Supporting Information for

Synthesis of β-Cyclopropylalanines by Photolysis of Diacyl Peroxides

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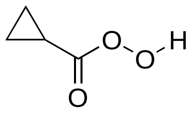
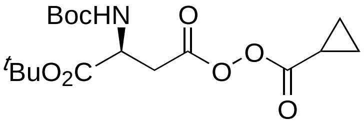


2

Cyclopropanepercarboxylic acid (2)

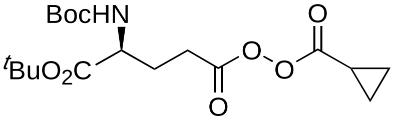
To neat cyclopropanecarboxylic acid (0.4 mL, 5 mmol) cooled at 0 °C was added conc. H_2SO_4 (0.625 mL) followed by drop wise addition of 50% H_2O_2 (0.51 mL, 7.5 mmol). The mixture was stirred at 0 °C, slowly allowed to warm to rt over a period of 2 h, and then stirred at rt for 1 h. It was then cooled to 0 °C and quenched by adding several folds of ice. The reaction mixture was diluted with ether (10 mL), ether layer was separated, washed with satd. aqueous $NaHCO_3$, dried ($MgSO_4$) and filtered. The resulting etheral solution of cyclopropanepercarboxylic acid (**2**) was used as such for the subsequent transformations.[11] For characterization purposes, a small aliquot of etheral solution was carefully concentrated under positive pressure of Ar to obtain neat cyclopropanepercarboxylic acid as clear colorless oil. IR (neat) 3400, 1731, 1556 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500MHz) δ 11.33 (br, 1H), 1.72-1.67 (m, 1H), 1.16-1.13 (m, 2H), 1.07-1.03 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.0, 9.7, 9.2.



3

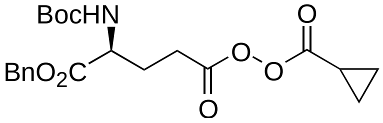
(2*S*)-2-*tert*-Butoxycarbonylamino-4-cyclopropanecarbonylperoxy-4-oxo-butyric acid *tert*-butyl ester (3)

The solution of cyclopropanepercarboxylic acid (**2**, prepared from cyclopropanecarboxylic acid (0.4 mL, 5 mmol), conc. H_2SO_4 (0.625 mL) and 50% H_2O_2 (0.51 mL, 7.5 mmol)) in 10 mL of ether was cooled to –40 °C and Boc-Asp-O-tBu (**1a**, 330 mg, 1.14 mmol) was added followed by DCC (282 mg, 1.37 mmol). The mixture was stirred at –40 °C for 7 h and then diluted by hexanes to precipitate the urea and warmed to rt. The precipitated urea was filtered and the filtrate was concentrated under reduced pressure. Purification by flash chromatography on silica gel (4/1 hexanes/ethyl acetate) provided 414 mg (89%) of **3** as white solid. $[\alpha]^{26}_{D}$= +50.2° (*c* 1.4, $CHCl_3$); IR ($CHCl_3$ cast) 3382, 1808, 1778, 1716, 1500 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300MHz) δ 5.46 (d, 1H, *J* = 7.5 Hz), 4.52 (dt, 1H, *J* = 4.5, 7.5 Hz), 3.06 (dd, 1H, *J* = 4.5, 16.8 Hz), 2.95 (dd, 1H, *J* = 4.5, 16.8 Hz), 1.76-1.65 (m, 1H), 1.46 (s, 9H), 1.44 (s, 9H), 1.17-1.11 (m, 2H), 1.09-1.03 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.3, 168.7, 166.7, 155.1, 83.0, 80.1, 50.3, 33.2, 28.3, 27.8, 9.5, 9.5, 9.3; HRMS (ES) Calcd for $C_{17}H_{27}NO_8Na$ 396.1628, found 396.1624.



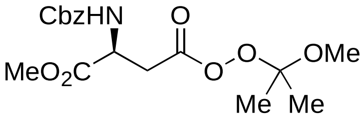
4

(2*S*)-2-*tert*-Butoxycarbonylamino-5-cyclopropanecarbonylperoxy-5-oxo-pentanoic acid *tert*-butyl ester (4) Prepared from cyclopropanecarboxylic acid (0.4 mL, 5 mmol), conc. H_2SO_4 (0.625 mL), 50% H_2O_2 (0.51 mL, 7.5 mmol), *N*-Boc-glutamic acid t-butyl ester (**1b**, 300 mg, 1 mmol) and DCC (270 mg, 1.3 mmol) as described for **3**. Purification by flash chromatography on silica gel (4/1 hexanes/ethyl acetate) provided 330 mg (85%) of **4** as white solid. $[\alpha]^{26}_{D}$= +16.7° (*c* 3.5, $CHCl_3$); IR ($CHCl_3$ cast) 3383, 1807, 1778, 1715, 1506 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 5.11 (d, 1H, *J* = 8.1 Hz), 4.19-4.12 (m, 1H), 2.54-2.35 (m, 2H), 2.24-2.12 (m, 1H), 1.99-1.86 (m, 1H), 1.70-1.58 (m, 1H), 1.40 (s, 9H), 1.37 (s, 9H), 1.10-1.05 (m, 2H), 1.04-0.96 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.6, 168.4, 155.2, 82.4, 79.8, 53.1, 28.1, 27.9, 27.8, 26.2, 9.2, 9.2; HRMS (ES) Calcd for $C_{18}H_{29}NO_8Na$ 410.1785, found 410.1785.



5

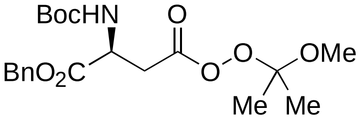
(2*S*)-2-*tert*-Butoxycarbonylamino-5-cyclopropanecarbonylperoxy-5-oxo-pentanoic acid benzyl ester (5) Prepared from cyclopropanecarboxylic acid (0.4 mL, 5 mmol), conc. H_2SO_4 (0.625 mL), 50% H_2O_2 (0.51 mL, 7.5 mmol), Boc-Glu-OBn (**1c**, 337 mg, 1 mmol) and DCC (268 mg, 1.3 mmol) as described for **3**. Purification by flash chromatography on silica gel (7/3 hexanes/ethyl acetate) provided 351 mg (83%) of **5** as white solid. $[\alpha]^{26}_{D}$= +3.8° (*c* 1, $CHCl_3$); IR ($CHCl_3$ cast) 3383, 1805, 1776, 1743, 1715, 1500 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ 7.30-7.25 (m, 5H), 5.28 (d, 1H, *J* = 8.0 Hz), 5.10 (s, 2H), 4.36-4.30 (m, 1H), 2.51-2.36 (m, 2H), 2.26-2.18 (m, 1H), 2.02-1.93 (m, 1H), 1.68-1.61 (m, 1H), 1.37 (s, 9H), 1.08-1.03 (m, 2H), 1.02-0.95 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.3, 170.5, 168.2, 155.1, 135.0, 128.4, 128.2, 128.0, 79.8, 67.1, 52.5, 28.0, 27.3, 26.1, 9.2, 9.0; HRMS (ES) Calcd for $C_{21}H_{27}NO_8Na$ 444.1628, found 444.1628.



6

(2*S*)-2-Benzyloxycarbonylamino-3-(1-methoxy-1-methyl-ethylperoxycarbonyl)-propionic acid methyl ester (6)

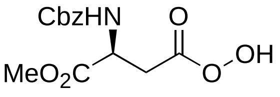
A solution of *N*-Cbz-aspartic acid-α-methyl ester (**1d**, 1 g, 3.56 mmol) in CH_2Cl_2 (5 mL) was cooled to –40 °C and 2-methoxyprop-2-yl hydroperoxide,[12] (1M solution in CH_2Cl_2, 5.34 mL, 5.34 mmol) was added followed by DCC (850 mg, 4.13 mmol) and DMAP (44 mg, 0.36 mmol). The mixture was slowly warmed to and stirred at rt for 4 h and then diluted by hexanes to precipitate the urea. The precipitated urea was filtered and the filtrate was washed with 0.5 M H_2SO_4 (10 mL x 2) followed by water (10 mL x 2), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash chromatography on silica gel (7/3 hexanes/ethyl acetate) provided 1.26 g (96%) of **6** as clear colorless oil. $[\alpha]^{26}_{D}$= +31.6° (*c* 2, $CHCl_3$); IR ($CHCl_3$ cast) 3351, 1777, 1731, 1519 cm^{-1}; ^1H NMR ($CDCl_3$, 500MHz) δ 7.35-7.27 (m, 5H), 5.75 (d, 1H, *J* = 7.5 Hz), 5.10 (s, 2H), 4.67 (dt, 1H, *J* = 4.5, 7.5 Hz), 3.75 (s, 3H), 3.28 (s, 3H), 3.03 (dd, 1H, *J* = 4.5, 17.0 Hz), 2.89 (dd, 1H, *J* = 4.5, 17.0 Hz), 1.41 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.4, 167.9, 155.7, 136.0, 128.4, 128.1, 127.9, 107.2, 67.0, 52.8, 50.2, 49.8, 33.8, 22.3, 22.3; HRMS (ES) Calcd for $C_{17}H_{23}NO_8Na$ 392.1315, found 392.1317.



7

(2*S*)-2-*tert*-Butoxycarbonylamino-3-(1-methoxy-1-methyl-ethylperoxycarbonyl)-propionic acid benzyl ester (7)

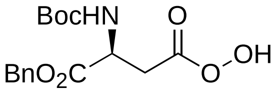
A solution of *N*-Boc-aspartic acid-α-benzyl ester (**1e**, 1.615 g, 5 mmol) in CH_2Cl_2 (10 mL) was cooled to –40 °C and 2-methoxyprop-2-yl hydroperoxide,[12] (1M solution in CH_2Cl_2, 7.5 mL, 7.5 mmol) was added followed by DCC (1.236 g, 6 mmol) and DMAP (61 mg, 0.5 mmol). The mixture was slowly warmed to and stirred at rt for 4 h and then diluted by hexanes to precipitate the urea. The precipitated urea was filtered and the filtrate was washed with 0.5 M H_2SO_4 (20 mL x 2) followed by water (20 mL x 2), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash chromatography on silica gel (7/3 hexanes/ethyl acetate) provided 1.95 g (95%) of **7** as clear colorless oil. $[\alpha]^{26}_{D}$= +19.3° (*c* 2, $CHCl_3$); IR ($CHCl_3$ cast) 3371, 1776, 1746, 1717, 1499 cm^{-1}; ^1H NMR ($CDCl_3$, 500MHz) δ 7.34-7.27 (m, 5H), 5.51 (d, 1H, *J* = 8.0 Hz), 5.16 (s, 2H), 4.61 (dt, 1H, *J* = 4.5, 8.0 Hz), 3.27 (s, 3H), 3.00 (dd, 1H, *J* = 4.5, 16.5 Hz), 2.88 (dd, 1H, *J* = 4.5, 16.5 Hz), 1.40 (s, 3H), 1.40 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.4, 167.9, 155.7, 136.0, 128.4, 128.1, 127.9, 107.2, 67.0, 52.8, 50.2, 49.8, 33.8, 22.3, 22.3; HRMS (ES) Calcd for $C_{20}H_{29}NO_8Na$ 434.1785, found 434.1786.



8

(2*S*)-2-Benzyloxycarbonylamino-3-hydroperoxycarbonyl-propionic acid methyl ester (8)

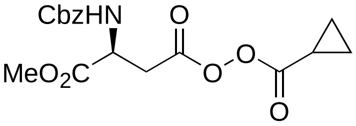
To a stirred solution of **6** (369 mg, 1mmol) in 10 mL of $CHCl_3$ at rt was added 50% aqueous TFA (2mL) and the mixture was stirred vigorously at rt for 15 min. The reaction was quenched by carefully adding excess satd. aqueous $NaHCO_3$ and then diluted with ether. The organic layer was separated, washed with water, dried ($MgSO_4$), and concentrated under reduced pressure to obtain 295 mg (99% crude) of **8** as clear colorless oil. $[\alpha]^{26}_{D}$= +33.5° (*c* 1.5, $CHCl_3$); IR ($CHCl_3$ cast) 3333, 1720, 1587 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ 7.37-7.28 (m, 5H), 5.69 (d, 1H, *J* = 6.8 Hz), 5.11 (s, 2H), 4.70 (dt, 1H, *J* = 4.4, 6.8 Hz), 3.76 (s, 3H), 3.06 (dd, 1H, *J* = 4.4, 16.4 Hz), 2.99 (dd, 1H, *J* = 4.4, 16.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.1, 170.2, 155.8, 135.7, 128.5, 128.3, 128.1, 67.4, 53.1, 50.1, 33.3; HRMS (ES) Calcd for $C_{13}H_{15}NO_7Na$ 320.0740, found 320.0738.



9

(2*S*)-2-*tert*-Butoxycarbonylamino-3-hydroperoxycarbonyl-propionic acid benzyl ester (9)

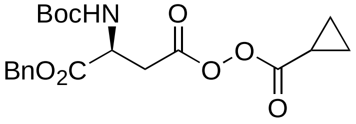
A mixture of **7** (411 mg, 1mmol) and 50% aqueous AcOH (6 mL) was stirred at rt for 3 h. Ether (40 mL) was added and then reaction was quenched by carefully adding excess satd. aqueous $NaHCO_3$. The organic layer was separated, washed with water (2 x 5 mL), dried ($MgSO_4$), and concentrated under reduced pressure to obtain 289 mg (85% crude) of **9** as white solid. $[\alpha]^{26}_{D}$= +16.9° (*c* 1.8, $CHCl_3$); IR ($CHCl_3$ cast) 3349, 1746, 1713, 1500 cm^{-1}; ^1H NMR ($CDCl_3$, 500MHz) δ 7.37-7.31 (m, 5H), 5.44 (d, 1H, *J* = 7.5 Hz), 5.18 (s, 2H), 4.72-4.78 (m, 1H), 3.02 (dd, 1H, *J* = 3.5, 16.5 Hz), 2.96 (dd, 1H, *J* = 5.0, 16.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.0, 170.0, 155.3, 134.8, 128.5, 128.4, 128.2, 80.7, 67.8, 49.9, 33.4, 28.1; HRMS (ES) Calcd for $C_{16}H_{21}NO_7Na$ 362.1210, found 362.1205.



10

(2*S*)-2-Benzyloxycarbonylamino-4-cyclopropanecarbonylperoxy-4-oxo-butyric acid methyl ester (10)

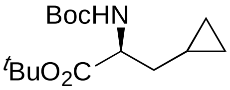
To a solution of crude **8** (295 mg, 0.99 mmol) in 10 mL CH_2Cl_2 cooled to –78 °C was added cyclopropanecarbonyl chloride (0.09 mL, 1 mmol) followed by pyridine (0.08 mL, 1 mmol). The reaction mixture was stirred at –78 °C for 12 h and then slowly allowed to warm to rt and stirred at rt overnight. Solvent was removed under reduced pressure and the residue purified by flash chromatography on silica gel (7/3 hexanes/ethyl acetate) to obtain 297 mg (81%) of **10** as clear colorless oil. $[\alpha]^{26}_{D}$= +42.3° (*c* 2.2, $CHCl_3$); IR ($CHCl_3$ cast) 3363, 1806, 1775, 1724, 1517 cm^{-1}; ^1H NMR ($CDCl_3$, 500MHz) δ 7.40-7.32 (m, 5H), 5.80 (d, 1H, *J* = 7.5 Hz), 5.15 (s, 2H), 4.75 (dt, 1H, *J* = 4.5, 7.5 Hz), 3.80 (s, 3H), 3.16 (dd, 1H, *J* = 4.5, 17.0 Hz), 3.05 (dd, 1H, *J* = 4.5, 17.0 Hz), 1.75-1.70 (m, 1H), 1.19-1.15 (m, 2H), 1.10-1.06 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.4, 170.0, 166.6, 155.7, 135.9, 128.4, 128.1, 127.9, 67.1, 52.9, 50.2, 33.0, 9.4, 9.1; HRMS (ES) Calcd for $C_{17}H_{19}NO_8Na$ 388.1002, found 388.1000.



11

(2*S*)-2-*tert*-Butoxycarbonylamino-4-cyclopropanecarbonylperoxy-4-oxo-butyric acid benzyl ester (11)

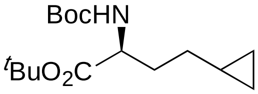
To a solution of crude **9** (120 mg, 0.35 mmol) in 2 mL CH_2Cl_2 cooled to –78 °C was added cyclopropanecarbonyl chloride (32 μL, 0.35 mmol) followed by pyridine (28 μL, 0.35 mmol). The reaction mixture was stirred at –78 °C for 12 h and then slowly allowed to warm to rt and stirred at rt overnight. Solvent was removed under reduced pressure and the residue purified by flash chromatography on silica gel (8/2 hexanes/ethyl acetate) to obtain 127 mg (88%) of **11** as clear colorless oil. $[\alpha]^{26}_{D}$= +14.0° (*c* 1.3, $CHCl_3$); IR ($CHCl_3$ cast) 3377, 1806, 1776, 1746, 1715, 1499 cm^{-1}; ^1H NMR ($CDCl_3$, 500MHz) δ 7.36-7.29 (m, 5H), 5.49 (d, 1H, *J* = 7.5 Hz), 5.20 (d, 1H, *J* = 12.0 Hz), 5.15 (d, 1H, *J* = 12.0 Hz), 4.66 (dt, 1H, *J* = 4.5, 7.5 Hz), 3.11 (dd, 1H, *J* = 4.5, 16.5 Hz), 2.99 (dd, 1H, *J* = 4.5, 16.5 Hz), 1.71-1.66 (m, 1H), 1.41 (S, 9H), 1.15-1.12 (m, 2H), 1.06-1.02 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.3, 169.8, 166.8, 155.1, 134.9, 128.5, 128.4, 128.3, 80.3, 67.7, 49.9, 33.0, 28.1, 9.4, 9.1; HRMS (ES) Calcd for $C_{20}H_{25}NO_8Na$ 430.1472, found 430.1474 .



12

(2*S*)-2-*tert*-Butoxycarbonylamino-3-cyclopropyl-propionic acid *tert*-butyl ester (12)

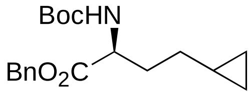
A solution of **3** (350 mg, 0.93 mmol) in $CHCl_3$ was transferred to a crystallization dish (150 mm x 75 mm) and solvent was evaporated with the aid of dry air, and finally purged with Ar gas in order to generate a thin film of compound at the bottom of container. The container was then covered with a quartz plate, cooled to –78 °C and photolyzed with 254 nm UV lamp (0.9 Amp) for 80 h at which point starting material was completely consumed. Purification of crude product by flash chromatography on silica gel (95/5 hexanes/ethyl acetate) provided 155 mg (58%) of **12** as clear colorless oil. $[\alpha]^{26}_{D}$= +8.9° (*c* 1, $CHCl_3$); IR ($CHCl_3$ cast) 3367, 1716, 1499 cm^{-1}; ^1H NMR (DMSO-d_6, +100 °C, 400MHz) δ 6.44 (bs, 1H), 3.91 (q, 1H, *J* = 9.5 Hz), 1.60-1.46 (m, 2H), 1.41 (s, 9H), 1.39 (s, 9H), 0.80-0.70 (m, 1H), 0.45-0.37 (m, 2H), 0.14-0.10 (m, 1H), 0.04-0.00 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.8, 155.2, 81.5, 79.4, 54.5, 37.5, 28.3, 27.9, 6.8, 4.3, 4.2; HRMS (ES) Calcd for $C_{15}H_{27}NO_4Na$ 308.1832, found 308.1837.



13

(2*S*)-2-*tert*-Butoxycarbonylamino-4-cyclopropyl-butyric acid *tert*-butyl ester (13)

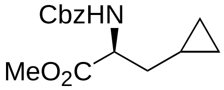
4 (170 mg, 0.44 mmol) was photolyzed at –78 °C with 254 nm UV lamp (0.9 Amp) for 80 h (as described for **12**), at which point starting material was completely consumed. Purification of crude product by flash chromatography on silica gel (95/5 hexanes/ethyl acetate) provided 76 mg (58%) of **13** as clear colorless oil. $[\alpha]^{26}_{D}$= +7.6° (*c* 1, $CHCl_3$); IR ($CHCl_3$ cast) 3357, 1716, 1499 cm^{-1}; ^1H NMR ($CDCl_3$, 500MHz) δ 4.95 (d, 1H, *J* = 7.0 Hz), 4.18-4.14 (m, 1H), 1.89-1.82 (m, 1H), 1.71-1.63 (m, 1H), 1.43 (s, 9H), 1.41 (s, 9H), 1.31-1.22 (m, 2H), 1.20-1.13 (m, 1H), 0.67-0.60 (m, 1H), 0.43-0.37 (m, 2H), 0.04-–0.03 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.9, 155.1, 81.5, 79.4, 53.8, 32.8, 30.3, 28.3, 28.0, 10.5, 4.6, 4.4; HRMS (ES) Calcd for $C_{16}H_{29}NO_4Na$ 322.1994, found 322.1996.



