Supporting Information

Electrochemical Methoxymethylation of Alcohols – A New Green and Safe Approach for the Preparation of MOM Ethers and Other Acetals

Xi-Ya Luo,[a] Xiaofeng Ma,[a] Frédéric Lebreux,[a] István E. Markó[a†] and Kevin Lam*[b]

[a] Université Catholique de Louvain, Laboratory of Organic and Medicinal Chemistry, Bâtiment Lavoisier, Place Louis Pasteur 1 bte L4.01.02., B-1348 Louvain-la-Neuve, Belgium
[†] Deceased on the 31st of July 2017
[b] Department of Pharmaceutical, Chemical and Environmental Sciences, Faculty of Engineering and Science, University of Greenwich, Central Avenue, Chatham Maritime, ME4 4TB, United Kingdom
E-mail: k.lam@greenwich.ac.uk

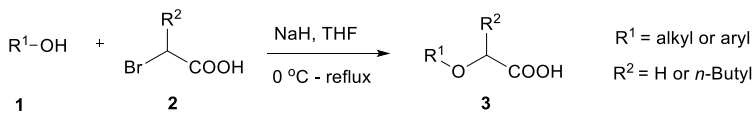
Contents

1. General Experimental Section

Commercial grade solvents were dried and purified by standard procedures as specified in Purification of Laboratory Chemicals, 4th Ed (Armarego, W. L. F.; Perrin, D. D. Butterworth Heinemann: 1997). NMR spectra were recorded at room temperature on a Bruker Avance 300 instrument operating at a frequency of 300 MHz for ^{1}H and 75 MHz for ^{13}C. Chemical shifts (δ) are reported in ppm from $CDCl_3$ (δ = 7.27 ppm) or DMSO-*d*6 (δ = 2.50 ppm) for ^{1}H NMR and relative to $CDCl_3$ (δ = 77.2 ppm) or DMSO-*d*6 (δ = 39.5 ppm) for ^{13}C NMR. Column chromatography was performed over ROCC Silica gel 60 (40-63μ mesh) eluting with ethyl acetate (or diethyl ether) and petroleum ether. Mass spectra were recorded using Varian Matt 44S and Finnigan-Matt TSQ-70 spectrometer. High-resolution mass data were obtained with a Kratos MS50TC instrument. Infrared spectra were recorded on a SHIMADZU-FTIR-8400S spectrometer and recorded in cm^{-1}. The electrolysis were carried out using a Thurlby/Thandar PL320QMT 30V coupled to a 2A Quad Mode Triple Output DC Power Supply or using an Electrasyn 2.0 equipped with graphite electrodes.

2. Procedure for the Synthesis of *α*-alkoxy Carboxylic Acids

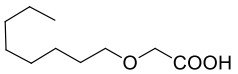
All starting materials were purchased from commercial suppliers and used without further purification.



Procedure: A flame dried 250 mL three-necked flask was equipped with a

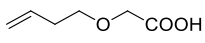
magnetic stir bar and a reflux condenser. Sodium hydride (1.20 g, 60% dispersion in mineral oil, 30 mmol) was then suspended in dry THF (20 mL) at 0 ºC under argon. Alcohol **1** (10 mmol), dissolved in dry THF (30 mL), was then added slowly. After 30 min, bromoacetic acid **2** (10 mmol), dissolved in dry THF (30 mL), was added dropwise. The mixture was heated to reflux, and the progress of the reaction was monitored by TLC. Upon completion of the reaction, as shown by TLC, the mixture was cooled down to room temperature and diluted with water (60 mL). The mixture was extracted with hexane (2 x 30 mL), the aqueous layer was acidified with HCl (2 M) until pH 2 was reached and extracted with diethyl ether (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, the solvent was removed under reduced pressure and the crude mixture was purified by column chromatography on silica gel (petroleum ether / ethyl acetate) to give the pure α-alkoxy carboxylic acids **3**.

2-(octyloxy)acetic acid (3a)



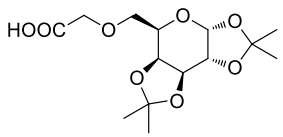
Pale yellow oil, 95% yield; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 10.09 (s, 1H), 4.12 (s, 2H), 3.55 (t, J = 6.7 Hz, 2H), 1.68-1.58 (m, 2H), 1.37-1.22 (m, 10H), 0.88 (t, J = 6.7 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 175.4, 72.3, 67.9, 31.9, 29.6, 29.5, 29.3, 26.0, 22.8, 14.2; **IR** (neat) ν 3507, 2923, 1728, 1465, 1242, 1124; **MS** (Cl) *m/z* (%): 189.2 (30), 143.2 (20), 113.2 (45), 77.0 (100).

2-(but-3-en-1-yloxy)acetic acid (3b)



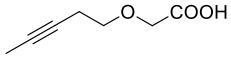
Pale yellow liquid, 87% yield; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 11.27 (s, 1H), 5.88-5.75 (m, 1H), 5.16-5.04 (m, 2H), 4.14 (s, 2H), 3.62 (t, J = 6.7 Hz, 2H), 2.39 (qt, J = 6.7, 1.3 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 175.9, 134.6, 117.1, 71.3, 67.9, 34.0; **IR** (neat) ν 3506, 2914, 2873, 1728, 1641, 1431, 1220, 1119, 997, 914; **MS** (Cl) *m/z* (%): 131.0 (17), 76.9 (23), 55.0 (100).

2-(((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)methoxy)acetic acid (3c)



Pale yellow oil, 85% yield; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 5.55 (d, J = 5.0 Hz, 1H), 4.66 (dd, J = 7.9, 2.5 Hz, 1H), 4.37 (dd, J = 5.0, 2.6 Hz, 1H), 4.31 (dd, J = 7.9, 2.1 Hz, 1H), 4.26-4.13 (m, 2H), 4.07-4.03 (m, 1H), 3.79-3.68 (m, 2H), 1.54 (s, 3H), 1.47 (s, 3H), 1.37 (s, 3H), 1.34 (s, 3H); **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 172.0, 110.0, 109.1, 96.3, 71.2, 71.0, 70.7, 70.5, 68.9, 66.3, 26.1, 26.0, 25.0, 24.6; **IR** (neat) ν 3501, 3215, 2987, 2935, 1738, 1456, 1371, 1253, 1213, 1164, 1064, 1003, 891; **ESI-HRMS**: m/z calcd for $C_{14}H_{23}O_8$ $[M+H]^+$: 319.1387; found: 319.1388.

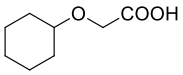
2-(pent-3-yn-1-yloxy)acetic acid (3d)



Pale yellow liquid, 81% yield; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 4.18 (s, 2H), 3.66 (t, J = 6.7 Hz, 2H), 2.50-2.44 (m, 2H), 1.79 (t, J = 2.5 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 174.3, 77.6, 75.4, 70.7, 68.1, 20.2, 3.6; **IR** (neat) ν 3517, 3479, 2922, 2565, 2538, 1732, 1429, 1429, 1221, 1124, 957;

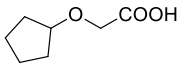
ESI-HRMS: m/z calcd for $C_7H_{11}O_3$ $[M+H]^+$: 143.0703; found: 143.0703.

2-(cyclohexyloxy)acetic acid (3e)



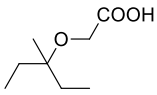
Colorless liquid, 82% yield; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 8.83 (s, 1H), 4.14 (s, 2H), 3.53-3.35 (m, 1H), 1.96-1.92 (m, 2H), 1.77-1.75 (m, 2H), 1.56-1.53 (m, 1H), 1.41-1.19 (m, 5H); **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 174.1, 79.2, 65.2, 32.0, 25.6, 24.0; **IR** (neat) ν 3064, 2932, 2856, 1728, 1448, 1358, 1217, 1113, 933, 887.

2-(cyclopentyloxy)acetic acid (3f)



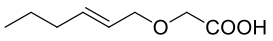
Colorless liquid, 80% yield; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 9.04 (s, 1H), 4.08 (s, 2H), 4.07-4.02 (m, 1H), 1.79-1.66 (m, 6H), 1.64-1.51 (m, 2H); **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 174.3, 83.0, 66.0, 32.2, 23.5; **IR** (neat) ν 3110, 2949, 2874, 1728, 1435, 1348, 1221, 1121, 982, 960.

2-((3-methylpentan-3-yl)oxy)acetic acid (3g)



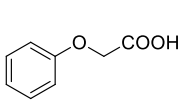
Colorless liquid, 82% yield; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 8.94 (s, 1H), 3.96 (s, 2H), 1.52 (q, J = 7.4 Hz, 4H), 1.14 (s, 3H), 0.86 (t, J = 7.5 Hz, 6H); **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 173.0, 80.0, 59.5, 29.9, 22.1, 8.0; **IR** (neat) ν 3105, 2970, 2941, 1728, 1435, 1375, 1209, 1117, 879; **ESI-HRMS**: m/z calcd for $C_8H_{16}O_3Na$ $[M+Na]^+$: 183.0992; found: 183.0992.

(*E*)-2-(hex-2-en-1-yloxy)acetic acid (3h)

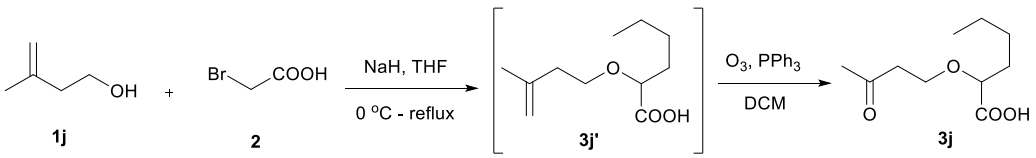


Pale yellow oil, 89% yield; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 10.17 (s, 1H), 5.80-5.70 (m, 1H), 5.60-5.50 (m, 1H), 4.11 (s, 2H), 4.06 (d, J=6.4, 2H), 2.04 (q, J=6.9, 2H), 1.48-1.35 (m, 2H), 0.90 (t, J=7.4, 3H); **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 175.7, 136.9, 125.0, 72.4, 66.2, 34.4, 22.2, 13.8; **IR** (neat) ν 2956, 1728, 1426, 1207, 1114, 1038, 971.

2-phenoxyacetic acid (3i)



White solid, 83% yield; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 9.59 (s, 1H), 7.34-7.26 (m, 2H), 7.02 (t, J = 7.3 Hz, 1H), 6.93 (d, J = 7.9 Hz, 2H), 4.68 (s, 2H); **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 174.7, 157.5, 129.9, 122.3, 114.8, 65.0; **IR** (neat) ν 3421, 3036, 2575, 2005, 1957, 1907, 1866, 1732, 1697, 1596, 1583, 1496, 1487, 1434, 1373, 1265, 1091, 835.

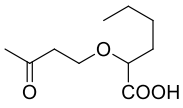


3j' was synthesised following the general procedure for the preparation of α-alkoxy carboxylic acids and used for the next step without further purification.

In a 250 three-necked flask, **3j'** (1.86 g, 9.2 mmol) was dissolved in dichloromethane (100 mL). The mixture was cooled to -78 °C and a gentle flux of ozone was passed through the solution until a persisting deep blue colour appeared. The excess of ozone was removed by passing a flow of dry air through the solution and then triphenylphosphine (2.66 g, 10.12 mmol) was

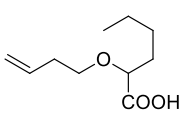
added. The solution was refluxed overnight and then washed with 0.5 M sulfuric acid (50 mL) and extracted with DCM (2 x 20 mL), the organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude mixture was then purified on silica gel by chromatography. The excess of phosphine and the formed phosphine oxide were eluted using a mixture of ethyl acetate / dichloromethane / triethylamine (2 : 2 : 1) and the ammonium salt of **3j** was eluted using pure methanol. The methanol was removed under reduced pressure and the residue was dissolved into dichloromethane and 1 M HCl (50 mL). The aqueous layer was extracted with dichloromethane, the organic layers were collected, dried over $MgSO_4$ and concentrated under reduced pressure to give **3j** as pale yellow oil.

2-(3-oxobutoxy)hexanoic acid (3j)



Yellowish oil, 92% yield; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 9.33 (s, 1H), 3.81 (ddd, J = 17.9, 8.5, 4.0 Hz, 2H), 3.60 (dt, J = 9.2, 4.6 Hz, 1H), 2.92-2.70 (m, 2H), 2.23 (s, 3H), 1.86-1.64 (m, 2H), 1.42-1.26 (m, 4H), 0.91-0.86 (m, 3H); **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 208.8, 175.9, 79.3, 65.2, 43.0, 32.7, 30.3, 27.4, 22.4, 14.0; **IR** (neat) ν 3508, 2929, 1743, 1714, 1651, 1467, 1359, 1193, 1123; **MS** (Cl) *m/z* (%): 203.4 (100), 157.3 (66), 87.4 (50).

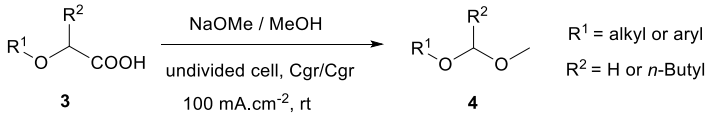
2-(but-3-en-1-yloxy)hexanoic acid (3k)



Yellowish oil, 90% yield; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 11.02 (s,

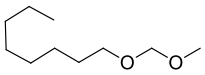
1H), 5.90-5.76 (m, 1H), 5.16-5.05 (m, 2H), 3.88 (dd, *J* = 7.1, 5.2 Hz, 1H), 3.67 (dt, *J* = 9.0, 6.7 Hz, 1H), 3.48 (dt, *J* = 9.0, 6.7 Hz, 1H), 2.42-2.35 (m, 2H), 1.85-1.69 (m, 2H), 1.49-1.26 (m, 4H), 0.91 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 178.0, 134.8, 117.1, 78.9, 70.3, 34.2, 32.4, 27.3, 22.5, 14.0; **IR** (neat) *v* 3447, 2957, 2930, 1717, 1643, 1124, 1101, 914; **MS** (Cl) *m/z* (%): 187.1 (100), 172.3 (65), 158.2 (15), 144.9 (12), 141.2 (45).

3. Procedure for the Electrolysis of Carboxylic Acids

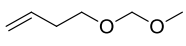


General Electrolysis Procedure: In an undivided beaker-type cell (100 mL) equipped with two graphite electrodes (2 cm × 3 cm), or in an Electrasyn 2.0, α-alkoxy carboxylic acid **3** (1.87 mmol) was dissolved in MeOH (50 mL). The acid was then partially neutralised with NaOMe (0.46 mmol) and a current density of 100 $mA.cm^{-2}$ was applied. The reaction was monitored by TLC. Upon completion of the reaction, as shown by TLC, the solvent was carefully removed under reduced pressure and then water (10 mL) was added (in the case the solution was not basic, 5 mL of 1 M KOH were added). The aqueous mixture was then extracted with diethylether (3 x 15 mL). The organic layers were collected, dried over Na_2CO_3, and concentrated under reduced pressure to yield the clean product **4** without the need for any further purifications.

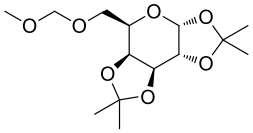
1-(methoxymethoxy)octane (4a)

 Colorless liquid, 90% yield; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 4.62 (s, 2H), 3.51 (t, J = 6.6 Hz, 2H), 3.36 (s, 3H), 1.63-1.54 (m, 2H), 1.37-1.27 (m, 10H), 0.88 (t, J = 6.7 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 96.5, 68.0, 55.2, 32.0, 29.9, 29.5, 29.4, 26.4, 22.8, 14.2; **IR** (neat) v 2925, 2854, 1737, 1465, 1151, 1110, 1039, 919; **MS** (EI) *m/z* (%): 175.2 (11) , 159.1 (1), 143.2 (100), 129.2 (15), 71 (46), 57 (27).

4-(methoxymethoxy)but-1-ene (4b)

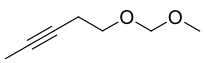
 Colorless liquid, 75% yield; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 5.90-5.77 (m, 1H), 5.15-5.03 (m, 2H), 4.63 (s, 2H), 3.59 (t, J = 6.7 Hz, 2H), 3.36 (s, 3H), 2.36 (qt, J = 6.7, 1.4 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 135.4, 116.6, 96.5, 67.1, 55.3, 34.3; **IR** (neat) v 2954, 2929, 1641, 1191, 1107, 1049, 914; **MS** (Cl) *m/z* (%): 115.2 (25), 101.2 (14), 85.2 (2), 75.1 (1.5), 55.1 (4).

(3aR,5R,5aS,8aS,8bR)-5-((methoxymethoxy)methyl)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran (4c)

 Colorless oil, 90% yield; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 5.55 (d, J = 4.9 Hz, 1H), 4.67 (s, 2H), 4.61 (dt, J = 7.9, 2.7 Hz, 1H), 4.34-4.31 (m, 1H), 4.26 (dt, J = 7.9, 2.7 Hz, 1H), 3.99 (t, J = 6.1 Hz, 1H), 3.78-3.65 (m, 2H), 3.38 (s, 3H), 1.55 (s, 3H), 1.45 (s, 3H), 1.34 (s, 6H); **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 109.5, 108.7, 96.9, 96.5, 71.3, 70.8, 70.6, 67.0, 66.7, 55.4, 26.2, 26.1, 25.1, 24.6; **IR** (neat) v 2987, 2935, 1737, 1716, 1456, 1371,

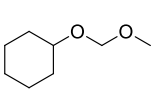
1253, 1211, 1166, 1108, 1070, 1039, 999, 918, 889, 865; **ESI-HRMS**: m/z calcd for $C_{14}H_{24}O_7Na$ $[M+Na]^+$: 327.1414; found: 327.1415.

5-(methoxymethoxy)pent-2-yne (4d)



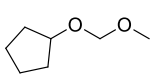
Colorless liquid, 93% yield; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 4.64 (s, 2H), 3.60 (t, J = 6.8 Hz, 2H), 3.36 (s, 3H), 2.45-2.38 (m, 2H), 1.77 (t, J = 2.5 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 96.5, 76.7, 76.0, 66.5, 55.3, 20.3, 3.6; **IR** (neat) v 2937, 1442, 1379, 1274, 1149, 1108, 1041, 918, 763; **ESI-HRMS**: m/z calcd for $C_7H_{13}O_2$ $[M+H]^+$: 129.0910; found: 129.0911.

(methoxymethoxy)cyclohexane (4e)



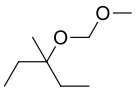
Colorless liquid, 88% yield; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 4.66 (s, 2H), 3.53-3.44 (m, 1H), 3.35 (s, 3H), 1.91-1.83 (m, 2H), 1.73-1.69 (m, 2H), 1.53-1.49 (m, 1H), 1.32-1.21 (m, 5H); **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 94.5, 75.2, 55.2, 32.9, 25.8, 24.3; **IR** (neat) v 3496, 2925, 2854, 1448, 1365, 1269, 1217, 1091.

(methoxymethoxy)cyclopentane (4f)



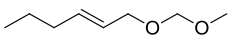
Colorless liquid, 84% yield; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 4.63 (s, 2H), 4.18-4.12 (m, 1H), 3.36 (s, 3H), 1.78-1.64 (m, 6H), 1.57-1.52 (m, 2H); **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 95.2, 78.9, 55.3, 32.8, 23.5; **IR** (neat) v 2927, 1456, 1261, 1091.

3-(methoxymethoxy)-3-methylpentane (4g)



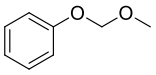
Colorless liquid, 83% yield; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 4.68 (s, 2H), 3.38 (s, 3H), 1.52 (q, J = 7.4 Hz, 4H), 1.15 (s, 3H), 0.86 (t, J = 7.5 Hz, 6H); **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 90.8, 78.9, 55.4, 31.1, 23.0, 8.2; **IR** (neat) v 2925, 1442, 1365, 1271, 1217, 1091, 1041, 918; **ESI-HRMS**: m/z calcd for $C_8H_{18}O_2Na$ $[M+Na]^+$: 169.1199; found: 169.1199.

