Supporting Information for

Cu-catalyzed *O*-alkylation of phenol derivatives with alkylsilyl peroxides

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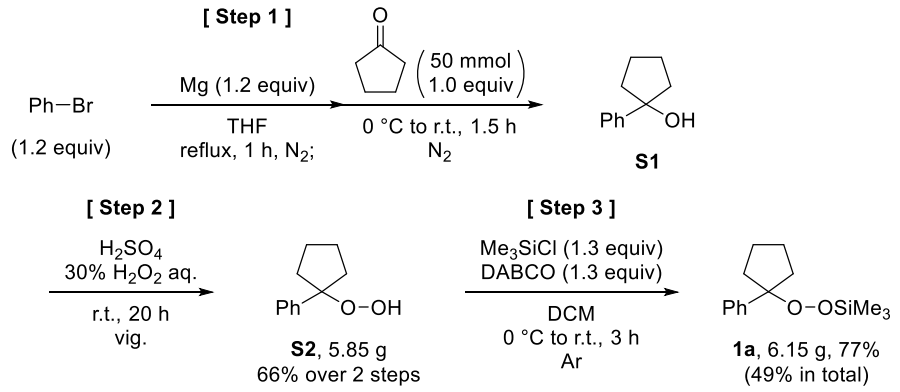
1. General Information

^{1}H NMR spectra were measured on JEOL JNM-ECA500 (500 MHz) spectrometer. Data were reported as follows: chemical shifts in ppm from tetramethylsilane as an internal standard in $CDCl_3$, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet-doublet, dt = doublet-triplet, dq = doublet-quartet, td = triplet-doublet, ddd = doublet-doublet-doublet, m = multiplet, br = broad, app = apparent), coupling constants (Hz), and assignment. ^{13}C NMR spectra were measured on JEOL JNM-ECA500 (125 MHz) spectrometer with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent as an internal standard. High-resolution mass spectra (HRMS) were performed on Thermo Exactive plus (ESI) spectrometer. High performance liquid chromatography (HPLC) was performed on Shimadzu 20A instruments using Daicel CHIRALPAK IC-3 (4.6 mm × 25 cm) column. Optical rotation was measured on a JASCO DIP-1000 digital polarimeter. For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (Merck, TLC Silica gel 60 F_{254}) were used. The products were purified by flash column chromatography on silica gel (Kanto Chemical, Silica gel 60 N, spherical, neutral, 40-50 μm or FUJIFILM Wako, Wakosil®, 60, spherical, 64-210 μm). Commercially available reagents and solvents were purchased from CHEM-IMPEX INT'L INC., FUJIFILM Wako, Oakwood Chemical, Sigma-Aldrich and TCI, and used as received. Alkylsilyl peroxides (ASPs) were prepared according to the literate procedures.[1] All reactions were performed under N_2 atmosphere, and NMR yields were determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

2. Synthesis of Alkylsilyl Peroxide (ASP) 1a



This procedure is a slightly modified version from the author's previously reported one.[1]

[Step 1]

To flame-dried Mg turnings (1.44 g, 60 mmol, 1.2 equiv) in anhydrous THF (100 mL) was added PhBr (6.3 mL, 60 mmol, 1.2 equiv) carefully under N_2 atmosphere. After being refluxed for 1 h, the obtained PhMgBr/THF solution was cooled down to 0 °C and then cyclopentanone (4.4 mL, 50 mmol, 1.0 equiv) was added dropwisely. After being

stirred at room temperature for 1.5 h, the reaction mixture was quenched with sat. NH_4Cl aq. at 0 °C and extracted with a solution of hexane / EtOAc (4 / 1) three times. The combined organic layer was dried over Na_2SO_4 and concentrated. The crude product **S1** was used for the next step without further purification.

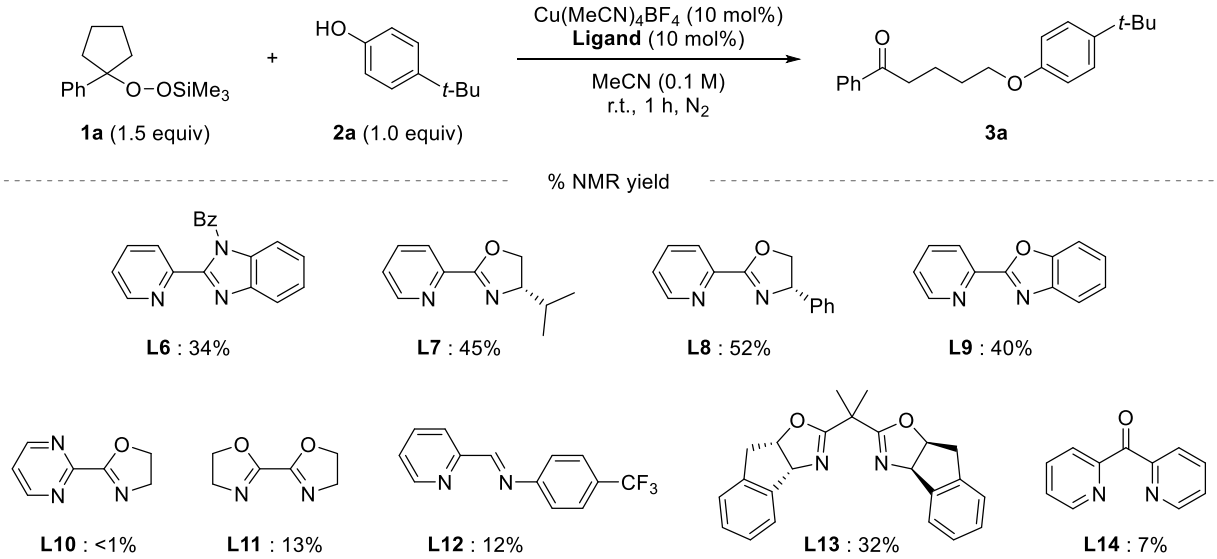
[Step 2]

To **S1** in a flask was added a solution of H_2SO_4 / 30% H_2O_2 aq. (1.5 mL / 50 mL) slowly. After being stirred vigorously at room temperature for 20 h, the reaction mixture was diluted with H_2O (100 mL) and then extracted with CH_2Cl_2 three times. The combined organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (hexane / CH_2Cl_2 = 1 / 1) to afford hydroperoxide **S2** as a pale-yellow oil (5.85 g, 66% over 2 steps). Spectral data of **S2** matched those previously reported in the literature.[1b]

[Step 3]

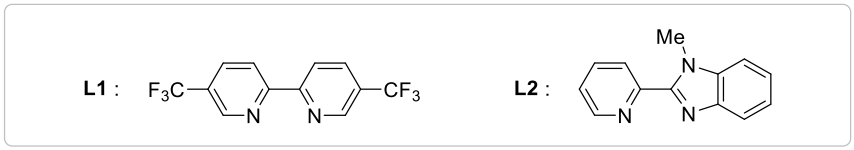
To a solution of **S2** (5.85 g, 33 mmol, 1.0 equiv) and 1,4-diazabicyclo[2.2.2]octane (DABCO, 4.8 g, 43 mmol, 1.3 equiv) in anhydrous CH_2Cl_2 (100 mL) was added Me_3SiCl (5.4 mL, 43 mmol, 1.3 equiv) dropwisely at 0 °C under argon atmosphere. After being stirred at room temperature for 3 h, the reaction mixture was diluted with hexane (80 mL) and passed through a celite pad to remove white precipitates, eluting with hexane. The obtained filtrate was concentrated and purified by flash column chromatography on silica gel (hexane / EtOAc = 20 / 1) to afford trimethyl((1-phenylcyclopentyl)peroxy)silane (**1a**) as a colorless oil (6.15 g, 77% [49% in total]). Spectral data of **1a** matched those previously reported in the literature.[1]

3. Further Ligand Screening

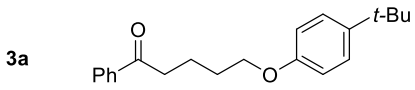


4. General Procedures for Cu-Catalyzed *O*-Alkylation of Phenol Derivatives with Alkylsilyl Peroxides (ASPs) and Spectral Data of Products 3 and 4

To the solution of a phenol derivative (0.2 mmol, 1.0 equiv), $Cu(MeCN)_4BF_4$ (6.2 mg, 0.02 mmol, 10 mol%) and a ligand (**L1**; 5.8 mg, 0.02 mmol, 10 mol% or **L2**; 4.2 mg, 0.02 mmol, 10 mol%) in MeCN (2.0 mL) was added ASP (0.5 mmol, 2.5 equiv) at room temperature under N_2 atmosphere. After being stirred at same temperature for 1 h, the reaction mixture was diluted with a solution of hexane / EtOAc (2 / 1, 3 mL) and then passed through a short silica gel / Na_2SO_4 plug eluting with a solution of hexane / EtOAc (2 / 1). The obtained solution was concentrated and the residue was purified by flash column chromatography on silica gel (hexane / EtOAc = 10 / 1) or washed with hexane to afford the following products **3** or **4**.



5-(4-(*Tert*-butyl)phenoxy)-1-phenylpentan-1-one (3a)



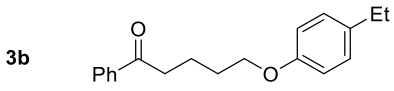
L2 was used for the reaction. Colorless oil, 52.8 mg, 85% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (2H, app d, J = 7.1 Hz), 7.56 (1H, app t, J = 7.4 Hz), 7.46 (2H, app t, J = 7.9 Hz), 7.29 (2H, d, J = 8.8 Hz), 6.82 (2H, d, J = 8.8 Hz), 4.00 (2H, t, J = 6.1 Hz), 3.06 (2H, t, J = 6.9 Hz), 1.97-1.85 (4H, m), 1.30 (9H, s).

^{13}C NMR (125 MHz, $CDCl_3$) δ 200.2, 156.8, 143.4, 137.1, 133.1, 128.7, 128.2, 126.3, 114.0, 67.7, 38.2, 34.2, 31.7, 29.0, 21.1.

HRMS (ESI) Calcd. For $C_{21}H_{27}O_2$: 311.2006 ($[M + H]^+$), Found: 311.2010 ($[M + H]^+$).

5-(4-Ethylphenoxy)-1-phenylpentan-1-one (3b)



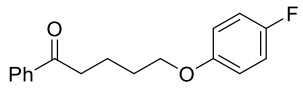
L2 was used for the reaction. White solid, 52.0 mg, 92% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (2H, app dt, J = 8.2, 1.6 Hz), 7.58-7.54 (1H, m), 7.48-7.45 (2H, m), 7.10 (2H, d, J = 8.8 Hz), 6.81 (2H, d, J = 8.8 Hz), 3.99 (2H, t, J = 6.1 Hz), 3.06 (2H, t, J = 7.1 Hz), 2.58 (2H, q, J = 7.7 Hz), 1.97-1.85 (4H, m), 1.21 (3H, t, J = 7.7 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ 200.2, 157.1, 137.1, 136.4, 133.1, 128.8, 128.7, 128.1, 114.5, 67.7, 38.2, 29.0, 28.1, 21.1, 16.0.

HRMS (ESI) Calcd. For $C_{19}H_{23}O_2$: 283.1693 ($[M + H]^+$), Found: 283.1693 ($[M + H]^+$).

5-(4-Fluorophenoxy)-1-phenylpentan-1-one (3c)

3c 

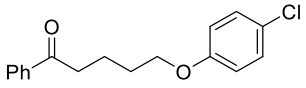
L2 was used for the reaction. White solid, 37.6 mg, 69% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (2H, app d, J = 7.1 Hz), 7.56 (1H, app t, J = 7.1 Hz), 7.46 (2H, app t, J = 7.8 Hz), 6.95 (2H, app t, J = 8.4 Hz), 6.82-6.80 (2H, m), 3.97 (2H, t, J = 6.0 Hz), 3.06 (2H, t, J = 6.9 Hz), 1.96-1.86 (4H, m).

^{13}C NMR (125 MHz, $CDCl_3$, C−F coupling) δ 200.1, 157.3 (d, J_{C-F} = 237.2 Hz), 155.2, 137.1, 133.1, 128.7, 128.2, 115.9 (d, J_{C-F} = 23.8 Hz), 115.5 (d, J_{C-F} = 8.3 Hz), 68.4, 38.2, 29.0, 21.0. (One C−F coupling was not observed.)

HRMS (ESI) Calcd. For $C_{17}H_{18}O_2F$: 273.1285 ($[M + H]^+$), Found: 273.1289 ($[M + H]^+$).

5-(4-Chlorophenoxy)-1-phenylpentan-1-one (3d)

3d 

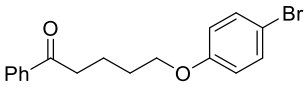
L2 was used for the reaction. White solid, 34.7 mg, 60% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97-7.95 (2H, m), 7.58-7.55 (1H, m), 7.48-7.45 (2H, m), 7.21 (2H, d, J = 9.1 Hz), 6.80 (2H, d, J = 9.1 Hz), 3.98 (2H, t, J = 6.1 Hz), 3.06 (2H, t, J = 7.1 Hz), 1.97-1.85 (4H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ 200.1, 157.7, 137.1, 133.2, 129.4, 128.7, 128.1, 125.5, 115.9, 68.0, 38.2, 28.9, 20.9.

HRMS (ESI) Calcd. For $C_{17}H_{18}O_2Cl$: 289.0990 ($[M + H]^+$), Found: 289.0986 ($[M + H]^+$).

5-(4-Bromophenoxy)-1-phenylpentan-1-one (3e)

3e 

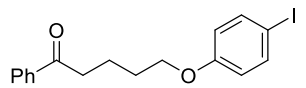
L1 was used for the reaction. White solid, 62 mg, 93% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (2H, app d, J = 8.2 Hz), 7.58-7.55 (1H, m), 7.46 (2H, app t, J = 7.8 Hz), 7.35 (2H, d, J = 8.2 Hz), 6.76 (2H, d, J = 8.2 Hz), 3.97 (2H, t, J = 6.0 Hz), 3.06 (2H, t, J = 6.8 Hz), 1.96-1.86 (4H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ 200.1, 158.2, 137.1, 133.2, 132.4, 128.8, 128.2, 116.4, 112.8, 68.0, 38.2, 28.8, 21.0.

HRMS (ESI) Calcd. For $C_{17}H_{17}O_2BrNa$: 355.0304 ($[M + Na]^+$), Found: 355.0303 ($[M + Na]^+$).

5-(4-Iodophenoxy)-1-phenylpentan-1-one (3f)

3f 

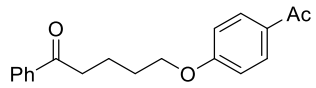
L1 was used for the reaction. White solid, 70 mg, 92% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (2H, app dd, J = 8.4, 1.3 Hz), 7.58-7.53 (3H, m), 7.46 (2H, app t, J = 7.7 Hz), 6.66 (2H, d, J = 8.8 Hz), 3.97 (2H, t, J = 6.1 Hz), 3.06 (2H, t, J = 7.1 Hz), 1.96-1.86 (4H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ 200.0, 159.0, 138.3, 137.1, 133.2, 128.8, 128.2, 117.0, 82.7, 67.9, 38.2, 28.8, 21.0.

HRMS (ESI) Calcd. For $C_{17}H_{17}O_2INa$: 403.0165 ($[M + Na]^+$), Found: 403.0160 ($[M + Na]^+$).

5-(4-Acetylphenoxy)-1-phenylpentan-1-one (3g)

3g 

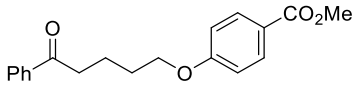
L1 was used for the reaction. The crude mixture was washed with hexane to afford pure **3g**. White solid, 48.0 mg, 81% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (2H, app dd, *J* = 8.2, 1.1 Hz), 7.92 (2H, d, *J* = 9.1 Hz), 7.58-7.55 (1H, m), 7.47 (2H, app t, *J* = 7.7 Hz), 6.91 (2H, d, *J* = 9.1 Hz), 4.08 (2H, t, *J* = 6.0 Hz), 3.07 (2H, t, *J* = 6.8 Hz), 2.55 (3H, s), 1.98-1.88 (4H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ 199.9, 196.9, 163.0, 137.0, 133.2, 130.7, 130.3, 128.7, 128.1, 114.2, 68.0, 38.1, 28.7, 26.4, 20.9.

HRMS (ESI) Calcd. For $C_{19}H_{20}O_3Na$: 319.1305 ($[M + Na]^+$), Found: 319.1304 ($[M + Na]^+$).

Methyl 4-((5-Oxo-5-phenylpentyl)oxy)benzoate (3h)

3h 

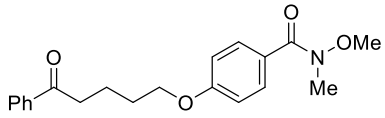
L1 was used for the reaction. The crude mixture was washed with hexane to afford pure **3h**. White solid, 53.1 mg, 85% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99-7.95 (4H, m), 7.58-7.55 (1H, m), 7.48-7.45 (2H, m), 6.89 (2H, d, *J* = 8.8 Hz), 4.07 (2H, t, *J* = 6.1 Hz), 3.88 (3H, s), 3.07 (2H, t, *J* = 6.9 Hz), 1.99-1.88 (4H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ 199.9, 167.0, 162.9, 137.0, 133.2, 131.7, 128.7, 128.1, 122.6, 114.1, 67.9, 51.9, 38.1, 28.8, 20.9.

HRMS (ESI) Calcd. For $C_{19}H_{20}O_4Na$: 335.1254 ($[M + Na]^+$), Found: 335.1251 ($[M + Na]^+$).

***N*-Methoxy-*N*-methyl-4-((5-oxo-5-phenylpentyl)oxy)benzamide (3i)**

3i 

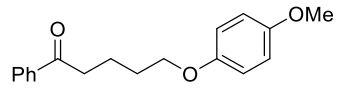
L1 was used for the reaction. The crude mixture was purified by flash column chromatography on silica gel (hexane / EtOAc = 2 / 1 to 1 / 1, gradient) to afford pure **3i**. White solid, 64.9 mg, 83% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (2H, app dd, *J* = 8.2, 1.1 Hz), 7.71 (2H, d, *J* = 9.1 Hz), 7.57 (1H, app t, *J* = 7.4 Hz), 7.47 (2H, app t, *J* = 7.8 Hz), 6.88 (2H, d, *J* = 9.1 Hz), 4.05 (2H, t, *J* = 6.0 Hz), 3.56 (3H, s), 3.35 (3H, s), 3.07 (2H, t, *J* = 6.9 Hz), 1.98-1.87 (4H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ 200.0, 169.5, 161.0, 137.0, 133.1, 130.6, 128.7, 128.1, 125.9, 113.8, 67.8, 61.0, 38.1, 34.0, 28.8, 20.9.

HRMS (ESI) Calcd. For $C_{20}H_{23}O_4NNa$: 364.1519 ($[M + Na]^+$), Found: 364.1521 ($[M + Na]^+$).

5-(4-Methoxyphenoxy)-1-phenylpentan-1-one (3j)

3j 

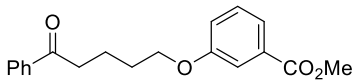
L2 was used for the reaction. White solid, 17.1 mg, 30% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97-7.96 (2H, m), 7.58-7.54 (1H, m), 7.48-7.45 (2H, m), 6.82 (4H, s), 3.96 (2H, t, J = 6.2 Hz), 3.77 (3H, s), 3.06 (2H, t, J = 7.2 Hz), 1.97-1.83 (4H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ 200.2, 153.9, 153.3, 137.1, 133.1, 128.7, 128.2, 115.6, 114.8, 68.4, 55.9, 38.3, 29.1, 21.1.

HRMS (ESI) Calcd. For $C_{18}H_{20}O_3Na$: 307.1305 ($[M + Na]^+$), Found: 307.1308 ($[M + Na]^+$).

Methyl 3-((5-Oxo-5-phenylpentyl)oxy)benzoate (3k)

3k 

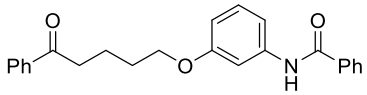
L1 was used for the reaction. The crude mixture was purified by flash column chromatography on silica gel (hexane / EtOAc = 8 / 1) to afford pure **3k**. White solid, 60.0 mg, 96% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97-7.96 (2H, m), 7.62 (1H, app dt, J = 7.7, 1.1 Hz), 7.58-7.54 (2H, m), 7.48-7.45 (2H, m), 7.33 (1H, app t, J = 8.1 Hz), 7.08 (1H, app dq, J = 8.2, 1.1 Hz), 4.06 (2H, t, J = 6.0 Hz), 3.91 (3H, s), 3.07 (2H, t, J = 6.9 Hz), 1.99-1.87 (4H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ 200.0, 167.1, 159.0, 137.0, 133.1, 131.5, 129.5, 128.7, 128.1, 122.0, 120.0, 114.7, 67.9, 52.2, 38.1, 28.8, 20.9.

HRMS (ESI) Calcd. For $C_{19}H_{20}O_4Na$: 335.1254 ($[M + Na]^+$), Found: 335.1254 ($[M + Na]^+$).

***N*-(3-((5-Oxo-5-phenylpentyl)oxy)phenyl)benzamide (3l)**

3l 

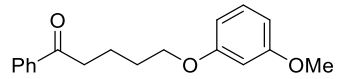
L1 was used for the reaction. The crude mixture was purified by flash column chromatography on silica gel (hexane / EtOAc = 4 / 1 to 2 / 1, gradient) to afford pure **3l**. White solid, 57.5 mg, 77% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98-7.96 (2H, m), 7.88-7.86 (2H, m), 7.78 (1H, br s), 7.58-7.54 (2H, m), 7.52-7.41 (5H, m), 7.25 (2H, app t, J = 8.2 Hz), 7.09 (1H, app d, J = 6.8 Hz), 6.69 (1H, app dd, J = 7.8, 2.1 Hz), 4.06 (2H, t, J = 6.0 Hz), 3.08 (2H, t, J = 6.9 Hz), 1.98-1.89 (4H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ 200.3, 166.0, 159.6, 139.3, 137.0, 135.1, 133.1, 131.9, 129.8, 128.8, 128.7, 128.2, 127.2, 112.4, 111.2, 106.5, 67.7, 38.2, 28.8, 21.0.

HRMS (ESI) Calcd. For $C_{24}H_{23}O_3NNa$: 396.1570 ($[M + Na]^+$), Found: 396.1570 ($[M + Na]^+$).

5-(3-Methoxyphenoxy)-1-phenylpentan-1-one (3m)

3m 

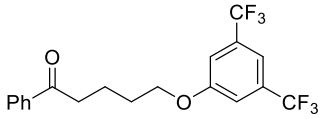
L2 was used for the reaction. Colorless oil, 39.8 mg, 70% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98-7.96 (2H, m), 7.58-7.54 (1H, m), 7.48-7.45 (2H, m), 7.17 (1H, app t, J = 8.2 Hz), 6.49 (2H, app ddd, J = 8.2, 3.6, 2.5 Hz), 6.45 (1H, app t, J = 2.4 Hz), 4.00 (2H, t, J = 6.1 Hz), 3.78 (3H, s), 3.06 (2H, t, J = 7.1 Hz), 1.98-1.85 (4H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ 200.1, 160.9, 160.3, 137.1, 133.1, 130.0, 128.7, 128.2, 106.7, 106.4, 101.0, 67.7, 55.4, 38.2, 28.9, 21.0.

HRMS (ESI) Calcd. For $C_{18}H_{20}O_3Na$: 307.1305 ($[M + Na]^+$), Found: 307.1309 ($[M + Na]^+$).

5-(3,5-Bis(trifluoromethyl)phenoxy)-1-phenylpentan-1-one (3n)

3n 

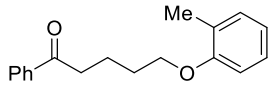
L1 was used for the reaction. Colorless oil, 25.8 mg, 33% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97-7.96 (2H, m), 7.57 (1H, app t, J = 7.4 Hz), 7.47 (2H, app t, J = 7.8 Hz), 7.44 (1H, s), 7.26 (2H, s), 4.09 (2H, t, J = 5.8 Hz), 3.09 (2H, t, J = 6.7 Hz), 2.00-1.92 (4H, m).

^{13}C NMR (125 MHz, $CDCl_3$, C−F coupling) δ 199.8, 159.6, 137.0, 133.3, 132.9 (q, J_{C-F} = 33.4 Hz), 128.8, 128.1, 123.3 (q, J_{C-F} = 273.0 Hz), 114.9, 114.3, 68.7, 38.0, 28.6, 20.8.

HRMS (ESI) Calcd. For $C_{19}H_{16}O_2F_6Na$: 391.1127 ($[M + Na]^+$), Found: 391.1125 ($[M + Na]^+$).

1-Phenyl-5-(*o*-tolyloxy)pentan-1-one (3o)

3o 

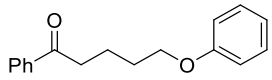
L2 was used for the reaction. Colorless oil, 29.5 mg, 55% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98-7.95 (2H, m), 7.58-7.54 (1H, m), 7.48-7.45 (2H, m), 7.16-7.12 (2H, m), 6.84 (1H, app td, J = 7.4, 0.9 Hz), 6.81 (1H, app d, J = 7.9 Hz), 4.02 (2H, t, J = 6.0 Hz), 3.08 (2H, t, J = 7.1 Hz), 2.21 (3H, s), 2.00-1.88 (4H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ 200.2, 157.2, 137.1, 133.1, 130.7, 128.7, 128.2, 126.9, 126.9, 120.3, 110.9, 67.6, 38.3, 29.1, 21.2, 16.4.

HRMS (ESI) Calcd. For $C_{18}H_{20}O_2Na$: 291.1356 ($[M + Na]^+$), Found: 291.1359 ($[M + Na]^+$).

5-Phenoxy-1-phenylpentan-1-one (3p)

3p 

L2 was used for the reaction. The reaction was performed in 6.0 mmol scale (Phenol; 564.7 mg, 6.0 mmol, ASP **1a**; 3.76 g, 15 mmol, $Cu(MeCN)_4BF_4$; 188.7 mg, 0.6 mmol, **L2**; 125.6 mg, 0.6 mmol, MeCN; 40 mL [0.15 M]). After

the reaction mixture was stirred for 1 h under N_2 atmosphere, the solvent was evaporated and then H_2O was poured into the residue. The aqueous layer was extracted with a solution of hexane / EtOAc (3 / 1). The obtained organic layer was concentrated and the residue was purified by flash column chromatography on silica gel (hexane / EtOAc = 20 / 1 to 15 / 1, gradient) to afford the desired product **3p**. White solid, 1.39 g, 91% yield.

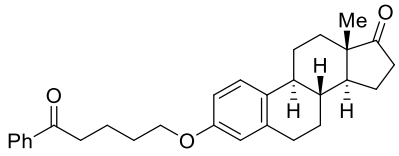
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97-7.96 (2H, m), 7.58-7.55 (1H, m), 7.48-7.45 (2H, m), 7.29-7.27 (2H, m), 6.93 (1H, app td, J = 7.4, 1.1 Hz), 6.89-6.88 (2H, m), 4.01 (2H, t, J = 5.7 Hz), 3.07 (2H, t, J = 6.7 Hz), 1.98-1.86 (4H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ 200.2, 159.1, 137.1, 133.1, 129.6, 128.7, 128.2, 120.7, 114.6, 67.6, 38.2, 29.0, 21.1.