14

(2*S*)-2-*tert*-Butoxycarbonylamino-4-cyclopropyl-butyric acid benzyl ester (14)

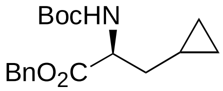
5 (300 mg, 0.71 mmol) was photolyzed at –78 °C with 254 nm UV lamp (0.9 Amp) for 48 h (as described for **12**), at which point starting material was completely consumed. Purification of crude product by flash chromatography on silica gel (9/1 hexanes/ethyl acetate) provided 126 mg (53%) of **14** as clear colorless oil. $[\alpha]^{26}_{D}$= -7.0° (*c* 1.3, $CHCl_3$); IR ($CHCl_3$ cast) 3364, 1740, 1715, 1499 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500MHz) δ 7.36-7.29 (m, 5H), 5.19 (d, 1H, *J* = 12.5 Hz). 5.10 (d, 1H, *J* = 12.5 Hz), 4.95 (d, 1H, *J* = 8.0 Hz), 4.35 (q, 1H, *J* = 8.0 Hz), 1.94-1.86 (m, 1H), 1.74-1.67 (m, 1H), 1.41 (s, 9H), 1.26-1.19 (m, 1H), 1.17-1.10 (m, 1H), 0.64-0.56 (m, 1H), 0.40-0.33 (m, 2H), –0.02-–0.09 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.8, 155.3, 135.5, 128.5, 128.3, 128.2, 79.7, 66.8, 53.3, 32.5, 30.2, 28.2, 10.3, 4.4, 4.3; HRMS (ES) Calcd for $C_{19}H_{27}NO_4Na$ 356.1837, found 356.1838.



15

(2*S*)-2-Benzyloxycarbonylamino-3-cyclopropyl-propionic acid methyl ester (15)

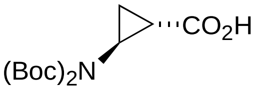
10 (120 mg, 0.32 mmol) was photolyzed at –78 °C with 254 nm UV lamp (0.9 Amp) for 30 h (as described for **12**), at which point starting material was completely consumed. Purification of crude product by flash chromatography on silica gel (3/1 hexanes/ethyl acetate) provided 52 mg (57%) of **15** as clear colorless oil. $[\alpha]^{26}_{D}$= +13.4° (*c* 1, $CHCl_3$); IR ($CHCl_3$ cast) 3342, 1723, 1525 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500MHz) δ 7.35-7.27 (m, 5H), 5.39 (d, *J* = 7.5 Hz, 1H), 5.09 (s, 2H), 4.46-4.42 (m, 1H), 3.72 (s, 3H), 1.72-1.59 (m, 2H), 0.71-0.63 (m, 1H), 0.48-0.40 (m, 2H), 0.09-0.00 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.8, 155.7, 136.3, 128.5, 128.1, 128.0, 66.9, 54.2, 52.2, 37.3, 6.7, 4.1, 4.0; HRMS (ES) Calcd for $C_{15}H_{19}NO_4Na$ 300.1206, found 300.1204.



16

(2*S*)-2-*tert*-Butoxycarbonylamino-3-cyclopropyl-propionic acid benzyl ester (16)

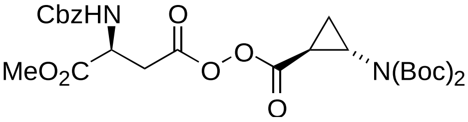
11 (203 mg, 0.5 mmol) was photolyzed at –78 °C with 254 nm UV lamp (0.9 Amp) for 30 h (as described for **12**), at which point starting material was completely consumed. Purification of crude product by flash chromatography on silica gel (3/1 hexanes/ethyl acetate) provided 83 mg (52%) of **16** as clear colorless oil. $[\alpha]^{26}_{D}$= -6.4° (*c* 1.5, EtOH); IR ($CHCl_3$ cast) 3364, 1715, 1498 cm^{-1}; ^1H NMR ($CDCl_3$, 500MHz) δ 7.35-7.29 (m, 5H), 5.16 (d, 1H, *J* = 12.3 Hz), and 5.12 (d, 1H, *J* = 12.3 Hz), 5.20-5.10 (br, 1H), 4.44-4.37 (m, 1H), 3.72 (s, 3H), 1.72-1.58 (m, 2H), 1.41 (s, 9H), 0.71-0.58 (m, 1H), 0.46-0.34 (m, 2H), 0.07--0.04 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.5, 155.1, 135.3, 128.5, 128.3, 128.2, 79.6, 66.8, 53.9, 37.3, 28.2, 6.8, 4.1, 4.0; HRMS (ES) Calcd for $C_{18}H_{25}NO_4Na$ 342.1675, found 342.1679.



19

(*1S,2S*)-2-[(*N*-bis-Boc)amino]cyclopropane-1-carboxylic acid (19)

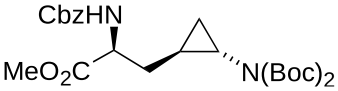
To a vigorously stirred mixture of (*S,S*)-(*N*-bis-Boc)aminocyclopropyl methanol **18**[16] (430 mg, 1.5 mmol) in $MeCN/CHCl_3/H_2O$ (15 mL/15 mL/22.5 mL) at rt was added $NaHCO_3$ (800 mg, 9.5 mmol) followed by $NaIO_4$ (1.75 g, 8.18 mmol) and then $RuCl_3$ (35 mg, 0.16 mmol). The mixture was vigorously stirred at rt for 2h at which point the reaction was complete by tlc. The reaction mixture was cooled to 0 °C and pH was carefully adjusted to 4 by adding 1M HCl. The reaction was diluted with ethyl acetate and the precipitated salts were removed by filtration. The organic layer was separated, aqueous layer was extracted with ethyl acetate, and the combined organic layer dried ($MgSO_4$) and concentrated. The crude product was filtered through a plug of silica gel (ethyl acetate) to obtain 337 mg (74%) of **19** as clear colorless oil. $[\alpha]^{26}_{D}$= +36.0° (*c* 1.8, $CHCl_3$); IR ($CHCl_3$ cast) 3250, 1788, 1735, 1700 cm^{-1}; ^1H NMR ($CDCl_3$, 500MHz) δ 3.10-3.07 (m, 1H), 1.83-1.79 (m, 1H), 1.63-1.59 (m, 1H), 1.48 (s, 18H), 1.30-1.26 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.9, 151.9, 82.8, 36.4, 27.8, 24.6, 18.8; HRMS (ES) Calcd for $C_{14}H_{23}NO_6Na$ 324.1417, found 324.1418.



20

(*2S*)-4-{(*1S,2S*)-2-[(*N*-bis-Boc)amino]cyclopropane-1-carbonylperoxy}-2-benzyloxycarbonylamino-4-oxo-butyric acid methyl ester (20)

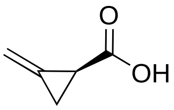
To a cooled (–40 °C) solution of **19** (130 mg, 0.43 mmol) in CH_2Cl_2 (2 mL) was added a solution of **8** (160 mg, 0.53 mmol) in CH_2Cl_2 (3 mL) followed by DCC (100 mg, 0.48 mmol). The reaction mixture was stirred at –40 °C for 5 min and then warmed to and vigorously stirred at 0 °C for 45 min. The precipitated urea was removed by filtration and the filtrate was concentrated under reduced pressure. Purification of crude product by flash chromatography on silica gel (3/1 hexanes/ethyl acetate) provided 215 mg (83%) of **20** as clear colorles oil. $[\alpha]^{26}_{D}$= +116.0° (*c* 1, $CHCl_3$); IR ($CHCl_3$ cast) 3354, 1777, 1747, 1728, 1522 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500MHz) δ 7.36-7.29 (m, 5H), 5.73 (d, *J* = 8.0 Hz, 1H), 5.11 (s, 2H), 4.70 (dt, 1H, *J* = 5.0, 8.0 Hz), 3.75 (s, 3H), 3.17-3.14 (m, 1H), 3.12 (dd, 1H, *J* = 5.0, 16.5), 3.01 (dd, 1H, *J* = 5.0, 16.5), 1.94-1.90 (m, 1H), 1.71-1.67 (m, 1H), 1.48 (s, 18H), 1.42-1.38 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.8, 167.6, 166.1, 155.5, 151.5, 135.8, 128.3, 128.0, 127.9, 83.2, 67.1, 53.0, 50.2, 36.6, 32.9, 27.9, 21.1, 19.3; HRMS (ES) Calcd for $C_{27}H_{36}N_2O_{12}Na$ 603.2160, found 603.2165.



21

(2*S*)-3-{(1*R*,2*S*)-2-[(*N*-bis-Boc)amino]-1-cyclopropyl}-2-benzyloxycarbonylamino-propionic acid methyl ester (21)

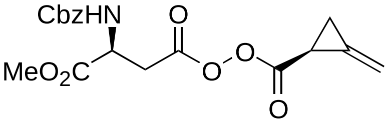
20 (40 mg, 0.07 mmol) was photolyzed at –78 °C with 254 nm UV lamp (0.9 Amp) for 36 h, as described for **12**. Purification of crude product by flash chromatography on silica gel (4/1 hexanes/ethyl acetate) provided 16 mg (47%) of **21** as clear colorless oil along with 15 mg (41%) of **22** as clear colorless oil. Data for **21**: $[\alpha]^{26}_{D}$= +11.1° (*c* 1, $CHCl_3$); IR ($CHCl_3$ cast) 3321, 1731, 1706, 1530 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500MHz) δ 7.36-7.26 (m, 5H), 7.01 (d, *J* = 9.0 Hz, 1H), 5.14 (d, 1H, *J* = 12.5 Hz), 5.08 (d, 1H, *J* = 12.5 Hz), 4.53 (dt, 1H, *J* = 4.5, 9.0 Hz), 3.70 (s, 3H), 2.41-2.38 (m, 1H), 2.06 (dt, 1H, *J* = 4.5, 14.5), 1.61-1.56 (m, 1H), 1.45 (s, 18H), 0.96-0.90 (m, 1H), 0.77-0.73 (m, 1H), 0.66 (q, 1H, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.3, 156.4, 153.4, 136.7, 128.3, 127.8, 127.7, 82.7, 66.5, 53.4, 52.1, 34.5, 34.4, 27.9, 18.2, 14.5; HRMS (ES) Calcd for $C_{25}H_{36}N_2O_8Na$ 515.2363, found 515.2361; Data for **22** $[\alpha]^{26}_{D}$= +40.0° (*c* 1, $CHCl_3$); IR ($CHCl_3$ cast) 3354, 1788, 1735, 1525 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.38-7.31 (m, 5H), 5.75 (d, 1H, *J* = 8.4 Hz), 5.12 (s, 2H), 4.66-4.61 (m, 1H), 4.51 (dd, 1H, *J* = 3.3, 11.7 Hz), 4.41 (dd, 1H, *J* = 3.3, 11.7 Hz), 3.77 (s, 3H), 3.03-2.97 (m, 1H), 1.83-1.76 (m, 1H), 1.60-1.51 (m, 1H), 1.47 (s, 18H), 1.28-1.21 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.6, 169.8, 155.7, 152.1, 136.0, 128.5, 128.2, 128.1, 82.9, 67.1, 64.2, 53.3, 52.8, 36.6, 27.9, 24.5, 18.4; HRMS (ES) Calcd for $C_{26}H_{36}N_2O_{10}Na$ 559.2262, found 559.2264.



24

(*S*)-Methylenecyclopropanecarboxylic acid (24)

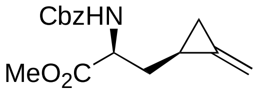
This compound was prepared by modification of reported procedure.[23] The suspension of *N*-[(*R*)-1'-phenyl-2'-hydroxyethyl]-(*1S*)-methylenecyclopropanecarboxamide (217 mg, 1 mmol) in 2N H_2SO_4 was heated to reflux (oil bath temperature 120 °C) for 2h at which point the reaction was complete by tlc (ethyl acetate). The resulting clear solution was cooled to rt and extracted with ether (4 x 5 mL). The combined organic layer was washed with brine (5 mL), dried ($MgSO_4$) and carefully concentrated under reduced pressure to obtain 91 mg (93%) of pure **24** as yellow oil. $[\alpha]^{26}_{D}$= +29.8° (*c* 1, $CHCl_3$); spectroscopic data was identical to that reported.[23]



(**25**)

(*2S*)-*2*-Benzyloxycarbonylamino-4-[(*S*)-2-methylene-cyclopropanecarbonylperoxy]-4-oxo-butyric acid methyl ester (25)

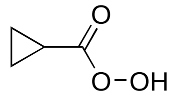
To a stirred solution of **24** (18 mg, 0.18 mmol) in CH_2Cl_2 (0.5 mL) was added at –78 °C a solution of **8** (55 mg, 0.18 mmol) in CH_2Cl_2 (0.5 mL) followed by DCC (60 mg, 0.29 mmol). The reaction mixture was stirred at –78 °C for 48 h. The precipitated urea was removed by filtration and the filtrate was concentrated under reduced pressure. Purification of crude product by flash chromatography on silica gel (3/1 hexanes/ethyl acetate) provided 32 mg (46%) of **25** as clear colorless oil. $[\alpha]^{26}_{D}$= +59.6° (*c* 1, $CHCl_3$); IR ($CHCl_3$ cast) 3368, 1806, 1777, 1724, 1515 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 7.45-7.27 (m, 5H), 5.78 (d, 1H, *J* = 7.5 Hz), 5.64-5.61 (m, 2H), 5.13 (s, 2H), 4.75-4.70 (dt, 1H, *J* = 7.5, 4.5 Hz), 3.78 (s, 3H), 3.14 (dd, 1H, *J* = 4.5, 16.5 Hz), 3.03 (dd, 1H, *J* = 4.5, 16.5 Hz), 2.38-2.33 (m, 1H), 1.99-1.93 (m, 1H), 1.88-1.81 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.0, 167.5, 166.6, 155.7, 136.0, 128.5, 128.2, 128.0, 127.9, 106.4, 67.2, 53.0, 50.2, 33.0, 13.9, 12.5; HRMS (ES) Calcd for $C_{18}H_{19}NO_8Na$ 400.1008, found 400.1004.



(**26**)

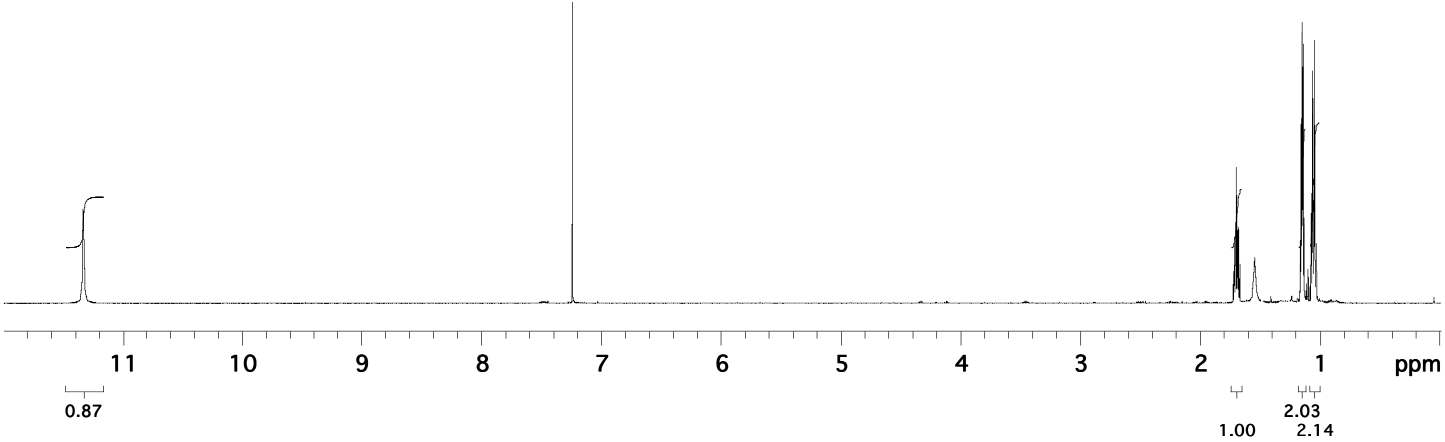
(2*S*)-2-Benzyloxycarbonylamino-3-[(*S*)-2-methylenecyclopropyl]-propionic acid methyl ester (26)

25 (60 mg, 0.16 mmol) was photolyzed at –78 °C with 254 nm UV lamp (0.9 Amp) for 30 h, as described for **12**. Purification of crude product by flash chromatography on silica gel (7/3 hexanes/ethyl acetate) provided 11 mg (24%) of **26** as clear colorless oil. $[\alpha]^{26}_{D}$= +6.6° (*c* 0.3, $CHCl_3$); IR ($CHCl_3$ cast) 3336, 1722, 1651, 1520 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500MHz) (mixture of rotamers) δ 7.36-7.28 (m, 5H), 5.46-5.34 (m, 3H), 5.10 (s, 2H), 4.49-4.44 (m, 1H), 3.73 and 3.72 (s, 3H), 2.00-1.65 (m, 2H), 1.43-1.35 (m, 1H), 1.29-1.23 (m, 1H), 0.81-0.73 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) (mixture of rotamers) δ 172.4, 155.7, 136.2, 134.5, 134.4, 128.5, 128.1, 128.1, 104.0, 66.9, 54.0, 52.2, 36.0, 35.8,11.6, 11.4, 9.5, 9.4; HRMS (ES) Calcd for $C_{16}H_{19}NO_4Na$ 312.1211, found 312.1212.

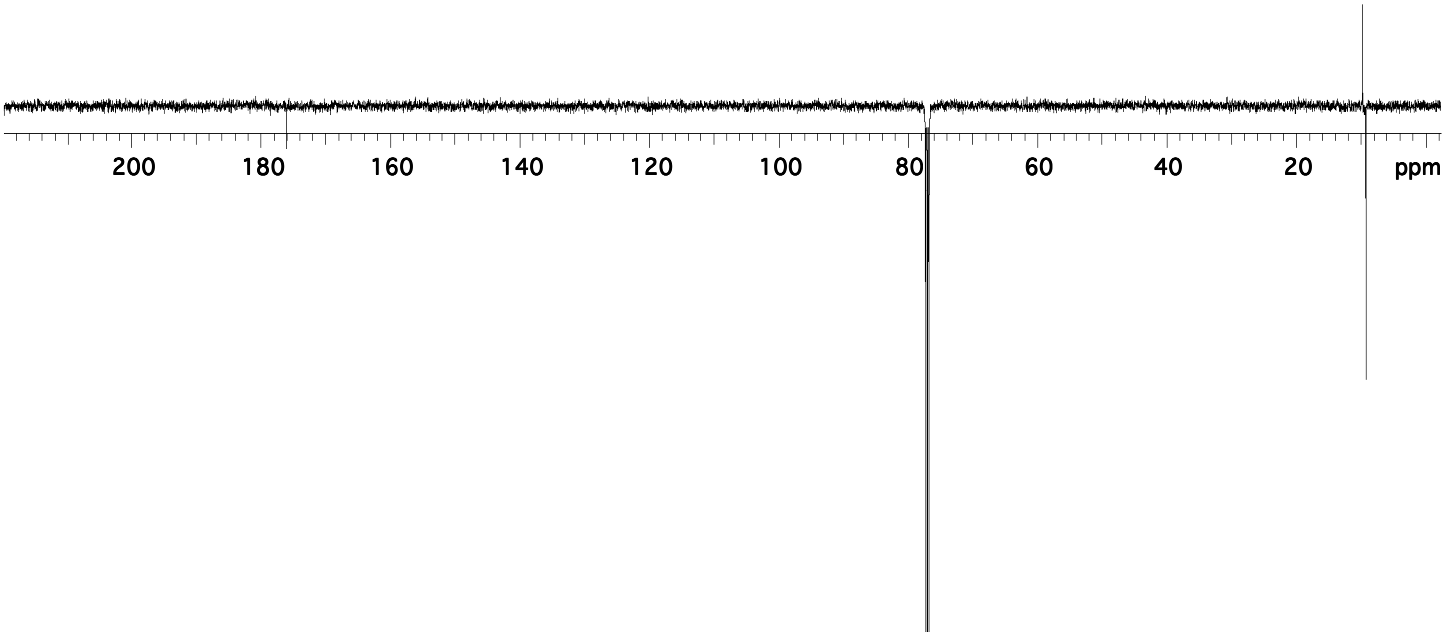


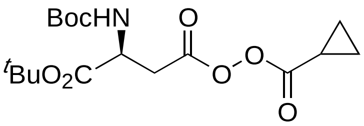
2

(500 MHz/$CDCl_3$)



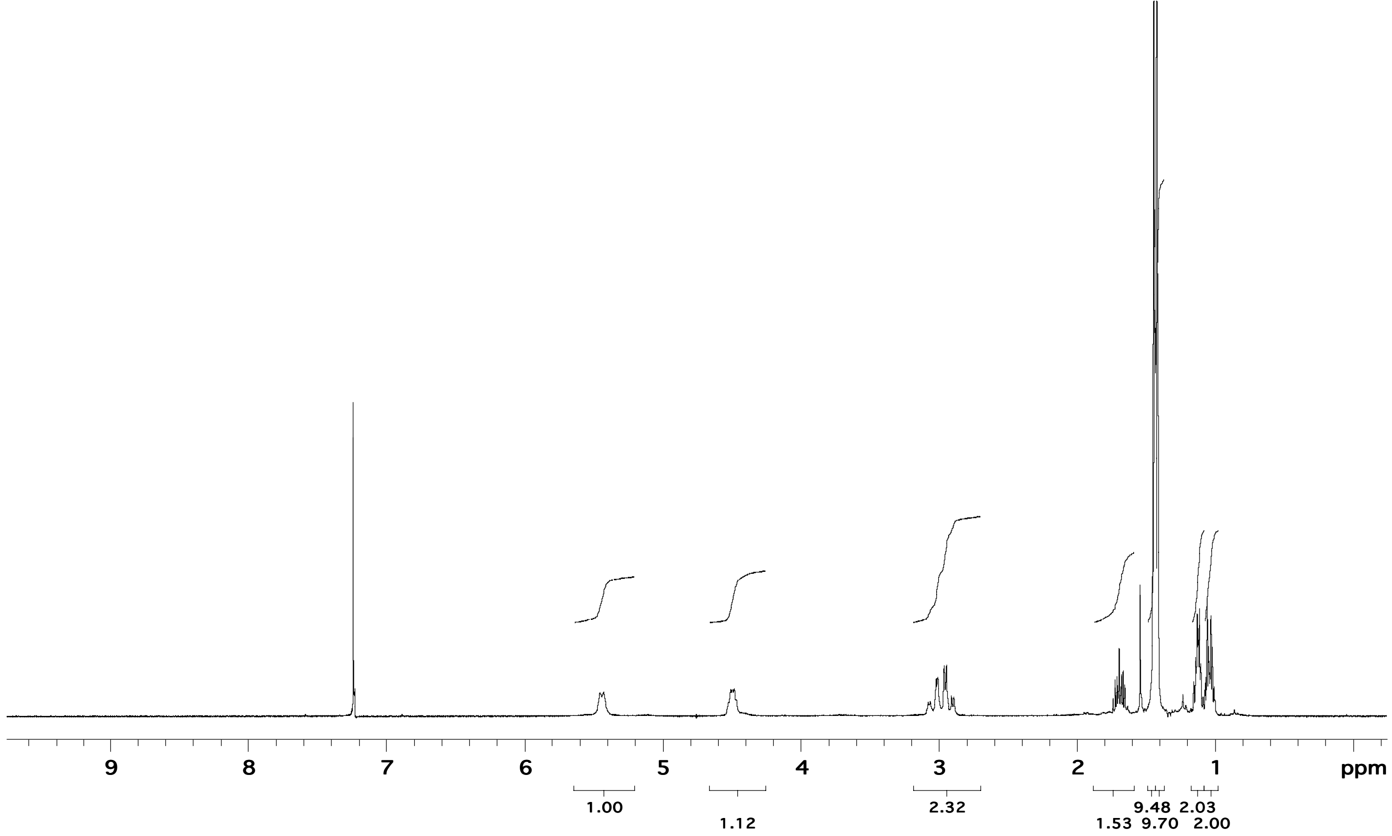
(125 MHz/$CDCl_3$)





