

Highly Chemoselective Synthesis of Hindered Amides via Cobalt-Catalyzed Intermolecular Oxidative Hydroamidation

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α -Tertiary amides are of great importance for medicinal chemistry. However, they are often challenging to access through conventional methods due to reactivity and chemoselectivity issues. Here we report a single-step approach towards such amides via cobalt-catalyzed intermolecular oxidative hydroamidation of unactivated alkenes, using nitriles of either solvent- or reagent-quantities. This protocol is orthogonal to groups that rapidly react under known carbocation amidation conditions such as tertiary alcohols, electron-rich alkenes, ketals, weak C–H bonds, and carboxylic acids. Straightforward access to a diverse array of hindered amides is demonstrated, including a rapid synthesis of an aminoadamantane-derived pharmaceutical intermediate.

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Supporting Information

Highly Chemoselective Synthesis of Hindered Amides via Cobalt-Catalyzed Intermolecular Oxidative Hydroamidation

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Table of Contents

I. General Information	S3
II. Procedures and Characterizations	S4
II-A. Synthesis and Characterizations of non-Commercial Compounds.....	S4
II-B. General Procedures for Cobalt-Catalyzed Intermolecular Oxidative Hydroamidation..	S7
II-C. Characterizations of Compounds.....	S9
III. Gram-Scale Hydroamidation and Application.....	S28
IV. Mechanistic Studies.....	S30
IV-A. With Deuterium-Labeled Silane (Scheme 4a).....	S30
IV-B. Test for Proton-Activation (Scheme 4b).....	S30
IV-C. Crossover Reaction (Scheme 4c).....	S31
IV-D. Effect of the Amount of Nitrile (Scheme 4d).....	S32
V. X-Ray Crystallography Analysis.....	S33
VI. SI References and Notes.....	S36
VII. NMR Spectra	S38

I. General Information

All reactions were carried out with dry solvents under anhydrous conditions, unless otherwise noted. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Anhydrous dichloromethane, 1,1,3,3-tetramethyldisiloxane (CAS # 3277-26-7), *N*-fluoro-2,4,6-trimethylpyridinium triflate (**5**) (CAS # 107264-00-6) and 2,6-lutidine (CAS # 108-48-5) were purchased from J&K. (R,R)-(-)-*N,N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) (CAS # 176763-62-5) was purchased from Strem and Energy Chemical. 1-Methylcyclopentene (**2e**) (CAS # 693-89-0) was purchased from 3A Chemical. 1-Methyl-cyclohexen (**2f**) (CAS # 591-49-1) was purchased from Alfa. 1-Dodecene (**2g**) (CAS # 112-41-4) and (+)-dihydrocarvone (**2r**) (CAS # 5524-05-0) were purchased from Energy Chemical. Alpha-terpineol (**2h**) (CAS # 98-55-5) was purchased from Bidepharm. CDCl₃ was purchased from Innochem. Oxone (CAS # 37222-66-5) was purchased from J&K and ground into fine powder (100 mesh). Anhydrous acetonitrile was purchased from Fisher and purified by passing through Vigor solvent purification system and stored under N₂. "PE" refers to petroleum ether. All chemicals were weighed on the bench top, in the air. Yields refer to chromatographically and spectroscopically (¹H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by ¹H NMR spectroscopy and thin-layer chromatography (TLC) carried out on silica gel plates (HSGF254) supplied by Yantai Chemicals (China), using UV light as a visualizing agent and phosphomolybdic acid in ethanol or KMnO₄ solution and heat as developing agents. Flash silica gel chromatography was performed using silica gel (200-300 mesh) supplied by Tsingtao Haiyang. ¹H and ¹³C NMR spectra were recorded on a Bruker 400 spectrometer and were calibrated using CDCl₃ as internal reference (CDCl₃: 7.26 ppm for ¹H NMR and 77.2 ppm for ¹³C NMR). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br = broad. IR spectra were recorded on a Thermo Scientific Nicolet iS5 FT-IR spectrometer (iD5 ATR). High-resolution mass data was recorded by a Solarix XR Fourier Transform Ion Cyclotron Resonance Mass Spectrometer.

II. Procedures and Characterizations

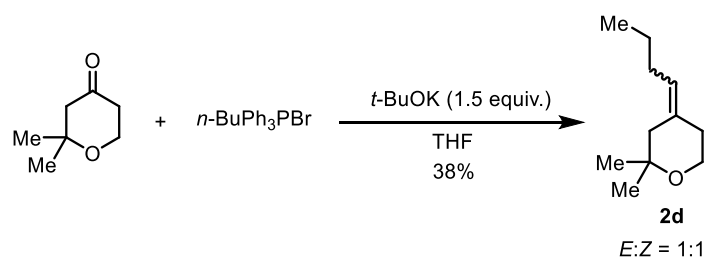
II-A. Synthesis and Characterizations of non-Commercial Compounds

O-3-Methylbut-3-en-1-yl-estrone (2j),¹ 6-methylhept-6-enoic acid (2k),²
(1*S*,4*S*,6*S*)-1-methyl-4-(prop-1-en-2-yl)-7-oxabicyclo[4.1.0]heptan-2-one (2s),³
3-methylbut-3-en-1-yl thiophene-2-carboxylate (2u),⁴
[N,N'-(1,1,2,2-tetramethylethylene)bis(3,5-di-*tert*-butylsalicylideneiminato)]cobalt(II) (1a),⁵
PhSiD₃⁶ were prepared according to literature procedures.

General Procedure for Substrate Preparation

To a 250 mL oven-dried round bottom flask equipped with a magnetic stir bar was added methyltriphenylphosphonium bromide (10 g, 28 mmol, 1.4 equiv.) and anhydrous THF (35 mL). Potassium *tert*-butoxide (3.4 g, 30 mmol, 1.5 equiv.) was added and the reaction mixture was stirred for 30 min at r.t., during which time the reaction mixture turned yellow. A solution of ketone (20 mmol, 1.0 equiv.) in anhydrous THF (20 mL) was added drop-wise to the reaction mixture. The reaction mixture was stirred for an additional 1.5 h at r.t. before quenched by the addition of 50 mL H₂O. The resulting mixture was extracted with ethyl acetate and the combined organic layers were dried over Na₂SO₄, filtered, concentrated *in vacuo* and purified by silica gel chromatography to get 1,1-disubstituted alkenes. Following this procedure, 2a,⁷ 2b,⁸ 2c,⁹ 2i,¹⁰ 2m,¹¹ 2p,¹² 2q,¹³ 2w¹⁴ were prepared, and their spectroscopic data matches literature reports.

4-Butylidene-2,2-dimethyltetrahydro-2H-pyran (2d)



Following the general procedure for substrates preparation with slight modification, 2d was synthesized from butyltriphenylphosphonium bromide (11.2 g, 28 mmol, 1.4 equiv.) and 2,2-dimethyltetrahydro-4H-pyran-4-one (2.6 g, 20 mmol, 1.0 equiv.). Purification by silica gel chromatography afforded 2d (510 mg, 38% yield, *E:Z* = 1:1) as a colorless oil.

¹H NMR (400 MHz, CDCl₃) δ 5.28 (tt, *J* = 7.3, 1.3 Hz, 0.5H), 5.13 (tt, *J* = 7.4, 1.3 Hz, 0.5H), 3.68 (dt, *J* = 12.3, 5.7 Hz, 2H), 2.22 – 1.91 (m, 6H), 1.36 (hd, *J* = 7.3, 6.1 Hz, 2H),

1.18 (d, $J = 6.0$ Hz, 6H), 0.90 (t, $J = 7.3$ Hz, 3H).

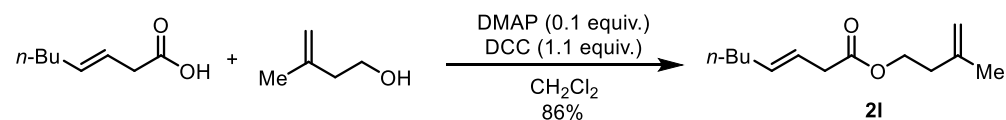
^{13}C NMR (101 MHz, CDCl_3) δ 133.07, 132.92, 124.60, 124.45, 73.12, 72.90, 63.06, 62.02, 47.83, 40.46, 36.46, 29.19, 29.05, 29.00, 26.38, 26.21, 23.18, 23.14, 13.88, 13.73.

HRMS (ESI) $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{11}\text{H}_{21}\text{O}$: 169.1587, found: 169.1587;

FTIR (cm^{-1}): 2958.7, 2927.9, 2862.4, 1363.5, 1257.4, 1186.8, 1083.3, 1048.6, 853.7, 744.4;

TLC: $R_f = 0.95$ (PE: ethyl acetate = 10:1).

3-Methylbut-3-en-1-yl (*E*)-oct-3-enoate (**2l**)



To a solution of 3-octenoic acid (1.4 g, 10.0 mmol, 1.0 equiv.) in CH_2Cl_2 (50 mL) at 25 °C was added 3-methylbut-3-en-1-ol (1.0 g, 11.0 mmol, 1.1 equiv.), followed by 4-dimethylaminopyridine (DMAP, 122.2 mg, 1.0 mmol, 0.10 equiv.) and *N,N*-dicyclohexylcarbodiimide (DCC, 2.3 g, 11 mmol, 1.1 equiv.). The resulting mixture was stirred at r.t. overnight. The reaction mixture was filtered through celite and the filter cake was washed with ethyl acetate (3×10 mL). The resulting filtrate was concentrated and purified by flash column chromatography to afford **2l** (1.8 g, 86% yield) as a colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 5.60 – 5.44 (m, 2H), 4.79 (s, 1H), 4.72 (s, 1H), 4.19 (t, $J = 6.9$ Hz, 2H), 3.01 (d, $J = 5.7$ Hz, 2H), 2.33 (t, $J = 6.9$ Hz, 2H), 2.02 (q, $J = 6.4, 5.9$ Hz, 2H), 1.75 (s, 3H), 1.32 (tdt, $J = 8.5, 3.6, 2.2$ Hz, 4H), 0.88 (t, $J = 7.0$ Hz, 3H).

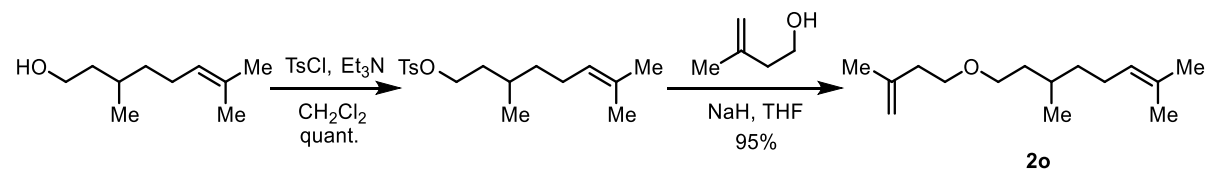
^{13}C NMR (101 MHz, CDCl_3) δ 172.16, 141.61, 134.80, 121.49, 112.25, 62.73, 38.12, 36.67, 32.14, 31.29, 22.49, 22.16, 13.91.

HRMS (ESI) $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{13}\text{H}_{23}\text{O}_2$: 211.1693, found: 211.1690;

FTIR (cm^{-1}): 2928.1, 2854.8, 2117.4, 1736.3, 1240.2, 1156.9, 967.8, 889.9, 842.1;

TLC: $R_f = 0.85$ (PE: ethyl acetate = 4:1).

2,6-Dimethyl-8-((3-methylbut-3-en-1-yl)oxy)oct-2-ene (**2o**)



To a solution of citronellol (3.2 g, 20.0 mmol, 1.0 equiv.), Et_3N (3.4 mL, 24.0 mmol, 1.20 equiv.) in dry CH_2Cl_2 (40 mL) was added TsCl (4.2 g, 22.0 mmol, 1.1 equiv.) and the

resulting mixture stirred at r.t. overnight. The reaction mixture was quenched with saturated aqueous NaHCO₃ (25 mL) and extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated *in vacuo* and purified via column chromatography (PE: ethyl acetate = 20:1) to yield 3,7-dimethyloct-6-en-1-yl 4-methylbenzenesulfonate as a colorless oil (quant.).¹⁵

In a 100-mL round-bottom flask equipped with a dropping funnel, a suspension of NaH (420 mg, 60% in mineral oil, 10.5 mmol) in THF (10 mL) was prepared under nitrogen atmosphere. A solution of 3-methyl-2-buten-1-ol (861 mg, 10 mmol) in THF (5 mL) was added dropwise under an ice bath, the mixture was stirred for 1 h, and 3,7-dimethyloct-6-en-1-yl 4-methylbenzenesulfonate was added. The resulting reaction mixture was stirred at r.t. overnight. The reaction mixture was quenched by H₂O, followed by addition of aqueous NaHCO₃ (20 mL) and extracted with Et₂O. The combined organic layers were dried over Na₂SO₄, filtered, concentrated *in vacuo* and purified by silica gel chromatography (PE: ethyl acetate = 15:1) to get **2o** (1.8 g, 95% yield) as a colorless oil.

¹H NMR (400 MHz, CDCl₃) δ 5.09 (tdd, *J* = 6.8, 2.8, 1.4 Hz, 1H), 4.76 (s, 1H), 4.72 (s, 1H), 3.54 – 3.41 (m, 4H), 2.34 – 2.26 (m, 2H), 1.96 (m, 2H), 1.74 (s, 3H), 1.67 (s, 3H), 1.65 – 1.50 (m, 5H), 1.44 – 1.28 (m, 2H), 1.20 – 1.10 (m, 1H), 0.89 (d, *J* = 6.5 Hz, 3H).

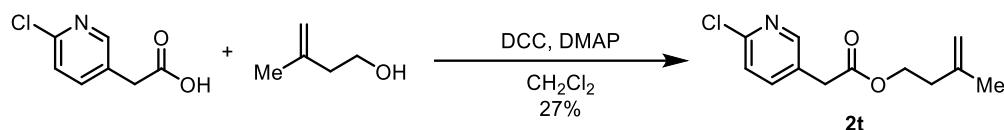
¹³C NMR (101 MHz, CDCl₃) δ 141.99, 130.07, 123.83, 110.27, 68.35, 68.21, 36.83, 36.21, 35.65, 28.57, 24.70, 24.46, 21.75, 18.55, 16.60.

HRMS (ESI) [*M* + *H*]⁺ calculated for C₁₅H₂₉O: 225.2213, found: 225.2213;

FTIR (cm⁻¹): 3411.2, 2986.4, 1716.6, 1458.2, 1377.2, 1275.3, 1259.0, 1105.3, 749.8;

TLC: R_f = 0.95 (PE: ethyl acetate = 10:1).

3-Methylbut-3-en-1-yl 2-(6-chloropyridin-3-yl)acetate (**2t**)



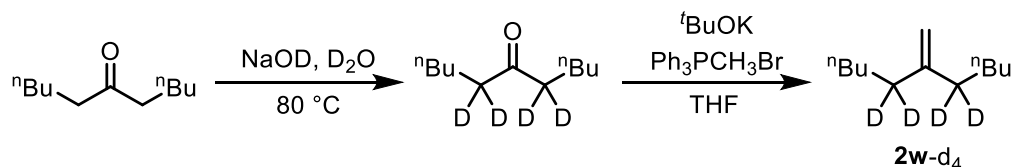
Following procedure for **2l**, **2t** was synthesized from 2-(6-chloropyridin-3-yl)acetic acid (2.6 g, 15.0 mmol). Purification by silica gel chromatography afforded **2t** (972 mg, 27% yield) as a colorless oil.

¹H NMR (400 MHz, CDCl₃) δ 8.28 (d, *J* = 2.5 Hz, 1H), 7.62 (dd, *J* = 8.2, 2.5 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 1H), 4.78 (s, 1H), 4.69 (s, 1H), 4.23 (t, *J* = 6.7 Hz, 2H), 3.61 (s, 2H), 2.33 (t, *J* = 6.8 Hz, 2H), 1.73 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 170.18, 150.30, 150.13, 141.27, 139.75, 128.74, 124.04, 112.54, 63.35, 37.62, 36.60, 22.31.

HRMS (ESI) $[M + H]^+$ calculated for $C_{12}H_{15}ClNO_2$: 240.0786, found: 240.0783;
 FTIR (cm^{-1}): 2968.4, 1731.5, 1650.9, 1587.9, 1566.5, 1459.2, 1384.8, 1335.2, 1139.4;
 TLC: R_f = 0.90 (PE: ethyl acetate = 1:1).

2w-d₄ (6-Methyleneundecane-5,5,7,7-d₄)



To a 25 mL oven-dried round bottom flask containing a magnetic stir bar was added undecan-6-one (1 mL, 4.90 mmol), NaOD (40% w/w in D_2O , 1 mL). The reaction mixture was refluxed overnight. The resulting mixture was dried over Na_2SO_4 , concentrated *in vacuo*. This sequence was repeated a total of three times to afford undecan-6-one-5,5,7,7-d₄ (267 mg, 31%) as the literature reported.¹⁶

To a 50 mL oven-dried round bottom flask equipped with a magnetic stir bar was added methyltriphenylphosphonium bromide (765 mg, 2.0 mmol, 1.4 equiv.) and anhydrous THF (15 mL). Potassium *tert*-butoxide (22.3 mg, 1.9 mmol, 1.3 equiv.) was added and the reaction mixture was stirred for 30 min at r.t., during which time the reaction mixture turned yellow. Undecan-6-one-5,5,7,7-d₄ (267 mg, 1.5 mmol, 1.0 equiv.) in anhydrous THF (3 mL) was added dropwise to the reaction mixture. The reaction mixture was stirred for an additional 1.5 h at r.t. before quenched by the addition of 5 mL H_2O . The resulting mixture was extracted with ethyl acetate and the combined organic layers were dried over Na_2SO_4 , filtered, concentrated *in vacuo* and purified by silica gel chromatography to get **2w-d₄** (> 97% D) as a colorless oil.

1H NMR (400 MHz, $CDCl_3$) δ 4.70 (s, 2H), 1.45 – 1.38 (m, 4H), 1.38 – 1.23 (m, 8H), 0.91 (t, J = 7.0 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.09, 108.28, 35.33 (quintet, J = 19.2 Hz), 31.50, 27.22, 22.48, 13.90.

HRMS (EI) calculated for $C_{12}H_{20}D_4$: 172.2129, found: 172.2124;

FTIR (cm^{-1}): 2956.3, 2922.4, 2858.9, 1637.2, 1465.8, 1377.9, 881.5.

II-B. General Procedures for Cobalt-Catalyzed Intermolecular Oxidative Hydroamidation

Evaluation of reaction conditions (Table 1, “Standard Conditions”): An oven-dried 10 mL re-sealable screw-cap vial equipped with a Teflon-coated magnetic stir bar was charged with Co catalyst **1a** (6.0 mg, 0.010 mmol, 0.10 equiv.) and oxone (100 mesh, 123 mg, 0.20 mmol, 2.0 equiv.). The reaction vessel was then briefly evacuated and backfilled

with nitrogen (this sequence was repeated a total of three times). Anhydrous acetonitrile (1.0 mL), **2a** (18.1 mg, 0.10 mmol, 1.0 equiv.), degassed H₂O (2 μ L, 0.11 mmol, 1.1 equiv.) and 1,1,3,3-tetramethyldisiloxane (73 μ L, 0.40 mmol, 4.0 equiv.) were added to the reaction vessel via syringe sequentially. The reaction mixture was stirred at r.t. for 18 h before an NMR internal standard (phenanthrene) was added. The mixture was filtered through a short pad of silica gel with another 5 mL CH₂Cl₂/MeOH (20/1) as an eluent. The solvents were removed *in vacuo* and the residue was analyzed by ¹H NMR spectroscopy.



Figure S1. Photos of the reaction mixture (Reaction time: 0 min, 5 min and 18 h)

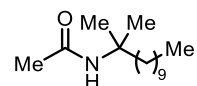
General Procedure A: An oven-dried 25 mL re-sealable Schlenk tube equipped with a Teflon-coated magnetic stir bar was charged with Co catalyst **1a** (15 mg, 0.025 mmol, 0.050 equiv.) and oxone (100 mesh, 922 mg, 1.5 mmol, 3.00 equiv.). The reaction vessel was then briefly evacuated and backfilled with nitrogen (this sequence was repeated a total of three times). Anhydrous acetonitrile (5.0 mL), **2** (0.50 mmol, 1.0 equiv.), H₂O (20 μ L, 1.1 mmol, 2.2 equiv.) and 1,1,3,3-tetramethyldisiloxane (275 μ L, 1.5 mmol, 3.0 equiv.) were added to the reaction vessel via syringe sequentially. The reaction mixture was stirred at r.t. for 18 h. The mixture was filtered through a short pad of silica gel with CH₂Cl₂/MeOH (20/1) as an eluent. The solvents were removed *in vacuo* and the residue was purified by silica gel column chromatography to afford corresponding amide product **3**.

General Procedure B: An oven-dried 25 mL re-sealable schlenk tube equipped with a Teflon-coated magnetic stir bar was charged with Co catalyst **1a** (30 mg, 0.050 mmol, 0.10 equiv.) and oxone (100 mesh, 922 mg, 1.5 mmol, 3.0 equiv.). The reaction vessel was then briefly evacuated and backfilled with nitrogen (this sequence was repeated a total of three times). Anhydrous dichloromethane (5.0 mL), nitrile (1.0 mmol, 2.5 equiv.), **2** (0.50 mmol, 1.0 equiv.), H₂O (20 μ L, 1.1 mmol, 2.2 equiv.) and 1,1,3,3-tetramethyldisiloxane (275 μ L, 1.5 mmol, 3.0 equiv.) were added to the reaction vessel via syringe sequentially. The reaction mixture was stirred at r.t. for 18 h. The mixture was filtered through a short pad of silica gel with CH₂Cl₂/MeOH (20/1) as an eluent. The solvents were removed *in vacuo* and the residue was purified by silica gel column chromatography to afford corresponding amide product **8**.

General Procedure C: An oven-dried 25 mL re-sealable schlenk tube equipped with a Teflon-coated magnetic stir bar was charged with Co catalyst **1a** (30 mg, 0.050 mmol, 0.10 equiv.) and oxone (100 mesh, 922 mg, 1.5 mmol, 3.0 equiv.). The reaction vessel was then briefly evacuated and backfilled with nitrogen (this sequence was repeated a total of three times). Anhydrous dichloromethane (5.0 mL), nitrile (2.5 mmol, 5.0 equiv.), **2** (0.50 mmol, 1.0 equiv.), H₂O (20 μ L, 1.1 mmol, 2.2 equiv.) and 1,1,3,3-tetramethyldisiloxane (275 μ L, 1.5 mmol, 3.0 equiv.) were added to the reaction vessel via syringe sequentially. The reaction mixture was stirred at r.t. for 18 h. The mixture was filtered through a short pad of silica gel with CH₂Cl₂/MeOH (20/1) as an eluent. The solvents were removed *in vacuo* and the residue was purified by silica gel column chromatography to afford corresponding amide product **8**.

II-C. Characterizations of Compounds

Compound 3a (*N*-(2-methyldodecan-2-yl)acetamide)

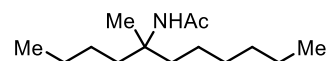


Following General Procedure A, the title compound was synthesized from 2-methyldodec-1-ene (**2a**) (90.2 mg, 0.50 mmol). The product was purified by silica gel flash column chromatography (PE: ethyl acetate = 10:1 to 1:1) to afford **3a** (114.0 mg, 94%) as a pale yellow solid. The spectroscopic data matches the literature reported.¹⁷

¹H NMR (400 MHz, CDCl₃) δ 5.19 (s, 1H), 1.91 (s, 3H), 1.69 – 1.58 (m, 2H), 1.32 – 1.22 (m, 22H), 0.87 (t, *J* = 6.8 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 169.39, 53.68, 40.34, 31.90, 30.01, 29.69, 29.65, 29.61, 29.33, 26.87, 24.48, 24.14, 22.67, 14.10.

Compound 3b (*N*-(5-methylundecan-5-yl)acetamide)



Following General Procedure A, the title compound was synthesized from 5-methyleneundecane (**2b**) (84.1 mg, 0.50 mmol). The product was purified by silica gel flash column chromatography (PE: ethyl acetate = 10:1 to 1:1) to afford **3b** (109.0 mg, 96%) as a pale yellow solid.

¹H NMR (400 MHz, CDCl₃) δ 5.30 (s, 1H), 1.86 (s, 3H), 1.67 (qd, *J* = 8.7, 3.6 Hz, 2H), 1.75 – 1.47 (m, 2H), 1.27 – 1.13 (m, 15H), 0.87 – 0.81 (m, 6H).

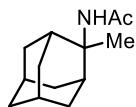
^{13}C NMR (101 MHz, CDCl_3) δ 169.31, 56.24, 38.33, 38.06, 31.87, 29.69, 25.90, 24.38, 24.35, 23.63, 23.08, 22.64, 14.13, 14.05.

FTIR (cm^{-1}): 3296.5, 2954.8, 2926.5, 2858.7, 2359.0, 1646.8, 1552.2, 1465.9, 1299.3;

HRMS (ESI) $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{14}\text{H}_{30}\text{NO}$: 228.2322, found: 228.2321;

TLC: R_f = 0.40 (PE: ethyl acetate = 1:1).

Compound 3c (*N*-((1*r*,3*r*,5*r*,7*r*)-2-methyladamantan-2-yl)acetamide)

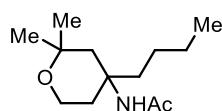


Following General Procedure A, the title compound was synthesized from 2-methylideneadamantane (**2c**) (75.0 mg, 0.50 mmol). The product was purified by silica gel flash column chromatography (PE: ethyl acetate = 10:1 to 1:1) to afford **3c** (98.5 mg, 95%) as a pale yellow solid. The spectroscopic data matches the literature reported.¹⁸

^1H NMR (400 MHz, CDCl_3) δ 5.40 (s, 1H), 2.12 (s, 2H), 1.90 – 1.97 (m, 7H), 1.77 (s, 2H), 1.70 – 1.59 (m, 4H), 1.59 – 1.52 (m, 2H), 1.47 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 168.81, 58.08, 38.12, 34.92, 32.90, 32.79, 27.14, 26.50, 24.21, 22.68.

Compound 3d (*N*-(4-butyl-2,2-dimethyltetrahydro-2H-pyran-4-yl)acetamide)



Following General Procedure A, the title compound was synthesized from 4-butyldiene-2,2-dimethyltetrahydro-2H-pyran (**2d**) (85.0 mg, 0.50 mmol). The product was purified by silica gel flash column chromatography (PE: ethyl acetate = 10:1 to 1:1) to afford **3d** (74.4 mg, 65%) as a pale yellow oil.

^1H NMR (400 MHz, CDCl_3) δ 5.53 (s, 1H), 3.75 (td, J = 12.3, 2.2 Hz, 1H), 3.61 (ddd, J = 12.4, 4.9, 2.4 Hz, 1H), 2.34 (dd, J = 14.5, 2.3 Hz, 1H), 1.97 – 1.76 (m, 5H), 1.53 – 1.35 (m, 2H), 1.31 – 1.03 (m, 11H), 0.83 (t, J = 7.2 Hz, 3H).

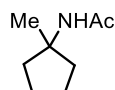
^{13}C NMR (101 MHz, CDCl_3) δ 169.57, 70.87, 57.27, 53.54, 42.88, 39.36, 34.79, 32.07, 24.69, 24.18, 22.97, 22.54, 13.84.

FTIR (cm⁻¹): 3294.7, 2928.6, 1647.8, 1551.9, 1367.8, 1301.0, 1116.8, 1040.6, 961.4;

HRMS (ESI) [M + H]⁺ calculated for C₁₃H₂₆NO₂: 228.1958, found: 228.1963;

TLC: R_f = 0.10 (PE: ethyl acetate = 1:1).

Compound 3e (*N*-(1-methylcyclopentyl)acetamide)

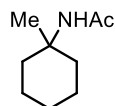


Following General Procedure A, the title compound was synthesized from 1-methylcyclopent-1-ene (**2e**) (42.0 mg, 0.50 mmol). The product was purified by silica gel flash column chromatography (PE: ethyl acetate = 10:1 to 1:1) to afford **3e** (60.3 mg, 86%) as a pale yellow solid. The spectroscopic data matches the literature reported.¹⁹

¹H NMR (400 MHz, CDCl₃) δ 5.66 (s, 1H), 1.95 – 1.86 (m, 5H), 1.69 – 1.56 (m, 6H), 1.36 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 169.69, 61.19, 39.35, 25.44, 24.31, 23.69.

Compound 3f (*N*-(1-methylcyclohexyl)acetamide)



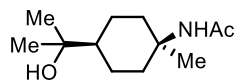
Following General Procedure A, the title compound was synthesized from 1-methylcyclohex-1-ene (**2f**) (49.0 mg, 0.50 mmol). The product was purified by silica gel flash column chromatography (PE: ethyl acetate = 10:1 to 1:1) to afford **3f** (53.6 mg, 69%) as a pale yellow solid. The spectroscopic data matches the literature reported.²⁰

¹H NMR (400 MHz, CDCl₃) δ 5.26 (s, 1H), 2.01 – 1.87 (m, 5H), 1.58 – 1.17 (m, 11H).

¹³C NMR (101 MHz, CDCl₃) δ 169.21, 53.04, 36.37, 25.86, 25.27, 24.32, 21.72.

Compound 3h

(*N*-((1*s*,4*s*)-4-(2-hydroxypropan-2-yl)-1-methylcyclohexyl)acetamide)



Following General Procedure A, the title compound was synthesized from alpha-terpineol (**2h**) (78.0 mg, 0.50 mmol). Diastereomeric ratio (3:1) was determined by ^1H NMR analysis of the crude reaction mixture. The product was purified by silica gel flash column chromatography (PE: ethyl acetate = 10:1 to 1:1) to afford **3h** (57.7 mg, 54%, mixture of diastereoisomers) as a colorless solid. The stereochemistry of the major diastereomer (shown above) was determined by X-ray single crystal diffraction of a recrystallized sample.

^1H NMR (400 MHz, CDCl_3) δ 5.27 (s, 1H), 2.26 – 2.19 (m, 2H), 1.90 (s, 3H), 1.62 (d, J = 9.5 Hz, 2H), 1.30 (s, 3H), 1.22 – 1.08 (m, 12H).

^{13}C NMR (101 MHz, CDCl_3) δ 169.46, 72.04, 52.43, 47.86, 36.17, 27.22, 26.80, 24.20, 22.28.

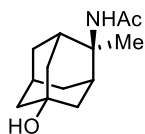
FTIR (cm^{-1}): 3304.8, 2933.6, 1650.6, 1548.7, 1445.7, 1371.6, 1180.4, 1133.5;

HRMS (ESI) $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{12}\text{H}_{24}\text{NO}_2$: 214.1802, found: 214.1800;

TLC: R_f = 0.05 (PE: ethyl acetate = 1:1).