HRMS (ESI) Calcd. For $C_{17}H_{18}O_2Na$: 277.1199 ([M + Na]$^+$), Found: 277.1203 ([M + Na]$^+$).

(8*R*,9*S*,13*S*,14*S*)-13-Methyl-3-((5-oxo-5-phenylpentyl)oxy)-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (3q)

3q



L2 was used for the reaction. The crude mixture was purified by flash column chromatography on silica gel (hexane / EtOAc = 8 / 1) to afford pure **3q**. White solid, 62.9 mg, 73% yield.

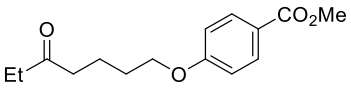
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97-7.96 (2H, m), 7.58-7.55 (1H, m), 7.48-7.45 (2H, m), 7.19 (1H, app d, J = 8.8 Hz), 6.70 (1H, app dd, J = 8.5, 2.8 Hz), 6.63 (1H, app d, J = 2.8 Hz), 3.99 (2H, t, J = 6.1 Hz), 3.06 (2H, t, J = 7.1 Hz), 2.89 (2H, dd, J = 9.8, 6.9 Hz), 2.50 (1H, dd, J = 18.8, 8.6 Hz), 2.42-2.37 (1H, m), 2.27-2.22 (1H, m), 2.18-2.10 (1H, m), 2.08-1.98 (2H, m), 1.96-1.85 (5H, m), 1.67-1.58 (2H, m), 1.53-1.41 (4H, m), 0.91 (3H, s).

^{13}C NMR (125 MHz, $CDCl_3$) δ 221.1, 200.1, 157.1, 137.8, 137.1, 133.1, 132.1, 128.7, 128.1, 126.4, 114.6, 112.2, 67.6, 50.5, 48.1, 44.1, 38.5, 38.2, 36.0, 31.7, 29.8, 29.0, 26.7, 26.0, 21.7, 21.1, 14.0.

HRMS (ESI) Calcd. For $C_{29}H_{34}O_3Na$: 453.2400 ([M + Na]$^+$), Found: 453.2401 ([M + Na]$^+$).

Methyl 4-((5-Oxoheptyl)oxy)benzoate (4a)

4a



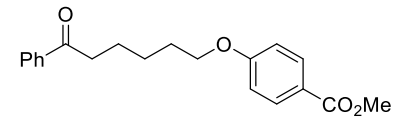
L1 was used for the reaction and the reaction was performed at 50 °C for 3 h. The crude mixture was purified by flash column chromatography on silica gel (hexane / EtOAc = 5 / 1) to afford pure **4a**. White solid, 37.5 mg, 71% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (2H, d, J = 8.8 Hz), 6.89 (2H, d, J = 9.1 Hz), 4.01 (2H, t, J = 6.0 Hz), 3.88 (3H, s), 2.50 (2H, t, J = 6.9 Hz), 2.44 (2H, q, J = 7.3 Hz), 1.84-1.74 (4H, m), 1.06 (3H, t, J = 7.2 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ 211.3, 167.0, 162.9, 131.7, 122.6, 114.1, 67.9, 52.0, 41.9, 36.1, 28.7, 20.5, 8.0.

HRMS (ESI) Calcd. For $C_{15}H_{20}O_4Na$: 287.1254 ([M + Na]$^+$), Found: 287.1258 ([M + Na]$^+$).

Methyl 4-((6-Oxo-6-phenylhexyl)oxy)benzoate (4b)

4b 

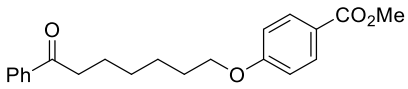
L1 was used for the reaction. The crude mixture was purified by flash column chromatography on silica gel (hexane / EtOAc = 5 / 1) to afford pure **4b**. White solid, 41.8 mg, 64% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99-7.95 (4H, m), 7.56 (1H, app t, J = 7.4 Hz), 7.46 (2H, app t, J = 7.8 Hz), 6.90 (2H, d, J = 8.8 Hz), 4.03 (2H, t, J = 6.5 Hz), 3.88 (3H, s), 3.02 (2H, t, J = 7.4 Hz), 1.90-1.80 (4H, m), 1.61-1.58 (2H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ 200.3, 167.0, 163.0, 137.1, 133.1, 131.7, 128.7, 128.1, 122.5, 114.2, 68.0, 52.0, 38.5, 29.1, 25.9, 24.0.

HRMS (ESI) Calcd. For $C_{20}H_{22}O_4Na$: 349.1410 ($[M + Na]^+$), Found: 349.1417 ($[M + Na]^+$).

Methyl 4-((7-Oxo-7-phenylheptyl)oxy)benzoate (4c)

4c 

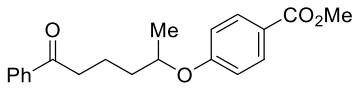
L1 was used for the reaction. The crude mixture was washed with hexane to afford pure **4c**. White solid, 60.6 mg, 89% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99-7.95 (4H, m), 7.57-7.54 (1H, m), 7.48-7.44 (2H, m), 6.89 (2H, d, J = 8.8 Hz), 4.01 (2H, t, J = 6.5 Hz), 3.88 (3H, s), 2.99 (2H, t, J = 7.2 Hz), 1.85-1.76 (4H, m), 1.56-1.43 (4H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ 200.4, 167.0, 163.0, 137.1, 133.0, 131.7, 128.7, 128.1, 122.4, 114.1, 68.1, 51.9, 38.5, 29.1, 29.0, 26.0, 24.2.

HRMS (ESI) Calcd. For $C_{21}H_{24}O_4Na$: 363.1567 ($[M + Na]^+$), Found: 363.1573 ($[M + Na]^+$).

Methyl 4-((6-Oxo-6-phenylhexan-2-yl)oxy)benzoate (4d)

4d 

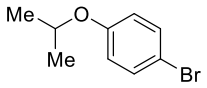
L1 was used for the reaction. The crude mixture was purified by flash column chromatography on silica gel (hexane / EtOAc = 5 / 1) to afford pure **4d**. Colorless oil, 62.0 mg, 95% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97-7.93 (4H, m), 7.57-7.54 (1H, m), 7.47-7.44 (2H, m), 6.88 (2H, d, J = 9.1 Hz), 4.54-4.49 (1H, m), 3.88 (3H, s), 3.05-3.00 (2H, m), 1.97-1.69 (4H, m), 1.35 (3H, d, J = 6.0 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ 200.0, 166.9, 162.0, 137.0, 133.1, 131.7, 128.7, 128.1, 122.3, 115.1, 76.9, 73.8, 51.9, 38.3, 35.9, 20.2, 19.6.

HRMS (ESI) Calcd. For $C_{20}H_{22}O_4Na$: 349.1410 ($[M + Na]^+$), Found: 349.1417 ($[M + Na]^+$).

1-Bromo-4-isopropoxybenzene (4e)

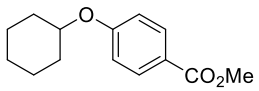
4e 

L1 was used for the reaction. The crude mixture was purified by flash column chromatography on silica gel (hexane) to afford pure **4e**. Colorless oil, 40.4 mg, 94% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (2H, d, *J* = 9.1 Hz), 6.76 (2H, d, *J* = 9.1 Hz), 4.53-4.45 (1H, m), 1.32 (6H, d, *J* = 6.0 Hz).

^{1}H NMR spectrum and other spectral data matched those reported in the literature.[2]

Methyl 4-(Cyclohexyloxy)benzoate (4f)

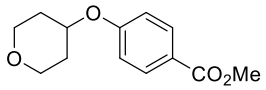
4f 

L1 was used for the reaction. Colorless oil, 44.5 mg, 95% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (2H, d, *J* = 9.1 Hz), 6.89 (2H, d, *J* = 8.8 Hz), 4.36-4.31 (1H, m), 3.88 (3H, s), 2.00-1.97 (2H, m), 1.84-1.79 (2H, m), 1.56-1.51 (3H, m), 1.43-1.28 (3H, m).

^{1}H NMR spectrum and other spectral data matched those reported in the literature.[3]

Methyl 4-((Tetrahydro-2*H*-pyran-4-yl)oxy)benzoate (4g)

4g 

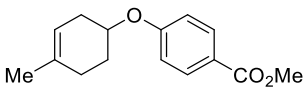
L1 was used for the reaction. The crude mixture was purified by flash column chromatography on silica gel (hexane / EtOAc = 10 / 1 to 3 / 1, gradient) to afford pure **4g**. Colorless oil, 45.4 mg, 96% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (2H, d, *J* = 9.1 Hz), 6.92 (2H, d, *J* = 8.8 Hz), 4.61-4.56 (1H, m), 4.01-3.96 (2H, m), 3.92-3.88 (3H, m), 3.62-3.58 (2H, m), 2.07-2.01 (2H, m), 1.84-1.78 (2H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 161.2, 131.7, 122.7, 115.2, 71.6, 65.0, 51.9, 31.7.

HRMS (ESI) Calcd. For $C_{13}H_{17}O_4$: 237.1121 ($[M + H]^+$), Found: 237.1121 ($[M + H]^+$).

Methyl 4-((4-Methylcyclohex-3-en-1-yl)oxy)benzoate (4h)

4h 

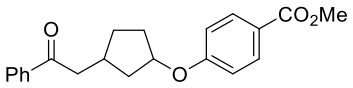
L1 was used for the reaction and the reaction was performed at 50 °C for 3 h. Colorless oil, 15.3 mg, 31% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (2H, d, *J* = 8.8 Hz), 6.91 (2H, d, *J* = 8.8 Hz), 5.32 (1H, app t, *J* = 1.4 Hz), 4.61-4.56 (1H, m), 3.88 (3H, s), 2.47-2.44 (1H, m), 2.23-1.99 (4H, m), 1.90-1.83 (1H, m), 1.69 (3H, s).

^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 161.9, 134.3, 131.7, 122.4, 117.9, 115.3, 72.7, 51.9, 31.1, 28.2, 27.7, 23.4.

HRMS (ESI) Calcd. For $C_{15}H_{18}O_3Na$: 269.1148 ($[M + Na]^+$), Found: 269.1145 ($[M + Na]^+$).

Methyl 4-((3-(2-Oxo-2-phenylethyl)cyclopentyl)oxy)benzoate (4i)

4i 

L1 was used for the reaction. The crude mixture was purified by flash column chromatography on silica gel (hexane / EtOAc = 5 / 1) to afford the single diastereomers A and B of **4i** (separable by flash column chromatography on silica gel).

· Diastereomer A (R_f = 0.29, hexane / EtOAc = 5 / 1), white solid, 31.8 mg, 47% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98-7.94 (4H, m), 7.57-7.54 (1H, m), 7.46 (2H, app t, *J* = 7.8 Hz), 6.86 (2H, d, *J* = 9.1 Hz), 4.86-4.82 (1H, m), 3.88 (3H, s), 3.18-3.09 (2H, m), 2.61-2.55 (1H, m), 2.51-2.45 (1H, m), 2.05-1.92 (3H, m), 1.54-1.50 (2H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ 199.8, 167.0, 161.9, 137.2, 133.2, 131.7, 128.7, 128.2, 122.3, 115.1, 79.3, 52.0, 44.9, 39.5, 34.5, 32.9, 31.0.

HRMS (ESI) Calcd. For $C_{21}H_{22}O_4Na$: 361.1410 ($[M + Na]^+$), Found : 361.1411 ($[M + Na]^+$).

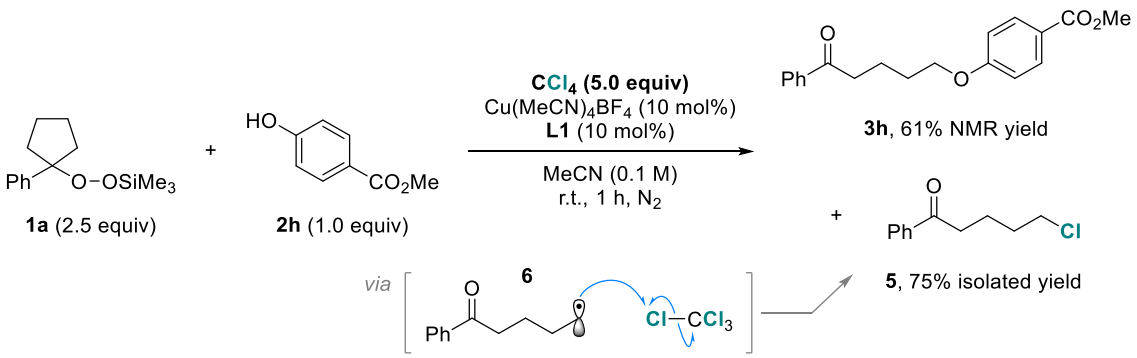
· Diastereomer B (R_f = 0.25, hexane / EtOAc = 5 / 1), white solid, 30.5 mg, 45% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (4H, app dt, *J* = 7.9, 1.1 Hz), 7.58-7.55 (1H, m), 7.47 (2H, app t, *J* = 7.9 Hz), 6.85 (2H, d, *J* = 8.5 Hz), 4.86 (1H, t, *J* = 6.1 Hz), 3.87 (3H, s), 3.05 (2H, d, *J* = 7.1 Hz), 2.80-2.73 (1H, m), 2.23-2.11 (3H, m), 1.91-1.85 (1H, m), 1.62-1.58 (1H, m), 1.36-1.28 (1H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ 199.7, 167.1, 161.9, 137.1, 133.2, 131.6, 128.7, 128.2, 122.2, 115.1, 79.0, 51.9, 44.3, 39.8, 34.2, 32.4, 31.1.

HRMS (ESI) Calcd. For $C_{21}H_{22}O_4Na$: 361.1410 ($[M + Na]^+$), Found: 361.1411 ($[M + Na]^+$).

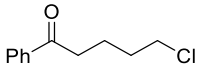
5. A Control Experiment using Tetrachloromethane



When tetrachloromethane (CCl_4, 97 μL, 5.0 equiv) was added to the reaction (0.2 mmol scale) using **1a** and methyl 4-hydroxybenzoate (**2h**), the yield of desired *O*-alkylated product (**3h**) was dropped down to 61% NMR yield and 5-chloro-1-phenylpentan-1-one (**5**) was obtained in 75% isolated yield (based on **2h**) as a white solid, which was purified by flash column chromatography on silica gel (hexane / EtOAc = 10 / 1, 29.5 mg). This result would also support that our Cu-catalyzed *O*-alkylation of phenol derivatives with ASPs proceeded via a radical mechanism.[4]

5-Chloro-1-phenylpentan-1-one (5)

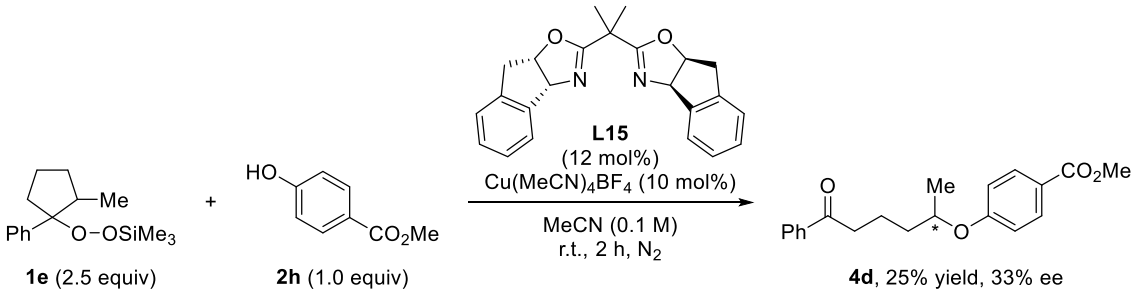
5



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97-7.95 (2H, m), 7.59-7.55 (1H, m), 7.49-7.45 (2H, m), 3.59 (2H, t, J = 6.4 Hz), 3.02 (2H, t, J = 6.9 Hz), 1.95-1.85 (4H, m).

^{1}H NMR spectrum and other spectral data matched those reported in the literature.[5]

6. Enantioselective Synthesis of 4d

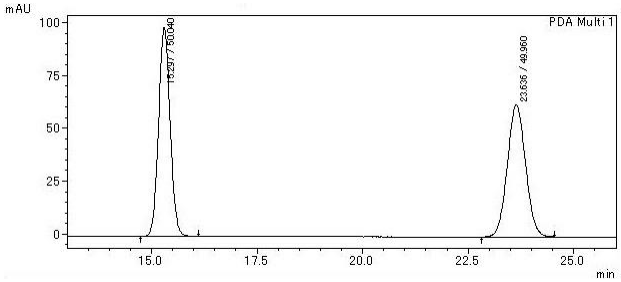


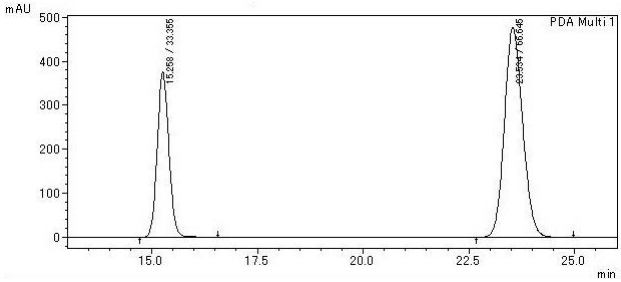
1e (2.5 equiv) **2h** (1.0 equiv) **4d**, 25% yield, 33% ee

The reaction (0.2 mmol scale) was performed for 2 h, using **1e**, **2h** and a chiral bis(oxazoline) (BOX) ligand **L15** (8.6 mg, 12 mol%) instead of **L1**. The enantiomeric excess (ee) of **4d** was determined by HPLC after purified by flash column chromatography on silica gel (16.3 mg, 25% yield, 33% ee).

$[\alpha]_D^{23}$ = −1.6 (*c* = 1.0, $CHCl_3$, 33% ee).

HPLC analysis: Daicel CHIRALPAK IC-3, hexane / ^{i}PrOH = 3 / 1, flow rate = 1.0 mL/min, λ = 254 nm, retention time: 15.3 min (minor) and 23.5 min (major).





254nm 4nm

RetTime [min]	Area [mAU*s]	Area [%]
15.258	7165401	33.355
23.534	14317108	66.645
		100.000

7. References

[1] (a) R. Sakamoto, S. Sakurai, and K. Maruoka, *Chem*. *Eur*. *J*. **2017**, *23*, 9030.

(b) R. Sakamoto, T. Kato, S. Sakurai, and K. Maruoka, *Org*. *Lett*. **2018**, *20*, 1400.

(c) T. Seihara, S. Sakurai, T. Kato, R. Sakamoto, and K. Maruoka, *Org*. *Lett*. **2019**, *21*, 2477.

(d) S. Sakurai, S. Tsuzuki, R. Sakamoto, and K. Maruoka, *J*. *Org*. *Chem*. **2020**, *85*, 3973.

(e) S. Sakurai, A. Matsumoto, T. Kano, and K. Maruoka, *J*. *Am*. *Chem*. *Soc*. **2020**, *142*, 19017.

[2] X. Xiong, F. Tan, and Y.-Y. Yeung, *Org*. *Lett*. **2017**, *19*, 4243.

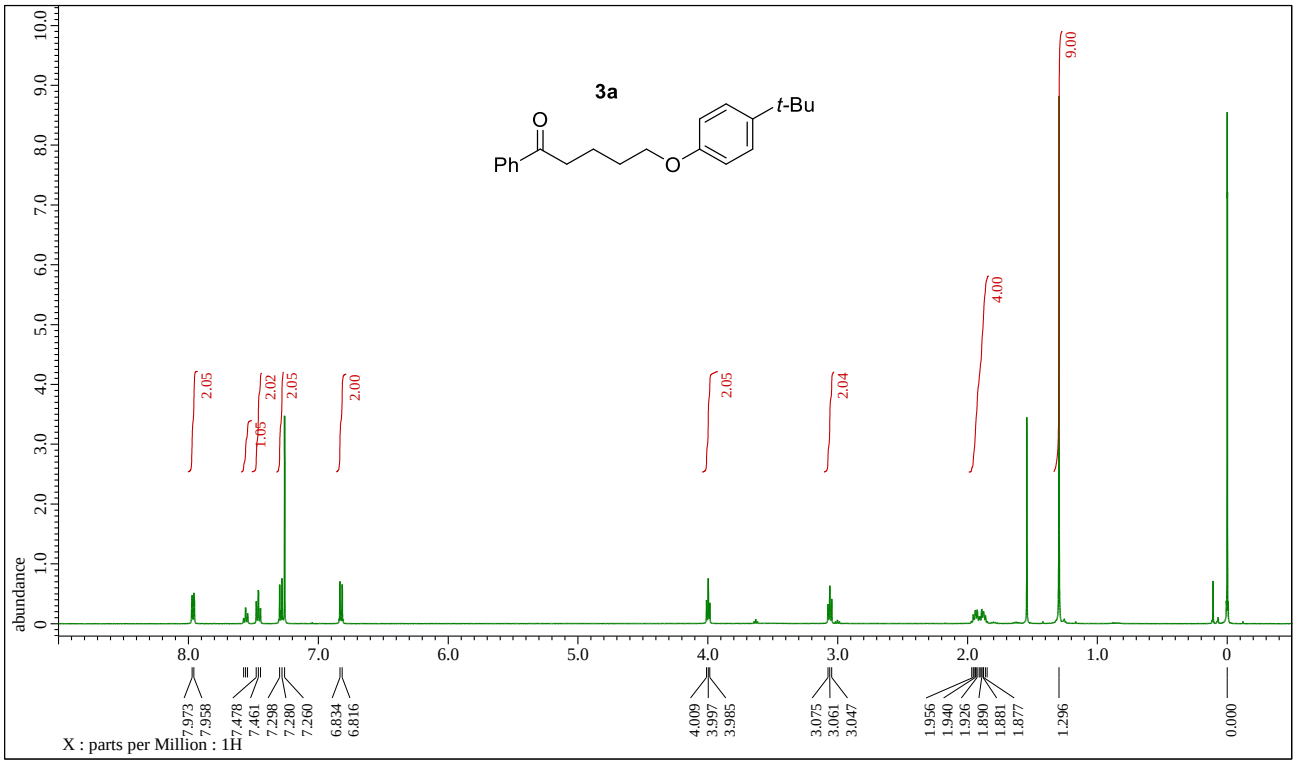
[3] L. Yang, H.-H. Lu, C.-H. Lai, G. Li, W. Zhang, R. Cao, F. Li, C. Wang, J. Xiao, and D. Xue, *Angew*. *Chem*. *Int*. *Ed*. **2020**, *59*, 12714.

[4] H. G. Yayla, H. Wang, K. T. Tarantino, H. S. Orbe, and R. R. Knowles, *J*. *Am*. *Chem*. *Soc*. **2016**, *138*, 10794.

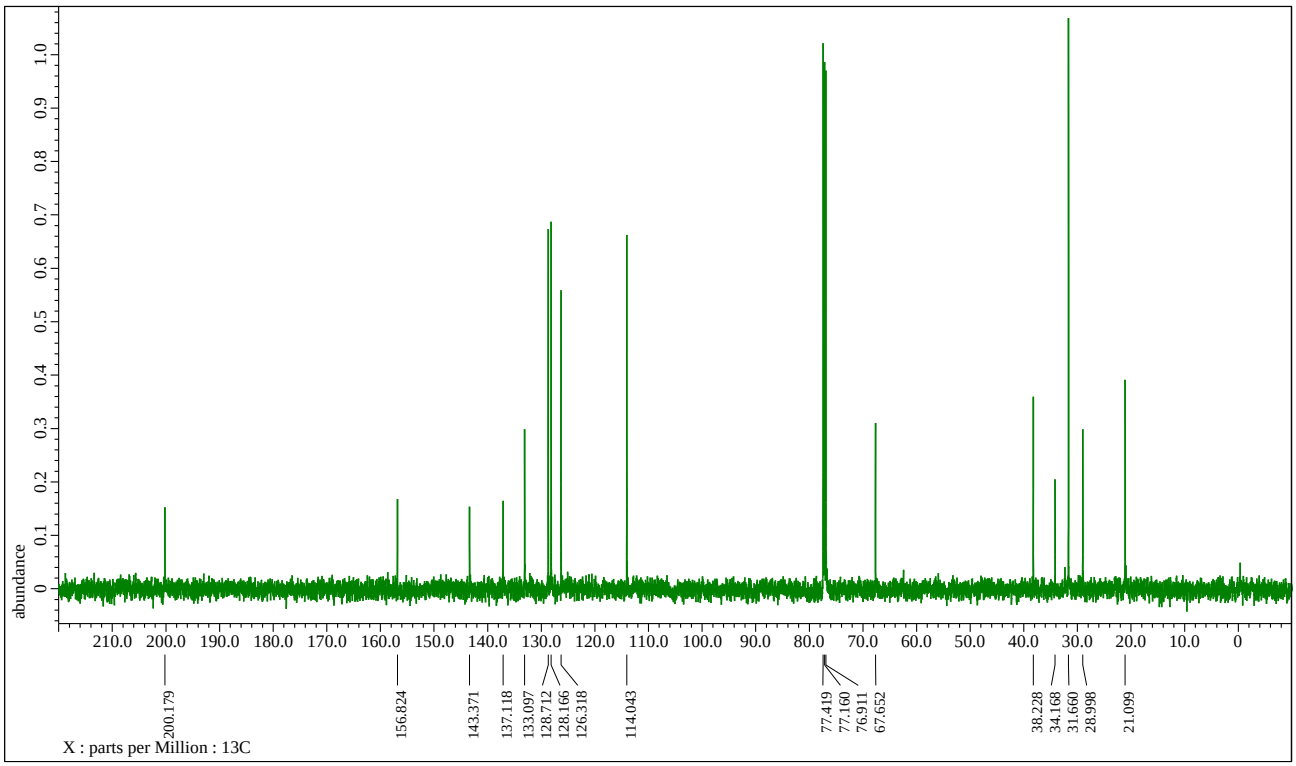
[5] C. Monasterolo, H. Műller-Bunz, and D. G. Gilheany, *Chem*. *Sci*. **2019**, *10*, 6531.

