Support Information

Sequential (3+2) cycloaddition and (5+n) annulation reactions for modular synthesis of dihydrobenzoxazines, tetrahydrobenzoxazepines and tetrahydrobenzoxazocines

Alex Muthengi,[a] Xiaofeng Zhang,[a] Gagan Dhawan,[b] Wenshen Zhang,[c] Francesca Corsini,[a] Wei Zhang[a]*

Content

1. General information

Chemicals and solvents were purchased from commercial suppliers and used as received. ^{1}H NMR (400 MHz) and ^{13}C NMR spectra (101 MHz) were recorded on Agilent NMR spectrometers. The chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.26) and carbon (chloroform δ 77.0). Multiplicities were indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), br s (broad singlet). Coupling constants were reported in hertz (Hz).

For compounds **6b** and **6c**, NMR experiments were performed in dimethyl sulfoxide-d_6. The residual DMSO ^{1}H NMR and ^{13}C signals were observed at 2.49 ppm and 40 ppm respectively.

LC–MS was performed on an Agilent 2100 LC with a 6130 quadrupole MS spectrometer, and a C18 column (5.0 μm, 6.0 × 50 mm) was used for separation. The mobile phases were MeOH and water; both containing 0.01% trifluoroacetic acid. A linear gradient of 50:50 (v/v) MeOH/H_2O to 100% MeOH was used over 7.0 min at a flow rate of 0.7 mL/min. The chromatograms were detected at UV wavelengths 210, 254, and 365 nm. Low resolution mass spectra were recorded in APCI (atmospheric pressure chemical ionization). The microwave reactions were performed on a Biotage Initiator 8 system. The final products were purified on Angela HP-100 pre-LC system with a Venusil PrepG C18 column (10 μm, 120 Å, 21.2 mm x 250 mm).

HRMS was analyzed by RP-LC-MS: 1 μL of each sample was combined and 500 mL of optima grade MeCN (0.1 % formic acid) and 500 mL of optima grade H_2O (0.1 % formic acid) were added to the mixture. This mixture was then diluted by another factor of 10 with a 75/25 mixture of the optima grade MeCN and H_2O. 1 mL (10 fmol of each on column) of this mixture was analyzed by RP-LC-MS.

2. General procedure for (3+2) cycloaddition & (5+n) annulation reactions for 4, 5, 6, 7 & 8

Representative procedure for (3+2) cycloaddition: A reaction vial was charged with the corresponding D-alanine methyl ester, glycine methyl ester or L-phenylalanine methyl ester **1** (1.2 mmol), maleimide or *E*-dimethyl fumarate **2** (1.1 mmol) and salicylaldehyde **3** (1.0 mmol). Then, it was dissolved in 2.5 mL of CH_3CN and heated under microwave irridiation at 125 ^{o}C for 30 min. The reaction mixture was kept for 2-3 h and a solid product was formed, washed with 1 mL of water, filtered and dried.

Note: Those products which did not form the solid products on cooling were concentrated and washed 2 times with 1 mL of water to obtain intermediate **4**. The intermediate products were used for the next reaction without further purification.

Representative procedure for (5+n) Annulations:

To a solution of (3+2) cycloaddition adduct **4** (39:1 dr, 1 mmol, 1 equiv.), 1,2-dibromoethane/ 1,3-dibromopropane (2.0 mmol, 2.0 equiv.) or *di(1H*-imidazol-1-yl)methanone (1.5 mmol, 1.5 equiv.) and K_2CO_3 (2.5 mmol, 2.5 equiv.) in 2.0 mL of CH_3CN. The reaction mixture was heated in a sealed reaction vial at 115 ^{o}C for 3.5-4 h for synthesis of compounds **5**, **7** and **8**. Compounds **6** were heated in a sealed reaction vial at 95 ^{o}C for 6 h. The completion of the reaction was

detected using LC-MS. The solvent was then removed under reduced pressure and the residue purified using flash chromatography or Angela HP-100 pre-LC system using a 70:30 mixture of MeOH/Water as eluent to provide the desired products **5, 7** and **8**. Products **6a-6c** were precipitated out from reaction mixture, and no further purification was required.

3. Characterization of products 5, 6, 7 and 8.

*Methyl (8R,8aS,11aR,11bS)-10-ethyl-2,8-dimethyl-9,11-dioxo-8a,9,10,11,11a,11b-hexahydro-6H,8H-benzo[e]pyrrolo[3',4':3,4]pyrrolo[1,2-c][1,3]oxazine-8-carboxylate (**5a**):* white solid (83% yield). MP: 136-138 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 1H), 6.91 (d, J = 8.0 Hz, 1H), 6.63 (d, J = 8.3 Hz, 1H), 5.04 (d, J = 9.2 Hz, 1H), 4.87 (d, J = 9.5 Hz, 1H), 4.66 (d, J = 9.5 Hz, 1H), 3.82 (d, J = 9.3 Hz, 1H), 3.52 (s, 3H), 3.42 (q, J = 7.2 Hz, 2H), 3.33 (d, J = 9.3 Hz, 1H), 2.31 (s, 3H), 1.59 (s, 3H), 1.02 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0, 174.0, 172.1, 151.7, 129.6, 129.3, 128.6, 120.1, 116.4, 67.4, 59.3, 55.7, 52.4, 46.5, 46.4, 33.9, 21.0, 20.7, 12.7. HRMS (ESI) m/z: $(M+H)^+$ Calcd for $C_{19}H_{22}N_2O_5$ 359.16073, found 359.1608.

*Methyl (8R,8aS,11aR,11bS)-10-cyclohexyl-8-methyl-9,11-dioxo-8a,9,10,11,11a,11b-hexahydro-6H,8H-benzo[e]pyrrolo[3',4':3,4]pyrrolo[1,2-c][1,3]oxazine-8-carboxylate (**5b**):* yellow oil (81% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 – 7.06 (m, 2H), 6.77 (dd, J = 22.7, 7.5 Hz, 2H), 5.07 (d, J = 9.1 Hz, 1H), 4.87 (dd, J = 9.6, 3.2 Hz, 1H), 4.70 (d, J = 9.6 Hz, 1H), 3.84 (d, J = 3.0 Hz, 2H), 3.82 – 3.79 (m, 2H), 3.49 (s, 3H), 2.00 – 1.91 (m, 3H), 1.74 (s, 3H), 1.18 (ddd, J = 18.8, 11.1, 4.7 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3, 174.2, 172.1, 157.9, 128.9, 127.9, 120.4, 119.3, 116.8, 67.4, 62.7, 59.4, 55.4, 54.0, 52.3, 51.9, 47.8, 46.1, 28.4, 25.8, 25.0, 21.2. HRMS (ESI) m/z: $(M+H)^+$ Calcd for $C_{22}H_{26}N_2O_5$ 399.19203, found 399.1909.

*Methyl (8R,8aS,11aR,11bS)-2-methoxy-8,10-dimethyl-9,11-dioxo-8a,9,10,11,11a,11b-hexahydro-6H,8H-benzo[e]pyrrolo[3',4':3,4]pyrrolo[1,2-c][1,3]oxazine-8-carboxylate (**5c**):* white solid (85% yield). MP: 190-192 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, J = 2.7 Hz, 1H), 6.69 – 6.62 (m, 2H), 5.15 (d, J = 9.6 Hz, 1H), 4.88 (d, J = 9.9 Hz, 1H), 4.67 (d, J = 10.0 Hz, 1H), 3.90 (t, J = 9.6 Hz, 1H), 3.82 (s, 3H), 3.50 (s, 3H), 3.37 (d, J = 9.5 Hz, 1H), 2.86 (s, 3H), 1.62 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 174.2, 172.3, 153.2, 148.0, 121.1, 117.3, 114.6, 113.5, 75.8, 67.3, 59.8, 55.9, 55.7, 52.6, 46.7, 25.0, 21.5. HRMS (ESI) m/z: $(M+H)^+$ Calcd for $C_{18}H_{20}N_2O_6$ 361.1400, found 361.1390.

*Methyl (8R,8aS,11aR,11bS)-8-methyl-9,11-dioxo-10-phenyl-8a,9,10,11,11a,11b-hexahydro-6H,8H-benzo[e]pyrrolo[3',4':3,4]pyrrolo[1,2-c][1,3]oxazine-8-carboxylate (**5d**):* orange oil (79% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 – 7.34 (m, 3H), 7.33 – 7.28 (m, 2H), 7.12 – 7.08 (m, 2H), 6.96 (td, J = 7.5, 1.2 Hz, 1H), 6.84 (dd, J = 8.2, 1.2 Hz, 1H), 4.99 (d, J = 8.3 Hz, 1H), 4.82 (d, J = 8.3 Hz, 1H), 4.51 (d, J = 7.4 Hz, 1H), 4.07 (d, J = 7.7 Hz, 1H), 3.80 (s, 3H), 3.75 – 3.70 (m, 1H), 1.72 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.08, 173.30, 173.06, 153.63, 131.58, 129.09, 129.04, 128.96, 128.82, 128.55, 128.54, 126.39, 120.50, 119.50, 117.18, 68.16, 67.41, 60.65, 52.73, 51.06, 45.69, 18.90. HRMS (ESI) m/z: $(M+H)^+$ Calcd for $C_{22}H_{20}N_2O_5$ 393.14508, found 393.1441.

*Methyl (8R,8aS,11aR,11bS)-2-bromo-10-ethyl-8-methyl-9,11-dioxo-8a,9,10,11,11a,11b-hexahydro-6H,8H-benzo[e]pyrrolo[3',4':3,4]pyrrolo[1,2-c][1,3]oxazine-8-carboxylate (**5e**):*

yellow oil (71% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.72 (dd, J = 2.4, 1.0 Hz, 1H), 7.20 (ddd, J = 8.7, 2.4, 0.9 Hz, 1H), 6.61 (d, J = 8.7 Hz, 1H), 5.09 (d, J = 9.5 Hz, 1H), 4.90 (d, J = 9.9 Hz, 1H), 4.68 (d, J = 9.9 Hz, 1H), 3.85 (d, J = 3.5 Hz, 1H), 3.49 (s, 3H), 3.44 (q, J = 7.2 Hz, 2H), 3.35 (d, J = 9.5 Hz, 1H), 1.61 (s, 3H), 1.03 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.78, 173.69, 172.03, 153.22, 131.87, 130.84, 122.39, 118.44, 112.67, 75.93, 67.37, 59.05, 55.67, 52.54, 46.44, 34.00, 21.53, 12.69. HRMS (ESI) m/z: $(M+H)^+$ Calcd for $C_{18}H_{19}N_2O_5Br$ 423.05559, found 423.0547.

*Methyl (8R,8aS,11aR,11bS)-10-ethyl-2,8-dimethyl-9,11-dioxo-6-phenyl-8a,9,10,11,11a,11b-hexahydro-6H,8H-benzo[e]pyrrolo[3',4':3,4]pyrrolo[1,2-c][1,3]oxazine-8-carboxylate **(5f)**:* yellow solid (81% yield). MP: 150-153 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 7.8 Hz, 2H), 7.28 (d, J = 6.9 Hz, 1H), 7.26 – 7.19 (m, 3H), 6.86 (d, J = 8.0 Hz, 1H), 6.73 (d, J = 8.2 Hz, 1H), 6.02 (s, 1H), 4.97 (d, J = 10.4 Hz, 1H), 3.96 (t, J = 10.5 Hz, 1H), 3.50 – 3.44 (m, 3H), 3.36 (s, 3H), 2.20 (s, 3H), 1.82 (s, 3H), 1.02 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.2, 174.3, 172.8, 149.9, 138.7, 129.4, 129.2, 129.0, 128.4, 128.4, 126.8, 126.7, 119.9, 116.4, 82.8, 67.8, 55.6, 54.7, 52.2, 47.6, 33.8, 24.7, 20.8, 12.7. HRMS (ESI) m/z: $(M+H)^+$ Calcd for $C_{25}H_{26}N_2O_5$ 435.19203, found 435.1920.

*Methyl (8R,8aS,11aR,11bS)-10-cyclohexyl-8-methyl-9,11-dioxo-6-phenyl-8a,9,10,11,11a,11b-hexahydro-6H,8H-benzo[e]pyrrolo[3',4':3,4]pyrrolo[1,2-c][1,3]oxazine-8-carboxylate **5g**):* white solid (79% yield). MP: 175-178 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.38 (m, 3H), 7.29 – 7.26 (m, 1H), 7.25 – 7.19 (m, 2H), 7.09 – 7.04 (m, 1H), 6.86 – 6.79 (m, 2H), 6.04 (s, 1H), 4.99 (d, J = 10.3 Hz, 1H), 3.93 (t, J = 10.5 Hz, 1H), 3.84 (tt, J = 12.3, 3.9 Hz, 1H), 3.44 (d, J = 10.7 Hz, 1H), 3.33 (s, 3H), 2.01 (dd, J = 15.5, 11.9 Hz, 2H), 1.81 (s, 3H), 1.75 (d, J = 12.7 Hz, 2H), 1.43 (d, J = 12.4 Hz, 2H), 1.30 – 1.11 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4, 174.5, 172.7, 152.3, 138.6, 128.8, 128.7, 128.5, 128.4, 127.8, 127.6, 126.8, 126.5, 120.5, 116.8, 82.9, 67.8, 55.3, 55.2, 52.1, 51.9, 51.7, 47.3, 47.1, 28.4, 25.7, 24.8. HRMS (ESI) m/z: $(M+H)^+$ Calcd for $C_{28}H_{30}N_2O_5$ 475.22333, found 475.2235.

*Methyl (8R,8aS,11aR,11bS)-10-cyclohexyl-8-methyl-6,9,11-trioxo-8a,9,10,11,11a,11b-hexahydro-6H,8H-benzo[e]pyrrolo[3',4':3,4]pyrrolo[1,2-c][1,3]oxazine-8-carboxylate **6a**):*
white solid (87% yield). MP: 230-234 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 7.7 Hz, 1H), 7.35 (t, J = 7.8 Hz, 1H), 7.22 (t, J = 7.6 Hz, 1H), 7.05 (d, J = 8.2 Hz, 1H), 5.29 (d, J = 6.9 Hz, 1H), 3.89 – 3.78 (m, 2H), 3.69 (s, 3H), 3.21 (d, J = 8.3 Hz, 1H), 1.99 (h, J = 12.1 Hz, 2H), 1.80 (s, 3H), 1.77 (d, J = 10.6 Hz, 1H), 1.56 (d, J = 21.8 Hz, 4H), 1.19 (dq, J = 26.3, 15.4, 12.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9, 172.9, 168.3, 149.1, 147.7, 129.8, 128.2, 128.0, 116.3, 115.4, 68.3, 57.7, 57.5, 53.1, 52.6, 52.4, 46.5, 46.3, 28.7, 25.7, 24.8, 20.9. HRMS (ESI) m/z: $(M+H)^+$ Calcd for $C_{22}H_{24}N_2O_6$ 413.1713, found 413.1717.

*Methyl (8R,8aS,11aR,11bS)-4,8,10-trimethyl-6,9,11-trioxo-8a,9,10,11,11a,11b-hexahydro-6H,8H-benzo[e]pyrrolo[3',4':3,4]pyrrolo[1,2-c][1,3]oxazine-8-carboxylate **6b**):* white solid (92% yield). MP: 270-273 °C. ^{1}H NMR (400 MHz, DMSO) δ 7.44 (d, J = 7.7 Hz, 1H), 7.16 (d, J = 7.5 Hz, 1H), 7.06 (t, J = 7.6 Hz, 1H), 5.41 (d, J = 6.8 Hz, 1H), 4.18 (t, J = 7.4 Hz, 1H), 3.47 (s, 3H), 3.14 (d, J = 5.1 Hz, 1H), 2.69 (s, 3H), 2.16 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 175.2, 174.5, 169.1, 147.6, 147.2, 130.8, 130.6, 126.8, 124.5, 117.0, 68.0, 57.4, 53.9,

52.9, 47.5, 25.1, 20.6, 15.9. HRMS (ESI) m/z: $(M+H)^+$ Calcd for $C_{18}H_{18}N_2O_6$ 359.12435, found 359.1238.

Methyl (8R,8aS,11aR,11bS)-10-ethyl-2,8-dimethyl-6,9,11-trioxo-8a,9,10,11,11a,11b-hexahydro-6H,8H-benzo[e]pyrrolo[3',4':3,4]pyrrolo[1,2-c][1,3]oxazine-8-carboxylate ***6c****):* white solid (91% yield). MP: 244-245 °C. ^{1}H NMR (400 MHz, DMSO) δ 7.47 (d, J = 2.1 Hz, 1H), 7.14 (dd, J = 8.4, 2.0 Hz, 1H), 6.92 (d, J = 8.3 Hz, 1H), 5.42 (d, J = 6.9 Hz, 1H), 4.20 (t, J = 7.5 Hz, 1H), 3.49 (s, 3H), 3.41 (d, J = 8.0 Hz, 1H), 3.27 (ddd, J = 21.9, 12.9, 6.1 Hz, 2H), 2.33 (s, 3H), 1.63 (s, 3H), 0.96 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 174.9, 174.3, 169.1, 147.8, 147.0, 132.7, 130.1, 129.2, 117.0, 115.5, 67.9, 57.3, 57.2, 53.7, 52.8, 47.2, 33.8, 20.9, 12.8. HRMS (ESI) m/z: $(M+H)^+$ Calcd for $C_{19}H_{20}N_2O_6$ 373.1400, found 373.1395.

*Methyl (9R,9aS,12aR,12bS)-9,11-dimethyl-10,12-dioxo-6,7,9a,10,11,12,12a,12b-octahydro-9H-benzo[f]pyrrolo[3',4':3,4]pyrrolo[1,2-d][1,4]oxazepine-9-carboxylate (****7a****):* yellow oil (79% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 7.7 Hz, 1H), 7.23 (t, J = 7.5 Hz, 1H), 7.15 – 7.07 (m, 1H), 6.98 (d, J = 8.0 Hz, 1H), 4.57 (d, J = 7.4 Hz, 1H), 4.30 (td, J = 10.5, 6.9 Hz, 1H), 3.92 – 3.85 (m, 2H), 3.80 (s, 3H), 3.56 – 3.38 (m, 2H), 3.16 (d, J = 7.6 Hz, 1H), 2.86 (s, 3H), 1.49 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.8, 174.6, 172.2, 155.5, 130.2, 128.9, 127.4, 123.2, 119.6, 70.7, 70.4, 67.4, 54.0, 52.6, 47.7, 44.2, 25.1, 15.3. HRMS (ESI) m/z: $(M+H)^+$ Calcd for $C_{18}H_{20}N_2O_5$ 345.14508, found 345.1448.

*Methyl (9R,9aS,12aR,12bS)-9-benzyl-11-methyl-10,12-dioxo-6,7,9a,10,11,12,12a,12b-octahydro-9H-benzo[f]pyrrolo[3',4':3,4]pyrrolo[1,2-d][1,4]oxazepine-9-carboxylate (****7b****):* white solid (85% yield). MP: 157-160 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 7.6 Hz, 1H), 7.28 (d, J = 6.2 Hz, 2H), 7.24 (d, J = 6.9 Hz, 1H), 7.12 (d, J = 6.4 Hz, 2H), 7.05 – 6.98 (m, 2H), 6.76 (dd, J = 13.7, 6.1 Hz, 1H), 5.07 (dd, J = 8.8, 5.6 Hz, 1H), 4.86 (d, J = 13.7 Hz, 1H), 4.52 (d, J = 6.0 Hz, 1H), 3.87 (s, 3H), 3.74 – 3.67 (m, 1H), 3.48 (d, J = 13.6 Hz, 1H), 3.41 (d, J = 7.6 Hz, 1H), 3.13 (d, J = 13.6 Hz, 1H), 2.76 (s, 3H), 2.43 (d, J = 4.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.7, 174.6, 171.3, 154.9, 148.8, 135.1, 129.6, 129.1, 128.8, 127.4, 127.3, 126.8, 123.3, 115.8, 95.6, 71.2, 55.6, 54.4, 52.3, 52.3, 47.9, 40.3, 24.9. HRMS (ESI) m/z: $(M+H)^+$ Calcd for $C_{24}H_{24}N_2O_5$ 421.17638, found 421.1758.

*Methyl (9R,9aS,12aR,12bS)-11-ethyl-10,12-dioxo-6,7,9a,10,11,12,12a,12b-octahydro-9H-benzo[f]pyrrolo[3',4':3,4]pyrrolo[1,2-d][1,4]oxazepine-9-carboxylate (****7c****):* yellow oil (84% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 7.8 Hz, 1H), 7.21 (d, J = 8.0 Hz, 1H), 7.10 (t, J = 7.5 Hz, 1H), 6.98 (d, J = 8.0 Hz, 1H), 4.23 (dddt, J = 10.8, 9.2, 5.3, 0.8 Hz, 1H), 4.12 (d, J = 6.4 Hz, 1H), 4.02 (dddt, J = 11.6, 4.5, 3.7, 0.8 Hz, 1H), 3.83 (s, 3H), 3.63 – 3.55 (m, 2H), 3.50 – 3.43 (m, 3H), 3.27 – 3.20 (m, 1H), 2.62 (ddd, J = 13.3, 9.2, 4.5 Hz, 1H), 1.08 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3, 174.4, 169.4, 157.1, 130.6, 128.9, 125.9, 122.5, 122.3, 70.6, 70.4, 68.9, 52.3, 50.3, 47.2, 45.6, 34.1, 12.6. HRMS (ESI) m/z: $(M+H)^+$ Calcd for $C_{18}H_{20}N_2O_5$ 345.14508, found 345.1449.

*Methyl (9R,9aS,12aR,12bS)-11-cyclohexyl-9-methyl-10,12-dioxo-6,7,9a,10,11,12,12a,12b-octahydro-9H-benzo[f]pyrrolo[3',4':3,4]pyrrolo[1,2-d][1,4]oxazepine-9-carboxylate (****7d****):* white solid (79% yield). MP: 195-197 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (dd, J = 7.5, 1.5 Hz, 1H), 7.22 (td, J = 7.7, 1.8 Hz, 1H), 7.11 (td, J = 7.4, 1.4 Hz, 1H), 6.98 (dd, J = 8.0, 1.3 Hz, 1H), 4.55

(d, J = 7.5 Hz, 1H), 4.35 – 4.25 (m, 1H), 3.88 – 3.81 (m, 2H), 3.80 (s, 3H), 3.33 (t, J = 7.5 Hz, 1H), 3.08 (d, J = 7.5 Hz, 1H), 2.92 (ddd, J = 13.8, 6.7, 1.3 Hz, 1H), 2.73 (ddd, J = 13.7, 10.9, 5.5 Hz, 1H), 2.03 – 1.86 (m, 2H), 1.72 (d, J = 12.9 Hz, 2H), 1.56 (d, J = 7.5 Hz, 3H), 1.46 (s, 3H), 1.27 – 1.05 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.8, 174.7, 172.3, 155.5, 130.2, 128.9, 127.8, 123.4, 123.2, 70.9, 70.3, 67.6, 53.7, 52.4, 52.0, 47.2, 43.7, 28.3, 28.1, 25.8, 25.8, 25.0, 15.3. HRMS (ESI) m/z: $(M+H)^+$ Calcd for $C_{23}H_{28}N_2O_5$ 413.20768, found 413.2079.

*Methyl (9R,9aS,12aR,12bS)-2-bromo-11-ethyl-9-methyl-10,12-dioxo-6,7,9a,10,11,12,12a,12b-octahydro-9H-benzo[f]pyrrolo[3',4':3,4]pyrrolo[1,2-d][1,4]oxazepine-9-carboxylate (**7e**):* yellow oil (57% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 3.0 Hz, 1H), 7.31 (dd, J = 8.4, 2.7 Hz, 1H), 6.86 (d, J = 8.6 Hz, 1H), 4.49 (d, J = 7.3 Hz, 1H), 4.31 – 4.25 (m, 1H), 3.86 – 3.83 (m, 1H), 3.80 (s, 3H), 3.71 (d, J = 5.6 Hz, 1H), 3.45 – 3.36 (m, 3H), 3.13 (d, J = 7.5 Hz, 1H), 2.93 – 2.87 (m, 1H), 1.47 (s, 3H), 1.04 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 174.1, 171.9, 154.7, 132.9, 131.9, 129.9, 125.2, 115.8, 70.9, 70.3, 67.0, 53.8, 52.5, 47.5, 43.7, 34.0, 15.4, 12.6. HRMS (ESI) m/z: $(M+H)^+$ Calcd for $C_{19}H_{21}N_2O_5Br$ 437.07124, found 437.0702.

*Methyl (9R,9aS,12aR,12bS)-11-ethyl-2,9-dimethyl-10,12-dioxo-6,7,9a,10,11,12,12a,12b-octahydro-9H-benzo[f]pyrrolo[3',4':3,4]pyrrolo[1,2-d][1,4]oxazepine-9-carboxylate (**7f**):* orange oil (89% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 – 7.00 (m, 2H), 6.87 (d, J = 8.2 Hz, 1H), 4.51 (d, J = 7.4 Hz, 1H), 4.31 – 4.21 (m, 1H), 3.80 (s, 3H), 3.46 – 3.34 (m, 4H), 3.12 (d, J = 7.5 Hz, 1H), 2.34 (s, 3H), 2.28 (d, J = 7.9 Hz, 2H), 1.47 (s, 3H), 1.04 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.6, 174.4, 172.2, 153.2, 132.6, 129.6, 127.3, 123.1, 117.0, 70.3, 68.2, 67.5, 53.9, 48.1, 47.5, 43.7, 33.9, 20.3, 15.3, 12.5. HRMS (ESI) m/z: $(M+H)^+$ Calcd for $C_{20}H_{24}N_2O_5$ 373.17638, found 373.1761.

*Methyl (9R,9aS,12aR,12bS)-2-methoxy-9-methyl-10,12-dioxo-11-propyl-6,7,9a,10,11,12,12a,12b-octahydro-9H-benzo[f]pyrrolo[3',4':3,4]pyrrolo[1,2-d][1,4]oxazepine-9-carboxylate (**7g**):* yellow oil (89% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (d, J = 8.6 Hz, 1H), 6.82 – 6.73 (m, 2H), 4.49 (d, J = 7.5 Hz, 1H), 4.24 (td, J = 10.6, 7.1 Hz, 1H), 3.80 (s, 6H), 3.36 (dt, J = 15.0, 7.4 Hz, 3H), 3.13 (d, J = 7.8 Hz, 1H), 2.88 (dd, J = 13.7, 7.0 Hz, 1H), 2.71 (ddd, J = 14.1, 10.9, 5.6 Hz, 1H), 1.62 (s, 3H), 1.48 – 1.46 (m, 3H), 0.84 (t, J = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.8, 174.5, 172.1, 155.2, 149.1, 128.6, 124.0, 115.1, 113.9, 70.3, 67.6, 55.6, 53.8, 52.4, 47.4, 43.6, 40.6, 20.9, 20.7, 15.2, 10.9. HRMS (ESI) m/z: $(M+H)^+$ Calcd for $C_{21}H_{26}N_2O_6$ 403.18695, found 403.1869.

*Trimethyl(1R,2S,3R,11bS)-3-methyl-1,2,3,5,6,11b-hexahydrobenzo[f]pyrrolo[1,2-d][1,4]oxazepine-1,2,3-tricarboxylate (**7h**):* colorless oil (90% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, J = 7.8, 1.6 Hz, 1H), 7.26 – 7.18 (m, 1H), 7.15 – 7.06 (m, 1H), 7.00 (dd, J = 7.8, 1.4 Hz, 1H), 4.64 (d, J = 9.6 Hz, 1H), 4.34 (ddd, J = 11.5, 6.0, 2.8 Hz, 1H), 4.23 (dd, J = 11.1, 9.6 Hz, 1H), 3.72 (s, 3H), 3.71 (s, 3H), 3.67 – 3.61 (m, 1H), 3.53 (s, 3H), 3.48 (d, J = 4.3 Hz, 1H), 3.05 (ddd, J = 13.2, 7.5, 2.8 Hz, 1H), 2.93 (ddd, J = 13.1, 6.1, 2.3 Hz, 1H), 1.67 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 172.7, 170.9, 158.1, 131.0, 128.9, 126.5, 123.8, 121.1, 72.6, 69.5, 65.5, 56.2, 52.5, 52.3, 51.9, 48.1, 46.6, 21.2. HRMS (ESI) m/z: $(M+H)^+$ Calcd for $C_{19}H_{23}NO_7$ 378.15531, found 378.1543.

*Methyl (10R,10aS,13aR,13bS)-10,12-dimethyl-11,13-dioxo-7,8,10a,11,12,13,13a,13b-octahydro-6H,10H-benzo[b]pyrrolo[3',4':3,4]pyrrolo[2,1-d][1,5]oxazocine-10-carboxylate (**8a**):* yellow oil (83% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (dddd, J = 7.9, 7.2, 1.8, 0.7 Hz, 1H), 7.23 (dd, J = 7.6, 1.8 Hz, 1H), 7.13 (tt, J = 7.4, 1.1 Hz, 1H), 6.92 (dd, J = 7.9, 1.2 Hz, 1H), 4.54 (ddd, J = 12.2, 10.2, 1.9 Hz, 1H), 4.25 (d, J = 8.6 Hz, 1H), 3.94 – 3.85 (m, 1H), 3.83 (s, 3H), 3.27 (t, J = 8.2 Hz, 1H), 3.09 (d, J = 7.7 Hz, 1H), 2.87 (s, 3H), 2.52 (dd, J = 12.6, 6.9 Hz, 1H), 1.67 – 1.52 (m, 3H), 1.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.9, 174.7, 172.5, 155.4, 132.0, 129.8, 129.8, 124.6, 123.9, 71.6, 71.1, 66.9, 54.2, 52.3, 48.7, 45.0, 25.0, 24.5, 14.2. HRMS (ESI) m/z: $(M+H)^+$ Calcd for $C_{19}H_{22}N_2O_5$ 359.16073, found 359.1599.

*Methyl (10R,10aS,13aR,13bS)-10-benzyl-12-methyl-11,13-dioxo-7,8,10a,11,12,13,13a,13b-octahydro-6H,10H-benzo[b]pyrrolo[3',4':3,4]pyrrolo[2,1-d][1,5]oxazocine-10-carboxylate (**8b**):* white solid (88% yield). MP: 168-170 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (dd, J = 7.6, 1.4 Hz, 1H), 7.27 (d, J = 7.3 Hz, 2H), 7.25 – 7.20 (m, 2H), 7.13 (dd, J = 7.7, 1.6 Hz, 2H), 6.90 (d, J = 7.7 Hz, 2H), 6.14 (ddt, J = 17.2, 10.5, 5.2 Hz, 1H), 5.48 (d, J = 18.9 Hz, 1H), 5.32 (d, J = 10.6 Hz, 1H), 5.09 (d, J = 9.0 Hz, 1H), 4.70 – 4.66 (m, 2H), 3.87 (s, 3H), 3.76 – 3.70 (m, 1H), 3.49 – 3.38 (m, 2H), 3.13 (d, J = 13.6 Hz, 1H), 2.75 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.9, 174.7, 171.4, 156.5, 135.3, 133.5, 129.6, 129.0, 128.7, 127.3, 126.6, 126.0, 120.7, 117.4, 111.3, 71.3, 69.2, 56.2, 54.6, 52.3, 47.9, 40.3, 24.9. HRMS (ESI) m/z: $(M+H)^+$ Calcd for $C_{25}H_{26}N_2O_5$ 435.19203, found 435.1915.

*Methyl (10R,10aS,13aR,13bS)-10-benzyl-12-ethyl-11,13-dioxo-7,8,10a,11,12,13,13a,13b-octahydro-6H,10H-benzo[b]pyrrolo[3',4':3,4]pyrrolo[2,1-d][1,5]oxazocine-10-carboxylate (**8c**):* white solid (82% yield). MP: 120-123 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (ddd, J = 7.4, 1.7, 0.7 Hz, 1H), 7.29 – 7.26 (m, 1H), 7.25 – 7.20 (m, 3H), 7.13 – 7.10 (m, 2H), 6.92 – 6.85 (m, 2H), 6.20 – 6.10 (m, 1H), 5.50 (dq, J = 17.2, 1.6 Hz, 1H), 5.33 (dq, J = 10.5, 1.5 Hz, 1H), 5.13 (dd, J = 9.1, 5.5 Hz, 1H), 4.74 – 4.65 (m, 2H), 3.87 (s, 3H), 3.71 (dd, J = 9.1, 7.5 Hz, 1H), 3.47 (d, J = 13.6 Hz, 1H), 3.39 – 3.22 (m, 3H), 3.12 (d, J = 13.6 Hz, 1H), 2.35 (d, J = 5.5 Hz, 1H), 0.93 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.6, 174.4, 171.4, 156.4, 135.2, 133.6, 129.6, 128.9, 128.8, 127.3, 126.4, 126.2, 120.5, 117.2, 111.2, 71.1, 69.1, 55.4, 54.3, 52.2, 52.1, 47.4, 47.3, 40.3, 33.8, 12.9. HRMS (ESI) m/z: $(M+H)^+$ Calcd for $C_{26}H_{28}N_2O_5$ 449.20768, found 449.2066.

*Methyl (10R,10aS,13aR,13bS)-12-cyclohexyl-10-methyl-11,13-dioxo-7,8,10a,11,12,13,13a,13b-octahydro-6H,10H-benzo[b]pyrrolo[3',4':3,4]pyrrolo[2,1-d][1,5]oxazocine-10-carboxylate (**8d**):* white solid (82% yield). MP: 161-163 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (dd, J = 7.6, 1.7 Hz, 1H), 7.22 (dd, J = 7.6, 1.7 Hz, 1H), 7.12 (dd, J = 7.4, 1.3 Hz, 1H), 6.91 (dd, J = 7.9, 1.2 Hz, 1H), 4.57 – 4.49 (m, 1H), 4.23 (d, J = 8.6 Hz, 1H), 3.93 – 3.86 (m, 1H), 3.82 (s, 3H), 3.79 (dd, J = 12.3, 3.9 Hz, 1H), 3.22 – 3.15 (m, 1H), 3.00 (d, J = 7.9 Hz, 1H), 2.91 – 2.83 (m, 1H), 2.51 (dd, J = 12.4, 6.9 Hz, 1H), 2.02 – 1.87 (m, 2H), 1.78 – 1.70 (m, 2H), 1.65 – 1.53 (m, 5H), 1.41 (s, 3H), 1.26 – 1.10 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.9, 174.5, 172.6, 155.4, 132.2, 129.8, 129.7, 124.6, 123.6, 71.3, 71.2, 67.1, 53.8, 52.2, 51.9, 48.3, 45.3, 28.2, 28.0, 25.9, 25.9, 25.0, 24.4, 14.2. HRMS (ESI) m/z: $(M+H)^+$ Calcd for $C_{24}H_{30}N_2O_5$ 427.22333, found 427.2227.