(*E*)-1-(methoxymethoxy)hex-2-ene (4h)



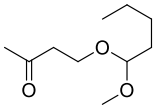
Colorless liquid, 91% yield; **^{1}H NMR** (DMSO-*d*6, 300 MHz) δ 5.71-5.61 (m, 1H), 5.55-5.46 (m, 1H), 4.54 (s, 2H), 3.93 (dd, J = 5.9, 1.0 Hz, 2H), 3.24 (s, 3H), 1.99 (q, J = 7.2 Hz, 2H), 1.36 (dd, J = 14.7, 7.3 Hz, 2H), 0.87 (t, J = 7.4 Hz, 3H); **^{13}C NMR** (DMSO-*d*6, 75 MHz) δ 133.3, 126.5, 94.8, 67.2, 54.5, 33.7, 21.8, 13.5; **IR** (neat) v 2937, 1664, 1563, 1051, 825.

(methoxymethoxy)benzene (4i)



Colorless liquid, 89% yield; **^{1}H NMR** (DMSO-*d*6, 300 MHz) δ 7.32-7.26 (m, 2H), 7.06-7.00 (m, 3H), 5.18 (s, 2H), 3.37 (s, 3H); **^{13}C NMR** (DMSO-*d*6, 75 MHz) δ 156.8, 129.5, 121.6, 116.1, 93.8, 55.5; **IR** (neat) v 2921, 1737, 1596, 1492, 1456, 1440, 1228, 1197, 1149, 1078; **MS** (Cl) *m/z* (%): 139.3 (20), 123.4 (25.), 107.2 (100), 94.2 (27), 61.2 (3).

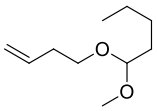
4-((1-methoxypentyl)oxy)butan-2-one (4j)



Colorless liquid, 87% yield; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 4.40 (t, J = 5.7 Hz, 1H), 3.86-3.79 (m, 1H), 3.73-3.65 (m, 1H), 3.30 (s, 3H), 2.67 (t, J = 6.2 Hz, 2H), 2.18 (s, 3H), 1.58-1.54 (m, 2H), 1.32-1.28 (m, 4H),

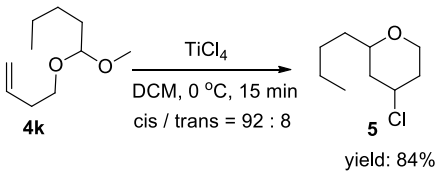
0.89 (t, *J* = 6.9 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 207.3, 104.3, 60.8, 52.9, 43.8, 32.7, 30.6, 26.8, 22.6, 14.1; **IR** (neat) *v* 2927, 1716, 1361, 1193, 1051; **MS** (Cl) *m/z* (%): 173.4 (5), 157.3 (100), 131.3 (25), 101.2 (91), 87.7 (25), 71.1 (54).

1-(but-3-en-1-yloxy)-1-methoxypentane (4k)



Colorless liquid, 92% yield; **^{1}H NMR** (DMSO-*d*6, 300 MHz) δ 5.88-5.74 (m, 1H), 5.11-5.00 (m, 2H), 4.39 (t, *J* = 5.7 Hz, 1H), 3.54 (dt, *J* = 9.4, 6.87 Hz, 1H), 3.44-3.33 (m, 1H), 3.20 (s, 3H), 2.25 (q, *J* = 6.6 Hz, 2H), 1.53-1.46 (m, 2H), 1.31-1.24 (m, 4H), 0.86 (t, *J* = 6.7 Hz, 3H); **^{13}C NMR** (DMSO-*d*6, 75 MHz) δ 135.7, 116.4, 103.1, 64.5, 52.1, 33.9, 32.2, 26.4, 22.0, 13.9; **IR** (neat) *v* 2955, 2932, 1641, 1465, 1193, 1110; **MS** (Cl) *m/z* (%): 171.5 (1), 141.5 (2), 115.3 (5), 101.1 (63), 70.9 (100), 56.8 (81).

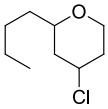
4. Synthesis of tetrahydro-2H-pyran from acetal (5)



Procedure: In a flame dried round bottom flask, at 0 °C, titanium (IV) chloride (1.161 mmol) was dissolved in dichloromethane (4.8 mL). Then the acetal **4k** (100 mg, 0.581 mmol), dissolved in dichloromethane (5 mL), was added dropwise. The reaction was stirred for 15 min and then quenched by adding methanol (1 mL) followed by 2M HCl (8 mL) saturated with NaCl. The reaction mixture was then extracted with DCM (2 x 20 mL), the organic layers

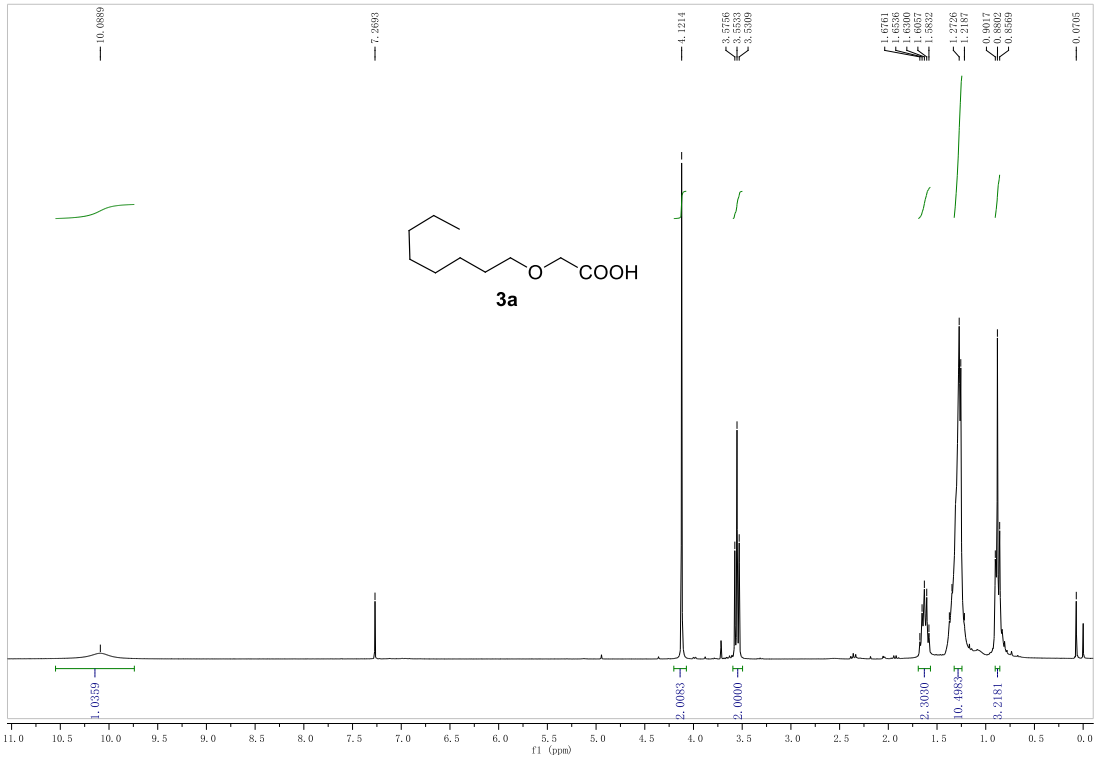
were then collected and dried over $MgSO_4$. The pure product was purified by distillation at atmospheric pressure.

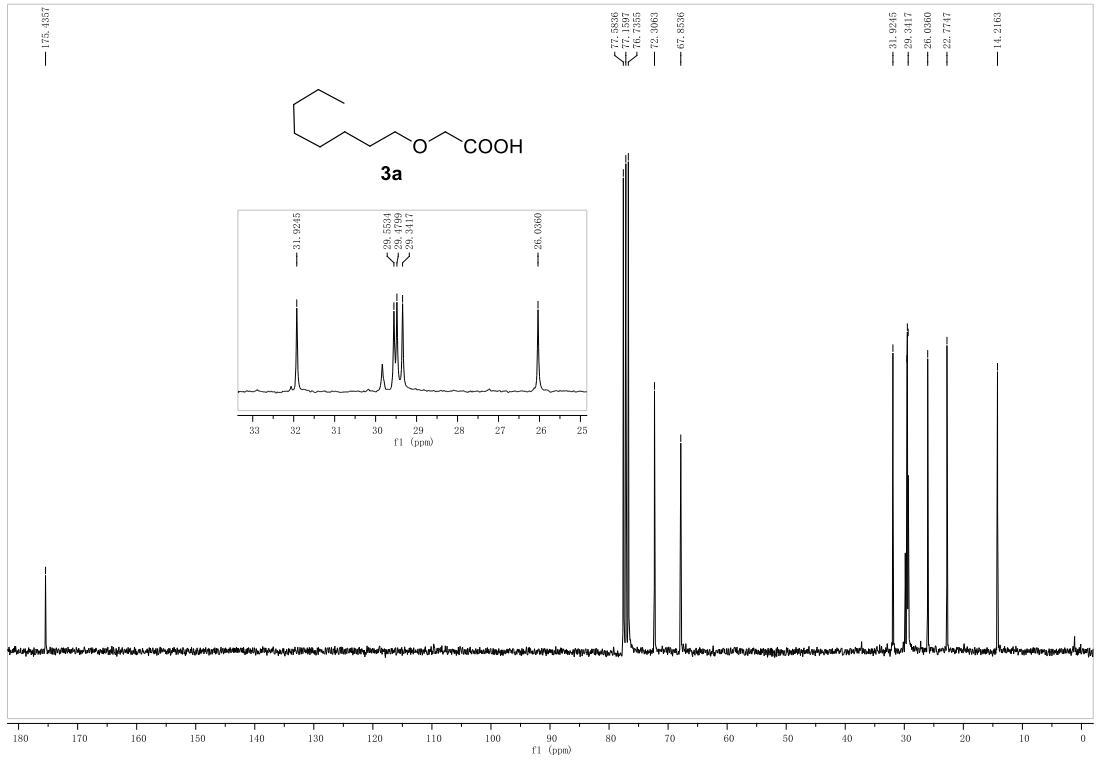
2-butyl-4-chlorotetrahydro-2H-pyran (5)

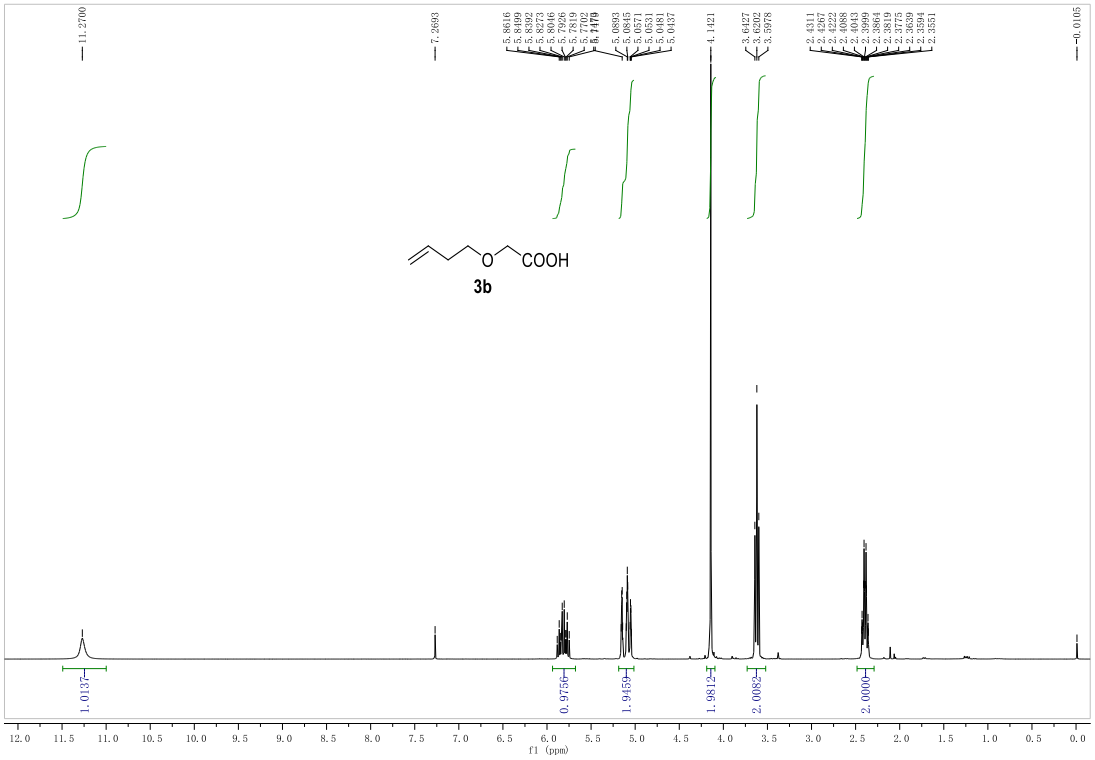


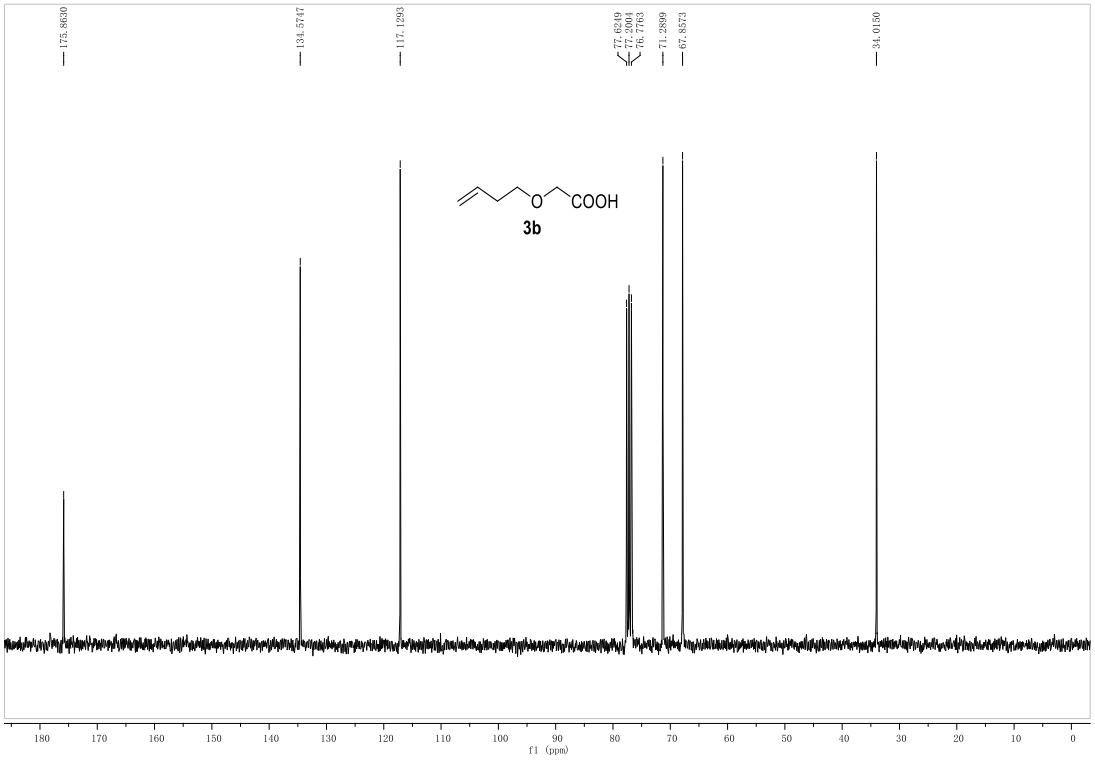
Pale yellow oil, 84% yield; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.00-3.86 (m, 2H), 3.48-3.27 (m, 2H), 2.28-1.69 (m, 3H), 1.52-1.21 (m, 7H), 0.85-0.81 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 77.6, 67.0, 56.0, 42.8, 37.1, 35.6, 27.5, 22.6, 14.1; IR (neat) ν 2956, 2929, 1149.

