Supporting Information

Flash Generation of α-(Trifluoromethyl)vinyllithium and an Application to Continuous Flow Three-Component Synthesis of α-Trifluoromethylamides

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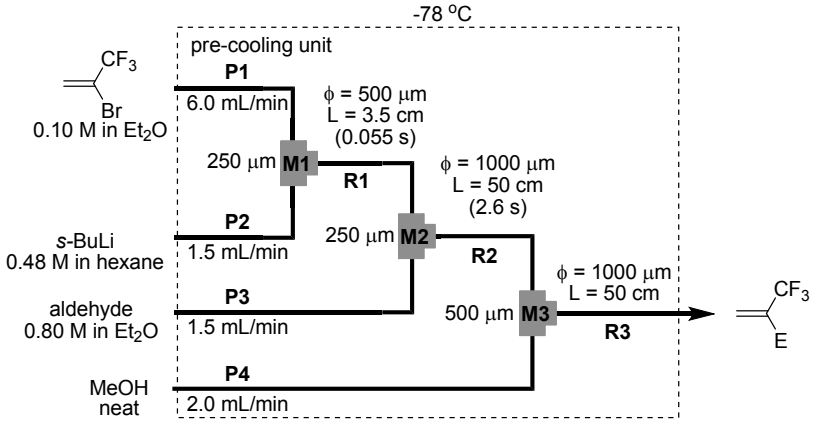
General

GC analysis was performed on a SHIMADZU GC-2014 gas chromatograph equipped with a flame ionization detector using a fused silica capillary column (column-a, CBP1; 0.22 mm x 25 m and column-b, Rtx-200; 0.25 mm x 30 m). ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on Varian MERCURY plus-400 (^{1}H 400 MHz, ^{13}C 100 MHz, and ^{19}F 377 MHz) spectrometer with an internal standard (Me_4Si, $CDCl_3$, and trifluorotoluene, respectively) in $CDCl_3$. Gel permeation chromatography (GPC) was carried out on Japan Analytical Industry LC-908 and LC-9201 using $CHCl_3$ as an eluent. EI mass spectra were recorded on JMS-MS700 spectrometer. ESI and APCI mass spectra were recorded on EXACTIVE spectrometer. Dry diethyl ether was purchased from Kanto Chemical Co., Inc., and was used without further purification. Hexane was purchased from Wako, distilled before use, and stored over molecular sieves 4A. 2-Bromo-3,3,3-trifluoro-1-propene, benzyl isocyanate, phenyl isocyanate, *n*-butyl isocyanate, benzaldehyde, 4-(trifluoromethyl)benzaldehyde, *trans*-cinnamaldehyde, diethyl malonate, dibenzyl malonate, di-*t*-butyl malonate, 4-(methoxy)thiophenol, methanol, acetic acid, and *s*-BuLi were obtained from commercial suppliers.

Stainless steel (SUS304) T-shaped micromixer with inner diameter of 250 and 500 μm were manufactured by Sanko Seiki Co., Inc. Stainless steel (SUS316) microtube reactors with inner diameter of 1000 μm purchased from GL Sciences were used. The micromixer and microtube reactors were connected with stainless steel fittings (GL Sciences, 1/16 OUW). The flow microreactor system was dipped in a cooling bath to control the temperature. Solutions were introduced to the flow microreactor system using syringe pumps, Harvard PHD 2000, equipped with gastight syringes purchased from SGE.

Typical Procedure for Br/Li Exchange Reaction of 2-Bromo-3,3,3-trifluoromethyl-1-propene Followed by Reaction with Aldehydes in an Integrated Flow Microreactor System (Quenching with Methanol).



A flow microreactor system consisting of three T-shaped micromixers (**M1**, **M2** and **M3**), three microtube reactors (**R1, R2** and **R3**), and four pre-cooling units (**P1** (inner diameter ϕ = 1000 μm, length L = 150 cm), **P2** (ϕ = 1000 μm, L = 50 cm) and **P3** (ϕ = 1000 μm, L = 50

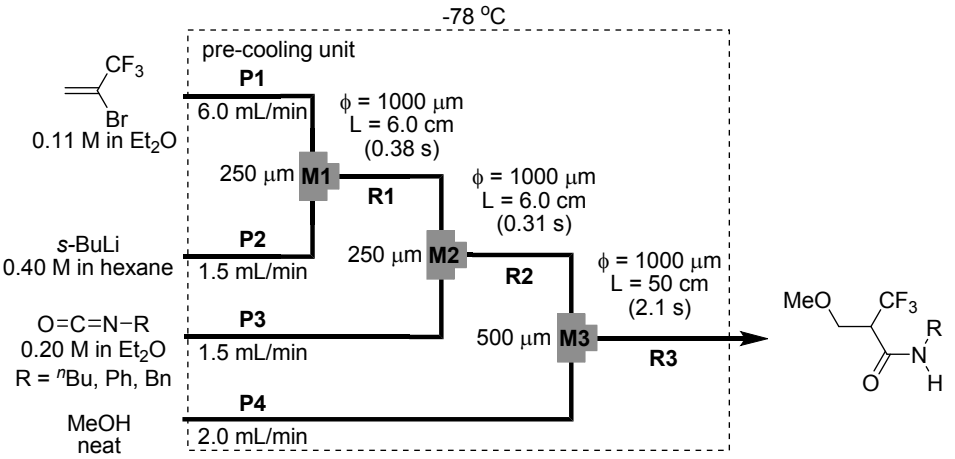
cm), **P4** (ϕ = 1000 μm, L = 50 cm)) was used. A solution of 2-bromo-3,3,3-trifluoro-1-propene (0.10 M in Et_2O) (flow rate: 6.0 mL min^{-1}) and a solution of *s*-BuLi (0.48 M in hexane/cyclohexane (57/43)) (flow rate: 1.5 mL min^{-1}) were introduced to **M1** (ϕ = 250 μm) by syringe pumps and was passed through **R1**. The resulting solution was mixed with a solution of an aldehyde (0.80 M in Et_2O) (flow rate: 1.5 mL min^{-1}) in **M2** (ϕ = 250 μm) and was passed through **R2** (ϕ = 1000 μm, L = 50 cm). The resulting solution was mixed with methanol (neat, flow rate: 2.0 mL min^{-1}) in **M3** (ϕ = 500 μm) and was passed through **R3** (ϕ = 1000 μm, L = 50 cm). After a steady state was reached, an aliquot of the product solution was collected for 30 s and was treated with sat. aq NH_4Cl solution. The reaction mixture was analyzed by GC using an internal standard.

1-Phenyl-2-(trifluoromethyl)prop-2-3n-1-ol. Obtained in 79% yield (GC yield, ^tR 13.5 min (initial oven temperature, 50 °C for 2 min; rate of temperature increase, 10 °C/min; final oven temperature, 250 °C for 10 min)). The spectral data were identical to those reported in the literature.[1]

2-(Trifluoromethyl)-1-(4-(trifluoromethyl)phenyl)prop-2-en-1-ol. Obtained in 72% yield (GC yield, ^tR 14.0 min (initial oven temperature, 50 °C for 2 min; rate of temperature increase, 10 °C/min; final oven temperature, 250 °C for 10 min)). The spectral data were identical to those reported in the literature.[1]

(*E*)-1-Phenyl-4-(trifluoromethyl)penta-1,4-dien-3-ol. Obtained in 90% yield (GC yield, ^tR 16.3 min (initial oven temperature, 50 °C for 2 min; rate of temperature increase, 10 °C/min; final oven temperature, 250 °C for 10 min)). The spectral data were identical to those reported in the literature.[1]

Typical Procedure for Br/Li Exchange Reaction of 2-Bromo-3,3,3-trifluoromethyl-1-propene Followed by Reaction with Isocyanates in an Integrated Flow Microreactor System (Quenching with Methanol).



An integrated flow microreactor system consisting of three T-shaped micromixers (**M1**, **M2** and **M3**), three microtube reactors (**R1, R2** and **R3**), and four pre-cooling units (**P1** (inner diameter ϕ = 1000 μm, length L = 150 cm), **P2** (ϕ = 1000 μm, L = 50 cm) and **P3** (ϕ = 1000 μm, L = 50 cm), **P4** (ϕ = 1000 μm, L = 50 cm)) was used. A solution of 2-bromo-3,3,3-trifluoro-1-propene (0.11 M in Et_2O) (flow rate: 6.0 mL min^{-1}) and a solution of *s*-BuLi (0.40 M in hexane/cyclohexane (65/35)) (flow rate: 1.5 mL min^{-1}) were introduced to **M1** (ϕ = 250 μm) by syringe pumps and was passed through **R1** (ϕ = 1000 μm, L = 6.0 cm). The

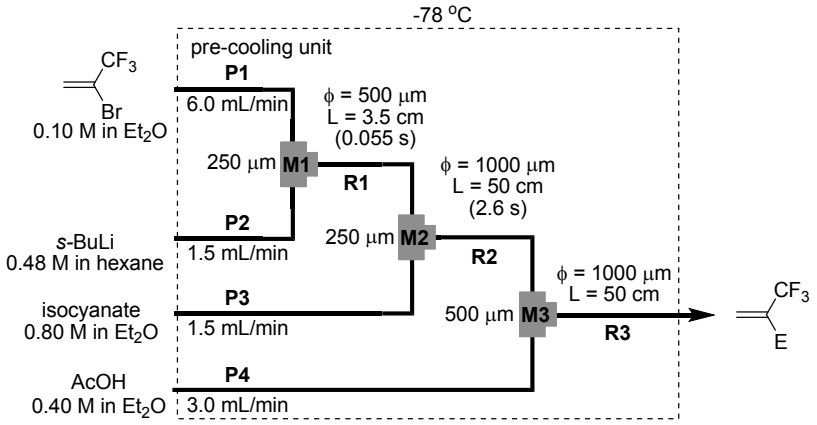
resulting solution was mixed with a solution of an isocyanate (0.20 M in Et_2O) (flow rate: 1.5 mL min^{-1}) in **M2** (ϕ = 250 μm) and was passed through **R2** (ϕ = 1000 μm, L = 6.0 cm). The resulting solution was mixed with MeOH (neat) (flow rate: 2.0 mL min^{-1}) in **M3** (ϕ = 500 μm) and was passed through **R3** (ϕ = 1000 μm, L = 50 cm). After a steady state was reached, an aliquot of the product solution was collected for 30 s and was treated with sat. aq NH_4Cl solution. The reaction mixture was analyzed by GC using an internal standard.

***N*-Benzyl-3,3,3-trifluoro-2-(methoxymethyl)propanamide.** Obtained in 80% yield (GC yield, ^tR 19.7 min (initial oven temperature, 50 °C for 2 min; rate of temperature increase, 10 °C/min; final oven temperature, 250 °C for 10 min)). After extraction, the crude product was purified by column chromatography (hexane/ethyl acetate = 5/1 to 3/1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.12-3.23 (m, 1H), 3.38 (s, 3H), 3.78 (dd, *J* = 4.0 Hz, *J* = 9.6 Hz, 1H), 3.88 (dd, *J* = 7.6 Hz, *J* = 9.6 Hz, 1H), 4.51 (dd, *J* = 2.0 Hz, *J* = 5.8 Hz, 2H), 6.43 (brs, 1H), 7.25-7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.6, 51.4 (q, *J* = 26.2 Hz), 59.2, 67.6 and 67.7 (two peaks), 124.1 (q, *J* = 278.5 Hz), 127.4, 127.5, 128.6, 137.5, 165.0 and 165.1 (two peaks); ^{19}F NMR (377 MHz, $CDCl_3$) δ -67.07 (d, *J* = 7.54 Hz); HRMS (ESI) *m/z* calcd for $C_{12}H_{15}F_3NO_2$ ($[MH]^+$): 262.1049, found: 262.1041.

3,3,3-Trifluoro-2-(methoxymethyl)-*N*-phenylpropanamide. Obtained in 65% yield (GC yield, ^tR 18.8 min (initial oven temperature, 50 °C for 2 min; rate of temperature increase, 10 °C/min; final oven temperature, 250 °C for 10 min)). After extraction, the crude product was purified by column chromatography (hexane/ethyl acetate = 5/1 to 3/1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.23-3.34 (m, 1H), 3.47 (s, 3H), 3.86 (dd, *J* = 3.6 Hz, J = 10.0 Hz, 1H), 3.94 (dd, *J* = 6.8 Hz, J = 10.0 Hz, 1H), 7.12-7.17 (m, 1H), 7.31-7.37 (m, 2H), 7.50-7.55 (m, 2H), 8.11 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.0 (q, *J* = 25.8 Hz), 59.3, 67.6 and 67.7 (two peaks), 120.3, 124.1 (q, *J* = 278.5 Hz), 124.9, 128.9, 137.1, 163.5 and 163.6 (two peaks); ^{19}F NMR (377 MHz, $CDCl_3$) δ -66.95 (d, *J* = 7.54 Hz); HRMS (APCI) *m/z* calcd for $C_{11}H_{13}F_3NO_2$ ($[MH]^+$): 248.0893, found: 248.0892.

***N*-Butyl-3,3,3-trifluoro-2-(methoxymethyl)propanamide.** Obtained in 83% yield (GC yield, ^tR 14.9 min (initial oven temperature, 50 °C for 2 min; rate of temperature increase, 10 °C/min; final oven temperature, 250 °C for 10 min)). After extraction, the crude product was purified by column chromatography (hexane/ethyl acetate = 5/1 to 3/1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, *J* = 7.6 Hz, 3H), 1.30-1.40 (m, 2H), 1.47-1.56 (m, 2H), 3.00-3.16 (m, 1H), 3.27-3.34 (m, 2H), 3.40 (s, 3H), 3.74 (dd, *J* = 3.6 Hz, *J* = 9.6 Hz, 1H), 3.85 (dd, *J* = 6.8 Hz, *J* = 9.6 Hz, 1H), 6.12 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5, 19.8, 31.2, 39.5, 51.4 (q, *J* = 25.8 Hz), 59,1, 67.8 and 67.8 (two peaks), 124.2 (q, *J* = 278.1 Hz), 164.9 and 165.0 (two peaks); ^{19}F NMR (377 MHz, $CDCl_3$) δ -67.23 (d, *J* = 7.54 Hz); HRMS (ESI) *m/z* calcd for $C_9H_{17}F_3NO_2$ ($[MH]^+$): 228.1206, found: 228.1205.

Typical Procedure for Br/Li Exchange Reaction of 2-Bromo-3,3,3-trifluoromethyl-1-propene Followed by Reaction with Isocyanates in an Integrated Flow Microreactor System (Quenching with Acetic Acid).



A flow microreactor system consisting of three T-shaped micromixers (**M1**, **M2** and **M3**), three microtube reactors (**R1, R2** and **R3**), and four pre-cooling units (**P1** (inner diameter ϕ = 1000 μm, length L = 150 cm), **P2** (ϕ = 1000 μm, L = 50 cm) and **P3** (ϕ = 1000 μm, L = 50 cm), **P4** (ϕ = 1000 μm, L = 50 cm)) was used. A solution of 2-bromo-3,3,3-trifluoro-1-propene (0.10 M in Et_2O) (flow rate: 6.0 mL min^{-1}) and a solution of *s*-BuLi (0.48 M in hexane/cyclohexane (57/43)) (flow rate: 1.5 mL min^{-1}) were introduced to **M1** (ϕ = 250 μm) by syringe pumps and was passed through **R1**. The resulting solution was mixed with a solution of an electrophile (0.80 M in Et_2O) (flow rate: 1.5 mL min^{-1}) in **M2** (ϕ = 250 μm) and was passed through **R2** (ϕ = 1000 μm, L = 50 cm). The resulting solution was mixed with acetic acid (0.40 M in Et_2O, flow rate: 3.0 mL min^{-1}) in **M3** (ϕ = 500 μm) and was passed through **R3** (ϕ = 1000 μm, L = 50 cm). After a steady state was reached, an aliquot of the product solution was collected for 30 s and was treated with sat. aq NH_4Cl solution. The reaction mixture was analyzed by GC using an internal standard.

