Supporting Information

Rapid access to 3-indolyl-1-trifluoromethyl-isobenzofurans by hybrid use of Lewis/Brønsted acid catalysts

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Supporting Information

General experimental procedures

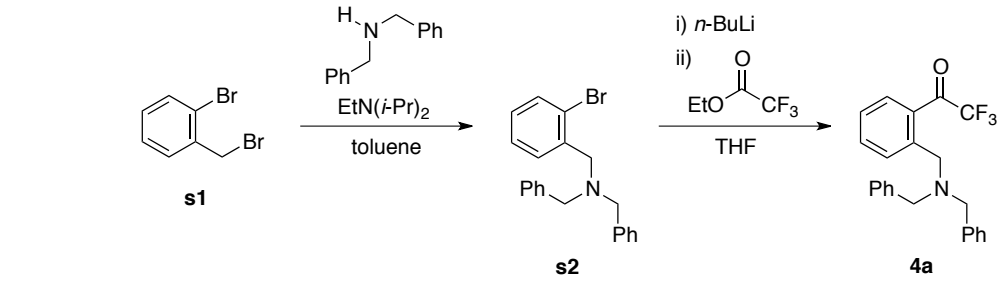
All reactions utilizing air- and moisture-sensitive reagents were performed in dried glassware under an atmosphere of dry nitrogen. Anhydrous ethereal solvents (THF, Et_2O) were purchased from Kanto Chemical Co., INC., and used directly. Dichloromethane and 1,2-dichloroethane were distilled over CaH_2. Aromatic solvents such as benzene, toluene, xylenes, and mesitylene were distilled over CaH_2, and stored over 4A molecular sieves.

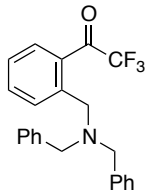
For thin-layer chromatography (TLC) analysis, Merck pre-coated plates (silica gel 60 F_{254}, Art 5715, 0.25 mm) were used. Column chromatography and preparative TLC (PTLC) were performed on Silica Gel 60N (spherical, neutral), Kanto Chemical Ltd. and Wakogel B-5F, Wako Pure Chemical Industries, respectively.

Melting point (mp) determinations were performed by using a AS ONE ATM-01 instrument and are uncorrected. ^{1}H NMR, ^{13}C NMR, ^{19}F NMR were measured on a AL-300 MR (JEOL Ltd., 300 MHz), and ECA-500 (JEOL Ltd., 500 MHz) spectrometers. Chemical shifts are expressed in parts per million (ppm) downfield from internal standard (tetramethylsilane for ^{1}H, 0.00 ppm, C_6F_6 for ^{19}F, 0.00 ppm), and coupling constants are reported as hertz (Hz). Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; sep, septet; m, multiplet. Infrared (IR) spectra were recorded on a FTIR-8600PC instrument (Shimadzu Co.). Elemental analysis (EA) was carried out on Flash2000 instrument (Amco Inc.).

1. Preparation of starting materials.

Scheme 1. Preparation of starting materials **4**. Preparation of **4a** was shown as a representative example.





Synthesis of 1-(2-((dibenzylamino)methyl)phenyl)-2,2,2-trifluoroethanone (4a):

To a solution of commercially available **s1** (1.98 g, 7.94 mmol) in toluene (7.90 mL) were successively added *i*-Pr_2NEt (2.77 mL, 15.9 mmol), and Bn_2NH (2.29 mL, 11.9 mmol). After the mixture was heated to reflux for 1 h, the reaction was quenched by addition of H_2O. The crude mixture was extracted with EtOAc (x3) and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 100/1) to give **s2** (2.77 g) as colorless oil. At this moment, **s2** could not be isolated as a pure compound, so this crude material was used for next reaction without further purification.

To a solution of **s2** in THF (37.8 mL) was added *n*-BuLi (1.57 M in hexane, 5.78 mL, 9.07 mmol) at –78 °C. The reaction mixture was stirred for 10 min at –78 °C, to which ethyl trifluoroacetate (1.35 mL, 11.3 mmol) was added. After being stirred for 2.5 h at –78 °C, the reaction was quenched by addition of saturated aqueous $NaHCO_3$ at –78 °C. The crude mixture was extracted with EtOAc (x3) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 50/1) to afford CF_3-ketone **s3** (2.41 g, 79% from **s1**) as yellow amorphous. Interestingly, not only target CF_3-ketone, but also intramolecular cyclization adduct were observed in the NMR spectrum.

CF_3-Ketone : intramolecular cyclization adduct = 5.5:1 (* indicates the peaks of intramolecular cyclization adduct).

IR (neat) 3365, 3063, 3030, 2927, 2802, 1715, 1602, 1573, 1516, 1496, 1454, 1365, 1320, 1285, 1183, 1146, 1048, 1030, 937 cm^{-1}.

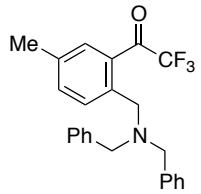
^1H NMR (300 MHz, $CDCl_3$) δ 3.56 (s, 4H), 3.82 (s, 2H), 7.18–7.40 (m, 11H), 7.57 (ddd, 1H, J = 1.2, 7.5, 7.5 Hz), 7.72 (d, 1H, J = 7.5 Hz), 7.85 (d, 1H, J = 7.5 Hz). Only the peaks of CF_3-ketone were described.

^{13}C NMR (75 MHz, $CDCl_3$) δ 55.5, 57.8, 116.4 (q, J_{C-F} = 290.4 Hz), 126.8, 127.0, 128.2, 129.0, 129.9, 130.3, 130.8, 133.3, 138.2, 143.0, 183.6 (q, J_{C-F} = 34.6 Hz).

Only the peaks of CF_3-ketone were described.

^{19}F NMR (283 MHz, $CDCl_3$) δ 77.8* (s), 89.5 (s).

Anal. Calcd for $C_{23}H_{20}F_3NO$: C, 72.05; H, 5.26; N, 3.65. Found: C, 72.29; H, 5.40; N, 3.86.



1-(2-((Dibenzylamino)methyl)-5-methylphenyl)-2,2,2-trifluoroethanone (**4g**).

Colorless oil.

Yield: 65% (synthesized from 2-bromo-1-(bromomethyl)-4-methylbenzene[1]).

CF_3-Ketone : intramolecular cyclization adduct = 5.2:1 (* indicates the peaks of intramolecular cyclization adduct).

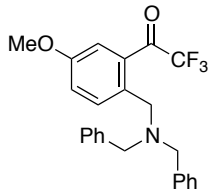
IR (neat) 3365, 3087, 3063, 3030, 2925, 2838, 1715, 1604, 1571, 1496, 1455, 1366, 1327, 1284, 1233, 1200, 1159, 1052, 1030, 992, 969, 910 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ 2.33 (s, 3H), 3.53 (s, 4H), 3.76 (s, 2H), 7.15–7.37 (m, 11H), 7.48 (s, 1H), 7.67 (d, 1H, J = 8.1 Hz). Only the peaks of CF_3-ketone were described.

^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8, 55.3, 57.6, 116.4 (q, J_{C-F} = 290.3 Hz), 127.0, 128.2, 129.0, 129.9, 130.3, 131.0, 133.9, 136.7, 138.2, 140.0, 183.8 (q, J_{C-F} = 33.9 Hz). Only the peaks of CF_3-ketone were described.

^{19}F NMR (283 MHz, $CDCl_3$) δ 77.9* (s), 89.6 (s).

Anal. Calcd for $C_{24}H_{22}F_3NO$: C, 72.53; H, 5.58; N, 3.52. Found: C, 72.64; H, 5.88; N, 3.46.



1-(2-((Dibenzylamino)methyl)-5-methoxyphenyl)-2,2,2-trifluoroethanone (**4h**).

Colorless amorphous.

Yield: 55% (synthesized from 2-bromo-1-(bromomethyl)- 4-methoxybenzene[2]).

CF_3-Ketone : intramolecular cyclization adduct = 1.5:1 (* indicates the peaks of intramolecular cyclization adduct).

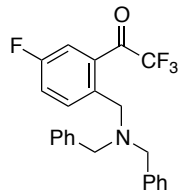
IR (neat) 3348, 3087, 3063, 3030, 2936, 2839, 1730, 1611, 1575, 1496, 1455, 1423, 1366, 1282, 1249, 1167, 1044, 996, 959, 910 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ 3.53 (s, 4H), 3.74 (s, 2H), 3.83 (s, 3H), 7.70 (dd, 1H, J = 2.4, 8.4 Hz), 7.15–7.40 (m, 11H), 7.70 (d, 1H, J = 8.4 Hz). Only the peaks of CF_3-ketone were described.

^{13}C NMR (75 MHz, $CDCl_3$) δ 54.9, 55.2, 55.4, 56.3, 57.5, 94.6 (q, J_{C-F} = 32.1 Hz), 114.3, 114.4 (q, J_{C-F} = 10.6 Hz), 116.2, 116.3 (q, J_{C-F} = 290.3 Hz), 118.3, 118.4, 126.8, 127.0, 127.7, 128.2, 128.4, 129.0, 129.9, 131.6, 131.9, 134.0, 134.2, 135.4, 138.2, 138.7, 158.0, 159.3, 183.5 (q, J_{C-F} = 34.5 Hz).

^{19}F NMR (283 MHz, $CDCl_3$) δ 77.9* (s), 89.3 (s).

Anal. Calcd for $C_{24}H_{22}F_3NO_2$: C, 69.72; H, 5.36; N, 3.39. Found: C, 69.47; H, 5.55; N, 3.16.



1-(2-((Dibenzylamino)methyl)-5-fluorophenyl)-2,2,2-trifluoroethanone (**4i**).

Colorless amorphous.

Yield: 70% (synthesized from 2-bromo-1-(bromomethyl)-4-fluorobenzene[3]).

CF_3-Ketone : intramolecular cyclization adduct = 1.2:1 (* indicates the peaks of

intramolecular cyclization adduct).

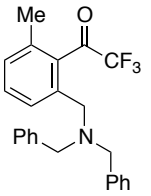
IR (neat) 3357, 3065, 3032, 2927, 2852, 1717, 1614, 1588, 1494, 1455, 1418, 1366, 1282, 1245, 1172, 1154, 1109, 1049, 984 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ 3.54 (s, 4H), 3.75 (s, 2H), 7.00 (ddd, 1H, J = 2.7, 8.1, 8.1 Hz), 7.12–7.42 (m, 10H), 7.53 (dd, 1H, J = 2.7, 10.8 Hz), 7.75 (dd, 1H, J = 5.4, 8.1 Hz). Only the peaks of CF_3-ketone were described.

^{13}C NMR (75 MHz, $CDCl_3$) δ 54.9, 56.6, 57.7, 58.5, 115.9 (d, J_{C-F} = 20.3 Hz), 116.0 (d, J_{C-F} = 20.9 Hz), 116.2 (q, J_{C-F} = 289.7 Hz), 117.7, 118.0, 120.2 (d, J_{C-F} = 21.0 Hz), 127.1, 127.9, 128.3, 128.5, 129.0, 129.9, 130.7 (d, J_{C-F} = 3.7 Hz), 132.1 (d, J_{C-F} = 6.2 Hz), 132.2 (d, J_{C-F} = 7.4 Hz), 134.4 (d, J_{C-F} = 7.4 Hz), 135.1, 137.9, 138.5 (d, J_{C-F} = 3.7 Hz), 160.8 (d, J_{C-F} = 246,7 Hz), 162.3 (d, J_{C-F} = 246.0 Hz), 182.5 (q, J_{C-F} = 34.5 Hz).

^{19}F NMR (283 MHz, $CDCl_3$) δ 47.8–48.0 (m, 1F), 48.9–49.1*(m, 1F), 77.7* (s, 3F), 89.1 (s, 3F).

Anal. Calcd for $C_{23}H_{19}F_4NO$: C, 68.82; H, 4.77; N, 3.49. Found: C, 68.63; H, 4.98; N, 3.21.



1-(2-((Dibenzylamino)methyl)-6-methylphenyl)-2,2,2-trifluoroethanone (**4j**).

Colorless amorphous.

Yield: 57% (synthesized from 1-(bromomethyl)-2-iodo-3-methylbenzene[4]).

CF_3-Ketone : intramolecular cyclization adduct = >20:1.

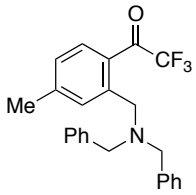
IR (neat) 3063, 3029, 2935, 2843, 2801, 1717, 1596, 1496, 1455, 1363, 1307, 1203, 1181, 1130, 1066, 1030, 932 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 2.89 (s, 3H), 3.57 (s, 4H), 3.62 (s, 2H), 7.15–7.22 (m, 5H), 7.23–7.28 (m, 3H), 7.28–7.38 (m, 5H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 19.2, 55.9, 56.4, 116.5 (q, J_{C-F} = 290.9 Hz), 126.2, 127.1, 128.2, 129.5, 129.8, 130.7, 133.1, 136.5, 136.5, 138.7, 187.5 (q, J_{C-F} = 35.8 Hz).

^{19}F NMR (283 MHz, $CDCl_3$) δ 85.1 (s, 3F).

Anal. Calcd for $C_{24}H_{22}F_3NO$: C, 72.53; H, 5.58; N, 3.52. Found: C, 72.42; H, 5.76; N, 3.35.



1-(2-((Dibenzylamino)methyl)-4-methylphenyl)-2,2,2-trifluoroethanone (**4k**).

Colorless amorphous.

Yield: 63% (synthesized from 1-bromo-2-(bromomethyl)-4-methylbenzene[5]).

CF_3-Ketone : intramolecular cyclization adduct = 4.0:1 (* indicates the peaks of intramolecular cyclization adduct).

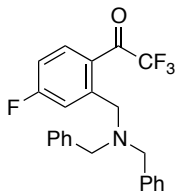
IR (neat) 3379, 3062, 3030, 2925, 2802, 1712, 1609, 1566, 1496, 1454, 1366, 1324, 1285, 1190, 1145, 1070, 1049, 1030, 956, 910 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ 2.43 (s, 3H), 3.56 (s, 4H), 3.83 (s, 2H), 7.15 (d, 1H, J = 7.8 Hz), 7.18–7.37 (m, 10H), 7.66 (dd, 1H, J = 1.5, 7.8 Hz), 7.70 (s, 1H). Only the peaks of CF_3-ketone were described.

^{13}C NMR (75 MHz, $CDCl_3$) δ 21.9, 55.7, 58.0, 116.5 (q, J_{C-F} = 291.0 Hz), 127.0, 127.4, 128.2, 128.4, 128.9, 129.9, 131.1, 138.5, 143.7, 144.6, 182.8 (q, J_{C-F} = 33.9 Hz). Only the peaks of CF_3-ketone were described.

^{19}F NMR (283 MHz, $CDCl_3$) δ 77.7* (s), 90.7 (s).

Anal. Calcd for $C_{24}H_{22}F_3NO$: C, 72.53; H, 5.58; N, 3.52. Found: C, 72.81; H, 5.40; N, 3.34.



1-(2-((Dibenzylamino)methyl)-4-fluorophenyl)-2,2,2-trifluoroethanone (**4l**).

Colorless amorphous.

Yield: 52% (synthesized from commercially available, 1-bromo-2-(bromomethyl)-4-fluorobenzene).

CF_3-Ketone : intramolecular cyclization adduct = 13.9:1 (* indicates the peaks of intramolecular cyclization adduct).

IR (neat) 3364, 3087, 3064, 3030, 2927, 2804, 2716, 1714, 1608, 1580, 1496, 1455,

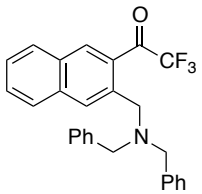
1430, 1367, 1329, 1291, 1201, 1181, 1146, 1076, 1051, 1030, 969, 923 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ 3.59 (s, 4H), 3.85 (s, 2H), 7.15 (d, 1H, J = 7.8 Hz), 6.95–7.07 (m, 1H), 7.18–7.40 (m, 10H), 7.70–7.86 (m, 2H). Only the peaks of CF_3-ketone were described.

^{13}C NMR (75 MHz, $CDCl_3$) δ 55.4, 58.3, 113.8 (d, J_{C-F} = 22.2 Hz), 116.3 (q, J_{C-F} = 290.4 Hz), 117.3 (d, J_{C-F} = 23.4 Hz), 126.1 (d, J_{C-F} = 3.1 Hz), 127.2, 128.4, 128.8, 182.8 (qd, J_{C-F} = 3.8, 9.8 Hz), 138.3, 148.8 (d, J_{C-F} = 8.6 Hz), 165.9 (d, J_{C-F} = 255.3 Hz), 181.5 (q, J_{C-F} = 33.9 Hz). Only the peaks of CF_3-ketone were described.

^{19}F NMR (283 MHz, $CDCl_3$) δ 49.1* (dd, 1F, J = 6.8, 15.8 Hz), 49.7 (dd, 1F, J = 9.1, 13.6 Hz), 77.6* (s, 3F), 90.2 (s, 3F).

Anal. Calcd for $C_{23}H_{19}F_4NO$: C, 68.82; H, 4.77; N, 3.49. Found: C, 69.05; H, 4.64; N, 3.66.



1-(3-((Dibenzylamino)methyl)naphthalen-2-yl)-2,2,2-trifluoroethanone (**4m**).

Colorless amorphous.

Yield: 48% (synthesized from 2-bromomethyl-3-iodo-naphthalene[6]).

CF_3-Ketone : intramolecular cyclization adduct = 4.3:1 (* indicates the peaks of intramolecular cyclization adduct).

IR (neat) 3434, 2965, 2929, 2867, 1723, 1652, 1613, 1513, 1463, 1438, 1377, 1314, 1302, 1273, 1245, 1196, 1177, 1135, 1092, 1038, 1017, 985 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ 3.59 (s, 4H), 3.98 (s, 2H), 7.17–7.38 (m, 10H), 7.52 (dd, 1H, J = 8.1, 8.1 Hz), 7.61 (dd, 1H, J = 8.1, 8.1 Hz), 7.83 (d, 1H, J = 8.1 Hz), 7.89 (d, 1H, J = 8.1 Hz), 8.07 (s, 1H), 8.26 (s, 1H). Only the peaks of CF_3-ketone were described.

^{13}C NMR (75 MHz, $CDCl_3$) δ 56.2, 57.4,

116.5 (q, J_{C-F} = 290.4 Hz),

127.0, 127.6, 127.8, 128.2, 128.5, 128.6, 129.1, 129.2, 129.3, 129.6, 130.0, 131.1, 131.4 (q, J_{C-F} = 3.1 Hz), 132.3, 134.9, 137.2, 138.0,

183.3 (q, J_{C-F} = 34.5 Hz).

Only the peaks of CF_3-ketone were described.

^{19}F NMR (283 MHz, $CDCl_3$) δ 77.5* (s), 90.3 (s).

Anal. Calcd for $C_{27}H_{22}F_3NO$: C, 74.81; H, 5.12; N, 3.23. Found: C, 74.55; H, 5.37; N, 3.10.

2. Synthesis of 3-indolyl-1-trifluoromethyl-isobenzofurans.

General Procedure of the formation of 1-amino-3-trifluoromethyl-isobenzofurans.

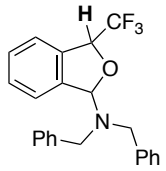
To a solution of trifluoromethyl ketone **4** (0.10 mmol) in *o*-xylene or *m*-xylene (1.0 mL) was added $Yb(OTf)_3$ (0.010 mmol, 10 mol%), and the mixture was heated at 100 °C. After completion of the reaction, the reaction was stopped by adding saturated aqueous $NaHCO_3$. The crude products were extracted with EtOAc (x3) and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by preparative TLC to give 1-amino-3-trifluoromethyl-isobenzofuran **5**.

General Procedure of the formation of 3-indolyl-1-trifluoromethyl-isobenzofurans from 1-amino-3-trifluoromethyl-isobenzofurans.

To a solution of 1-amino-3-trifluoromethyl-isobenzofuran **5** (0.10 mmol) in *o*-xylene or *m*-xylene (1.0 mL) were successively added Tf_2NH (1 M in CH_2Cl_2, 100 μL, 0.10 mmol, 1.0 equiv.) and indole derivative (0.15 mmol, 1.5 equiv.), and the mixture was heated at reflux. After completion of the reaction, the reaction was stopped by adding saturated aqueous $NaHCO_3$. The crude products were extracted with EtOAc (x3) and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by preparative TLC to give 3-indolyl-1-trifluoromethyl-isobenzofuran **10**.

General Procedure of the formation of 3-indolyl-1-trifluoromethyl-isobenzofurans derivatives (one-pot reaction).

To a solution of trifluoromethyl ketone **4** (0.10 mmol) in *o*-xylene or *m*-xylene (1.0 mL) was added $Yb(OTf)_3$ (0.010 mmol, 10 mol%), and the mixture was heated at 100 °C for 24 h. After cooling to room temperature, Tf_2NH (1 M in CH_2Cl_2, 100 μL, 0.10 mmol, 1.0 equiv.) and indole derivative (0.15 mmol, 1.5 equiv.) were successively added to the mixture, and then heated at reflux for appropriate time (3~6 h). After cooling to room temperature, the reaction was stopped by adding saturated aqueous $NaHCO_3$. The crude products were extracted with EtOAc (x3) and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by preparative TLC to give 3-indolyl-1-trifluoromethyl-isobenzofuran **10**.



N,*N*-Dibenzyl-3-(trifluoromethyl)-1,3-dihydroisobenzofuran-1-amine (**5a**).

Colorless amorphous.

Yield: 90%, *d.r.* = 1.6:1.

* shows minor diastereomer.

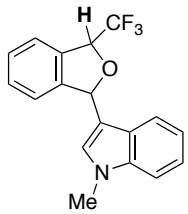
IR (neat) 3085, 3062, 3030, 2896, 2851, 1495, 1455, 1397, 1363, 1335, 1280, 1249, 1164, 1135, 1051, 1027, 973, 910 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 3.68–3.77 (m, 4H+3H*), 3.80* (d, 1H, *J* = 14.5 Hz), 5.30* (dq, 1H, *J* = 2.5, 6.0 Hz), 5.49 (dq, 1H, *J* = 2.5, 6.5 Hz), 6.12* (d, 1H, *J* = 1.0 Hz, 6.25 (d, 1H, *J* = 2.5 Hz), 7.19–7.27 (m, 2H+2H*). 7.27–7.48 (m, 12H+12H*).

^{13}C NMR (125 MHz, $CDCl_3$) δ 52.5, 52.6, 78.3 (q, J_{C-F} = 33.4 Hz), 79.4 (q, J_{C-F} = 33.4 Hz), 97.6, 98.4, 122.6, 122.9, 123.0, 123.1, 124.2 (q, J_{C-F} = 280.0 Hz), 124.3 (q, J_{C-F} = 280.1 Hz), 127.0, 127.1, 128.3, 128.3, 128.7, 128.8, 129.1, 129.2, 129.6, 129.7, 134.3, 134.5, 138.9, 139.1, 139.4, 139.7.

^{19}F NMR (283 MHz, $CDCl_3$) δ 83.5 (d, J_{C-F} = 6.8 Hz), 85.2* (d, J_{C-F} = 7.1 Hz).

Anal. Calcd for $C_{23}H_{20}F_3NO$: C, 72.05; H, 5.26; N, 3.65. Found: C, 72.28; H, 5.02; N, 3.47.



1-Methyl-3-(3-(trifluoromethyl)-1,3-dihydroisobenzofuran-1-yl)-1*H*-indole (**10a**).

Pale yellow amorphous.

Yield: 92%, *d.r.* = 2.0:1.

* shows minor diastereomer.

IR (neat) 3051, 2917, 2884, 1615, 1553, 1474, 1426, 1373, 1333, 1287, 1240, 1212, 1163, 1134, 1054, 917 cm^{-1}.

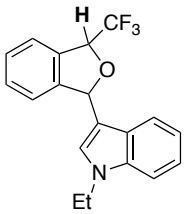
^1H NMR (500 MHz, $CDCl_3$) δ 3.72* (s, 3H), 3.74 (s, 3H), 5.56* (dq, 1H, *J* = 2.5, 6.5

Hz), 5.65 (dq, 1H, J = 2.0, 6.5 Hz), 6.66* (s, 1H), 6.70 (d, 1H, J = 2.5 Hz), 6.97 (dd, 1H, J = 7.5, 7.5 Hz), 7.01–7.07 (m, 1H+2H*), 7.09 (s, 1H), 7.12–7.44 (m, 6H+6H*), 7.46–7.53 (m, 1H+1H*).

^{13}C NMR (125 MHz, $CDCl_3$) δ 32.8, 32.8, 80.2 (q, J_{C-F} = 33.4 Hz), 80.3 (q, J_{C-F} = 33.4 Hz), 80.8, 81.3, 109.4, 109.5, 113.4, 113.6, 119.4, 119.4, 119.6, 119.6, 121.9, 122.1, 122.5, 122.8, 122.9, 126.2, 126.6, 128.2, 128.2, 128.9, 129.1, 129.4, 129.6, 124.0 (q, J_{C-F} = 280.0 Hz), 124.5 (q, J_{C-F} = 280.1 Hz), 133.3, 133.5, 137.3, 137.7, 142.5, 142.6.

^{19}F NMR (283 MHz, $CDCl_3$) δ 83.7 (d, J_{C-F} = 6.8 Hz), 84.6* (d, J_{C-F} = 6.8 Hz).

Anal. Calcd for $C_{18}H_{14}F_3NO$: C, 68.13; H, 4.45; N, 4.41. Found: C, 68.41; H, 4.19; N, 4.67.



1-Ethyl-3-(3-(trifluoromethyl)-1,3-dihydroisobenzofuran-1-yl)-1*H*-indole (**10b**).

Pale green amorphous.

Yield: 81%, *d.r.* = 2.5:1.

* shows minor diastereomer.

IR (neat) 3062, 2979, 2937, 2880, 1614, 1552, 1462, 1361, 1287, 1274, 1213, 1163, 1134, 1055, 919 cm^{-1}.

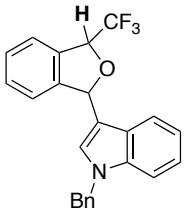
^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44* (t, 3H, J = 7.0 Hz), 1.45 (t, 3H, J = 7.0 Hz), 4.12* (q, 2H, J = 7.0 Hz), 4.14 (q, 2H, J = 7.0 Hz), 5.56* (dq, 1H, J = 2.0, 6.5 Hz), 5.66 (dq, 1H, J = 2.0, 6.5 Hz), 6.66* (d, 1H, J = 1.8 Hz), 6.71 (d, 1H, J = 2.0 Hz), 6.96 (dd, 1H, J = 7.5, 7.5 Hz), 7.01–7.06 (m, 1H+1H*), 7.10* (s, 1H), 7.12–7.44 (m, 6H+6H*), 7.46–7.53 (m, 1H+1H*).

^{13}C NMR (125 MHz, $CDCl_3$) δ 15.3, 41.0, 50.0, 50.1, 80.2 (q, J_{C-F} = 3 Hz), 80.3 (q, J_{C-F} = 32.3 Hz), 80.9, 81.5, 109.5, 109.6, 113.4, 113.6, 119.5, 119.6, 121.8, 121.9, 122.5, 122.8, 122.9, 124.0 (q, J_{C-F} = 281.0 Hz), 124.5 (q, J_{C-F} = 281.4 Hz), 126.3, 126.8, 127.2, 127.4, 128.2, 128.2, 129.5, 129.6, 133.4, 133.5, 136.4, 136.7, 142.6, 142.6.

^{19}F NMR (283 MHz, $CDCl_3$) δ 83.7 (d, J_{C-F} = 7.1 Hz), 84.6* (d, J_{C-F} = 6.8 Hz).

Anal. Calcd for $C_{19}H_{16}F_3NO$: C, 68.87; H, 4.87; N, 4.23. Found: C, 68.95; H, 4.80; N,

4.11.



1-Benzyl-3-(3-(trifluoromethyl)-1,3-dihydroisobenzofuran-1-yl)-1*H*-indole (**10c**).

Pale red amorphous.

Yield: 64%, *d.r.* = 2.0:1.

* shows minor diastereomer.

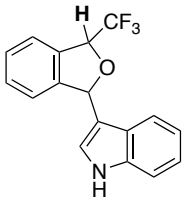
IR (neat) 3060, 3033, 2920, 2876, 1614, 1554, 1496, 1468, 1360, 1334, 1287, 1275, 1211, 1165, 1134, 1055, 1027, 910 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.21* (s, 2H), 5.22 (s, 2H), 5.55* (dq, 1H, *J* = 2.5, 6.5 Hz), 5.66 (q, 1H, *J* = 6.0 Hz), 6.64* (s, 1H), 6.69 (d, 1H, *J* = 2.5 Hz), 6.95 (dd, 1H, *J* = 7.5, 7.5 Hz), 7.00–7.42 (m, 12H+13H*), 7.46–7.52 (m, 1H+1H*).

^{13}C NMR (125 MHz, $CDCl_3$) δ 50.0, 50.1, 80.2 (q, J_{C-F} = 33.4 Hz), 80.3 (q, J_{C-F} = 33.4 Hz), 80.8, 81.4, 110.0, 110.0, 114.0, 114.2, 119.5, 119.6, 119.8, 119.9, 122.1, 122.3, 122.5, 122.7, 122.9, 124.0 (q, J_{C-F} = 281.5 Hz), 124.4 (q, J_{C-F} = 282.1 Hz), 126.3, 126.7, 126.8, 127.6, 127.7, 128.2, 128.2, 128.3, 128.6, 128.7, 128.7, 129.4, 129.6, 133.2, 133.5, 136.9, 137.0, 137.3, 142.2, 142.5.

^{19}F NMR (283 MHz, $CDCl_3$) δ 83.7 (d, J_{C-F} = 7.1 Hz), 84.6* (d, J_{C-F} = 6.8 Hz).

Anal. Calcd for $C_{24}H_{18}F_3NO$: C, 73.27; H, 4.61; N, 3.56. Found: C, 73.43; H, 4.56; N, 3.75.



3-(3-(Trifluoromethyl)-1,3-dihydroisobenzofuran-1-yl)-1*H*-indole (**10d**).

Pale yellow amorphous.

Yield: 68%, *d.r.* = 1.9:1.

* shows minor diastereomer.

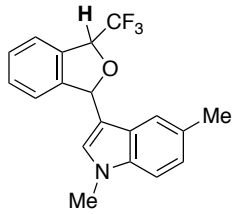
IR (neat) 3408, 3054, 2924, 2853, 1555, 1458, 1422, 1371, 1286, 1274, 1212, 1166, 1135, 1049, 919 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ 5.59* (dq, 1H, J = 2.1, 6.6 Hz), 5.68 (dq, 1H, J = 2.7, 6.6 Hz), 6.68* (s, 1H), 6.73 (d, 1H, J = 2.7 Hz), 6.96–7.44 (m, 8H+8H*), 7.48–7.57 (m, 1H+1H*), 8.18 (brs, 1H+1H*).

^{13}C NMR (125 MHz, $CDCl_3$) δ 80.3 (q, J_{C-F} = 33.4 Hz), 80.4 (q, J_{C-F} = 33.4 Hz), 80.9, 81.5, 111.3, 111.4, 114.8, 115.0, 119.3, 119.4, 120.0, 120.0, 122.4, 122.5, 122.7, 122.9, 124.0 (q, J_{C-F} = 281.0 Hz), 124.5 (q, J_{C-F} = 281.4 Hz), 124.5, 124.7, 125.5, 126.0, 128.2, 128.3, 129.5, 129.7, 133.2, 133.4, 136.5, 136.8, 142.4, 142.5.

^{19}F NMR (283 MHz, $CDCl_3$) δ 83.7 (d, J_{C-F} = 7.1 Hz), 84.6* (d, J_{C-F} = 6.8 Hz).

Anal. Calcd for $C_{17}H_{12}F_3NO$: C, 67.32; H, 3.99; N, 4.62. Found: C, 67.08; H, 4.17; N, 4.78.



1,5-Dimethyl-3-(3-(trifluoromethyl)-1,3-dihydroisobenzofuran-1-yl)-1*H*-indole (**10e**).

Pale yellow amorphous.

Yield: 72%, *d.r.* = 1.7:1.

* shows minor diastereomer.

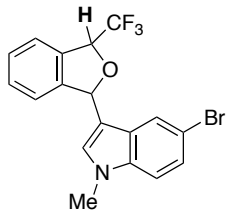
IR (neat) 3035, 2919, 2857, 1623, 1577, 1552, 1492, 1461, 1427, 1372, 1315, 1286, 1275, 1241, 1213, 1202, 1162, 1134, 1054, 1024, 919 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 2.32 (s, 3H), 2.38* (s, 3H), 3.69* (s, 3H), 3.70 (s, 3H), 5.56* (dq, 1H, J = 2.5, 6.5 Hz), 5.65 (dq, 1H, J = 2.0, 6.5 Hz), 6.65* (s, 1H), 6.69 (d, 1H, J = 2.5 Hz), 6.90 (s, 1H), 6.92* (s, 1H), 6.98–7.43 (m, 6H+6H*), 7.45–7.53 (m, 1H+1H*).

^{13}C NMR (125 MHz, $CDCl_3$) δ 21.4, 32.8, 32.8, 80.2 (q, J_{C-F} = 32.3 Hz), 80.7, 81.3, 109.1, 109.2, 112.9, 113.2, 118.9, 118.9, 112.5, 122.8, 122.9, 123.6, 123.7, 124.0 (q, J_{C-F} = 284.0 Hz), 124.5 (q, J_{C-F} = 285.1 Hz), 126.5, 127.0, 128.1, 128.2, 128.8, 128.9, 128.9, 129.4, 129.6, 133.4, 133.5, 135.7, 136.1, 142.6, 142.7.

^{19}F NMR (283 MHz, $CDCl_3$) δ 83.8 (d, J_{C-F} = 6.8 Hz), 84.6* (d, J_{C-F} = 6.8 Hz).

Anal. Calcd for $C_{19}H_{16}F_3NO$: C, 68.87; H, 4.87; N, 4.23. Found: C, 68.93; H, 4.53; N, 4.48.



5-Bromo-1-methyl-3-(3-(trifluoromethyl)-1,3-dihydroisobenzofuran-1-yl)-1*H*-indole (**10f**).

Pale yellow amorphous.

Yield: 80%, *d.r.* = 1.8:1.

* shows minor diastereomer.

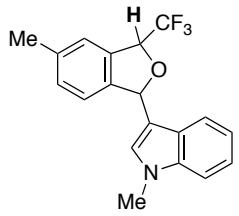
IR (neat) 3078, 3043, 2922, 2883, 1612, 1550, 1474, 1424, 1369, 1311, 1284, 1239, 1210, 1164, 1135, 1053, 1024, 910 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 3.71* (s, 3H), 3.74 (s, 3H), 5.56* (dq, 1H, *J* = 2.0, 6.5 Hz), 5.66 (dq, 1H, *J* = 2.0, 6.5 Hz), 6.60* (s, 1H), 6.64 (d, 1H, *J* = 2.0 Hz), 6.98* (s, 1H), 7.08 (s, 1H), 7.10–7.56 (m, 7H+7H*).

^{13}C NMR (125 MHz, $CDCl_3$) δ 33.0, 33.0, 80.2 (q, J_{C-F} = 33.4 Hz), 80.3 (q, J_{C-F} = 33.4 Hz), 80.3, 80.9, 111.0, 111.1, 113.2, 113.2, 113.5, 121.8, 121.9, 122.6, 123.1, 124.0 (q, J_{C-F} = 280.2 Hz), 124.4 (q, J_{C-F} = 280.3 Hz), 124.9, 125.0, 127.8, 128.3, 128.4, 128.4, 129.6, 129.7, 129.9, 133.2, 133.4, 135.9, 136.3, 142.1, 142.1.

^{19}F NMR (283 MHz, $CDCl_3$) δ 89.9 (s, 3F).

Anal. Calcd for $C_{18}H_{13}BrF_3NO$: C, 54.57; H, 3.31; N, 3.54. Found: C, 54.30; H, 3.37; N, 3.28.



1-Methyl-3-(5-methyl-3-(trifluoromethyl)-1,3-dihydroisobenzofuran-1-yl)-1*H*-indole (**10g**).

Pale yellow amorphous.

Yield: 85%, *d.r.* = 2.0:1.

* shows minor diastereomer.

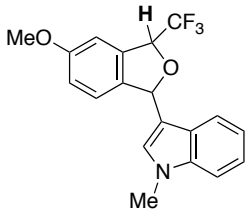
IR (neat) 3053, 2924, 2890, 1617, 1554, 1474, 1426, 1375, 1333, 1284, 1239, 1162, 1134, 1059, 1013, 947, 909 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 3.43 (s, 3H+3H*), 3.72* (s, 3H), 3.73 (s, 3H), 5.52* (q, 1H, J = 6.5 Hz), 5.60 (dq, 1H, J = 2.5, 6.5 Hz), 6.61* (s, 1H), 6.66 (d, 1H, J = 2.5 Hz), 6.95–7.32 (m, 8H+7H*), 7.34* (d, 1H, J = 8.0 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 32.7, 32.8, 80.1 (q, J_{C-F} = 33.4 Hz), 80.2 (q, J_{C-F} = 33.4 Hz), 80.6, 81.1, 109.4, 109.5, 113.6, 113.8, 119.4, 119.5, 119.6, 121.8, 122.0, 122.4, 122.8, 123.3, 124.0 (q, J_{C-F} = 281.0 Hz), 124.5 (q, J_{C-F} = 281.4 Hz), 126.2, 126.7, 128.9, 129.1, 130.4, 130.6, 133.6, 133.7, 137.3, 137.6, 138.1, 138.2, 139.7, 139.8.

^{19}F NMR (283 MHz, $CDCl_3$) δ 83.8 (d, J_{C-F} = 6.8 Hz), 84.7* (d, J_{C-F} = 6.8 Hz).

Anal. Calcd for $C_{19}H_{16}F_3NO$: C, 68.87; H, 4.87; N, 4.23. Found: C, 69.08; H, 4.73; N, 4.04.



3-(5-Methoxy-3-(trifluoromethyl)-1,3-dihydroisobenzofuran-1-yl)-1-methyl-1*H*-indole (**10h**).