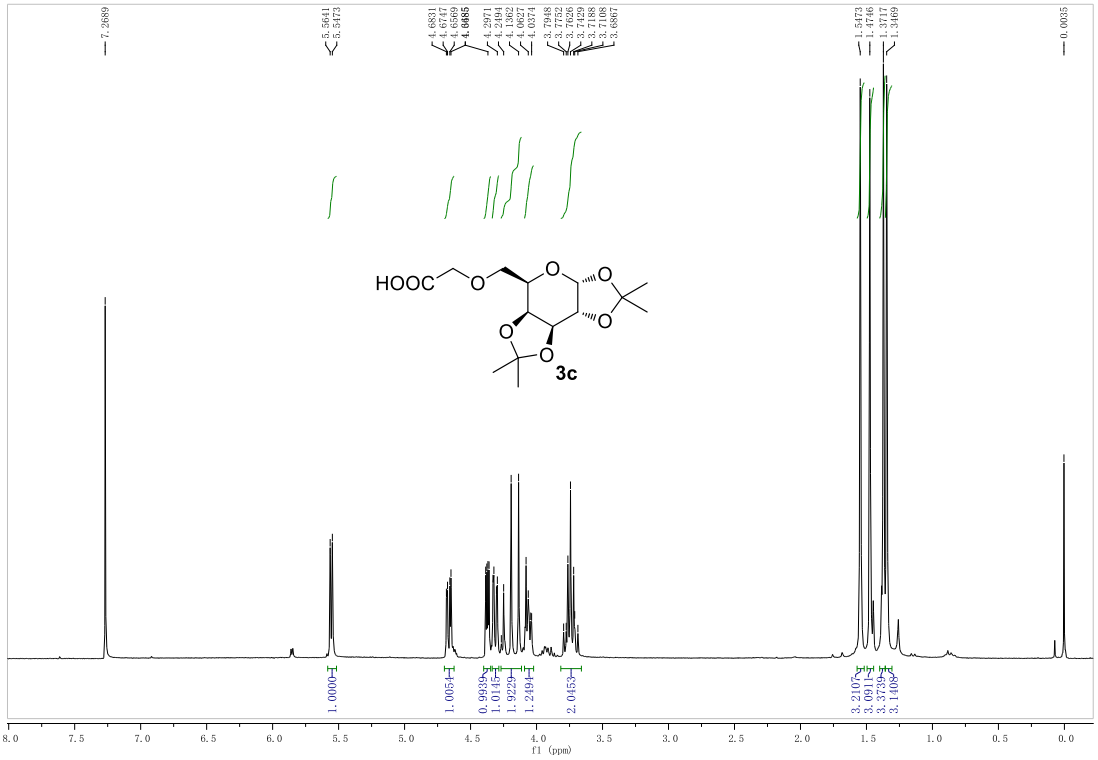
5. NMR spectra

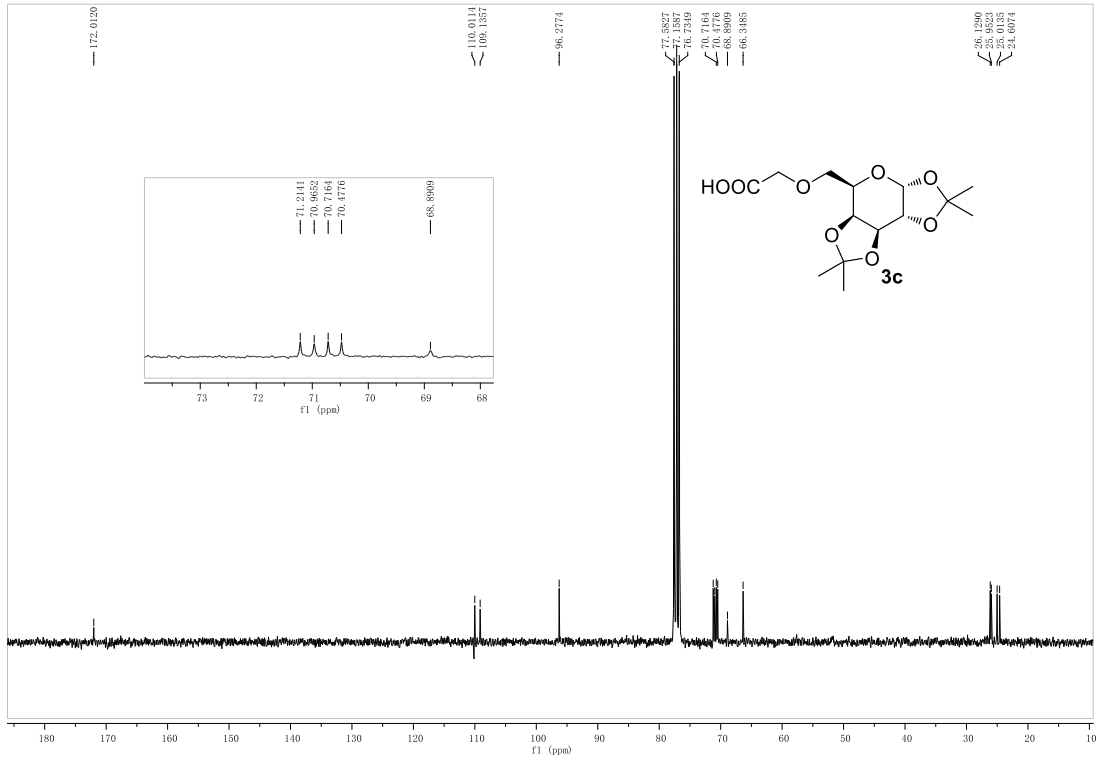


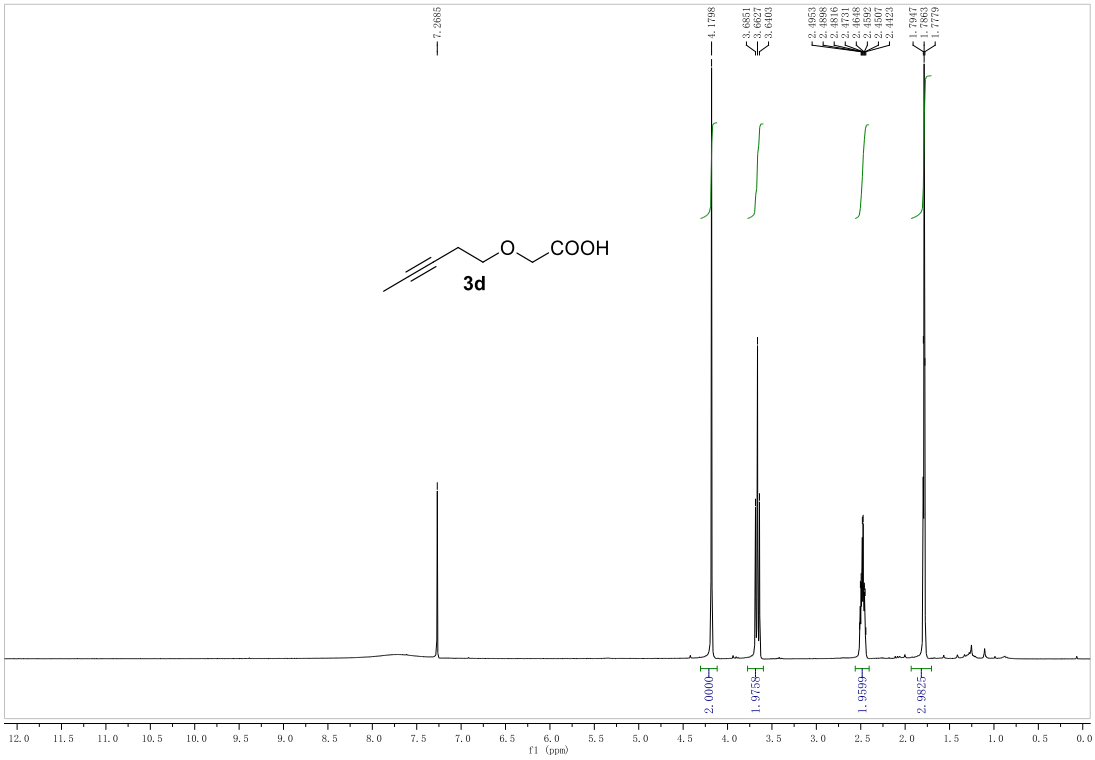


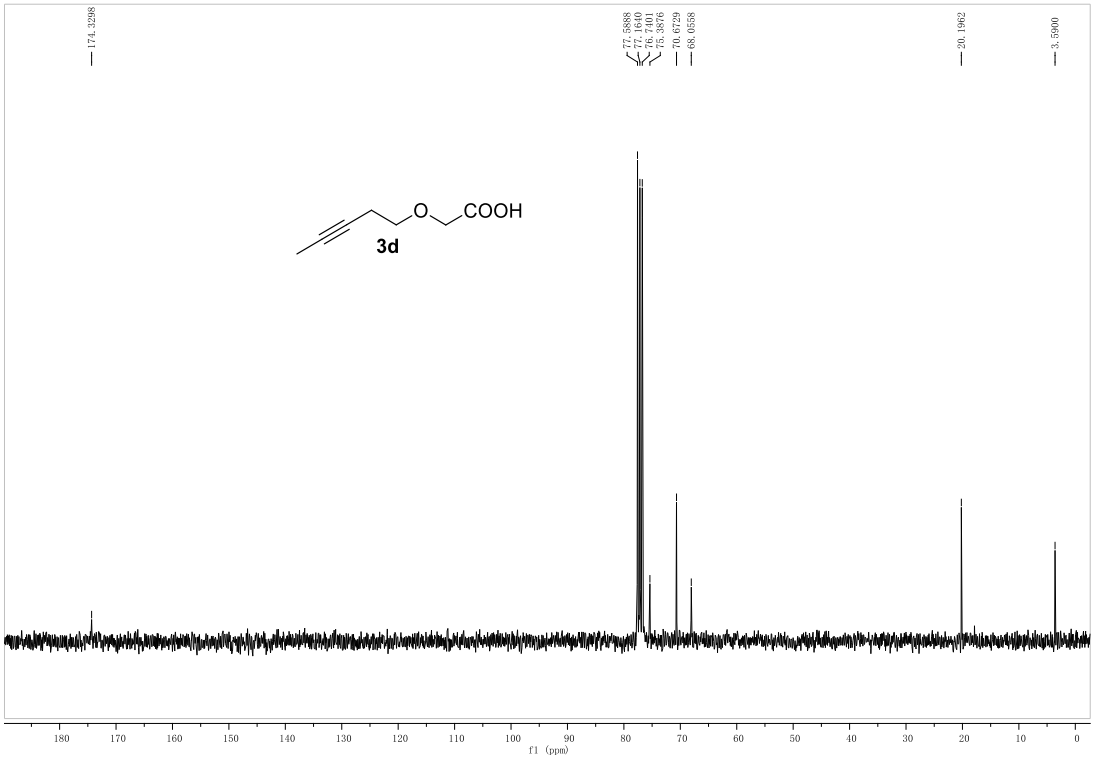

11.2700
7.2693
5.8616
5.8499
5.8382
5.8273
5.8046
5.7926
5.7819
5.7702
5.7585
5.7478
5.0893
5.0845
5.0571
5.0531
5.0181
5.0137
4.1421
3.6427
3.6202
3.5978
2.4311
2.4197
2.4022
2.4088
2.4043
2.3960
2.3864
2.3819
2.3775
2.3639
2.3594
2.3351
0.0105
O
COOH
3b
1.0137
0.9756
1.9459
1.9812
2.0082
2.0000
f1 (ppm)

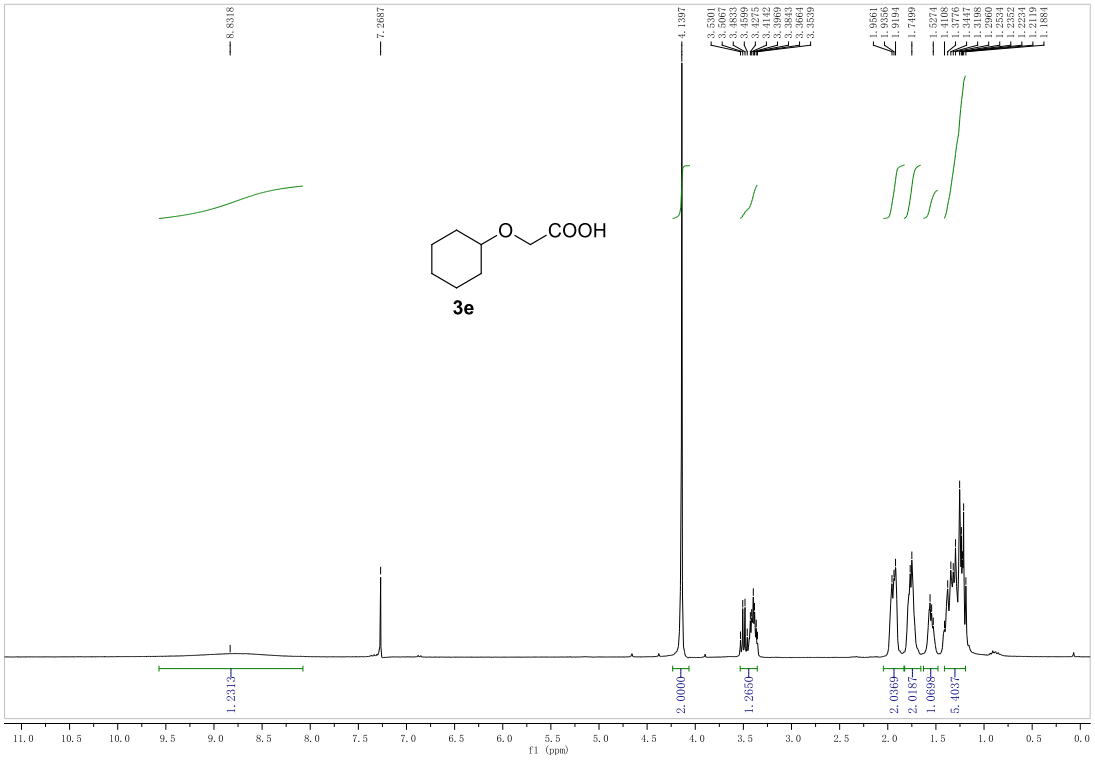

175.8830
134.5747
117.1293
77.6249
77.2904
76.7783
71.2899
67.8573
34.0150
O
COOH
3b
f1 (ppm)

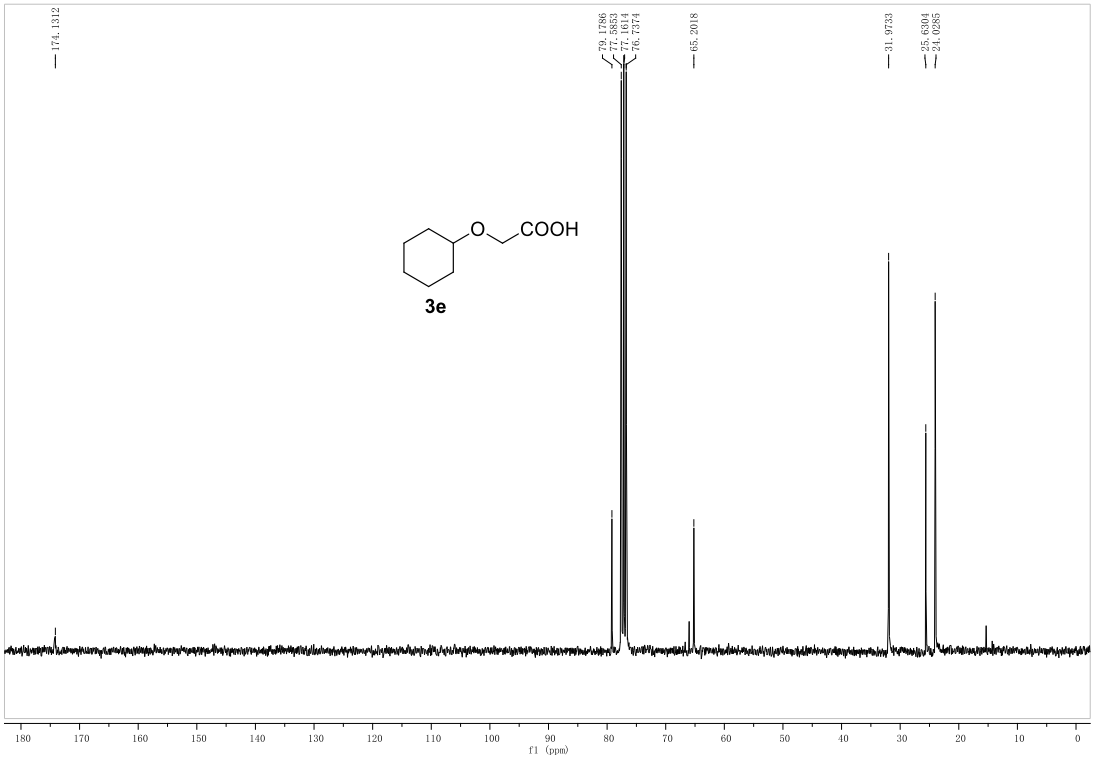

7.2689
5.5641
5.5473
4.6831
4.6747
4.6589
4.6485
4.2971
4.2494
4.1362
4.0627
4.0054
3.7948
3.7732
3.7626
3.7429
3.7188
3.7106
3.6867
1.5473
1.4746
1.3737
1.3469
0.0035
HOOC
O
O
O
O
O
O
3c
1.0000
1.0054
0.9939
1.0145
1.9229
1.2494
2.0453
3.2107
3.4911
3.3739
3.1408
f1 (ppm)

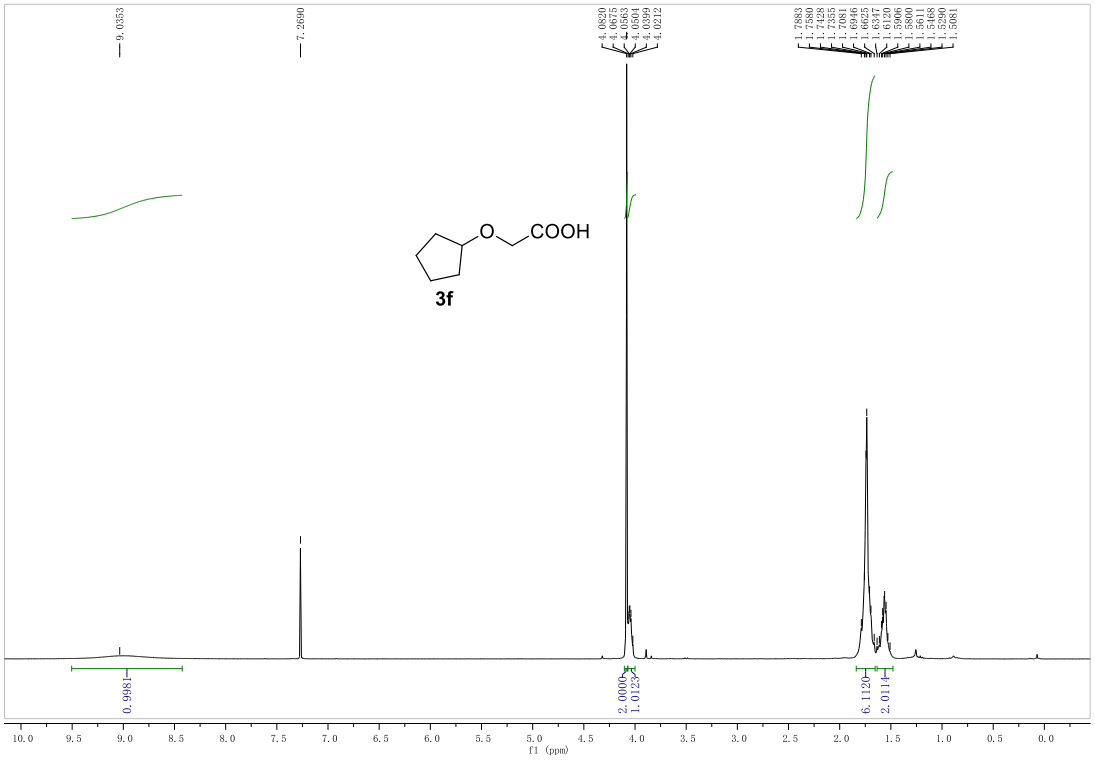

172.0120
110.0114
109.1357
96.2774
77.5827
77.1587
76.7349
70.7164
70.4776
68.8909
66.3485
26.1290
25.9523
25.0135
24.6074
71.2141
70.9652
70.7164
70.4776
68.8909
HOOC
O
O
O
O
O
O
3c
f1 (ppm)

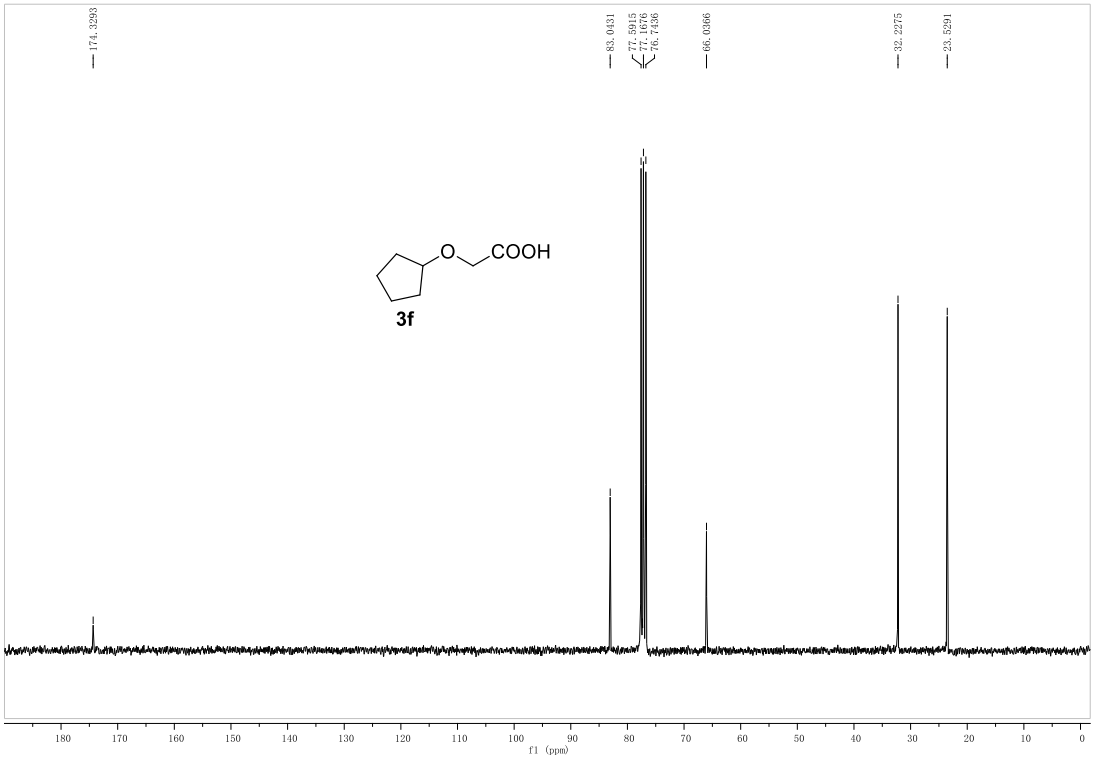

7.2685
4.1708
3.6851
3.6627
3.6403
2.4953
2.4808
2.4816
2.4731
2.4648
2.4592
2.4507
2.4423
1.7947
1.7863
1.7779
O
COOH
3d
2.0000
1.9758
1.9599
2.9825
f1 (ppm)

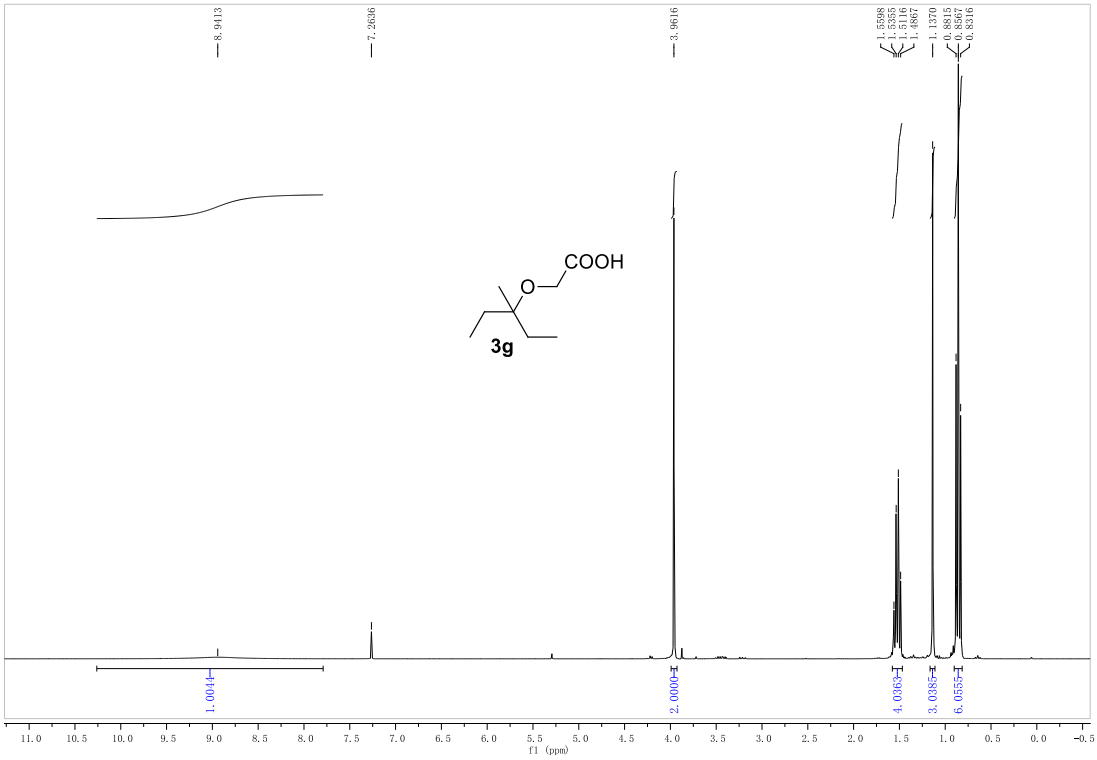

174.3298
77.5888
77.1640
76.7401
75.3876
70.6729
68.0558
20.1962
3.5900
O
COOH
3d
f1 (ppm)