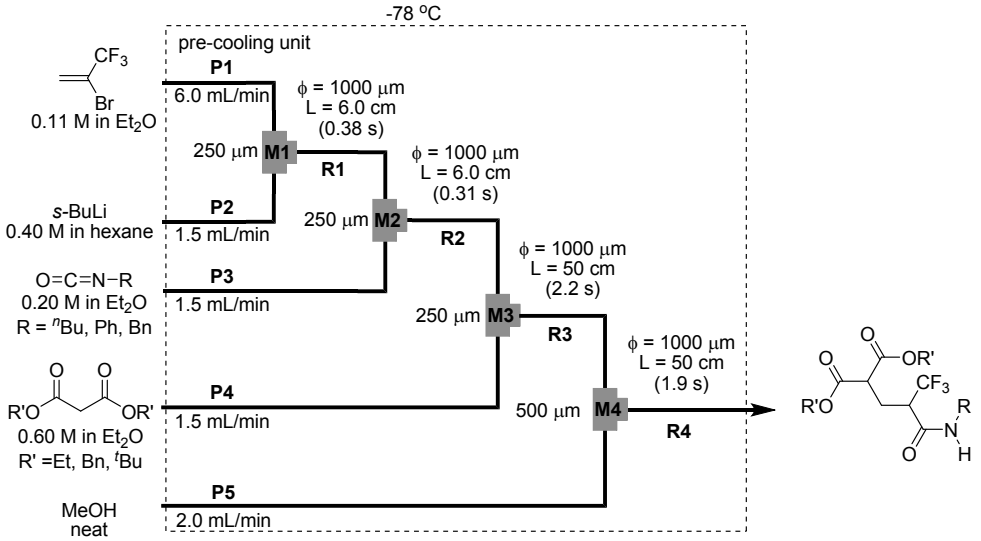
***N*-Benzyl-2-(trifluoromethyl)acrylamide.** Obtained in 62% yield (GC yield, ^tR 17.1 min (initial oven temperature, 50 °C for 2 min; rate of temperature increase, 10 °C/min; final oven temperature, 250 °C for 10 min)). After extraction, the crude product was purified by column chromatography (hexane/ethyl acetate = 5/1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.57 (d, *J* = 5.6 Hz, 2H), 6.1-6.3 (brs, 1H), 6.27 (q, *J* = 1.6 Hz, 1H), 6.61 (q, *J* = 1.6 Hz, 1H), 7.27-7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.6, 121.9 (q, *J* = 270.9 Hz), 127.4, 127.5, 128.1 (d, *J* = 4.7 Hz), 128.6, 133.9 (q, *J* = 30.6 Hz), 137.3, 161.3; ^{19}F NMR (377 MHz, $CDCl_3$) δ -64.6; HRMS (ESI) *m/z* calcd for $C_{11}H_{11}F_3NO$ ($[MH]^+$): 230.0787, found: 230.0787.

***N*-Phenyl-2-(trifluoromethyl)acrylamide.** Obtained in 63% yield (GC yield, ^tR 15.8 min (initial oven temperature, 50 °C for 2 min; rate of temperature increase, 10 °C/min; final oven temperature, 250 °C for 10 min)). After extraction, the crude product was purified by column chromatography (hexane/ethyl acetate = 5/1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36 (q, *J* = 1.6 Hz, 1H), 6.76 (q, *J* = 1.6 Hz, 1H), 7.16-7.22 (m, 1H), 7.35-7.40 (m, 2H), 7.53-7.57 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 122.0 (q, *J* = 271.4 Hz), 120.7, 125.4, 129.1, 129.3 (q, *J* = 5.1 Hz), 134.5 (q, *J* = 30.5 Hz), 136.8, 159.3; ^{19}F NMR (377 MHz, $CDCl_3$) δ -64.4; HRMS (ESI) *m/z* calcd for $C_{10}H_8F_3NONa$ ($[M+Na]^+$): 238.0450, found: 238.0446.

***N*-Butyl-2-(trifluoromethyl)acrylamide.** Obtained in 72% yield (GC yield, ^tR 11.0 min (initial oven temperature, 50 °C for 2 min; rate of temperature increase, 10 °C/min; final oven temperature, 250 °C for 10 min)). After extraction, the crude product was purified by column chromatography (hexane/ethyl acetate = 5/1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, *J* = 7.2 Hz, 3H), 1.32-1.42 (m, 2H), 1.52-1.60 (m, 2H), 3.38 (dt, *J* = 2.8 Hz, *J* = 6.8 Hz, 2H), 5.90 (brs,

1H), 6.23 (q, J = 1.6 Hz, 1H), 6.58 (q, J = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5, 19.9, 31.2, 39.7, 122.1 (q, J = 271.0 Hz), 128.3, 134.1 (q, J = 29.3 Hz), 161.0; ^{19}F NMR (377 MHz, $CDCl_3$) δ -64.6; HRMS (EI) *m/z* calcd for $C_8H_{12}F_3NO$ (M^+): 195.0871, found: 195.0879.

Typical Procedure for Reactions of 1-Trifluoromethyvinyllithium with Isocyanates Followed by Reactions with Malonic Esters in an Integrated Flow Microreactor System.



An integrated flow microreactor system consisting of four T-shaped micromixers (**M1**, **M2, M3 and M4**), four microtube reactors (**R1, R2**, **R3 and R4**), and five pre-cooling units (**P1** (inner diameter ϕ = 1000 μm, length L = 150 cm), **P2** (ϕ = 1000 μm, L = 50 cm) and **P3** (ϕ = 1000 μm, L = 50 cm), **P4** (ϕ = 1000 μm, L = 50 cm), **P5** (ϕ = 1000 μm, L = 50 cm)) was used. A solution of 2-bromo-3,3,3-trifluoro-1-propene (0.11 M in Et_2O) (flow rate: 6.0 mL min^{-1}) and a solution of *s*-BuLi (0.40 M in hexane/cyclohexane(65/35)) (flow rate: 1.5 mL min^{-1}) were introduced to **M1** (ϕ = 250 μm) by syringe pumps and was passed through **R1** (ϕ = 1000 μm, L = 6.0 cm). The resulting solution was mixed with a solution of an isocyanate (0.20 M in Et_2O) (flow rate: 1.5 mL min^{-1}) in **M2** (ϕ = 250 μm) and was passed through **R2** (ϕ = 1000 μm, L = 6.0 cm). The resulting solution was mixed with a solution of an active methylene compound (0.60 M in Et_2O) (flow rate: 1.5 mL min^{-1}) in **M3** (ϕ = 250 μm) and was passed through **R3** (ϕ = 1000 μm, L = 50 cm). The resulting solution was mixed with MeOH (neat) (flow rate: 2.0 mL min^{-1}) in **M4** (ϕ = 500 μm) and was passed through **R4** (ϕ = 1000 μm, L = 50 cm). After a steady state was reached, an aliquot of the product solution was collected for 30 s and was treated with sat. aq NH_4Cl solution. The reaction mixture was analyzed by GC using an internal standard.

Diethyl 2-(2-(benzylcarbamoyl)-3,3,3-trifluoropropyl)malonate. Obtained in 80% yield (GC yield, ^tR 26.5 min (initial oven temperature, 50 °C for 2 min; rate of temperature increase, 10 °C/min; final oven temperature, 250 °C for 10 min)). After extraction, the crude product was purified by column chromatography (hexane/ethyl acetate = 5/1 to 3/1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, J = 7.2 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H), 2.36 (ddd, J = 4.4 Hz, J = 9.9 Hz, J = 14.2 Hz, 1H), 2.52 (ddd, J = 5.2 Hz, J = 10.2 Hz, J = 14.2 Hz, 1H), 3.09-3.20 (m, 1H), 3.46 (dd, J = 5.2 Hz, J = 9.9 Hz, 1H), 4.13-4.26 (m, 4H), 4.42-4.56 (m, 2H), 6.13 (brs, 1H), 7.25-7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6 and 13.6, 24.6, 43.5, 47.9 (q, J = 26.6 Hz), 48.6, 61.6 and 61.7 (two peaks), 124.7 (q, J = 278.5 Hz), 127.3, 127.3, 128.4, 137.3, 165.1 and 165.1 (two peaks), 168.2 and 168.4; ^{19}F NMR (377 MHz, $CDCl_3$) δ -69.02 (d, J =

11.31 Hz); HRMS (ESI) *m/z* calcd for $C_{18}H_{23}F_3NO_5$ ([MH]$^+$): 390.1523, found: 390.1515.

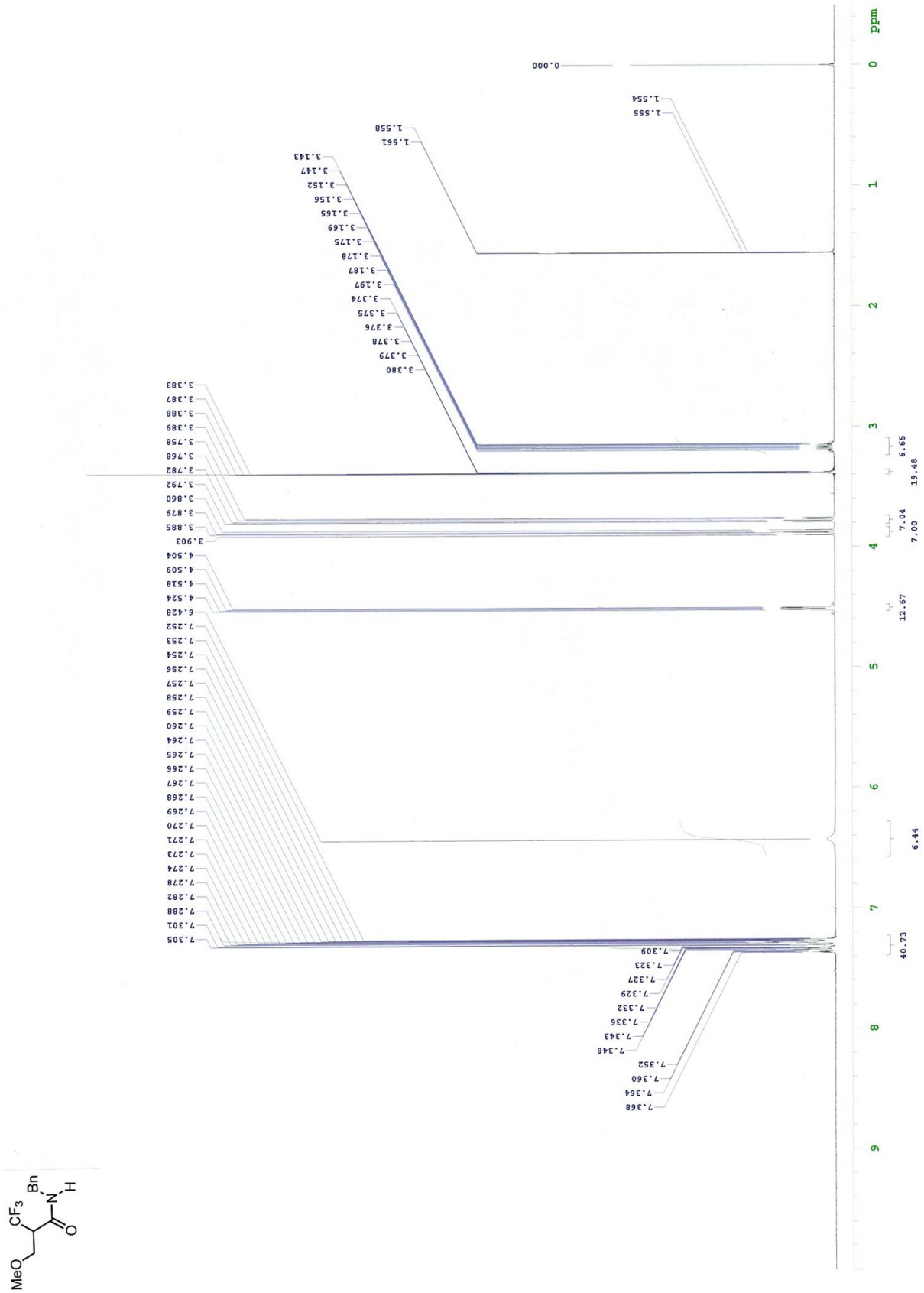
Diethyl 2-(3,3,3-trifluoro-2-(phenylcarbamoyl)propyl)malonate. Obtained in 65% yield (GC yield, ^tR 25.5 min (initial oven temperature, 50 ^{o}C for 2 min; rate of temperature increase, 10 ^{o}C/min; final oven temperature, 250 ^{o}C for 10 min)). After extraction, the crude product was purified by column chromatography (hexane/ethyl acetate = 5/1 to 3/1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.2 Hz, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 2.41 (ddd, *J* = 4,4 Hz, *J* = 9.4 Hz, *J* = 14.3 Hz, 1H), 2.59 (ddd, *J* = 6.0 Hz, *J* = 9.6 Hz, *J* = 14.3 Hz, 1H), 3.26-3.37 (m, 1H), 3.53 (dd, *J* = 6.0 Hz, 9.4 Hz, 1H), 4.15-4.27 (m, 4H), 7.13-7.18 (m, 1H), 7.32-7.37 (m, 2H), 7.51-7.57 (m, 2H), 7.74 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8 and 13.9, 25.0 and 25.0, 48.8, 49.0 (q, *J* = 26.6 Hz), 62.0 and 62.1 (two peaks), 120.1, 124.8 (q, *J* = 278.1 Hz), 125.1, 129.0, 137.0, 163.4, 168.5 and 168.8 (two peaks); ^{19}F NMR (377 MHz, $CDCl_3$) δ -68.98 (d, *J* = 7.54 Hz); HRMS (APCI) *m/z* calcd for $C_{17}H_{21}F_3NO_5$ ([MH]$^+$): 376.1366, found: 376.1366.

Diethyl 2-(2-(butylcarbamoyl)-3,3,3-trifluoropropyl)malonate. Obtained in 73% yield (GC yield, ^tR 22.7 min (initial oven temperature, 50 ^{o}C for 2 min; rate of temperature increase, 10 ^{o}C/min; final oven temperature, 250 ^{o}C for 10 min)). After extraction, the crude product was purified by column chromatography (hexane/ethyl acetate = 5/1 to 3/1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, *J* = 7.6 Hz, 3H), 1.28 (t, *J* = 6.8 Hz, 6H), 1.31-1.40 (m, 2H), 1.47-1.55 (m, 2H), 2.38 (ddd, *J* = 4.4 Hz, *J* = 10.1 Hz, *J* = 14.1 Hz, 1H), 2.48 (ddd, *J* = 5.6 Hz, *J* = 10.4 Hz, *J* = 14.1 Hz, 1H), 3.02-3.13 (m, 1H), 3.23-3.38 (m, 2H), 3.44 (dd, *J* = 5.6 Hz, *J* = 10.0 Hz, 1H), 4.15-4.28 (m, 4H), 5.81 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6 and 13.9, 19.8, 24.8 and 24.9, 31.3, 39.7, 48.4 (q, *J* = 26.6 Hz), 48.8, 61.8, 77.2, 124.9 (q, *J* = 278.4 Hz), 164.8, 168.3 and 168.7 (two peaks); ^{19}F NMR (377 MHz, $CDCl_3$) δ -69.18 (d, *J* = 11.31 Hz); HRMS (APCI) *m/z* calcd for $C_{15}H_{25}F_3NO_5$ ([MH]$^+$): 356.1679, found: 356.1678.

