Direct Synthesis of Medium-Bridged Twisted Amides via a Transannular Cyclization Strategy

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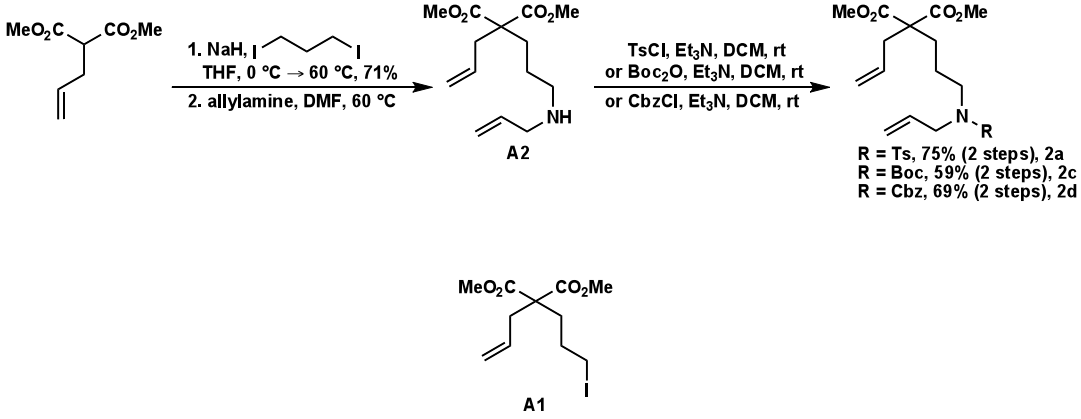
List of Known Compounds

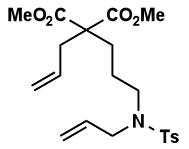
The following compounds are known: N-Allyl-2-nitrobenzenesulfonamide[1], N-(But-3-enyl)-2-nitrobenzenesulfonamide[2], 2-Nitro-N-(pent-4-enyl)benzenesulfonamide[2], Dimethyl 2-allyl-2-(2-bromoethyl)malonate[3], Methyl allylphenylacetate[4], Phenyl allylphenylacetate[5]. Dimethyl 2-allylmalonate, Grubbs 1, Grubbs 2 and Hoveyda-Grubbs 2 were purchased from Aldrich and used as received. Fürstner catalyst was purchased from Strem and used as received. All nitrobenzenosulfonamides were preapred by method of Cluzeau *et al*.[1] Phenyl allylphenylacetate was obtained by alkylation of commercially available phenyl phenylacetate following a procedure by Molander *et al*.[6]

Preparation of Starting Materials

Scheme A. *Synthesis of Compounds* ***2a, 2c, 2d***.



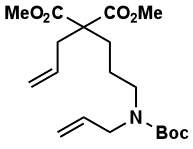
Dimethyl 2-allyl-2-(3-iodopropyl)malonate (A1). To a suspension of sodium hydride (60%, suspension in mineral oil) (0.111 g, 2.78 mmol, 1.1 equiv) in 10 mL of THF at 0° C was added dimethyl 2-allylmalonate (0.434 g, 2.52 mmol, 1.0 equiv) dropwise in 10 mL of THF and the resulting solution was stirred at rt for 30 min. 1,3-diiodopropane (1.15 mL, 10.1 mmol, 4.0 equiv) was added in one portion at 0 °C and the resulting solution was stirred for 30 min at room temperature followed by heating to 60-65 °C for 1 h. The reaction was cooled to room temperature, diluted with ether (20 mL) and quenched with brine (10 mL). The aqueous layer was extracted with ether (3 x 50 mL), and the combined organic layers were washed brine (20 mL). The organic layer was dried (Na_2SO_4) and concentrated. Chromatography (3-5% EtOAc/hexanes) afforded the title compound as a colorless oil (R_f = 0.30, 10% EtOAc/hexanes). Yield 71% (0.609 g, 1.79 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.72-1.80 (m, 2H), 1.96-2.02 (m, 2H), 2.64-2.68 (m, 2H), 3.17 (t, *J* = 6.8, 2H), 3.75 (s, 6H), 5.11-5.17 (m, 1H), 5.60-5.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.6, 28.3, 33.5, 37.4, 52.5, 57.0, 119.4, 132.0, 171.3; IR (neat) 2950, 1731, 1435, 1221 cm^{-1}; HRMS calcd for $C_{11}H_{17}IO_4Na$ (M^+ + Na) 363.0069, found 363.0072.



2a

Dimethyl 2-allyl-2-(3-(N-allyl-4-methylphenylsulfonamido)propyl)malonate (2a). To a solution of iodide **A2** (0.381 g, 1.12 mmol, 1.0 equiv) in DMF (12.0 mL) was added Et_3N (0.31 mL, 2.24 mmol, 2.0 equiv), followed by allylamine (0.43 mL, 5.61 mmol, 5.0 equiv) under Ar. The septum was sealed with Teflon tape, Ar atmosphere was removed, and the reaction mixture was heated at 60 °C for 30 min. The reaction was cooled to room temperature, diluted with ether (20 mL), quenched with water (10 mL), and extracted with ether (3 x 50 mL). The organic layer was washed with water (4 x 50 mL), and brine (1 x 50 mL), dried (Na_2SO_4), and concentrated. The resulting amine **A2** was used in the next step w/o further purification.

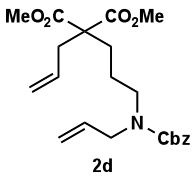
To a solution the crude amine **A2** (1.12 mmol) in DCM (20 mL), Et_3N (0.23 mL, 1.68 mmol, 1.5 equiv) was added, followed by TsCl (0.265 g, 1.34 mmol, 1.2 equiv). The reaction mixture was stirred for 19 h at rt. The solvent was removed under reduced pressure, and the reaction mixture was purified directly by flash chromatography (1/6-1/4 EtOAc/hexanes) to afford the title compound **2a** as a light oil (R_f = 0.25, 1/4 EtOAc/hexanes), yield 75% for two steps (0.353 g, 0.83 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40-1.48 (m, 2H), 1.78-1.84 (m, 2H), 2.44 (s, 3H), 2.62 (d, *J* = 7.4 Hz, 2H), 3.10 (t, *J* = 7.4 Hz, 2H), 3.72 (s, 6H), 3.79 (d, *J* = 6.5 Hz, 2H), 5.06-5.19 (m, 4H), 5.55-5.67 (m, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.69 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 23.0, 29.6, 37.4, 47.2, 50.7, 52.4, 57.3, 118.9, 119.1, 127.2, 129.7, 132.2, 133.2, 136.9, 143.2, 171.4; IR (neat) 2951, 2926, 1734, 1340, 1215, 1159 cm^{-1}; HRMS calcd for $C_{21}H_{29}NO_6SNa$ (M^+ + Na) 446.1613, found 446.1610.



2c

Dimethyl 2-allyl-2-(3-(allyl(tert-butoxycarbonyl)amino)propyl)malonate (2c). To a solution of the crude amine **A2** (0.60 mmol) in DCM (15 mL), Et_3N (0.12 mL, 0.90 mmol, 1.5 equiv) was added, followed by Boc_2O (0.16 g, 0.72 mmol, 1.2 equiv). The reaction mixture was stirred for 20 h at rt. The solvent was removed under reduced pressure, and the reaction mixture was purified directly by flash chromatography (1/8-1/4 EtOAc/hexanes) to afford the title compound **2c** as colorless oil (R_f = 0.43, 1/4 EtOAc/hexanes), yield 59% for two steps (0.13 g, 0.35 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37-1.52 (m, 2H), 1.47 (s, 9H), 1.82-1.88 (m, 2H), 2.66 (d, *J* = 7.4 Hz, 2H), 3.17-3.25 (m, 2H), 3.73 (s, 6H), 3.75-3.85 (m, 2H), 5.07-5.16 (m, 4H), 5.57-5.69 (m, 1H), 7.71-5.83 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of rotamers) δ 22.8, 23.1, 28.4, 29.7, 37.2, 46.5, 49.4, 52.4, 57.3, 79.5, 116.4, 119.1, 132.3, 134.3, 155.4, 171.5; IR

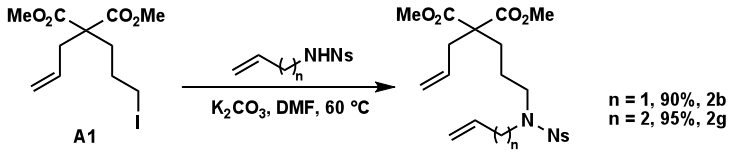
(neat) 2976, 1735, 1695, 1410, 1244, 1207, 1149 cm^{-1}; HRMS calcd for $C_{19}H_{31}NO_6Na$ (M^+ + Na) 392.2049, found 392.2052.

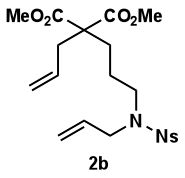


2d

Dimethyl 2-allyl-2-(3-(allyl(benzyloxycarbonyl)amino)propyl)malonate (2d). To a solution of the crude amine **A2** (0.60 mmol) in DCM (15 mL), Et_3N (0.12 mL, 0.90 mmol, 1.5 equiv) was added, followed by CBzCl (0.10 mL, 0.72 mmol, 1.2 equiv). The reaction mixture was stirred for 5 h at rt. The solvent was removed under reduced pressure, and the reaction mixture was purified directly by flash chromatography (1/4 EtOAc/hexanes) to afford the title compound **2d** as colorless oil (R_f = 0.35, 1/4 EtOAc/hexanes), yield 69% for two steps (0.165 g, 0.41 mmol). ^1H NMR (400 MHz, $CDCl_3$) δ 1.47 (br, 2H), 1.85 (br, 2H), 2.63 (br, 2H), 3.25 (br, 2H), 3.70 (s, 6H), 3.90 (br, 2H), 4.98-5.22 (br, 4H), 5.15 (s, 2H), 5.52-5.86 (m, 2H), 7.29-7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of rotamers) δ 22.6, 23.1, 29.6, 37.3, 46.4, 47.0, 49.5, 50.0, 52.4, 57.3, 67.2, 116.6, 117.1, 119.1, 127.9, 128.5, 132.2, 133.8, 136.8, 156.0, 171.5; IR (neat) 2951, 1734, 1699, 1238, 1215 cm^{-1}; HRMS calcd for $C_{22}H_{30}NO_6$ (M^+ + H) 404.2073, found 404.2067.

Scheme B. *Synthesis of Compounds **2b** and **2g**.*

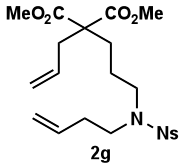




2b

Dimethyl 2-allyl-2-(3-(N-allyl-2-nitrophenylsulfonamido)propyl)malonate (2b). To a round bottom flask charged with N-allyl-2-nitrobenzenesulfonamide[1] (0.0475 g, 0.20 mmol, 1.0 equiv), K_2CO_3 (0.060 g, 0.43 mmol, 2.2 equiv) and DMF (12 mL), iodide **A1** (0.100 g, 0.29 mmol, 1.5 equiv) was added as a solution in DMF (3 mL) at rt, and the reaction mixture was heated at 60 °C for 30 min. The reaction was cooled to room temperature, diluted with ether (20 mL), quenched with water (10 mL), and extracted with ether (3 x 30 mL). The organic layer was washed with water (4 x 20 mL), and brine (1 x 20 mL), dried (Na_2SO_4), and concentrated. Chromatography (1/2 EtOAc/hexanes) afforded the title compound as a colorless oil (R_f = 0.56, 1/1 EtOAc/hexanes). Yield 90%

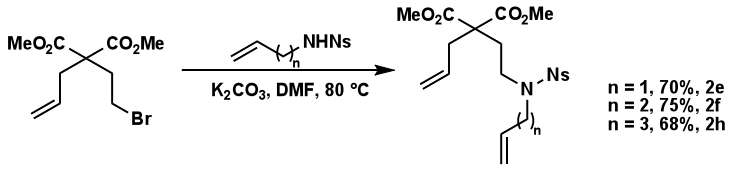
(0.0801 g, 0.18 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42-1.52 (m, 2H), 1.74-1.80 (m, 2H), 2.61 (d, *J* = 7.4 Hz, 2H), 3.29 (t, *J* = 7.4 Hz, 2H), 3.72 (s, 6H), 3.94 (d, *J* = 6.4 Hz, 2H), 5.06-5.13 (m, 2H), 5.18-5.26 (m, 2H), 5.54-5.76 (m, 2H), 7.63-7.75 (m, 3H), 8.03-8.07 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5, 29.5, 37.5, 46.7, 49.8, 52.4, 57.2, 119.2, 119.4, 124.2, 131.0, 131.7, 132.2, 132.7, 133.5, 133.7, 148.0, 171.3; IR (neat) 2952, 1732, 1543, 1352, 1215, 1163 cm^{-1}; HRMS calcd for $C_{20}H_{26}N_2O_8SNa$ (M^+ + Na) 477.1308, found 477.1309.

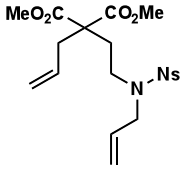


2g

Dimethyl 2-allyl-2-(3-(N-(but-3-enyl)-2-nitrophenylsulfonamido)propyl) malonate (2g). According to the procedure for **2b**, the reaction of N-(but-3-enyl)-2-nitrobenzenesulfonamide[2] (0.165 g, 0.64 mmol, 1.0 equiv), K_2CO_3 (0.197 g, 1.41 mmol, 2.2 equiv) and iodide **A1** (0.33 g, 0.97 mmol, 1.5 equiv) in DMF (20 mL) at 60 °C for 60 min afforded after chromatography (1/4-1/2 EtOAc/hexanes) the title compound as a colorless oil (R_f = 0.63, 1/1 EtOAc/hexanes). Yield 95% (0.284 g, 0.61 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44-1.54 (m, 2H), 1.76-1.82 (m, 2H), 2.24-2.33 (m, 2H), 2.62 (d, *J* = 7.4 Hz, 2H), 3.28-3.39 (m, 4H), 3.72 (s, 6H), 5.00-5.13 (m, 4H), 5.54-5.76 (m, 2H), 7.63-7.74 (m, 3H), 8.00-8.04 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 29.6, 32.5, 37.6, 46.5, 47.1, 52.5, 57.2, 117.5, 119.3, 124.2, 130.8, 131.6, 132.1, 133.4, 133.6, 134.1, 148.0, 171.3; IR (neat) 2952, 1732, 1545, 1373, 1346, 1215, 1159 cm^{-1}; HRMS calcd for $C_{21}H_{29}N_2O_8S$ (M^+ + H) 469.1645, found 469.1654.

Scheme C. *Synthesis of Compounds **2e, 2f** and **2h**.*

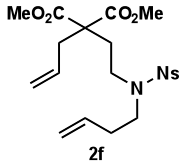




2e

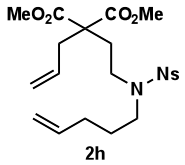
Dimethyl 2-allyl-2-(2-(N-allyl-2-nitrophenylsulfonamido)ethyl)malonate (2e). According to the procedure for **2b**, the reaction of N-allyl-2-nitrobenzenesulfonamide[1] (0.11 g, 0.45 mmol, 1.0 equiv), K_2CO_3 (0.138 g, 0.99 mmol, 2.2 equiv) and dimethyl 2-allyl-2-(2-bromoethyl)malonate[3] (0.25 g, 0.91 mmol, 2.0 equiv) in DMF (15 mL) at 80 °C for 7 h afforded after chromatography (1/4-1/2 EtOAc/hexanes) the title compound as a

colorless oil (R_f = 0.66, 1/1 EtOAc/hexanes). Yield 70% (0.139 g, 0.32 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.09-2.16 (m, 2H), 2.64 (d, *J* = 7.4 Hz, 2H), 3.25-3.32 (m, 2H), 3.74 (s, 6H), 3.97 (d, *J* = 6.4 Hz, 2H), 5.09-5.32 (m, 4H), 5.55-5.75 (m, 2H), 7.62-7.74 (m, 3H), 8.00-8.05 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.8, 37.6, 42.6, 50.1, 52.6, 56.1, 119.6, 119.7, 125.0, 130.9, 131.7, 131.8, 132.5, 133.5, 133.6, 148.0, 170.9; IR (neat) 2952, 1732, 1545, 1371, 1356, 1224, 1163 cm^{-1}; HRMS calcd for $C_{19}H_{25}N_2O_8S$ (M^+ + H) 441.1332, found 441.1332.



2f

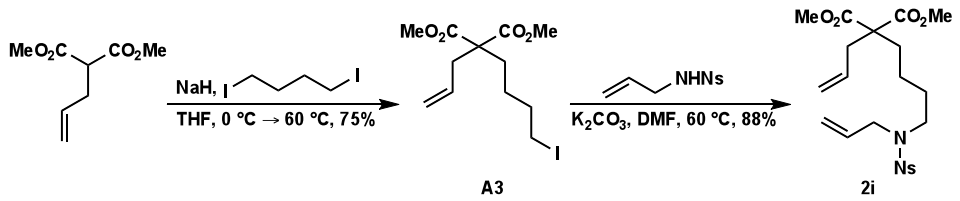
Dimethyl 2-allyl-2-(2-(N-(but-3-enyl)-2-nitrophenylsulfonamido)ethyl) malonate (2f). According to the procedure for **2b**, the reaction of N-(but-3-enyl)-2-nitrobenzenesulfonamide[2] (0.16 g, 0.62 mmol, 1.0 equiv), K_2CO_3 (0.22 g, 1.6 mmol, 2.5 equiv) and dimethyl 2-allyl-2-(2-bromoethyl)malonate[3] (0.52 g, 1.9 mmol, 3.0 equiv) in DMF (15 mL) at 80 °C for 13 h afforded after chromatography (1/4-1/3-1/1 EtOAc/hexanes) the title compound as a colorless oil (R_f = 0.77, 1/1 EtOAc/hexanes). Yield 75% (0.21 g, 0.46 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.10-2.16 (m, 2H), 2.28-2.36 (m, 2H), 2.66 (d, *J* = 7.4 Hz, 2H), 3.30-3.37 (m, 2H), 3.37-3.42 (m, 2H), 3.76 (s, 6H), 5.02-5.18 (m, 4H), 5.58-5.77 (m, 2H), 7.61-7.74 (m, 3H), 7.99-8.04 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.4, 32.6, 38.0, 43.2, 47.0, 52.7, 56.1, 117.5, 119.7, 124.2, 130.8, 131.6, 131.9, 133.4, 133.6, 134.2, 148.0, 170.9; IR (neat) 2952, 1732, 1545, 1373, 1350, 1222, 1161 cm^{-1}; HRMS calcd for $C_{20}H_{27}N_2O_8S$ (M^+ + H) 455.1488, found 455.1490.

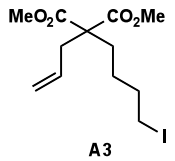


2h

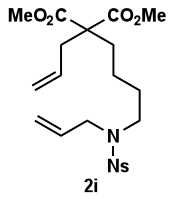
Dimethyl 2-allyl-2-(2-(2-nitro-N-(pent-4-enyl)phenylsulfonamido)ethyl) malonate (2h). According to the procedure for **2b**, the reaction of 2-nitro-N-(pent-4-enyl)benzenesulfonamide[2] (0.114 g, 0.42 mmol, 1.0 equiv), K_2CO_3 (0.147 g, 1.05 mmol, 2.5 equiv) and dimethyl 2-allyl-2-(2-bromoethyl)malonate[3] (0.35 g, 1.25 mmol, 3.0 equiv) in DMF (15 mL) at 80 °C for 13 h afforded after chromatography (1/4-1/2 EtOAc/hexanes) the title compound as a colorless oil (R_f = 0.14, 1/4 EtOAc/hexanes). Yield 68% (0.133 g, 0.28 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61-1.69 (m, 2H), 2.01-2.08 (m, 2H), 2.09-2.16 (m, 2H), 2.66 (d, *J* = 7.4 Hz, 2H), 3.27-3.35 (m, 4H), 3.76 (s, 6H), 4.97-5.05 (m, 2H), 5.09-5.18 (m, 2H), 5.57-5.68 (m, 2H), 5.70-5.81 (m, 2H), 7.60-7.73 (m, 3H), 7.98-8.02 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.2, 30.6, 31.5, 37.9, 43.2, 47.3, 52.7, 56.1, 115.5, 119.7, 124.2, 130.8, 131.6, 131.9, 133.4, 133.5, 137.2, 148.1, 170.9; IR (neat) 2952, 1732, 1545, 1373, 1350, 1219, 1161 cm^{-1}; HRMS calcd for $C_{21}H_{28}N_2O_8SNa$ (M^+ + H) 491.1164, found 491.1465.

Scheme D. *Synthesis of Compound **2i**.*



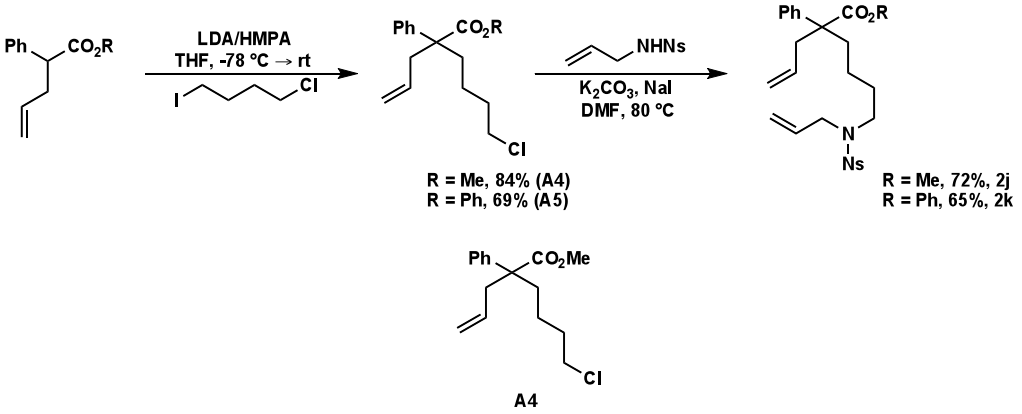


Dimethyl 2-allyl-2-(4-iodobutyl)malonate (A3). According to the procedure for **A1**, the reaction of sodium hydride (60%, suspension in mineral oil) (0.26 g, 6.4 mmol, 1.1 equiv), dimethyl 2-allylmalonate (1.0 g, 5.8 mmol, 1.0 equiv), and 1,4-diiodopropane (2.3 mL, 17.4 mmol, 3.0 equiv) in THF (20 mL) afforded after chromatography (2-5% EtOAc/hexanes) the title compound as a colorless oil (R_f = 0.42, 10% EtOAc/hexanes). Yield 75% (1.54 g, 4.4 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22-1.37 (m, 2H), 1.78-1.92 (m, 4H), 2.67 (d, *J* = 7.4 Hz, 2H), 3.19 (t, *J* = 6.9 Hz, 2H), 3.74 (s, 6H), 5.08-55.14 (m, 2H), 5.57-5.69 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.3, 24.8, 31.1, 33.3, 37.1, 52.5, 57.4, 119.2, 132.3, 171.6; IR (neat) 2951, 1732, 1435, 1215 cm^{-1}; HRMS calcd for $C_{12}H_{20}IO_4$ (M^+ + H) 355.0406, found 355.0394.

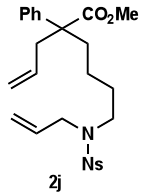


Dimethyl 2-allyl-2-(4-(N-allyl-2-nitrophenylsulfonamido)butyl)malonate (2i). According to the procedure for **2b**, the reaction of N-allyl-2-nitrobenzenesulfonamide[1] (0.173 g, 0.72 mmol, 1.0 equiv), K_2CO_3 (0.22 g, 1.57 mmol, 2.2 equiv) and iodide **A3** (0.38 g, 1.07 mmol, 1.5 equiv) in DMF (15 mL) at 60 °C for 60 min afforded after chromatography (1/4-1/2 EtOAc/hexanes) the title compound as a colorless oil (R_f = 0.72, 1/1 EtOAc/hexanes). Yield 88% (0.295 g, 0.63 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05-1.15 (m, 2H), 1.52 (p, *J* = 7.5 Hz, 2H), 1.78-1.87 (m, 2H), 2.58 (d, *J* = 7.4 Hz, 2H), 3.28 (t, *J* = 7.5 Hz, 2H), 3.71 (s, 6H), 3.92 (d, *J* = 6.2 Hz, 2H), 5.04-5.27 (m, 4H), 5.54-5.76 (m, 2H), 7.62-7.75 (m, 3H), 8.01-8.06 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 27.9, 32.1, 37.1, 46.6, 49.7, 52.4, 57.5, 119.0, 119.2, 124.3, 130.9, 131.6, 132.3, 132.8, 133.5, 133.7, 147.9, 171.5; IR (neat) 2952, 1732, 1543, 1373, 1352, 1211, 1161 cm^{-1}; HRMS calcd for $C_{21}H_{29}N_2O_8S$ (M^+ + H) 469.1645, found 469.1638.

Scheme E. *Synthesis of Compounds **2j** and **2k**.*

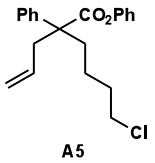


Methyl 2-allyl-6-chloro-2-phenylhexanoate (A4). To solution of LDA prepared from diisopropylamine (0.37 mL, 2.62 mmol, 1.15 equiv) and n-butyllithium (2.3 M in hexanes) (1.09 mL, 2.50 mmol, 1.10 equiv) in THF (10 mL), HMPA (1.0 mL) was added dropwise at -78 °C. After stirring for 30 min at -78 °C methyl allylphenylacetate[4] in THF (5 mL) was added dropwise. After next 45 min at -78 °C, 1-chloro-4-iodobutane (0.42 mL, 3.4 mmol, 1.5 equiv) was added dropwise, and after 15 min the reaction mixture was allowed to warm to room temperature. After stirring for additional 3 h, the reaction was quenched with brine (10 mL). The aqueous layer was extracted with ether (3 x 50 mL), and the combined organic layers were washed brine (20 mL). The organic layer was dried (Na_2SO_4) and concentrated. Chromatography (1-2-5% EtOAc/hexanes) afforded the title compound as a colorless oil (R_f = 0.47, 10% EtOAc/hexanes). Yield 84% (0.534 g, 1.90 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23-1.33 (m, 2H), 1.78 (p, *J* = 7.5 Hz, 2H), 1.98-2.08 (m, 2H), 2.84 (dq, *J* = 7.7, 14 Hz, 2H), 3.52 (dt, *J* = 1.5, 6.6 Hz, 2H), 3.68 (s, 3H), 5.05-5.15 (m, 2H), 5.49-5.61 (m, 1H), 7.24-7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 32.9, 33.7, 39.1, 44.6, 52.1, 53.7, 118.5, 126.3, 126.9, 128.4, 133.5, 142.0, 175.8; IR (neat) 2951, 1730, 1496, 1446, 1271, 1217, 1155 cm^{-1}; HRMS calcd for $C_{16}H_{21}ClO_2Na$ (M^+ + Na) 303.1128, found 3303.1117.



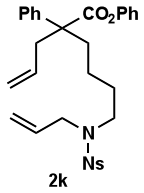
Methyl 2-allyl-6-(N-allyl-2-nitrophenylsulfonamido)-2-phenylhexanoate (2j). To a round bottom flask charged with N-allyl-2-nitrobenzenesulfonamide[1] (0.215 g, 0.89 mmol, 1.0 equiv), K_2CO_3 (0.273 g, 1.96 mmol, 2.2 equiv), NaI (0.67g, 4.5 mmol, 5 equiv) and DMF (10 mL), chloride **A4** (0.50 g, 1.78 mmol, 2.0 equiv) was added as a solution in DMF (5 mL) at rt, and the reaction mixture was heated at 80 °C for 14 h. The reaction was cooled to room temperature, diluted with ether (20 mL), quenched with water (10 mL), and extracted with ether (3 x 50 mL). The organic layer was washed with water (4 x 50 mL), and brine (1 x 50 mL), dried (Na_2SO_4), and concentrated.

Chromatography (1/4-1/3 EtOAc/hexanes) afforded the title compound as a yellow oil (R_f = 0.76, 1/1 EtOAc/hexanes). Yield 72% (0.313 g, 0.64 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96-1.06 (m, 2H), 1.44-1.56 (m, 2H), 1.90-1.99 (m, 2H), 2.74 (dq, *J* = 6.8, 14 Hz, 2H), 3.24 (d, *J* = 7.7 Hz, 2H), 3.65 (s, 3H), 3.91 (d, *J* = 6.2 Hz, 2H), 5.02-5.09 (m, 2H), 5.19 (dt, *J* = 1.2, 10.0 Hz, 2H), 5.44-5.56 (m, 1H), 5.63-5.75 (m, 1H), 7.19-7.38 (m, 5H), 7.62-7.73 (m, 3H), 8.00-8.04 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 28.1, 34.1, 39.2, 46.8, 49.7, 52.1, 53.7, 118.4, 119.1, 124.2, 126.3, 126.9, 128.4, 130.9, 131.6, 132.8, 133.4, 133.5, 133.8, 141.9, 147.9, 175.8; IR (neat) 2949, 1728, 1545, 1371, 1352, 1163 cm^{-1}; HRMS calcd for $C_{25}H_{30}N_2O_6SNa$ (M^+ + Na) 509.1722, found 509.1724.



A5

Phenyl 2-allyl-6-chloro-2-phenylhexanoate (A5). According to the procedure for **A4**, the reaction of LDA (prepared from diisopropylamine (0.27 mL, 1.91 mmol, 1.15 equiv) and n-butyllithium (2.3 M in hexanes) (0.79 mL, 1.83 mmol, 1.10 equiv) in THF (10 mL)), HMPA (1.0 mL), phenyl allylphenylacetate[5] (0.42 g, 1.66 mmol, 1.0 equiv), and 1-chloro-4-iodobutane (0.31 mL, 2.5 mmol, 1.5 equiv) afforded after chromatography (hexanes-1-2-5% EtOAc/hexanes) the title compound as a colorless oil (R_f = 0.35, 10% EtOAc/hexanes). The compound was contaminated with inseparable impurity (ca. 10-15% by ^{1}H NMR). Yield (corrected by impurity) 69% (0.39 g, 1.14 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33-1.52 (m, 2H), 1.83 (p, *J* = 7.0 Hz, 2H), 2.07-2.24 (m, 2H), 2.97 (dq, *J* = 6.6, 14.1 Hz, 2H), 3.52-3.62 (m, 2H), 5.18-5.24 (m, 2H), 5.63-5.74 (m, 1H), 6.94-6.99 (m, 2H), 7.19-7.24 (m, 1H), 7.29-7.45 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 32.9, 33.6, 39.0, 44.7, 53.8, 118.9, 121.4, 125.8, 126.4, 127.1, 128.6, 129.4, 133.1, 141.6, 150.8, 174.0; IR (neat) 2952, 1749, 1593, 1492, 11.92, 1161 cm^{-1}; HRMS calcd for $C_{21}H_{23}ClO_2Na$ (M^+ + Na) 365.1284, found 365.1251.



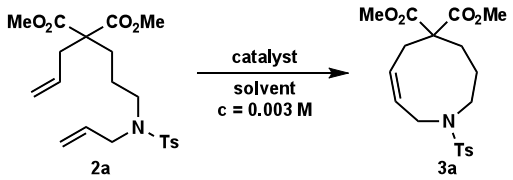
2k

Phenyl 2-allyl-6-(N-allyl-2-nitrophenylsulfonamido)-2-phenylhexanoate (2k). According to the procedure for **2j**, the reaction of N-allyl-2-nitrobenzenesulfonamide[1] (0.109 g, 0.45 mmol, 1.0 equiv), K_2CO_3 (0.138 g, 0.99 mmol, 2.2 equiv), NaI (0.34 g, 2.3 mmol, 5 equiv) and chloride **A5** (0.39 g, 1.14 mmol, 2.5 equiv) in DMF (15 mL) at 80 °C for 14 h afforded after chromatography (1/5-1/4 EtOAc/hexanes) the title compound as oil (R_f = 0.74, 1/1 EtOAc/hexanes). Yield 65% (0.161 g, 0.29 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10- 1.20 (m, 2H), 1.51-1.62 (m, 2H), 2.02-2.16 (m, 2H), 2.89 (dq, *J* = 6.6, 14.0 Hz, 2H), 3.28 (t, *J* = 7.6 Hz, 2H), 3.92 (d, *J* = 6.3 Hz, 2H), 5.12- 5.25 (m, 4H), 5.58-5.76 (m, 2H), 6.92-6.97 (m, 2H), 7.19-7.24 (m, 1H), 7.28-7.43 (m, 7H), 7.60-7.71 (m, 3H), 8.01-8.05 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 28.2, 34.1, 39.0, 46.7,

49.8, 53.8, 118.9, 119.1, 121.3, 124.2, 125.8, 126.4, 127.1, 128.6, 129.4, 130.9, 131.6, 132.8, 133.1, 133.4, 133.7, 141.5, 147.9, 150.8, 173.9; IR (neat) 2935, 1747, 1543, 1371, 1352, 1161, 1124 cm^{-1}; HRMS calcd for $C_{30}H_{32}N_2O_6SNa$ (M^+ + Na) 571.1878, found 571.1880.

RCM Reactions

***Scheme F**. Optimization of RCM (Table 1).*



Entry 1. To a 25 ml round-bottom flask charged with olefin and solvent (c = 0.003 M), 50 mol% of Grubbs 1 catalyst was added as solid under nitrogen. The reaction was stirred at 40 °C for 16 h. The reaction was cooled to rt, 50 mol% of Grubbs 1 catalyst was added, and stirring at 40 °C was continued for next 10 h. The reaction was cooled to rt, solvent was removed under reduced pressure. Known amount of nitromethane was added as the internal standard, and the reaction was analyzed by ^{1}H NMR. Purification by flash chromatograhy afforded the final product: **(Z)-Dimethyl 1-tosyl-3,4,6,9-tetrahydro-1H-azonine-5,5(2H)-dicarboxylate (3a).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.72 (s, 2H), 2.15 (s, 2H), 2.45 (s, 3H), 2.7-3.2 (br s, 2H), 3.17 (s, 2H), 3.66 (s, 2H), 3.76 (s, 6H), 5.49 (q, *J* = 10.4 Hz, 1H), 5.81 (m, 1H), 7.33 (d, *J* = 8.0 Hz), 7.71 (d, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 23.9, 27.8, 30.3, 46.5, 50.8, 52.7, 56.7, 127.3, 128.4, 129.5, 129.7, 135.3, 143.4, 171.6; IR (neat) 2952, 2926, 1733, 1339, 1210, 1160, 1090 cm^{-1}; HRMS calcd for $C_{19}H_{26}NO_6SNa$ (M^+ + Na) 418.1300, found 418.1296.

Entry 2 and 3. To a 25 ml round-bottom flask charged with olefin and solvent (c = 0.003 M), Fürstner catalyst was added in one portion as solid under nitrogen. The reaction was stirred at rt (entry 2) or 40 °C (entry 3) for specified period of time. Solvent was removed under reduced pressure. Known amount of nitromethane was added as the internal standard, and the reaction was analyzed by ^{1}H NMR.

Entry 4 and 5. To a 25 ml round-bottom flask charged with olefin. Grubbs 2 catalyst followed by solvent (c = 0.003 M) was added as solid under nitrogen. The reaction was stirred at 40 °C (entry 4) or 80 °C (entry 5) for specified period of time. Solvent was removed under reduced pressure. Known amount of nitromethane was added as the internal standard, and the reaction was analyzed by ^{1}H NMR.

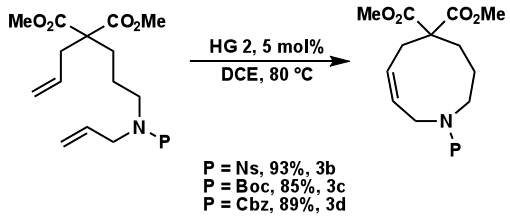
Entry 7. To a 25 ml round-bottom flask charged with olefin. Grubbs 2 catalyst followed by solvent (c = 0.003 M) was added as solid under nitrogen. Ti(O*i*Pr)$_4$ (5 equiv) was added and the reaction was stirred at 80 °C for specified period of time. Solvent was removed under reduced pressure. Known amount of nitromethane was added as the internal standard, and the reaction was analyzed by ^{1}H NMR.

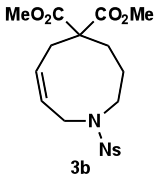
Entry 6 and 8. A 25 ml round-bottom flask charged with olefin and solvent (c = 0.003 M) was heated to 80 °C for 30-45 min. Grubbs 2 (entry 6) or Hoveyda-Grubbs 2 catalyst (entry 8) was added in DCE and the reaction was stirred at 80 °C for specified period of time. Solvent was removed under reduced pressure. Known amount of nitromethane was added as the internal standard, and the reaction was analyzed by ^{1}H NMR.

Entry 9. A 25 ml round-bottom flask charged with olefin (0.0150 g, 0.036 mmol, 1.0 equiv) and solvent (c = 0.003 M) was heated to 80 °C for 15 min. Hoveyda-Grubbs 2 catalyst was added in DCE. Argon was bubbled through the reaction while it was stirred at 80 °C for specified period of time. Solvent was removed under reduced pressure. Purification of the residue by flash chromatography (1/7-1/4 EtOAc/Hexanes) afforded the title compound in 87% yield (0.0122 g, 0.031 mmol).

Entry 10. A 25 ml round-bottom flask charged with olefin (0.0144 g, 0.034 mmol, 1.0 equiv) and solvent (c = 0.003 M) was sealed with a septum under argon and heated to 80 °C for 15 min. Hoveyda-Grubbs 2 catalyst was added in DCE. The reaction was stirred at 80 °C for 8 h. A needle was inserted once every hour to open the reaction to air and release ethylene. Solvent was removed under reduced pressure. Purification of the residue by flash chromatography (1/7-1/4 EtOAc/Hexanes) afforded the title compound in 95% yield (0.0127 g, 0.032 mmol).

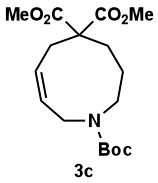
Scheme G. *Synthesis of Compounds **3b, 3c, 3d** (Table 1, entries 11, 12 and 13).*





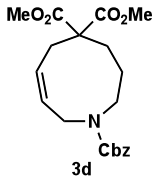
(Z)-Dimethyl 1-(2-nitrophenylsulfonyl)-3,4,6,9-tetrahydro-1H-azonine-5,5(2H)-dicarboxylate (3b). A 100 ml round-bottom flask charged with olefin **2b** (0.0610 g, 0.134 mmol, 1.0 equiv) and DCE (45 mL, c = 0.003 M) was heated to 80 °C for 15 min. Hoveyda-Grubbs 2 catalyst (0.0042 g, 0.0067 mmol, 0.05 equiv) was added in DCE (1.0 mL). Argon was bubbled through the reaction while it was stirred at 80 °C for 16 h. Solvent was removed under reduced pressure. Purification of the residue by

flash chromatography (1/7-1/1 EtOAc/Hexanes) afforded the title compound as an oil (R_f = 0.33, 1/1 EtOAc/hexanes). Yield 93% (0.0532 g, 0.125 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.75 (s, 2H), 2.16 (s, 2H), 2.94 (s, 2H), 3.39 (t, *J* = 6.0 Hz, 2H), 3.76 (s, 6H), 3.85 (d, *J* = 7.0 Hz, 2H), 5.51-5.59 (m, 1H), 5.86-5.94 (m, 1H), 7.60-7.64 (m, 1H), 7.67-7.75 (m, 2H), 7.96-7.99 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 27.1, 30.4, 46.2, 50.9, 52.7, 56.6, 124.1, 129.0, 129.7, 130.7, 131.5, 132.0, 133.6, 148.5, 171.5; IR (neat) 2952, 2924, 1732, 1541, 1373, 1346, 1207, 1165 cm^{-1}; HRMS calcd for $C_{18}H_{22}N_2O_8SNa$ (M^+ + Na) 449.0994, found 449.0992.