Methyl (10R,10aS,13aR,13bS)-4,10,12-trimethyl-11,13-dioxo-7,8,10a,11,12,13,13a,13b-octahydro-6H,10H-benzo[b]pyrrolo[3',4':3,4]pyrrolo[2,1-d][1,5]oxazocine-10-carboxylate. ***(8e)****:* white solid (92% yield). MP: 160-162 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, J = 7.8 Hz, 1H), 7.06 – 6.98 (m, 2H), 4.50 (t, J = 11.3 Hz, 1H), 4.24 (d, J = 8.7 Hz, 1H), 3.97 (d, J = 10.3 Hz, 1H), 3.84 (s, 3H), 3.30 – 3.22 (m, 1H), 3.09 (d, J = 7.7 Hz, 1H), 2.98 – 2.87 (m, 1H), 2.86 (s, 3H), 2.50 (dd, J = 12.4, 6.7 Hz, 1H), 2.20 (s, 3H), 1.60 – 1.45 (m, 2H), 1.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.9, 174.7, 172.6, 153.1, 133.4, 131.6, 131.0, 127.4, 123.3, 70.9, 68.9, 67.0, 54.2, 52.2, 48.7, 44.9, 25.0, 24.8, 15.8, 14.2. HRMS (ESI) m/z: $(M+H)^+$ Calcd for $C_{20}H_{24}N_2O_5$ 373.17638, found 373.1755.

*Methyl (10R,10aS,13aR,13bS)-2-methoxy-10-methyl-11,13-dioxo-12-propyl-7,8,10a,11,12,13,13a,13b-octahydro-6H,10H-benzo[b]pyrrolo[3',4':3,4]pyrrolo[2,1-d][1,5]oxazocine-10-carboxylate (****8f****):* white solid (91% yield). MP: 149-151 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 – 6.81 (m, 2H), 6.78 (d, J = 9.5 Hz, 1H), 4.45 (t, J = 11.2 Hz, 1H), 4.17 (d, J = 8.3 Hz, 1H), 3.85 (d, J = 10.3 Hz, 1H), 3.80 (s, 6H), 3.40 – 3.26 (m, 2H), 3.23 (t, J = 8.1 Hz, 1H), 3.04 (d, J = 7.8 Hz, 1H), 2.82 (dd, J = 23.1, 8.3 Hz, 1H), 2.52 (dd, J = 12.4, 6.8 Hz, 1H), 1.69 – 1.48 (m, 4H), 1.43 (s, 3H), 0.88 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.9, 174.5, 172.4, 155.4, 148.9, 132.6, 124.8, 115.4, 113.9, 71.4, 71.1, 66.9, 55.4, 53.9, 52.2, 48.6, 45.2, 40.7, 24.3, 20.5, 14.2, 11.2. HRMS (ESI) m/z: $(M+H)^+$ Calcd for $C_{22}H_{28}N_2O_6$ 417.2026, found 417.2020.

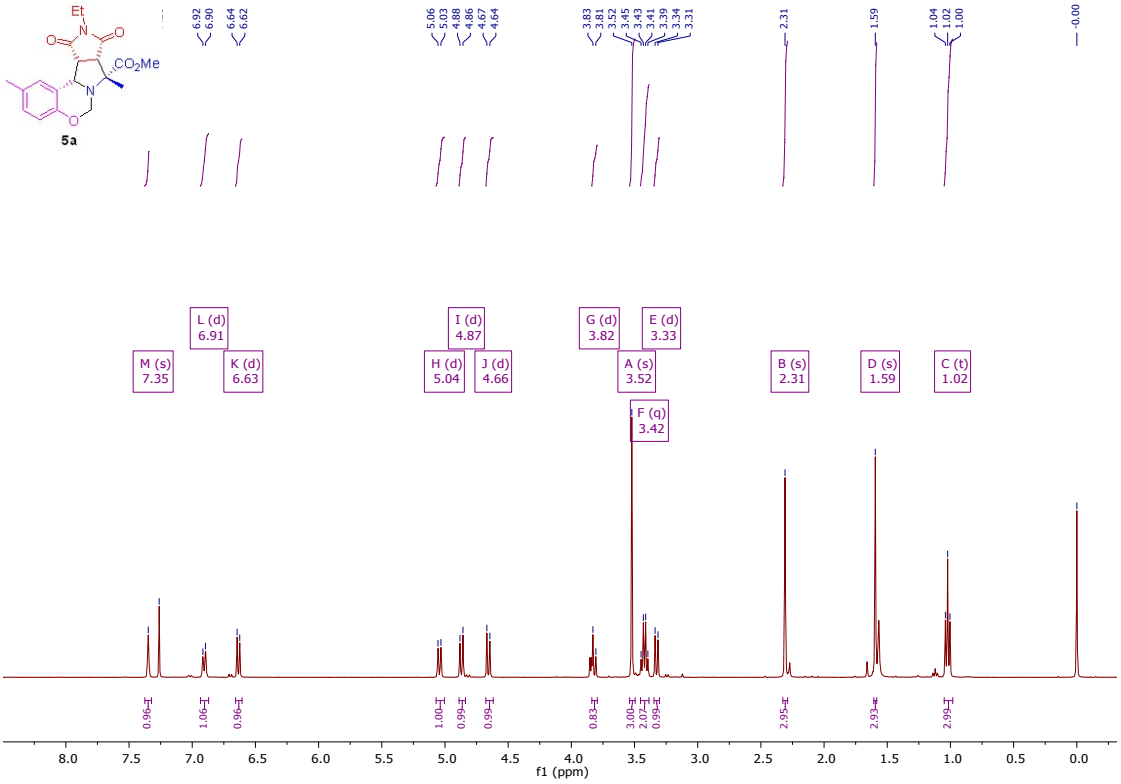
Methyl (10R,10aS,13aR,13bS)-12-ethyl-2,10-dimethyl-11,13-dioxo-7,8,10a,11,12,13,13a,13b-octahydro-6H,10H-benzo[b]pyrrolo[3',4':3,4]pyrrolo[2,1-d][1,5]oxazocine-10-carboxylate ***(8g)****:* white solid (90% yield). MP: 138-141 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (dd, J = 8.2, 2.0 Hz, 1H), 6.87 (d, J = 2.0 Hz, 1H), 6.70 (d, J = 8.2 Hz, 1H), 5.76 – 5.63 (m, 1H), 5.11 – 5.00 (m, 2H), 4.24 (d, J = 9.6 Hz, 1H), 3.75 (s, 3H), 3.58 – 3.35 (m, 4H), 3.35 – 3.29 (m, 1H), 3.15 (d, J = 8.8 Hz, 1H), 3.05 (dd, J = 14.0, 9.4 Hz, 1H), 2.28 (s, 3H), 1.55 (s, 3H), 1.14 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.5, 173.5, 172.0, 155.2, 132.6, 130.7, 130.0, 128.6, 119.5, 116.8, 69.9, 69.2, 55.2, 52.5, 51.6, 47.7, 34.3, 20.6, 17.1, 12.2. HRMS (ESI) m/z: $(M+H)^+$ Calcd for $C_{21}H_{26}N_2O_5$ 387.19203, found 387.1913.

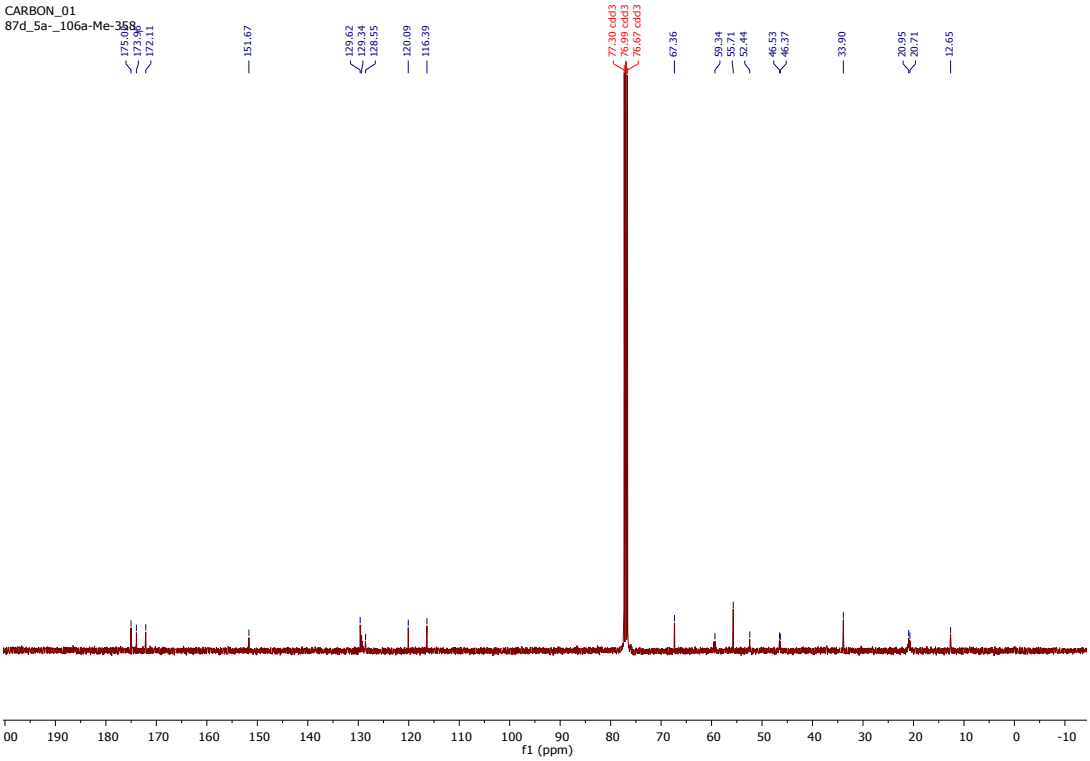
*Methyl (10R,10aS,13aR,13bS)-2-bromo-12-ethyl-10-methyl-11,13-dioxo-7,8,10a,11,12,13,13a,13b-octahydro-6H,10H-benzo[b]pyrrolo[3',4':3,4]pyrrolo[2,1-d][1,5]oxazocine-10-carboxylate (****8h****):* yellow solid (61% yield). MP: 148-150 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.37 (m, 2H), 6.81 – 6.77 (m, 1H), 4.53 (t, J = 12.3 Hz, 1H), 4.16 (d, J = 8.3 Hz, 1H), 3.89 (d, J = 10.2 Hz, 1H), 3.82 (s, 3H), 3.49 – 3.39 (m, 2H), 3.36 (d, J = 7.9 Hz, 1H), 3.22 (t, J = 8.1 Hz, 1H), 3.04 (d, J = 7.9 Hz, 1H), 2.87 – 2.77 (m, 1H), 2.51 (dd, J = 12.5, 7.1 Hz, 1H), 1.66 – 1.58 (m, 1H), 1.42 (s, 3H), 1.10 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.6, 174.3, 172.7, 155.5, 133.0, 131.5, 129.2, 117.8, 113.1, 69.5, 67.3, 56.9, 55.3, 52.6, 48.2, 33.9, 23.9, 22.7, 14.1, 13.0. HRMS (ESI) m/z: $(M+H)^+$ Calcd for $C_{20}H_{23}N_2O_5Br$ 451.08689, found 451.0863.

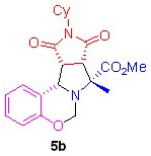
*Trimethyl(1R,2S,3R,12bS)-3-methyl-1,2,3,6,7,12b-hexahydro-5H-benzo[b]pyrrolo[2,1-d][1,5]oxazocine-1,2,3-tricarboxylate (****8i****):* yellow oil (92% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, J = 7.9, 1.5 Hz, 1H), 7.30 (ddt, J = 7.3, 1.4, 0.6 Hz, 1H), 7.16 (dddd, J = 8.0, 7.3, 1.3, 0.7 Hz, 1H), 7.03 (dd, J = 7.9, 1.2 Hz, 1H), 4.83 (d, J = 9.1 Hz, 1H), 4.41 (dt, J = 12.0, 4.0 Hz,

1H), 4.08 – 4.01 (m, 1H), 3.81 – 3.73 (m, 1H), 3.72 (s, 3H), 3.61 (s, 3H), 3.56 (s, 3H), 3.50 – 3.44 (m, 1H), 2.99 (dd, J = 14.5, 8.3 Hz, 1H), 2.38 – 2.30 (m, 1H), 1.96 – 1.79 (m, 2H), 1.66 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 173.3, 171.2, 159.2, 131.3, 129.7, 127.5, 124.6, 122.1, 76.3, 68.7, 59.7, 55.9, 52.3, 52.1, 51.7, 46.9, 43.5, 31.3, 22.5. HRMS (ESI) m/z: $(M+H)^+$ Calcd for $C_{20}H_{25}NO_7$ 392.17096, found 392.1704.

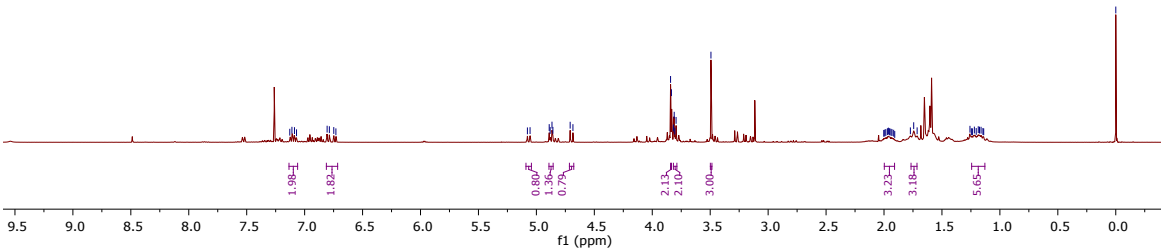
4. NMR Spectra of Products 5, 6, 7 and 8.



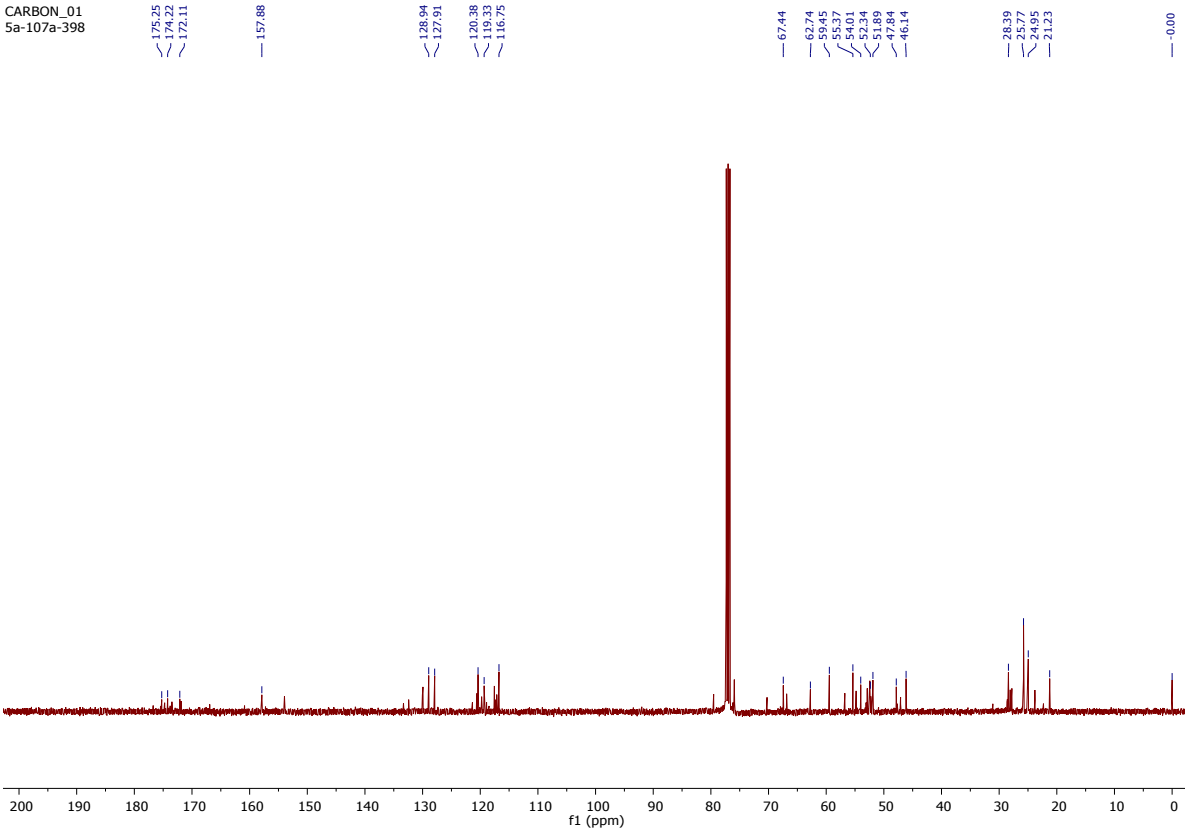


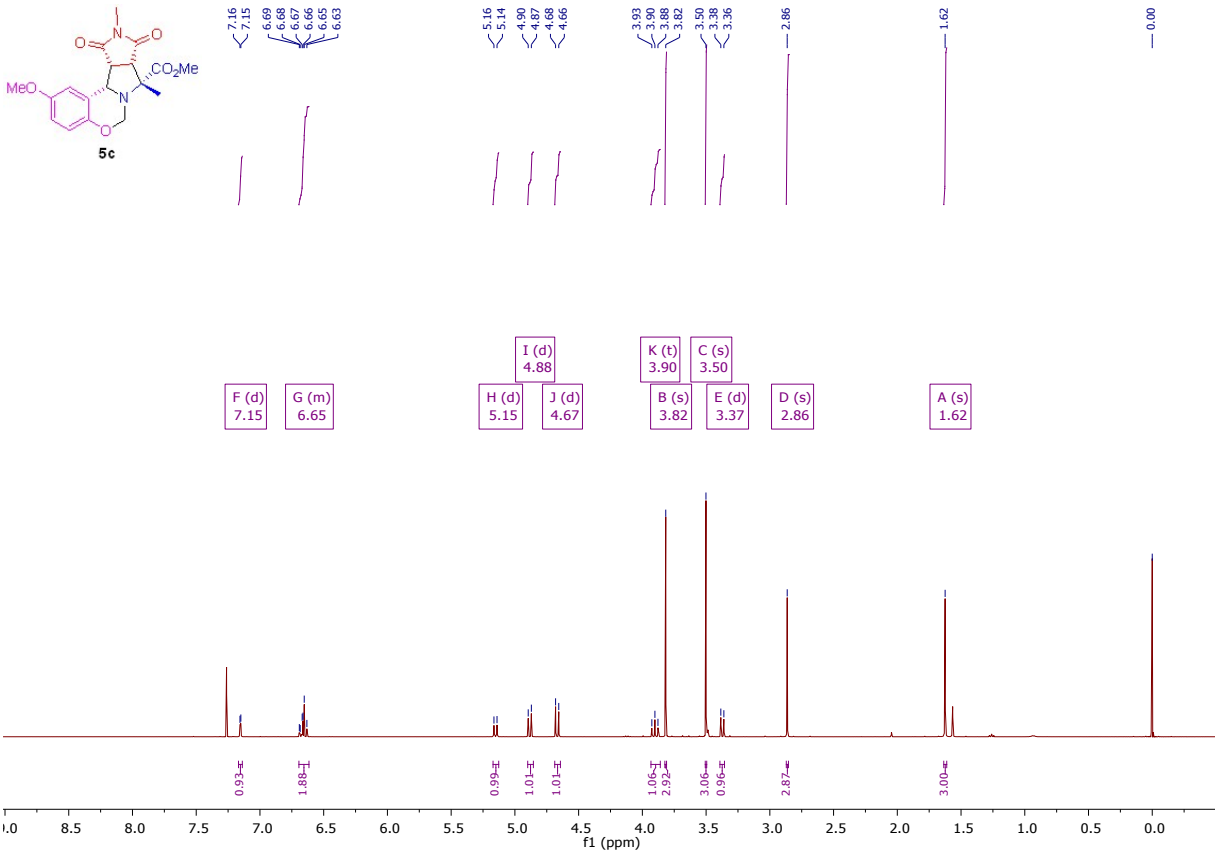


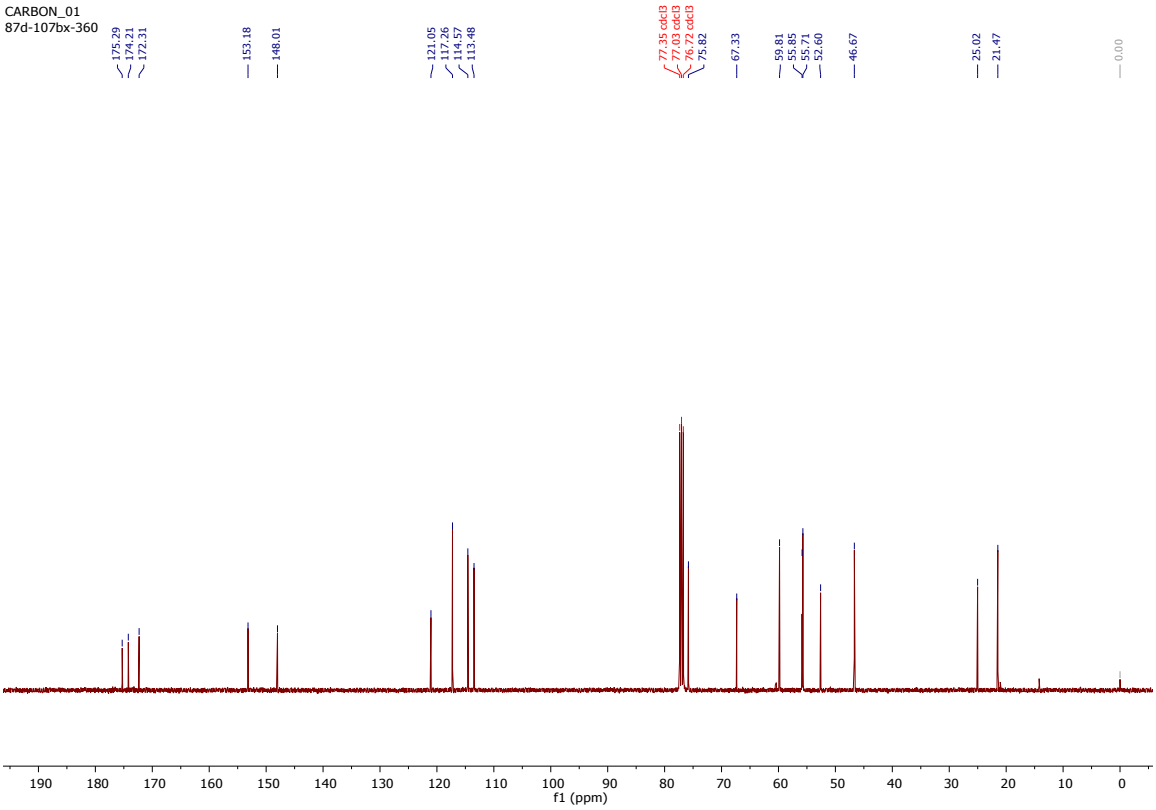
5b

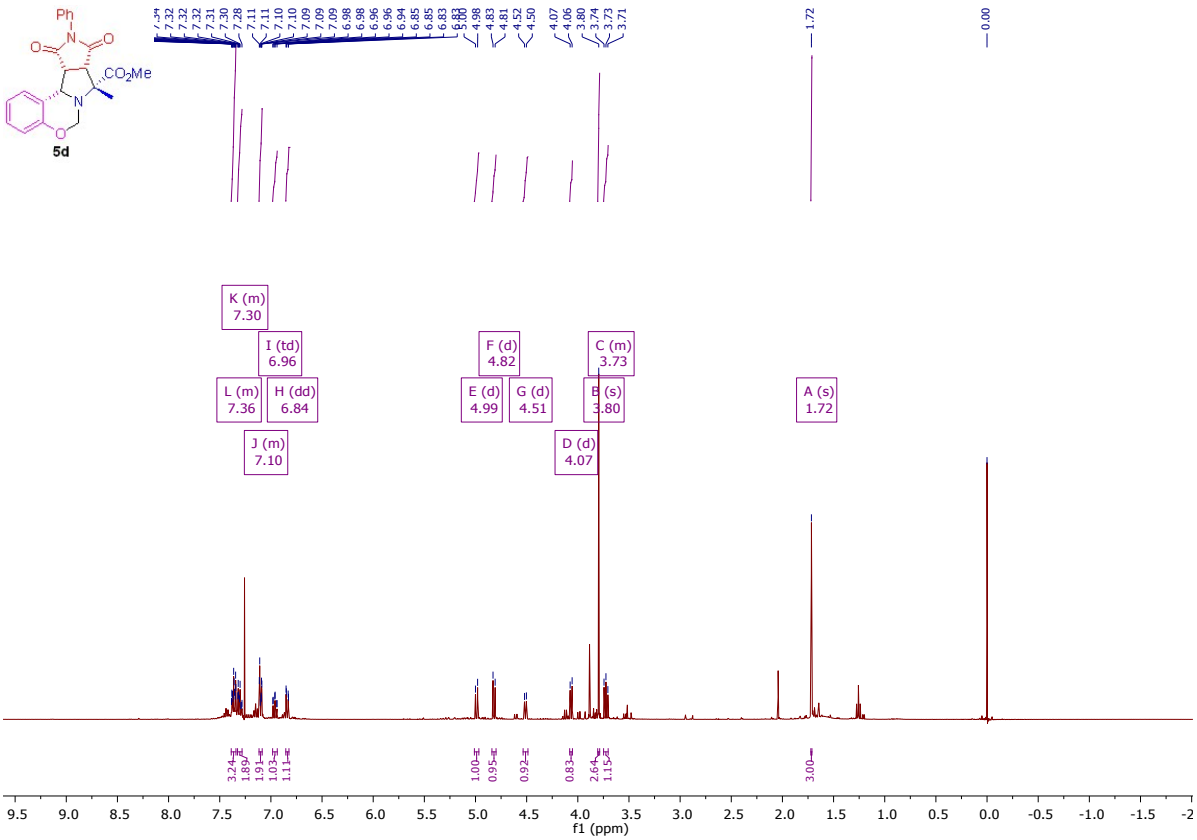


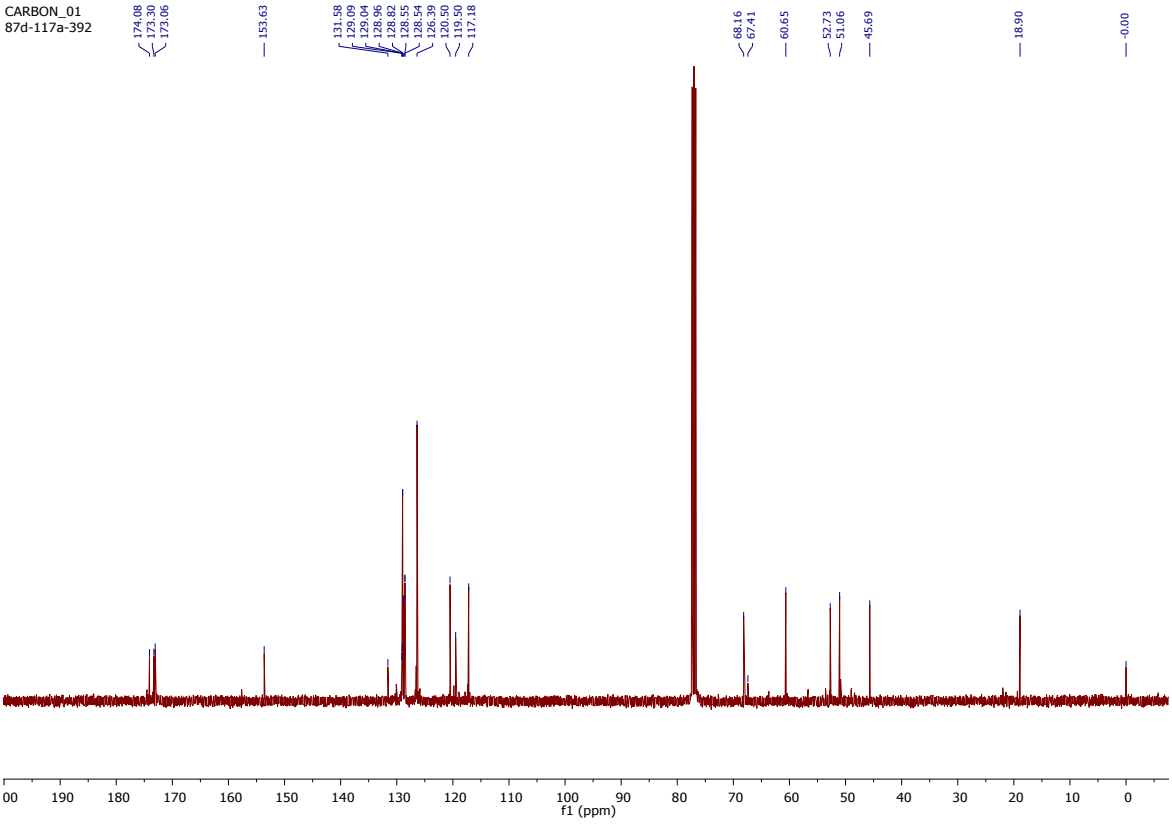
CARBON_01
5a-107a-398

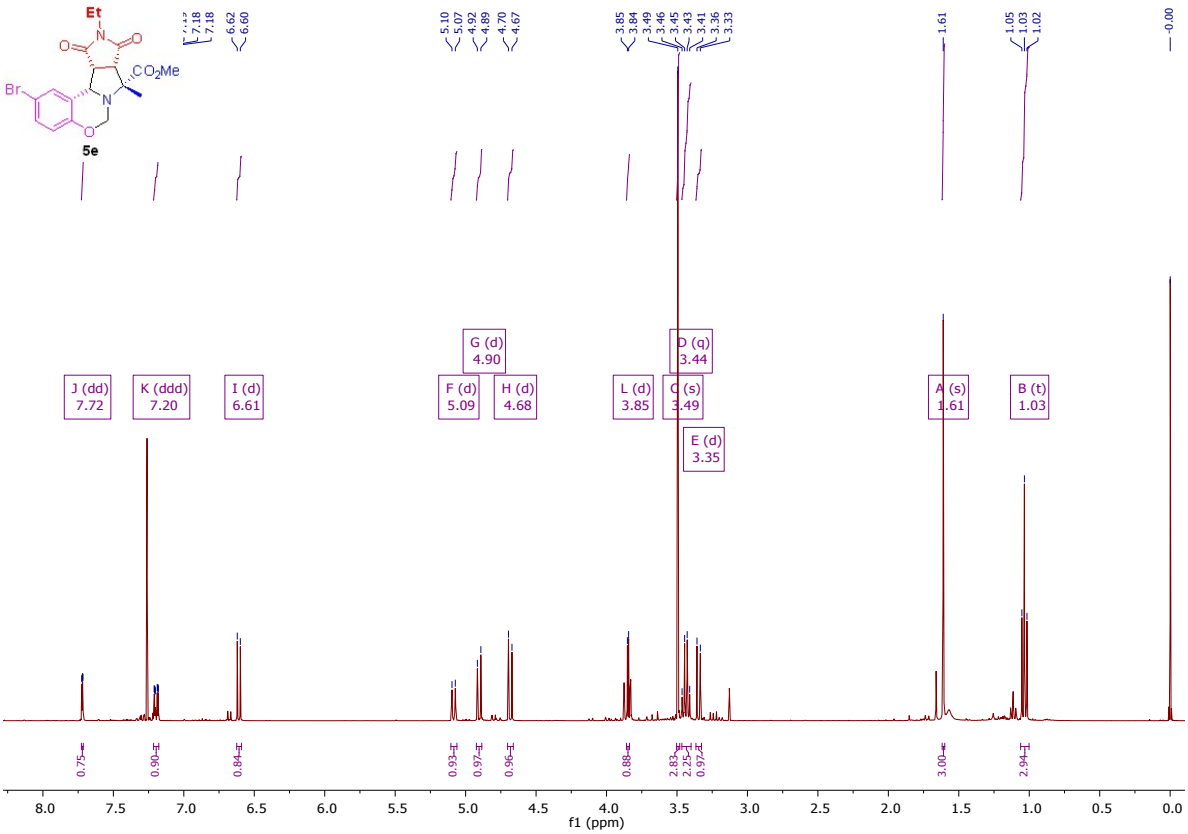


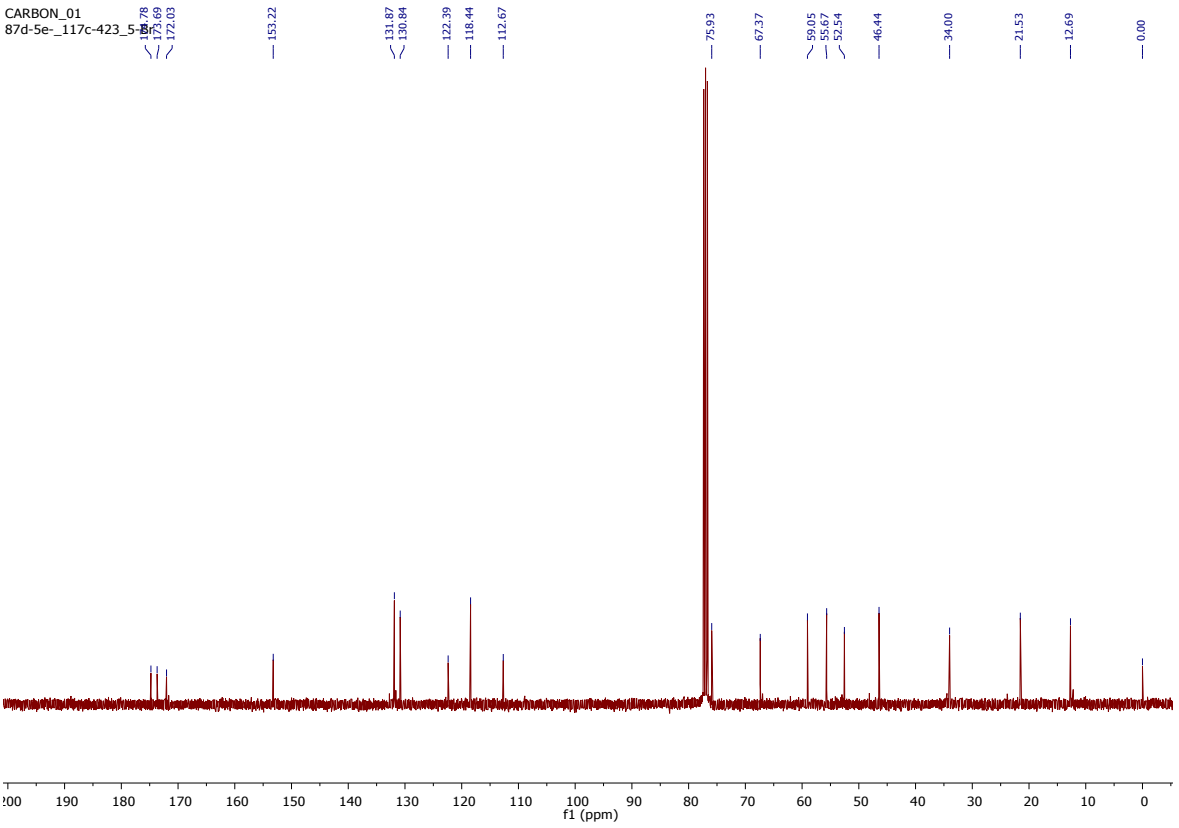

5c
F (d) 7.15
G (m) 6.65
I (d) 4.88
H (d) 5.15
J (d) 4.67
K (t) 3.90
B (s) 3.82
C (s) 3.50
E (d) 3.37
D (s) 2.86
A (s) 1.62
f1 (ppm)

