Supplementary Material (ESI) for Chemical Communications

Supplementary Information

Biomimetic trifunctional organocatalyst showing a great acceleration for the transesterification between vinyl ester and alcohol

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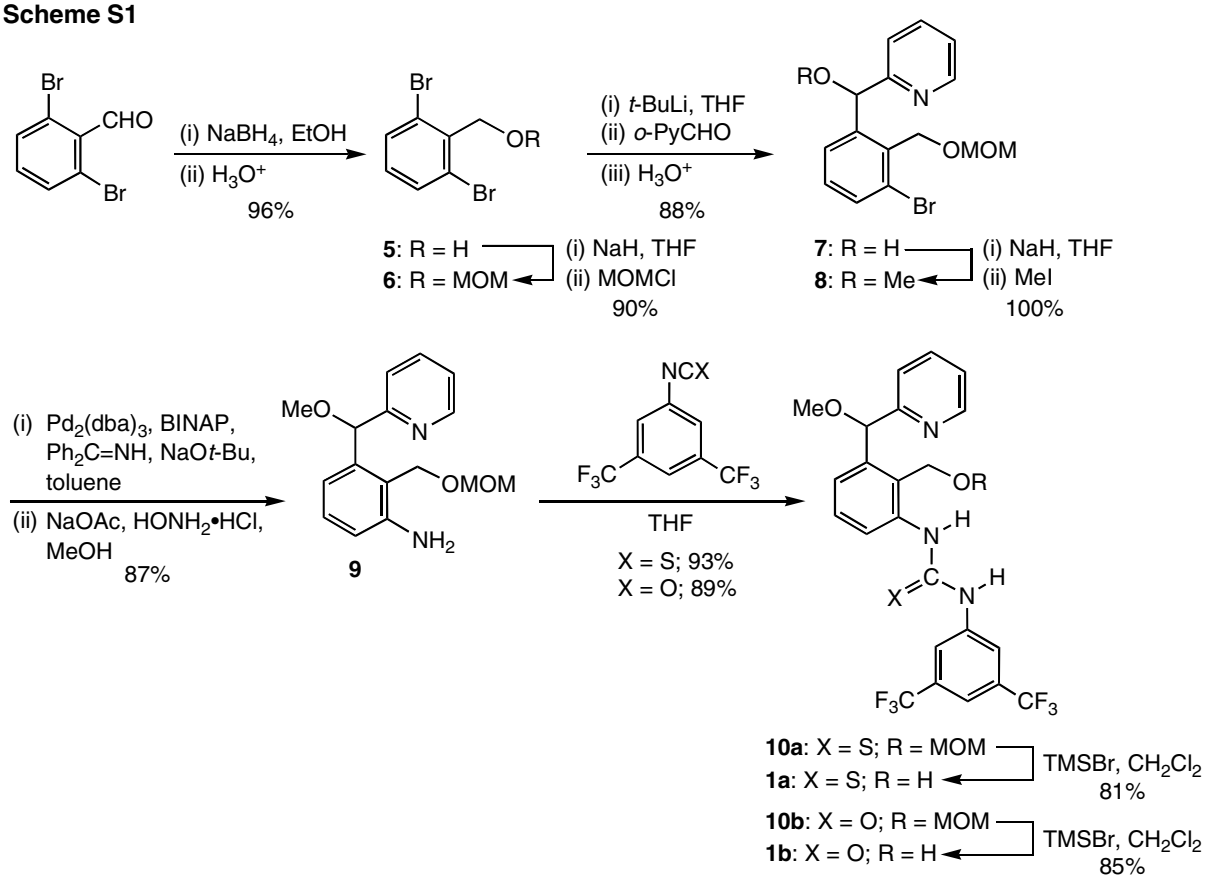
Synthetic Procedures for 1–4.

Scheme S1



2,6-Dibromobenzyl alcohol (5).

To a solution of 2,6-dibromobenzaldehyde[1] (1.51 g, 5.70 mmol) in EtOH (48 mL) in an ice bath was added $NaBH_4$ (237 mg, 6.26 mmol), and the mixture was stirred under N_2 at room temperature for 5 h. The reaction was quenched with saturated aqueous NH_4Cl and 3% HCl, and the mixture was extracted with Et_2O, dried over $MgSO_4$, and concentrated. The product was purified by silica gel column chromatography (hexane/EtOAc (5:1)) to afford **5** as white crystals (1.45 g, 96%): mp 113–114 ºC; ^{1}H NMR ($CDCl_3$, 600 MHz) δ2.18 (br s, 1H), 5.00 (s, 2H), 7.02 (t, J = 8.0 Hz, 1H), 7.55 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ65.4, 125.7, 130.6, 132.5, 138.4; IR (KBr) 3323, 2953, 1575, 1553, 1429, 1120, 1059 cm^{-1}; Anal. Calcd for $C_7H_6OBr_2$: C, 31.62; H, 2.27. Found: C, 31.77; H, 2.36.

2,6-Dibromobenzyl methoxymethyl ether (6).

To a suspension of NaH (60% oil suspension, 550 mg, 13.8 mmol) in dry THF (12 mL) under N_2 was added dropwise a solution of **5** (2.38 g, 8.95 mmol) in dry THF (6 mL) at room temperature over 15 min. The mixture was stirred for 2.5 h. MOMCl (0.91 mL, 12 mmol) was added, and the mixture was stirred for 16 h. The mixture was filtered through Celite, and concentrated. The product was purified by silica gel column chromatography (hexane/EtOAc (25:1)) to afford **6** as a pale yellow oil (2.50 g, 90%): ^{1}H NMR ($CDCl_3$, 600 MHz) δ3.47 (s, 3H),

4.78 (s, 2H), 4.91 (s, 2H), 7.03 (t, J = 8.2 Hz, 1H), 7.56 (d, J = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 55.7, 69.5, 96.6, 126.6, 130.8, 132.4, 136.1; IR (neat) 3071, 2926, 1553, 1431, 1151, 1063 cm^{-1}; Anal. Calcd for $C_9H_{10}O_2Br_2$: C, 34.87; H, 3.25. Found: C, 34.92; H, 3.26.

2-Bromo-6-[1-hydroxy-1-(2-pyridyl)methyl]benzyl methoxymethyl ether (7).

To a solution of **6** (1.31 g, 4.22 mmol) in dry THF (17 mL) under N_2 was added dropwise *t*-BuLi (1.57 M in *n*-pentane, 4.0 mL, 6.4 mmol) dropwise at –94 °C over 5 min. The mixture was stirred at –90 °C for 1.3 h, and a solution of 2-formylpyridine (0.47 mL, 4.9 mmol) in dry THF (4 mL) was added. The mixture was stirred at –90 °C for 1.5 h. The reaction was quenched with saturated aqueous NH_4Cl, and the solution was adjusted to pH 5. The mixture was extracted with Et_2O (15 mL × 3), dried over $MgSO_4$, and concentrated. The product was purified by silica gel column chromatography (hexane/EtOAc (2:1)) to afford **7** as a colorless oil (1.26 g, 88%): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 3.42 (s, 3H), 4.70 (d, J = 6.7 Hz, 1H), 4.72 (d, J = 6.7 Hz, 1H), 4.94 (d, J = 11.1 Hz, 1H), 5.00 (d, J = 11.1 Hz, 1H), 5.43 (br s, 1H), 6.15 (s, 1H), 7.10–7.13 (m, 2H), 7.20–7.22 (m, 1H), 7.25 (dd, J = 0.9, 6.6 Hz, 1H), 7.52–7.56 (m, 1H), 7.63 (dt, J = 1.7, 6.6 Hz, 1H), 8.57 (ddd, J = 0.9, 1.7, 6.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 55.8, 66.0, 71.7, 96.3, 121.7, 122.5, 126.5, 128.0, 130.1, 132.6, 134.7, 136.9, 145.4, 147.8, 160.5; IR (neat) 3400, 3064, 2937, 1589, 1435, 1205, 1150, 1035 cm^{-1}; HRMS (FAB, nitrobenzyl alcohol) calcd for $C_{15}H_{17}NO_3Br$ 338.0392, found 338.0373 (M + H).

2-Bromo-6-[1-methoxy-1-(2-pyridyl)methyl]benzyl methoxymethyl ether (8).

To a suspension of NaH (60% oil suspension, 223 mg, 5.58 mmol) in dry THF (40 mL) under N_2 in an ice bath was added dropwise a solution of **7** (1.25 g, 3.70 mmol) in dry THF (10 mL) over 15 min, and the mixture was stirred at 0 °C for 2.5 h. MeI (0.65 mL, 10 mmol) was added, and the mixture was stirred for 3 h. The mixture was filtered through Celite, and concentrated. The product was purified by silica gel column chromatography (hexane/EtOAc (5:1)) to afford **8** as a colorless oil (1.2 g, 100%): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 3.43 (s, 3H), 3.46 (s, 3H), 4.70 (d, J = 6.6 Hz, 1H), 4.73 (d, J = 6.6 Hz, 1H), 4.85 (d, J = 10.8 Hz, 1H), 5.03 (d, J = 10.8 Hz, 1H), 5.82 (s, 1H), 7.13–7.15 (m, 1H), 7.19 (t, J = 7.9 Hz, 1H), 7.41 (d, J = 7.9 Hz, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.53 (dd, J = 1.2, 7.9 Hz, 1H), 7.65 (dt, J = 1.8, 7.8 Hz, 1H), 8.52–8.53 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 55.7, 57.3, 65.6, 82.7, 96.3, 120.9, 122.4, 126.4, 126.7, 129.9, 132.5, 134.8, 136.7, 143.0, 149.1, 160.7; IR (neat) 2988, 2934, 1589, 1572, 1433, 1150, 1101, 1039 cm^{-1}; Anal. Calcd for $C_{16}H_{18}NO_3Br$: C, 54.56; H, 5.15; N, 3.98. Found: C, 54.39; H, 5.18; N, 3.64; HRMS (FAB, nitrobenzyl alcohol) calcd for $C_{16}H_{19}NO_3Br$ 352.0548, found 352.0563 (M + H).

2-Amino-6-[1-methoxy-1-(2-pyridyl)methyl]benzyl methoxymethyl ether (9).

A Schlenk tube was charged with $Pd_2(dba)_3$ (12.0 mg, 0.0131 mmol), (*R*)-BINAP (14.1 mg, 0.0226 mmol) and NaO^{t}Bu (192 mg, 2.00 mmol), and purged with Ar. Toluene (5.6 mL), benzophenone imine (0.29 mL, 1.7 mmol), and a solution of **8** (467 mg, 1.43 mmol) in toluene (2 mL) was added, and the mixture was heated under Ar at 80 °C for 21 h. The mixture was

cooled to room temperature, diluted with Et_2O (20 mL), filtered, and concentrated to afford diphenyl ketimine adduct. A mixture of the diphenyl ketimine adduct, NaOAc (200 mg, 2.44 mmol), and $HONH_2$•HCl (167 mg, 2.40 mmol) in MeOH (22 mL) was stirred at room temperature for 4 h. The mixture was concentrated, and the solution was adjusted to pH 10. The mixture was extracted with CH_2Cl_2 (10 mL × 3), dried over Na_2SO_4, and concentrated. The product was purified by silica gel column chromatography (hexane/EtOAc (5:4) to (1:2)) to afford **9** as a pale yellow oil (359 mg, 87%): ^{1}H NMR ($CDCl_3$, 600 MHz) δ3.38 (s, 3H), 3.43 (s, 3H), 4.18 (br s, 2H), 4.59 (d, J = 6.5 Hz, 1H), 4.62 (d, J = 6.5 Hz, 1H), 4.63 (d, J = 12.1 Hz, 1H), 4.92 (d, J = 12.1 Hz, 1H), 5.67 (s, 1H), 6.64 (dd, J = 0.9, 7.8 Hz, 1H), 6.88 (dd, J = 0.9, 7.8 Hz, 1H), 7.11–7.14 (m, 2H), 7.40 (d, J = 7.1 Hz, 1H), 7.62 (dt, J = 1.8, 7.1 Hz, 1H), 8.52 (ddd, J = 0.8, 1.8, 7.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ55.6, 57.2, 62.1, 83.5, 95.1, 115.7, 117.3, 120.2, 121.0, 122.1, 129.1, 136.5, 140.3, 147.2, 148.9, 161.3; IR (neat) 3445, 3366, 2887, 1589, 1470, 1435, 1304, 1150, 918, 783, 756 cm^{-1}; Anal. Calcd for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72. Found: C, 66.58; H, 6.97; N, 9.52; HRMS (FAB, nitrobenzyl alcohol) calcd for $C_{16}H_{21}N_2O_3$ 289.1552, found 289.1544 (M + H).

***N*-[3,5-Bis(trifluoromethyl)phenyl]-*N*'-{2-(methoxymethoxymethyl)-3-[1-methoxy-1-(2-pyridyl)methyl]phenyl}thiourea (10a).**

To a solution of **9** (810 mg, 2.81 mmol) in dry THF (7 mL) under N_2 in an ice bath was added 3,5-bis(trifluoromethyl)phenyl isothiocyanate (0.56 mL, 3.1 mmol). The mixture was stirred at room temperature for 22 h, and concentrated. The product was purified by silica gel column chromatography (hexane/EtOAc (2:1) to (1:2)) to afford **10a** as yellow crystals (1.47 g, 93%): mp 45 ºC (dec); ^{1}H NMR ($CDCl_3$, 600 MHz) δ3.35 (s, 3H), 3.47 (s, 3H), 4.62 (d, J = 6.6 Hz, 1H), 4.64 (d, J = 6.6 Hz, 1H), 4.71 (d, J = 12.0 Hz, 1H), 4.99 (d, J = 12.0 Hz, 1H), 5.78 (s, 1H), 7.19 (ddd, J = 1.1, 5.0, 7.7 Hz, 1H), 7.42–7.43 (m, 1H), 7.46 (t, J = 7.7 Hz, 1H), 7.51 (dd, J = 1.5, 7.7 Hz, 1H), 7.56 (d, J = 7.7 Hz, 1H), 7.66 (s, 1H), 7.73 (dt, J = 1.9, 7.7 Hz, 1H), 7.95 (s, 1H), 8.00 (s, 2H), 8.50 (ddd, J = 1.1, 1.9, 5.0 Hz, 1H), 8.58 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 55.7, 57.4, 62.2, 82.6, 96.0, 118.9 (sept, J_{CF} = 3.8 Hz), 121.1, 122.7, 122.9 (q, J_{CF} = 271.5 Hz), 124.1 (d, J_{CF} = 3.5 Hz), 126.4, 127.3, 129.8, 131.8 (q, J_{CF} = 33.0 Hz), 132.0, 136.7, 137.0, 139.9, 142.5, 149.0, 160.4, 180.4; ^{19}F NMR ($CDCl_3$, 565 MHz) δ–64.0; IR (KBr) 3271, 2939, 2891, 1591, 1522, 1472, 1383, 1279, 1180, 1134, 1026, 887, 683 cm^{-1}; HRMS (FAB, nitrobenzyl alcohol) calcd for $C_{25}H_{24}N_3O_3F_6S$ 560.1443, found 560.1447 (M + H).

***N*-[3,5-Bis(trifluoromethyl)phenyl]-*N*'-{2-(hydroxymethyl)-3-[1-methoxy-1-(2-pyridyl)methyl]phenyl}thiourea (1a).**

To a solution of **10a** (500 mg, 0.894 mmol) in dry CH_2Cl_2 (17 mL) under N_2 was added TMSBr (1.2 mL, 9.2 mmol) at –65 °C under N_2. The mixture was stirred at –50 °C for 3 h, and allowed to warm up slowly to –30 °C. The reaction was quenched with saturated aqueous $NaHCO_3$, and the solution was adjusted to pH 10. The mixture was extracted with CH_2Cl_2 (10 mL × 3), dried over Na_2SO_4, and concentrated. The product was purified by basic alumina column

chromatography (hexane/EtOAc (1:50) to EtOAc/MeOH (7:1)) to afford **1a** as pale yellow crystals (374 mg, 81%): mp 128 ºC (dec); ^{1}H NMR ($CDCl_3$, 600 MHz) δ3.48 (s, 3H), 4.97 (d, J = 12.6 Hz, 1H), 5.10 (d, J = 12.6 Hz, 1H), 5.81 (s, 1H), 7.16–7.18 (m, 1H), 7.29–7.31 (m, 1H), 7.36 (dt, J = 1.8, 7.8 Hz, 1H), 7.54 (d, J = 7.8 Hz, 1H), 7.59 (s, 1H), 7.73 (br s, 1H), 7.79–7.82 (m, 2H), 8.12 (s, 2H), 8.27 (d, J = 4.8 Hz, 1H), 8.73 (br s, 1H), 9.34 (br s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ56.2, 57.4, 80.7, 118.3 (sept, J_{CF} = 3.8 Hz), 119.6, 122.7, 123.1 (q, J_{CF} = 271.3 Hz), 123.6 (d, J_{CF} = 3.5 Hz), 126.6, 127.3, 129.9, 131.5 (q, J_{CF} = 33.4 Hz), 135.9, 136.2, 138.6, 140.9, 142.1, 147.5, 160.1, 182.0; ^{19}F NMR ($CDCl_3$, 565 MHz) δ–64.0; IR (KBr) 3163, 3001, 2901, 2831, 1597, 1528, 1474, 1389, 1281, 1180, 1126, 1003, 887, 702, 679 cm^{-1}; HRMS (FAB, nitrobenzyl alcohol) calcd for $C_{23}H_{20}N_3O_2F_6S$ 516.1180, found 516.1201 (M + H).

***N*-[3,5-Bis(trifluoromethyl)phenyl]-*N*'-{2-(methoxymethoxymethyl)-3-[1-methoxy-1-(2-pyridyl)methyl]phenyl}urea (10b).**

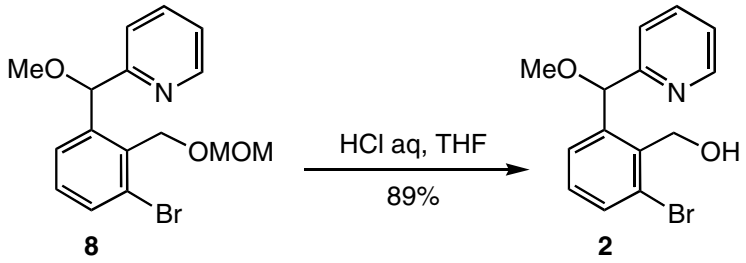
To a solution of **9** (236 mg, 0.820 mmol) in dry THF (2 mL) under N_2 in an ice bath was added 3,5-bis(trifluoromethyl)phenyl isocyanate (0.16 mL, 0.93 mmol). The mixture was stirred at room temperature for 12 h, and concentrated. The product was purified by silica gel column chromatography (hexane/EtOAc (1:1) to (1:2)) to afford **10b** as pale yellow crystals (395 mg, 89%): mp 140–142 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ3.30 (s, 3H), 3.42 (s, 3H), 4.49 (d, J = 6.6 Hz, 1H), 4.53 (d, J = 6.6 Hz, 1H), 4.64 (d, J = 12.1 Hz, 1H), 4.94 (d, J = 12.1 Hz, 1H), 5.71 (s, 1H), 7.19 (ddd, J = 1.5, 4.8, 7.2 Hz, 1H), 7.25–7.27 (m, 1H), 7.33 (t, J = 7.8 Hz, 1H), 7.47–7.48 (m, 2H), 7.68–7.72 (m, 2H), 7.78 (br s, 1H), 7.89 (s, 2H), 7.99 (br s, 1H), 8.50–8.51 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ55.8, 57.3, 62.6, 83.4, 95.9, 116.0 (sept, J_{CF} = 3.9 Hz), 118.6 (d, J_{CF} = 3.2 Hz), 121.2, 122.6, 123.2 (q, J_{CF} = 271.3 Hz), 123.5, 124.0, 127.1, 129.4, 132.1 (q, J_{CF} = 33.3 Hz), 137.0, 138.0, 140.4, 140.7, 148.9, 152.6, 160.8; ^{19}F NMR ($CDCl_3$, 565 MHz) δ –64.1; IR (KBr) 3348, 3092, 2939, 1574, 1474, 1389, 1277, 1180, 1130, 702 cm^{-1}; Anal. Calcd for $C_{25}H_{23}N_3O_4F_6$: C, 55.25; H, 4.27; N, 7.73. Found: C, 55.38; H, 4.30; N, 7.33; HRMS (FAB, nitrobenzyl alcohol) calcd for $C_{25}H_{24}N_3O_4F_6$ 544.1671, found 544.1642 (M + H).

***N*-[3,5-Bis(trifluoromethyl)phenyl]-*N*'-{2-(hydroxymethyl)-3-[1-methoxy-1-(2-pyridyl)methyl]phenyl}urea (1b).**

To a solution of **10b** (284 mg, 0.522 mmol) in dry CH_2Cl_2 (10 mL) under N_2 was added TMSBr (0.7 mL, 5.4 mmol) at –65 °C under N_2. The mixture was stirred at –60 °C for 3 h, and allowed to warm up slowly to –40 °C. The reaction was quenched with saturated aqueous $NaHCO_3$, and the solution was adjusted to pH 10. The mixture was extracted with CH_2Cl_2 (6 mL × 3), dried over Na_2SO_4, and concentrated. The product was purified by silica gel column chromatography (hexane/EtOAc (3:2) to (1:1)) to afford **1b** as pale yellow crystals (220 mg, 85%): mp 162 ºC (dec); ^{1}H NMR ($CDCl_3$, 600 MHz) δ3.50 (s, 3H), 5.08 (dd, J = 7.2, 12.8 Hz, 1H), 5.16 (dd, J = 7.2, 12.8 Hz, 1H), 5.83 (s, 1H), 7.12 (t, J = 5.6 Hz, 1H), 7.32–7.38 (m, 2H), 7.41 (s, 1H), 7.62 (t, J = 6.6 Hz, 1H), 7.76 (s, 2H), 7.78–7.84 (m, 2H), 8.01 (br s, 1H), 8.20–8.26 (m, 2H), 8.81 (br s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ56.2, 57.3, 80.9, 115.6 (sept, J_{CF} = 3.4 Hz), 118.4, 119.9,

122.5, 123.05, 123.12 (q, J_{CF} = 271.4 Hz), 124.9, 129.5, 131.9 (q, J_{CF} = 33.1 Hz), 136.8, 138.6, 140.8, 141.0, 147.4, 154.0, 160.5; ^{19}F NMR ($CDCl_3$, 565 MHz) δ–64.2; IR (KBr) 3317, 3117, 2901, 1681, 1574, 1474, 1389, 1281, 1180, 756 cm^{-1}; HRMS (FAB, nitrobenzyl alcohol) calcd for $C_{23}H_{20}N_3O_3F_6$ 500.1409, found 500.1394 (M + H).

Scheme S2

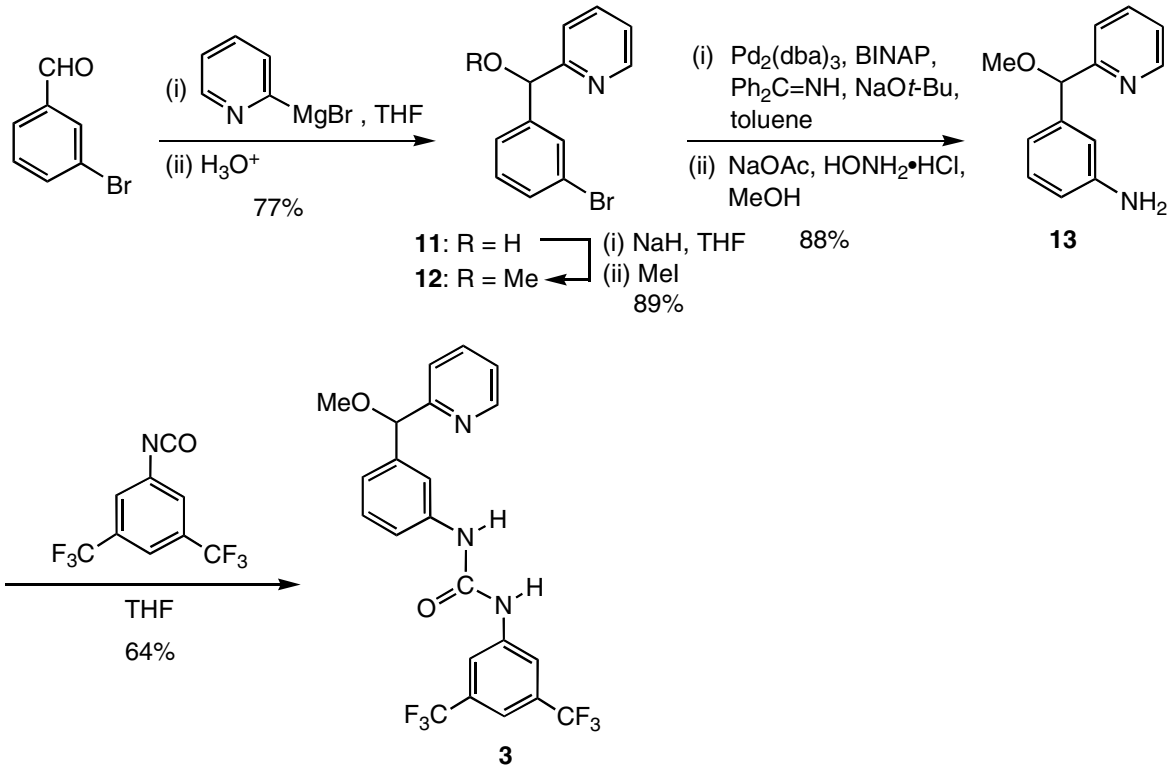


8 **2**

2-Bromo-6-[1-methoxy-1-(2-pyridyl)methyl]benzyl alcohol (2).

To a solution of **8** (176 mg, 0.500 mmol) in THF (3 mL) was added 2N HCl (3 mL), and the solution was heated at reflux for 9 h. The mixture was neutralized with saturated aqueous $NaHCO_3$, extracted with EtOAc (5 mL × 3), dried over Na_2SO_4, and concentrated. The product was purified by silica gel column chromatography (hexane/EtOAc (5:1) to afford **2** as white crystals (138 mg, 89%): mp 109–110 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ3.44 (s, 3H), 5.08 (d, J = 12.6 Hz, 1H), 5.11 (d, J = 12.6 Hz, 1H), 5.83 (s, 1H), 6.49 (br s, 1H), 7.11 (t, J = 8.0 Hz, 1H), 7.12–7.14 (m, 1H), 7.40 (dd, J = 1.2, 8.0 Hz, 1H), 7.51 (dd, J = 1.2, 8.0 Hz, 1H), 7.74–7.77 (m, 2H), 8.36 (dt, J = 1.2, 5.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ57.2, 60.9, 81.2, 119.2, 122.3, 125.4, 126.1, 129.6, 132.5, 138.0, 138.4, 142.4, 148.1, 160.4; IR (KBr) 3418, 3186, 2932, 2862, 2824, 1589, 1574, 1481, 1435, 1188, 1103, 1018, 972, 718, 679 cm^{-1}; HRMS (FAB, nitrobenzyl alcohol) calcd for $C_{14}H_{15}NO_2Br$ 308.0286, found 308.0286 (M + H).

