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Supporting Information

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DNA-Based Catalytic Enantioselective Michael Reactions in Water

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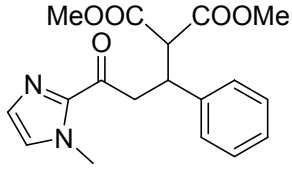
General Remarks.
Salmon testes and calf thymus DNA were obtained from Sigma. Copper complexes **L1-3**,[1] Michael's acceptors **1a** and **1f**[2] and **1b-e**[3] were prepared following published procedures. ^{1}H-NMR, and ^{13}C-NMR spectra were recorded on a Varian 400 (400 and 100 MHz) or Varian 200 (200 and 50 MHz) in $CDCl_3$. Chemical shifts (δ) are denoted in ppm using residual solvent peaks as internal standard (δ_C=77.0 and δ_H=7.26 for $CDCl_3$). Mass spectra (HRMS) were recorded on an AEI MS-902. Mass spectra (CI-MS) were recorded on a Jeol JMS 600H. Optical rotations were measured on a Schmidt and Haensch Polartronic MH8. Enantiomeric excess determinations were performed by HPLC analysis (Chiracel-OD or Chiralpak-AD) using UV-detection. Flash chromatography was performed using silica gel 60 Å (Merck, 200-400 mesh).

Representative procedure DNA-CuL3$(NO_3)_2$ catalyzed Michael addition reaction.
A catalyst solution of copper(II) complex (0.3 mM) and salmon testes DNA (1.3 mg/mL) in 20 mM MOPS buffer, pH 6.5, was prepared by adding to a solution of [Cu**L3**$(NO_3)_2$] in water (5 mL, concentration 0.9 mM), a salmon testes DNA solution (10 mL, 2 mg/mL in 30 mM MOPS buffer, pH 6.5; prepared 24h in advance). To this was added 30 μL of a fresh stock solution of Michael acceptor in CH_3CN. After addition of nitromethane (1 mL) or dimethymalonate (174 μL) at 0°C, the reaction was mixed for 3 days by continuous inversion at 5°C. The product was isolated by extraction with Et_2O (2 x 10 mL). After drying (Na_2SO_4) and removal of the solvent the crude product was analyzed by NMR and HPLC.

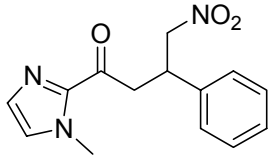
Synthesis Michael addition products

dimethyl 2-(3-(1-methyl-1H-imidazol-2-yl)-3-oxo-1-phenylpropyl)malonate (2a)



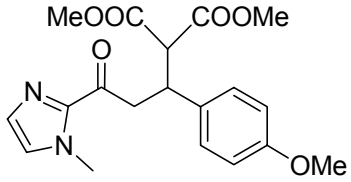
A colourless oil was obtained after column chromatography (SiO_2, EtOAc/hexane 4:6). $[\alpha]_D^{25}$ = -56.1° (c = 10.5 in $CHCl_3$, 85% e.e. according to HPLC); ^{1}H-NMR ($CDCl_3$, 400 MHz, 300 K) δ=7.26 (d, J = 7.2 Hz, 2H), 7.19 (t, J = 7.2 Hz, 2H), 7.11 (d, J = 6.9 Hz, 1H), 7.03 (d, J = 0.9 Hz, 1H), 6.91 (s, 1H), 4.13 (td, J = 4.5, 9.8 Hz, 1H), 3.84-3.76 (m, 2H), 3.80 (s, 3H), 3.67 (s, 3H), 3.45-3.39 (m, 1H), 3.41 (s, 3H); ^{13}C-NMR ($CDCl_3$, 50 MHz, 300 K) δ=189.7, 168.7, 168.2, 143.0, 140.6, 129.1, 128.5, 128.4, 127.2, 127.1, 57.8, 52.8, 52.5, 42.9, 40.5, 36.1; HRMS: *m/z*: 344.1366 [M^+] (Calcd 344.1372). The e.e. was determined by HPLC analysis (Chiralpak-AD, *n*-heptane/iPrOH 90:10, 1 ml/min). Retention times: 22.9 and 27.7 min.

1-(1-methyl-1H-imidazol-2-yl)-4-nitro-3-phenylbutan-1-one (3a)



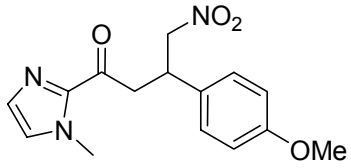
A white solid was obtained after purification by column chromatography (SiO_2, EtOAc/hexane 4:6). m.p. 93.4°C; $[\alpha]_D^{25}$ = -48.8° (c = 4.9 in $CHCl_3$, 84% e.e. according to HPLC); ^{1}H-NMR ($CDCl_3$, 400 MHz, 300 K) δ=7.38-7.20 (m, 5H), 7.09 (d, J = 0.9 Hz, 1H), 6.99 (s, 1H), 4.72 (dd, J = 6.8, 12.5 Hz, 1H), 4.62 (dd, J = 8.3, 12.5 Hz, 1H), 4.19 (quint, J = 7.2 Hz, 1H), 3.90 (s, 3H), 3.70 (dd, J = 7.2, 17.4 Hz, 1H), 3.46 (dd, J = 7.2, 17.4 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz, 300 K) δ=189.3, 142.7, 139.2, 129.5, 129.1, 127.9, 127.7, 127.6, 80.1, 42.0, 39.5, 36.3; MS (CI): *m/z* (%): 274.2 (100) [M+H^+] (Calcd 274.1). The e.e. was determined by HPLC analysis (Chiralpak-AD, *n*-heptane/iPrOH 95:5, 1 ml/min). Retention times: 28.4 and 35.0 min.

dimethyl 2-(1-(4-methoxyphenyl)-3-(1-methyl-1H-imidazol-2-yl)-3-oxopropyl)malonate (2b)



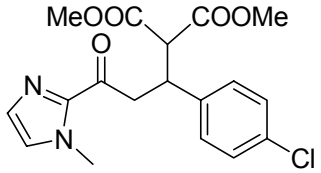
A colourless oil was obtained after column chromatography (SiO_2, EtOAc/hexane 4:6). ^{1}H-NMR ($CDCl_3$, 400 MHz, 300 K) δ=7.19 (d, J = 8.7 Hz, 2H), 7.07 (s, 1H), 7.94 (s, 1H), 6.75 (d, J = 8.7 Hz, 2H), 4.71 (td, J = 5.6, 9.9 Hz, 1H), 3.87-3.71 (m, 2H), 3.85 (s, 3H), 3.72 (s, 3H), 3.70 (s, 3H), 3.46 (s, 3H), 3.44-3.34 (m, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz, 300 K) δ=189.9, 168.8, 168.3, 158.6, 143.0, 132.6, 129.5, 129.1, 127.7, 113.9, 58.0, 55.3, 52.8, 52.6, 43.1, 39.8, 36.3; HRMS: *m/z*: 374.1489 [M^+] (Calcd 374.1478). The e.e. was determined by HPLC analysis (Chiralpak-AD, *n*-heptane/iPrOH 90:10, 1 ml/min). Retention times: 23.5 and 29.0 min.

3-(4-methoxyphenyl)-1-(1-methyl-1H-imidazol-2-yl)-4-nitrobutan-1-one (3b)



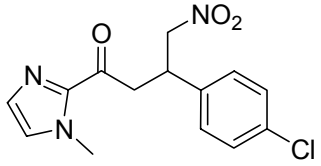
A colourless oil was obtained after purification by column chromatography (SiO_2, EtOAc/hexane 4:6). ^{1}H-NMR ($CDCl_3$, 400 MHz, 300 K) δ=7.21 (d, J = 6.9 Hz, 2H), 7.12 (s, 1H), 7.02 (s, 1H), 6.83 (d, J = 6.9 Hz, 2H), 4.71 (dd, J = 6.9, 12.3 Hz, 1H), 4.59 (dd, J = 8.3, 12.3 Hz, 1H), 4.16 (quint, J = 7.7 Hz, 1H), 3.94 (s, 3H), 3.76 (s, 3H), 3.69 (dd, J = 7.2, 17.4 Hz, 1H), 3.45 (dd, J = 7.2, 17.4 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz, 300 K) δ=131.1, 129.5, 129.5, 128.9, 128.8, 127.5, 114.5, 80.3, 55.4, 55.4, 55.3, 42.1, 38.8; MS (CI): *m/z* (%): 304.2 (100) [M+H$^+$] (Calcd 304.1). The e.e. was determined by HPLC analysis (Chiralpak-AD, *n*-heptane/iPrOH 95:5, 1 ml/min). Retention times: 34.3 and 38.4 min.

dimethyl 2-(1-(3-chlorophenyl)-3-(1-methyl-1H-imidazol-2-yl)-3-oxopropyl)malonate (2c)



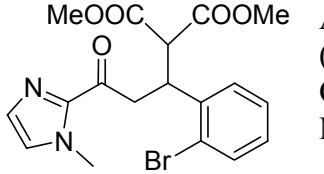
A colourless oil was obtained after column chromatography (SiO_2, EtOAc/hexane 4:6). ^{1}H-NMR ($CDCl_3$, 400 MHz, 300 K) δ=7.21 (m, 4H), 7.07 (s, 1H), 6.95 (s, 1H), 4.12 (m, 1H), 3.86 (s, 3H), 3.83-3.75 (m, 2H), 3.71 (s, 3H), 3.48 (s, 3H) 3.44-3.38 (m, 2H); ^{13}C-NMR ($CDCl_3$, 50 MHz, 300 K) δ=189.6, 168.5, 168.1, 142.9, 139.2, 133.0, 129.9, 129.3, 128.7, 127.2, 57.6, 52.9, 52.6, 42.8, 39.9, 36.2; HRMS: *m/z*: 378.0965 [M^+] (Calcd 378.0982). The e.e. was determined by HPLC analysis (Chiralpak-AD, *n*-heptane/iPrOH 90:10, 1 ml/min). Retention times: 26.0 and 31.0 min.

3-(3-chlorophenyl)-1-(1-methyl-1H-imidazol-2-yl)-4-nitrobutan-1-one (3c)



A colourless oil was obtained after purification by column chromatography (SiO_2, EtOAc/hexane 4:6). ^{1}H-NMR ($CDCl_3$, 400 MHz, 300 K) δ=7.25 (m, 4H), 7.11 (s, 1H), 7.02 (s, 1H), 4.71 (m, 1H), 4.61 (m, 1H), 4.18 (quint, J = 7.7 Hz, 1H), 3.92 (s, 3H), 3.69 (dd, J = 7.5, 17.5 Hz, 1H), 3.45 (dd, J = 7.0, 17.5 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz, 300 K) δ=188.9, 142.7, 137.7, 133.8, 129.9, 129.6, 129.5, 129.3, 129.2, 127.7, 79.9, 41.9, 38.9, 36.3; MS (CI): *m/z* (%): 308.1 (100) [M+H$^+$] (Calcd 308.1). The e.e. was determined by HPLC analysis (Chiralpak-AD, *n*-heptane/iPrOH 95:5, 1 ml/min). Retention times: 35.2 and 40.7 min.