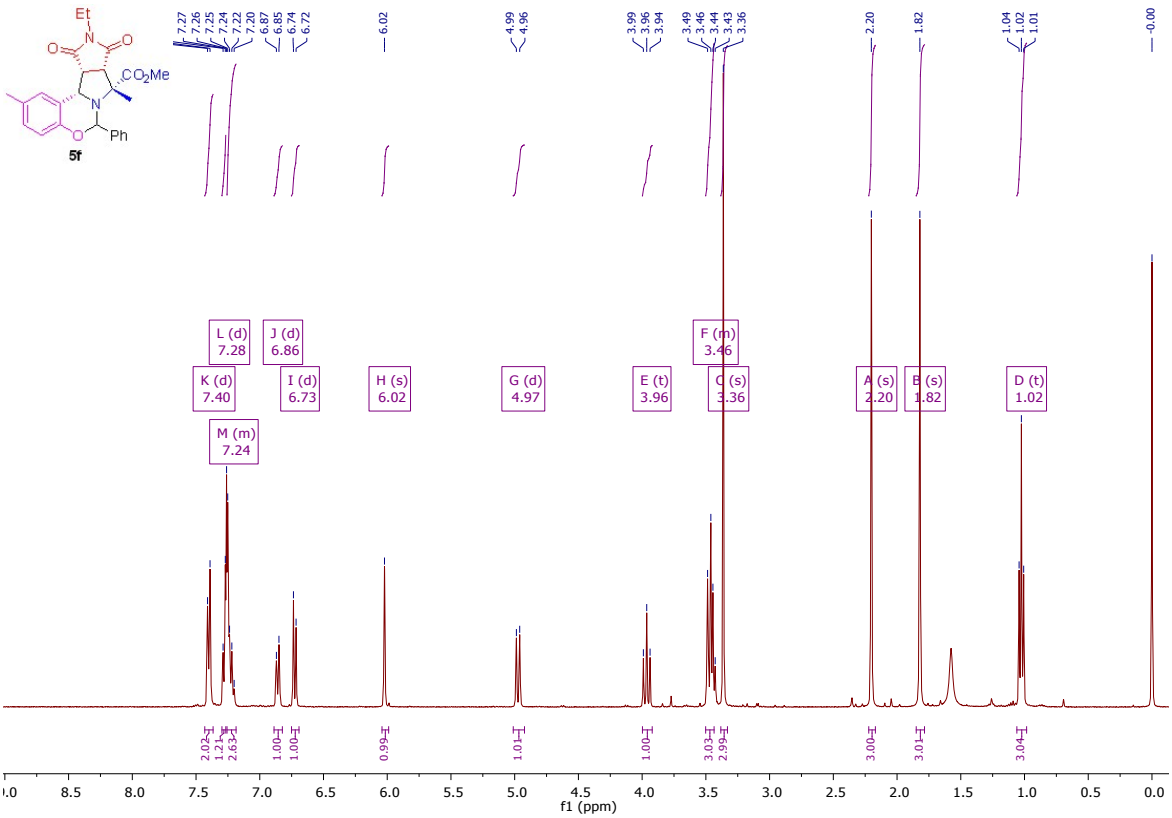

CARBON_01
87d-107bx-360
f1 (ppm)

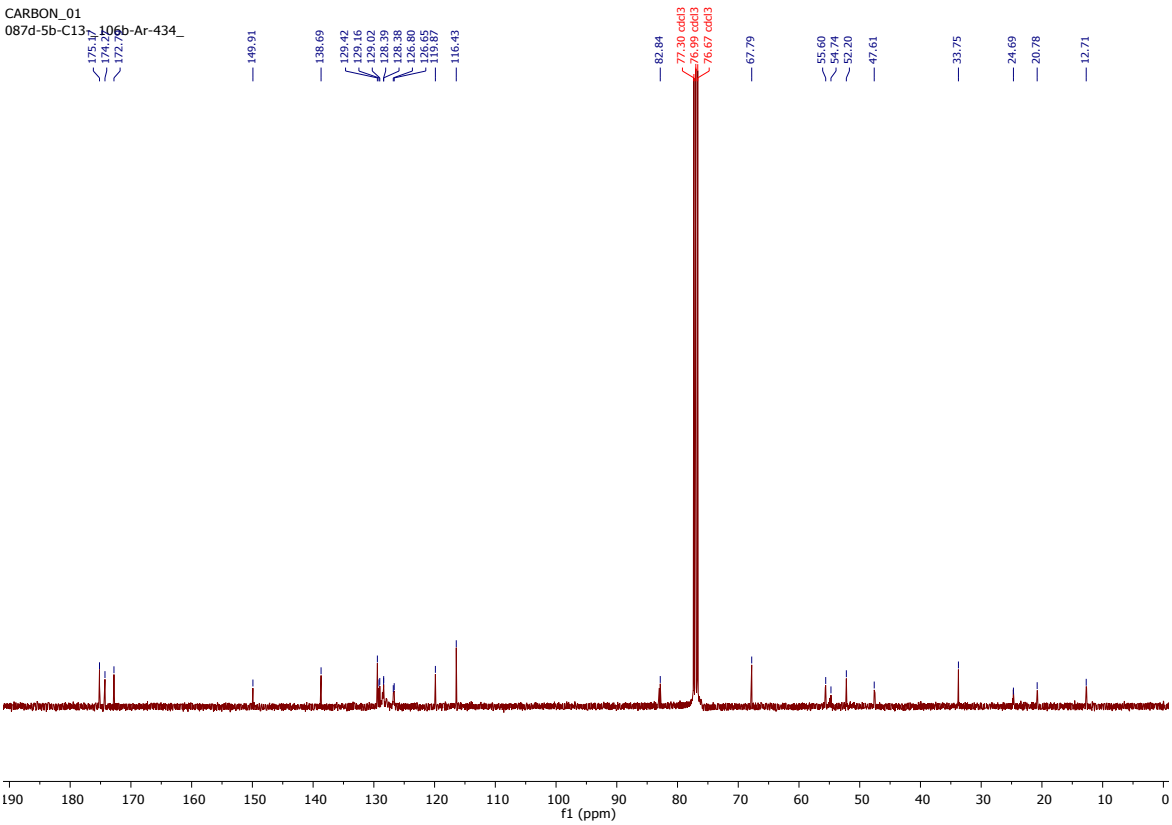

Ph
N
O
O
CO2Me
N
O
5d
K (m) 7.30
I (td) 6.96
L (m) 7.36
H (dd) 6.84
J (m) 7.10
F (d) 4.82
E (d) 4.99
G (d) 4.51
C (m) 3.73
B (s) 3.80
D (d) 4.07
A (s) 1.72
f1 (ppm)

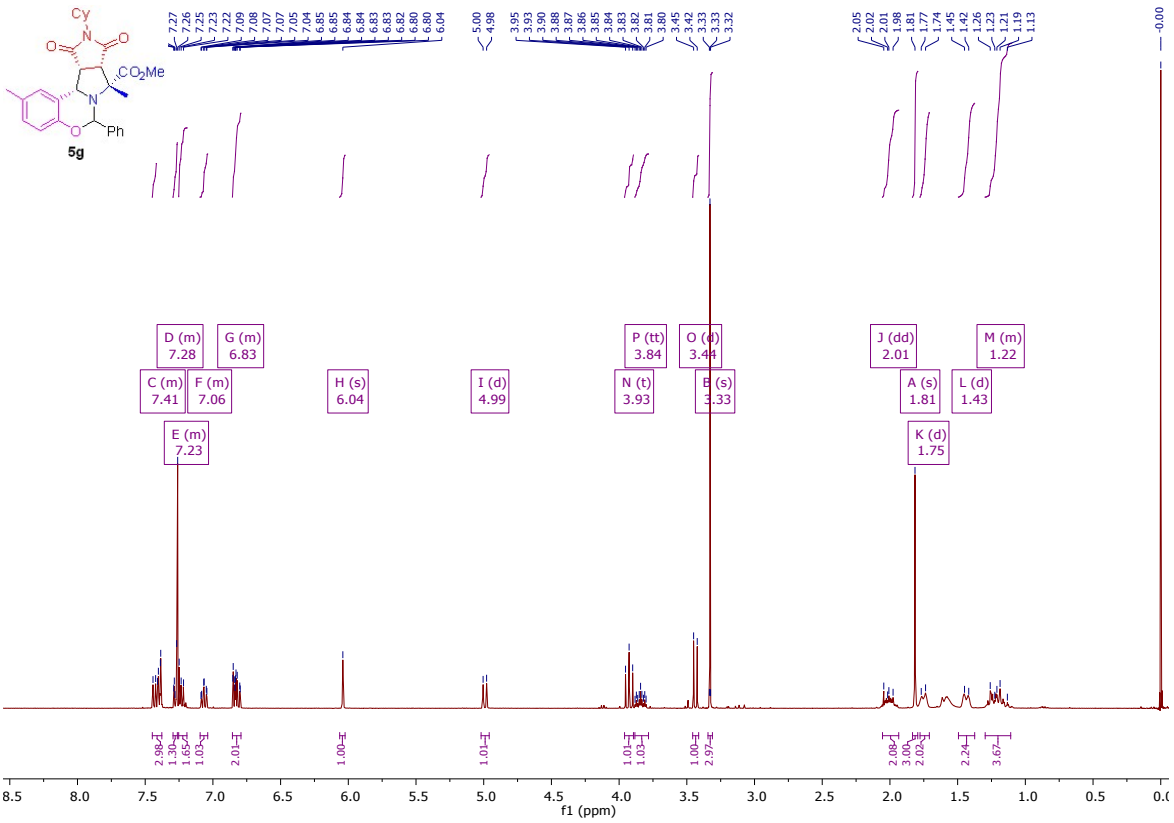

CARBON_01
87d-117a-392
f1 (ppm)

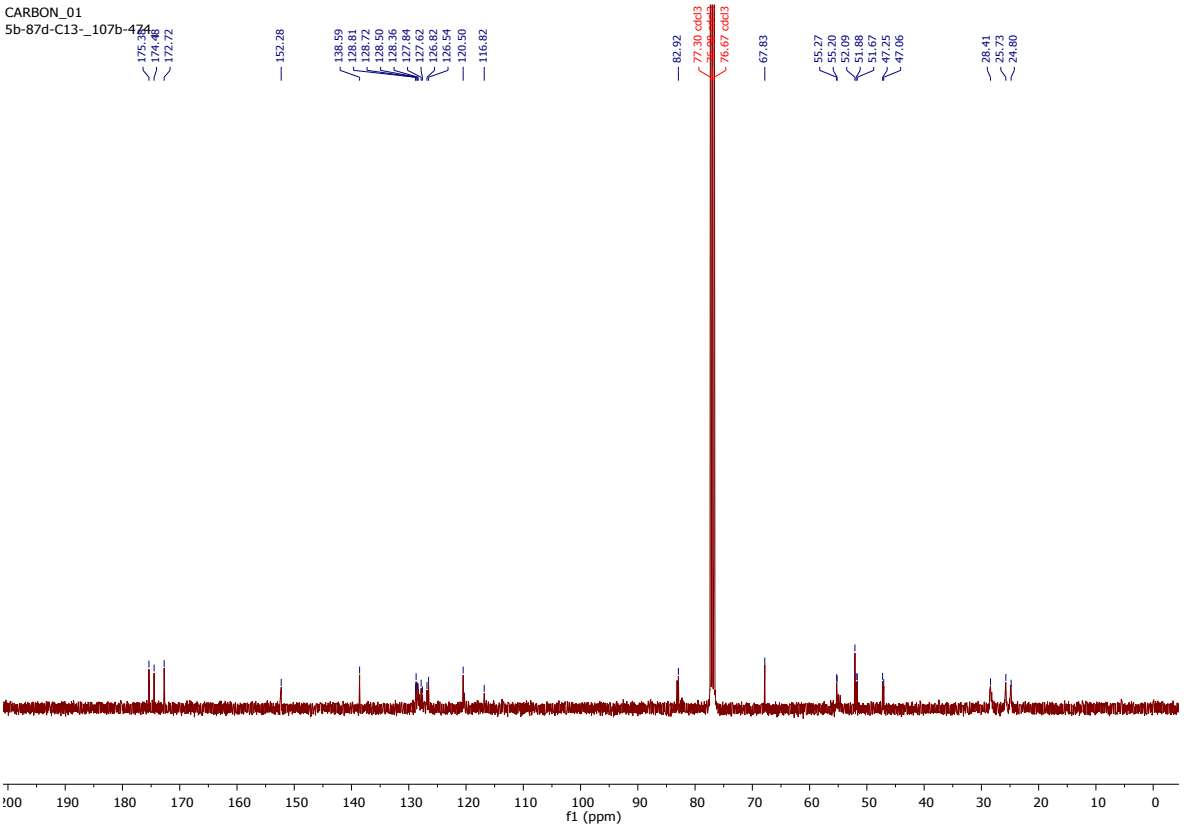

Et
CO2Me
Br
5e
J (dd) 7.72
K (ddd) 7.20
I (d) 6.61
F (d) 5.09
G (d) 4.90
H (d) 4.68
L (d) 3.85
O (s) 3.49
D (q) 3.44
E (d) 3.35
A (s) 1.61
B (t) 1.03
f1 (ppm)

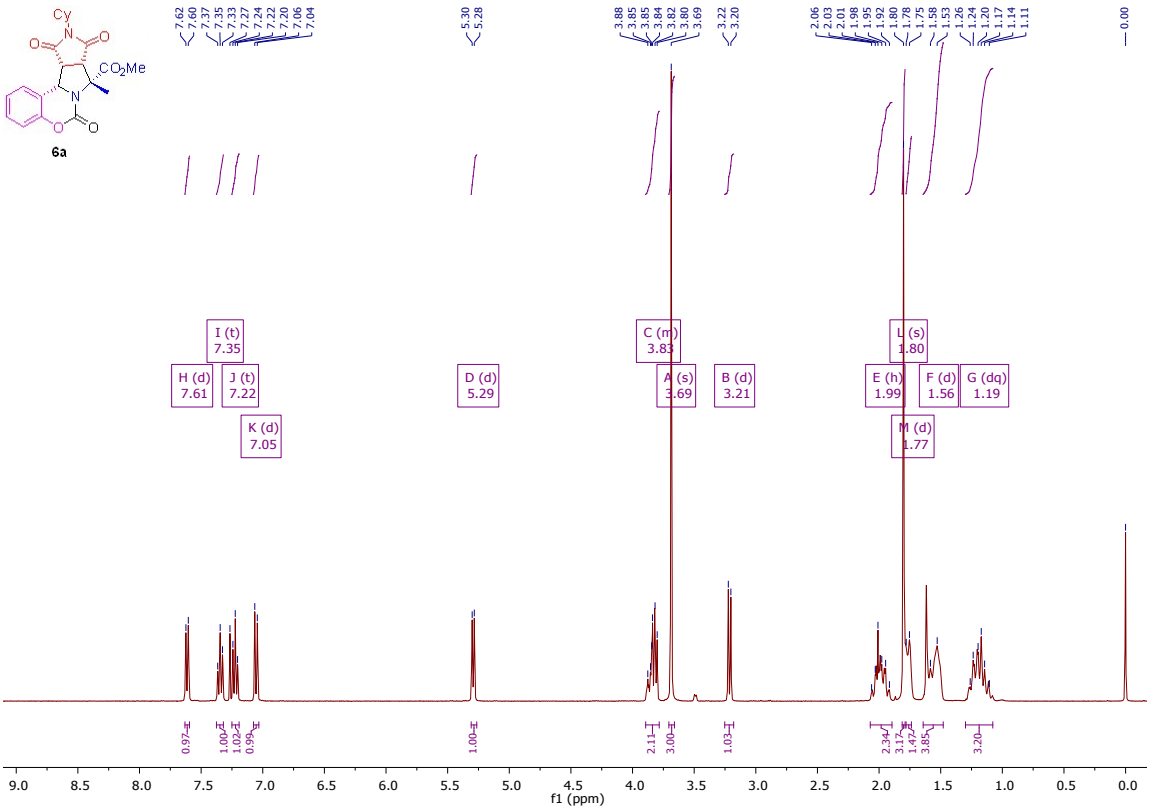

CARBON_01
87d-5e-_117c-423_5-3
f1 (ppm)

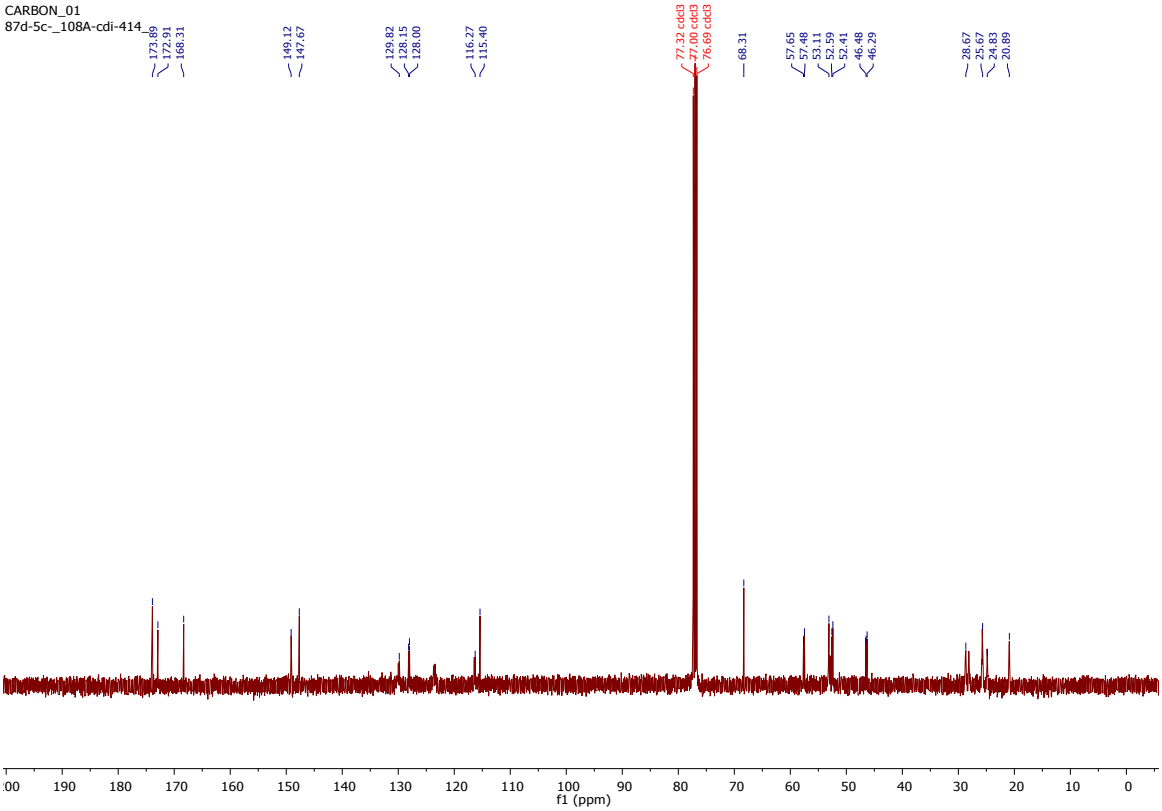

Et
CO2Me
Ph
5f
L (d) 7.28
J (d) 6.86
F (m) 3.46
K (d) 7.40
I (d) 6.73
H (s) 6.02
G (d) 4.97
E (t) 3.96
C (s) 3.36
A (s) 2.20
B (s) 1.82
D (t) 1.02
M (m) 7.24
f1 (ppm)

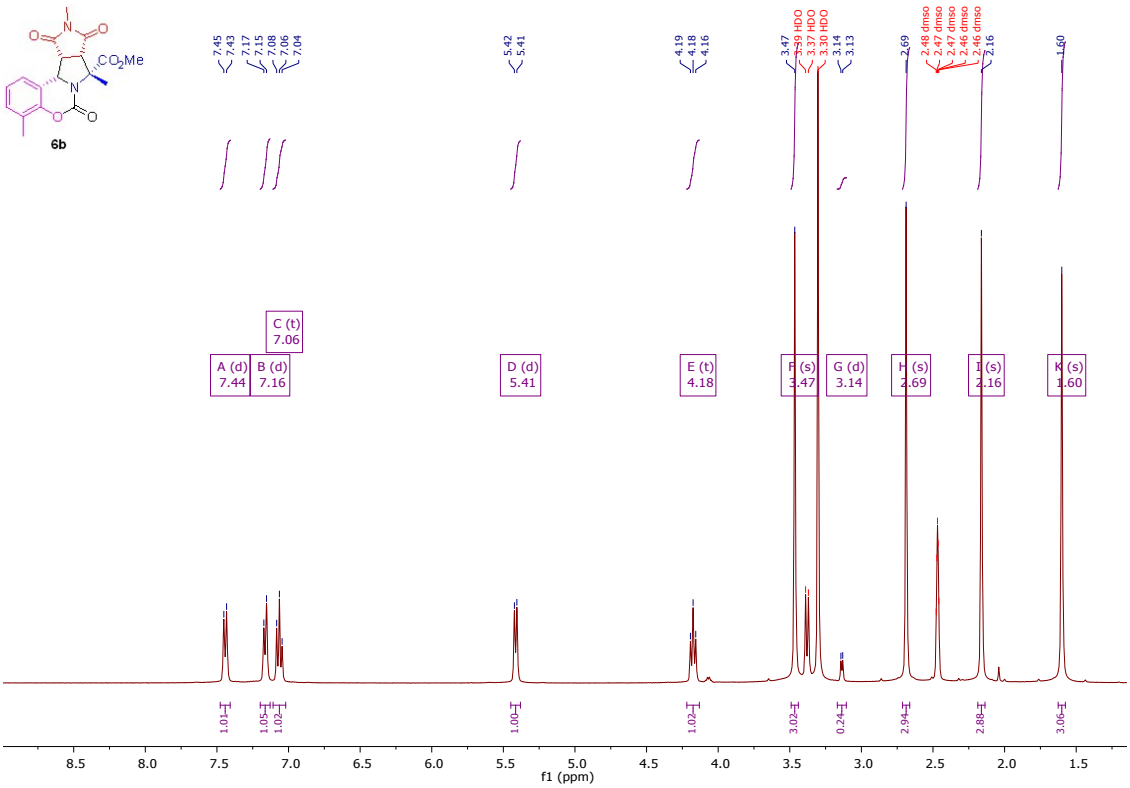

CARBON_01
087d-5b-C13-106b-Ar-434_
f1 (ppm)

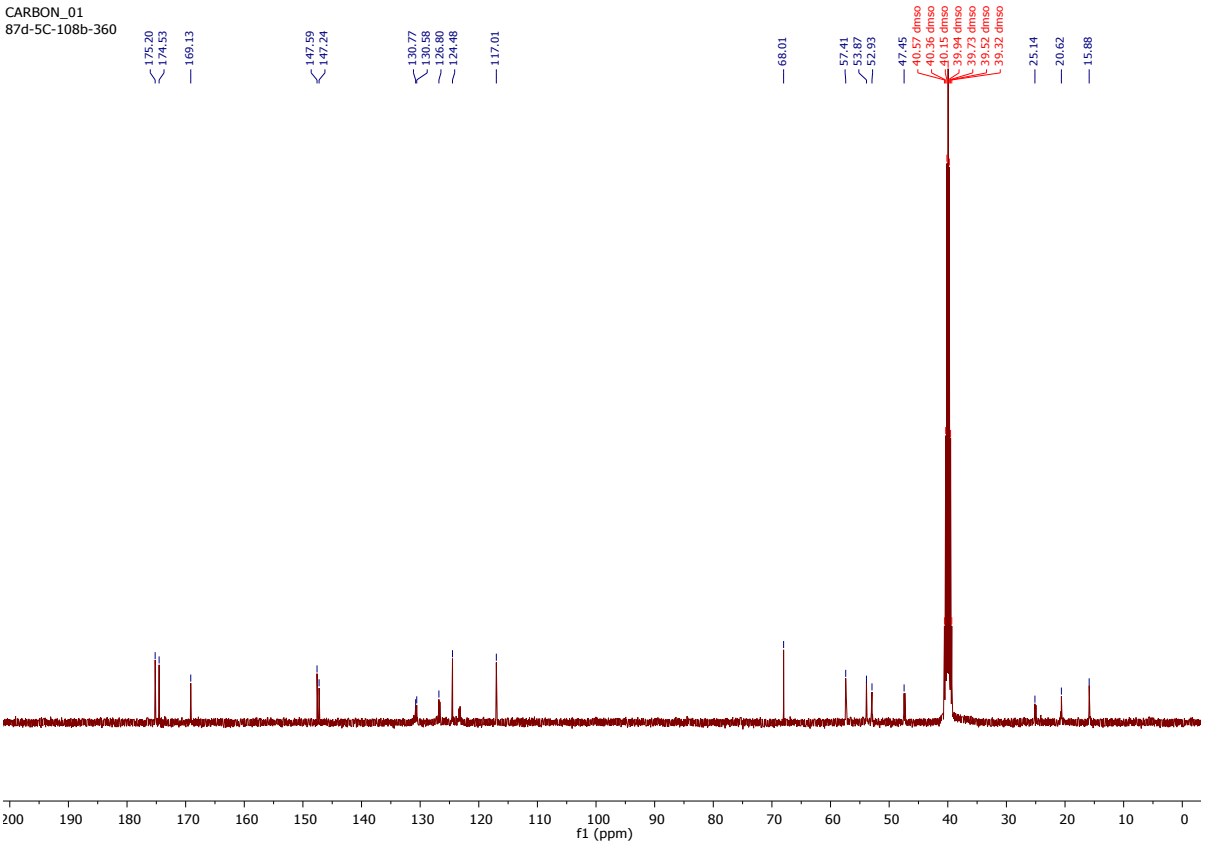

5g
D (m) 7.28
G (m) 6.83
C (m) 7.41
F (m) 7.06
E (m) 7.23
H (s) 6.04
I (d) 4.99
P (tt) 3.84
O (d) 3.44
N (t) 3.93
B (s) 3.33
J (dd) 2.01
M (m) 1.22
A (s) 1.81
L (d) 1.43
K (d) 1.75
f1 (ppm)

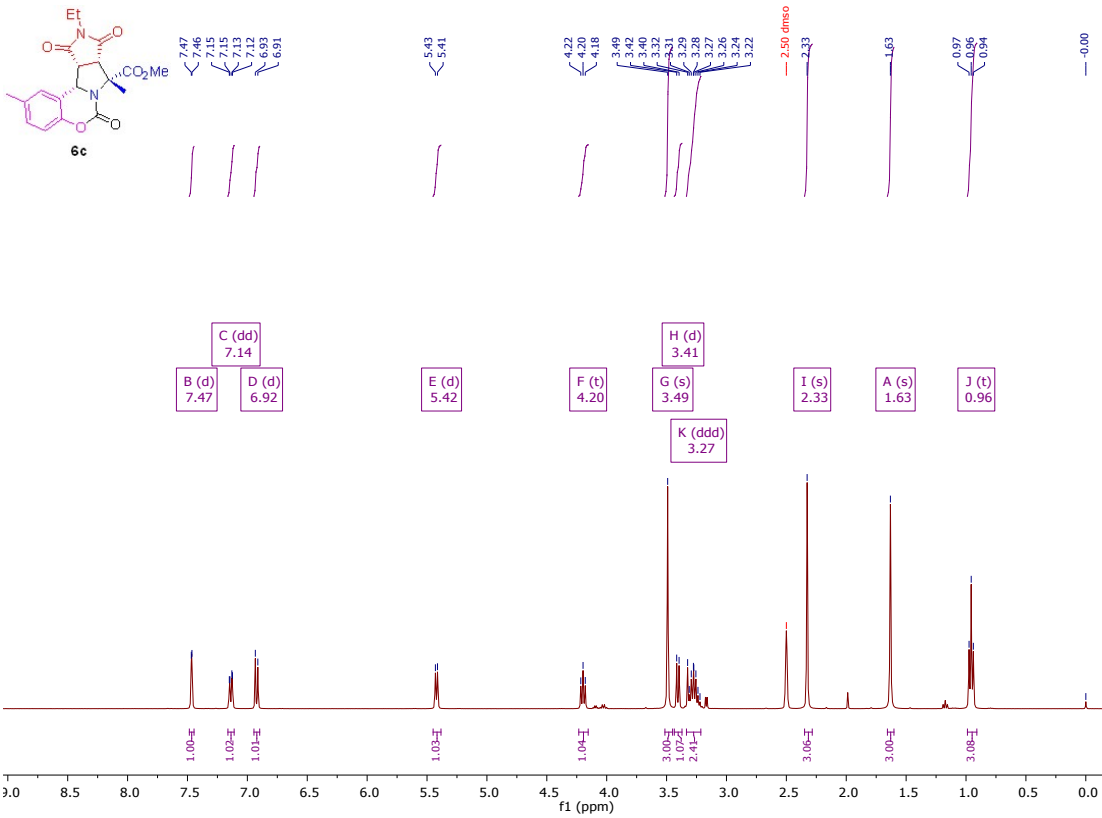

CARBON_01
5b-87d-C13-_107b-474
f1 (ppm)

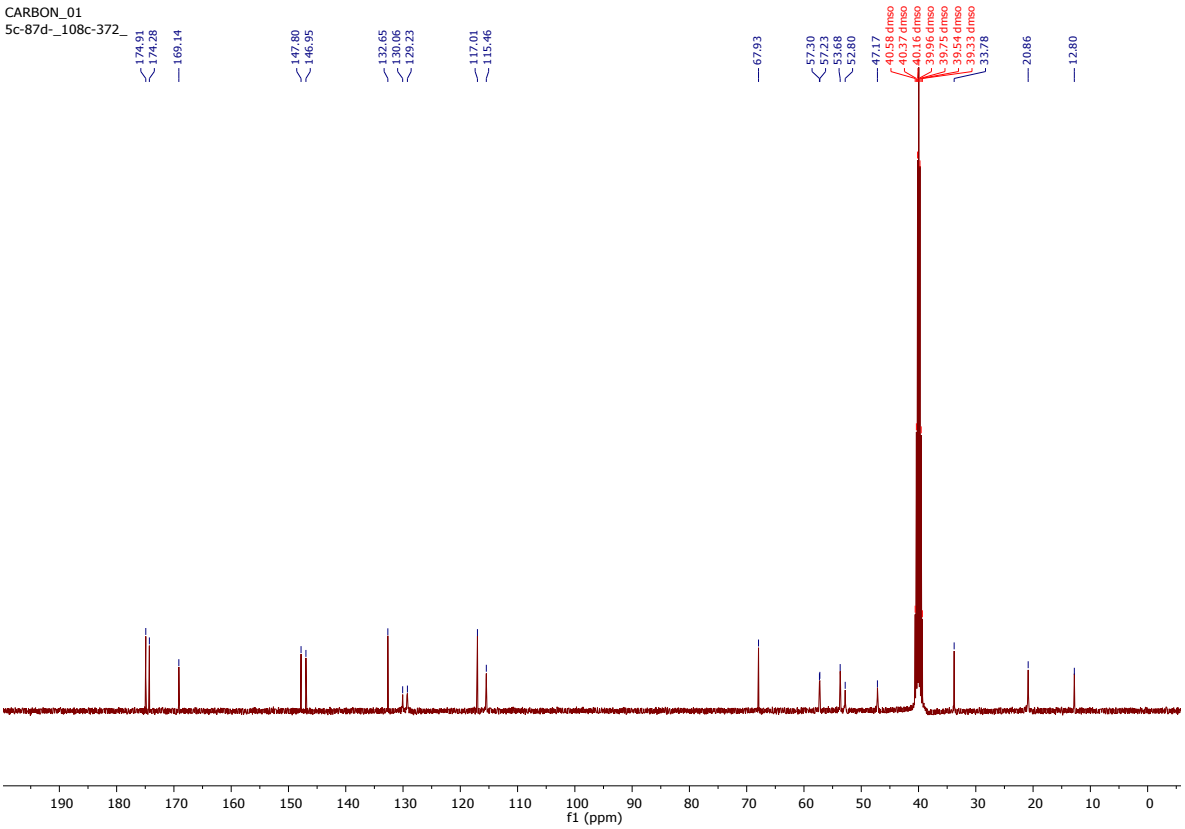

Cy
CO2Me
6a
I (t) 7.35
H (d) 7.61
J (t) 7.22
K (d) 7.05
D (d) 5.29
C (m) 3.83
A (s) 3.69
B (d) 3.21
L (s) 1.80
E (h) 1.99
F (d) 1.56
G (dq) 1.19
M (d) 1.77
f1 (ppm)

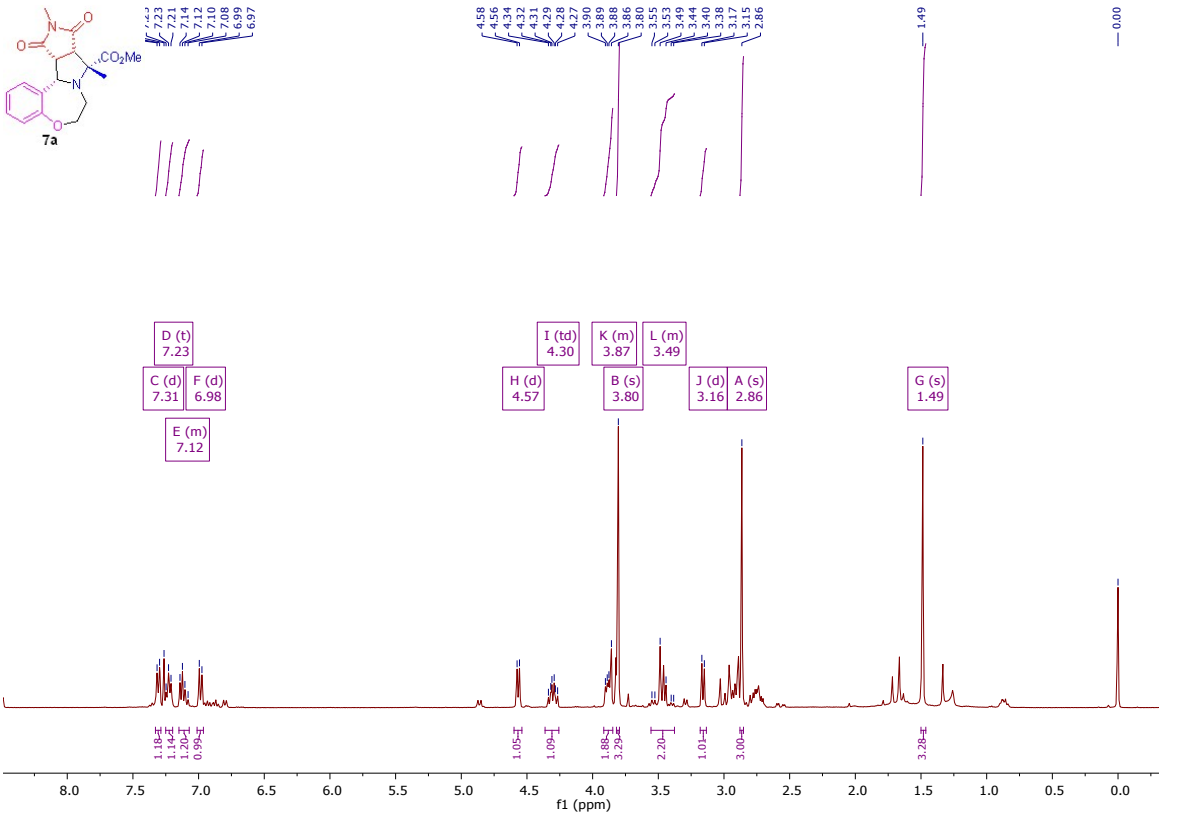

CARBON_01
87d-5c-_108A-cdi-414_
f1 (ppm)

