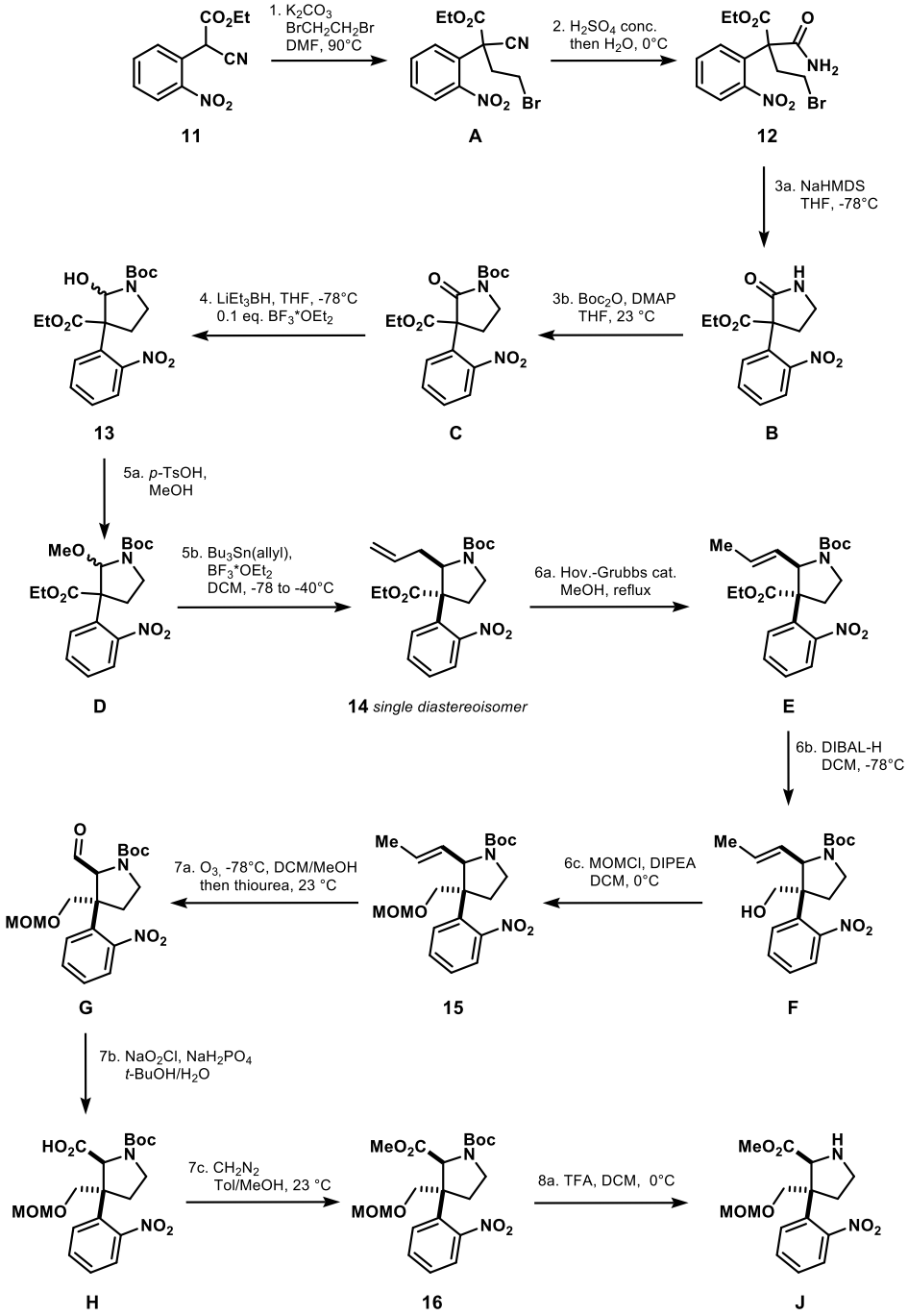
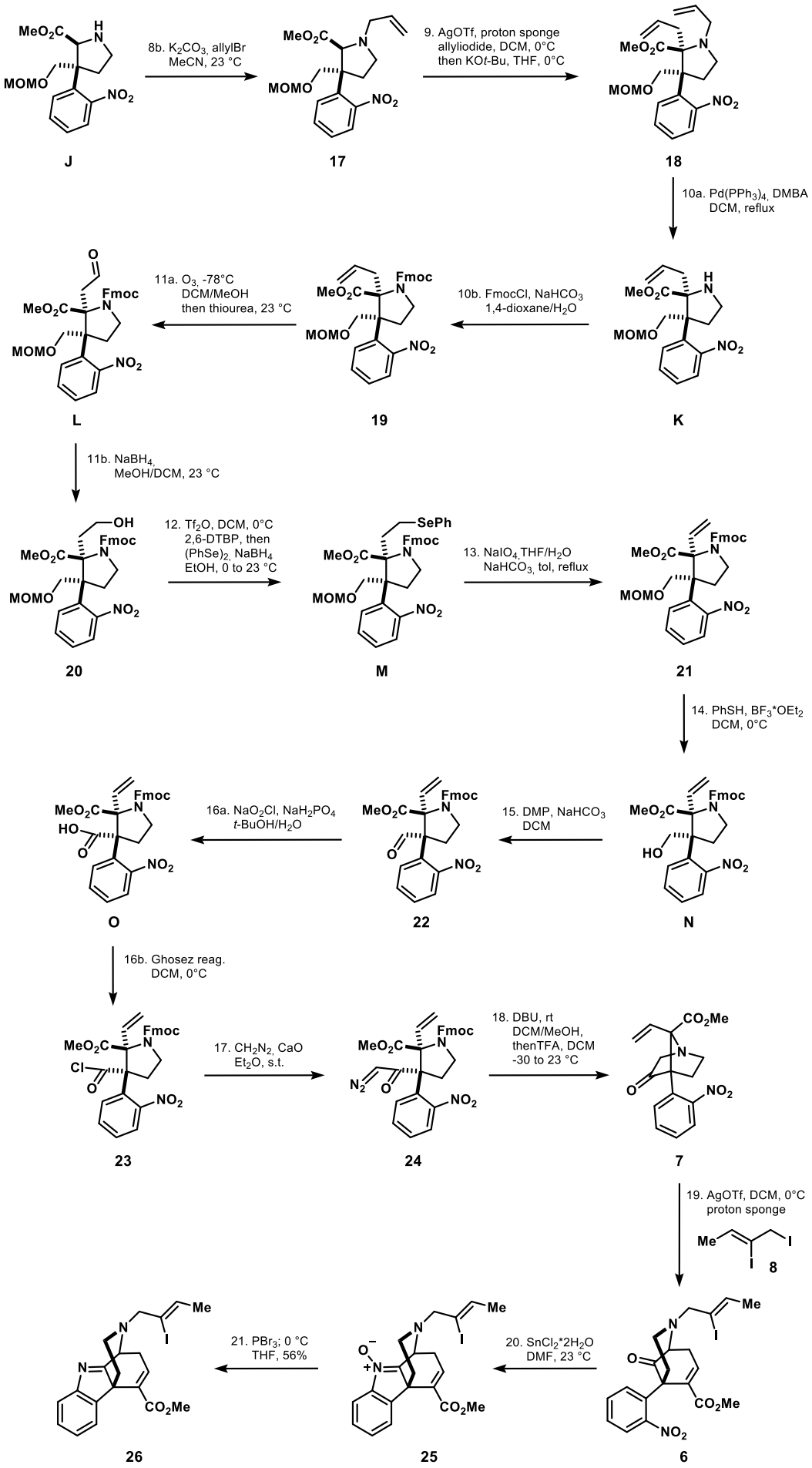
1. General

All reactions were carried out in oven- or flame-dried glassware. Anhydrous CH_2Cl_2 (DCM) was distilled from CaH_2 under argon atmosphere and andydrous THF was distilled from Na and benzophenone under argon atmosphere. Other anhydrous solvents (Et_2O, DMF, CH_3CN, toluene, methanol, ethanol) were obtained by filtration through drying columns on a Glass-Contour system. Reactions were magnetically stirred and monitored by thin layer chromatography (TLC) with silica gel 60-F254 plates. Flash column chromatography was performed with silica gel 60 Å from Acros. Preparative thin layer chromatography was performed with silica gel 60-F254 aluminum plates from Merck. Yields refer to chromatographically and spectroscopically pure compounds unless stated otherwise. NMR spectra were recorded on a 400 MHz spectrometer or a 600 MHz spectrometer with cryoplattform (Avance III 600) from Bruker. All NMR spectra were measured in $CDCl_3$ solution and referenced to the residual $CHCl_3$ signal (^1H, δ = 7.26 ppm, ^{13}C, δ = 77.16 ppm). All ^1H and ^{13}C shifts are given in ppm (s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet, b = broad signal). Assignments of proton resonance were confirmed, when possible, by correlated spectroscopy. High resolution mass spectra were measured on a Micromass LCT spectrometer via loop-mode injection from a Waters (Alliance 2695) HPLC system. Alternatively, a Micromass Q-TOF in combination with a Waters Aquity Ultraperformance LC system was employed. Ionization was achieved by ESI. Modes of ionization, calculated and found mass are given. IR spectra were measured with a Bruker Vector 22 FT-IR spectrometer or a PerkinElmer Spectrum 100 FT-IR spectrometer. Commercially available reagents were used as supplied unless stated otherwise. Eluents used for flash chromatography were distilled prior to use.

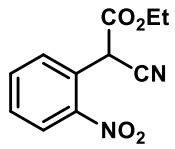
2. Experimental Procedures

Graphical overview:




8b. K2CO3, allylBr MeCN, 23 °C
9. AgOTf, proton sponge allyliodide, DCM, 0°C then KOt-Bu, THF, 0°C
10a. Pd(PPh3)4, DMBA DCM, reflux
10b. FmocCl, NaHCO3 1,4-dioxane/H2O
11a. O3, -78°C DCM/MeOH then thiourea, 23 °C
11b. NaBH4, MeOH/DCM, 23 °C
12. Tf2O, DCM, 0°C 2,6-DTBP, then (PhSe)2, NaBH4 EtOH, 0 to 23 °C
13. NaIO4 THF/H2O NaHCO3, tol, reflux
14. PhSH, BF3*OEt2 DCM, 0°C
15. DMP, NaHCO3 DCM
16a. NaO2Cl, NaH2PO4 t-BuOH/H2O
16b. Ghosez reag. DCM, 0°C
17. CH2N2, CaO Et2O, s.t.
18. DBU, rt DCM/MeOH, thenTFA, DCM -30 to 23 °C
19. AgOTf, DCM, 0°C proton sponge
20. SnCl2*2H2O DMF, 23 °C
21. PBr3; 0 °C THF, 56%
J
17
18
K
19
L
M
20
21
N
22
O
23
24
7
8
6
25
26

Ethyl 2-cyano-2-(2-nitrophenyl)acetate (11)



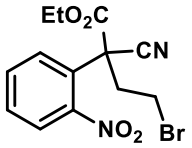
11

Sodium hydride (33.4 g, 834 mmol, 2.2 eq, 60% dispersion in mineral oil) was put in a 4 L two necked flask and 500 mL anhydrous THF were added. The mixture was cooled to 0 °C. A dropping funnel was connected to the flask and loaded with ethyl cyanoacetate (94.3 g, 89.0 mL, 834 mmol, 2.2 eq) dissolved in 300 mL anhydrous THF. The ethyl cyano acetate solution was added dropwise at 0 °C. After complete addition the mixture was allowed to warm up to 23 °C and stirred until no more gas evolution was observed. 2-Fluoro nitrobenzene (53.5 g, 40.0 mL, 379 mmol, 1 eq) dissolved in 300 mL anhydrous THF was put into the dropping funnel and added dropwise to the reaction mixture at 23 °C. After complete addition 1 L anhydrous THF was added and the mixture was heated to reflux for 7 h. During the reaction an intensive red colour appeared. After cooling to room temperature the mixture was concentrated under reduced pressure and poured onto water (5 L). The aqueous phase was extracted with Et_2O (2 x 1 L). The ether phase was disposed. The aqueous phase was acidified to pH=6 with 1 M HCl and extracted with DCM (3 x 1 L). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. Ethyl 2-cyano-2-(2-nitrophenyl)acetate (**11**, 65.7 g, 280 mmol, 74%) was obtained as a yellow viscous fluid. NMR data were in agreement with literature values and required no further characterization of **11**.[1]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.23 - 8.21 (m, 1H), 7.79 - 7.74 (m, 2H), 7.66 - 7.62 (m, 1H), 5.66 (s, 1H), 4.30 (q, J = 7.2 Hz, 2H), 1.32 (t, J = 7.0 Hz, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 163.6, 147.5, 134.7, 131.7, 130.9, 126.3, 125.4, 114.6, 64.0, 41.5, 13.9 ppm.

Ethyl 4-bromo-2-cyano-2-(2-nitrophenyl)butanoate (A)



A

Ethyl 2-cyano-2-(2-nitrophenyl)acetate (**11**, 65.0 g, 278 mmol, 1 eq) dissolved in 300 mL anhydrous DMF was put in a 1 L flask. K_2CO_3 (46.0 g, 333 mmol, 1.2 eq) and 1,2-dibromoethane (120 mL, 261 g, 1.39 mol, 5 eq) were sequentially added. The solution was heated to 90 °C for 5 h. After cooling to room temperature the mixture was poured onto water (3 L). The aqueous phase was extracted with Et_2O (3 x 1 L). The combined organic phases were dried over $MgSO_4$, filtrated und concentrated under reduced pressure. MeOH was added until crystallization of the product was observed. After storage in the frigde over night the precipitate was collected and washed with MeOH (200 mL). Ethyl 4-bromo-2-cyano-2-(2-nitrophenyl)butanoate (**A**, 67.3 g, 197 mmol, 71%) was obtained as colourless crystals.

MP: 85 °C

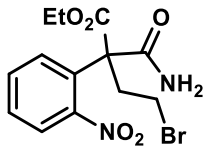
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.17 (dd, J_1 = 7.9 Hz, J_2 = 1.4 Hz, 1H), 7.85 (dd, J_1 = 8.0 Hz, J_2 = 1.5 Hz, 1H), 7.80 - 7.76 (m, 1H), 7.65 (ddd, J_1 = 8.1 Hz, J_2 = 7.5 Hz, J_3 = 1.5 Hz, 1H), 4.30 (q, J = 7.0 Hz, 2H), 3.56 (ddd, J_1 = 11.0 Hz, J_2 = 10.2 Hz, J_3 = 5.4 Hz, 1H), 3.34 (ddd, J_1 = 11.0 Hz, J_2 = 10.2 Hz, J_3 = 5.2 Hz, 1H), 3.16 (ddd, J_1 = 14.2 Hz, J_2 = 11.1 Hz, J_3 = 5.5 Hz, 1H), 2.97 (ddd, J_1 = 14.2 Hz, J_2 = 11.1 Hz, J_3 = 5.3 Hz, 1H), 1.29 (t, J = 7.2 Hz, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 165.1, 147.8, 134.3, 130.7, 130.4, 128.4, 126.9, 116.8, 64.2, 52.8, 39.1, 25.7, 13.9 ppm.

IR (neat): 3001, 2987, 2941, 2364, 1735, 1604, 1577, 1527, 1479, 1442, 1396, 1354, 1300, 1278, 1251, 1226, 1176, 1153, 1112, 1085, 1070, 1051, 1029, 1008, 931, 850, 808, 788, 775, 759, 738, 705, 694, 669, 644, 590, 561, 536, 474, 437, 416 cm^{-1}.

CHN: Anal. calc. for $C_{13}H_{13}BrN_2O_4$: C, 45.77; H, 3.84; N, 8.21; found: C, 45.91; H, 3.88; N, 8.09.

Ethyl 4-bromo-2-carbamoyl-2-(2-nitrophenyl)butanoate (12)



12

Ethyl 4-bromo-2-cyano-2-(2-nitrophenyl)butanoate (**A**, 67.0 g, 196 mmol, 1 eq) was milled by a mortar and dissolved in concentrated sulfuric acid (2 L). After complete dissolution the mixture was transferred to a dropping funnel. A 5 L Erlenmeyer flask was packed with ice and water (2 L) and positioned in an ice bath. The reaction mixture was added dropwise under stirring so that the inner temperature did not rise above 10 °C. After complete addition the precipitate was collected and washed with water (1 L). The precipitate was dissolved in DCM (1 L), transferred to a seperation funnel and washed with saturated NaCl solution (1 L). The organic phase was dried over $MgSO_4$, filtrated and concentrated under reduced pressure. Ethyl 4-bromo-2-carbamoyl-2-(2-nitrophenyl)butanoate (**12**, 67.6 g, 188 mmol, 96%) was obtained as a slightly brown amorphous solid.

MP: 115 °C

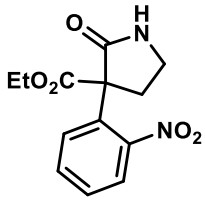
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.11 (dd, J_1 = 8.5 Hz, J_2 = 1.3 Hz, 1H), 8.02 (bs, 1H), 7.73 - 7.69 (m, 1H), 7.55 - 7.50 (m, 2H), 5.81 (bs, 1H), 4.12 (dq, J_1 = 10.8 Hz, J_2 = 7.2 Hz, 1H), 4.08 (dq, J_1 = 10.8, J_2 = 7.1 Hz, 1H), 3.43 - 3.30 (m, 2H), 3.02 (ddd, J_1 = 14.0 Hz, J_2 = 11.5 Hz, J_3 = 5.1 Hz, 1H), 2.93 (ddd, J_1 = 14.1 Hz, J_2 = 11.7 Hz, J_3 = 5.9 Hz, 1H), 1.10 (t, J = 7.2 Hz, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.8, 170.2, 148.5, 133.7, 132.6, 129.5, 129.0, 126.1, 62.8, 61.8, 39.8, 26.7, 13.7 ppm.

IR (neat): 3390, 3263, 3170, 2987, 2358, 1737, 1714, 1681, 1577, 1523, 1477, 1460, 1442, 1354, 1340, 1301, 1251, 1213, 1178, 1153, 1112, 1082, 1062, 1031, 1012, 977, 960, 914, 854, 808, 788, 738, 705, 690, 669, 655, 623, 590, 536, 516, 472, 433, 416 cm^{-1}.

HRMS (ESI): calc. for $C_{13}H_{15}N_2O_5Br^+$: 359.0243, found: 359.0248

Ethyl 3-(2-nitrophenyl)-2-oxopyrroldine-3-carboxylate (B)



B

Ethyl 4-bromo-2-carbamoyl-2-(2-nitrophenyl)butanoate (**12**, 67.0 g, 187 mmol, 1 eq) was dissolved in anhydrous THF (9 L) and cooled to -78°C. Sodium bis(trimethylsilyl)amide (94.2 mL, 188 mmol, 1.01 eq, 2 M solution in THF) dissolved in anhydrous THF (1 L) was put to a dropping funnel and added dropwise to the mixture at -78°C. After complete addition the mixture was poured onto saturated NH_4Cl solution (10 L) and afterwards allowed to warm to 23 °C. The organic phase was separated and the aqueous phase extracted with Et_2O (2 x 2 L). The combined organic phases were washed with saturated NaCl solution (5 L), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. An analytical sample was purified by flash column chromatography (SiO_2, PE/EtOAc = 2:1 to 1:1) to obtain lactam **B** as a colourless solid.

MP: 116 °C

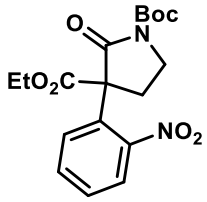
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.08 (dd, J_1 = 8.2 Hz, J_2 = 1.4 Hz, 1H), 7.67 - 7.62 (m, 2H), 7.53 (dd, J_1 = 7.9 Hz, J_2 = 1.4 Hz, 1H), 7.51 - 7.47 (m, 1H), 4.21 (dq, J_1 = 10.6 Hz, J_2 = 7.2 Hz, 1H), 4.15 (dq, J_1 = 10.8 Hz, J_2 = 7.1 Hz, 1H), 3.64 - 3.51(m, 2H), 3.35 - 3.30 (m, 1H), 2.40 - 2.33 (m, 1H), 1.20 (t, J = 7.2 Hz, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 174.6, 169.2, 148.5, 134.4, 134.0, 130.1, 128.8, 126.0, 62.6, 61.5, 39.9, 35.4, 13.9 ppm.

IR (neat): 3196, 3111, 3072, 2989, 2885, 2360, 1734, 1672, 1610, 1577, 1521, 1458, 1350, 1317, 1284, 1226, 1089, 1051, 1014, 954, 850, 769, 752, 707, 661, 653, 603, 569, 536, 507, 416 cm^{-1}.

HRMS (ESI): calc. for $C_{13}H_{14}N_2O_5Na^+$: 301.0800, found: 301.0801

1-(*tert*-Butyl) 3-ethyl 3-(2-nitrophenyl)-2-oxopyrrolidine-1,3-dicarboxylate (C)



C

Crude material from lactam **B** was dissolved in anhydrous THF (1 L). 4-Dimethylaminopyridin (1.14 g, 9.33 mmol, 0.05 eq) and di-*tert*-butyl dicarbonate (48.9 g, 224 mmol, 1.2 eq) were sequentially added and the resulting mixture was stirred at 23 °C for 24 h. The solvent was concentrated under reduced pressure and the crude material was purified by flash column chromatography (SiO_2, PE/EtOAc = 3:1 to 2:1) to obtain 1-(*tert*-butyl) 3-ethyl 3-(2-nitrophenyl)-2-oxopyrrolidine-1,3-dicarboxylate (**C**, 53.0 g, 140 mmol, 75%) as a colourless solid.

MP: 102 °C.

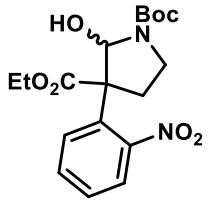
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.09 (dd, J_1 = 8.0 Hz, J_2 = 1.5 Hz, 1H), 7.63 (ddd, J_1 = 7.7 Hz, J_2 = 7.7 Hz, J_3 = 1.5 Hz, 1H), 7.50 (ddd, J_1 = 8.1 Hz, J_2 = 7.6 Hz, J_3 = 1.3 Hz, 1H), 7.41 (dd, J_1 = 7.9 Hz, J_2 = 1.4 Hz, 1H), 4.17 (q, J = 7.2 Hz, 2H), 4.00 (ddd, J_1 = 10.6 Hz, J_2 = 8.5 Hz, J_3 = 5.5 Hz, 1H), 3.64 (ddd, J_1 = 10.6 Hz, J_2 = 8.4 Hz, J_3 = 6.3 Hz, 1H), 3.39 (ddd, J_1 = 13.7 Hz, J_2 = 8.5 Hz, J_3 = 6.1 Hz, 1H), 2.27 (ddd, J_1 = 13.6 Hz, J_2 = 8.1 Hz, J_3 = 5.4 Hz, 1H), 1.57 (s, 9H), 1.19 (t, J = 7.2 Hz, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.0, 168.2, 149.8, 148.4, 134.0, 133.9, 130.0, 129.0, 126.2, 84.1, 63.8, 62.9, 44.0, 31.6, 28.1, 13.9 ppm.

IR (neat): 2981, 2081, 1783, 1726, 1608, 1575, 1529, 1479, 1451, 1365, 1293, 1258, 1229, 1147, 1101, 1069, 1009, 922, 850, 780, 738, 704, 674 cm^{-1}.

HRMS (ESI): calc. for $C_{18}H_{22}N_2O_7Na^+$: 401.1325, found: 401.1322

1-(*tert*-Butyl) 3-ethyl 2-hydroxy-3-(2-nitrophenyl)pyrrolidine-1,3-dicarboxylate (13)



13

1-(*tert*-Butyl) 3-ethyl 3-(2-nitrophenyl)-2-oxopyrrolidine-1,3-dicarboxylate (**C**, 49.6 g, 131 mmol, 1 eq) was dissolved in anhydrous THF (1.5 L) and cooled to -78 °C. Boron trifluoride diethyl etherate (3.50 mL, 13.1 mmol, 0.1 eq, 48% solution) and lithium triethylborohydride (80.8 mL, 137 mmol, 1.05 eq, 1.7 M solution in THF) were rapidly added. The resulting mixture was stirred at -78°C for 30 min, then poured onto saturated NH_4Cl solution (1 L) and allowed to warm to 23 °C. The aqueous phase was extracted with Et_2O (2 x 500 mL) and the combined organic phases were washed with saturated NaCl solution (1 L), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The resulting colourless solid was collected and washed with EtOAc (31.4 g, 82.5 mmol, 0.63 eq). The residue was purified by flash column chromatography (SiO_2, PE/EtOAc = 3:1 to 2:1) to obtain the title compound (13.0 g, 34.1 mmol, 0.26 eq). In total, 1-(*tert*-butyl) 3-ethyl 2-hydroxy-3-(2-nitrophenyl)pyrrolidine-1,3-dicarboxylate (**13**, 44.4 g, 117 mmol, 89%) was obtained as a colourless solid.

MP: 148 °C

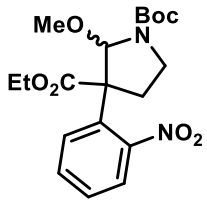
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.99 - 7.89 (m, 1H), 7.60 (dd, J_1 = 7.9 Hz, J_2 = 7.9 Hz, 1H), 7.50 - 7.30 (m, 2H), 5.85 - 5.66 (m, 1H), 4.35 - 3.71 (m, 4H), 3.28 - 3.09 (m, 2H), 2.40 - 2.15 (m, 1H), 1.48 (s, 9H), 1.19 (t, J = 7.2 Hz, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$, rotamers): δ = 170.3, 169.6, 154.8, 153.2, 149.0, 148.7, 134.4, 134.0, 133.5, 133.2, 128.8, 128.6, 128.4, 127.9, 126.1, 125.8, 86.3, 86.1, 81.5, 81.3, 62.1, 61.9, 60.6, 60.0, 44.3, 43.7, 31.7, 31.3, 28.5, 14.0 ppm.

IR (neat): 3435 (bs), 2980, 2362, 1679, 1530, 1479, 1390, 1363, 1298, 1246, 1168, 1134, 1068, 893, 854, 781, 742, 668 cm^{-1}.

HRMS (ESI): calc. for $C_{18}H_{24}N_2O_7Na^+$: 403.1481, found: 403.1477

1-(*tert*-Butyl) 3-ethyl 2-methoxy-3-(2-nitrophenyl)pyrrolidine-1,3-dicarboxylate (D)

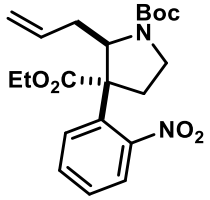


D

1-(*tert*-Butyl) 3-ethyl 2-hydroxy-3-(2-nitrophenyl)pyrrolidine-1,3-dicarboxylate (**13**, 44.0 g, 116 mmol, 1 eq) was dissolved in MeOH (500 mL) and *p*-toluenesulfonic acid monohydrate (1.10 g, 5.80 mmol, 0.05 eq) was added. The mixture was stirred at 23 °C for 14 h, then poured onto saturated $NaHCO_3$ solution (500 mL) and extracted with Et_2O (3 x 500 mL). The combined organic phases were washed with saturated NaCl solution (500 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. An analytical sample was purified by flash column chromatography (SiO_2, PE/EtOAc = 3:1 to 2:1) to obtain 1-(*tert*-butyl) 3-ethyl 2-methoxy-3-(2-nitrophenyl)pyrrolidine-1,3-dicarboxylate (**D**) as a colourless viscous fluid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.75 - 7.73 (m, 1H), 7.59 - 7.48 (m, 2H), 7.41 - 7.37 (m, 1H), 5.59 - 5.48 (m, 1H), 4.18 - 4.11 (m, 2H), 3.54 - 3.37 (m, 2H), 3.17 - 3.12 (m, 3H), 2.72 - 2.56 (m, 2H), 1.51 - 1.48 (m, 9H), 1.19 (t, J = 7.0 Hz, 3H) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$, rotamers): δ = 171.5, 171.3, 155.6, 155.3, 149.5, 149.3, 133.5, 132.6, 132.4, 131.3, 131.1, 128.1, 124.2, 89.6, 89.6, 80.8, 80.1, 61.8, 60.7, 60.0, 56.3, 55.9, 44.2, 43.6, 33.9, 33.4, 28.4, 14.1, 14.0 ppm.
IR (neat): 2978, 2933, 2900, 2835, 1732, 1697, 1608, 1577, 1525, 1477, 1456, 1363, 1309, 1247, 1228, 1168, 1153, 1128, 1093, 1072, 1022, 991, 979, 925, 896, 852, 781, 769, 731, 717, 690, 636, 599, 538, 511, 487, 459 cm^{-1}.
HRMS (ESI): calc. for $C_{19}H_{26}N_2O_7Na^+$: 417.1638, found: 417.1643

1-(*tert*-Butyl) 3-ethyl 2-allyl-3-(2-nitrophenyl)pyrrolidine-1,3-dicarboxylate (14)



14

Crude material from **D** was dissolved in anhydrous DCM (600 mL) and cooled to –78 °C. Allyltributylstannane (53.4 mL, 57.6 g, 174 mmol, 1.5 eq) and boron trifluoride diethyl etherate (33.8 mL, 128 mmol, 1.1 eq, 48% solution) were added. The resulting mixture was allowed to warm to -40 °C over a period of 4 h, then poured onto saturated $NaHCO_3$ solution (1 L) and allowed to warm to 23 °C. After seperation of the organic phase the aqueous phase was extracted with DCM (2 x 500 mL) and the combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO_2, PE/EtOAc = 5:1 to 3:1 to 2:1 to 1:1) to obtain 1-(*tert*-butyl) 3-ethyl 2-allyl-3-(2-nitrophenyl)pyrrolidine-1,3-dicarboxylate (**14**, 42.5 g, 105 mmol, 80%) as a colourless foam.

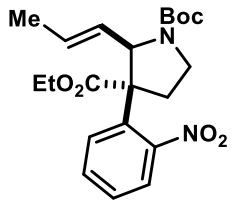
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.92 - 7.90 (m, 1H), 7.65 - 7.57 (m, 2H), 7.51 - 7.46 (m, 1H), 5.57 - 5.46 (m, 1H), 4.86 - 4.68 (m, 2H), 4.51 - 4.38 (m, 1H), 4.18 - 4.10 (m, 2H), 3.55 - 3.49 (m, 1H), 3.45 - 3.33 (m, 1H), 2.83 - 2.75 (m, 1H), 2.42 - 2.32 (m, 1H), 2.22 - 1.96 (m, 1H), 1.79 - 1.69 (m, 1H), 1.50 - 1.48 (m, 9H), 1.19 (t, J = 7.2 Hz, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$, rotamers): δ = 173.0, 172.8, 155.3, 154.6, 149.7, 149.5, 134.3, 134.2, 133.1, 132.9, 132.9, 130.7, 130.6, 128.9, 128.9, 125.4, 117.0, 116.8, 80.0, 79.4, 61.8, 61.7, 60.2, 60.1, 59.4, 58.7, 43.9, 43.4, 37.8, 37.2, 33.6, 33.0, 28.6, 14.1, 14.1 ppm.

IR (neat): 2977, 2926, 1785, 1731, 1693, 1530, 1455, 1389, 1364, 1300, 1234, 1174, 1024, 917, 855, 780 cm^{-1}.

HRMS (ESI): calc. for $C_{21}H_{28}N_2O_6Na^+$: 427.1845, found: 427.1848

1-(*tert*-Butyl) 3-ethyl 3-(2-nitrophenyl)-2-((*E*)-prop-1-en-1-yl)pyrrolidine-1,3-dicarboxylate (E)



E

1-(*tert*-Butyl) 3-ethyl 2-allyl-3-(2-nitrophenyl)pyrrolidine-1,3-dicarboxylate (**14**, 33.6 g, 83.1 mmol, 1 eq) was dissolved in anhydrous MeOH (800 mL). Hoveyda-Grubbs catalyst 2nd generation (521 mg, 830 μmol, 0.01 eq) was added and the mixture was heated to reflux for 4 h. Additional Hoveyda-Grubbs catalyst 2nd generation (521 mg, 830 μmol, 0.01 eq) was added and the mixture was heated to reflux for 8 h. After cooling to 23 °C, the solvent was removed under reduced pressure. An analytical sample was purified by flash column chromatography (SiO_2, PE/EtOAc = 3:1 to 2:1) to obtain 1-(*tert*-butyl) 3-ethyl 3-(2-nitrophenyl)-2-((*E*)-prop-1-en-1-yl)pyrrolidine-1,3-dicarboxylate (**E**) as a colourless viscous fluid.

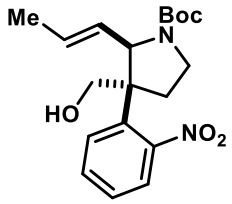
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.88 (dd, J_1 = 8.3 Hz, J_2 = 1.5 Hz, 1H), 7.64 - 7.58 (m, 1H), 7.55 - 7.50 (m, 1H), 7.44 (dd, J_1 = 7.7 Hz, J_2 = 7.7 Hz, 1H), 5.56 - 5.38 (m, 1H), 5.09 - 4.91 (m, 1H), 4.75 - 4.56 (m, 1H), 4.20 . 4.14 (m, 2H), 3.62 - 3.52 (m, 1H), 3.41 - 3.34 (m, 1H), 2.68 - 2.60 (m, 1H), 2.52 - 2.43 (m, 1H), 1.46 - 1.44 (m, 9H), 1.39 (dd, J_1 = 6.5 Hz, J_2 = 1.0 Hz, 3H), 1.20 (t, J = 7.0 Hz, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$, rotamers): δ = 172.9, 172.8, 155.0, 154.3, 149.5, 149.3, 133.9, 133.8, 133.3, 133.0, 130.6, 130.6, 130.1, 129.9, 128.6, 127.0, 126.9, 125.3, 79.7, 79.4, 63.0, 62.8, 61.8, 61.7, 59.5, 58.8, 44.0, 43.3, 33.8, 33.4, 28.7, 28.6, 17.7, 17.5, 14.1 ppm.

IR (film): 2976, 2933, 2893, 1732, 1689, 1608, 1575, 1527, 1477, 1454, 1388, 1363, 1352, 1303, 1259, 1217, 1176, 1122, 1082, 1024, 962, 921, 896, 852, 785, 767, 731, 709, 692, 636 cm^{-1}.

HRMS (ESI): calc. for $C_{21}H_{28}N_2O_6Na^+$: 427.1845, found: 427.1845

***tert*-Butyl 3-(hydroxymethyl)-3-(2-nitrophenyl)-2-((*E*)-prop-1-en-1-yl)pyrrolidine-1-carboxylate (F)**



F

Crude ethyl ester **E** was dissolved in anhydrous DCM (1 L) and cooled to -78 °C. Diisobutylaluminium hydride (498 mL, 498 mmol, 6 eq, 1 M solution in hexane) was transferred to a dropping funnel and added dropwise over a period of 2 h. The mixture was poured onto a saturated Na/K-tartrate solution (2 L) and was allowed to warm to 23 °C. Et_2O (2 L) was added and the resulting mixture was vigourously stirred for 48 h at 23 °C. The organic phase was separated and the aqueous phase extracted with Et_2O (2 x 500 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. An analytical sample was purified by flash column chromatography (SiO_2, PE/EtOAc = 2:1 to 1:1) to obtain *tert*-butyl 3-(hydroxymethyl)-3-(2-nitrophenyl)-2-((*E*)-prop-1-en-1-yl)pyrrolidine-1-carboxylate (**F**) as a colourless viscous fluid.

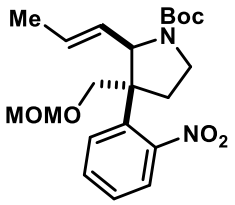
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.65 - 7.49 (m, 2H), 7.43 - 7.35 (m, 2H), 5.65 - 5.48 (m, 1H), 4.92 - 4.81 (m, 1H), 4.69 - 4.47 (m, 1H), 4.23 - 4.07 (m, 1H), 3.68 (d, J = 10.9 Hz, 1H), 3.53 - 3.38 (m, 2H), 2.70 - 2.54 (m, 1H), 2.17 - 2.08 (m, 1H), 1.95 - 1.70 (m, 1H), 1.49 (dd, J_1 = 6.7 Hz, J_2 = 1.5 Hz, 3H), 1.45 - 1.43 (m, 9H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$, rotamers): δ = 154.7, 154.2, 151.6, 151.3, 134.7, 134.1, 133.6, 133.4, 131.7, 131.3, 131.2, 130.6, 128.1, 128.0, 126.1, 126.1, 125.3, 124.8, 79.9, 79.7, 66.1, 65.5, 62.8, 62.5, 56.0, 55.2, 43.2, 42.5, 29.2, 28.7, 24.0, 18.0, 17.8 ppm.

IR (film): 3419 (bs), 2976, 2933, 2891, 1666, 1604, 1573, 1527, 1477, 1454, 1398, 1365, 1354, 1292, 1257, 1172, 1153, 1126, 1072, 1043, 962, 902, 848, 781, 734, 711, 682, 644 cm^{-1}.

HRMS (ESI): calc. $C_{19}H_{27}N_2O_5^+$: 363.1920, found: 363.1920

1-*tert*-Butyl 3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)-2-((*E*)-prop-1-en-1-yl)pyrrolidine-1-carboxylate (15)



15

Crude alcohol **F** was dissolved in anhydrous DCM (500 mL) and cooled to 0 °C. *N*,*N*-Diisopropylethylamine (174 mL, 128 g, 997 mmol, 12 eq) and chloromethyl methyl ether (63.1 mL, 66.9 g, 830 mmol, 10 eq) were sequentially added. The mixture was stirred for 20 h and allowed to warm to 23 °C during this time. Additional *N*,*N*-diisopropylethylamine (58.1 mL, 43.0 g, 332 mmol, 4 eq) and chloromethyl methyl ether (18.9 mL, 20.0 g, 249 mmol, 3 eq) were added at 23 °C and the mixture was stirred for 18 h. Water (1 L) was added and the organic phase was seperated. The aqueous phase was extracted with DCM (2 x 300 mL), the combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO_2, PE/EtOAc = 3:1 to 2:1 to 1:1) to obtain *tert*-butyl 3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)-2-((*E*)-prop-1-en-1-yl)pyrrolidine-1-carboxylate (**15**, 27.4 g, 67.4 mmol, 81%) as a colourless foam.

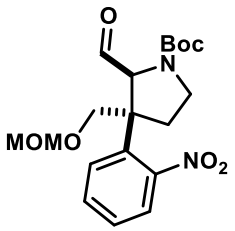
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.65 - 7.54 (m, 1H), 7.52 - 7.41 (m, 2H), 7.39 - 7.33 (m, 1H), 5.65 - 5.48 (m, 1H), 4.94 - 4.82 (m, 1H), 4.80 - 4.53 (m, 1H), 4.49 - 4.42 (m, 2H), 4.13 - 3.97 (m, 1H), 3.65 - 3.62 (m, 1H), 3.55 - 3.40 (m, 2H), 3.15 - 3.14 (m, 3H), 2.70 - 2.49 (m, 1H), 2.23 - 2.13 (m, 1H), 1.49 (dd, J_1 = 6.6 Hz, J_2 = 1.5 Hz, 3H), 1.46 - 1.44 (m, 9H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$, rotamers): δ = 154.6, 153.9, 151.3, 151.0, 135.2, 134.4, 133.8, 133.5, 131.4, 130.9, 130.9, 130.2, 127.9, 127.8, 126.3, 126.1, 125.1, 124.5, 96.5, 79.7, 79.5, 70.1, 69.8, 63.0, 62.5, 55.3, 55.2, 54.4, 53.5, 43.2, 42.5, 29.7, 28.7, 18.0, 17.8 ppm.

IR (film): 2974, 2931, 2887, 2823, 1691, 1529, 1477, 1454, 1394, 1363, 1292, 1255, 1174, 1149, 1111, 1045, 960, 918, 848, 781, 732, 711, 684 cm^{-1}.

HRMS (ESI): calc. for $C_{21}H_{30}N_2O_6Na^+$: 429.2002, found: 429.2002

***tert*-Butyl 2-formyl-3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)pyrrolidine-1-carboxylate (G)**



G

tert-Butyl 3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)-2-((*E*)-prop-1-en-1-yl)pyrrolidine-1-carboxylate (**15**, 24.0 g, 59.0 mmol, 1 eq) was dissolved in DCM/MeOH = 4:1 (500 mL) and cooled to -78 °C. Ozone was passed through the solution until its colour stayed blue. Afterwards oxygen was passed through the solution until its colour turned to slightly yellow. Thiourea (4.50 g, 59.0 mmol, 1 eq) was added and the mixture was allowed to warm up to 23 °C and stirred for 1 h. The resulting mixture was poured onto water (1 L). After seperation of the phases the aqueous phase was extracted with DCM (2 x 300 mL). The combined organic phases were washed with saturated NaCl solution (500 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. An analytical sample was purified by flash column chromatography (SiO_2, PE/EtOAc = 3:1 to 2:1) to obtain aldehyde **G** as a colourless foam.

