Supporting Information

Palladium-Catalyzed sp^3 C–H Acetoxylation of α,α-Disubstituted α-Amino Acids

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EXPERIMENTAL SECTION

General. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, for $CDCl_3$ and DMSO-d_6 solution. NMR measurements were performed at 80 ºC if necessary. HRMS data were obtained by DART using a TOF mass spectrometer. The structures of all products listed below were unambiguously determined by ^{1}H and ^{13}C NMR and X-ray crystal structure analysis.

Amino acid derivative **1** and **3** [35,42-45] and mono-*N*-protected amino acid ligand **L6** [46] were prepared according to published procedures. Other reagents were purchased from commercial resources and used without further purification.

The following experimental procedures may be regarded as typical in methodology and scale.

Procedure for *N*-Phthalimide Protection of Amino Acids

Procedure A [42]: Amino acid (1.0 equiv.) and phthalic anhydride (1.2 equiv.) were placed into a round-bottom flask and heated to 190 ºC until visible formation of water vapor ceased (approximately 45 min.). The reaction mixture was allowed to cool slightly before adding the contents to sat. $NaHCO_3$ (aq.). The reaction flask was rinsed with sat. $NaHCO_3$ (aq.) and 1% NaOH (aq.). The combined aqueous portions were filtered, and the filtrate was acidified to a pH below 2 with concentrated HCl (aq.). The resulting precipitate was isolated by filtration and dried under vacuum to give the corresponding *N*-phthalimide protected amino acid, which was used without further purification.

Procedure B [43]: 1M toluene solution of amino acid (1.0 equiv.) and phthalic anhydride (1.0 equiv.) was prepared in a round-bottom flask. Then, NEt_3 (0.10 eq.) were added to the solution. The suspension was refluxed at 130 ºC overnight equipped with a Dean-Stark system to collect the water produced during the reaction. The resulting mixture was cooled down to room temperature and solvents were removed under vacuum. The crude product was then dissolved in DCM and washed by aqueous 1 M HCl (aq., 3 times). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure to obtain the corresponding *N*-phthalimide protected amino acid, which was used without further purification. If the crude product was not colorless, it was dissolved in DCM and extracted with saturated $NaHCO_3$ (aq.). The combined aqueous portions were filtered, and the filtrate was acidified to a pH below 2 with concentrated HCl (aq.). The resulting precipitate was isolated by filtration and dried under vacuum to give the corresponding *N*-phthalimide protected amino acid, which was used without further purification.

Procedure C [44]: Amino acid (1.0 equiv.) and Na_2CO_3 (1.0 equiv.) were dissolved in water (1 M) at room temperature. *N*-Ethoxycarbonylphthalimide (1.0 equiv.) was added to the solution in small portions. The mixture was stirred for 3 hours at room temperature, and then the aqueous solution was cooled to 0 ºC and slowly acidified with 6 M HCl (aq.) until pH of 1-2 was attained and white

precipitate was observed. The precipitate was collected and washed with 1 M HCl (aq.) and EtOAc/hexanes = 1/5 to give the corresponding *N*-phthalimide protected amino acid, which was used without further purification.

Preparation of 1a-e and 1g-k [43]

To a round-bottom flask were added the amino acid (1.0 equiv.), DCM (0.50 M) and a few drops of DMF. Oxalyl chloride (2.0 eq.) was added slowly to the mixture and then the resulting mixture was stirred for 3 h at room temperature. The excess of oxalyl chloride and DCM were removed in vacuo. The crude acid chloride was dissolved in DCM (0.5 M) and primary or secondary amine (1.5 equiv.) and *N,N*-diisopropylethylamine (1.5 equiv.) were added dropwise under cooling with an ice bath. The mixture was stirred for 2 hours at room temperature and then quenched with sat. $NaHCO_3$ (aq.). The aqueous layer was extracted with EtOAc (3 times). The combined organic layers were washed with 1 M HCl (aq., 3 times) and brine (3 times), dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by column chromatography on silica gel using hexane−EtOAc as eluent to afford substrate **1**.

Preparation of 1f [45]

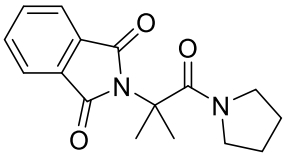
To a stirring solution of 1-(1,3-dioxoisoindolin-2-yl)cyclopropane-1-carboxylic acid (1.3 mmol) and *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (307 mg, 1.6 mmol) in DCM (5.2 mL) were added pyrrolidine (134 μL, 1.6 mmol) and a small amount of 4-(dimethylamino)pyridine (15.9 mg, 0.13 mmol). The reaction mixture was stirred for 24 h at room temperature. Upon completion, the organic layer was washed with 0.2 M HCl (aq.) and sat. Na_2CO_3 (aq.). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel using hexane−EtOAc as eluent to afford substrate **1f** (238 mg, 64%).

Preparation of 3a-b [35]

To a solution of amino acid methyl ester hydrochloride (3.6 mmol) and NEt_3 (1.7 mmol) in DMF (10 mL) were added 2-(1,3-dioxoisoindolin-2-yl)-2-methylpropanoic acid (3 mmol) and 1-hydroxy-7-azabenzotriazole (HOAt, 3.03 mmol). The mixture was cooled in an ice bath and subsequently 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide hydrochloride (EDCI, 3.6 mmol) was added in one portion. After 1.5 h at 0 ºC and 6 h (**3a**) or 3 d (**3b**) at room temperature, the mixture was partitioned between H_2O and EtOAc. The aqueous phase was extracted with EtOAc (3 times). The organic phase was washed successively with H_2O, 0.5 M HCl (aq.), sat. $NaHCO_3$ (aq.) and brine. Then it was dried

over anhydrous Na_2SO_4, filtered, and concentrated. The crude residue was purified by column chromatography on silica gel using hexane−EtOAc as eluent to afford substrate **3**.

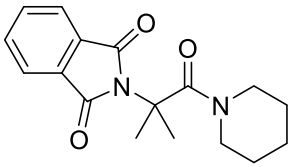
Characterization Data of 1 and 3



2-(2-Methyl-1-oxo-1-(pyrrolidin-1-yl)propan-2-yl)isoindoline-1,3-dione (**1a**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, J = 5.5, 3.0 Hz, 2H), 7.73 (dd, J = 5.5, 3.0 Hz, 2H), 3.56 (t, J = 6.8 Hz, 2H), 3.20 (t, J = 6.2 Hz, 2H), 1.84 (s, 6H), 1.82–1.73 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 168.3, 134.4, 131.6, 123.4, 61.3, 47.9, 46.8, 27.2, 24.8, 23.1; HRMS: *m/z* calcd for $C_{16}H_{19}N_2O_3$ $[M+H]^+$ 287.13957, found: 287.13826.

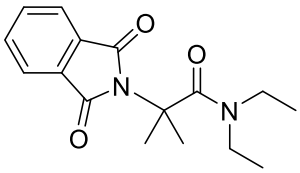
N-Phthalimide protection was performed by Procedure A.



2-(2-Methyl-1-oxo-1-(piperidin-1-yl)propan-2-yl)isoindoline-1,3-dione (**1b**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 (d, J = 0.8 Hz, 4H), 3.40–3.37 (m, 4H), 1.72 (d, J = 1.0 Hz, 6H), 1.52–1.46 (m, 2H), 1.38–1.32 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.4, 167.2, 134.3, 130.9, 122.5, 59.9, 44.5, 25.0, 24.9, 24.7, 23.5; HRMS: *m/z* calcd for $C_{17}H_{21}N_2O_3$ $[M+H]^+$ 301.15522, found: 301.15555.

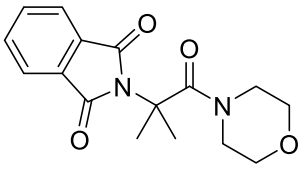
N-Phthalimide protection was performed by Procedure A.



2-(1,3-Dioxoisoindolin-2-yl)-*N*,*N*-diethyl-2-methylpropanamide (**1c**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, J = 5.5, 3.0 Hz, 2H), 7.73 (dd, J = 5.5, 3.0 Hz, 2H), 3.35 (br s, 4H), 1.84 (s, 6H), 1.15 (br s, 3H), 0.95 (br s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 168.2, 134.3, 131.8, 123.3, 61.1, 41.5, 41.1, 25.8, 13.5, 12.5; HRMS: *m/z* calcd for $C_{16}H_{21}N_2O_3$ $[M+H]^+$ 289.15522, found: 289.15469.

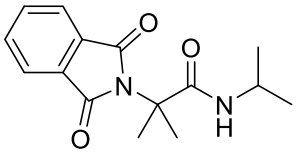
N-Phthalimide protection was performed by Procedure A.



2-(2-Methyl-1-morpholino-1-oxopropan-2-yl)isoindoline-1,3-dione (1d)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 (d, J = 1.4 Hz, 4H), 3.48–3.40 (m, 8H), 1.72 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.0, 167.2, 134.3, 130.9, 122.6, 65.4, 59.7, 44.2, 24.7; HRMS: *m/z* calcd for $C_{16}H_{19}N_2O_4$ $[M+H]^+$ 303.13448, found: 303.13354.

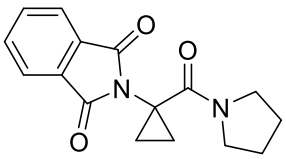
N-Phthalimide protection was performed by Procedure A.



2-(1,3-Dioxoisoindolin-2-yl)-*N*-isopropyl-2-methylpropanamide (1e)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.82 (s, 4H), 7.68 (d, J = 7.9 Hz, 1H), 3.85 (dp, J = 7.9, 6.6 Hz, 1H), 1.64 (s, 6H), 0.99 (d, J = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.2, 168.3, 134.2, 131.9, 122.6, 60.6, 40.7, 24.8, 22.1; HRMS: *m/z* calcd for $C_{15}H_{19}N_2O_3$ $[M+H]^+$ 275.13957, found: 275.13969.

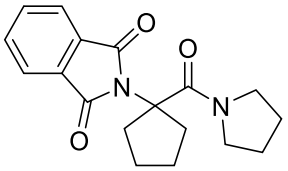
N-Phthalimide protection was performed by Procedure A.



2-(1-(Pyrrolidine-1-carbonyl)cyclopropyl)isoindoline-1,3-dione (1f)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87 (d, J = 1.1 Hz, 4H), 3.32–3.28 (m, 4H), 1.74–1.70 (m, 4H), 1.63–1.60 (m, 2H), 1.42–1.39 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.5, 166.9, 134.3, 130.8, 122.8, 46.3, 33.2, 24.3, 14.5; HRMS: *m/z* calcd for $C_{16}H_{17}N_2O_3$ $[M+H]^+$ 285.12392, found: 285.12352.

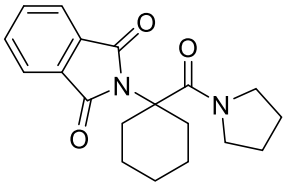
N-Phthalimide protection was performed by Procedure C.



2-(1-(Pyrrolidine-1-carbonyl)cyclopentyl)isoindoline-1,3-dione (**1g**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, J = 5.5, 3.1 Hz, 2H), 7.73 (dd, J = 5.5, 3.1 Hz, 2H), 3.53 (t, J = 6.8 Hz, 2H), 3.20 (t, J = 6.4 Hz, 2H), 2.66–2.59 (m, 2H), 2.50–2.43 (m, 2H), 1.84–1.72 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 168.4, 134.3, 131.6, 123.4, 70.9, 47.6, 46.6, 35.5, 27.1, 24.9, 23.3; HRMS: *m/z* calcd for $C_{18}H_{21}N_2O_3$ $[M+H]^+$ 313.15522, found: 313.15321.

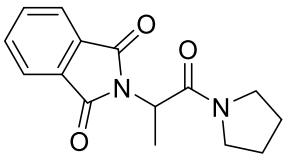
N-Phthalimide protection was performed by Procedure B.



2-(1-(Pyrrolidine-1-carbonyl)cyclohexyl)isoindoline-1,3-dione (**1h**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, J = 5.5, 3.1 Hz, 2H), 7.73 (dd, J = 5.5, 3.1 Hz, 2H), 3.54 (br s, 2H), 3.20 (br s, 2H), 2.58 (ddd, J = 12.7, 8.1, 3.7 Hz, 2H), 2.24 (ddd, J = 13.4, 8.7, 3.8 Hz, 2H), 1.83–1.77 (m, 6H), 1.65–1.57 (m, 2H), 1.52–1.48 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 168.7, 134.3, 131.5, 123.3, 65.7, 48.1, 46.6, 31.9, 27.3, 25.1, 23.0, 22.9; HRMS: *m/z* calcd for $C_{19}H_{23}N_2O_3$ $[M+H]^+$ 327.17087, found: 327.17166.

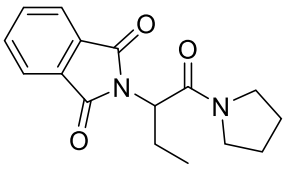
N-Phthalimide protection was performed by Procedure B.



2-(1-Oxo-1-(pyrrolidin-1-yl)propan-2-yl)isoindoline-1,3-dione (**1i**) [S1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, J = 5.5, 3.1 Hz, 2H), 7.72 (dd, J = 5.5, 3.1 Hz, 2H), 4.99 (q, J = 7.2 Hz, 1H), 3.52–3.41 (m, 3H), 3.27–3.21 (m, 1H), 1.94–1.85 (m, 3H), 1.83–1.74 (m, 1H), 1.71 (d, J = 7.2 Hz, 3H); HRMS: *m/z* calcd for $C_{15}H_{17}N_2O_3$ $[M+H]^+$ 273.12392, found: 273.12338.

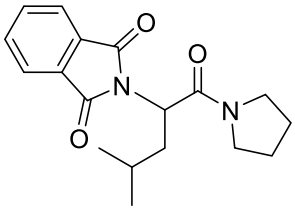
N-Phthalimide protection was performed by Procedure C.



2-(1-Oxo-1-(pyrrolidin-1-yl)butan-2-yl)isoindoline-1,3-dione (**1j**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, J = 5.5, 3.0 Hz, 2H), 7.72 (dd, J = 5.5, 3.0 Hz, 2H), 4.79 (dd, J = 10.4, 5.2 Hz, 1H), 3.50–3.43 (m, 3H), 3.29 (dt, J = 10.1, 7.1 Hz, 1H), 2.41 (ddq, J = 14.8, 10.4, 7.4 Hz, 1H), 2.15 (dqd, J = 14.8, 7.4, 5.2 Hz, 1H), 1.93–1.71 (m, 4H), 0.96 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 167.3, 134.2, 131.7, 123.5, 54.8, 46.5, 46.5, 26.5, 23.9, 22.0, 11.1; HRMS: *m/z* calcd for $C_{16}H_{19}N_2O_3$ $[M+H]^+$ 287.13957, found: 287.13883.

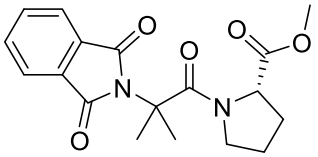
N-Phthalimide protection was performed by Procedure A.



2-(4-Methyl-1-oxo-1-(pyrrolidin-1-yl)pentan-2-yl)isoindoline-1,3-dione (**1k**) [S2]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, J = 5.5, 3.0 Hz, 2H), 7.71 (dd, J = 5.5, 3.0 Hz, 2H), 5.00 (dd, J = 11.4, 4.3 Hz, 1H), 3.51–3.45 (m, 3H), 3.40–3.34 (m, 1H), 2.61–2.53 (m, 1H), 1.98–1.90 (m, 2H), 1.89–1.70 (m, 3H), 1.59–1.51 (m, 1H), 0.95 (dd, J = 6.6, 5.4 Hz, 6H); HRMS: *m/z* calcd for $C_{18}H_{23}N_2O_3$ $[M+H]^+$ 315.17087, found: 315.17149.

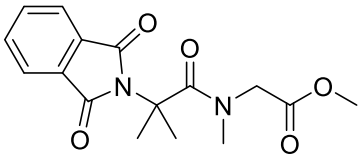
N-Phthalimide protection was performed by Procedure B.



Methyl (2-(1,3-dioxoisoindolin-2-yl)-2-methylpropanoyl)-L-prolinate (**3a**) [S3]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, J = 5.5, 3.0 Hz, 2H), 7.74 (dd, J = 5.5, 3.0 Hz, 2H), 4.56 (dd, J = 8.5, 3.7 Hz, 1H), 3.74 (s, 3H), 3.62–3.57 (m, 1H), 3.16–3.10 (m, 1H), 2.08–1.95 (m, 5H), 1.90–1.85 (m, 1H), 1.82–1.77 (m, 1H), 1.73 (s, 3H); HRMS: *m/z* calcd for $C_{18}H_{21}N_2O_5$ $[M+H]^+$ 345.14505, found: 345.14554.

N-Phthalimide protection was performed by Procedure A.



Methyl N-(2-(1,3-dioxoisoindolin-2-yl)-2-methylpropanoyl)-*N*-methylglycinate (3b)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.74 (dd, *J* = 5.4, 3.1 Hz, 2H), 4.08 (s, 2H), 3.74 (s, 3H), 3.00 (s, 3H), 1.87 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 172.1, 169.8, 168.0, 134.4, 131.7, 123.4, 60.8, 52.1, 51.4, 37.0, 25.1; HRMS: *m/z* calcd for $C_{16}H_{19}N_2O_5$ $[M+H]^+$ 319.12940, found: 319.13002.

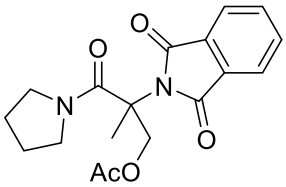
N-Phthalimide protection was performed by Procedure A.

Amino acid methyl ester hydrochloride was prepared according to literature report [S4].

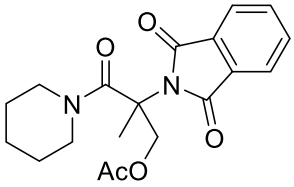
General Procedure for Pd-Catalyzed Acetoxylation of 1 and 3

To a flame dried 5 mL vial or 15 mL pressure resistant tube were added **1** or **3** (0.3 mmol), $PhI(OAc)_2$ (0.9 mmol, 290 mg), $Pd(CH_3CN)_4(BF_4)_2$ (0.015 mmol, 7 mg), *N*-acetyl-L-valine (**L1**, 0.03 mmol, 5 mg) and HFIP/DME/Ac_2O (5/4/1, 0.7 mL). The mixture was stirred under Ar (1 atm) at 80 °C (hot plate temperature or oil bath) for 20 h. The mixture was diluted with EtOAc (1 mL) and then passed through a short column with activated alumina to remove insoluble solids. After removal of the solvents under vacuum, the crude residue was purified by column chromatography on silica gel using hexane−EtOAc as eluent to afford acetoxylated products **2** or **4**. Further purification by GPC (gel permeation chromatography) was performed, if needed.

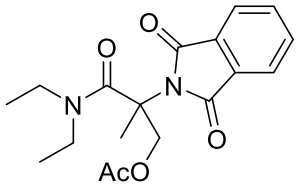
Characterization Data of Products



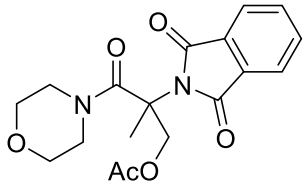
2-(1,3-Dioxoisoindolin-2-yl)-2-methyl-3-oxo-3-(pyrrolidin-1-yl)propyl Acetate (2a): white solid; 67 mg (65%); m.p. 95-97 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.84 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.75 (dd, *J* = 5.5, 3.1 Hz, 2H), 4.87 (d, *J* = 11.7 Hz, 1H), 4.64 (d, *J* = 11.7 Hz, 1H), 3.61–3.44 (m, 3H), 2.97 (q, *J* = 7.6 Hz, 1H), 2.00 (s, 3H), 1.94 (s, 3H), 1.84–1.65 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 170.7, 168.4, 168.3, 134.6, 131.4, 123.6, 66.8, 62.9, 47.7, 46.4, 27.2, 23.0, 20.9, 19.4; HRMS: *m/z* calcd for $C_{18}H_{21}N_2O_5$ $[M+H]^+$ 345.14505, found: 345.14492.



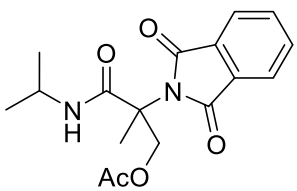
2-(1,3-Dioxoisoindolin-2-yl)-2-methyl-3-oxo-3-(piperidin-1-yl)propyl Acetate (**2b**): white solid; 58 mg (54%); m.p. 142-144 ºC; ^{1}H NMR (400 MHz, DMSO-d_6, 80 ℃) δ 7.88 (d, J = 1.1 Hz, 4H), 4.73 (d, J = 11.5 Hz, 1H), 4.38 (d, J = 11.5 Hz, 1H), 3.46 – 3.34 (m, 4H), 1.93 (s, 3H), 1.86 (d, J = 1.1 Hz, 3H), 1.54 – 1.46 (m, 2H), 1.36 (td, J = 12.0, 6.1 Hz, 4H); ^{13}C NMR (100 MHz, DMSO-d_6, 80 ℃) δ 169.5, 167.3, 166.7, 134.5, 130.5, 122.8, 66.3, 61.5, 44.1, 24.8, 23.4, 19.9, 19.2; HRMS: *m/z* calcd for $C_{19}H_{23}N_2O_5$ $[M+H]^+$ 359.16070, found: 359.16146.



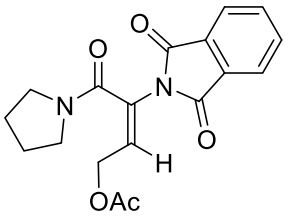
3-(Diethylamino)-2-(1,3-dioxoisoindolin-2-yl)-2-methyl-3-oxopropyl Acetate (**2c**): white solid; 53 mg (51%); m.p. 91-93 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, J = 5.5, 3.1 Hz, 2H), 7.74 (dd, J = 5.5, 3.1 Hz, 2H), 4.87 (d, J = 11.7 Hz, 1H), 4.54 (d, J = 11.7 Hz, 1H), 3.42–3.27 (m, 4H), 2.01 (s, 3H), 1.90 (s, 3H), 1.13 (t, J = 7.1 Hz, 3H), 0.92 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 168.8, 168.3, 134.5, 131.5, 123.4, 67.3, 62.7, 41.1, 40.8, 20.8, 20.1, 13.4, 12.4; HRMS: *m/z* calcd for $C_{18}H_{23}N_2O_5$ $[M+H]^+$ 347.16070, found: 347.16035.



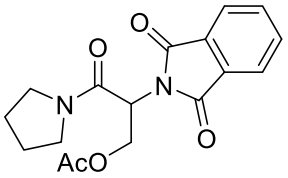
2-(1,3-Dioxoisoindolin-2-yl)-2-methyl-3-morpholino-3-oxopropyl Acetate (**2d**): white solid; 28 mg (26%); m.p. 138-140 ºC; ^{1}H NMR (400 MHz, DMSO-d_6, 80 ºC) δ 7.88 (d, J = 0.7 Hz, 4H), 4.70 (d, J = 11.5 Hz, 1H), 4.41 (d, J = 11.5 Hz, 1H), 3.53 – 3.41 (m, 8H), 1.93 (s, 3H), 1.86 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, 80 ºC) δ 169.5, 167.3, 167.2, 134.5, 130.5, 122.8, 66.1, 65.3, 61.4, 43.9, 19.89, 19.3; HRMS: *m/z* calcd for $C_{18}H_{21}N_2O_6$ $[M+H]^+$ 361.13996, found: 361.14043.



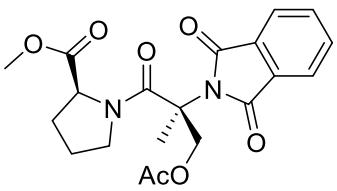
2-(1,3-Dioxoisoindolin-2-yl)-3-(isopropylamino)-2-methyl-3-oxopropyl Acetate (**2e**): white solid; 22 mg (22%); m.p. 191-193 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, J = 5.5, 3.1 Hz, 2H), 7.73 (dd, J = 5.5, 3.1 Hz, 2H), 5.66 (br d, J = 8.0 Hz, 1H), 4.77 (d, J = 11.6 Hz, 1H), 4.69 (d, J = 11.6 Hz, 1H), 4.11 (dp, J = 8.0, 6.6 Hz, 1H), 2.00 (s, 3H), 1.86 (s, 3H), 1.15 (dd, J = 6.6, 4.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 169.2, 168.5, 134.4, 131.8, 123.4, 65.9, 63.3, 42.0, 22.6, 20.9, 20.8; HRMS: *m/z* calcd for $C_{17}H_{21}N_2O_5$ $[M+H]^+$ 333.14505, found: 333.14550.