Compound 3i

(*rac*-*N*-((1*R*,2*R*,3*S*,5*S*,7*S*)-5-hydroxy-2-methyladamantan-2-yl)acetamide)



Following General Procedure A, the title compound was synthesized from *rac*-(1*S*,3*R*,5*S*,7*S*)-4-methyleneadamantan-1-ol (**2i**) (82.2 mg, 0.50 mmol). Diastereomeric ratio (5:1) was determined by ^1H NMR analysis of the crude reaction mixture. The product was purified by silica gel flash column chromatography (PE: ethyl acetate = 5:1 to 1:1) to afford the major diastereomer **3i** (71.5 mg, 64%, single diastereoisomer) as a pale yellow solid. The stereochemistry of the major diastereomer (shown above) was determined by X-ray single crystal diffraction of a recrystallized sample.

^1H NMR (400 MHz, CDCl_3) δ 5.28 (s, 1H), 2.61 (s, 1H), 2.37 (s, 2H), 2.16 (d, J = 3.1 Hz, 1H), 2.09 (p, J = 3.1 Hz, 1H), 1.98 – 1.93 (m, 5H), 1.91 – 1.84 (m, 2H), 1.68 (s, 2H), 1.54 – 1.50 (m, 1H), 1.48 (s, 3H), 1.23 (s, 2H).

^{13}C NMR (101 MHz, CDCl_3) δ 169.32, 69.55, 67.24, 57.25, 53.82, 46.11, 40.61, 37.77, 31.79, 29.73, 29.28, 24.58, 22.19.

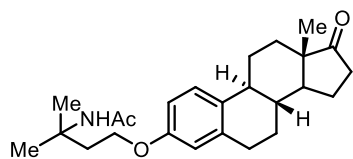
FTIR (cm⁻¹): 3290.9, 2989.6, 2920.3, 1634.4, 1557.2, 1358.9, 1304.1, 1114.3, 1084.5

HRMS (ESI) [M + H]⁺ calculated for C₁₃H₂₂NO₂: 224.1645, found: 224.1644;

TLC: R_f = 0.45 (PE: acetone = 1:1).

Compound 3j

N-(2-methyl-4-(((8R,9S,13S)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl)oxy)butan-2-yl)acetamide



Following General Procedure A, the title compound was synthesized from O-3-methylbut-3-en-1-yl-estrone (**2j**) (169.3 mg, 0.50 mmol). The product was purified by silica gel flash column chromatography (PE: ethyl acetate = 5:1 to 1:1) to afford **3j** (184.9 mg, 93%) as a pale yellow solid.

¹H NMR (400 MHz, CDCl₃) δ 7.16 (d, *J* = 8.6 Hz, 1H), 6.67 (dd, *J* = 8.6, 2.7 Hz, 1H), 6.60 (s, 1H), 6.27 (s, 1H), 4.02 (t, *J* = 5.9 Hz, 2H), 2.86 (q, *J* = 5.1, 4.1 Hz, 2H), 2.46 (dd, *J* = 18.7, 8.7 Hz, 1H), 2.33 (dd, *J* = 9.3, 4.5 Hz, 1H), 2.24 – 1.83 (m, 10H), 1.71 – 1.15 (m, 12H), 0.86 (s, 3H).

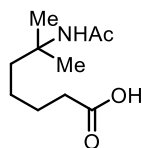
¹³C NMR (101 MHz, CDCl₃) δ 220.96, 169.61, 156.50, 137.94, 132.40, 126.49, 114.33, 112.05, 64.85, 53.26, 50.40, 48.02, 43.98, 39.65, 38.36, 35.89, 31.58, 29.69, 27.09, 27.07, 26.53, 25.93, 24.64, 21.60, 13.87.

FTIR (cm⁻¹): 2927.2, 1733.5, 1655.1, 1608.3, 1541.0, 1498.2, 1452.5, 1367.5, 1280.4;

HRMS (ESI) [M + H]⁺ calculated for C₂₅H₃₆NO₃: 398.2690, found: 398.2687;

TLC: R_f = 0.30 (PE: ethyl acetate = 1:1).

Compound 3k (6-acetamido-6-methylheptanoic acid)



Following General Procedure A, the title compound was synthesized from 6-methylhept-6-enoic acid (**2k**) (71.1 mg, 0.50 mmol). The product was purified by silica

gel flash column chromatography (PE: ethyl acetate = 5:1 to 1:1) to afford **3k** (83.5 mg, 83%) as a pale yellow solid.

^1H NMR (400 MHz, CDCl_3) δ 10.75 (br, 1H), 5.48 (s, 1H), 2.33 (t, $J = 7.3$ Hz, 2H), 1.92 (s, 3H), 1.73 – 1.66 (m, 2H), 1.61 (p, $J = 7.5$ Hz, 2H), 1.34 – 1.21 (m, 9H).

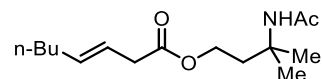
^{13}C NMR (101 MHz, CDCl_3) δ 178.37, 170.30, 53.85, 39.46, 34.00, 26.95, 24.94, 24.28, 23.51.

FTIR (cm^{-1}): 2929.3, 1707.3, 1623.5, 1548.5, 1370.3, 1126.0, 1038.3, 738.0, 610.1;

HRMS (ESI) $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{10}\text{H}_{20}\text{NO}_3$: 202.1438, found: 202.1437;

TLC: $R_f = 0.30$ (PE: acetone = 1:1).

Compound 3l (3-acetamido-3-methylbutyl (*E*)-oct-3-enoate)



Following General Procedure A, the title compound was synthesized from 3-methylbut-3-en-1-yl (*E*)-oct-3-enoate (**2l**) (105.2 mg, 0.50 mmol). The product was purified by silica gel flash column chromatography (PE: ethyl acetate = 10:1 to 1:1) to afford **3l** (118.2 mg, 88%) as a pale yellow solid.

^1H NMR (400 MHz, CDCl_3) δ 5.61 – 5.42 (m, 3H), 4.11 (t, $J = 6.8$ Hz, 2H), 2.98 (d, $J = 6.1$ Hz, 2H), 2.07 (t, $J = 6.8$ Hz, 2H), 2.00 (q, $J = 6.6$ Hz, 2H), 1.90 (s, 3H), 1.38 – 1.21 (m, 12H), 0.86 (t, $J = 6.9$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 172.03, 169.45, 134.84, 121.00, 61.28, 52.48, 37.99, 37.70, 31.91, 31.05, 27.13, 24.18, 21.93, 13.67.

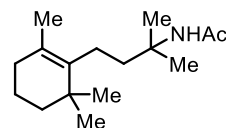
FTIR (cm^{-1}): 3304.15, 2926.4, 1734.9, 1652.4, 1549.5, 1450.0, 1161.5, 968.3, 608.9;

HRMS (ESI) $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{15}\text{H}_{28}\text{NO}_3$: 270.2064, found: 270.2062;

TLC: $R_f = 0.50$ (PE: ethyl acetate = 1:1).

Compound 3m

(*N*-(2-methyl-4-(2,6,6-trimethylcyclohex-1-en-1-yl)butan-2-yl)acetamide)



Following General Procedure A, the title compound was synthesized from 1,3,3-trimethyl-2-(3-methylbut-3-en-1-yl)cyclohex-1-ene (**2m**) (96.2 mg, 0.50 mmol). The product was purified by silica gel flash column chromatography (PE: ethyl acetate = 10:1 to 1:1) to afford **3m** (112.6 mg, 90%) as a pale yellow solid.

^1H NMR (400 MHz, CDCl_3) δ 5.48 (s, 1H), 1.95 – 1.83 (m, 7H), 1.76 – 1.67 (m, 2H), 1.58 – 1.50 (m, 5H), 1.40 – 1.33 (m, 2H), 1.29 (s, 6H), 0.93 (s, 6H).

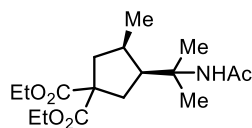
^{13}C NMR (101 MHz, CDCl_3) δ 169.37, 136.33, 127.14, 53.87, 39.87, 39.85, 34.99, 32.79, 28.68, 26.71, 24.40, 22.95, 19.72, 19.50.

FTIR (cm^{-1}): 3292.4, 3077.9, 2925.1, 1644.6, 1550.9, 1472.9, 1303.17, 1176.04, 606.3;

HRMS (ESI) $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{16}\text{H}_{30}\text{NO}$: 252.2322, found: 252.2321;

TLC: R_f = 0.70 (PE: ethyl acetate = 1:1).

Compound **3n** **(Diethyl (3*S*,4*R*)-3-(2-acetamidopropan-2-yl)-4-methylcyclopentane-1,1-dicarboxylate)**



Following General Procedure A, the title compound was synthesized from diethyl (3*S*,4*R*)-3-(2-acetamidopropan-2-yl)-4-methylcyclopentane-1,1-dicarboxylate (**2n**) (134.2 mg, 0.50 mmol). The product was purified by silica gel flash column chromatography (PE: ethyl acetate = 5:1 to 1:1) to afford **3n** (78.6 mg, 48%, single diastereoisomer) as a pale yellow solid. The stereochemistry of the major diastereomer was assigned by analogy with a structurally related literature compound.²¹

^1H NMR (400 MHz, CDCl_3) δ 5.36 (s, 1H), 4.21 – 4.10 (m, 4H), 2.44 – 2.26 (m, 4H), 2.19 (d, J = 13.1 Hz, 1H), 2.03 (d, J = 13.9 Hz, 1H), 1.89 (s, 3H), 1.39 (s, 6H), 1.22 (t, J = 7.1 Hz, 6H), 0.93 (d, J = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 173.07, 172.71, 169.25, 61.54, 61.51, 57.78, 55.00, 51.31, 41.89, 34.88, 32.67, 26.28, 26.02, 24.72, 17.10, 14.02.

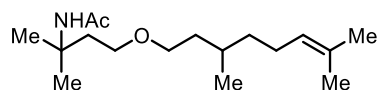
FTIR (cm^{-1}): 3309.2, 2977.0, 1724.4, 1653.2, 1544.5, 1445.2, 1365.7, 1273.8, 1248.5;

HRMS (ESI) $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{17}\text{H}_{30}\text{NO}_5$: 328.2118, found: 328.2119;

TLC: R_f = 0.2 (PE: ethyl acetate = 1:1).

Compound 3o

(*N*-(4-((3,7-dimethyloct-6-en-1-yl)oxy)-2-methylbutan-2-yl)acetamide)



Following General Procedure A, the title compound was synthesized from 2,6-dimethyl-8-((3-methylbut-3-en-1-yl)oxy)oct-2-ene (**2o**) (112.2 mg, 0.50 mmol). The product was purified by silica gel flash column chromatography (PE: ethyl acetate = 10:1 to 1:1) to afford **3o** (75.1 mg, 53%) as a pale yellow solid.

^1H NMR (400 MHz, CDCl_3) δ 6.65 (s, 1H), 5.05 (dddd, J = 8.6, 5.7, 2.8, 1.3 Hz, 1H), 3.58 (t, J = 6.5 Hz, 2H), 3.41 (t, J = 6.7 Hz, 2H), 2.04 – 1.86 (m, 2H), 1.83 (s, 3H), 1.77 (t, J = 6.3 Hz, 2H), 1.68 – 1.42 (m, 8H), 1.41 – 1.21 (m, 8H), 1.19 – 1.07 (m, 1H), 0.90 (d, J = 6.6 Hz, 3H).

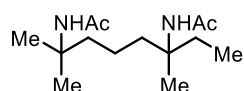
^{13}C NMR (101 MHz, CDCl_3) δ 169.12, 130.95, 124.30, 69.16, 67.40, 52.96, 41.11, 36.88, 36.48, 29.18, 25.98, 25.94, 25.40, 25.10, 24.26, 19.15, 17.31.

FTIR (cm^{-1}): 3309.6, 2923.1, 1653.9, 1544.3, 1453.8, 1370.5, 1275.4, 1258.9, 1107.3;

HRMS (ESI) $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{17}\text{H}_{34}\text{NO}_2$: 284.2584, found: 284.2586;

TLC: R_f = 0.75 (PE: ethyl acetate = 1:1).

Compound 3o' (*N, N'*-(2,6-dimethyloctane-2,6-diyl)diacetamide)



Adapted from a literature procedure.²² An oven-dried 10 mL re-sealable screw-cap vial equipped with a Teflon-coated magnetic stir bar was charged with concentrated sulfuric acid (1 mL) and glacial acetic acid (2 mL). MeCN (1 mL) was added at 0 °C. Then **2o** (112.2 mg, 0.5 mmol in 1 mL MeCN) was added dropwise. The mixture was stirred for 5 h at r.t. before quenched with 5 mL H_2O . The pH of reaction mixture was adjusted to 7 – 8 with saturated aqueous Na_2CO_3 (10 mL) and extracted with diethyl ether (3×10 mL). The combined organic layers were dried over Na_2SO_4 , filtered, concentrated *in vacuo* and purified via column chromatography (PE: ethyl acetate = 1:1) to yield **3o'** (19.0 mg, 15%) as a pale yellow solid.

^1H NMR (400 MHz, CDCl_3) δ 5.38 (s, 1H), 5.22 (s, 1H), 1.91 (s, 3H), 1.90 (s, 3H), 1.84 – 1.47 (m, 5H), 1.30 – 1.16 (m, 12H), 0.79 (t, J = 7.4 Hz, 3H).

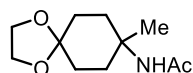
^{13}C NMR (101 MHz, CDCl_3) δ 169.30, 169.25, 56.33, 53.49, 40.29, 37.96, 30.58, 26.70, 26.61, 24.22, 24.17, 23.62, 17.94, 7.73.

FTIR (cm^{-1}): 3295.5, 2988.2, 1645.6, 1551.6, 1458.6, 1275.4, 1258.9, 749.8, 479.0, 434.7;

HRMS (ESI) $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{14}\text{H}_{29}\text{N}_2\text{O}_2$: 257.2224, found: 257.2222;

TLC: R_f = 0.30 (PE: ethyl acetate = 1:1).

Compound 3p (*N*-(8-methyl-1,4-dioxaspiro[4.5]decan-8-yl)acetamide)



Following a slightly modified General Procedure A where additional 2.0 equiv. 2,6-lutidine was added. The title compound was synthesized from 8-methylene-1,4-dioxaspiro[4.5]decan-8-yl (2p) (78.0 mg, 0.50 mmol). The product was purified by silica gel flash column chromatography (PE: ethyl acetate = 10:1 to 1:1) to afford 3p (90.6 mg, 85%) as a pale yellow solid.

^1H NMR (400 MHz, CDCl_3) δ 5.23 (s, 1H), 3.93 (s, 4H), 2.12 – 2.05 (m, 2H), 1.93 (s, 3H), 1.72 – 1.52 (m, 6H), 1.38 (s, 3H).

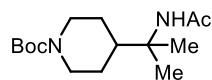
^{13}C NMR (101 MHz, CDCl_3) δ 169.92, 108.13, 64.29, 64.28, 52.52, 34.10, 30.74, 24.57.

FTIR (cm^{-1}): 3303.0, 2930.9, 1643.9, 1544.5, 1443.7, 1365.2, 1300.7, 1095.0, 937.0;

HRMS (ESI) $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{11}\text{H}_{20}\text{NO}_3$: 214.1438, found: 214.1437;

TLC: R_f = 0.10 (PE: ethyl acetate = 1:1).

Compound 3q (tert-butyl 4-(2-acetamidopropan-2-yl)piperidine-1-carboxylate)



Following General Procedure A, the title compound was synthesized from tert-butyl 4-(prop-1-en-2-yl)piperidine-1-carboxylate (2q) (113.0 mg, 0.50 mmol). The product was purified by silica gel flash column chromatography (PE: ethyl acetate = 10:1 to 1:1) to afford 3q (128.2 mg, 90%) as a pale yellow solid.

^1H NMR (400 MHz, CDCl_3) δ 5.47 (s, 1H), 4.10 (s, 2H), 2.59 (t, J = 13.0 Hz, 2H), 2.24 (tt, J = 12.3, 3.3 Hz, 1H), 1.87 (s, 3H), 1.56 (d, J = 12.9, 2H), 1.39 (s, 9H), 1.20 (s, 6H), 1.10 (td, J = 12.6, 4.4 Hz, 2H).

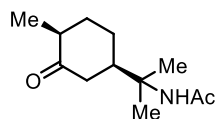
^{13}C NMR (101 MHz, CDCl_3) δ 169.46, 154.70, 79.27, 56.09, 42.15, 28.44, 26.78, 24.42, 24.25.

FTIR (cm^{-1}): 3311.9, 2972.6, 2942.9, 2855.0, 1654.8, 1547.4, 1424.8, 1364.9, 1243.3;

HRMS (ESI) $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{15}\text{H}_{29}\text{N}_2\text{O}_3$: 285.2173, found: 285.2173;

TLC: R_f = 0.05 (PE: ethyl acetate = 1:1).

Compound 3r (*N*-(2-((1*R*,4*S*)-4-methyl-3-oxocyclohexyl)propan-2-yl)acetamide)



Following General Procedure A, the title compound was synthesized from (+)-dihydrocarvone (**2r**) (77.0 mg, 0.50 mmol). The product was purified by silica gel flash column chromatography (PE: ethyl acetate = 10:1 to 1:1) to afford **3r** (100.4 mg, 95%) as a pale yellow solid.

^1H NMR (400 MHz, CDCl_3) δ 5.77 (s, 1H), 2.48 (ddt, J = 13.6, 12.1, 3.4 Hz, 1H), 2.31 (ddd, J = 13.0, 3.7, 2.4 Hz, 1H), 2.21 (tdd, J = 12.8, 6.4, 1.5 Hz, 1H), 2.07 – 1.94 (m, 2H), 1.83 (s, 3H), 1.81 – 1.72 (m, 1H), 1.38 (qd, J = 12.7, 3.4 Hz, 1H), 1.30 – 1.10 (m, 7H), 0.91 (d, J = 6.5 Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 212.32, 169.21, 55.44, 45.21, 44.30, 42.85, 33.89, 26.10, 23.93, 23.91, 23.61, 13.90.

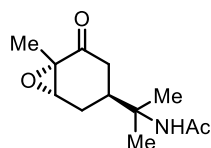
FTIR (cm^{-1}): 3307.0, 2969.9, 1705.7, 1652.3, 1541.6, 1449.1, 1367.0, 966.8, 603.7;

HRMS (ESI) $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{12}\text{H}_{22}\text{NO}$: 212.1645, found: 212.1645;

TLC: R_f = 0.05 (PE: ethyl acetate = 1:1).

Compound 3s

N-(2-((1*S*,3*S*,6*S*)-6-methyl-5-oxo-7-oxabicyclo[4.1.0]heptan-3-yl)propan-2-yl)acetamide)



Following a slightly modified General Procedure A where additional 2.0 equiv.

2,6-lutidine was added. The title compound was synthesized from (1*S*,4*S*,6*S*)-1-methyl-4-(prop-1-en-2-yl)-7-oxabicyclo[4.1.0]heptan-2-one (**2s**) (83.1 mg, 0.50 mmol). The product was purified by silica gel flash column chromatography (PE: ethyl acetate = 10:1 to 1:1) to afford **3s** (48.0 mg, 43%) as a pale yellow solid.

¹H NMR (400 MHz, CDCl₃) δ 5.25 (s, 1H), 3.42 (d, *J* = 3.3 Hz, 1H), 2.83 – 2.70 (m, 1H), 2.50 (ddd, *J* = 17.9, 5.3, 1.5 Hz, 1H), 2.39 – 2.26 (m, 1H), 1.91 (s, 4H), 1.77 (ddd, *J* = 14.7, 12.0, 0.9 Hz, 1H), 1.38 (s, 3H), 1.30 (s, 3H), 1.24 (s, 3H).

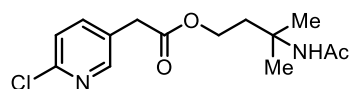
¹³C NMR (101 MHz, CDCl₃) δ 206.71, 170.05, 61.74, 59.33, 55.87, 39.01, 35.40, 25.40, 25.19, 24.93, 24.67, 15.58.

FTIR (cm⁻¹): 3307.8, 2974.1, 2931.6, 2359.2, 2342.5, 1702.4, 1652.6, 1540.9, 1367.5;

HRMS (ESI) [*M* + *H*]⁺ calculated for C₁₂H₂₀NO₃: 226.1438, found: 226.1436;

TLC: R_f = 0.80 (PE: acetone = 1:1).

Compound 3t (3-acetamido-3-methylbutyl 2-(6-chloropyridin-3-yl)acetate)



Following General Procedure A, the title compound was synthesized from 3-methylbut-3-en-1-yl 2-(6-chloropyridin-3-yl)acetate (**2t**) (119.9 mg, 0.50 mmol). The product was purified by silica gel flash column chromatography (PE: ethyl acetate = 10:1 to 1:1) to afford **3t** (134.2 mg, 90%) as a pale yellow solid.

¹H NMR (400 MHz, CDCl₃) δ 8.16 (d, *J* = 2.5 Hz, 1H), 7.52 (dd, *J* = 8.2, 2.5 Hz, 1H), 7.20 (d, *J* = 8.2 Hz, 1H), 5.88 (s, 1H), 4.05 (t, *J* = 7.0 Hz, 2H), 3.50 (s, 2H), 2.03 (t, *J* = 7.0 Hz, 2H), 1.79 (s, 3H), 1.19 (s, 6H).

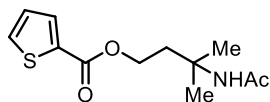
¹³C NMR (101 MHz, CDCl₃) δ 169.81, 169.38, 149.70, 149.55, 139.40, 128.23, 123.63, 61.89, 51.93, 37.03, 36.90, 26.95, 23.72.

FTIR (cm⁻¹): 2970.0, 1731.5, 1650.9, 1587.8, 1566.5, 1384.8, 1355.3

HRMS (ESI) [*M* + *H*]⁺ calculated for C₁₄H₂₀ClN₂O₃: 299.1157, found: 299.1150;

TLC: R_f = 0.05 (PE: ethyl acetate = 1:1).

Compound 3u (3-acetamido-3-methylbutyl thiophene-2-carboxylate)



Following General Procedure A, the title compound was synthesized from 3-methylbut-3-en-1-yl thiophene-2-carboxylate (**2u**) (98.1 mg, 0.50 mmol). The product was purified by silica gel flash column chromatography (PE: ethyl acetate = 10:1 to 1:1) to afford **3u** (121.4 mg, 95%) as a pale yellow solid.

^1H NMR (400 MHz, CDCl_3) δ 7.69 (d, J = 3.8 Hz, 1H), 7.48 (d, J = 5.0 Hz, 1H), 7.01 (t, J = 5.0 Hz, 1H), 6.01 (s, 1H), 4.27 (t, J = 6.6 Hz, 2H), 2.16 (t, J = 6.6 Hz, 2H), 1.84 (s, 3H), 1.31 (s, 6H).

^{13}C NMR (101 MHz, CDCl_3) δ 173.75, 57.89, 40.77, 38.43, 35.33, 33.23, 33.12, 27.46, 26.82, 25.33, 23.10, 17.96.

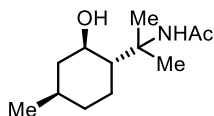
FTIR (cm^{-1}): 2988.0, 2921.3, 1651.2, 1649.8, 1550.4, 1525.4, 1418.0, 1375.8

HRMS (ESI) $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{12}\text{H}_{18}\text{NO}_3\text{S}$: 256.1002, found: 256.1000;

TLC: R_f = 0.20 (PE: ethyl acetate = 1:1).

Compound 3v

(*N*-(2-((1*S*,2*R*,4*R*)-2-hydroxy-4-methylcyclohexyl)propan-2-yl)acetamide)

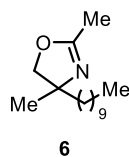


Following a slightly modified General Procedure A where 5 mL aqueous NaOH (1 M) was added during workup. The mixture was stirred for additional 10 minutes and extracted with dichloromethane (3×15 mL). The title compound was synthesized from (-)-isopulegol (**2v**) (78.0 mg, 0.50 mmol). The product was purified by silica gel flash column chromatography (PE: ethyl acetate = 10:1 to 1:1) to afford **3v** (101.3 mg, 95%) as a pale yellow solid. The spectroscopic data matches the literature reported.²²

^1H NMR (400 MHz, CDCl_3) δ 7.45 (s, 1H), 3.66 (td, J = 10.4, 4.4 Hz, 1H), 3.10 (s, 1H), 1.91 (dtd, J = 12.2, 3.9, 2.2 Hz, 1H), 1.86 (s, 3H), 1.82 – 1.72 (m, 1H), 1.68 – 1.61 (m, 1H), 1.46 (s, 4H), 1.30 (s, 3H), 1.26 (s, 2H), 1.11 – 1.06 (m, 1H), 0.89 (d, J = 6.5 Hz, 4H).

^{13}C NMR (101 MHz, CDCl_3) δ 169.54, 72.05, 56.64, 51.37, 45.60, 34.23, 31.22, 25.36, 24.84, 21.69, 21.27.

Compound 6 (4-decyl-2,4-dimethyl-4,5-dihydrooxazole)

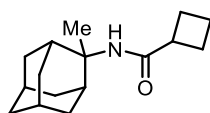


Compound **6** detected by ^1H NMR spectroscopic analysis of the crude reaction mixture (ca. 10%). The structure was assigned based on analogy with literature compounds.²³

Characteristic ^1H NMR signals (protonated form): 4.55 (d, $J = 9.3$ Hz, 1H), 4.48 (d, $J = 9.3$ Hz, 1H), 2.50 (s, 3H), 1.04 (s, 3H).²²

Compound 7a

(±)- (*N*-((1*R*,3*R*,5*R*,7*R*)-2-methyladamantan-2-yl)cyclobutanecarboxamide)



Following General Procedure B, the title compound was synthesized from 2-methylideneadamantane (**2c**) (75.0 mg, 0.50 mmol) and cyanocyclobutane (81.0 mg, 1.0 mmol). The product was purified by silica gel flash column chromatography (PE: ethyl acetate = 50:1 to 10:1) to afford **7a** (86.6 mg, 70%) as a pale yellow solid.

^1H NMR (400 MHz, CDCl_3) δ 5.16 (s, 1H), 2.93 (p, $J = 8.5$ Hz, 1H), 2.26 – 2.15 (m, 2H), 2.14 – 2.03 (m, 4H), 1.95 – 1.73 (m, 8H), 1.66 – 1.52 (m, 6H), 1.45 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 173.47, 57.61, 40.49, 38.15, 35.05, 32.95, 32.85, 27.18, 26.55, 25.05, 22.82, 17.68.

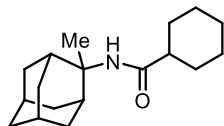
FTIR (cm^{-1}): 3316.8, 2896.0, 2856.4, 1637.6, 1540.6, 1446.2, 1273.4, 1222.8, 1124.4;

HRMS (ESI) $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{16}\text{H}_{26}\text{NO}$: 248.2009, found: 248.2005;

TLC: $R_f = 0.90$ (PE: ethyl acetate = 2:1).

Compound 7b

(±)- (*N*-((1*R*,3*R*,5*R*,7*R*)-2-methyladamantan-2-yl)cyclohexanecarboxamide)



Following General Procedure B, the title compound was synthesized from 2-methylideneadamantane (**2c**) (75.0 mg, 0.50 mmol) and cyclohexanecarbonitrile (109.2 mg, 1.0 mmol). The product was purified by silica gel flash column chromatography (PE: ethyl acetate = 50:1 to 10:1) to afford **7b** (89.5 mg, 65%) as a pale yellow solid.

^1H NMR (400 MHz, CDCl_3) δ 5.26 (s, 1H), 2.12 (s, 2H), 2.03 – 1.87 (m, 5H), 1.84 – 1.71 (m, 6H), 1.66 – 1.53 (m, 7H), 1.44 (m, 2H), 1.40 – 1.10 (m, 6H).

^{13}C NMR (101 MHz, CDCl_3) δ 174.92, 57.82, 46.50, 38.44, 35.32, 33.24, 33.15, 29.90, 27.48, 26.85, 25.80, 23.12.

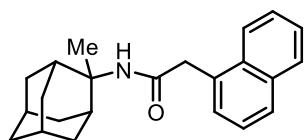
FTIR (cm^{-1}): 3316.6., 2918.4, 2854.0, 1645.3, 1533.5, 1448.3, 1368.4, 1211.3, 959.6;

HRMS (ESI) $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{18}\text{H}_{30}\text{NO}$: 276.2322, found: 276.2322;

TLC: R_f = 0.80 (PE: ethyl acetate = 5:1).

Compound 7c

(±)- (*N*-((1*R*,3*R*,5*R*,7*R*)-2-methyladamantan-2-yl)-2-(naphthalen-1-yl)acetamide)



Following General Procedure B, the title compound was synthesized from 2-methylideneadamantane (**2c**) (75.0 mg, 0.50 mmol) and 1-naphthyl acetonitrile (167.2 mg, 1.0 mmol). The product was purified by silica gel flash column chromatography (PE: ethyl acetate = 50:1 to 10:1) to afford **7c** (96.7 mg, 58%) as a pale yellow solid.

^1H NMR (400 MHz, CDCl_3) δ 8.05 – 7.99 (m, 1H), 7.89 – 7.82 (m, 1H), 7.80 (d, J = 8.1 Hz, 1H), 7.55 – 7.47 (m, 2H), 7.47 – 7.37 (m, 2H), 5.09 (s, 1H), 3.98 (s, 2H), 1.92 – 1.77 (m, 4H), 1.68 (p, J = 3.1 Hz, 1H), 1.54 – 1.44 (m, 4H), 1.40 (s, 3H), 1.32 – 1.16 (m, 5H).

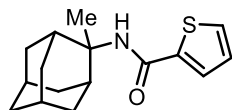
^{13}C NMR (101 MHz, CDCl_3) δ 169.22, 133.65, 131.72, 131.60, 128.45, 128.08, 127.87, 125.92, 125.35, 123.79, 57.91, 42.81, 38.03, 34.91, 32.83, 32.35, 27.04, 26.25, 22.50.

FTIR (cm^{-1}): 3309.1, 2908.0, 1643.8, 1538.0, 1448.1, 1353.2, 1129.9, 781.6;

HRMS (ESI) $[M + H]^+$ calculated for $C_{23}H_{28}NO$: 334.2165, found: 334.2163;

Compound 7d

(±)- (*N*-((1*R*,3*R*,5*R*,7*R*)-2-methyladamantan-2-yl)thiophene-2-carboxamide)



Following General Procedure B, the title compound was synthesized from 2-methylideneadamantane (**2c**) (75.0 mg, 0.50 mmol) and 2-thiophenecarbonitrile (109.2 mg, 1.0 mmol). The product was purified by silica gel flash column chromatography (PE: ethyl acetate = 50:1 to 10:1) to afford **7d** (78.5 mg, 57%) as a pale yellow solid.

