

## Supporting Information

### Furoic Acid and Derivatives as Atypical Dienes in Diels-Alder Reactions

Răzvan C. Cioc,<sup>a</sup> Tom J. Smak,<sup>a</sup> Marc Crockatt,<sup>b</sup> Jan C. van der Waal,<sup>b</sup> and Pieter C. A. Bruijninx<sup>\*a</sup>

---

a Dr. R. C. Cioc, MSc. T. J. Smak, Prof. Dr. P. C. A. Bruijninx  
Organic Chemistry and Catalysis, Debye Institute for Nanomaterials Science, Faculty of Science, Utrecht University  
Universiteitsweg 99, 3584 CG, Utrecht (The Netherlands)  
E-mail: p.c.a.bruijninx@uu.nl

b M. Crockatt, Dr. J. C. van der Waal  
Department of Sustainable Process and Energy Systems, TNO  
Leeghwaterstraat 44, 2628 CA Delft (The Netherlands)

## General information

Unless stated otherwise, all solvents and commercially available reagents were used as purchased. The esters of 2-furoic acid (ethyl, isopropyl) were prepared by esterification of furoyl chloride in the respective alcohol solvent;<sup>[1]</sup> the *tert*-butyl ester was prepared as described below. Similarly, the amide derivatives were prepared by acylation the corresponding amines with 2-furoyl chloride. Spectral data was in agreement with literature values.<sup>[1][2][3]</sup>

Nuclear magnetic resonance (NMR) spectra were recorded on an Agilent MRF 400 equipped with a OneNMR probe and Optima Tune system or a Varian VNMR-S-400 equipped with a PFG probe. Resonances were referenced to residual solvent peaks (<sup>1</sup>H: δ 7.26 ppm, <sup>13</sup>C{<sup>1</sup>H}: δ 77.16 ppm for CDCl<sub>3</sub>, <sup>1</sup>H: δ 2.50 ppm, <sup>13</sup>C{<sup>1</sup>H}: δ 39.52 ppm for DMSO-d<sub>6</sub>, <sup>1</sup>H: δ 2.05 ppm, <sup>13</sup>C{<sup>1</sup>H}: δ 29.84 ppm for acetone-d<sub>6</sub> and <sup>1</sup>H: 4.79 ppm for D<sub>2</sub>O) Chemical shifts (δ) are given in ppm and coupling constants (*J*) are quoted in hertz (Hz). Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), br (broad singlet) and m (multiplet) or combinations thereof. Electrospray Ionization (ESI) mass spectrometry was carried out using an Agilent technologies 6560 ion mobility Q-TOF instrument.

## Stereochemical information

The *exo*- and *endo*- configurations for the Diels-Alder adducts were assigned following the rationale described in our previous study.<sup>[4]</sup>

## Experimental procedures

### *Reaction optimization*

In a vial, 2-furoic acid **1a** (56 mg, 0.5 mmol, 1 equiv) and *N*-methyl maleimide **2a** (83 mg, 0.75 mmol, 1.5 equiv) and additive were dissolved in solvent (0.5 mL, 1 M). The vial was sealed and the mixture was stirred at 50 °C for the indicated time. The reaction was stopped, the mixture was allowed to cool to ambient temperature and the conversion was determined by crude <sup>1</sup>H-NMR analysis.

### *General synthesis of adducts of furoic acids 3a-j*

2-furoic acid **1** (5 mmol, 1 equiv) was dissolved in demineralized H<sub>2</sub>O (5 mL, 1 M). 50 wt.% NaOH solution (5 mmol, 1 equiv) and maleimide **2** (7.5 mmol, 1.5 equiv) were then added. The mixture was stirred at 50 °C for 16 hours and then the crude conversion was determined by <sup>1</sup>H-NMR analysis. The reaction was stopped and the mixture was allowed to cool to ambient temperature. The mixture was then transferred to a separatory funnel and washed with dichloromethane (3x 2.5 mL). The aqueous phase was transferred to a round bottom flask and solid NaCl (1 g) was then added. The solution was acidified with 85% H<sub>3</sub>PO<sub>4</sub> to a pH of 1-2 and cooled to 0-5 °C. The Diels-Alder adduct **3** precipitated and the suspension was stirred at 0-5 °C for at least one hour prior to filtration. The precipitate was washed twice with cold H<sub>2</sub>O (2x 1 mL), collected and dried *in vacuo*.

### *General synthesis of adducts of furoic acid derivatives 3k-s*

2-Furoic acid ester or amide **1** (5 mmol, 1 equiv) was diluted with in demineralized H<sub>2</sub>O (5 mL, 1 M). Maleimide **2** (7.5 mmol, 1.5 equiv) was then added. The mixture was stirred at 50 °C for 16 hours and then the crude conversion was determined by <sup>1</sup>H-NMR analysis.. The reaction was stopped and the mixture was allowed to cool to ambient temperature. If precipitation had occurred, the product was isolated by filtration; otherwise, the product was extracted in dichloromethane and purified by column chromatography on silicagel.

### Recycling experiment

2-Furoic acid **1a** (5 mmol, 1 equiv) was dissolved in demineralized H<sub>2</sub>O (2.5 mL, 2 M) after which *N*-methyl maleimide **2a** (5 mmol, 1 equiv). The mixture was stirred at 50 °C for 16 hours. In time, the solution turns into a very thick paste. The mixture was allowed to cool to ambient temperature and diluted with petroleum ether (5 mL) to make the suspension more mobile. The suspension was stirred for one hour prior filtration. The filtrate was used as rinse and the product was washed with H<sub>2</sub>O (0.5 mL). The product **3a** was collected and dried *in vacuo*. A white solid was obtained of sufficient purity according to <sup>1</sup>H-NMR (700 mg, 63%). The petroleum ether layer in the filtrate was decanted and the aqueous layer was concentrated to dryness *in vacuo* (55 °C). Additional **1a** and **2a** (up to 5 mmol) and H<sub>2</sub>O (2.5 mL) were added and the sequence of steps was repeated. A white solid was obtained containing 2 wt-% **1a** according to <sup>1</sup>H-NMR (725 mg, 65%, corrected).

### Reaction profiles

Formation of **3a** in D<sub>2</sub>O (with addition of NaOH)

2-Furoic acid (56 mg, 0.5 mmol, 1 equiv) was dissolved in D<sub>2</sub>O (1 mL, 0.5 M) in a glass vial (note that the higher dilution was used to prevent product crystallization in the NMR-tube later on). If specified, 50 wt-% NaOH was added (0.5 mmol, 1 equiv). *N*-methyl maleimide **2a** (55 mg, 0.5 mmol, 1 equiv) was added and the mixture was homogenized. The solution was transferred to an NMR tube and the conversion at 50 °C was monitored *in situ*.

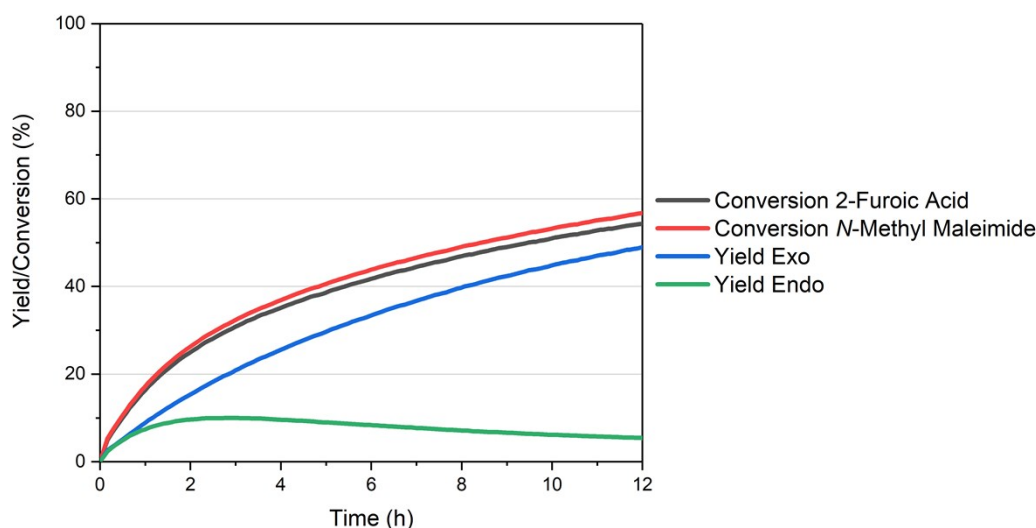


Figure S1. Kinetic profile of reaction between **1a** and **2a** (D<sub>2</sub>O)

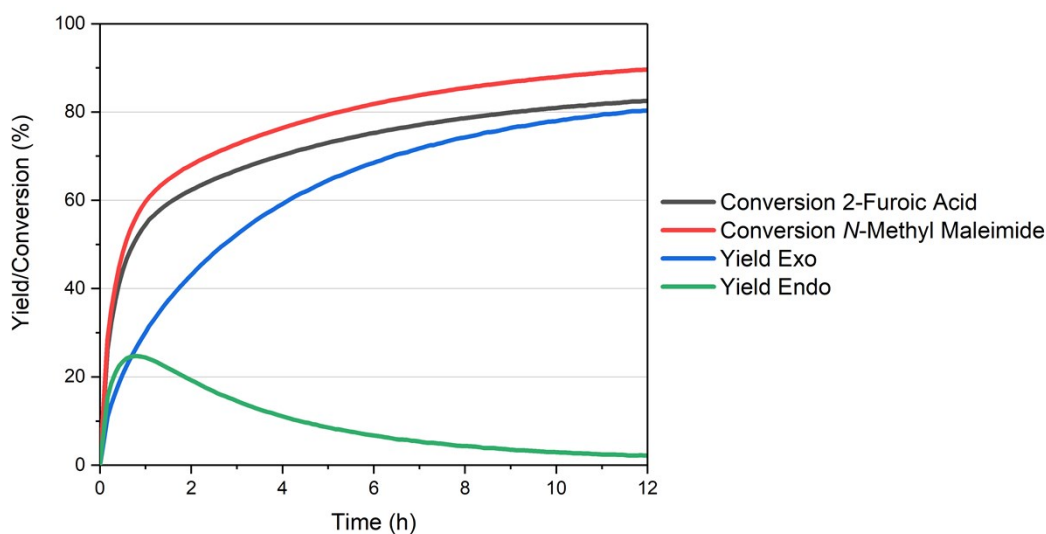


Figure S2. Kinetic profile of reaction between **1a** and **2a** with addition of NaOH (D<sub>2</sub>O)

Formation of **3a** in organic solvents (with addition of  $\text{NEt}_3$ )  
 2-Furoic acid (56 mg, 0.5 mmol, 1 equiv) was dissolved in  $\text{CDCl}_3$  and  $\text{CD}_3\text{OD}$  (1 mL, 0.5 M) respectively, in a glass vial. If specified,  $\text{NEt}_3$  was added (0.5 mmol, 1 equiv). *N*-methyl maleimide **2a** (55 mg, 0.5 mmol, 1 equiv) was added and the mixture was homogenized. The solutions were transferred to NMR tubes and the conversions at 50 °C were monitored *in situ*.

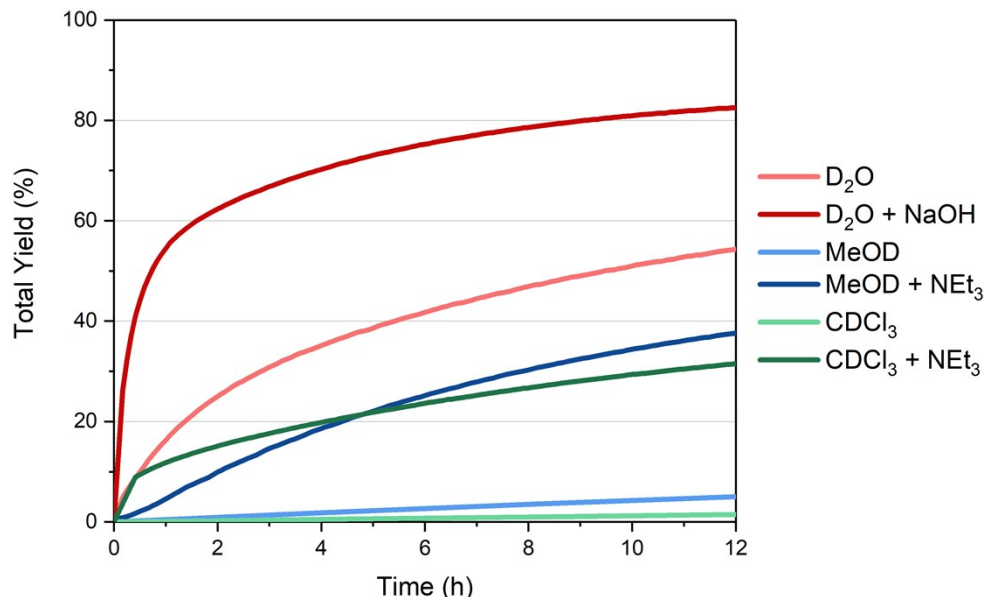


Figure S3. Kinetic profile of reaction between **1a** and **2a** in selected solvents, with or without the addition of base

Determination of equilibrium conversion  
 2-Furoic acid (56 mg, 0.5 mmol, 1 equiv) was dissolved in  $\text{D}_2\text{O}$  and  $\text{CD}_3\text{OD}$  (2 mL, 0.25 M) respectively. Note that the higher dilution was used to prevent product crystallization. *N*-methyl maleimide **2a** (83 mg, 0.75 mmol, 1.5 equiv) was added and the mixture was stirred at 50 °C. The reaction mixture was periodically sampled for  $^1\text{H-NMR}$  analysis over the course of 8 days.

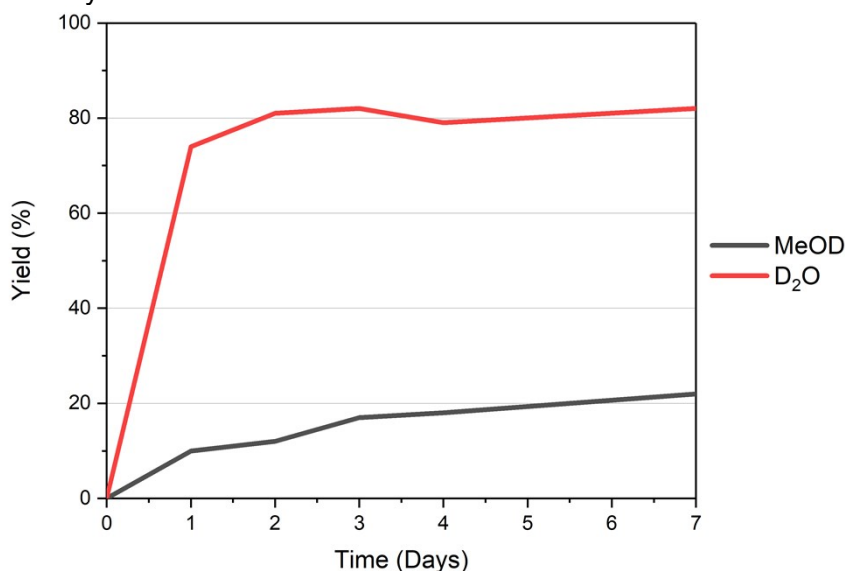


Figure S4. Kinetic profile of reaction between **1a** and **2a** in  $\text{D}_2\text{O}$  and  $\text{CD}_3\text{OD}$ : determination of equilibrium conversion

### Substituent effect

(5-Substituted-) 2-furoic acid (2 mmol, 1 equiv) was dissolved in H<sub>2</sub>O (2 mL) in a glass vial. NaOH solution (1 M) was added (2 mL, 2 mmol, 1 equiv). *N*-methyl maleimide **2a** (2 mmol, 1 equiv) was then added and the mixture was homogenized. The mixture was stirred at 50 °C and the conversion was monitored by <sup>1</sup>H-NMR spectroscopy (samples diluted in D<sub>2</sub>O, water suppression, 20 sec relaxation delay).

Figure S5 (both left and right) indicates that the fastest equilibration occurs for R<sup>1</sup> = Me (approx. 7 h); however, this diene does not afford the highest equilibrium conversion. In general, it is not trivial to distinguish between kinetic and thermodynamic effects when comparing the performance of various substrates (unless the conversion profile is recorded, as shown herein).

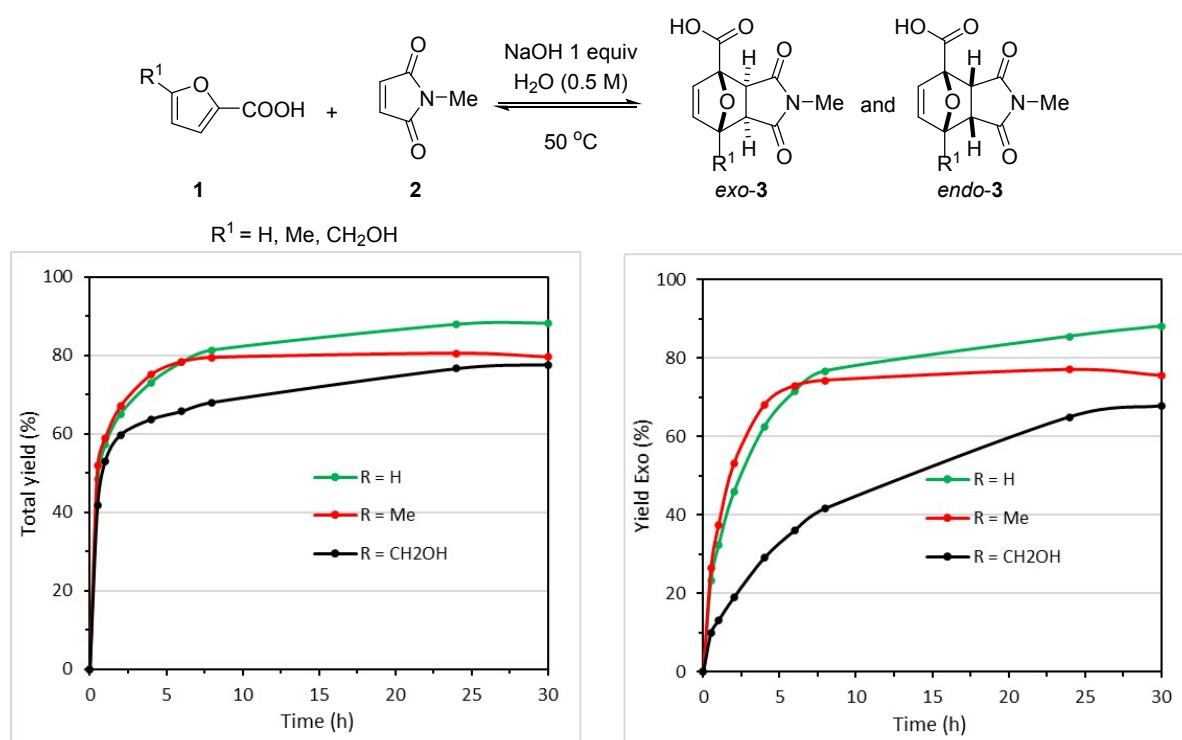


Figure S5. Kinetic profile of reaction between 5-substituted-2-furoic acids and **2a** (H<sub>2</sub>O, 0.5 M, 1 equiv NaOH): total yield (left) and yield *exo*-**3a** (right)

### Determination of pK<sub>a</sub>

The pK<sub>a</sub> of DA adduct **3b** was determined by pH titration. **3b** was selected as representative product based on its highest aqueous solubility. 1 mmol of **3b** was dissolved in water (approx. 30 mL) and titrated with NaOH 0.05 M. The pH was recorded during the titration using a WTW pH 315i electrode. As control, the pK<sub>a</sub> of 2-furoic acid **1a** was also analogously determined.

The pK<sub>a</sub> is the intercept of the plot of the solution pH as function of log([**3b**-Na]/[**3b**]). We have thus calculated the pK<sub>a</sub> = 2.55 for **3b** and pK<sub>a</sub> = 3.13 for **1a** (lit. 3.12<sup>[5]</sup>).

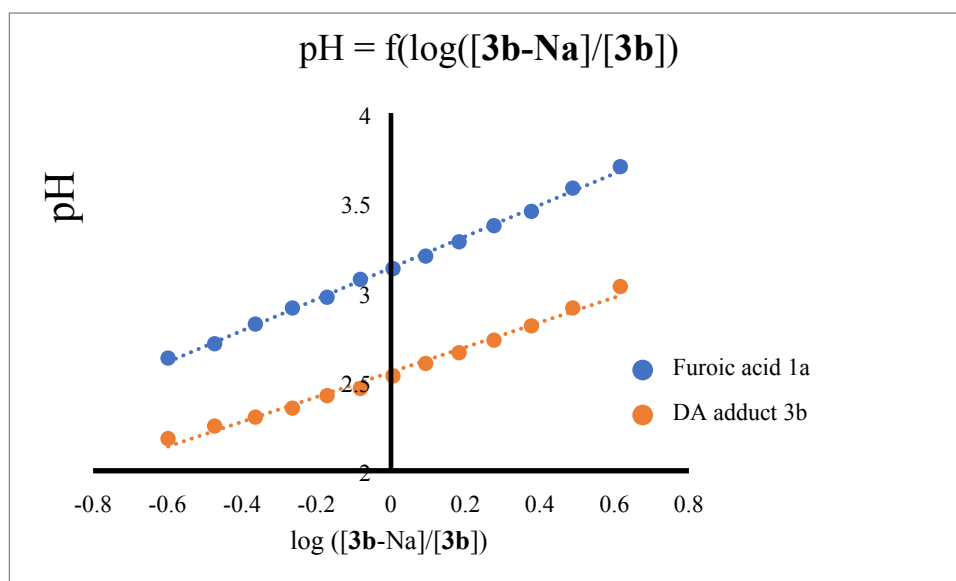


Figure S6. Determination of the  $pK_a$  of adduct **3b**

The difference in  $pK_a$  values translates into a difference in the reaction Gibbs free energy (at 50 °C, assuming  $\Delta pK_a$  is temperature independent) of  $2.303 RT(pK_a^{3b} - pK_a^{1a}) = -3.6$  kJ/mol or in other words, the equilibrium constant is 4 times larger in reaction (2) compared to (1).

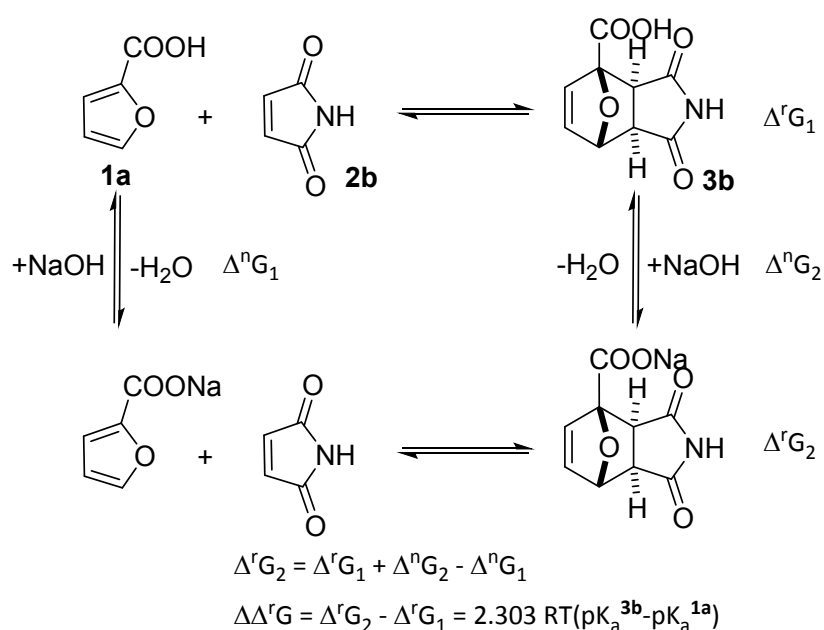
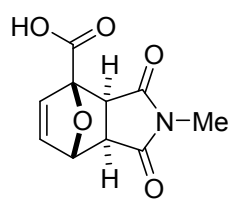


Figure S7. Calculation of  $\Delta\Delta^r G$  according to the thermodynamics law of Hess

#### Tert-butyl 2-furoate

KOtBu (941 mg, 8.4 mmol, 1.1 equiv) was dissolved in THF (7 mL). The solution was cooled to 0-5 °C and 2-furoyl chloride (1000 mg, 7.7 mmol, 1 equiv) was then added dropwise. The mixture was stirred for 5 minutes and then DMAP (94 mg, 0.77 mmol, 0.1 equiv) was added. This mixture was stirred for 1 hour. The product was purified by column chromatography on silicagel using petroleum ether/acetone (95:5) mixture as eluent. The product was obtained as a colourless oil in 39% yield (504 mg, 3.0 mmol). Product identity was confirmed by comparison to literature spectra.<sup>[1]</sup>

## Characterization of novel compounds

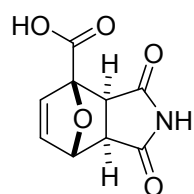


Diels-Alder adduct *exo*-**3a**<sup>[4]</sup>

Prepared from furoic acid **1a** (560 mg, 5 mmol, 1 equiv) and *N*-methyl maleimide **2a** (826 mg, 7.5 mmol, 1.5 equiv) according to the general synthetic procedure. The product was obtained as a white solid in 77% yield (858 mg, 3.86 mmol).

Prepared from furoic acid **1a** (4.48 g, 40 mmol, 1 equiv) and *N*-methyl maleimide **2a** (6.66 g, 60 mmol, 1.5 equiv) according to the general synthetic procedure. The product was obtained as a white solid in 92% yield (8.23 g, 36.9 mmol).

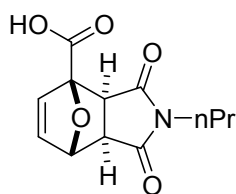
<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 400 MHz): δ 6.67 (dd, *J* = 5.5, 1.8 Hz, 1H), 6.56 (d, *J* = 5.5 Hz, 1H), 5.17 (d, *J* = 1.8 Hz, 1H), 3.16 (d, *J* = 6.5 Hz, 1H), 3.06 (d, *J* = 6.5 Hz, 1H), 2.80 (s, 3H), ppm. <sup>13</sup>C{<sup>1</sup>H}-NMR (DMSO-d<sub>6</sub>, 100 MHz): δ 175.8, 174.1, 167.9, 137.9, 136.3, 88.6, 80.4, 49.9, 48.7, 24.5, ppm. IR (ATR):  $\tilde{\nu}$  = 3515 (m), 3433 (w), 1769 (w), 1698 (s), 1679 (s), 1445 (m), 1381 (w), 1285 (m), 1223 (w), 1145 (m), 961 (m), 722 (w), 655 (w), 591 (w). ESI-MS: *m/z* [*M*-H]<sup>-</sup> calculated for C<sub>10</sub>H<sub>8</sub>NO<sub>5</sub>, 222.0408, found 222.0428.