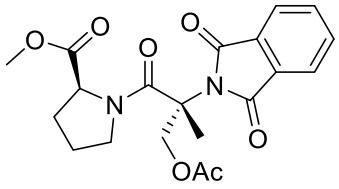
(E)-3-(1,3-Dioxoisoindolin-2-yl)-4-oxo-4-(pyrrolidin-1-yl)but-2-en-1-yl Acetate (**2f'**): white solid; 47 mg (46%); m.p. 148-150 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, J = 5.5, 3.1 Hz, 2H), 7.75 (dd, J = 5.5, 3.1 Hz, 2H), 6.26 (t, J = 7.3 Hz, 1H), 4.83 (d, J = 7.3 Hz, 2H), 3.57–3.48 (m, 4H), 2.08 (s, 3H), 1.93 (dq, J = 6.8, 4.0 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 166.3, 162.6, 134.8, 131.5, 129.0, 124.0, 123.7, 60.5, 48.2, 45.9, 26.0, 24.4, 20.9; HRMS: *m/z* calcd for $C_{18}H_{19}N_2O_5$ $[M+H]^+$ 343.12940, found: 343.12997.



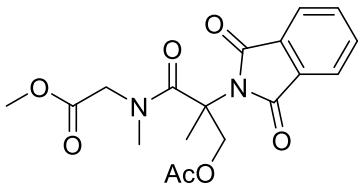
2-(1,3-Dioxoisoindolin-2-yl)-3-oxo-3-(pyrrolidin-1-yl)propyl Acetate (**2i**): pale yellow oil; 21 mg (21%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, J = 5.5, 3.1 Hz, 2H), 7.76 (dd, J = 5.5, 3.1 Hz, 2H), 5.18 (dd, J = 10.0, 4.5 Hz, 1H), 4.89 (dd, J = 11.9, 4.5 Hz, 1H), 4.74 (dd, J = 11.9, 10.0 Hz, 1H), 3.51–3.44 (m, 3H), 3.16 (dt, J = 10.4, 7.4 Hz, 1H), 1.97 (s, 3H), 1.93–1.85 (m, 3H), 1.79–1.72 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 167.5, 164.5, 134.5, 131.6, 123.8, 61.3, 51.4, 46.6, 46.5, 26.5, 23.9, 20.8; HRMS: *m/z* calcd for $C_{17}H_{19}N_2O_5$ $[M+H]^+$ 331.12940, found: 331.12932.



Methyl ((S)-3-Acetoxy-2-(1,3-dioxoisoindolin-2-yl)-2-methylpropanoyl)-L-prolinate (**(S)-4a**): white solid; 30 mg (24%); m.p. 174-175 ºC; $[\alpha]_D^{20}$ = -89.4 (*c* = 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.75 (dd, *J* = 5.5, 3.1 Hz, 2H), 4.85 (d, *J* = 11.8 Hz, 1H), 4.57 – 4.52 (m, 2H), 3.72 (s, 3H), 3.67 (ddd, *J* = 9.8, 7.2, 3.1 Hz, 1H), 3.02 (td, *J* = 8.9, 6.3 Hz, 1H), 2.06 (s, 3H), 2.04–1.88 (m, 6H), 1.80 (dt, *J* = 8.6, 3.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 170.7, 168.9, 168.2, 134.6, 131.3, 123.6, 66.6, 62.6, 60.3, 52.3, 47.0, 27.9, 25.6, 20.8, 18.7; HRMS: *m/z* calcd for $C_{20}H_{23}N_2O_7$ $[M+H]^+$ 403.15053, found: 403.14996.



Methyl ((R)-3-Acetoxy-2-(1,3-dioxoisoindolin-2-yl)-2-methylpropanoyl)-L-prolinate (**(R)-4a**): colorless oil; 10 mg (8%); $[\alpha]_D^{20}$ = 17.1 (*c* = 0.48, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.76 (dd, *J* = 5.5, 3.0 Hz, 2H), 4.88 (d, *J* = 11.8 Hz, 1H), 4.77 (d, *J* = 11.8 Hz, 1H), 4.52 (dd, *J* = 8.7, 5.2 Hz, 1H), 3.76 (s, 3H), 3.44 – 3.41 (m, 2H), 2.15–2.07 (m, 1H), 2.00– 1.80 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 170.5, 168.7, 167.9, 134.6, 131.5, 123.7, 66.2, 63.0, 61.0, 52.3, 47.1, 28.1, 26.0, 20.9, 20.4; HRMS: *m/z* calcd for $C_{20}H_{23}N_2O_7$ $[M+H]^+$ 403.15053, found: 403.14996.

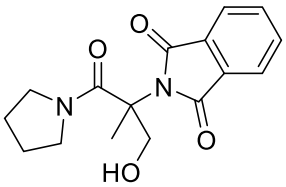


Methyl N-(3-Acetoxy-2-(1,3-dioxoisoindolin-2-yl)-2-methylpropanoyl)-N-methylglycinate (**4b**): pale yellow oil; 24 mg (21%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.76 (dd, *J* = 5.5, 3.0 Hz, 2H), 4.85 (d, *J* = 11.8 Hz, 1H), 4.57 (d, *J* = 11.8 Hz, 1H), 4.49 (d, *J* = 17.2 Hz, 1H), 3.74 (s, 3H), 3.66 (d, *J* = 17.2 Hz, 1H), 3.00 (s, 3H), 2.09 (s, 3H), 1.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 170.3, 169.6, 168.1, 134.6, 131.4, 123.6, 66.9, 62.4, 52.3, 51.0, 36.6, 20.8, 19.4; HRMS: *m/z* calcd for $C_{18}H_{21}N_2O_7$ $[M+H]^+$ 377.13488, found: 377.13509.

Procedure for Methanolysis of 2a [47]

To a 50 mL flask were added **2a** (0.26 mmol, 89 mg), HCl-MeOH (5-10%, 10 mL) and MeOH (5 mL). The mixture was stirred under air (1 atm) at 60 ºC for 0.5 h. After removal of the solvents under

vacuum, product was purified by column chromatography on silica gel using hexane−EtOAc as eluent. Further purification by GPC (gel permeation chromatography) was performed to afford **5** (63 mg, 80%).



2-(3-Hydroxy-2-methyl-1-oxo-1-(pyrrolidin-1-yl)propan-2-yl)isoindoline-1,3-dione (**5**): colorless oil; 63 mg (80%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, J = 5.5, 3.1 Hz, 2H), 7.74 (dd, J = 5.5, 3.1 Hz, 2H), 4.01–3.92 (m, 2H), 3.76 (dd, J = 8.0, 6.6 Hz, 1H), 3.61–3.52 (m, 2H), 3.34 (dd, J = 10.7, 5.8 Hz, 1H), 3.18–3.15 (m, 1H), 1.91 (s, 3H), 1.83–1.76 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 168.6, 134.6, 131.5, 123.6, 67.4, 64.2, 47.7, 46.8, 27.0, 23.1, 18.8; HRMS: *m/z* calcd for $C_{16}H_{19}N_2O_4$ $[M+H]^+$ 303.13448, found: 303.13263.

X-ray Crystal structure Analysis

The structure of **2f'** has been determined for white needle-like crystals obtained from hexane/DCM (**Figure S1**). CCDC 2240420 contains the crystallographic data of **2f'**.

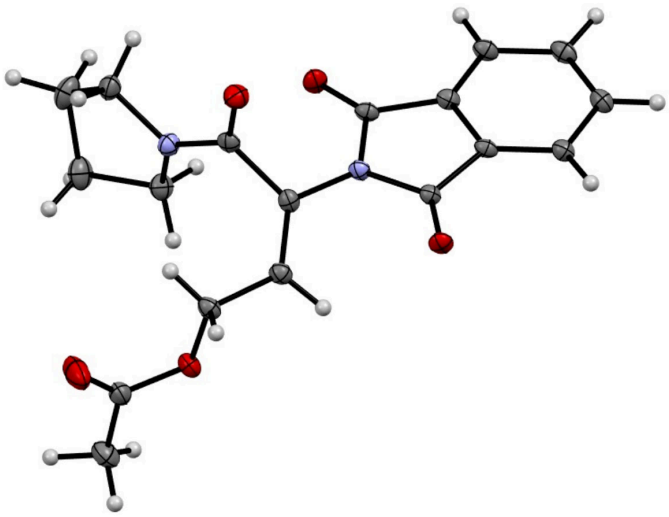


Figure S1. ORTEP drawing of compound **2f'**. Crystal data : $C_{18}H_{18}N_2O_5$, Mw = 342.34, monoclinic, space group C 2/c, T = 110 K, a = 31.8056(9), b = 7.9378(2), c = 13.0969(4), β = 94.205(3), V = 3297.63(16), Z = 8, 14902 reflections measured, R = 0.0527, wR2 = 0.1424.

The structure of **4a** has been determined for white needle-like crystals obtained from hexane/DCM (**Figure S2**). CCDC 2240422 contains the crystallographic data of **4a**.

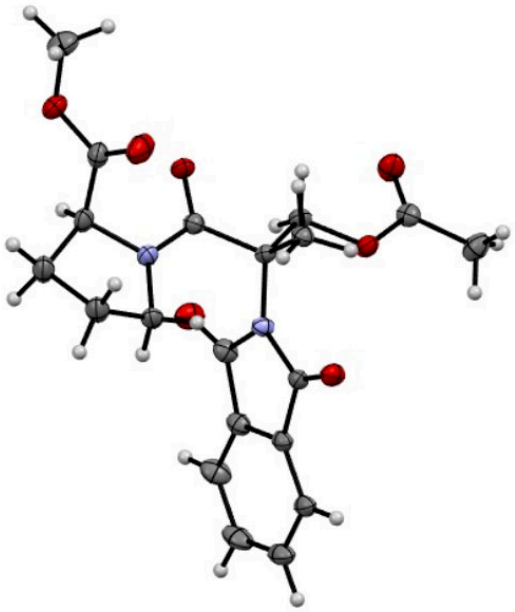


Figure S2. ORTEP drawing of compound (*S*)-**4a**. Crystal data: $C_{20}H_{22}N_2O_7$, Mw = 402.39, orthorhombic, space group *P* 21 21 21, *T* = 110 K, a = 9.863(4), b = 10.830(4), c = 18.514(7), β = 90, *V* = 1977.5(13), *Z* = 4, 20287 reflections measured, *R* = 0.0326, wR2 = 0.0696.

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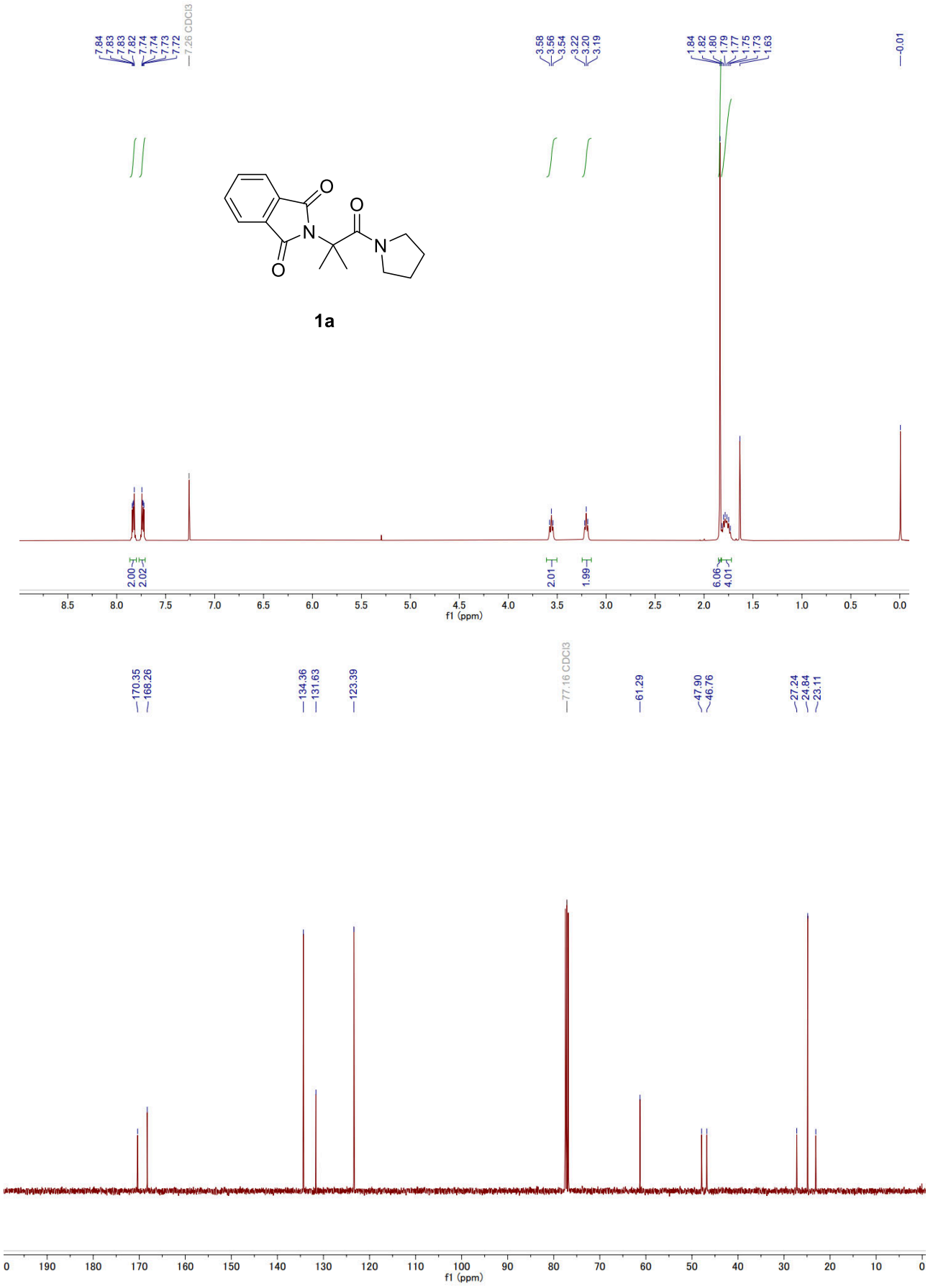
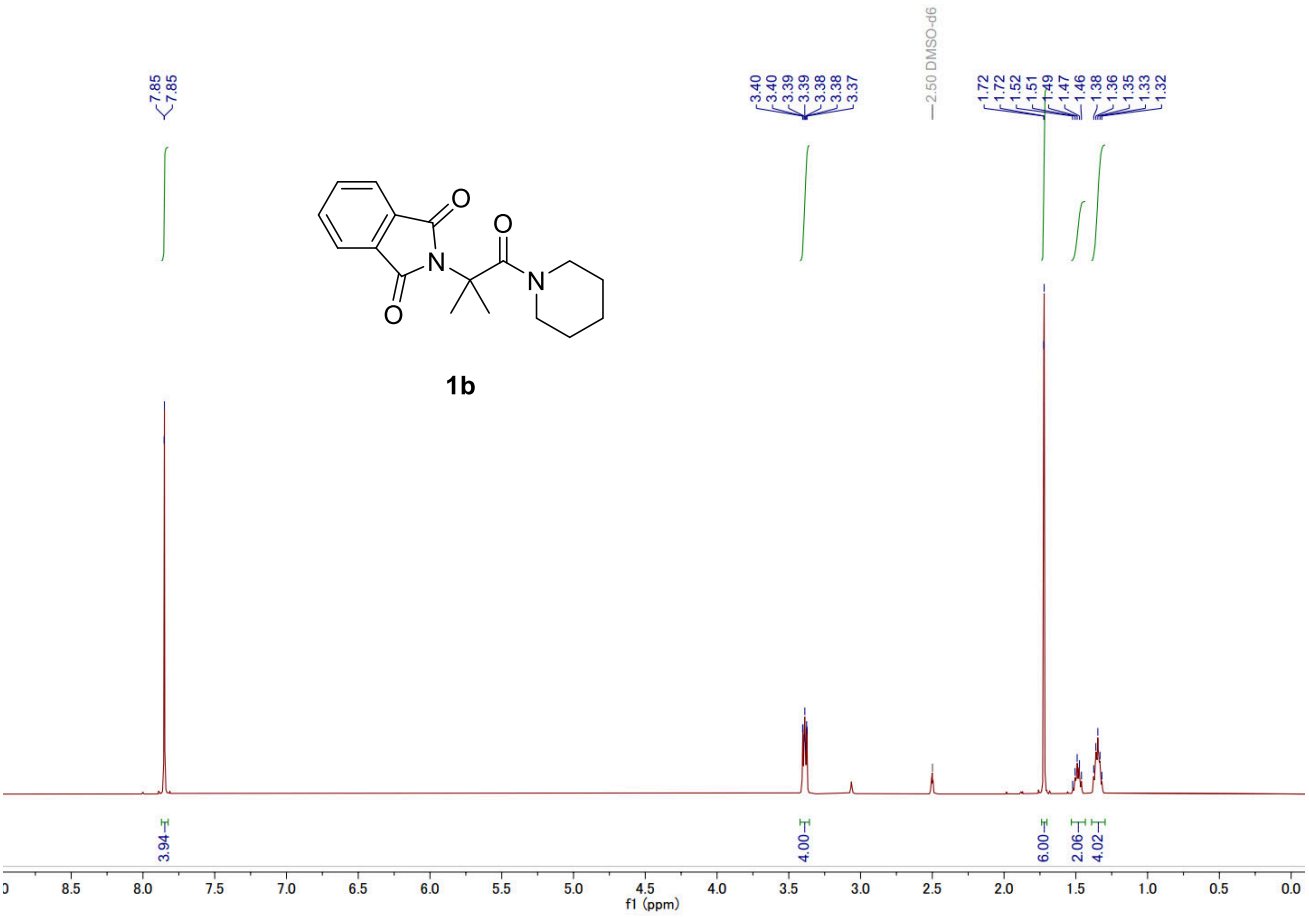
^{1}H and ^{13}C NMR Spectra of Starting Materials



1a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7.85
3.40
3.40
3.39
3.39
3.38
3.38
3.37
2.50 DMSO-d6
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1.52
1.51
1.49
1.47
1.46
1.38
1.36
1.35
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N
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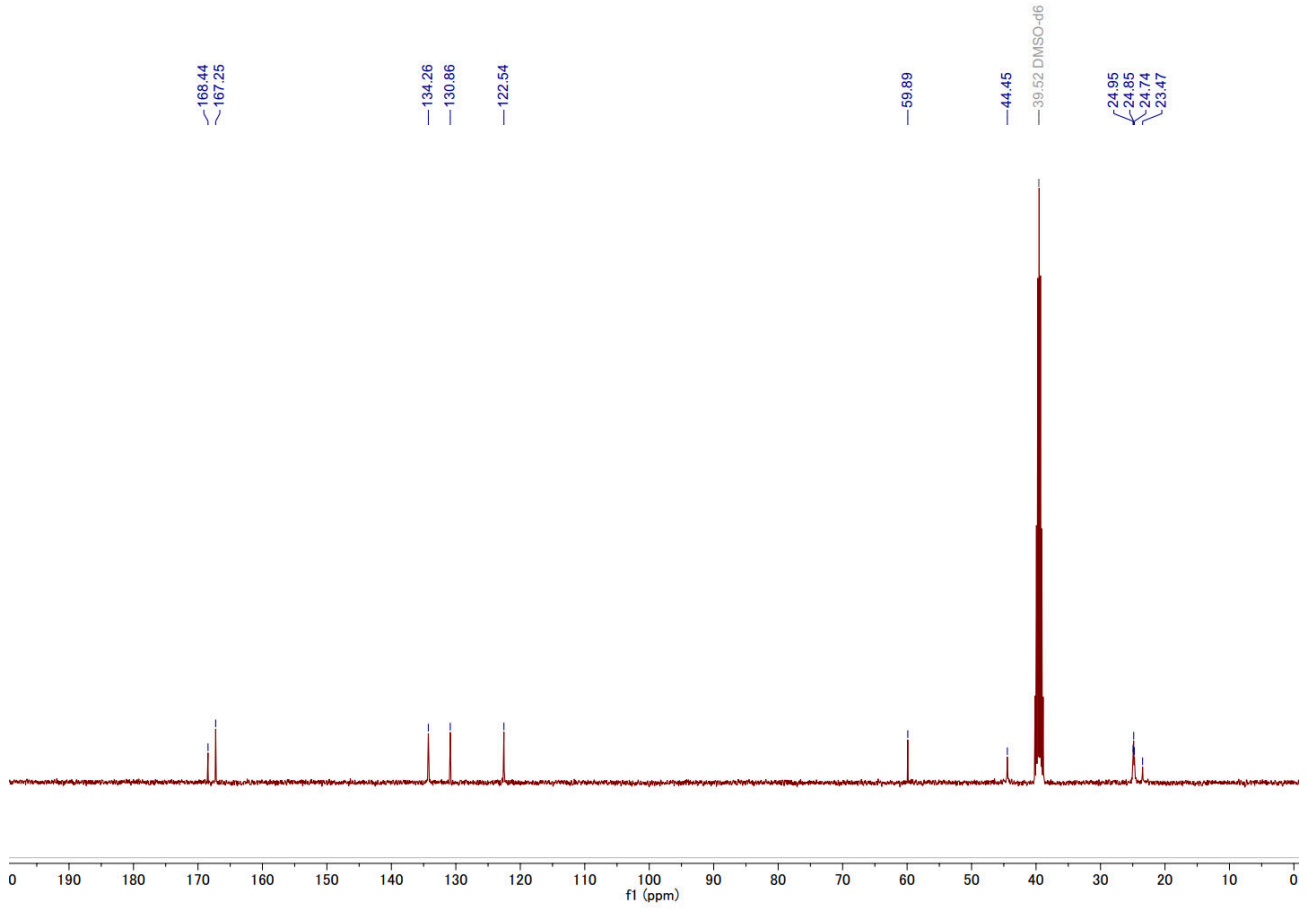
6.00
2.06
4.02
f1 (ppm)

