Supporting Information

Perfluoroalkylation in Flow Microreactors: Generation of Perfluoroalkyllithiums in the Presence and Absence of Electrophiles

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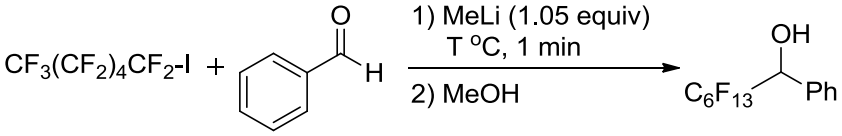
General

GC analysis was performed on a SHIMADZU GC-2014 gas chromatograph equipped with a flame ionization detector using a fused silica capillary column (column, CBP1; 0.22 mm x 25 m). ^{1}H NMR spectra were recorded on Varian MERCURYplus-400 (400 MHz) spectrometer with Me_4Si or $CDCl_3$ as a standard in $CDCl_3$ unless otherwise noted. ^{13}C NMR spectra were recorded on JEOL ECA-600P (150 MHz) spectrometer with $CDCl_3$ as a standard in $CDCl_3$ unless otherwise noted. ^{19}F NMR spectra were recorded on Varian MERCURYplus-400 (377 MHz) spectrometer with trifluorotoluene as a standard in $CDCl_3$ unless otherwise noted. ^{119}Sn NMR spectrum was recorded on JEOL ECA-600P (224 MHz) spectrometer with tetramethyltin as an external standard in $CDCl_3$. EI mass spectra were recorded on JMS-SX102A spectrometer. APCI mass spectra were recorded on EXACTIVE spectrometer. FT-IR spectrum was recorded on SHIMADZU IRAffinity-1 spectrometer. Gel permeation chromatography (GPC) was carried out on Japan Analytical Industry LC-908 and LC-9201. Diethyl ether was purchased from Kanto Chemical Co., Inc. as a dry solvent and used without further purification. Perfluoroalkyl halide, benzaldehyde, acetophenone, phenyl isocyanate, *n*-butyl isocyanate, chlorotributylstanane, trimethylsilyl triflate, methanol, MeLi were commercially available. All solutions used for flow reactions were prepared under the argon atmosphere using dry solvents.

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 was purchased from GL Sciences. The micromixer and microtube reactors were connected with stainless steel fittings (GL Sciences, 1/16 OUW). The microflow system was dipped in a cooling bath to control the temperature. Solutions were introduced to the flow microreactor system using syringe pumps, Harvard Model 11, equipped with gastight syringes purchased from SGE.

Generation of Tridecafluorohexyllithium in the Presence of Benzaldehyde in a Macro Batch System

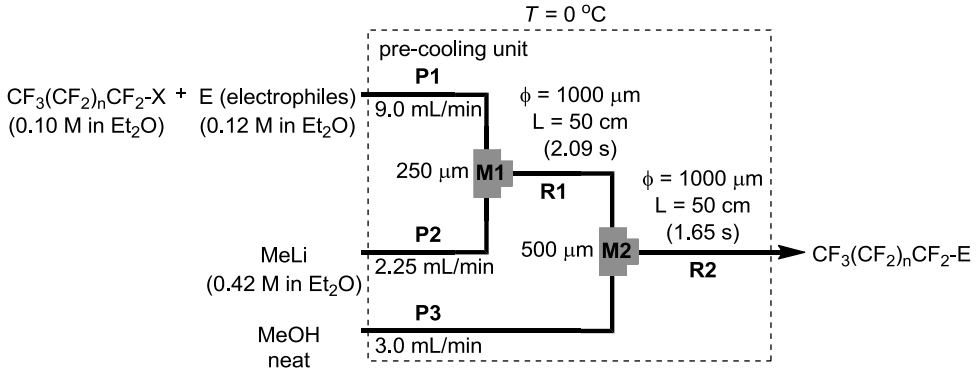


A solution of MeLi (0.42 M in Et_2O, 2.25 mL) was added dropwise to a mixture solution of tridecafluorohexyl iodide (0.10 M) and benzaldehyde (0.12 M) in Et_2O (9 mL) at T °C at regular pace for 1.0 min. After stirring for 1 min, methanol (neat, 3.0 mL) was added dropwise to this mixture at regular pace for 1.0 min. After stirring at T °C for 10 min, a cooling bath was removed. When the reaction mixture reached room temperature, the yield of 1-phenyl-2,2,3,3,4,4,5,5,6,6,7,7,7-tridecafluoroheptan-1-ol were determined by GC analysis using an internal standard (pentadecane). The results are summarized in Table S-1.

Table S-1. The reaction of tridecafluorohexyllithium with benzaldehyde using a conventional batch macro reactor.

T (°C)	yield (%)
-78	67
0	46

Typical Procedure for Generation of Perfluoroalkyllithiums in the Presence of Electrophiles in the Flow Microreactor System



A flow microreactor system consisting of two T-shaped micromixers (**M1** and **M2**), two microtube reactors (**R1** and **R2**), and three tube 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)) was used. A mixing solution of $CF_3(CF_2)_nCF_2X$ (0.10 M in Et_2O) and an electrophile (0.12 M in Et_2O) (flow rate: 9.0 mL min^{-1}) and a solution of MeLi (0.42 M in Et_2O) (flow rate: 2.25 mL min^{-1}) were introduced to **M1** (ϕ = 250 μm) by syringe pumps. The resulting solution was passed through **R1** (ϕ = 1000 μm, L = 50 cm) and was mixed with methanol (neat) (flow rate: 3.0 mL min^{-1}) in **M2** (ϕ = 500 μm). The resulting solution was passed through **R2** (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. aqueous NH_4Cl solution. The reaction mixture was analyzed by GC using an internal standard.

1-Phenyl-2,2,3,3,3-pentafluoropropan-1-ol: Obtained in 84% yield (GC ^tR 11.6 min). The spectral data were identical to those reported in the literature.[1]

1-Phenyl-2,2,3,3,4,4,4-heptafluorobutan-1-ol: Obtained in 80% yield (GC ^tR 12.4 min). The spectral data were identical to those reported in the literature.[2]

1-Phenyl-2,2,3,3,4,4,5,5,5-nonafluoropentan-1-ol: Obtained in 85% yield (GC ^tR 13/4 min). The spectral data were identical to those reported in the literature.[2]

1-Phenyl-2,2,3,3,4,4,5,5,6,6,6-undecafluorohexan-1-ol: Obtained in 86% yield (GC ^tR 14.3 min). After extraction, the crude product was purified by column chromatography (hexane/ethyl acetate = 20/1 to 10/1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.51 (d, *J* = 5.2 Hz, 1H), 5.22 (dt, *J* = 5.6 Hz, *J* = 17.6 Hz, 1H), 7.41-7.49 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 72.3 (dd, *J* = 23.0 Hz, *J* = 28.0 Hz), 106.2-107.4 (m), 108.0-115.4 (m), 116.2-117.1 (m), 118.3 (t, *J* = 33.0 Hz), 120.3 (t, *J* = 33.0 Hz), 128.1, 128.6, 129.7, 134.0; ^{19}F NMR (377 MHz, $CDCl_3$) δ -81.2 (t, *J* = 10.2 Hz, 3F), -118.0-(-127.6) (m, 8F) ; HRMS (APCI) *m/z* calcd for $C_{12}H_7F_{11}OCl$ ($[M+Cl]^-$): 411.0004, found: 441.0014.

1-Phenyl-2,2,3,3,4,4,5,5,6,6,7,7,7-tridecafluoroheptan-1-ol: Obtained in 74% yield (GC ^tR 15.2 min). Isolated yield was 74% (purified by column chromatography (hexane/ethyl acetate = 10/1)). The spectral data were identical to those reported in the literature.[2]

1-Methyl-1-phenyl-2,2,3,3,4,4,5,5,6,6,7,7,7-tridecafluoroheptan-1-ol: Obtained in 70% yield (GC ^tR 15.5 min). The spectral data were identical to those reported in the literature.[3]

2,2,3,3,4,4,5,5,6,6,7,7,7-Tridecafluoro-*N*-phenylheptanamide: Obtained in 79% yield (GC ^tR 16.1 min). After extraction, the crude product was purified by column chromatography (hexane/ethyl acetate = 5/1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.28 (m, 1H), 7.38-7.43 (m, 2H), 7.55-7.58 (m, 2H), 7.15-7.22 (m, 3H), 7.91 (brs, 1H); ^{13}C NMR (150 MHz, DMSO) δ 105.5-112.7 (m), 113.8 (t, *J* = 33.0 Hz), 115.7 (t, *J* = 33.0 Hz), 117.6 (t, *J* = 33.0 Hz), 119.5 (t, *J* = 33.0 Hz), 121.3, 125.7, 128.7, 136,3, 155.1 (t, *J* = 25.8 Hz); ^{19}F NMR (377 MHz, DMSO) δ -82.3 (t, *J* = 10.2 MHz, 3F), -120.0-(-127.8) (m, 10F); HRMS (EI) *m/z* calcd for $C_{13}H_6ONF_{13}$ (M^+): 439.0242, found: 270.439.0233.

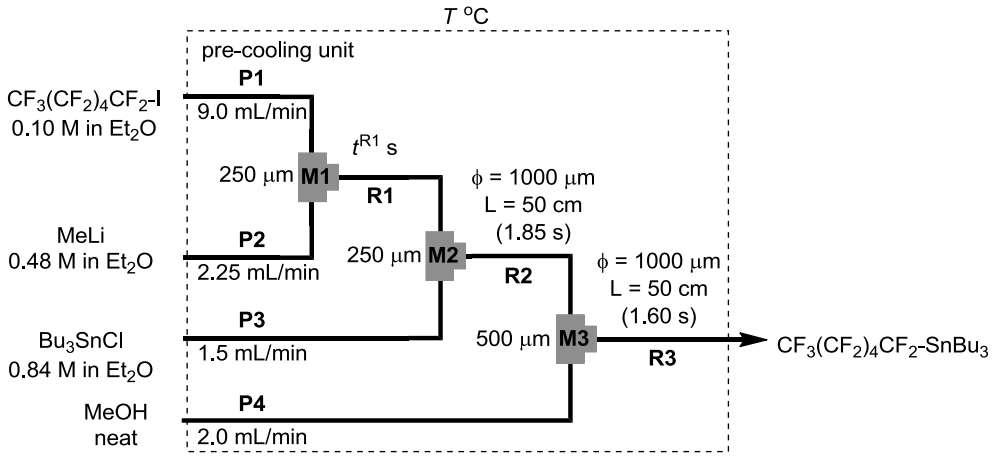
2,2,3,3,4,4,5,5,6,6,7,7,7-Tridecafluoro-*N*-*n*-butylheptanamide: Obtained in 86% yield (GC

^tR 12.5 min). After extraction, the crude product was purified by column chromatography (hexane/ethyl acetate = 10/1 to 5/1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, *J* = 7.2 Hz, 3H), 1.32-1.42 (m, 2H), 1.53-1.61 (m, 2H), 3.39 (dt, *J* = 6.4 Hz, *J* = 6.4 Hz, 3H), 6.30 (brs, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.1, 19.8, 30.8, 40.0, 106.2-113.2 (m), 114.4 (t, *J* = 33.0 Hz), 116.3 (t, *J* = 33.0 Hz), 118,2 (t, *J* = 33.0 Hz), 120.1 (t, *J* = 33.0 Hz), 158.1 (t, *J* = 25.9 Hz); ^{19}F NMR (377 MHz, $CDCl_3$) δ -81.2 (t, *J* = 10.2 Hz, 3F), 120.1-(-236.7) (m, 10F); HRMS (APCI) *m/z* calcd for $C_{11}H_{11}NOF_{13}$ ($[MH]^+$): 420.0628, found: 420.0618.

Trimethyl(1,1,2,2,3,3,4,4,5,5,6,6,6-tridecafluorohexyl)silane: Obtained in 30% yield (GC ^tR 4.3 min). After extraction, the crude product was purified by GPC: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.30 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ -4.8, 106.5-107.8 (m), 108.3-114.1 (m), 114.6-115.6 (m), 116.7 (t, *J* = 33.0 Hz), 118.6 (t, *J* = 33.0 Hz), 120.5 (t, *J* = 33.0 Hz), 121.6 (t, *J* = 44.5 Hz), 123.4 (t, *J* = 44.5 Hz), 125.2 (t, *J* = 46.0 Hz); ^{19}F NMR (377 MHz, $CDCl_3$) δ -81.3 (t, *J* = 10.2 Hz, 3F), -119.4-(-128.9) (m, 10F).

Tri-*n*-butyl(1,1,2,2,3,3,4,4,5,5,6,6,6-tridecafluorohexyl)stannane: Obtained in 2% yield (GC ^tR 19.9 min). The spectral data were identical to those reported in the literature.[4]

The I-Li Exchange Reaction of Tridecafluorohexyl Iodide Followed by Reaction with Chlorotributylstannane in the Flow Microreactor System



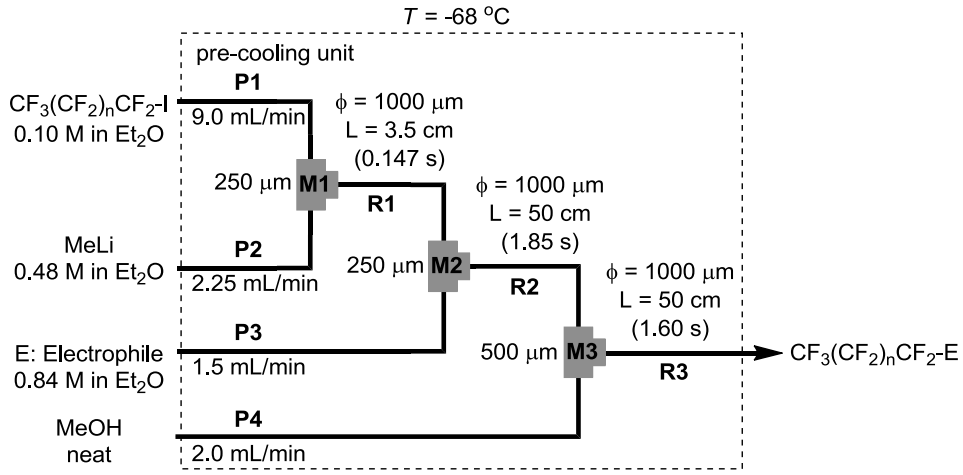
A flow microreactor system consisting of three T-shaped micromixers (**M1**, **M2** and **M3**), three microtube reactors (**R1, R2** and **R3**), and four tube pre-cooling units (**P1** (inner diameter ϕ = 1000 μm, length L = 150 cm), **P2** (ϕ = 1000 μm, L = 50 cm) and **P3** (ϕ = 1000 μm, L = 50 cm), **P4** (ϕ = 1000 μm, L = 50 cm)) was used. A solution of tridecafluorohexyl iodide (0.10 M in Et_2O) (flow rate: 9.0 mL min^{-1}) and a solution of MeLi (0.48 M in Et_2O) (flow rate: 2.25 mL min^{-1}) were introduced to **M1** (ϕ = 250 μm) by syringe pumps. The resulting solution was passed through **R1** and was mixed with a solution of chlorotributylstanane (0.84 M in Et_2O) (flow rate: 1.5 mL min^{-1}) in **M2** (ϕ = 250 μm). The resulting solution was passed through **R2** (ϕ = 1000 μm, L = 50 cm) and was mixed with methanol (neat) (flow rate: 2.0 mL min^{-1}) in **M3** (ϕ = 500 μm). The resulting solution 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. aqueous $NaHCO_3$ solution. The reaction mixture was analyzed by GC using an internal standard. The results are summarized in Table S-1.