Diels-Alder adduct *exo*-**3b**

Prepared from furoic acid **1a** (560 mg, 5 mmol, 1 equiv) and maleimide **2b** (728 mg, 7.5 mmol, 1.5 equiv) according to the general synthetic procedure. The product was obtained as a white solid in 68% yield (710 mg, 3.40 mmol).

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ 11.24 (s, 1H), 6.65 (dd, *J* = 5.5, 2.0 Hz, 1H), 6.54 (d, *J* = 5.5 Hz, 1H), 5.16 (d, *J* = 2.0 Hz, 1H), 3.09 (d, *J* = 6.5 Hz, 1H), 2.99 (d, *J* = 6.5 Hz, 1H), ppm. <sup>13</sup>C{<sup>1</sup>H}-NMR (DMSO-d<sub>6</sub>) δ 177.1, 175.4, 168.1, 137.8, 136.5, 88.8, 80.5, 51.0, 49.9, ppm. IR (ATR):  $\tilde{\nu}$  = 3600-2600 (br), 1764 (w), 1736 (s), 1682 (s), 1424 (w), 1348 (m), 1290 (m), 1167 (s), 996 (m), 939 (m), 858 (m), 728 (w), 626 (m), 498 (w). ESI-MS: *m/z* [*M*-H]<sup>-</sup> calculated for C<sub>9</sub>H<sub>6</sub>NO<sub>5</sub>, 208.0251, found 208.0257.

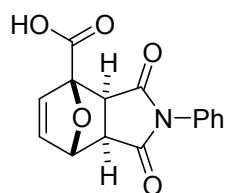


Diels-Alder adduct *exo*-**3c**

Prepared from furoic acid **1a** (560 mg, 5 mmol, 1 equiv) and *N*-propyl maleimide **2c** (1044 mg, 7.5 mmol, 1.5 equiv) according to the general synthetic procedure. The product was obtained as a white solid in 72% yield (905 mg, 3.60 mmol).

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ 6.67 (dd, *J* = 5.5, 2.0 Hz, 1H), 6.57 (d, *J* = 5.5 Hz, 1H), 5.18 (d, *J* = 2.0 Hz, 1H), 3.30 (t, *J* = 7.0 Hz, 2H), 3.15 (d, *J* = 6.5 Hz, 1H), 3.06 (d, *J* = 6.5 Hz, 1H), 1.44 (sext, *J* = 7.0 Hz, 2H), 0.79 (t, *J* = 7.4 Hz, 3H), ppm. <sup>13</sup>C{<sup>1</sup>H}-NMR (DMSO-d<sub>6</sub>) δ 175.8, 174.1, 167.8, 137.8, 136.4, 88.7, 80.5, 49.7, 48.5, 39.6, 20.4, 10.9, ppm. IR (ATR):  $\tilde{\nu}$  = 3600-2600 (br), 1767 (w), 1727 (s), 1675 (s), 1410 (m), 1328 (m), 1209 (w), 1058 (w), 963 (w), 863 (w), 724 (w), 658 (w). ESI-MS: *m/z* [*M*-H]<sup>-</sup> calculated for C<sub>12</sub>H<sub>12</sub>NO<sub>5</sub>, 250.0721, found 250.0729.

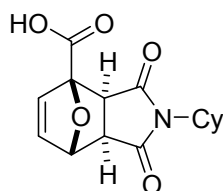
Diels-Alder adduct *exo*-**3d**



Prepared from furoic acid **1a** (560 mg, 5 mmol, 1 equiv) and *N*-Phenyl maleimide **2d** (1289 mg, 7.5 mmol, 1.5 equiv) according to the general synthetic procedure. The crude product was washed extensively with water on the filter to remove unreacted **1a**. The product was obtained as a

white solid in 21% yield (297 mg, 1.04 mmol). Contains a minor amount of *N*-Phenyl maleamic acid.

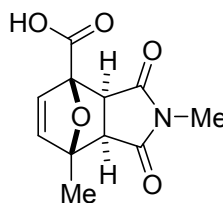
$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$  7.50 (t,  $J$  = 7.5 Hz, 2H), 7.42 (t,  $J$  = 7.5 Hz, 1H), 7.20 (d,  $J$  = 7.5 Hz, 2H), 6.73 (dd,  $J$  = 5.5, 2.0 Hz, 1H), 6.65 (d,  $J$  = 5.5 Hz, 1H), 5.31 (d,  $J$  = 2.0 Hz, 1H), 3.31 (d,  $J$  = 6.5 Hz, 1H), 3.24 (d,  $J$  = 6.5 Hz, 1H), ppm.  $^{13}\text{C}\{^1\text{H}\}$ -NMR (DMSO- $d_6$ )  $\delta$  175.0, 173.3, 167.9, 138.0, 136.5, 132.0, 129.0, 128.6, 126.7, 89.1, 81.0, 50.2, 48.9, ppm. IR (ATR):  $\tilde{\nu}$  = 3300-2600 (br), 1757 (m), 1667 (s), 1389 (m), 1269 (m), 1200 (m), 1169 (m), 1062 (m), 812 (w), 651 (w). ESI-MS:  $m/z$  [ $M-H$ ] $^-$  calculated for  $\text{C}_{15}\text{H}_{10}\text{NO}_5$ , 284.0564, found 284.0576.



#### Diels-Alder adduct *exo*-3e

Prepared from furoic acid **1a** (560 mg, 5 mmol, 1 equiv) and *N*-cyclohexyl maleimide **2e** (1344 mg, 7.5 mmol, 1.5 equiv) according to the general synthetic procedure (a 1:4 mixture of water:methanol was used instead of 100% water). The product was obtained as a white solid in 31% yield (451 mg, 1.55 mmol).

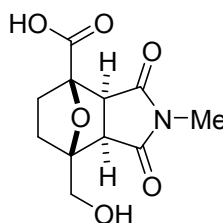
$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$  6.66 (dd, 1H), 6.56 (d,  $J$  = 5.5 Hz, 1H), 5.16 (d,  $J$  = 2.0 Hz, 1H), 3.75 (tt,  $J$  = 12.5, 3.5 Hz, 1H), 3.08 (d,  $J$  = 6.5 Hz, 1H), 3.00 (d,  $J$  = 6.5 Hz, 1H), 1.97 (qd,  $J$  = 12.5, 3.5 Hz, 2H), 1.75 (d,  $J$  = 13.0 Hz, 2H), 1.59 (d,  $J$  = 13.0 Hz, 1H), 1.47 (d,  $J$  = 13.0 Hz, 2H), 1.23 (qt,  $J$  = 13.0, 3.5 Hz, 2H), 1.08 (qt,  $J$  = 13.0, 3.5 Hz, 1H), ppm.  $^{13}\text{C}\{^1\text{H}\}$ -NMR (DMSO- $d_6$ )  $\delta$  175.8, 174.0, 167.8, 137.8, 136.5, 88.8, 80.6, 50.9, 49.4, 48.1, 28.5, (28.3), 25.3, (25.3), 24.8, ppm (signals due to conformers observed, listed in brackets). IR (ATR):  $\tilde{\nu}$  = 3552 (m), 3459 (w), 3300-2400 (br), 1779 (w), 1704 (s), 1493 (m), 1385 (m), 1302 (w), 1194 (m), 1077 (w), 950 (w), 723 (w), 642 (w). ESI-MS:  $m/z$  [ $M-H$ ] $^-$  calculated for  $\text{C}_{15}\text{H}_{16}\text{NO}_5$ , 290.1034, found 290.1040.



#### Diels-Alder adduct *exo*-3f

Prepared from 5-methyl 2-furoic acid **1b** (378 mg, 3 mmol, 1 equiv) and *N*-methyl maleimide **2a** (500 mg, 4.5 mmol, 1.5 equiv) according to the general synthetic procedure. The crude product was washed extensively with water on the filter to remove unreacted **1b**. The product was obtained as a white solid in 75% yield (531 mg, 2.24 mmol).

$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$  6.56 (d,  $J$  = 5.5 Hz, 1H), 6.51 (d,  $J$  = 5.5 Hz, 1H), 3.27 (d,  $J$  = 6.5 Hz, 1H), 2.93 (d,  $J$  = 6.5 Hz, 1H), 2.80 (s, 3H), 1.58 (s, 3H), ppm.  $^{13}\text{C}\{^1\text{H}\}$ -NMR (DMSO- $d_6$ )  $\delta$  174.4, 174.0, 168.0, 141.4, 136.8, 88.2, 87.6, 52.8, 50.7, 24.5, 15.4, ppm. IR (ATR):  $\tilde{\nu}$  = 3530 (m), 3474 (m), 3100-2400 (br), 1772 (w), 1734 (m), 1682 (s), 1440 (w), 1385 (w), 1293 (m), 1243 (w), 1105 (m), 1001 (w), 865 (m), 725 (w). ESI-MS:  $m/z$  [ $M-H$ ] $^-$  calculated for  $\text{C}_{11}\text{H}_{10}\text{NO}_5$ , 236.0564, found 236.0567.



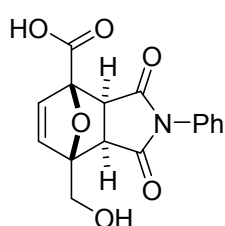
#### Hydrogenated Diels-Alder adduct *exo*-3g

Prepared from 5-hydroxymethyl 2-furoic acid **1b** (284 mg, 2 mmol, 1 equiv) and *N*-methyl maleimide **2a** (333 mg, 3 mmol, 1.5 equiv) according to the general synthetic procedure. At the end of the reaction, the mixture was cooled to ambient temperature, diluted with water (1 mL) and subjected to hydrogenation on 10% Pd/C (71 mg) using a  $\text{H}_2$  balloon. After 7 hours stirring at ambient temperature, the mixture was filtered over Celite and the filter was rinsed with water (2x). The solution was then transferred to a separatory funnel and unreacted **2a** was washed away with dichloromethane (3x 2 mL). The aqueous phase was then subjected to. The solution was acidified using 35% HCl to pH approx. 2 and the water was removed *in vacuo* leaving a white powder as a residue. The product was separated from NaCl by



extracting in MeOH as  $\text{NEt}_3$  salt (free **3g** dissolved poorly in MeOH and other organic solvents). The extraction was done in three stages, using in total a mixture of MeOH (4 mL) and 4 mmol  $\text{NEt}_3$ . After filtering off the inorganic salts, the filtrate was evaporated *in vacuo*. The solid residue was redissolved in MeOH (1 mL) and **3g** was precipitated by the addition of 35% HCl (208 mg). The resulting suspension was stirred at 0-5 °C for 1 hour and then filtered. The product was rinsed with a small volume of cold MeOH and dried *in vacuo*. The product was obtained as a white powder (258 mg, 1.01 mmol, 51%).

$^1\text{H-NMR}$  ( $\text{D}_2\text{O}$ )  $\delta$  4.02 (d,  $J = 12.0$  Hz, 1H), 3.92 (d,  $J = 12.0$  Hz, 1H), 3.66 (d,  $J = 7.0$  Hz, 1H), 3.38 (d,  $J = 7.0$  Hz, 1H), 2.93 (s, 3H), 2.28-2.18 (m, 1H), 2.18-2.00 (m, 2H), 1.94-1.82 (m, 1H), ppm.  $^{13}\text{C}\{^1\text{H}\}$ -NMR ( $\text{D}_2\text{O}$ )  $\delta$  177.6, 174.4, 172.1, 88.7, 86.7, 59.8, 53.1, 50.7, 32.7, 30.2, 24.7, ppm. IR (ATR):  $\tilde{\nu} = 3427$  (s), 1749 (s), 1687 (s), 1440 (m), 1381 (w), 1297 (m), 1257 (w), 1187 (w), 1003 (m), 847 (m), 682 (m). ESI-MS:  $m/z$   $[M-H]^-$  calculated for  $\text{C}_{11}\text{H}_{12}\text{NO}_6$ , 254.0670, found 254.0684.



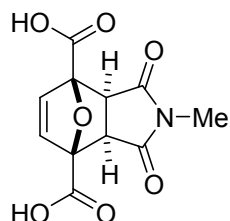
#### Diels-Alder adduct *exo*-**3h**

Prepared from furoic acid **1c** (711 mg, 5 mmol, 1 equiv) and *N*-Phenyl maleimide **2a** (1289 mg, 7.5 mmol, 1.5 equiv) according to the general synthetic procedure. The crude product was washed extensively with water on the filter to remove unreacted **1c**. The product was obtained as a white solid in 11% yield (169 mg, 0.54 mmol). Contains a minor amount of *N*-Phenyl maleamic acid.

$^1\text{H-NMR}$  (acetone- $d_6$ )  $\delta$  7.48 (t,  $J = 8.0$  Hz, 2H), 7.40 (t,  $J = 6.0$  Hz, 1H), 7.26 (d,  $J = 7.0$  Hz, 2H), 6.79 (d,  $J = 5.5$  Hz, 1H), 6.69 (d,  $J = 5.5$  Hz, 1H), 4.24 (d,  $J = 12.5$  Hz, 1H), 4.01 (d,  $J = 12.5$  Hz, 1H), 3.55 (d,  $J = 6.5$  Hz, 1H), 3.31 (d,  $J = 6.5$  Hz, 1H), ppm.  $^{13}\text{C}\{^1\text{H}\}$ -NMR (DMSO- $d_6$ )  $\delta$  173.3, 173.1, 168.0, 139.6, 136.6, 132.0, 129.0, 128.5, 126.7, 92.3, 88.7, 58.8, 52.8, 49.4, ppm. IR (ATR):  $\tilde{\nu} = 3600$ -2800 (br), 1773 (w), 1705 (s), 1493 (m), 1383 (m), 1192 (m), 995 (m), 854 (w), 742 (w), 513 (w). ESI-MS:  $m/z$   $[M-H]^-$  calculated for  $\text{C}_{16}\text{H}_{12}\text{NO}_6$ , 314.0670, found 314.0683.

#### Diels-Alder adduct *exo*-**3i**

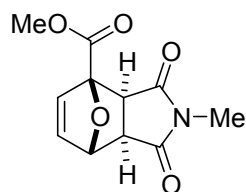
The reaction with 5-formyl-2-furoic acid lead to very little conversion. Isolation of adduct **3i** was not attempted.



#### Diels-Alder adduct *exo*-**3j**

Prepared from 2,5-furan dicarboxylic acid **1e** (312 mg, 2 mmol, 1 equiv) and *N*-methyl maleimide **2a** (333 mg, 3 mmol, 1.5 equiv) according to the general synthetic procedure (2 M concentration was used). At the end of the reaction, the mixture was cooled to 0-5 °C. A this suspension formed. Acetone was added gradually (2 mL). The solids (likely unreacted **2a**) rapidly redissolved while a second, dense (oily) phase began to form. This biphasic mixture was stirred at 0-5 °C for 2 hours but crystallization did not occur. The acetone layer was decanted off and the mixture was washed two more times with acetone (2x 2 mL) in a similar manner. The residual oily mixture was sampled, diluted in  $\text{D}_2\text{O}$  and characterized by crude NMR analysis. Various attempts to isolate **3j** (either as dicarboxylic acid or bis-Na salt) failed due to high water solubility, facile cycloreversion and difficult separation from unreacted **1e**.

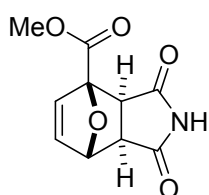
$^1\text{H-NMR}$  ( $\text{D}_2\text{O}$ , water suppression)  $\delta$  6.71 (s, 2H), 3.39 (s, 2H), 2.94 (s, 3H), ppm.  $^{13}\text{C}\{^1\text{H}\}$ -NMR ( $\text{D}_2\text{O}$ )  $\delta$  176.7, 165.9, 138.4, 90.7, 51.2, 24.7, ppm. ESI-MS:  $m/z$   $[M-H]^-$  calculated for  $\text{C}_{11}\text{H}_8\text{NO}_7$ , 266.0306, found 266.0326.



#### Diels-Alder adduct *exo*-3k

Prepared from methyl 2-furoate (378 mg, 3 mmol, 1 equiv) and *N*-methyl maleimide **2a** (500 mg, 4.5 mmol, 1.5 equiv) according to the general synthetic procedure. The product was isolated by filtration. The product was obtained as a white solid in 52% yield (370 mg, 1.56 mmol).

$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$  6.71 (dd,  $J = 5.5, 2.0$  Hz, 1H), 6.59 (d,  $J = 5.5$  Hz, 1H), 5.23 (d,  $J = 2.0$  Hz, 1H), 3.78 (s, 3H), 3.22 (d,  $J = 6.5$  Hz, 1H), 3.09 (d,  $J = 6.5$  Hz, 1H), 2.80 (s, 3H), ppm.  $^{13}\text{C}\{^1\text{H}\}$ -NMR (DMSO- $d_6$ )  $\delta$  175.6, 174.1, 166.9, 138.1, 135.6, 88.4, 80.6, 52.4, 50.3, 48.5, 24.5, ppm. IR (ATR):  $\tilde{\nu} = 3600\text{-}2800$  (br), 1768 (w), 1753 (m), 1704 (s), 1688 (s), 1438 (m), 1285 (m), 1130 (m), 915 (w), 718 (w), 589 (w). ESI-MS:  $m/z$   $[M+H]^+$  calculated for  $\text{C}_{11}\text{H}_{12}\text{NO}_5$ , 238.0710 found 238.0712.

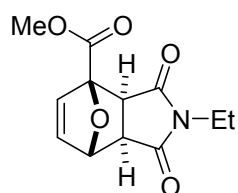


#### Diels-Alder adduct *exo*-3l

Prepared from methyl 2-furoate (378 mg, 3 mmol, 1 equiv) and maleimide **2b** (437 mg, 4.5 mmol, 1.5 equiv) according to the general synthetic procedure. The product was isolated by filtration. The product was obtained as a white solid in 43% yield (286 mg, 1.28 mmol).

Alternatively, the Diels-Alder adduct **3l** was prepared by reacting methyl 2-furoate (504 mg, 4 mmol, 1 equiv) and maleimide **2b** (582 mg, 6 mmol, 1.5 equiv) in  $\text{H}_2\text{O}$  (1 mL, 4 M). The reaction mixture was heated for 24 hours at 50  $^\circ\text{C}$ , a suspension formed in time. The mixture was cooled to room temperature and diluted with  $\text{H}_2\text{O}$  (1 mL). The suspension was filtered and the product was washed with  $\text{H}_2\text{O}$  (2x 1 mL). The product was dried *in vacuo*. A white solid was obtained in 82% yield (732 mg, 3.28 mmol).

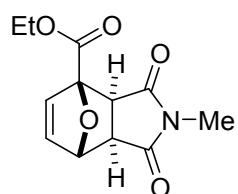
$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$  11.30 (s, 1H), 6.69 (dd,  $J = 5.6, 2.0$  Hz, 1H), 6.57 (d,  $J = 5.5$  Hz, 1H), 5.21 (d,  $J = 2.0$  Hz, 1H), 3.77 (s, 3H), 3.15 (d,  $J = 6.5$  Hz, 1H), 3.02 (d,  $J = 6.5$  Hz, 1H), ppm.  $^{13}\text{C}\{^1\text{H}\}$ -NMR (DMSO- $d_6$ )  $\delta$  176.9, 175.4, 167.1, 138.2, 135.8, 88.6, 80.8, 52.3, 51.5, 49.7, ppm. IR (ATR):  $\tilde{\nu} = 3294$  (s), 3200-2900 (br), 1772 (w), 1746 (m), 1711 (s), 1440 (w), 1328 (m), 1165 (m), 1066 (m), 921 (m), 767 (m), 629 (m), 427 (w). ESI-MS:  $m/z$   $[M+Na]^+$  calculated for  $\text{C}_{10}\text{H}_9\text{NNaO}_5$ , 246.0373, found 246.0379.



#### Diels-Alder adduct *exo*-3m

Prepared from methyl 2-furoate (378 mg, 3 mmol, 1 equiv) and *N*-ethyl maleimide **2f** (563 mg, 4.5 mmol, 1.5 equiv) according to the general synthetic procedure. The product was isolated by filtration. The product was obtained as a white solid in 47% yield (352 mg, 1.40 mmol).

$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$  6.71 (dd,  $J = 5.5, 2.0$  Hz, 1H), 6.60 (d,  $J = 5.5$  Hz, 1H), 5.23 (d,  $J = 2.0$  Hz, 1H), 3.78 (s, 3H), 3.32 (q,  $J = 7.0$  Hz, 2H), 3.20 (d,  $J = 6.5$  Hz, 1H), 3.09 (d,  $J = 6.5$  Hz, 1H), 1.00 (t,  $J = 7.0$  Hz, 3H), ppm.  $^{13}\text{C}\{^1\text{H}\}$ -NMR (DMSO- $d_6$ )  $\delta$  175.3, 173.8, 166.9, 138.1, 135.7, 88.5, 80.7, 52.3, 50.2, 48.4, 33.1, 12.6, ppm. IR (ATR):  $\tilde{\nu} = 3200\text{-}2800$  (br), 1786 (w), 1750 (m), 1694 (s), 1403 (w), 1352 (m), 1223 (m), 1137 (m), 1058 (w), 839 (w), 720 (w), 656 (w). ESI-MS: the exact mass of this DA adduct could not be confirmed by ESI-MS.

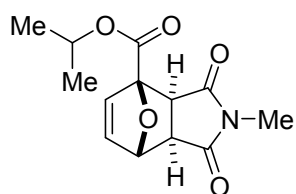


#### Diels-Alder adduct *exo*-3n

Prepared from ethyl 2-furoate (420 mg, 3 mmol, 1 equiv) and *N*-methyl maleimide **2a** (500 mg, 4.5 mmol, 1.5 equiv) according to the general

synthetic procedure. The product was isolated by extraction in dichloromethane (3x 1 mL) and purification by column chromatography on silicagel using petroleum ether/ethyl acetate (60:40) as eluent. The product was obtained as a white solid in 29% yield (220 mg, 0.87 mmol).

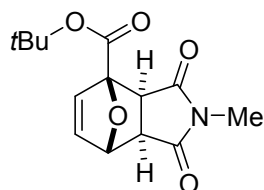
$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$  6.71 (dd,  $J$  = 5.5, 2.0 Hz, 1H), 6.59 (d,  $J$  = 5.5 Hz, 1H), 5.22 (d,  $J$  = 2.0 Hz, 1H), 4.32-4.20 (m, 2H), 3.21 (d,  $J$  = 6.5 Hz, 1H), 3.09 (d,  $J$  = 6.5 Hz, 1H), 2.81 (s, 3H), 1.27 (t,  $J$  = 7.0 Hz, 3H), ppm.  $^{13}\text{C}\{^1\text{H}\}$ -NMR (DMSO- $d_6$ )  $\delta$  175.6, 174.0, 166.4, 138.1, 135.7, 88.4, 80.6, 61.3, 50.3, 48.6, 24.5, 14.0, ppm. IR (ATR):  $\tilde{\nu}$  = 3100-2900 (br), 1766 (w), 1744 (m), 1688 (s), 1437 (m), 1296 (m), 1132 (m), 1061 (m), 720 (w), 659 (w). ESI-MS:  $m/z$  [ $M+\text{Na}$ ] $^+$  calculated for  $\text{C}_{12}\text{H}_{13}\text{NNaO}_5$ , 274.0686 found 274.0693.



#### Diels-Alder adduct *exo*-3o

Prepared from isopropyl 2-furoate (462 mg, 3 mmol, 1 equiv) and *N*-methyl maleimide **2a** (500 mg, 4.5 mmol, 1.5 equiv) according to the general synthetic procedure. The product was isolated by extraction in dichloromethane (3x 1 mL) and purification by column chromatography on silicagel using petroleum ether/ethyl acetate (60:40) as eluent. The product was obtained as a white solid in 26% yield (209 mg, 0.79 mmol).

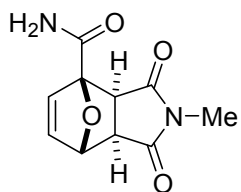
$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$  6.70 (dd,  $J$  = 5.5, 2.0 Hz, 1H), 6.57 (d,  $J$  = 5.5 Hz, 1H), 5.21 (d,  $J$  = 2.0 Hz, 1H), 5.08 (sept,  $J$  = 6.5 Hz, 1H), 3.18 (d,  $J$  = 6.5 Hz, 1H), 3.08 (d,  $J$  = 6.5 Hz, 1H), 2.80 (s, 3H), 1.29 (d,  $J$  = 6.5 Hz, 3H), 1.26 (d,  $J$  = 6.5 Hz, 3H), ppm.  $^{13}\text{C}\{^1\text{H}\}$ -NMR ( $\text{CDCl}_3$ )  $\delta$  175.1, 173.4, 165.9, 137.1, 136.7, 88.9, 81.2, 70.2, 50.1, 48.8, 25.0, 21.7, 21.6, ppm. IR (ATR):  $\tilde{\nu}$  = 3100-2900 (br), 1774 (w), 1741 (m), 1698 (s), 1435 (w), 1366 (m), 1287 (m), 1135 (w), 1057 (m), 960 (w), 708 (w), 602 (w). ESI-MS:  $m/z$  [ $M+\text{Na}$ ] $^+$  calculated for  $\text{C}_{13}\text{H}_{15}\text{NNaO}_5$ , 288.0842, found 288.0844.



#### Diels-Alder adduct *exo*-3p

Prepared from *tert*-butyl 2-furoate (504 mg, 3 mmol, 1 equiv) and *N*-methyl maleimide **2a** (500 mg, 4.5 mmol, 1.5 equiv) according to the general synthetic procedure. The product was isolated by extraction in dichloromethane (3x 1 mL) and purification by column chromatography on silicagel using petroleum ether/ethyl acetate (60:40) as eluent. The product was obtained as a colorless oil in 25% yield (210 mg, 0.75 mmol).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  6.58-6.54 (m, 2H), 5.30 (s, 1H), 3.13 (d,  $J$  = 6.5 Hz, 1H), 2.96 (s, 3H), 2.94 (d,  $J$  = 6.5 Hz, 1H), 1.57 (s, 9H), ppm.  $^{13}\text{C}\{^1\text{H}\}$ -NMR ( $\text{CDCl}_3$ )  $\delta$  175.3, 173.7, 165.4, 137.3, 137.2, 89.3, 84.0, 81.2, 50.1, 49.2, 28.2, 25.2, ppm. IR (ATR):  $\tilde{\nu}$  = 3100-2900 (br), 1731 (m), 1698 (s), 1435 (w), 1371 (w), 1333 (w), 1289 (w), 1132 (m), 1061 (m), 960 (w), 839 (w), 720 (w). ESI-MS:  $m/z$  [ $M+\text{Na}$ ] $^+$  calculated for  $\text{C}_{14}\text{H}_{17}\text{NNaO}_5$ , 302.0999, found 302.1001.