Scheme S3



1-Bromo-3-[1-hydroxy-1-(2-pyridyl)methyl]benzene (11).

To a suspension of Mg (426 mg, 17.5 mmol) in dry THF (30 mL) under N_2 was added dropwise 1,2-dibromoethane (0.75 mL, 8.7 mmol) at room temperature, and subsequently 2-bromopyridine (0.85 mL, 8.8 mmol) was added. The mixture was stirred for 1 h. To the slurry was added *m*-bromobenzaldehyde (1.1 mL, 9.0 mmol), and the mixture was stirred at room temperature for 1.3 h. The reaction was quenched with saturated aqueous NH_4Cl, and the solution was adjusted to pH 5. The mixture was extracted with Et_2O (10 mL × 3), dried over $MgSO_4$, and concentrated. The product was purified by silica gel column chromatography (hexane/EtOAc (3:1) to (1:1)) to afford **11** as white crystals (1.77 g, 77%): mp 92–94 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ5.38 (br s, 1H), 5.70 (s, 1H), 7.14–7.16 (m, 1H), 7.20 (t, J = 7.2 Hz, 1H), 7.21–7.23 (m, 1H), 7.31–7.33 (m, 1H), 7.40 (ddd, J = 1.1, 1.8, 7.9 Hz, 1H), 7.53 (t, J = 1.8 Hz, 1H), 7.64 (dt, J = 1.3, 7.2 Hz, 1H), 8.57 (dt, J = 1.3, 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ74.2, 121.3, 122.66, 122.7, 125.6, 130.0, 130.1, 130.9, 137.0, 145.5, 147.9, 160.0; IR (KBr) 3109, 2909, 2862, 2708, 1597, 1574, 1474, 1435, 1319, 1188, 1065, 1003, 771, 694 cm^{-1}; HRMS (FAB, nitrobenzyl alcohol) calcd for $C_{12}H_{11}NOBr$ 264.0024, found 264.0020 (M + H).

1-Bromo-3-[1-methoxy-1-(2-pyridyl)methyl]benzene (12).

To a suspension of NaH (60% oil suspension, 400 mg, 10.0 mmol) in dry THF (55 mL) under N_2 in an ice bath was added dropwise a solution of **11** (1.74 g, 6.63 mmol) in dry THF (18 mL) over 15 min. The mixture was stirred for 2 h, and MeI (1.2 mL, 19 mmol) was added. The mixture was stirred for 1.5 h, filtered through Celite, and concentrated. The product was purified by silica gel column chromatography (hexane/EtOAc (4:1) to (2:1)) to afford **12** as a

pale yellow oil (1.63 g, 89%): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 3.43 (s, 3H), 5.32 (s, 1H), 7.15–7.19 (m, 2H), 7.34–7.38 (m, 2H), 7.46 (d, J = 8.4 Hz, 1H), 7.59 (t, J = 1.3 Hz, 1H), 7.68 (dt, J = 1.3, 6.8 Hz, 1H), 8.54 (dt, J = 1.3, 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 57.2, 85.6, 120.4, 122.6, 125.5, 129.7, 130.0, 130.7, 136.9, 143.2, 149.0, 160.8; IR (neat) 3055, 2928, 2824, 1587, 1572, 1470, 1433, 1194, 1107, 995, 980, 779 cm^{-1}; HRMS (FAB, nitrobenzyl alcohol) calcd for $C_{13}H_{13}NOBr$ 278.0181, found 278.0206 (M + H).

1-Amino-3-[1-methoxy-1-(2-pyridyl)methyl]benzene (13).

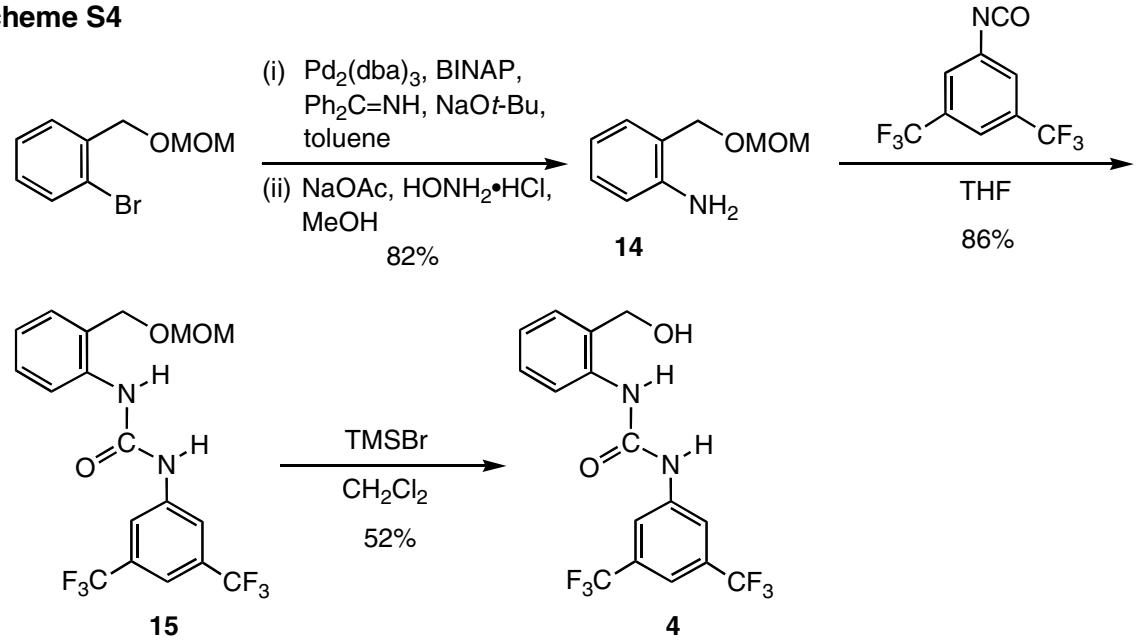
A two-necked flask was charged with $Pd_2(dba)_3$ (16.7 mg, 0.0182 mmol), (*R*)-BINAP (11.7 mg, 0.0188 mmol) and NaO^{t}Bu (253 mg, 2.63 mmol), and purged with Ar. To the flask was added toluene (7.5 mL), benzophenone imine (0.40 mL, 2.4 mmol), and a solution of **12** (522 mg, 1.88 mmol) in toluene (2.5 mL), and the mixture was heated under Ar at 80 °C for 18 h. The mixture was cooled to room temperature, diluted with Et_2O (20 mL), filtered, and concentrated to afford diphenyl ketimine adduct. A mixture of the diphenyl ketimine adduct, NaOAc (264 mg, 3.22 mmol), and $HONH_2$•HCl (222 mg, 3.19 mmol) in MeOH (25 mL) was stirred at room temperature for 2 h. The mixture was concentrated, and the solution was adjusted to pH 10. The mixture was extracted with CH_2Cl_2 (10 mL × 3), dried over Na_2SO_4, and concentrated. The product was purified by silica gel column chromatography (hexane/EtOAc (1:1) to (1:3)) to afford **13** as a pale yellow oil (356 mg, 88%): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 3.42 (s, 3H), 3.64 (br s, 2H), 5.27 (s, 1H), 6.57 (ddd, J = 1.2, 2.3, 7.8 Hz, 1H), 6.77 (t, J = 2.3 Hz, 1H), 6.82 (d, J = 7.8 Hz, 1H), 7.11 (t, J = 7.8 Hz, 1H), 7.13–7.16 (m, 1H), 7.47 (d, J = 6.7 Hz, 1H), 7.66 (dt, J = 1.8, 6.7 Hz, 1H), 8.53 (ddd, J = 1.1, 1.8, 6.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 57.1, 86.4, 113.4, 114.5, 117.1, 120.5, 122.3, 129.3, 136.7, 141.9, 146.5, 148.9, 161.5; IR (neat) 3441, 3348, 3217, 2932, 2824, 1589, 1458, 1304, 1088, 995, 756, 702 cm^{-1}; HRMS (FAB, nitrobenzyl alcohol) calcd for $C_{13}H_{15}N_2O$ 215.1184, found 215.1187 (M + H).

***N*-[3,5-Bis(trifluoromethyl)phenyl]-*N*'-{3-[1-methoxy-1-(2-pyridyl)methyl]phenyl}urea (3).**

To a solution of **13** (193 mg, 0.899 mmol) in dry THF (7 mL) under N_2 in an ice bath was added 3,5-bis(trifluoromethyl)phenyl isocyanate (0.17 mL, 0.99 mmol) under N_2. The mixture was stirred at room temperature for 16 h, and concentrated. The product was purified by silica gel column chromatography (hexane/EtOAc (3:1)) to afford **3** as white crystals (269 mg, 64%): mp 164 ºC (dec); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 3.35 (s, 3H), 5.34 (s, 1H), 7.08 (d, J = 7.8 Hz, 1H), 7.17 (t, J = 1.5 Hz, 1H), 7.22 (ddd, J = 1.3, 4.8, 7.6 Hz, 1H), 7.25 (t, J = 7.8 Hz, 1H), 7.41 (d, J = 7.6 Hz, 1H), 7.45 (s, 1H), 7.51 (dd, J = 1.5, 7.8 Hz, 1H), 7.75 (dt, J = 1.3, 7.6 Hz, 1H), 7.85 (s, 2H), 8.33 (br s, 1H), 8.39–8.41 (m, 1H), 8.80 (br s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 56.9, 85.3, 115.6 (sept, J_{CF} = 3.8 Hz), 118.3, 119.8, 122.7, 122.9, 123.1 (q, J_{CF} = 271.5 Hz), 123.6, 129.5, 132.0 (q, J_{CF} = 33.5 Hz), 138.0, 139.1, 140.2, 140.7, 148.7, 152.1, 153.0, 159.9; ^{19}F NMR ($CDCl_3$, 565 MHz) δ –64.1; IR (KBr) 3348, 3094, 2939, 2839, 1713, 1666, 1558, 1474, 1389, 1281, 1173, 1126, 880, 702 cm^{-1}; HRMS (FAB, nitrobenzyl alcohol) calcd for

$C_{22}H_{18}N_3O_2F_6$ 470.1303, found 470.1300 (M + H).

Scheme S4



2-Aminobenzyl methoxymethyl ether (14).

A Schlenk tube was charged with $Pd_2(dba)_3$ (14.2 mg, 0.0155 mmol), (*R*)-BINAP (16.0 mg, 0.0257 mmol) and NaO^{t}Bu (220 mg, 2.29 mmol), and purged with Ar. Toluene (7 mL), benzophenone imine (0.34 mL, 2.0 mmol), and a solution of 2-bromobenzyl methoxymethyl ether[2] (392 mg, 1.70 mmol) in toluene (2 mL) was added, and the mixture was heated under Ar at 80 °C for 19 h. The mixture was cooled to room temperature, diluted with Et_2O (20 mL), filtered, and concentrated to afford diphenyl ketimine adduct. A mixture of diphenyl ketimine adduct, NaOAc (230 mg, 2.80 mmol), and $HONH_2$•HCl (195 mg, 2.81 mmol) in MeOH (25 mL) was stirred at room temperature for 4 h. The mixture was concentrated, and the solution was adjusted to pH 10. The mixture was extracted with CH_2Cl_2 (10 mL × 3), dried over Na_2SO_4, and concentrated. The product was purified by silica gel column chromatography (hexane/EtOAc (4:1) to (1:2)) to afford **14** as a pale yellow oil (224 mg, 82%): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 3.41 (s, 3H), 4.10 (br s, 2H), 4.60 (s, 2H), 4.67 (s, 2H), 6.69–6.74 (m, 2H), 7.10–7.16 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 55.5, 67.6, 95.0, 115.8, 118.1, 121.7, 129.5, 130.5, 146.3; IR (neat) 3456, 3371, 3240, 2939, 2885, 1620, 1497, 1458, 1150, 1034 756 cm^{-1}; Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.35; H, 7.69; N, 8.27.

***N*-[3,5-Bis(trifluoromethyl)phenyl]-*N*'-[2-(methoxymethoxymethyl)phenyl]urea (15).**

To a solution of **14** (326 mg, 1.95 mmol) in dry THF (10 mL) under N_2 in an ice bath was added 3,5-bis(trifluoromethyl)phenyl isocyanate (0.40 mL, 2.3 mmol). The mixture was stirred at room temperature for 17 h, and concentrated. The product was purified by silica gel column chromatography (hexane/EtOAc (3:1)) to afford **15** as white crystals (709 mg, 86%): mp 143–144 ºC; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 3.40 (s, 3H), 4.67 (s, 2H), 4.68 (s, 2H), 7.13 (dt, *J* =

1.2, 7.6 Hz, 1H), 7.29 (dd, J = 1.2, 7.6 Hz, 1H), 7.36–7.39 (m, 2H), 7.52 (s, 1H), 7.78 (s, 1H), 7.84 (d, J = 7.6 Hz, 1H), 7.88 (s, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 55.8, 68.0, 95.8, 116.3 (sept, J_{CF} = 3.8 Hz), 118.9 (d, J_{CF} = 2.9 Hz), 123.1 (q, J_{CF} = 271.2 Hz), 123.2, 124.8, 128.0, 129.7, 130.4, 132.3 (q, J_{CF} = 33.2 Hz), 136.9, 140.1, 152.5; ^{19}F NMR ($CDCl_3$, 565 MHz) δ –64.1; IR (KBr) 3356, 3263, 3086, 2993, 2954, 1659, 1574, 1389, 1281, 1173, 1126, 1026, 895, 748, 702 cm^{-1}; Anal. Calcd for $C_{18}H_{16}N_2O_3F_6$: C, 51.19; H, 3.82; N, 6.63. Found: C, 51.33; H, 3.86; N, 6.28; HRMS (FAB, nitrobenzyl alcohol) calcd for $C_{18}H_{17}N_2O_3F_6$ 423.1143, found 423.1166 (M + H).

***N*-[3,5-Bis(trifluoromethyl)phenyl]-*N*'-[2-(hydroxymethyl)phenyl]urea (4).**

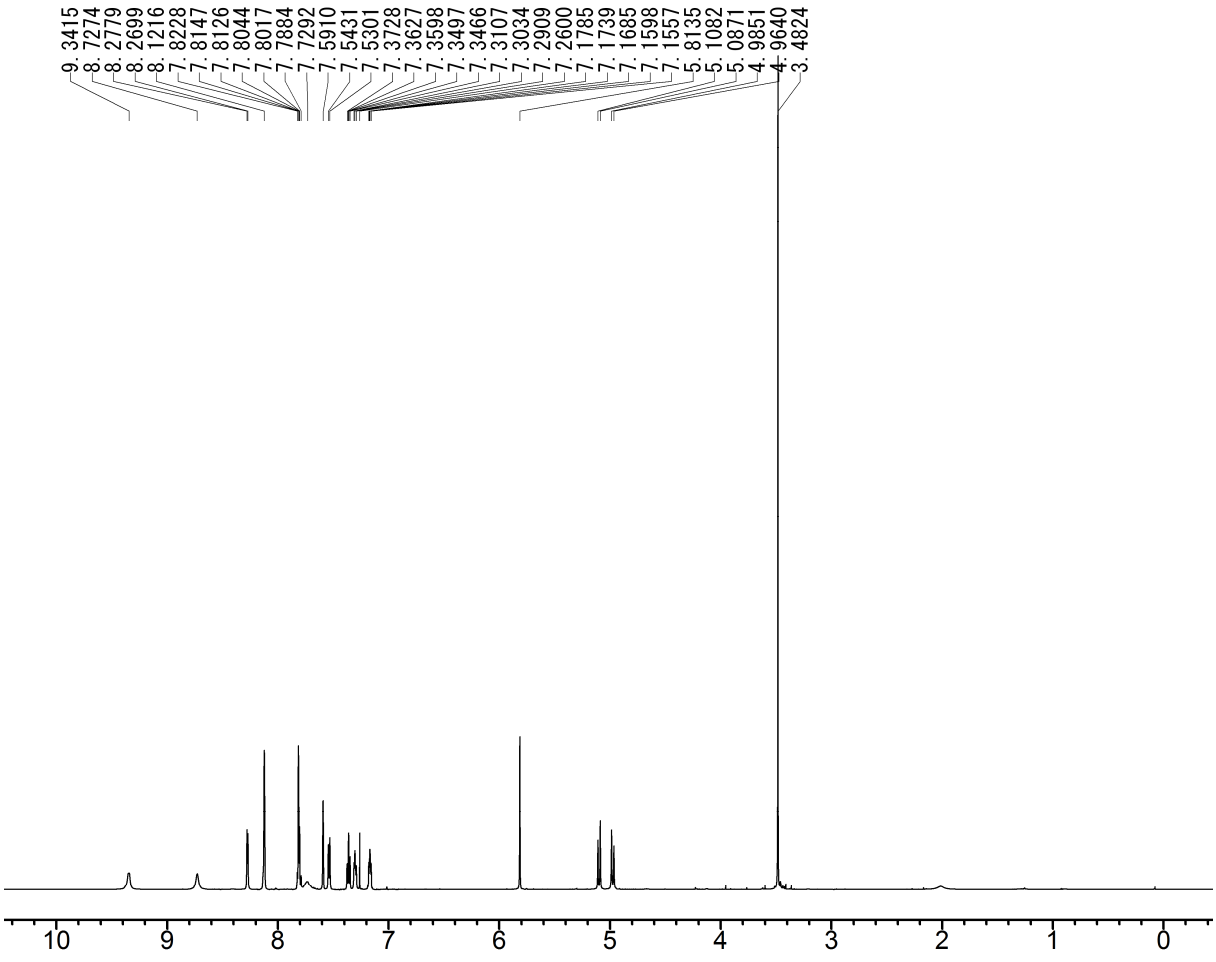
To a solution of **15** (300 mg, 0.710 mmol) in dry CH_2Cl_2 (13 mL) under N_2 was added TMSBr (0.92 mL, 7.1 mmol) at –78 °C. The mixture was stirred at –65 °C for 3 h, and allowed to warm up slowly to –55 °C. The reaction was quenched with saturated aqueous $NaHCO_3$, and the solution was adjusted to pH 10. The mixture was extracted with CH_2Cl_2 (50 mL × 1, 20 mL × 2), dried over Na_2SO_4, and concentrated. Recrystallization from CH_2Cl_2 afforded **4** as a white solid (140 mg, 52%): mp 184.5–185.5 ºC; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 4.77 (s, 2H), 7.09 (s, 1H), 7.13 (t, J = 7.4 Hz, 1H), 7.25 (d, J = 7.4 Hz, 1H), 7.39 (t, J = 7.3 Hz, 1H), 7.54 (s, 1H), 7.85 (s, 1H), 7.90 (d, J = 7.3 Hz, 1H), 7.94 (s, 2H); ^{13}C NMR (d_6-acetone, 150 MHz) δ 63.8, 115.3 (sept, J_{CF} = 3.9 Hz), 118.8 (d, J_{CF} = 2.9 Hz), 122.6, 123.8, 124.5 (q, J_{CF} = 270.4 Hz), 128.8, 129.2, 131.6, 132.4 (q, J_{CF} = 32.7 Hz), 138.9, 143.3, 153.2; ^{19}F NMR ($CDCl_3$, 565 MHz) δ –64.1; IR (KBr) 3317, 3101, 1666, 1574, 1389, 1281, 1134, 887, 756 cm^{-1}; HRMS (FAB, nitrobenzyl alcohol) calcd for $C_{16}H_{13}N_2O_2F_6$ 379.0881, found 379.0897 (M + H).

References

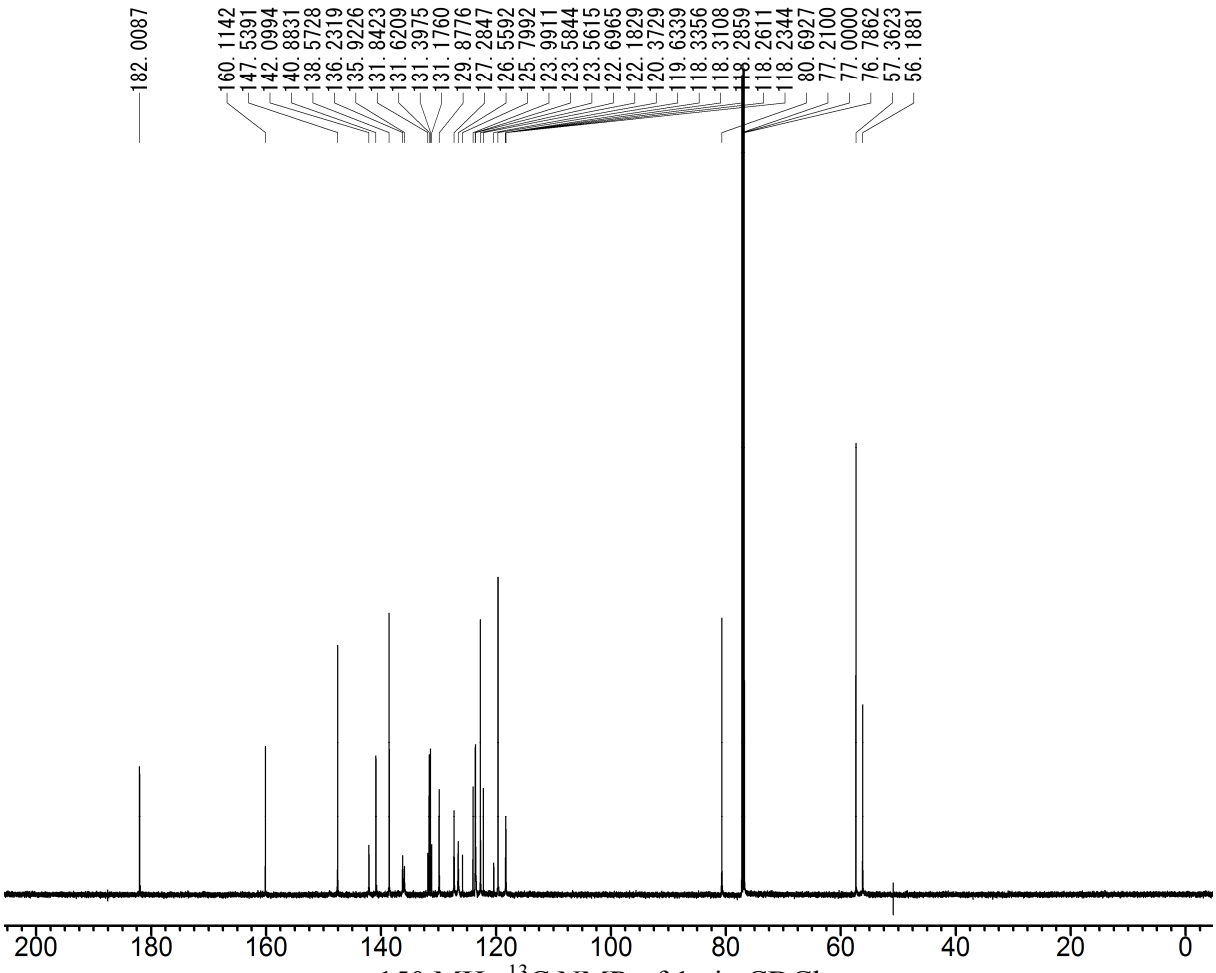
1 S. Lulinski and J. Serwatowski, *J. Org. Chem.*, 2003, **68**, 5384–5387.

2 S. J. Baker, Y.-K. Zhang, T. Akama, A. Lau, H. Zhou, V. Hernandez, W. Mao, M. R. K. Alley, V. Sanders and J. J. Plattner, *J. Med. Chem*., 2006, **49**, 4447–4450.

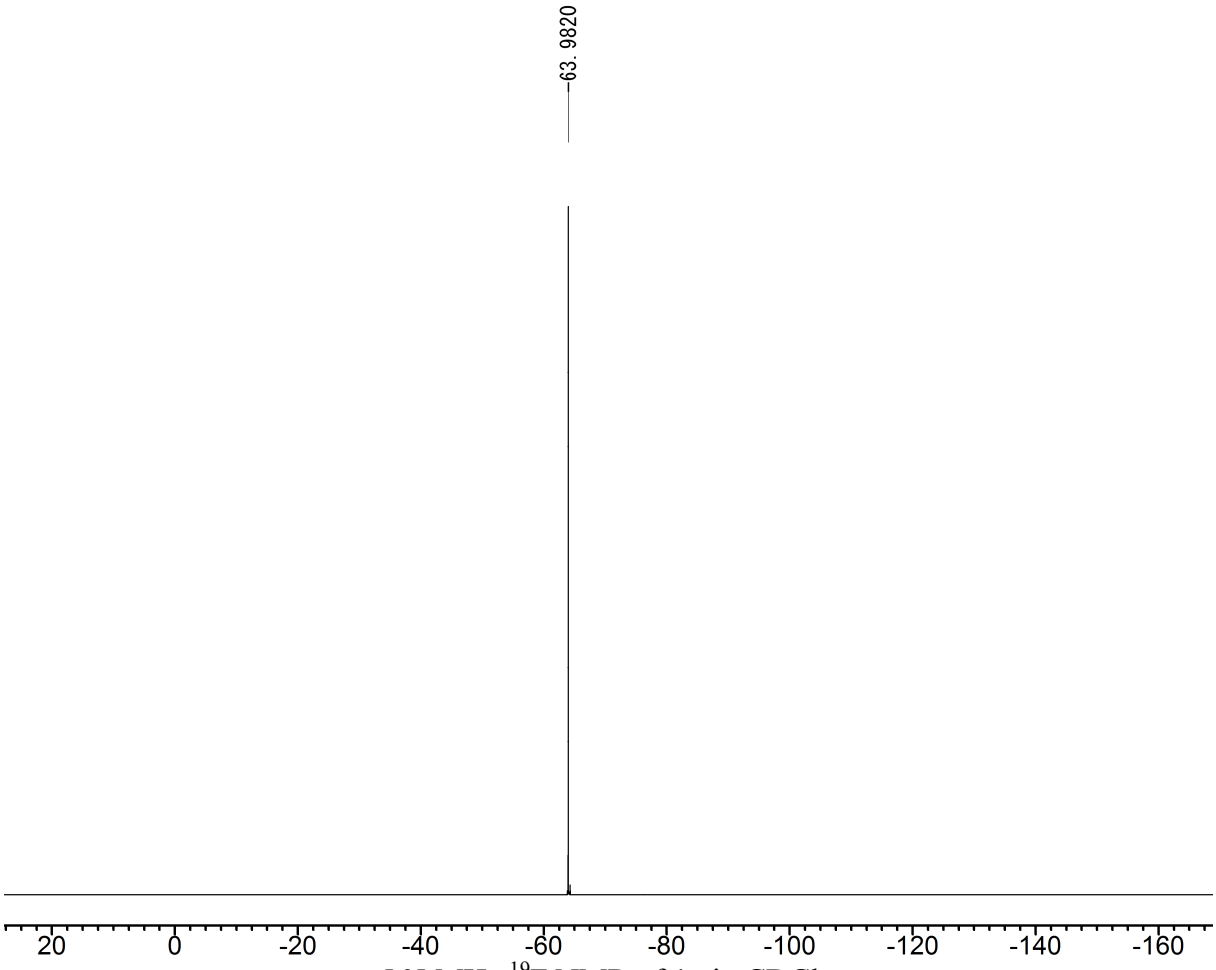
^{1}H, ^{13}C, and ^{19}F NMR Spectra.