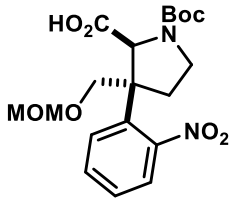
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.58 - 9.48 (m, 1H), 7.61 - 7.38 (m, 4H), 5.11 - 4.90 (m, 1H), 4.47 - 4.45 (m, 2H), 3.82 - 3.77 (m, 1H), 3.74 - 3.58 (m, 2H), 3.52 - 3.41 (m, 1H), 3.15 - 3.14 (m, 3H), 2.45 - 2.31 (m, 2H), 1.46 - 1.42 (m, 9H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$, rotamers): δ = 199.2, 198.3, 154.4, 154.0, 151.2, 151.1, 132.0, 131.9, 131.8, 131.7, 131.6, 128.8, 128.7, 125.0, 124.8, 96.4, 80.8, 80.6, 70.0, 58.3, 67.8, 55.4, 55.4, 52.9, 52.0, 43.8, 43.3, 30.1, 29.7, 28.5, 28.4 ppm.

IR (film): 2976, 2935, 2889, 2825, 1732, 1691, 1604, 1573, 1529, 1477, 1456, 1390, 1365, 1257, 1149, 1136, 1109, 1043, 918, 848, 773, 734, 680, 636, 542, 416, 403 cm^{-1}.

HRMS (ESI): calc. for $C_{19}H_{27}N_2O_7^+$: 395.1818, found: 395.1818

1-(*tert*-Butoxycarbonyl)-3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)-pyrrolidine-2-carboxylic acid (H)



H

Crude aldehyde **G** was dissolved in *t*BuOH (200 mL) and 2-methyl 2-butene (50 mL) was added. NaO_2Cl (66.7 g, 590 mmol, 10 eq, 80%) and NaH_2PO_4 (66.7 g) were dissolved in water (200 mL) and the resulting solution was added to the first mixture under cooling with an ice bath. The reaction mixture was vigourously stirred for 15 h and allowed to warm to 23 °C during this time. The mixture was poured onto water (1 L) and extracted with Et_2O (500 mL). 1 M HCl solution (200 mL) was added and the aqoueous phase was extracted with Et_2O (2 x 200 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. An analytical sample was purified by acid/base wash (1 M NaOH/Et_2O and 1 M HCl/Et_2O) to obtain carboxylic acid **H** as a colourless solid.

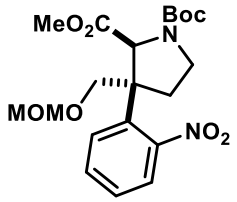
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.68 (bs, 1H), 7.62 - 7.53 (m, 1H), 7.51 - 7.43 (m, 2H), 7.39 - 7.34 (m, 1H), 5.00 - 4.84 (m, 1H), 4.45 (s, 2H), 3.90 - 3.73 (s, 1H), 3.72 - 3.54 (m, 2H), 3.50 - 3.40 (m, 1H), 3.14 - 3.13 (m, 3H), 2.66 - 2.46 (m, 1H), 2.39 - 2.33 (m, 1H), 1.45 - 1.36 (m, 9H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$, rotamers): δ = 175.4, 173.1, 155.5, 154.1, 150.6, 150.5, 133.0, 132.7, 132.6, 132.3, 131.3, 131.2, 128.5, 128.2, 124.9, 124.6, 96.5, 96.4, 81.6, 81.1, 70.0, 69.9, 64.1, 64.0, 55.4, 55.3, 54.7, 53.1, 44.3, 44.0, 29.9, 28.9, 28.5, 28.4 ppm.

IR (film): 3062 (bs), 2976, 2935, 2893, 1735, 1697, 1647, 1575, 1531, 1477, 1415, 1392, 1367, 1350, 1244, 1170, 1151, 1111, 1043, 916, 850, 777, 756, 731, 680, 559, 416, 405 cm^{-1}.

HRMS (ESI): calc. for $C_{19}H_{27}N_2O_8^+$: 411.1767, found: 411.1773

1-(*tert*-Butyl) 2-methyl 3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)-pyrrolidine-1,2-dicarboxylate (16)



16

Crude carboxylic acid **H** was dissolved in PhMe/MeOH = 3:1 (400 mL). A freshly prepared ethereal diazomethane solution[2] starting from *N*-methyl-*N*-nitrotoluene-*p*-sulfonamide (37.9 g, 177 mmol, 3 eq) was transferred to the solution. The resulting mixture was stirred at 23 °C for 12 h in an opened flask. The solvent was concentrated under reduced pressure and the crude product was purified by flash column chromatography (SiO_2, PE/EtOAc = 3:1 to 2:1) to obtain 1-(*tert*-butyl) 2-methyl 3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)pyrrolidine-1,2-dicarboxylate (**16**, 20.8 g, 49.0 mmol, 83%) as a colourless viscous fluid.

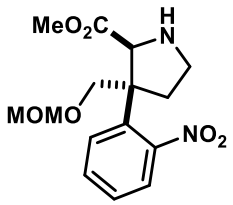
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.69 - 7.58 (m, 1H), 7.54 - 7.45 (m, 2H), 7.41 - 7.34 (m, 1H), 5.05 - 4.87 (m, 1H), 4.50 - 4.45 (m, 2H), 4.05 - 3.89 (m, 1H), 3.76 - 3.60 (m, 2H), 3.54 - 3.45 (m, 1H), 3.38 - 3.37 (m, 3H), 3.16 - 3.15 (m, 3H), 2.67 - 2.53 (m, 1H), 2.50 - 2.36 (m, 1H), 1.45 - 1.41 (m, 9H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$, rotamers): δ = 171.8, 171.5, 154.4, 154.0, 150.8, 150.5, 133.3, 133.0, 132.8, 132.7, 131.4, 130.9, 128.4, 128.3, 125.1, 124.7, 96.5, 96.5, 80.7, 80.5, 70.0, 69.9, 63.9, 63.8, 55.4, 55.3, 54.8, 53.9, 51.9, 51.8, 44.4, 44.0, 29.6, 29.3, 28.5, 28.4 ppm.

IR (film): 2976, 2951, 2891, 1741, 1697, 1531, 1477, 1456, 1435, 1392, 1365, 1244, 1172, 1151, 1134, 1109, 1043, 981, 918, 850, 777, 725, 561, 462, 408 cm^{-1}.

HRMS (ESI): calc. for $C_{20}H_{29}N_2O_8^+$: 425.1924, found: 425.1925

Methyl 3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)pyrrolidine-2-carboxylate (J)

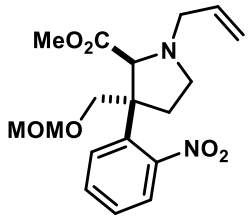


J

1-(*tert*-Butyl) 2-methyl 3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)pyrrolidine-1,2-dicarboxylate (**16**, 20.8 g, 49.0 mmol, 1 eq) was dissolved in DCM (300 mL) and cooled to 0 °C. Trifluoroacetic acid (70 mL) was added and the resulting mixture was stirred at 0 °C for 5 h. The organic phase was washed with 8 M NH_4OH solution (1 L) and after seperation of the phases the aqueous phase was extracted with DCM (2 x 200 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. An analytical sample was purified by acid/base wash (1 M HCl/Et_2O and 8 M NH_4OH/Et_2O) followed by flash column chromatography (SiO_2, DCM/MeOH = 50:1 to 40:1 to 30:1 to 20:1) to obtain secondary amine **J** as a colourless viscous fluid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.55 - 7.53 (m, 1H), 7.45 - 7.41 (m, 2H), 7.36 - 7.30 (m, 1H), 4.52 (d, J = 6.5 Hz, 1H), 4.49 (d, J = 6.5 Hz, 1H), 4.46 (s, 1H), 3.82 (s, 2H), 3.44 (s, 3H), 3.28 (ddd, J_1 = 10.3 Hz, J_2 = 10.3 Hz, J_3 = 3.4 Hz, 1H), 3.22 - 3.16 (m, 1H), 3.19 (s, 3H), 2.47 (ddd, J_1 = 12.4 Hz, J_2 = 10.3 Hz, J_3 = 7.4 Hz, 1H), 2.21 (ddd, J_1 = 12.3 Hz, J_2 = 8.5 Hz, J_3 = 3.6 Hz, 1H), 2.12 (bs, 1H) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 173.0, 151.0, 135.7, 132.3, 130.8, 127.7, 124.4, 96.6, 71.7, 66.2, 55.4, 55.1, 51.7, 44.8, 31.2 ppm.
IR (film): 2949, 2885, 1735, 1653, 1527, 1436, 1365, 1244, 1193, 1170, 1149, 1109, 1041, 952, 916, 852, 781, 759, 723, 696, 542 cm^{-1}.
HRMS (ESI): calc. for $C_{15}H_{21}N_2O_6^+$: 325.1400, found: 325.1396

Methyl 1-allyl-3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)pyrrolidine-2-carboxylate (17)



17

Crude amine **J** was dissolved in anhydrous MeCN (50 mL) and K_2CO_3 (13.5 g, 98.0 mmol, 2 eq) was added followed by allyl bromide (21.2 mL, 29.6 g, 245 mmol, 5 eq). The resulting mixture was stirred at 23 °C for 18 h. The reaction mixture was poured onto H_2O (500 mL) and the aqueous phase was extracted with Et_2O (3 x 200 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, PE/EtOAc = 10:1 to 5:1 to 3:1) to obtain methyl 1-allyl-3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)pyrrolidine-2-carboxylate (**17**, 13.4 g, 36.8 mmol, 75%) as a yellow viscous fluid.

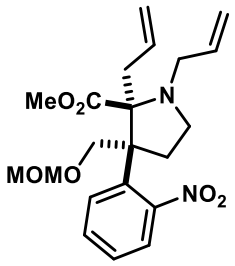
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.50 (dd, J_1 = 7.7 Hz, J_2 = 1.2 Hz, 1H), 7.43 - 7.37 (m, 2H), 7.30 (ddd, J_1 = 8.0 Hz, J_2 = 6.7 Hz, J_3 = 2.1 Hz, 1H), 5.85 (ddt, J_1 = 16.9 Hz, J_2 = 10.4 Hz, J_3 = 6.4 Hz, 1H), 5.19 (ddd, J_1 = 17.2 Hz, J_2 = 3.2 Hz, J_3 = 1.6 Hz, 1H), 5.11 (ddd, J_1 = 10.1 Hz, J_2 = 2.7 Hz, J_3 = 1.2 Hz, 1H), 4.52 (d, J = 6.5 Hz, 1H), 4.46 (d, J = 6.5 Hz, 1H), 4.34 (s, 1H), 3.99 (d, J = 9.2 Hz, 1H), 3.84 (d, J = 9.2 Hz, 1H), 3.44 (s, 3H), 3.26 (dddd, J_1 = 13.7 Hz, J_2 = 6.0 Hz, J_3 = 1.3 Hz, J_4 = 1.3 Hz, 1H), 3.17 (s, 3H), 3.11 - 3.04 (m, 2H), 2.79 (ddd, J_1 = 10.6 Hz, J_2 = 8.9 Hz, J_3 = 4.1 Hz, 1H), 2.42 (ddd, J_1 = 12.6 Hz, J_2 = 10.6 Hz, J_3 = 5.5 Hz, 1H), 2.09 (ddd, J_1 = 12.5 Hz, J_2 = 8.4 Hz, J_3 = 4.1 Hz, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.7, 150.8, 136.0, 135.4, 132.4, 130.4, 127.5, 124.3, 117.1, 96.5, 71.7, 70.0, 55.2, 54.8, 54.4, 51.0, 49.5, 30.3 ppm.

IR (film): 2949, 2885, 2843, 1732, 1527, 1436, 1363, 1193, 1151, 1109, 1045, 918, 854, 781, 759, 723, 684, 561, 418 cm^{-1}.

HRMS (ESI): calc. for $C_{18}H_{25}N_2O_6^+$: 365.1713, found: 365.1709

Methyl 1,2-diallyl-3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)pyrrolidine-2-carboxylate (18)



18

Silver trifluoromethanesulfonate (46.9 g, 183 mmol, 5 eq) was put in a Schlenk tube under argon. Anhydrous DCM (120 mL) was added and the suspension was subjected to ultrasonic for 30 min. The mixture was cooled to 0 °C and freshly prepared allyl iodide (16.7 mL, 30.7 g, 183 mmol, 5 eq) was added. After stirring for 5 min 1-allyl-3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)pyrrolidine-2-carboxylate (**17**, 13.3 g, 36.5 mmol, 1 eq) and 1,8-*bis*(*N,N*-dimethylamino)naphthalene (23.5 g, 110 mmol, 3 eq) dissolved in anhydrous DCM (200 mL) were added and the resulting mixture was stirred at 0 °C for 1 h. After warming up to 23 °C the suspension was filtrated over Celite into a flask containing K_2CO_3 (50.4 g, 365 mmol, 10 eq). The solvent was removed under reduced pressure and the crude ammonium salt was dissolved in anhydrous THF (600 mL) and cooled to 0 °C. Potassium *tert*-butoxide (110 mL, 110 mmol, 3 eq, 1 M solution in *t*BuOH) was added and the mixture was stirred at 0 °C for 15 min. The mixture was poured onto water (2 L) and the aqueous phase was extracted with Et_2O (3 x 500 mL). The aqueous phase was adjusted to pH=12 with KOH and extracted with Et_2O (2 x 500 mL). The combined organic phases were washed with saturated NaCl solution (500 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, PE/EtOAc = 10:1 to 5:1 to 3:1) to obtain methyl 1,2-diallyl-3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)pyrrolidine-2-carboxylate (**18**, 7.82 g, 19.3 mmol, 53%, dr > 99:1) as a colourless crystalline solid. An analytical sample for X-ray spectroscopy was crystallized from Et_2O/pentane. 1-Allyl-3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)pyrrolidine-2-carboxylate (**17**, 2.79 g, 7.66 mmol, 0.21 eq) could be recovered and used in a second cycle.

MP: 67.6 °C

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.57 (dd, J_1 = 8.2 Hz, J_2 = 1.0 Hz, 1H), 7.42 - 7.38 (m, 1H), 7.35 - 7.27 (m, 2H), 6.07 (dddd, J_1 = 17.1 Hz, J_2 = 10.4 Hz, J_3 = 6.7 Hz, J_4 = 6.7 Hz, 1H), 5.77 (dddd, J_1 = 17.2 Hz, J_2 = 10.0 Hz, J_3 = 7.4 Hz, J_4 = 4.4 Hz, 1H), 5.20 - 5.18 (m, 1H), 5.16 - 5.13 (m, 1H), 5.06 - 5.02 (m, 2H), 4.43 (d, J = 6.5 Hz, 1H), 4.40 (d, J = 6.8 Hz, 1H), 4.06 (d, J = 9.9 Hz, 1H), 3.91 (d, J = 10.2 Hz, 1H), 3.43 - 3.37 (m, 1H), 3.32 (s, 3H), 3.24 (ddd, J_1 = 8.7 Hz, J_2 = 8.7 Hz, J_3 = 5.6 Hz, 1H), 3.20 - 3.14 (m, 2H), 3.08 (s, 3H), 2.69 - 2.58 (m, 2H), 2.53 - 2.46 (m, 1H), 2.09 (ddd, J_1 = 12.5 Hz, J_2 = 8.7 Hz, J_3 = 3.8 Hz, 1H) ppm.

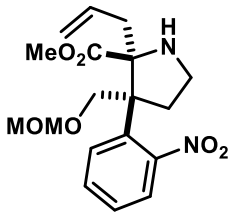
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 172.9, 151.6, 136.0, 135.5, 135.3, 130.7, 129.8, 127.5, 124.3, 116.4, 116.3, 96.5, 77.5, 71.5, 57.7, 55.3, 53.6, 51.2, 49.9, 36.5, 31.6 ppm.

IR (film): 3076, 2978, 2949, 2885, 2843, 1720, 1635, 1529, 1485, 1435, 1365, 1276, 1217, 1151, 1107, 1041, 916, 846, 777, 740, 688, 561 cm^{-1}.

HRMS (ESI): calc. for $C_{21}H_{29}N_2O_6^+$: 405.2026, found: 405.2026

Single crystal diffraction data (see Spectroscopic Data)

Methyl 2-allyl-3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)pyrrolidine-2-carboxylate (K)

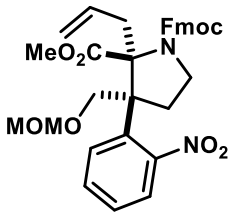


K

Tetrakis(triphenylphosphine)palladium(0) (1.13 g, 979 μmol, 0.05 eq) and 1,3-dimethylbarbituric acid (6.11 g, 39.2 mmol, 2 eq) were put in a Schlenk tube under argon. 1,2-Diallyl-3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)pyrrolidine-2-carboxylate (**18**, 7.92 g, 19.6 mmol, 1 eq) was dissolved in degassed anhydrous DCM (200 mL) and added to the Schlenk tube. The resulting mixture was heated to reflux for 1 h. After cooling to 23 °C the reaction mixture was poured onto 8 M NH_4OH solution (500 mL) and the aqueous phase was extracted with DCM (2 x 200 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under redued pressure. An analytical sample was purified by acid/base wash (1 M HCl/Et_2O, saturated Na_2CO_3/Et_2O) followed by flash column chromatography (SiO_2, PE/EtOAc = 1:1 to 0:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, J = 8.2 Hz, 1H), 7.48 - 7.43 (m, 1H), 7.35 - 7.31 (m, 2H), 5.78 (dddd, J_1 = 17.1 Hz, J_2 = 10.1 Hz, J_3 = 8.1 Hz, J_4 = 6.1 Hz, 1H), 5.16 - 5.07 (m, 2H), 4.54 (s, 2H), 4.10 (d, J = 9.9 Hz, 1H), 3.8 (d, J = 9.9 Hz, 1H), 3.31 (s, 3H), 3.30 - 3.24 (m, 1H), 3.24 (s, 3H), 3.16 - 3.10 (m, 2H), 2.52 - 2.44 (m, 2H), 2.37 (ddd, J_1 = 12.9 Hz, J_2 = 8.1 Hz, J_3 = 3.7 Hz, 1H), 2.10 (bs, 1H) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 173.8, 151.9, 134.1, 133.4, 131.1, 130.0, 127.9, 124.2, 118.8, 96.8, 76.0, 71.3, 56.8, 55.7, 52.0, 43.8, 38.9, 34.1 ppm.
IR (film): 3367, 3076, 2949, 2885, 1728, 1639, 1529, 1485, 1435, 1371, 1296, 1217, 1151, 1107, 1041, 999, 918, 848, 773, 678 cm^{-1}.
HRMS (ESI): calc. for $C_{18}H_{25}N_2O_6^+$: 365.1713, found: 365.1711

1-((9*H*-Fluoren-9-yl)methyl) 2-methyl 2-allyl-3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)pyrrolidine-1,2-dicarboxylate (19)



19

Crude secondary amine **K** was dissolved in 1,4-dioxane (120 mL) and water (30 mL). $NaHCO_3$ (3.46 g, 41.1 mmol, 2.1 eq) and fluorenylmethyloxycarbonyl chloride (5.32 g, 20.6 mmol, 1.05 eq) were sequentially added and the resulting mixture was stirred at 23 °C for 7 h. The mixture was poured onto water (1 L) and the aqueous phase was extracted with Et_2O (3 x 500 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO_2, PE/EtOAc = 5:1 to 3:1 to 2:1 to 1:1) to obtain 1-((9*H*-fluoren-9-yl)methyl) 2-methyl 2-allyl-3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)pyrrolidine-1,2-dicarboxylate (**19**, 9.31 g, 15.9 mmol, 81%) as a colourless foam.

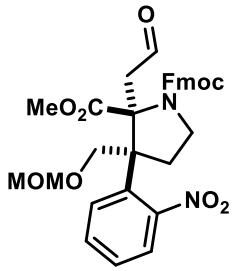
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.79 - 7.71 (m, 3H), 7.63 - 7.58 (m, 2H), 7.50 - 7.26 (m, 7H), 5.86 - 5.46 (m, 1H), 5.27 - 4.98 (m, 2H), 4.60 - 4.23 (m, 5H), 4.10 - 3.83 (m, 3H), 3.71 - 3.52 (m, 1H), 3.52 - 3.39 (m, 1H), 3.27 - 2.76 (m, 7H), 2.72 - 2.50 (m, 1H), 2.41 - 2.28 (m, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$, rotamers): δ = 171.9, 171.4, 154.4, 154.1, 151.6, 151.5, 144.2, 143.9, 143.7, 141.5, 141.4, 134.0, 133.8, 131.4, 130.9, 130.6, 130.4, 129.9, 129.9, 127.9, 127.8, 127.8, 127.7, 127.3, 127.2, 127.2, 127.1, 125.2, 125.1, 124.6, 124.4, 123.9, 120.2, 120.1, 118.2, 117.7, 96.6, 96.5, 74.4, 73.3, 70.5, 67.5, 67.3, 60.2, 59.1, 55.6, 55.5, 52.4, 52.2, 47.4, 47.3, 46.7, 46.0, 36.3, 36.0, 29.0 ppm.

IR (film): 3072, 2949, 2889, 2357, 2341, 1741, 1699, 1529, 1450, 1408, 1355, 1346, 1244, 1213, 1192, 1149, 1109, 1074, 1039, 979, 918, 850, 759, 740, 669, 621, 584, 570, 545 cm^{-1}.

HRMS (ESI): calc. for $C_{33}H_{34}N_2O_8Na^+$: 609.2213, found: 609.2212

1-((9*H*-Fluoren-9-yl)methyl) 2-methyl 3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)-2-(2-oxoethyl)pyrrolidine-1,2-dicarboxylate (L)



L

1-((9*H*-Fluoren-9-yl)methyl) 2-methyl 2-allyl-3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)pyrrolidine-1,2-dicarboxylate (**19**, 2.09 g, 3.56 mmol, 1 eq) was dissolved in anhydrous DCM (200 mL) and anhydrous MeOH (50 mL) and cooled to -78 °C. Ozone was passed through the solution until a blue color appeared followed by oxygen until the blue color disappeared. Thiourea (271 mg, 3.56 mmol, 1 eq) was added and the mixture was allowed to warm to 23 °C. The reaction mixture was poured onto water (500 mL) and the aqueous phase was extracted with Et_2O (3 x 300 mL). The combined organic phases were washed with saturated NaCl solution (300 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO_2, PE/EtOAc = 3:1 to 2:1 to 1:1) to obtain aldehyde **L** (1.57 g, 2.67 mmol, 75%) as a colourless foam.

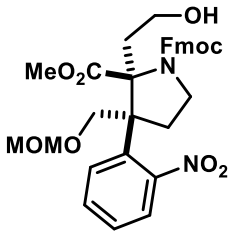
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.64 - 8.91 (m, 1H), 7.78 - 7.76 (m, 2H), 7.66 - 7.30 (m, 10H), 4.93 - 4.21 (m, 5H), 4.12 - 3.73 (m, 4H), 3.66 - 3.46 (m, 1H), 3.29 - 2.85 (m, 7H), 2.78 - 2.54 (m, 1H), 2.42 - 2.22 (m, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$, rotamers): δ = 198.7, 198.4, 171.2, 154.7, 151.2, 143.9, 143.7, 141.5, 130.8, 130.3, 130.2, 130.1, 129.0, 128.8, 127.9, 127.2, 125.2, 125.0, 124.3, 124.2, 124.0, 120.5, 120.2, 120.2, 120.1, 96.5, 82.7, 73.2, 70.9, 70.7, 67.7, 66.5, 58.3, 55.9, 55.8, 52.7, 52.4, 47.4, 47.3, 46.5, 46.3, 45.0, 30.3 ppm.

IR (film): 3064, 2951, 2891, 1741, 1695, 1529, 1477, 1450, 1408, 1357, 1336, 1265, 1247, 1217, 1193, 1149, 1107, 1037, 977, 918, 848, 759, 738, 702, 621, 582, 547, 426 cm^{-1}.

HRMS (ESI): calc. for $C_{32}H_{33}N_2O_9^+$: 589.2186; found: 589.2183

1-((9*H*-Fluoren-9-yl)methyl) 2-methyl 2-(2-hydroxyethyl)-3-((methoxymethoxy)-methyl)-3-(2-nitrophenyl)pyrrolidine-1,2-dicarboxylate (20)



20

Aldehyde **L** (1.57 g, 2.67 mmol, 0.75 eq) was dissolved in anhydrous MeOH (150 mL) and anhydrous DCM (30 mL). Sodium borohydride (112 mg, 2.95 mmol, 0.83 eq) was added and the mixture was stirred at 23 °C for 30 min. Water (50 mL) was added and the mixture was stirred for 5 min at 23 °C. The resulting mixture was poured onto water (500 mL) and the aqueous phase was extracted with Et_2O (3 x 300 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude alcohol was purified by flash column chromatography (SiO_2, PE/EtOAc = 1:1 to 0:1) to obtain 1-((9*H*-fluoren-9-yl)methyl) 2-methyl 2-(2-hydroxyethyl)-3-((methoxymethoxy)-methyl)-3-(2-nitrophenyl)pyrrolidine-1,2-dicarboxylate (**20**, 1.48 g, 2.51 mmol, 71%) as a colourless foam.

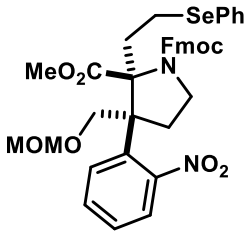
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.83 - 7.77 (m, 2H), 7.66 - 7.15 (m, 10H), 4.90 - 4.39 (m, 4H), 4.26 - 4.10 (m, 1H), 4.00 - 3.68 (m, 5H), 3.55 - 3.31 (m, 1H), 3.22 - 2.82 (m, 7H), 2.69 - 1.81 (m, 4H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$, rotamers): δ = 171.6, 171.1, 155.4, 154.5, 151.3, 151.2, 143.9, 143.9, 143.8, 142.1, 141.5, 141.4, 131.2, 130.6, 130.4, 130.0, 129.8, 128.6, 128.5, 127.9, 127.9, 127.8, 127.4, 127.2, 127.2, 127.0, 125.1, 125.0, 124.2, 124.0, 123.9, 123.8, 120.4, 120.2, 120.2, 96.7, 96.6, 74.4, 72.5, 71.1, 70.2, 67.7, 66.4, 59.8, 59.6, 59.4, 59.2, 55.7, 55.6, 52.3, 52.2, 47.3, 46.9, 46.4, 36.6, 35.2, 29.8, 27.8 ppm.

IR (film): 3466 (bs), 3064, 2949, 2891, 1739, 1697, 1529, 1450, 1406, 1371, 1344, 1265, 1244, 1213, 1192, 1149, 1105, 1035, 916, 848, 758, 731, 702, 669, 621, 584, 563, 545, 426 cm^{-1}.

HRMS (ESI): calc. for $C_{32}H_{34}N_2O_9Na^+$: 613.2162; found: 613.2163

1-((9*H*-fluoren-9-yl)methyl) 2-methyl 3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)-2-(2-phenylselanyl)ethyl)pyrrolidine-1,2-dicarboxylate (M)



M

1-((9*H*-Fluoren-9-yl)methyl) 2-methyl 2-(2-hydroxyethyl)-3-((methoxymethoxy)-methyl)-3-(2-nitrophenyl)pyrrolidine-1,2-dicarboxylate (**20**, 1.48 g, 2.51 mmol, 1 eq) was dissolved in anhydrous DCM (50 mL) and cooled to 0 °C. 2,6-Di-*tert*-butylpyridine (1.35 mL, 1.15 g, 6.01 mmol, 2.4 eq) and trifluoromethanesulfonic anhydride (505 μL, 848 mg, 3.01 mmol, 1.2 eq) were sequentially added. The mixture was allowed to warm to 23 °C and was stirred for 1 h. The organic phase was washed with saturated $NaHCO_3$ solution (100 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. Diphenyldiselenid (430 mg, 1.38 mmol, 0.55 eq) was dissolved in anhydrous EtOH (10 mL) and cooled to 0 °C. Sodium borohydride (114 mg, 3.01 mmol, 1.2 eq) was added and the resulting mixture was stirred for 10 min at 0 °C under gas evolution. The crude triflate was dissolved in anhydrous EtOH (15 mL) and added to the colourless selenid solution. After being allowed to warm to 23 °C, the resulting mixture was stirred for 45 min and was then poured onto saturated $NaHCO_3$ solution (300 mL). The aqueous phase was extracted with Et_2O (3 x 300 mL) and the combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The material was purified by flash column chromatography (SiO_2, PE/EtOAc = 5:1 to 2:1) to obtain seleno ether **M** (1.54 g, 2.10 mmol, 84%) as a colourless foam.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.79 - 7.75 (m, 2H), 7.63 - 7.20 (m, 15H), 4.53 - 4.21 (m, 5H), 4.02 - 3.64 (m, 3H), 3.53 - 3.38 (m, 1H), 3.20 - 2.40 (m, 11H), 2.34 - 2.22 (m, 1H) ppm.

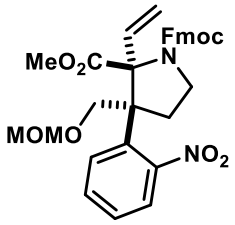
^{13}C-NMR (100 MHz, $CDCl_3$, rotamers): δ = 171.4, 154.9, 151.1, 143.9, 143.9, 141.5, 133.9, 132.9, 131.2, 130.4, 130.2, 129.9, 129.3, 129.2, 128.5, 127.9, 127.7, 127.5, 127.3, 127.2, 127.0, 125.1, 125.0, 125.0, 124.5, 124.5, 123.9, 120.3, 120.2, 96.7,

96.5, 75.2, 70.8, 69.9, 67.5, 67.4, 59.1, 55.8, 55.7, 52.3, 52.3, 47.3, 46.5, 35.1, 30.3, 29.6, 23.4 ppm.

IR (film): 3068, 2949, 2891, 1741, 1699, 1577, 1531, 1477, 1450, 1436, 1404, 1371, 1338, 1244, 1213, 1149, 1109, 1041, 1022, 918, 848, 759, 740, 692 cm^{-1}.

HRMS (ESI): calc. for $C_{38}H_{39}N_2O_8Se^+$: 731.1872; found: 731.1866

1-((9*H*-Fluoren-9-yl)methyl) 2-methyl 3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)-2-vinylpyrrolidine-1,2-dicarboxylate (21)



21

Seleno ether **M** was dissolved in THF/H_2O = 4:1 (40 mL) and sodium periodate (4.50 g, 21.1 mmol, 8.4 eq) was added. After stirring at 23 °C for 3 h the colourless suspension was transferred to a refluxing mixture of $NaHCO_3$ (354 mg, 4.21 mmol, 1.68 eq) in toluene (100 mL) and stirred for 10 min. After cooling down to 23 °C the solvent was removed under reduced pressure. H_2O (300 mL) and $Na_2S_2O_3$ solution (50 mL) were added and the aqueous phase was extracted with Et_2O (3 x 300 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO_2, PE/EtOAc = 3:1 to 2:1 to 1:1) to obtain 1-((9*H*-fluoren-9-yl)methyl) 2-methyl 3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)-2-vinylpyrrolidine-1,2-dicarboxylate (**21**, 861 mg, 1.50 mmol, 60%) as a colourless foam.

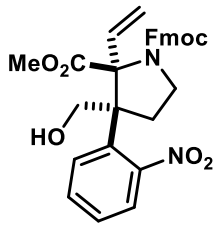
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.79 - 7.71 (m, 2H), 7.62 - 7.58 (m, 2H), 7.54 - 7.45 (m, 2H), 7.44 - 7.21 (m, 6H), 6.68 - 6.39 (m, 1H), 5.44 - 5.15 (m, 2H), 4.52 - 3.94 (m, 6H), 3.76 - 3.56 (m, 3H), 3.32 - 3.17 (m, 3H), 3.10 - 3.06 (m, 3H), 2.79 - 2.62 (m, 1H), 2.52 - 2.44 (m, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$, rotamers): δ = 170.5, 170.2, 154.7, 151.6, 144.0, 143.9, 143.9, 141.5, 141.5, 141.4, 141.4, 132.3, 131.8, 131.1, 130.7, 130.3, 130.0, 129.9, 128.7, 128.6, 127.9, 127.9, 127.7, 127.2, 127.2, 127.1, 127.0, 125.1, 125.1, 125.0, 124.9, 123.8, 123.7, 120.2, 120.0, 120.0, 117.2, 117.0, 96.5, 96.4, 76.0, 75.3, 71.6, 71.3, 67.7, 67.5, 58.8, 57.9, 55.5, 55.4, 52.6, 52.5, 47.4, 47.3, 46.6, 45.9, 28.2 ppm.

IR (film): 3066, 2951, 2891, 1741, 1705, 1531, 1450, 1408, 1373, 1354, 1340, 1246, 1213, 1193, 1151, 1107, 1087, 1043, 918, 850, 759, 740 cm^{-1}.

HRMS (ESI): calc. for $C_{32}H_{33}N_2O_8^+$: 573.2237; found: 573.2237

1-((9*H*-Fluoren-9-yl)methyl) 2-methyl 3-(hydroxymethyl)-3-(2-nitrophenyl)-2-vinylpyrrolidine-1,2-dicarboxylate (N)



N

1-((9*H*-Fluoren-9-yl)methyl) 2-methyl 3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)-2-vinylpyrrolidine-1,2-dicarboxylate (**21**, 861 mg, 1.50 mmol, 1 eq) was dissolved in anhydrous DCM (30 mL) and cooled to 0 °C. Thiophenol (184 μL, 199 mg, 1.80 mmol, 1.2 eq) and boron trifluoride diethyl etherate (476 μL, 1.80 mmol, 1.2 eq, 48% solution) were sequentially added. The reaction mixture was stirred for 13 h and was thereby allowed to warm to 23 °C. Saturated $NaHCO_3$ solution (100 mL) was added and the aqueous phase was extracted with DCM (2 x 100 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, PE/EtOAc = 2:1 to 1:1) to obtain alcohol **N** (715 mg, 1.35 mmol, 90%) as a colourless foam.

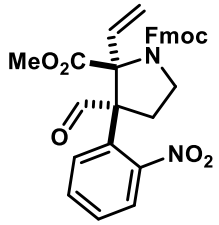
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.79 - 7.23 (m, 12H), 6.74 - 6.42 (m, 1H), 5.48 - 5.10 (m, 2H), 4.48 - 3.44 (m, 7H), 3.29 - 3.12 (m, 3H), 2.74 - 2.58 (m, 1H), 2.53 - 2.30 (m, 1H), 1.70 - 1.59 (m, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$, rotamers): δ = 170.9, 170.7, 154.2, 152.1, 144.0, 143.9, 141.5, 141.5, 132.8, 132.8, 132.5, 131.5, 130.5, 130.4, 129.0, 128.9, 127.9, 127.7, 127.3, 127.1, 127.0, 125.1, 125.1. 125.0, 124.9, 124.0, 124.0, 120.2, 120.0, 117.0, 116.8, 116.7, 76.2, 75.5, 67.6, 67.5, 67.4, 67.1, 59.7, 57.9, 52.5, 52.4, 47.4, 47.3, 46.6, 46.0, 28.3 ppm.

IR (film): 3458 (bs), 2951, 2893, 1741, 1701, 1529, 1450, 1409, 1373, 1354, 1340, 1255, 1246, 1209, 1157, 1082, 1066, 1043, 929, 848, 761, 740, 667, 420 cm^{-1}.

HRMS (ESI): calc. for $C_{30}H_{29}N_2O_7^+$: 529.1975; found: 529.1975

1-((9*H*-Fluoren-9-yl)methyl) 2-methyl 3-formyl-3-(2-nitrophenyl)-2-vinyl-pyrrolidine-1,2-dicarboxylate (22)



22

Alcohol **N** was dissolved in anhydrous DCM (15 mL). $NaHCO_3$ (682 mg, 8.12 mmol, 5.4 eq) and Dess-Martin periodinane (1.72 g, 4.06 mmol, 2.7 eq) were added at 23 °C and the resulting mixture was stirred for 3 h. After that the mixture was poured onto saturated $NaHCO_3$ solution (100 mL) and the aqueous phase was extracted with DCM (2 x 100 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO_2, PE/EtOAc = 3:1 to 2:1 to 1:1) to obtain 1-((9*H*-fluoren-9-yl)methyl) 2-methyl 3-formyl-3-(2-nitrophenyl)-2-vinylpyrrolidine-1,2-dicarboxylate (**22**, 594 mg, 1.13 mmol, 75%) as a colourless foam.

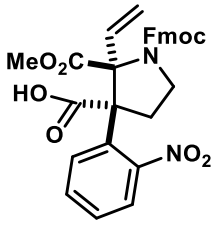
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.75 (s, 1H), 7.93 (dd, J_1 = 8.2 Hz, J_2 = 1.4 Hz, 1H), 7.79 - 7.28 (m, 11H), 6.80 - 6.55 (m, 1H), 5.53 - 5.32 (m, 1H), 5.19 - 5.08 (m, 1H), 4.59 - 4.47 (m, 1H), 4.40 - 4.31 (m, 1H), 4.25 - 4.11 (m, 1H), 4.03 - 3.96 (m, 1H), 3.88 - 3.68 (m, 1H), 3.36 - 3.09 (m, 3H), 2.62 - 2.55 (m, 1H), 2.46 - 2.36 (m, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 196.0, 169.5, 153.7, 144.0, 143.9, 141.6, 141.5, 136.8, 133.6, 133.3, 133.0, 132.0, 131.9, 130.6, 129.5, 127.9, 127.9, 127.3, 127.2, 127.0, 125.8, 125.1, 125.0, 120.2, 117.5, 67.8, 67.4, 65.4, 52.8, 47.5, 46.5, 31.3 ppm.

IR (film): 3064, 2949, 2897, 1741, 1705, 1606, 1575, 1527, 1477, 1450, 1404, 1340, 1265, 1211, 1155, 1114, 1093, 1058, 1006, 937, 854, 786, 758, 738, 725, 700, 621, 542 cm^{-1}.

HRMS (ESI): calc. for $C_{30}H_{26}N_2O_7Na^+$: 549.1638; found: 549.1638

1-(((9*H*-Fluoren-9-yl)carbonyl)-2-(methoxycarbonyl)-3-(2-nitrophenyl)-2-vinylpyrrolidine-3-carboxylic acid (O)



O

1-((9*H*-Fluoren-9-yl)methyl) 2-methyl 3-formyl-3-(2-nitrophenyl)-2-vinyl-pyrrolidine-1,2-dicarboxylate (**22**, 448 mg, 851 μmol, 1 eq) was dissolved in *t*BuOH (10 mL) and 2-methyl-2-butene (2 mL) was added. NaO_2Cl (960 mg, 8.51 mmol, 10 eq, 80%) and $NaH_2PO_4*H_2O$ (939 mg, 6.81 mmol, 8 eq) were dissolved in H_2O (10 mL). The aqueous solution was added to the aldehyde and the mixture was vigorously stirred at 23 °C for 22 h. The reaction mixture was poured onto H_2O (100 mL) and the aqueous phase was extracted with Et_2O (200 mL). 1 M HCl (50 mL) was addded and the aqueous phase was extracted with Et_2O (2 x 100 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure.

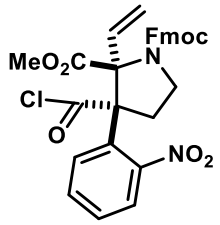
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, J = 7.5 Hz, 3H), 7.63 - 7.49 (m, 4H), 7.43 - 7.37 (m, 3H), 7.30 (dd, J_1 = 7.5 Hz, J_2 = 7.5 Hz, 2H), 6.73 - 6.42 (m, 1H), 5.43 - 5.10 (m, 2H), 4.47 - 4.22 (m, 3H), 4.04 - 3.98 (m, 1H), 3.89 - 3.83 (m, 1H), 3.48 - 3.16 (m, 3H), 2.78 - 2.62 (m, 2H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.2, 170.8, 154.4, 150.2, 144.1, 143.8, 141.5, 141.5, 132.6, 131.7, 131.3, 131.1, 128.9, 127.8, 127.2, 125.2, 125.1, 124.8, 120.1, 117.2, 67.6, 66.9, 52.9, 47.6, 47.3, 31.5, 29.8 ppm.

IR (film): 3064, 2953, 2926, 1735, 1707, 1575, 1529, 1477, 1450, 1408, 1357, 1338, 1247, 1220, 1197, 1157, 1095, 1053, 977, 910, 848, 758, 731, 648, 621, 543 cm^{-1}.

HRMS (ESI): calc. for $C_{30}H_{26}N_2O_8Na^+$: 565.1587; found: 565.1583

1-((9*H*-Fluoren-9-yl)methyl) 2-methyl 3-(chlorocarbonyl)-3-(2-nitrophenyl)-2-vinylpyrrolidine-1,2-dicarboxylate (23)



23

Crude carboxylic acid **O** was dissolved in anhydrous DCM (10 mL) and was cooled to 0 °C. Ghosez reagent (560 μL, 568 mg, 4.25 mmol, 5 eq) was added and the mixture was stirred at 0 °C for 30 min. The solvent was removed under reduced pressure and the crude material was purified by flash column chromatography (SiO_2, PE/EtOAc = 3:1 to 2:1 to 1:1) to obtain 1-((9*H*-fluoren-9-yl)methyl) 2-methyl 3-(chlorocarbonyl)-3-(2-nitrophenyl)-2-vinylpyrrolidine-1,2-dicarboxylate (**23**, 382 mg, 681 μmol, 80%) as a colourless foam.