1b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167.25
134.26
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122.54
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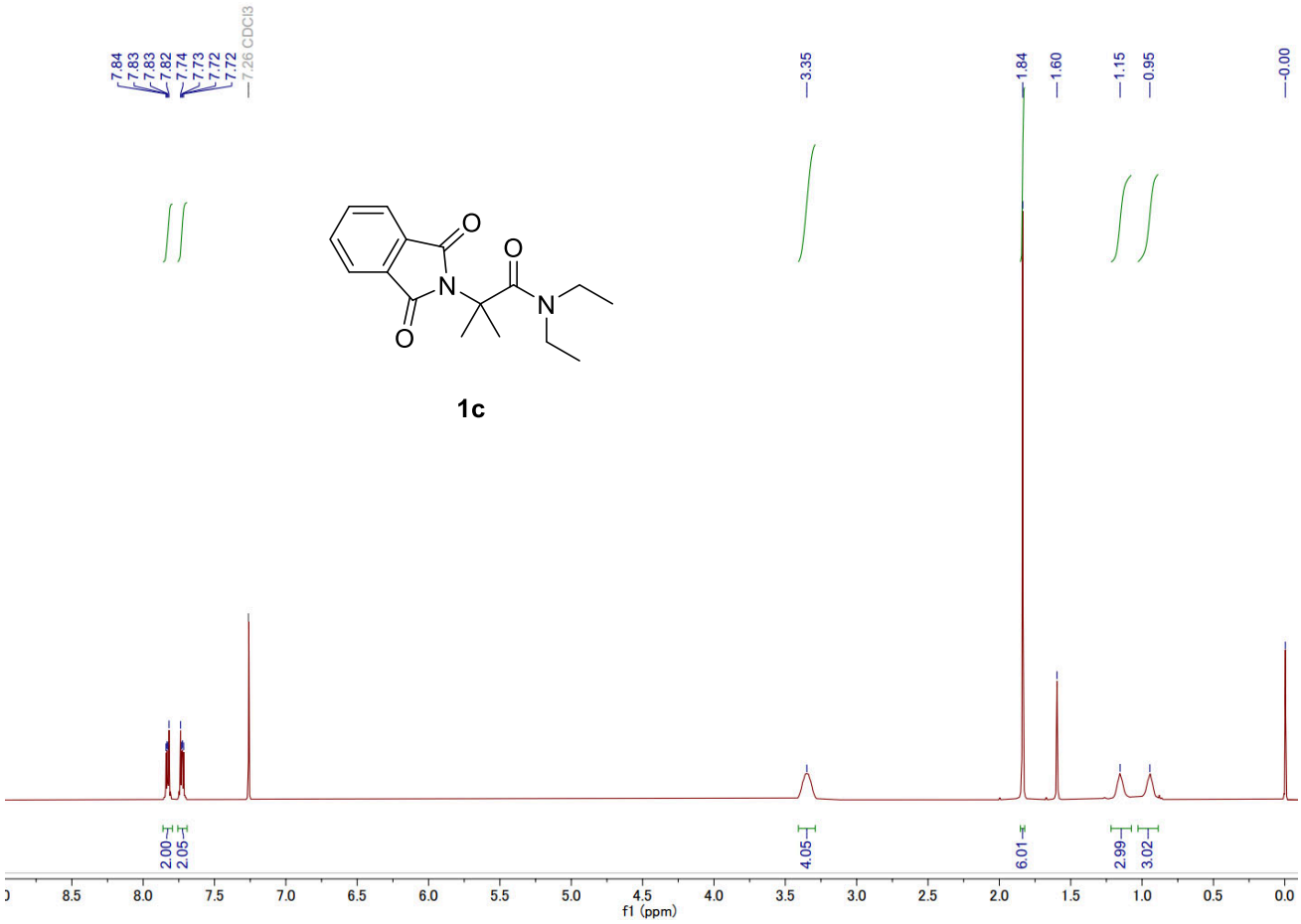
44.45
39.52 DMSO-d6
24.95
24.85
24.74
23.47
f1 (ppm)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7.83
7.83
7.82
7.74
7.73
7.72
7.72
7.26 CDCl3
3.35
1.84
1.60
1.15
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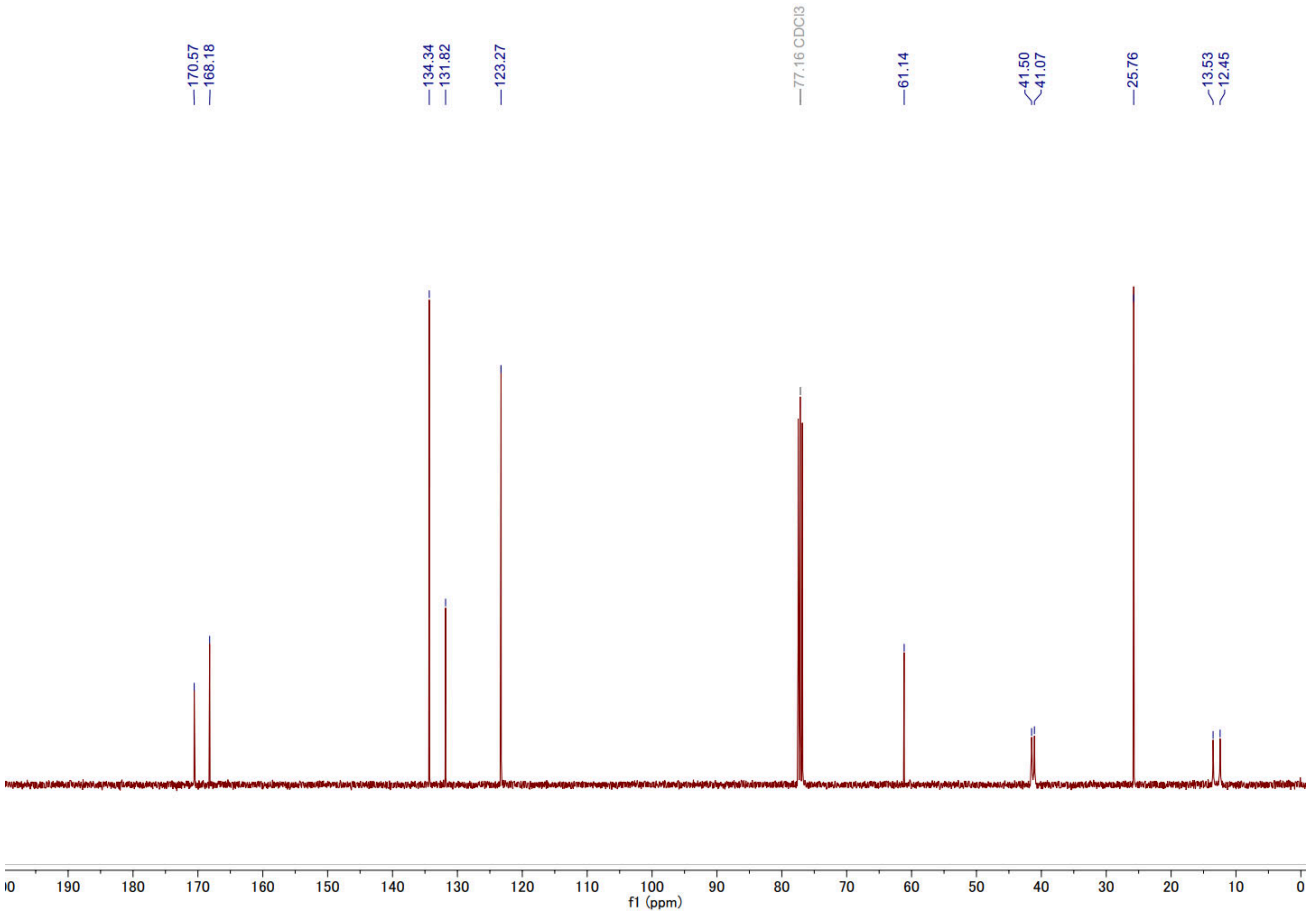
0.00
2.00
2.05
4.05
6.01
2.99
3.02
f1 (ppm)

1c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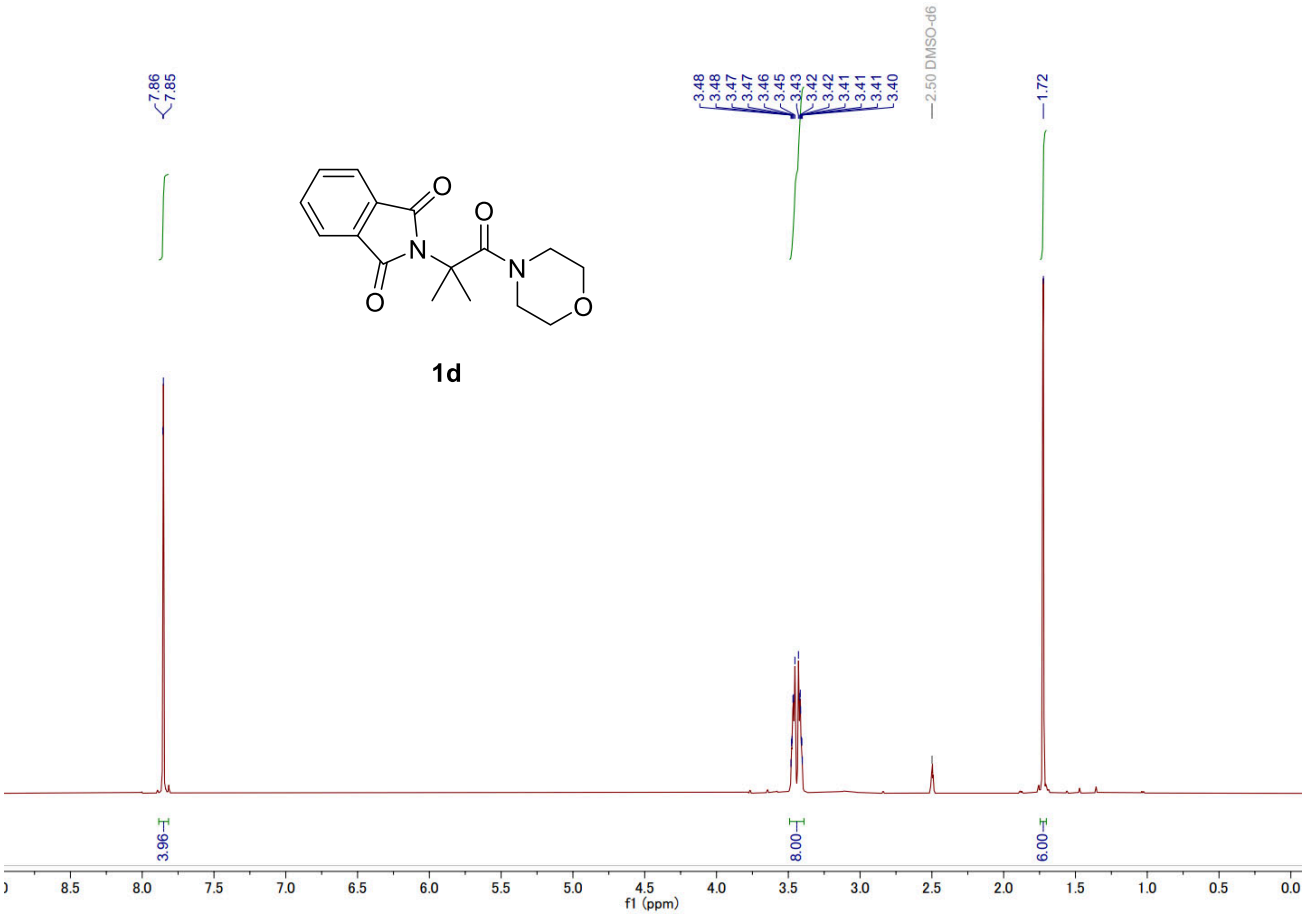
12.45
f1 (ppm)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3.45
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3.42
3.42
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6.00
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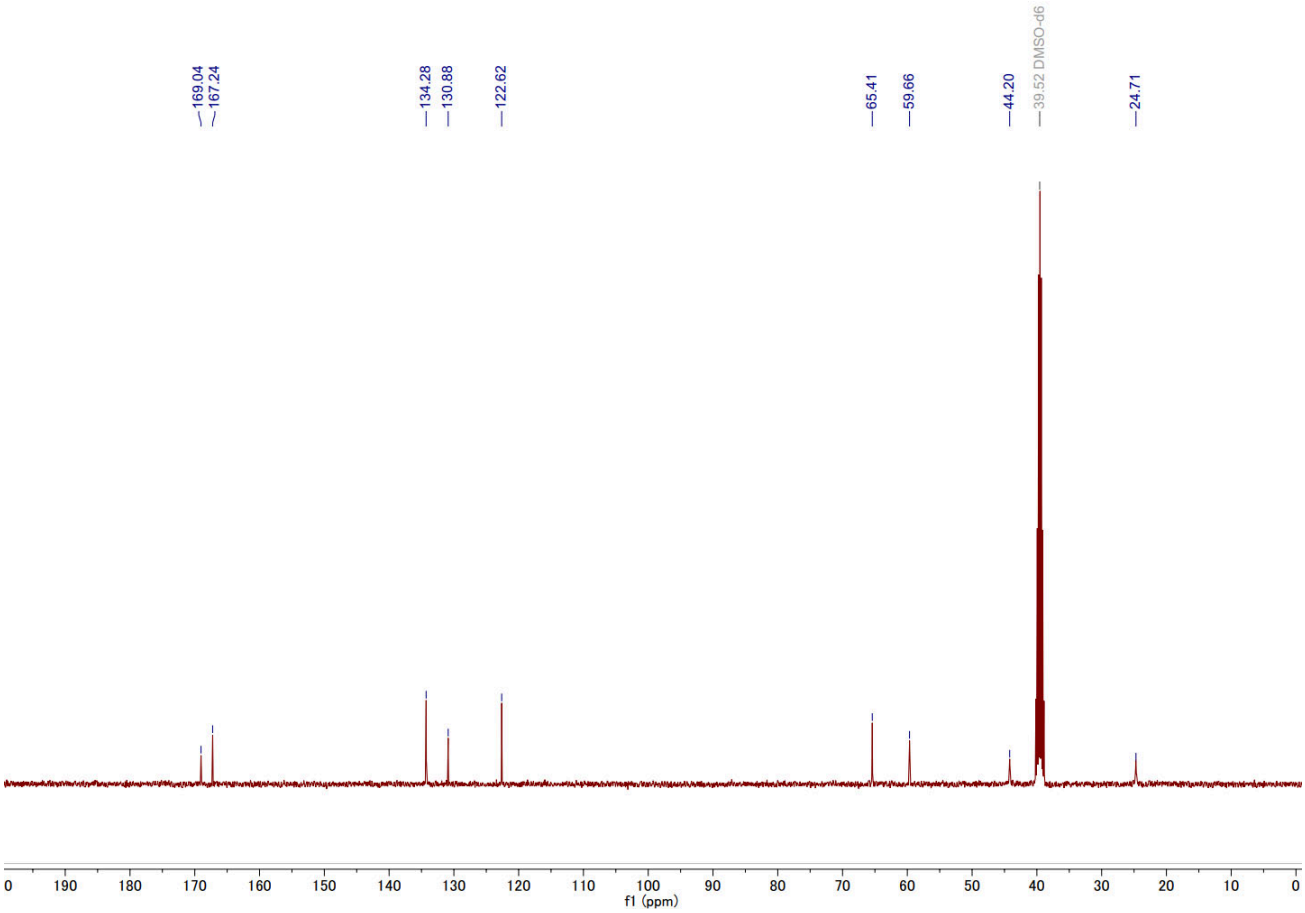
1d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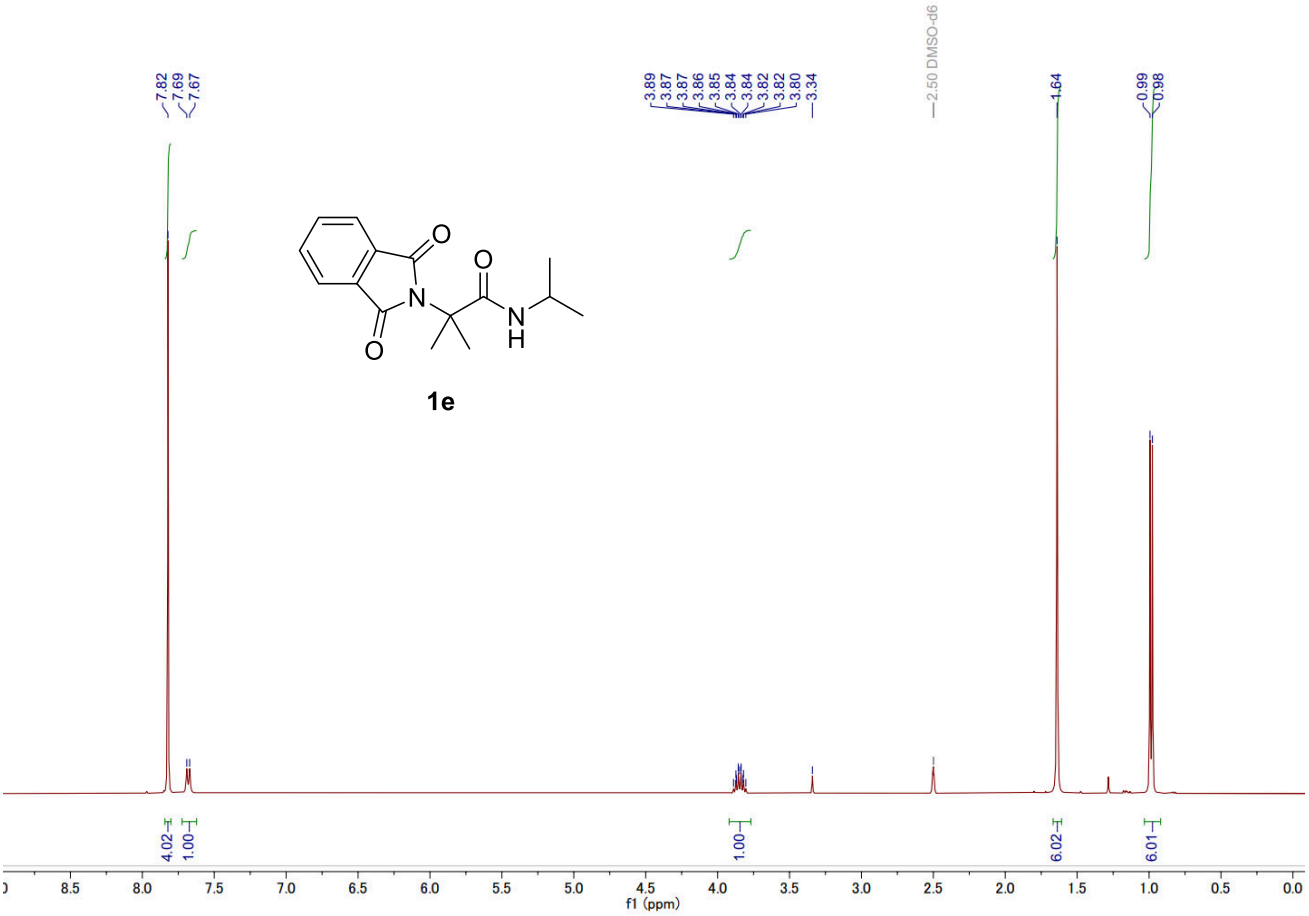
f1 (ppm)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3.34
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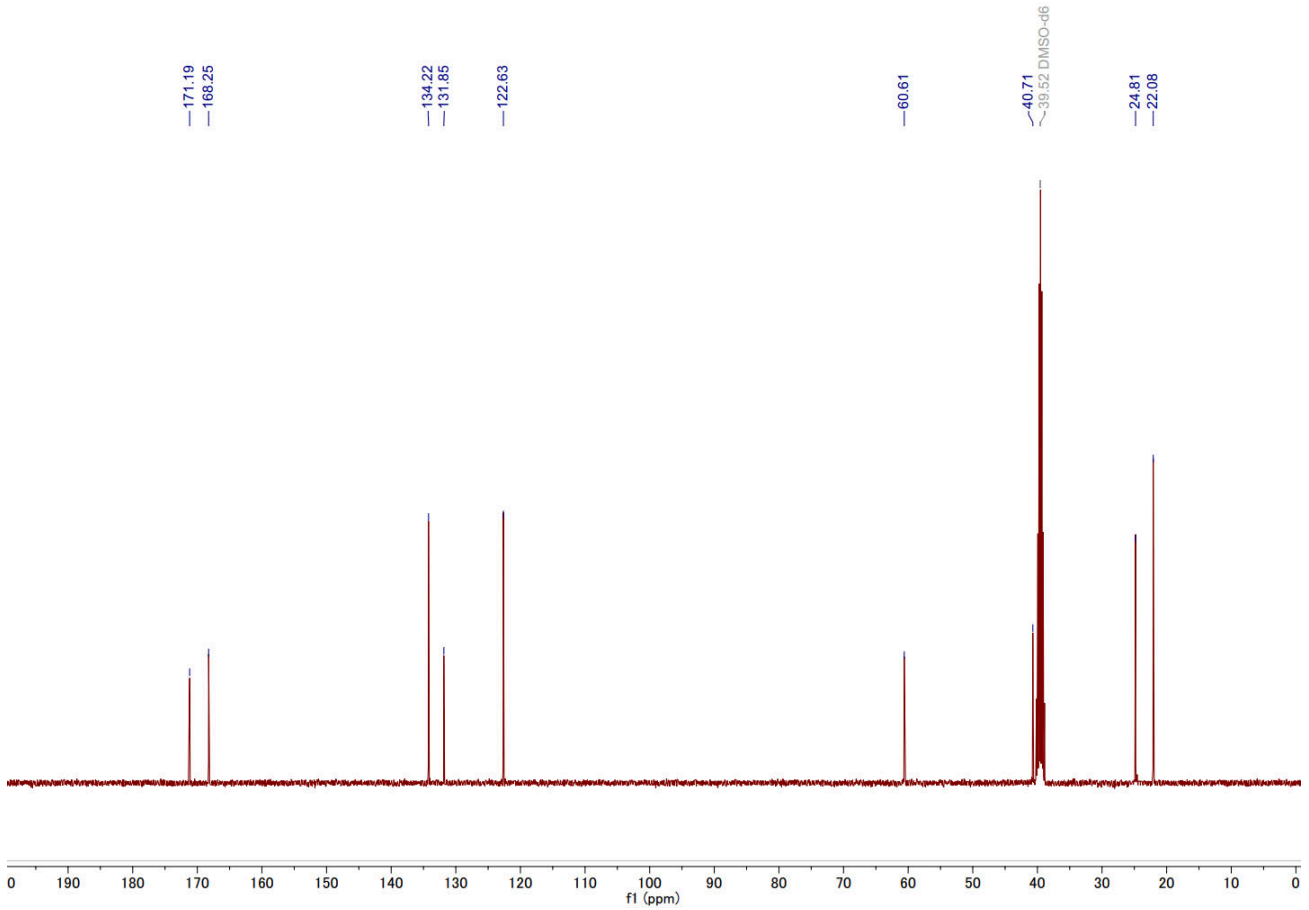
f1 (ppm)