Pale yellow amorphous.

Yield: 60%, *d.r.* = 1.7:1.

* shows minor diastereomer.

IR (neat) 3057, 3004, 2936, 2016, 2882, 2839, 1615, 1594, 1553, 1496, 1468, 1435, 1362, 1330, 1312, 1283, 1255, 1133, 1059, 1032, 943 cm^{-1}.

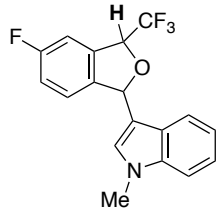
^1H NMR (500 MHz, $CDCl_3$) δ 3.74* (s, 3H), 3.75 (s, 3H), 3.85 (s, 3H+3H*), 5.52* (dq, 1H, J = 2.0, 6.5 Hz), 5.60 (dq, 1H, J = 2.0, 6.5 Hz), 6.60* (d, 1H, J = 2.0 Hz), 6.65 (d, 1H, J = 2.0 Hz), 6.89–6.95 (m, 1H+1H*), 6.97–7.26 (m, 6H+5H*), 7.27–7.38 (m, 1H+2H*).

^{13}C NMR (125 MHz, $CDCl_3$) δ 32.8, 32.8, 55.6, 80.1 (q, J_{C-F} = 32.1 Hz), 80.1 (q, J_{C-F} = 33.4 Hz), 80.5, 81.0, 107.2, 107.7, 109.4, 109.5, 113.8, 113.9, 116.1, 116.1, 119.5,

119.5, 119.5, 119.6, 121.9, 122.1, 123.5, 124.0 (q, J_{C-F} = 280.0 Hz), 124.4 (q, J_{C-F} = 280.1 Hz), 126.2, 126.7, 128.9, 129.1, 134.5, 134.6, 134.9, 135.0, 137.4, 137.7, 160.0, 160.0.

^{19}F NMR (283 MHz, $CDCl_3$) δ 83.8 (d, J_{C-F} = 4.5 Hz), 84.7* (d, J_{C-F} = 6.8 Hz).

Anal. Calcd for $C_{19}H_{16}F_3NO_2$: C, 65.70; H, 4.64; N, 4.03. Found: C, 65.48; H, 4.87; N, 4.25.



3-(5-Fluoro-3-(trifluoromethyl)-1,3-dihydroisobenzofuran-1-yl)-1-methyl-1*H*-indole (**10i**).

Pale yellow amorphous.

Yield: 53%, *d.r.* = 1.9:1.

* shows minor diastereomer.

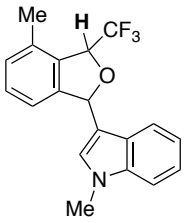
IR (neat) 3060, 2917, 2884, 1618, 1606, 1555, 1491, 1475, 1437, 1375, 1362, 1328, 1279, 1249, 1207, 1164, 1146, 1129, 1093, 1060, 1014, 960 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.74* (s, 3H), 3.75 (s, 3H), 5.52* (dq, 1H, *J* = 2.0, 6.5 Hz), 5.61 (dq, 1H, *J* = 2.5, 6.5 Hz), 6.61* (s, 1H), 6.65 (s, 1H), 6.97–7.26 (m, 7H+6H*), 7.28–7.34 (m, 1H+2H*).

^{13}C NMR (125 MHz, $CDCl_3$) δ 32.8, 32.8, 79.8 (q, J_{C-F} = 31.0 Hz), 79.9 (q, J_{C-F} = 31.0 Hz), 80.5, 81.0, 109.5, 109.6, 109.8 (d, J_{C-F} = 23.9 Hz), 110.2 (d, J_{C-F} = 25.0 Hz), 113.1, 113.2, 116.9, 117.0, 117.2, 119.3, 119.3, 119.7, 119.8, 122.1, 122.2, 123.7 (q, J_{C-F} = 280.3 Hz), 124.1 (d, J_{C-F} = 9.6 Hz), 124.2 (d, J_{C-F} = 8.4 Hz), 124.2 (q, J_{C-F} = 280.3 Hz), 126.0, 126.5, 129.0, 129.2, 135.3 (d, J_{C-F} = 8.3 Hz), 135.5 (d, J_{C-F} = 9.6 Hz), 137.4, 137.7, 138.1, 138.2, 162.8 (d, J_{C-F} = 244.5 Hz), 162.9 (d, J_{C-F} = 244.4 Hz).

^{19}F NMR (283 MHz, $CDCl_3$) δ 47.5–47.9 (d, 1F+1F*), 83.8 (d, 3F, J_{C-F} = 7.1 Hz), 84.7* (d, 3F, J_{C-F} = 6.8 Hz).

Anal. Calcd for $C_{18}H_{13}F_4NO$: C, 64.48; H, 3.91; N, 4.18. Found: C, 64.22; H, 4.16; N, 4.34.



1-Methyl-3-(4-methyl-3-(trifluoromethyl)-1,3-dihydroisobenzofuran-1-yl)-1*H*-indole (**10j**).

Pale yellow amorphous.

Yield: 77%, *d.r.* = 4.3:1.

* shows minor diastereomer.

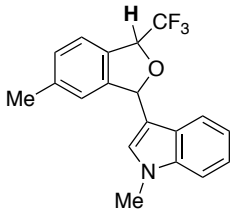
IR (neat) 3052, 2932, 2881, 1615, 1606, 1556, 1475, 1426, 1376, 1356, 1333, 1307, 1281, 1264, 1227, 1182, 1166, 1130, 1058, 1034, 1013, 913 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 2.42* (s, 3H), 2.45 (s, 3H), 3.72* (s, 3H), 3.74 (s, 3H), 5.59* (q, 1H, J = 6.5 Hz), 5.66 (dq, 1H, J = 2.0, 6.5 Hz), 6.65* (s, 1H), 6.69 (s, 1H), 6.90–7.33 (m, 8H+7H*), 7.55* (d, 1H, J = 8.0 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ 19.5, 32.8, 79.6 (q, J_{C-F} = 32.3 Hz), 81.1, 109.5, 113.4, 119.5, 119.5, 120.2, 122.0, 125.3 (q, J_{C-F} = 283.9 Hz), 126.2, 129.1, 129.7, 129.7, 132.4, 133.7, 137.6, 143.6 (the peaks derived from major diastereomer was only described)

^{19}F NMR (283 MHz, $CDCl_3$) δ 86.0 (d, J_{C-F} = 6.8 Hz), 87.5* (d, J_{C-F} = 7.1 Hz).

Anal. Calcd for $C_{19}H_{16}F_3NO$: C, 68.87; H, 4.87; N, 4.23. Found: C, 68.63; H, 5.03; N, 4.48.



1-Methyl-3-(6-methyl-3-(trifluoromethyl)-1,3-dihydroisobenzofuran-1-yl)-1*H*-indole (**10k**).

Pale yellow amorphous.

Yield: 78%, *d.r.* = 2.3:1.

* shows minor diastereomer.

IR (neat) 3056, 2919, 2882, 1617, 1554, 1475, 1426, 1365, 1332, 1284, 1241, 1200,

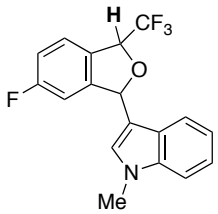
1163, 1135, 1056, 1013, 916 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 2.31* (s, 3H), 2.32 (s, 3H), 3.74* (s, 3H), 3.75 (s, 3H), 5.52* (q, 1H, J = 6.5 Hz), 5.62 (dq, 1H, J = 2.0, 6.5 Hz), 6.61* (s, 1H), 6.66 (d, 1H, J = 2.0 Hz), 6.94–7.25 (m, 6H+5H*), 7.27–7.39 (m, 2H+3H*).

^{13}C NMR (125 MHz, $CDCl_3$) δ 21.3, 21.4, 32.8, 32.8, 19.5, 32.8, 80.1 (q, J_{C-F} = 33.4 Hz), 80.1 (q, J_{C-F} = 33.4 Hz), 109.4, 109.5, 113.6, 113.8, 119.4, 119.5, 119.6, 119.6, 121.9, 122.1, 122.2, 122.6, 123.1, 123.1, 124.1 (q, J_{C-F} = 281.0 Hz), 124.5 (q, J_{C-F} = 281.4 Hz), 126.2, 126.7, 128.9, 129.0, 129.1, 129.2, 130.5, 130.6, 137.3, 137.7, 139.6, 139.8, 142.9.

^{19}F NMR (283 MHz, $CDCl_3$) δ 83.5 (d, J_{C-F} = 6.8 Hz), 84.5* (d, J_{C-F} = 7.4 Hz).

Anal. Calcd for $C_{19}H_{16}F_3NO$: C, 68.87; H, 4.87; N, 4.23. Found: C, 69.17; H, 4.63; N, 4.51.



3-(6-Fluoro-3-(trifluoromethyl)-1,3-dihydroisobenzofuran-1-yl)-1-methyl-1*H*-indole (**10l**).

Pale yellow amorphous.

Yield: 61%, *d.r.* = 1.4:1.

* shows minor diastereomer.

IR (neat) 3060, 2918, 2884, 1616, 1606, 1555, 1490, 1476, 1440, 1427, 1373, 1334, 1275, 1252, 1165, 1135, 1094, 1057, 1014, 920 cm^{-1}.

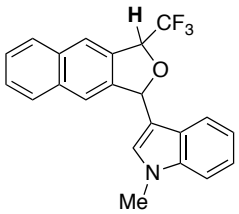
^1H NMR (500 MHz, $CDCl_3$) δ 3.76* (s, 3H), 3.77 (s, 3H), 5.53* (q, 1H, J = 6.5 Hz), 5.62 (dq, 1H, J = 2.0, 6.5 Hz), 6.62* (s, 1H), 6.66 (d, 1H, J = 2.0 Hz), 6.81–6.86 (m, 1H+1H*), 7.00 (dd, 1H, J = 8.0, 8.0 Hz), 7.03–7.37 (m, 5H+6H*), 7.41–7.47 (m, 1H+1H*).

^{13}C NMR (125 MHz, $CDCl_3$) δ 32.8, 32.9, 79.8 (q, J_{C-F} = 33.4 Hz), 79.9 (q, J_{C-F} = 32.3 Hz), 80.5 (d, J_{C-F} = 2.4 Hz), 81.1 (d, J_{C-F} = 2.4 Hz), 109.5, 109.6, 110.0 (d, J_{C-F} = 12.0 Hz), 110.2 (d, J_{C-F} = 11.9 Hz), 112.7, 112.9, 115.8 (d, J_{C-F} = 23.9 Hz), 115.8 (d, J_{C-F} = 23.9 Hz), 119.2, 119.8, 119.8, 122.1, 122.2, 123.8 (q, J_{C-F} = 280.1 Hz), 124.0 (d, J_{C-F} =

9.5 Hz), 124.3 (q, J_{C-F} = 280.1 Hz), 124.4 (d, J_{C-F} = 9.5 Hz), 126.0, 126.5, 128.8, 129.0, 129.1, 137.4, 137.7, 145.2 (d, J_{C-F} = 8.4 Hz), 145.3 (d, J_{C-F} = 8.4 Hz), 163.9 (d, J_{C-F} = 246.8 Hz), 164.9 (d, J_{C-F} = 246.8 Hz).

^{19}F NMR (283 MHz, $CDCl_3$) δ 49.4–49.7* (d, 1F), 49.7–50.0 (d, 1F), 83.4 (d, 3F, J_{C-F} = 7.1 Hz), 84.3* (d, 3F, J_{C-F} = 6.8 Hz).

Anal. Calcd for $C_{18}H_{13}F_4NO$: C, 64.48; H, 3.91; N, 4.18. Found: C, 64.74; H, 3.80; N, 4.26.



1-Methyl-3-(3-(trifluoromethyl)-1,3-dihydronaphtho[2,3-*c*]furan-1-yl)-1*H*-indole (**10m**).

Pale yellow amorphous.

Yield: 61%, *d.r.* = 2.2:1.

* shows minor diastereomer.

IR (neat) 3057, 2919, 2851, 1615, 1555, 1505, 1474, 1425, 1360, 1335, 1272, 1165, 1132, 1059, 1014, 930 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.77* (s, 3H), 3.79 (s, 3H), 5.71* (q, 1H, J = 6.5 Hz), 5.78 (q, 1H, J = 2.0, 6.5 Hz), 6.77* (s, 1H), 6.83 (s, 1H), 6.94 (dd, 1H, J = 7.5, 7.5 Hz), 7.00–7.38 (m, 4H+5H*), 7.91–8.02 (m, 2H+2H*), 7.57–7.63 (m, 1H+1H*), 7.72–7.77 (m, 1H+1H*), 7.91–8.02 (m, 2H+2H*).

^{13}C NMR (125 MHz, $CDCl_3$) δ 32.8, 79.6 (q, J_{C-F} = 33.4 Hz), 79.6 (q, J_{C-F} = 33.4 Hz), 80.2, 80.7, 109.4, 109.5, 113.5, 113.6, 119.5, 119.6, 119.6, 119.7, 121.4, 121.5, 121.7, 122.0, 122.1, 122.4, 124.0 (q, J_{C-F} = 281.0 Hz), 124.4 (q, J_{C-F} = 281.4 Hz), 126.2, 126.3, 126.6, 126.7, 128.1, 128.1, 128.3, 128.3, 129.1, 129.3, 132.3, 132.4, 133.2, 133.2, 134.0, 134.1, 137.4, 137.7, 140.4, 140.4.

^{19}F NMR (283 MHz, $CDCl_3$) δ 83.8 (d, J_{C-F} = 4.5 Hz), 84.7* (d, J_{C-F} = 6.8 Hz).

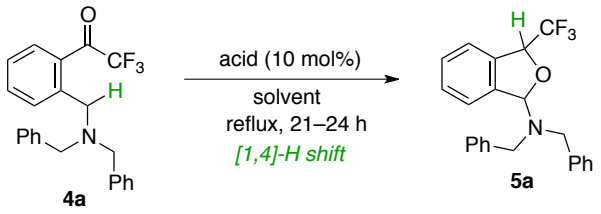
Anal. Calcd for $C_{22}H_{16}F_3NO$: C, 71.93; H, 4.39; N, 3.81. Found: C, 72.18; H, 4.32; N, 4.07.

3. Examination of the reaction conditions and substrates.

Initial trial was conducted with trifluoromethyl ketone **4a** with *N*,*N*-dibenzylaminomethy group at *ortho*-position as the substrate: a solution of **4a** in $ClCH_2CH_2Cl$ was heated to reflux in the presence of 10 mol% of various acid catalysts (Figure S1). When the reaction was conducted with $Sc(OTf)_3$, the desired reaction proceeded smoothly to afford **5a** in good chemical yields with 1.6:1 diastereoselectivity (61%, entry 1). The chemical yield of **5a** was significantly improved to 91% when $Yb(OTf)_3$ was employed (entry 2). Other metal triflates such as $Gd(OTf)_3$, $Zn(OTf)_2$, and $Hf(OTf)_4$ were also effective, however, chemical yield remained low to moderate level (entries 3–5). Substantial amount of starting material **4a** was recovered with common strong Lewis acids such as $SnCl_4$ and BF_3•OEt_2 (entries 6 and 7). Unfortunately, the desired reaction did not proceed with Tf_2NH, and starting material **4a** was recovered completely (86%, entry 7). This result is mainly ascribed to loss of the catalytic activity of Tf_2NH by formation of the ammonium salt with substrate **4a** bearing basic trialkylamine moiety.

Next, our attention moved to the examination of the reaction solvents with $Yb(OTf)_3$ as the catalyst. The chemical yield was slightly dropped compared to $ClCH_2CH_2Cl$ when common aromatic solvents such as benzene and toluene were employed (entries 8 and 9). Same situation was observed in the case of PhCl and $PhCF_3$ (entries 10 and 11). Although the chemical yield remained moderate level (76%) when the reaction was conducted at refluxing temperature of *p*-xylene (138 °C, entry 12), improvement of the chemical yield to 86% was accomplished by lowering the reaction temperature to 100 °C (entry 13). Satisfactory chemical yields (82% and 86% respectively) were also achieved in *m*- and *o*-xylenes when the reaction was conducted at 100 °C (entries 14 and 15).

Table S1. Examination of the reaction conditions.[a]



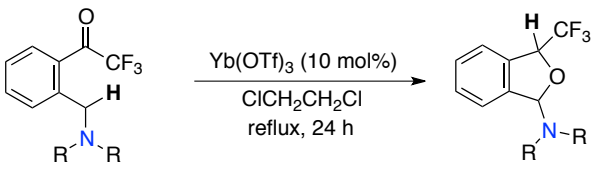
Entry	Catalyst	Solvent	Yield (%)[b]

			5a	D.r.	**4a**
1	$Sc(OTf)_3$	$ClCH_2CH_2Cl$	61	1.6:1	7
2	$Yb(OTf)_3$	$ClCH_2CH_2Cl$	91	1.6:1	–
3	$Gd(OTf)_3$	$ClCH_2CH_2Cl$	65	1.7:1	19
4	$Zn(OTf)_2$	$ClCH_2CH_2Cl$	18	1.7:1	53
5	$Hf(OTf)_4$	$ClCH_2CH_2Cl$	22	1.7:1	75
5	$SnCl_4$	$ClCH_2CH_2Cl$	11	1.8:1	76
6	BF_3•OEt_2	$ClCH_2CH_2Cl$	13	1.6:1	84
7	Tf_2NH	$ClCH_2CH_2Cl$	–	–	86
8	$Yb(OTf)_3$	benzene	55	1.7:1	–
9	$Yb(OTf)_3$	toluene	81	1.6:1	–
10	$Yb(OTf)_3$	PhCl	66	1.8:1	–
11	$Yb(OTf)_3$	$PhCF_3$	83	1.7:1	–
12	$Yb(OTf)_3$	*p*-xylene	76	1.6:1	–
13[c]	$Yb(OTf)_3$	*p*-xylene	86	1.6:1	–
14[c]	$Yb(OTf)_3$	*m*-xylene	82	1.6:1	–
15[c]	$Yb(OTf)_3$	*o*-xylene	86	1.6:1	–

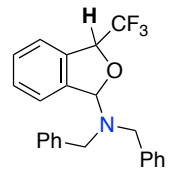
[a] Unless otherwise noted, all reactions were conducted with 0.10 mmol of **4a** in the presence of 10 mol% of catalyst in $ClCH_2CH_2Cl$ (1.0 mL) at refluxing temperature for 21–24 h. [b] Isolated yield. [c] At 100 °C.

The examination of the substituent on the nitrogen atom suggested that *N*,*N*-dibenzyl amine moiety was specifically effective to achieve the reaction as shown in Figure S1. Exposure of the substrate **s3** with *N*,*N*-diethylamine group to the optimized reaction conditions (10 mo% of $Yb(OTf)_3$, $ClCH_2CH_2Cl$, reflux, 24 h) afforded the adduct **s6** in 29% chemical yield (*d.r.* = 2.2:1, recovery of **s3**: 33%). Both substrates **s4** with *N*,*N*-diphenylamine group and **s5** with pyrrolidine group did not afford the desired adducts **s7** and **s8**, and recovery of starting material was observed in both cases (**s4**: 98%, **s5**: 65%). In the case of the substrate **6** with *N*-benzyl-*N*-phenylamine group, various unindetified materials were observed and the desired adduct **7** was not obtaind at all.

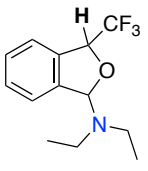
Figure S1. Examination of the substituents on amine portion.[a]



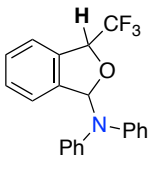
4a, s3–5, 6 → **5a, s6–8, 7**



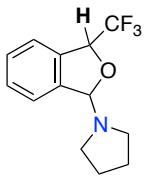
5a: 91%, *d.r.* = 1.6:1



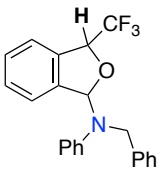
s6: 29%, *d.r.* = 2.2:1 (**SM**: 33%)



s7: – (**SM**: 98%)



s8: – (**SM**: 65%)



7: complex mixture

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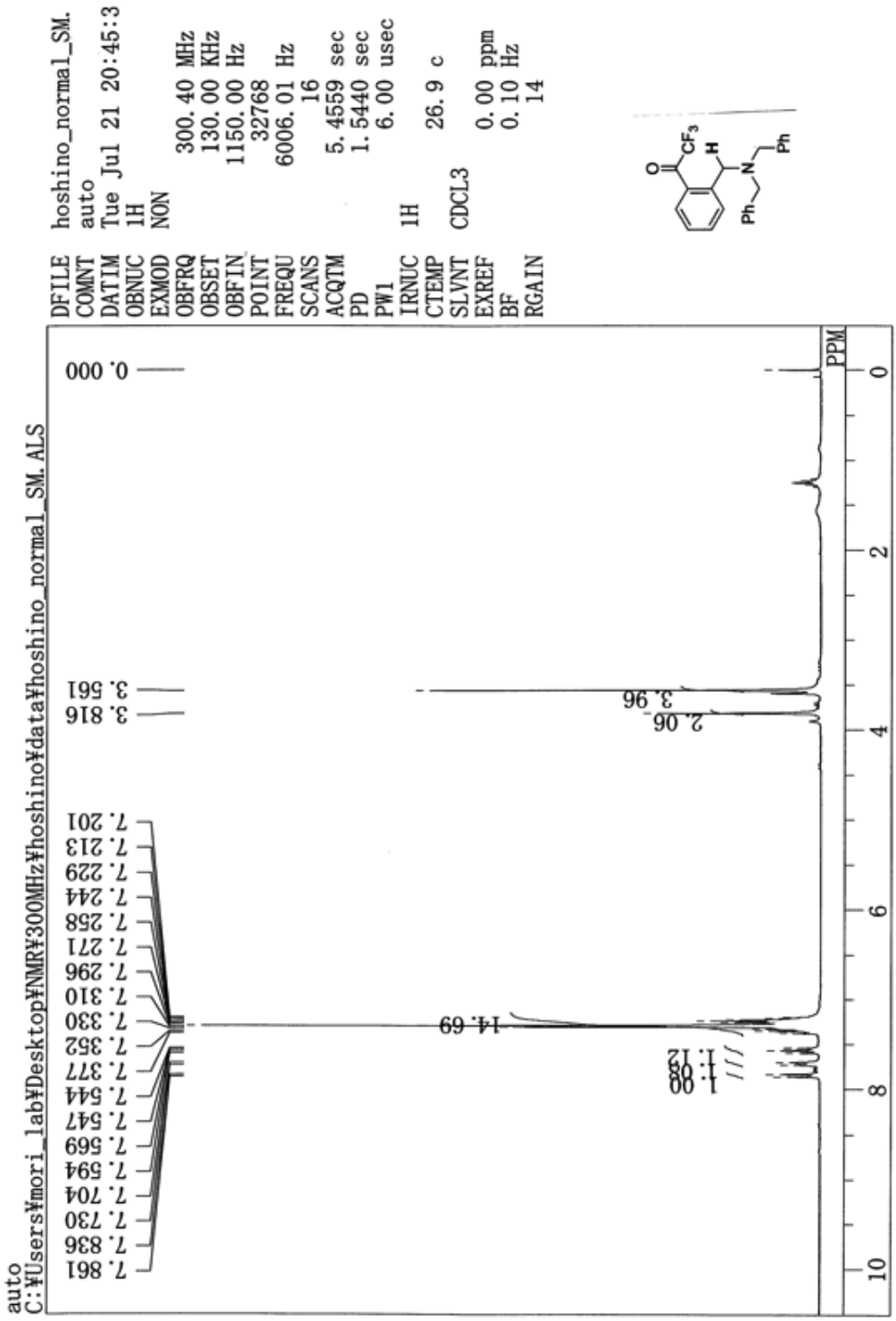
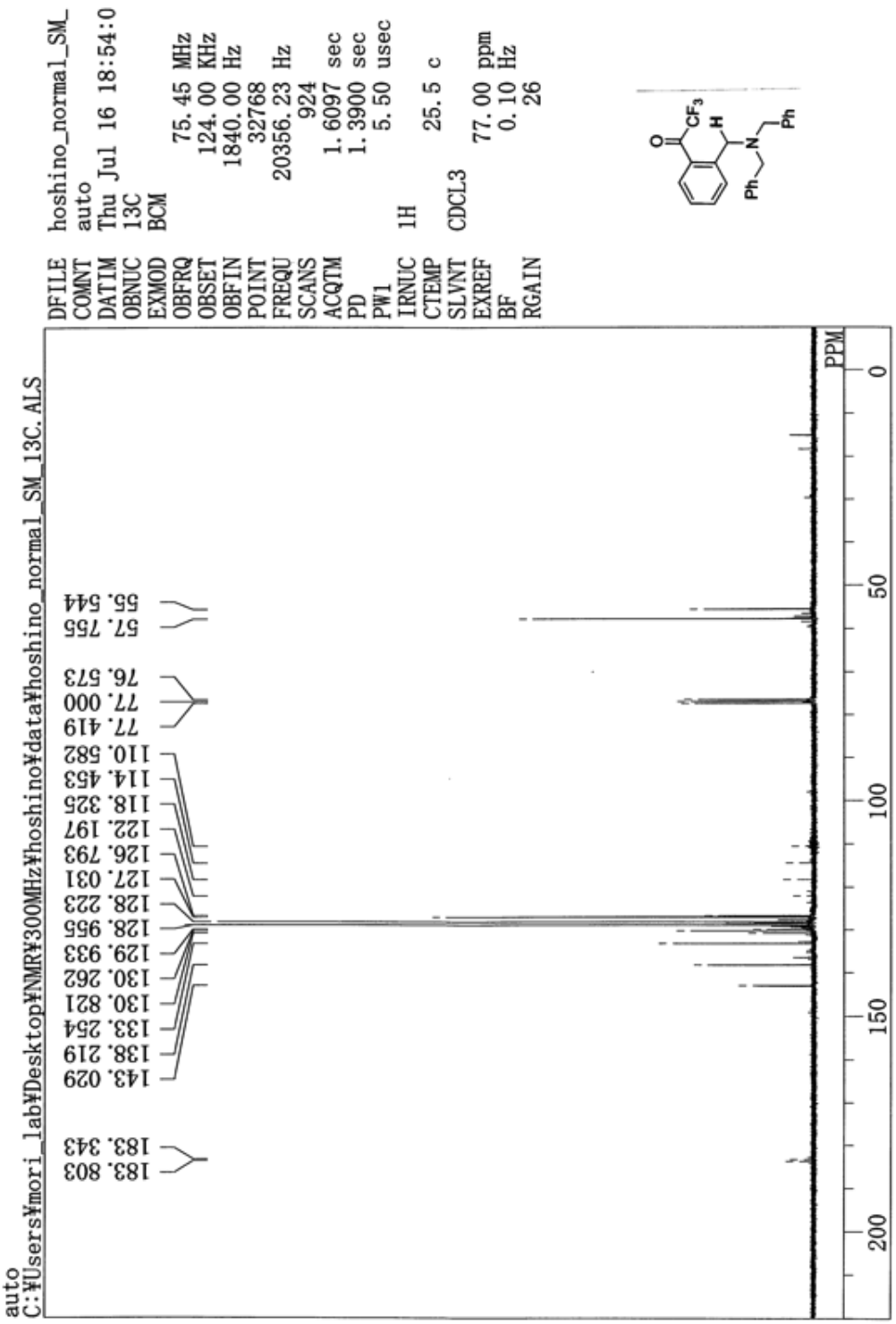
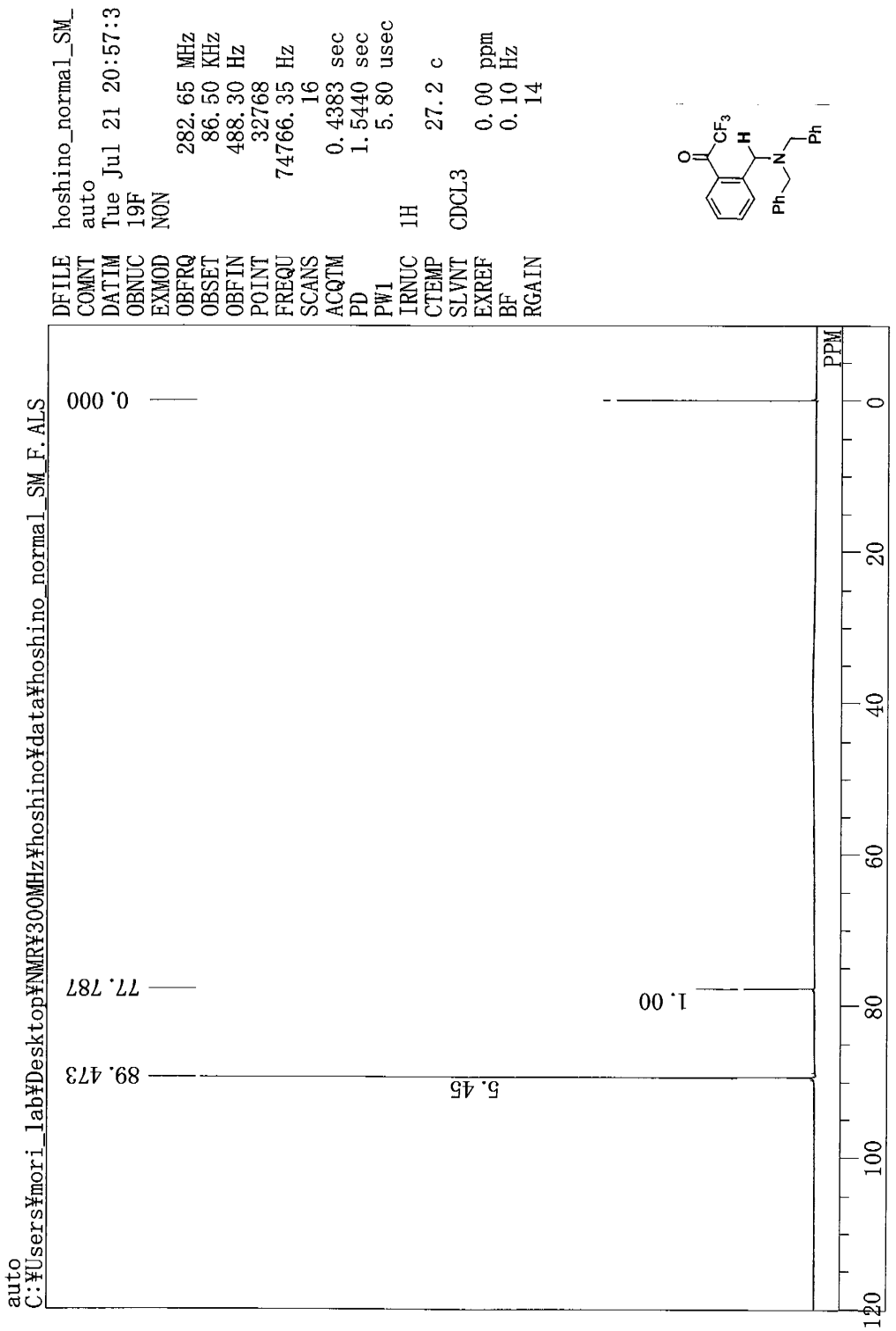
^{1}H NMR spectrum of **4a** ($CDCl_3$, 300 MHz).



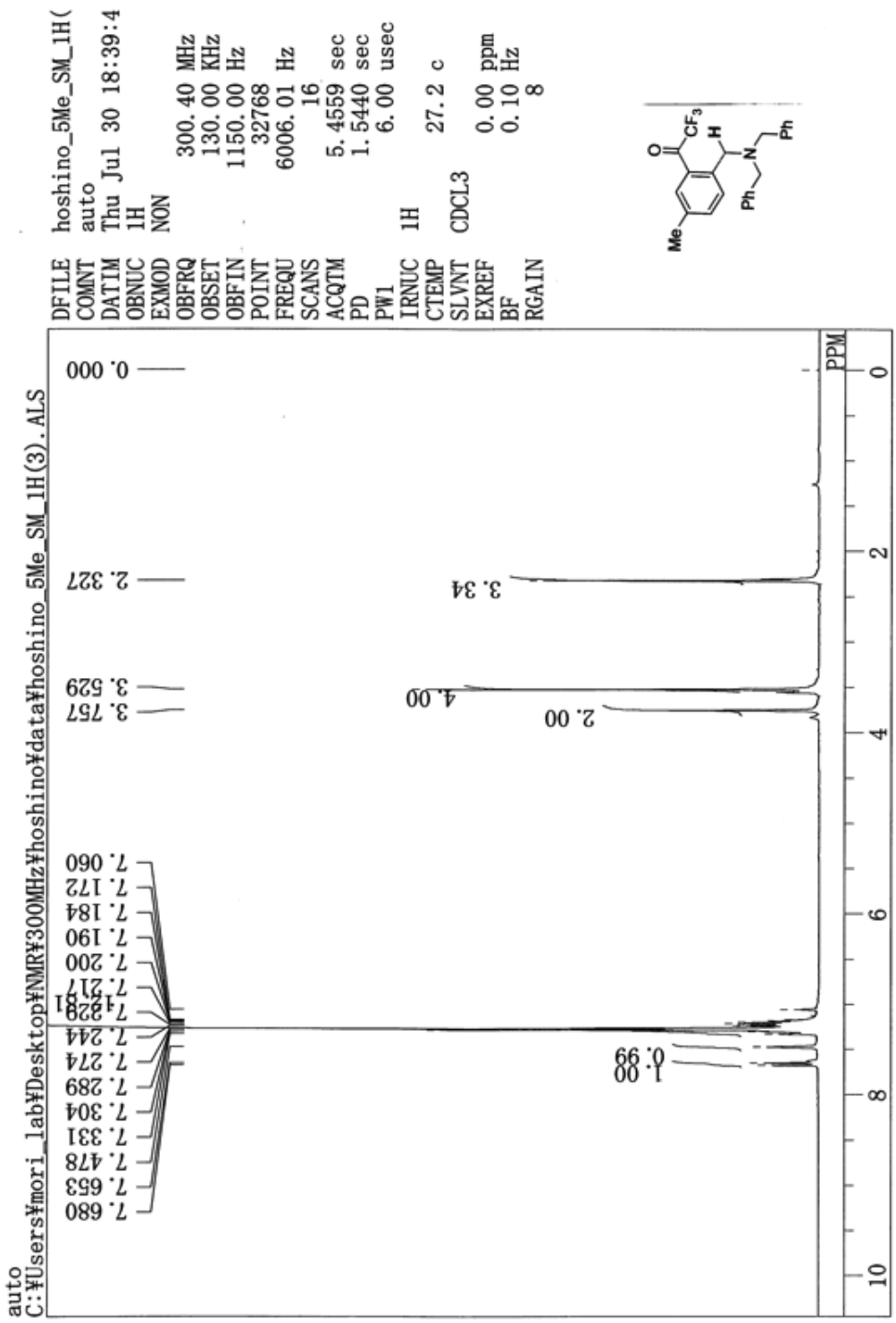
^{13}C NMR spectrum of **4a** ($CDCl_3$, 75 MHz).



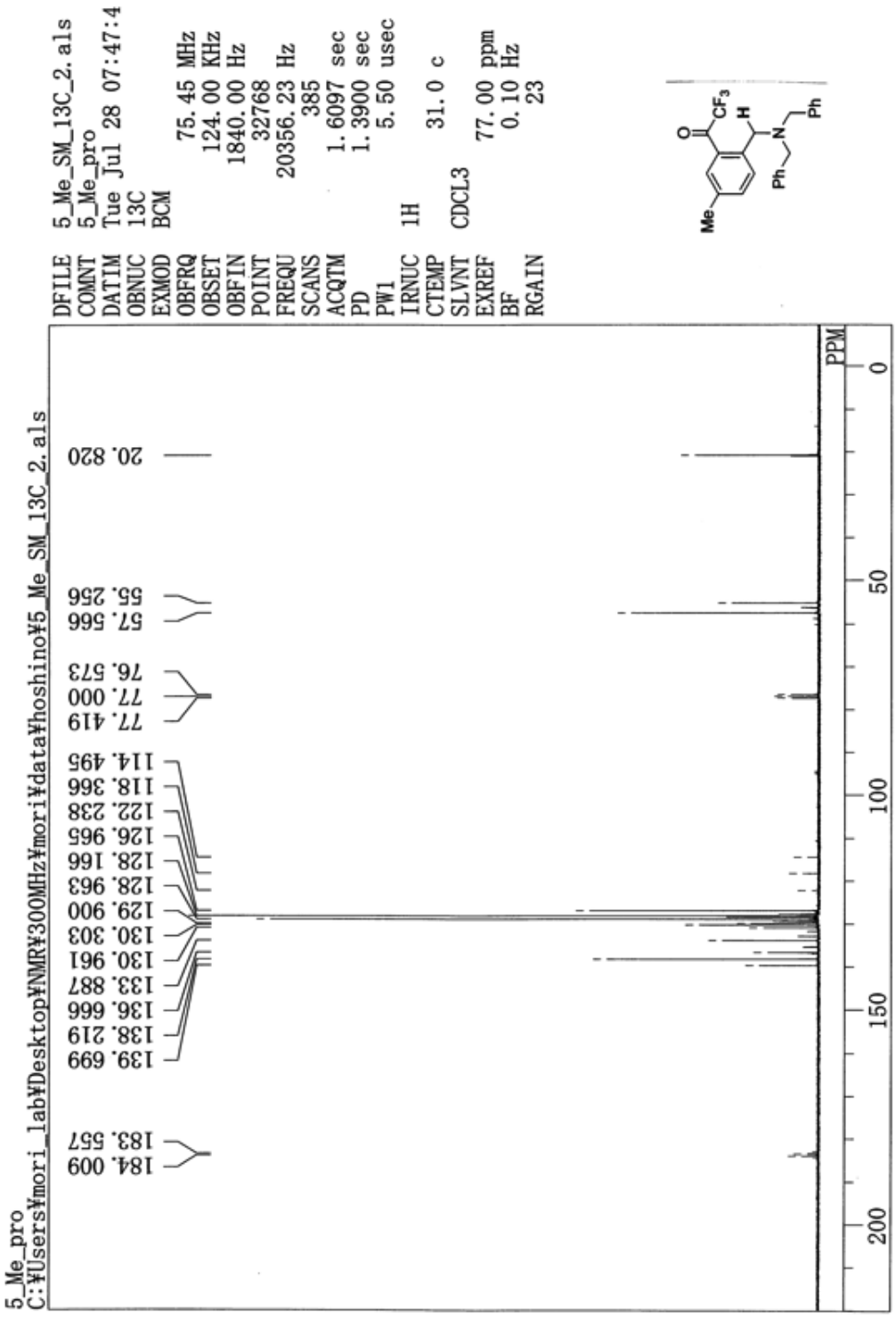
^{19}F NMR spectrum of **4a** ($CDCl_3$, 283 MHz).