Table S-1. The I-Li exchange reaction of tridecafluorohexyl iodide followed by reaction with chlorotributylstannate in flow microreactor systems.

inner diameter of **R1** (μm)	length of **R1** (cm)	t^{R1} (s)	*T* (°C)	yield (%)
1000	3.5	0.147	-48	47
1000	6.0	0.251		31
1000	12.5	0.524		8
1000	25	1.05		2
1000	50	2.09		0
1000	100	4.19		0
1000	200	8.38		0
1000	3.5	0.147	-58	72
1000	6.0	0.251		68

1000	12.5	0.524		56
1000	25	1.05		31
1000	50	2.09		11
1000	100	4.19		4
1000	200	8.38		2
1000	3.5	0.147	-68	87
1000	6.0	0.251		85
1000	12.5	0.524		84
1000	25	1.05		72
1000	50	2.09		55
1000	100	4.19		23
1000	200	8.38		15
1000	3.5	0.147	-78	75
1000	6.0	0.251		80
1000	12.5	0.524		80
1000	25	1.05		77
1000	50	2.09		71
1000	100	4.19		63
1000	200	8.38		41

Typical Procedure for Generation of Perfluoroalkyllithiums in the Absence of Electrophiles in the Flow Microreactor System



A flow microreactor system consisting of three T-shaped micromixers (**M1**, **M2** and **M3**), three microtube reactors (**R1, R2** and **R3**), and four tube 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 perfluoroalkyl halide (0.10 M in Et_2O) (flow rate: 9.0 mL min^{-1}) and a solution of MeLi (0.48 M in Et_2O) (flow rate: 2.25 mL min^{-1}) were introduced to **M1** (ϕ = 250 μm) by syringe pumps. The resulting solution was passed through **R1** and was mixed with a solution of an electrophile (0.84 M in Et_2O) (flow rate: 1.5 mL min^{-1}) in **M2** (ϕ = 250 μm). The resulting solution was passed through **R2** (ϕ = 1000 μm, L = 50 cm) and was quenched by mixing with methanol (flow rate: 2.0 mL min^{-1}) in **M3** (ϕ = 500 μm). The resulting solution 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. aqueous $NaHCO_3$ solution. The reaction mixture was analyzed by GC using an internal standard.

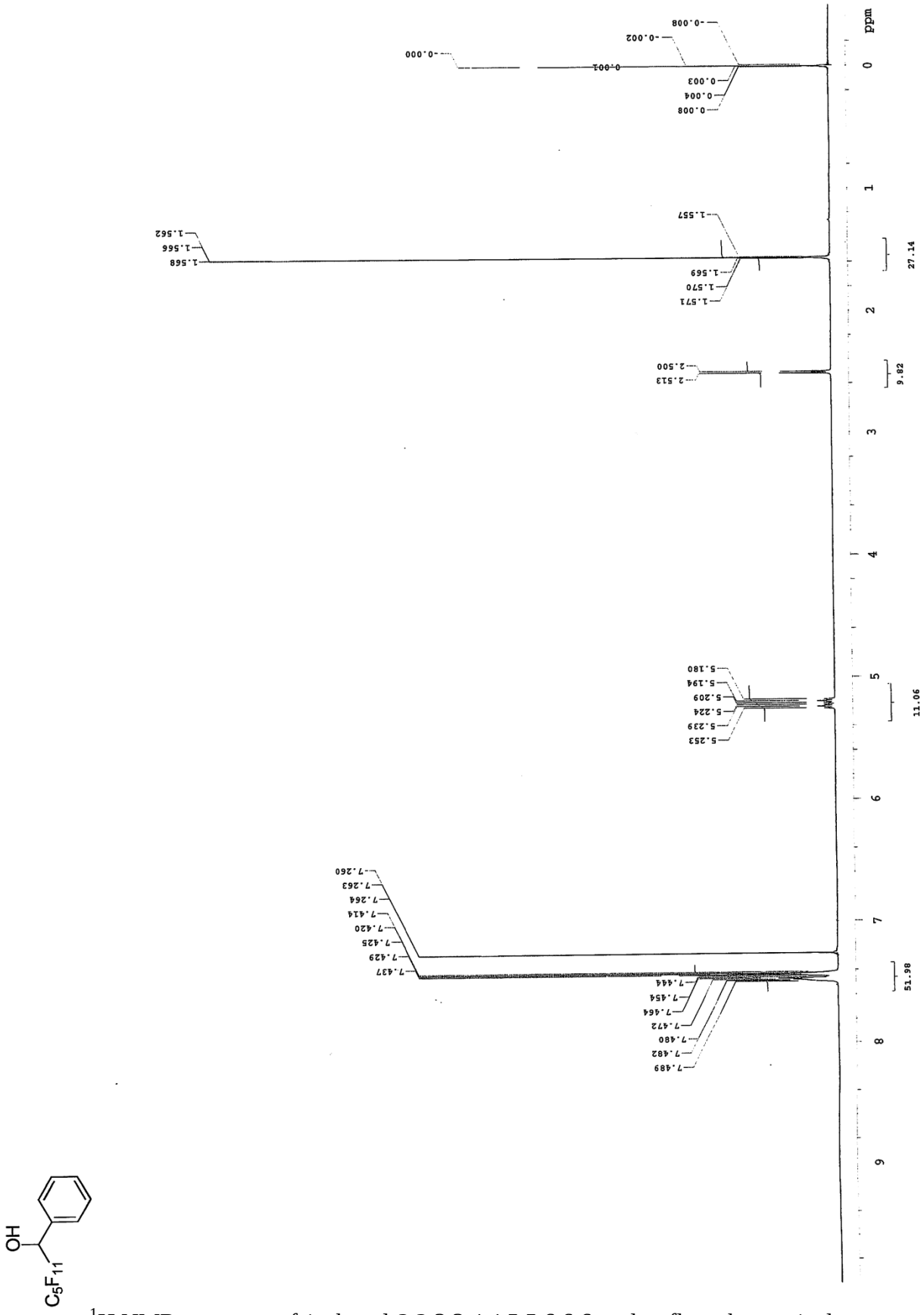
Tri-*n*-butyl(1,1,2,2,2-pentafluroroethyl)stannane: Obtained in 98% yield (GC ^tR 18.0 min). The spectral data were identical to those commercially available Tributyl(perfluoroethyl)stannane.

Tri-*n*-butyl(1,1,2,2,3,3,3-heptafluorooopropyl)stannane: Obtained in 70% yield (GC ^tR 18.2 min). The spectral data were identical to those reported in the literature.[5]

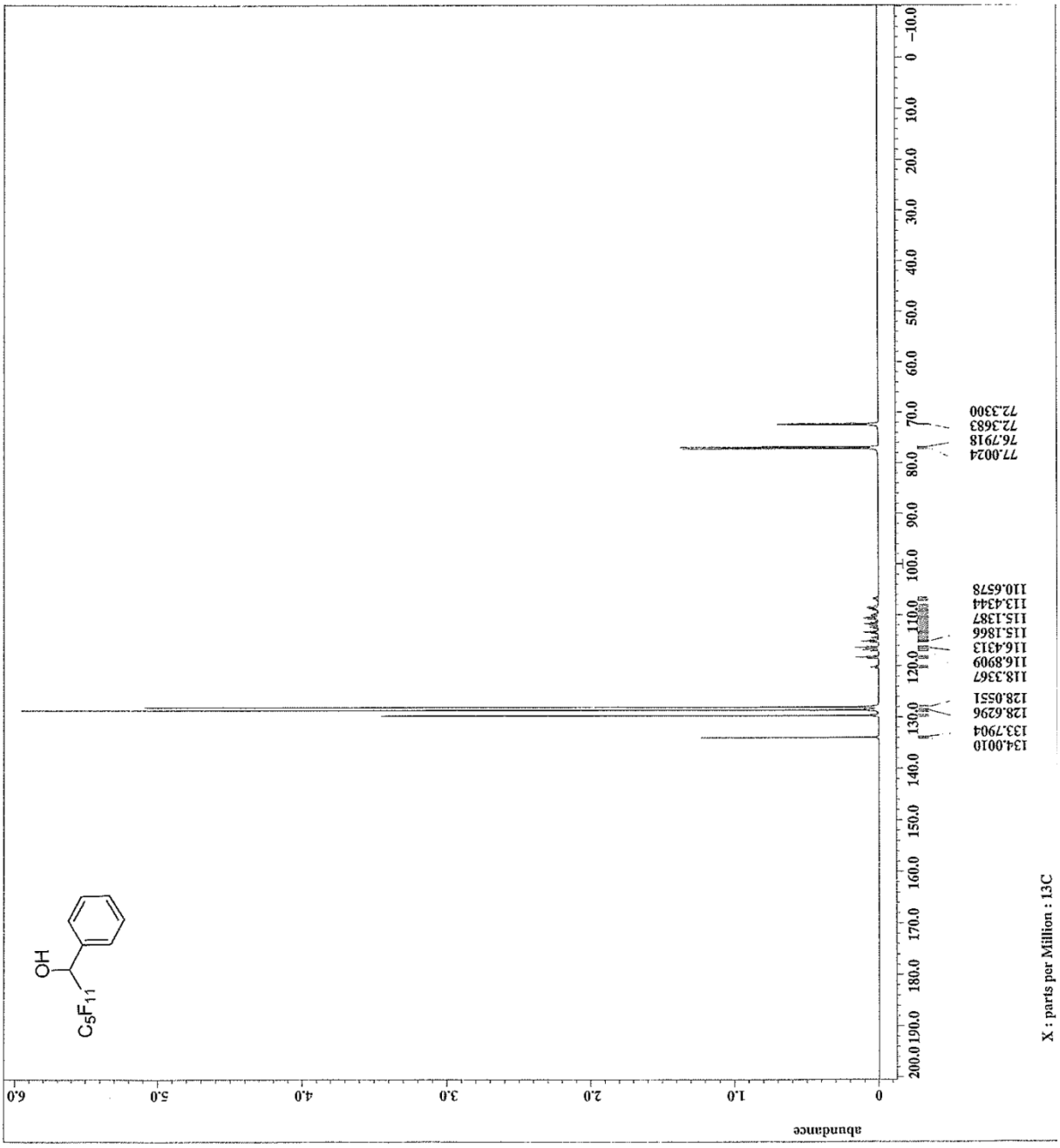
Tri-*n*-butyl(1,1,2,2,3,3,4,4,4-nonafluorobutyl)stannane: Obtained in 84% yield (GC ^tR 18.7 min). The spectral data were identical to those reported in the literature.[4]

Tri-*n*-butyl(1,1,2,2,3,3,4,4,5,5,5-undecafluoropentyl)stannane: Obtained in 90% yield (GC ^{t}R 19.2 min). After extraction, the crude product was purified by GPC: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.30 (s, 9H), 0.92 (t, J = 7.4 Hz, 3H), 1.10-1.39 (m, 4H), 1.46-1.67 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 10.7, 13.4, 27.3, 28.5, 106.4-107.6 (m), 108.2-115.1 (m), 116.8 (t, J = 33.0 Hz), 118.7 (t, J = 33.0 Hz), 120.6 (t, J = 33.0 Hz), 127.7-133.2 (m); ^{19}F NMR (377 MHz, $CDCl_3$) δ -81.3 (t, J = 10.2 Hz, 3F), -117.8-(-126.8) (m, 8F); ^{119}Sn NMR (224 MHz, $CDCl_3$) δ 0.51 (t, J = 191 Hz); HRMS (EI) *m/z* calcd for $C_{13}H_{18}F_{11}Sn$ ($[M\text{-}Bu]^+$): 503.0255, found: 503.0254.

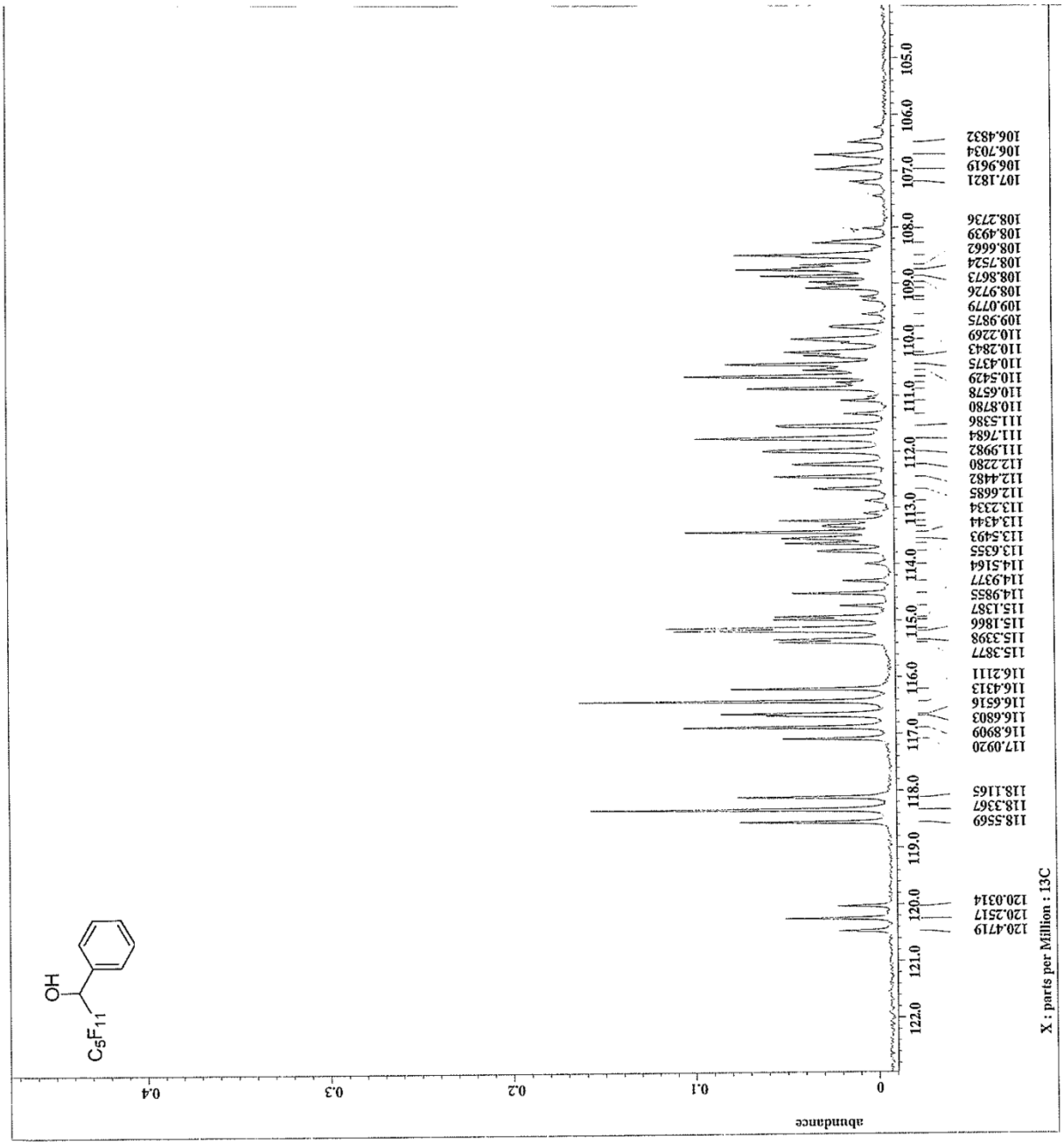
[1] G. K. S. Prakash, Y. Wang, R. Mogi, J. Hu, T. Mathew, G. A. Olah, *Org. Lett*., 2010, **12**, 2932.
[2] K. Mikami, T. Murase, Y. Itoh, *J. Am. Chem. Soc*., 2007, **129**, 11686.
[3] G. Santini, M. L. Blanc, J. G. Riess, *J. Organomet. Chem*., 1977, **140**, 1.
[4] J. E. Stanley, A. C. Swain, K. C. Molloy, D. W. H. Rankin, H. E. Robertson, B. F. Johnston, *Appl. Organometal. Chem*., 2005, **19**, 644.
[5] D. J. Burton, V. Jairaj, *J. Fluorine Chem*., 2005, **126**, 797.