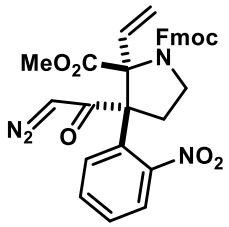
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.96 - 7.29 (m, 12H), 6.74 - 5.99 (m, 1H), 5.45 - 5.02 (m, 2H), 4.48 - 3.73 (m, 5H), 3.47 - 2.57 (m, 5H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 179.9, 169.8, 154.0, 149.2, 144.1, 143.9, 143.8, 141.5, 133.2, 131.1, 130.4, 130.1, 129.9, 129.0, 127.9, 127.2, 126.0, 125.2, 125.0, 120.1, 119.4, 72.4, 67.6, 52.9, 47.3, 45.4, 32.5, 31.7 ppm.

IR (film): 3064, 2951, 2902, 1797, 1741, 1707, 1606, 1577, 1531, 1450, 1408, 1355, 1342, 1298, 1246, 1219, 1195, 1157, 1095, 1051, 1002, 908, 854, 758, 736, 646, 420 cm^{-1}.

HRMS (ESI): calc. for $C_{30}H_{25}N_2O_7ClNa^+$: 583.1248; found: 583.1248

1-((9*H*-Fluoren-9-yl)methyl) 2-methyl 3-(2-diazoacetyl)-3-(2-nitrophenyl)-2-vinylpyrrolidine-1,2-dicarboxylate (24)



24

CaO (76.4 mg, 1.36 mmol, 2 eq) was put in a sealed tube and freshly prepared diazomethane[2] in anhydrous Et_2O (20 mL, solution prepared starting from 5.00 g *N*-methyl-*N*-(*p*-tolylsulfonyl)nitrosamide) was added. 1-((9*H*-Fluoren-9-yl)methyl) 2-methyl 3-(chlorocarbonyl)-3-(2-nitrophenyl)-2-vinylpyrrolidine-1,2-dicarboxylate (**23**, 382 mg, 681 μmol, 1 eq) was dissolved in anhydrous Et_2O (5 mL) and added to the sealed tube. The tube was sealed and the mixture was stirred at 23 °C for 2 d. After complete reaction the solids were removed by filtration over celite and the solvent was concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO_2, PE/EtOAc = 2:1 to 1:1 to 0:1) to obtain 1-((9*H*-fluoren-9-yl)methyl) 2-methyl 3-(2-diazoacetyl)-3-(2-nitrophenyl)-2-vinylpyrrolidine-1,2-dicarboxylate (**24**, 251 mg, 443 μmol, 65%) as a slightly yellow foam.

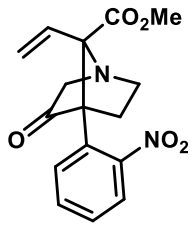
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.77 - 7.70 (m, 3H), 7.61 - 7.46 (m, 5H), 7.41 - 7.38 (m, 2H), 7.34 - 7.29 (m, 2H), 6.66 - 6.31 (m, 1H), 5.46 - 5.07 (m, 2H), 4.90 (s, 1H), 4.47 - 4.43 (m, 1H), 4.29 - 4.08 (m, 3H), 3.93 - 3.85 (m, 1H), 3.41 - 3.15 (m, 3H), 2.65 - 2.58 (m, 2H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 191.8, 171.2, 154.5, 151.1, 144.1, 143.9, 141.5, 141.4, 131.9, 131.3, 131.2, 131.0, 127.8, 127.2, 125.3, 125.1, 120.1, 118.7, 68.9, 67.6, 57.3, 52.9, 48.0, 47.4, 47.3, 31.9 ppm.

IR (film): 2953, 2108, 1739, 1706, 1636, 1531, 1449, 1405, 1338, 1244, 1155, 1099, 1051, 911, 853, 739, 649 cm^{-1}.

HRMS (ESI): calc. for $C_{31}H_{27}N_4O_7^+$: 567.1880; found: 567.1878

Methyl 4-(2-nitrophenyl)-3-oxo-7-vinyl-1-azabicyclo[2.2.1]heptane-7-carboxylate (7)



7

3-(2-Diazoacetyl)-3-(2-nitrophenyl)-2-vinylpyrrolidine-1,2-dicarboxylate (**24**, 55.0 mg, 97.1 μmol, 1 eq) was dissolved in DCM/MeOH = 1:1 (6 mL). 1,8-Diazabicyclo[5.4.0]undec-7-ene (29.0 μL, 29.6 mg, 194 μmol, 2 eq) was added and the mixture was stirred at 23 °C for 4.5 h. The reaction mixture was poured onto 1 M $NaHSO_4$ solution (50 mL) and the aqueous phase was extracted with PE (2 x 50 mL). Solid Na_2CO_3 was added to the aqueous phase until no more gas evolution occured followed by solid NaCl until saturation. The aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure to obtain the secondary amine as a colourless foam.

The crude secondary amine was dissolved in anhydrous DCM (6 mL) and cooled to -30 °C. Trifluoroacetic acid (73.8 μL, 110 mg, 971 μmol, 10 eq) was added and the mixture was stirred for 23 h and was thereby allowed to warm to 23 °C. Saturated K_2CO_3 solution (50 mL) was added and the aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic phases were concentrated under reduced pressure and poured onto 1 M HCl solution (100 mL). The aqueous phase was extracted with EtOAc (2 x 50 mL). 8 M NH_4OH solution was added to the aqueous phase until pH = 10 followed by extraction with EtOAc (3 x 100 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure to obtain methyl 4-(2-nitrophenyl)-3-oxo-7-vinyl-1-azabicyclo[2.2.1]heptane-7-carboxylate (**7**, 16.6 mg, 52.4 μmol, 54%) as a colourless foam.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.88 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 7.63 - 7.56 (m, 2H), 7.48 (ddd, J_1 = 8.2 Hz, J_2 = 7.0 Hz, J_3 = 1.6 Hz, 1H), 6.01 (dd, J_1 = 17.4 Hz, J_2 = 10.9 Hz, 1H), 5.55 (d, J = 17.4 Hz, 1H), 5.46 (d, J = 11.3 Hz, 1H), 3.80 - 3.75 (m,

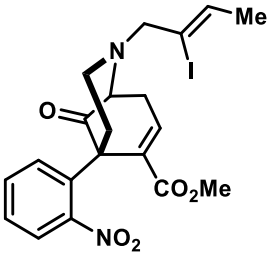
1H), 3.78 (s, 3H), 3.51 - 3.43 (m, 1H), 3.15 (d, J = 17.4 Hz, 1H), 2.91 - 2.80 (m, 2H), 2.39 - 2.32 (m, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 212.0, 169.7, 151.3, 133.3, 131.7, 131.6, 129.0, 127.2, 125.8, 121.2, 84.6, 65.0, 63.3, 53.0, 51.5, 33.1 ppm.

IR (film): 2954, 2924, 2852, 1739, 1573, 1529, 1481, 1458, 1436, 1357, 1273, 1255, 1207, 1163, 1139, 1078, 1066, 950, 852, 802, 786, 769, 740, 698 cm^{-1}.

HRMS (ESI): calc. for $C_{16}H_{17}N_2O_5^+$: 317.1137; found: 317.1147

Methyl (*Z*)-2-(2-iodobut-2-en-1-yl)-5-(2-nitrophenyl)-9-oxo-2-azabicyclo[3.3.1]-non-6-ene-6-carboxylate (6)



6

(*Z*)-2-iodobut-2-en-1-ol (500 mg, 2.53 mmol, 1 eq) was dissolved in DCM (10 mL). Triphenylphosphine (629 mg, 2.40 mmol, 0.95 eq) and imidazole (172 mg, 2.53 mmol, 1 eq) were added and the mixture was cooled to 0 °C. Iodine (641 mg, 2.53 mmol, 1 eq) was added and the resulting mixture was stirred at 0 °C for 2 h. Aqueous thiosulfate solution (50 mL) was added and the aqueous phase was extracted with DCM (50 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude iodide was purified by flash column chromatography (SiO_2, pentane/Et_2O = 10:1) to afford (*Z*)-1,2-diiodobut-2-ene (**8**, 360 mg, 971 μmol, 38%) as a slightly yellow fluid.

AgOTf (29.2 mg, 114 μmol, 6 eq) was put in a Schlenk tube under argon. Anhydrous DCM (200 μL) was added and the resulting suspension was cooled to 0 °C. Freshly prepared (*Z*)-1,2-diiodobut-2-ene (**8**, 35.0 mg, 114 μmol, 6 eq) dissolved in anhydrous DCM (100 μL) was added and the mixture was stirred for 1 min at 0 °C. Methyl 4-(2-nitrophenyl)-3-oxo-7-vinyl-1-azabicyclo[2.2.1]heptane-7-carboxylate (**7**, 6.00 mg, 19.0 μmol, 1 eq) and 1,8-bis(*N*,*N*-dimethylamino)naphtalene (24.4 mg, 114 μmol, 6 eq) dissolved in anhydrous DCM (500 μL) were added to the Schlenk tube and the resulting suspension was stirred at 0 °C for 4 h. During this time the mixture was allowed to warm to 23 °C slowly. The mixture was directly submitted to flash column chromatography (SiO_2, PE/EtOAc = 5:1 to 2:1) to obtain methyl (*Z*)-2-(2-iodobut-2-en-1-yl)-5-(2-nitrophenyl)-9-oxo-2-azabicyclo[3.3.1]-non-6-ene-6-carboxylate (**6**, 4.00 mg, 8.06 μmol, 42%) as a colourless foam.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.93 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 7.68 - 7.60 (m, 2H), 7.45 (ddd, J_1 = 8.3 Hz, J_2 = 6.9 Hz, J_3 = 1.5 Hz, 1H), 7.34 (dd, J_1 = 4.6 Hz, J_2 = 2.9 Hz, 1H), 5.88 (q, J = 6.5 Hz, 1H), 3.50 (s, 3H), 3.41 - 3.26 (m, 4H), 2.97 (ddd,

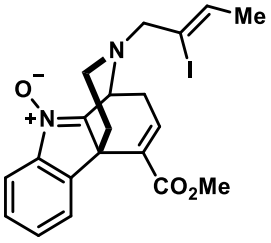
J_1 = 20.5 Hz, J_2 = 5.5 Hz, J_3 = 3.1 Hz, 1H), 2.92 - 2.81 (m, 2H), 2.76 - 2.67 (m, 2H), 1.78 (d, J = 6.5 Hz, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 205.6, 165.1, 149.2, 139.8, 134.6, 133.9, 132.7, 130.8, 130.2, 128.3, 125.6, 107.8, 65.4, 61.4, 55.7, 51.9, 44.3, 38.4, 29.9, 21.9 ppm.

IR (film): 2954, 2924, 2854, 1716, 1643, 1527, 1462, 1438, 1354, 1284, 1238, 1176, 1118, 1095, 1060, 1014, 964, 852, 783, 732, 574, 474 cm^{-1}.

HRMS (ESI): calc. for $C_{20}H_{22}N_2O_5I^+$: 497.0573; found: 497.0568

(*Z*)-12-(2-iodobut-2-en-1-yl)-4-(methoxycarbonyl)-1,2-dihydro-1,4a-(epimino-ethano)carbazole 9-oxide (25)

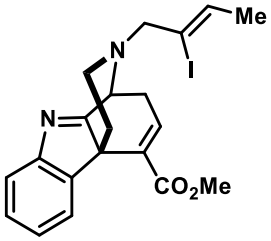


25

Methyl (*Z*)-2-(2-iodobut-2-en-1-yl)-5-(2-nitrophenyl)-9-oxo-2-azabicyclo[3.3.1]-non-6-ene-6-carboxylate (**6**, 4.00 mg, 8.06 μmol, 1 eq) was dissolved in anhydrous DMF (1 mL). Tin(II) chloride dihydrate (54.6 mg, 242 μmol, 30 eq) was added and the mixture was stirred at 23 °C for 29 h. The reaction mixture was poured onto saturated $NaHCO_3$ solution (15 mL) and the aqueous phase was extracted with Et_2O (4 x 5 mL). The combined organic phases were washed with saturated NaCl solution (5 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude material was purified by preparative thin layer chromatography (SiO_2, DCM/Et_2O = 5:1) to obtain (*Z*)-12-(2-iodobut-2-en-1-yl)-4-(methoxycarbonyl)-1,2-dihydro-1,4a-(epimino-ethano)carbazole 9-oxide (**25**, 2.30 mg, 4.95 μmol, 61%) as a yellow foam.

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 8.06 (d, J = 7.6 Hz, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.56 - 7.51 (m, 1H), 7.47 - 7.42 (m, 1H), 7.10 (t, J = 3.6 Hz, 1H), 6.01 (q, J = 6.3 Hz, 1H), 4.58 (m, 1H), 3.77 (s, 3H), 3.41 (d, J = 13.9 Hz, 1H), 3.21 (d, J = 14.0 Hz, 1H), 3.12 - 3.05 (m, 1H), 2.87 - 2.83 (m, 2H), 2.78 - 2.72 (m, 1H), 2.68 - 2.62 (m, 1H), 1.81 (d, J = 6.2 Hz, 3H), 1.74 - 1.66 (m, 1H) ppm.
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 165.9, 149.1, 148.2, 142.4, 136.3, 134.6, 129.4, 129.1, 128.7, 126.9, 115.3, 107.4, 65.6, 52.1, 48.7, 47.7, 43.9, 35.6, 33.1, 22.1 ppm.
IR (neat): 2922, 2851, 1715, 1626, 1592, 1436, 1377, 1300, 1258, 1204, 1112, 1088, 1057, 1040, 997, 904, 768, 750 cm^{-1}.
HRMS (ESI): calc. for $C_{20}H_{22}N_2O_3I^+$: 465.0675; found: 465.0673

Methyl (*Z*)-12-(2-iodobut-2-en-1-yl)-1,2-dihydro-1,4a-(epiminoethano)carbazole-4-carboxylate (26)



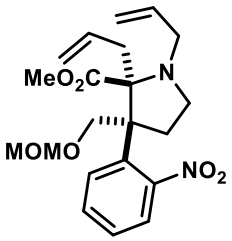
26

(*Z*)-12-(2-iodobut-2-en-1-yl)-4-(methoxycarbonyl)-1,2-dihydro-1,4a-(epimino-ethano)-carbazole 9-oxide (**25**, 2.50 mg, 5.38 μmol, 1 eq) was dissolved in anhydrous THF (1 mL) and the resulting mixture was cooled to 0 °C. Freshly distilled phosphorus tribromide (1.52 μL, 16.2 μmol, 3 eq) was added and the reaction mixture was stirred at 0 °C for 40 min. H_2O (6 mL) was added and the aqueous phase was extracted with Et_2O (3 x 5 mL). The combined organic phases were dried over Na_2SO_4, filtrated and concentrated under reduced pressure. The crude material was purified by preparative thin layer chromatography (SiO_2, DCM/Et_2O = 15:1) to yield methyl (*Z*)-12-(2-iodobut-2-en-1-yl)-1,2-dihydro-1,4a-(epiminoethano)carbazole-4-carboxylate (**26**, 1.40 mg, 3.12 μmol, 58%) as a colorless oil. ^{1}H- and ^{13}C-NMR data are in almost full agreement with data published by Zhu and co-workers[3] and provide even better resolution for some proton signals. Data obtained from HRMS and IR are also highly comparable and further confirm successful preparation of compound **26**.

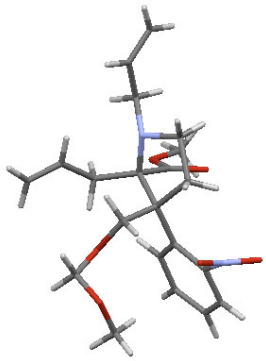
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.91 (d, J = 7.6 Hz, 1H), 7.67 (d, J = 7.6 Hz, 1H), 7.38 (dt, J_1 = 1.3 Hz, J_2 = 7.6 Hz, 1H), 7.24 (dt, J_1 = 1.1 Hz, J_2 = 7.5 Hz, 1H), 7.06 (t, J = 3.6 Hz, 1H), 5.89 (q, J = 6.4 Hz, 1H), 3.95 (d, J = 6.4 Hz, 1H), 3.76 (s, 3H), 3.39 (d, J = 14.1 Hz, 1H), 3.23 (d, J = 14.0 Hz, 1H), 3.06 (dt, J_1 = 2.9 Hz, J_2 = 13.8 Hz, 1H), 2.93 (dd, J_1 = 4.2 Hz, J_2 = 20.5 Hz, 1H), 2.82 - 2.75 (m, 1H), 2.72 - 2.62 (m, 2H), 1.79 (d, J = 6.4 Hz, 3H), 1.57 (dt, J_1 = 4.2 Hz, J_2 = 12.8 Hz, 1H) ppm.
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 183.2, 166.0, 156.1, 141.3, 140.3, 133.1, 129.9, 128.5, 126.4, 125.6, 120.9, 108.6, 65.2, 55.4, 54.8, 51.8, 43.3, 36.0, 34.1, 21.9 ppm.
IR (neat): 2922, 2852, 1717, 1631, 1464, 1376, 1261, 1231, 1092, 1062, 1019, 912, 804, 775, 749 cm^{-1}.
HRMS (ESI): calc. for $C_{20}H_{22}N_2O_2I^+$: 449.0726; found: 449.0725

3. Spectroscopic Data

Methyl 1,2-diallyl-3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)pyrrolidine-2-carboxylate (18)



18



Computing details

Data collection: Bruker *APEX2*; cell refinement: Bruker *SAINT*; data reduction: Bruker *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL2014*/7 (Sheldrick, 2014).

Compound **18** submitted for X-ray structure analysis

CCDC number 1474384

Crystal data

$C_{21}H_{28}N_2O_6$	V = 2161.0 (5) Å^3
M_r = 404.45	Z = 4
Monoclinic, $P2_1/n$	F(000) = 864
a = 12.5404 (19) Å	D_x = 1.243 Mg m^{-3}
b = 9.1067 (11) Å	μ = 0.09 mm^{-1}
c = 19.609 (3) Å	T = 200 K
β = 105.204 (5)°	0.50 × 0.30 × 0.20 mm

Data collection

23305 measured reflections	θ_{max} = 25.1°, θ_{min} = 2.5°
3820 independent reflections	h = −14→14
2627 reflections with $I > 2\sigma(I)$	k = −10→8

R_{int} = 0.069	l = −23→23

Refinement

Refinement on F^2	Primary atom site location: structure-invariant direct methods
Least-squares matrix: full	Secondary atom site location: difference Fourier map
$R[F^2 > 2\sigma(F^2)]$ = 0.046	Hydrogen site location: inferred from neighbouring sites
$wR(F^2)$ = 0.157	H-atom parameters constrained
S = 1.01	$w = 1/[\sigma^2(F_o^2) + (0.0986P)^2 + 0.0386P]$ where $P = (F_o^2 + 2F_c^2)/3$
3820 reflections	$(\Delta/\sigma)_{max}$ = 0.011
264 parameters	$\Delta\rho_{max}$ = 0.32 e Å^{-3}
0 restraints	$\Delta\rho_{min}$ = −0.25 e Å^{-3}

Special details

Refinement

Refinement of F^2 against ALL reflections. The weighted *R*-factor *wR* and goodness of fit *S* are based on F^2, conventional *R*-factors *R* are based on *F*, with *F* set to zero for negative F^2. The threshold expression of $F^2 > \sigma(F^2)$ is used only for calculating *R*-factors(gt) *etc*. and is not relevant to the choice of reflections for refinement. *R*-factors based on F^2 are statistically about twice as large as those based on *F*, and *R*-factors based on ALL data will be even larger.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
O1	0.62440 (16)	0.0340 (2)	0.24763 (10)	0.0758 (5)
O2	0.45543 (13)	0.01682 (14)	0.16261 (7)	0.0482 (4)
O3	0.22066 (14)	0.38788 (16)	0.00065 (8)	0.0549 (4)
O4	0.15943 (15)	0.17662 (17)	−0.05191 (7)	0.0637 (5)
O5	0.5314 (2)	0.60103 (18)	0.16361 (10)	0.0877 (7)
O6	0.54433 (15)	0.40870 (18)	0.22669 (8)	0.0663 (5)

N1	0.15283 (14)	0.21257 (18)	0.11189 (8)	0.0429 (4)
N2	0.53050 (15)	0.4686 (2)	0.16979 (9)	0.0486 (5)
C1	0.6917 (3)	0.0582 (4)	0.2010 (2)	0.1158 (13)
H1A	0.7143	−0.0364	0.1855	0.174*
H1B	0.7574	0.1141	0.2254	0.174*
H1C	0.65	0.1137	0.1598	0.174*
C2	0.5323 (2)	−0.0520 (3)	0.21860 (13)	0.0626 (7)
H2A	0.4955	−0.0769	0.256	0.075*
H2B	0.5567	−0.145	0.2013	0.075*
C3	0.39648 (18)	0.1324 (2)	0.18554 (10)	0.0420 (5)
H3A	0.4473	0.1877	0.2241	0.05*
H3B	0.337	0.0903	0.2042	0.05*
C4	0.34585 (16)	0.23720 (19)	0.12400 (9)	0.0345 (4)
C5	0.23587 (16)	0.1710 (2)	0.07423 (10)	0.0364 (5)
C6	0.03702 (18)	0.1927 (3)	0.07303 (12)	0.0548 (6)
H6A	0.0283	0.0964	0.0488	0.066*
H6B	0.0159	0.27	0.0365	0.066*
C7	−0.0385 (2)	0.1997 (3)	0.12058 (14)	0.0604 (6)
H7	−0.0247	0.1352	0.16	0.072*
C8	−0.1217 (2)	0.2887 (3)	0.11101 (16)	0.0790 (8)
H8A	−0.1374	0.3544	0.072	0.095*
H8B	−0.167	0.2883	0.143	0.095*
C9	0.30196 (18)	0.3750 (2)	0.15534 (11)	0.0433 (5)
H9A	0.3355	0.3806	0.2069	0.052*
H9B	0.3213	0.4655	0.1333	0.052*
C10	0.17770 (19)	0.3602 (2)	0.14013 (12)	0.0506 (6)
H10A	0.1535	0.3728	0.1839	0.061*
H10B	0.1402	0.4346	0.1052	0.061*
C11	0.23229 (18)	0.0010 (2)	0.06295 (10)	0.0431 (5)
H11A	0.1777	−0.0206	0.0176	0.052*
H11B	0.3055	−0.0309	0.0582	0.052*
C12	0.2038 (2)	−0.0907 (2)	0.11969 (14)	0.0606 (7)
H12	0.1479	−0.0536	0.1396	0.073*
C13	0.2468 (4)	−0.2118 (3)	0.14334 (18)	0.1024 (12)
H13A	0.3031	−0.2535	0.1251	0.123*
H13B	0.2229	−0.2612	0.1794	0.123*
C14	0.20787 (17)	0.2578 (2)	0.00396 (10)	0.0417 (5)
C15	0.1214 (3)	0.2569 (4)	−0.11801 (13)	0.1002 (12)
H15A	0.0683	0.3323	−0.1129	0.15*
H15B	0.0856	0.1888	−0.1558	0.15*
H15C	0.1845	0.3037	−0.1299	0.15*
C16	0.43532 (16)	0.27133 (19)	0.08552 (9)	0.0343 (4)
C17	0.44120 (17)	0.1926 (2)	0.02545 (10)	0.0400 (5)
H17	0.3883	0.1174	0.0088	0.048*
C18	0.51975 (18)	0.2183 (2)	−0.01103 (11)	0.0475 (5)
H18	0.5202	0.1604	−0.0512	0.057*

C19	0.59737 (19)	0.3272 (2)	0.01047 (12)	0.0526 (6)
H19	0.651	0.3459	−0.0149	0.063*
C20	0.59590 (18)	0.4086 (2)	0.06935 (12)	0.0499 (5)
H20	0.6484	0.4848	0.0849	0.06*
C21	0.51735 (17)	0.3788 (2)	0.10590 (10)	0.0395 (5)

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0687 (12)	0.0743 (12)	0.0703 (11)	0.0030 (10)	−0.0068 (10)	−0.0001 (9)
O2	0.0591 (10)	0.0395 (8)	0.0423 (8)	0.0079 (7)	0.0068 (7)	0.0017 (6)
O3	0.0658 (11)	0.0449 (9)	0.0485 (9)	0.0002 (8)	0.0056 (8)	0.0044 (7)
O4	0.0893 (13)	0.0604 (10)	0.0339 (8)	−0.0056 (9)	0.0029 (8)	−0.0071 (7)
O5	0.140 (2)	0.0410 (10)	0.0720 (12)	−0.0081 (10)	0.0105 (12)	−0.0084 (8)
O6	0.0816 (13)	0.0670 (10)	0.0416 (9)	−0.0157 (9)	0.0007 (8)	−0.0013 (8)
N1	0.0398 (10)	0.0456 (10)	0.0465 (9)	−0.0033 (8)	0.0168 (8)	−0.0122 (8)
N2	0.0484 (11)	0.0434 (10)	0.0477 (11)	−0.0075 (9)	0.0015 (9)	−0.0013 (8)
C1	0.063 (2)	0.150 (3)	0.134 (3)	0.017 (2)	0.024 (2)	0.048 (3)
C2	0.0754 (18)	0.0482 (13)	0.0587 (14)	0.0055 (13)	0.0079 (13)	0.0155 (11)
C3	0.0520 (13)	0.0407 (11)	0.0335 (10)	−0.0016 (10)	0.0117 (9)	−0.0010 (8)
C4	0.0392 (11)	0.0317 (9)	0.0329 (9)	−0.0029 (8)	0.0100 (8)	−0.0048 (8)
C5	0.0385 (11)	0.0367 (10)	0.0364 (10)	−0.0022 (9)	0.0139 (9)	−0.0060 (8)
C6	0.0413 (13)	0.0638 (14)	0.0591 (14)	−0.0061 (11)	0.0128 (11)	−0.0174 (11)
C7	0.0435 (14)	0.0684 (15)	0.0711 (16)	−0.0049 (12)	0.0184 (12)	−0.0088 (13)
C8	0.0484 (16)	0.107 (2)	0.0833 (19)	−0.0007 (16)	0.0206 (14)	−0.0230 (17)
C9	0.0479 (13)	0.0413 (11)	0.0425 (11)	−0.0017 (10)	0.0149 (10)	−0.0111 (9)
C10	0.0486 (14)	0.0516 (13)	0.0545 (12)	−0.0002 (11)	0.0185 (11)	−0.0176 (10)
C11	0.0476 (13)	0.0386 (11)	0.0429 (11)	−0.0082 (9)	0.0117 (10)	−0.0105 (9)
C12	0.0761 (18)	0.0428 (12)	0.0735 (16)	−0.0091 (13)	0.0384 (14)	−0.0047 (12)
C13	0.174 (4)	0.0508 (16)	0.110 (2)	0.0064 (19)	0.087 (3)	0.0082 (16)
C14	0.0394 (12)	0.0476 (13)	0.0379 (10)	0.0012 (10)	0.0098 (9)	−0.0068 (9)
C15	0.153 (3)	0.094 (2)	0.0357 (13)	−0.011 (2)	−0.0074 (17)	0.0022 (13)
C16	0.0360 (11)	0.0319 (9)	0.0341 (9)	0.0025 (8)	0.0076 (8)	0.0025 (8)
C17	0.0413 (12)	0.0393 (10)	0.0400 (10)	0.0013 (9)	0.0118 (9)	−0.0002 (8)
C18	0.0492 (13)	0.0539 (12)	0.0430 (11)	0.0106 (11)	0.0183 (10)	0.0044 (10)
C19	0.0429 (13)	0.0637 (14)	0.0562 (13)	0.0038 (11)	0.0219 (11)	0.0109 (12)
C20	0.0377 (12)	0.0506 (12)	0.0600 (14)	−0.0035 (10)	0.0103 (10)	0.0089 (11)
C21	0.0379 (12)	0.0378 (10)	0.0395 (10)	0.0025 (9)	0.0045 (9)	0.0052 (8)

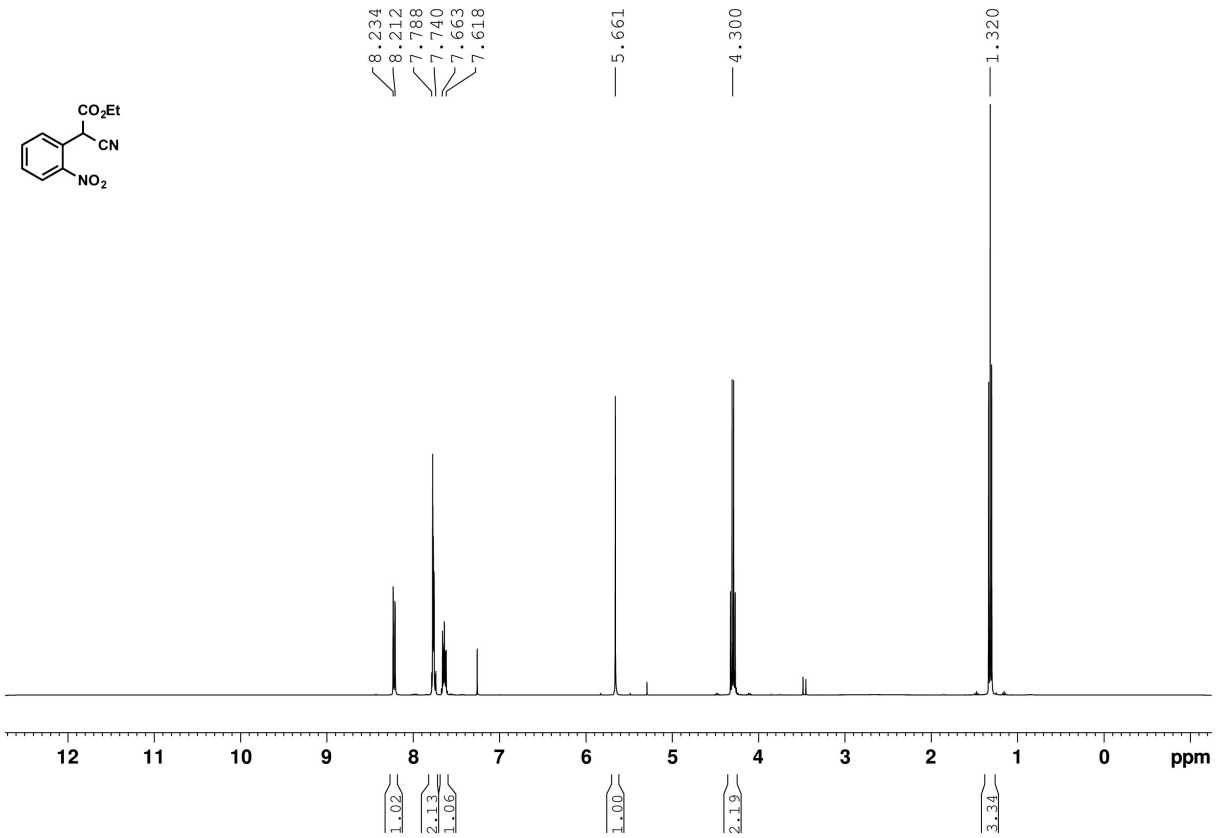
Bond lengths (Å)

O1—C2	1.388 (3)	C7—C8	1.295 (3)
O1—C1	1.415 (4)	C7—H7	0.95
O2—C2	1.404 (3)	C8—H8A	0.95
O2—C3	1.425 (2)	C8—H8B	0.95
O3—C14	1.199 (2)	C9—C10	1.514 (3)
O4—C14	1.329 (2)	C9—H9A	0.99
O4—C15	1.456 (3)	C9—H9B	0.99
O5—N2	1.212 (2)	C10—H10A	0.99
O6—N2	1.213 (2)	C10—H10B	0.99
N1—C10	1.456 (2)	C11—C12	1.507 (3)
N1—C6	1.464 (3)	C11—H11A	0.99
N1—C5	1.475 (2)	C11—H11B	0.99
N2—C21	1.469 (3)	C12—C13	1.261 (4)
C1—H1A	0.98	C12—H12	0.95
C1—H1B	0.98	C13—H13A	0.95
C1—H1C	0.98	C13—H13B	0.95
C2—H2A	0.99	C15—H15A	0.98
C2—H2B	0.99	C15—H15B	0.98
C3—C4	1.539 (3)	C15—H15C	0.98
C3—H3A	0.99	C16—C17	1.397 (3)
C3—H3B	0.99	C16—C21	1.400 (3)
C4—C16	1.539 (3)	C17—C18	1.381 (3)
C4—C9	1.560 (3)	C17—H17	0.95
C4—C5	1.585 (3)	C18—C19	1.376 (3)
C5—C14	1.547 (3)	C18—H18	0.95
C5—C11	1.562 (3)	C19—C20	1.376 (3)
C6—C7	1.494 (3)	C19—H19	0.95
C6—H6A	0.99	C20—C21	1.389 (3)
C6—H6B	0.99	C20—H20	0.95

Bond angles(º)

C2—O1—C1	113.3 (2)	C10—C9—C4	107.57 (16)
C2—O2—C3	112.92 (17)	C10—C9—H9A	110.2
C14—O4—C15	115.26 (19)	C4—C9—H9A	110.2
C10—N1—C6	113.35 (16)	C10—C9—H9B	110.2
C10—N1—C5	108.58 (15)	C4—C9—H9B	110.2
C6—N1—C5	116.23 (15)	H9A—C9—H9B	108.5
O5—N2—O6	122.45 (19)	N1—C10—C9	105.31 (16)
O5—N2—C21	118.07 (18)	N1—C10—H10A	110.7
O6—N2—C21	119.41 (17)	C9—C10—H10A	110.7
O1—C1—H1A	109.5	N1—C10—H10B	110.7
O1—C1—H1B	109.5	C9—C10—H10B	110.7