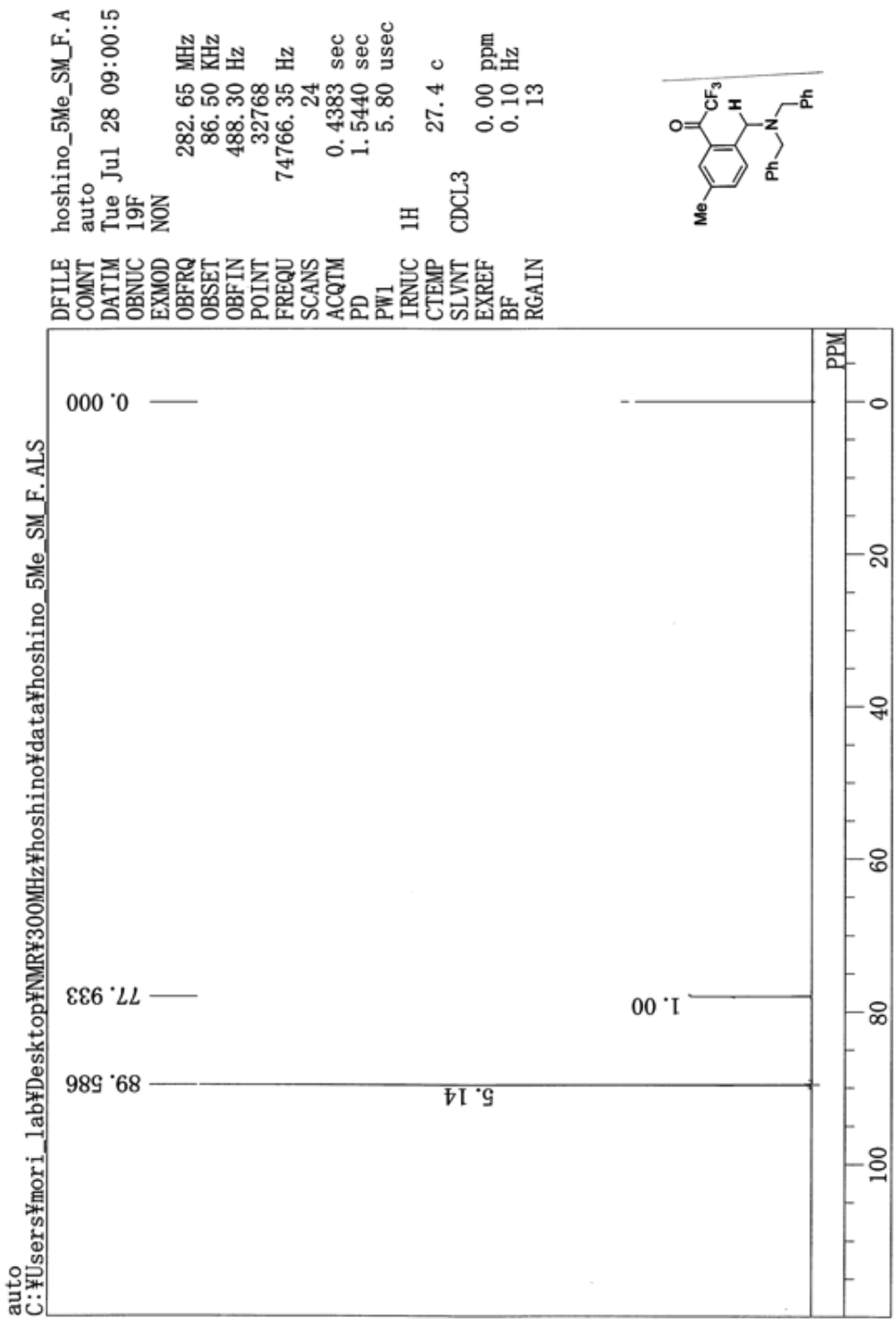
^{1}H NMR spectrum of **4g** ($CDCl_3$, 300 MHz).



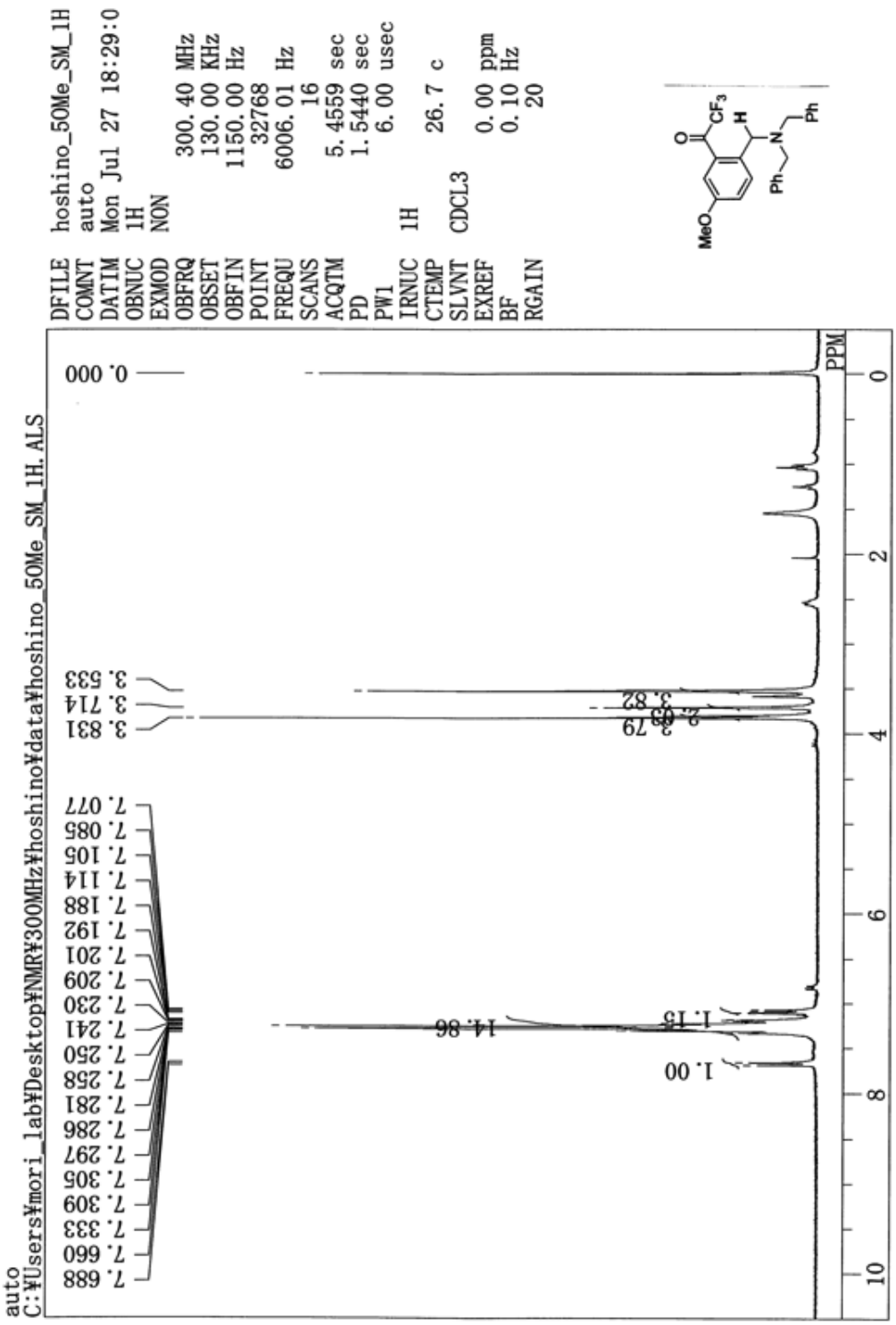
^{13}C NMR spectrum of **4g** ($CDCl_3$, 75 MHz).



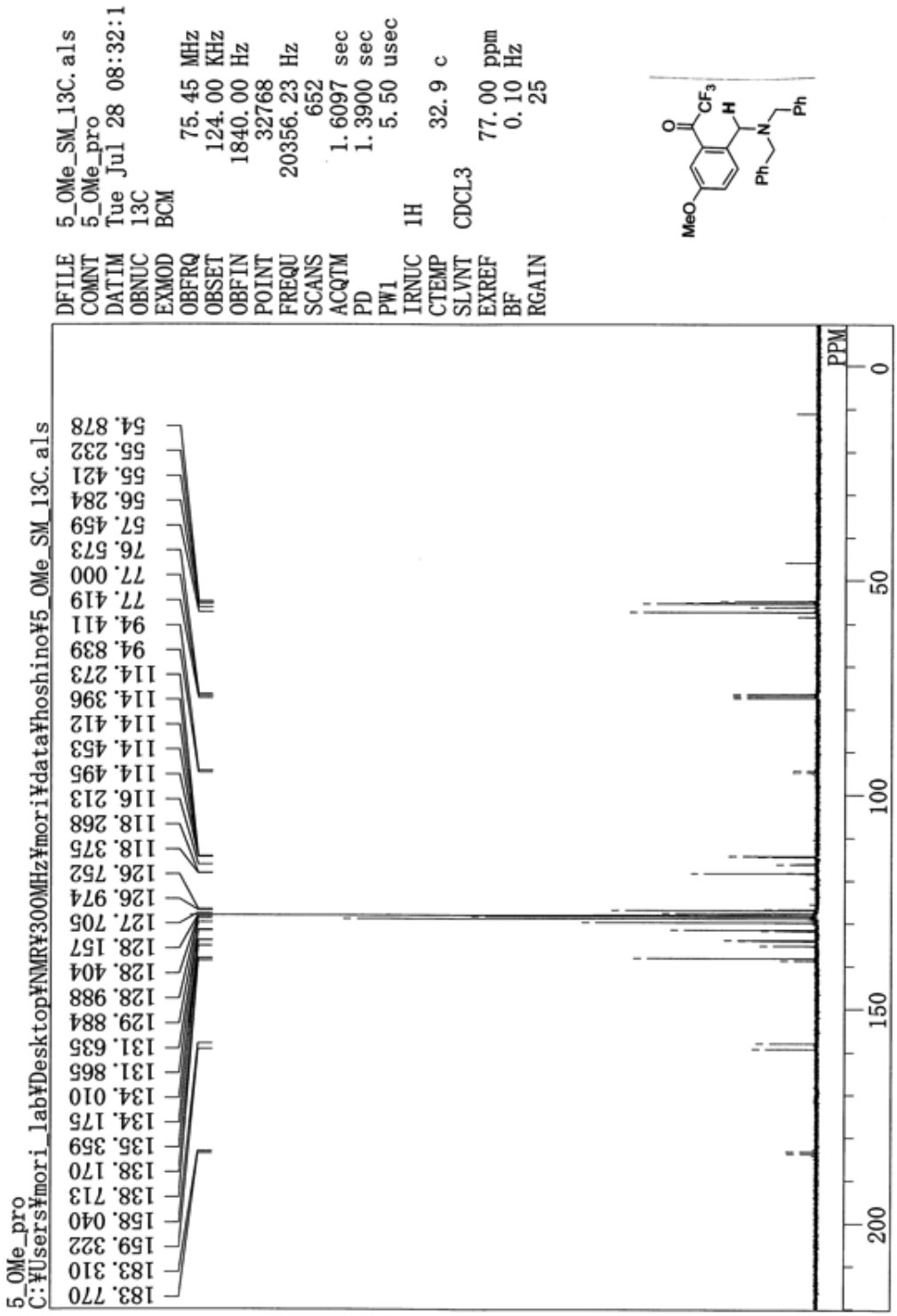
^{19}F NMR spectrum of **4g** ($CDCl_3$, 283 MHz).



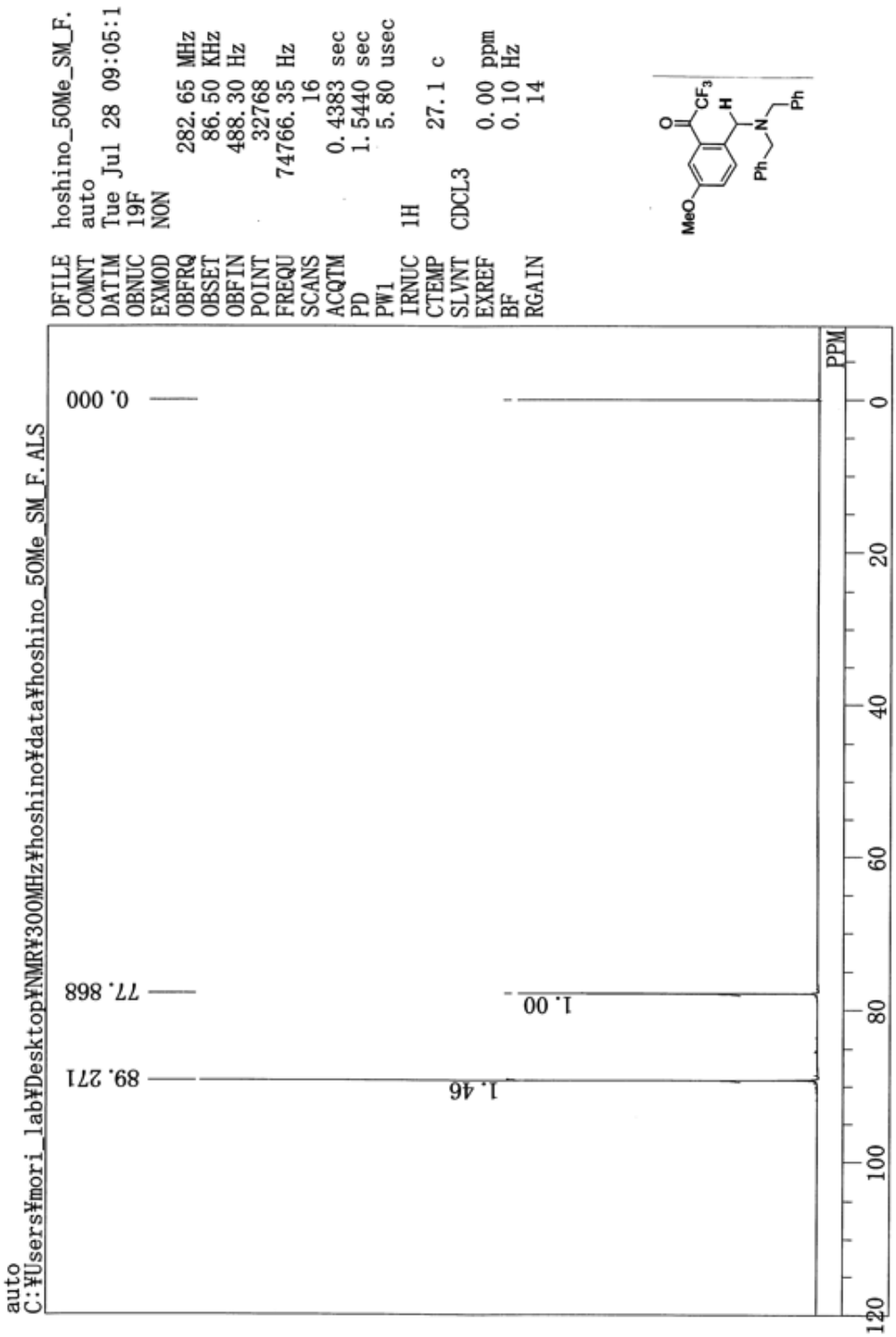
^{1}H NMR spectrum of **4h** ($CDCl_3$, 300 MHz).



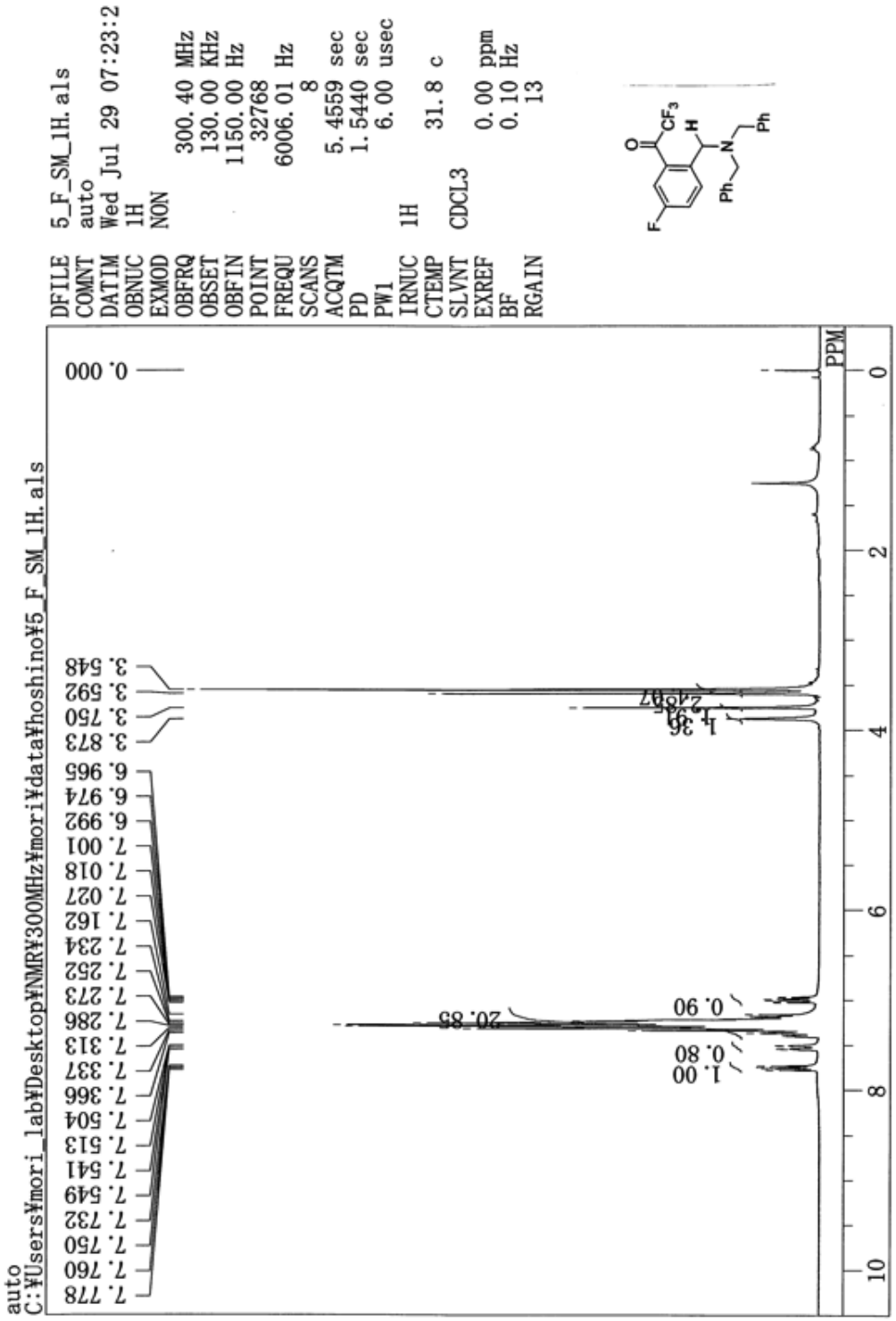
^{13}C NMR spectrum of **4h** ($CDCl_3$, 75 MHz).



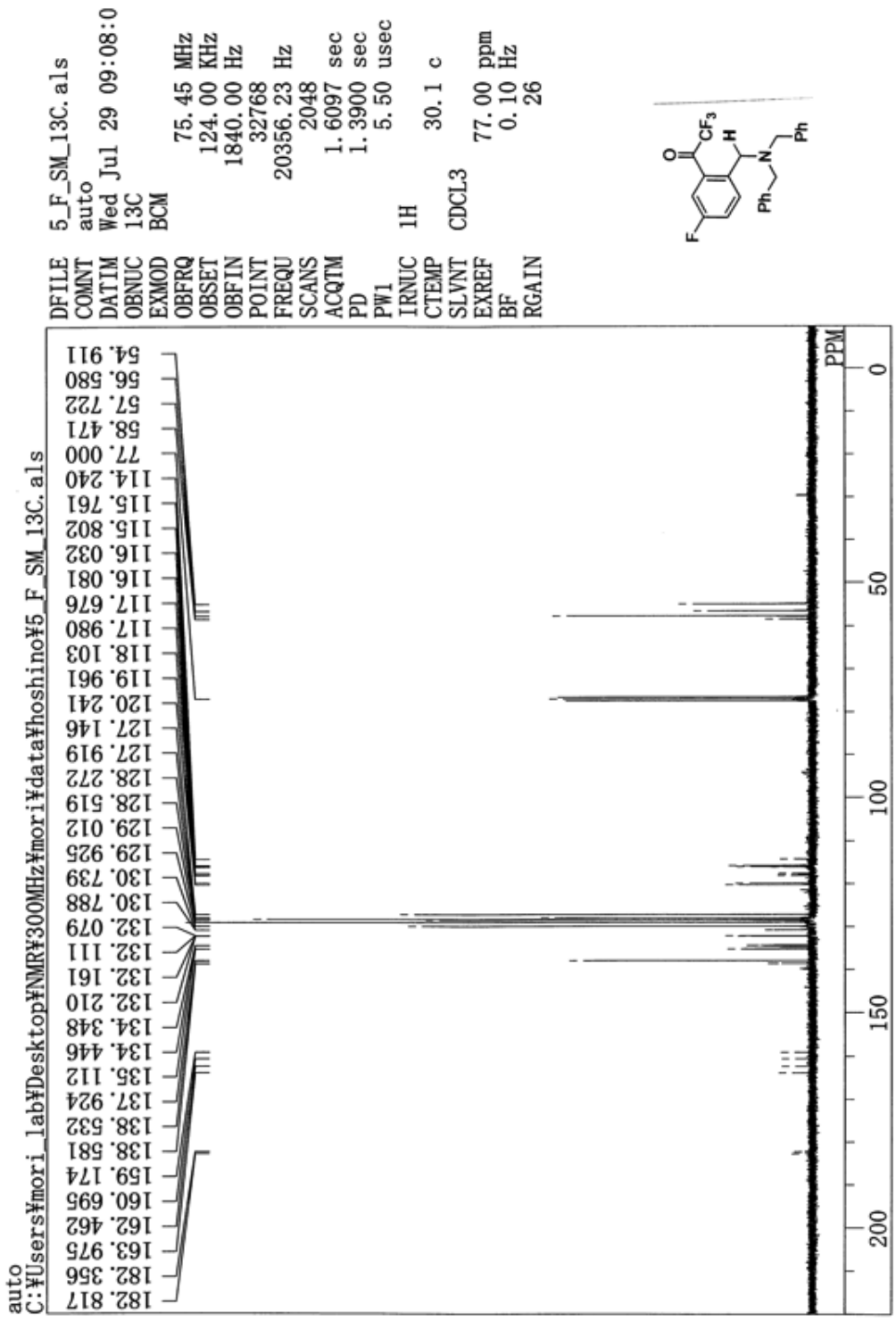
^{19}F NMR spectrum of **4h** ($CDCl_3$, 283 MHz).



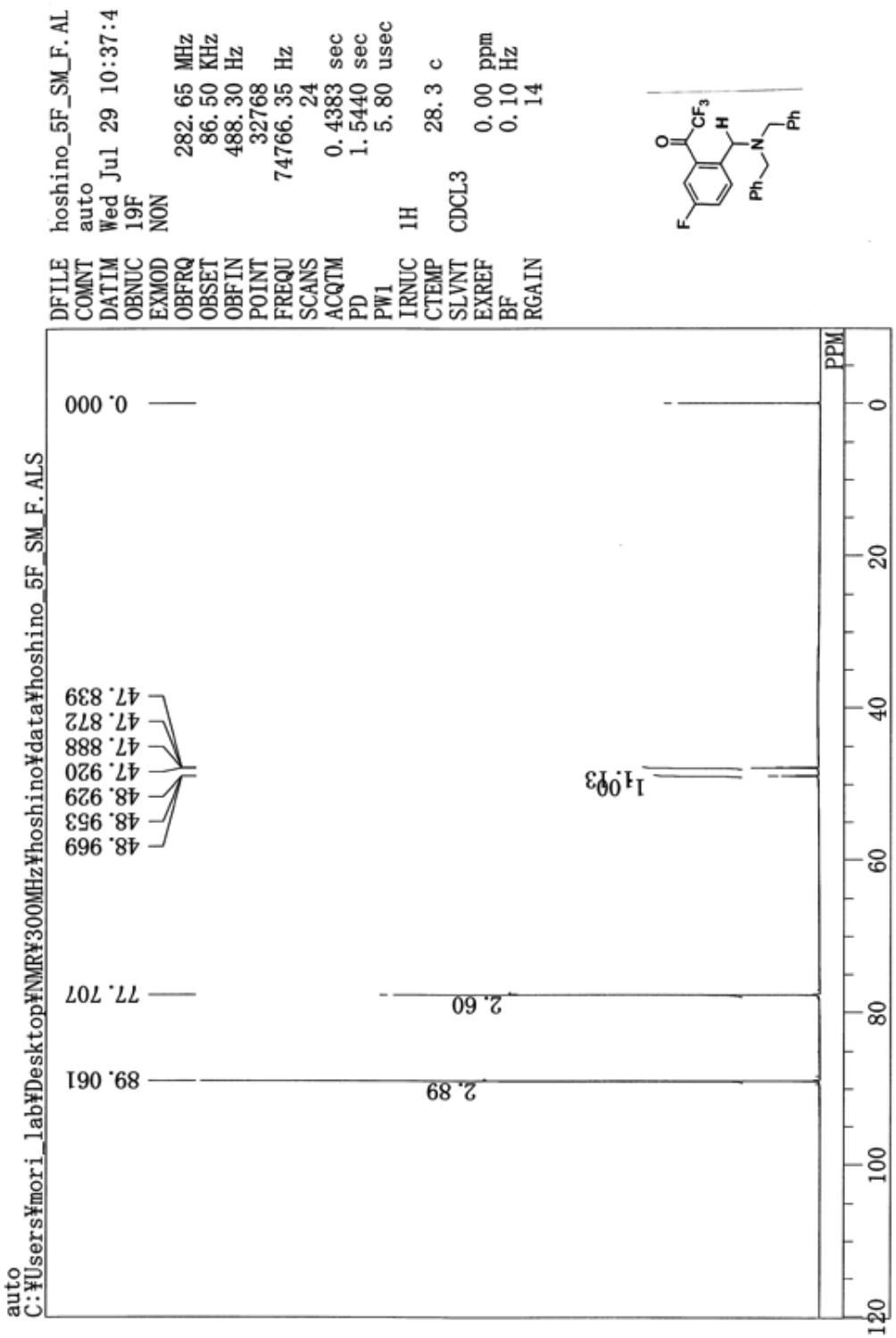
^{1}H NMR spectrum of **4i** ($CDCl_3$, 300 MHz).



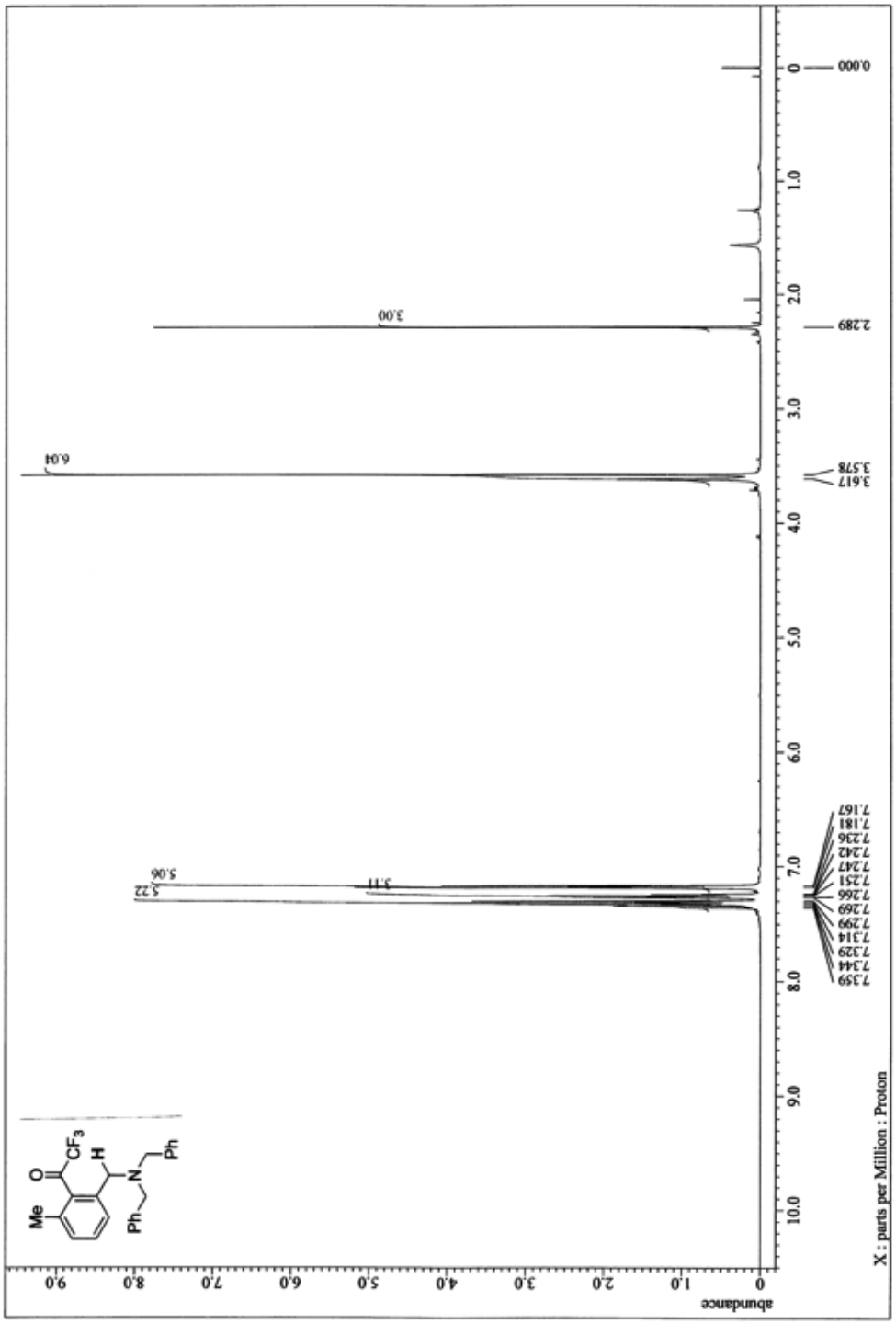
^{13}C NMR spectrum of **4i** ($CDCl_3$, 75 MHz).



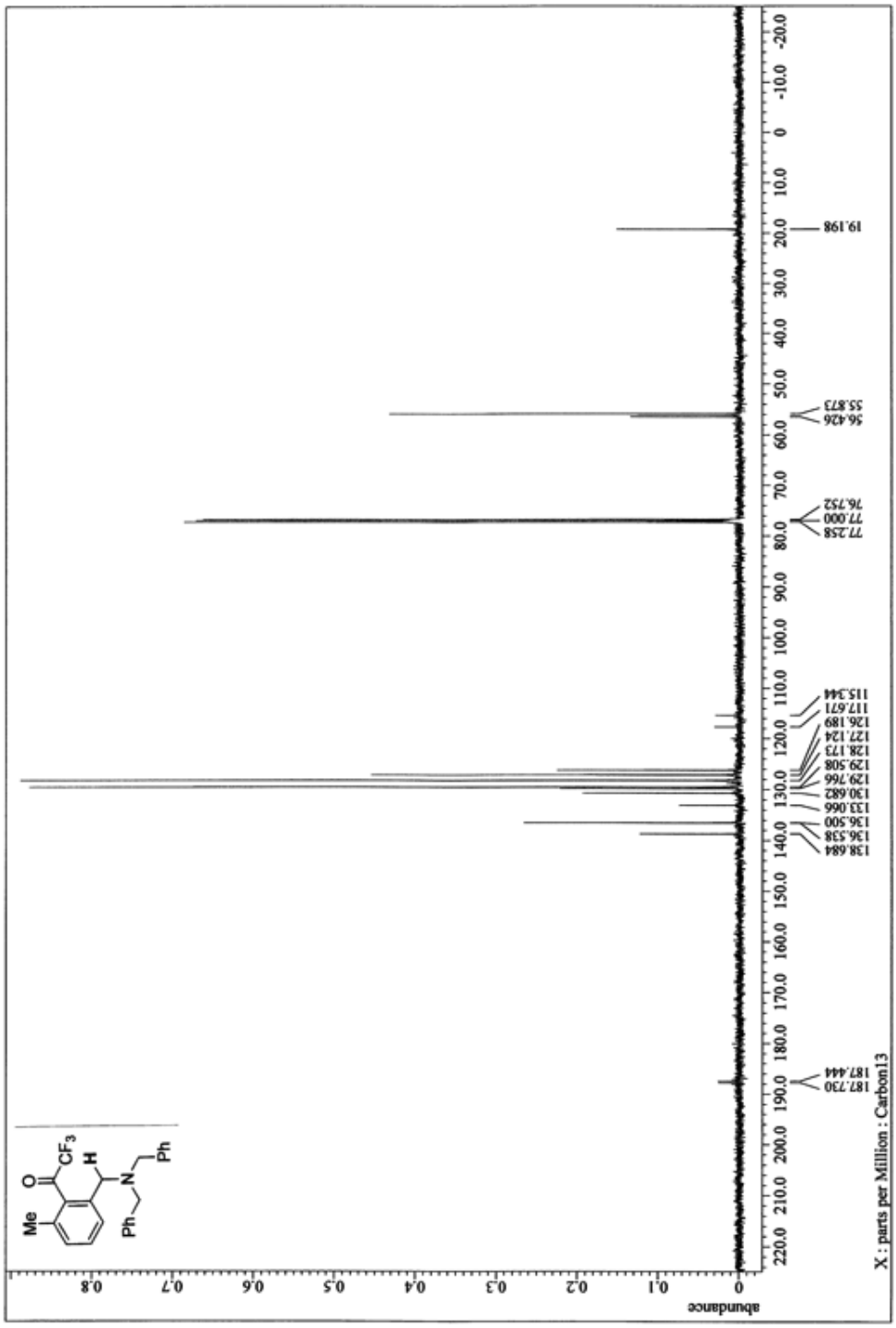
^{19}F NMR spectrum of **4i** ($CDCl_3$, 283 MHz).



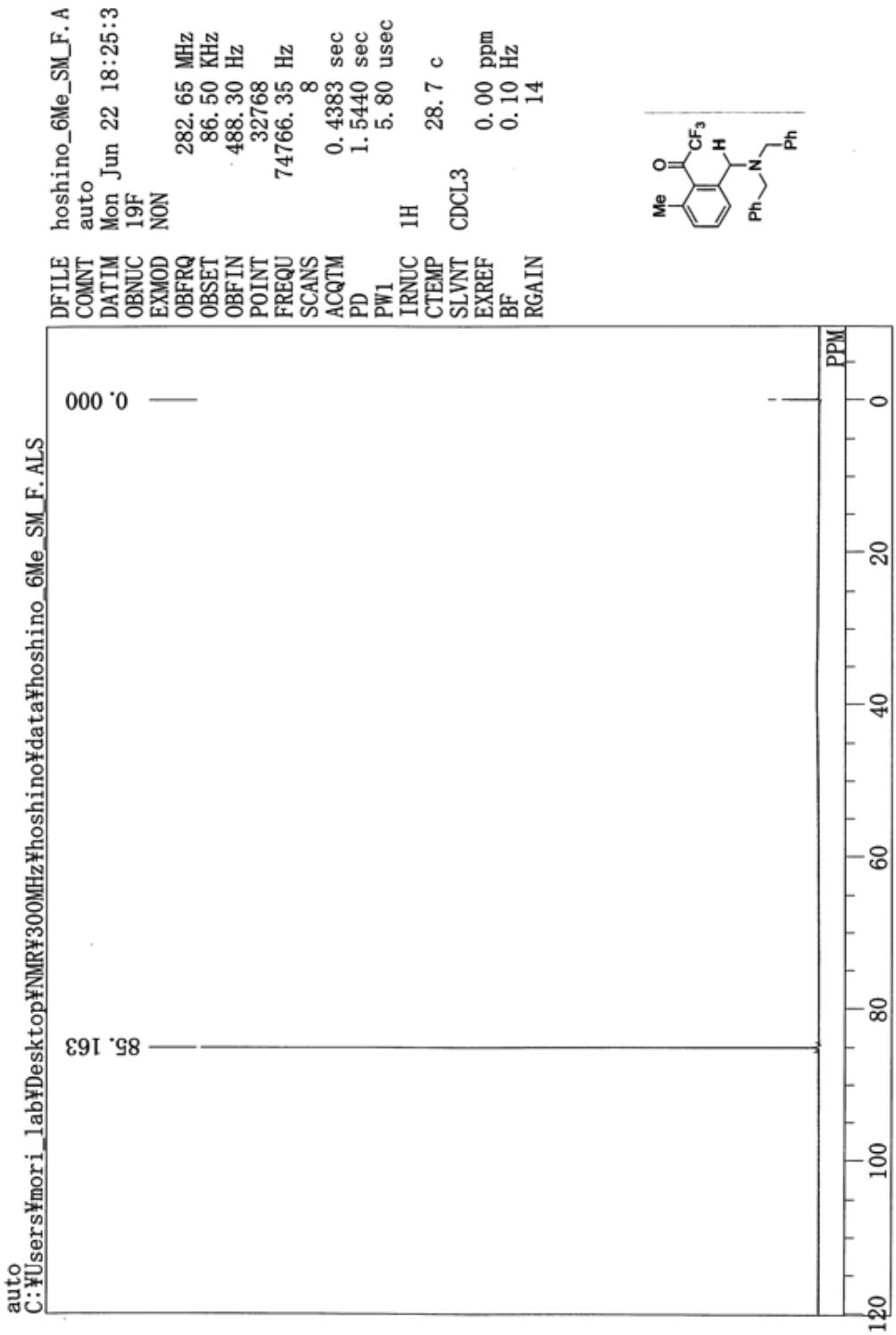
^{1}H NMR spectrum of **4j** ($CDCl_3$, 500 MHz).