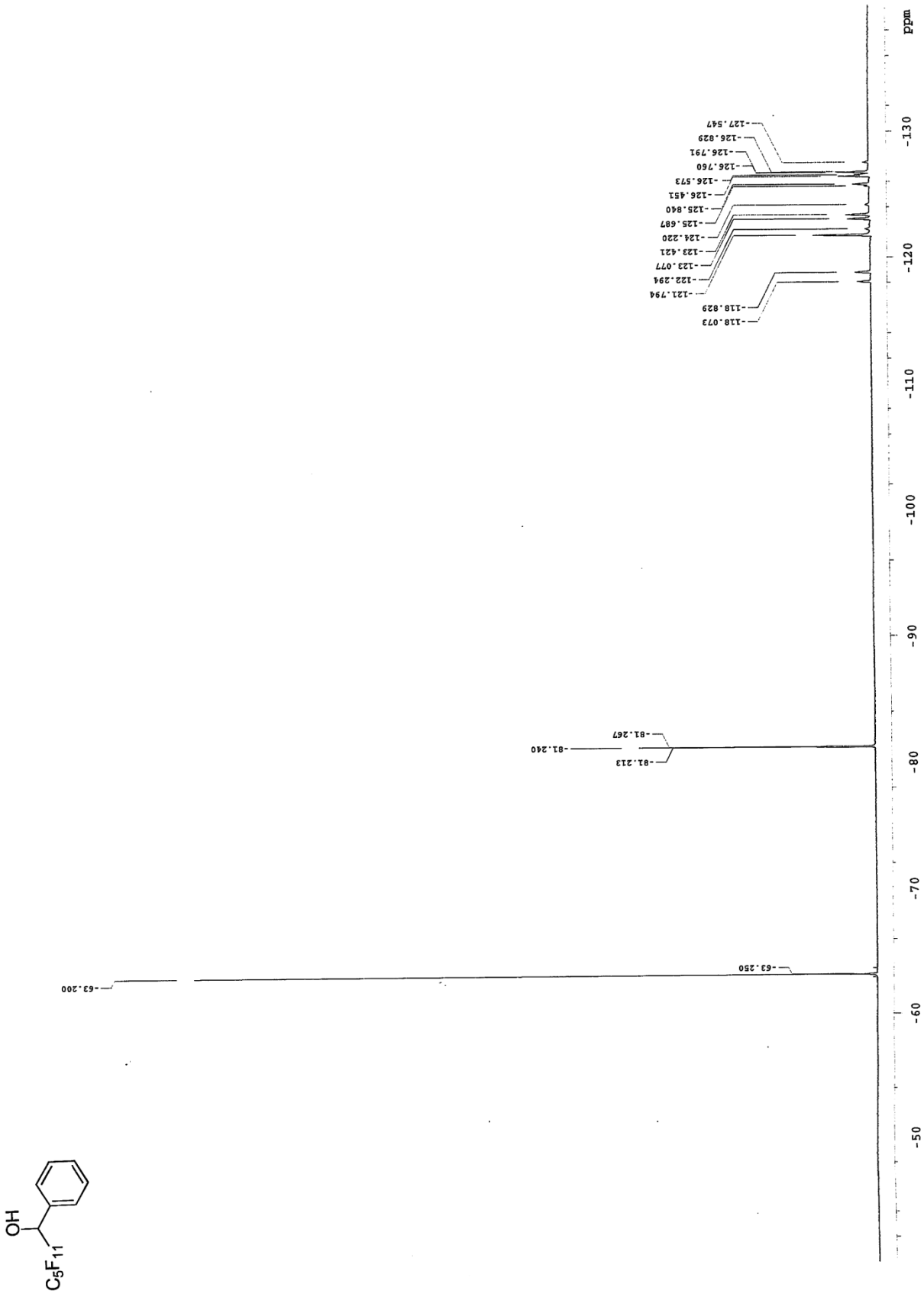
^{1}H NMR spectrum of 1-phenyl-2,2,3,3,4,4,5,5,6,6,6-undecafluorohexan-1-ol



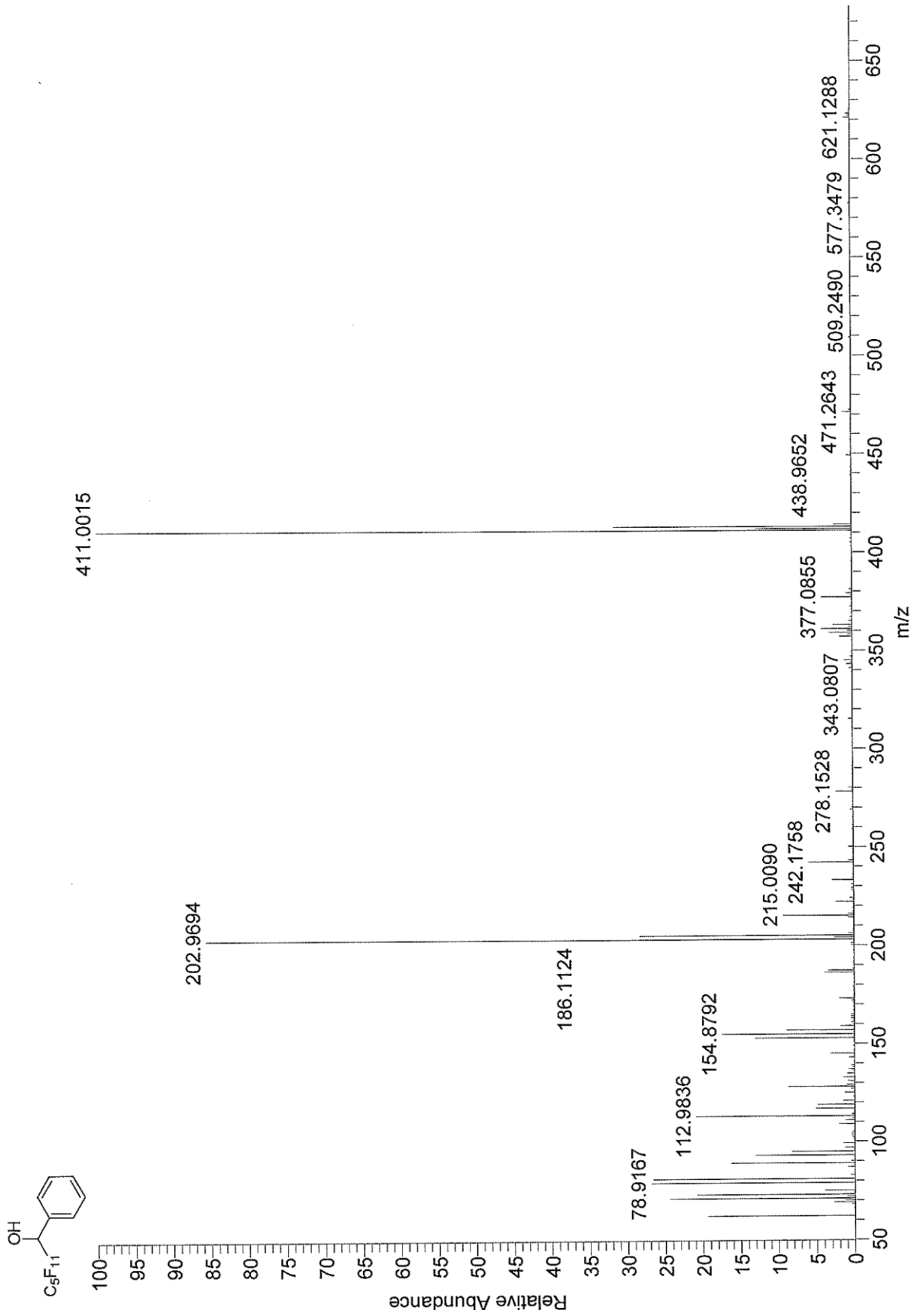
^{13}C NMR spectrum of 1-phenyl-2,2,3,3,4,4,5,5,6,6,6-undecafluorohexan-1-ol



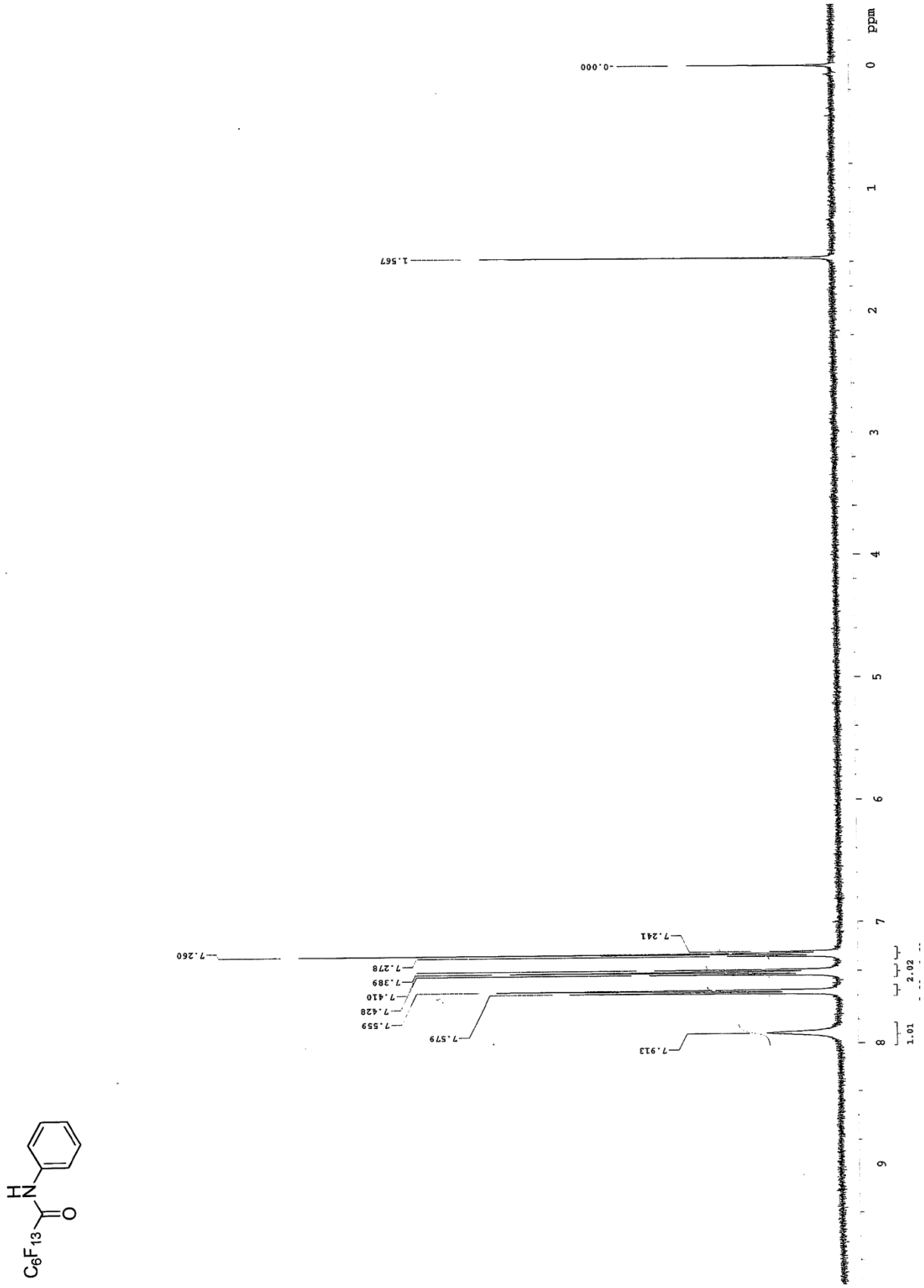
^{13}C NMR spectrum of 1-phenyl-2,2,3,3,4,4,5,5,6,6,6-undecafluorohexan-1-ol



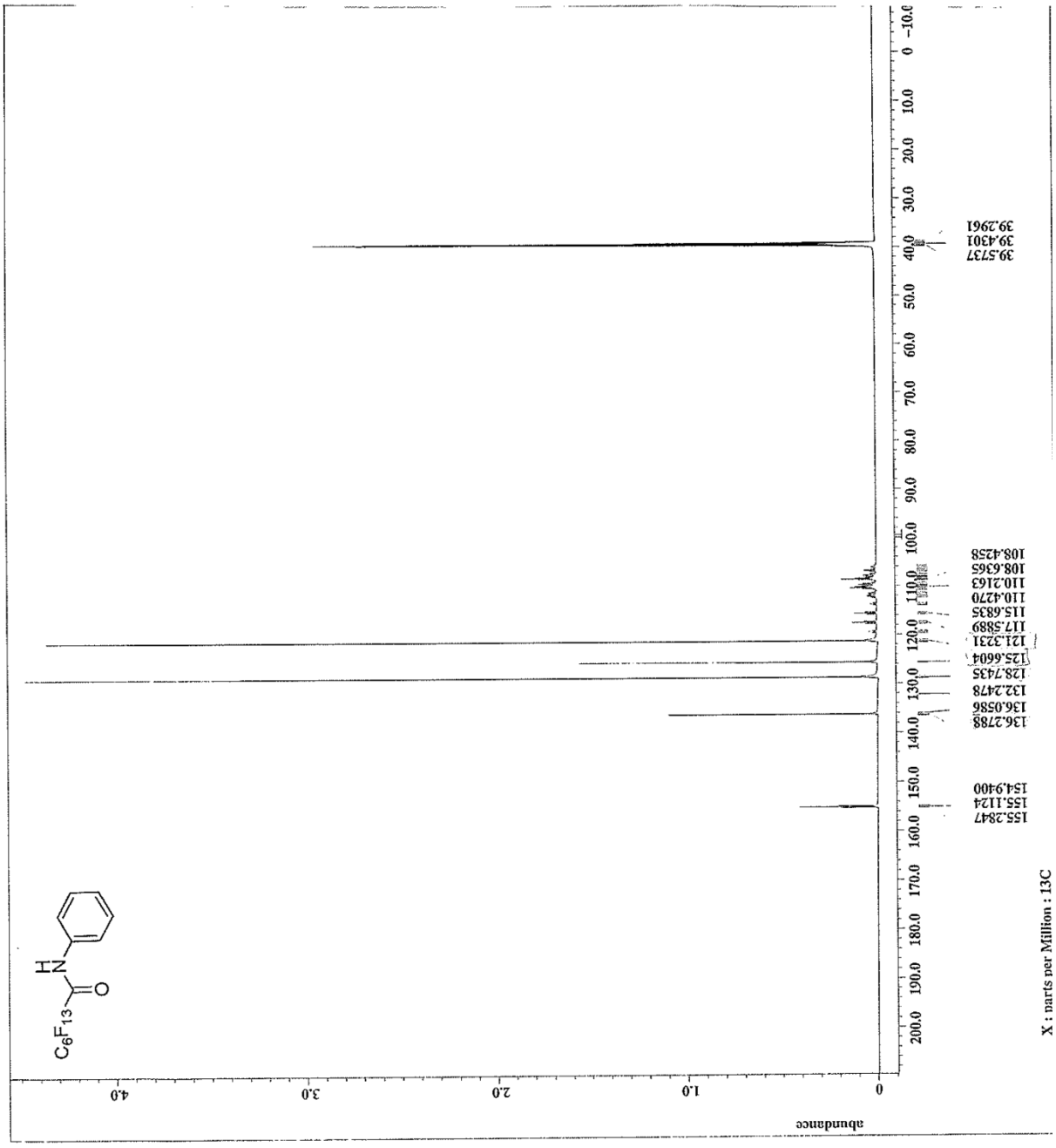
^{19}F NMR spectrum of 1-phenyl-2,2,3,3,4,4,5,5,6,6,6-undecafluorohexan-1-ol