H1A—C1—H1B	109.5	H10A—C10—H10B	108.8
O1—C1—H1C	109.5	C12—C11—C5	116.61 (16)
H1A—C1—H1C	109.5	C12—C11—H11A	108.1
H1B—C1—H1C	109.5	C5—C11—H11A	108.1
O1—C2—O2	113.27 (18)	C12—C11—H11B	108.1
O1—C2—H2A	108.9	C5—C11—H11B	108.1
O2—C2—H2A	108.9	H11A—C11—H11B	107.3
O1—C2—H2B	108.9	C13—C12—C11	126.5 (3)
O2—C2—H2B	108.9	C13—C12—H12	116.8
H2A—C2—H2B	107.7	C11—C12—H12	116.8
O2—C3—C4	110.62 (15)	C12—C13—H13A	120.0
O2—C3—H3A	109.5	C12—C13—H13B	120.0
C4—C3—H3A	109.5	H13A—C13—H13B	120.0
O2—C3—H3B	109.5	O3—C14—O4	122.93 (19)
C4—C3—H3B	109.5	O3—C14—C5	123.42 (17)
H3A—C3—H3B	108.1	O4—C14—C5	113.42 (17)
C16—C4—C3	107.81 (15)	O4—C15—H15A	109.5
C16—C4—C9	114.12 (15)	O4—C15—H15B	109.5
C3—C4—C9	107.80 (15)	H15A—C15—H15B	109.5
C16—C4—C5	113.80 (14)	O4—C15—H15C	109.5
C3—C4—C5	111.11 (15)	H15A—C15—H15C	109.5
C9—C4—C5	102.05 (15)	H15B—C15—H15C	109.5
N1—C5—C14	106.82 (16)	C17—C16—C21	113.71 (17)
N1—C5—C11	109.12 (15)	C17—C16—C4	121.07 (16)
C14—C5—C11	112.89 (15)	C21—C16—C4	125.22 (16)
N1—C5—C4	102.03 (14)	C18—C17—C16	123.53 (19)
C14—C5—C4	108.14 (15)	C18—C17—H17	118.2
C11—C5—C4	116.88 (16)	C16—C17—H17	118.2
N1—C6—C7	112.00 (18)	C19—C18—C17	120.5 (2)
N1—C6—H6A	109.2	C19—C18—H18	119.8
C7—C6—H6A	109.2	C17—C18—H18	119.8
N1—C6—H6B	109.2	C20—C19—C18	118.8 (2)
C7—C6—H6B	109.2	C20—C19—H19	120.6
H6A—C6—H6B	107.9	C18—C19—H19	120.6
C8—C7—C6	123.7 (3)	C19—C20—C21	119.7 (2)
C8—C7—H7	118.2	C19—C20—H20	120.2
C6—C7—H7	118.2	C21—C20—H20	120.2
C7—C8—H8A	120.0	C20—C21—C16	123.84 (19)
C7—C8—H8B	120.0	C20—C21—N2	113.28 (18)
H8A—C8—H8B	120.0	C16—C21—N2	122.86 (18)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10
9
8
7
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5
4
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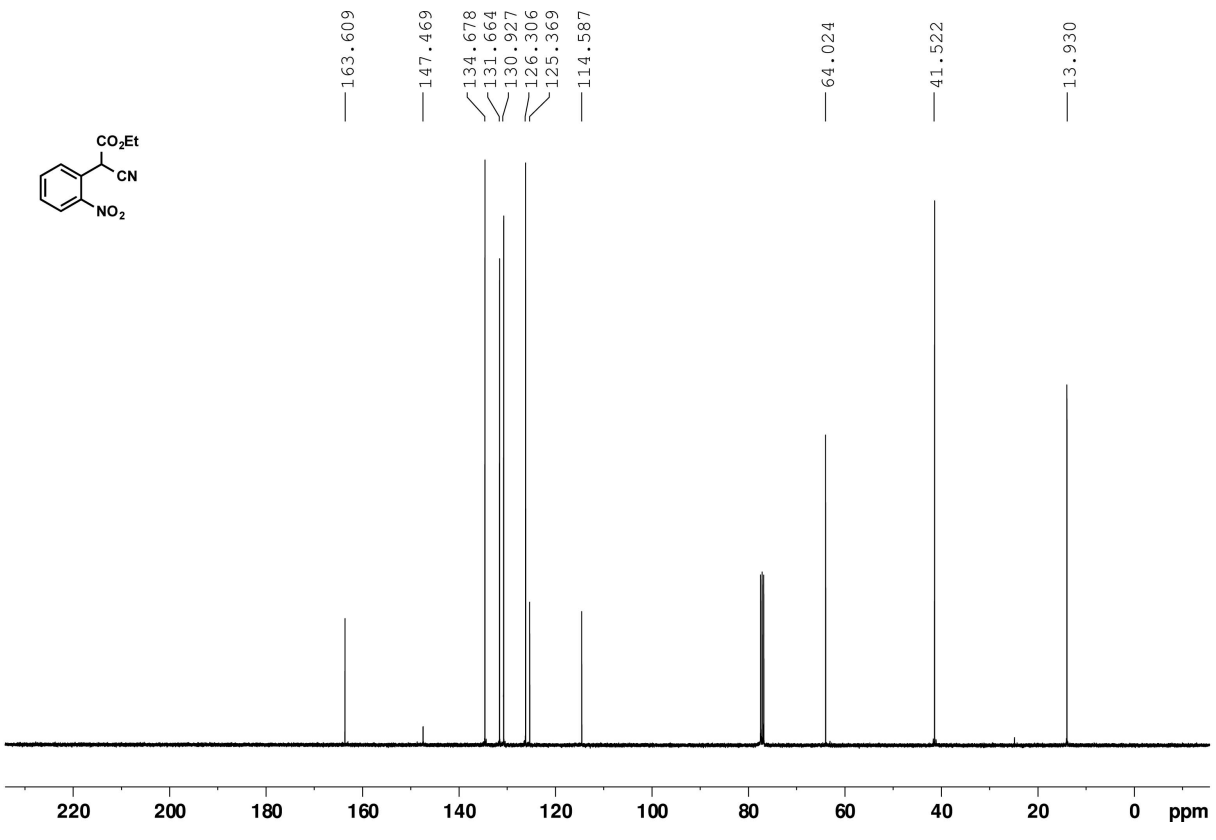
3.34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NO2
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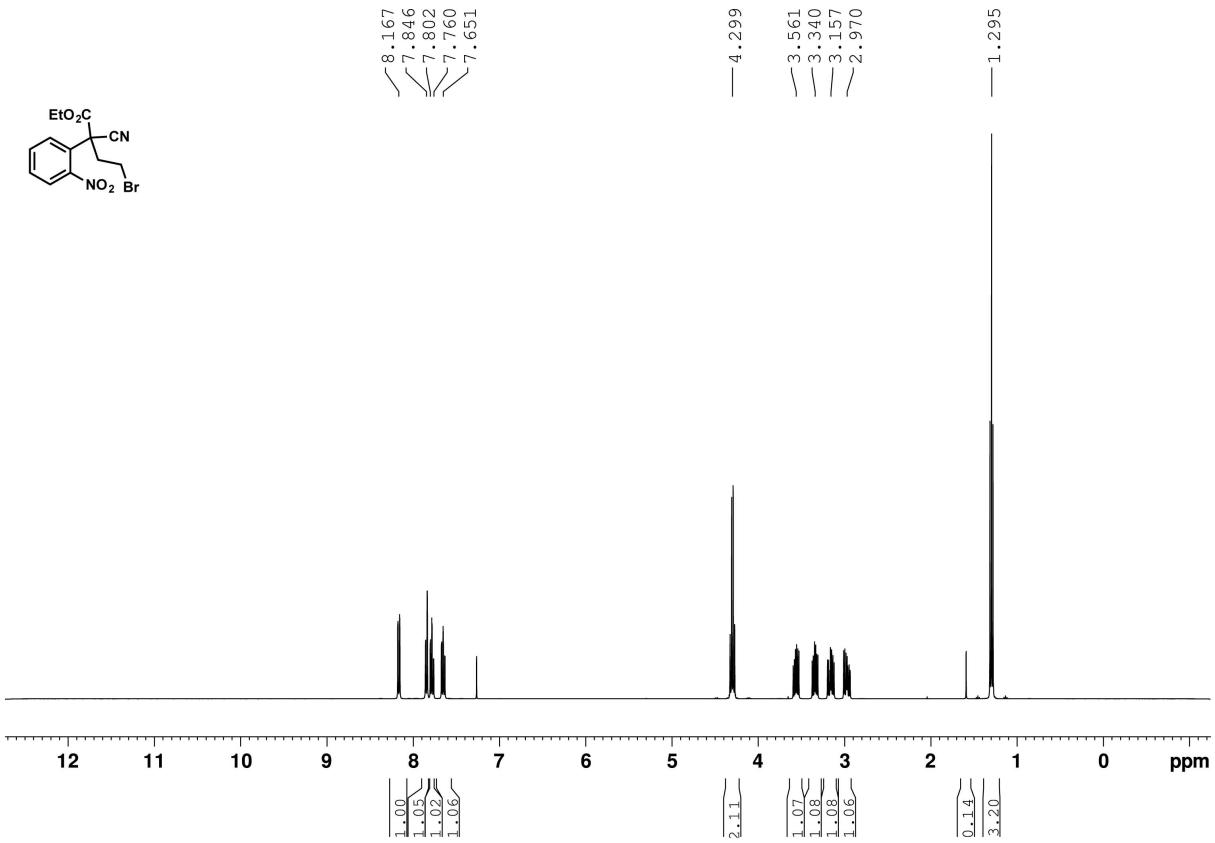
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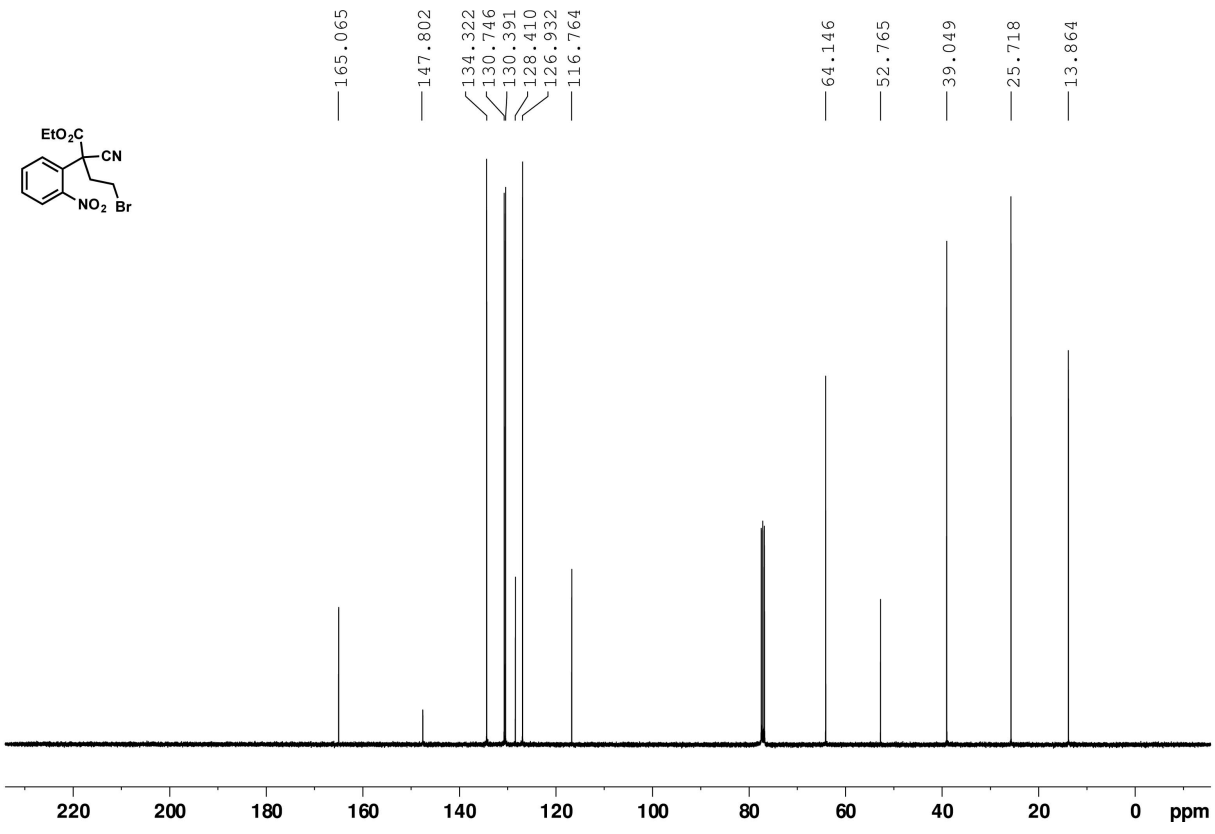
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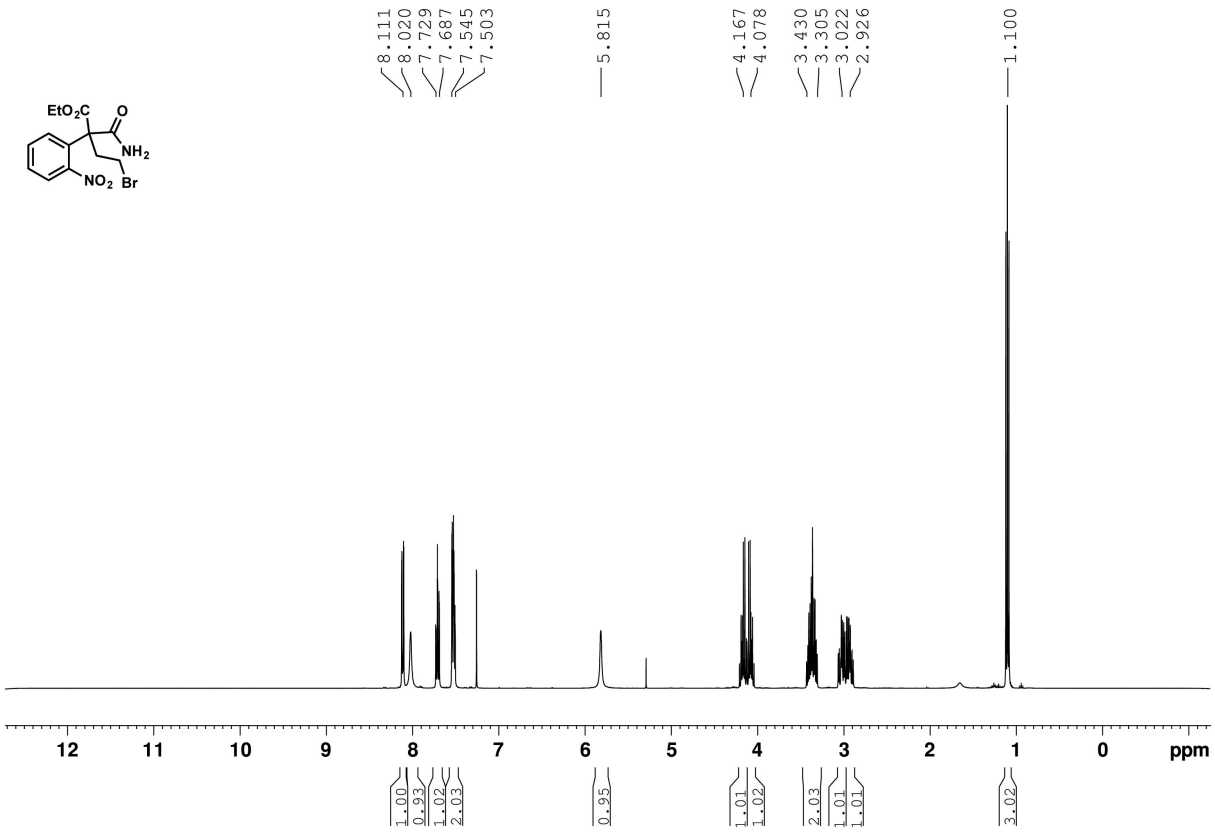
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10
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8
7
6
5
4
3
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ppm
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1.02
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1.01
1.02
2.03
1.01
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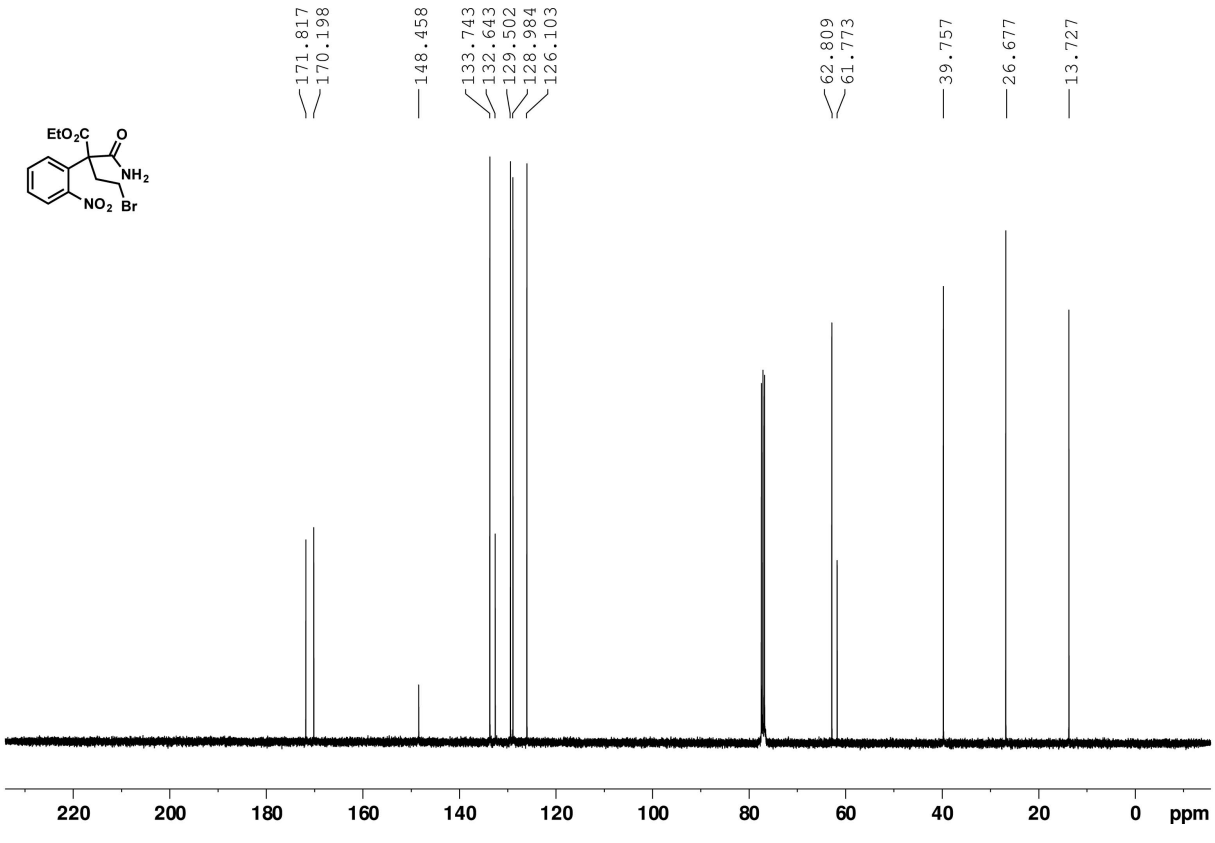
3.02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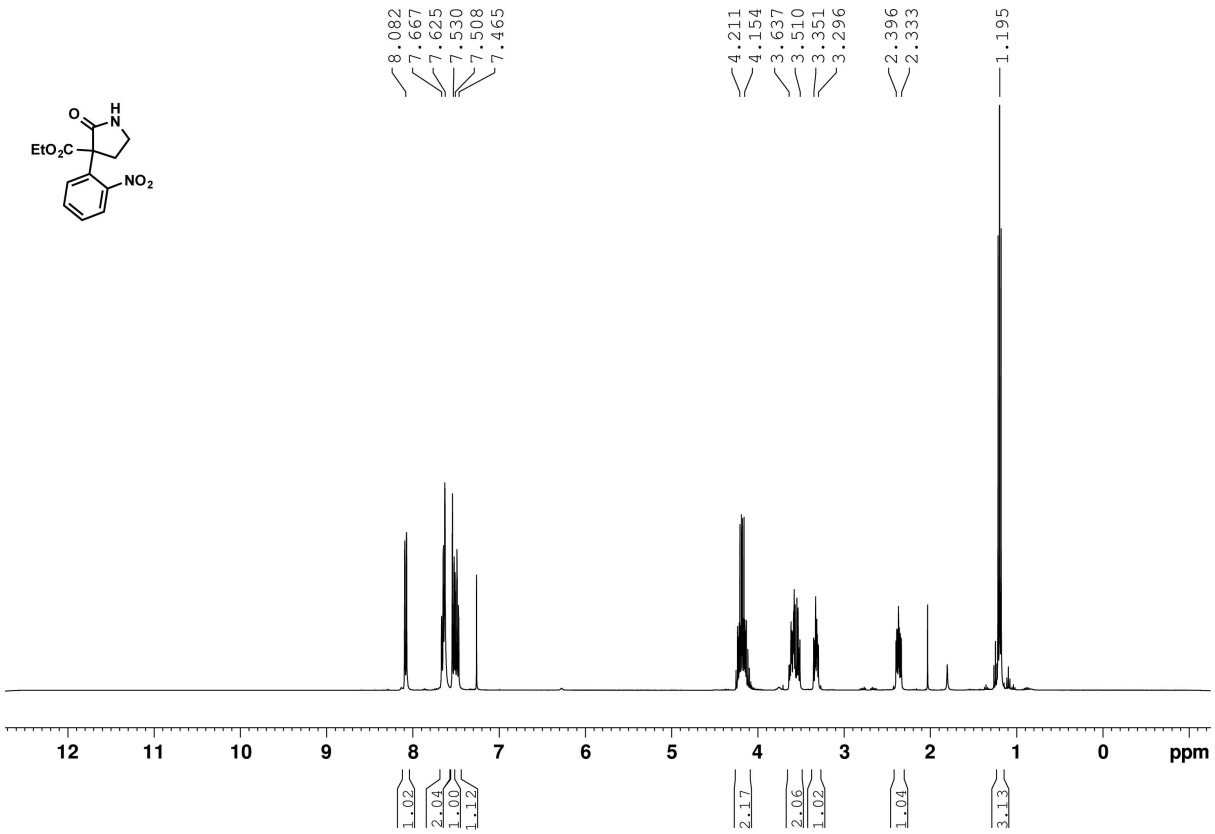
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10
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8
7
6
5
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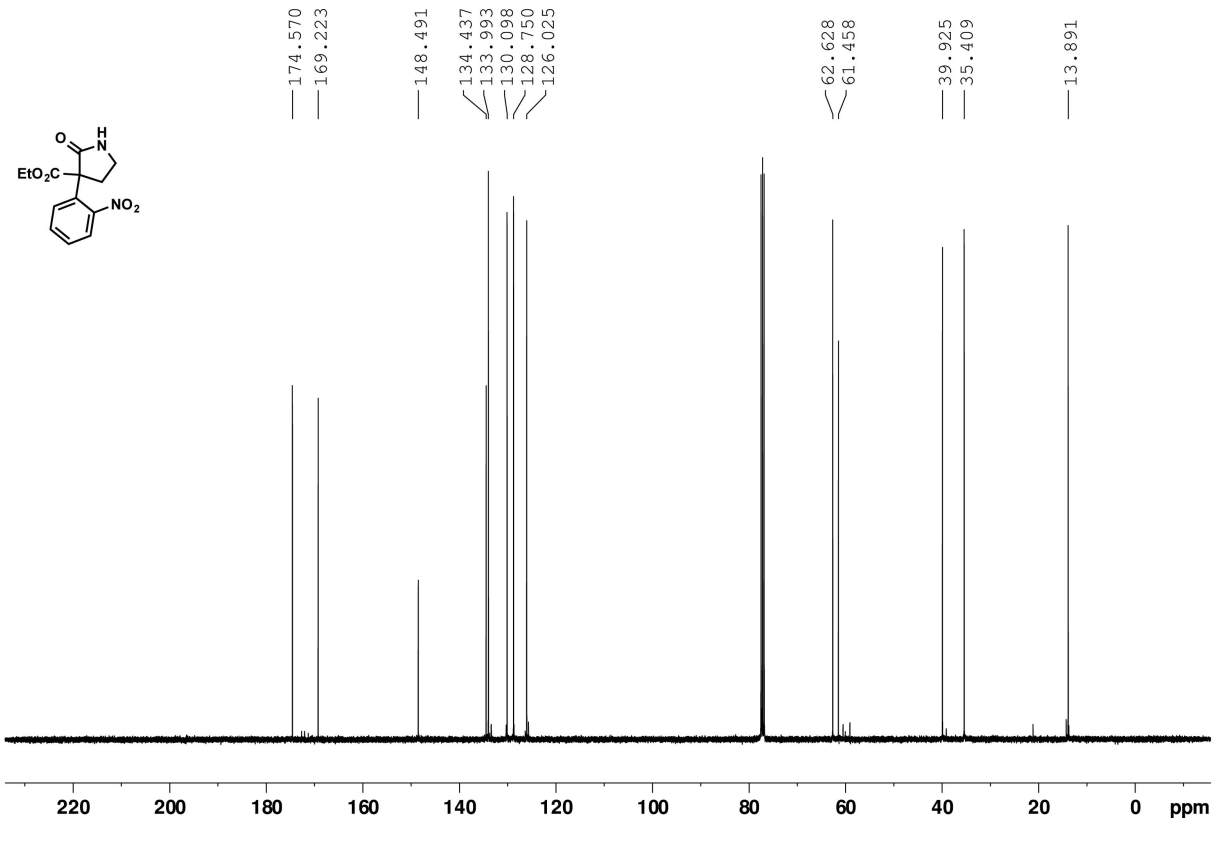
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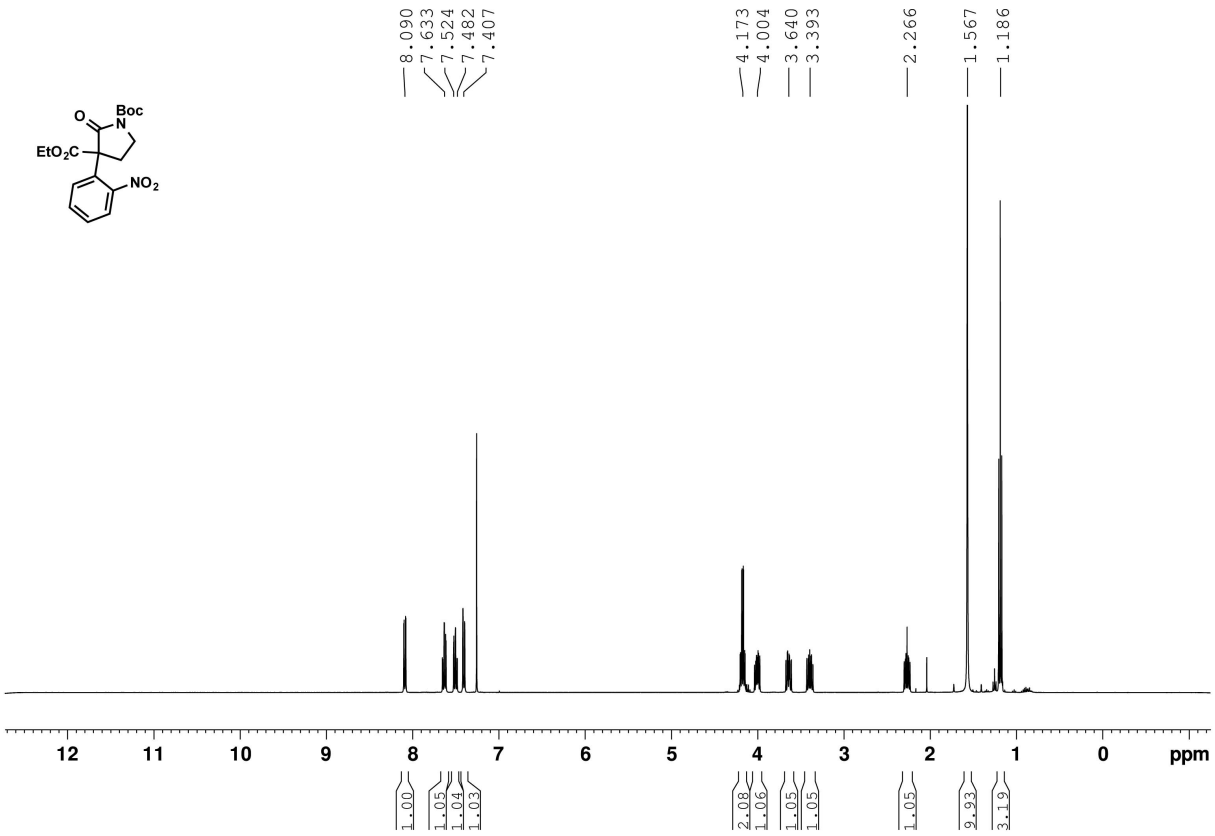
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Boc
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N
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10
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8
7
6
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4
3
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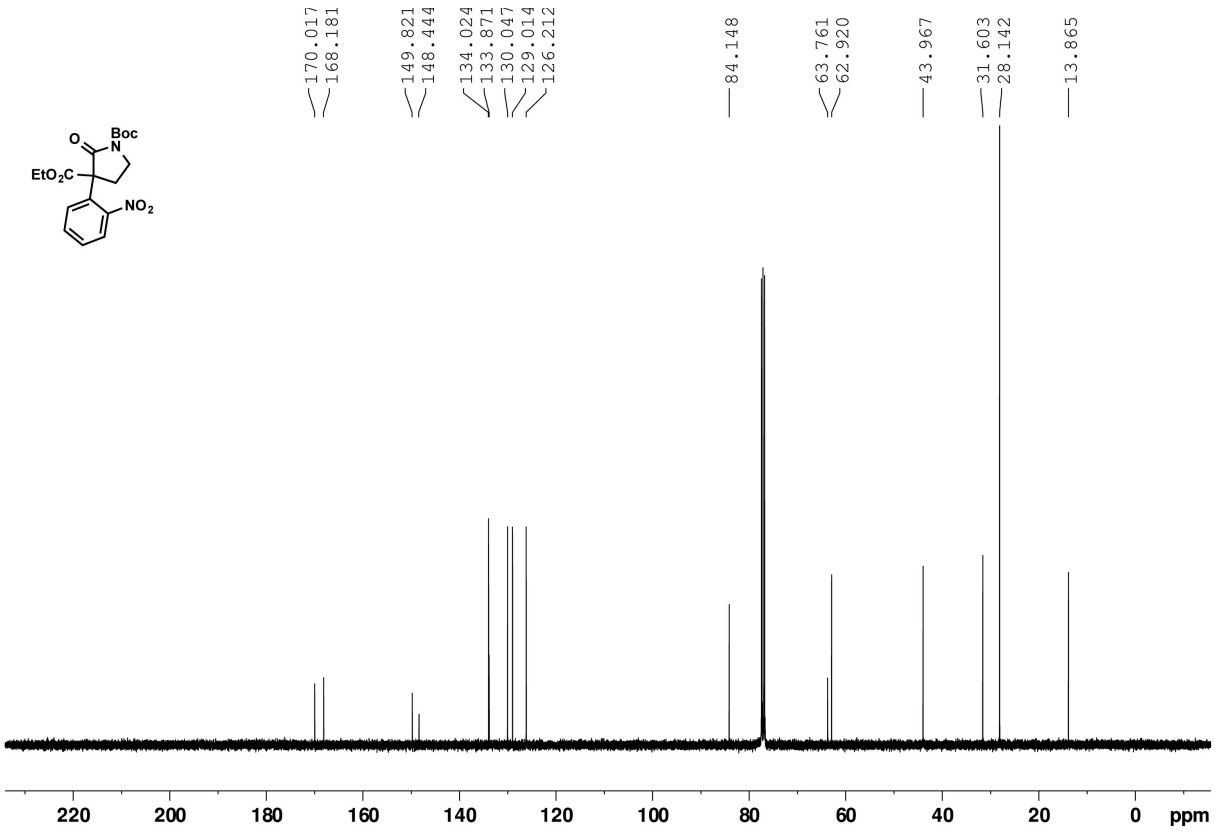
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28.142
13.865
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EtO2C
NO2
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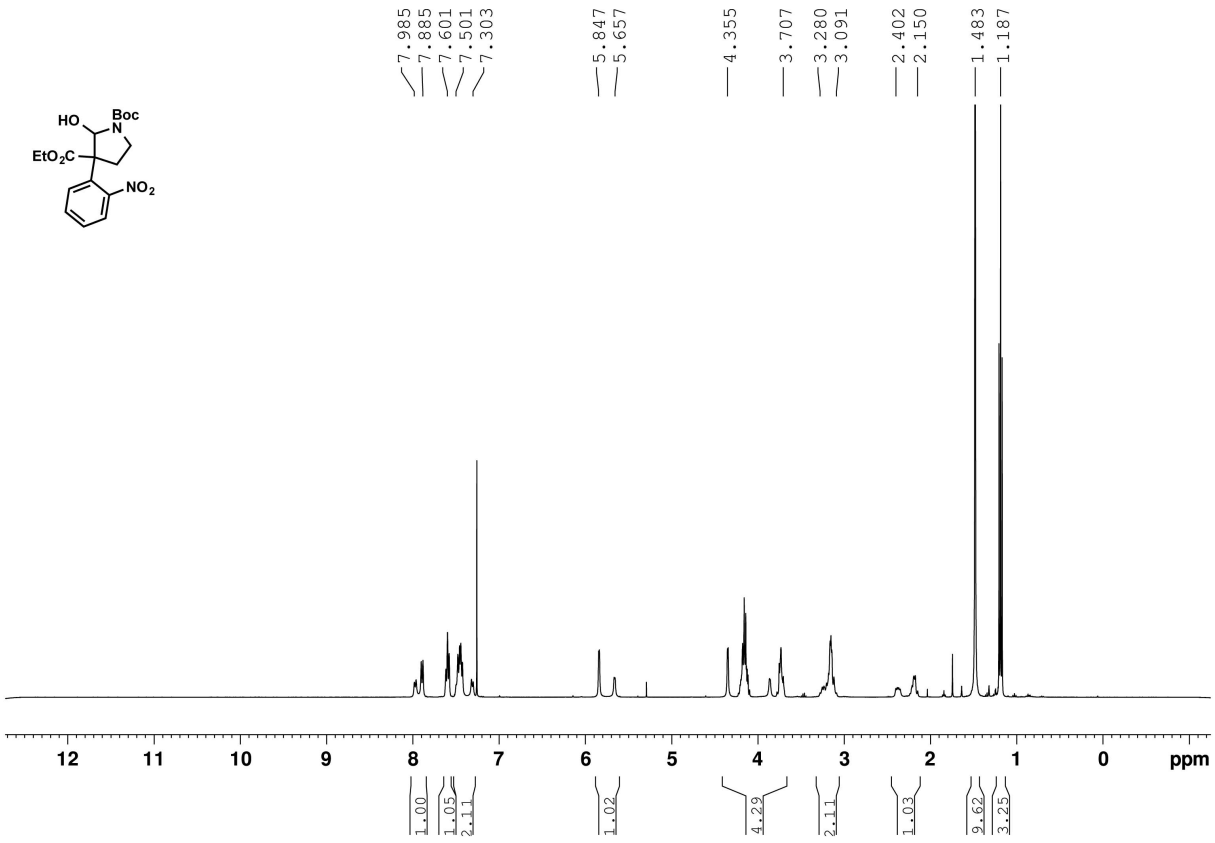
ppm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2.150
1.483
1.187
HO
Boc
N
EtO2C
NO2
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11
10
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8
7
6
5
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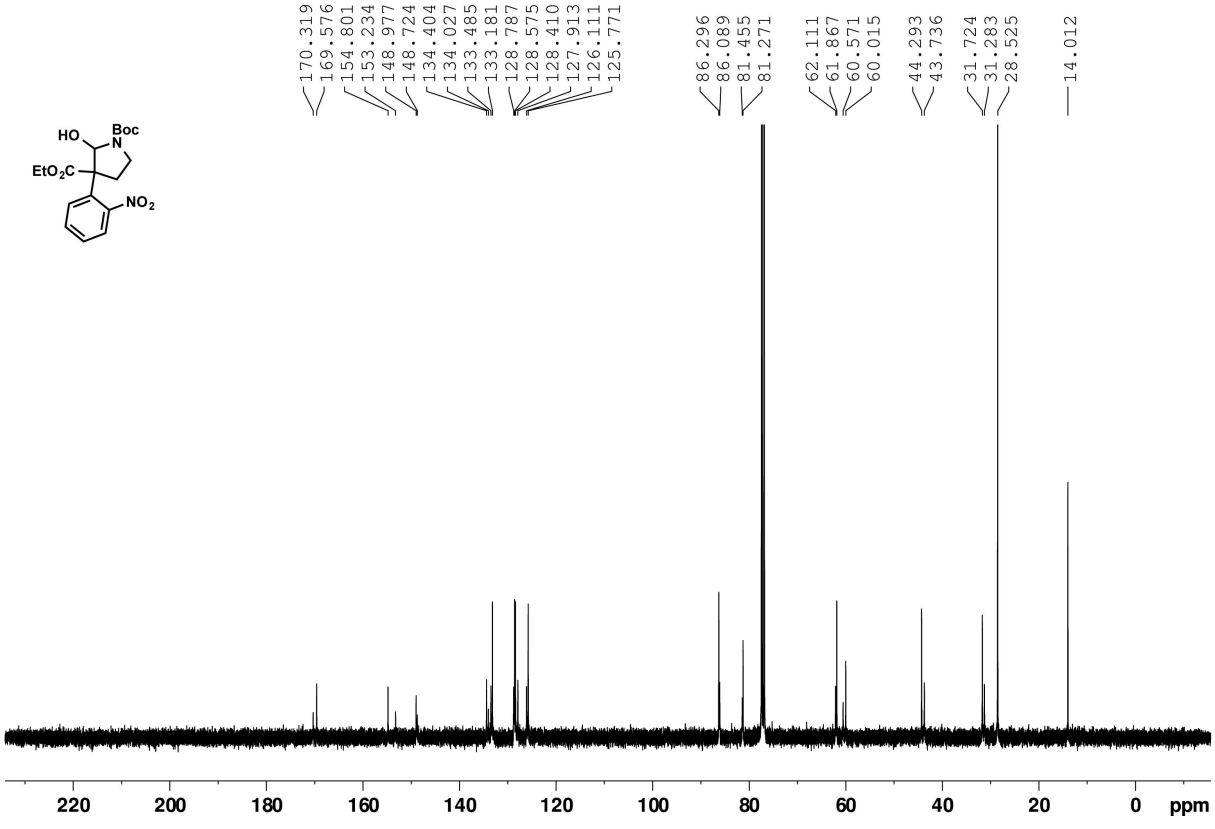
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126.111