3c

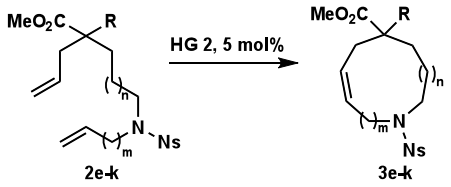
(Z)-1-*tert*-Butyl 5,5-dimethyl 3,4-dihydro-1H-azonine-1,5,5(2H,6H,9H)-tricarboxylate (3c). According to the procedure for **3b**, the reaction of **2c** (0.0840 g, 0.23, 1.0 equiv) and Hoveyda-Grubbs catalyst 2 (0.0071 g, 0.011 mmol, 0.05 equiv) in DCE (57 mL = 0.004 M) at 80 °C for 17 h afforded after chromatography (1/7-1/5 EtOAc/hexanes) the title compound as a colorless oil (R_f = 0.33, 1/4 EtOAc/hexanes). Yield 85% (0.0662 g, 0.194 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (s, 9H), 1.6-2.2 (m, 4H), 2.5-3.0 (m, 2H), 3.37 (s, 2H), 3.75 (s, 6H), 3.75-4.05 (m, 2H), 5.27-5.42 (m, 1H), 5.83-5.92 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of rotamers) δ 21.8, 23.1, 26.9, 27.7, 28.5, 28.5, 29.7, 30.4, 30.5, 46.6, 47.8, 49.9, 50.8, 52.6, 52.6, 57.0, 57.3, 79.6, 79.8, 125.9, 126.6, 130.9, 131.2, 155.5, 171.7; IR (neat) 2952, 1733, 1693, 1456, 1411, 1395, 1125, 1170 cm^{-1}; HRMS calcd for $C_{17}H_{27}NO_6Na$ (M^+ + Na) 374.1736, found 364.1706.

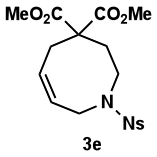


3d

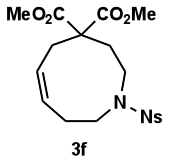
(Z)-1-Benzyl 5,5-dimethyl 3,4-dihydro-1H-azonine-1,5,5(2H,6H,9H)-tricarboxylate (3d). According to the procedure for Table 1, entry 10, the reaction of **2d** (0.0170 g, 0.042, 1.0 equiv) and Hoveyda-Grubbs catalyst 2 (0.0013 g, 0.0021 mmol, 0.05 equiv) in DCE (15 mL = 0.003 M) at 80 °C for 8 h afforded after chromatography (1/7-1/5 EtOAc/hexanes) the title compound as a colorless oil (R_f = 0.68, 1/1 EtOAc/hexanes). Yield 89% (0.0141 g, 0.038 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.11 (s, 2H), 2.79 (s, 2H), 3.42 (t, *J* = 6.0 Hz, 2H), 3.76 (s, 6H), 3.85 (s, 2H), 3.92 (d, *J* = 6.2 Hz, 2H), 5.35-5.44 (m, 1H), 5.88-6.01 (m, 1H), 7.31-7.42 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of rotamers) δ 21.8, 23.0, 26.6, 27.1, 30.7, 30.8, 46.0, 47.3, 50.0, 50.3, 52.6, 52.7, 56.9, 57.0, 67.1, 67.3, 127.0, 127.4, 127.8, 127.9, 128.0, 128.5, 130.5, 130.7, 136.7, 136.9, 155.8, 156.3, 171.6; IR (neat) 2950, 1731, 1699, 1417, 1251, 1230, 1214, 1089 cm^{-1}; HRMS calcd for $C_{20}H_{26}NO_6$ (M^+ + H) 376.1760, found 376.1758.

Scheme H. *Synthesis of Compounds **3e-k** (Table 2, Step 1).*

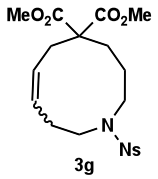




(Z)-Dimethyl 1-(2-nitrophenylsulfonyl)-1,2,3,8-tetrahydroazocine-4,4(5H)-dicarboxylate (3e). According to the procedure for Table 1, entry 10, the reaction of **2e** (0.0689 g, 0.157 mmol, 1.0 equiv) and Hoveyda-Grubbs catalyst 2 (0.0049 g, 0.0080 mmol, 0.05 equiv) in DCE (53 mL = 0.003 M) at 80 °C for 2.5 h (needle was inserted every 15-30 min) afforded after chromatography (1/7-1/1 EtOAc/hexanes) the title compound as white solid (Mp = 158 °C; R_f = 0.43, 1/1 EtOAc/hexanes). Yield 90% (0.0583 g, 0.142 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (m, 2H), 3.03 (d, *J* = 7.6 Hz, 2H), 3.55 (m, 2H), 3.76 (s, 6H), 4.00 (d, *J* = 4.1 Hz, 2H), 5.72-5.86 (m, 2H), 7.62-7.75 (m, 3H), 7.98-8.04 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.7, 31.1, 45.3, 46.8, 52.9, 57.5, 124.2, 127.6, 129.2, 131.1, 131.7, 132.6, 133.6, 148.0, 171.2; IR (neat) 2954, 1732, 1541, 1373, 1346, 1221, 1163, 1130 cm^{-1}; HRMS calcd for $C_{17}H_{20}N_2O_8SNa$ (M^+ + Na) 435.0838, found 435.0833.

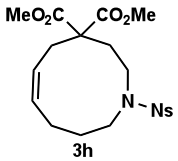


(Z)-Dimethyl 1-(2-nitrophenylsulfonyl)-2,3,8,9-tetrahydro-1H-azonine-4,4(5H)-dicarboxylate (3f). According to the procedure for **3e**, the reaction of **2f** (0.0663 g, 0.146 mmol, 1.0 equiv) and Hoveyda-Grubbs catalyst 2 (0.0046 g, 0.0073 mmol, 0.05 equiv) in DCE (50 mL = 0.003 M) at 80 °C for 2.5 h (needle was inserted every 15-30 min) afforded after chromatography (1/7-1/1 EtOAc/hexanes) the title compound as yellowish foam (R_f = 0.47, 1/1 EtOAc/hexanes). Yield 94% (0.0586 g, 0.138 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.24 (t, *J* = 5.7 Hz, 2H), 2.52 (s, 2H), 3.04 (d, *J* = 8.4 Hz, 2H), 3.25 (s, 2H), 3.34 (s, 2H), 3.80 (s, 6H), 5.47-5.56 (m, 1H), 5.84-5.92 (m, 1H), 7.58-7.62 (m, 1H), 7.67-7.75 (m, 2H), 7.88-7.93 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.8, 29.8, 31.9, 46.1, 49.2, 52.9, 56.6, 124.0, 128.3, 130.7, 131.1, 131.4, 131.4, 133.6, 148.7, 171.2; IR (neat) 2952, 1733, 1542, 1456, 1437, 1373, 1350, 1221, 1167 cm^{-1}; HRMS calcd for $C_{18}H_{23}N_2O_8S$ (M^+ + H) 427.1175, found 427.1173.



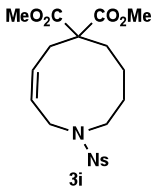
3g

Dimethyl 1-(2-nitrophenylsulfonyl)-1,2,3,4,9,10-hexahydroazecine-5,5(6H)-dicarboxylate (3g). According to the procedure for **3e**, the reaction of **2g** (0.0578 g, 0.123 mmol, 1.0 equiv) and Hoveyda-Grubbs catalyst 2 (0.0039 g, 0.0062 mmol, 0.05 equiv) in DCE (42 mL = 0.003 M) at 80 °C for 2 h afforded after chromatography (1/7-1/1 EtOAc/hexanes) the title compound (5:1 mixture of Z/E isomers) as oil (R_f = 0.43, 1/1 EtOAc/hexanes). Yield 90% (0.0495 g, 0.110 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of Z/E isomers) δ 1.45-1.80 (m, 2.7H), 1.90-2.50 (m, 3.9H), 2.62 (s, 1.3H), 3.00 (m, 4.5H), 3.75 (s, 8.2H), 3.93 (s, 1.1H), 5.42-5.51 (m, 1H, Z isomer), 5.50-5.61 (m, 1H, E isomer), 5.65-5.70 (m, 1H, E isomer), 5.71-5.79 (m, 1H, Z isomer), 7.58-7.64 (m, 1.07H), 7.65-7.73 (m, 2.36H), 7.86-7.93 (m, 1.18H); ^{13}C NMR (100 MHz, $CDCl_3$) (Z isomer) δ 22.9, 25.6, 28.4, 28.7, 49.1, 49.8, 52.6, 55.7, 124.1, 125.7, 127.8, 130.2, 131.1, 131.5, 133.4, 148.3, 171.8; IR (neat) 2952, 1730, 1543, 1437, 1373, 1344, 1273, 1257, 1209, 1141 cm^{-1}; HRMS calcd for $C_{19}H_{25}N_2O_8S$ (M^+ + H) 441.1332, found 441.1334.



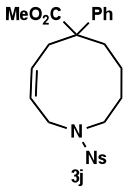
3h

(Z)-Dimethyl 1-(2-nitrophenylsulfonyl)-2,3,5,8,9,10-hexahydroazecine-4,4(1H)-dicarboxylate (3h). A 100 ml round-bottom flask charged with olefin **2h** (0.0587 g, 0.125 mmol, 1.0 equiv) and DCE (62 mL, c = 0.003 M) was heated to 80 °C for 15 min open to air. Hoveyda-Grubbs 2 catalyst (0.0039 g, 0.0063 mmol, 0.05 equiv) was added in DCE (0.5 mL) at 80 °C. After stirring for 1.5 h at 80 °C, the solvent was removed under reduced pressure. Purification of the residue by flash chromatography (1/7-1/4-/1/2 EtOAc/Hexanes) afforded the title compound as oil (R_f = 0.47, 1/1 EtOAc/hexanes). Yield 92% (0.0508 g, 0.116 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80-2.40 (m, 4.6H), 2.50-2.85 (m, 2H), 3.10 (m, 3.5H), 3.25-3.65 (m, 1.9H), 3.80 (s, 6H), 5.27-5.35 (m, 1H), 5.54-5.63 (m, 1H), 7.56-7.61 (m, 1H), 7.67-7.76 (m, 2H), 7.89-7.92 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 27.1, 27.1, 30.0, 44.5, 46.7, 52.9, 56.5, 123.9, 126.0, 130.0, 131.0, 131.2, 132.2, 133.8, 148.9, 171.3; IR (neat) 2952, 1732, 1545, 1460, 1373, 1357, 1222, 1172, 1126 cm^{-1}; HRMS calcd for $C_{19}H_{24}N_2O_8SNa$ (M^+ + Na) 463.1151, found 463.1147.



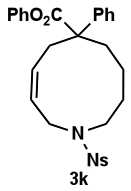
3i

(Z)-Dimethyl 1-(2-nitrophenylsulfonyl)-1,2,7,8,9,10-hexahydroazecine-6,6(5H)-dicarboxylate (3i). According to the procedure for **3e**, the reaction of **2i** (0.0587 g, 0.125 mmol, 1.0 equiv) and Hoveyda-Grubbs catalyst 2 (0.0039 g, 0.0063 mmol, 0.05 equiv) in DCE (42 mL = 0.003 M) at 80 °C for 3 h afforded after chromatography (1/7-1/3-1/1 EtOAc/hexanes) the title compound as oil (R_f = 0.71, 1/1 EtOAc/hexanes). Yield 79% (0.0435 g, 0.099 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 3H), 1.76 (s, 1H), 1.92 (s, 1H), 2.03 (s, 1H), 2.57 (m, 1H), 3.17 (m, 1H), 3.30 (m, 1H), 3.52 (m, 1H), 3.76 (s, 6H), 4.05 (m, 1H), 2.29 (m, 1H), 5.53-5.69 (m, 2H), 7.64-7.75 (m, 3H), 8.06-8.11 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.0, 27.6, 28.6, 28.7, 41.6, 44.9, 52.8, 55.8, 124.3, 127.2, 131.2, 131.3, 131.7, 133.2, 133.5, 148.0, 171.2, 171.7; IR (neat) 2952, 1730, 1543, 1437, 1371, 1340, 1161 cm^{-1}; HRMS calcd for $C_{19}H_{24}N_2O_8SNa$ (M^+ + Na) 463.1151, found 463.1141.



3j

(Z)-Methyl 1-(2-nitrophenylsulfonyl)-6-phenyl-1,2,3,4,5,6,7,10-octahydroazecine-6-carboxylate (3j). According to the procedure for **3e**, the reaction of **2j** (0.0678 g, 0.148 mmol, 1.0 equiv) and Hoveyda-Grubbs catalyst 2 (0.0046 g, 0.0074 mmol, 0.05 equiv) in DCE (60 mL = 0.003 M) at 80 °C for 5 h afforded after chromatography (1/7-1/3 EtOAc/hexanes) the title compound as oil (R_f = 0.68, 1/1 EtOAc/hexanes). Yield 76% (0.0482 g, 0.112 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers) δ 1.21 (m, 0.9H), 1.36 (m, 0.5H), 1.43-1.66 (m, 1.1H), 1.78-2.06 (m, 2.1H), 2.15-2.33 (m, 1.1H), 2.50 (dd, *J* = 3.4, 14.0 Hz, 0.6H), 2.94-3.02 (m, 0.4H), 3.17 (t, *J* = 12.5 Hz, 0.5H), 3.31-3.44 (m, 1.6H), 3.48-3.70 (m, 1.2H), 3.67 (s, 3H), 3.94-4.10 (m, 1H), 4.31-4.42 (m, 1H), 5.34 (dt, *J* = 4.6, 11.8 Hz, 0.6H), 5.47 (dt, *J* = 4.6, 11.6 Hz, 0.6H), 5.60 (dt, *J* = 4.7, 11.6 Hz, 0.4H), 5.81 (dt, *J* = 4.6, 12.1 Hz, 0.4H), 7.25-7.40 (m, 6H), 7.64-7.75 (m, 3H), 8.06-8.13 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of rotamers) δ 18.9, 19.6, 28.8, 29.1, 29.3, 30.0, 30.4, 33.0, 41.9, 45.2, 52.1, 52.2, 52.3, 52.5, 124.3, 126.0, 126.1, 126.3, 126.3, 127.2, 128.6, 131.3, 131.6, 132.6, 133.2, 133.3, 133.5, 140.8, 142.2, 148.0, 175.6, 175.7; IR (neat) 2951, 1726, 1543, 1371, 1354, 1340, 1219, 1161 cm^{-1}; HRMS calcd for $C_{23}H_{26}N_2O_6SNa$ (M^+ + Na) 481.1409, found 481.1408.

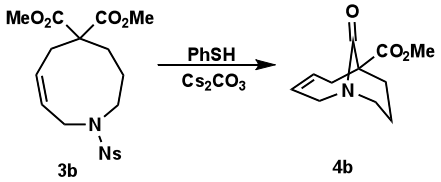


3k

(Z)-Phenyl 1-(2-nitrophenylsulfonyl)-6-phenyl-1,2,3,4,5,6,7,10-octahydroazecine-6-carboxylate (3k). According to the procedure for **3h**, the reaction of **2k** (0.0397 g, 0.0723 mmol, 1.0 equiv) and Hoveyda-Grubbs catalyst 2 (0.0023 g, 0.0036 mmol, 0.05 equiv) in DCE (61 mL = 0.0012 M) at 80 °C for 13 h afforded after chromatography (1/7-1/41/2 EtOAc/hexanes) the title compound as oil (R_f = 0.50, 1/2 EtOAc/hexanes). Yield 60% (0.0227 g, 0.044 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers) δ 1.25-1.45 (m, 1H), 1.55 (m, 1H), 1.70-1.95 (m, 2H), 2.09 (m, 1H), 2.39 (m, 1H), 2.57 (dd, *J* = 3.6, 13.7 Hz, 0.6H), 3.11-319 (m, 0.4H), 3.26-3.49 (m, 2H), 3.52-3.58 (m, 0.4H), 3.62-3.70 (m, 0.6H), 3.99 (dd, *J* = 4.8, 14.2 Hz, 0.6H), 4.06-4.13 (m, 0.4H), 4,40 (m, 1H), 5.40 (dd, *J* = 4.8, 12.0 Hz, 0.6H), 5.52 (dd, *J* = 4.9, 11.4 Hz, 0.6H), 5.69 (dd, *J* = 4.6, 11.2 Hz, 0.4H), 5.95-6.03 (m, 0.4H), 6.93 (t, *J* = 8.2 Hz, 2H), 7.22 (t, *J* = 7.5 Hz, 1H), 7.30-7.52 (m, 7H), 7.64-7.76 (m, 3H), 8.08-8.14 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of rotamers) δ 18.9, 19.7, 28.7, 29.1, 29.3, 29.7, 30.0, 30.4, 33.0, 41.9, 42.0, 45.2, 52.4, 52.6, 121.3, 124.3, 125.9, 126.1, 126.3, 126.8, 127.4, 128.8, 129.4, 131.3, 131.7, 132.4, 132.9, 133.1, 133.5, 140.3, 141.7, 148.0, 150.8, 173.7; IR (neat) 2916, 1745, 1542, 1371, 1340, 1194, 1163 cm^{-1}; HRMS calcd for $C_{28}H_{28}N_2O_6SNa$ (M^+ + Na) 543.1565, found 543.1565.

Transannular Cyclization Reactions

Scheme I. *Synthesis of Compound **4b** (Scheme 2).*

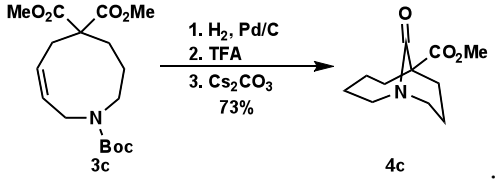


3b 4b

Methyl 10-oxo-1-azabicyclo[4.3.1]dec-3-ene-6-carboxylate (4b). To a solution of **3b** (0.0206 g, 0.0484 mmol, 1.0 equiv) and Cs_2CO_3 (0.088 g, 0.27 mmol, 5.5 equiv) in CH_3CN (5 mL), thiophenol (0.0297 g, 0.27 mmol, 5.5 equiv) was added, and the resulting mixture was heated at 55-60 °C for 2.5 h. Solvent was removed under reduced pressure, and the reaction was analyzed by ^{1}H NMR Yield 89% (vs. 2-nitrophenylphenylsulfide). Purification by PTLC (1:1 EtOAc/hexanes) afforded the title compound as oil (R_f = 0.57, 1/1 EtOAc/hexanes). Yield 54% (0.0055 g, 0.0263 mmol). Note: the compound is unstable on silica. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.78-1.88 (m, 2H), 1.93-2.02 (m, 1H), 2.32-2.40 (m, 1H), 2.50-2.56 (m, 1H), 3.03-3.11 (m, 1H), 3.19 (m, 1H), 3.29-3.37 (m, 1H), 3.41-3.48 (m, 1H), 3.80 (s, 3H), 3.40-3.48 (m, 1H), 5.55-5.62 (m, 1H), 5.67-5.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 34.2, 35.4, 50.4,

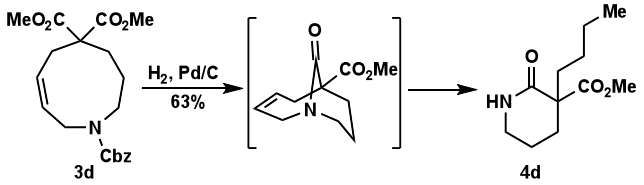
52.7, 54.9, 59.5, 126.6, 126.7, 172.8, 181.9; IR (neat) 2916, 1739, 1683, 1458, 1437, 1242, 1182, 1116 cm^{-1}; HRMS calcd for $C_{11}H_{15}NO_3Na$ (M^+ + Na) 232.0949, found 232.0951.

Scheme J. *Synthesis of Compound **4c** (Scheme 3, top).*



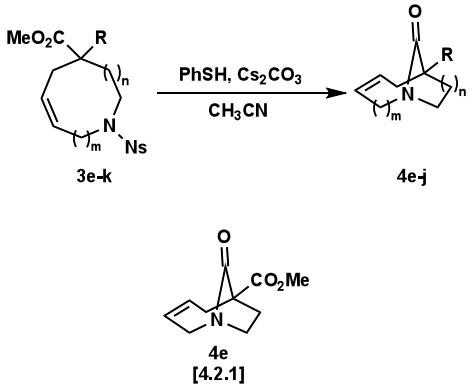
Methyl 10-oxo-1-azabicyclo[4.3.1]decane-6-carboxylate (4c). A 10 mL round-bottom flask charged with **3c** (0.0245 g, 0.072 mmol, 1.0 equiv), EtOAc (5 mL) and Pd/C (5%, ca. 50 mg) was stirred under H_2 balloon for 22 h at rt. The reaction mixture was filtered through a pad of celite and concentrated. The residue was taken in 8 mL of DCM and 3 mL of TFA was added at rt After stirring for 2 h at rt, the solvent was removed under reduced pressure, CH_3CN was added, followed by Cs_2CO_3 (0.47 g, 1.44 mmol, 20 equiv), and the reaction mixture was stirred at 60 °C for 3 h. Solvent removal, followed by chromatography (1/2-1/1 EtOAc/hexanes) afforded the title compound as oil (R_f = 0.72, 1/1 EtOAc/hexanes). Yield 73% (0.0111 g, 0.053 mmol). Note: in contrast to **18**, the compound is stable on silica. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.64-1.97 (m, 8H), 2.41-2.55 (m, 2H), 2.77-2.84 (m, 1H), 3.30-3.37 (m, 1H), 3.44 (dt, *J* = 4.0, 11.2 Hz, 1H), 3.79 (s, 3H), 3.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 23.7, 26.3, 32.4, 35.4, 49.1, 50.2, 52.5, 58.6, 173.3, 181.0; IR (neat) 2945, 1737, 1680, 1444, 1255, 1240, 1176 cm^{-1}; HRMS calcd for $C_{11}H_{17}NO_3Na$ (M^+ + Na) 234.1106, found 234.1105.

Scheme K. *Synthesis of Compound **4d** (Scheme 3, bottom).*

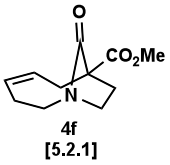


Methyl 3-butyl-2-oxopiperidine-3-carboxylate (4d). A 10 mL round-bottom flask charged with **3d** (0.0140 g, 0.0373 mmol, 1.0 equiv), MeOH (5 mL) and Pd/C (5%, ca. 30 mg) was stirred under H_2 balloon for 24 h at rt. The reaction mixture was filtered through a pad of celite and concentrated. Purification by chromatography (EtOAc-1/4 MeOH/EtOAc) afforded the title compound as oil (R_f = 0.37, EtOAc). Yield 63% (0.0050 g, 0.024 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, *J* = 7.0 Hz, 3H), 1.14-1.39 (m, 4H), 1.79-2.04 (m, 5H), 2.19-2.27 (m, 1H), 3.36 (m, 2H), 3.76 (s, 3H), 5.83 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 19.8, 23.1, 26.7, 29.5, 35.4, 42.5, 52.6, 54.0, 170.9, 173.5; IR (neat) 3209, 2954, 1734, 1668, 1558, 1489, 1456, 1197 cm^{-1}; HRMS calcd for $C_{11}H_{20}NO_3$ (M^+ + Na) 214.1443, found 214.1440.

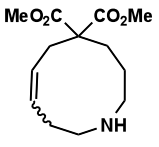
Scheme L. *Synthesis of Compounds **4e-k** (Table 2, Step 2).*



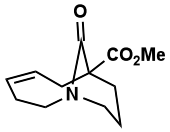
Methyl 9-oxo-1-azabicyclo[4.2.1]non-3-ene-6-carboxylate (4e). According to the procedure for **4b**, the reaction of **3e** (0.0190 g, 0.046 mmol, 1.0 equiv), Cs_2CO_3 (0.15 g, 0.46 mmol, 10 equiv), PhSH (0.0254 g, 0.23 mmol, 5.0 equiv) in CH_3CN (5 mL) at 60 °C for 2 h afforded the title compound in 92 % yield (^{1}H NMR, vs. 2-nitrophenylphenylsulfide) and in 75% yield (0.0067 g, 0.034 mmol) after purification by PTLC (1:1 EtOAc/hexanes) (R_f = 0.57, 1/1 EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.03 (dd, *J* = 7.9, 12.5 Hz, 1H), 2.16-2.24 (m, 1H), 2.60-2.70 (m, 1H), 2.92-3.01 (m, 1H), 3.08-3.18 (m, 1H), 3.32-3.39 (m, 1H), 3.53 (t, *J* = 9.4 Hz, 1H), 3.81 (s, 3H), 4.24-4.33 (m, 1H), 5.38 (dp, *J* = 3.0, 12.7 Hz, 1H), 5.63-5.71 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.8, 32.1, 46.8, 52.1, 52.7, 57.1, 122.6, 127.6, 171.1, 183.8; IR (neat) 2952, 1739, 1720, 1437, 1242, 1197, 1134 cm^{-1}; HRMS calcd for $C_{10}H_{13}NO_3Na$ (M^+ + Na) 218.0793, found 218.0785.



Methyl 10-oxo-1-azabicyclo[5.2.1]dec-4-ene-7-carboxylate (4f). According to the procedure for **4b**, the reaction of **3f** (0.0213 g, 0.050 mmol, 1.0 equiv), Cs_2CO_3 (0.16 g, 0.50 mmol, 10 equiv), PhSH (0.0275 g, 0.25 mmol, 5.0 equiv) in CH_3CN (5 mL) at 60 °C for 13 h afforded the title compound after chromatography (1/2-1/1 EtOAc/hexanes) as oil (R_f = 0.39, 1/1 EtOAc/hexanes). Yield 85% (0.00890 g, 0.043 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.94-2.02 (m, 1H), 2,12 (ddd, *J* = 2.4, 8.0, 10.5 Hz, 1H), 2.50-2.77 (m, 3H), 2.96 (dd, *J* = 6.0, 14.3 Hz, 1H), 3.04-3.14 (m, 1H), 3.57-3.67 (m, 2H), 3.73-3.81 (m, 4H), 5.77-5.93 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.5, 26.5, 33.8, 43.4, 49.8, 52.6, 60.1, 129.1, 132.7, 171.3, 180.2; IR (neat) 2949, 1737, 1697, 1456, 1400, 1251, 1194 cm^{-1}; HRMS calcd for $C_{11}H_{16}NO_3$ (M^+ + H) 210.1130, found 210.1128.



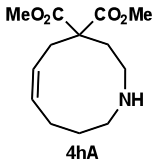
4gA



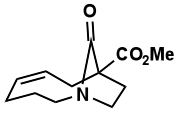
4g
[5.3.1]

Dimethyl 1,2,3,4,9,10-hexahydroazecine-5,5(6H)-dicarboxylate (4gA). According to the procedure for **4b**, the reaction of **3g** (0.104 g, 0.24 mmol, 1.0 equiv), Cs_2CO_3 (0.78 g, 2.4 mmol, 10 equiv), PhSH (0.13 g, 1.2 mmol, 5.0 equiv) in CH_3CN (12 mL) at 60 °C for 30 min afforded the title compound (5:1 mixture of Z/E isomers) after chromatography (0/0/100-1/4/95-1/9/90 NH_4OH/MeOH/DCM) as oil (R_f = 0.19, 1/9/90 NH_4OH/MeOH/DCM). Yield 99% (0.0614 g, 0.24 mmol). ^1H NMR (400 MHz, $CDCl_3$) (5:1 mixture of Z/E isomers) δ 1.50 (m, 2H), 2.00 (m, 2H), 2.11 (s, 1H), 2.52-2.59 (m, 1H), 2.80 (m, 4H), 2.97-3.19 (m, 2H), 3.76 (s, 6H), 5.38-5.48 (m, 1H, Z isomer), 5.56-5.65 (m, 1H), 5.75 (dt, *J* = 7.3, 21.5 Hz, 1H, E isomer); ^{13}C NMR (100 MHz, $CDCl_3$) (Z isomer) δ 23.9, 25.4, 27.8, 29.7, 46.3, 46.9, 52.6, 56.4, 126.7, 131.4, 171.9; IR (neat) 2951, 1732, 1437, 1269, 1248, 1205, 1180, 1138 cm^{-1}; HRMS calcd for $C_{13}H_{21}NO_4Na$ (M^+ + Na) 278.1368, found 278.1369.

Methyl 11-oxo-1-azabicyclo[5.3.1]undec-4-ene-7-carboxylate (4g). 10 mL MW vial (Biotage) was charged with amine **4gA** (0.0198 g, 0.078 mmol, 1.0 equiv), toluene (3.0 mL), and DBU (0.12 g, 0.78 mmol, 10 equiv). The vial was sealed with metal septum, placed in an oil bath preheated to 200 °C and stirred for 3 h. The reaction was cooled to rt, solvent was removed under vacuum and the residue was purified by chromatography (1/1 EtOAc/hexanes) to afford the title compound as oil (R_f = 0.67, 1/1 EtOAc/hexanes). Yield 65% (0.0093 g, 0.042 mmol out of possible 0.065 mmol). ^1H NMR (400 MHz, $CDCl_3$) δ 1.84-1.96 (m, 3H), 2.04-2.12 (m, 1H), 2.21-2.26 (m, 1H), 2.50-2.66 (m, 2H), 2.75-2.86 (m, 2H), 3.24-3.31 (m, 1H), 3.54-3.61 (m, 1H), 3.78 (s, 3H), 4.05 (dt, *J* = 4.6, 13.4 Hz, 1H), 5.80-5.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 24.5, 29.9, 36.4, 46.9, 50.4, 52.3, 60.7, 129.8, 132.3, 173.1, 177.3; IR (neat) 2928, 1739, 1653, 1452, 1329, 1248, 1192, 1118 cm^{-1}; HRMS calcd for $C_{12}H_{18}NO_3$ (M^+ + H) 224.1287, found 224.1279.



4hA

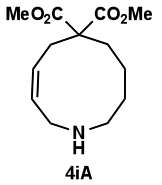


4h
[6.2.1]

(Z)-Dimethyl 2,3,5,8,9,10-hexahydroazecine-4,4(1H)-dicarboxylate (4hA). According to the procedure for **4gA**, the reaction of **3h** (0.0329 g, 0.075 mmol, 1.0 equiv), Cs_2CO_3 (0.24 g, 0.75 mmol, 10 equiv), PhSH (0.041 g, 0.37 mmol, 5.0 equiv) in CH_3CN (6 mL) at 60 °C for 1 h afforded the title compound after chromatography (0/0/100-1/4/95-1/9/90 NH_4OH/MeOH/DCM) as oil (R_f = 0.64, 1/9/90 NH_4OH/MeOH/DCM). Yield 98% (0.0187 g, 0.073 mmol). ^1H NMR (400 MHz, $CDCl_3$) δ 1.35-1.60 (m, 2H), 1.72-1.88 (m, 2H), 2.23 (t, *J* = 12.5, 1H), 2.44 (m, 2H), 2.56-2.68

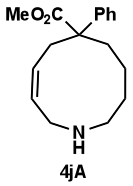
(m, 2H), 2.77 (m, 2H), 3.75 (s, 6H), 3.98 (t, *J* = 13.4 Hz, 1H), 5.19-5.26 (m, 1H), 5.41-5.51 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2, 26.2, 27.2, 31.4, 41.7, 44.9, 52.5, 58.1, 126.2, 131.2, 172.1, 172.7; IR (neat) 3352, 2918, 1732, 1437, 1228, 1182, 1126 cm^{-1}; HRMS calcd for $C_{13}H_{22}NO_4$ (M^+ + H) 256.1549, found 256.1545.

Methyl 11-oxo-1-azabicyclo[6.2.1]undec-5-ene-8-carboxylate (4h). According to the procedure for **4g**, the reaction of **4hA** (0.0100 g, 0.0392 mmol, 1.0 equiv) and DBU (0.12 g, 0.78 mmol, 20 equiv) in toluene (3.0 mL) at 180 °C for 12 h afforded the title compound after chromatography (1/1 EtOAc/hexanes) as oil (R_f = 0.33, 1/1 EtOAc/hexanes). Yield 44% (0.0038 g, 0.017 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.81-2.03 (m, 3H), 2.11 (ddd, *J* = 1.4, 8.6, 13.1 Hz, 1H), 2.18-2.31 (m, 1H), 2.45-2.55 (m, 1H), 2.61-2.69 (m, 1H), 2.85-2.92 (m, 2H), 3.22 (dt, *J* = 1.4, 9.2 Hz, 1H), 3.50 (q, *J* = 8.6 Hz, 1H), 3.79 (s, 3H), 3.22 (dt, *J* = 6.1, 13.6 Hz, 1H), 5.57-5.68 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.1, 24.4, 29.0, 32.5, 41.8, 45.7, 52.7, 55.4, 122.2, 138.6, 172.4, 177.1; IR (neat) 2925, 1735, 1685, 1456, 1431, 1257, 1205, 1116, 1077 cm^{-1}; HRMS calcd for $C_{12}H_{18}NO_3$ (M^+ + H) 224.1287, found 224.1288.

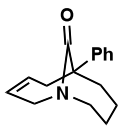


4iA

(Z)-Dimethyl 1,2,7,8,9,10-hexahydroazecine-6,6(5H)-dicarboxylate (4iA). According to the procedure for **4gA**, the reaction of **3i** (0.0444 g, 0.10 mmol, 1.0 equiv), Cs_2CO_3 (0.32 g, 1.0 mmol, 10 equiv), PhSH (0.056 g, 0.50 mmol, 5.0 equiv) in CH_3CN (6 mL) at 60 °C for 45 min afforded the title compound after chromatography (0/0/100-1/4/95-1/9/90 NH_4OH/MeOH/DCM) as oil (R_f = 0.44, 1/9/90 NH_4OH/MeOH/DCM). Yield 99% (0.027 g, 0.10 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33-1.58 (m, 3H), 1.64 (m, 1H), 1.96 (m, 3H), 2.50 (s, 1H), 2.71 (s, 1H), 2.95 (s, 1H), 3.18-3.42 (m, 2H), 3.76 (s, 6H), 3.84 (m, 1H), 5.40-5.48 (m, 1H), 5.60-5.68 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 26.7, 29.1, 29.3, 40.3, 44.7, 52.5, 56.4, 127.8, 132.2, 172.1; IR (neat) 2951, 1732, 1456, 1435, 1286, 1203, 1178 cm^{-1}; HRMS calcd for $C_{13}H_{21}NO_4Na$ (M^+ + Na) 278.1368, found 278.1363. Note: attempted heating of **4iA** with various bases at temperatures ranging from 110-220 °C led only to decomposition products.



4jA



4j
[4.4.1]

(Z)-Methyl 6-phenyl-1,2,3,4,5,6,7,10-octahydroazecine-6-carboxylate (4jA). According to the procedure for **4gA**, the reaction of **3j** (0.0277 g, 0.064 mmol, 1.0 equiv), Cs_2CO_3 (0.21 g, 0.64 mmol, 10 equiv), PhSH (0.0354 g, 0.32 mmol, 5.0 equiv) in

CH_3CN (6 mL) at 60 °C for 1 h afforded the title compound after chromatography (0/0/100-1/4/95-1/9/90 NH_4OH/MeOH/DCM) as oil (R_f = 0.46, 1/9/90 NH_4OH/MeOH/DCM). Yield 98% (0.0154 g, 0.063 mmol). ^1H NMR (400 MHz, $CDCl_3$) (mixture of rotamers) δ 1.22-1.42 (m, 1H), 1.45-1.82 (m, 3H), 1.98-2.22 (m, 3H), 2.42 (dd, *J* = 4.0, 14.0 Hz, 0.5H), 2.64-2.78 (m, 1H), 2.86 (m, 0.5H), 3.05 (q, *J* = 11.5 Hz, 1H), 3.22-3.38 (m, 1.5H), 3.47 (t, *J* = 13.4, 0.6H), 3.67 (s, 3H), 3.91 (t, *J* = 10.7 Hz, 0.9H), 5.06-5.19 (m, 0.6H), 5.48-5.72 (m, 1.4H), 7.23-7.41 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of rotamers) δ 19.9, 20.7, 28.0, 29.5, 29.7, 29.9, 30.4, 33.4, 40.5, 45.0, 52.1, 52.3, 52.8, 125.9, 126.2, 126.4, 126.8, 128.2, 128.4, 129.0, 129.7, 131.2, 131.6, 141.7, 142.9, 176.2; IR (neat) 2945, 2917, 1727, 1446, 1433, 1221, 1180, 1138 cm^{-1}; HRMS calcd for $C_{17}H_{24}NO_2$ (M^+ + H) 274.1807, found 274.1816.

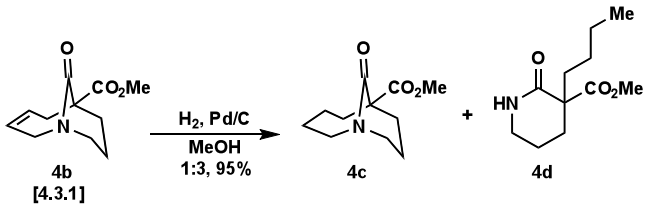
6-Phenyl-1-azabicyclo[4.4.1]undec-3-en-11-one (4j). From 4jA. According to the procedure for **4g**, the reaction of **4jA** (0.0042 g, 0.0171 mmol, 1.0 equiv) and DBU (0.052 g, 0.34 mmol, 20 equiv) in toluene (3.0 mL) at 220 °C for 10 h afforded the title compound after chromatography (1/2 EtOAc/hexanes) as a white film (R_f = 0.39, 1/1 EtOAc/hexanes). Yield 34% (0.0014 g, 0.0058 mmol). ^1H NMR (400 MHz, $CDCl_3$) δ 1.75-1.89 (m, 2H), 1.92-2.03 (m, 3H), 2.16 (dd, *J* = 7.7, 14.4 Hz, 1H), 2.22-2.29 (m, 1H), 2.76-2.85 (m, 1H), 3.02-3.11 (m, 1H), 3.66-3.71 (m, 1H), 3.85-3.99 (m, 2H), 5.88-5.96 (m, 1H), 6.12-6.22 (m, 1H), 7.21-7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 25.2, 33.3, 39.4, 49.7, 51.7, 63.8, 126.4, 126.9, 128.0, 128.3, 133.0, 146.0, 186.2; IR (neat) 2924, 2854, 1653, 1444, 1290, 1236, 1186, 1149 cm^{-1}; HRMS calcd for $C_{16}H_{20}NO$ (M^+ + H) 242.1545, found 242.1546. Note: no conversion was observed at temperatures lower than 220 °C.

6-Phenyl-1-azabicyclo[4.4.1]undec-3-en-11-one (4j). From 3k. To a solution of **3k** (0.0187 g, 0.0359 mmol, 1.0 equiv) and Cs_2CO_3 (0.12 g, 0.35 mmol, 10 equiv) in CH_3CN (6 mL), thiophenol (0.0197 g, 0.18 mmol, 5 equiv) was added, and the resulting mixture was heated at 60 °C for 2 h. Solvent was removed under reduced pressure, the residue was taken in toluene (10 mL), and DBU (0.10 mL, 0.70 mmol, 20 equiv) was added. The reaction mixture was heated at 110 °C for 16 h, solvent was removed under reduced pressure, and the residue was purified by chromatography (1/6-1/4 EtAc/hexanes) to give the title compound. Yield 86% (0.0074 g, 0.031 mmol).

Hydrogenolysis of Twisted Amides

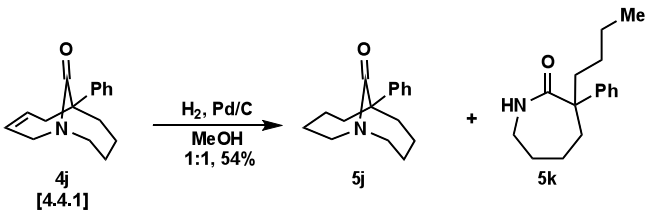
General procedure: To a solution of twisted amides in MeOH (5 mL), Pd/C (5%), ca. 30-40 mg was added, and the reaction was stirred under H_2 ballon at rt. Filtration through cotton or celite pad, followed by chromatography afforded the products.