1H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, $J = 3.7, 1.2$ Hz, 1H), 7.40 (dd, $J = 5.0, 1.2$ Hz, 1H), 7.03 (dd, $J = 5.0, 3.7$ Hz, 1H), 5.85 (s, 1H), 2.27 (s, 2H), 2.07 – 1.95 (m, 4H), 1.83 (m, 2H), 1.74 – 1.58 (m, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.80, 140.71, 129.28, 127.52, 127.39, 59.14, 38.42, 35.54, 33.28, 27.45, 26.83, 23.16.

FTIR (cm^{-1}): 3338.0, 2915.8, 2857.0, 1628.0, 1539.3, 1506.6, 1300.8, 1155.3, 1130.6;

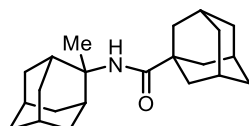
HRMS (ESI) $[M + H]^+$ calculated for $C_{16}H_{22}NOS$: 276.1417, found: 276.1417;

TLC: $R_f = 0.85$ (PE: ethyl acetate = 2:1).

Compound 7e

(±)-

((3*R*,5*R*,7*R*)-*N*-((1*R*,3*R*,5*R*,7*R*)-2-methyladamantan-2-yl)adamantane-1-carboxamide)



Following General Procedure C, the title compound was synthesized from 2-methylideneadamantane (**2c**) (75.0 mg, 0.50 mmol) and 1-adamantanecarbonitrile (403.2 mg, 2.5 mmol). The product was purified by silica gel flash column

chromatography (PE: ethyl acetate = 50:1 to 10:1) to afford **7e** (83.6 mg, 51%) as a pale yellow solid.

^1H NMR (400 MHz, CDCl_3) δ 5.42 (s, 1H), 2.16 (s, 2H), 2.03 (s, 3H), 1.99 (m, 1H), 1.96 (m, 1H), 1.93 – 1.90 (m, 1H), 1.88 (m, 1H), 1.84 (m, 6H), 1.80 (p, J = 3.0 Hz, 1H), 1.69 (m, 9H), 1.65 – 1.56 (m, 3H), 1.47 (s, 3H), 1.28 – 1.20 (m, 1H).

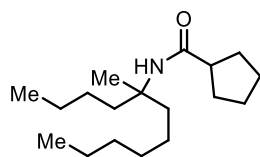
^{13}C NMR (101 MHz, CDCl_3) δ 176.29, 57.25, 41.04, 39.33, 38.28, 36.38, 35.20, 33.09, 33.05, 28.08, 27.31, 26.69, 22.87.

FTIR (cm^{-1}): 3365.7, 2903.0, 2852.8, 1639.1, 1518.7, 1453.7, 1278.2 1180.9, 800.7;

HRMS (ESI) $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{22}\text{H}_{34}\text{NO}$: 328.2635, found: 328.2634;

TLC: R_f = 0.90 (PE: ethyl acetate = 3:1).

Compound **7f** (\pm)- (*N*-(5-methylundecan-5-yl)cyclopentanecarboxamide)



Following General Procedure C, the title compound was synthesized from 5-methyleneundecane (**2b**) (84.1 mg, 0.50 mmol) and cyanocyclopentane (238.0 mg, 2.5 mmol). The product was purified by silica gel flash column chromatography (PE: ethyl acetate = 50:1 to 10:1) to afford **7f** (87.0 mg, 62%) as a pale yellow solid.

^1H NMR (400 MHz, CDCl_3) δ 5.05 (s, 1H), 2.47 – 2.33 (m, 1H), 1.85 – 1.62 (m, 8H), 1.62 – 1.46 (m, 4H), 1.42 – 1.09 (m, 15H), 0.87 (t, J = 6.8 Hz, 6H).

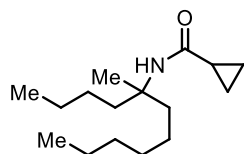
^{13}C NMR (101 MHz, CDCl_3) δ 175.40, 56.06, 46.80, 38.55, 38.30, 32.00, 30.61, 29.80, 26.03, 24.64, 23.75, 23.20, 22.75, 14.27, 14.18.

FTIR (cm^{-1}): 3315.8, 2927.3, 2860.0, 1644.6, 1541.5, 1466.3, 1378.6, 1263.3, 1090.4;

HRMS (ESI) $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{18}\text{H}_{36}\text{NO}$: 282.2791, found: 282.2787;

TLC: R_f = 0.50 (PE: ethyl acetate = 10:1).

Compound **7g** (\pm)- (*N*-(5-methylundecan-5-yl)cyclopropanecarboxamide)



Following General Procedure C, the title compound was synthesized from 5-methyleneundecane (**2b**) (84.1 mg, 0.50 mmol) and cyclopropanecarbonitrile (167.8 mg, 2.5 mmol). The product was purified by silica gel flash column chromatography (PE: ethyl acetate = 50:1 to 10:1) to afford **7g** (88.8 mg, 70%) as a pale yellow solid.

^1H NMR (400 MHz, CDCl_3) δ 5.24 (s, 1H), 1.76 – 1.64 (m, 2H), 1.63 – 1.51 (m, 2H), 1.35 – 1.11 (m, 16H), 0.95 – 0.80 (m, 8H), 0.69 – 0.57 (m, 2H).

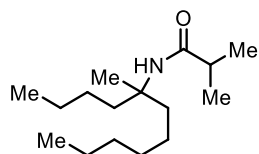
^{13}C NMR (101 MHz, CDCl_3) δ 172.11, 56.07, 38.39, 38.14, 31.68, 29.50, 25.73, 24.39, 23.44, 22.91, 22.46, 15.17, 13.98, 13.90, 6.34.

FTIR (cm^{-1}): 3312.0, 2954.8, 2927.1, 2858.9, 2358.8, 1643.6, 1545.1, 1466.2, 1271.9;

HRMS (ESI) $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{16}\text{H}_{32}\text{NO}$: 254.2478, found: 254.2475;

TLC: R_f = 0.90 (PE: ethyl acetate = 1:1).

Compound 7h (\pm)- (*N*-(5-methylundecan-5-yl)isobutyramide)



Following General Procedure C, the title compound was synthesized from 5-methyleneundecane (**2b**) (84.1 mg, 0.50 mmol) and isobutyronitrile (173.0 mg, 2.5 mmol). The product was purified by silica gel flash column chromatography (PE: ethyl acetate = 50:1 to 10:1) to afford **7h** (58.0 mg, 45%) as a pale yellow solid.

^1H NMR (400 MHz, CDCl_3) δ 5.02 (s, 1H), 2.23 (heptet, J = 6.9 Hz, 1H), 1.76 – 1.64 (m, 2H), 1.62 – 1.47 (m, 2H), 1.35 – 1.13 (m, 15H), 1.10 (d, J = 6.9 Hz, 6H), 0.87 (t, J = 6.8 Hz, 6H).

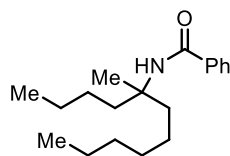
^{13}C NMR (101 MHz, CDCl_3) δ 176.07, 55.83, 38.40, 38.14, 36.49, 31.88, 29.68, 25.91, 24.49, 23.62, 23.08, 22.63, 19.84, 14.16, 14.07.

FTIR (cm^{-1}): 3315.2, 2956.8, 2926.4, 2858.9, 1646.4, 1541.5, 1466.6, 1379.9, 1094.6;

HRMS (ESI) $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{16}\text{H}_{34}\text{NO}$: 256.2634, found: 256.2636;

TLC: R_f = 0.60 (PE: ethyl acetate = 10:1).

Compound 7i (±)- (*N*-(5-methylundecan-5-yl)benzamide)



Following General Procedure C, the title compound was synthesized from 5-methyleneundecane (**2b**) (84.1 mg, 0.50 mmol) and benzonitrile (257.8 mg, 2.5 mmol). The product was purified by silica gel flash column chromatography (PE: ethyl acetate = 50:1 to 10:1) to afford **7i** (81.1 mg, 56%) as a pale yellow solid.

^1H NMR (400 MHz, CDCl_3) δ 7.78 – 7.65 (m, 2H), 7.54 – 7.32 (m, 3H), 5.78 (s, 1H), 1.86 (m, 2H), 1.71 (m, 2H), 1.39 – 1.17 (m, 15H), 0.87 (t, J = 6.8 Hz, 6H).

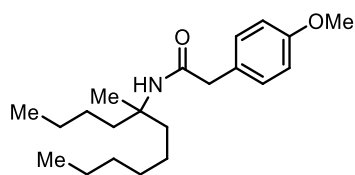
^{13}C NMR (101 MHz, CDCl_3) δ 165.72, 135.08, 129.97, 127.45, 125.64, 55.68, 37.50, 37.22, 30.85, 28.69, 24.98, 23.49, 22.72, 22.09, 21.64, 13.15, 13.07.

FTIR (cm^{-1}): 3311.5, 2954.9, 2927.1, 2858.4, 1639.9, 1534.2, 1488.9, 1466.1, 1292.3;

HRMS (ESI) $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{19}\text{H}_{32}\text{NO}$: 290.2478, found: 290.2474;

TLC: R_f = 0.60 (PE: ethyl acetate = 10:1).

Compound 7j (±)- (2-(4-methoxyphenyl)-*N*-(5-methylundecan-5-yl)acetamide)



Following General Procedure C, the title compound was synthesized from 5-methyleneundecane (**2b**) (84.1 mg, 0.50 mmol) and 4-methoxybenzyl cyanide (368.0 mg, 2.5 mmol). The product was purified by silica gel flash column chromatography (PE: ethyl acetate = 50:1 to 10:1) to afford **7j** (68.4 mg, 41%) as a pale yellow solid.

^1H NMR (400 MHz, CDCl_3) δ 7.19 – 7.04 (m, 2H), 6.91 – 6.83 (m, 2H), 4.99 (s, 1H), 3.79 (s, 3H), 3.41 (s, 2H), 1.61 (m, 2H), 1.55 – 1.41 (m, 2H), 1.29 – 1.14 (m, 11H), 1.11 – 1.00 (m, 4H), 0.87 (t, J = 6.8 Hz, 6H).

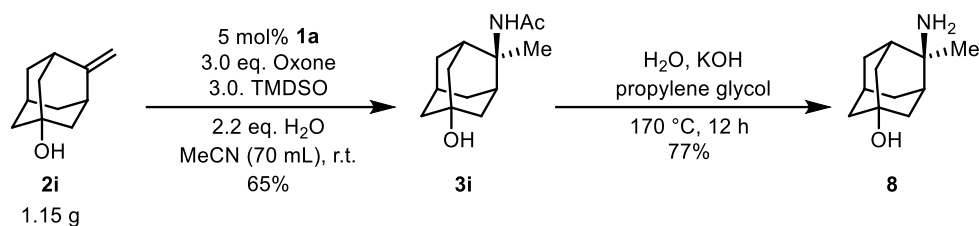
^{13}C NMR (101 MHz, CDCl_3) δ 170.19, 158.37, 130.00, 127.21, 113.96, 55.86, 54.87, 43.71, 37.94, 37.65, 31.46, 29.22, 25.43, 23.80, 23.13, 22.63, 22.21, 13.73, 13.6

FTIR (cm^{-1}): 3308.1, 2928.1, 2858.6, 1646.00, 1511.0, 1246.7 1176.9, 1037.4, 802.4;

HRMS (ESI) $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{21}\text{H}_{36}\text{NO}$: 334.2741, found: 334.2741;

TLC: $R_f = 0.25$ (PE: ethyl acetate = 10:1).

III. Gram-Scale Hydroamidation and Application



To a 250 mL oven-dried round bottom flask containing a magnetic stir bar was added **2i** (1.15 g, 7.00 mmol, 1.00 equiv.), Co catalyst **1a** (212 mg, 0.350 mmol, 0.0500 equiv.) and oxone (100 mesh, 12.9 g, 21.0 mmol, 3.00 equiv.). The reaction vessel was then briefly evacuated and backfilled with nitrogen (this sequence was repeated a total of three times). Anhydrous acetonitrile (70 mL), H₂O (280 μ L, 15.4 mmol, 2.20 equiv.) and 1,1,3,3-tetramethyldisiloxane (3.80 mL, 21.0 mmol, 3.00 equiv.) were added to the reaction vessel via syringe sequentially. The reaction mixture was stirred at r.t. for 21 h. The resulting mixture was filtered and dried over Na₂SO₄, concentrated *in vacuo* and purified by silica gel chromatography to afford **3i** (major diastereomer, 1.02 g, 65%) as a yellow solid.



Figure S2. Reaction mixture of gram-scale experiment

A mixture of potassium hydroxide (powder, 0.34 g, 6.0 mmol), water (33 μ L), and propylene glycol (0.25 mL) was stirred at room temperature for 1 h, to which was added **3i** (0.12 g, 0.50 mol). The mixture was stirred at 170 °C for 12 h, cooled to r.t. followed by the addition of ice-cold water (10 mL). The reaction mixture was extracted with dichloromethane. The combined organic layers were dried over Na₂SO₄, filtered and concentrated *in vacuo* to afford **8** (69.8 mg, 77% yield) as a pale yellow solid.

¹H NMR (400 MHz, CDCl₃) δ 2.12 – 2.06 (m, 3H), 1.88 (m, 2H), 1.80 (s, 3H), 1.73 (s,

2H), 1.66 (s, 2H), 1.54 – 1.49 (m, 3H), 1.27 – 1.23 (m, 1H), 1.21 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 67.62, 52.06, 46.26, 41.64, 40.65, 33.05, 29.52, 27.01.

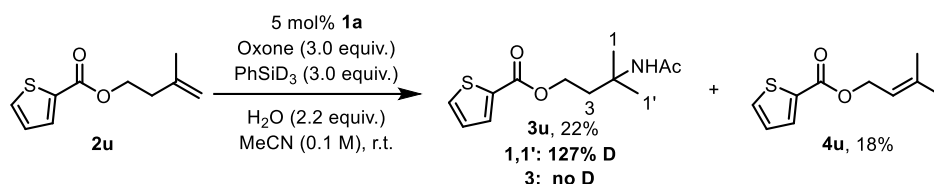
FTIR (cm^{-1}): 3539.4, 2920.8, 2851.9, 1659.1, 1114.4, 832.0;

HRMS (ESI) $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{11}\text{H}_{20}\text{NO}$: 182.1539, found: 182.1539;

TLC: $R_f = 0.25$ (CHCl_3 : CH_3OH : acetone: $\text{NH}_3 \cdot \text{H}_2\text{O} = 9:1.5:1:0.014$, ninhydrin in *n*-butyl alcohol as a visualizing agent)

IV. Mechanistic Investigation

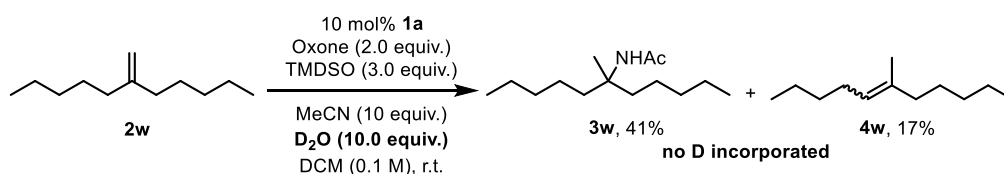
IV-A. With Deuterium-Labeled Silane (Scheme 4a)



An oven-dried 10 mL re-sealable screw-cap vial equipped with a Teflon-coated magnetic stir bar was charged with Co catalyst **1a** (3.0 mg, 0.0050 mmol, 0.050 equiv.) and oxone (100 mesh, 184 mg, 0.30 mmol, 3.0 equiv.). The reaction vessel was then briefly evacuated and backfilled with nitrogen (this sequence was repeated a total of three times). Anhydrous acetonitrile (1.0 mL), **2u** (19.6 mg, 0.10 mmol, 1.0 equiv.), degassed H₂O (4 μ L, 0.22 mmol, 2.2 equiv.) and PhSiD₃ (33 mg, 0.30 mmol, 3.0 equiv.) were added to the reaction vessel via syringe sequentially. The reaction mixture was stirred at r.t. for 18 h before an NMR internal standard (phenanthrene, 0.10 mmol, 18 mg) was added. The mixture was filtered through a short pad of silica gel with another 5 mL CH₂Cl₂/MeOH (20/1) as an eluent. The solvents were removed *in vacuo* and the residue was analyzed by ¹H NMR spectroscopy.

The levels of deuteration in each position (1, 1' and 3) were measured by ¹H NMR spectroscopy. **3u** with multiple deuterium substitution at the 1,1' position was noticed by ¹H and ¹³C NMR, as well as GCMS analysis. The ¹H NMR spectrum of **3u** showed that 127% deuterium incorporation at C1 and no deuterium incorporation at C3.

IV-B. Test for Proton-Activation (Scheme 4b)



An oven-dried 10 mL re-sealable screw-cap vial equipped with a Teflon-coated magnetic stir bar was charged with Co catalyst **1a** (6.0 mg, 0.010 mmol, 0.010 equiv.) and oxone (100 mesh, 123 mg, 0.20 mmol, 2.0 equiv.). The reaction vessel was then briefly evacuated and backfilled with nitrogen (this sequence was repeated a total of three times). Anhydrous CH₂Cl₂ (1.0 mL), **2w** (17 mg, 0.10 mmol, 1.0 equiv.), degassed D₂O (20 μ L, 1.0 mmol, 10 equiv.) and MeCN (54 μ L, 1.0 mmol, 10 equiv.) were added to the reaction vessel via syringe sequentially. The reaction mixture was stirred at r.t. for 18 h before an NMR internal standard (phenanthrene, 0.10 mmol, 18 mg) was added. The mixture was filtered through a short pad of silica gel with another 5 mL CH₂Cl₂/MeOH (20/1) as an

eluent. The solvents were removed *in vacuo* and the residue was analyzed by ^1H NMR spectroscopy to obtain the yields. Purification by silica gel chromatography afforded **3w** as a colorless oil. **4w** (ca. 1:1 mixture of E/Z isomers) could not be separated from the hydrogenation byproduct. Characteristic ^1H NMR signals of **4w**: 1.57 (s, 3H), 1.66 (d, J = 1.3 Hz, 3H). A standard sample of **3w** was independently prepared following General Procedure A with slight modification, where **2w** (0.10 mmol) was used. Deuterium incorporation in **3w** and **4w** was excluded by comparing their ^1H NMR spectra and GCMS data with standard samples prepared under D-free conditions.

N-(6-methylundecan-6-yl)acetamide (3w): ^1H NMR (400 MHz, CDCl_3) δ 5.09 (s, 1H), 1.90 (s, 3H), 1.76 – 1.63 (m, 2H), 1.56 (dt, J = 13.8, 6.9 Hz, 2H), 1.23 (m, 15H), 0.87 (t, J = 6.9 Hz, 6H).

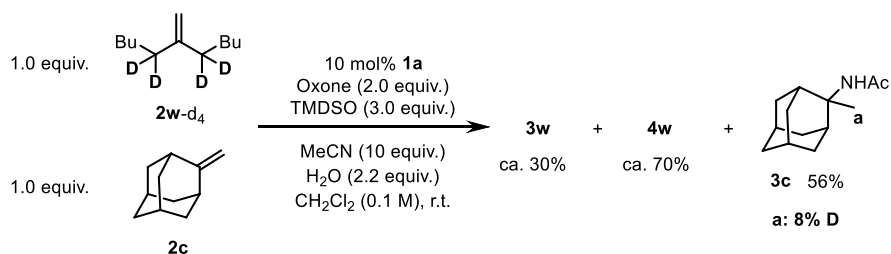
^{13}C NMR (101 MHz, CDCl_3) δ 169.09, 56.16, 38.10, 32.01, 24.30, 23.16, 22.49, 13.86.

FTIR (cm^{-1}): 3298.7, 2924.9, 2857.9, 1647.6, 1553.0, 1465.7, 1370.6, 1302.3;

HRMS (ESI) $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{14}\text{H}_{30}\text{NO}$: 228.2322, found: 228.2322;

TLC: R_f = 0.90 (PE: ethyl acetate = 1:1).

IV-C. Crossover Reaction (Scheme 4c)



An oven-dried 10 mL re-sealable screw-cap vial equipped with a Teflon-coated magnetic stir bar was charged with Co catalyst **1a** (18 mg, 0.030 mmol, 0.010 equiv.) and oxone (369 mg, 0.60 mmol, 2.0 equiv.). The reaction vessel was then briefly evacuated and backfilled with nitrogen (this sequence was repeated a total of three times). Anhydrous CH_2Cl_2 (1.0 mL), **2w-d₄** (52 mg, 0.30 mmol, 1.0 equiv.), **2c** (45 mg, 0.30 mmol, 1.0 equiv.), degassed H_2O (12 μL , 0.66 mmol, 2.2 equiv.) and MeCN (162 μL , 3.0 mmol, 10 equiv.) were added to the reaction vessel via syringe sequentially. The reaction mixture was stirred at r.t. for 18 h before an NMR internal standard (phenanthrene, 0.10 mmol, 18 mg) was added. The mixture was filtered through a short pad of silica gel with another 5 mL $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (20/1) as an eluent. The solvents were removed *in vacuo* and the residue was analyzed by ^1H NMR spectroscopy to obtain the yields. The product was purified by silica gel flash column chromatography to afford **3c**.

The level of deuteration at C(a) were measured by ^1H NMR spectroscopy to be 8% and confirmed by GCMS analysis.

IV-D. Effect of the amount of nitrile (Scheme 4d)

An oven-dried 10 mL re-sealable screw-cap vial equipped with a Teflon-coated magnetic stir bar was charged with Co catalyst **1a** (6.0 mg, 0.010 mmol, 0.10 equiv.) and oxone (100 mesh, 123 mg, 0.20 mmol, 2.0 equiv.). The reaction vessel was then briefly evacuated and backfilled with nitrogen (this sequence was repeated a total of three times). Anhydrous dichloromethane (1.0 mL), **2w** (16.8 mg, 0.10 mmol, 1.0 equiv.), degassed H_2O (4 μL , 0.22 mmol, 2.2 equiv.), 1,1,3,3-tetramethyldisiloxane (55 μL , 0.30 mmol, 3.0 equiv.) and cyclopropanecarbonitrile (X equiv., X = 1, 2, 3, 4 or 5) were added to the reaction vessel via syringe sequentially. The reaction mixture was stirred at r.t. for 18 h before an NMR internal standard (phenanthrene) was added. The mixture was filtered through a short pad of silica gel with another 5 mL $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (20/1) as an eluent. The solvents were removed *in vacuo* and the residue was analyzed by ^1H NMR spectroscopy. Characteristic ^1H NMR signals: 0.64 – 0.56 (m, 2H).

N-(6-methylundecan-6-yl)cyclopropanecarboxamide (3x): ^1H NMR (400 MHz, CDCl_3) δ 5.33 (s, 1H), 1.73 – 1.67 (m, 2H), 1.60 – 1.55 (m, 2H), 1.31 – 1.17 (m, 16H), 0.87 – 0.82 (m, 8H), 0.64 – 0.56 (m, 2H).

^{13}C NMR (101 MHz, CDCl_3) δ 171.99, 55.93, 38.18, 31.88, 24.22, 22.98, 22.32, 14.95, 13.70, 6.14.

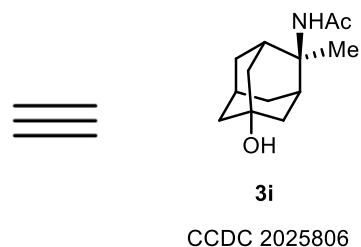
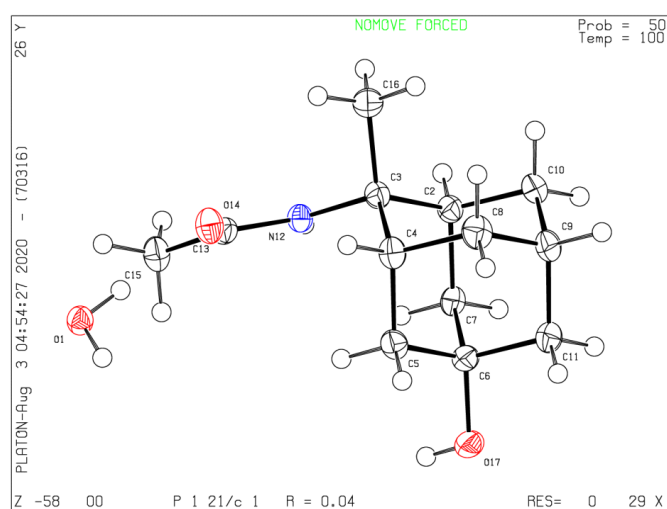
FTIR (cm^{-1}): 2930.7, 1656.5, 1511.5, 1466.8, 1258.3, 1032.4, 921.5, 801.2, 736.3;

TLC: R_f = 0.70 (PE: ethyl acetate = 3:1).

ρ g/cm ³	1.117
μ /mm ⁻¹	0.591
F(000)	472.0
Radiation	CuK α (λ = 1.54184)
h,k,l _{max}	10,10,24
N _{ref}	2628[1538]
T _{min} , T _{max}	0.932, 0.971

Crystallographic Data of Compound **3i**

Compound **3i** was dissolved in diethyl ether. The solvent was slowly evaporated at ambient temperature to afford the single crystal.



Empirical formula	C ₁₃ H ₂₁ NO ₂
Formula weight	223.32
Temperature/K	100
Space group	P21/c
Hall group	-P2ybc
a/Å	12.8834(1)

$b/\text{\AA}$	7.9504(1)
$c/\text{\AA}$	13.1471(1)
$\alpha/^\circ$	90
$\beta/^\circ$	94.302(1)
$\gamma/^\circ$	90
Volume/ \AA^3	1342.84(2)
Z	4
ρ g/cm ³	1.194
μ/mm^{-1}	0.676
F(000)	528.0
Radiation	CuK α ($\lambda = 1.54184$)
h,k,l _{max}	16,9,16
N _{ref}	2780
T _{min} , T _{max}	0.922, 0.987