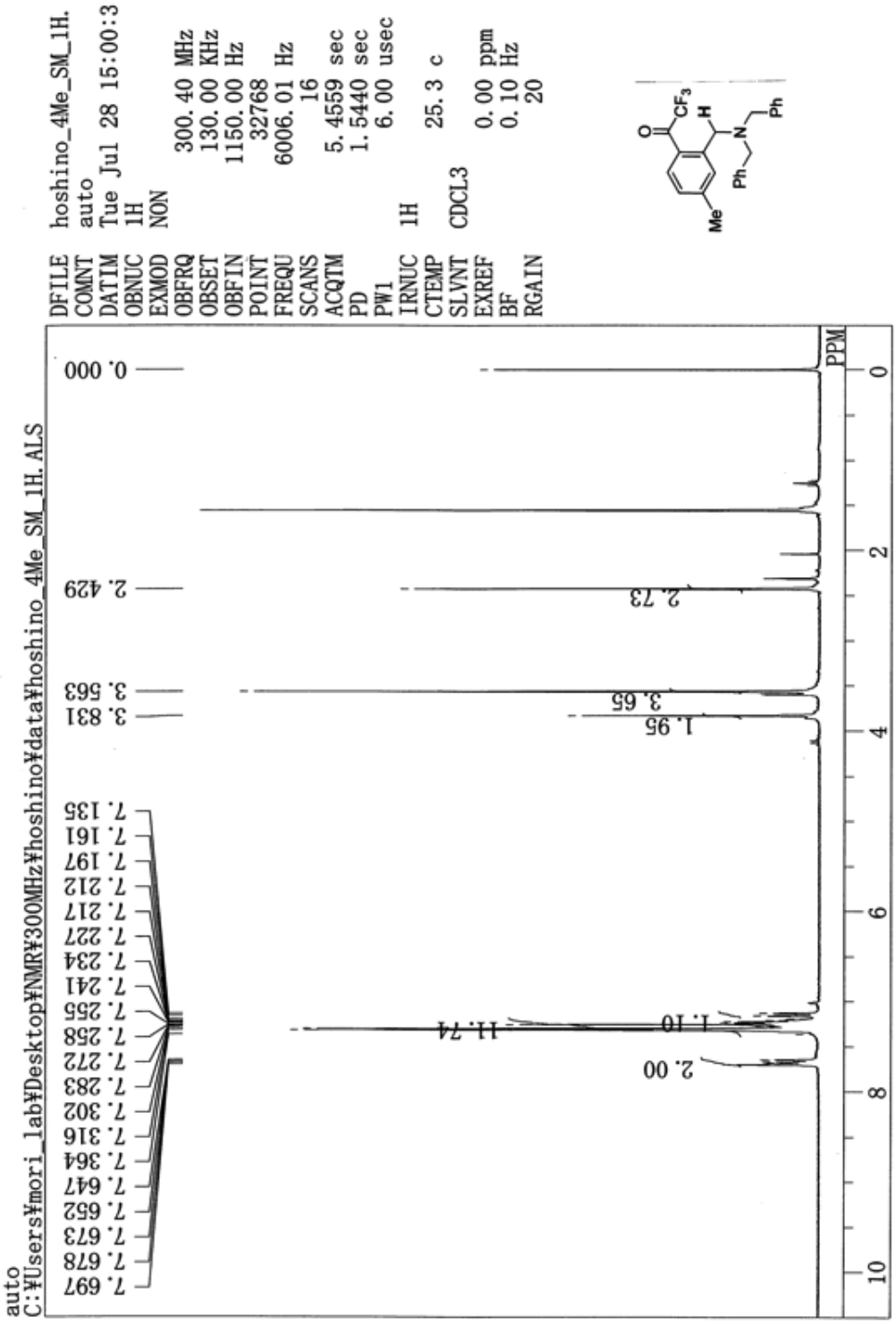
^{13}C NMR spectrum of **4j** ($CDCl_3$, 125 MHz).



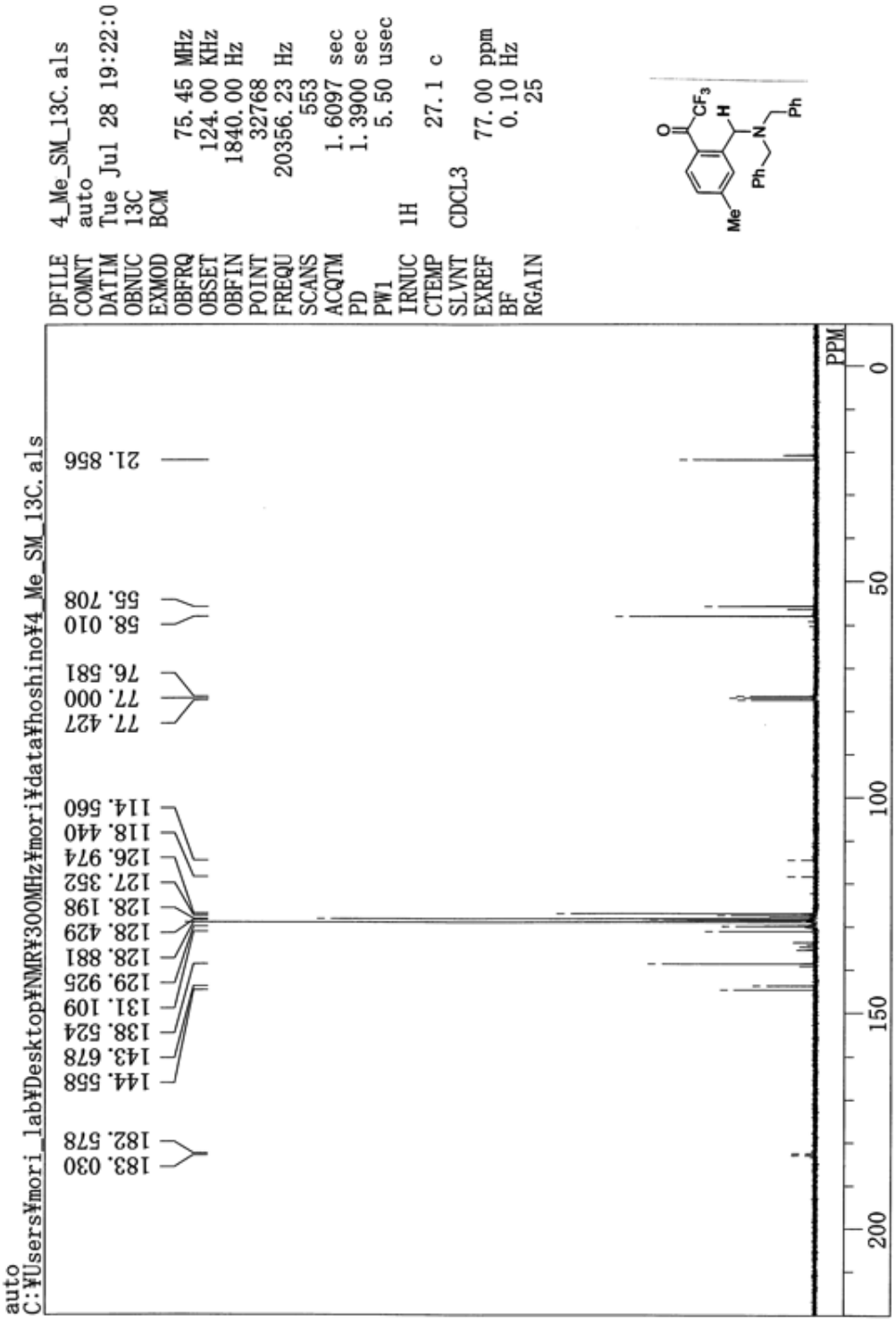
^{19}F NMR spectrum of **4j** ($CDCl_3$, 283 MHz).



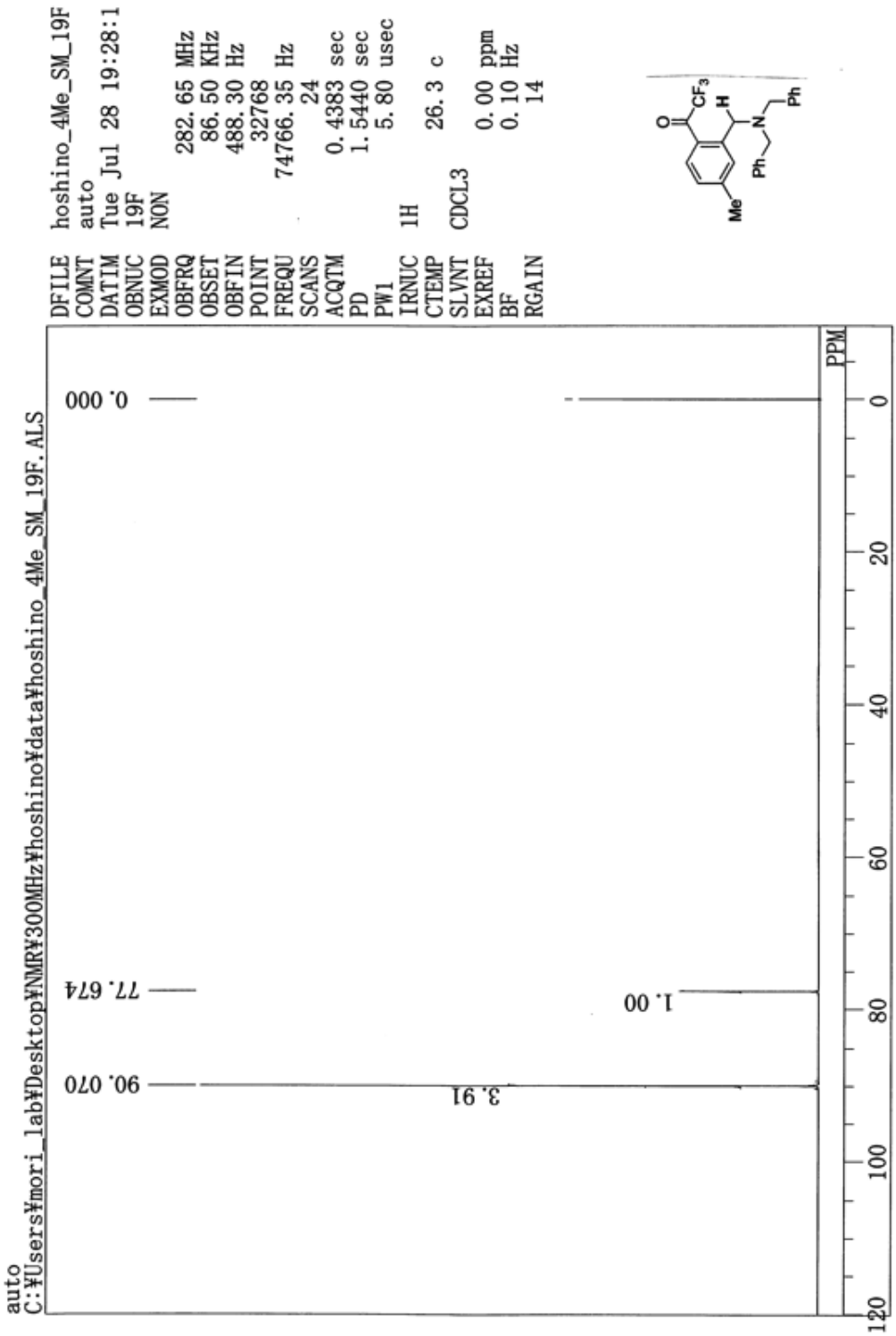
^{1}H NMR spectrum of **4k** ($CDCl_3$, 300 MHz).



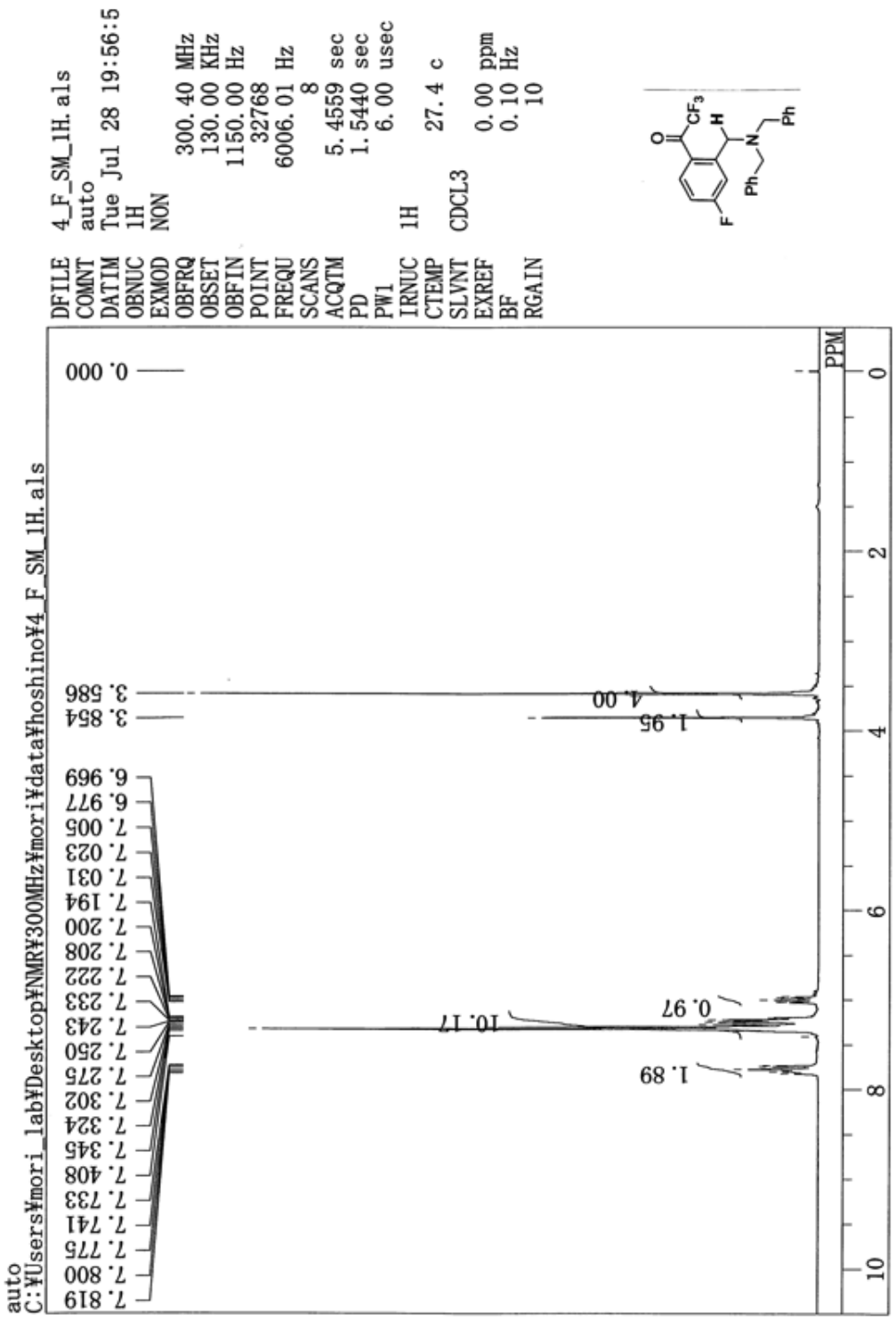
^{13}C NMR spectrum of **4k** ($CDCl_3$, 75 MHz).



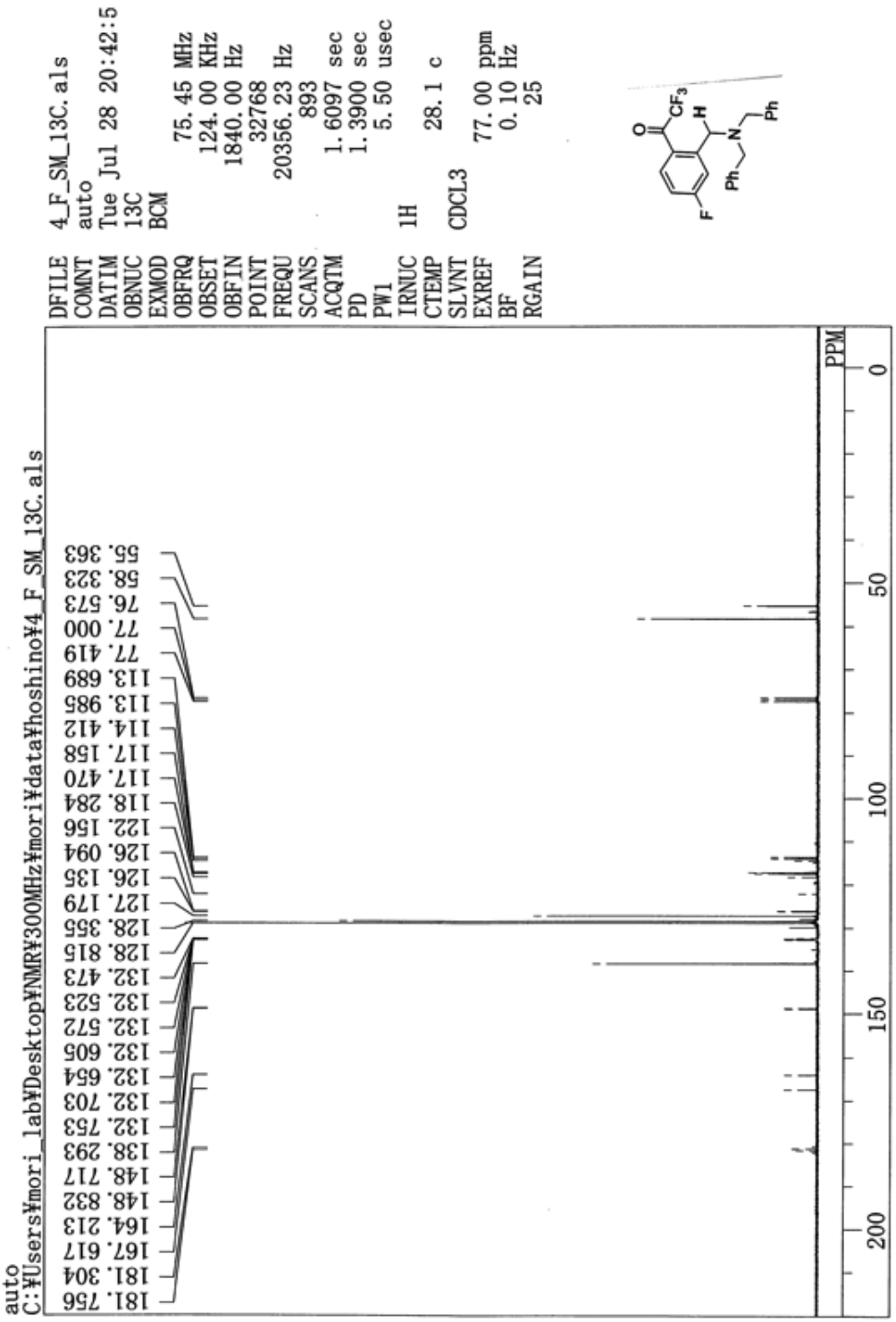
^{19}F NMR spectrum of **4k** ($CDCl_3$, 283 MHz).



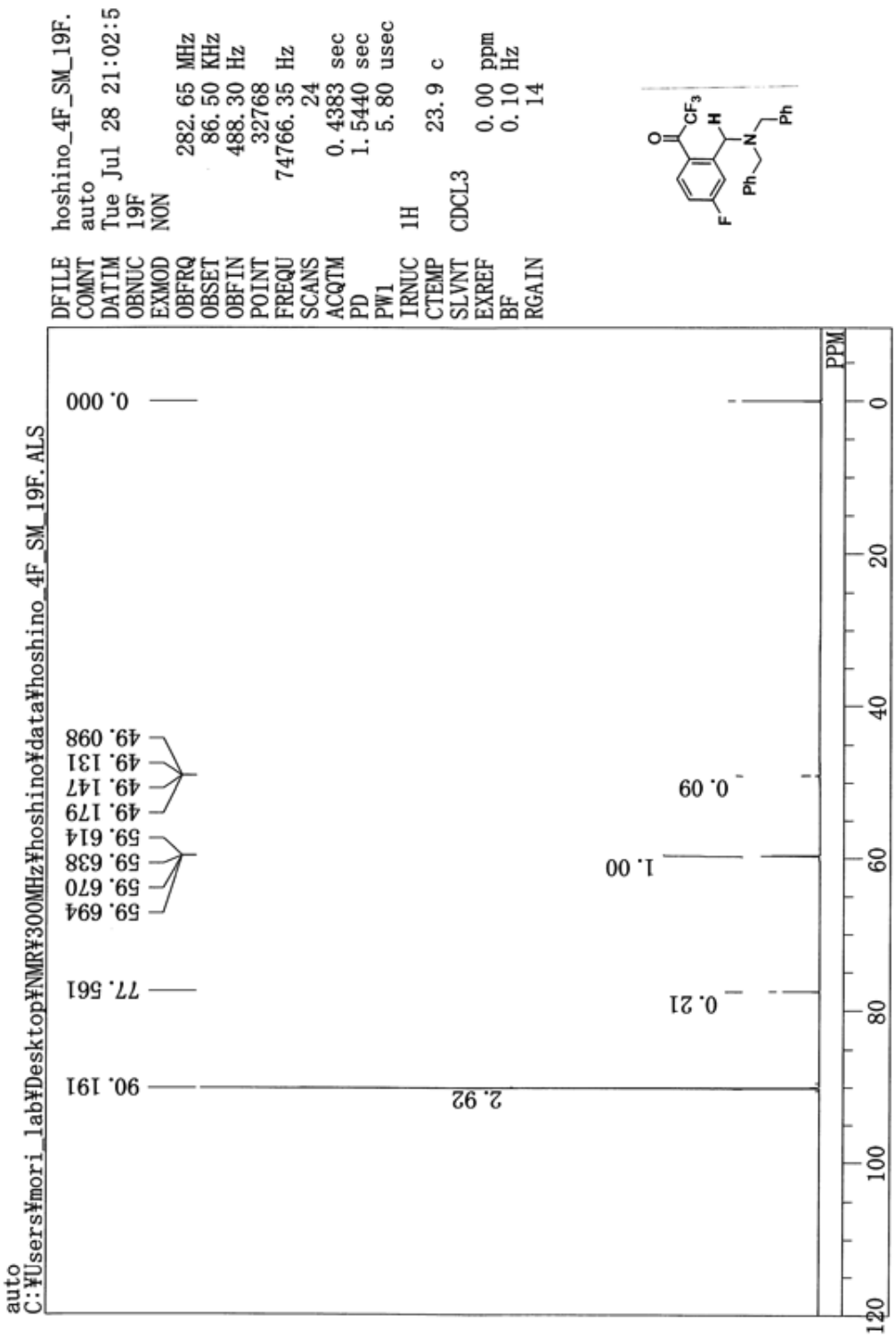
^{1}H NMR spectrum of **4** ($CDCl_3$, 300 MHz).



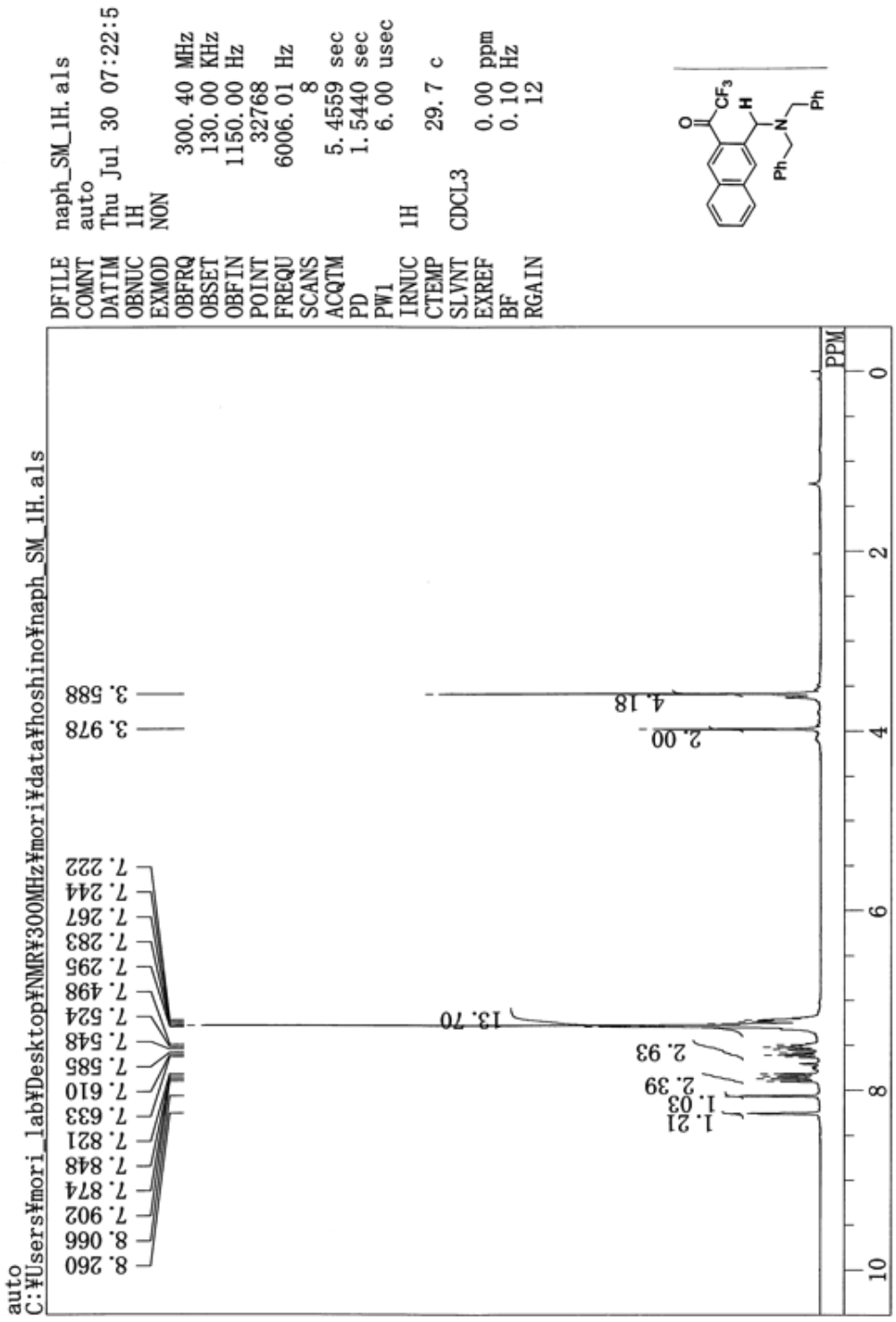
^{13}C NMR spectrum of **4l** ($CDCl_3$, 75 MHz).



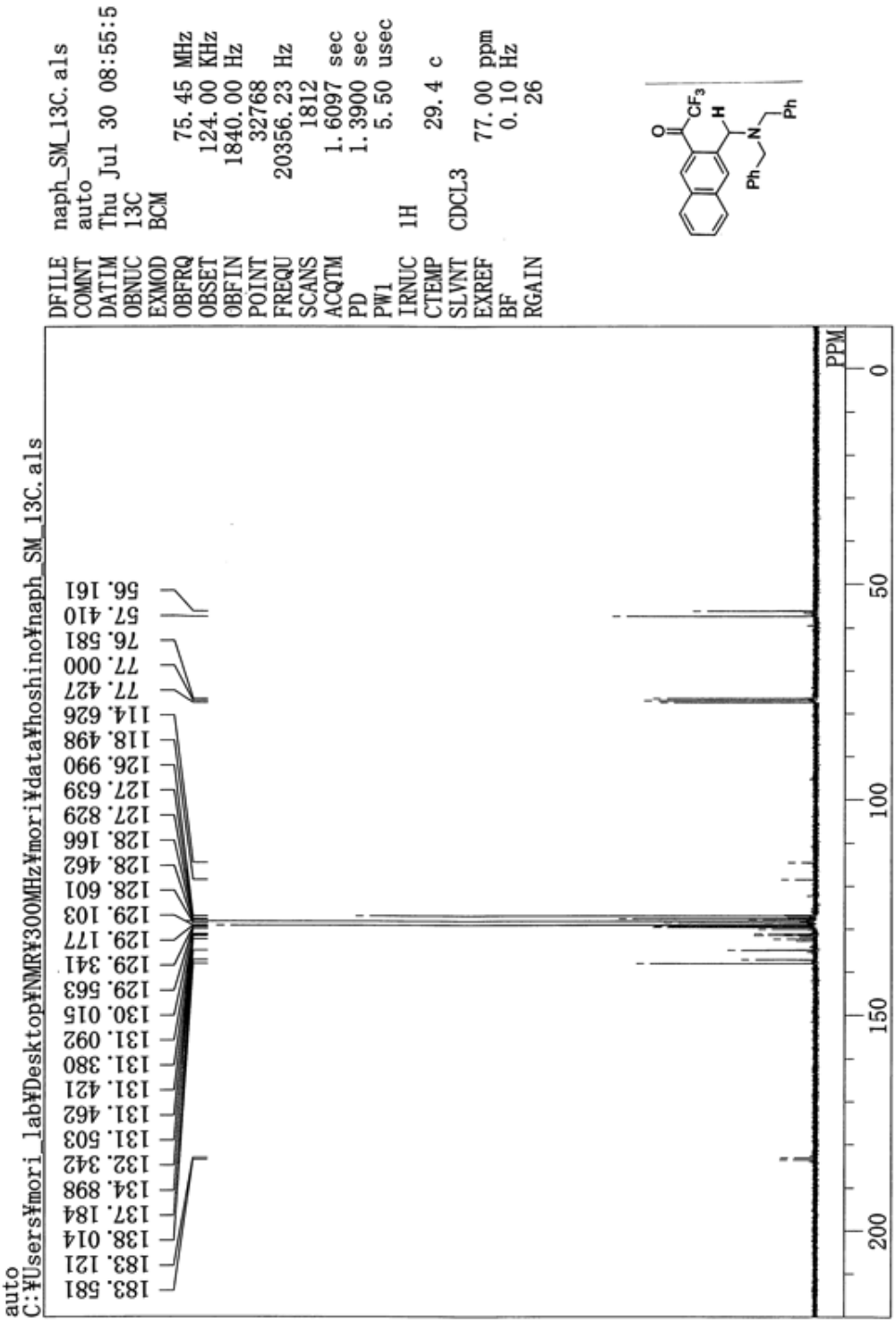
^{19}F NMR spectrum of **4l** ($CDCl_3$, 283 MHz).



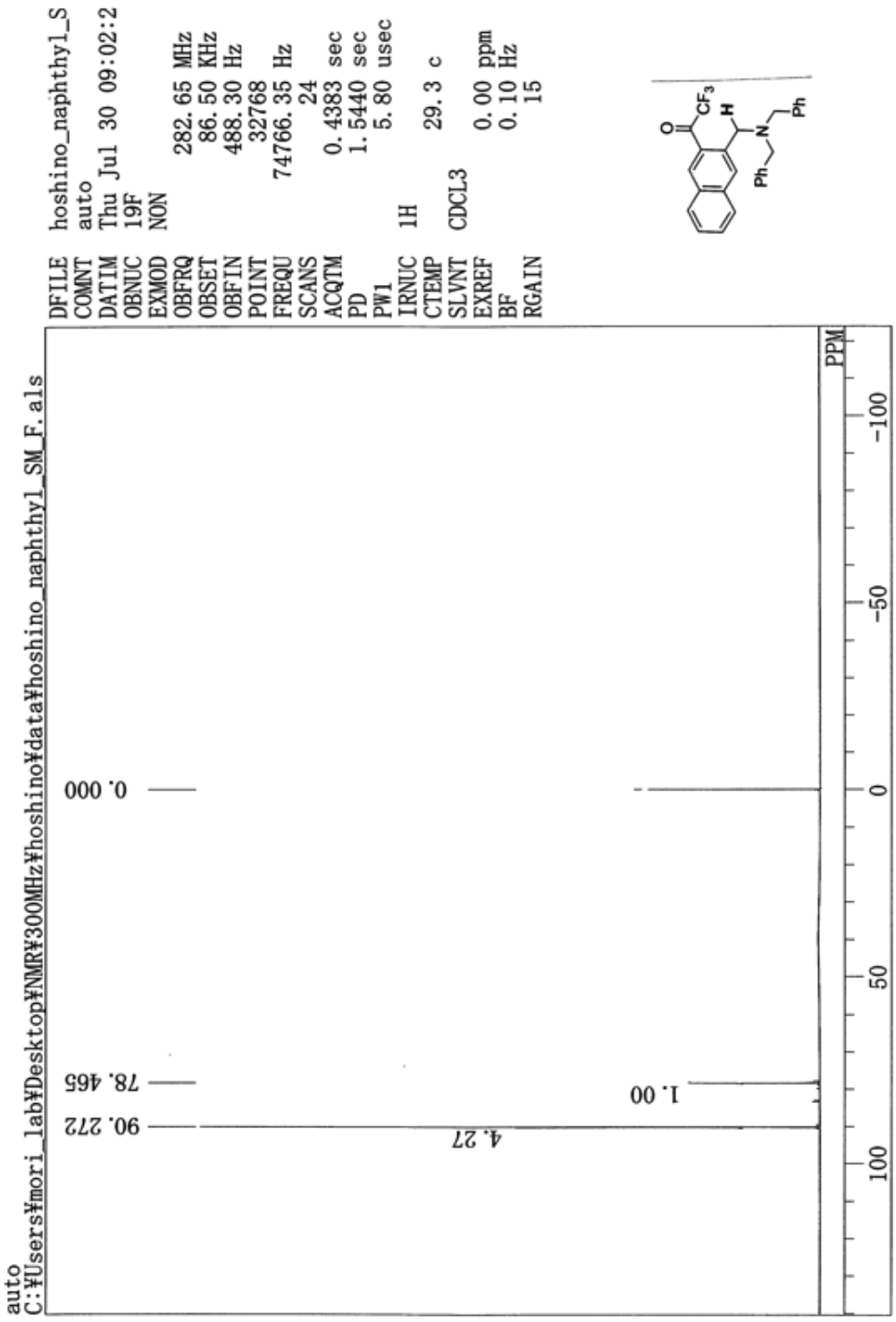
^{1}H NMR spectrum of **4m** ($CDCl_3$, 300 MHz).



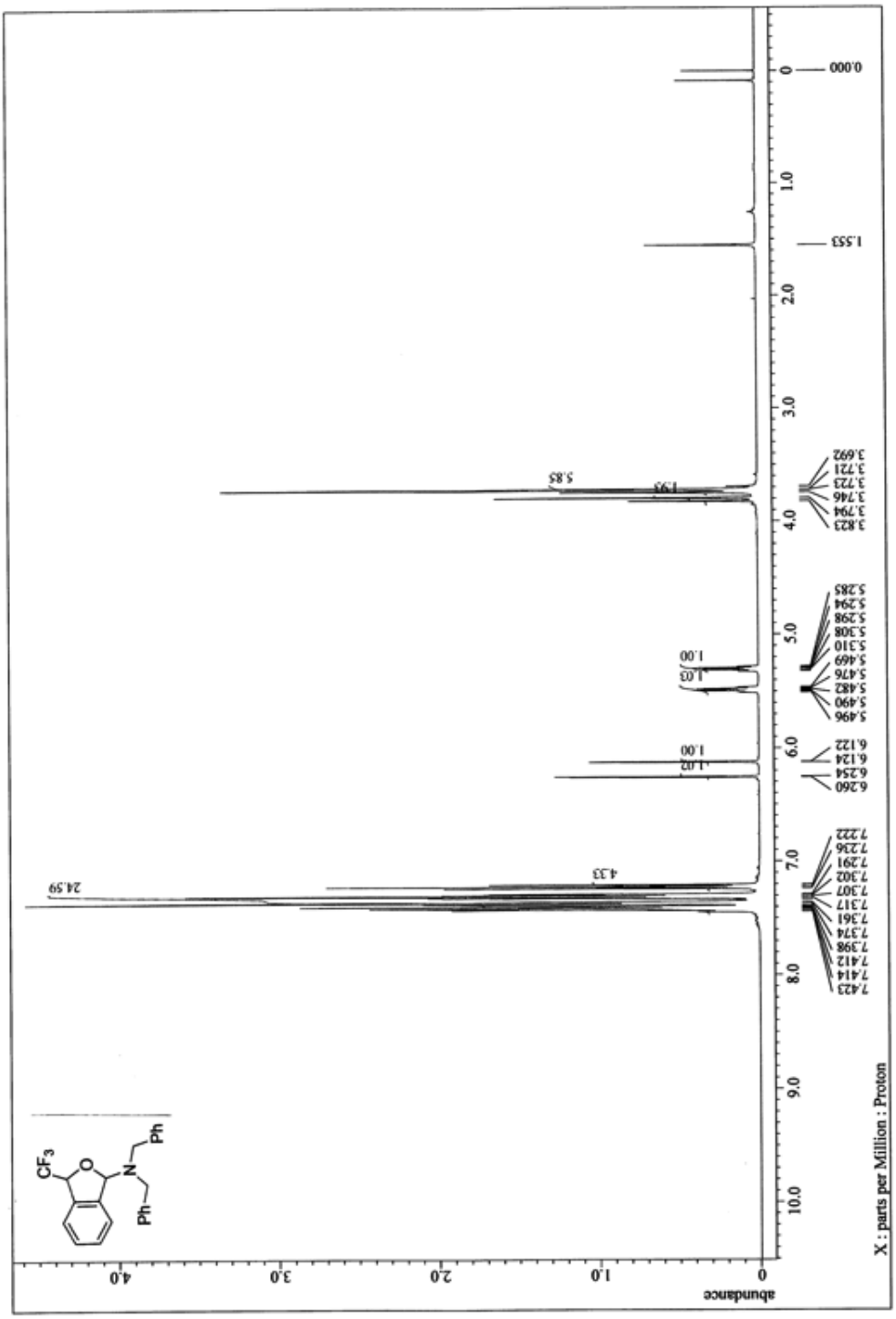
^{13}C NMR spectrum of **4m** ($CDCl_3$, 75 MHz).