Scheme M. *Hydrogenolysis of Compound **4b** (Table 3, entry 1).*



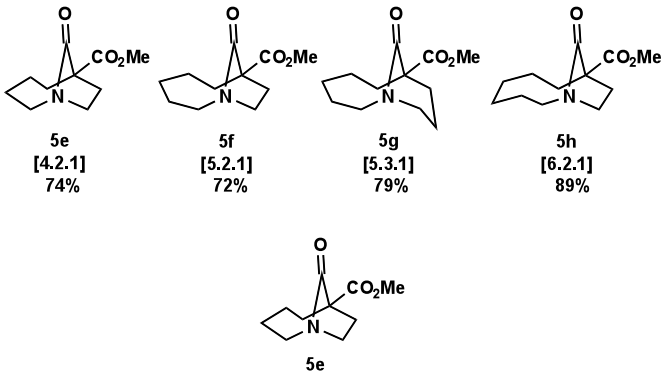
Methyl 10-oxo-1-azabicyclo[4.3.1]decane-6-carboxylate (4c) and Methyl 3-butyl-2-oxopiperidine-3-carboxylate (4d). According to the general procedure, the reaction of **4b** (0.0042 g, 0.0020 mmol, 1.0 equiv) and Pd/C (5%) (ca. 25 mg) in MeOH (4 mL) for 22 h at rt afforded 1:3 mixture of **4c** and **4d** (0.0040 g, 0.0190 mmol). Yield 95%. Spectroscopic properties matched those previously described.

Scheme N. *Hydrogenolysis of Compound **4j** (Table 3, entry 2).*

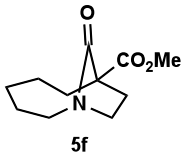


6-Phenyl-1-azabicyclo[4.4.1]undecan-11-one (5j) and 3-Butyl-3-phenylazepan-2-one (5k). According to the general procedure, the reaction of **4j** (0.0105 g, 0.0044 mmol, 1.0 equiv) and Pd/C (5%) (ca. 40 mg) in MeOH (6 mL) for 18 h at rt afforded 1.1:1.0 mixture of **5j** and **5k** (0.0057 g, 0.0240 mmol). Yield 54%. Further purification by PTLC (1/1 EtOAc/hexanes) afforded analytical samples of **5j** and **5k**. Compound **5j**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.73-1.93 (m, 8H), 1.95-2.04 (m, 2H), 2.17-2.25 (m, 2H), 3.10-3.18 (m, 2H), 3.54 (ddd, J = 3.8, 6.4, 10.0 Hz, 2H), 7.21-7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2, 25.5, 35.5, 50.3, 59.9, 126.1, 127.3, 127.9, 145.0, 186.3; IR (neat) 2951, 2910, 1643, 1492, 1437, 1413, 1302, 1219 cm^{-1}; HRMS calcd for $C_{16}H_{21}NONa$ (M^+ + Na) 266.1521, found 266.1523. Compound **5k**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (t, J = 7.3 Hz, 3H), 1.03-1.13 (m, 1H), 1.17-1.32 (m, 3H), 1.36-1.46 (m, 1H), 1.62-1.98 (m, 6H), 2.31 (dt, J = 2.5, 14.0 Hz, 1H), 2.62-2.72 (m, 1H), 2.80-2.88 (m, 1H), 5.93 (s, 1H), 7.21-7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 23.3, 24.8, 27.4, 29.0, 33.0, 41.8, 44.9, 53.9, 126.2, 127.2, 128.4, 141.2, 179.4; IR (neat) 3284, 3219, 2929, 2858, 1654, 1465, 1446, 1363, 1280 cm^{-1}; HRMS calcd for $C_{16}H_{24}NO$ (M^+ + H) 246.1858, found 246.1852.

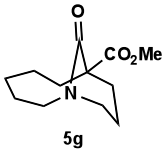
Scheme O. *Synthesis of Compounds **5e-h** (Table 3, entry 3).*



Methyl 9-oxo-1-azabicyclo[4.2.1]nonane-6-carboxylate (5e). According to the general procedure, the reaction of **4e** (0.0042 g, 0.022 mmol, 1.0 equiv) and Pd/C (5%) (ca. 30 mg) in MeOH (5 mL) for 18 h at rt afforded **5e** (0.0031 g, 0.016 mmol). Yield 74%. (R_f = 0.39, 1/1 EtOAc/hexanes) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.71-1.92 (m, 4H), 2.02 (ddd, *J* = 1.3, 8.6, 9.9 Hz, 1H), 2.34 (m, 1H), 2.57-2.67 (m, 1H), 2.77-2.85 (m, 1H), 3.17-3.26 (m, 1H), 3.58 (t, *J* = 9.6 Hz, 1H), 3.68-3.78 (m, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9, 24.3, 28.6, 32.4, 47.1, 48.6, 52.6, 57.1, 171.7, 183.4; IR (neat) 2924, 1739, 1716, 1458, 1437, 1282, 1186, 1123 cm^{-1}; HRMS calcd for $C_{10}H_{16}NO_3$ (M^+ + H) 198.1130, found 198.1126.

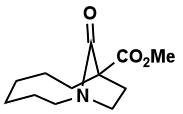


Methyl 10-oxo-1-azabicyclo[5.2.1]decane-7-carboxylate (5f). According to the general procedure, the reaction of **4f** (0.0070 g, 0.033 mmol, 1.0 equiv) and Pd/C (5%) (ca. 40 mg) in MeOH (5 mL) for 18 h at rt afforded **5f** (0.0050 g, 0.024 mmol). Yield 72%. (R_f = 0.39, 1/1 EtOAc/hexanes) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36-1.55 (m, 2H), 1.68-1.84 (m, 2H), 1.96-2.15 (m, 4H), 2.42-2.52 (m, 1H), 2.62-2.71 (m, 1H), 2.93 (dd, *J* = 5.4, 13.8 Hz, 1H), 3.44 (dt, *J* = 1.6, 10.3 Hz, 1H), 3.66 (q, *J* = 9.0 Hz, 1H), 3.78 (s, 3H), 4.18 (dt, *J* = 4.8, 13.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.3, 24.5, 26.3, 31.8, 41.7, 44.0, 44.9, 52.5, 54.8, 172.4, 180.1; IR (neat) 2931, 1739, 1693, 1435, 1418, 1271, 1248, 1195 cm^{-1}; HRMS calcd for $C_{11}H_{18}NO_3$ (M^+ + H) 212.1287, found 212.1288.



Methyl 11-oxo-1-azabicyclo[5.3.1]undecane-7-carboxylate (5g). According to the general procedure, the reaction of **4g** (0.0089 g, 0.040 mmol, 1.0 equiv) and Pd/C

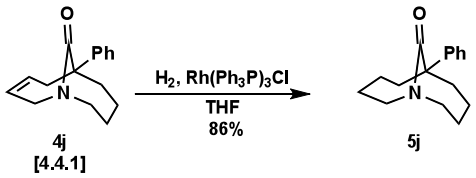
(5%) (ca. 50 mg) in MeOH (5 mL) for 24 h at rt afforded **5g** (0.0071 g, 0.032 mmol). Yield 79%. (R_f = 0.32, 1/1 EtOAc/hexanes) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40-1.59 (m, 2H), 1.70-1.83 (m, 3H), 1.88-2.16 (m, 6H), 2.43 (t, *J* = 12.4 Hz, 1H), 2.75 (dd, *J* = 4.8, 13.6 Hz, 1H), 3.27-3.33 (m, 1H), 3.68 (dt, *J* = 3.2, 11.7 Hz, 1H), 3.75 (s, 3H), 4.62 (dt, *J* = 4.0, 13.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 23.2, 24.8, 31.0, 32.4, 43.7, 48.2, 49.3, 52.2, 54.5, 174.1, 176.6; IR (neat) 2929, 1743, 1647, 1491, 1444, 1244, 1192, 1122 cm^{-1}; HRMS calcd for $C_{12}H_{20}NO_3$ (M^+ + H) 226.1443, found 226.1440.



5h

Methyl 11-oxo-1-azabicyclo[6.2.1]undecane-8-carboxylate (5h). According to the general procedure, the reaction of **4h** (0.0056 g, 0.025 mmol, 1.0 equiv) and Pd/C (5%) (ca. 40 mg) in MeOH (5 mL) for 16 h at rt afforded **5h** (0.0050 g, 0.022 mmol). Yield 89%. (R_f = 0.33, 1/1 EtOAc/hexanes) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11-1.21 (m, 1H), 1.26-1.38 (m, 1H), 1.42-1.52 (m, 1H), 1.71-1.90 (m, 6H), 2.02 (ddd, *J* = 2.1, 9.1, 13.3 Hz, 1H), 2.20 (t, *J* = 11.5 Hz, 1H), 2.67-2.77 (m, 1H), 2.86-2.93 (m, 1H), 3.45 (dt, *J* = 2.0, 10.6 Hz, 1H), 3.74 (q, *J* = 9.2 Hz, 1H), 3.78 (s, 3H), 3.94-4.02 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 23.6, 25.9, 26.0, 27.5, 36.4, 43.3, 46.2, 52.5, 55.3, 172.9, 173.4; IR (neat) 2924, 1737, 1685, 1458, 1437, 1255, 1120 cm^{-1}; HRMS calcd for $C_{12}H_{20}NO_3$ (M^+ + H) 226.1443, found 226.1439.

Scheme P. *Hydrogenolysis of Compound **4j** in the presence of Willkinson's catalyst (Table 3, entry 4).*



4j [4.4.1] 5j

To a solution of **4j** (0.0074 g, 0.031 mmol, 1.0 equiv) in THF (5 mL), $Rh(PPh_3)_3Cl$ (0.0284 g, 0.031 mmol, 1.0 equiv) was added under nitrogen. H_2 atmosphere was established, H_2 was bubbled through the solution for ca. 30 s, and the reaction was stirred under H_2 balloon for 19 h. Solvent was removed under reduced pressure, and the residue was purified by chromatography to give the title compound (0.0065 g, 0.027 mmol) in 86% yield. Spectroscopic properties matched those previously described.

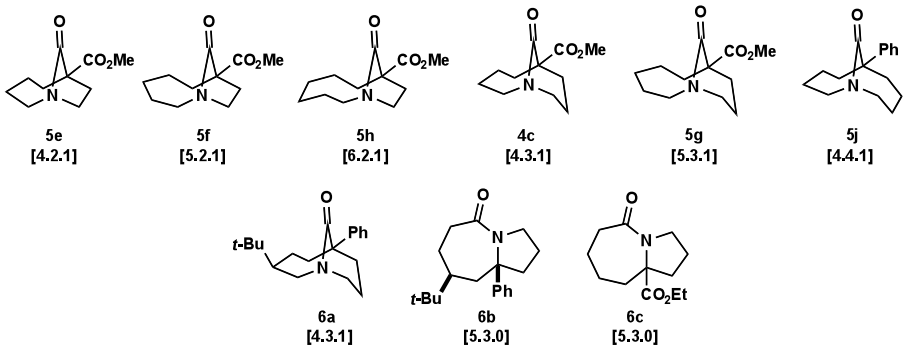
.

Comparison of Spectroscopic Properties of Twisted Amides

Table 4 including three additional examples (entries 7, 8 and 9)[7,8] to allow comparison between ester and phenyl substituents in α position of bridged amides (entries 4, 6 and 7), and between bridged and fused amides (entries 4, 6, 8 and 9).

Table 4. *Spectroscopic properties of saturated lactams.*

Entry	Lactam	Ring system	Lactam C=O ^{13}C [ppm]	Lactam IR νC=O [cm^{-1}]
1	**5e**	[4.2.1]	183.4	1716
2	**5f**	[5.2.1]	180.1	1693
3	**5h**	[6.2.1]	173.4	1685
4	**4c**	[4.3.1]	181.0	1679
5	**5g**	[5.3.1]	176.6	1647
6	**5j**	[4.4.1]	186.3	1643
7	**6a**	[4.3.1]	184.4	1668
8	**6b**	[5.3.0]	172.4	1635
9	**6c**	[5.3.0]	173.2	1630