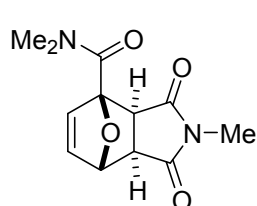


#### Diels-Alder adduct *exo*-3q

Prepared from 2-furamide (444 mg, 4 mmol, 1 equiv) and *N*-methyl maleimide **2a** (666 mg, 6 mmol, 1.5 equiv) according to the general synthetic procedure. The product was isolated by filtration. The product was obtained as a white solid in 77% yield (690 mg, 3.11 mmol).

$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$  7.42 (s, 1H), 7.27 (s, 1H), 6.63 (dd,  $J$  = 5.5, 2.0 Hz, 1H), 6.55 (d,  $J$  = 5.5 Hz, 1H), 5.20 (d,  $J$  = 2.0 Hz, 1H), 3.12 (d,  $J$  = 6.5 Hz, 1H), 3.07 (d,  $J$  = 6.5 Hz, 1H), 2.80 (s, 3H), ppm.  $^{13}\text{C}\{^1\text{H}\}$ -NMR (DMSO- $d_6$ )  $\delta$  175.9, 173.7, 167.6, 137.1, 89.8, 80.6, 49.3, 49.0, 24.5, ppm. IR (ATR):  $\tilde{\nu}$  = 3365 (m), 3300-2700 (br), 1767 (w), 1708 (m), 1690

(s), 1638 (s), 1431 (m), 1381 (m) 1291(m), 1105 (m), 994 (m), 904(m), 796 (w), 700 (m), 647 (m), 588 (m), 503(w). ESI-MS:  $m/z$   $[M+Na]^+$  calculated for  $C_{10}H_{10}N_2NaO_4$ , 245.0533, found 245.0539.

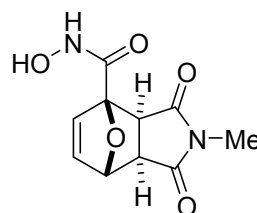


#### Diels-Alder adduct *exo-3r*

Prepared from *N,N*-dimethyl 2-furamide (556 mg, 4 mmol, 1 equiv) and *N*-methyl maleimide **2a** (666 mg, 6 mmol, 1.5 equiv) according to the general synthetic procedure. The mixture was a solution throughout the reaction. Upon cooling to ambient temperature, a precipitate formed.

The suspension was cooled to 0-5 °C and stirred for 5 hours before filtering. The solid was washed with water (0.5 mL). <sup>1</sup>H-NMR analysis indicated that the precipitate was mainly unreacted **2a**. The filtrate was divided in two portions of equal weight. One portion was transferred to a separatory funnel and washed with diethyl ether (4x 2 mL) to remove **2a**. The product was then extracted from the aqueous phase into dichloromethane (2x 5 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to yield a white solid. The solid was triturated with diethyl ether (2x 2 mL) to remove traces of unreacted furamide. The product was dried affording 206 mg of a white powder (41%, 0.82 mmol).

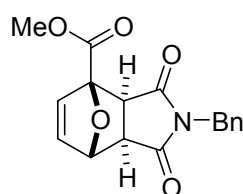
<sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) δ 6.69 (d, *J* = 5.5 Hz, 1H), 6.65 (dd, *J* = 5.5, 2.0 Hz, 1H), 5.22 (d, *J* = 2.0 Hz, 1H), 3.24 (d, *J* = 6.5 Hz, 1H), 3.10 (d, *J* = 6.5 Hz, 1H), 2.97 (s, 3H), 2.89 (s, 3H), 2.81 (s, 3H), ppm. <sup>13</sup>C{<sup>1</sup>H}-NMR (DMSO-*d*<sub>6</sub>) δ 175.6, 174.3, 164.9, 138.0, 136.9, 90.9, 80.7, 50.1, 48.8, 36.5, 36.3, 24.4, ppm. IR (ATR):  $\tilde{\nu}$  = 3100-2900 (br), 1765 (w), 1693 (s), 1628 (s), 1435 (w), 1380 (m), 1137 (w), 1049 (m), 854 (w), 730 (w), 658 (w). ESI-MS:  $m/z$   $[M+H]^+$  calculated for  $C_{12}H_{15}N_2O_4$ , 251.1026, found 251.1026.



#### Diels-Alder adduct *exo-3s*

Prepared from furan hydroxamic acid (64 mg, 0.5 mmol, 1 equiv) and *N*-methyl maleimide **2a** (83 mg, 0.75 mmol, 1.5 equiv) according to the general synthetic procedure. The product was isolated by filtration. The product was obtained as a white solid in 69% yield (82 mg, 0.34 mmol). Contains a minor amount of *endo-3s*.

<sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) δ 10.62 (s, 1H), 8.95 (s, 1H), 6.64 (dd, *J* = 5.5, 2.0 Hz, 1H), 6.56 (d, *J* = 5.5 Hz, 1H), 5.21 (d, *J* = 2.0 Hz, 1H), 3.14 (d, *J* = 6.5 Hz, 1H), 3.07 (d, *J* = 6.5 Hz, 1H), 2.80 (s, 3H), ppm. <sup>13</sup>C{<sup>1</sup>H}-NMR (DMSO-*d*<sub>6</sub>) δ 175.8, 173.6, 162.1, 137.1, 137.0, 89.0, 80.9, 49.4, 48.9, 24.6, ppm. IR (ATR):  $\tilde{\nu}$  = 3400-2800 (br), 1767 (w), 1691 (s), 1645 (s), 1550 (w), 1431 (m), 1381 (w), 1140 (w), 944 (w), 588 (w). ESI-MS:  $m/z$   $[M+Na]^+$  calculated for  $C_{10}H_{10}N_2NaO_5$ , 261.0482, found 261.0483.



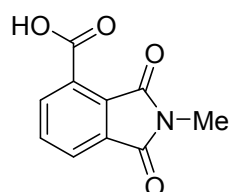
#### Diels-Alder adduct *exo-3t*

Adduct **3i** (0.5 mmol, 1 equiv) was suspended in dimethyl formamide (1 mL). K<sub>2</sub>CO<sub>3</sub> was added, which lead to the nearly complete dissolution of **3i**. Benzyl bromide (0.5 mmol, 1.0 equiv) was added and the resulting cloudy mixture was stirred at ambient temperature overnight. Precipitation occurred within hours. Crude <sup>1</sup>H-NMR analysis indicated the complete conversion of **3i** into **3t**. Water (2 mL) was added and the mixture was stirred for 2 hours prior filtration. The product was washed with water (2x 0.5 mL), collected and dried *in vacuo*. **3t** was obtained as a white solid (138 mg, 0.44 mmol, 88%).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.36-7.20 (m, 5H), 6.62 (d,  $J = 5.5$ , 1H), 6.58 (d,  $J = 5.5$  Hz, 1H), 5.34 (s, 1H), 4.65 (d,  $J = 14.5$  Hz, 1H), 4.60 (d,  $J = 14.5$  Hz, 1H), 3.89 (s, 3H), 3.16 (d,  $J = 6.5$  Hz, 1H), 2.96 (d,  $J = 6.5$  Hz, 1H), ppm.  $^{13}\text{C}\{^1\text{H}\}$ -NMR ( $\text{CDCl}_3$ )  $\delta$  174.7, 173.4, 166.9, 137.3, 136.6, 135.3, 128.7, 128.3, 127.9, 89.3, 81.4, 53.0, 50.4, 48.9, 42.7, ppm. IR (ATR):  $\tilde{\nu} = 1758$  (m), 1751 (m), 1692 (s), 1438 (m), 1397 (m), 1176 (m), 1163 (w), 1131 (w), 1070 (m), 909 (w), 721 (w), 593 (w). ESI-MS:  $m/z$  [ $M+H$ ] $^+$  calculated for  $\text{C}_{17}\text{H}_{16}\text{NO}_5$ , 314.1023, found 314.1025.

#### Esterification of **exo-3a** towards **exo-3n**

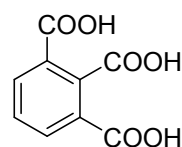
Adduct **3a** (1 mmol, 1 equiv) was suspended in ethanol (2 mL). Thionyl chloride (1.2 mmol, 1.2 equiv) was added and the mixture was stirred at ambient temperature for 2 hours. The suspension was then heated at 50 °C for 1 hour. Crude  $^1\text{H-NMR}$  analysis indicated the complete conversion of **3a** into **3n**. The mixture was concentrated to dryness *in vacuo*, resulting in a colorless oil which slowly solidifies upon standing. **3n** was obtained as a white solid (226 mg, 90%).



#### Phthalimide **4**

Diels-Alder adduct **3a** (223 mg, 1 mmol) and 33 wt-% HBr/AcOH (3.2 mL) were added in a vial. The mixture was stirred at 30 °C (to allow better dissolution of **3a**) for 18 hours. The resulting yellow solution was then stirred at 60 °C for 4 hours. The mixture turns brownish. The solution was then allowed to cool to ambient temperature and diluted with acetic acid (5 mL). HBr was neutralized by the careful (!), portionwise addition of solid  $\text{NaHCO}_3$  (1.5 g). This suspension was then stirred for 1 hour before concentrating to dryness *in vacuo*. The resulting white solid was suspended in water (4 mL) and filtered. After washing with water (2x 1 mL) the product was left to dry on the filter. Then, the product was dissolved in acetone on the filter and the filtrate was concentrated to dryness *in vacuo*. Phthalimide **4** was obtained as a pale brown solid (135 mg, 66%).

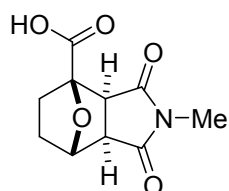
$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  8.49 (dd,  $J = 7.5$ , 1.0 Hz, 1H), 8.05 (dd,  $J = 7.5$ , 1.0 Hz, 1H), 7.87 (t,  $J = 7.5$  Hz, 1H), 3.24 (s, 3H), ppm.  $^{13}\text{C}\{^1\text{H}\}$ -NMR ( $\text{CDCl}_3$ )  $\delta$  171.4, 166.7, 163.6, 138.4, 135.2, 132.2, 129.4, 129.4, 127.5, 24.7, ppm. IR (ATR):  $\tilde{\nu} = 3600$ -2500 (br), 1781 (m), 1712 (s), 1634 (s), 1594 (s), 1479 (m), 1452 (s), 1298 (s), 1268 (m), 1018 (m), 720 (m), 619 (w), 446 (w). ESI-MS:  $m/z$  [ $M-H$ ] $^-$  calculated for  $\text{C}_{10}\text{H}_6\text{NO}_4$ , 204.0302, found 204.0305.



#### Hemimellitic acid **5**

**4** (45 mg, 0.22 mmol) was dissolved in 35% HCl (1 mL) in a microwave vial. The mixture was stirred at 100 °C for 24 hours. The reaction mixture was then allowed to cool to ambient temperature and diluted with water (1 mL). Crude  $^1\text{H-NMR}$  analysis indicated 94% conversion of **4**. Upon cooling, a white precipitate was formed. Most of the acid was neutralized by the careful (!), portionwise addition of solid  $\text{Na}_2\text{CO}_3$  (580 mg). The product was extracted in ethyl acetate (5x 2 mL). The combined organic layer was dried over  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo*. The product was obtained as a brown solid (46 mg, 94 mol-% **5**, contains trace of unreacted **4**). Product identity was confirmed by comparison to literature spectra.<sup>[6]</sup>

$^1\text{H-NMR}$  (acetone- $d_6$ )  $\delta$  8.20 (d,  $J = 7.5$  Hz, 2H), 7.68 (t,  $J = 7.5$  Hz, 1H), ppm.  $^{13}\text{C}\{^1\text{H}\}$ -NMR (acetone- $d_6$ )  $\delta$  168.9, 166.7, 138.2, 134.5, 130.4, 129.9, ppm. ESI-MS:  $m/z$  [ $M-H$ ] $^-$  calculated for  $\text{C}_9\text{H}_5\text{O}_6$ , 209.0092, found 209.0242.



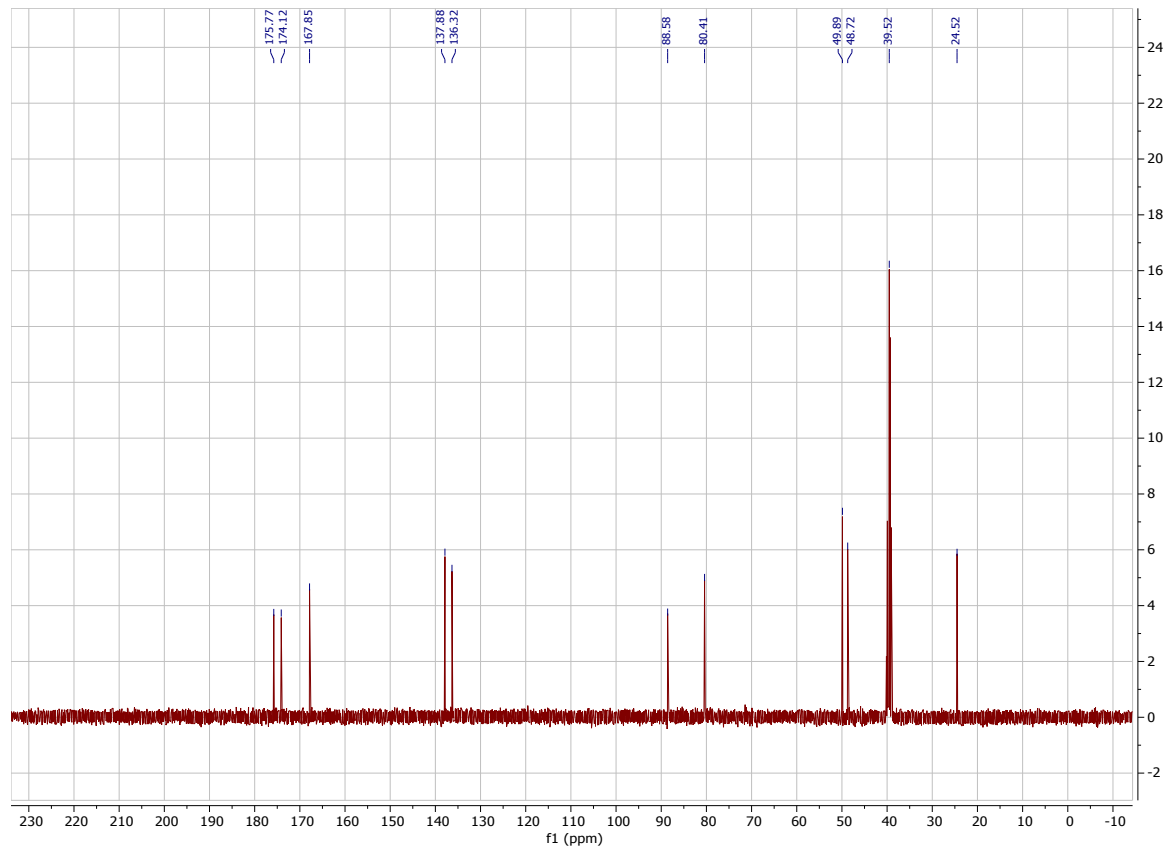
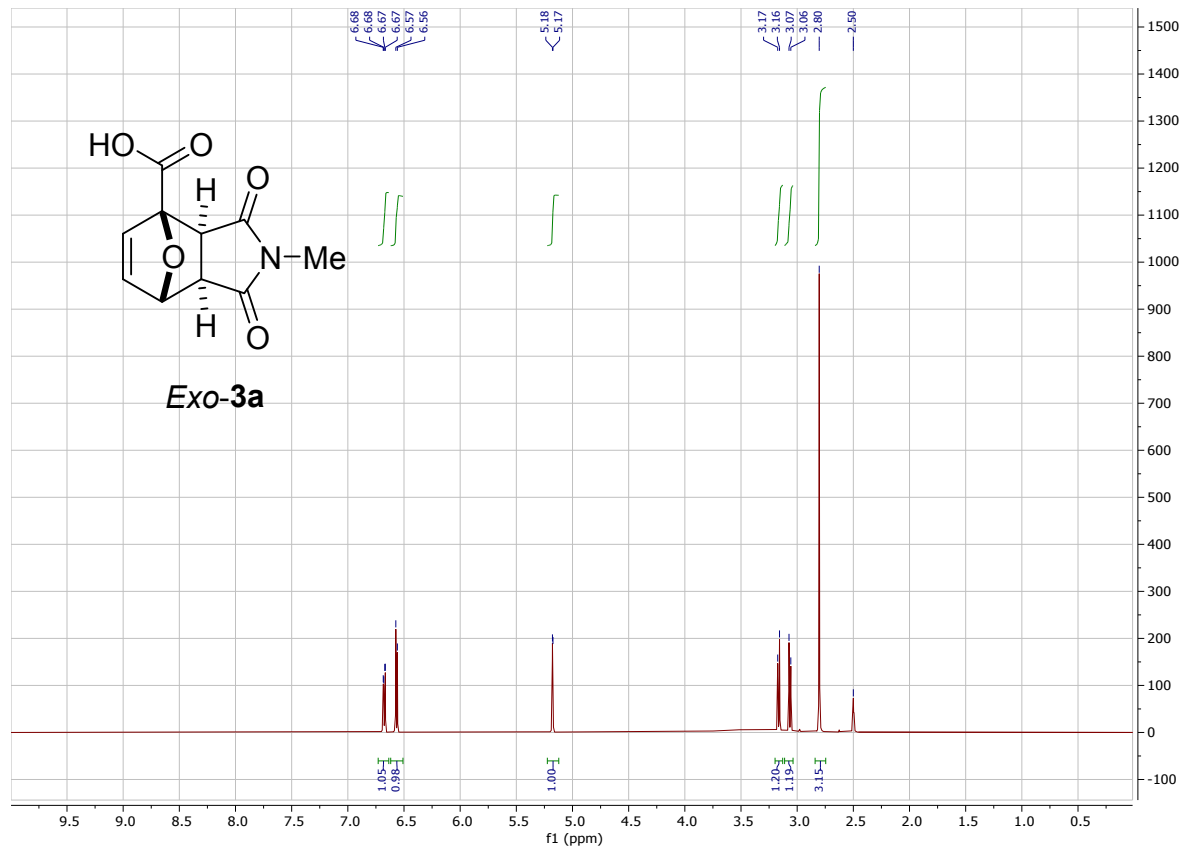
#### Hydrogenated Diels-Alder adduct **exo-6**

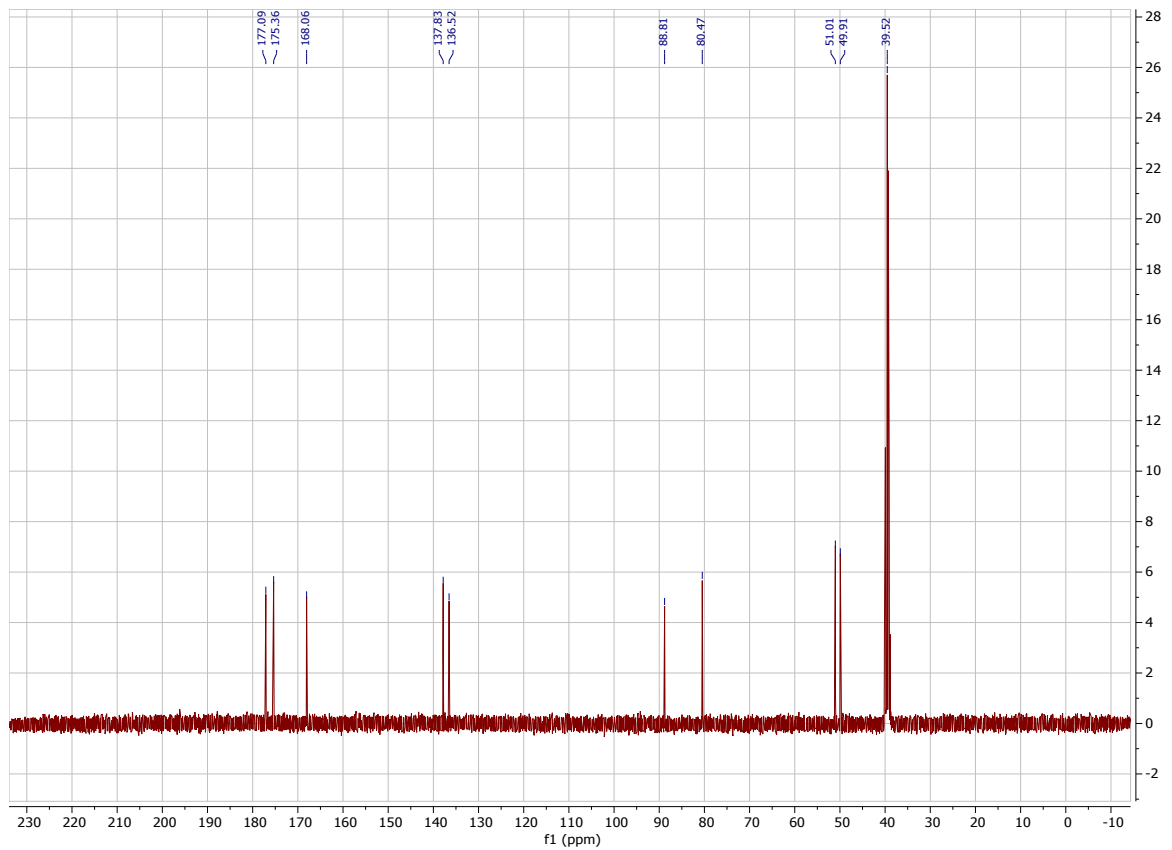
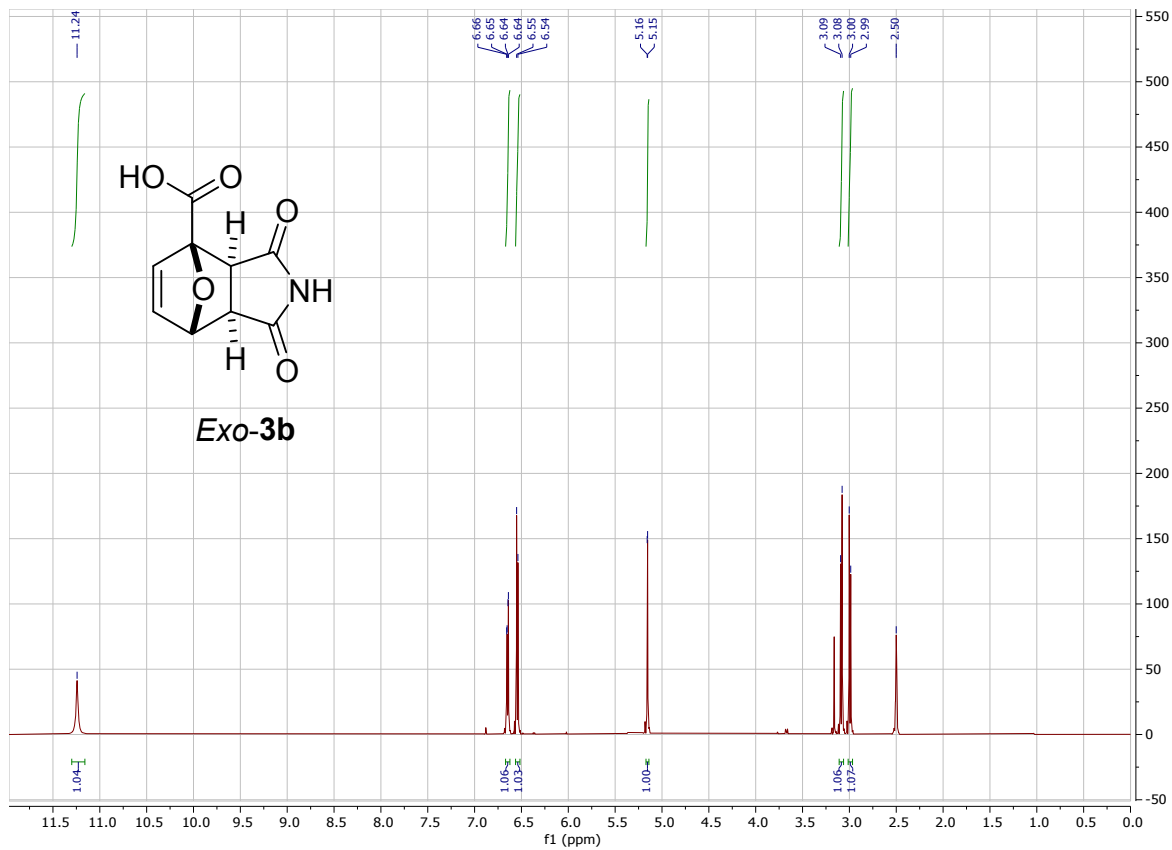
2-Furoic acid (560 mg, 5 mmol, 1 equiv.) was dissolved in water (5 mL); 50 wt.% NaOH solution (400 mg, 5 mmol, 1 equiv) and *N*-methyl

maleimide (833 mg, 7.5 mmol, 1.5 equiv) were then added. The resulting clear solution and was stirred for 16 hours at 50 °C. The reaction mixture was allowed to cool to ambient temperature and washed with dichloromethane (3x 2.5 mL) to remove excess *N*-methyl maleimide. The aqueous phase was then added to a round bottom flask containing 10 wt.% Pd/C (265 mg). The suspension was then stirred for three hours at ambient temperature under H<sub>2</sub> atmosphere (balloon). The reaction mixture was filtered over Celite and the filter was rinsed with water (2 mL). The reaction mixture was cooled to 0 °C and solid NaCl (1 g) was added. The reaction mixture was acidified with 85% H<sub>3</sub>PO<sub>4</sub> leading to precipitation of the product. The product was collected by filtration and washed with water (2 mL). The product was dried *in vacuo*; a white solid was obtained (1084 mg, 4.86 mmol, 97%).

