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Supporting Information
for

Highly efficient and environmentally benign preparation of Weinreb amides in the biphasic system 2-MeTHF / water

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Materials and methods.

All ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance spectrometers operating at 200, 300 or 400 MHz and at 50, 75 or 100 MHz, respectively, from $CDCl_3$ solutions. The (residual) solvent peak was used as an internal standard which was related to TMS with δ 7.26 ppm (^{1}H) and δ 77.0 ppm (^{13}C). The ^{15}N and ^{19}F NMR experiments were conducted on a Bruker Avance 400 spectrometer (40 MHz and 377 MHz, respectively). The ^{15}N NMR spectra were referenced against external nitromethane, for the ^{19}F NMR spectra absolute referencing via the Ξ ratio was used. Spin-spin coupling constants (*J*) are given in Hz. Full and unambiguous assignment of all ^{1}H, ^{13}C, ^{15}N and ^{19}F-NMR resonances was achieved by combining standard NMR techniques, such as fully ^{1}H-coupled ^{13}C-NMR spectra, APT, DEPT, HSQC, HMBC, and NOESY experiments.

All melting points are uncorrected. Column chromatography purifications were conducted on silica gel 60 (40-63 μm). TLC was carried out on aluminum sheets precoated with silica gel 60F254; the spots were visualized under UV light (λ = 254 nm) and/or $KMnO_4$ (aq.) was used as revealing system.

Elementary microanalyses were carried out using a Leco® CHNS 932 equipment. IR absorption spectra were recorded on a Perkin-Elmer System 2000 FT-IR spectrophotometer.

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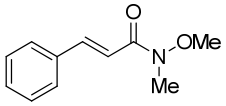
General Procedure for *N,O*-acylation of alcohols and amines: Preparation of Weinreb amides 1a-22a.
To a solution of acyl halide (1.0 equiv.) in 2-MeTHF was added *N,O*-dimethylhydroxylamine hydrochloride (DMHA) (1.1 equiv.) and the resulting suspension was cooled to 0°C. Afterwards, an aqueous solution of potassium carbonate (2.2 equiv.) was added during 2 min. After removing the cooling bath, the resulting mixture was stirred for 1 h and subsequently 1 M HCl was added. The two resulting phases were separated and, the organic phase (2-MeTHF) was dried over anhydrous $MgSO_4$, filtered and removed *in vacuo* to give the desired Weinreb amides in a pure form without needing to perform further purifications.

(2*E*)-*N*-methoxy-*N*-methyl-3-phenylacrylamide[1] (1a)



Following the General Procedure, starting from cinnamoyl chloride (1.55 g, 9.32 mmol), DMHA (1 g, 10.25 mmol) and potassium carbonate (2.83 g, 20.50 mmol) in 2-MeTHF – H_2O (20 mL, v/v), Weinreb amide **1a** was obtained in 97% yield (1.73 g) as a white crystalline solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.73 (d, *J* = 15.8 Hz, 1H, =CHAr), 7.57 (m, 2H, Ph H-2,6), 7.37 (m, 2H, Ph H-3,5), 7.36 (m, 1H, Ph H-4), 7.03 (d, *J* = 15.8 Hz, 1H, =CHCO), 3.76 (s, 3H, OCH_3), 3.51 (s, 3H, NCH_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 166.9 (C=O), 143.4 (=CHAr), 135.1 (Ph C-1), 129.8 (Ph C-4), 128.7 (Ph C-3,5), 128.0 (Ph C-2,6), 115.7 (=CHCO), 61.8 (OCH_3), 32.5 (NCH_3).

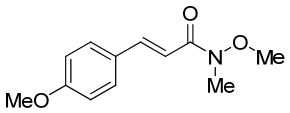
^{15}N NMR (40 MHz, $CDCl_3$) δ: -194.0 (amide N).

IR (NaCl, ν_{max}, cm^{-1}) 3064, 2932, 2825, 1659, 1622, 1456, 1413, 1381, 1184, 1102, 991, 765.

Mp: 48-50 °C (lit.[1] 56-59 °C)

Elemental Analysis (%) for $C_{11}H_{13}NO_2$. Calcd: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.21; H, 6.73; N, 7.19.

(2*E*)-*N*-methoxy-3-(4-methoxyphenyl)-*N*-methylacrylamide[2] (2a)



Following the General Procedure, starting from (*E*)-3-(4-methoxyphenyl)acryloyl chloride (1.83 g, 9.32 mmol), DMHA (1 g, 10.25 mmol) and potassium carbonate (2.83 g, 20.50 mmol) in 2-MeTHF – H_2O (20 mL, v/v), Weinreb amide **2a** was obtained in 94% yield (1.85 g) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.65 (d, *J* = 15.8 Hz, 1H, =CH), 7.54 – 7.40 (m, 2H, Ar-H) 6.99 – 6.69 (m, 2H, Ar-H), 6.87 (d, *J* = 15.8 Hz, 1H, =CHCO) 3.77 (s, 3H, OCH_3), 3.71 (s, 3H , OCH_3), 3.25 (s, 3H, NCH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.8, 160.5, 142.6, 129.2, 127.4, 113.8, 112.9, 61.4, 54.9, 32.1.

IR (NaCl, ν_{max}, cm^{-1}) 1649, 1599, 1511, 1422, 1250, 907.

Elemental Analysis (%) for $C_{12}H_{15}NO_3$. Calcd: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.30; H, 6.69; N, 6.43

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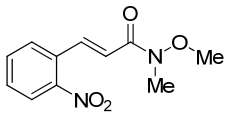
(2*E*)-*N*-methoxy-*N*-methyl-3-(2-nitrophenyl)acrylamide (3a)



Following the General Procedure, starting from (*E*)-3-(2-nitrophenyl)acryloyl chloride (1.97 g, 9.32 mmol), DMHA (1 g, 10.25 mmol) and potassium carbonate (2.83 g, 20.50 mmol) in 2-MeTHF – H_2O (20 mL, v/v), Weinreb amide **3a** was obtained in 92% yield (2.03 g) as a yellow thick oil.

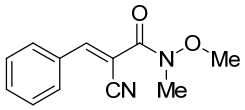
^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.02 (d, *J* = 15.6 Hz, 1H, =CH), 7.96 – 7.88 (m, 1H, Ar-H), 7.60 (qd, *J* = 7.9, 1.8 Hz, 2H, =CH), 7.46 (ddd, *J* = 8.6, 6.7, 2.2 Hz, 1H, Ar-H), 6.90 (d, *J* = 15.6 Hz, 1H, =CH), 3.70 (s, 3H, OCH_3), 3.24 (s, 3H, NCH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.6, 148.4, 138.5, 133.4, 131.2, 129.9, 129.2, 124.7, 121.0, 62.0, 32.4.

IR (NaCl, ν_{max}, cm^{-1}) 1656, 1602, 1538, 1361, 917.

Elemental Analysis (%) for $C_{11}H_{12}N_2O_4$. Calcd: C, 55.93; H, 5.12; N, 11.86. Found: C, 56.11; H, 5.29; N, 11.71.

***(*2*E*)*-2-cyano-*N*-methoxy-*N*-methyl-3-phenylacrylamide (4a)**



Following the General Procedure, starting from *(E)*-2-cyano-3-phenylacryloyl chloride (1.79 g, 9.32 mmol), DMHA (1 g, 10.25 mmol) and potassium carbonate (2.83 g, 20.50 mmol) in 2-MeTHF – H_2O (20 mL, v/v), Weinreb amide **4a** was obtained in 83% yield (1.83 g) as a light yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.09 (s, 1H, =CHAr), 7.96 (m, 2H, Ph H-2,6), 7.49 (m, 1H, Ph H-4), 7.48 (m, 2H, Ph H-3,5), 3.86 (s, 3H, OCH_3), 3.31 (s, 3H, NCH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.9 (C=O), 154.4 (=CHAr), 132.4 (Ph C-4), 132.1 (Ph C-1), 130.7 (Ph C-2,6), 129.0 (Ph C-3,5), 116.0 (C≡N), 104.2 (=CHCO), 61.7 (OCH_3), 33.5 (NCH_3).

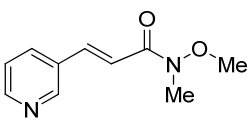
^{15}N NMR (40 MHz, $CDCl_3$) δ: -195.5 (amide N).

IR (NaCl, ν_{max}, cm^{-1}) 3083, 2245, 1642, 1597, 1343, 1225, 909.

Mp: 71-73°C.

Elemental Analysis (%) for $C_{12}H_{12}N_2O_2$. Calcd: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.49; H, 5.44; N, 13.17.

(2*E*)-*N*-methoxy-*N*-methyl-3-(3-pyridinyl)acrylamide[3] (5a)



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Following the General Procedure, starting from (*E*)-3-(pyridin-3-yl)acryloyl chloride (1.56 g, 9.32 mmol), DMHA (1 g, 10.25 mmol) and potassium carbonate (2.83 g, 20.50 mmol) in 2-MeTHF – H_2O (20 mL, v/v), Weinreb amide **5a** was obtained in 86% yield (1.54 g) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.77 (m, 1H, Pyr H-2), 8.57 (m, 1H, Pyr H-6), 7.85 (m, 1H, Pyr H-4), 7.70 (d, J = 15.9 Hz, 1H, =CHAr), 7.31 (m, 1H, Pyr H-5), 7.09 (d, J = 15.9 Hz, 1H, =CHCO), 3.76 (s, 3H, OCH_3), 3.30 (s, 3H, NCH_3).

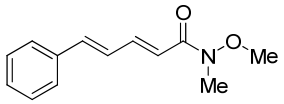
^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.1 (C=O), 150.5 (Pyr C-6), 149.5 (Pyr C-2), 139.7 (=CHAr), 134.4 (Pyr C-4), 130.9 (Pyr C-3), 123.6 (Pyr C-5), 117.9 (=CHCO), 61.9 (OCH_3), 32.5 (NCH_3).

^{15}N NMR (40 MHz, $CDCl_3$) δ: -69.1 (pyridine N), -193.8 (amide N).

IR (NaCl, ν_{max}, cm^{-1}) 3064, 1659, 1512, 1235.

Elemental Analysis (%) for $C_{10}H_{12}N_2O_2$. Calcd: C, 62.49; H, 6.29; N, 14.57. Found: C, 62.40; H, 6.19; N, 14.71.

(4*E*)-*N*-methoxy-*N*-methyl-5-phenyl-2,4-pentadienamide[4] (6a)



Following the General Procedure, starting from (2*E*,4*E*)-5-phenylpenta-2,4-dienoyl chloride (1.80 g, 9.32 mmol), DMHA (1 g, 10.25 mmol) and potassium carbonate (2.83 g, 20.50 mmol) in 2-MeTHF – H_2O (20 mL, v/v), Weinreb amide **6a** was obtained in 97% yield (1.96 g) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.50 (dd, J = 15.1Hz, 9.5 Hz, 1H, CH=CHCO), 7.46 (m, 2H, Ph H-2,6), 7.35 (m, 2H, Ph H-3,5), 7.29 (m, 1H, Ph H-4), 6.95 (dd, J = 15.6 Hz, 9.5 Hz, (1H, ArCH=CH), 6.90 (1H, d, J = 15.6 Hz, ArCH=), 6.60 (1H, d, J = 15.1 Hz, =CHCO), 3.74 (3H, s, OCH_3), 3.28 (3H, s, NCH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.2 (C=O), 143.3 (CH=CHCO), 139.7 (ArCH=), 136.3 (Ph C-1), 128.7 (Ph C-3,4,5), 127.0 (Ph C-2,6), 126.9 (ArCH=CH), 119.1 (=CHCO), 61.8 (OCH_3), 32.5 (NCH_3).

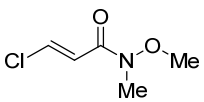
^{15}N NMR (40 MHz, $CDCl_3$) δ: -194.2 (amide N).

IR (NaCl, ν_{max}, cm^{-1}) 3064,1651, 1383, 905.

Mp: 64-66 °C.

Elemental Analysis (%) for $C_{13}H_{15}NO_2$. Calcd: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.74; H, 7.16; N, 6.5.

(2*E*)-3-chloro-*N*-methoxy-*N*-methylacrylamide (7a)



Following the General Procedure, starting (*E*)-3-chloroacryloyl chloride (1.16 g, 9.32 mmol), DMHA (1 g, 10.25 mmol) and potassium carbonate (2.83 g, 20.50 mmol) in 2-MeTHF – H_2O (20 mL, v/v), Weinreb amide **7a** was obtained in 92% yield (1.28 g) as a yellow oil.

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^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.27 (d, *J* = 13.3 Hz, 1H, ClCH=), 6.75 (d, *J* = 13.3 Hz, 1H, =CHCO), 3.64 (s, 3H, OCH_3), 3.16 (s, 3H, NCH_3).

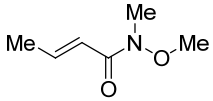
^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.0 (C=O), 136.0 (ClCH=), 122.3 (=CHCO), 61.8 (OCH_3), 33.0 (NCH_3).

^{15}N NMR (40 MHz, $CDCl_3$) δ: -195.1 (amide N).

IR (NaCl, ν_{max}, cm^{-1}) 1647, 1380, 1002, 909.

Elemental Analysis (%) for $C_5H_8ClNO_2$. Calcd: C, 40.15; H, 5.39; N, 9.36. Found: C, 40.02; H, 5.52; N, 9.48.

(2E)-*N*-methoxy-*N*-methyl-2-butenamide[5] (8a)



Following the General Procedure, starting from (*E*)-but-2-enoyl chloride (0.97 g, 0.90 ml, 9.32 mmol), DMHA (1 g, 10.25 mmol) and potassium carbonate (2.83 g, 20.50 mmol) in 2-MeTHF – H_2O (20 mL, v/v), Weinreb amide **8a** was obtained in 91% yield (1.10 g) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.95 (qd, *J* = 15.3, 6.9 Hz, 1H), 6.40 (qd, *J* = 15.3, 1.7 Hz, 1H), 3.67 (s, 3H), 3.21 (s, 3H OCH_3,), 1.89 (dd, *J* =6.9, 1.7 Hz, 1H, NCH_3).

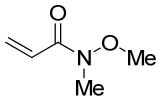
^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.9 (C=O), 142.8 (Me-CH=), 120.1 (=CHCO), 61.6 (OCH_3), 33.2 (NCH_3), 18.1 (=$CHCH_3$).

^{15}N NMR (40 MHz, $CDCl_3$) δ: -195.4 (amide N).

IR (NaCl, ν_{max}, cm^{-1}) 1660, 1461, 1421, 1180, 998.

Elemental Analysis (%) for $C_6H_{11}NO_2$. Calcd: C, 55.80; H, 8.58; N, 10.84. Found: C, 55.77; H, 8.67; N, 10.98.

N-methoxy-*N*-methylacrylamide[6] (9a)



Following the General Procedure, starting from acryloyl chloride (0.84 g, 0.76 mL, 9.32 mmol), DMHA (1 g, 10.25 mmol) and potassium carbonate (2.83 g, 20.50 mmol) in 2-MeTHF – H_2O (20 mL, v/v), Weinreb amide **9a** was obtained in 89% yield (0.95 g) as a light brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.75-6.70 (m, 1H), 6.42 (dd, *J* = 10.5 Hz, *J* = 1.5 Hz, 1H), 5.75 (dd, *J* = 7.0 Hz, *J* = 1.5 Hz, 1H), 3.70 (s, 3H, OCH_3), 3.26 (s, 3H, NCH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.5 (C=O), 129.1, 125.9, 61.8 (OCH_3), 32.3 (NCH_3).