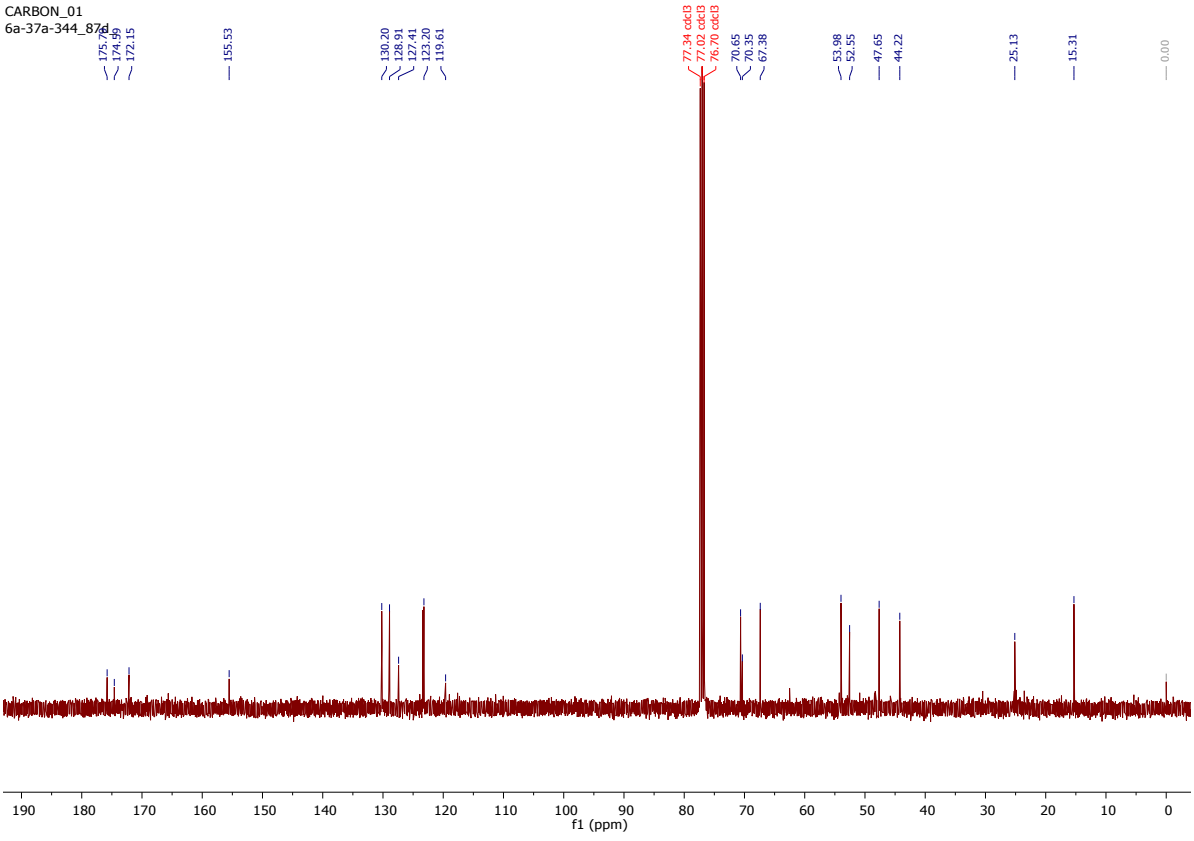

6b
7.45
7.43
7.17
7.15
7.08
7.06
7.04
5.42
5.41
4.19
4.18
4.16
3.47
3.39 HDO
3.37 HDO
3.30 HDO
3.14
3.13
2.69
2.48 dmso
2.47 dmso
2.47 dmso
2.46 dmso
2.46 dmso
2.16
1.60
A (d) 7.44
B (d) 7.16
C (t) 7.06
D (d) 5.41
E (t) 4.18
F (s) 3.47
G (d) 3.14
H (s) 2.69
I (s) 2.16
K (s) 1.60
1.01
1.05
1.02
1.00
1.02
3.02
0.24
2.94
2.88
3.06
f1 (ppm)

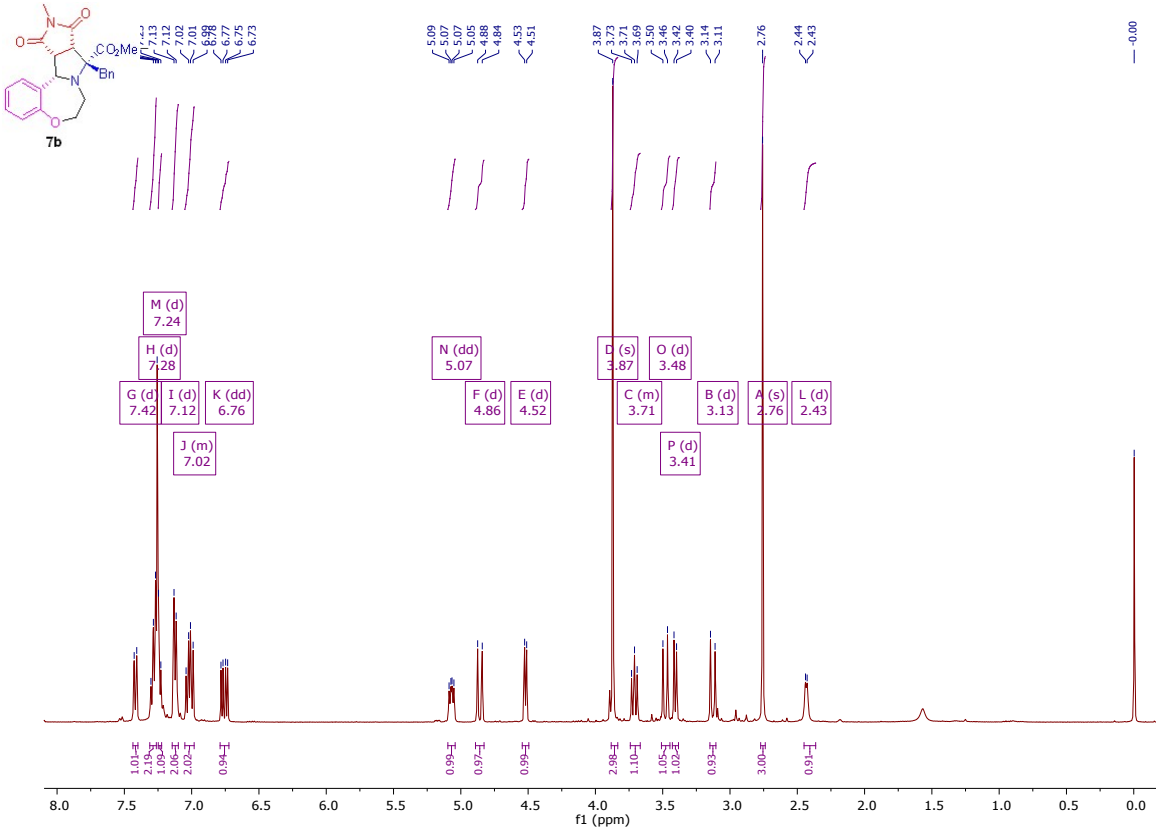

CARBON_01
87d-5C-108b-360
175.20
174.53
169.13
147.59
147.24
130.77
130.58
126.80
124.48
117.01
68.01
57.41
53.87
52.93
47.45
40.57 dmso
40.36 dmso
40.15 dmso
39.94 dmso
39.73 dmso
39.52 dmso
39.32 dmso
25.14
20.62
15.88
f1 (ppm)

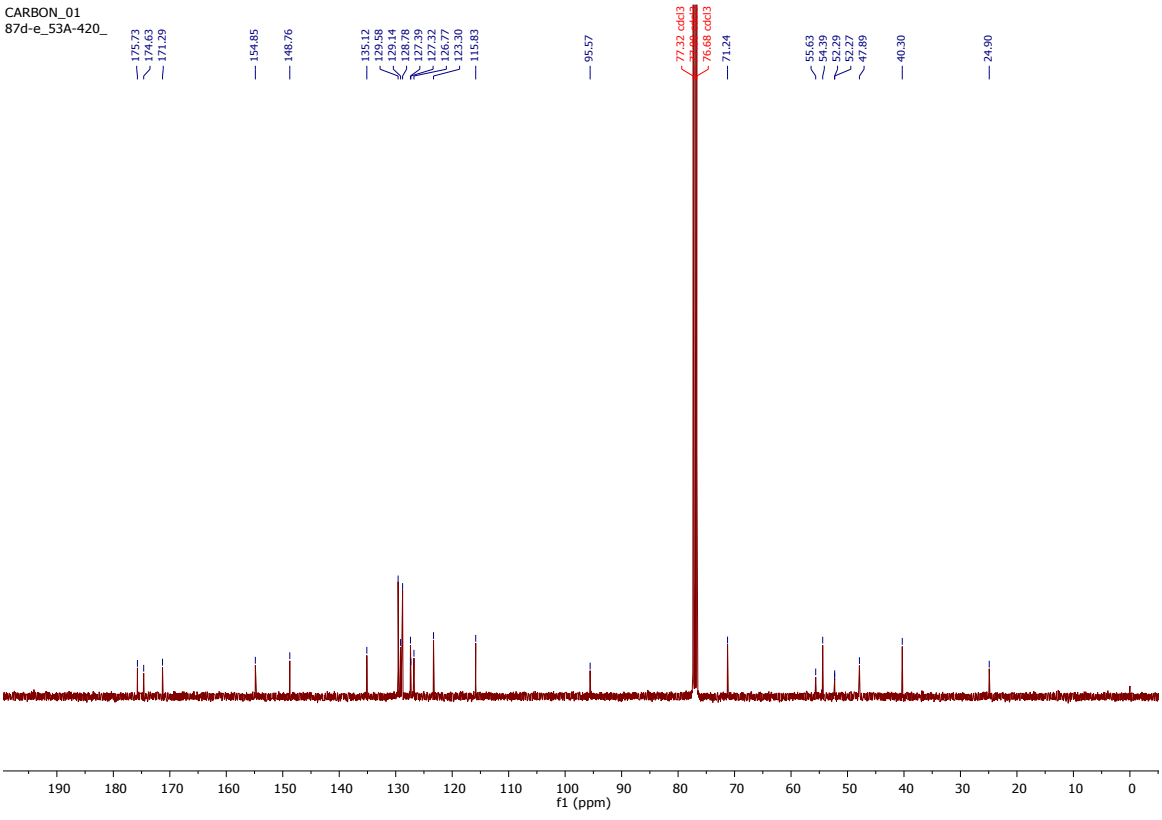

Et
CO2Me
6c
7.47
7.46
7.15
7.15
7.13
7.12
6.93
6.91
5.43
5.41
4.22
4.20
4.18
3.49
3.42
3.40
3.32
3.31
3.29
3.28
3.27
3.26
3.24
3.22
2.50 dmso
2.33
1.63
0.97
0.96
0.94
-0.00
B (d) 7.47
C (dd) 7.14
D (d) 6.92
E (d) 5.42
F (t) 4.20
G (s) 3.49
H (d) 3.41
K (ddd) 3.27
I (s) 2.33
A (s) 1.63
J (t) 0.96
1.00
1.02
1.01
1.03
1.04
3.00
1.07
2.41
3.06
3.00
3.08
f1 (ppm)

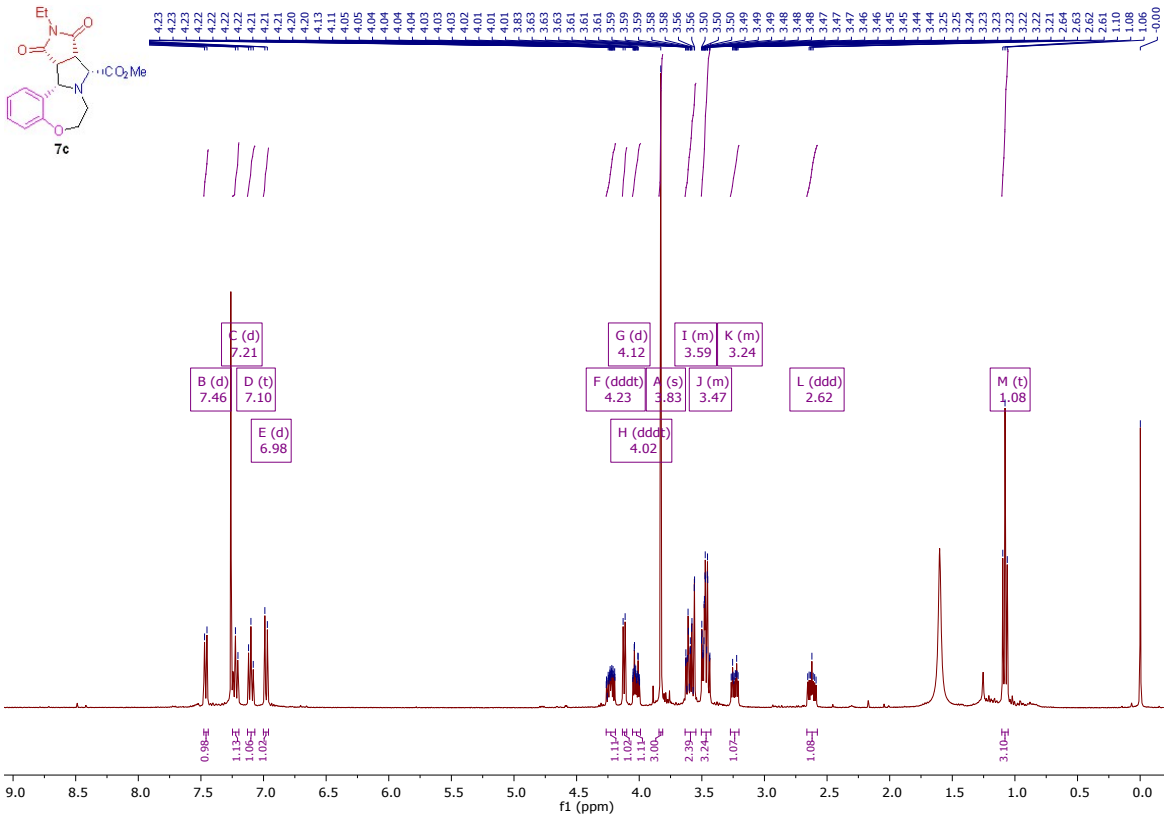

CARBON_01
5c-87d-_108c-372_
174.91
174.28
169.14
147.80
146.95
132.65
130.06
129.23
117.01
115.46
67.93
57.30
57.23
53.68
52.80
47.17
40.59 dmso
40.37 dmso
40.16 dmso
39.96 dmso
39.75 dmso
39.54 dmso
39.33 dmso
33.78
20.86
12.80
f1 (ppm)

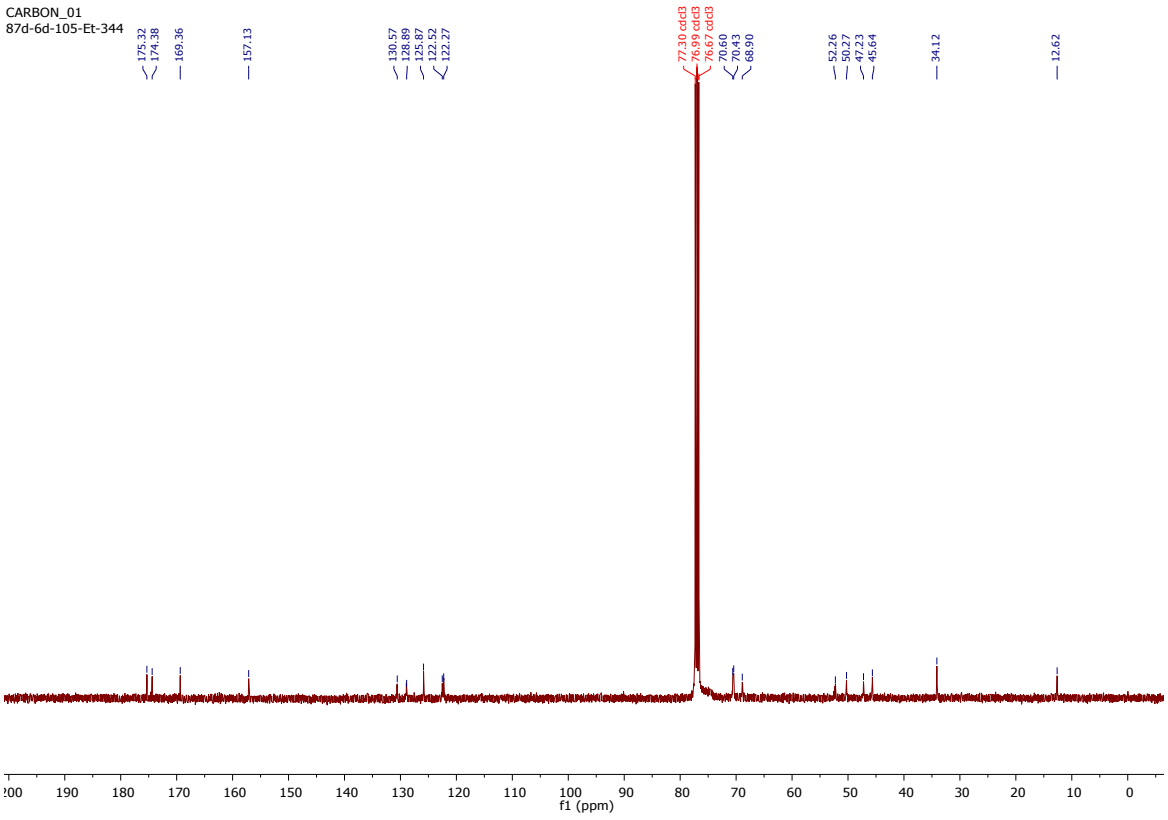

7a
D (t) 7.23
C (d) 7.31
F (d) 6.98
E (m) 7.12
I (td) 4.30
H (d) 4.57
K (m) 3.87
B (s) 3.80
L (m) 3.49
J (d) 3.16
A (s) 2.86
G (s) 1.49
f1 (ppm)

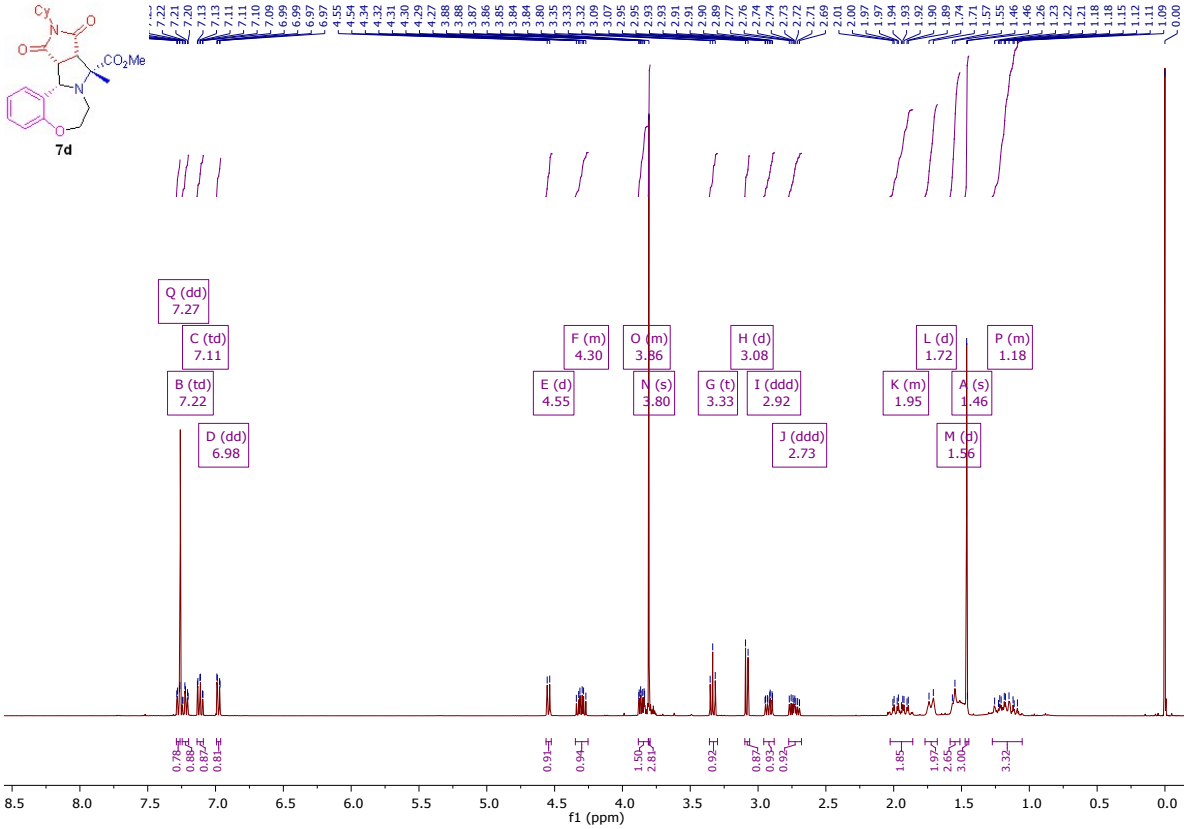

CARBON_01
6a-37a-344_87d
175.79
174.99
172.15
155.53
130.20
128.91
127.41
123.20
119.61
77.34 cdcl3
77.02 cdcl3
76.70 cdcl3
70.65
70.35
67.38
53.98
52.55
47.65
44.22
25.13
15.31
f1 (ppm)

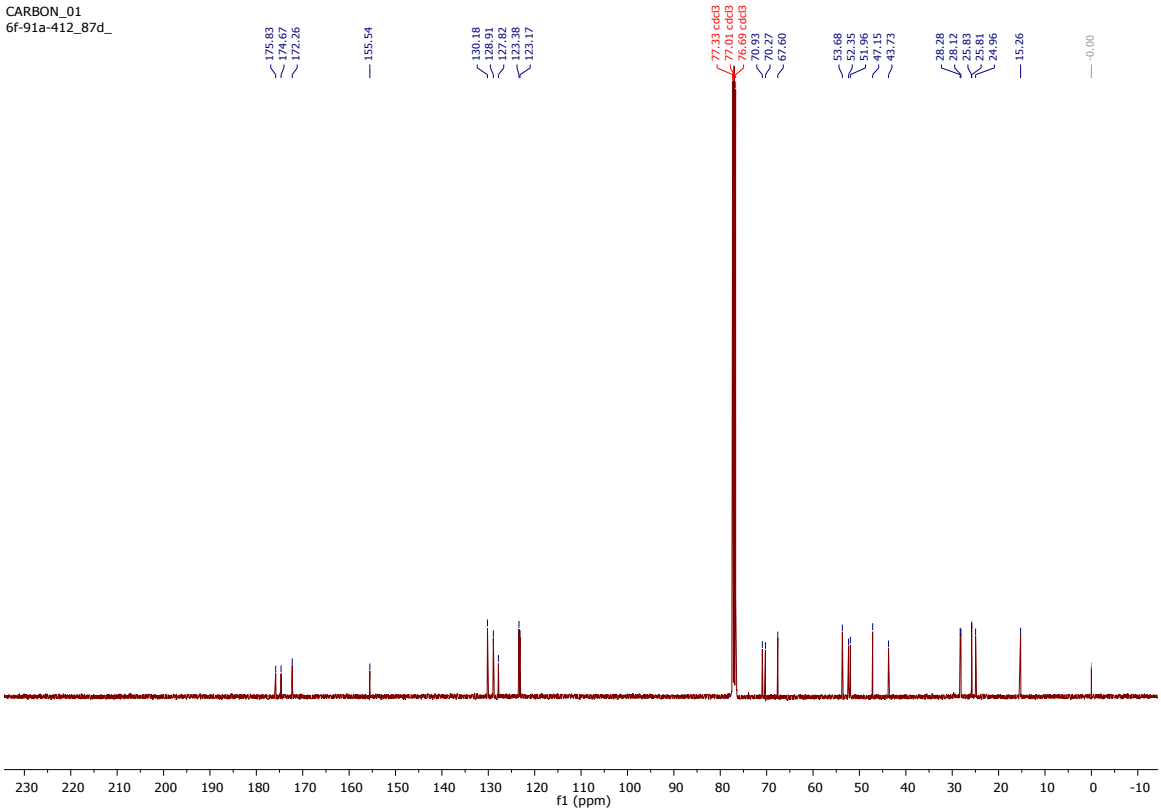

7b
M (d) 7.24
H (d) 7.28
G (d) 7.42
I (d) 7.12
K (dd) 6.76
J (m) 7.02
N (dd) 5.07
F (d) 4.86
E (d) 4.52
D (s) 3.87
C (m) 3.71
O (d) 3.48
P (d) 3.41
B (d) 3.13
A (s) 2.76
L (d) 2.43
f1 (ppm)

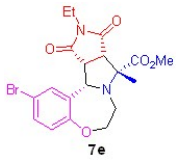

CARBON_01
87d-e_53A-420_
175.73
174.63
171.29
154.85
148.76
135.12
129.58
129.14
128.78
127.39
127.32
126.77
123.30
115.83
95.57
77.32 cdcl3
76.68 cdcl3
71.24
55.63
54.39
52.29
52.27
47.89
40.30
24.90
f1 (ppm)


Et
CO2Me
7c
C (d) 7.21
B (d) 7.46
D (t) 7.10
E (d) 6.98
G (d) 4.12
I (m) 3.59
K (m) 3.24
F (dddt) 4.23
A (s) 3.83
J (m) 3.47
H (dddt) 4.02
L (ddd) 2.62
M (t) 1.08
f1 (ppm)


CARBON_01
87d-6d-105-Et-344
175.32
174.38
169.36
157.13
130.57
128.89
125.87
122.52
122.27
77.30 cdcl3
76.99 cdcl3
76.67 cdcl3
70.60
70.43
68.90
52.26
50.27
47.23
45.64
34.12
12.62
f1 (ppm)

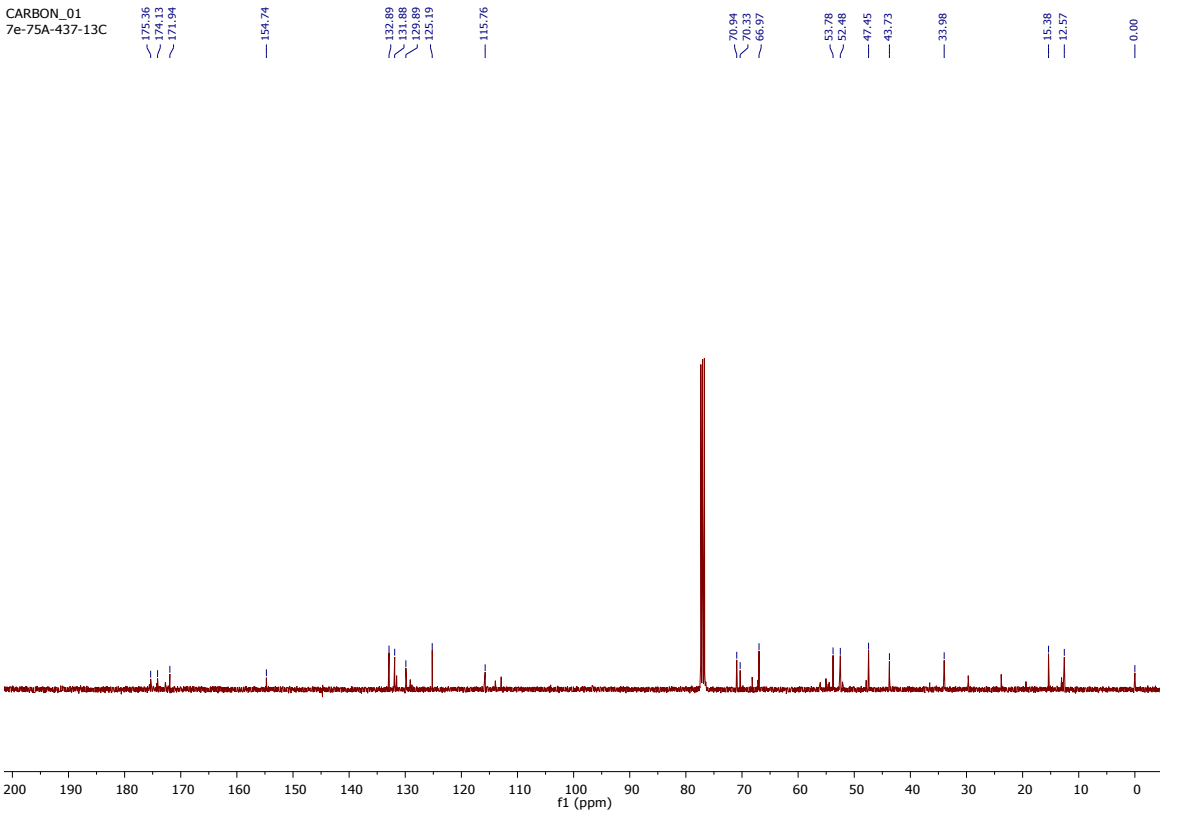

7d
Q (dd) 7.27
C (td) 7.11
B (td) 7.22
D (dd) 6.98
E (d) 4.55
F (m) 4.30
O (m) 3.86
N (s) 3.80
G (t) 3.33
H (d) 3.08
I (ddd) 2.92
J (ddd) 2.73
K (m) 1.95
L (d) 1.72
A (s) 1.46
M (d) 1.56
P (m) 1.18
f1 (ppm)

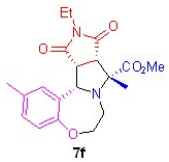

CARBON_01
6f-91a-412_87d_
175.83
174.67
172.26
155.54
130.18
128.91
127.82
123.38
123.17
77.33 cdcl3
77.01 cdcl3
76.69 cdcl3
70.93
70.27
67.60
53.68
52.35
51.96
47.15
43.73
28.28
28.12
25.83
25.81
24.96
15.26
f1 (ppm)


Et
O
O
N
CO2Me
Br
N
O

7e

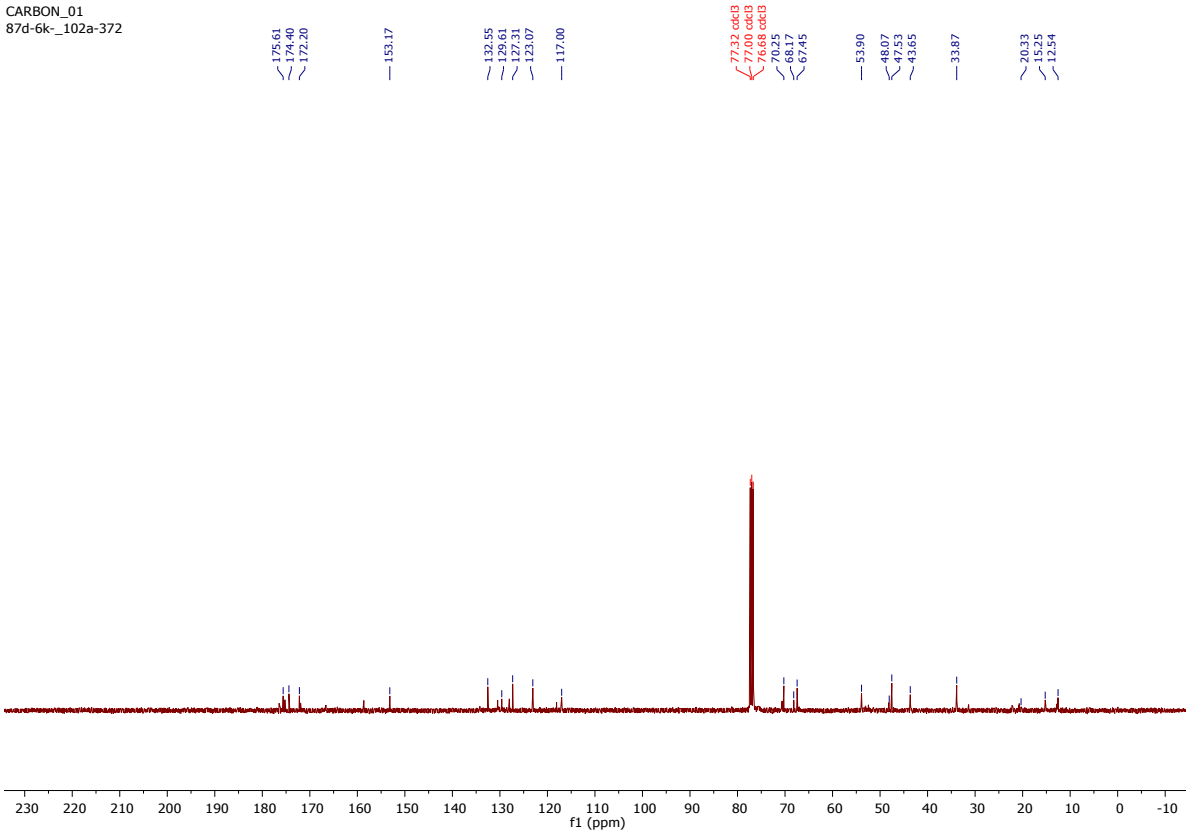
7.42
7.41
7.32
7.31
7.30
7.29
6.87
6.85
4.50
4.48
4.31
4.30
4.28
4.27
4.25
3.86
3.85
3.84
3.83
3.80
3.72
3.71
3.45
3.43
3.41
3.40
3.38
3.36
3.14
3.12
2.94
2.92
2.90
2.88
1.47
1.06
1.04
1.02
-0.00
D (dd) 7.31
C (d) 7.41
E (d) 6.86
H (m) 4.28
L (m) 3.85
J (d) 3.13
G (d) 4.49
B (s) 3.80
I (m) 3.40
K (m) 2.90
M (d) 3.71
A (s) 1.47
F (t) 1.04
0.94
0.98
0.94
1.05
0.98
1.03
2.81
1.20
3.41
0.96
1.05
3.00
3.08
f1 (ppm)