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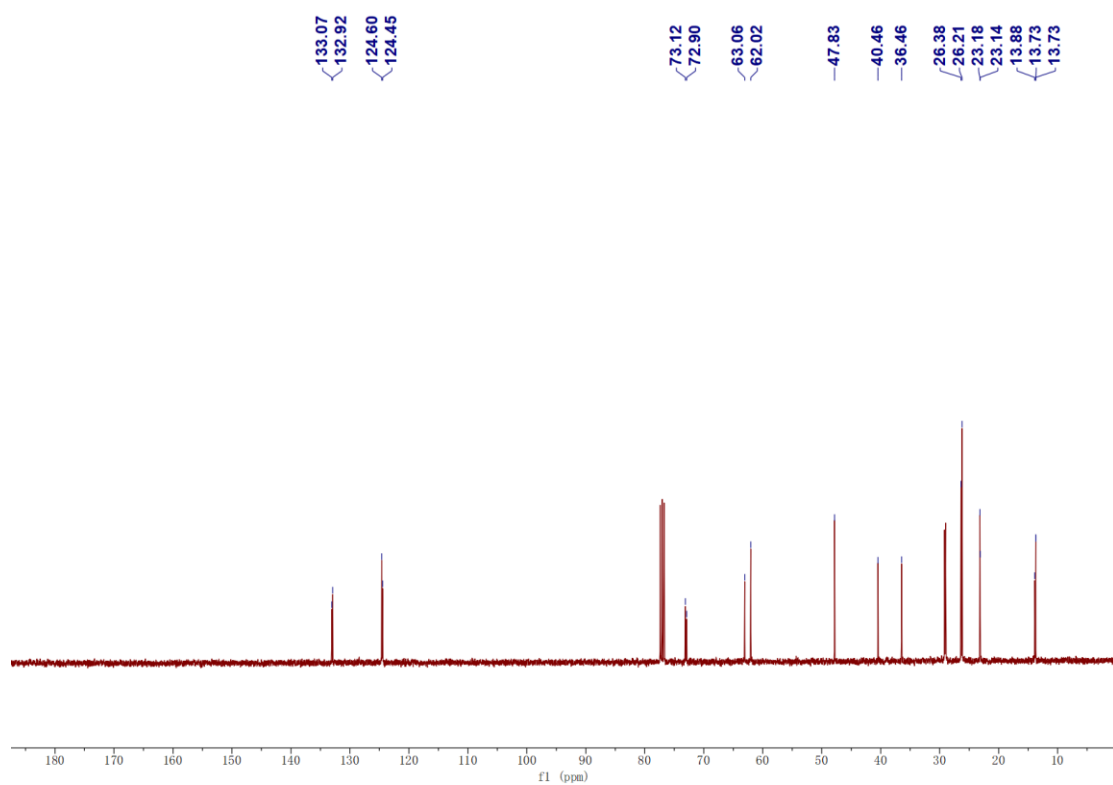
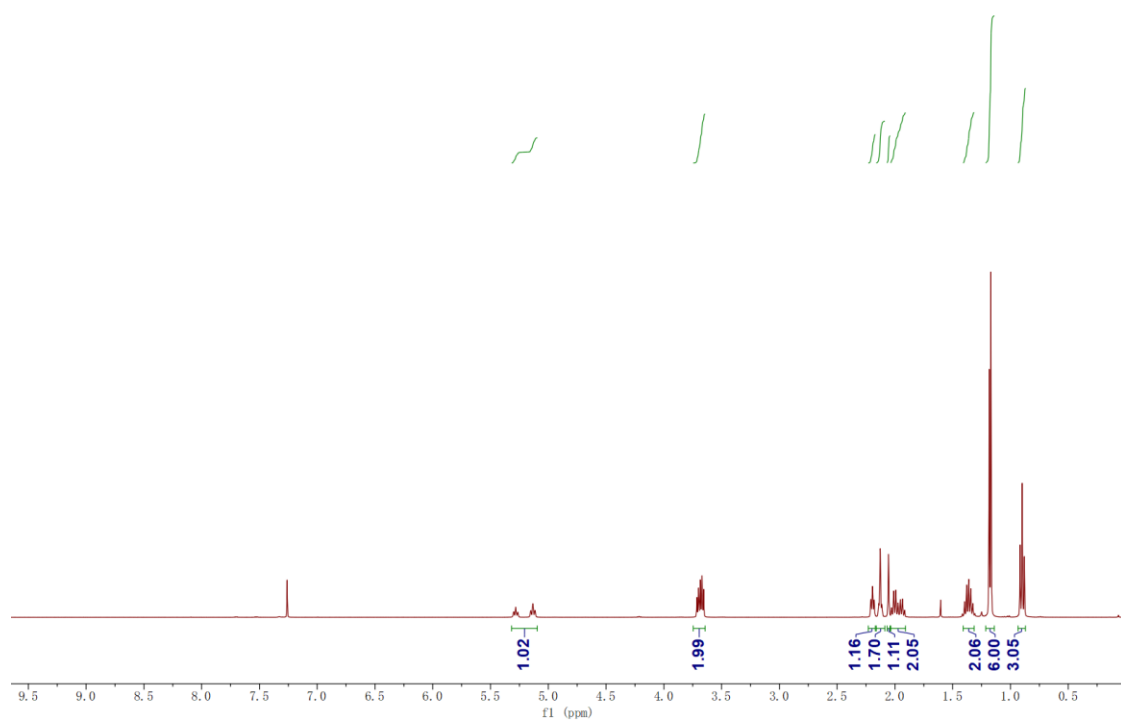
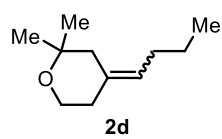
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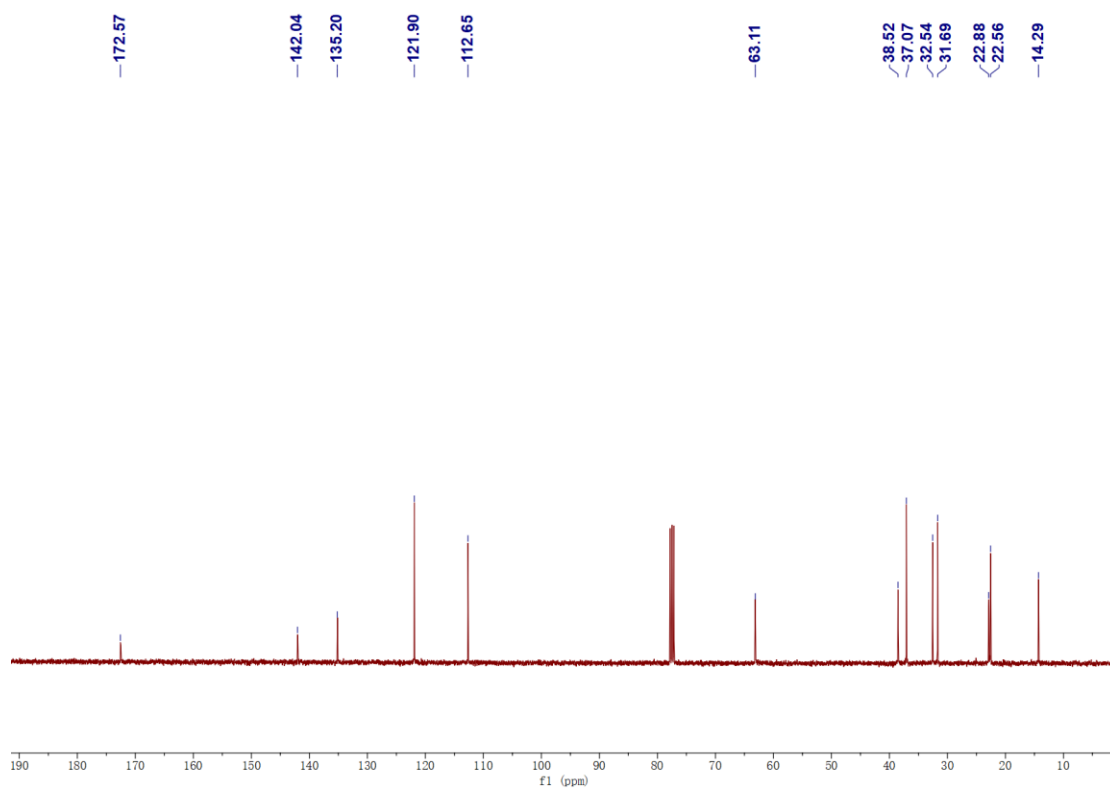
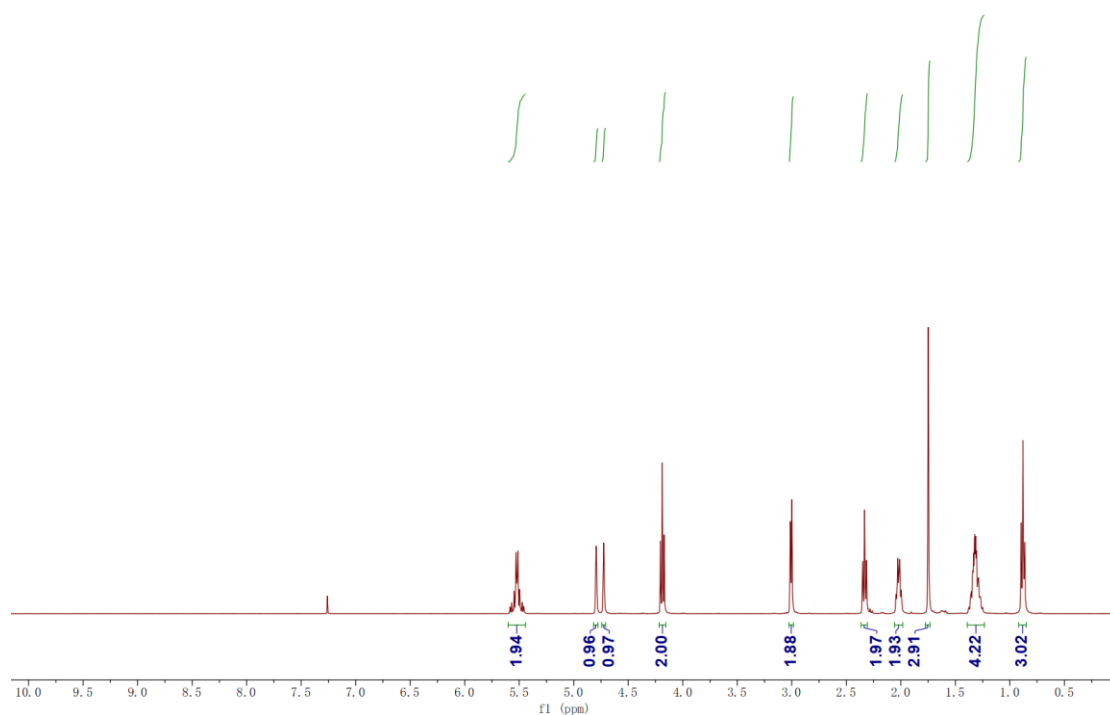
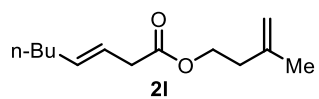
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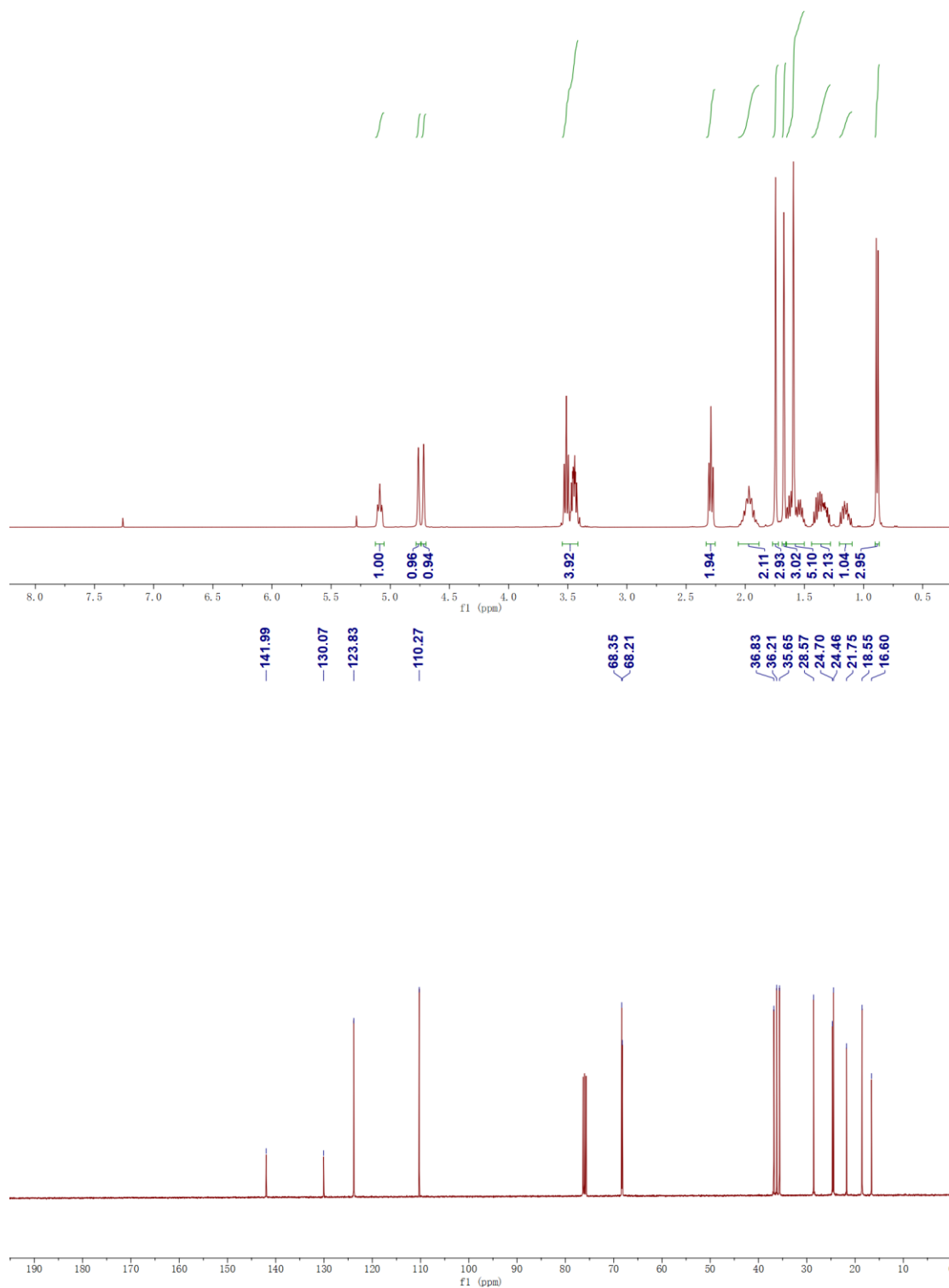
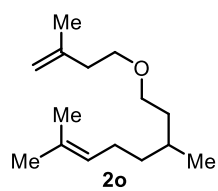
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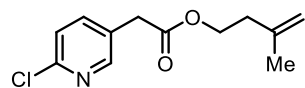
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VI. NMR Spectra

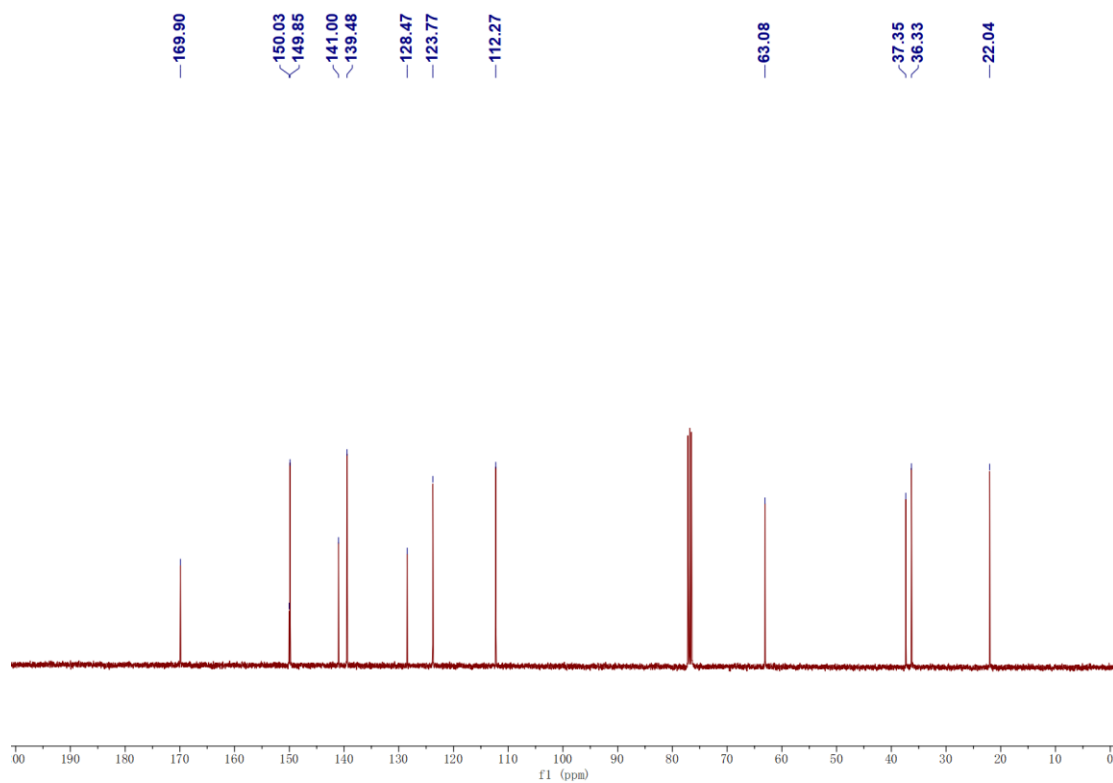
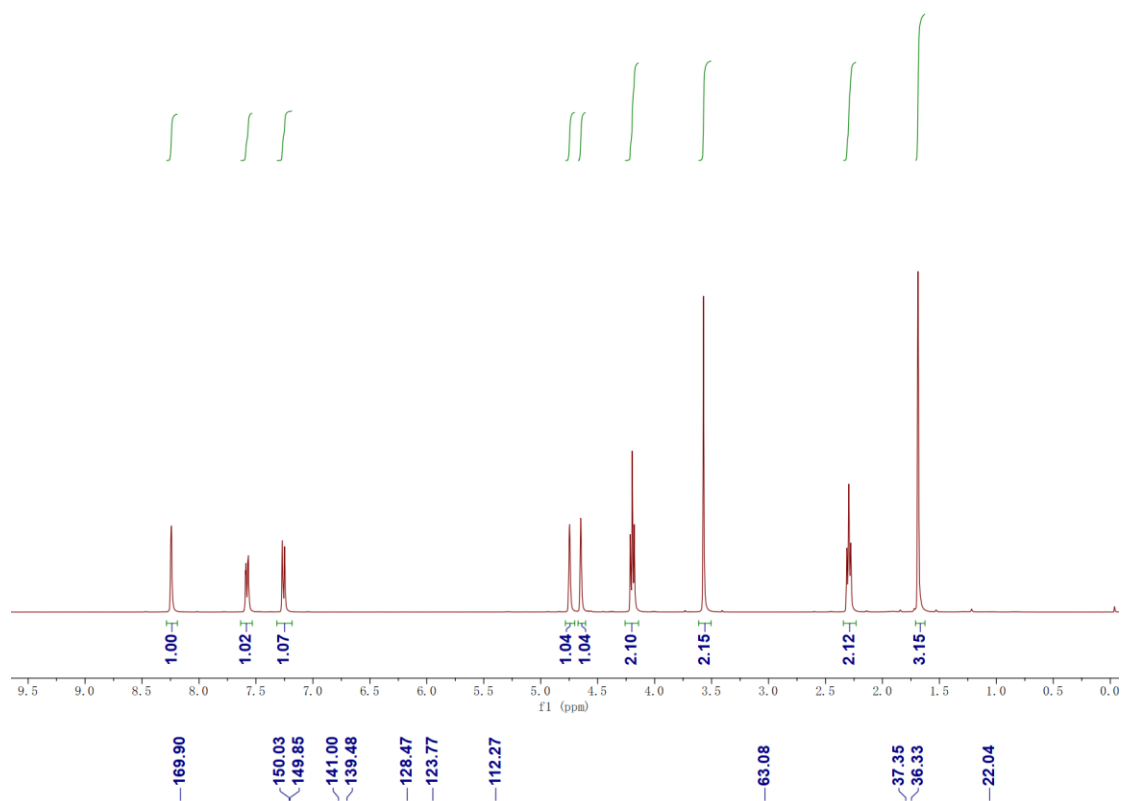


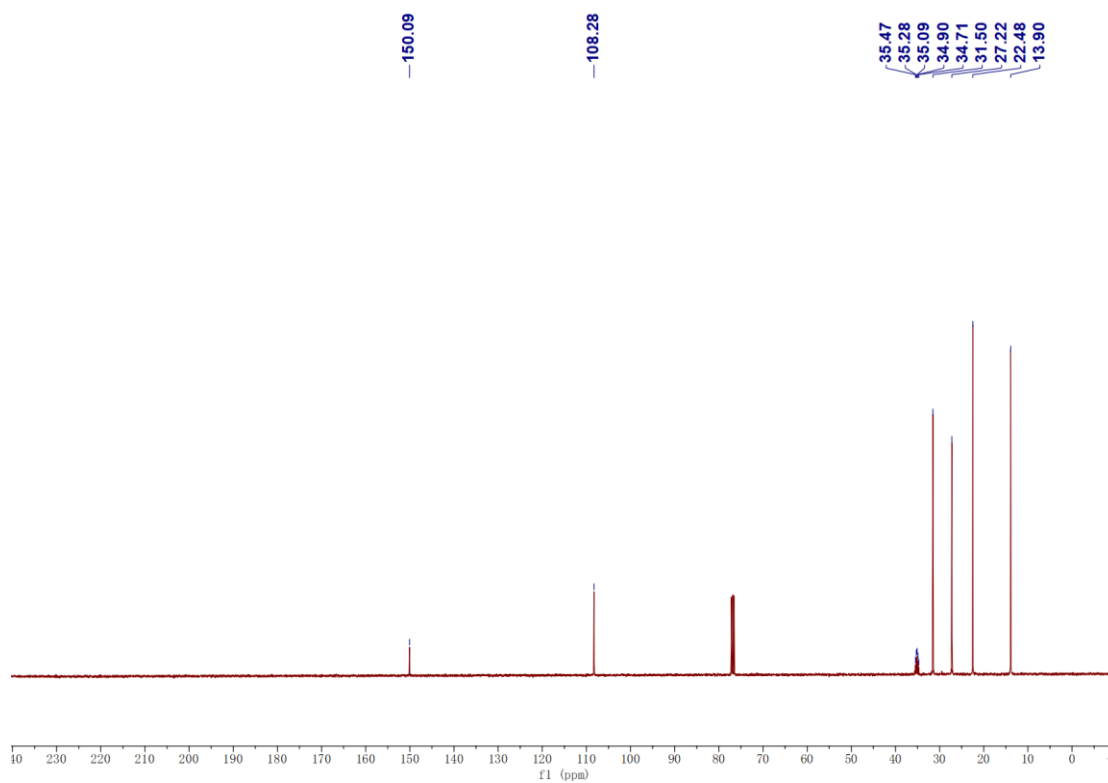
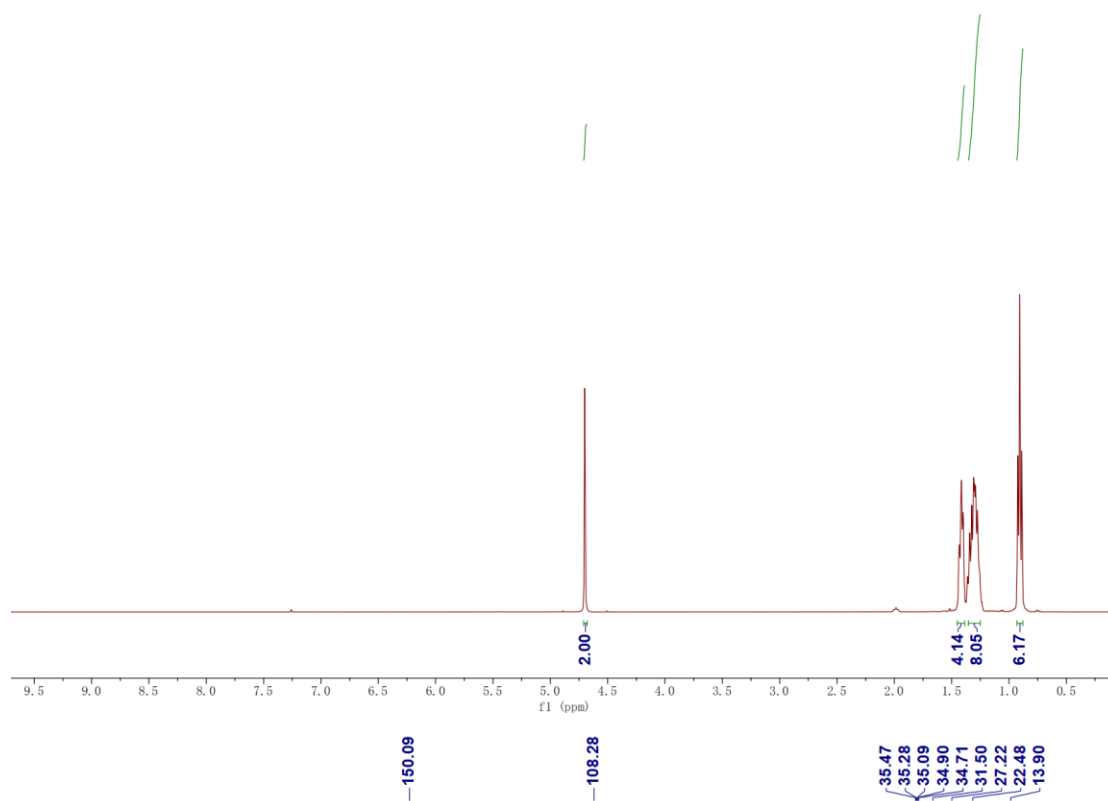
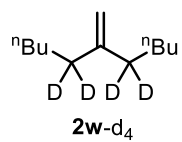


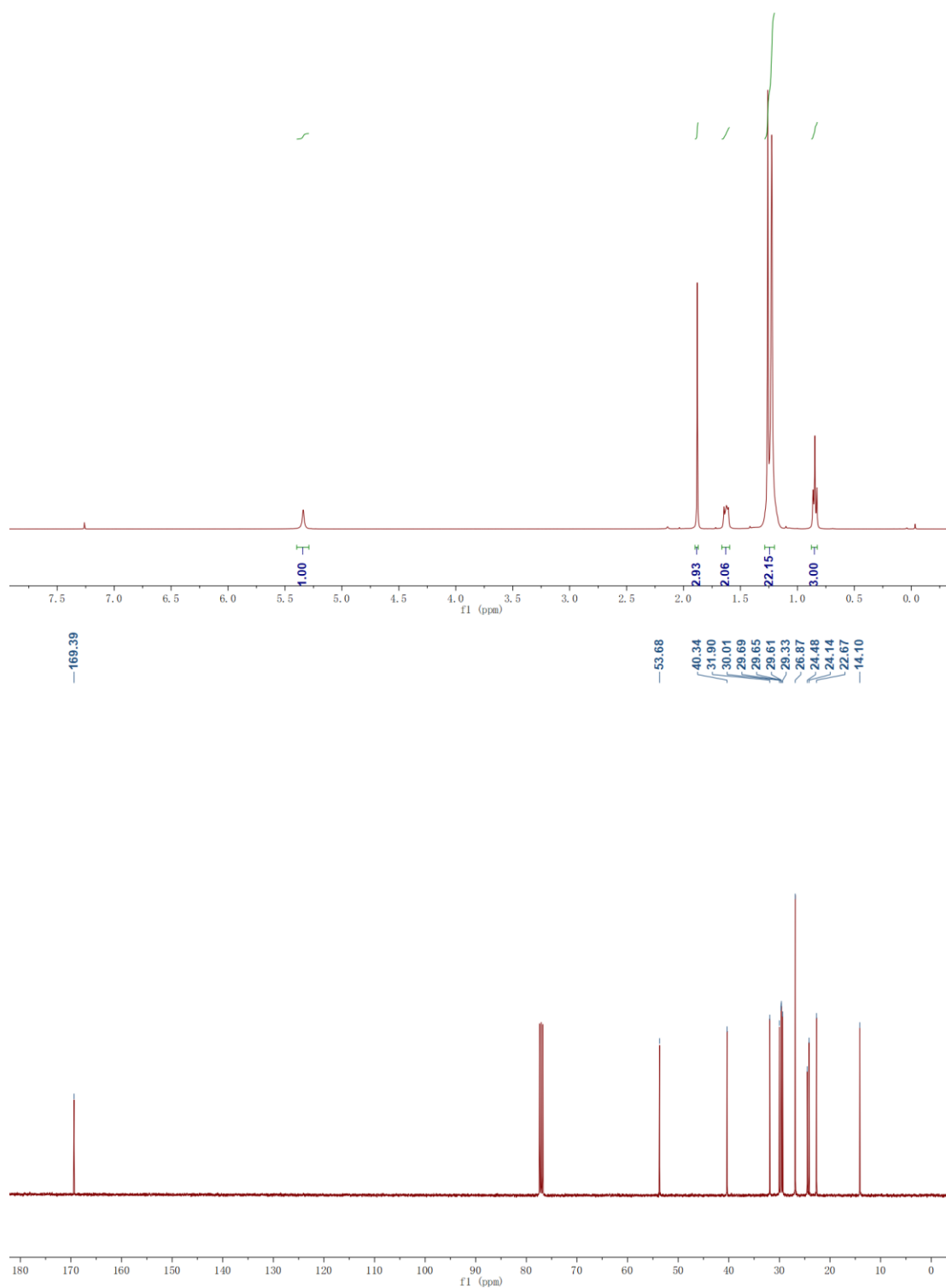


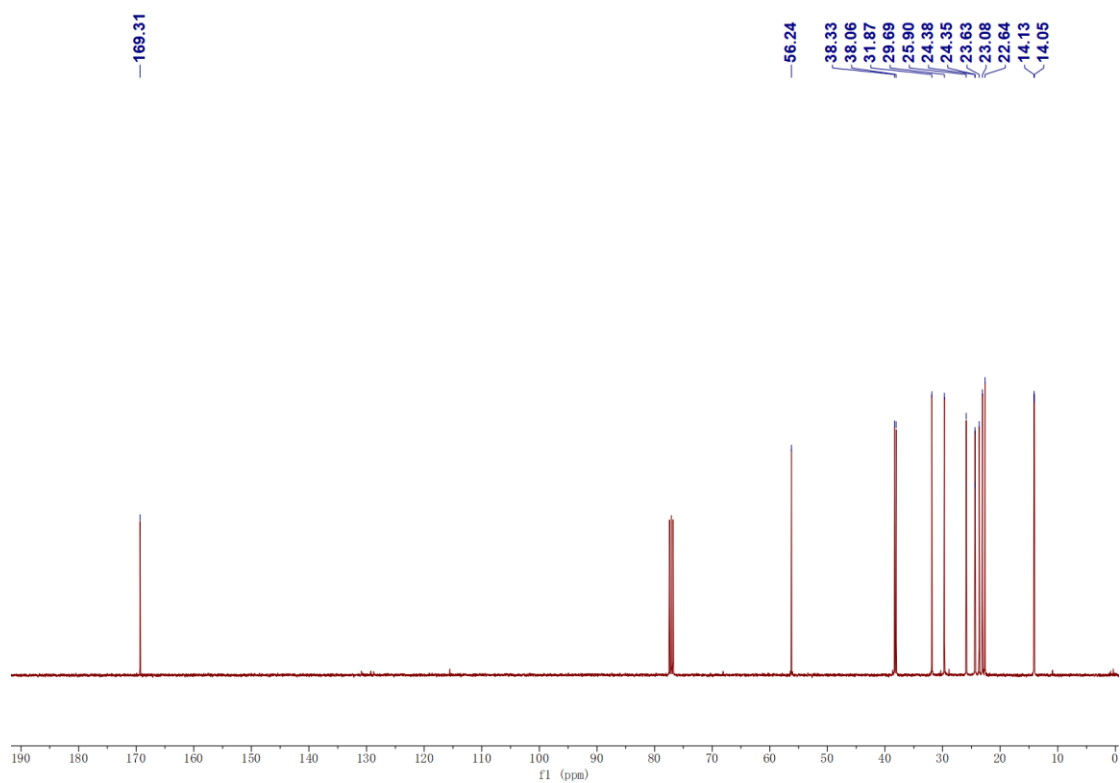
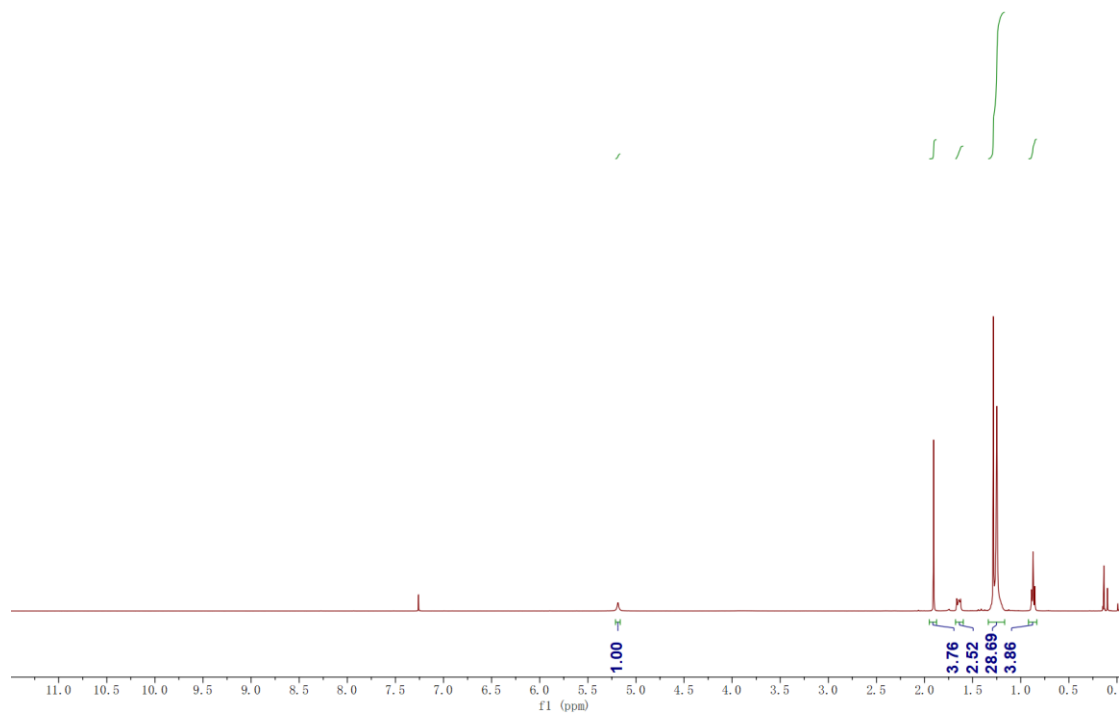
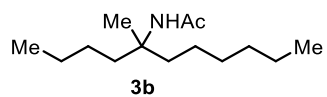