3

(300 MHz/CDCl$_3$)



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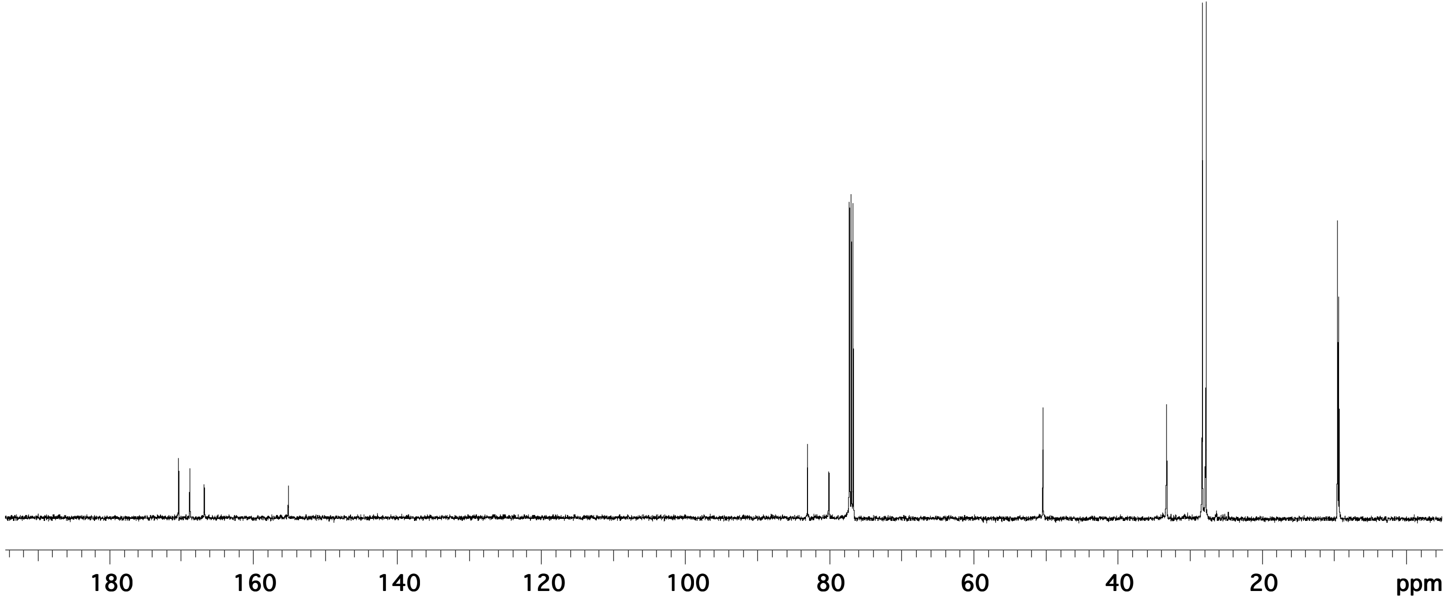
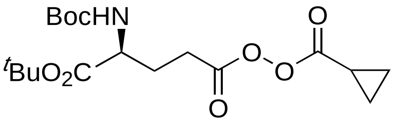
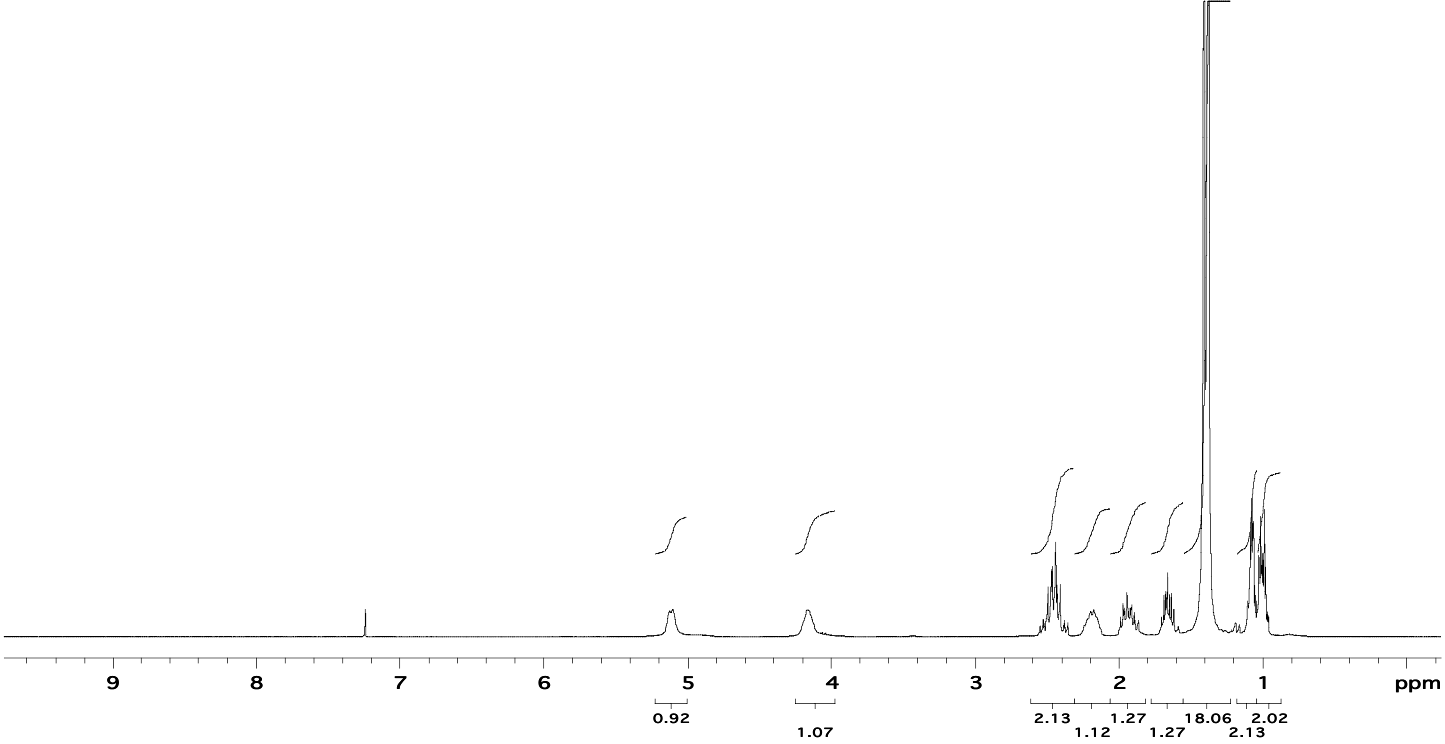


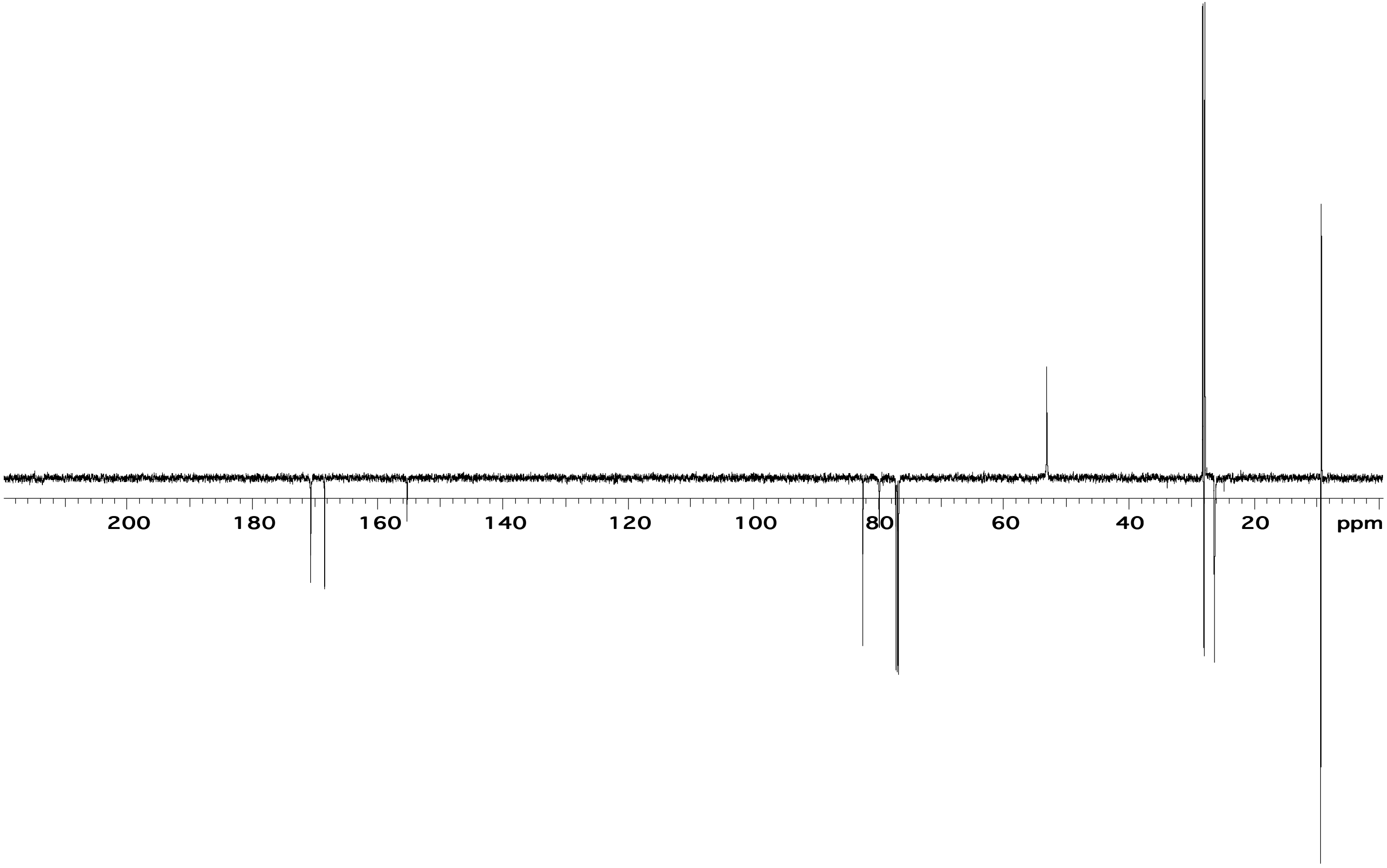


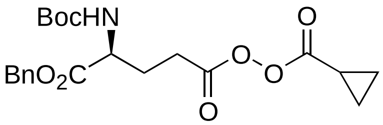
4

(300 MHz/$CDCl_3$)



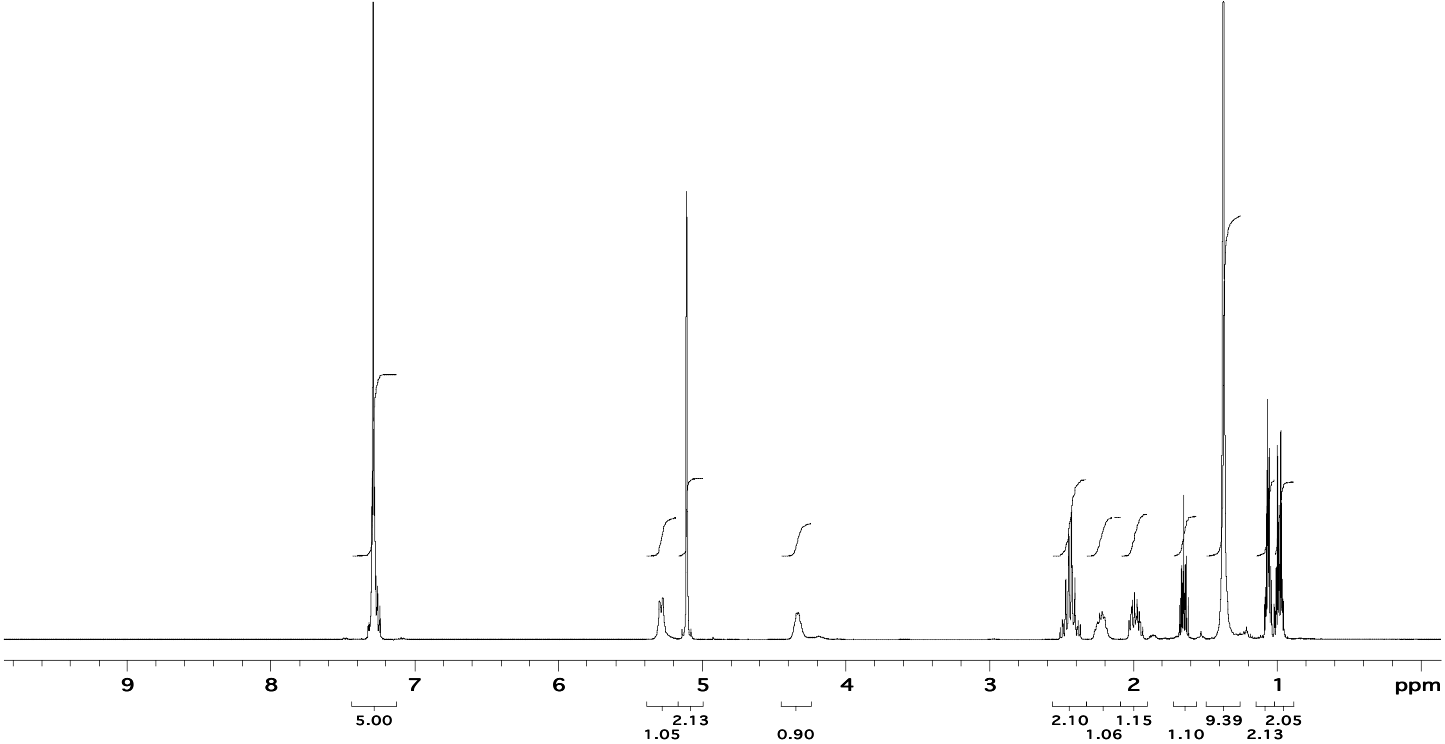
(125 MHz/$CDCl_3$)



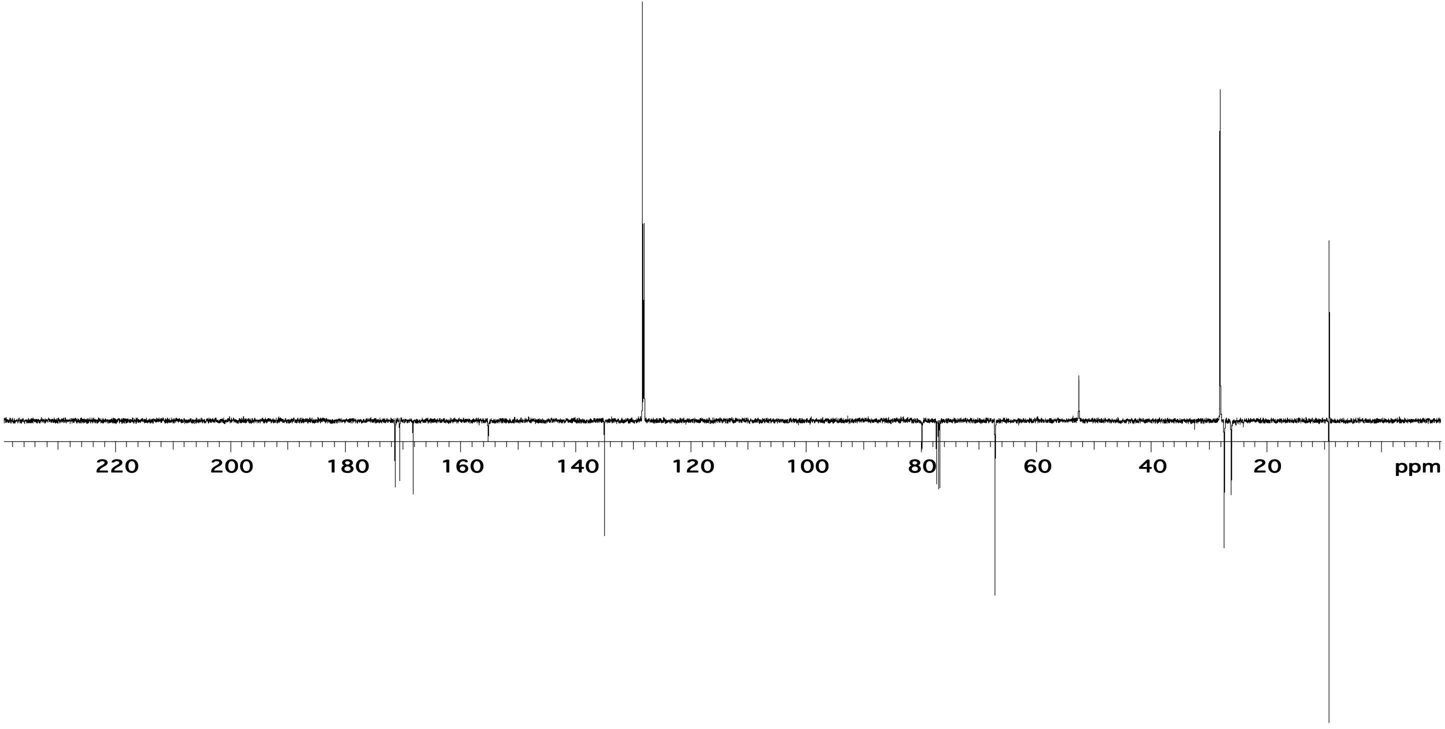


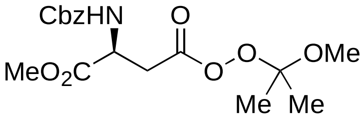
5

(400 MHz/CDCl$_3$)



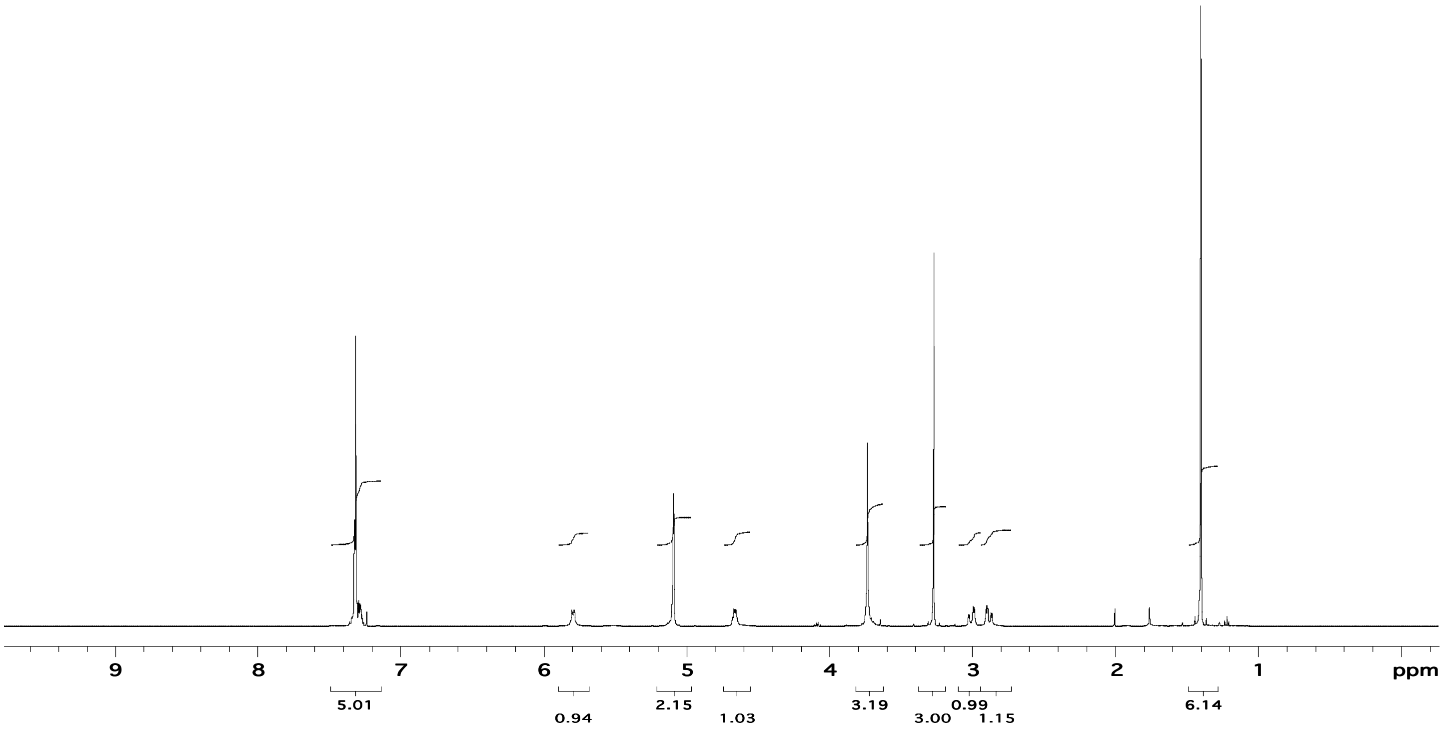
(100 MHz/CDCl$_3$)