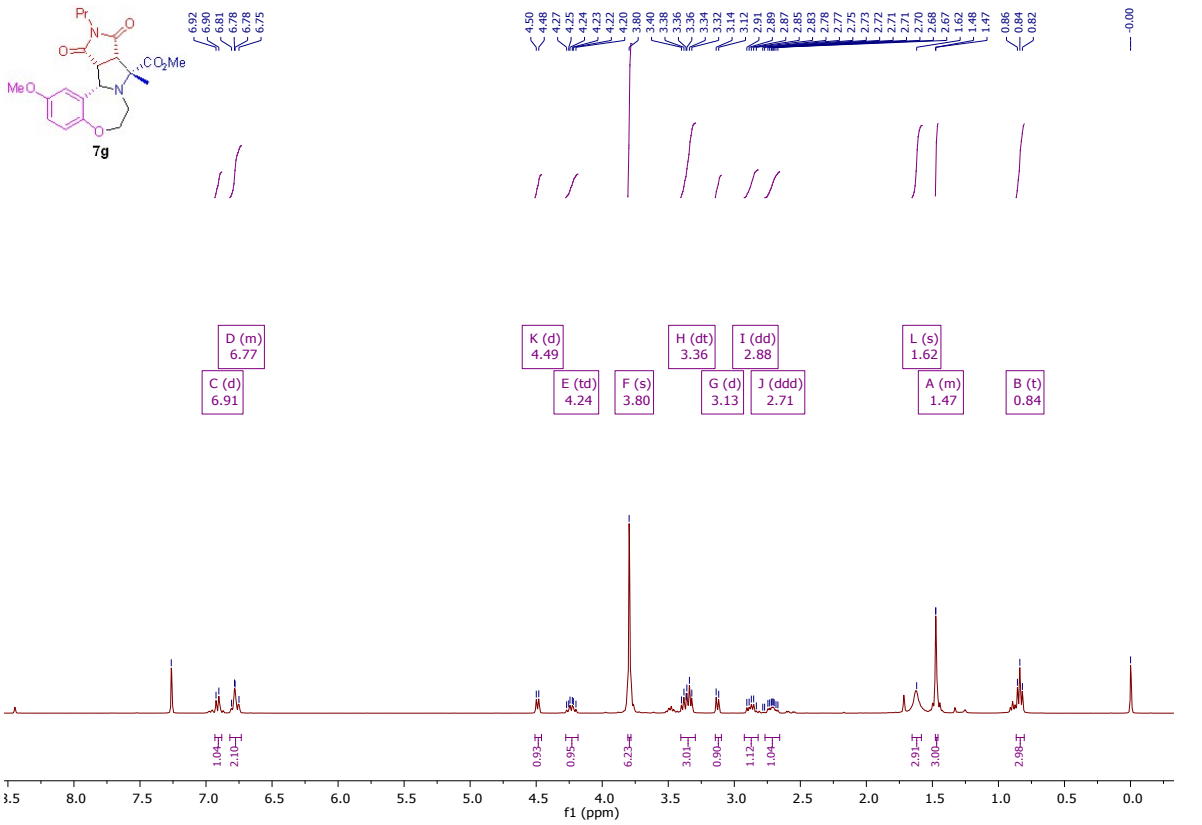

CARBON_01
7e-75A-437-13C
175.36
174.13
171.94
154.74
132.89
131.88
129.89
125.19
115.76
70.94
70.33
66.97
53.78
52.48
47.45
43.73
33.98
15.38
12.57
0.00
f1 (ppm)

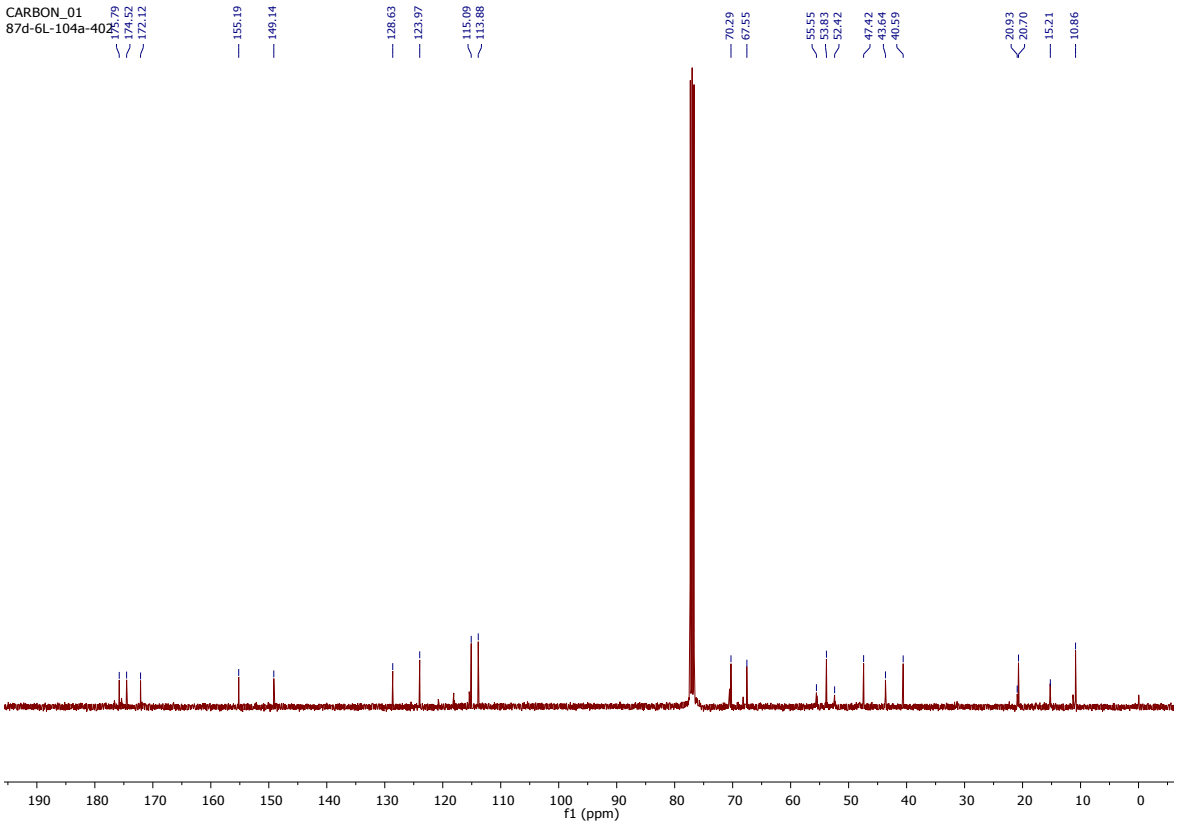


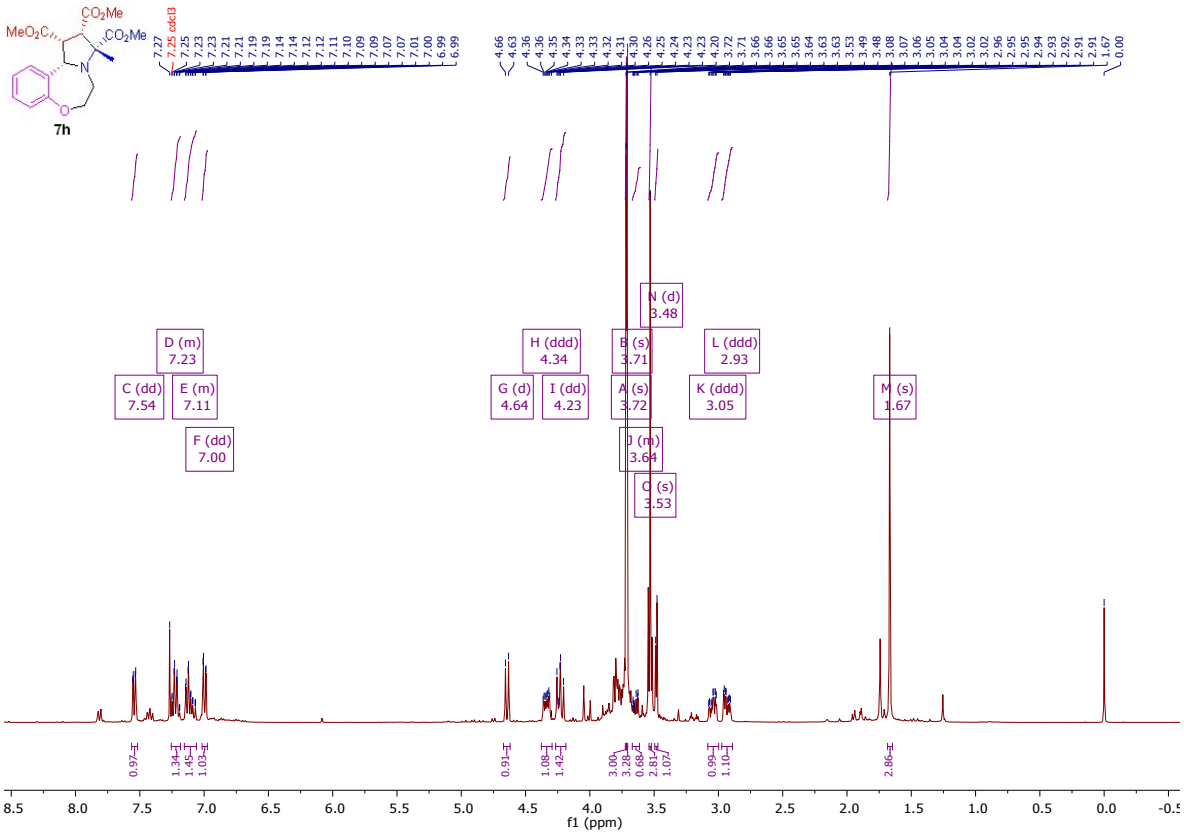
7f

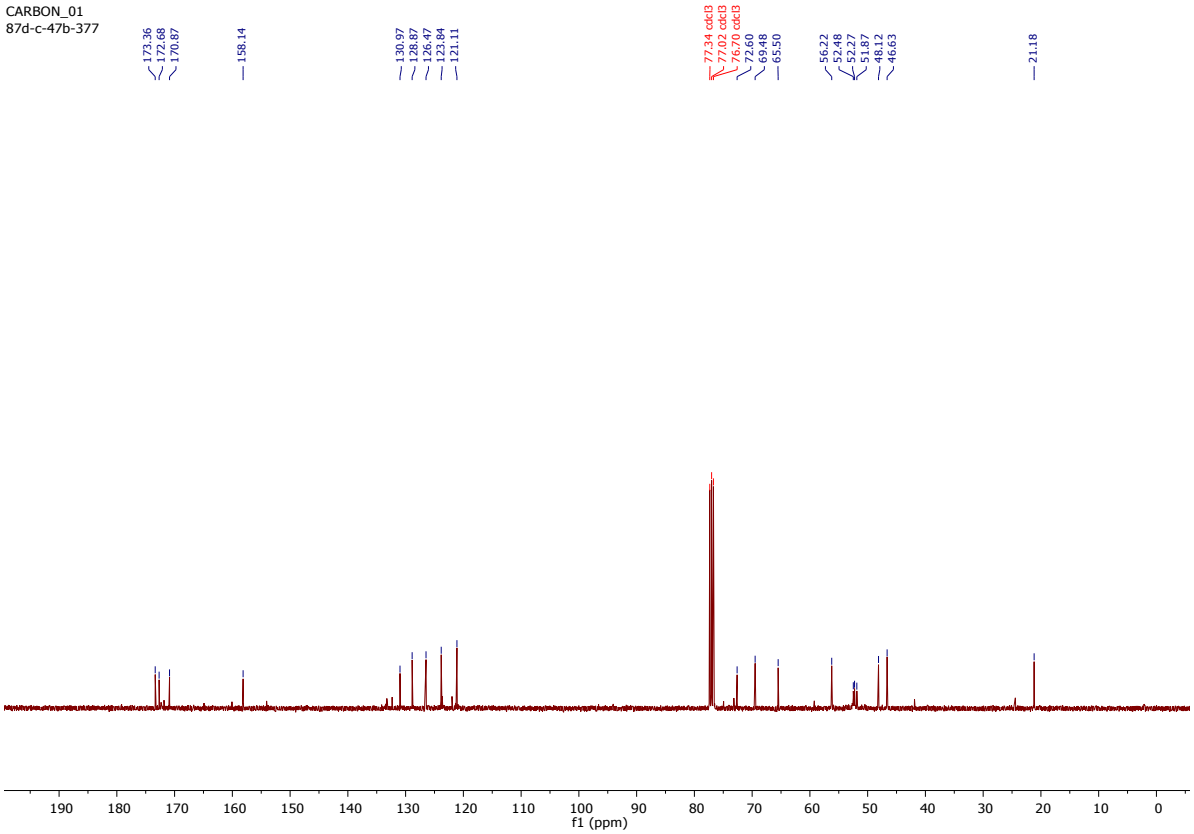
CARBON_01
87d-6k-_102a-372

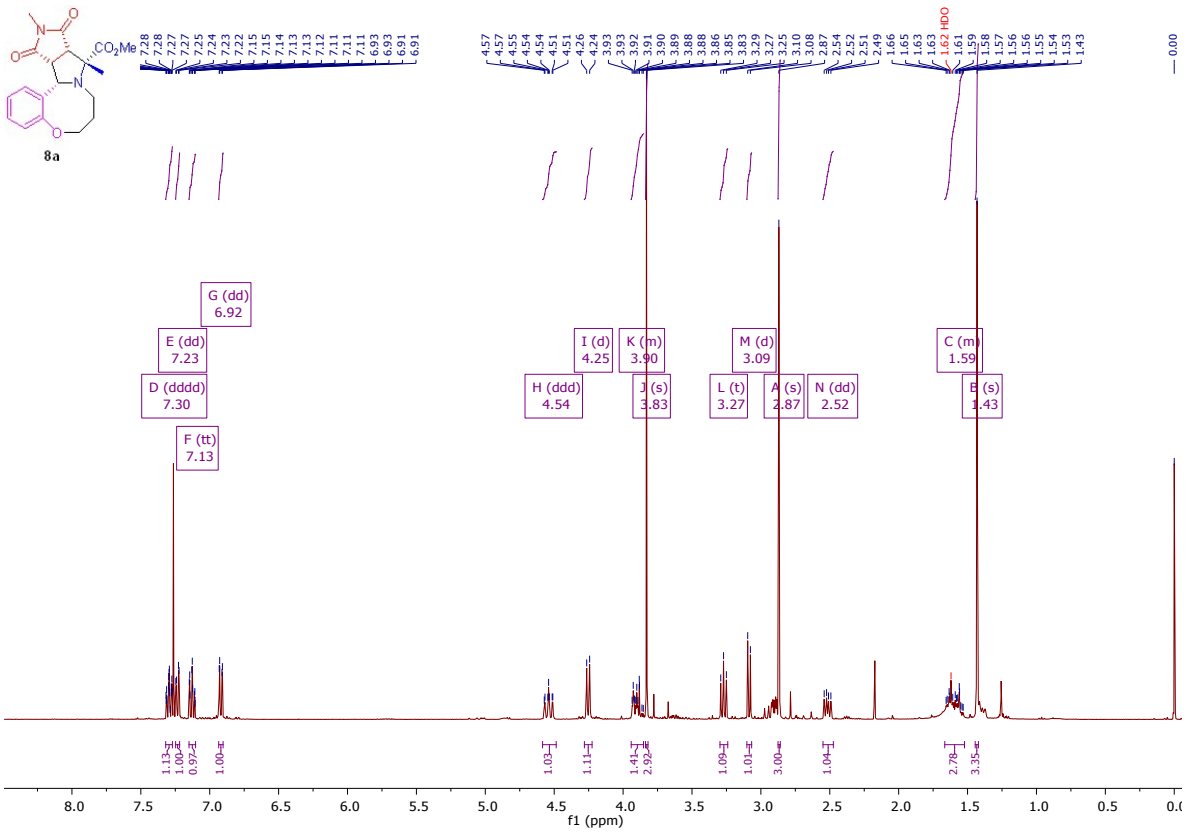


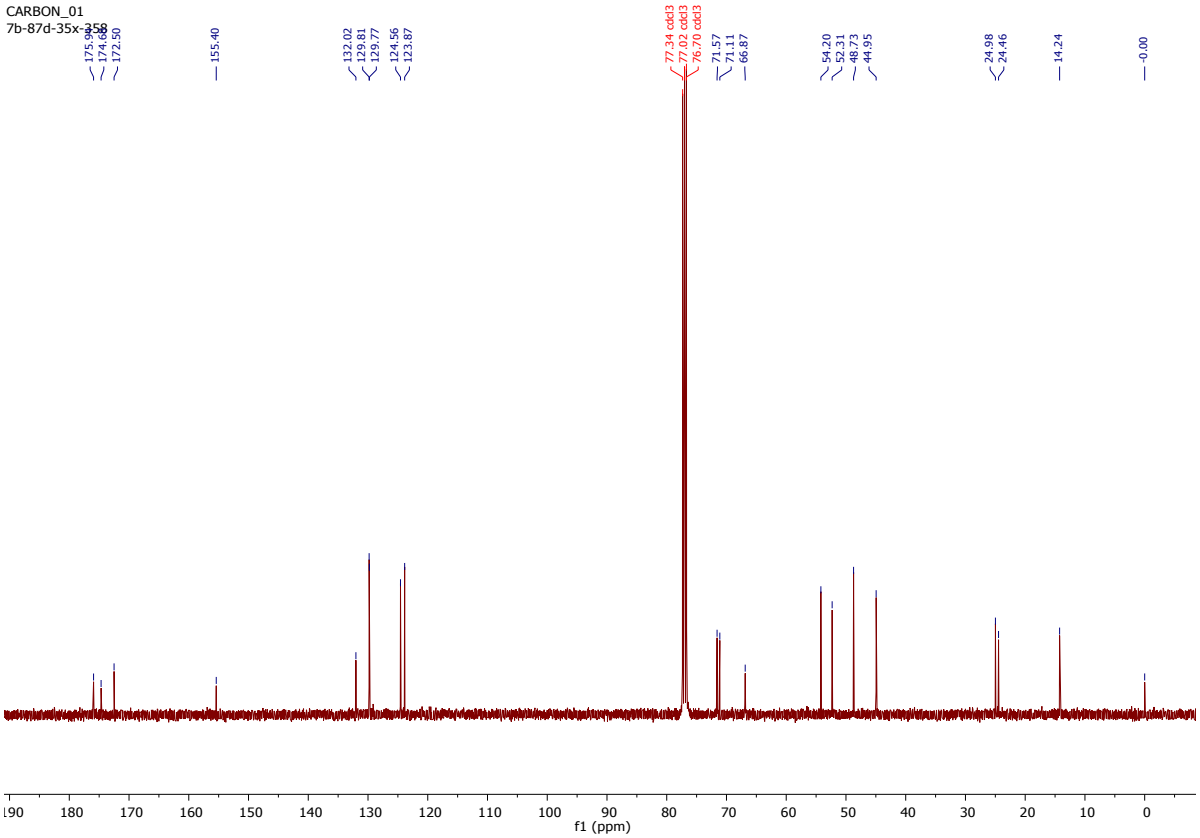

Pr
O
O
N
CO2Me
MeO
N
O
7g
6.92
6.90
6.81
6.78
6.78
6.75
4.50
4.48
4.27
4.25
4.24
4.23
4.22
4.20
3.80
3.40
3.38
3.36
3.36
3.34
3.32
3.14
3.12
2.91
2.89
2.87
2.85
2.83
2.78
2.77
2.75
2.73
2.72
2.71
2.71
2.70
2.68
2.67
1.62
1.48
1.47
0.86
0.84
0.82
-0.00
D (m) 6.77
C (d) 6.91
K (d) 4.49
E (td) 4.24
F (s) 3.80
H (dt) 3.36
G (d) 3.13
I (dd) 2.88
J (ddd) 2.71
L (s) 1.62
A (m) 1.47
B (t) 0.84
1.04
2.10
0.93
0.95
6.23
3.01
0.90
1.12
1.04
2.91
3.00
2.98
f1 (ppm)

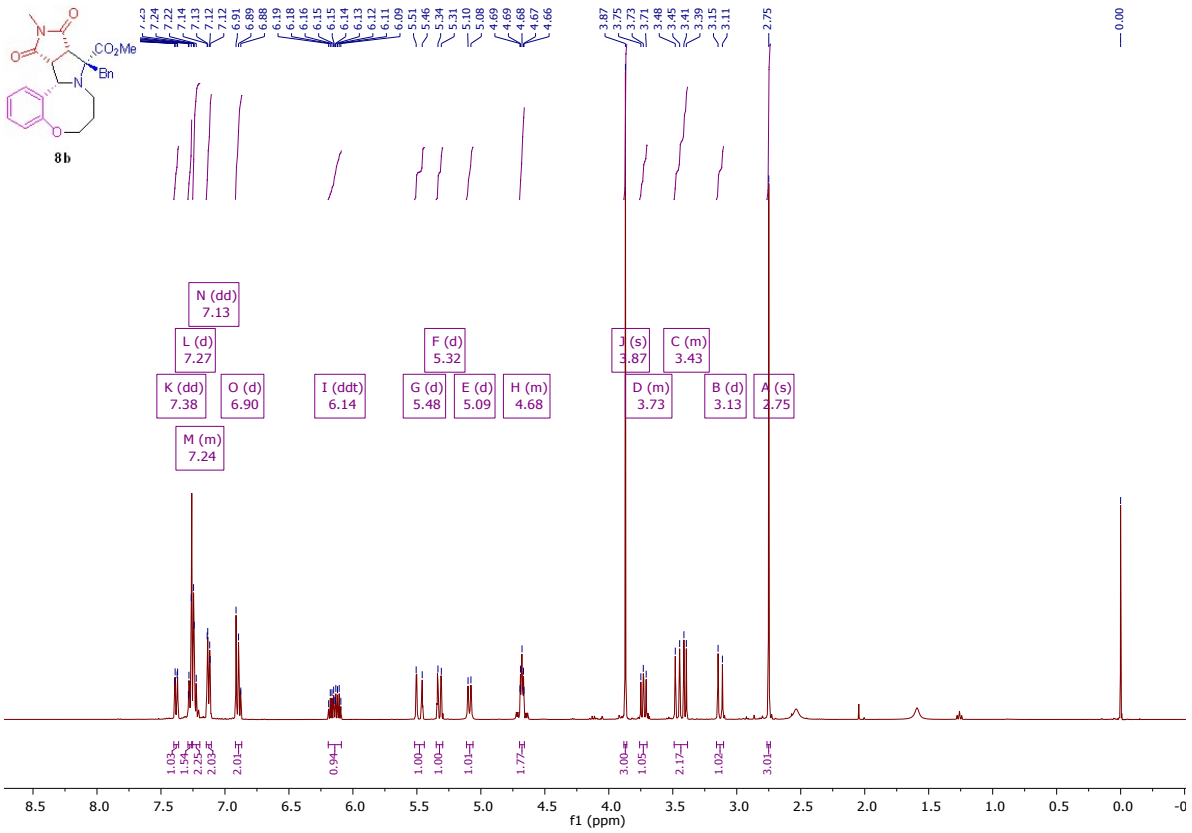

CARBON_01
87d-6L-104a-402
175.79
174.52
172.12
155.19
149.14
128.63
123.97
115.09
113.88
70.29
67.55
55.55
53.83
52.42
47.42
43.64
40.59
20.93
20.70
15.21
10.86
f1 (ppm)

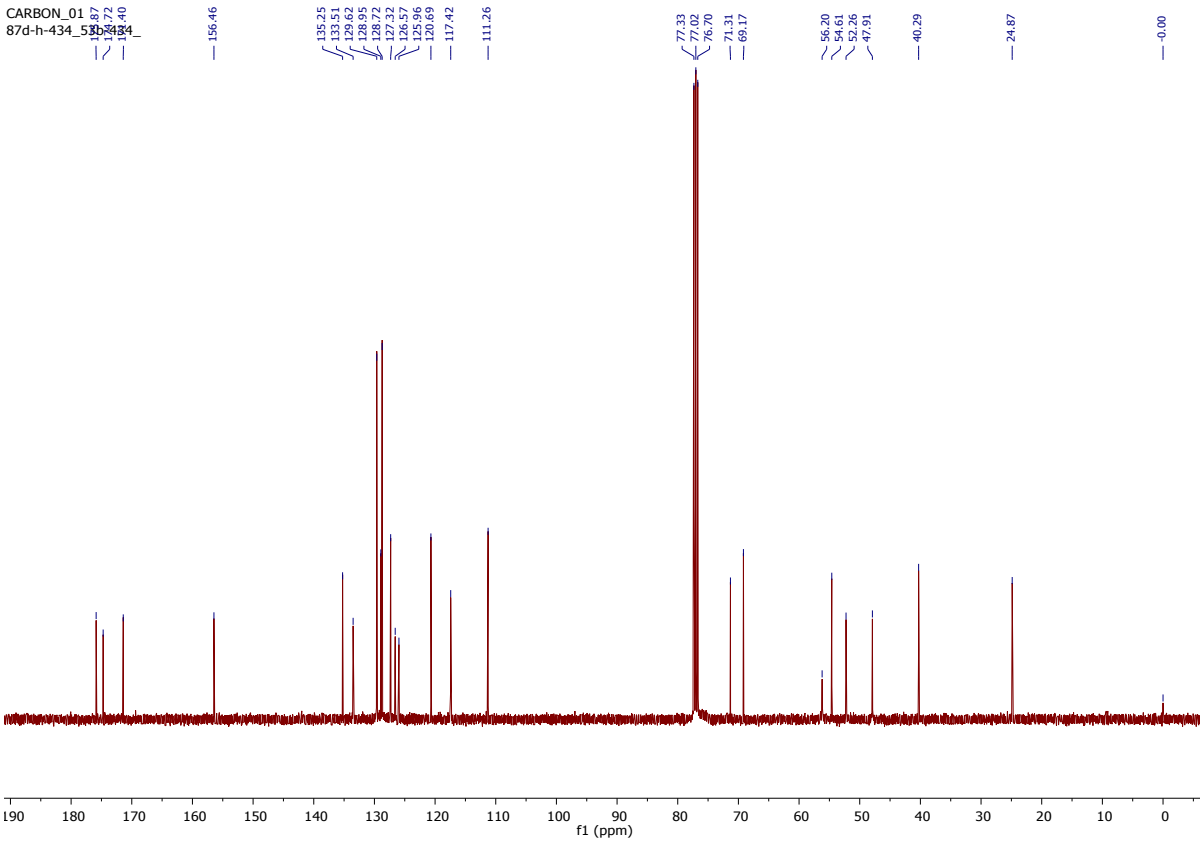

7h
D (m) 7.23
C (dd) 7.54
E (m) 7.11
F (dd) 7.00
H (ddd) 4.34
G (d) 4.64
I (dd) 4.23
B (s) 3.71
A (s) 3.72
N (d) 3.48
J (m) 3.64
O (s) 3.53
L (ddd) 2.93
K (ddd) 3.05
M (s) 1.67
f1 (ppm)

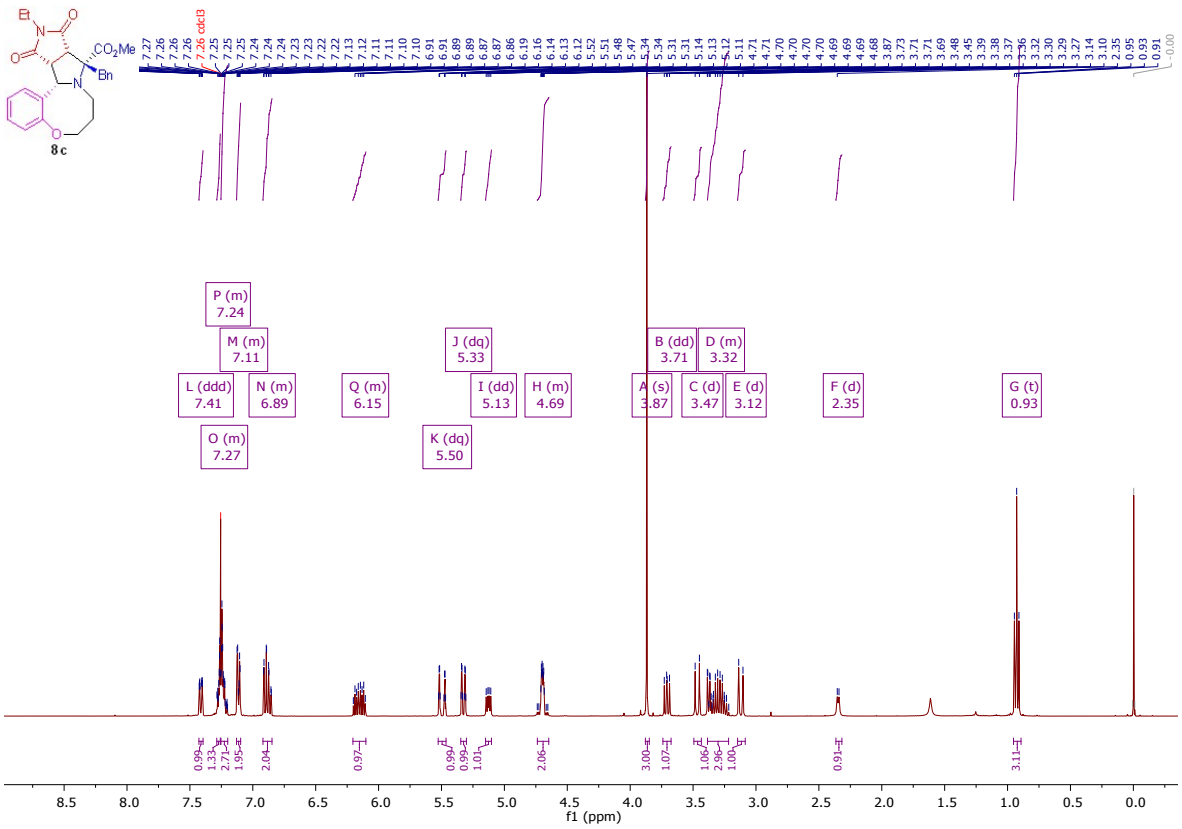

CARBON_01
87d-c-47b-377
f1 (ppm)

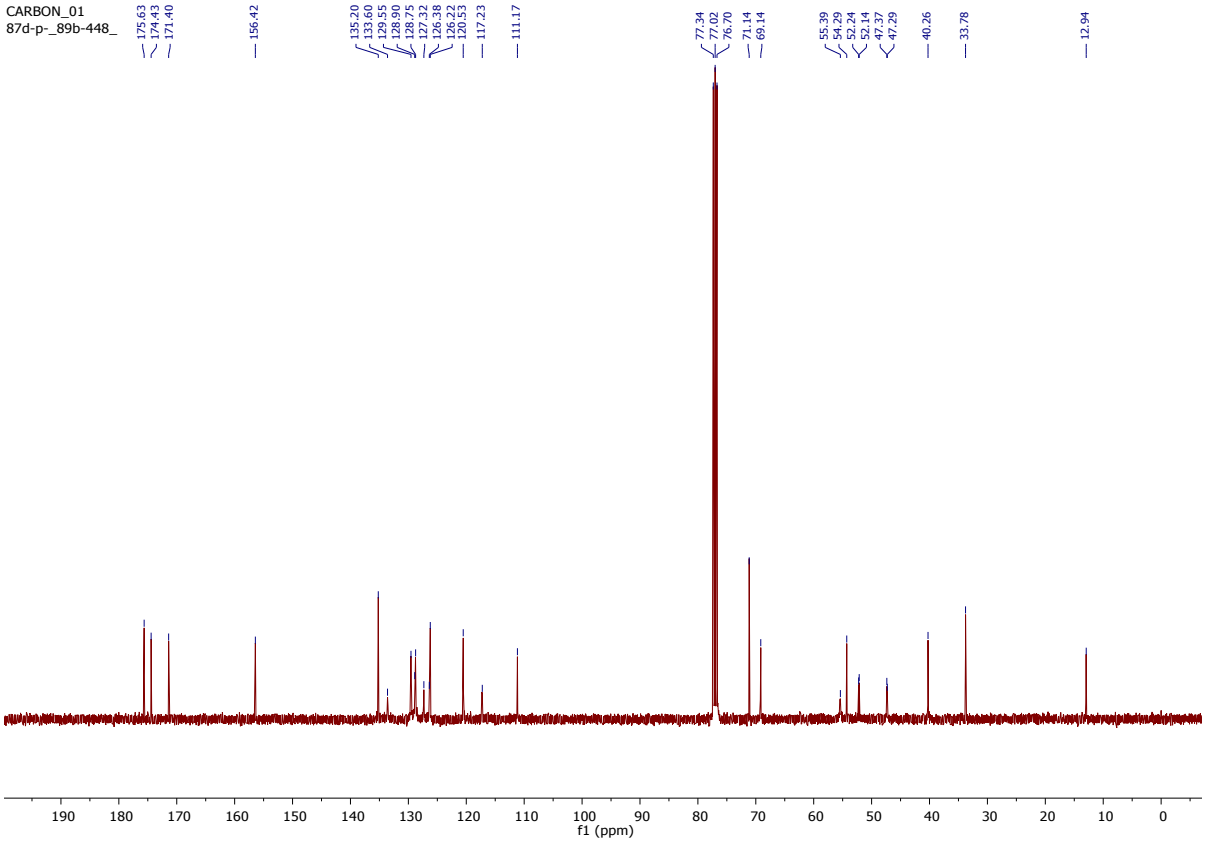

8a
G (dd) 6.92
E (dd) 7.23
D (dddd) 7.30
F (tt) 7.13
I (d) 4.25
K (m) 3.90
H (ddd) 4.54
J (s) 3.83
M (d) 3.09
L (t) 3.27
A (s) 2.87
N (dd) 2.52
C (m) 1.59
B (s) 1.43
1.62 HDO
f1 (ppm)

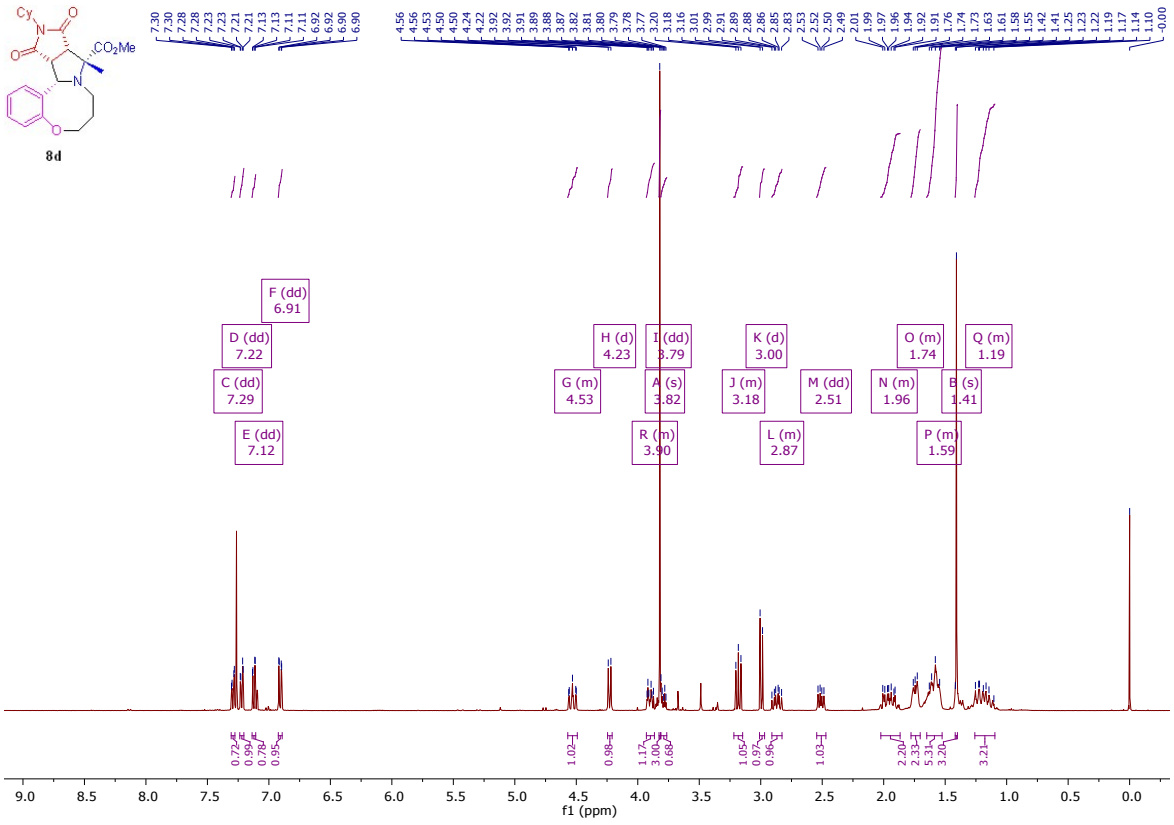

CARBON_01
7b-87d-35x-358
175.98
174.68
172.50
155.40
132.02
129.81
129.77
124.56
123.87
77.34 cdd3
77.02 cdd3
76.70 cdd3
71.57
71.11
66.87
54.20
52.31
48.73
44.95
24.98
24.46
14.24
-0.00
f1 (ppm)