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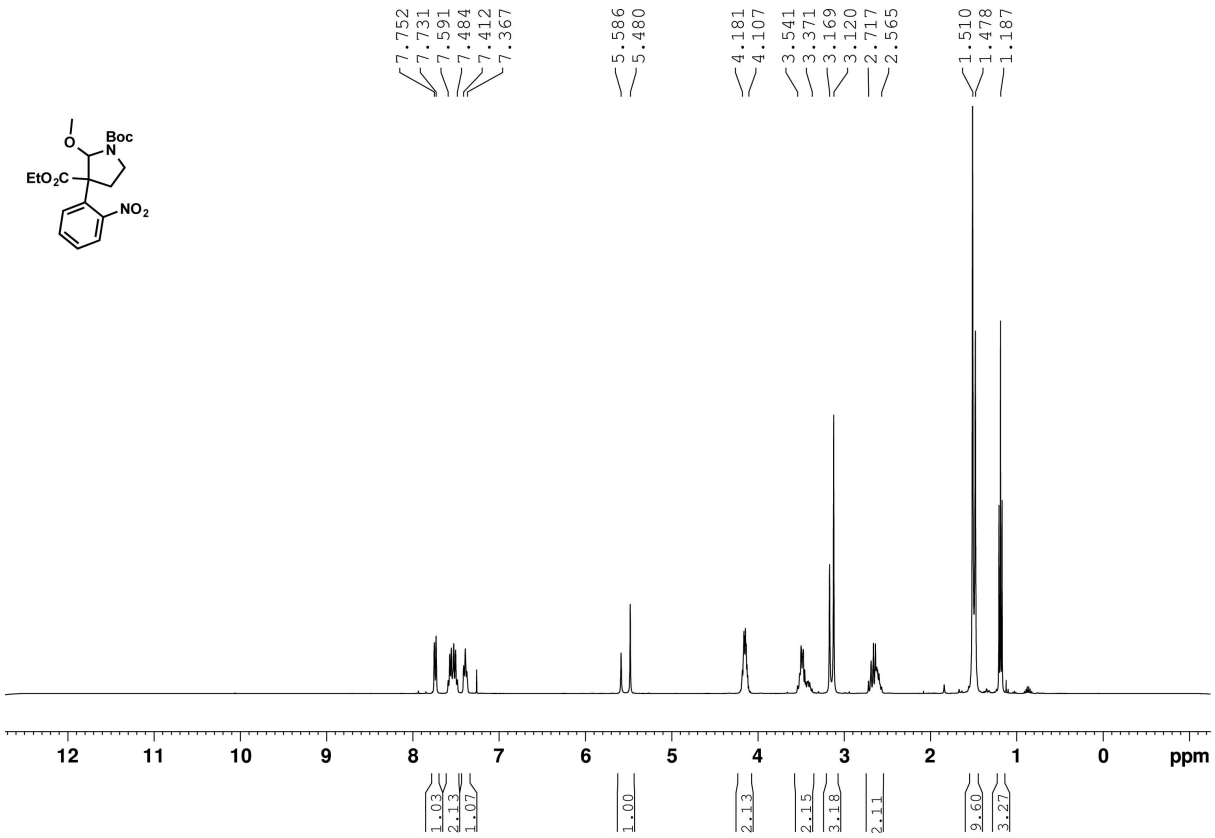
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2.565
1.510
1.478
1.187
Boc
N
O
EtO2C
NO2
12
11
10
9
8
7
6
5
4
3
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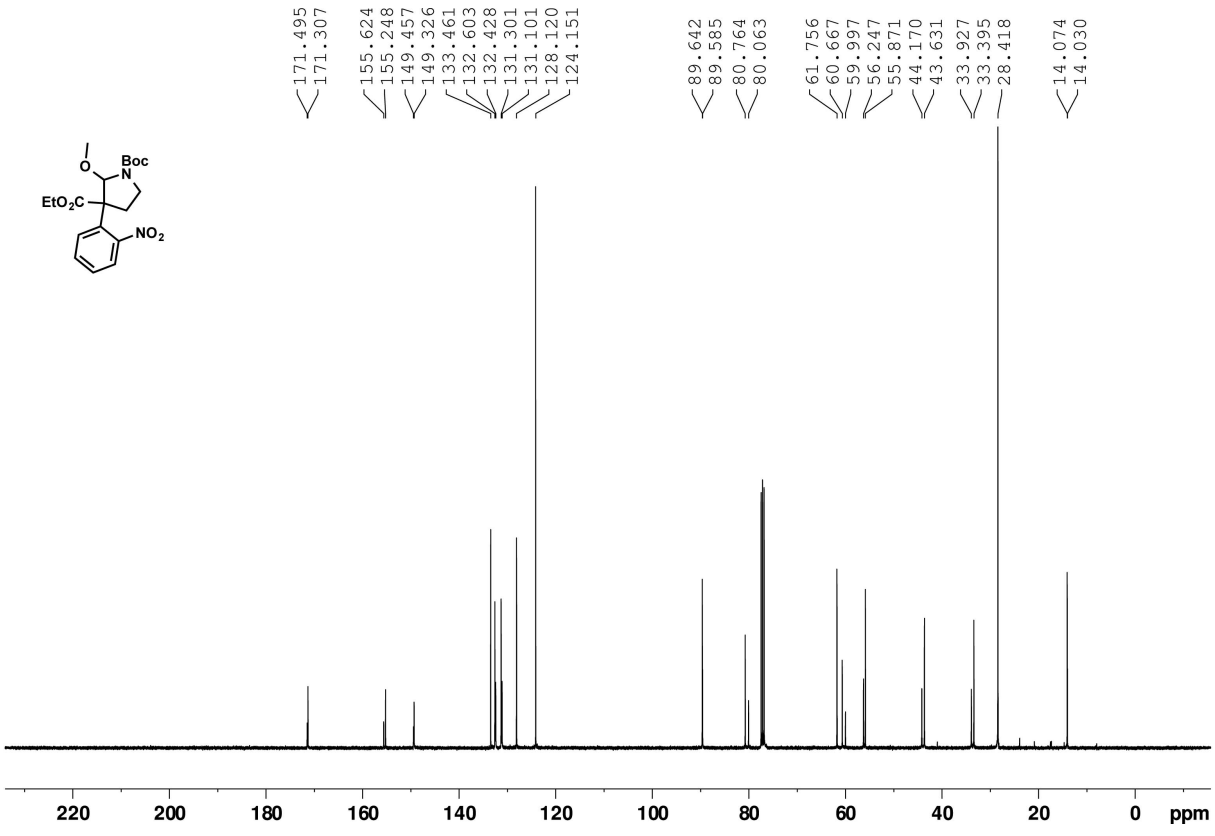
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44.170
43.631
33.927
33.395
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EtO2C
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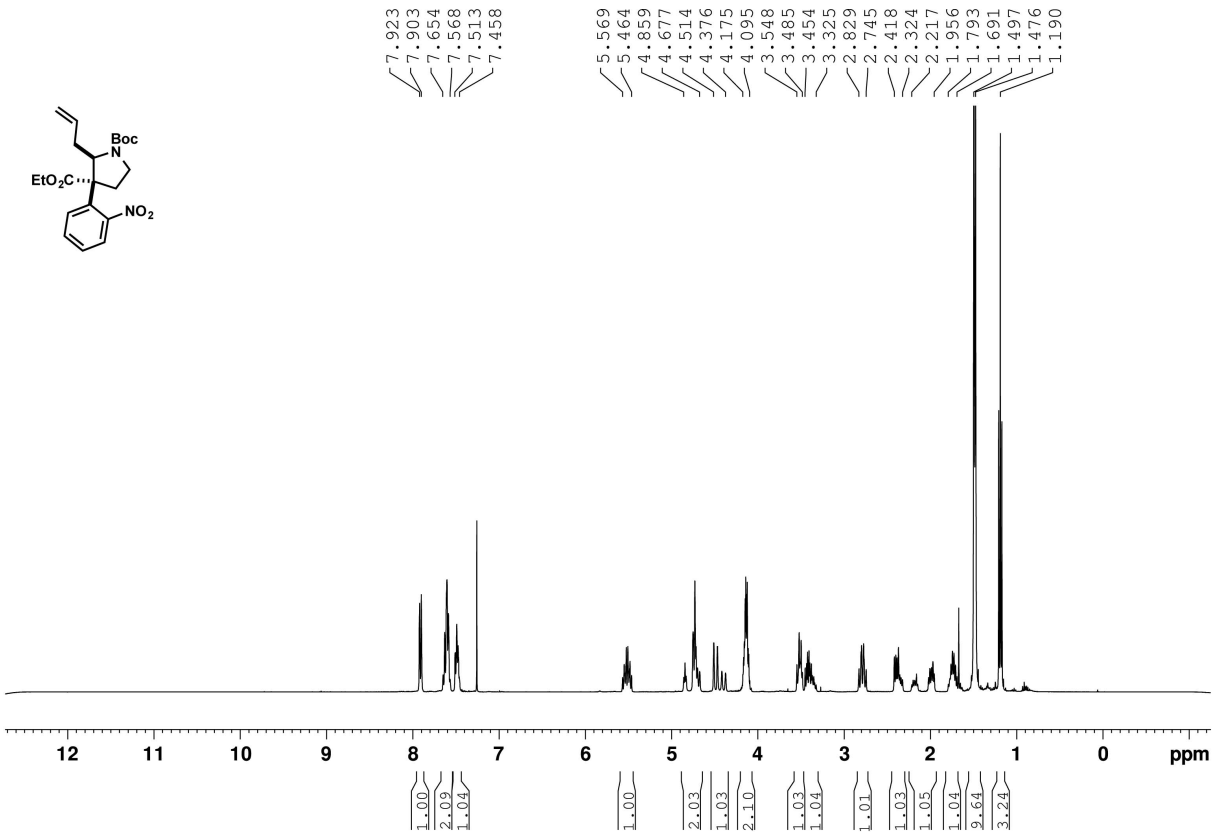
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4.175
4.095
3.548
3.485
3.454
3.325
2.829
2.745
2.418
2.324
2.217
1.956
1.793
1.691
1.497
1.476
1.190
Boc
N
EtO2C
NO2
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11
10
9
8
7
6
5
4
3
2
1
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ppm
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1.04
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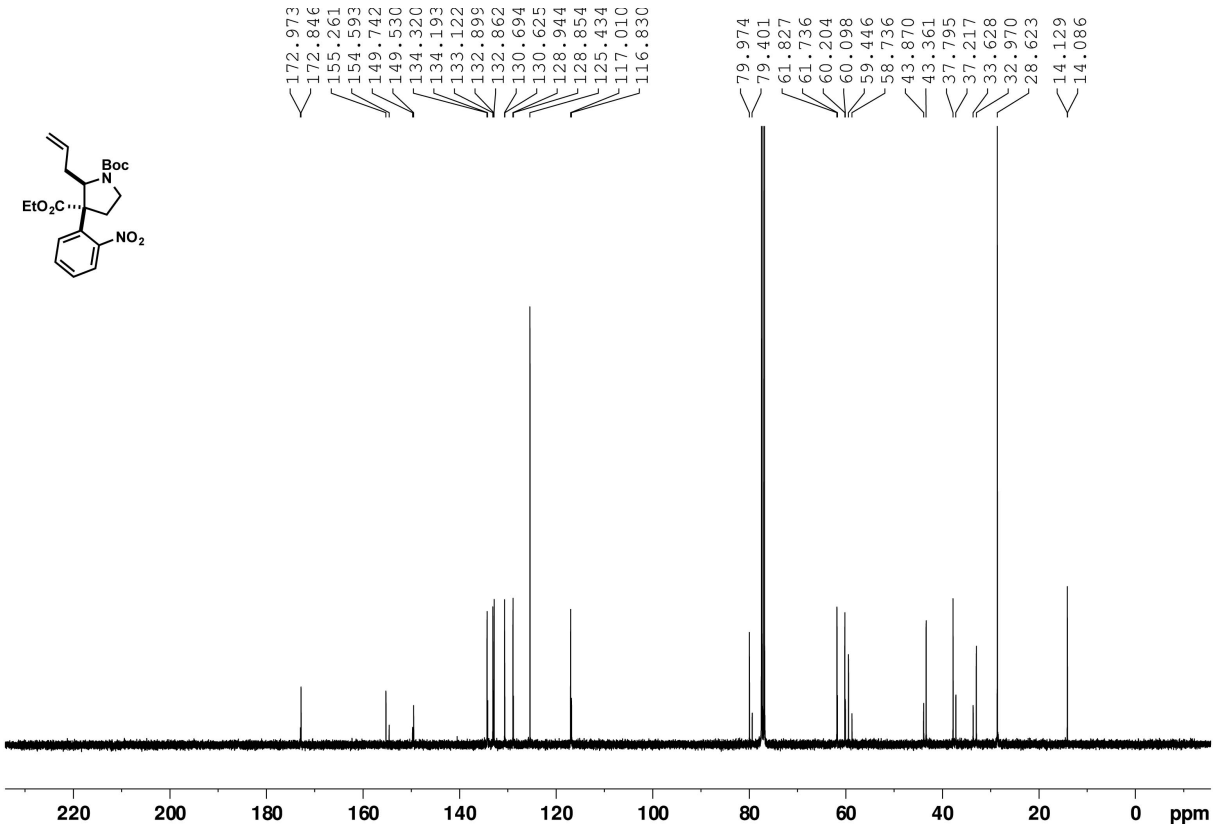
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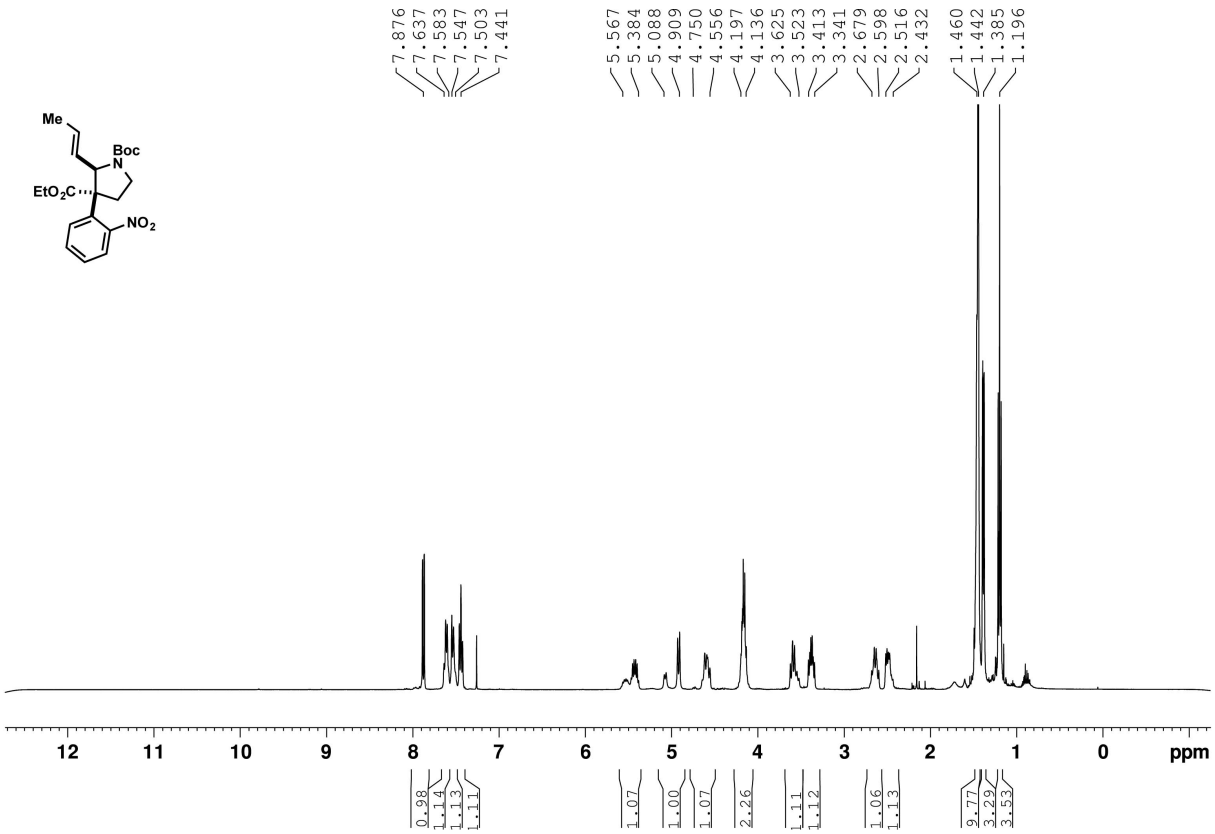
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3.413
3.341
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2.598
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1.442
1.385
1.196
Me
Boc
N
EtO2C
NO2
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
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1.13
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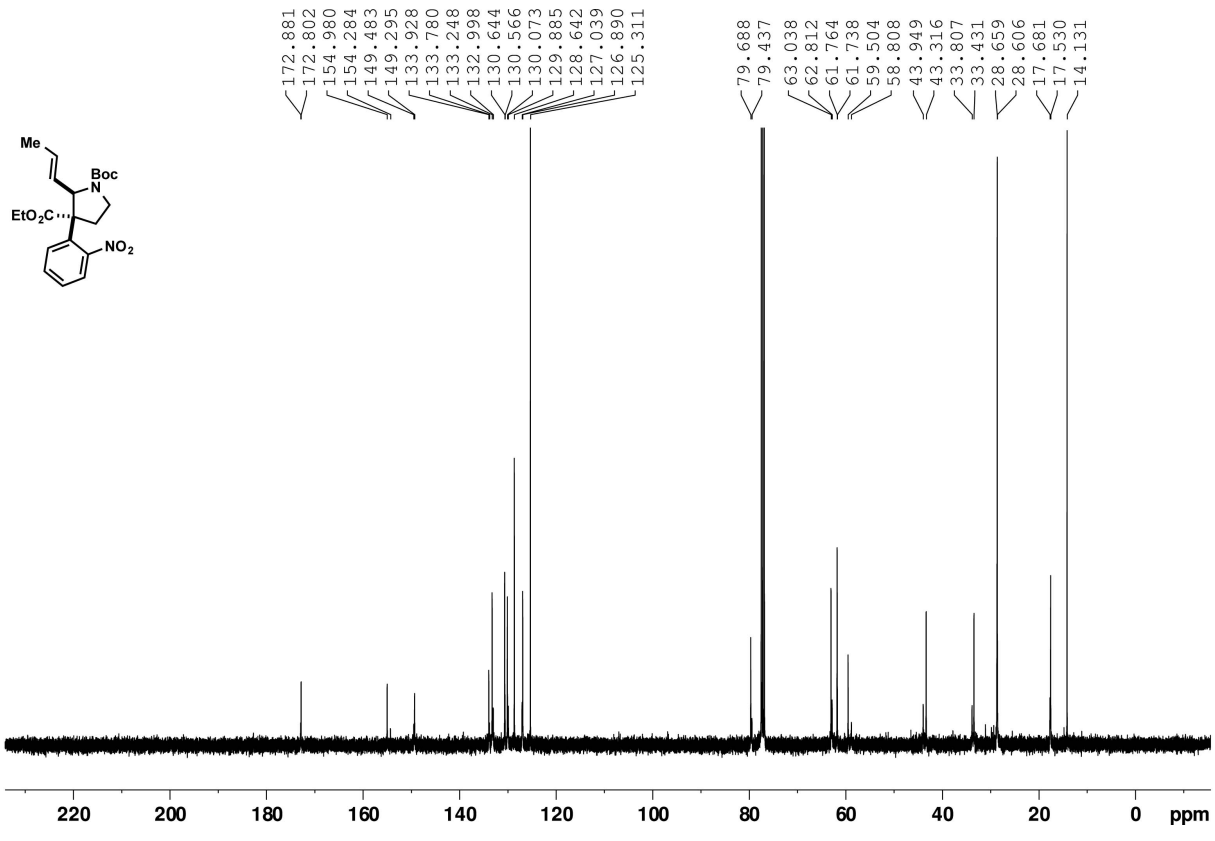
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127.039
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61.764
61.738
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17.530
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Boc
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EtO2C
NO2
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40
20
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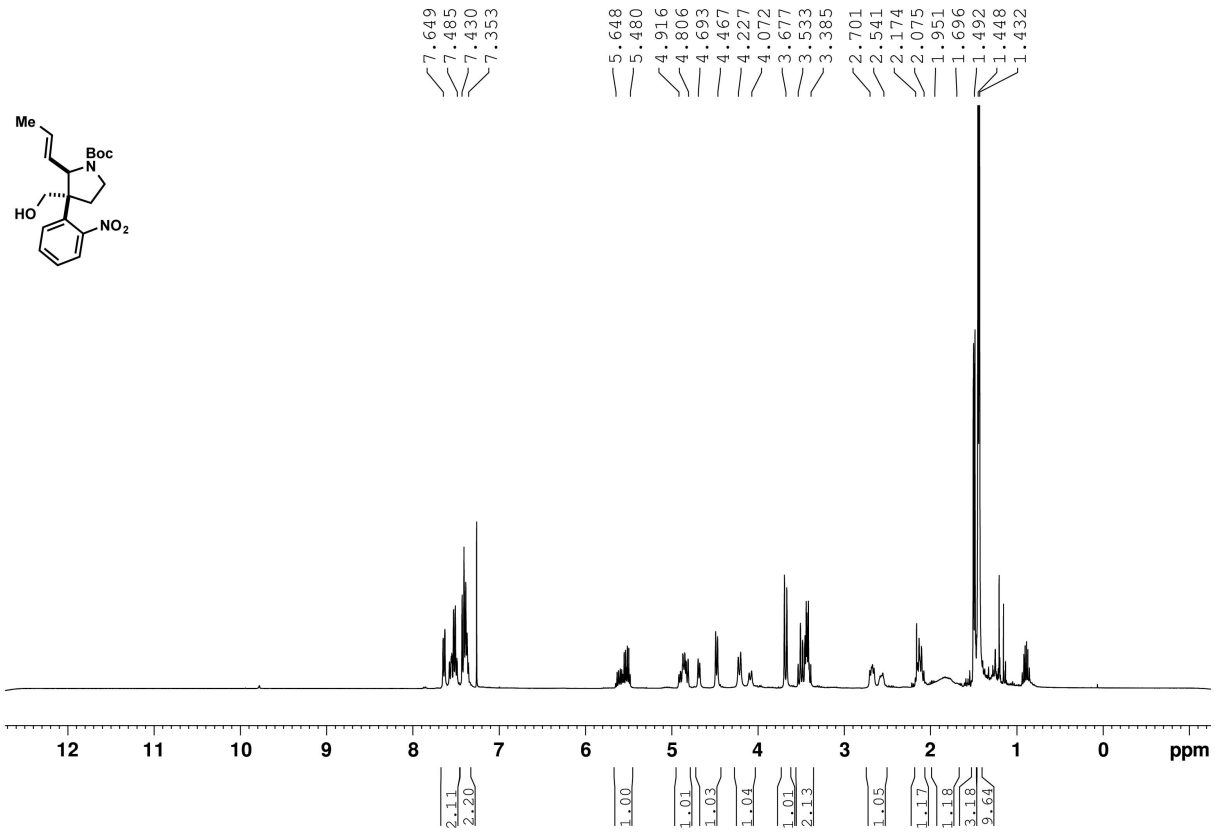
ppm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3.385
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2.541
2.174
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1.951
1.696
1.492
1.448
1.432
Me
Boc
N
HO
NO2
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11
10
9
8
7
6
5
4
3
2
1
0
ppm
2.11
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1.03
1.04
1.01
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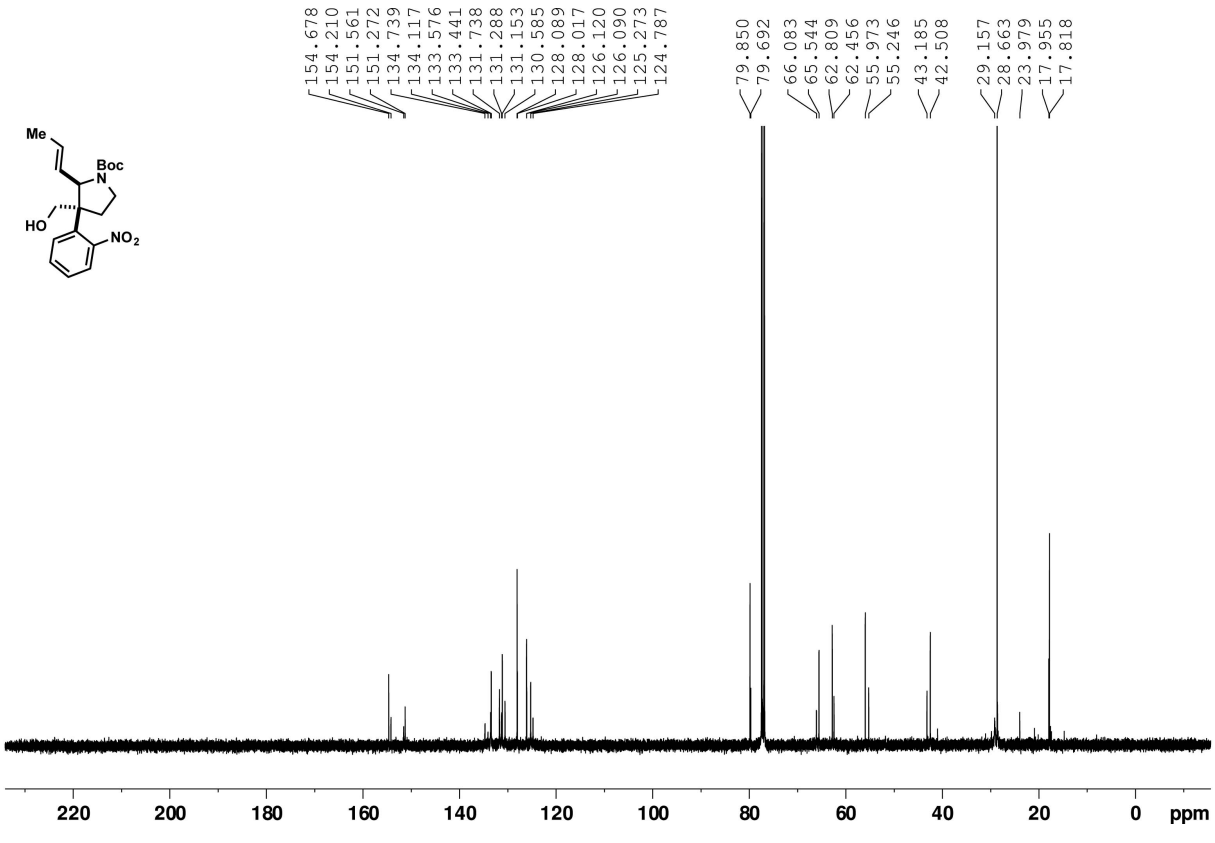
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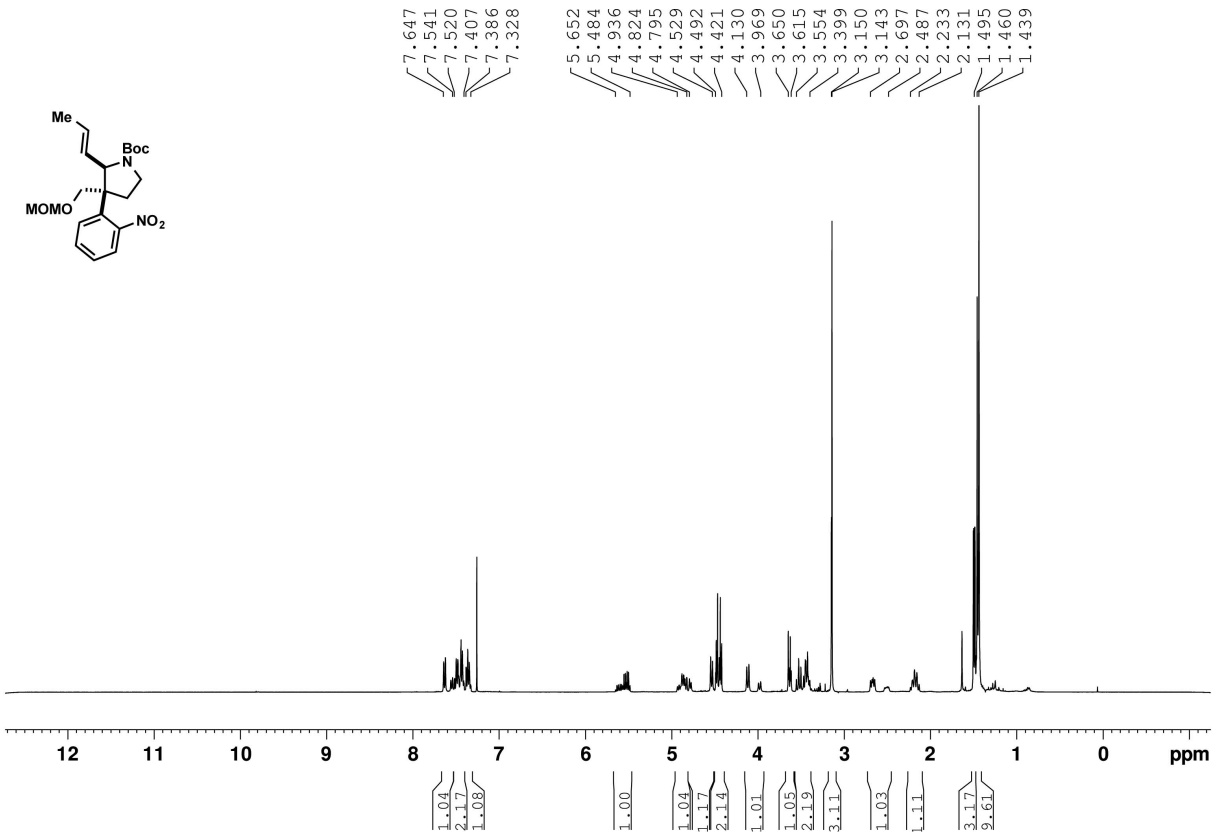
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Boc
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MOMO
NO2
12
11
10
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8
7
6
5
4
3
2
1
0
ppm
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2.17
1.08
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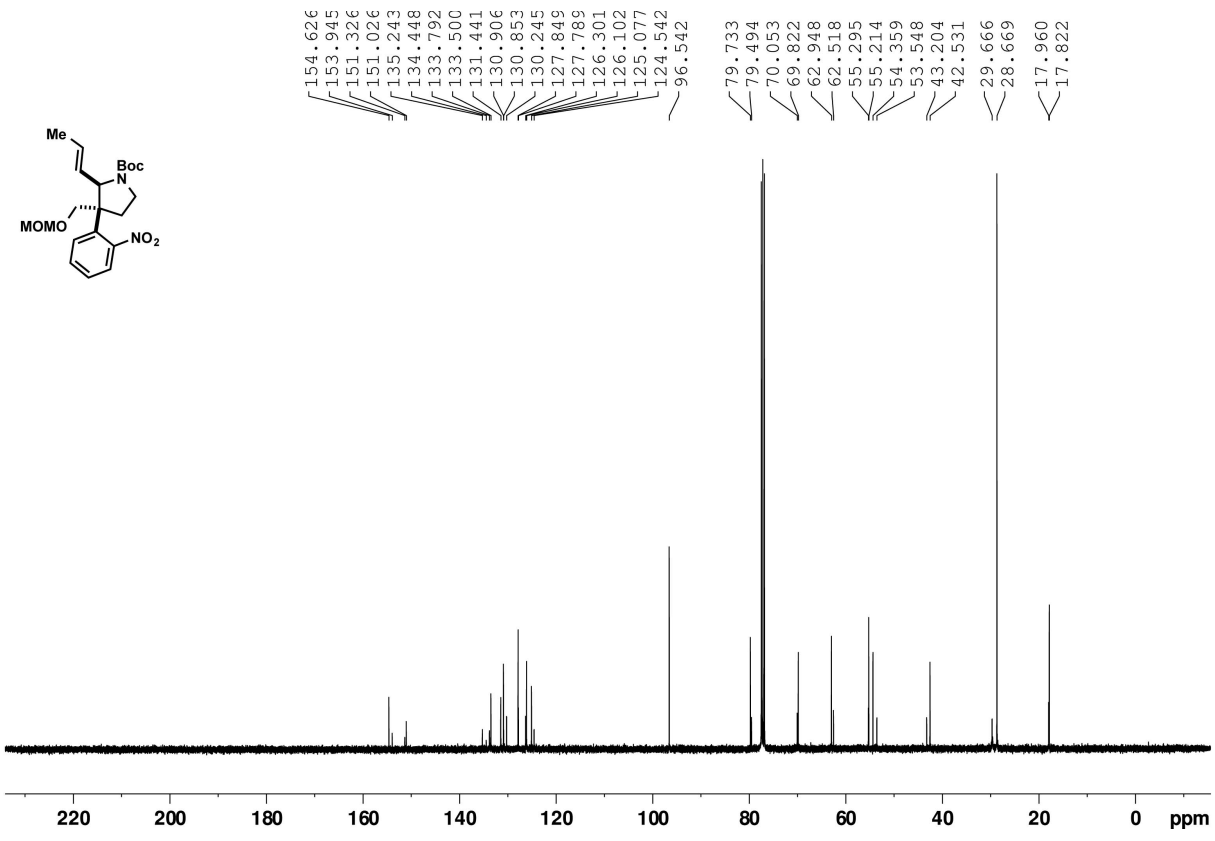
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17.822
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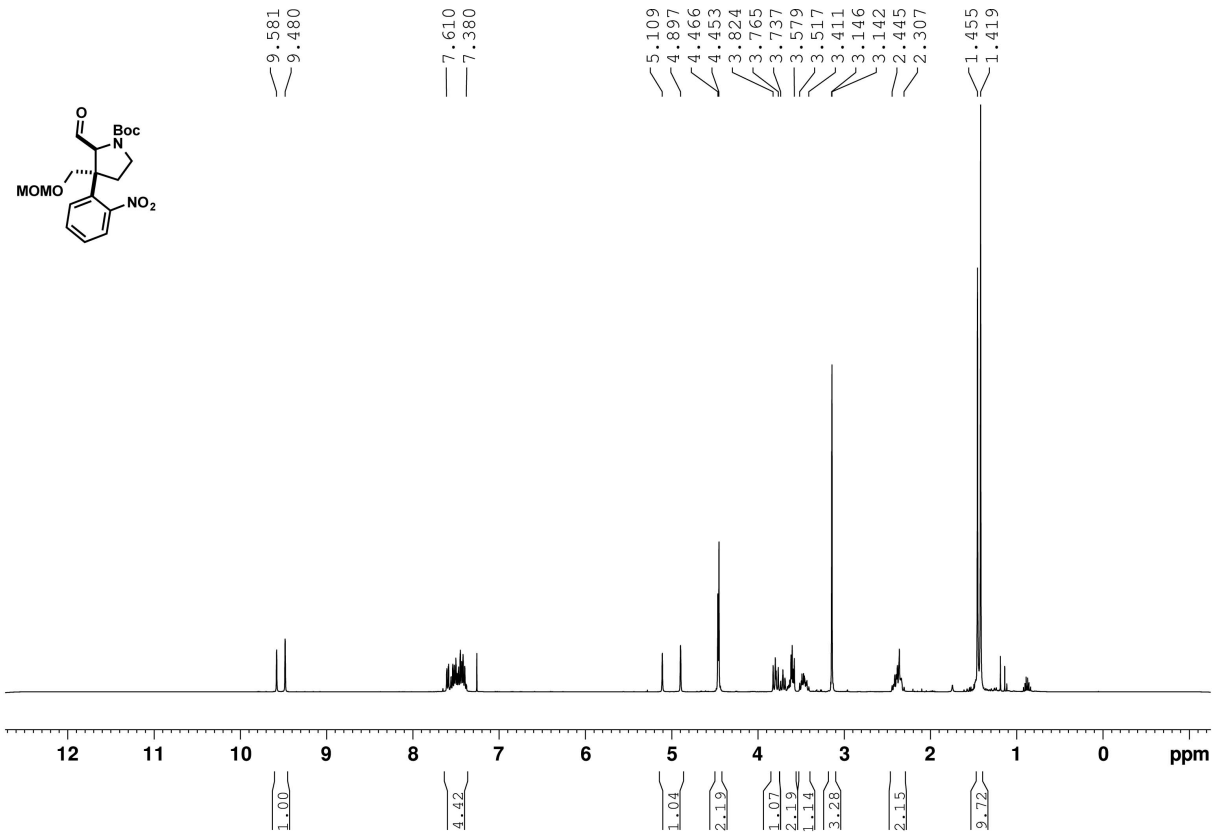
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Boc
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O
MOMO
NO2
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11
10
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8
7
6
5
4
3
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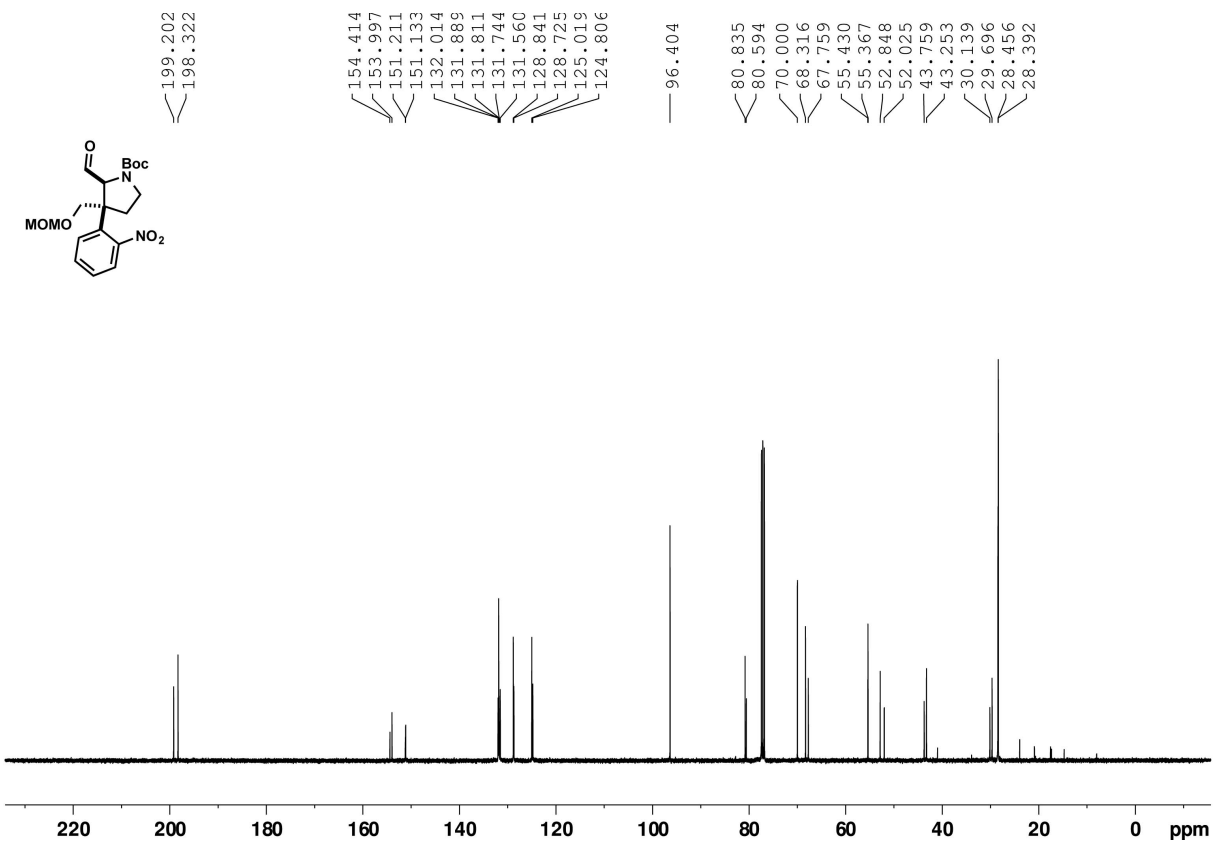
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NO2
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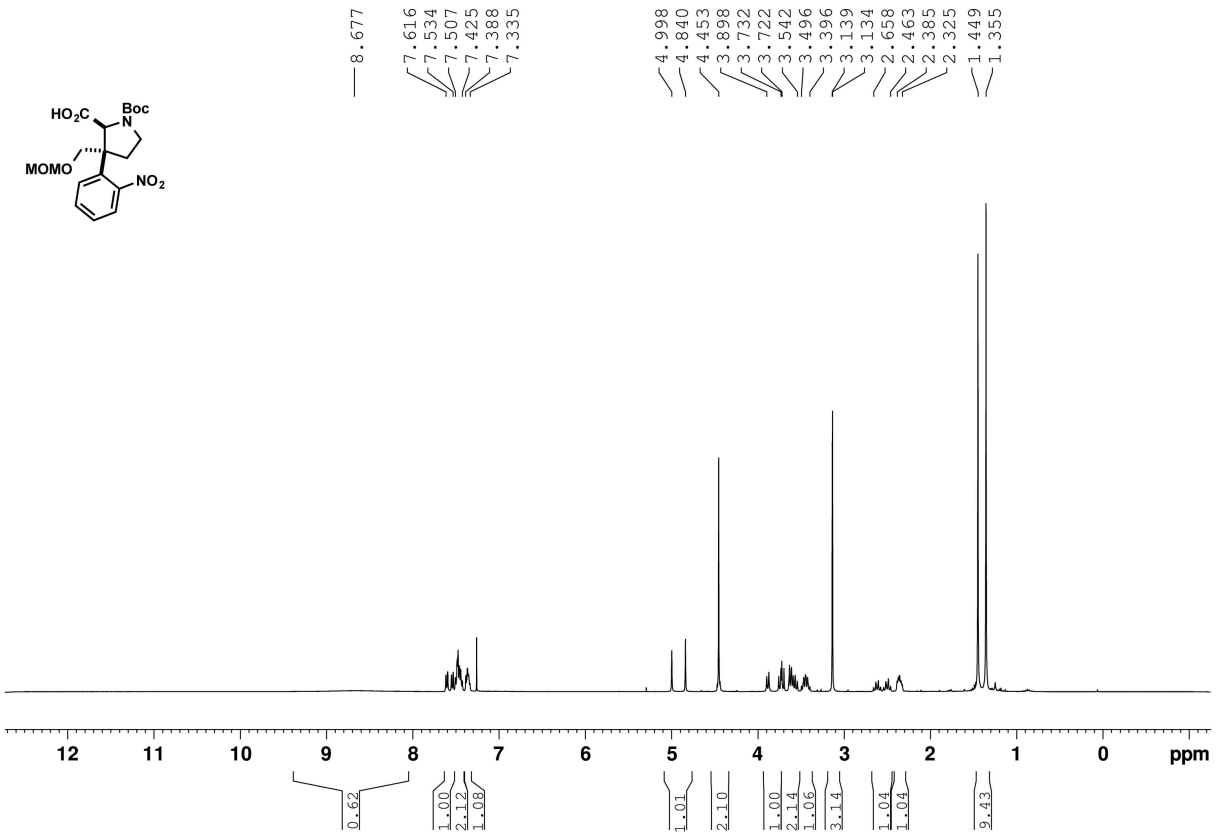
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3.496
3.396
3.139
3.134
2.658
2.463
2.385
2.325
1.449
1.355
HO2C
Boc
N
MOMO
NO2
12
11
10
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8
7
6
5
4
3
2
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ppm