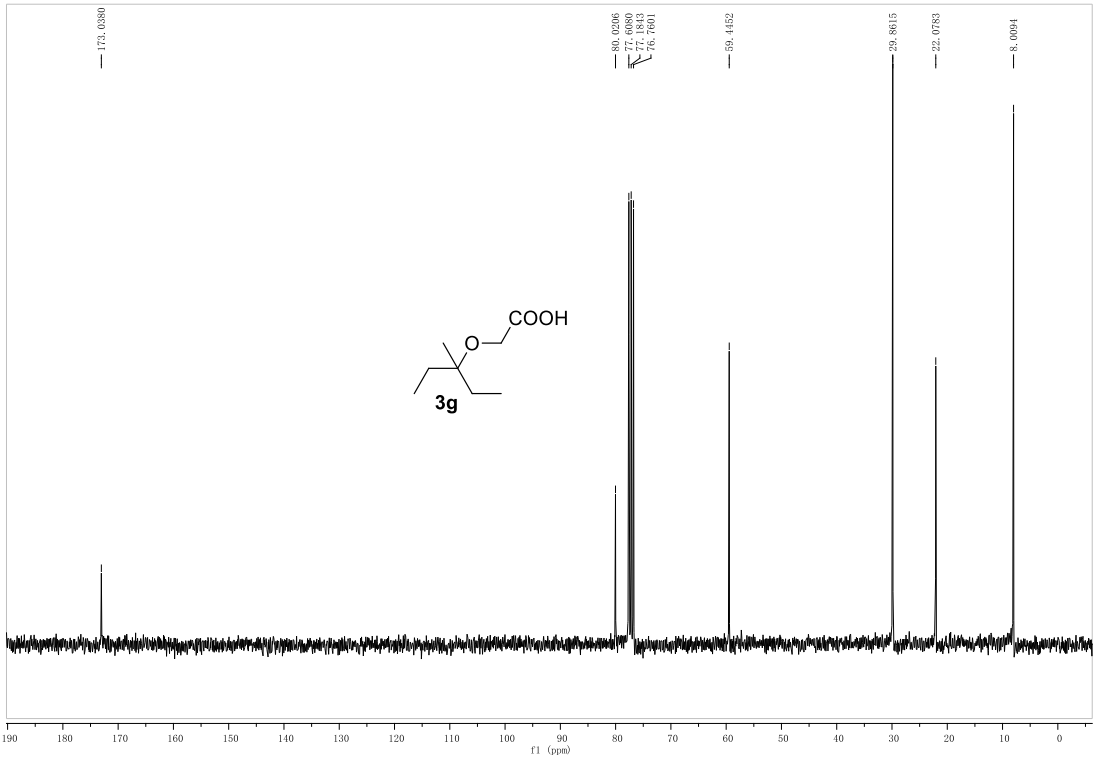

8.8318
7.2687
4.1397
3.5301
3.5067
3.4833
3.4599
3.4275
3.4142
3.3969
3.3843
3.3664
3.3539
1.9561
1.9356
1.9194
1.7499
1.5274
1.4108
1.3776
1.3447
1.3106
1.2960
1.2534
1.2352
1.2234
1.2149
1.1884
O
COOH
3e
1.2313
2.0000
1.2650
2.0369
2.0187
1.0698
5.4037
f1 (ppm)

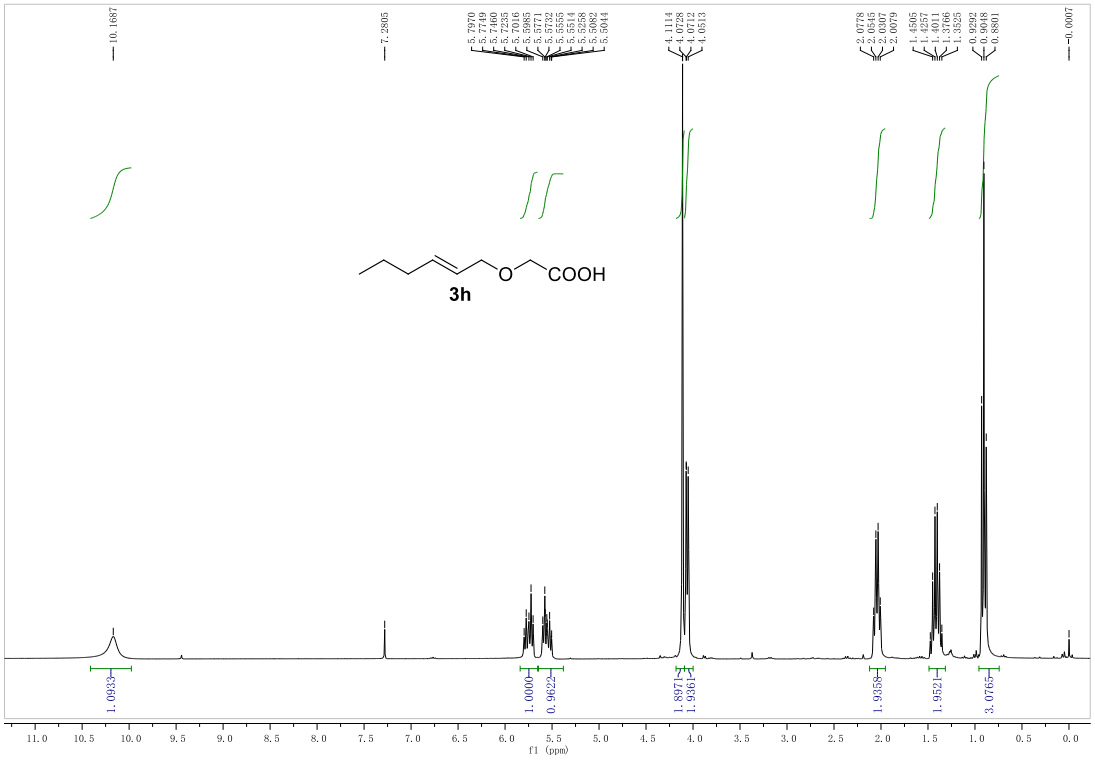

174.1312
79.1786
77.3853
77.1614
76.7374
65.2018
31.9733
25.6304
24.9285
O
COOH
3e
f1 (ppm)

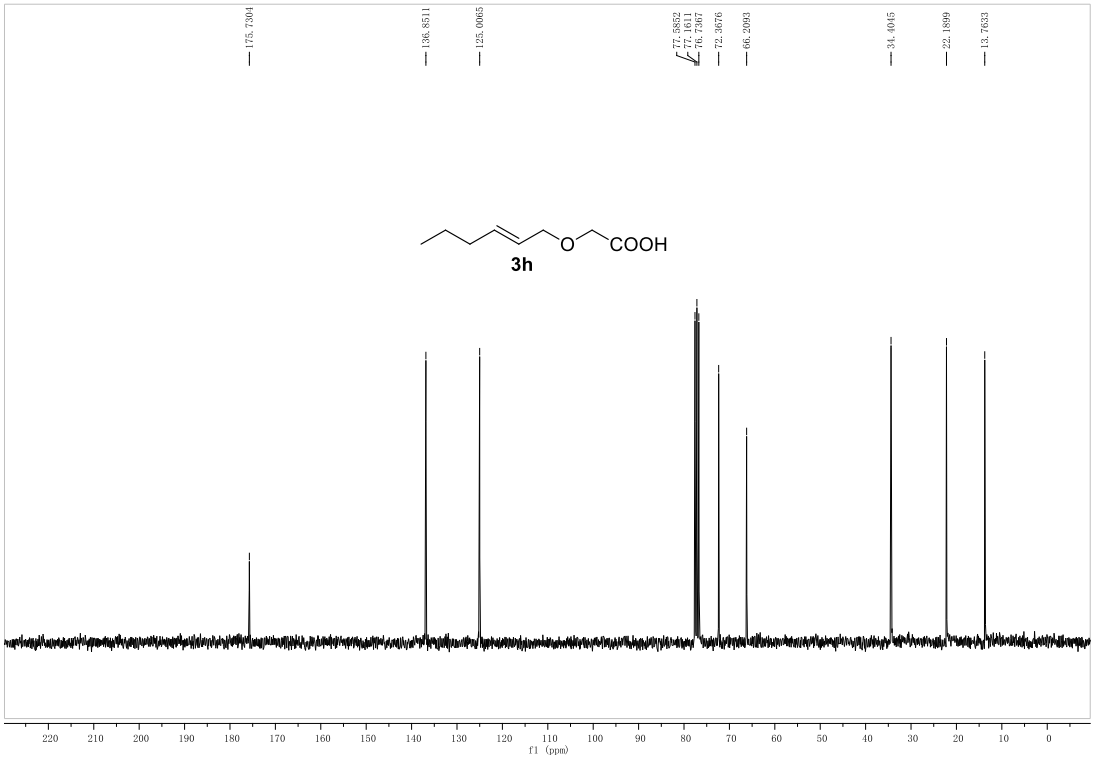

9.0353
7.2690
4.0820
4.0663
4.0504
4.0399
4.0212
1.7883
1.7590
1.7428
1.7355
1.7081
1.6946
1.6625
1.6347
1.6120
1.5906
1.5800
1.5611
1.5468
1.5290
1.5081
O
COOH
3f
0.9981
2.0000
1.0123
6.1126
2.0114
f1 (ppm)

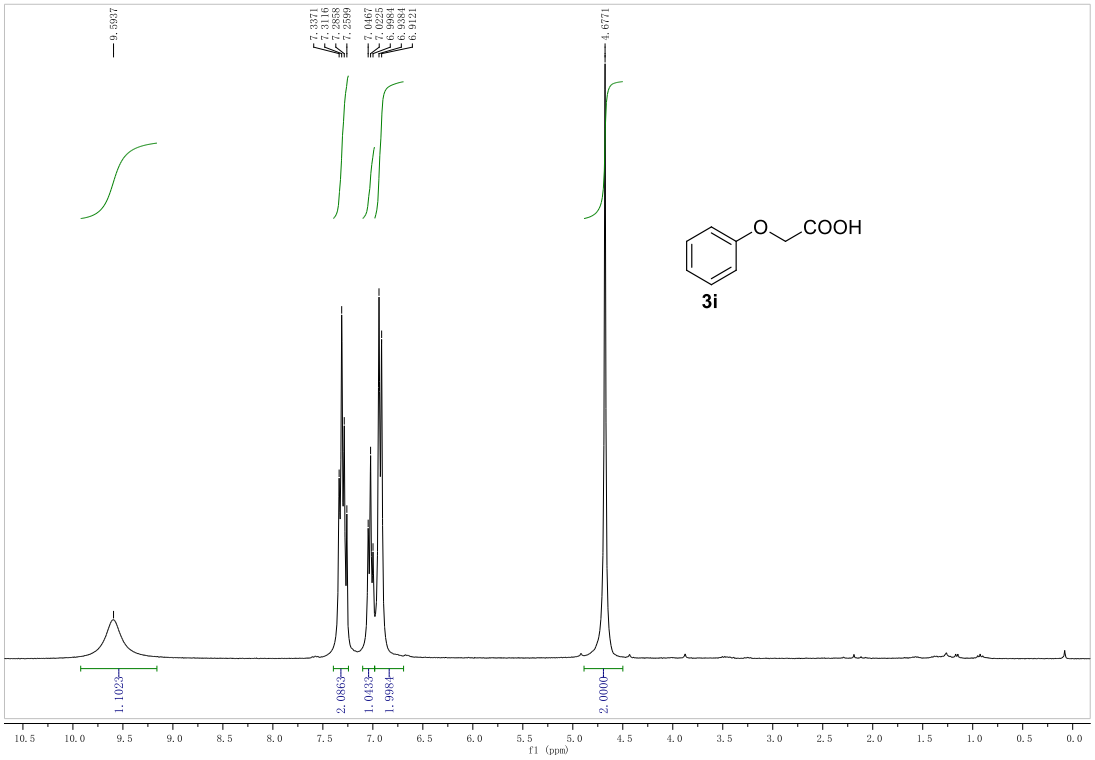

174.3293
83.0431
77.5915
77.1676
76.7436
66.0366
32.2275
23.5291
O
COOH
3f
f1 (ppm)

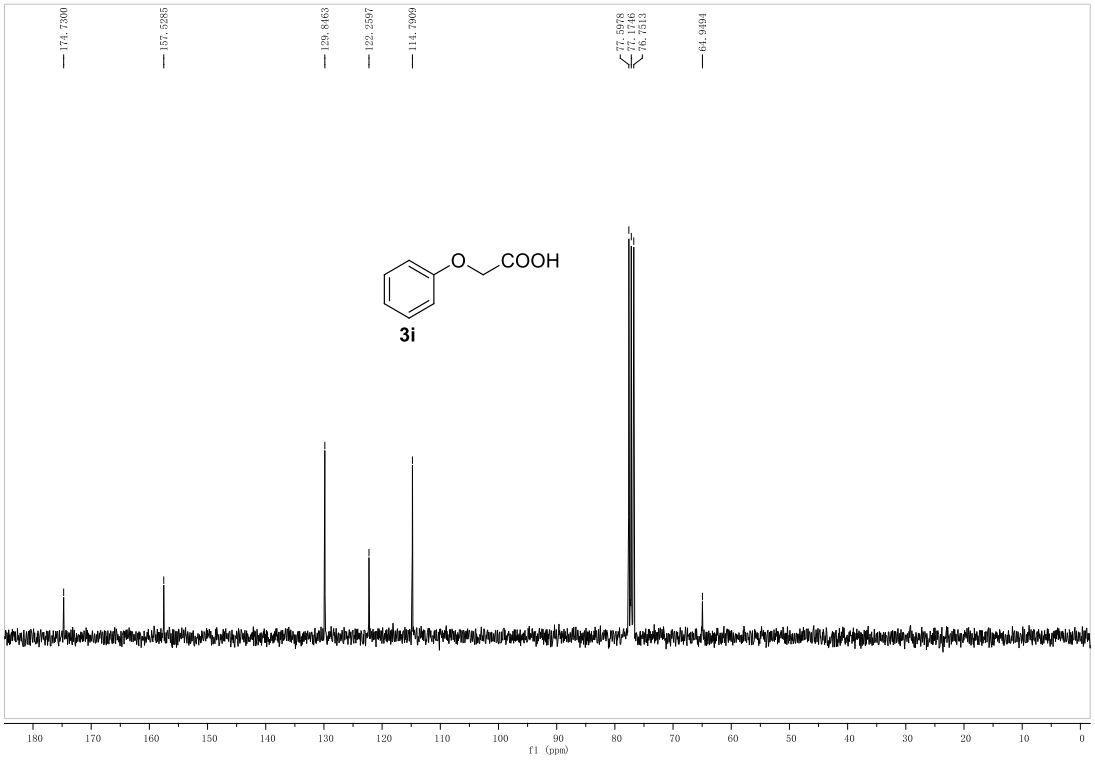

8.9413
7.2636
3.9616
1.5598
1.5355
1.5116
1.4867
1.1370
0.8815
0.8567
0.8316
COOH
O
3g
1.0044
2.0000
4.0363
3.0388
6.0555
f1 (ppm)

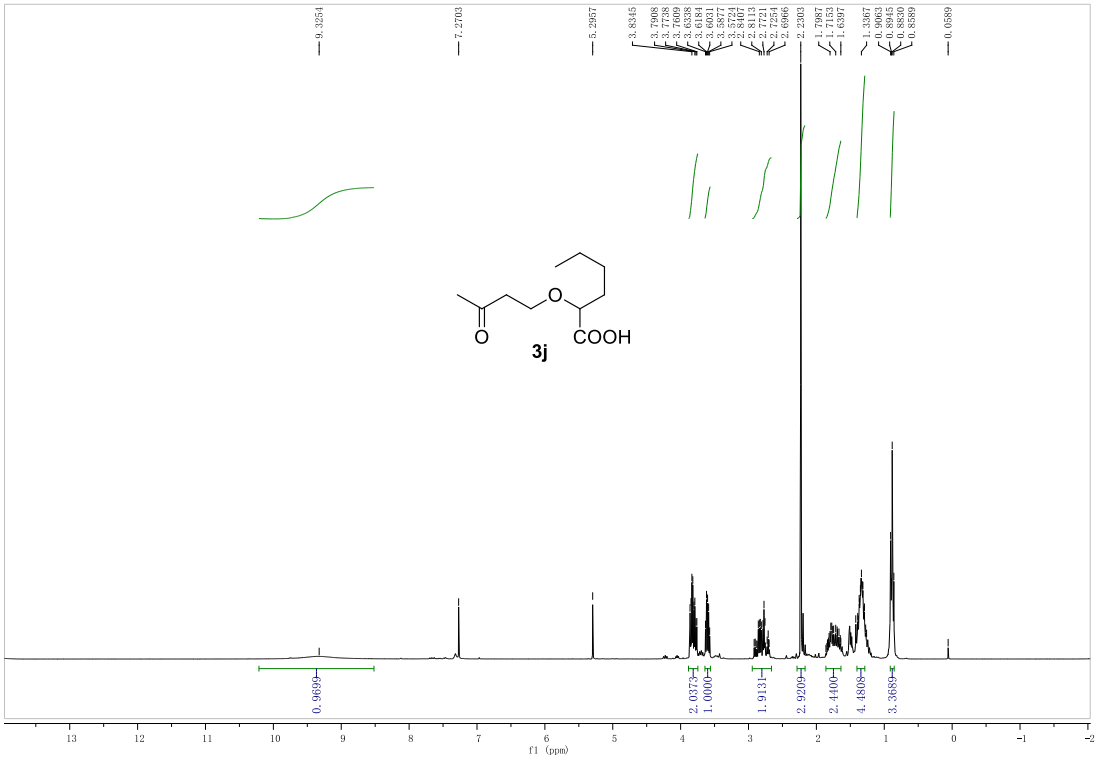

173.0380
80.0206
77.6080
77.1843
76.7601
59.4452
29.8615
22.0783
8.0094
COOH
O
3g
f1 (ppm)