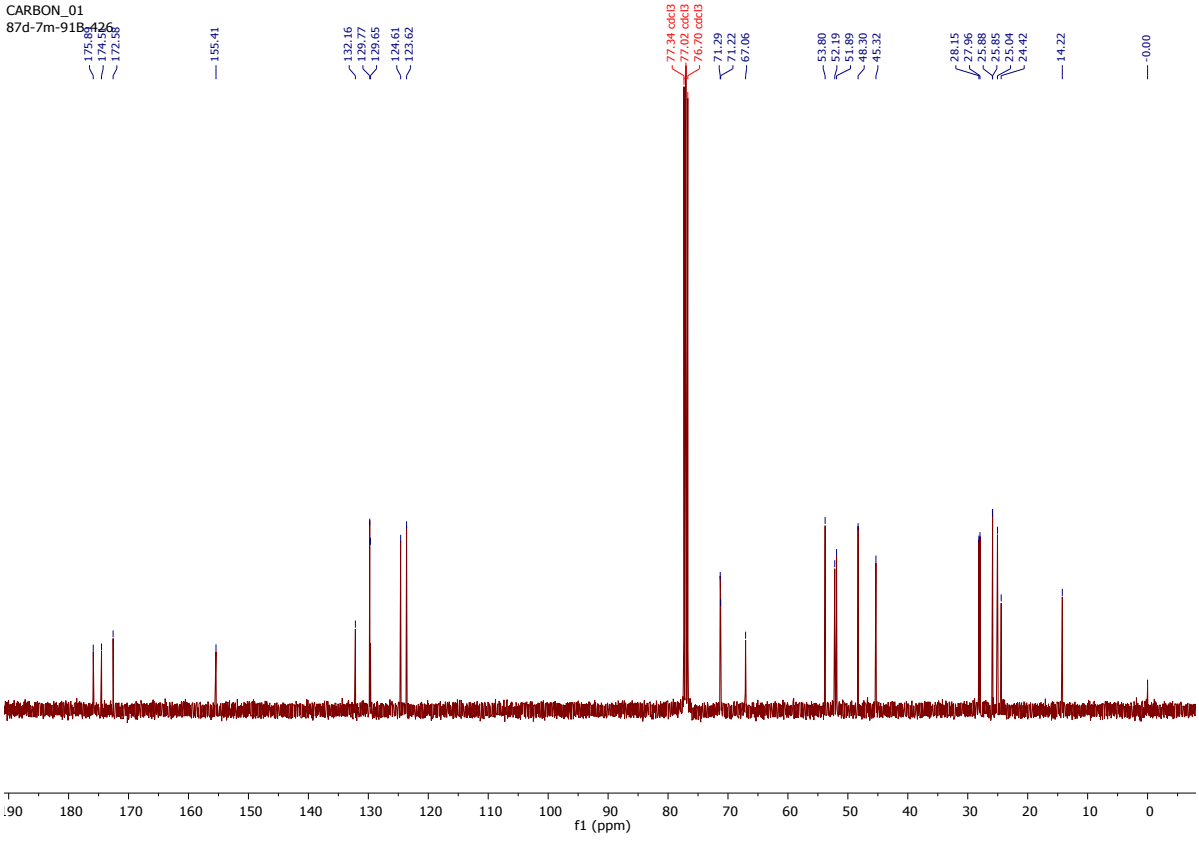

8b
N (dd) 7.13
L (d) 7.27
K (dd) 7.38
O (d) 6.90
M (m) 7.24
I (ddt) 6.14
F (d) 5.32
G (d) 5.48
E (d) 5.09
H (m) 4.68
J (s) 3.87
C (m) 3.43
D (m) 3.73
B (d) 3.13
A (s) 2.75
f1 (ppm)

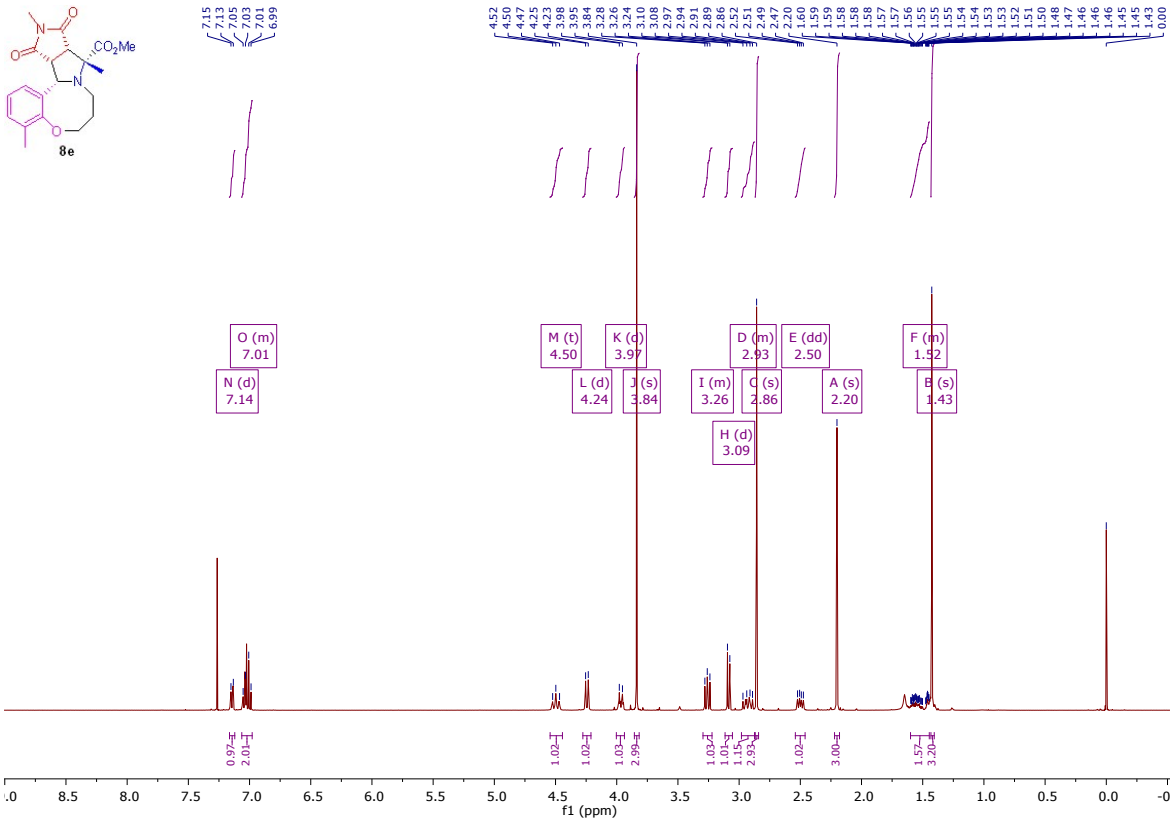

CARBON_01
87d-h-434_53
156.46
135.25
133.51
129.62
128.95
128.72
127.32
126.57
125.96
120.69
117.42
111.26
77.33
77.02
76.70
71.31
69.17
56.20
54.61
52.26
47.91
40.29
24.87
-0.00
f1 (ppm)

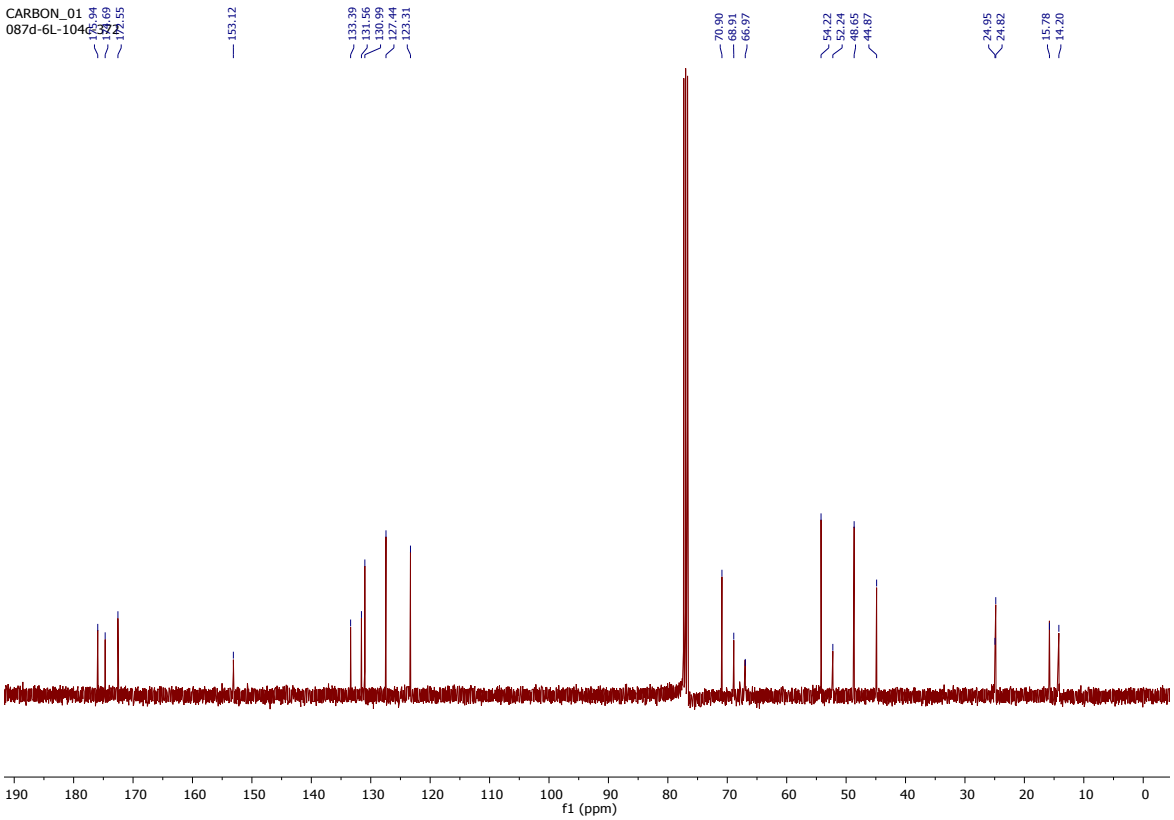

8c
P (m) 7.24
M (m) 7.11
L (ddd) 7.41
N (m) 6.89
O (m) 7.27
Q (m) 6.15
J (dq) 5.33
K (dq) 5.50
I (dd) 5.13
H (m) 4.69
B (dd) 3.71
D (m) 3.32
A (s) 3.87
C (d) 3.47
E (d) 3.12
F (d) 2.35
G (t) 0.93
f1 (ppm)

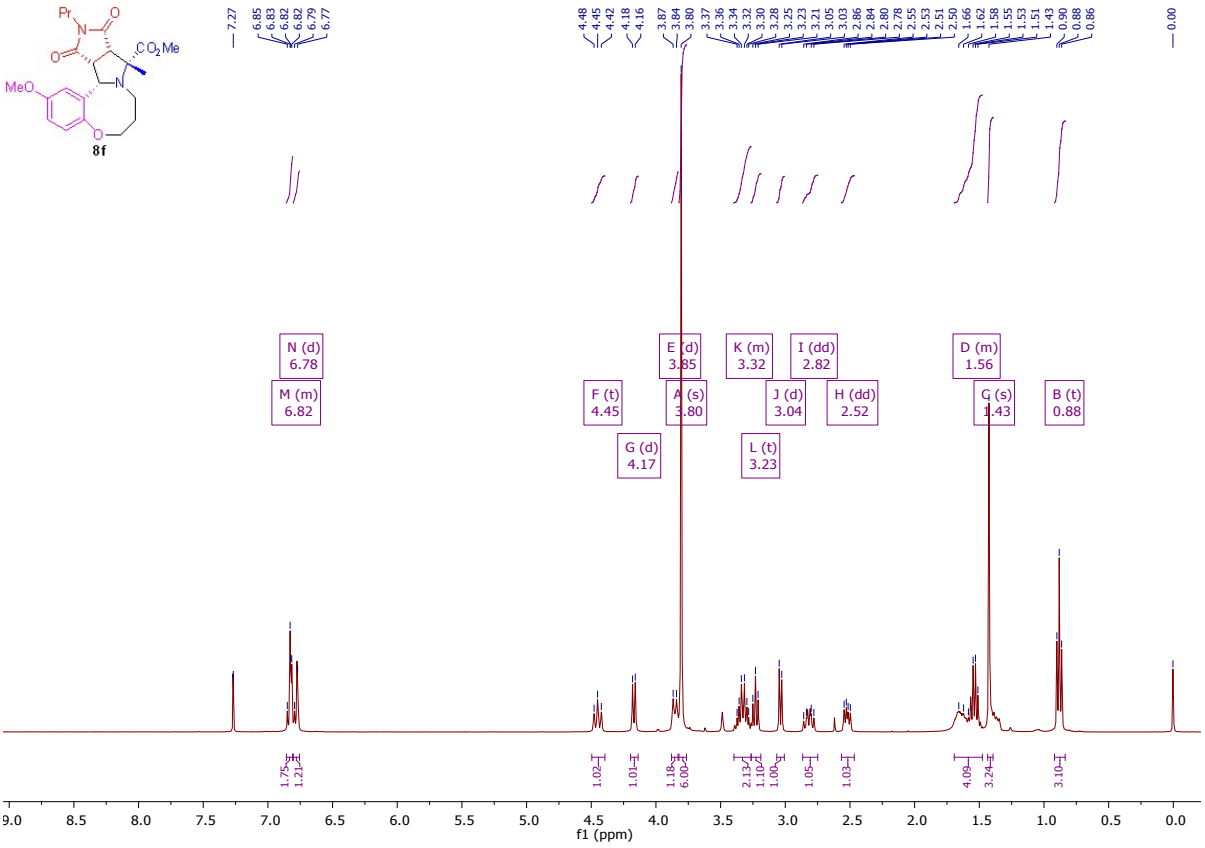

CARBON_01
87d-p-_89b-448_
f1 (ppm)

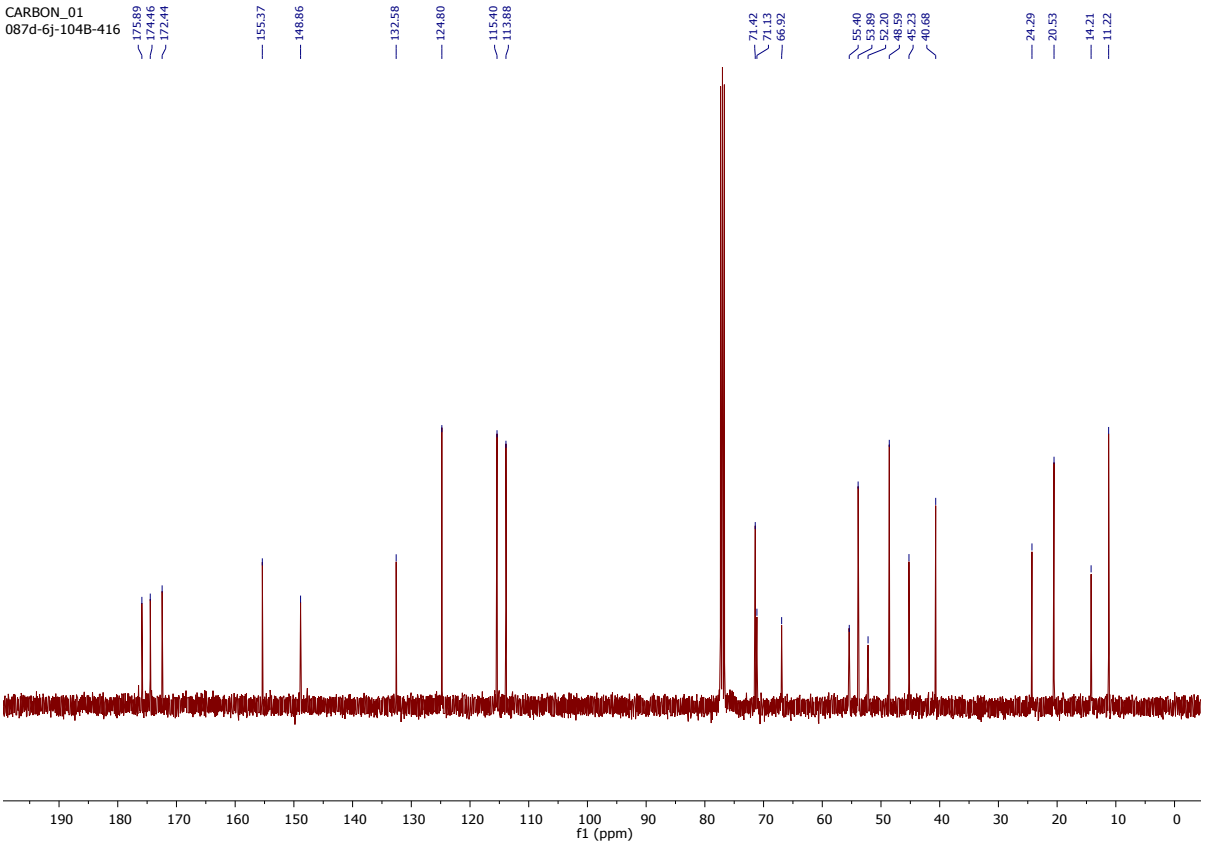

8d
F (dd) 6.91
D (dd) 7.22
C (dd) 7.29
E (dd) 7.12
H (d) 4.23
I (dd) 3.79
G (m) 4.53
A (s) 3.82
R (m) 3.90
K (d) 3.00
J (m) 3.18
L (m) 2.87
M (dd) 2.51
O (m) 1.74
Q (m) 1.19
N (m) 1.96
B (s) 1.41
P (m) 1.59
f1 (ppm)

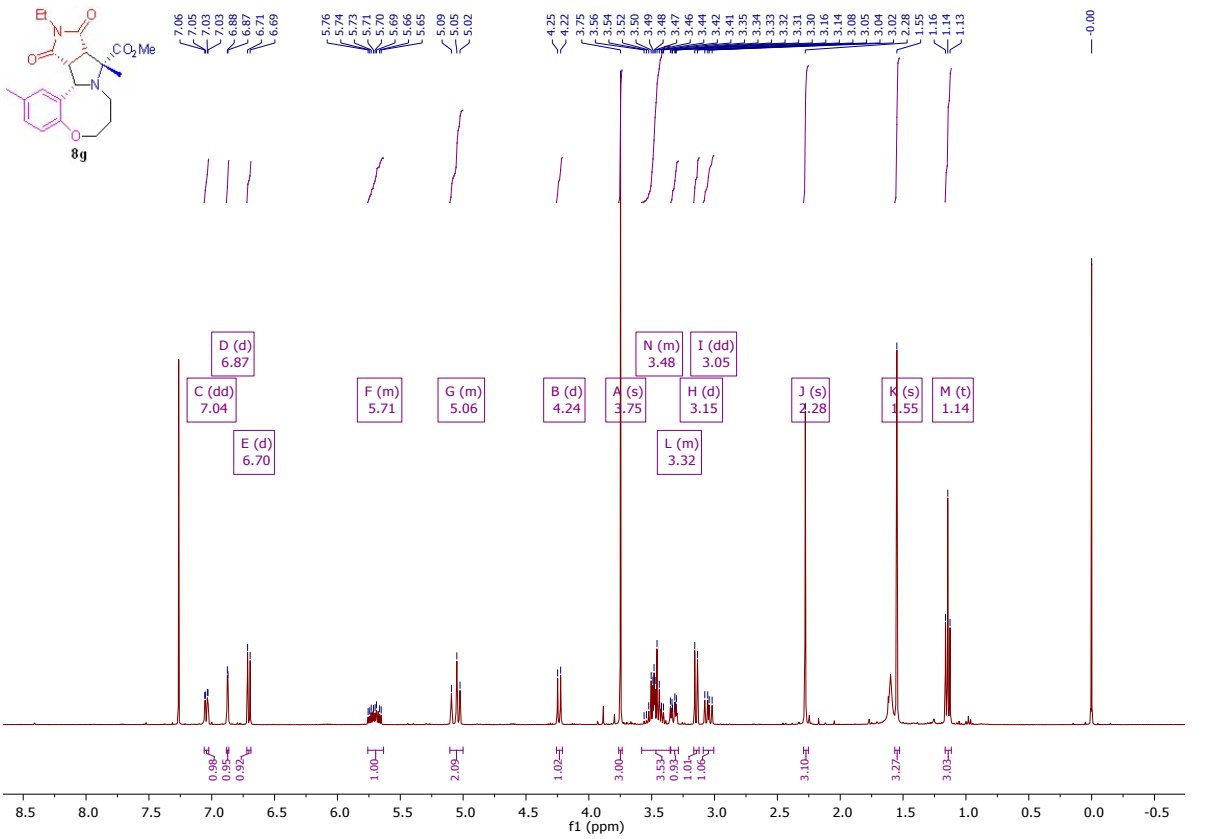

CARBON_01
87d-7m-91B-426
f1 (ppm)

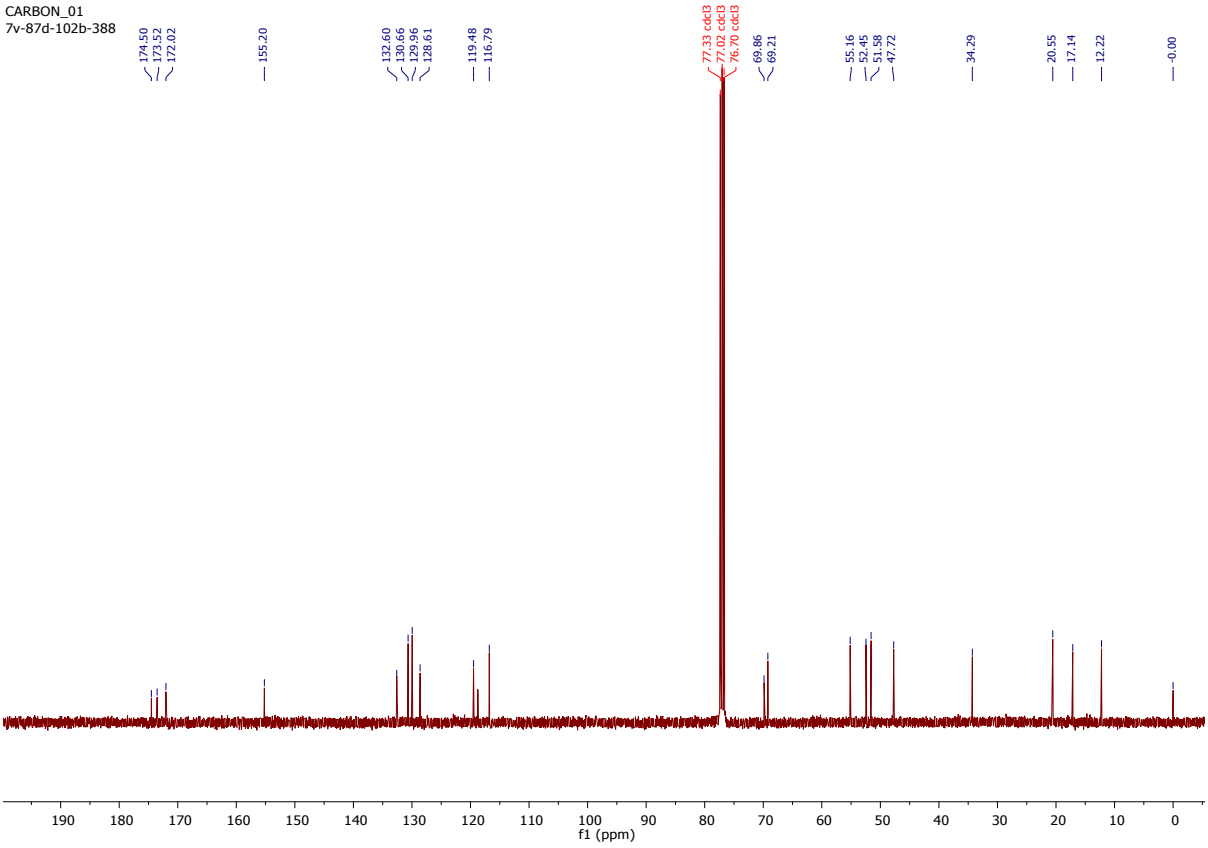

8e
O (m) 7.01
N (d) 7.14
M (t) 4.50
K (d) 3.97
L (d) 4.24
J (s) 3.84
D (m) 2.93
E (dd) 2.50
I (m) 3.26
C (s) 2.86
H (d) 3.09
A (s) 2.20
F (m) 1.52
B (s) 1.43
f1 (ppm)

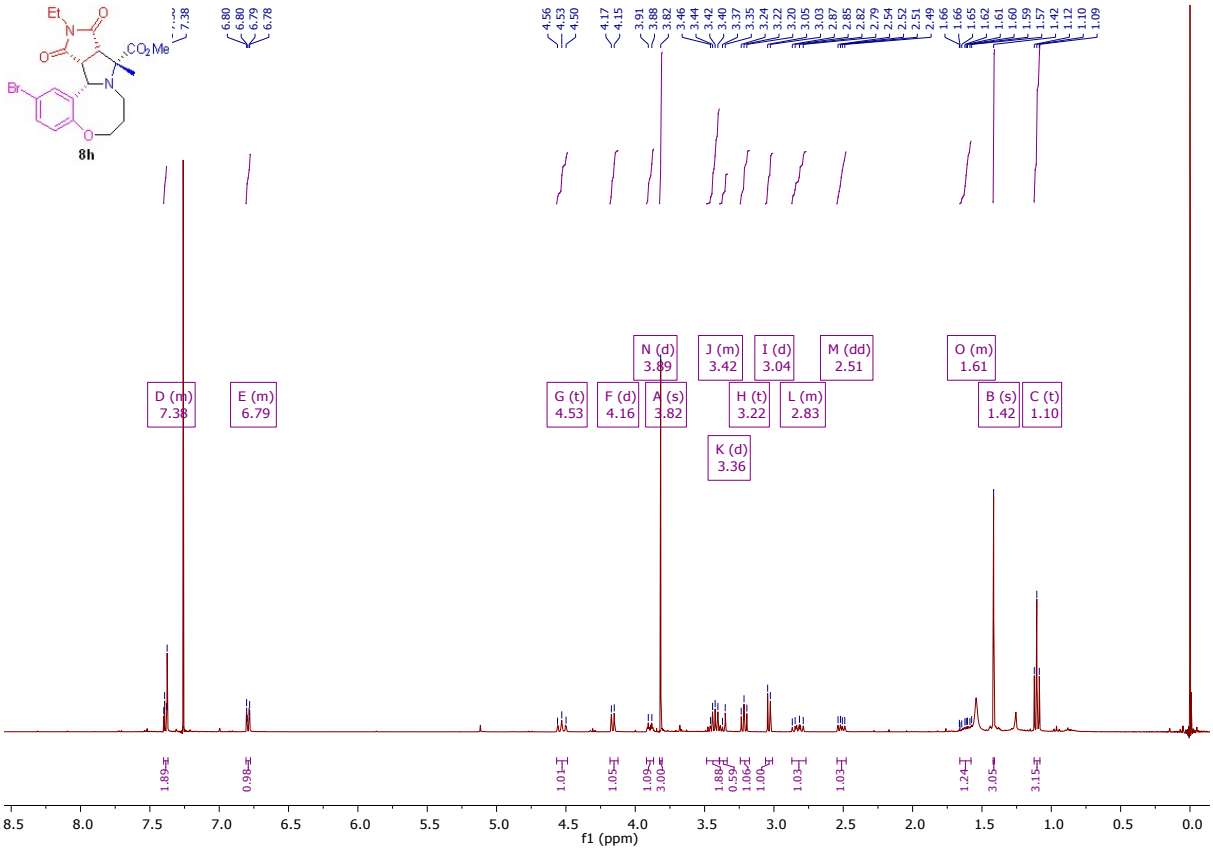

CARBON_01
087d-6L-104
f1 (ppm)

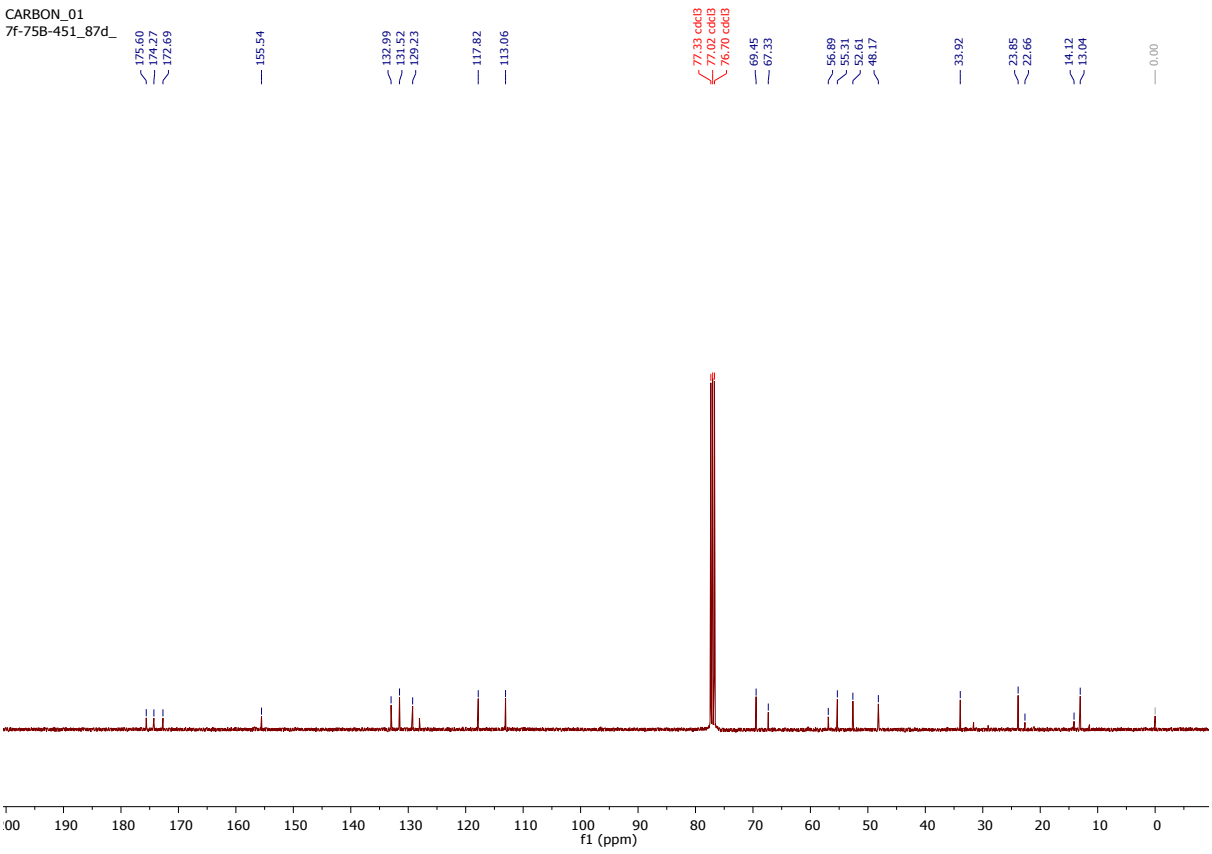

8f
N (d) 6.78
M (m) 6.82
F (t) 4.45
G (d) 4.17
E (d) 3.85
A (s) 3.80
K (m) 3.32
L (t) 3.23
I (dd) 2.82
J (d) 3.04
H (dd) 2.52
D (m) 1.56
C (s) 1.43
B (t) 0.88
f1 (ppm)

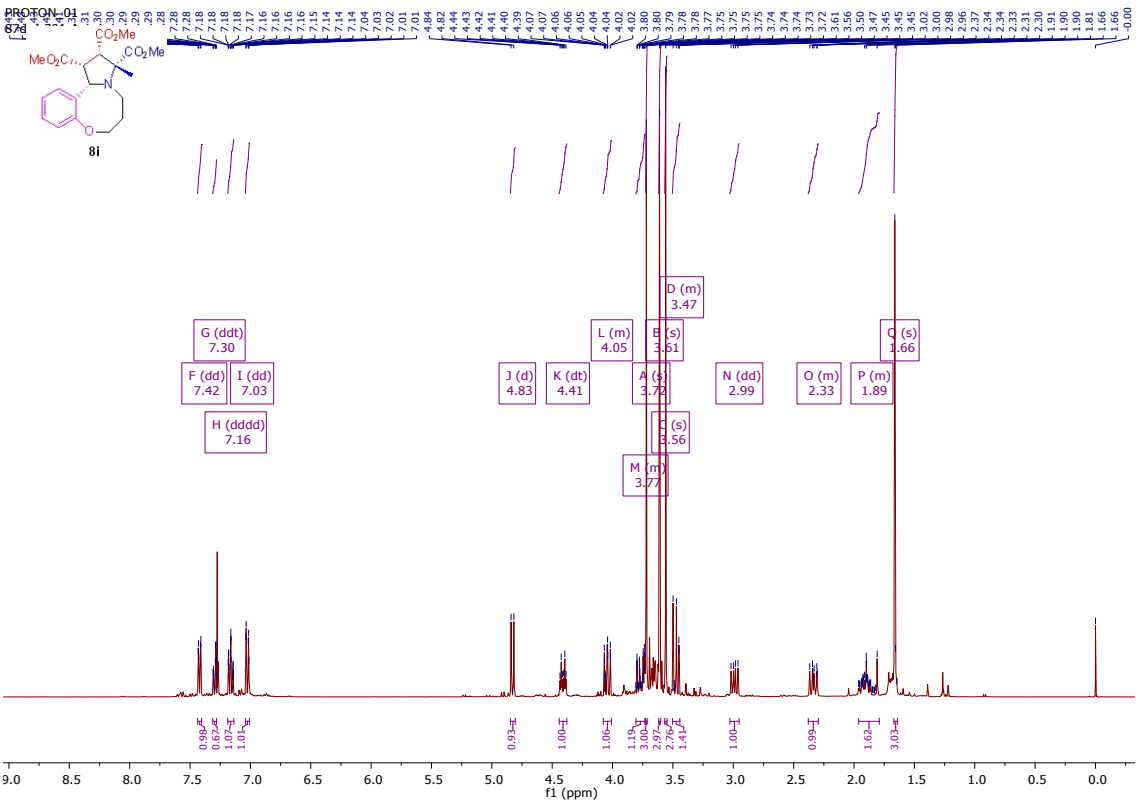

CARBON_01
087d-6j-104B-416
f1 (ppm)