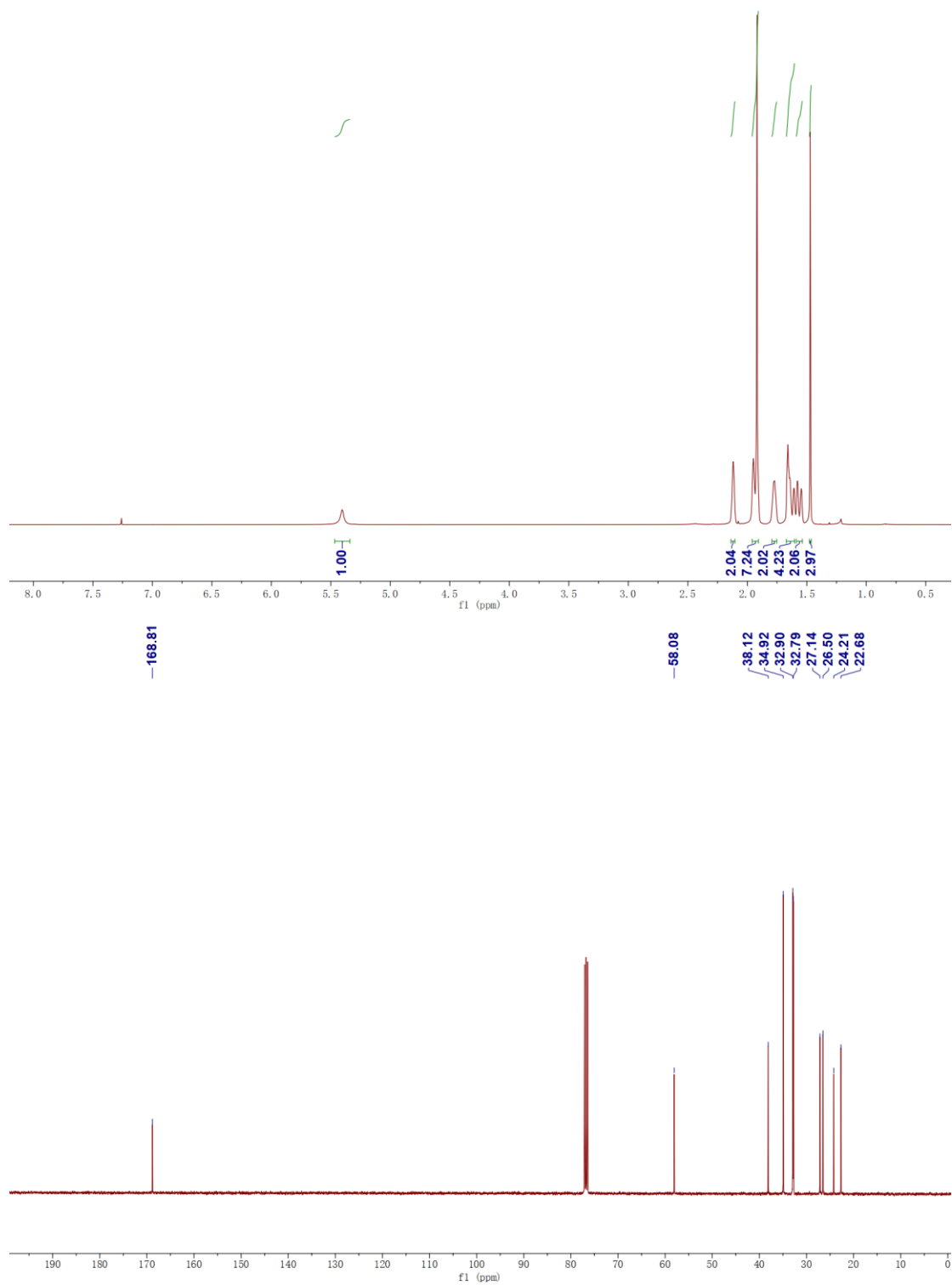
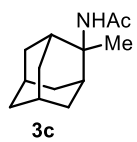
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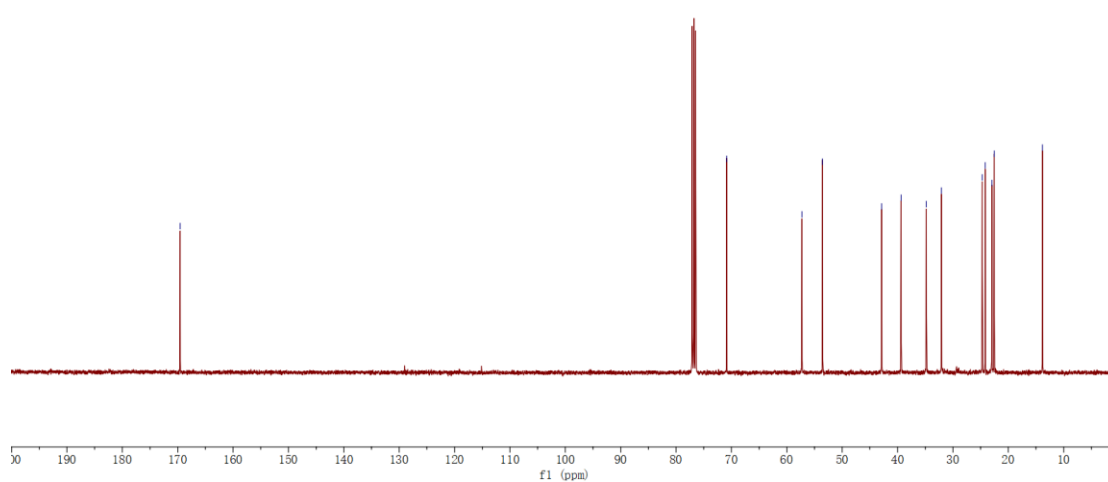
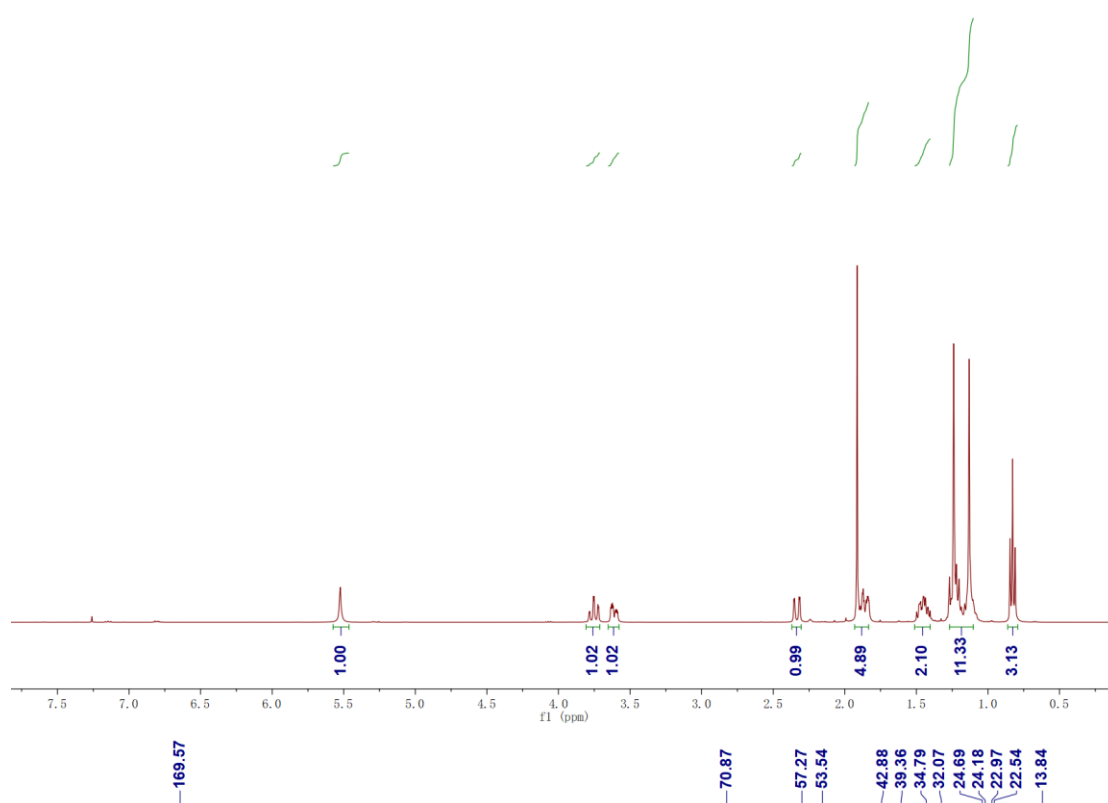
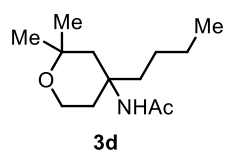


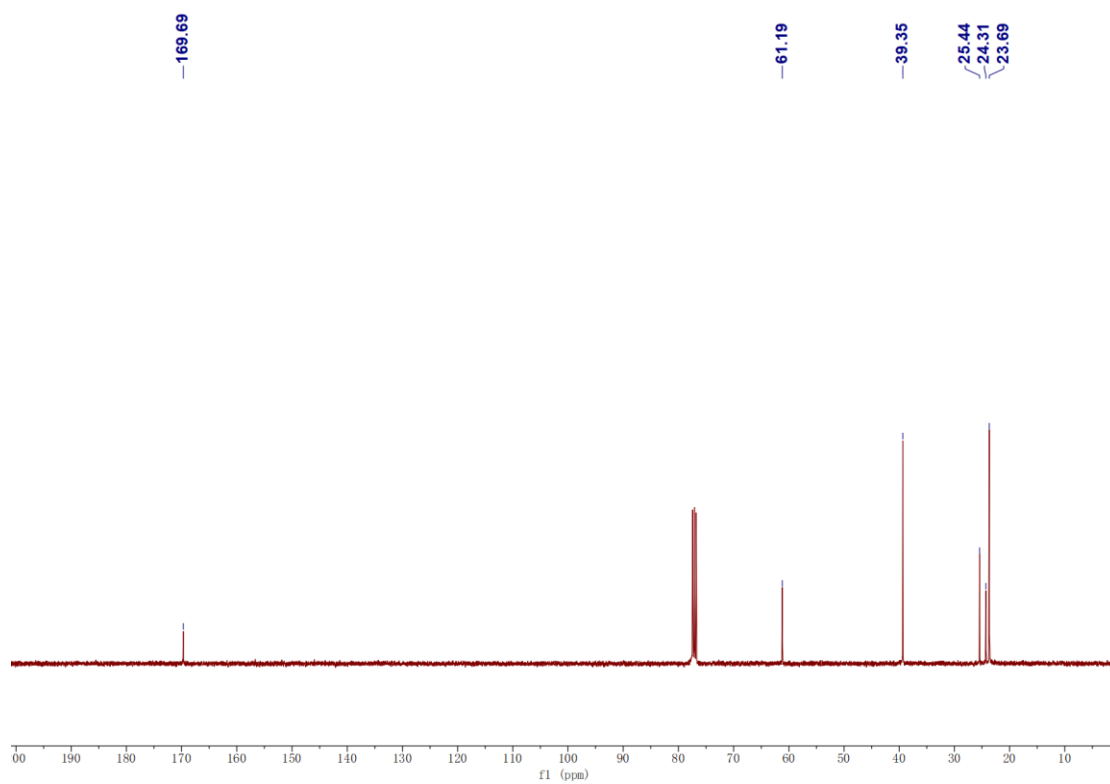
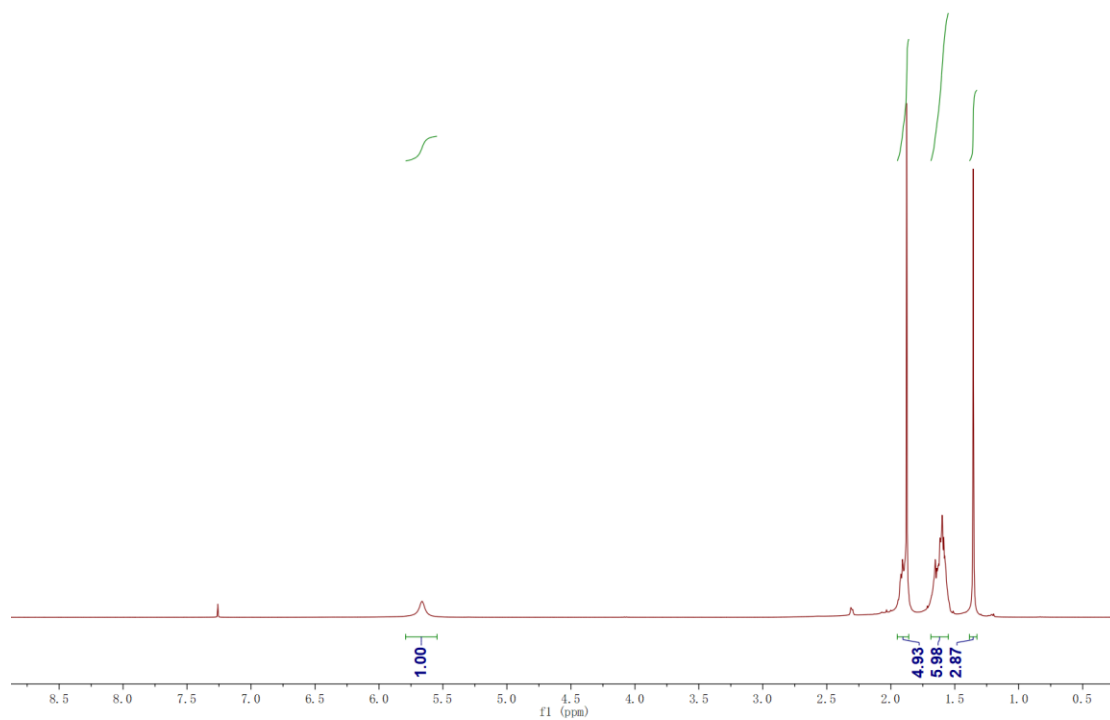
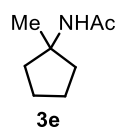


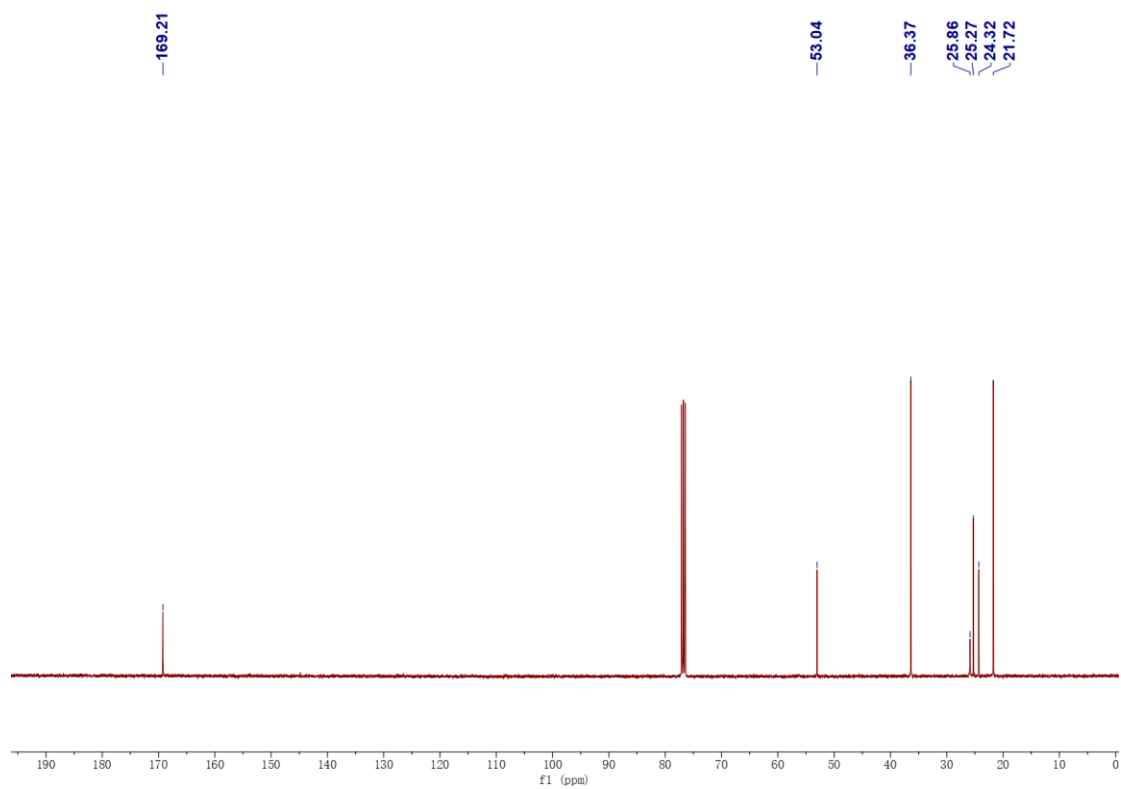
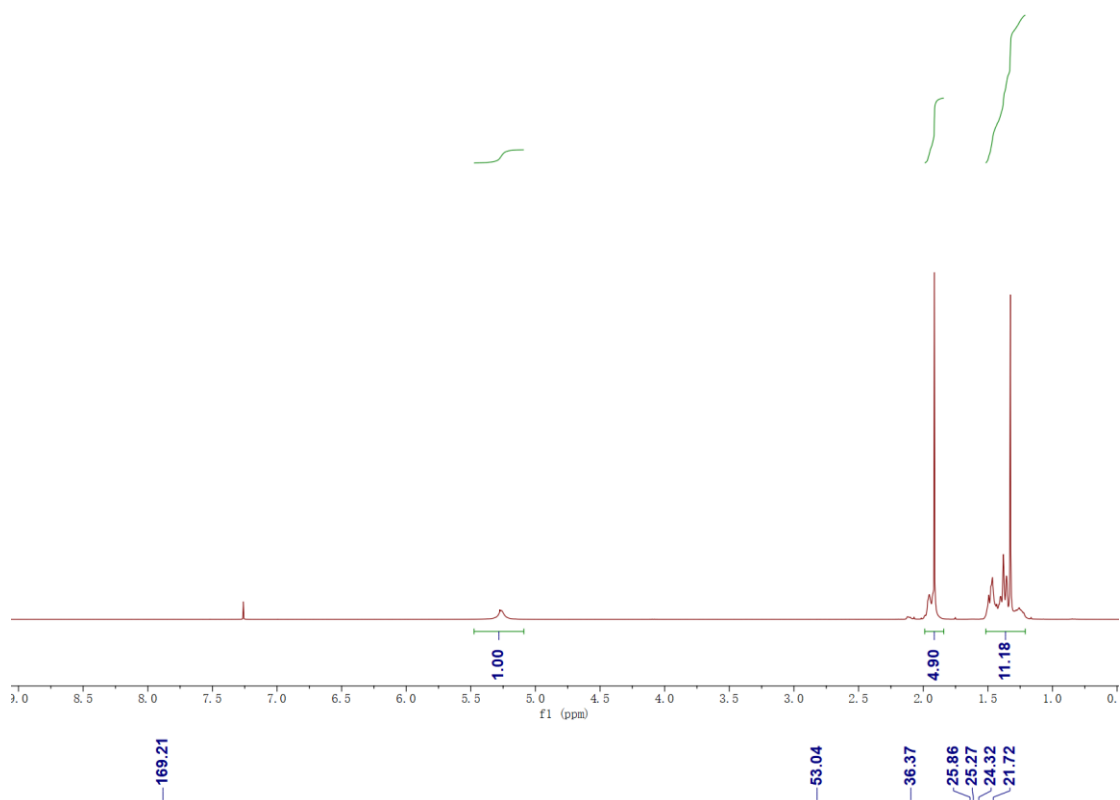
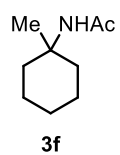


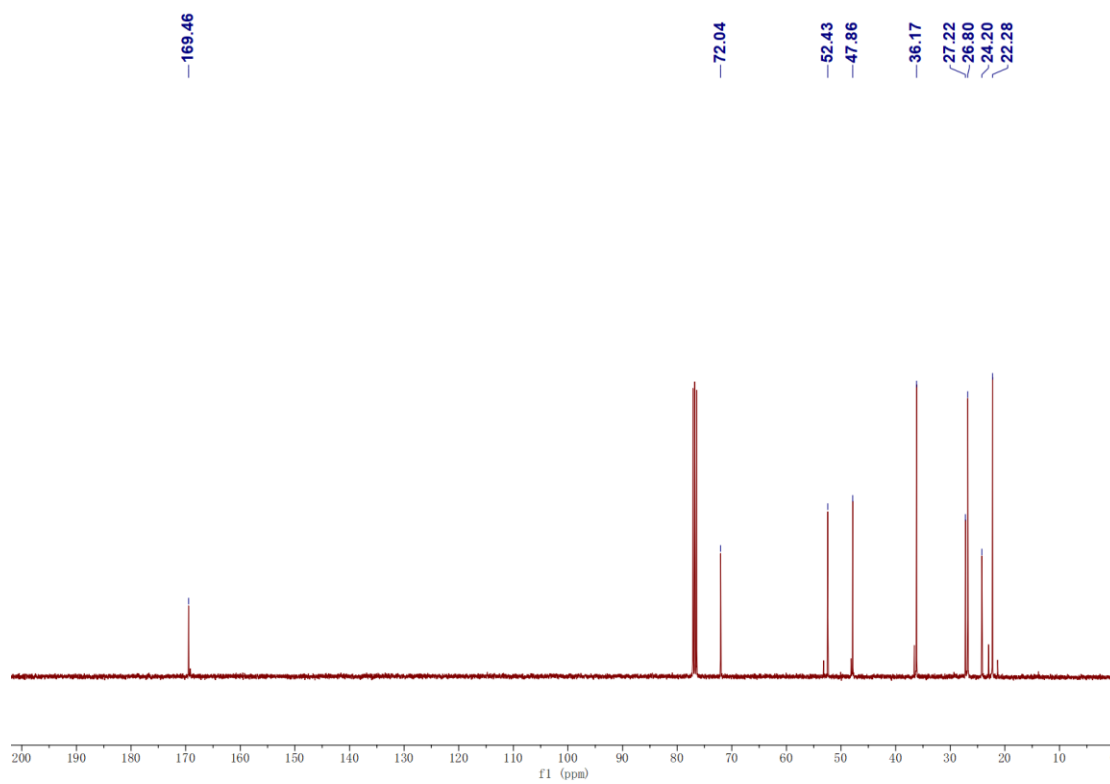
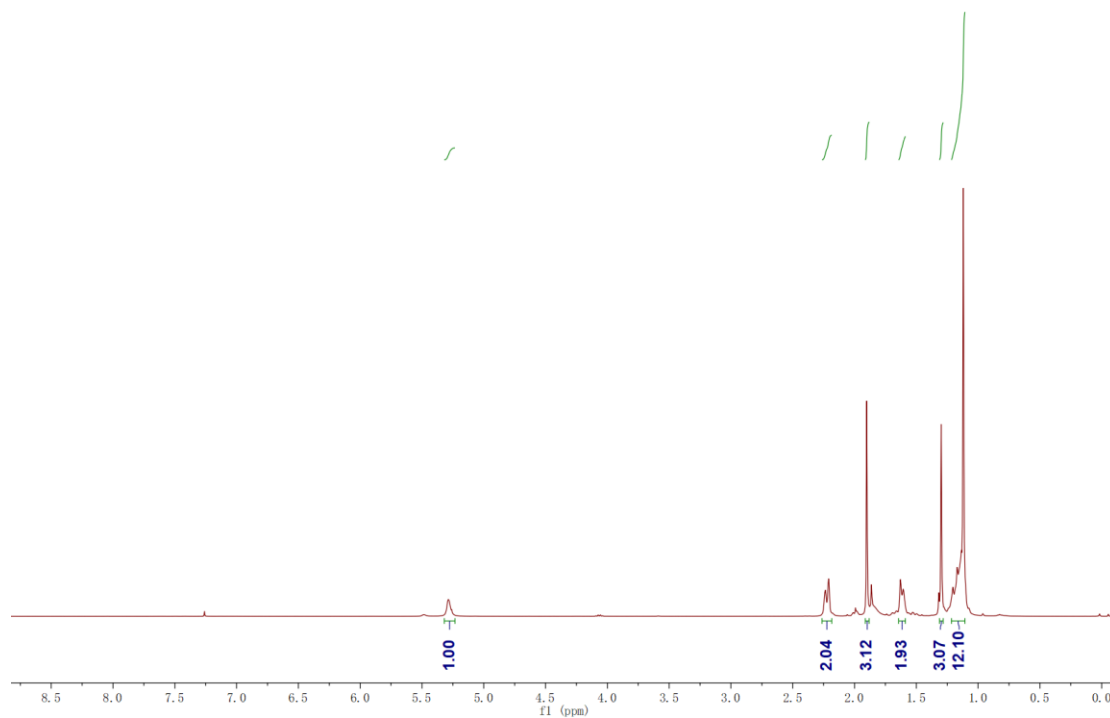
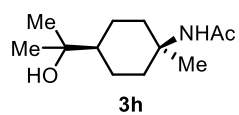


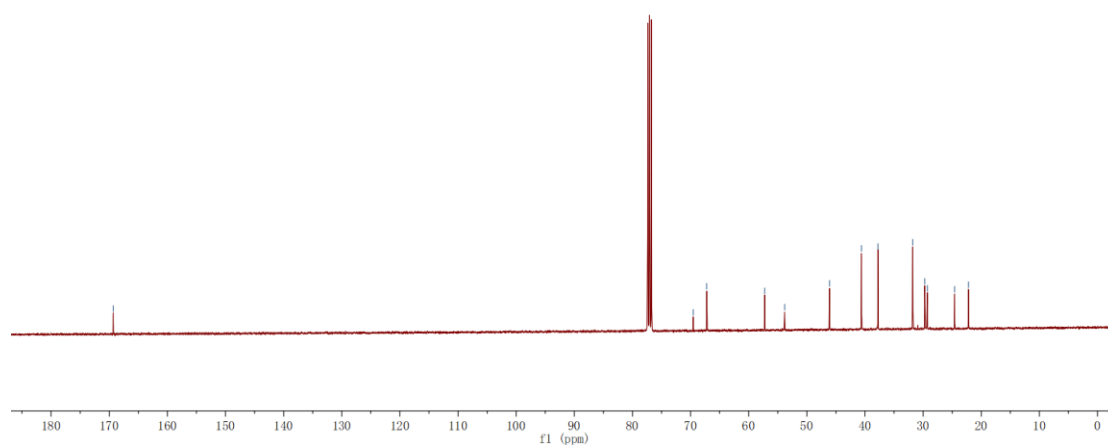
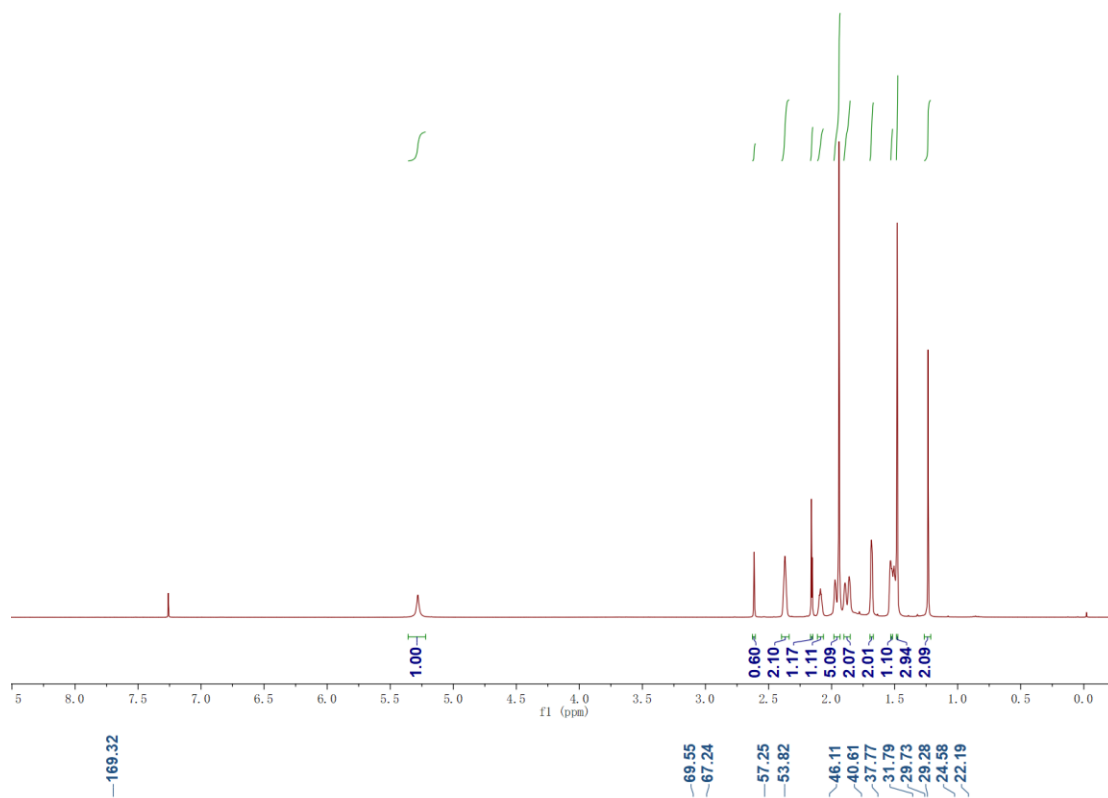
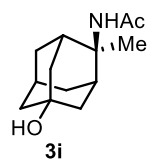