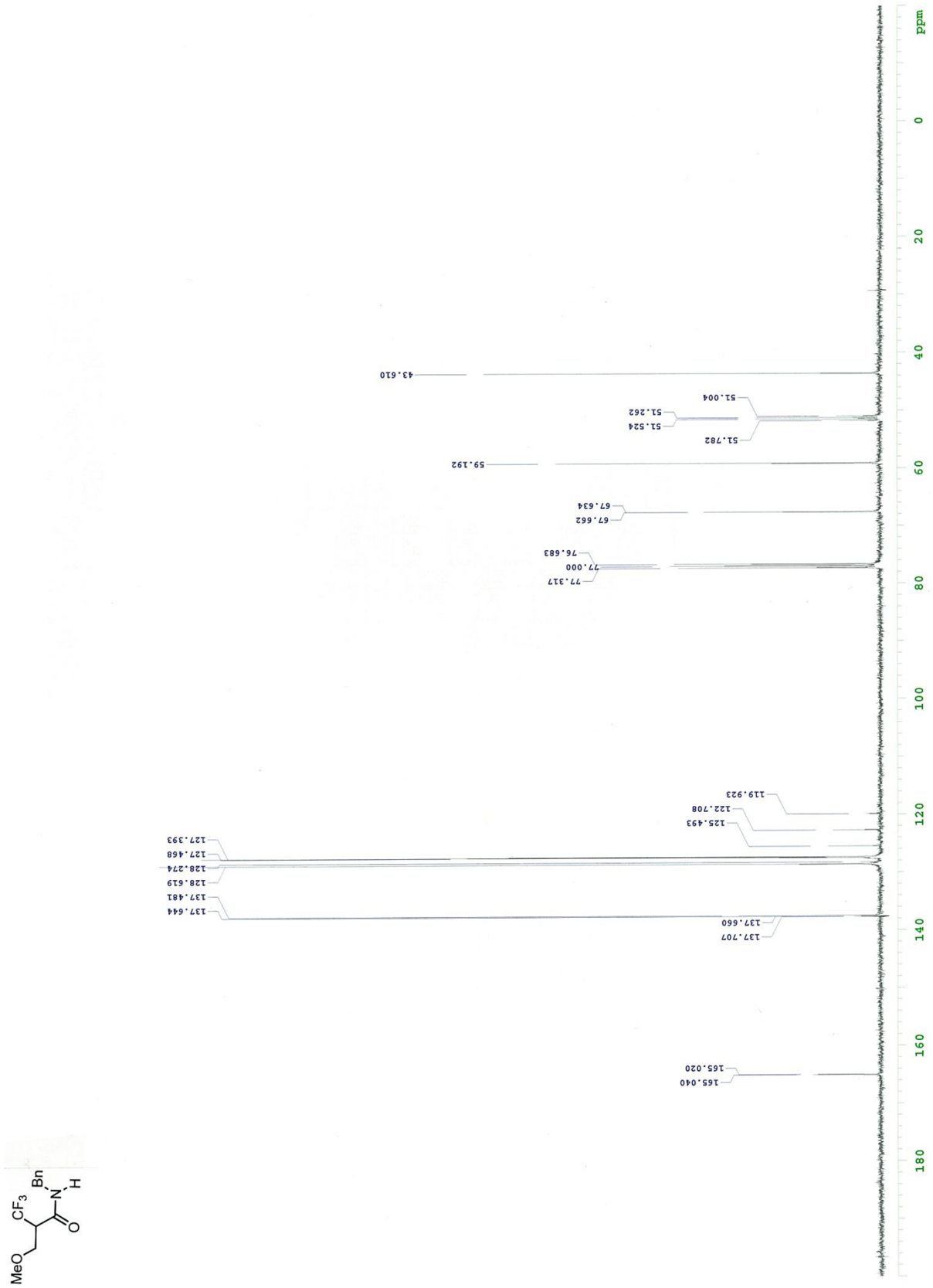
Dibenzyl 2-(2-(benzylcarbamoyl)-3,3,3-trifluoropropyl)malonate. Obtained in 51% yield (GC yield, ^tR 22.7 min (initial oven temperature, 50 ^{o}C for 2 min; rate of temperature increase, 10 ^{o}C/min; final oven temperature, 250 ^{o}C for 10 min)). After extraction, the crude product was purified by column chromatography (hexane/ethyl acetate = 5/1 to 3/1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (ddd, *J* = 4.4 Hz, *J* = 10.3 Hz, *J* = 14.0 Hz, 1H), 2.55 (ddd, *J* = 5.2 Hz, *J* = 10.4 Hz, *J* = 14.0 Hz, 1H), 2.85-2.96 (m, 1H), 3.55 (dd, *J* = 5.2 Hz, *J* = 10.3 Hz, 1H), 4.31-4.50(m, 2H), 5.08-5.18 (m, 4H), 5.75 (brs, 1H), 7.20-7.35 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 43.6, 48.0 (q, *J* = 26.6 Hz), 67.2 and 67.3 (two peaks), 124.7 (q, *J* = 278.9 Hz), 127.4, 128.0, 128.3, 128.4, 128.4, 128.5, 134.8, 134.8, 137.1, 164.8, 167.8 and 168.1 (two peaks); ^{19}F NMR (377 MHz, $CDCl_3$) δ -69.08 (d, *J* = 7.54 Hz); HRMS (ESI) *m/z* calcd for $C_{28}H_{27}F_3NO_5$ ([MH]$^+$): 514.1836, found: 514.1835.

Di-*tert*-butyl 2-(2-(benzylcarbamoyl)-3,3,3-trifluoropropyl)malonate. Obtained in 66% yield (GC yield, ^tR 16.3 min (initial oven temperature, 50 ^{o}C for 2 min; rate of temperature increase, 10 ^{o}C/min; final oven temperature, 250 ^{o}C for 10 min)). After extraction, the crude product was purified by column chromatography (hexane/ethyl acetate = 5/1 to 3/1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.46 (s, 9H), 2.26 (ddd, *J* = 4.4 Hz, *J* = 10.2 Hz, *J* = 14.0 Hz, 1H), 2.43 (ddd, *J* = 5.4 Hz, *J* = 10.2 Hz, *J* = 14.0 Hz, 1H), 3.05-3.16 (m, 1H), 2.23 (dd, *J* = 5.3 Hz, *J* = 10.2 Hz, 1H), 4.41-4.58 (m, 2H), 6.12 (brs, 1H), 7.25-7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9, 27.7 and 27.8, 43.8, 48.4 (q, *J* = 26.6 Hz), 50.6, 82.1 and 82.3 (two peaks), 124.9 (q, *J* = 278.1 Hz), 127.6, 127.6, 128.7, 137.3, 165.2, 167.4 and 168.1 (two peaks); ^{19}F NMR (377 MHz, $CDCl_3$) δ -69.03 (d, *J* = 11.31 Hz); HRMS (ESI) *m/z* calcd for $C_{22}H_{31}F_3NO_5$ ([MH]$^+$): 446.2149, found: 446.2142.

[1] R. Nadano, K. Fuchibe, M. Ikeda, H. Takahashi, J. Ichikawa, *Chem. Asian J.* **2010**, *5*, 1875.

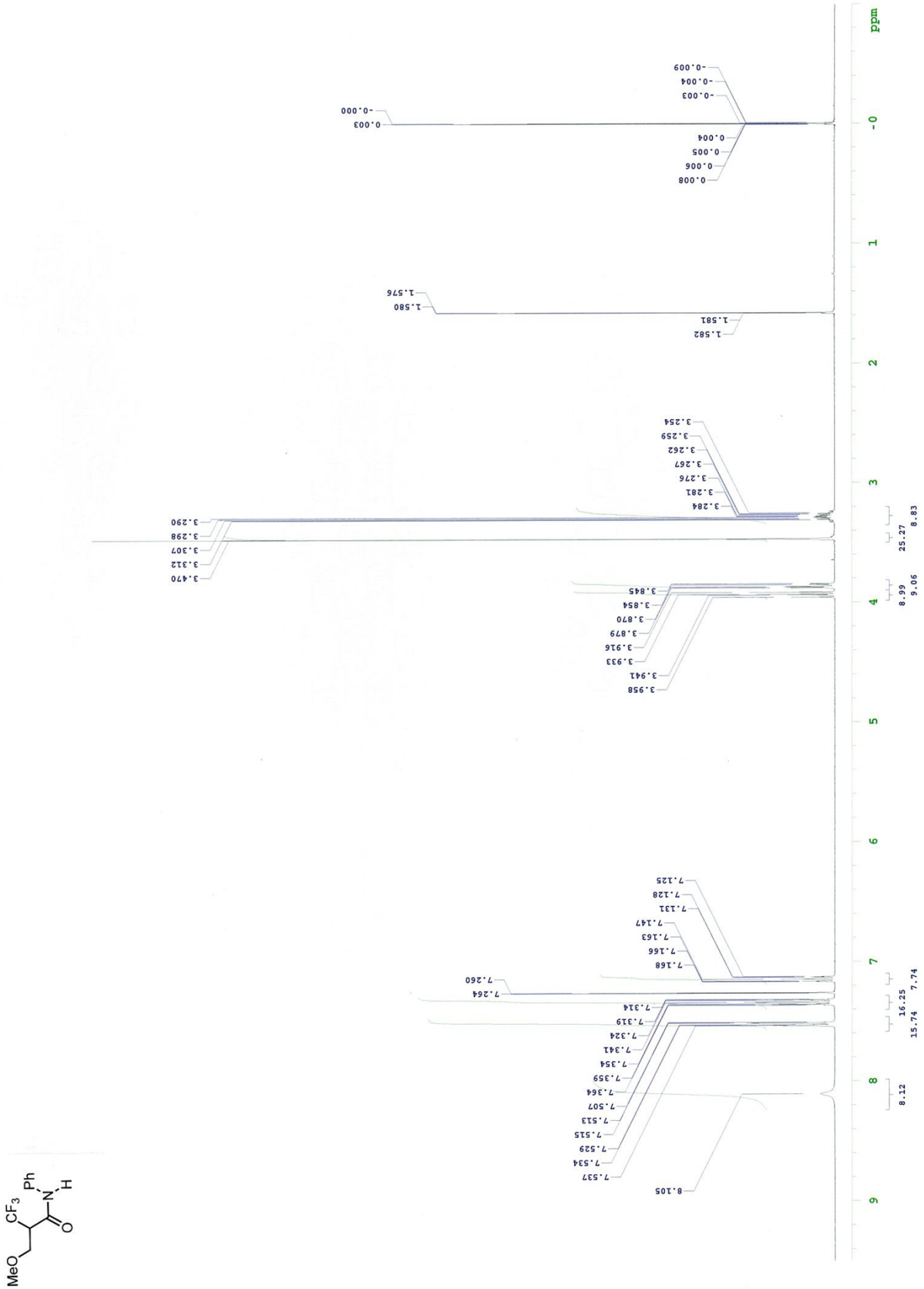


^{1}H spectrum of *N*-benzyl-3,3,3-trifluoro-2-(methoxymethyl)propanamide

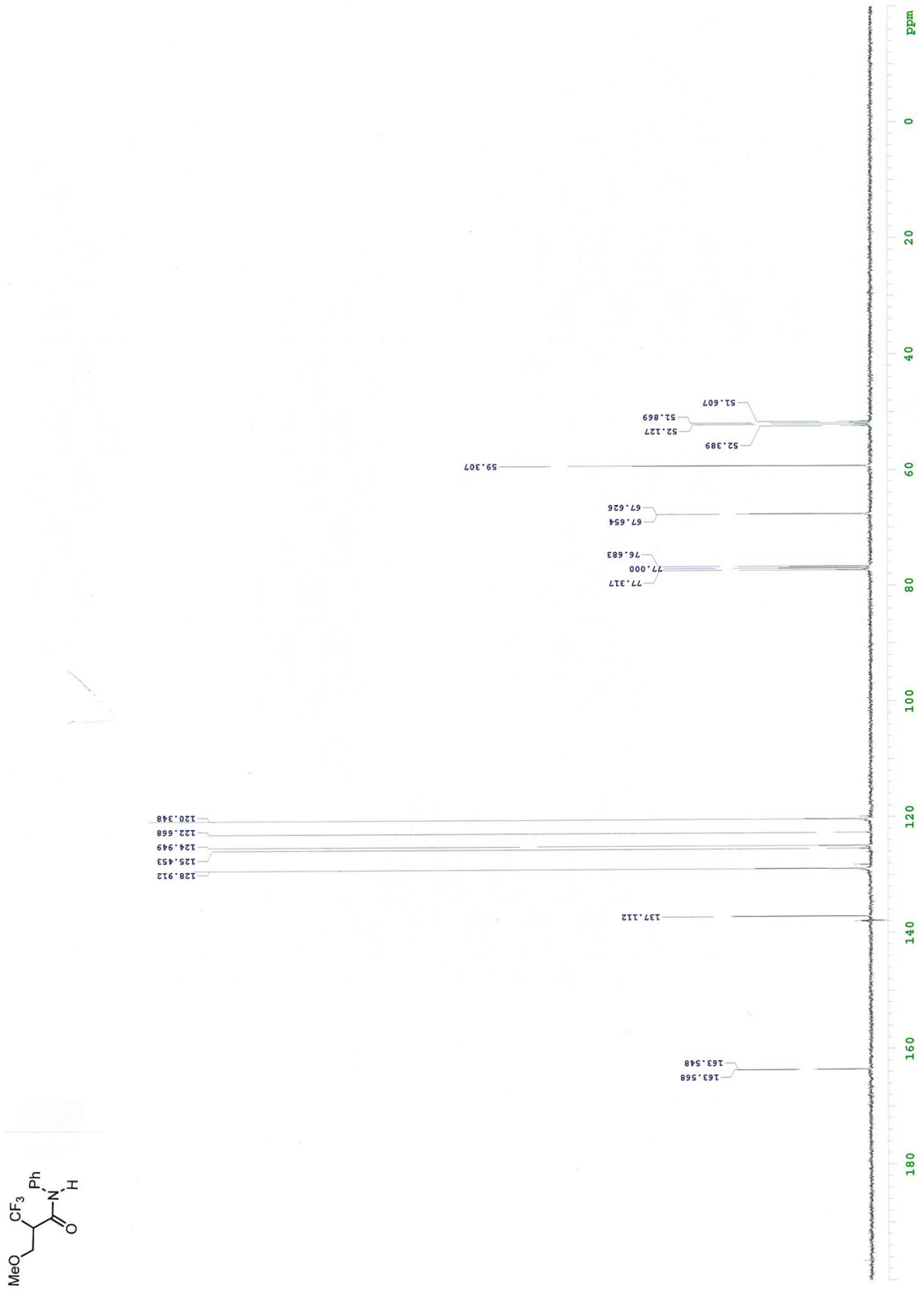


^{13}C spectrum of *N*-benzyl-3,3,3-trifluoro-2-(methoxymethyl)propanamide

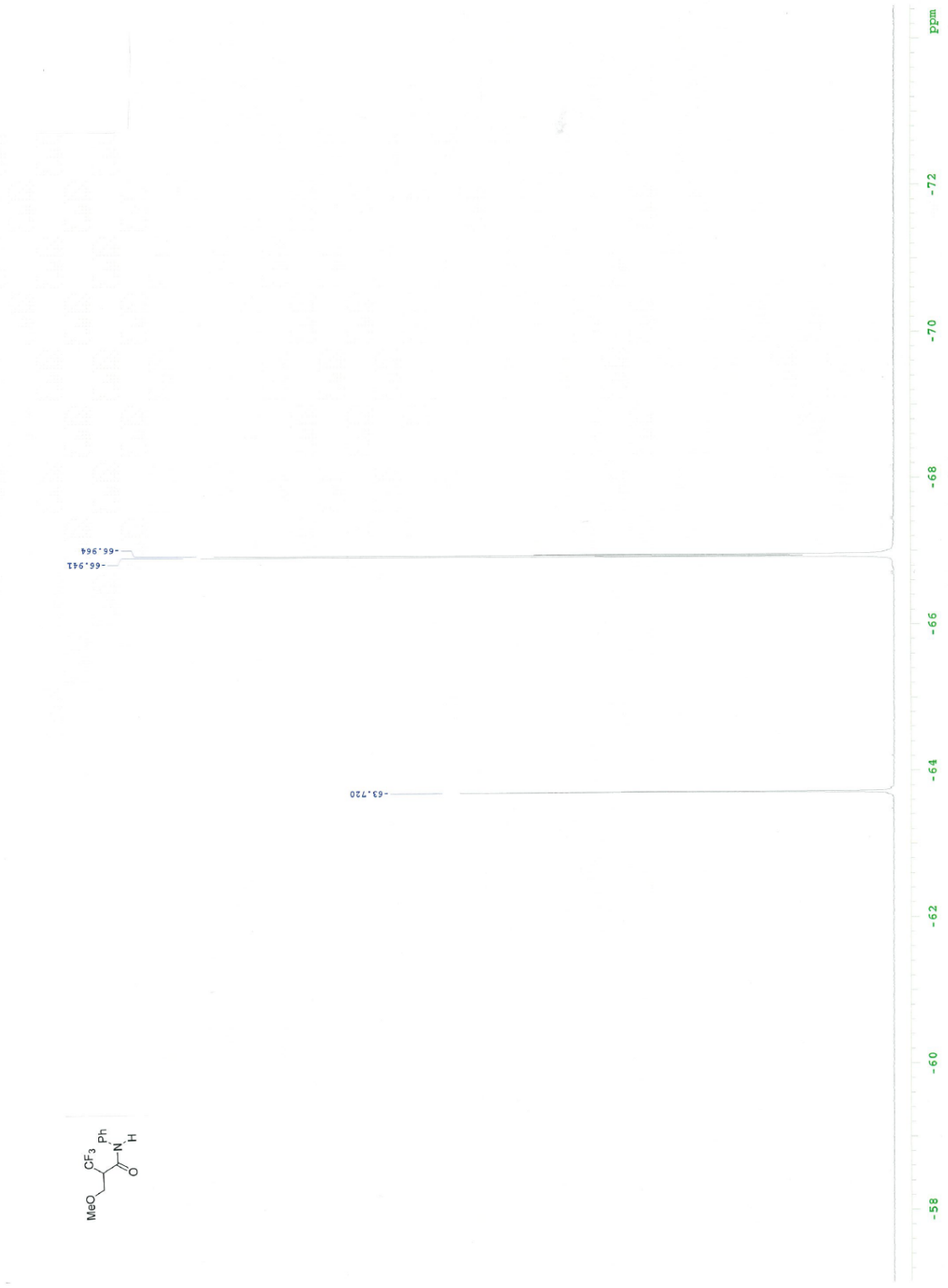
^{19}F spectrum of *N*-benzyl-3,3,3-trifluoro-2-(methoxymethyl)propanamide