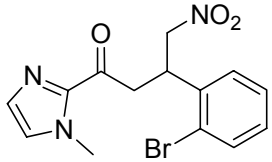
dimethyl 2-(1-(2-bromophenyl)-3-(1-methyl-1H-imidazol-2-yl)-3-oxopropyl)malonate (2d)



A colourless oil was obtained after column chromatography (SiO_2, EtOAc/hexane 4:6). $[\alpha]_D^{25}$ = -67.4° (c = 48.8 in $CHCl_3$, 99% e.e. according to HPLC); ^{1}H-NMR ($CDCl_3$, 400 MHz, 300 K) δ=7.52 (d, J = 7.7 Hz, 1H), 7.31 (d, J = 6.7 Hz,

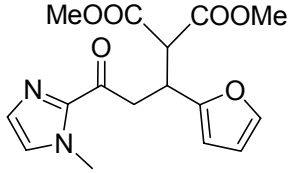
1H), 7.19 (t, J = 6.9 Hz, 1H), 7.07 (s, 1H), 7.03 (t, J = 6.4 Hz, 1H), 6.95 (s, 1H), 4.63 (m, 1H), 3.99-3.91 (m, 2H), 3.87 (s, 3H), 3.67 (s, 3H), 3.64-3.60 (m, 1H), 3.56 (s, 3H); ^{13}C-NMR ($CDCl_3$, 50 MHz, 300 K) δ=189.8, 168.5, 168.3, 143.0, 139.9, 133.6, 129.3, 128.7, 127.7, 127.1, 55.8, 52.7, 52.7, 41.4, 39.2, 36.2; HRMS: *m/z*: 422.0464 [M^+] (Calcd 422.0477). The e.e. was determined by HPLC analysis (Chiralpak-AD, *n*-heptane/iPrOH 90:10, 1 ml/min). Retention times: 21.3 and 29.5 min.

3-(2-bromophenyl)-1-(1-methyl-1H-imidazol-2-yl)-4-nitrobutan-1-one (3d)



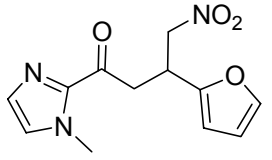
A colourless oil was obtained after purification by column chromatography (SiO_2, EtOAc/hexane 4:6). ^{1}H-NMR ($CDCl_3$, 400 MHz, 300 K) δ=7.56 (d, 1H), 7.30-7.23 (m, 2H), 7.11-7.08 (m, 2H), 7.02 (s, 1H), 4.76-4.74 (m, 2H), 4.72-4.65 (m, 1H), 3.92 (s, 3H), 3.73 (dd, J = 6.5, 17.8 Hz, 1H), 3.62 (dd, J = 7.4, 17.8 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz, 300 K) δ=189.1, 142.7, 138.1, 133.8, 129.6, 129.3, 128.3, 128.1, 127.6, 124.8, 78.2, 40.9, 38.2, 36.3; MS (CI): *m/z* (%): 352.0 (100) [M+H]$^+$ (Calcd 352.0). The e.e. was determined by HPLC analysis (Chiralpak-AD, *n*-heptane/iPrOH 95:5, 1 ml/min). Retention times: 28.6 and 31.8 min.

dimethyl 2-(1-(furan-2-yl)-3-(1-methyl-1H-imidazol-2-yl)-3-oxopropyl)malonate (2e)



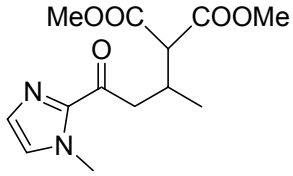
A colourless oil was obtained after column chromatography (SiO_2, EtOAc/hexane 4:6). ^{1}H-NMR ($CDCl_3$, 400 MHz, 300 K) δ=7.23 (m, 1H), 7.07 (s, 1H), 6.98 (s, 1H), 6.18 (m, 1H), 6.10 (d, J = 3.2 Hz, 1H), 4.25 (td, J = 4.4, 9.1 Hz, 1H), 3.90 (s, 3H), 3.86-3.78 (m, 2H), 3.68 (s, 3H), 3.58 (s, 3H), 3.41 (dd, J = 3.6, 17.6 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz, 300 K) δ=189.6, 168.3, 168.3, 153.7, 142.9, 141.8, 129.3, 127.2, 110.3, 107.1, 55.3, 52.8, 52.7, 40.4, 36.2, 34.1; HRMS: *m/z*: 334.1160 [M^+] (Calcd 334.1165). The e.e. was determined by HPLC analysis (Chiralpak-AD, *n*-heptane/iPrOH 90:10, 1 ml/min). Retention times: 23.7 and 26.9 min.

3-(furan-2-yl)-1-(1-methyl-1H-imidazol-2-yl)-4-nitrobutan-1-one (3e)



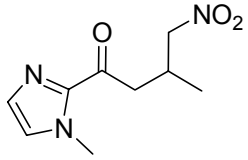
A colourless oil was obtained after purification by column chromatography (SiO_2, EtOAc/hexane 4:6). ^{1}H-NMR ($CDCl_3$, 400 MHz, 300 K) δ=7.39 (d, J = 1.9 Hz, 1H), 7.11 (s, 1H), 7.03 (s, 1H), 6.24 (dd, J = 1.9, 3.2 Hz, 1H), 6.17 (d, J = 3.3 Hz, 1H), 4.70 (d, J = 6.6 Hz, 2H), 4.29 (quint, J = 4.3 Hz, 1H), 3.95 (s, 3H), 3.71 (dd, J = 6.8, 17.6 Hz, 1H), 3.48 (dd, J = 7.1, 17.6 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz, 300 K) δ=188.9, 152.1, 142.6, 142.5, 129.6, 127.7, 110.5, 107.3, 77.6, 39.7, 36.3, 33.3; HRMS: *m/z*: 263.0901 [M^+] (Calcd 263.0906). The e.e. was determined by HPLC analysis (Chiralpak-AD, *n*-heptane/iPrOH 95:5, 1 ml/min). Retention times: 30.6 and 40.0 min.

dimethyl 2-(4-(1-methyl-1H-imidazol-2-yl)-4-oxobutan-2-yl)malonate (2f)



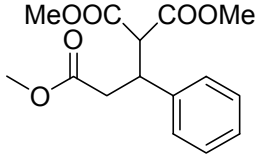
A colourless oil was obtained after column chromatography (SiO_2, EtOAc/hexane 4:6). ^{1}H-NMR ($CDCl_3$, 400 MHz, 300 K) δ=7.08 (s, 1H), 7.00 (s, 1H), 3.96 (s, 3H), 3.69 (s, 3H), 3.68 (s, 3H), 3.48 (d, J = 7.4 Hz, 1H), 3.19 (d, J = 6.6 Hz, 2H), 2.91 (quint, J = 6.8 Hz, 1H), 1.04 (d, J = 6.8 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 50 MHz, 300 K) δ=191.2, 169.2, 169.1, 143.1, 129.2, 127.2, 56.3, 52.6, 52.5, 43.2, 36.3, 29.5, 17.9; HRMS: *m/z*: 282.1205 [M^+] (Calcd 282.1215). The e.e. was determined by HPLC analysis (Chiralpak-AD, *n*-heptane/iPrOH 95:5, 1 ml/min). Retention times: 23.0 and 24.8 min.

3-methyl-1-(1-methyl-1H-imidazol-2-yl)-4-nitrobutan-1-one (3f)



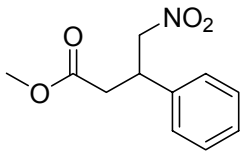
A colourless oil was obtained after purification by column chromatography (SiO_2, EtOAc/hexane 4:6). ^{1}H-NMR ($CDCl_3$, 400 MHz, 300 K) δ=7.08 (s, 1H), 7.02 (s, 1H), 4.47 (dd, J = 5.8, 12.0 Hz, 1H), 4.29 (dd, J = 7.7, 12.0 Hz, 1H), 3.95 (s, 3H), 3.18 (d, J = 2.1 Hz, 1H), 3.14 (d, J = 1.2 Hz, 1H), 2.93 (oct, J = 6.7 Hz, 1H), 1.07 (d, J = 6.7 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 50 MHz, 300 K) δ=190.3, 167.1, 129.4, 127.6, 80.8, 42.4, 36.3, 28.9, 17.8; MS (CI): *m/z* (%):212.1 (100) [M+H^+] (Calcd 212.1). The e.e. was determined by HPLC analysis (Chiralcel-OD, *n*-heptane/iPrOH 98:2, 1 ml/min). Retention times: 30.0 and 30.5 min.

(R)-trimethyl 2-phenylpropane-1,1,3-tricarboxylate (4a)



To a dried vial under N_2 atmosphere was added **2a** (56 mg, 0.16 mmol, 1 equiv), powdered 4 Å mol. sieves and acetonitrile (0.5 mL). The mixture was stirred for 2 hours at room temperature and methyl triflate (20 μL, 0.18 mmol) was added. After stirring for 3h, dried MeOH (0.5 mL) and DBU (0.20 mL) were added successively. The mixture was stirred for another 30 minutes and then diluted with 30 mL EtOAc. The organic phase was washed with bicarbonate saturated solution and brine, dried on Na_2SO_4 and the solvent was evaporated under reduced pressure. Column chromatography purification (SiO_2, 3:7 EtOAc/Hexane) provided **4a** as a colourless oil (19 mg, 48%). The NMR spectrum was as published.[4] $[\alpha]_D^{25}$ = -10.8° (c = 15 in $CHCl_3$, 85% e.e (*R*)), lit: $[\alpha]_D^{25}$ = -29.0 (*R*).[4]

(S)-methyl 4-nitro-3-phenylbutanoate (5a)



To a dried vial under N_2 atmosphere was added **3a** (79 mg, 0.3 mmol, 1 equiv), powdered 4 Å mol. sieves and acetonitrile (0.6 mL). The mixture was stirred for 2 hours at room temperature and methyl triflate (33 μL, 0.3 mmol) was added. After stirring for 3h, dried MeOH (0.6 mL) and DBU (0.30 mL) were added successively. The mixture was stirred for 30 minutes and then diluted with 30 mL

EtOAc. The organic phase was washed with bicarbonate saturated solution and brine, dried on Na_2SO_4 and the solvents was evaporated under reduced pressure. Column chromatography purification (SiO_2, 3:7 EtOAc/Hexane) provided **5a** as a colourless oil (52 mg, 81%). The NMR spectrum was as published.[5] $[\alpha]_D^{25}$ = -14.5° (c = 34 in $CHCl_3$, 84% e.e. (*S*)), lit: $[\alpha]_D^{25}$ = +8.7 (*R*).[5]

Table S1. Results of Michael addition catalyzed by DNA-Cu**L3**$(NO_3)_2$, pH dependence.[a]

pH	buffer	dimethylmalonate		$MeNO_2$	
		Conv[b]	ee[c]	conv[b]	ee[c]
5	MES	83	91	14	66
6.5	MOPS	full	91	full	85
6.5	Phosphate	93	92	82	81
7.5	MOPS	full	89	94	81

[a] All experiments were carried out with salmon testes DNA (1,3 mg mL^{-1}), 0.3 mM [Cu**L3**$(NO_3)_2$], 1 mM **1a** and 1000 equivalents of nitromethane or 100 equivalents of dimethylmalonate in buffer (20 mM) for 3 days at 5°C. [b] Conversion values were the average of experiments in duplo and were determined by ^{1}H NMR (standard variation ± 3%). [c] ee measured on analytical chiral HPLC (Chiralpak-AD), in all experiments and for each nucleophile the same enantiomer was obtained in excess.

Table S2. Control and additional experiments[a]

Modification	dimethylmalonate		$MeNO_2$	
	conv[b]	ee[c]	conv[b]	ee[c]
DNA source = Calf thymus	full	89	full	85
DNA (0.67 mg mL^{-1})	97	88		
DNA (0.27 mg mL^{-1})	full	83		
Without DNA	54	-	36	-
Without copper complex	0	0	0	0
$[Cu(H_2O)_32NO_3]$ / DNA	26	< 2	0	n.d.
Reaction at room temperature	95	87		
Substrate = chalcone	0	n.d.		