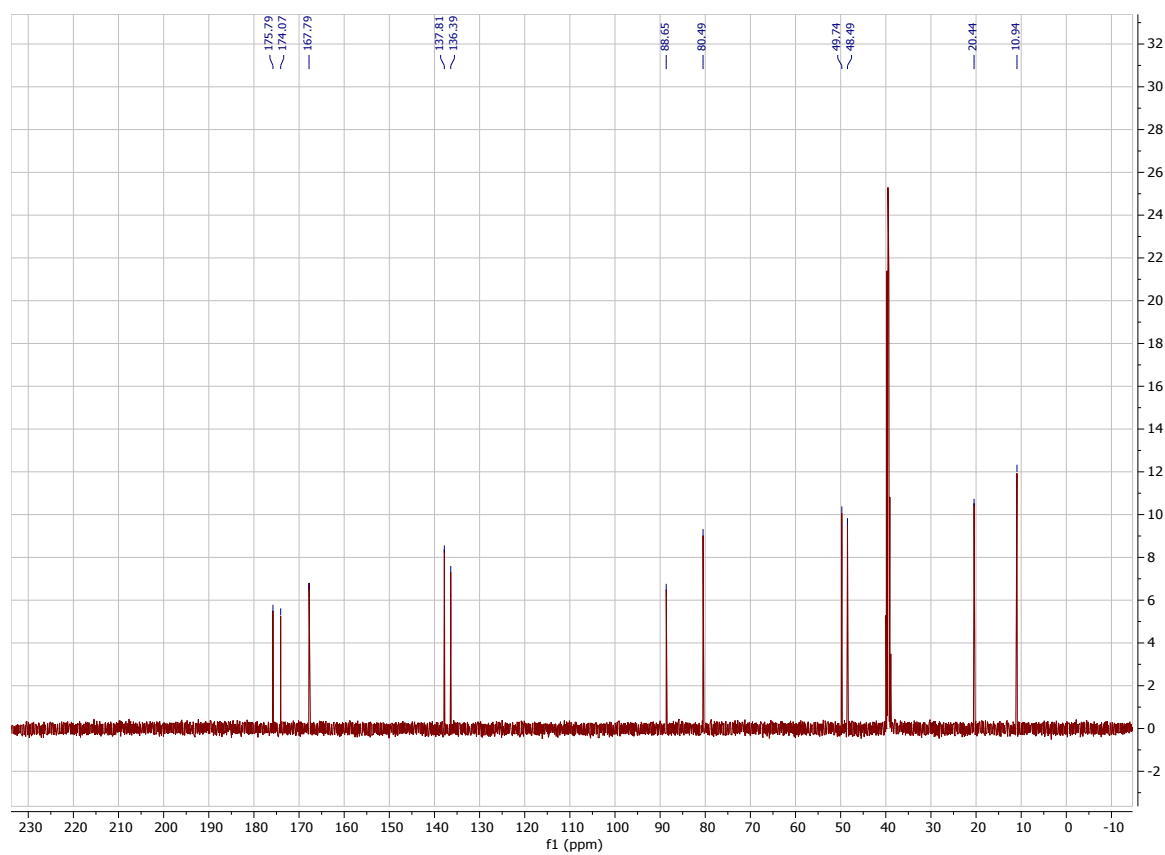
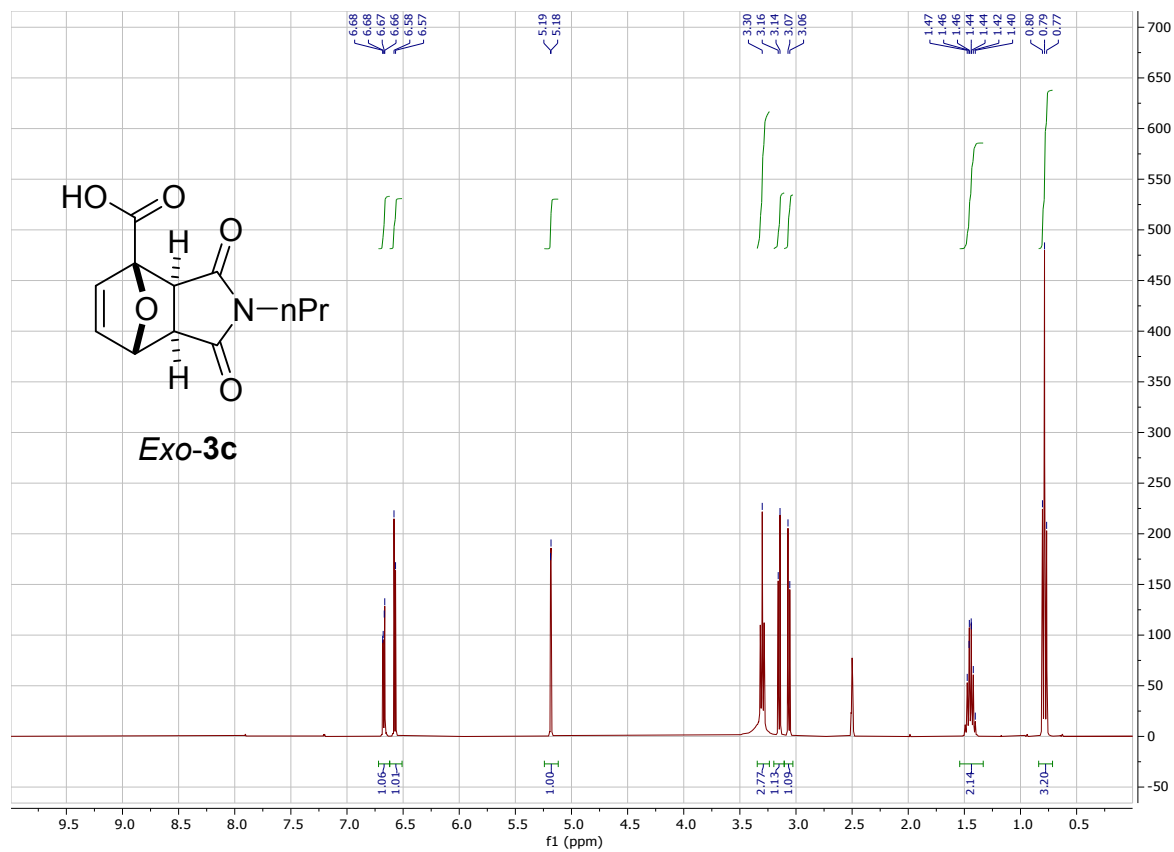
<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ 4.68 (d, J = 4.0 Hz, 1H), 3.30 (d, J = 7.0 Hz, 1H), 3.15 (d, J = 7.0 Hz, 1H), 2.78 (s, 3H), 1.99-1.87 (m, 1H), 1.83-1.66 (m, 3H), ppm. <sup>13</sup>C{<sup>1</sup>H}-NMR (DMSO-d<sub>6</sub>) δ 177.0, 175.3, 169.5, 86.4, 78.5, 51.8, 50.0, 32.3, 28.6, 24.7, ppm. IR (ATR):  $\tilde{\nu}$  = 3542 (m), 3465 (w), 3100-2400 (br), 1778 (w), 1684 (s), 1434 (w), 1286 (m), 1063 (w), 987 (w), 858 (w), 743 (w), 540 (w). ESI-MS: *m/z* [*M*-H]<sup>-</sup> calculated for C<sub>10</sub>H<sub>10</sub>NO<sub>5</sub>, 224.0564, found 224.0569.

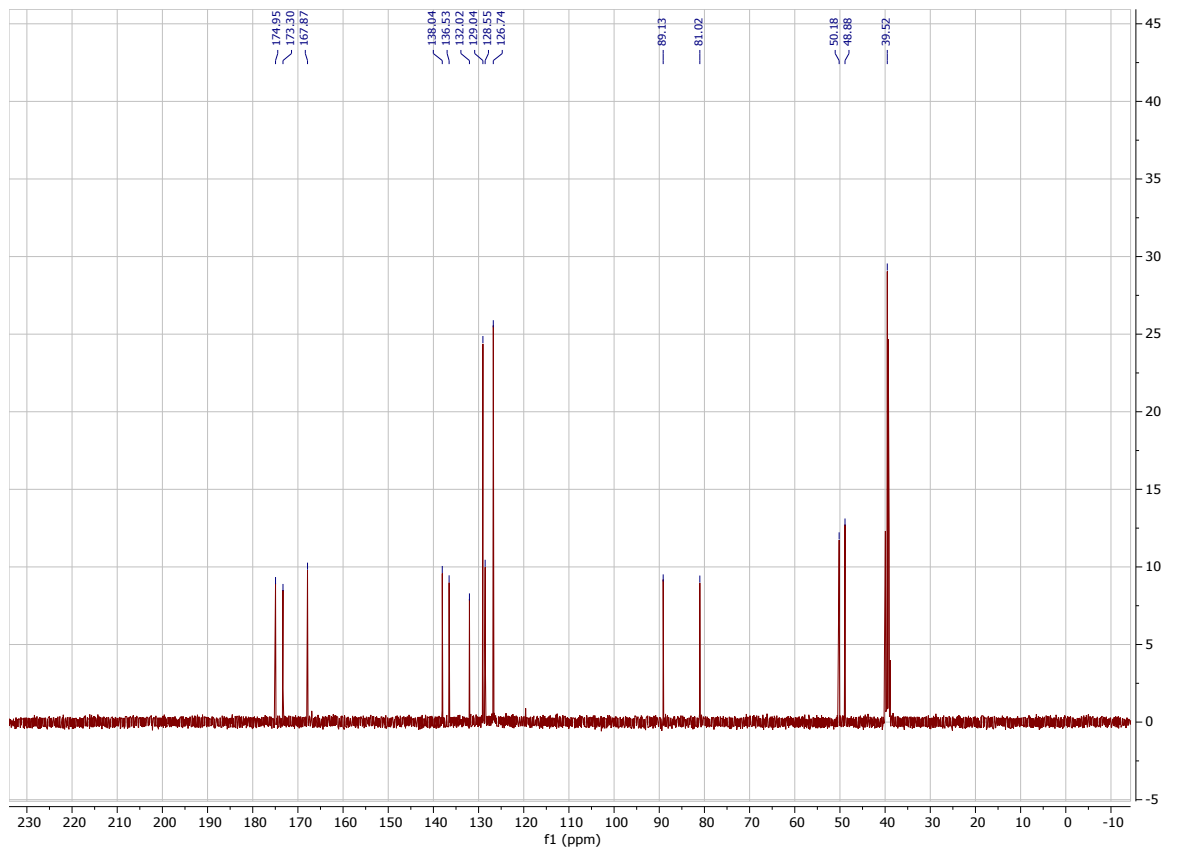
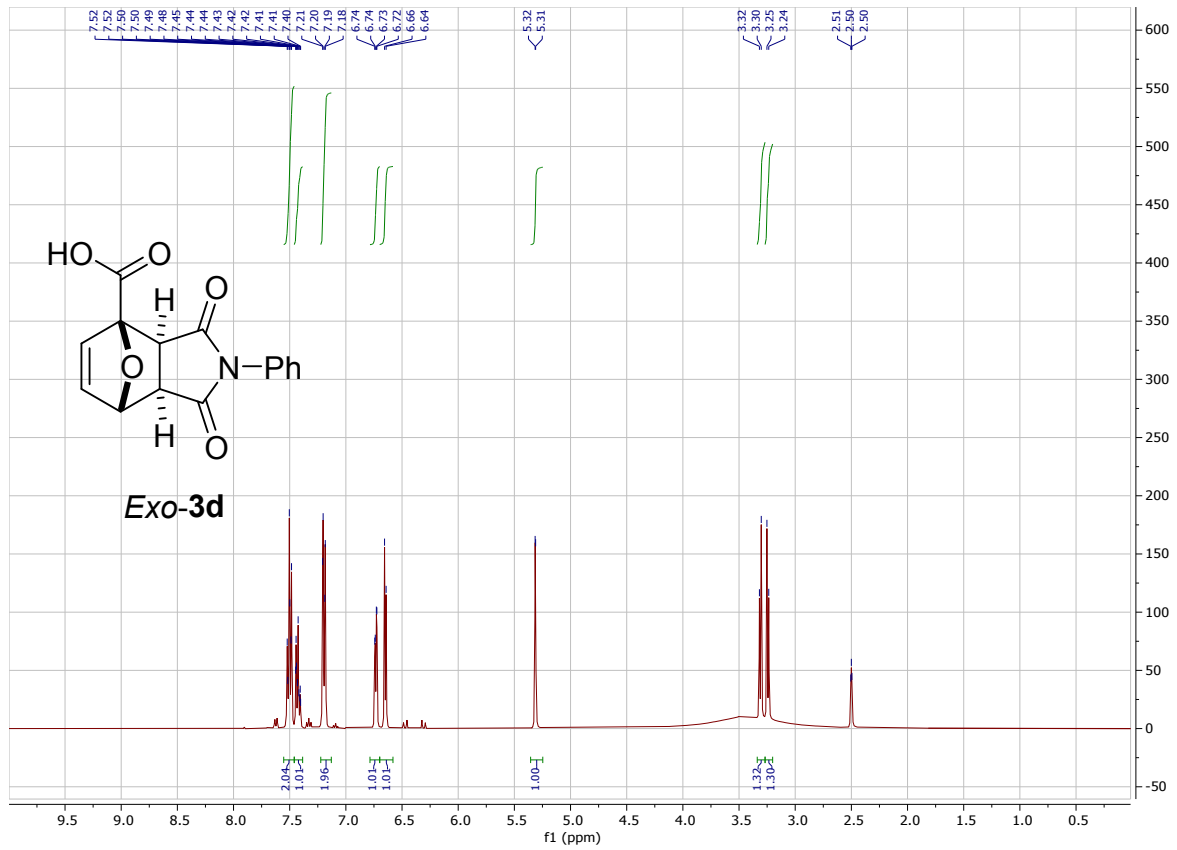
# NMR spectral data

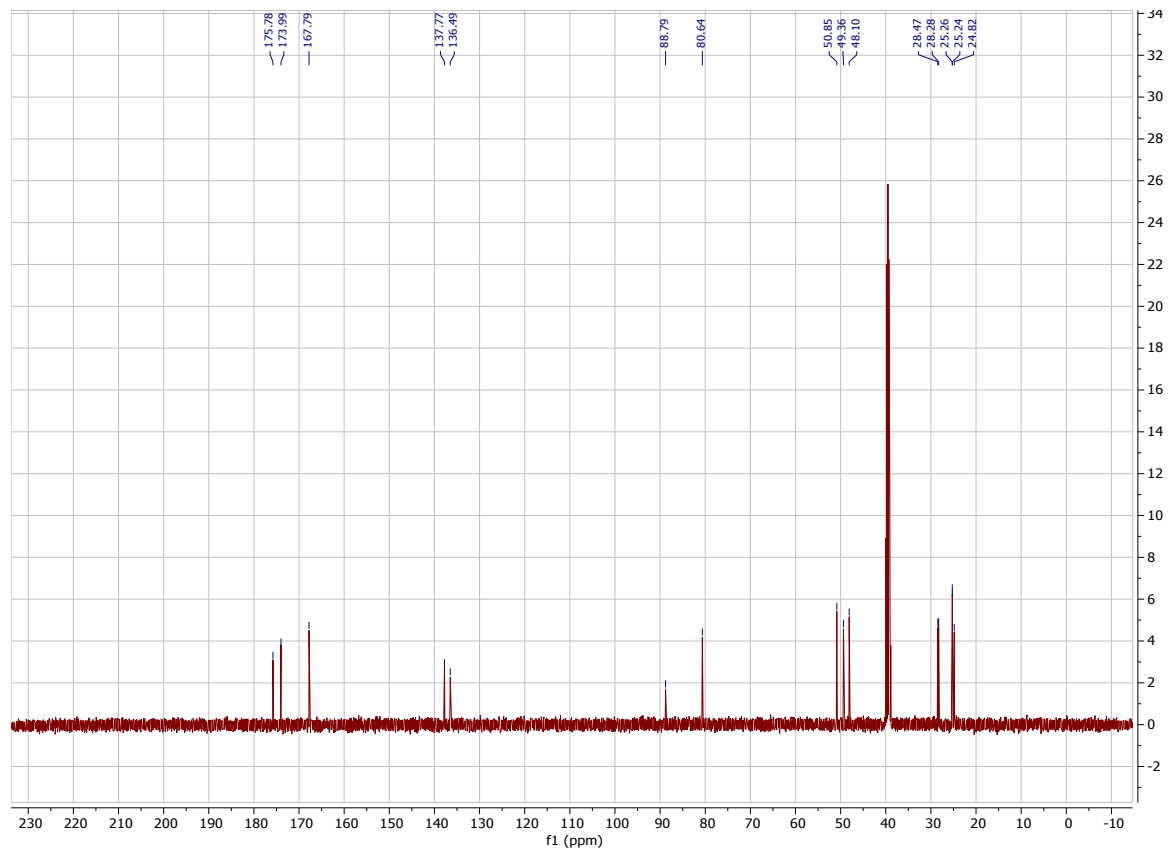
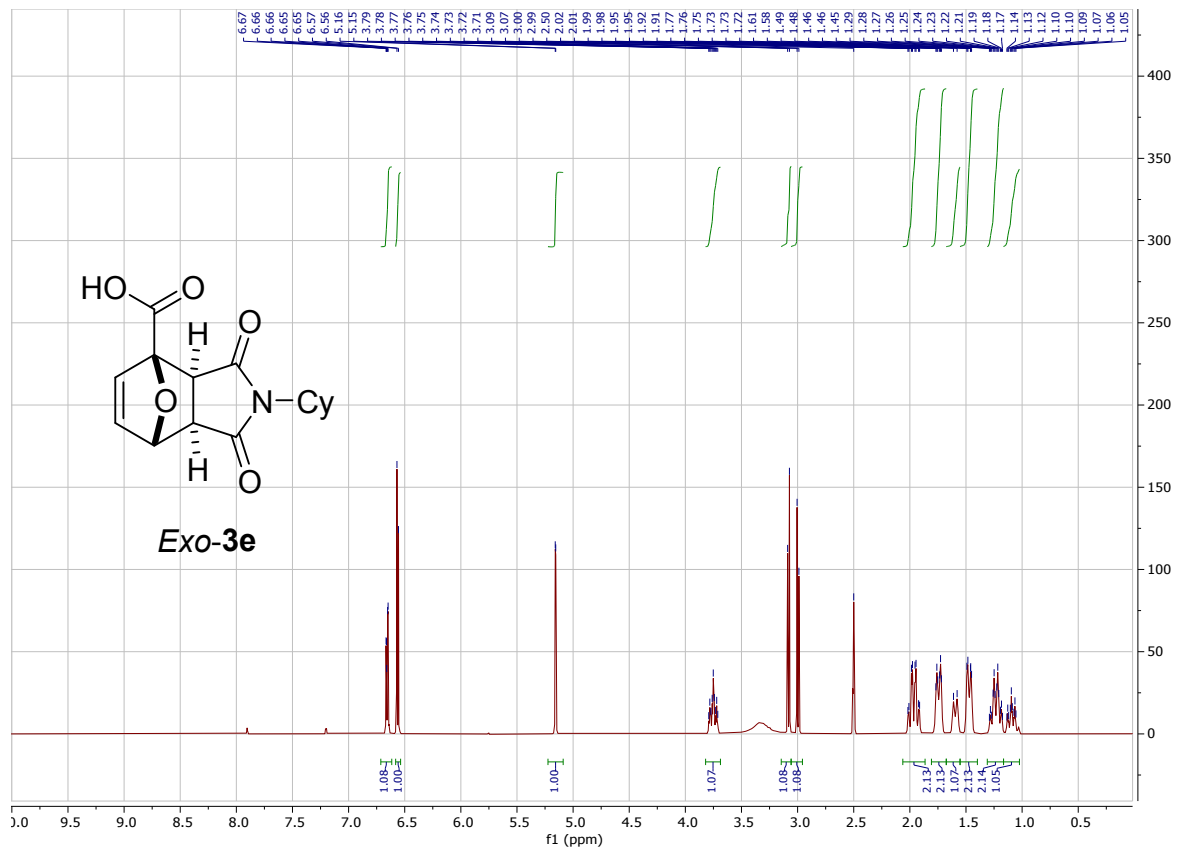


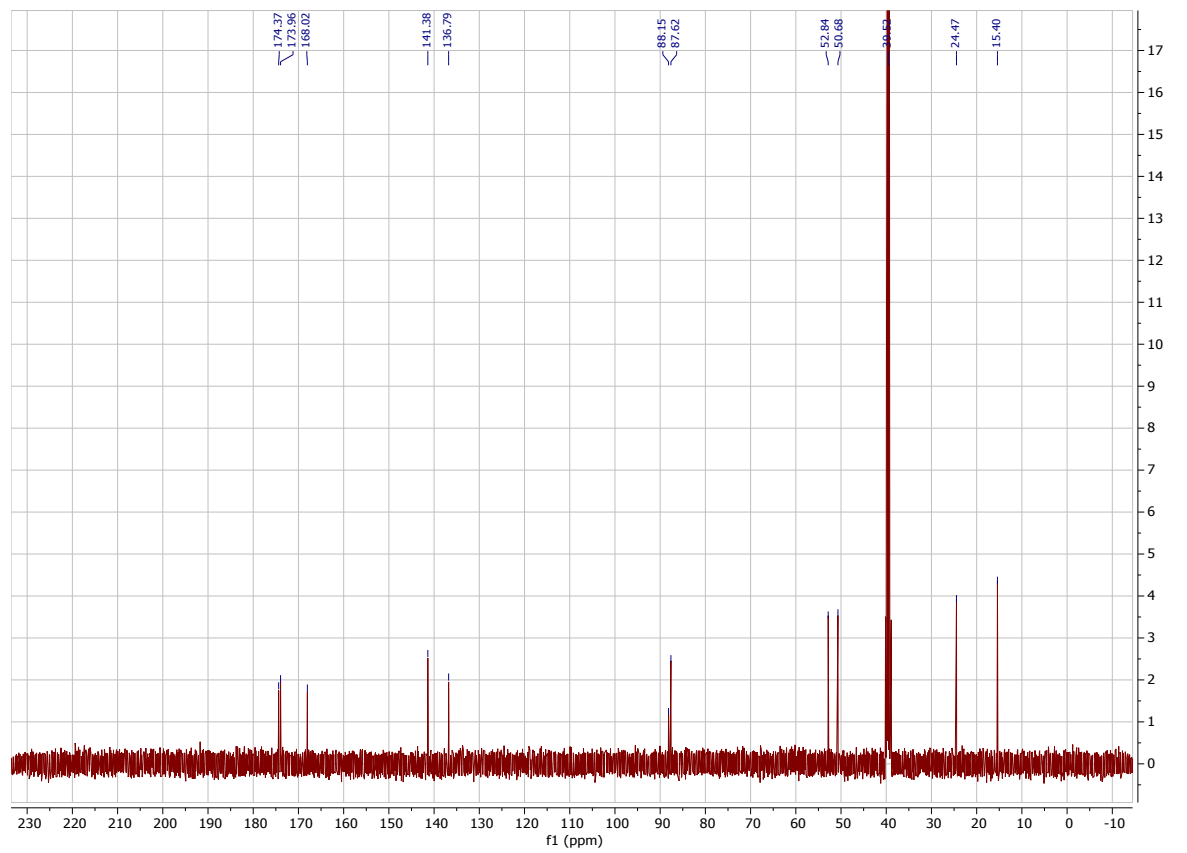
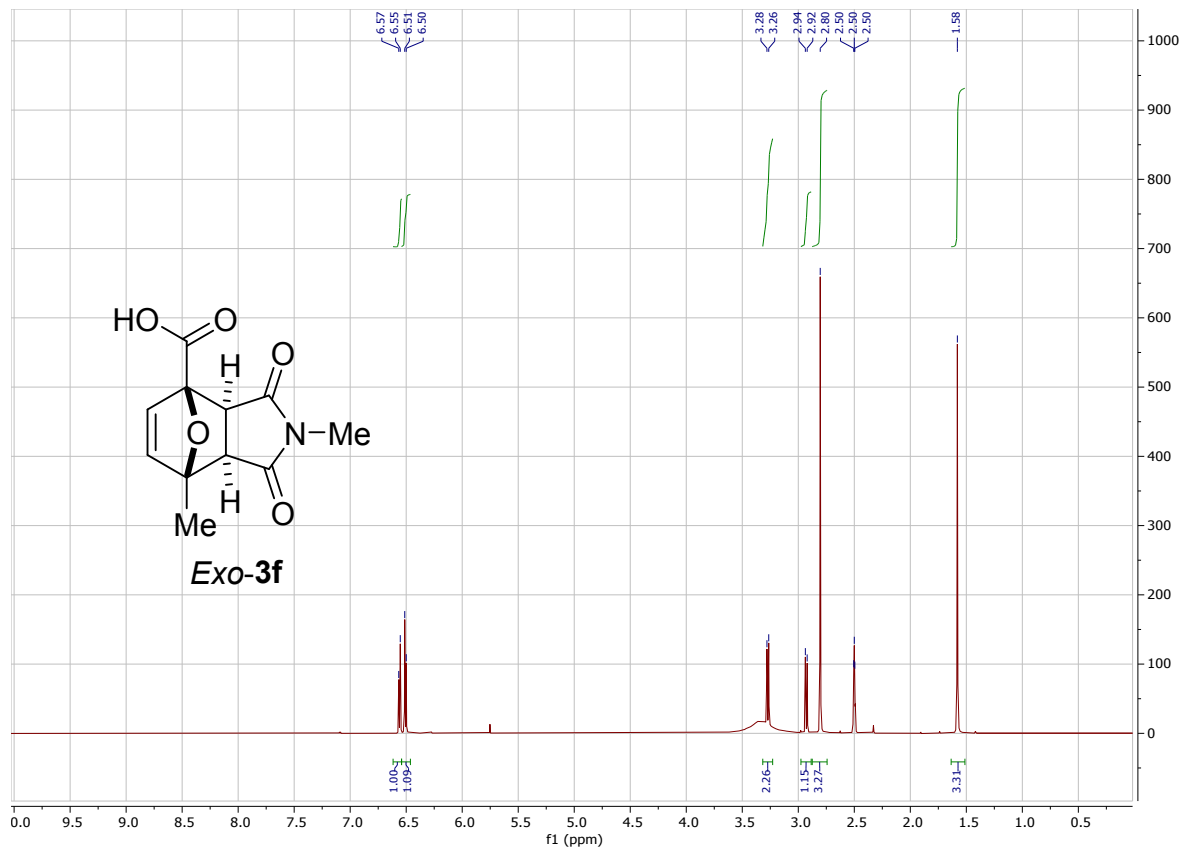


