Supporting Information

Direct Diels-Alder reaction of chitin derived 3-acetamido-5-acetylfuran

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General information:

All solvents were distilled prior to use. All reagents were used as received from commercial suppliers, unless otherwise stated. 3-acetamido-5-acetylfuran (3A5AF) was prepared according to Padovan's procedure.[1] *N*-(5-(1-hydroxyethyl)furan-3-yl)acetamide was prepared from 3A5AF according to Sperry's procedure.[2] Non-commercial maleimides were prepared in accordance with reported procedure.[3] ^{1}H and ^{13}C NMR spectra were acquired on Bruker MX300 spectrometer. HPLC analysis was performed on a Thermo Scientific Dionex Ultimate 3000 apparatus with a LPG-3400SD Pump, a UV MWD-3000(RS) detector and an autosampler ACC-3000, equipped with a 20 µL loop, using a reversed-phase EC 250/4 Nucleodur 100-5 C18ec column (250×4 mm, 5 µm) Thermo Scientific™ Dionex™.

General procedure A:

To a solution of *N*-(5-acetylfuran-3-yl)acetamide (60 mg, 0.36 mmol) and the corresponding maleimide (1.2 eq, 0.43 mmol) in DMSO-d6 (0.4 mL) was added a pH 4 aqueous solution (acetic acid-sodium acetate 0.1M, 0.4 mL). The reaction mixture was stirred at 50ºC for 24 hours. The reaction mixture was cooled down to room temperature and extracted with ethyl acetate (5 x 5 mL). The combined organic layers were dried with anhydrous Mg_2SO_4, filtered, and concentrated under reduced pressure. The product was isolated by flash chromatography, yielding the pure product.

General procedure B:

To a solution of *N*-(5-acetylfuran-3-yl)acetamide (20 mg, 0.12 mmol) and the corresponding maleimide (1.2 eq, 0.14 mmol) in DMSO-d6 (0.133 mL) was added pH 4 aqueous solution (acetic acid-sodium acetate 0.1M, 0.133 mL). The reaction mixture was stirred at 50ºC for 24 hours. The reaction mixture was cooled down to room temperature and 2-mercaptopropanoic acid (0.14 mmol) was added and stirred for 15 minutes. The reaction mixture was extracted with ethyl acetate:$NaHCO_3$ saturated solution (5 x 5 mL). The combined organic layers were dried with anhydrous Mg_2SO_4, filtered, and concentrated under reduced pressure, yielding the pure products. In some cases, it was possible to observe traces of starting material that was not present in the crude ^{1}H-NMR evaluation, possible due to retro-Diels-Alder reaction.

Comparison of the scope from GPA and GPB:

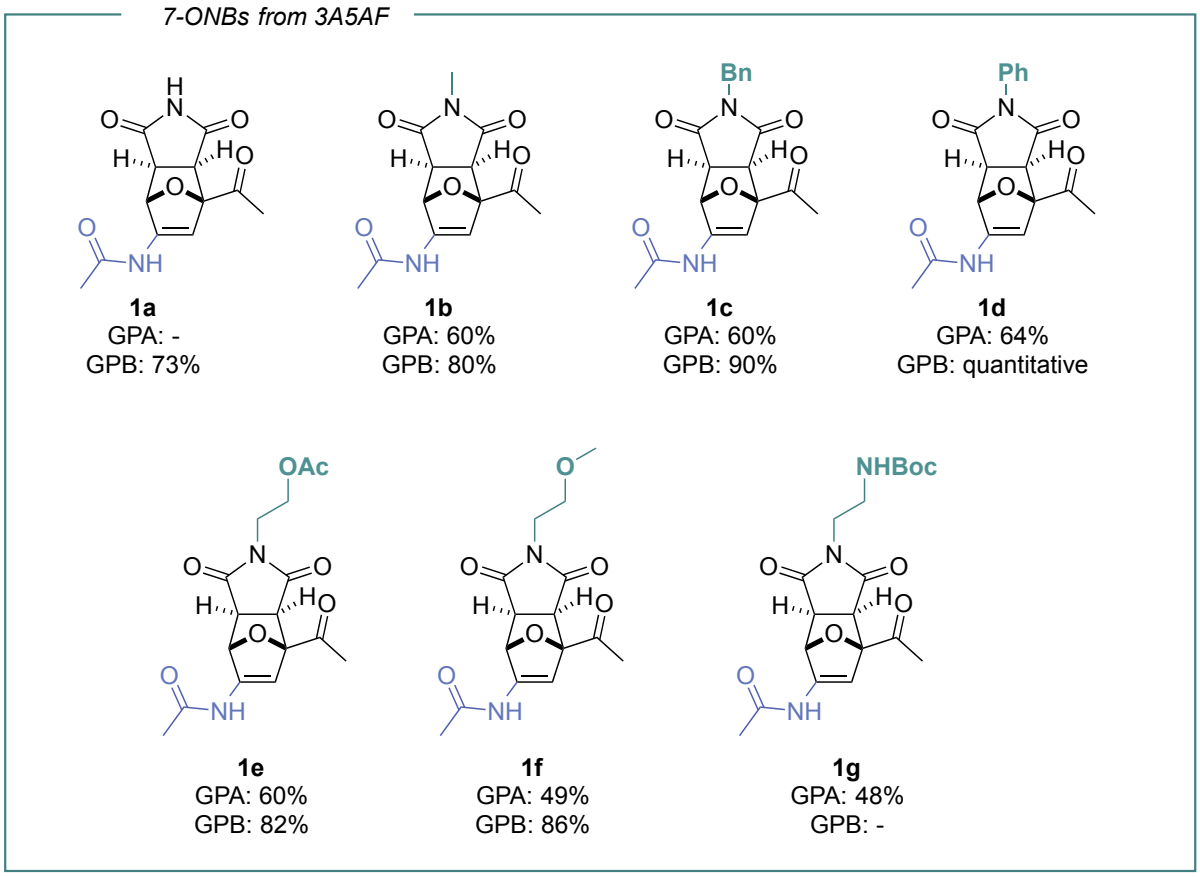


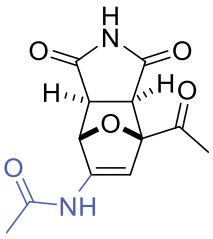
Figure 1. Isolated yield comparison of the scope from General procedure A and General procedure B.

General procedure C:

To a solution of *N*-(5-acetylfuran-3-yl)acetamide (6 mg, 0.036 mmol) and the corresponding maleimide (1.2 eq 0.043 mmol) in DMSO-d6 (0.4 mL) was added a acetic acid-sodium acetate buffer solution 0.1 M (0.4 mL) at pH 2.6. The reaction mixture was stirred at 50ºC for 24 hours. The reaction mixtures were cooled down to room temperature and washed with ethyl acetate:H_2O (5 x 5 mL). The combined aqueous layers were concentrated under reduced pressure and further freeze dried, yielding the pure products.

Scope of 7-ONBs:

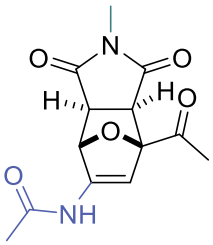
***N*-(7-acetyl-2-methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-epoxyisoindol-5-yl)acetamide (1a)**



The title compound was prepared according to the general procedure A using 100 mg of 3A5AF. The product was obtained in 73% yield (115 mg) as a hygroscopic yellow solid characterized as a mixture of 2:8 of starting materials:**1a** due to retro-DA.

^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ 6.11 (s, 1H), 5.16 (s, 1H), 3.39 (d, *J* = 6.50 Hz, 1H), 3.11 (d, *J* = 6.52 Hz, 1H), 2.25 (s, 3H), 1.97 (s, 3H) ppm. **^{13}C NMR (75 MHz, $(CD_3)_2SO$)** δ 202.9, 177.1, 176.1, 169.2, 169.1, 144.8, 110.4, 94.8, 80.1, 53.9, 50.3, 27.2, 23.4 ppm. **HRMS (ESI-MS)** *m/z* calculated for 279.09755 [M+H$^+$], found 279.09771.

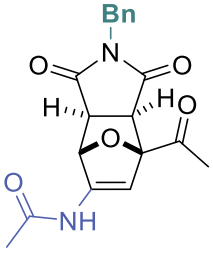
***N*-(7-acetyl-2-methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-epoxyisoindol-5-yl)acetamide (1b)**



The title compound was prepared according to the general procedure B. The product was obtained in 80% yield (27 mg) as a pale yellow hygroscopic solid.

^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ 10.28 (s, 1H), 6.13 (s, 1H), 5.18 (s, 1H), 3.45 (d, *J* = 6.50 Hz, 1H), 3.18 (d, *J* = 6.49 Hz, 1H), 2.81 (s, 3H), 2.25 (s, 3H), 1.98 (s, 3H) ppm. **^{13}C NMR (75 MHz, $(CD_3)_2CO$)** δ 203.0, 176.2, 175.2, 169.1, 145.9, 111.7, 95.7, 81.6, 53.7, 50.1, 27.0, 24.9, 23.5 ppm. **HRMS (ESI-MS)** *m/z* calculated for 279.09755 [M+H$^+$], found 279.09771.

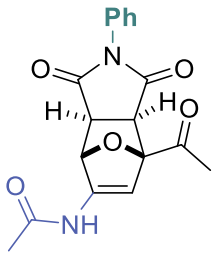
***N*-(7-acetyl-2-benzyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-epoxyisoindol-5-yl)acetamide (1c)**



The title compound was prepared according to the general procedure B using 60 mg of *N*-(5-acetylfuran-3-yl)acetamide. The product was isolated with 90% yield (114 mg) as a white solid. m.p. 137-140ºC.

^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ 10.30 (s, 1H), 7.35-7.20 (m, 5H), 6.14 (s, 1H), 5.22 (s, 1H), 4.55 (s, 2H), 3.50 (d, *J* = 6.47 Hz, 1H), 3.27 (d, *J* = 6.51 Hz, 1H), 2.16 (s, 3H), 1.99 (s, 3H) ppm. **^{13}C NMR (75 MHz, $(CD_3)_2CO$)** δ 203.1, 175.8, 174.8, 169.0, 145.6, 136.8, 129.1, 128.3, 111.6, 95.6, 81.5, 53.5, 49.9, 42.5, 26.8, 23.3 ppm. **HRMS (ESI-MS)** *m/z* calculated for $C_{19}H_{19}N_2O_5$ [M+H$^+$] 355.12885, found 355.12867.

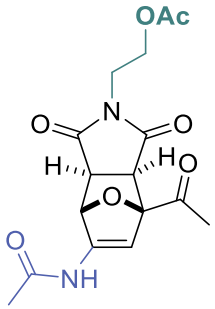
_N_-(7-acetyl-1,3-dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1_H_-4,7-epoxyisoindol-5-yl)acetamide (1d)



The title compound was prepared according to the general procedure B. The product was obtained in quantitative yield (41 mg) as a white solid. m.p.145-148ºC

^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 7.51-7.38 (m, 3H), 7.27-7.24 (m, 2H), 6.27 (s, 1H), 5.40 (s, 1H), 3.59 (d, *J* = 6.60 Hz, 1H), 3.40 (d, *J* = 3.40 Hz, 1H), 2.28 (s, 3H), 2.07 (s, 3H) ppm. **^{13}C NMR (75 MHz, $(CD_3)_2CO$)** δ 203.0, 175.4, 174.3, 169.2, 146.0, 133.4, 129.8, 129.3, 127.7, 111.9, 96.1, 82.1, 53.9, 50.2, 27.1, 23.5 ppm. **HRMS (ESI-MS)** *m/z* calculated for $C_{18}H_{17}N_2O_5$ [M+H$^+$] 341.11320, found 341.11290.

2-(6-acetamido-4-acetyl-1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2H-4,7-epoxyisoindol-2-yl)ethyl acetate (1e)

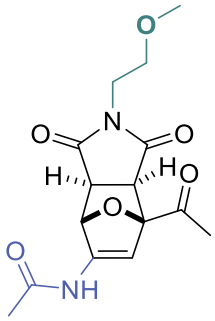


The title compound was prepared according to the general procedure B. The product was isolated with 82% yield (30.3 mg) as a yellow solid. m.p 79-81ºC.

^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ 10.29 (s, 1H), 6.11 (s, 1H), 5.20 (s, 1H), 4.09-4.05 (m, 2H), 3.60 (td, *J* = 5.19 Hz, *J* = 1.11 Hz, 2H), 3.45 (d, *J* = 6.50 Hz, 1H), 3.20 (d, *J* = 6.52 Hz, 1H), 2.24 (s, 3H), 1.98 (s, 3H), 1.93 (s, 3H) ppm **^{13}C NMR (75 MHz, $(CD_3)_2CO$)** δ 203.0, 175.9, 174.8, 169.0, 145.6, 111.4, 95.4,

81.4, 60.9, 53.3, 49.7, 38.1, 26.9, 23.2 ppm. **HRMS (ESI-MS)** *m/z* calculated for $C_{16}H_{19}N_2O_7$ [M+H$^+$] 351.11868, found 351.11812.

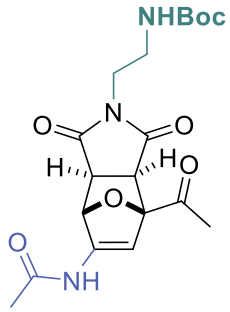
***N*-(7-acetyl-2-(2-methoxyethyl)-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-epoxyisoindol-5-yl)acetamide (1f)**



The title compound was prepared according to the general procedure B. The product was isolated with 86% yield (33 mg) as a yellow oil.

^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ 10.32 (s, 1H), 6.11 (s, 1H), 5.20 (s, 1H), 3.54-3.49 (m, 2H), 3.42-3.39 (m, 4H), 3.19 (s, 3H), 2.21 (s, 3H), 1.98 (s, 3H) ppm. **^{13}C NMR (75 MHz, $(CD_3)_2CO$)** δ 203.3, 175.9, 174.7, 169.0, 145.4, 111.5, 95.3, 81.3, 68.8, 58.1, 53.3, 49.5, 38.4, 26.7, 23.2 ppm. **HRMS (ESI-MS)** *m/z* calculated for compound $C_{15}H_{19}N_2O_6$ [M+H$^+$] 323.12376, found 323.12343.

***tert*-butyl(2-(6-acetamido-4-acetyl-1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-4,7-epoxyisoindol-2-yl)ethyl)carbamate (1g)**

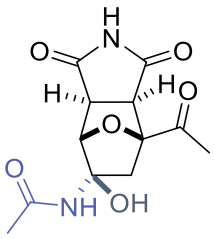


The compound was prepared according to the general procedure A. The crude mixture was isolated by flash chromatography using hexane:ethyl acetate (1:6) affording the product with 48% yield (48 mg) as an hygroscopic white solid characterized as amixture of 8.6:1.4 of **1g**:starting materials due to retro-DA.

^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ 9.42 (s, 1H), 6.19 (s, 1H), 5.26 (s, 1H), 3.57-3.52 (m, 2H), 3.38 (d, *J* = 6.45 Hz), 3.25-3.18 (m, 3H), 2.23 (s, 3H), 1.38 (s, 9H) ppm. **^{13}C NMR (75 MHz, $(CD_3)_2CO$)** δ 203.2, 176.1, 175.1, 169.1, 156.6, 145.8, 111.6, 95.6, 81.6, 78.8, 53.6, 49.9, 39.3, 38.6, 28.5, 27.0, 23.4 ppm. **HRMS (ESI-MS)** *m/z* calculated for $C_{19}H_{26}N_3O_7$ [M+H$^+$] 408.17653, found 408.17634.

Scope of Hemi-Acylaminals:

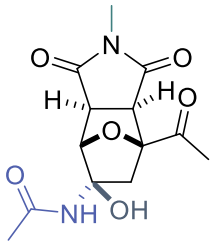
***N*-(7-acetyl-5-hydroxy-1,3-dioxooctahydro-1*H*-4,7-epoxyisoindol-5-yl)acetamide (2a)**



The title compound was prepared according to the general procedure C using 50 mg of 3A5AF. The product was isolated in quantitative yield (84 mg) as a white solid. m.p 140-143ºC.

^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ 11.39 (s, 1H), 8.79 (s, 1H), 5.93 (s, 1H), 4.85 (s, 1H), 3.29 (d, *J* = 6.99 Hz, 1H), 3.10 (d, *J* = 6.95 Hz, 1H), 2.24 (d, *J* = 13.08 Hz, 1H), 2.16 (s, 3H), 1.88 (d, *J* = 13.17 Hz, 1H), 1.84 (s, 3H) ppm. **^{13}C NMR (75 MHz, $(CD_3)_2SO$)** δ 203.2, 178.2, 176.9, 169.9, 90.6, 85.9, 85.8, 52.3, 47.8, 47.3, 27.2, 23.0 ppm. **HRMS (ESI-MS)** *m/z* calculated for $C_{12}H_{15}N_2O_6$ [M+H$^+$] 283.09246, found 283.09228.

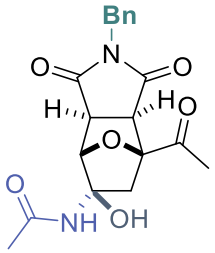
***N*-(7-acetyl-5-hydroxy-2-methyl-1,3-dioxooctahydro-1*H*-4,7-epoxyisoindol-5-yl)acetamide (2b)**



The compound was prepared according to the general procedure C. The product was isolated in quantitative yield (10.6 mg) as a yellow/brown oil.

^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.89 (s, 1H), 4.85 (s, 1H), 3.37 (d, *J* = 6.89 Hz, 1H), 3.14 (d, *J* = 6.89 Hz, 1H), 2.79 (s, 3H), 2.30 (d, *J* = 13.09 Hz, 1H), 2.16 (s, 3H), 1.89 (d, *J* = 13.04 Hz, 1H), 1.84 (s, 3H) ppm. **^{13}C NMR (100 MHz, $(CD_3)_2SO$)** δ 203.4, 176.7, 175.3, 170.0, 90.5, 85.9, 85.6, 51.0, 47.7, 46.1, 27.3, 24.8, 23.0 ppm. **HRMS (ESI-MS)** *m/z* calculated for $C_{13}H_{17}N_2O_6$ [M+H$^+$] 297.10811, found 297.10886.

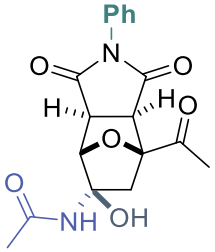
***N*-(7-acetyl-2-benzyl-5-hydroxy-1,3-dioxooctahydro-1*H*-4,7-epoxyisoindol-5-yl)acetamide (2c)**



The title compound was prepared according to the general procedure C. The product was isolated with 79% yield (10.6 mg) as a white solid. No melting point is given due to decomposition observed at 160ºC.

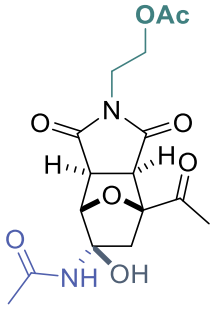
^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ 8.87 (s, 1H), 7.31-7.25 (m, 3H), 7.20 (d, *J* = 7.4 Hz, 2H), 6.03 (s, 1H), 4.91 (s, 1H), 4.54 (s, 2H), 3.42 (d, *J* = 6.92 Hz, 1H), 3.25 (d, *J* = 6.91 Hz, 1H), 2.30 (d, *J* = 13.09 Hz, 1H), 2.07 (s, 3H), 1.91 (d, *J* = 13.04 Hz, 1H), 1.85 (s, 3H) ppm. **^{13}C NMR (100 MHz, $(CD_3)_2SO$)** δ 203.2, 176.5, 175.1, 170.0, 135.6, 128.5, 127.4, 127.0, 90.7, 85.8, 51.0, 47.9, 46.1, 41.6, 27.1, 23.0 ppm. **HRMS (ESI-MS)** *m/z* calculated for $C_{19}H_{21}N_2O_6$[M+H$^+$] 373.13941, found 373.13972.

***N*-(7-acetyl-5-hydroxy-1,3-dioxo-2-phenyloctahydro-1*H*-4,7-epoxyisoindol-5-yl)acetamide (2d)**



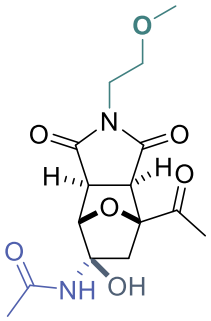
The title compound was prepared according to the general procedure C using a PBS buffer solution 0.1 M at pH 7. The product was isolated in quantitative yield (12.8 mg) as a hygroscopic yellow solid.
^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.97 (s, 1H), 7.52-7.43 (m, 3H), 7.17 (d, *J* = 7.7, 2H), 4.99 (s, 1H), 3.32 (d, *J* = 7.0, 1H), 2.38 (d, *J* = 13.0, 1H), 2.22 (s, 3H), 1.97 (d, *J* = 13.4, 1H), 1.88 (s, 3H) ppm. **^{13}C NMR (100 MHz, $(CD_3)_2SO$)** δ 203.4, 176.0, 174.6, 170.1, 132.1, 129.2, 128.7, 126.8, 90.9, 86.2, 86.0, 51.2, 44.5, 27.3, 23.0 ppm. **HRMS (ESI-MS)** *m/z* calculated for $C_{18}H_{19}N_2O_6$ [M+H$^+$] 359.12376, found 359.12447.

***2-(6-acetamido-4-acetyl-6-hydroxy-1,3-dioxooctahydro-2H-4,7-epoxyisoindol-2-yl)ethyl acetate* (2e)**



The title compound was prepared according to the general procedure C. The was isolated in 98% yield (13.1 mg) as a yellow/brown oil.
^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ 8.89 (s, 1H), 4.87 (s, 1H), 4.10-4.00 (m, 2H), 3.63-3.55 (m, 2H), 3.39 (d, *J* = 6.94 Hz, 1H), 3.16 (d, *J* = 6.93 Hz, 1H), 2.29 (d, *J* = 13.08 Hz, 1H), 2.16 (s, 3H), 1.89 (d, *J* = 13.11 Hz, 1H) ppm. **^{13}C NMR (100 MHz, $(CD_3)_2SO$)** δ 203.3, 176.6, 175.1, 170.4, 170.0, 90.6, 85.9, 85.8, 60.2, 50.9, 47.8, 46.0, 37.5, 27.1, 23.0, 20.6 ppm. **HRMS (ESI-MS)** *m/z* calculated for $C_{16}H_{21}N_2O_8$ [M+H$^+$] 369.12924, found 369.12832.

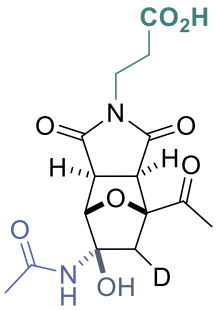
***N*-(7-acetyl-5-hydroxy-2-(2-methoxyethyl)-1,3-dioxooctahydro-1*H*-4,7-epoxyisoindol-5-yl)acetamide (2f)**



The title compound was prepared according to the general procedure C. The product was isolated with yield 84% (10.3 mg) as a yellow oil.

^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.84 (s, 1H), 6.00 (s, 1H), 4.88 (s, 1H), 3.56 – 3.48 (m, 2H), 3.39 – 3.32 (m, 3H), 3.18 (s, 1H), 2.24 (s, 1H), 2.14 (s, 3H) ppm. **^{13}C NMR (100 MHz, $(CD_3)_2SO$)** δ 203.8, 176.6, 175.1, 170.1, 90.5, 85.9, 85.9, 67.9, 57.9, 51.0, 47.9, 46.0, 37.9, 27.1, 23.0 ppm. **HRMS (ESI-MS)** *m/z* calculated for $C_{15}H_{21}N_2O_7$ [M+H$^+$] 341.13433, found 341.13396.

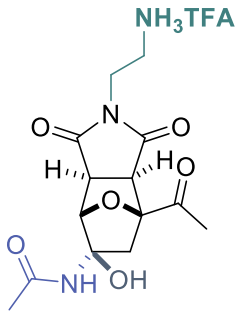
3-(6-acetamido-4-acetyl-6-hydroxy-1,3-dioxooctahydro-2*H*-4,7-epoxyisoindol-2-yl)propanoic acid (2g)



The title compound was prepared according to the general procedure A. The crude mixture was washed with ethyl acetate affording the product with 91% yield (116 mg) as a yellow oil.

^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.86 (s, 1H), 4.86 (s, 1H), 3.53 (t, *J* = 7.27 Hz, 2H), 3.33 (d, *J* = 6.90 Hz, 1H), 3.13 (d, *J* = 6.90 Hz, 1H), 2.39 (t, *J* = 7.33 Hz, 2H), 2.25 (br s, 1H), 2.15 (s, 3H), 1.84 (s, 3H) ppm. **^{13}C NMR (100 MHz, $(CD_3)_2SO$)** δ 203.7, 176.5, 175.1, 172.1, 170.3, 90.6, 86.0, 85.8, 51.0, 47.9, 46.1, 34.6, 31.9, 27.3, 23.0 ppm. **HRMS (ESI-MS)** *m/z* calculated for $C_{15}H_{18}D_1N_2O_8$ [M+H$^+$] 356.11987, found 356.11966.

2-(6-acetamido-4-acetyl-6-hydroxy-1,3-dioxooctahydro-2*H*-4,7-epoxyisoindol-2-yl)ethan-1-aminium 2,2,2-trifluoroacetate (2h)

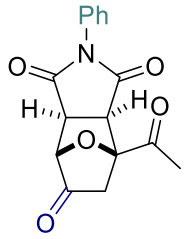


The compound was prepared according to the general procedure C. The product was obtained in quantitative yield with traces of maleimide (16 mg) as yellow/brown oil.

^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ 4.89 (s, 1H), 3.62-3.52 (m, 2H), 3.41 (d, *J* = 6.97 Hz, 1H), 3.14 (d, *J* = 6.97 Hz, 1H), 2.99-2.88 (m, 2H), 2.31-2.29 (m, 1H), 2.16 (s, 3H), 2.04-2.01 (m, 1H), 1.84 (s, 3H) ppm.**^{13}C NMR (75 MHz, $(CD_3)_2CO$)** δ 204.5, 177.6, 176.2, 174.6, 174.1, 173.2, 172.2, 160.8, 160.3, 159.9, 159.5, 135.5, 91.3, 86.6, 86.3, 51.6, 46.9, 37.6, 36.8, 27.9, 23.4, 21.8 ppm. **HRMS (ESI-MS)** *m/z* calculated for $C_{14}H_{20}N_3O_6$ [M+H+] 326.13466, found 326.13504.

Derivatization procedures

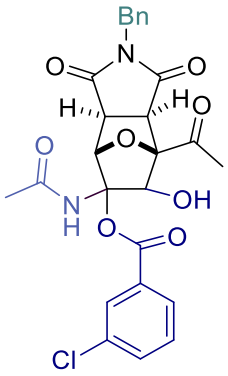
7-acetyl-2-phenyltetrahydro-1H-4,7-epoxyisoindole-1,3,5(2H,4H)-trione (3)



To a solution of **2d** (10 mg, 0.029 mmol) in DMF (590 µL, 0.05 M) was added *p*-toluenosulfonic acid (5 mg, 0.029 mmol). The reaction mixture was stirred for 2h at 80ºC. The crude was diluted with $NaHCO_3$ (sat. aq.) (5 mL) and extracted with ethyl acetate (5 mL × 3). The combined organic layers were dried with anhydrous Mg_2SO_4, filtered, and concentrated under reduced pressure. The product was isolated by flash chromatography using EtOAc:Hex (8:2) affording the product in 91% yield (8 mg) as a yellow oil.

^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 7.53 – 7.42 (m, 3H), 7.30 – 7.27 (m, 2H), 4.88 (s, 1H), 4.02 (d, *J* = 7.16 Hz, 1H), 3.62 (d, *J* = 7.16 Hz, 1H), 2.87-2.82 (m, 1H), 2.68 (d, *J* = 17.76 Hz, 1H), 2.33 (s, 3H) ppm. **^{13}C NMR (100 MHz, $(CD_3)_2CO$)** δ 205.3, 201.8, 174.6, 174.4, 133.3, 129.9, 129.6, 127.7, 92.6, 83.6, 52.3, 46.6, 44.2, 27.2 ppm. **HRMS (ESI-MS)** *m/z* calculated for $C_{16}H_{13}NO_5$ [M+H$^+$] 300.08665, found 300.08631.