IR (NaCl, ν_{max}, cm^{-1}) 1659, 1621, 1457, 1422, 1180, 788.

Elemental Analysis (%) for $C_5H_9NO_2$. Calcd: C, 52.16; H, 7.88; N, 12.17. Found: C, 51.99; H, 7.69; N, 12.02.

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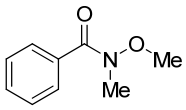
***N*-methoxy-*N*-methylbenzamide[7] (10a)**



Following the General Procedure, starting from benzoyl chloride (1.31 g, 9.32 mmol), DMHA (1 g, 10.25 mmol) and potassium carbonate (2.83 g, 20.50 mmol) in 2-MeTHF – H_2O (20 mL, v/v), Weinreb amide **10a** was obtained in 96% yield (1.48 g) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.61 (m, 2H, Ph H-2,6), 7.38 (m, 1H, Ph H-4), 7.33 (m, 2H, Ph H-3,5), 3.48 (s, 3H, OCH_3), 3.29 (s, 3H, NCH_3).

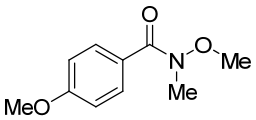
^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.7 (C=O), 133.9 (Ph C-1), 130.3 (Ph C-4), 127.9 (Ph C-2,6), 127.8 (Ph C-3,5), 60.8 (OCH_3), 33.5 (NCH_3).

^{15}N NMR (40 MHz, $CDCl_3$) δ: -195.8 (amide N).

IR (NaCl, ν_{max}, cm^{-1}) 3063, 2968, 2936, 2819, 1644, 1576, 1451, 1416, 1377, 1213, 982, 787, 708.

Elemental Analysis (%) for $C_9H_{11}NO_2$. Calcd: Cal. C, 65.44; H, 6.71; N, 8.48. Found: C, 65.65; H, 6.58; N, 8.36.

***N*,4-dimethoxy-*N*-methylbenzamide[8] (11a)**



Following the General Procedure, starting from 4-methoxybenzoyl chloride (1.59 g, 1.31 ml, 9.32 mmol), DMHA (1 g, 10.25 mmol) and potassium carbonate (2.83 g, 20.50 mmol) in 2-MeTHF – H_2O (20 mL, v/v), Weinreb amide **11a** was obtained in 94% yield (1.71 g) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.73 (m, 2H, Ph H-2,6), 6.90 (m, 2H, Ph H-3,5), 3.84 (s, 3H, Ar-O$\underline{C}H_3$), 3.56 (s, 3H, $NOCH_3$), 3.35 (s, 3H, NCH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.4 (C=O), 161.5 (Ph C-4), 130.5 (Ph C-2,6), 126.0 (Ph C-1), 113.2 (Ph C-3,5), 60.9 ($NOCH_3$), 55.3 (Ar-O$\underline{C}H_3$), 33.9 (NCH_3).

^{15}N NMR (40 MHz, $CDCl_3$) δ: -196.2 (amide N).

IR (NaCl, ν_{max}, cm^{-1}) 3284, 3072, 2935, 2842, 1637, 1512, 1460, 1421, 1373, 1254, 1174, 1027, 980, 842, 756.

Elemental Analysis (%) for $C_{10}H_{13}NO_3$. Calcd: Cal: C, 61.53; H, 6.71; N, 7.18. Found: C, 61.65; H, 6.83; N, 7.30.

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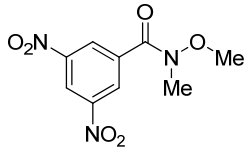
_N_-methoxy-_N_-methyl-3,5-dinitrobenzamide[9] (12a)



Following the General Procedure, starting from 3,5-dinitrobenzoyl chloride (2.15 g, 9.32 mmol), DMHA (1 g, 10.25 mmol) and potassium carbonate (2.83 g, 20.50 mmol) in 2-MeTHF – H_2O (20 mL, v/v), Weinreb amide **12a** was obtained in 90% yield (2.14 g) as a light yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.12 (t, J = 2.1 Hz 1H, Ph H-4), 8.90 (d, J = 2.1 Hz, 2H, Ph H-2,6), 3.61 (s, 3H, OCH_3), 3.44 (s, 3H, NCH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.6 (C=O), 148.1 (Ph C-3,5), 137.1 (Ph C-1), 128.8 (Ph C-2,6), 120.4 (Ph C-4), 61.7 (OCH_3), 33.1 (NCH_3).

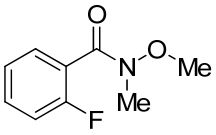
^{15}N NMR (40 MHz, $CDCl_3$) δ: -194.3 (amide N).

IR (NaCl, ν_{max}, cm^{-1}) 3091, 2930, 1652, 1541, 1453, 1417, 1377, 1199, 1167, 1116, 1062, 987.

Mp: 100 °C (lit.[9] 99-101 °C).

Elemental Analysis (%) for $C_9H_9N_3O_6$. Calcd: C, 42.36; H, 3.55; N, 16.47. Found: C, 42.21; H, 3.66; N, 16.61.

2-fluoro-_N_-methoxy-_N_-methylbenzamide[10] (13a)



Following the General Procedure, starting from 2-fluorobenzoyl chloride (1.48 g, 9.32 mmol), DMHA (1 g, 10.25 mmol) and potassium carbonate (2.83 g, 20.50 mmol) in 2-MeTHF – H_2O (20 mL, v/v), Weinreb amide **13a** was obtained in 96% yield (1.64 g) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38 (m, 1H, Ph H-6), 7.35 (m, 1H, Ph H-4), 7.14 (m, 1H, Ph H-5), 7.05(m, 1H, Ph H-3), 3.50 (br s, 3H, OCH_3), 3.29 (br s, 3H, NCH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.1 (very br, C=O), 158.5 (d, ^1J(C,F) = 249.1 Hz, Ph C-2), 131.4 (br d, ^3J(C,F) = 5.7 Hz, Ph C-4), 128.7 (br, Ph C-6), 123.9 (br, Ph C-5), 123.3 (d, ^2J(C,F) = 17.3 Hz, Ph C-1), 115.5 (d, ^2J(C,F) = 21.5 Hz, Ph C-3), 61.1 (OCH_3), 32.2 (very br, NCH_3).

^{19}F NMR (**377** MHz, $CDCl_3$) δ: -114.2 (br s).

IR (NaCl, ν_{max}, cm^{-1}) 1658, 1422, 1181, 989.

Elemental Analysis (%) for $C_9H_{10}FNO_2$. Calcd: C, 42.36; H, 3.55; N, 16.47. Found: C, 42.24; H, 3.46; N, 16.59.

_N_-methoxy-_N_-methyl-2-thiophenecarboxamide[8] (14a)

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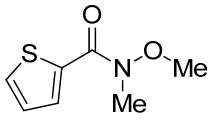


Following the General Procedure, starting from thiophene-3-carbonyl chloride (1.37 g, 1.0 ml, 9.32 mmol), DMHA (1 g, 10.25 mmol) and potassium carbonate (2.83 g, 20.50 mmol) in 2-MeTHF – H_2O (20 mL, v/v), Weinreb amide **14a** was obtained in 89% yield (1.42g) as a brown oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.96 (dd, ^3J = 3.8, ^4J =1.3 Hz, 1H, Th H-3), 7.55 (dd, ^2J = 5.0 Hz, ^4J = 1.3 Hz, 1H, Th H-5), 7.10 (dd, ^3J = 5.0 Hz, ^3J = 3.8 Hz, 1H, Th H-4), 3.77 (s, 3H, OCH_3), 3.37 (s, 3H, NCH_3).

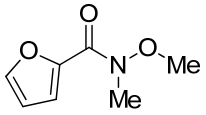
^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.2 (C=O), 134.4 (Th C-3), 133.2 (Th C-2), 132.2 (Th C-5), 126.8 (Th C-4), 61.5 (OCH_3), 33.0 (NCH_3).

^{15}N NMR (40 MHz, $CDCl_3$) δ: -197.1 (amide N).

IR (NaCl, ν_{max}, cm^{-1}) 3112, 2968, 2939, 2822, 1629, 1521, 1461, 1430, 1383, 1348, 1220, 1185, 1157, 1074, 982, 934.

Elemental Analysis (%) for $C_7H_9NO_2S$: C, 49.10; H, 5.30; N, 8.18; S, 18.73. Found: C, 48.96; H, 5.17; N, 8.32; S, 18.61.

***N*-methoxy-*N*-methyl-2-furamide (15a)**



Following the General Procedure, starting from furan-3-carbonyl chloride (1.22 g, 0.92 ml, 9.32 mmol), DMHA (1 g, 10.25 mmol) and potassium carbonate (2.83 g, 20.50 mmol) in 2-MeTHF – H_2O (20 mL, v/v), Weinreb amide **15a** was obtained in 92% yield (1.33 g) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58 (dd, ^3J = 1.7 Hz, ^4J = 0.8 Hz, 1H, Fur H-5), 7.14 (dd, ^3J = 3.5 Hz, ^4J = 0.8 Hz, 1H, Fur H-3), 6.50 (dd, ^3J = 3.4, ^3J = 1.7 Hz, 1H, Fur H-4), 3.76 (s, 3H, OCH_3), 3.34 (s, 3H, NCH_3).

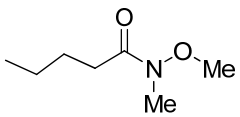
^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.1 (C=O), 145.7 (Fur C-2), 145.2 (Fur C-5), 117.3 (Fur C-3), 111.5 (Fur C-4), 61.3 (OCH_3), 33.1 (NCH_3).

^{15}N NMR (40 MHz, $CDCl_3$) δ: -198.2 (amide N).

IR (NaCl, ν_{max}, cm^{-1}) 3287, 3133, 2935, 1638, 1566, 1481, 1424, 1175, 1020, 979.

Elemental Analysis (%) for $C_7H_9NO_3$. Calcd: C, 54.19; H, 5.85; N, 9.03. Found: C, 54.25; H, 5.99; N, 8.89.

***N*-methoxy-*N*-methylpentanamide[11] (16a)**



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Following the General Procedure, starting from pentanoyl chloride (1.12 g, 1.13 ml, 9.32 mmol), DMHA (1 g, 10.25 mmol) and potassium carbonate (2.83 g, 20.50 mmol) in 2-MeTHF – H_2O (20 mL, v/v), Weinreb amide **16a** was obtained in 93% yield (1.26 g) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.67 (s, 3H, OCH_3), 3.17 (s, 3H, NCH_3), 2.41 (t, ^3J = 7.7 Hz, 2H, $COCH_2$), 1.61(m, 2H, $COCH_2\underline{CH_2}$), 1.36 (m, 2H, $CH_3\underline{CH_2}$), 0.92 (t, ^3J = 7.3 Hz, 3H, CH_3).

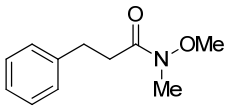
^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.8 (C=O), 61.2 (OCH_3), 32.2 (NCH_3), 31.6 ($CO\underline{C}H_2$), 26.7 ($COCH_2\underline{C}H_2$), 22.5 ($CH_3\underline{C}H_2$), 13.8 ($\underline{C}H_3CH_2$).

^{15}N NMR (40 MHz, $CDCl_3$) δ: -193.7 (amide N).

IR (NaCl, ν_{max}, cm^{-1}) 2838, 1659, 1614, 1515, 1461, 1440, 1416, 1389.

Elemental Analysis (%) for $C_7H_{15}NO_2$. Calcd: C, 57.90; H, 10.41; N, 9.65. Found: C, 57.78; H, 10.29; N, 9.49.

_N_-methoxy-_N_-methyl-3-phenylpropanamide[12] (17a)



Following the General Procedure, starting from phenylpropionyl chloride (1.57 g, 1.39 mL 9.32 mmol), DMHA (1 g, 10.25 mmol) and potassium carbonate (2.83 g, 20.50 mmol) in 2-MeTHF – H_2O (20 mL, v/v), Weinreb amide **17a** was obtained in 90% yield (1.62 g) as a light brown oil.

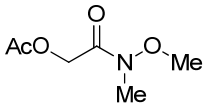
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.34-7.20 (m, 5H, Ar-H), 3.62 (s, 3H, OCH_3), 3.20 (s, 3H, NCH_3), 2.98 (m, 2H, CH_2), 2.76 (m, 2H, CH_2).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.3, 151.6, 141.4, 128.5, 126.1, 61.2, 33.8, 32.2, 30.7.

IR (NaCl, ν_{max}, cm^{-1}) 3060, 3022, 2939, 2818, 1660, 1452, 1421, 1381, 1176, 1111, 993, 754.

Elemental Analysis (%) for $C_{11}H_{15}NO_2$. Calcd: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.50; H, 7.69; N, 7.11.

2-[methoxy(methyl)amino]-2-oxoethyl acetate[13] (18a)



Following the General Procedure, starting from 2-chloro-2-oxoethyl acetate (1.27 g, 1.00 mL 9.32 mmol), DMHA (1 g, 10.25 mmol) and potassium carbonate (2.83 g, 20.50 mmol) in 2-MeTHF – H_2O (20 mL, v/v), Weinreb amide **18a** was obtained in 88% yield (1.32 g) as a light yellow oil.

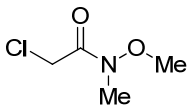
^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.53 (s, 2H, CH_2), 3.46 (s, 3H, $NOCH_3$), 2.90 (s, 3H, NCH_3), 1.86 (s, 3H, $COCH_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.6, 168.1, 61.62, 61.2, 32.3, 20.6.

IR (NaCl, ν_{max}, cm^{-1}) 3567.35, 1746.53, 1685.48, 1425.93, 1233.65, 1066.07, 982.

Elemental Analysis (%) for $C_6H_{11}NO_4$: C, 44.72; H, 6.88; N, 8.69. Found: C, 44.85; H, 7.01; N, 8.57.

2-chloro-*N*-methoxy-*N*-methylacetamide[14] (19a)



Following the General Procedure, starting from 2-chloroacetyl chloride (1.05 g, 0.74 mL 9.32 mmol), DMHA (1 g, 10.25 mmol) and potassium carbonate (2.83 g, 20.50 mmol) in 2-MeTHF – H_2O (20 mL, v/v), Weinreb amide **19a** was obtained in 95% yield (1.21 g) as a light brown crystalline solid.

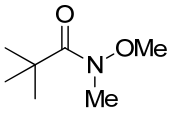
^{1}H NMR (200 MHz, $CDCl_3$) δ: 4.27 (s, 2H, CH_2), 3.78 (s, 3H, OCH_3), 3.26 (s, 2H, NCH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.5, 61.7, 40.8, 32.6.

IR (NaCl, ν_{max}, cm^{-1}) 1681, 1422, 1230.

Elemental Analysis (%) for $C_4H_8ClNO_2$. Calcd: C, 34.92; H, 5.86; N, 10.18. Found: C, 35.09; H, 5.74; N, 10.30.

***N*-methoxy-*N*-methylpivalamide[9] (20a)**



Following the General Procedure, starting from pivaloyl chloride (1.12 g, 1.15 mL 9.32 mmol), DMHA (1 g, 10.25 mmol) and potassium carbonate (2.83 g, 20.50 mmol) in 2-MeTHF – H_2O (20 mL, v/v), Weinreb amide **20a** was obtained in 97% yield (1.31 g) as a colorless oil.