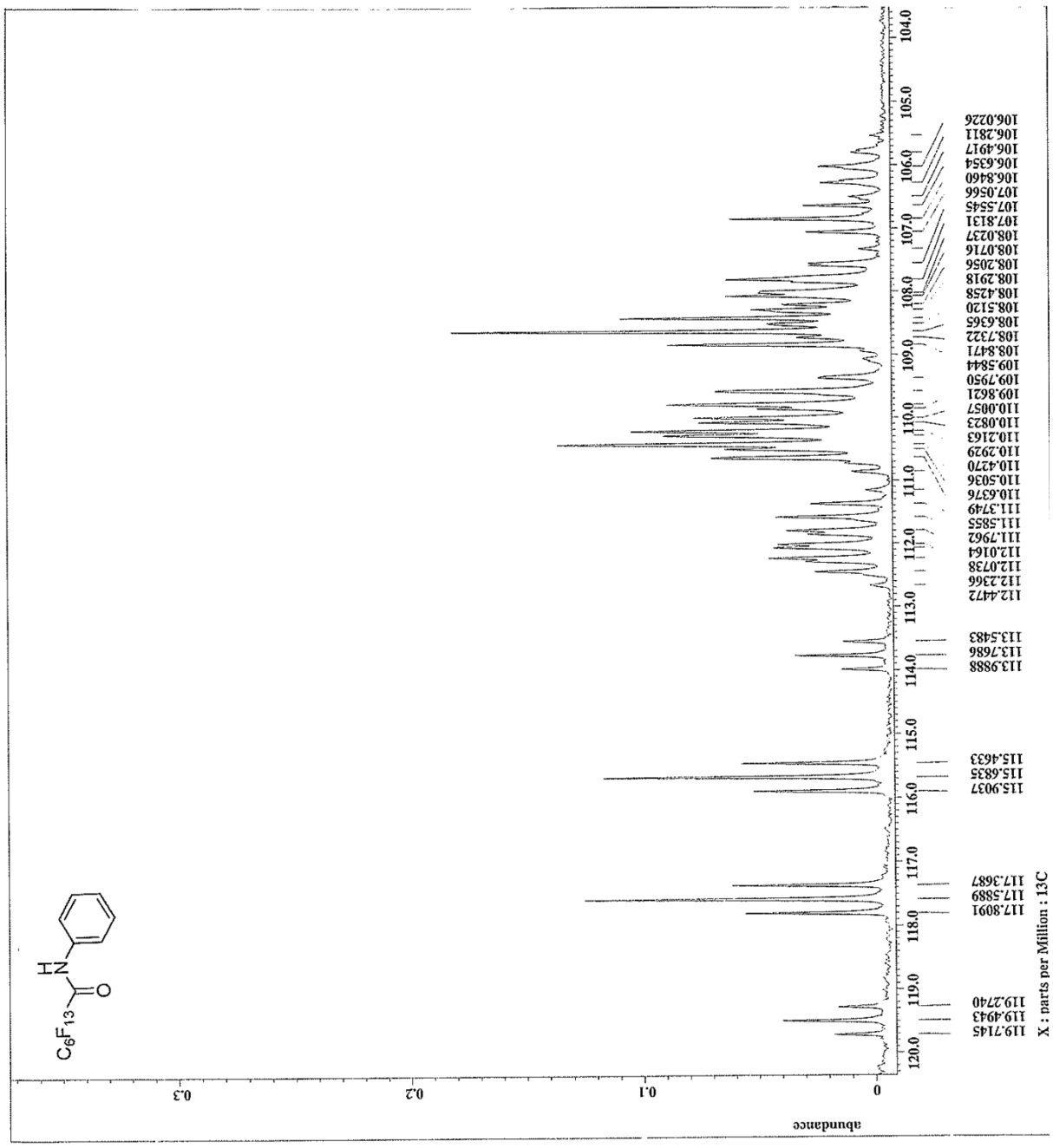
APCI mass spectrum of 1-phenyl-2,2,3,3,4,4,5,5,6,6,6-undecafluorohexan-1-ol



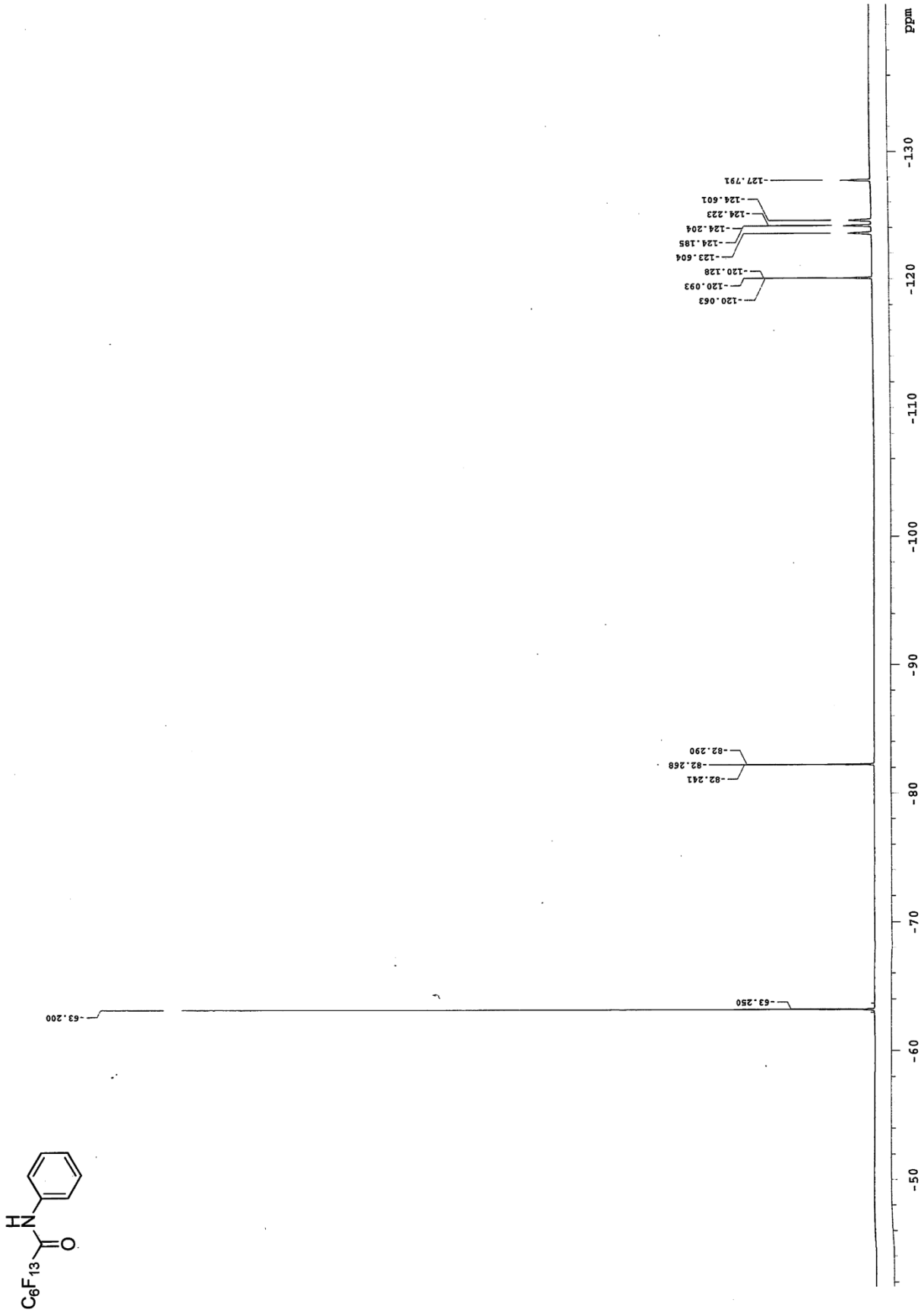
^{1}H NMR spectrum of 2,2,3,3,4,4,5,5,6,6,7,7,7-tridecafluoro-*N*-phenylheptanamide



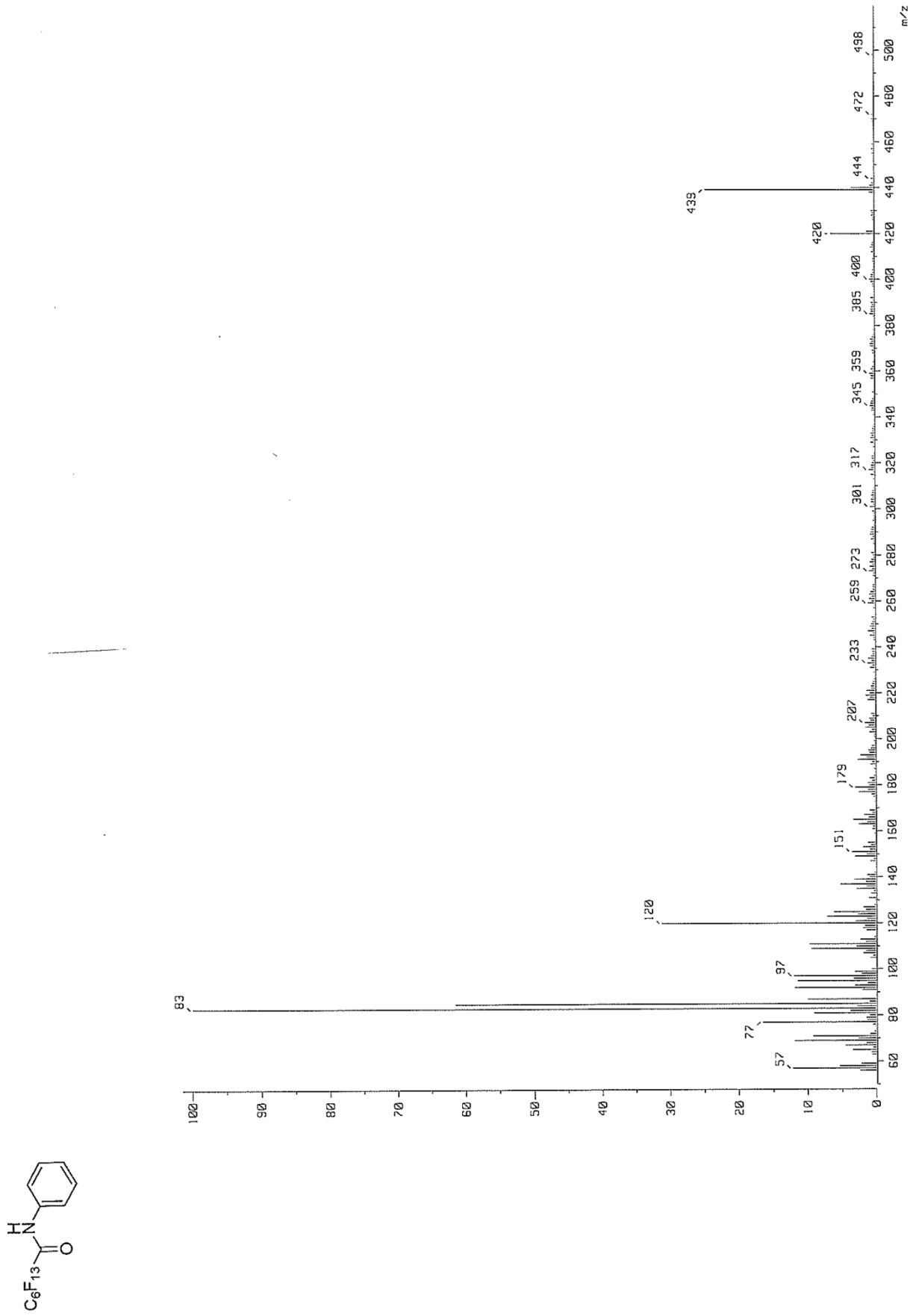
^{13}C NMR spectrum of 2,2,3,3,4,4,5,5,6,6,7,7,7-tridecafluoro-*N*-phenylheptanamide



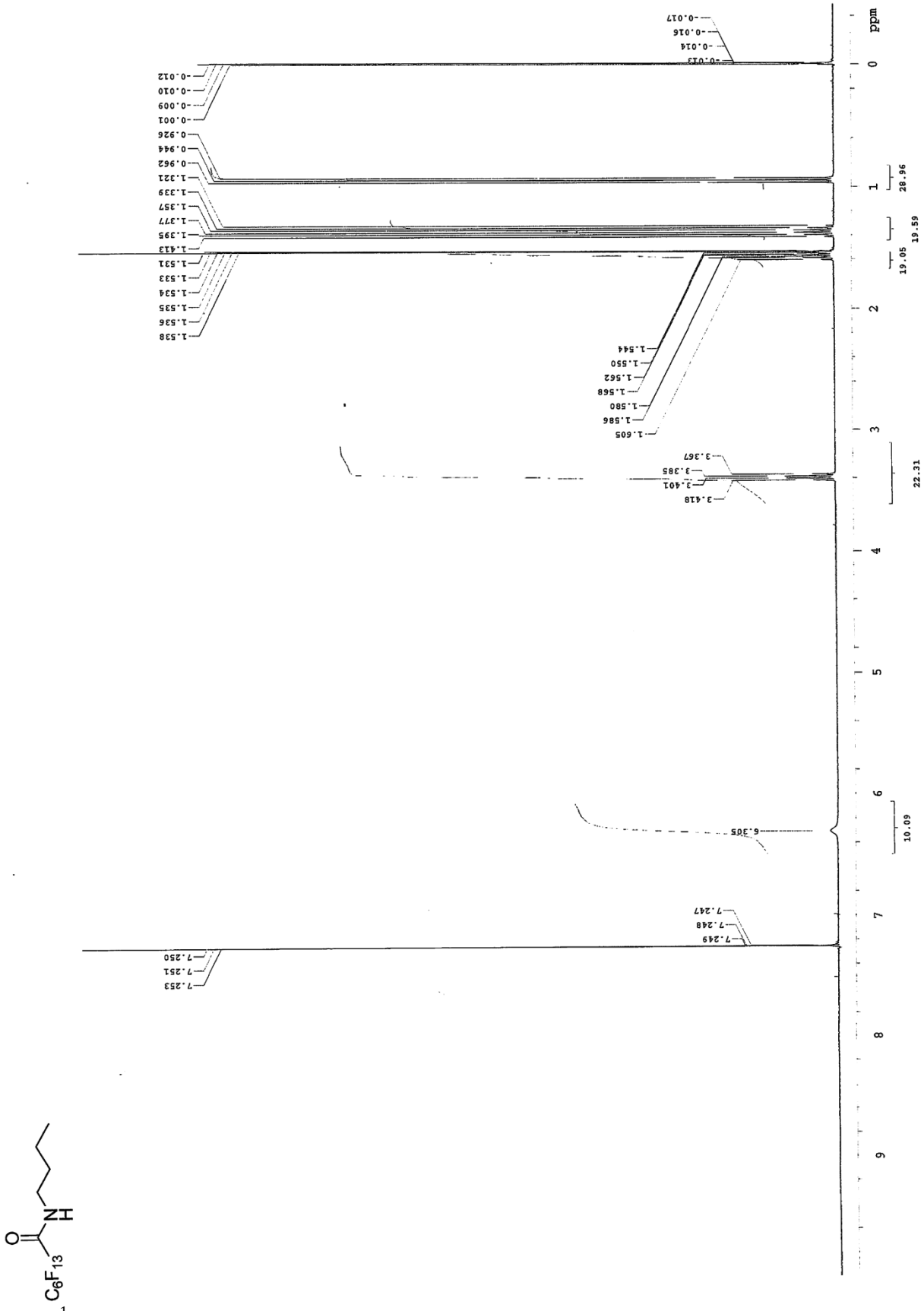
^{13}C NMR spectrum of 2,2,3,3,4,4,5,5,6,6,7,7,7-tridecafluoro-*N*-phenylheptanamide