5-acetamido-7-acetyl-2-benzyl-6-hydroxy-1,3-dioxooctahydro-1*H*-4,7-epoxyisoindol-5-yl 3-methylbenzoate (4)

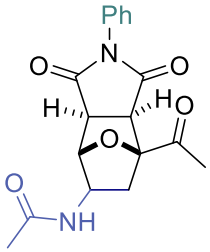


To a solution of *N*-(7-acetyl-2-benzyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-epoxyisoindol-5-yl)acetamide (20 mg, 0.056 mmol) in dichloromethane (565 µL, 0.1 M) was added 3-chloroperbenzoic acid 50-55% (24 mg, 0.068 mmol). The reaction mixture was stirred overnight at 40ºC. The reaction mixture was cooled down to 0ºC to precipitate the m-CPBA/3-chlorobenzoic acid. The crude mixture was washed with a saturated solution of $Na_2S_2O_3$ and extracted with dichloromethane (5x5 mL) and then washed with a saturated solution of $NaHCO_3$. The combined organic layers were dried with anhydrous Mg_2SO_4, filtered, and concentrated under reduced pressure affording 5-acetamido-7-acetyl-

2-benzyl-6-hydroxy-1,3-dioxooctahydro-1*H*-4,7-epoxyisoindol-5-yl 3-methylbenzoate with 58% yield (16.5 mg) as a pale yellow hygroscopic solid.

^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 8.03 (br, 1H), 7.92-7.89 (m, 2H), 7.70-7.68 (m, 1H), 7.55 (t, *J* = 7.78 Hz, 1H), 7.34-7.25 (m, 5H), 5.39 (s, 1H), 5.30 (s, 1H), 4.68-4.59 (m, 2H), 3.77 (d, *J* = 6.94 Hz, 1H), 3.52 (d, *J* = 6.96 Hz, 1H), 2.21 (s, 3H), 2.01 (s, 3H) ppm. **^{13}C NMR (100 MHz, $(CD_3)_2CO$)** δ 200.6, 176.2, 174.6, 171.6, 165.1, 136.5, 134.8, 134.2, 131.7, 131.3, 129.9, 129.2, 128.8, 128.3, 128.2, 93.4, 88.2, 87.1, 82.8, 49.6, 46.5, 42.9, 28.1, 23.1 ppm. **HRMS (ESI-MS)** *m/z* calculated for $C_{26}H_{24}ClN_2O_8$ [M+H$^+$] 527.12157, found 527.12225.

***N*-(7-acetyl-1,3-dioxo-2-phenyloctahydro-1*H*-4,7-epoxyisoindol-5-yl)acetamide (5)**

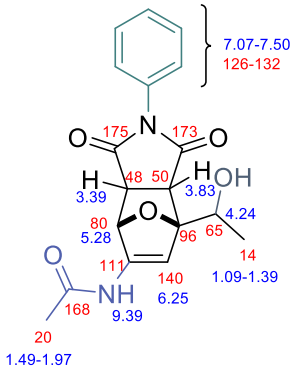


To a solution of *N*-(7-acetyl-1,3-dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-epoxyisoindol-5-yl)acetamide (20 mg, 0.059 mmol) in methanol (0.1 M) was added palladium on carbon (6.25 mg, Pd/C 10% w/w). The reaction was stirred overnight at 8 bar of H_2 after which the crude mixture was filtered through celite. The solvent was evaporated under reduced pressure. The product was isolated by flash chromatography using EtOAc:MeOH (4%) affording *N*-(7-acetyl-1,3-dioxo-2-phenyloctahydro-1*H*-4,7-epoxyisoindol-5-yl)acetamide in 80% yield (16 mg) as an orange hygroscopic solid.

^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 7.51-7.38 (m, 3H), 7.26-7.23 (m, 2H),5.03 (d, *J* = 4.84 Hz, 1H), 4.31-4.22 (m, 1H),3.69 (d, *J* = 7.19 Hz, 1H), 3.63 (d, *J* = 7.19 Hz, 1H), 2.31 (dd, *J* = 13.08 Hz, *J* = 11.44 Hz, 1H), 2.23 (s, 3H), 1.96-1.90 (m, 4H) ppm. **^{13}C NMR (75 MHz, $(CD_3)_2CO$)** δ 204.0, 177.1, 175.1, 170.9, 133.4, 129.8, 129.3, 127.6, 93.4, 82.4, 53.4, 51.4, 45.6, 37.9, 27.4, 22.7 ppm. **HRMS (ESI-MS)** *m/z* calculated for $C_{18}H_{19}N_2O_5$ [M+H$^+$] 343.12885, found 343.12890.

Diels-Alder reaction of the 3A5AF alcohol.

N-(7-(1-hydroxyethyl)-1,3-dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1H-4,7-epoxyisoindol-5-yl)acetamide (8)



To a solution of *N*-(5-(1-hydroxyethyl)furan-3-yl)acetamide (20 mg, 0.12 mmol) in a mixture of water:acetonitrile 8:2 (1.2 mL) was added N-phenyl-maleimide (24 mg, 0.14 mmol, 1.2 eq). The reaction was stirred at room temperature for 5 minutes. 2-mercaptopropanoic acid (0.14 mmol) was added and the mixture was further stirred for 15 minutes. The reaction mixture was extracted with ethyl acetate:$NaHCO_3$ saturated solution (3 x 3 mL). The combined organic layers were dried with anhydrous Mg_2SO_4, filtered, and concentrated under reduced pressure, yielding N-(7-(1-hydroxyethyl)-1,3-dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1H-4,7-epoxyisoindol-5-yl)acetamide as a white powder in 99% yield (40 mg). The product was characterized a mixture of 4 diastereoisomers (*endo*-(R), *endo*-(S), *exo*-(R), *exo*-(S)).

^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 9.39 (s, 1H), 7.50 – 7.36 (m, 3H), 7.28 – 7.24 (m, 1H), 7.09 – 7.07 (m, 1H), 6.29 – 6.20 (s, 1H), 5.30 – 5.26 (s, 1H), 4.31 – 4.17 (m, 1H), 3.90 – 3.76 (m, 1H), 3.43 – 3.36 (m, 1H), 1.97 – 1.95 and 1.37 – 1.51 (m, 3H), 1.09 – 1.36 (3H) ppm.**^{13}C NMR (75 MHz, $(CD_3)_2CO$)** δ 175.1, 175.0, 174.9 (× 2), 174.5 173.9, 173.3, 173.1, 168.1 (× 4), 144.5, 144.3, 141.9, 141.5, 132.8, 132.7 (× 2), 132.6, 128.8, 128.7, 128.7, 128.4, 128.3, 128.2, 127.3, 127.3, 126.8, 111.4, 111.3, 109.8, 109.2, 96.8, 95.9(× 2), 95.8, 80.9, 80.7, 79.0, 78.9, 66.9, 65.9, 65.6, 65.1, 51.2, 50.7, 50.5, 484.9, 48.8, 48.7, 47.7, 22.6, 22.5, 18.7, 18.5, 17.8, 14.7, 13.6, 13.1 ppm. **HRMS (ESI-MS)** *m/z* calculated for $C_{18}H_{18}N_2O_5$ [M+H$^+$] 343.12885, found 343.12855.

Competitive reaction of 3A5AF and acetylfuran (AF)

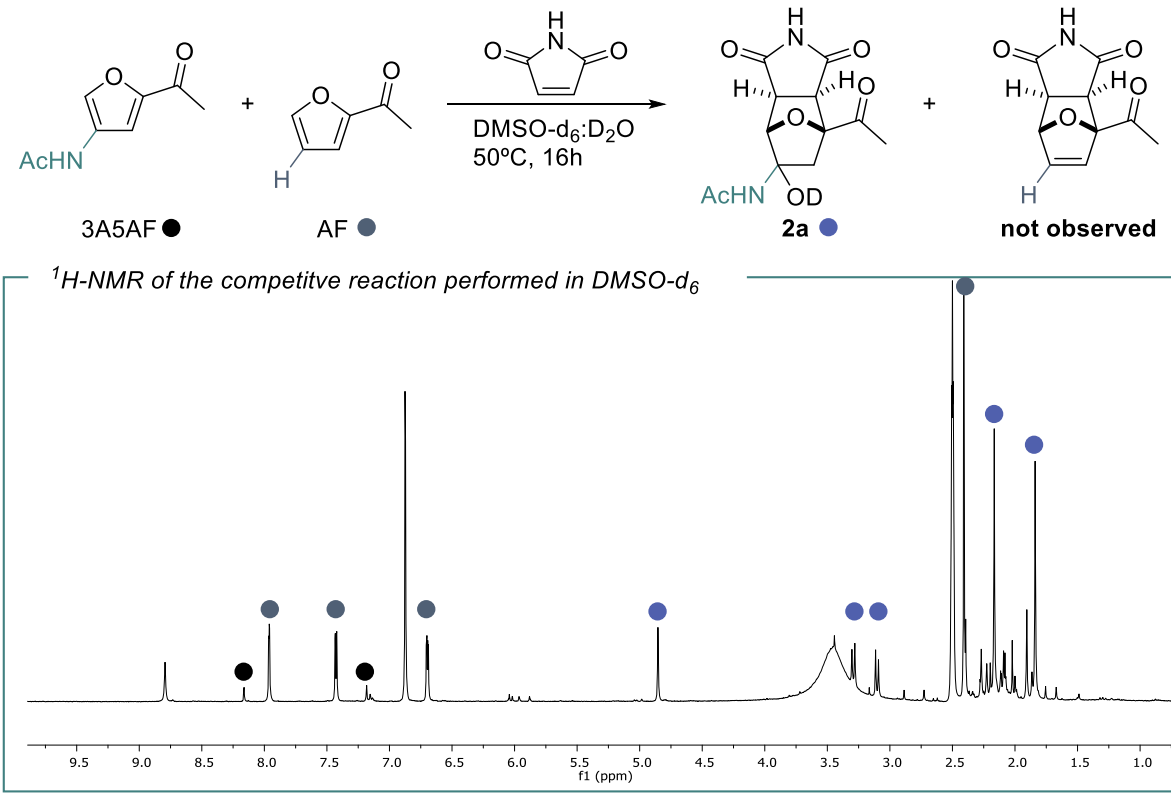


Figure S2. Competitive reaction of 3A5AF and AF. No 7-ONB derived from AF was detected, highlighting the remarkable effect of the 3-amido group.

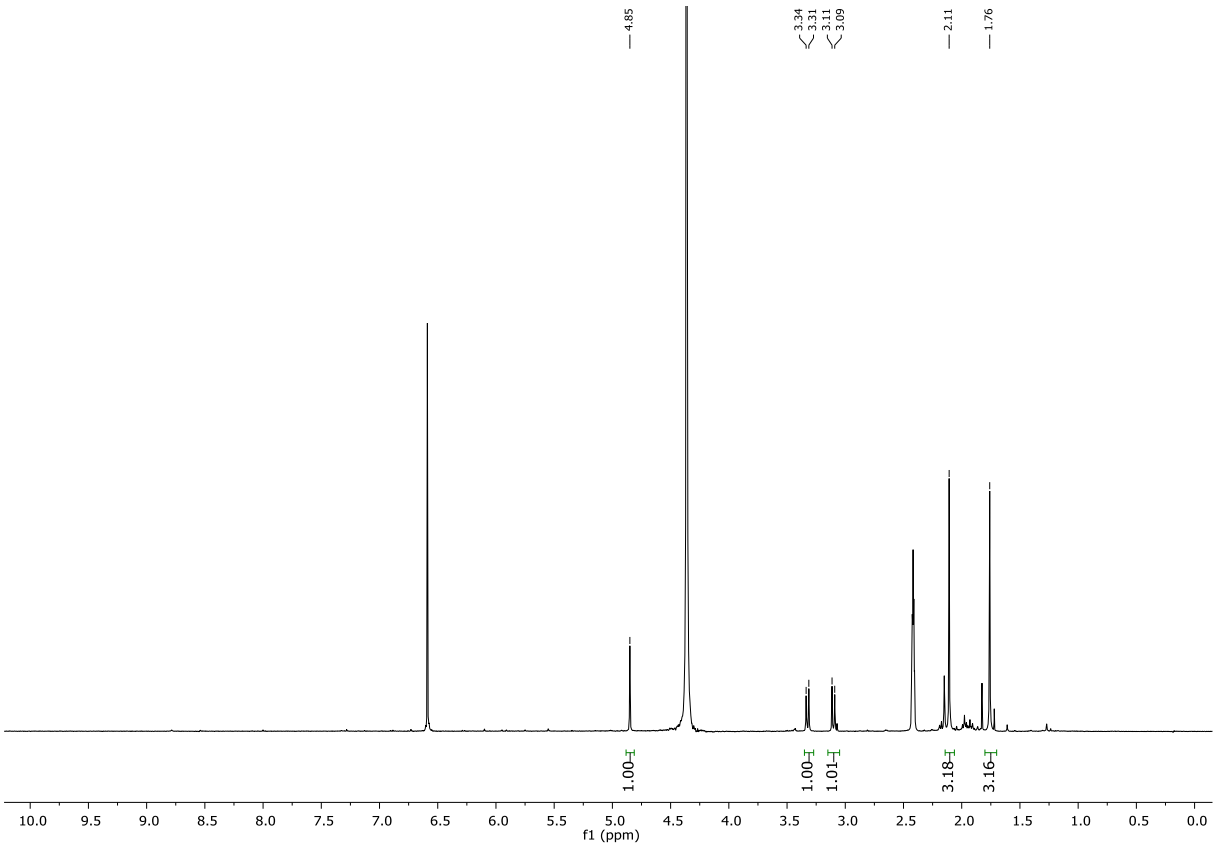


Figure S3. ^{1}H-NMR of the crude reaction mixture for the preparation of **2a**.

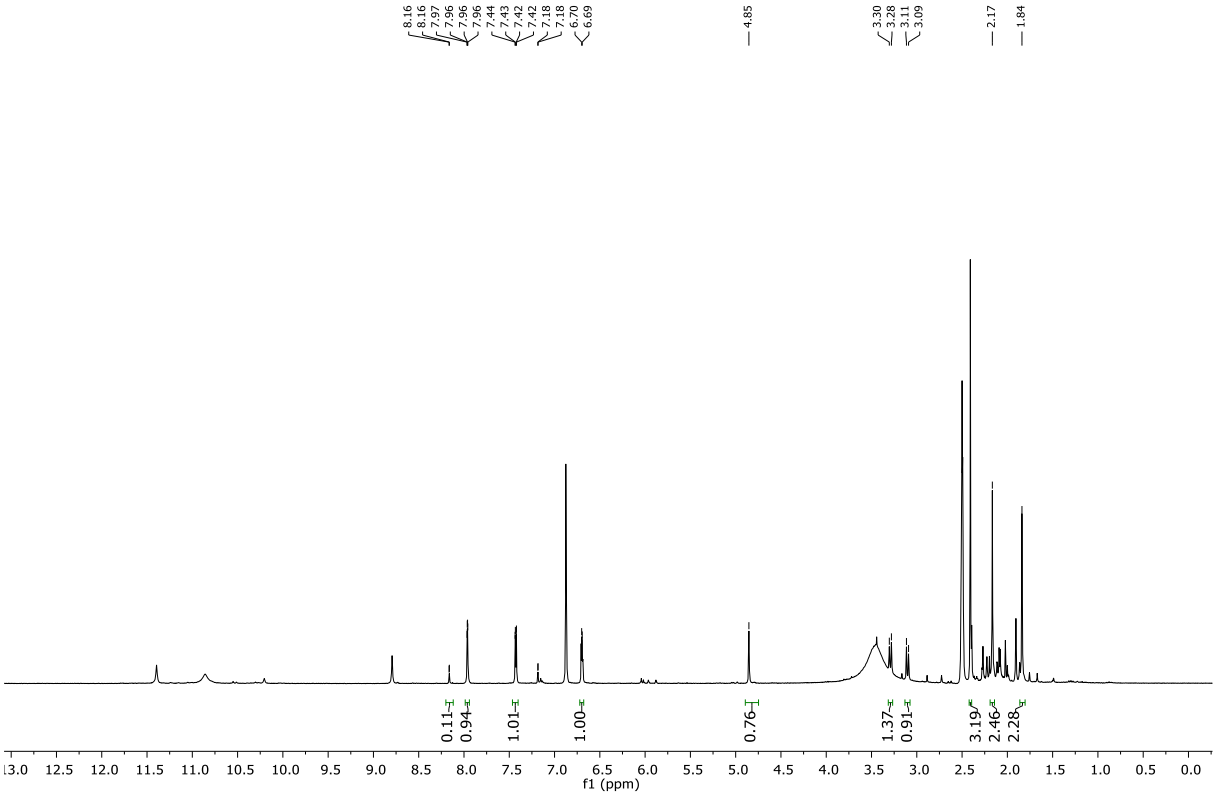


Figure S4. ^{1}H-NMR of the crude reaction mixture for the competitive assay of 3A5AF and AF.

General procedure for the retro-Diels-Alder studies of 7-ONBs

A solution of *N*-(7-acetyl-2-benzyl-5-hydroxy-1,3-dioxooctahydro-1*H*-4,7-epoxyisoindol-5-yl)acetamide in DMSO-d6 (45 mM) was stirred overnight at 80ºC or 150ºC. The conversion to 3A5AF was analyzed at different times (5 min – 20 h) by HPLC.

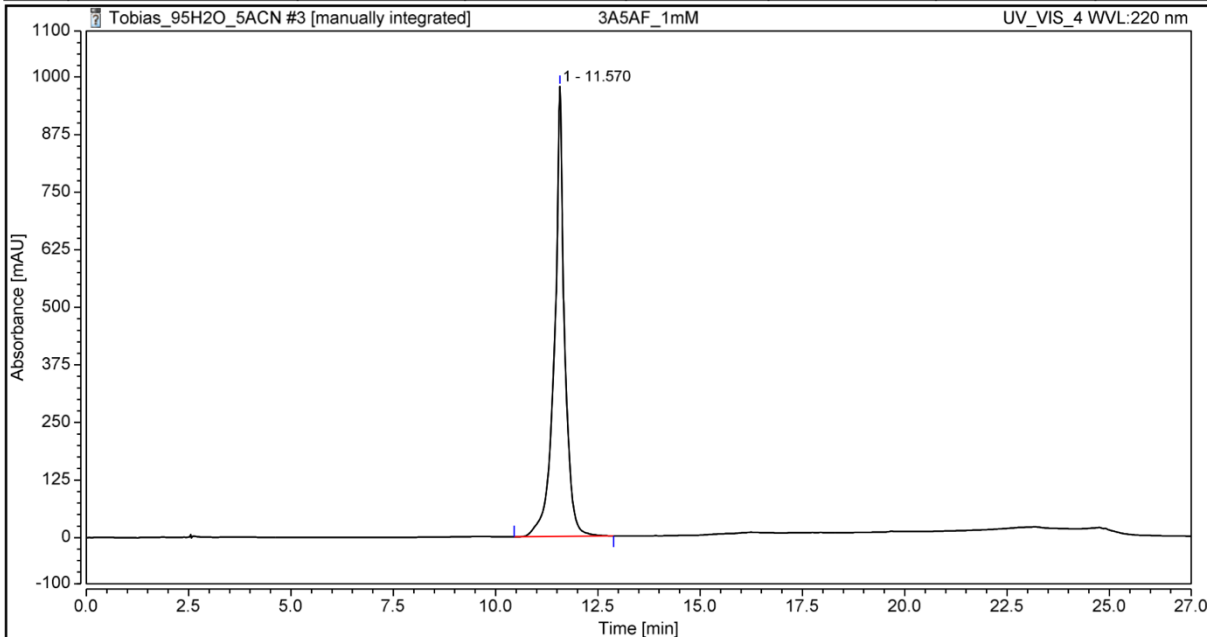
Each HPLC sample was diluted to final concentration of 1mM. The injection volume was 20 µL and the flow rate was set to 1 mL/min.

Examples of HPLC chromatograms

3A5AF

Injection Details			
Injection Name:	**3A5AF_1mM**	*Run Time (min):*	**27.00**
Vial Number:	**GC1**	*Injection Volume:*	**20.00**
Injection Type:	**Unknown**	*Channel:*	**UV_VIS_4**
Calibration Level:		*Wavelength:*	**220**
Instrument Method:	**TCOS_95H2O5ACN**	*Bandwidth:*	**4**
Processing Method:	**JMR_Process**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**09/Apr/21 12:48**	*Sample Weight:*	**1.0000**

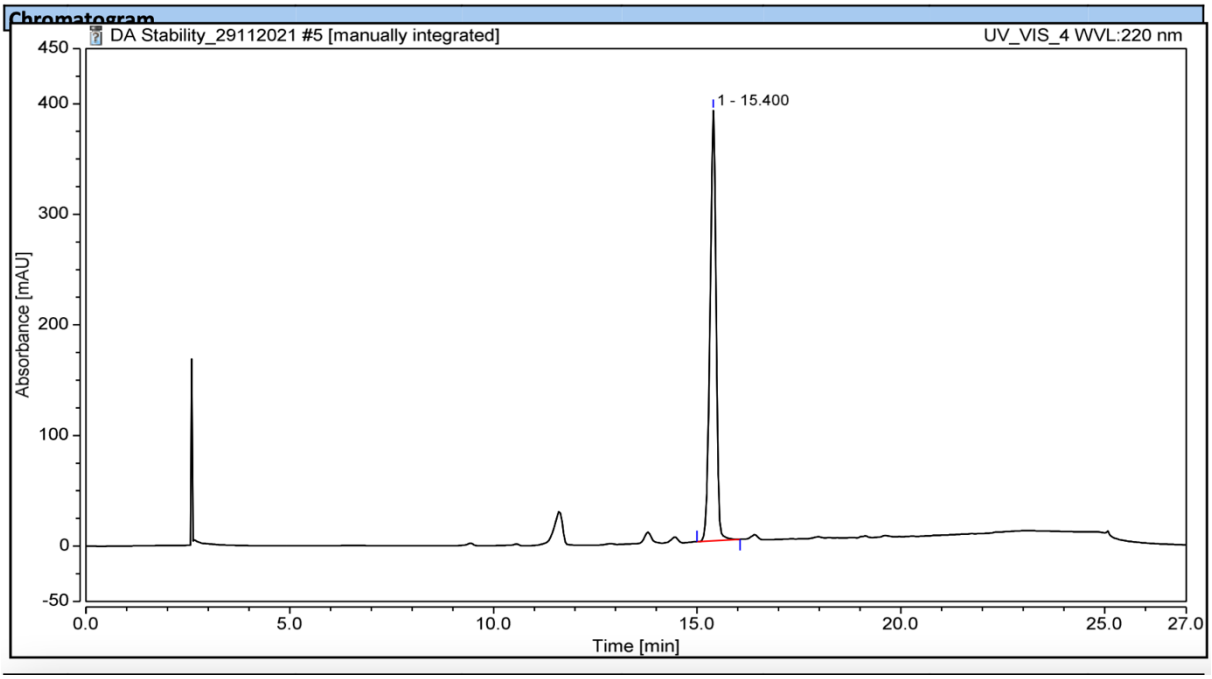
Chromatogram



N-(7-acetyl-2-benzyl-5-hydroxy-1,3-dioxooctahydro-1H-4,7-epoxyisoindol-5-yl)acetamide

Injection Details			
Injection Name:	**JP722_Padrao_1mM_29112021**	*Run Time (min):*	**27.00**
Vial Number:	**RD4**	*Injection Volume:*	**20.00**
Injection Type:	**Unknown**	*Channel:*	**UV_VIS_4**
Calibration Level:		*Wavelength:*	**220**
Instrument Method:	**TCOS_95H2O5ACN**	*Bandwidth:*	**4**
Processing Method:	**FBBA**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**29/Nov/21 17:41**	*Sample Weight:*	**1.0000**

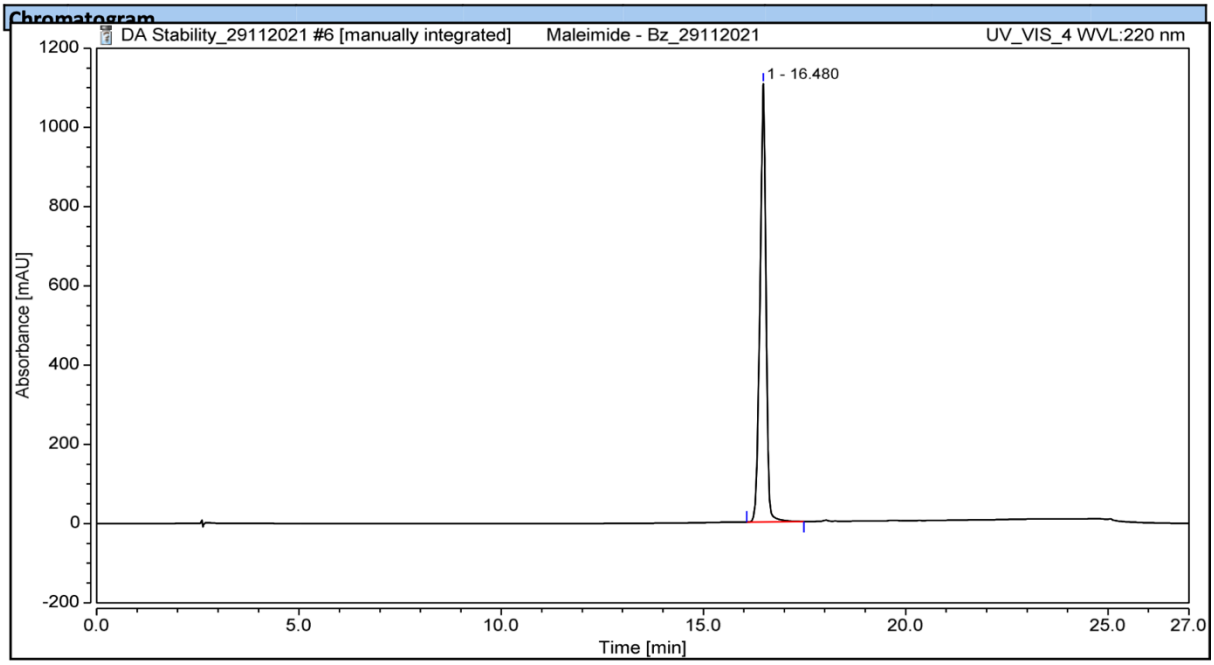
Chromatogram



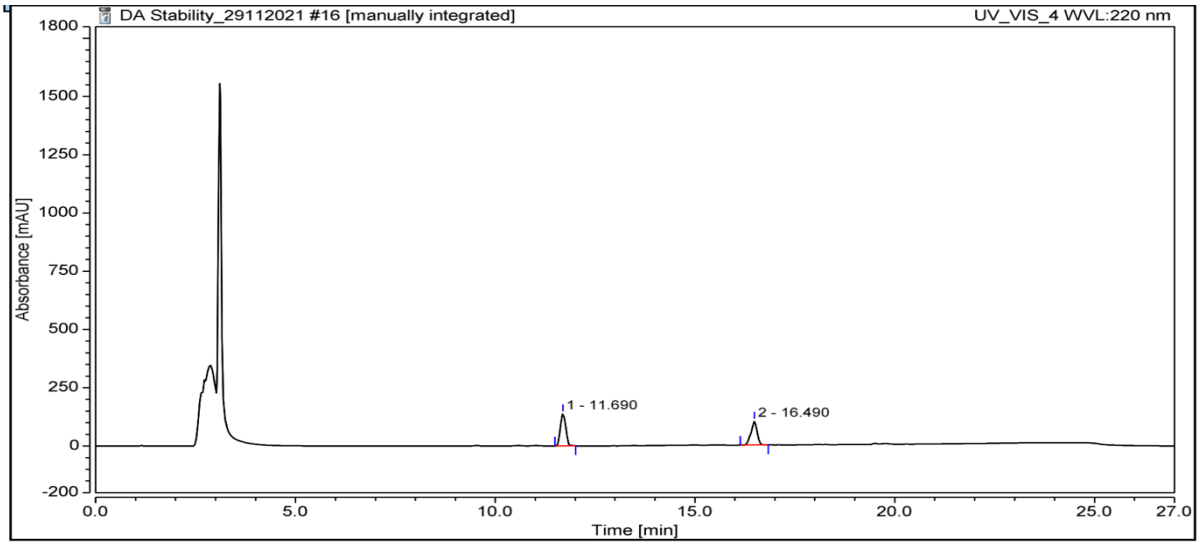
N-benzyl-maleimide

Injection Details			
Injection Name:	**Maleimide - Bz_29112021**	*Run Time (min):*	**27.00**
Vial Number:	**RD5**	*Injection Volume:*	**20.00**
Injection Type:	**Unknown**	*Channel:*	**UV_VIS_4**
Calibration Level:		*Wavelength:*	**220**
Instrument Method:	**TCOS_95H2O5ACN**	*Bandwidth:*	**4**
Processing Method:	**FBBA**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**29/Nov/21 18:09**	*Sample Weight:*	**1.0000**

Chromatogram



150ºC – 5 min

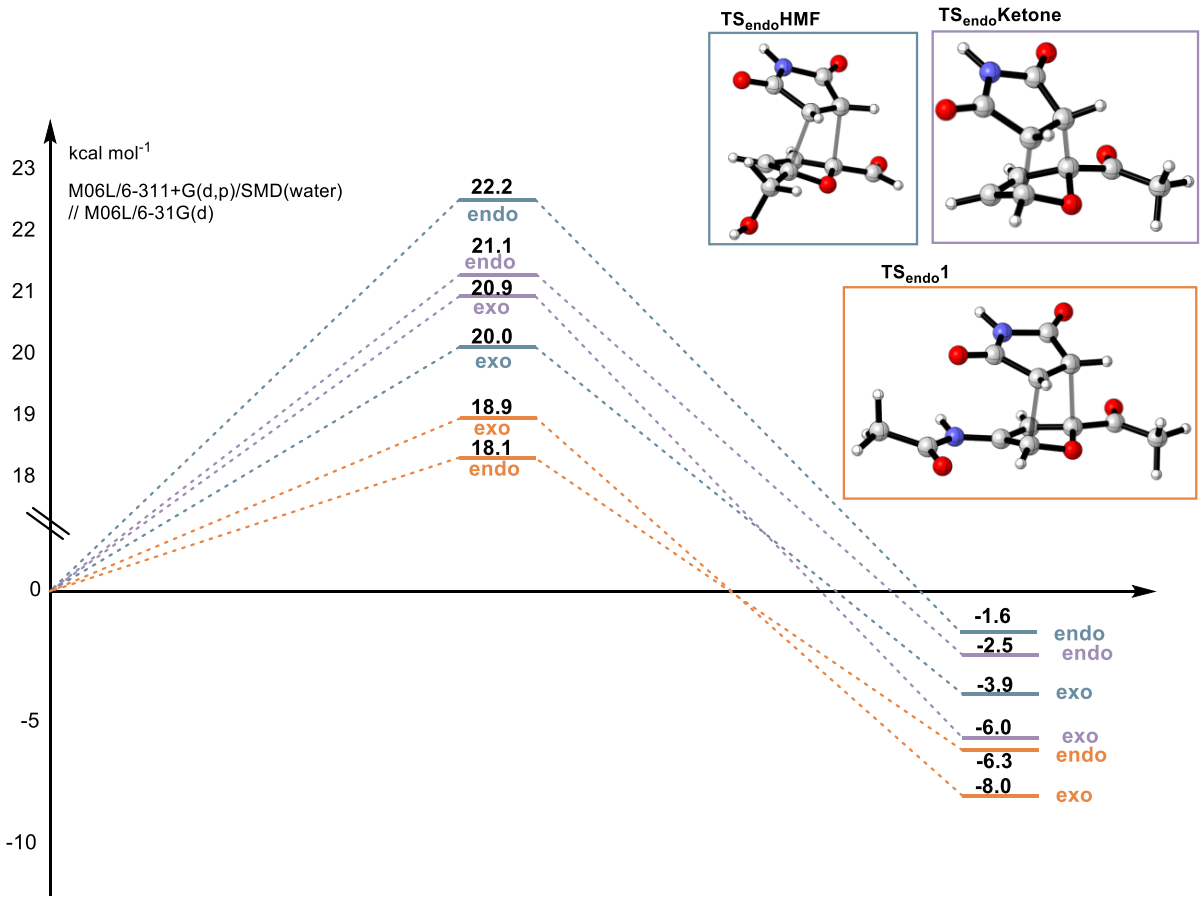

DA Stability_29112021 #16 [manually integrated]
UV_VIS_4 WVL:220 nm
Absorbance [mAU]
1800
1500
1250
1000
750
500
250
0
-200
1 - 11.690
2 - 16.490
0.0
5.0
10.0
15.0
20.0
25.0
27.0
Time [min]

Computational studies

Geometry optimizations and frequency calculations were carried out using Gaussian 09 software, Revision D.01. Vibrational frequencies and intensities were calculated at the M06L/6- 31G(d) level of theory, since such functional/basis-set combination was reported to provide a good energetics accuracy cycloadditions. All the geometry optimizations were carried out at the M06L level of theory with the 6-31G(d) basis set. All of the optimized geometries were verified by frequency computations as minima (zero imaginary frequencies) or transition states (a single imaginary frequency corresponding to the desired reaction coordinate). Single-point energy calculations on the optimized geometries were then evaluated using the same functional (M06L) and the 6-311+G(d,p) basis set . Solvent effects in water were evaluated at the M06L/6-311+G(d,p) level with a self-consistent reaction field (SCRF) using the CPCM model on the gas-phase-optimized structures. Graphical representation of the optimized geometries was generated by using CYLView.