8. ^{1}H NMR and ^{13}C NMR Spectra

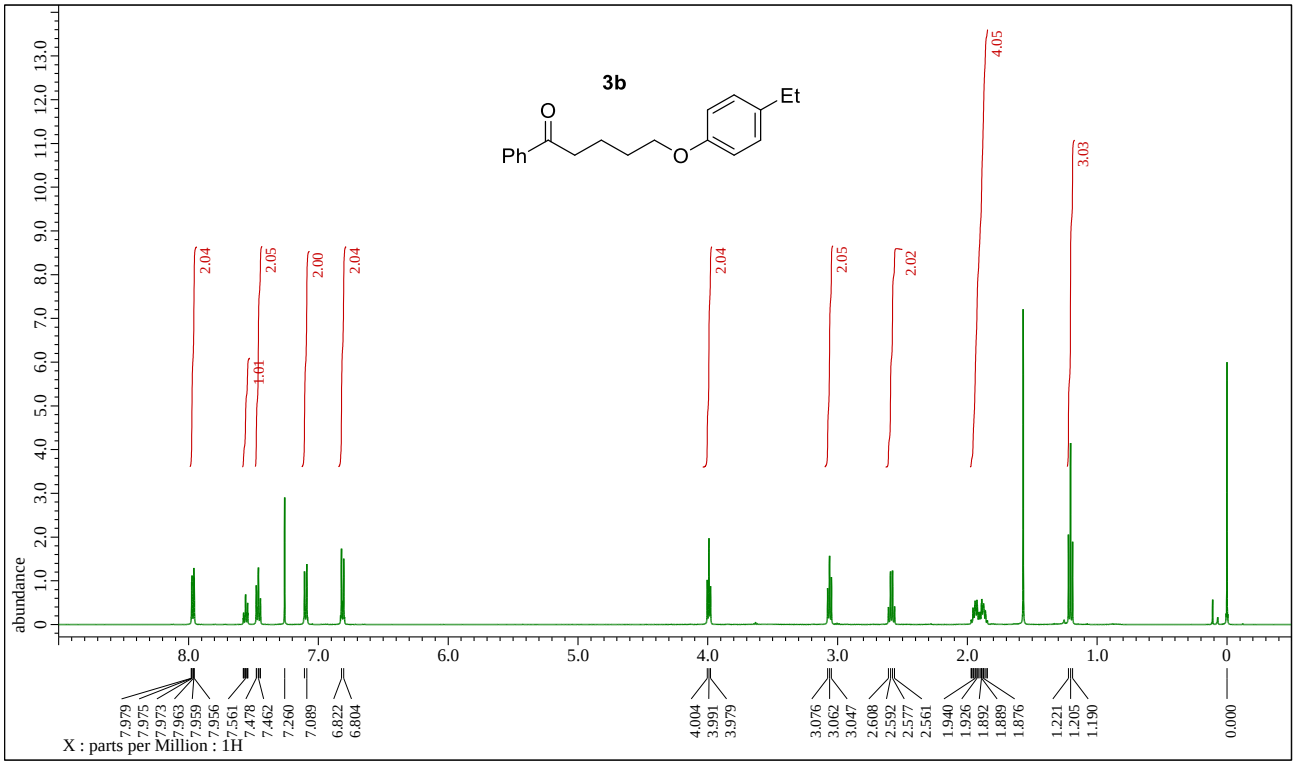
^{1}H NMR spectrum of **3a** (500 MHz, $CDCl_3$)



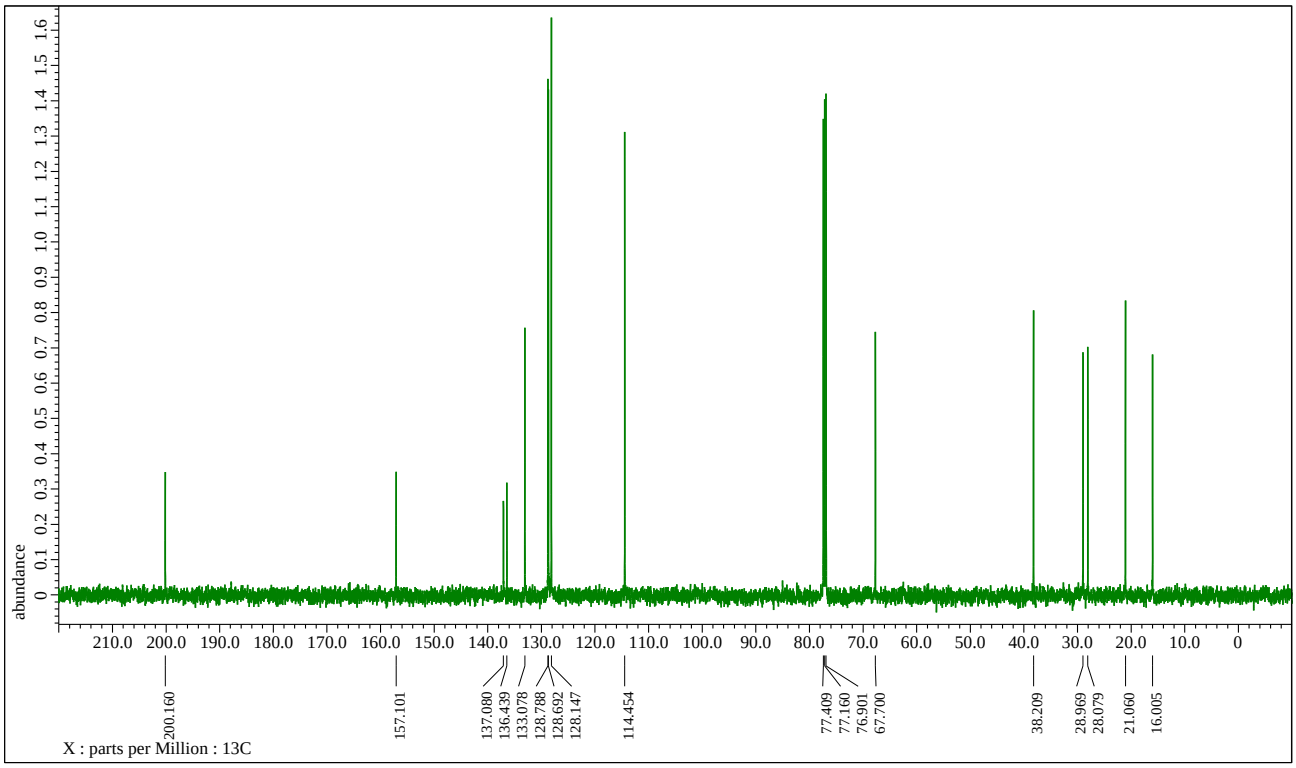
^{13}C NMR spectrum of **3a** (125 MHz, $CDCl_3$)



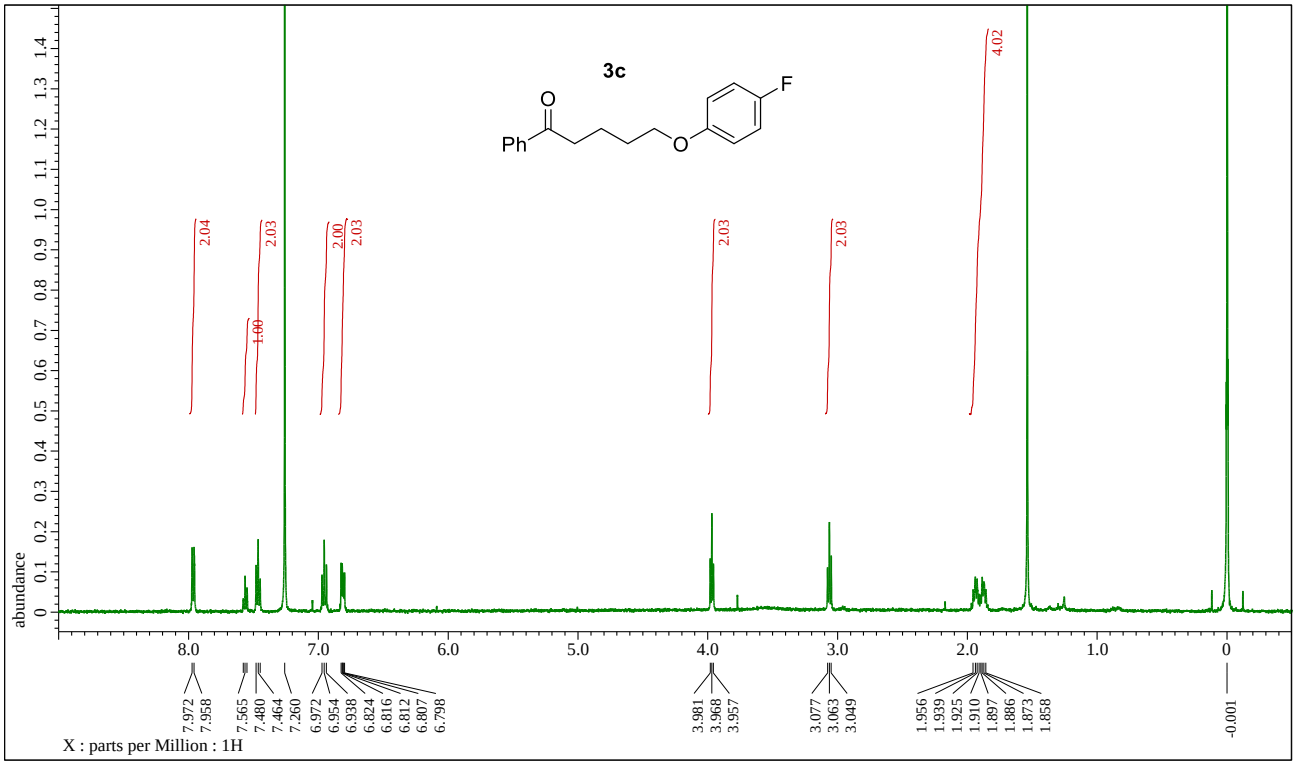
^{1}H NMR spectrum of **3b** (500 MHz, $CDCl_3$)



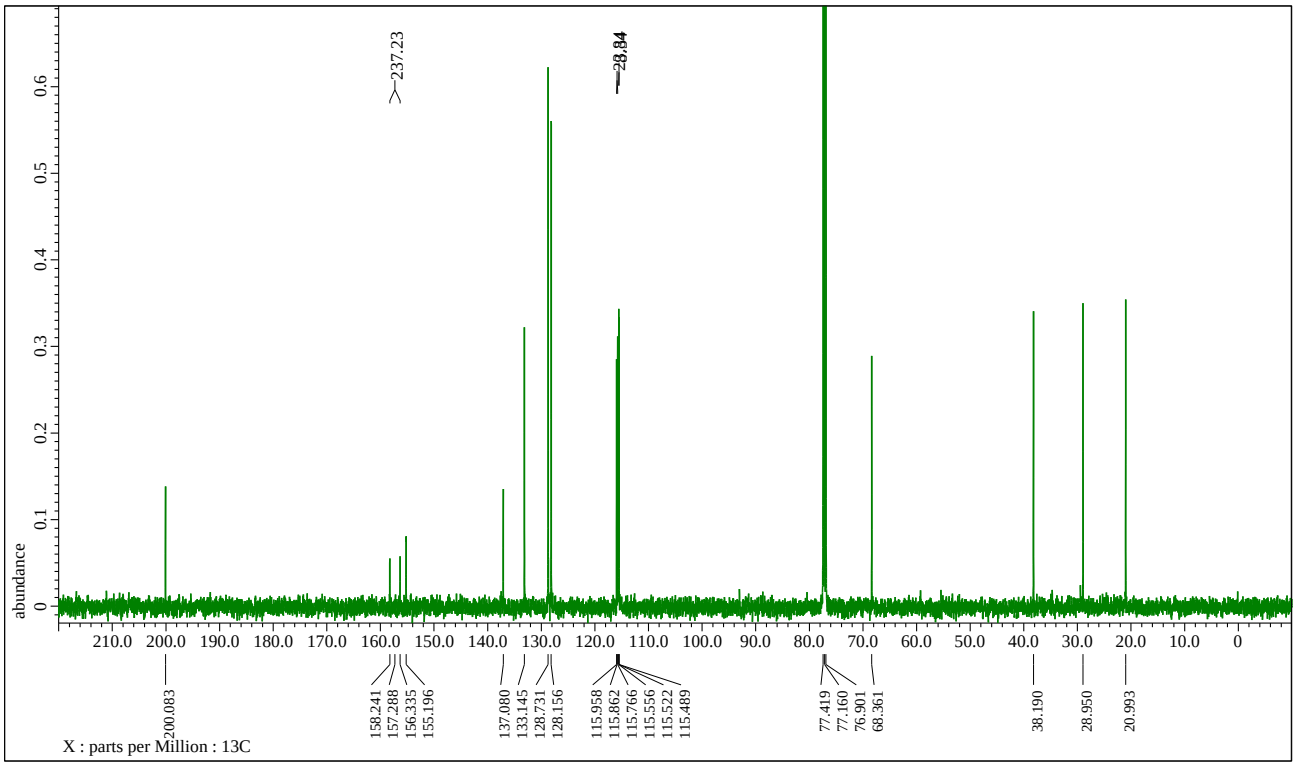
^{13}C NMR spectrum of **3b** (125 MHz, $CDCl_3$)



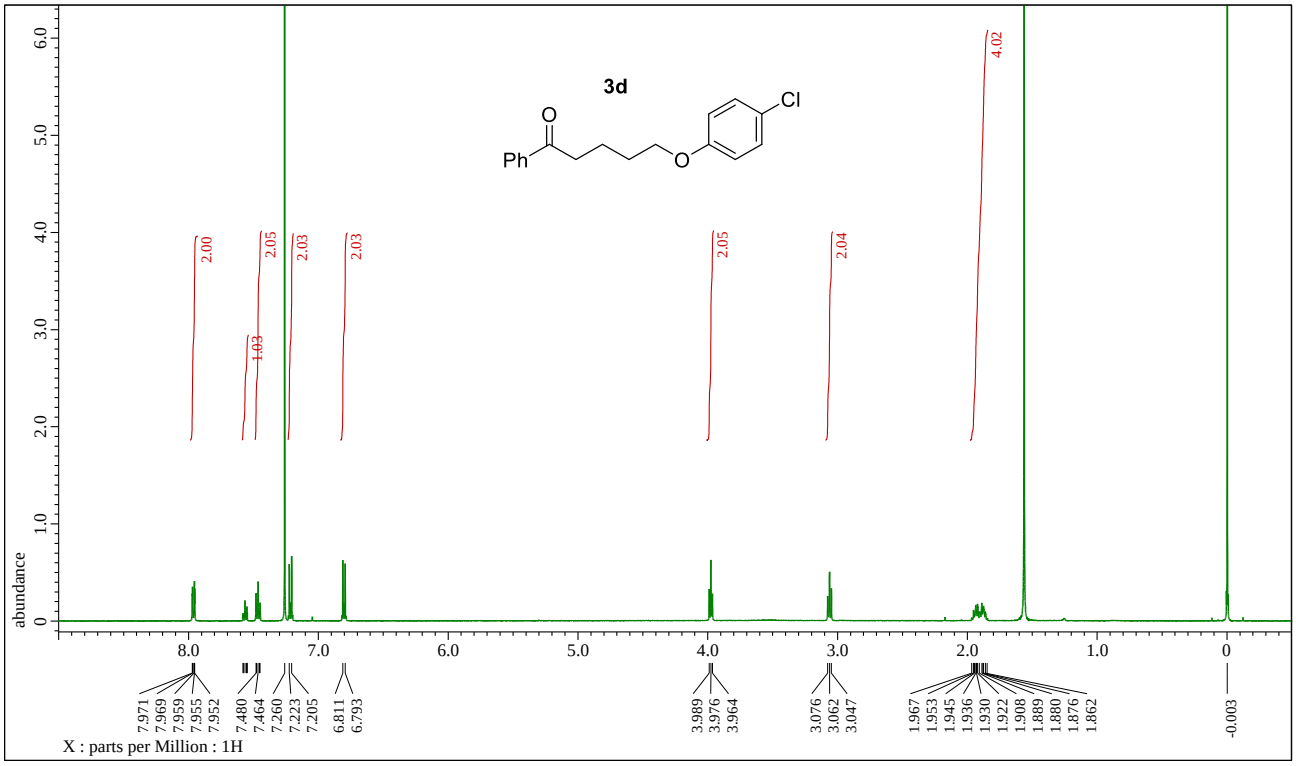
^{1}H NMR spectrum of **3c** (500 MHz, $CDCl_3$)



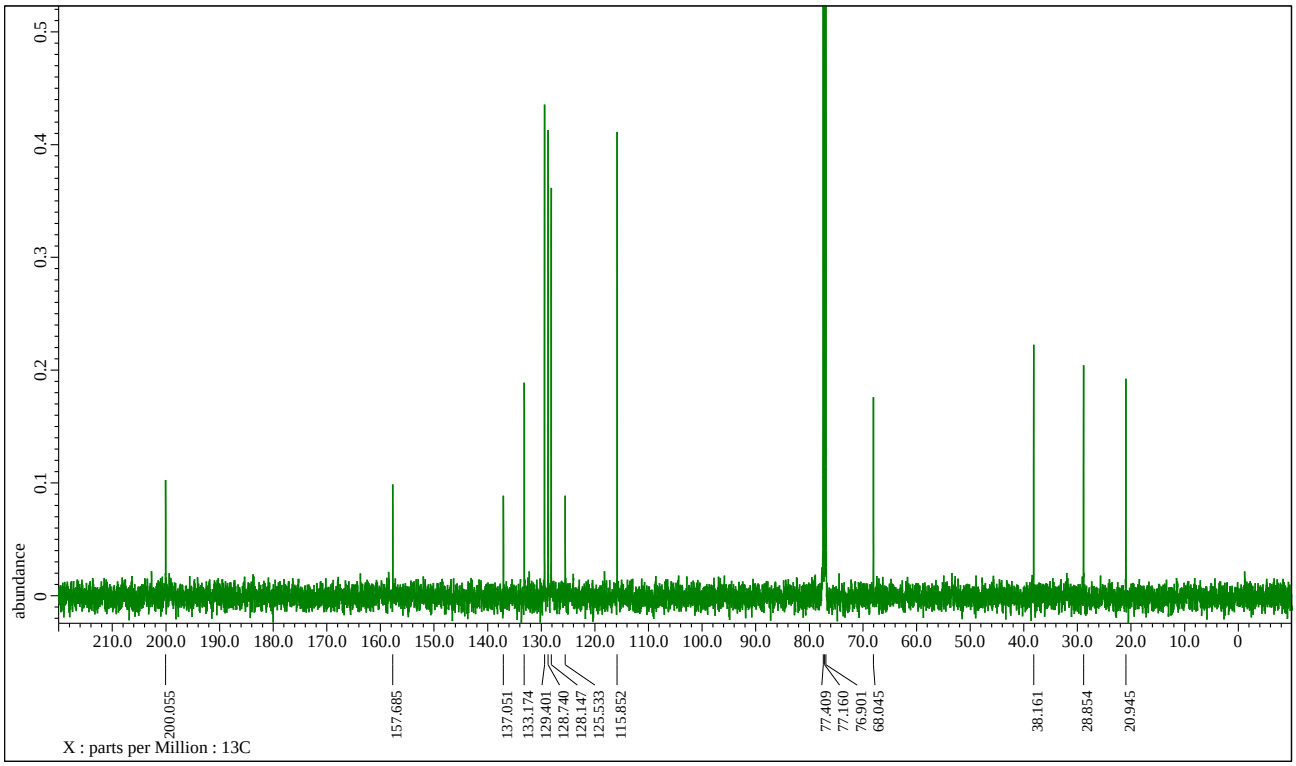
^{13}C NMR spectrum of **3c** (125 MHz, $CDCl_3$)



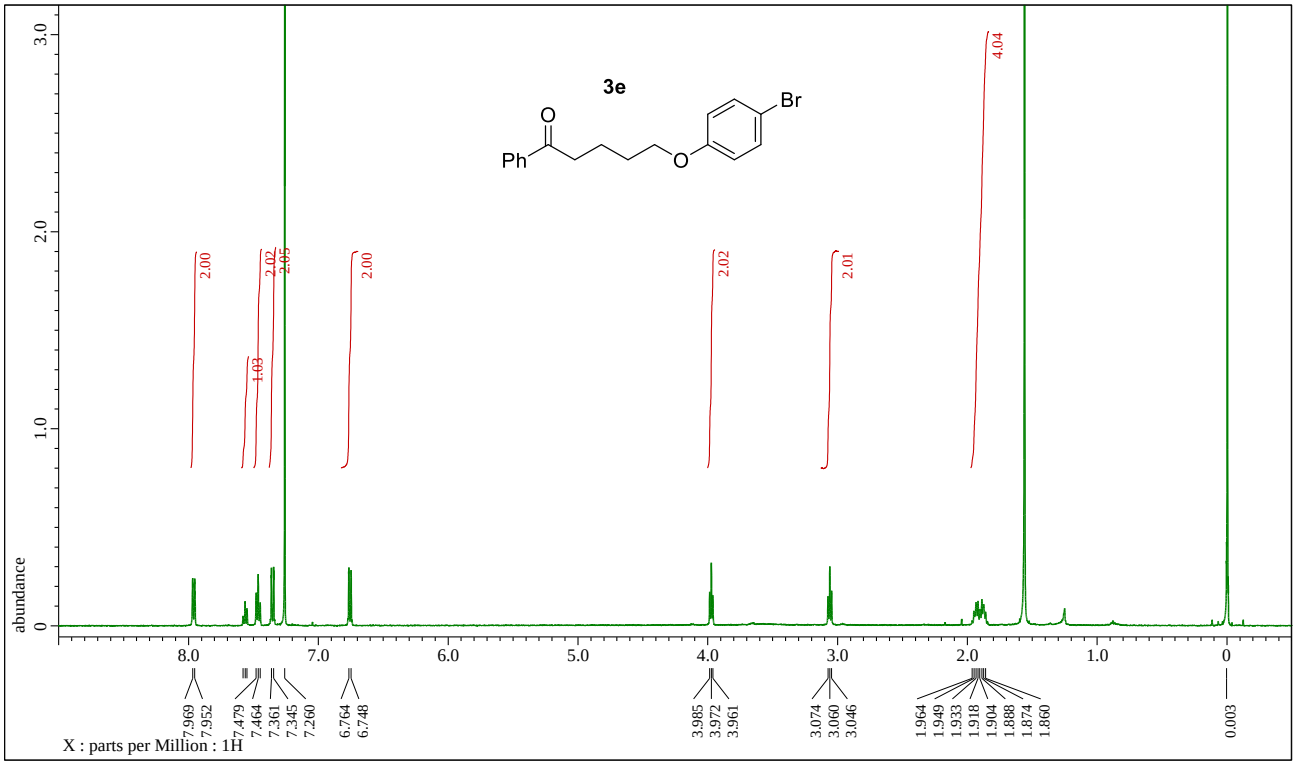
^{1}H NMR spectrum of **3d** (500 MHz, $CDCl_3$)



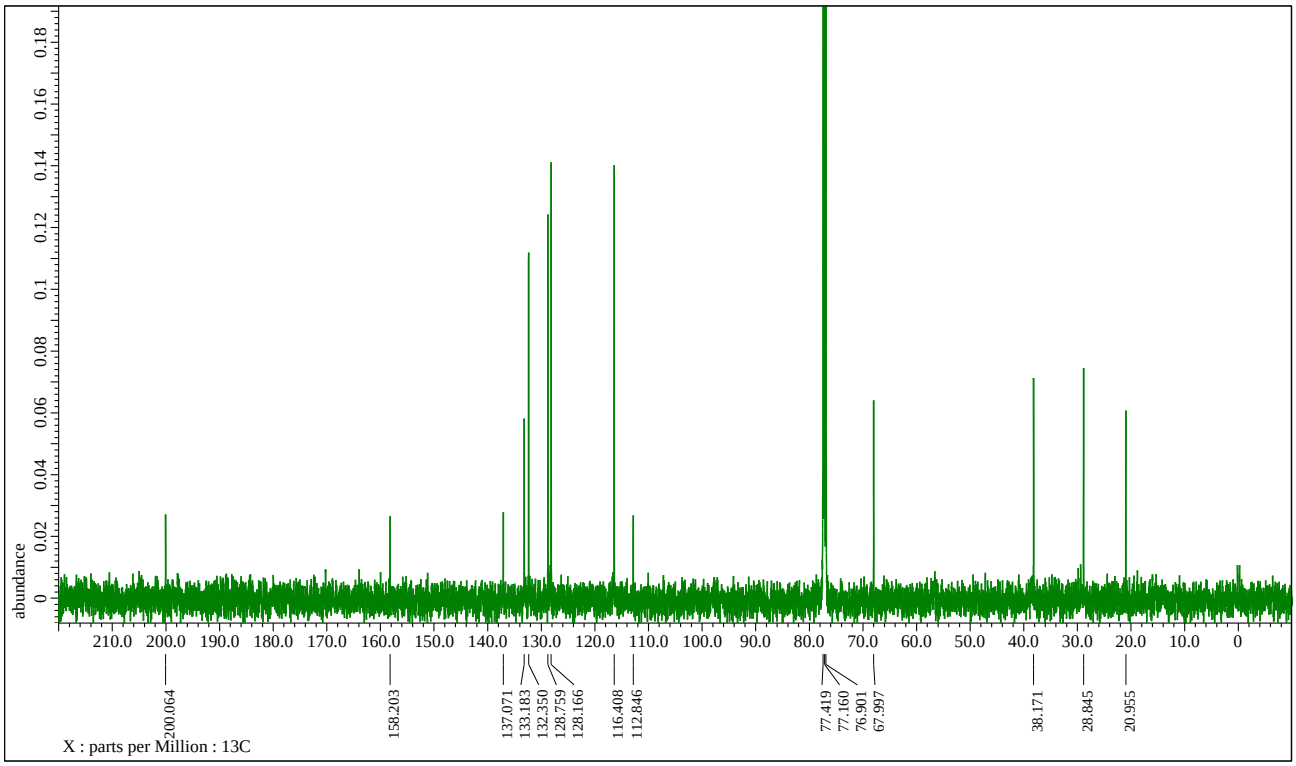
^{13}C NMR spectrum of **3d** (125 MHz, $CDCl_3$)



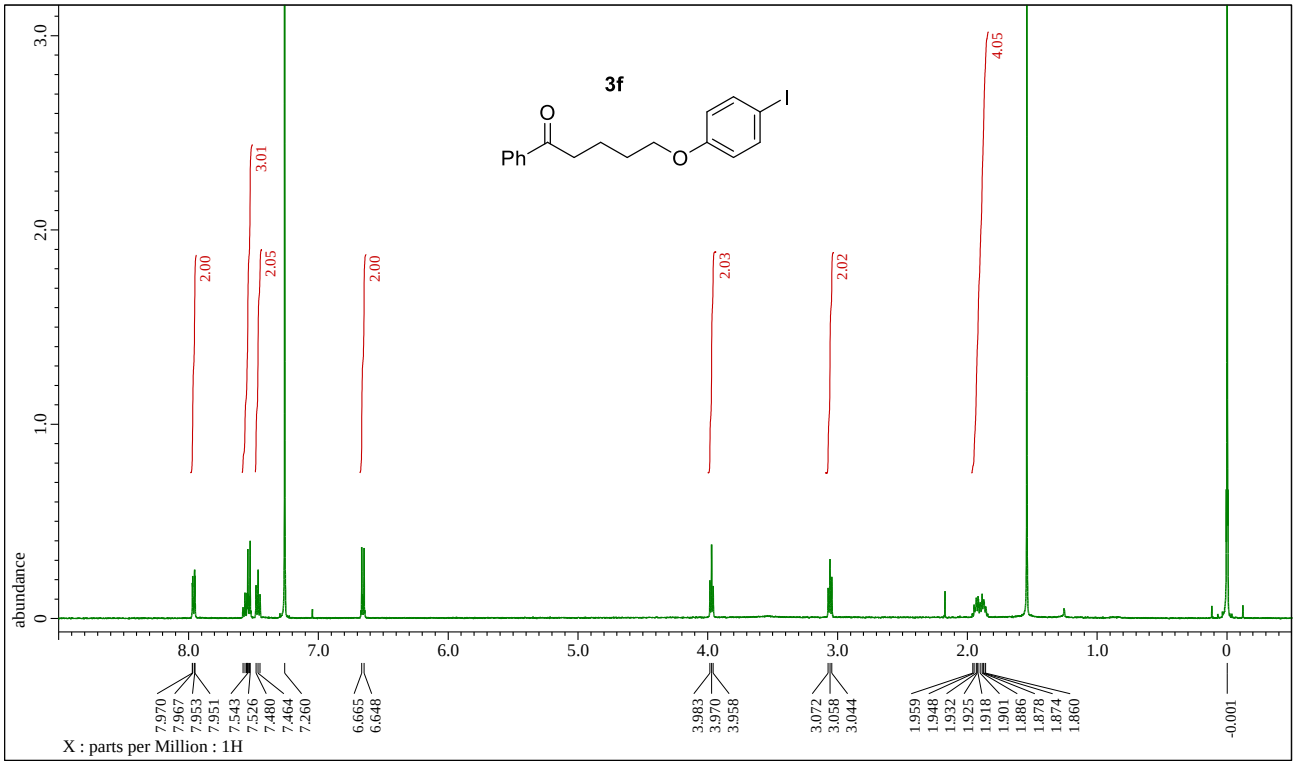
^{1}H NMR spectrum of **3e** (500 MHz, $CDCl_3$)