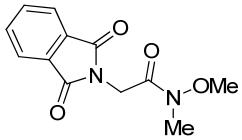
^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.58 (s, 3H, OCH_3), 3.08 (s, 3H, NCH_3), 1.15 (s, 9H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 179.2, 60.6, 39.4, 33.8, 27.2.

IR (NaCl, ν_{max}, cm^{-1}) 2962, 2932, 1653, 1486, 1457, 1403, 1356, 1169, 998.

Elemental Analysis (%) for $C_7H_{15}NO_2$. Calcd: C, 57.90; H, 10.41; N, 9.65. Found: C, 58.02; H, 10.55; N, 9.43.

2-(1,3-dioxoisoindolin-2-yl)-*N*-methoxy-*N*-methylacetamide (21a)



Following the General Procedure, starting from phthalylglycyl chloride (2.08 g, 9.32 mmol), DMHA (1 g, 10.25 mmol) and potassium carbonate (2.83 g, 20.50 mmol) in 2-MeTHF – H_2O (20 mL, v/v), Weinreb amide **21a** was obtained in 96% yield (2.22 g) as a light brown oil.

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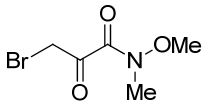
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.85-7.82 (m, 2H, Ar-H), 7.61-7.68 (m, 2H, Ar-H), 4.60 (s, 2H, CH_2), 3.60 (s, 3H, OCH_3), 3.19 (s, 3H, NCH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.0, 167.0, 134.2, 134.1, 132.2, 132.0, 124.1, 123.5, 61.5, 38.6, 38.5, 32.5.

IR (NaCl, ν_{max}, cm^{-1}) 1715, 1677, 1418, 1390, 1089, 1001, 718.

Elemental Analysis (%) for $C_{12}H_{12}NO_4$. Calcd: C, 58.06; H, 4.87; N, 11.29. Found: C, 57.94; H, 5.05; N, 11.42.

3-bromo-*N*-methoxy-*N*-methyl-2-oxopropanamide (22a)



Following the General Procedure, starting from 3-bromo-2-oxopropanoyl chloride[15] (1.73 g, 9.32 mmol), DMHA (1 g, 10.25 mmol) and potassium carbonate (2.83 g, 20.50 mmol) in 2-MeTHF – H_2O (20 mL, v/v), Weinreb amide **22a** was obtained in 89% yield (1.74 g) as a light yellow oil.

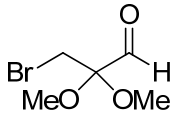
^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.23 (s, 2H, CH_2), 3.72 (s, 3H, OCH_3), 3.24 (s, 3H, NCH_3,).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 190.2, 165.4, 62.5, 46.0, 31.8. 31.5.

IR (NaCl, ν_{max}, cm^{-1}) 1740, 1699, 1221, 1181, 1033.

Elemental Analysis (%) for $C_5H_8BrNO_3$. Calcd: C, 28.59; H, 3.84; N, 6.67. Found: C, 28.73; H, 3.99; N, 6.56.

3-bromo-2,2-dimethoxypropanal[16] (23)



Weinreb amide **22a** (1.30 g, 6.19 mmol) was dissolved in anhydrous methanol (20 mL) and subsequently, trimethyl orthoformate (3.28 g, 3.38 mL, 30.95 mmol, 5.0 equiv.) and sulfuric acid (*oleum*, 1 mL) were added. The resulting mixture was refluxed in a Dean-Stark apparatus during 24 h, and then cooled to 0 °C. Saturated $NaHCO_3$ (30 mL) was added and the resulting solution was extracted with 2-MeTHF (2 x 15 mL) and dried over anhydrous Na_2SO_4. After filtration the solution was cooled at 0 °C and $LiAlH_4$ was added portionwise (258 mg, 6.81 mmol, 1.1 equiv.) and the resulting mixture was stirred for 2 h, before AcOEt (2 mL) was added. After adjusting the pH to 4 (HCl, 1M) the organic phase was separated, dried (Na_2SO_4) and filtered. Aldehyde **23** was obtained as a colorless oil in 79% yield (963 mg).

^{1}H NMR (200 MHz, $CDCl_3$) δ: 9.53 (s, 1H, CHO), 3.52 (s, 2H, CH_2), 3.39 (s, 6H, $(OCH_3)_2$).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 199.0, 50.3, 28.4.

IR (NaCl, ν_{max}, cm^{-1}) 1741, 1226, 967.

Elemental Analysis (%) for $C_5H_9BrO_3$. Calcd.: C, 30.48; H, 4.60. Found: C, 30.64; H, 4.85.

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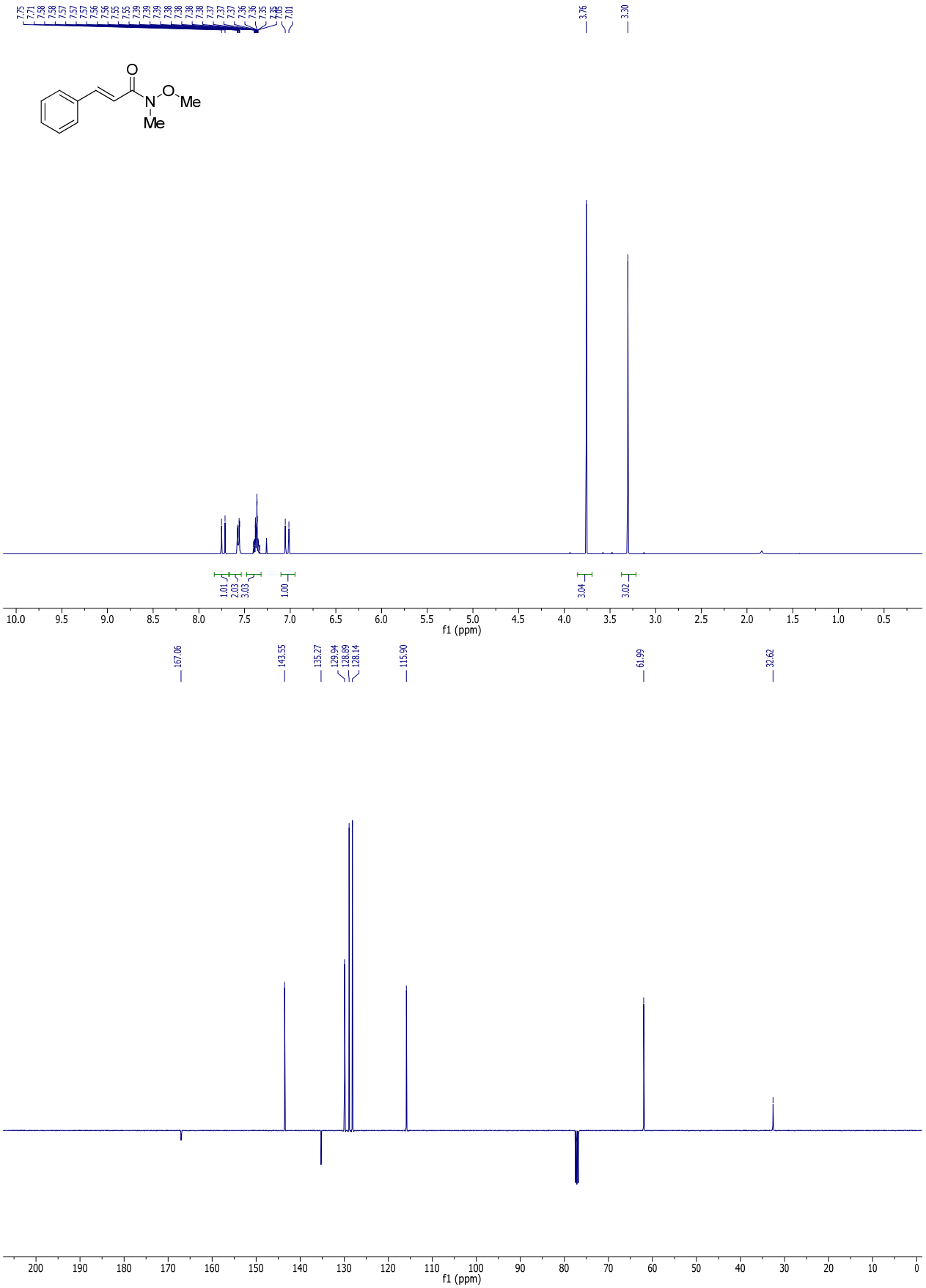

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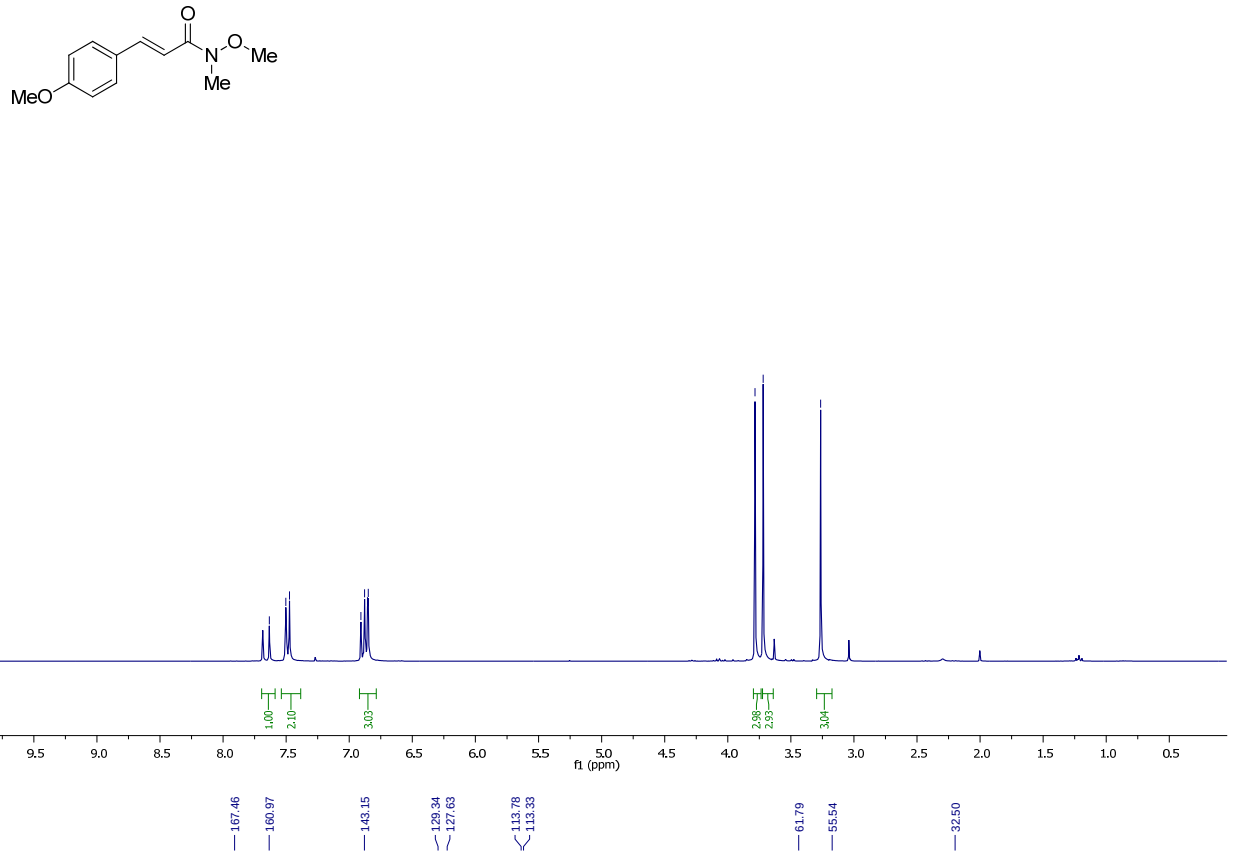

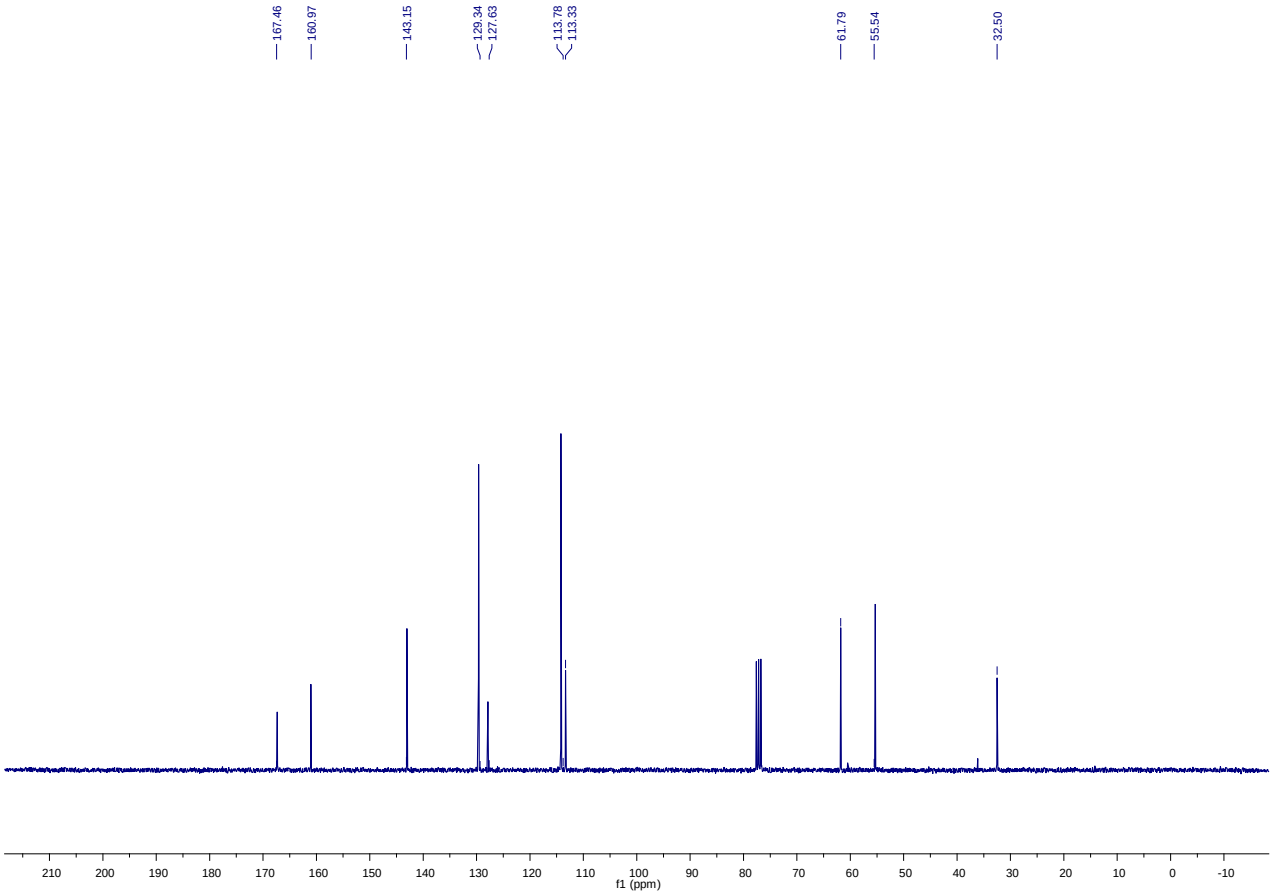

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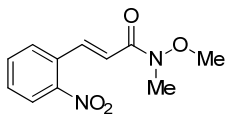