Table S 1- Summary of the calculations performed at M06L/6-311+G(d,p)/SMD(water)// M06L/6-31G(d) level of theory for pre-complexes, TS and products

	M06L/6-311+G(d,p)/SMD(water)// M06L/6-31G(d)	
	ΔG (H)	ΔG_{rel} (kcal/mol)
Pre-complex HMF endo	-817.130151221	0.0
TS HMF endo	-817.094824575	22.2
Product HMF endo	-817.132685973	-1.6
Pre-complex HMF exo	-817.127813393	0.0
TS HMF exo	-817.092804827	22.0
Product HMF exo	-817.134039245	-3.9
Pre-complex ketone endo	-741.917097284	0.0
TS ketone endo	-741.883791001	20.9
Product ketone endo	-741.921057098	-2.5
Pre-complex ketone exo	-741.882658850	0.0
TS ketone exo	-741.916211304	21.1
Product ketone exo	-741.925767059	-6.0
Pre-complex **1** endo	-949.874802400	0.0
TS **1** endo	-949.845996720	18.1
Product **1** endo	-949.884813582	-6.3
Pre-complex VI	-949.876308590	0.0
TS VI	-949.846201949	18.9
Product VI	-949.889029967	-8.0


TS$_{endo}$HMF
TS$_{endo}$Ketone
TS$_{endo}$1
kcal mol^{-1}
M06L/6-311+G(d,p)/SMD(water)
// M06L/6-31G(d)
23
22
21
20
19
18
0
-5
-10
22.2
endo
21.1
endo
20.9
exo
20.0
exo
18.9
exo
18.1
endo
-1.6
endo
-2.5
endo
-3.9
exo
-6.0
exo
-6.3
endo
-8.0
exo

Cartesian coordinates

HMF R endo

SCF energy = -817.271491448 Hartree
Free energy correction= 0.141340227 Hartree

6	-1.301979000	-0.494729000	1.288827000
6	0.059287000	-0.888883000	1.409204000
6	-1.739617000	-0.999105000	0.094919000
6	0.352338000	-1.599425000	0.277825000
8	-0.731098000	-1.677831000	-0.523612000
6	-3.014098000	-0.909720000	-0.609525000
8	-3.955939000	-0.271222000	-0.195297000
1	-3.054273000	-1.467196000	-1.565958000
6	1.606273000	-2.290856000	-0.171861000
8	2.690934000	-1.938388000	0.643278000
1	-1.897073000	0.092671000	1.973818000
1	0.746764000	-0.693929000	2.218625000
1	1.470341000	-3.375593000	-0.092563000
1	1.785051000	-2.061252000	-1.232005000
1	3.032595000	-1.092309000	0.309721000
6	0.484395000	0.989768000	-1.528545000
6	-0.497057000	1.704160000	-0.978428000
6	1.697576000	1.081732000	-0.650341000
6	0.015926000	2.329813000	0.291365000
7	1.360578000	1.948239000	0.371938000
8	2.757227000	0.507235000	-0.784753000
8	-0.573964000	3.008802000	1.087845000
1	0.480213000	0.394918000	-2.432395000
1	-1.516664000	1.854436000	-1.309515000
1	1.953460000	2.145282000	1.166378000

HMF TS endo

SCF energy = -817.239079386 Hartree
Free energy correction= 0.144254811 Hartree
Imaginary Frequency= -508.2679 icm^{-1}

6	-0.459597000	-0.821789000	1.339961000
6	0.820829000	-0.344818000	1.306266000
6	-0.697312000	-1.361194000	0.046801000
6	1.304552000	-0.590576000	-0.016784000
8	0.493199000	-1.533109000	-0.588260000
6	-1.835886000	-2.189533000	-0.400304000
8	-2.859784000	-2.270696000	0.230252000
1	-1.683846000	-2.704884000	-1.368694000
6	2.734114000	-0.541365000	-0.452135000
8	3.477984000	-1.420904000	0.363501000
1	-1.211482000	-0.729261000	2.111570000
1	1.350281000	0.228880000	2.054802000
1	2.783626000	-0.818921000	-1.514641000
1	3.065828000	0.501737000	-0.346207000
1	4.413866000	-1.317063000	0.142377000
6	0.378341000	0.906182000	-1.061954000
6	-0.964304000	0.496949000	-1.061996000
6	0.500736000	2.081267000	-0.141072000
6	-1.718966000	1.383799000	-0.126822000
7	-0.758219000	2.244442000	0.424168000
8	1.487311000	2.732755000	0.112035000
8	-2.893876000	1.388993000	0.139677000
1	1.032147000	0.853368000	-1.925372000
1	-1.483850000	0.042988000	-1.896377000
1	-0.972753000	2.942223000	1.123963000

HMF P endo

SCF energy = -817.281099159 Hartree
Free energy correction= 0.148413186 Hartree

6	-0.436608000	-0.799033000	1.323048000
6	0.827177000	-0.380540000	1.312728000
6	-0.760382000	-1.099316000	-0.128055000
6	1.261852000	-0.416528000	-0.147668000
8	0.494313000	-1.510826000	-0.659672000
6	-1.848357000	-2.098305000	-0.426108000
8	-2.747499000	-2.328989000	0.337482000
1	-1.764595000	-2.592059000	-1.415227000
6	2.733153000	-0.522714000	-0.440871000
8	3.276117000	-1.518875000	0.392288000
1	-1.152828000	-0.863703000	2.131793000
1	1.436010000	-0.007004000	2.126276000
1	2.857381000	-0.758048000	-1.508410000
1	3.174641000	0.467534000	-0.249946000
1	4.224590000	-1.580033000	0.218143000
6	0.533685000	0.768130000	-0.883459000
6	-0.921955000	0.282838000	-0.885074000
6	0.526007000	2.072115000	-0.107649000
6	-1.705170000	1.342651000	-0.128271000
7	-0.791426000	2.325741000	0.250286000
8	1.477666000	2.755993000	0.177494000
8	-2.881816000	1.352664000	0.120672000
1	0.961957000	0.913925000	-1.878440000
1	-1.347473000	0.126545000	-1.879322000
1	-1.056354000	3.117130000	0.825286000

HMF R exo

SCF energy = -817.271629120 Hartree
Free energy correction= 0.143815727 Hartree

6	-1.019611000	-1.936954000	0.914248000
6	0.385647000	-2.087718000	0.778980000
6	-1.429367000	-1.182467000	-0.149705000
6	0.732452000	-1.423588000	-0.367375000
8	-0.357707000	-0.871168000	-0.938737000
6	-2.739208000	-0.659899000	-0.540101000
8	-3.730109000	-0.836539000	0.133905000
1	-2.758279000	-0.085145000	-1.484046000
6	2.046943000	-1.291303000	-1.081133000
8	3.120956000	-1.438484000	-0.192243000
1	-1.666788000	-2.318339000	1.691015000
1	1.072034000	-2.625679000	1.415845000
1	2.133769000	-2.089582000	-1.826712000
1	2.069324000	-0.335464000	-1.623515000
1	3.224279000	-0.589134000	0.269395000
6	-0.734620000	1.429856000	1.183729000
6	0.512790000	1.121108000	1.539480000
6	-0.707822000	2.021568000	-0.199230000
6	1.439422000	1.493341000	0.420451000
7	0.644761000	2.072187000	-0.552837000
8	-1.632485000	2.370307000	-0.885058000
8	2.636639000	1.315125000	0.346973000
1	-1.661999000	1.295121000	1.725166000
1	0.876878000	0.663551000	2.449515000
1	0.979340000	2.361770000	-1.461593000

HMF TS exo

SCF energy = -817.240251646 Hartree

Free energy correction= 0.147446819 Hartree
Imaginary Frequency= -507.6318 icm^{-1}

6	-0.966722000	-2.014179000	0.698288000
6	0.389204000	-2.163501000	0.633906000
6	-1.277894000	-0.933790000	-0.178827000
6	0.855931000	-1.187784000	-0.298716000
8	-0.207554000	-0.733412000	-1.009945000
6	-2.625505000	-0.572394000	-0.683680000
8	-3.618461000	-0.894983000	-0.079590000
1	-2.652094000	0.015816000	-1.617610000
6	2.215623000	-1.123617000	-0.948251000
8	3.219793000	-1.046315000	0.027461000
1	-1.685748000	-2.497067000	1.345082000
1	1.038104000	-2.795152000	1.224979000
1	2.377182000	-2.042176000	-1.522833000
1	2.236007000	-0.280113000	-1.649392000
1	3.305191000	-0.100840000	0.252794000
6	-0.689166000	0.641333000	1.070692000
6	0.702578000	0.441606000	1.097037000
6	-0.956370000	1.808091000	0.160330000
6	1.329690000	1.489781000	0.248252000
7	0.293170000	2.218737000	-0.310342000
8	-2.012927000	2.299038000	-0.150354000
8	2.512571000	1.676902000	0.029672000
1	-1.376441000	0.466302000	1.888290000
1	1.271403000	0.034425000	1.921571000
1	0.422619000	2.944535000	-1.002631000

HMF P exo

SCF energy = -817.284816801 Hartree
Free energy correction= 0.150777556 Hartree

6	0.998653000	-2.010977000	-0.682136000
6	-0.317957000	-2.191175000	-0.614132000
6	1.257699000	-0.713372000	0.065728000
6	-0.858590000	-1.004458000	0.170670000
8	0.227174000	-0.696727000	1.048795000
6	2.633370000	-0.517985000	0.660850000
8	3.619252000	-0.908562000	0.091837000
1	2.668226000	0.001839000	1.635401000
6	-2.178318000	-1.153006000	0.905485000
8	-3.246818000	-1.103393000	-0.008530000
1	1.764301000	-2.576257000	-1.197322000
1	-0.939640000	-2.949370000	-1.074361000
1	-2.206095000	-2.124366000	1.407109000
1	-2.246749000	-0.371597000	1.673411000
1	-3.415969000	-0.160348000	-0.180091000
6	0.752894000	0.449646000	-0.867589000
6	-0.767323000	0.207911000	-0.837599000
6	0.945230000	1.794728000	-0.176539000
6	-1.359093000	1.466980000	-0.232665000
7	-0.318482000	2.312809000	0.093127000
8	1.987855000	2.316851000	0.121867000
8	-2.533141000	1.692344000	-0.031787000
1	1.233706000	0.447588000	-1.846684000
1	-1.247145000	-0.016124000	-1.790520000
1	-0.455219000	3.185119000	0.591268000

Ketone R endo

SCF energy = -742.052661389 Hartree
Free energy correction= 0.135564105 Hartree

6	-0.835826000	0.240501000	1.580238000
6	0.133995000	-0.762061000	1.868246000
6	-1.591504000	-0.249209000	0.552590000
6	-0.103764000	-1.779550000	0.991898000
8	-1.151680000	-1.485530000	0.194773000
6	-2.710686000	0.336848000	-0.207125000
8	-3.103549000	1.453990000	0.058268000
1	0.371097000	-2.734115000	0.820423000
1	-0.962696000	1.207584000	2.045145000
6	1.158370000	-0.301296000	-1.466275000
6	0.752103000	0.933456000	-1.172625000
6	2.359901000	-0.632290000	-0.625572000
6	1.662553000	1.504930000	-0.117712000
7	2.623413000	0.520373000	0.109383000
8	2.973214000	-1.668727000	-0.574664000
8	1.594686000	2.574224000	0.430757000
1	0.743054000	-1.015556000	-2.165353000
1	-0.079342000	1.502872000	-1.568288000
1	3.343615000	0.588678000	0.814310000
1	0.909083000	-0.734348000	2.619744000
6	-3.302877000	-0.506518000	-1.312500000
1	-3.664619000	-1.459657000	-0.915079000
1	-4.121192000	0.043475000	-1.776671000
1	-2.537838000	-0.742070000	-2.059960000

Ketone TS endo

SCF energy = -742.024317008 Hartree
Free energy correction= 0.140526007 Hartree
Imaginary Frequency= -535.7655 icm^{-1}

6	-0.381560000	-0.398986000	1.538153000
6	0.587138000	-1.359242000	1.412416000
6	-1.150213000	-0.467145000	0.346235000
6	0.381906000	-1.950985000	0.132316000
8	-0.883660000	-1.649275000	-0.280248000
6	-2.459752000	0.193395000	0.085511000
8	-2.790288000	1.134320000	0.769646000
1	0.776808000	-2.891168000	-0.229678000
1	-0.510918000	0.355570000	2.301592000
6	1.190650000	-0.510578000	-1.094759000
6	0.227633000	0.507589000	-1.010355000
6	2.412101000	-0.043715000	-0.358468000
6	0.801639000	1.629581000	-0.208909000
7	2.061649000	1.179711000	0.205250000
8	3.473961000	-0.603724000	-0.231242000
8	0.317787000	2.700476000	0.058249000
1	1.318654000	-1.166196000	-1.947571000
1	-0.520874000	0.727953000	-1.761392000
1	2.686344000	1.729324000	0.779712000
1	1.436844000	-1.546261000	2.054266000
6	-3.290951000	-0.364288000	-1.043179000
1	-3.568187000	-1.399887000	-0.821002000
1	-4.185759000	0.246336000	-1.161698000
1	-2.718412000	-0.381785000	-1.975985000

Ketone P endo

SCF energy = -742.066290631 Hartree
Free energy correction= 0.145233533 Hartree

6	-0.357030000	-0.391464000	1.540213000
6	0.585883000	-1.328401000	1.450896000
6	-0.989941000	-0.329832000	0.161956000
6	0.530108000	-1.819710000	0.011679000
8	-0.852789000	-1.669413000	-0.307611000
6	-2.409541000	0.193236000	0.065417000
8	-2.780003000	1.048383000	0.833050000

1	0.879101000	-2.826971000	-0.204736000
1	-0.612232000	0.277839000	2.351519000
6	1.138397000	-0.687293000	-0.893170000
6	0.043579000	0.387115000	-0.801100000
6	2.391156000	-0.032852000	-0.332796000
6	0.721540000	1.617147000	-0.221240000
7	2.054884000	1.275180000	-0.004899000
8	3.473517000	-0.537281000	-0.171655000
8	0.228512000	2.687812000	0.019024000
1	1.317967000	-1.058045000	-1.903629000
1	-0.432920000	0.628960000	-1.753899000
1	2.713119000	1.911817000	0.429070000
1	1.322747000	-1.626832000	2.185756000
6	-3.271479000	-0.403768000	-1.016637000
1	-3.428297000	-1.465727000	-0.802413000
1	-4.225431000	0.121950000	-1.053653000
1	-2.768179000	-0.350321000	-1.987508000

Ketone R exo

SCF energy = -742.053088423 Hartree

Free energy correction= 0.136877119 Hartree

6	-1.086821000	2.003225000	-0.551709000
6	0.063969000	2.644994000	-0.179241000
6	-1.057680000	0.740886000	0.099156000
6	0.762439000	1.729742000	0.658983000
8	-0.118044000	0.782653000	1.084736000
6	-2.200595000	-0.212482000	0.221335000
8	-3.054844000	-0.188499000	-0.635617000
1	1.598390000	1.918081000	1.321286000
1	-1.842383000	2.299148000	-1.265447000
6	0.381796000	-0.186679000	-1.246734000
6	1.530190000	0.503369000	-0.829052000
6	0.414381000	-1.547396000	-0.625552000
6	2.312468000	-0.411708000	0.069929000
7	1.552519000	-1.572131000	0.180603000
8	-0.374260000	-2.455096000	-0.744803000
8	3.363129000	-0.200408000	0.625423000
1	-0.157061000	-0.050975000	-2.174556000
1	2.076021000	1.231563000	-1.414243000
1	1.804308000	-2.353598000	0.770658000
1	0.458374000	3.584293000	-0.541036000
6	-2.225982000	-1.119517000	1.422192000
1	-2.412653000	-0.521301000	2.321055000
1	-3.020044000	-1.854268000	1.291318000
1	-1.265435000	-1.623832000	1.552997000

Ketone TS exo

SCF energy = -742.023957913 Hartree

Free energy correction= 0.141299063 Hartree

Imaginary Frequency= -519.4815 icm^{-1}

6	1.241815000	1.941913000	0.663023000
6	0.126703000	2.662998000	0.153275000
6	1.354821000	0.817613000	-0.104405000
6	-0.358159000	1.920485000	-0.883861000
8	0.383076000	0.807442000	-1.059351000
6	2.338523000	-0.286699000	-0.060899000
8	3.080525000	-0.370316000	0.895793000
1	-1.192393000	2.044493000	-1.558737000
1	1.892223000	2.200317000	1.485738000
6	-0.806616000	-0.628303000	1.484982000
6	-1.817516000	0.202709000	1.230661000
6	-0.731161000	-1.646634000	0.382085000
6	-2.471103000	-0.206163000	-0.060481000
7	-1.791259000	-1.350427000	-0.470812000
8	0.075659000	-2.531014000	0.235877000
8	-3.377471000	0.332556000	-0.645408000
1	-0.103025000	-0.633223000	2.307216000
1	-2.161490000	1.059187000	1.794273000
1	-1.956678000	-1.819827000	-1.349887000
1	-0.268743000	3.605142000	0.503092000
6	2.408410000	-1.213853000	-1.248818000
1	3.007005000	-0.731409000	-2.030360000
1	2.893376000	-2.141193000	-0.944351000
1	1.419924000	-1.424232000	-1.659957000

Ketone P exo

SCF energy = -742.070111942 Hartree

Free energy correction= 0.144344883 Hartree

6	-1.131692000	1.955395000	-0.572075000
6	-0.053914000	2.633320000	-0.185498000
6	-0.925829000	0.538613000	-0.054529000
6	0.816719000	1.618586000	0.539340000
8	-0.150215000	0.745315000	1.124430000
6	-2.191916000	-0.277430000	0.153146000
8	-3.010750000	-0.280281000	-0.736077000
1	1.534078000	1.967618000	1.280643000
1	-1.971661000	2.254865000	-1.184995000
6	0.163195000	-0.112374000	-0.987374000
6	1.412942000	0.688840000	-0.572652000
6	0.453650000	-1.542776000	-0.546642000
6	2.359811000	-0.329832000	0.043906000
7	1.734189000	-1.568203000	-0.016037000
8	-0.294543000	-2.486628000	-0.607954000
8	3.442413000	-0.115895000	0.525756000
1	-0.119932000	-0.084723000	-2.040049000
1	1.917594000	1.245206000	-1.363292000
1	2.134318000	-2.402272000	0.397784000
1	0.227045000	3.654522000	-0.409159000
6	-2.344976000	-1.006256000	1.458091000
1	-2.217824000	-0.307865000	2.290607000
1	-3.325334000	-1.481257000	1.493290000
1	-1.560789000	-1.765275000	1.543919000

5AF Ketone R endo

SCF energy = -950.061971248 Hartree

Free energy correction= 0.187168848 Hartree

6	0.235204000	-1.049371000	-1.123927000
6	-0.934529000	-1.277011000	-0.344048000
6	1.292739000	-1.280234000	-0.294093000
6	-0.500041000	-1.659967000	0.898955000
8	0.850196000	-1.657617000	0.933373000
6	2.739940000	-1.126599000	-0.546556000
8	3.111654000	-0.856179000	-1.669974000
1	-1.019137000	-1.916714000	1.805680000
1	0.303594000	-0.725614000	-2.153169000
6	-0.521721000	1.395759000	1.192332000
6	0.768539000	1.418334000	1.527791000
6	-0.650184000	1.833701000	-0.241888000
6	1.569994000	1.883628000	0.348394000
7	0.632822000	2.181405000	-0.644500000
8	-1.646602000	1.861106000	-0.927457000
8	2.767153000	1.979017000	0.246818000
1	-1.386328000	1.087764000	1.767431000
1	1.238933000	1.143437000	2.462738000

1	0.886809000	2.400030000	-1.598043000
7	-2.244740000	-1.050095000	-0.772453000
1	-2.340006000	-0.744451000	-1.731978000
6	-3.222808000	-0.629473000	0.104763000
8	-3.088570000	-0.735152000	1.310164000
6	-4.432756000	-0.012778000	-0.552226000
1	-5.268314000	-0.038003000	0.146281000
1	-4.190674000	1.027995000	-0.792093000
1	-4.704221000	-0.530663000	-1.475857000
6	3.673400000	-1.256224000	0.629568000
1	3.367171000	-2.058137000	1.305376000
1	4.685965000	-1.422903000	0.261672000
1	3.652321000	-0.309900000	1.182848000

5AF Ketone TS endo

SCF energy = -950.037009033 Hartree
Free energy correction= 0.191012313 Hartree
Imaginary Frequency= -505.4221 icm^{-1}

6	-0.547120000	-0.682940000	1.201408000
6	0.646871000	-0.952218000	0.570794000
6	-1.540214000	-0.833021000	0.209070000
6	0.313495000	-1.248144000	-0.796810000
8	-1.020081000	-1.526572000	-0.841558000
6	-3.013170000	-0.842528000	0.419493000
8	-3.462010000	-0.373462000	1.440494000
1	0.933484000	-1.763721000	-1.512648000
1	-0.725751000	-0.294176000	2.194380000
6	0.057492000	0.655836000	-1.487397000
6	-1.211620000	0.997010000	-0.984549000
6	1.066861000	1.500674000	-0.757276000
6	-1.042569000	2.027271000	0.069399000
7	0.350136000	2.171511000	0.225410000
8	2.262291000	1.577911000	-0.928631000
8	-1.871576000	2.635199000	0.698536000
1	0.260440000	0.402532000	-2.521172000
1	-2.142207000	0.945085000	-1.534804000
1	0.761397000	2.870924000	0.829034000
7	1.919996000	-0.732850000	1.065095000
1	1.989046000	-0.161515000	1.896547000
6	3.077080000	-0.958261000	0.329905000
8	3.059577000	-1.576903000	-0.711051000
6	4.315362000	-0.326968000	0.914397000
1	5.192106000	-0.834995000	0.514596000
1	4.332625000	0.720048000	0.593580000
1	4.328243000	-0.365236000	2.007020000
6	-3.855888000	-1.446455000	-0.676013000
1	-3.670420000	-2.525002000	-0.723865000
1	-4.907883000	-1.261399000	-0.460138000
1	-3.587093000	-1.034089000	-1.652912000

5AF Ketone P endo

SCF energy = -950.079060610 Hartree
Free energy correction= 0.194247028 Hartree

6	-0.496769000	-0.657167000	1.158689000
6	0.672482000	-0.874852000	0.541110000
6	-1.515270000	-0.595028000	0.043420000
6	0.342102000	-0.951183000	-0.951612000
8	-0.975754000	-1.481500000	-0.933648000
6	-2.956444000	-0.904491000	0.398083000
8	-3.376864000	-0.606832000	1.490295000
1	1.006032000	-1.520258000	-1.590309000
1	-0.713304000	-0.422614000	2.192392000
6	0.051778000	0.531361000	-1.389016000
6	-1.317443000	0.776999000	-0.731787000
6	0.982153000	1.566766000	-0.769245000
6	-1.135868000	1.989250000	0.161875000
7	0.206519000	2.357717000	0.068912000
8	2.172501000	1.685477000	-0.926084000
8	-1.960693000	2.542991000	0.840077000
1	0.051084000	0.619545000	-2.476725000
1	-2.136662000	0.938785000	-1.436216000
1	0.597526000	3.118698000	0.611748000
7	1.955894000	-0.777727000	1.051927000
1	2.043882000	-0.392839000	1.982891000
6	3.121617000	-0.966189000	0.321419000
8	3.126714000	-1.448851000	-0.788792000
6	4.366871000	-0.464935000	1.014047000
1	5.231858000	-0.975613000	0.592610000
1	4.455910000	0.607138000	0.809311000
1	4.337076000	-0.615507000	2.096533000
6	-3.780639000	-1.570677000	-0.673093000
1	-3.378510000	-2.571554000	-0.860039000
1	-4.819177000	-1.633057000	-0.348562000
1	-3.707257000	-1.022077000	-1.617644000