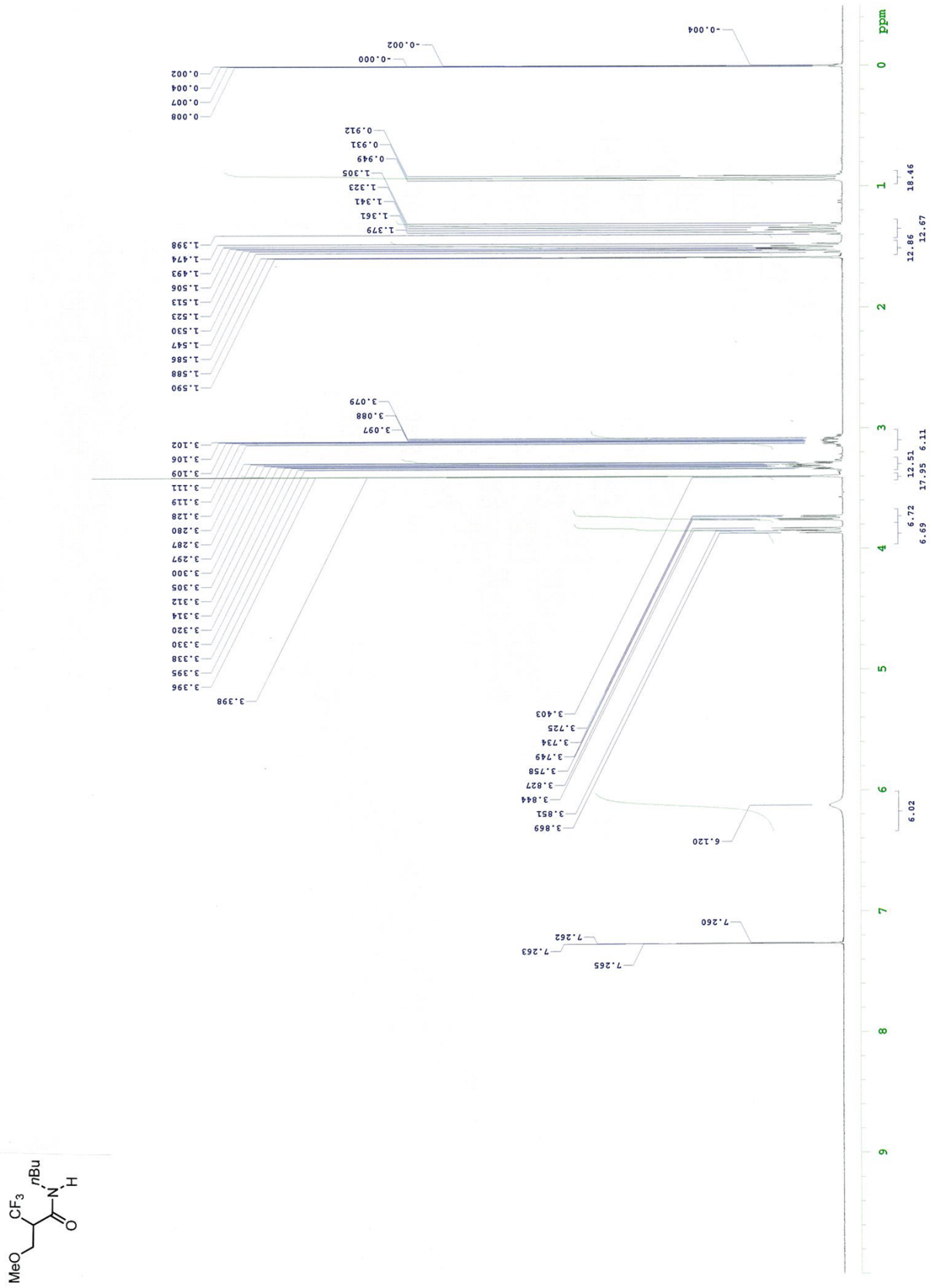
^{1}H spectrum of 3,3,3-trifluoro-2-(methoxymethyl)-*N*-phenylpropanamide



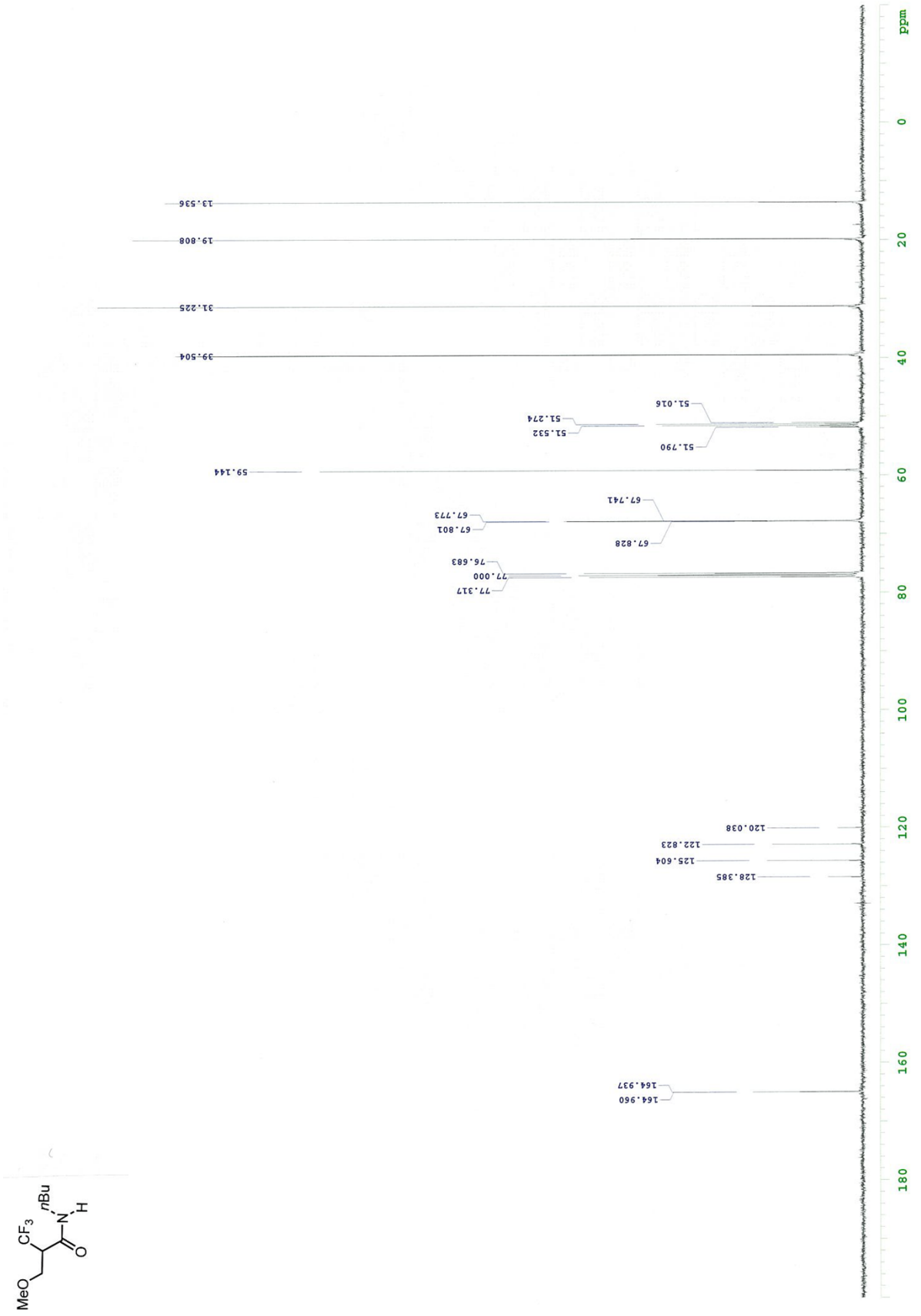
^{13}C spectrum of 3,3,3-trifluoro-2-(methoxymethyl)-*N*-phenylpropanamide