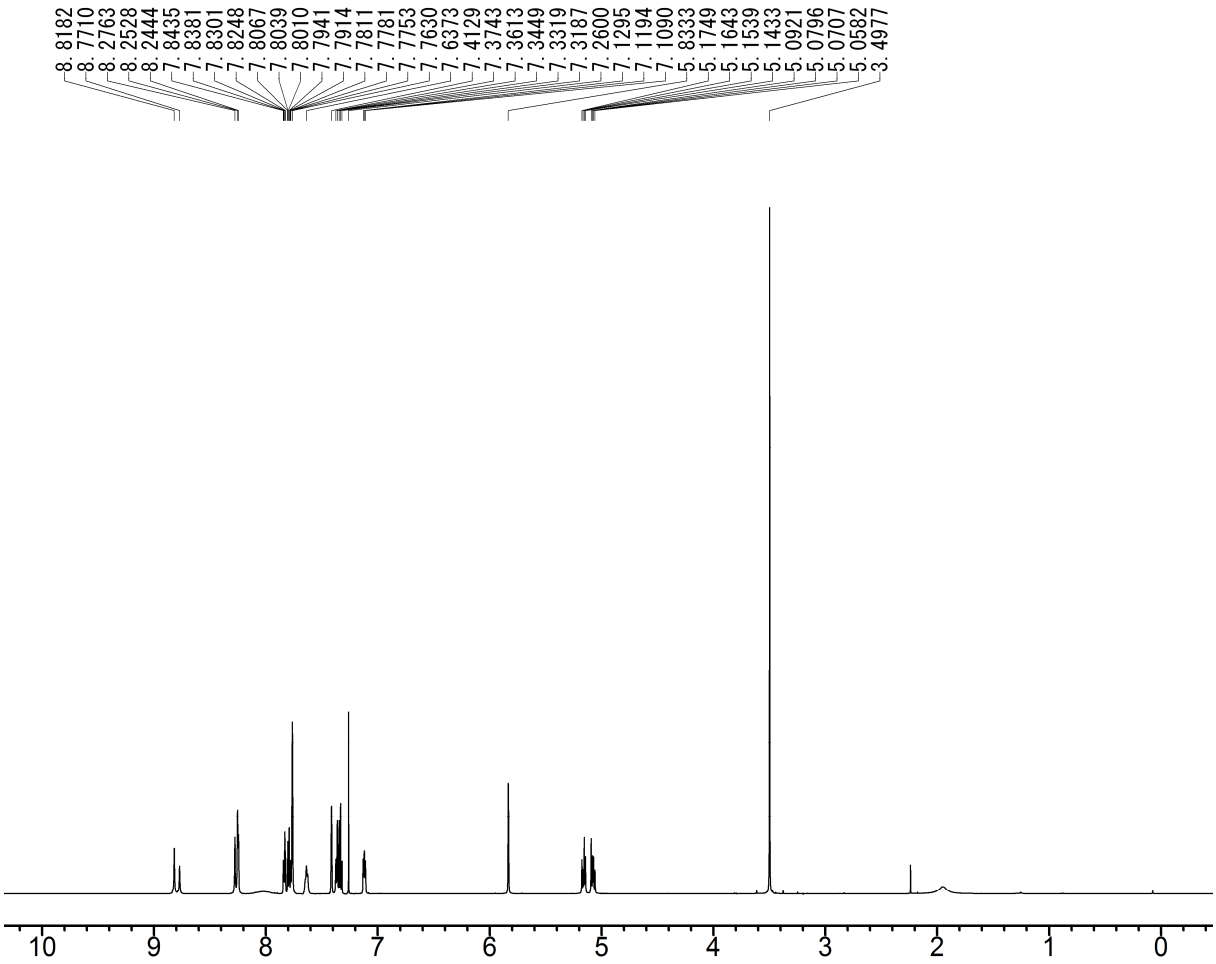
600 MHz ^{1}H NMR of **1a** in $CDCl_3$.



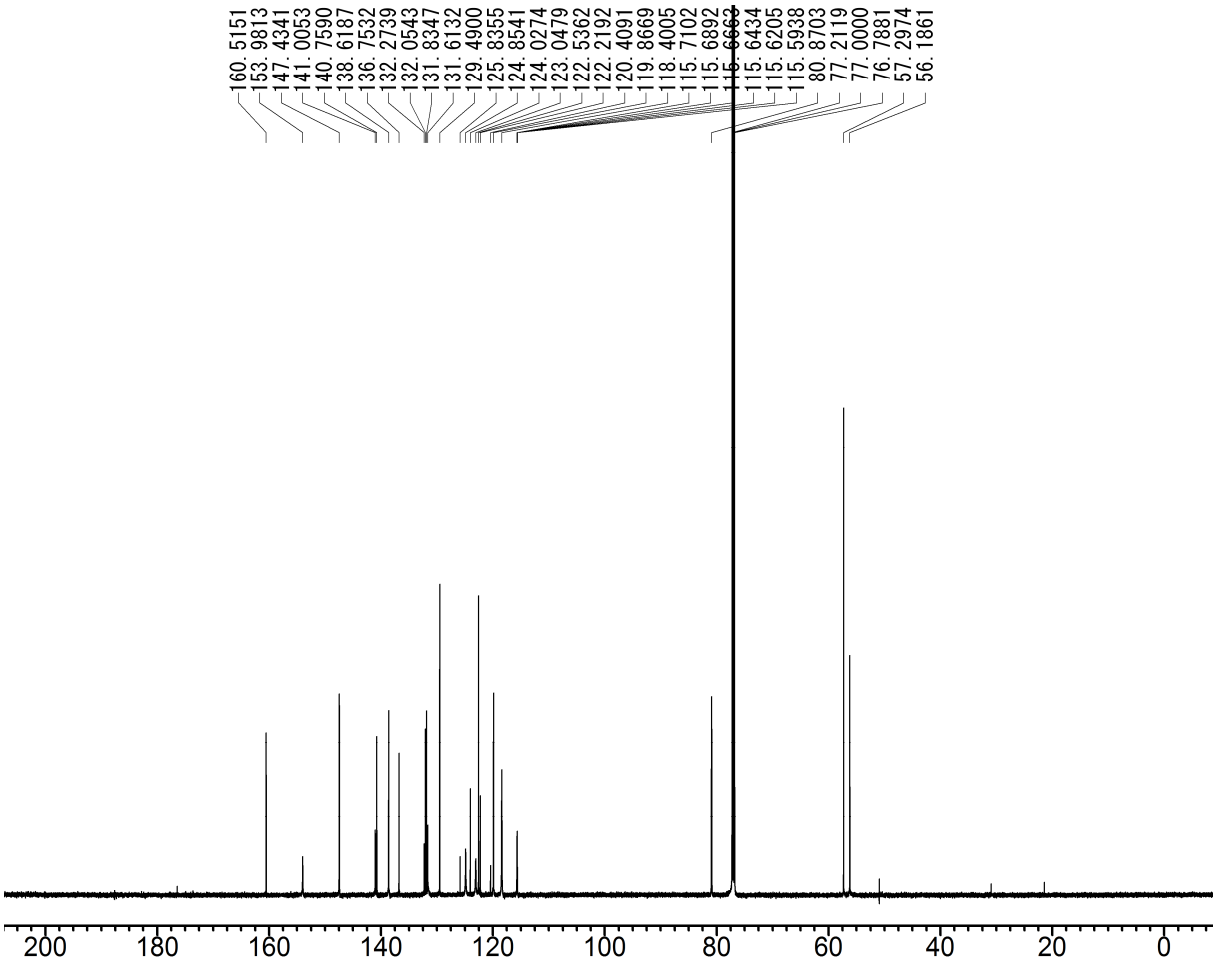
150 MHz ^{13}C NMR of **1a** in $CDCl_3$.



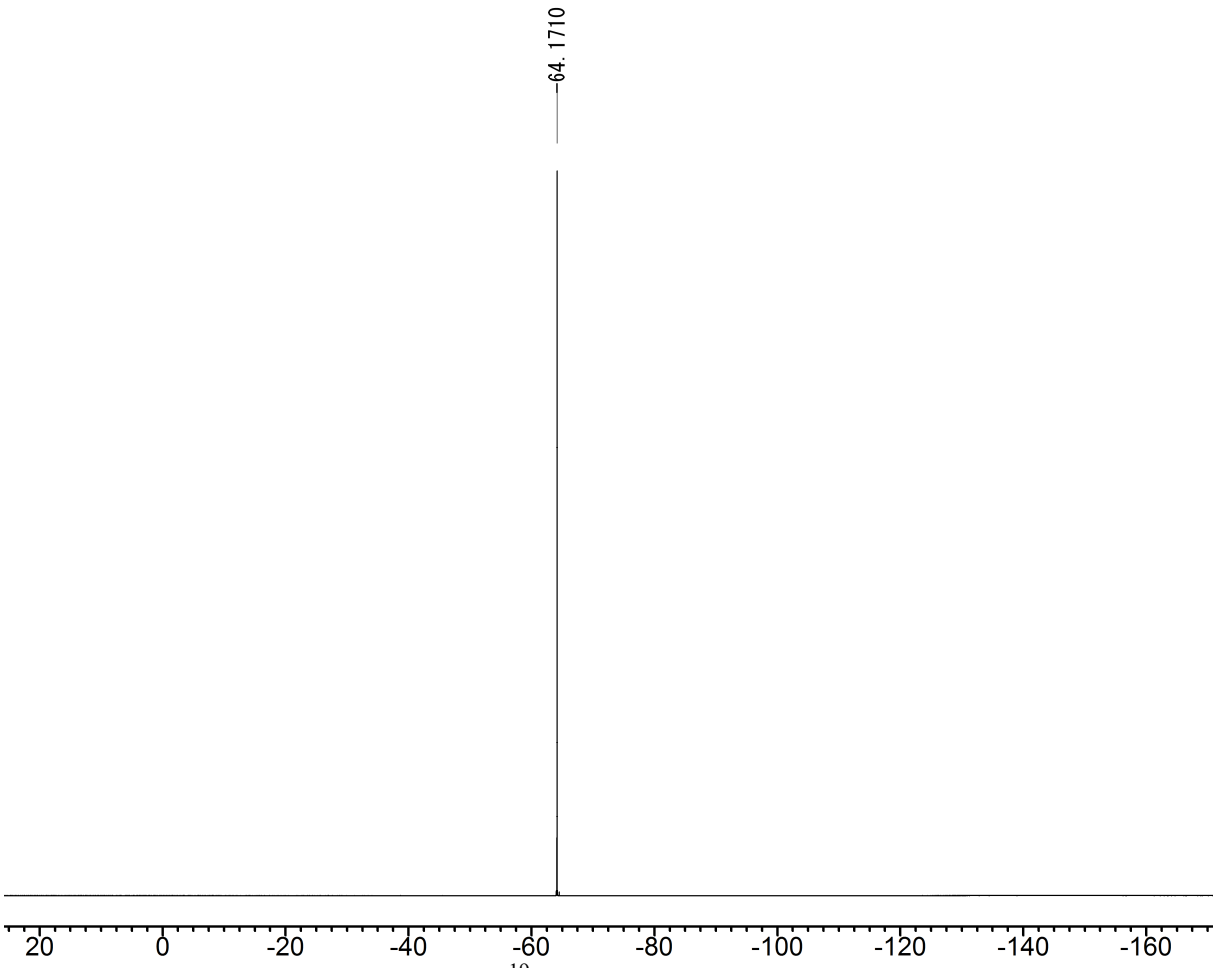
565 MHz ^{19}F NMR of **1a** in $CDCl_3$.



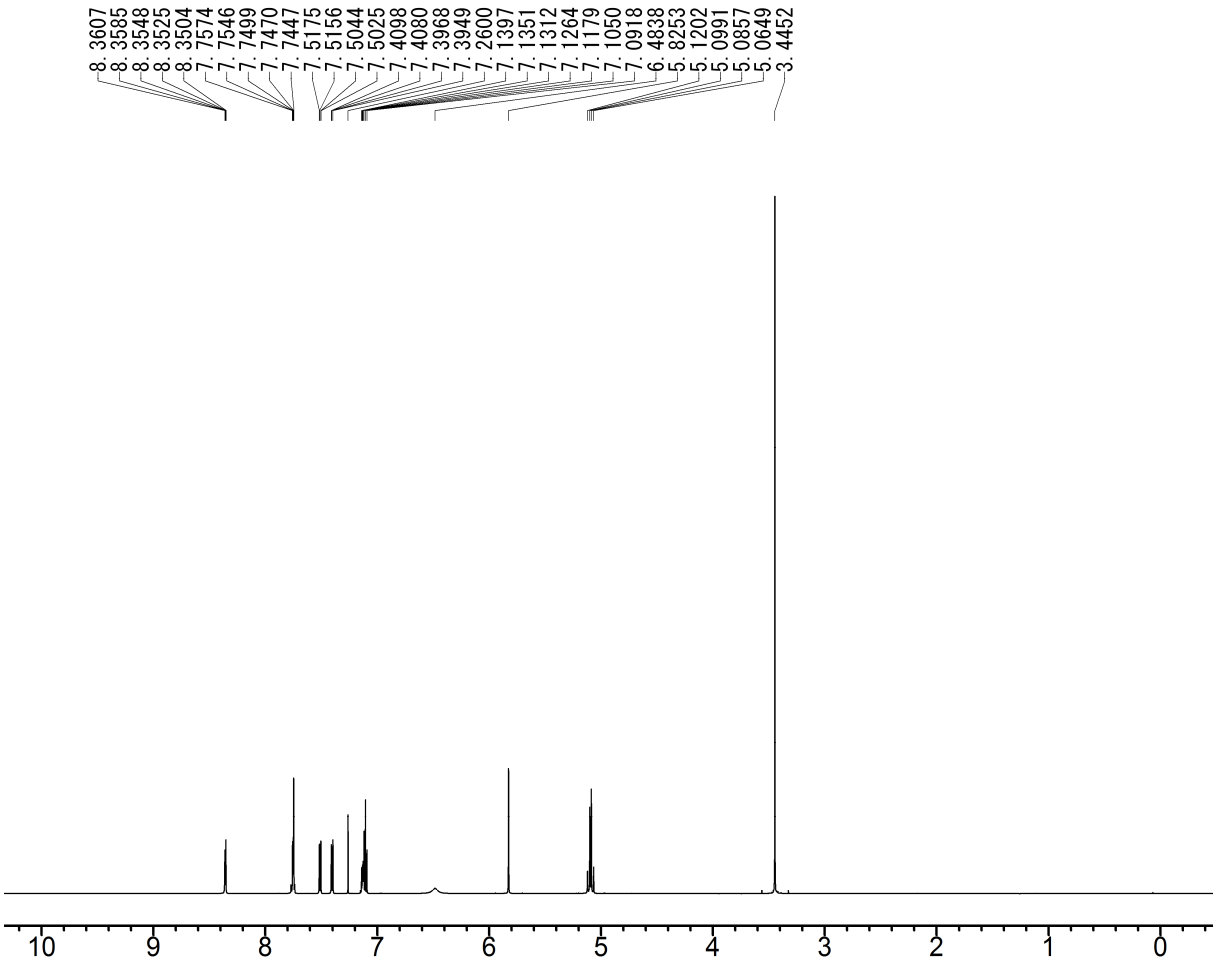
600 MHz ^{1}H NMR of **1b** in $CDCl_3$.



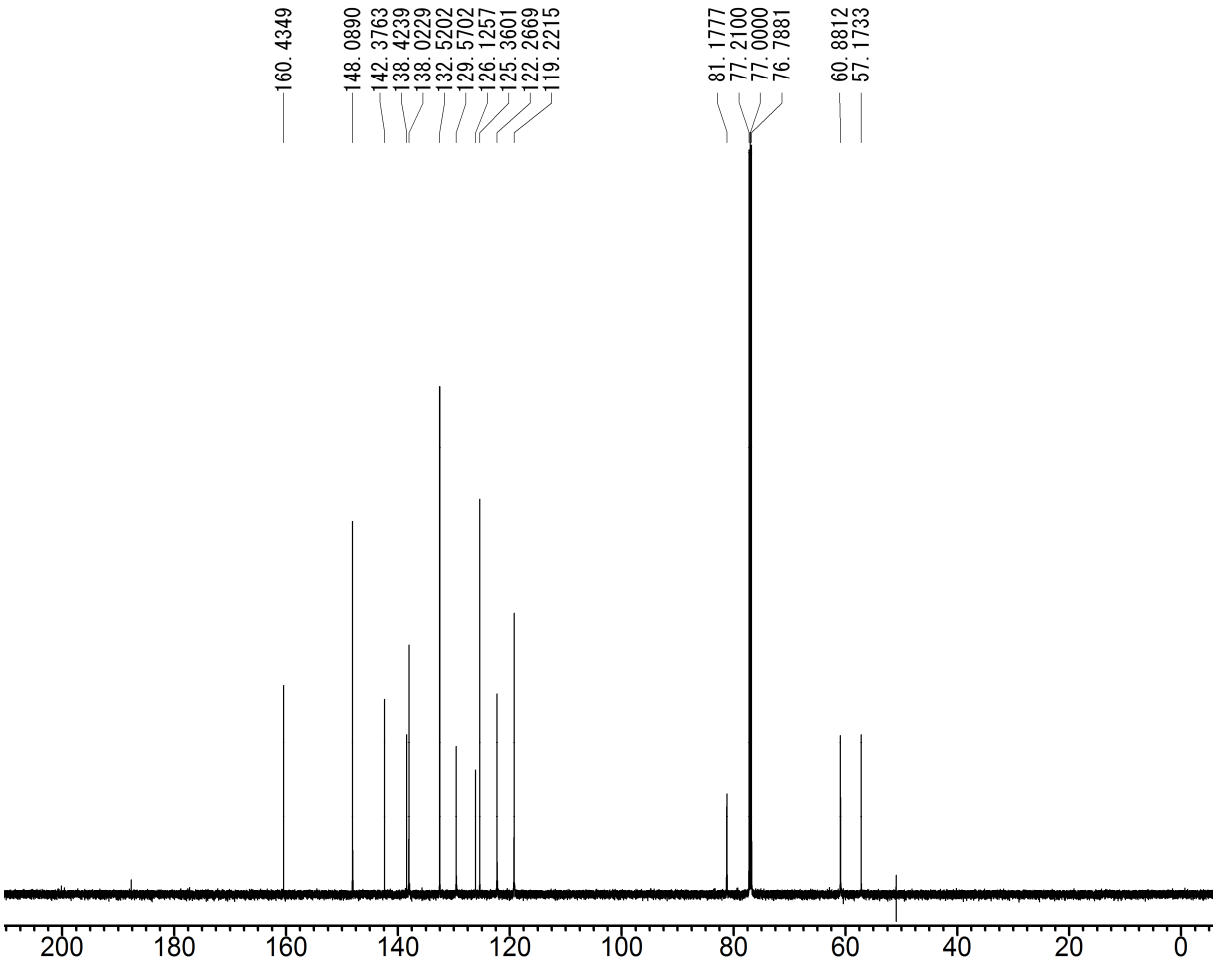
150 MHz ^{13}C NMR of **1b** in $CDCl_3$.



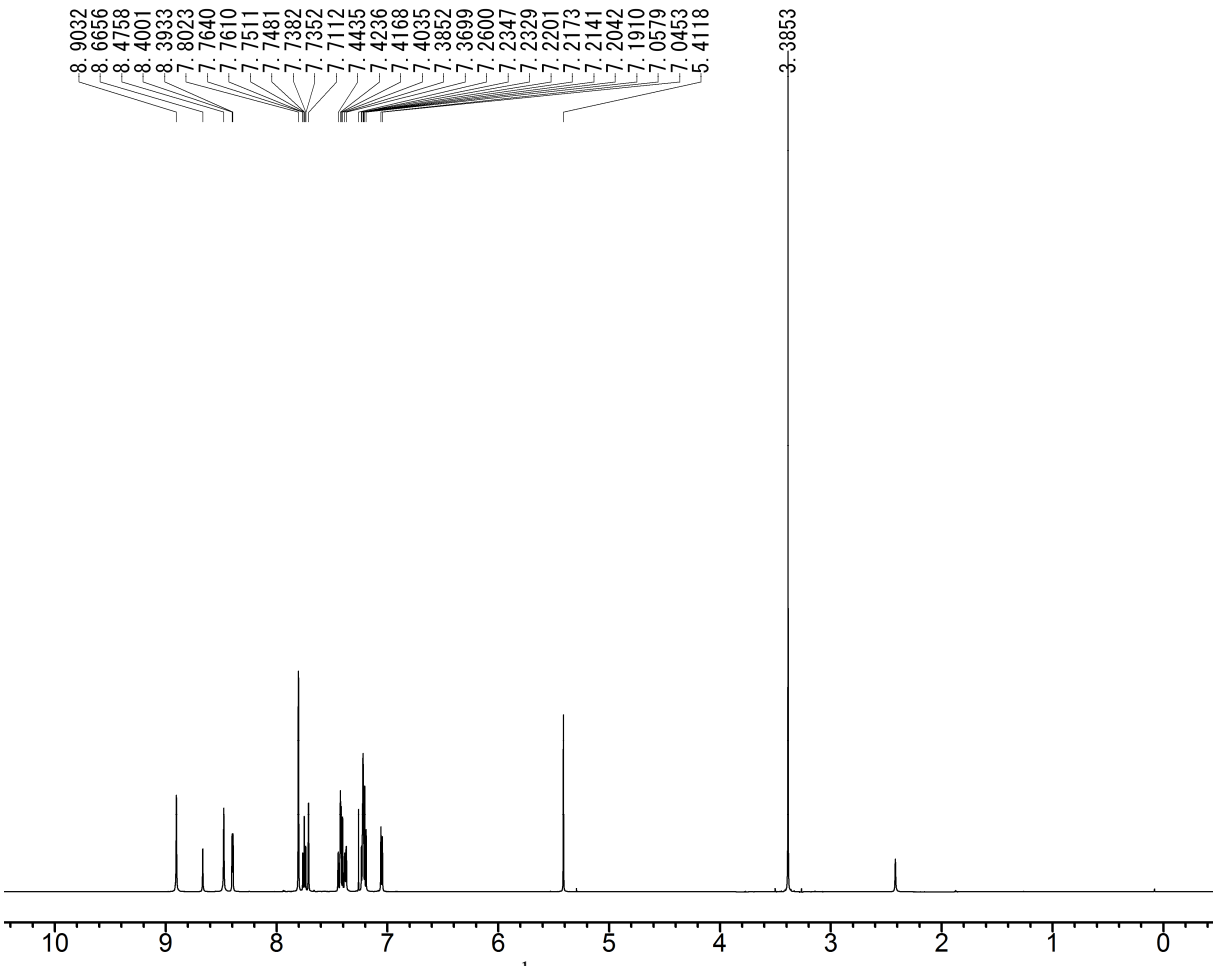
565 MHz ^{19}F NMR of **1b** in $CDCl_3$.



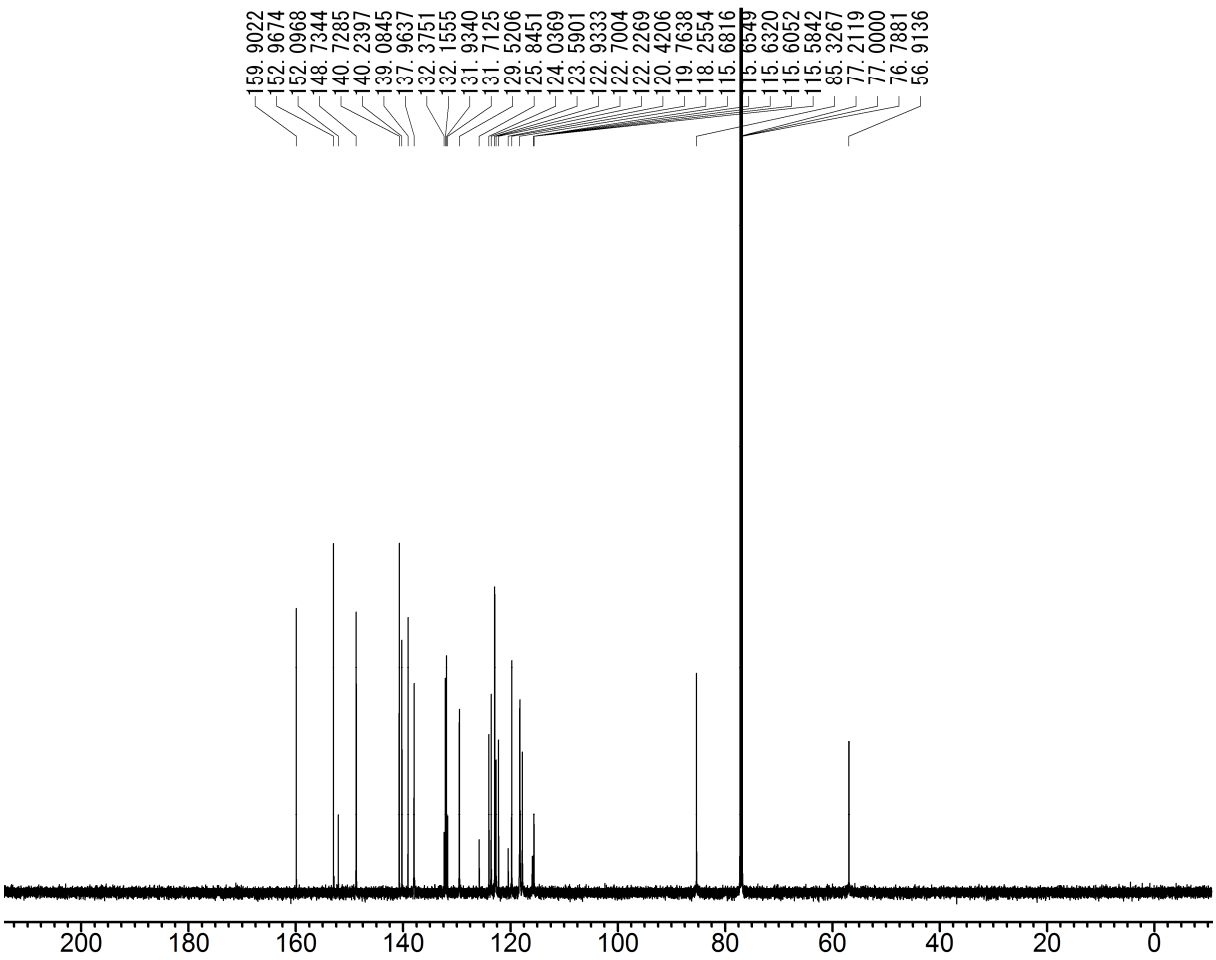
600 MHz ^{1}H NMR of **2** in $CDCl_3$.