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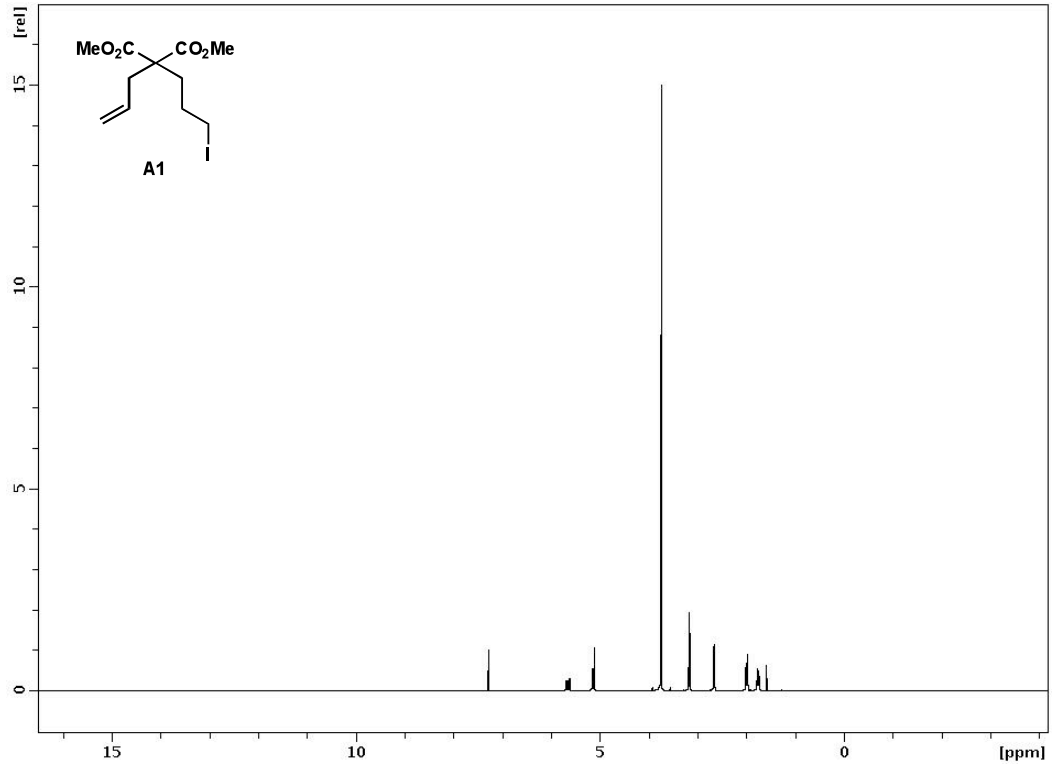
8. Milligan, G. L.; Mossman, C. J.; Aubé, J. *J. Am. Chem. Soc.*, **1995**, *117*, 10449-10459.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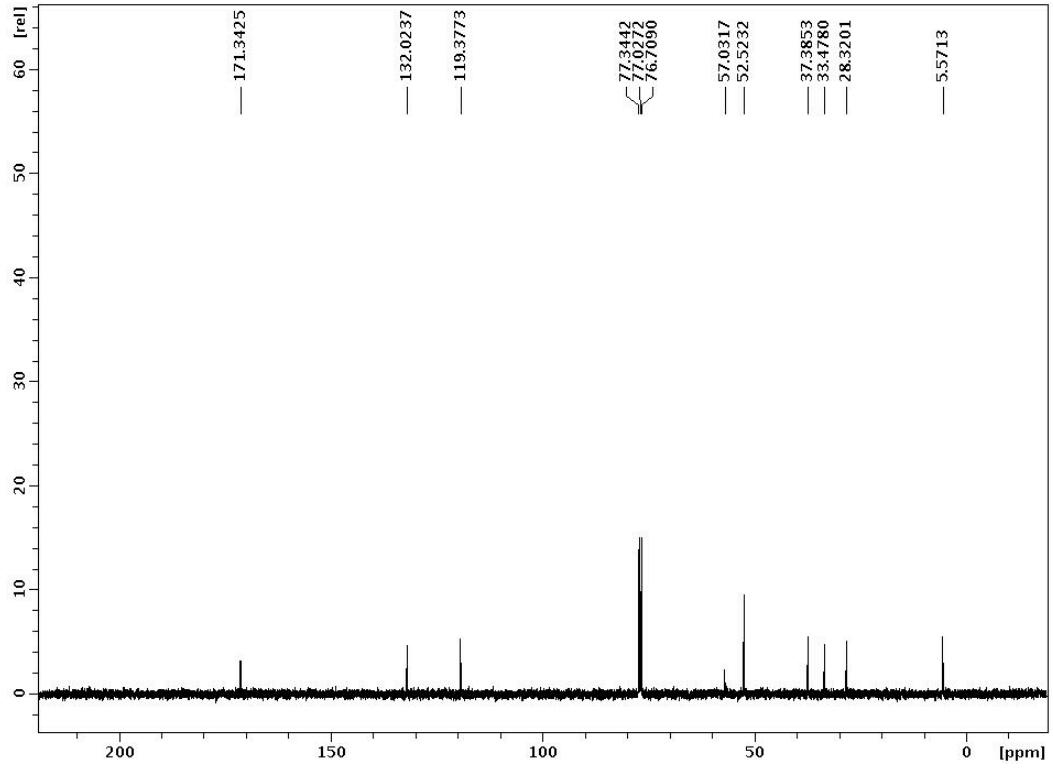
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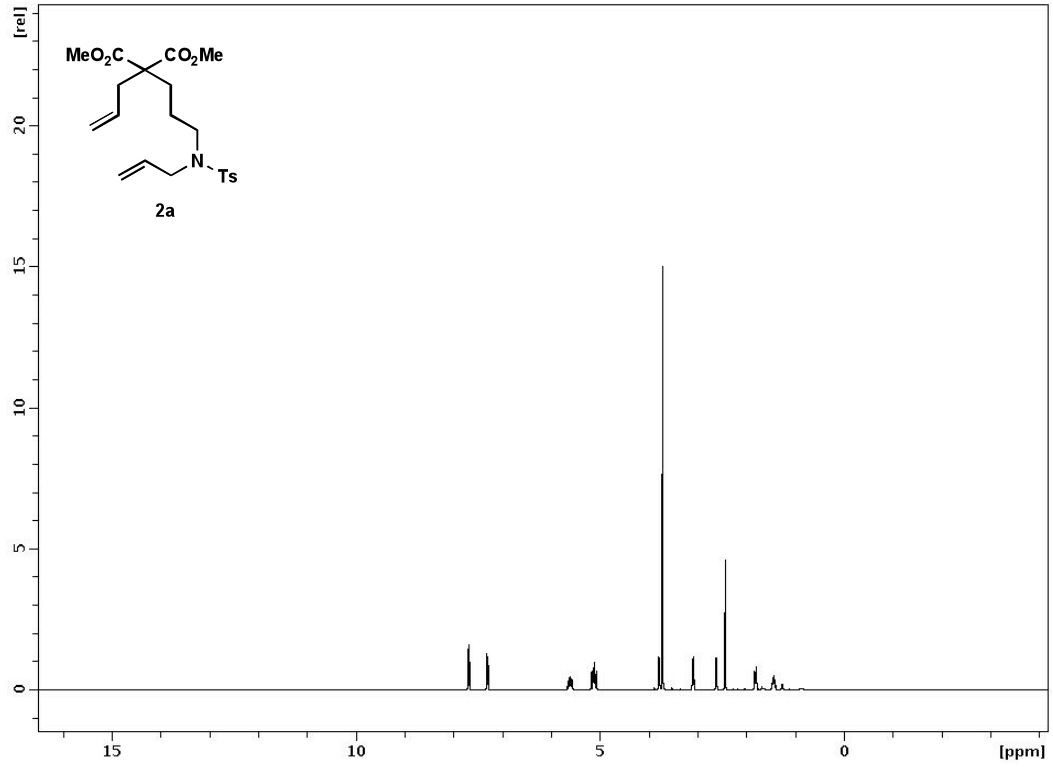
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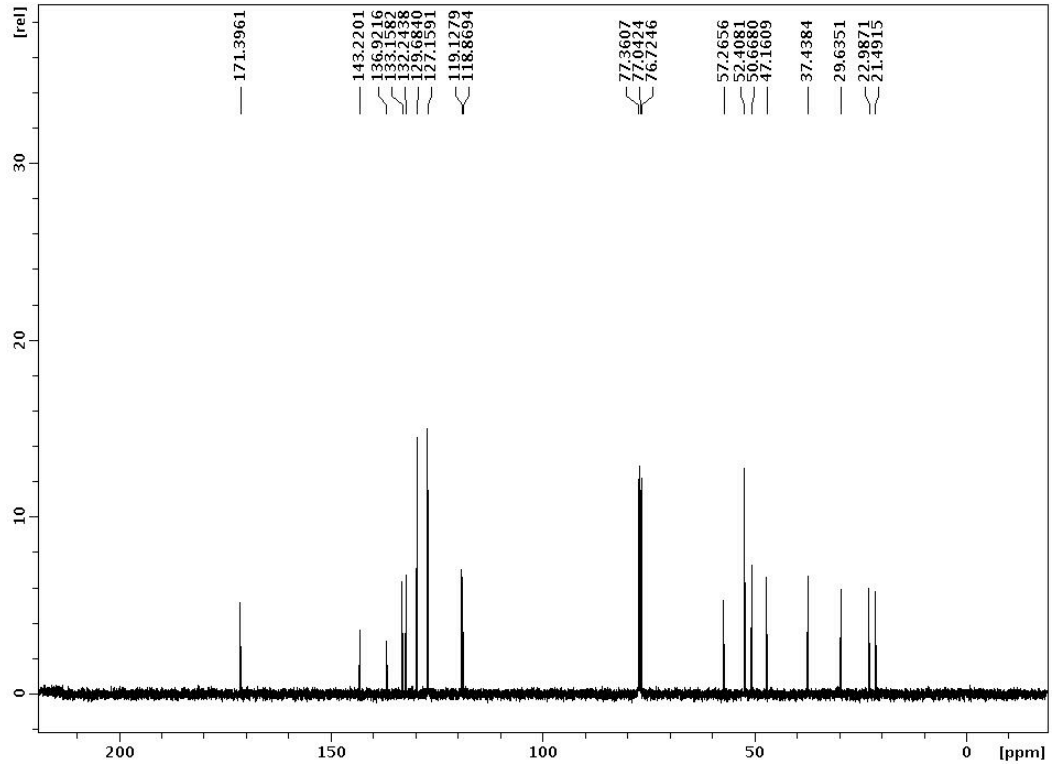
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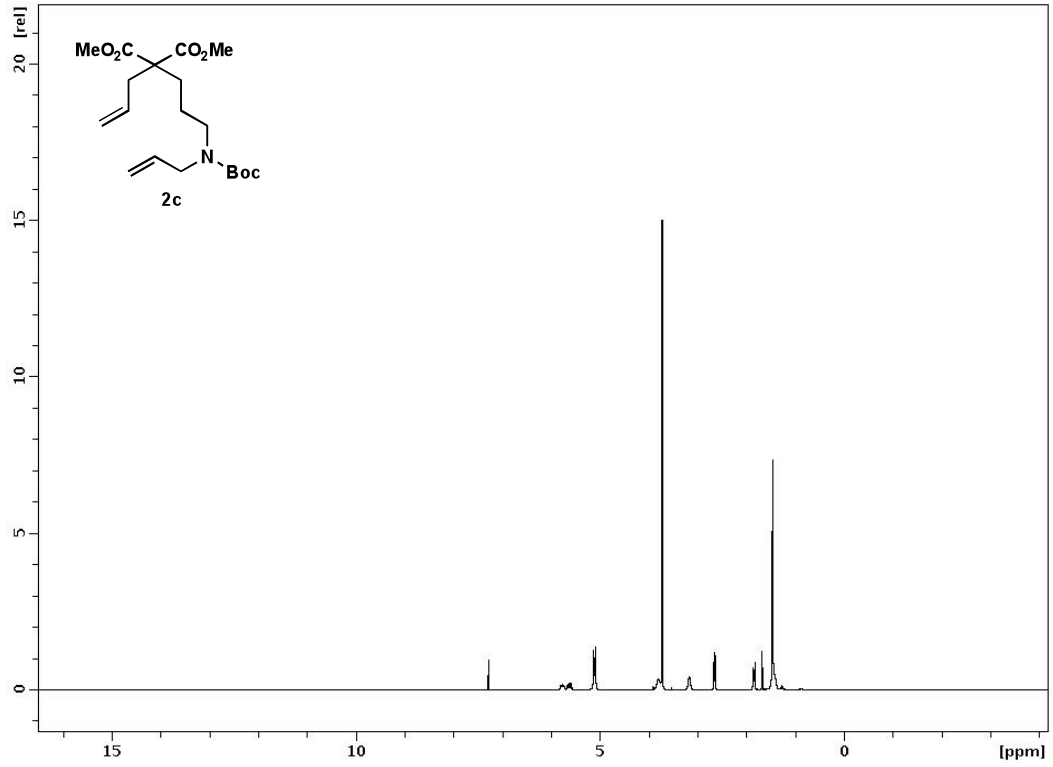
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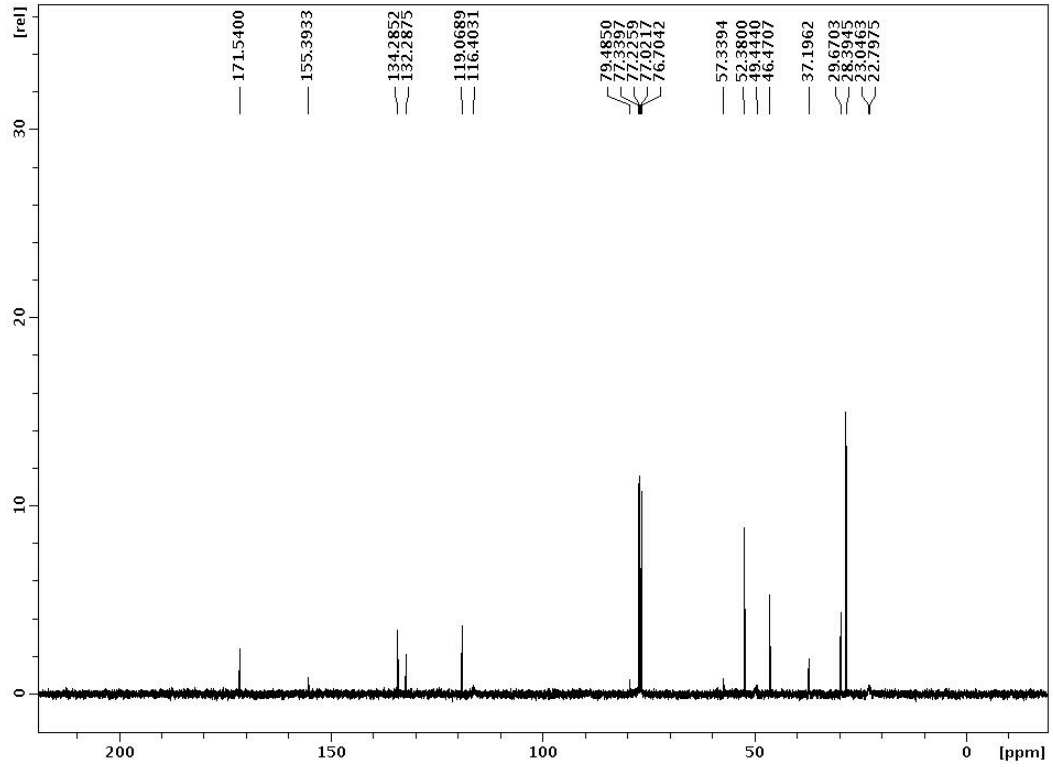
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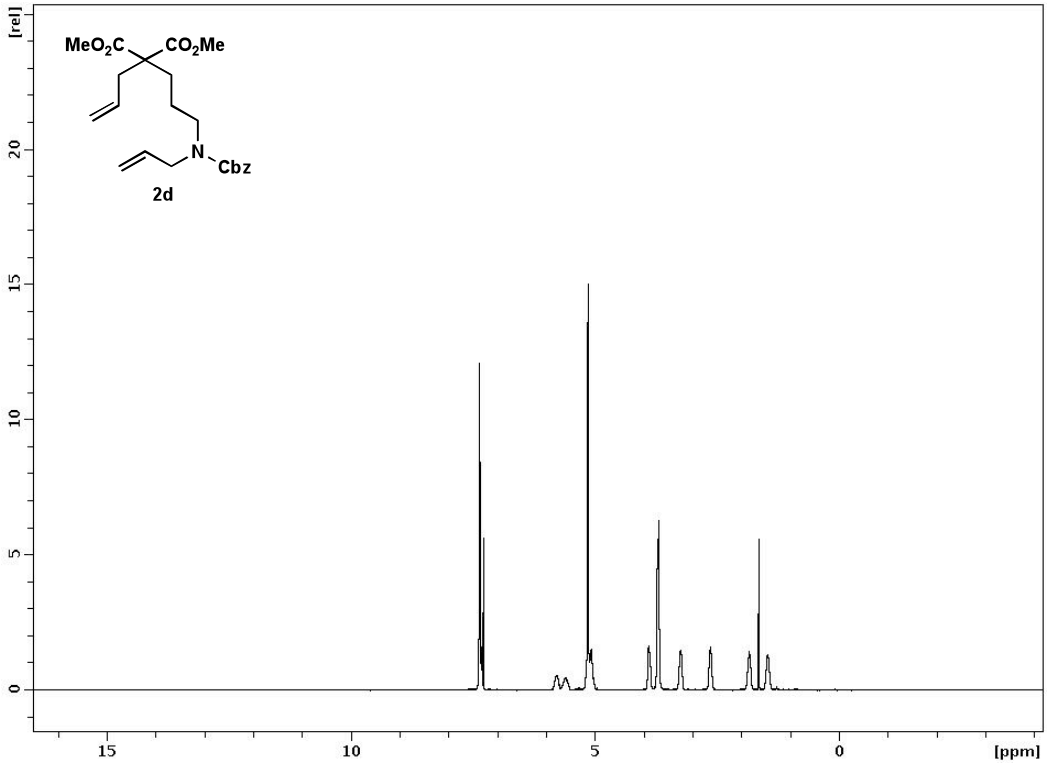
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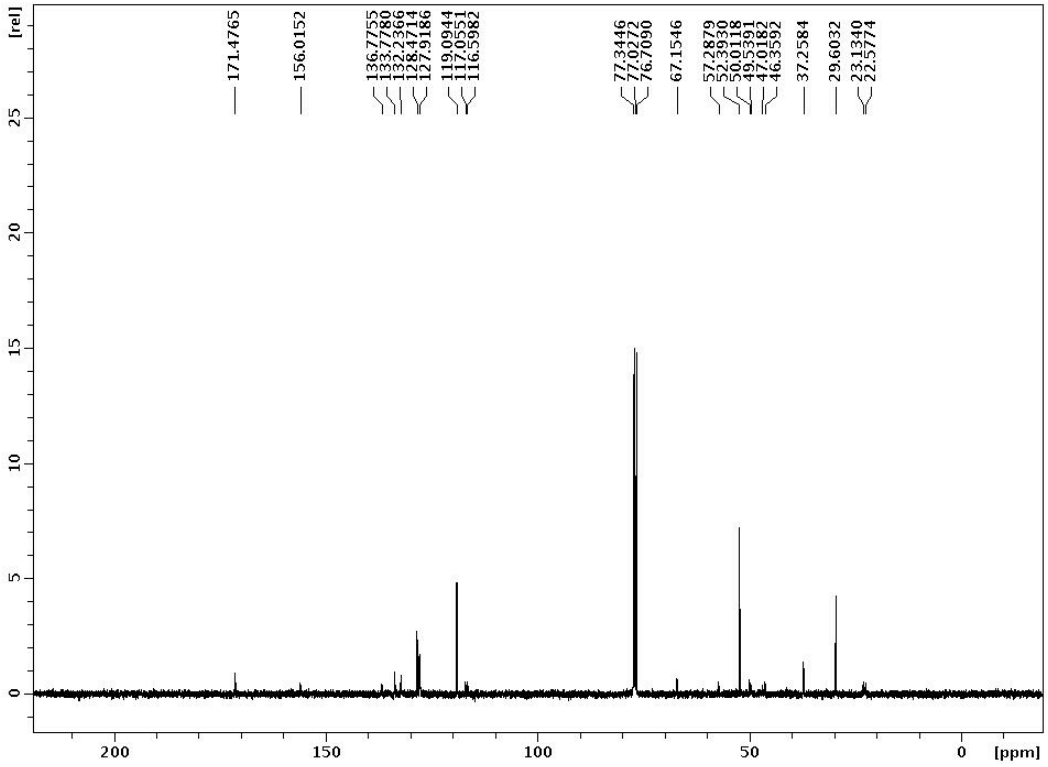
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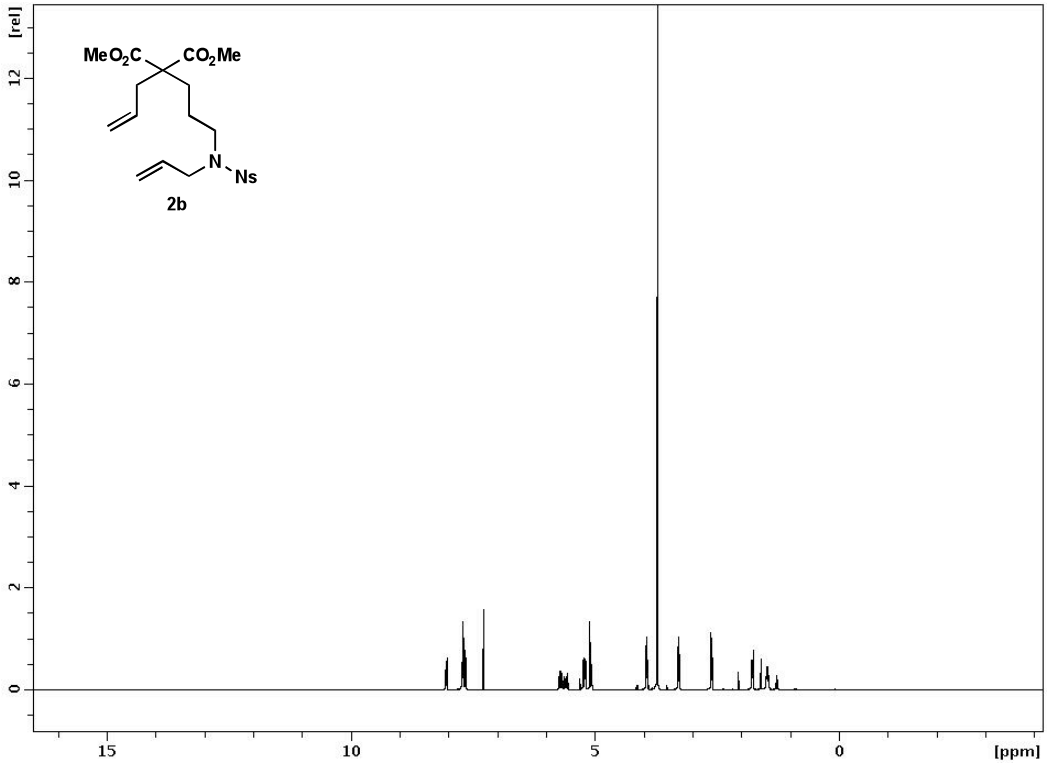
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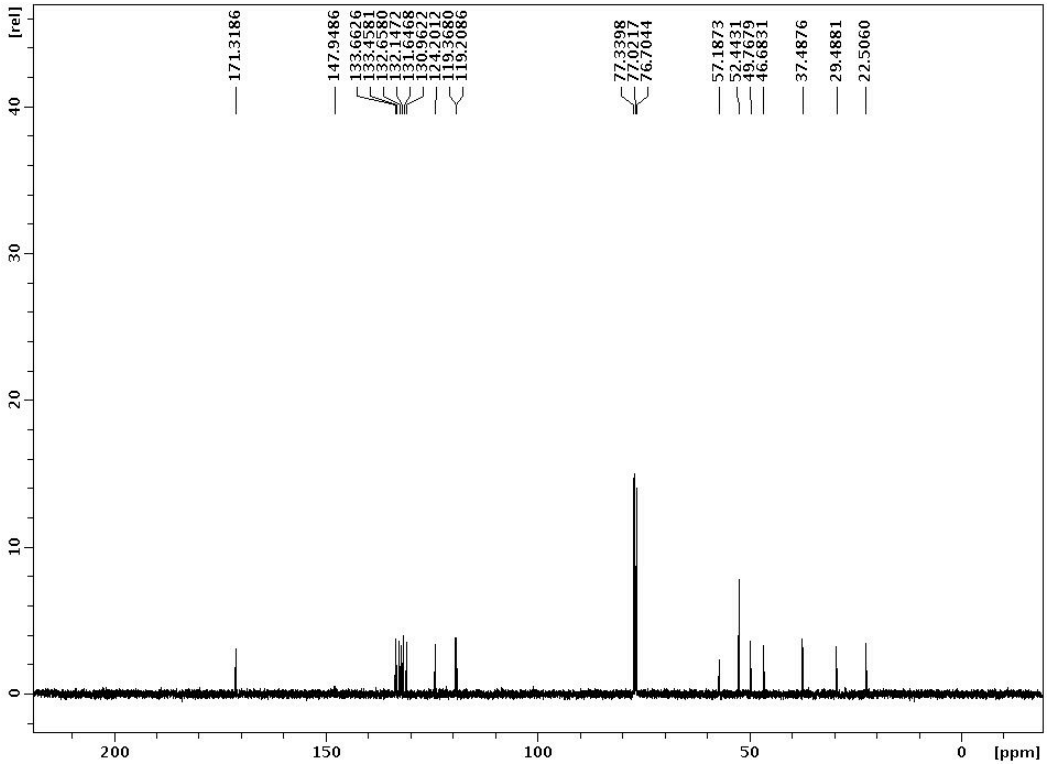
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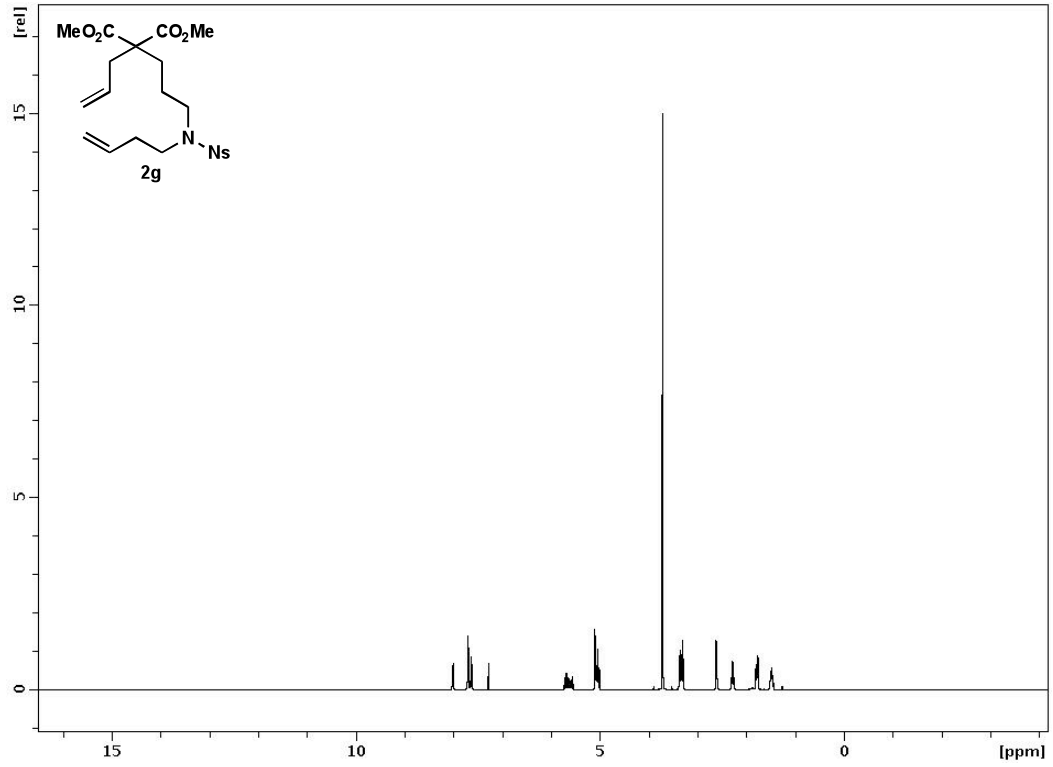
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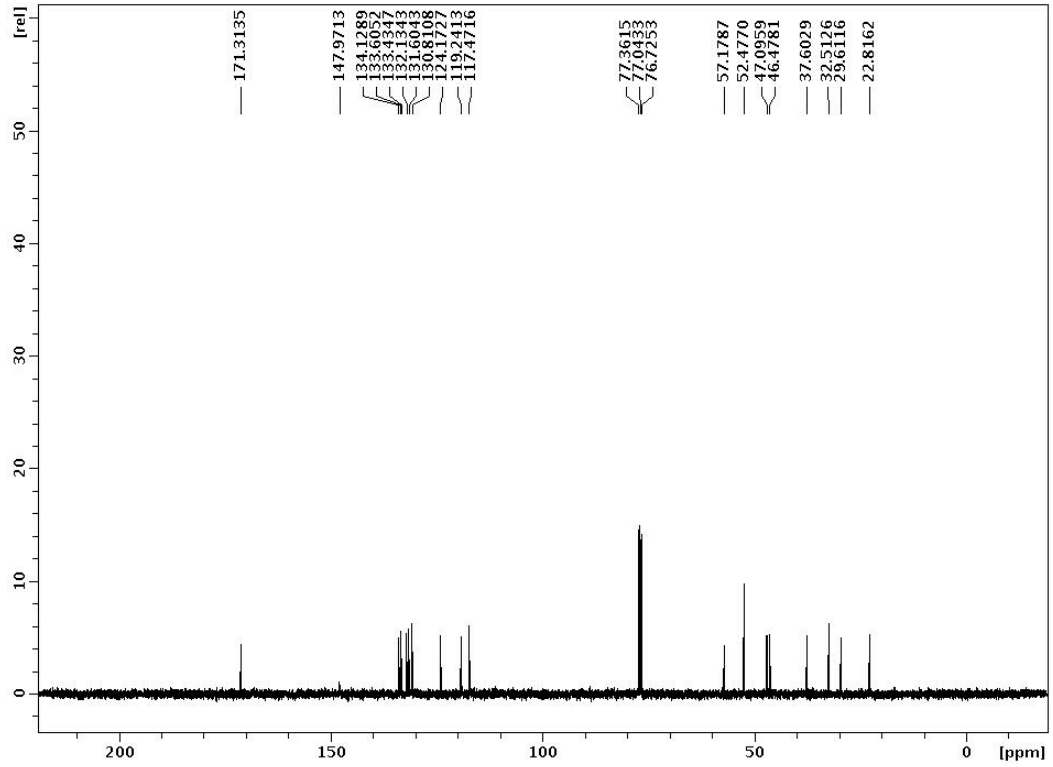
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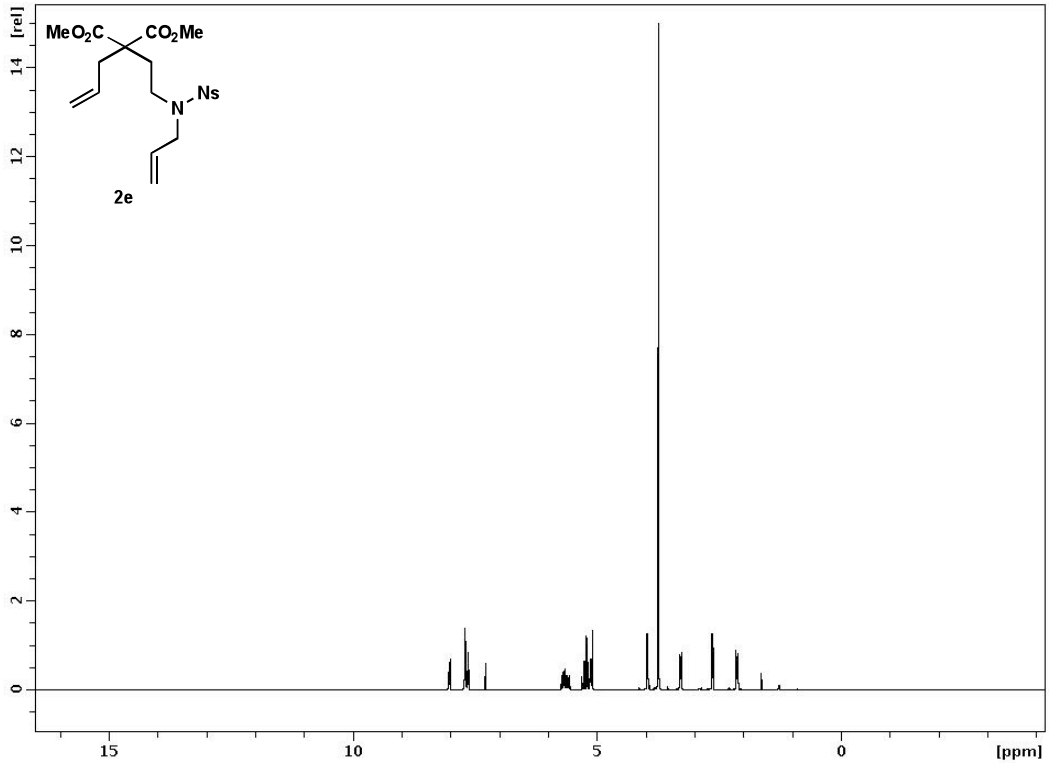
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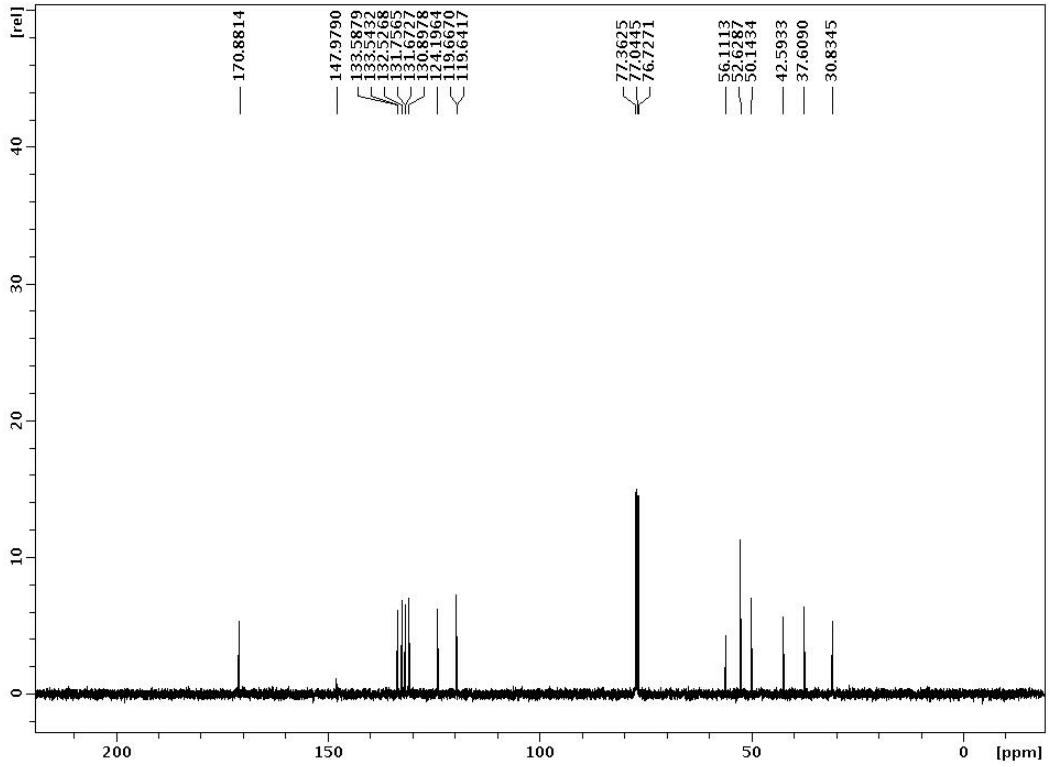
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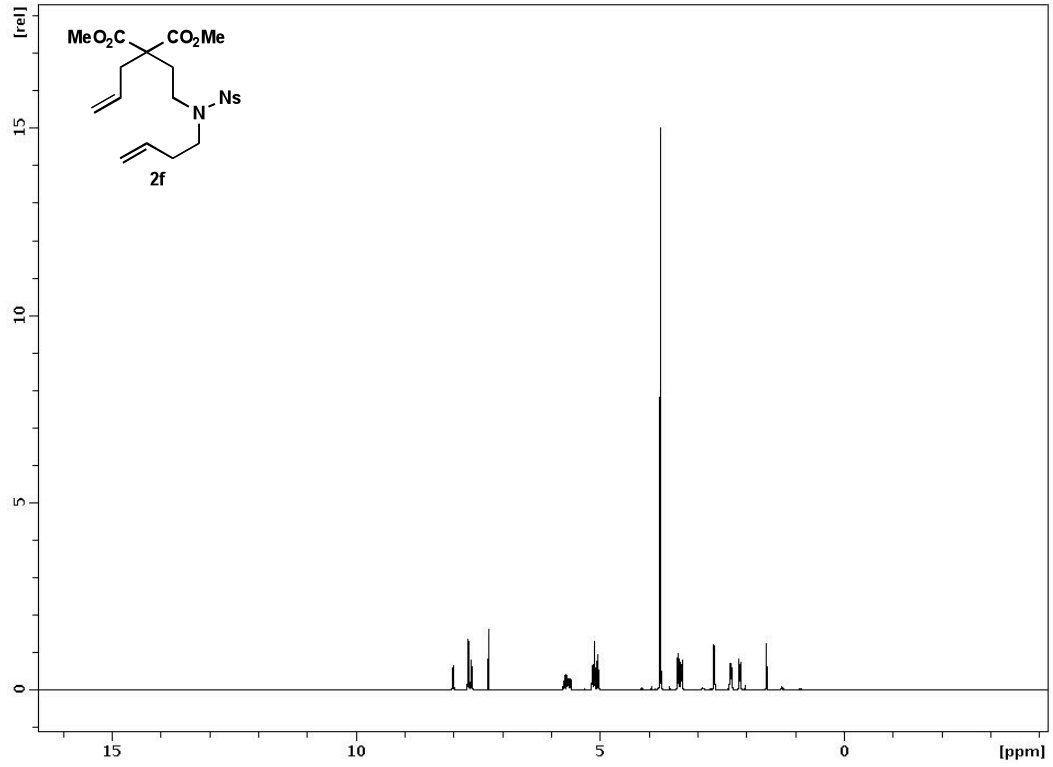
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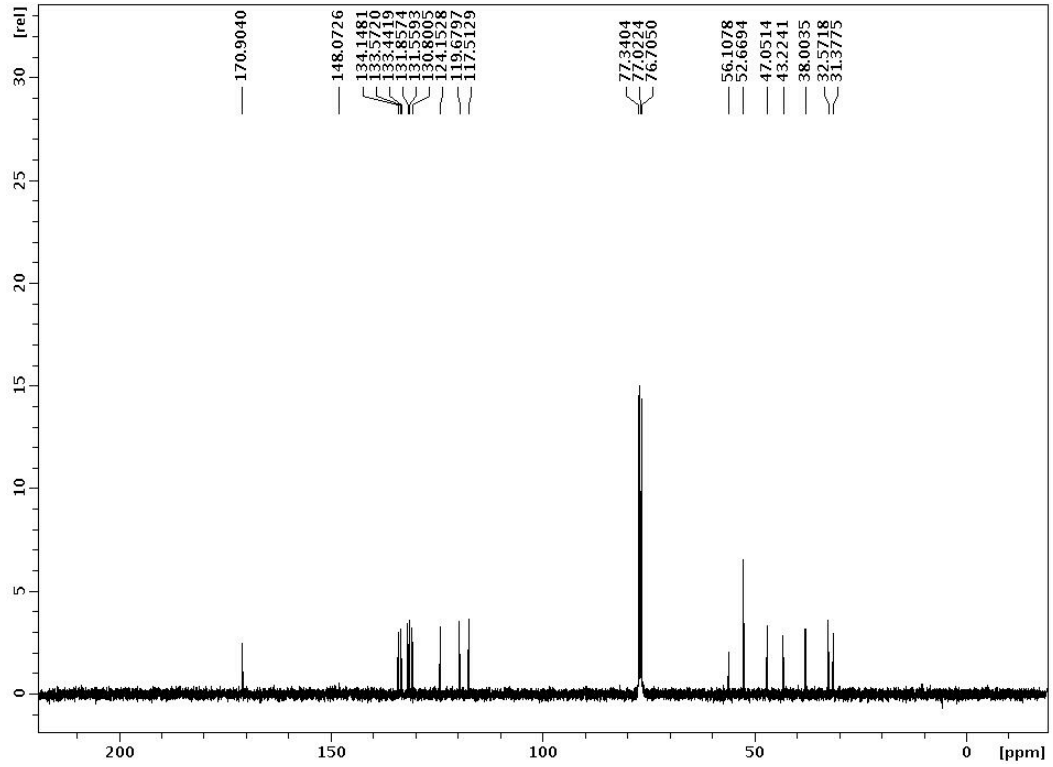
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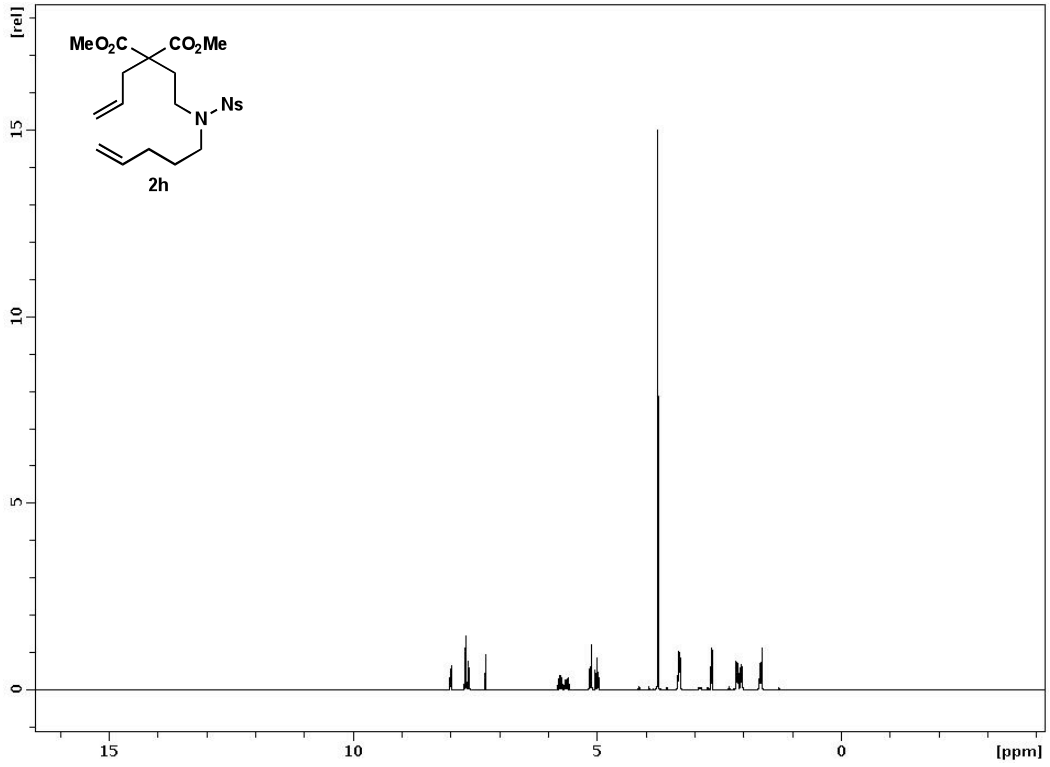
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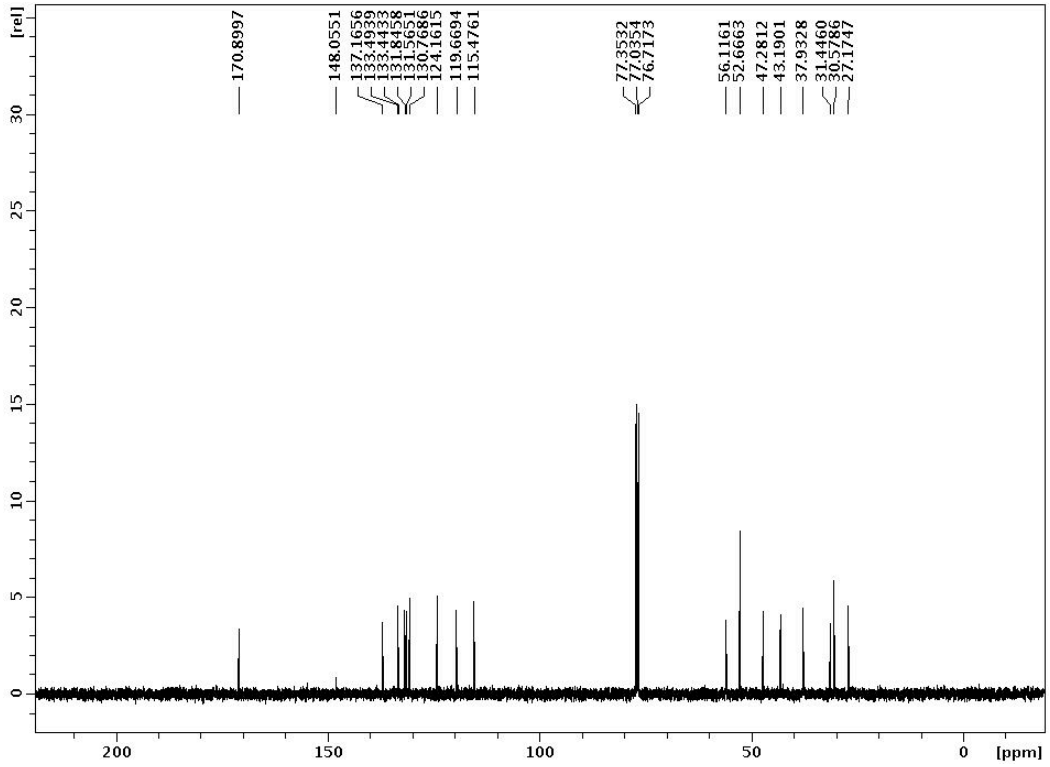
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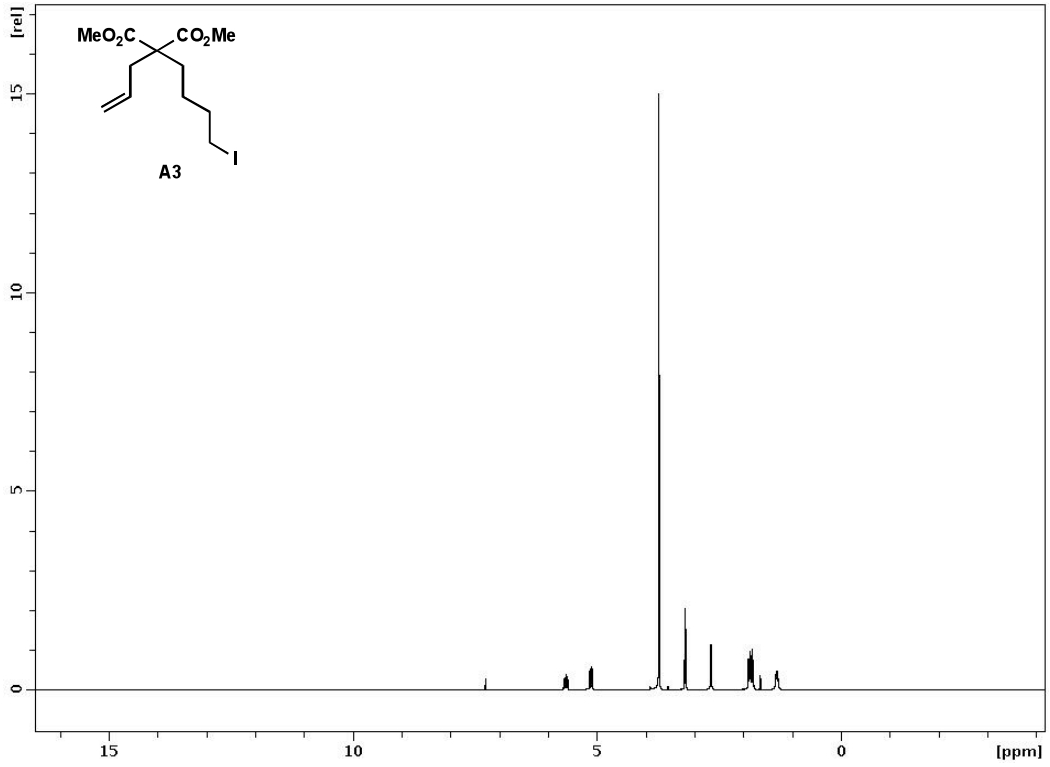
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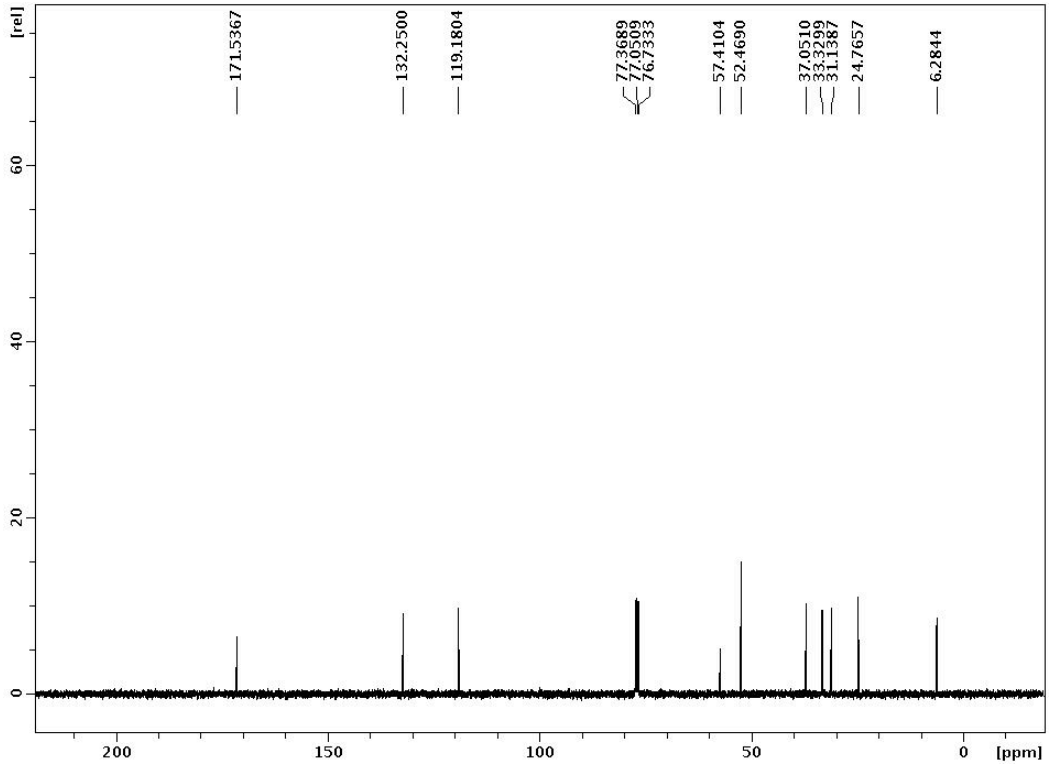
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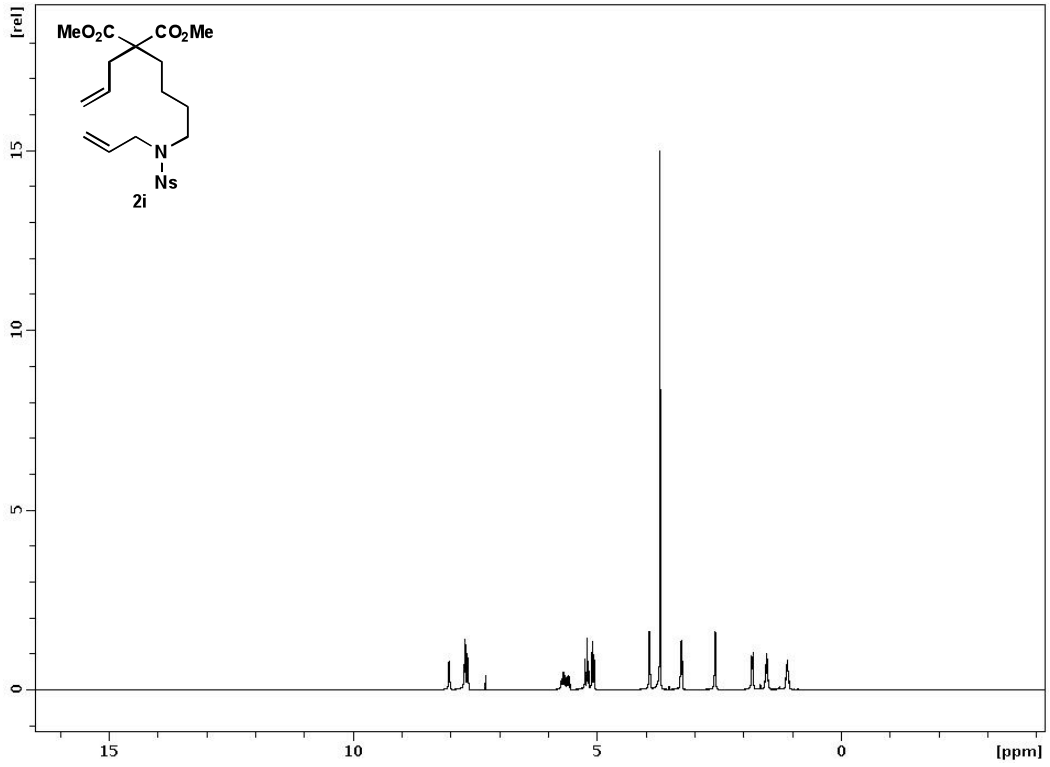
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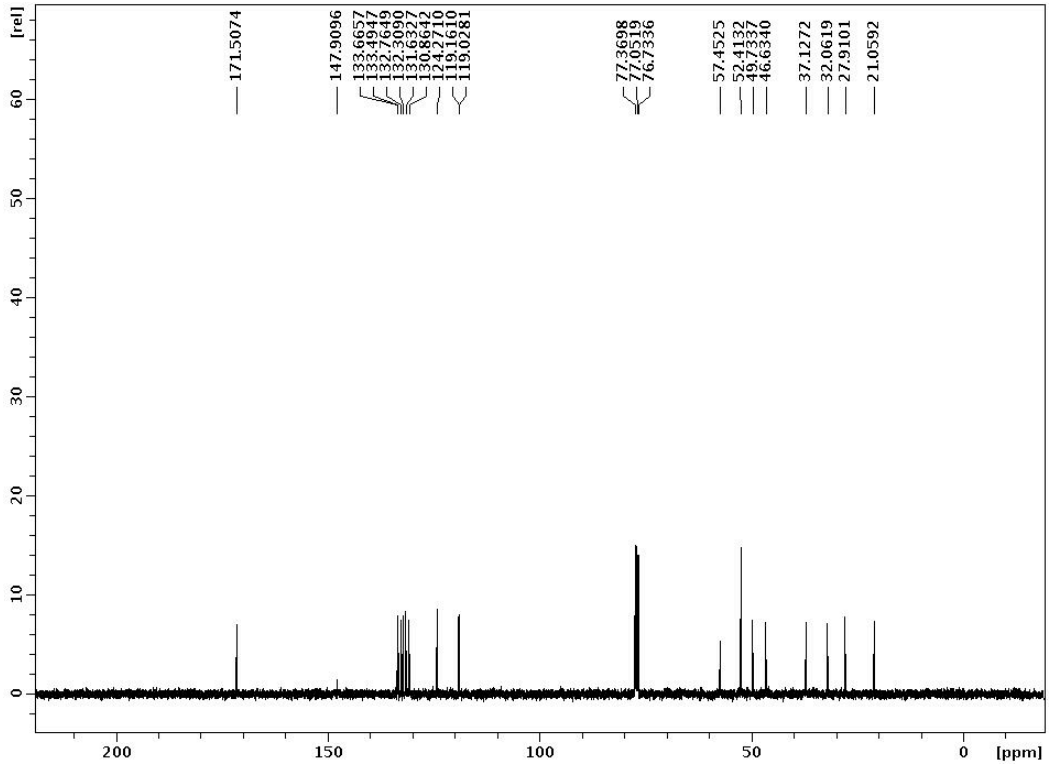
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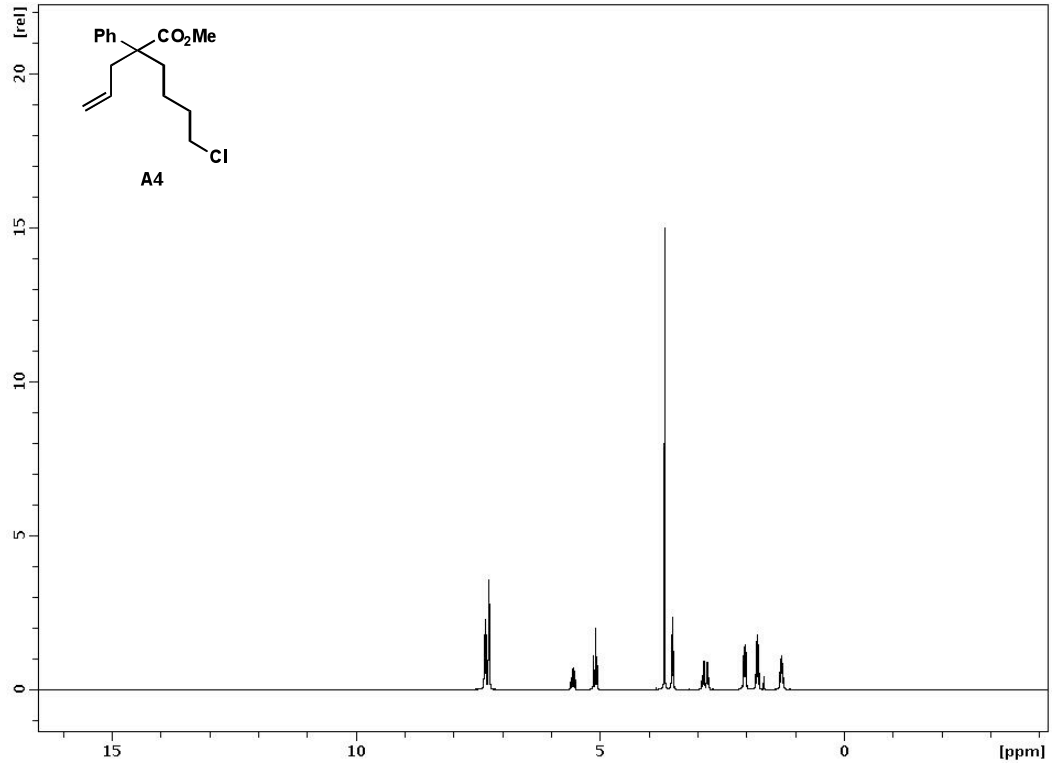
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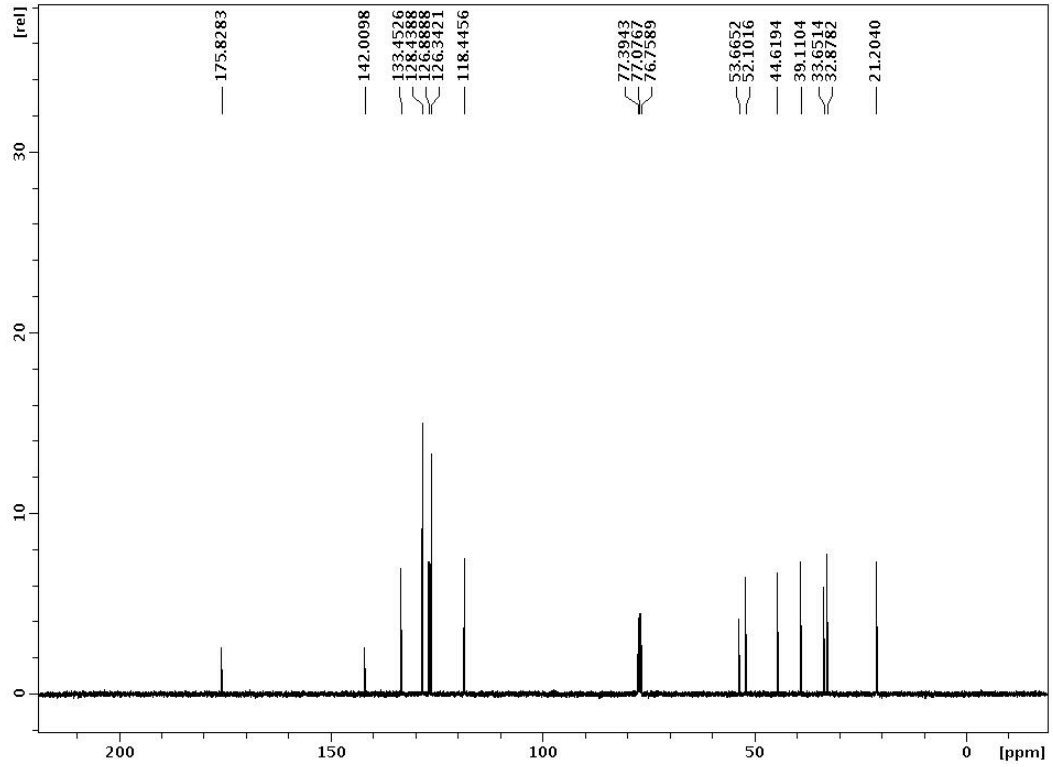