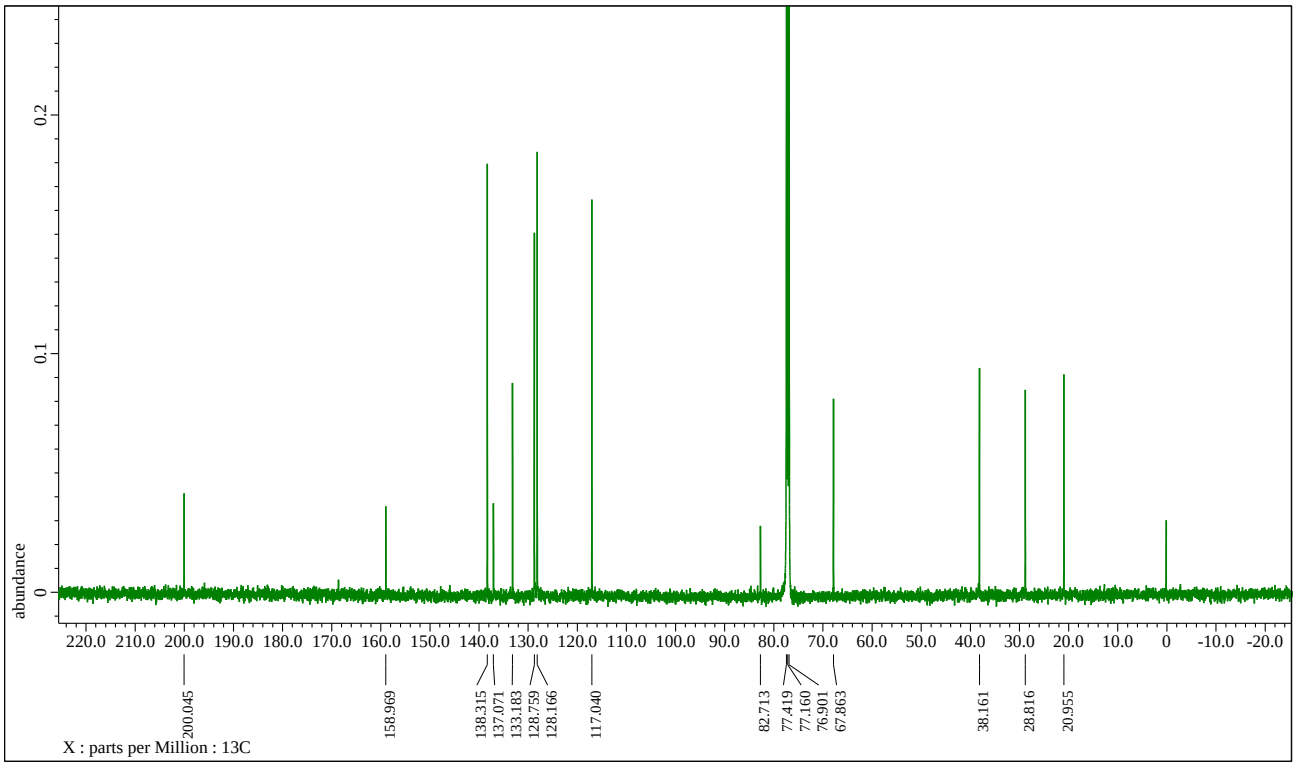
^{13}C NMR spectrum of **3e** (125 MHz, $CDCl_3$)



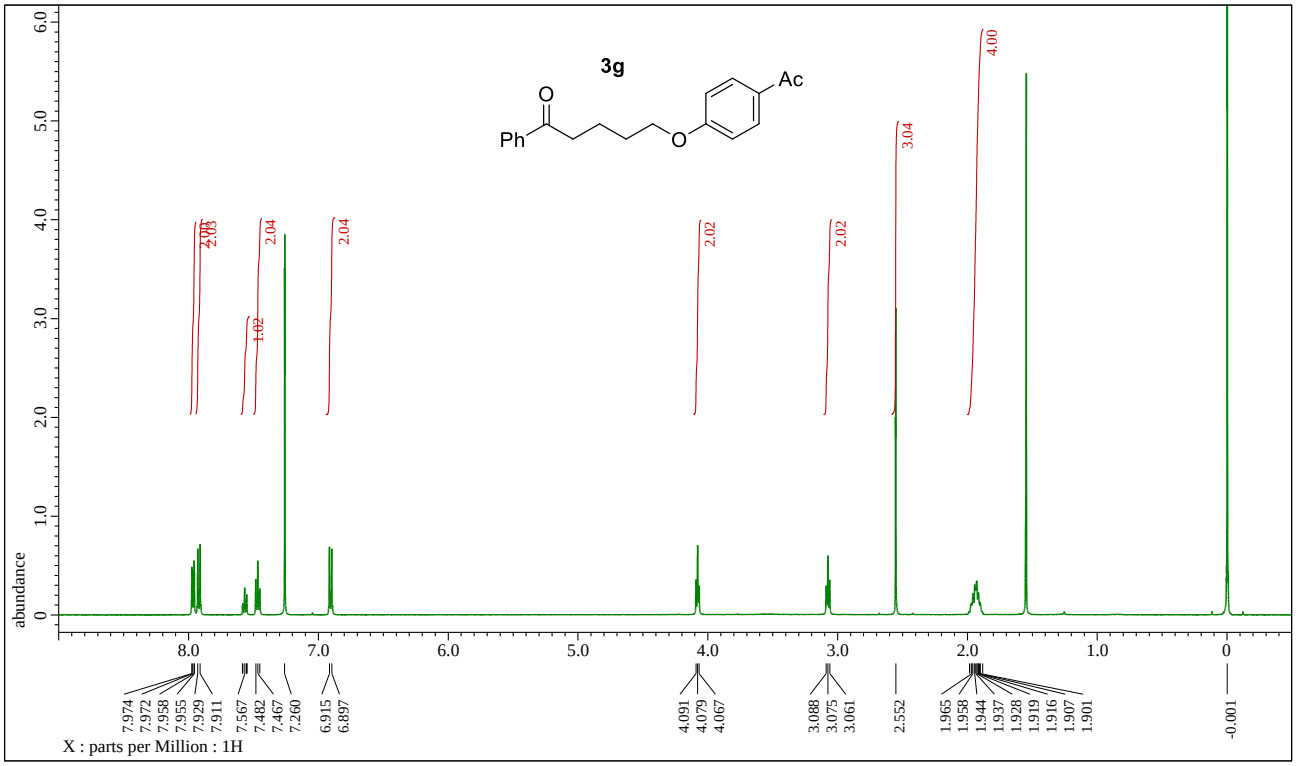
^{1}H NMR spectrum of **3f** (500 MHz, $CDCl_3$)



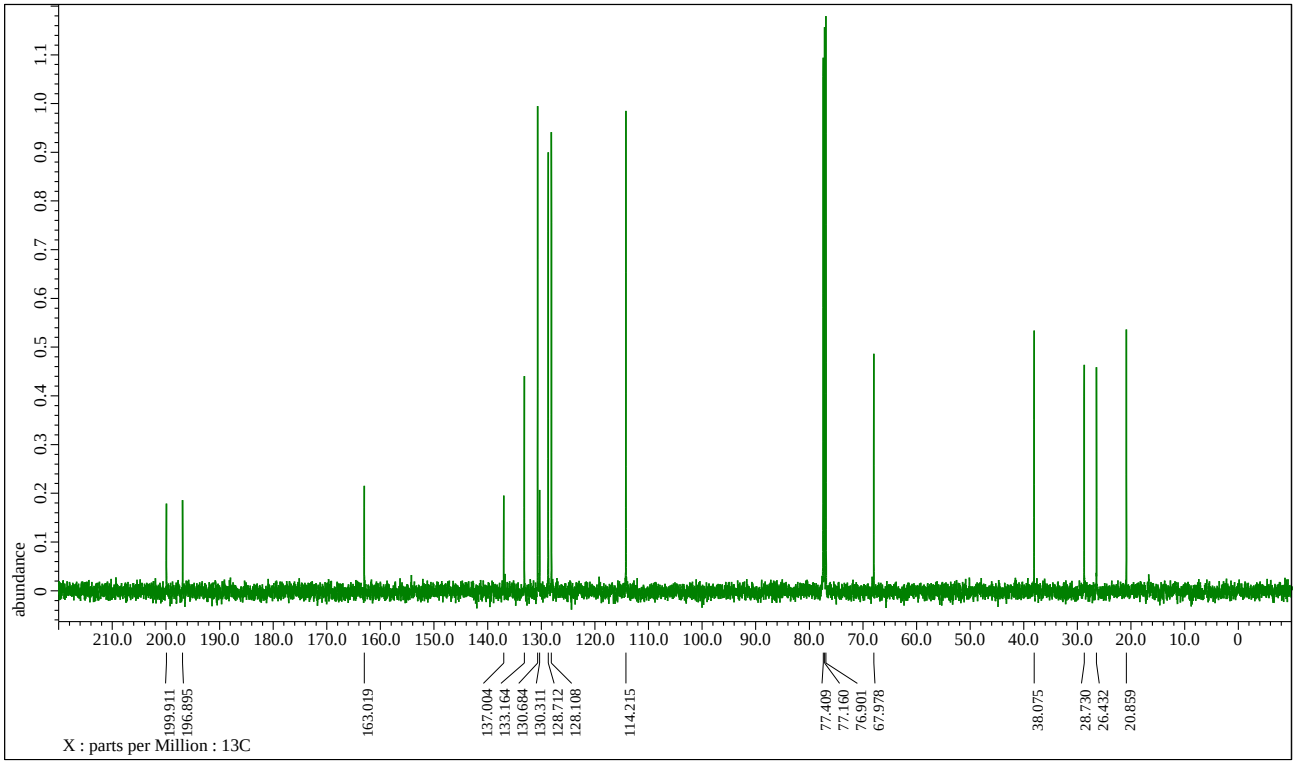
^{13}C NMR spectrum of **3f** (125 MHz, $CDCl_3$)



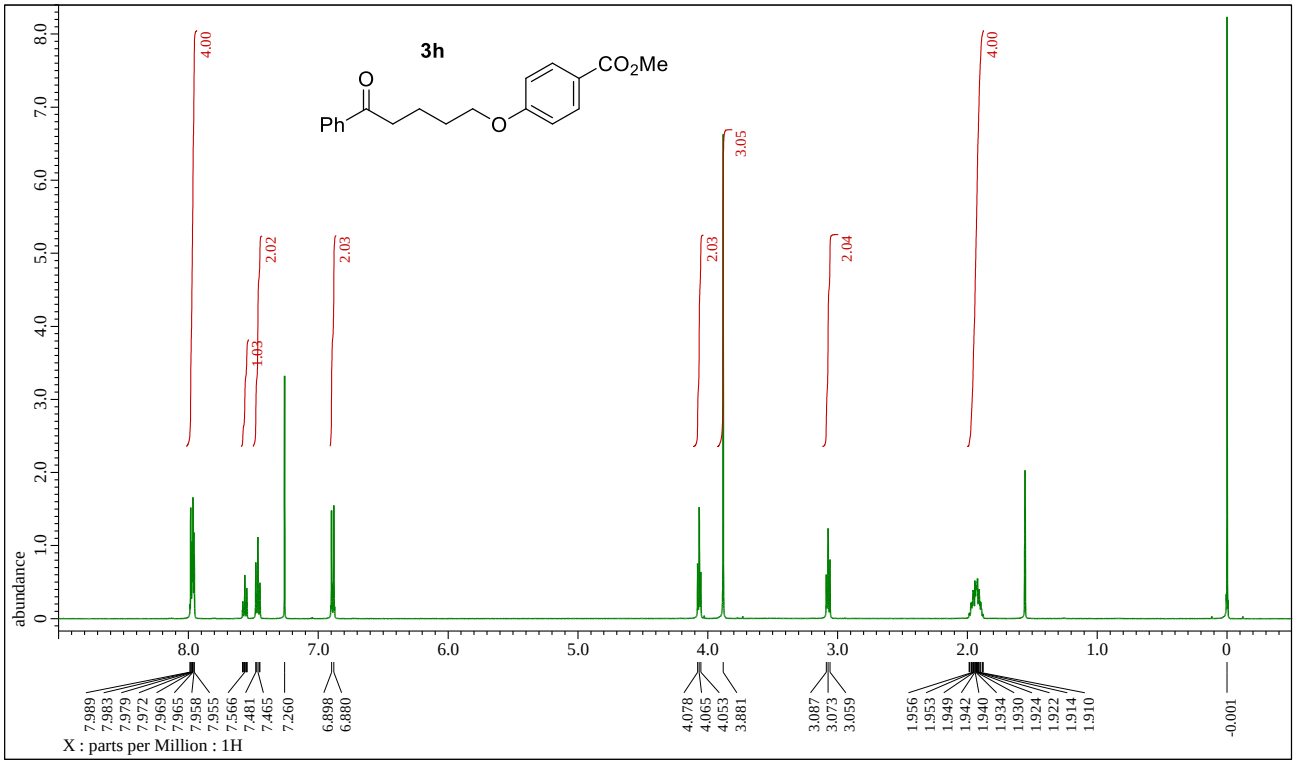
^{1}H NMR spectrum of **3g** (500 MHz, $CDCl_3$)



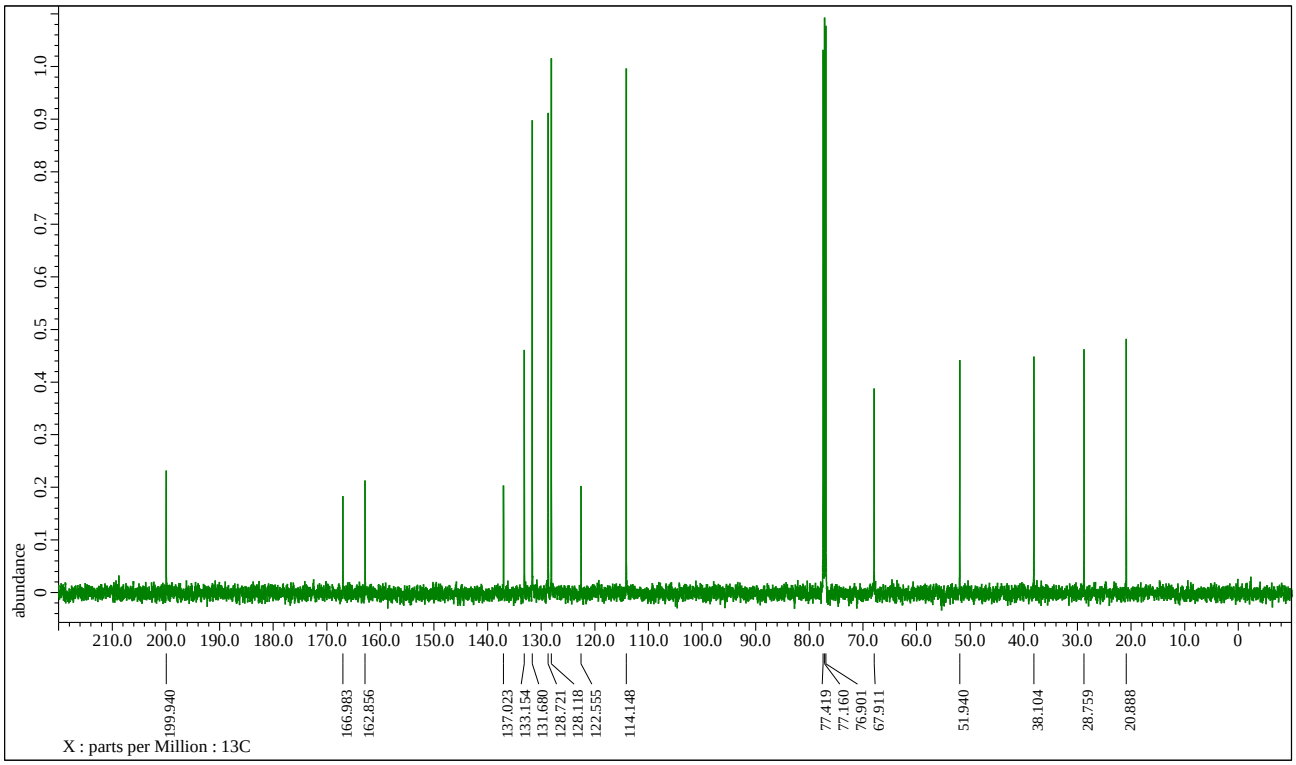
^{13}C NMR spectrum of **3g** (125 MHz, $CDCl_3$)



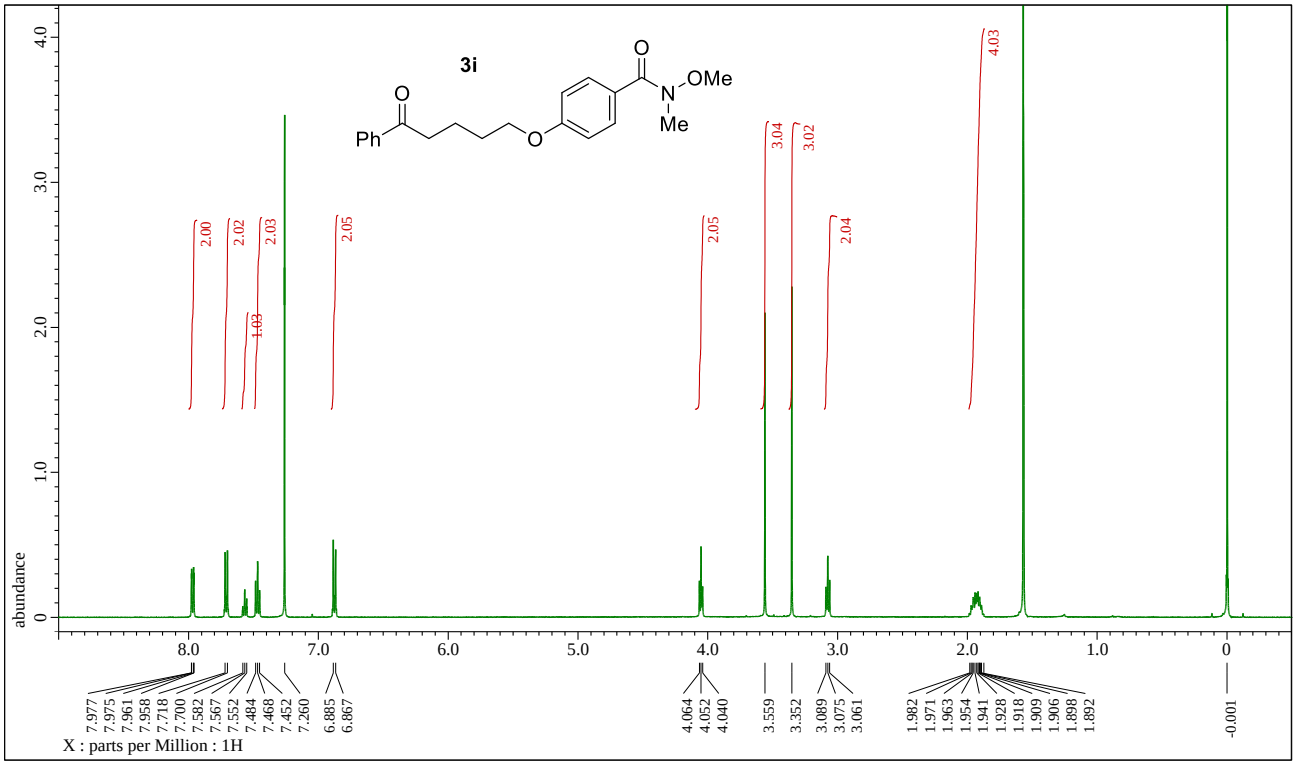
^{1}H NMR spectrum of **3h** (500 MHz, $CDCl_3$)



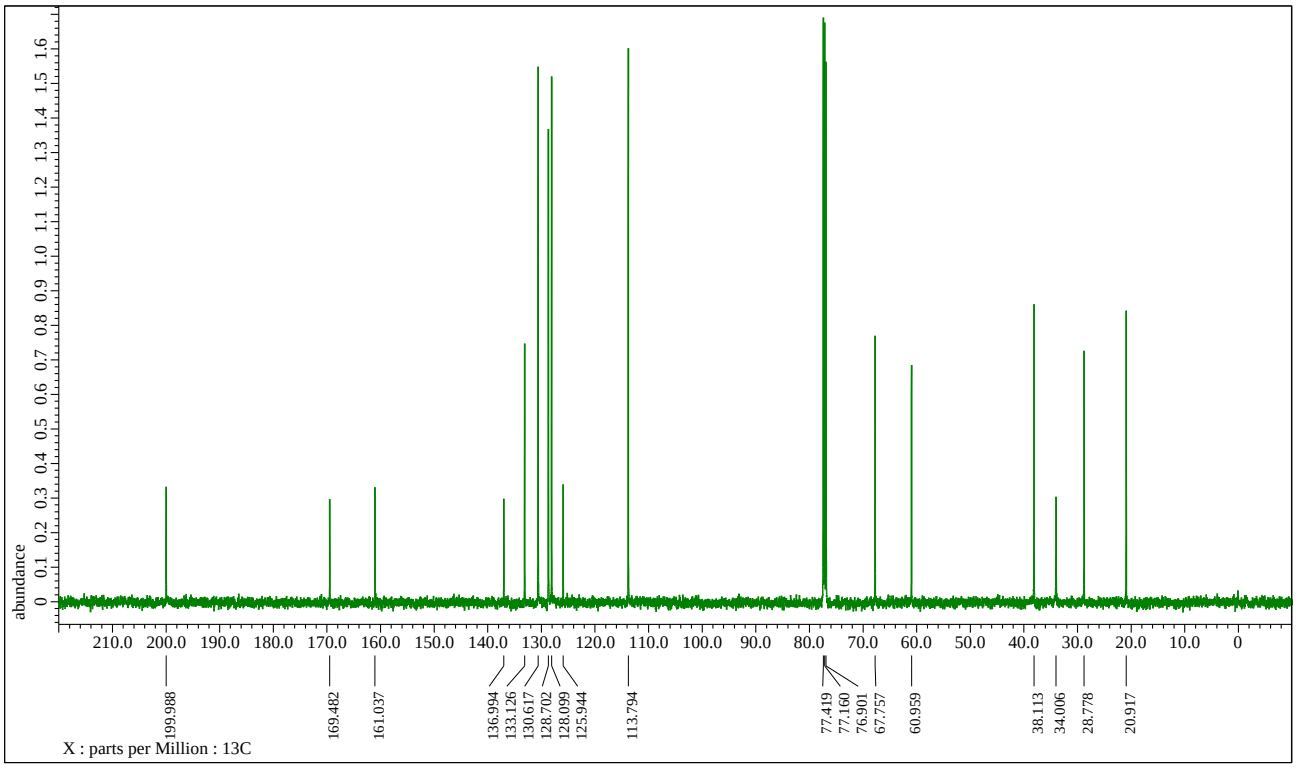
^{13}C NMR spectrum of **3h** (125 MHz, $CDCl_3$)



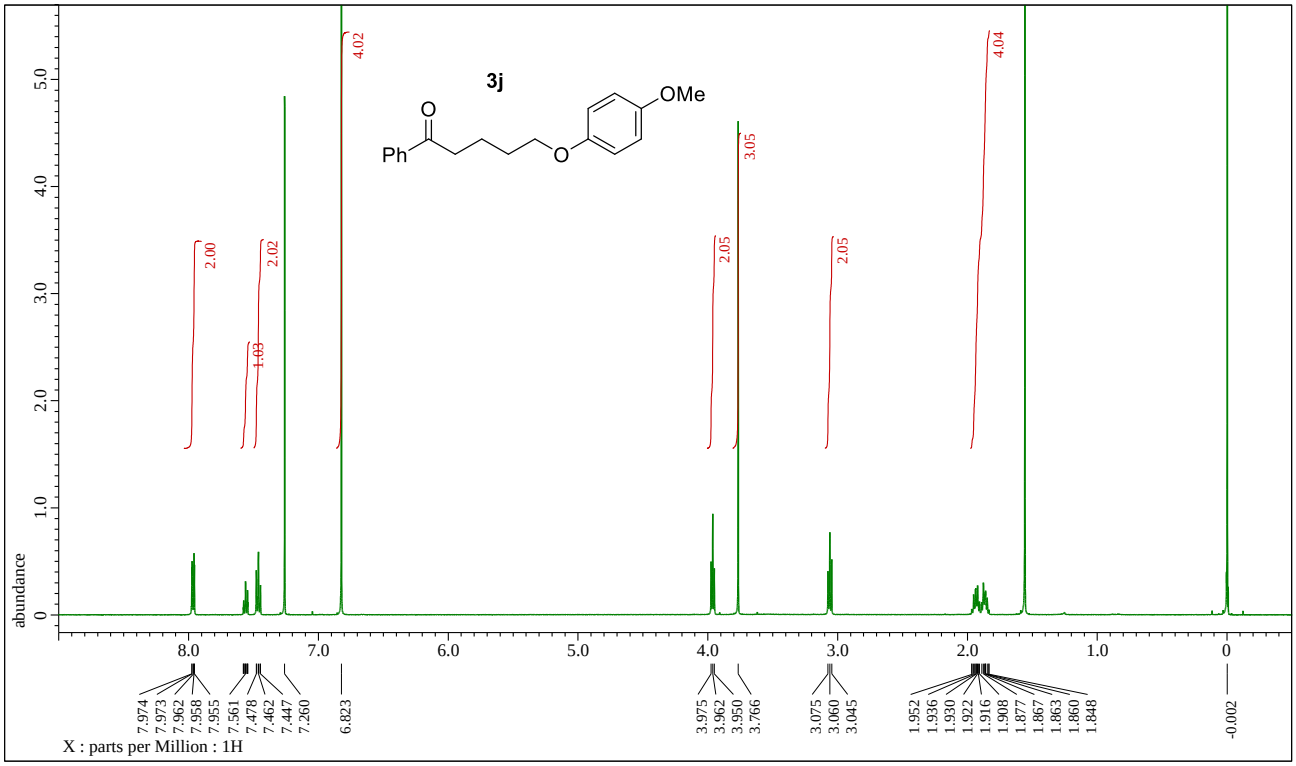
^{1}H NMR spectrum of **3i** (500 MHz, $CDCl_3$)