5AF Ketone R exo

SCF energy = -950.062245173 Hartree
Free energy correction= 0.185936583 Hartree

6	0.387540000	-1.840883000	0.340170000
6	1.445211000	-1.018224000	-0.136023000
6	-0.732835000	-1.437845000	-0.327709000
6	0.894132000	-0.169580000	-1.063934000
8	-0.428700000	-0.433883000	-1.185322000
6	-2.117323000	-1.953396000	-0.259742000
8	-2.377066000	-2.828603000	0.538916000
1	1.295345000	0.636361000	-1.654871000
1	0.425894000	-2.628739000	1.079296000
6	-0.933686000	1.009506000	1.621100000
6	-0.043472000	1.771403000	0.984076000
6	-2.256711000	1.114318000	0.915391000
6	-0.720939000	2.429933000	-0.188243000
7	-2.050897000	2.017402000	-0.123283000
8	-3.286634000	0.536142000	1.161702000
8	-0.240577000	3.152603000	-1.022769000
1	-0.808354000	0.380236000	2.491970000
1	1.007641000	1.931988000	1.186581000
1	-2.749635000	2.257587000	-0.812213000
7	2.766439000	-1.079514000	0.312783000
1	3.018279000	-1.858887000	0.902720000
6	3.713525000	-0.133478000	0.009295000
8	3.454078000	0.833067000	-0.681411000
6	5.094327000	-0.403683000	0.565814000
1	5.693624000	-0.908567000	-0.197775000
1	5.567880000	0.552374000	0.789871000
1	5.078853000	-1.025315000	1.464458000
6	-3.127235000	-1.394225000	-1.231990000
1	-3.088357000	-1.984845000	-2.154393000
1	-4.120675000	-1.480110000	-0.791965000
1	-2.913315000	-0.354981000	-1.488337000

5AF Ketone TS exo

SCF energy = -950.036225936 Hartree
Free energy correction= 0.190023987 Hartree
Imaginary Frequency= -492.7112 icm^{-1}

6	-0.323431000	-1.814317000	-0.262049000
6	-1.359582000	-0.982808000	0.095925000
6	0.839592000	-1.218922000	0.267990000
6	-0.766458000	0.106933000	0.818792000
8	0.484783000	-0.291054000	1.190632000
6	2.210396000	-1.801059000	0.291137000
8	2.460995000	-2.698704000	-0.482708000
1	-1.260447000	0.815764000	1.466674000
1	-0.326970000	-2.672892000	-0.919067000
6	0.957690000	0.437516000	-1.272071000
6	-0.111489000	1.191995000	-0.768004000
6	2.229094000	1.061967000	-0.820360000
6	0.481363000	2.342095000	0.010104000
7	1.857276000	2.143101000	-0.014517000
8	3.368761000	0.728633000	-1.051468000
8	-0.094125000	3.240460000	0.572077000
1	0.959665000	-0.194152000	-2.149060000
1	-1.061353000	1.355808000	-1.264578000
1	2.518133000	2.739534000	0.464427000
7	-2.671782000	-1.064365000	-0.346699000
1	-2.895310000	-1.826789000	-0.971160000
6	-3.684729000	-0.207532000	0.041264000
8	-3.479510000	0.735459000	0.775148000
6	-5.050601000	-0.559775000	-0.503551000
1	-5.534706000	-1.271824000	0.172098000
1	-5.652836000	0.347590000	-0.536697000
1	-5.001670000	-1.006354000	-1.499930000
6	3.196598000	-1.249364000	1.287370000
1	3.156794000	-1.867893000	2.191331000
1	4.197055000	-1.308323000	0.858007000
1	2.965302000	-0.220363000	1.567740000
1	2.401460000	-1.691945000	2.286538000
1	3.838199000	-2.310959000	1.396927000
1	3.416552000	-0.573943000	1.373266000

5AF Ketone P exo

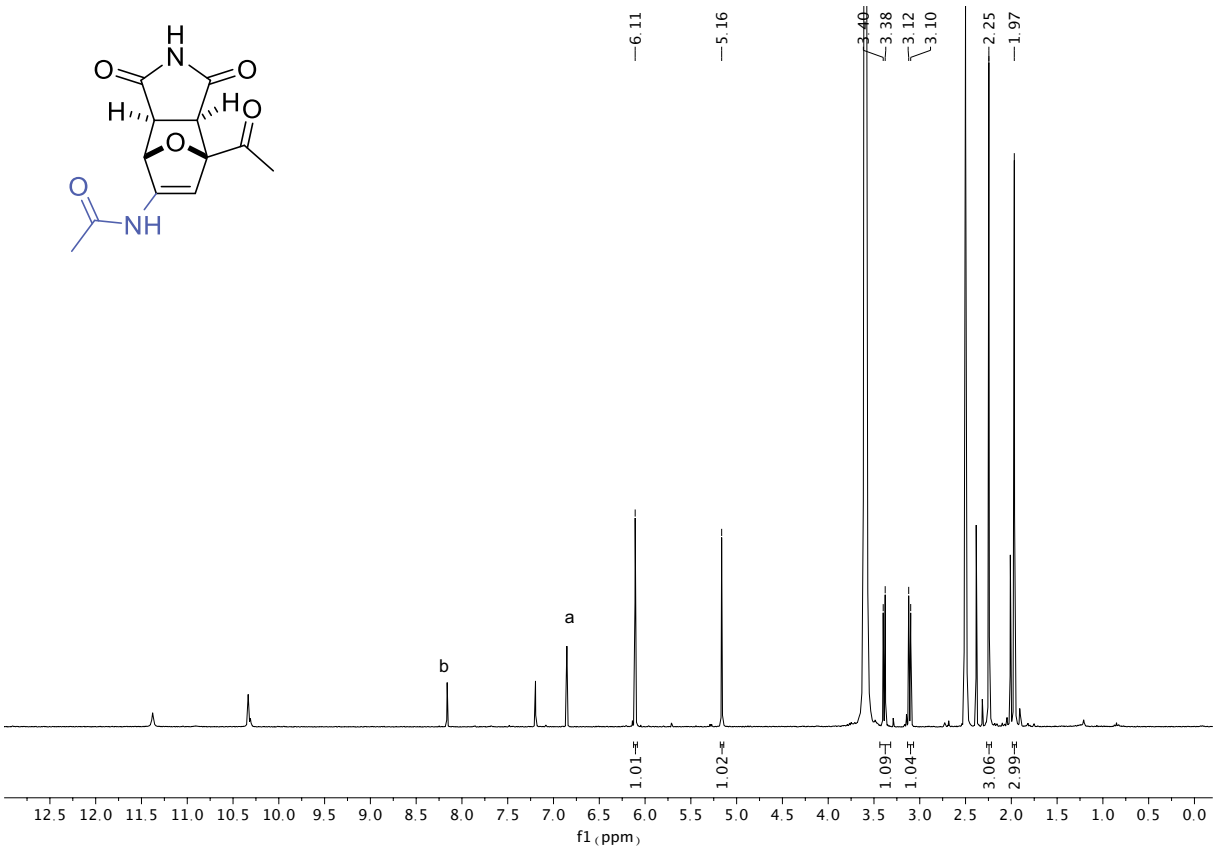
SCF energy = -950.082330551 Hartree

Free energy correction= 0.193300584 Hartree

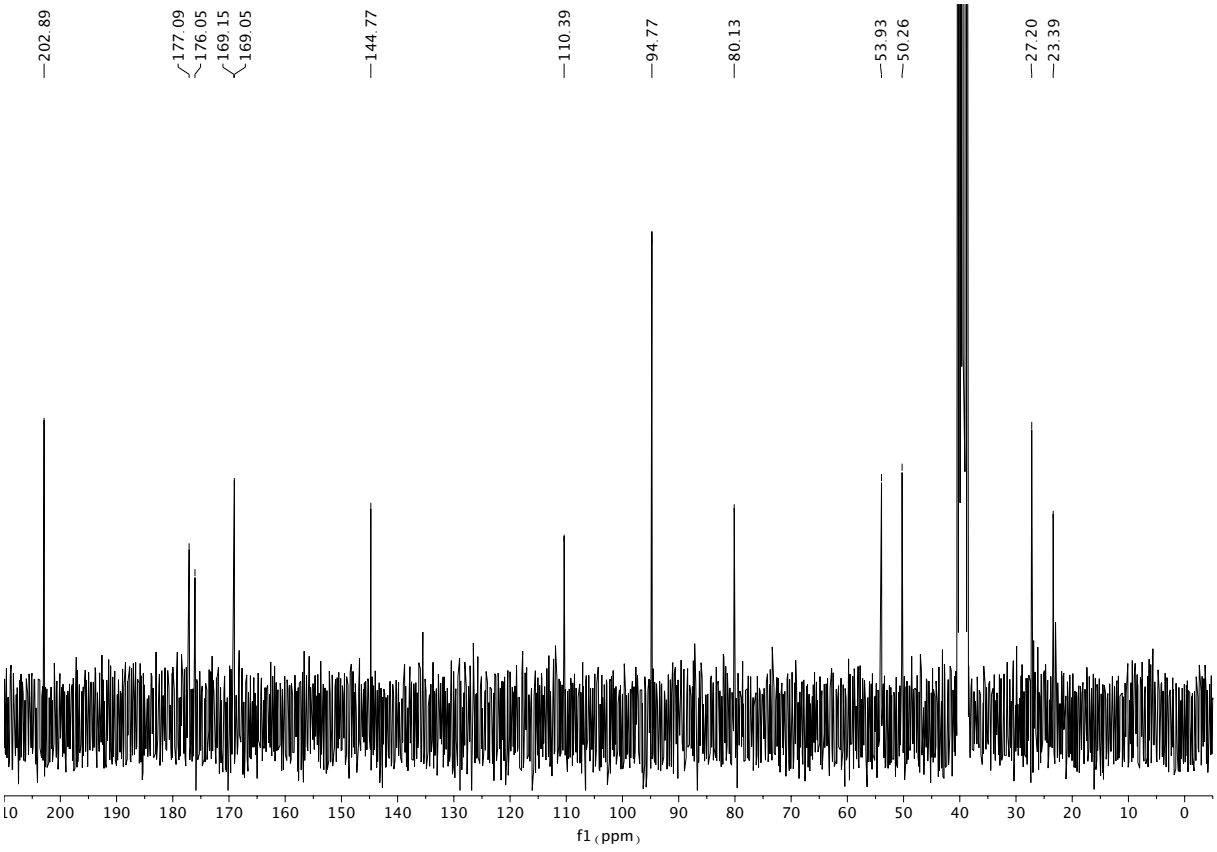
6	-0.329080000	-1.751279000	-0.389584000
6	-1.344924000	-0.993683000	0.032105000
6	0.916484000	-0.979697000	0.009483000
6	-0.708454000	0.237915000	0.679391000
8	0.505306000	-0.307939000	1.198751000
6	2.174782000	-1.819403000	0.164490000
8	2.419063000	-2.634819000	-0.694321000
1	-1.270146000	0.776140000	1.436720000
1	-0.318891000	-2.667691000	-0.963926000
6	1.024459000	0.244642000	-0.977849000
6	-0.161721000	1.106883000	-0.494400000
6	2.265102000	1.075648000	-0.677204000
6	0.468756000	2.382885000	0.048588000
7	1.843824000	2.278579000	-0.137337000
8	3.415142000	0.747058000	-0.839414000
8	-0.090881000	3.311774000	0.569079000
1	1.018578000	-0.069349000	-2.021901000
1	-0.933743000	1.347675000	-1.225593000
1	2.491546000	2.980568000	0.200859000
7	-2.712592000	-1.197319000	-0.110909000
1	-3.010859000	-2.118529000	-0.402564000
6	-3.653838000	-0.188964000	-0.041882000
8	-3.342023000	0.968967000	0.145842000
6	-5.083993000	-0.657292000	-0.193685000
1	-5.402770000	-1.174086000	0.716879000
1	-5.718031000	0.214376000	-0.348719000
1	-5.195878000	-1.347423000	-1.034912000
6	3.017847000	-1.593317000	1.387989000

Copies of NMR spectra:

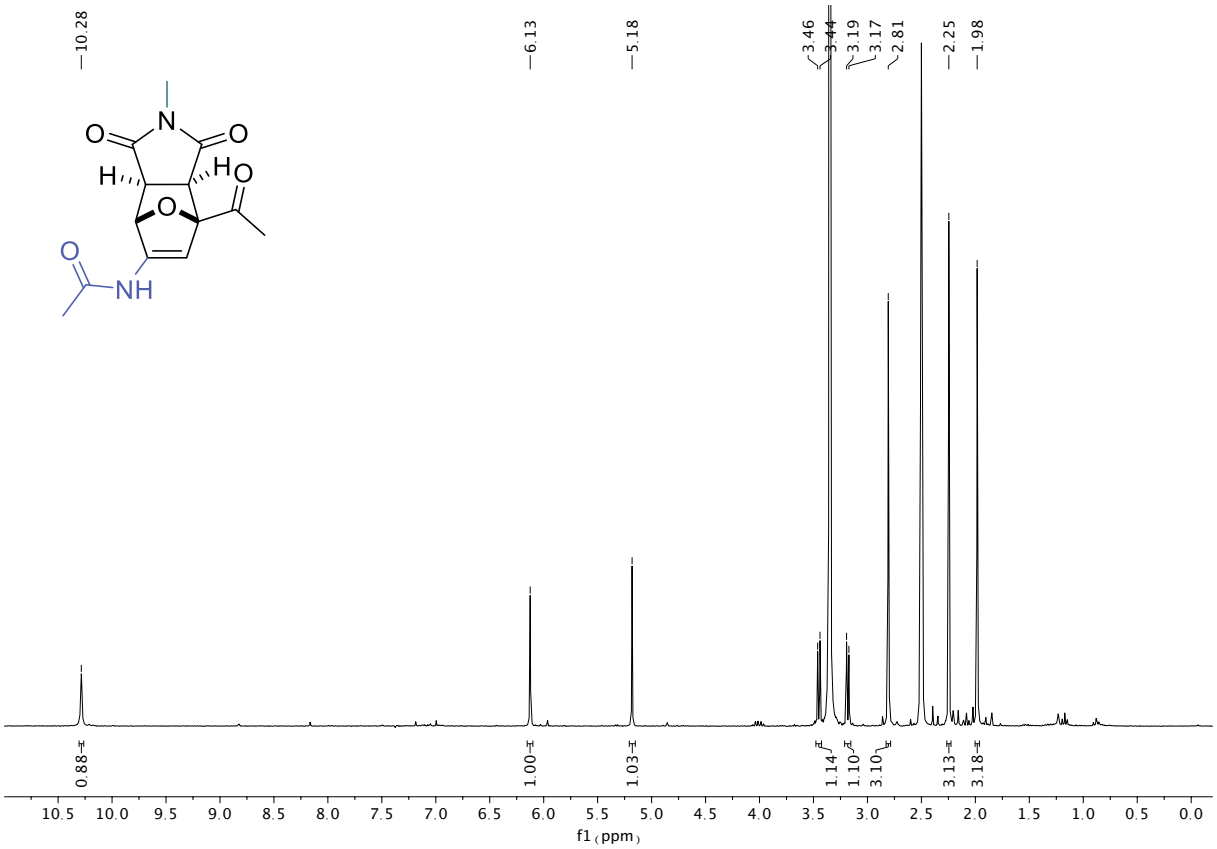
^{1}H and ^{13}C NMR of product 1a

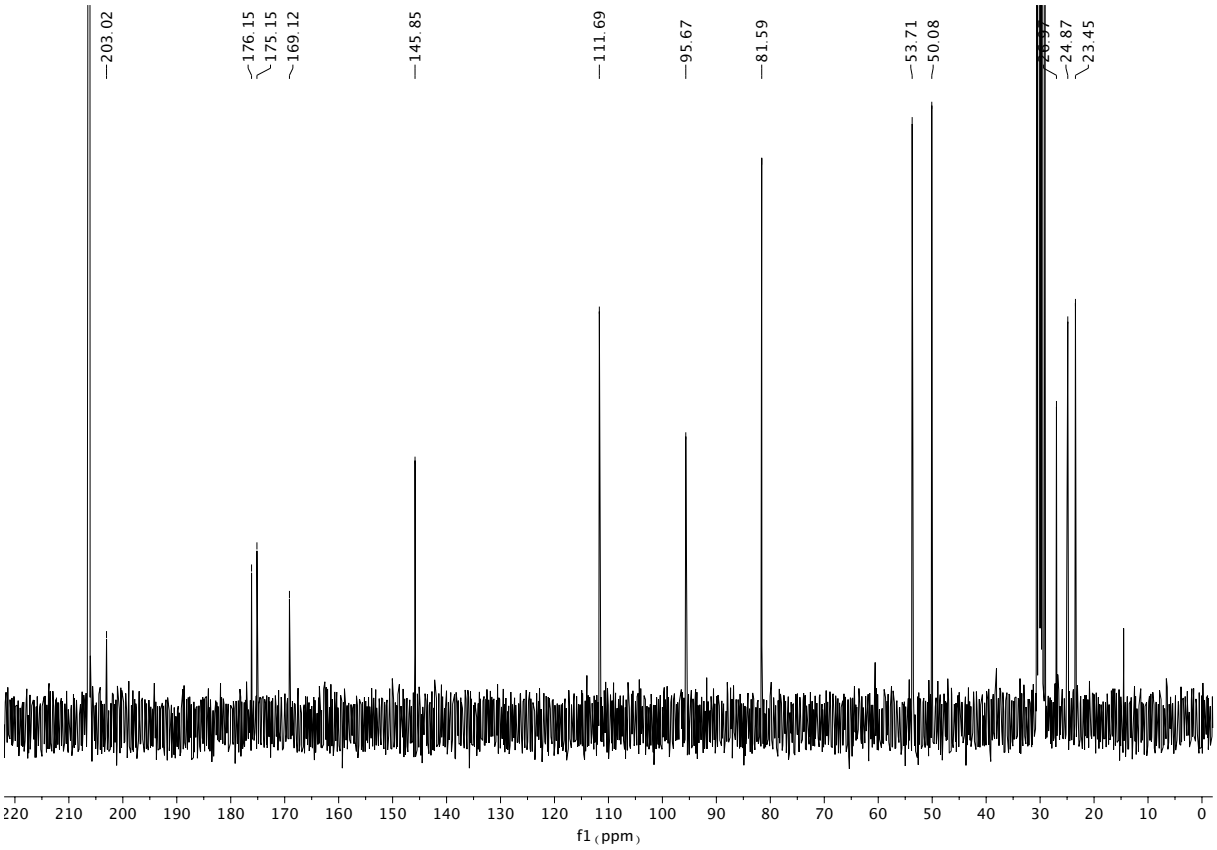


[a] corresponds to maleimide whereas [b] corresponds to 3A5AF.