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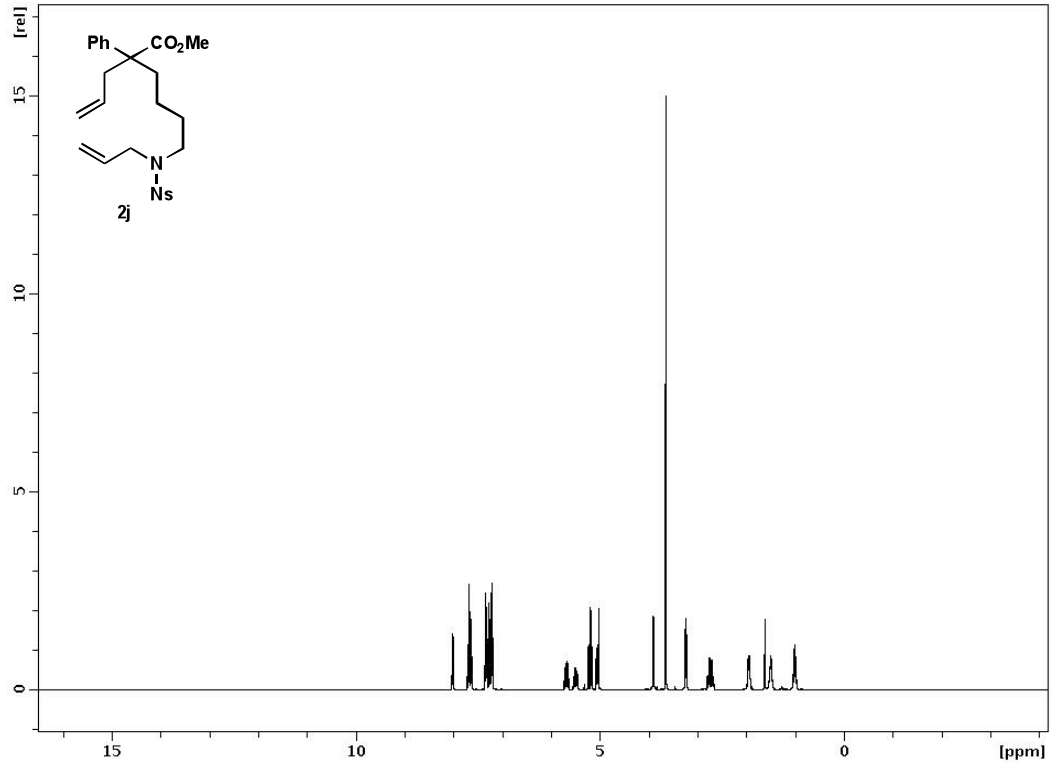
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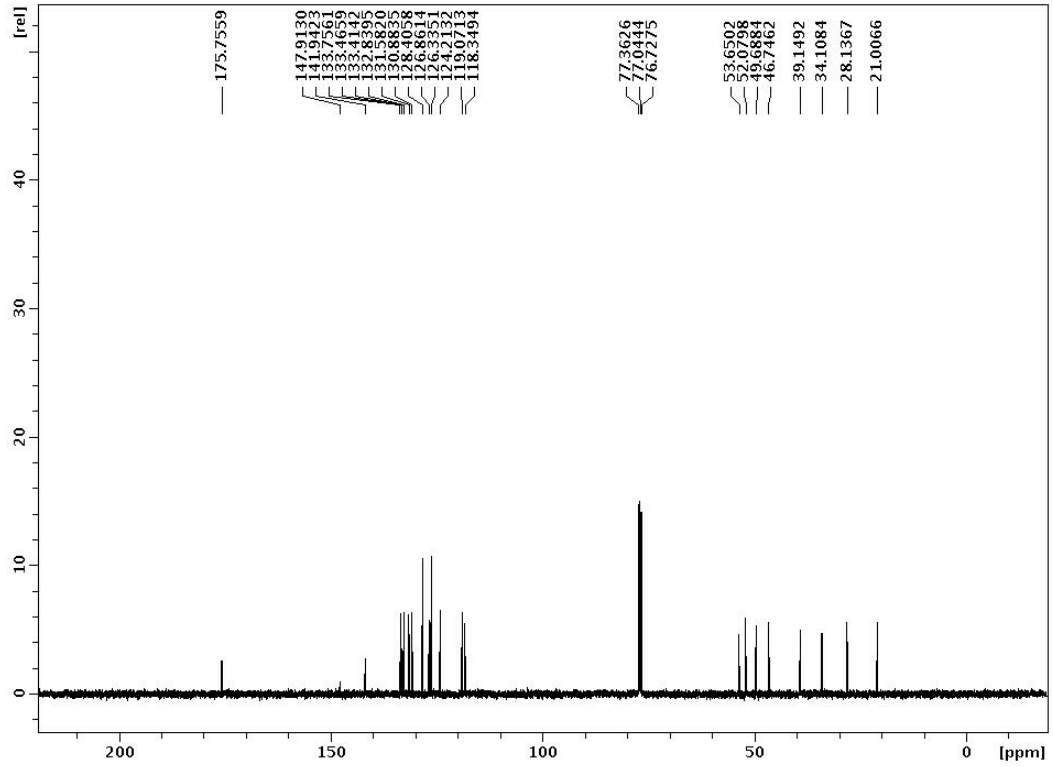
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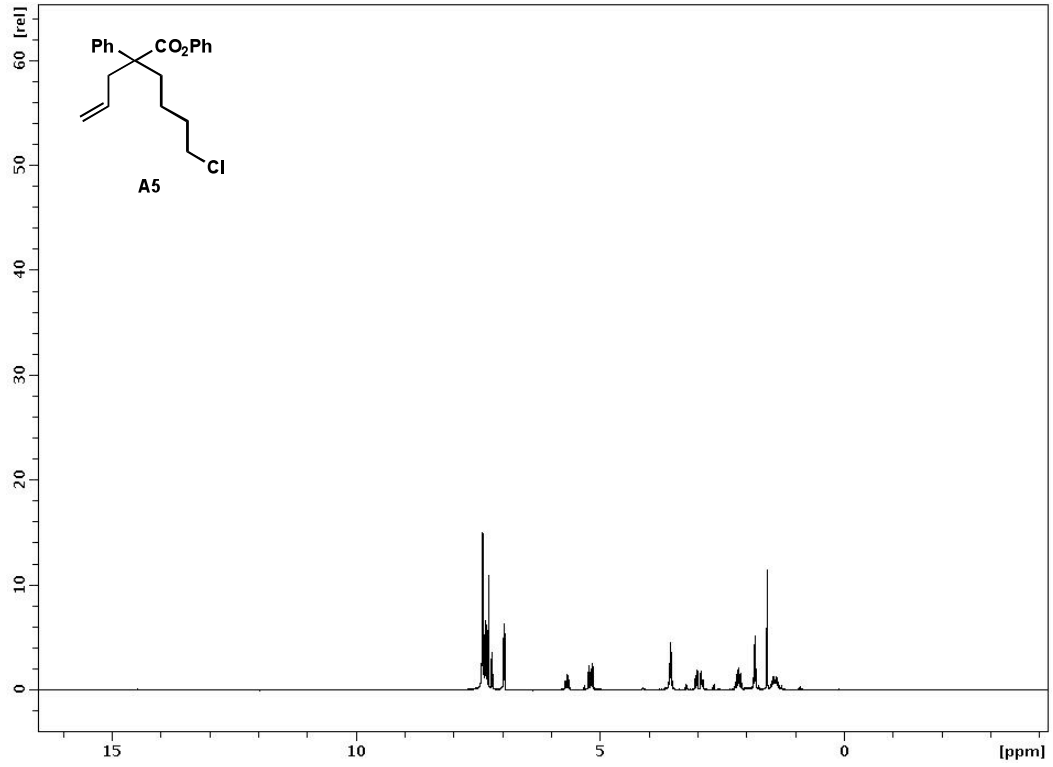
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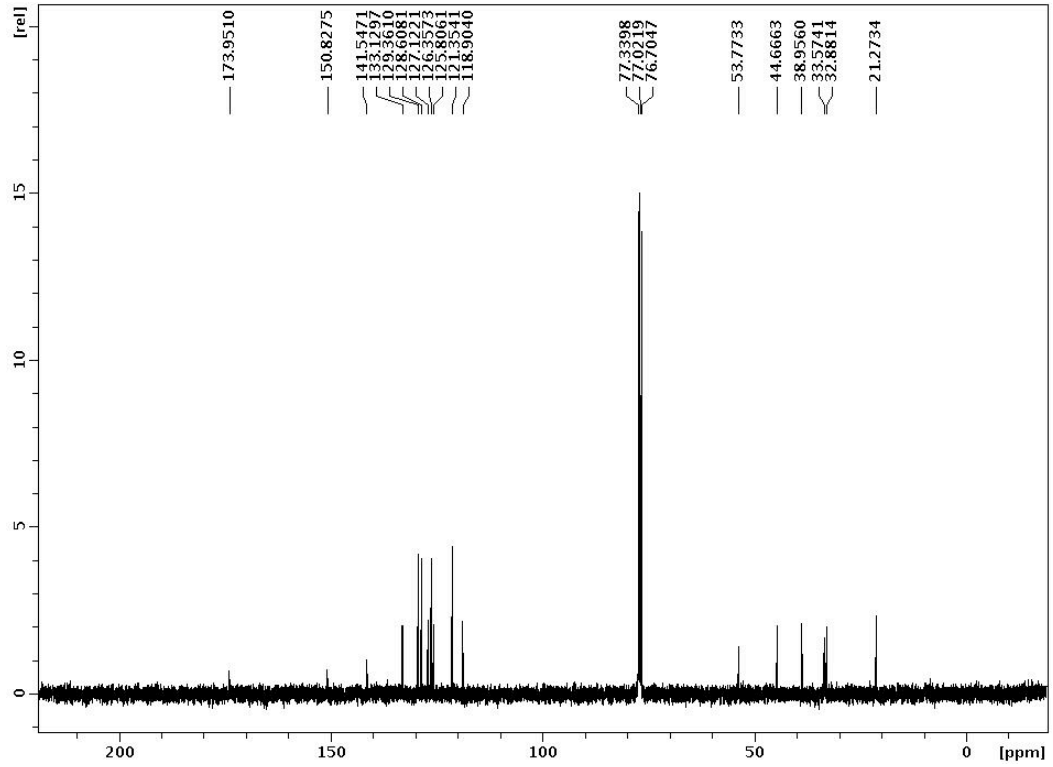
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77.3398
77.0219
76.7047
53.7733
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32.8814
21.2734
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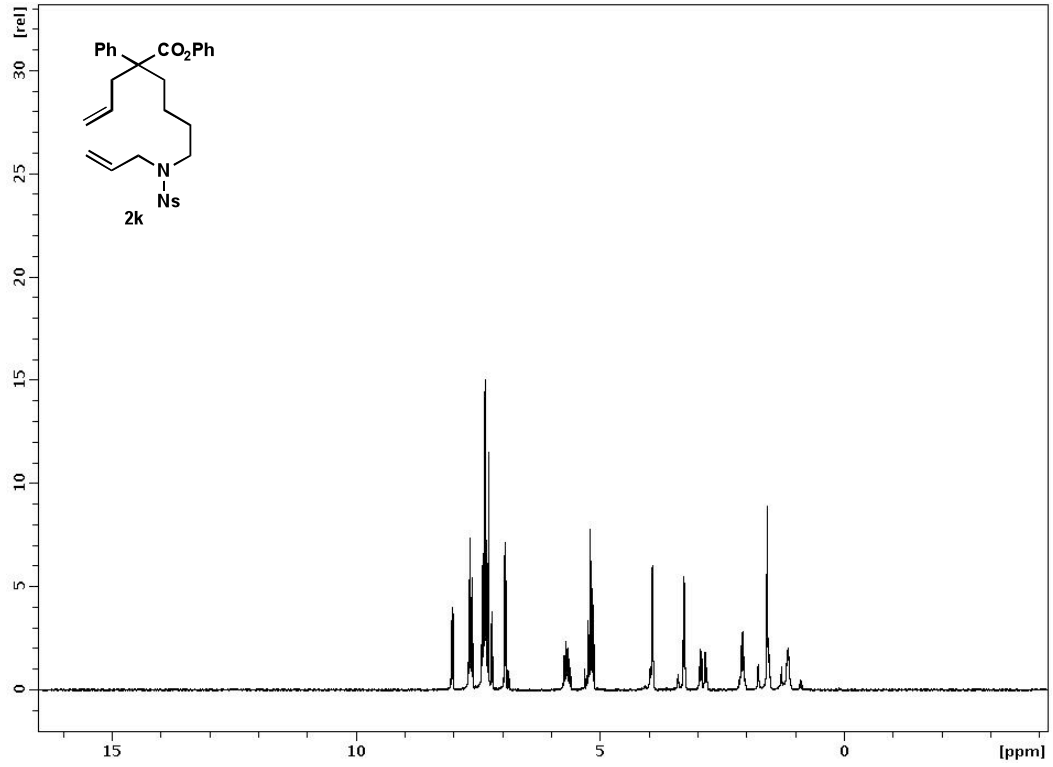
Ph
CO2Ph
N
Ns
2k
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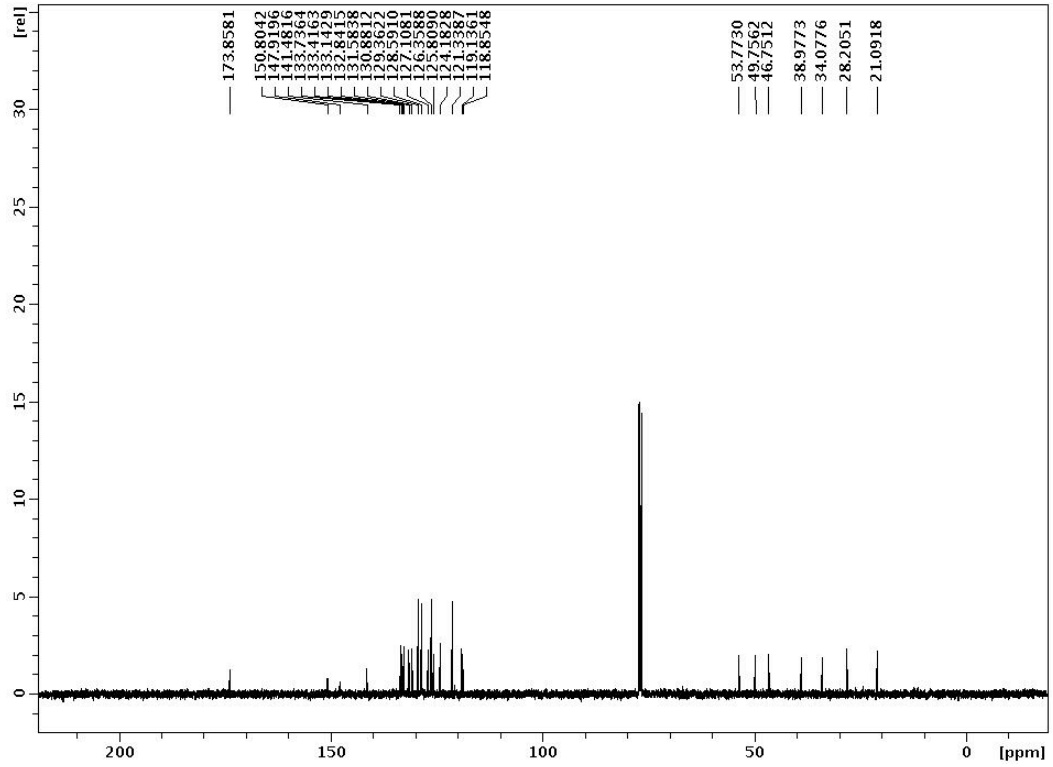
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128.5910
127.1081
126.3588
125.8090
124.1828
121.3387
119.1361
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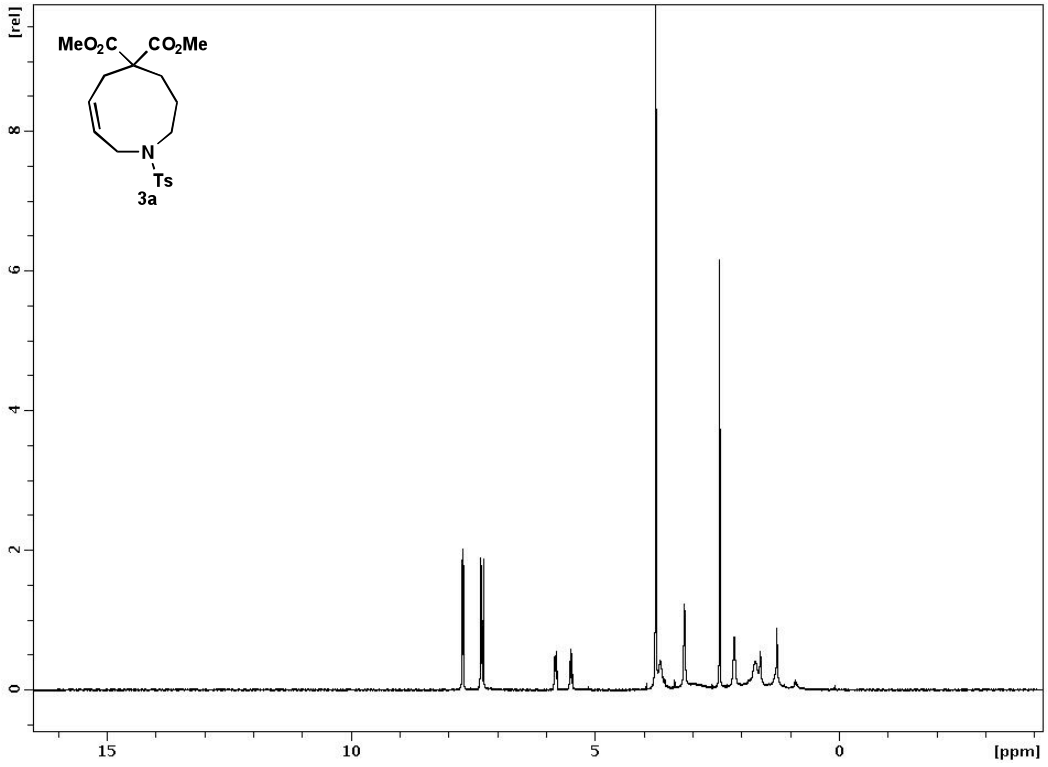
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CO2Me
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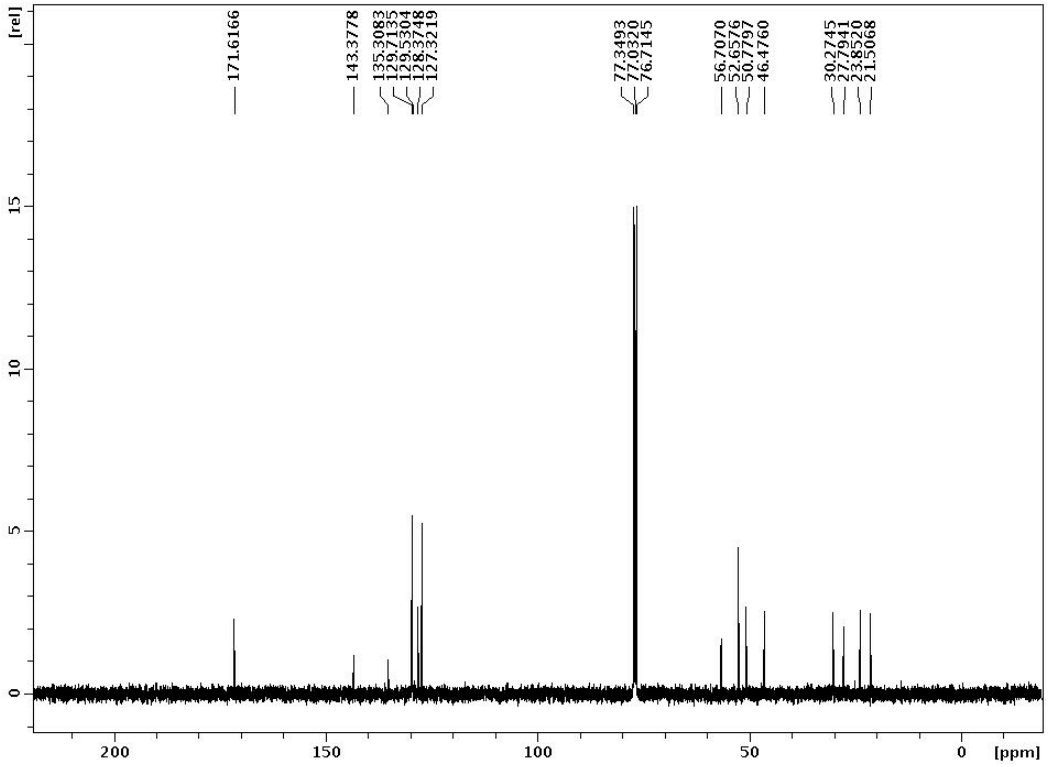
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77.0320
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50.7797
46.4760
30.2745
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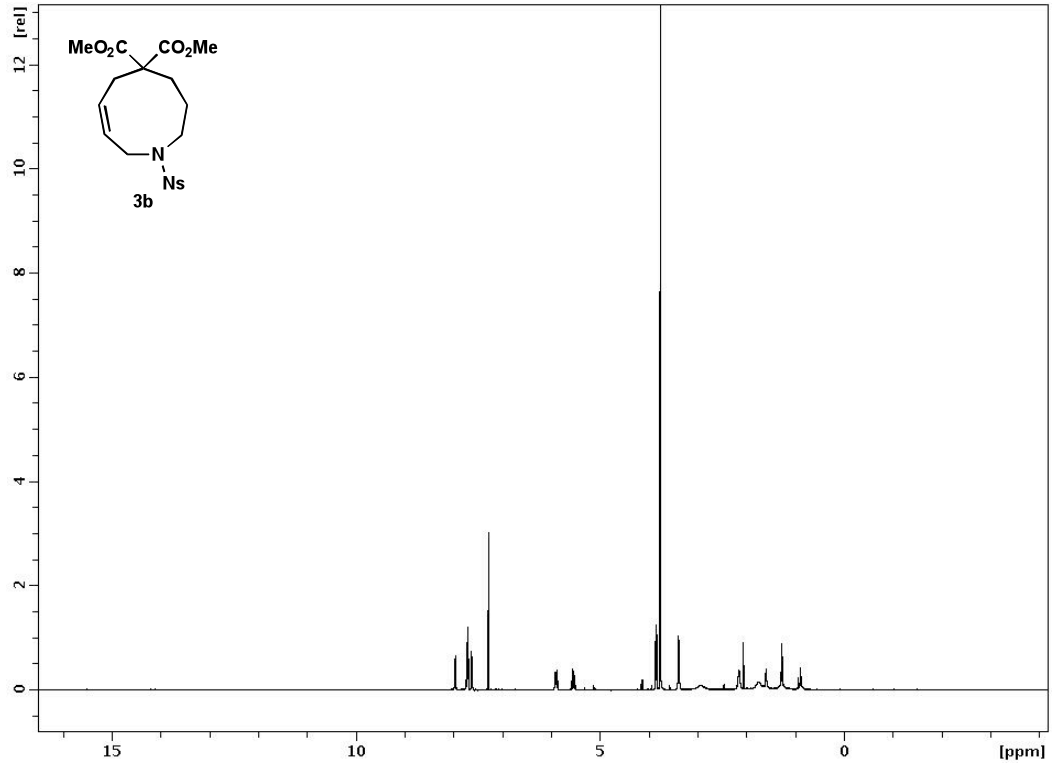
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CO2Me
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Ns
3b
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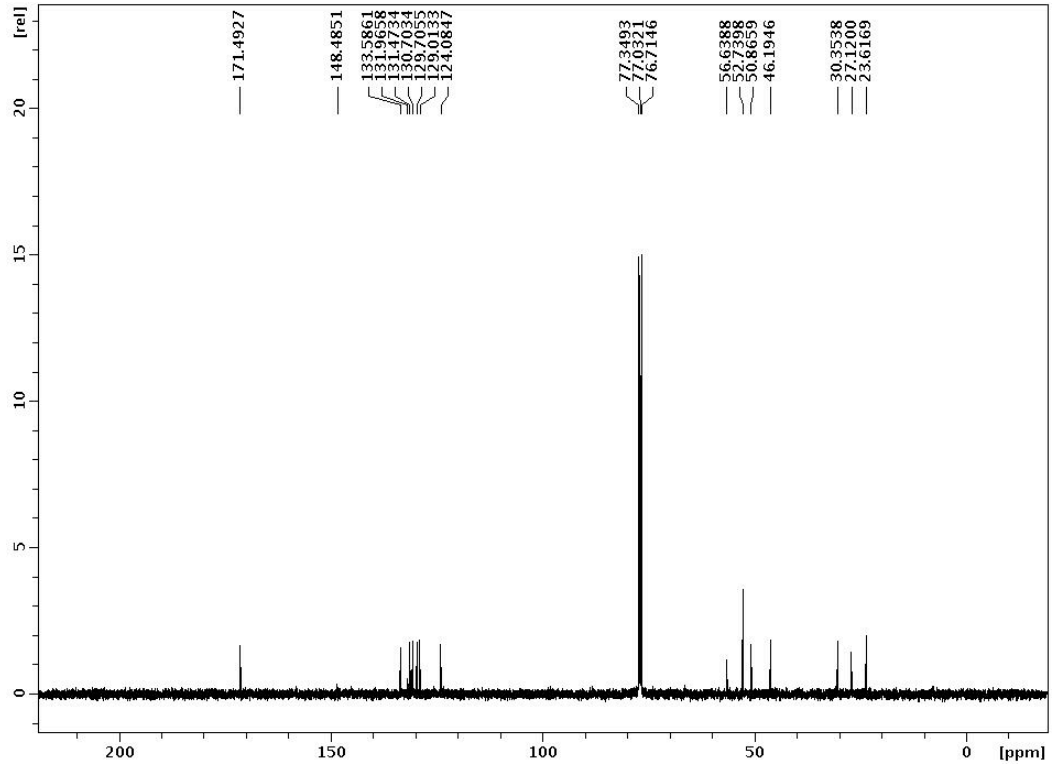
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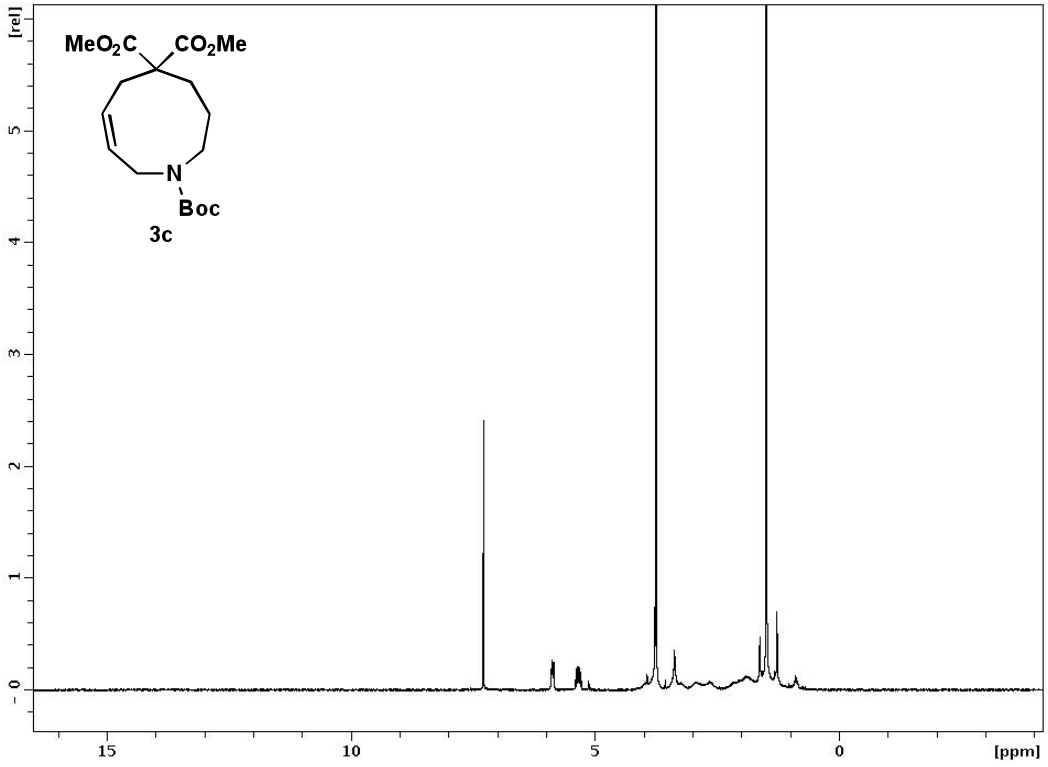
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Boc
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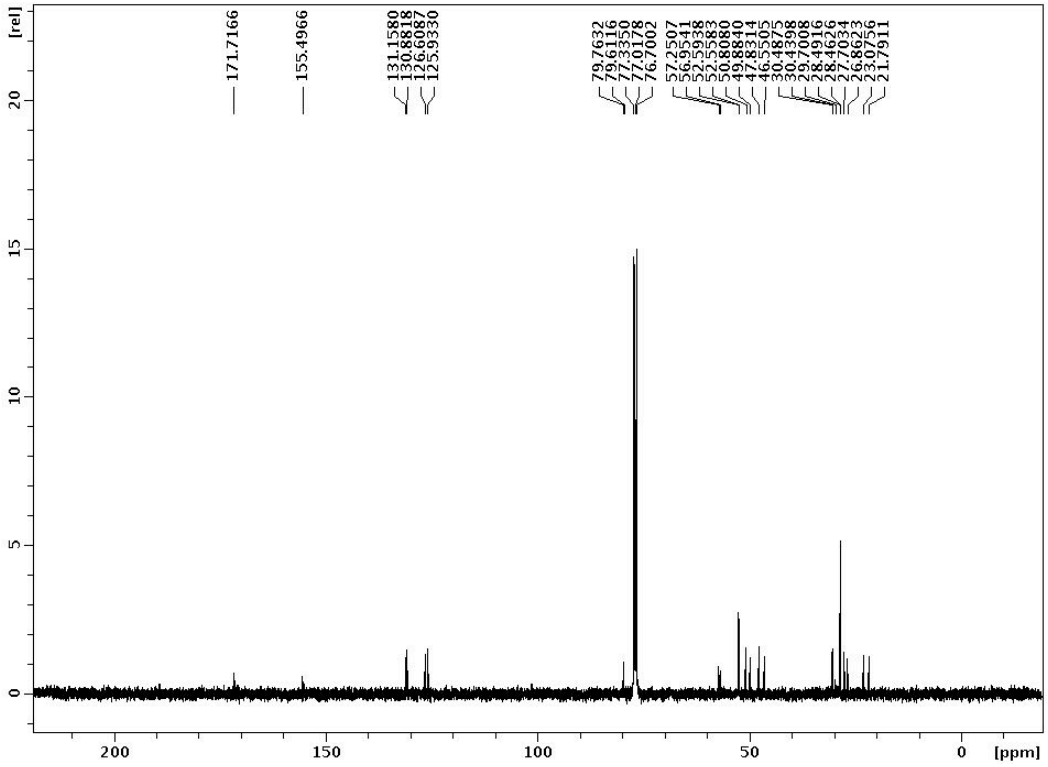
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46.5505
30.4875
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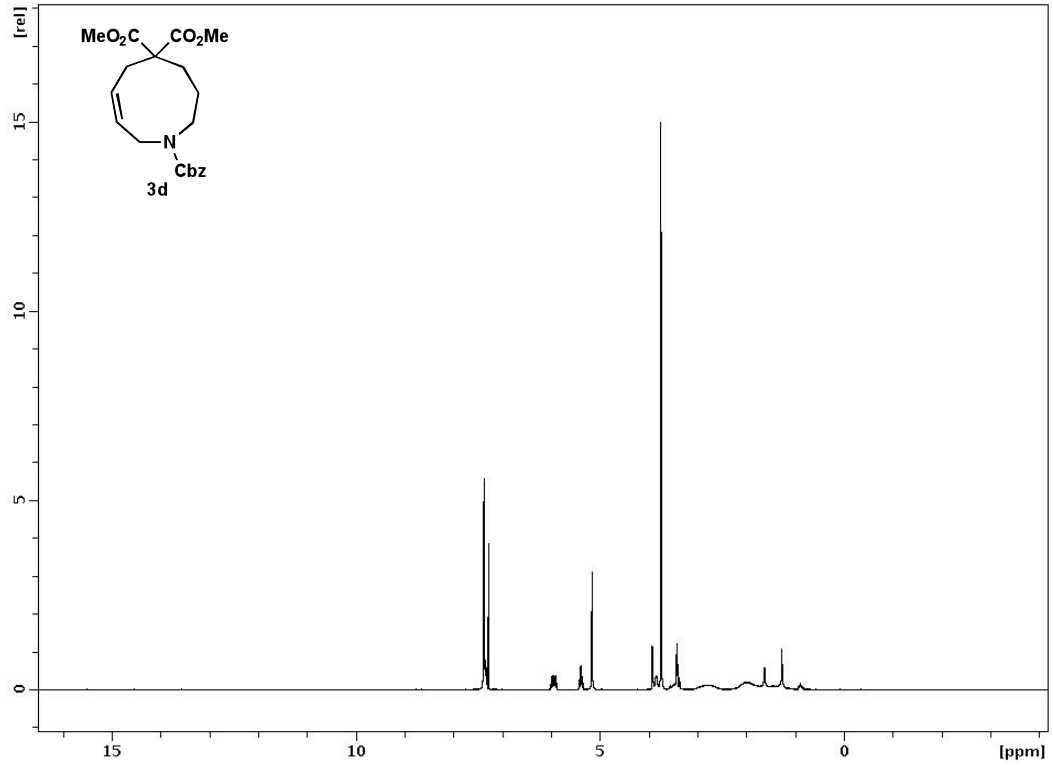
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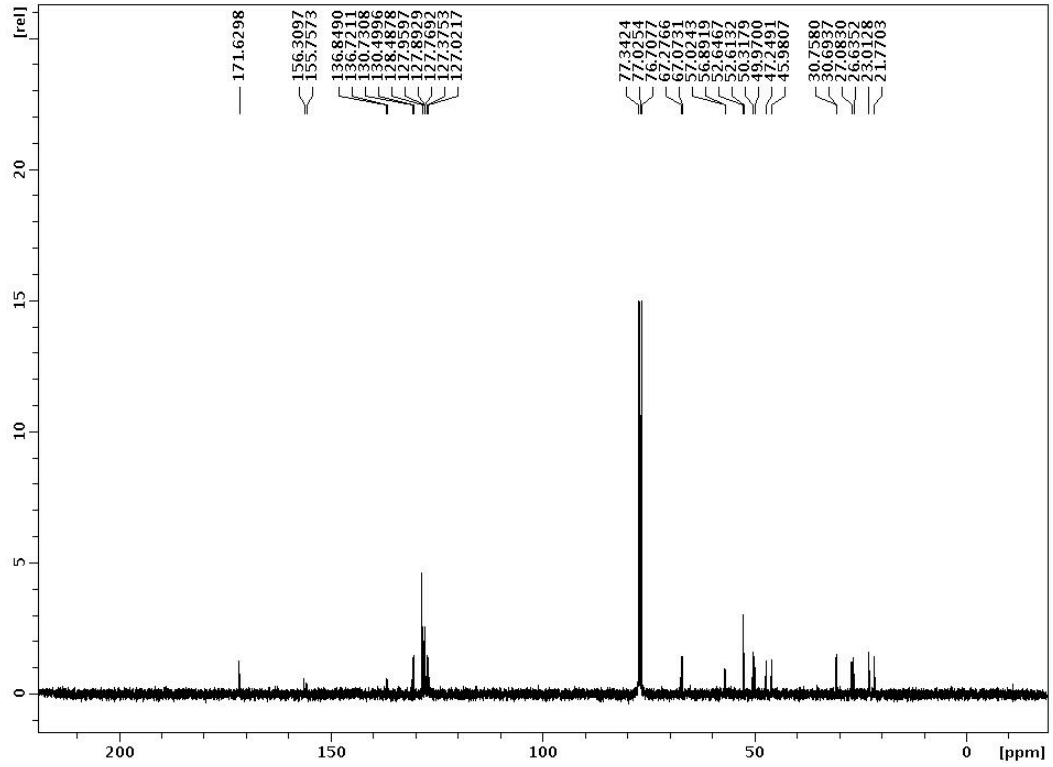
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127.3753
127.0217
77.3424
77.0234
76.7076
67.0791
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56.8919
52.6467
52.6132
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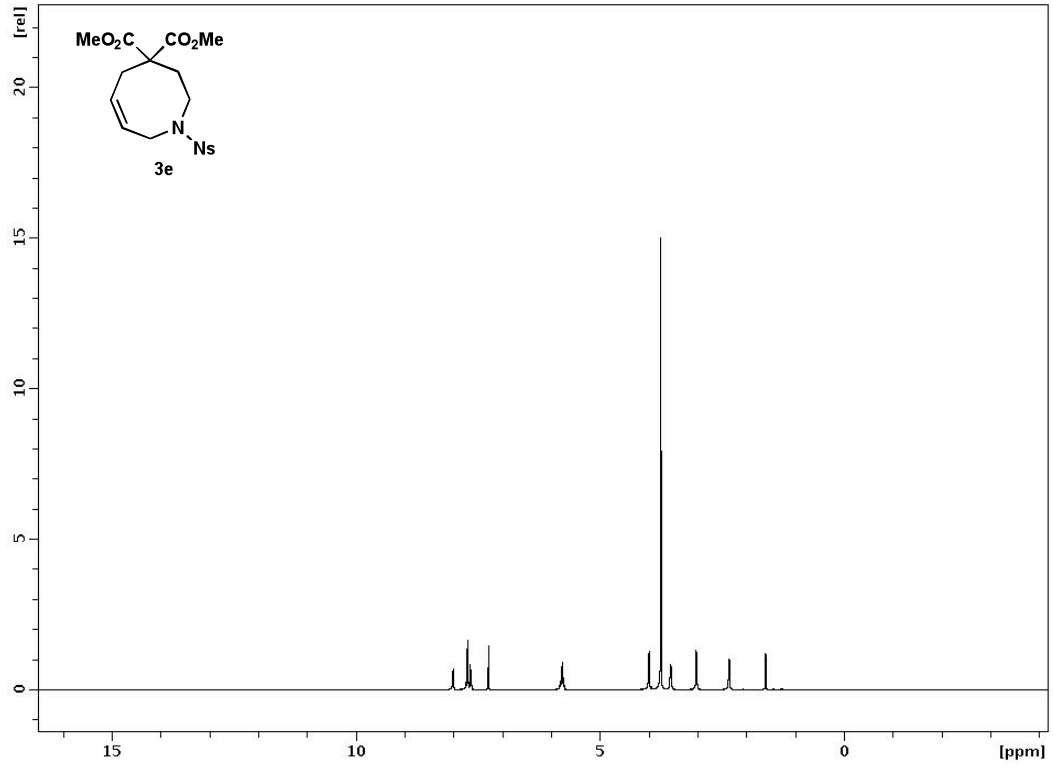