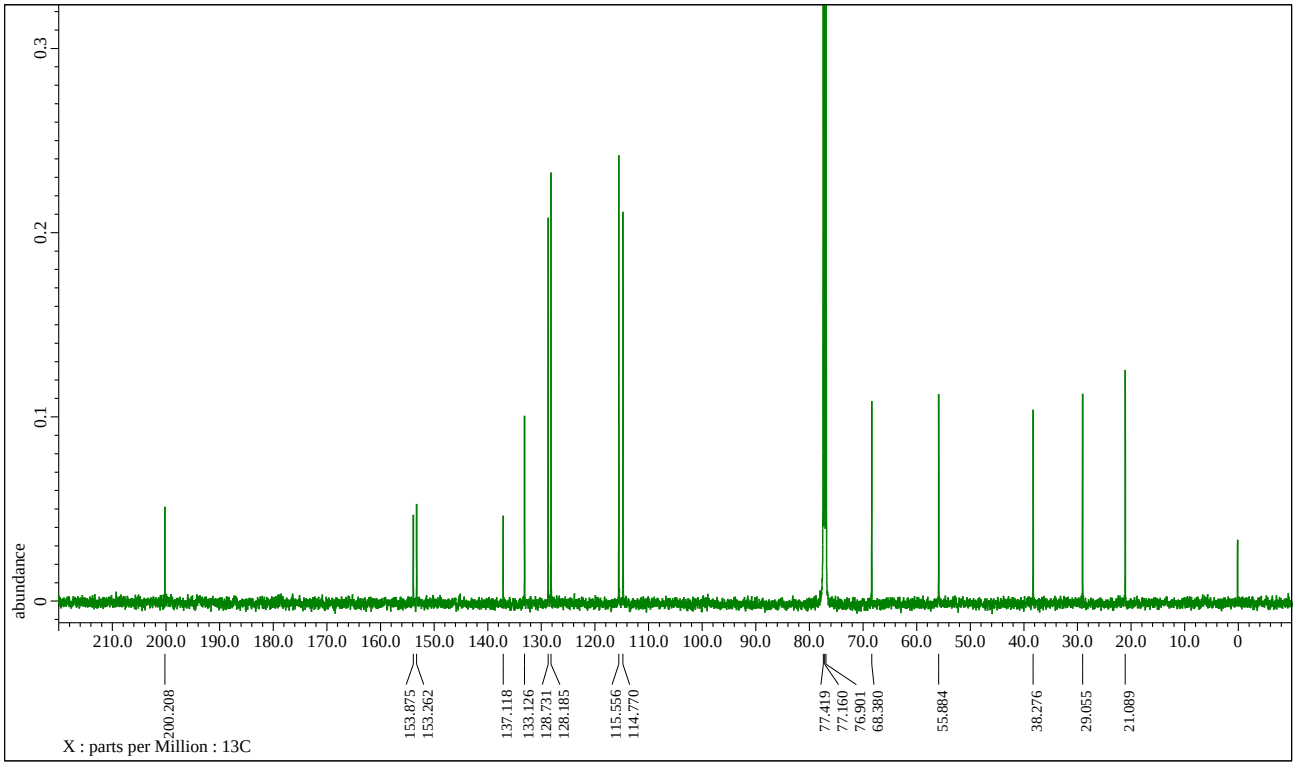
^{13}C NMR spectrum of **3i** (125 MHz, $CDCl_3$)



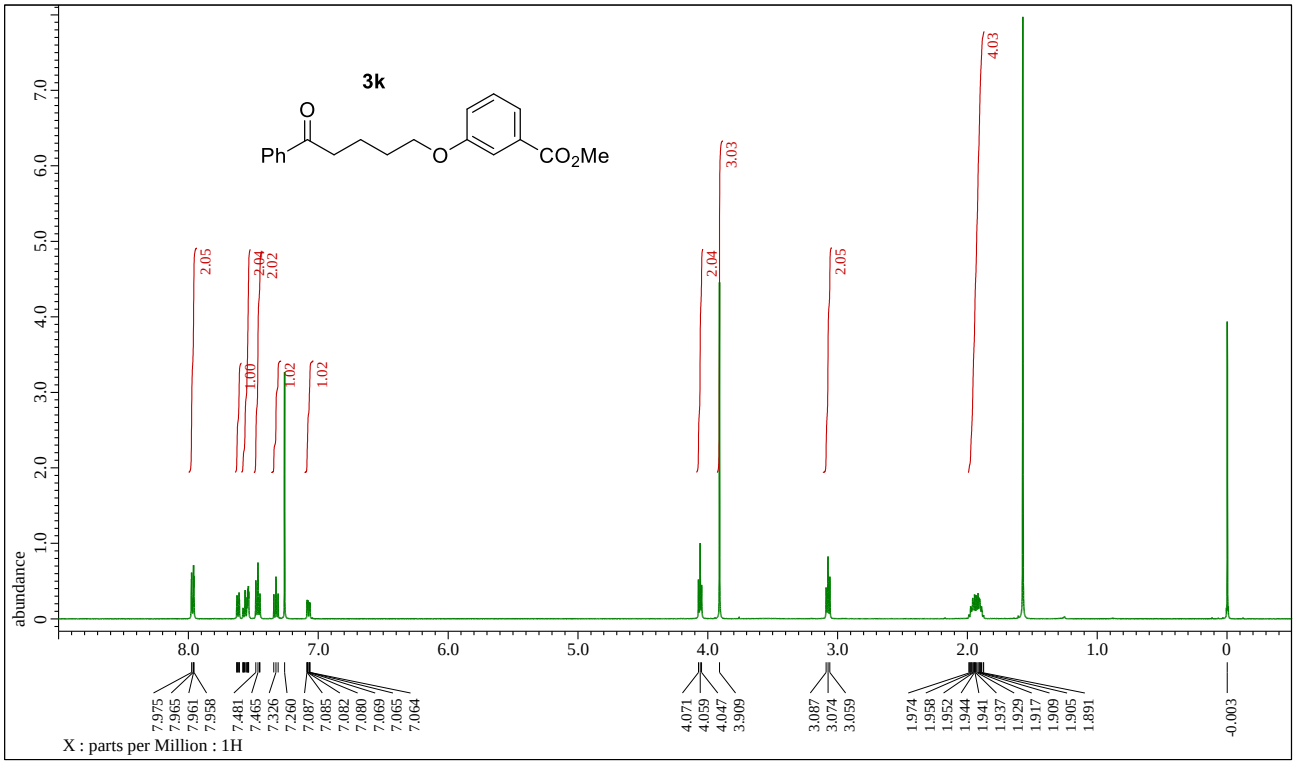
^{1}H NMR spectrum of **3j** (500 MHz, $CDCl_3$)



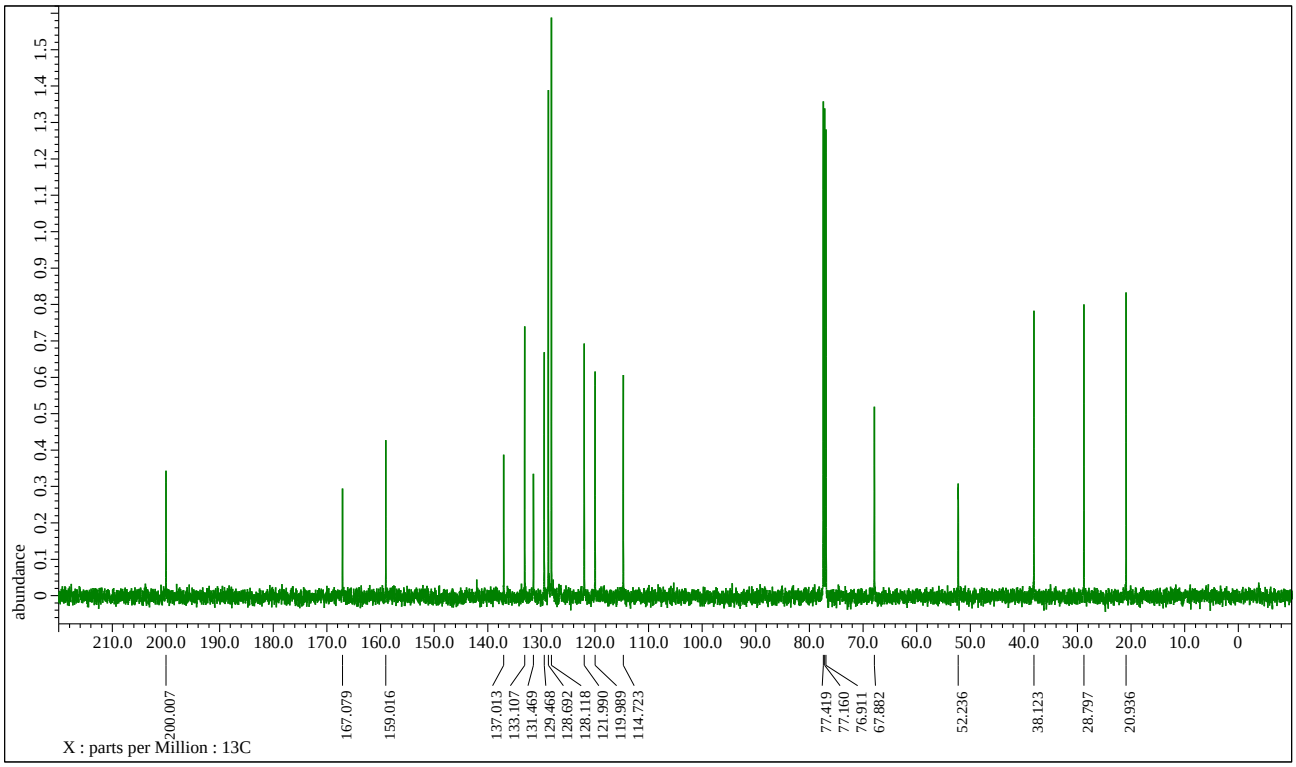
^{13}C NMR spectrum of **3j** (125 MHz, $CDCl_3$)



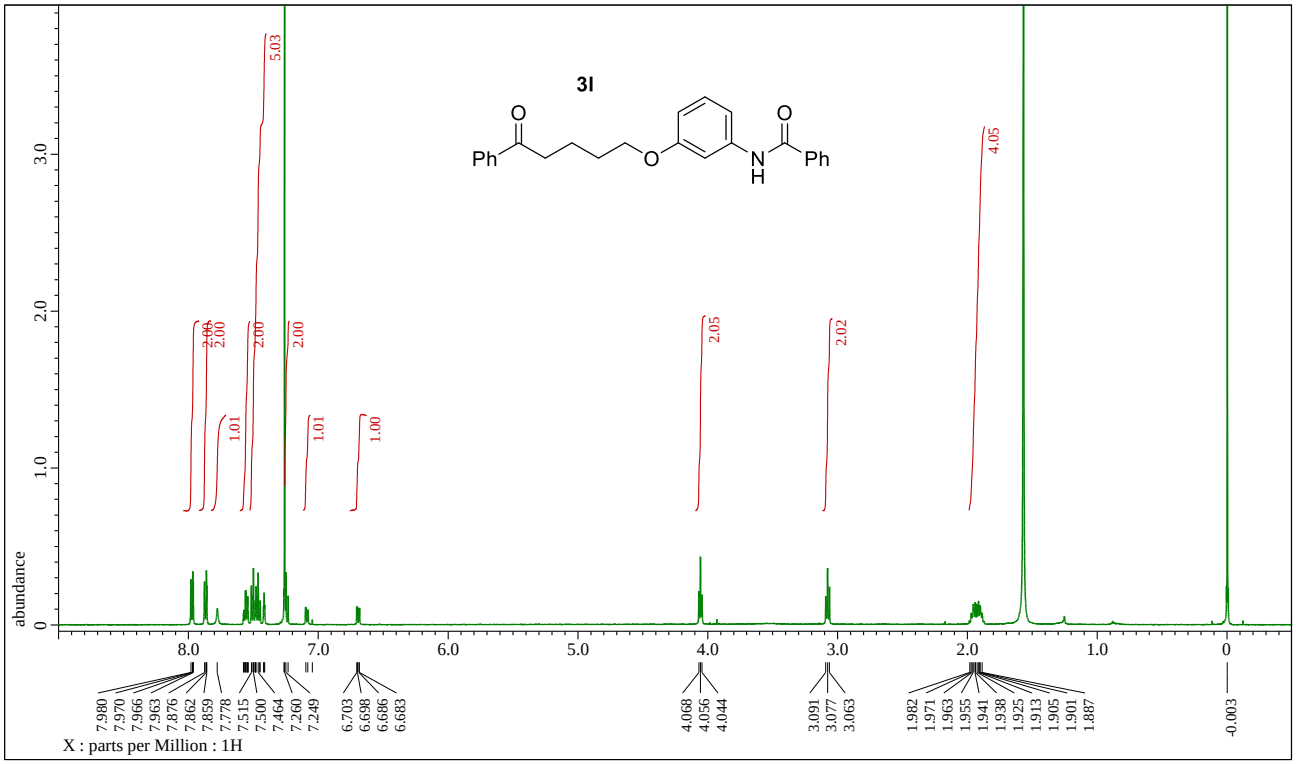
^{1}H NMR spectrum of **3k** (500 MHz, CDCl3)



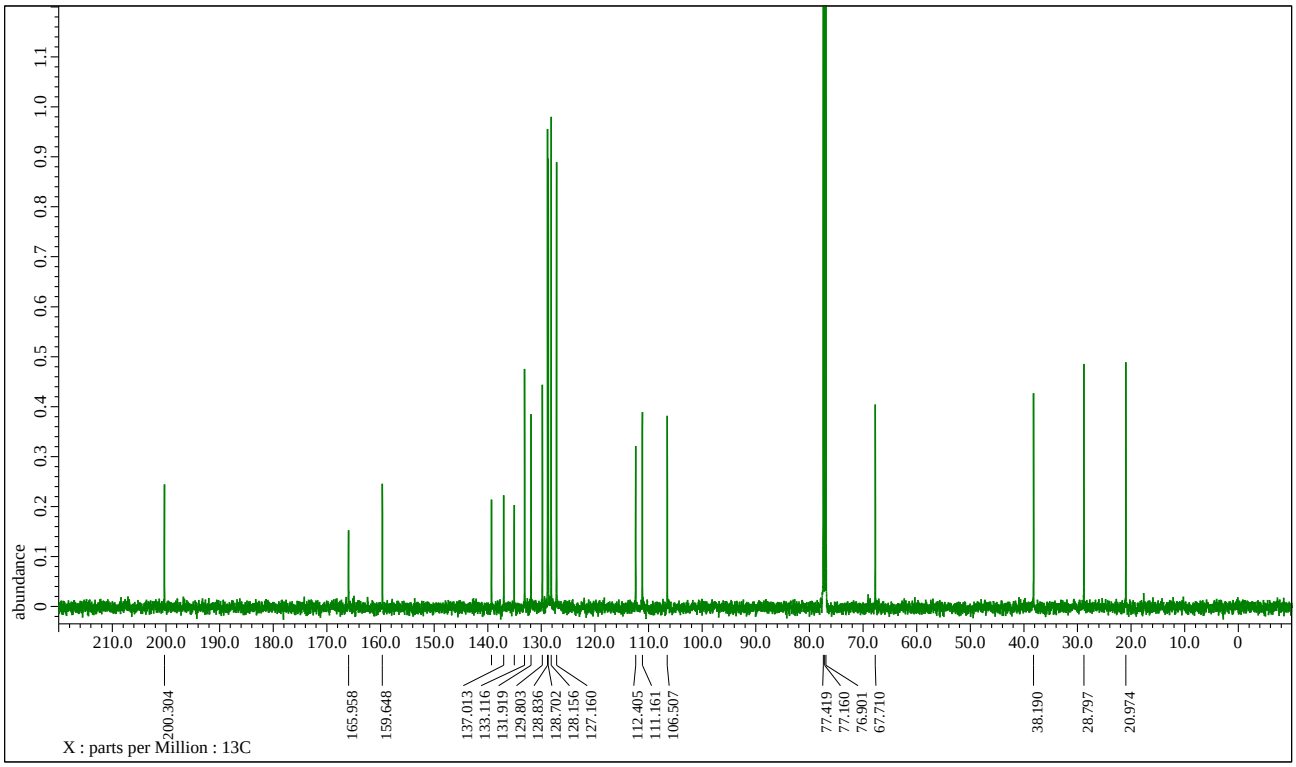
^{13}C NMR spectrum of **3k** (125 MHz, $CDCl_3$)



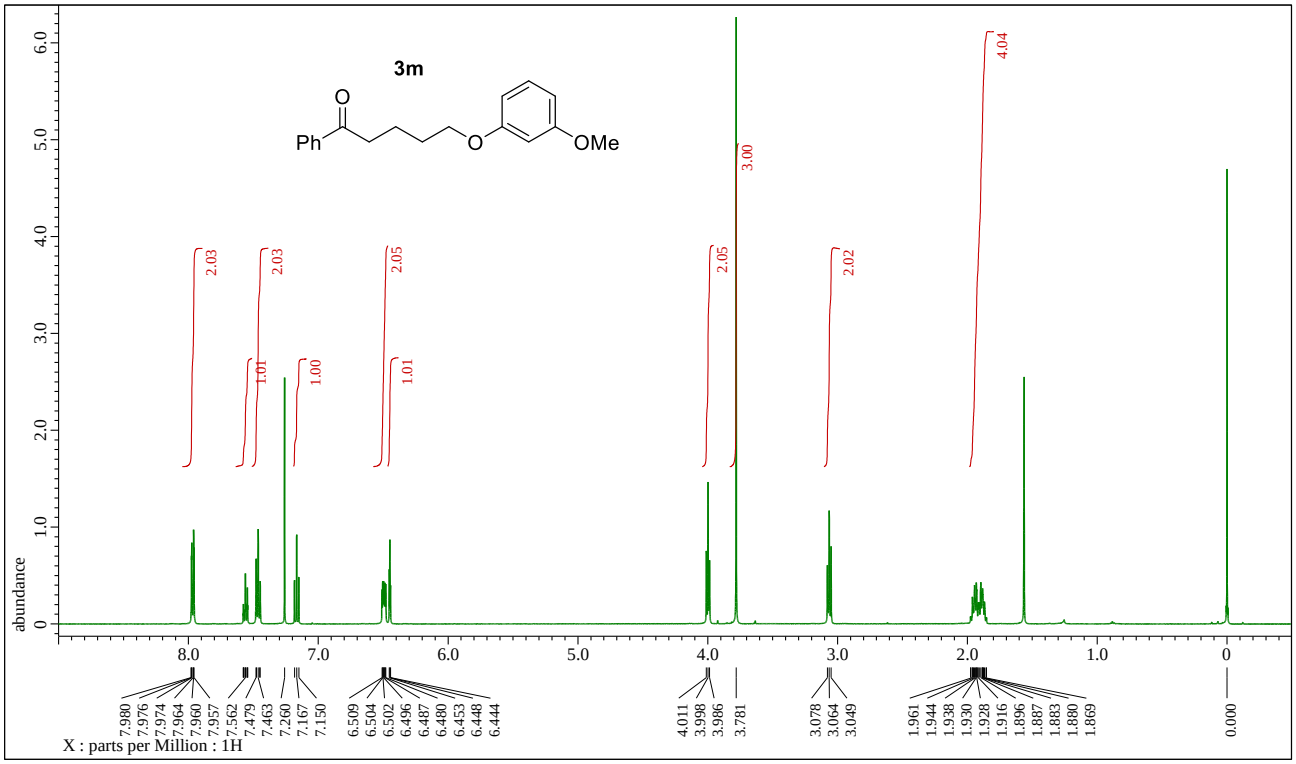
^{1}H NMR spectrum of **3l** (500 MHz, $CDCl_3$)



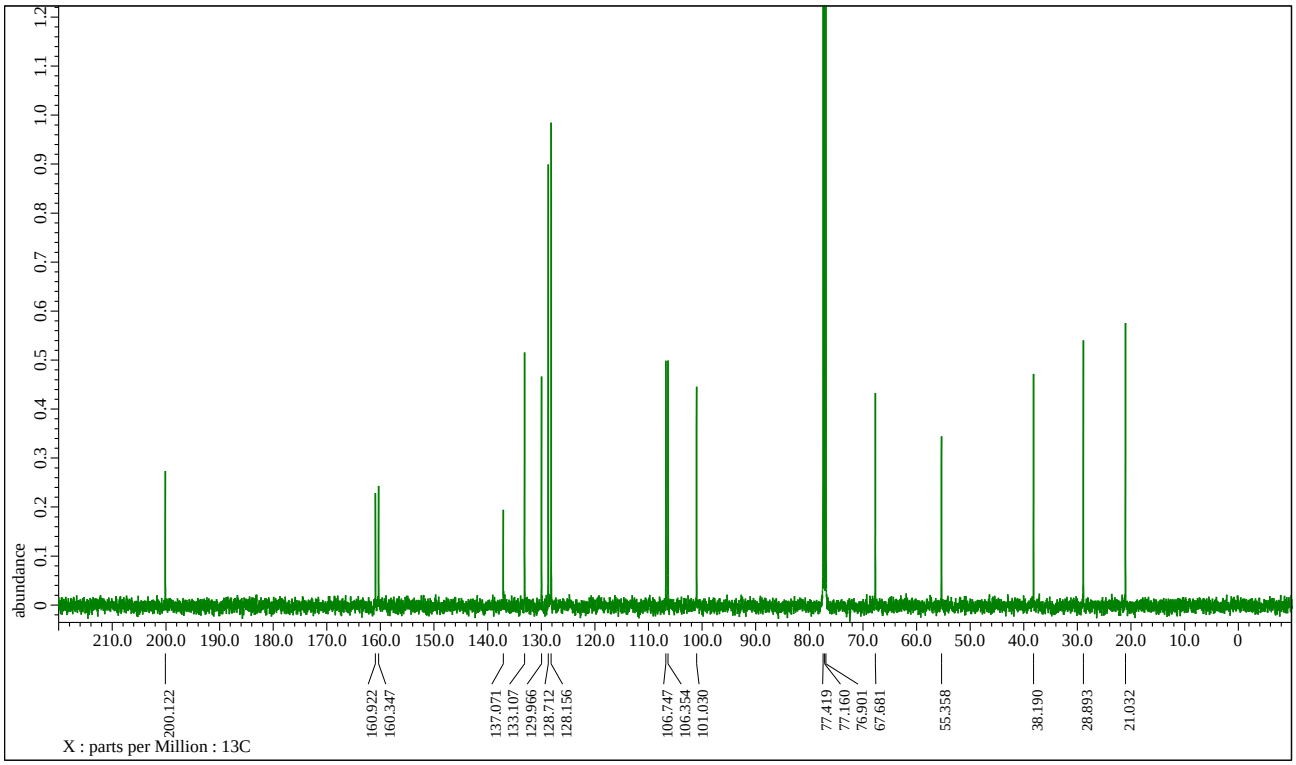
^{13}C NMR spectrum of **3l** (125 MHz, $CDCl_3$)



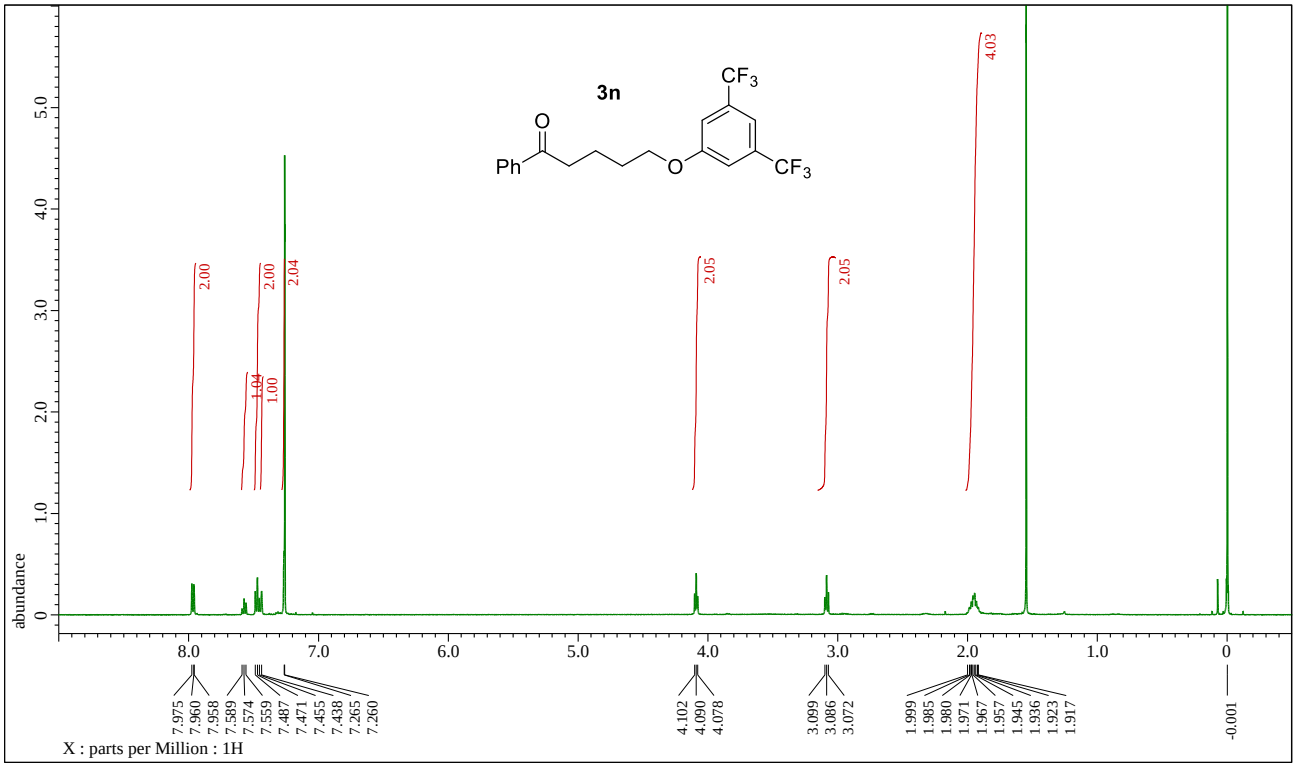
^{1}H NMR spectrum of **3m** (500 MHz, $CDCl_3$)