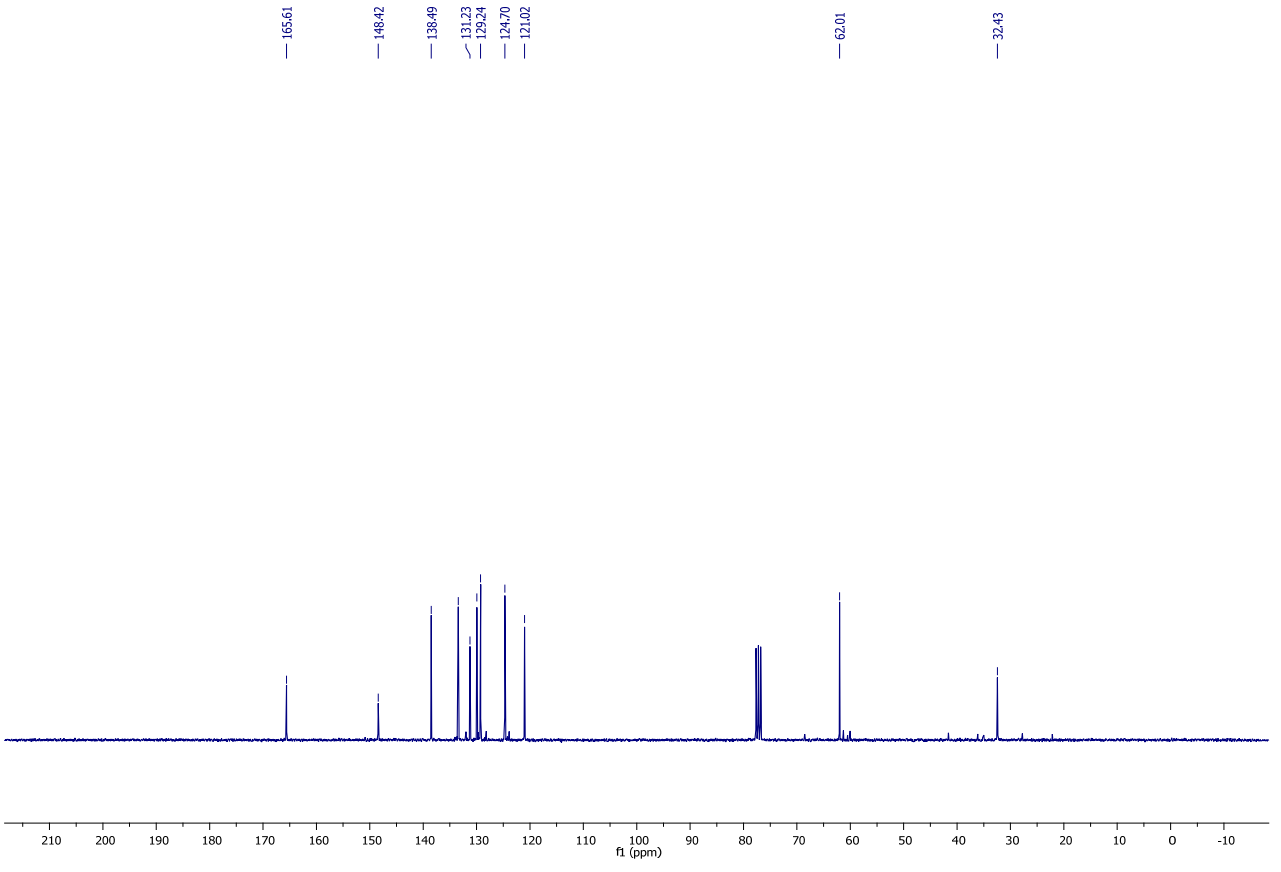

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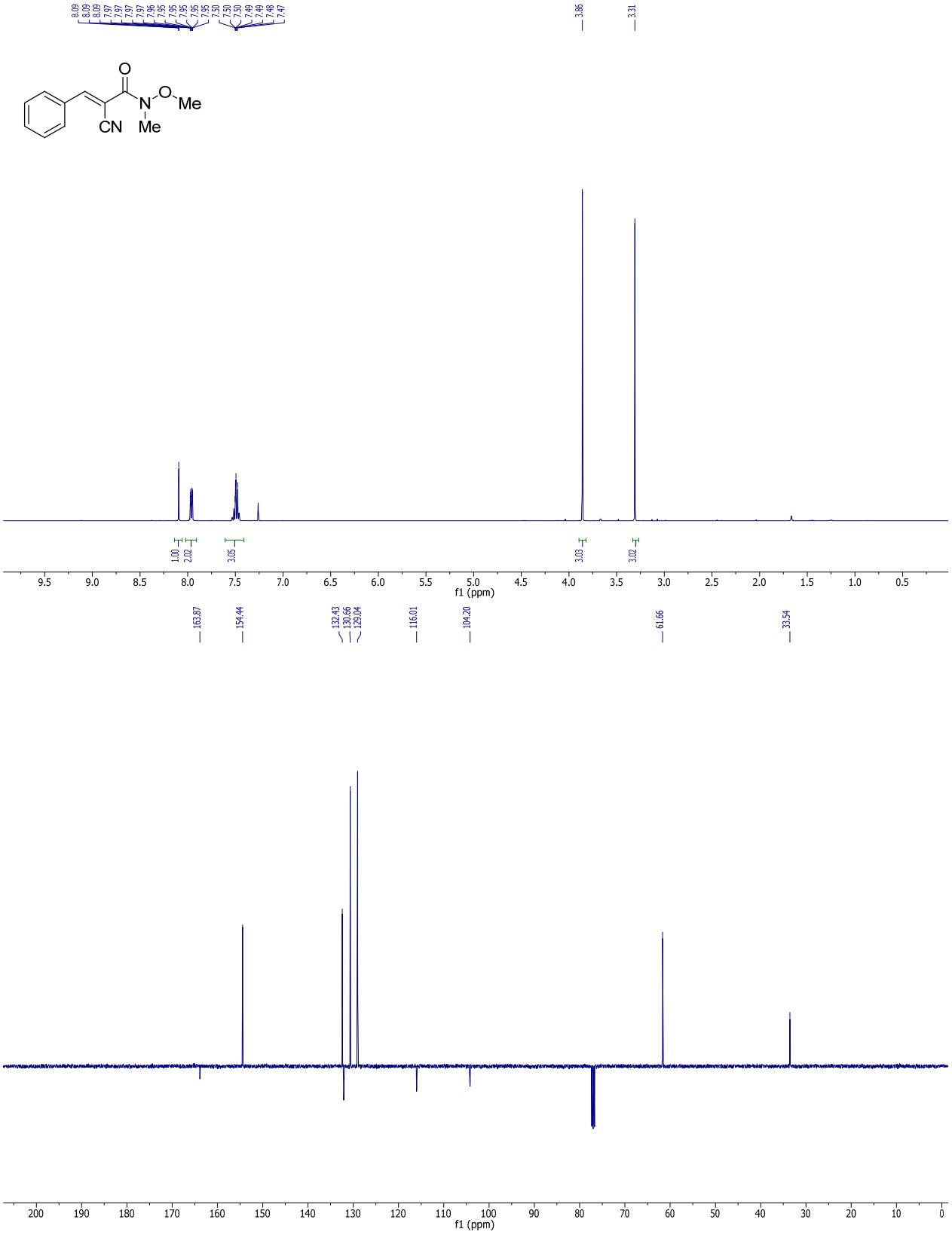

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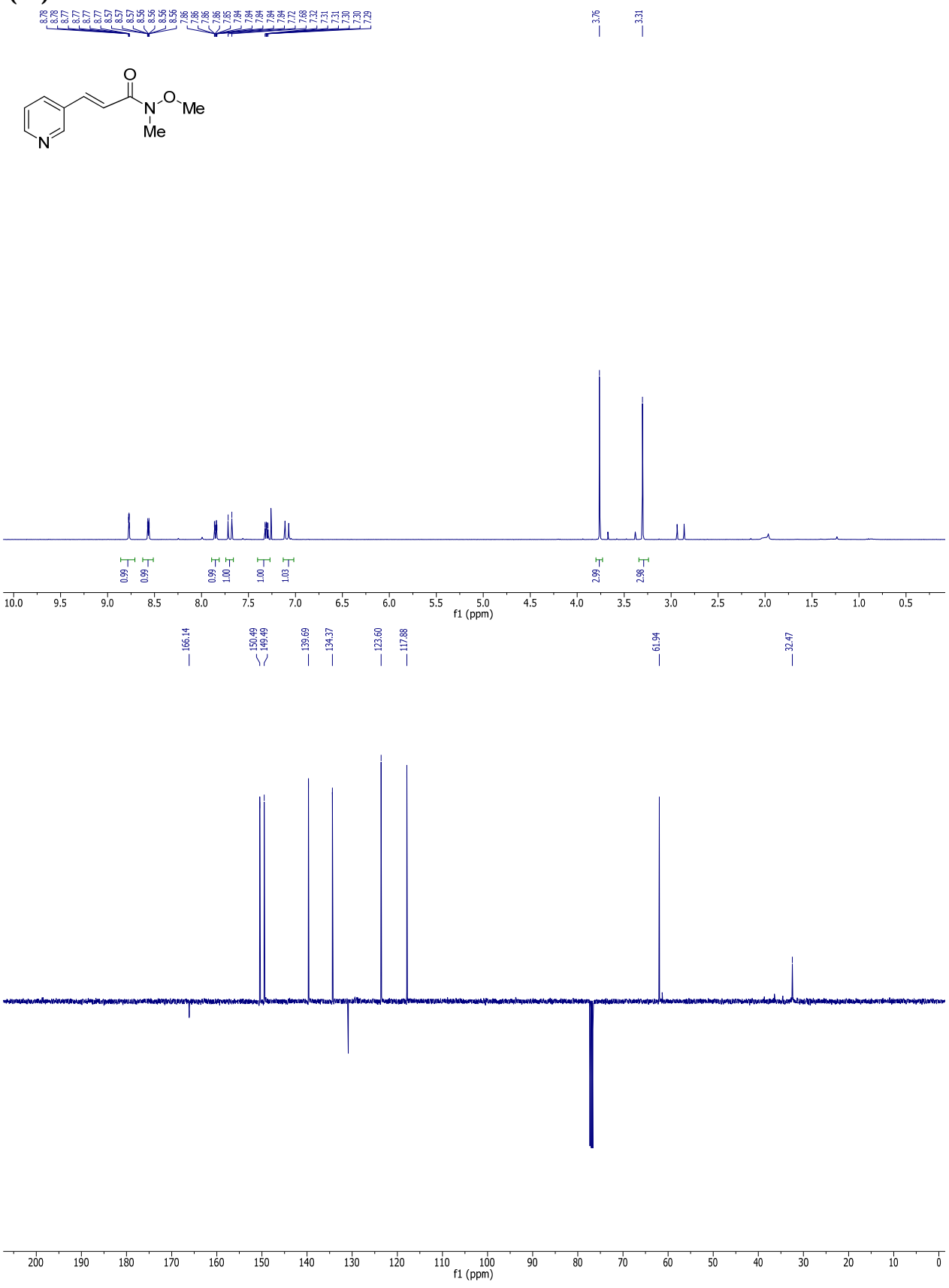

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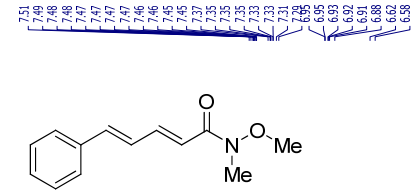