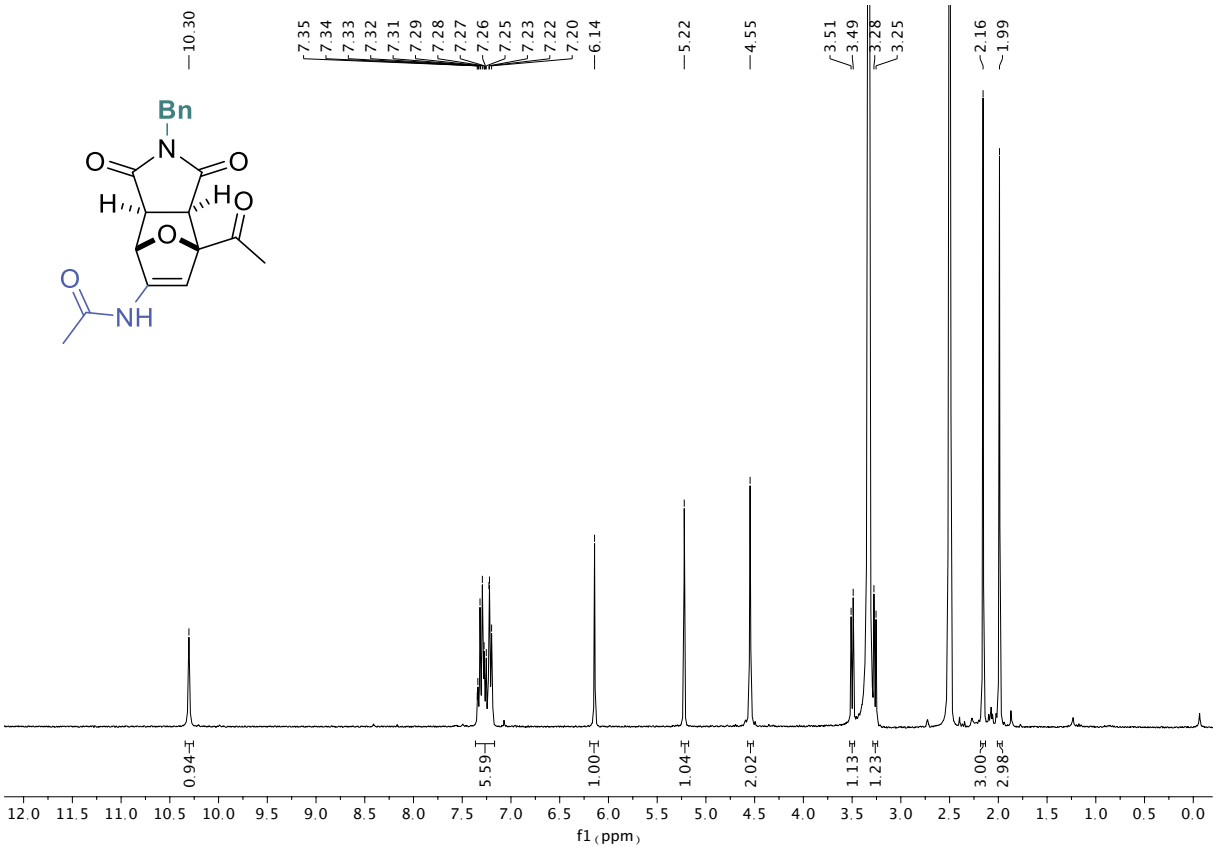


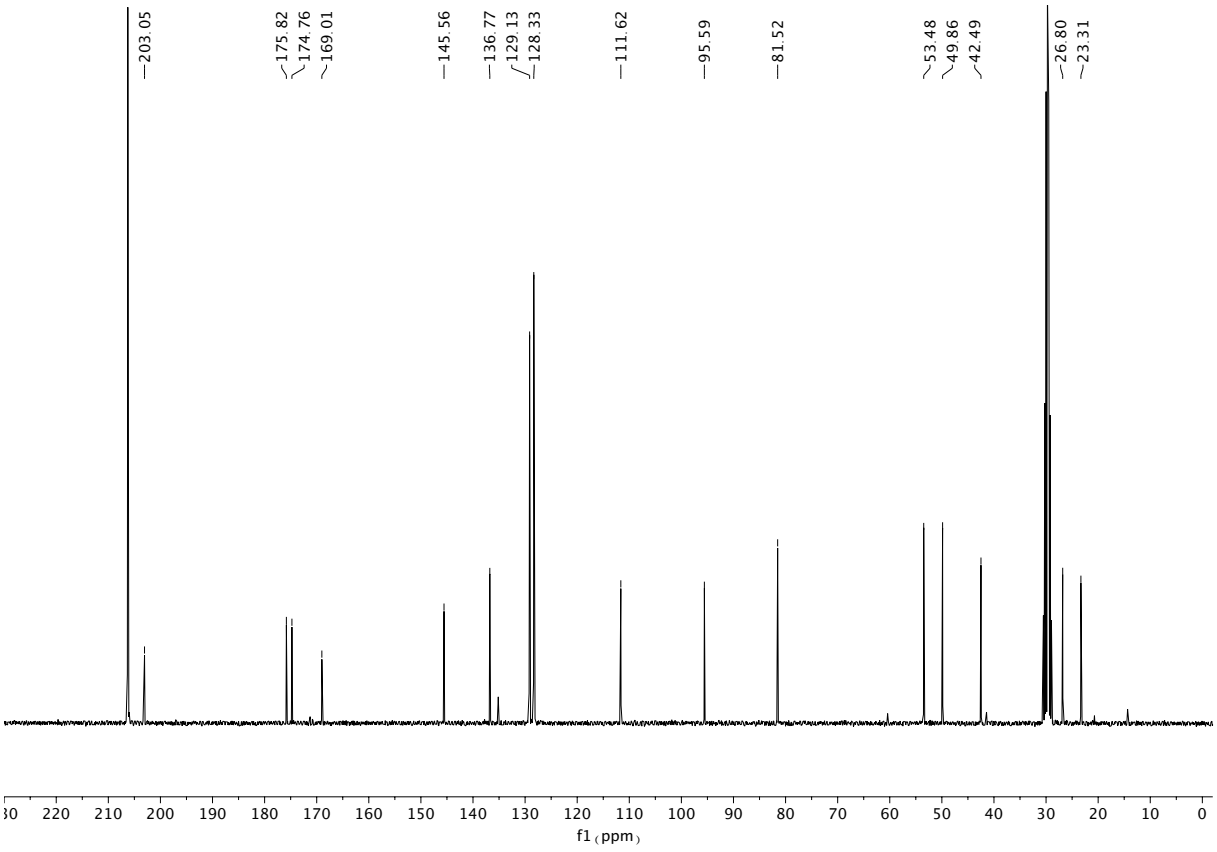
^{1}H and ^{13}C NMR of product 1b



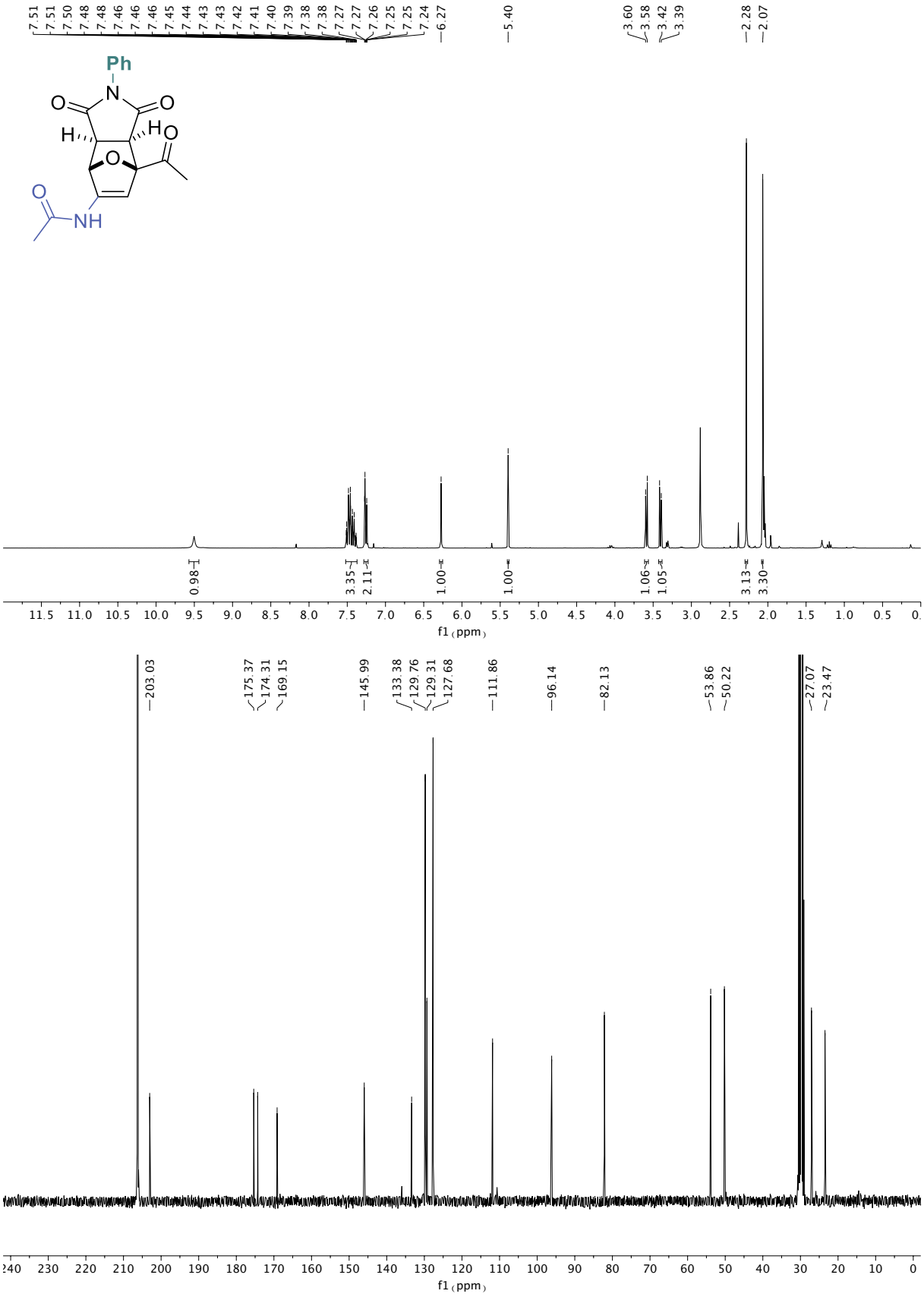


^{1}H and ^{13}C NMR of product 1c

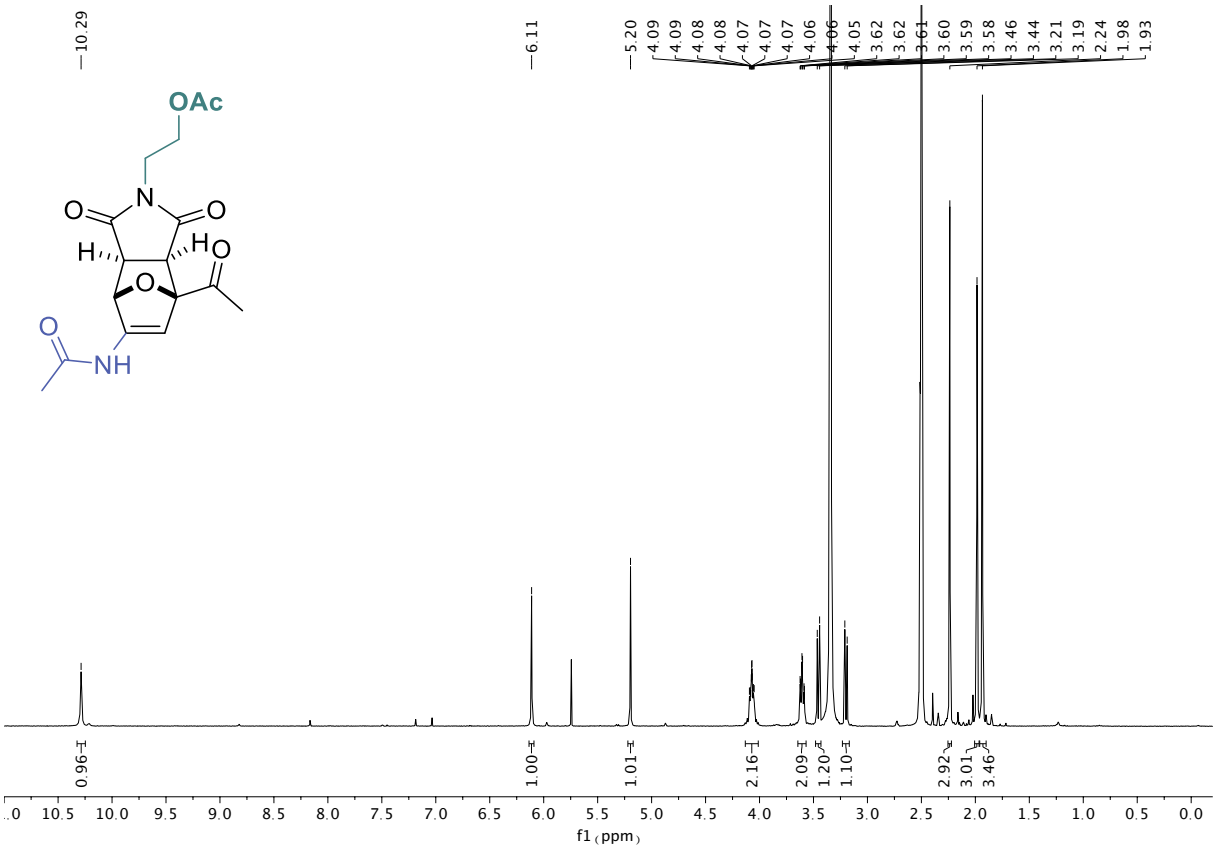


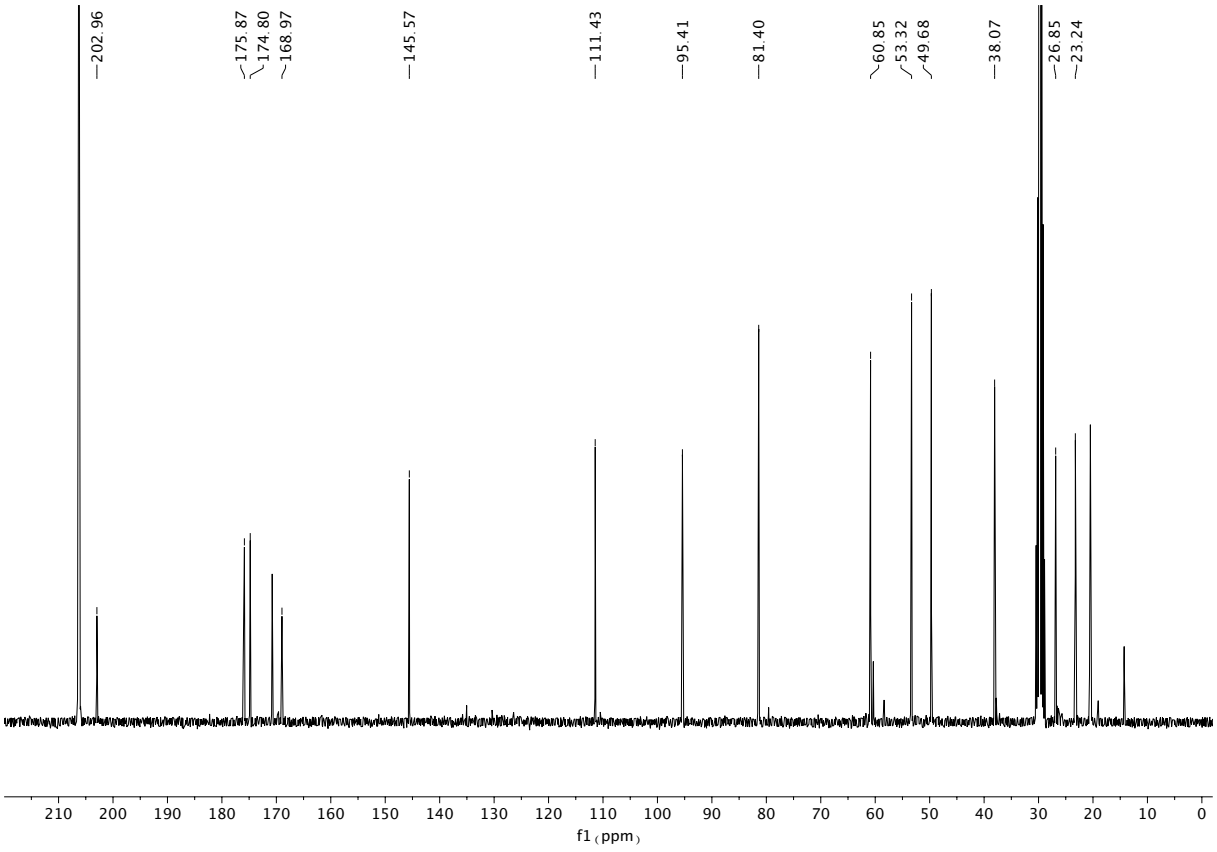


^{1}H and ^{13}C NMR of product 1d

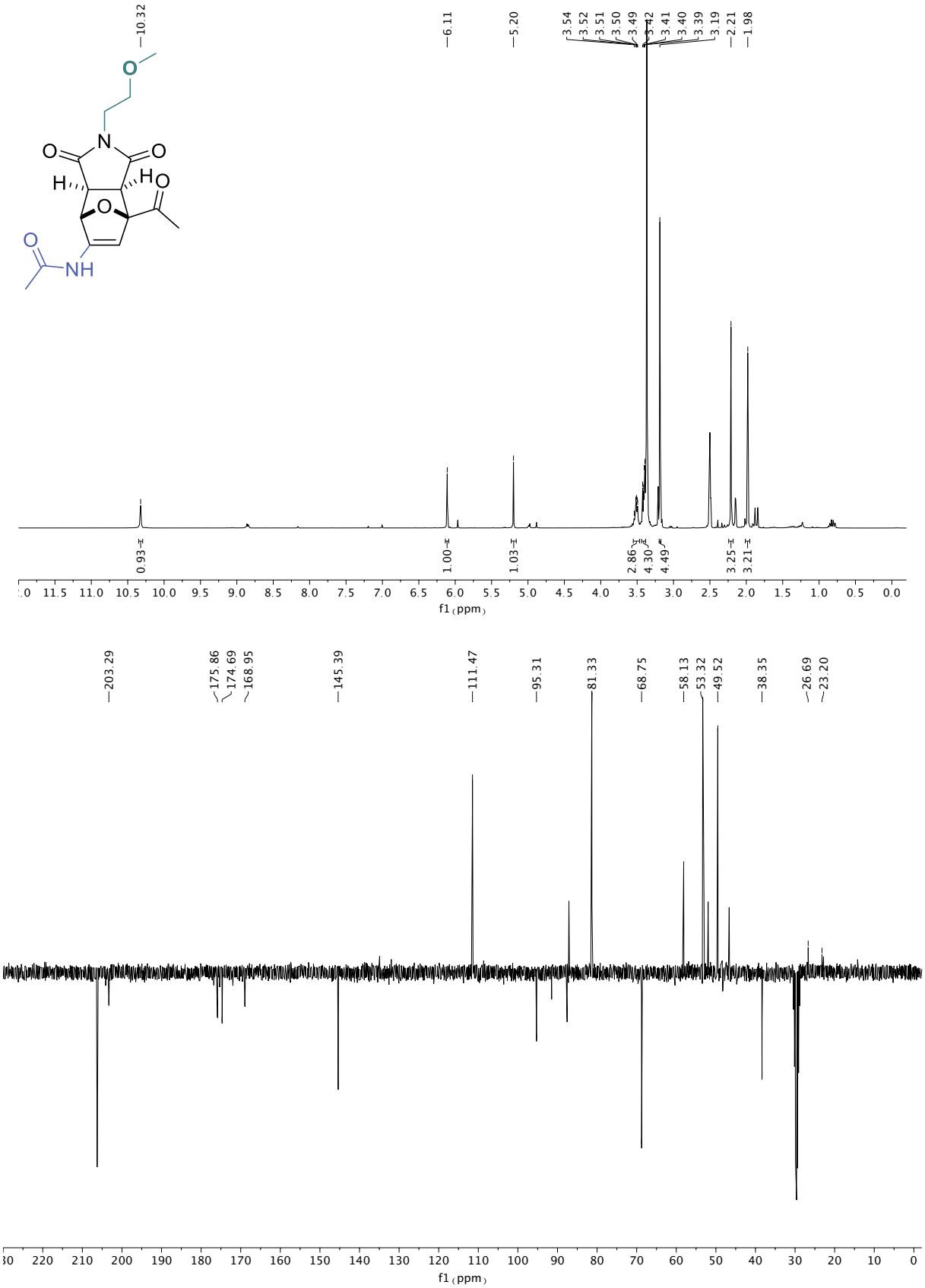


^{1}H and ^{13}C NMR of product 1e



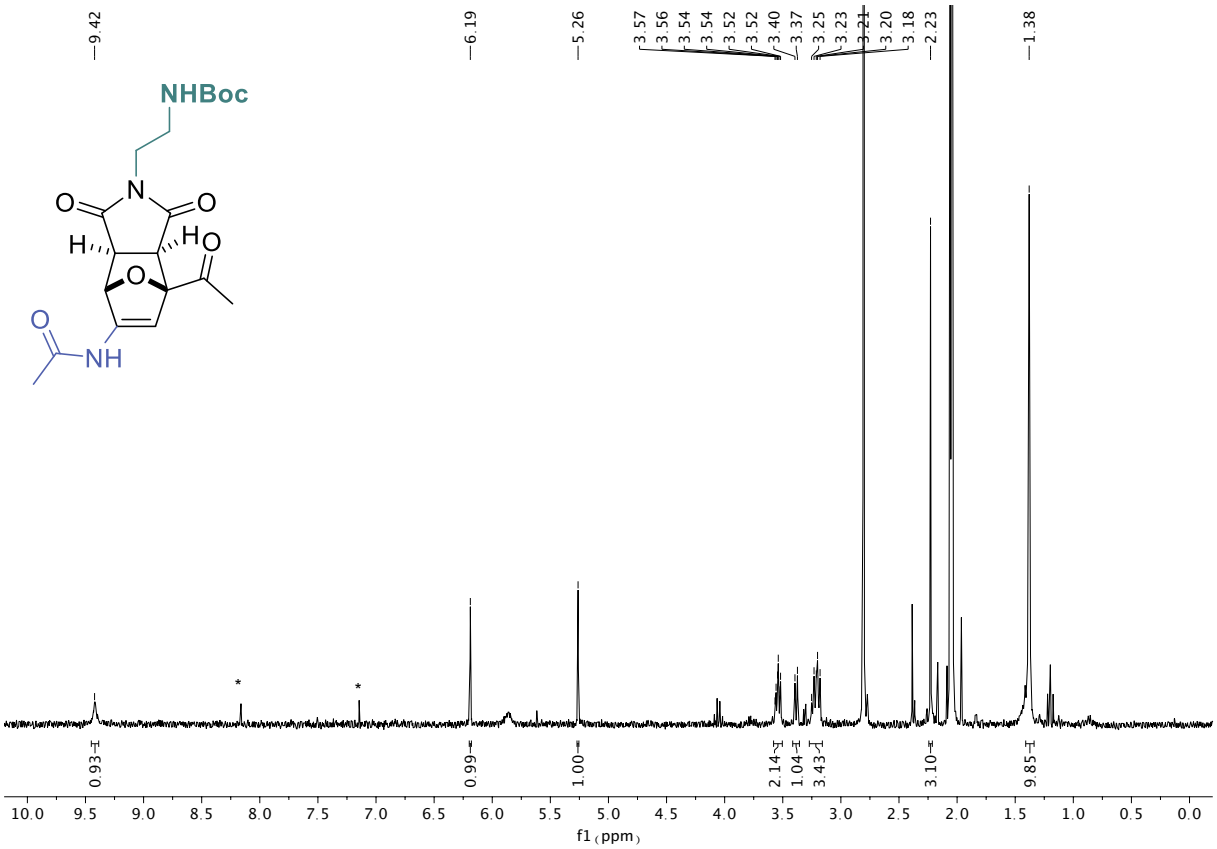


^{1}H and ^{13}C NMR of product 1f

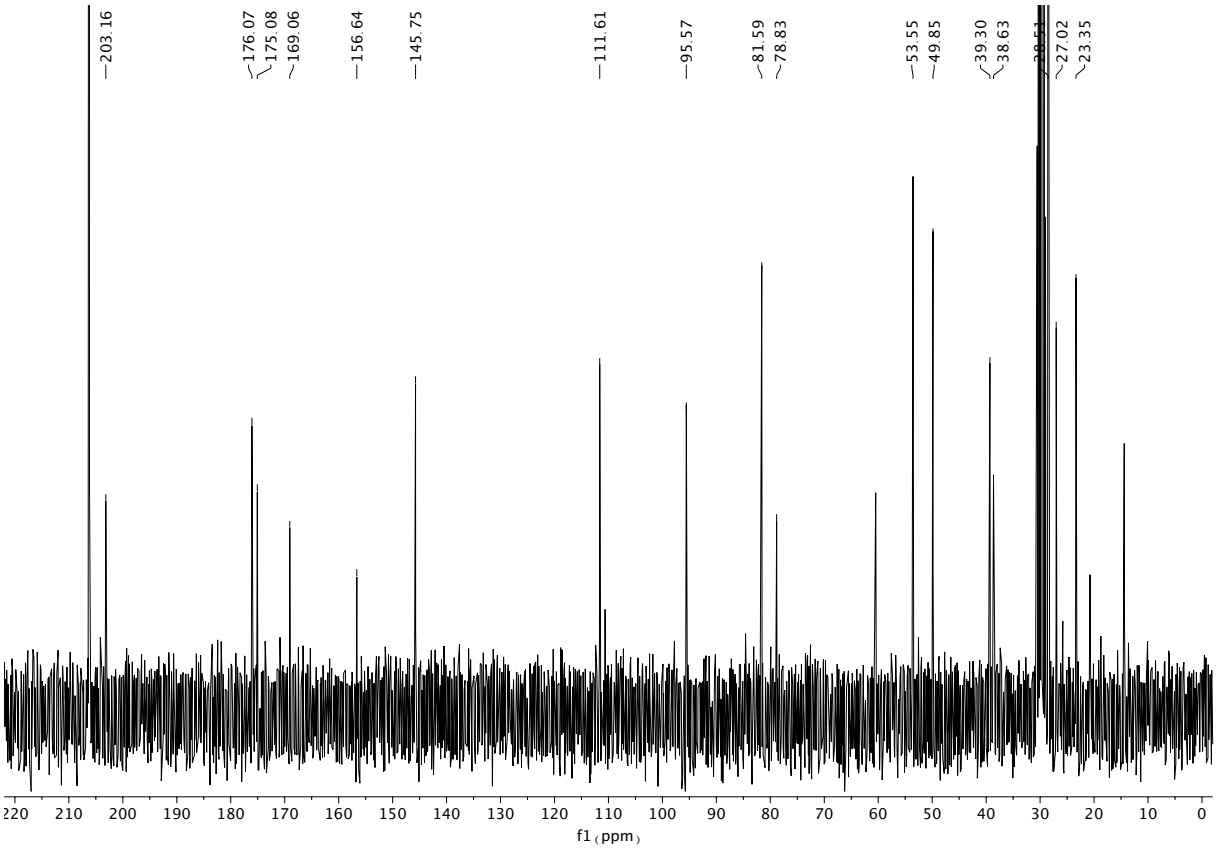


Note: Peaks from the corresponding hemi-acylaminal **2f** are present on the ^{13}C due to partial hydrolysis on the NMR tube.

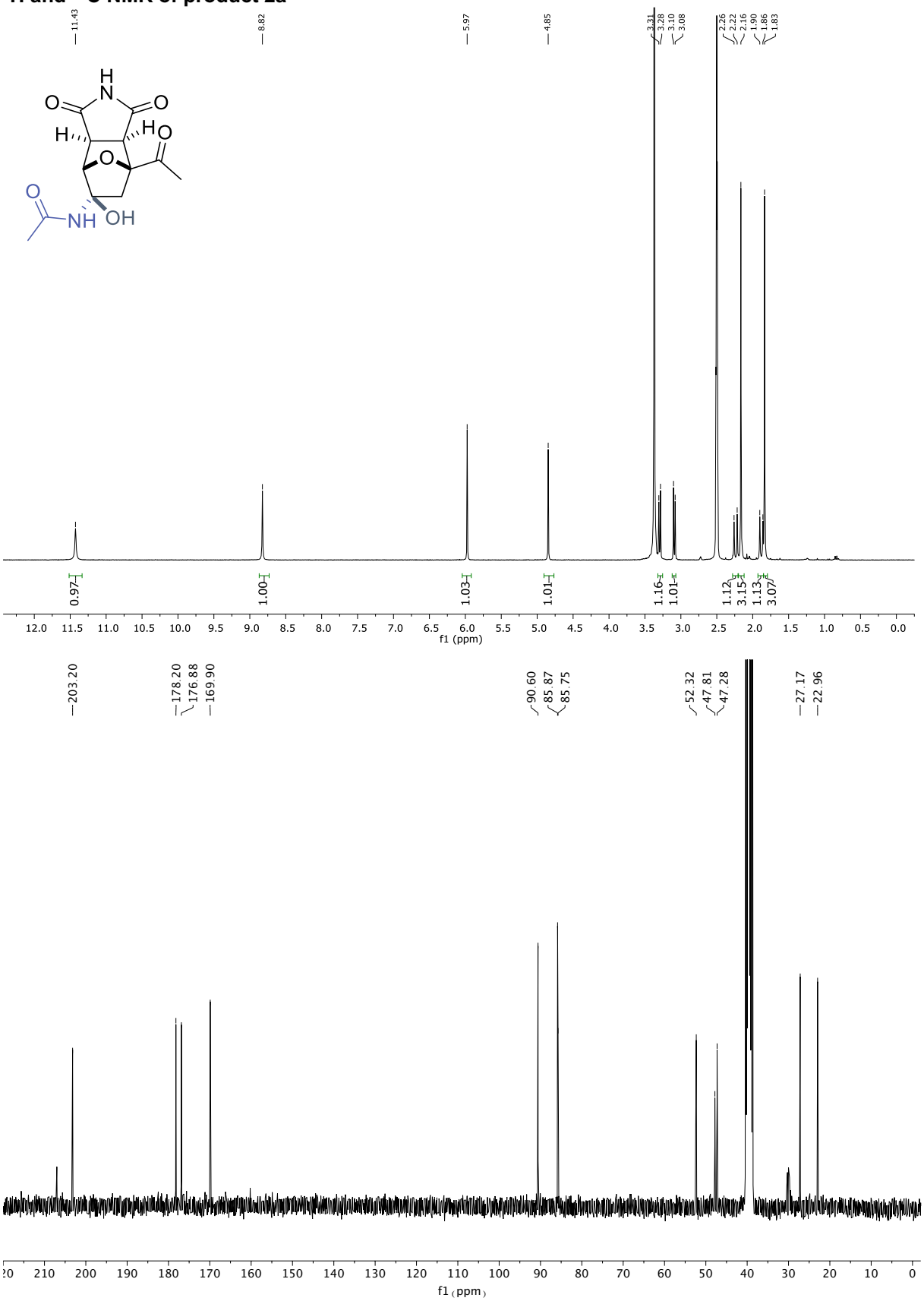
^{1}H and ^{13}C NMR of product 1g



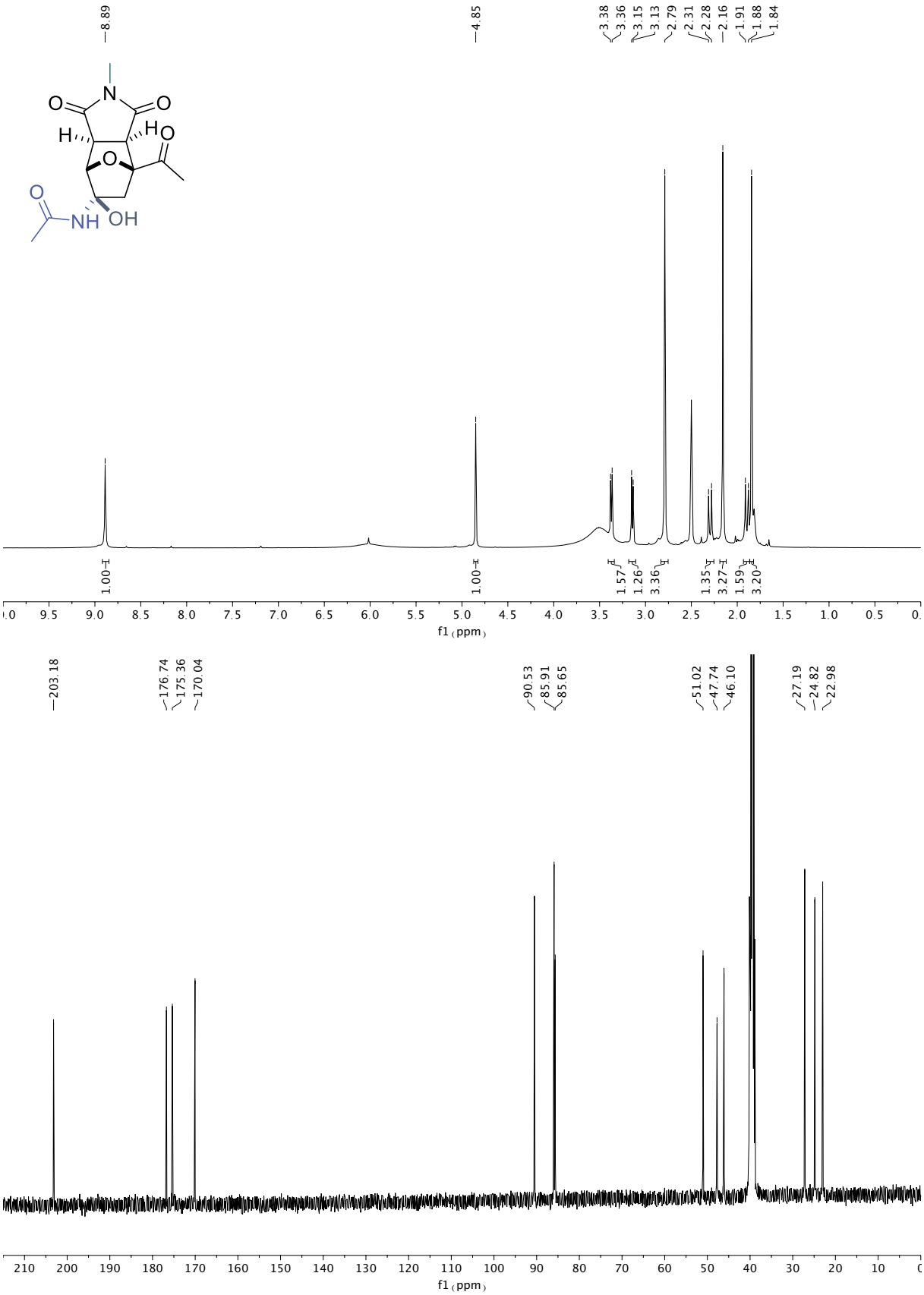
[a] Corresponds to 3A5AF.