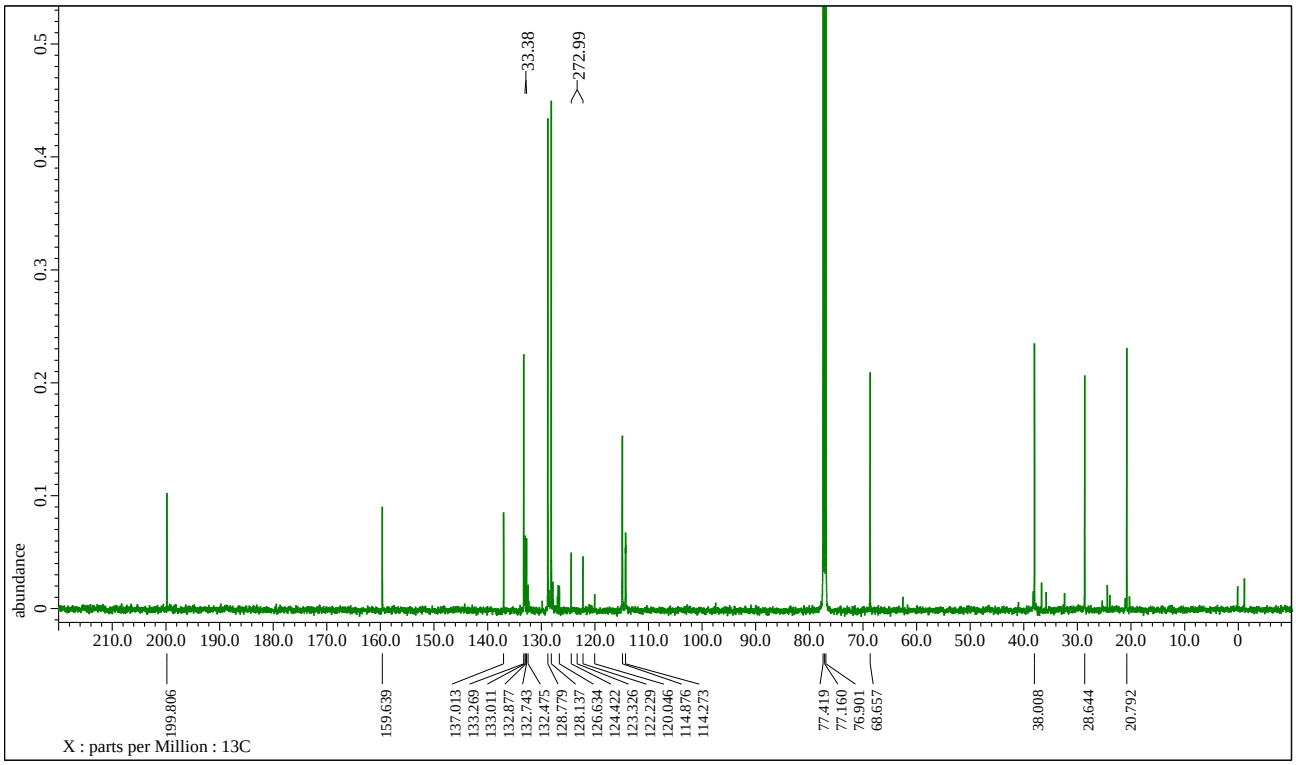
^{13}C NMR spectrum of **3m** (125 MHz, $CDCl_3$)



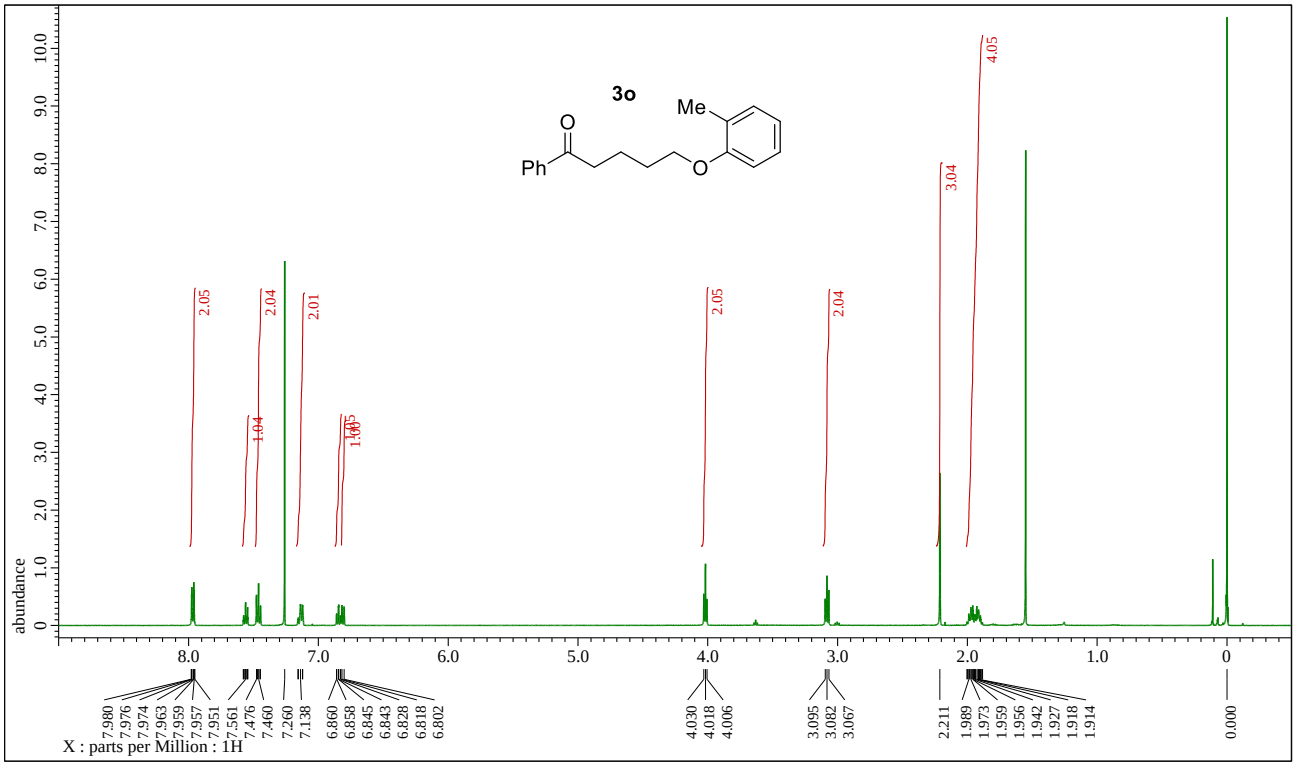
^{1}H NMR spectrum of **3n** (500 MHz, $CDCl_3$)



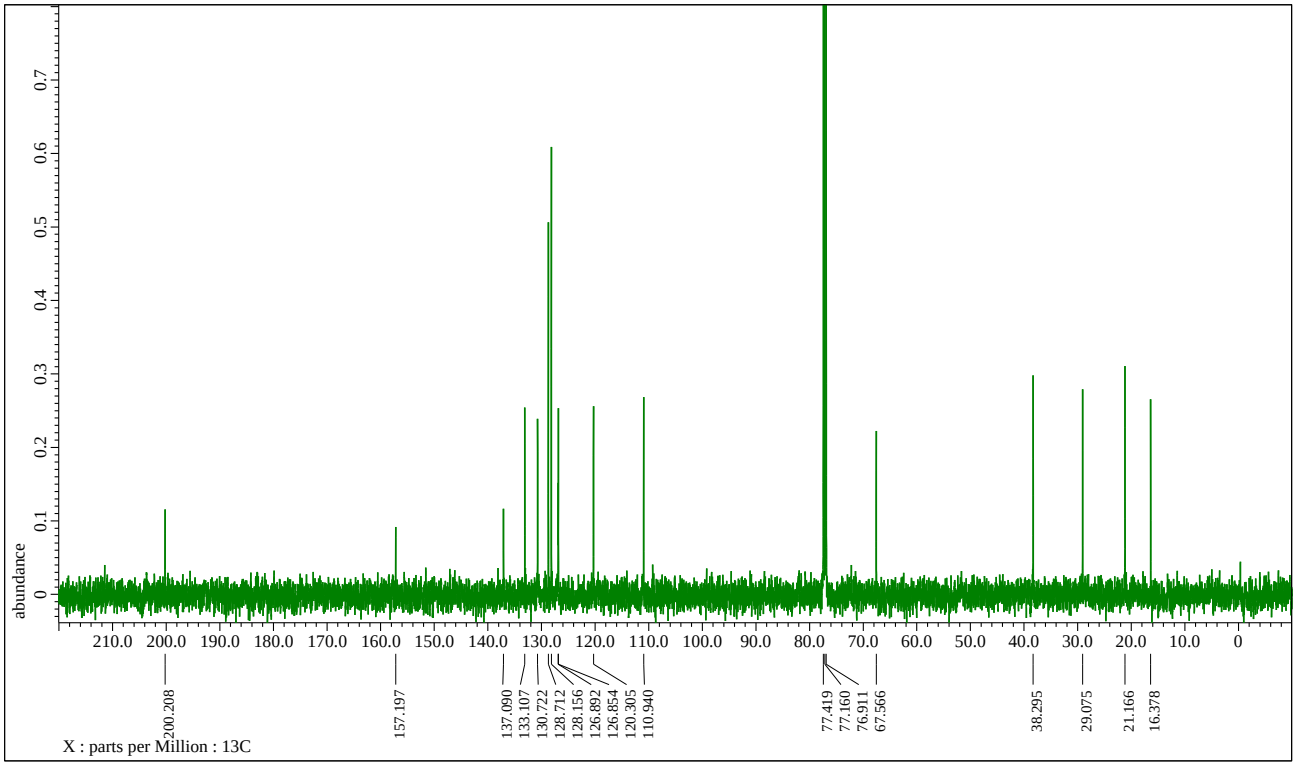
^{13}C NMR spectrum of **3n** (125 MHz, $CDCl_3$)



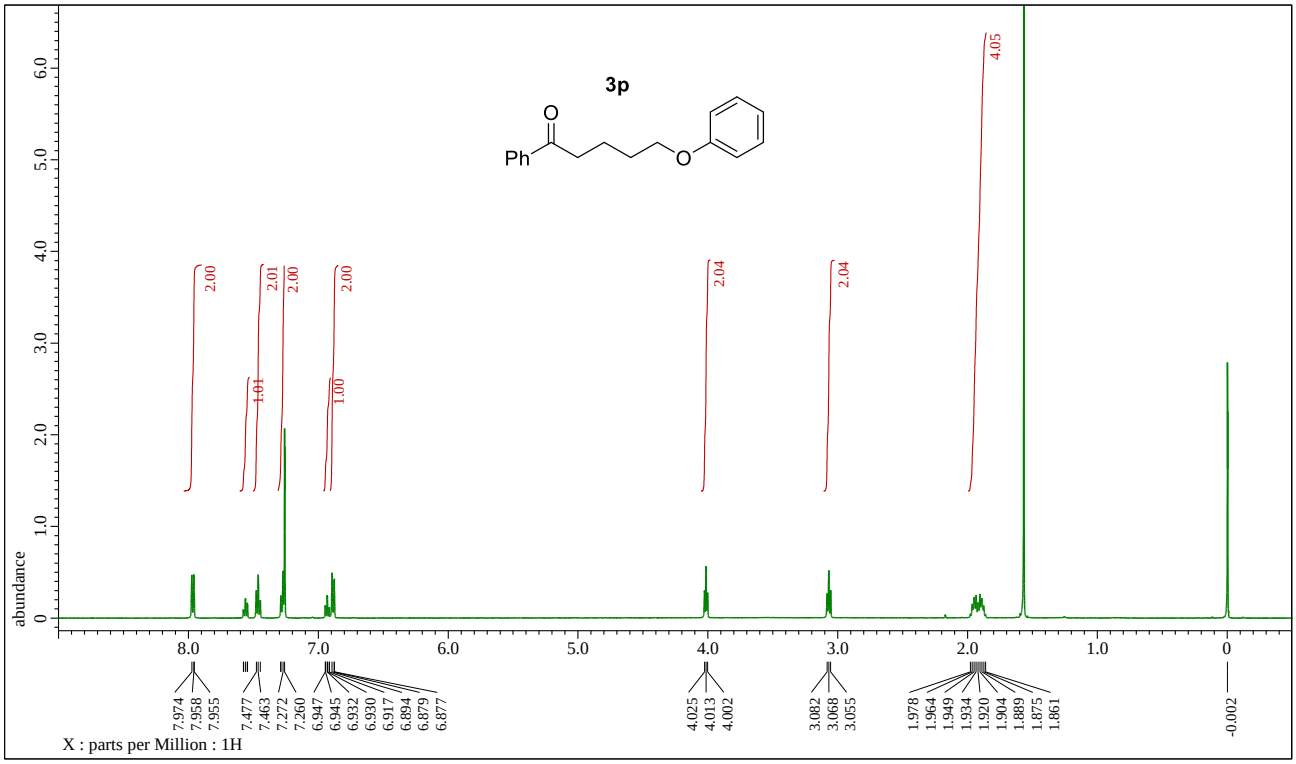
^{1}H NMR spectrum of **3o** (500 MHz, $CDCl_3$)



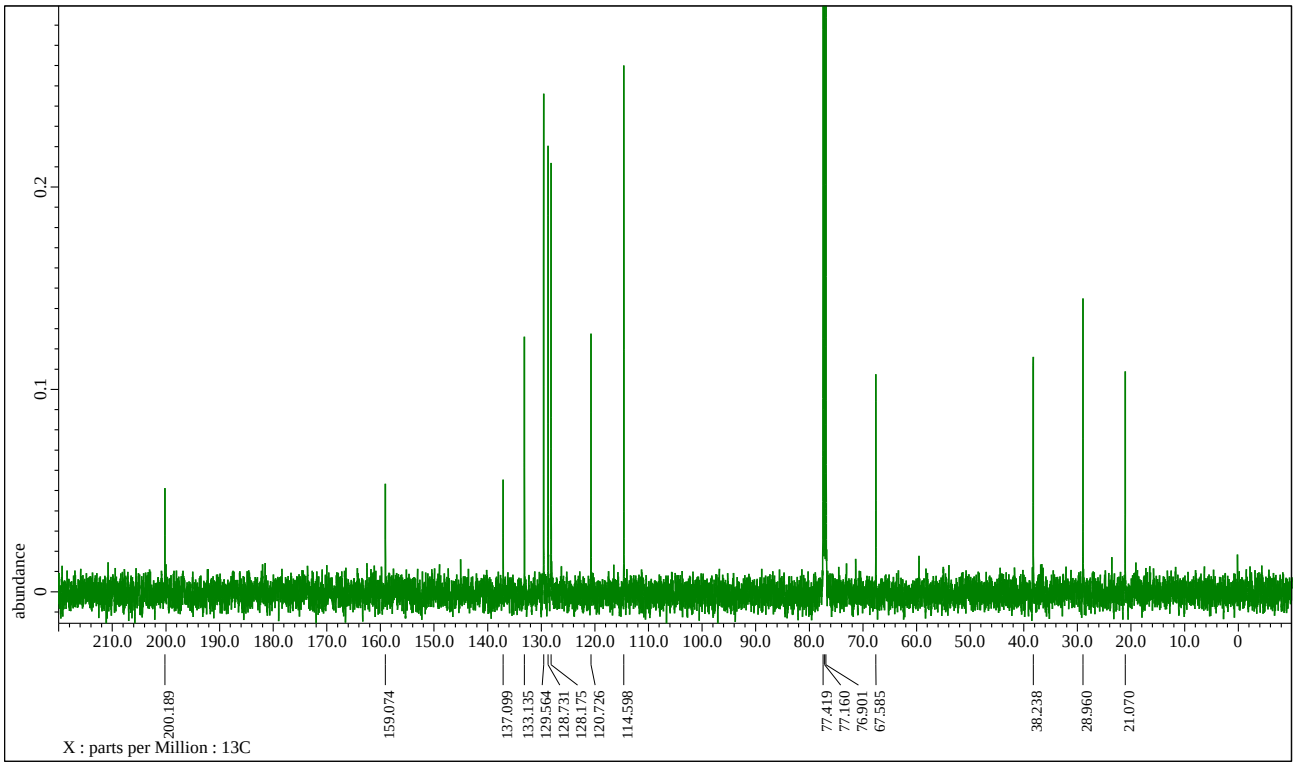
^{13}C NMR spectrum of **3o** (125 MHz, $CDCl_3$)



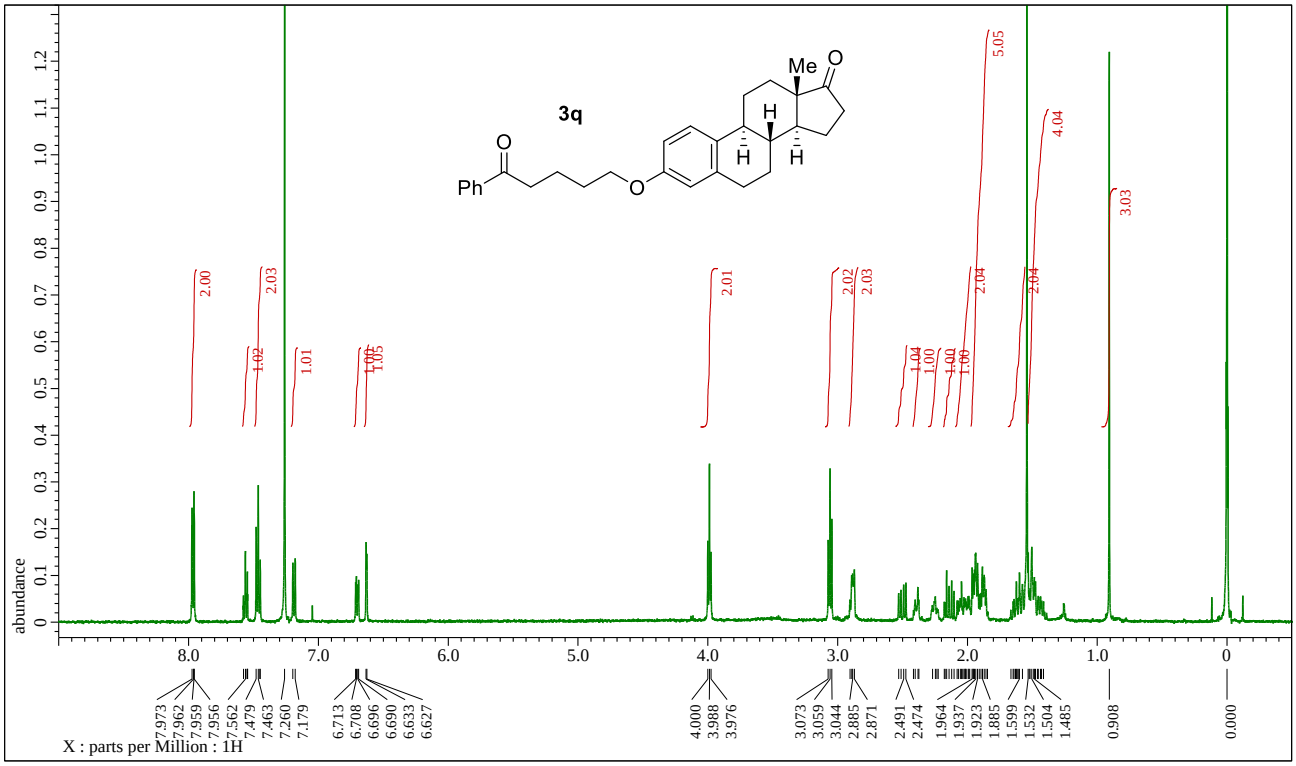
^{1}H NMR spectrum of **3p** (500 MHz, $CDCl_3$)



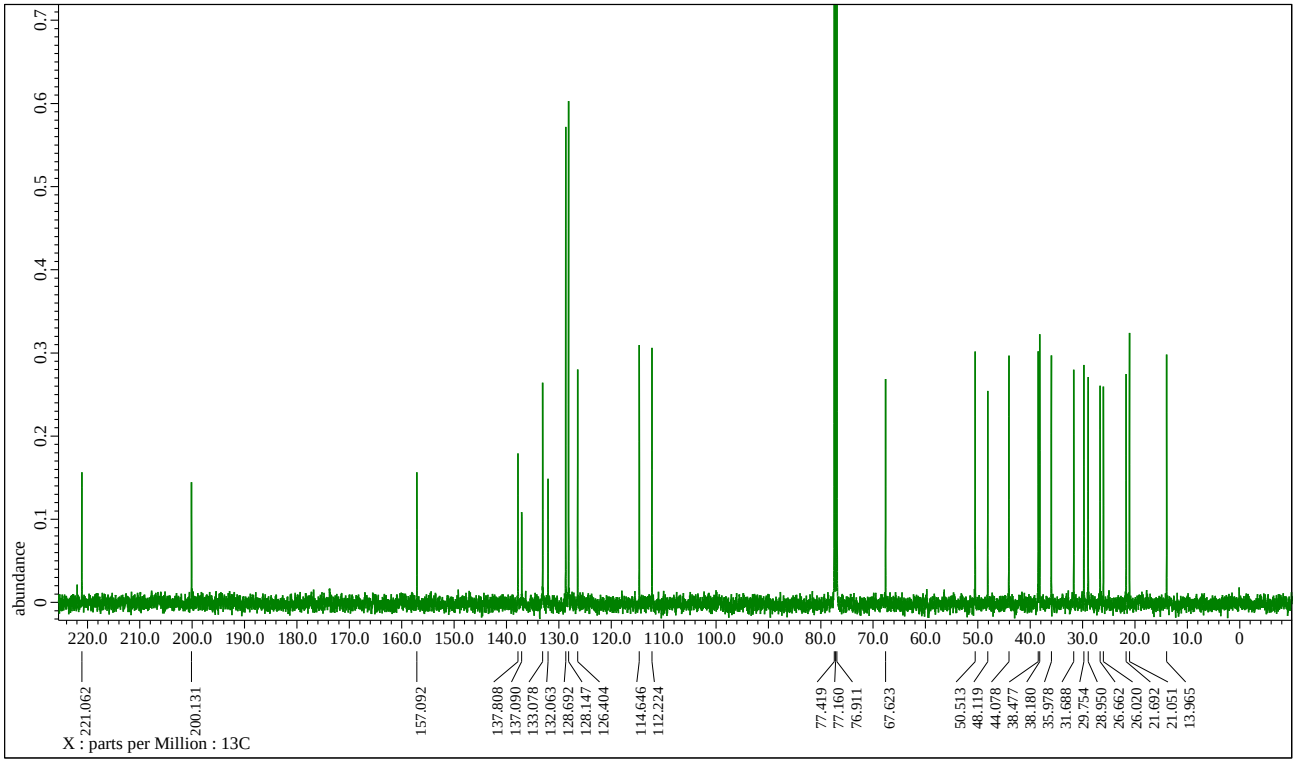
^{13}C NMR spectrum of **3p** (125 MHz, $CDCl_3$)



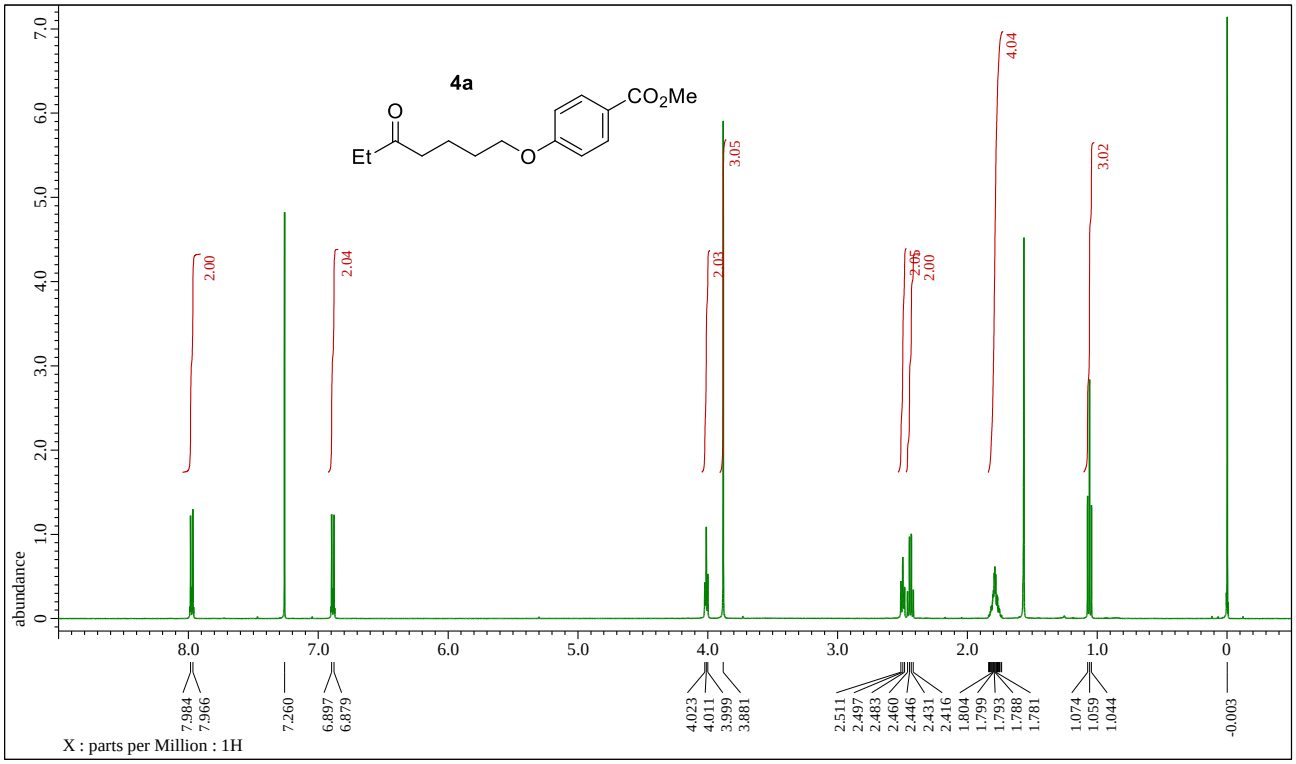
^{1}H NMR spectrum of **3q** (500 MHz, $CDCl_3$)