[a] Except as noted otherwise, all experiments were carried out with DNA (1,3 mg mL^{-1}), 0.3 mM [Cu**L3**$(NO_3)_2$], 1 mM of **1a** in MOPS buffer (20 mM pH 6.5) for 3 days at 5°C, using 1000 equivalents of nitromethane or 100 equivalents of dimethylmalonate as nucleophile. [b] Conversion values were the average of experiments in duplo and were determined by ^{1}H NMR (standard variation ± 2%). [c] ee measured on analytical chiral HPLC (Chiralpak-AD).

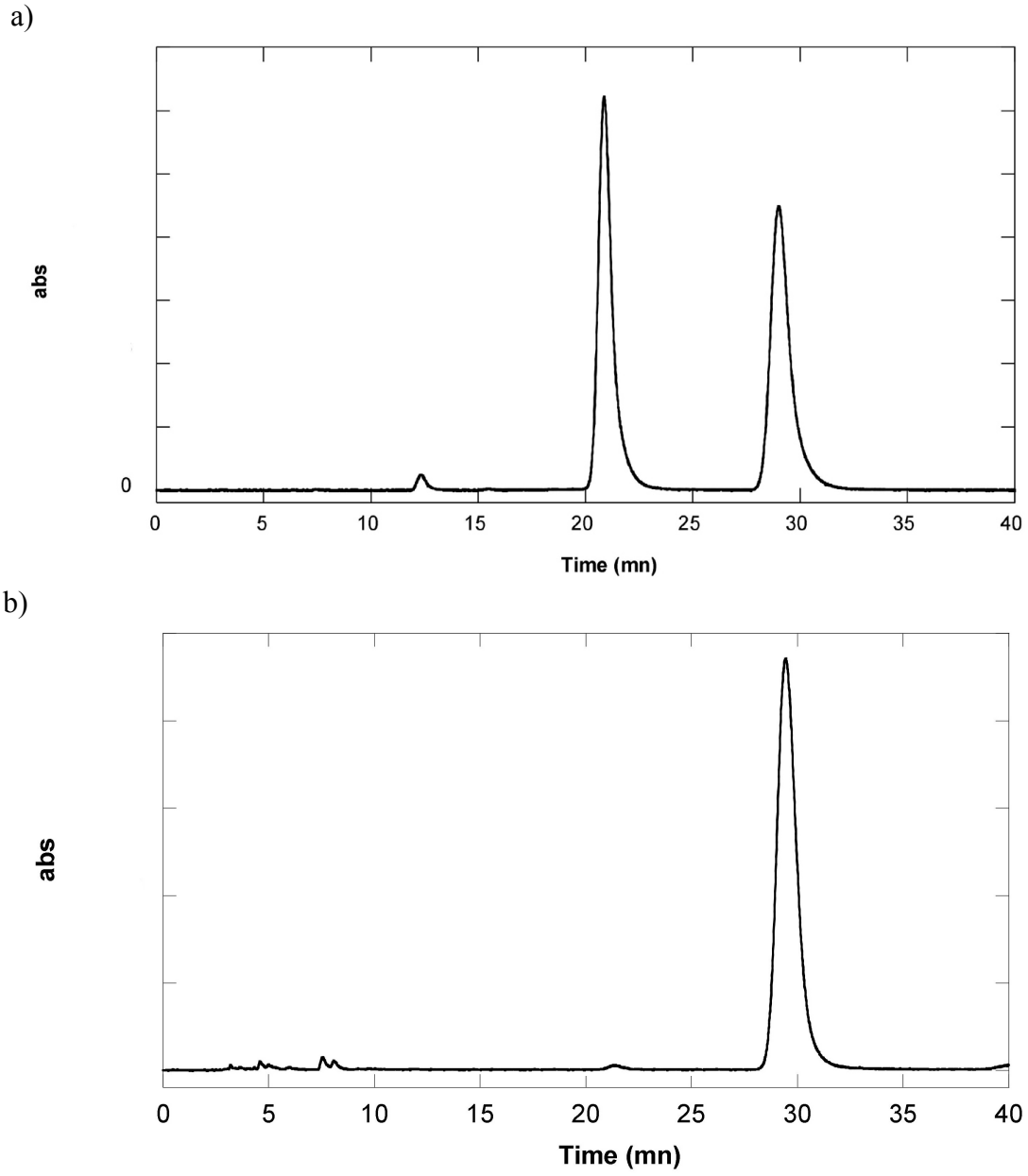


Figure S1. HPLC trace (Chiralpak-AD 90/10 *n*-heptane/*iso*-propanol) of a) racemic **2d** after purification by column chromatography; b) crude **2d** obtained by [Cu**L3**$(NO_3)_2$] /st-DNA catalyzed reaction. Retention times for both enantiomers: 21.3 min and 29.5 min.

References

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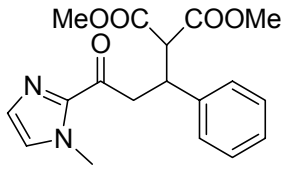
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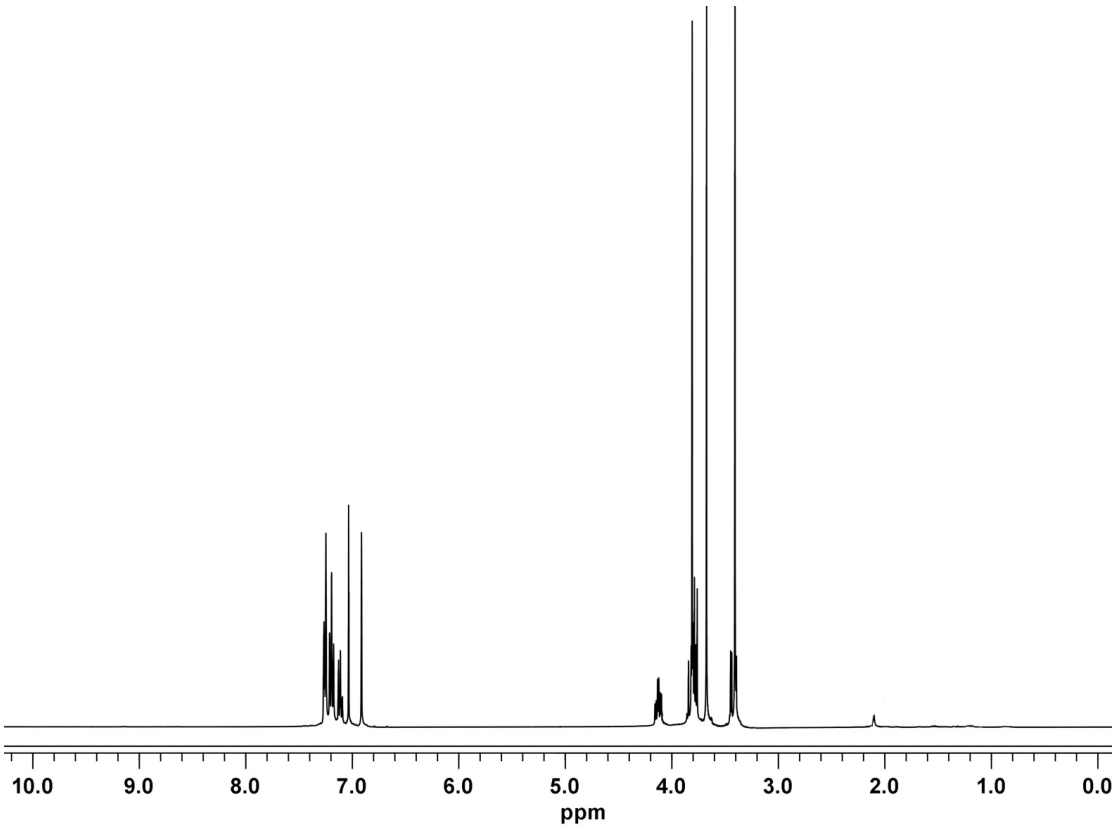
N