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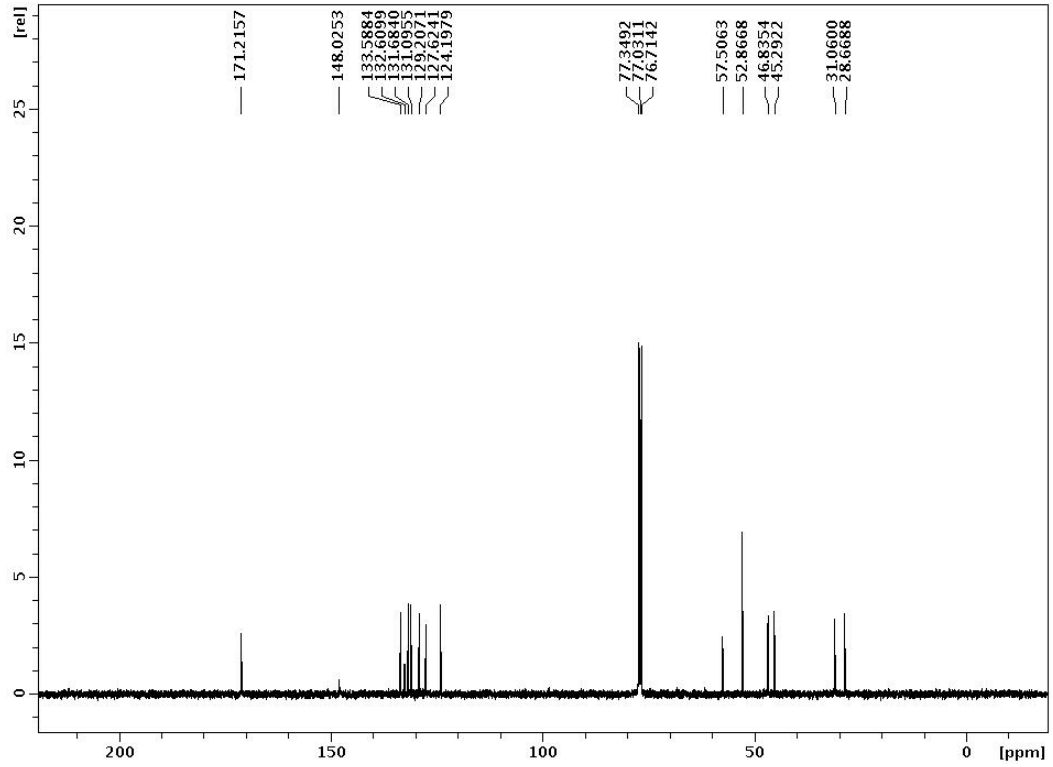
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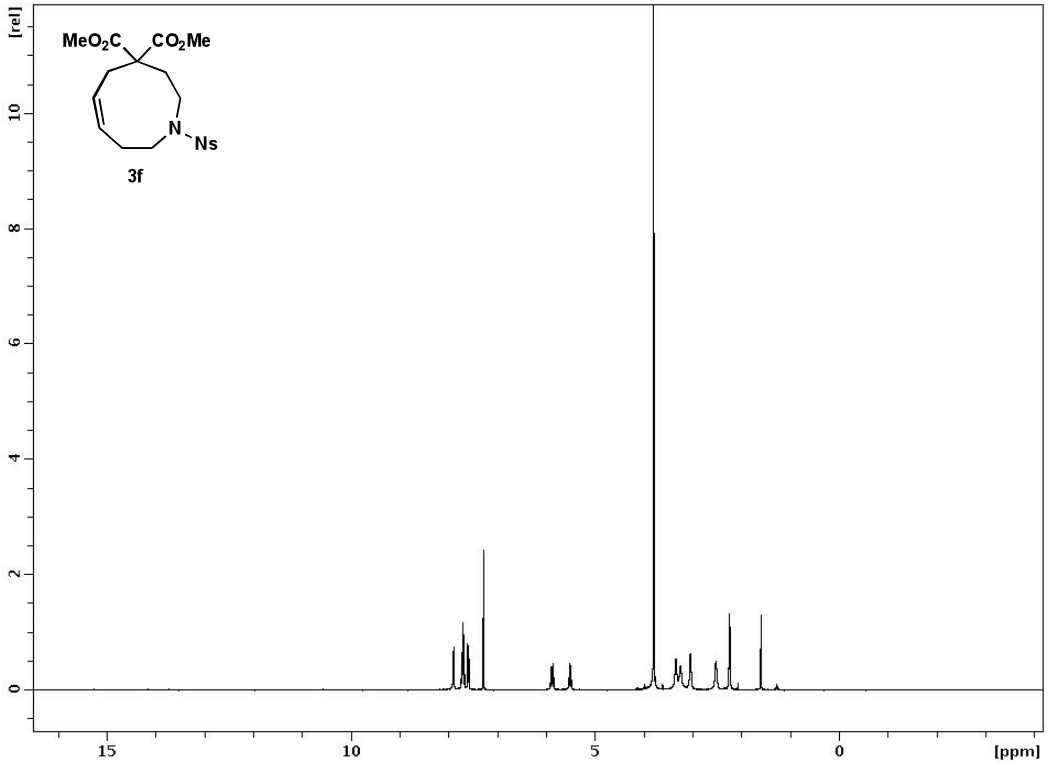
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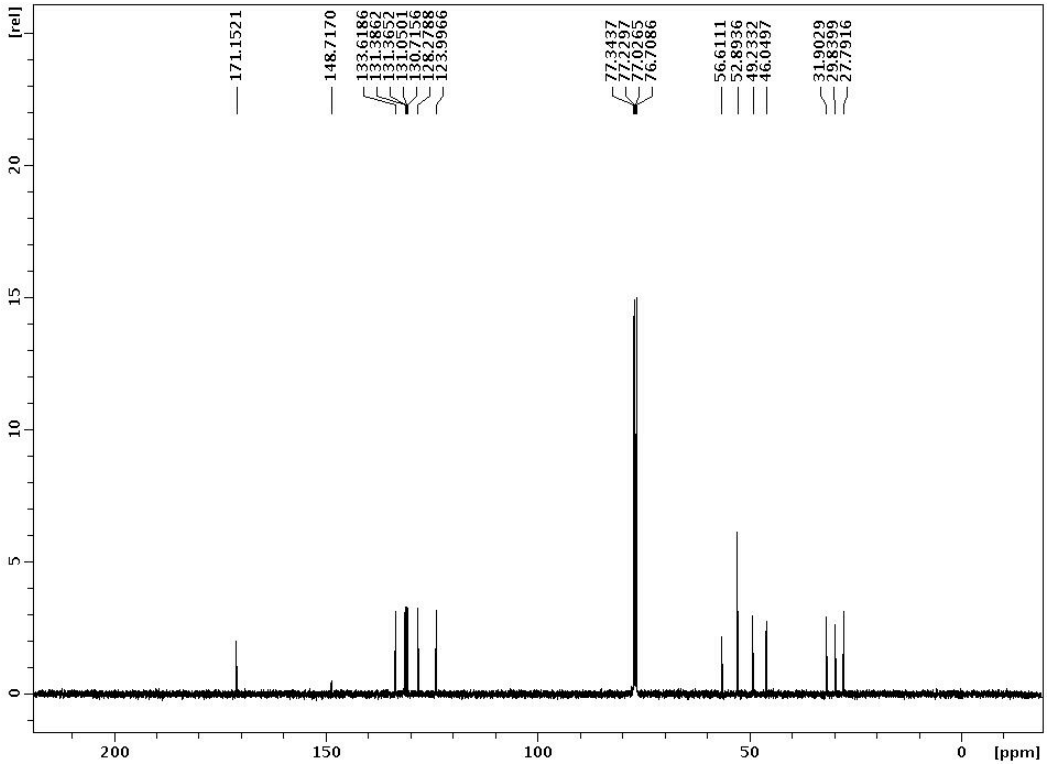
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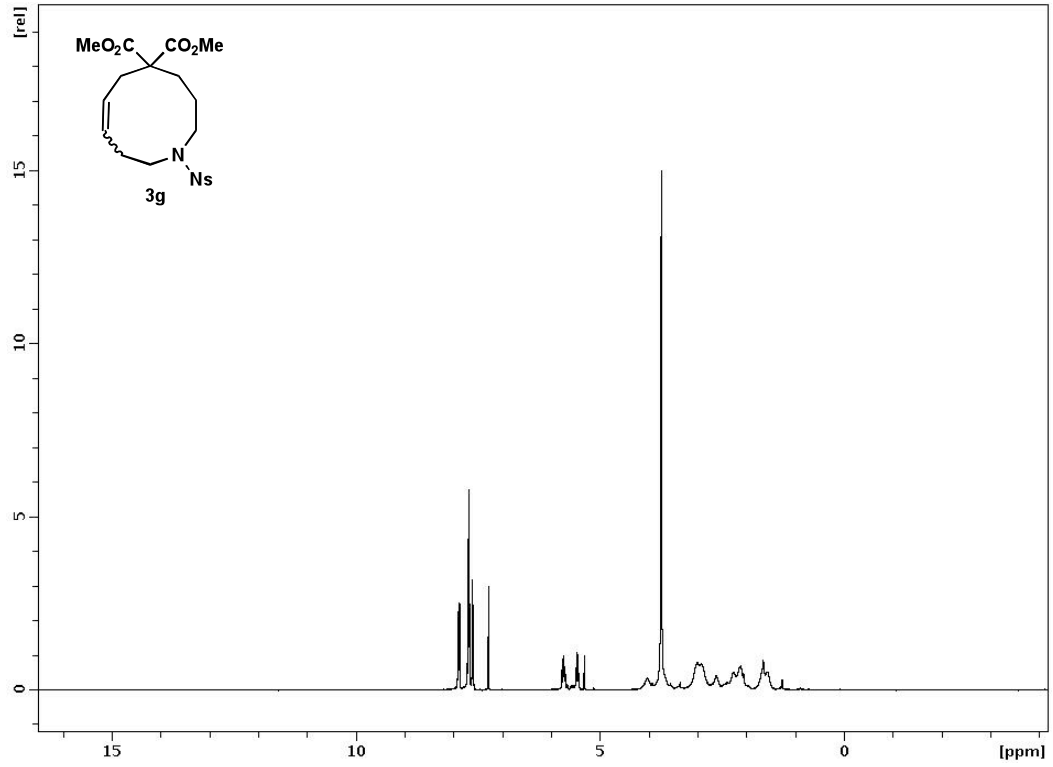
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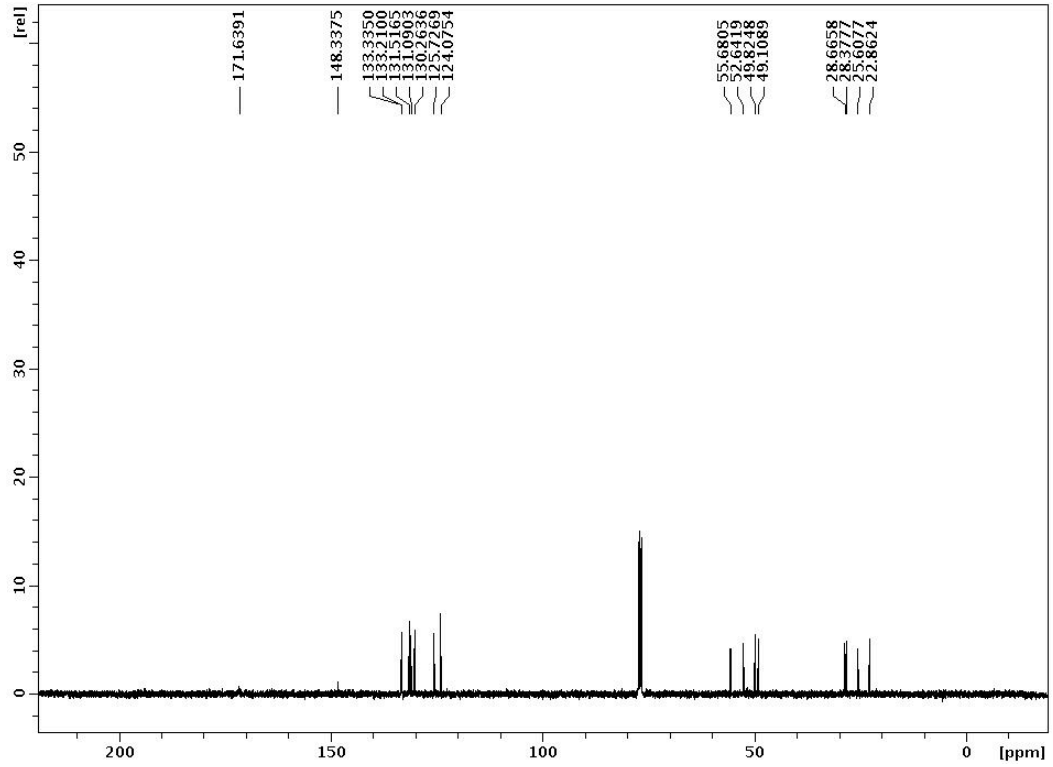
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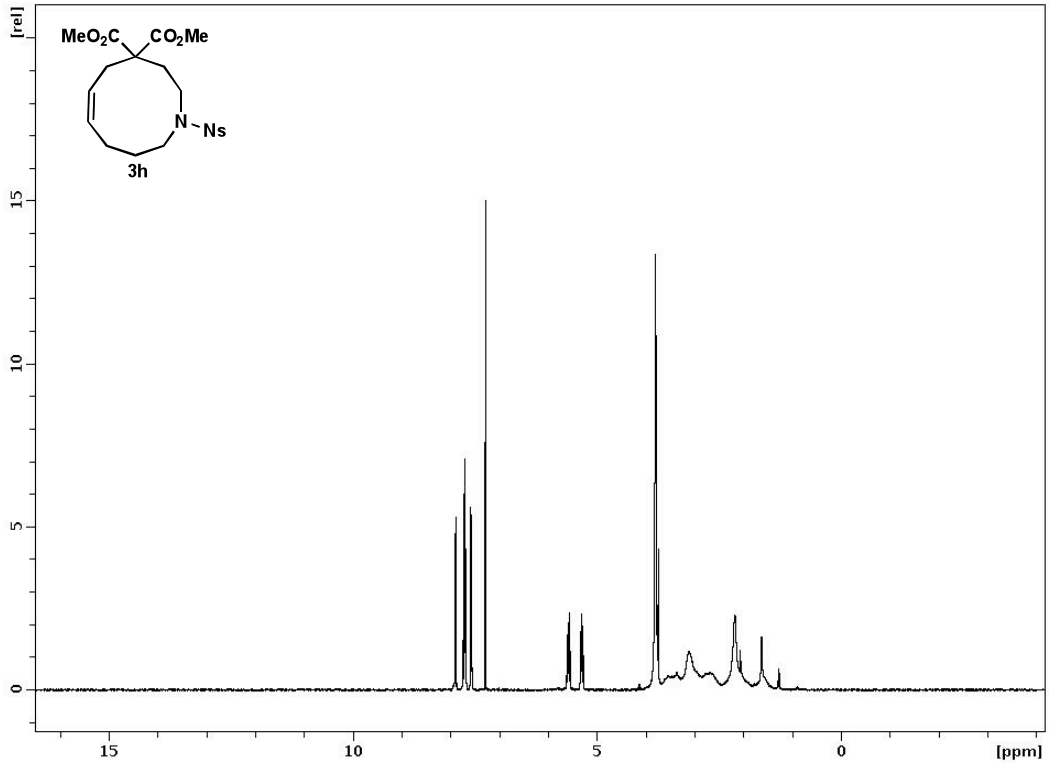
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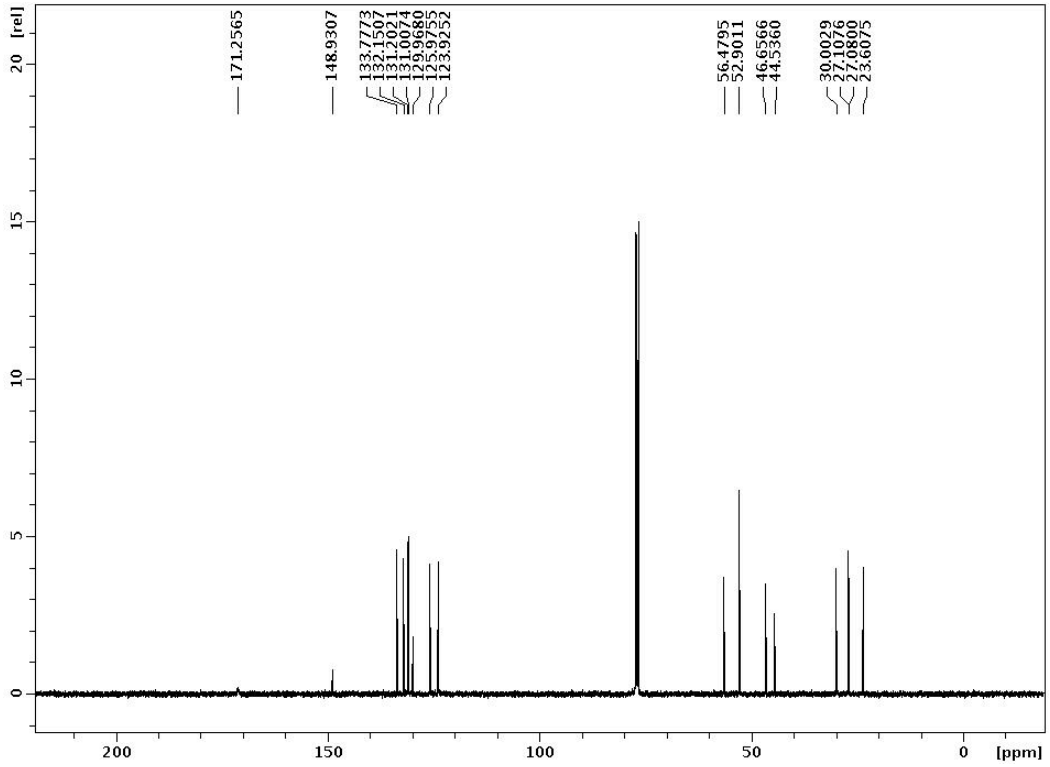
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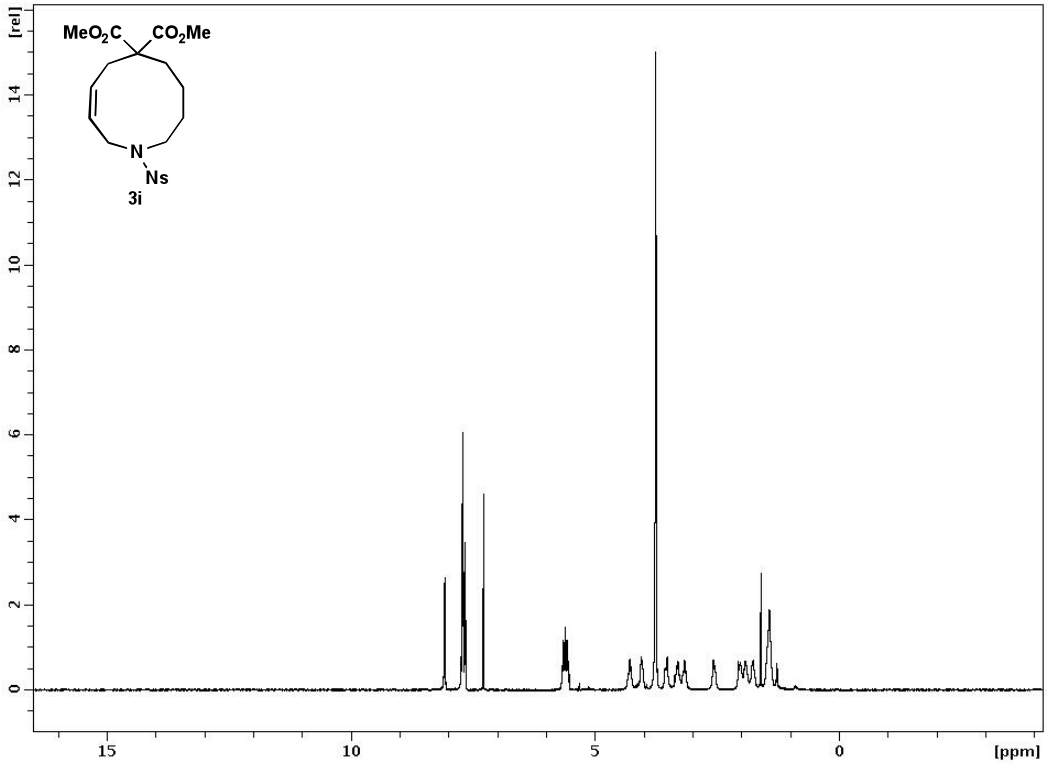
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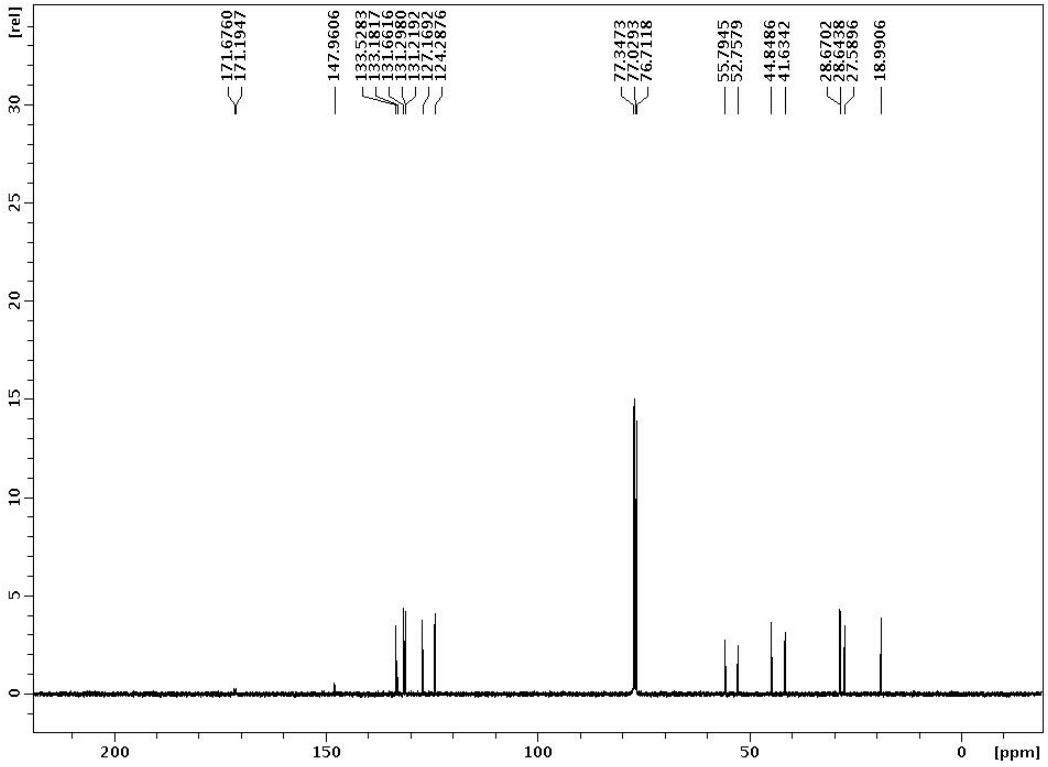
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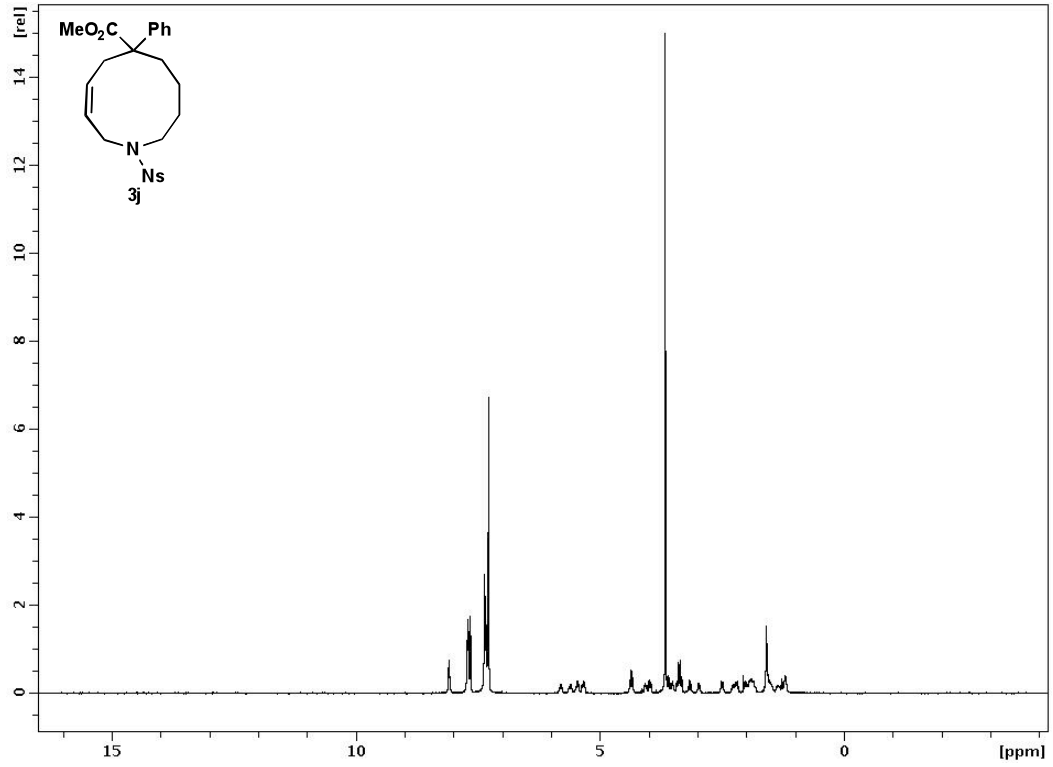
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Ph
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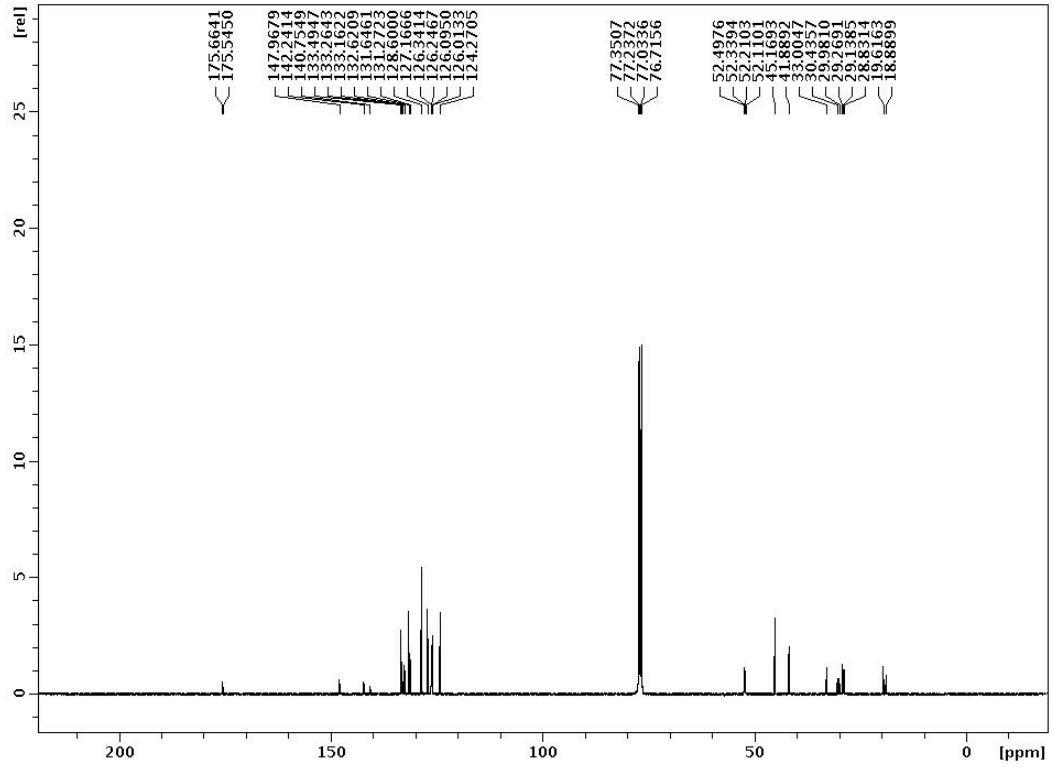
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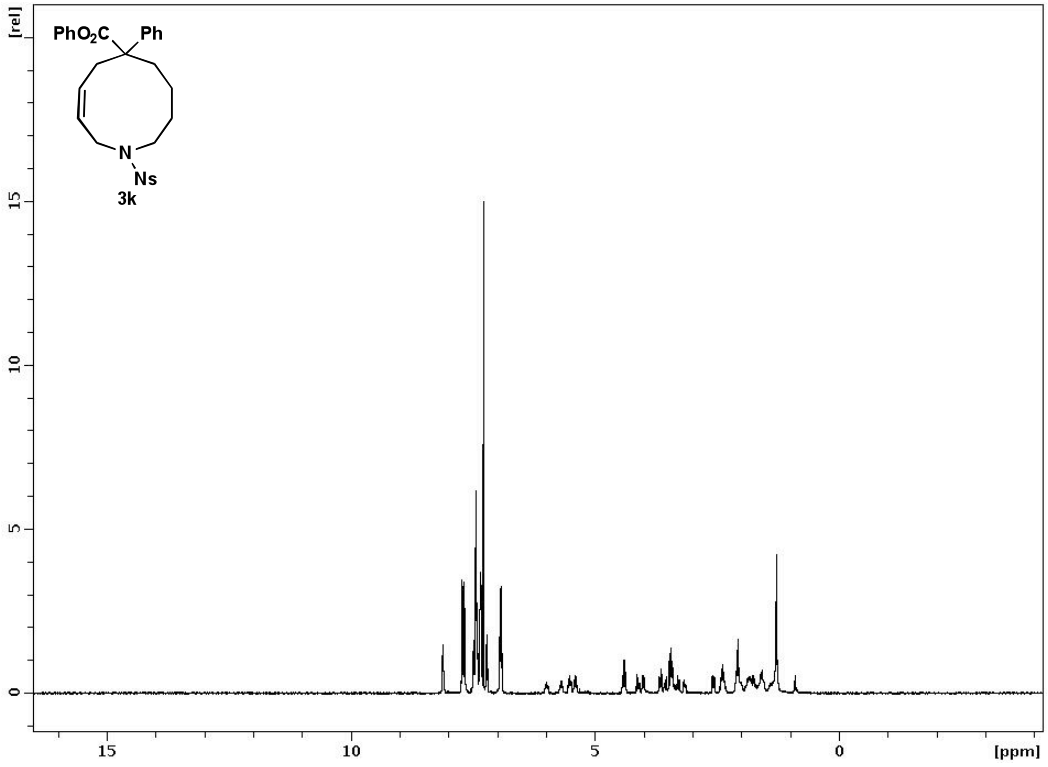
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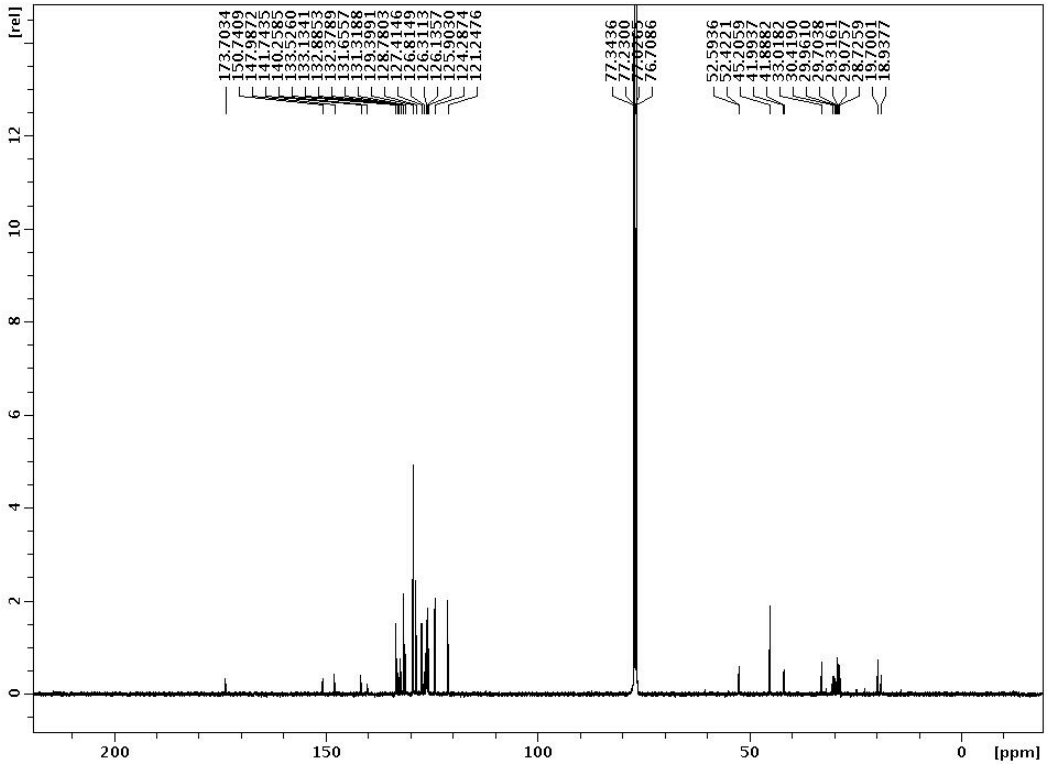
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76.7086
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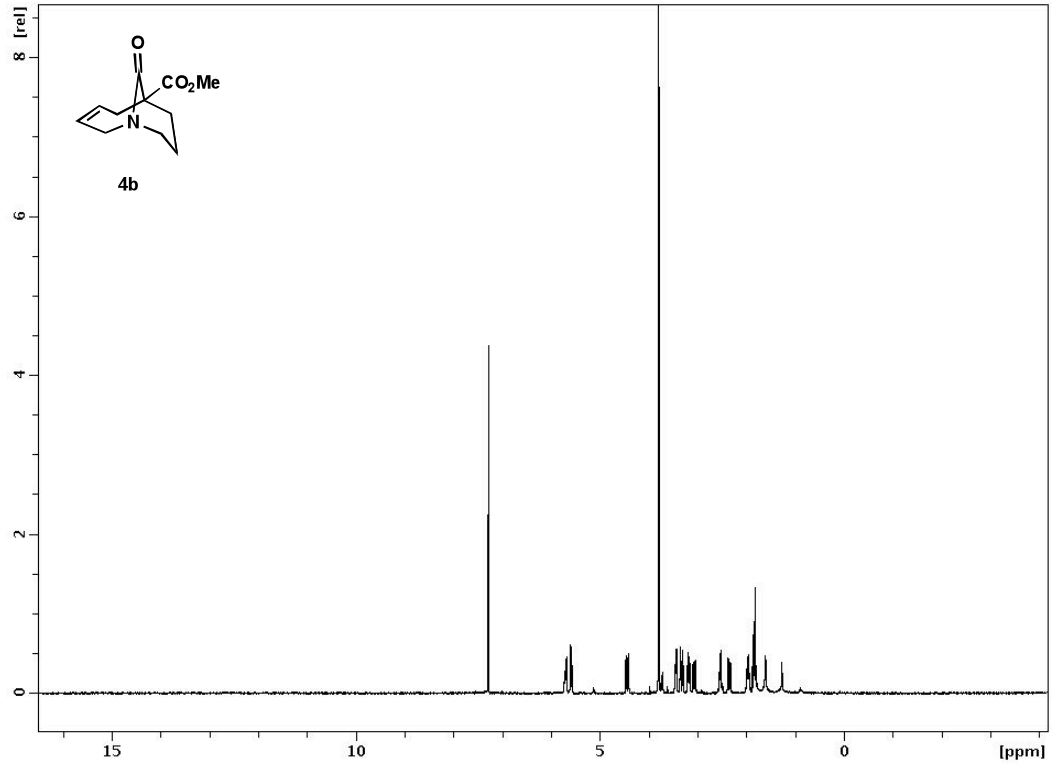
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CO2Me
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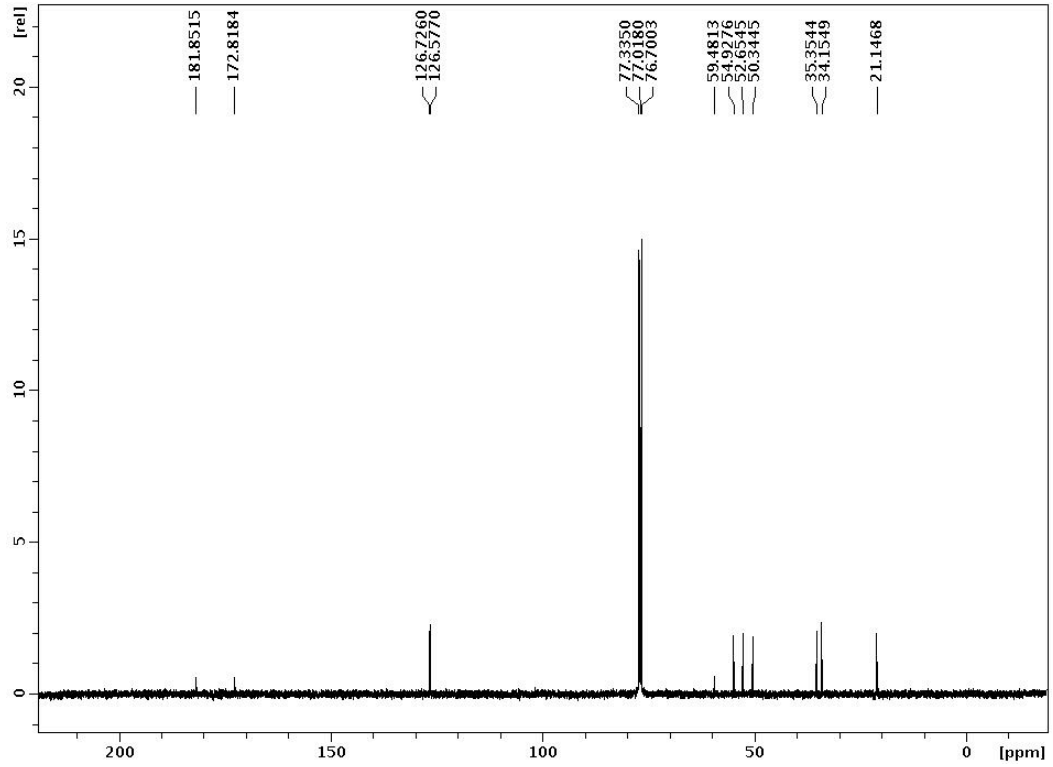
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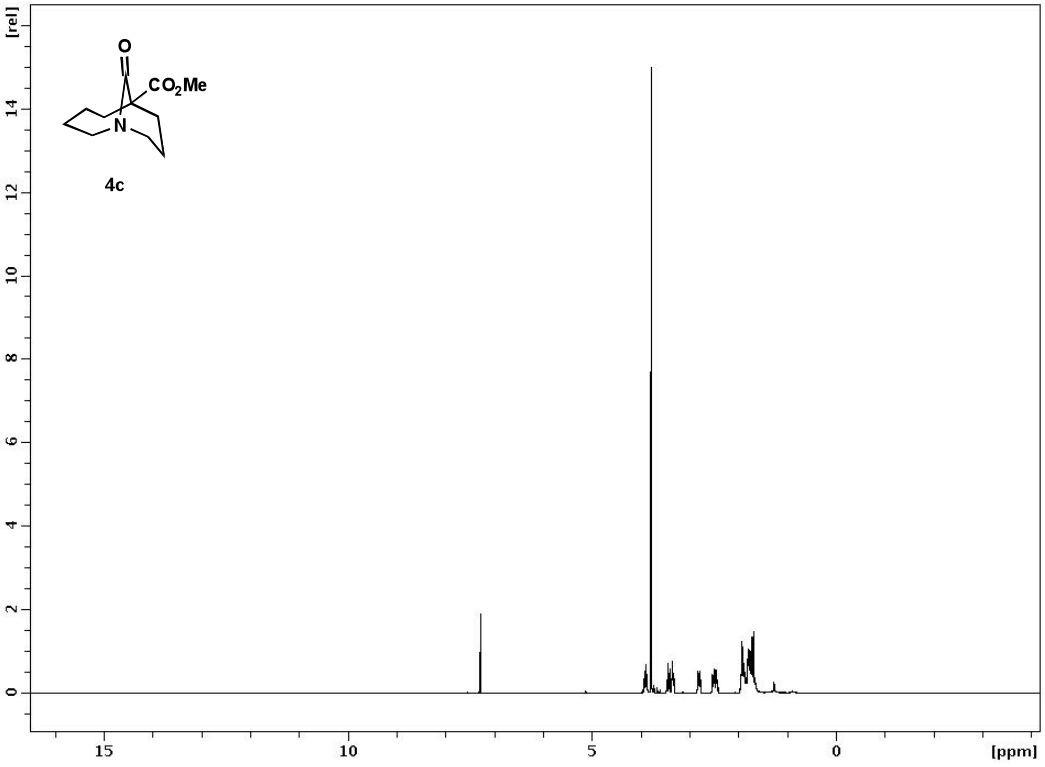
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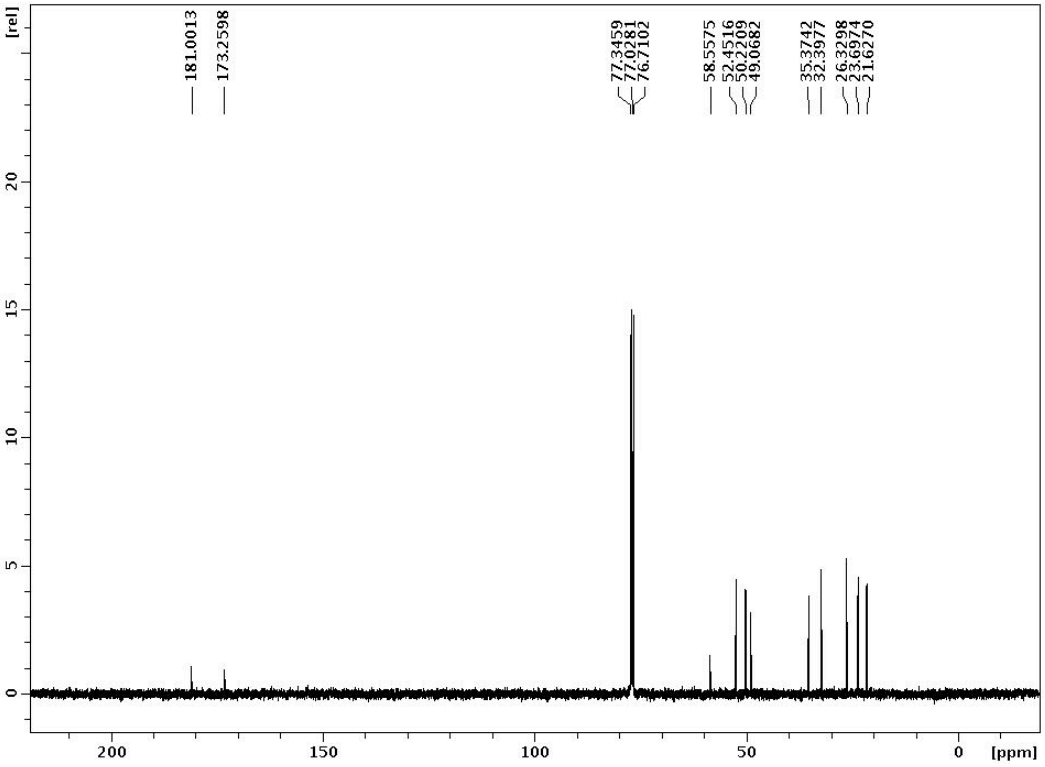
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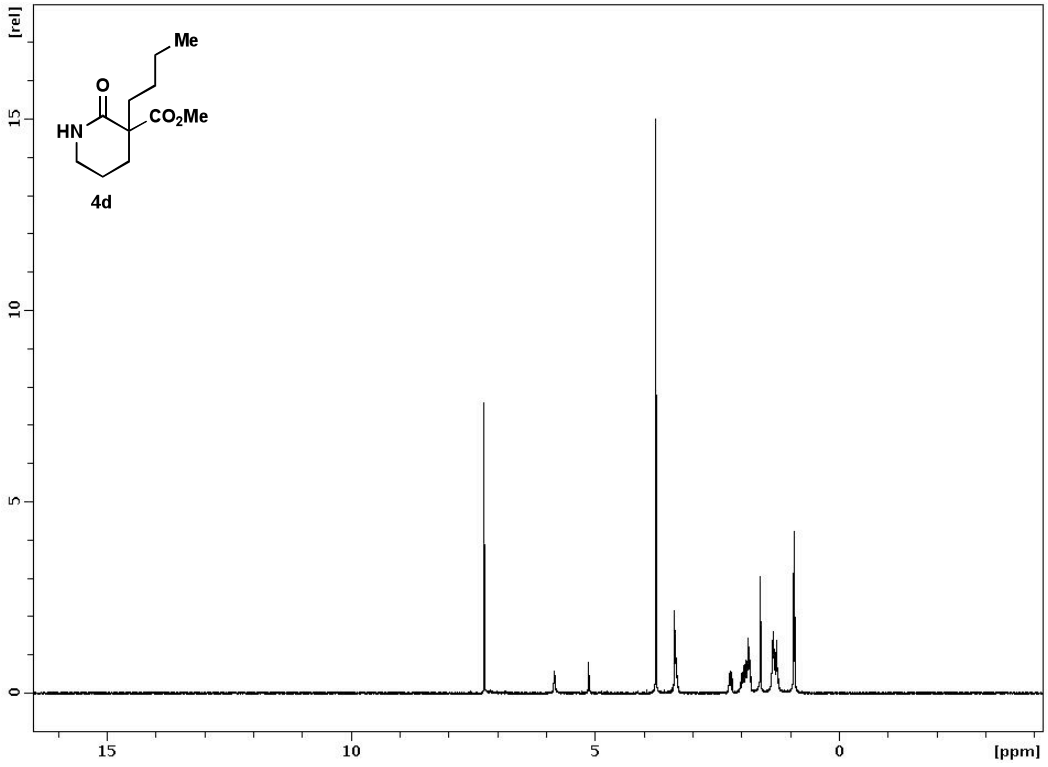
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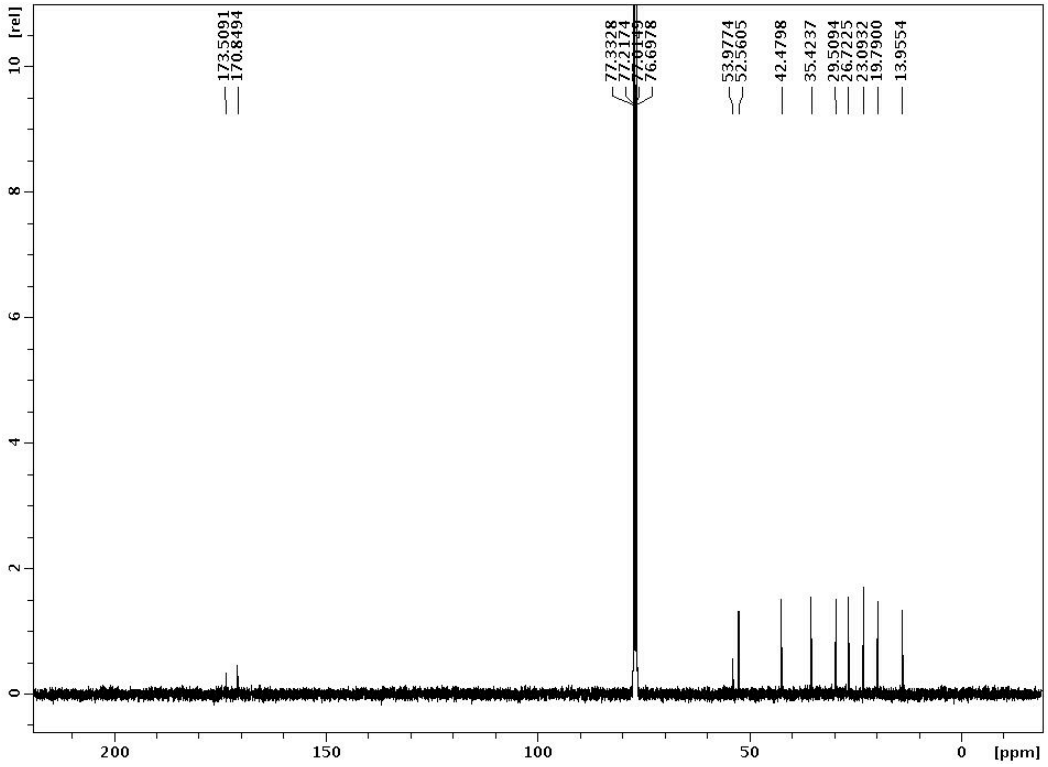
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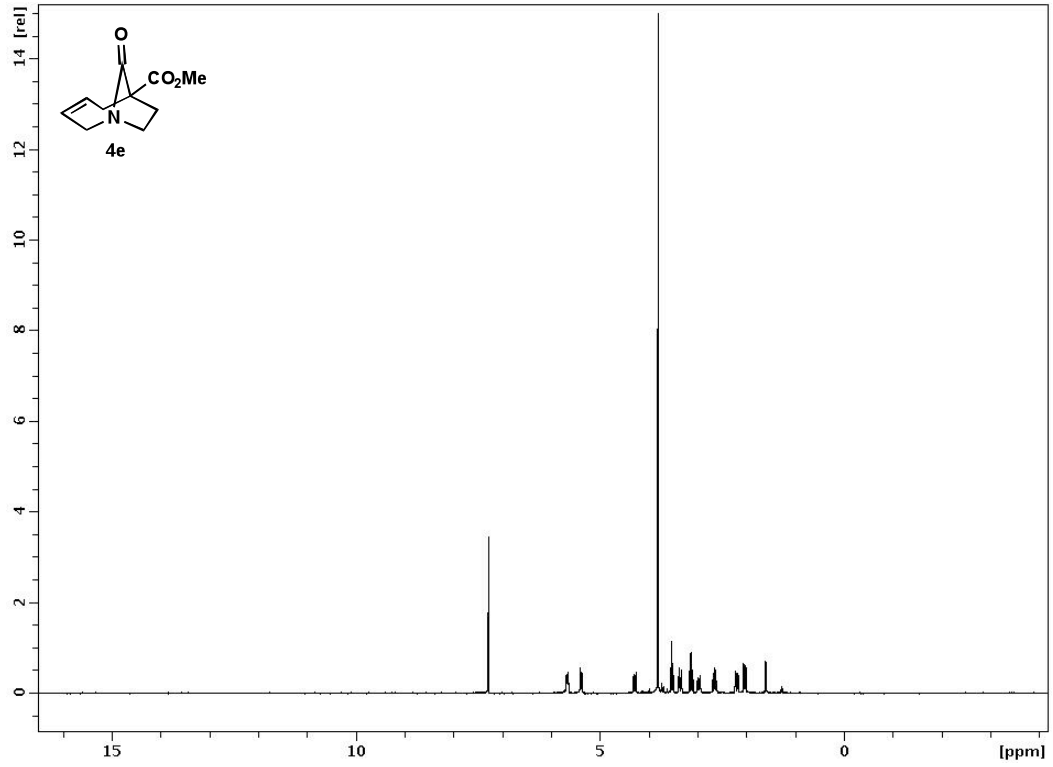
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N
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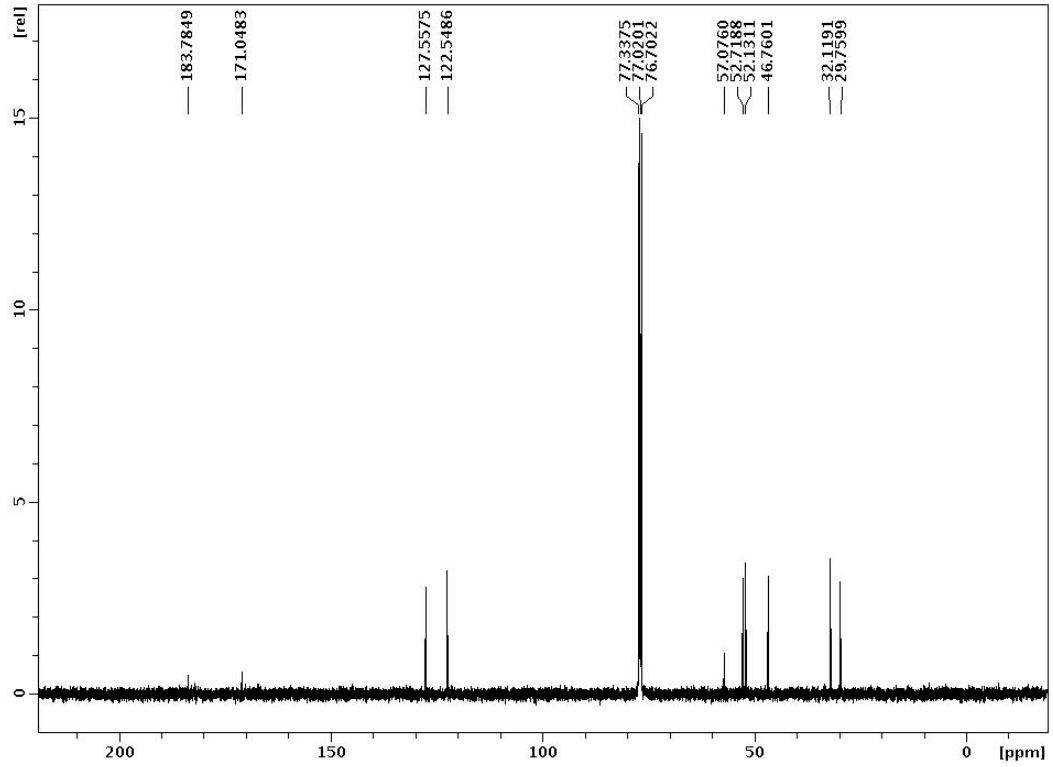
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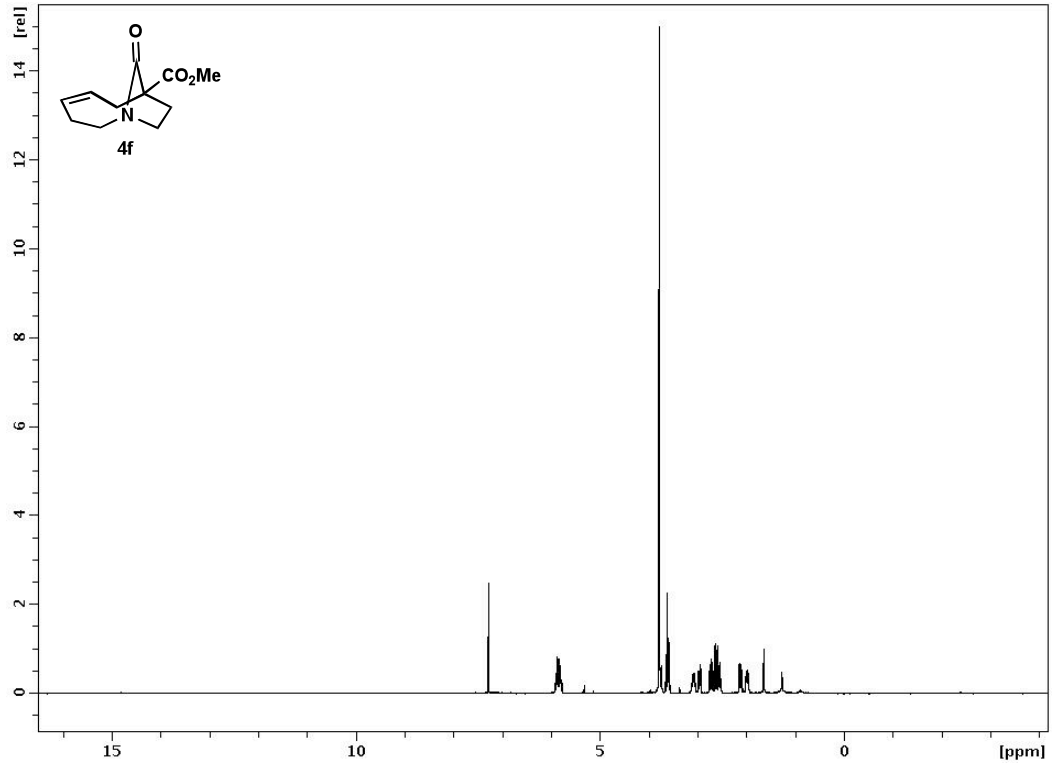