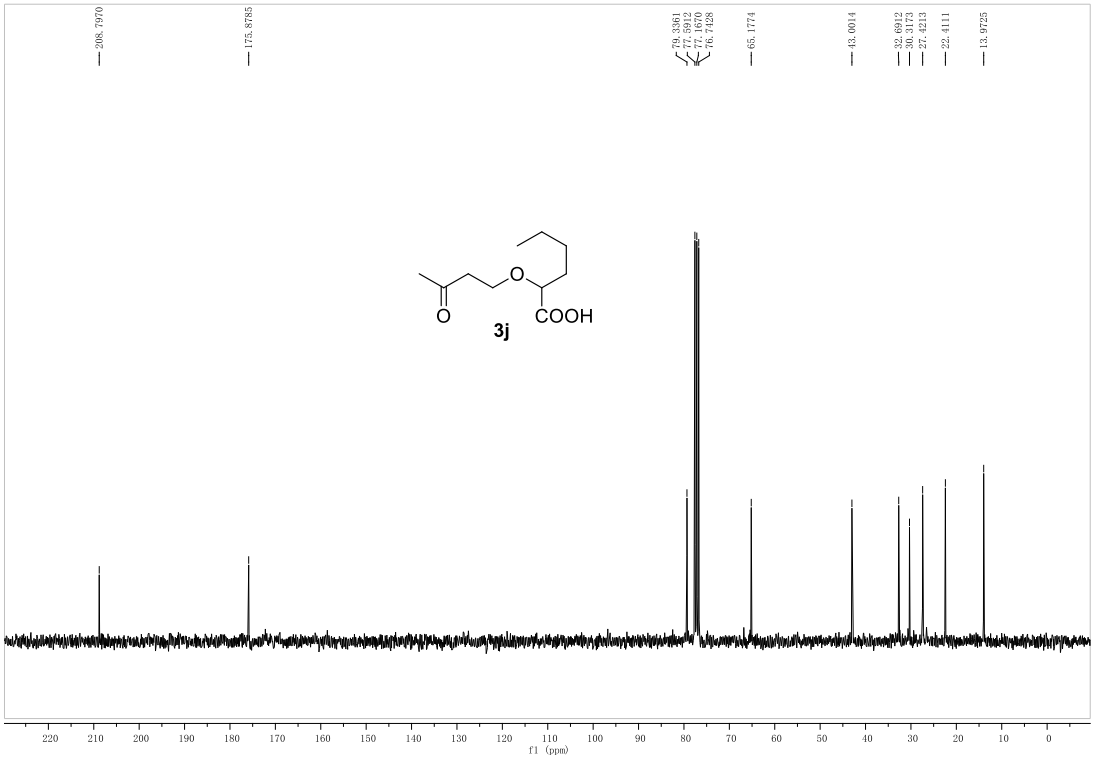

10.1687
7.2805
5.7970
5.7749
5.7460
5.7235
5.7016
5.5985
5.5771
5.5732
5.5555
5.5354
5.5258
5.5082
5.5044
4.1114
4.0728
4.0712
4.0513
2.0778
2.0545
2.0307
2.0079
1.4505
1.4257
1.4041
1.3766
1.3525
0.9292
0.9048
0.8801
0.0007
O
COOH
3h
1.0933
1.0000
0.9622
1.8971
1.9361
1.9358
1.9521
3.0765
f1 (ppm)

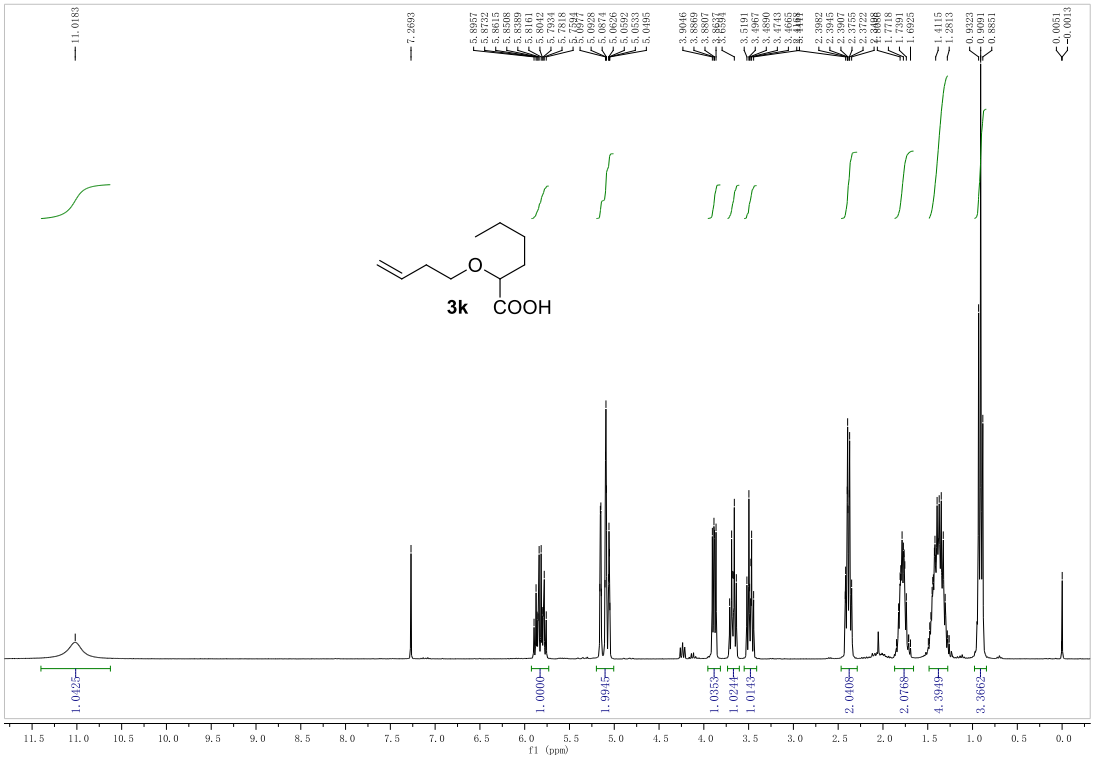

175.7304
136.8511
125.0065
77.5852
77.1611
76.7367
72.3676
66.2093
34.4045
22.1899
13.7633
O
COOH
3h
f1 (ppm)

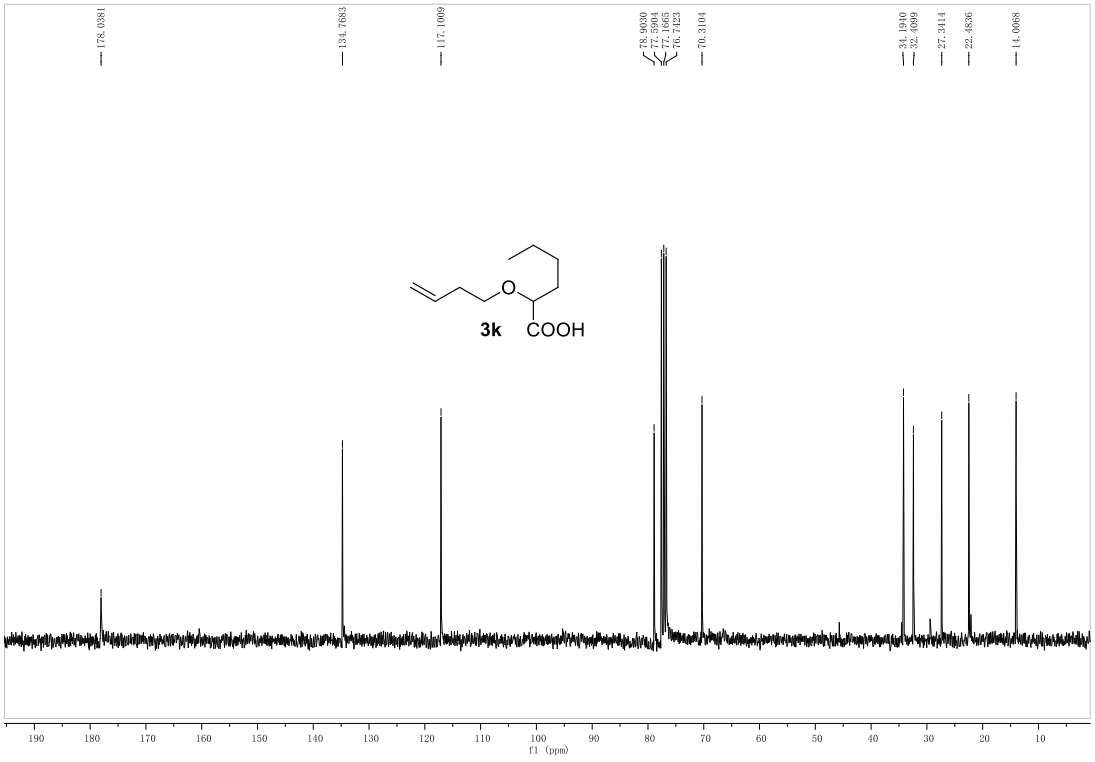

9.5937
7.3371
7.3116
7.2858
7.2599
7.0467
7.0225
6.9984
6.9884
6.9121
4.6771
O
COOH
3i
1.1023
2.0863
1.0433
1.9984
2.0000
f1 (ppm)

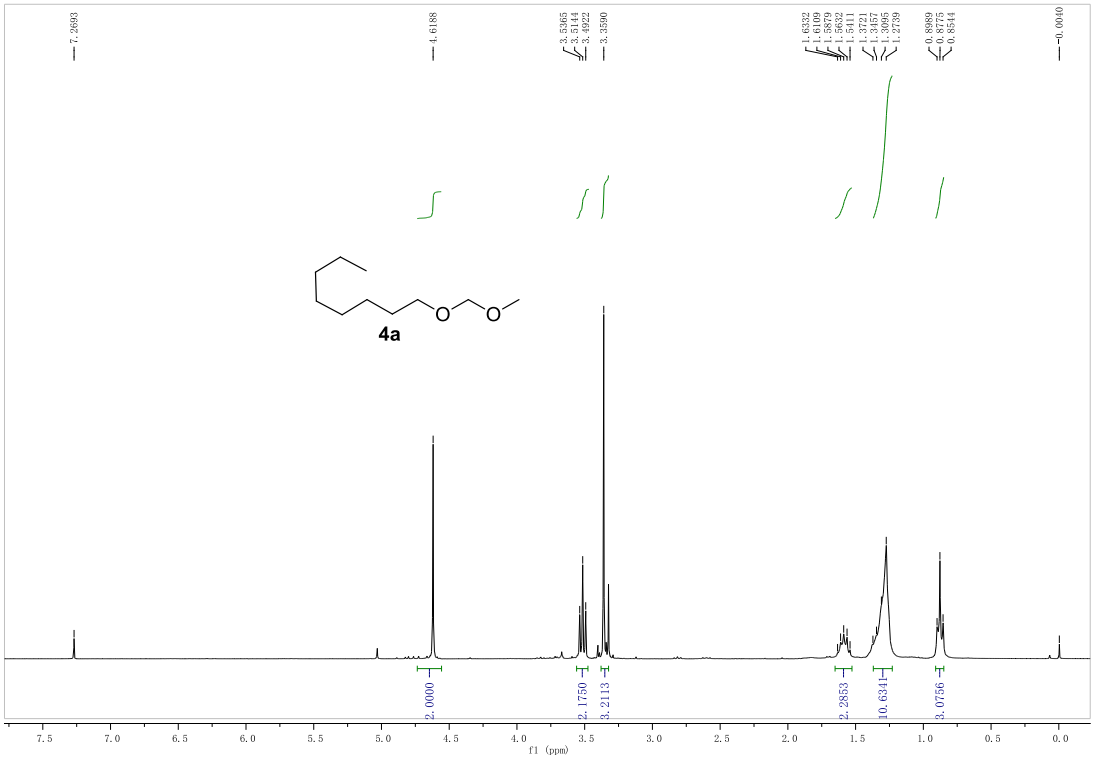

174.7300
157.5285
129.8463
122.2597
114.7909
77.5978
77.1746
76.7513
64.9494
O
COOH
3i
f1 (ppm)

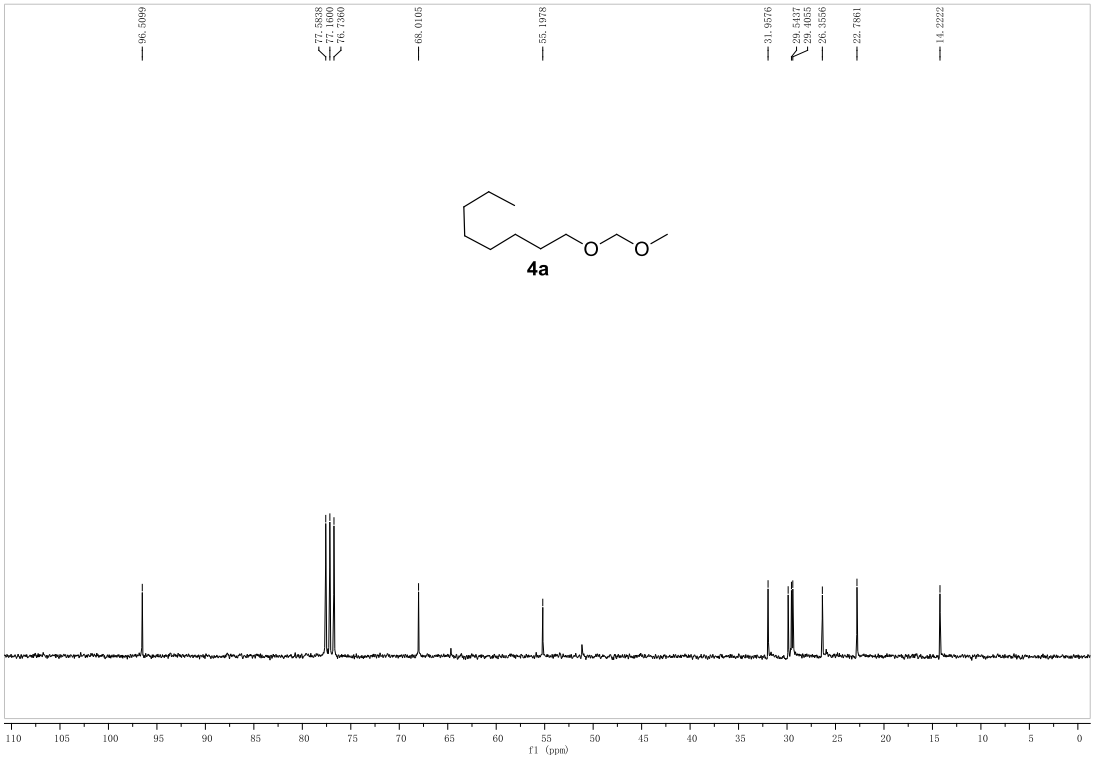

9.3254
7.2703
5.2957
3.8345
3.7908
3.7738
3.7609
3.6538
3.6184
3.6001
3.5877
3.5724
3.5475
2.8113
2.7721
2.7254
2.6966
2.2303
1.7987
1.7153
1.6397
1.3367
0.9065
0.8945
0.8830
0.8589
0.0589
O
O
COOH
3j
0.9699
2.0373
1.0000
1.9131
2.9209
2.4400
4.4808
3.3689
f1 (ppm)

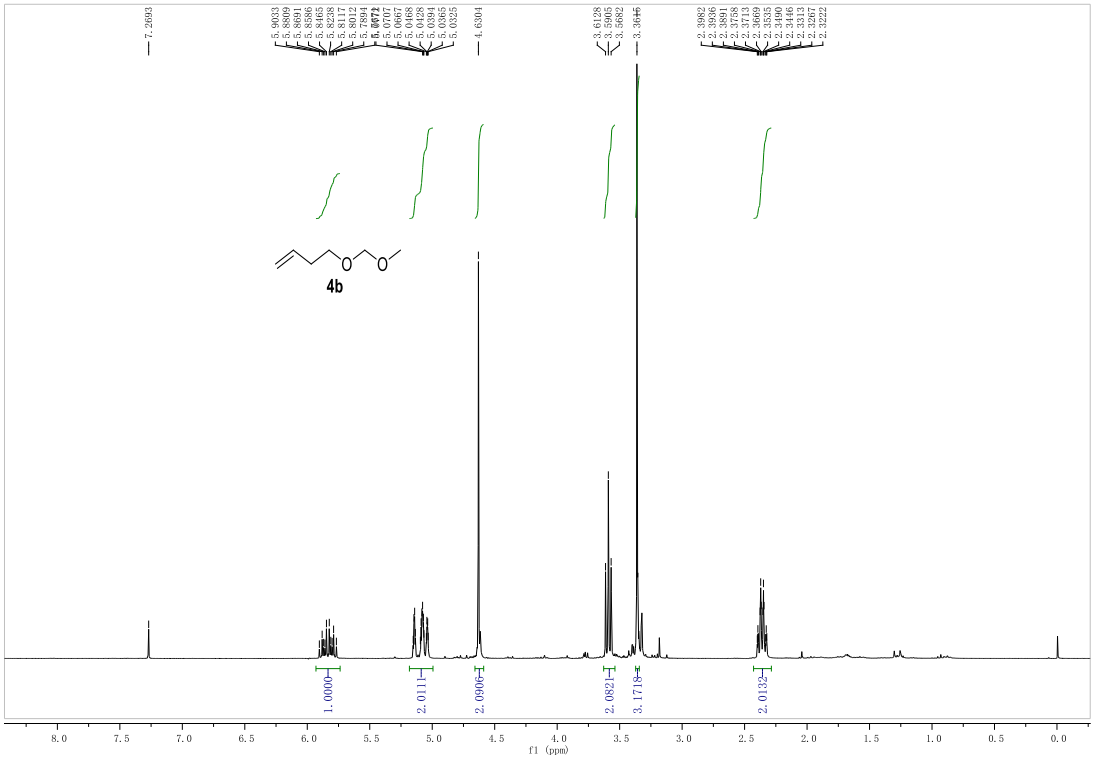

208.7970
175.8785
79.3361
77.3912
77.1800
76.7428
65.1774
43.0014
32.6912
30.3173
27.4213
22.4111
13.9725
O
O
COOH
3j
f1 (ppm)

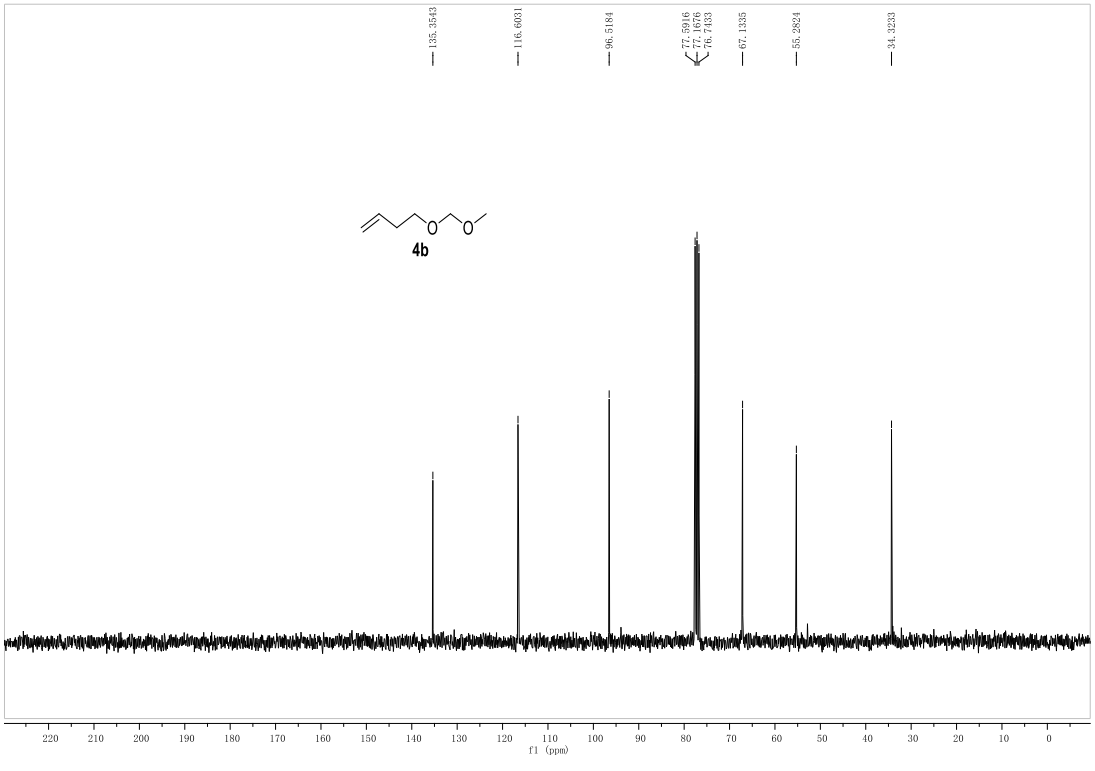

11.0183
7.2693
5.8957
5.8732
5.8615
5.8508
5.8389
5.8310
5.8042
5.7934
5.7818
5.0974
5.0928
5.0874
5.0695
5.0592
5.0533
5.0495
3.9046
3.8889
3.8807
3.8654
3.8594
3.5191
3.4967
3.4896
3.4743
3.4665
2.3982
2.3945
2.3907
2.3755
2.3722
1.7718
1.7391
1.6925
1.4115
1.2813
0.9323
0.9091
0.8851
0.0051
-0.0013
3k
COOH
1.0425
1.0000
1.9945
1.0353
1.0244
1.0143
2.0408
2.0768
4.3949
3.3662
f1 (ppm)