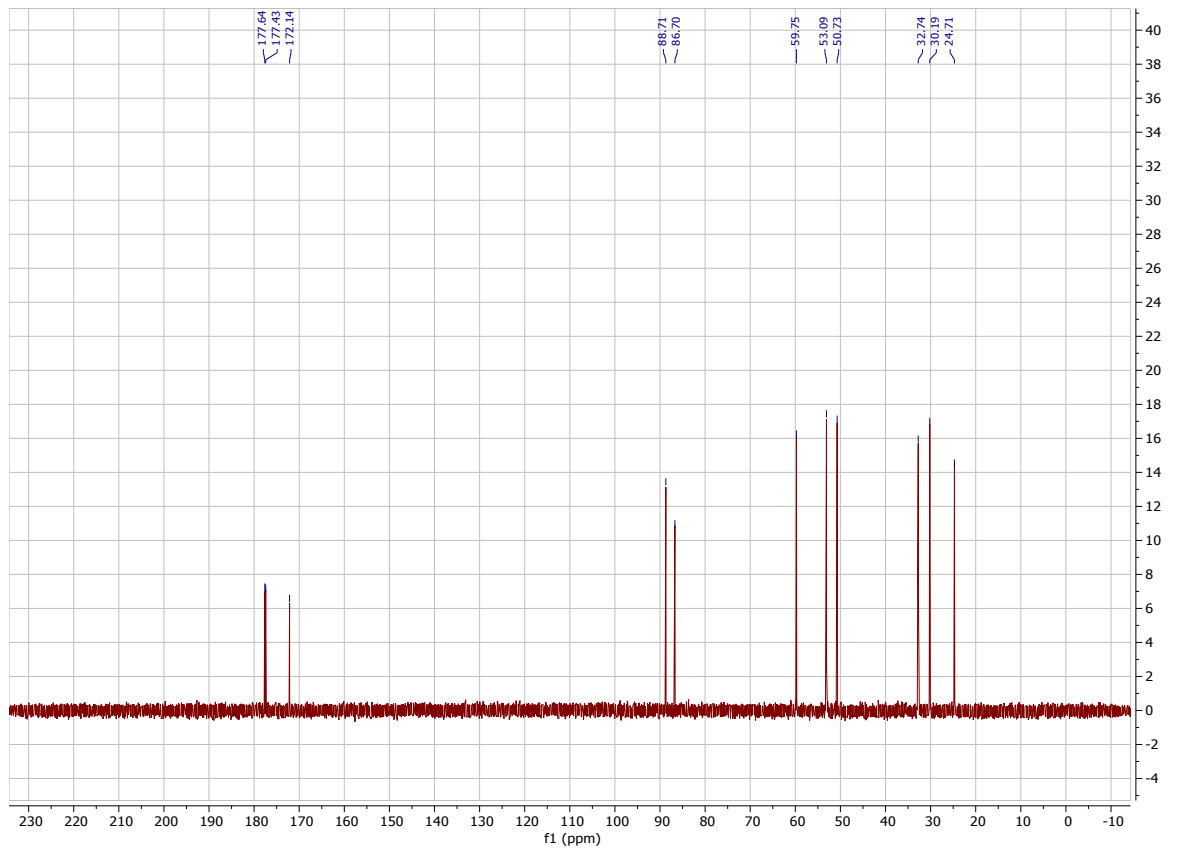
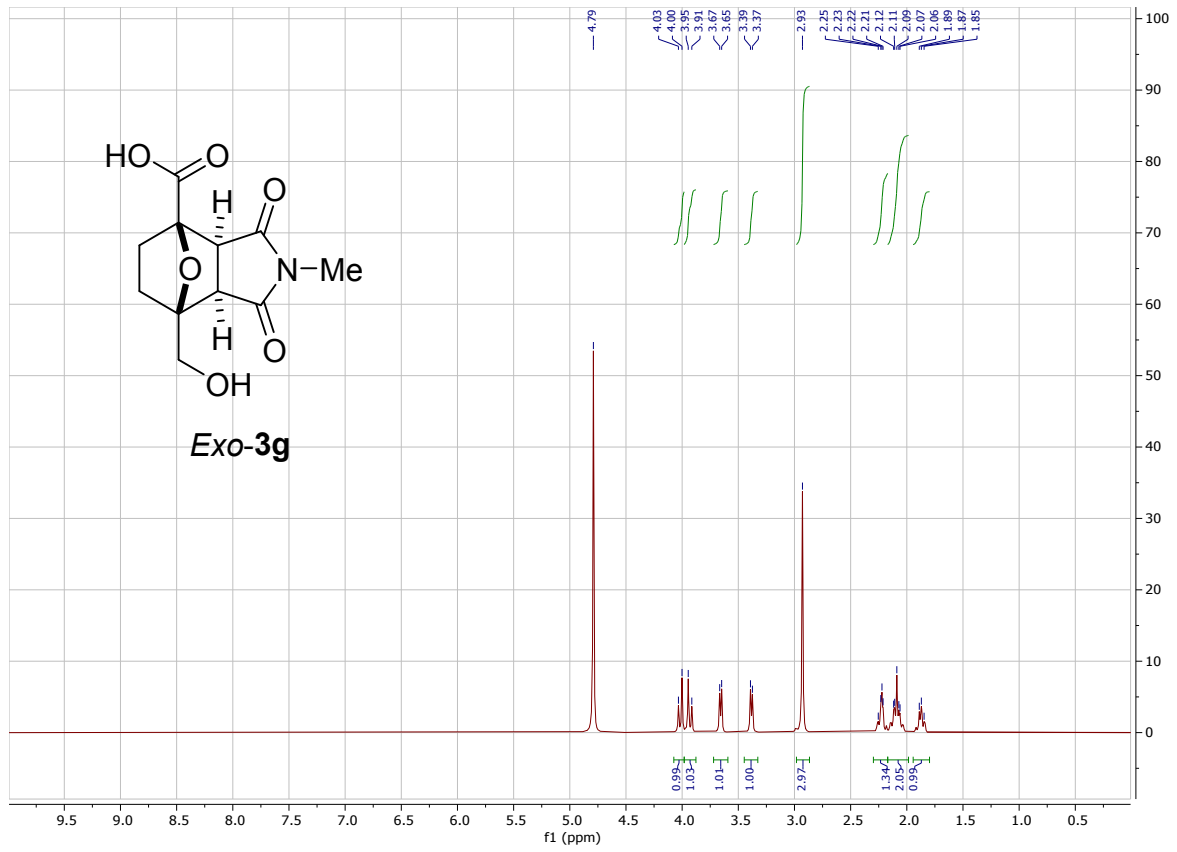


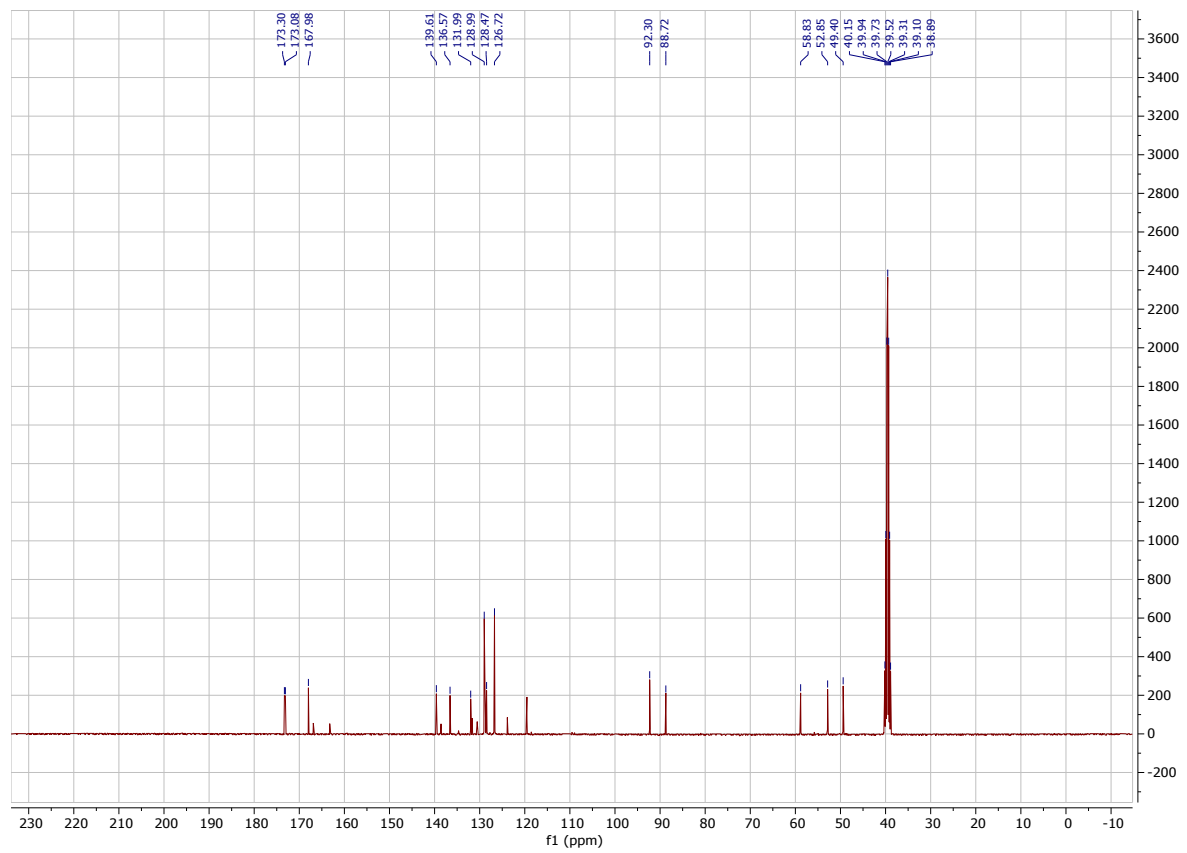
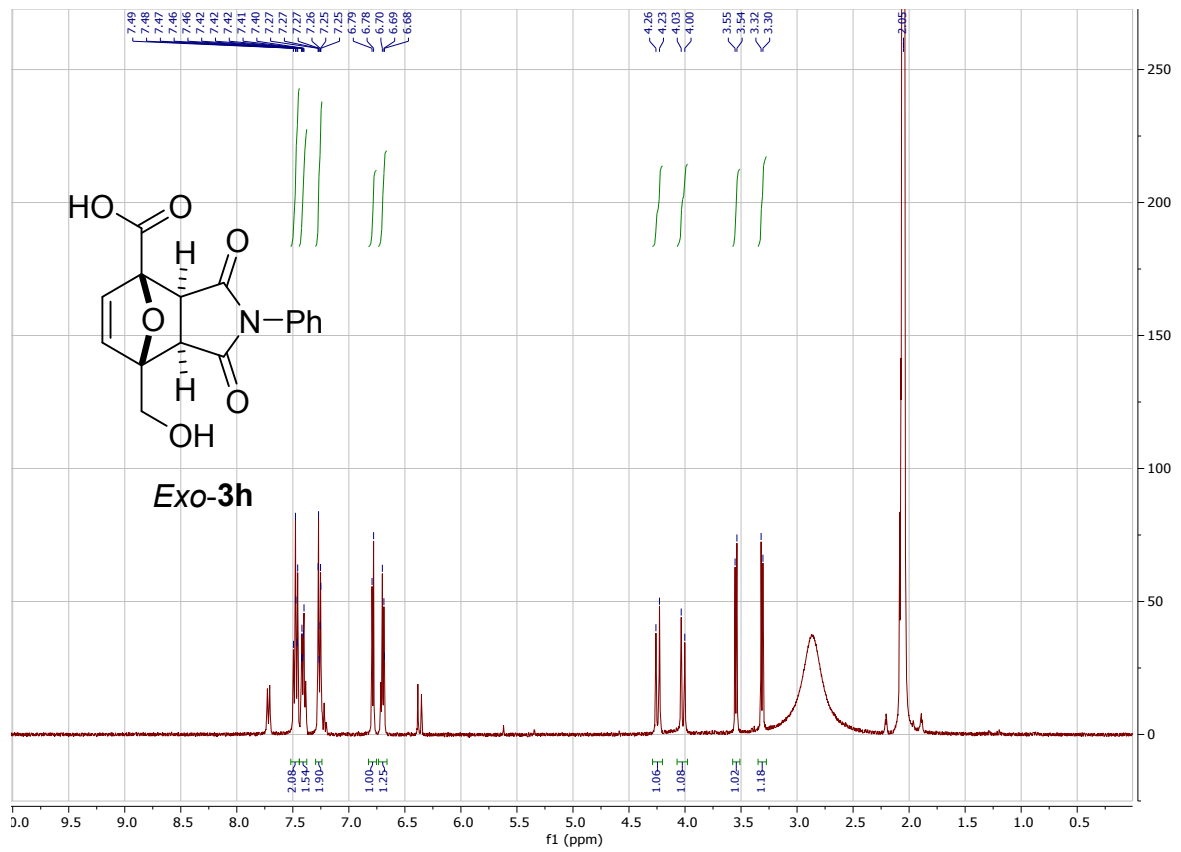


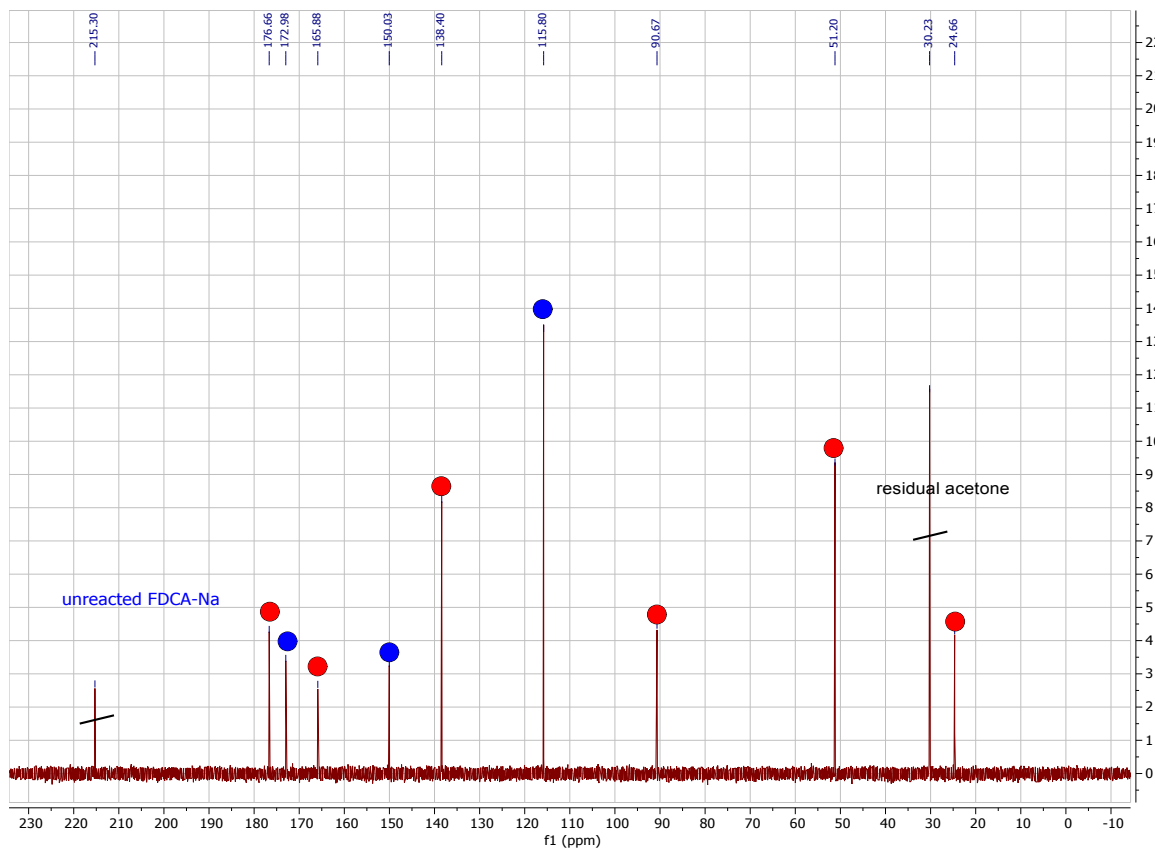
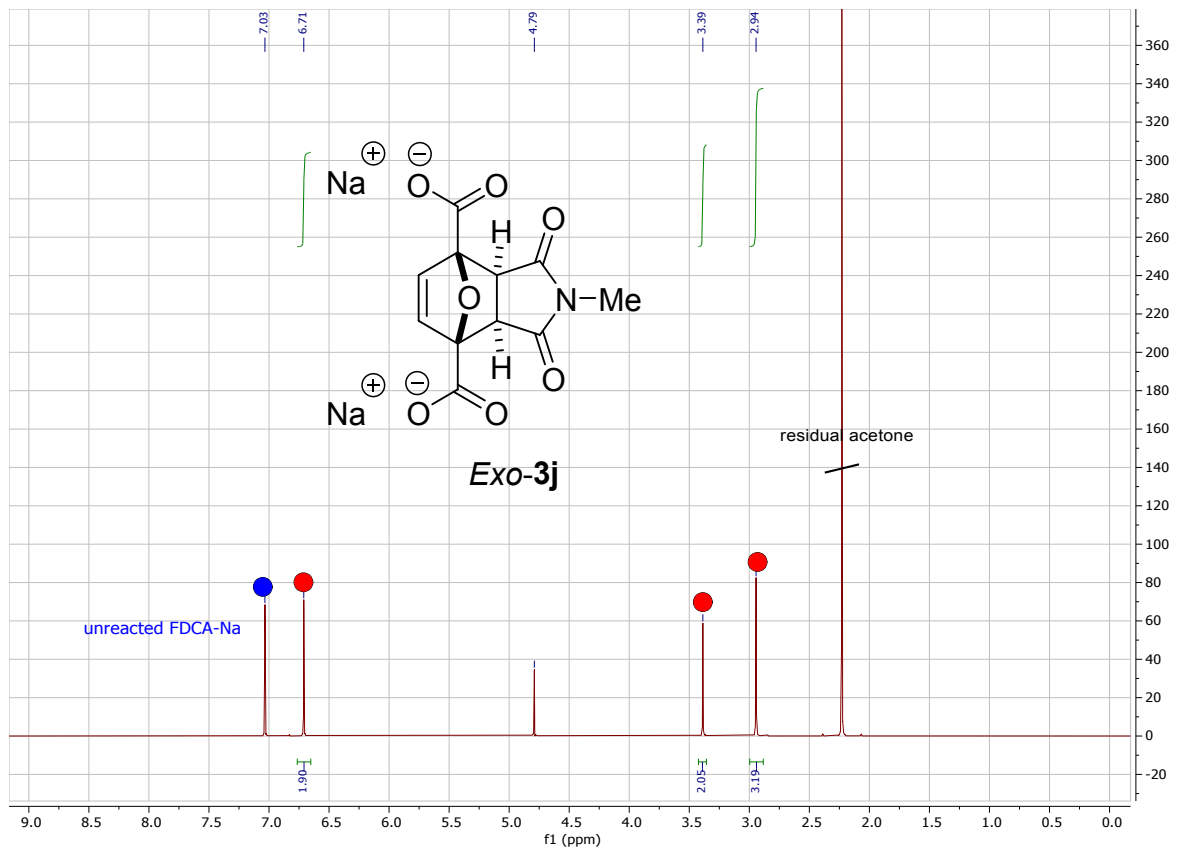