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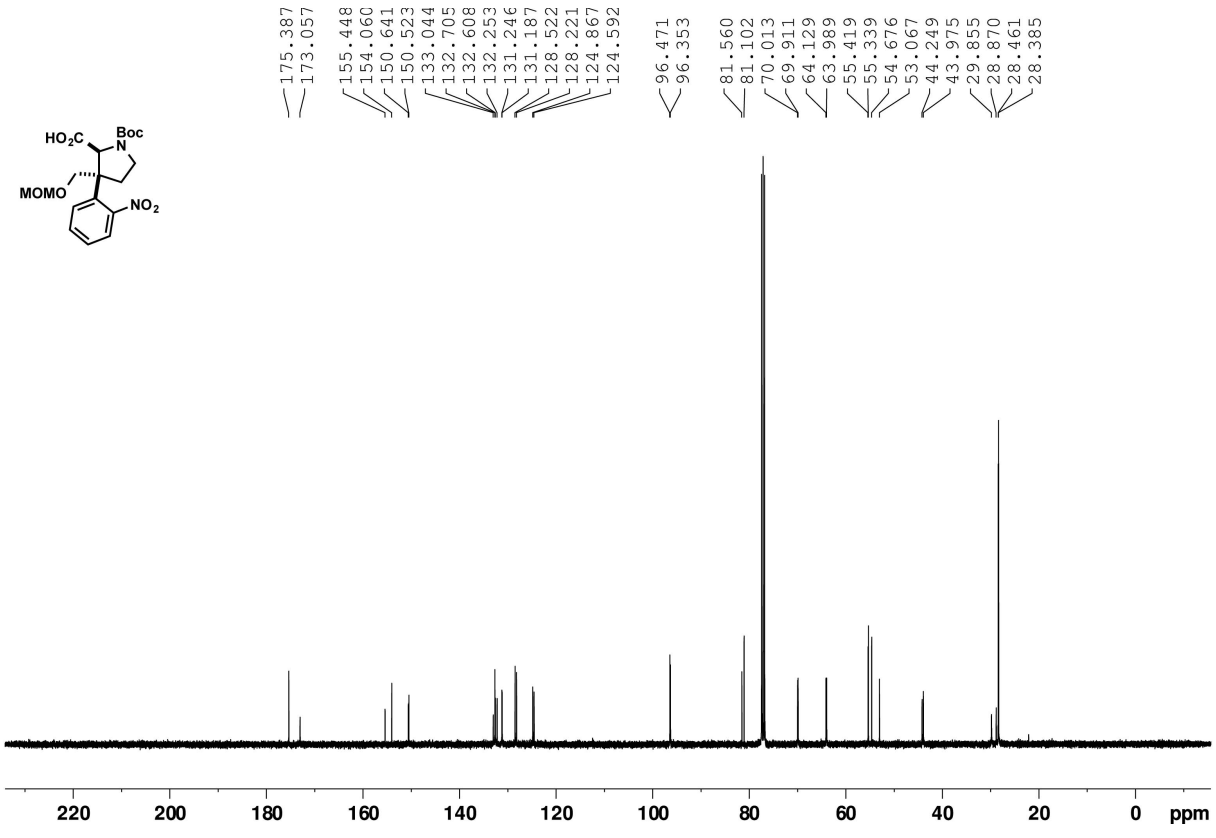
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NO2
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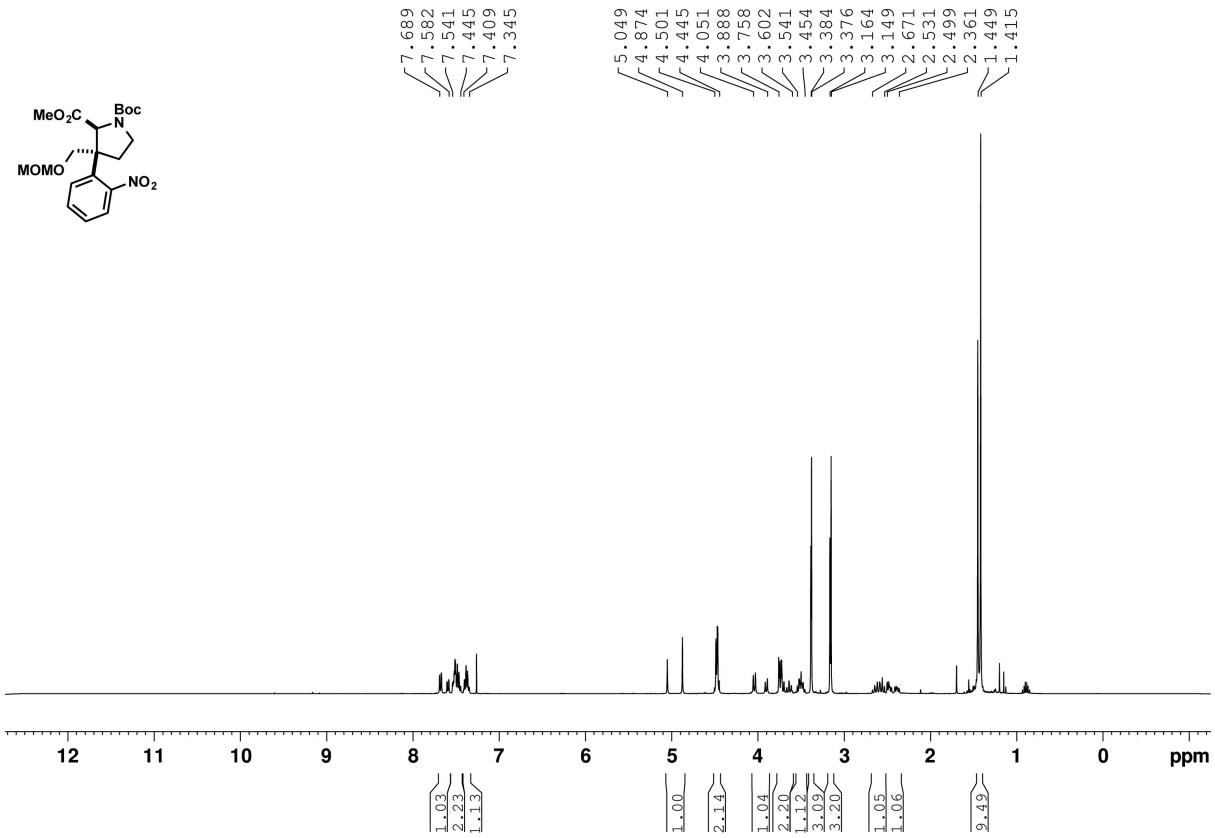
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MeO2C
Boc
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MOMO
NO2
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11
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5
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3
2
1
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ppm
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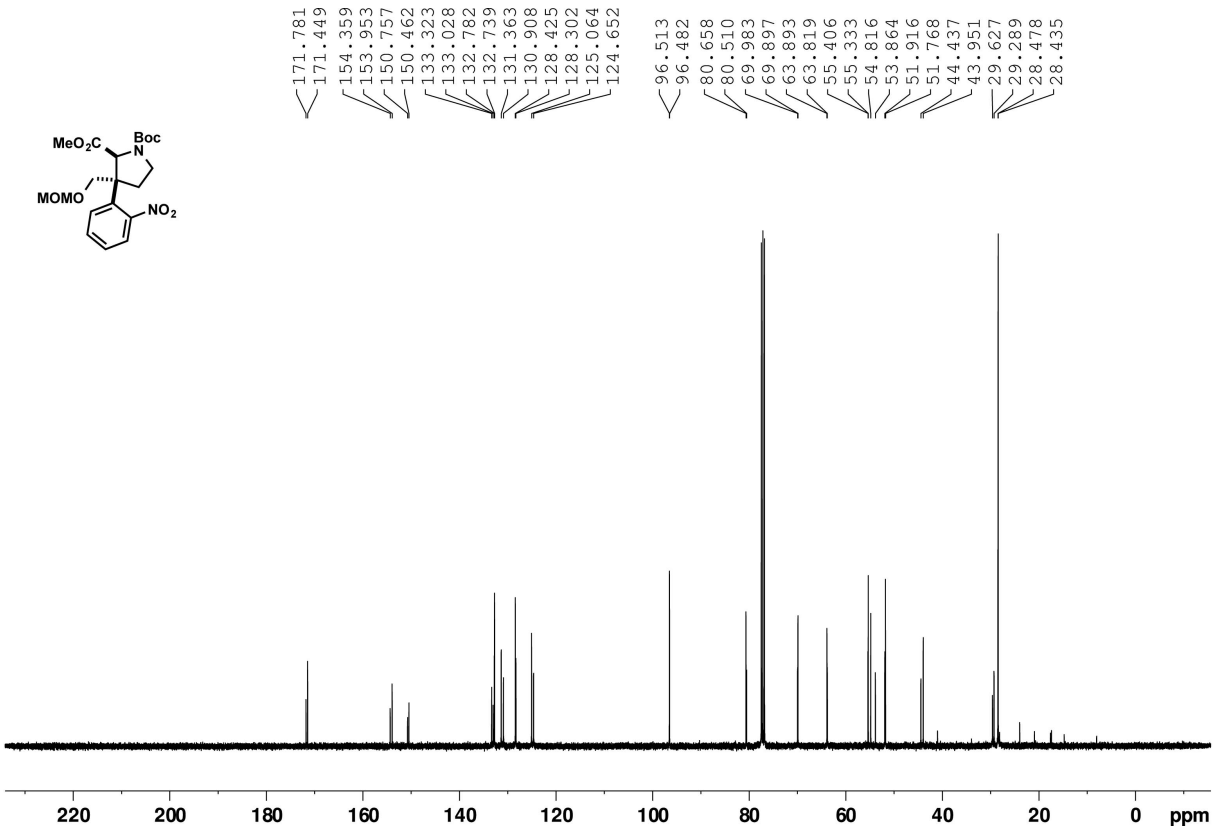
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28.435
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Boc
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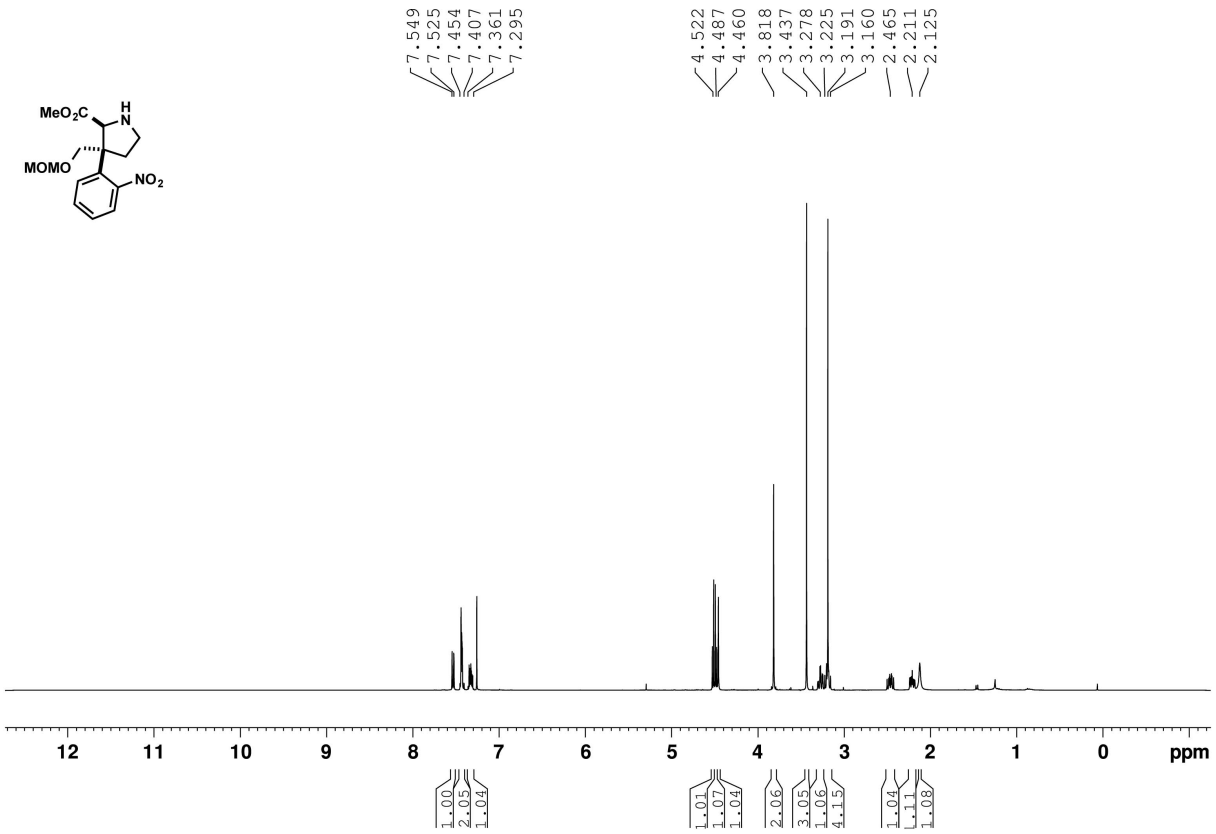
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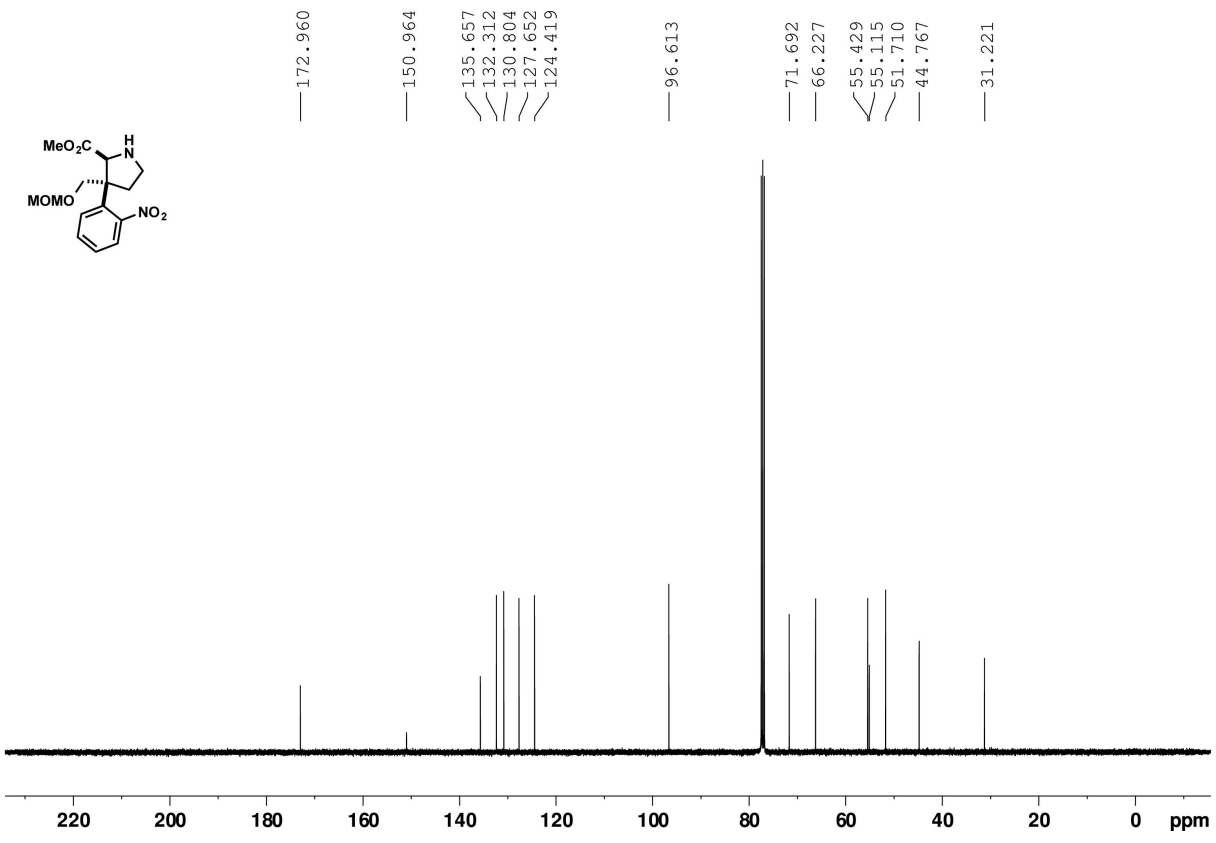
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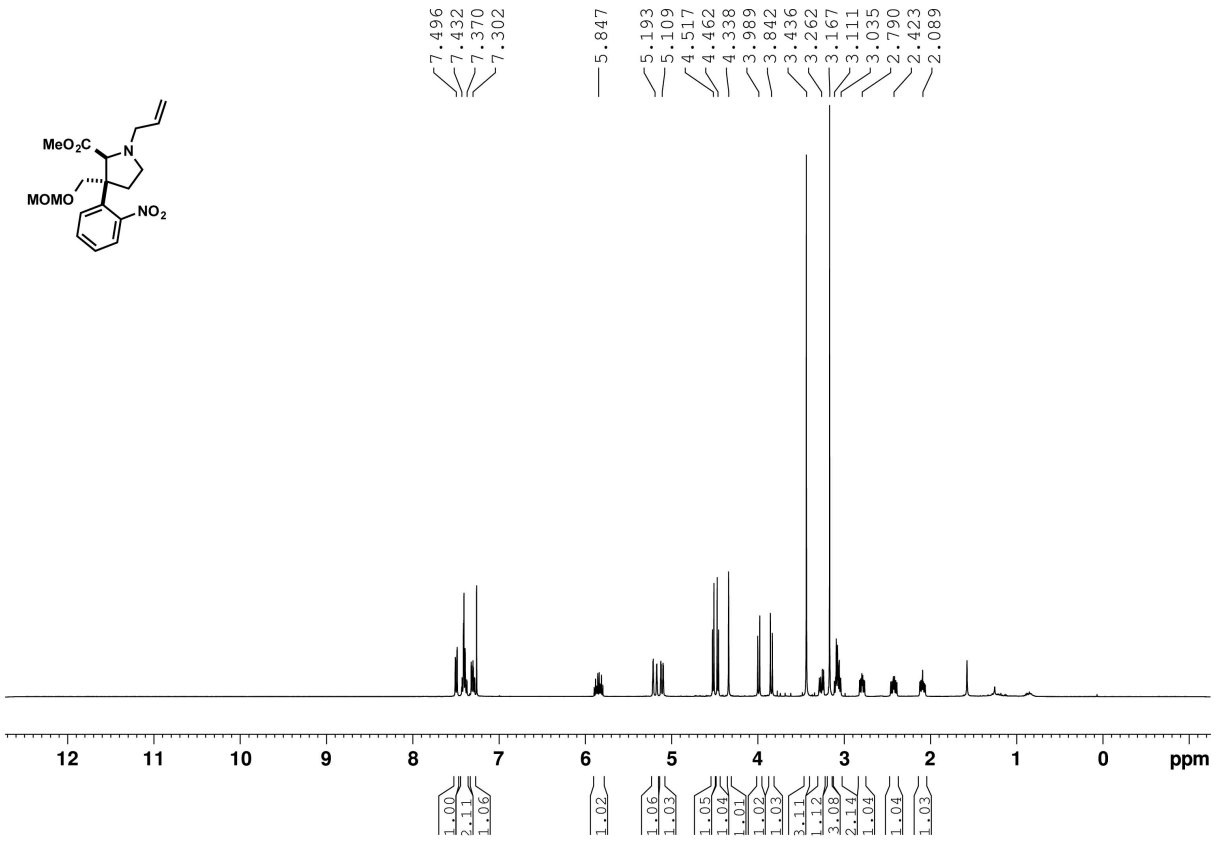
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MOMO
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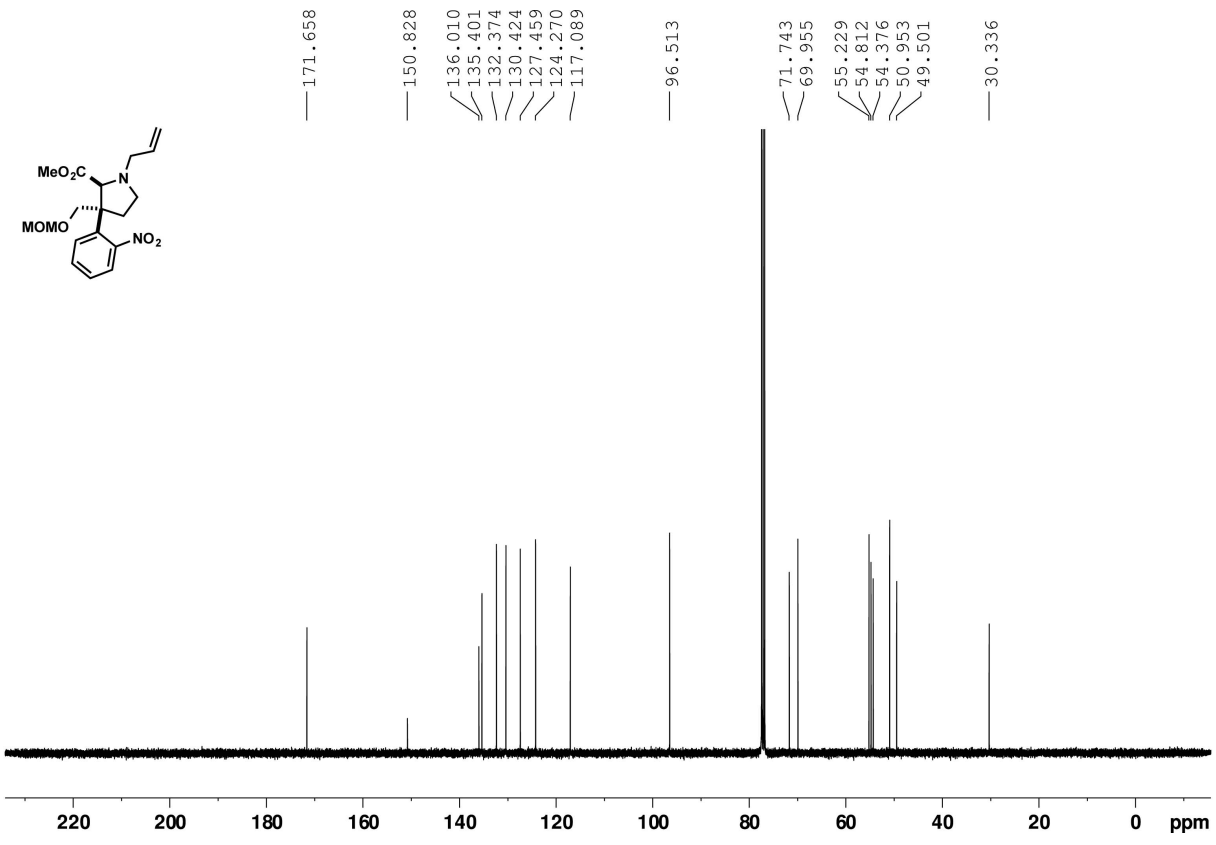
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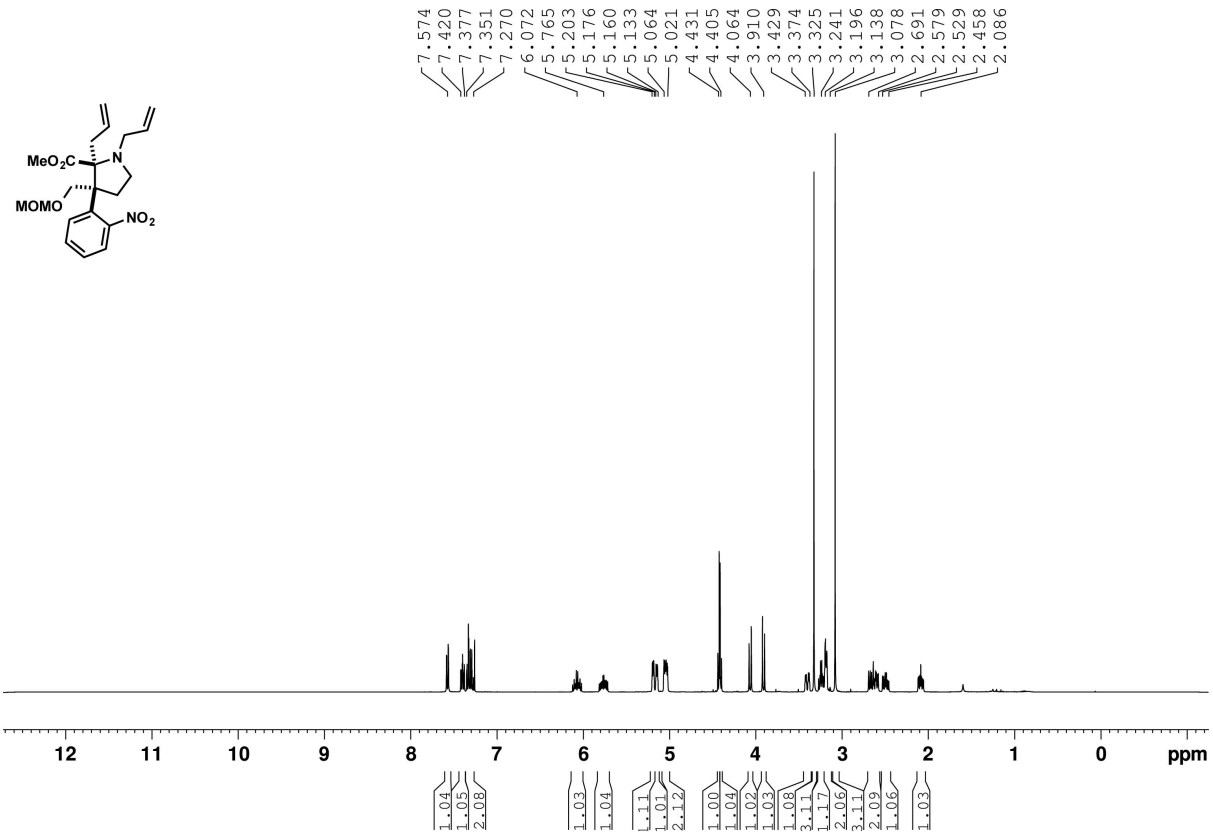
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4.405
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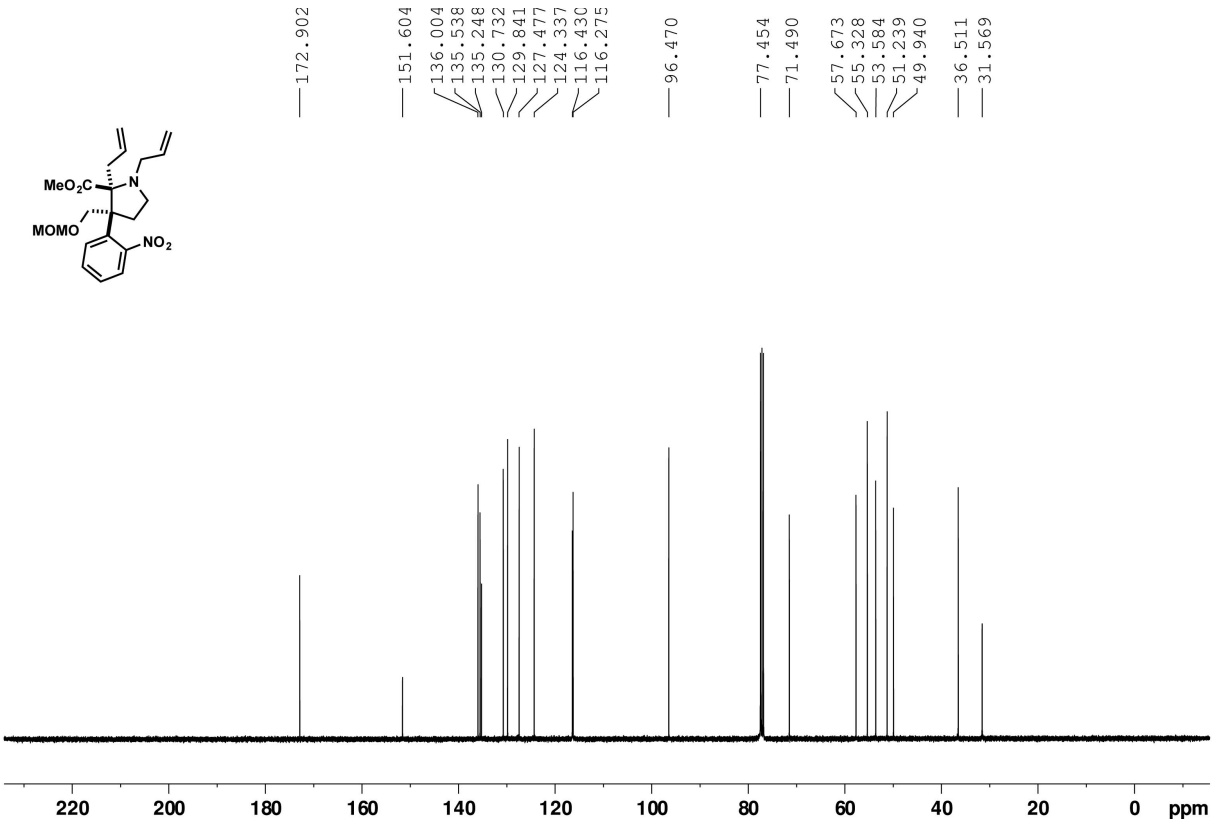
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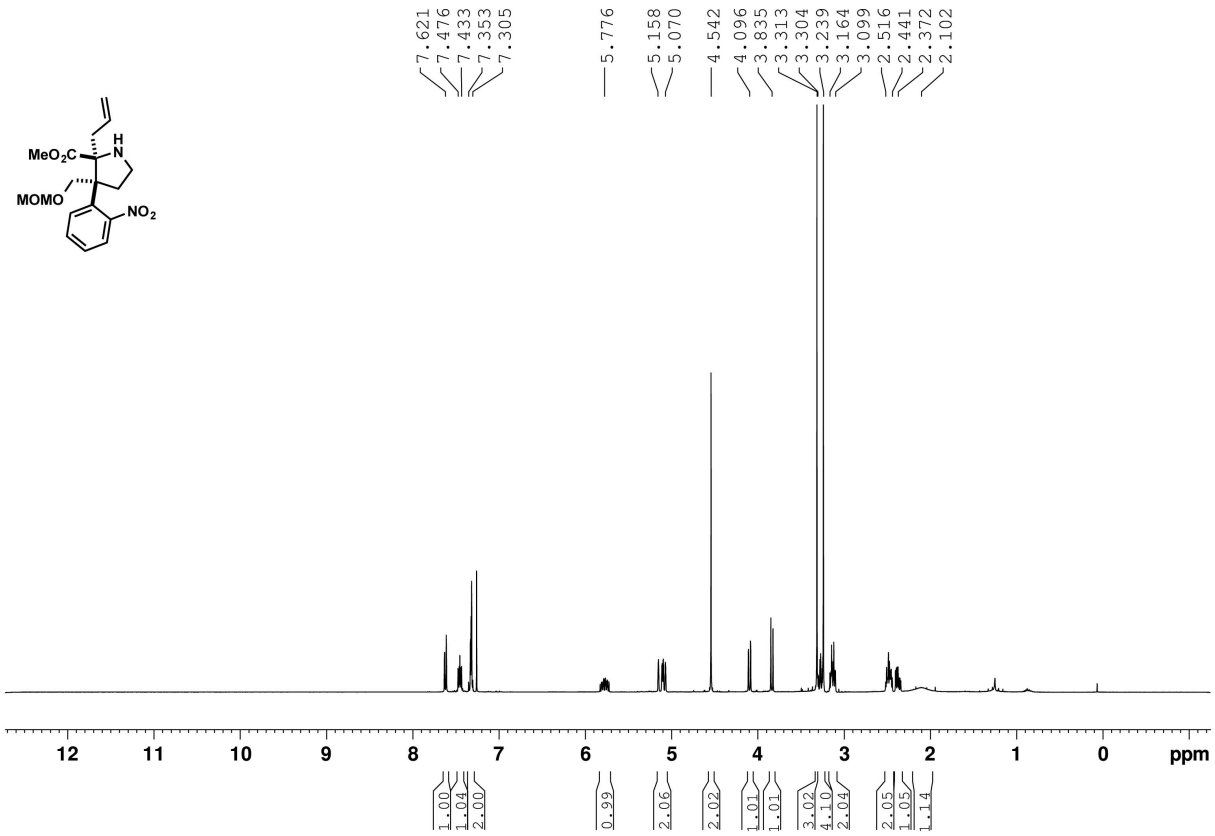
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2.372
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MeO2C
H
N
MOMO
NO2
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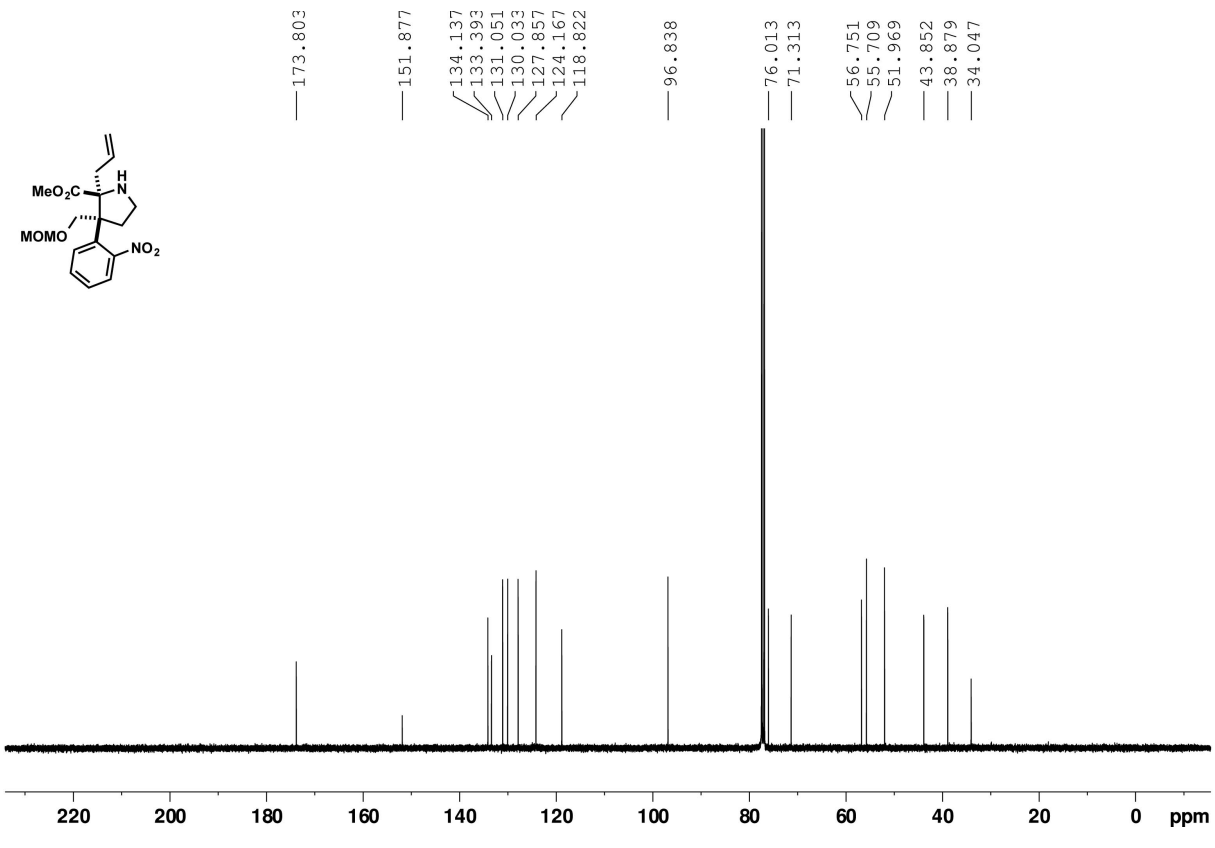
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56.751
55.709
51.969
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H
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MOMO
NO2
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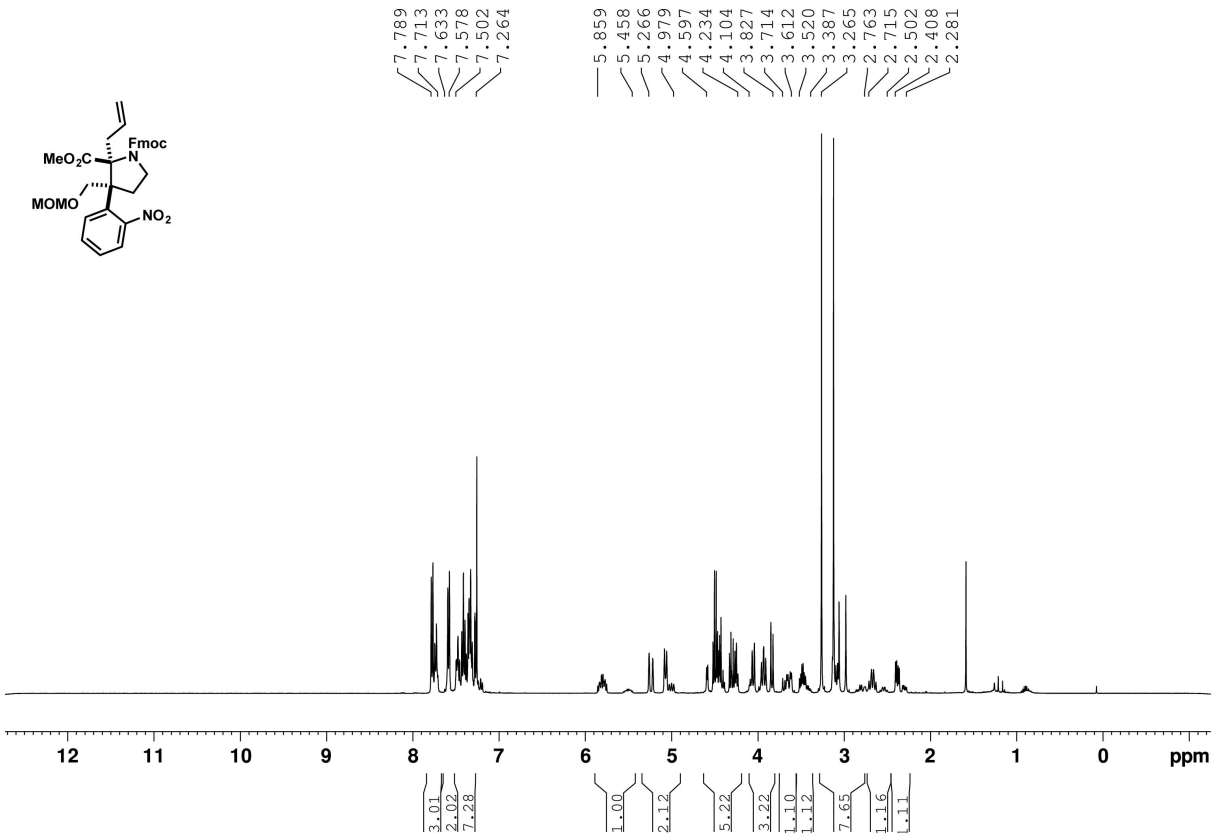
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4.104
3.827
3.714
3.612
3.520
3.387
3.265
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2.715
2.502
2.408
2.281
Fmoc
N
MeO2C
MOMO
NO2
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11
10
9
8
7
6
5
4
3
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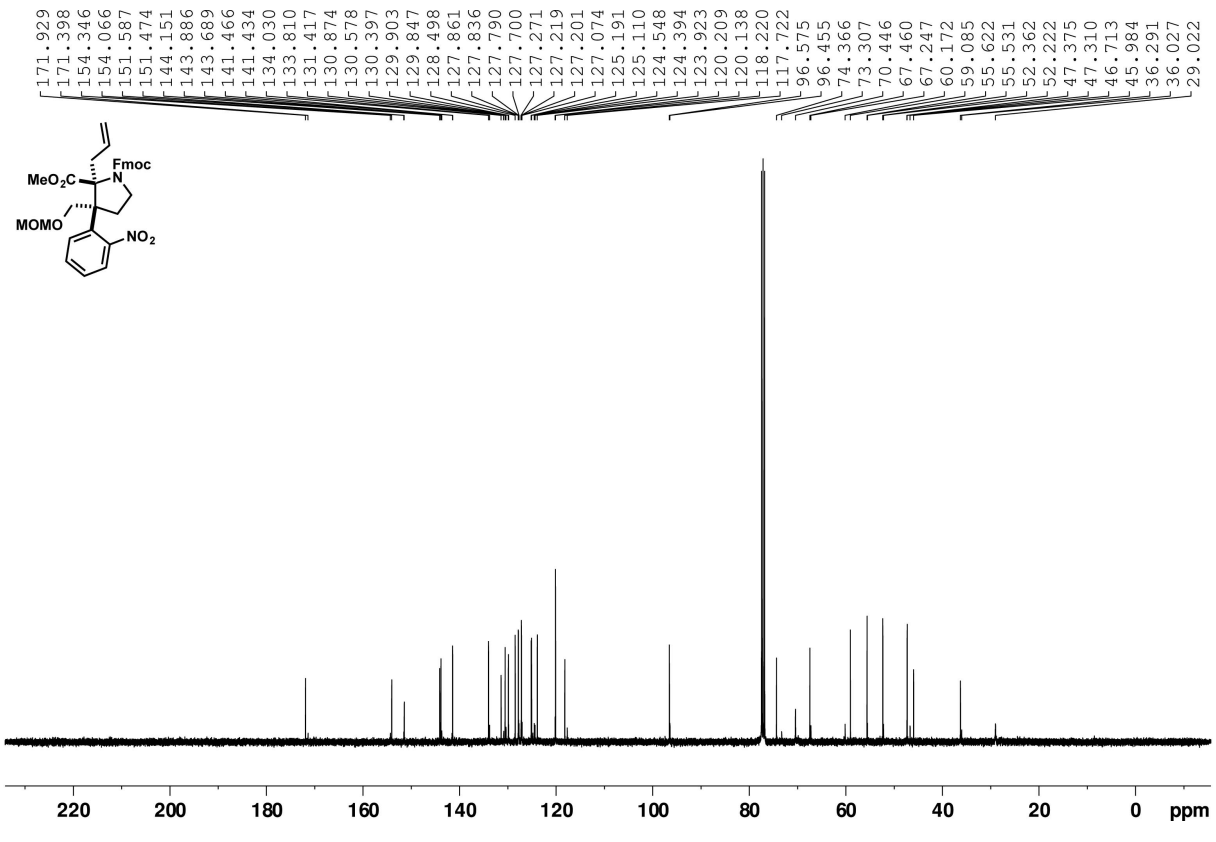
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47.310
46.713
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MOMO
NO2
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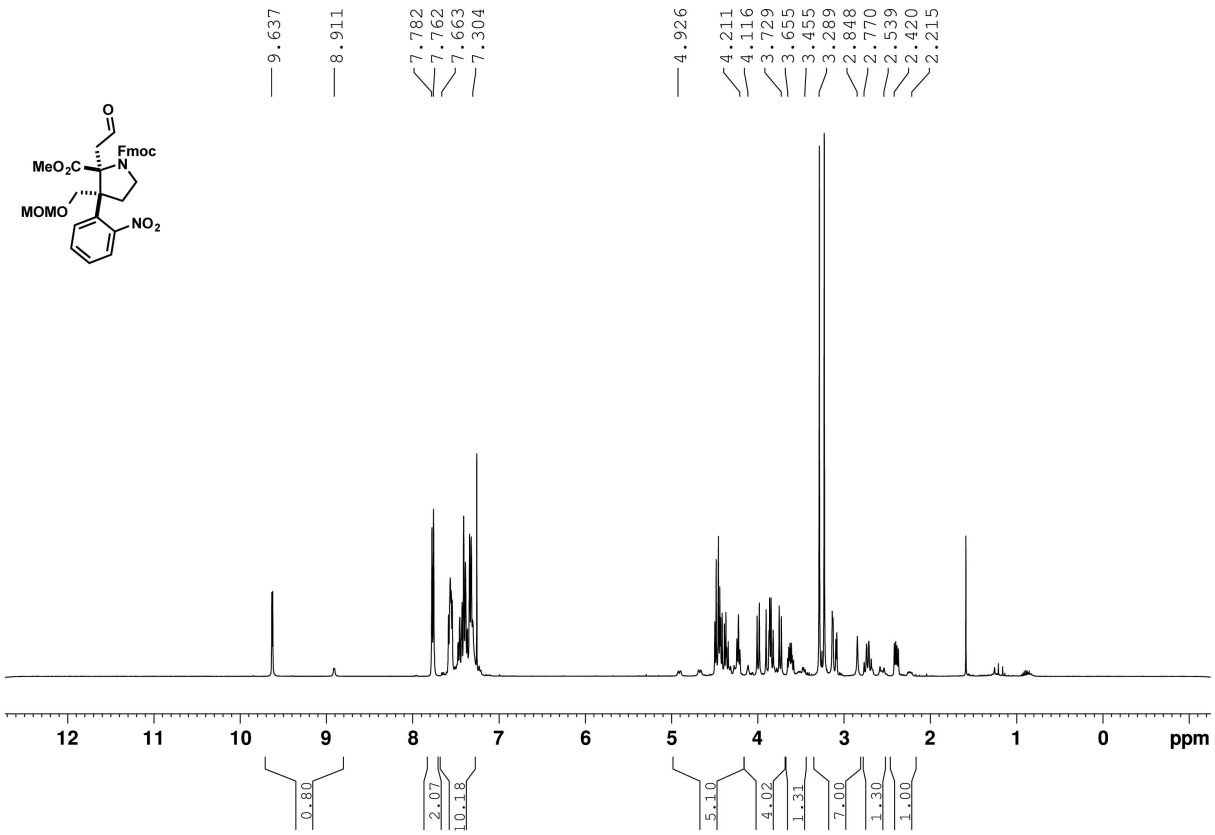
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2.848
2.770
2.539
2.420
2.215
O
Fmoc
N
MeO2C
MOMO
NO2
12
11
10
9
8
7
6
5
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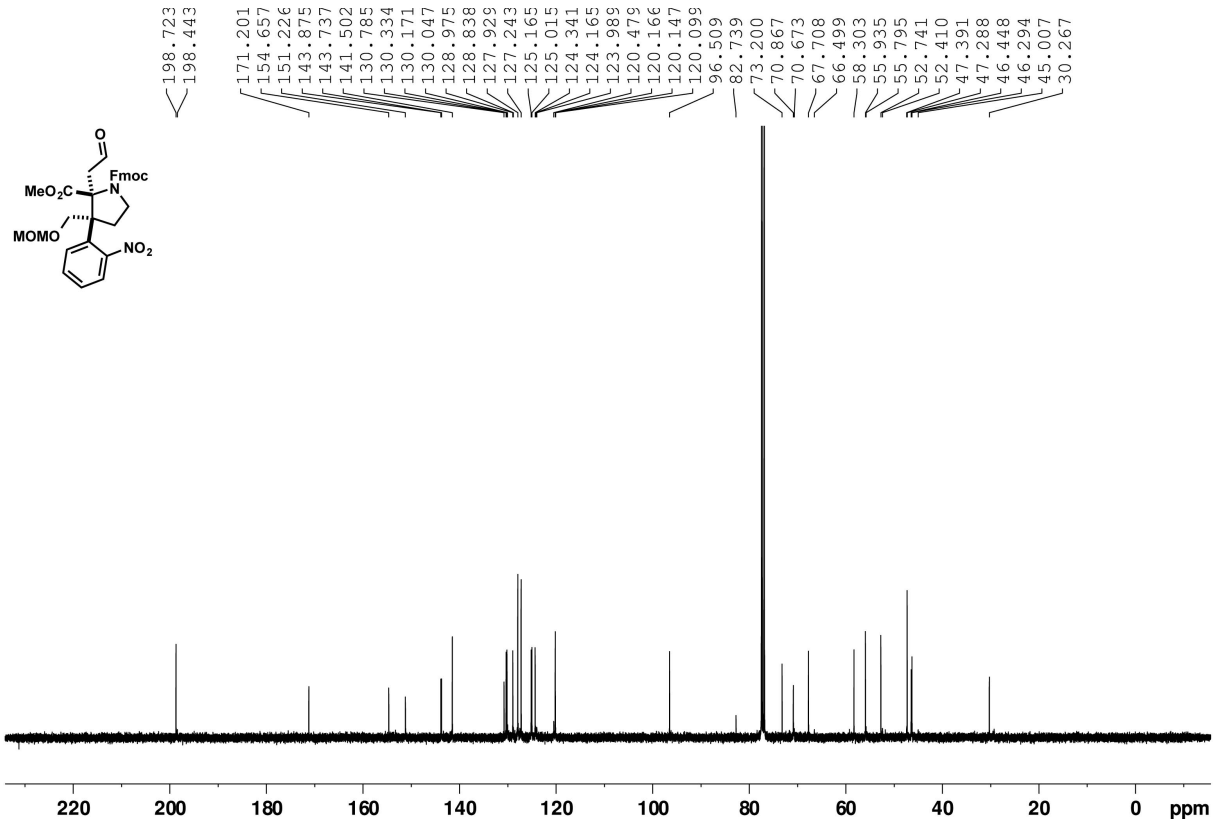
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O
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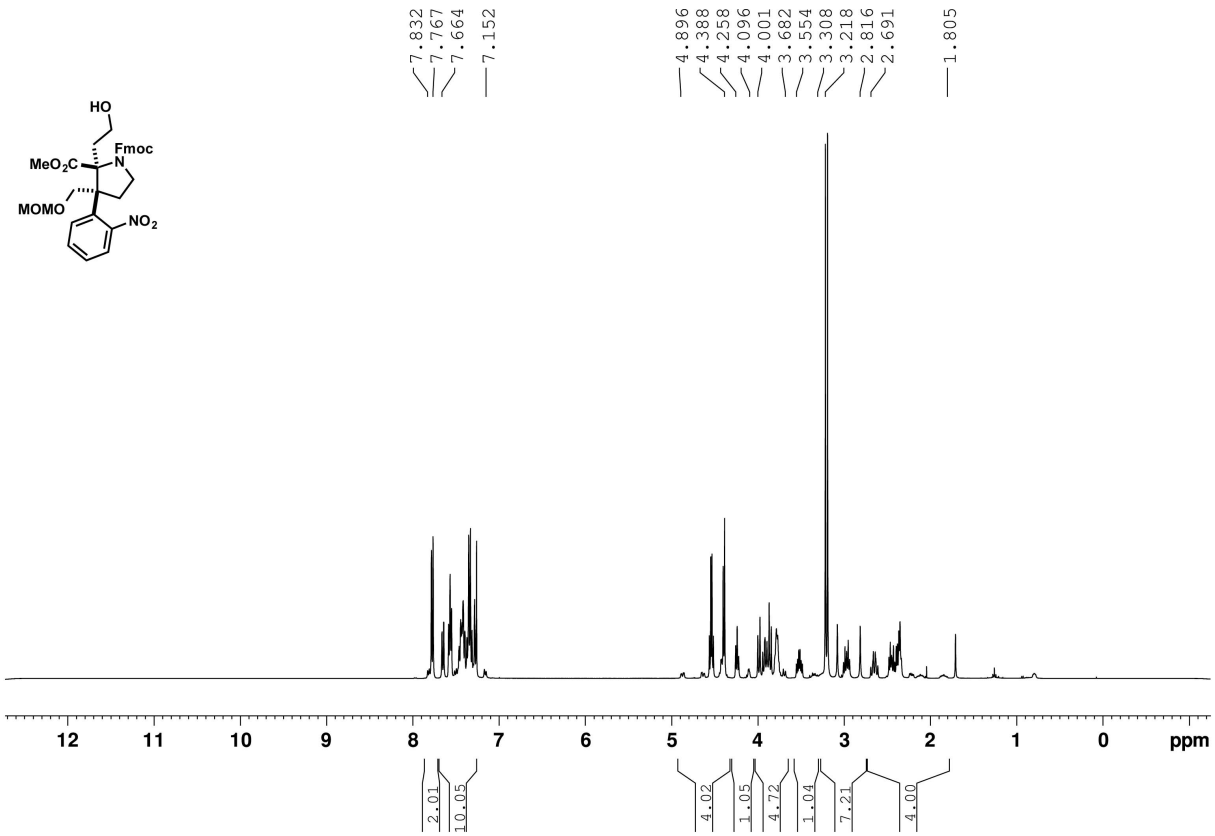
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1.805
HO
Fmoc
MeO2C
N
MOMO
NO2
12
11
10
9
8
7
6
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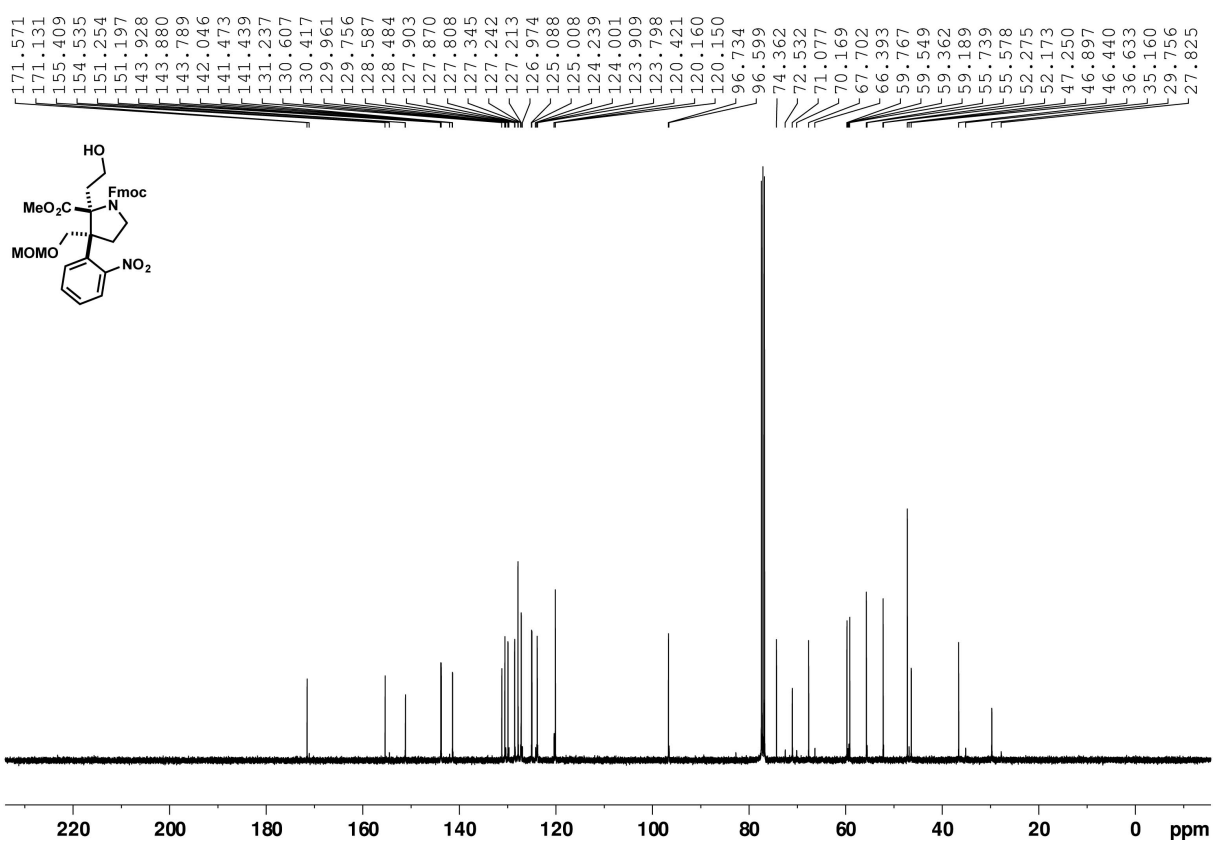
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127.242
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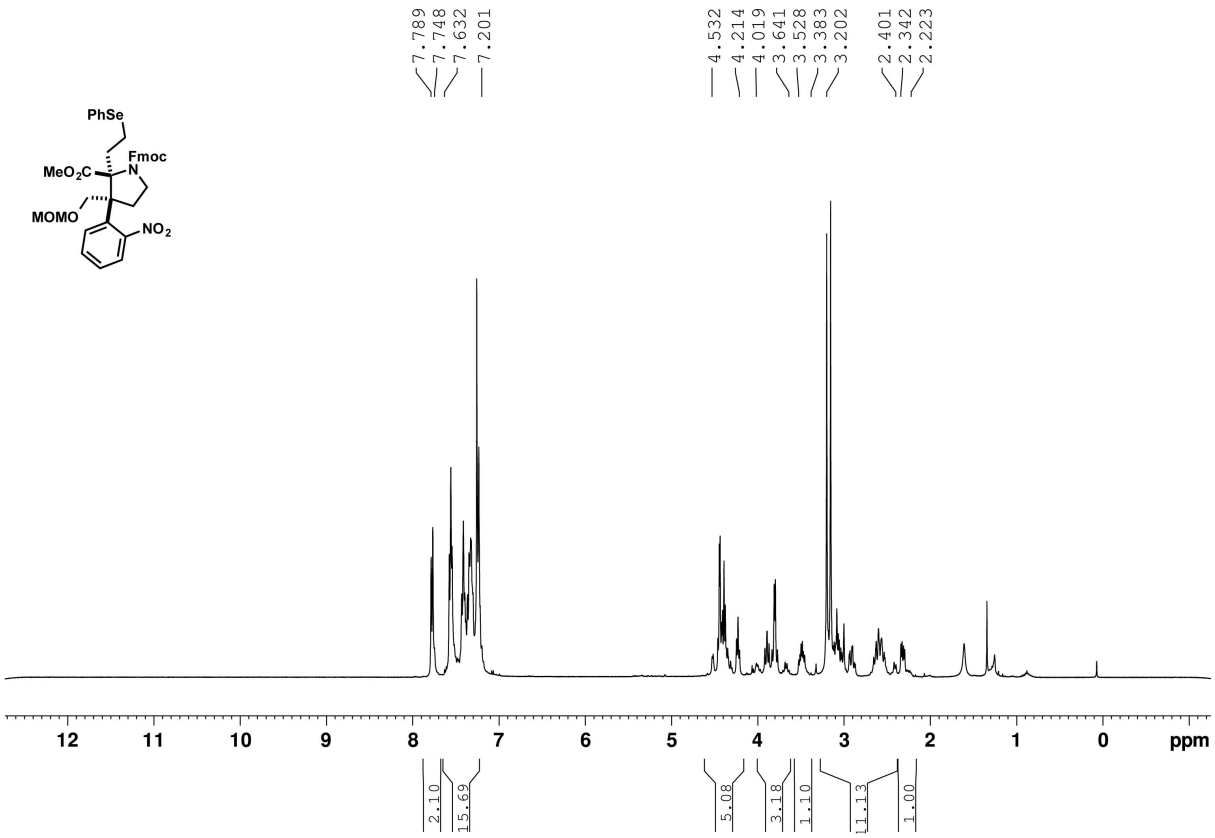
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MeO2C
N
MOMO
NO2
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11
10
9
8
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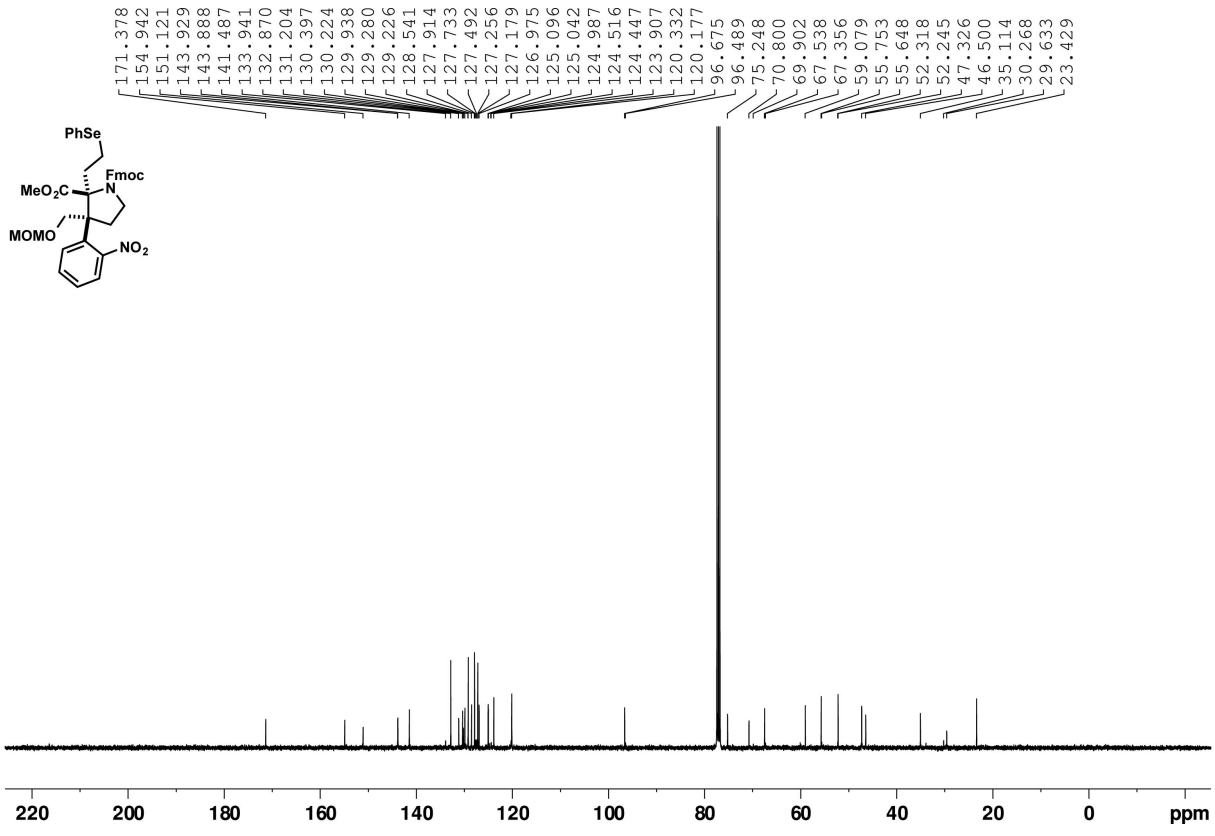
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PhSe
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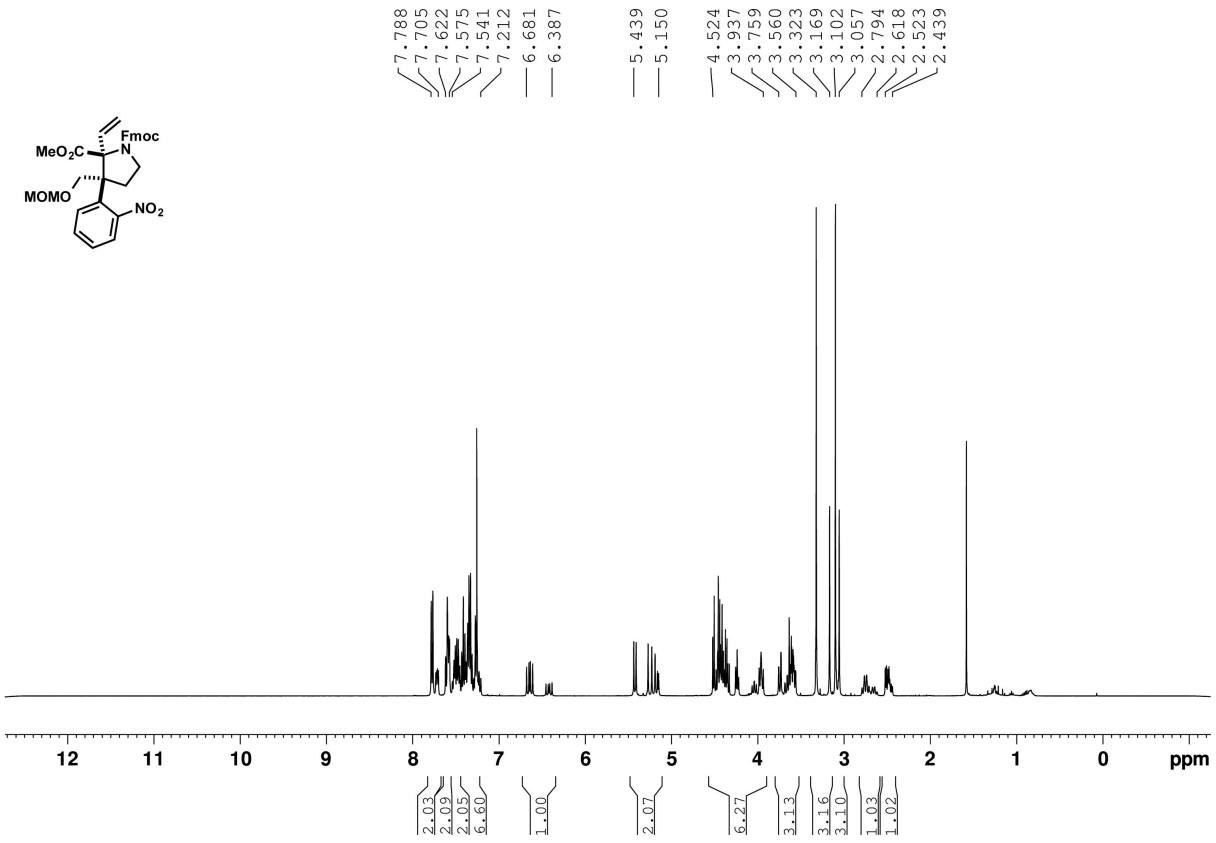
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3.102
3.057