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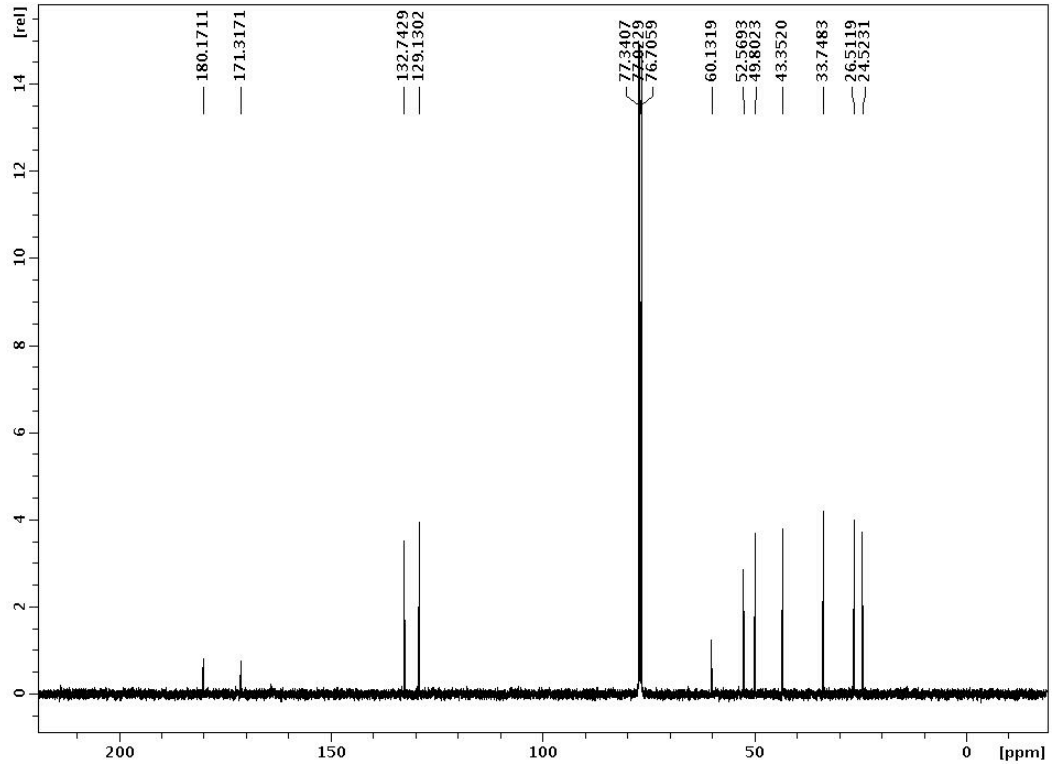
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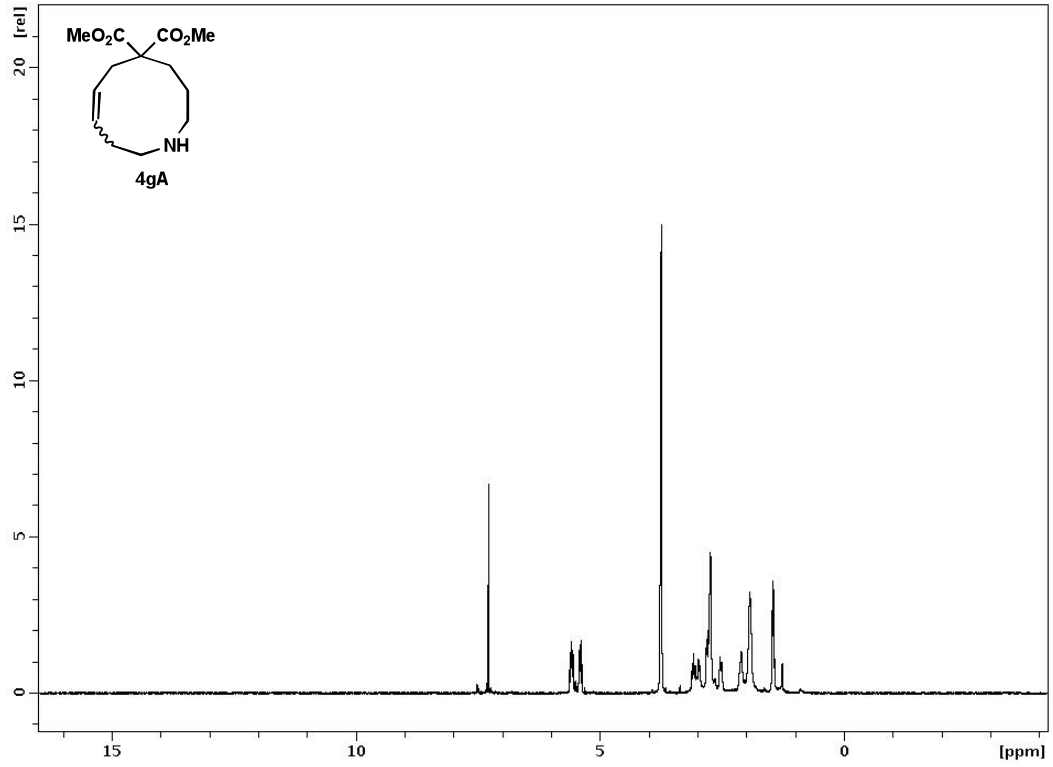
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CO2Me
NH
4gA
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5
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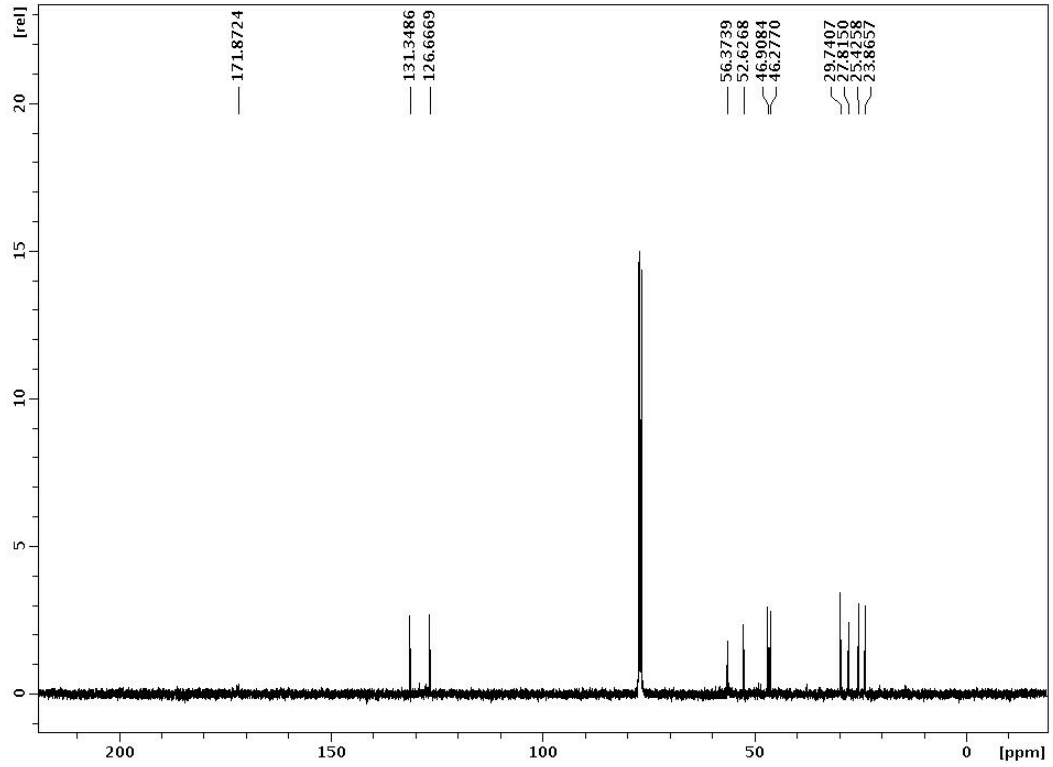
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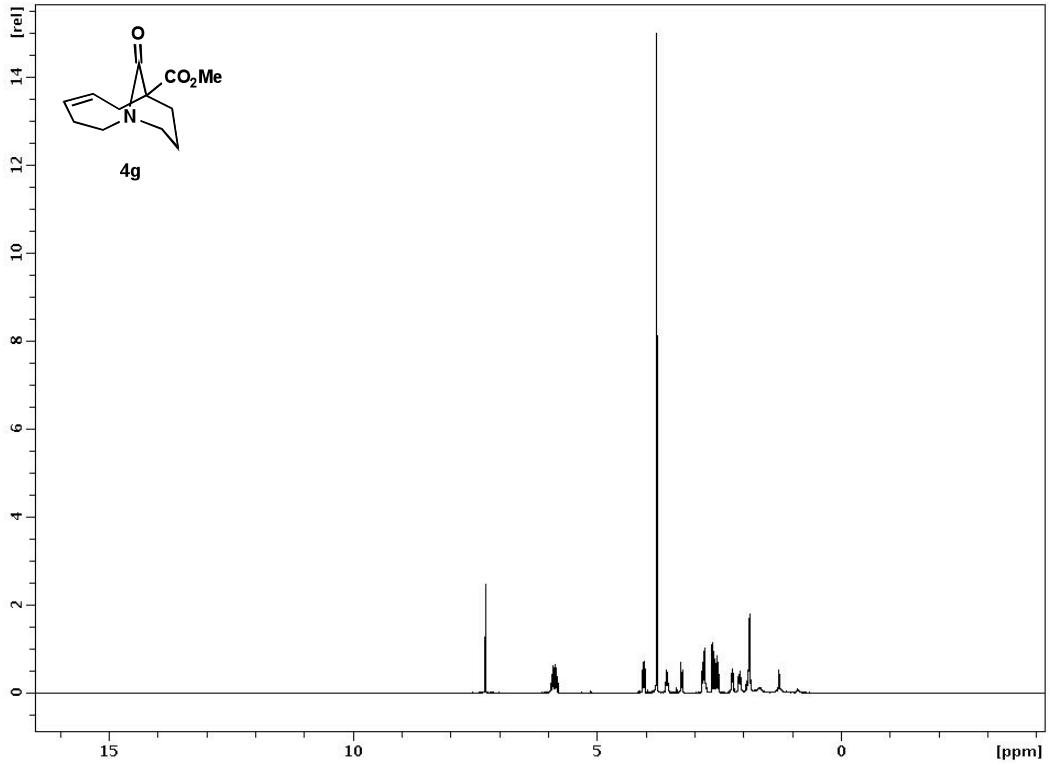
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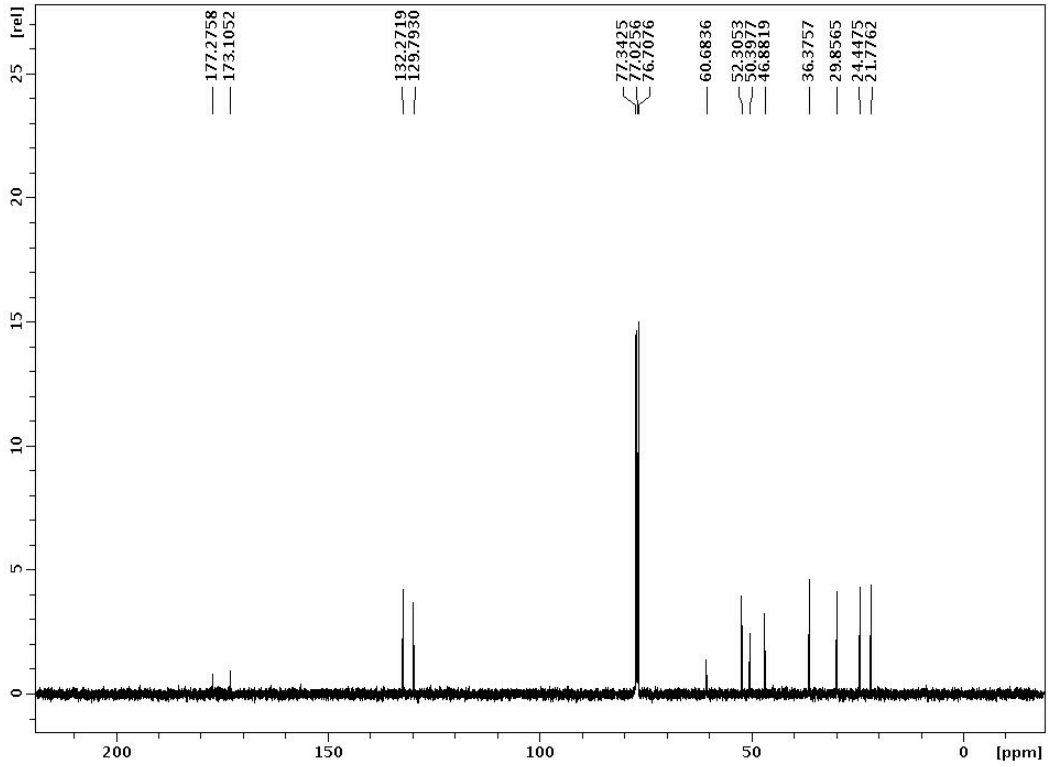
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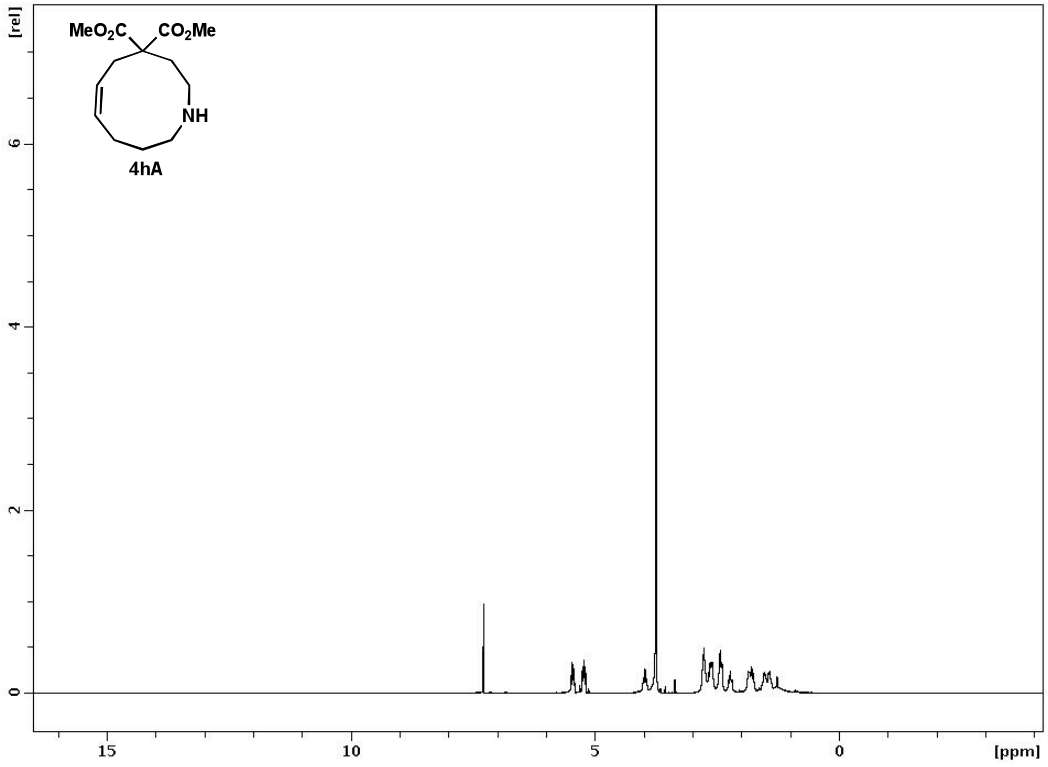
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CO2Me
NH
4hA
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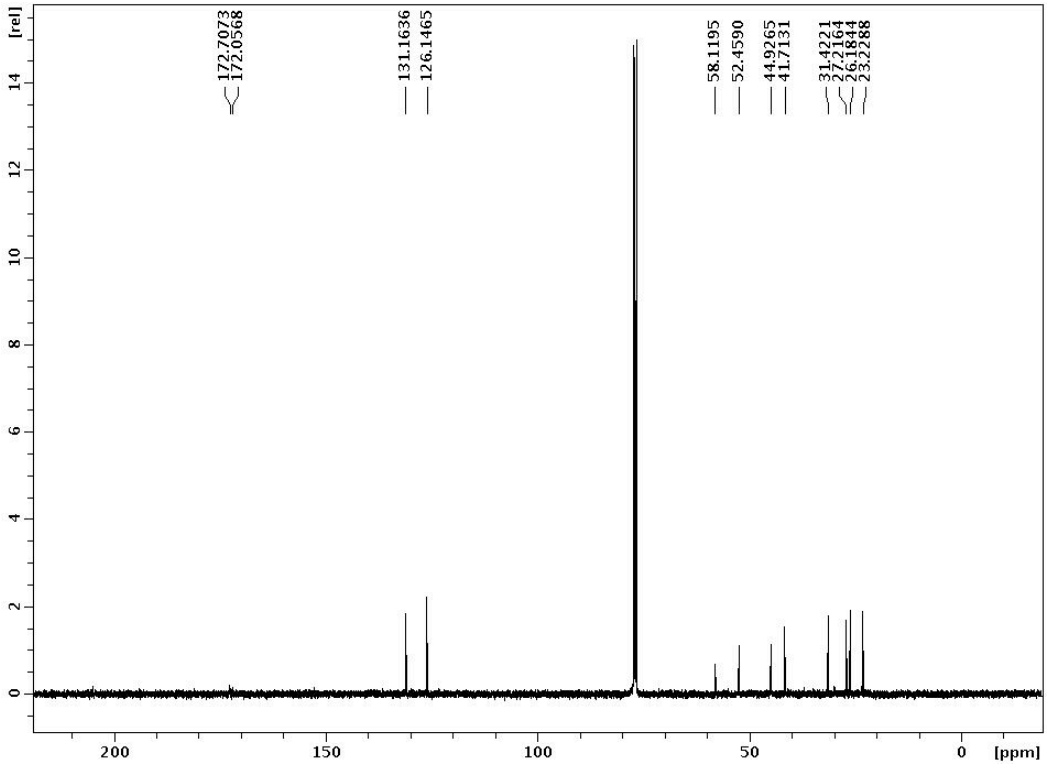
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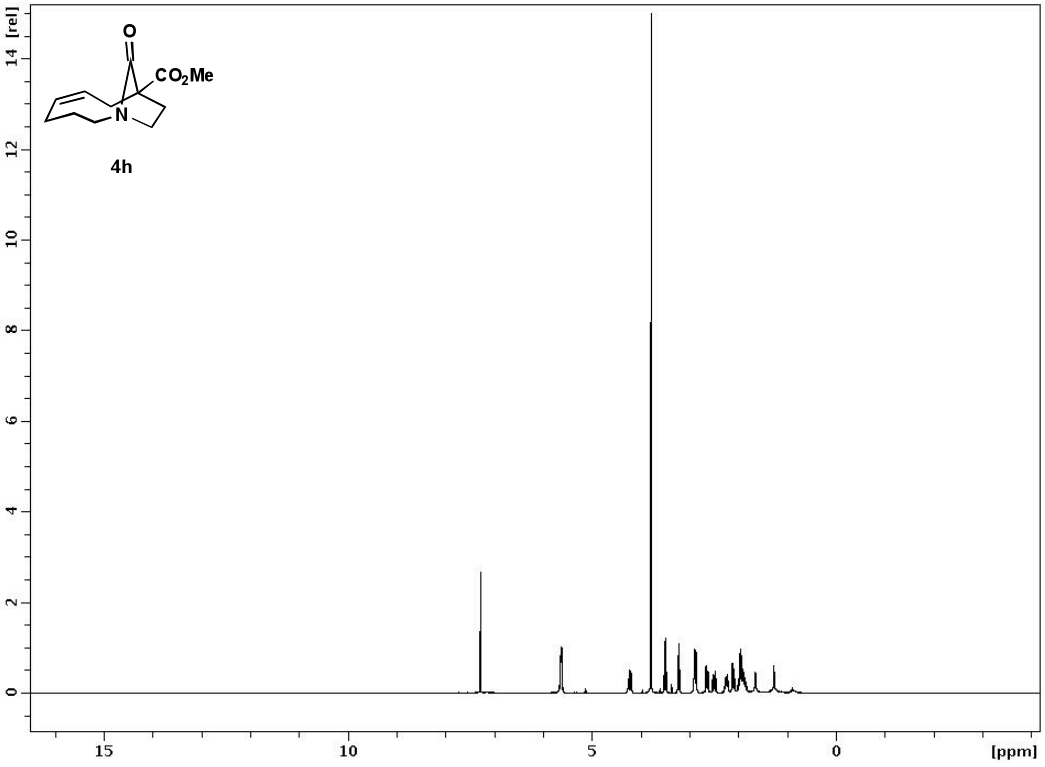
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CO2Me
N
4h
[rel]
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10
8
6
4
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15
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5
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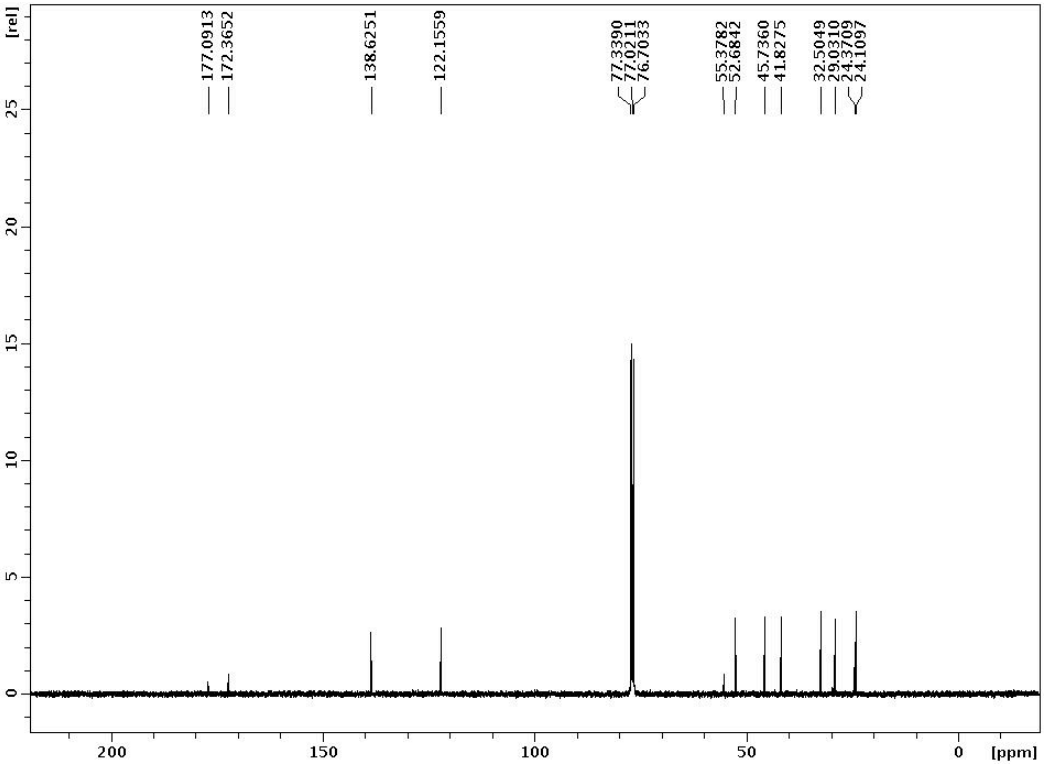
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25
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10
5
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50
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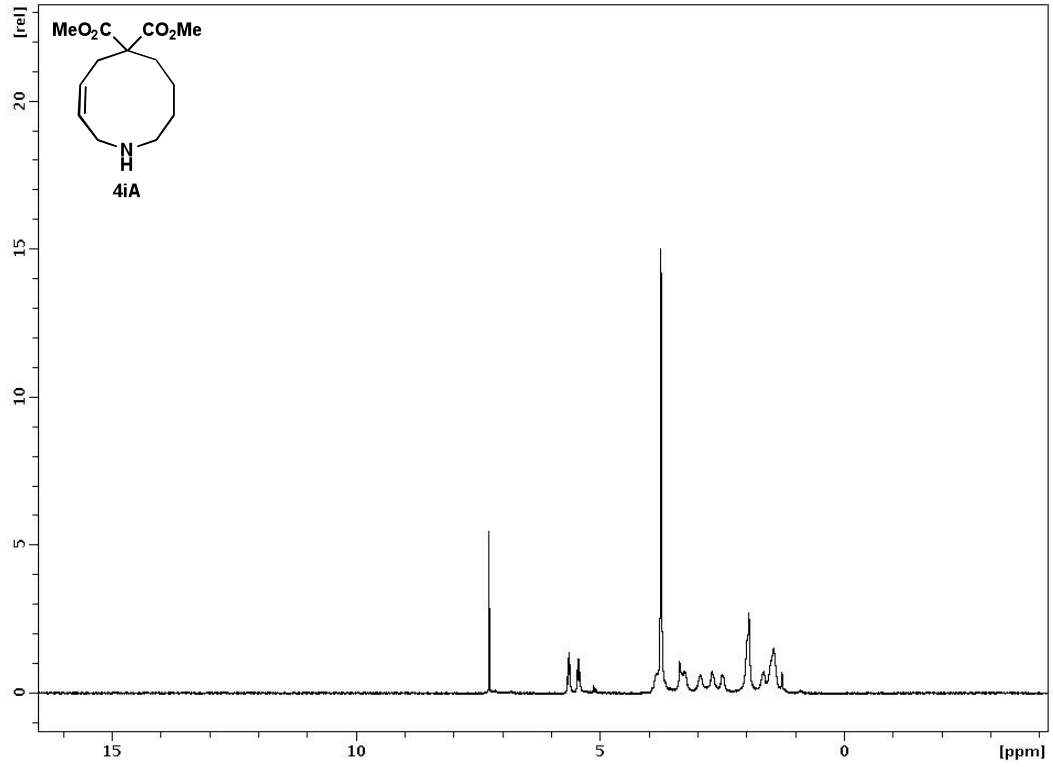
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CO2Me
N
H
4iA
[rel]
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10
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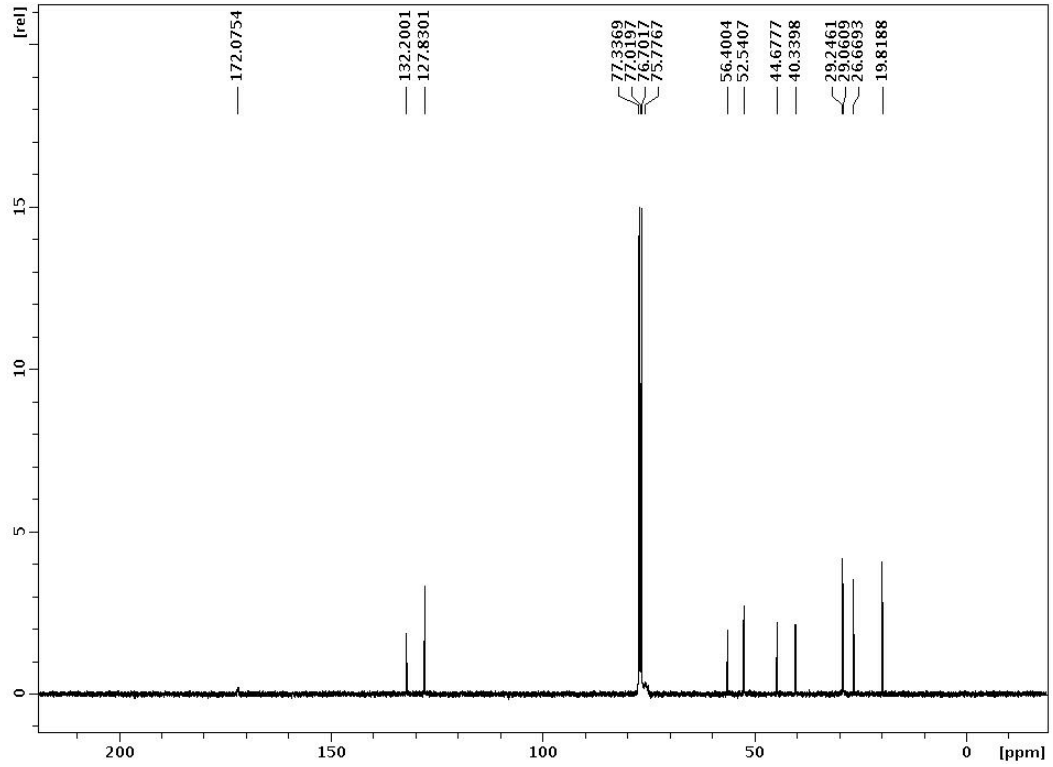
10
5
0
[ppm]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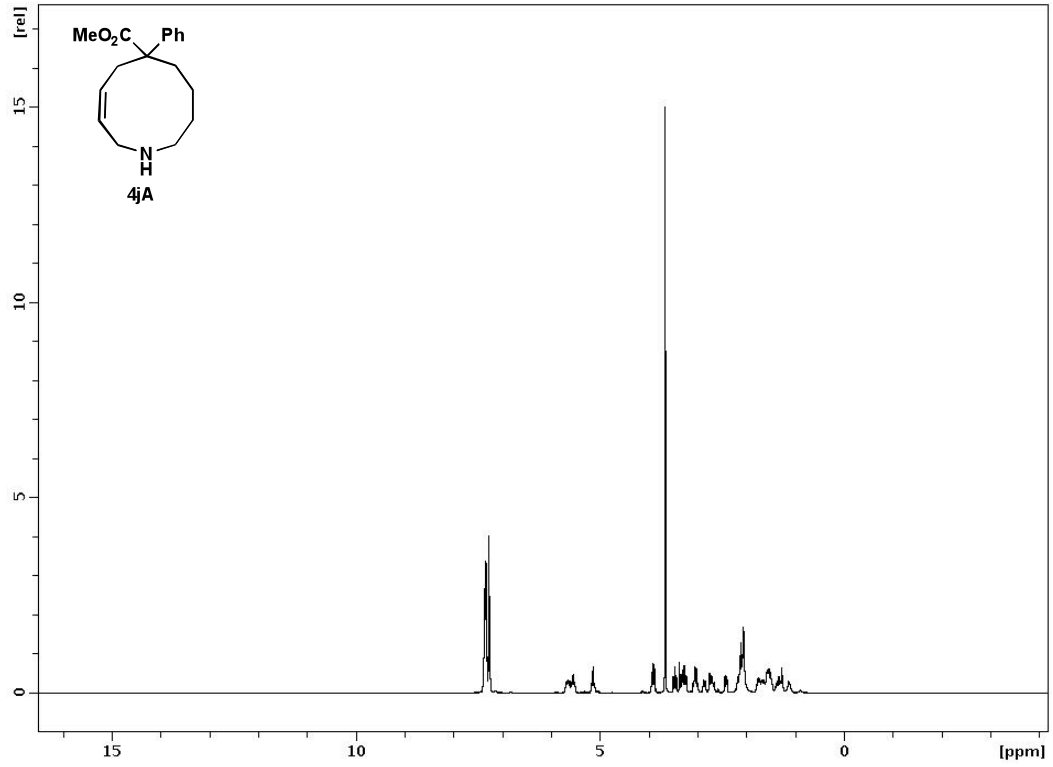
MeO2C
Ph
N
H
4jA
[rel]
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15
10
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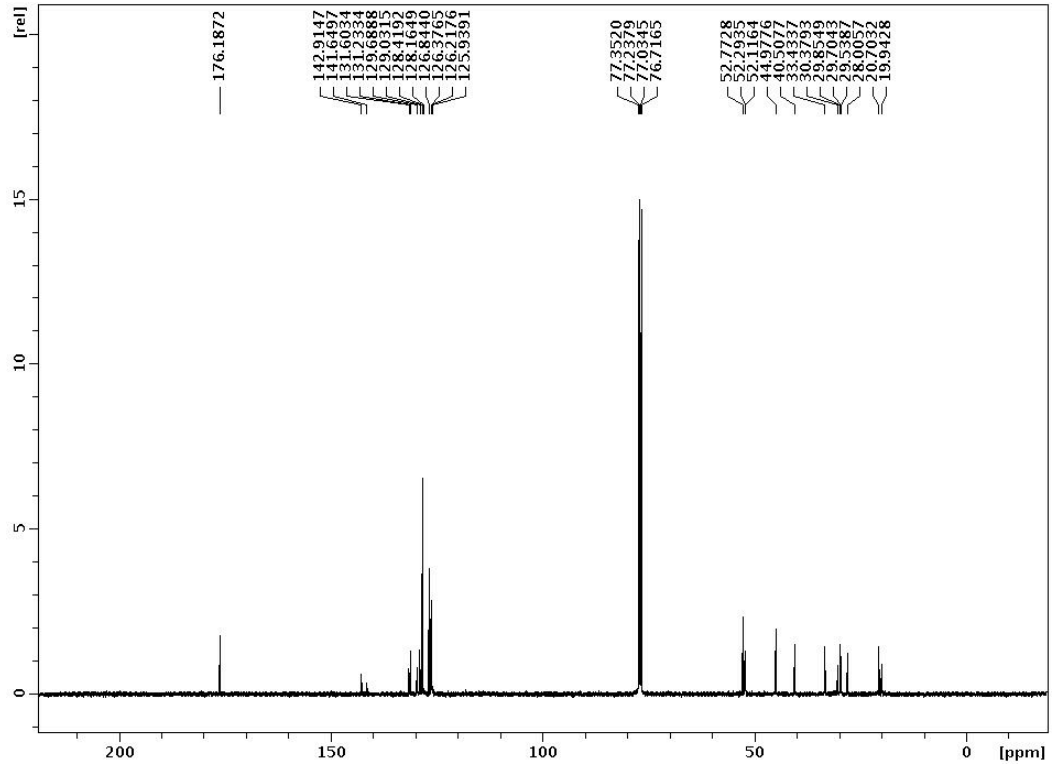
[ppm]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126.2176
125.9391
77.3520
77.2379
77.0345
76.7165
52.7728
52.2935
52.1164
44.9776
40.5077
33.4337
30.3733
29.9549
29.5387
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20.7032
19.9428
15
10
5