1e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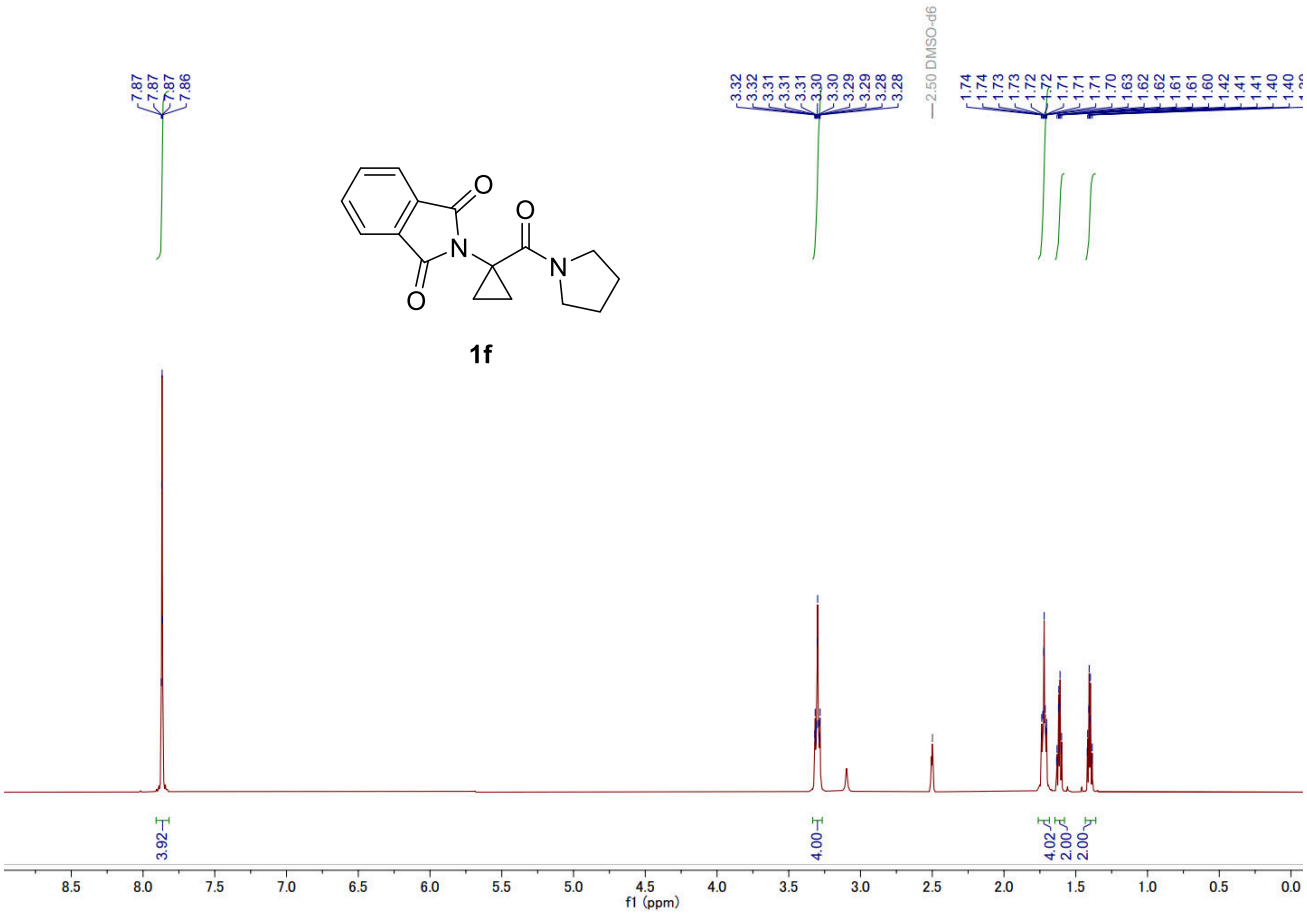
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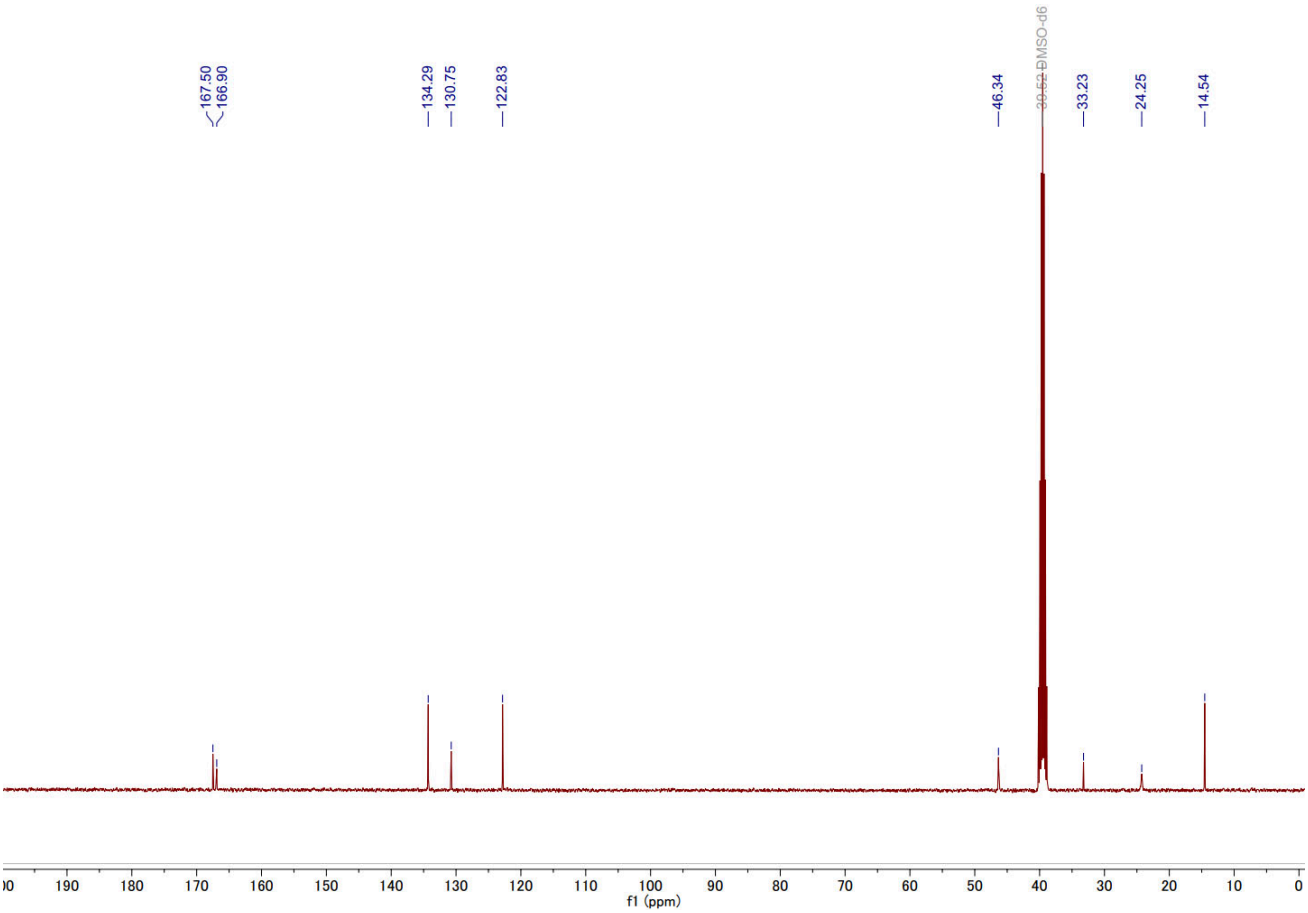
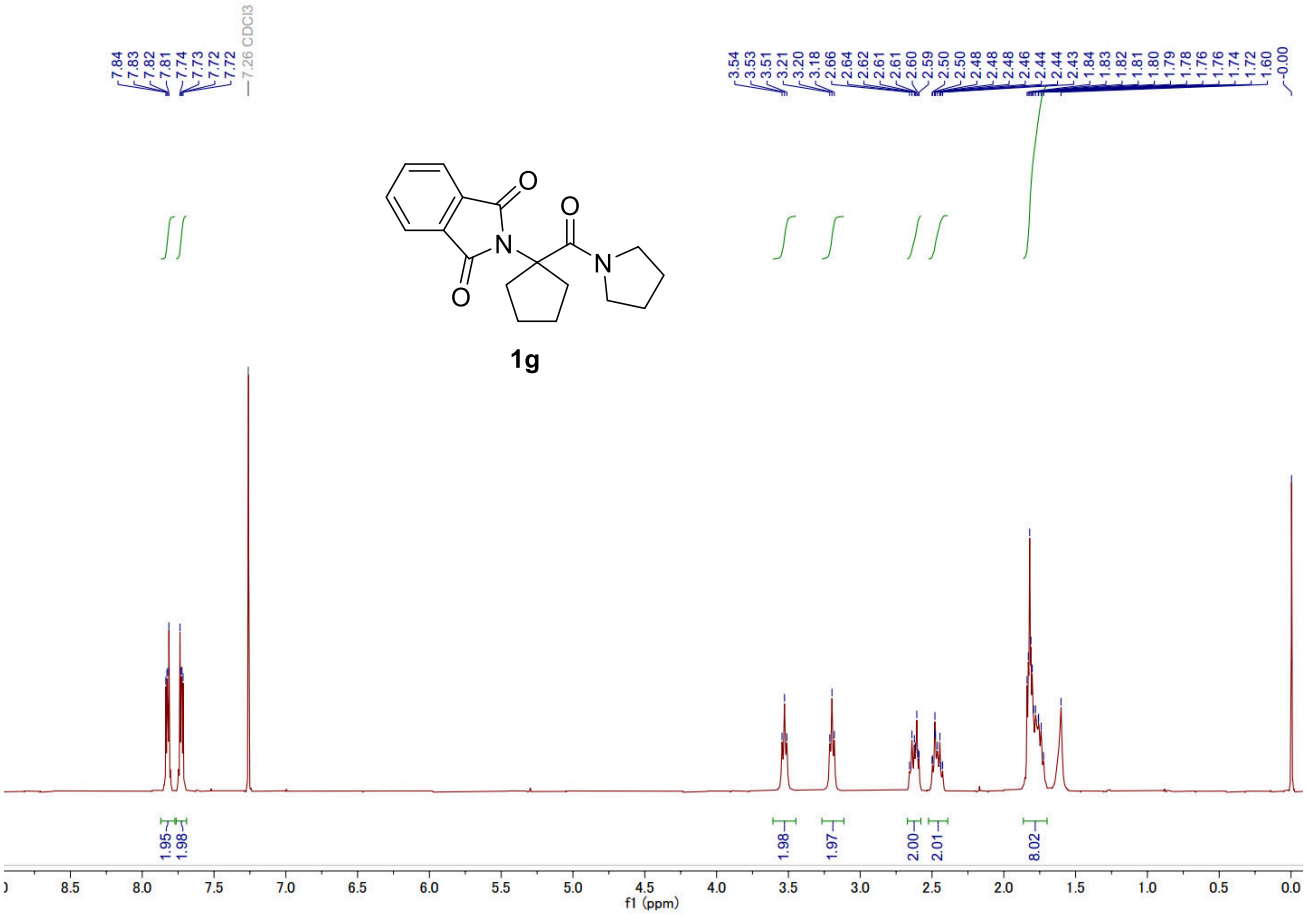
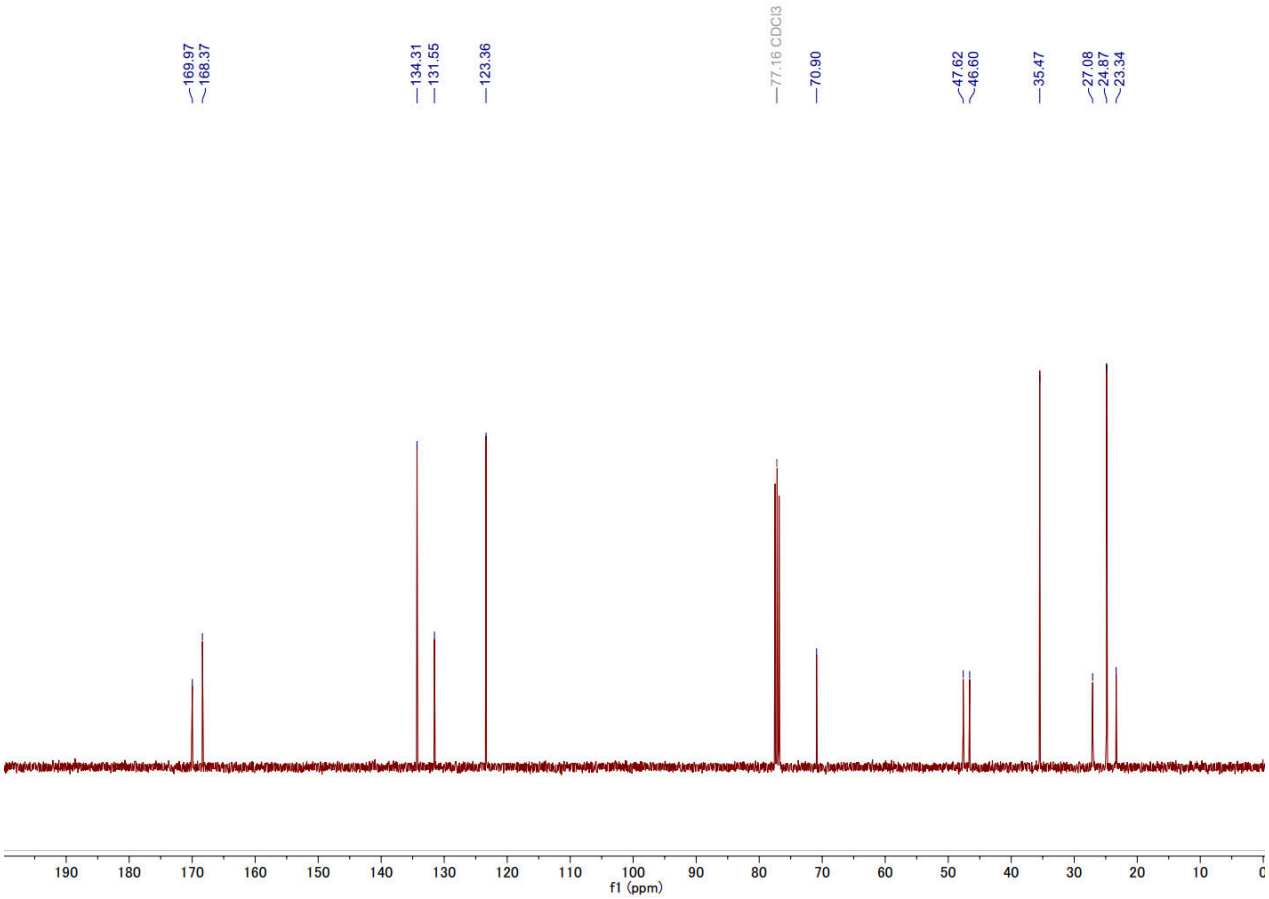
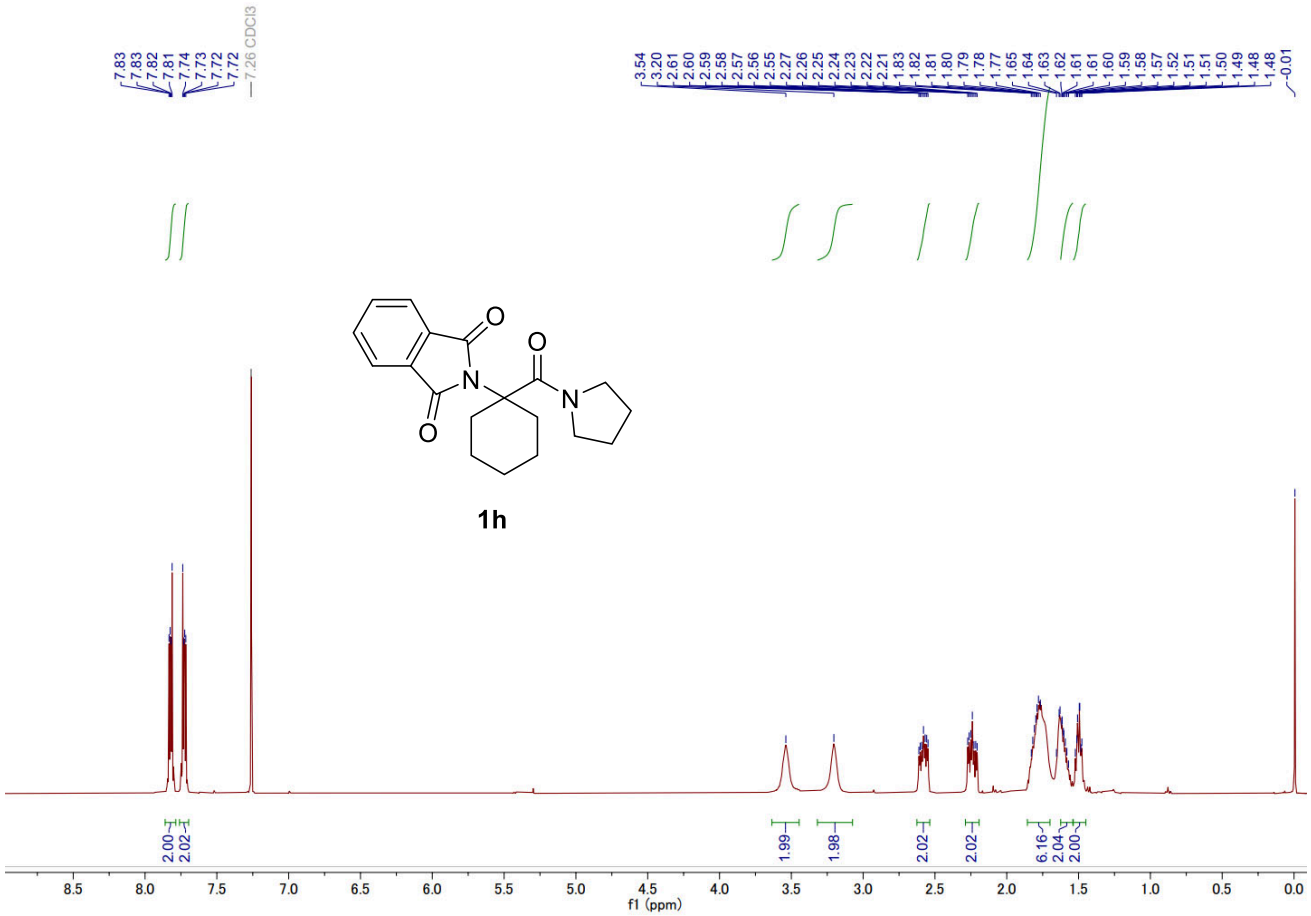
3.30
3.30
3.29
3.29
3.28
3.28
2.50 DMSO-d6
1.74
1.74
1.73
1.73
1.72
1.72
1.71
1.71
1.71
1.70
1.63
1.62
1.62
1.61
1.61
1.60
1.42
1.41
1.41
1.40
O
O
N
O
N
3.92
4.00
4.02
2.00
2.00
f1 (ppm)

1f

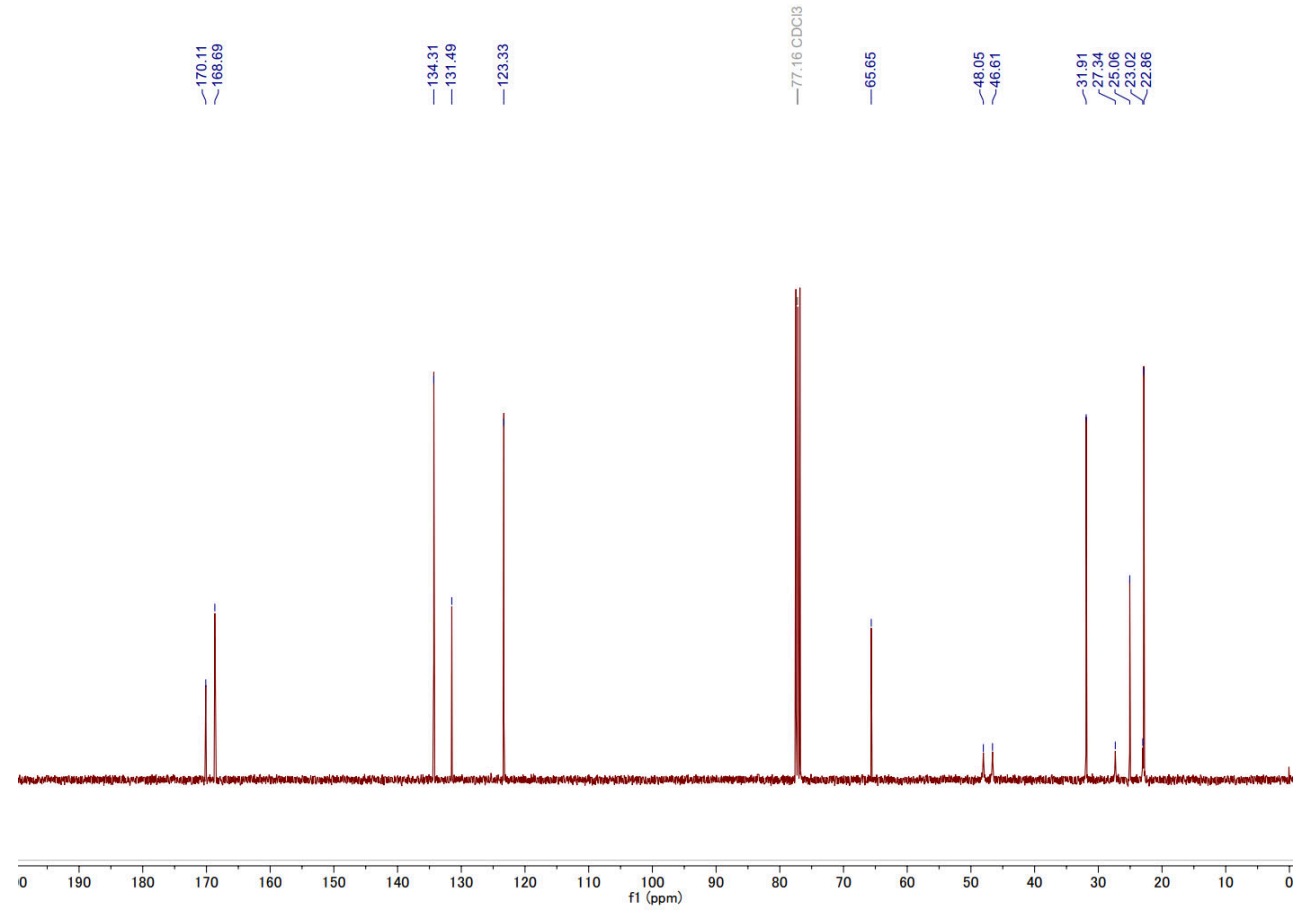

167.50
166.90
134.29
130.75
122.83
46.34
39.52 DMSO-d6
33.23
24.25
14.54
f1 (ppm)

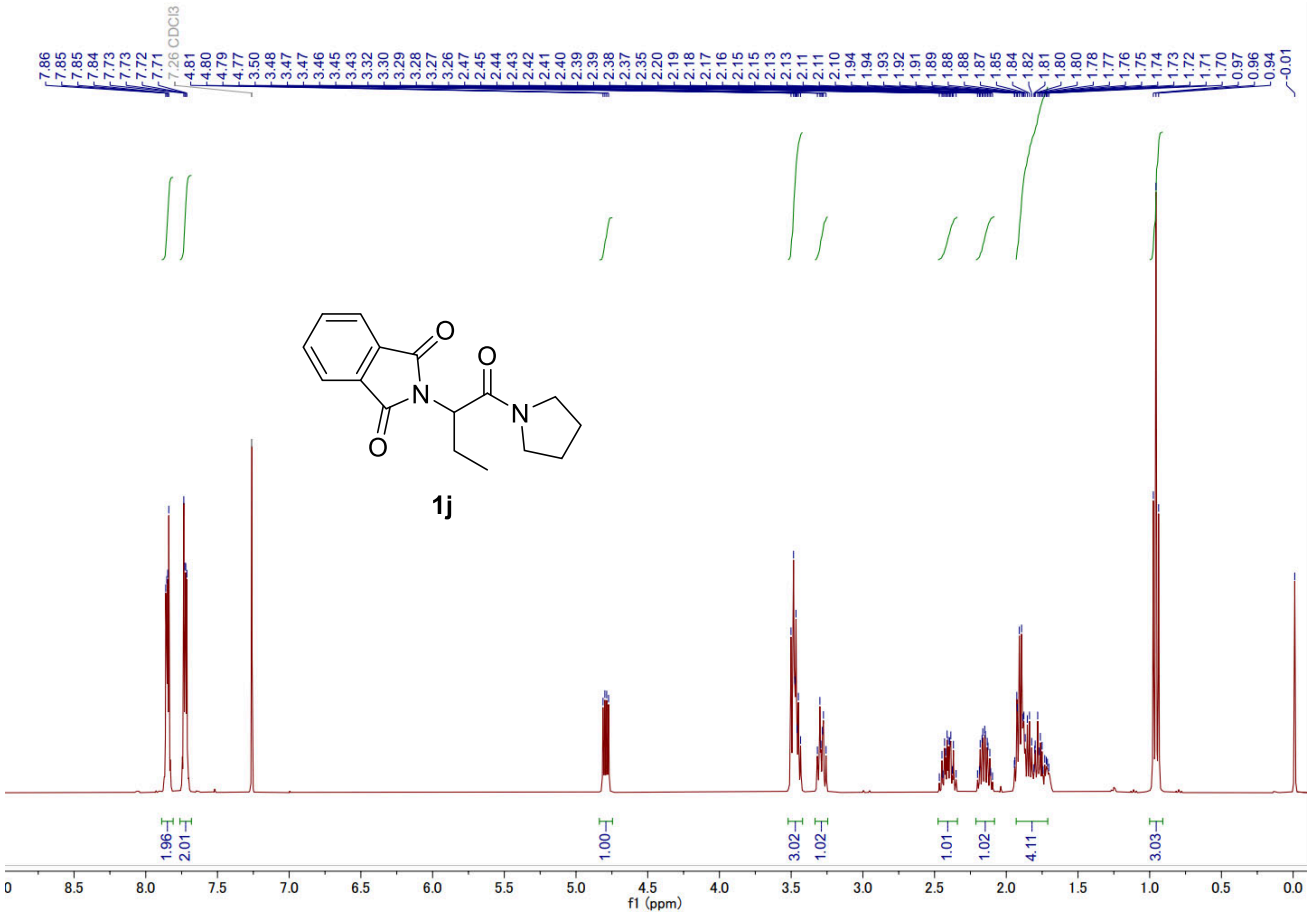

7.84
7.83
7.82
7.81
7.74
7.73
7.72
7.72
7.26 CDCl3
3.54
3.53
3.51
3.21
3.20
3.18
2.66
2.64
2.62
2.61
2.61
2.60
2.59
2.50
2.50
2.48
2.48
2.48
2.46
2.44
2.44
2.43
1.84
1.83
1.82
1.81
1.80
1.79
1.78
1.76
1.76
1.74
1.72
1.60
0.00
O
O
N
O
N
1g
1.95
1.98
1.98
1.97
2.00
2.01
8.02
f1 (ppm)