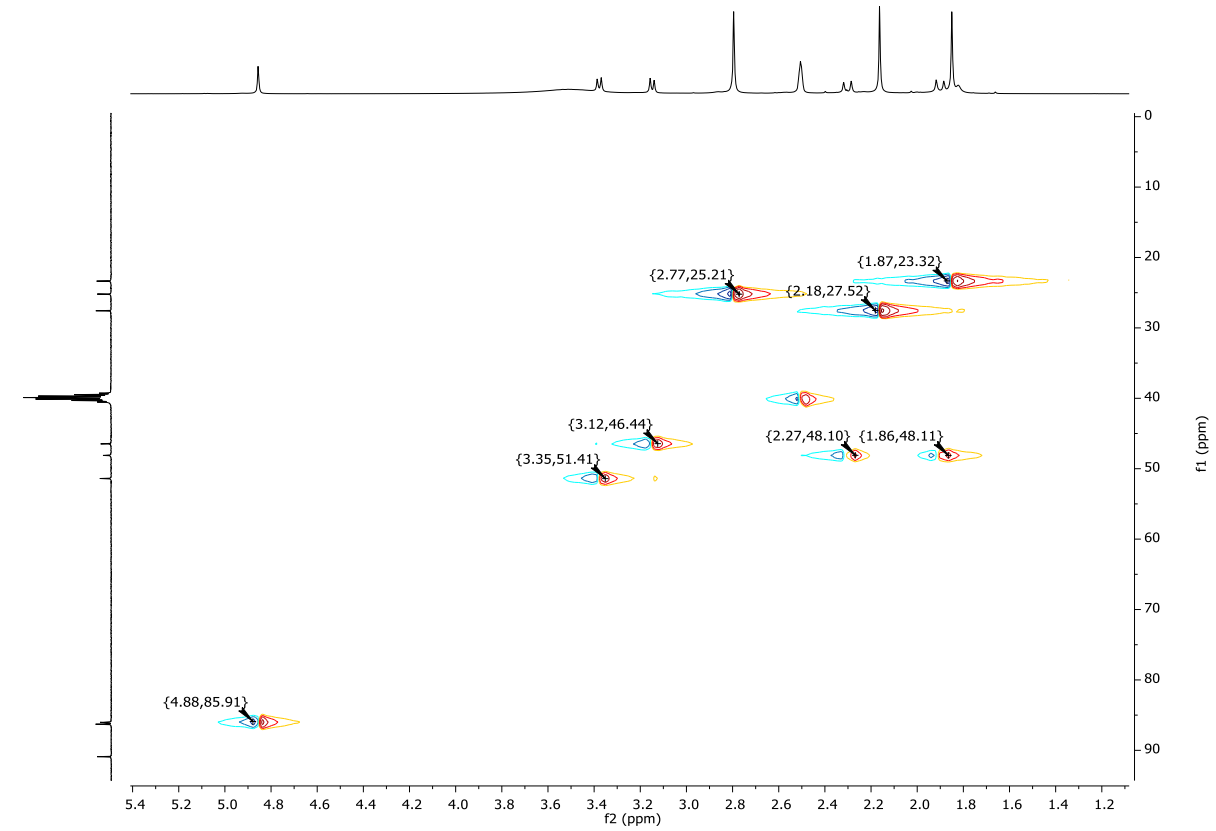
^{1}H and ^{13}C NMR of product 2a

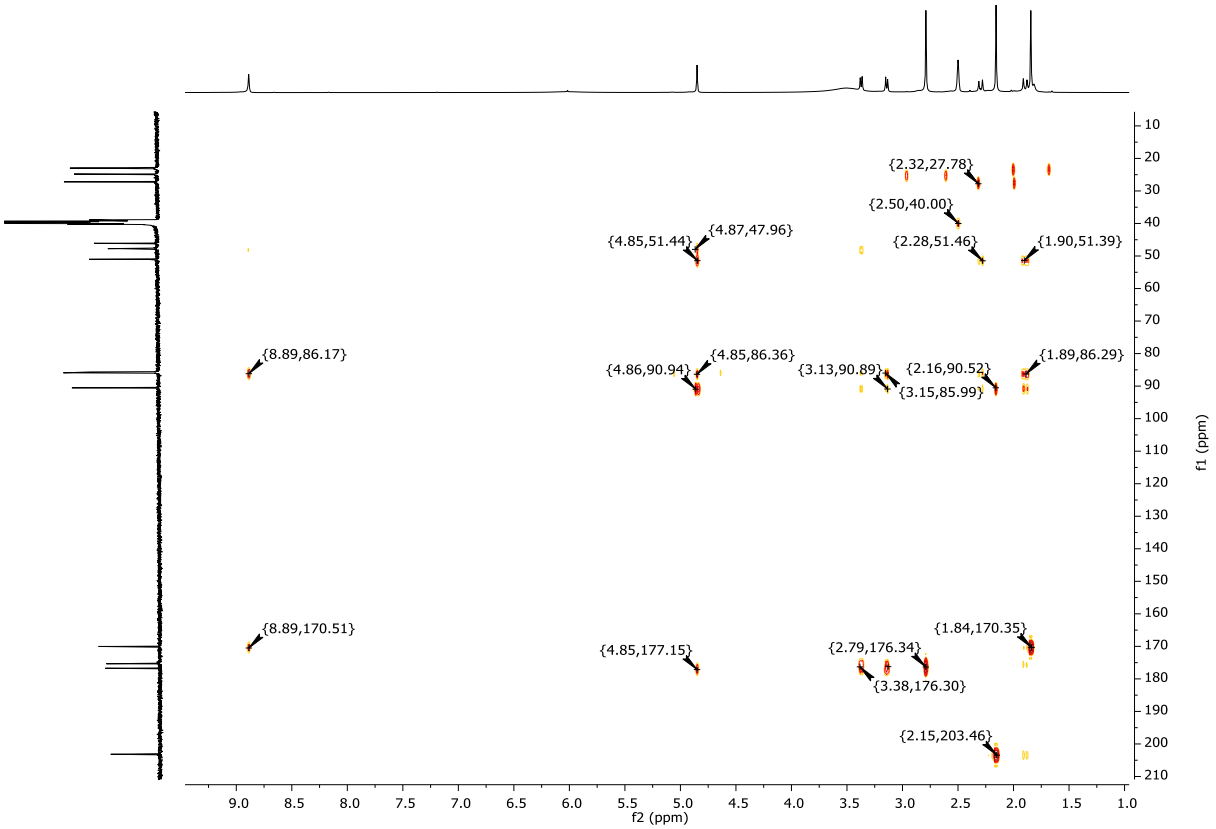


^{1}H and ^{13}C NMR of product 2b

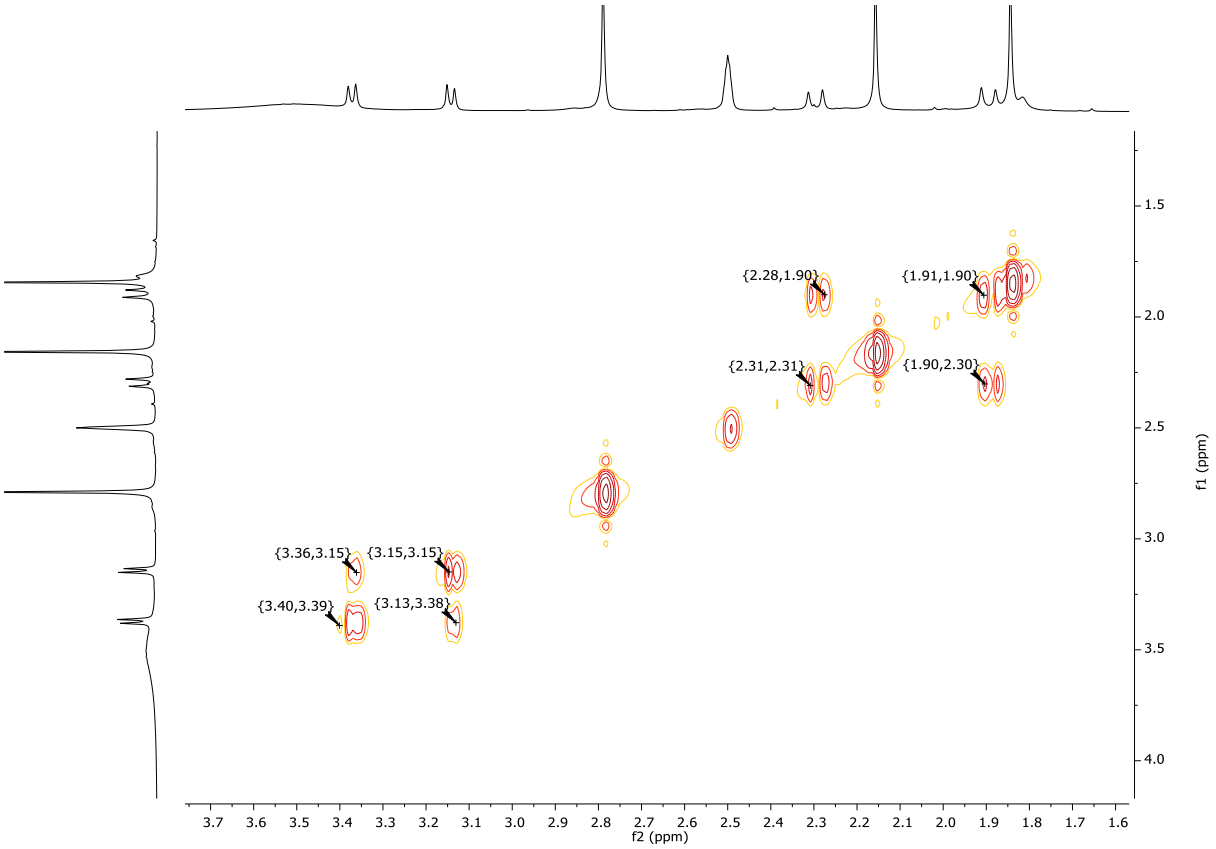


HSQC and HMBC of product 2b

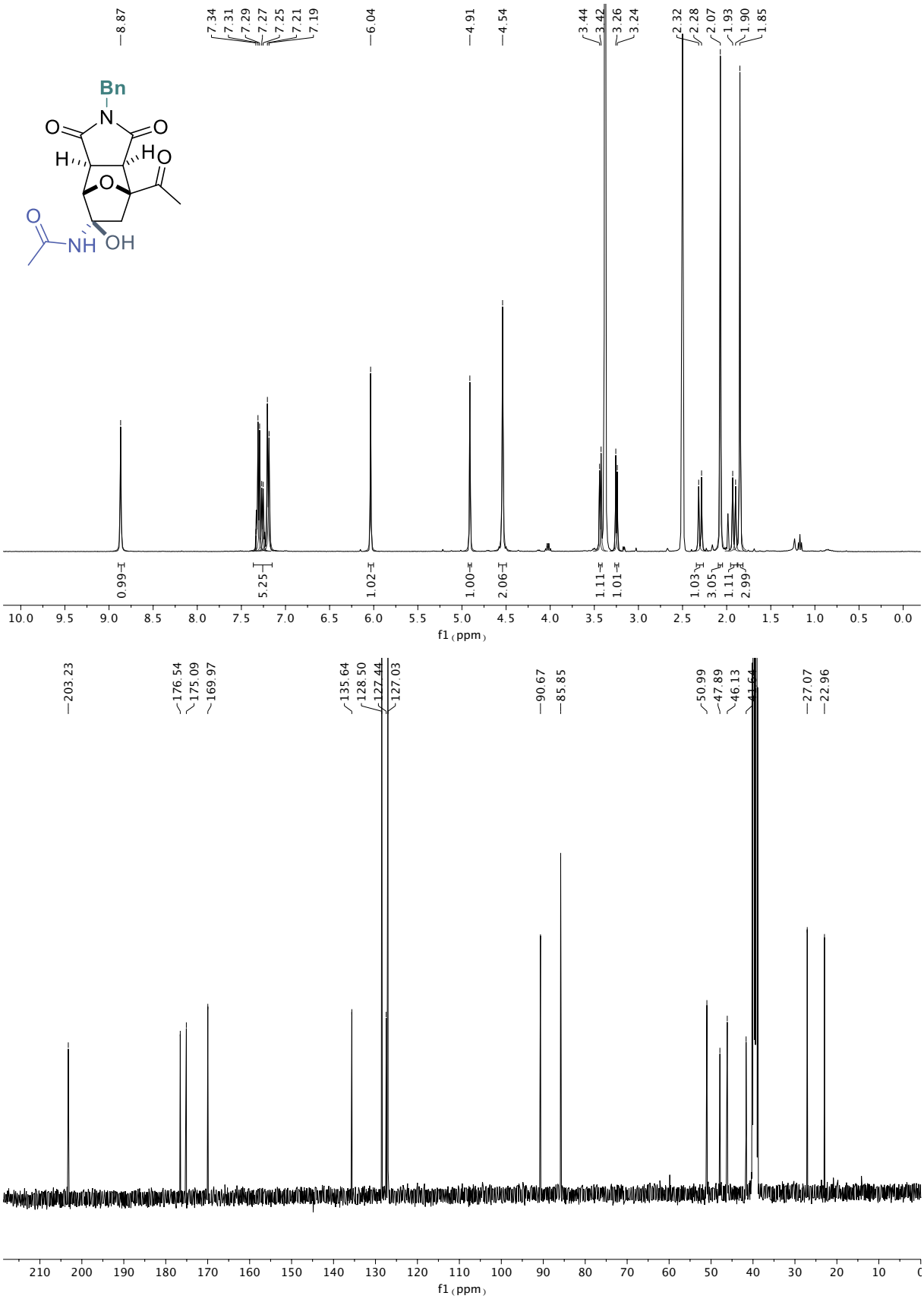




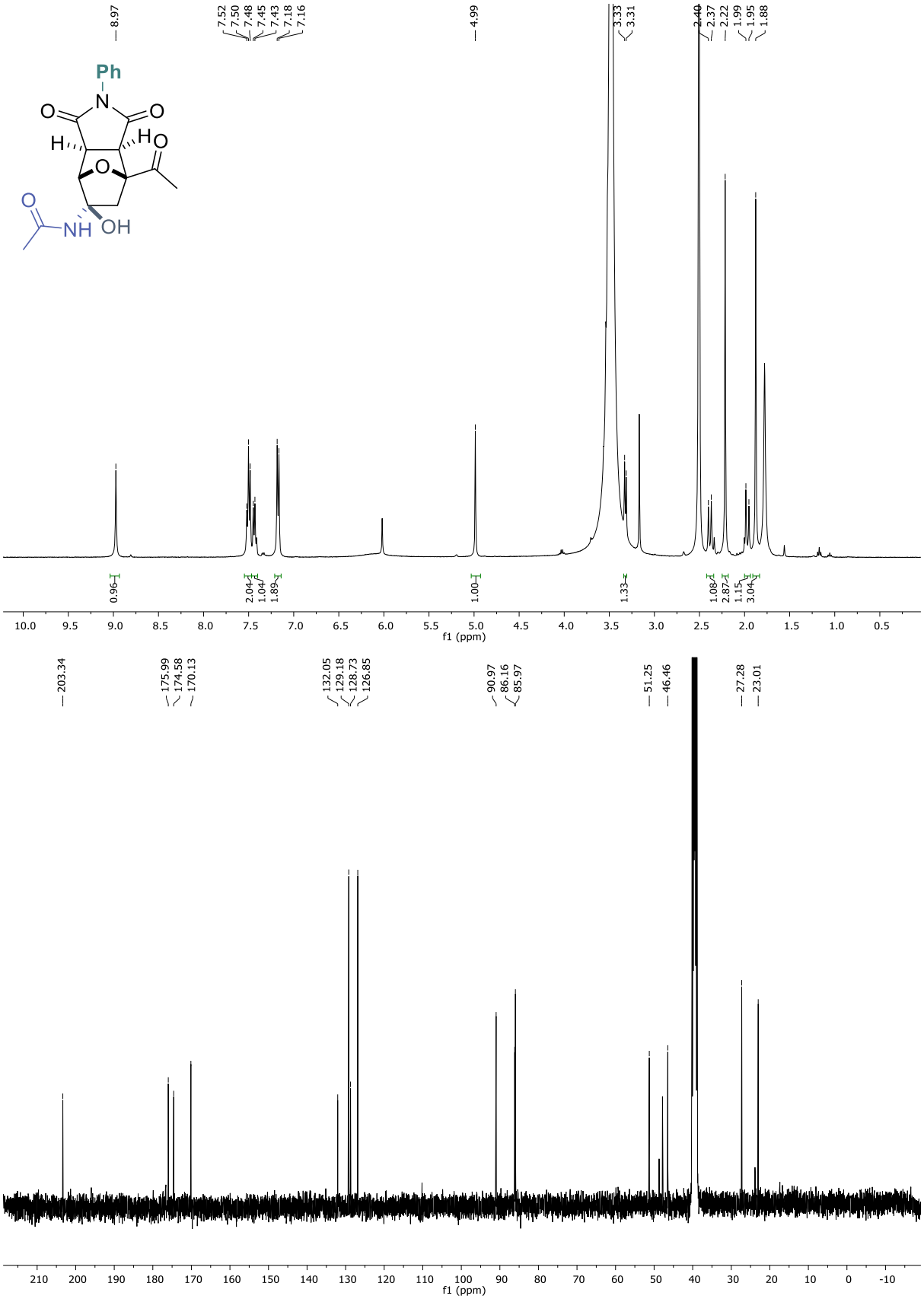
COSY of product 2b



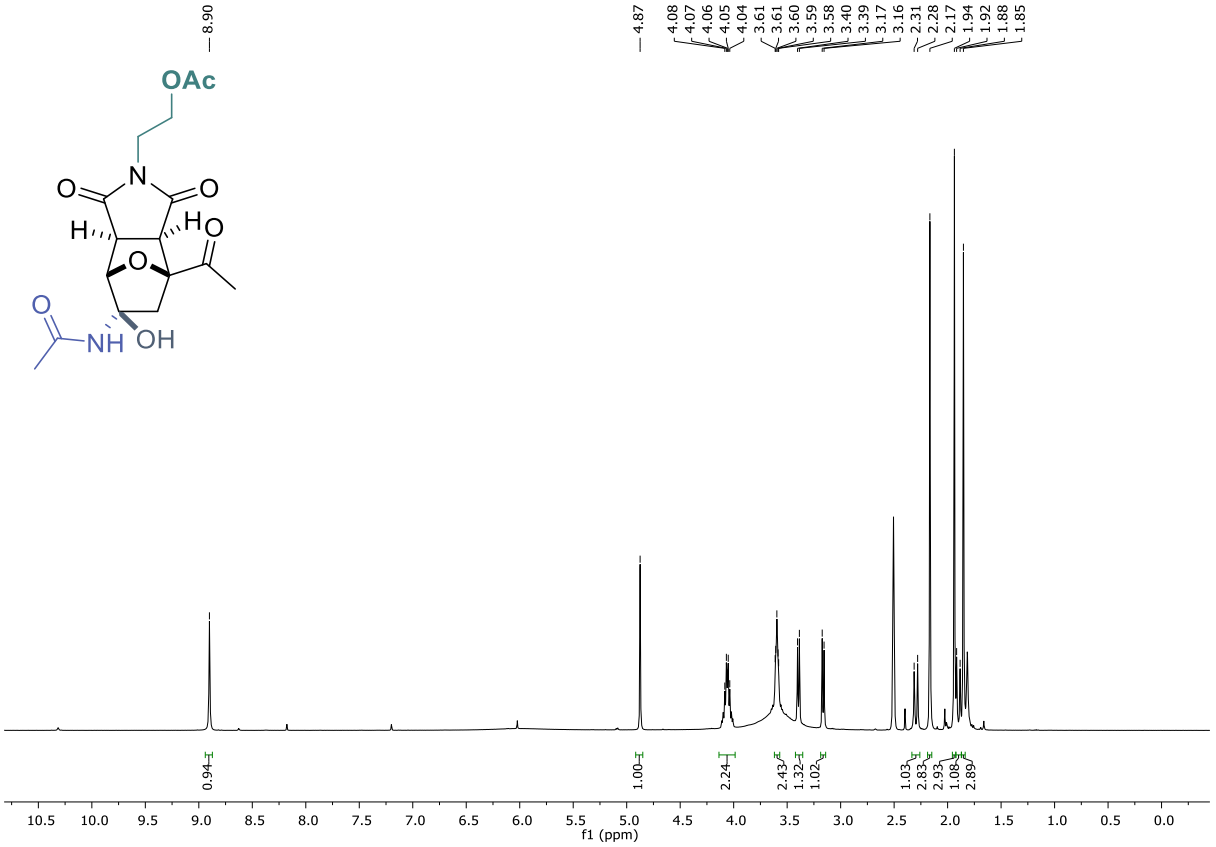
^{1}H and ^{13}C NMR of product 2c

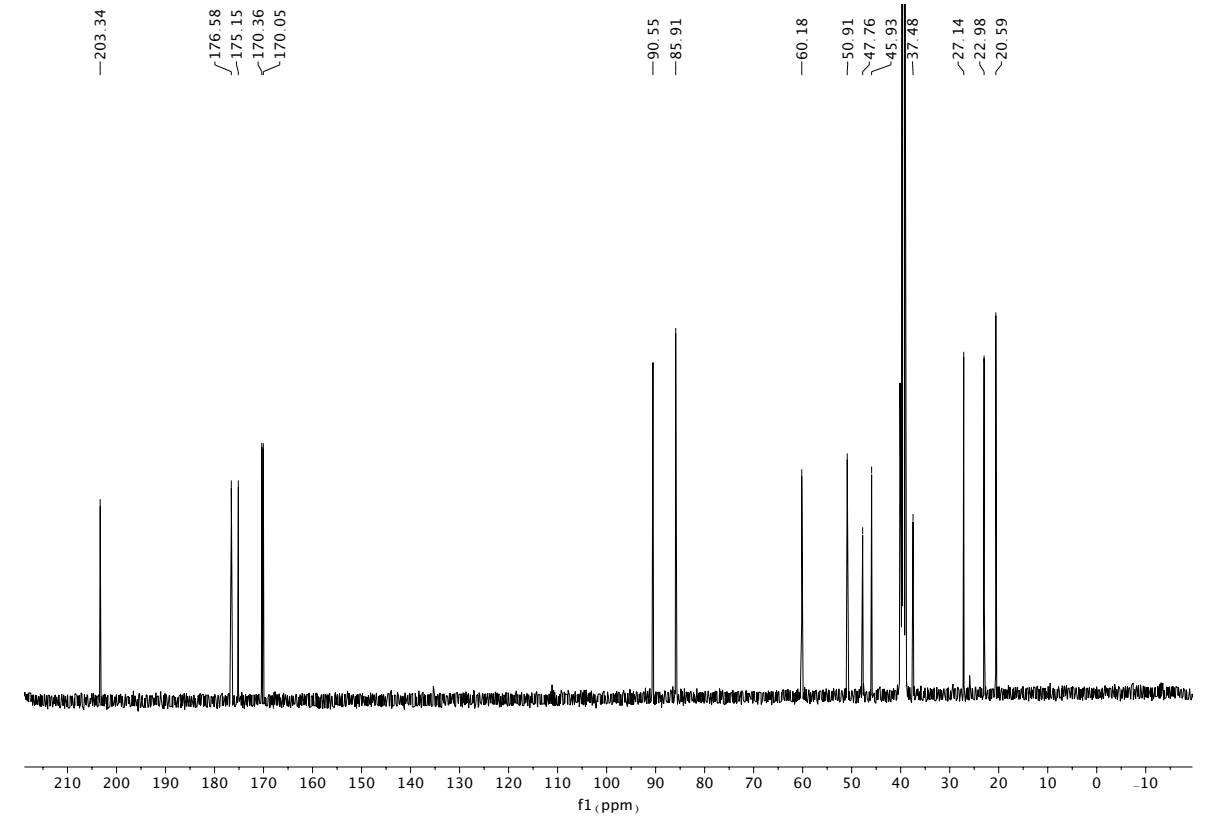


^{1}H and ^{13}C NMR of product 2d

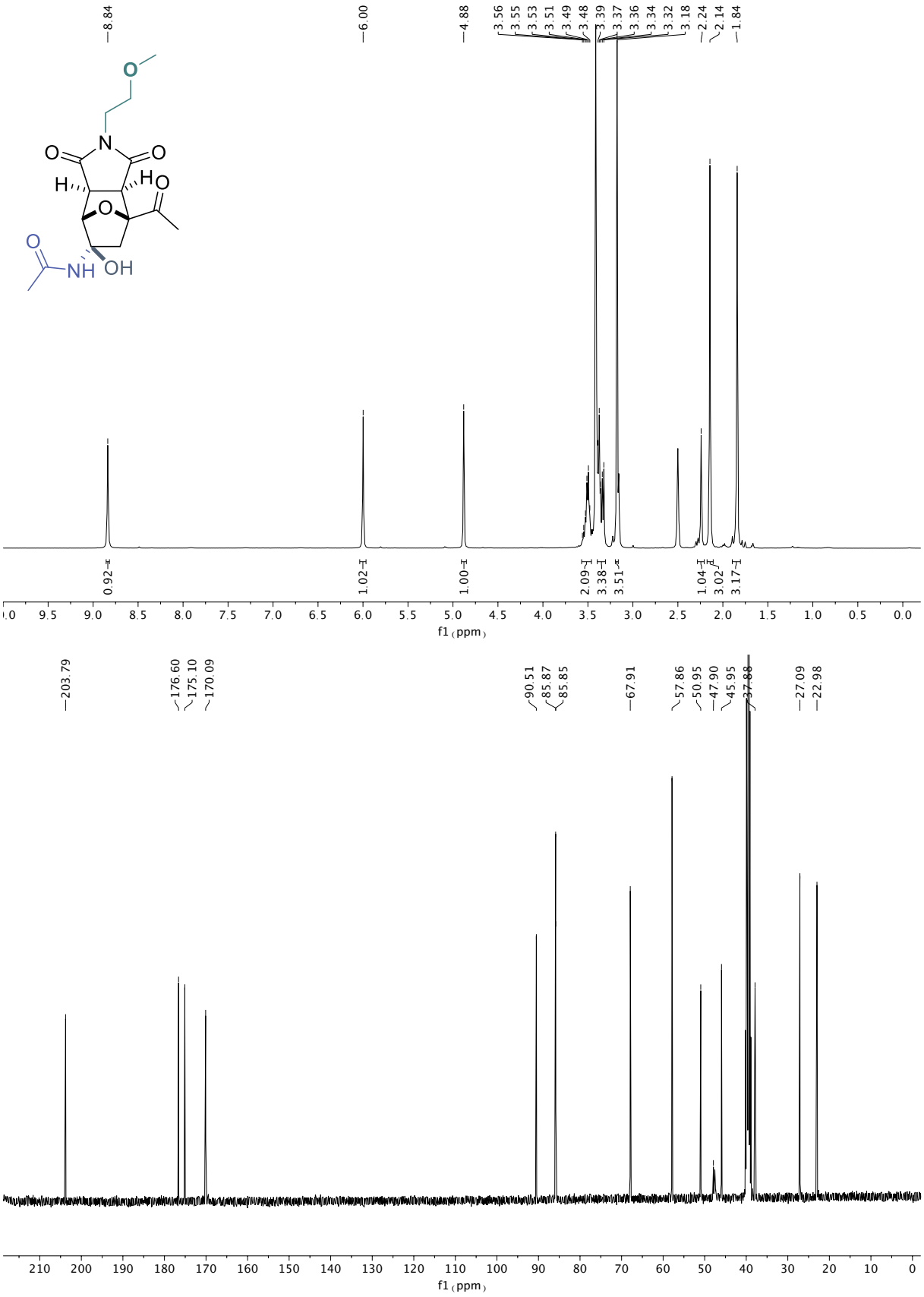


^{1}H and ^{13}C NMR of product 2e

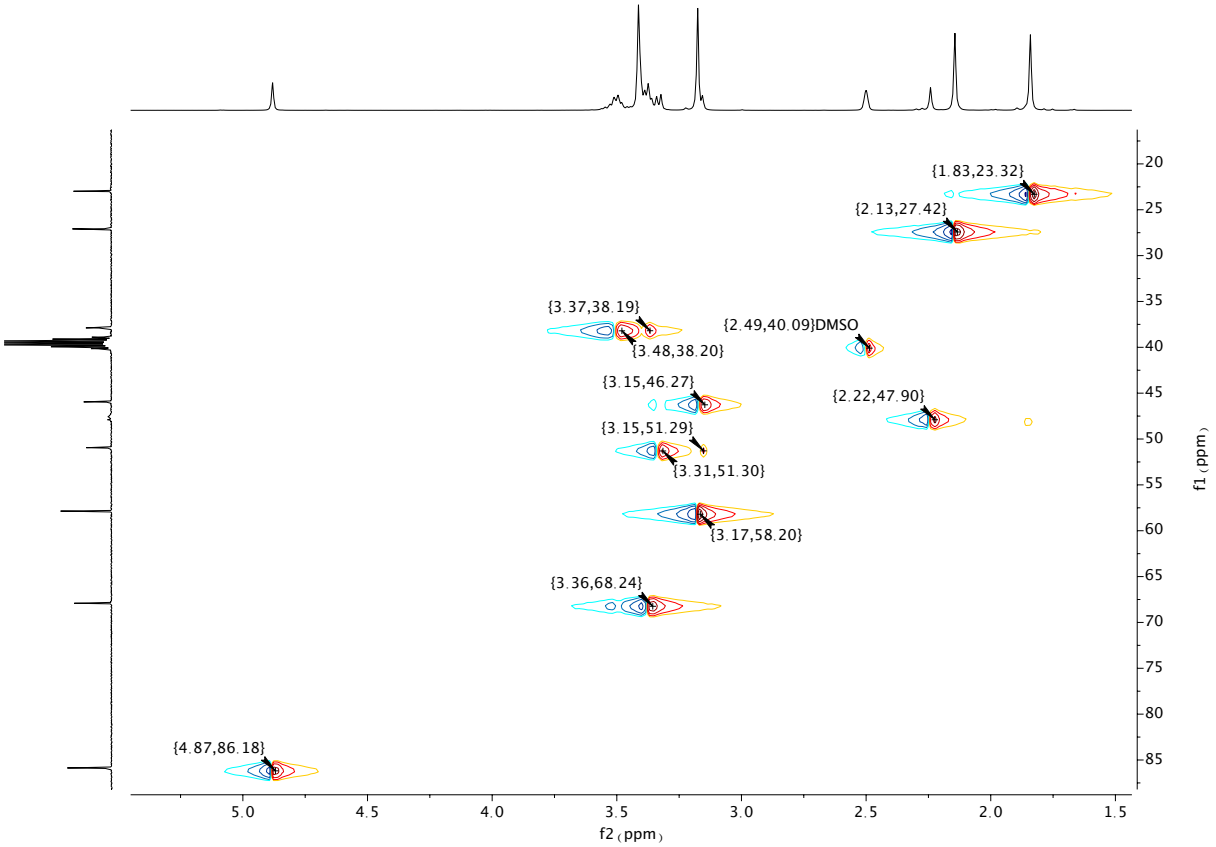


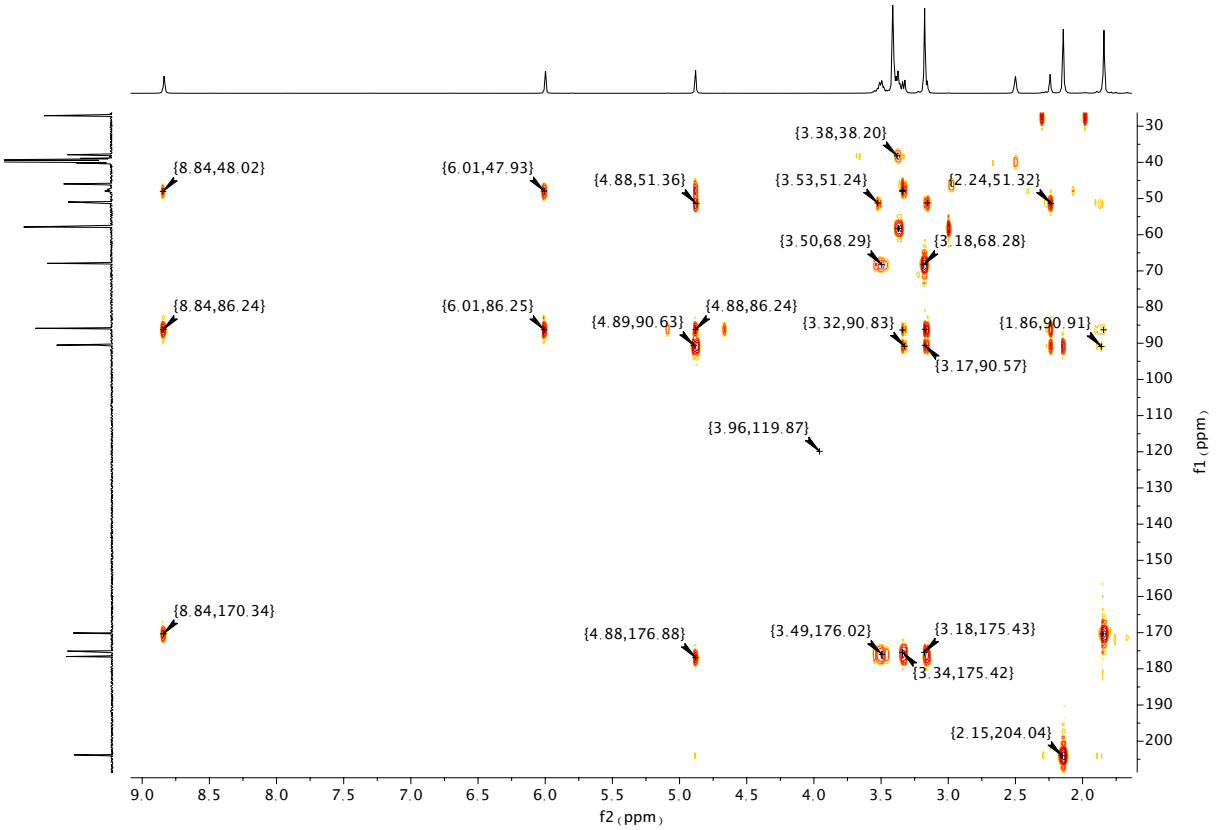


^{1}H and ^{13}C NMR of product 2f

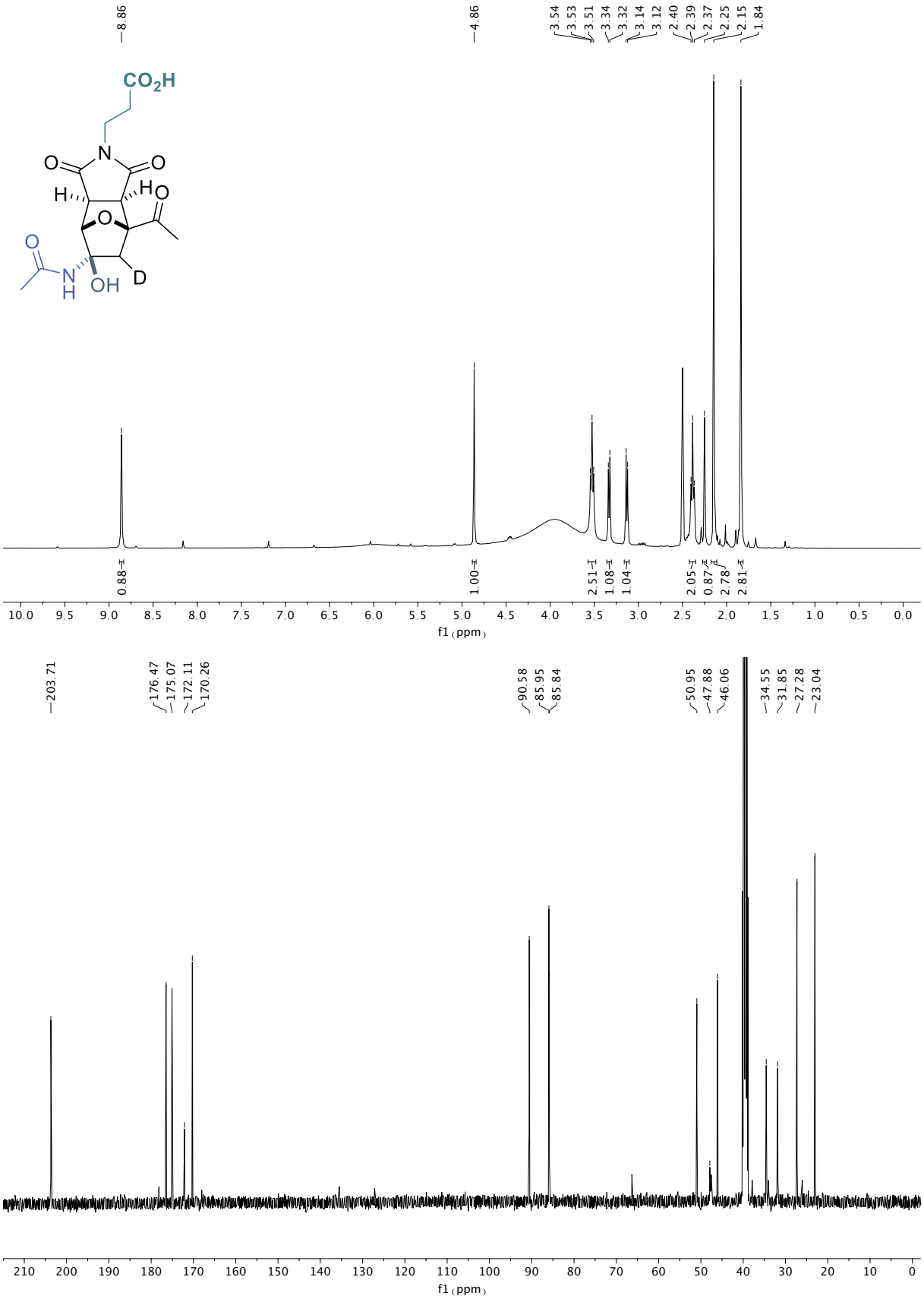


HSQC and HMBC of product 2f

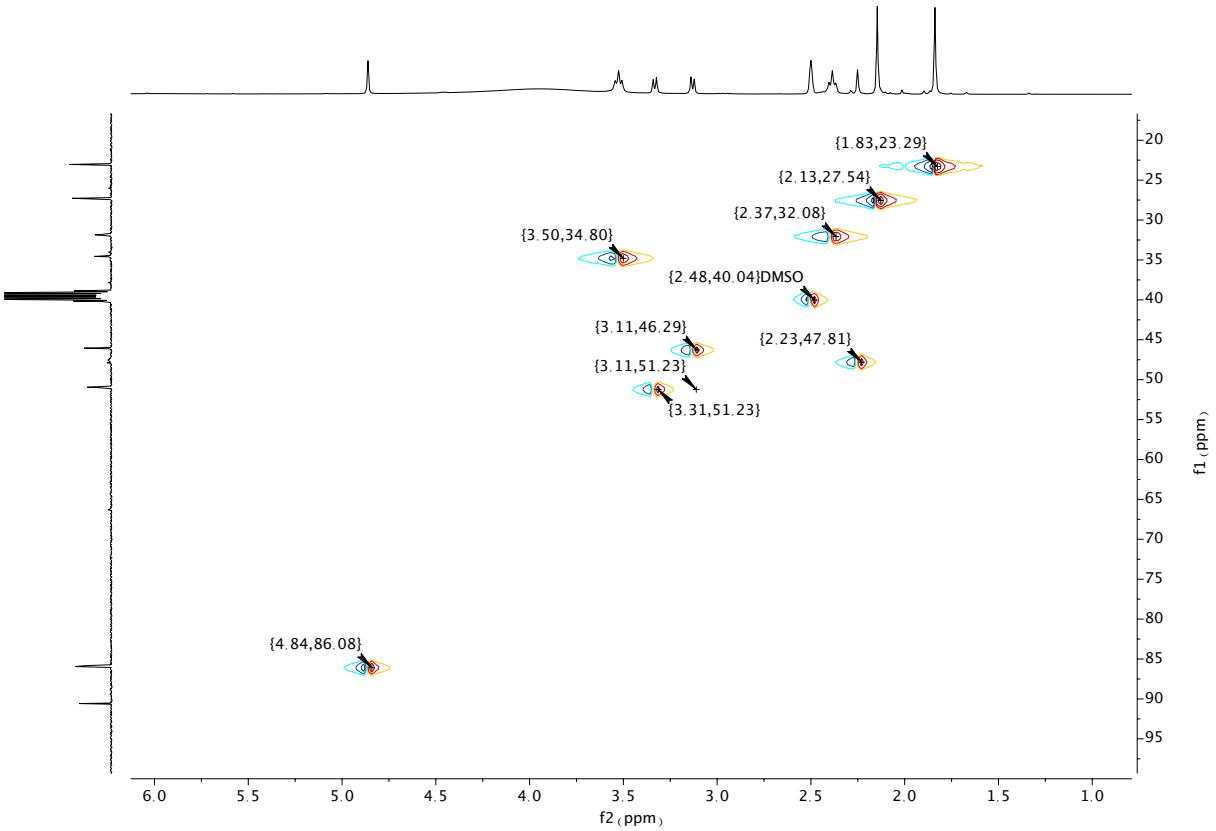


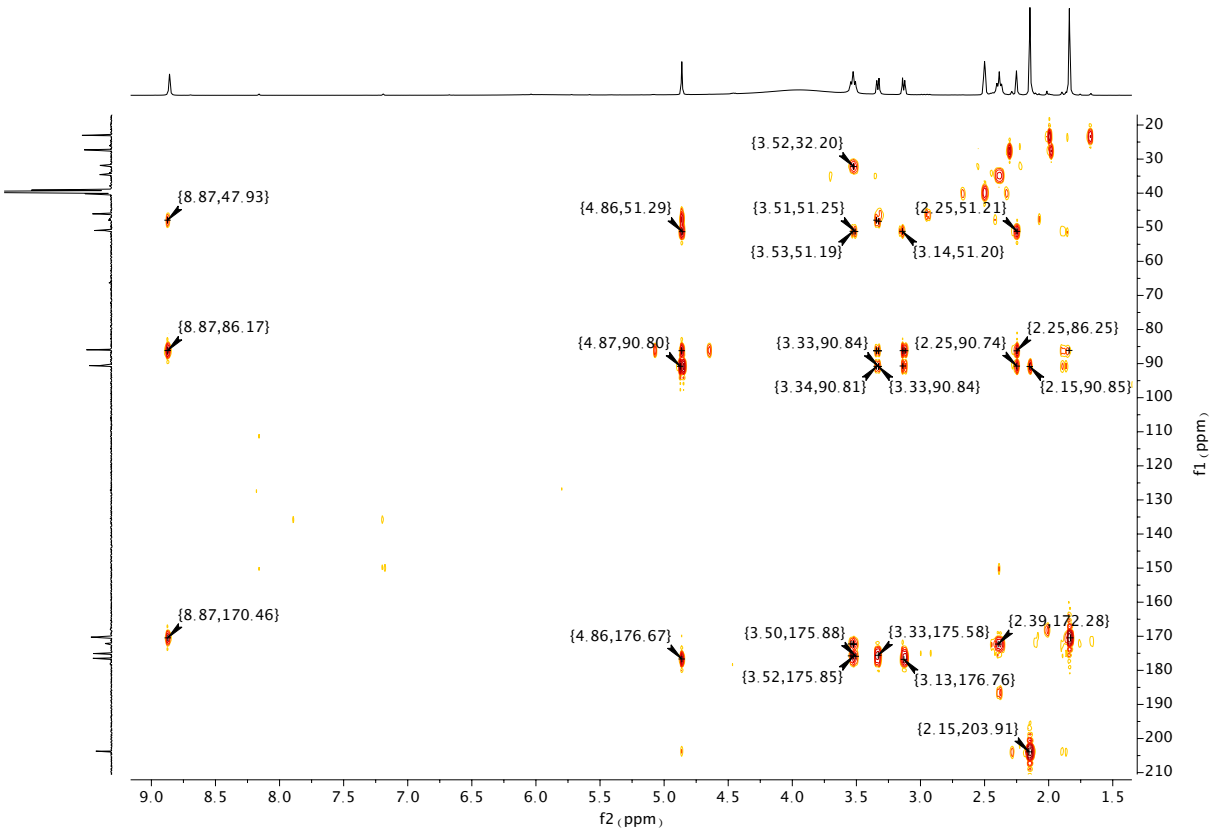

{3.38,38.20}
{8.84,48.02}
{6.01,47.93}
{4.88,51.36}
{3.53,51.24}
{2.24,51.32}
{3.50,68.29}
{3.18,68.28}
{8.84,86.24}
{6.01,86.25}
{4.89,90.63}
{4.88,86.24}
{3.32,90.83}
{1.86,90.91}
{3.17,90.57}
{3.96,119.87}
{8.84,170.34}
{4.88,176.88}
{3.49,176.02}
{3.18,175.43}
{3.34,175.42}
{2.15,204.04}
f2 (ppm)
f1 (ppm)