2a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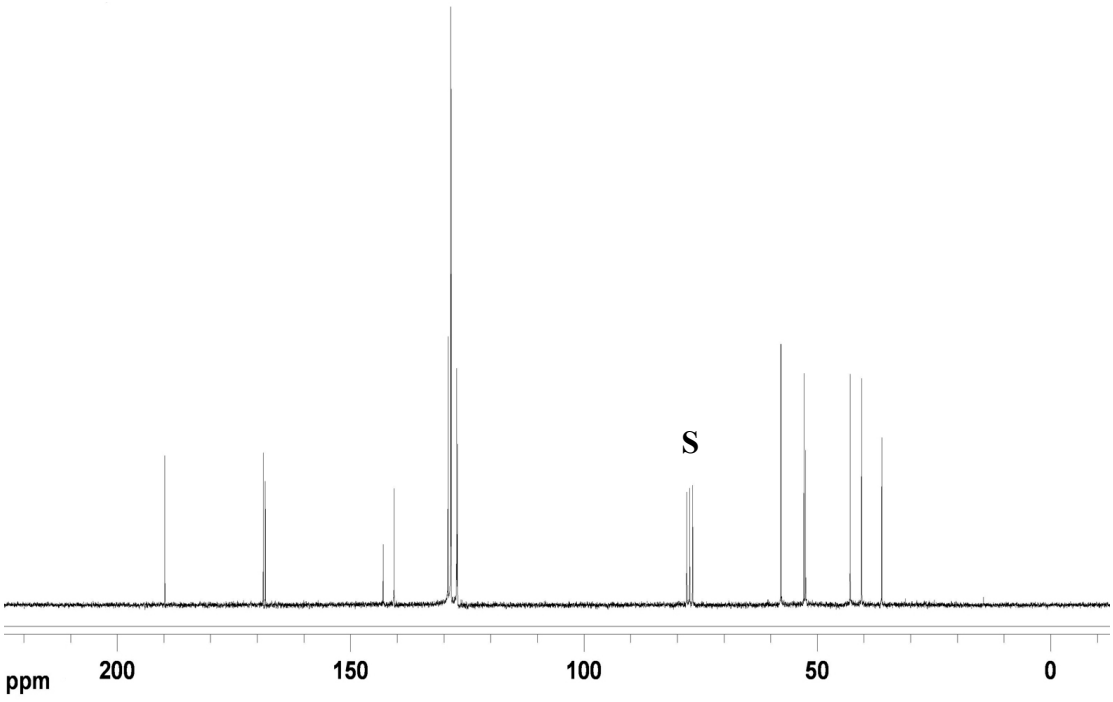
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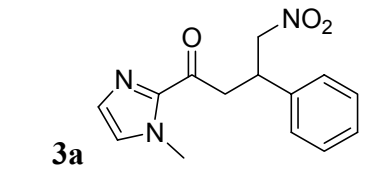
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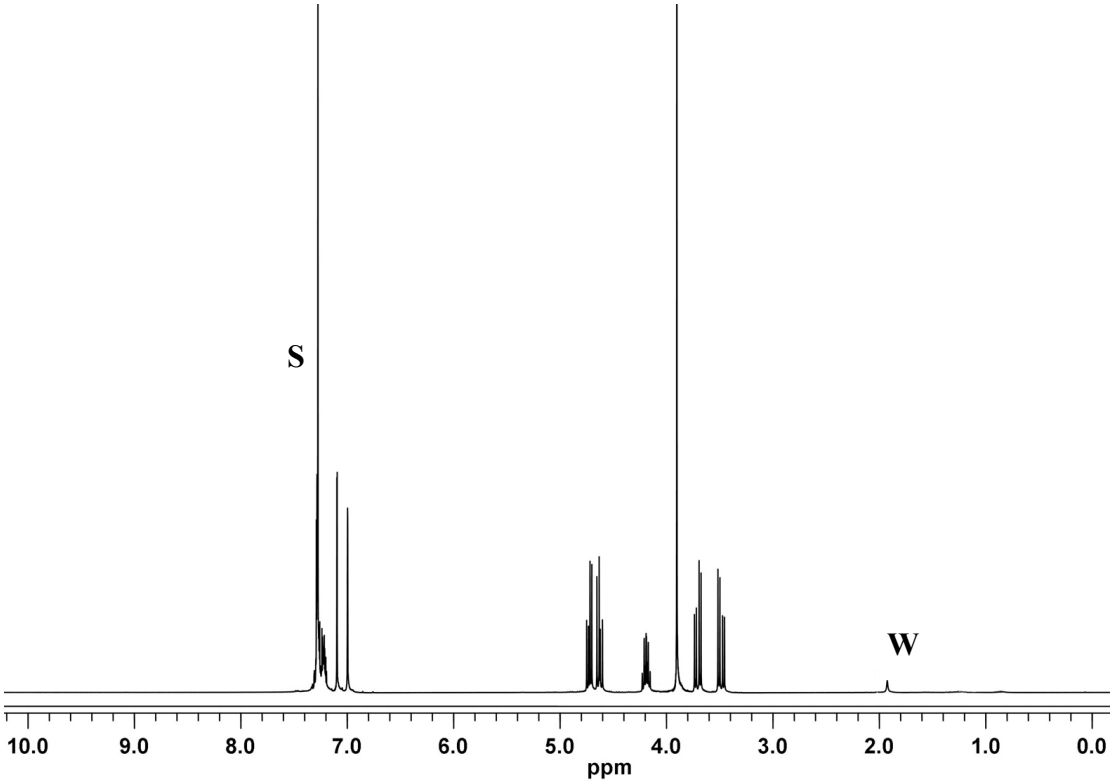
3a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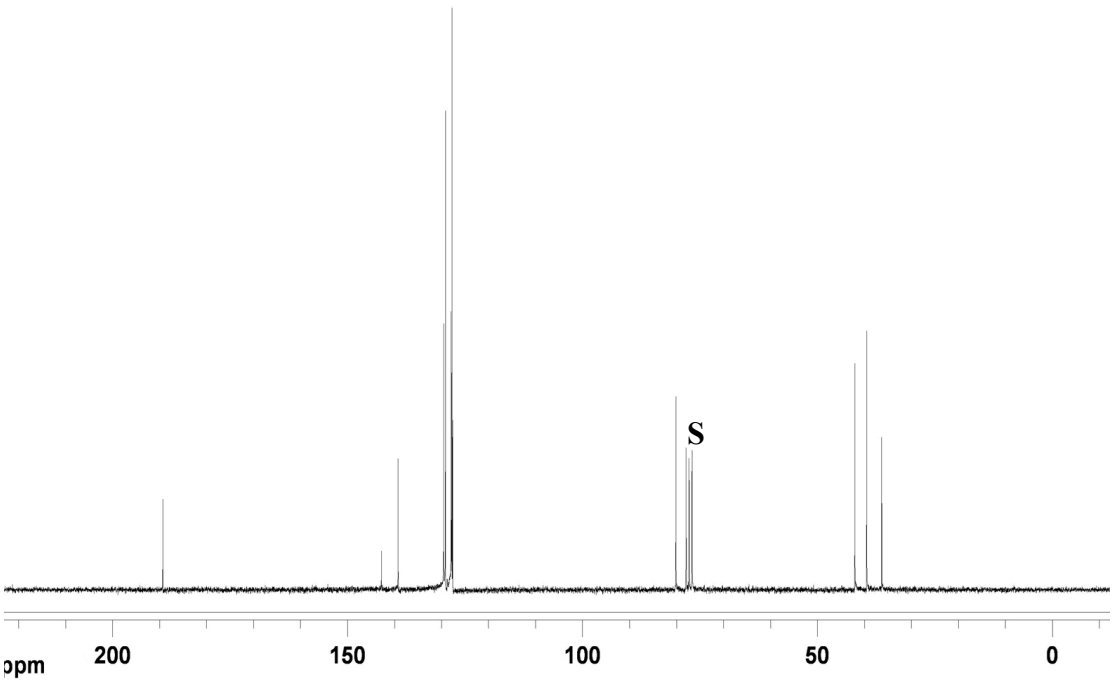
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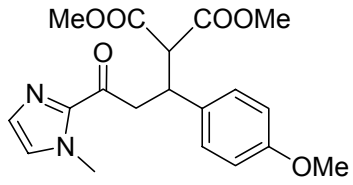
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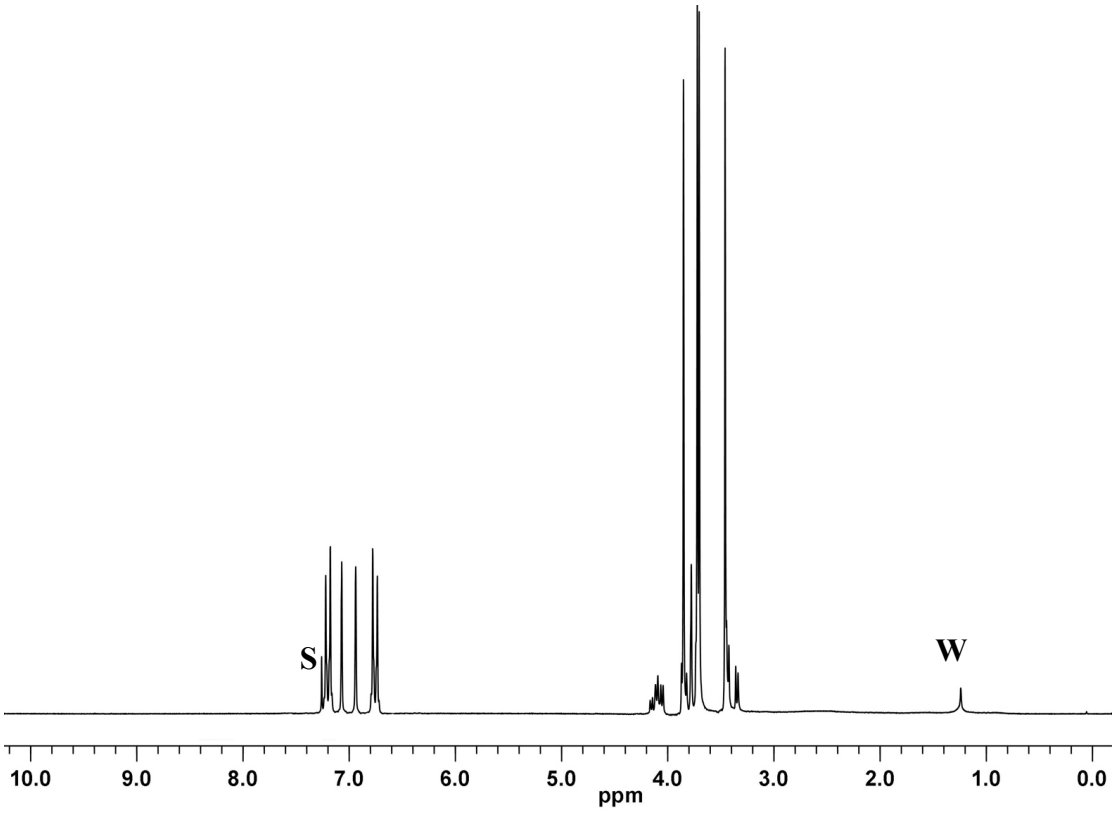
2b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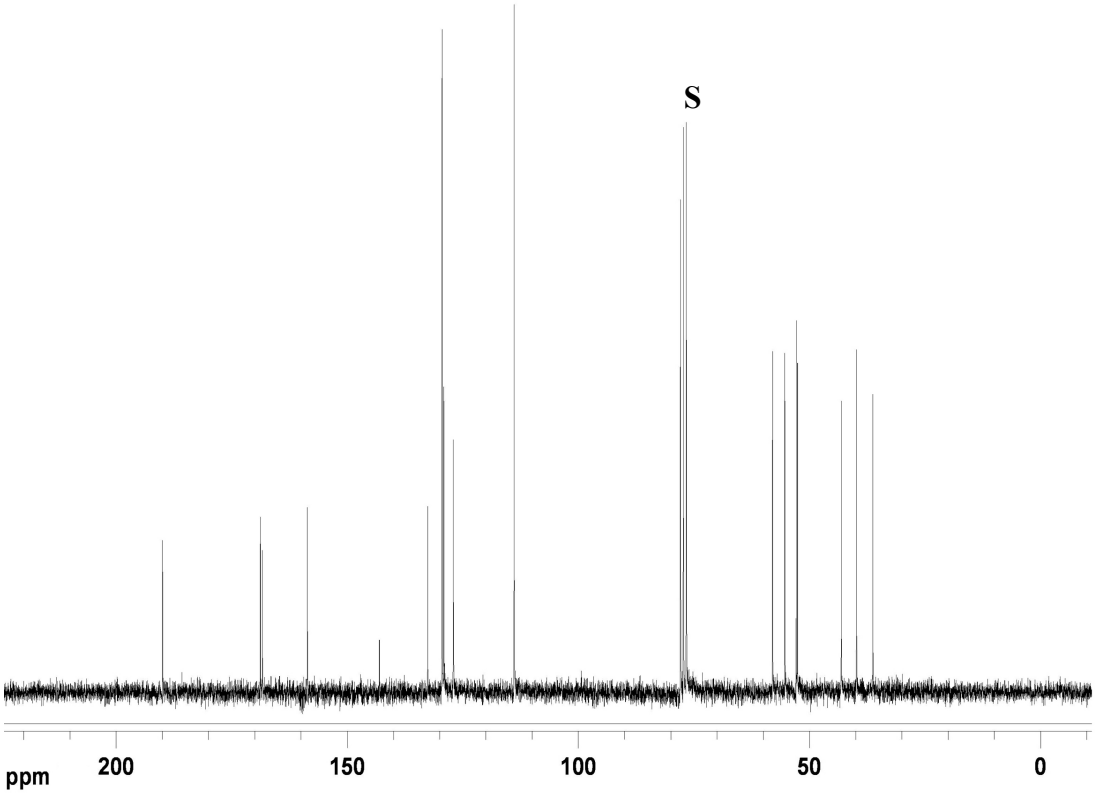
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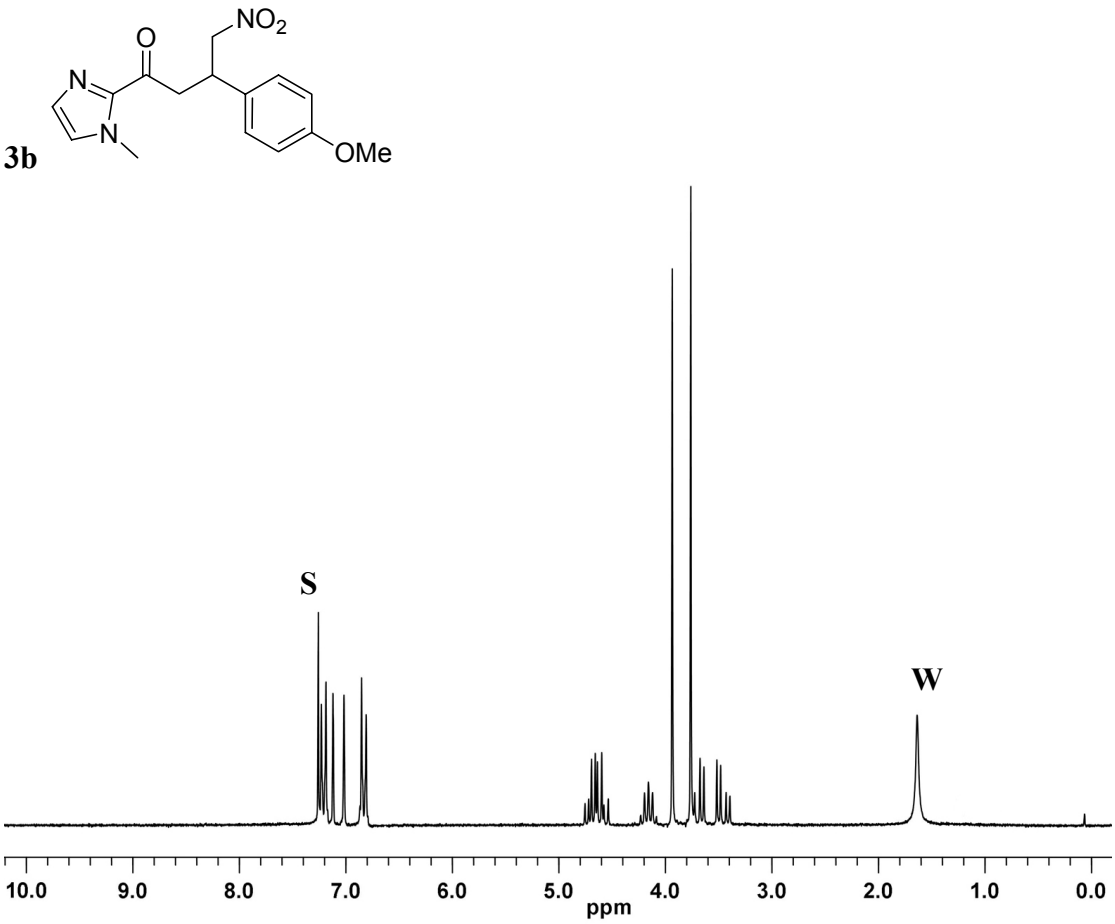