169.97
168.37
134.31
131.55
123.36
77.16 CDCl3
70.90
47.62
46.60
35.47
27.08
24.87
23.34
f1 (ppm)

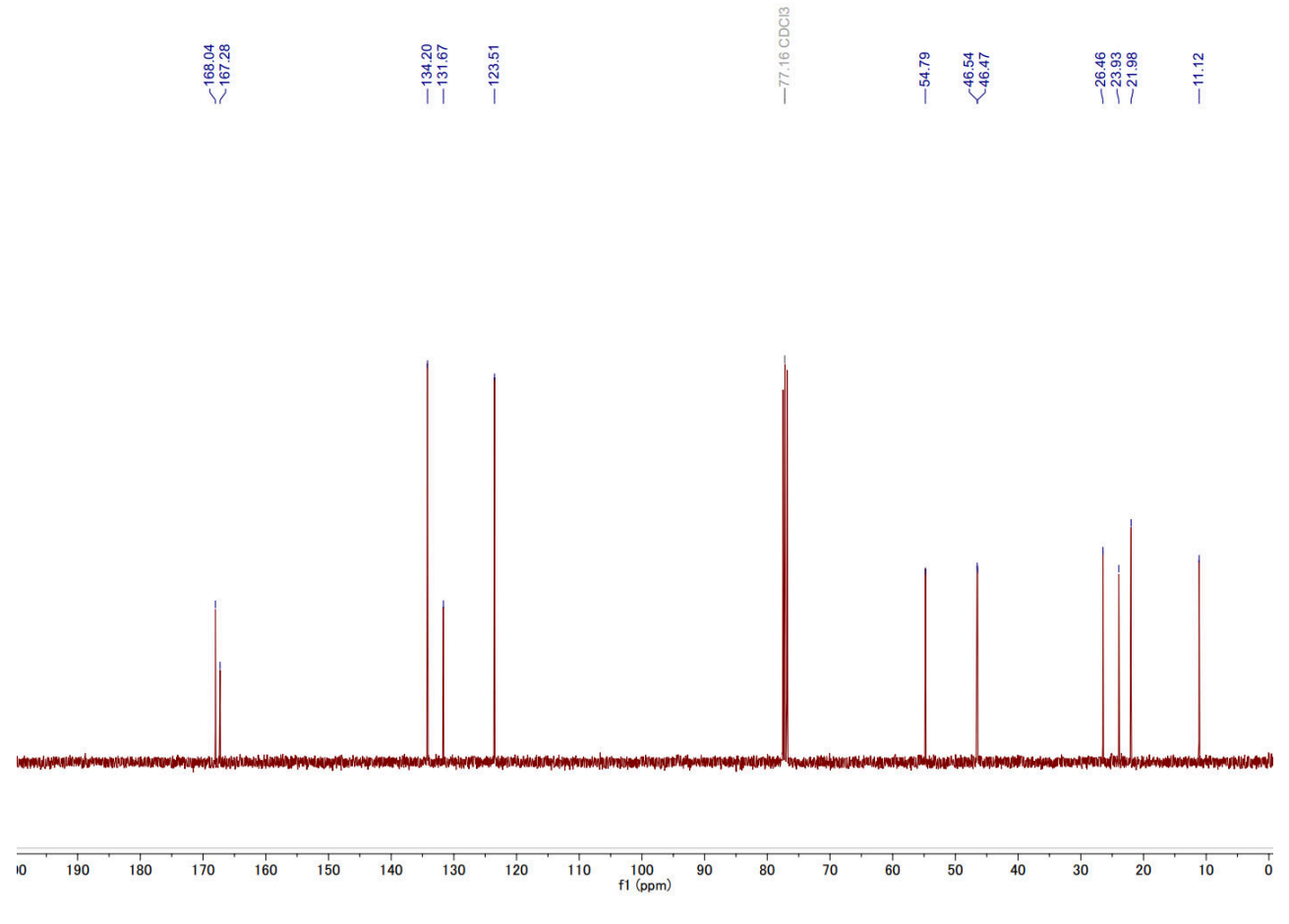

7.83
7.83
7.82
7.81
7.74
7.73
7.72
7.72
7.26 CDCl3
3.54
3.20
2.61
2.60
2.59
2.58
2.57
2.56
2.55
2.27
2.26
2.25
2.24
2.23
2.22
2.21
1.83
1.82
1.81
1.80
1.79
1.78
1.77
1.65
1.64
1.63
1.62
1.61
1.61
1.60
1.59
1.58
1.57
1.52
1.51
1.51
1.50
1.49
1.48
1.48
0.01
O
O
N
O
N
2.00
2.02
1.99
1.98
2.02
2.02
6.16
2.04
2.00
f1 (ppm)

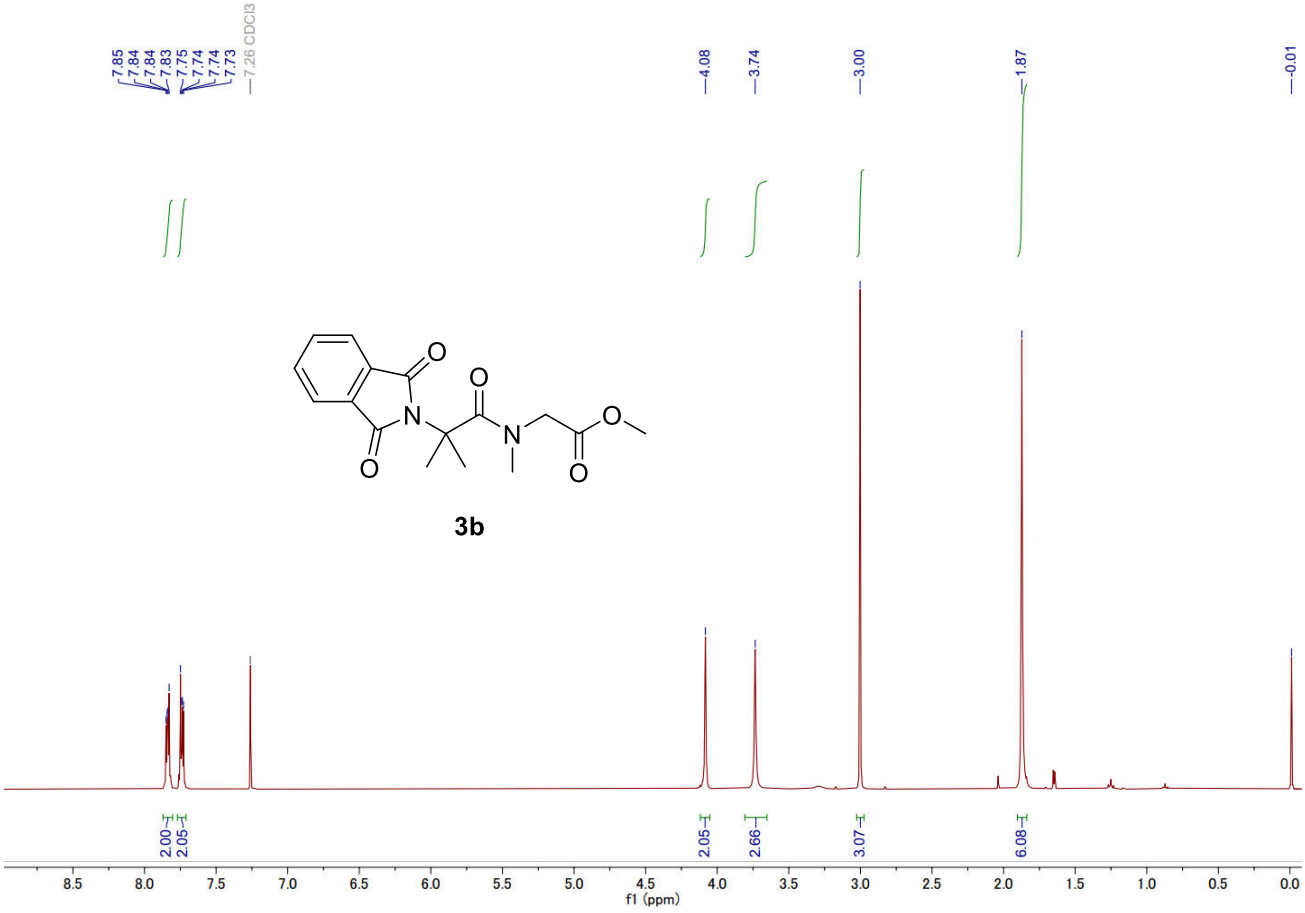
1h


170.11
168.69
134.31
131.49
123.33
77.16 CDCl3
65.65
48.05
46.61
31.91
27.34
25.06
23.02
22.86
f1 (ppm)

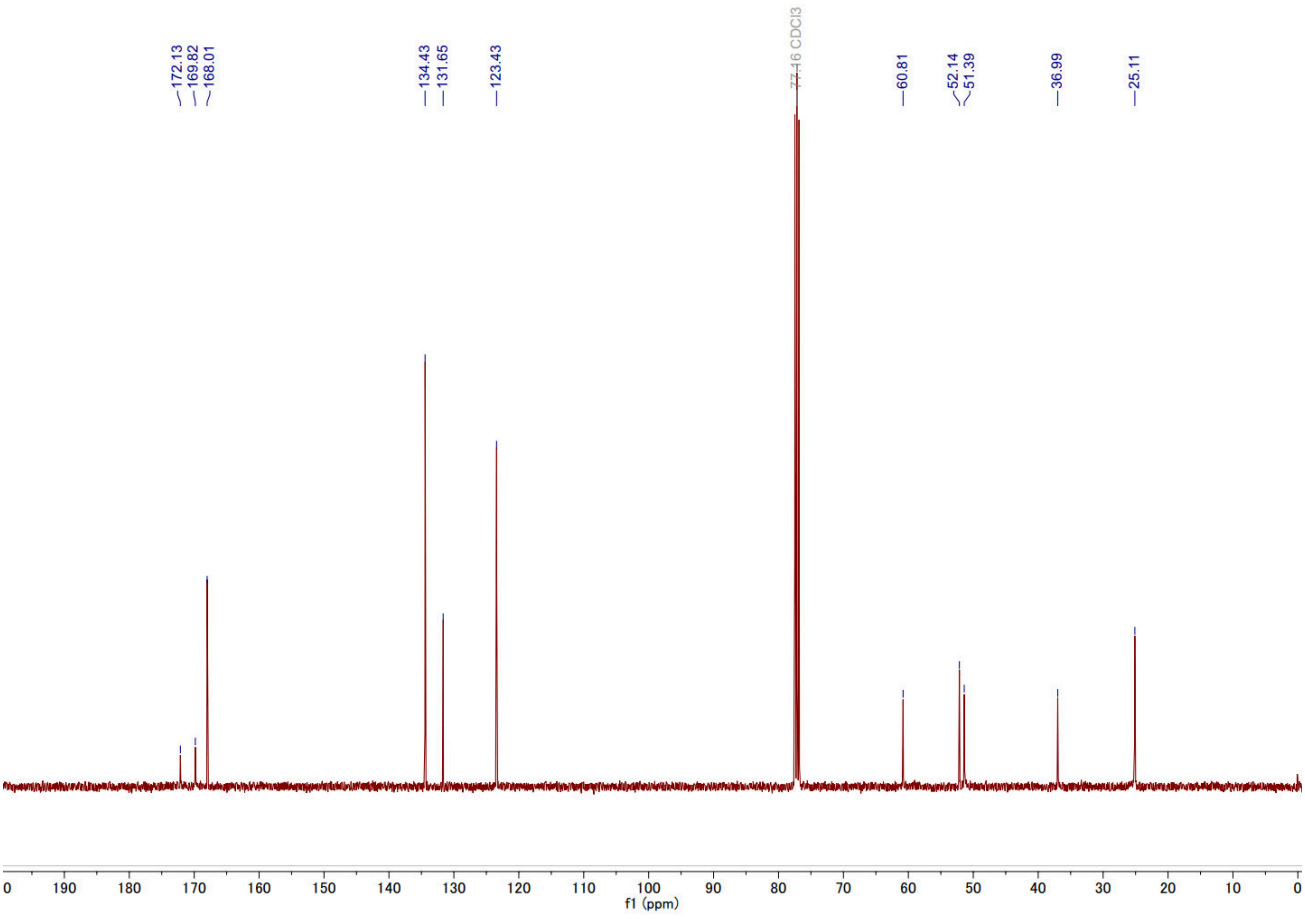

7.86
7.85
7.85
7.84
7.73
7.73
7.72
7.71
7.26 CDCl3
4.81
4.80
4.79
4.77
3.50
3.48
3.47
3.47
3.46
3.45
3.43
3.32
3.30
3.29
3.28
3.27
3.26
2.47
2.45
2.44
2.43
2.42
2.41
2.40
2.39
2.39
2.38
2.37
2.35
2.20
2.19
2.18
2.17
2.16
2.15
2.15
2.13
2.11
2.11
2.10
1.94
1.94
1.93
1.92
1.91
1.89
1.88
1.88
1.87
1.85
1.84
1.82
1.81
1.80
1.80
1.78
1.77
1.76
1.75
1.74
1.73
1.72
1.71
1.70
0.97
0.96
0.94
0.01
O
O
N
O
N
1.96
2.01
1.00
3.02
1.02
1.01
1.02
4.11
3.03
f1 (ppm)

1j

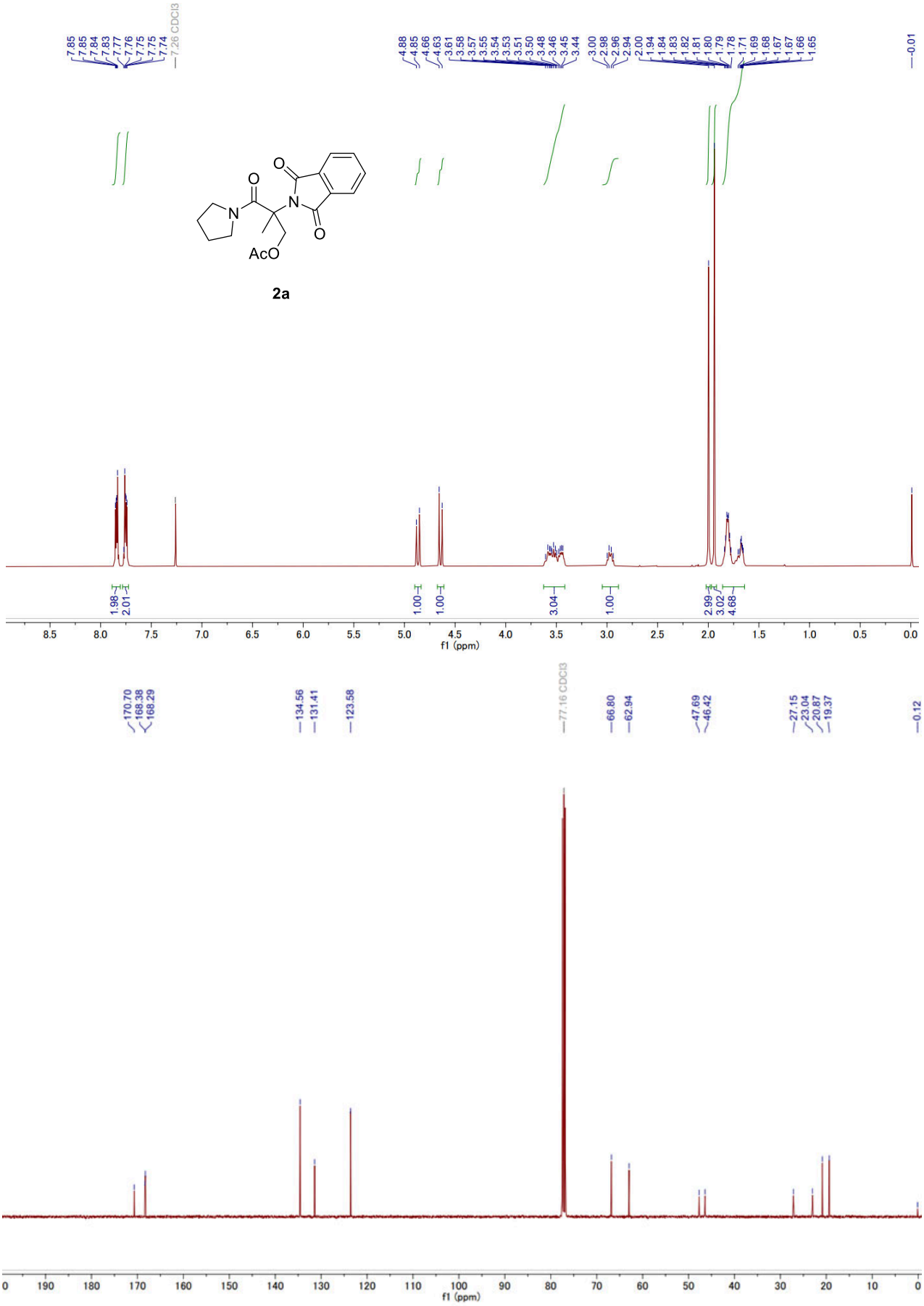

168.04
167.28
134.20
131.67
123.51
77.16 CDCl3
54.79
46.54
46.47
26.46
23.93
21.98
11.12
f1 (ppm)

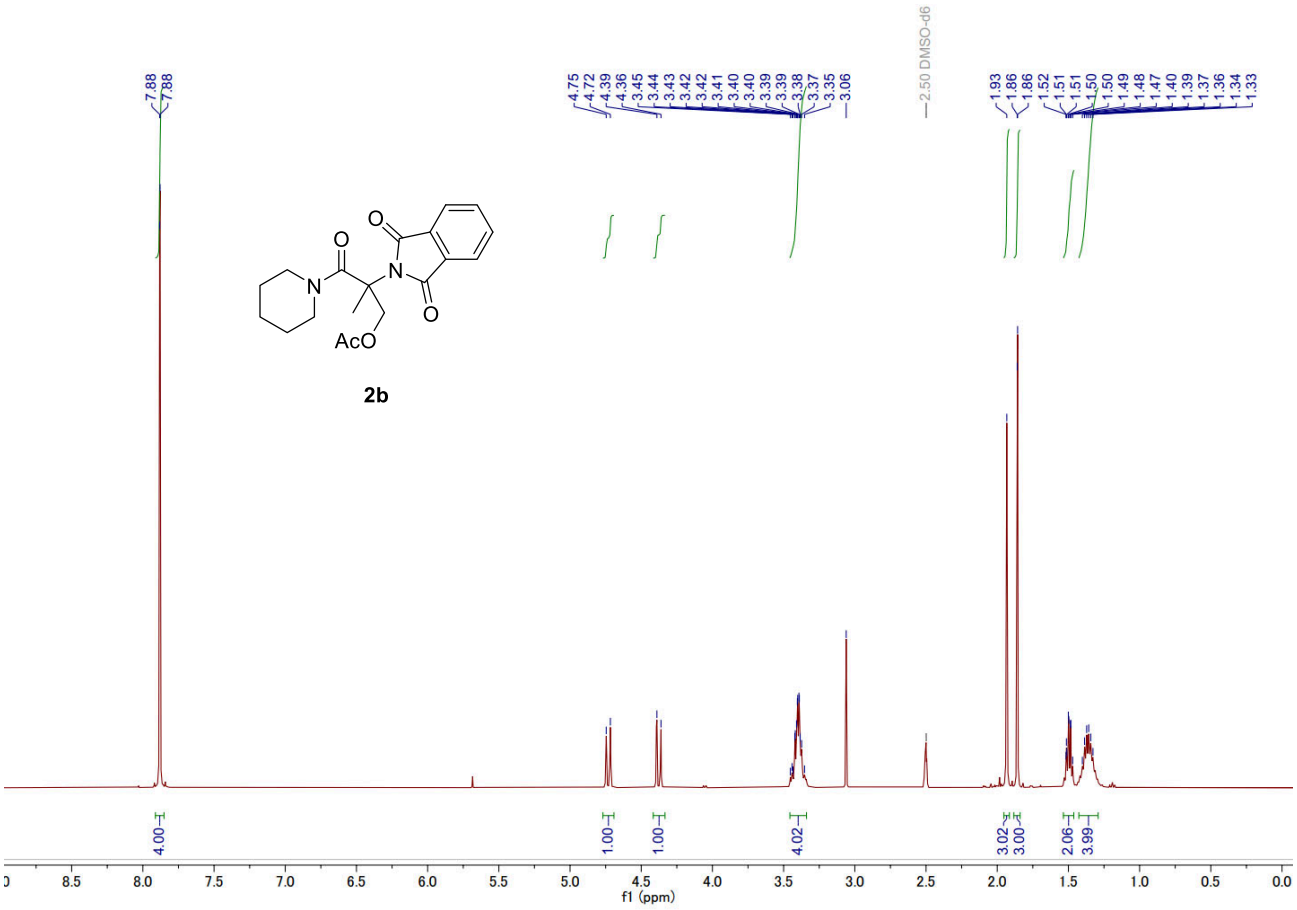

7.85
7.84
7.84
7.83
7.75
7.74
7.74
7.73
7.26 CDCl3
4.08
3.74
3.00
1.87
0.01
2.00
2.05
2.05
2.66
3.07
6.08
f1 (ppm)

3b

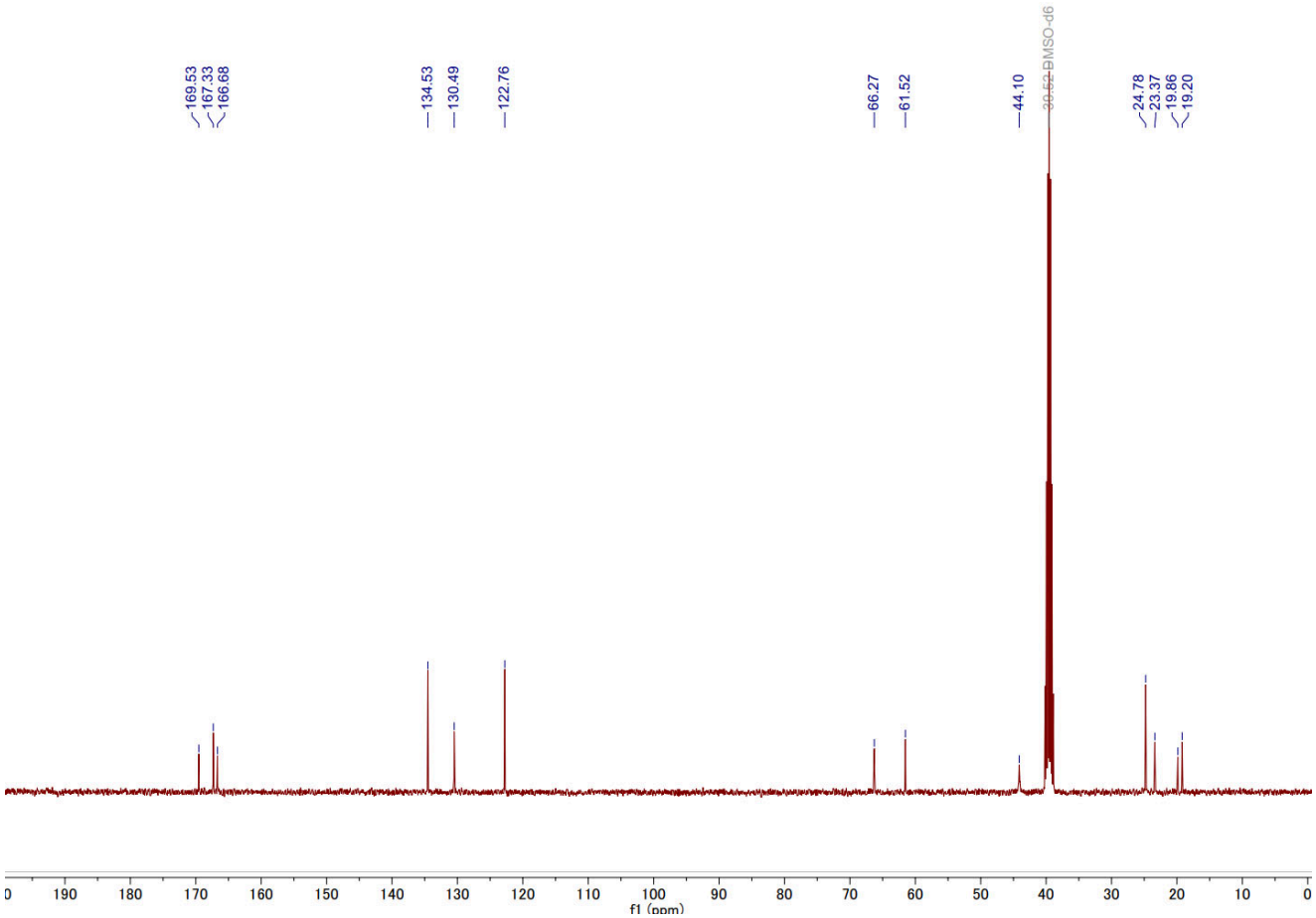

172.13
169.82
168.01
134.43
131.65
123.43
77.16 CDCl3
60.81
52.14
51.39
36.99
25.11
f1 (ppm)