^{1}H and ^{13}C NMR of product 2g

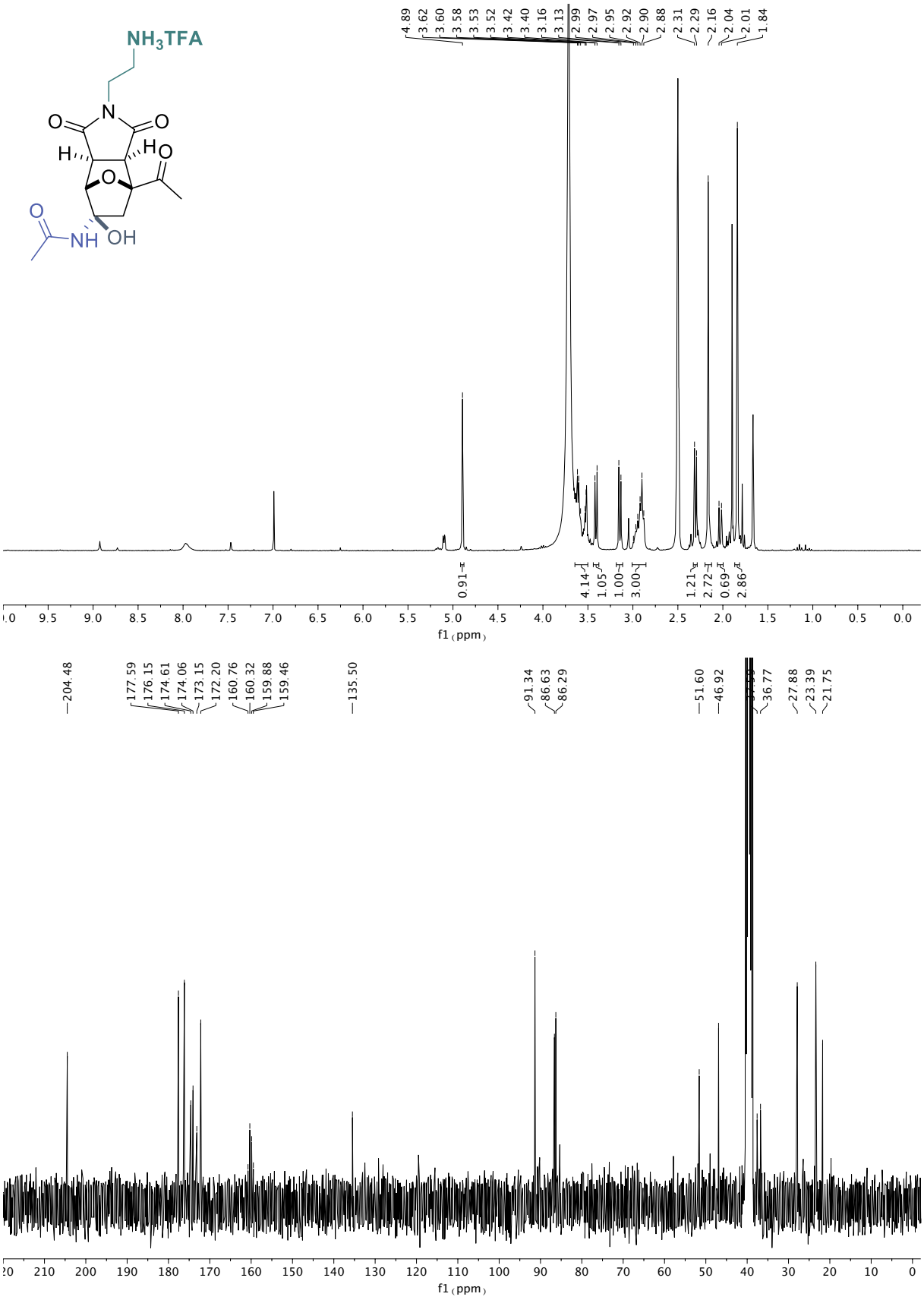


HSQC and HMBC of product 2g

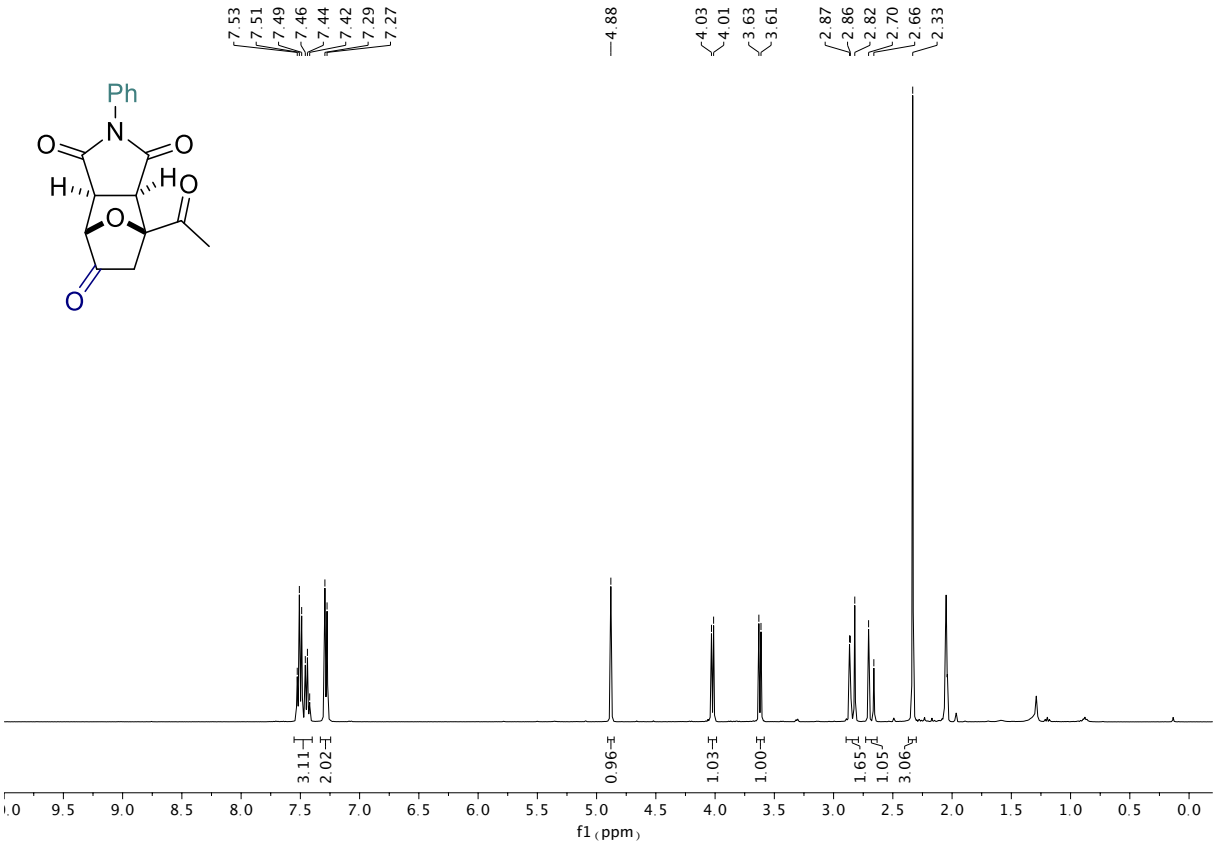


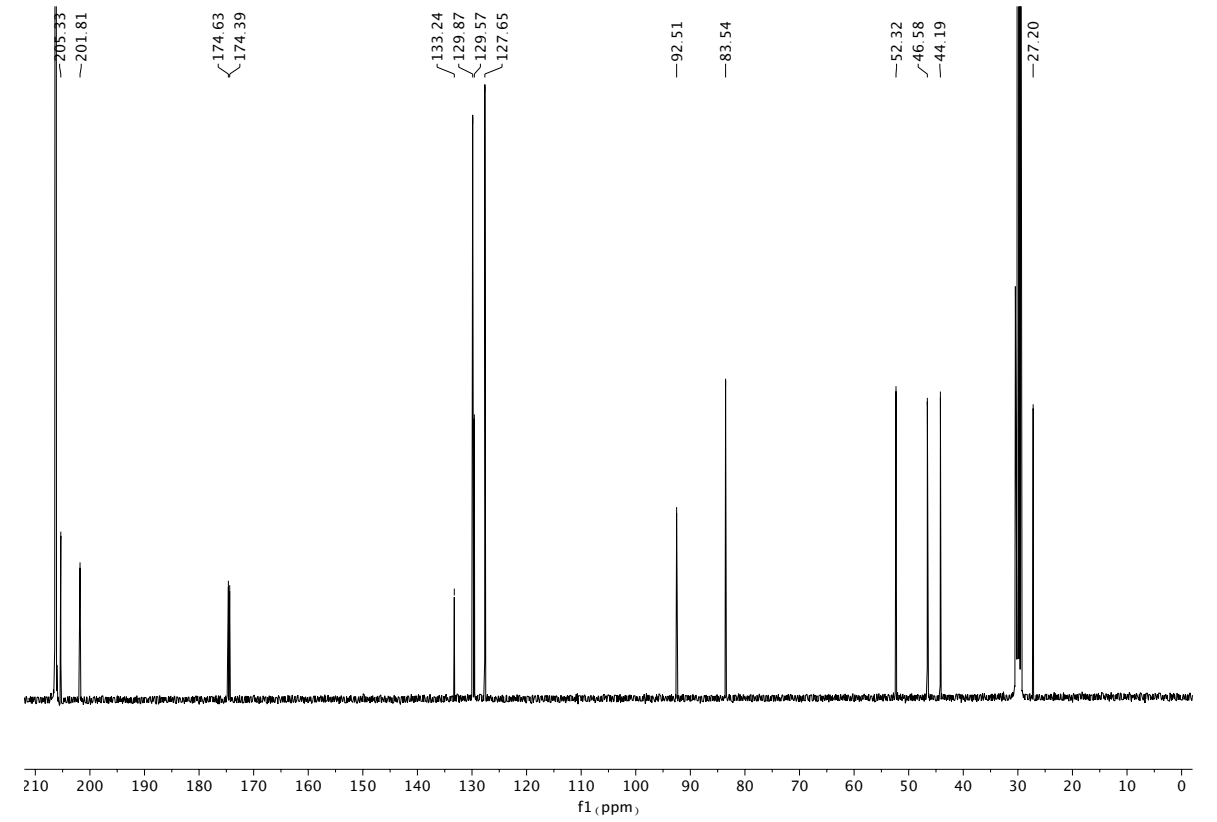


^{1}H and ^{13}C NMR of product 2h

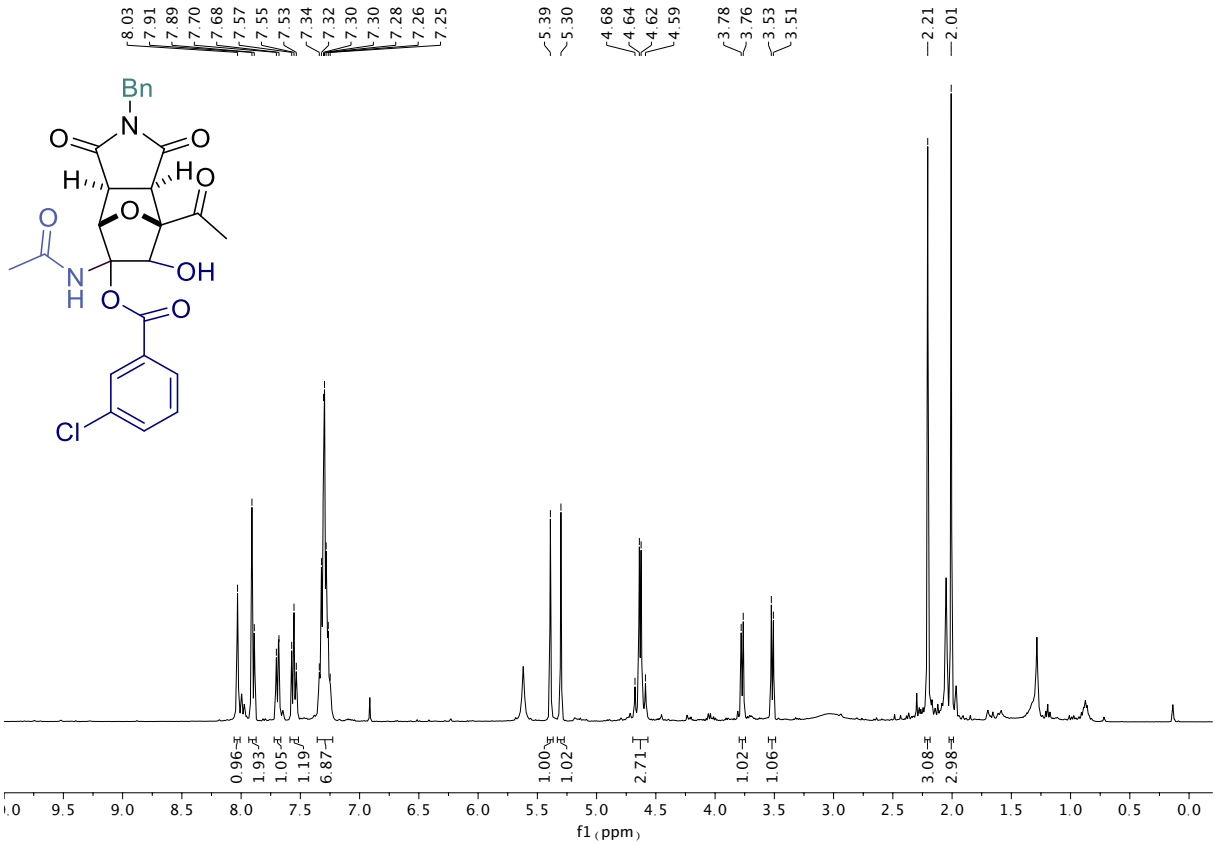


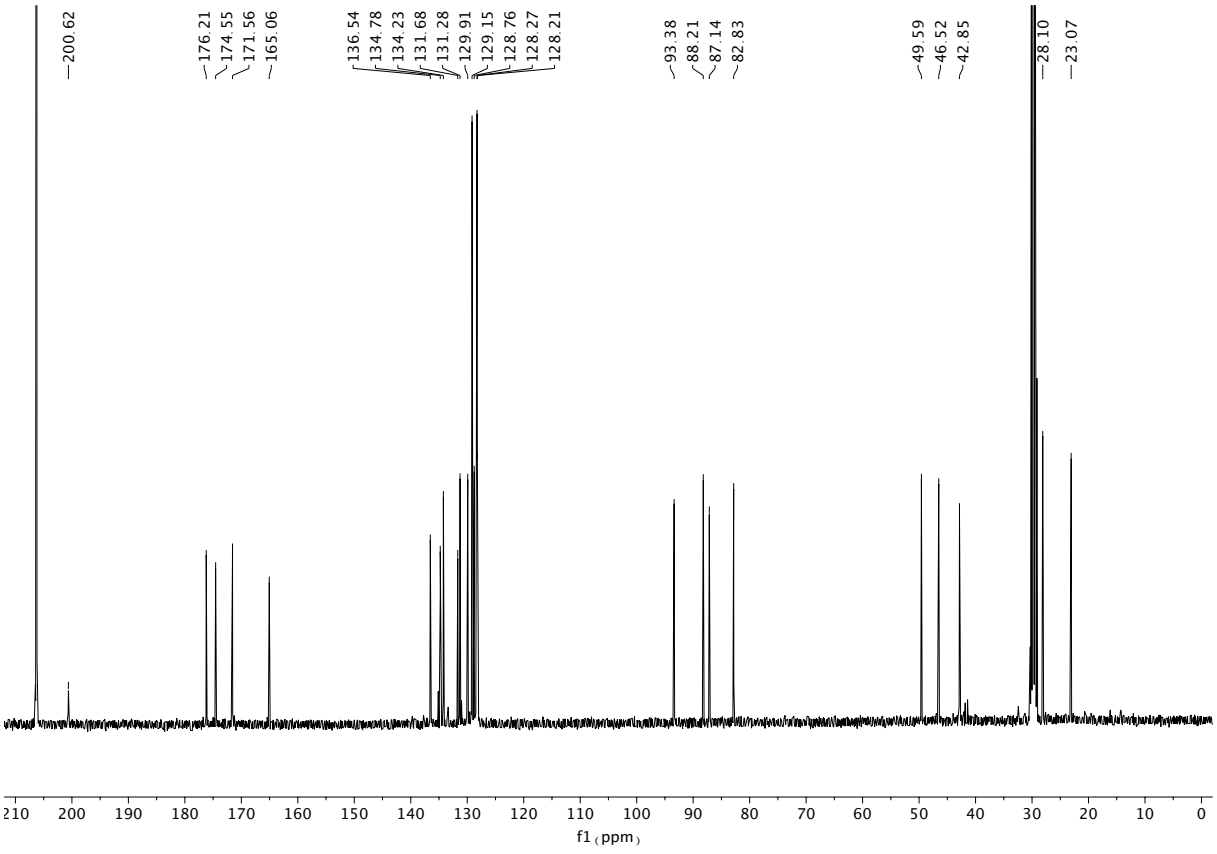
^{1}H and ^{13}C NMR of product 3



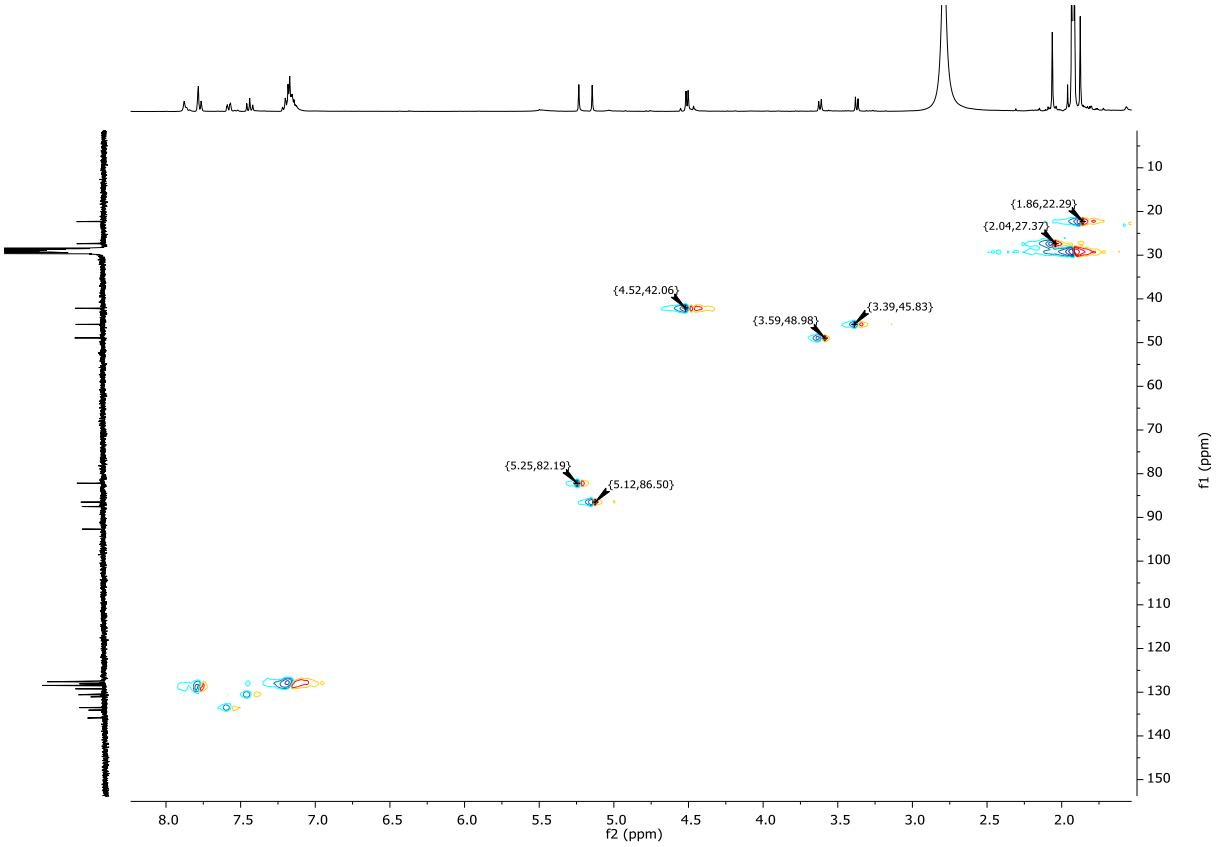


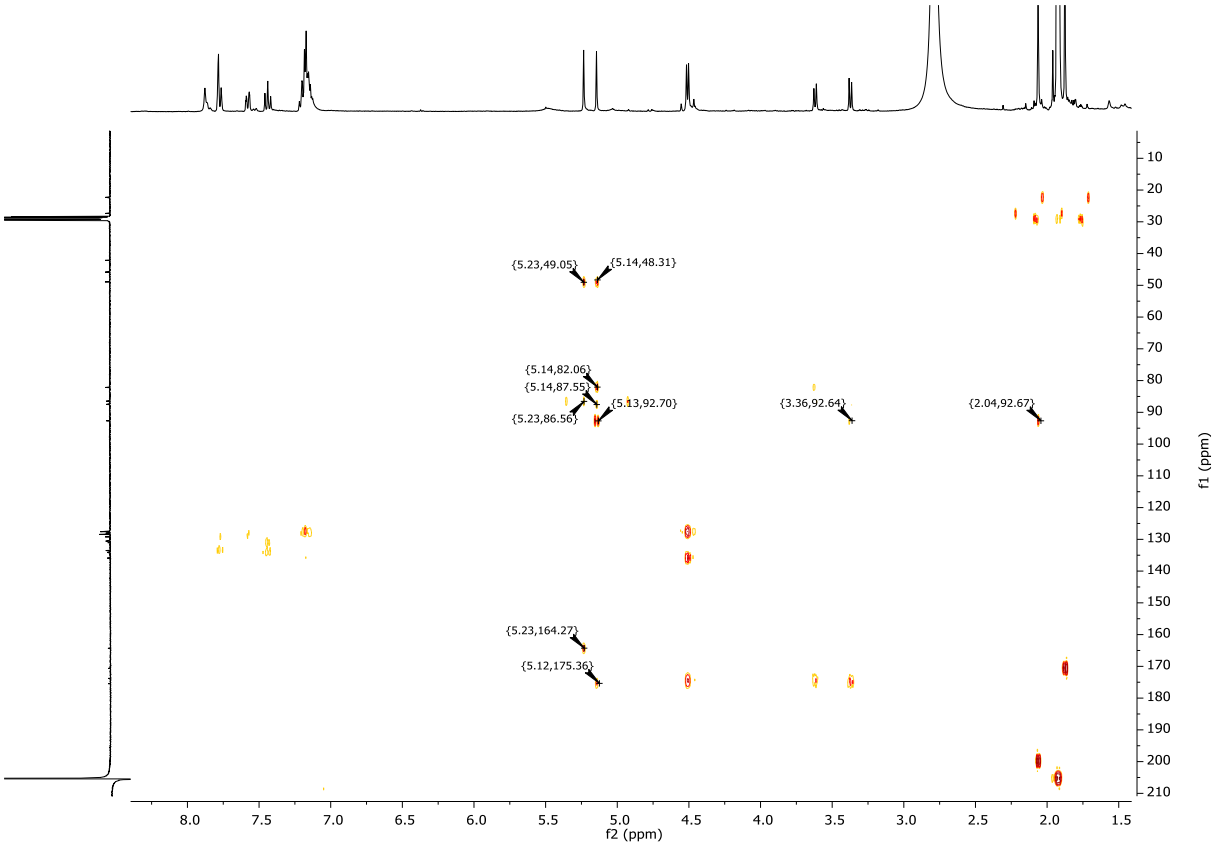
^{1}H and ^{13}C NMR of product 4



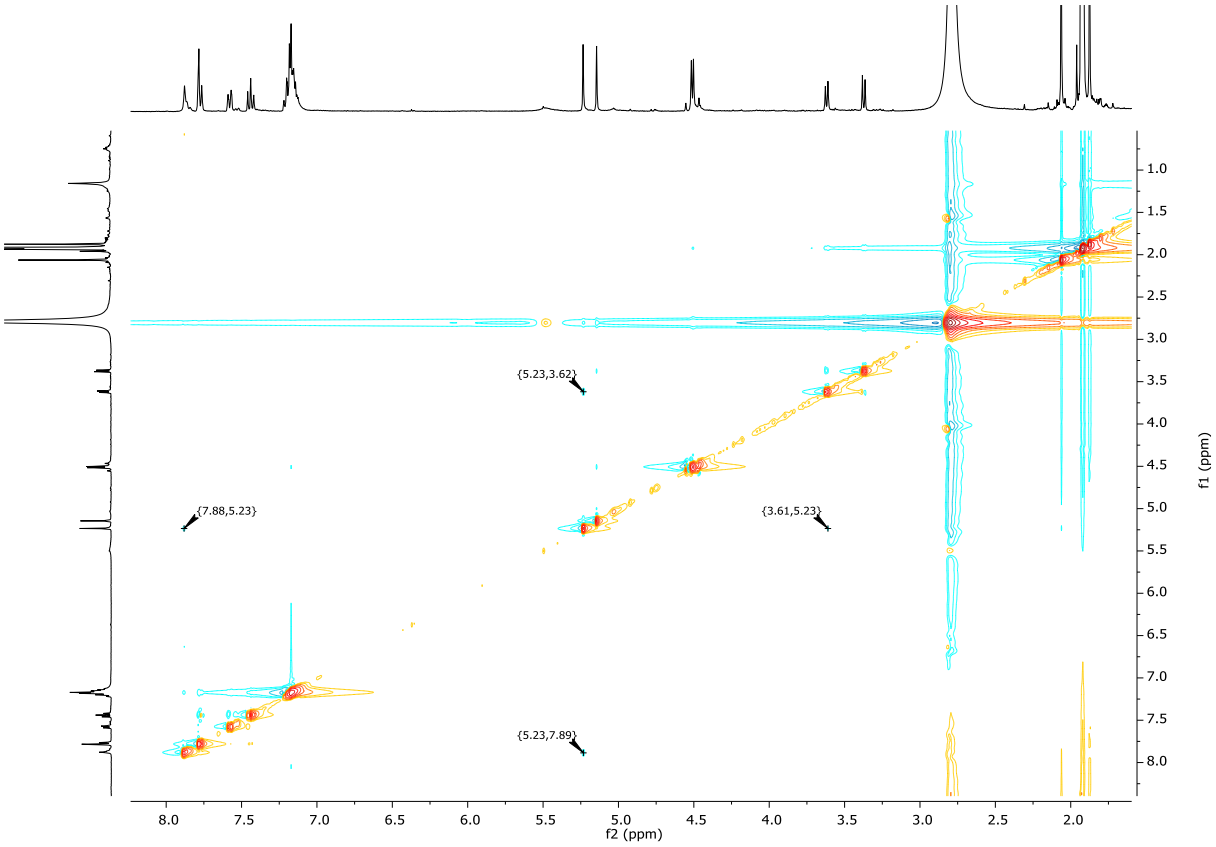