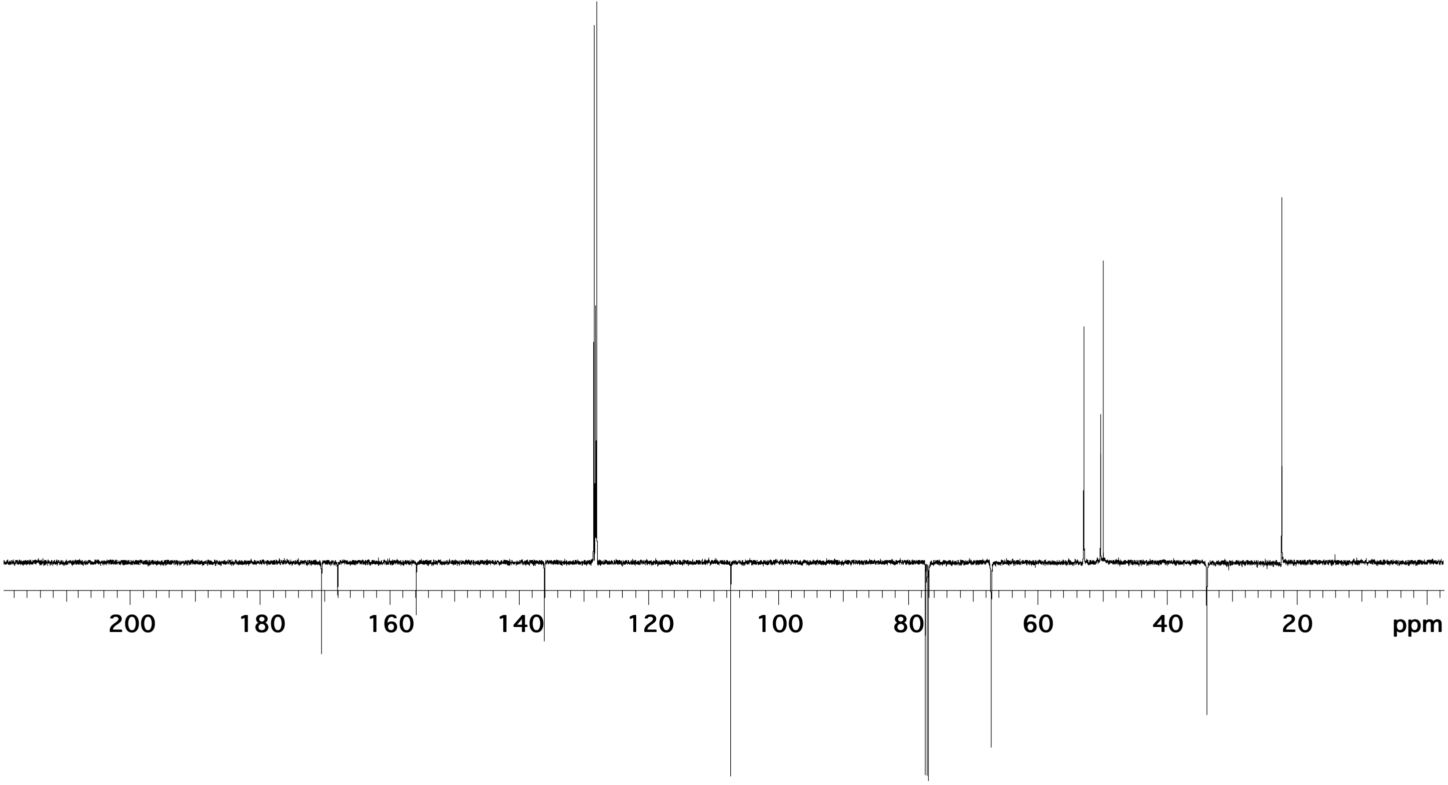


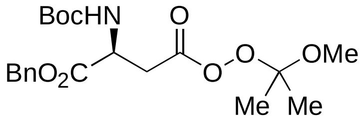
6

(500MHz/$CDCl_3$)



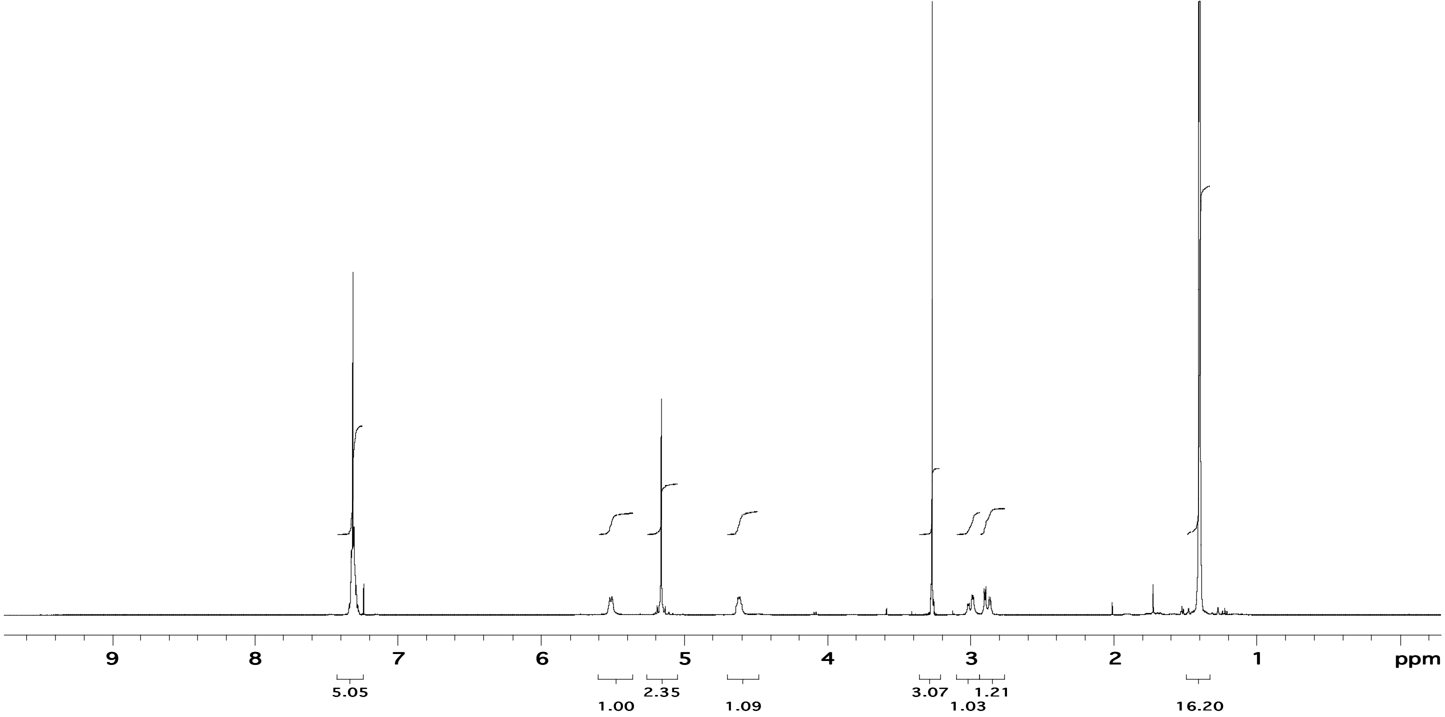
(125 MHz/$CDCl_3$)



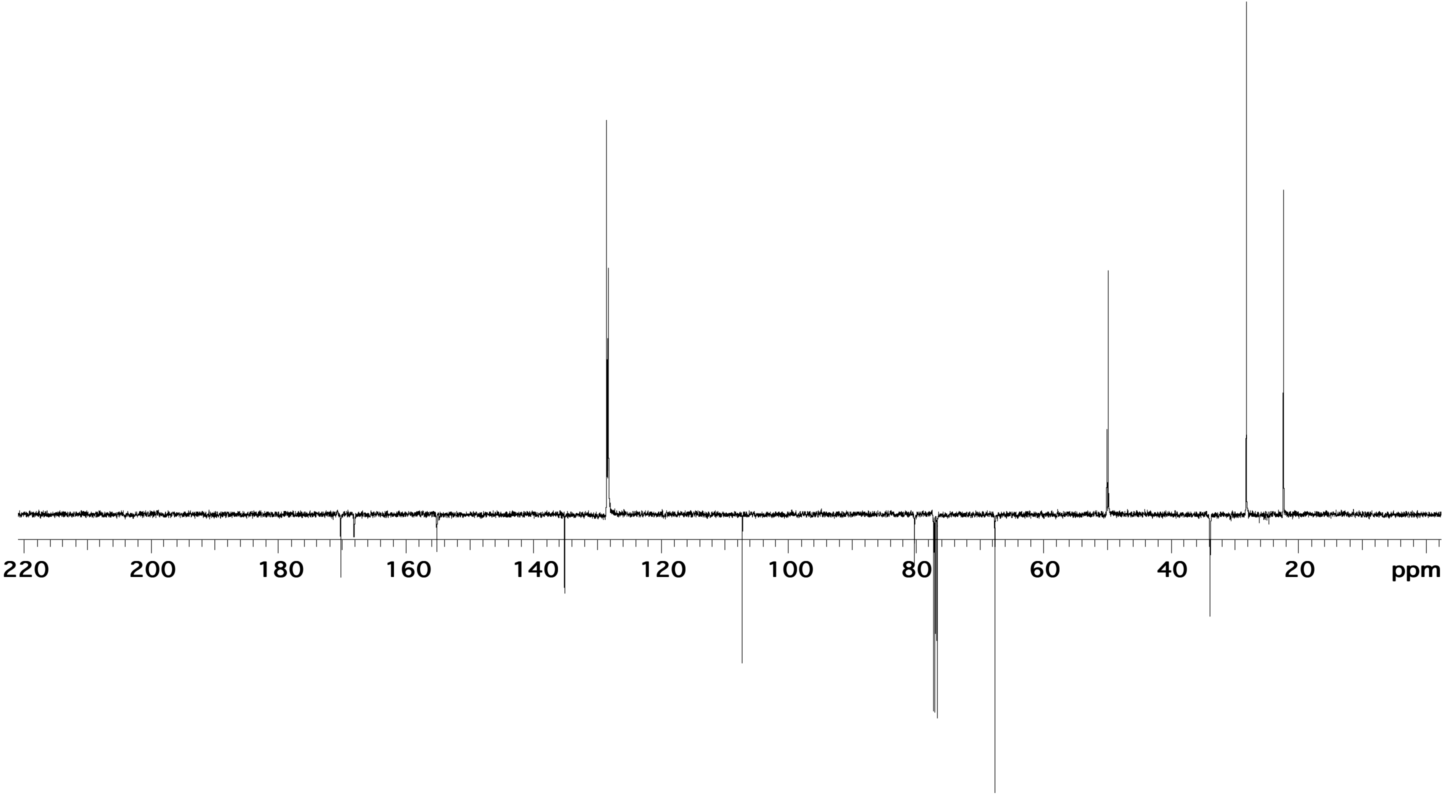


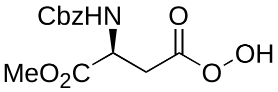
(**7**)

(500 MHz/CDCl$_3$)

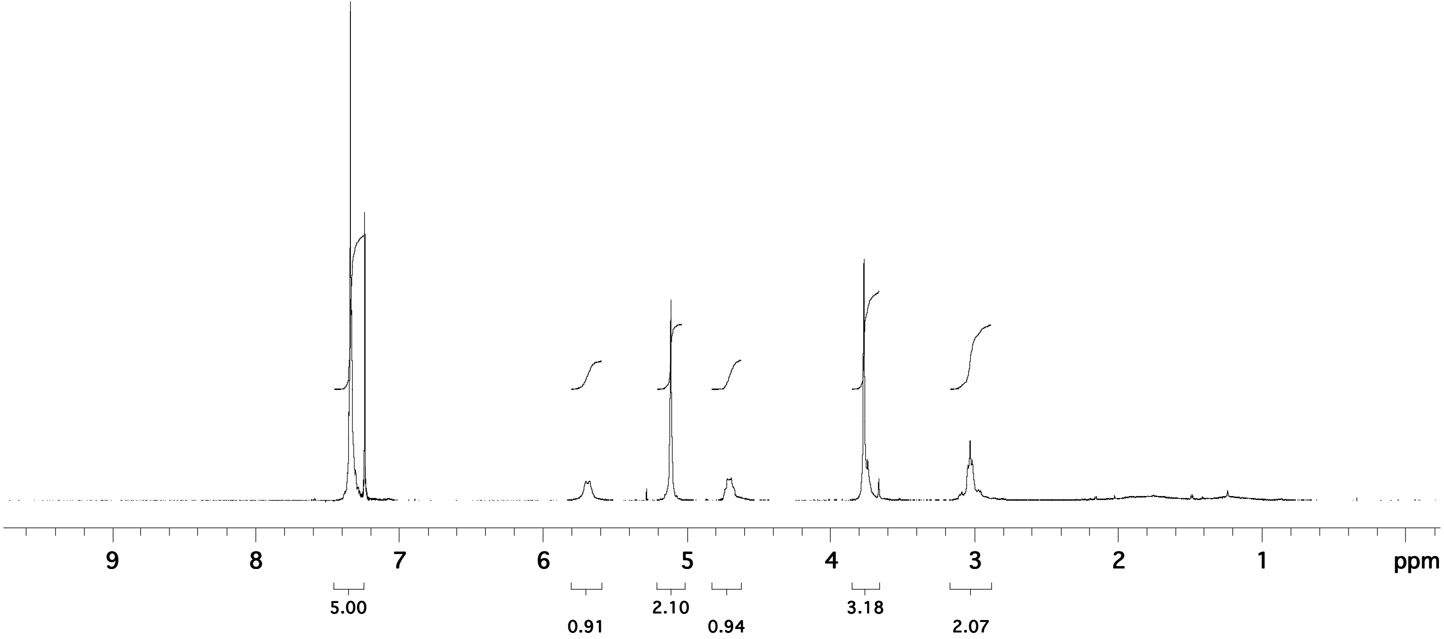


(125 MHz/CDCl$_3$)

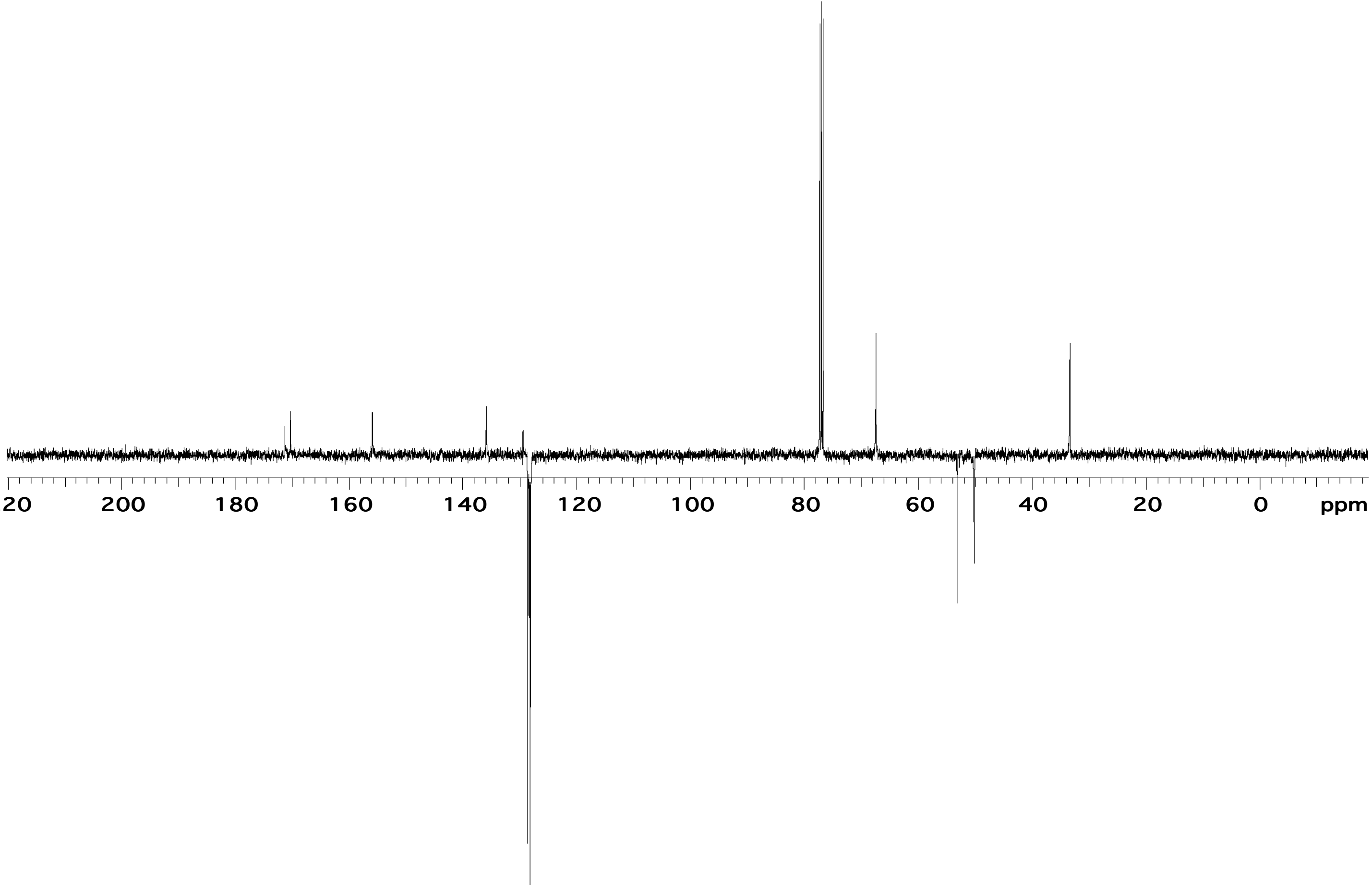


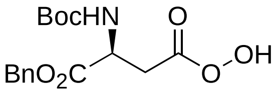


8 (crude product)
(300 MHz/$CDCl_3$)



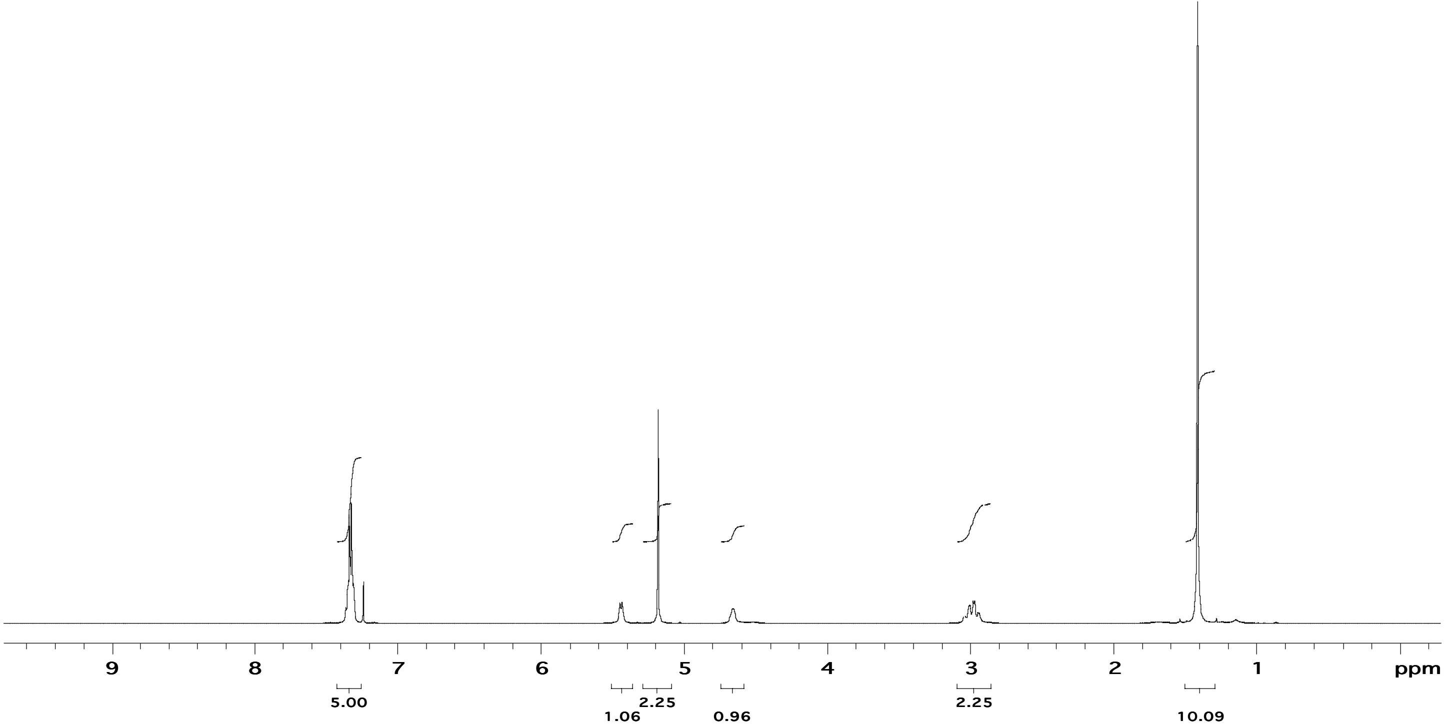
(100 MHz/$CDCl_3$)