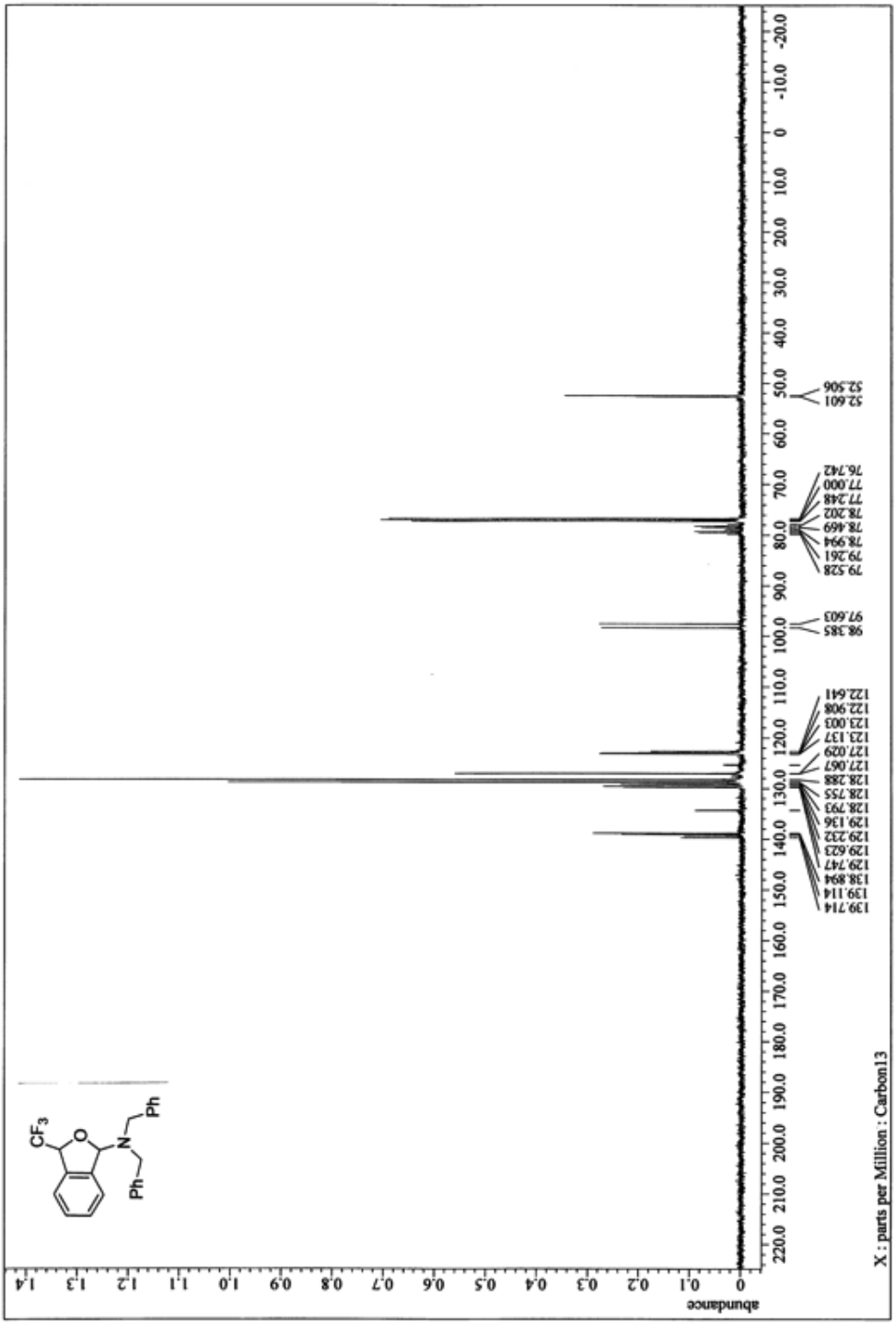
^{19}F NMR spectrum of **4m** ($CDCl_3$, 283 MHz).



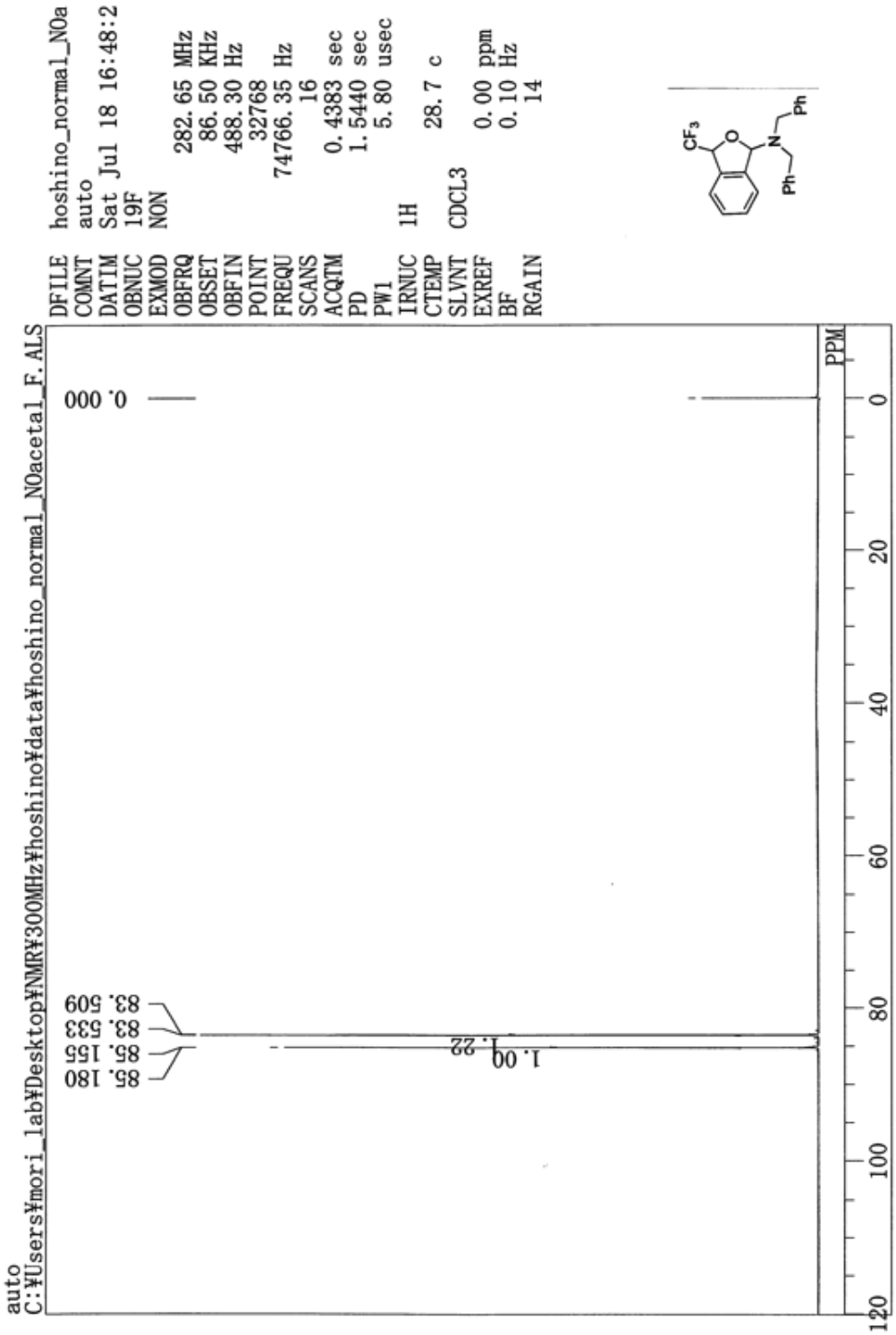
^{1}H NMR spectrum of **5a** ($CDCl_3$, 500 MHz).



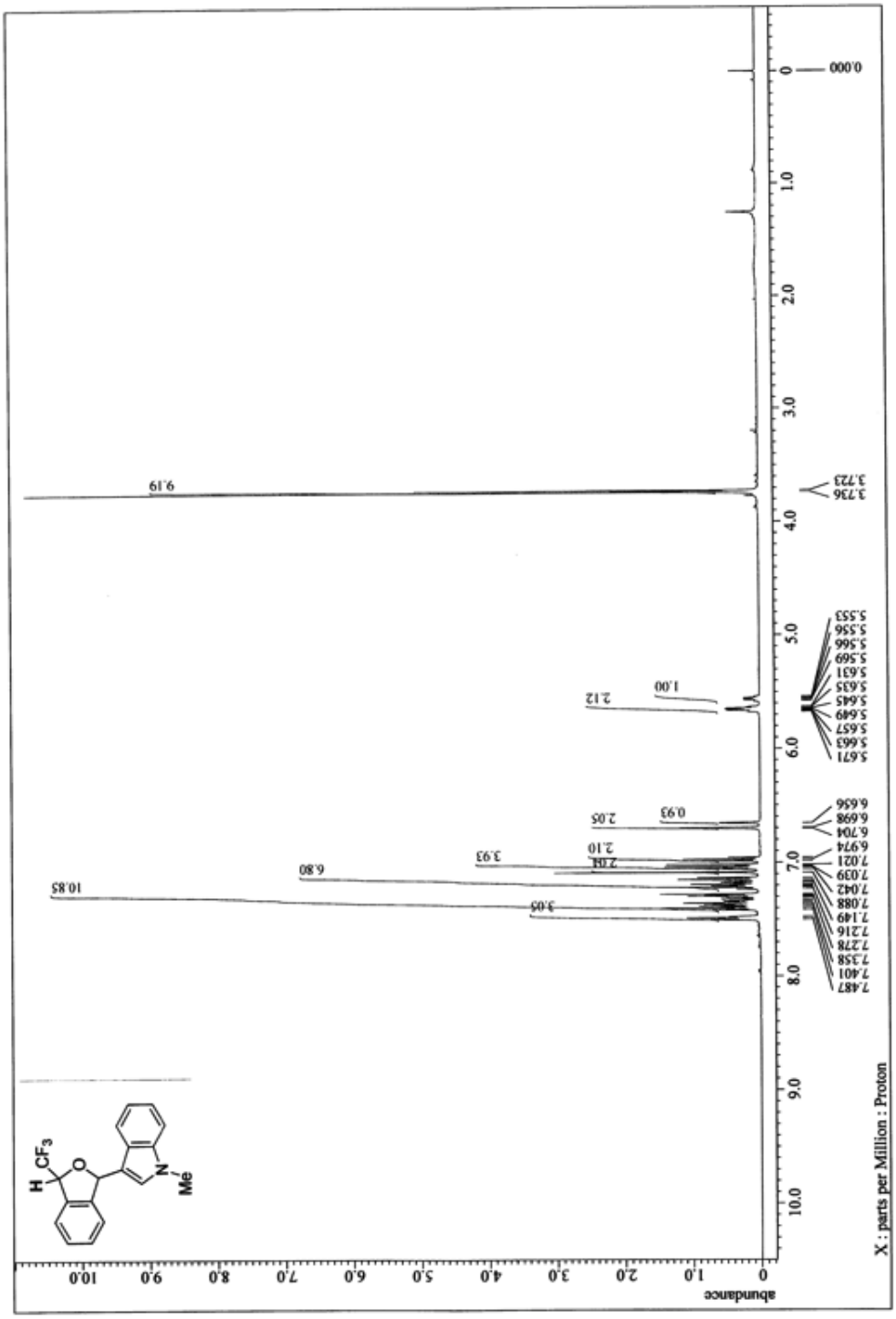
^{13}C NMR spectrum of **5a** ($CDCl_3$, 125 MHz).



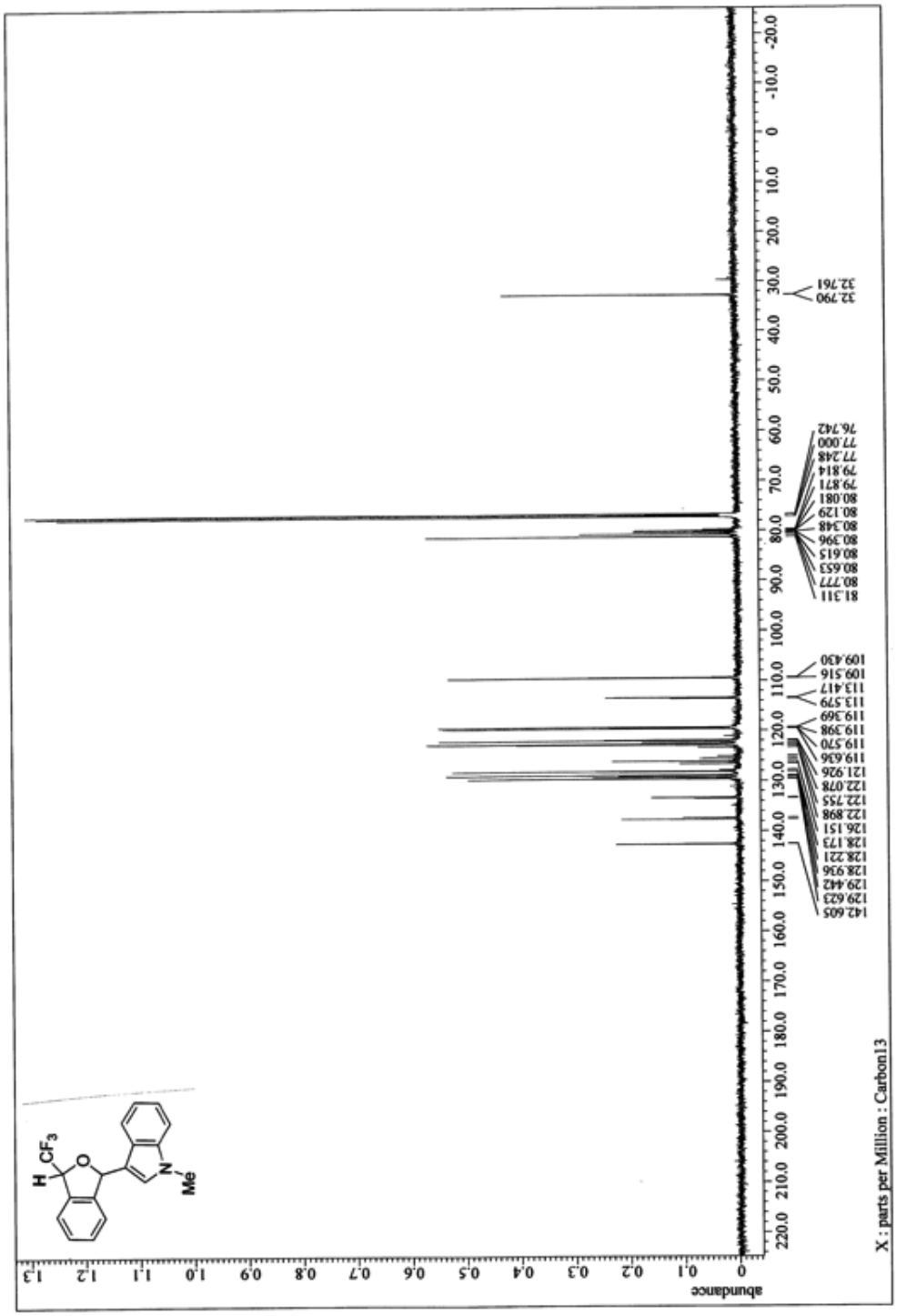
^{19}F NMR spectrum of **5a** ($CDCl_3$, 283 MHz).



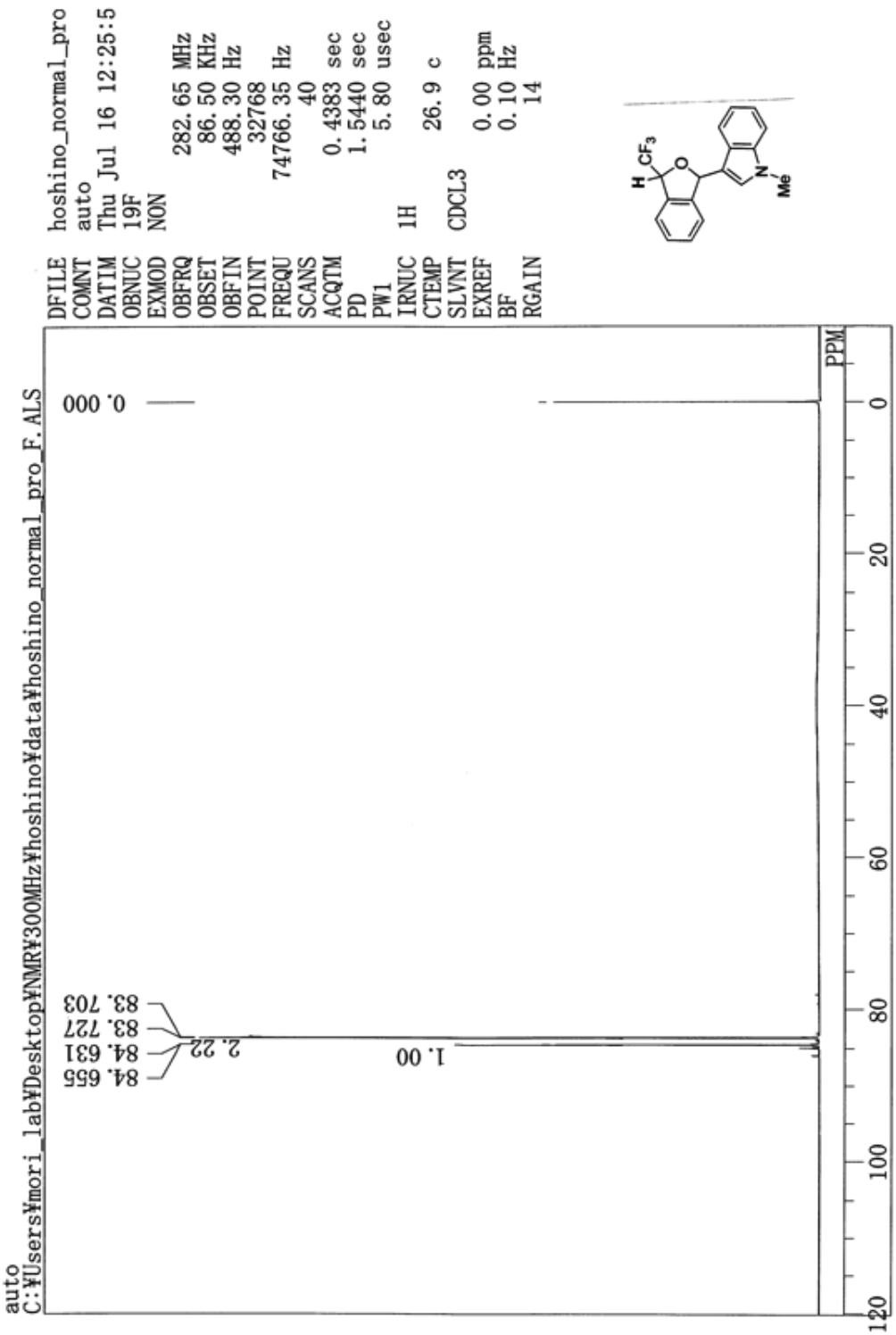
^{1}H NMR spectrum of **10a** ($CDCl_3$, 500 MHz).



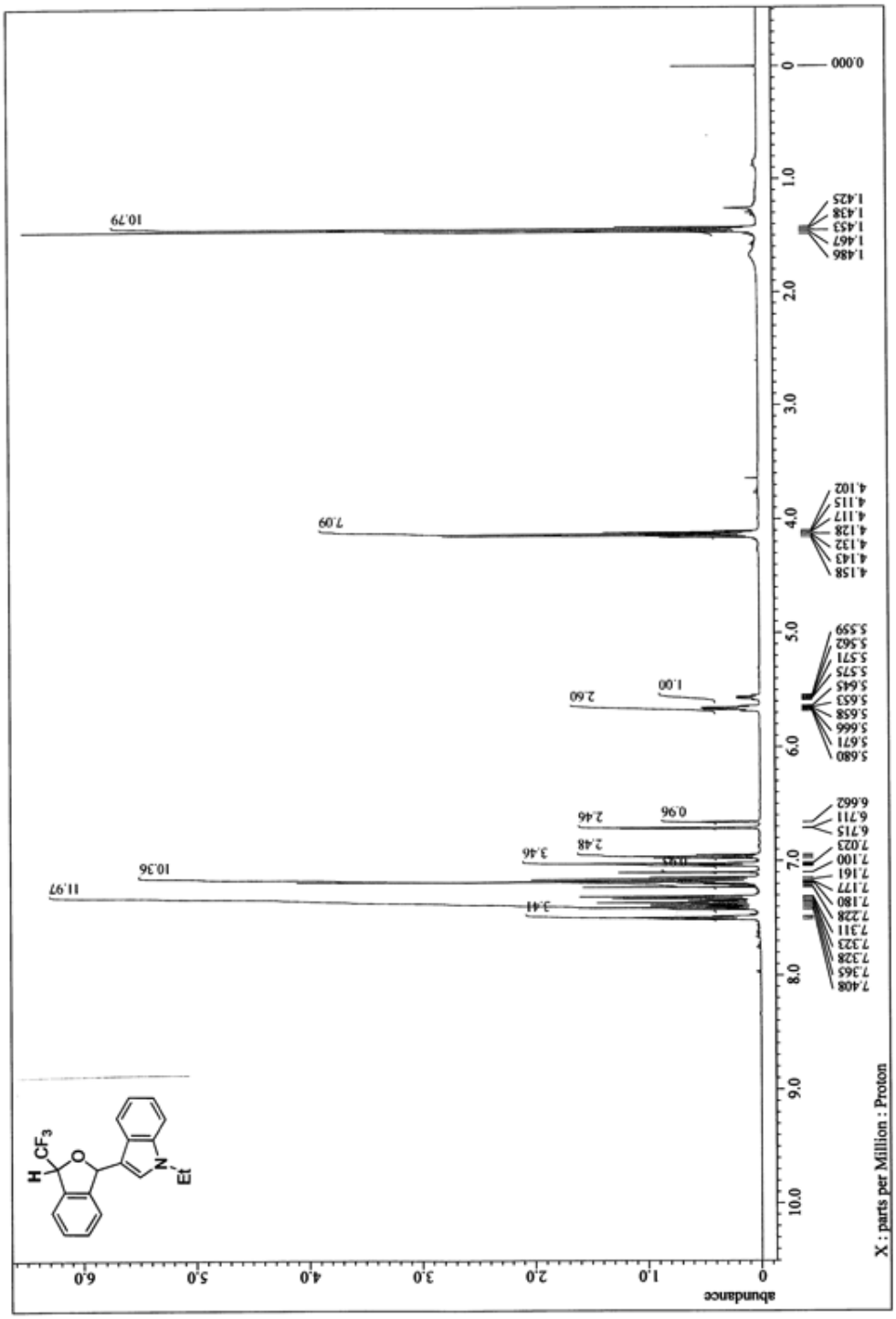
^{13}C NMR spectrum of **10a** ($CDCl_3$, 125 MHz).



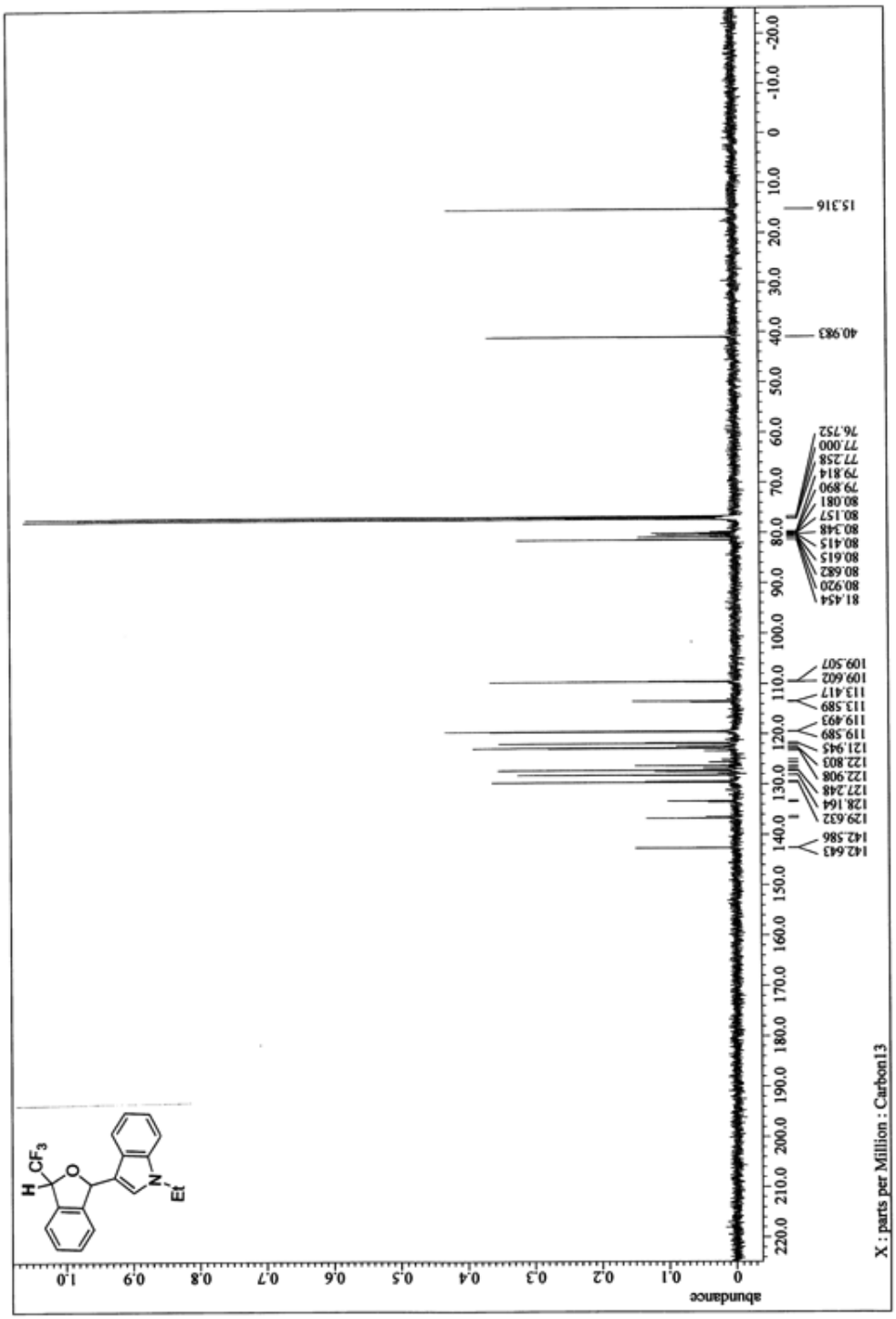
^{19}F NMR spectrum of **10a** ($CDCl_3$, 283 MHz).



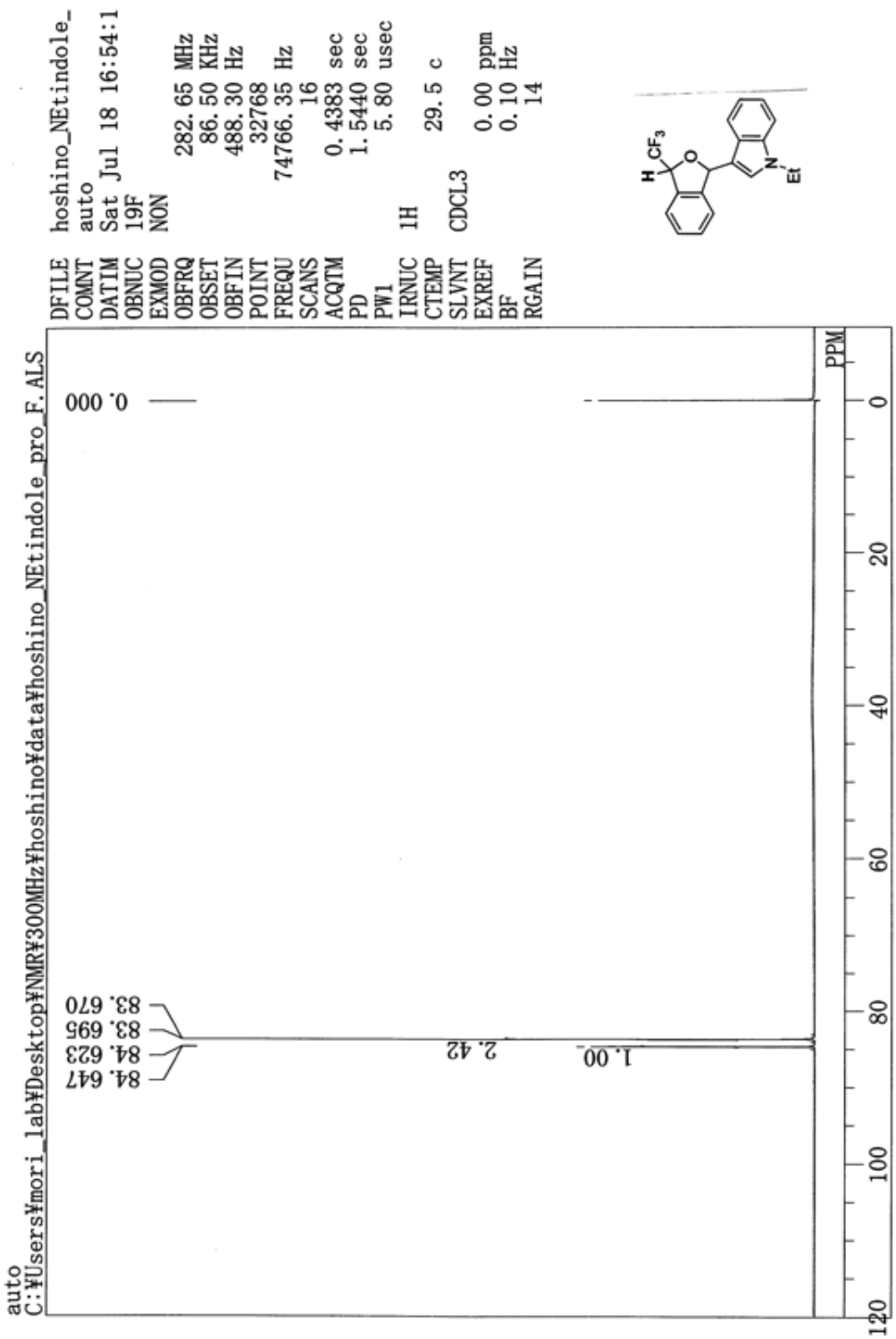
^{1}H NMR spectrum of **10b** ($CDCl_3$, 500 MHz).



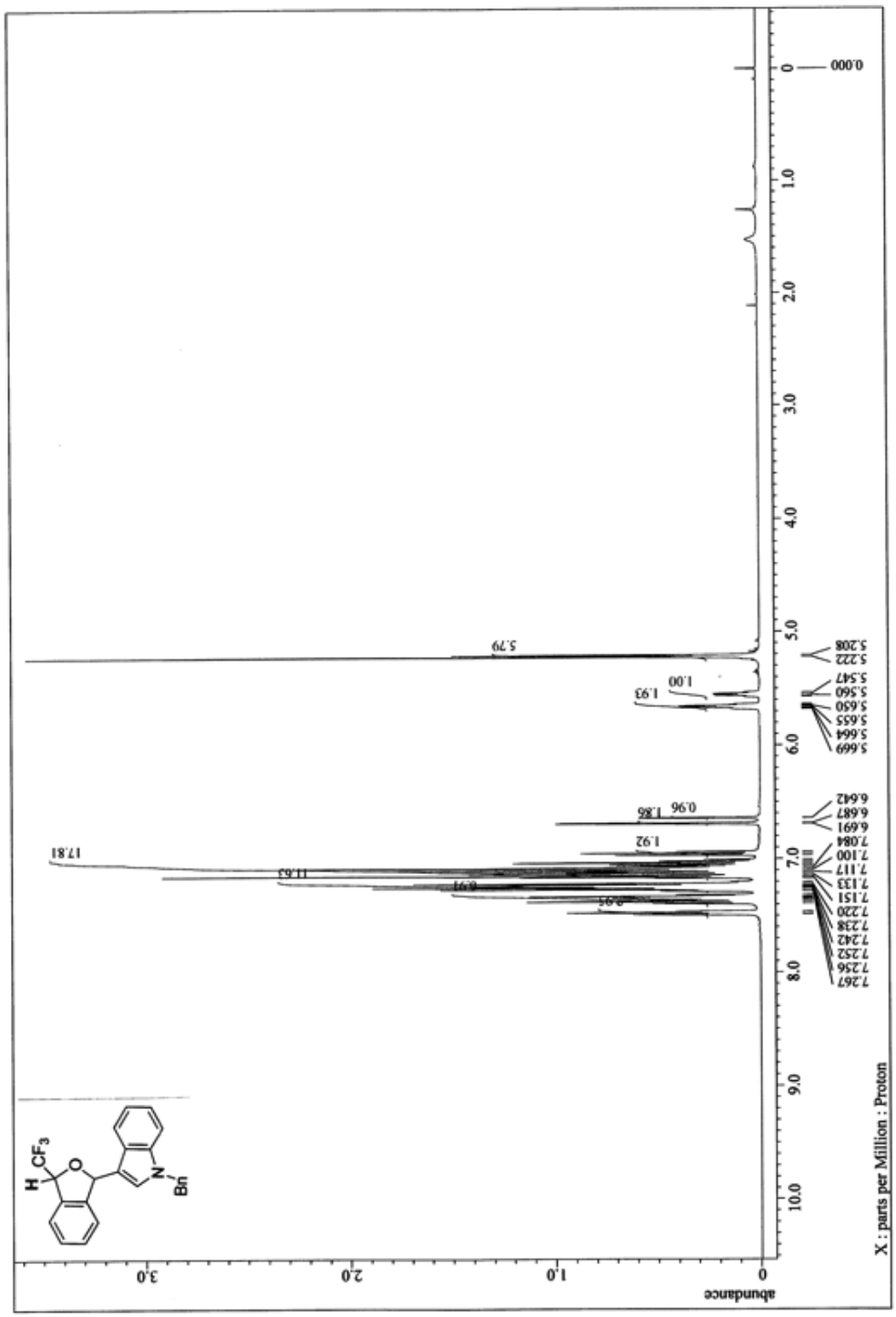
^{13}C NMR spectrum of **10b** ($CDCl_3$, 125 MHz).



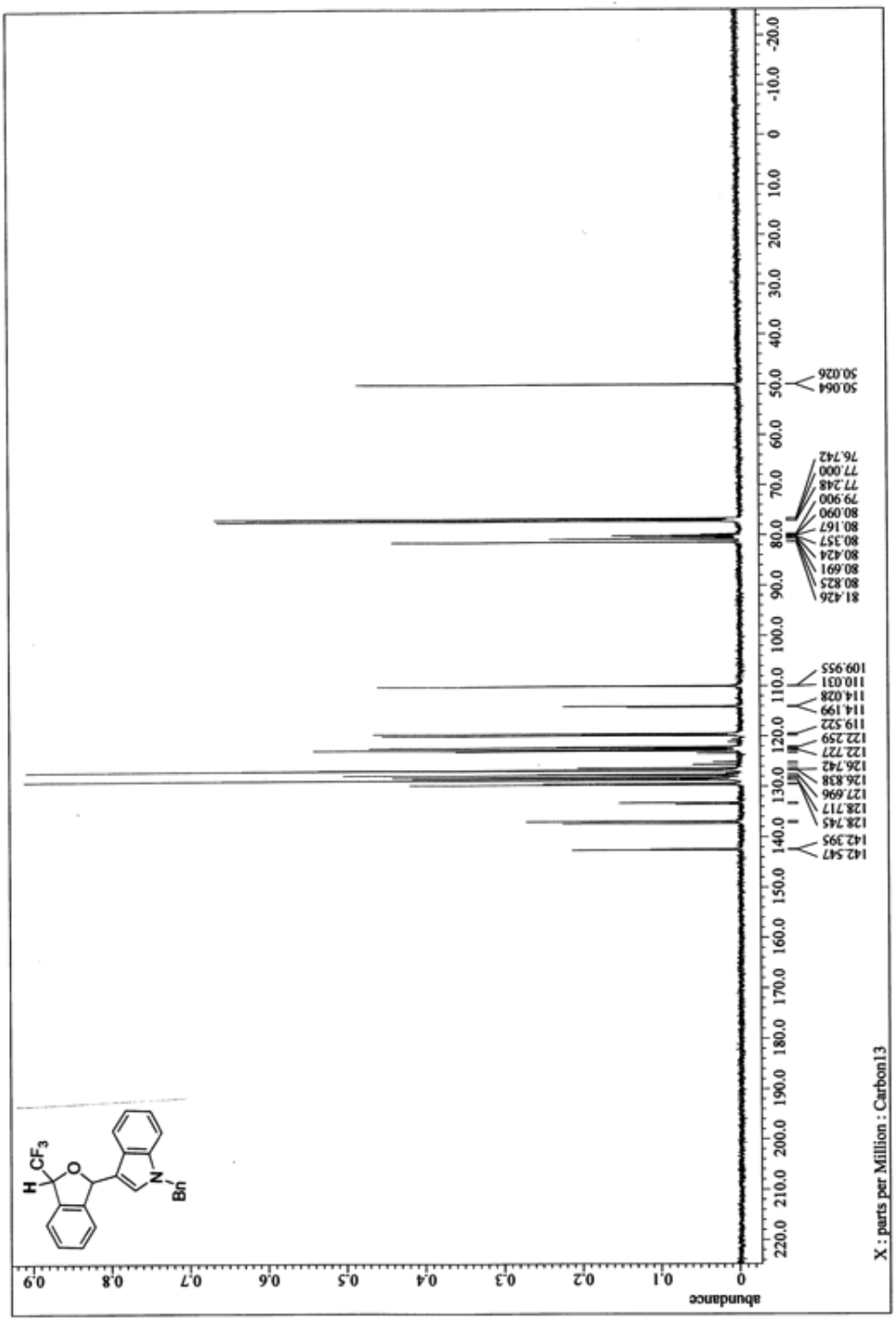
^{19}F NMR spectrum of **10b** ($CDCl_3$, 283 MHz).