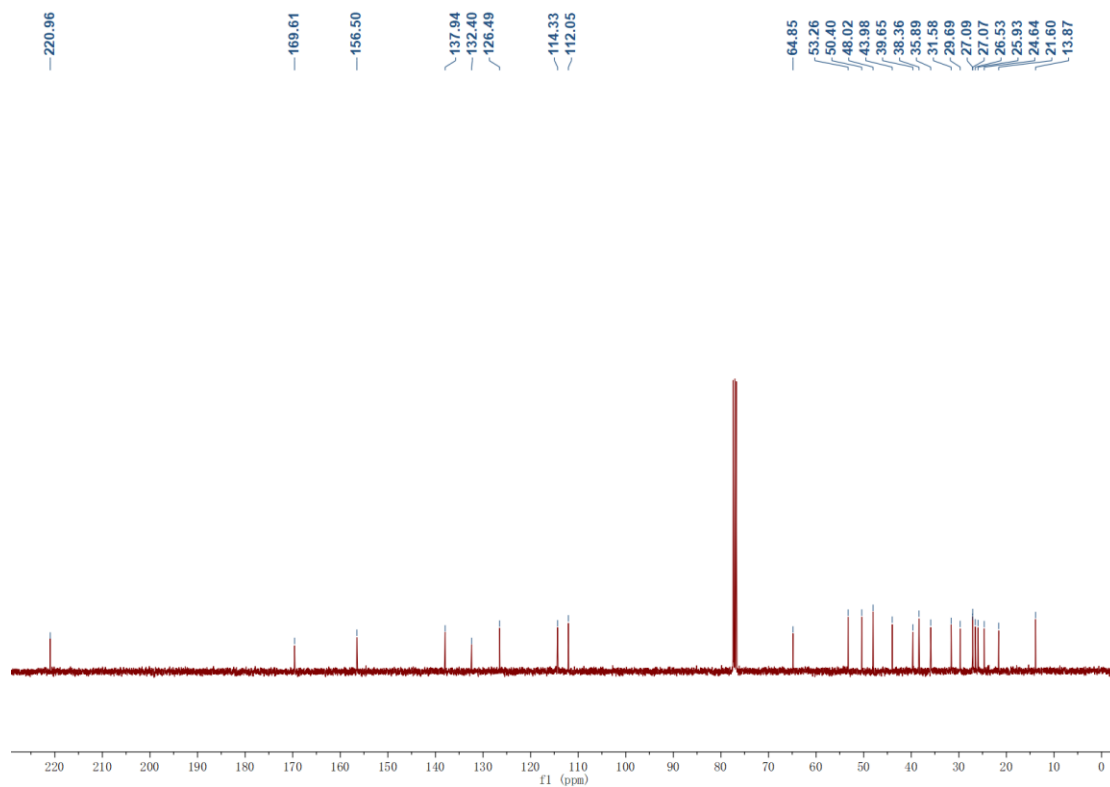
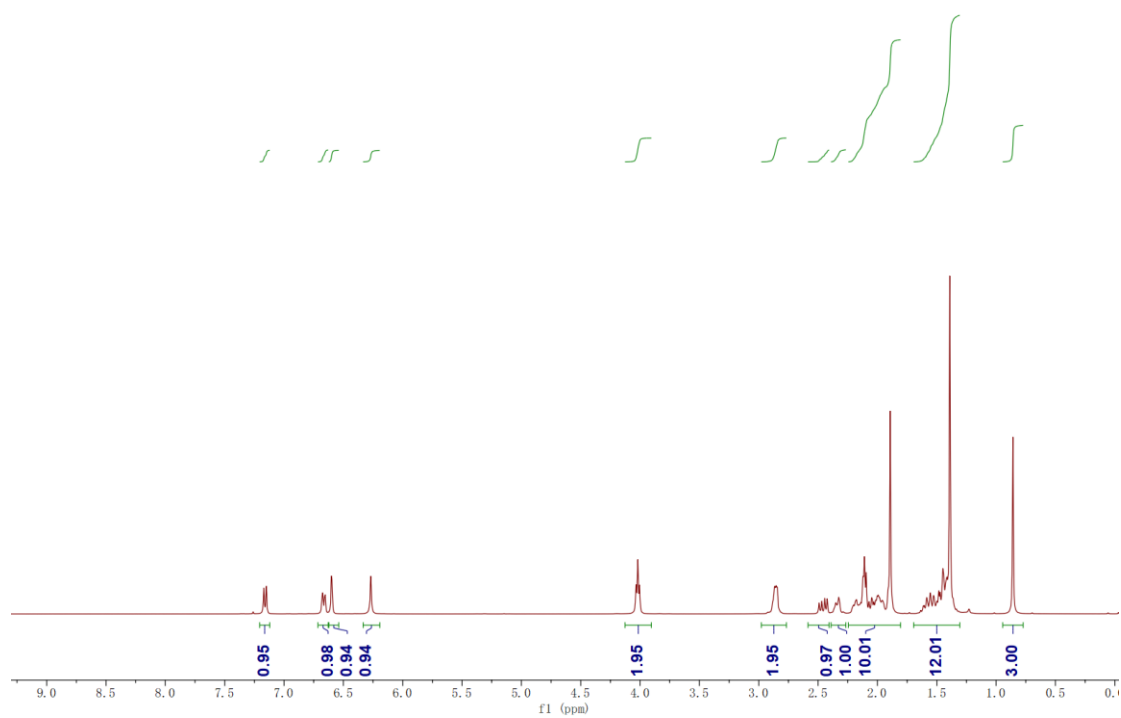
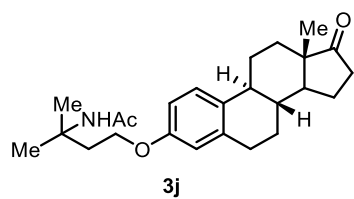


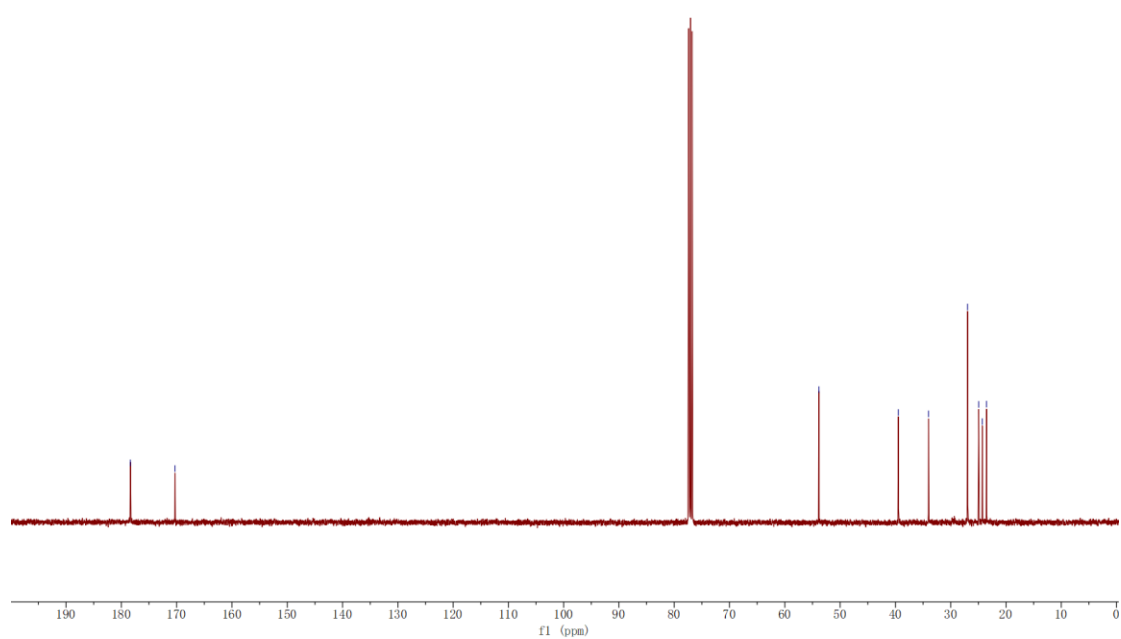
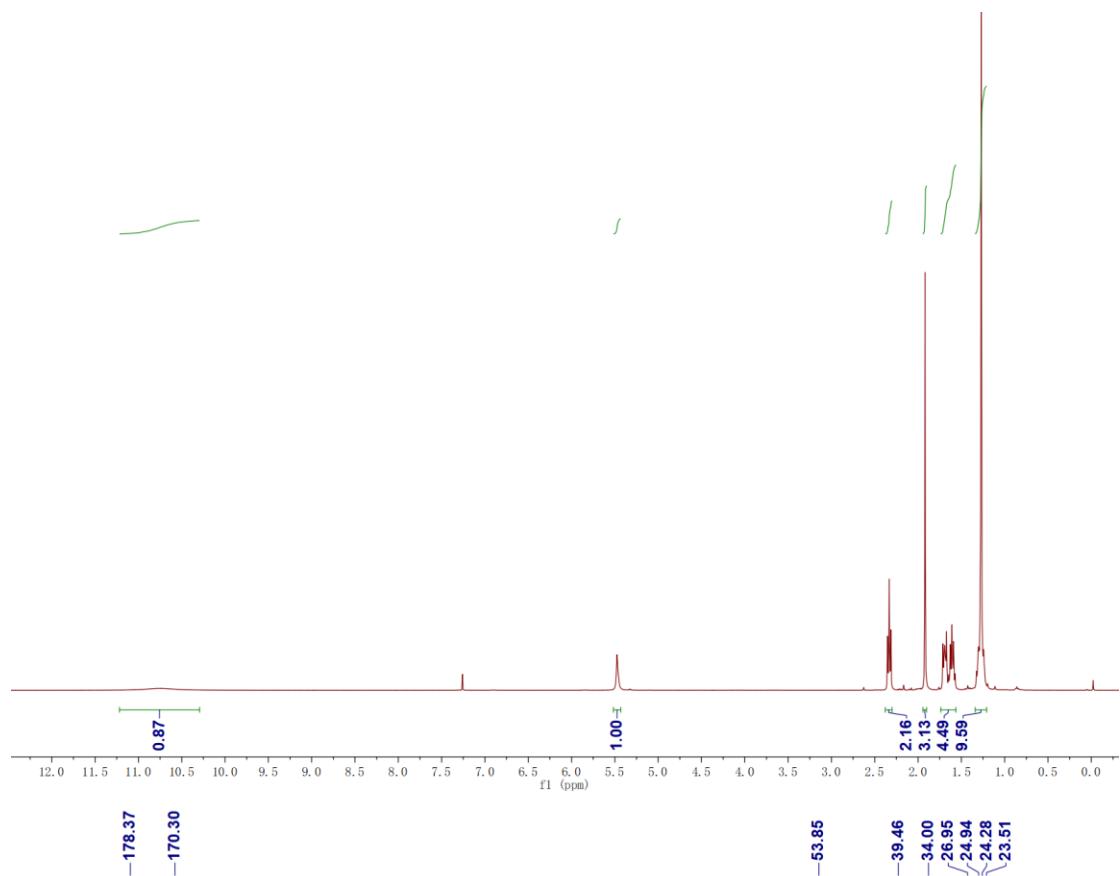
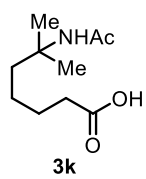


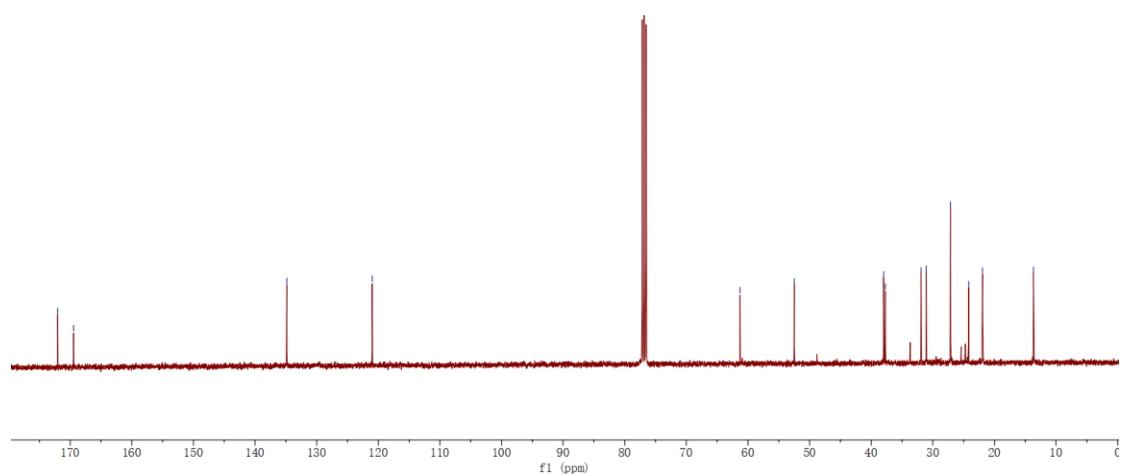
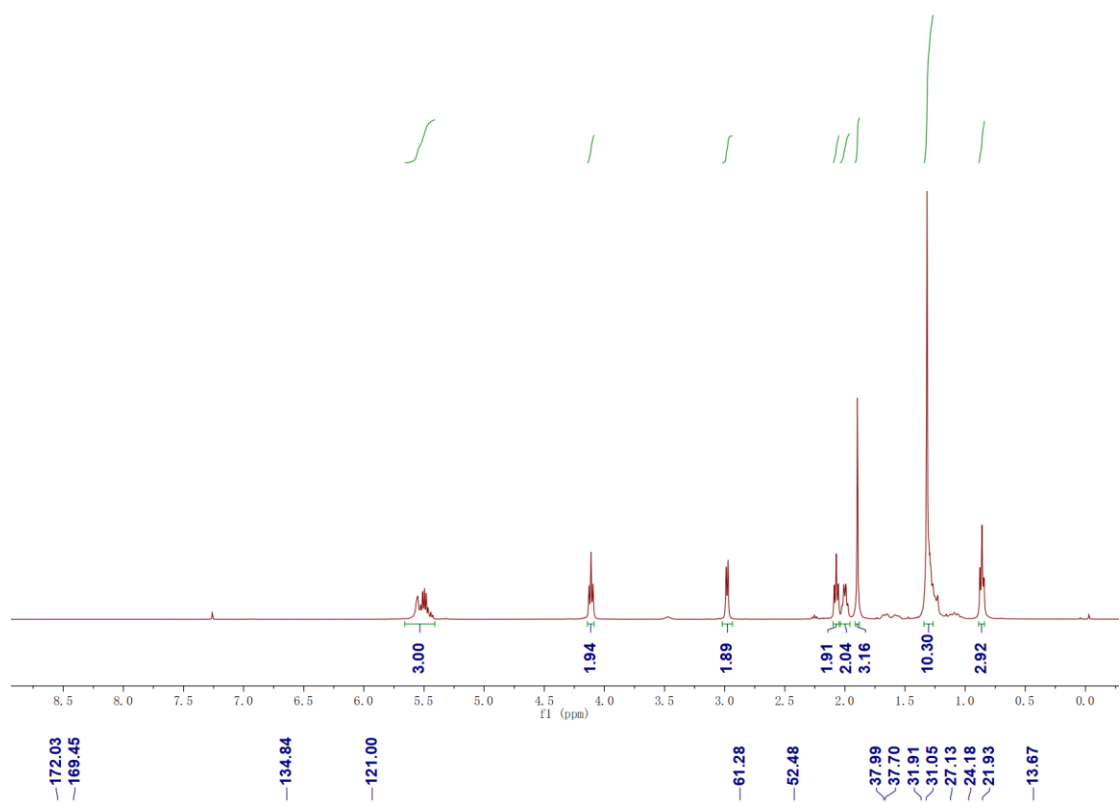
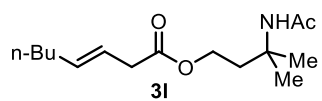


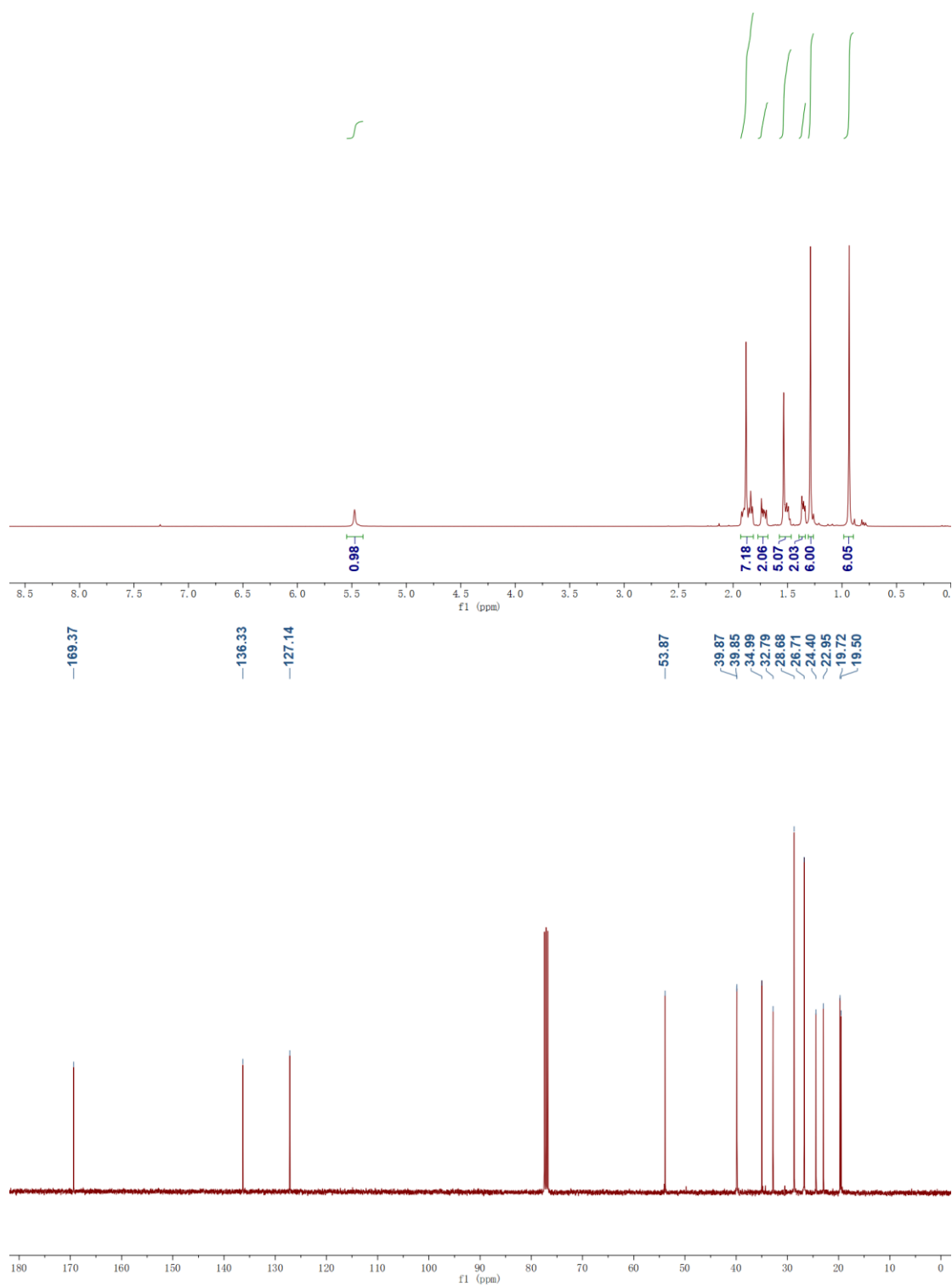
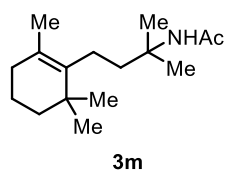


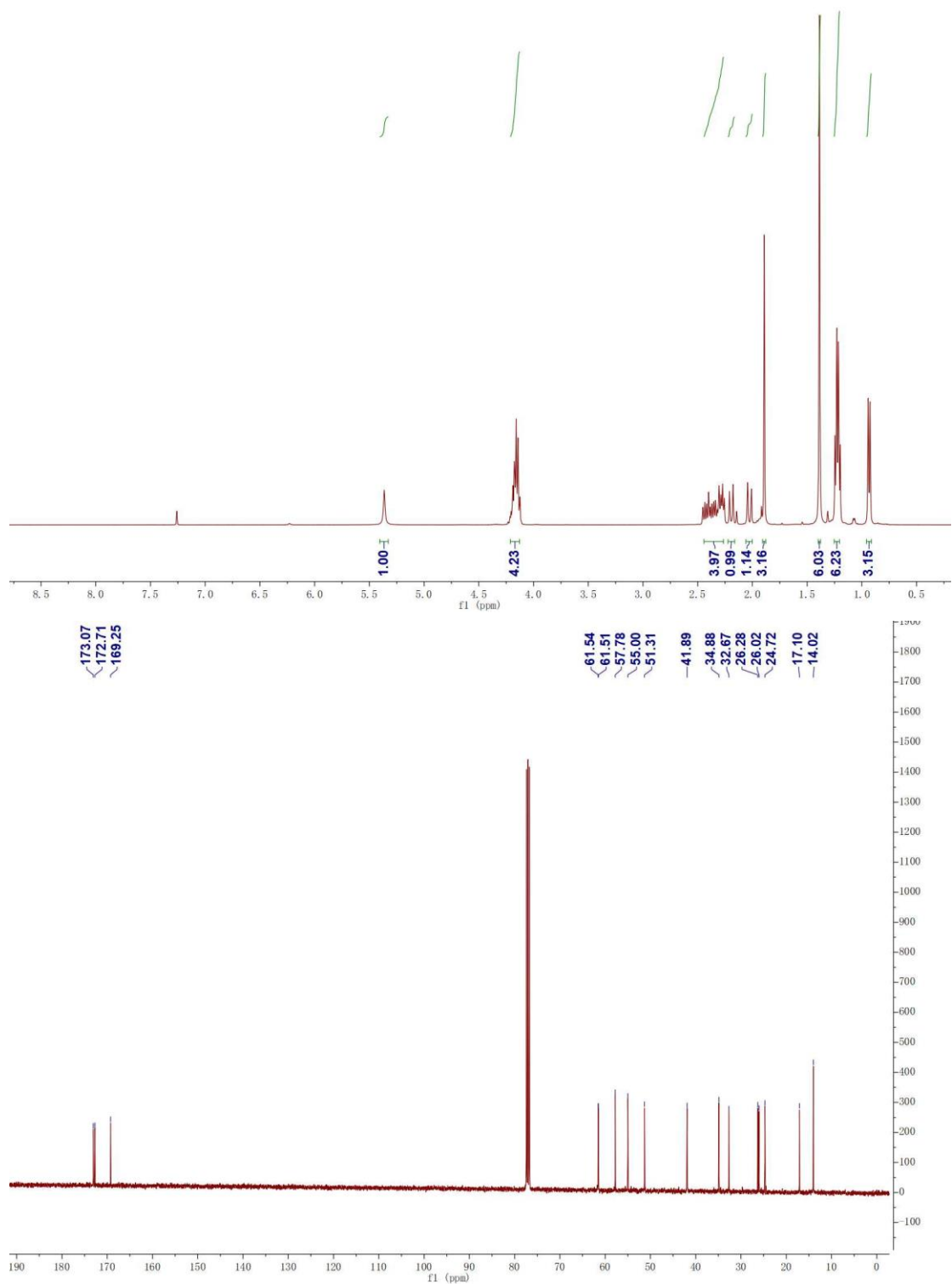


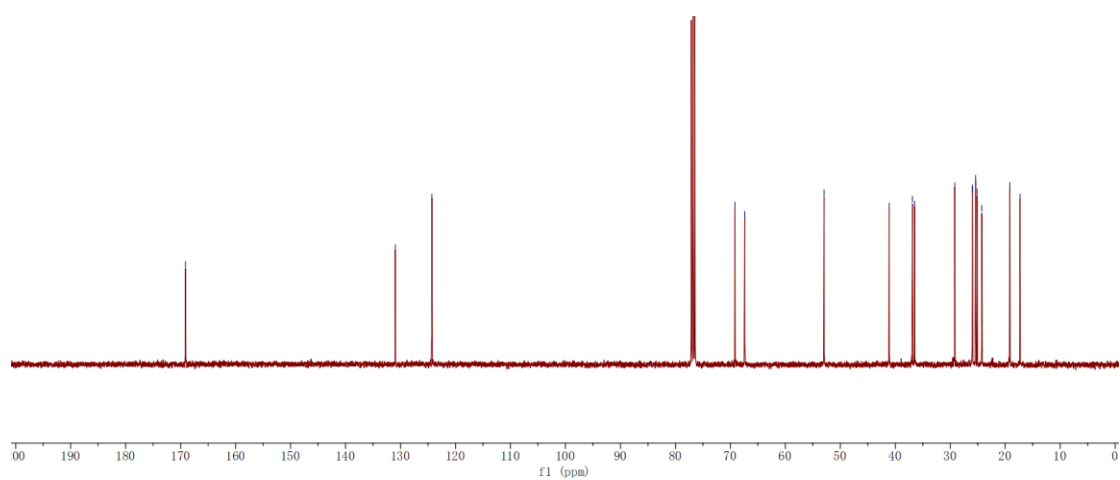
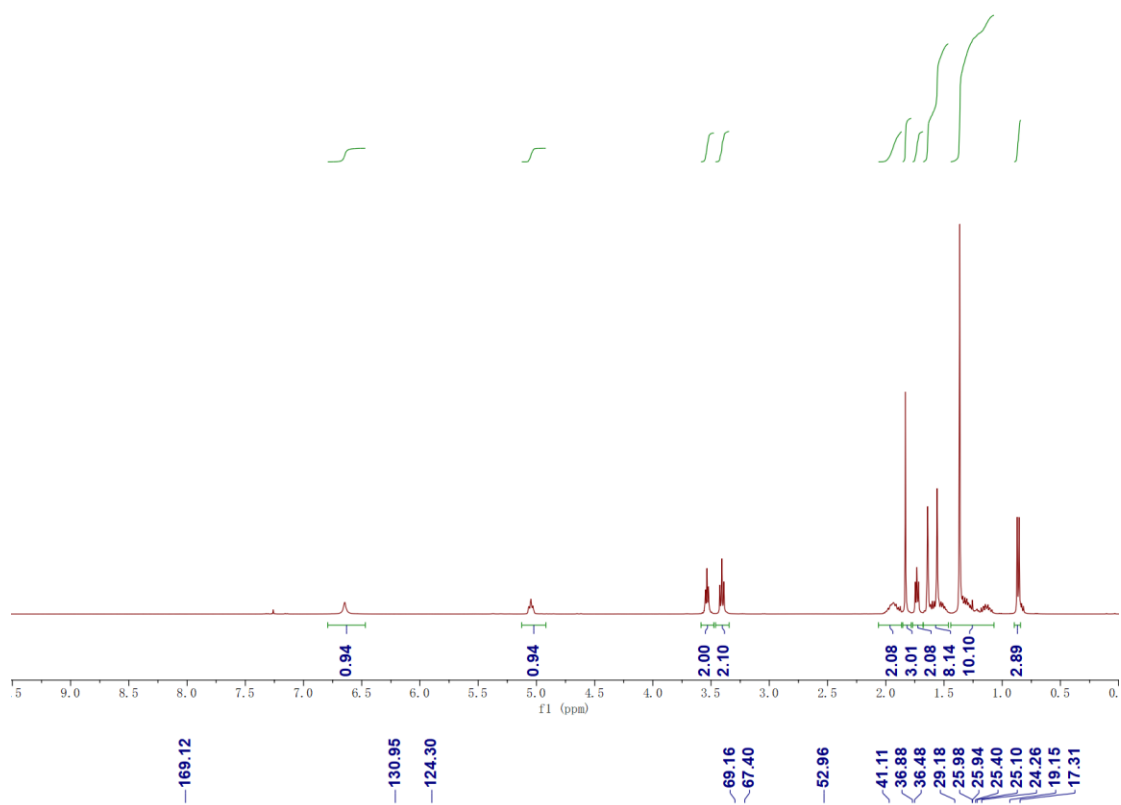
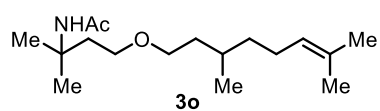


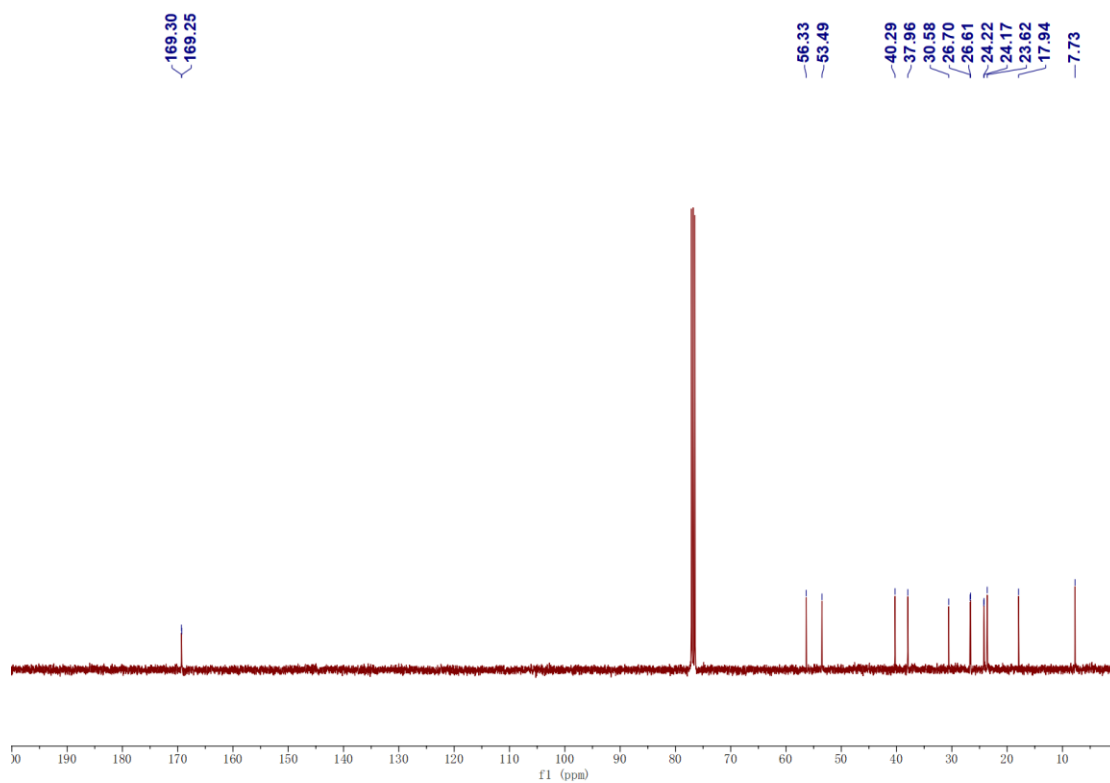
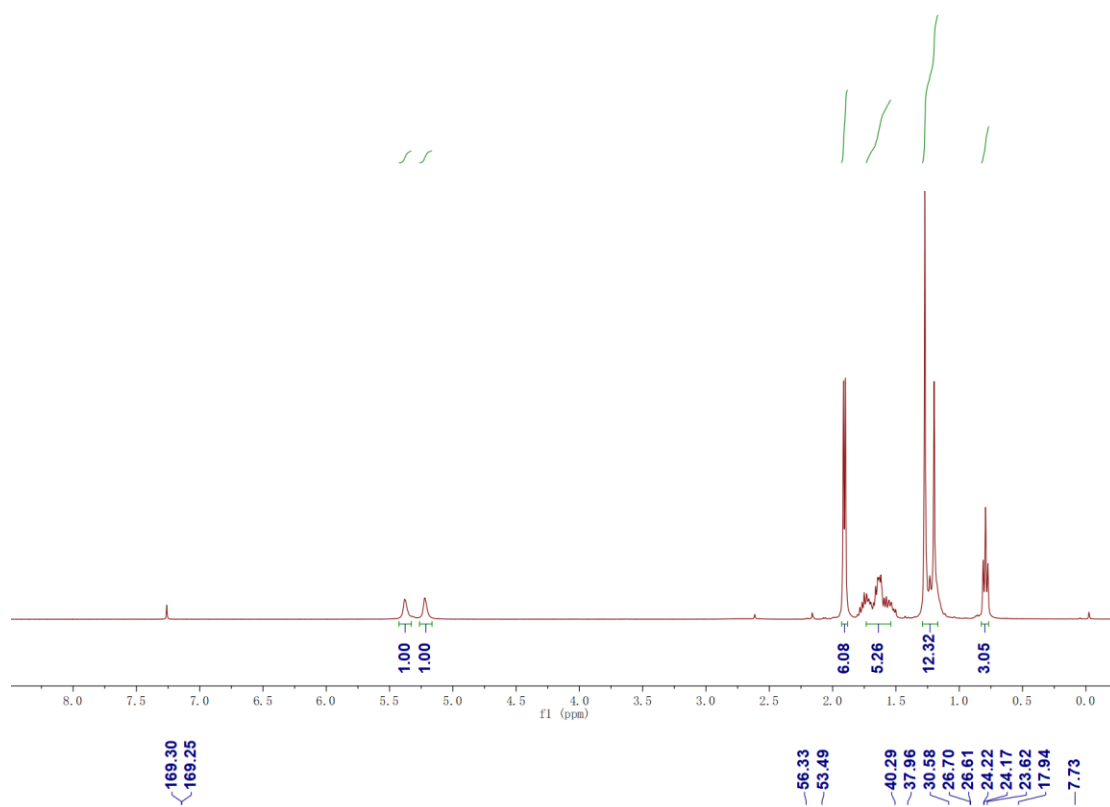
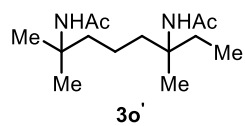