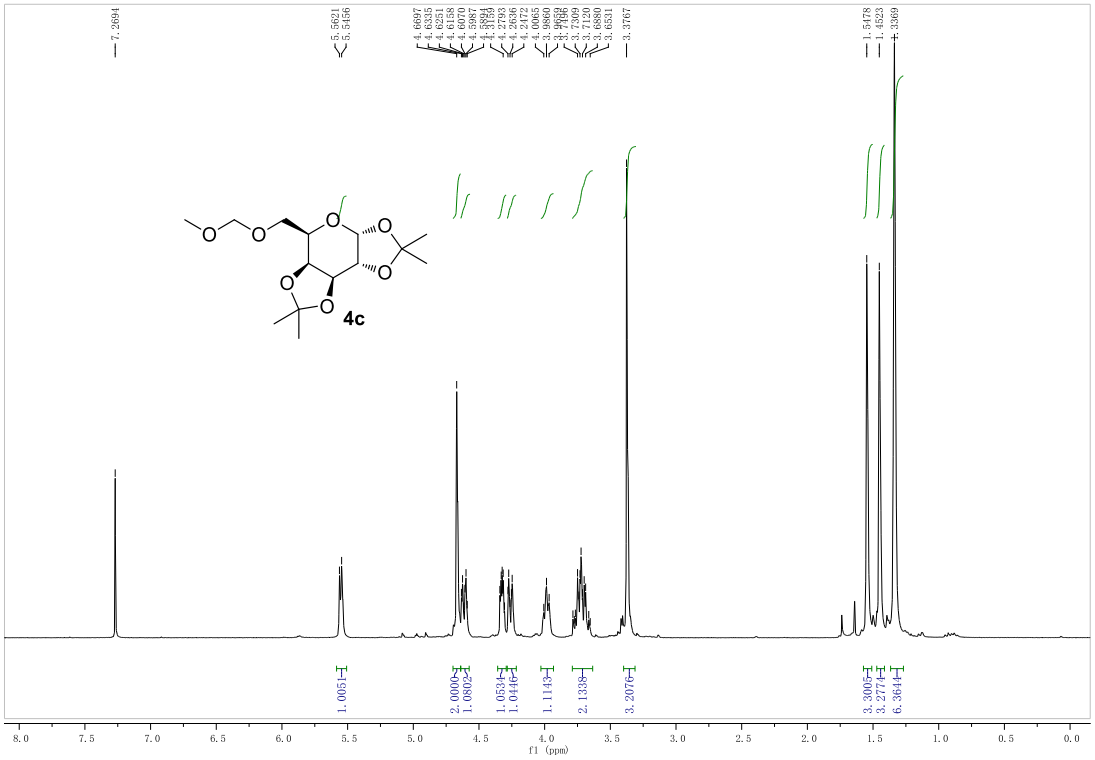

178.0381
134.7683
117.1009
78.9830
77.3904
77.1665
76.7423
70.3104
34.1940
32.4099
27.3414
22.4836
14.0068
3k
COOH
f1 (ppm)

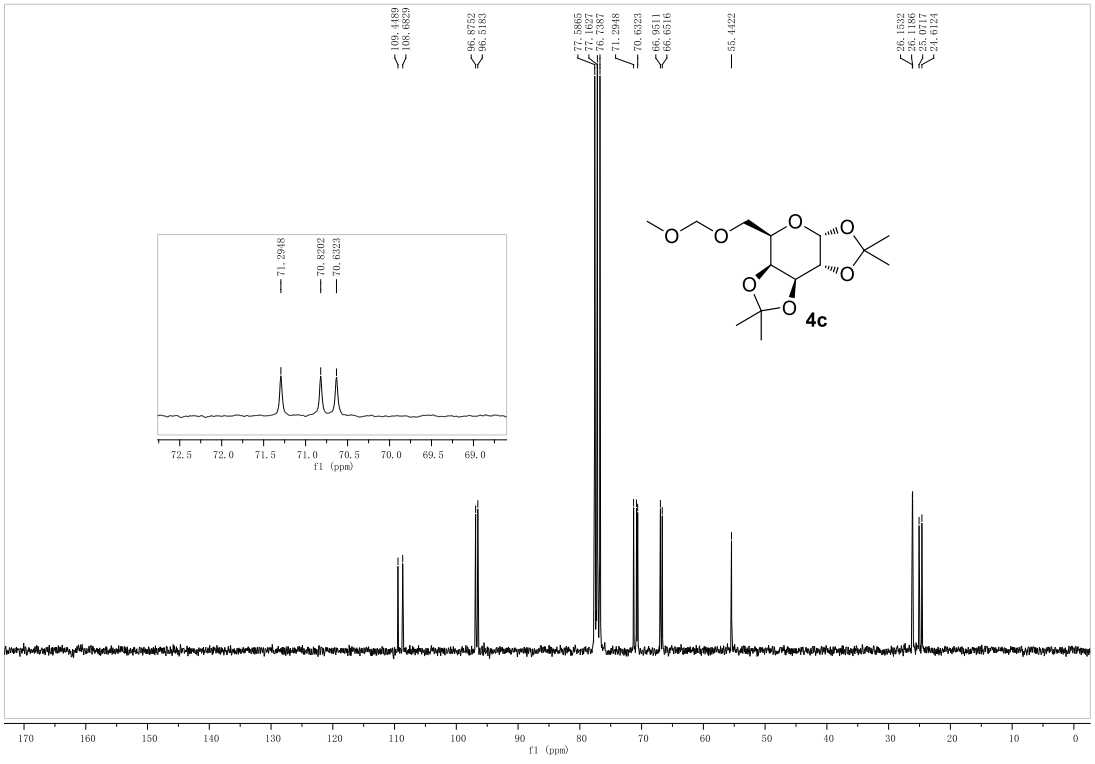

7.2693
4.6188
3.5365
3.5144
3.4922
3.3590
1.6332
1.6109
1.5879
1.5632
1.5411
1.3721
1.3457
1.3095
1.2739
0.8989
0.8775
0.8544
0.0040
4a
2.0000
2.1750
3.2113
2.2853
10.6341
3.0756
f1 (ppm)

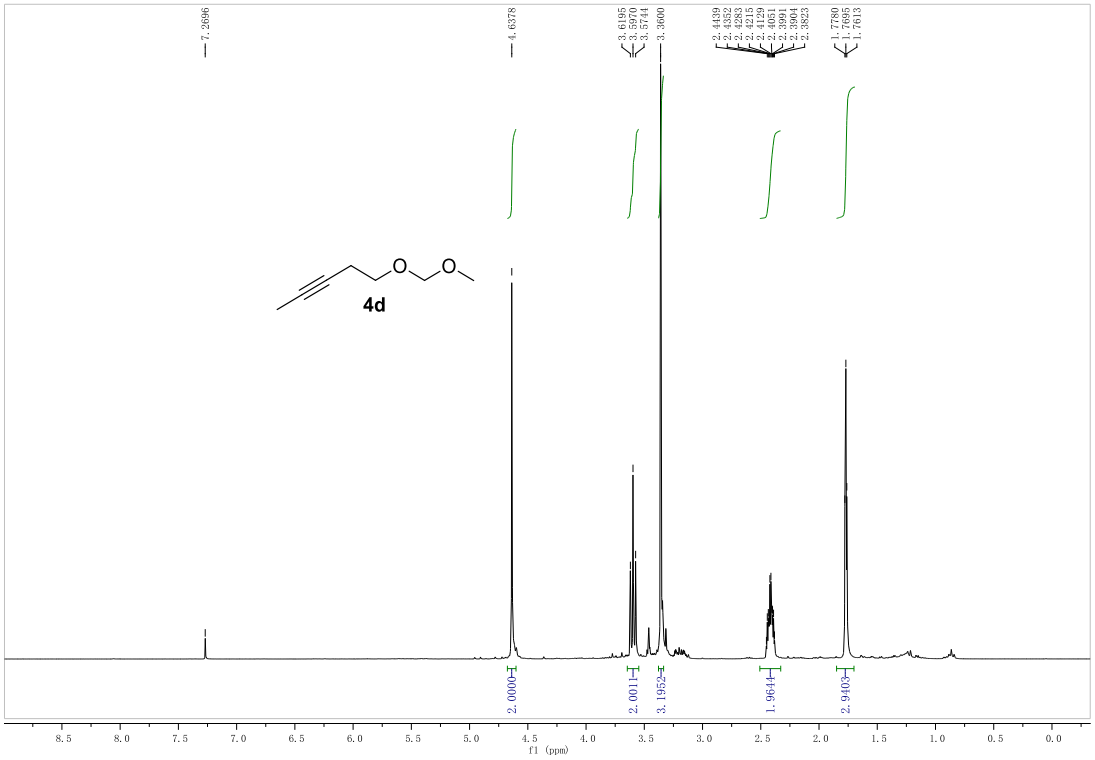

96.5099
77.5838
77.1600
76.7360
68.0105
55.1978
31.9576
29.5437
29.4055
26.3556
22.7861
14.2222
4a
f1 (ppm)

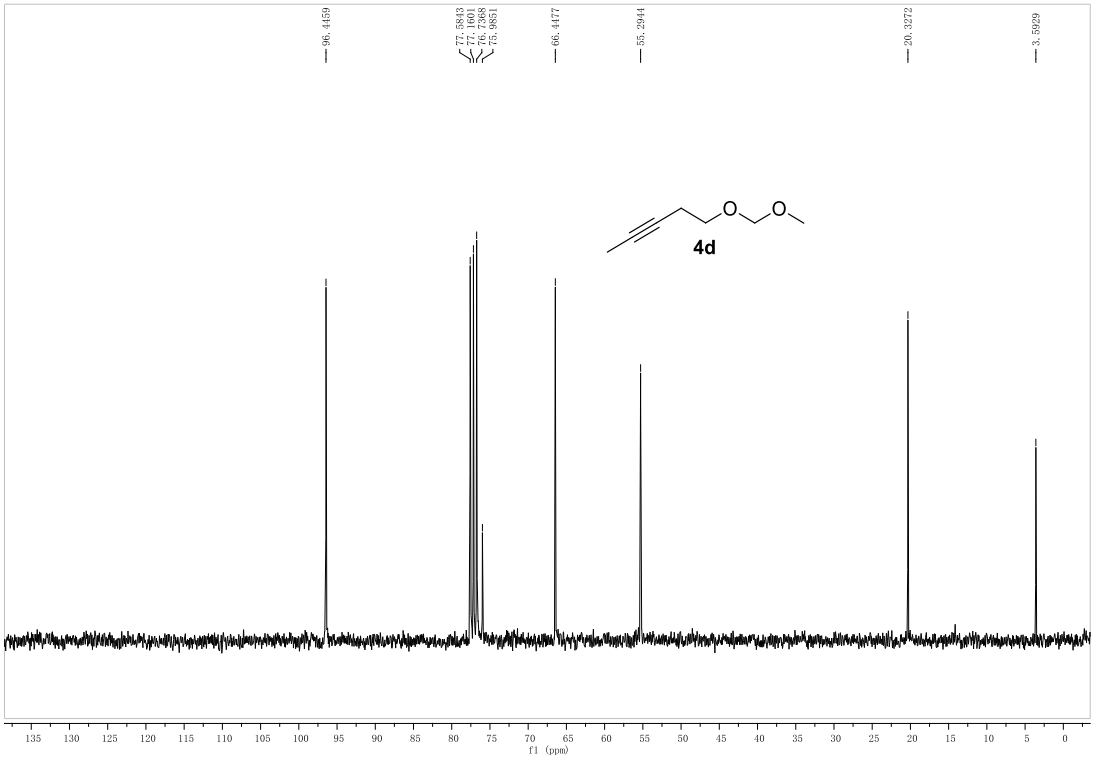

7.2693
5.9033
5.8809
5.8691
5.8586
5.8455
5.8228
5.8117
5.8012
5.7894
5.7707
5.7677
5.0667
5.0468
5.0428
5.0394
5.0365
5.0325
4.6304
3.6128
3.5905
3.5682
3.3646
2.3982
2.3806
2.3691
2.3758
2.3713
2.3669
2.3535
2.3490
2.3446
2.3313
2.3267
2.3222
4b
1.0000
2.0111
2.0906
2.0821
3.1718
2.0132
f1 (ppm)

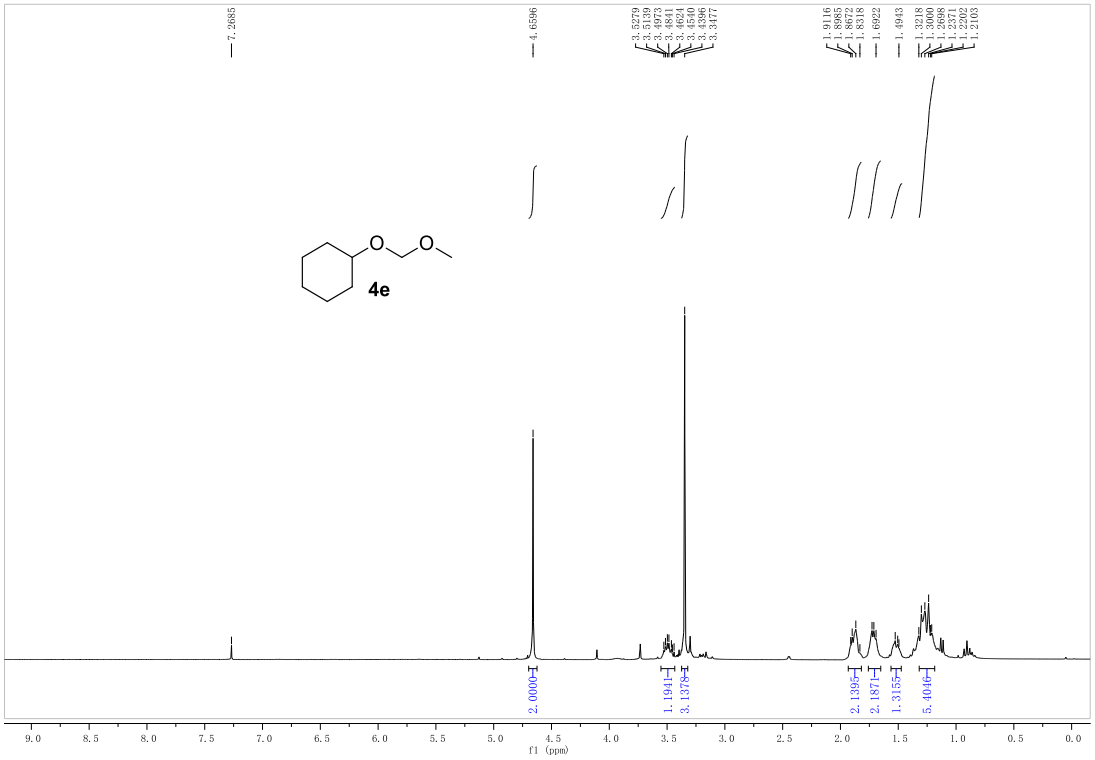

135.3543
116.6031
96.5184
77.5916
77.1795
76.7433
67.1335
55.2824
34.3233
4b
f1 (ppm)

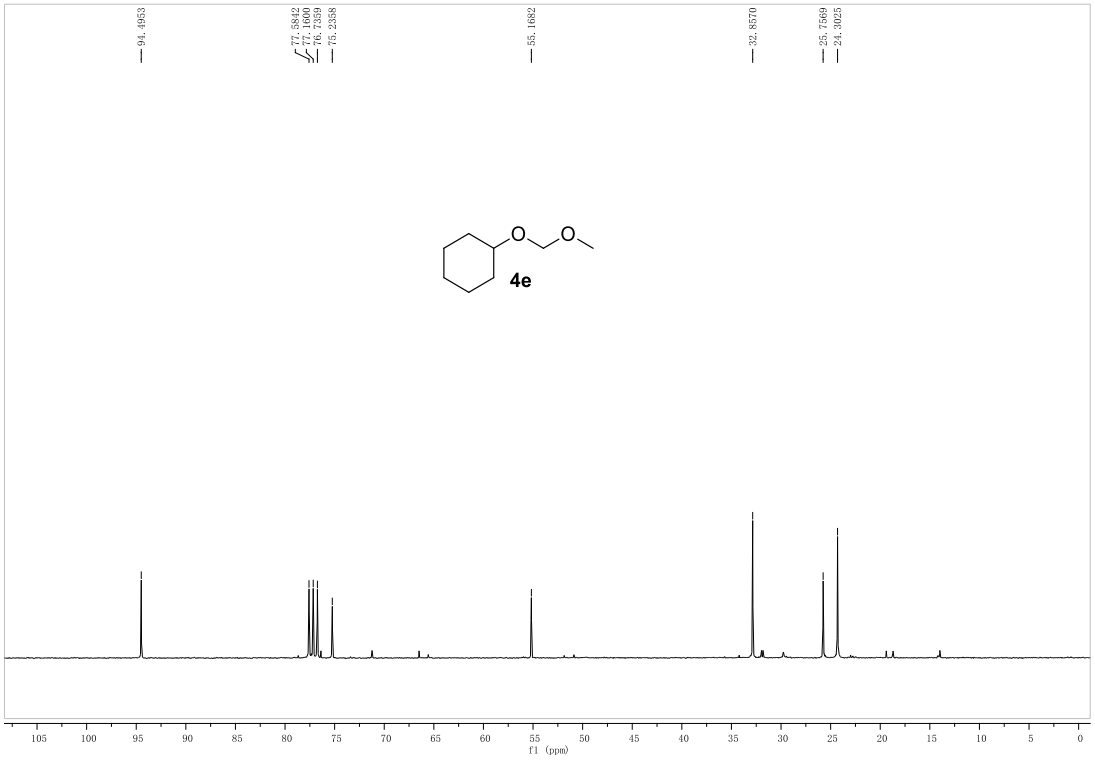

7.2694
5.5621
5.5486
4.6697
4.6335
4.6251
4.6158
4.6070
4.5985
4.3894
4.3759
4.3733
4.2636
4.2472
4.0065
3.9860
3.9698
3.9496
3.7309
3.7130
3.6880
3.6531
3.3767
1.5478
1.4523
1.3369
4c
1.0051
2.0000
1.0802
1.0534
1.0446
1.1143
2.1338
3.2076
3.3005
3.2774
6.3644
f1 (ppm)

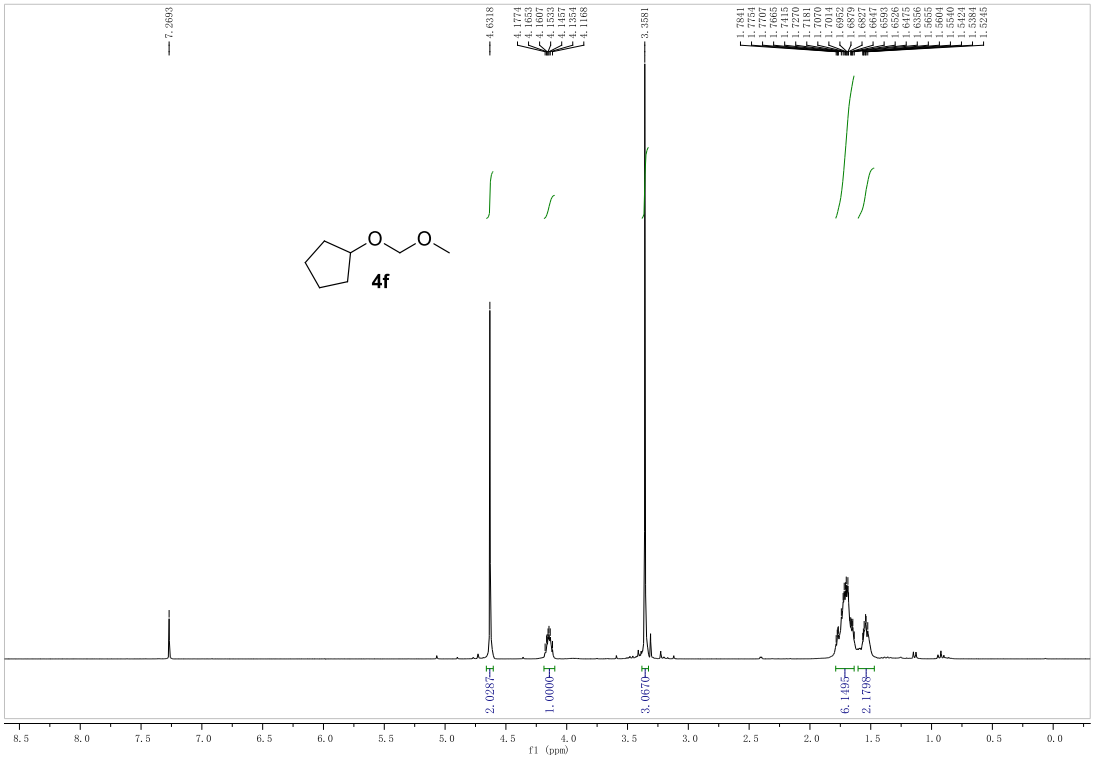

109.4489
108.6829
96.8752
96.5183
77.5865
77.1627
76.7387
71.2948
70.6323
66.9511
66.6516
55.4422
26.1532
26.1186
25.6717
24.6194
71.2948
70.8202
70.6323
4c
f1 (ppm)