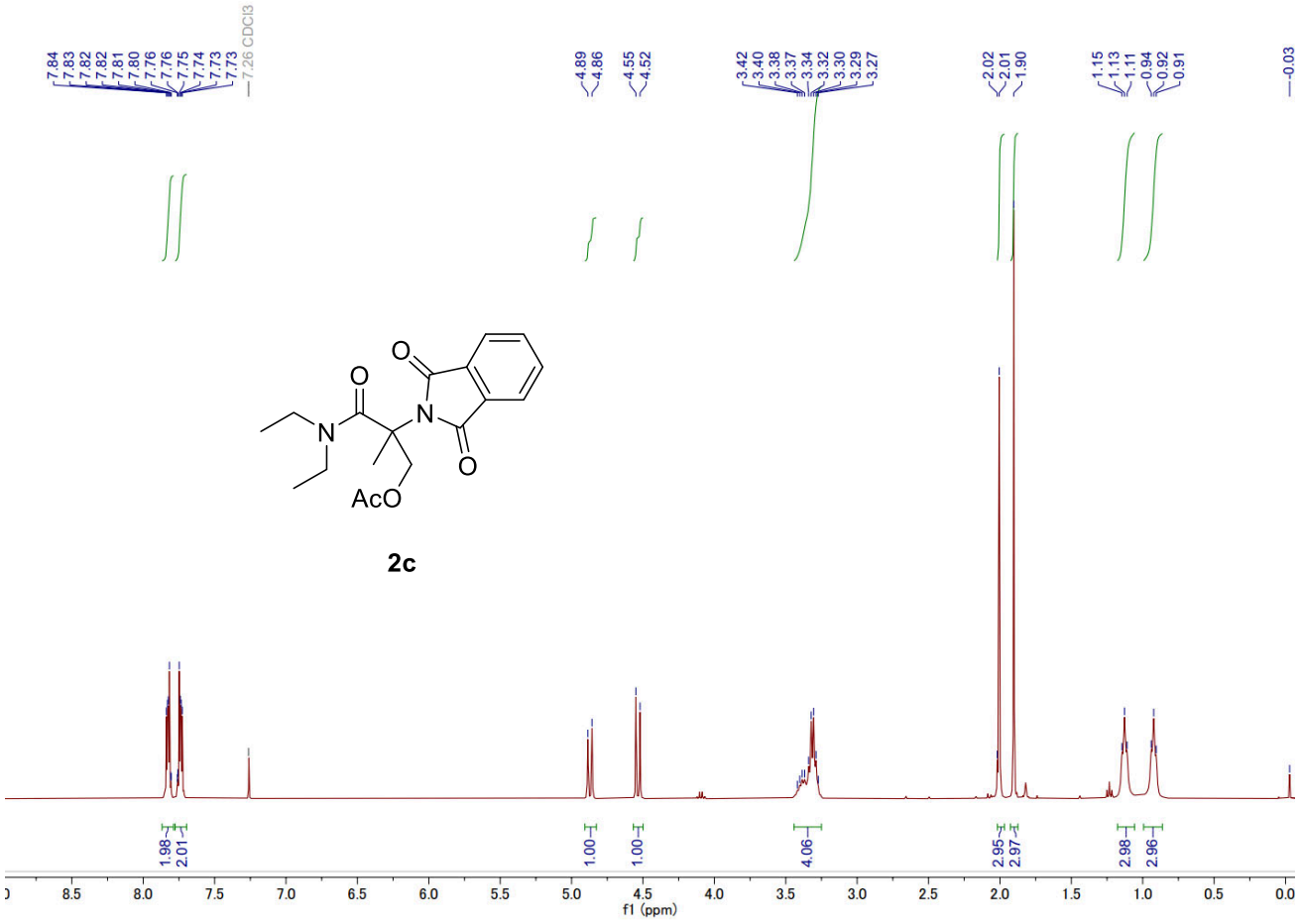
^{1}H and ^{13}C NMR Spectra of Products



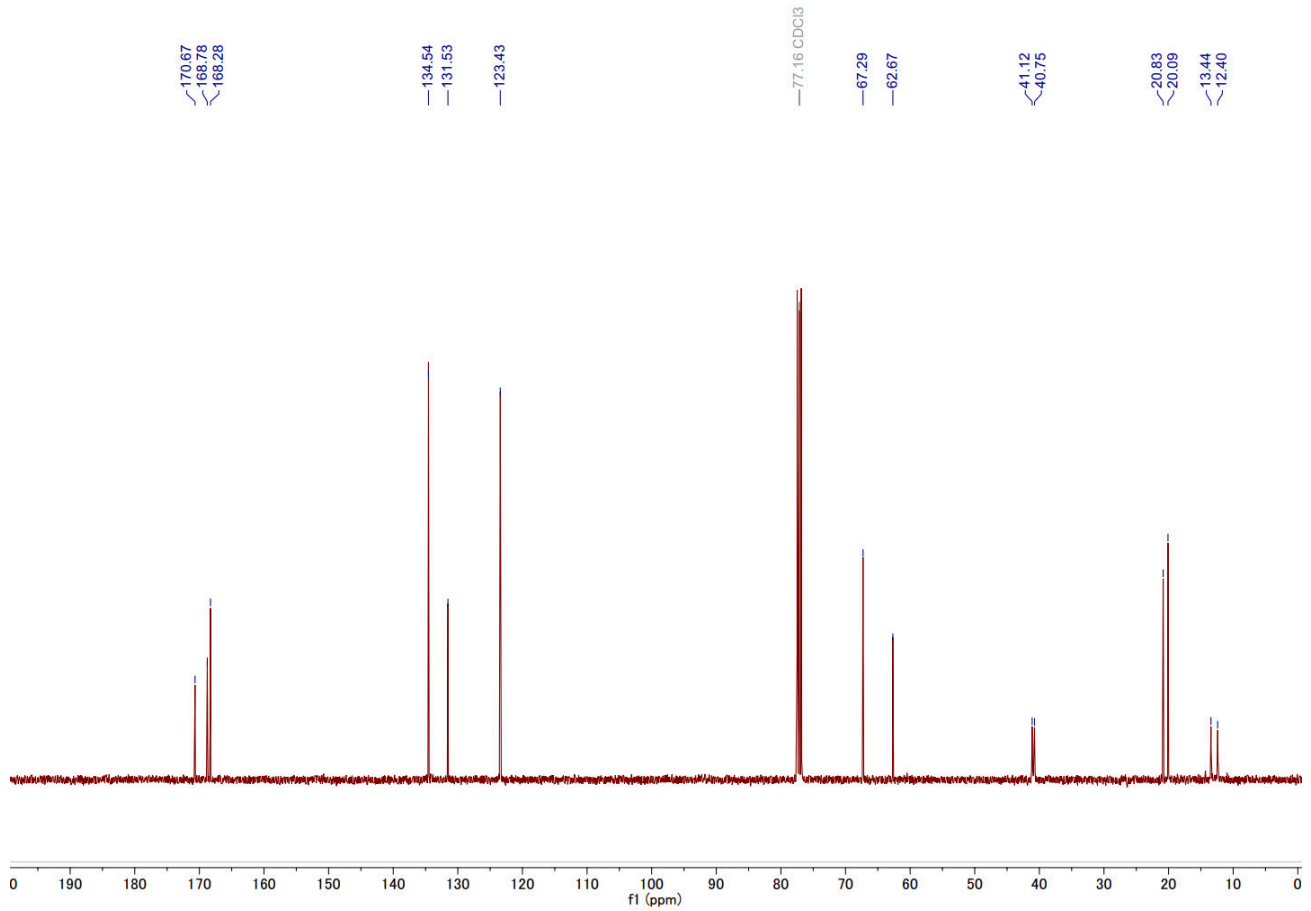

7.88
7.88
4.75
4.72
4.39
4.36
3.45
3.44
3.43
3.42
3.42
3.41
3.40
3.40
3.39
3.39
3.38
3.37
3.35
3.06
2.50 DMSO-d6
1.93
1.86
1.86
1.52
1.51
1.51
1.50
1.50
1.49
1.48
1.47
1.40
1.39
1.37
1.36
1.34
1.33
O
O
N
N
O
O
AcO
4.00
1.00
1.00
4.02
3.02
3.00
2.06
3.99
f1 (ppm)

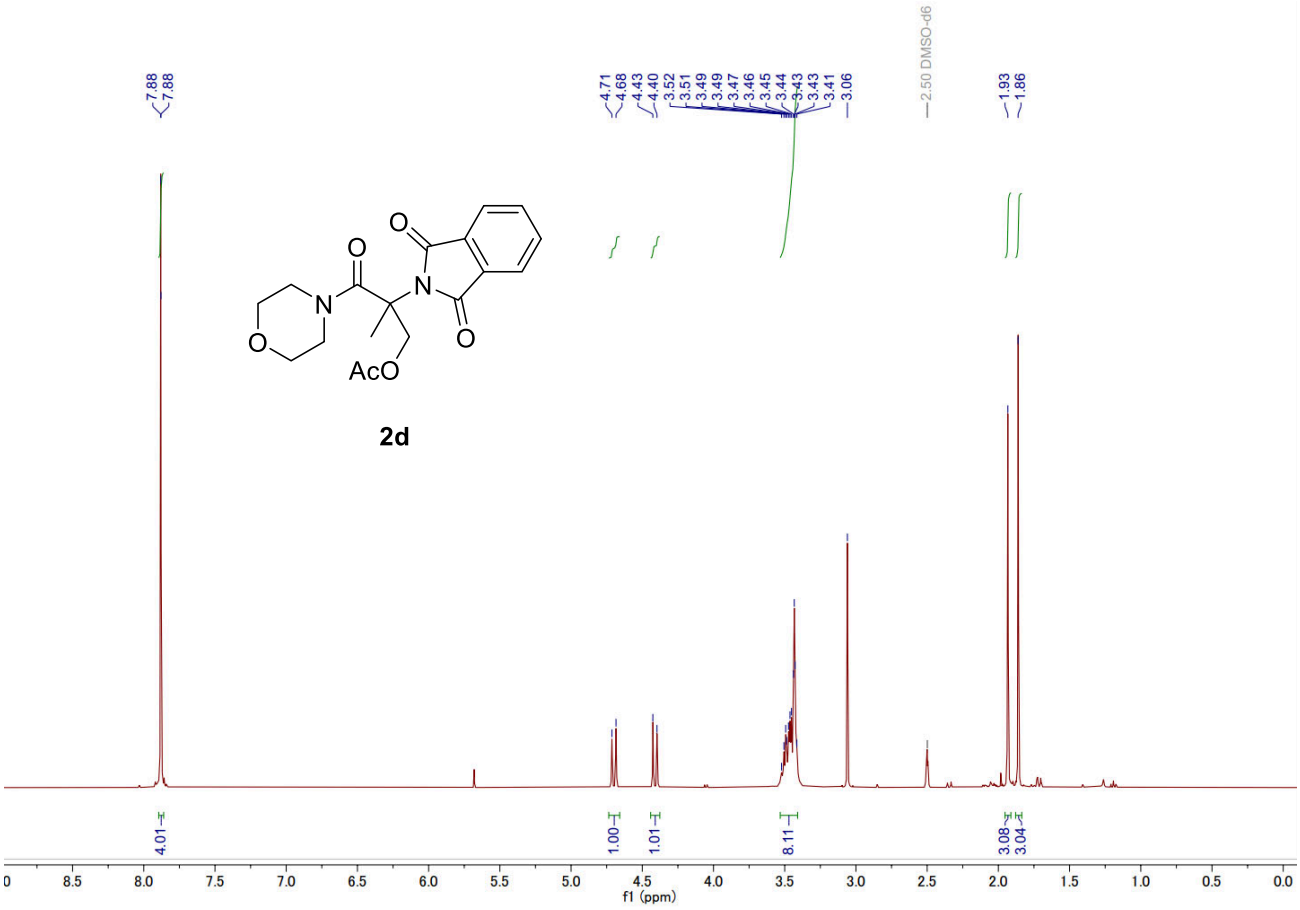
2b


169.53
167.33
166.68
134.53
130.49
122.76
66.27
61.52
44.10
39.52 DMSO-d6
24.78
23.37
19.86
19.20
f1 (ppm)

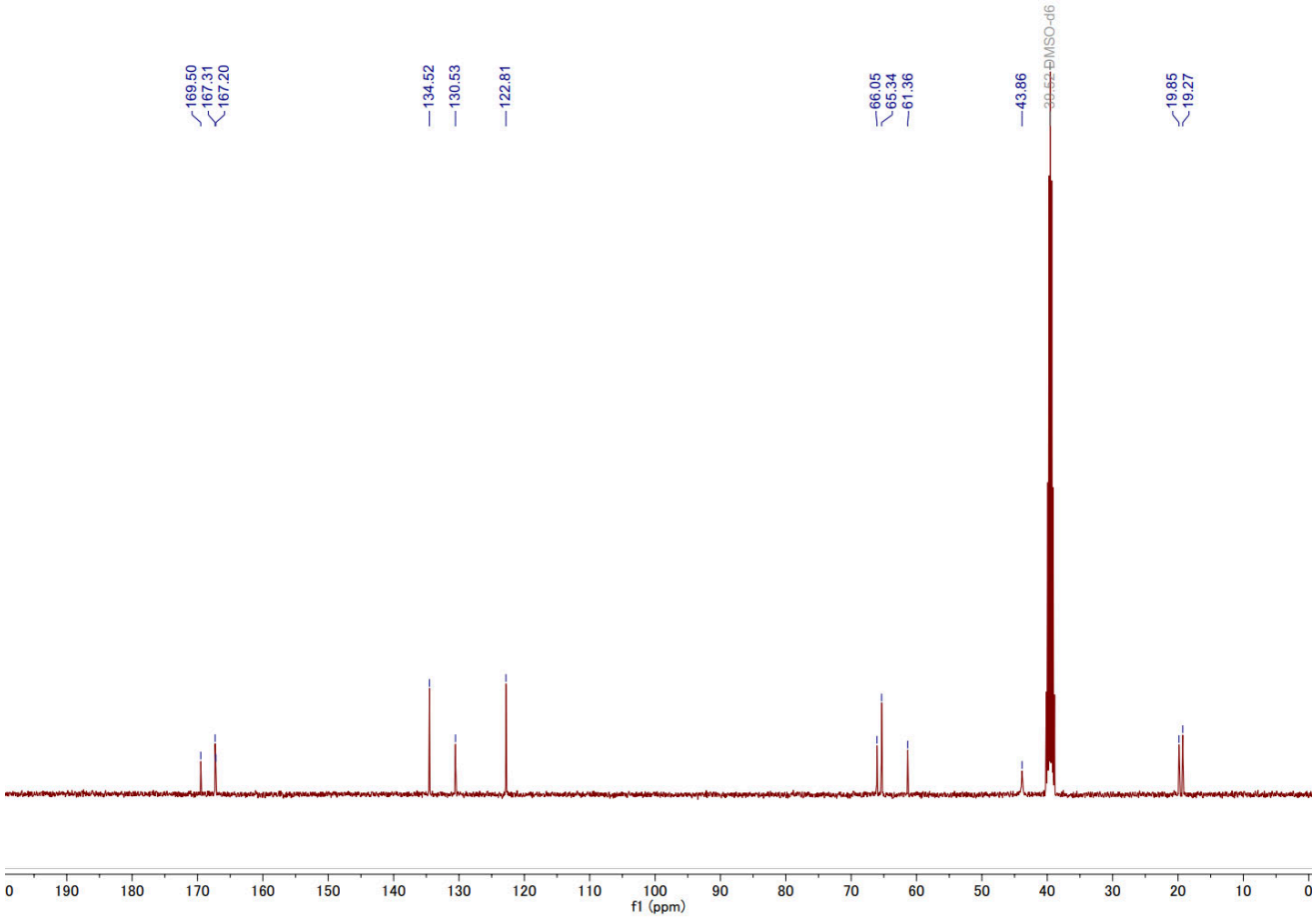

7.84
7.83
7.82
7.82
7.81
7.80
7.76
7.76
7.75
7.74
7.73
7.73
7.26 CDCl3
4.89
4.86
4.55
4.52
3.42
3.40
3.38
3.37
3.34
3.32
3.30
3.29
3.27
2.02
2.01
1.90
1.15
1.13
1.11
0.94
0.92
0.91
0.03
O
O
N
N
O
AcO
1.98
2.01
1.00
1.00
4.06
2.95
2.97
2.98
2.96
f1 (ppm)

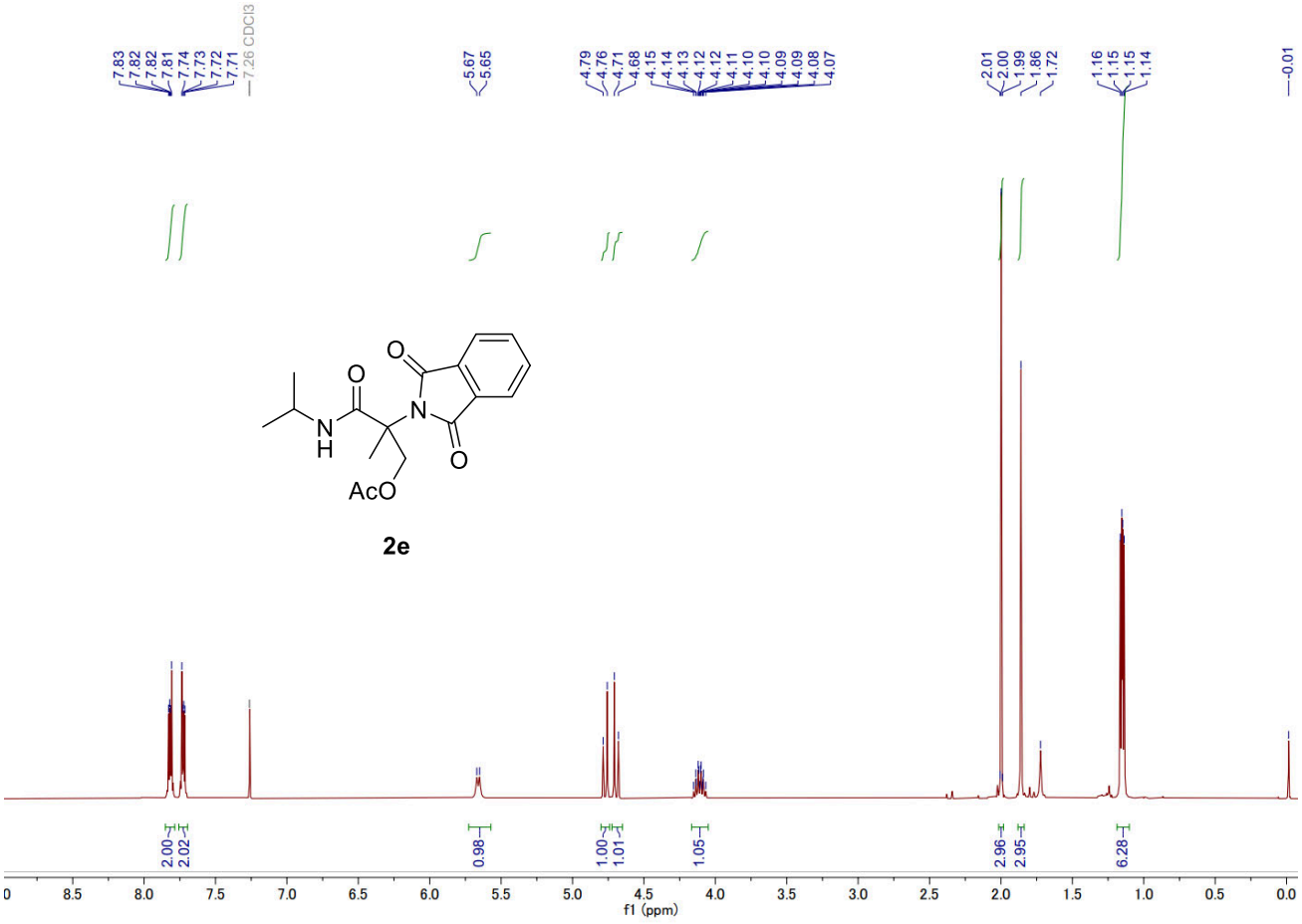
2c


170.67
168.78
168.28
134.54
131.53
123.43
77.16 CDCl3
67.29
62.67
41.12
40.75
20.83
20.09
13.44
12.40
f1 (ppm)

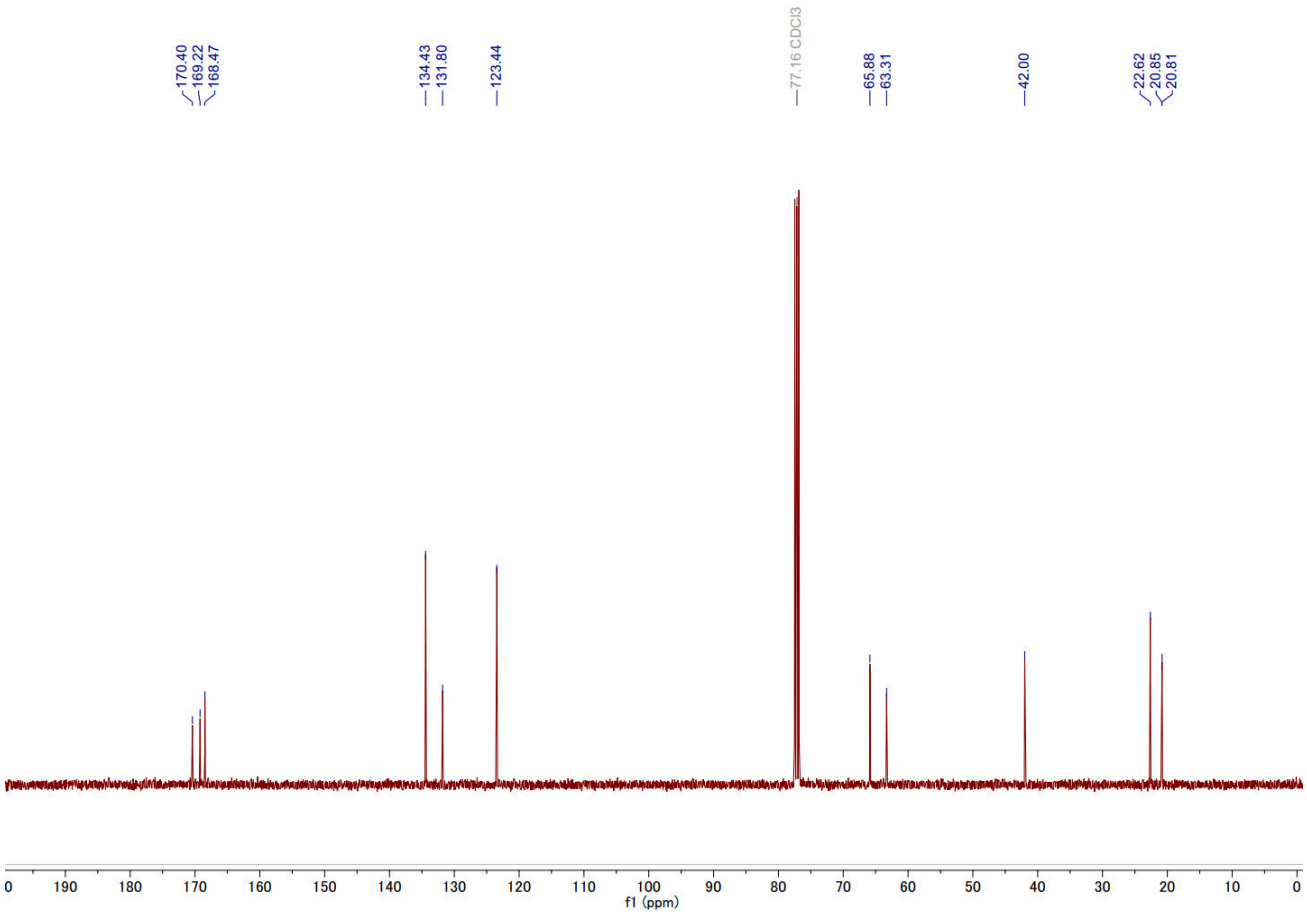

7.88
7.88
4.71
4.68
4.43
4.40
3.52
3.51
3.49
3.49
3.47
3.46
3.45
3.44
3.43
3.43
3.41
3.06
2.50 DMSO-d6
1.93
1.86
O
O
N
N
O
O
O
AcO
4.01
1.00
1.01
8.11
3.08
3.04
f1 (ppm)