^{19}F spectrum of 3,3,3-trifluoro-2-(methoxymethyl)-*N*-phenylpropanamide

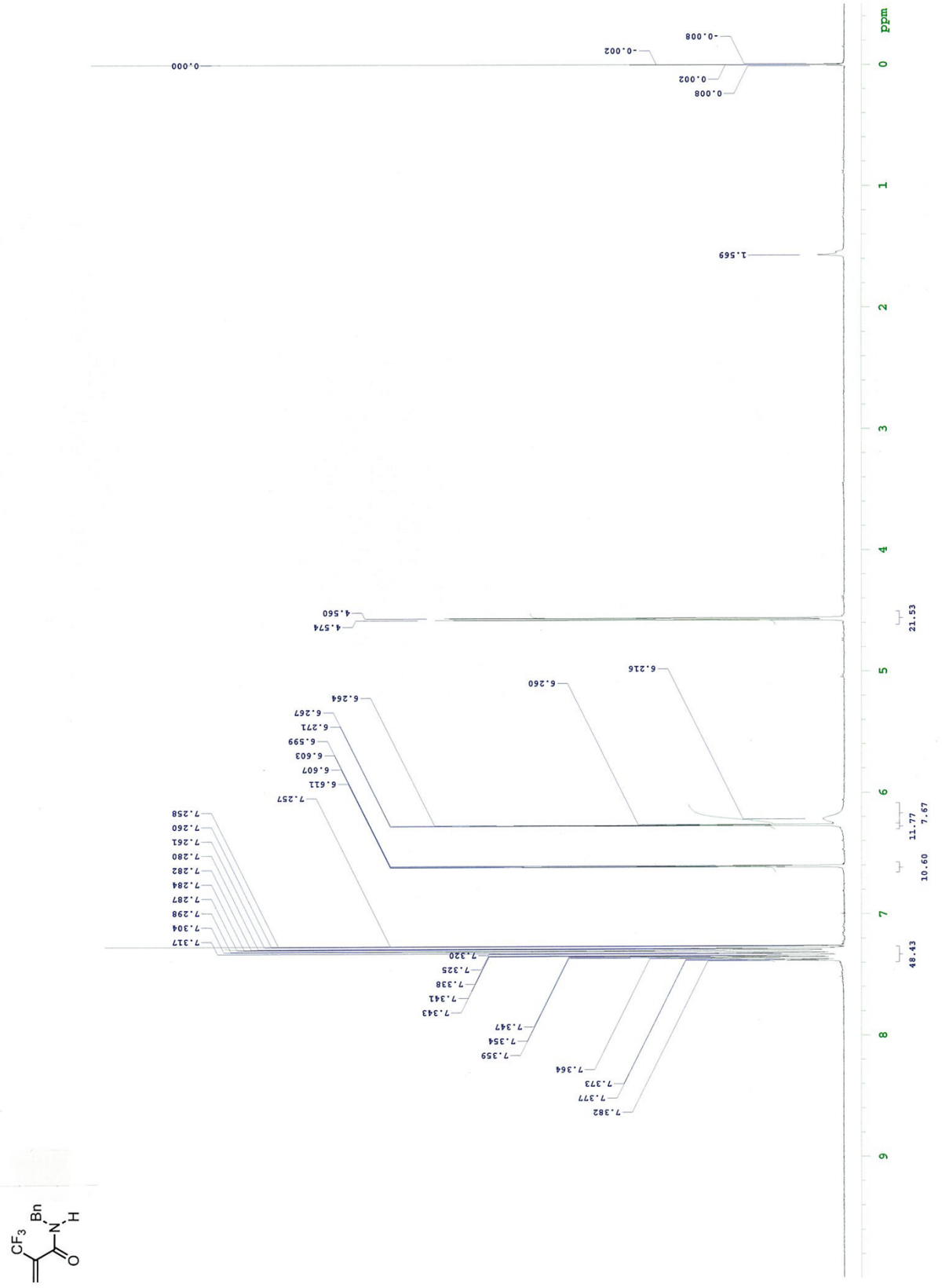


^{1}H spectrum of *N*-butyl-3,3,3-trifluoro-2-(methoxymethyl)propanamide

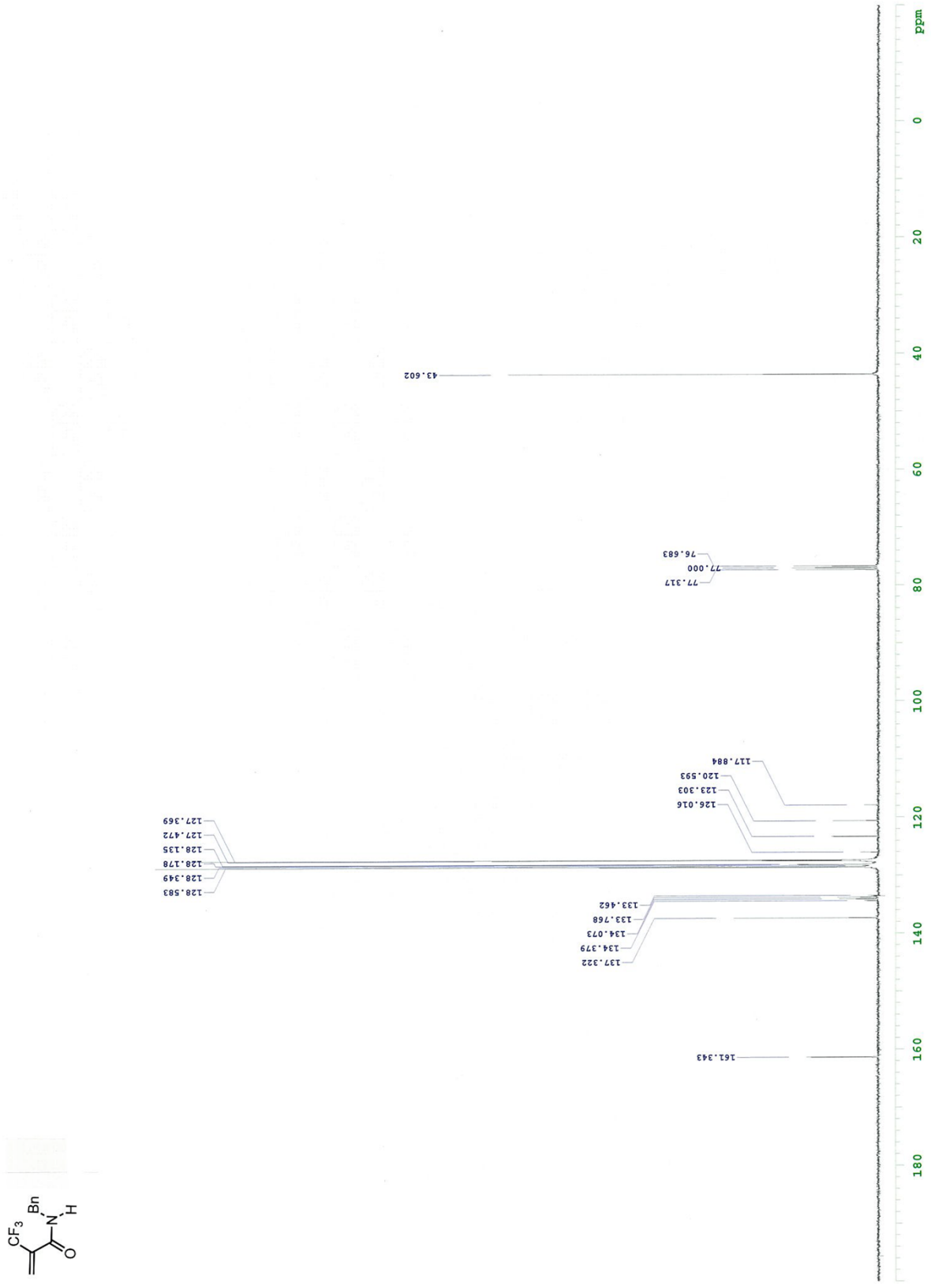


^{13}C spectrum of *N*-butyl-3,3,3-trifluoro-2-(methoxymethyl)propanamide

^{19}F spectrum of *N*-butyl-3,3,3-trifluoro-2-(methoxymethyl)propanamide



^{1}H spectrum of *N*-benzyl-2-(trifluoromethyl)acrylamide



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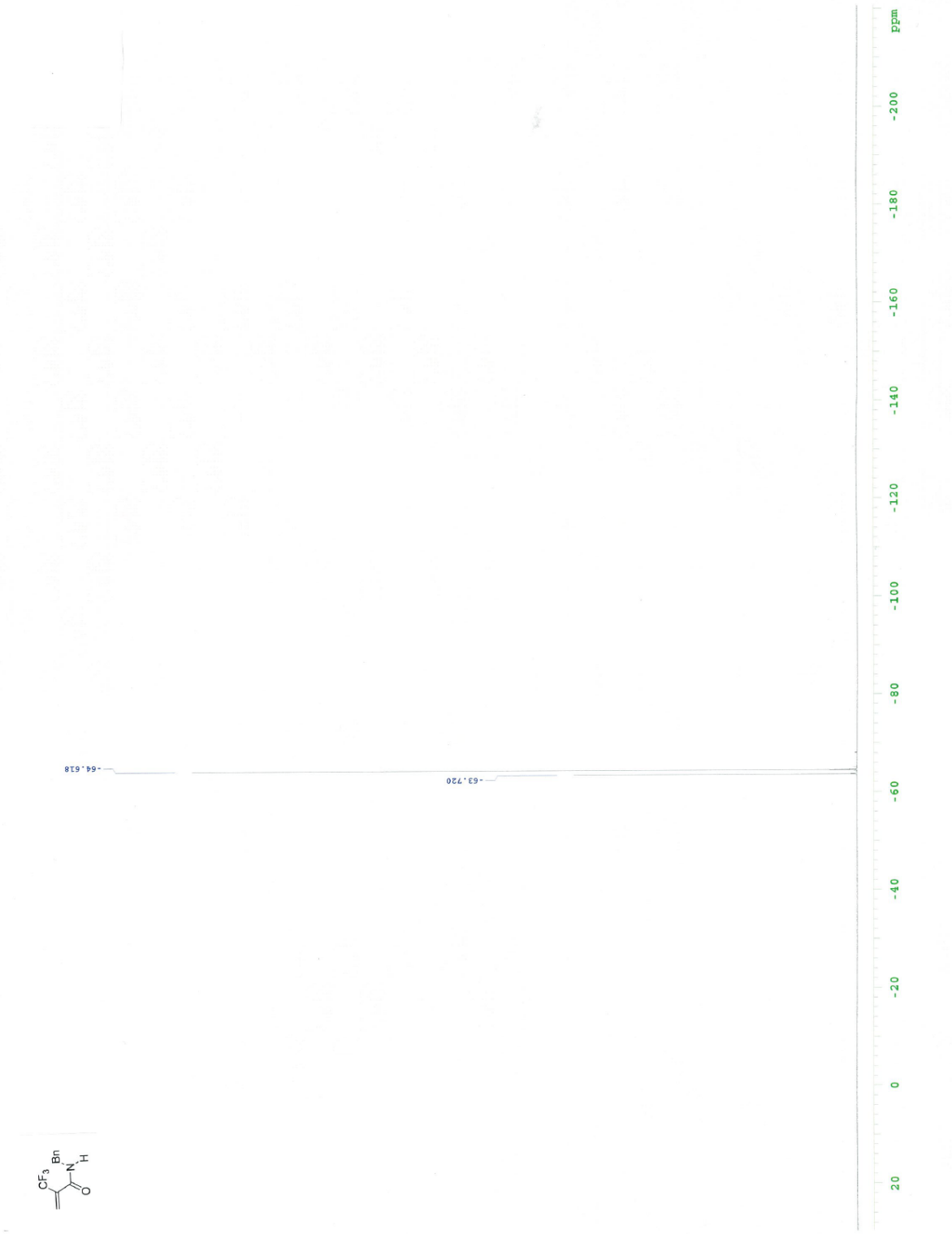

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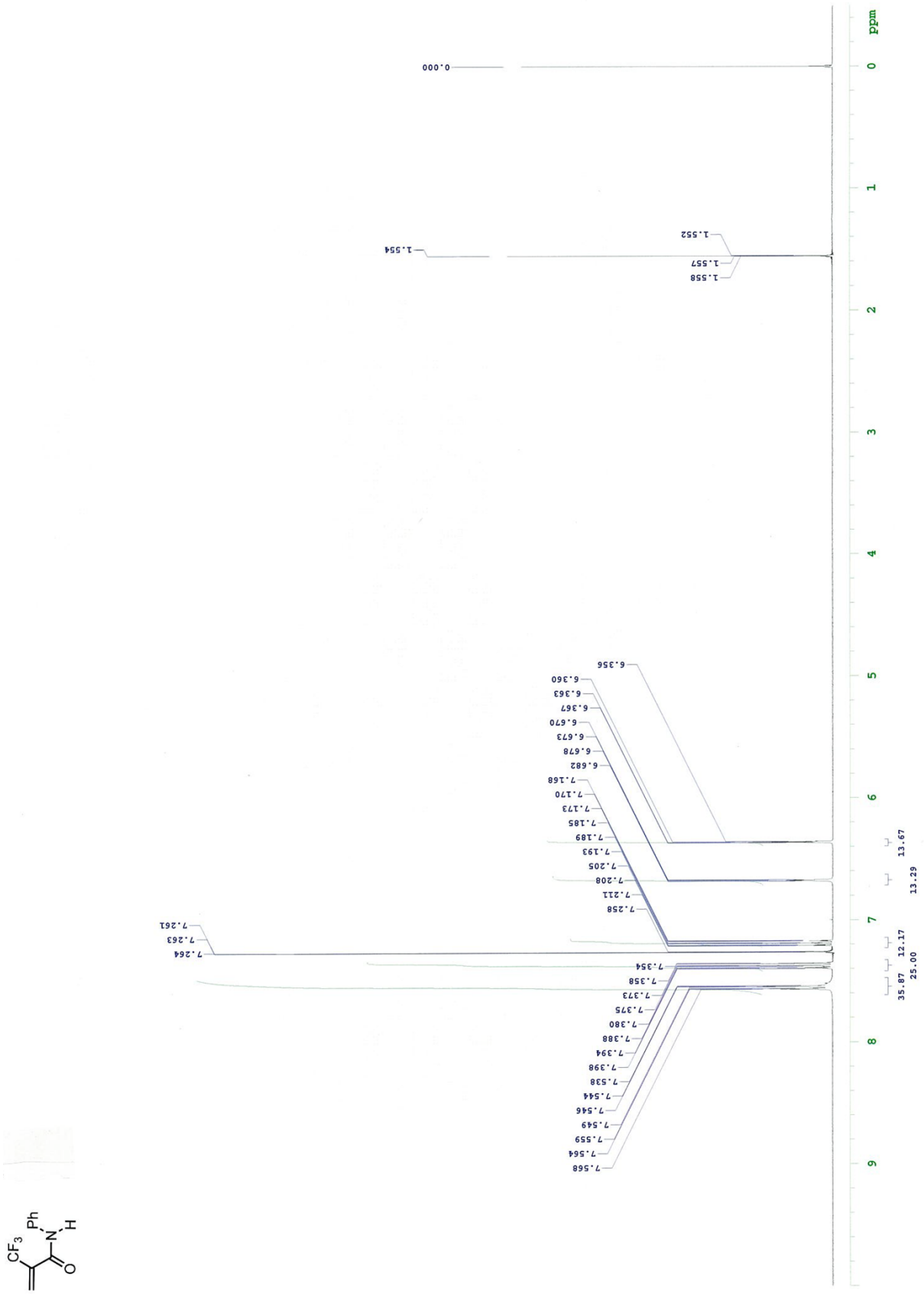

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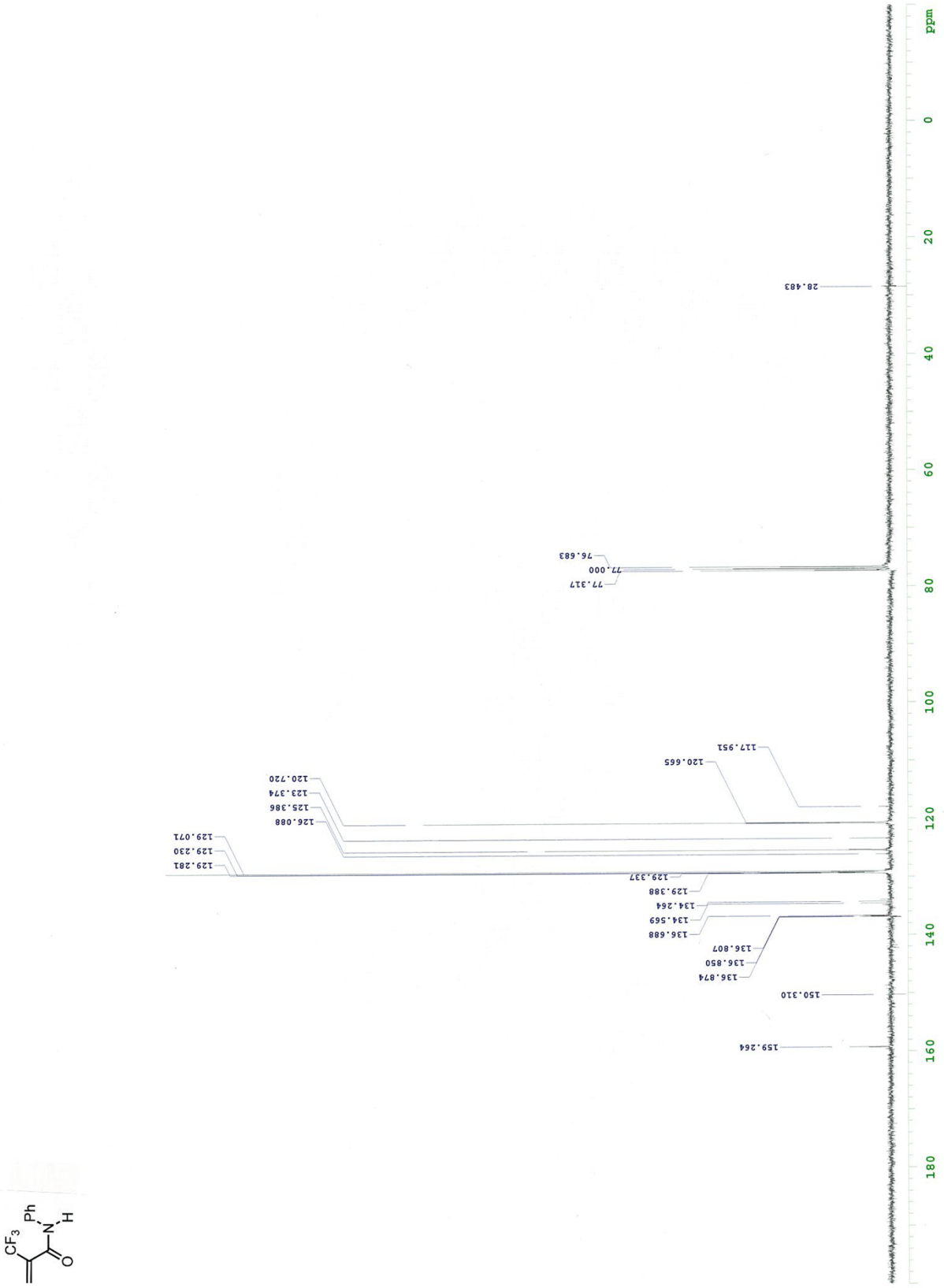
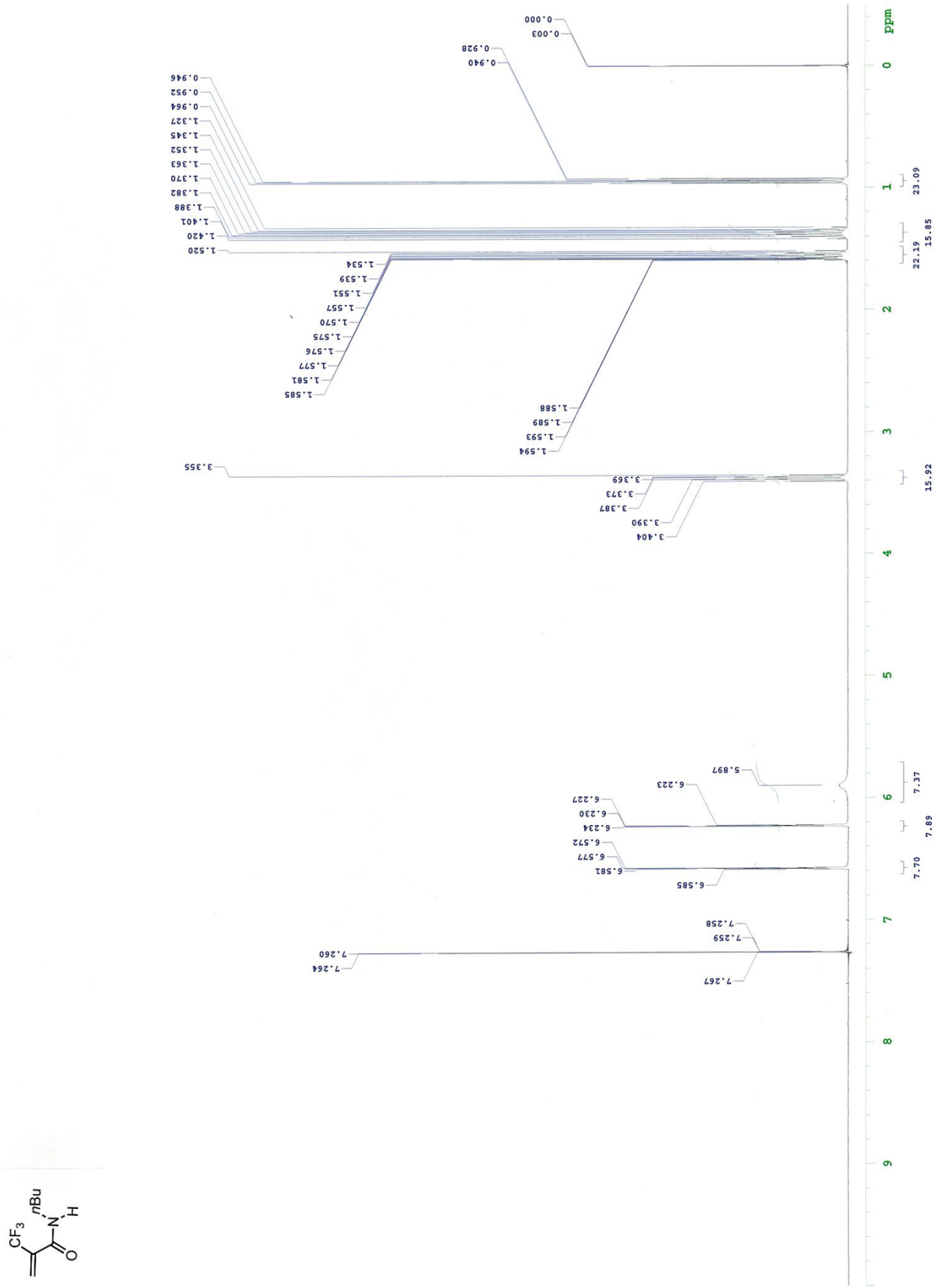
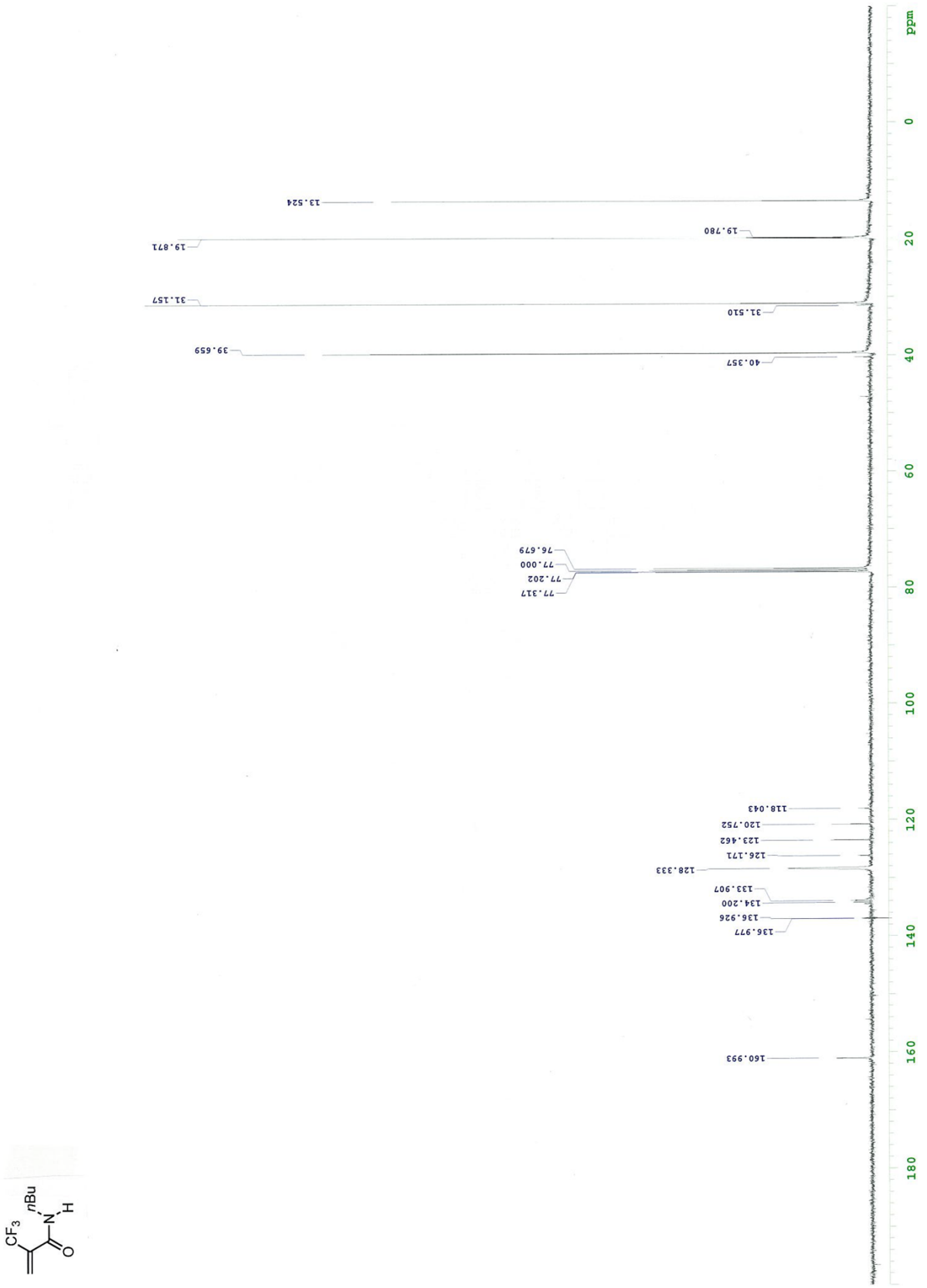