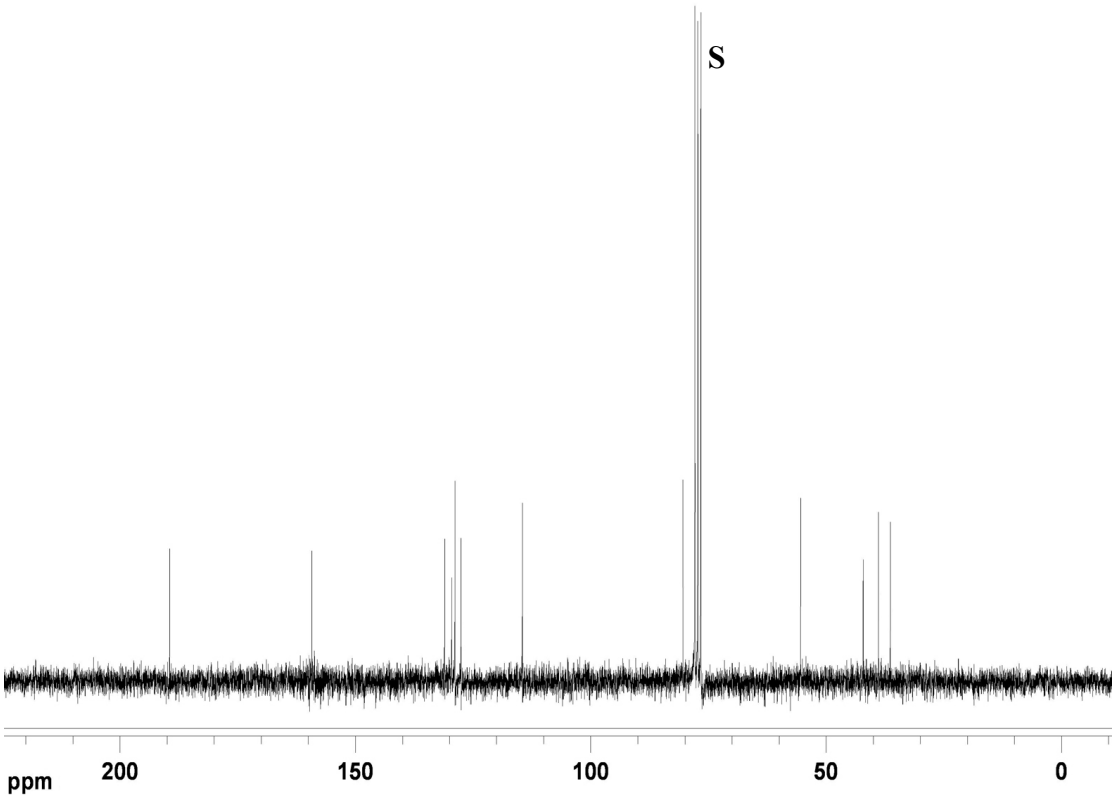

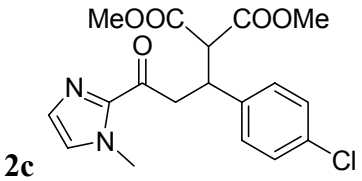
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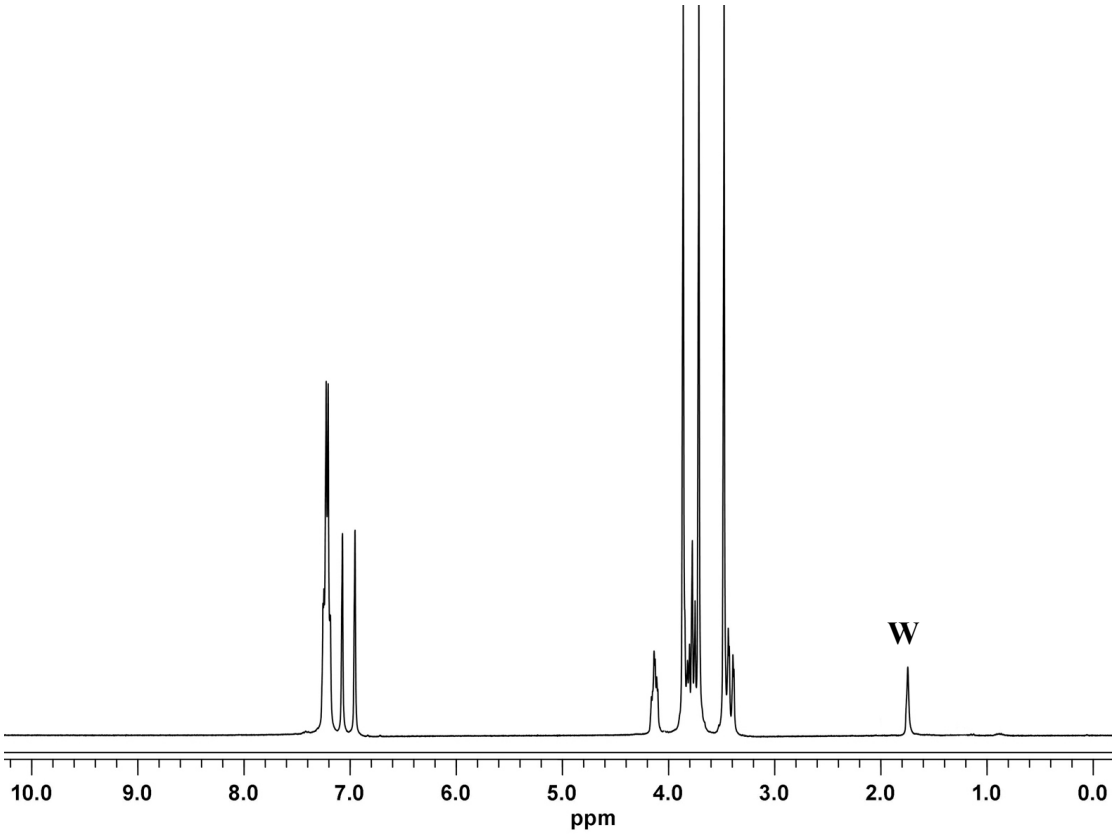
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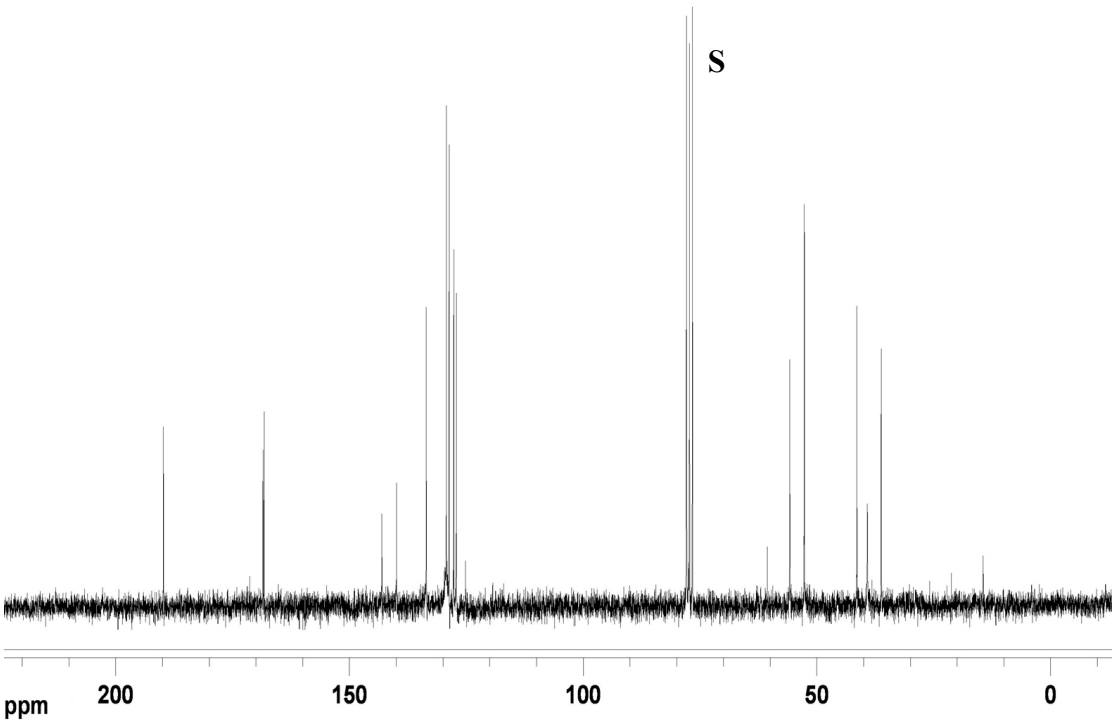
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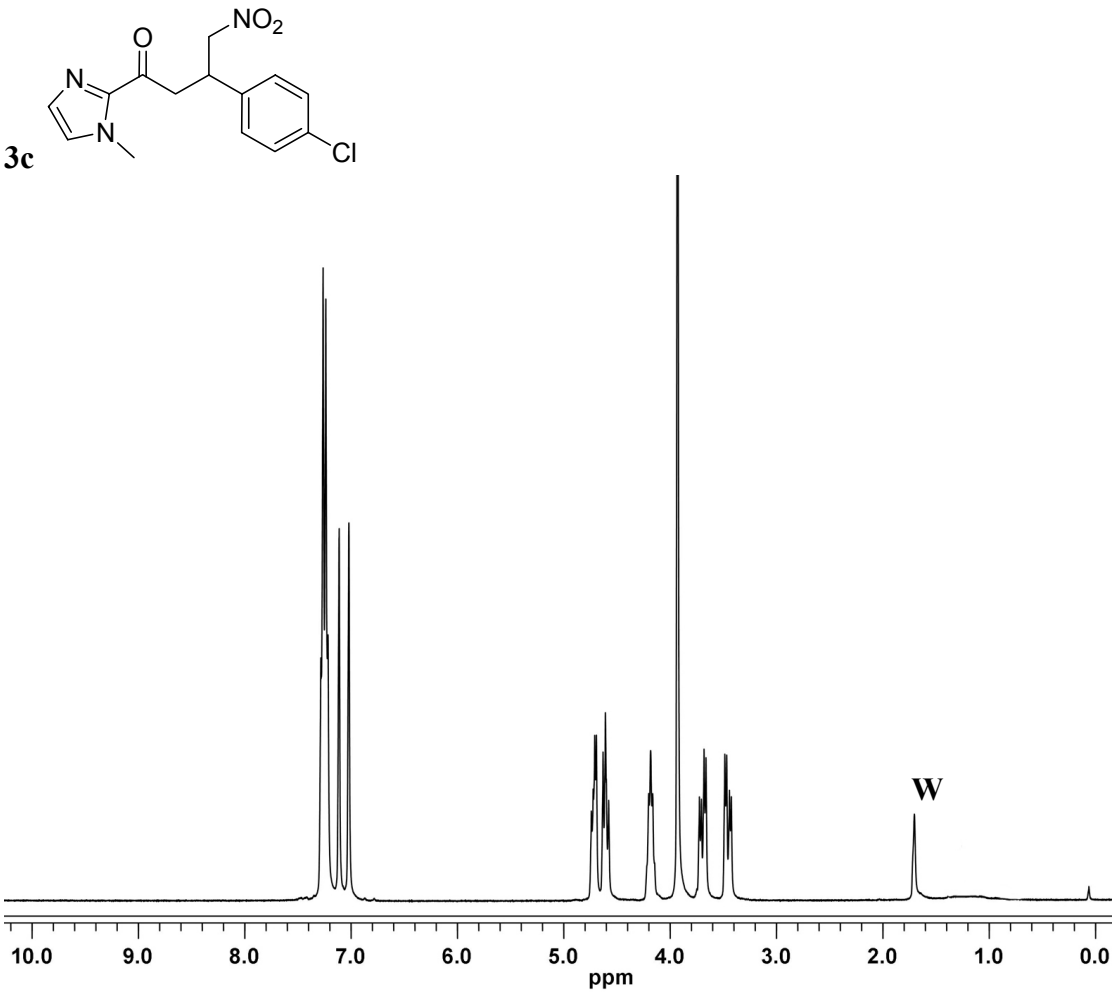