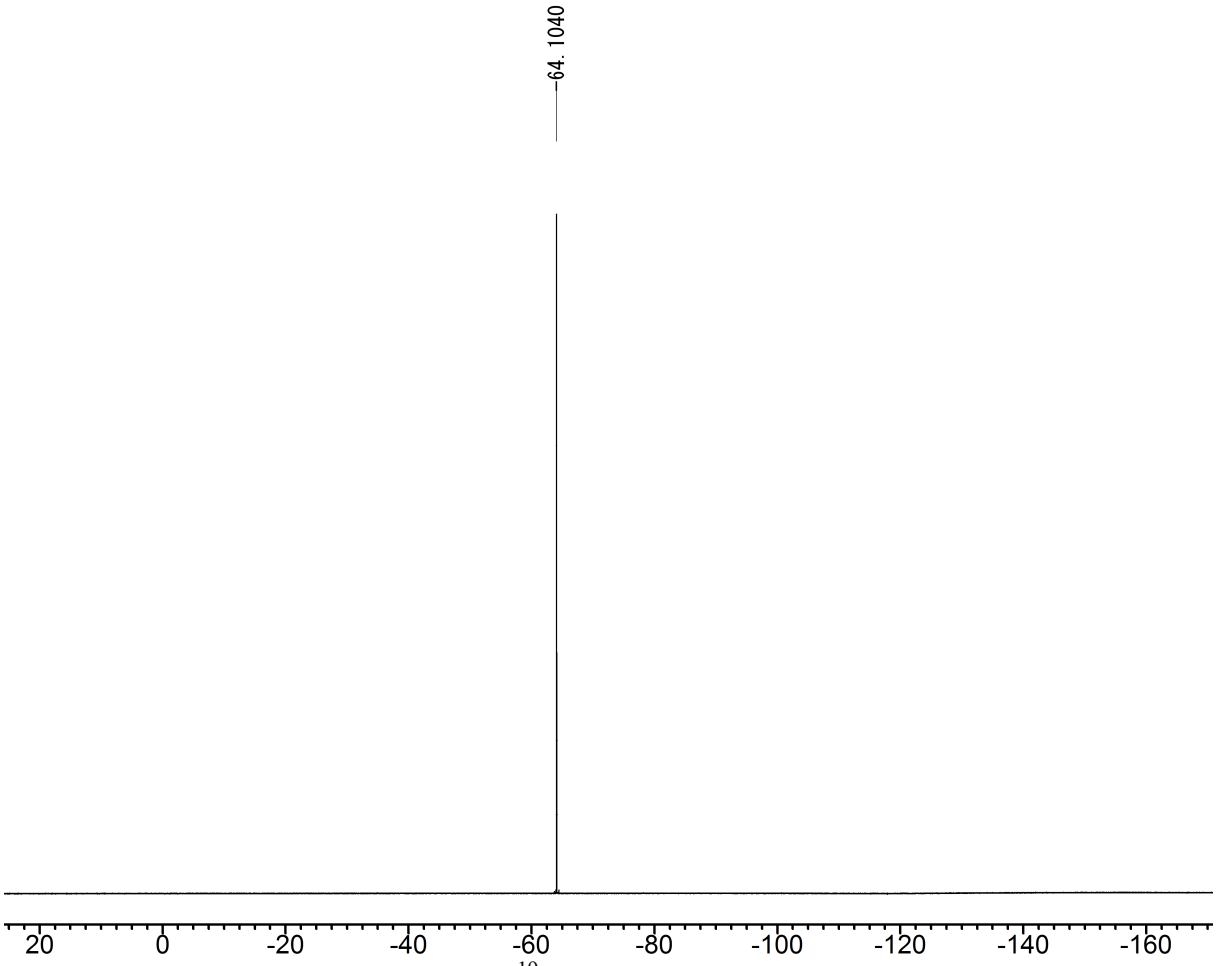
150 MHz ^{13}C NMR of **2** in $CDCl_3$.



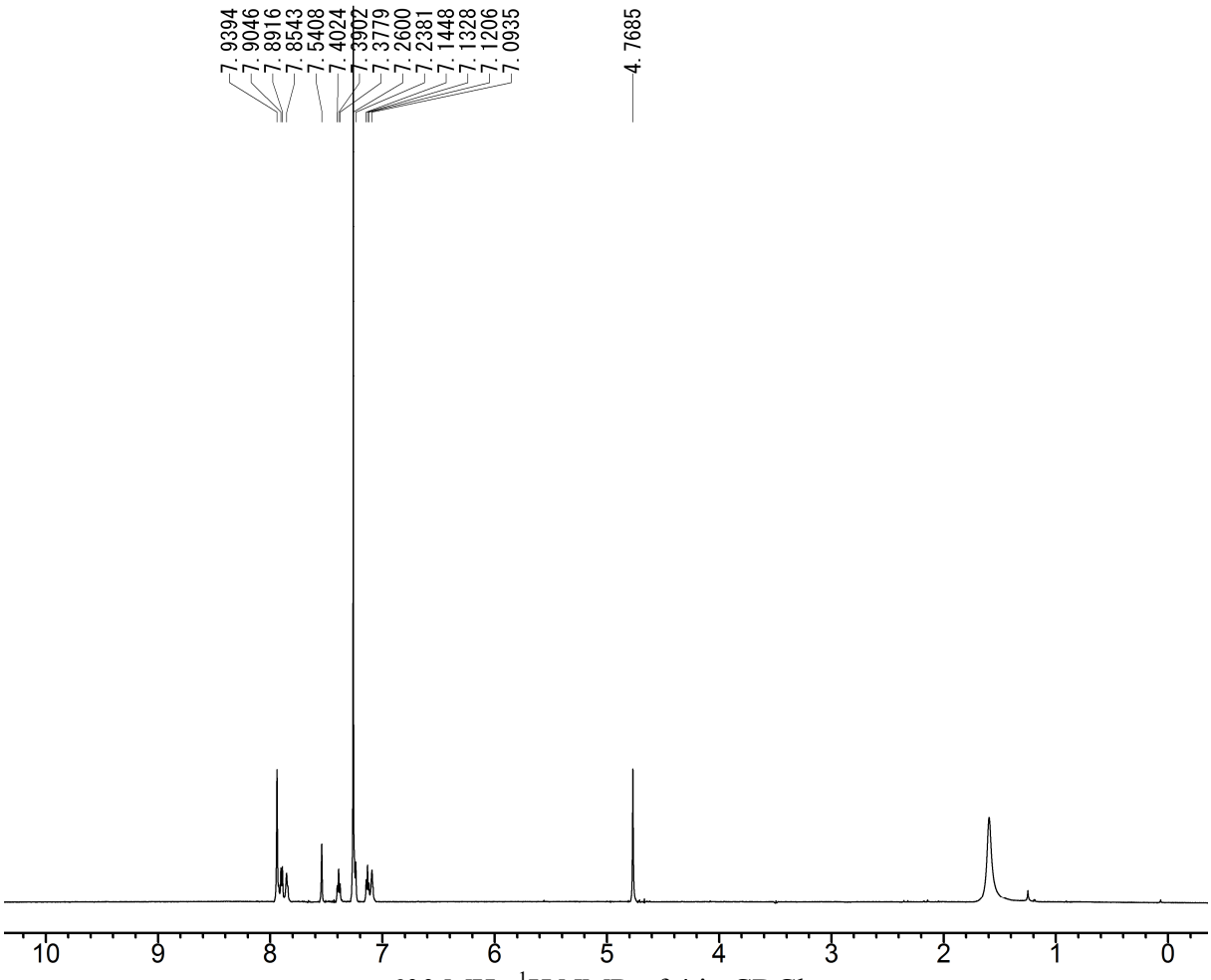
600 MHz ^{1}H NMR of **3** in $CDCl_3$.



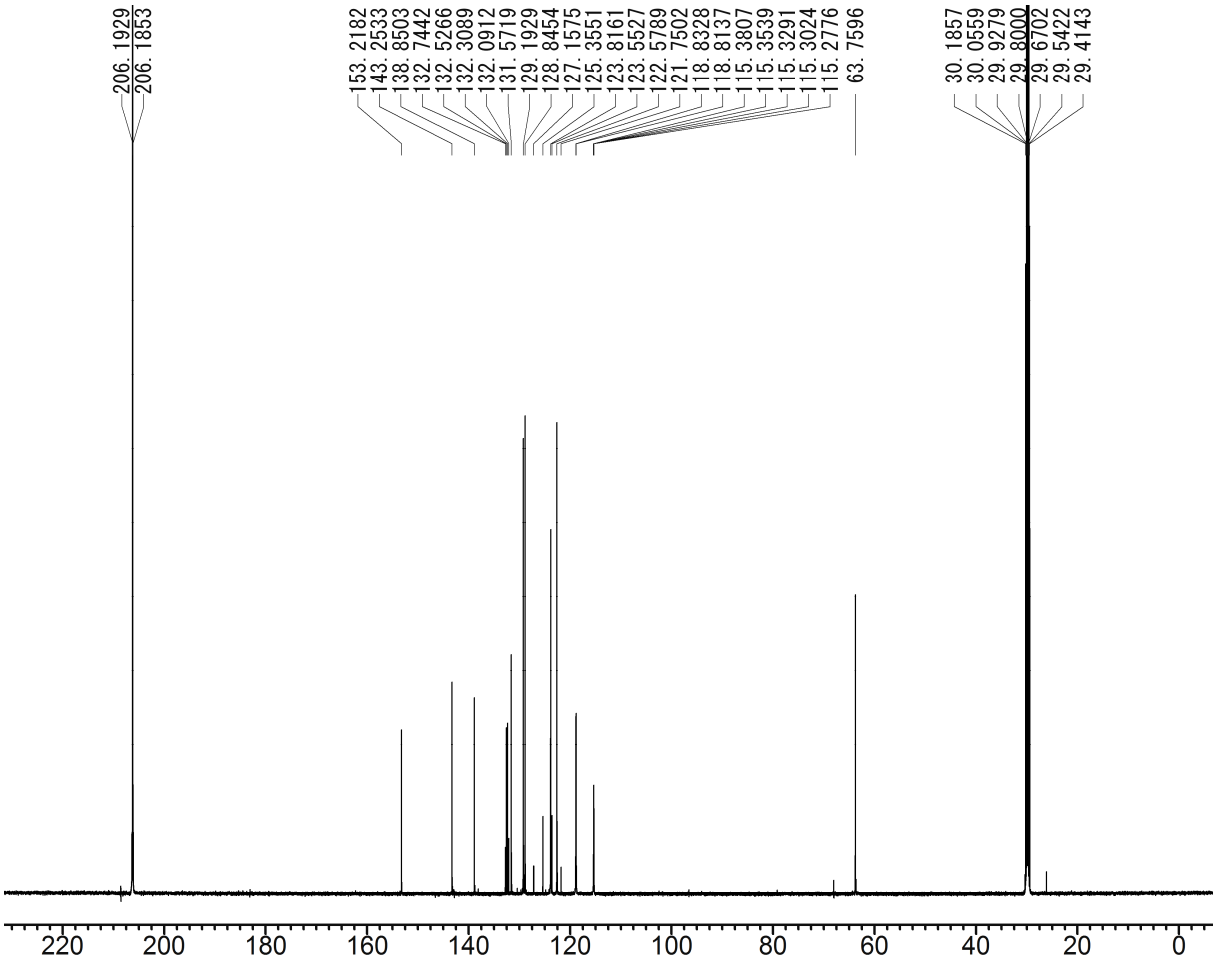
150 MHz ^{13}C NMR of **3** in $CDCl_3$.



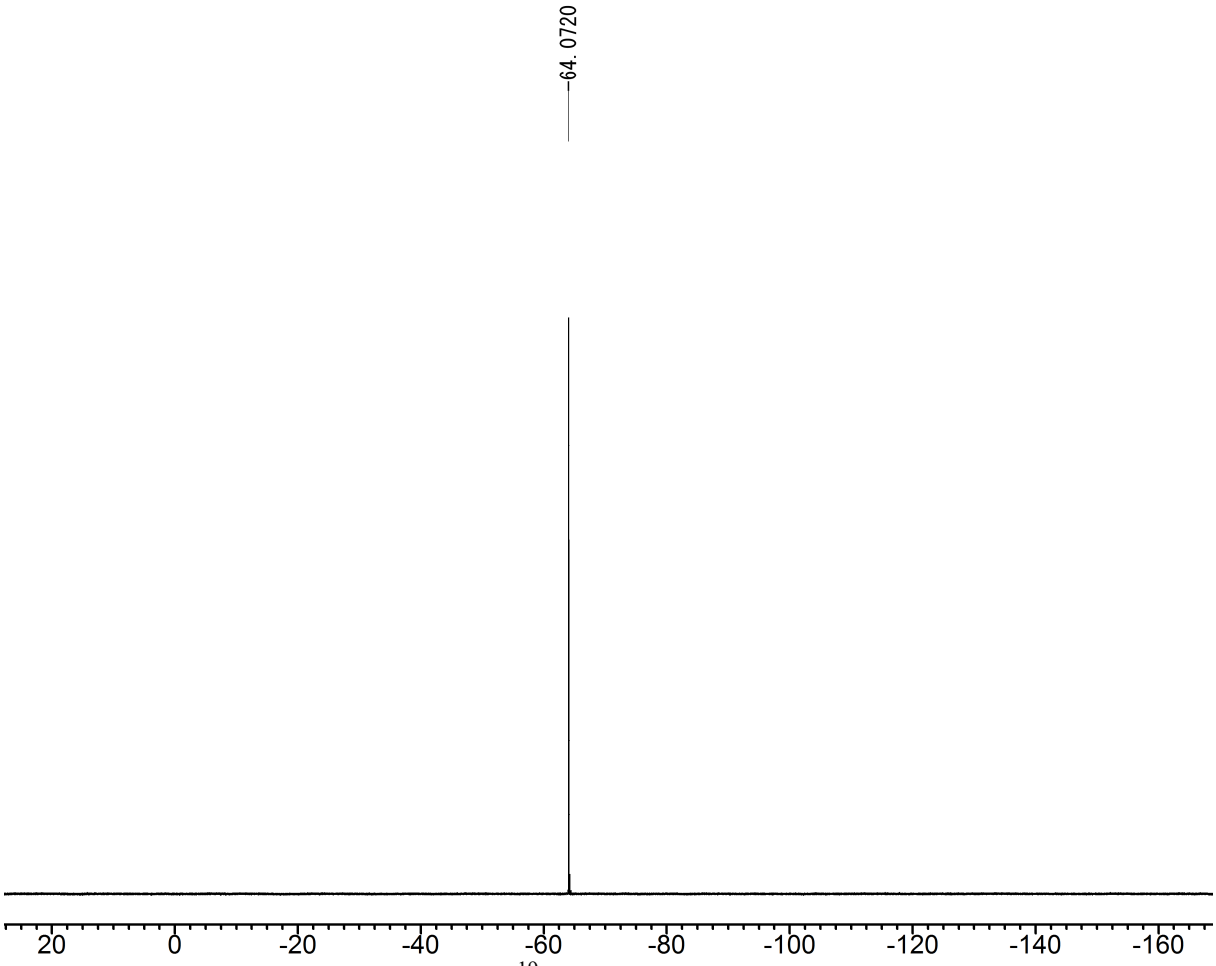
565 MHz ^{19}F NMR of **3** in $CDCl_3$.



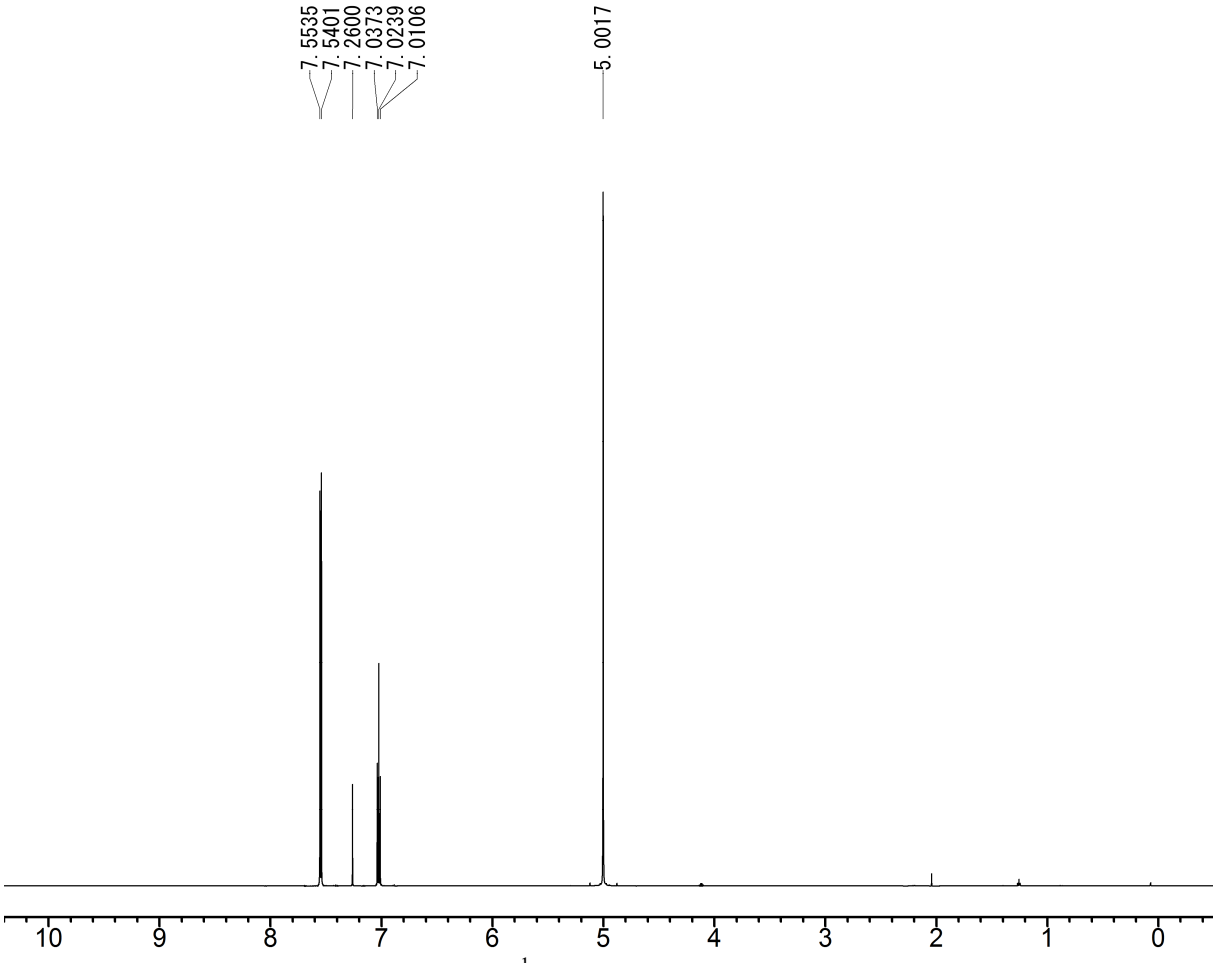
600 MHz ^{1}H NMR of **4** in $CDCl_3$.



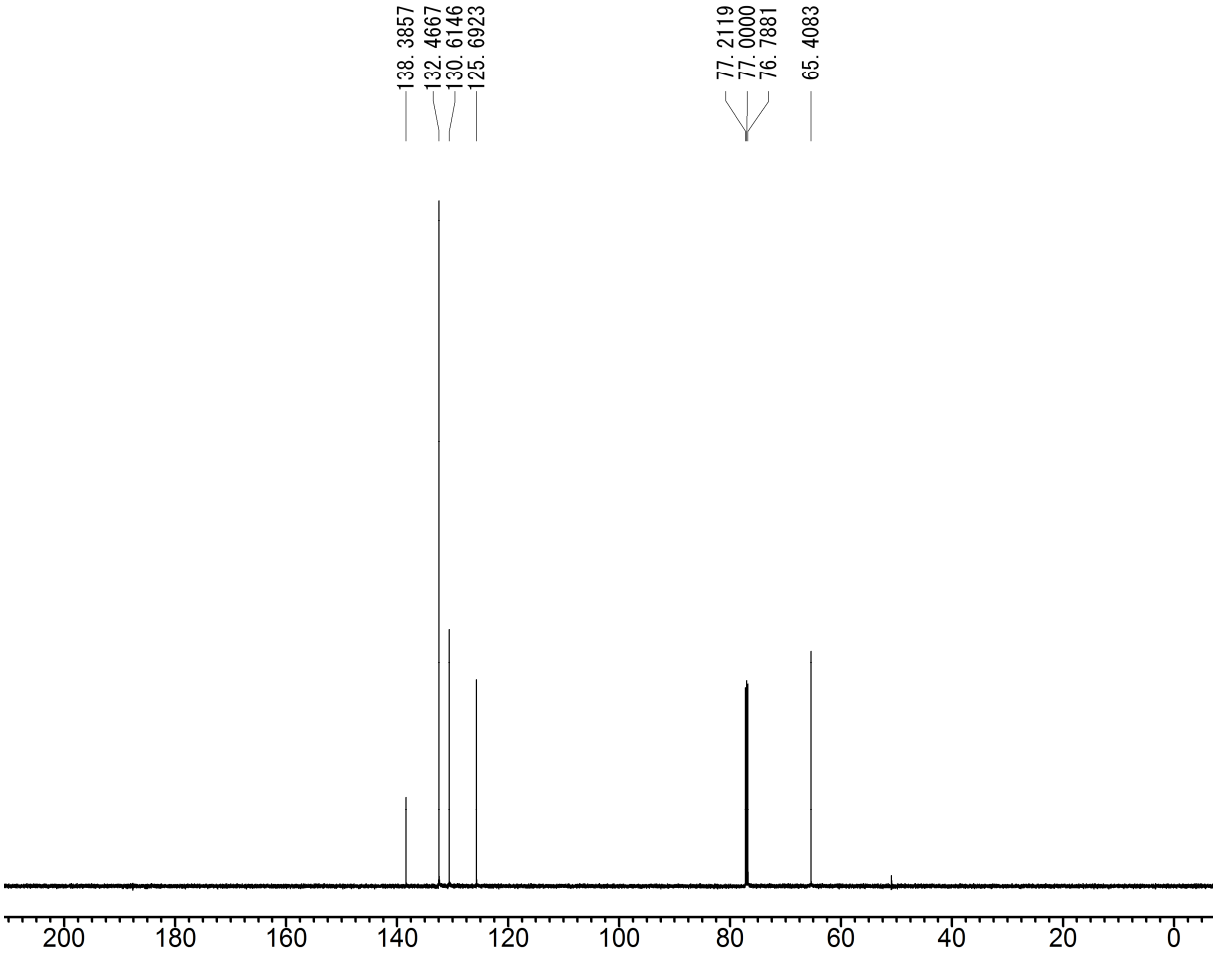
150 MHz ^{13}C NMR of **4** in d_6-acetone.



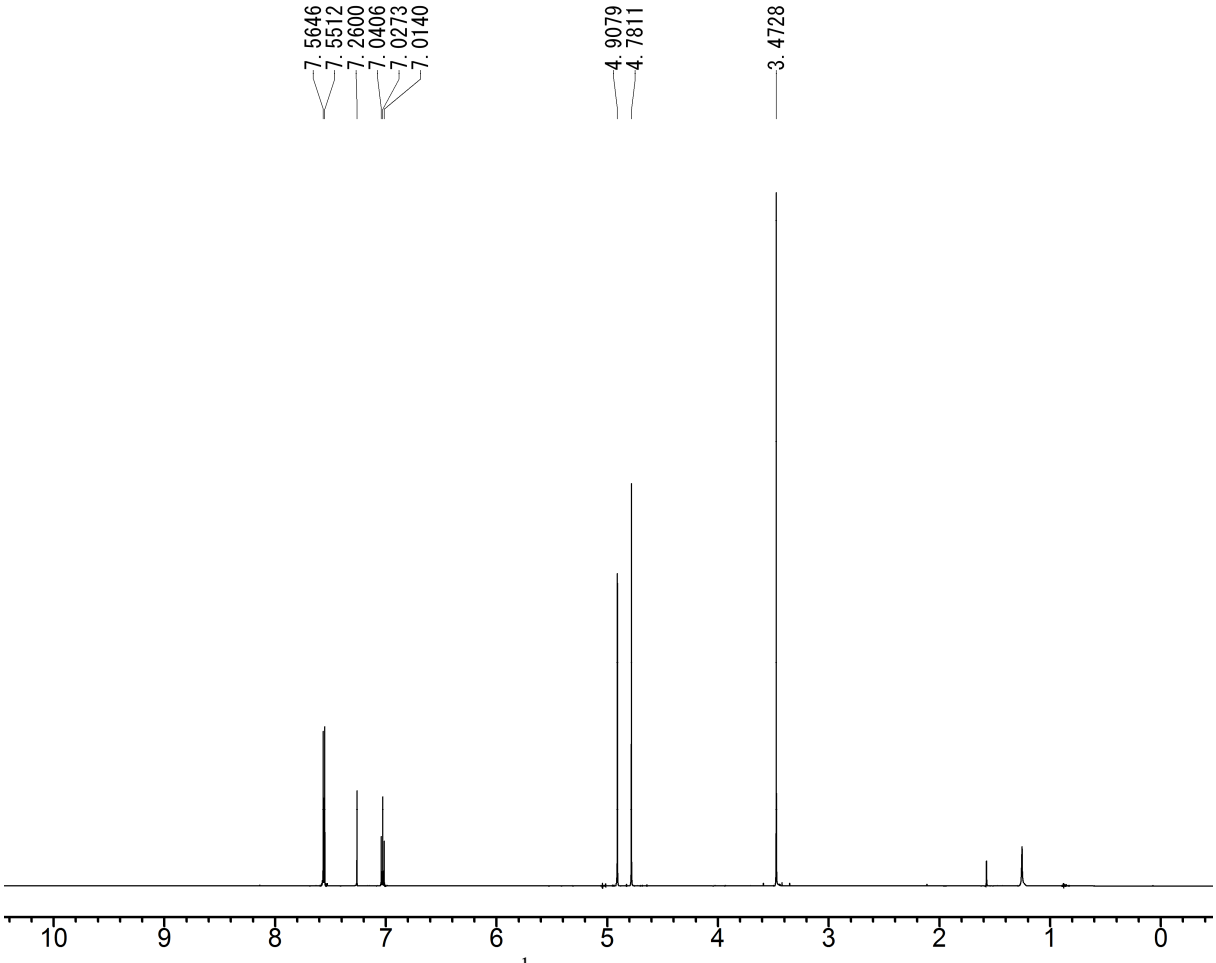
565 MHz ^{19}F NMR of **4** in $CDCl_3$.