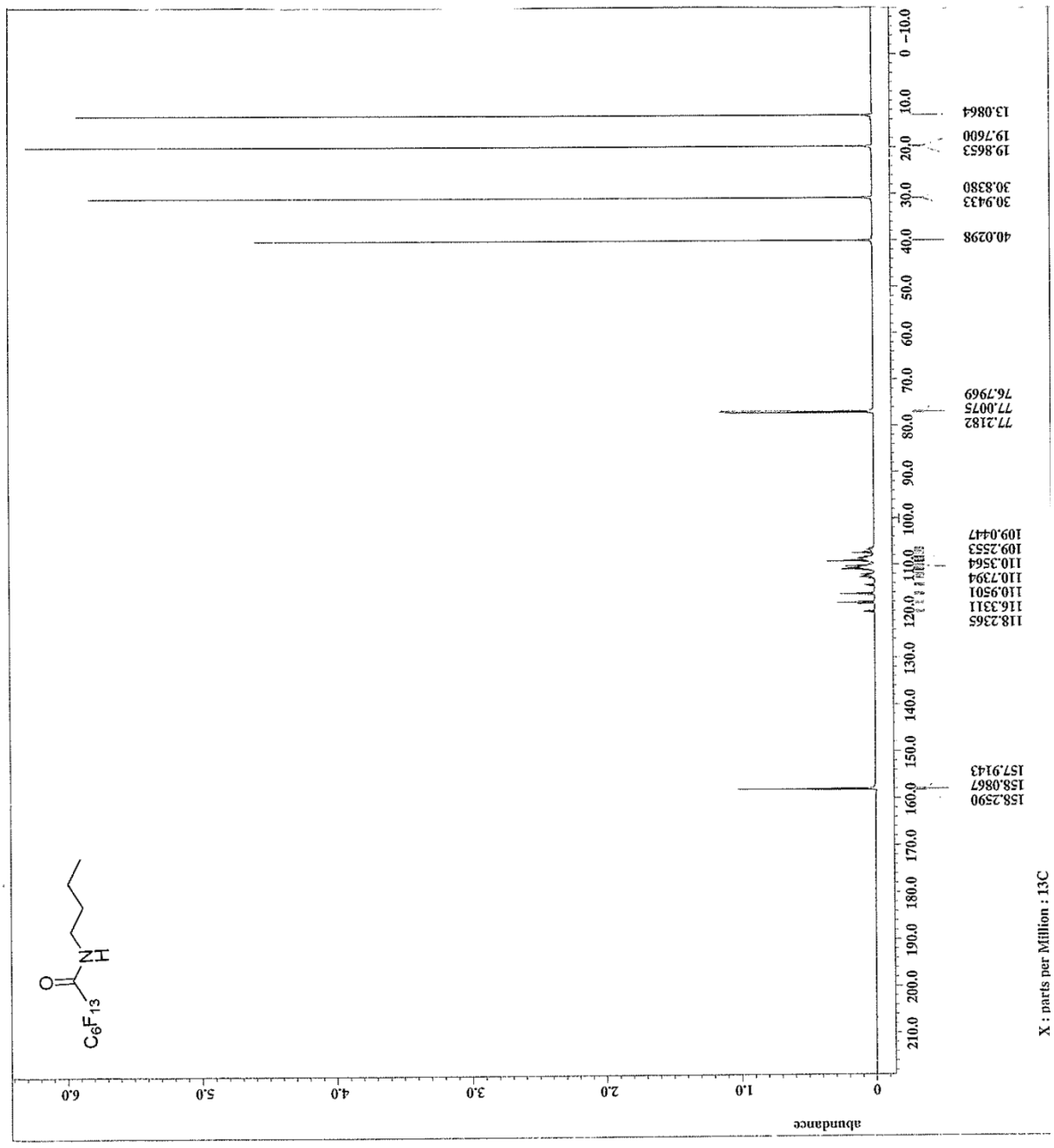
^{19}F NMR spectrum of 2,2,3,3,4,4,5,5,6,6,7,7,7-tridecafluoro-*N*-phenylheptanamide



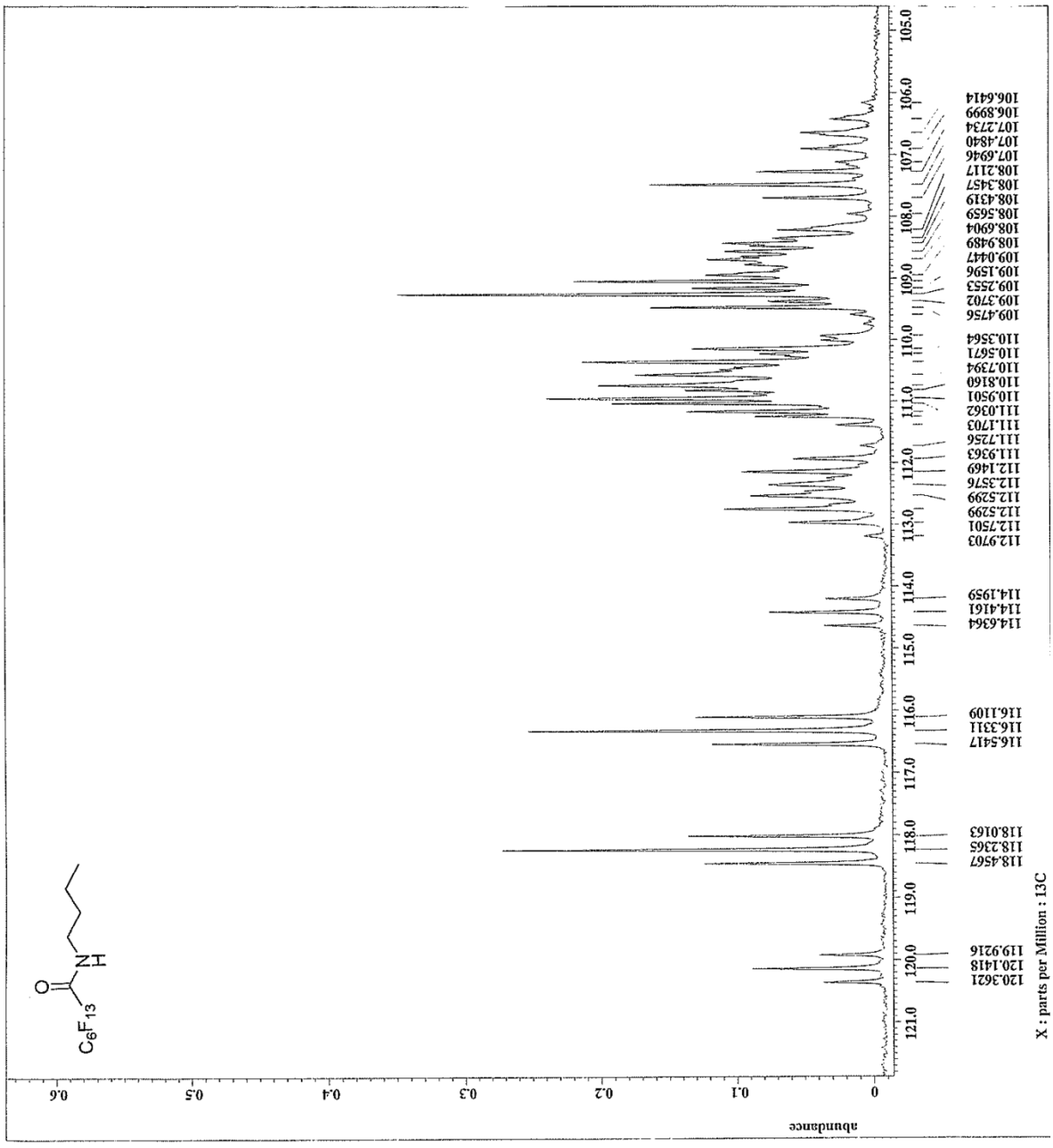
EI mass spectrum of 2,2,3,3,4,4,5,5,6,6,7,7,7-tridecafluoro-*N*-phenylheptanamide



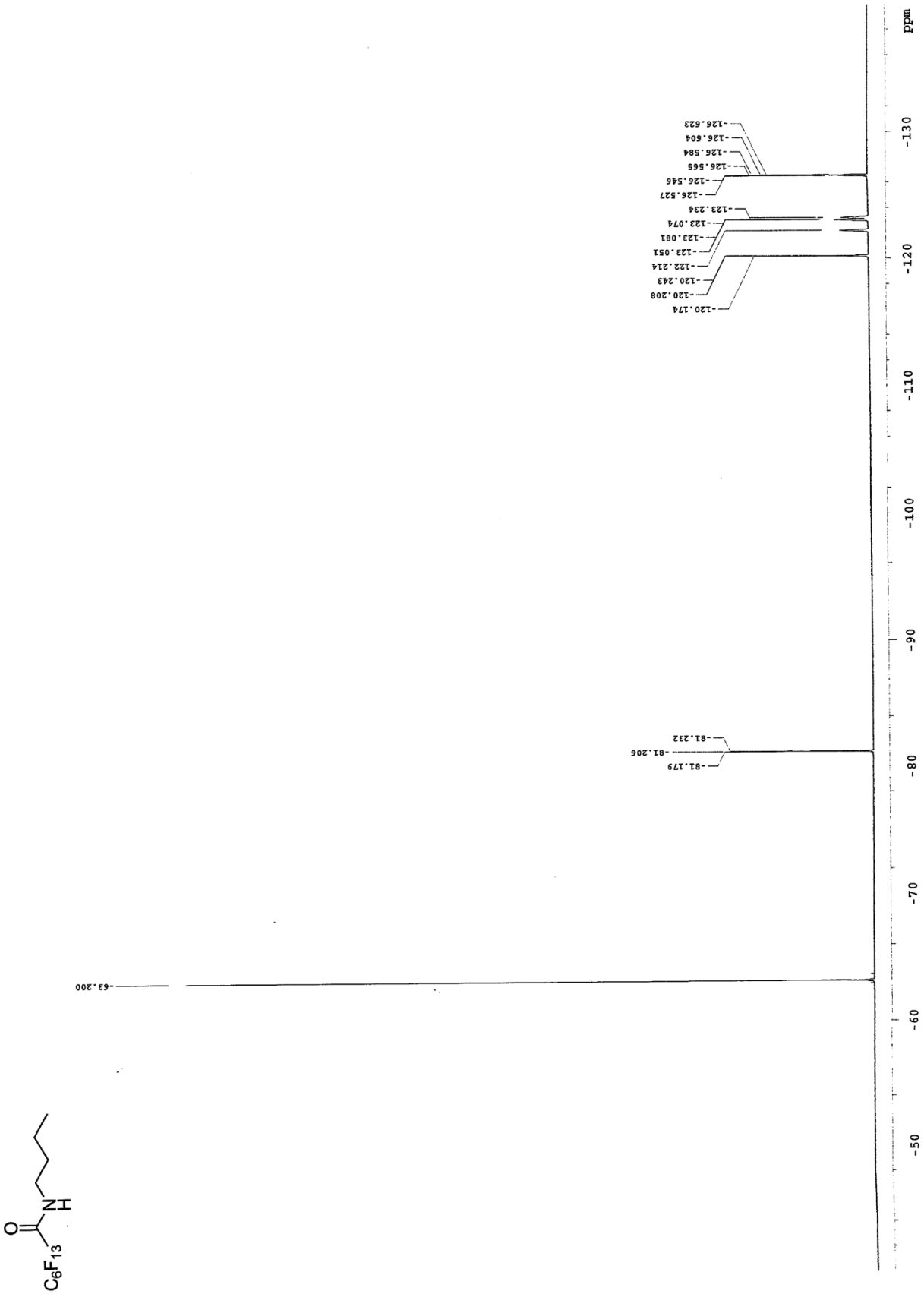
^{1}H NMR spectrum of 2,2,3,3,4,4,5,5,6,6,7,7,7-tridecafluoro-*N*-*n*-butylheptanamide