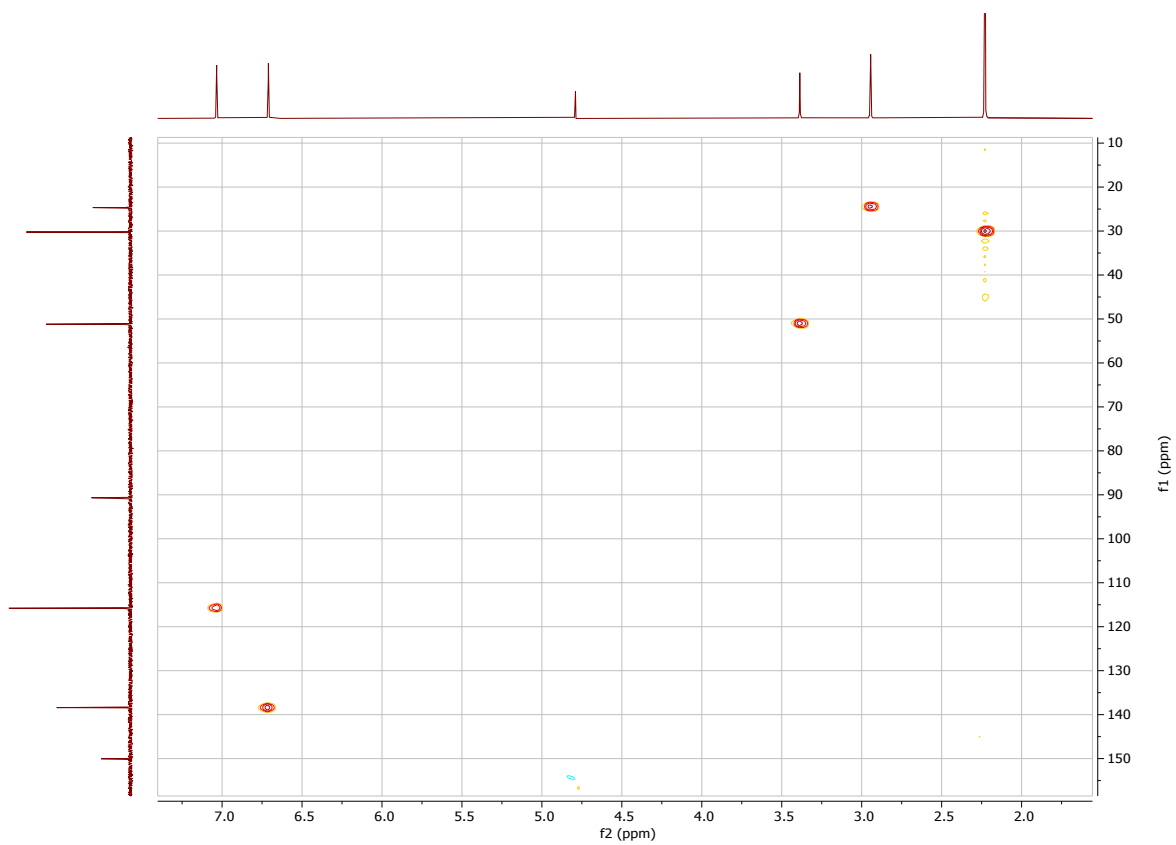
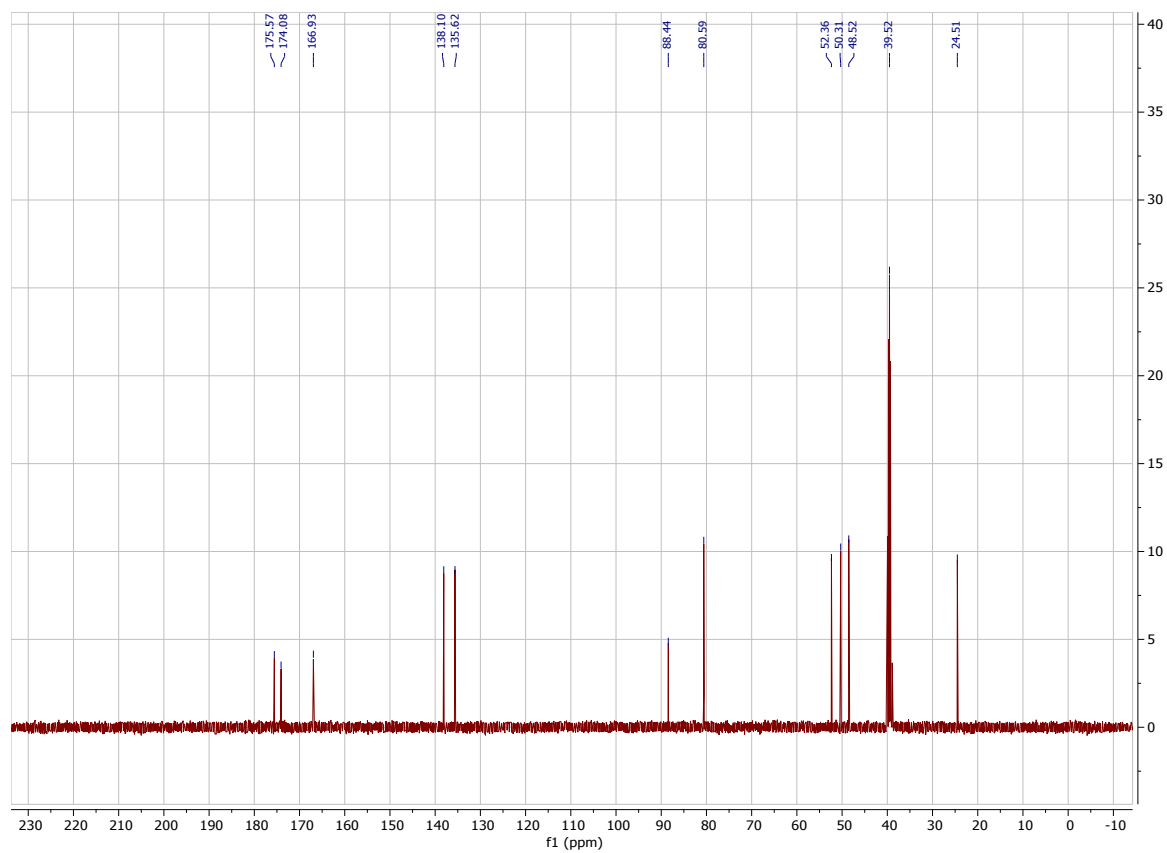
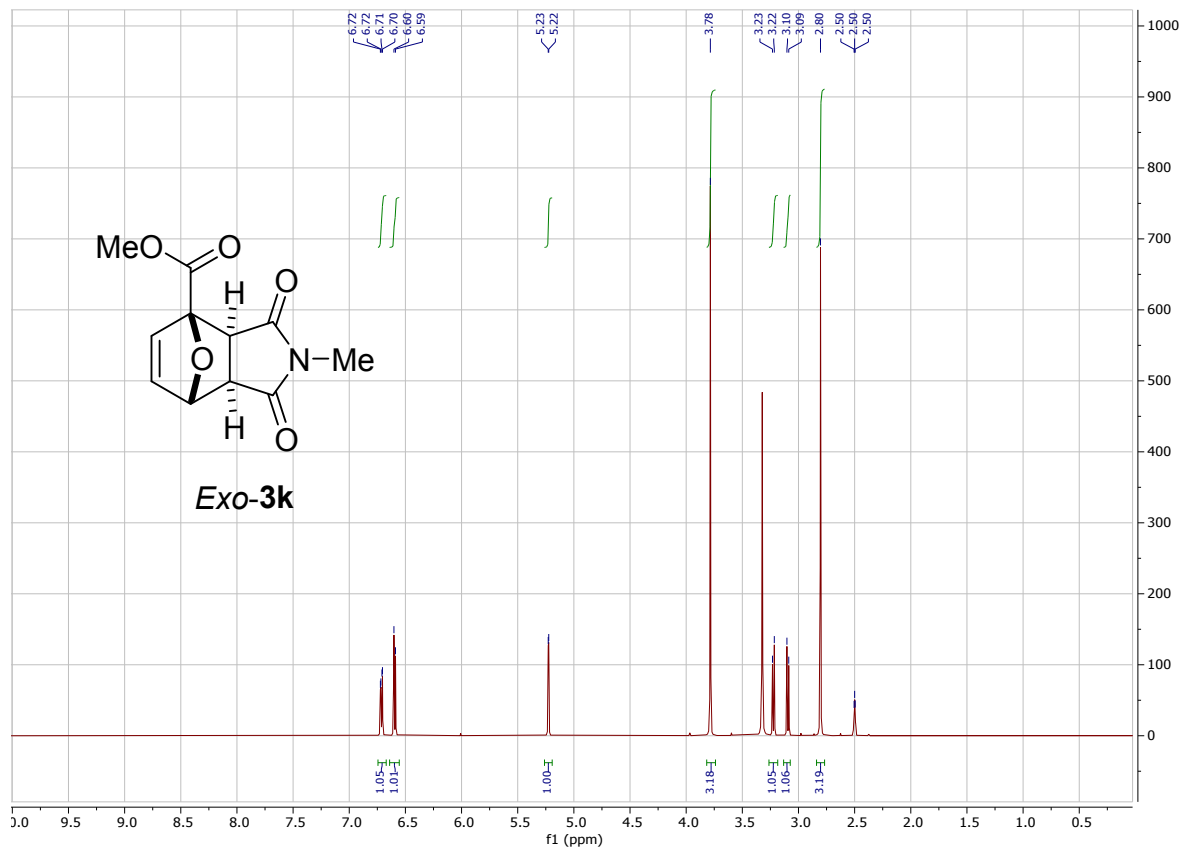
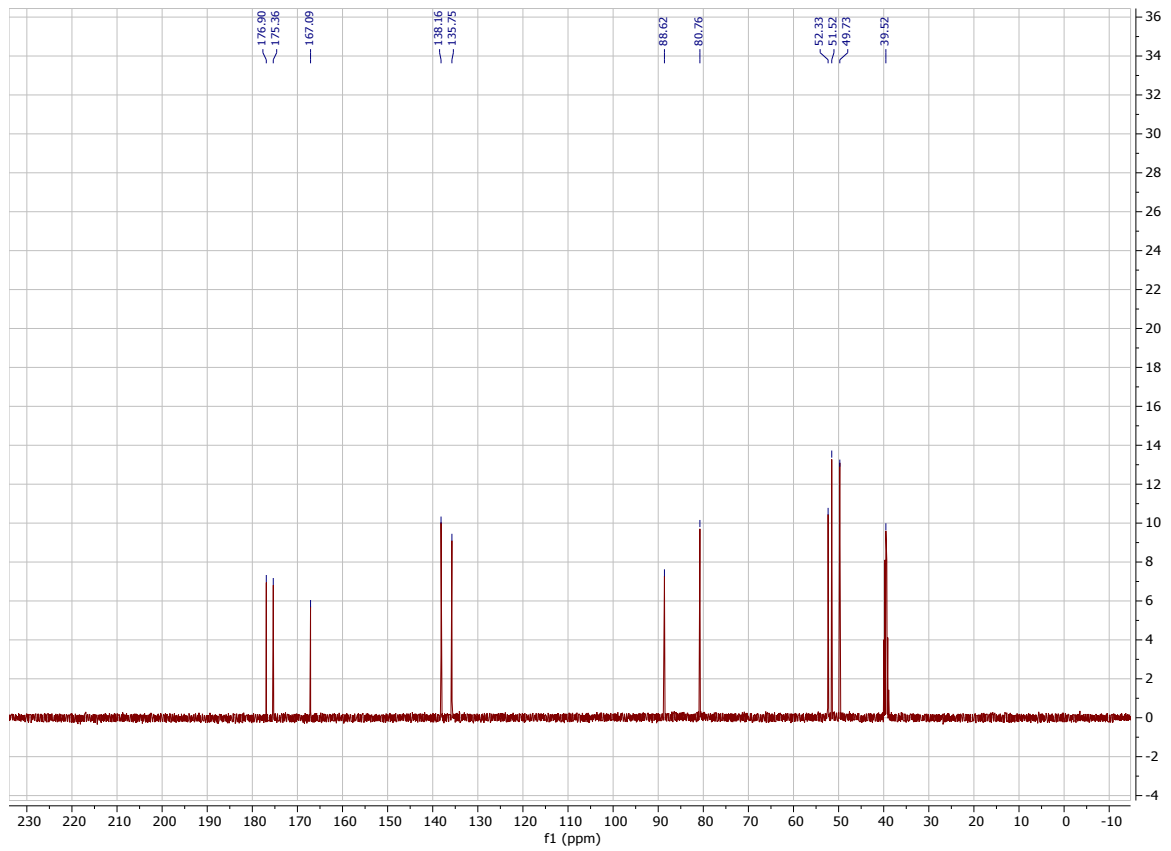
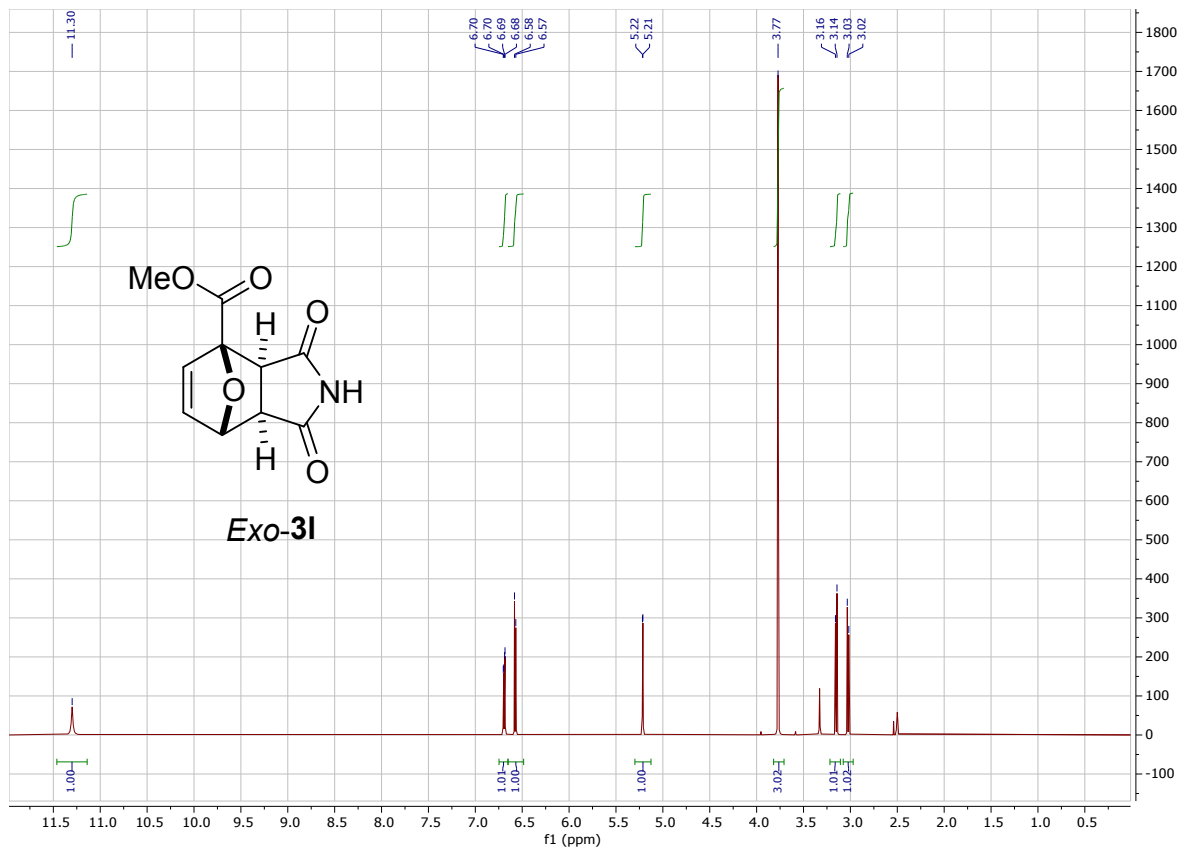
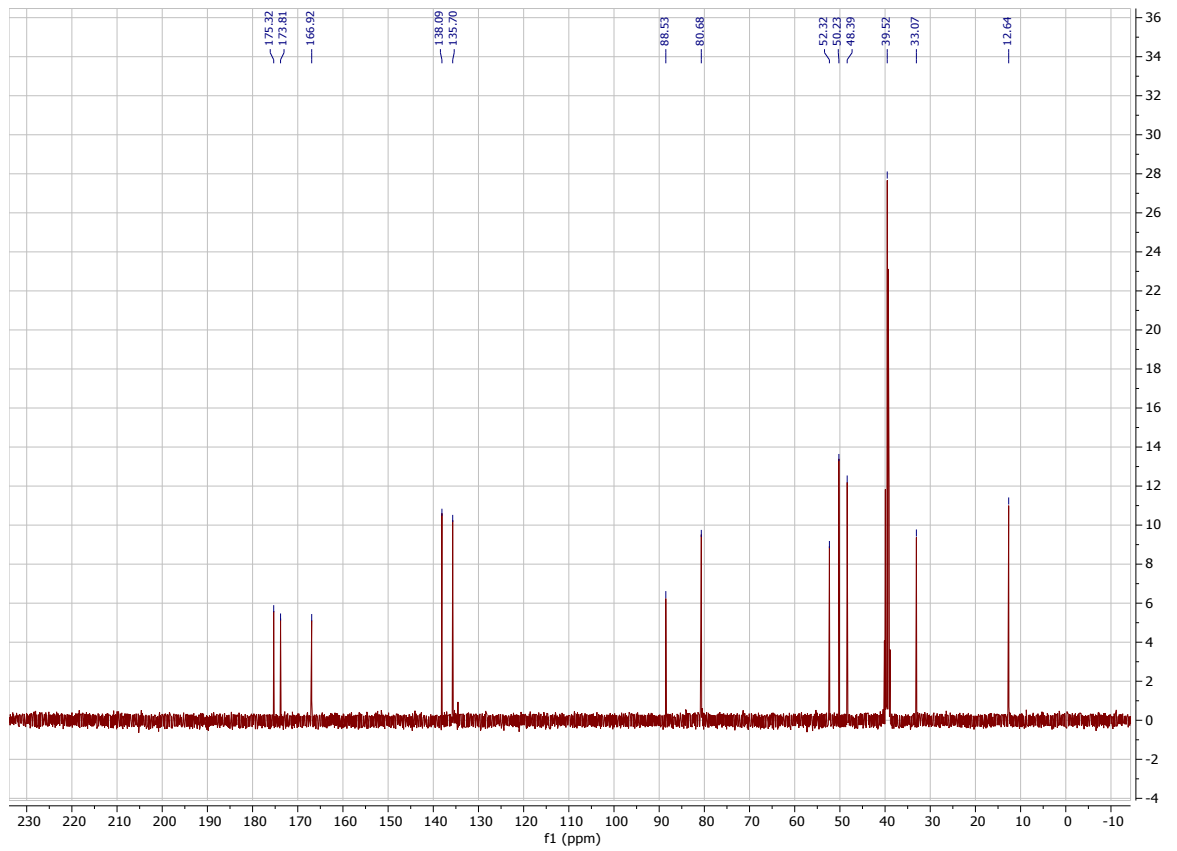
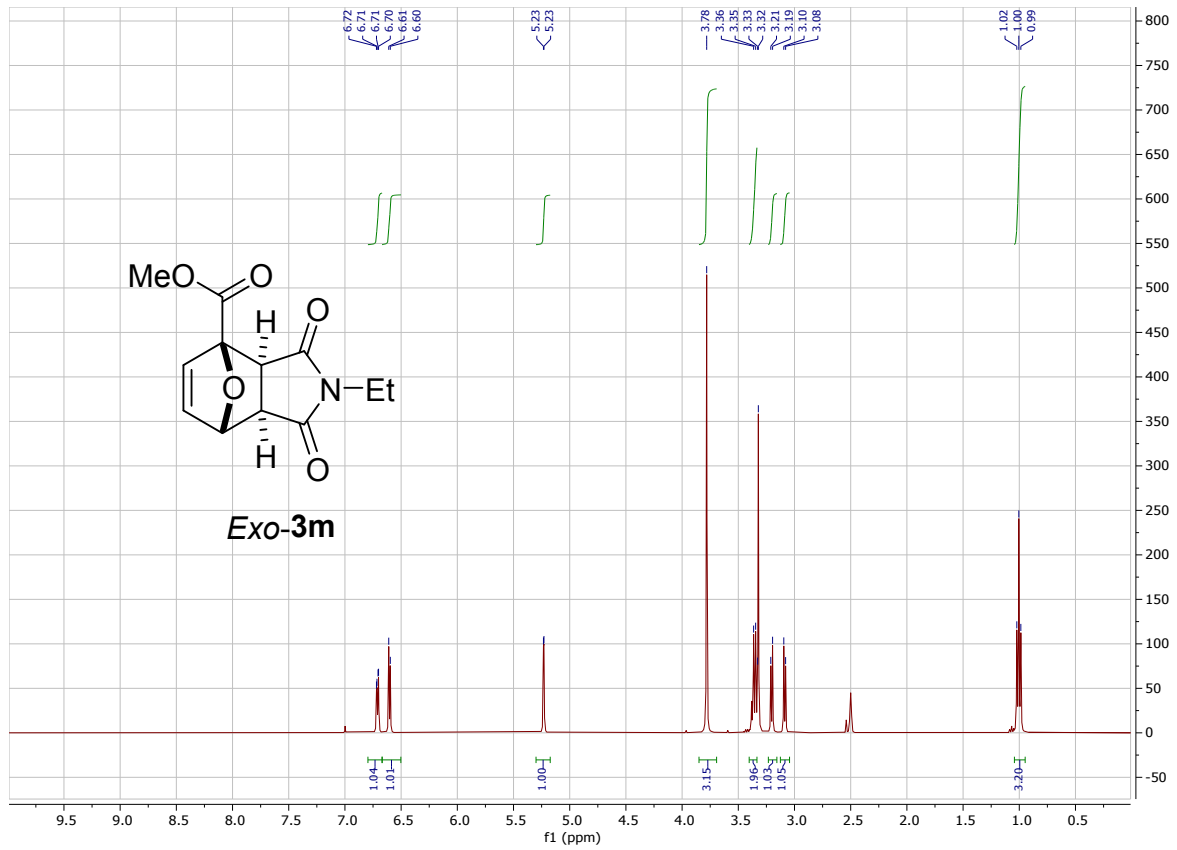


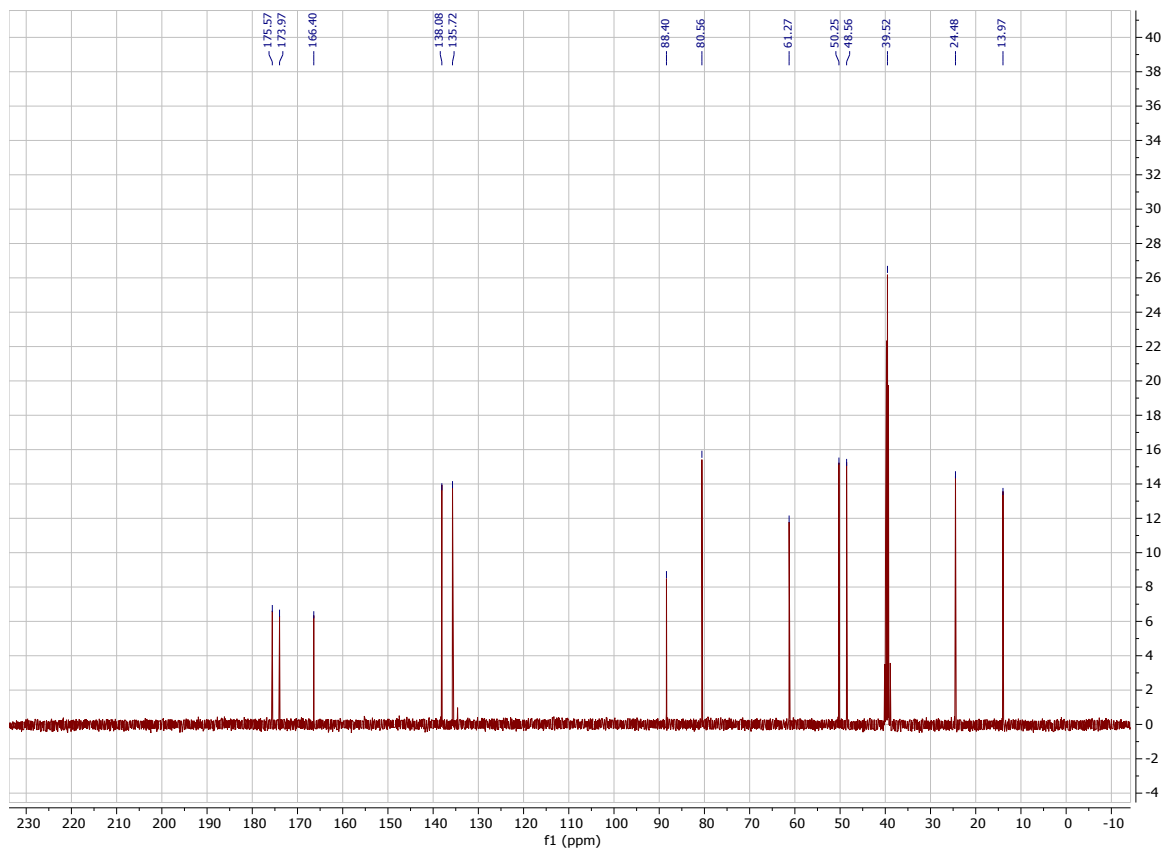
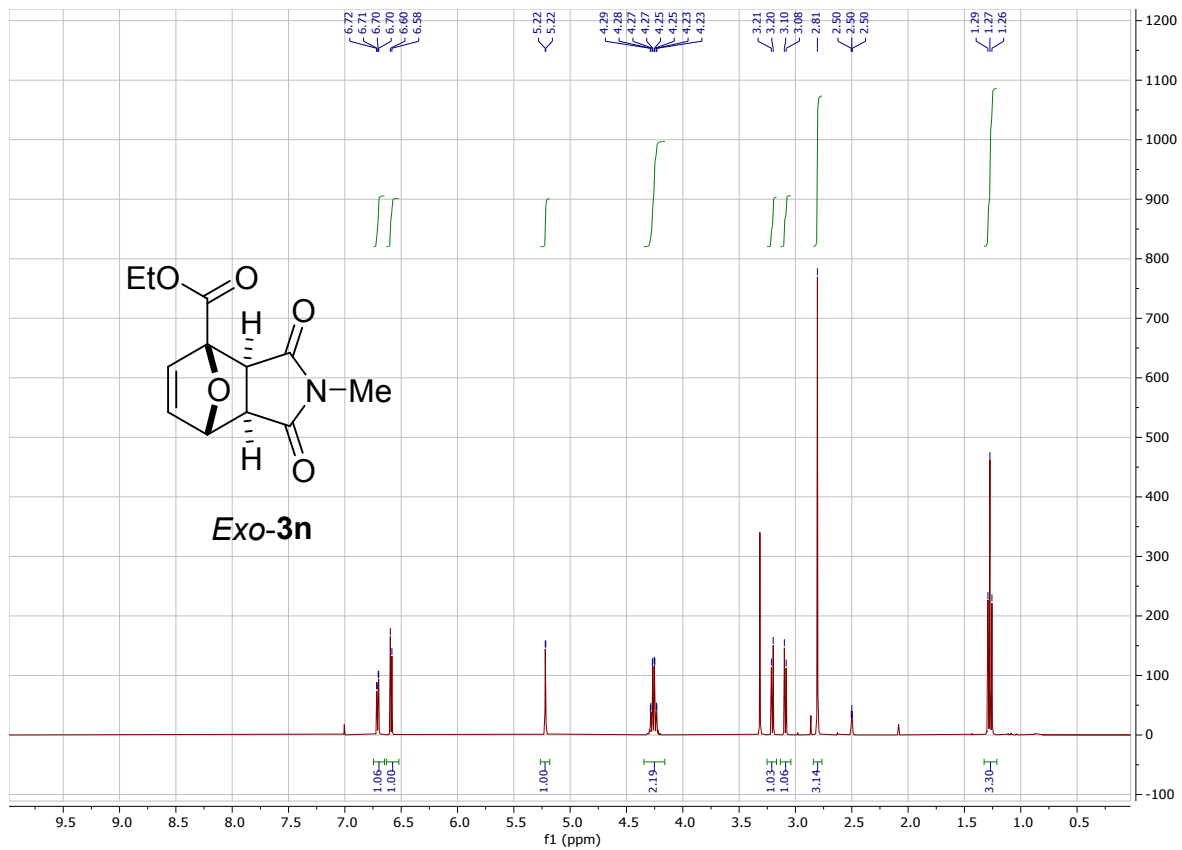
Figure S8. ASAP-HMQC  $^1\text{H}$ - $^{13}\text{C}$  correlation spectrum of crude reaction mixture 3j

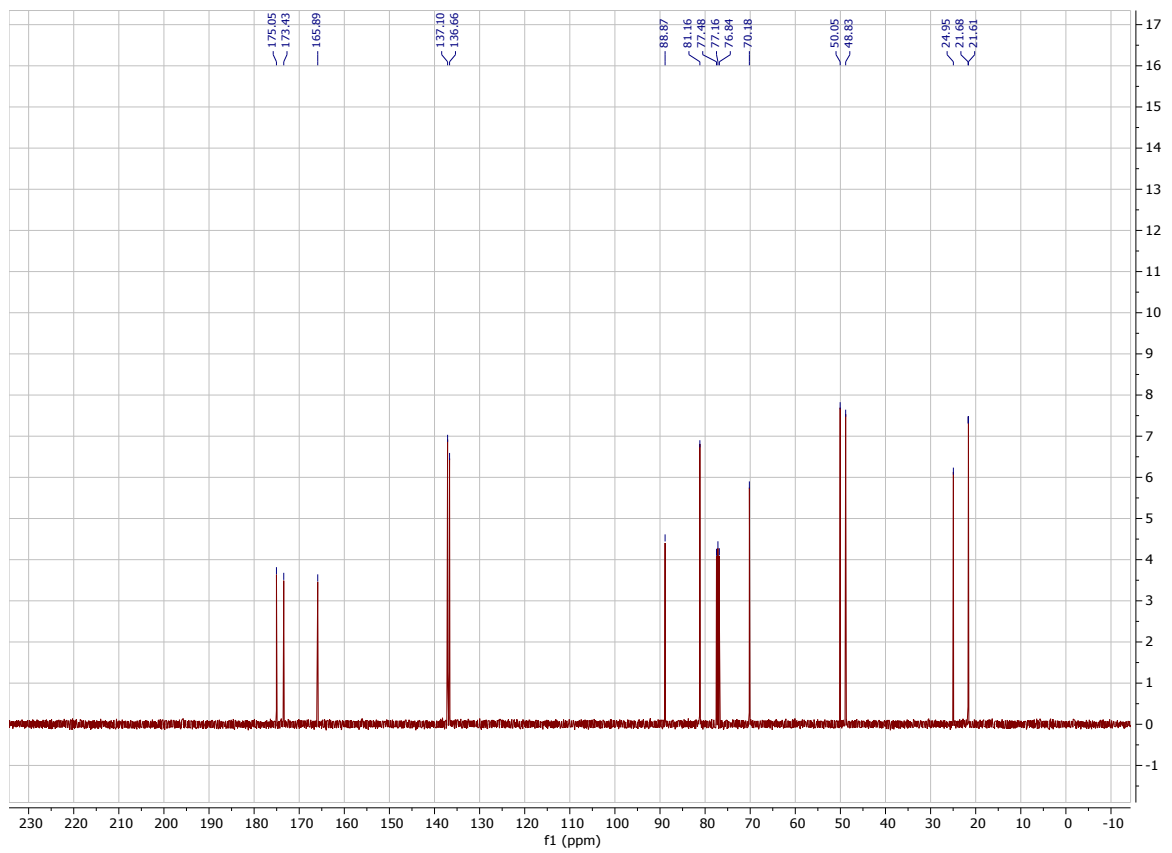
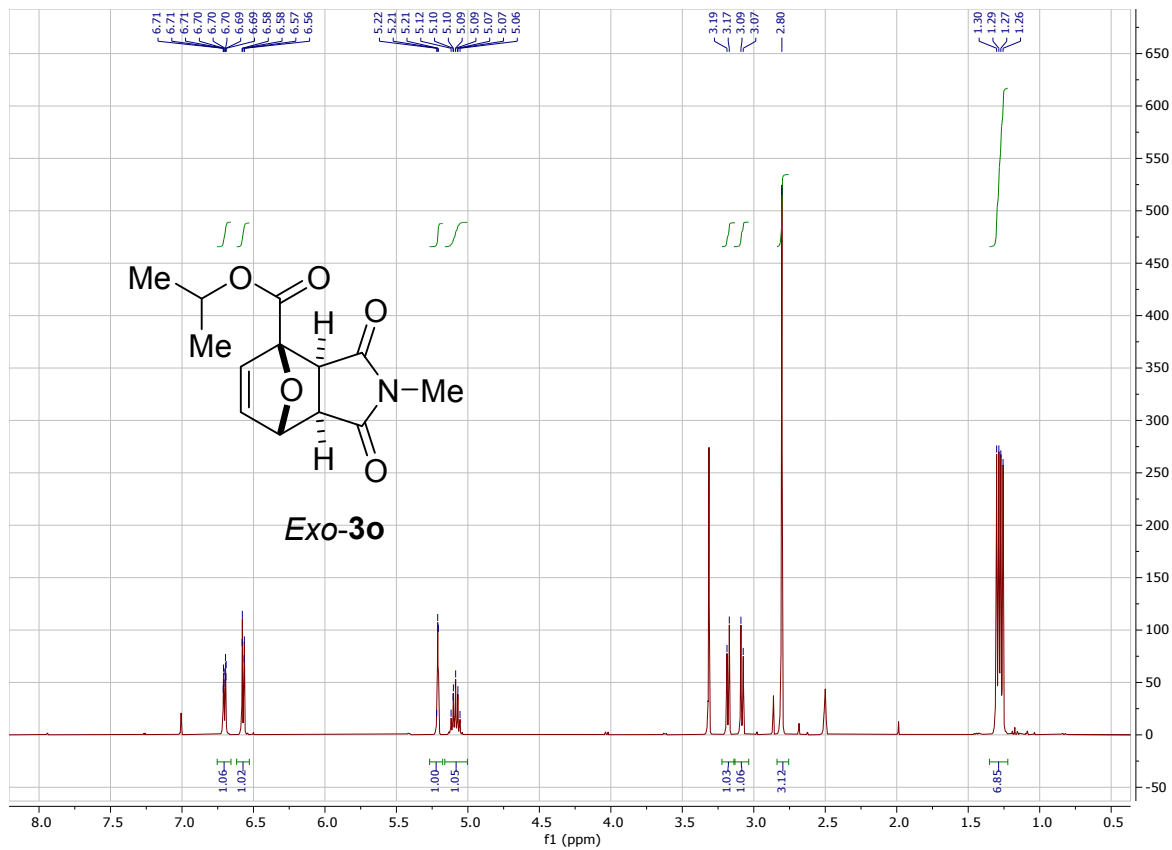