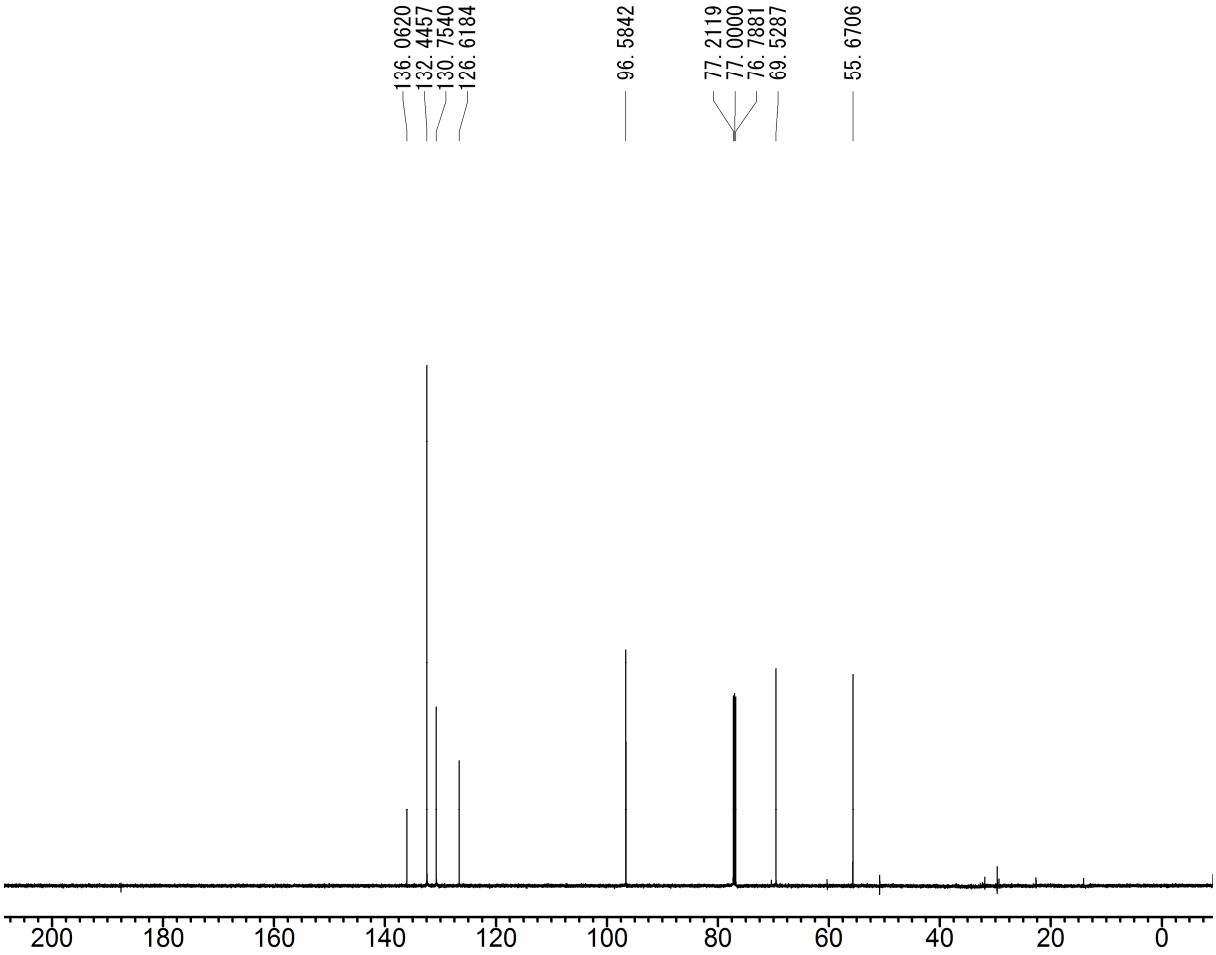
600 MHz ^{1}H NMR of **5** in $CDCl_3$.



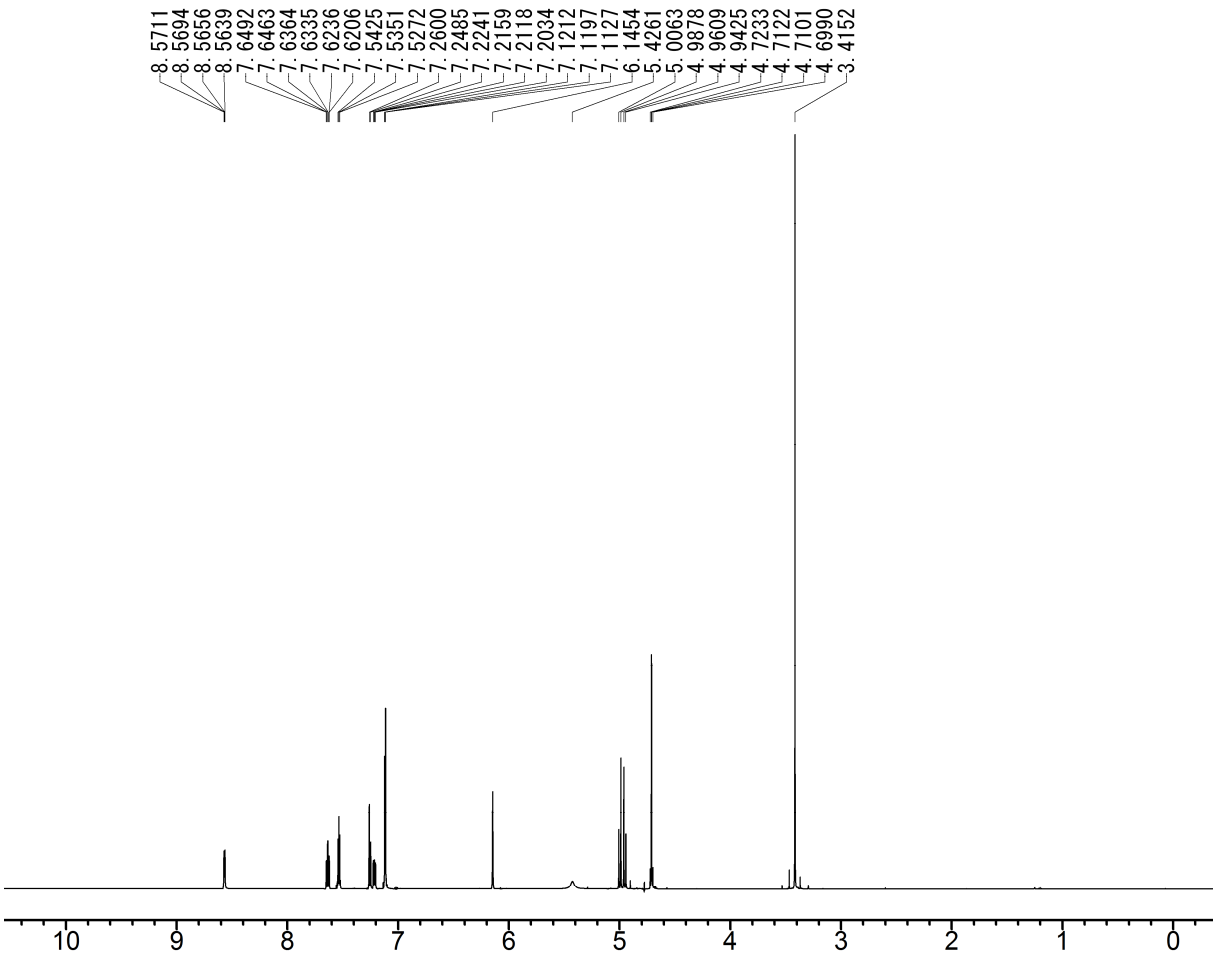
150 MHz ^{13}C NMR of **5** in $CDCl_3$.



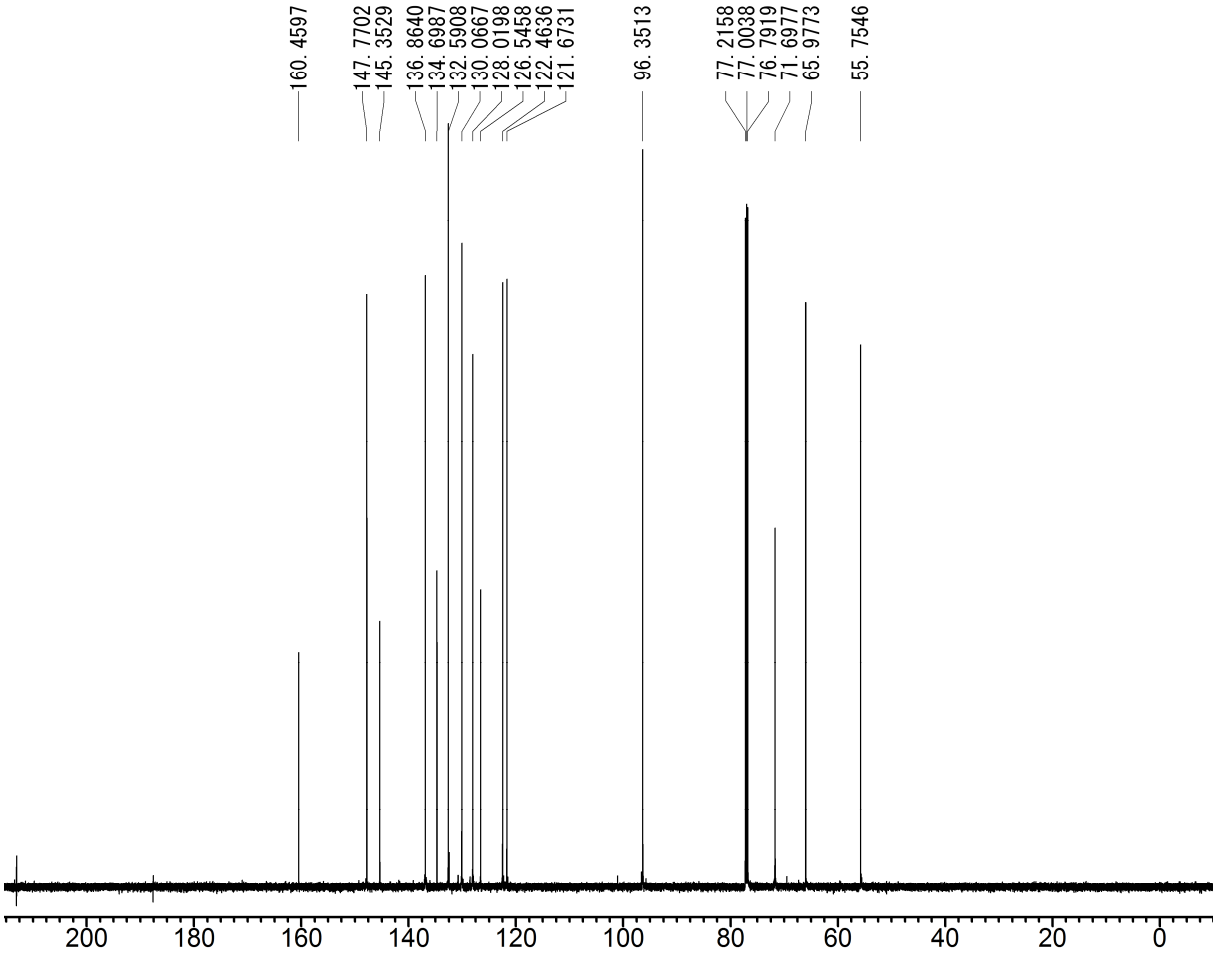
600 MHz ^{1}H NMR of **6** in $CDCl_3$.



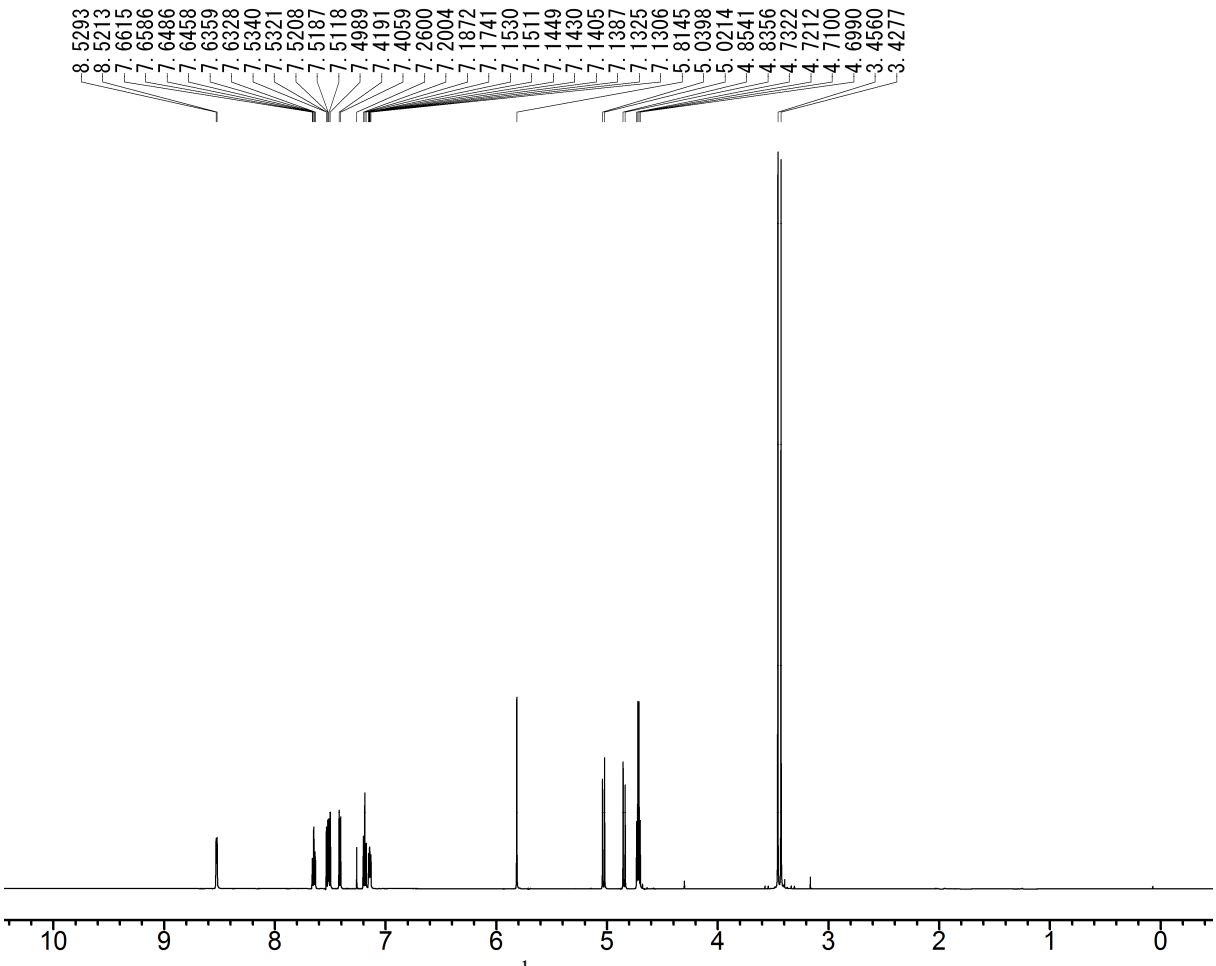
150 MHz ^{13}C NMR of **6** in $CDCl_3$.



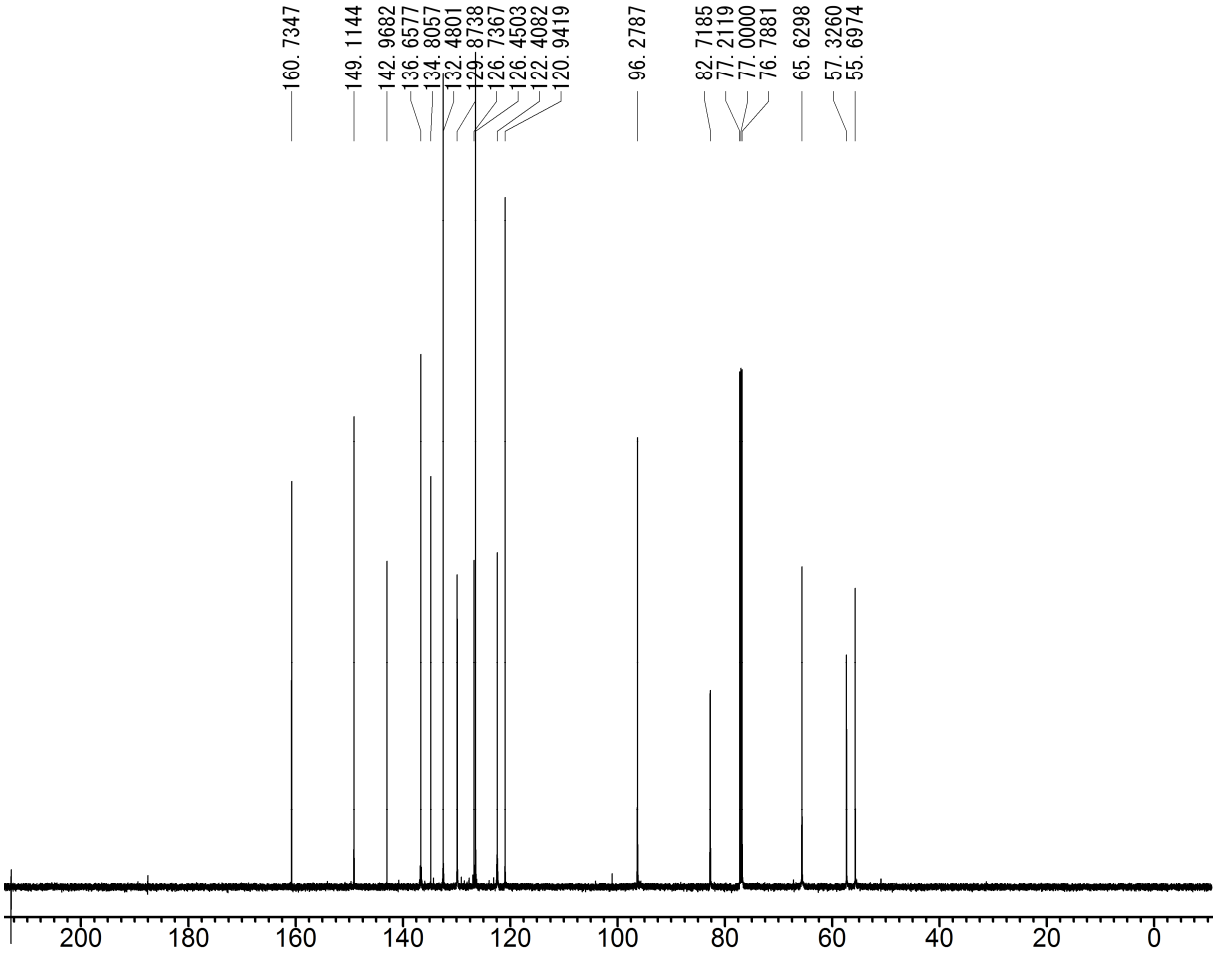
600 MHz ^{1}H NMR of **7** in $CDCl_3$.



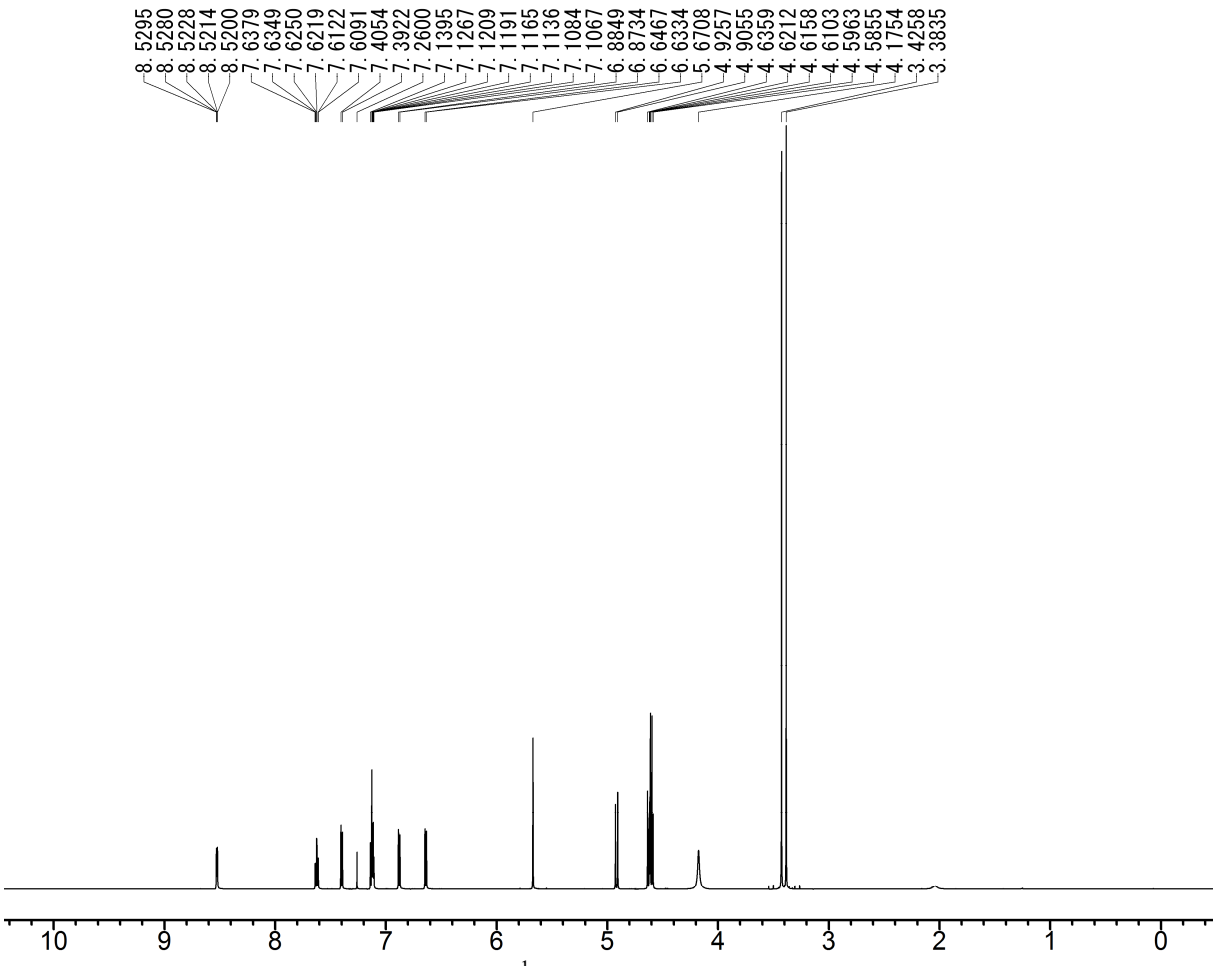
150 MHz ^{13}C NMR of **7** in $CDCl_3$.



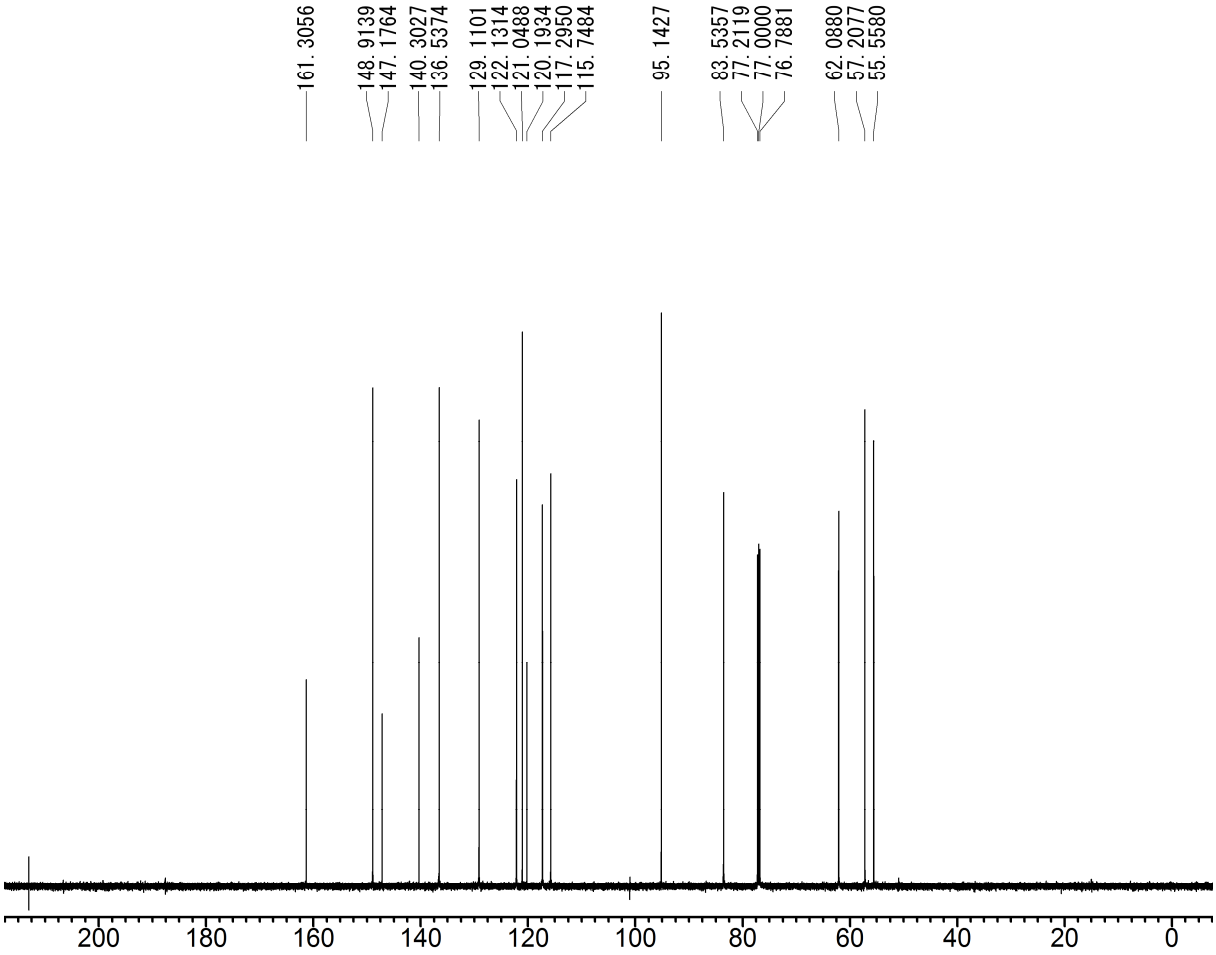
600 MHz ^{1}H NMR of **8** in $CDCl_3$.