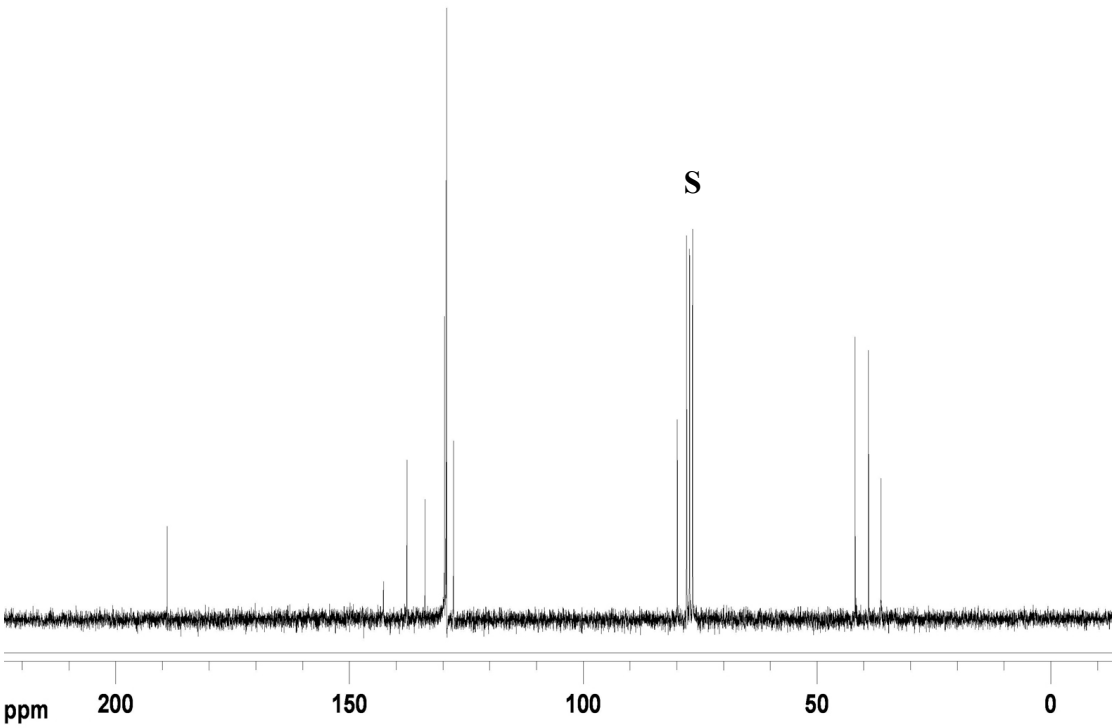

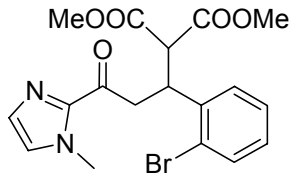
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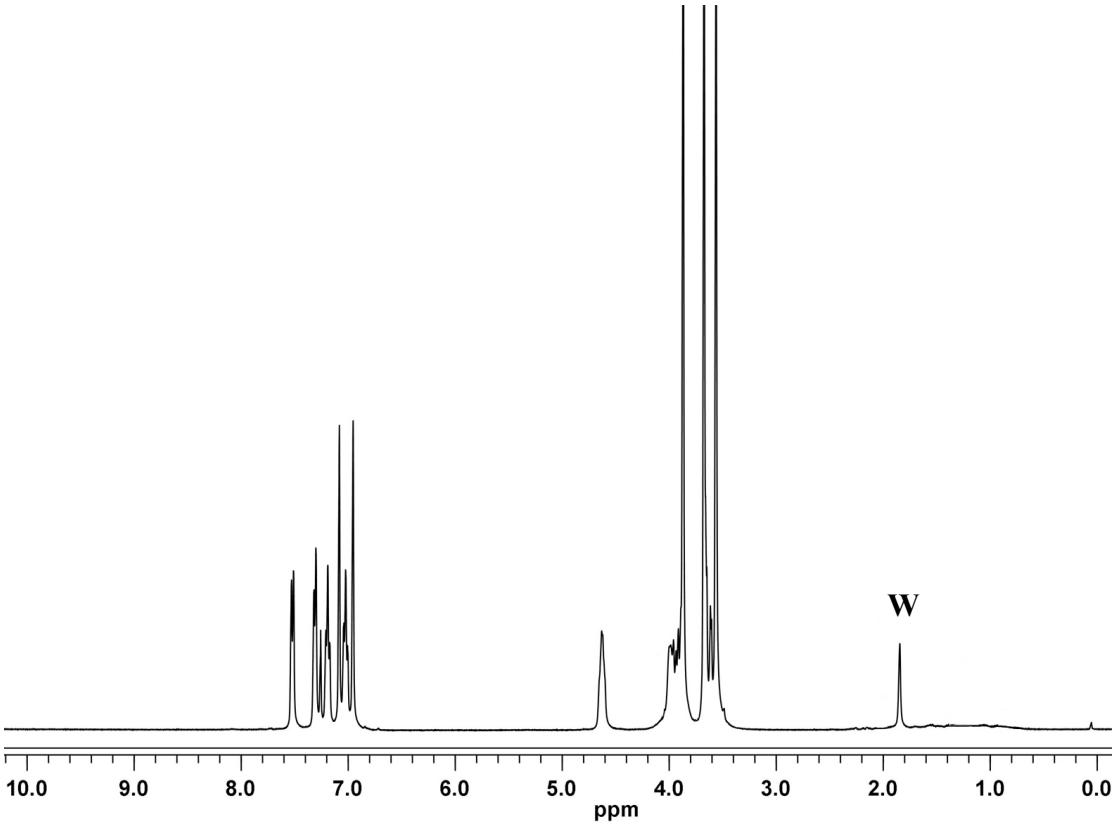
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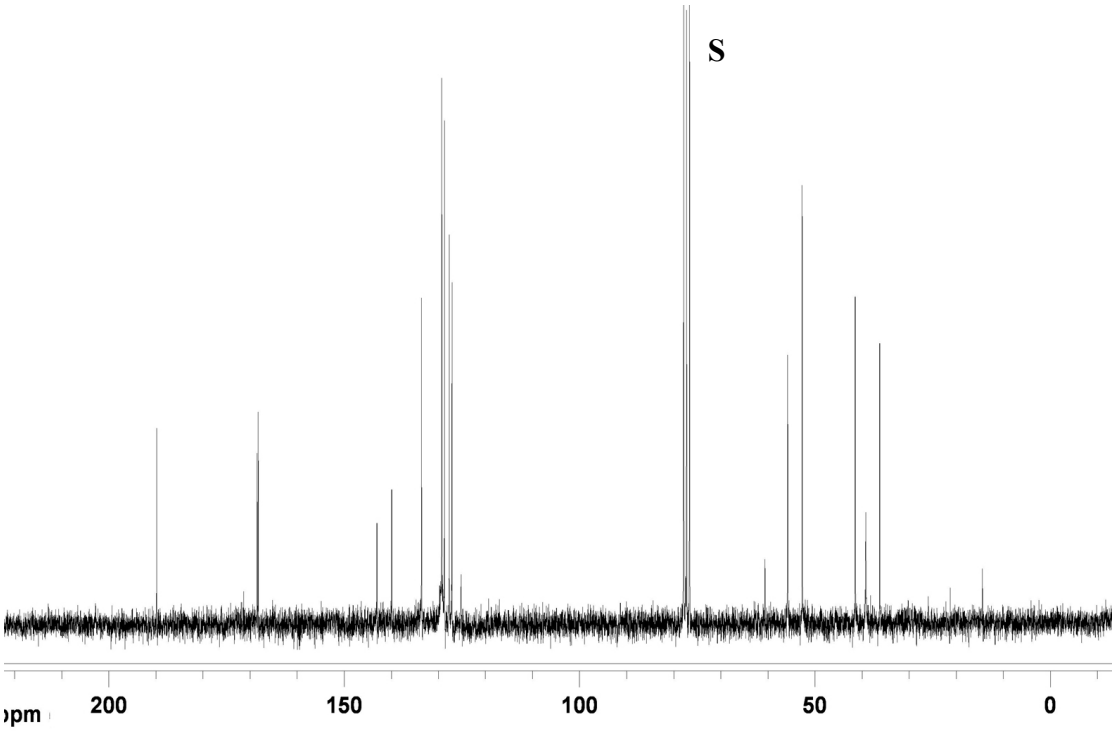
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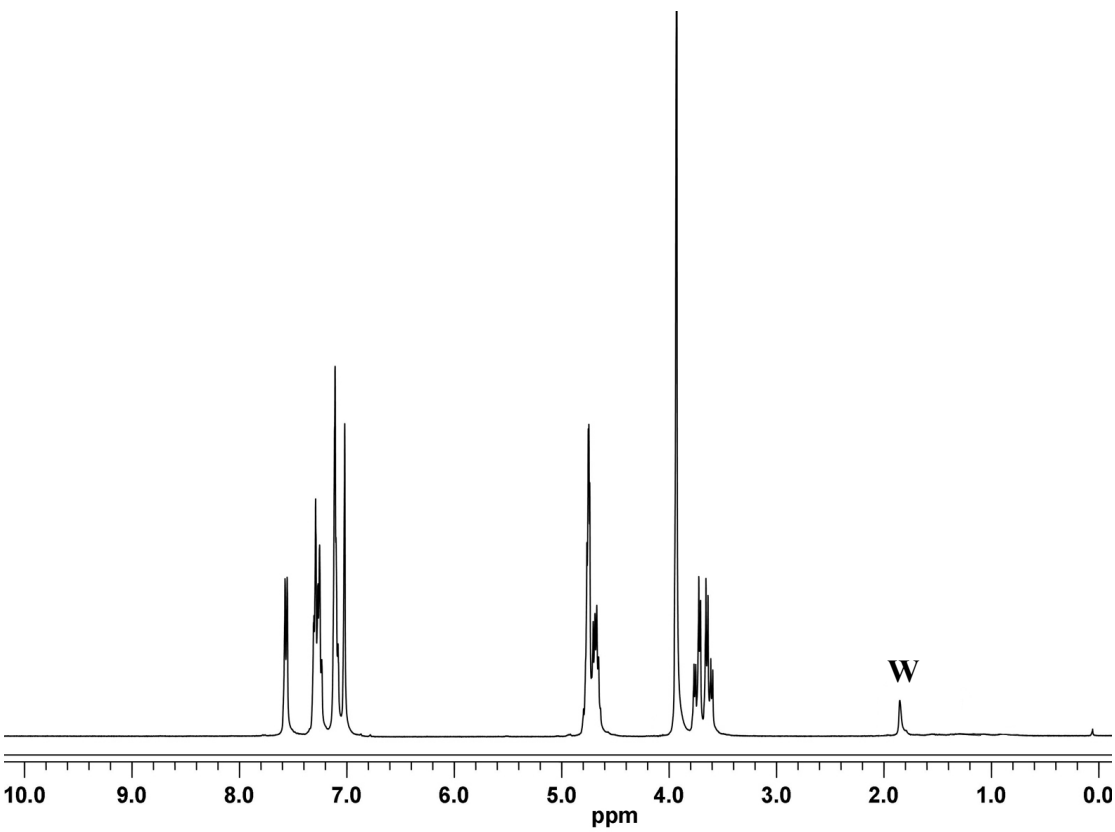