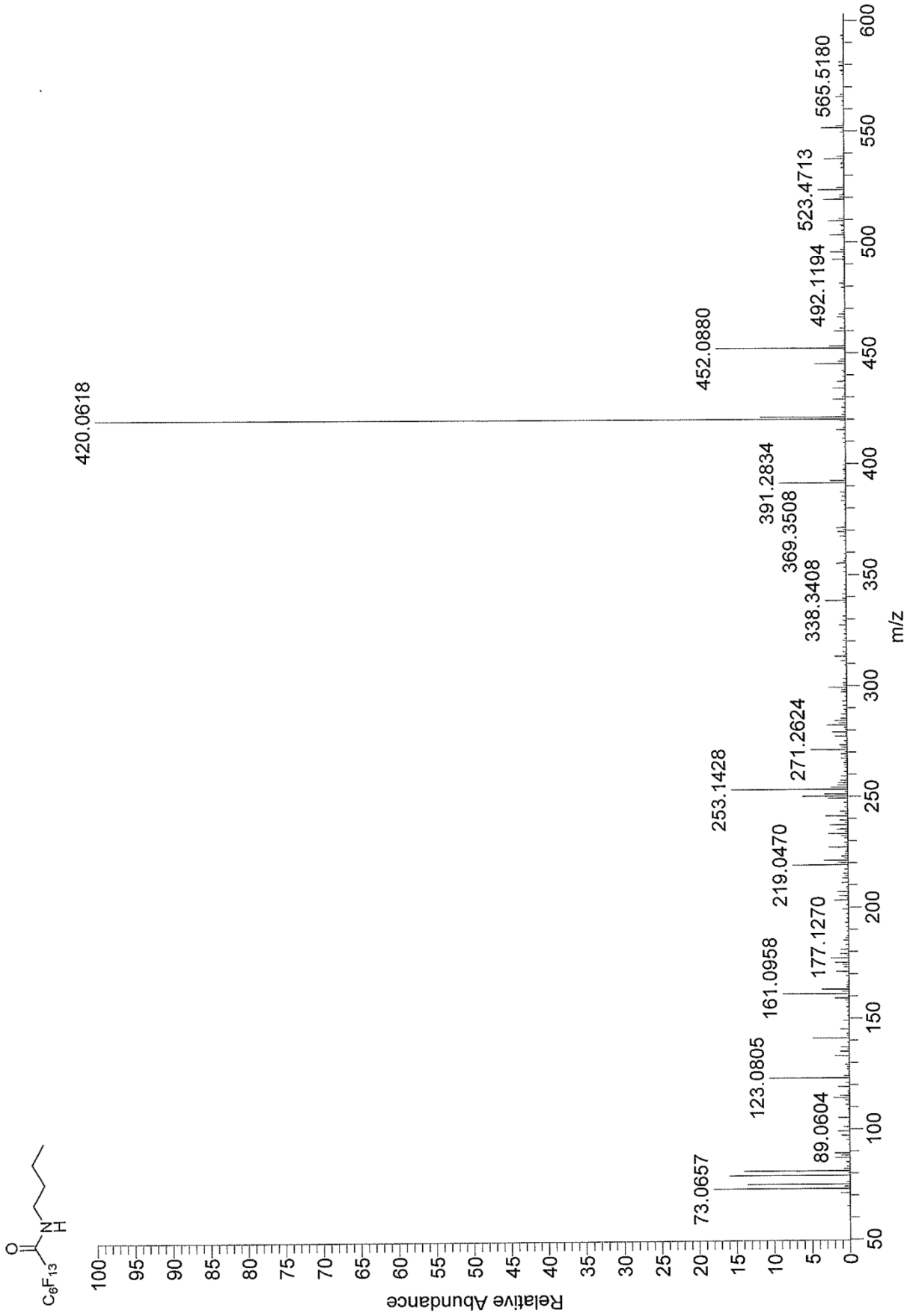
^{13}C NMR spectrum of 2,2,3,3,4,4,5,5,6,6,7,7,7-tridecafluoro-*N*-*n*-butylheptanamide



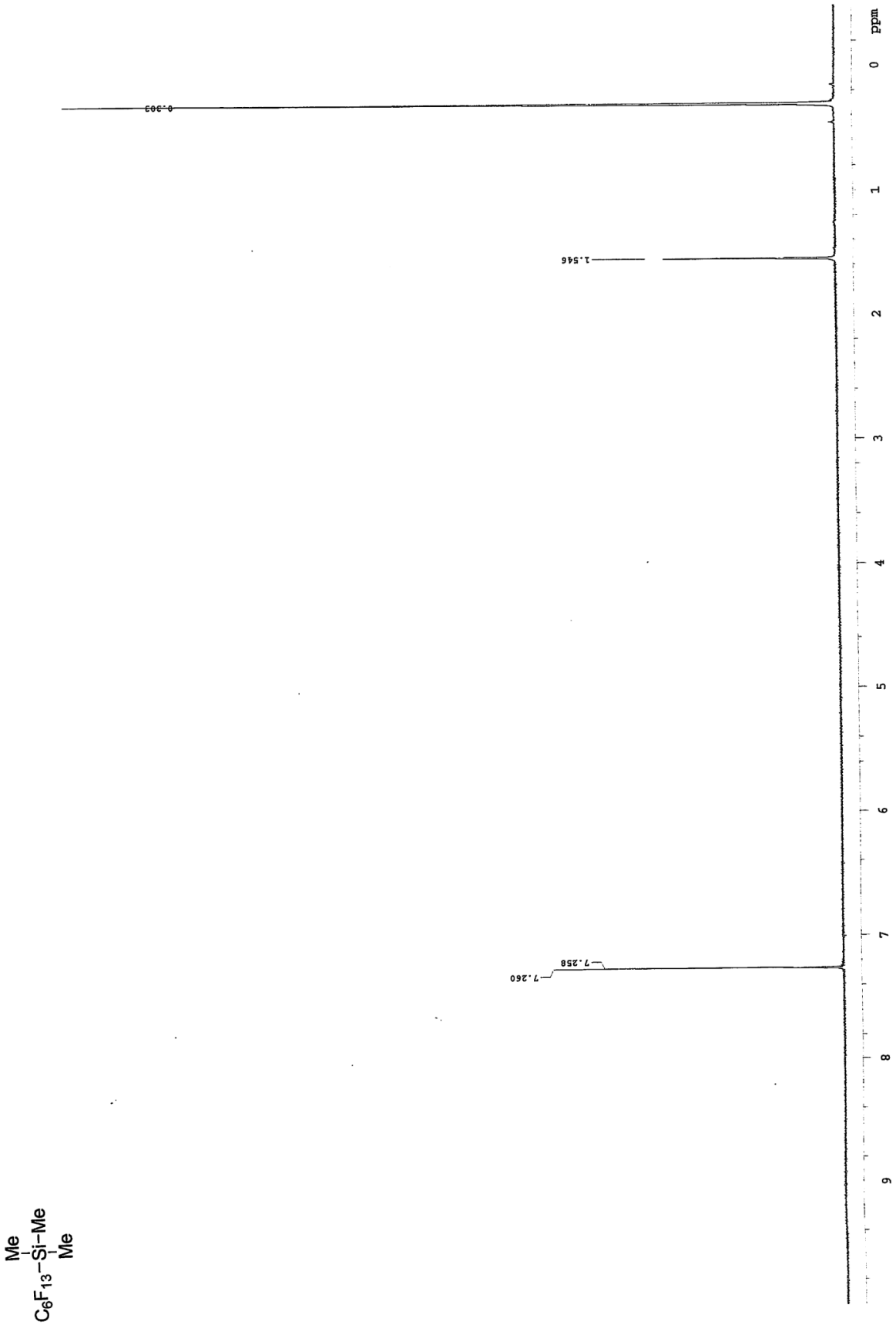
^{13}C NMR spectrum of 2,2,3,3,4,4,5,5,6,6,7,7,7-tridecafluoro-*N*-*n*-butylheptanamide



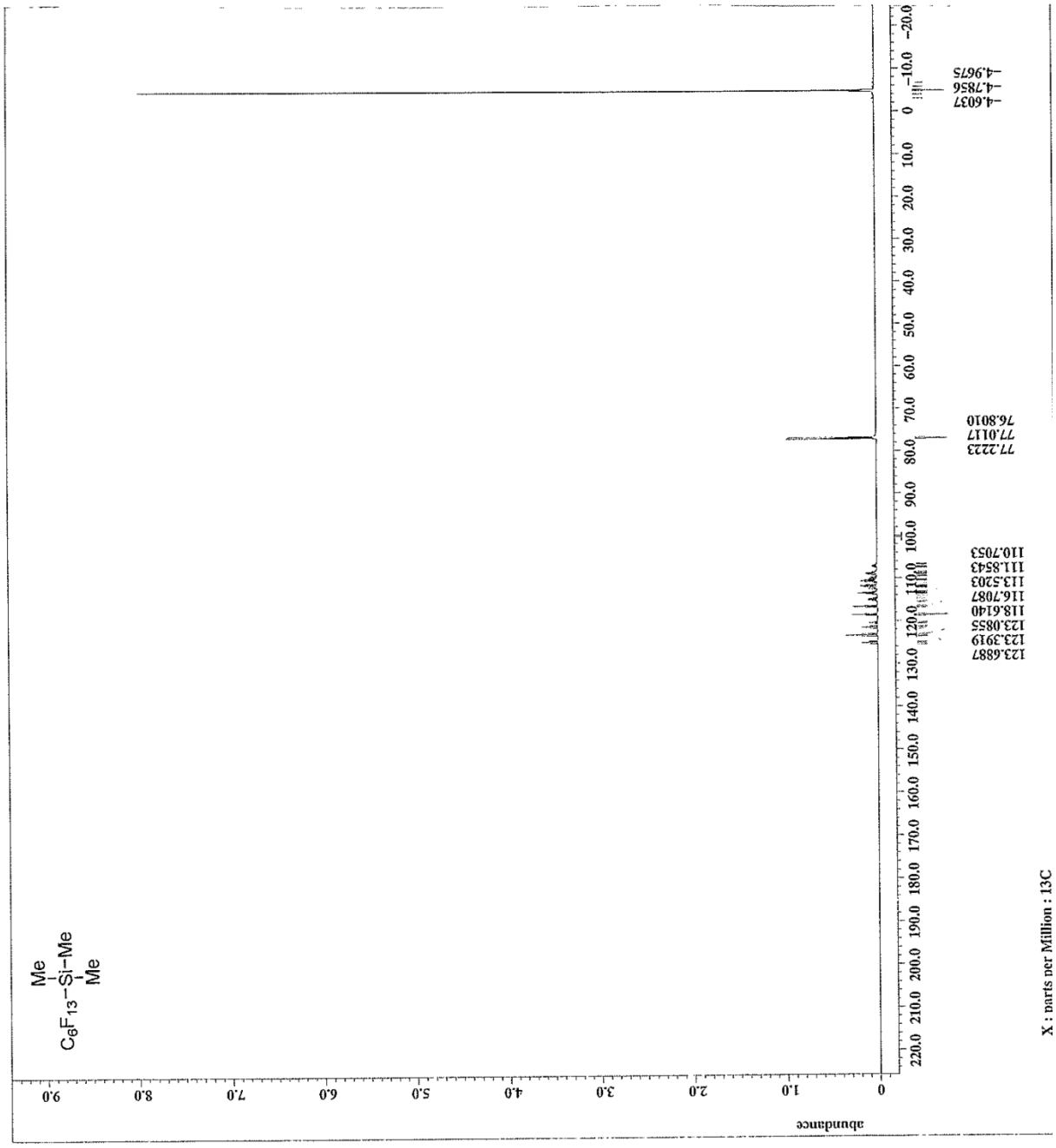
^{19}F NMR spectrum of 2,2,3,3,4,4,5,5,6,6,7,7,7-tridecafluoro-*N*-*n*-butylheptanamide



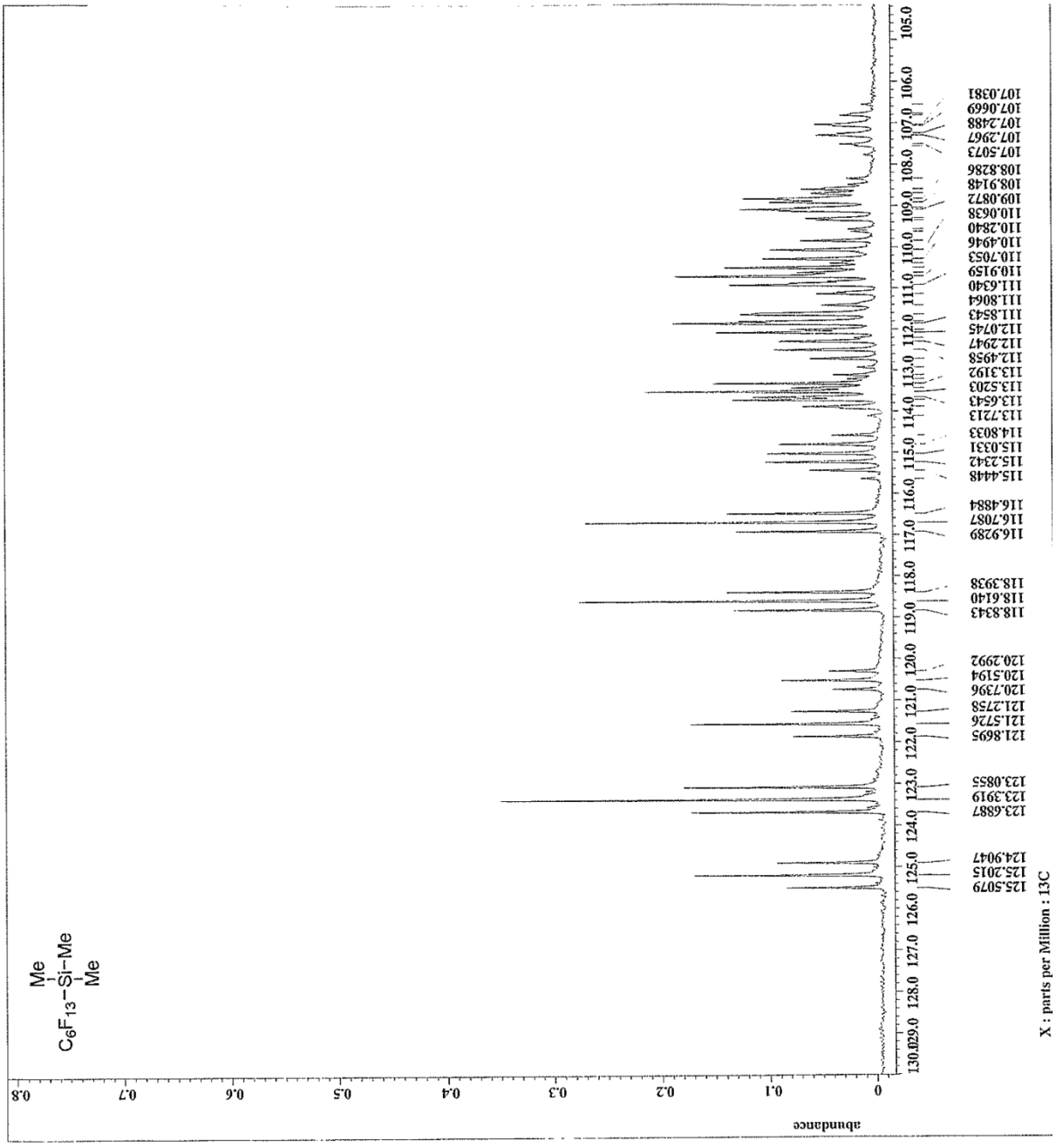
APCI mass spectrum of 2,2,3,3,4,4,5,5,6,6,7,7,7-tridecafluoro-*N*-*n*-butylheptanamide