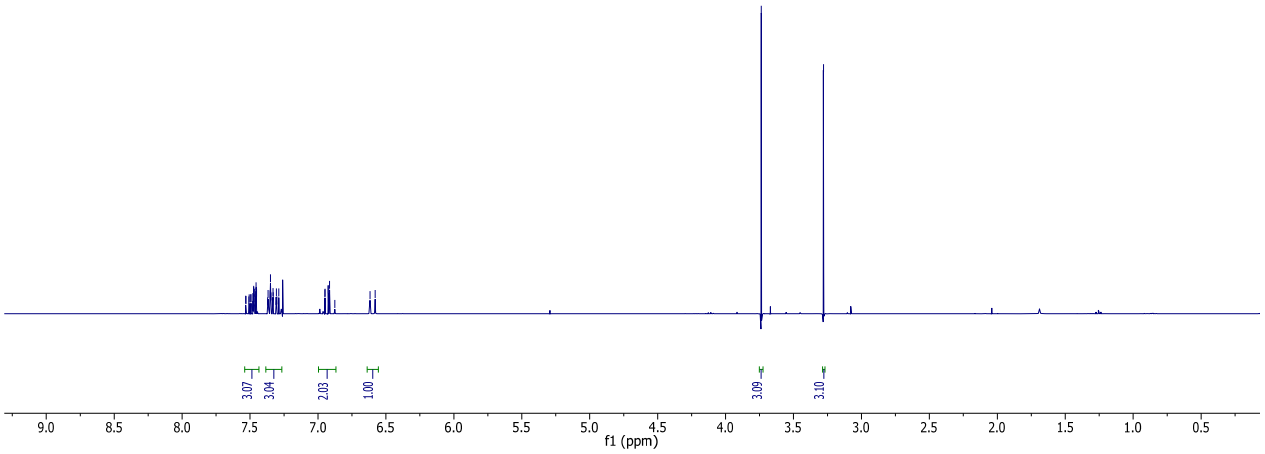

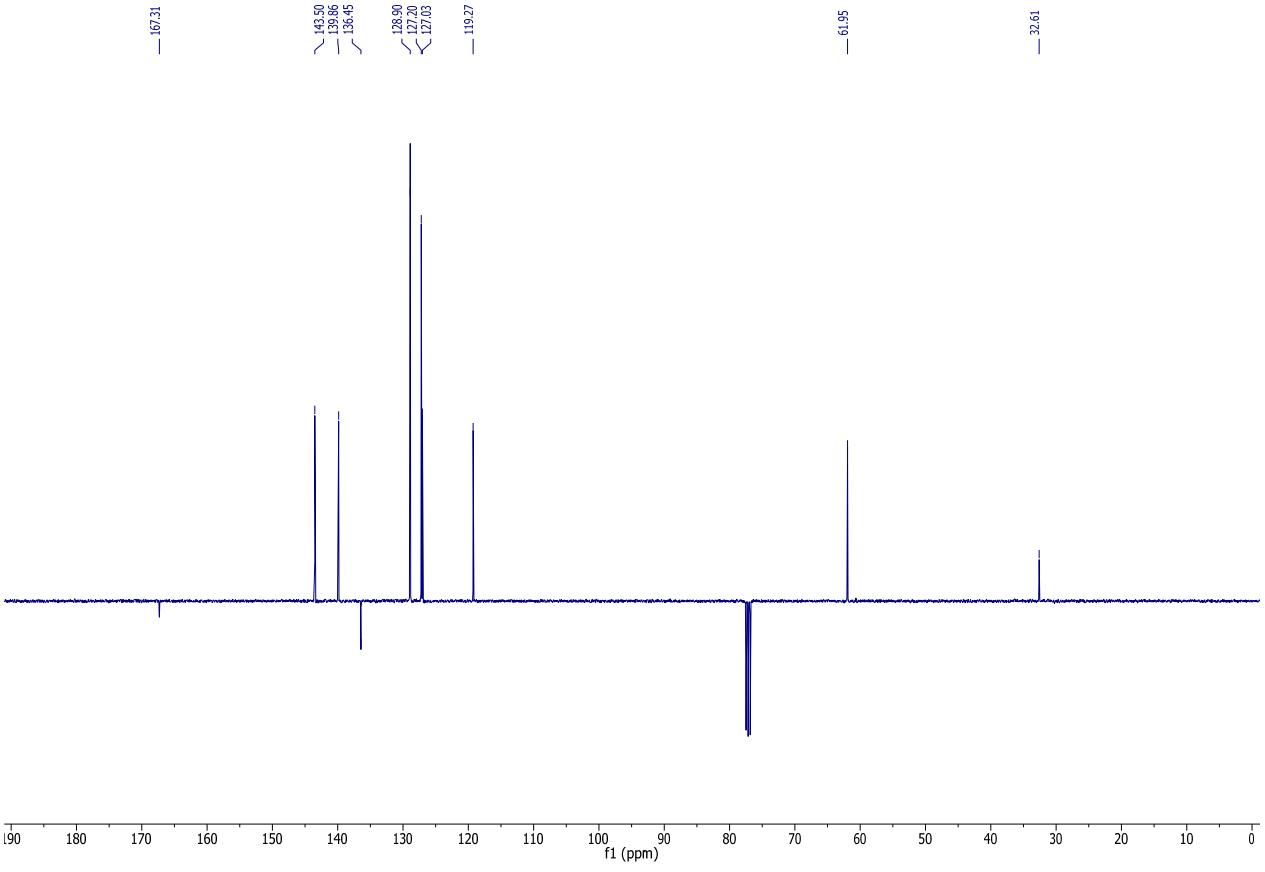

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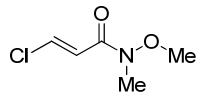
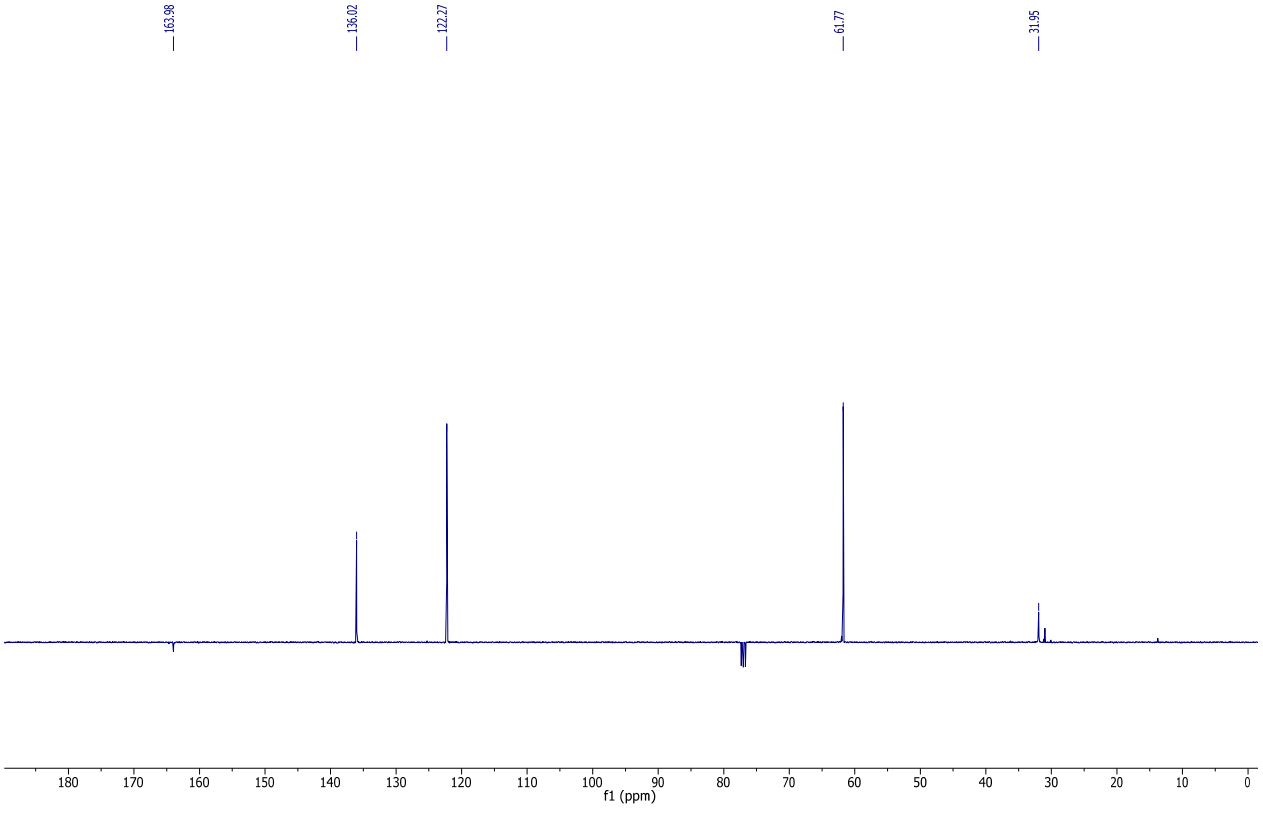
(7a)





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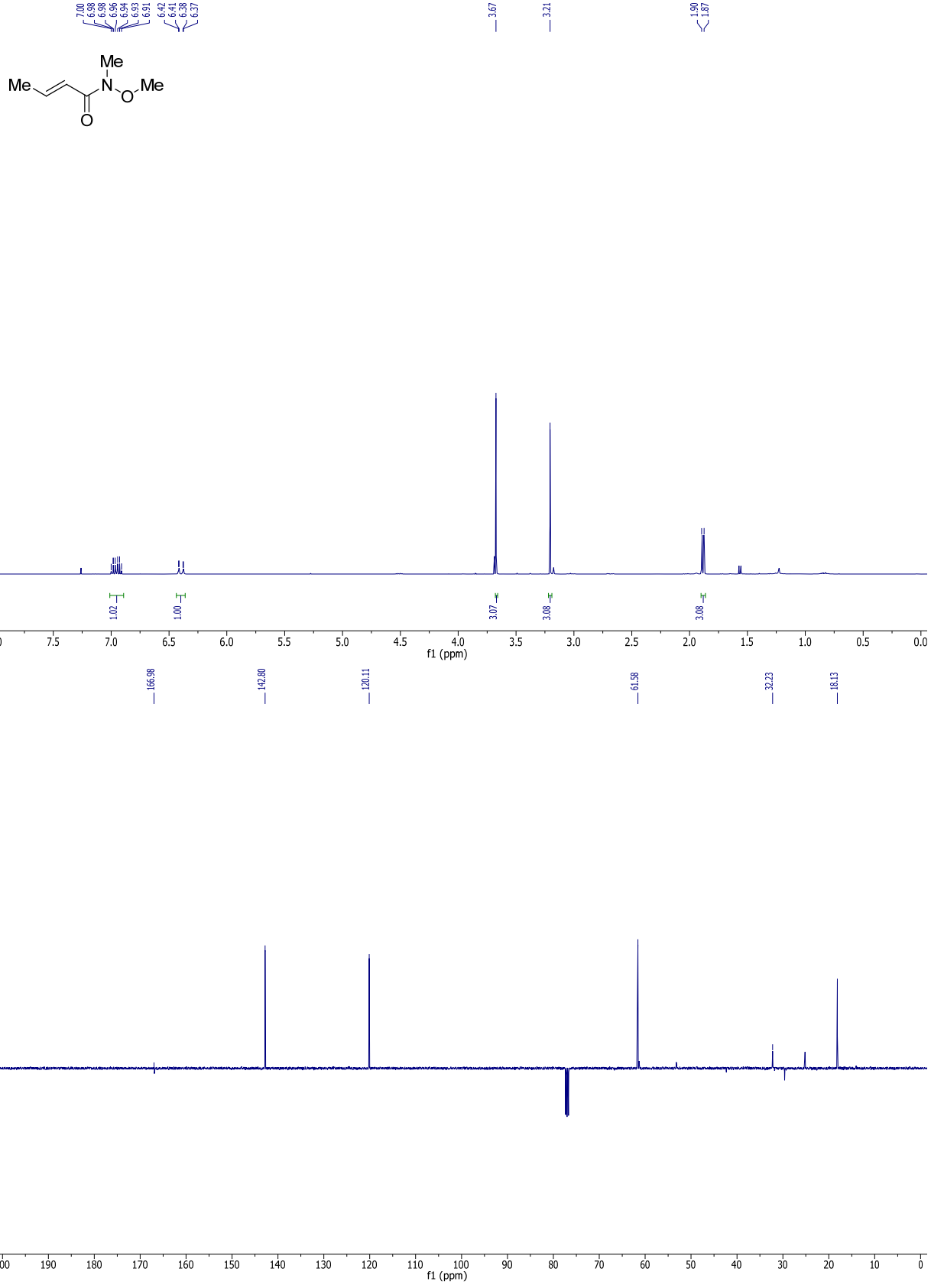
(8a)



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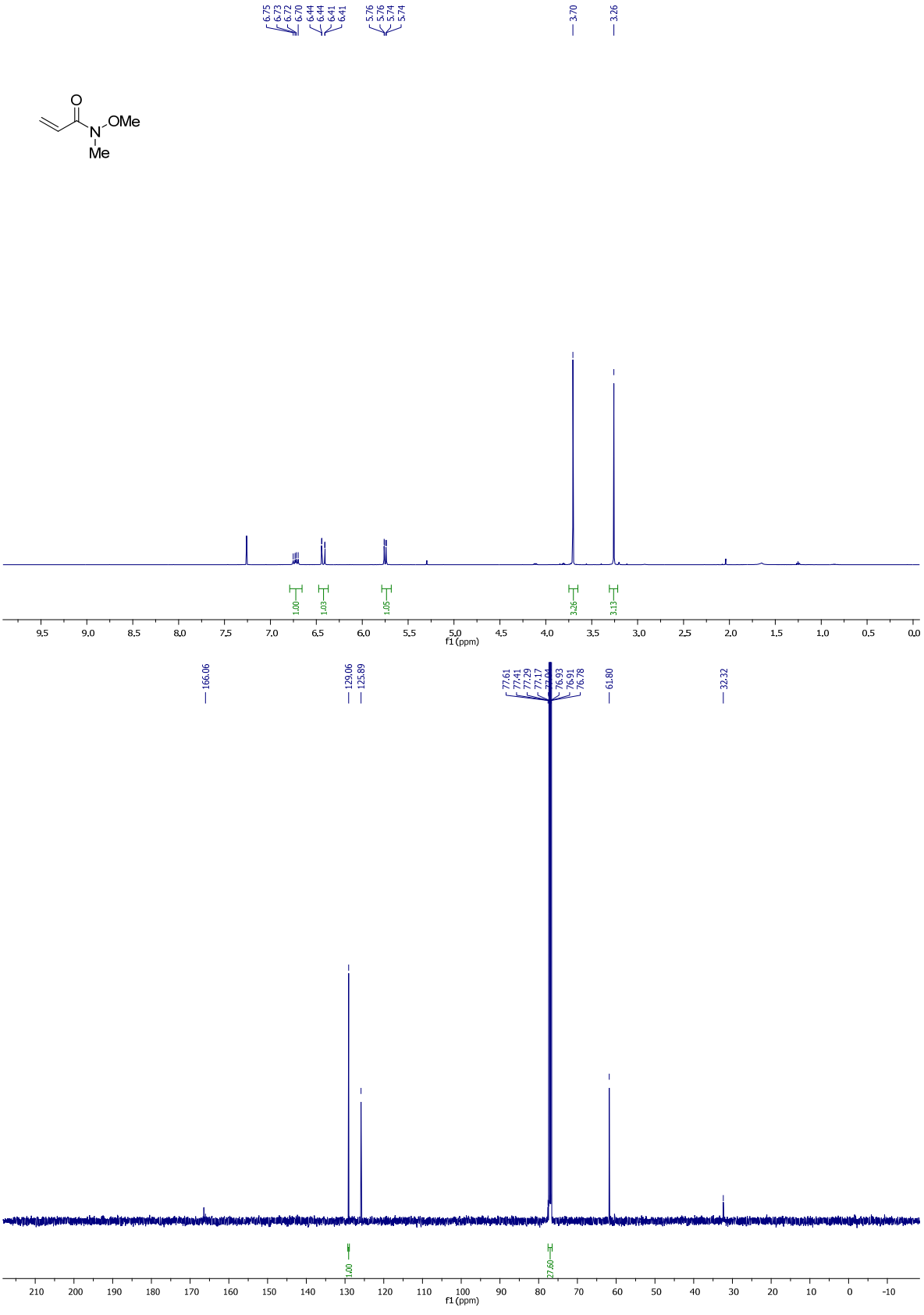
(9a)



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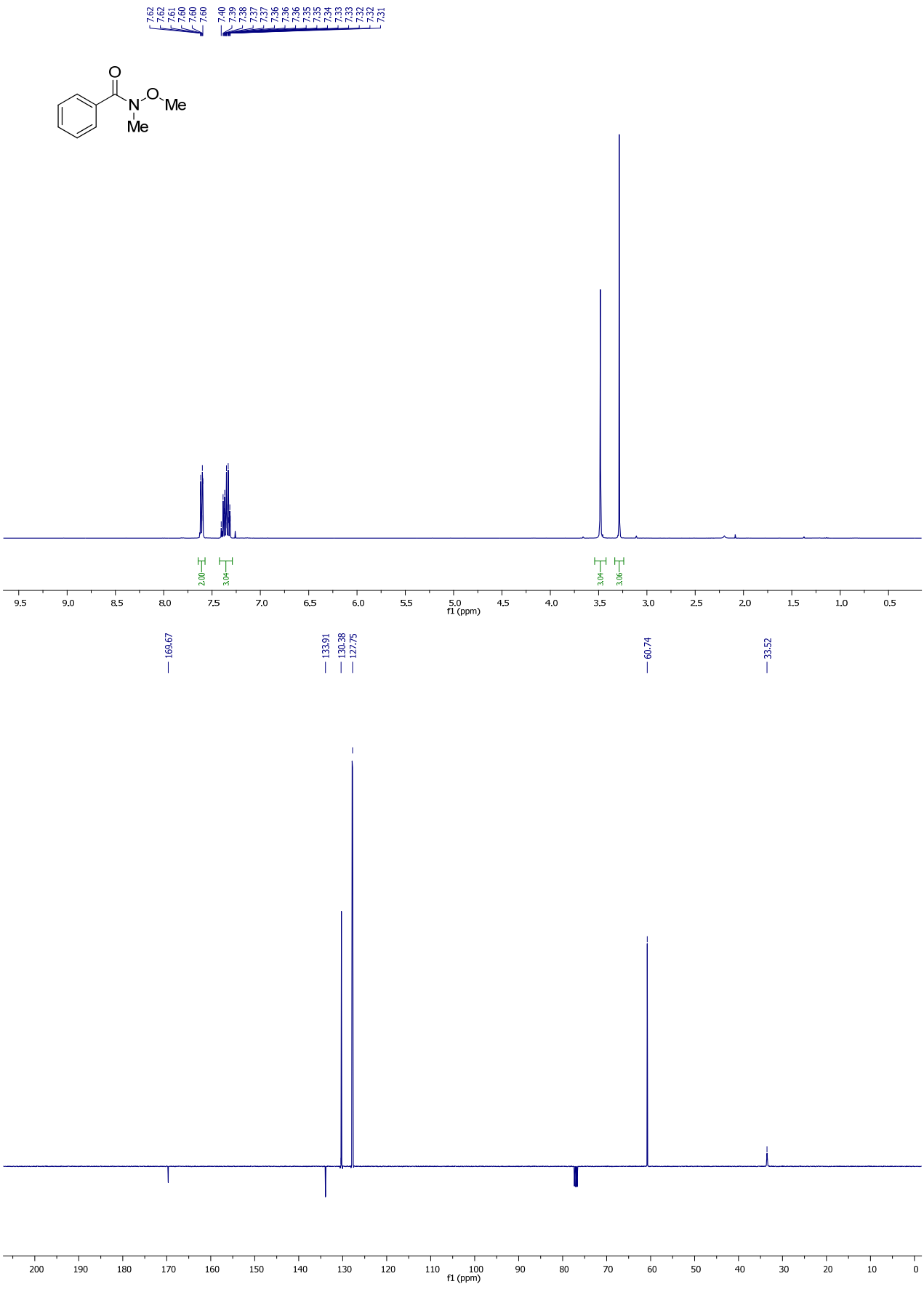
(10a)