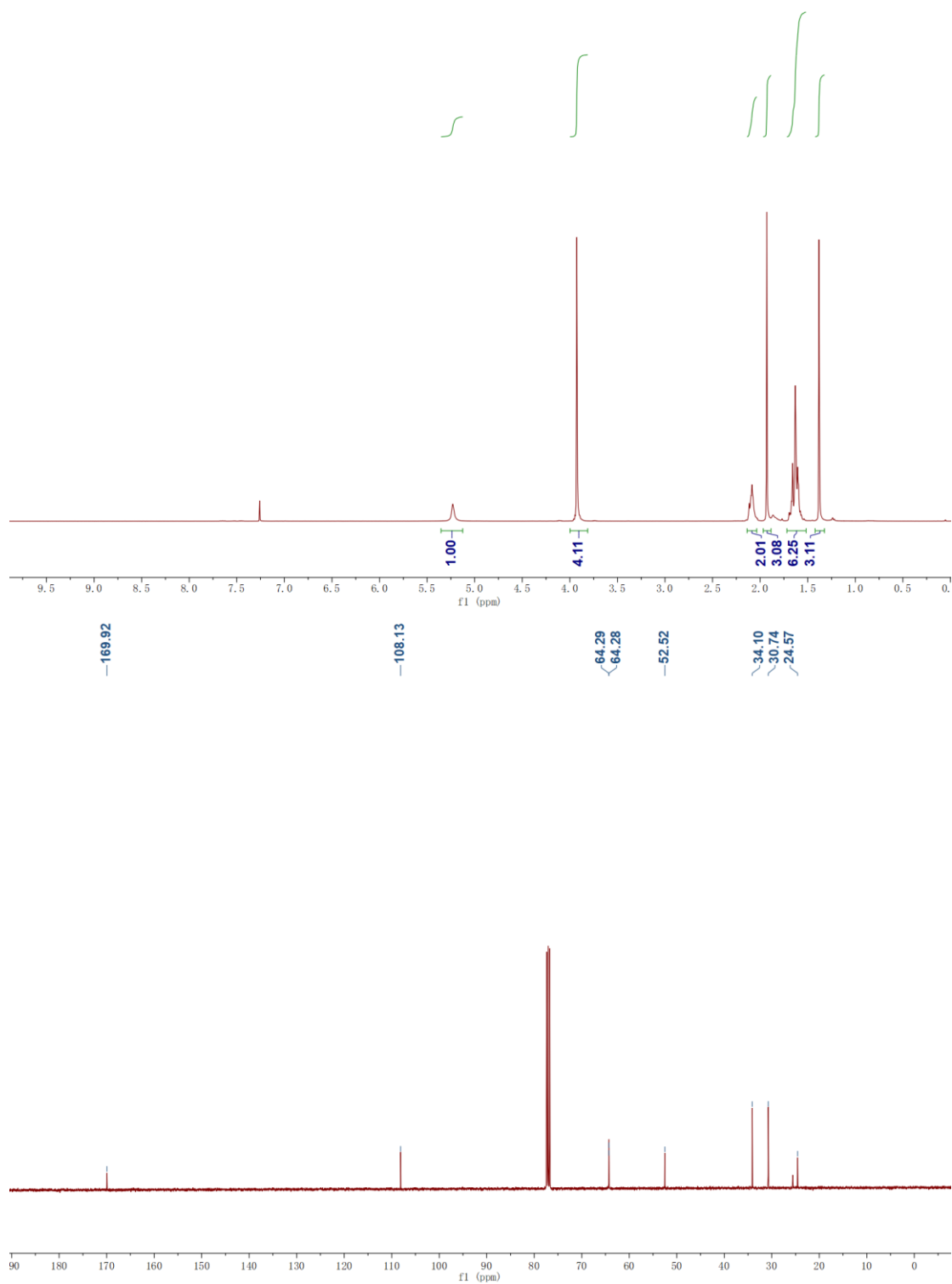
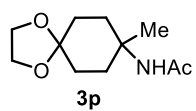


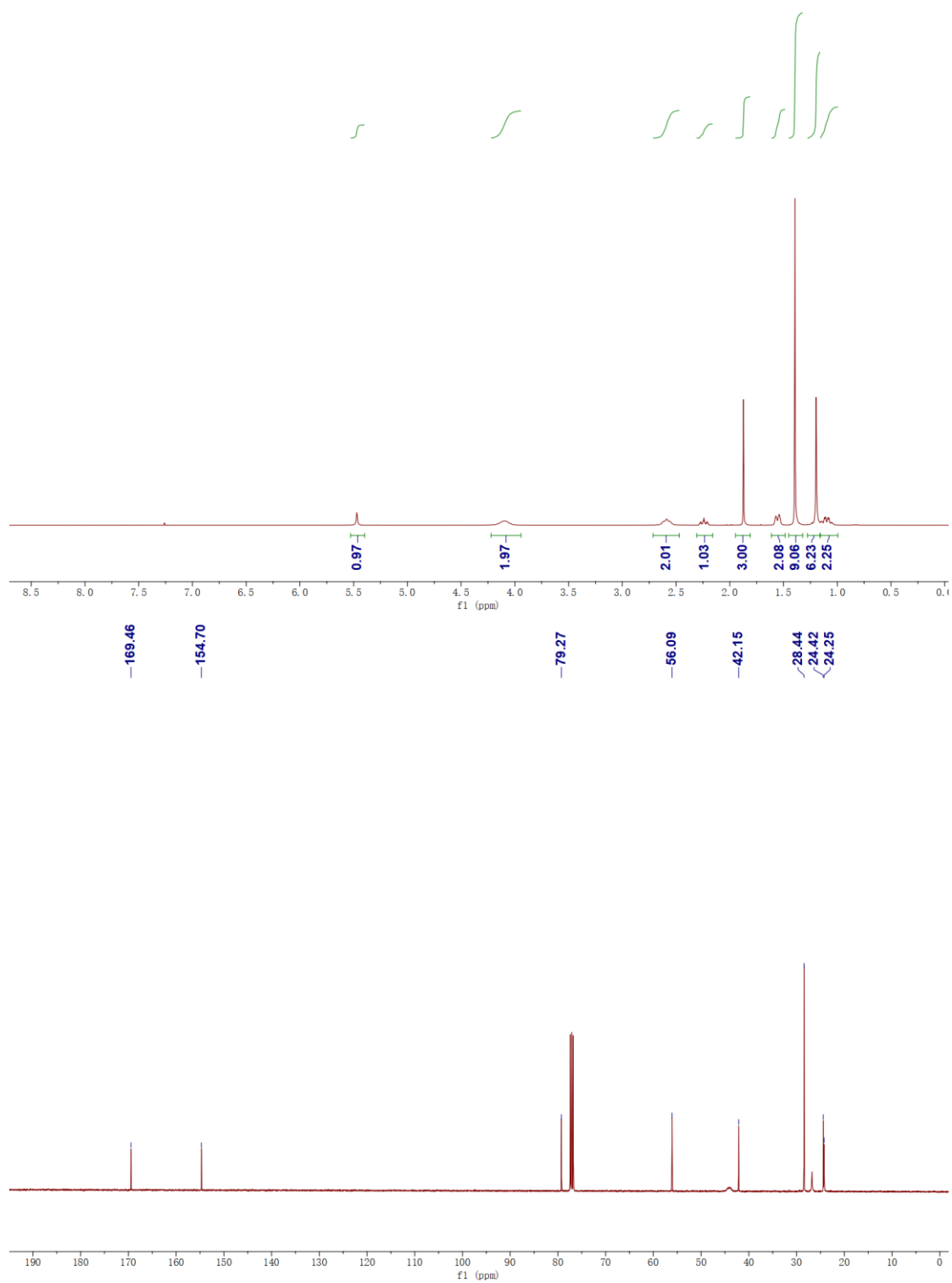
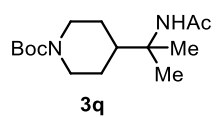


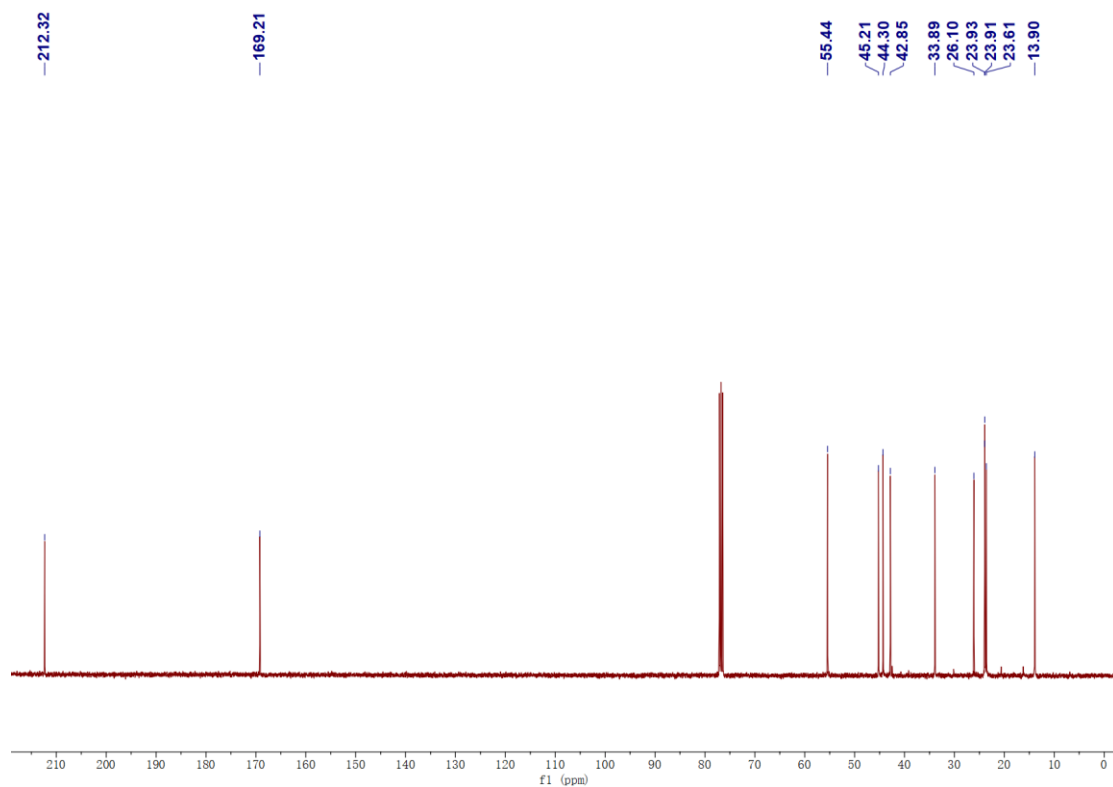
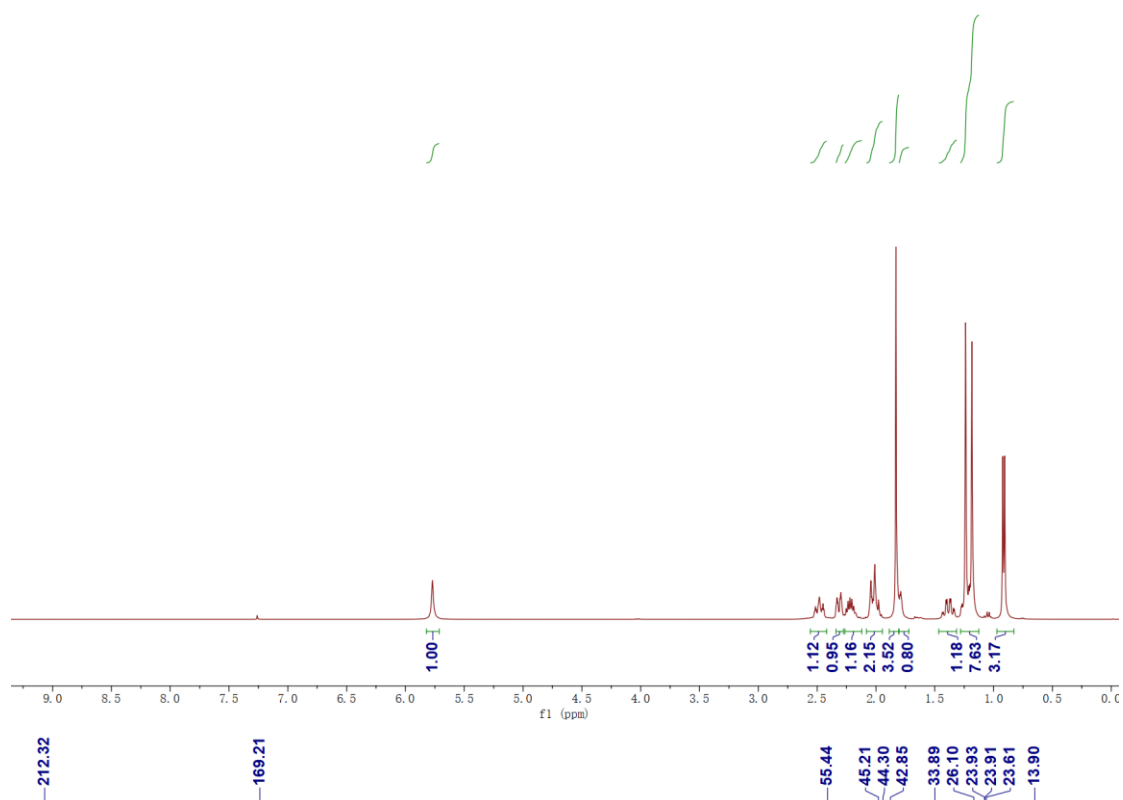
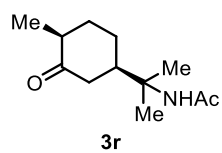


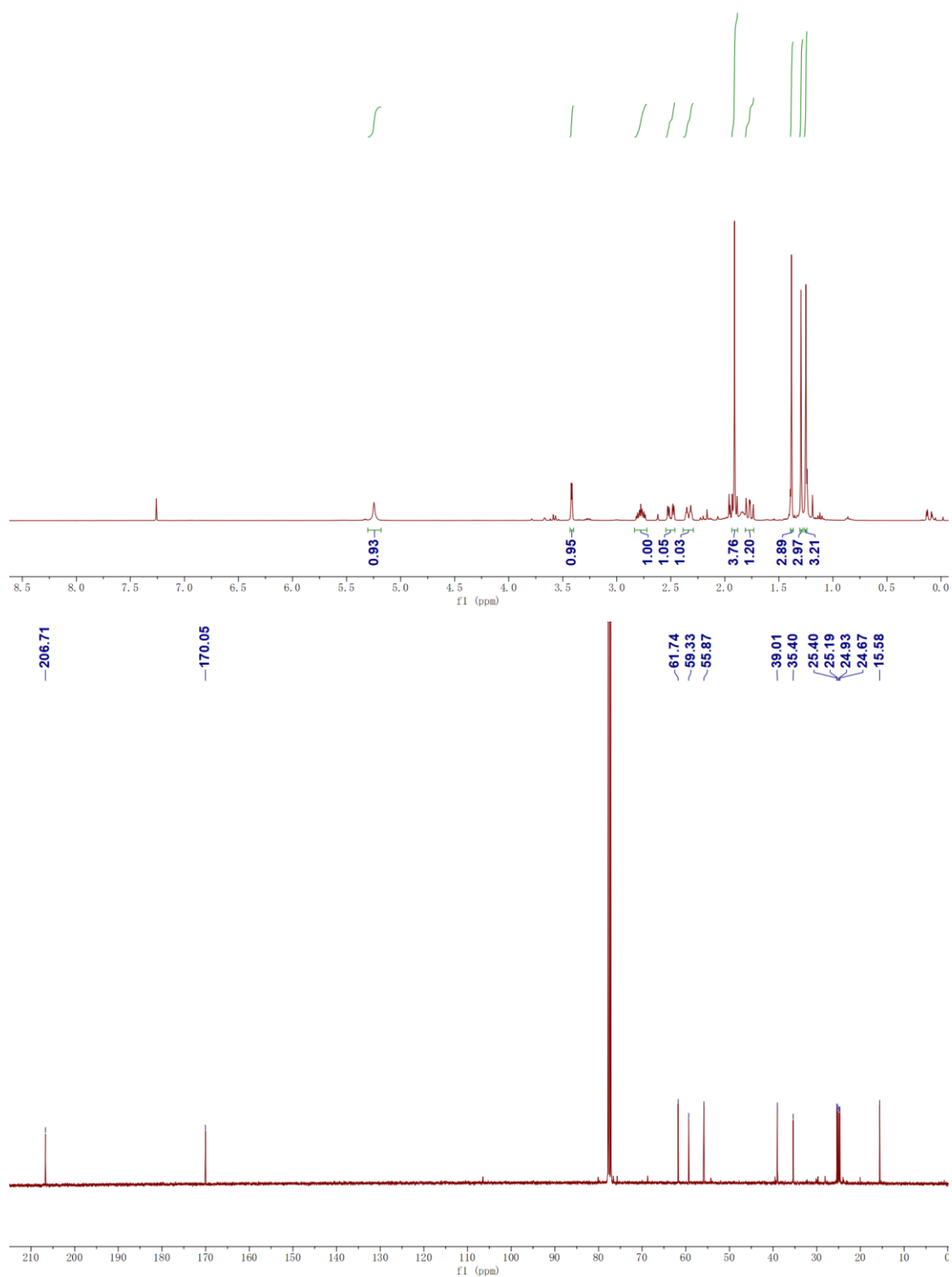
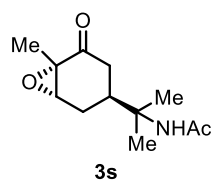


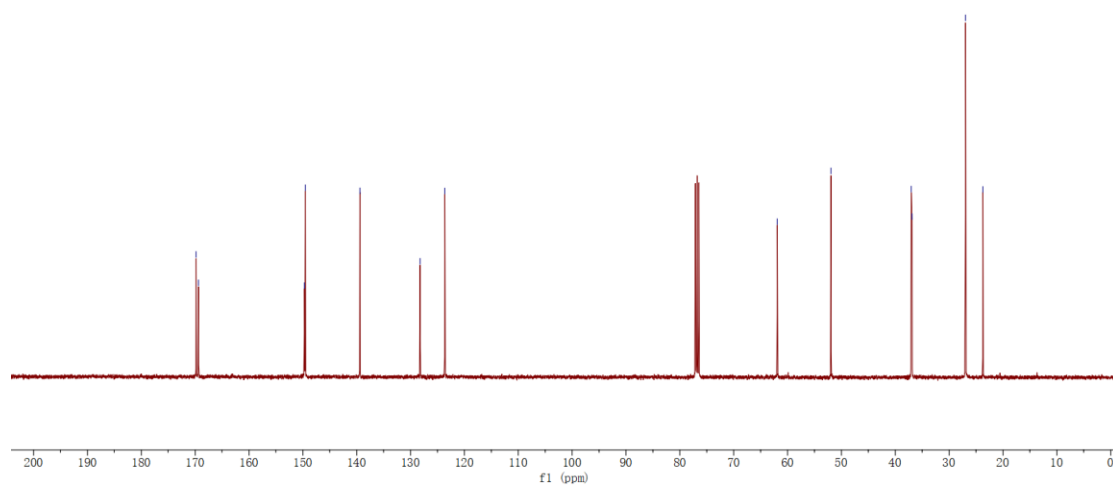
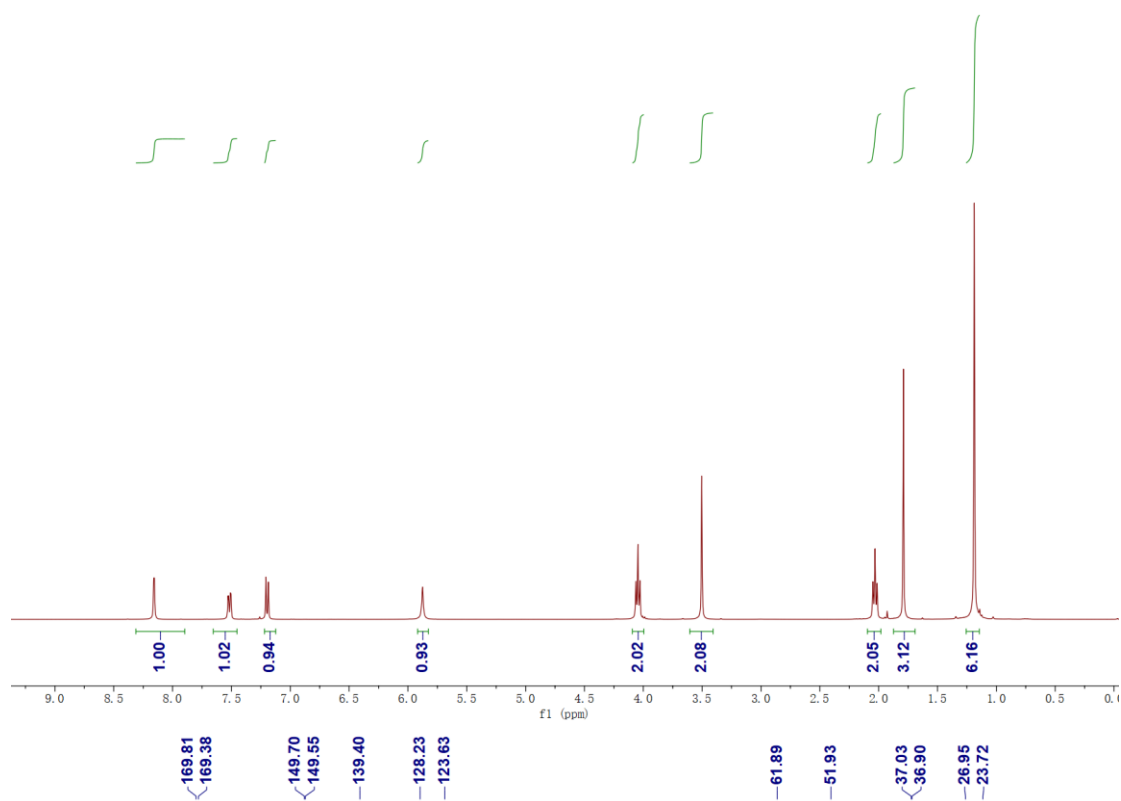
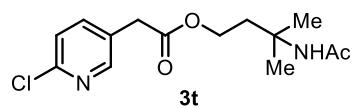


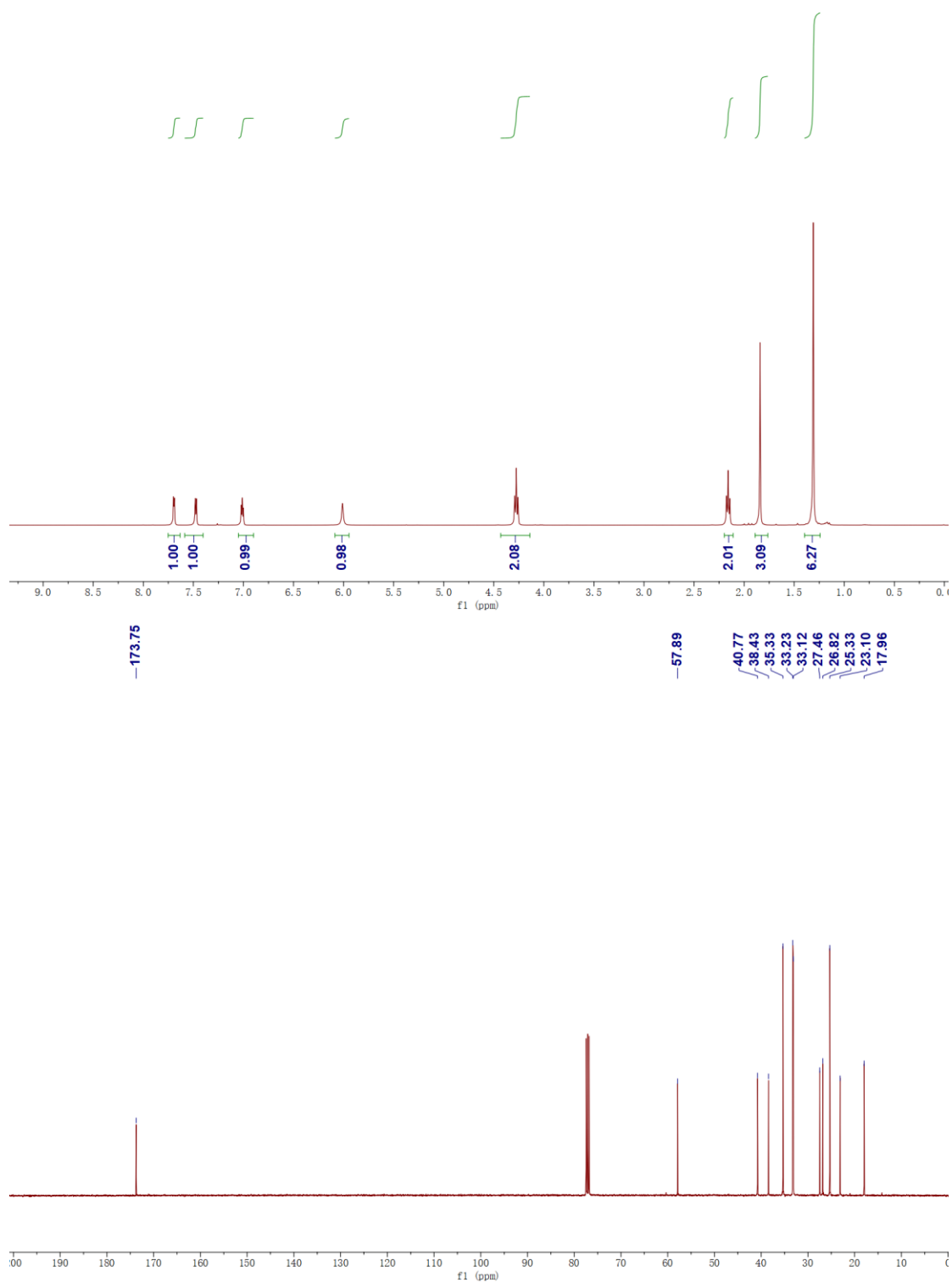
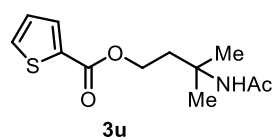


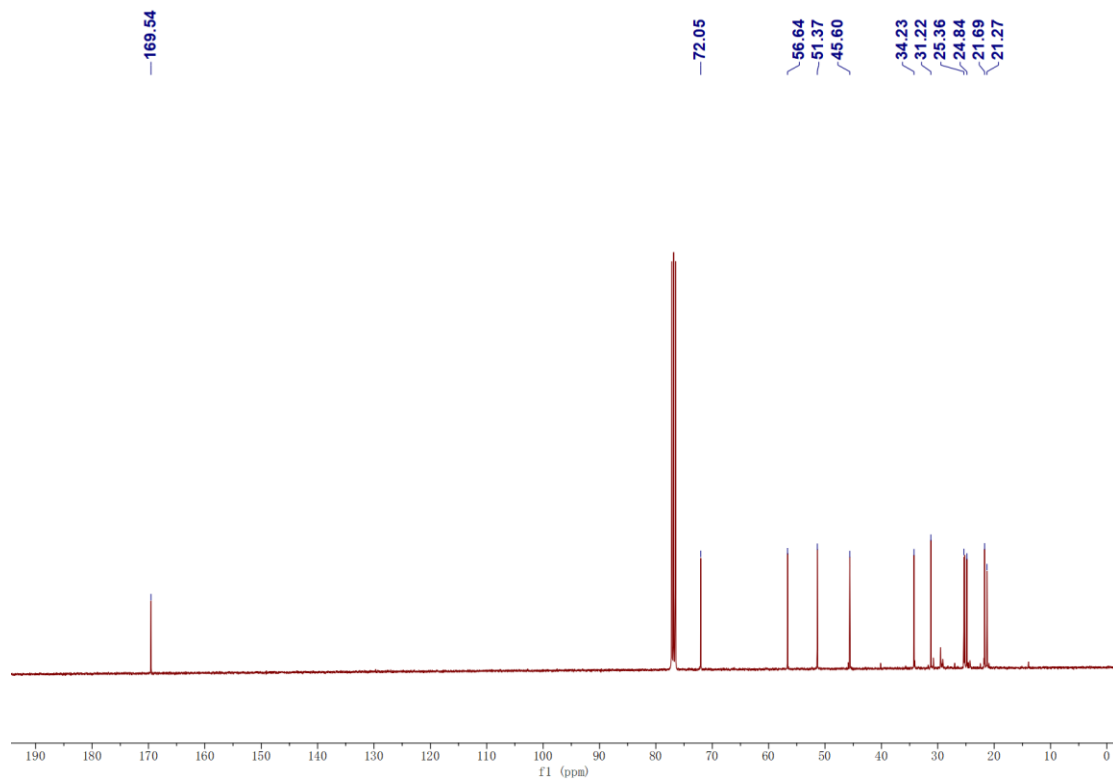
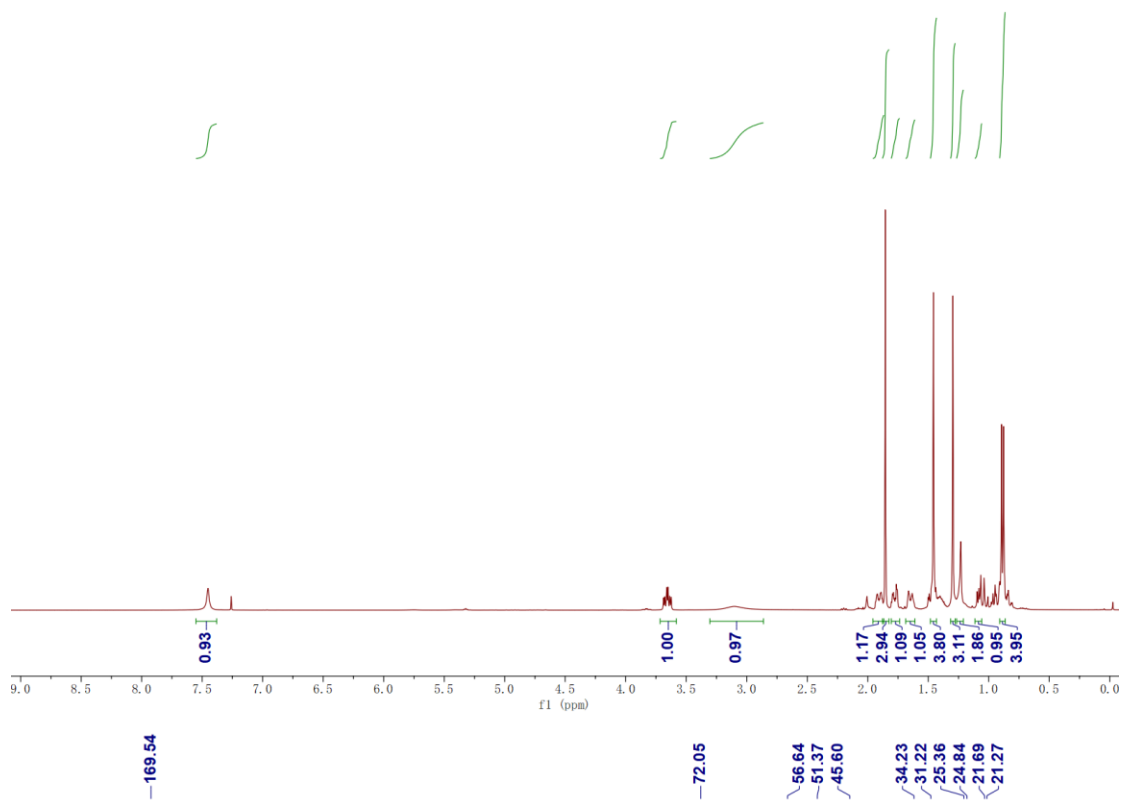
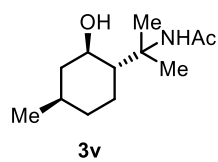