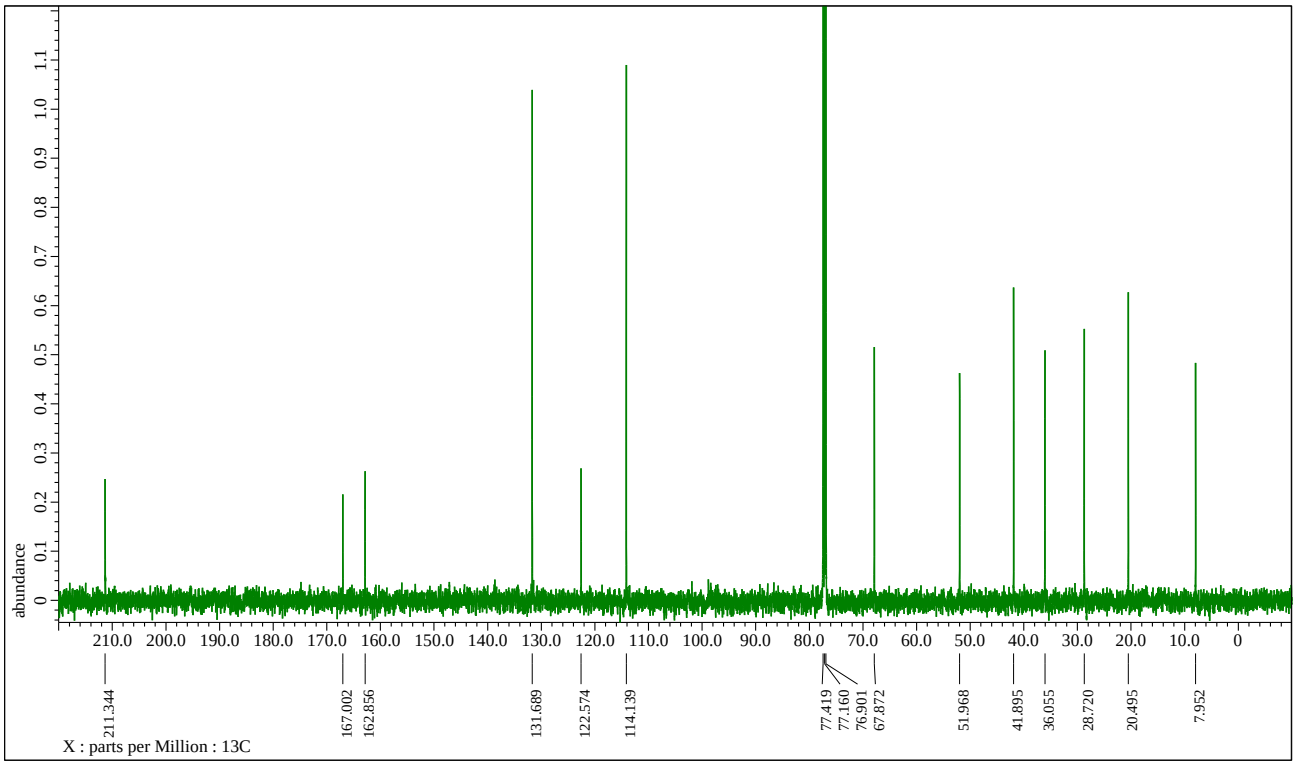
^{13}C NMR spectrum of **3q** (125 MHz, $CDCl_3$)



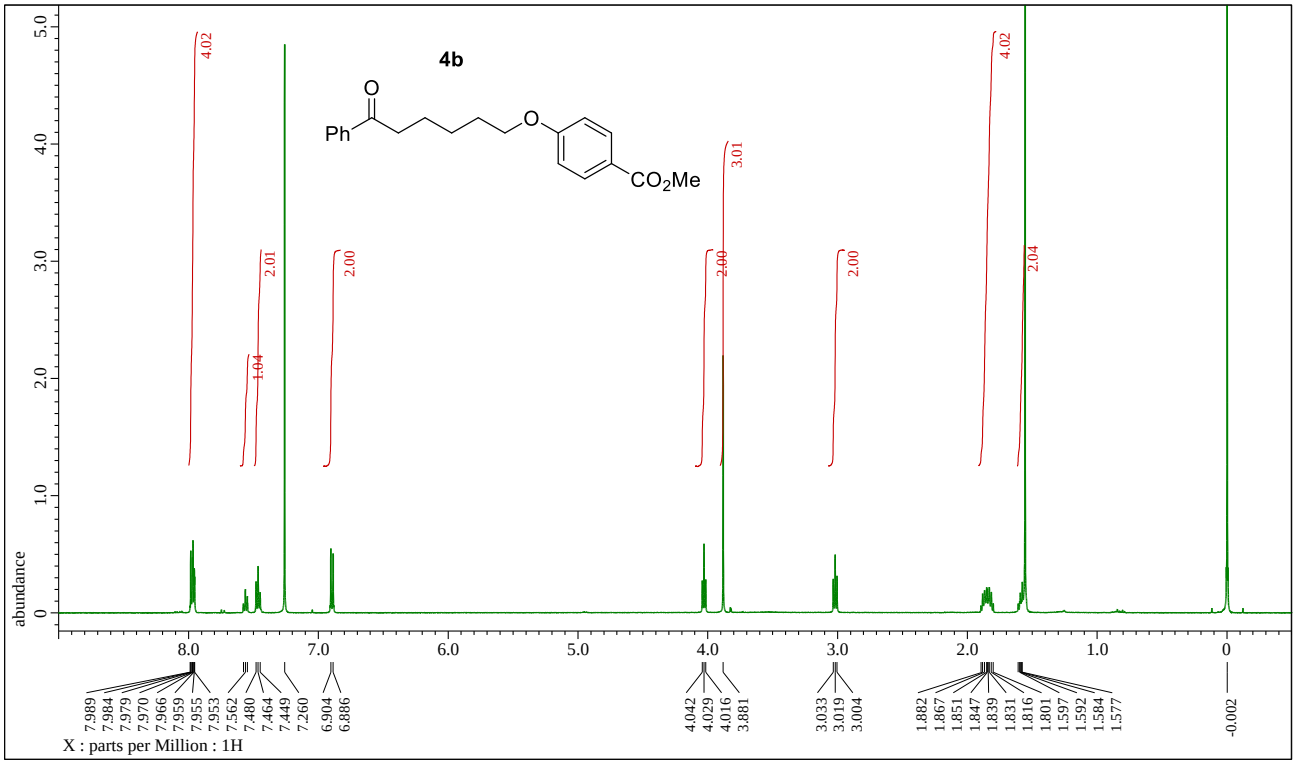
^{1}H NMR spectrum of **4a** (500 MHz, $CDCl_3$)



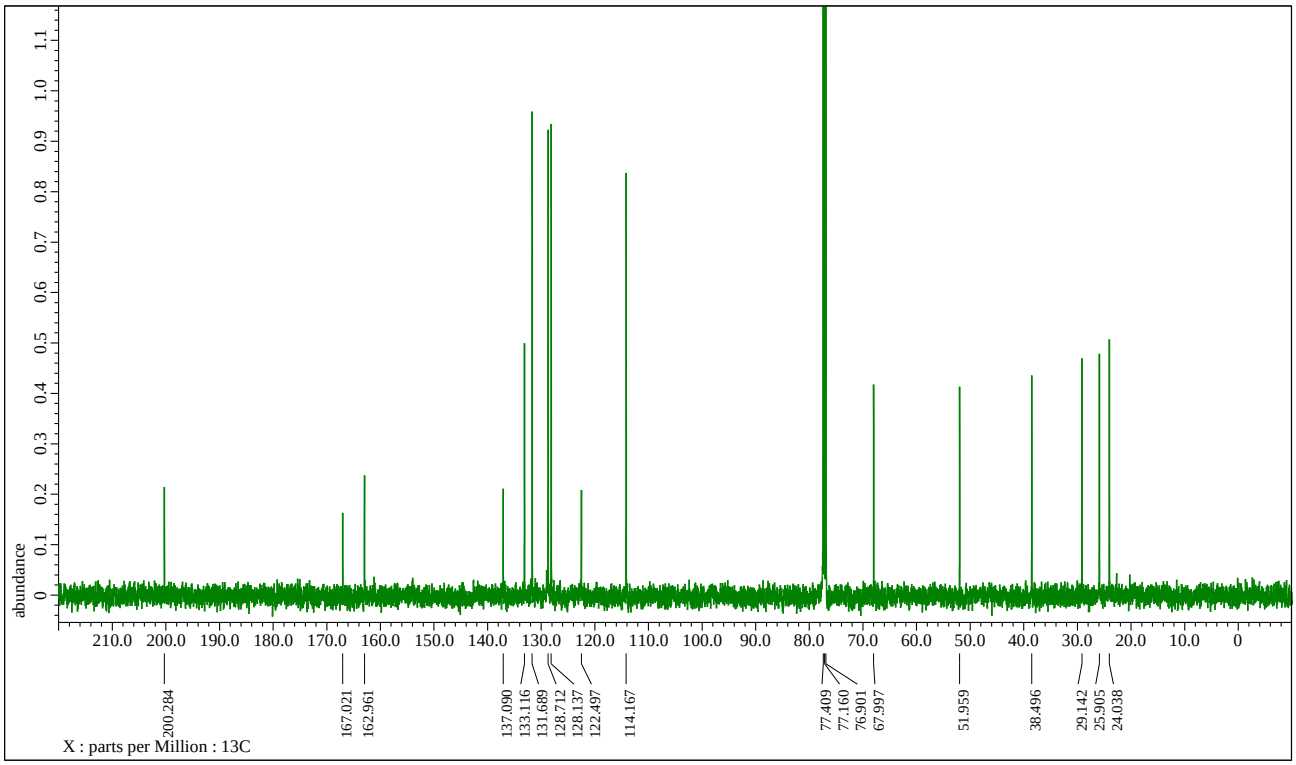
^{13}C NMR spectrum of **4a** (125 MHz, $CDCl_3$)



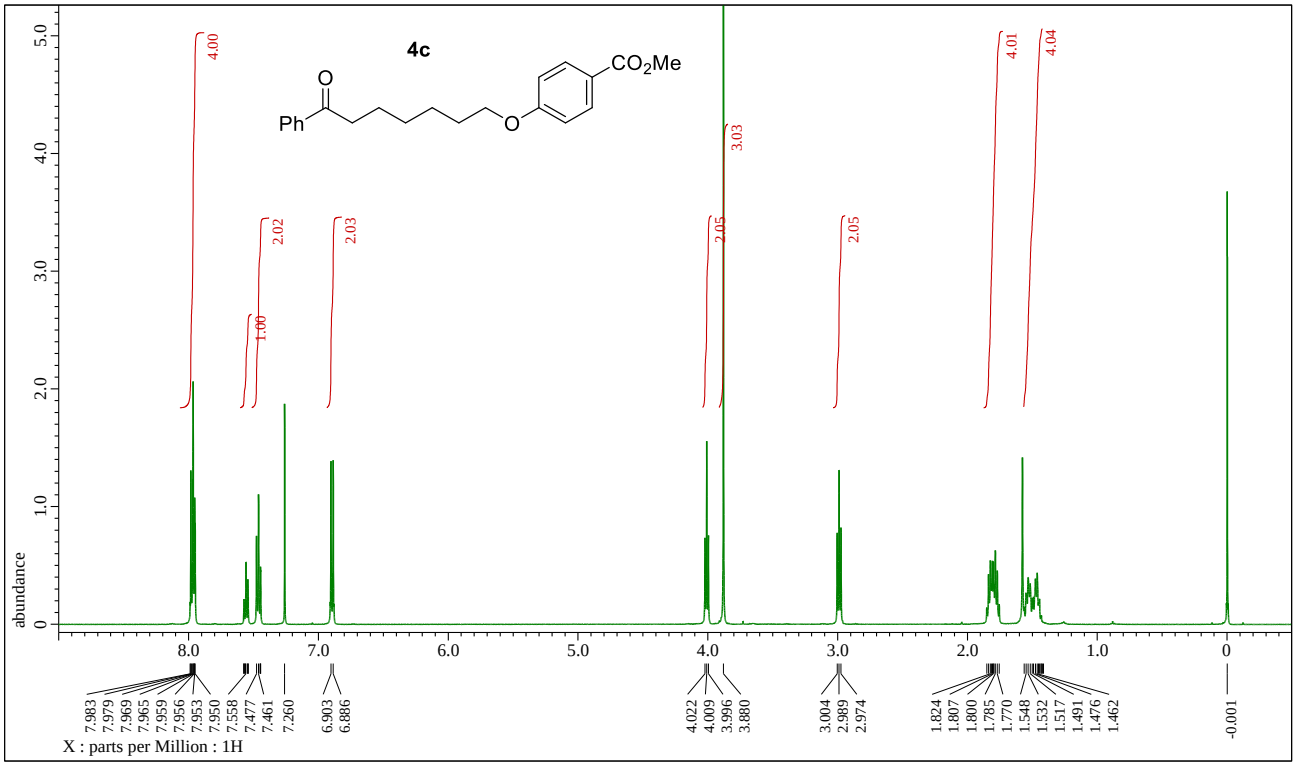
^{1}H NMR spectrum of **4b** (500 MHz, $CDCl_3$)



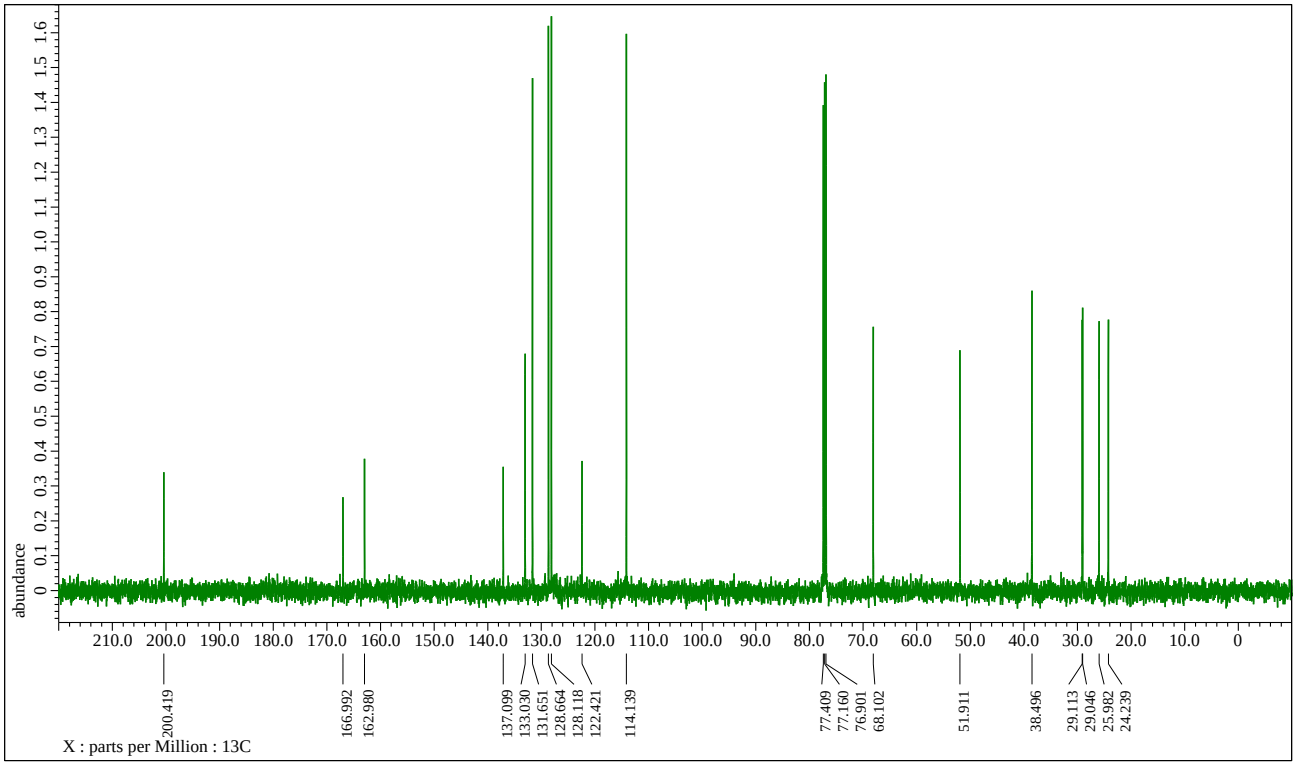
^{13}C NMR spectrum of **4b** (125 MHz, $CDCl_3$)



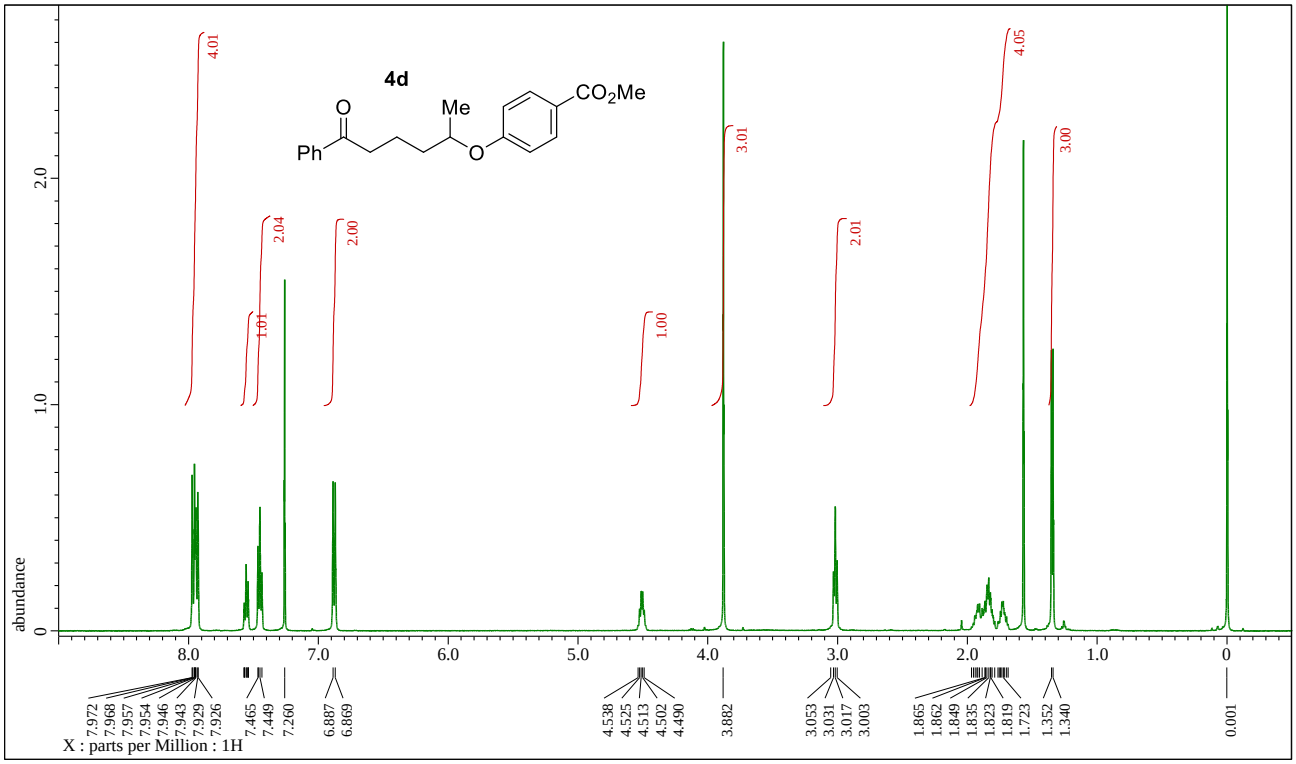
^{1}H NMR spectrum of **4c** (500 MHz, $CDCl_3$)



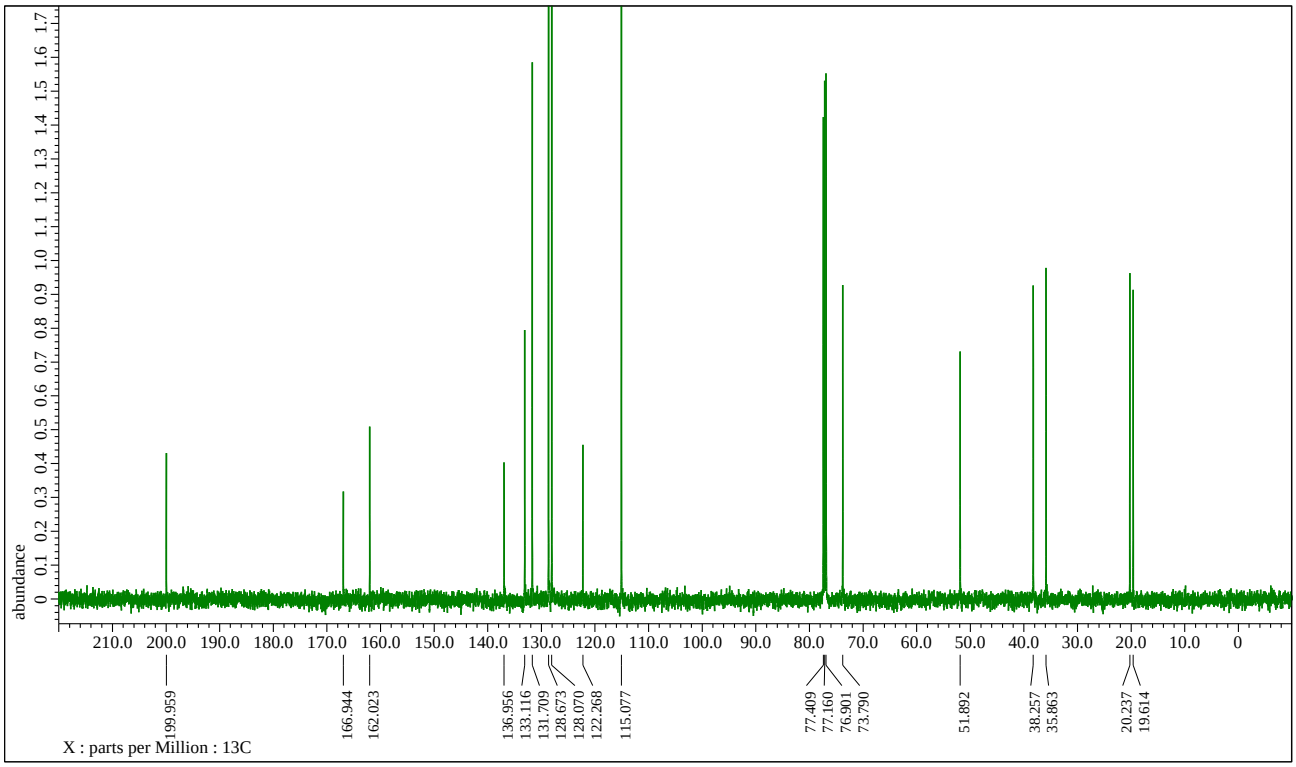
^{13}C NMR spectrum of **4c** (125 MHz, $CDCl_3$)



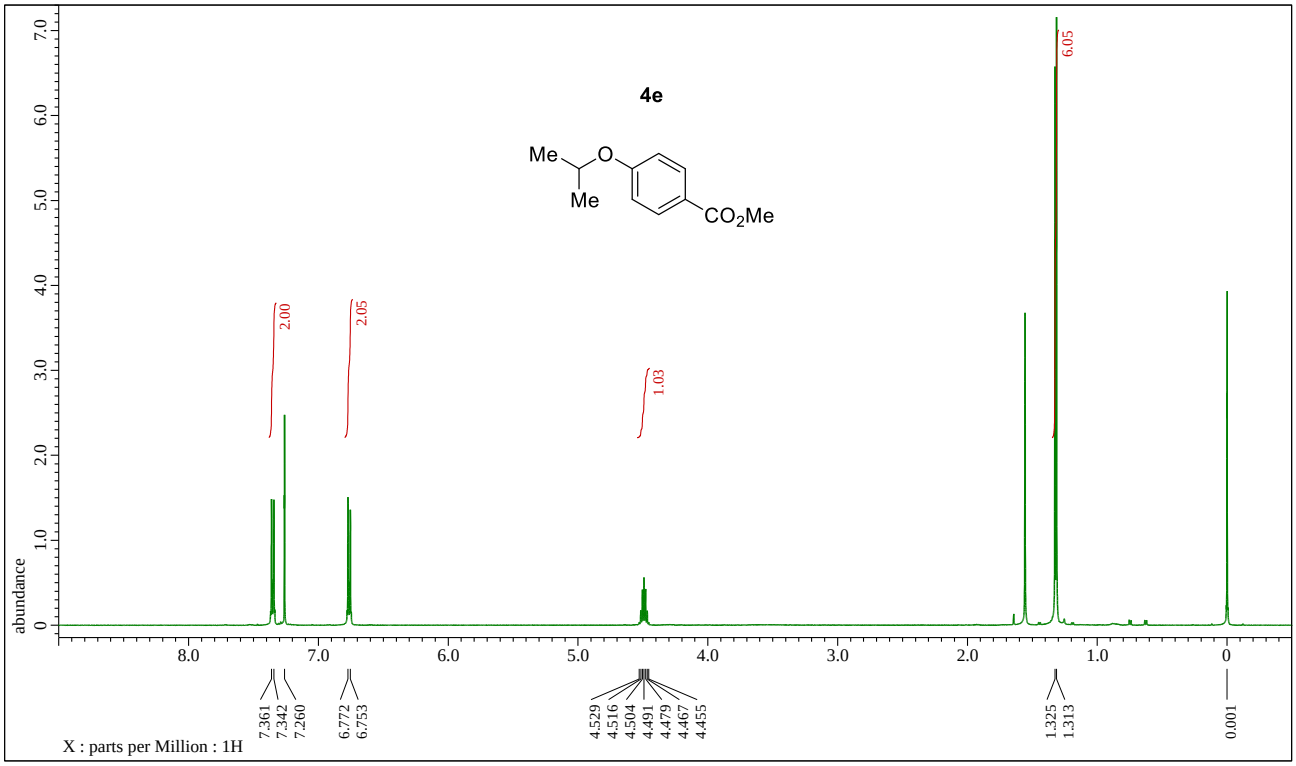
^{1}H NMR spectrum of **4d** (500 MHz, $CDCl_3$)



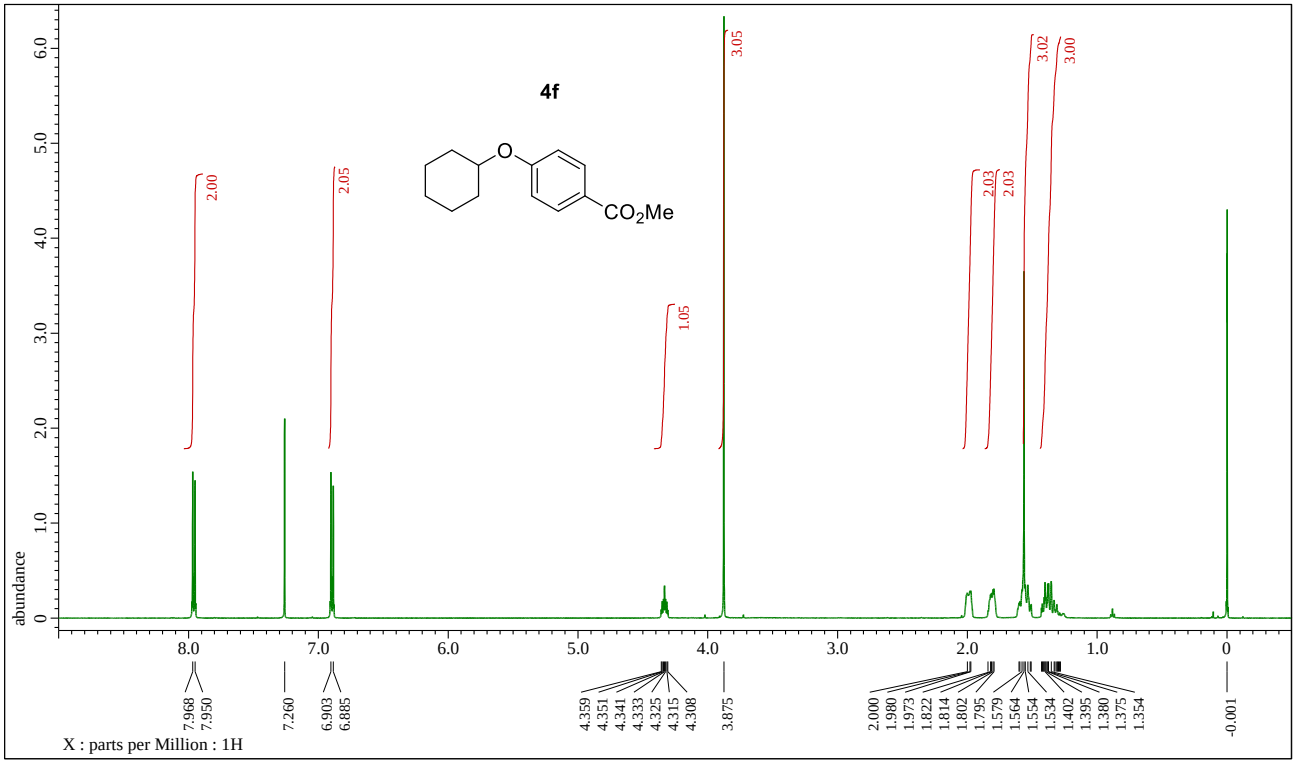
^{13}C NMR spectrum of **4d** (125 MHz, $CDCl_3$)