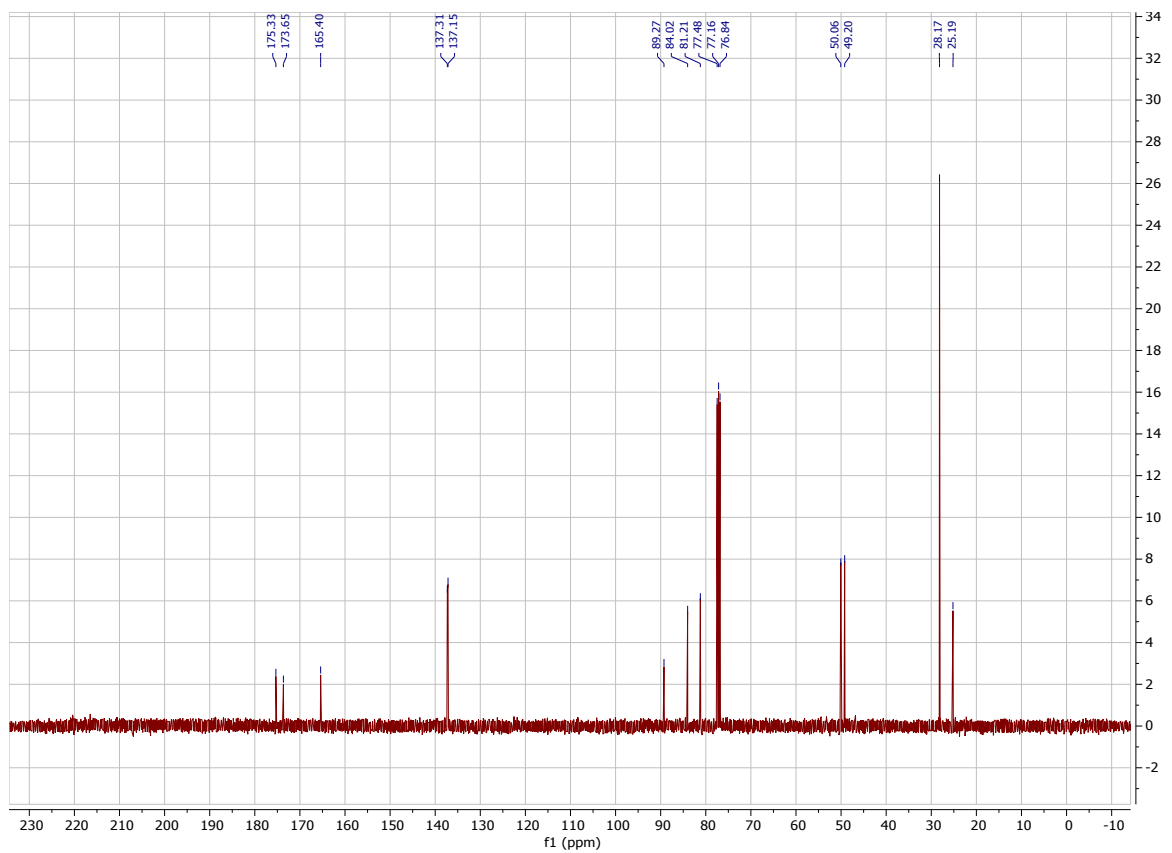
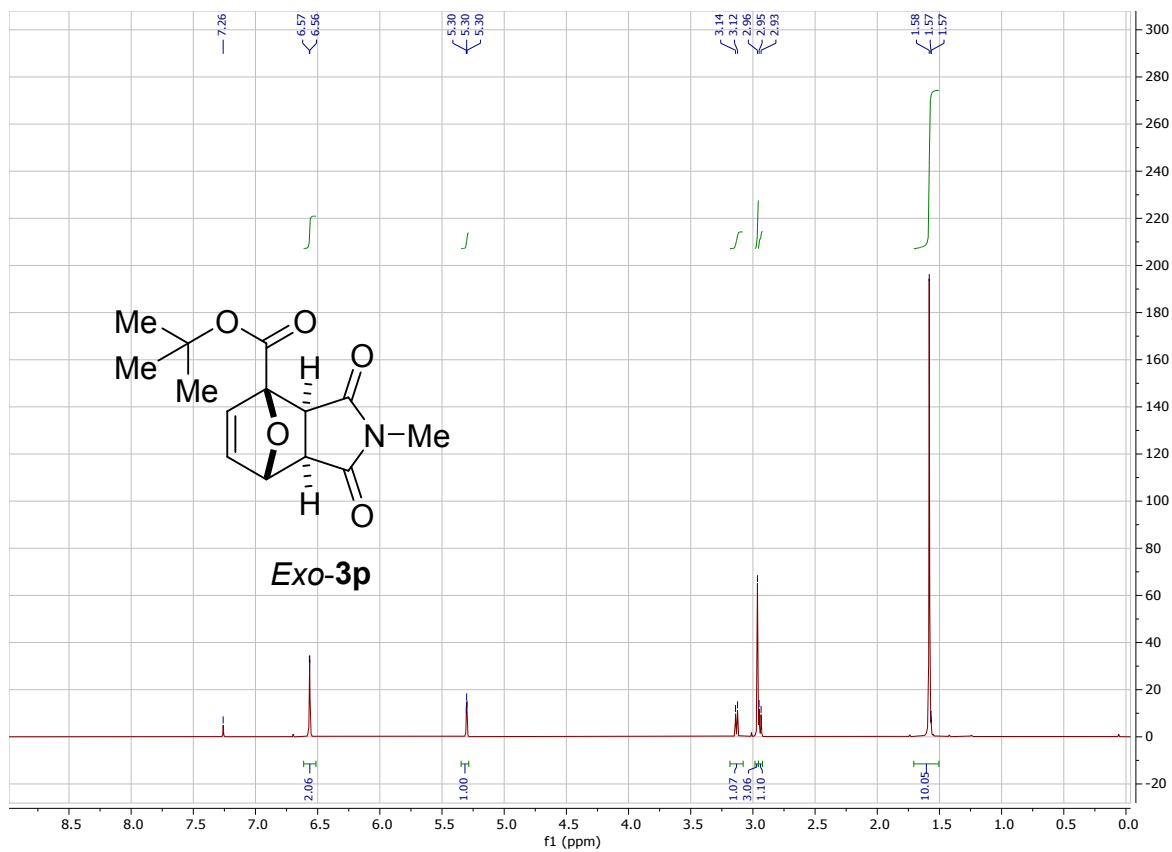


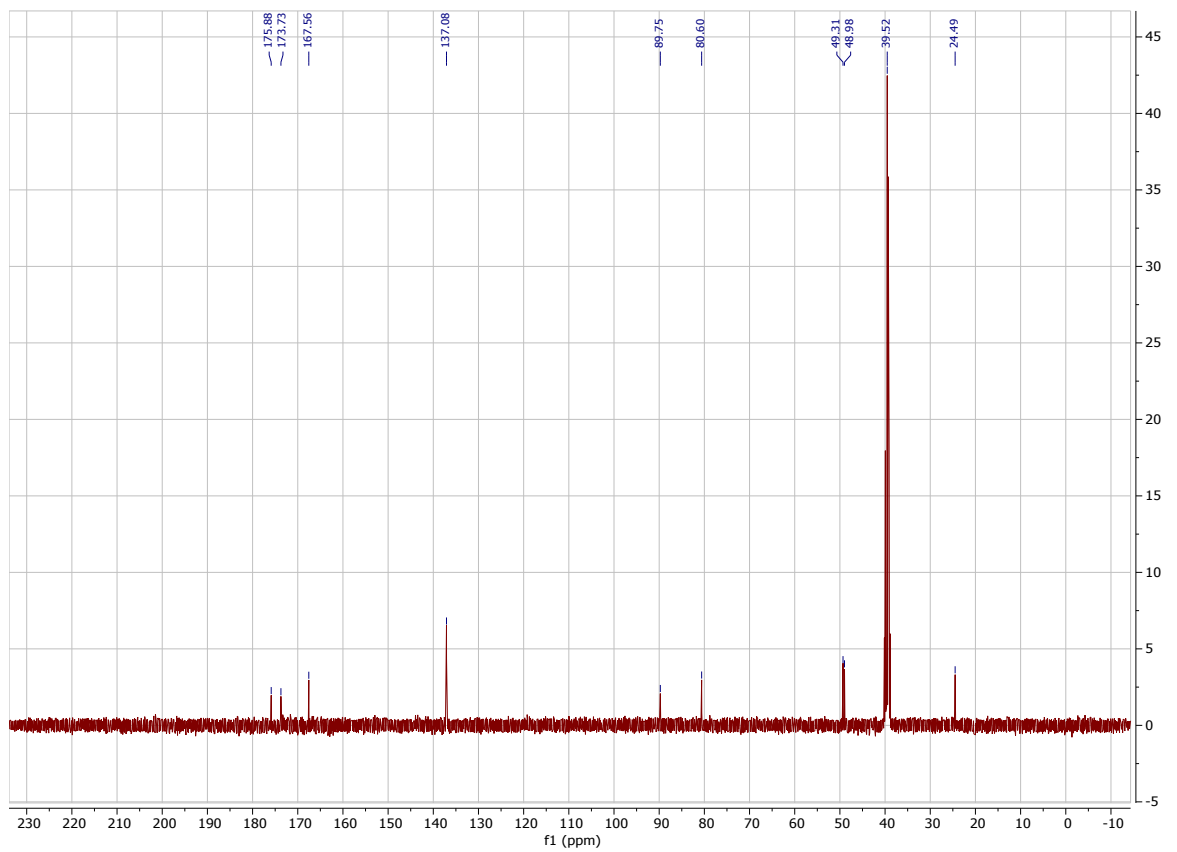
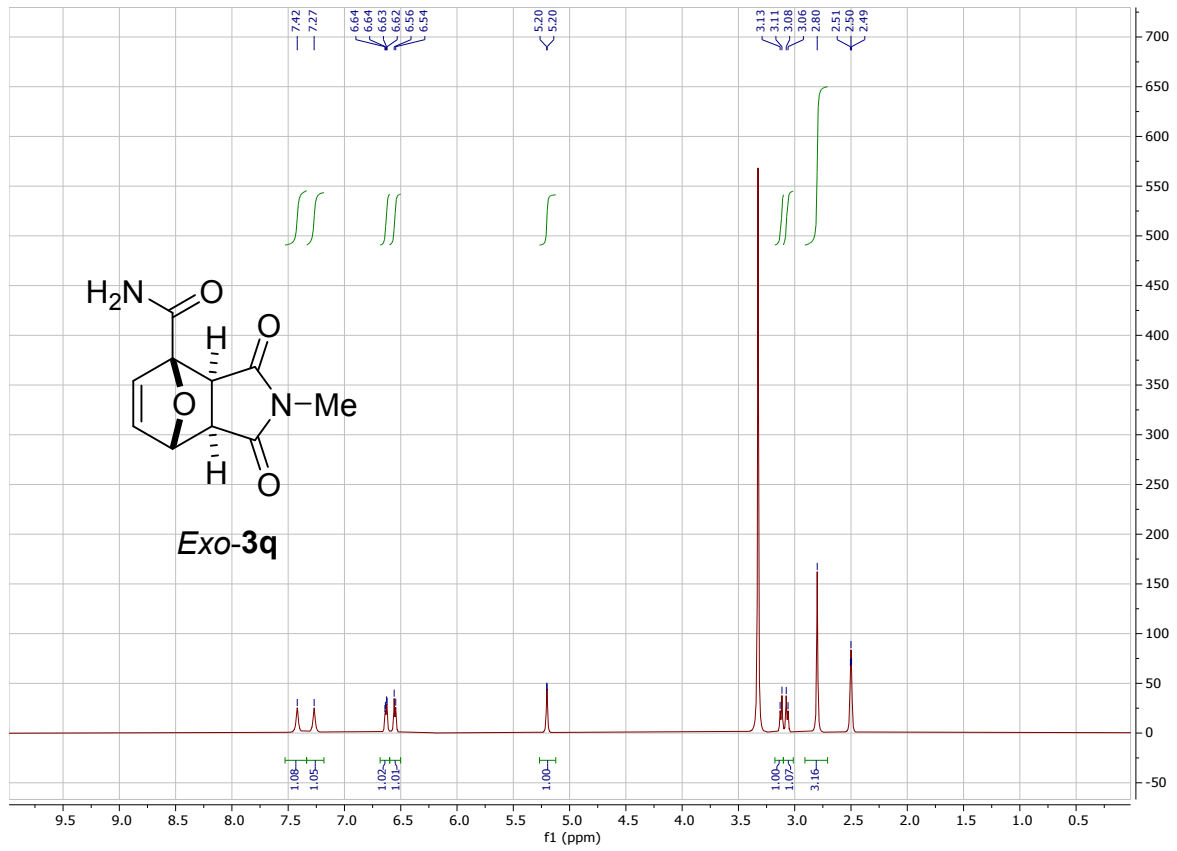


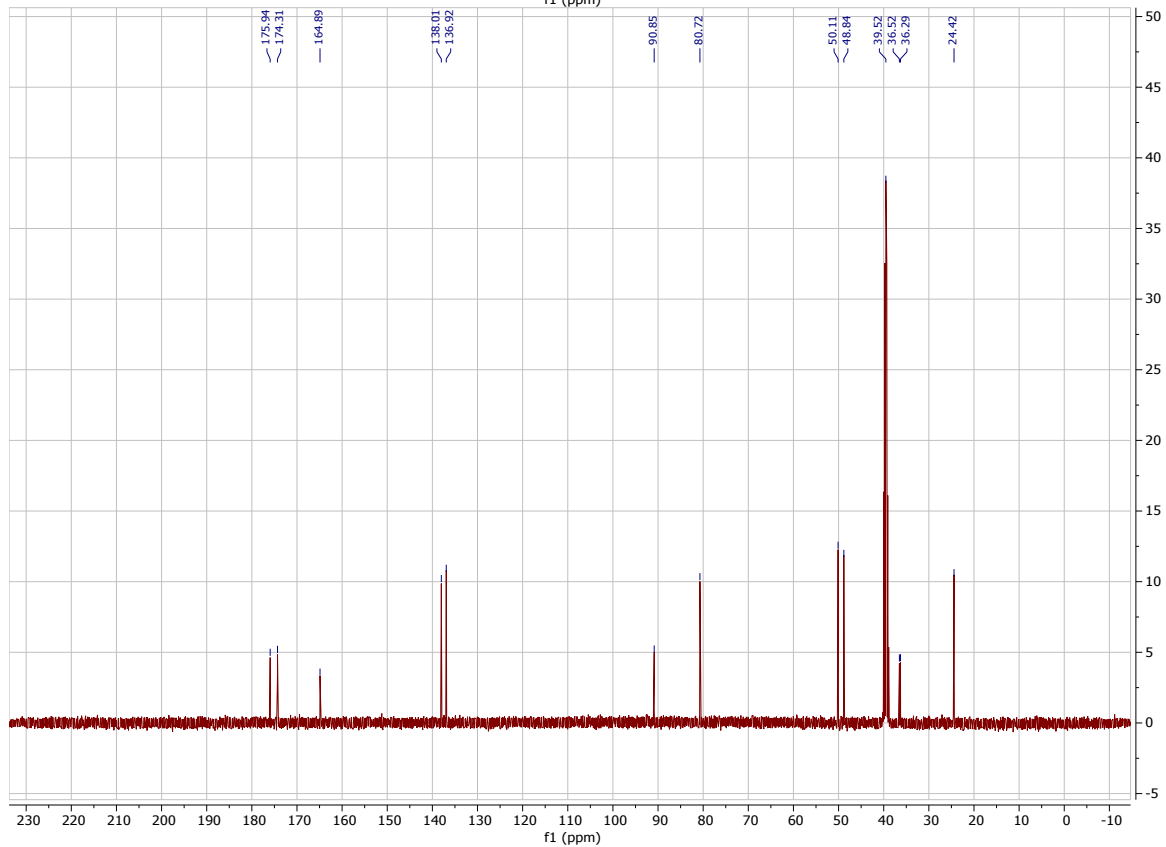
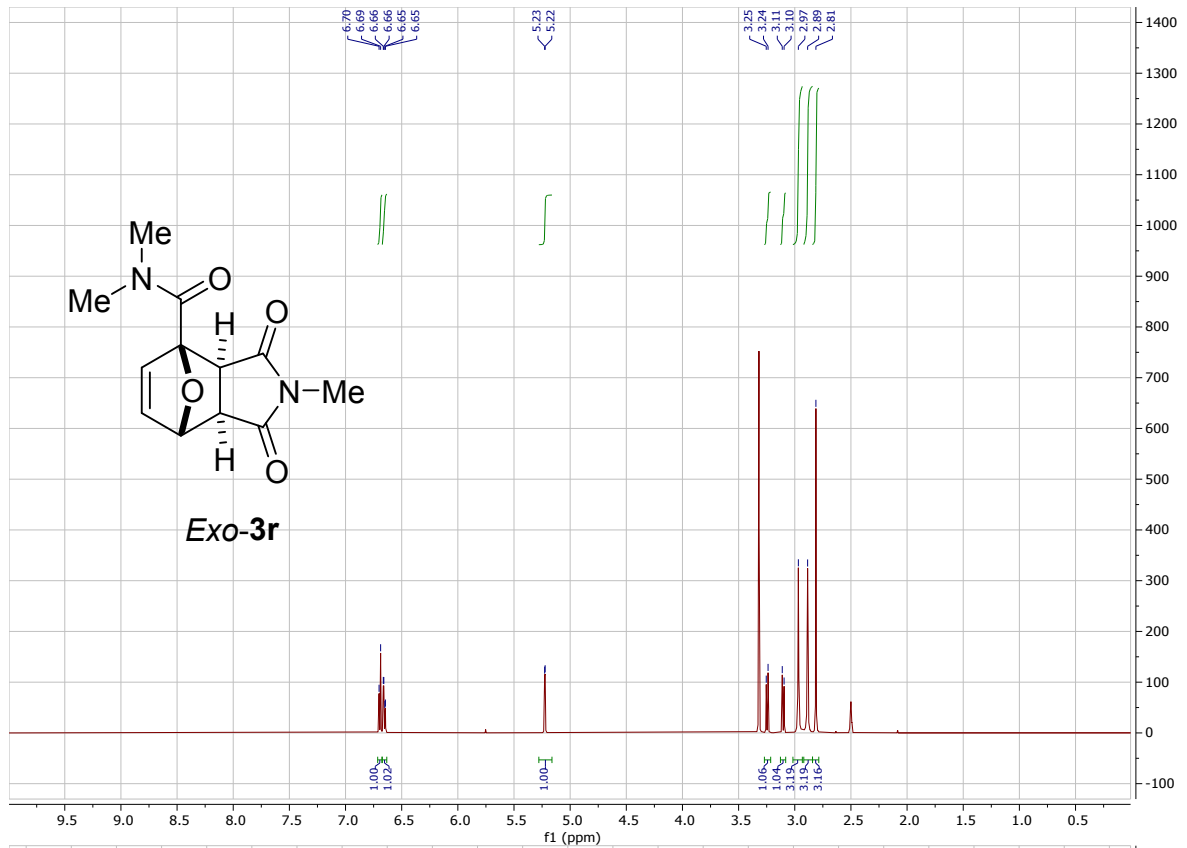




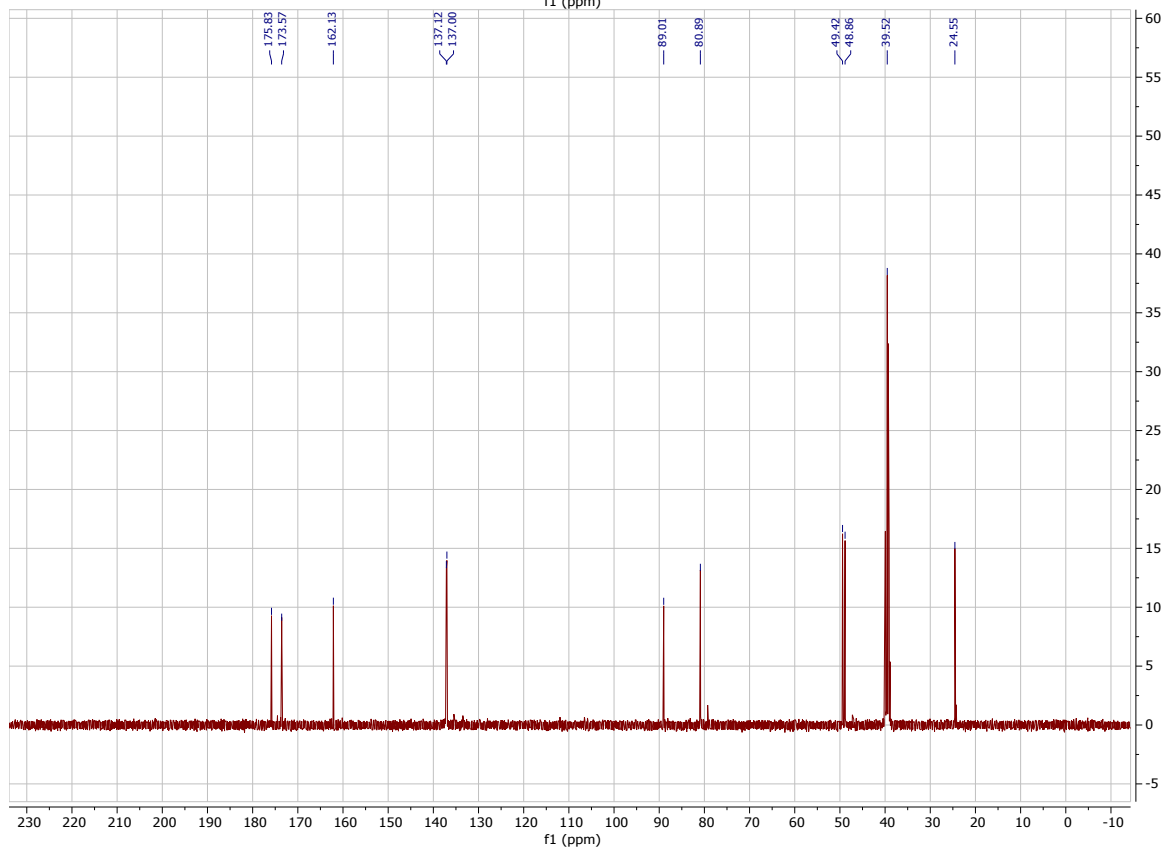
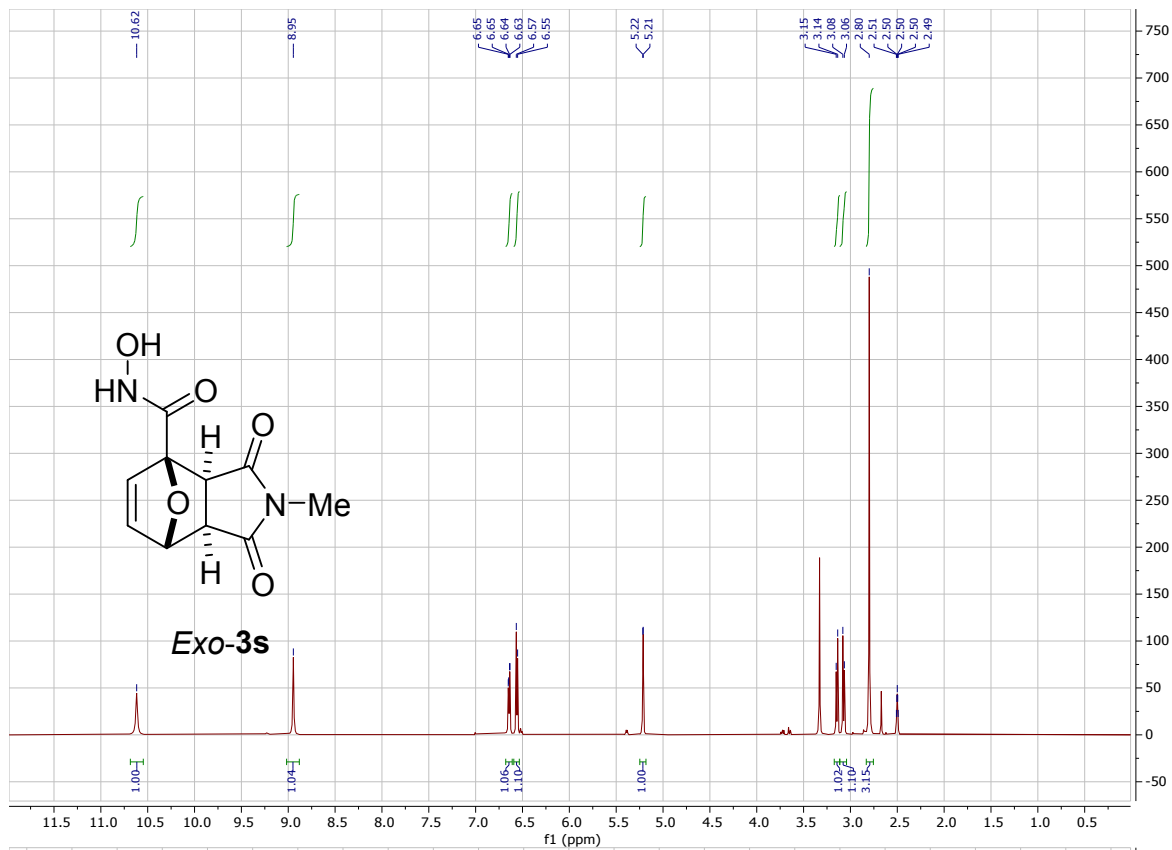