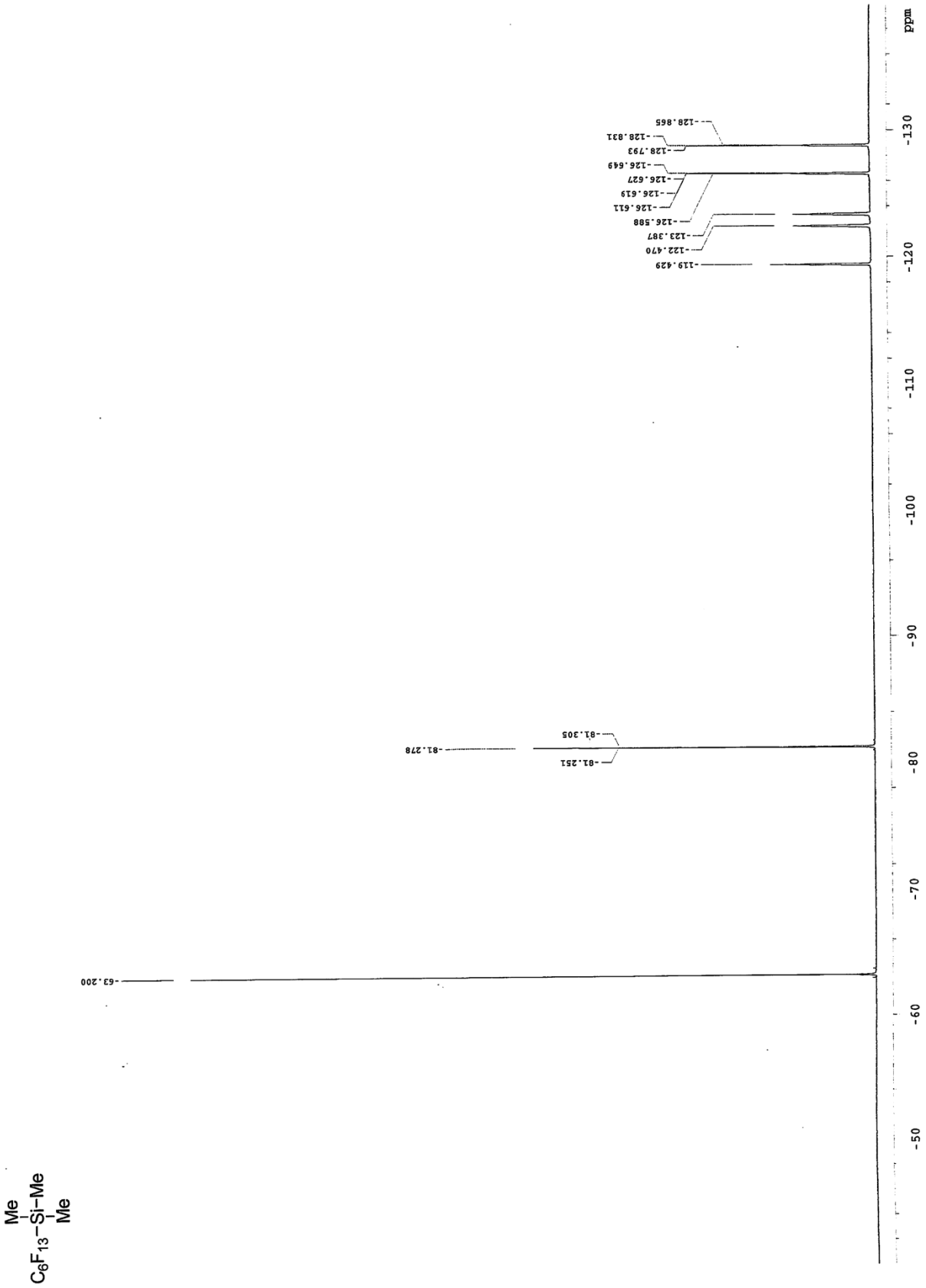
^{1}H NMR spectrum of trimethyl(1,1,2,2,3,3,4,4,5,5,6,6,6-tridecafluorohexyl)silane



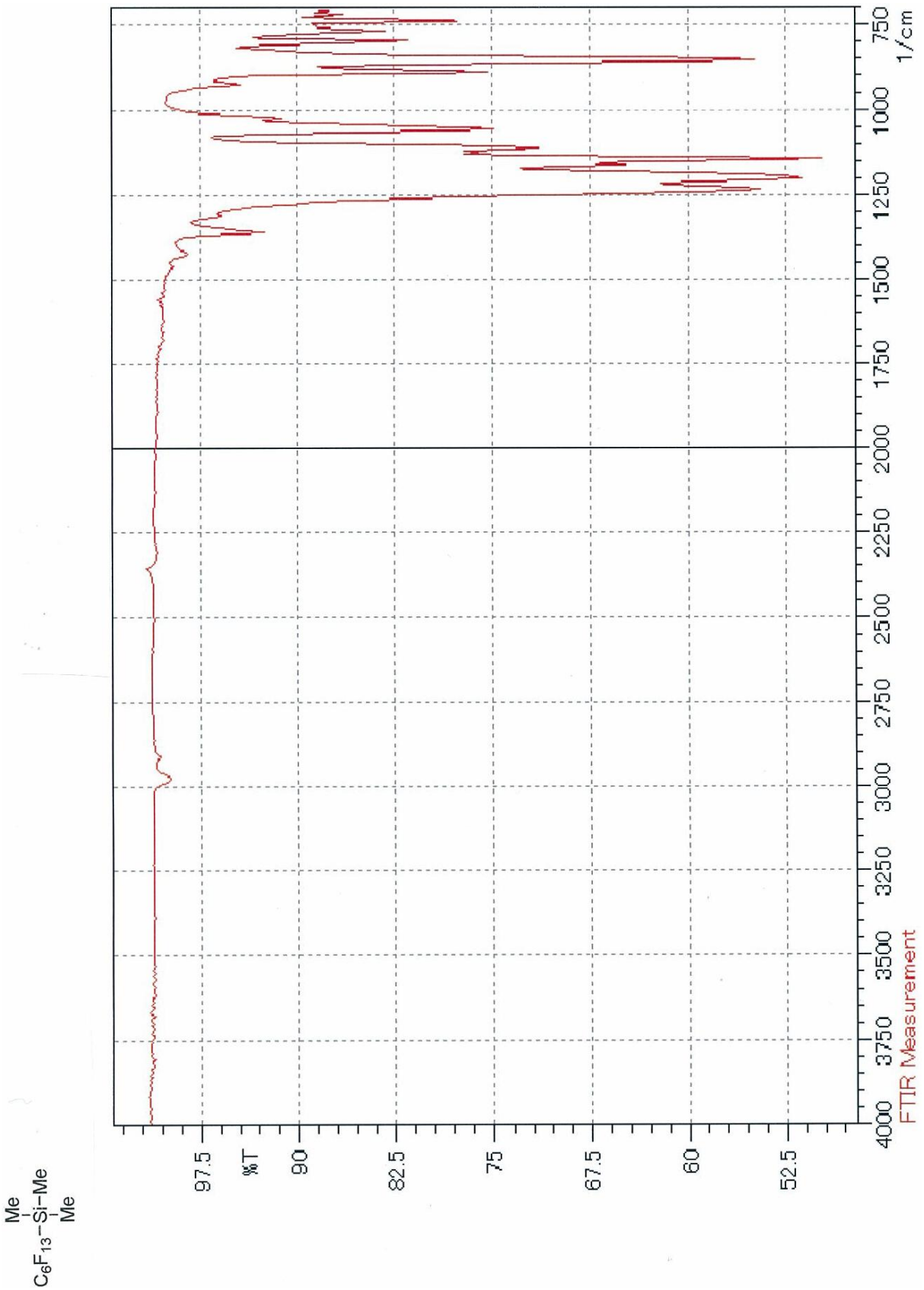
^{13}C NMR spectrum of trimethyl(1,1,2,2,3,3,4,4,5,5,6,6,6-tridecafluorohexyl)silane



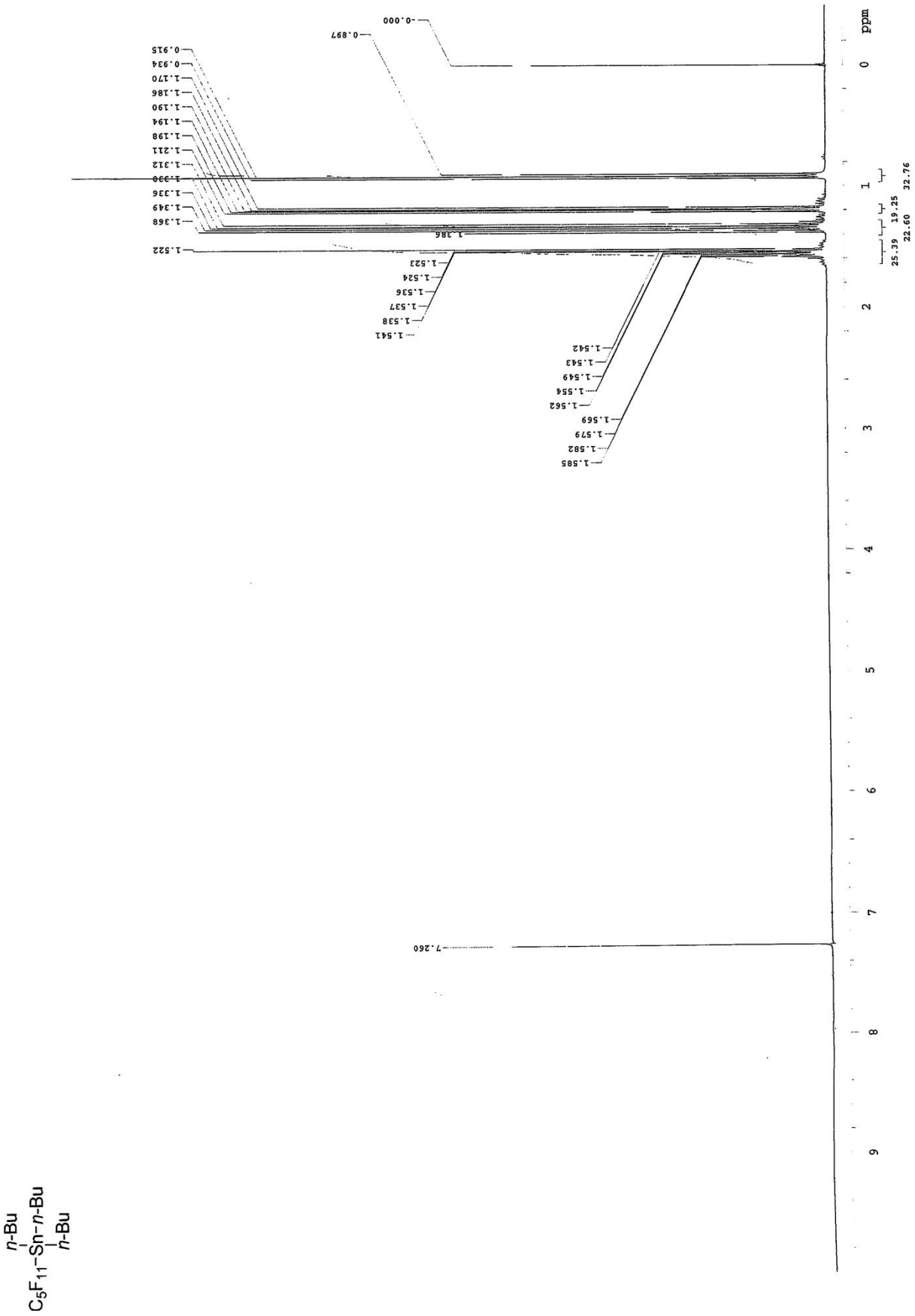
^{13}C NMR spectrum of trimethyl(1,1,2,2,3,3,4,4,5,5,6,6,6-tridecafluorohexyl)silane



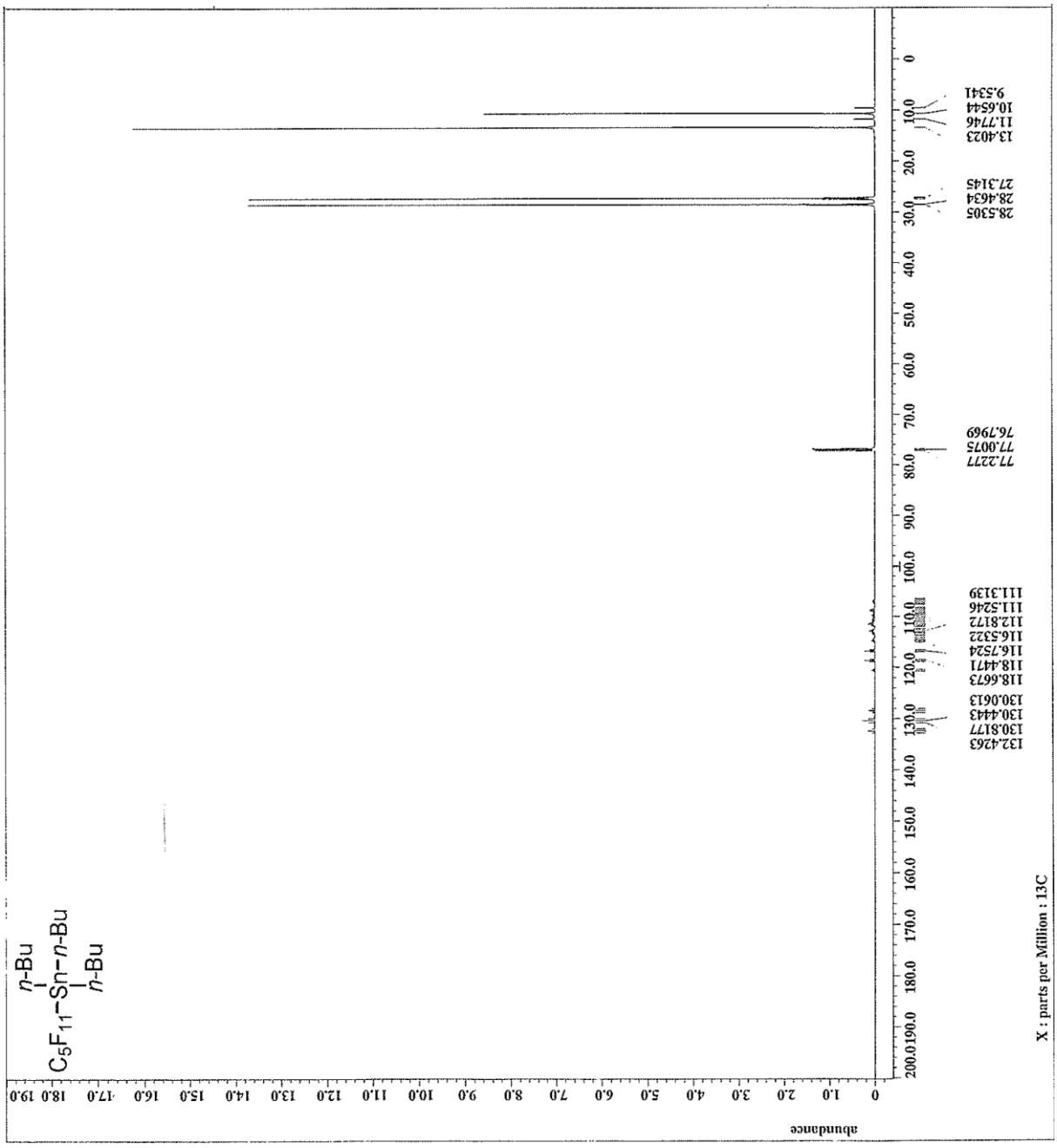
^{19}F NMR spectrum of trimethyl(1,1,2,2,3,3,4,4,5,5,6,6,6-tridecafluorohexyl)silane