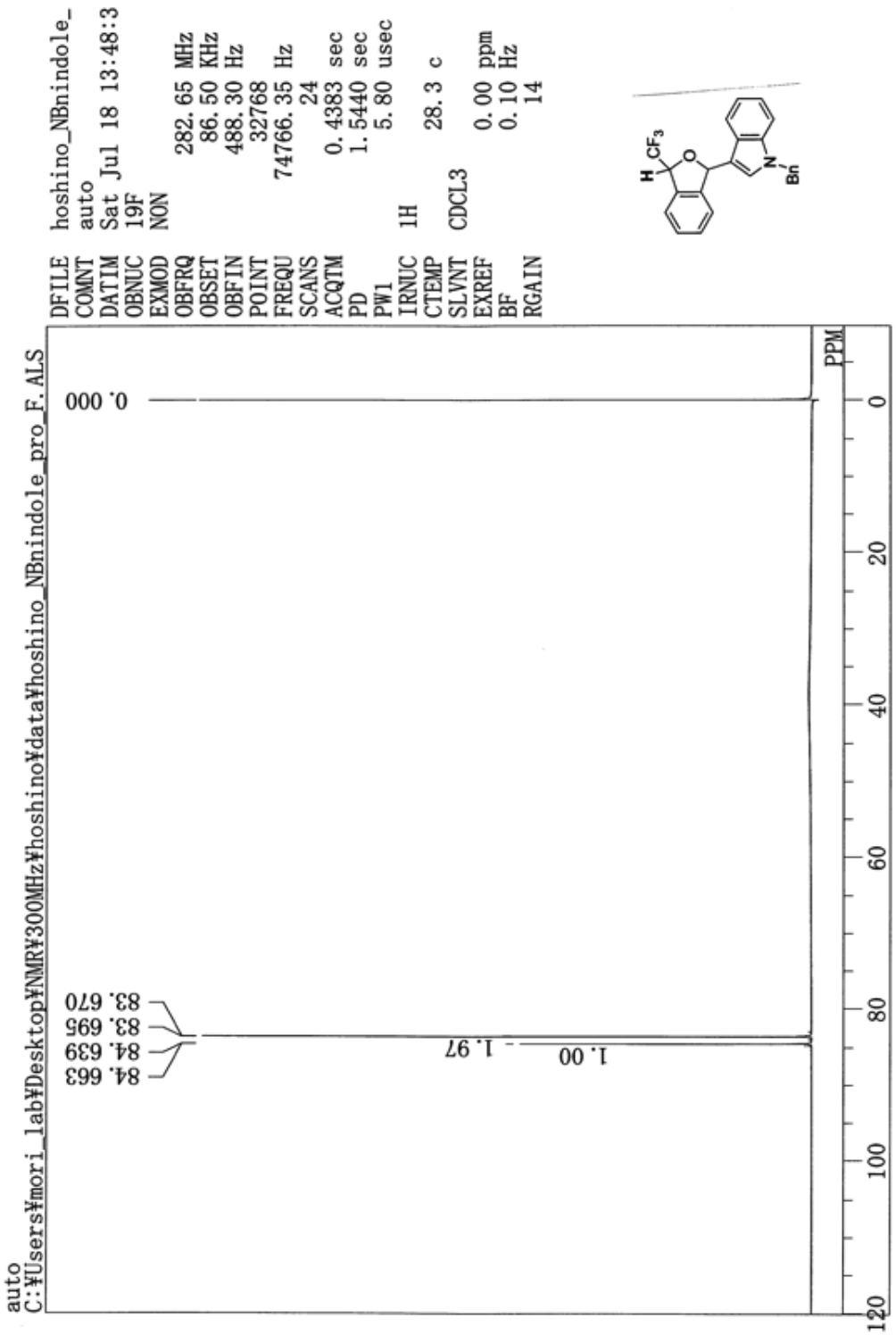
^{1}H NMR spectrum of **10c** ($CDCl_3$, 500 MHz).



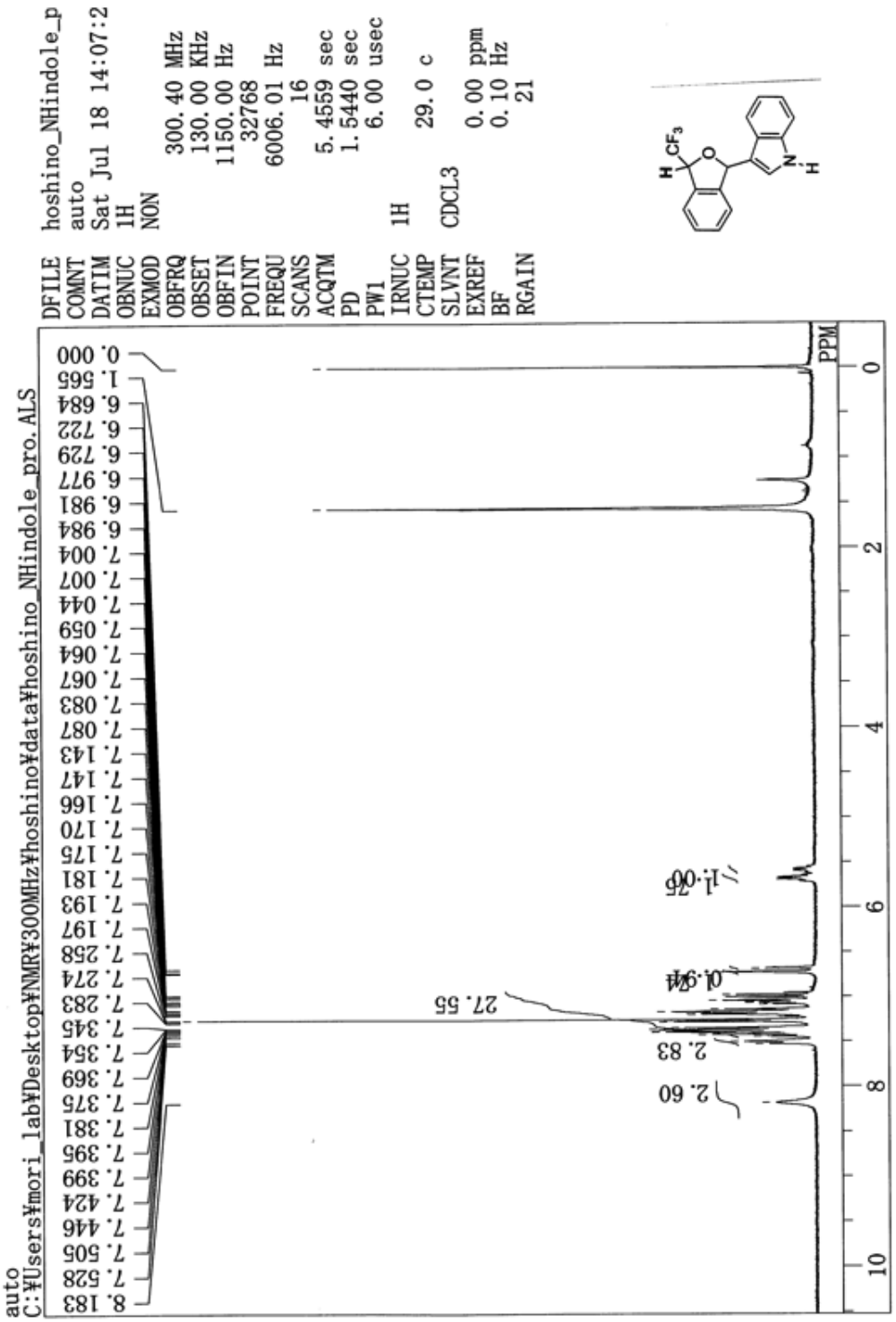
^{13}C NMR spectrum of **10c** ($CDCl_3$, 125 MHz).



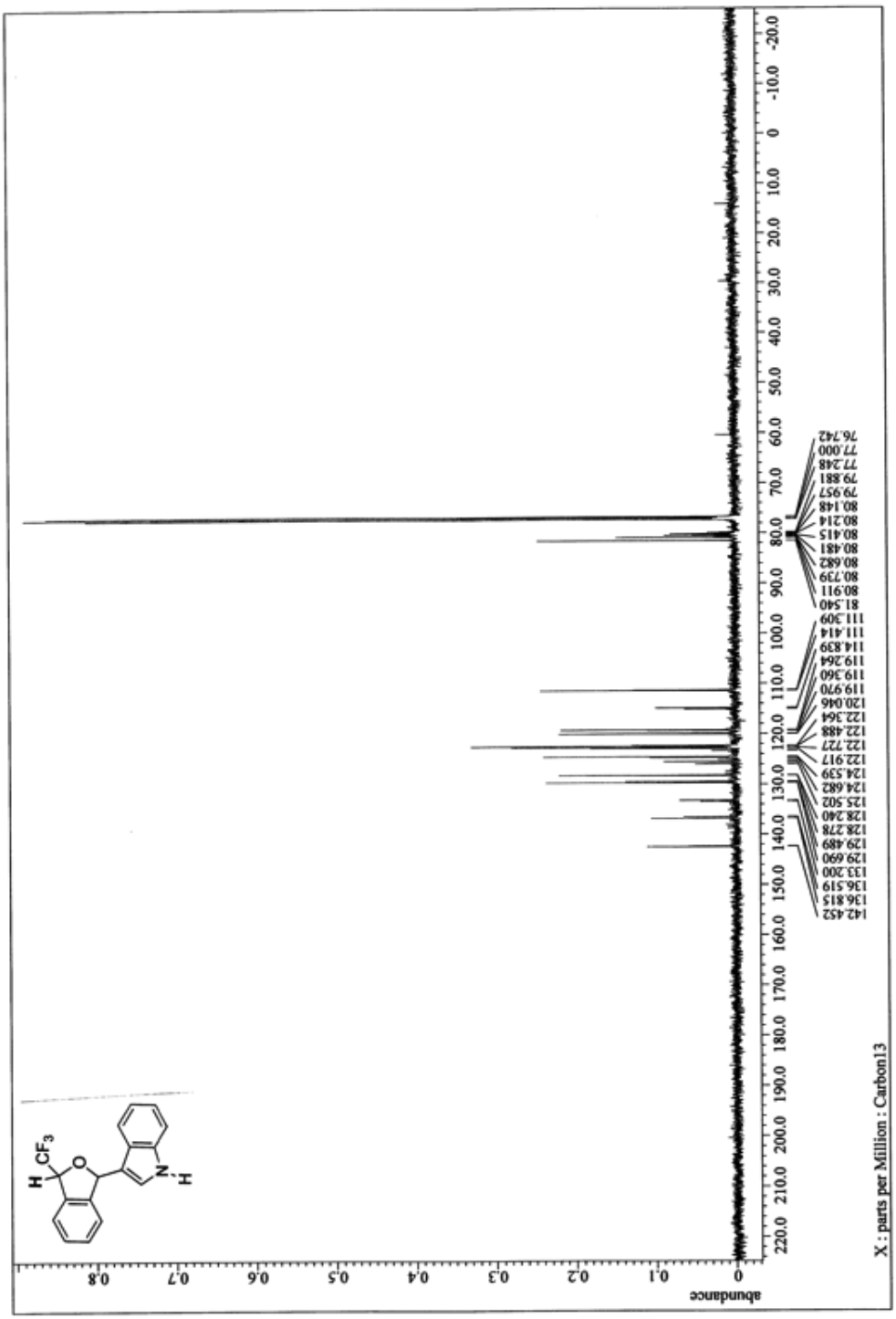
^{19}F NMR spectrum of **10c** ($CDCl_3$, 283 MHz).



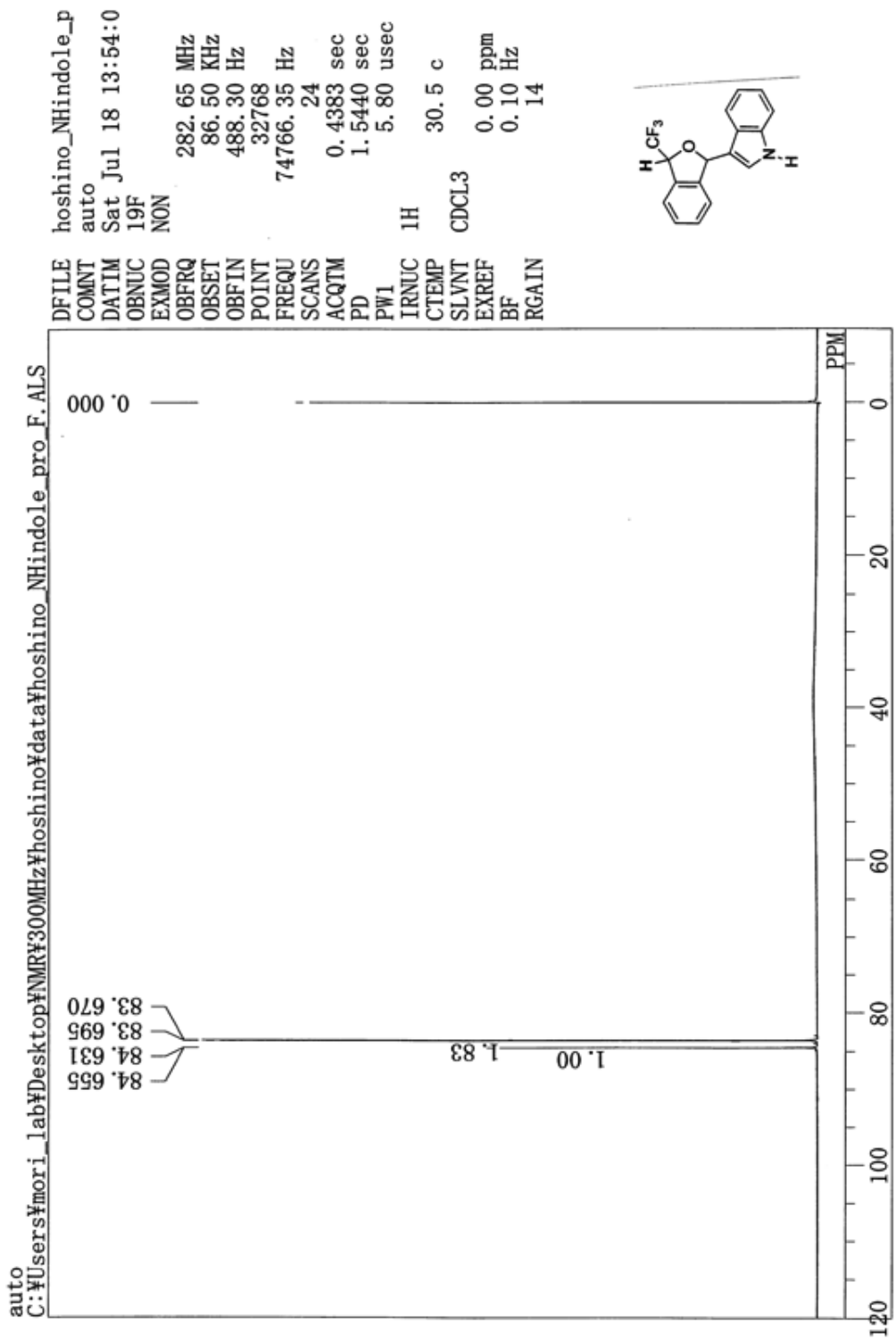
^{1}H NMR spectrum of **10d** ($CDCl_3$, 300 MHz).



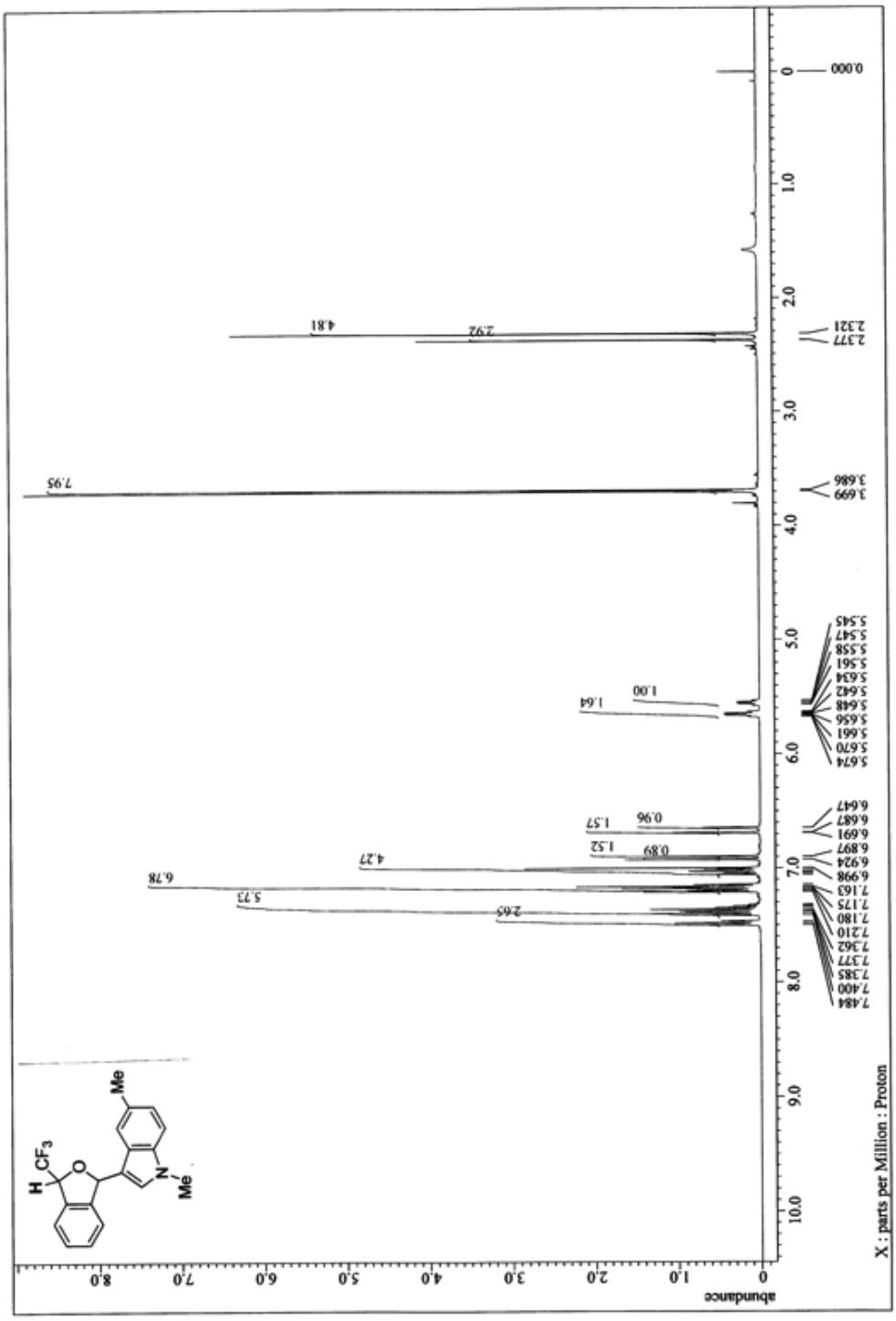
^{13}C NMR spectrum of **10d** ($CDCl_3$, 125 MHz).



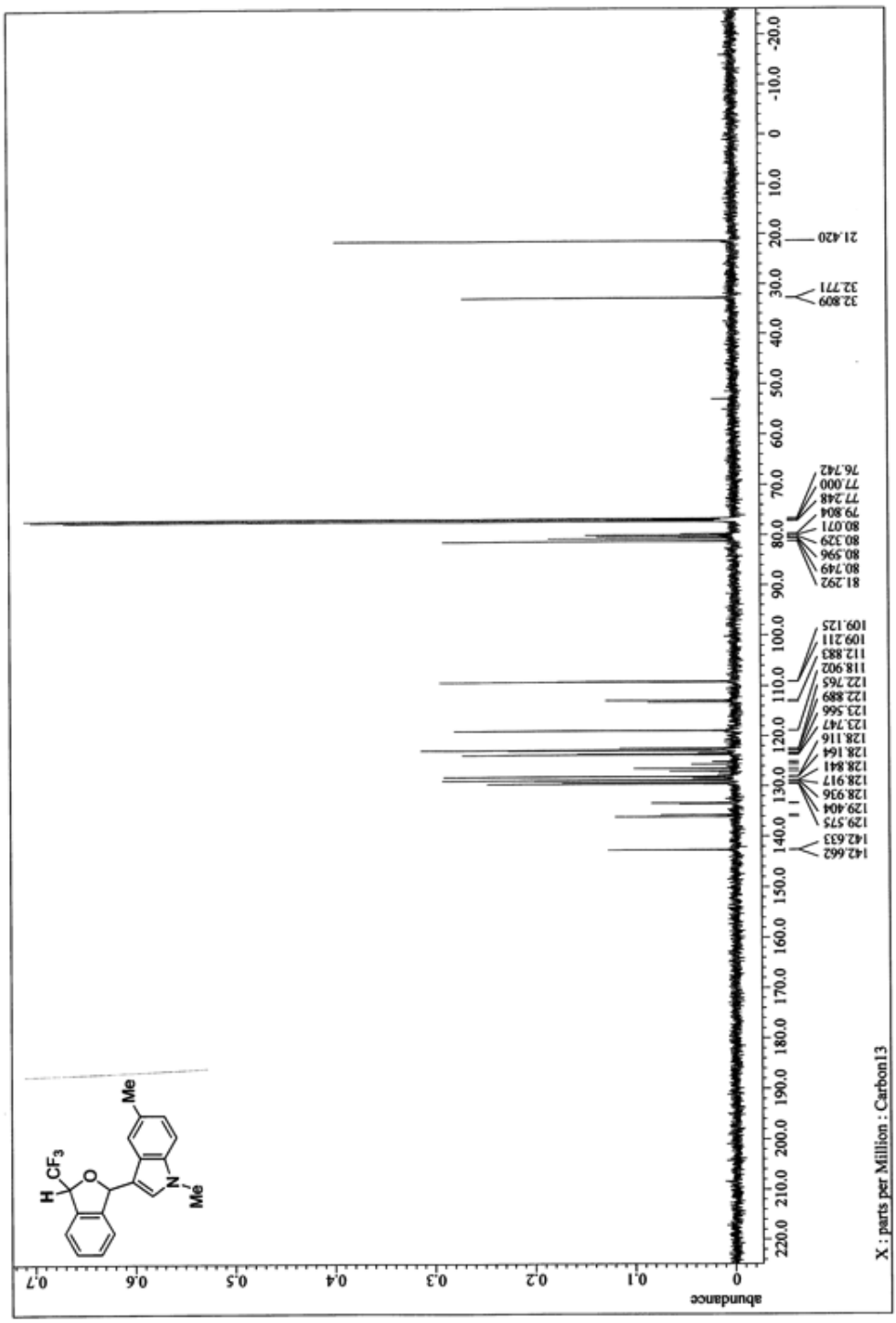
^{19}F NMR spectrum of **10d** ($CDCl_3$, 283 MHz).



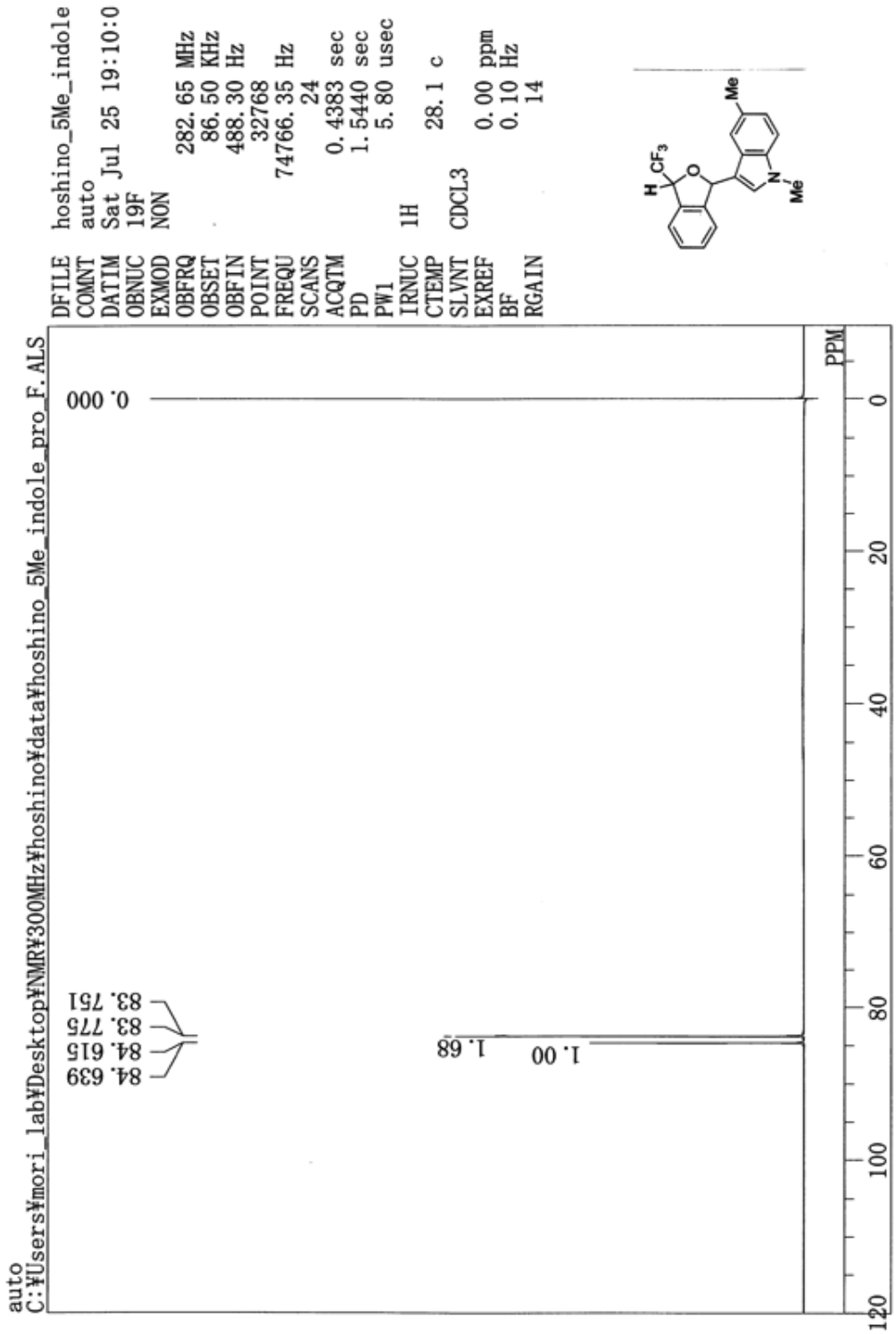
^{1}H NMR spectrum of **10e** ($CDCl_3$, 500 MHz).



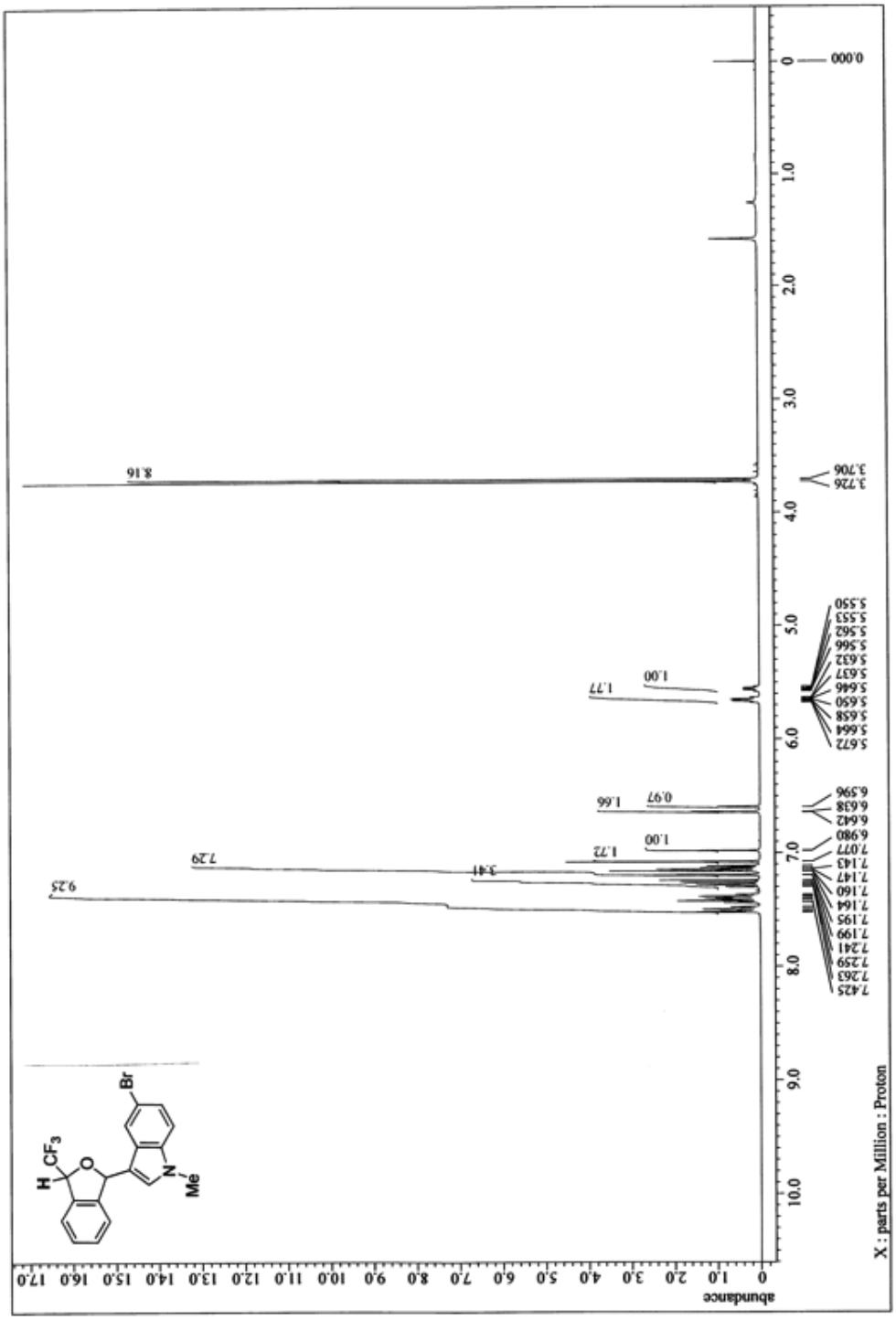
^{13}C NMR spectrum of **10e** ($CDCl_3$, 125 MHz).



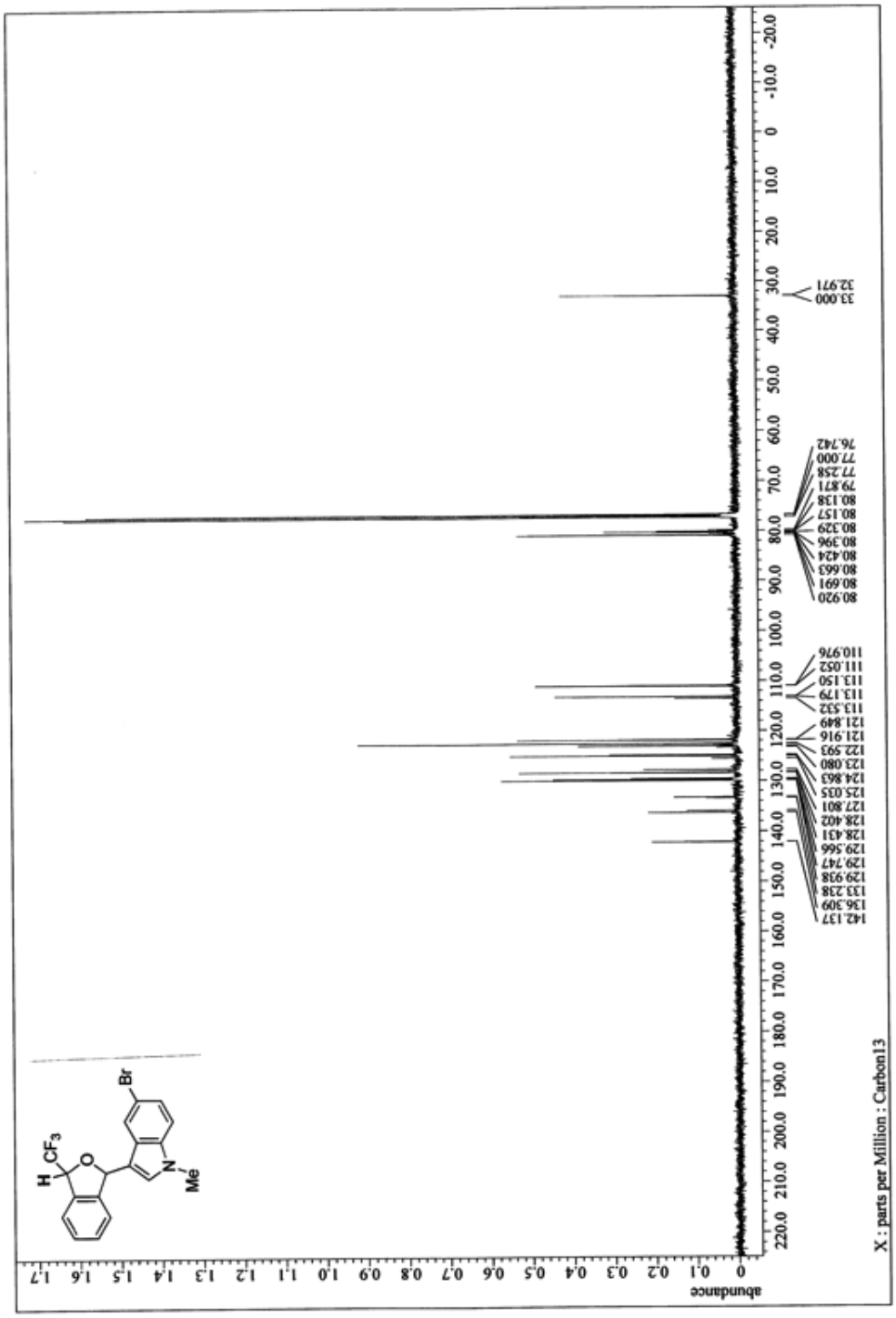
^{19}F NMR spectrum of **10e** ($CDCl_3$, 283 MHz).



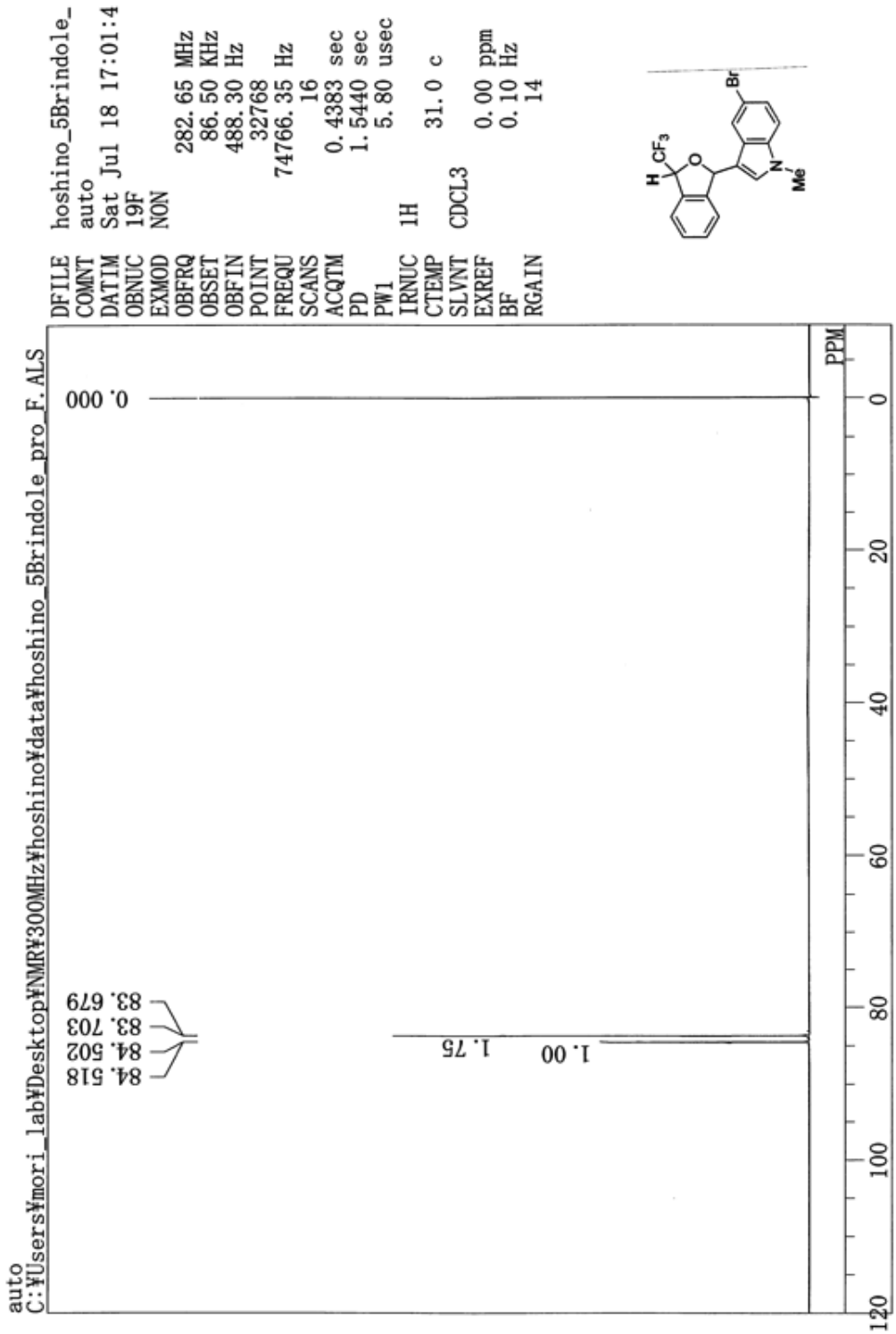
^{1}H NMR spectrum of **10f** ($CDCl_3$, 500 MHz).