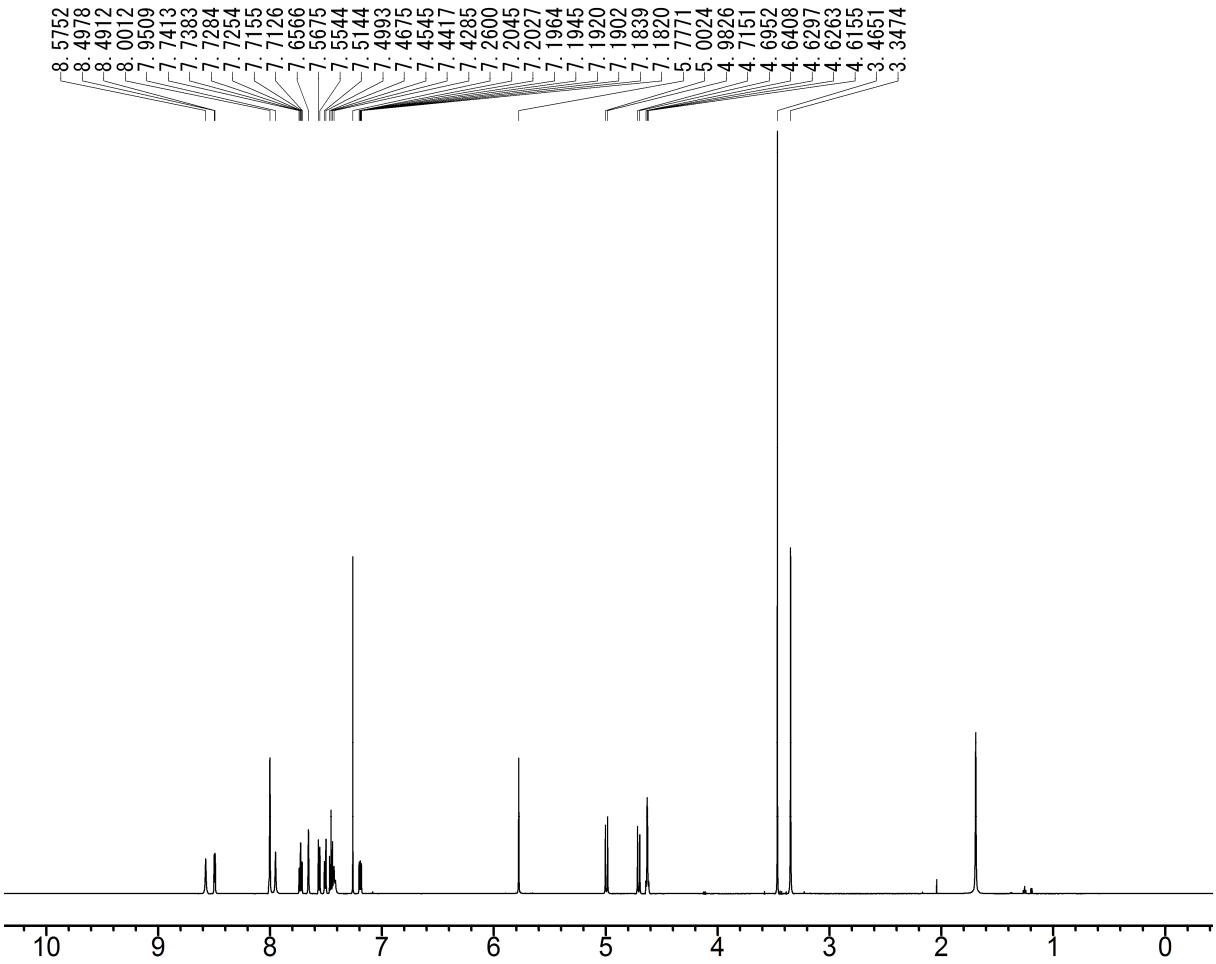
150 MHz ^{13}C NMR of **8** in $CDCl_3$.



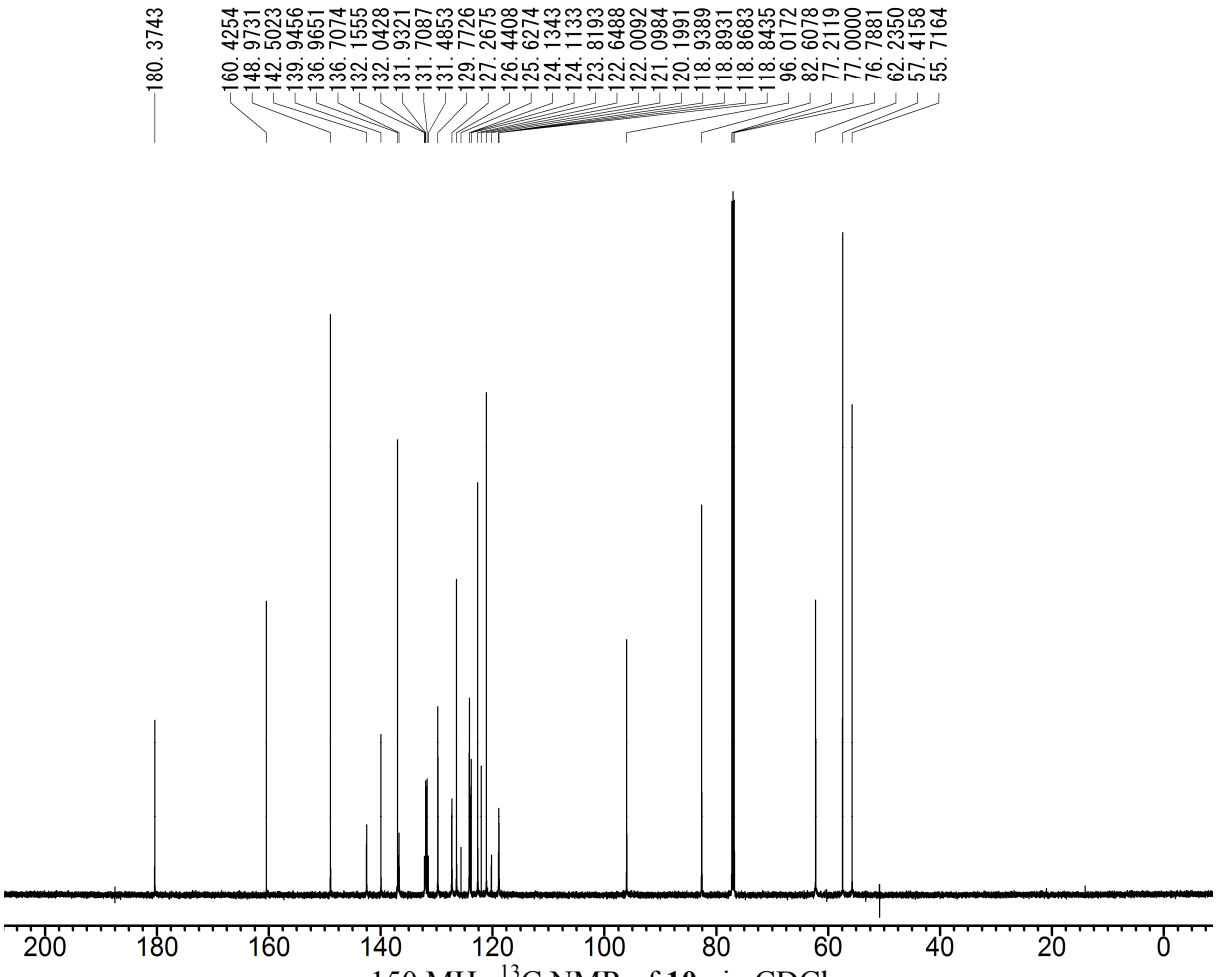
600 MHz ^{1}H NMR of **9** in $CDCl_3$.



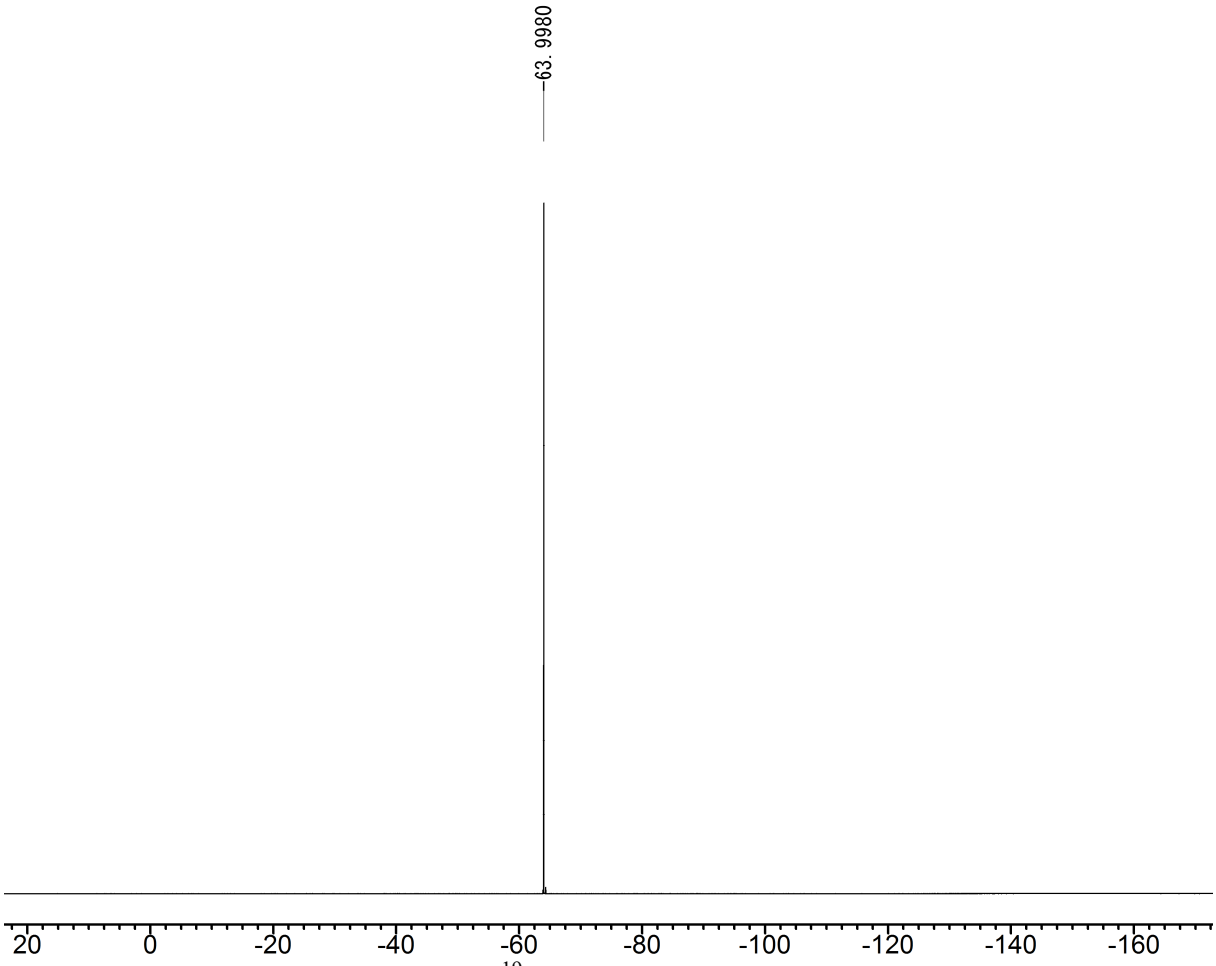
150 MHz ^{13}C NMR of **9** in $CDCl_3$.



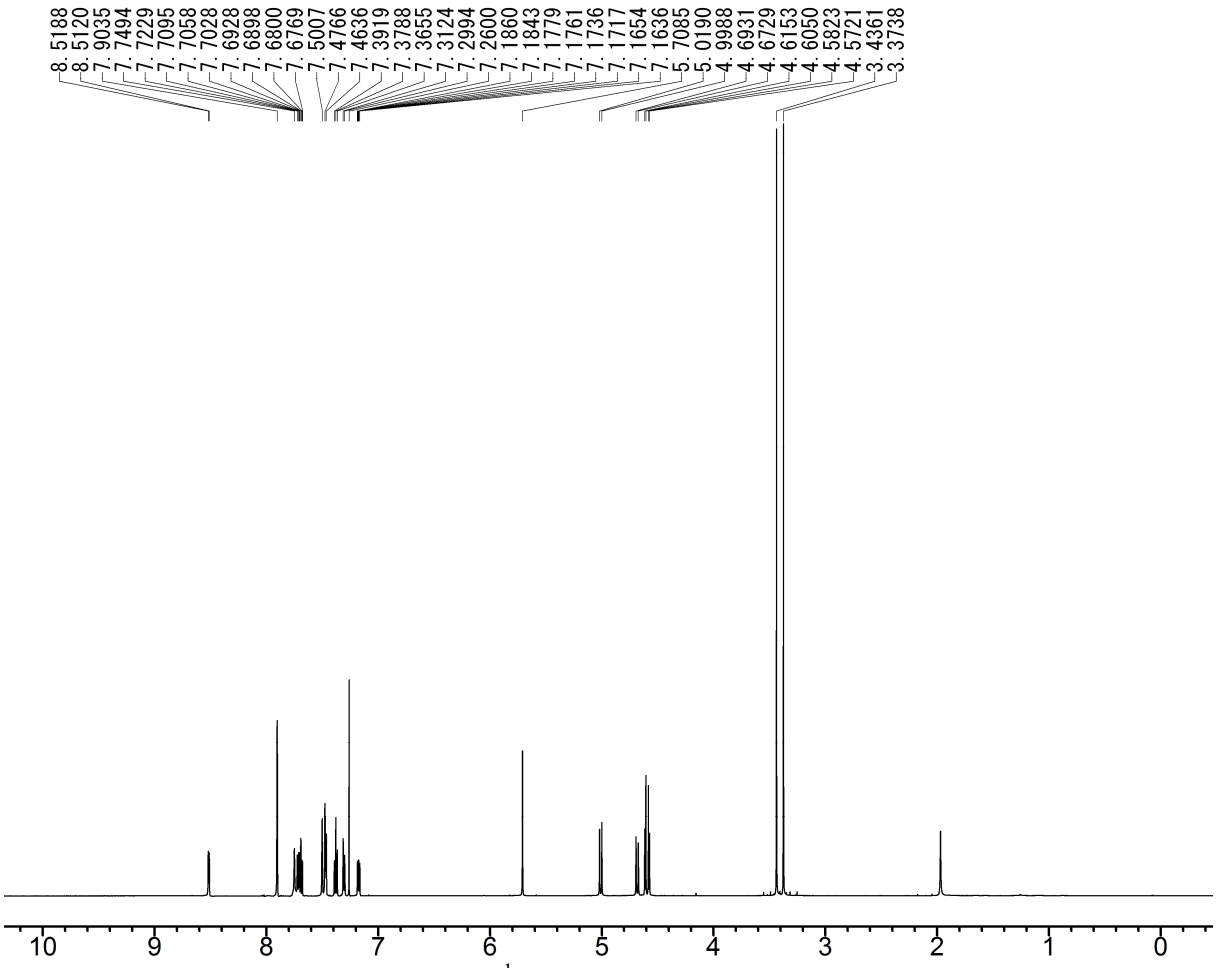
600 MHz ^{1}H NMR of **10a** in $CDCl_3$.



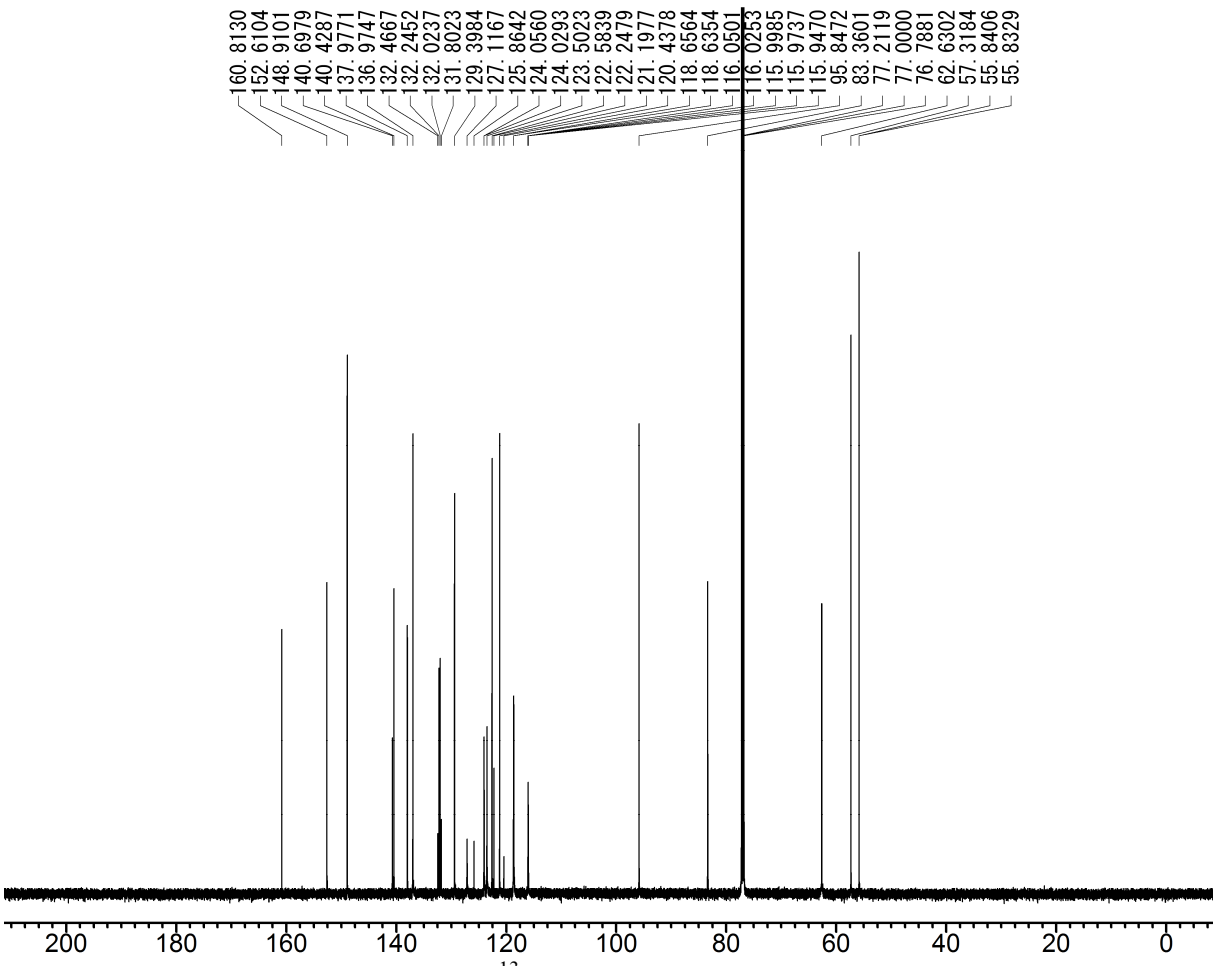
150 MHz ^{13}C NMR of **10a** in $CDCl_3$.



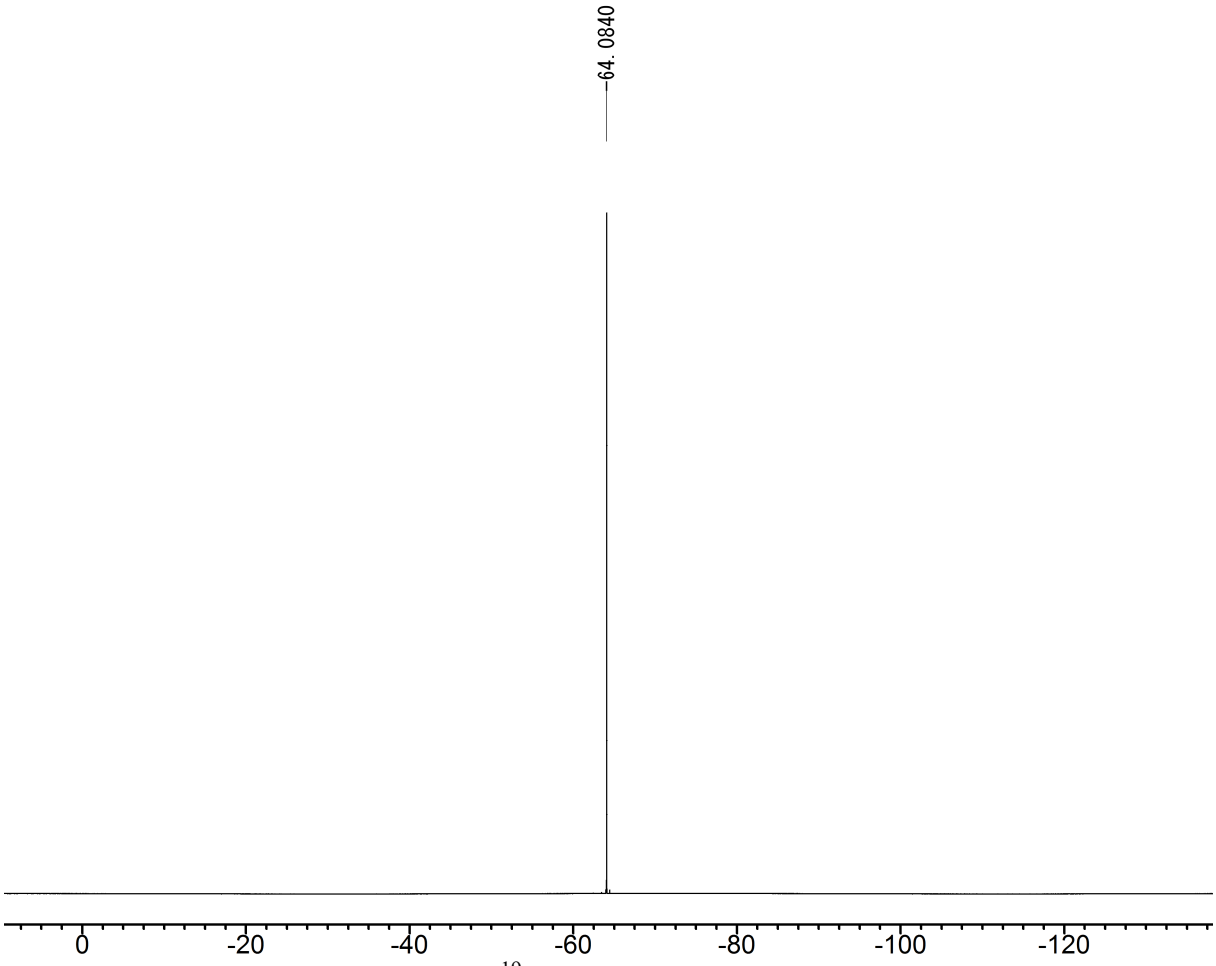
565 MHz ^{19}F NMR of **10a** in $CDCl_3$.



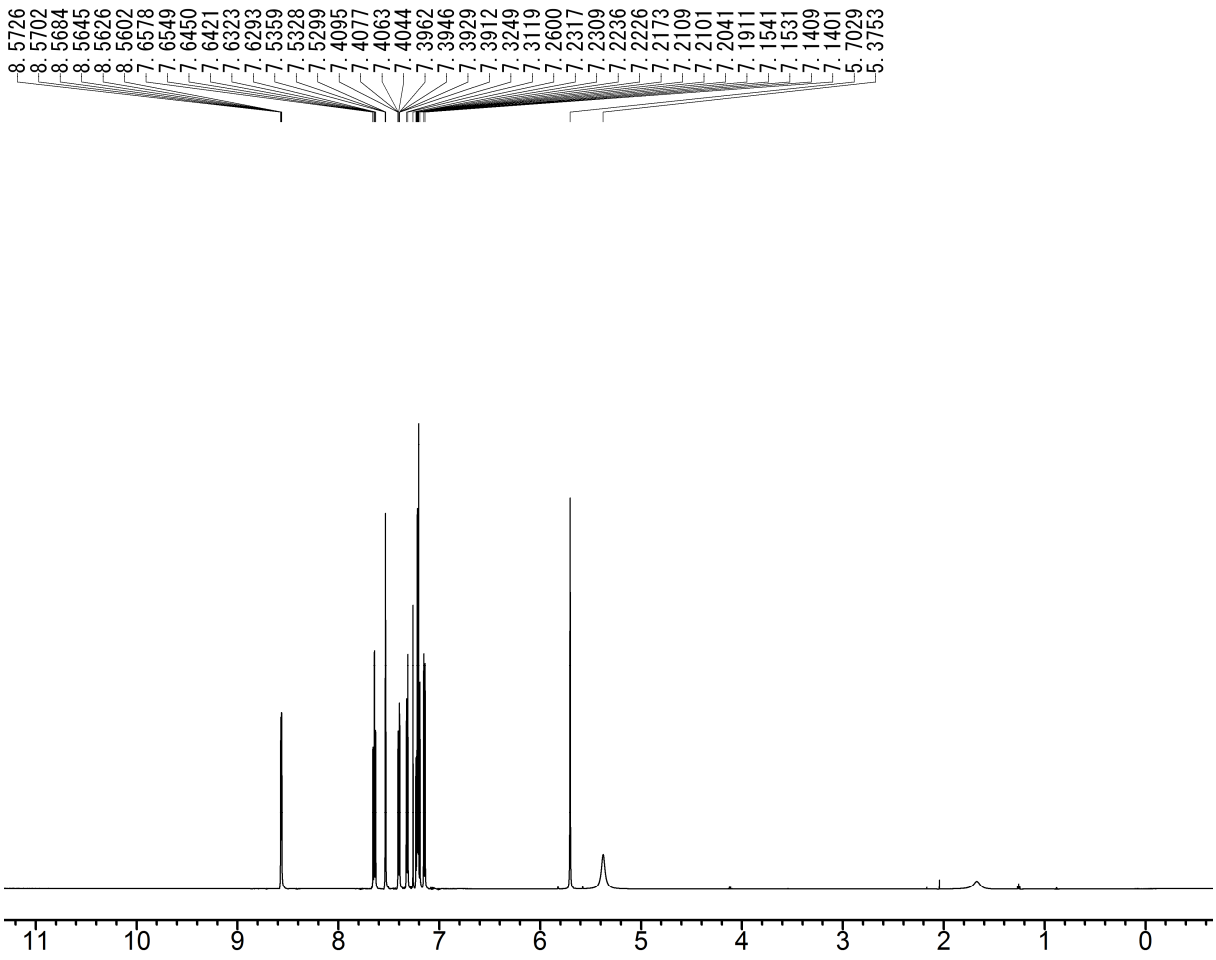
600 MHz ^{1}H NMR of **10b** in $CDCl_3$.