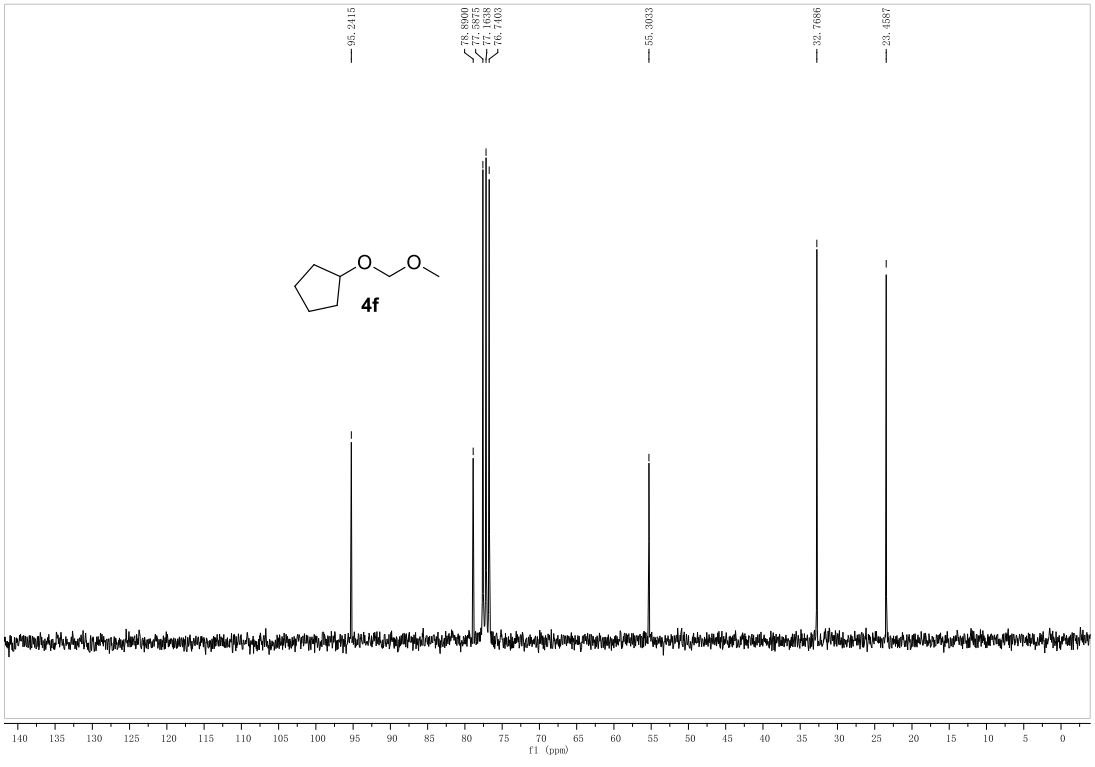

7.2696
4.6378
3.6195
3.5970
3.5744
3.3600
2.4439
2.4352
2.4258
2.4215
2.4129
2.4051
2.3991
2.3944
2.3823
1.7780
1.7695
1.7613
4d
2.0000
2.0011
3.1952
1.9644
2.9403
f1 (ppm)

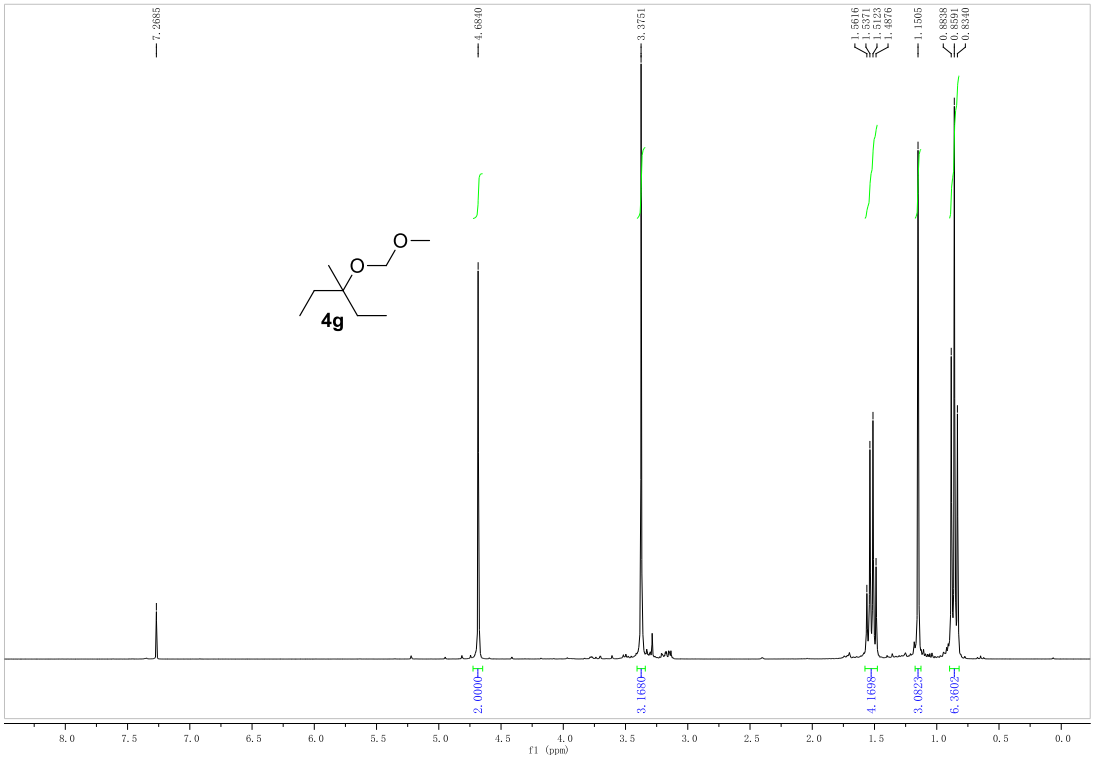

96.4459
77.5843
77.1601
76.7368
75.9851
66.4477
55.2944
20.3272
3.5929
4d
f1 (ppm)

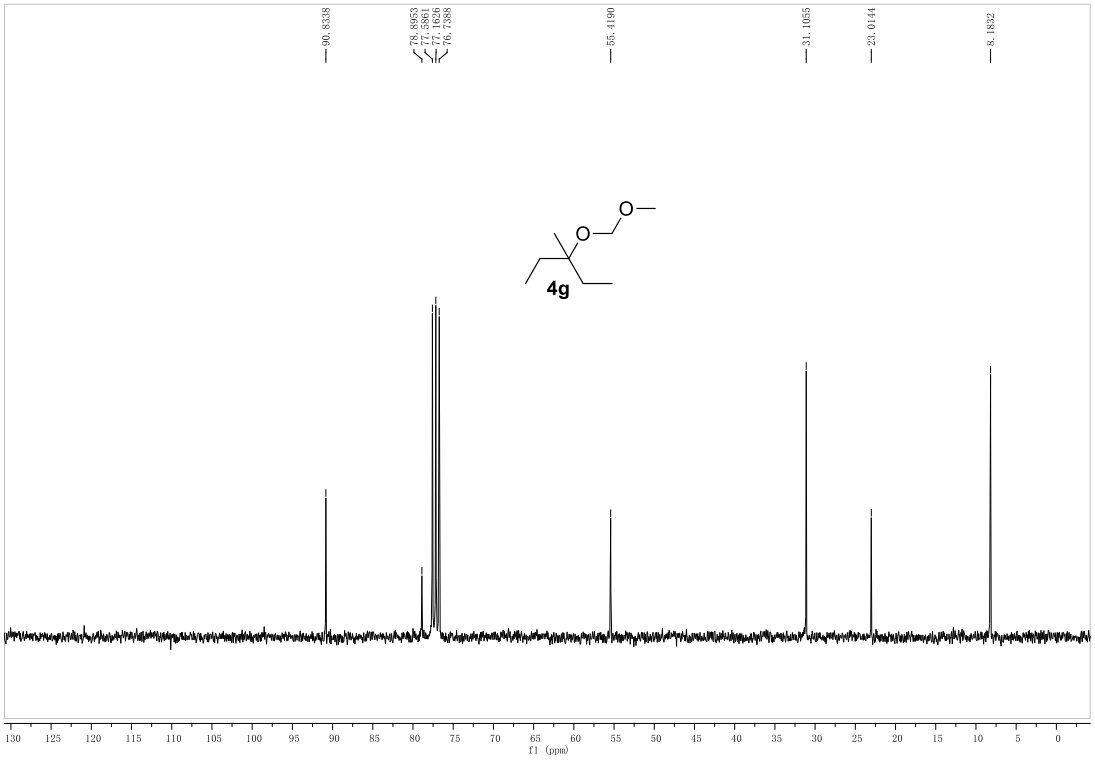

7.2685
4.6596
3.5279
3.5139
3.4973
3.4841
3.4624
3.4540
3.4396
3.3477
1.9116
1.8955
1.8672
1.8318
1.6922
1.4943
1.3218
1.3000
1.2698
1.2371
1.2092
1.2103
4e
2.0000
1.1941
3.1378
2.1395
2.1871
1.3155
5.4046
f1 (ppm)

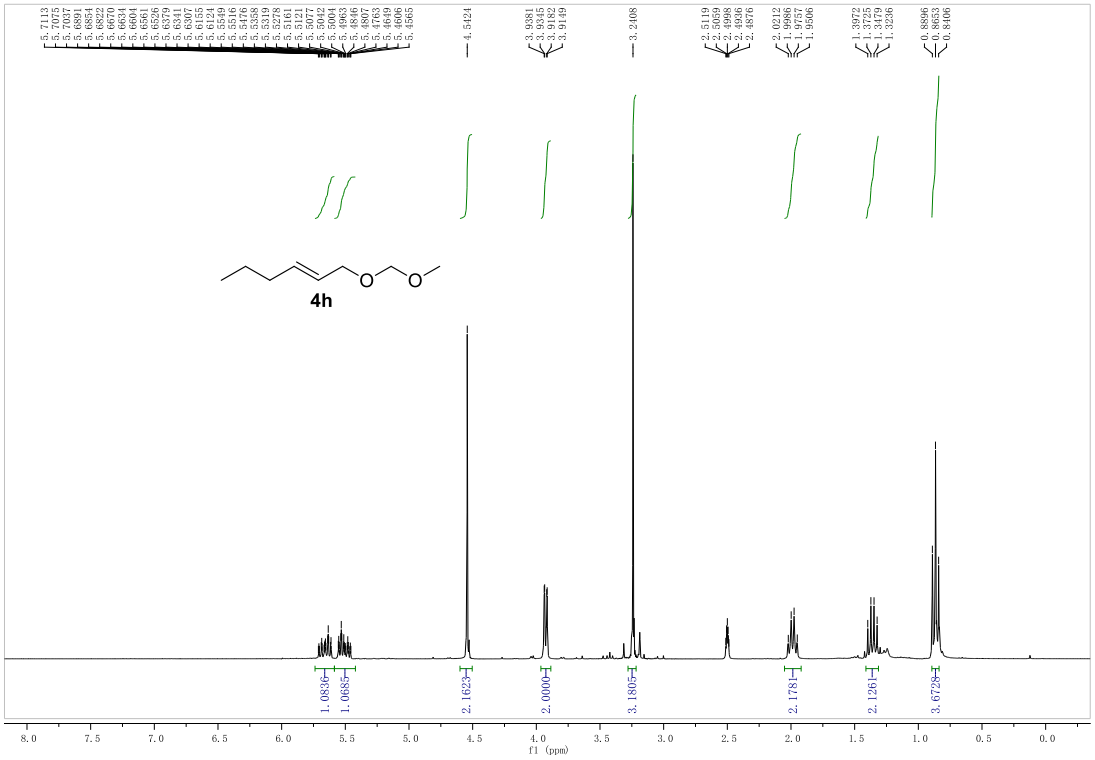

94.4953
77.5842
77.1660
76.7359
75.2358
55.1682
32.8570
25.7569
24.3025
4e
f1 (ppm)

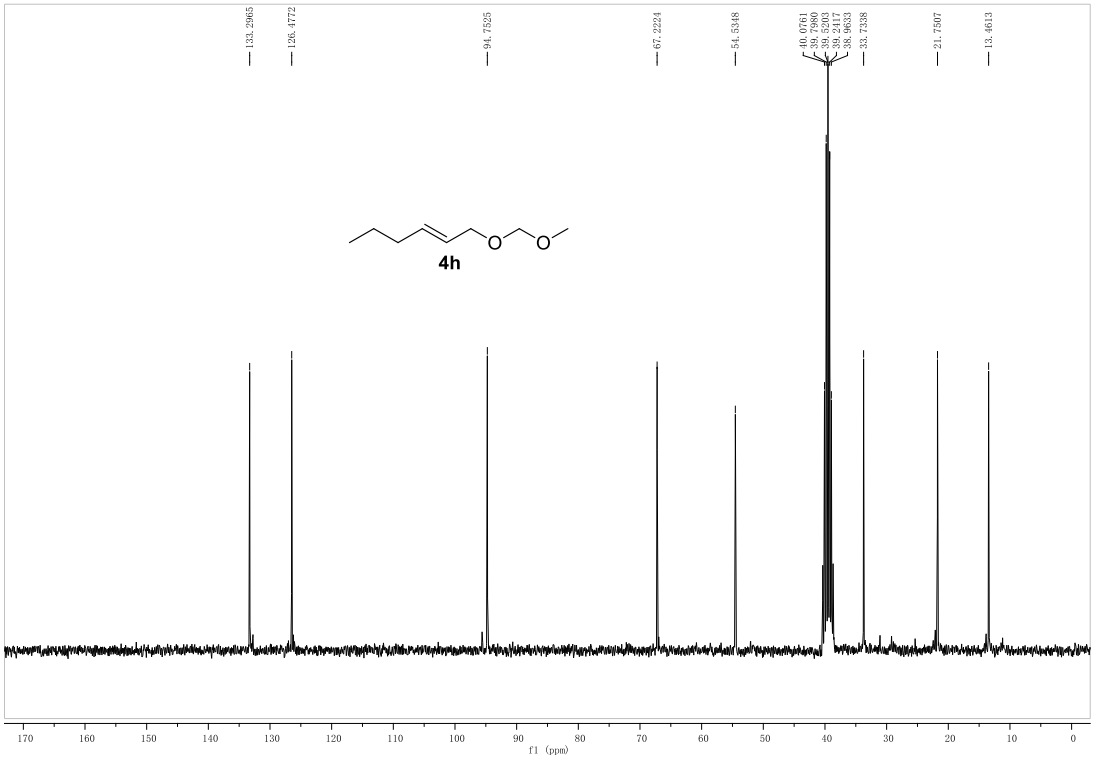

7.2693
4.6318
4.1774
4.1655
4.1607
4.1533
4.1457
4.1354
4.1108
3.3581
1.7841
1.7734
1.7707
1.7665
1.7415
1.7270
1.7181
1.7070
1.7014
1.6952
1.6879
1.6827
1.6647
1.6593
1.6526
1.6475
1.6356
1.5655
1.5604
1.5540
1.5429
1.5384
1.5245
4f
2.0287
1.0000
3.0670
6.1495
2.1798
f1 (ppm)

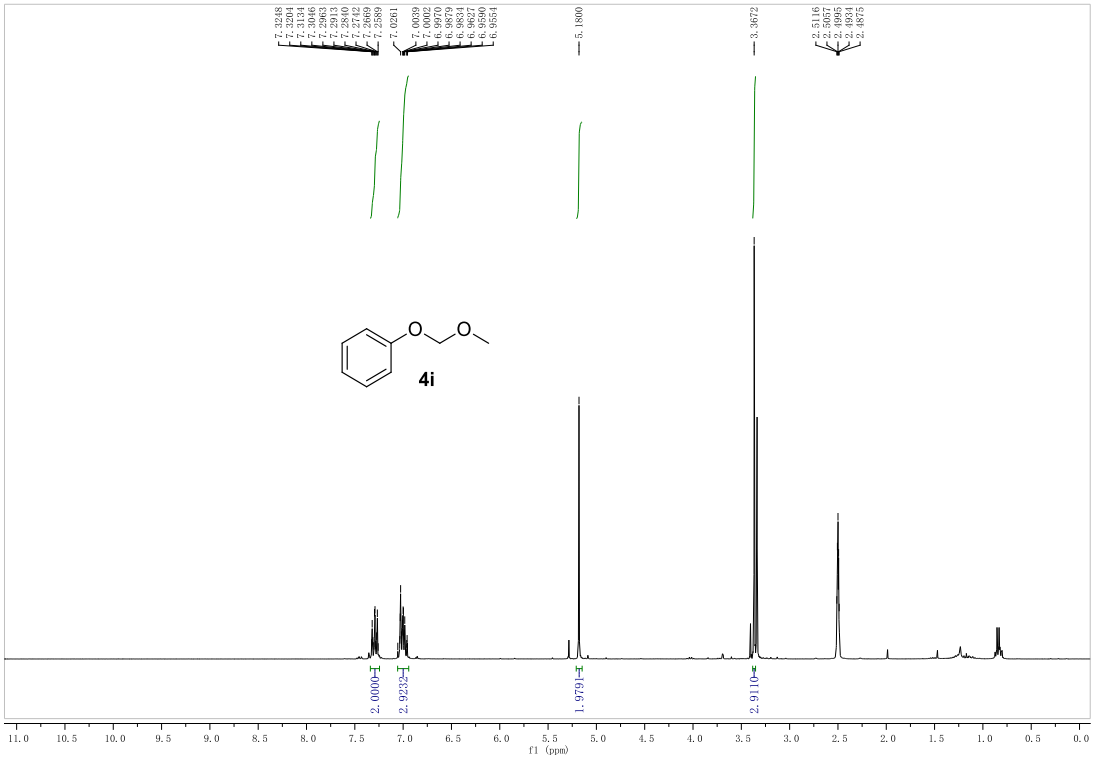

95.2415
78.8900
77.5875
77.1658
76.7403
55.3033
32.7686
23.4587
4f
f1 (ppm)

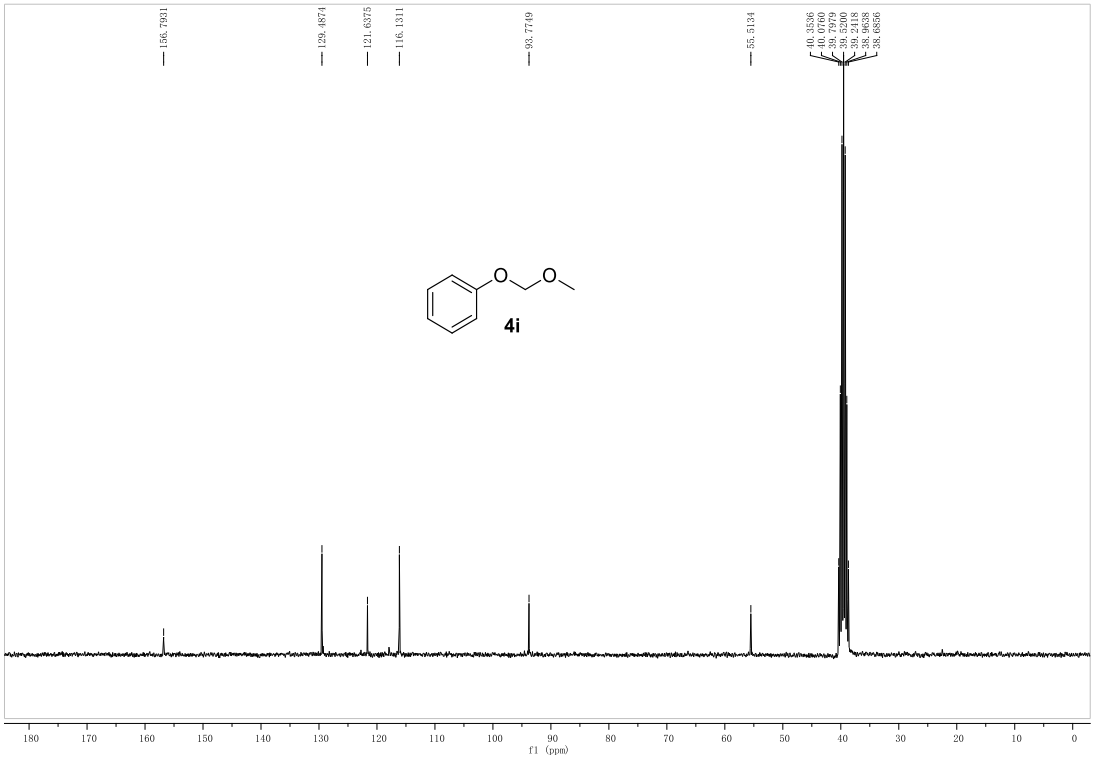

7.2685
4.6840
3.3751
1.5616
1.5371
1.5123
1.4876
1.1505
0.8838
0.8591
0.8340
4g
2.0000
3.1680
4.1699
3.0823
6.3602
f1 (ppm)