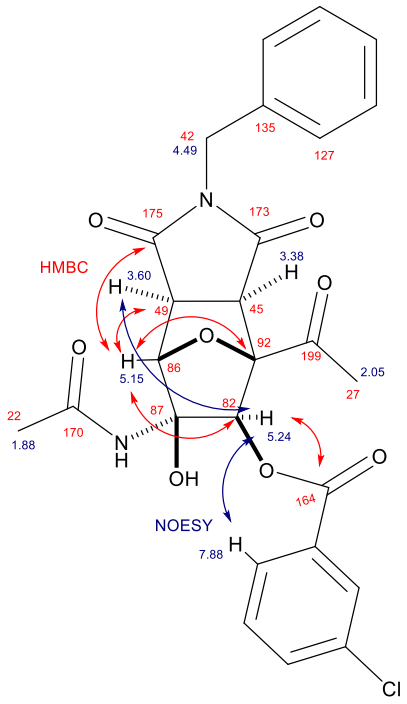
HSQC and HMBC of product 4



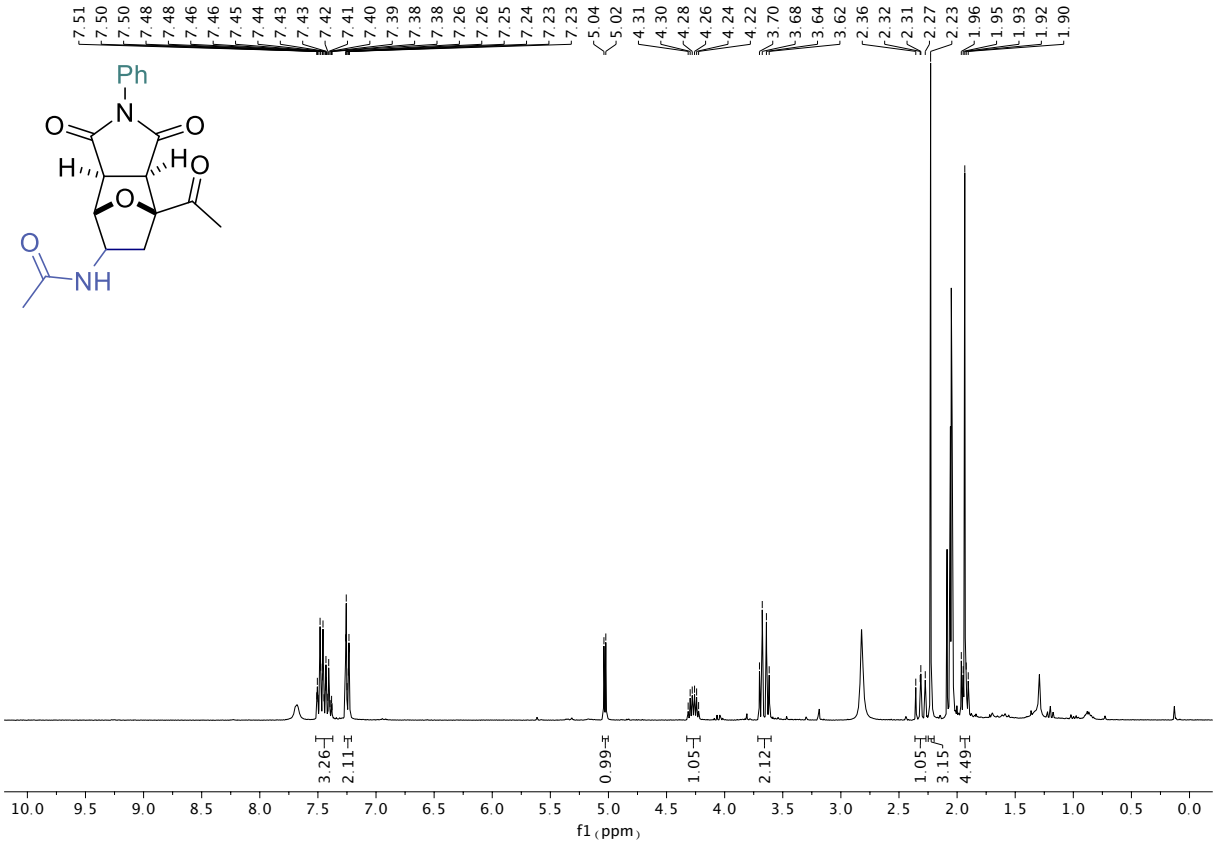


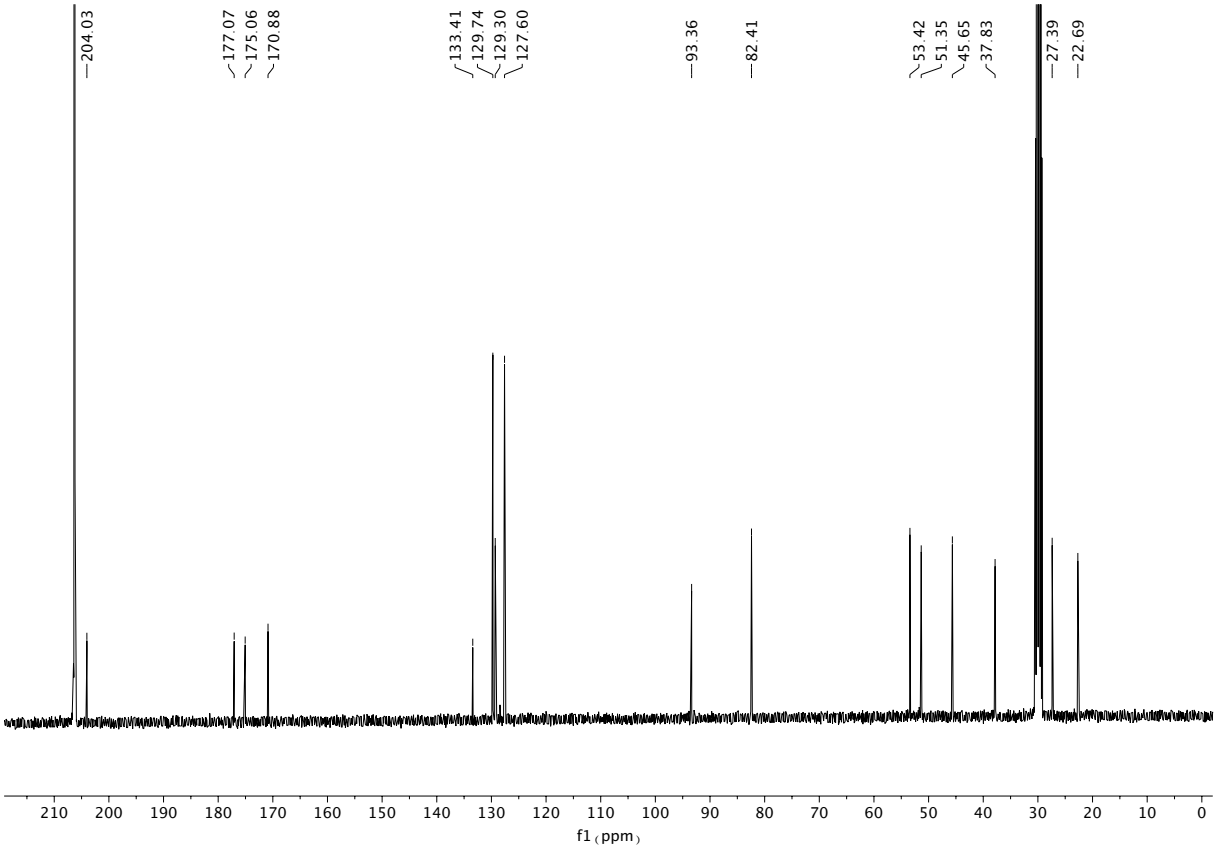
NOESY and attributed correlations of product 4



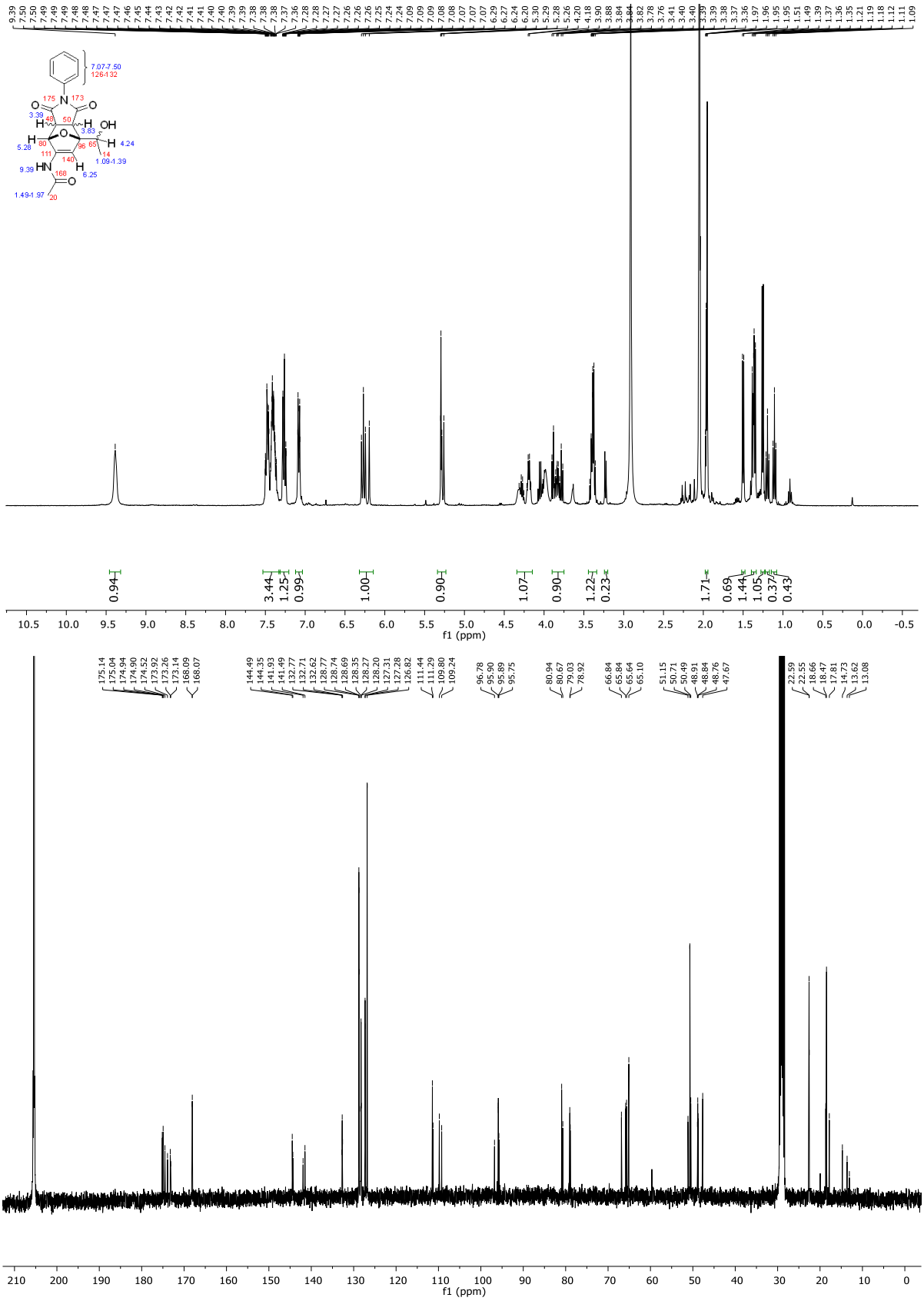


^{1}H and ^{13}C NMR of product 5

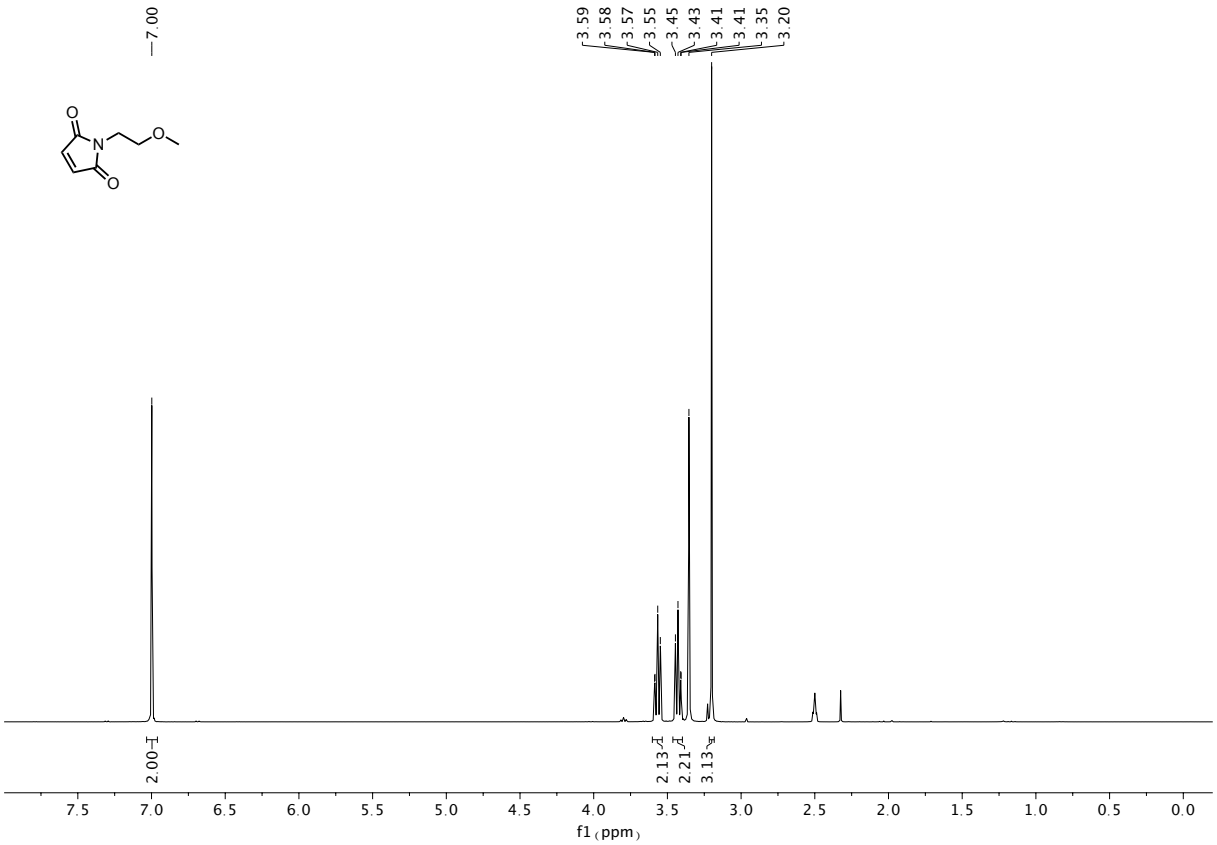


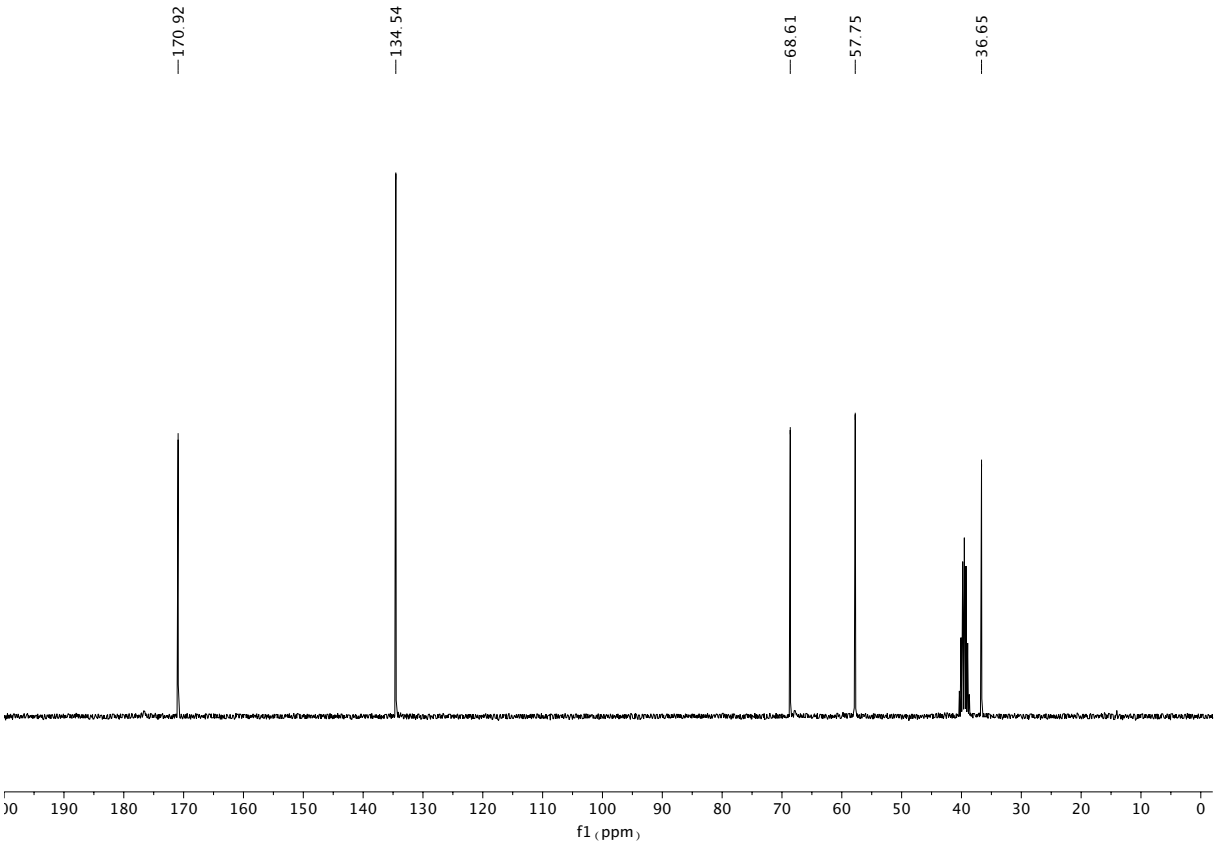


^{1}H and ^{13}C NMR of product 8



^{1}H and ^{13}C NMR of 1-(2-methoxyethyl)-1H-pyrrole-2,5-dione





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