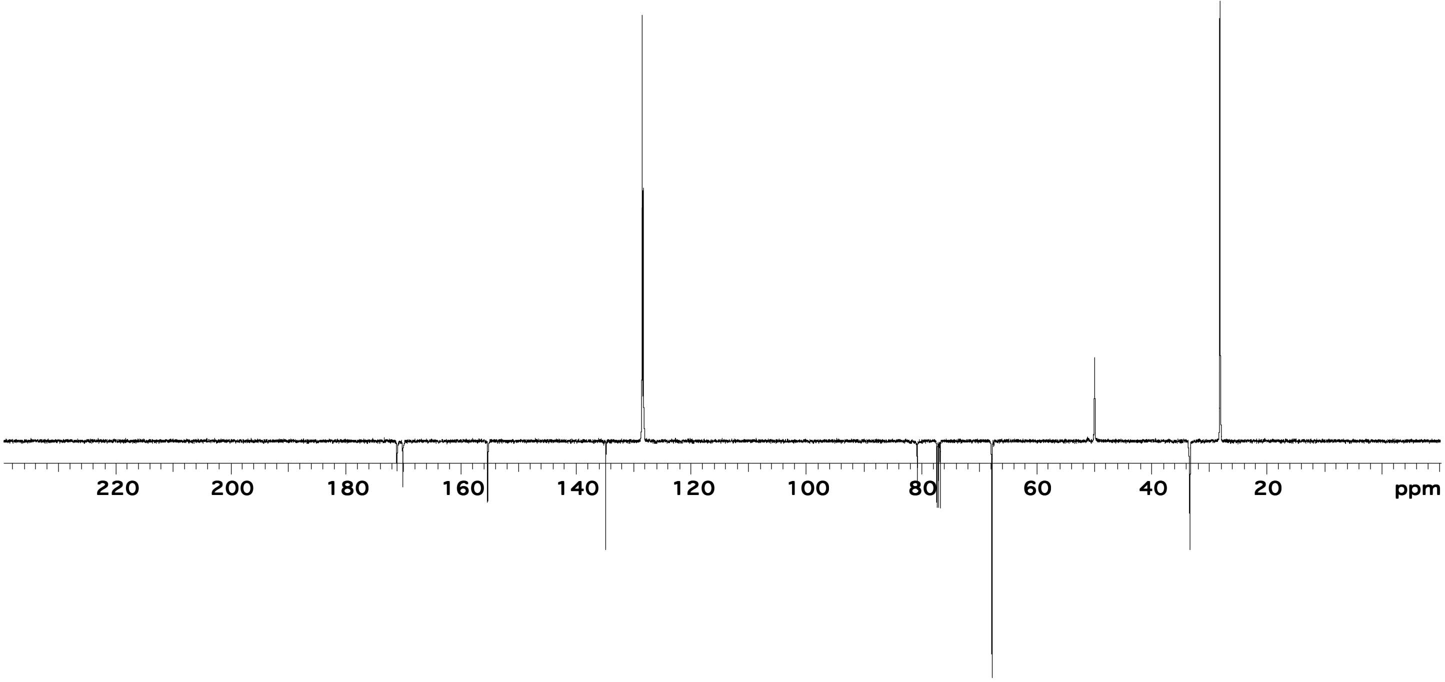


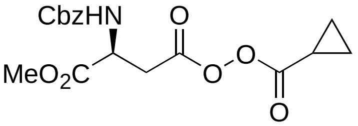
9

(500 MHz/$CDCl_3$)



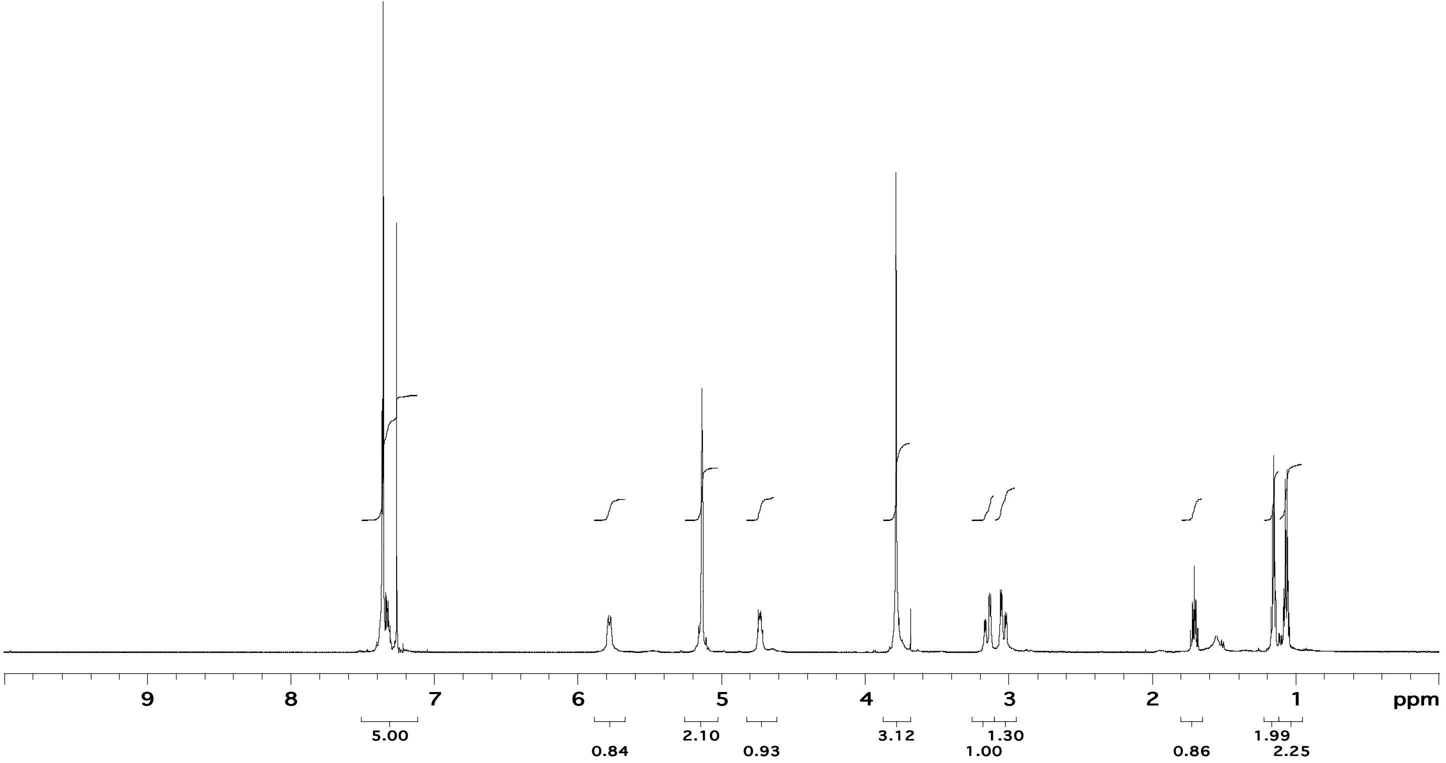
(125 MHz/$CDCl_3$)



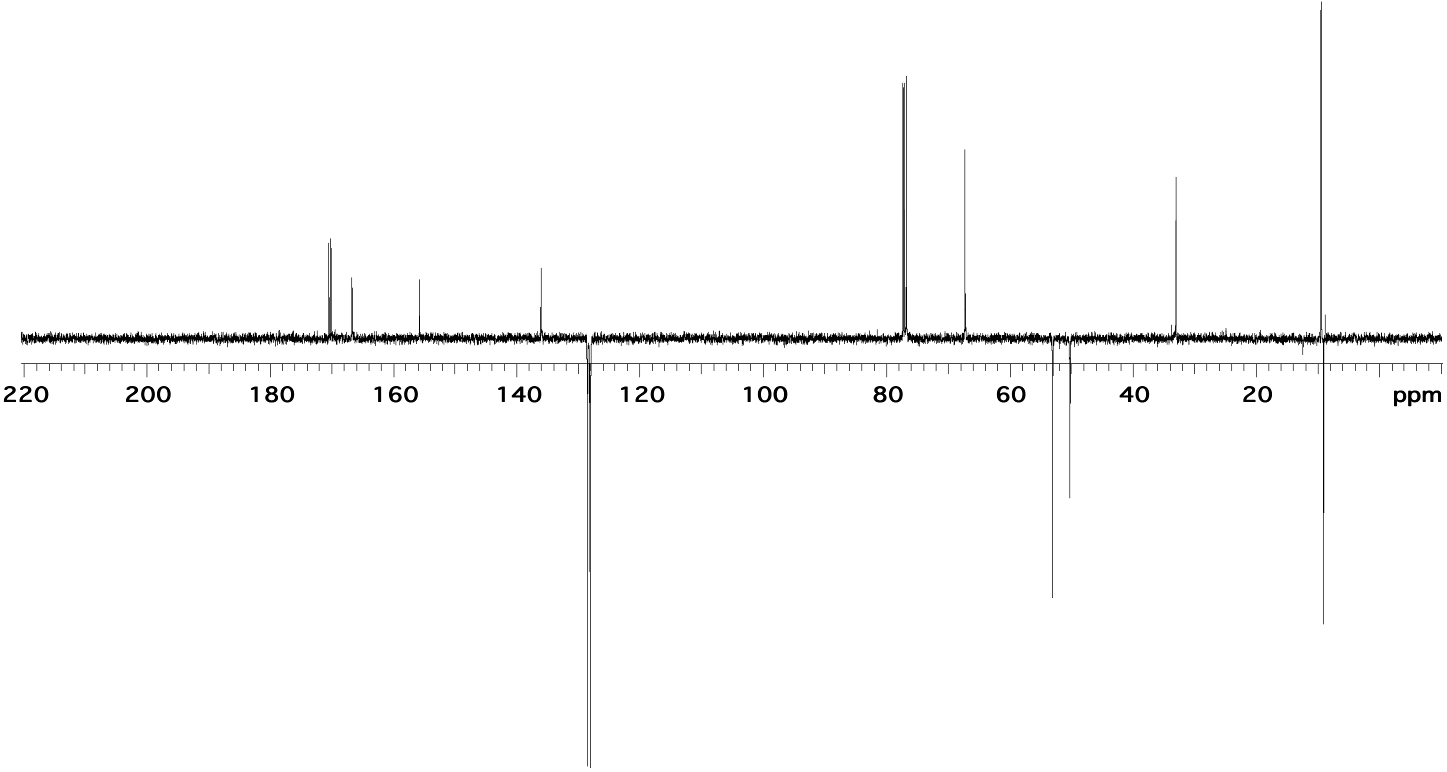


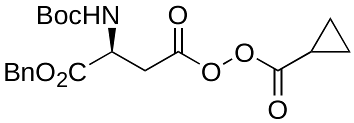
10

(500 MHz/CDCl$_3$)



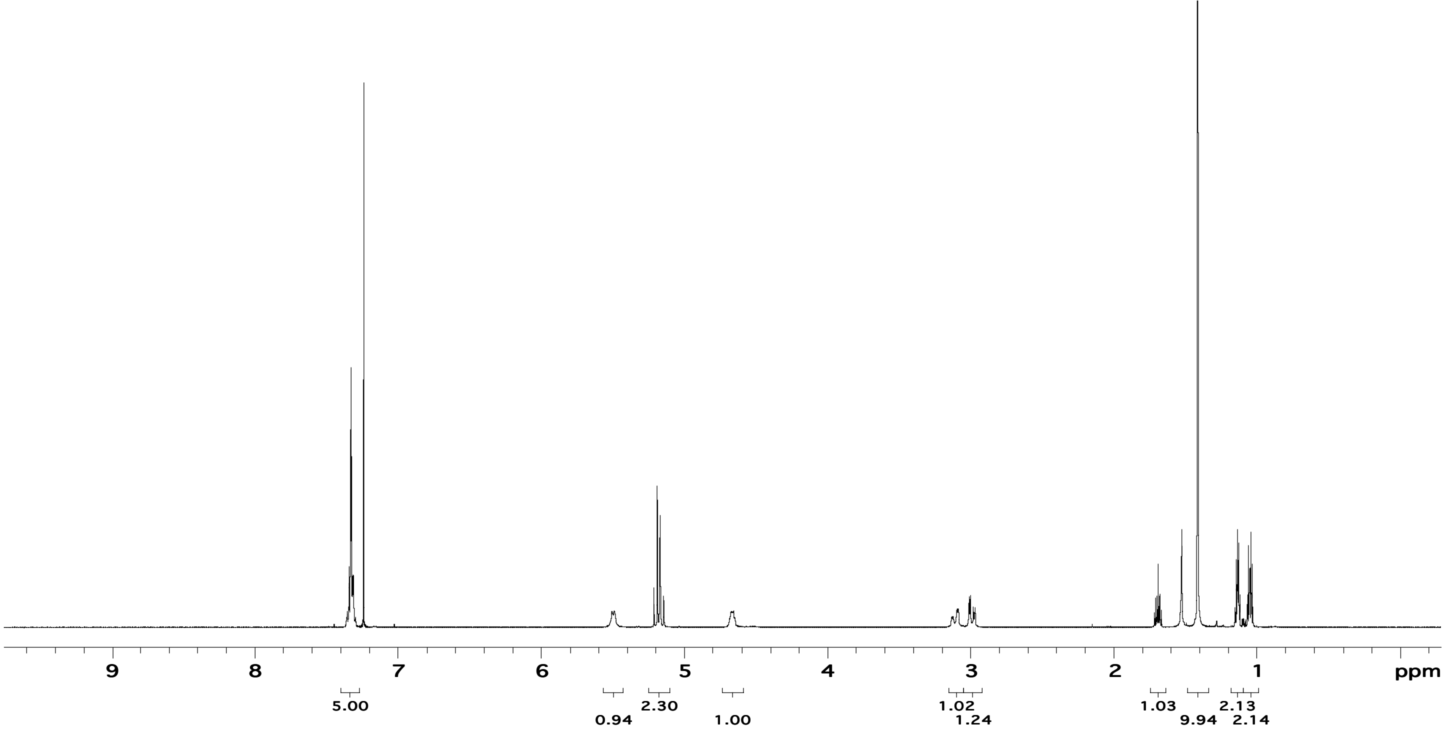
(125 MHz/CDCl$_3$)



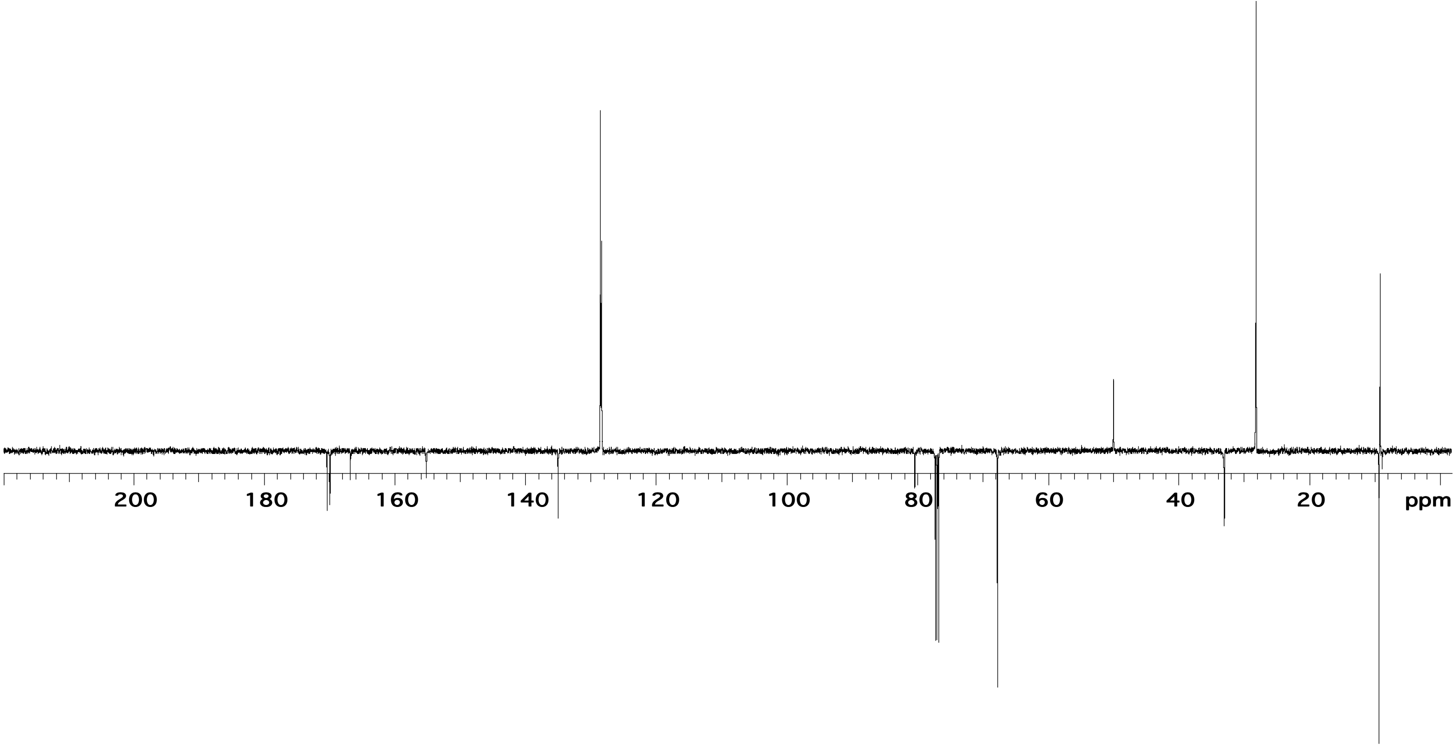


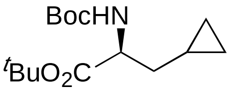
11

(500 MHz/CDCl$_3$)



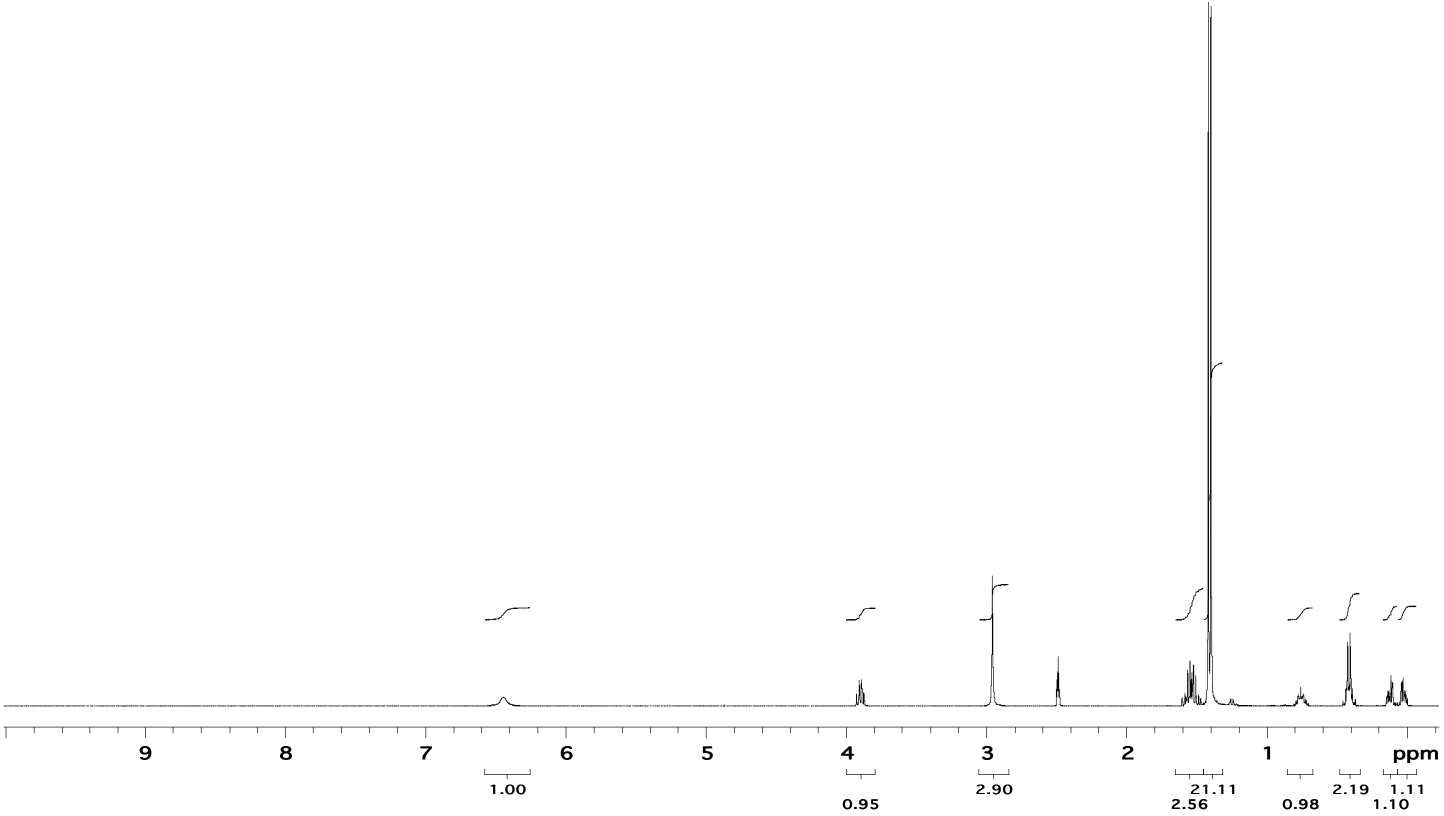
(125 MHz/CDCl$_3$)