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MeO2C
N
MOMO
NO2
12
11
10
9
8
7
6
5
4
3
2
1
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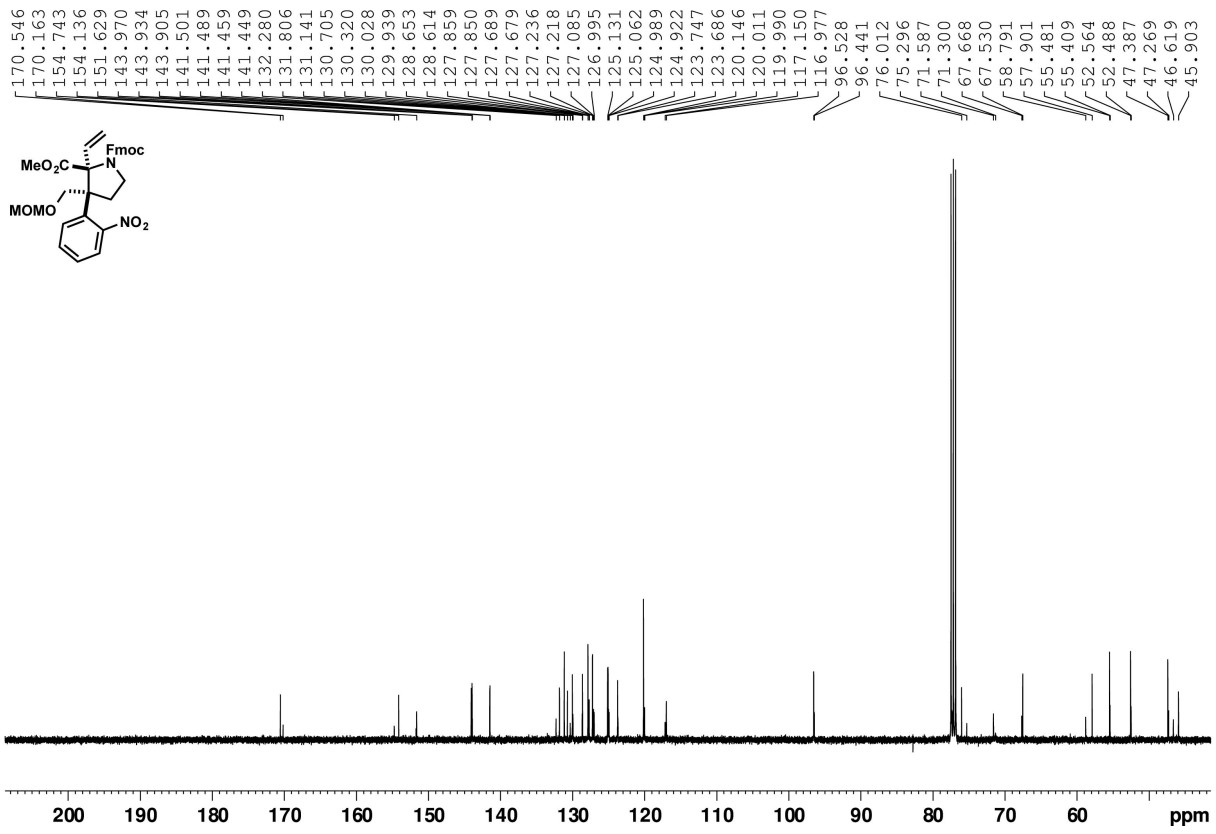
1.02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MeO2C
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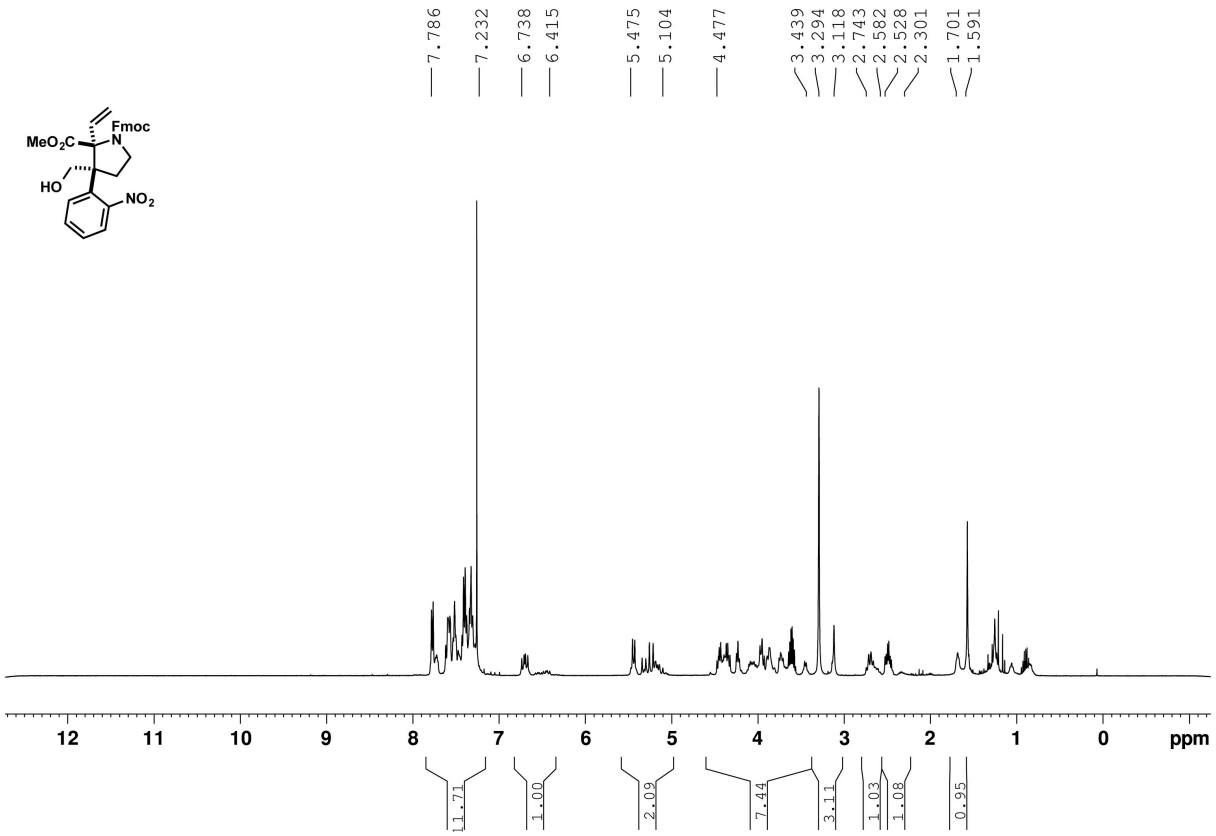
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MeO2C
HO
NO2
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6
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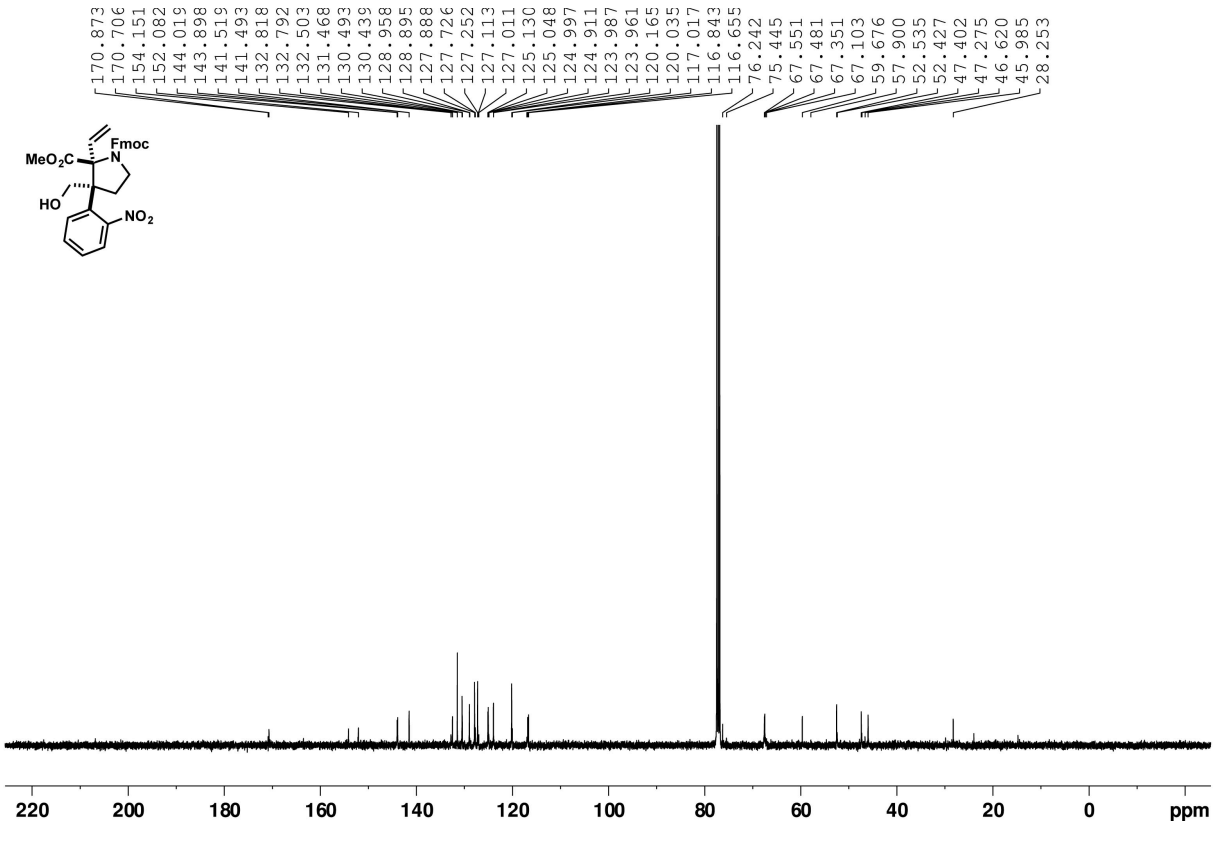
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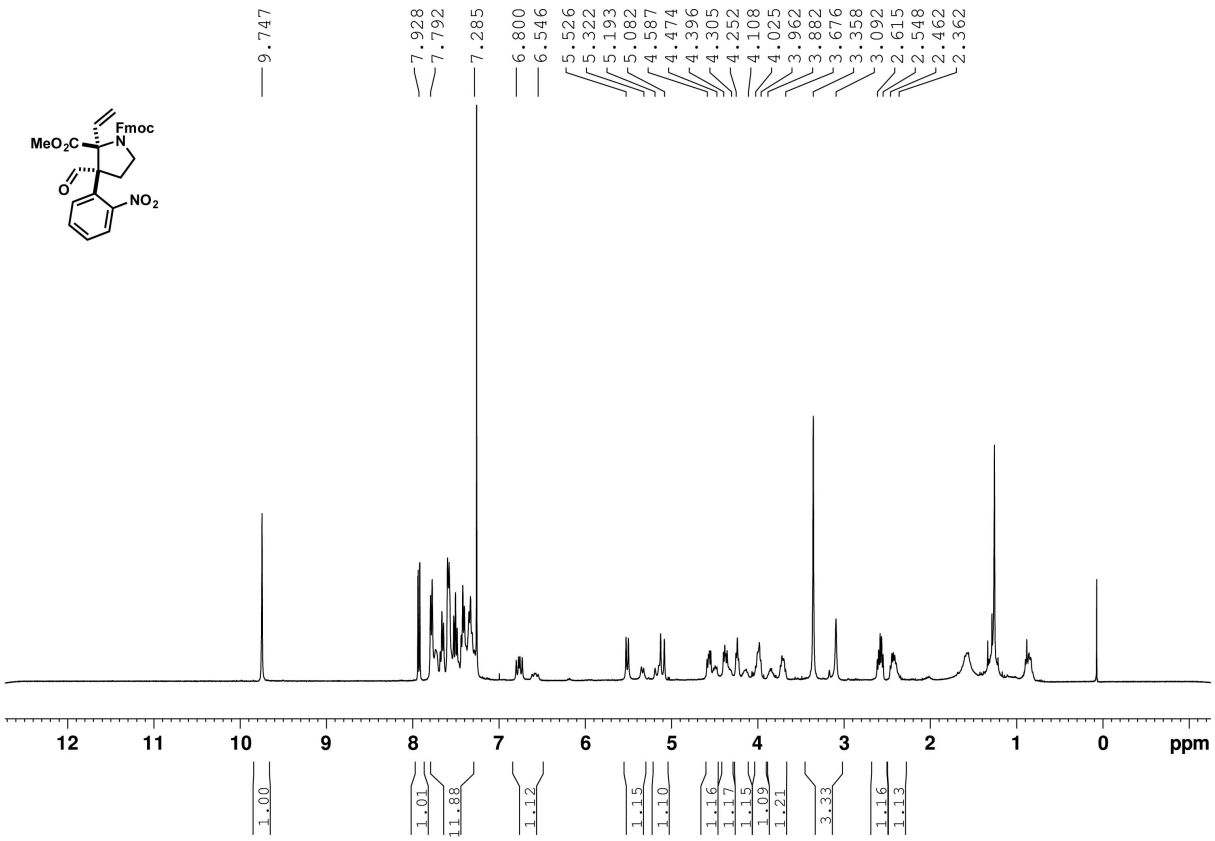
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Fmoc
MeO2C
O
NO2
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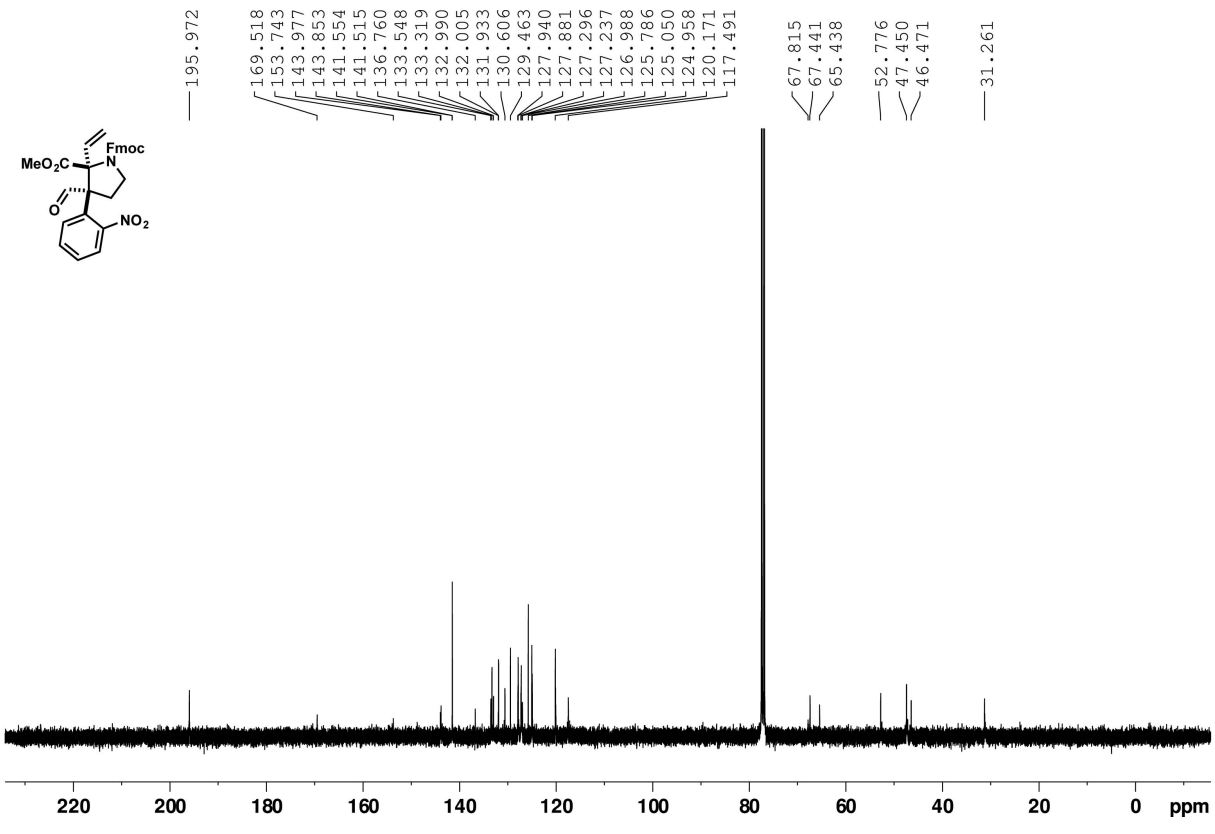
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31.261
Fmoc
MeO2C
O
NO2
220
200
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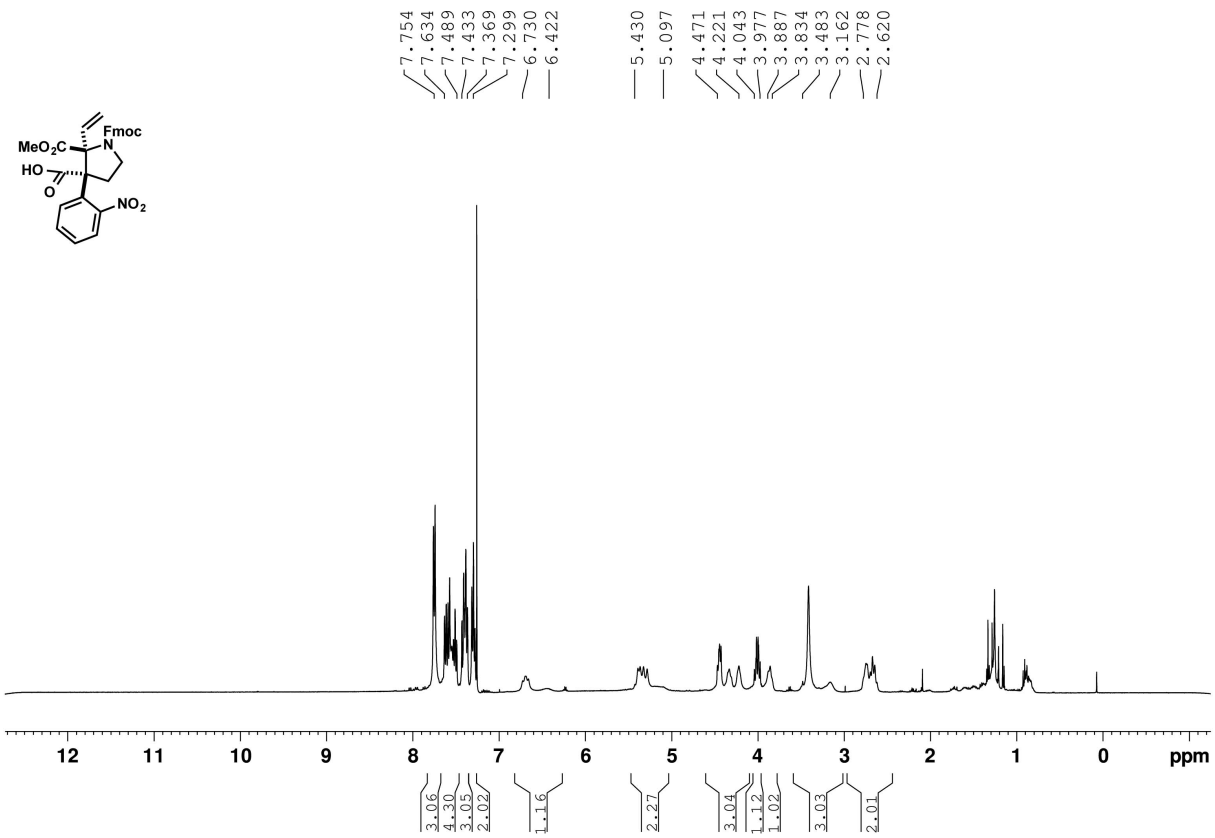
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5.430
5.097
4.471
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4.043
3.977
3.887
3.834
3.483
3.162
2.778
2.620
Fmoc
MeO2C
HO
O
NO2
12
11
10
9
8
7
6
5
4
3
2
1
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4.30
3.05
2.02
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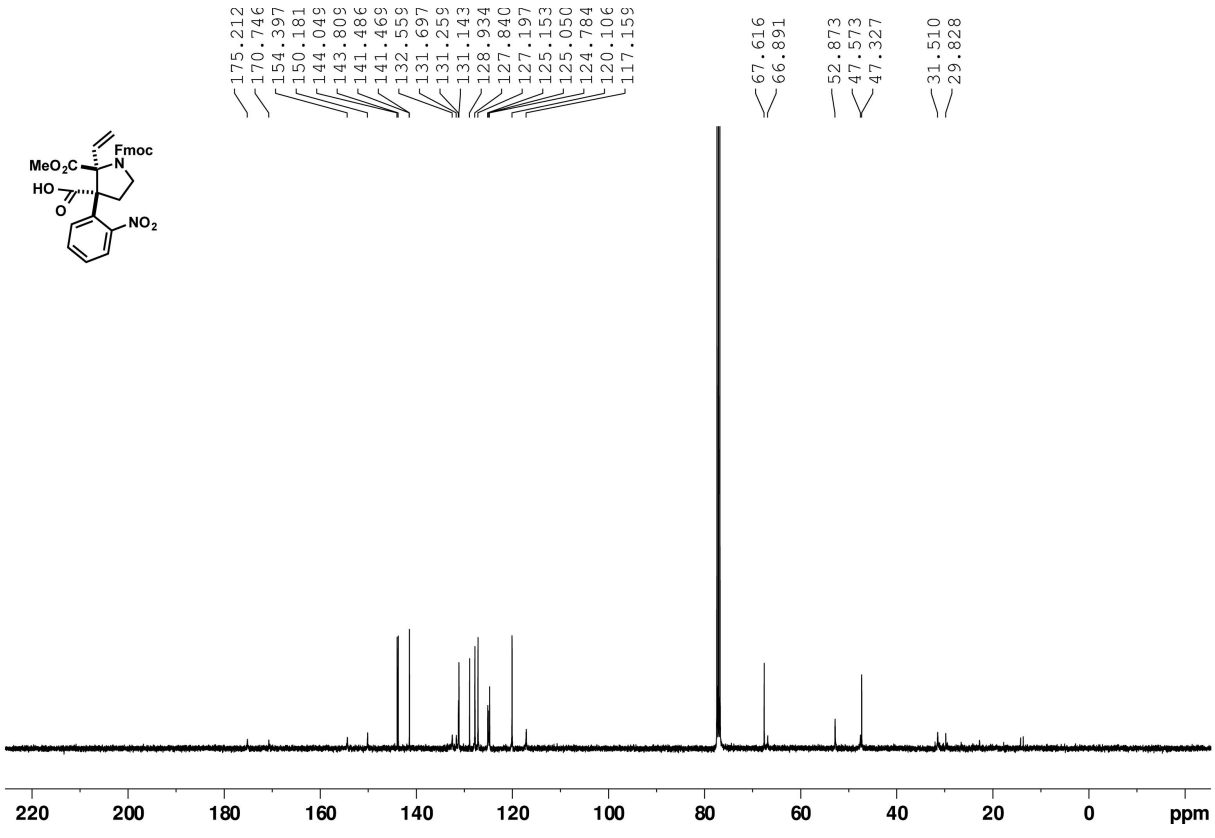
2.27
3.04
1.12
1.02
3.03
2.01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154.397
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144.049
143.809
141.486
141.469
132.559
131.697
131.259
131.143
128.934
127.840
127.197
125.153
125.050
124.784
120.106
117.159
67.616
66.891
52.873
47.573
47.327
31.510
29.828
Fmoc
MeO2C
HO
O
NO2
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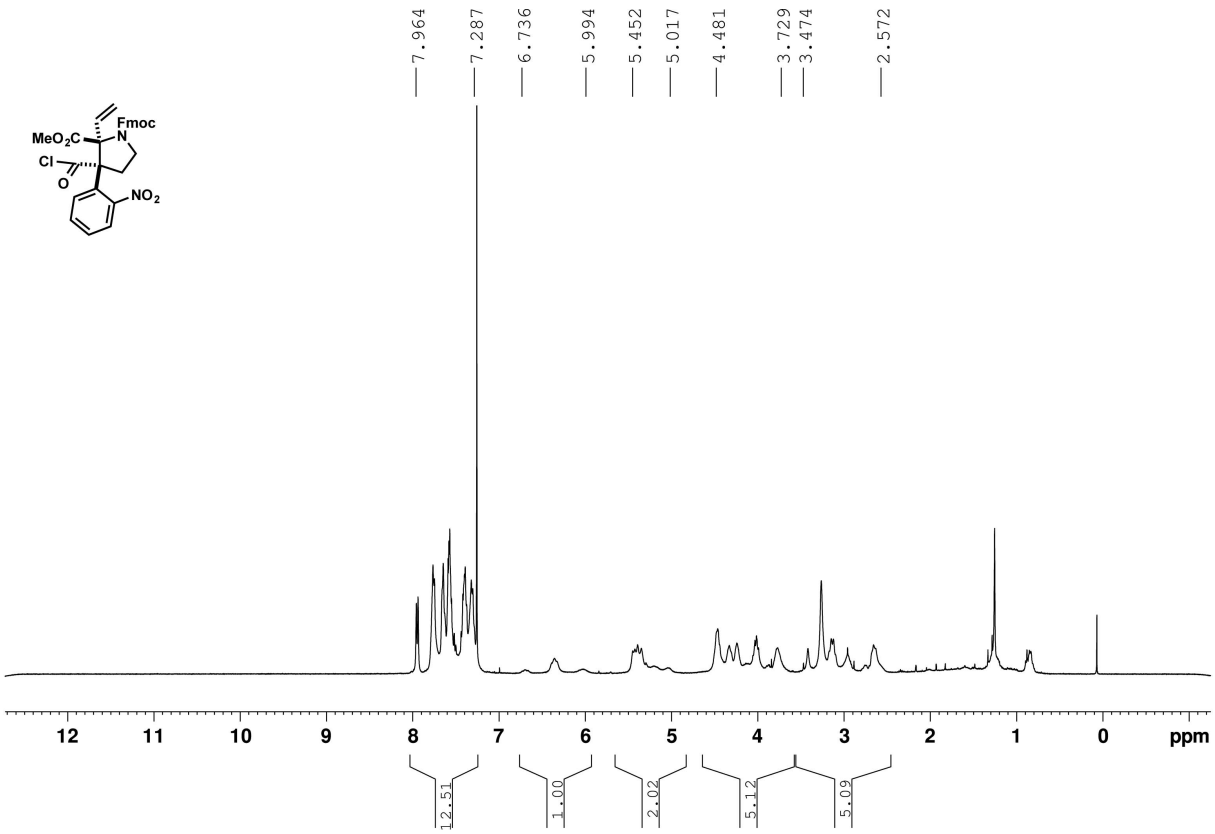
200
180
160
140
120
100
80
60
40
20
0
ppm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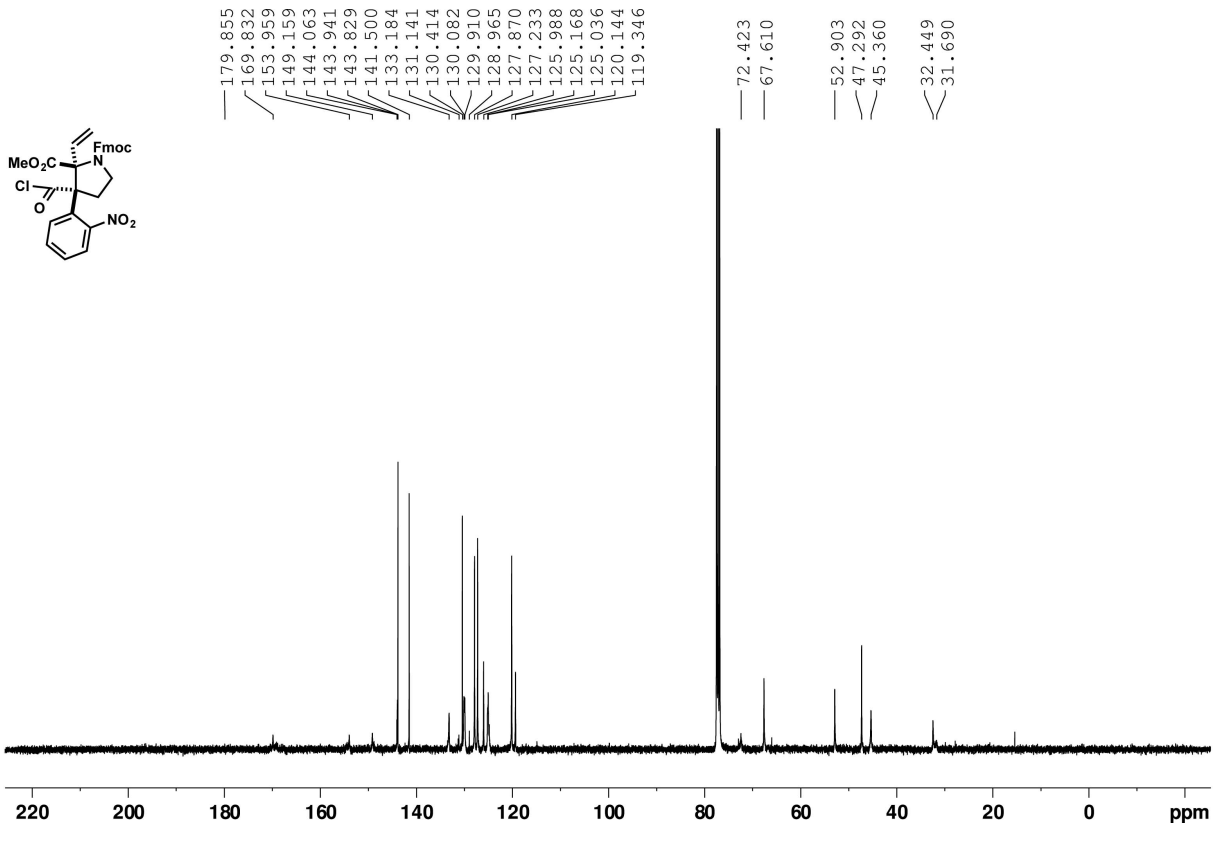
6.736
5.994
5.452
5.017
4.481
3.729
3.474
2.572
Fmoc
MeO2C
Cl
O
NO2
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
12.51
1.00
2.02
5.12
5.09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153.959
149.159
144.063
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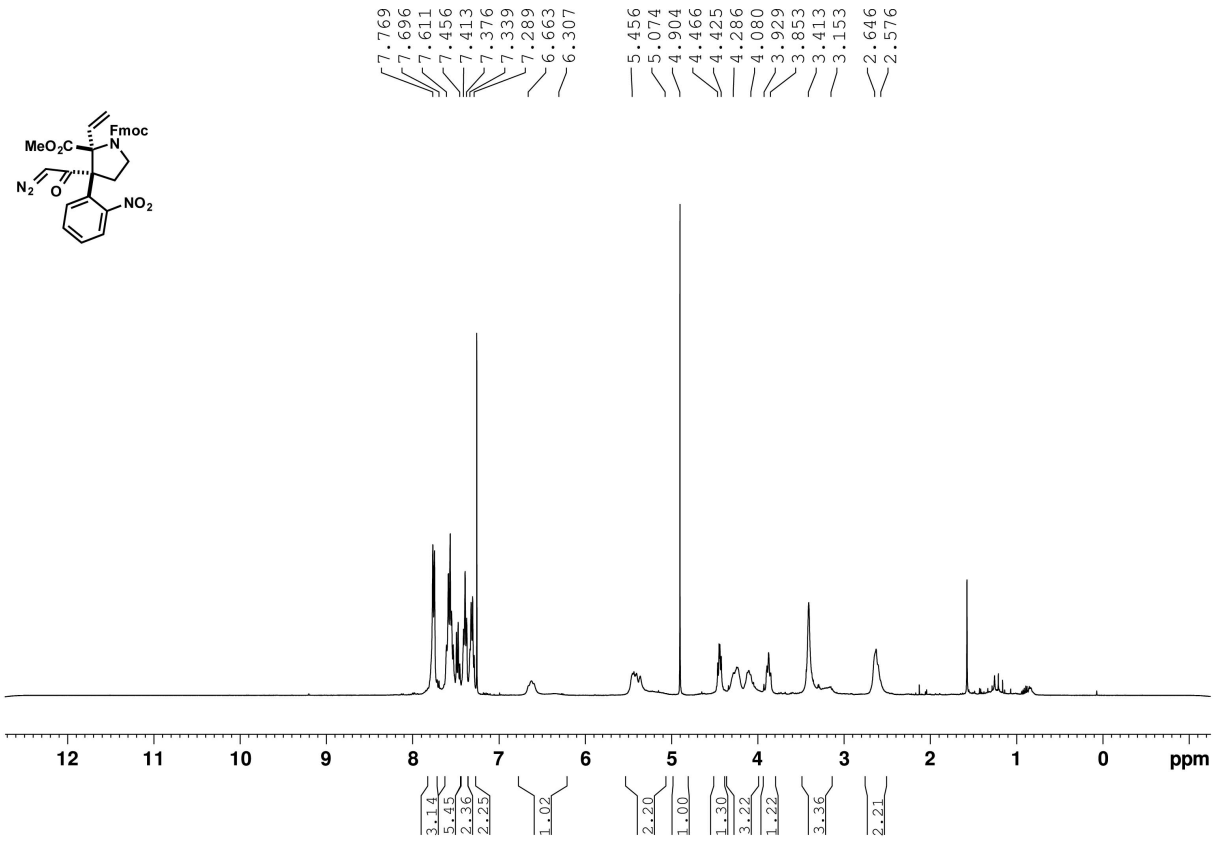
143.829
141.500
133.184
131.141
130.414
130.082
129.910
128.965
127.870
127.233
125.988
125.168
125.036
120.144
119.346
72.423
67.610
52.903
47.292
45.360
32.449
31.690
Fmoc
MeO2C
Cl
O
NO2
220
200
180
160
140
120
100
80
60
40
20
0
ppm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7.611
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7.413
7.376
7.339
7.289
6.663
6.307
5.456
5.074
4.904
4.466
4.425
4.286
4.080
3.929
3.853
3.413
3.153
2.646
2.576
Fmoc
MeO2C
N2
O
NO2
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
3.14
5.45
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2.25
1.02
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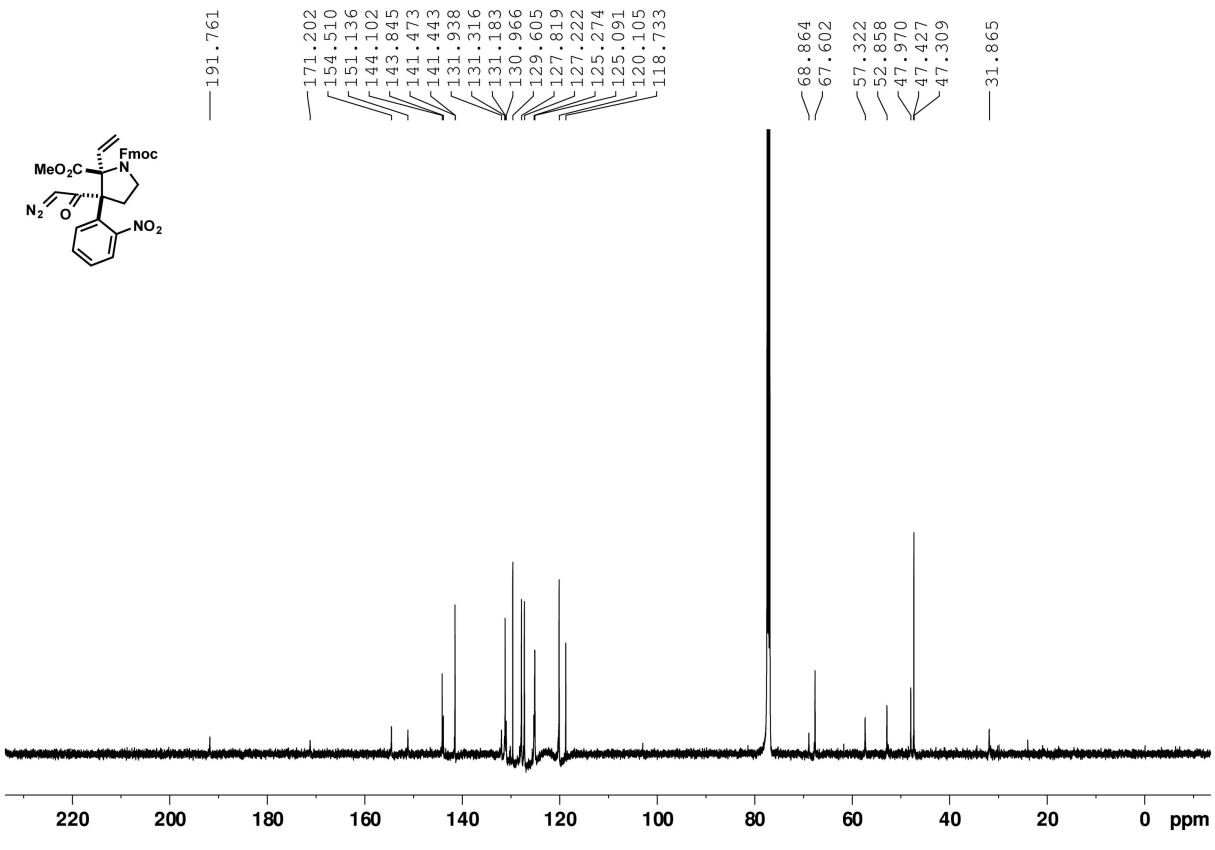
1.00
1.30
3.22
1.22
3.36
2.21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171.202
154.510
151.136
144.102
143.845
141.473
141.443
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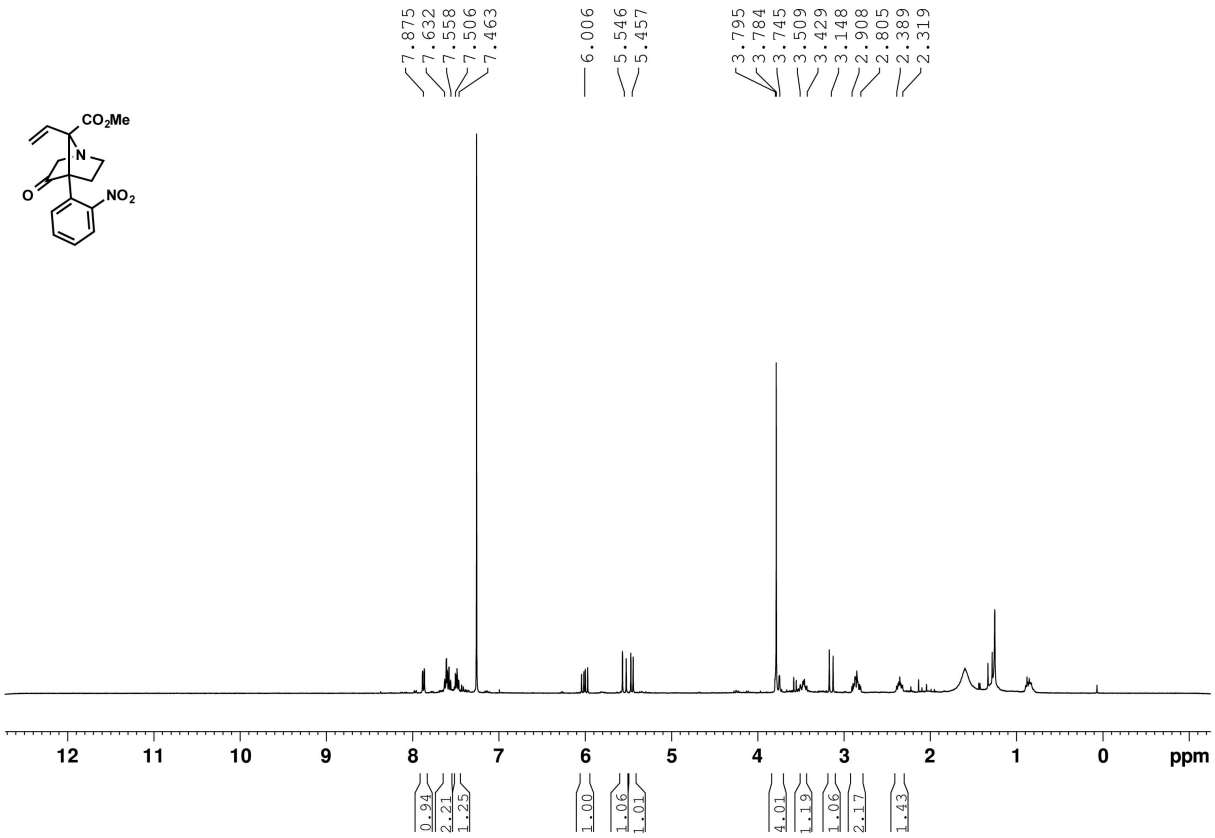
131.316
131.183
130.966
129.605
127.819
127.222
125.274
125.091
120.105
118.733
68.864
67.602
57.322
52.858
47.970
47.427
47.309
31.865
Fmoc
MeO2C
N2
O
NO2
220
200
180
160
140
120
100
80
60
40
20
0
ppm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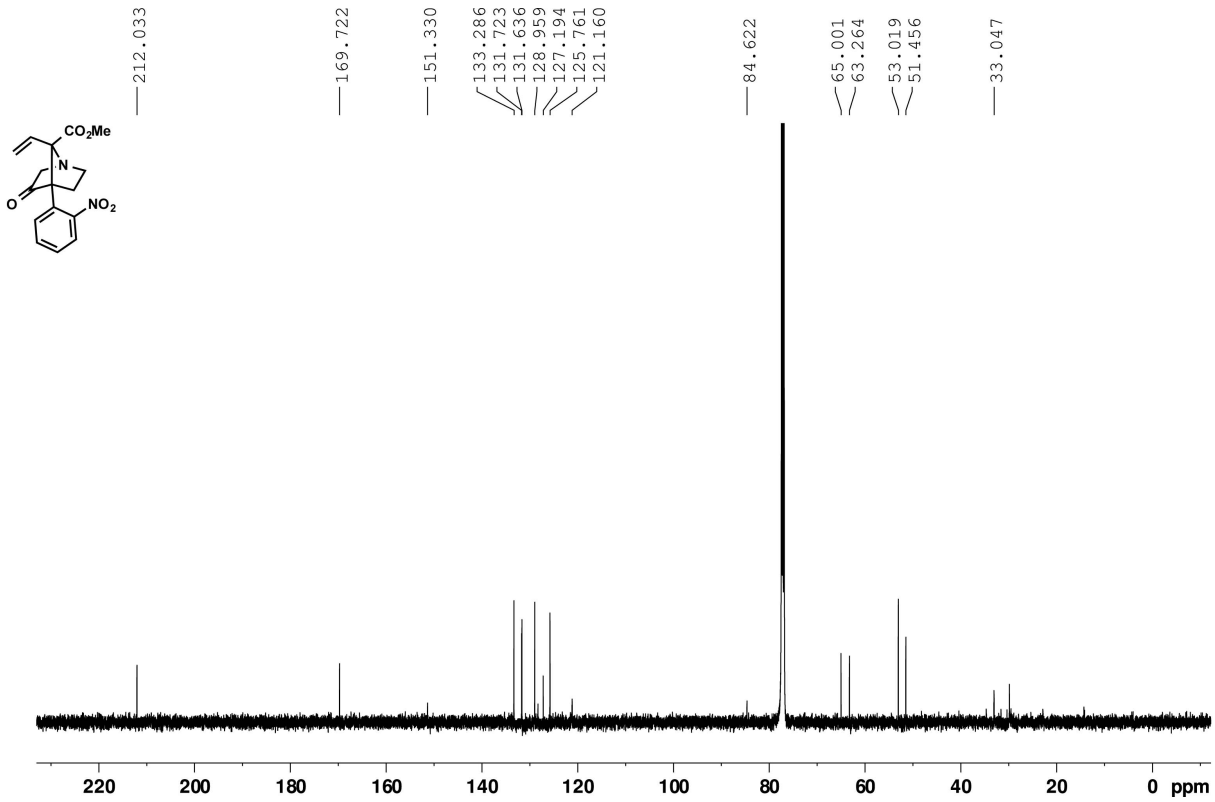
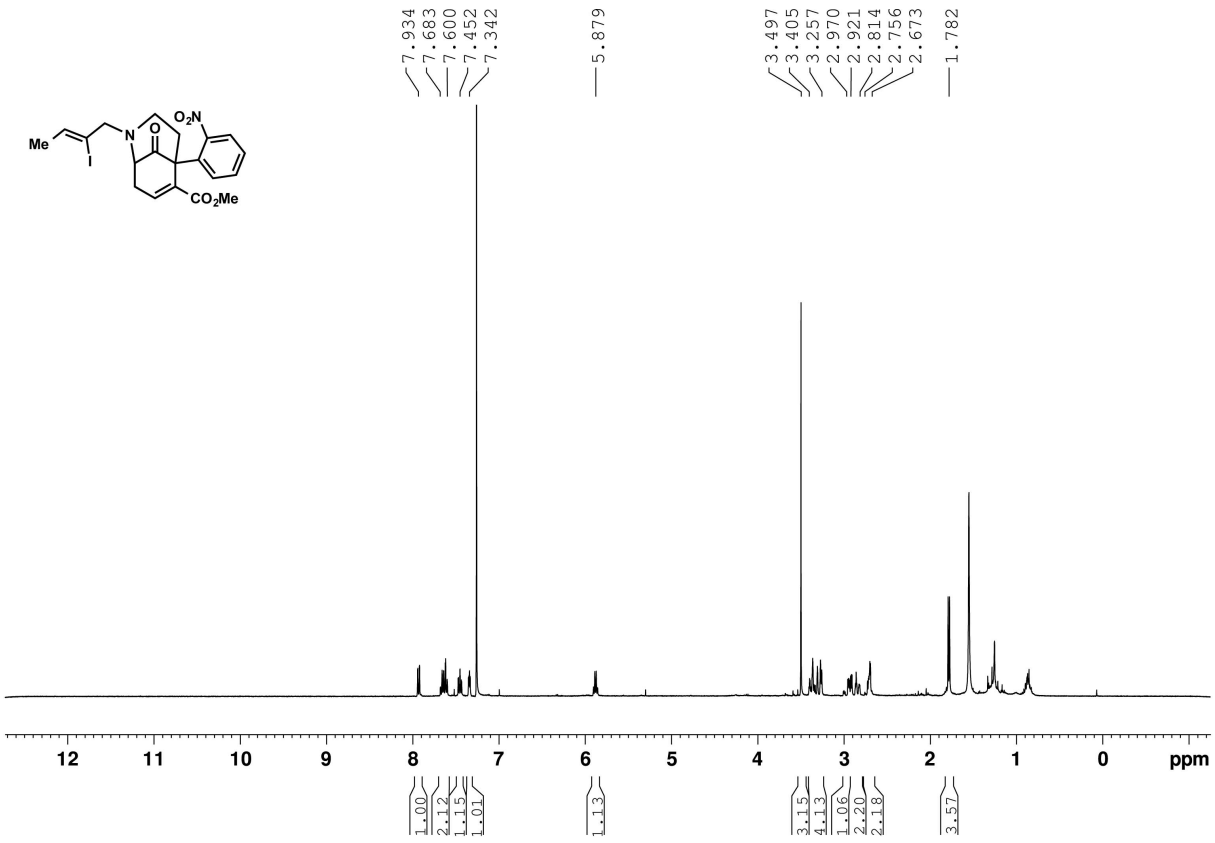
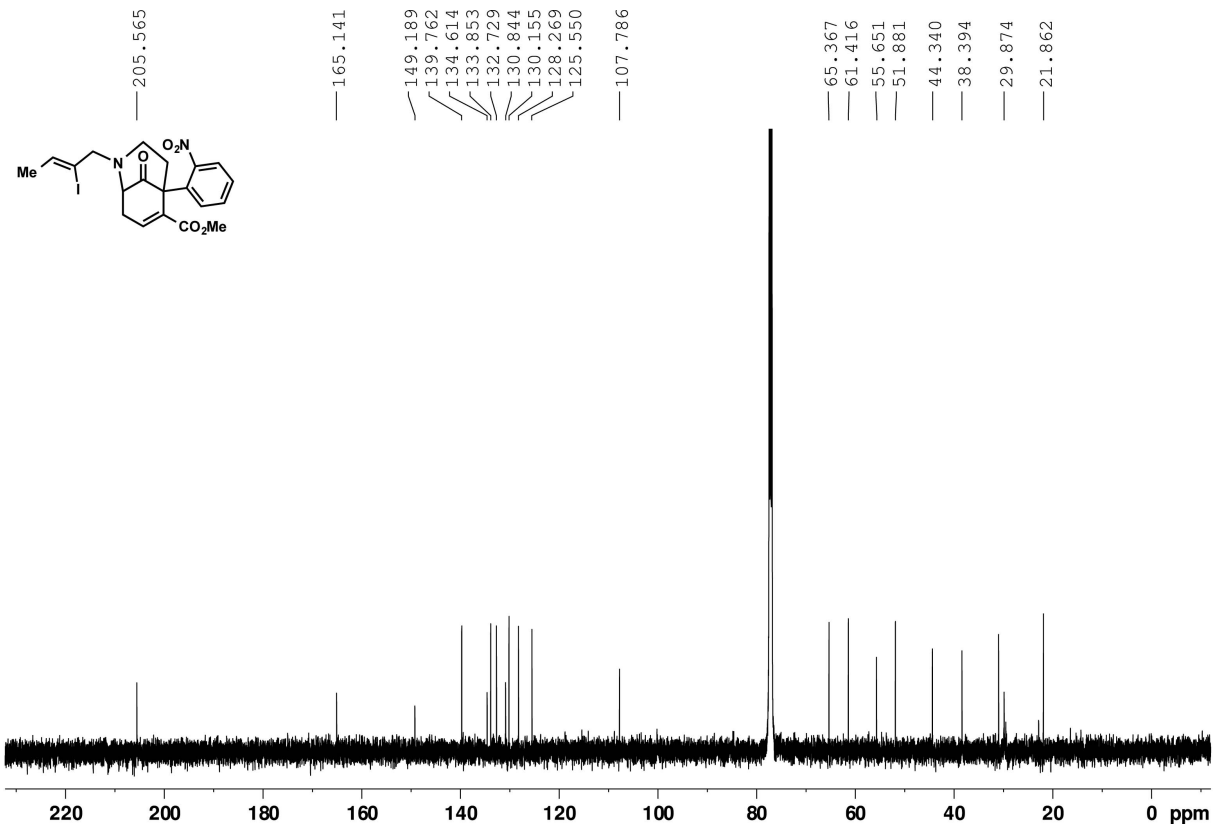
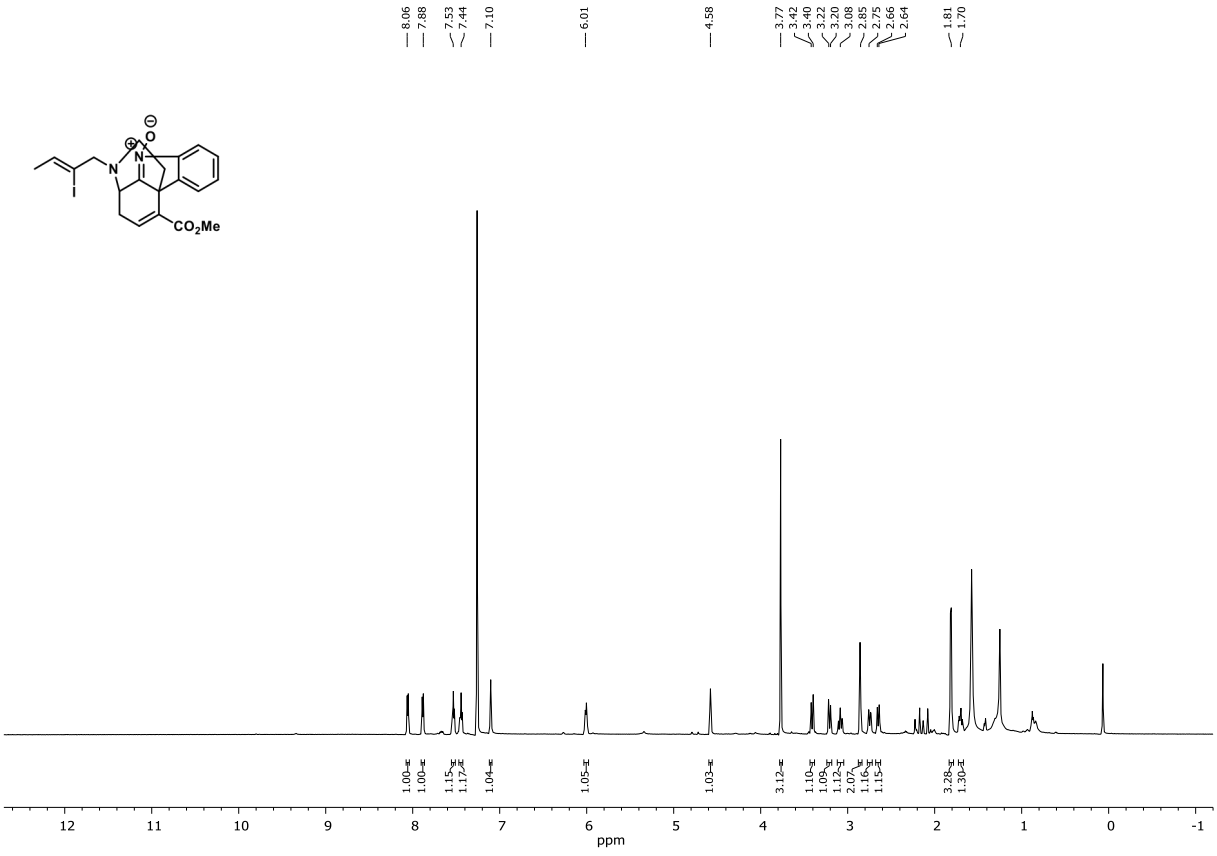
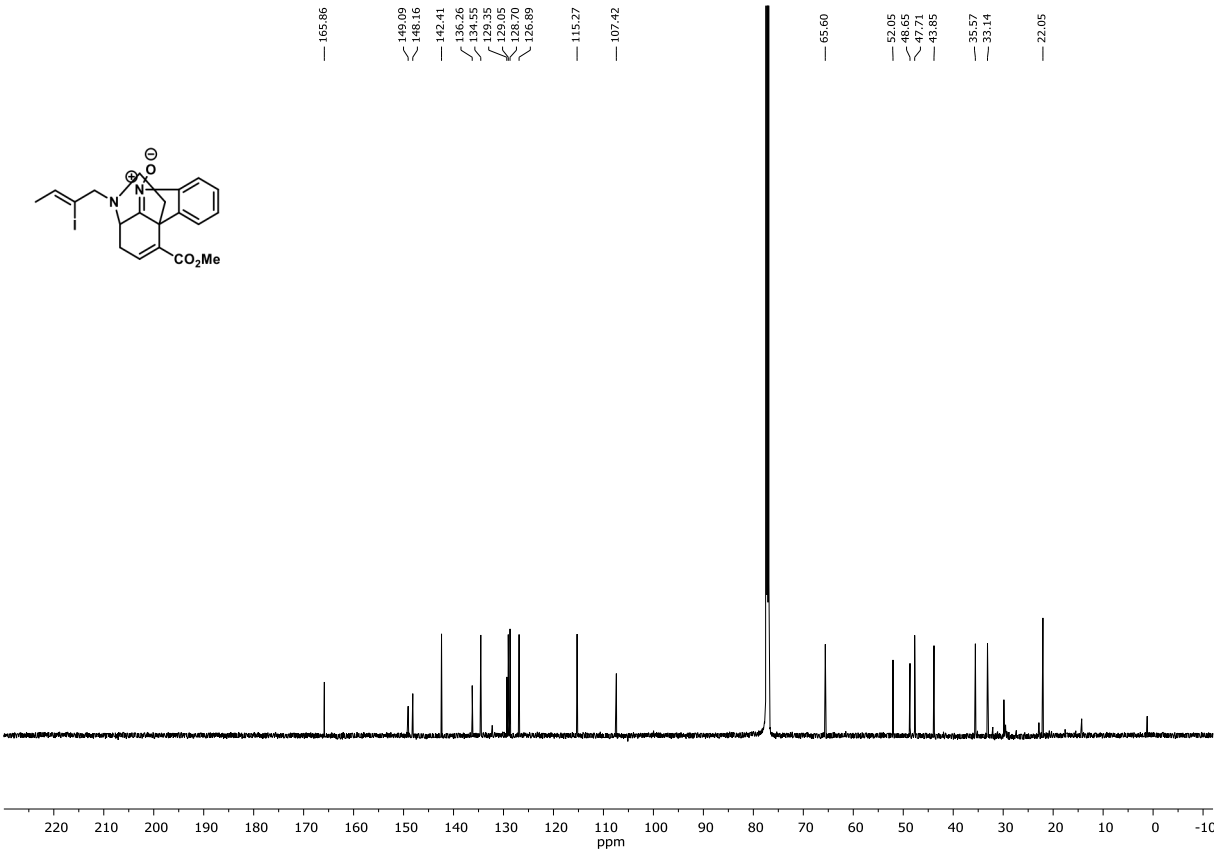
7.506
7.463
6.006
5.546
5.457
3.795
3.784
3.745
3.509
3.429
3.148
2.908
2.805
2.389
2.319
CO2Me
N
O
NO2
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.94
2.21
1.25
1.00
1.06
1.01
4.01
1.19
1.06
2.17
1.43