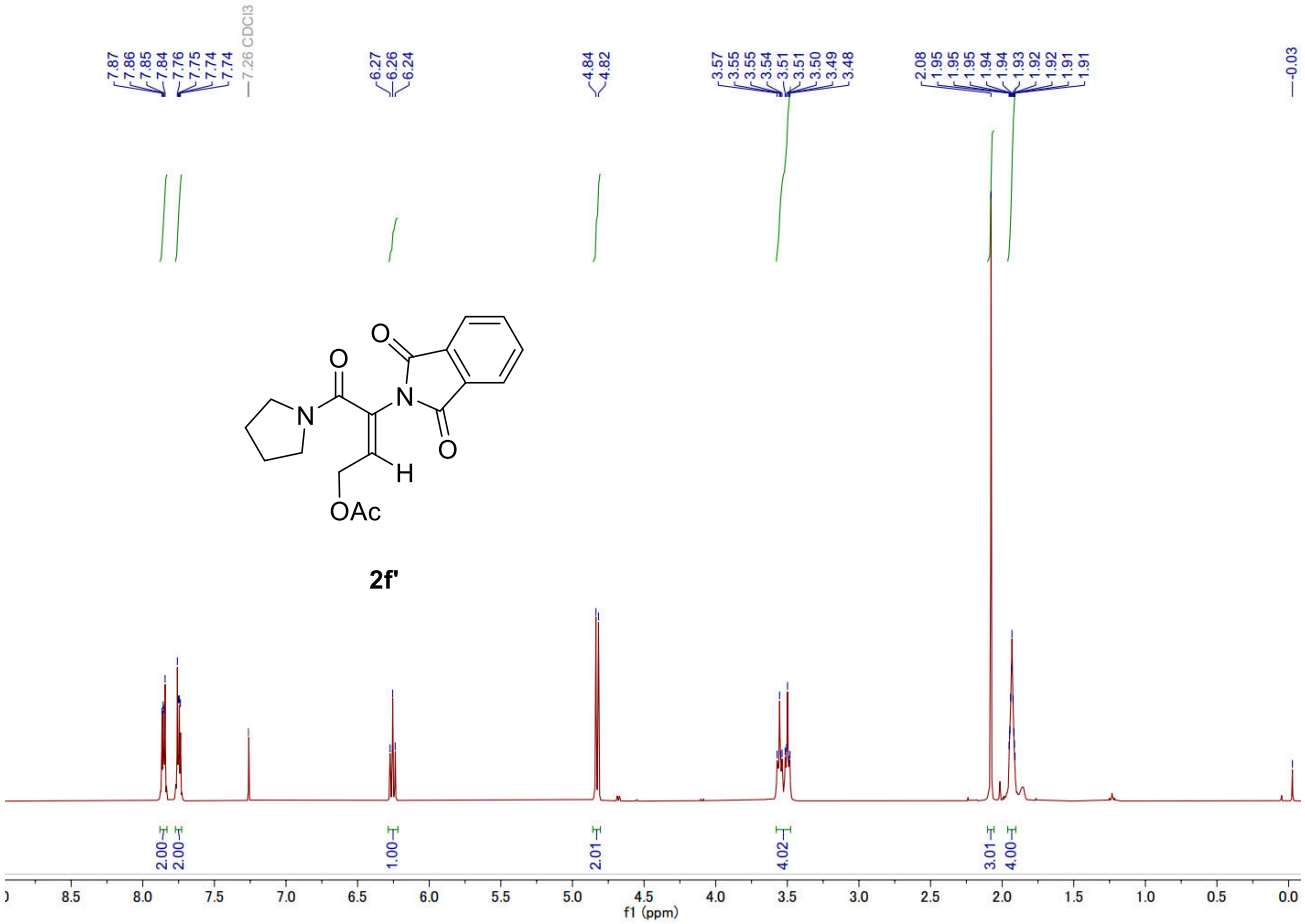
2d


169.50
167.31
167.20
134.52
130.53
122.81
66.05
65.34
61.36
43.86
39.52 DMSO-d6
19.85
19.27
f1 (ppm)

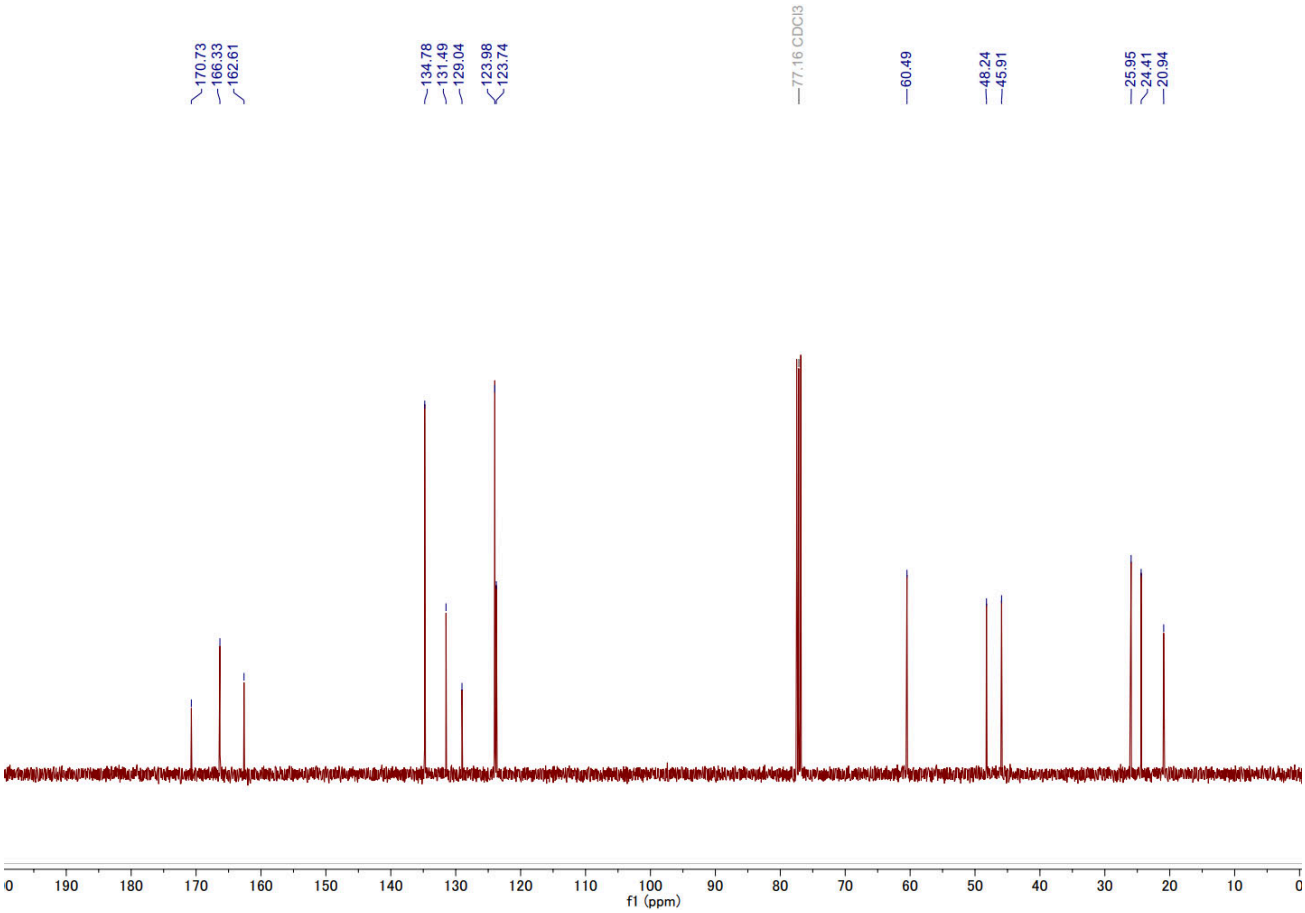

7.83
7.82
7.82
7.81
7.74
7.73
7.72
7.71
7.26 CDCl3
5.67
5.65
4.79
4.76
4.71
4.68
4.15
4.14
4.13
4.12
4.12
4.11
4.10
4.10
4.09
4.09
4.08
4.07
2.01
2.00
1.99
1.86
1.72
1.16
1.15
1.15
1.14
0.01
O
O
N
H
N
O
O
AcO
2.00
2.02
0.98
1.00
1.01
1.05
2.96
2.95
6.28
f1 (ppm)

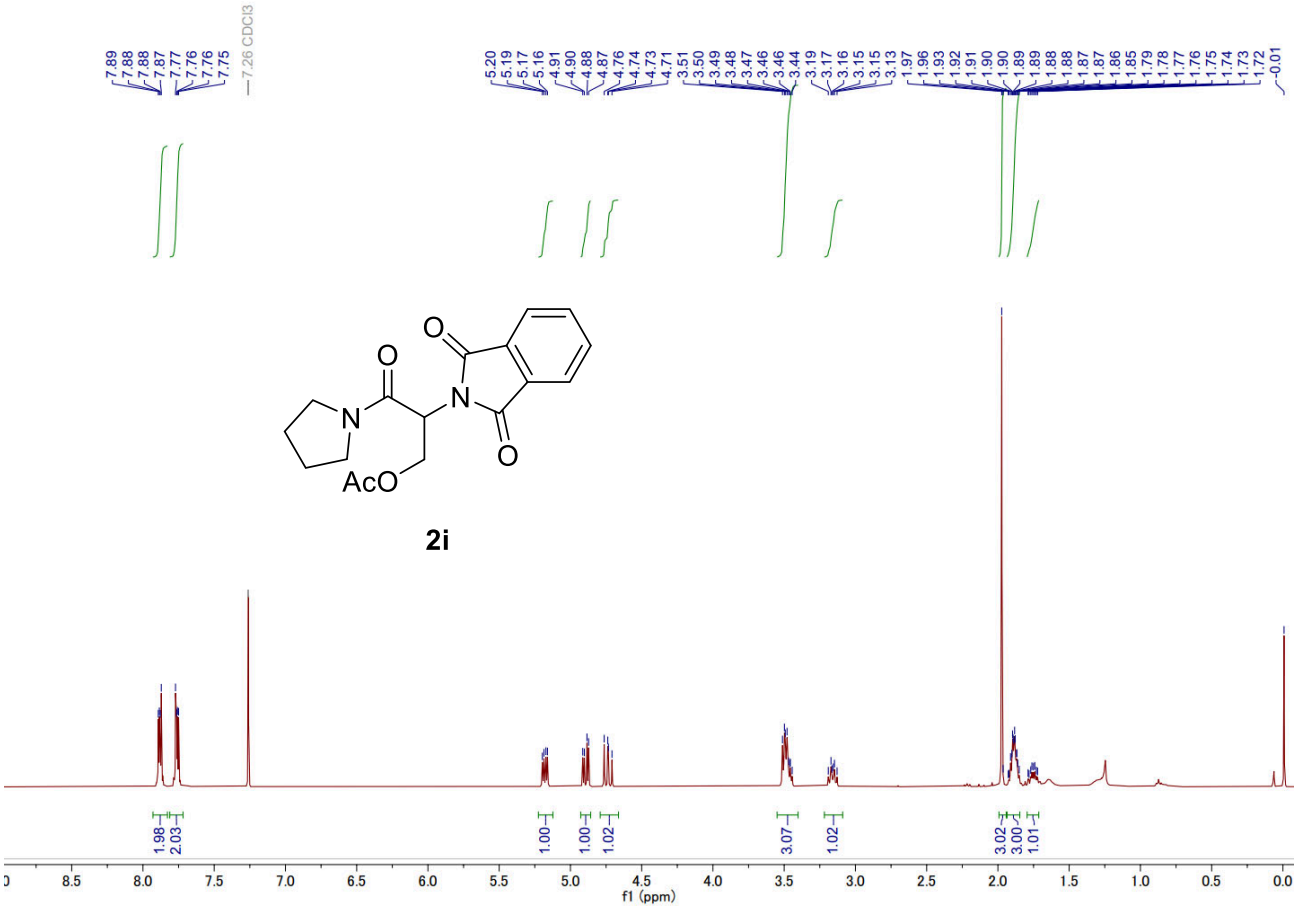
2e


170.40
169.22
168.47
134.43
131.80
123.44
77.16 CDCl3
65.88
63.31
42.00
22.62
20.85
20.81
f1 (ppm)

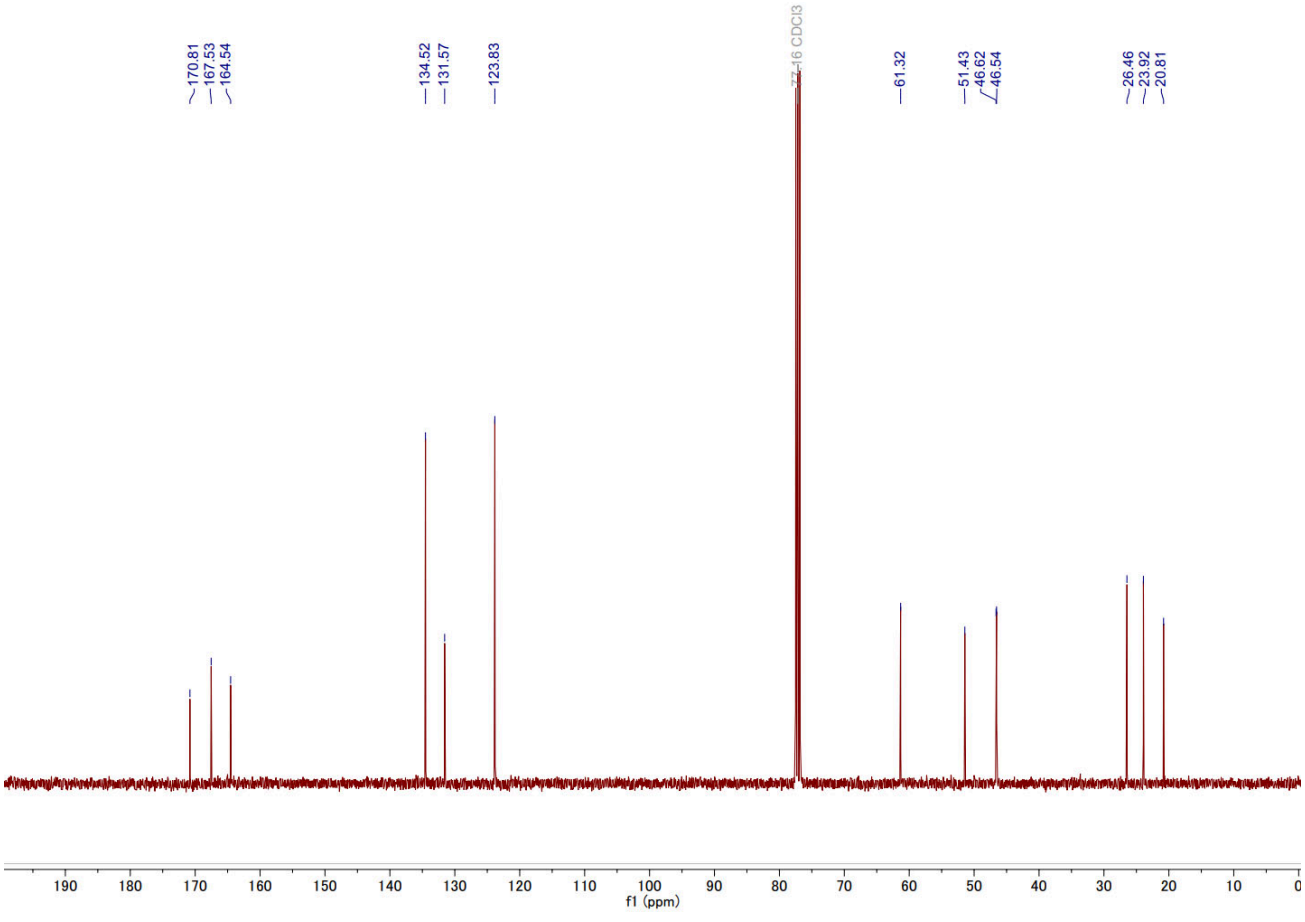

7.87
7.86
7.85
7.84
7.76
7.75
7.74
7.74
7.26 CDCl3
6.27
6.26
6.24
4.84
4.82
3.57
3.55
3.55
3.54
3.51
3.51
3.50
3.49
3.48
2.08
1.95
1.95
1.95
1.94
1.94
1.93
1.92
1.92
1.91
1.91
0.03
O
O
N
N
O
H
OAc
2.00
2.00
1.00
2.01
4.02
3.01
4.00
f1 (ppm)

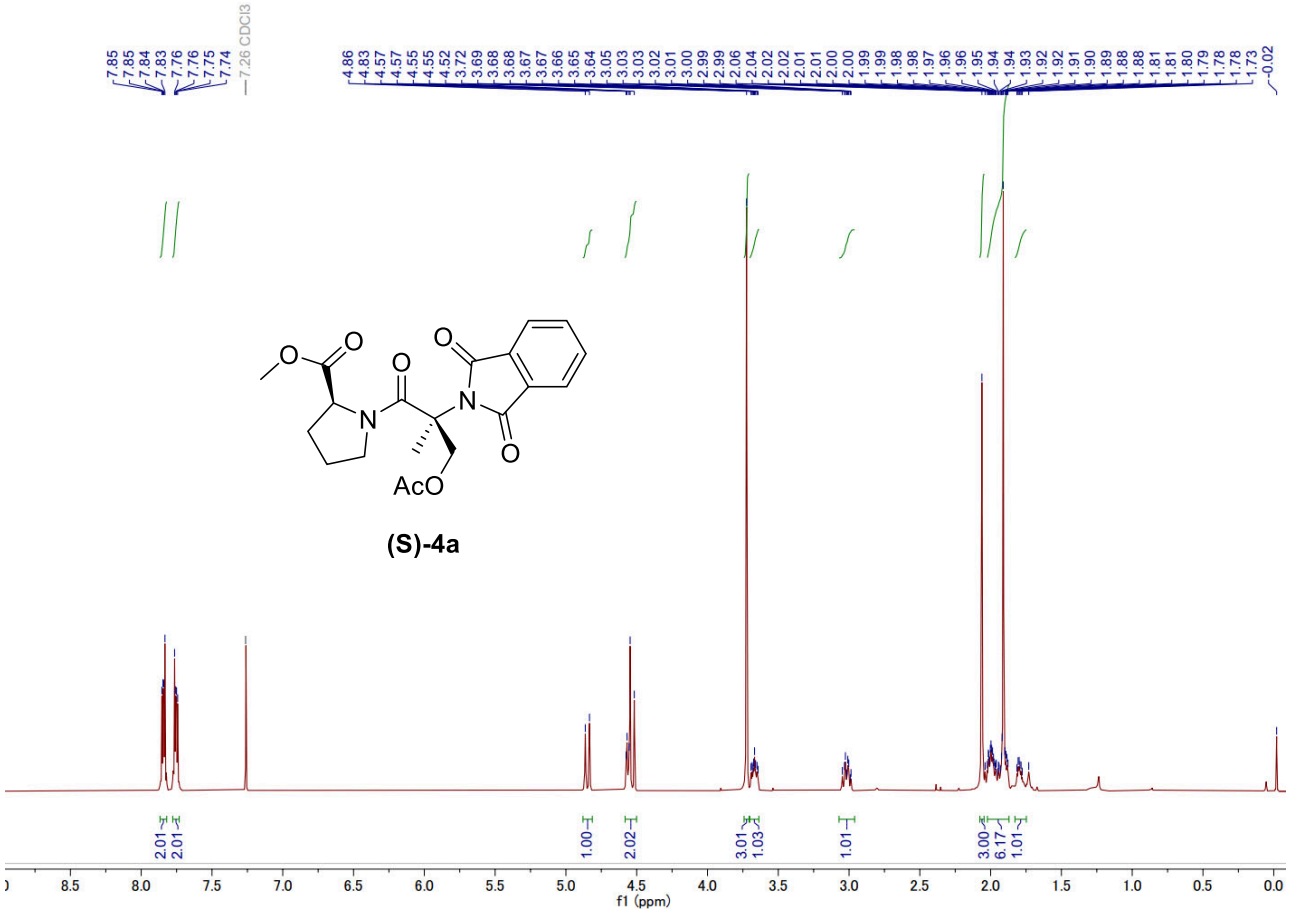
2f'


170.73
166.33
162.61
134.78
131.49
129.04
123.98
123.74
77.16 CDCl3
60.49
48.24
45.91
25.95
24.41
20.94
f1 (ppm)

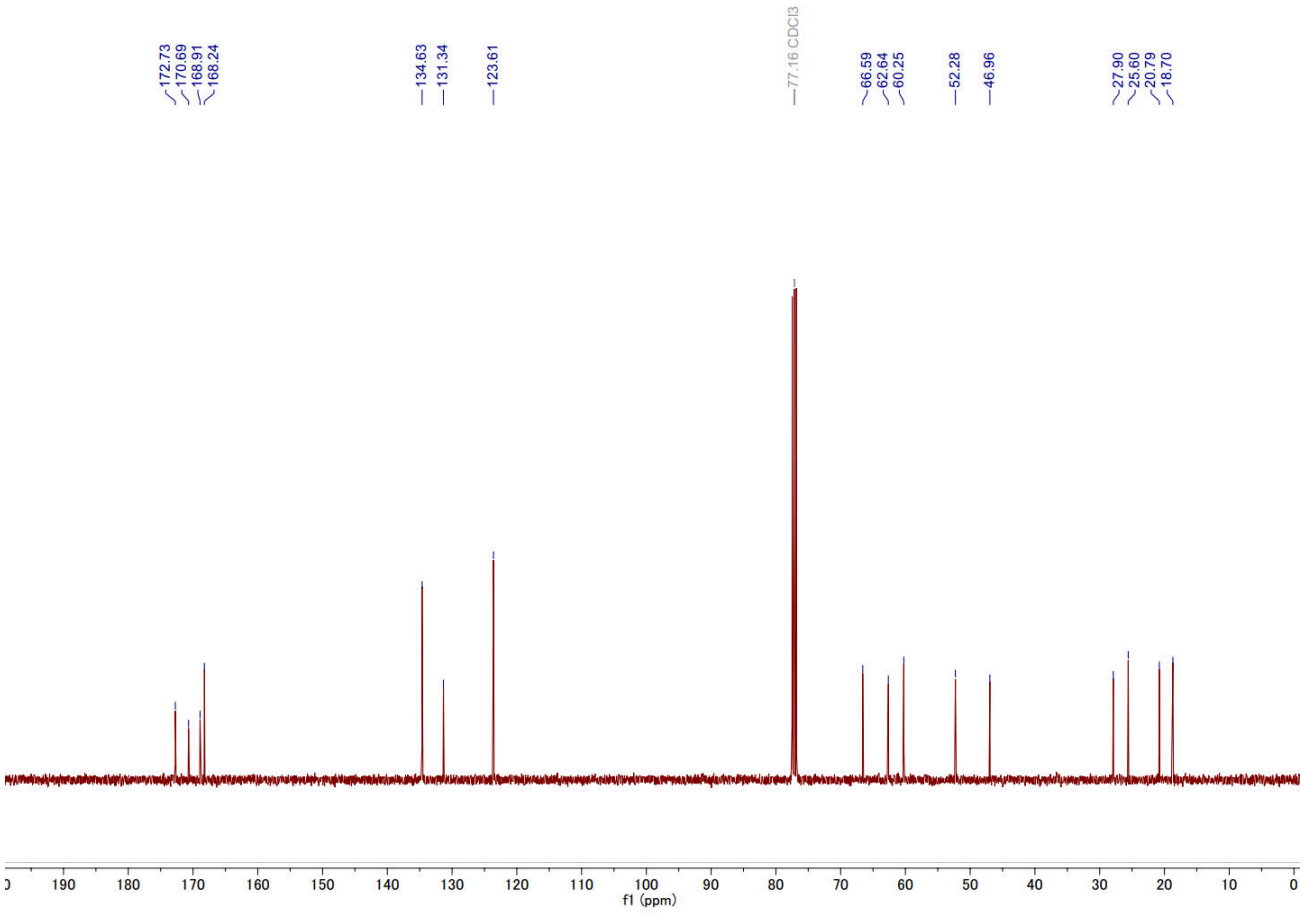

7.89
7.88
7.88
7.87
7.77
7.76
7.76
7.75
7.26 CDCl3
5.20
5.19
5.17
5.16
4.91
4.90
4.88
4.87
4.76
4.74
4.73
4.71
3.51
3.50
3.49
3.48
3.47
3.46
3.46
3.44
3.19
3.17
3.16
3.15
3.15
3.13
1.97
1.96
1.93
1.92
1.91
1.90
1.90
1.89
1.89
1.88
1.88
1.87
1.87
1.86
1.85
1.79
1.78
1.77
1.76
1.75
1.74
1.73
1.72
-0.01
O
O
N
N
O
AcO
1.98
2.03
1.00
1.00
1.02
3.07
1.02
3.02
3.00
1.01
f1 (ppm)