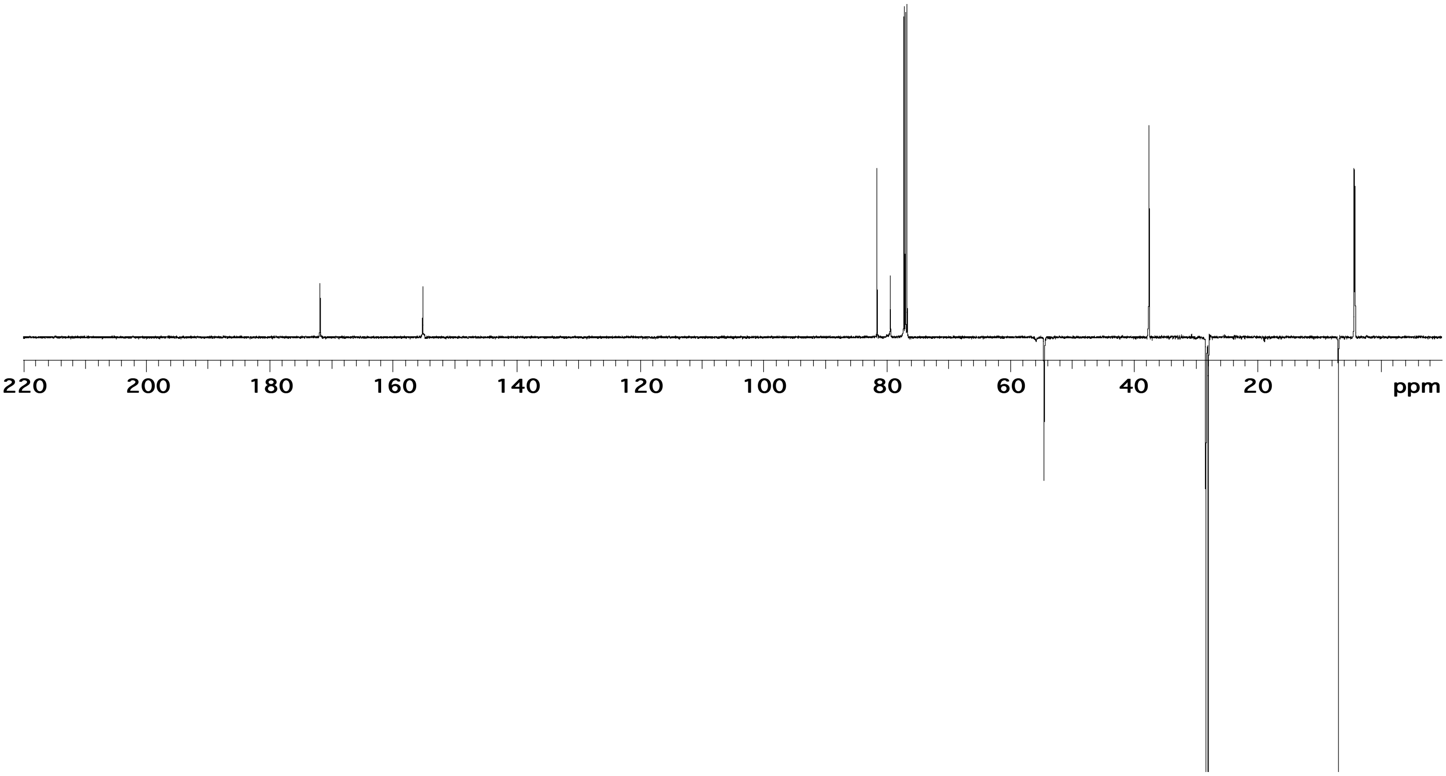


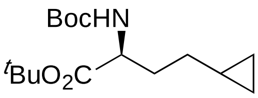
12

(400 MHz/ DMSO-d$_6$/100 °C)



(125 MHz/CDCl$_3$)





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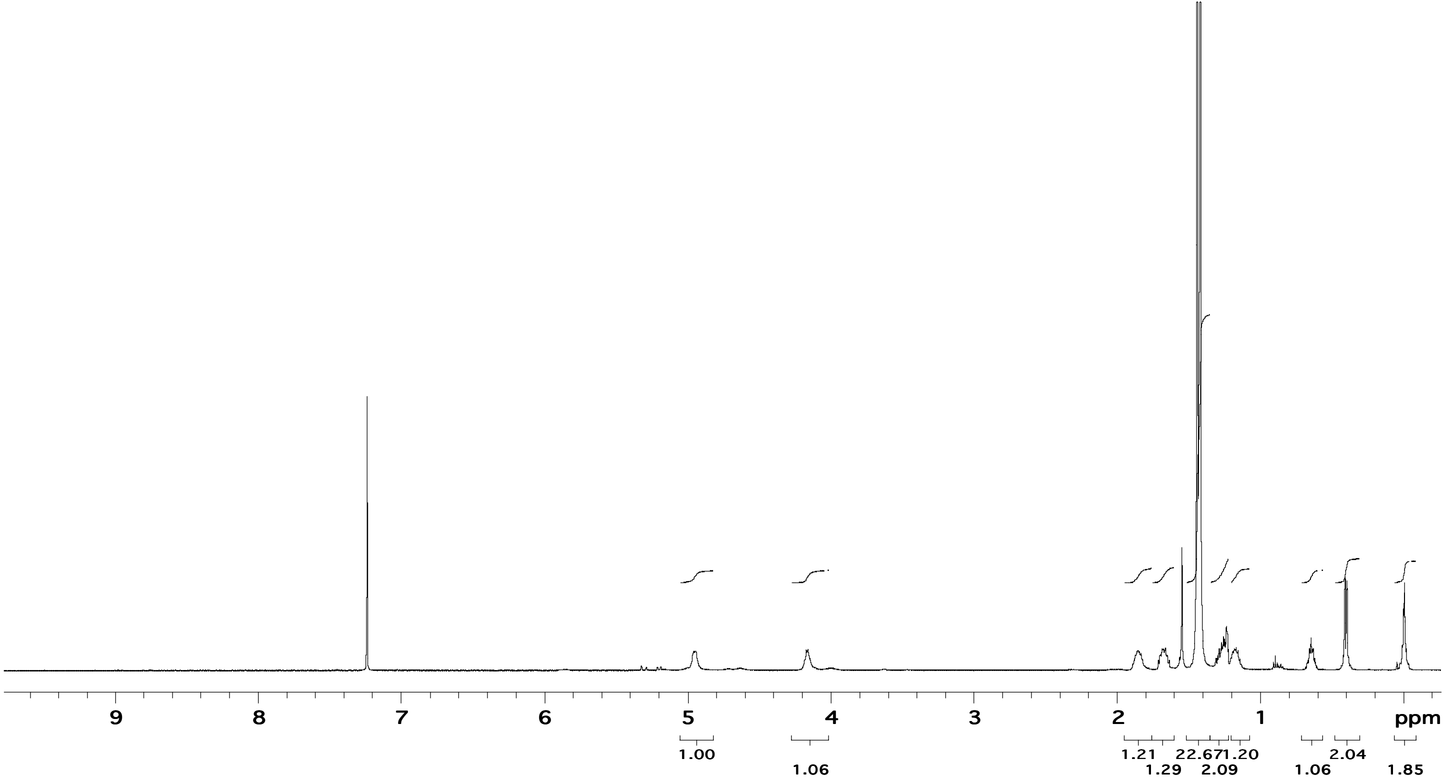
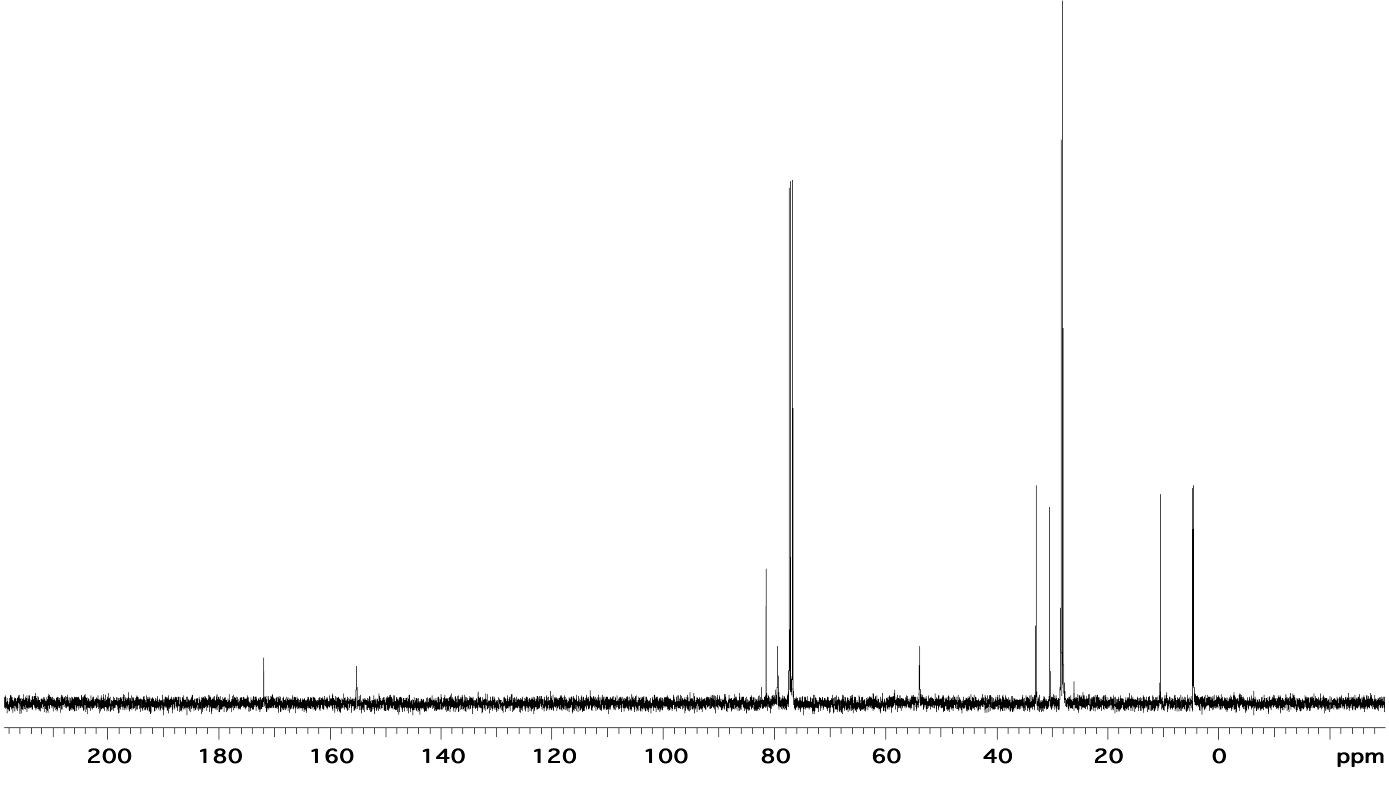
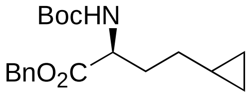
(500 MHz/CDCl$_3$)



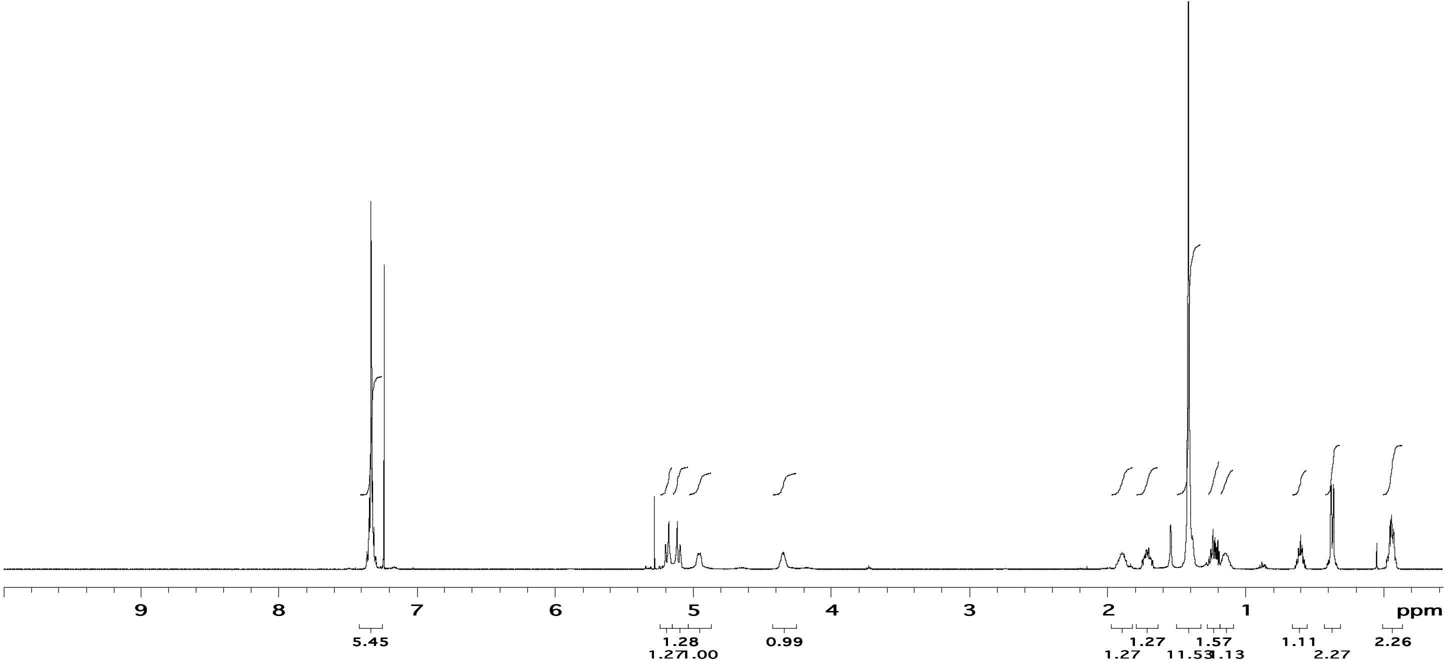
(100 MHz/CDCl$_3$)



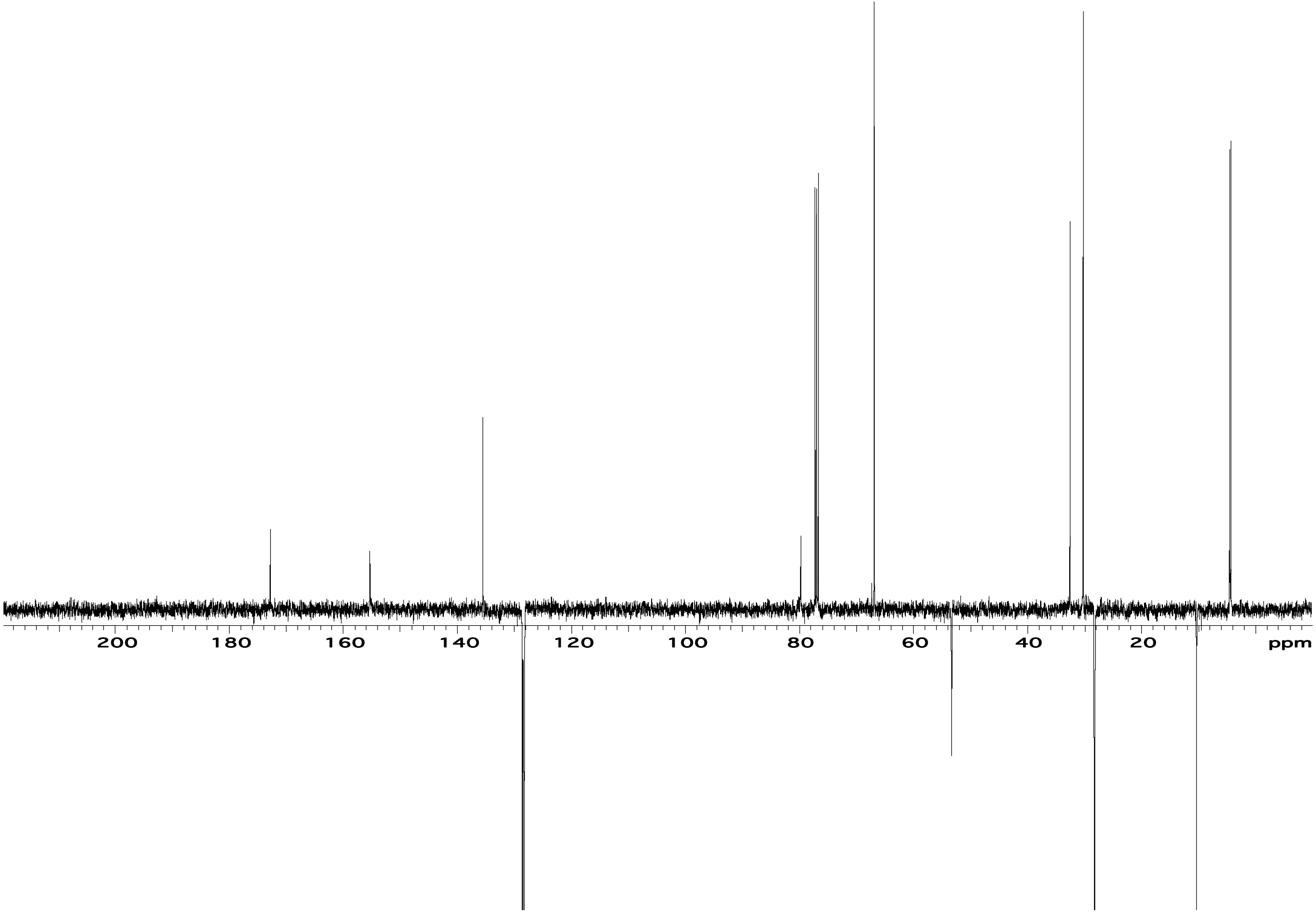


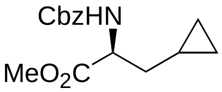
14

(500 MHz/CDCl$_3$**)**



(125 MHz/CDCl$_3$)





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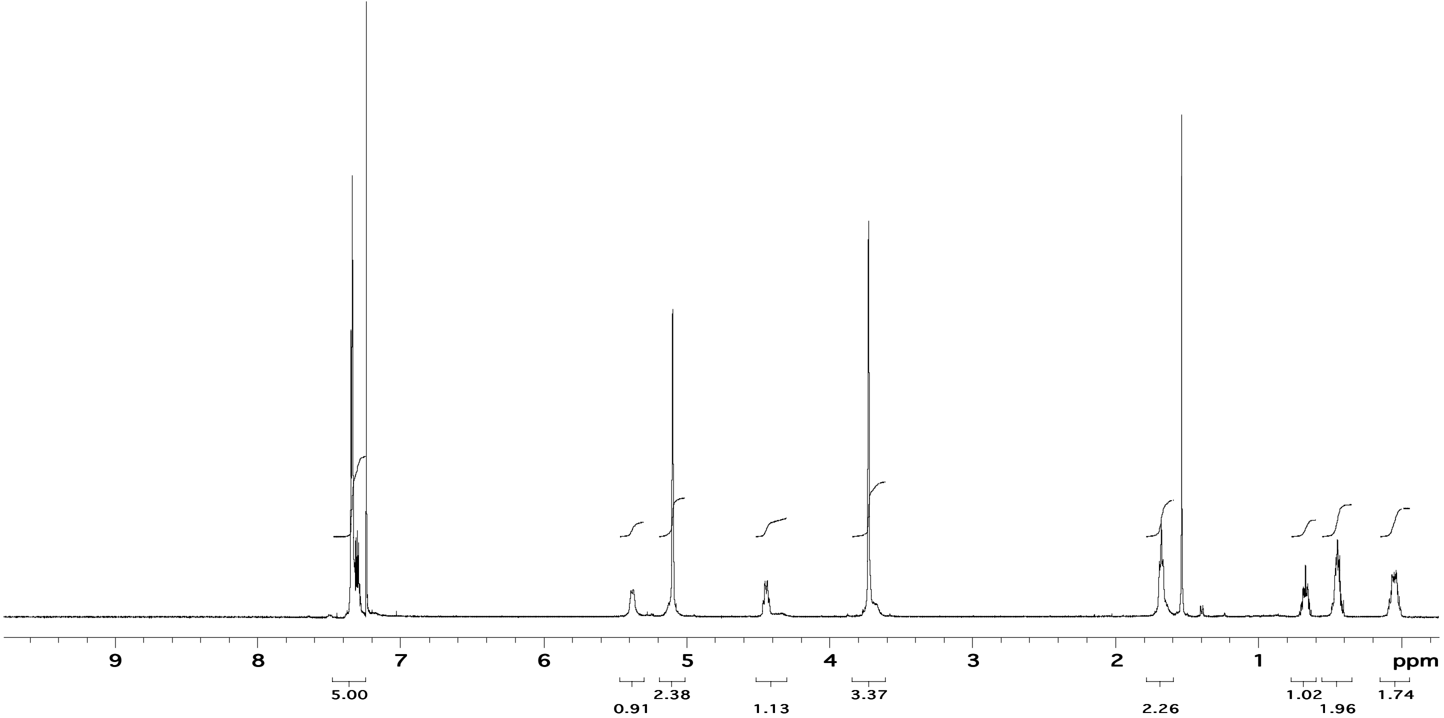
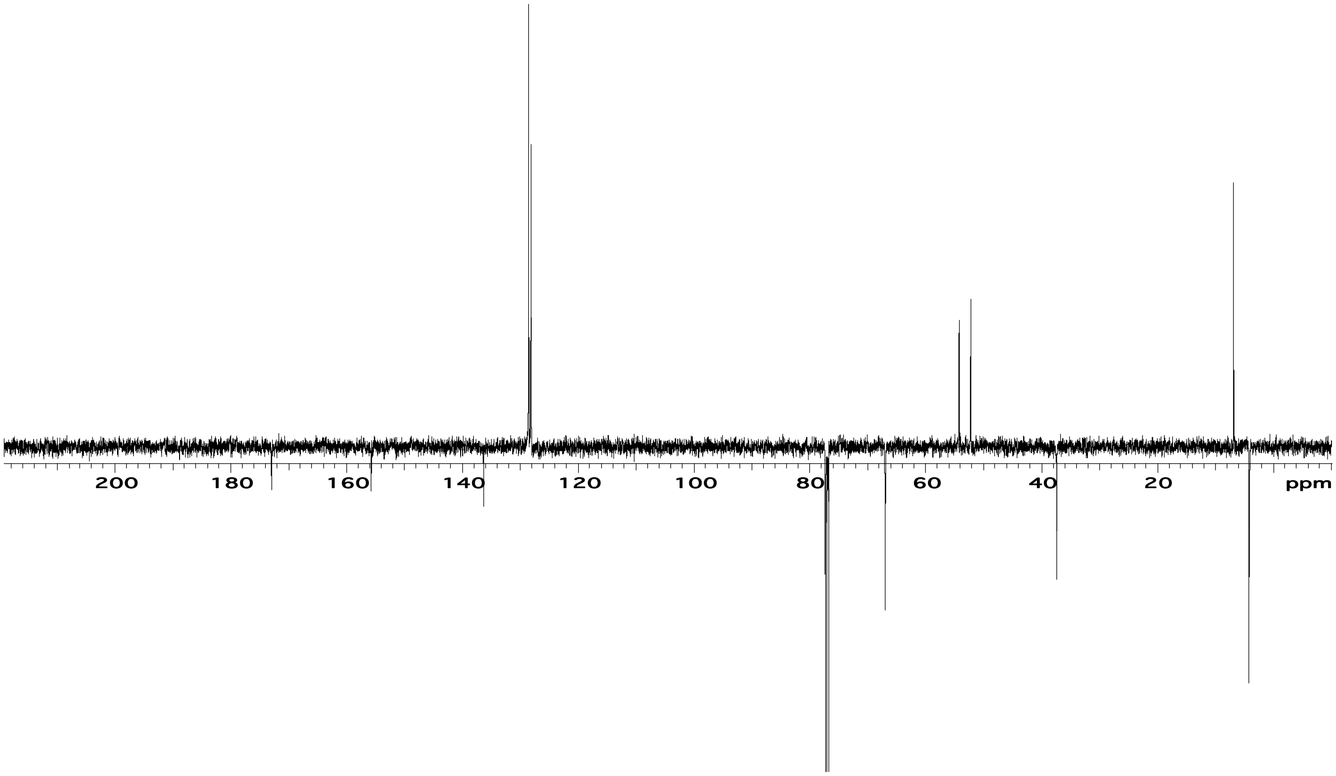
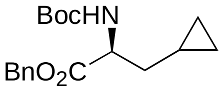
(500 MHz/$CDCl_3$)