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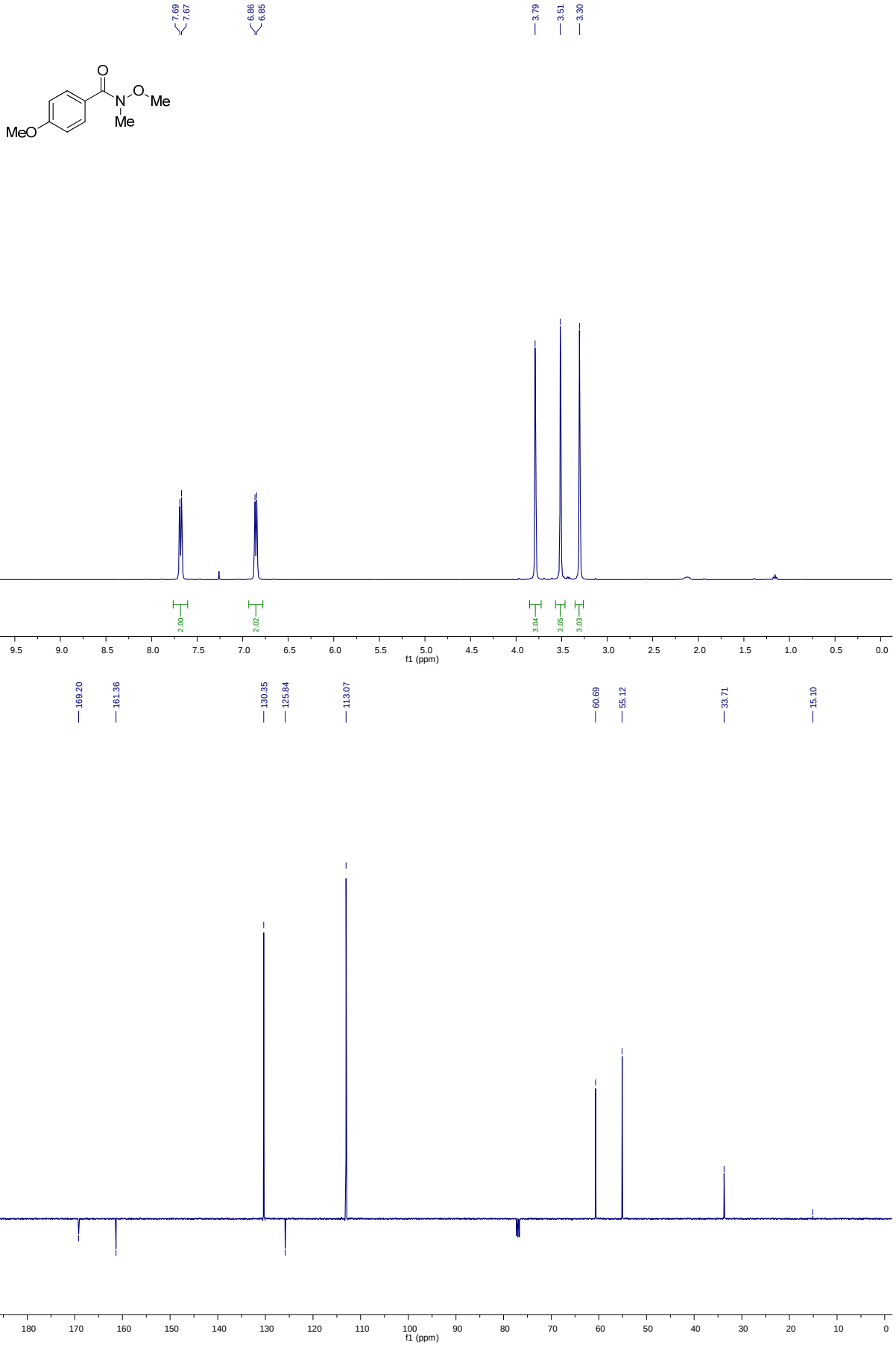
(11a)



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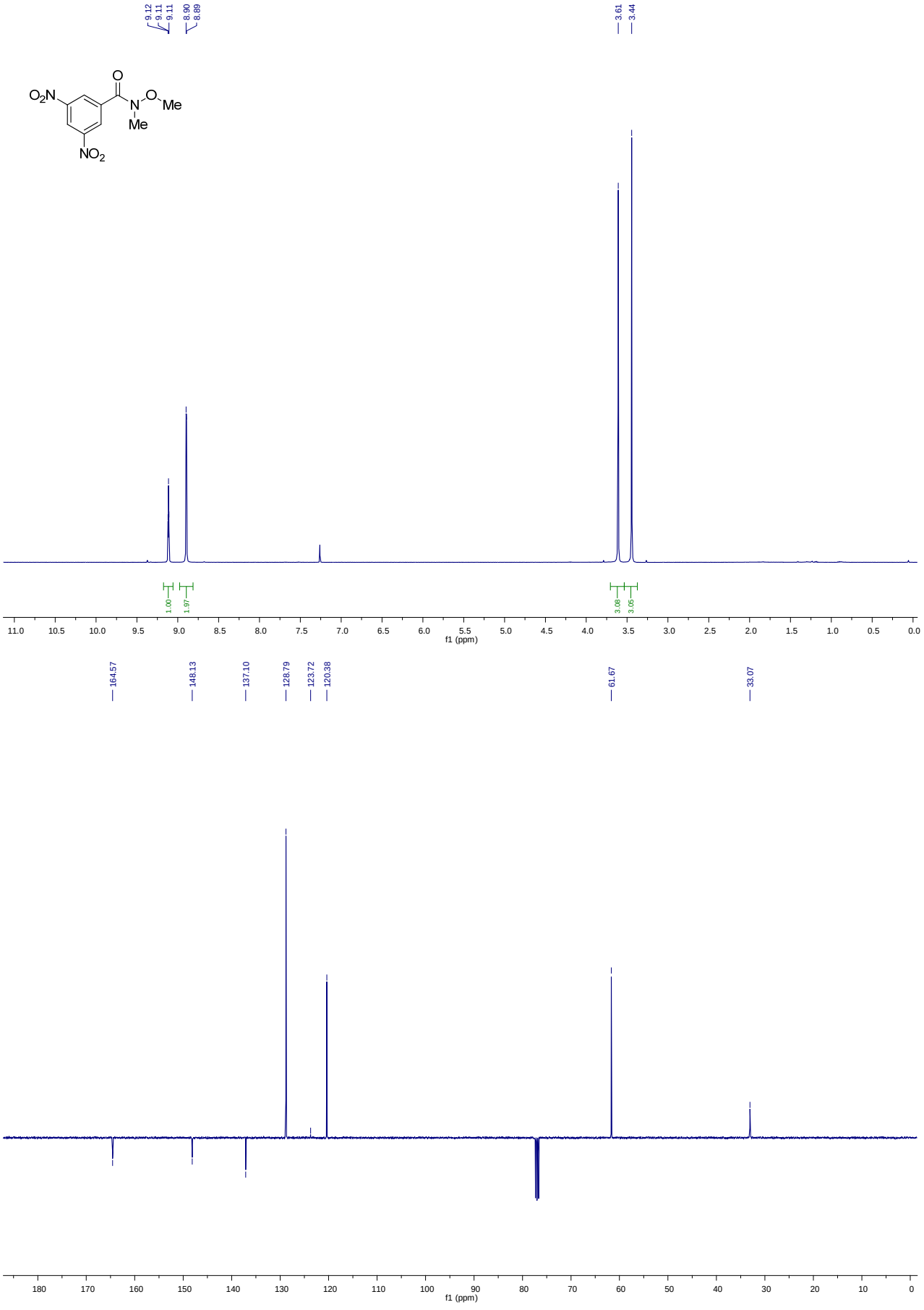
(12a)



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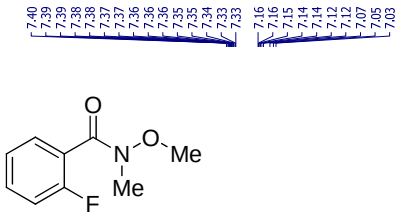
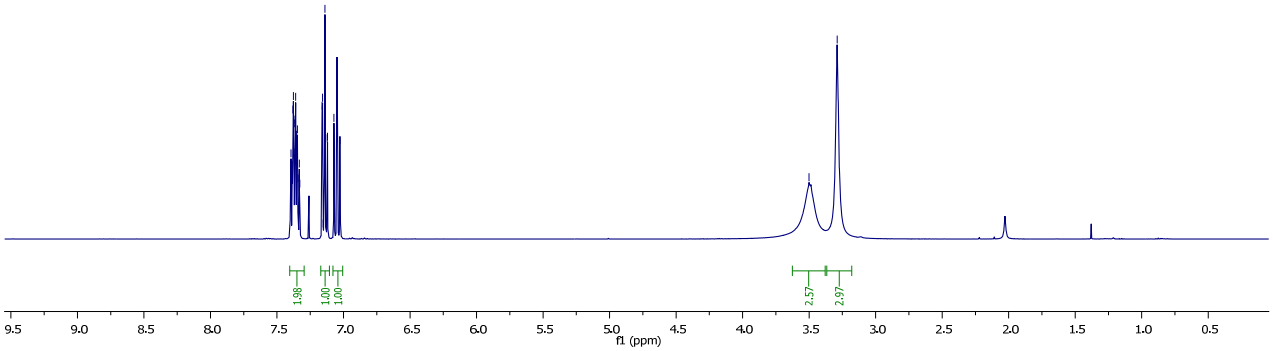
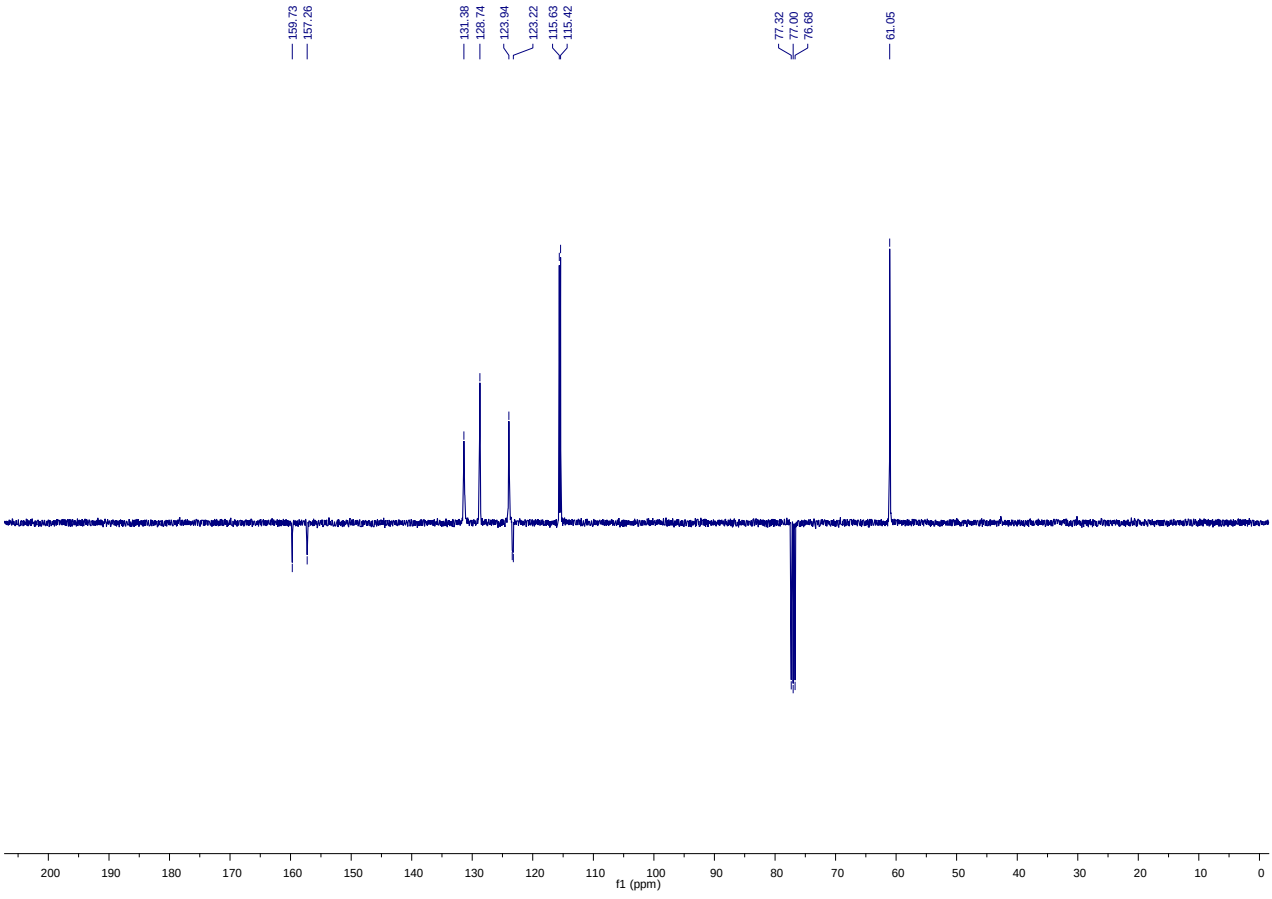
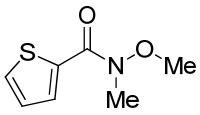
(13a)