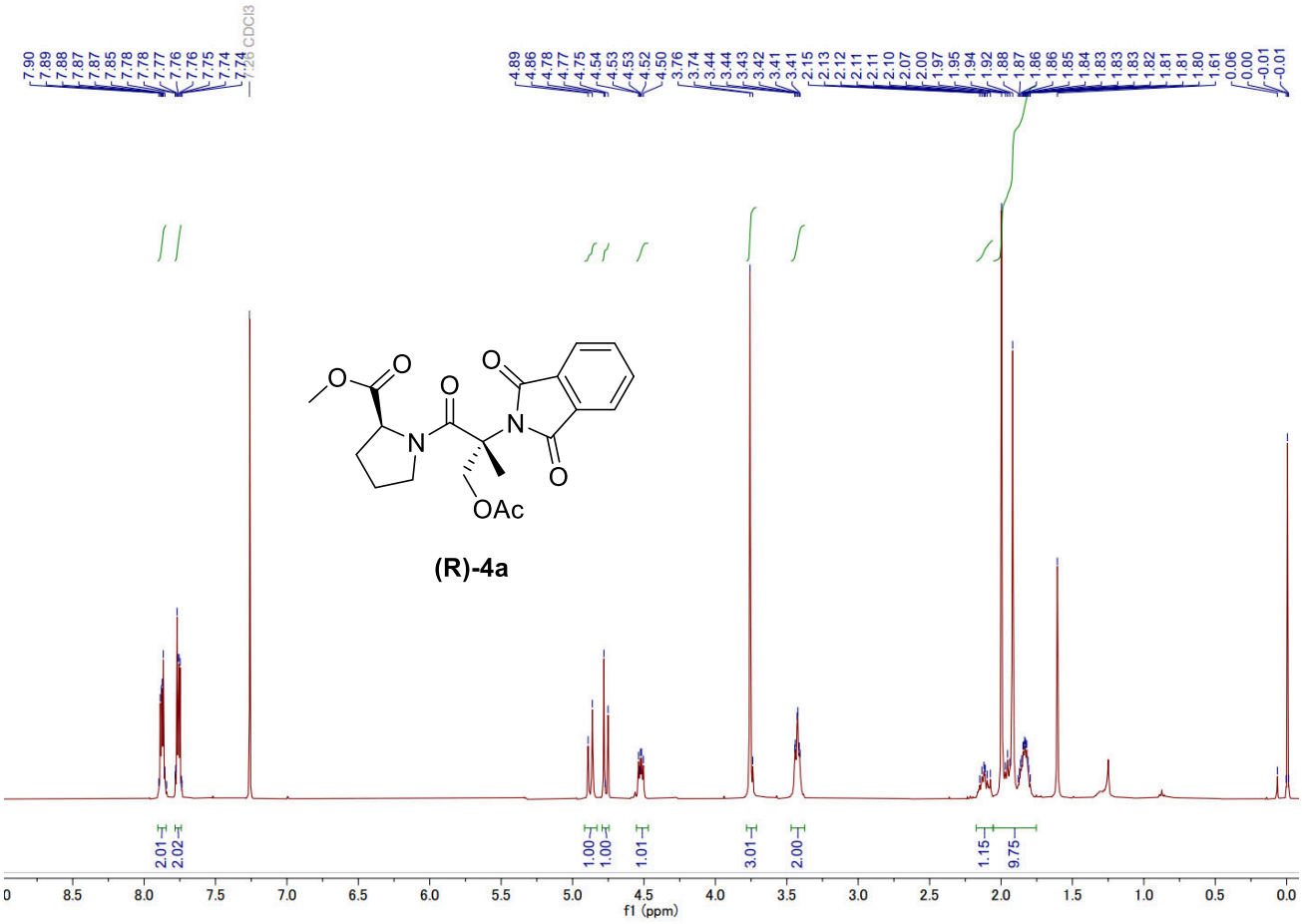
2i

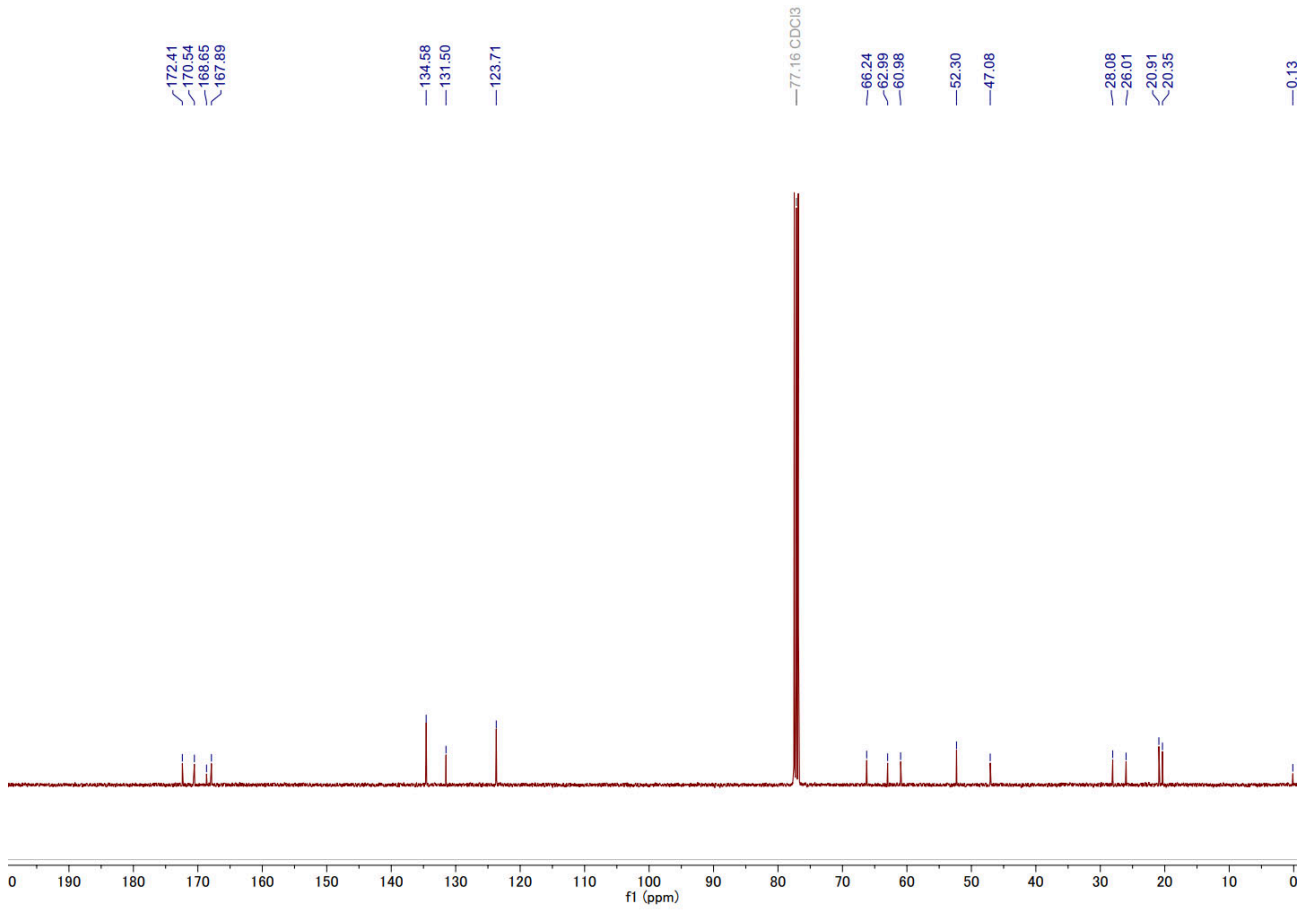

170.81
167.53
164.54
134.52
131.57
123.83
77.16 CDCl3
61.32
51.43
46.62
46.54
26.46
23.92
20.81
f1 (ppm)

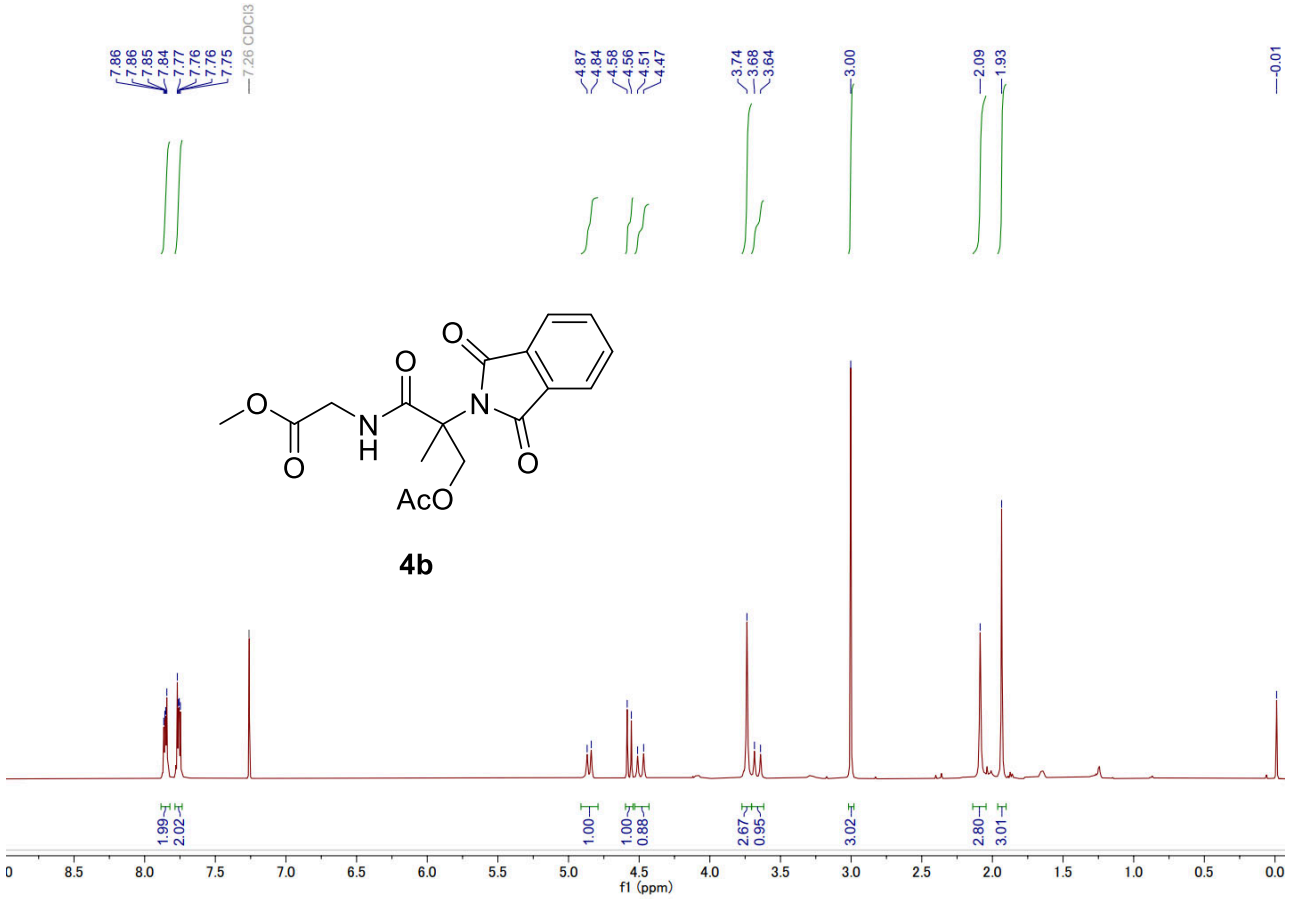

7.85
7.85
7.84
7.83
7.76
7.76
7.75
7.74
7.26 CDCl3
4.86
4.83
4.57
4.57
4.55
4.55
4.52
3.72
3.69
3.68
3.68
3.67
3.67
3.66
3.65
3.64
3.05
3.03
3.03
3.02
3.01
3.00
2.99
2.99
2.06
2.04
2.02
2.02
2.01
2.01
2.00
2.00
1.99
1.99
1.98
1.98
1.97
1.96
1.96
1.95
1.94
1.94
1.93
1.92
1.92
1.91
1.90
1.89
1.88
1.88
1.81
1.81
1.80
1.79
1.78
1.78
1.73
-0.02
O
O
O
N
O
N
O
AcO
2.01
2.01
1.00
2.02
3.01
1.03
1.01
3.00
6.17
1.01
f1 (ppm)

(S)-4a

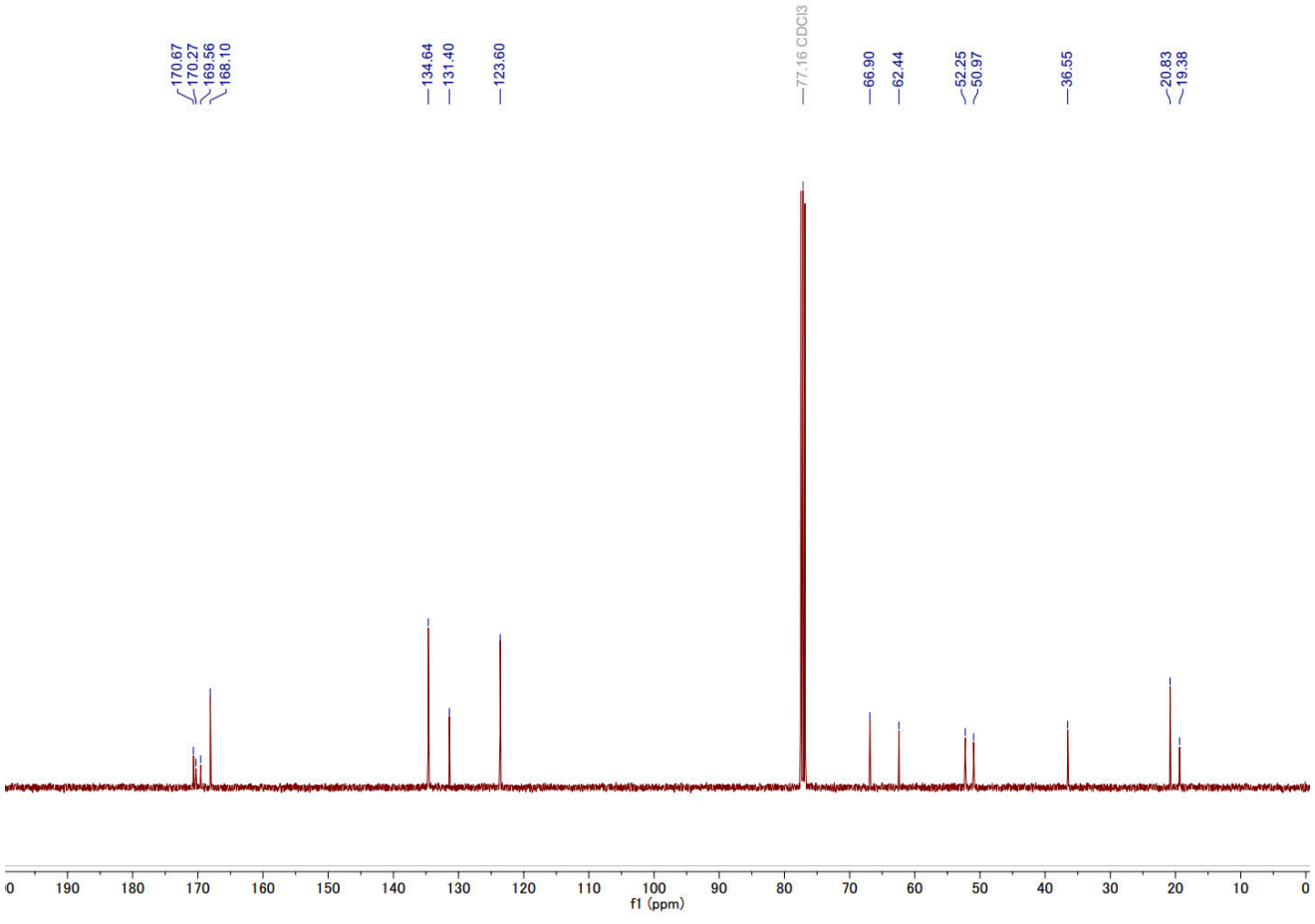

172.73
170.69
168.91
168.24
134.63
131.34
123.61
77.16 CDCl3
66.59
62.64
60.25
52.28
46.96
27.90
25.60
20.79
18.70
f1 (ppm)

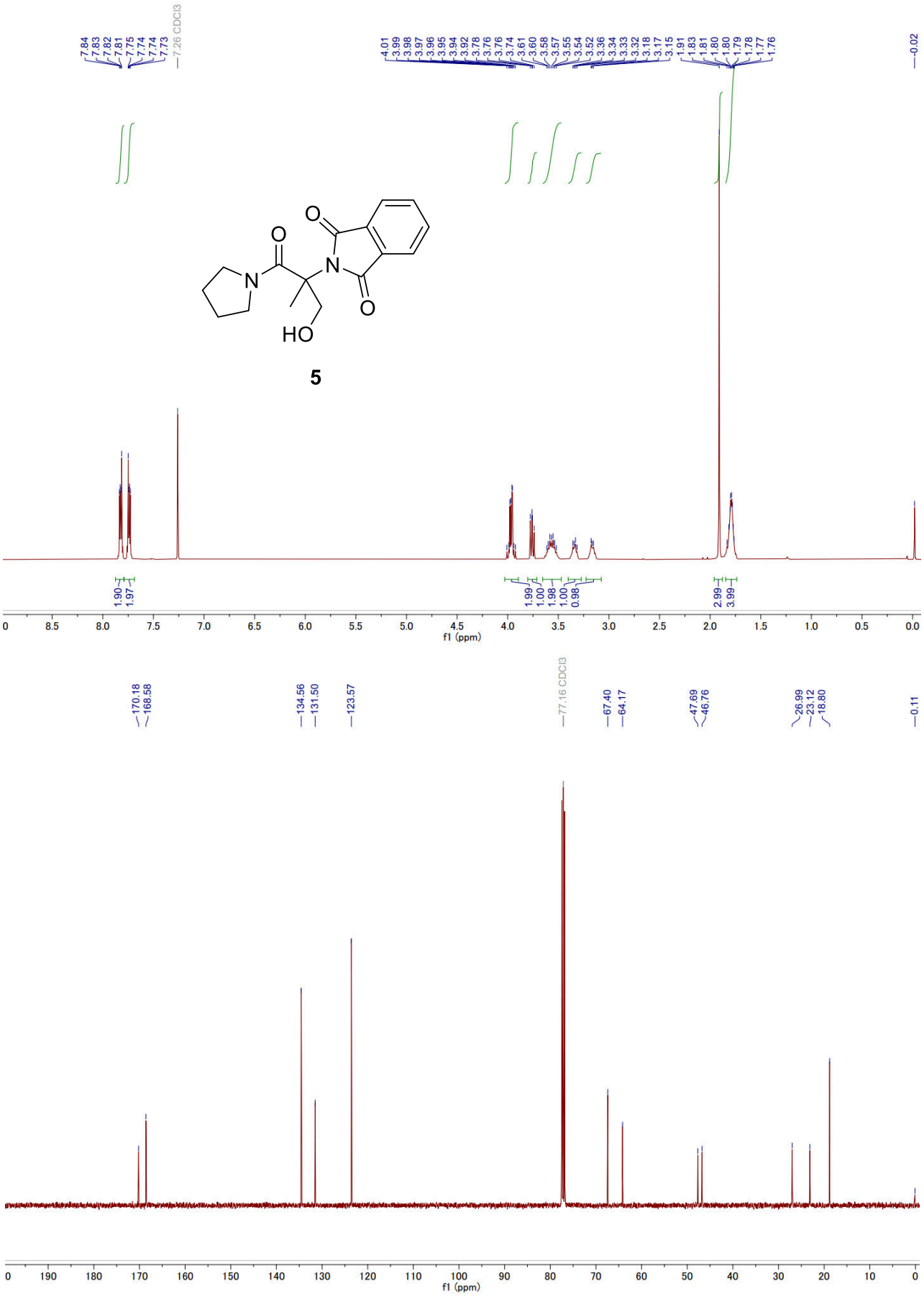

7.90
7.89
7.88
7.87
7.87
7.85
7.78
7.78
7.77
7.76
7.76
7.75
7.74
7.74
7.28 CDCl3
4.89
4.86
4.78
4.77
4.75
4.54
4.53
4.53
4.52
4.50
3.76
3.74
3.44
3.44
3.43
3.42
3.41
3.41
2.15
2.13
2.12
2.11
2.11
2.10
2.07
2.00
1.97
1.95
1.94
1.92
1.88
1.87
1.86
1.86
1.85
1.84
1.83
1.83
1.82
1.81
1.81
1.80
1.61
0.06
0.00
-0.01
-0.01
O
O
O
N
O
N
O
OAc
(R)-4a
2.01
2.02
1.00
1.00
1.01
3.01
2.00
1.15
9.75
f1 (ppm)


172.41
170.54
168.65
167.89
134.58
131.50
123.71
77.16 CDCl3
66.24
62.99
60.98
52.30
47.08
28.08
26.01
20.91
20.35
0.13
f1 (ppm)


7.86
7.86
7.85
7.84
7.77
7.76
7.76
7.75
7.26 CDCl3
4.87
4.84
4.58
4.56
4.51
4.47
3.74
3.68
3.64
3.00
2.09
1.93
0.01
O
O
O
N
N
H
O
O
AcO
1.99
2.02
1.00
1.00
0.88
2.67
0.95
3.02
2.80
3.01
f1 (ppm)

4b


170.67
170.27
169.56
168.10
134.64
131.40
123.60
77.16 CDCl3
66.90
62.44
52.25
50.97
36.55
20.83
19.38
f1 (ppm)


7.84
7.83
7.82
7.81
7.75
7.74
7.74
7.73
7.26 CDCl3
4.01
3.99
3.98
3.97
3.96
3.95
3.94
3.92
3.78
3.76
3.76
3.74
3.61
3.60
3.58
3.57
3.55
3.54
3.52
3.36
3.34
3.33
3.32
3.18
3.17
3.15
1.91
1.83
1.81
1.80
1.80
1.79
1.78
1.77
1.76
0.02
O
O
N
N
O
O
HO
5
1.90
1.97
1.99
1.00
1.98
1.00
0.98
2.99
3.99
f1 (ppm)
170.18
168.58
134.56
131.50
123.57
77.16 CDCl3
67.40
64.17
47.69
46.76
26.99
23.12
18.80
0.11
f1 (ppm)