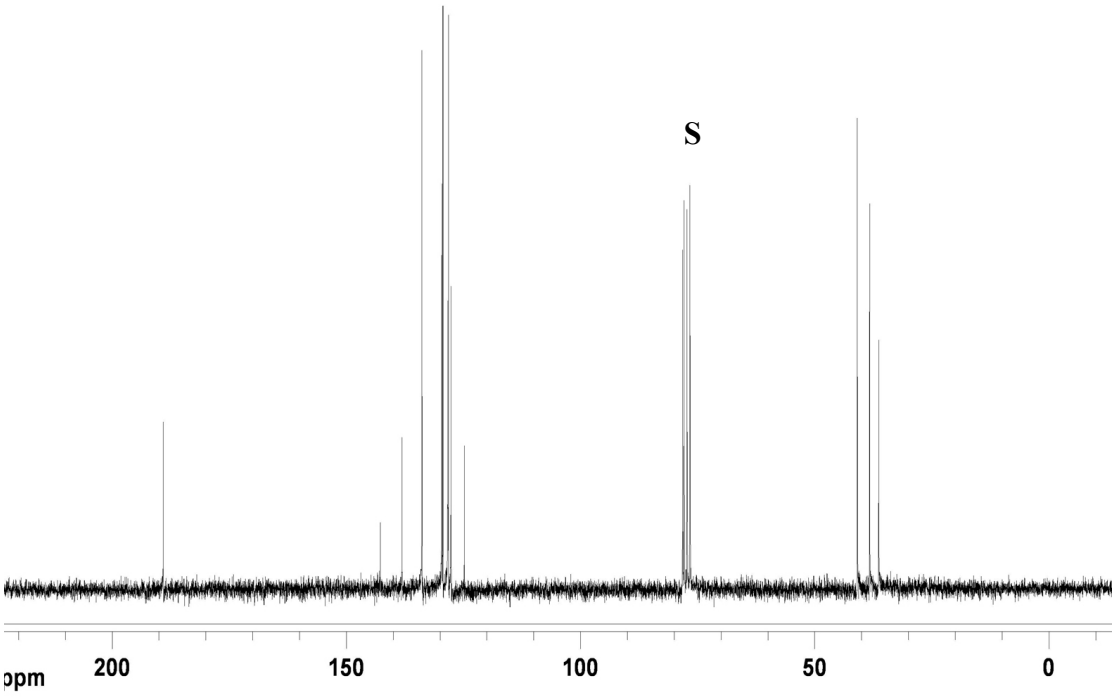

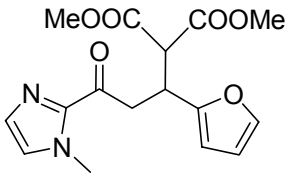
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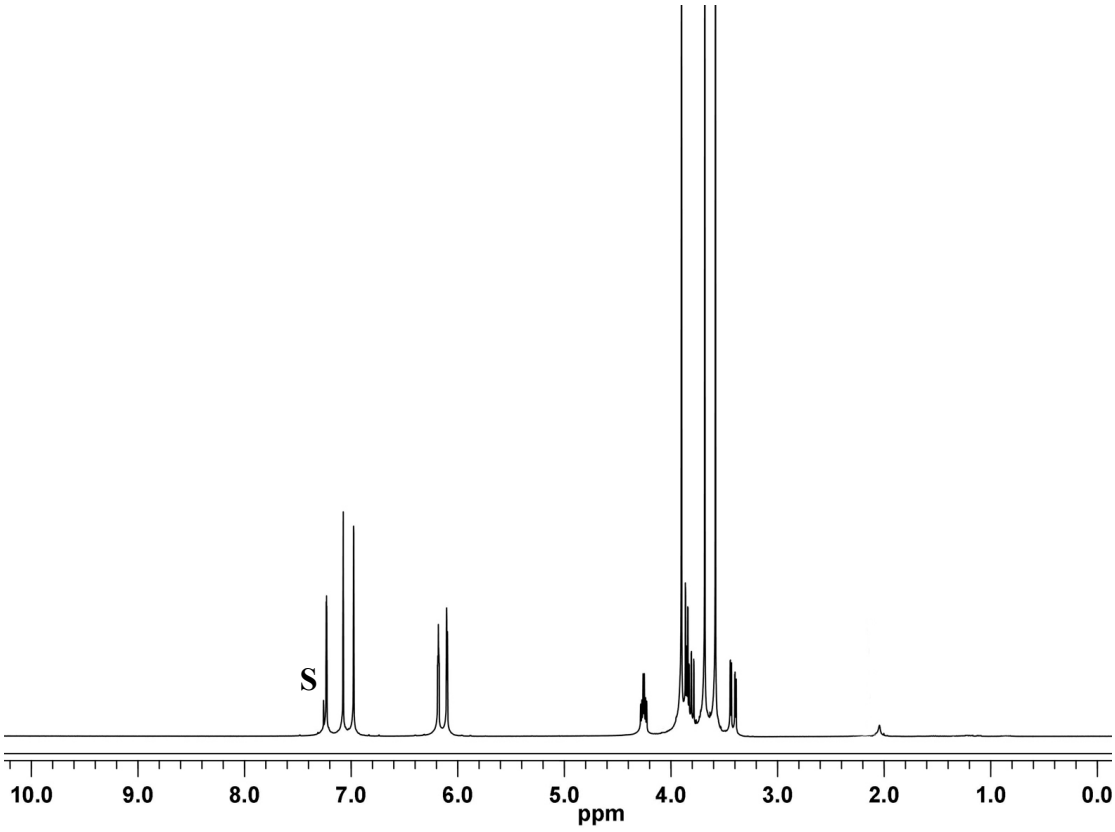
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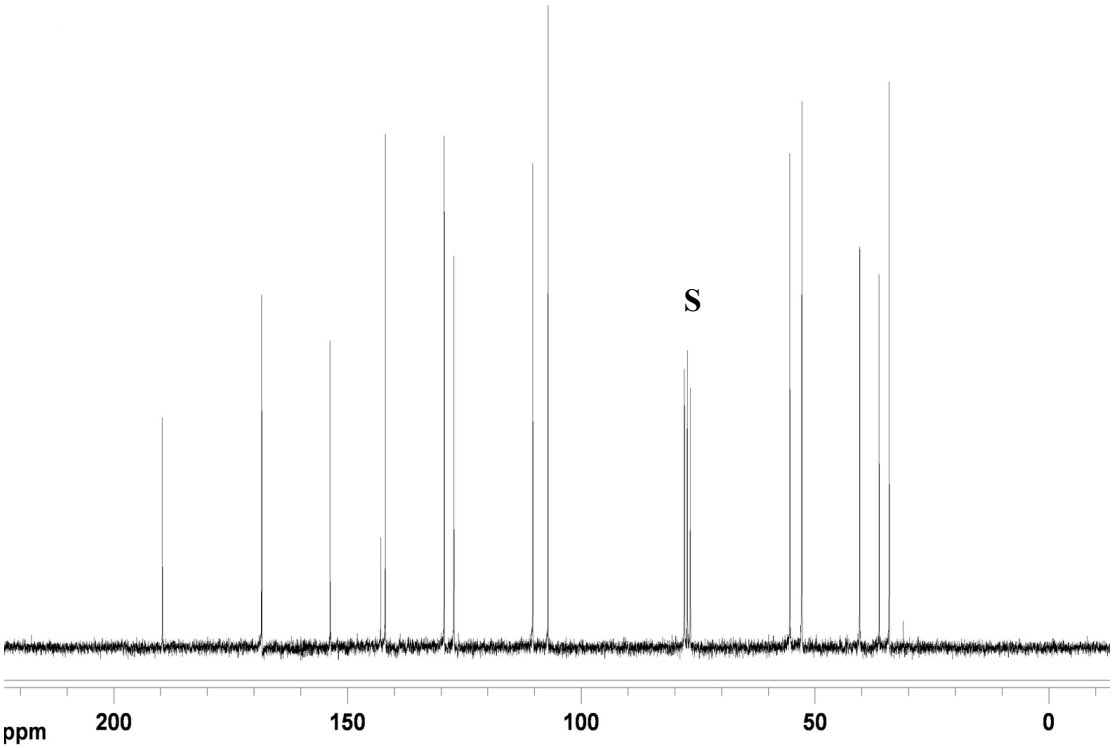
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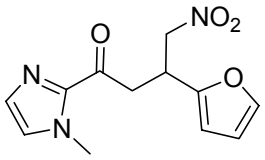
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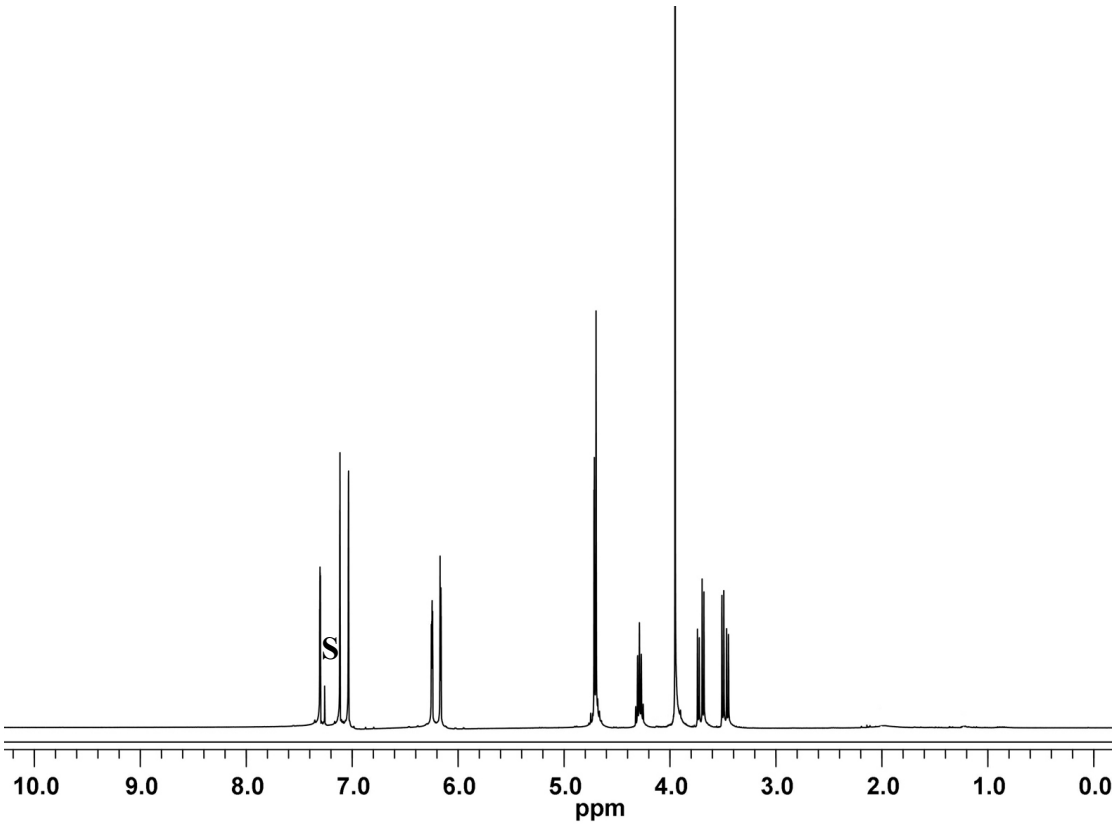