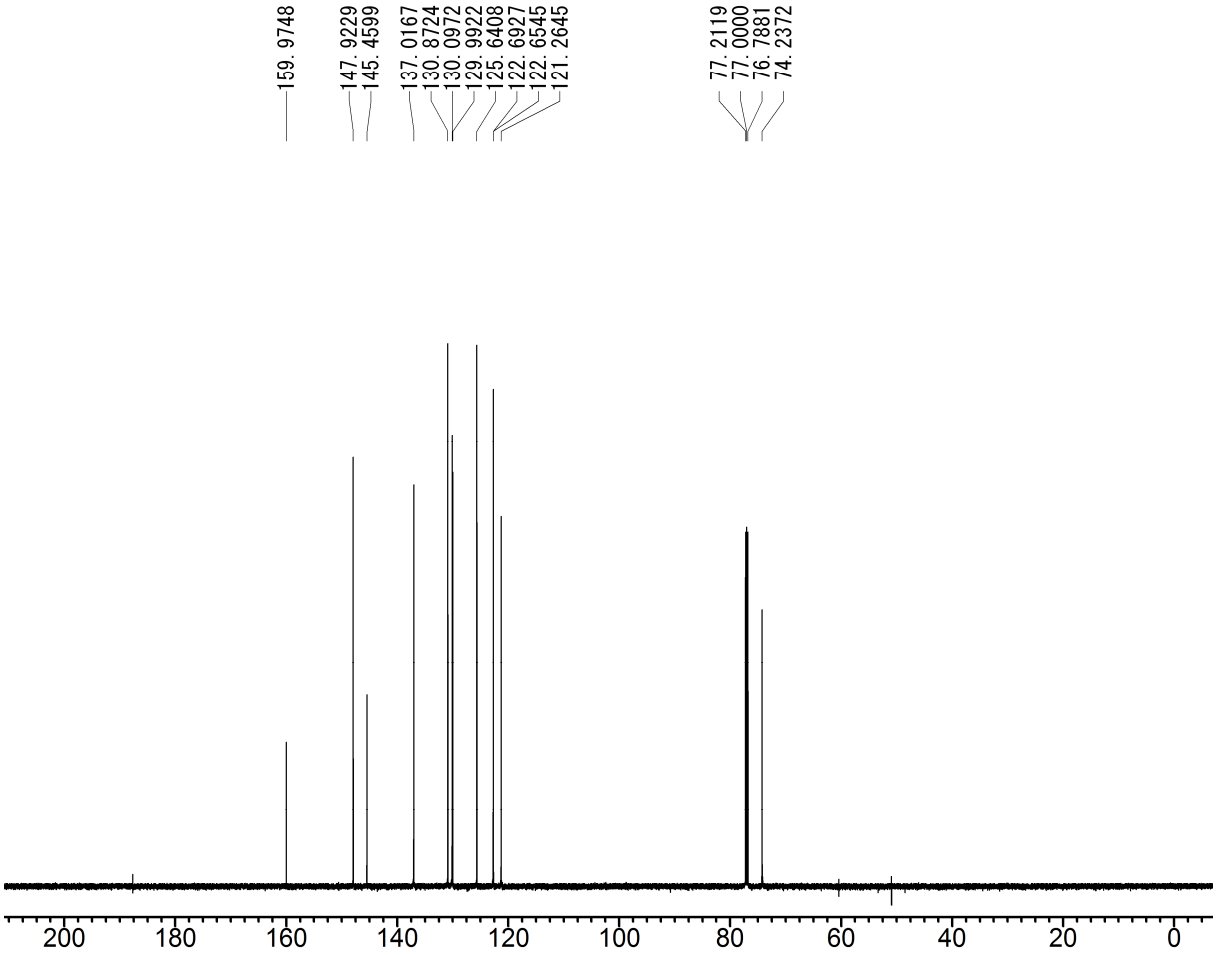
150 MHz ^{13}C NMR of **10b** in $CDCl_3$.



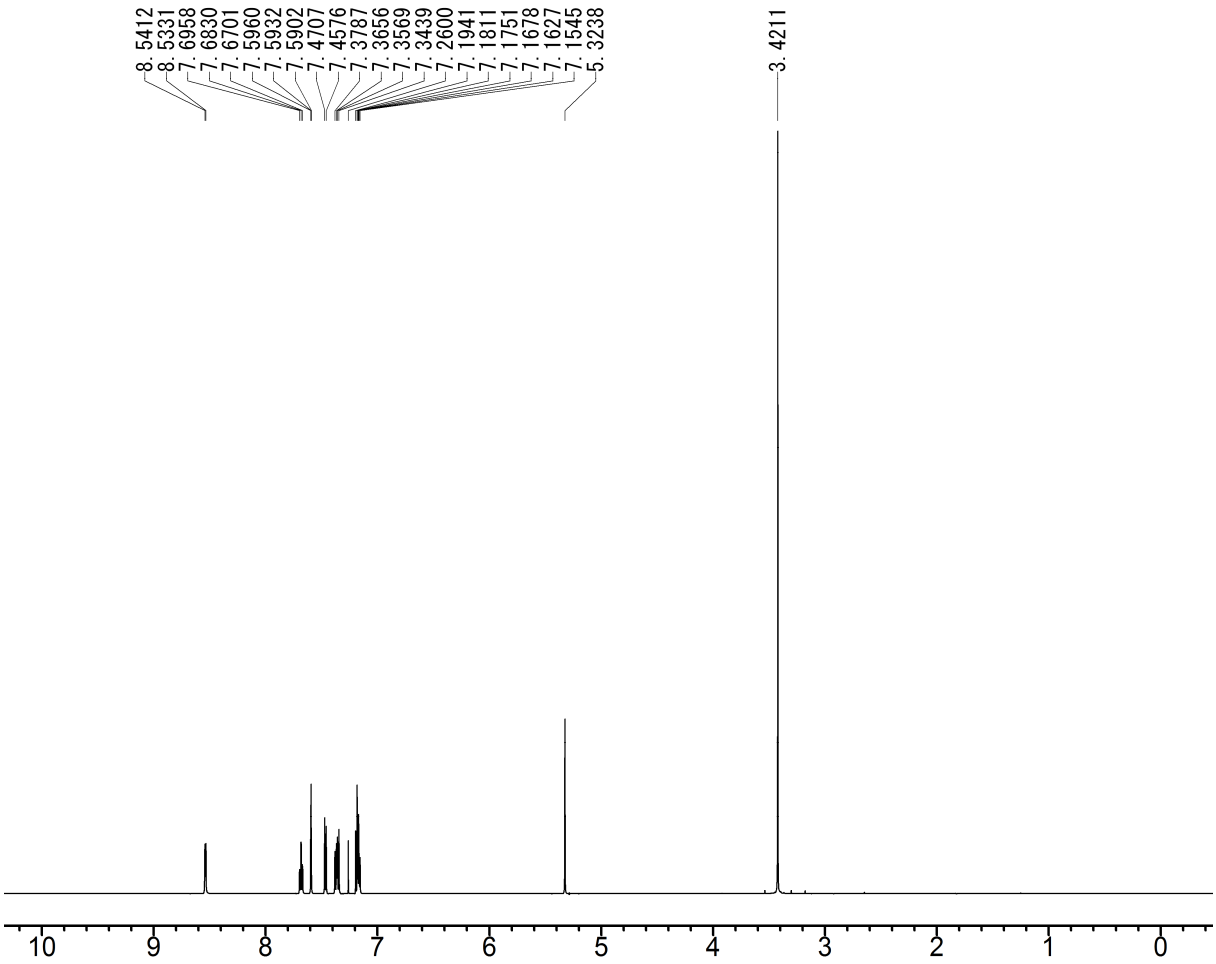
565 MHz ^{19}F NMR of **10b** in $CDCl_3$.



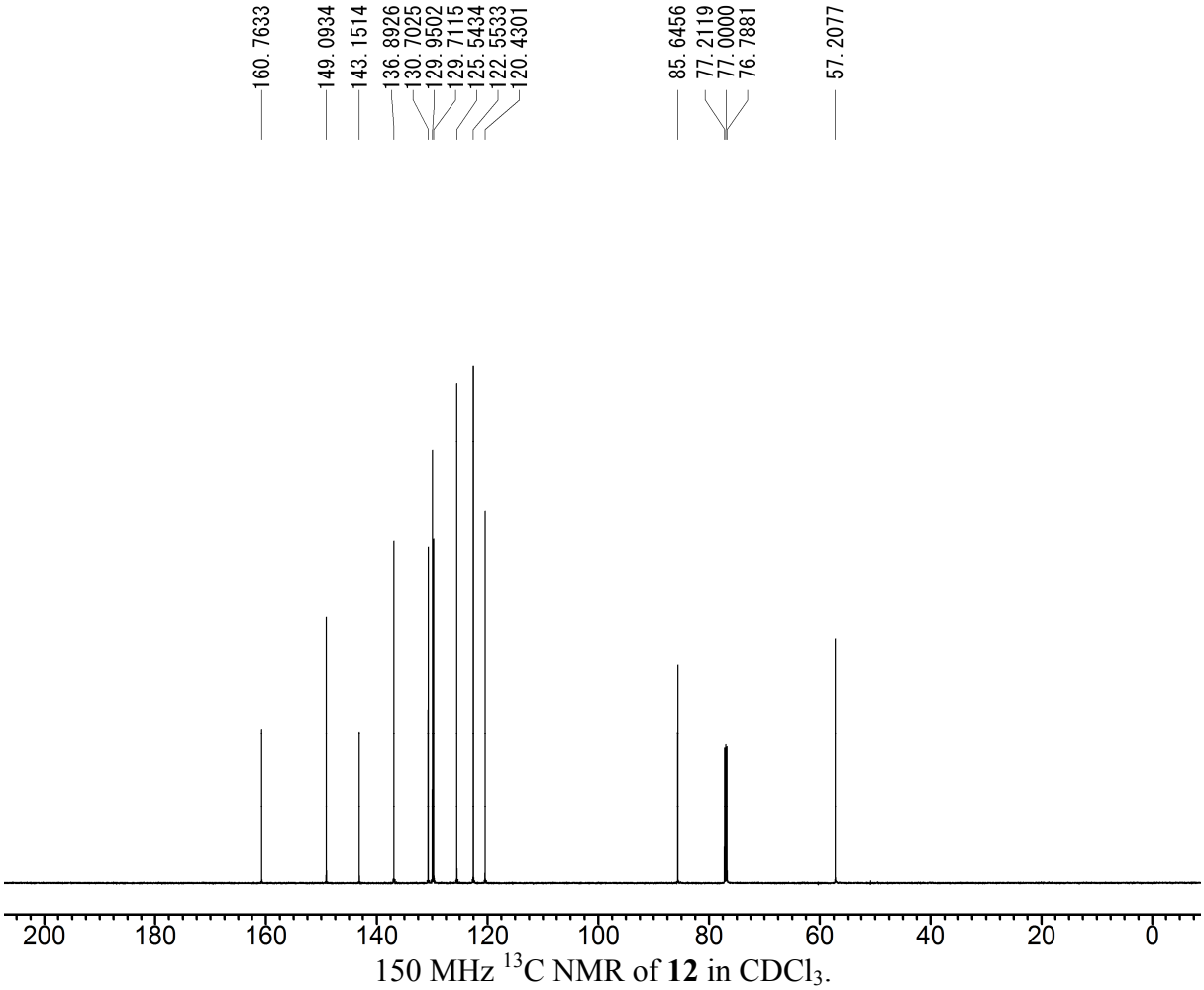
600 MHz ^{1}H NMR of **11** in $CDCl_3$.



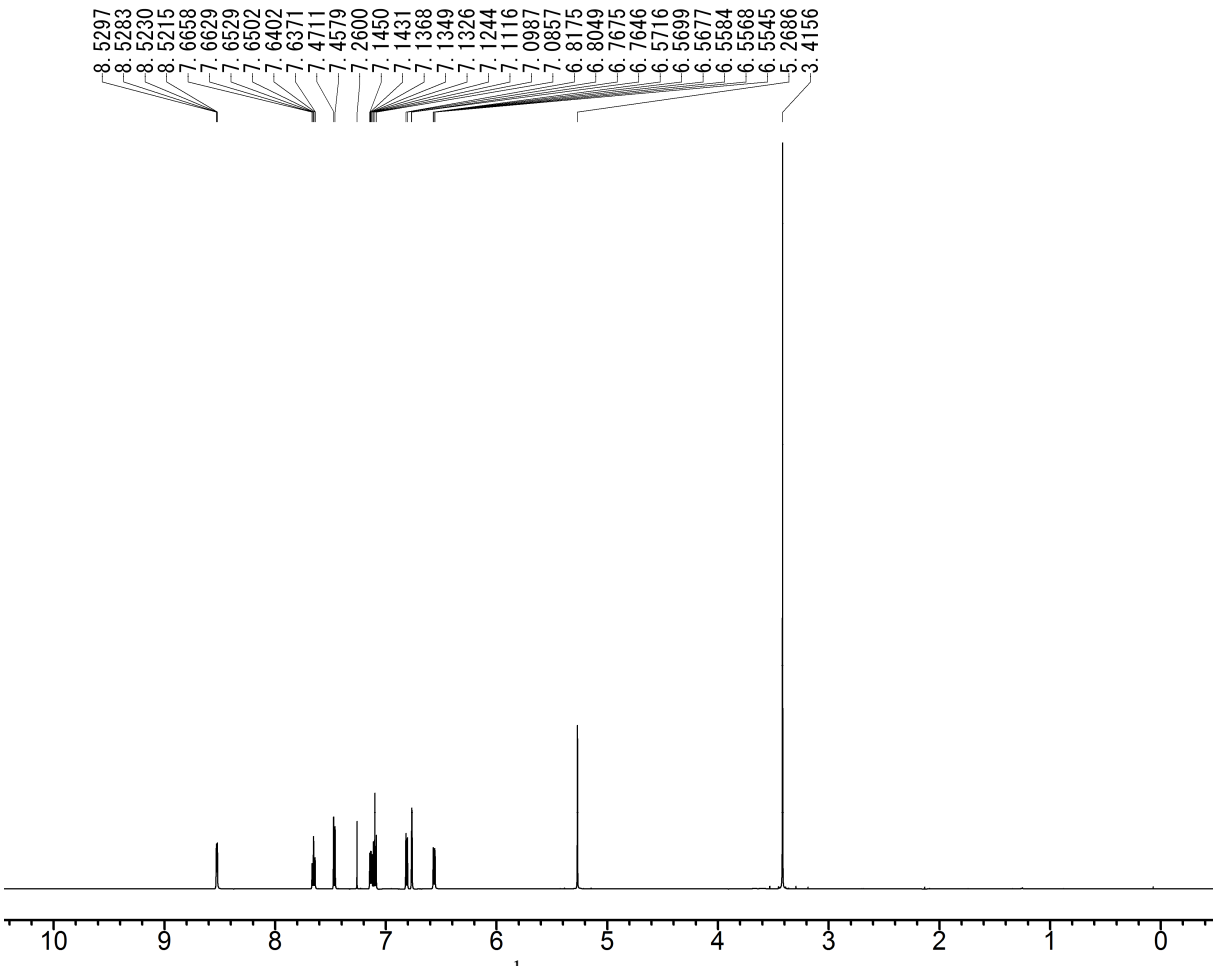
150 MHz ^{13}C NMR of **11** in $CDCl_3$.



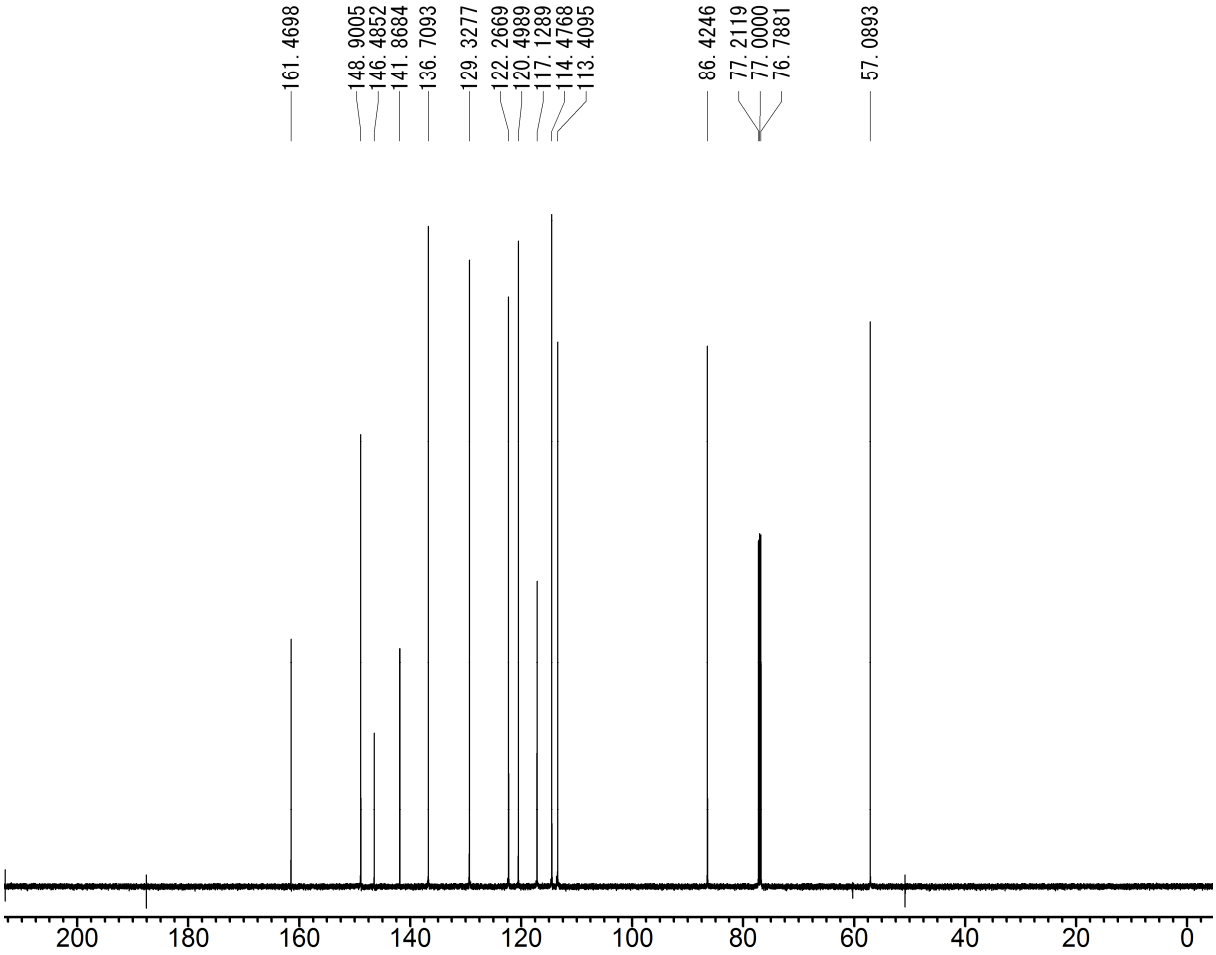
600 MHz ^{1}H NMR of **12** in $CDCl_3$.



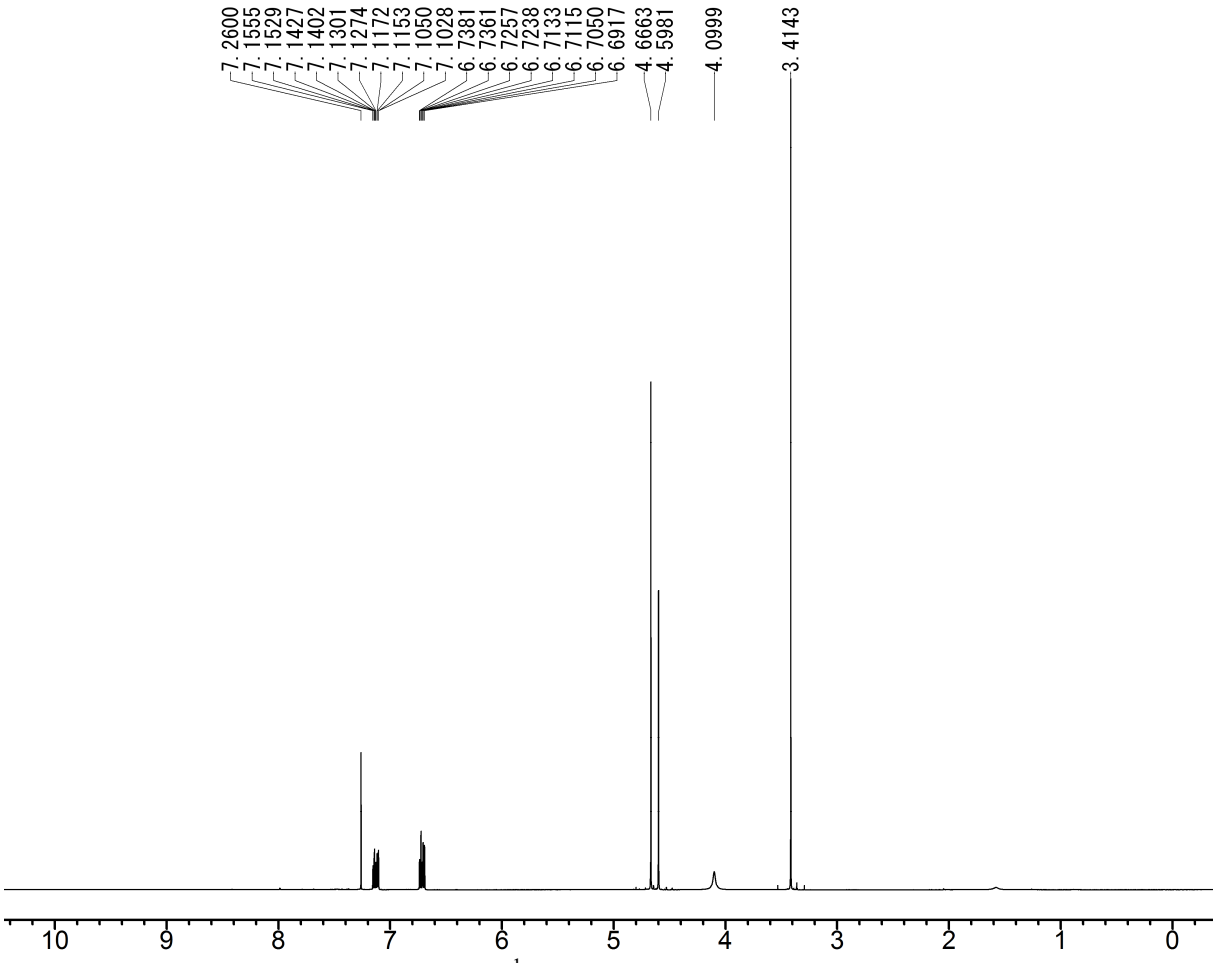
150 MHz ^{13}C NMR of **12** in $CDCl_3$.



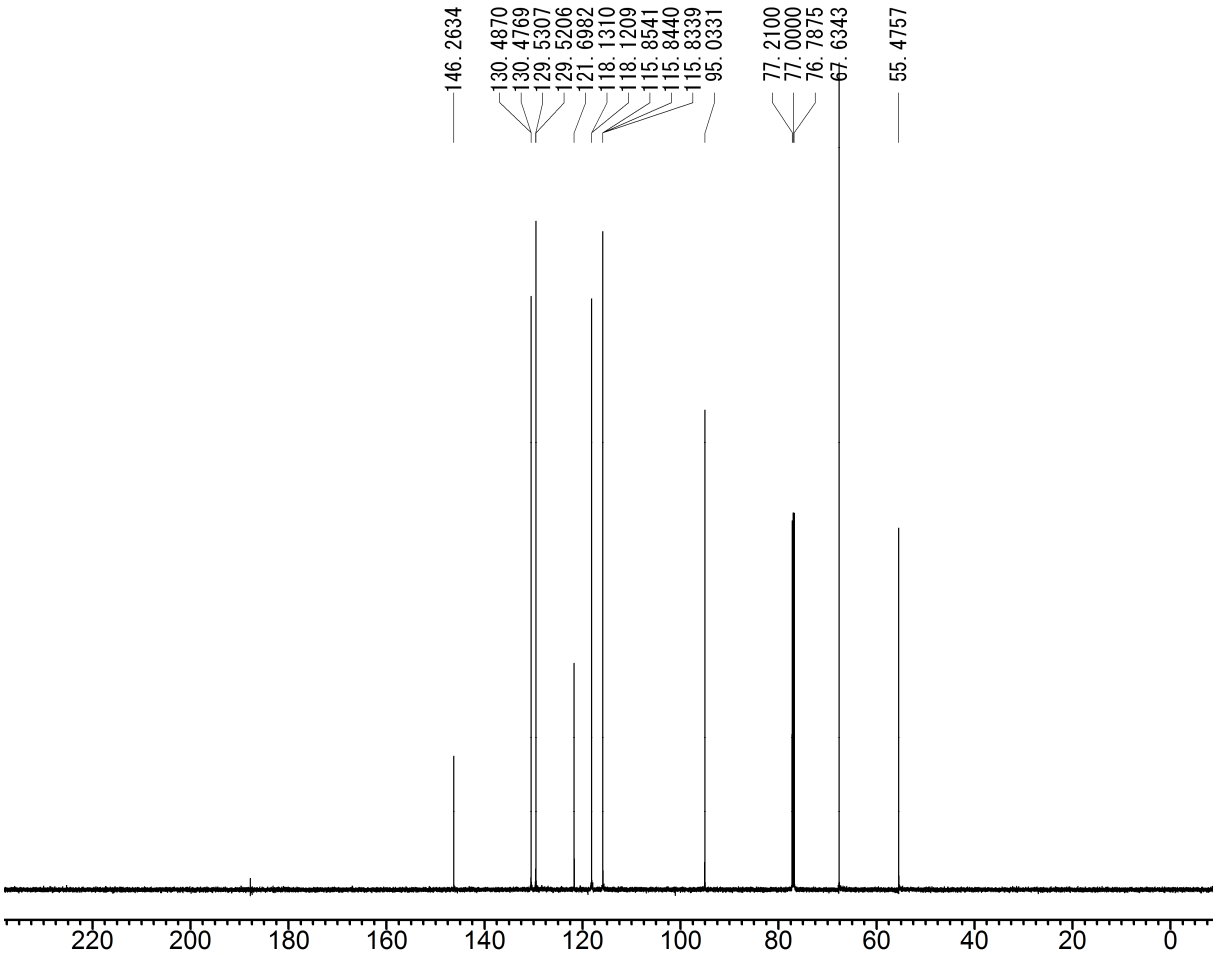
600 MHz ^{1}H NMR of **13** in $CDCl_3$.