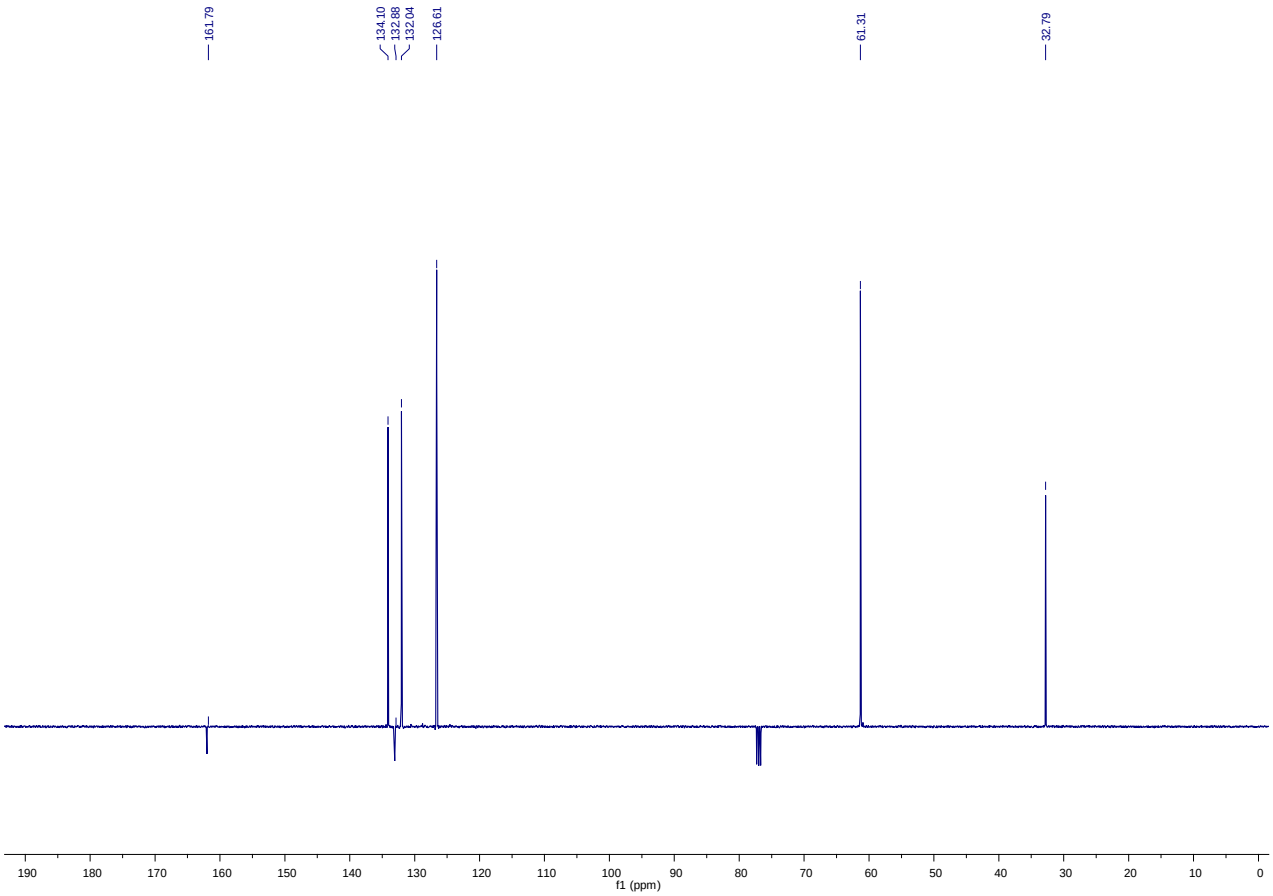




(14a)


O
S
N
O
Me
Me

7.91
7.90
7.06
7.05
7.03
3.72
3.31
0.99
1.00
1.00
3.03
3.06
f1 (ppm)


161.79
134.10
132.88
132.04
126.61
61.31
32.79
f1 (ppm)

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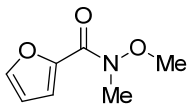
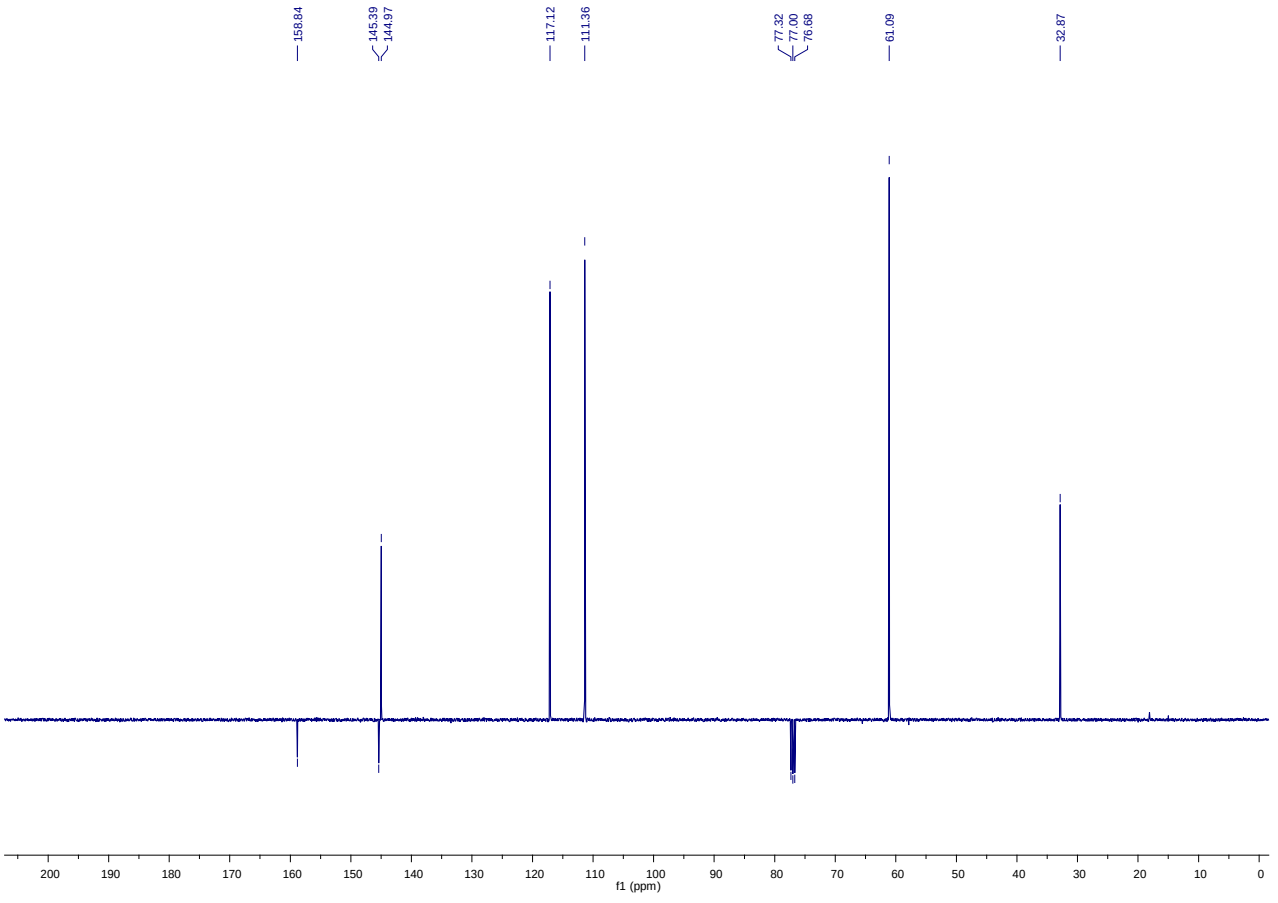
(15a)





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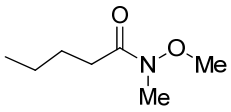
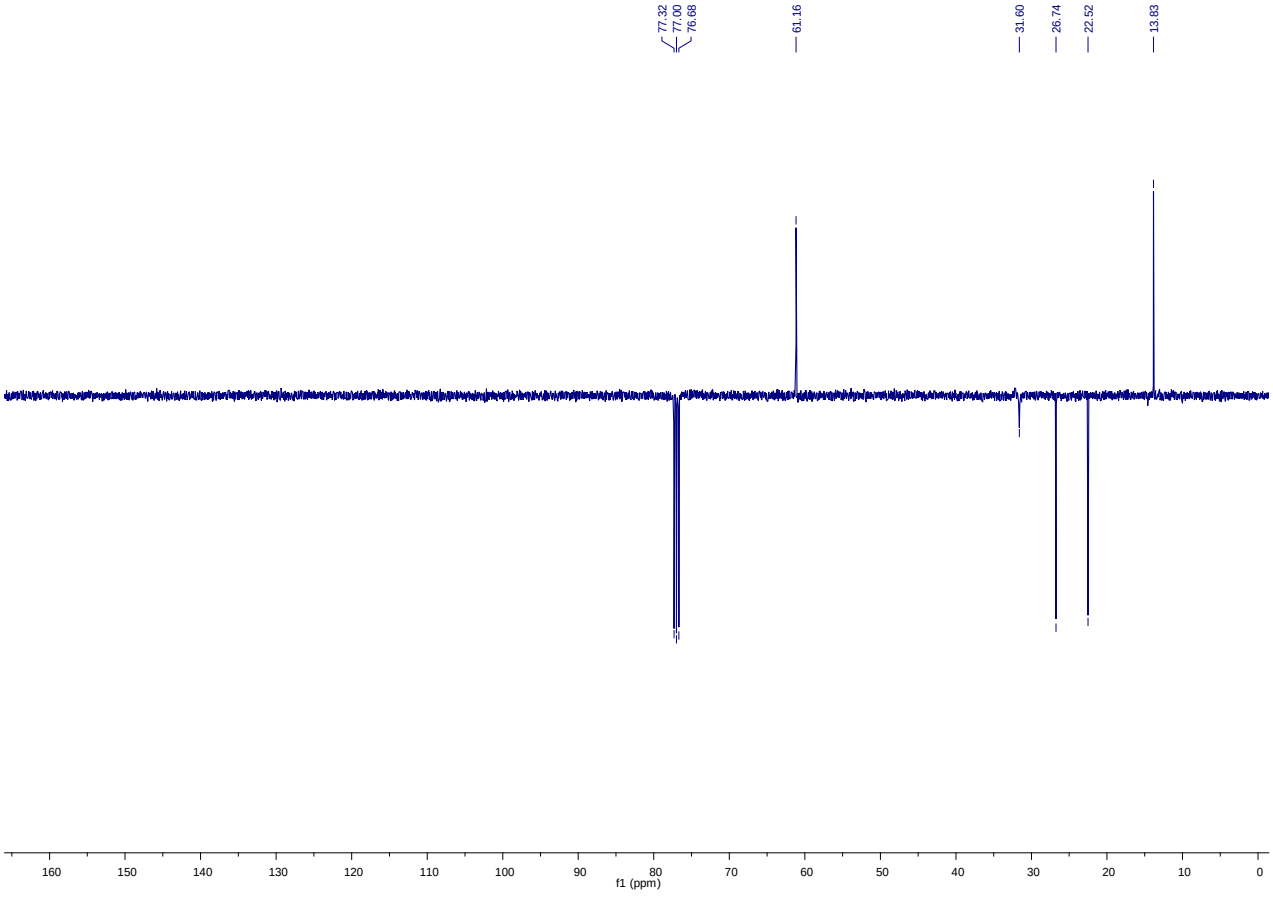
(16a)





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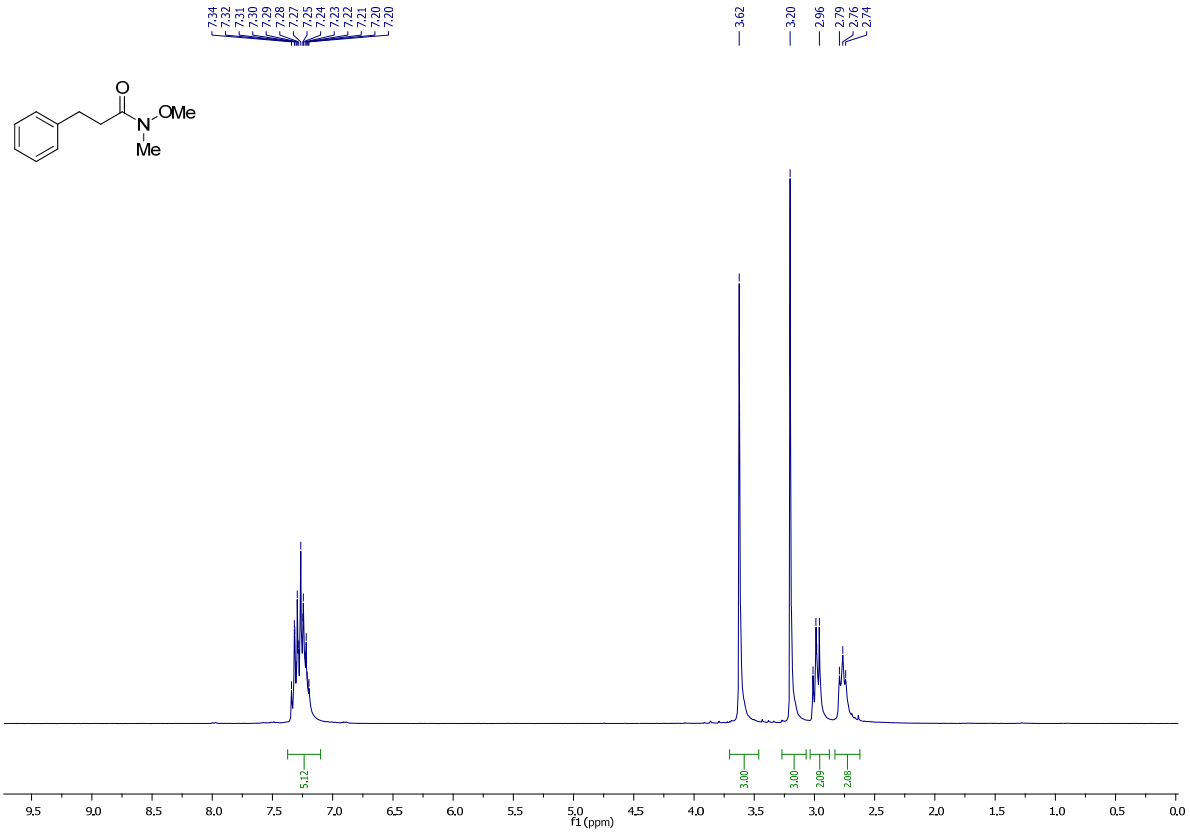
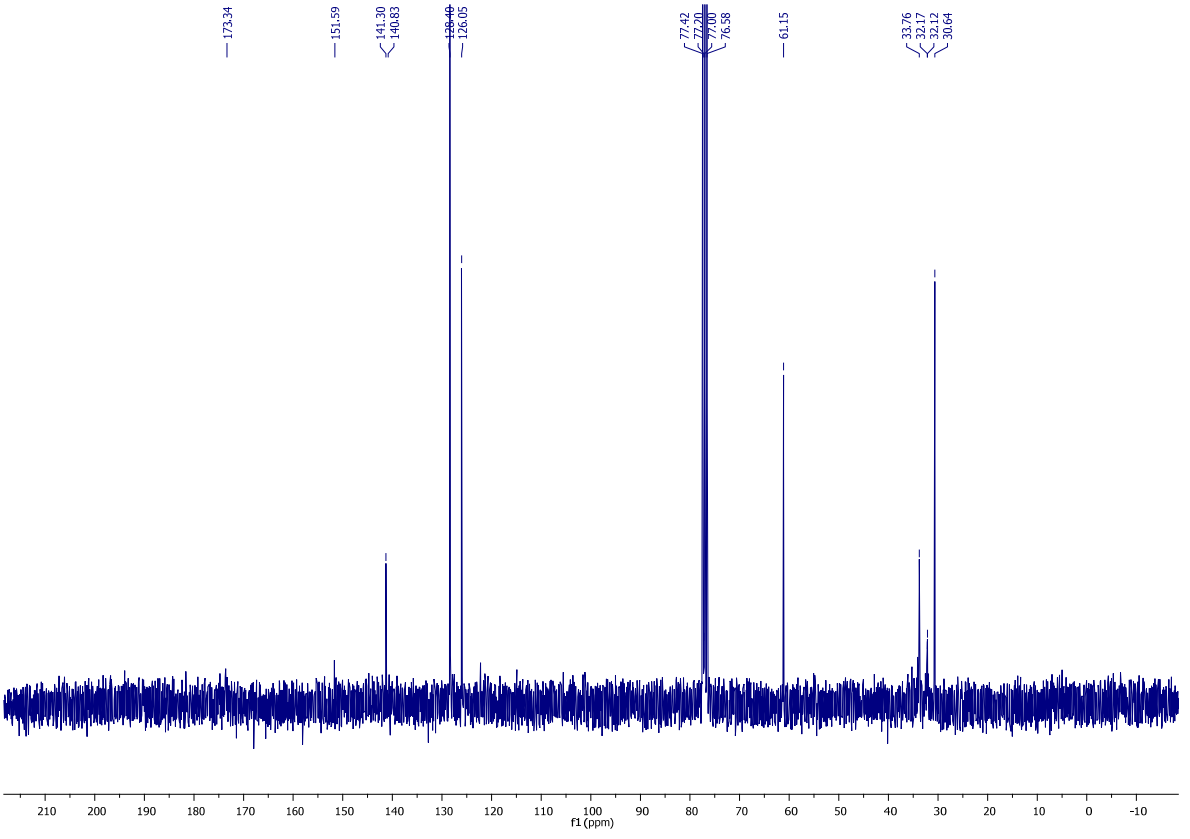
(17a)