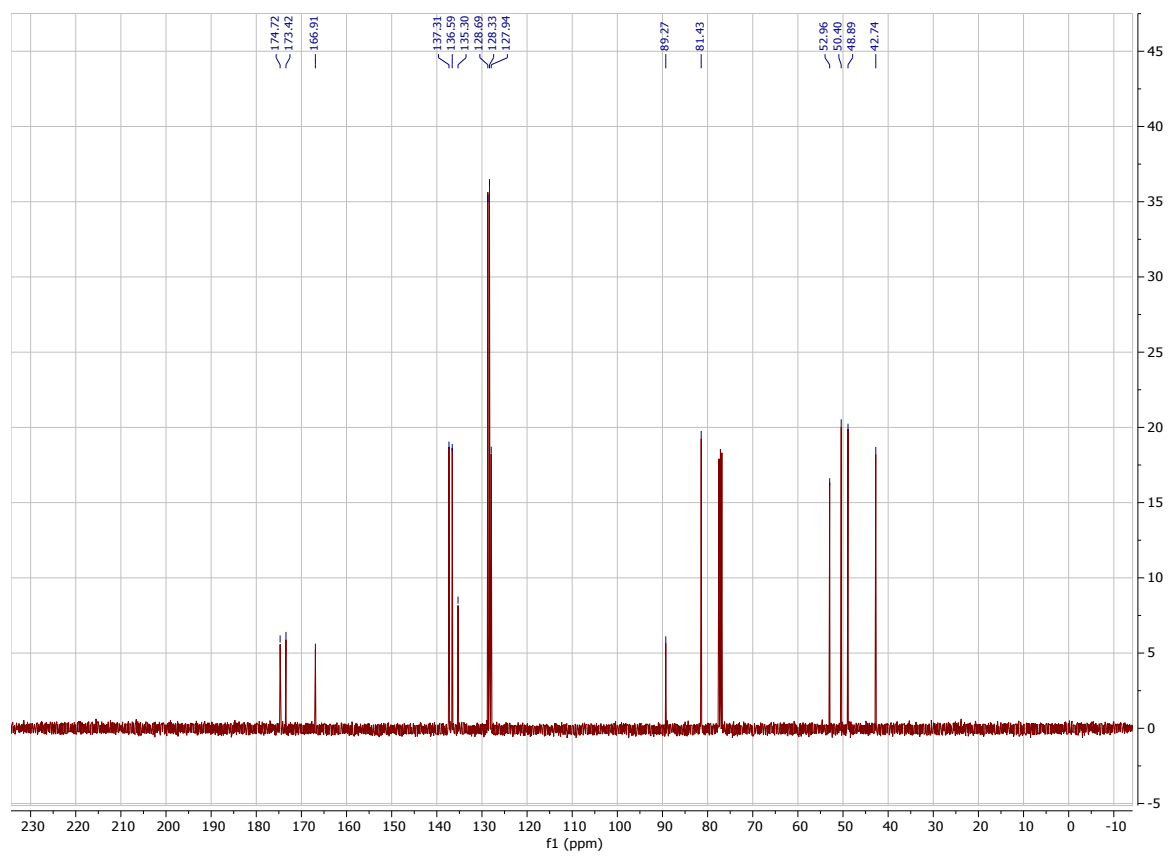
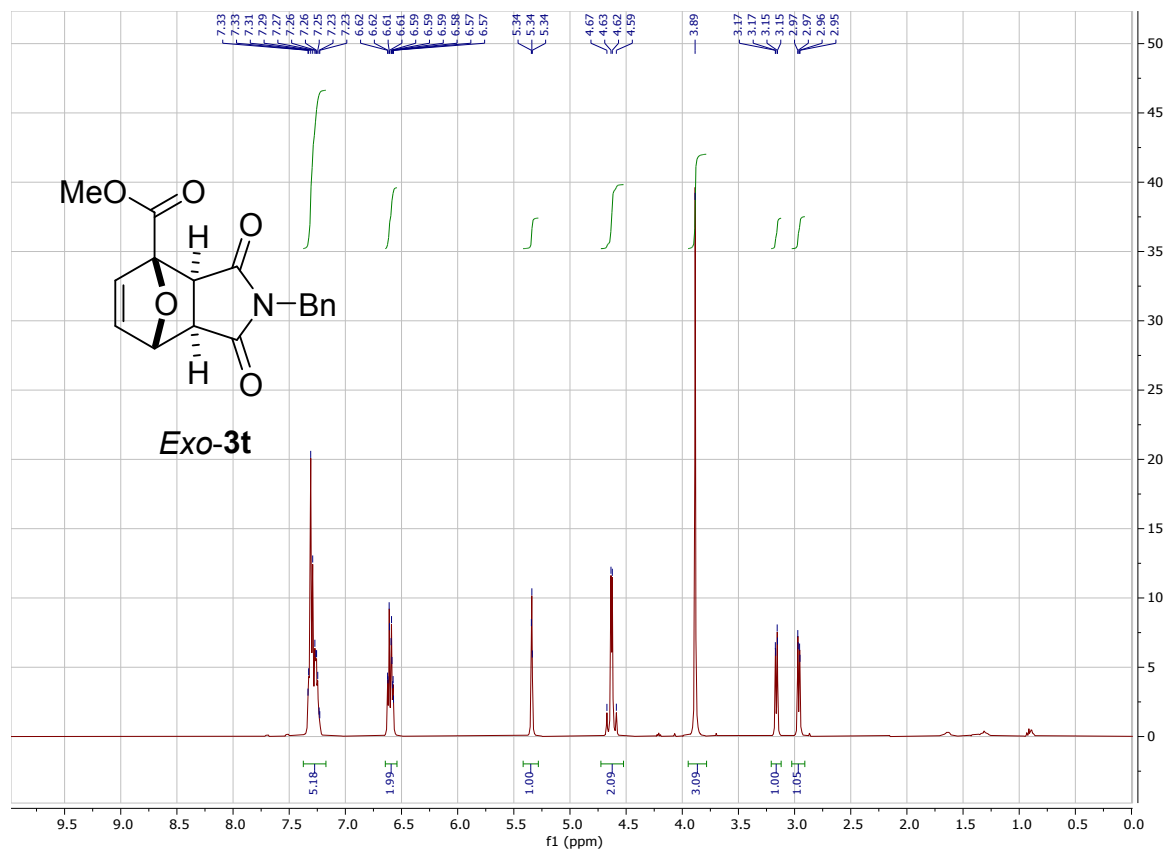


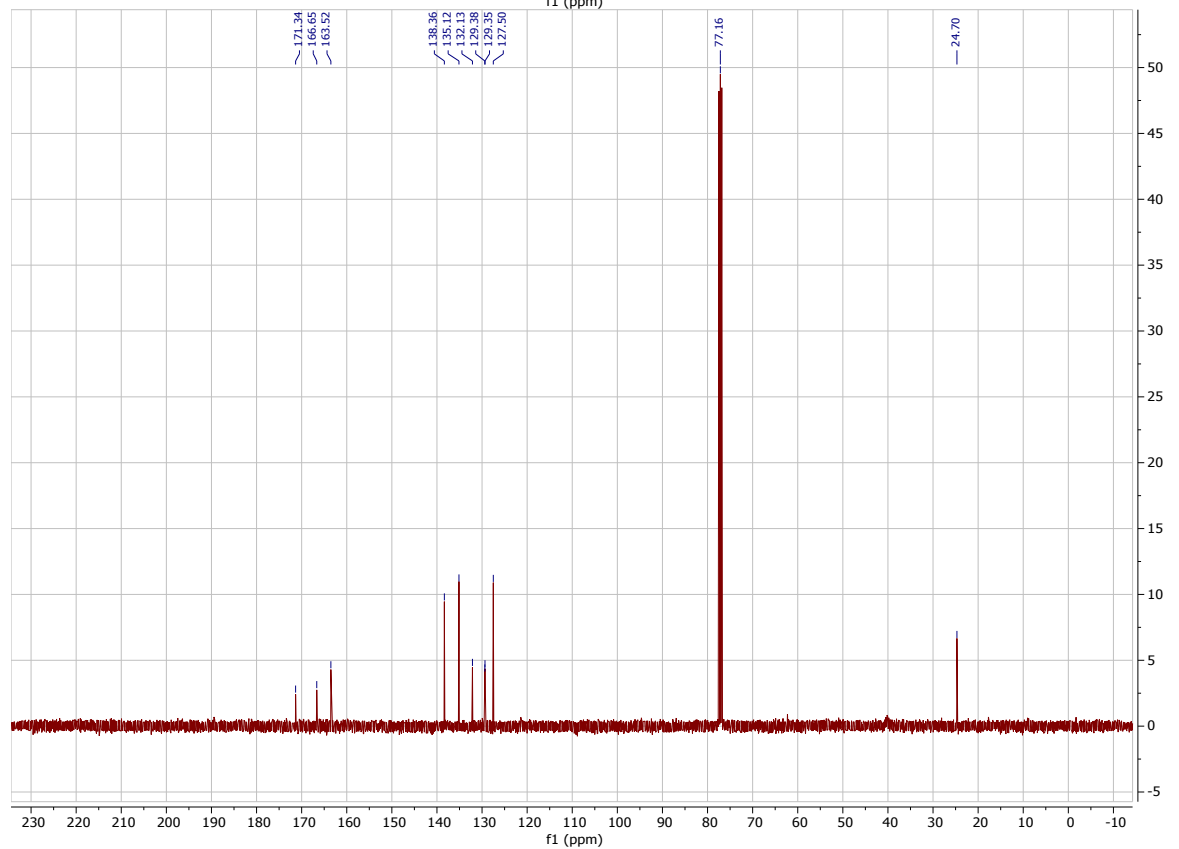
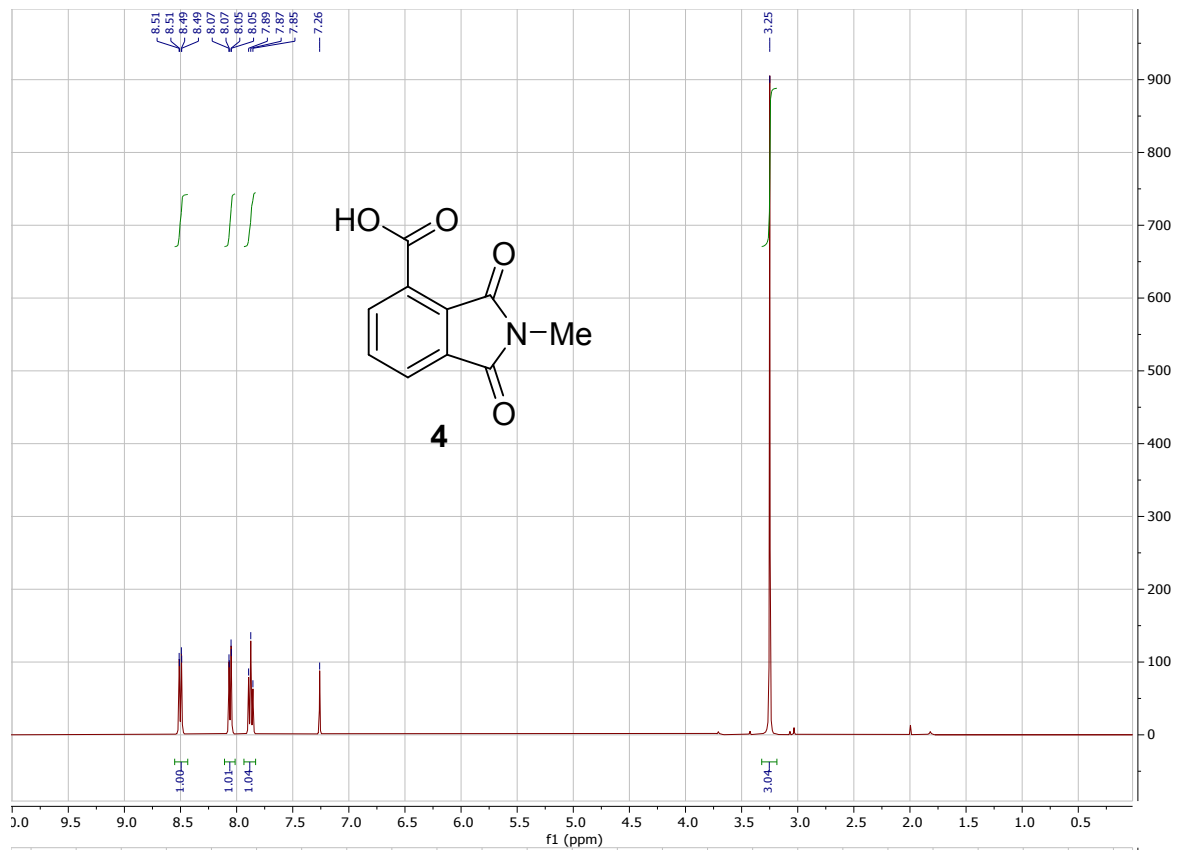


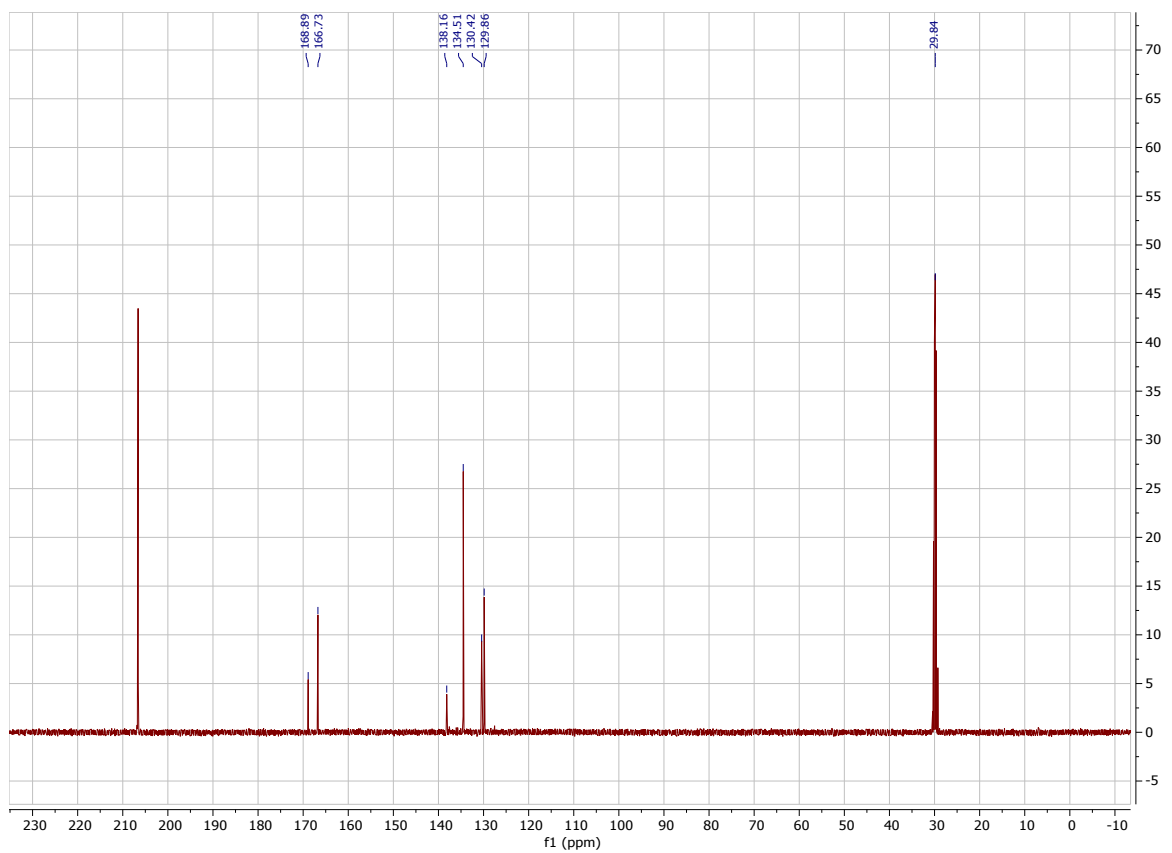
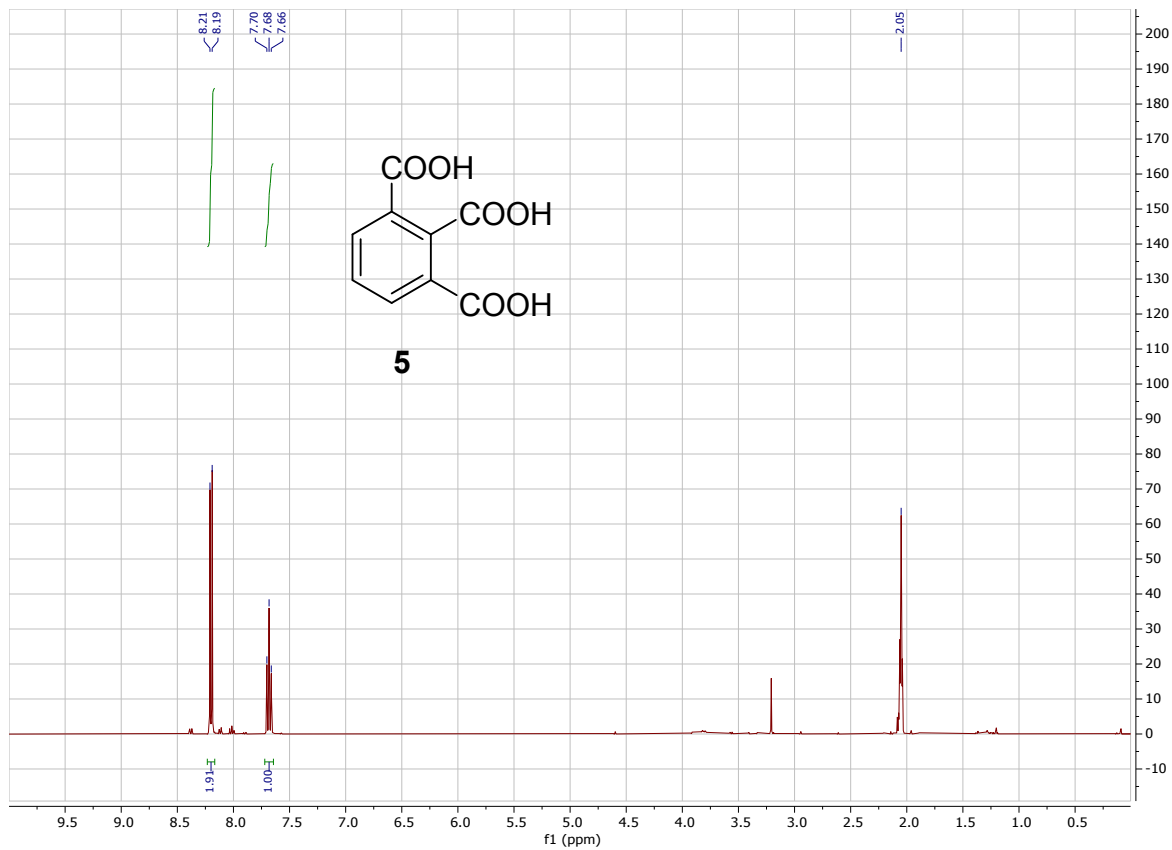


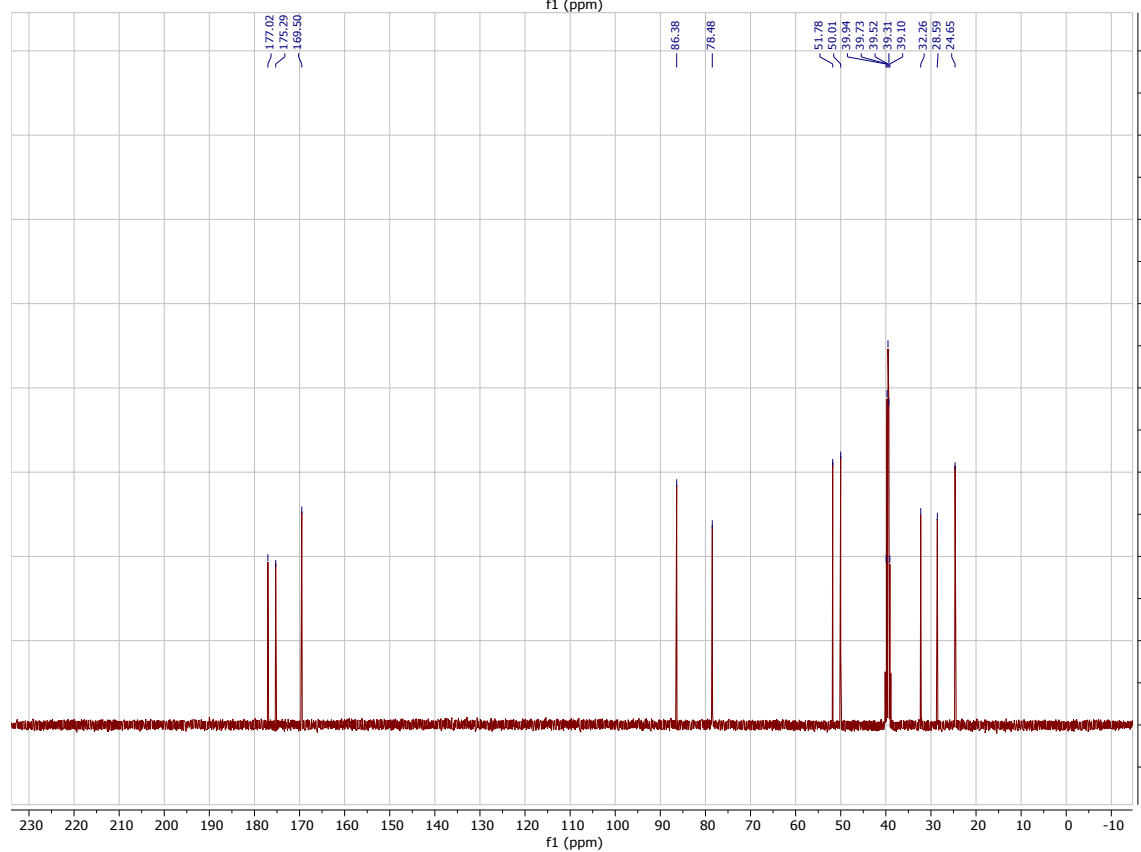
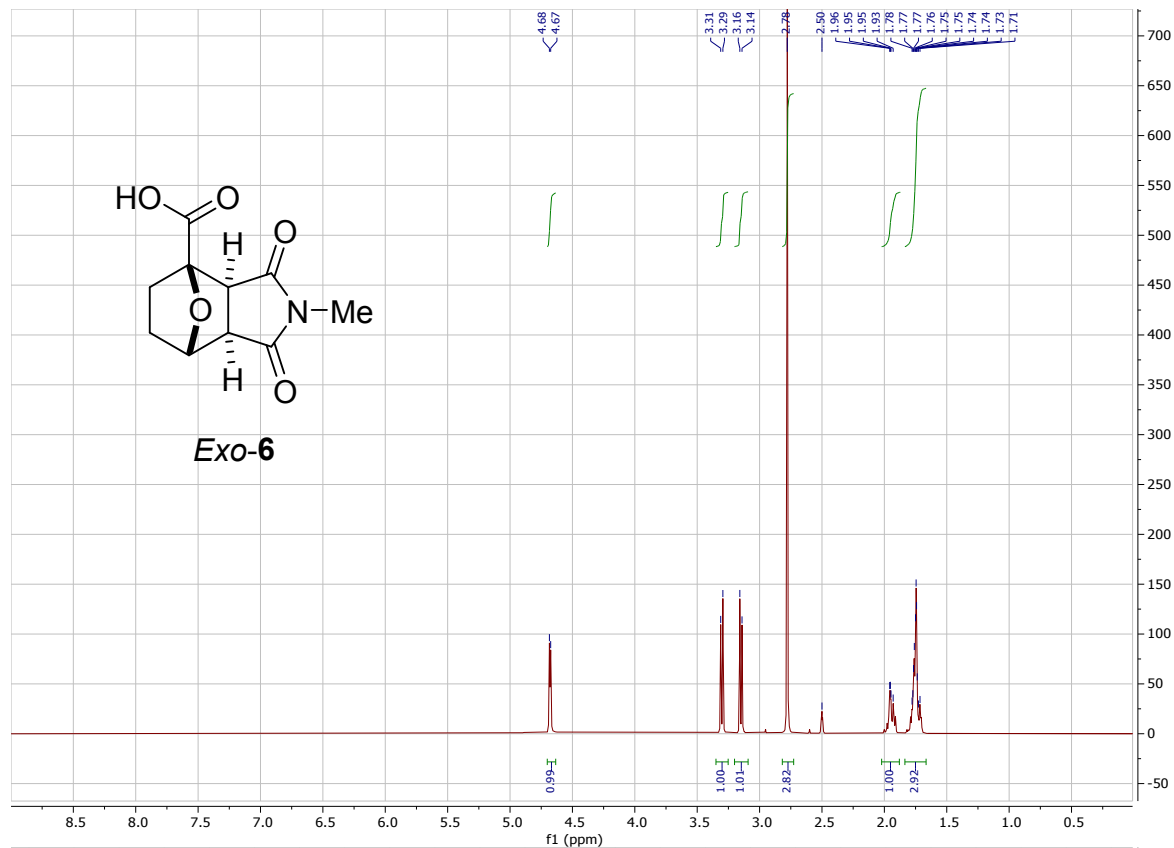












## References

- [1] W. Luo, K. Jiang, Y. Li, H. Jiang, B. Yin, *Org. Lett.* **2020**, *22*, 2093–2098.
- [2] M. Jia, H. Zhang, Y. Lin, D. Chen, Y. Chen, Y. Xia, *Org. Biomol. Chem.* **2018**, *16*, 3615–3624.
- [3] A. Joshi, R. Kumar, R. Semwal, D. Rawat, S. Adimurthy, *Green Chem.* **2019**, *21*, 962–967.
- [4] R. C. Cioc, M. Lutz, E. A. Pidko, M. Crockatt, J. C. van der Waal, P. C. A. Bruijnincx, *Green Chem.* **2021**, *23*, 367–373.
- [5] <https://www.drugfuture.com/chemdata/2-Furoic-Acid.html>, retrieved 04-Feb-2021.
- [6] <https://www.sigmaaldrich.com/catalog/product/aldrich/b4201?lang=en&region=NL>, retrieved 09 April 2021.