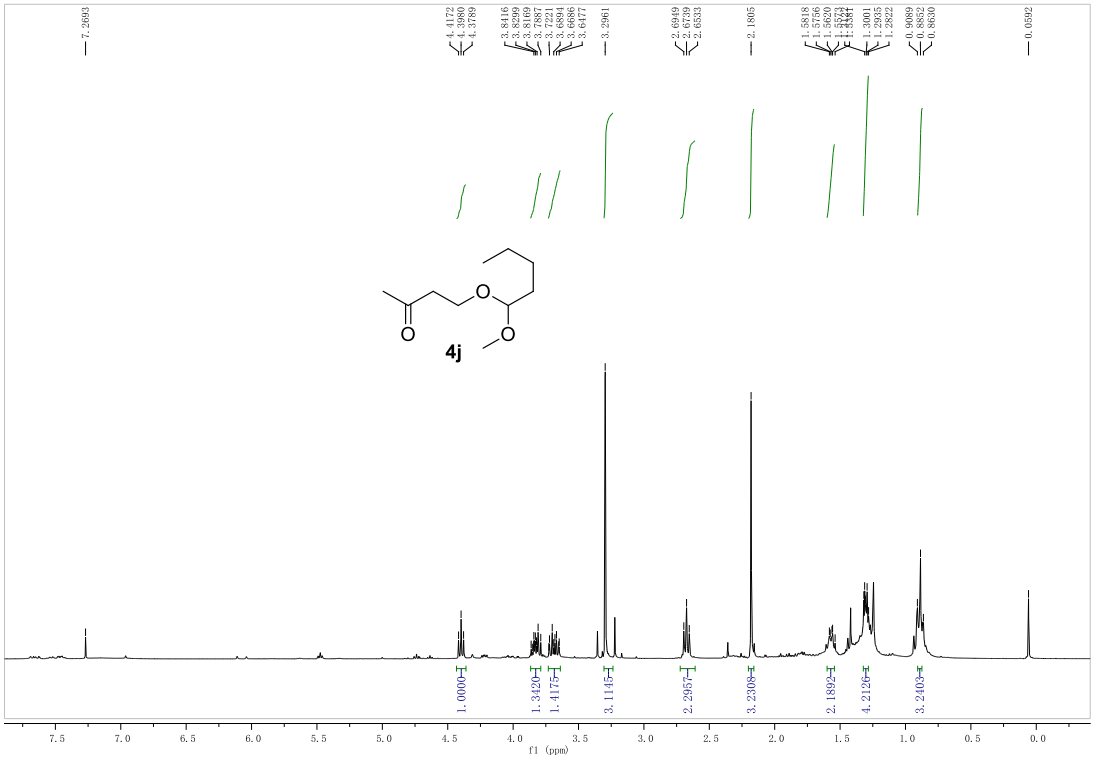

90.8338
78.8953
77.5861
77.1626
76.7388
55.4190
31.1055
23.0144
8.1832
4g
f1 (ppm)

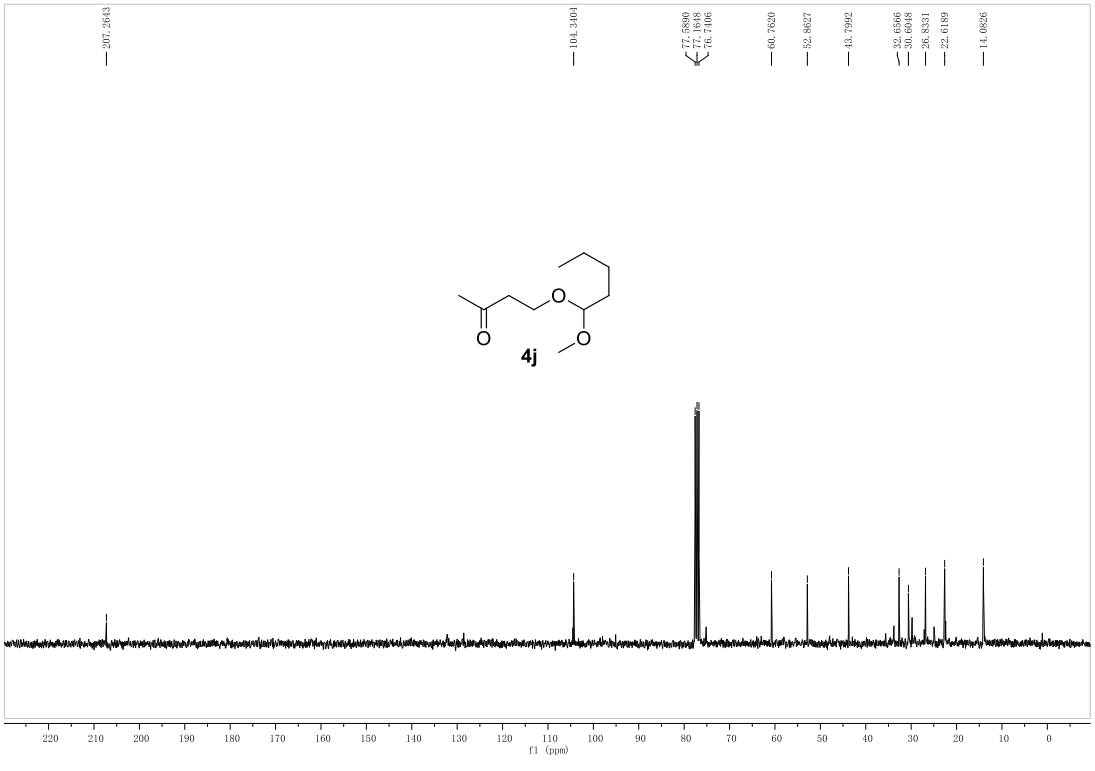

4h
f1 (ppm)

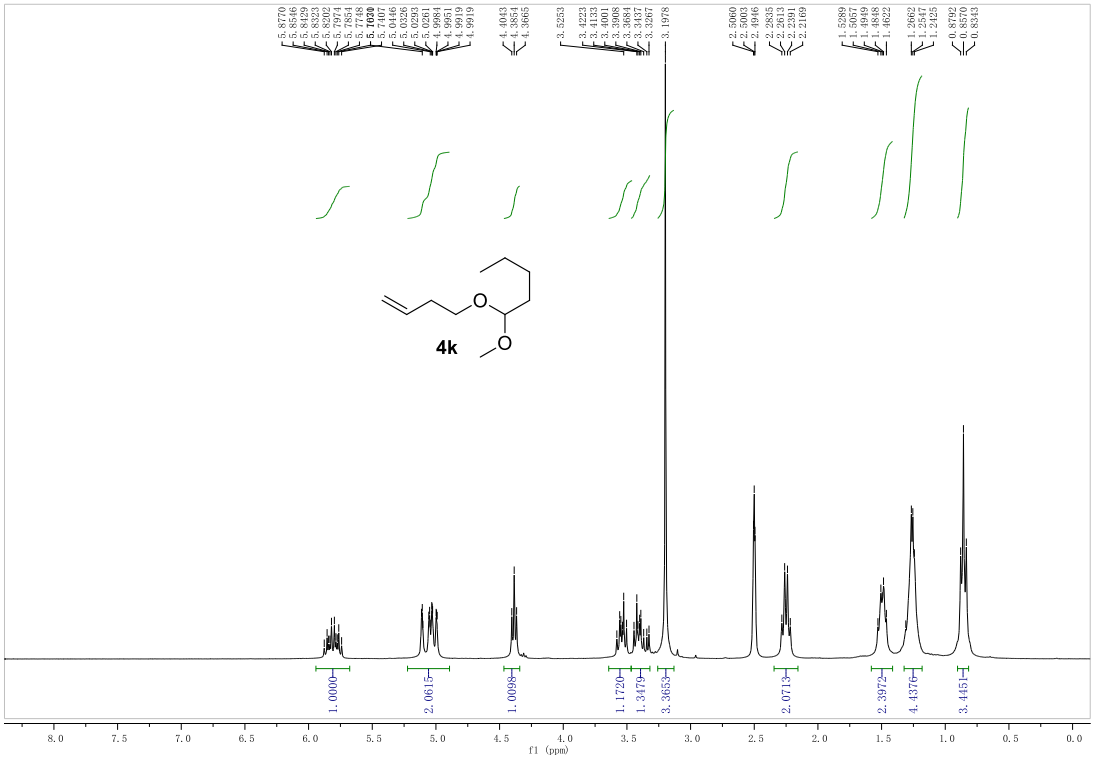

4h
f1 (ppm)

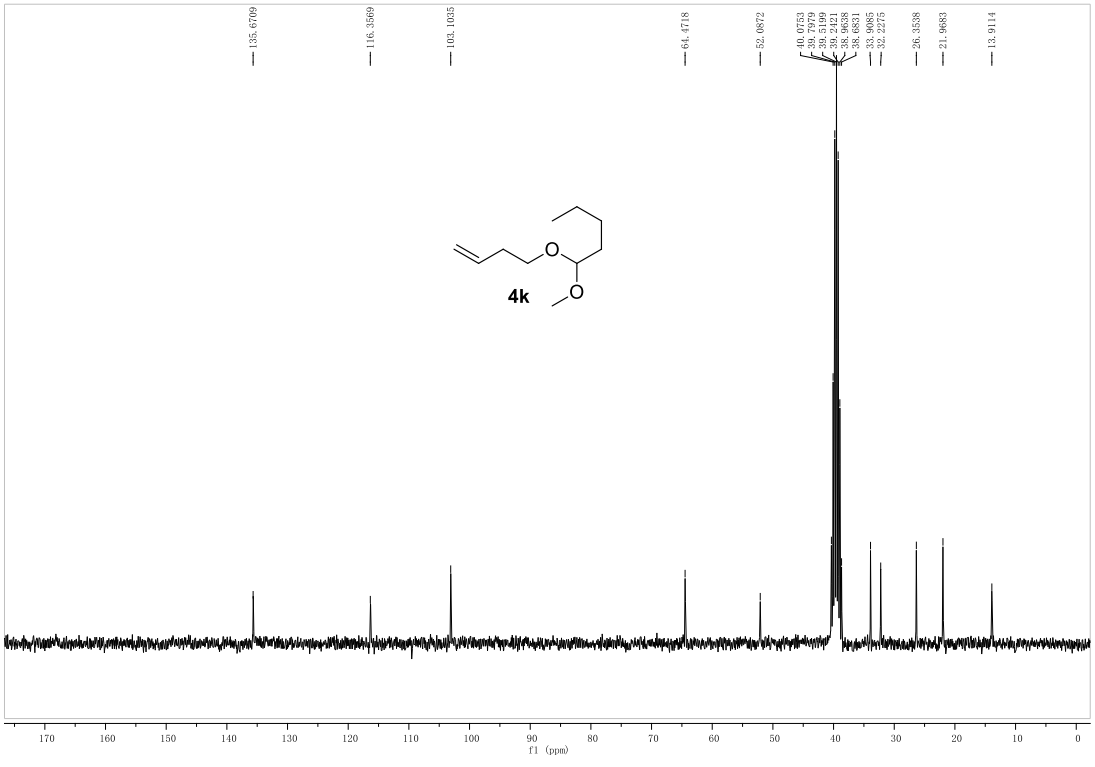

7.3248
7.3204
7.3134
7.3046
7.2963
7.2913
7.2840
7.2742
7.2669
7.2589
7.0261
7.0039
7.0002
6.9970
6.9879
6.9654
6.9627
6.9590
6.9554
5.1800
3.3672
2.5116
2.5057
2.4995
2.4934
2.4875
O
O
4i
2.0000
2.9232
1.9791
2.9110
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

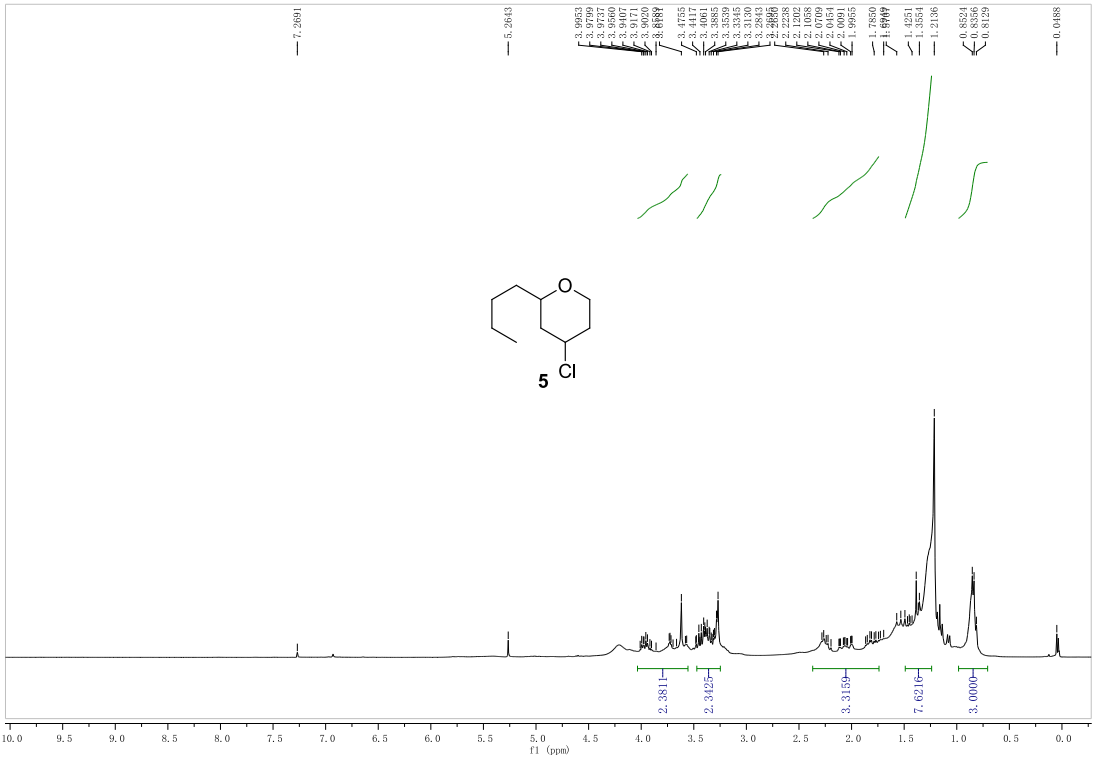

156.7931
129.4874
121.6375
116.1311
93.7749
55.5134
40.3536
40.0760
39.7979
39.5200
39.2418
38.9638
38.6856
O
O
4i
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

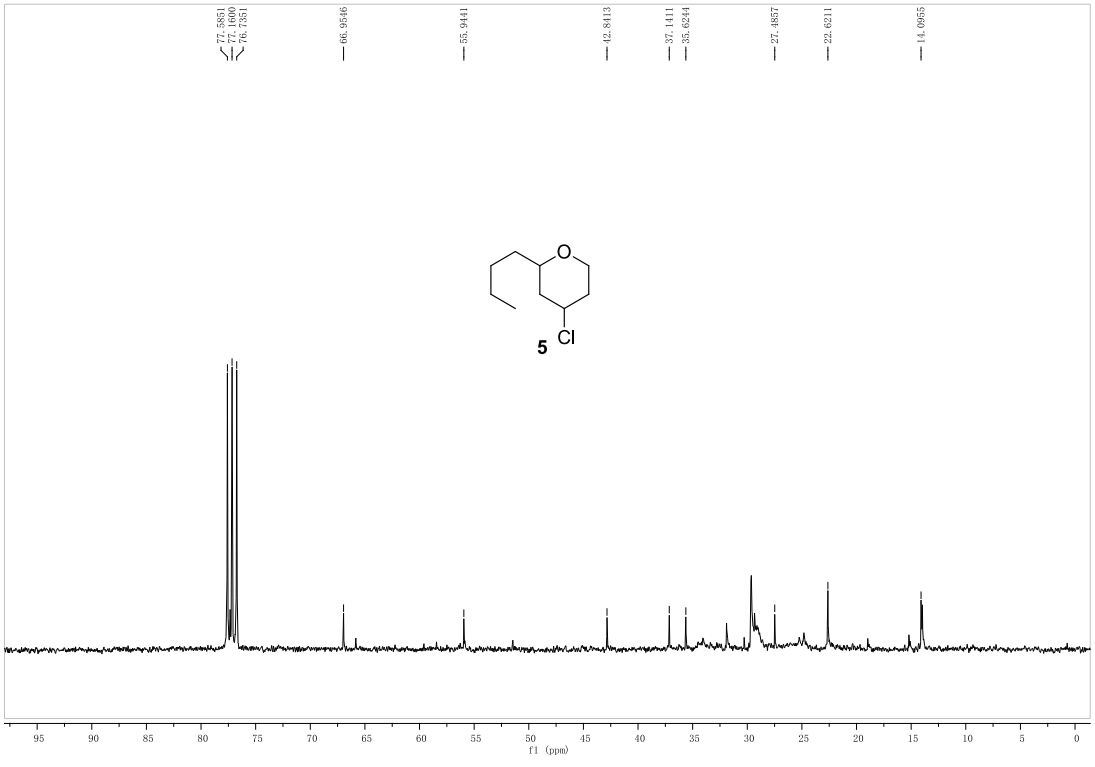

7.2693
4.4172
4.3980
4.3789
3.8416
3.8290
3.8169
3.7887
3.7221
3.6884
3.6686
3.6477
3.2961
2.6949
2.6739
2.6533
2.1805
1.5818
1.5756
1.5620
1.5523
1.5435
1.3001
1.2935
1.2822
0.9089
0.8852
0.8630
0.0592
4j
1.0000
1.3420
1.4175
3.1145
2.2957
3.2308
2.1892
4.2126
3.2403
f1 (ppm)


207.2643
104.3404
77.5890
77.1658
76.7406
60.7620
52.8627
43.7992
32.6566
30.6048
26.8331
22.6189
14.0826
4j
f1 (ppm)


5.8770
5.8546
5.8459
5.8323
5.8202
5.7974
5.7764
5.7748
5.7630
5.7407
5.0146
5.0036
5.0293
5.0261
4.9984
4.9951
4.9919
4.9919
4.4043
4.3851
4.3665
3.5253
3.4223
3.4133
3.4001
3.3988
3.3964
3.3437
3.3267
3.1978
2.5060
2.5003
2.4946
2.2835
2.2613
2.2391
2.2169
1.5289
1.5057
1.4849
1.4848
1.4622
1.2662
1.2557
1.2425
0.8792
0.8570
0.8343
4k
1.0000
2.0615
1.0098
1.1720
1.3479
3.3653
2.0713
2.3972
4.4376
3.4451
f1 (ppm)


135.6709
116.3569
103.1035
64.4718
52.0872
40.0753
39.7979
39.5189
39.2421
38.9638
38.6831
33.9085
32.2275
26.3538
21.9683
13.9114
4k
f1 (ppm)


7.2691
5.2643
3.4755
3.4417
3.4061
1.7850
1.4251
1.3554
1.2136
0.8524
0.8356
0.8129
0.0488
O
Cl
5
2.3811
2.3425
3.3159
7.6216
3.0000
f1 (ppm)


77.5851
77.1600
76.7351
66.9546
55.9441
42.8413
37.1411
35.6244
27.4857
22.6211
14.0955
O
Cl
5
f1 (ppm)