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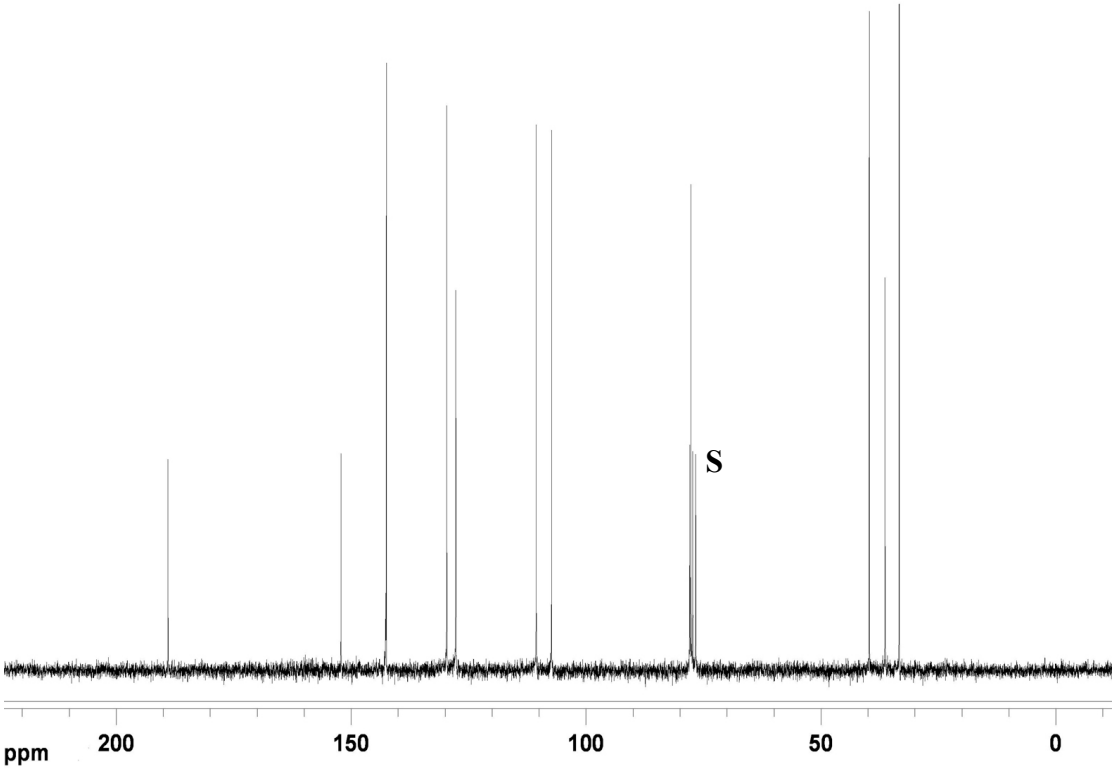
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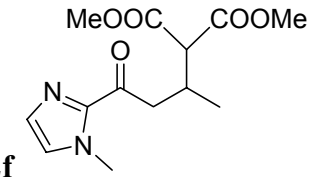
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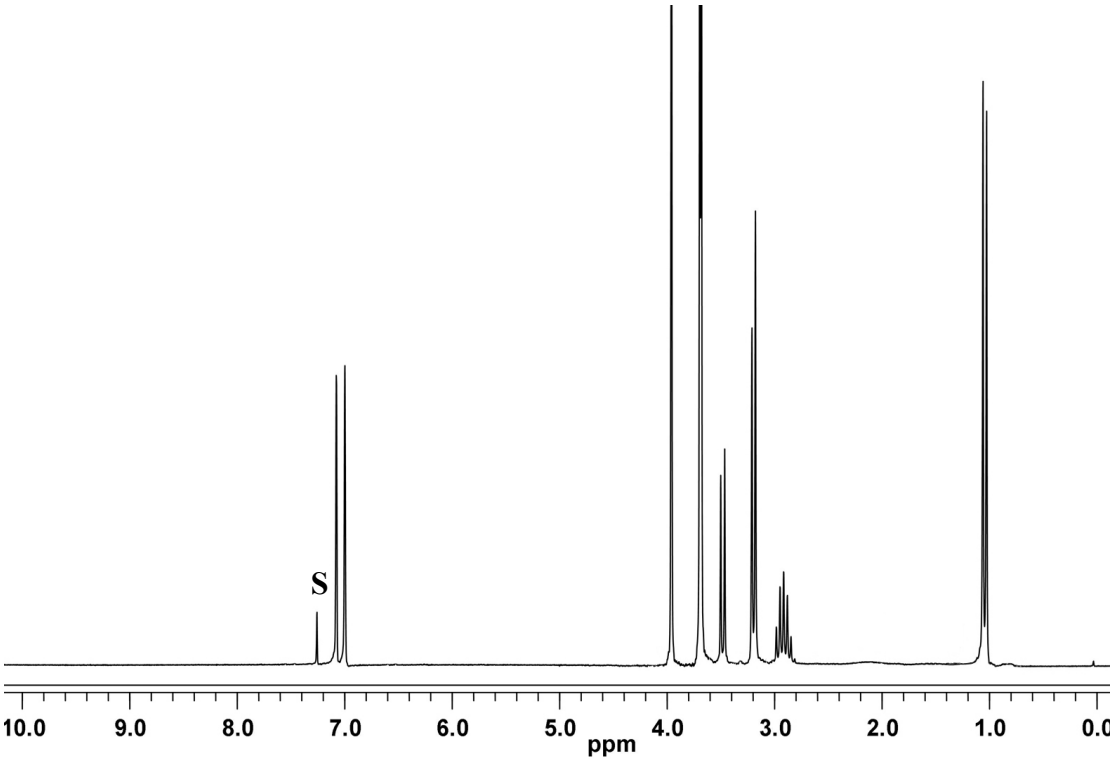
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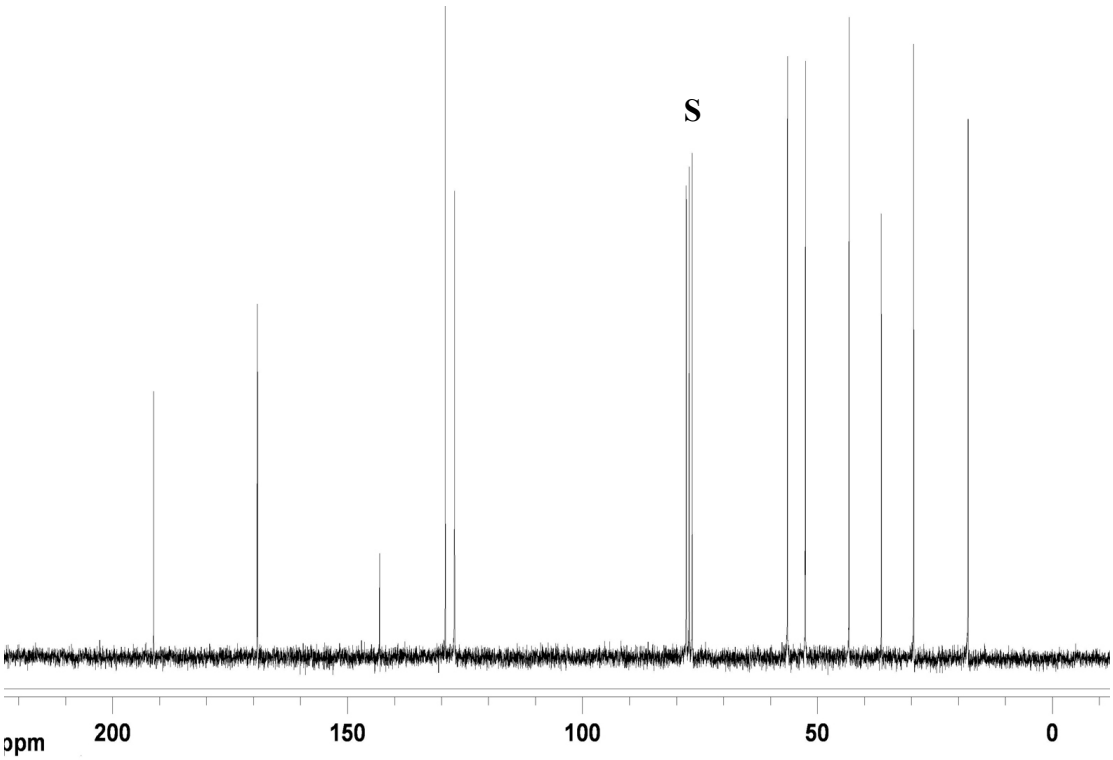
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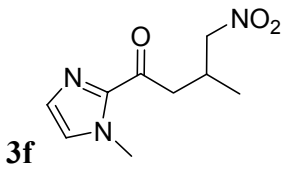

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