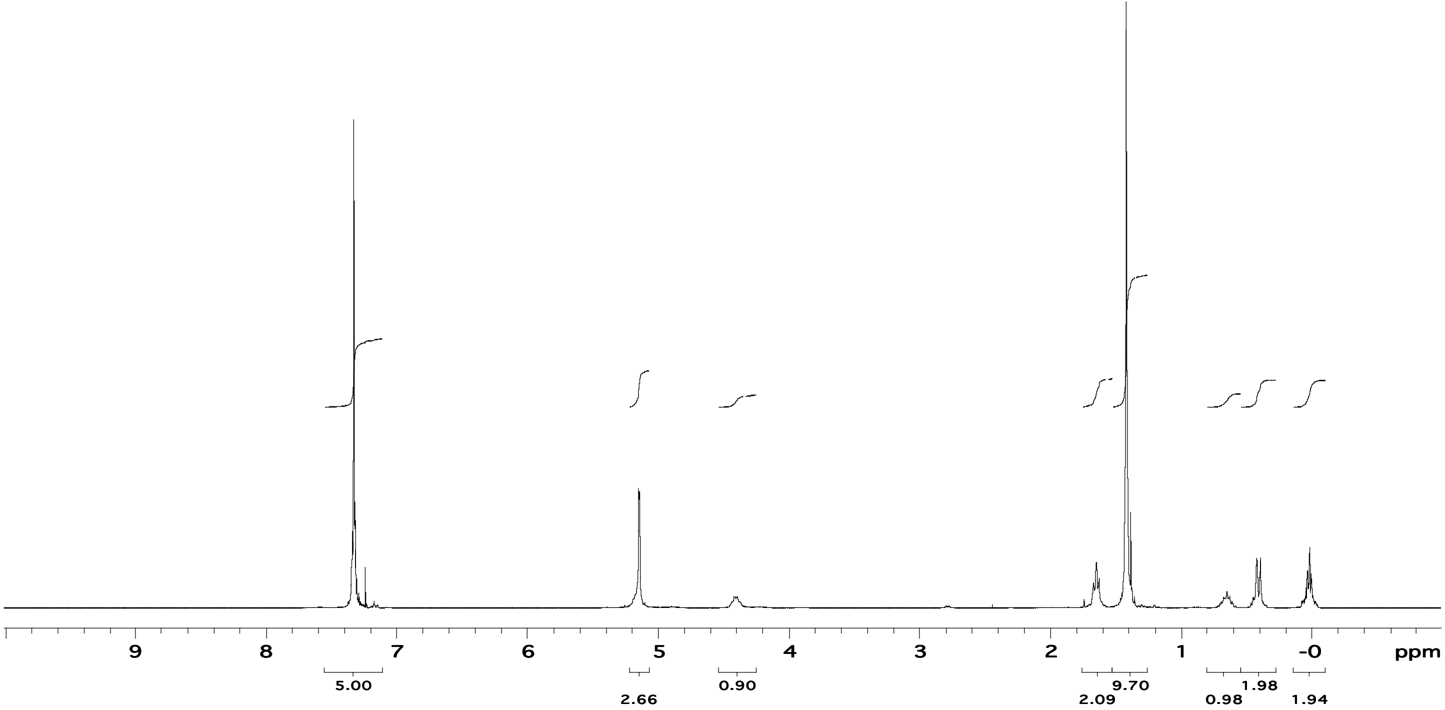
(125 MHz/$CDCl_3$)



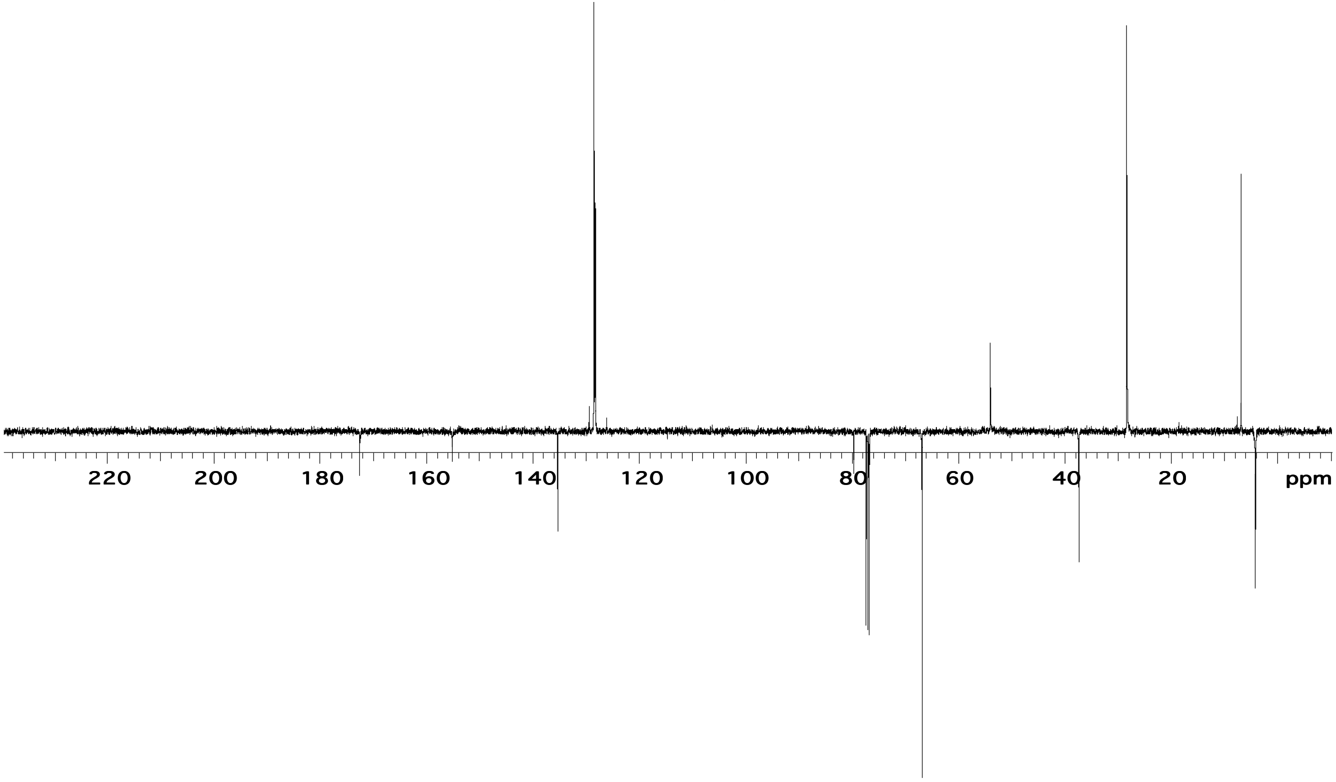


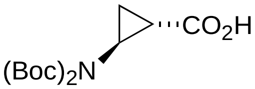
(**16**)

(300 MHz, $CDCl_3$)



(125 MHz, $CDCl_3$)





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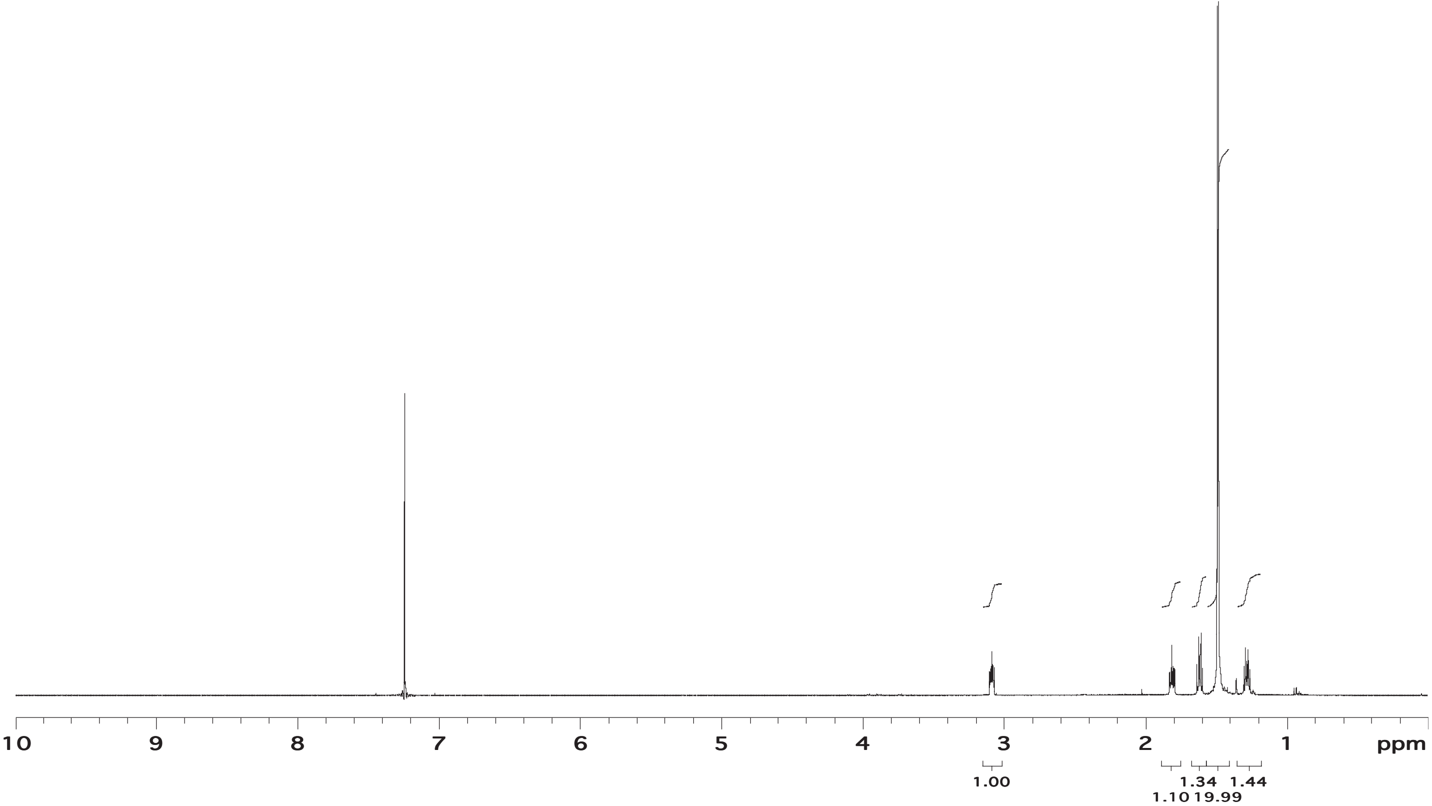
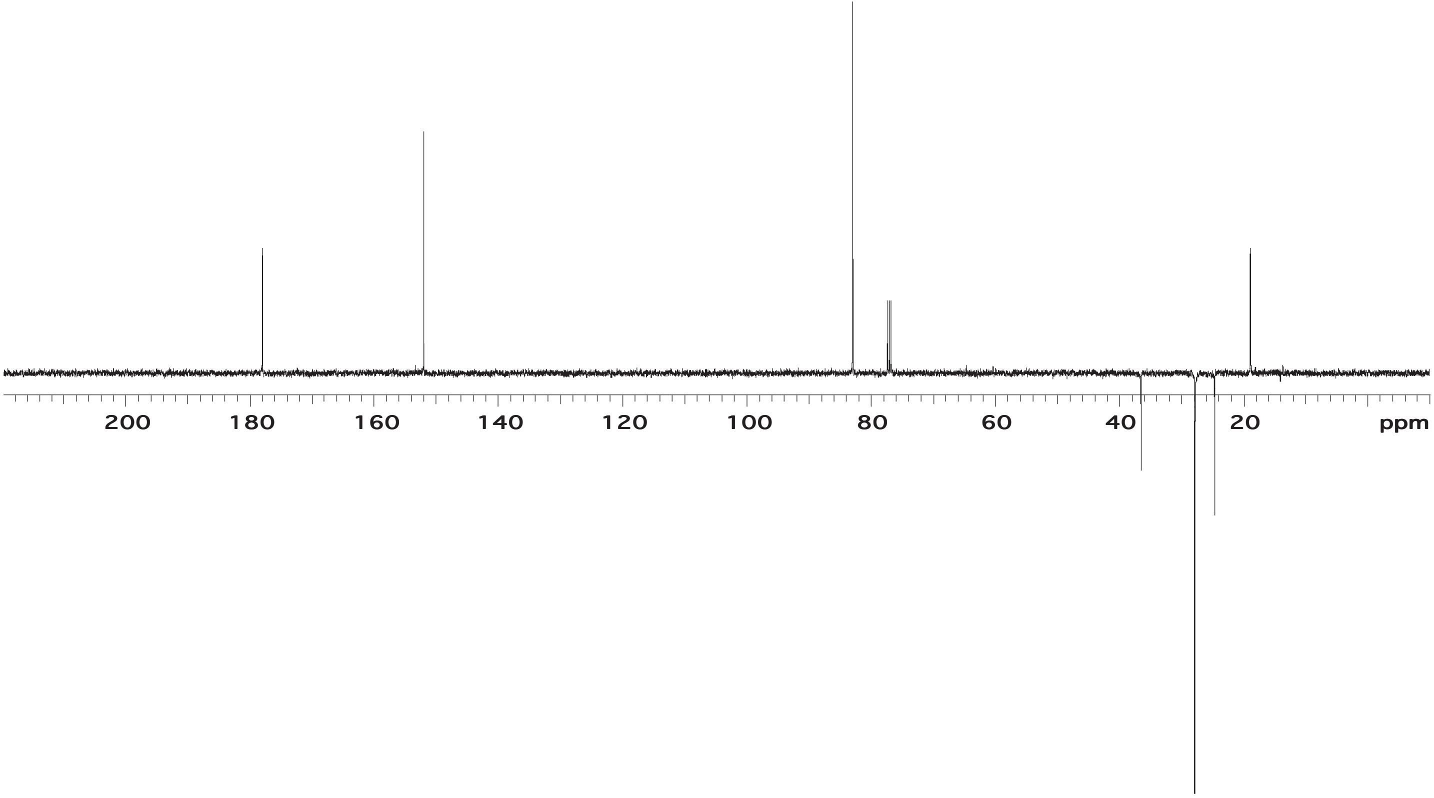
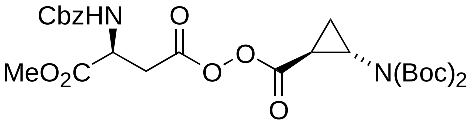
(500MHz, $CDCl_3$)



(125 MHz, $CDCl_3$)





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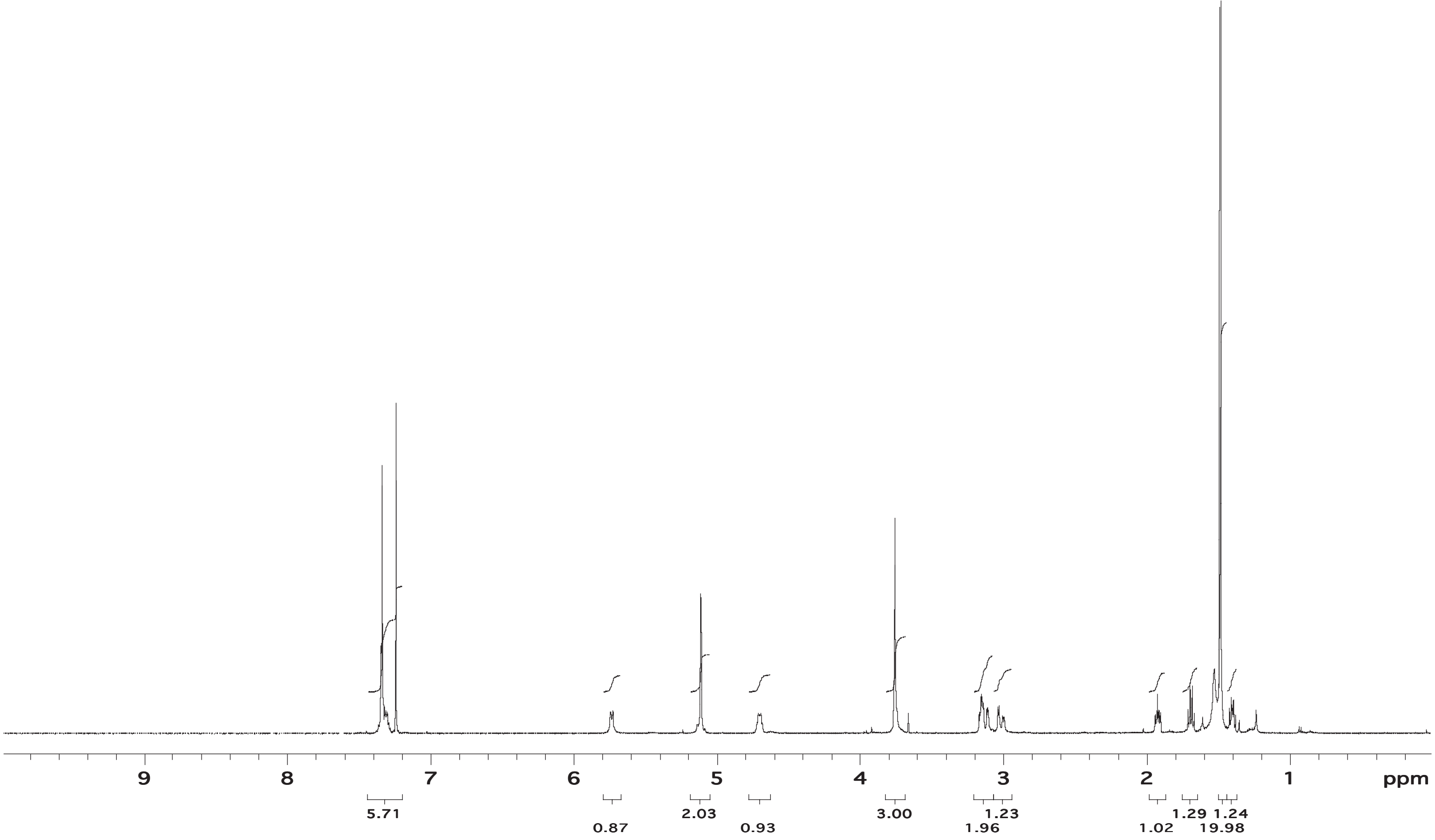
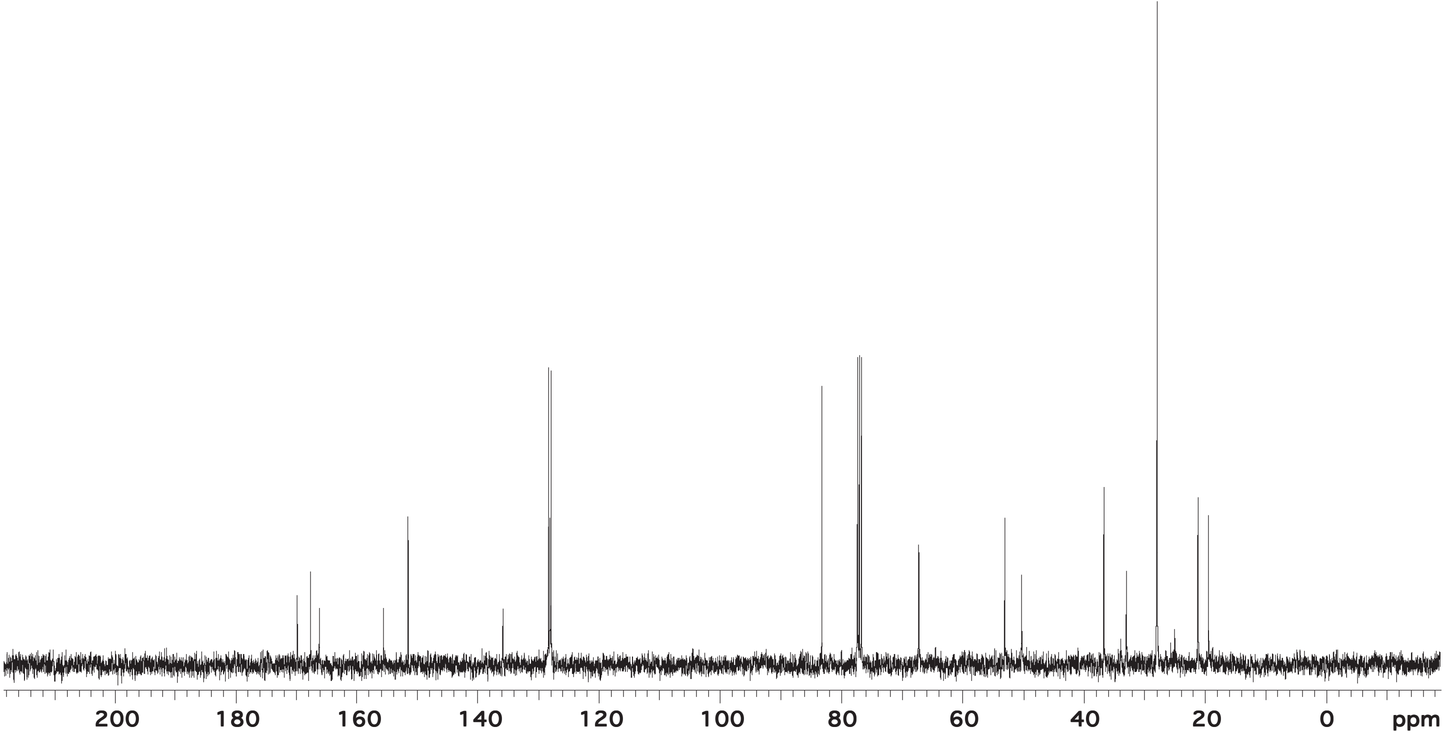
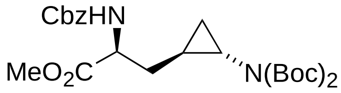
(500MHz/CDCl$_3$)