0
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100
50
0
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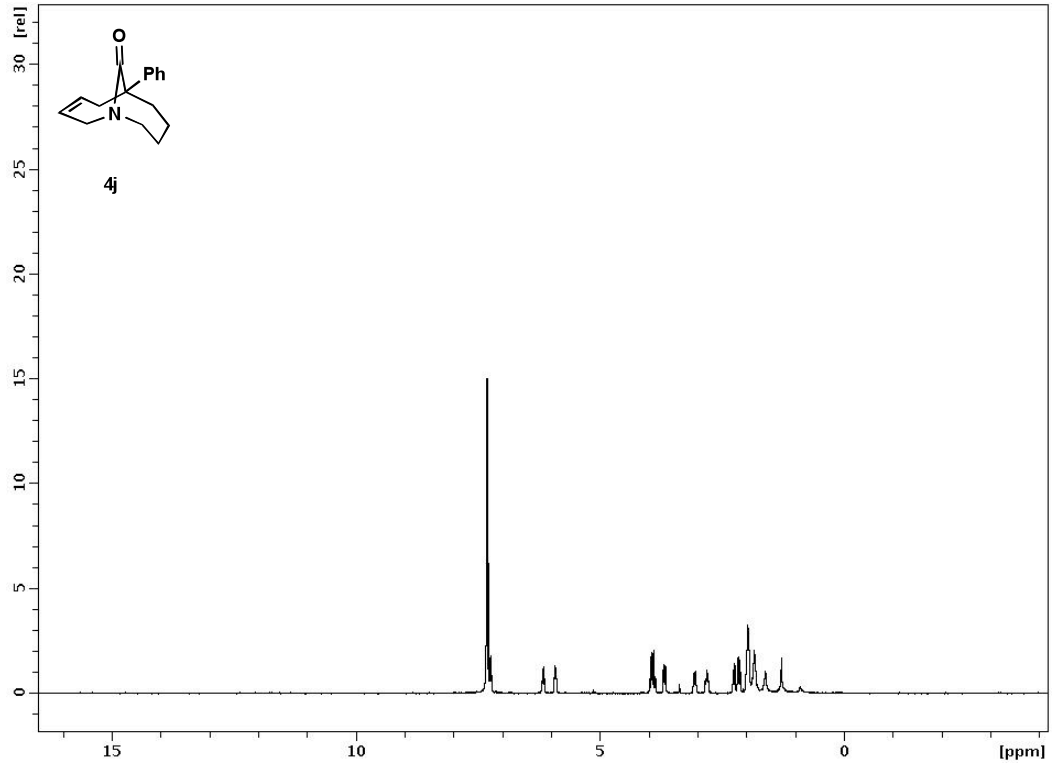
O
Ph
N
4j
[rel]
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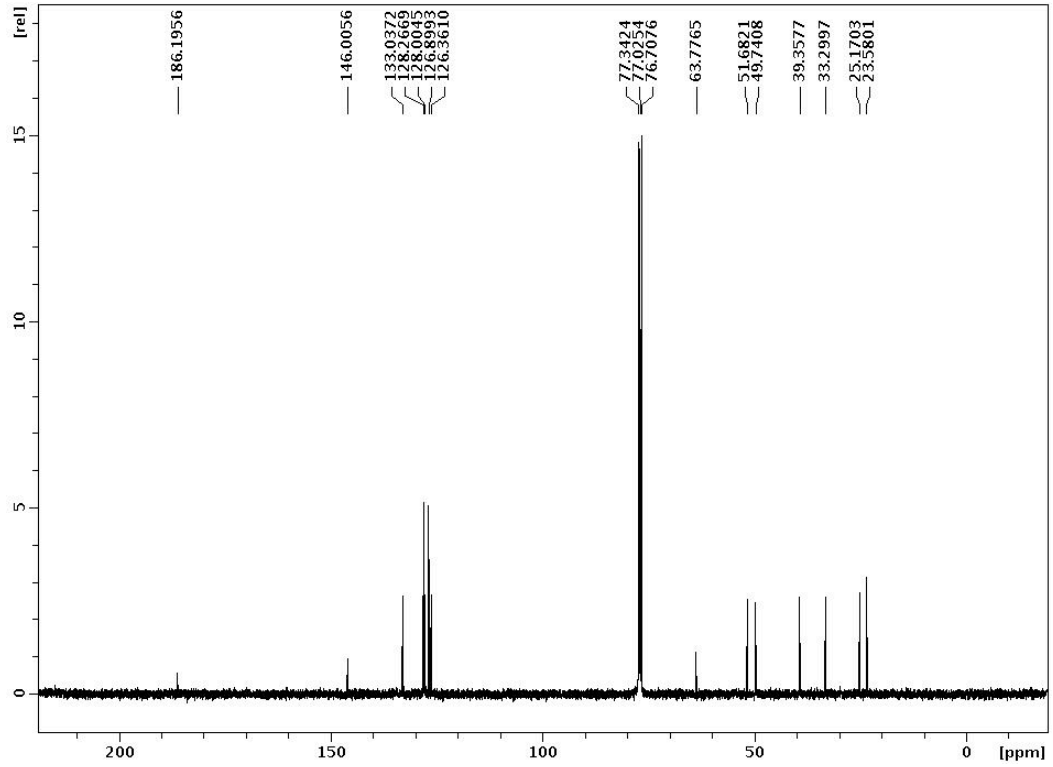
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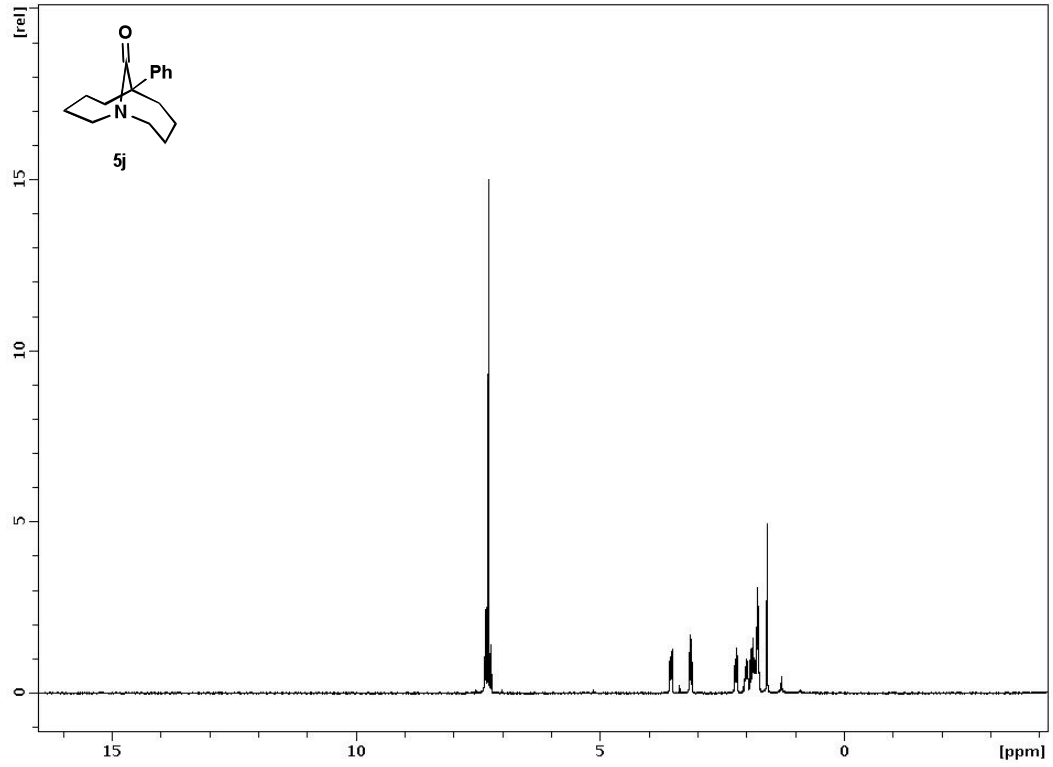
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Ph
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10
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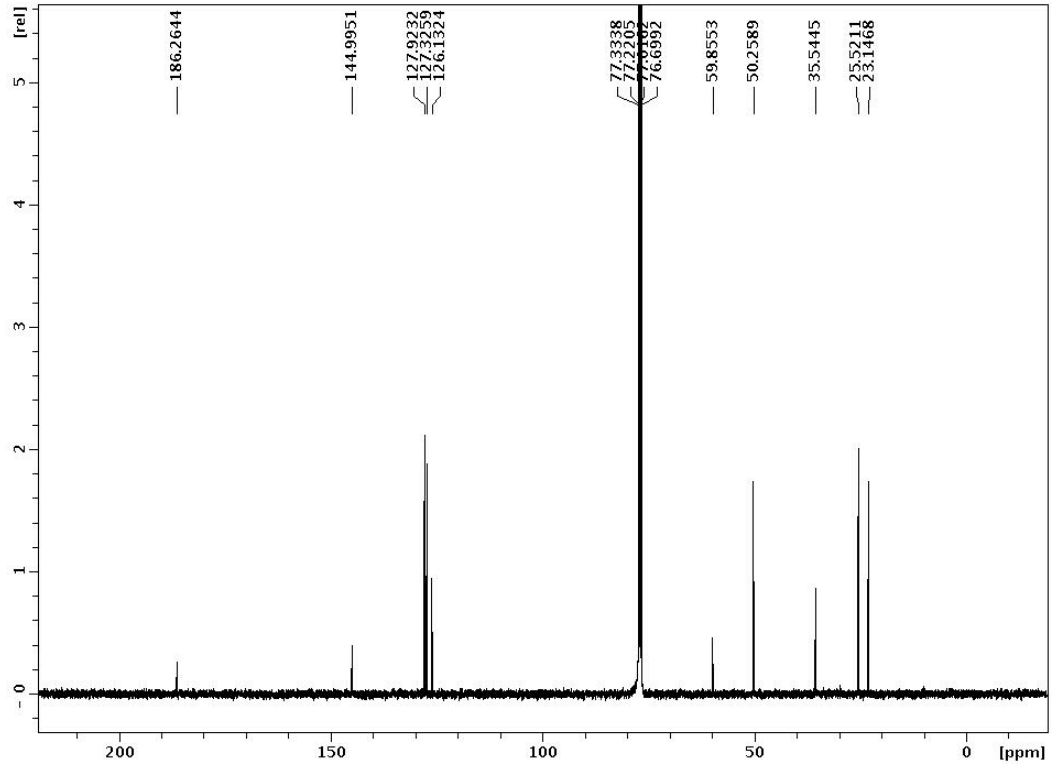
[ppm]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25.5211
23.1468
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4
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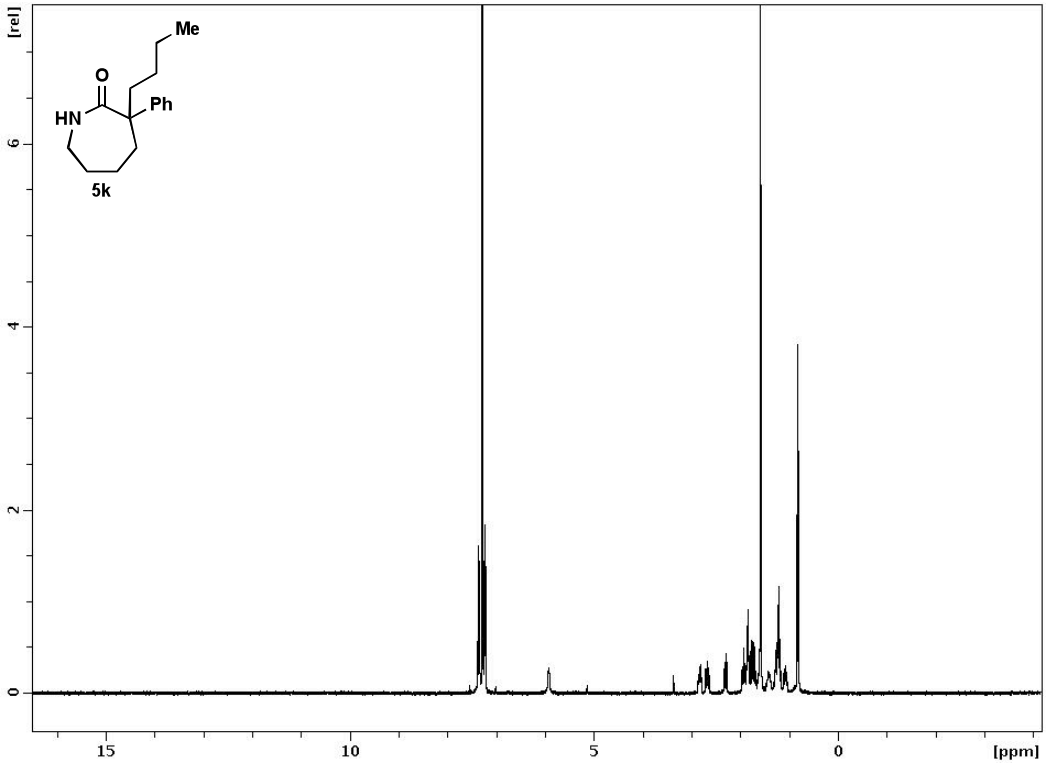
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HN
Ph
5k
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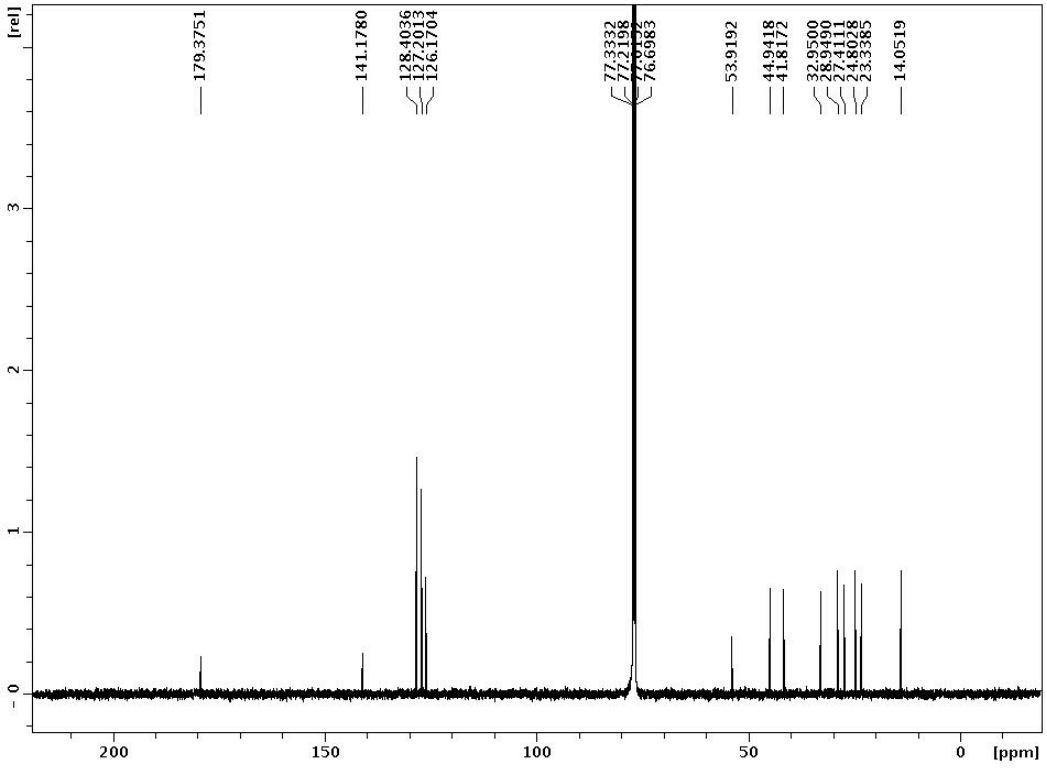
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32.9500
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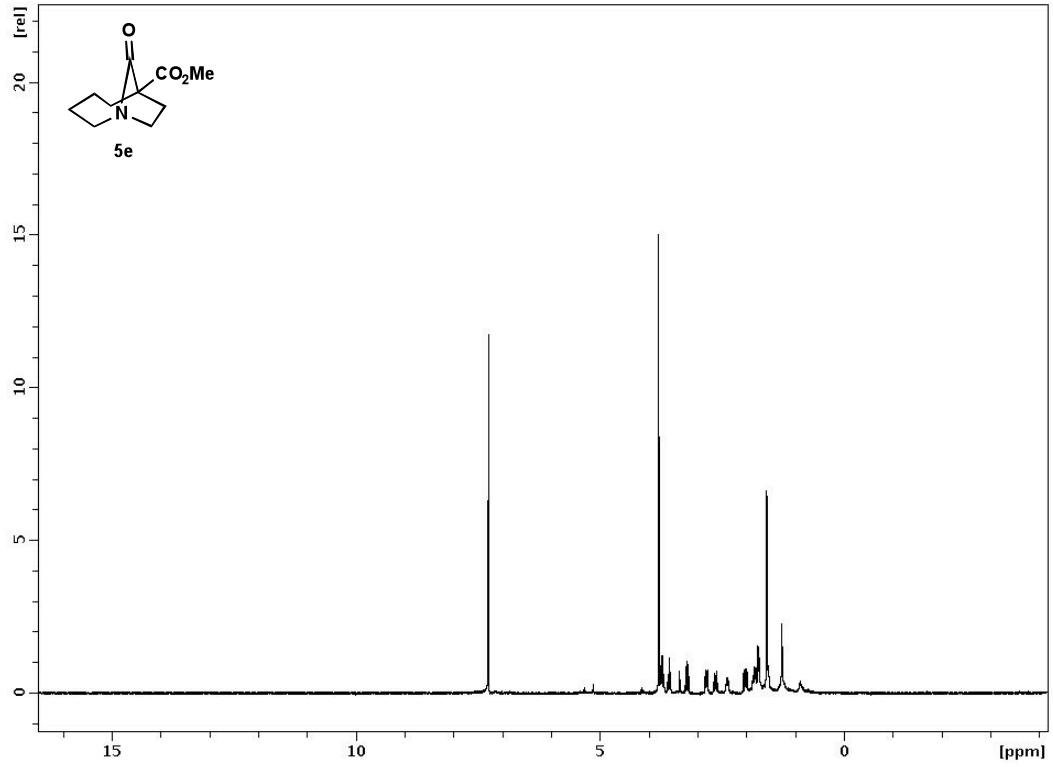
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N
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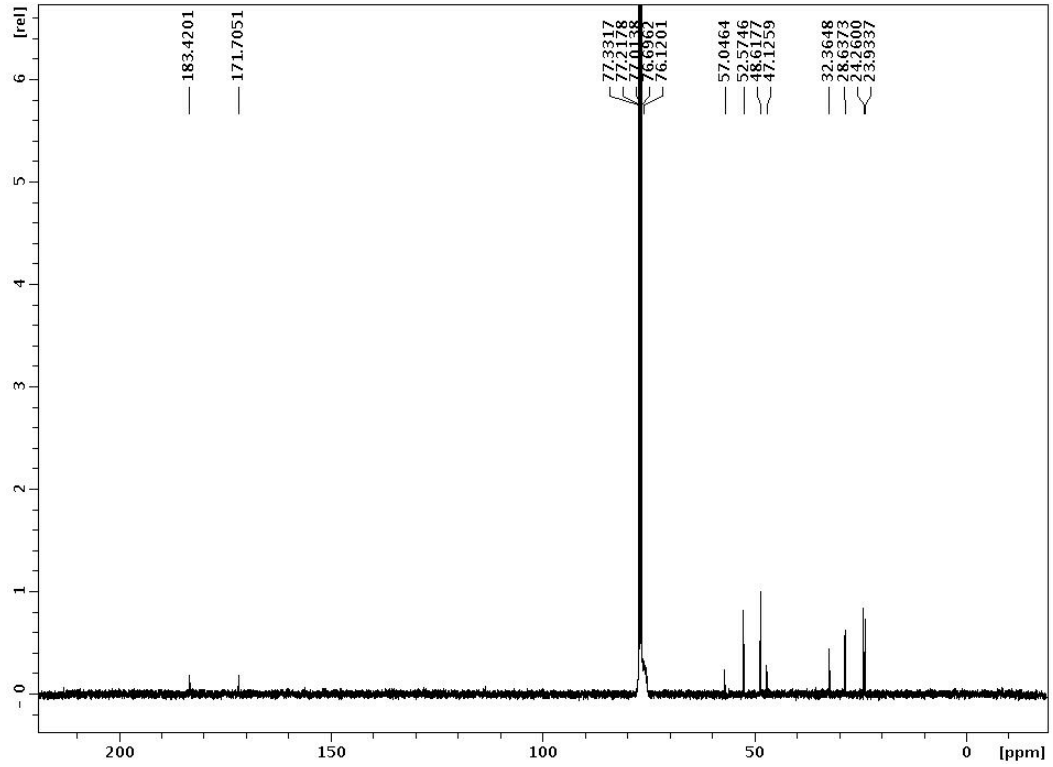
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47.1259
32.3648
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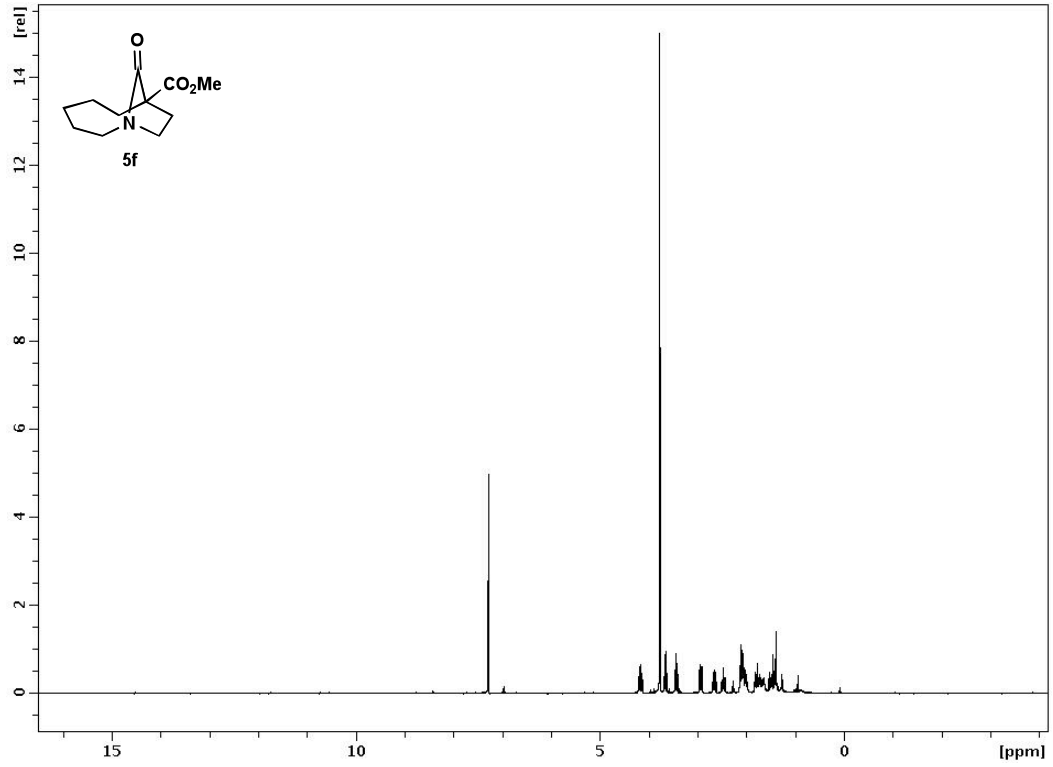
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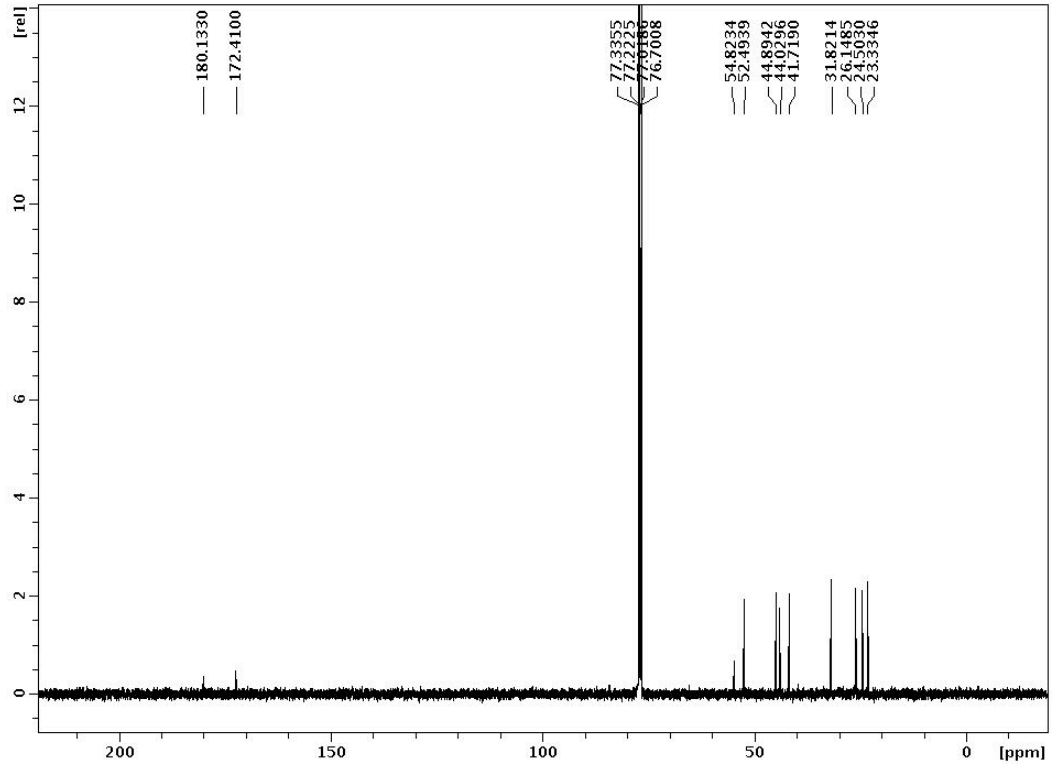
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23.3346
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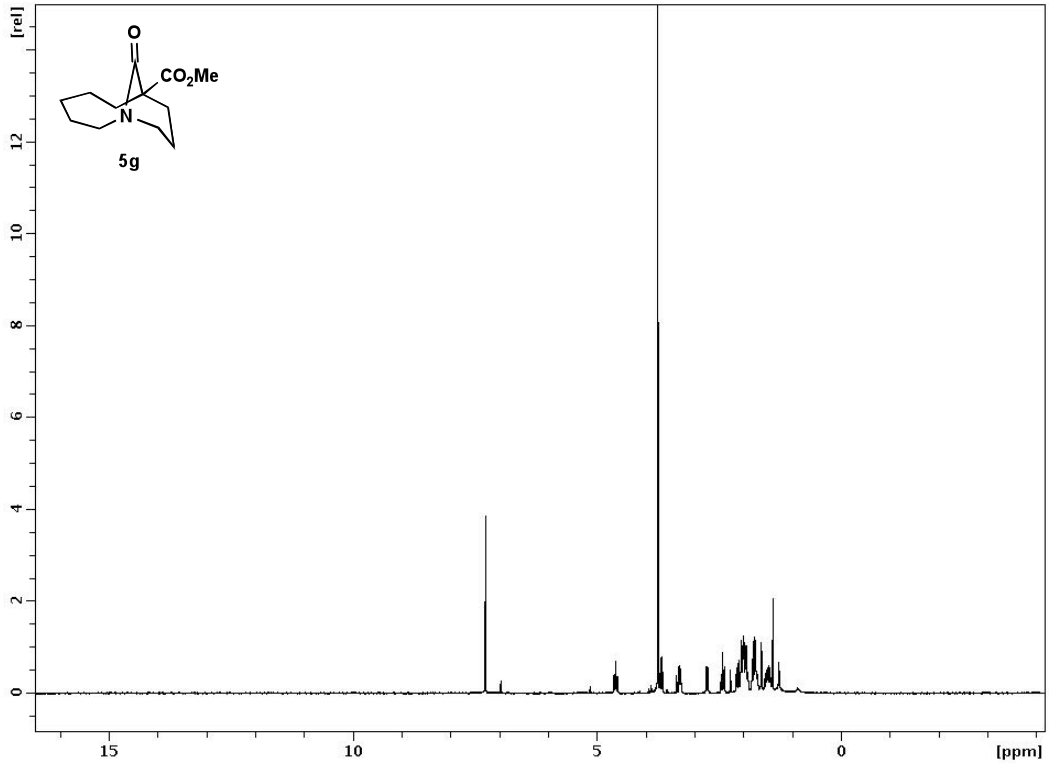
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CO2Me
N
5g
[rel]
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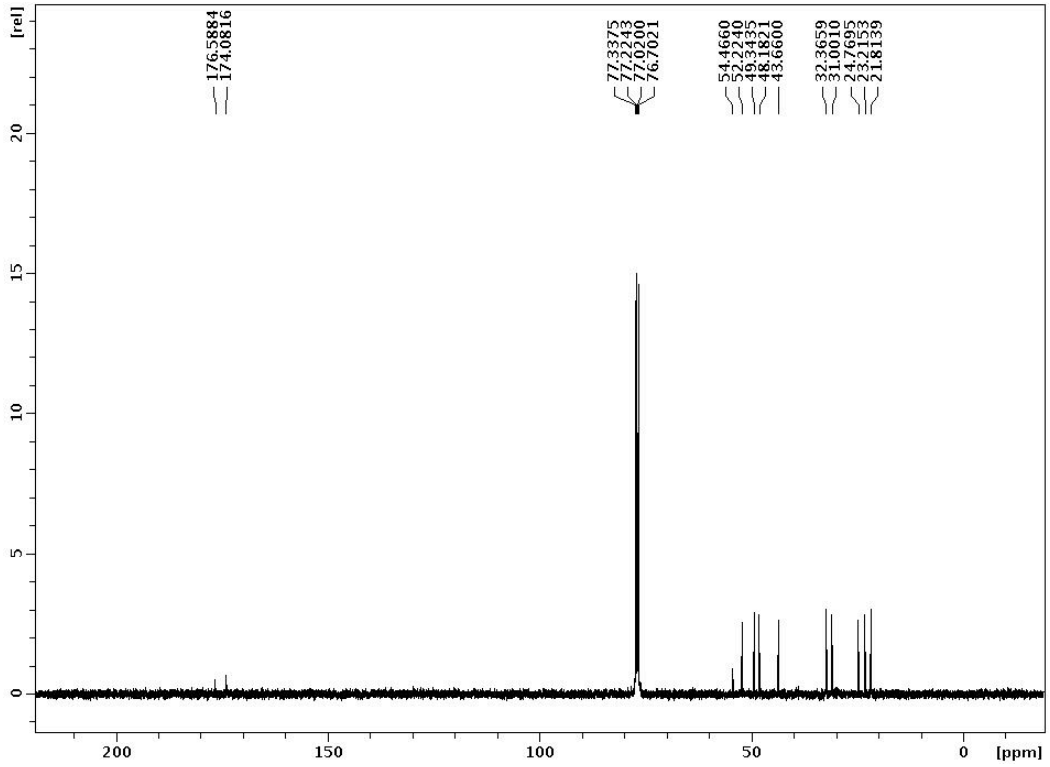
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43.6600
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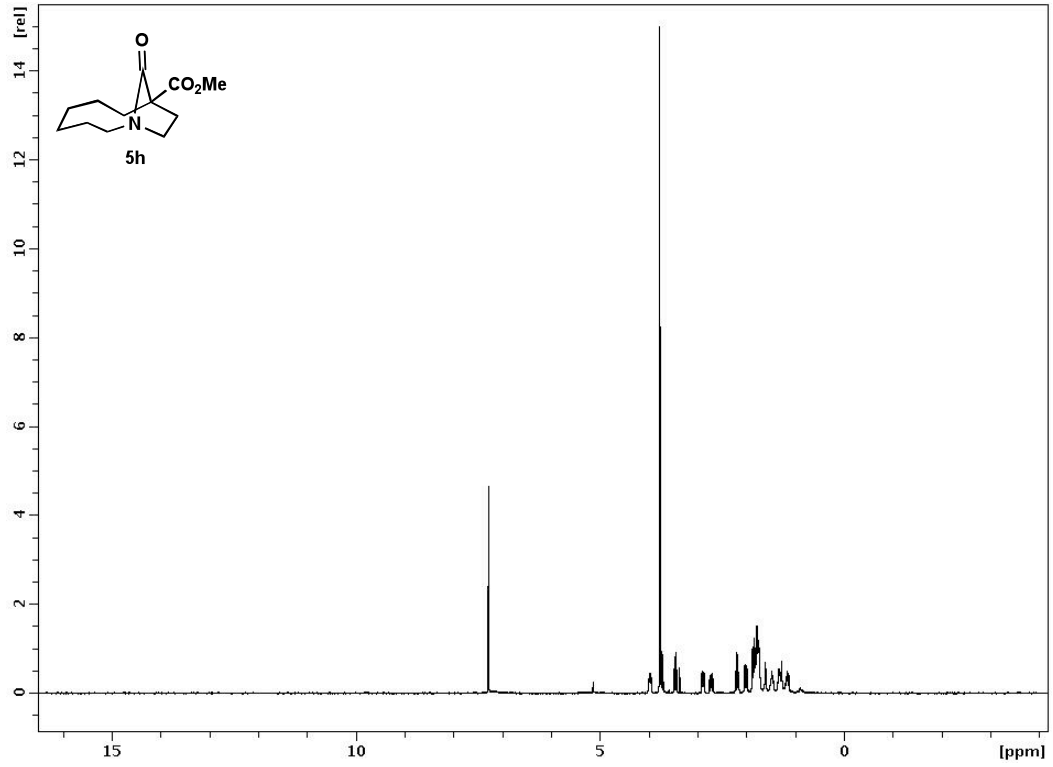
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CO2Me
N
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[rel]
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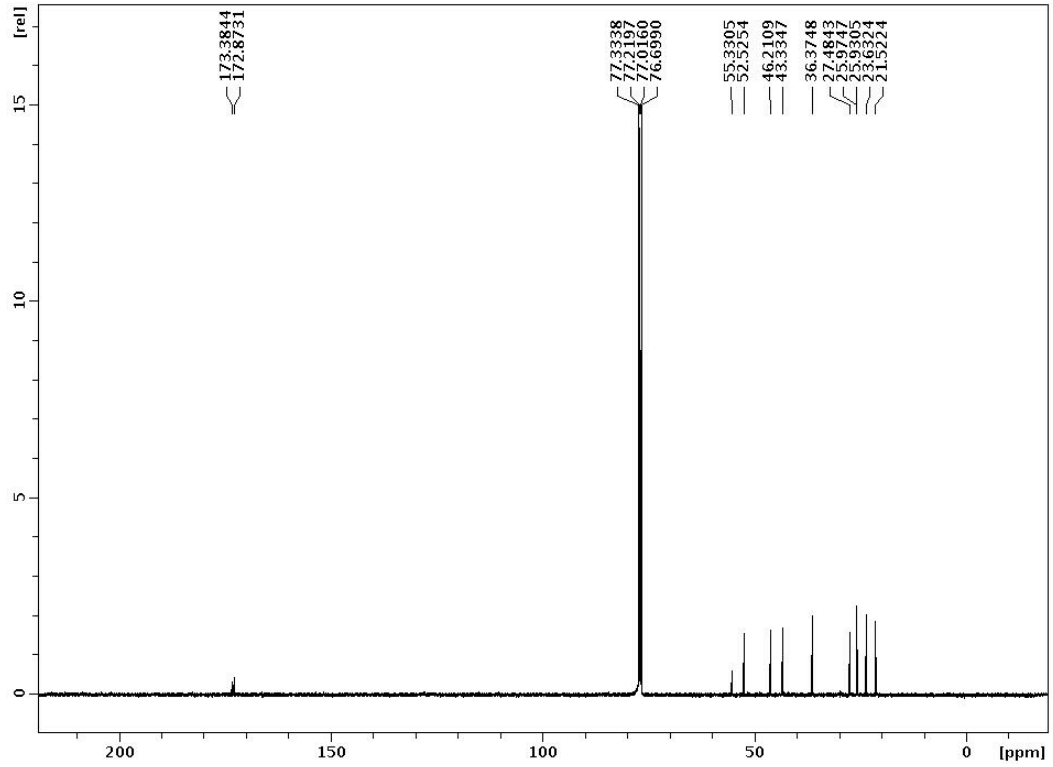
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23.6324
21.5224
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