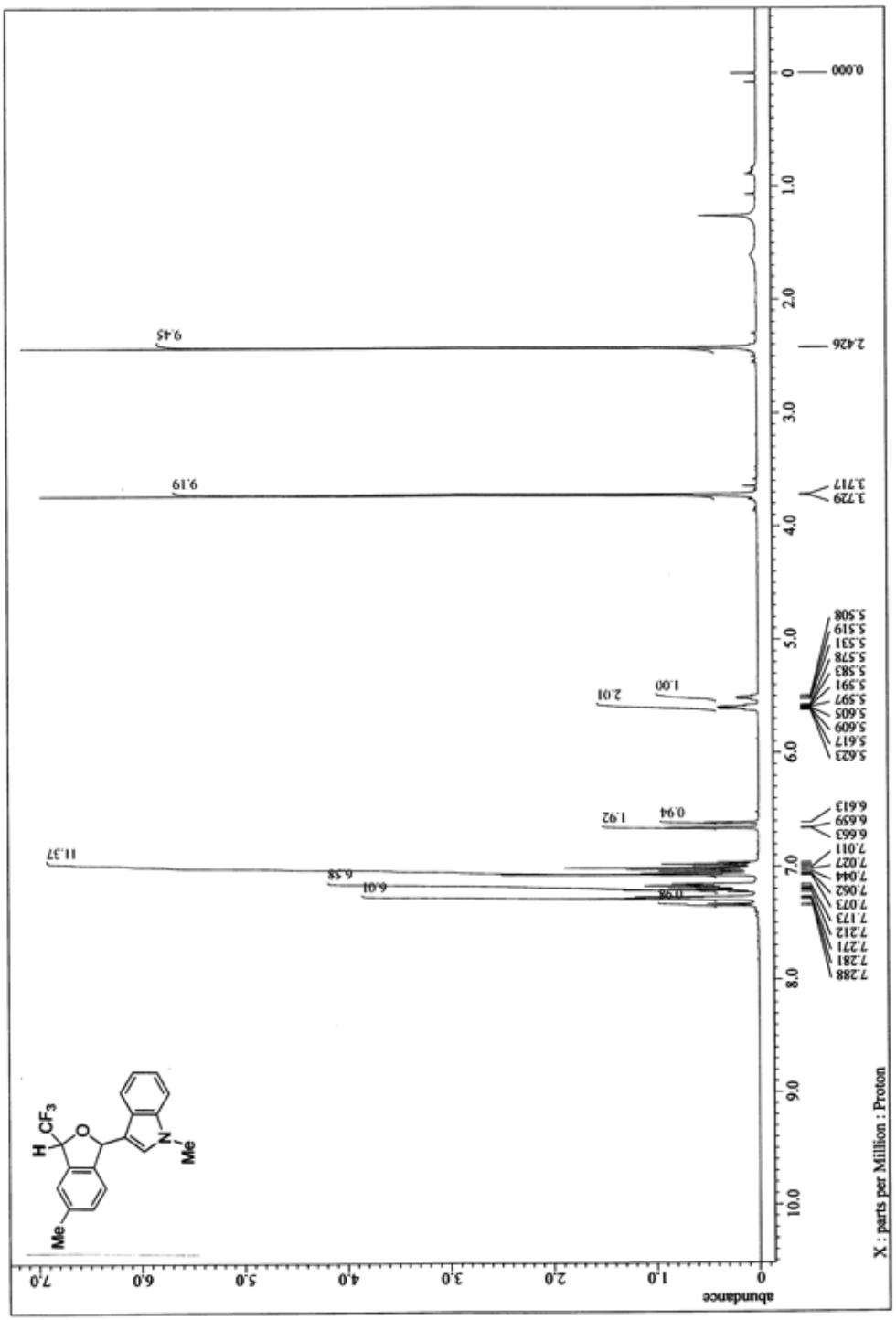
^{13}C NMR spectrum of **10f** ($CDCl_3$, 125 MHz).



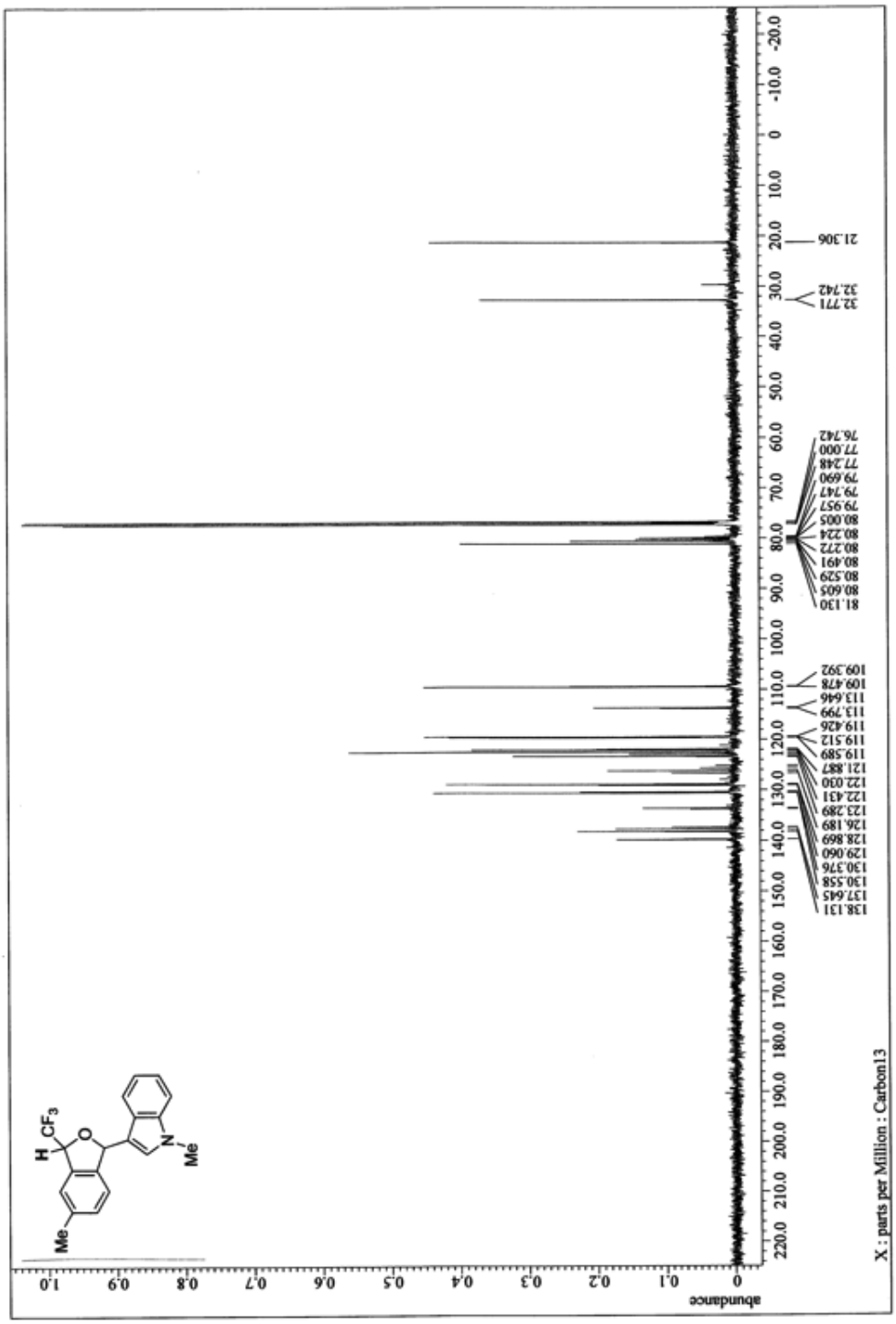
^{19}F NMR spectrum of **10f** ($CDCl_3$, 283 MHz).



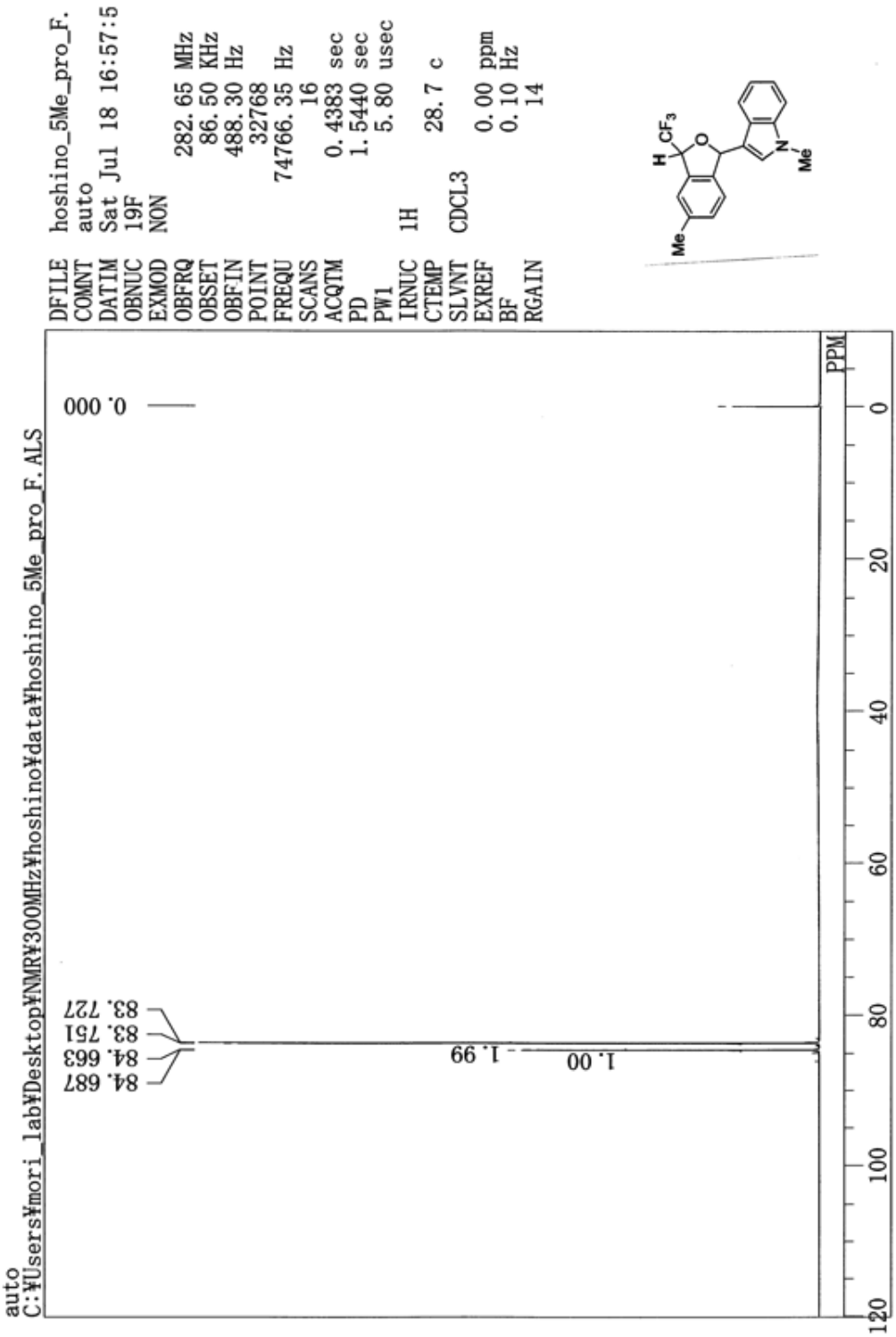
^{1}H NMR spectrum of **10g** ($CDCl_3$, 500 MHz).



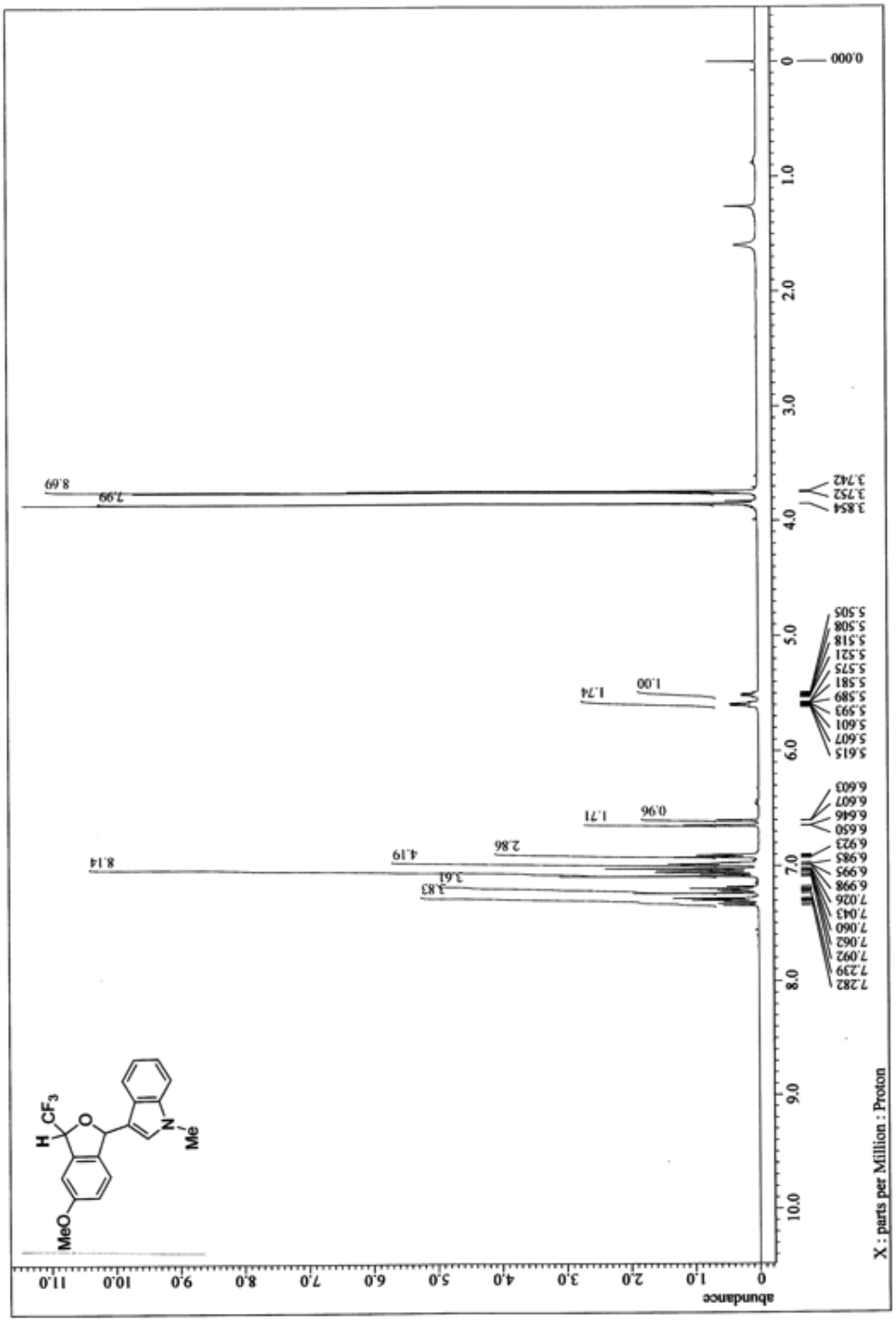
^{13}C NMR spectrum of **10g** ($CDCl_3$, 125 MHz).



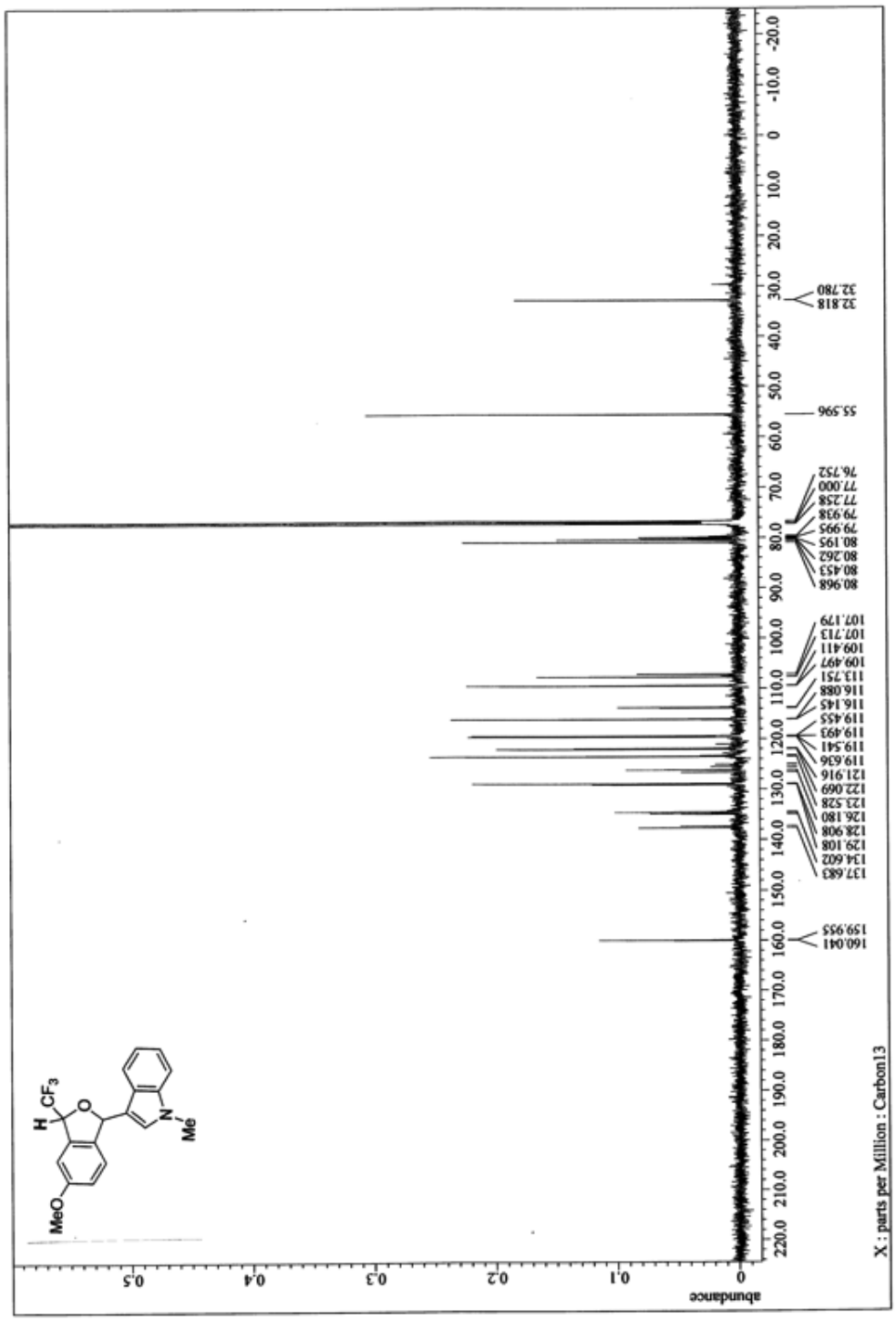
^{19}F NMR spectrum of **10g** ($CDCl_3$, 283 MHz).



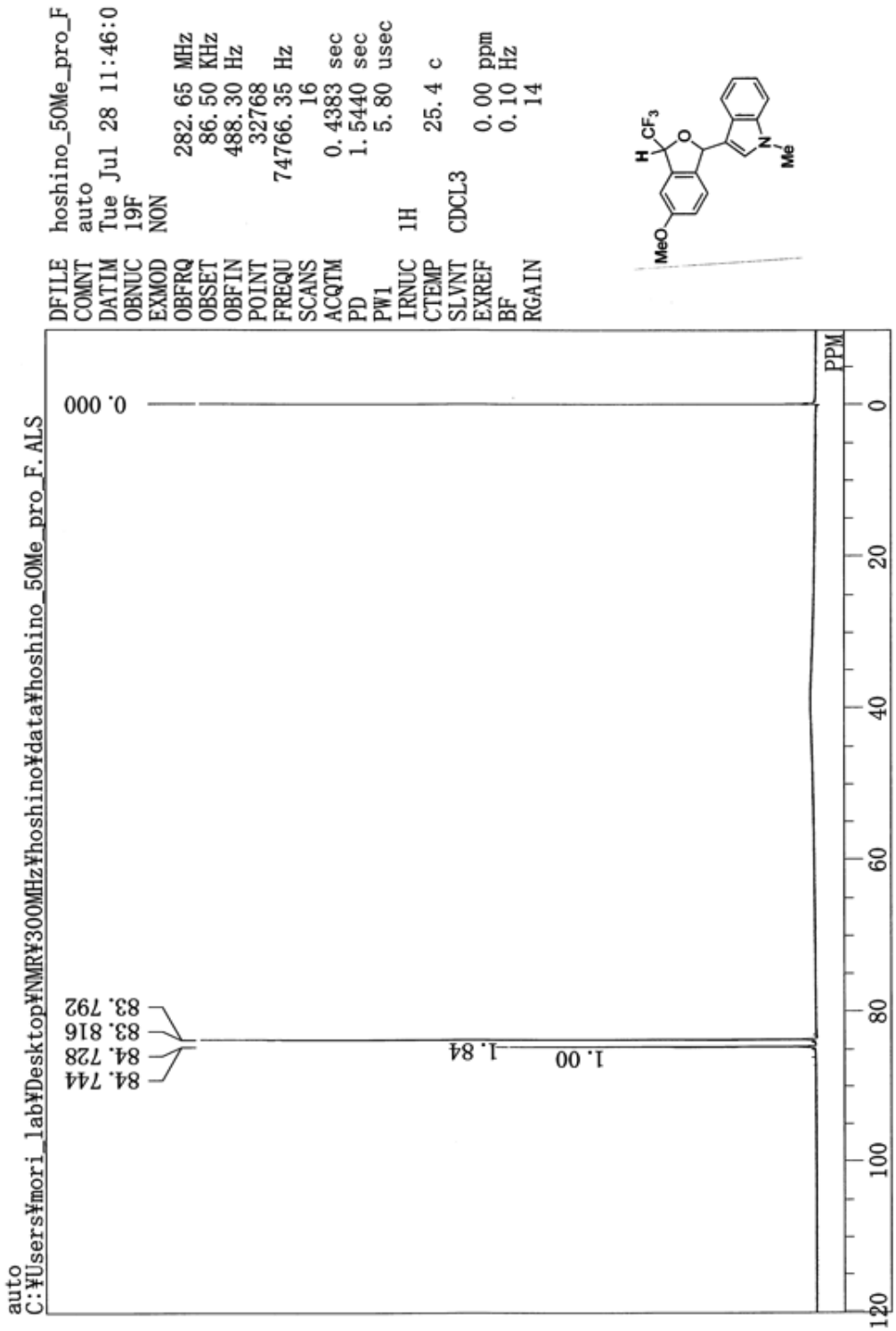
^{1}H NMR spectrum of **10h** ($CDCl_3$, 500 MHz).



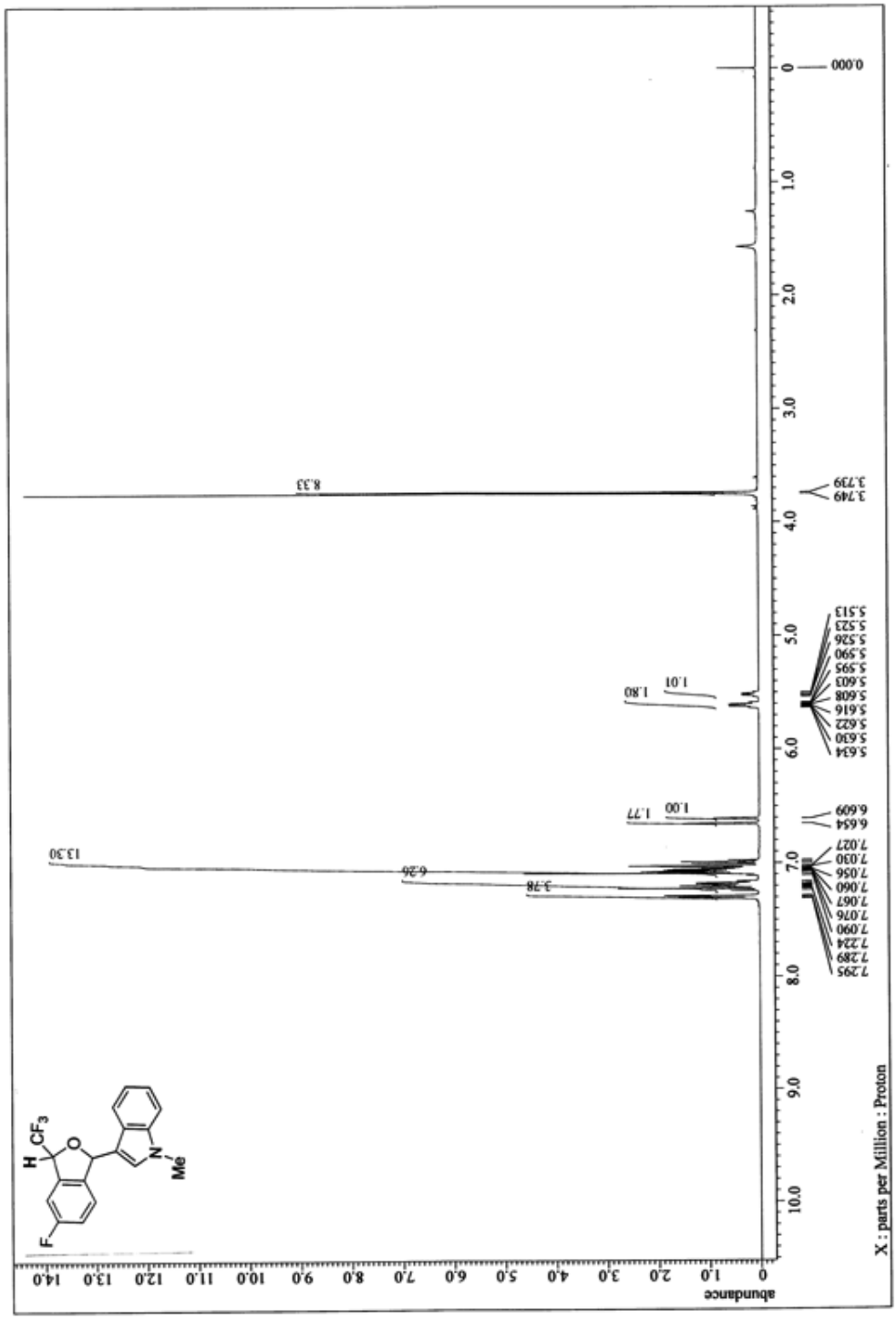
^{13}C NMR spectrum of **10h** ($CDCl_3$, 125 MHz).



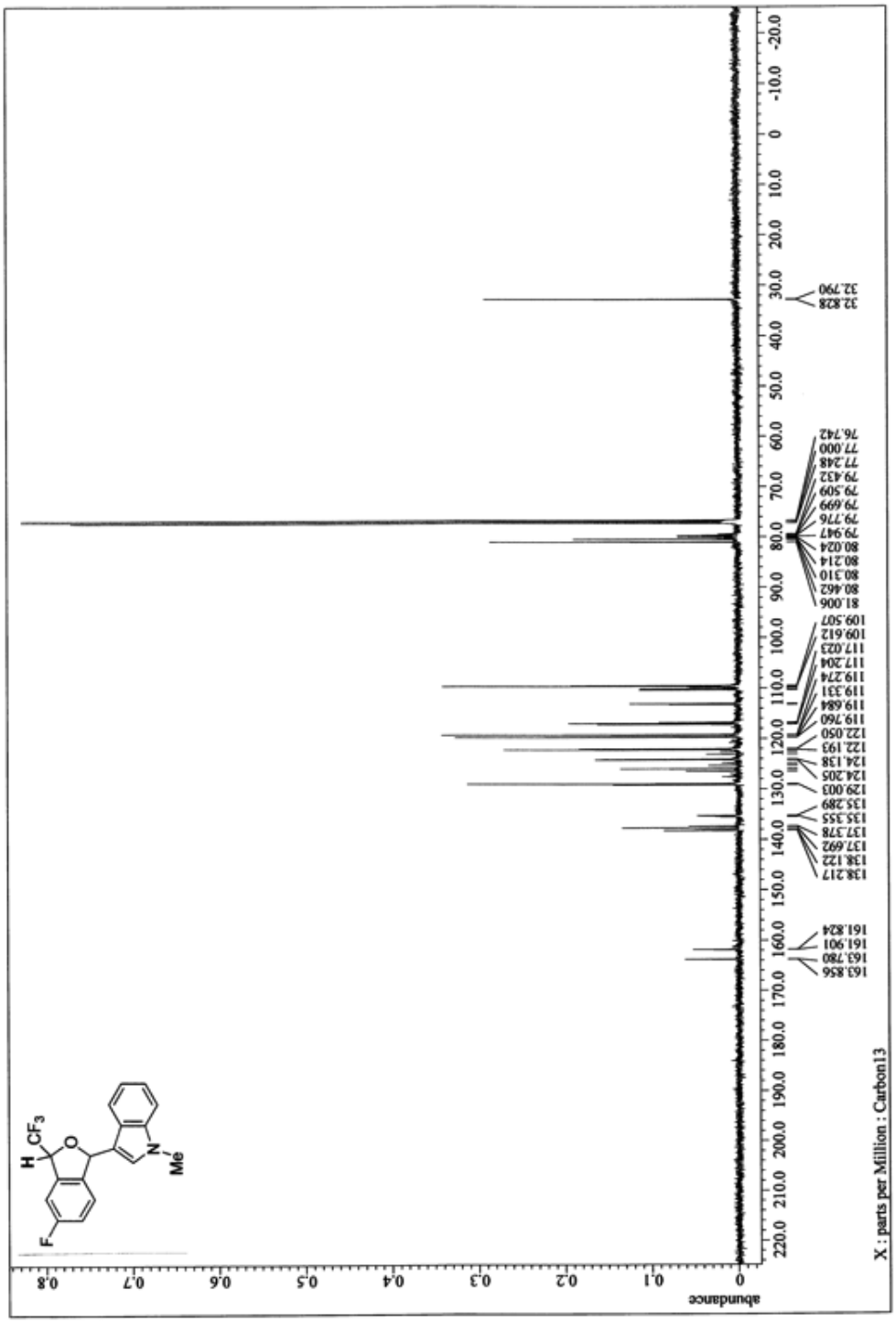
^{19}F NMR spectrum of **10h** ($CDCl_3$, 283 MHz).



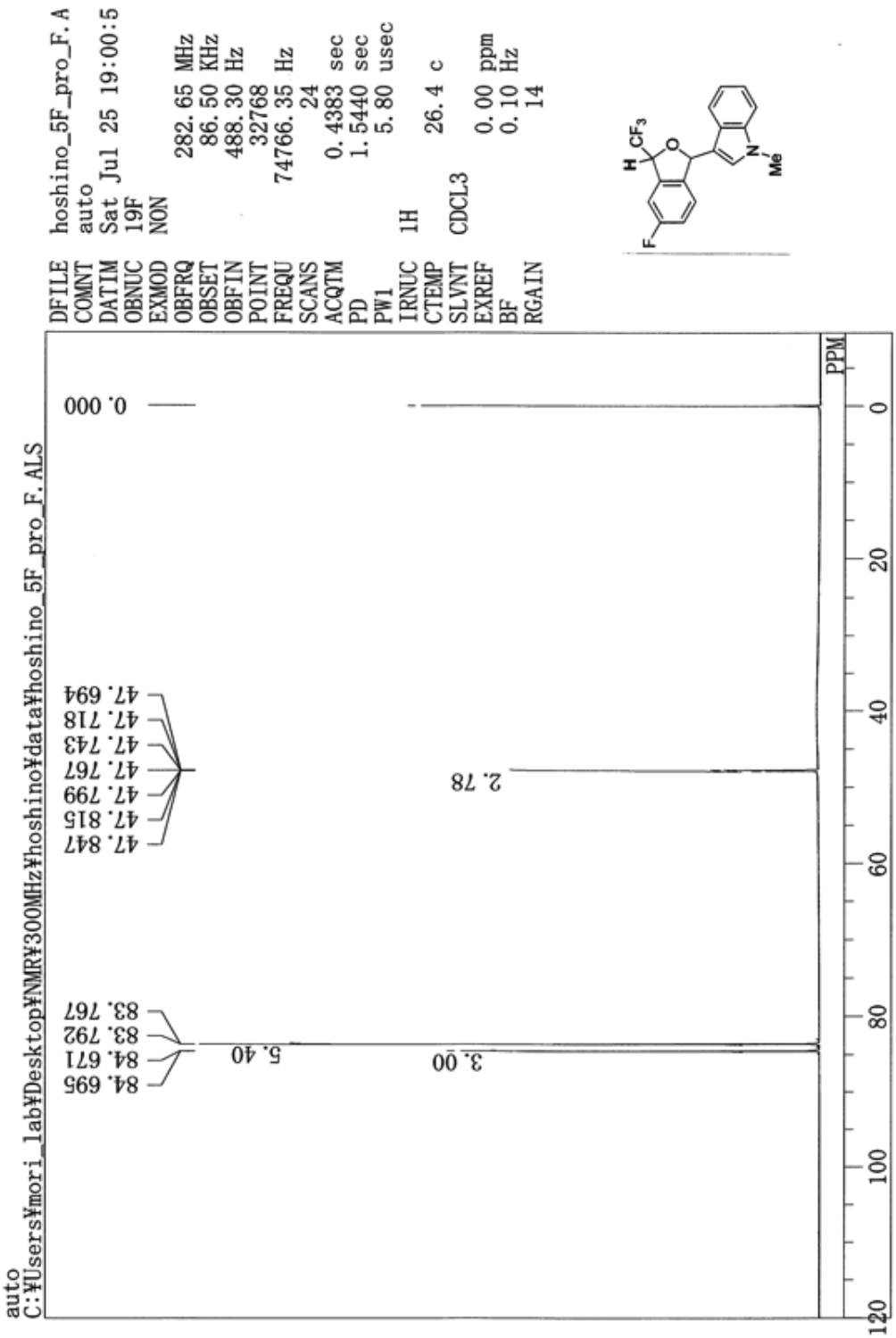
^{1}H NMR spectrum of **10i** ($CDCl_3$, 500 MHz).



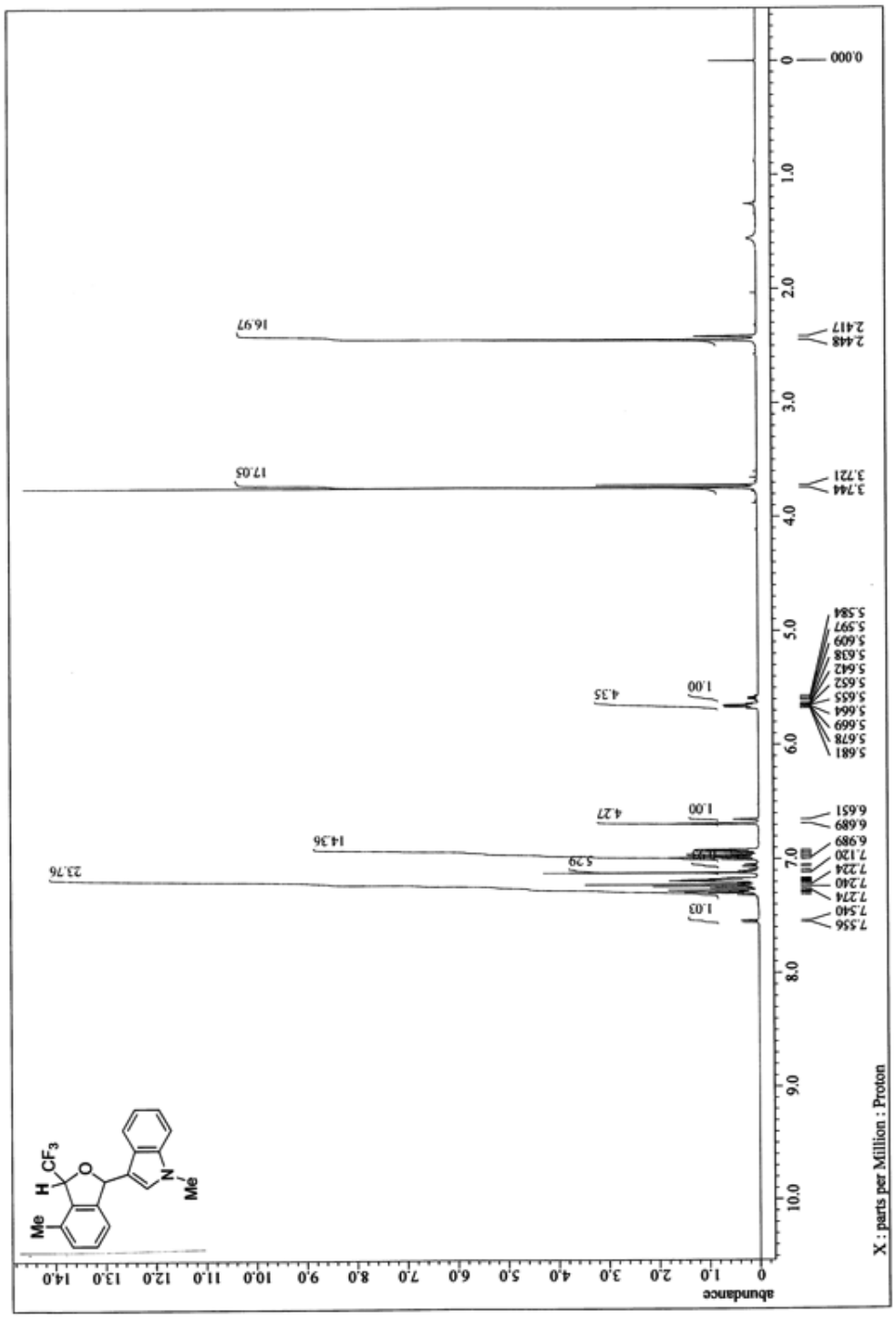
^{13}C NMR spectrum of **10i** ($CDCl_3$, 125 MHz).