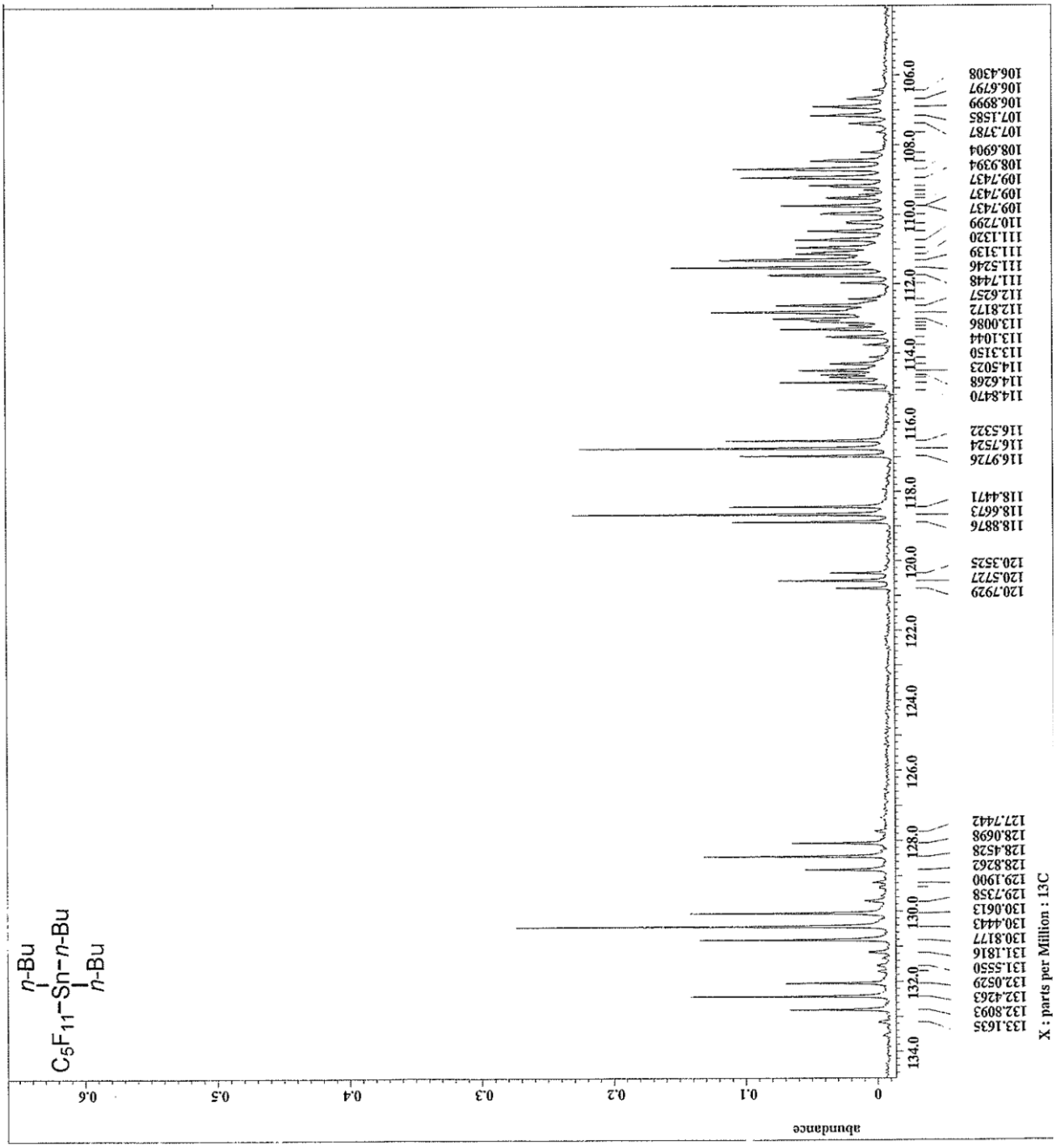
FT-IR spectrum of trimethyl(1,1,2,2,3,3,4,4,5,5,6,6,6-tridecafluorohexyl)silane



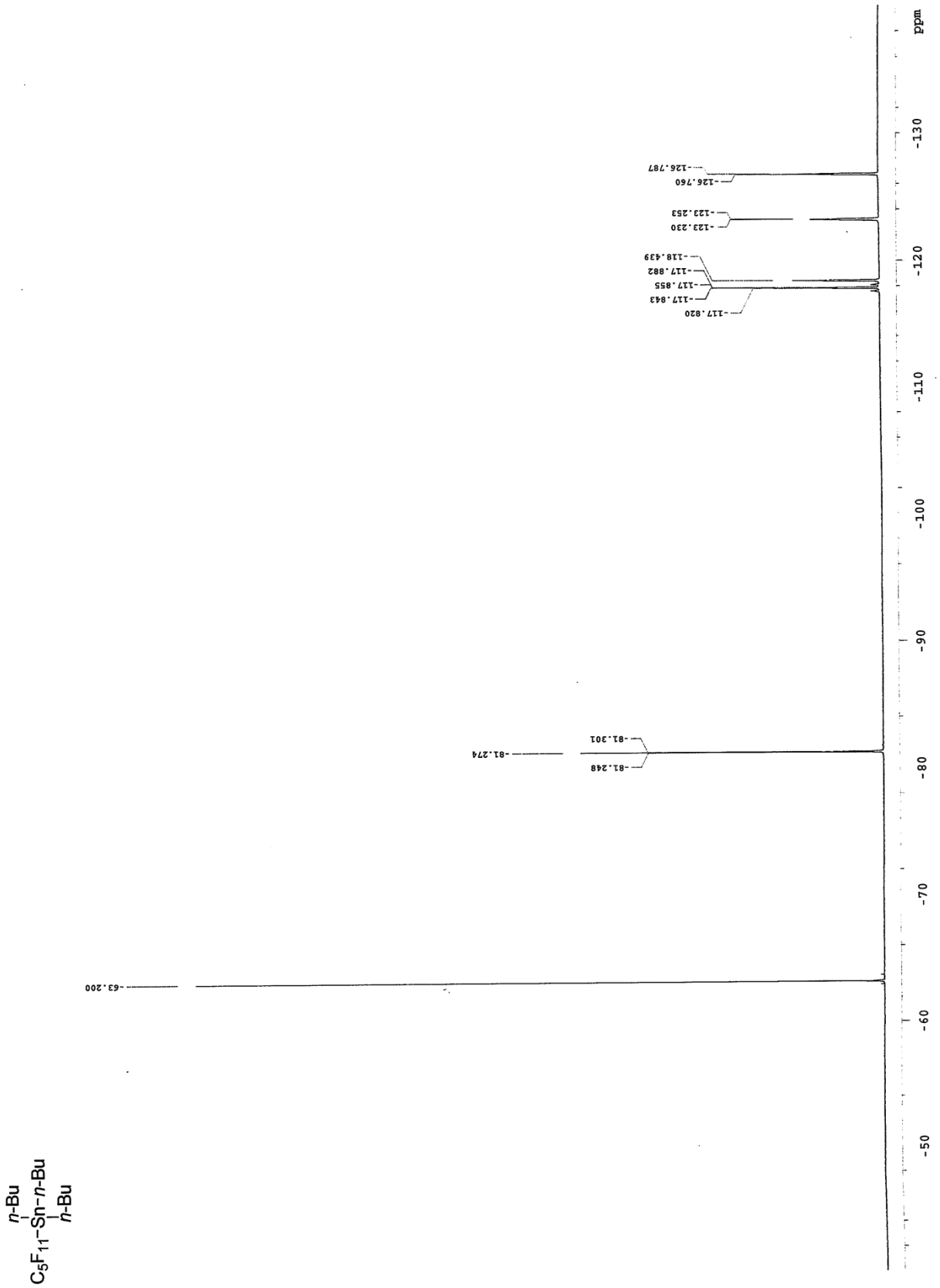
^{1}H NMR spectrum of tri-*n*-butyl(1,1,2,2,3,3,4,4,5,5,5-undecafluoropentyl)stannane



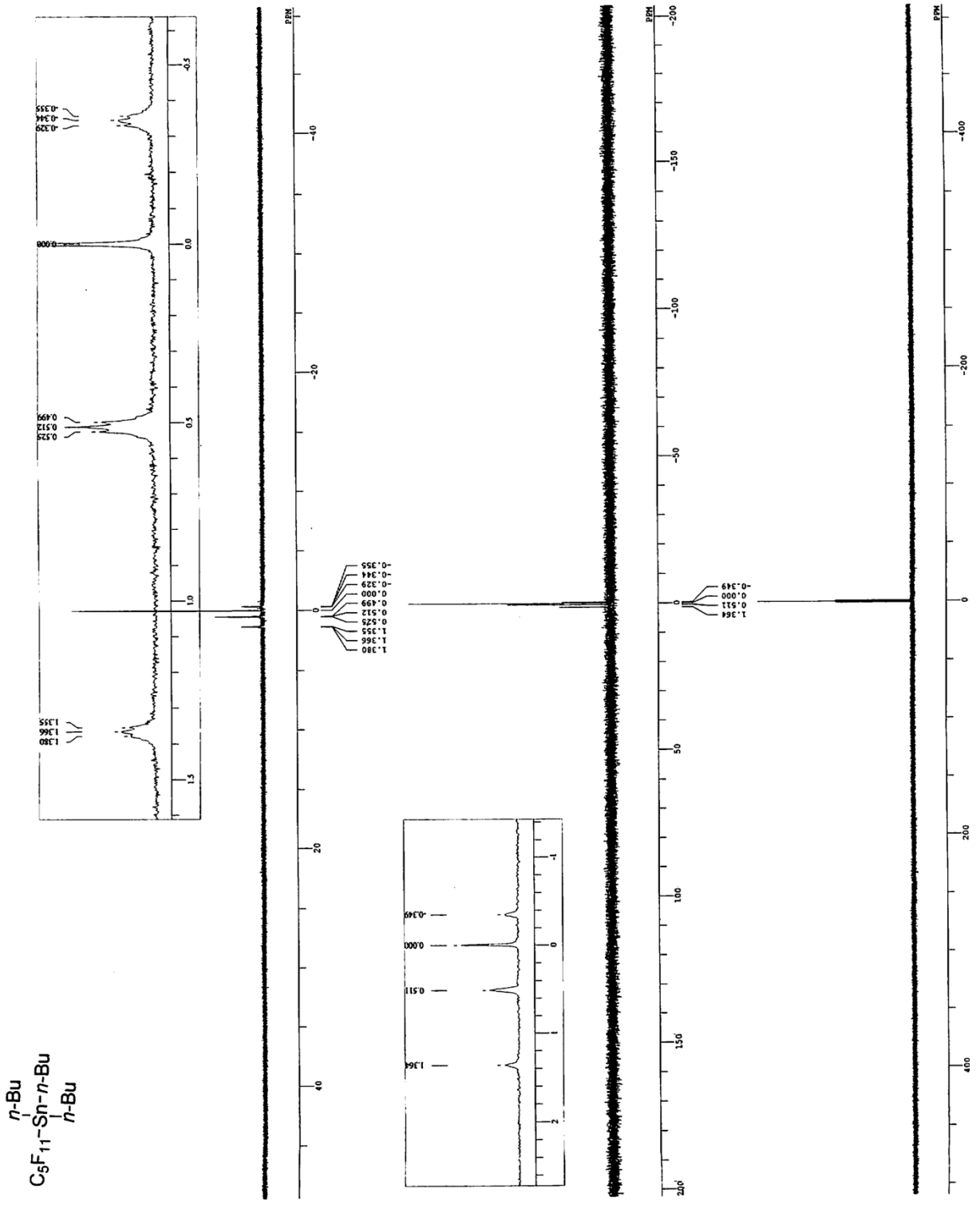
^{13}C NMR spectrum of tri-*n*-butyl(1,1,2,2,3,3,4,4,5,5,5-undecafluoropentyl)stannane



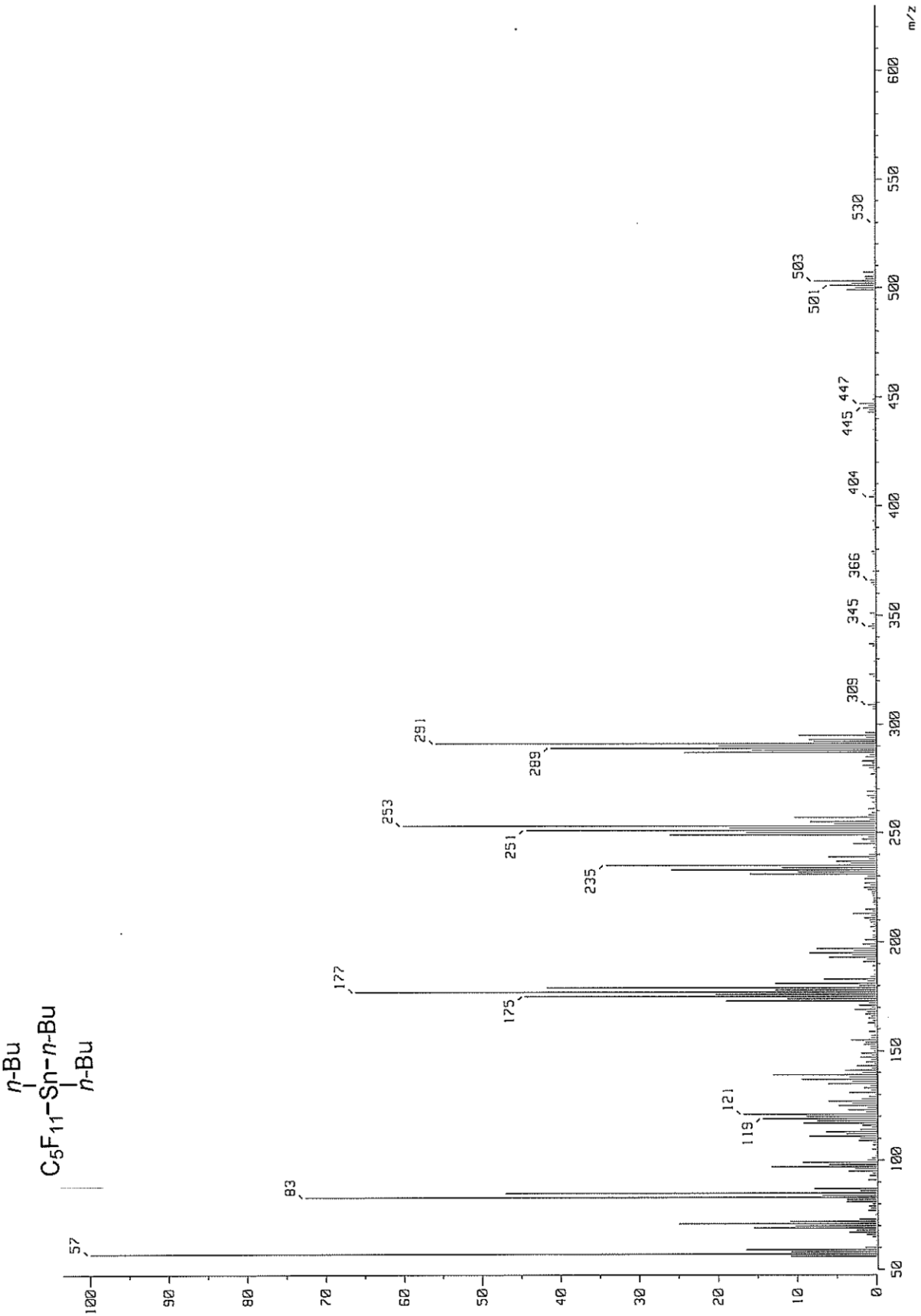
^{13}C NMR spectrum of tri-*n*-butyl(1,1,2,2,3,3,4,4,5,5,5-undecafluoropentyl)stannane



^{19}F NMR spectrum of tri-*n*-butyl(1,1,2,2,3,3,4,4,5,5,5-undecafluoropentyl)stannane



^{119}Sn NMR spectrum of tri-*n*-butyl(1,1,2,2,3,3,4,4,5,5,5-undecafluoropentyl)stannane



EI mass spectrum of tri-*n*-butyl(1,1,2,2,3,3,4,4,5,5,5-undecafluoropentyl)stannane