^{13}C spectrum of *N*-phenyl-2-(trifluoromethyl)acrylamide

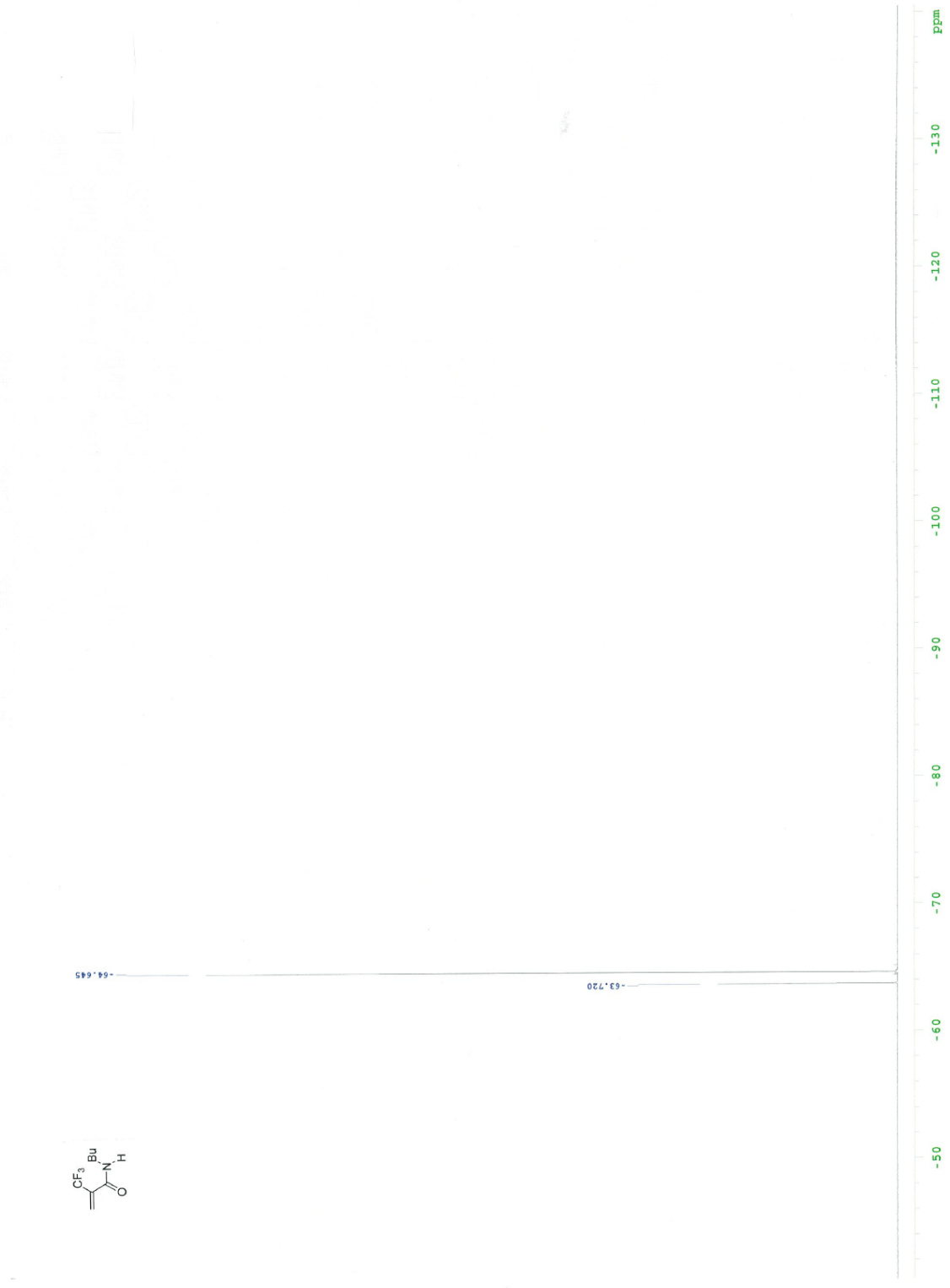
^{19}F spectrum of *N*-phenyl-2-(trifluoromethyl)acrylamide



[1]H spectrum of *N*-butyl-2-(trifluoromethyl)acrylamide



^{13}C spectrum of *N*-butyl-2-(trifluoromethyl)acrylamide



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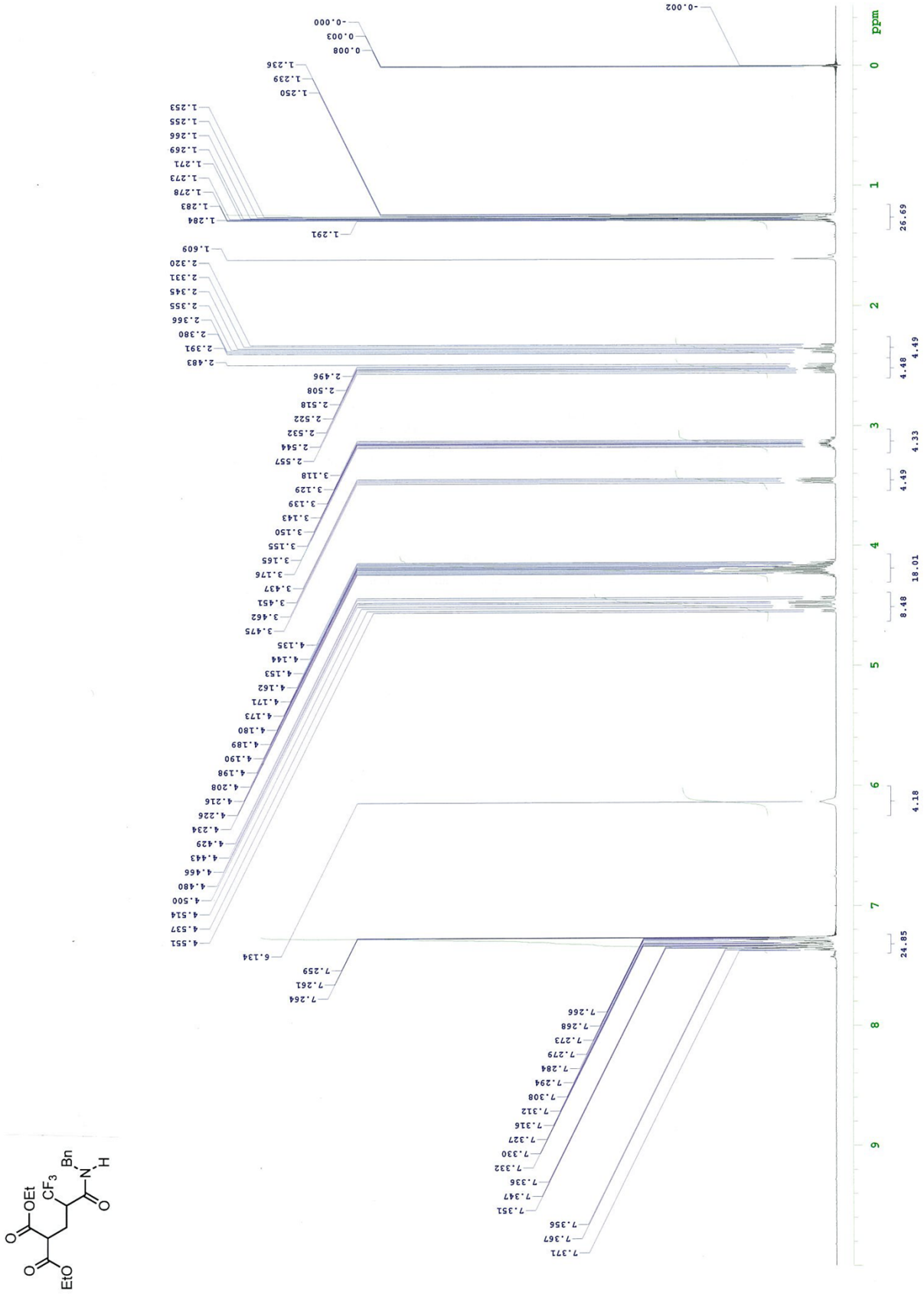
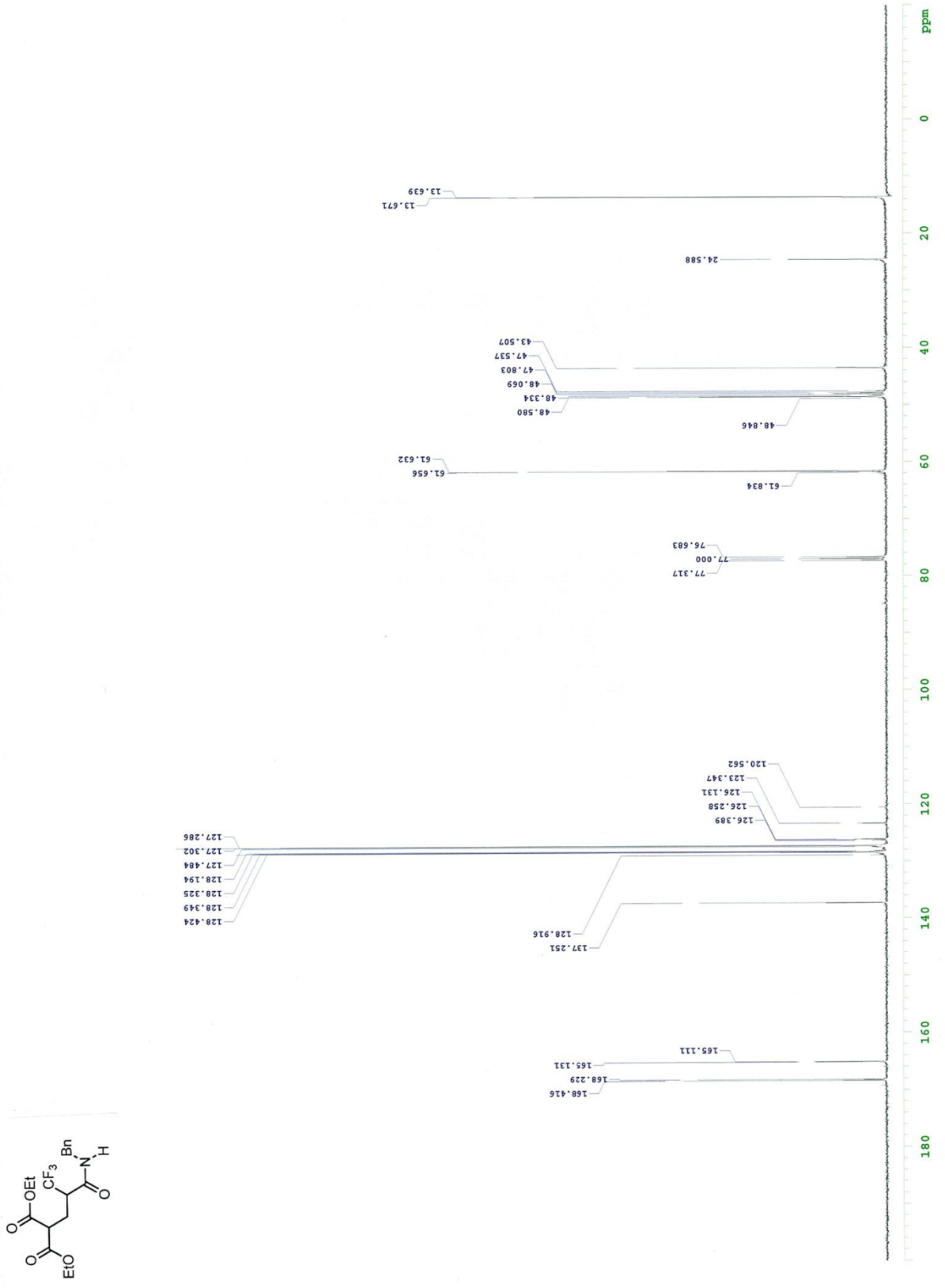
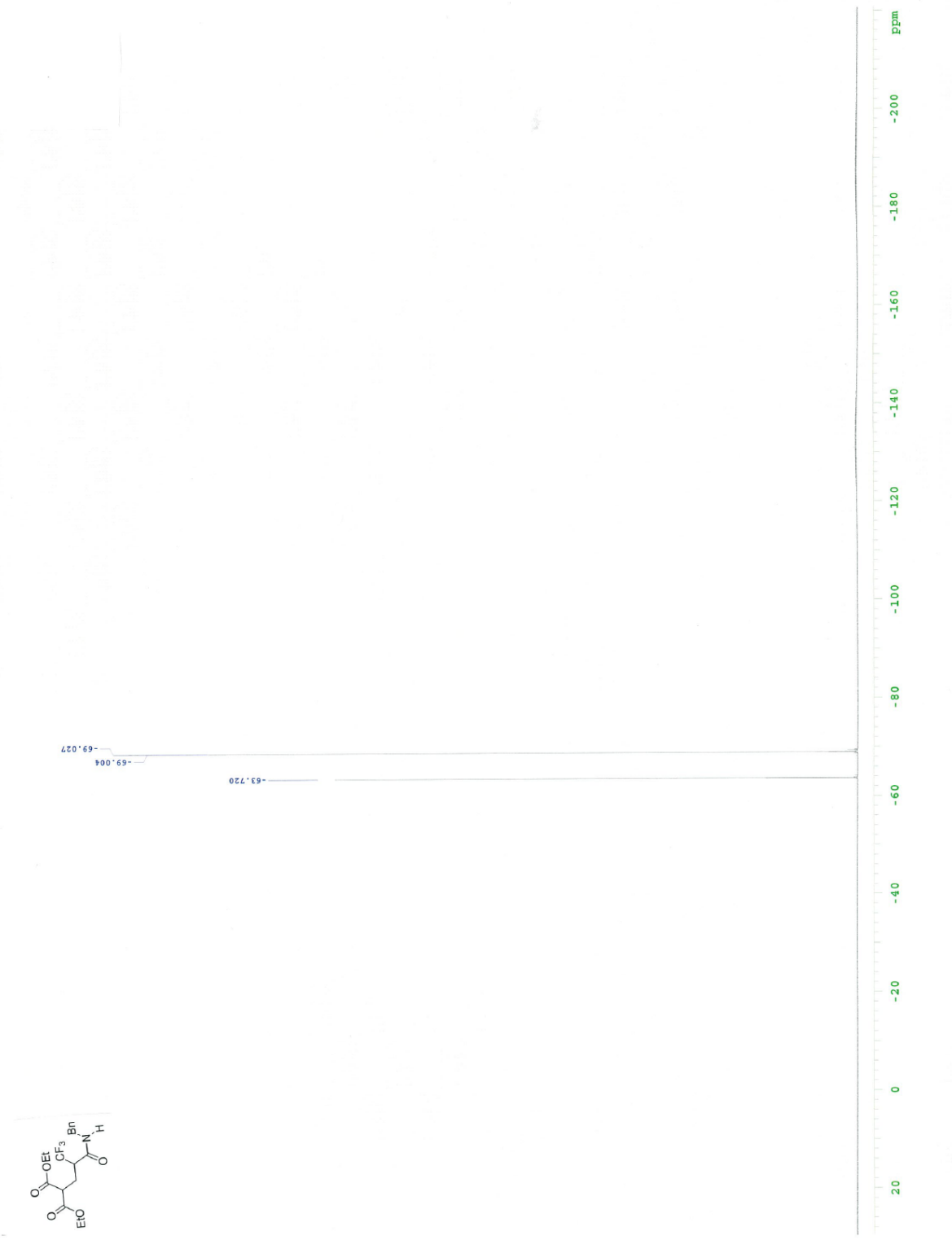