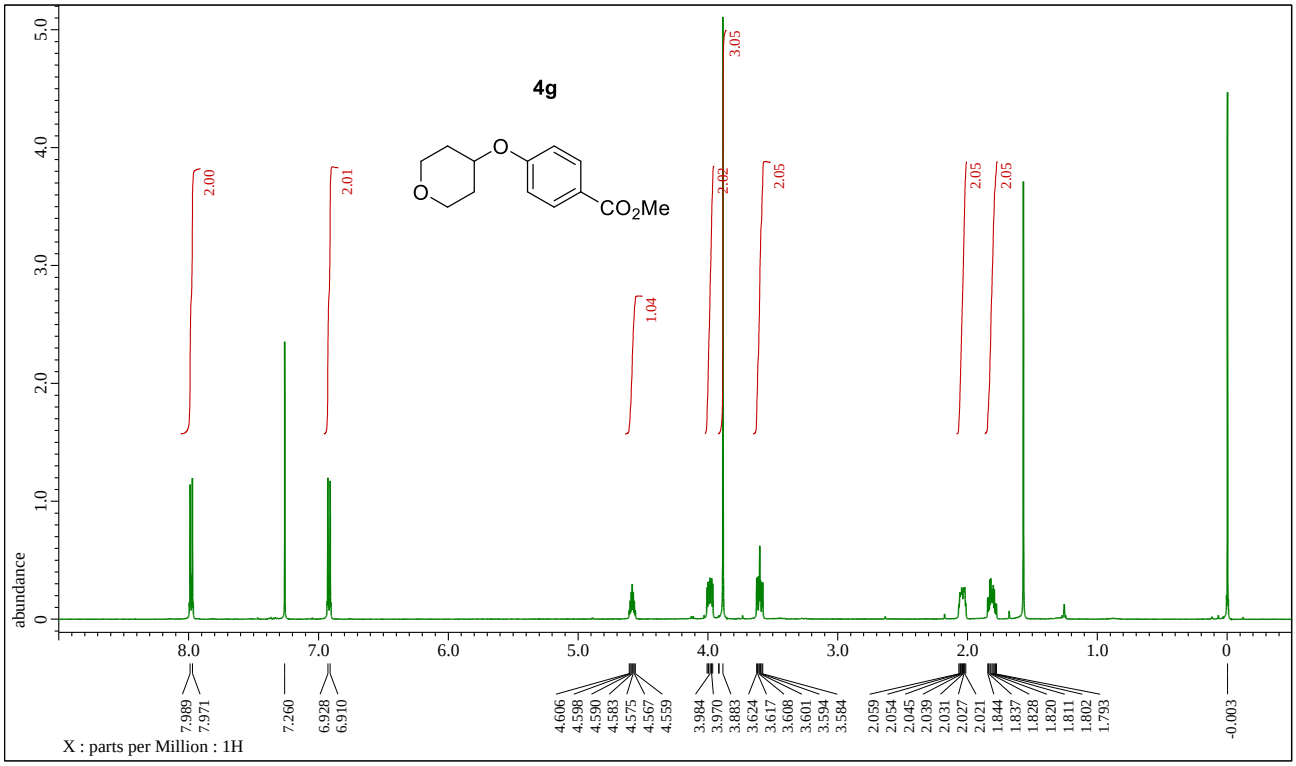
^{1}H NMR spectrum of **4e** (500 MHz, $CDCl_3$)



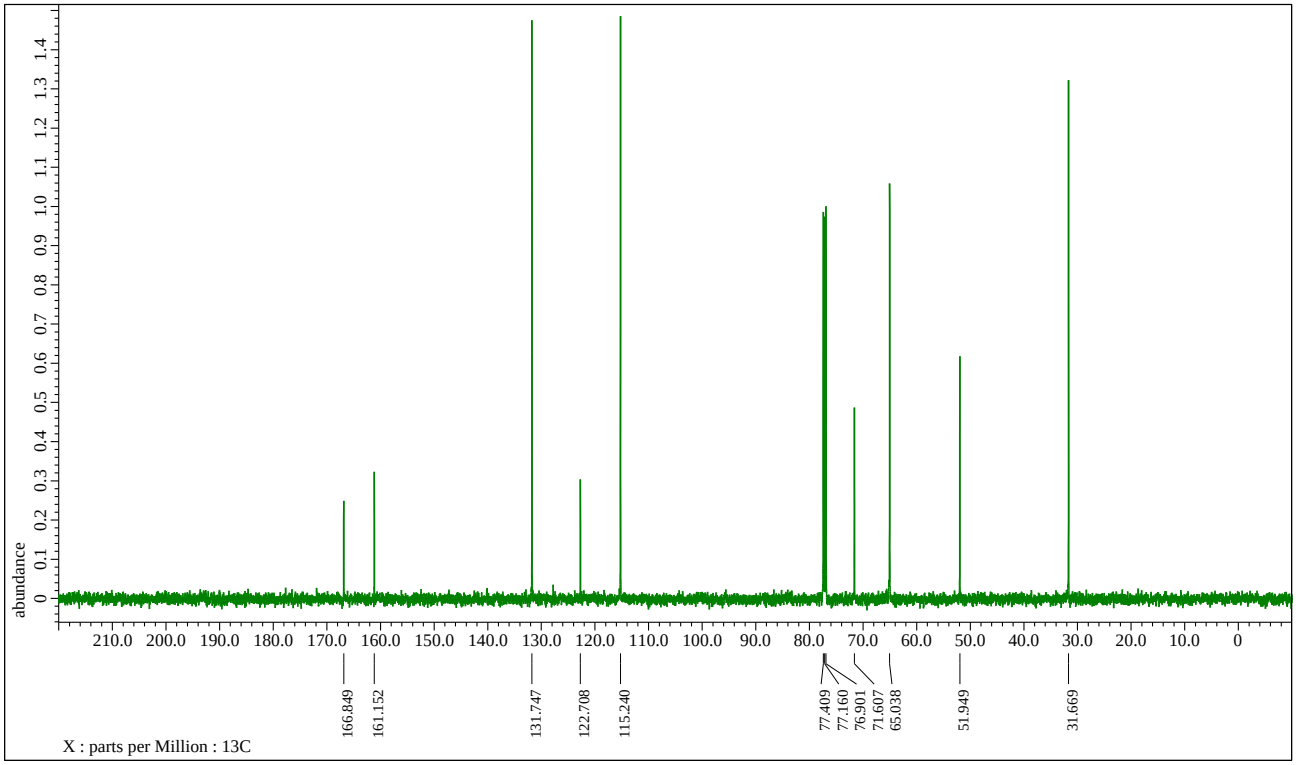
^{1}H NMR spectrum of **4f** (500 MHz, $CDCl_3$)



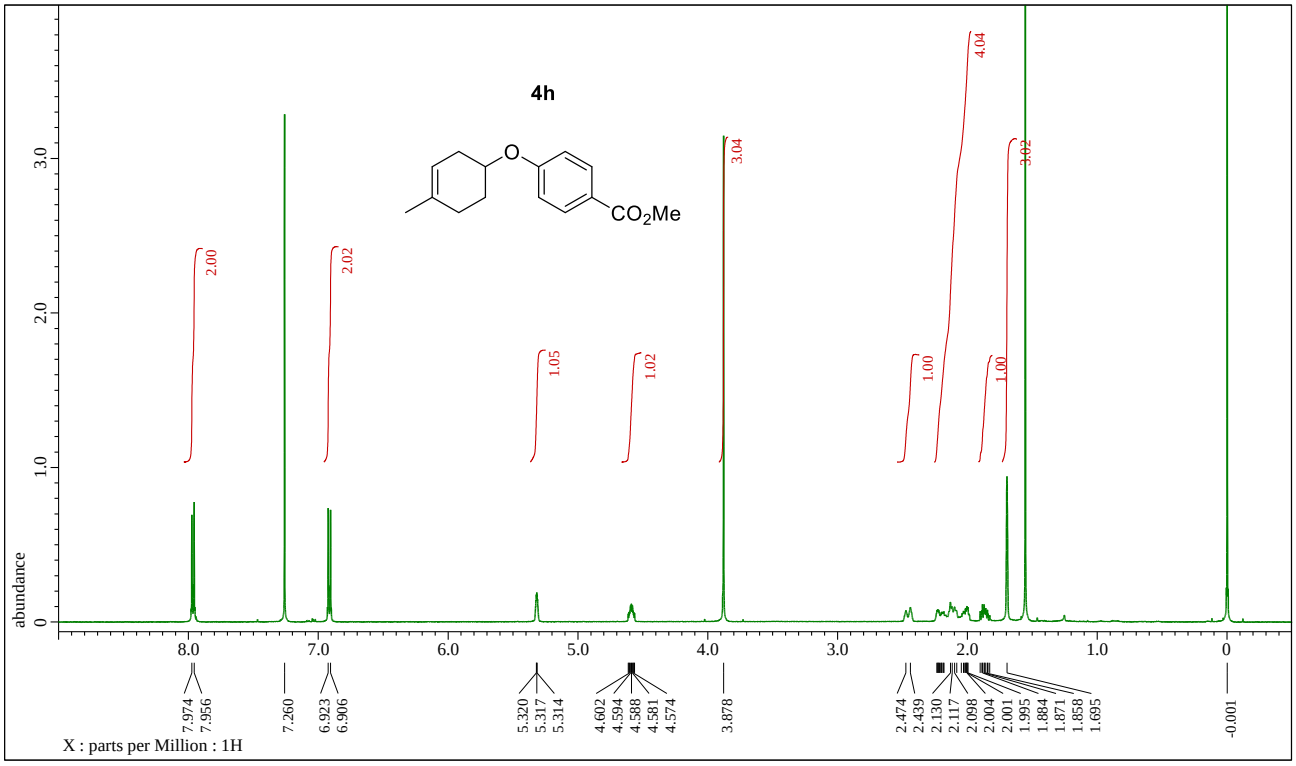
^{1}H NMR spectrum of **4g** (500 MHz, $CDCl_3$)



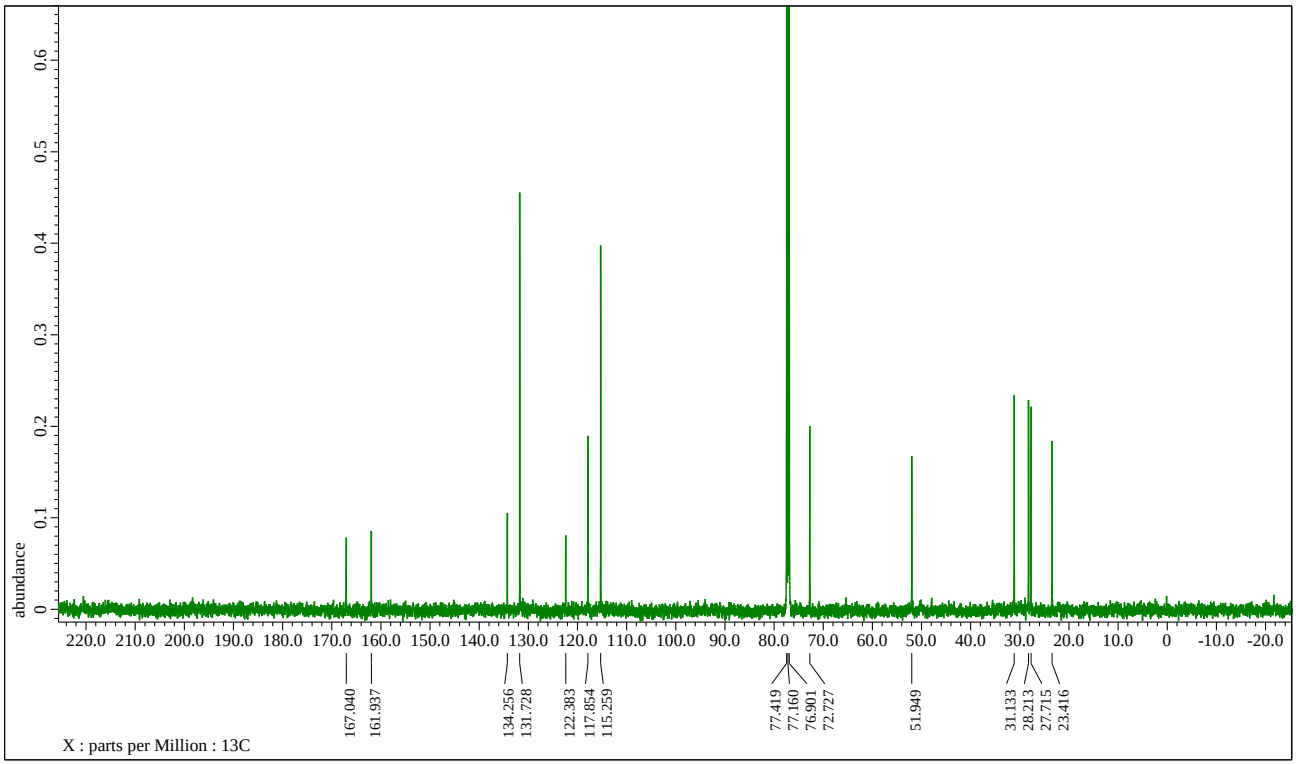
^{13}C NMR spectrum of **4g** (125 MHz, $CDCl_3$)



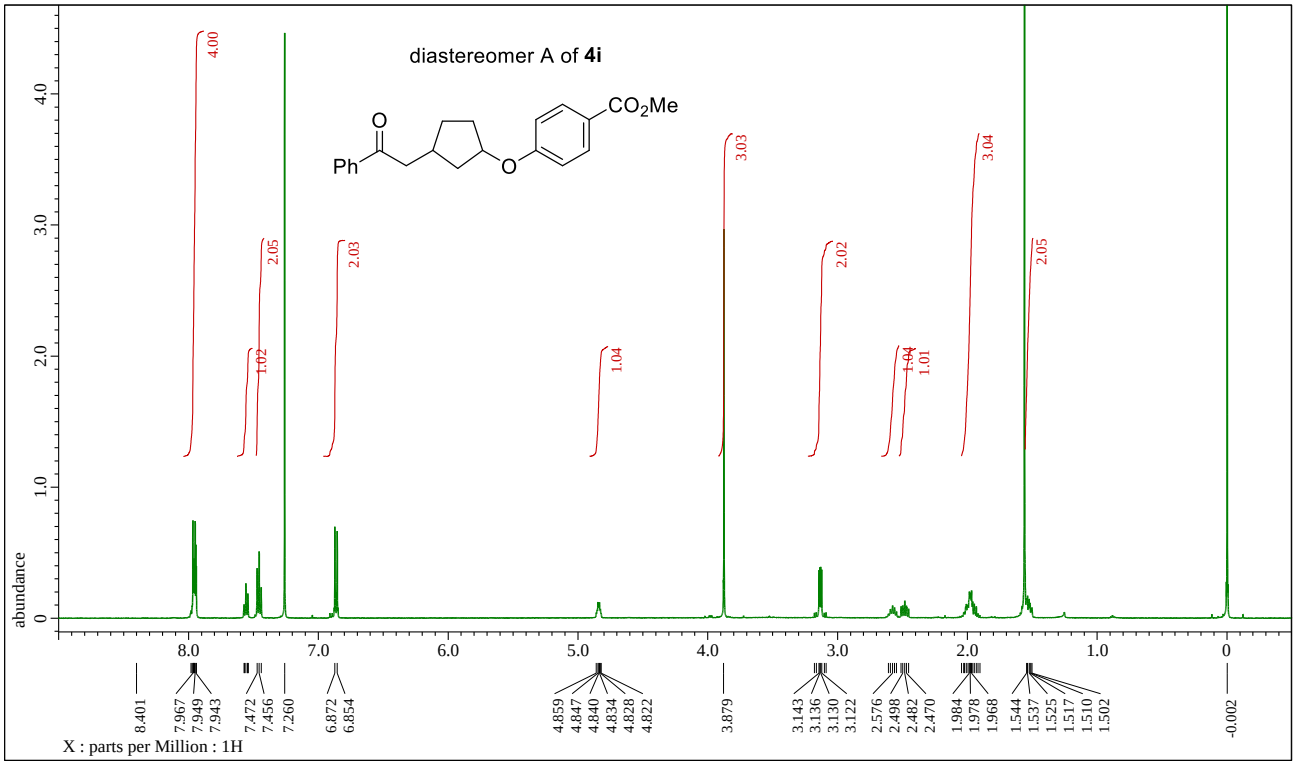
^{1}H NMR spectrum of **4h** (500 MHz, $CDCl_3$)



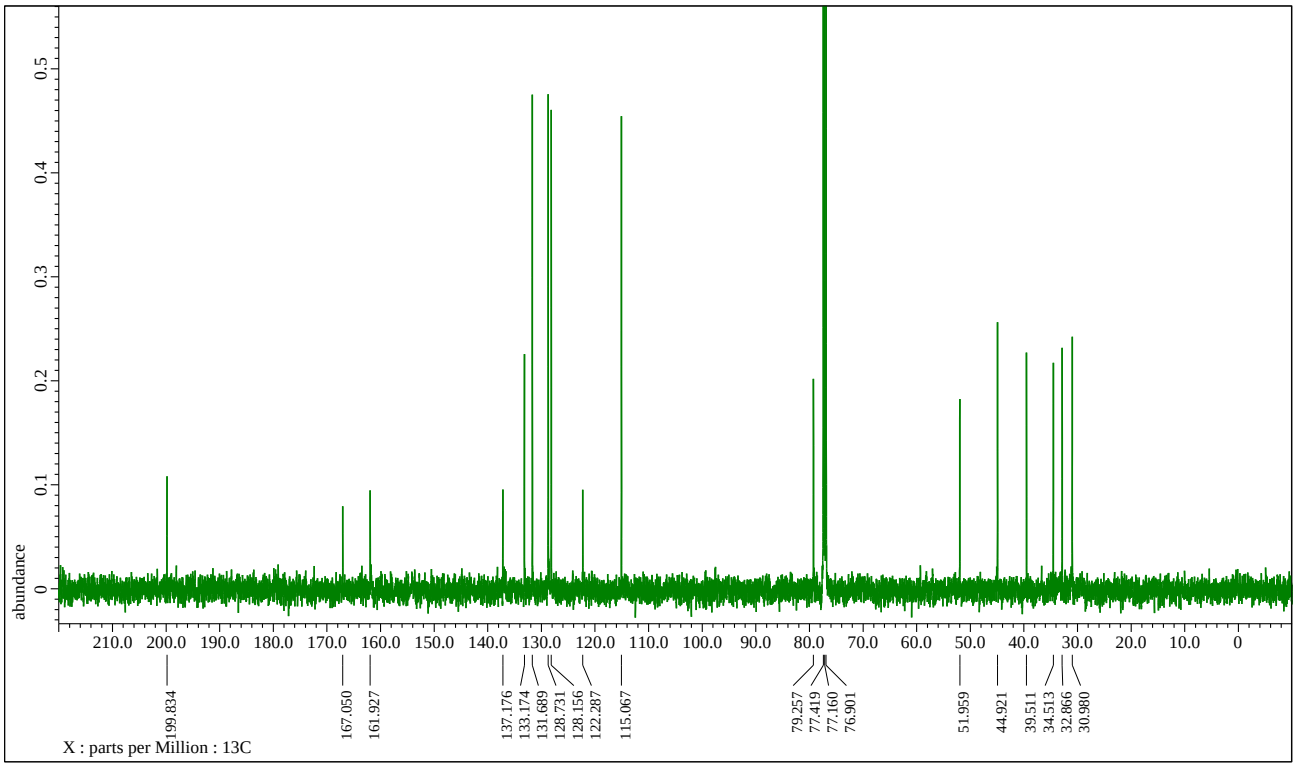
^{13}C NMR spectrum of **4h** (125 MHz, $CDCl_3$)



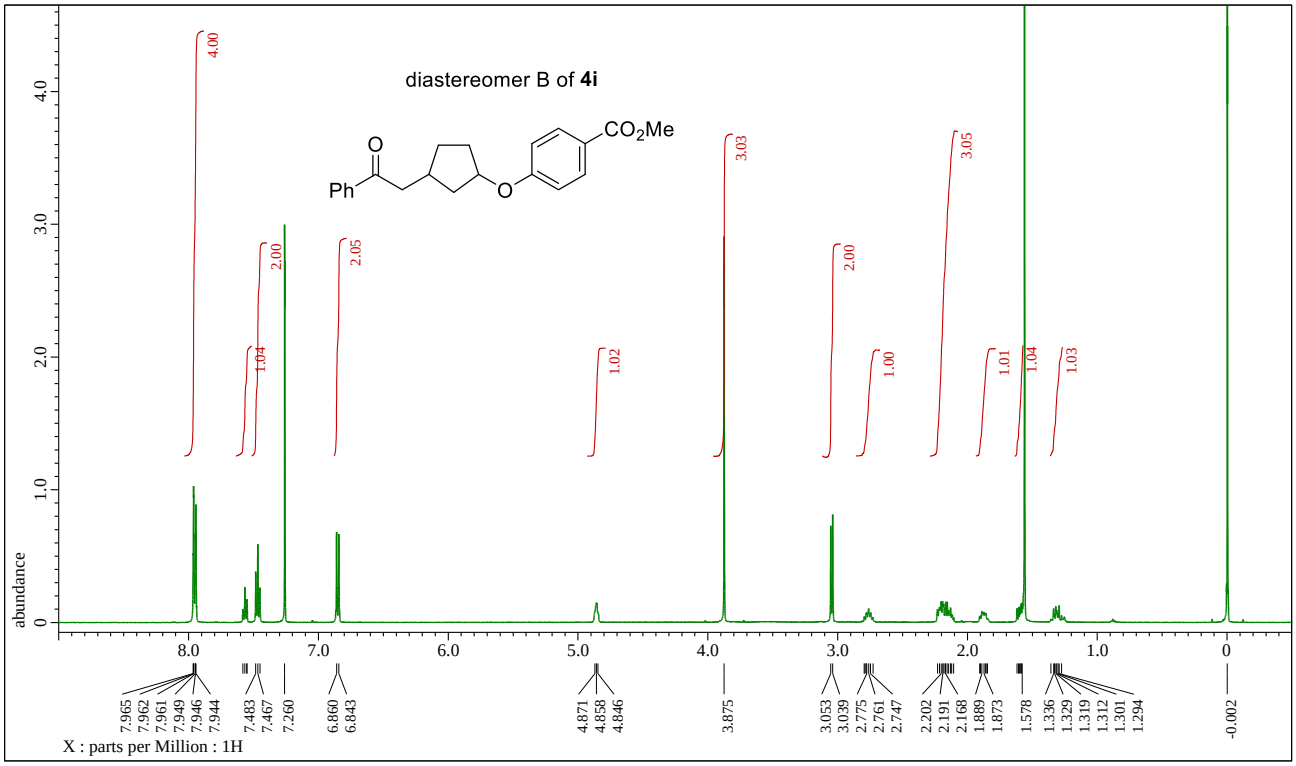
^{1}H NMR spectrum of diastereomer A of **4i** (500 MHz, $CDCl_3$)



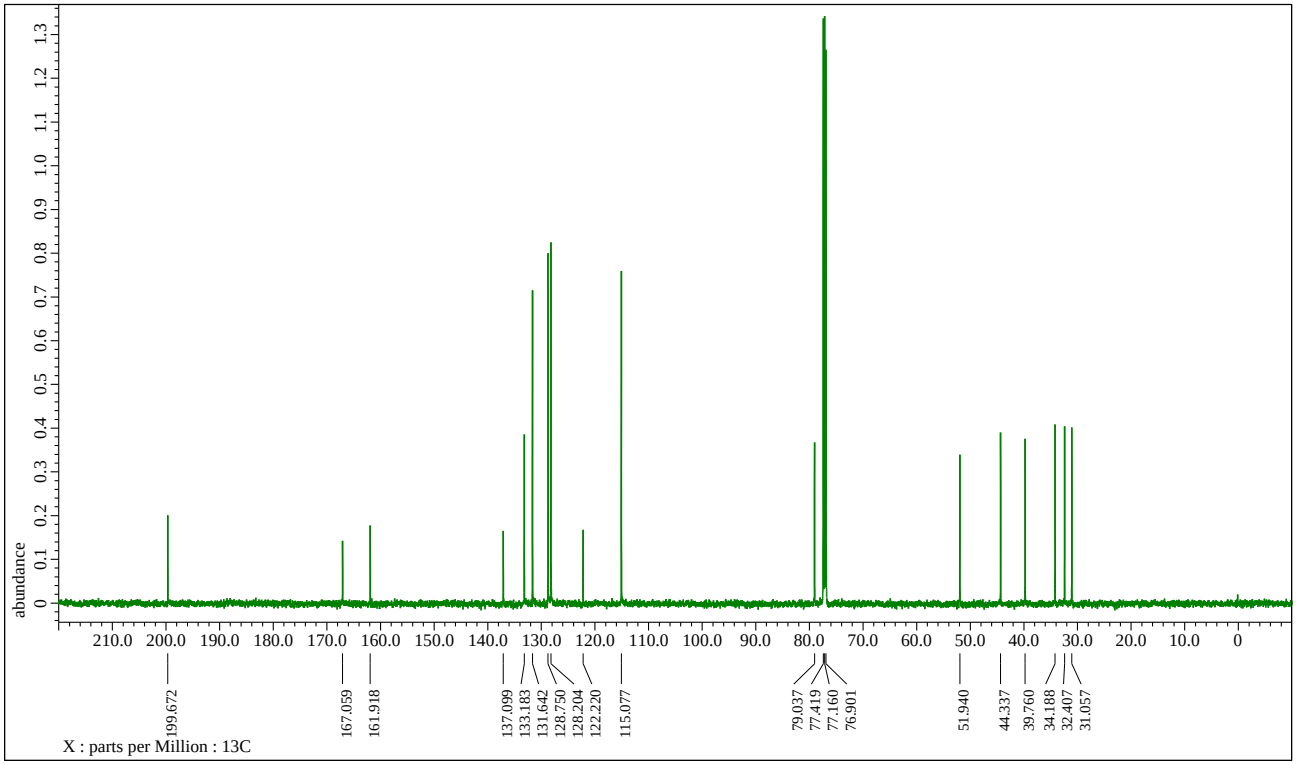
^{13}C NMR spectrum of diastereomer A of **4i** (125 MHz, $CDCl_3$)



^{1}H NMR spectrum of diastereomer B of **4i** (500 MHz, $CDCl_3$)



^{13}C NMR spectrum of diastereomer B of **4i** (125 MHz, $CDCl_3$)



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