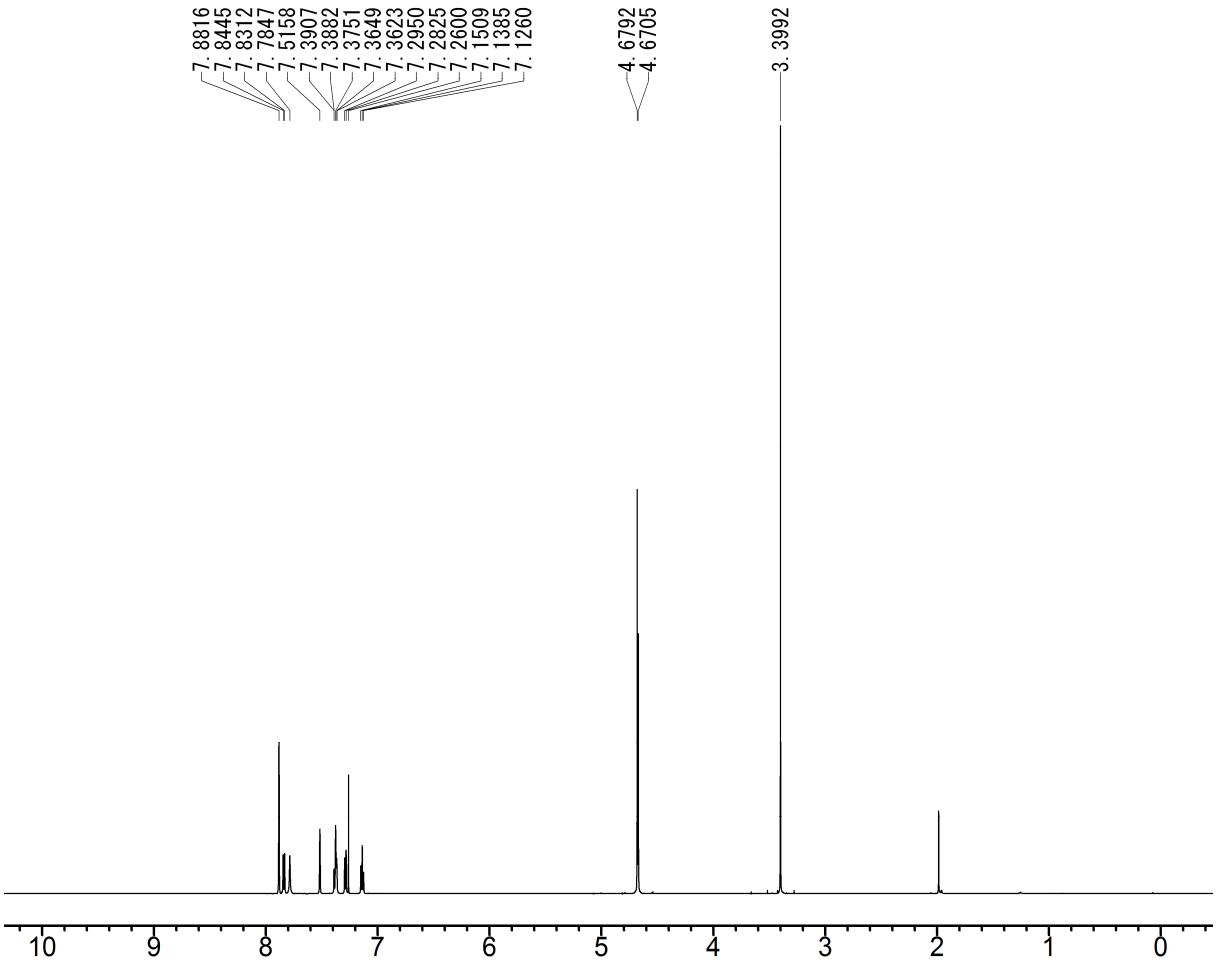
150 MHz ^{13}C NMR of **13** in $CDCl_3$.



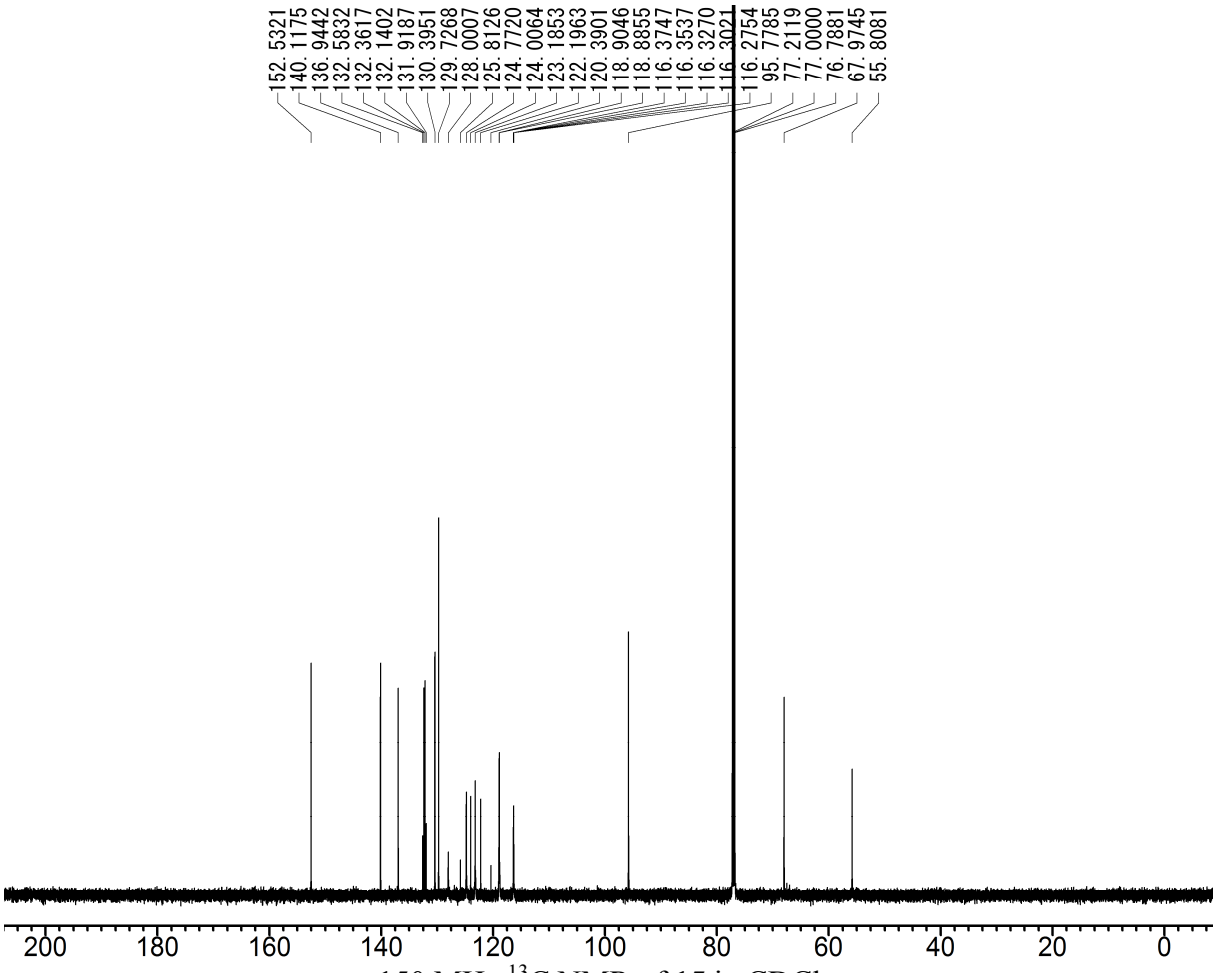
600 MHz ^{1}H NMR of **14** in $CDCl_3$.



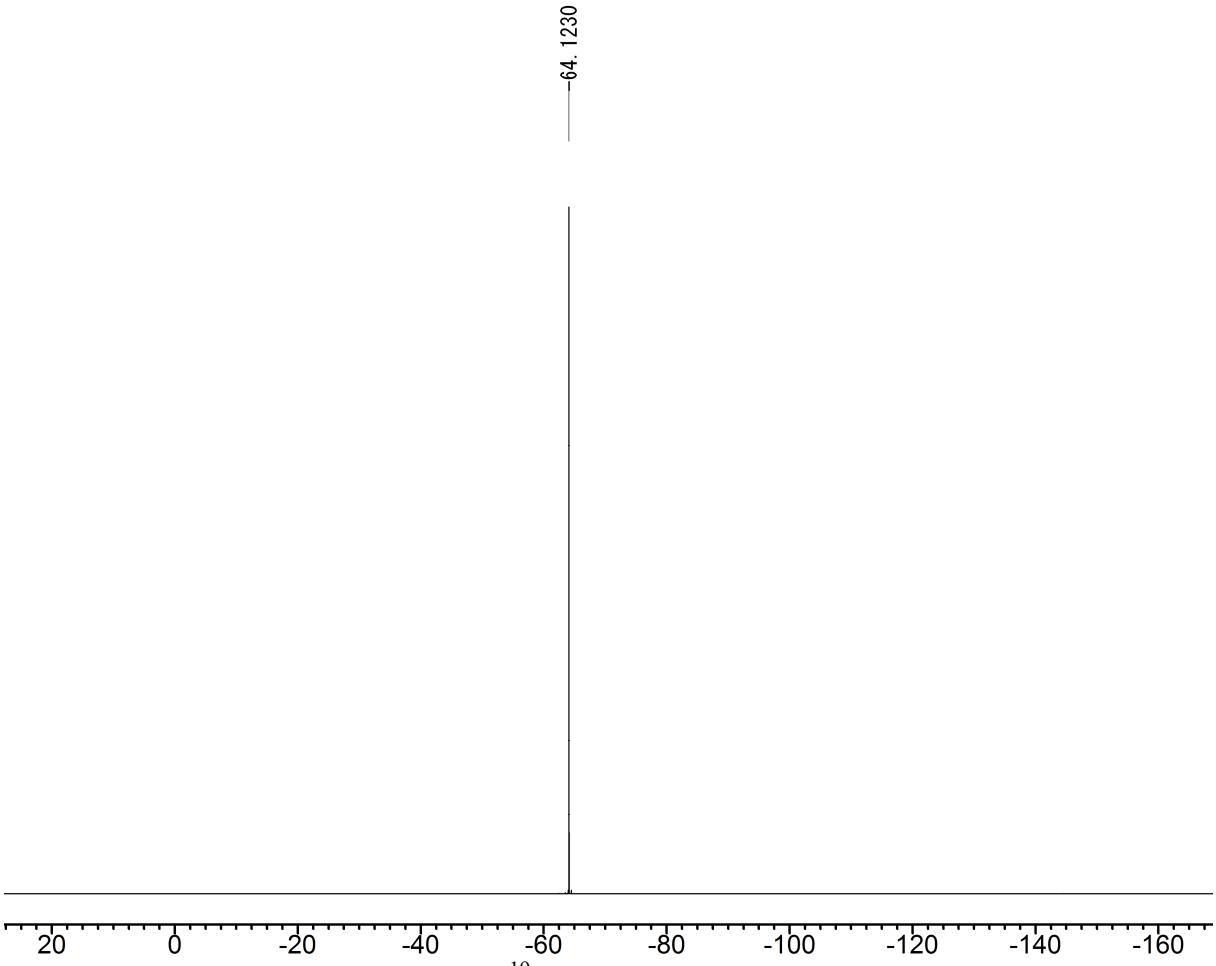
150 MHz ^{13}C NMR of **14** in $CDCl_3$.



600 MHz ^{1}H NMR of **15** in $CDCl_3$.

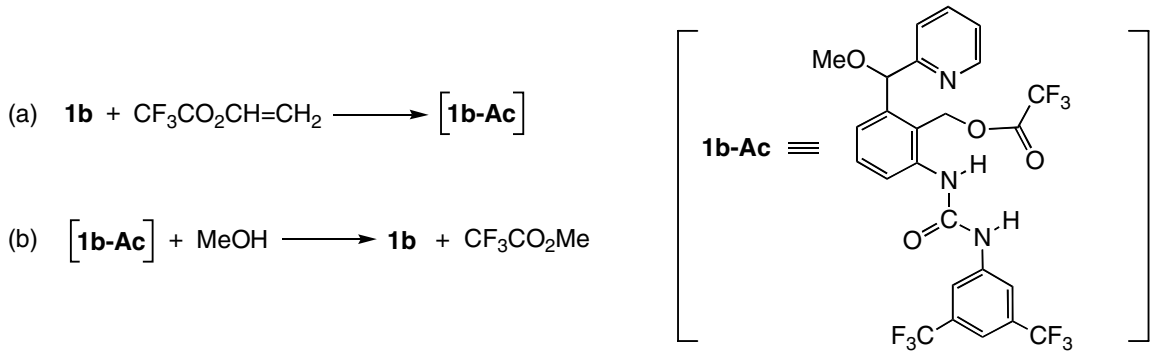


150 MHz ^{13}C NMR of **15** in $CDCl_3$.



565 MHz ^{19}F NMR of **15** in $CDCl_3$.

Spectroscopic Detection of Acyl-Catalyst Intermediate.



The formation of the acyl-catalyst intermediate, **1b-Ac**, was confirmed by ^{19}F NMR. Dry $CDCl_3$ was prepared in advance by passing through a basic alumina short column, and it was stored over molecular sieves 3A. The addition of $CF_3CO_2CH=CH_2$ to **1b** in dry $CDCl_3$ in the absence of MeOH generated **1b-Ac** immediately at room temperature (Figure S1a). Although dry $CDCl_3$ was used, **1b-Ac** was gradually hydrolyzed by a trace amount of H_2O to give CF_3CO_2H, and therefore the signals for the trifluoroacetyl groups of **1b-Ac** and CF_3CO_2H were observed. The signal for a small amount of the remaining $CF_3CO_2CH=CH_2$ can also be seen. Subsequent addition of 5 equiv of MeOH to this solution gave the signal for CF_3CO_2Me together with that for CF_3CO_2H (Figure S1b).

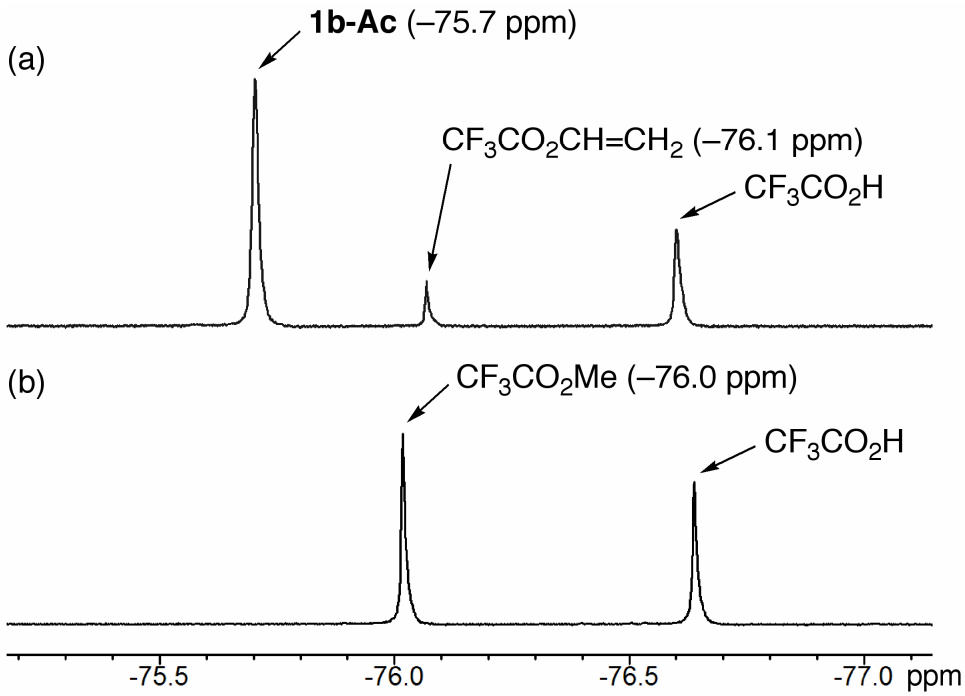
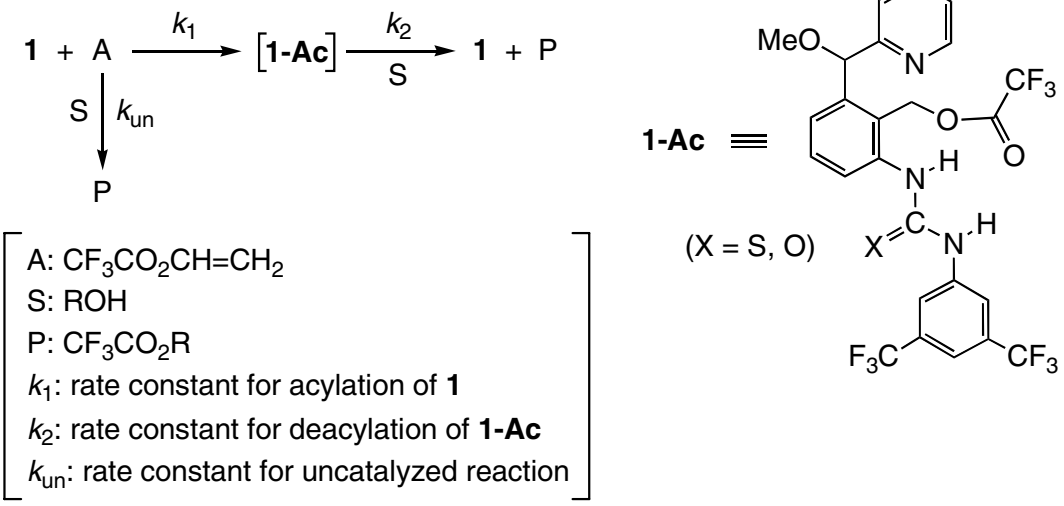


Figure S1 (a) 565 MHz ^{19}F NMR spectrum just after addition of $CF_3CO_2CH=CH_2$ (20 mM) to **1b** (20 mM) in $CDCl_3$ at 22 ºC. (b) ^{19}F NMR spectrum after the subsequent addition of MeOH (100 mM) to the solution indicated in (a).

Derivation of Equations and Determination of Rate Constants.

(a) Derivation of the equations

Scheme S5



Assuming the catalytic cycle shown in Scheme S5, equation 1 can be derived as follows:

The steady-state approximation for the acyl-catalyst intermediate, **1-Ac**, gives

$$\frac{d[\mathbf{1\text{-}Ac}]}{dt} = k_1[\mathbf{1}][A] - k_2[\mathbf{1\text{-}Ac}][S] = 0 \qquad (2)$$

The initial concentration of **1** is related by

$$[\mathbf{1}]_0 = [\mathbf{1}] + [\mathbf{1\text{-}Ac}] \qquad (3)$$

The reaction rate is expressed by

$$v = k_2[\mathbf{1\text{-}Ac}][S] + k_{un}[A][S] \qquad (4)$$

Substitution of equation 2 by equation 3 gives

$$[\mathbf{1\text{-}Ac}] = \frac{k_1[\mathbf{1}]_0[A]}{k_1[A] + k_2[S]} \qquad (5)$$

Equation 4 can therefore be written as

$$v = \frac{k_1k_2[\mathbf{1}]_0[A][S]}{k_1[A] + k_2[S]} + k_{un}[A][S] \qquad (1)$$

Under pseudo-first-order conditions ([S] >> [A])

$$v_{obs} = k_{obs}[A] \qquad (6)$$

From equations 1 and 6

$$k_{obs}[A] = \frac{k_1k_2[\mathbf{1}]_0[A][S]}{k_1[A] + k_2[S]} + k_{un}[A][S] \qquad (7)$$

Rearranging equation 7 gives

$$\frac{1}{k_{obs} - k_{un}[S]} = \frac{[A]}{k_2[\mathbf{1}]_0[S]} + \frac{1}{k_1[\mathbf{1}]_0} \qquad (8)$$

The apparent rate constants, k_{obs}, are determined at various concentrations of A, while k_{un} can be determined independently without the catalyst. Plotting $1/(k_{obs} - k_{un}[S])$ against [A] gives a straight line, from which k_1 and k_2 can be determined.

(b) Determination of the rate constants

To a solution of **1** and ROH in $CDCl_3$ was added a solution of $CF_3CO_2CH{=}CH_2$ in $CDCl_3$. The progress of the reaction was immediately monitored at 22 ºC by ^{19}F NMR, and the initial conversions were measured at appropriate time intervals to give the k_{obs} value. The k_{obs} values were determined at several concentrations of $CF_3CO_2CH{=}CH_2$.

Table S1. Determination of Rate Constants for **1a**-Catalyzed Acylation of MeOH[a]

	[A] (M)				
	0.01	0.03	0.05	0.08	0.1
k_{obs} (s^{-1})	0.0002875	0.0002755	0.0002432	0.00021525	0.00020863
$1/(k_{obs} - k_{un}[S])$ (s)	4726	5010	5978	7177	7535

[a] The final concentrations: [**1a**] = 0.1 mM, [S] = 1.0 M. The rate constant for the uncatalyzed reaction: $k_{un} = 7.6 \times 10^{-5}$ M^{-1} s^{-1}.

Plotting $1/(k_{obs} - k_{un}[S])$ against [A] gave a straight line, from which the rate constants for the **1a**-catalyzed acylation of MeOH were obtained: k_1 = 2.4 M^{-1} s^{-1} and k_2 = 0.29 M^{-1} s^{-1}.

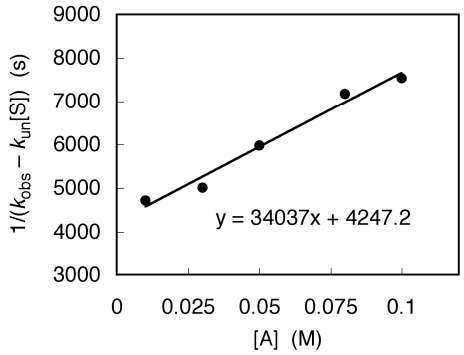


Table S2. Determination of Rate Constants for **1b**-Catalyzed Acylation of MeOH[a]

	[A] (M)			
	0.01	0.03	0.05	0.08
k_{obs} (s^{-1})	0.0005409	0.00033808	0.00025534	0.0001929
$1/(k_{obs} - k_{un}[S])$ (s)	1988	3332	4600	6453

[a] The final concentrations: [**1b**] = 0.05 mM, [S] = 0.5 M. The rate constant for the uncatalyzed reaction: $k_{un} = 7.6 \times 10^{-5}$ M^{-1} s^{-1}.

Plotting $1/(k_{obs} - k_{un}[S])$ against [A] gave a straight line, from which the rate constants for the **1b**-catalyzed acylation of MeOH were obtained: k_1 = 14.4 M^{-1} s^{-1} and k_2 = 0.63 M^{-1} s^{-1}.

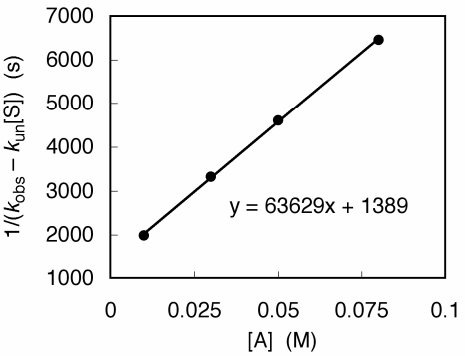


Table S3. Determination of Rate Constants for **1a**-Catalyzed Acylation of *i*-PrOH[a]

	[A] (M)			
	0.01	0.03	0.05	0.08
k_{obs} (s^{-1})	0.00021321	0.00016025	0.00012947	0.00009653
$1/(k_{obs} - k_{un}[S])$ (s)	4780	6400	7971	10808

[a] The final concentrations: [**1a**] = 0.1 mM, [S] = 1.0 M. The rate constant for the uncatalyzed reaction: $k_{un} = 4.0 \times 10^{-6}$ M^{-1} s^{-1}.

Plotting $1/(k_{obs} - k_{un}[S])$ against [A] gave a straight line, from which the rate constants for the **1a**-catalyzed acylation of *i*-PrOH were obtained: $k_1 = 2.6$ M^{-1} s^{-1} and $k_2 = 0.12$ M^{-1} s^{-1}.

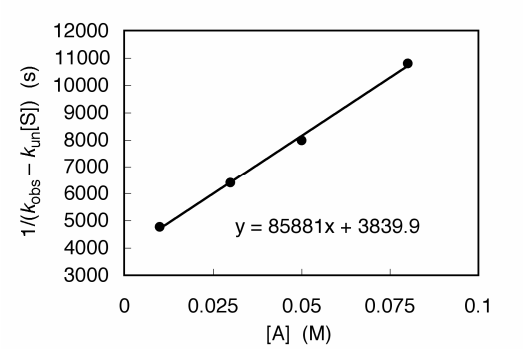


Table S4. Determination of Rate Constants for **1b**-Catalyzed Acylation of *i*-PrOH[a]

	[A] (M)				
	0.01	0.03	0.05	0.08	0.1
k_{obs} (s^{-1})	0.000449	0.000315	0.000231	0.000155	0.000126
$1/(k_{obs} - k_{un}[S])$ (s)	2237	3195	4367	6536	8065

[a] The final concentrations: [**1b**] = 0.05 mM, [S] = 0.5 M. The rate constant for the uncatalyzed reaction: $k_{un} = 4.0 \times 10^{-6}$ M^{-1} s^{-1}.

Plotting $1/(k_{obs} - k_{un}[S])$ against [A] gave a straight line, from which the rate constants for the **1b**-catalyzed acylation of *i*-PrOH were obtained: $k_1 = 14.9$ M^{-1} s^{-1} and $k_2 = 0.61$ M^{-1} s^{-1}.