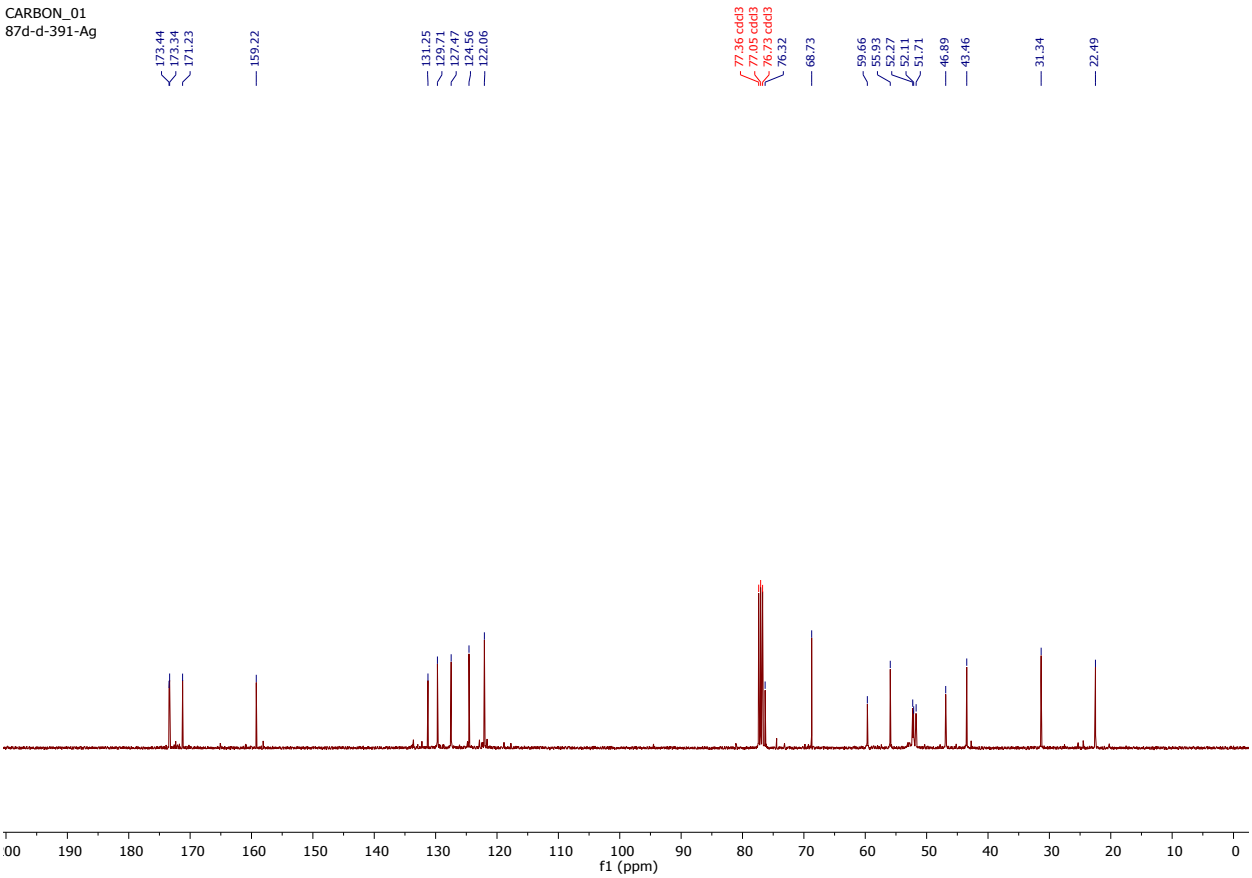

8g
D (d) 6.87
C (dd) 7.04
E (d) 6.70
F (m) 5.71
G (m) 5.06
B (d) 4.24
A (s) 3.75
N (m) 3.48
I (dd) 3.05
H (d) 3.15
L (m) 3.32
J (s) 2.28
K (s) 1.55
M (t) 1.14
f1 (ppm)


CARBON_01
7v-87d-102b-388
f1 (ppm)


8h
D (m) 7.38
E (m) 6.79
G (t) 4.53
F (d) 4.16
A (s) 3.82
N (d) 3.89
K (d) 3.36
J (m) 3.42
H (t) 3.22
I (d) 3.04
L (m) 2.83
M (dd) 2.51
O (m) 1.61
B (s) 1.42
C (t) 1.10
f1 (ppm)

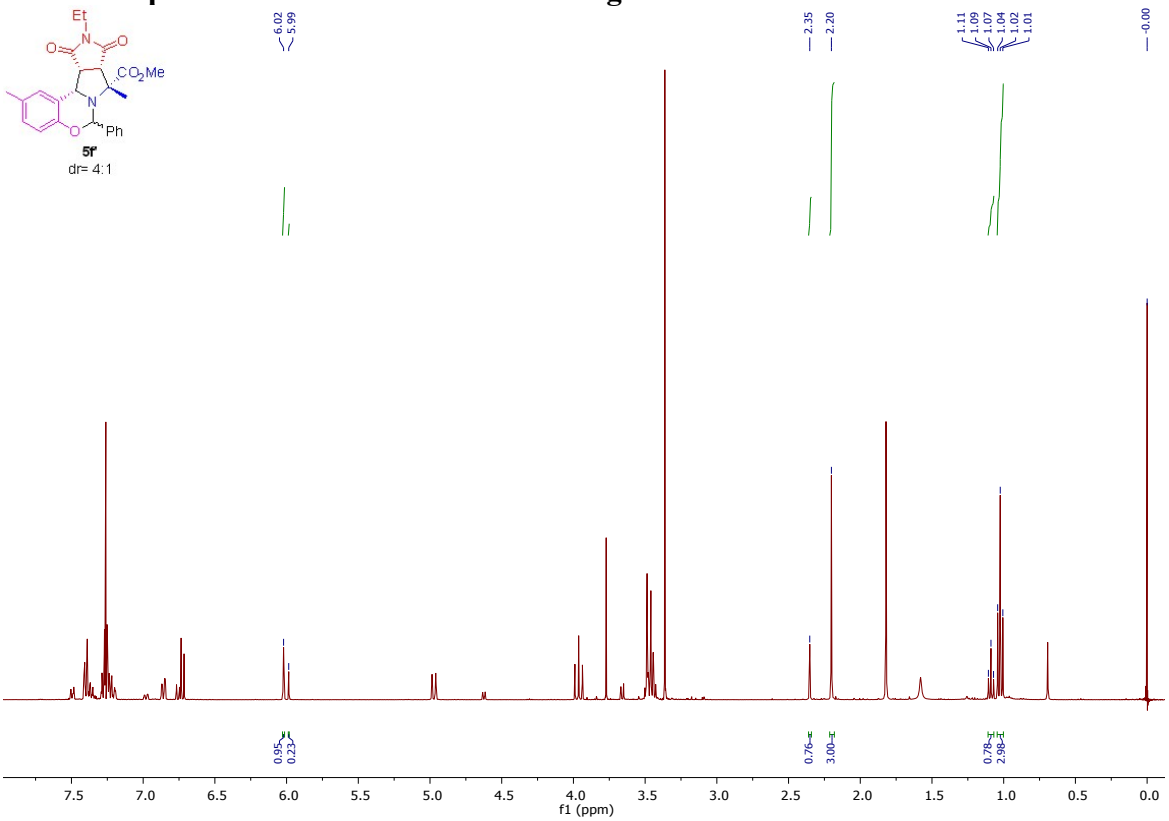

CARBON_01
7f-75B-451_87d_
f1 (ppm)

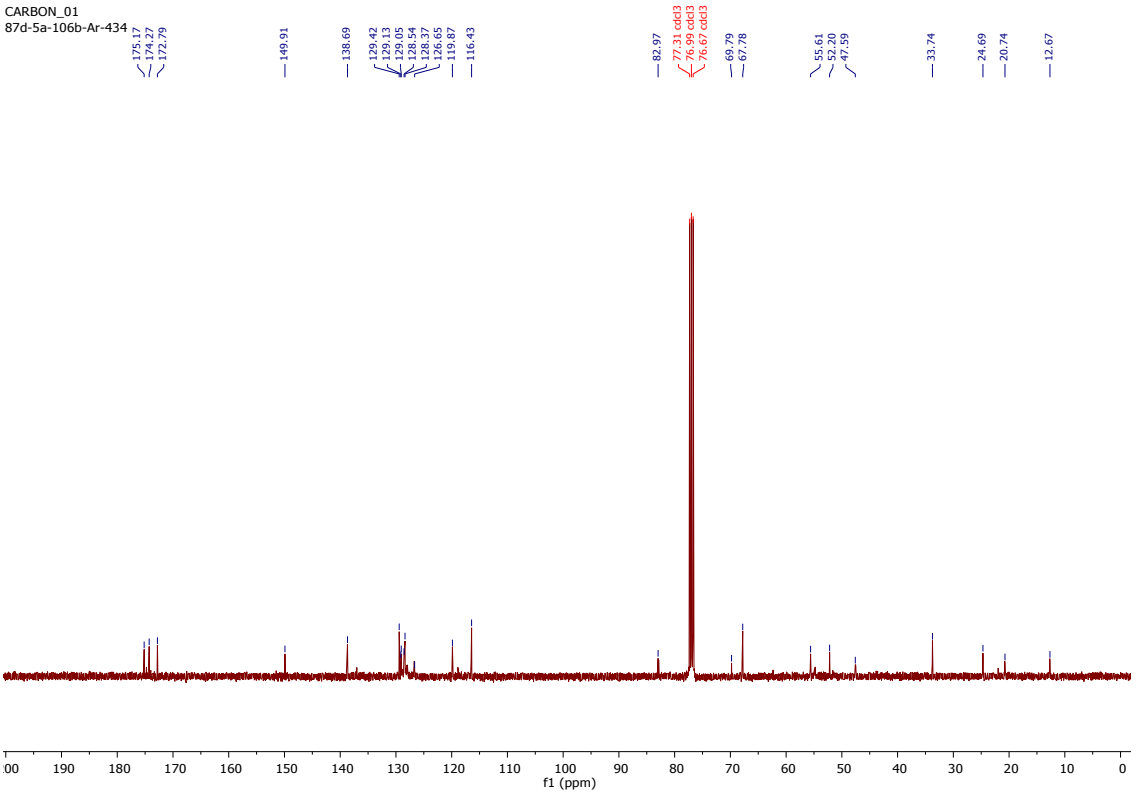

PROTON_01
87d
8i
G (ddt) 7.30
F (dd) 7.42
I (dd) 7.03
H (dddd) 7.16
J (d) 4.83
K (dt) 4.41
L (m) 4.05
D (m) 3.47
B (s) 3.61
A (s) 3.72
C (s) 3.56
M (m) 3.77
N (dd) 2.99
O (m) 2.33
P (m) 1.89
Q (s) 1.66
f1 (ppm)


CARBON_01
87d-d-391-Ag
173.44
173.34
171.23
159.22
131.25
129.71
127.47
124.56
122.06
77.36 cdd3
77.05 cdd3
76.73 cdd3
76.32
68.73
59.66
55.93
52.27
52.11
51.71
46.89
43.46
31.34
22.49
f1 (ppm)

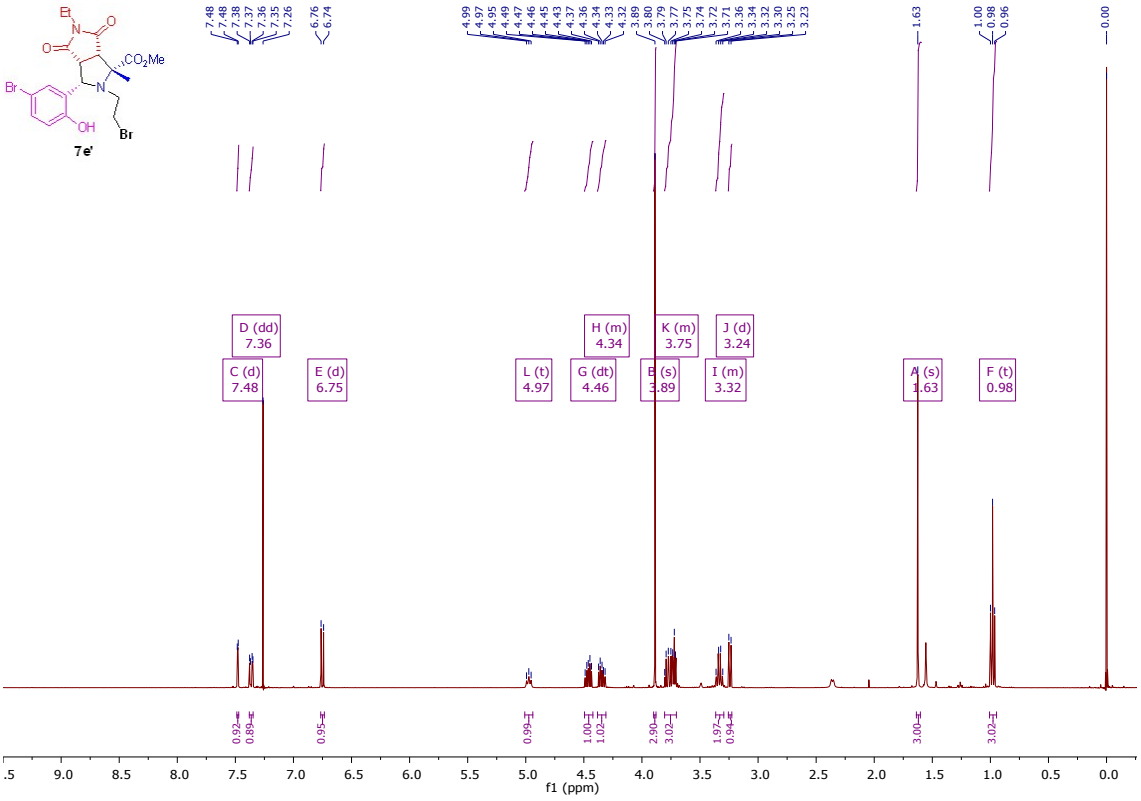
5.0 Spectra of 5f', 7e, 7e', 7h and 7j

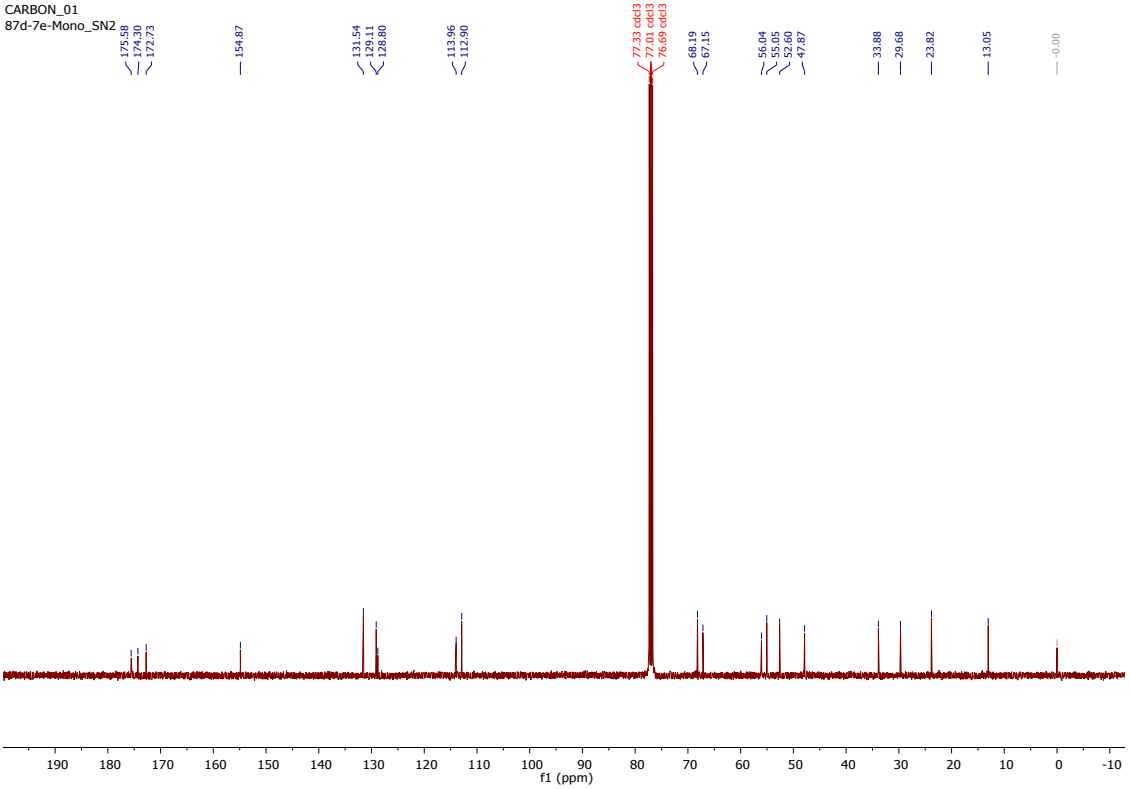
5.1 NMR spectra of 5f' diastereomer showing dr ratio



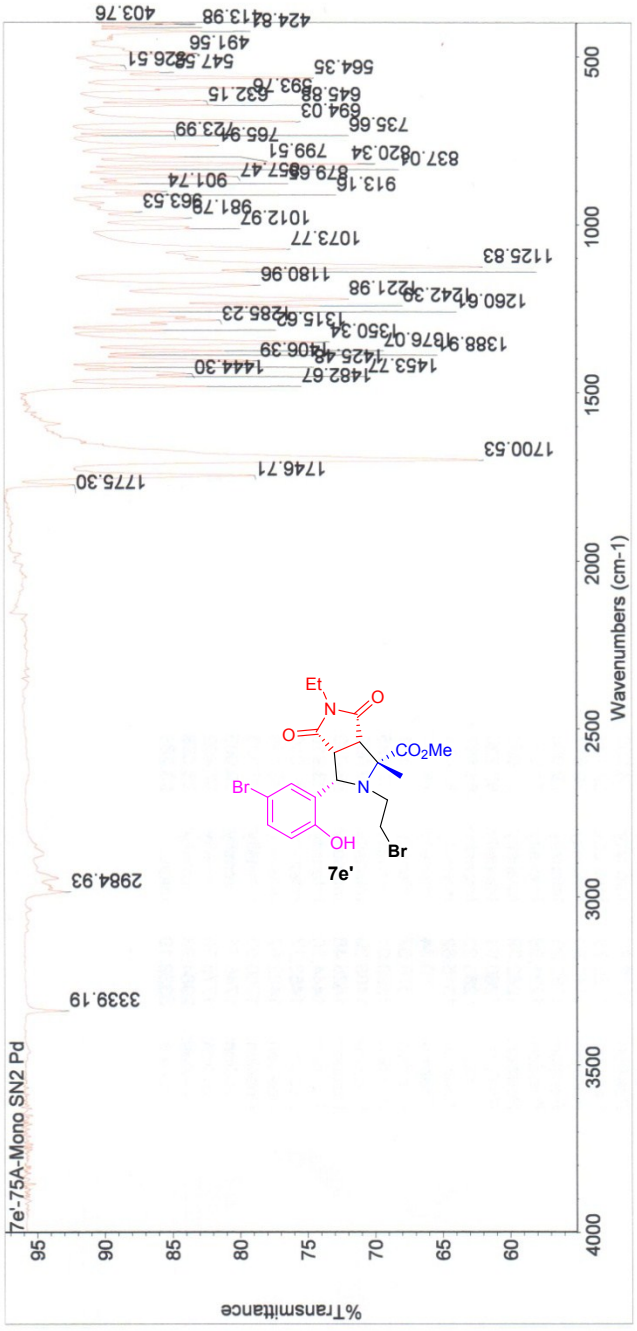


5.2 NMR spectra of mono S_N2 product 7e'





5.3 IR spectrum of mono S_N2 product 7e'



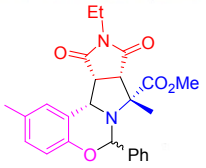
Tue Mar 06 14:29:45 2018 (GMT-05:00)
FIND PEAKS:
Spectrum: 7e'-75A-Mono SN2 Pd
Region: 4000.00 400.00
Absolute threshold: 93.735
Sensitivity: 50
Peak list:

Position:	403.76	Intensity:	84.388
Position:	413.98	Intensity:	88.238
Position:	424.81	Intensity:	82.874
Position:	491.56	Intensity:	83.302
Position:	526.51	Intensity:	88.787
Position:	547.52	Intensity:	85.901
Position:	564.35	Intensity:	74.639
Position:	593.76	Intensity:	79.552

5.4 LC-MS of 5f', 7h, 7e and 7j

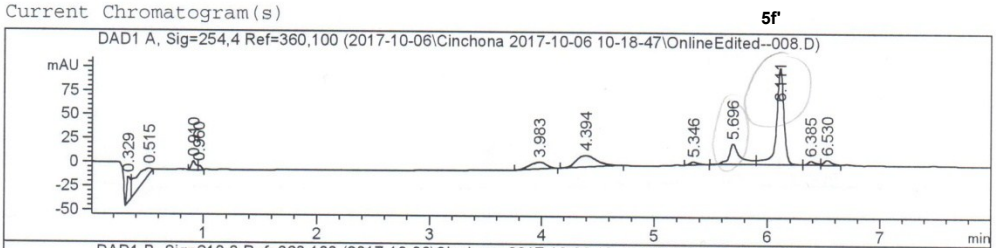
Print of all graphic windows
Data File : C:\Chem32\1\Data\2017-10-06\Cinchona 2017-10-06 10-18-47\OnlineEdited--008.D
Sample Name : 10B-Ar-434

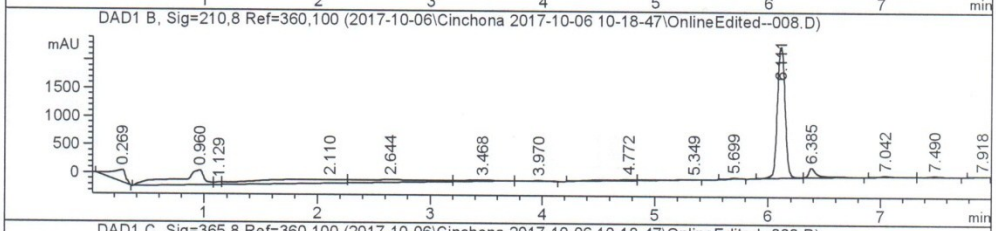
Acq. Operator : SYSTEM Seq. Line : 8
Acq. Instrument : LCMS Location : 23
Injection Date : 10/6/2017 11:23:04 AM Inj : 1
Inj Volume : 4.000 µl
Method : C:\Chem32\1\Data\2017-10-06\Cinchona 2017-10-06 10-18-47\XFnormal_A.M (Sequence Method)
Last changed : 10/6/2017 10:18:47 AM by SYSTEM
Method Info : created 09/11/2015 by Kenny Pham

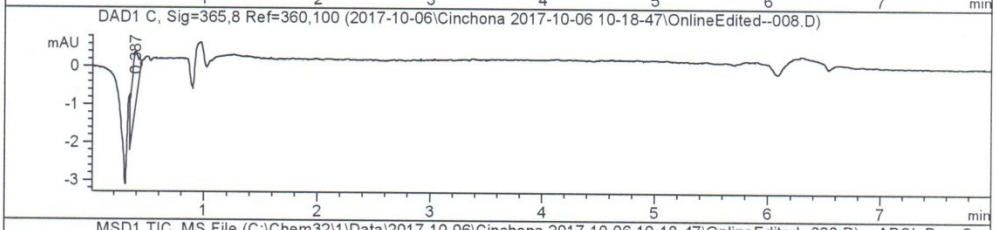


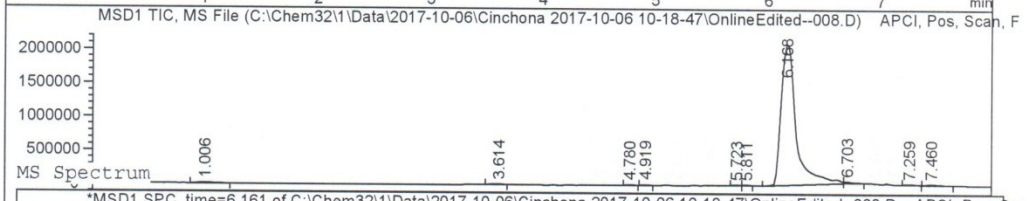
5f'

Current Chromatogram(s)

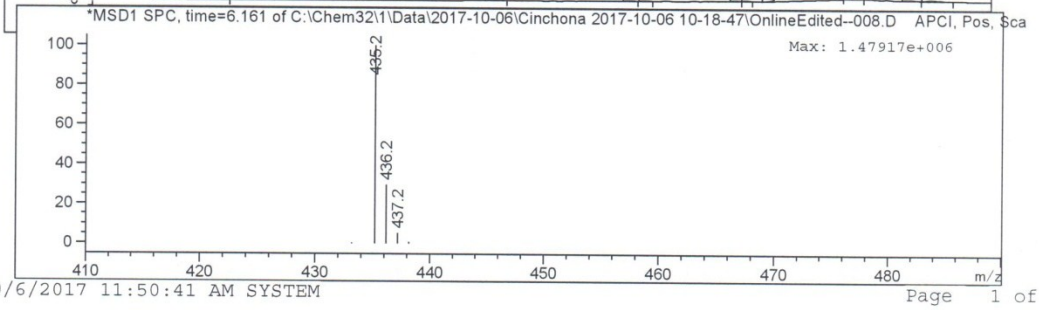








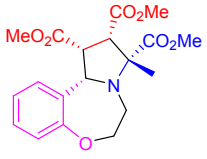
MS Spectrum



LCMS 10/6/2017 11:50:41 AM SYSTEM

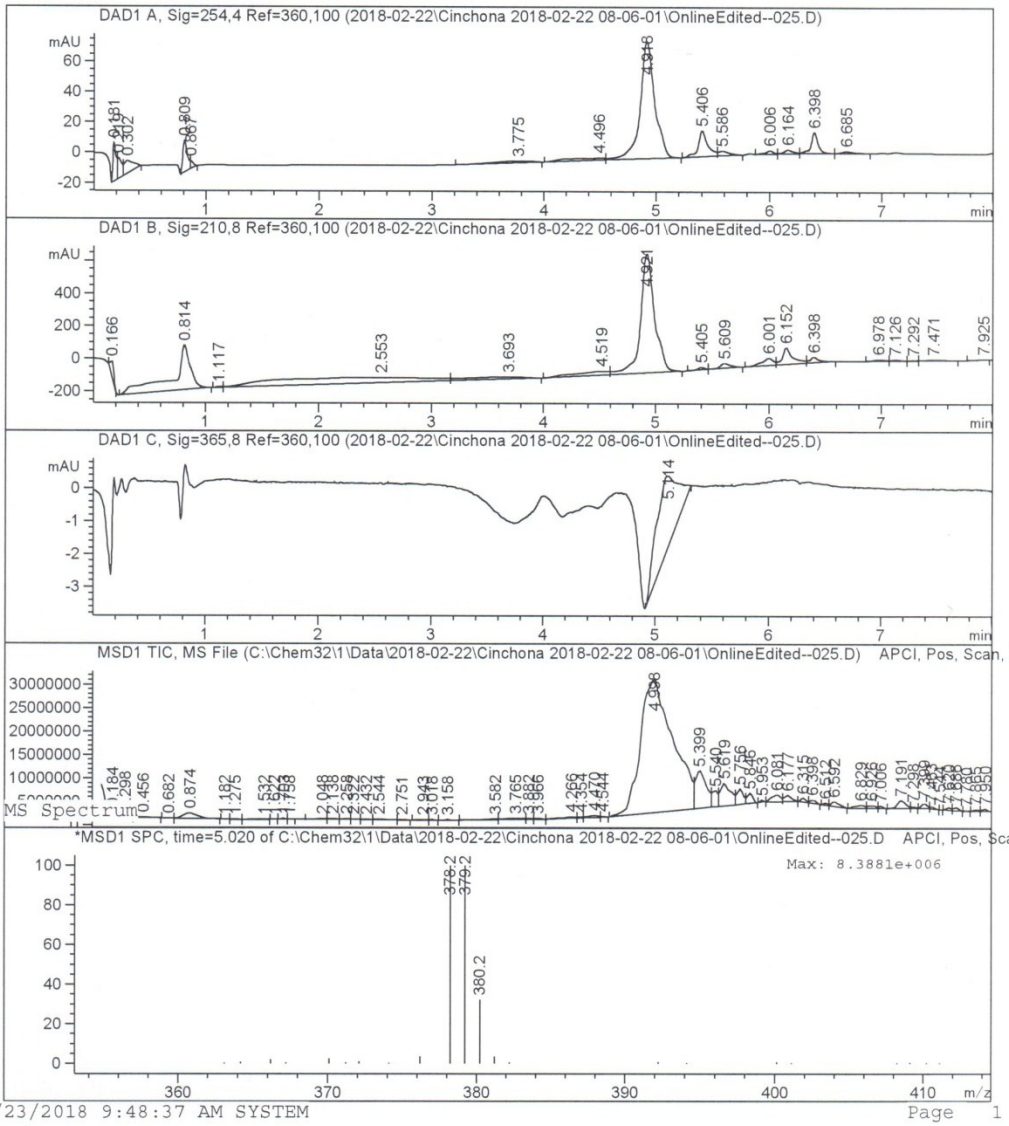
Print of all graphic windows
Data File : C:\Chem32\1\Data\2018-02-22\Cinchona 2018-02-22 08-06-01\OnlineEdited--025.D
Sample Name : 47B-E-377

Acq. Operator : SYSTEM Seq. Line : 25
Acq. Instrument : LCMS Location : 56
Injection Date : 2/22/2018 11:43:06 AM Inj : 1
Inj Volume : 4.000 µl
Method : C:\Chem32\1\Data\2018-02-22\Cinchona 2018-02-22 08-06-01\XFnormal_A.M (Sequence Method)
Last changed : 2/22/2018 8:06:01 AM by SYSTEM
Method Info : created 09/11/2015 by Kenny Pham



7h

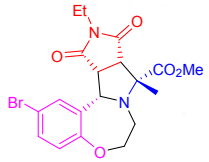
Current Chromatogram(s)



LCMS 2/23/2018 9:48:37 AM SYSTEM

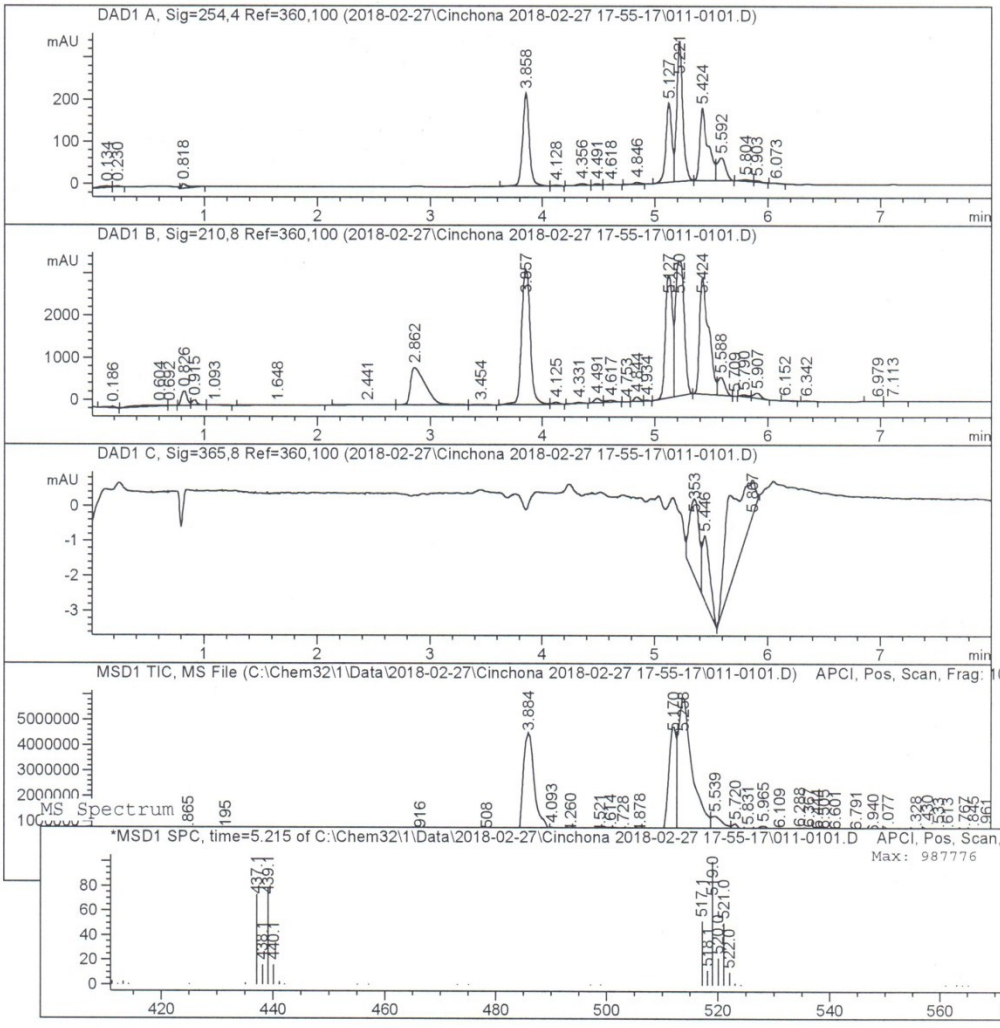
Print of all graphic windows
Data File : C:\Chem32\1\Data\2018-02-27\Cinchona 2018-02-27 17-55-17\011-0101.D
Sample Name : 75A-7E

Acq. Operator : SYSTEM Seq. Line : 1
Acq. Instrument : LCMS Location : 11
Injection Date : 2/27/2018 5:56:17 PM Inj : 1
Inj Volume : 4.000 µl
Method : C:\Chem32\1\Data\2018-02-27\Cinchona 2018-02-27 17-55-17\XFnormal_A.M (Sequence Method)
Last changed : 2/27/2018 5:55:17 PM by SYSTEM
Method Info : created 09/11/2015 by Kenny Pham



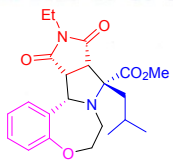
7e

Current Chromatogram(s)

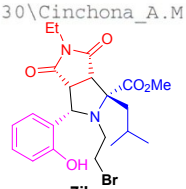


Print of all graphic windows
Data File : C:\Chem32\1\Data\2016-12-14\Cinchona 2016-12-14 15-28-30\OnlineEdited--014.D
Sample Name : 57b-et-399

Acq. Operator : SYSTEM Seq. Line : 14
Acq. Instrument : LCMS Location : 24
Injection Date : 12/14/2016 5:14:00 PM Inj : 1
Inj Volume : 4.000 µl
Method : C:\Chem32\1\Data\2016-12-14\Cinchona 2016-12-14 15-28-30\Cinchona_A.M (Sequence Method)
Last changed : 12/14/2016 3:28:30 PM by SYSTEM
Method Info : created 09/11/2015 by Kenny Pham