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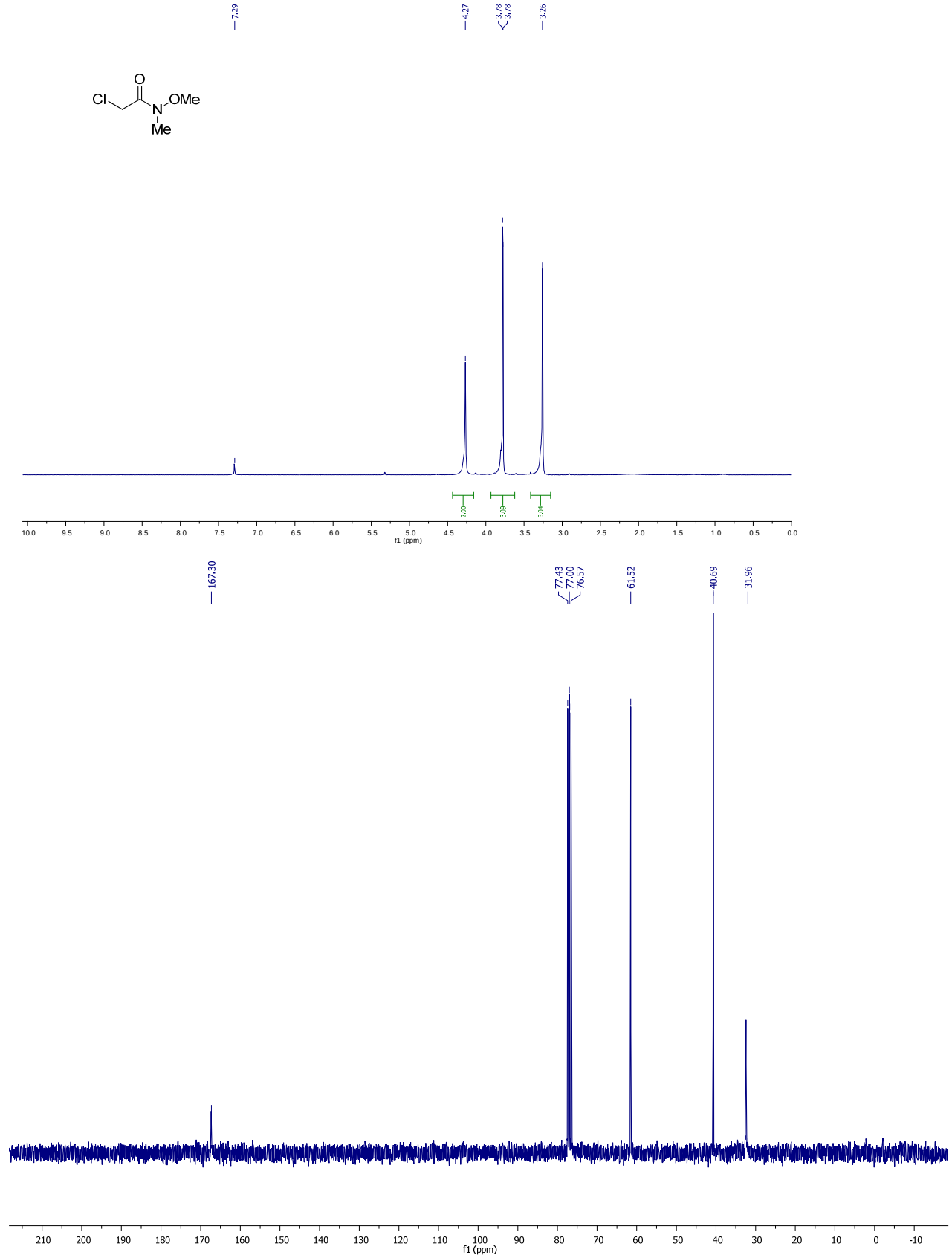
7.29
4.27
3.78
3.78
3.26
Cl
O
N
OMe
Me
2.00
3.09
3.04
f1 (ppm)
167.30
77.43
77.00
76.57
61.52
40.69
31.96
f1 (ppm)

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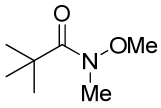
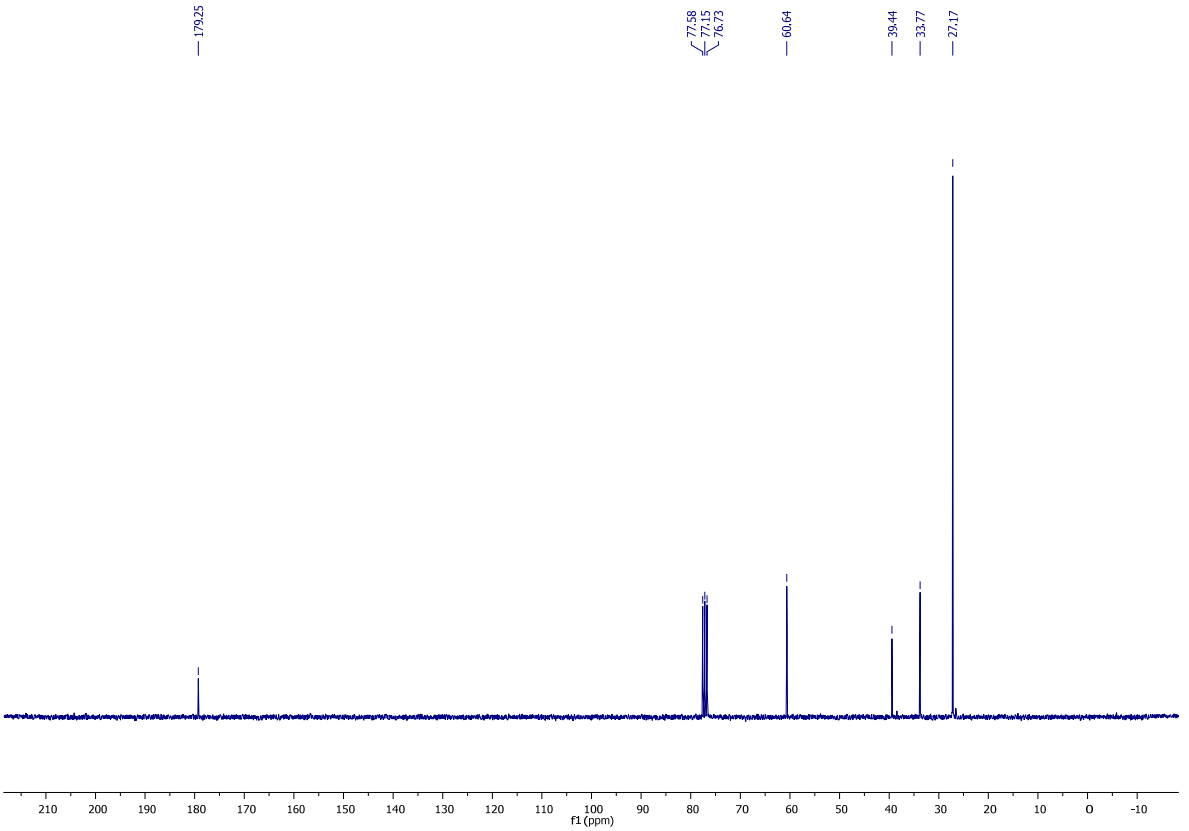
(20a)





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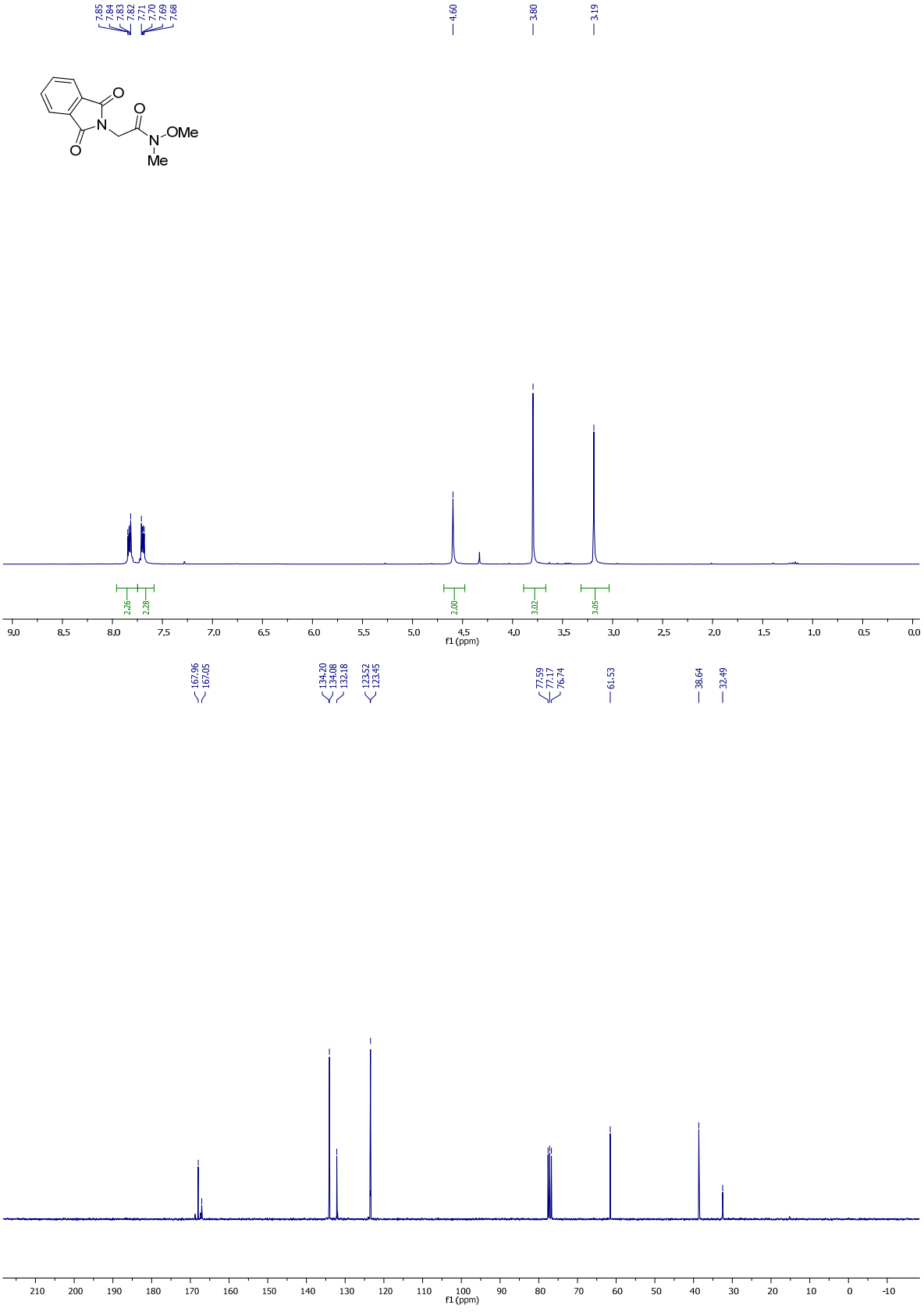
(21a)



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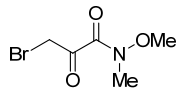
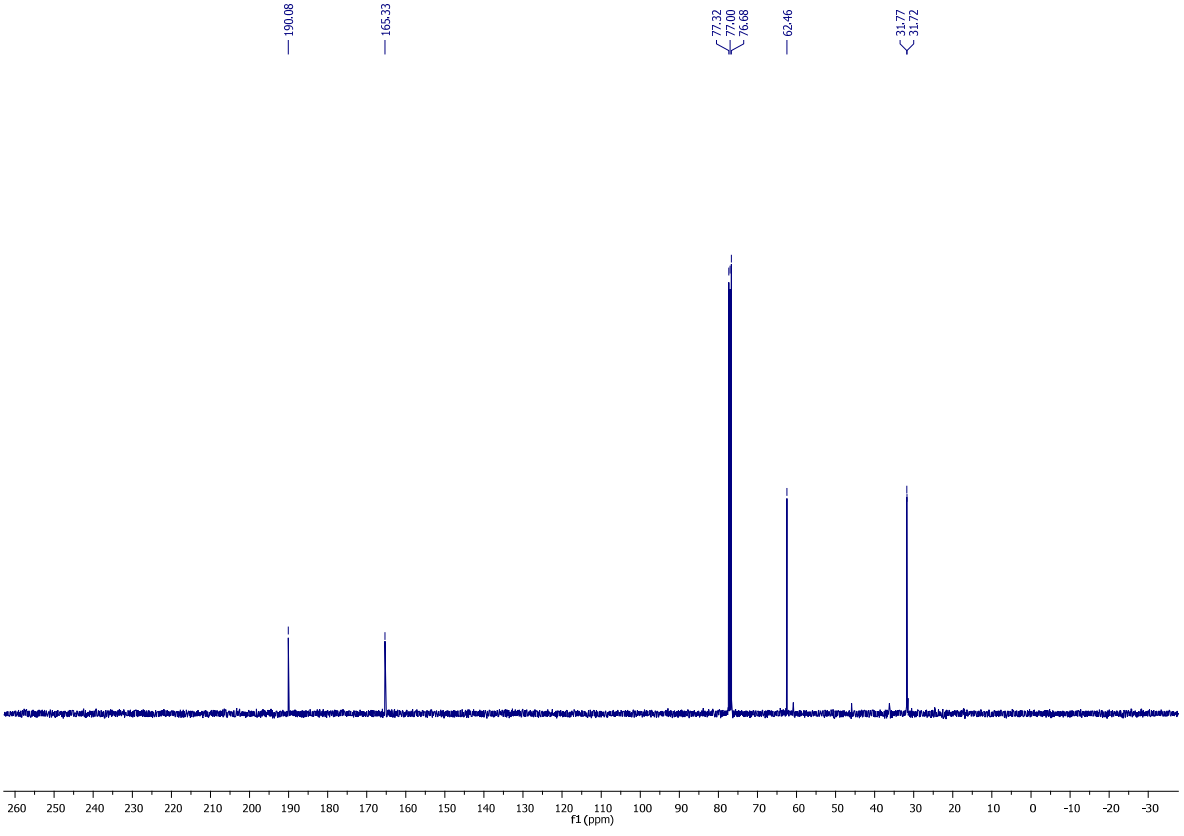
(22a)





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(23)