212.033
169.722
151.330
133.286
131.723
131.636
128.959
127.194
125.761
121.160
84.622
65.001
63.264
53.019
51.456
33.047
CO2Me
N
O
NO2
220
200
180
160
140
120
100
80
60
40
20
0
ppm


7.934
7.683
7.600
7.452
7.342
5.879
3.497
3.405
3.257
2.970
2.921
2.814
2.756
2.673
1.782
Me
I
N
O
O2N
CO2Me
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
2.12
1.15
1.01
1.13
3.15
4.13
1.06
2.20
2.18
3.57


205.565
165.141
149.189
139.762
134.614
133.853
132.729
130.844
130.155
128.269
125.550
107.786
65.367
61.416
55.651
51.881
44.340
38.394
29.874
21.862
Me
I
N
O
O2N
CO2Me
220
200
180
160
140
120
100
80
60
40
20
0 ppm


8.06
7.88
7.53
7.44
7.10
6.01
4.58
3.77
3.42
3.40
3.22
3.20
3.08
2.85
2.75
2.66
2.64
1.81
1.70
CO2Me
1.00
1.00
1.15
1.17
1.04
1.05
1.03
3.12
1.10
1.09
1.12
2.07
1.16
1.15
3.28
1.30
ppm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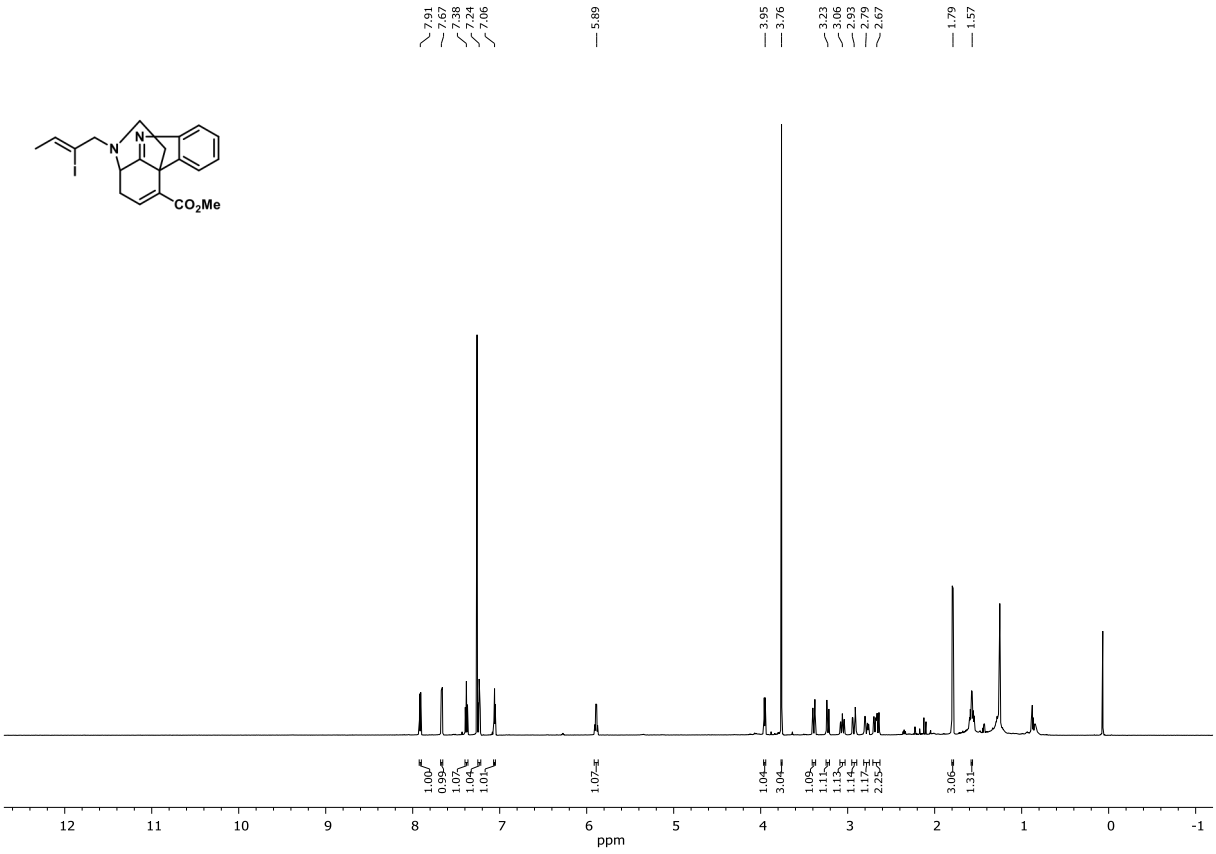
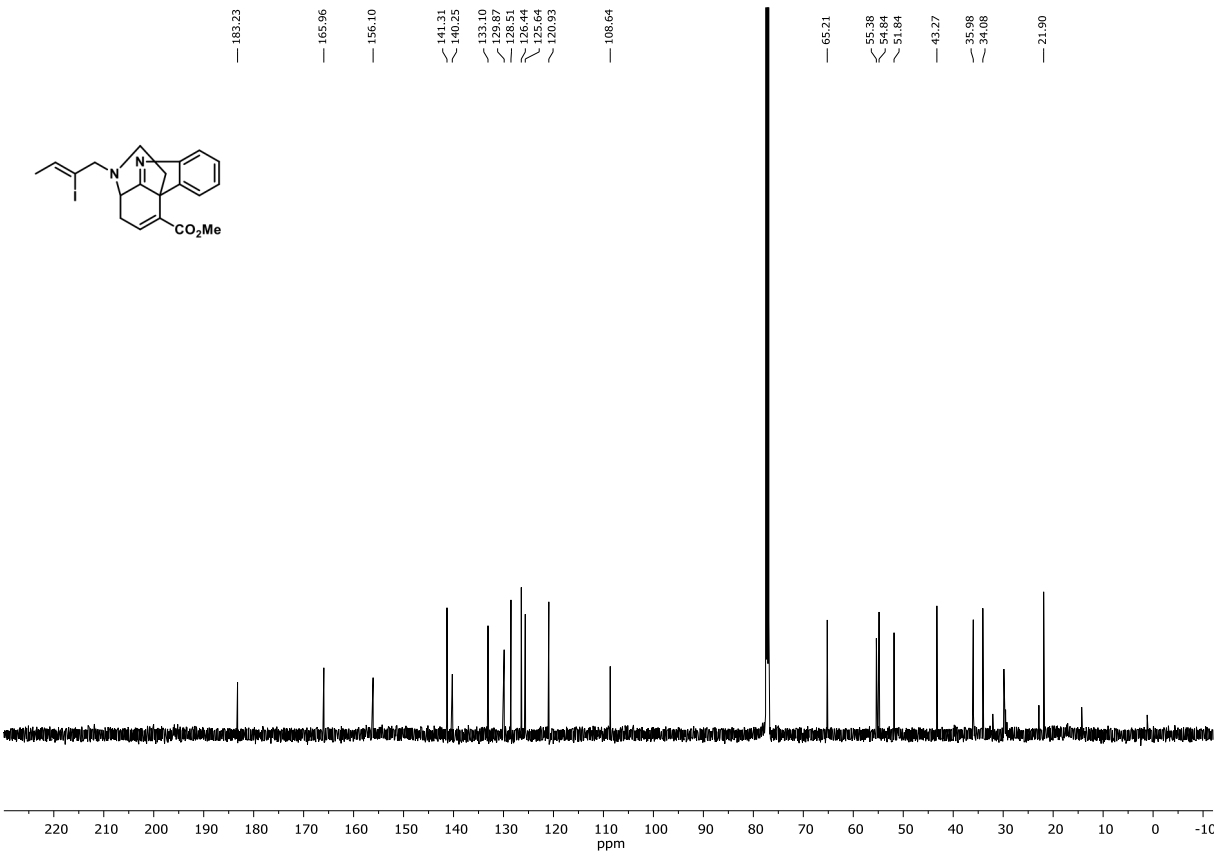
148.16
142.41
136.26
134.55
129.35
129.05
128.70
126.89
115.27
107.42
65.60
52.05
48.65
47.71
43.85
35.57
33.14
22.05
CO2Me
ppm


7.91
7.67
7.38
7.24
7.06
5.89
3.95
3.76
3.23
3.06
2.93
2.79
2.67
1.79
1.57
CO2Me
ppm


183.23
165.96
156.10
141.31
140.25
133.10
129.87
128.51
126.44
125.64
120.93
108.64
65.21
55.38
54.84
51.84
43.27
35.98
34.08
21.90
CO2Me
ppm

4. References

[1] S. H. Kim, K. H. Kim and J. N. Kim, *Adv. Synth. Catal.*, 2011, **353**, 3335.

[2] V. Pace, G. Verniest, J.-V. Sinisterra, A. R. Alcántara and N. De Kimpe, *J. Org. Chem.*, 2010, **75**, 5760.

[3] W. Ren, Q. Wang and J. Zhu, *Angew. Chem., Int. Ed.*, 2016, **55**, 3500.