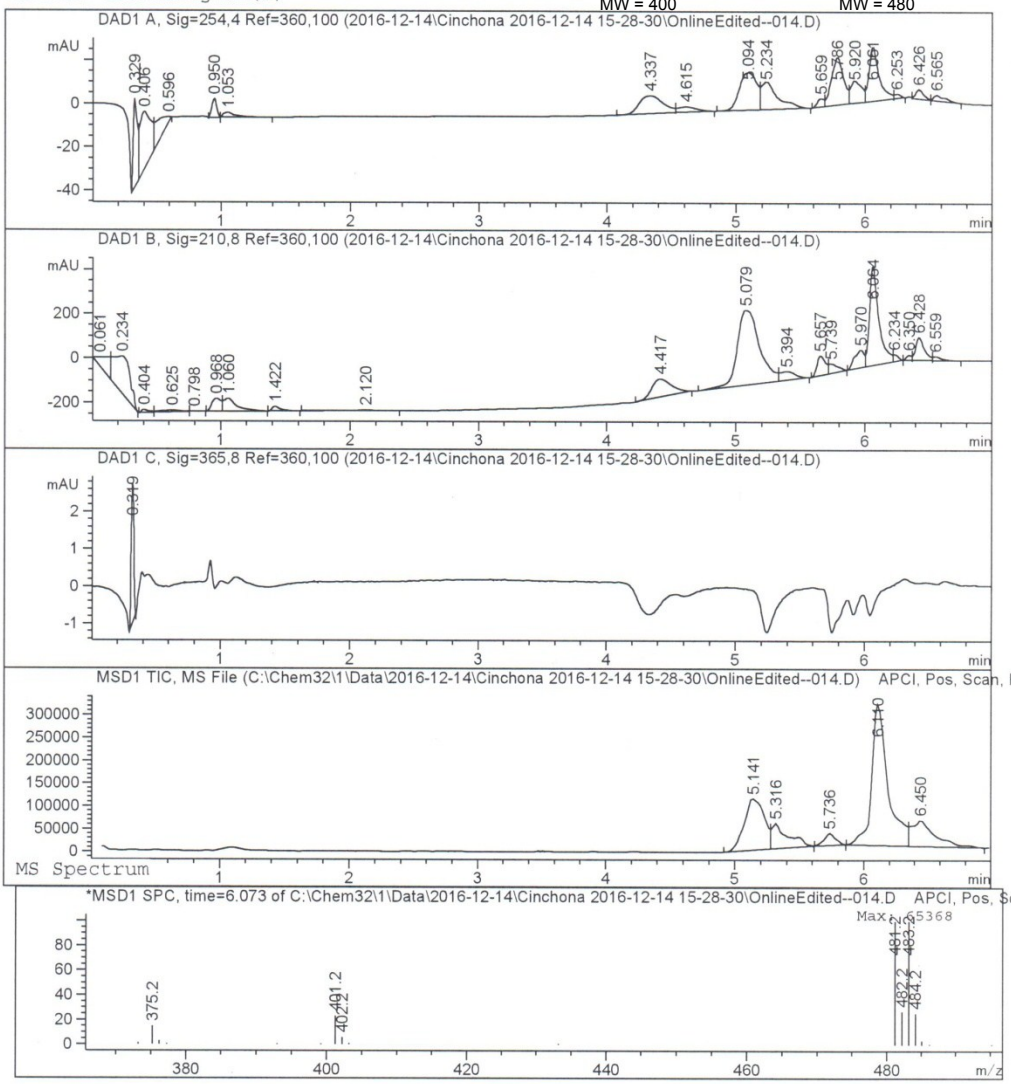


7j
MW = 400



7j'
MW = 480

Current Chromatogram(s)



LCMS 3/6/2018 7:13:46 PM SYSTEM

6.0 Green chemistry metrics analysis

The following formulae were used for calculating Atom Economy (AE), Atom Efficiency (AEf), Carbon Efficiency (CE), Reaction Mass Efficiency (RME), Optimum Efficiency (OE), Process Mass Intensity (PMI), E factor, Solvent and Water Intensity (SI and WI).[1-14]

$$AE = \frac{Molecular\ weight\ of\ product}{Total\ molecular\ weight\ of\ reactants} X\ 100$$

$$AEf = AE\ X\ yield\%$$

$$CE = \frac{Amount\ of\ carbon\ in\ the\ product}{Total\ carbon\ present\ in\ reactants} X\ 100$$

$$RME = \frac{Mass\ of\ isolated\ \ product}{Total\ mass\ of\ reactants} X\ 100$$

$$OE = \frac{RME}{AE} X\ 100$$

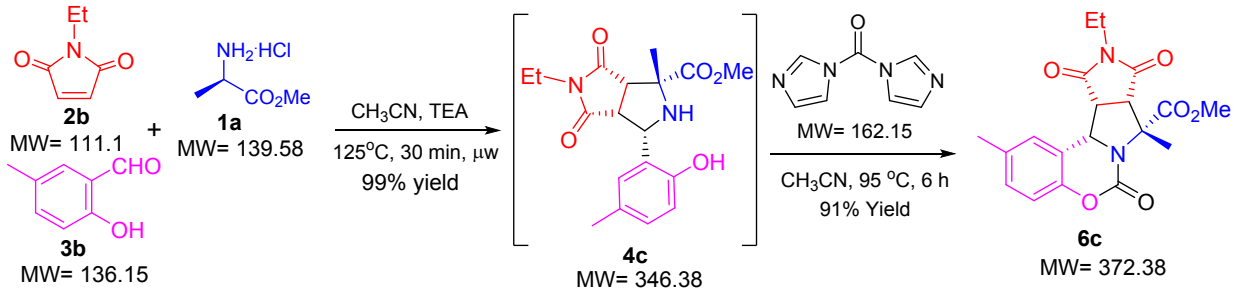
$$PMI = \frac{Total\ mass\ of\ input\ material\ in\ the\ whole\ process}{Mass\ of\ product}$$

$$E\ Factor = PMI - 1$$

$$SI = \frac{Total\ mass\ of\ solvents\ excl.\ water\ in\ the\ whole\ process}{Mass\ of\ product}$$

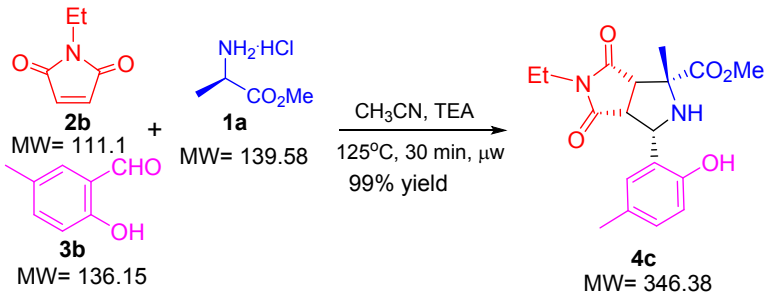
$$WI = \frac{Total\ mass\ of\ water\ used\ in\ the\ whole\ process}{Mass\ of\ product}$$

6.1. Process A, (3+2) cycloaddition and (5+1) annulation (synthesis of compound 6c)



This is a two step synthesis with one purification step to obtain the final product.

Step 1: Synthesis of methyl (1R,3S,3aR,6aS)-5-ethyl-3-(2-hydroxy-5-methylphenyl)-1-methyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (4c)



Experimental procedure: A reaction vial was charged with the corresponding D-alanine methyl ester **1a** (0.167 g, 1.2 mmol), *N*-ethylmaleimide **2b** (0.137 g, 1.1 mmol) and 2-hydroxy-5-methylbenzaldehyde **3b** (0.136 g, 1.0 mmol). Then, it was dissolved in 2.0 mL of CH_3CN and heated under microwave irridiation at 125 °C for 30 min. The solvent was evaporated and the residue washed 2 times with 1 mL of water, filtered and dried to afford 0.343 g of intermediate **4c** in 99% yield.
The intermediate product was used for the next reaction without further purification

Materials used for metrics calculations: D-alanine methyl ester **1a** (0.167 g, 1.2 mmol), and *N*-ethylmaleimide **2b** (0.137 g, 1.1 mmol), 2-hydroxy-5-methylbenzaldehyde **3b** (0.136 g, 1.0 mmol), CH_3CN (2.0 mL, 1.572 g), water (2.0 mL, 2 g) and compound **4c** (0.343 g, 0.99 mmole).

$$AE\ (4c) = \frac{346.38}{136.15 + 139.58 + 125.13} X\ 100 = 86.41$$

$$AEf\ (4) = \frac{86.41}{100} X\ 99 = 85.55$$

$$CE\ (4c) = \frac{18\ X\ 0.00099}{8\ X\ 0.001 + 4\ X\ 0.0012 + 6X0.0011} X\ 100 = 91.86$$

$$RME\ (4c) = \frac{0.343}{0.136 + 0.167 + 0.137} X\ 100 = 78.00$$

$$OE\ (4c) = \frac{78}{85.55} X\ 100 = 91.17$$

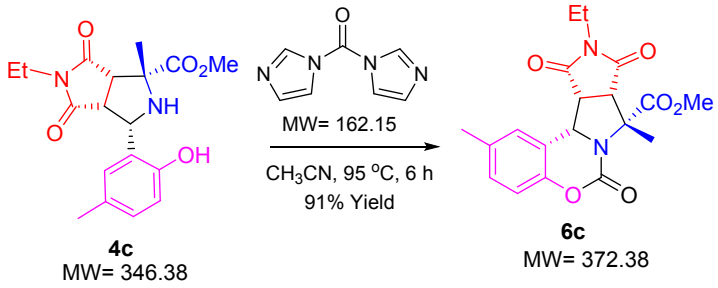
$$PMI\ (4c) = \frac{0.136 + 0.167 + 0.137 + 1.572 + 2.0}{0.343} = 11.70$$

$$E\ Factor\ (4) = 11.70 - 1 = 10.70$$

$$SI\ (4c) = \frac{1.572}{0.343} = 4.58$$

$$WI\ (4c) = \frac{2.0}{0.343} = 5.83$$

Step 2: Synthesis of methyl (8R,8aS,11aR,11bS)-10-ethyl-2,8-dimethyl-6,9,11-trioxo-8a,9,10,11,11a,11b-hexahydro-6H,8H-benzo[e]pyrrolo[3',4':3,4]pyrrolo[1,2-c][1,3]oxazine-8-carboxylate (6c).



Experimental procedure: To a solution of (3+2) cycloaddition adduct **4c** (0.104 g, 0.3 mmol) *di(1H*-imidazol-1-yl)methanone (0.073 g, 0.45 mmol) in 1.5 mL of CH_3CN. The reaction mixture was heated at 95 °C for 6 h. The completion of the reaction was detected using LC-MS. On cooling the desired product, **6c**, precipitated out from reaction mixture, filtered and dried to afford 0.102 g (91 %) as a white solid. and no further purification was required.

Materials used for metrics calculations: Compound **4c** (0.104 g, 0.3 mmol) *di(1H*-imidazol-1-yl)methanone (0.073 g, 0.45 mmol), CH_3CN (1.5 mL, 1.179 g), and compound **6c** (0.102 g, 0.276 mmole).

$$AE\ (6c) = \frac{372.38}{346.38 + 162.15} X\ 100 = 73.23$$

$$AEf\ (6c) = \frac{73.23}{100} X\ 91 = 66.64$$

$$CE\ (6c) = \frac{19\ X\ 0.00027}{18X\ 0.0003 + 7\ X\ 0.00045} X\ 100 = 60.00$$

$$RME\ (6c) = \frac{0.102}{0.104 + 0.073} X\ 100 = 57.63$$

$$OE\ (6c) = \frac{57.06}{73.23} X\ 100 = 78.70$$

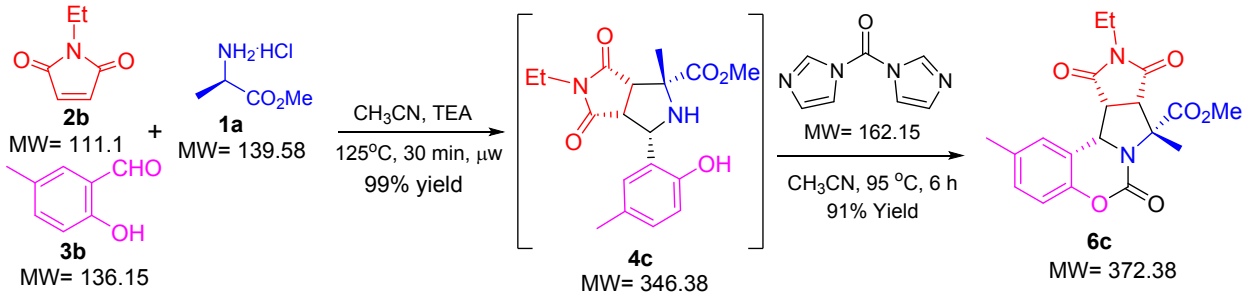
$$PMI\ (6c) = \frac{0.104 + 0.073 + 1.179}{0.102} = 13.29$$

$$E\ Factor\ (6c) = 13.29 - 1 = 12.29$$

$$SI\ (6c) = \frac{1.179}{0.101} = 11.67$$

$$WI\ (6c) = \frac{0}{0.101} = 0$$

Cumulative metrics for process A (synthesis of compound 6c)



Materials used for metrics calculations: D-alanine methyl ester **1a** (0.167 g, 1.2 mmol), and *N*-ethylmaleimide **2b** (0.137 g, 1.1 mmol), 2-hydroxy-5-methylbenzaldehyde **3b** (0.136 g, 1.0 mmol CH_3CN (2.0 mL, 1.572 g), water (2.0 mL, 2 g). Compound **4c** (0.104 g, 0.3 mmol), *di(1H*-imidazol-1-yl)methanone (0.073 g, 0.45 mmol), CH_3CN (1.5 mL, 1.179 g) and compound **6c** (0.102 g, 0.276 mmole).

$$AE\ (6c\ cumulative) = \frac{372.38}{136.15 + 139.58 + 125.13 + 162.15} X\ 100 = 66.14$$

$$AEf\ (6c\ cumulative) = \frac{66.14}{100} X\ 91 = 60.19$$

$$CE\ (6c\ Cum.) = \frac{19\ X\ 0.00027}{8\ X\ 0.001 + 4\ X\ 0.0012 + 6X0.0011 + 7\ X\ 0.00045} X\ 100 = 22.75$$

$$RME\ (6c\ cumulative) = \frac{0.102}{\frac{0.104}{0.78} + 0.073} X\ 100 = 49.43$$

$$OE\ (6c\ cumulative) = \frac{49.43}{66.14} X\ 100 = 74.74$$

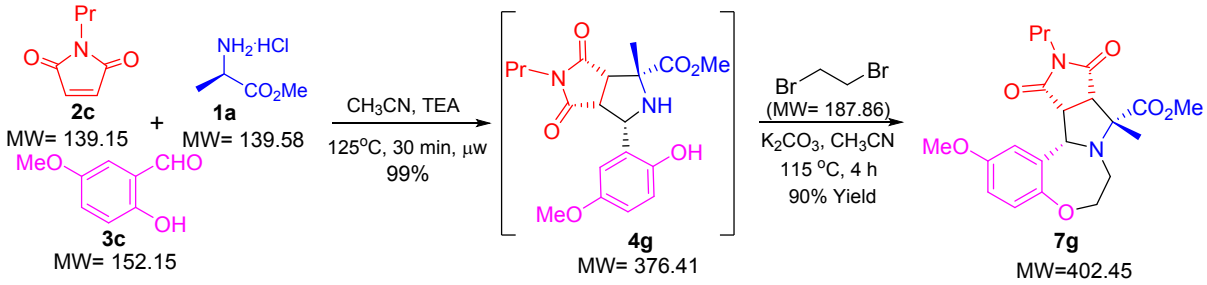
$$PMI\ (6c\ Cum) = \frac{0.136 + 0.167 + 0.137 + 0.104 + 0.073 + 2.751 + 1.0}{0.102} = 42.82$$

$$E\ Factor\ (6c\ cumulative) = 42.82 - 1 = 41.82$$

$$SI\ (6c\ cumulative) = \frac{2.751}{0.101} = 27.24$$

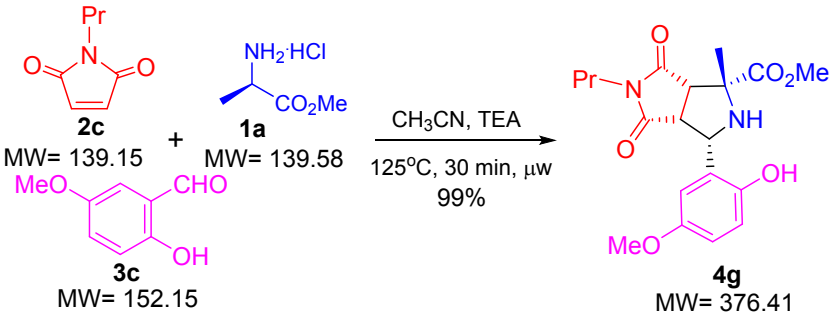
$$WI\ (6c\ cumulative) = \frac{2.0}{0.101} = 19.80$$

6.2. Process B, (3+2) cycloaddition and (5+2) annulation (synthesis of compound 7g)



This is a two step synthesis with one purification step to obtain the final product.

Step 1: Synthesis of methyl (1R,3S,3aR,6aS)-3-(2-hydroxy-5-methoxyphenyl)-1-methyl-4,6-dioxo-5-propyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (4g)



Experimental procedure: A reaction vial was charged with the corresponding D-alanine methyl ester **1a** (0.167 g, 1.2 mmol), *N*-propylmaleimide **2c** (0.153 g, 1.1 mmol) and 2-hydroxy-5-methoxybenzaldehyde **3c** (0.152 g, 1.0 mmol). Then, it was dissolved in 2.0 mL of CH_3CN and

heated under microwave irridiation at 125 °C for 30 min. The solvent was evaporated and the residue washed 2 times with 1 mL of water, filtered and dried to afford 0.372 g of intermediate **4g** in 99% yield.
The intermediate product was used for the next reaction without further purification.

Materials used for metrics calculations: D-alanine methyl ester **1a** (0.167 g, 1.2 mmol), *N*-propylmaleimide **2c** (0.153 g, 1.1 mmol) and 2-hydroxy-5-methoxybenzaldehyde **3c** (0.152 g, 1.0 mmol), CH_3CN (2.0 mL, 1.572 g), water (2.0 mL, 2 g) and compound **4g** (0.372 g, 0.99 mmole).

$$AE\ (4g) = \frac{376.41}{152.15 + 139.58 + 139.15} X\ 100 = 87.36$$

$$AEf\ (4g) = \frac{87.36}{100} X\ 99 = 86.48$$

$$CE\ (4g) = \frac{19\ X\ 0.00099}{8\ X\ 0.001 + 4\ X\ 0.0012 + 7X0.0011} X\ 100 = 91.76$$

$$RME\ (4g) = \frac{0.372}{0.152 + 0.167 + 0.153} X\ 100 = 78.81$$

$$OE\ (4g) = \frac{78.81}{87.36} X\ 100 = 90.22$$

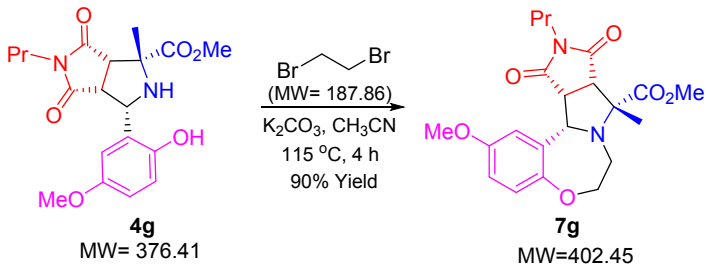
$$PMI\ (4g) = \frac{0.152 + 0.167 + 0.153 + 1.572 + 2.0}{0.372} = 10.87$$

$$E\ Factor\ (4g) = 10.87 - 1 = 9.87$$

$$SI\ (4g) = \frac{1.572}{0.372} = 4.23$$

$$WI\ (4g) = \frac{2.0}{0.372} = 5.38$$

Step 2: Synthesis of methyl (9R,9aS,12aR,12bS)-2-methoxy-9-methyl-10,12-dioxo-11-propyl-6,7,9a,10,11,12,12a,12b-octahydro-9H-benzo[f]pyrrolo[3',4':3,4]pyrrolo[1,2-d][1,4]oxazepine-9-carboxylate 7g).



4g
MW= 376.41

7g
MW=402.45

Experimental procedure: To a solution of (3+2) cycloaddition adduct **4g** (0.151 g, 0.4 mmol) (1,2-dibromoethane (0.150 g, 0.8 mmol) and K_2CO_3 (0.136 g, 1 mmol) in 2.0 mL of CH_3CN. The reaction mixture was heated at 115 °C for 4 h. The completion of the reaction was detected using LC-MS. The solvent was then removed under reduced pressure and the residue purified on Angela HP-100 pre-LC system with a Venusil PrepG C18 column (10 µm, 120 Å, 21.2 mm × 250 mm) to afford compound **7g** as a white solid (90 %).

Materials used for metrics calculations: Compound **4g** (0.151 g, 0.4 mmol), 1,2-dibromoethane (0.150 g, 0.8 mmol) and K_2CO_3 (0.136 g, 1 mmol) in 2.0 mL of CH_3CN (2.0 mL 1.572 g) and compound **7g** (0.145 g, 0.36 mmole).

$$AE\ (7g) = \frac{402.45}{376.41 + 187.86} X\ 100 = 71.32$$

$$AEf\ (7g) = \frac{71.32}{100} X\ 90 = 64.19$$

$$CE\ (7g) = \frac{21\ X\ 0.00036}{19X\ 0.0004 + 2\ X\ 0.0008} X\ 100 = 82.17$$

$$RME\ (7g) = \frac{0.145}{0.151 + 0.150} X\ 100 = 48.17$$

$$OE\ (7g) = \frac{48.17}{71.32} X\ 100 = 67.54$$

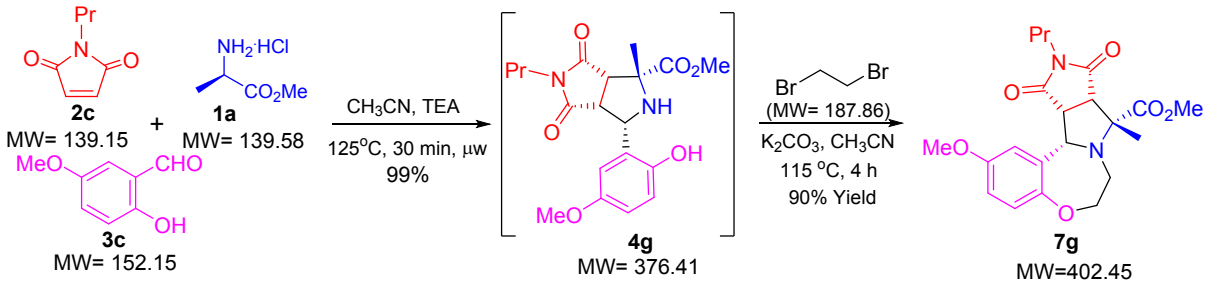
$$PMI\ (7g) = \frac{0.151 + 0.150 + 0.136 + 1.572}{0.145} = 13.86$$

$$E\ Factor\ (7g) = 13.86 - 1 = 12.86$$

$$SI\ (7g) = \frac{1.572}{0.145} = 10.84$$

$$WI\ (7g) = \frac{0}{0.145} = 0$$

Cumulative metrics for process B (synthesis of compound 7g)



Materials used for metrics calculations: D-alanine methyl ester **1a** (0.167 g, 1.2 mmol), *N*-propylmaleimide **2c** (0.153 g, 1.1 mmol) and 2-hydroxy-5-methoxybenzaldehyde **3c** (0.152 g, 1.0 mmol). CH_3CN (2.0 mL, 1.572 g), water (2.0 mL, 2 g), compound **4g** (0.151 g, 0.4 mmol), 1,2-dibromoethane (0.150 g, 0.8 mmol) and K_2CO_3 (0.136 g, 1 mmol) in 2.0 mL of CH_3CN (2.0 mL, 1.572 g) and compound **7g** (0.145 g, 0.36 mmole).

$$AE\ (7g\ cumulative) = \frac{402.45}{152.15 + 139.58 + 139.15 + 187.86} X\ 100 = 65.04$$

$$AEf\ (7g\ cumulative) = \frac{65.04}{100} X\ 90 = 58.54$$

$$CE\ (7g\ Cum.) = \frac{21\ X\ 0.00036}{8\ X\ 0.001 + 4\ X\ 0.0012 + 7X0.0011 + 2\ X\ 0.0008} X\ 100 = 34.21$$

$$RME\ 7g = \frac{0.145}{\frac{0.151}{0.7881} + 0.150} X\ 100 = 42.45$$

$$OE\ (7g\ cumulative) = \frac{42.45}{65.04} X\ 100 = 65.26$$

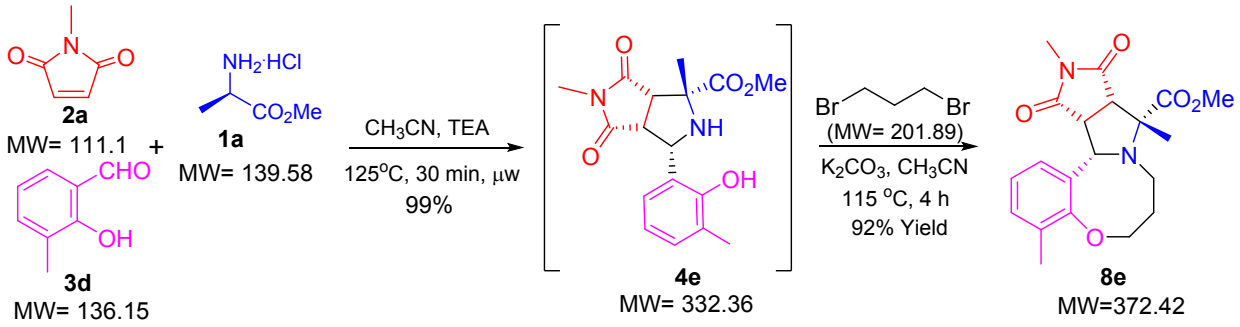
$$PMI\ (7g\ Cum) = \frac{0.152 + 0.167 + 0.153 + 3.144 + 0.136 + 2.0}{0.145} = 39.67$$

$$E\ Factor\ (7g\ cumulative) = 39.67 - 1 = 38.67$$

$$SI\ (7g\ cumulative) = \frac{3.144}{0.145} = 21.68$$

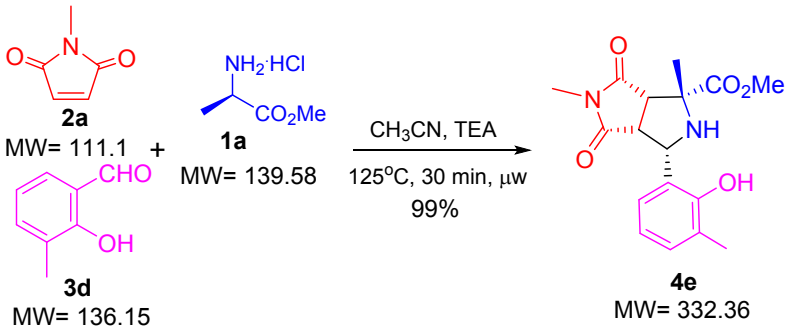
$$WI\ (7g\ cumulative) = \frac{2.0}{0.145} = 13.79$$

6.3. Process C, (3+2) cycloaddition and (5+3) annulation (synthesis of compound 8e)



This is a two step synthesis with one purification step to obtain the final product.

Step 1: Synthesis of methyl (1R,3S,3aR,6aS)-3-(2-hydroxy-3-methylphenyl)-1,5-dimethyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (4e)



Experimental procedure: A reaction vial was charged with the corresponding D-alanine methyl ester **1a** (0.167 g, 1.2 mmol), *N*-methylmaleimide **2a** (0.122 g, 1.1 mmol) and 2-hydroxy-5-methylbenzaldehyde **3d** (0.136 g, 1.0 mmol). Then, it was dissolved in 2.0 mL of CH_3CN and heated under microwave irridiation at 125 °C for 30 min. The solvent was evaporated and the residue washed 2 times with 1 mL of water, filtered and dried to afford 0.329 g of intermediate **4e** in 99% yield.
The intermediate product was used for the next reaction without further purification

Materials used for metrics calculations: D-alanine methyl ester **1a** (0.167 g, 1.2 mmol), *N*-methylmaleimide **2a** (0.122 g, 1.1 mmol) and 2-hydroxy-5-methylbenzaldehyde **3d** (0.136 g, 1.0 mmol), CH_3CN (2.0 mL, 1.572 g), water (2.0 mL, 2 g) and compound **4e** (0.329 g, 0.99 mmole).

$$AE\ (4e) = \frac{332.36}{136.15 + 139.58 + 111.1} X\ 100 = 85.92$$

$$AEf\ (4e) = \frac{85.92}{100} X\ 99 = 85.06$$

$$CE\ (4e) = \frac{17\ X\ 0.00099}{8\ X\ 0.001 + 4\ X\ 0.0012 + 5X0.0011} X\ 100 = 91.97$$

$$RME\ (4e) = \frac{0.329}{0.136 + 0.167 + 0.122} X\ 100 = 77.41$$

$$OE\ (4e) = \frac{77.41}{85.92} X\ 100 = 90.10$$

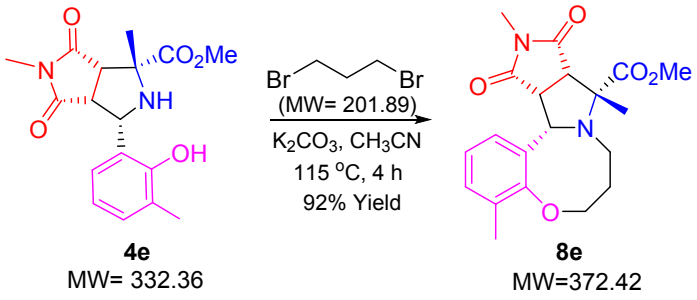
$$PMI\ (4e) = \frac{0.136 + 0.167 + 0.122 + 1.572 + 2.0}{0.329} = 12.15$$

$$E\ Factor\ (4e) = 12.15 - 1 = 11.15$$

$$SI\ (4e) = \frac{1.572}{0.329} = 4.78$$

$$WI\ (4e) = \frac{2.0}{0.329} = 6.08$$

Step 2: Synthesis of methyl (10R,10aS,13aR,13bS)-4,10,12-trimethyl-11,13-dioxo-7,8,10a,11,12,13,13a,13b-octahydro-6H,10H-benzo[b]pyrrolo[3',4':3,4]pyrrolo[2,1-d][1,5]oxazocine-10-carboxylate (8e).



4e
MW= 332.36

8e
MW=372.42

Experimental procedure: To a solution of (3+2) cycloaddition adduct **4e** (0.133 g, 0.4 mmol,) (1,3-dibromopropane (0.162 g, 0.8 mmol) and K_2CO_3 (0.136 g, 1 mmol) in 2.0 mL of CH_3CN. The reaction mixture was heated at 115 °C for 4 h. The completion of the reaction was detected using LC-MS. The solvent was then removed under reduced pressure and the residue purified on Angela HP-100 pre-LC system with a Venusil PrepG C18 column (10 µm, 120 Å, 21.2 mm × 250 mm) to afford compound **8e** as a white solid (92 %).

Materials used for metrics calculations: Compound **4c** (0.133 g, 0.4 mmol), 1,3-dibromopropane (0.162 g, 0.8 mmol) and K_2CO_3 (0.136 g, 1 mmol) in CH_3CN (2.0 mL 1.572 g) and compound **8e** (0.138 g, 0.37 mmole).

$$AE\ (8e) = \frac{372.42}{332.36 + 201.89} X\ 100 = 69.71$$

$$AEf\ (8e) = \frac{69.71}{100} X\ 92 = 64.13$$

$$CE\ (8e) = \frac{20\ X\ 0.00037}{17X\ 0.0004 + 3\ X\ 0.0008} X\ 100 = 80.43$$

$$RME\ (8e) = \frac{0.138}{0.133 + 0.162} X\ 100 = 46.78$$

$$OE\ (8e) = \frac{46.78}{69.71} X\ 100 = 67.11$$

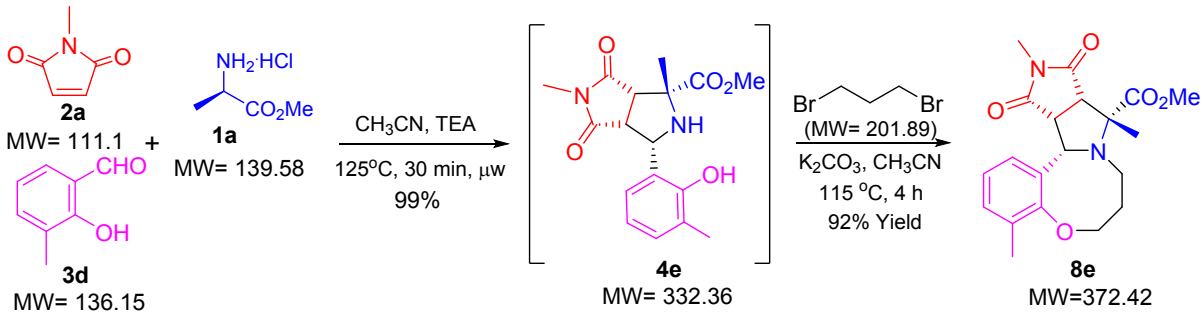
$$PMI\ (8e) = \frac{0.133 + 0.162 + 0.136 + 1.572}{0.138} = 14.51$$

$$E\ Factor\ (8e) = 14.51 - 1 = 13.51$$

$$SI\ (8e) = \frac{1.572}{0.138} = 11.39$$

$$WI\ (8e) = \frac{0}{0.138} = 0$$

Cumulative metrics for process C (synthesis of compound 8e)



Materials used for metrics calculations: D-alanine methyl ester **1a** (0.167 g, 1.2 mmol), *N*-methylmaleimide **2a** (0.122 g, 1.1 mmol) and 2-hydroxy-5-methylbenzaldehyde **3d** (0.136 g, 1.0 mmol), CH_3CN (2.0 mL, 1.572 g), water (2.0 mL, 2 g), compound **4e** (0.133 g, 0.4 mmol) (1,3-dibromopropane (0.162 g, 0.8 mmol), K_2CO_3 (0.136 g, 1 mmol) in CH_3CN (2.0 mL 1.572 g) and compound **8e** (0.138 g, 0.37 mmole).

$$AE\ (8e\ cumulative) = \frac{372.42}{136.15 + 139.58 + 111.1 + 201.89} X\ 100 = 63.26$$

$$AEf\ (8e\ cumulative) = \frac{63.26}{100} X\ 92 = 58.20$$

$$CE\ (8e\ Cum.) = \frac{20\ X\ 0.00037}{8\ X\ 0.001 + 4\ X\ 0.0012 + 5X0.0011 + 3\ X\ 0.0008} X\ 100 = 35.75$$

$$RME\ (8e\ Cum.) = \frac{0.138}{\frac{0.133}{0.7741} + 0.162} X\ 100 = 41.34$$

$$OE\ (8e\ cumulative) = \frac{41.34}{63.26} X\ 100 = 65.35$$

$$PMI\ (8e\ Cum) = \frac{0.136 + 0.167 + 0.122 + 3.144 + 0.136 + 2.0}{0.138} = 41.34$$

$$E\ Factor\ (8e\ cumulative) = 41.34 - 1 = 40.34$$

$$SI\ (8e\ cumulative) = \frac{3.144}{0.138} = 22.78$$

$$WI\ (8e\ cumulative) = \frac{2.0}{0.138} = 14.49$$

7.0 References for Green Metrics

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