^{1}H spectrum of diethyl 2-(2-(benzylcarbamoyl)-3,3,3-trifluoropropyl)malonate



^{13}C spectrum of diethyl 2-(2-(benzylcarbamoyl)-3,3,3-trifluoropropyl)malonate



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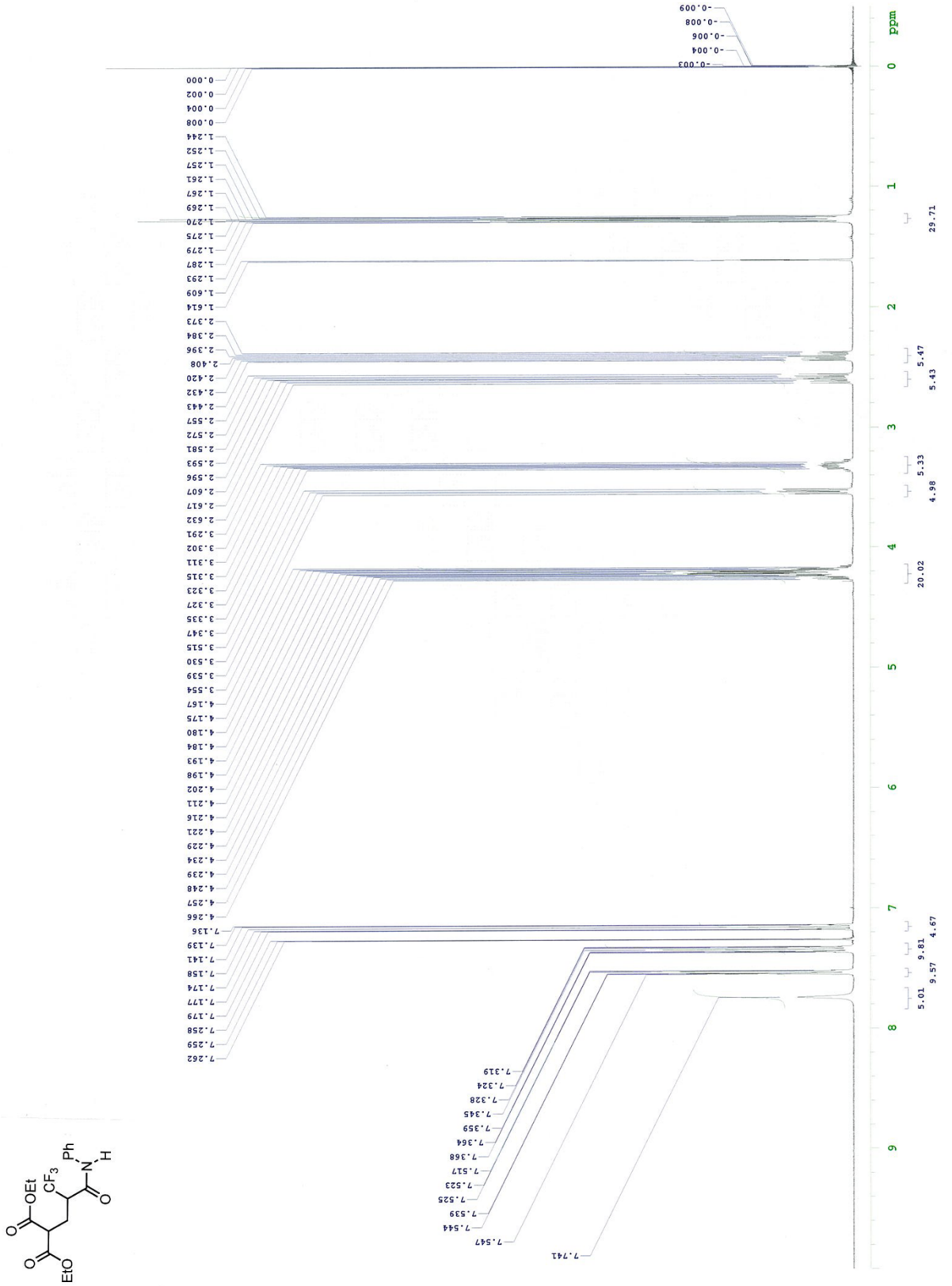
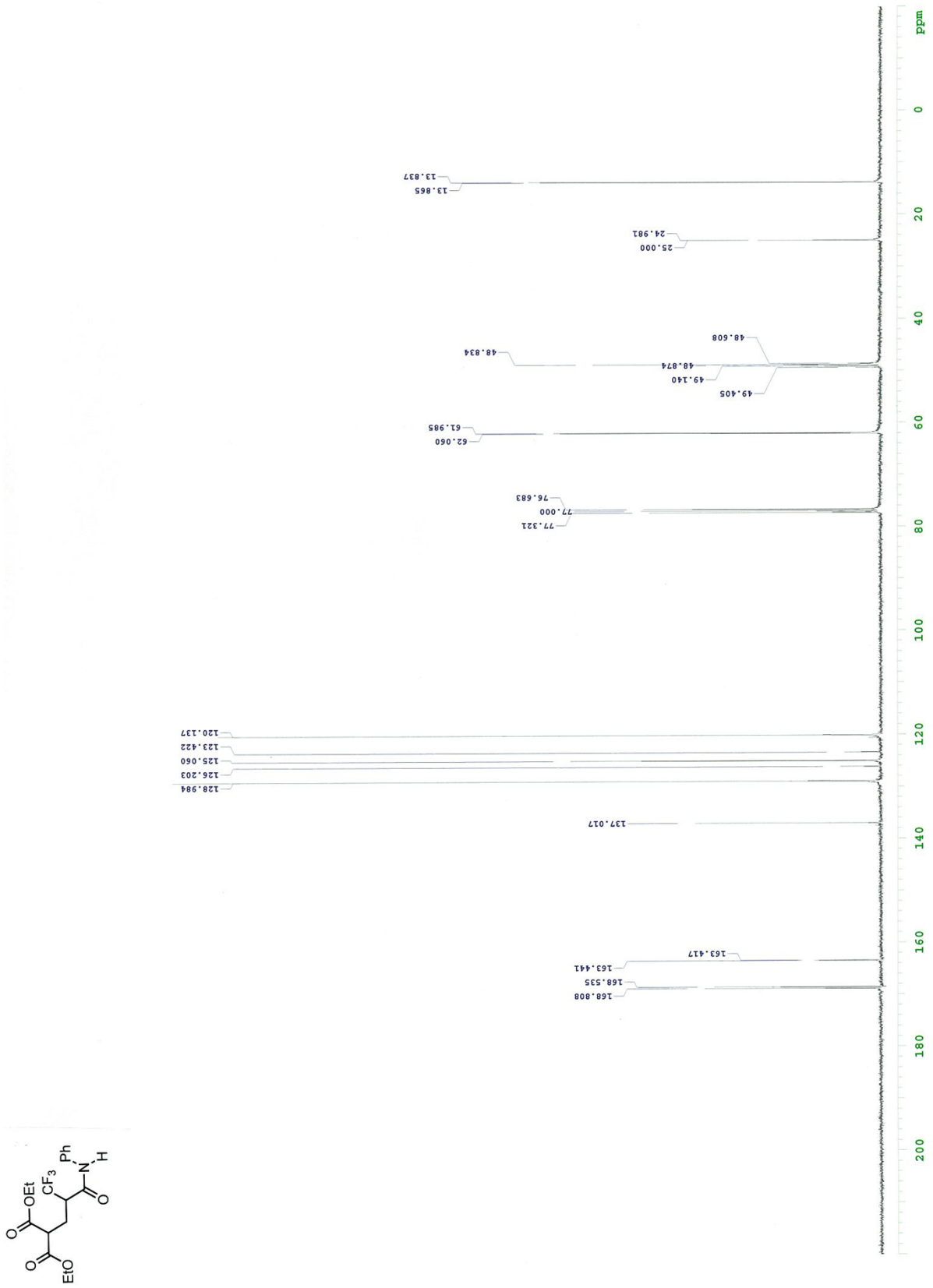
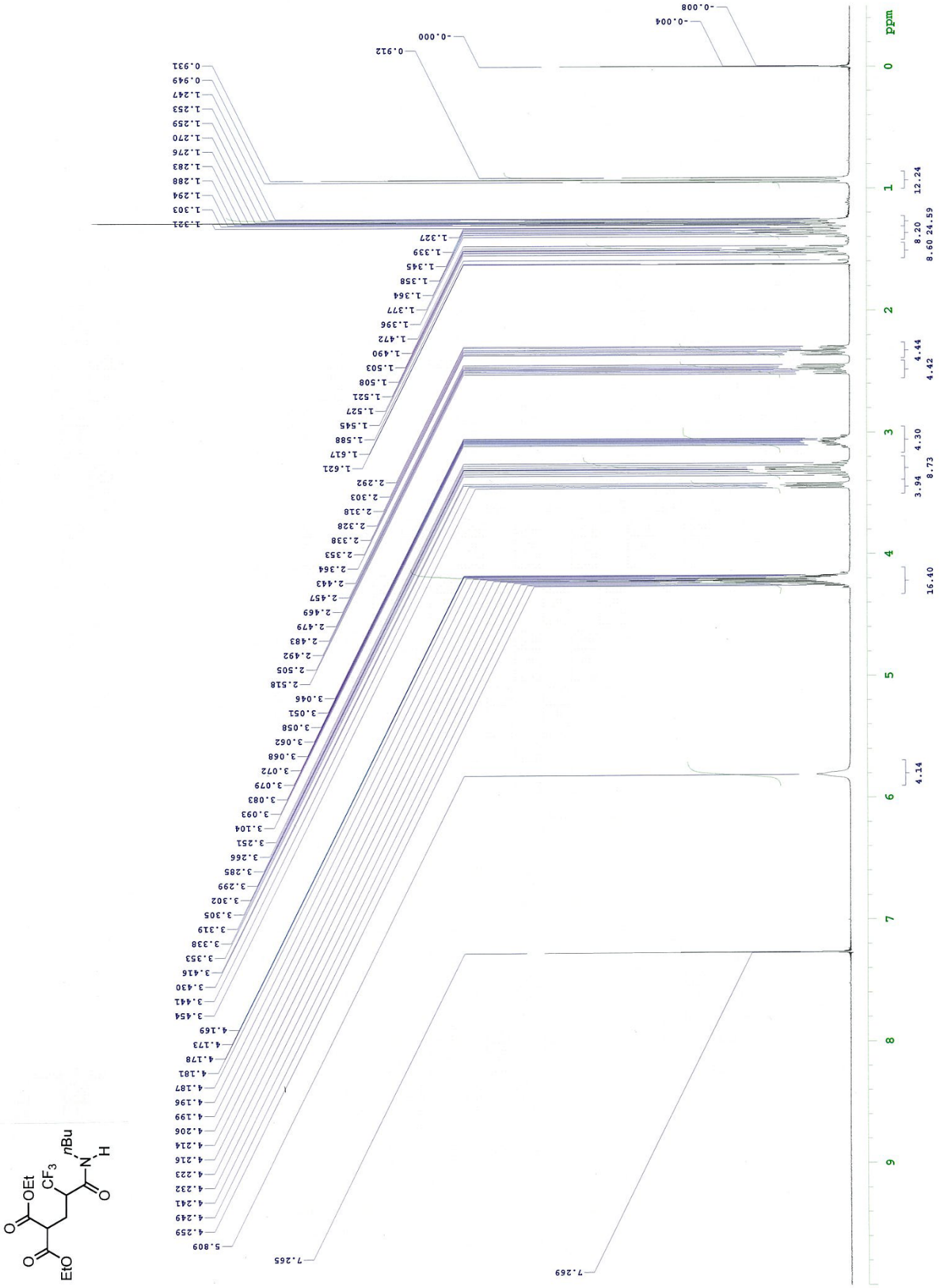