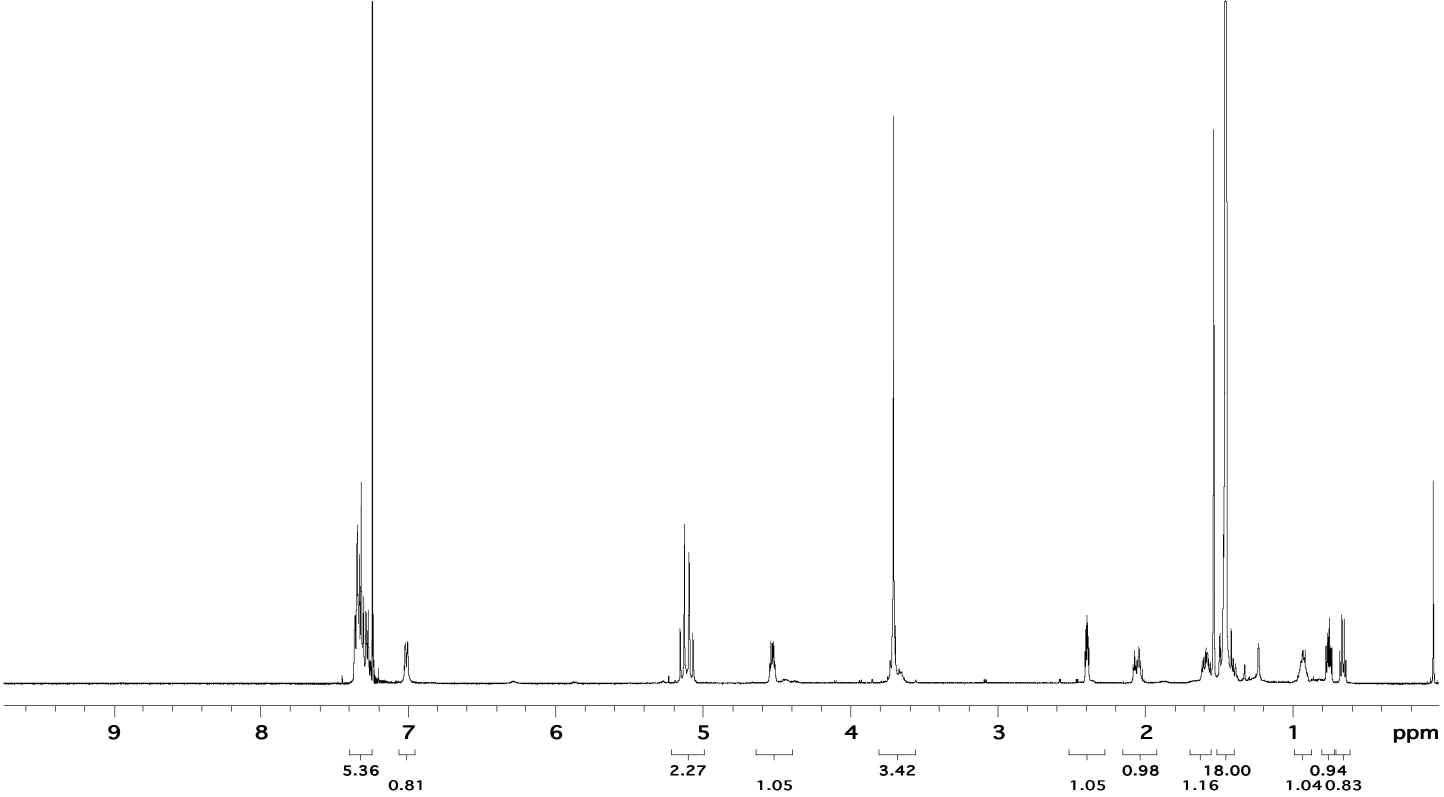
(100 MHz/CDCl$_3$)



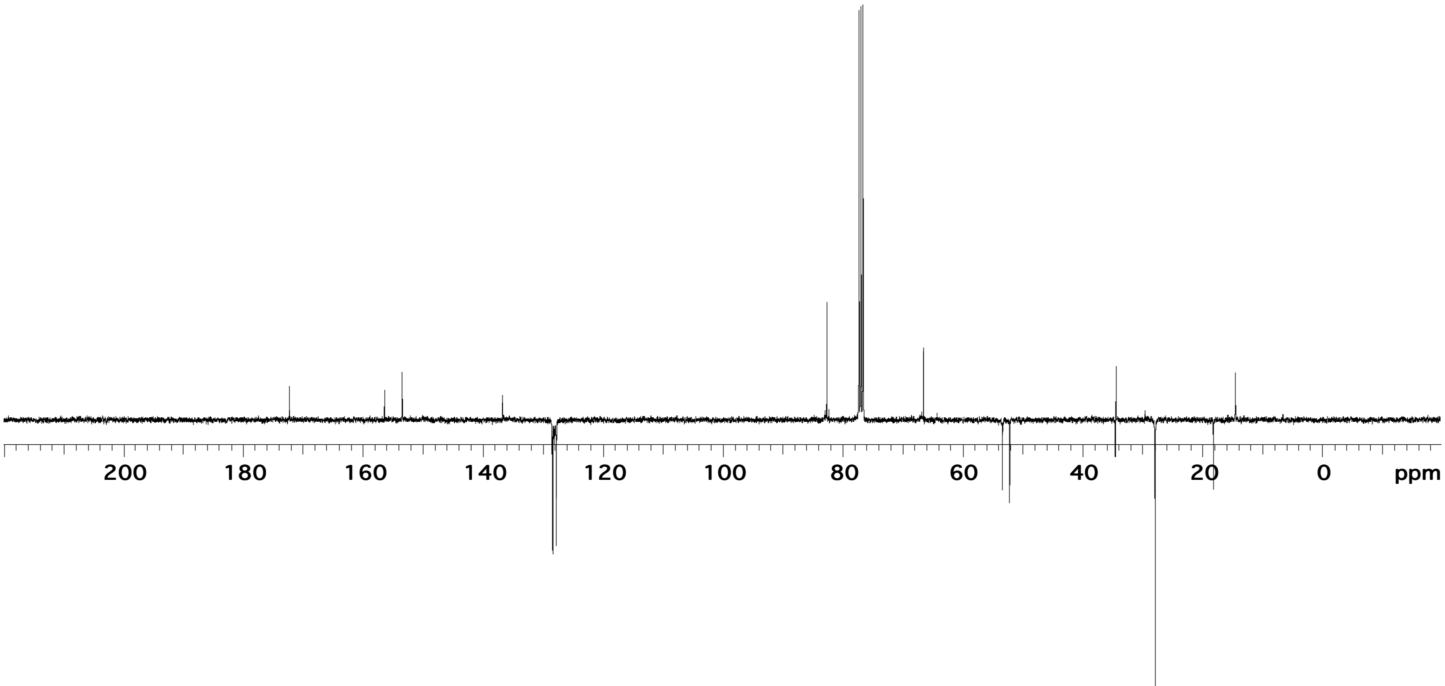


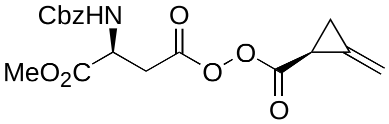
21

(500 MHz/CDCl$_3$)



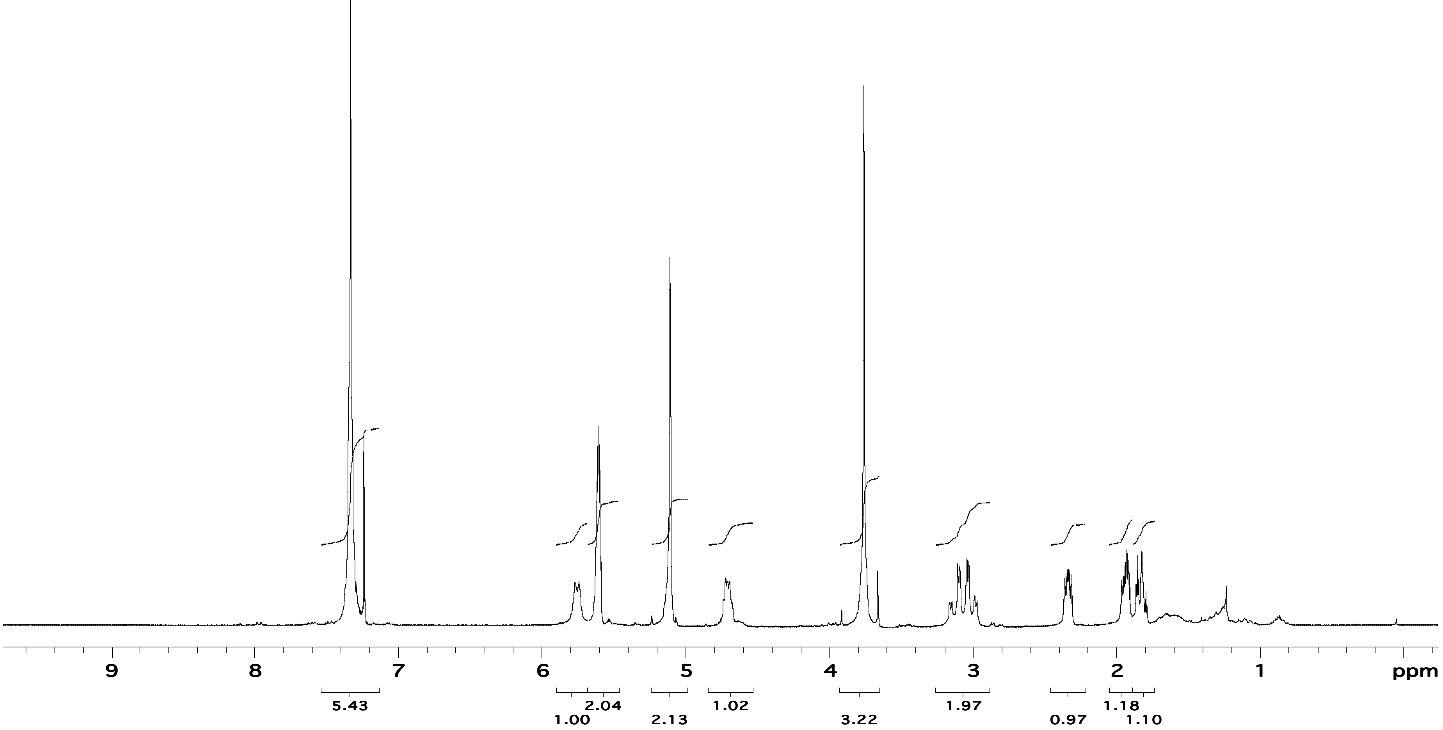
(100 MHz/CDCl$_3$)



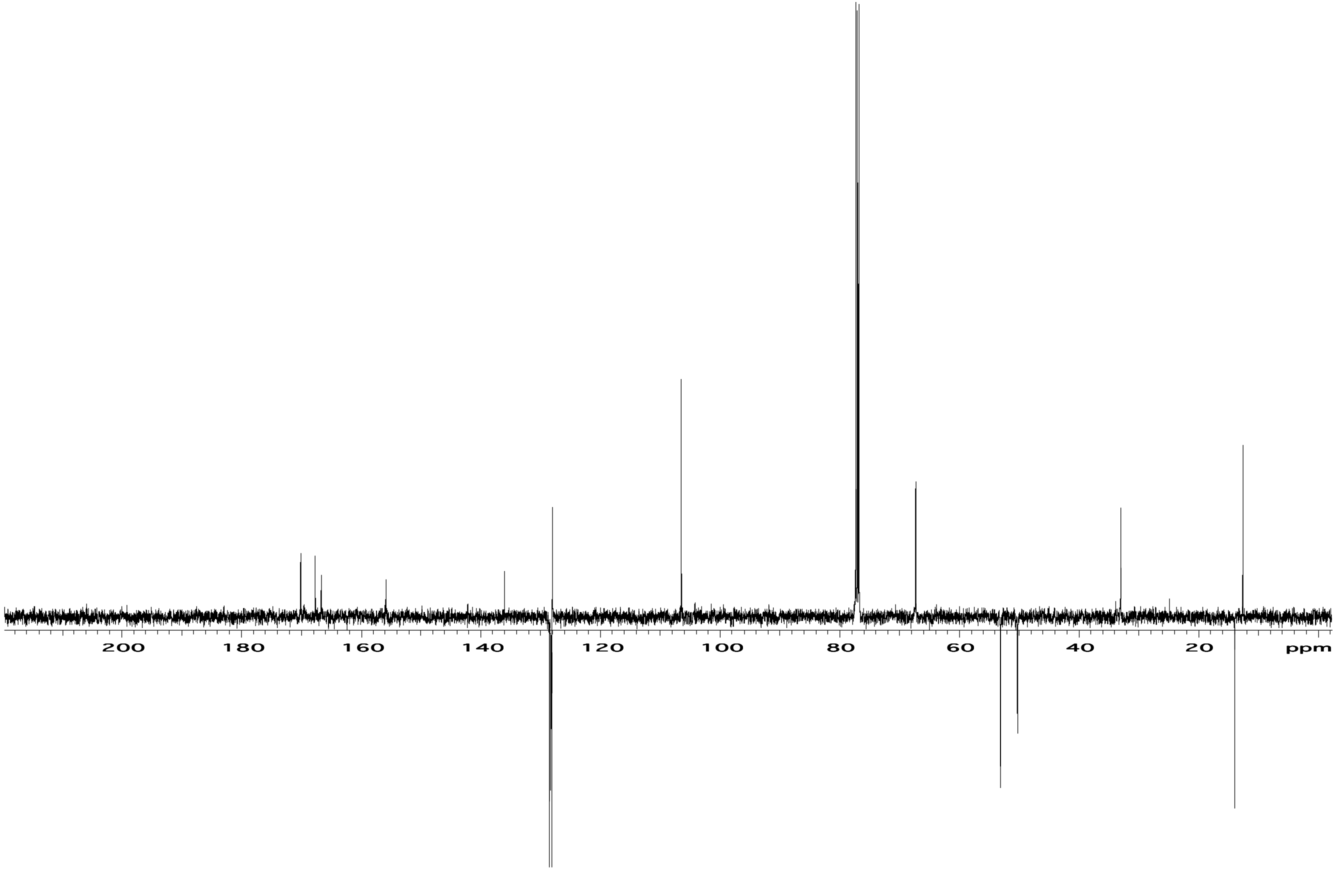


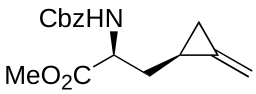
(**25**)

(300 MHz/CDCl$_3$)



(125 MHz/CDCl$_3$)





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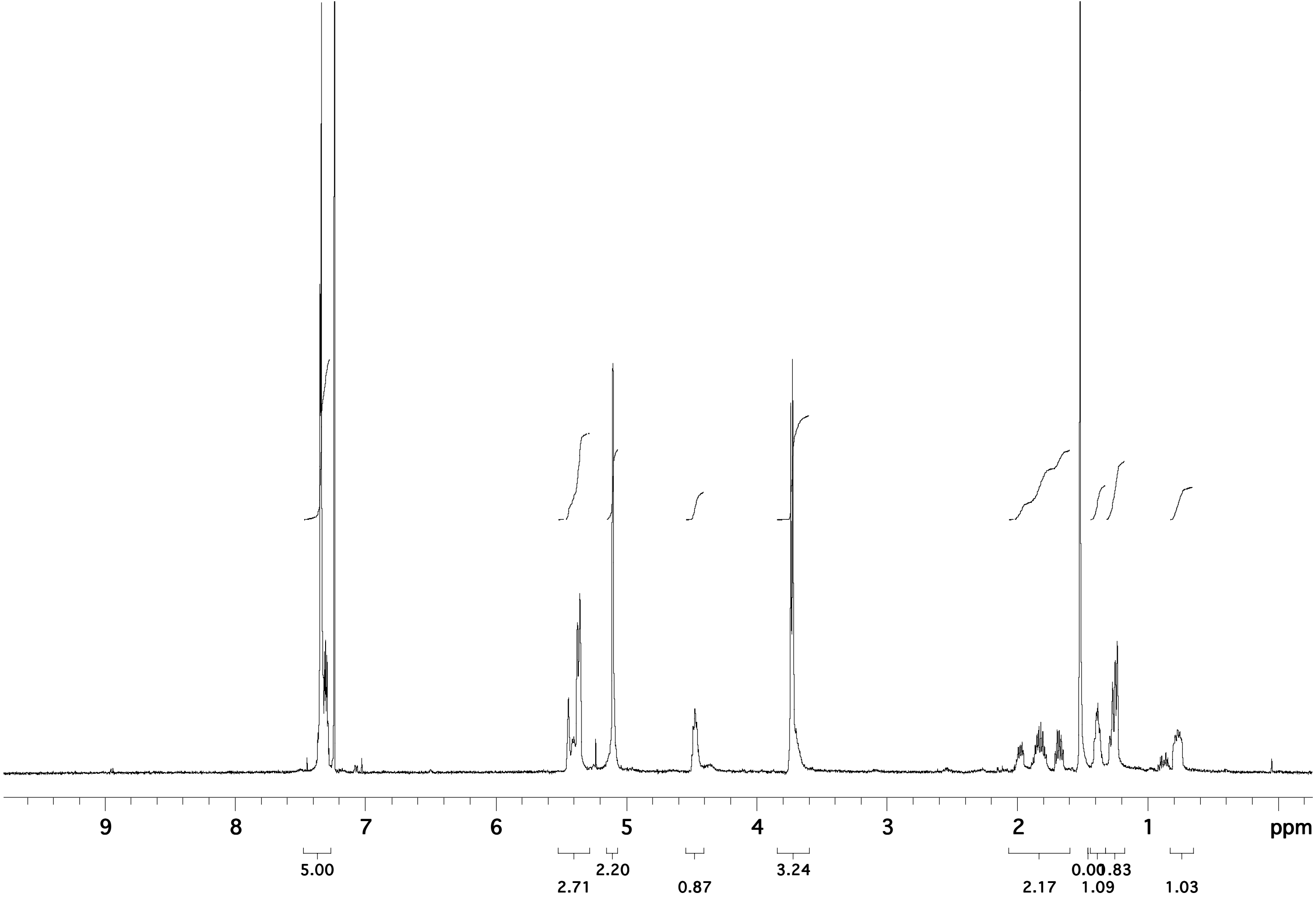
(500 MHz/CDCl$_3$)



(125 MHz/CDCl$_3$)