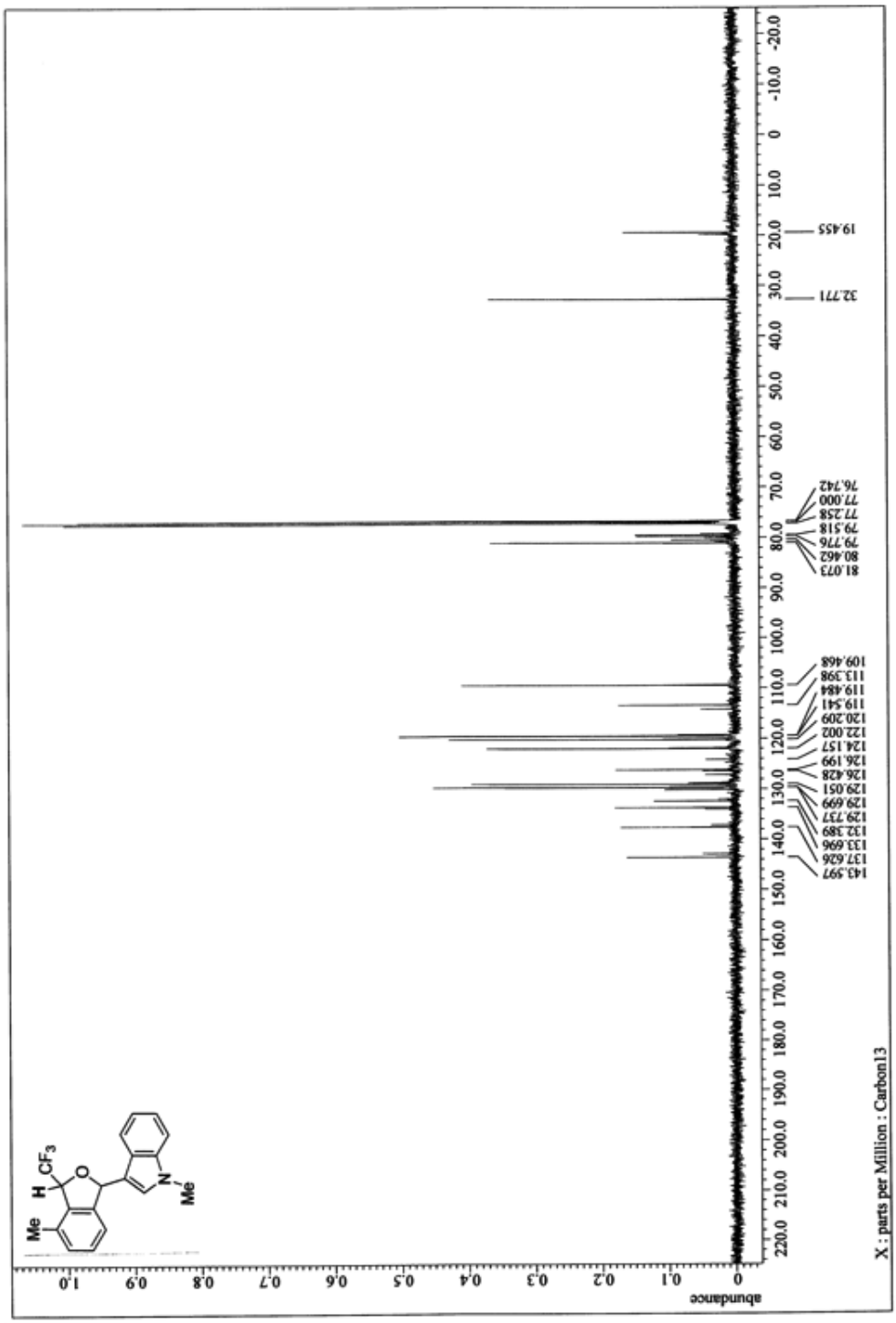
^{19}F NMR spectrum of **10i** ($CDCl_3$, 283 MHz).



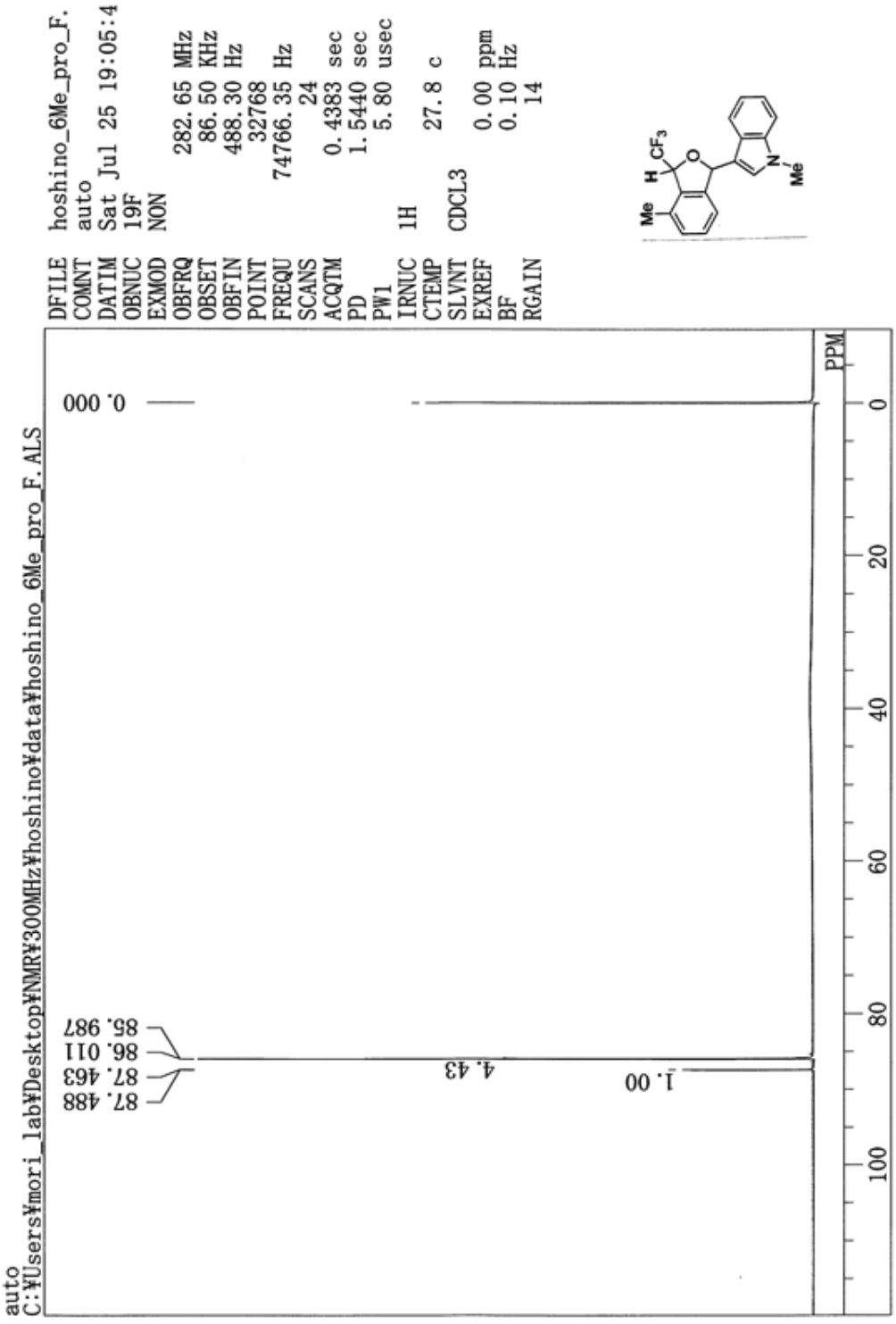
^{1}H NMR spectrum of **10j** ($CDCl_3$, 500 MHz).



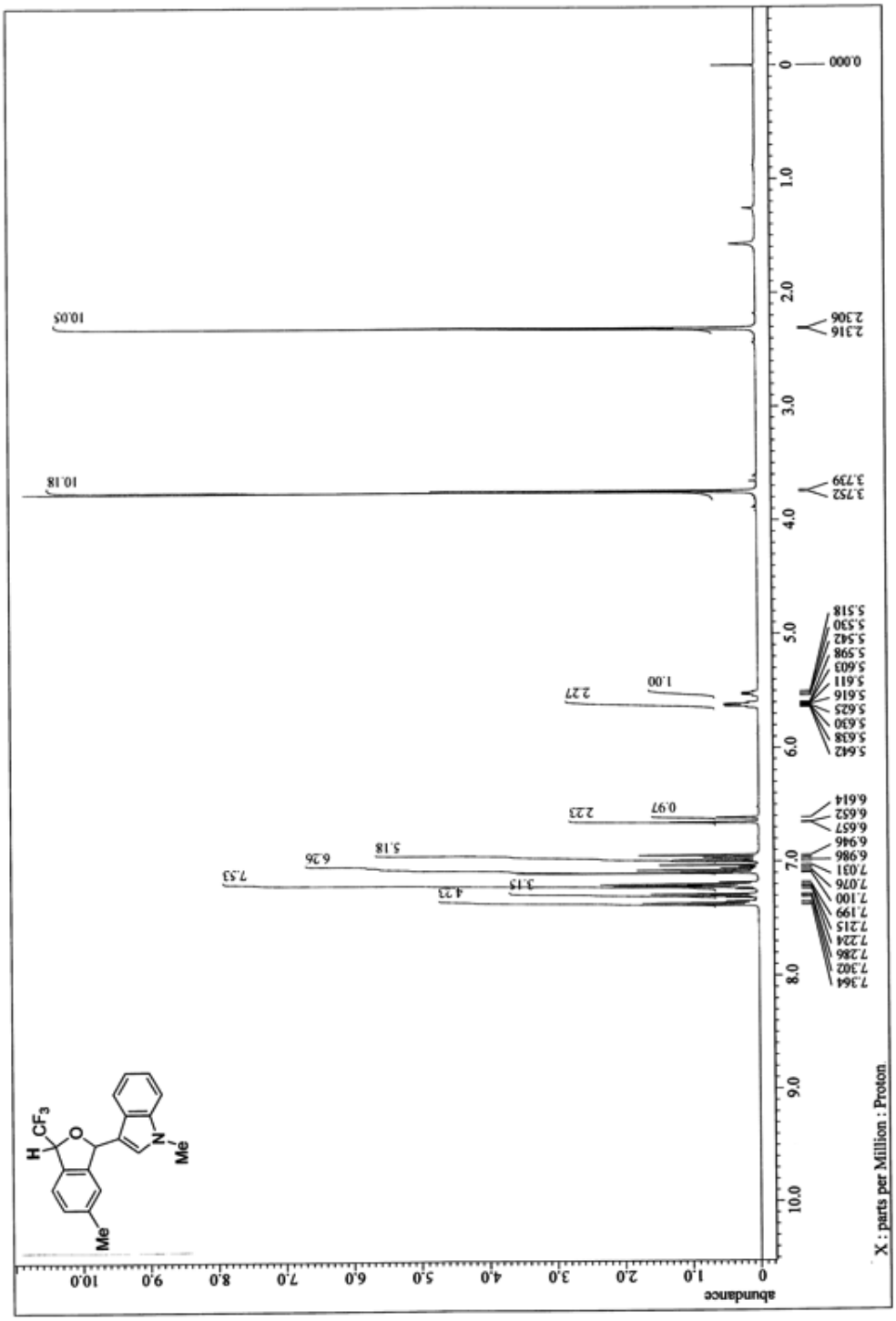
^{13}C NMR spectrum of **10j** ($CDCl_3$, 125 MHz).



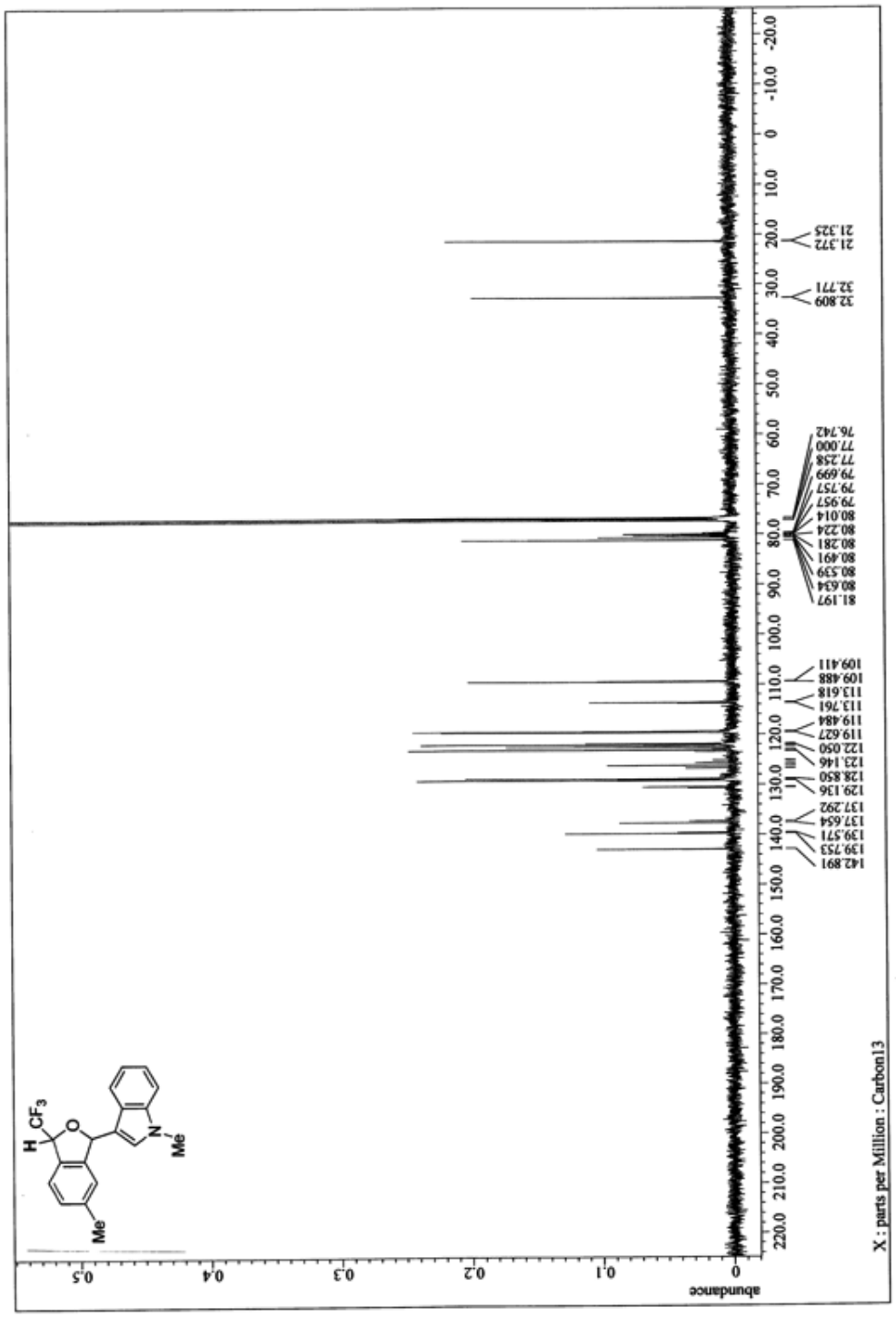
^{19}F NMR spectrum of **10j** ($CDCl_3$, 283 MHz).



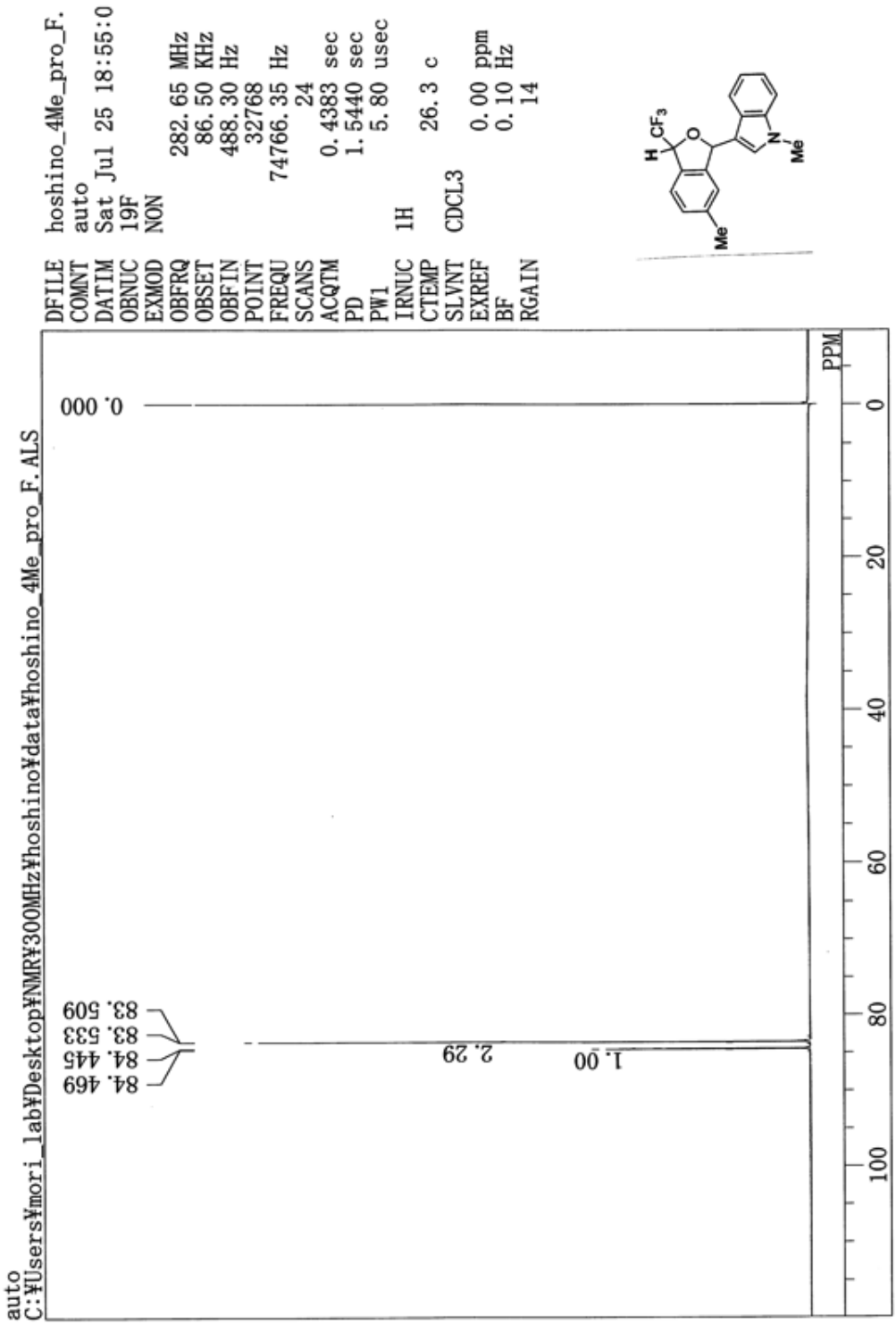
^{1}H NMR spectrum of **10k** ($CDCl_3$, 500 MHz).



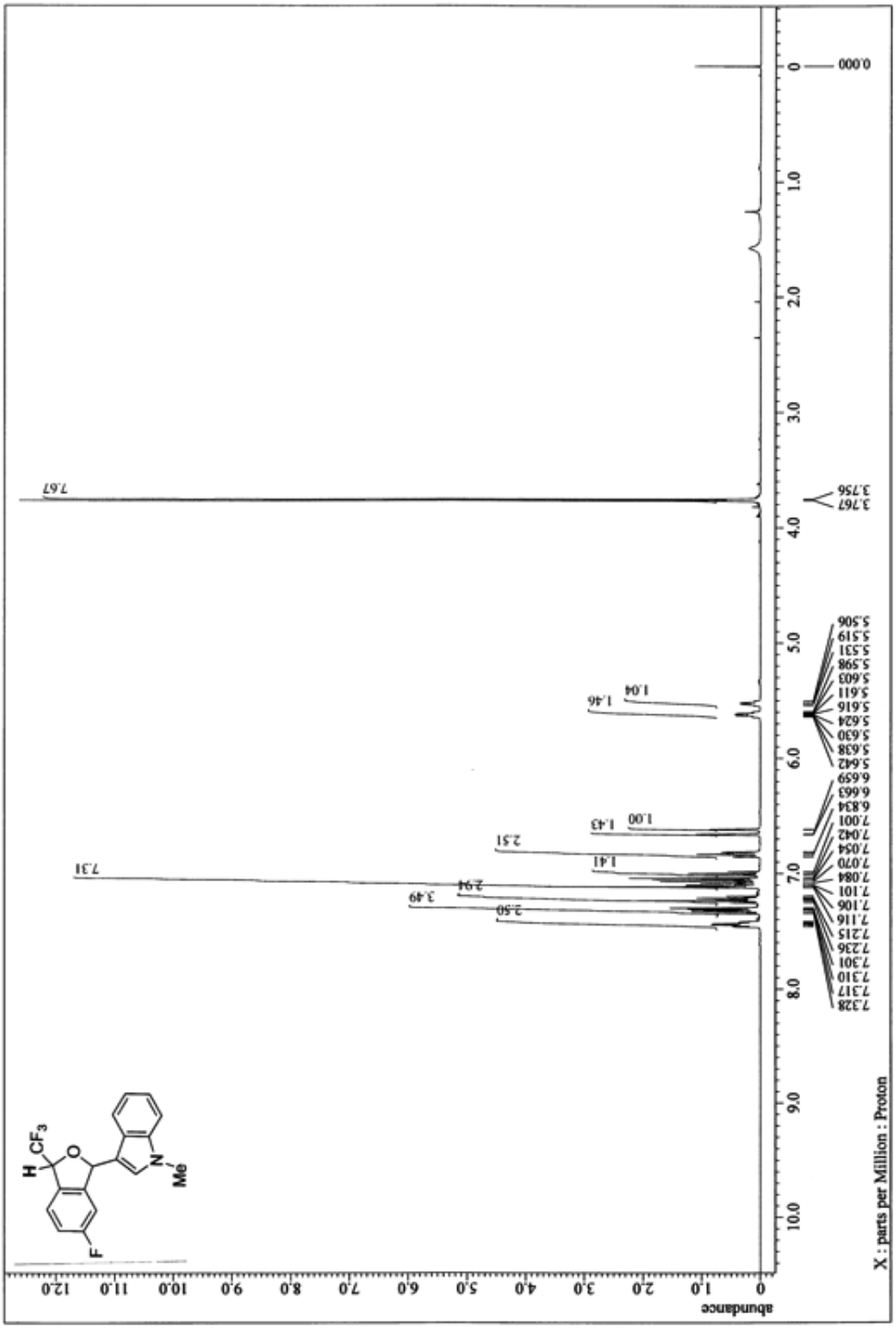
^{13}C NMR spectrum of **10k** ($CDCl_3$, 125 MHz).



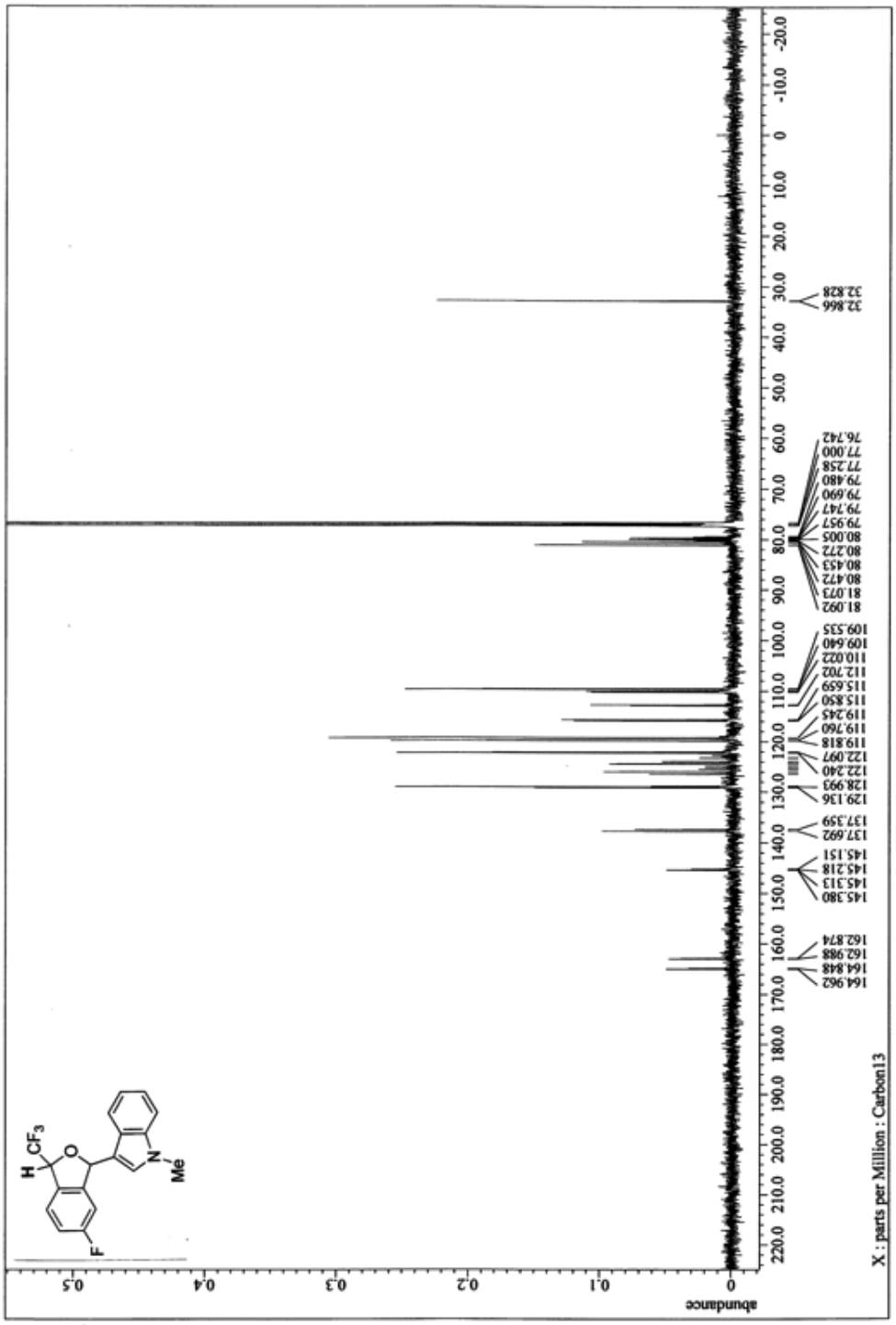
^{19}F NMR spectrum of **10k** ($CDCl_3$, 283 MHz).



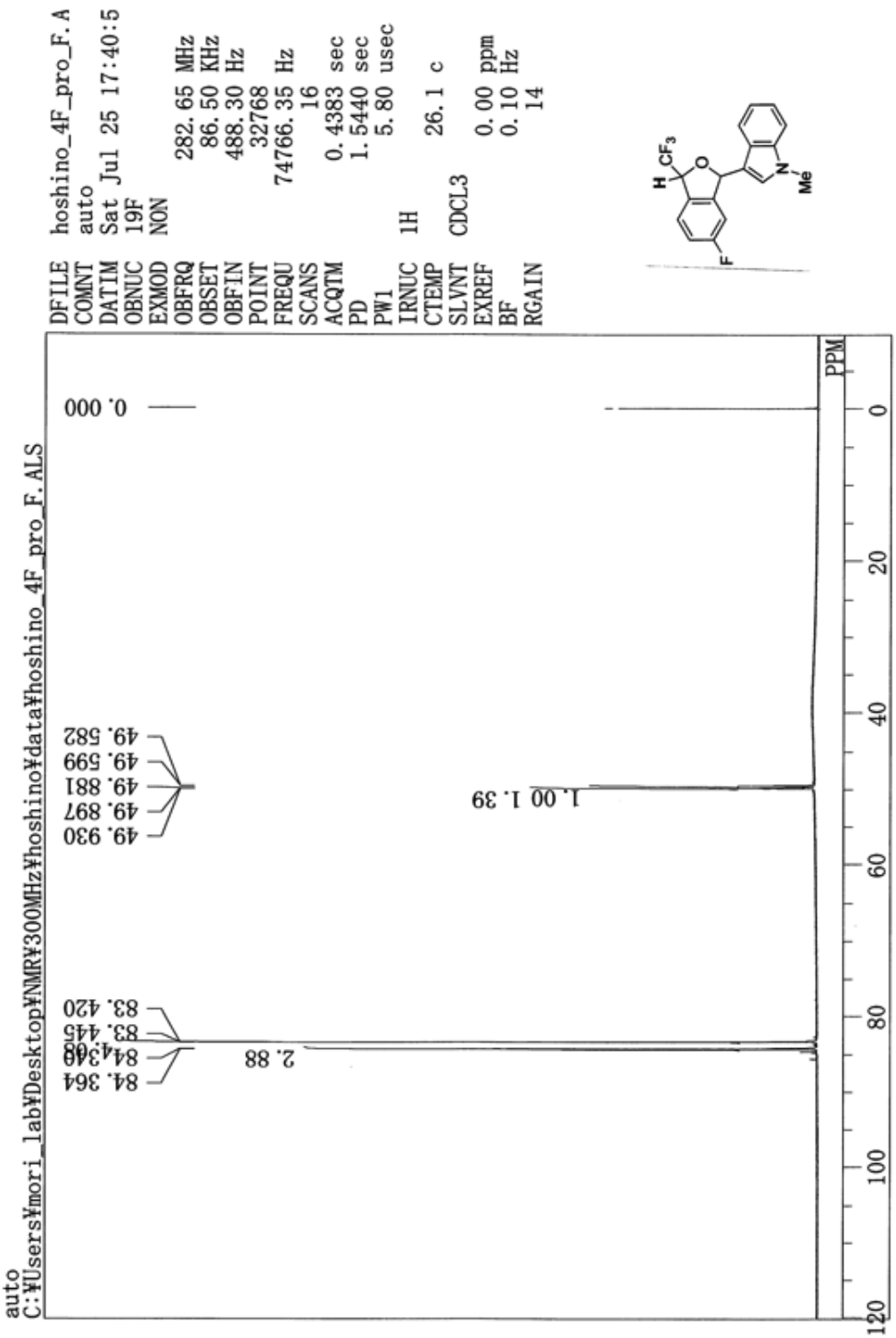
^{1}H NMR spectrum of **10l** ($CDCl_3$, 500 MHz).



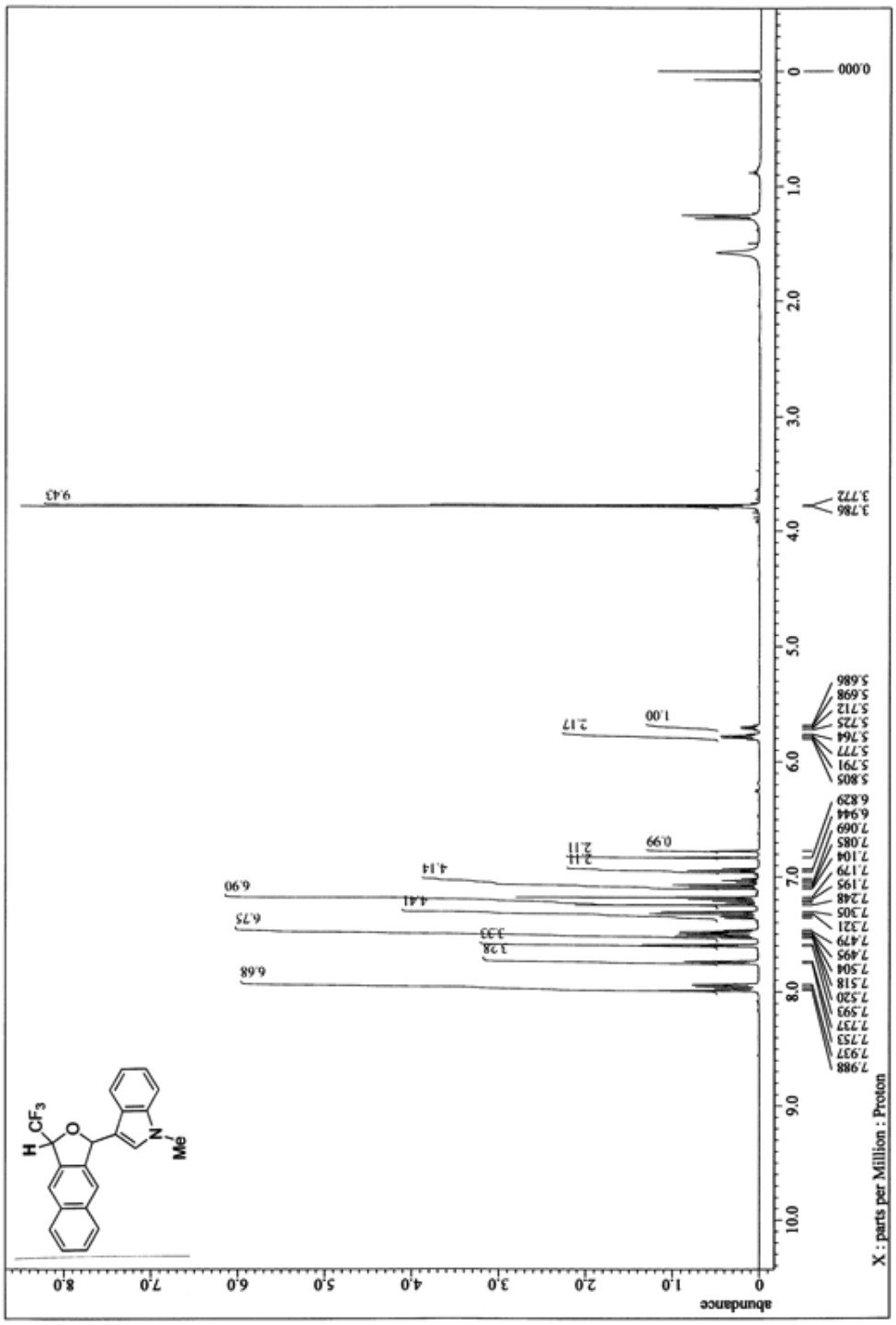
^{13}C NMR spectrum of **10l** ($CDCl_3$, 125 MHz).



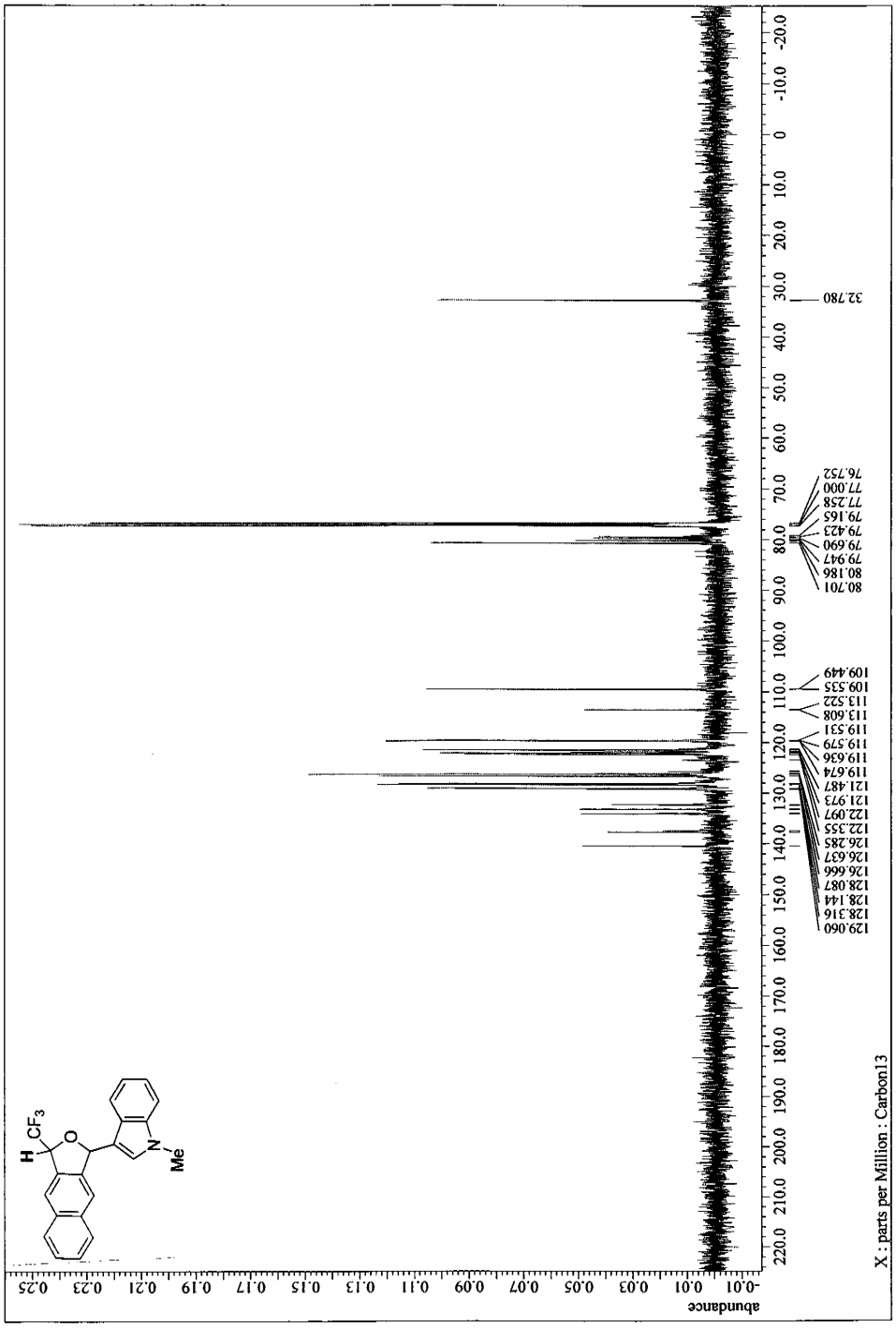
^{19}F NMR spectrum of **10l** ($CDCl_3$, 283 MHz).



^{1}H NMR spectrum of **10m** ($CDCl_3$, 500 MHz).



^{13}C NMR spectrum of **10m** ($CDCl_3$, 125 MHz).



^{19}F NMR spectrum of **10m** ($CDCl_3$, 283 MHz).