^{1}H spectrum of diethyl 2-(3,3,3-trifluoro-2-(phenylcarbamoyl)propyl)malonate

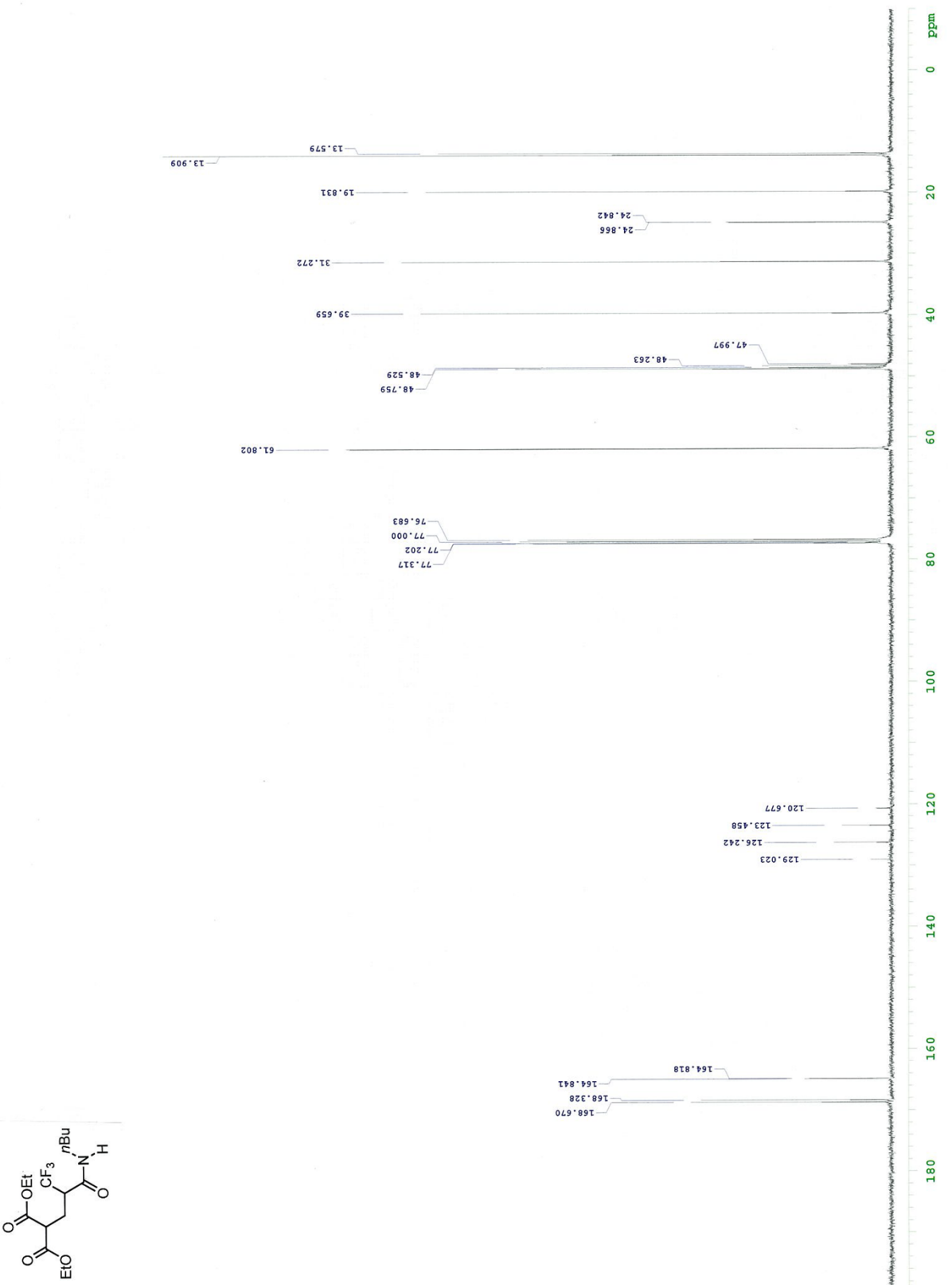


^{13}C spectrum of diethyl 2-(3,3,3-trifluoro-2-(phenylcarbamoyl)propyl)malonate

^{19}F spectrum of diethyl 2-(3,3,3-trifluoro-2-(phenylcarbamoyl)propyl)malonate

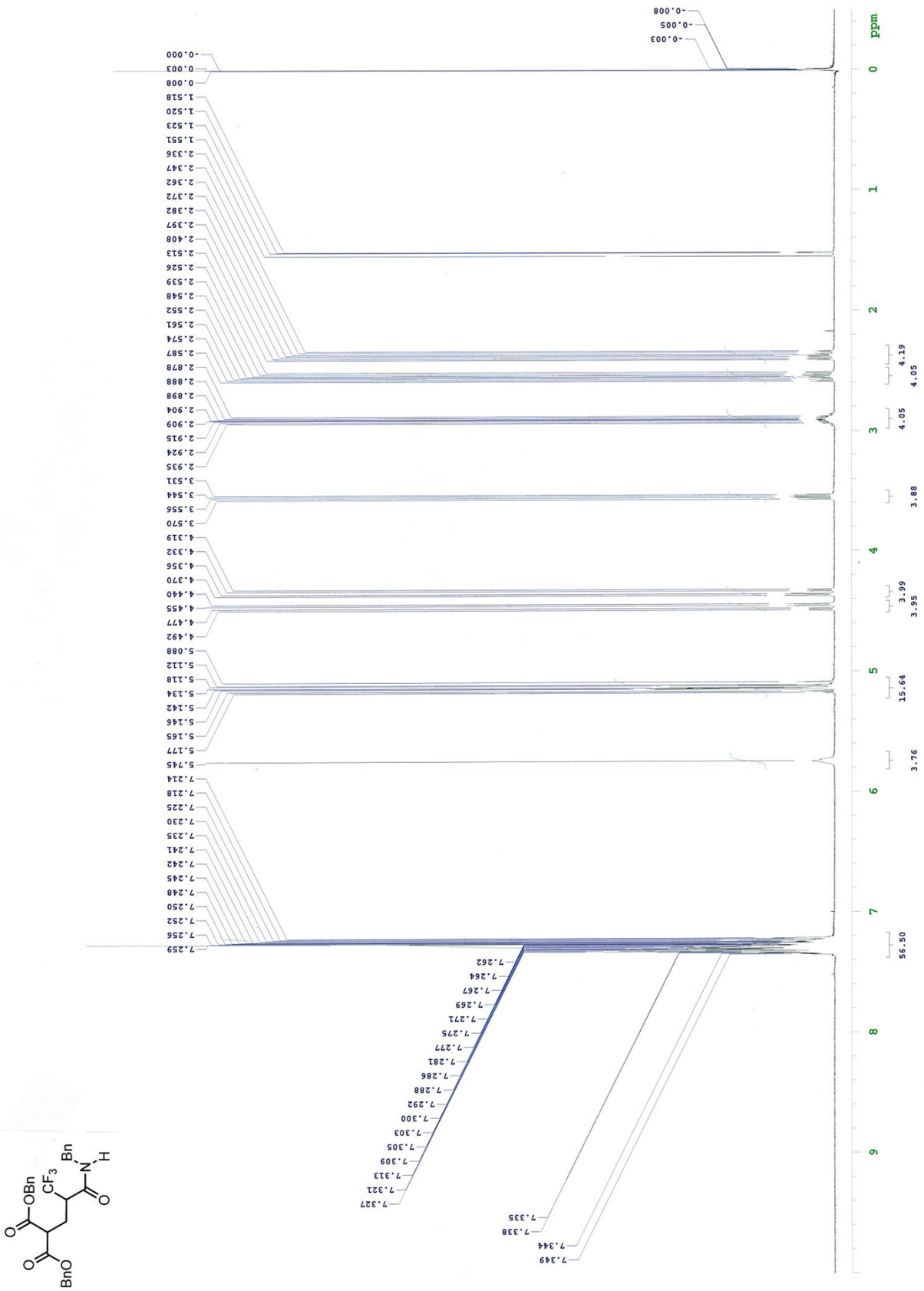


^{1}H spectrum of diethyl 2-(2-(butylcarbamoyl)-3,3,3-trifluoropropyl)malonate



^{13}C spectrum of diethyl 2-(2-(butylcarbamoyl)-3,3,3-trifluoropropyl)malonate

^{19}F spectrum of diethyl 2-(2-(butylcarbamoyl)-3,3,3-trifluoropropyl)malonate



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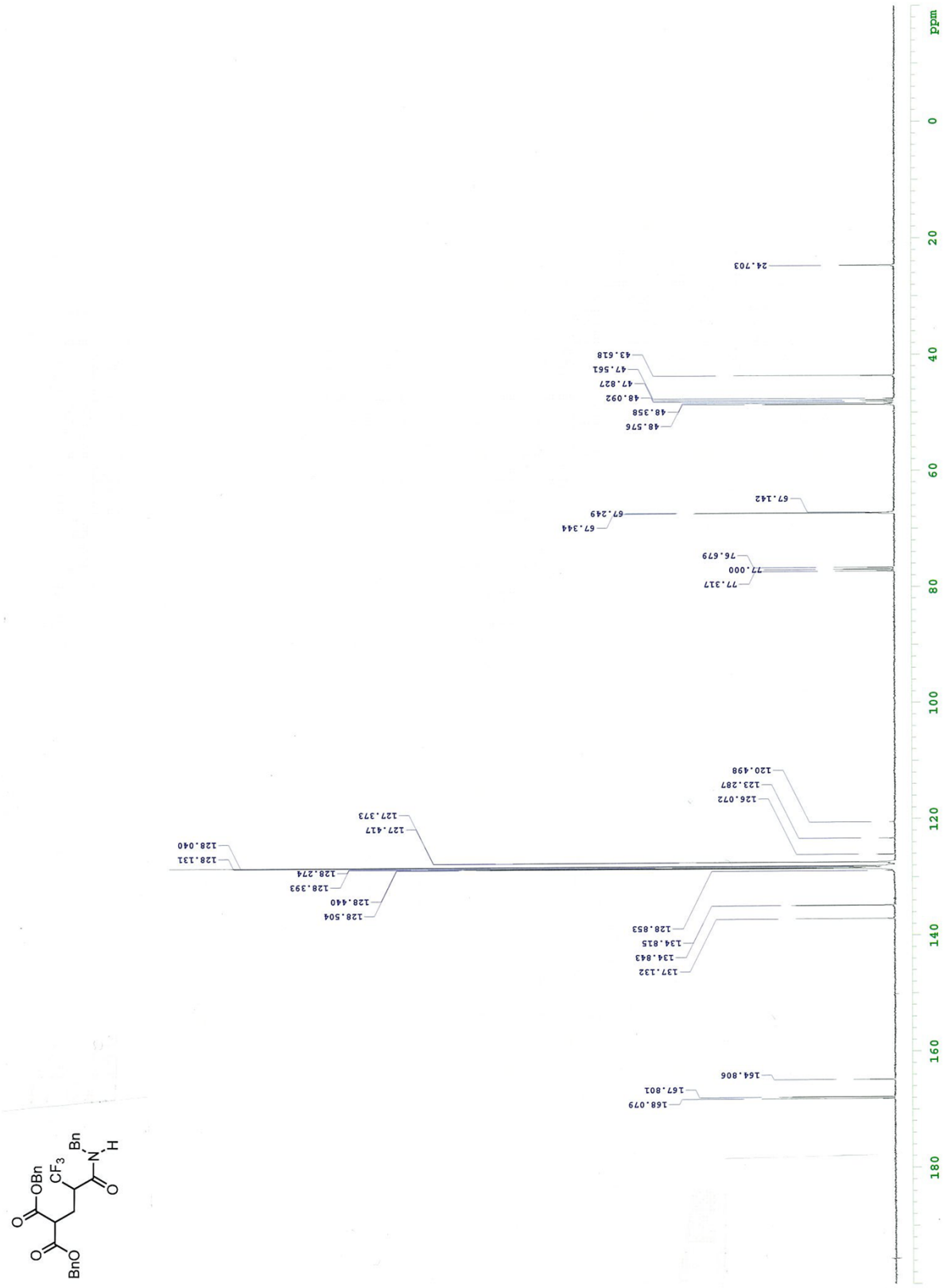
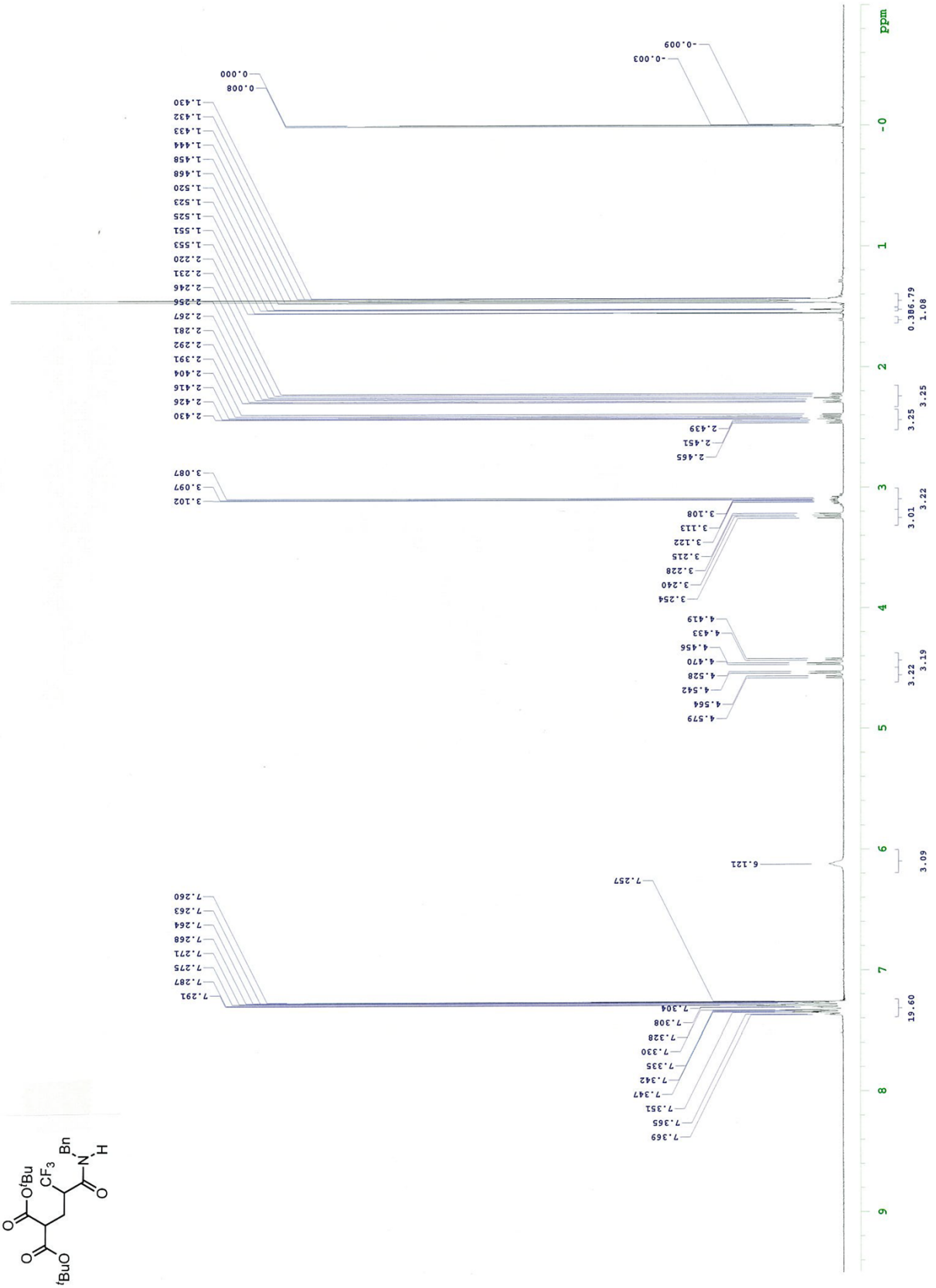


^{13}C spectrum of dibenzyl 2-(2-(benzylcarbamoyl)-3,3,3-trifluoropropyl)malonate

^{19}F spectrum of dibenzyl 2-(2-(benzylcarbamoyl)-3,3,3-trifluoropropyl)malonate



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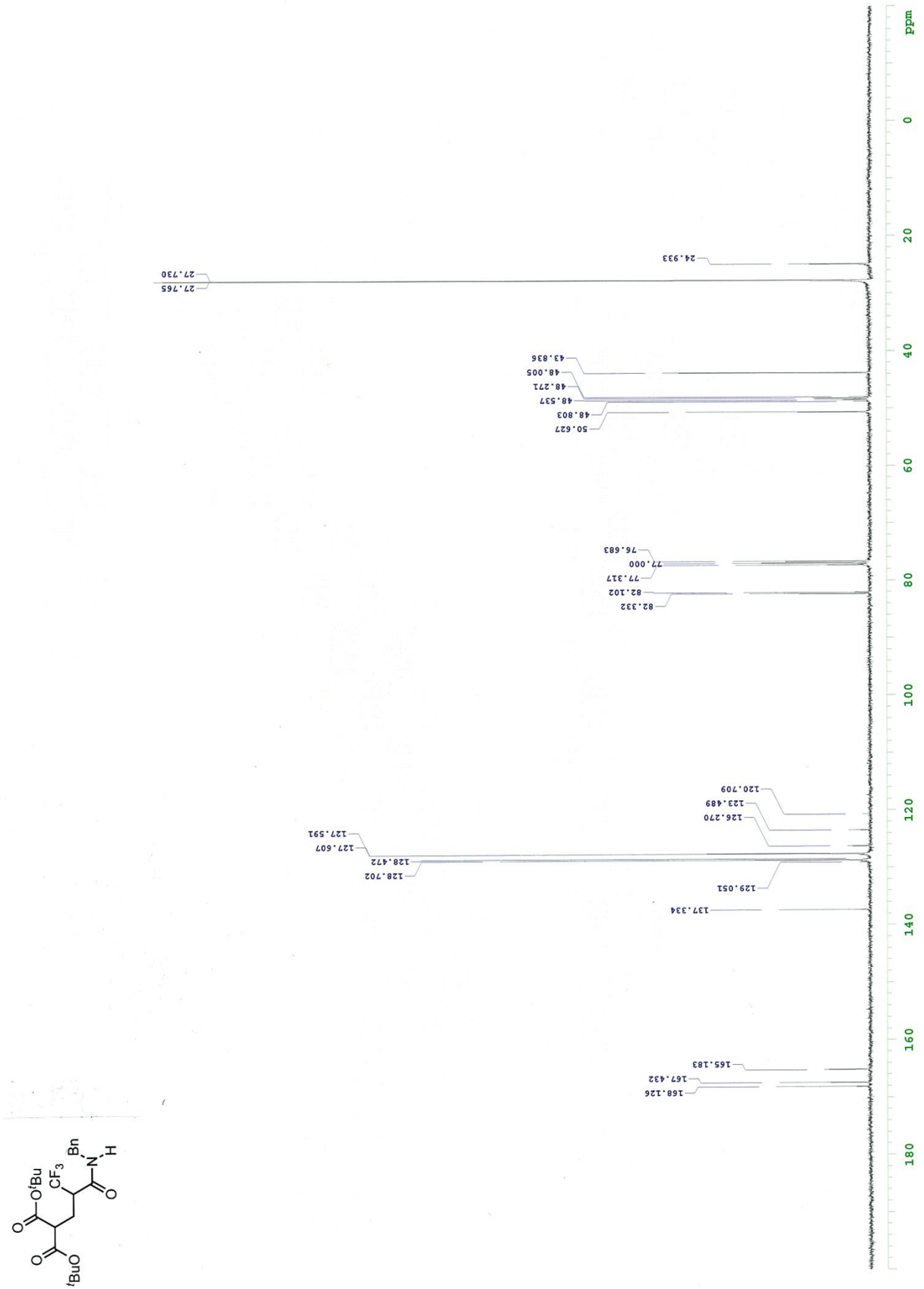

^{13}C spectrum of di-*tert*-butyl 2-(2-(benzylcarbamoyl)-3,3,3-trifluoropropyl)malonate

^{19}F spectrum of di-*tert*-butyl 2-(2-(benzylcarbamoyl)-3,3,3-trifluoropropyl)malonate