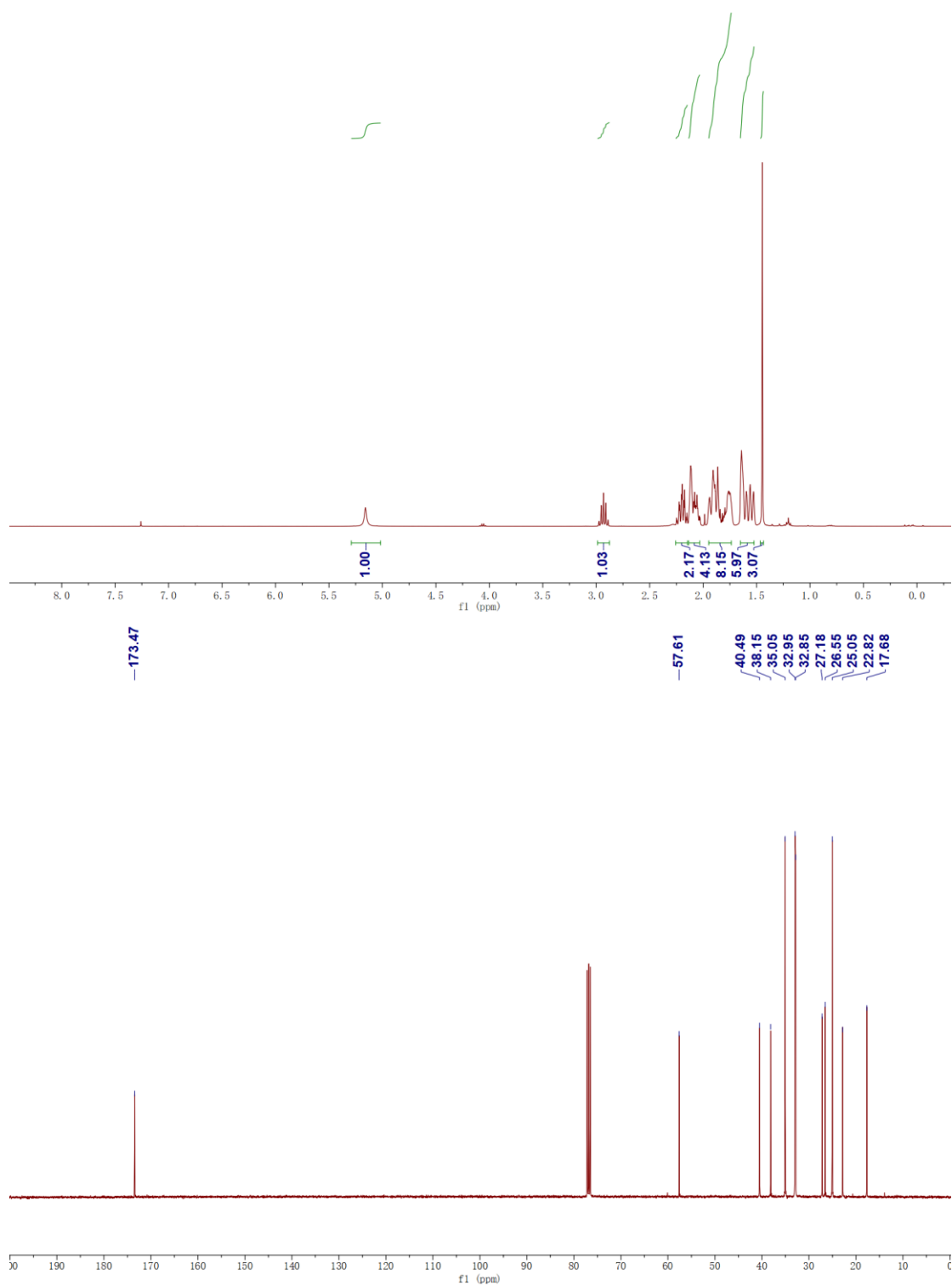
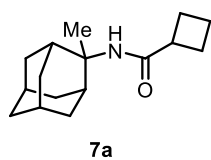


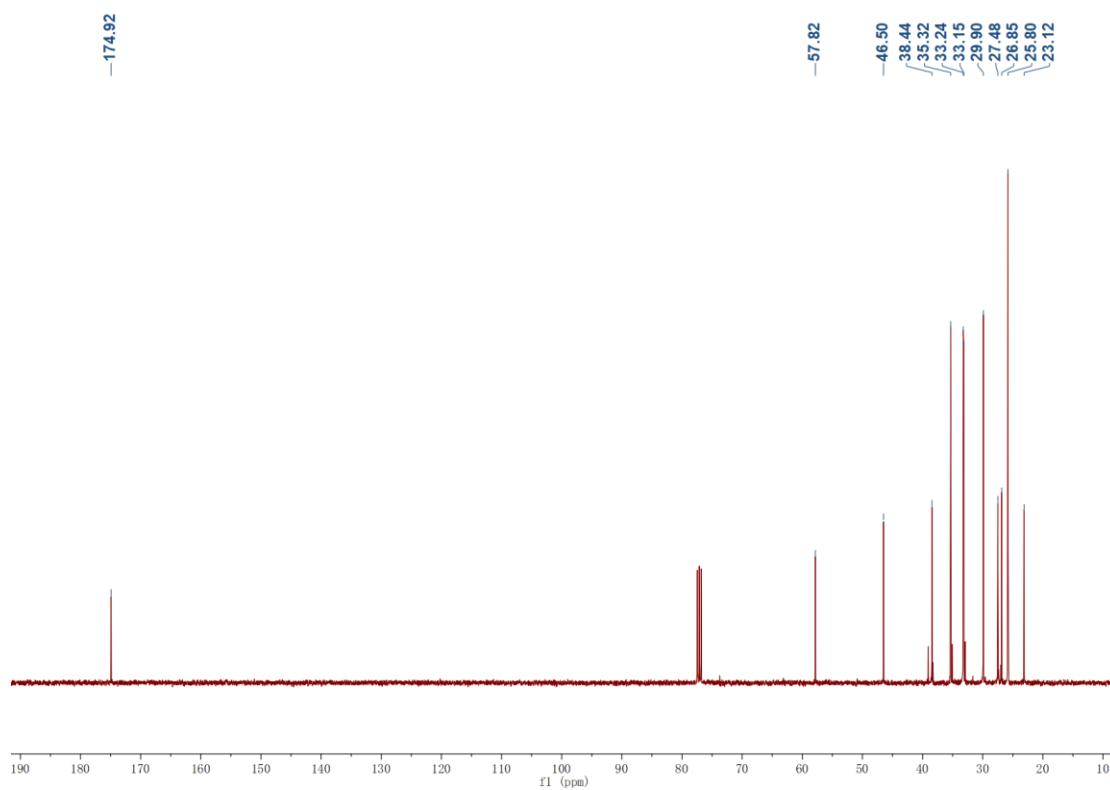
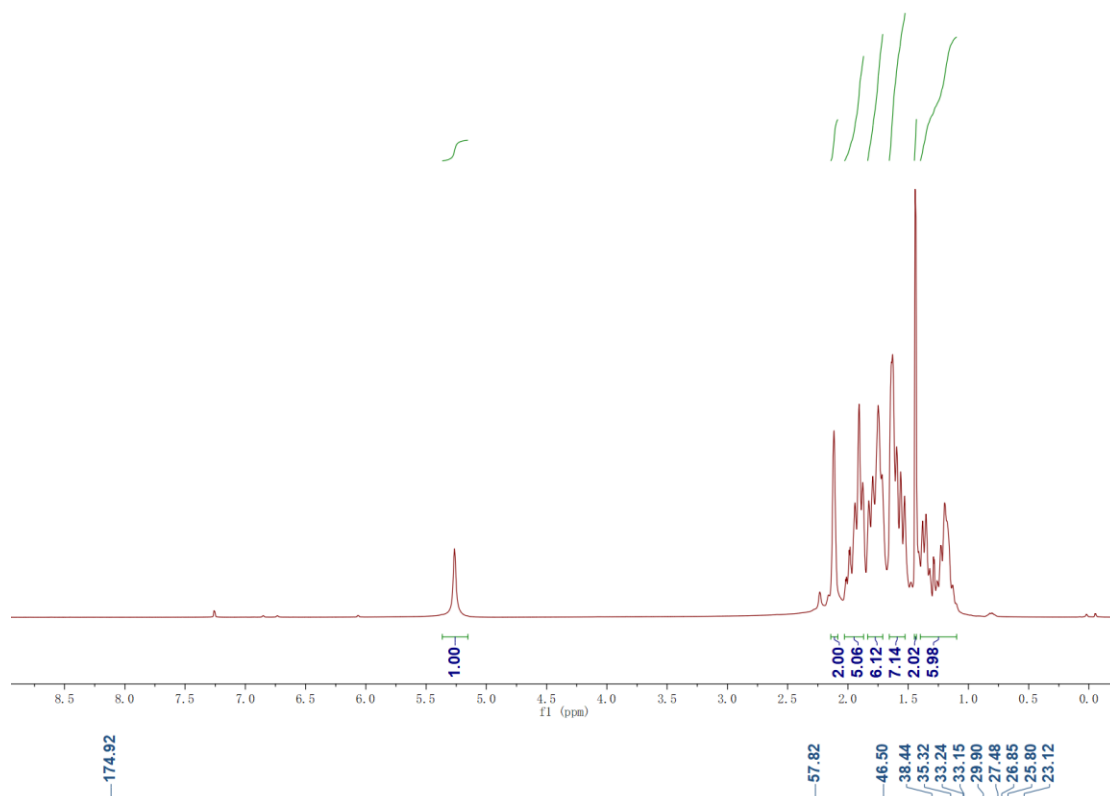
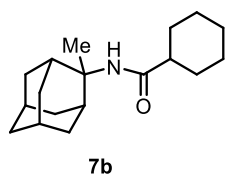


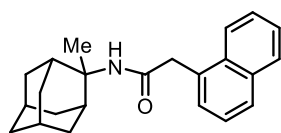




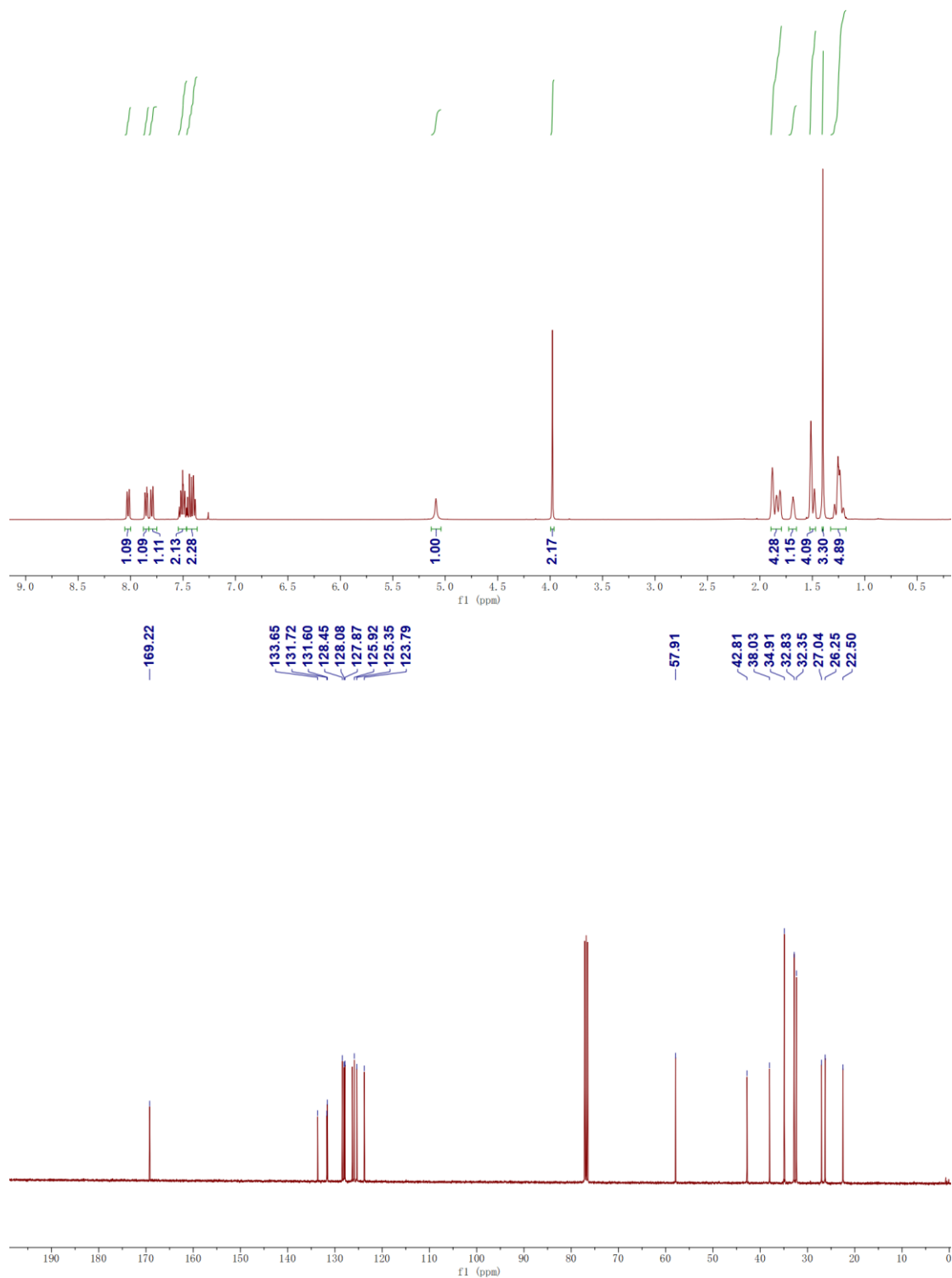


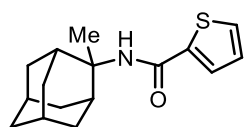




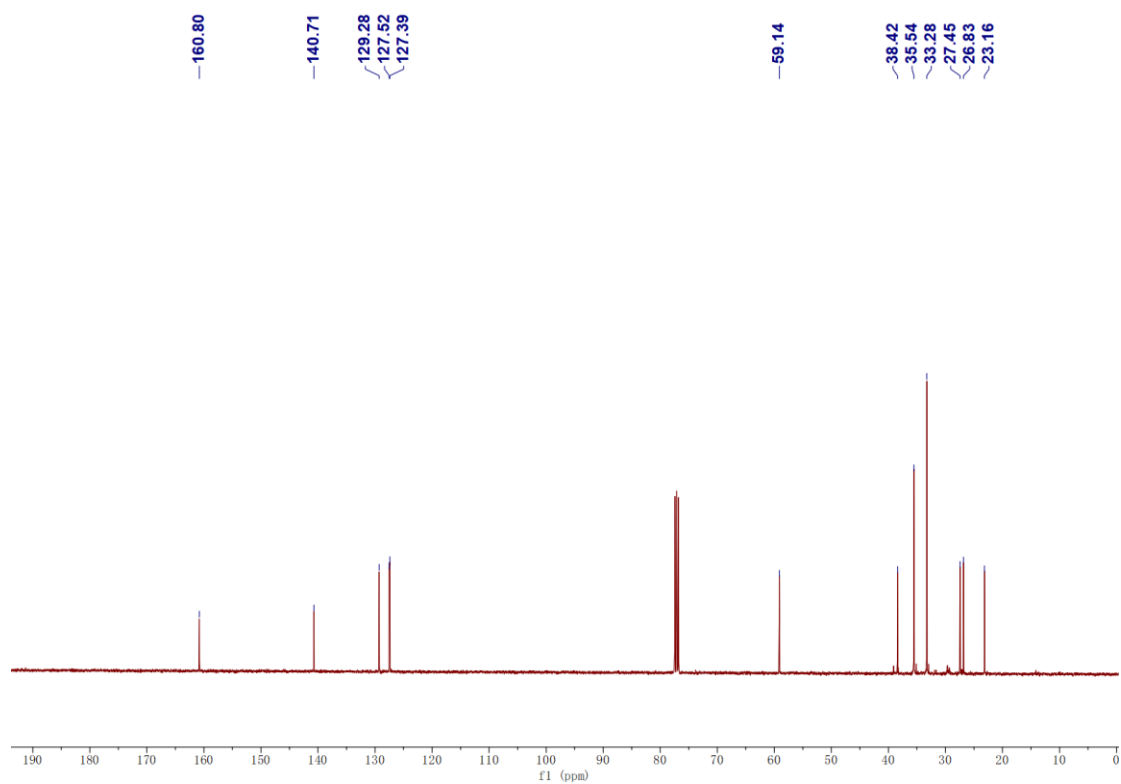
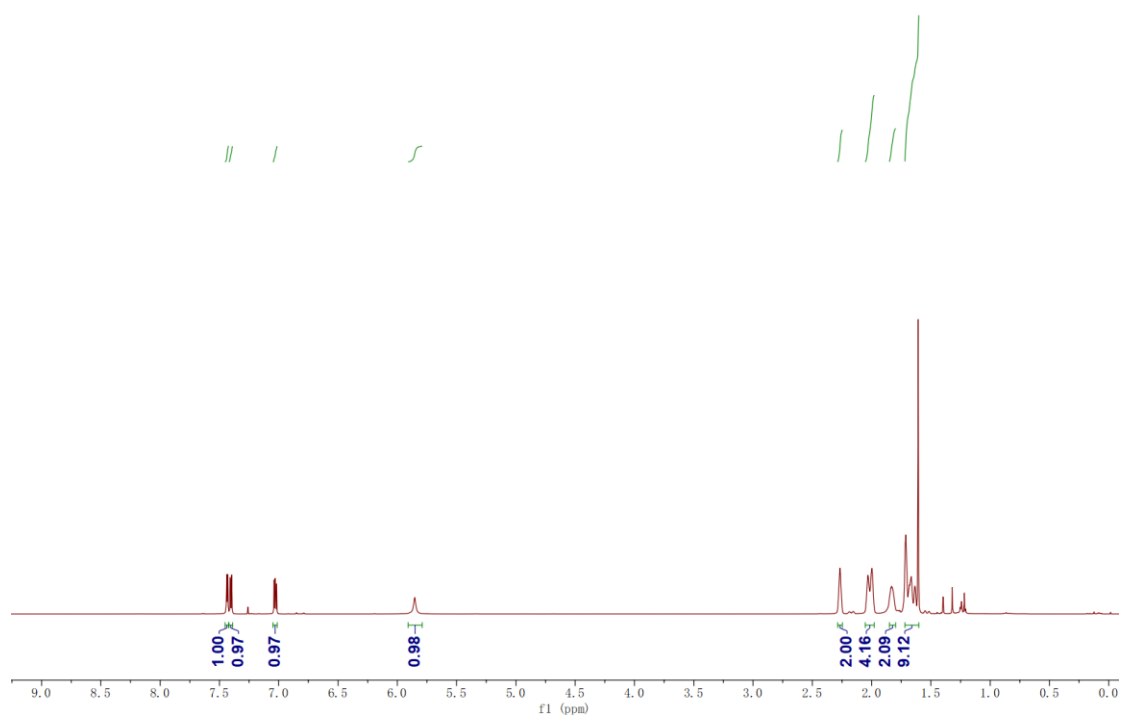


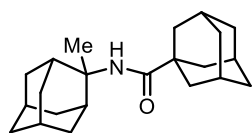
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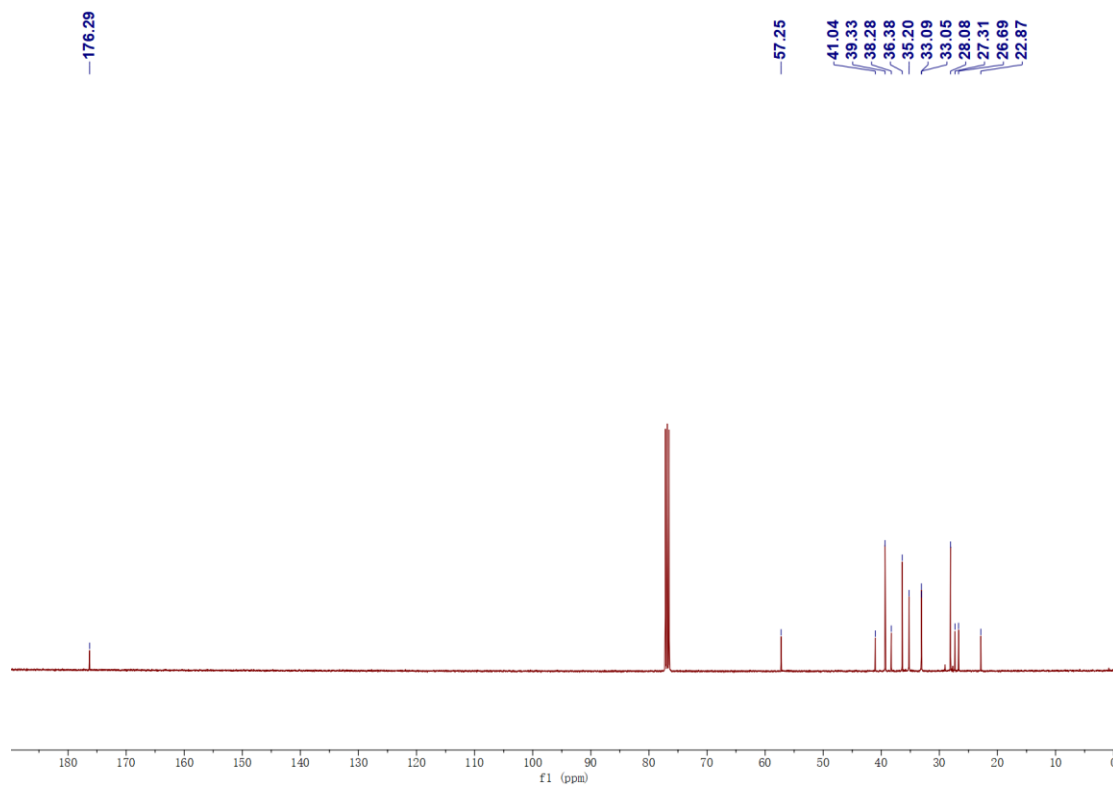
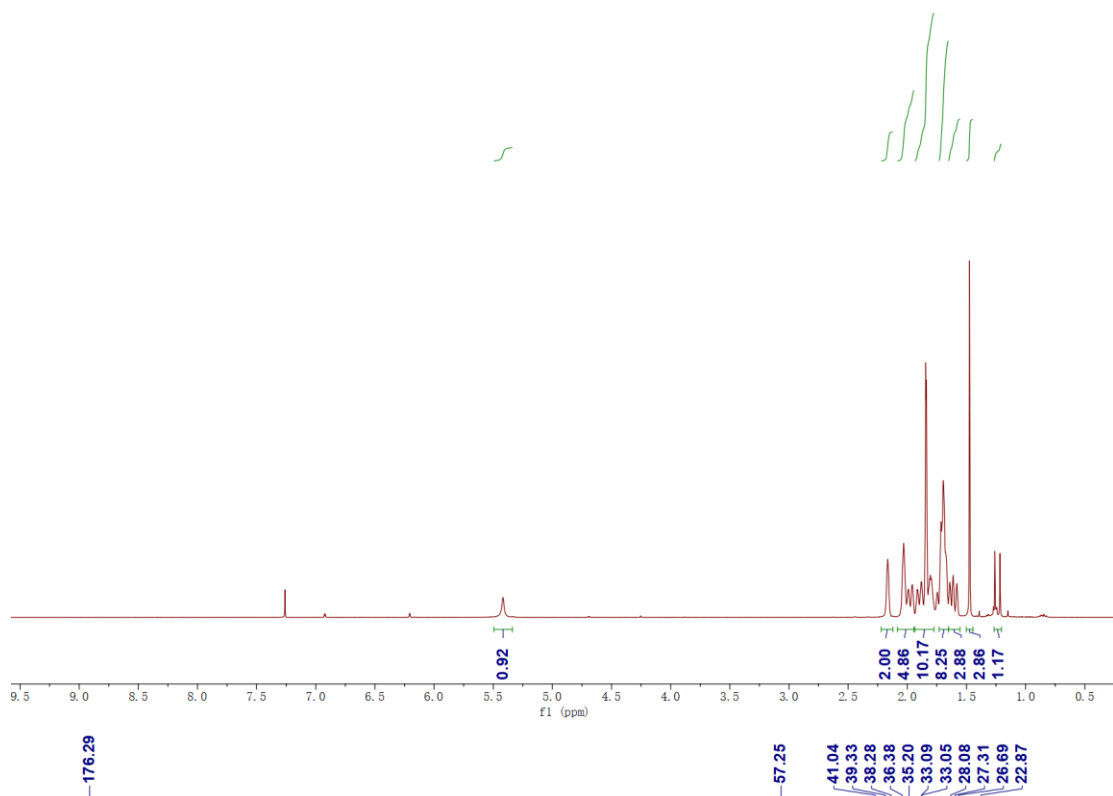


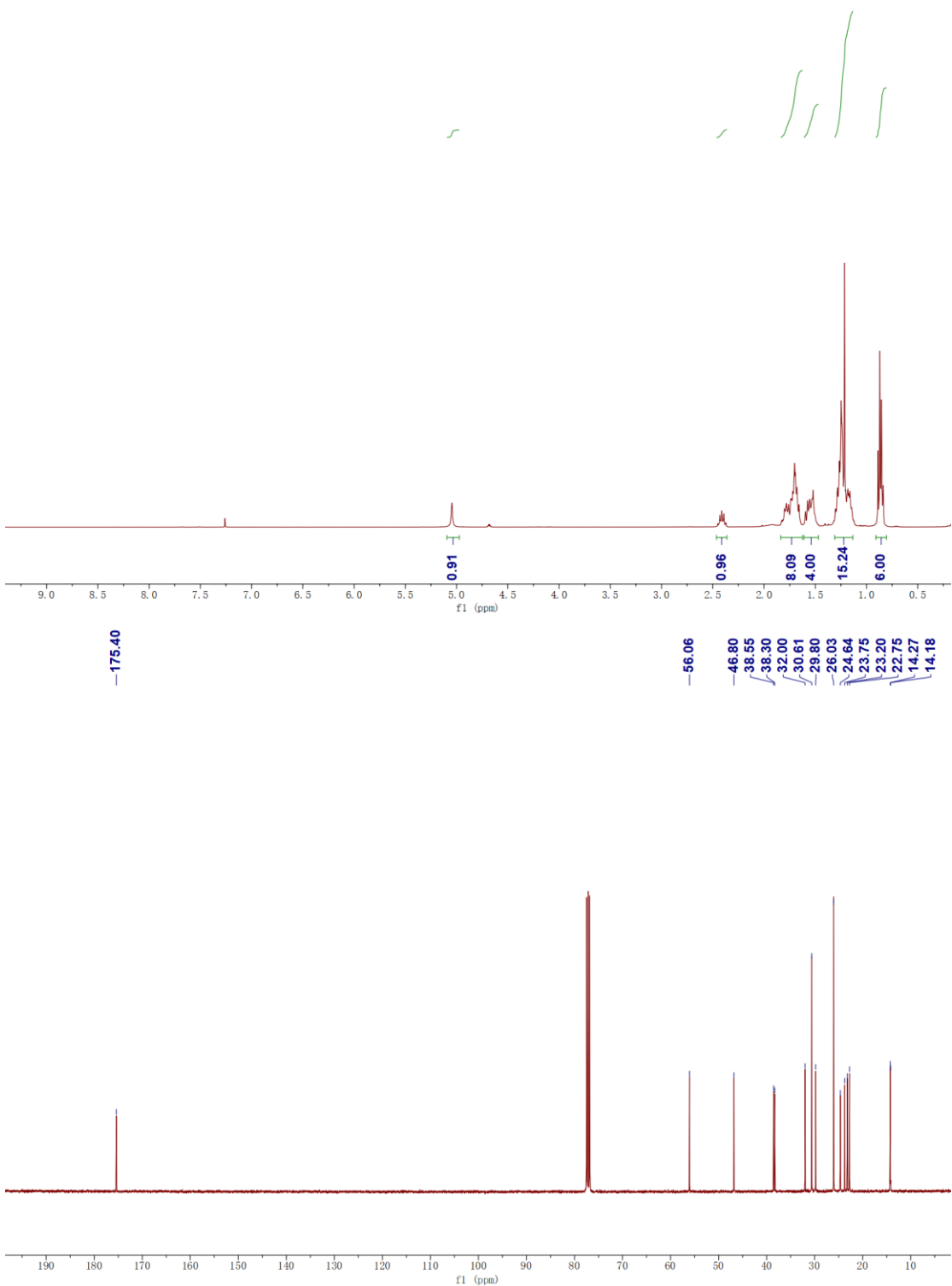
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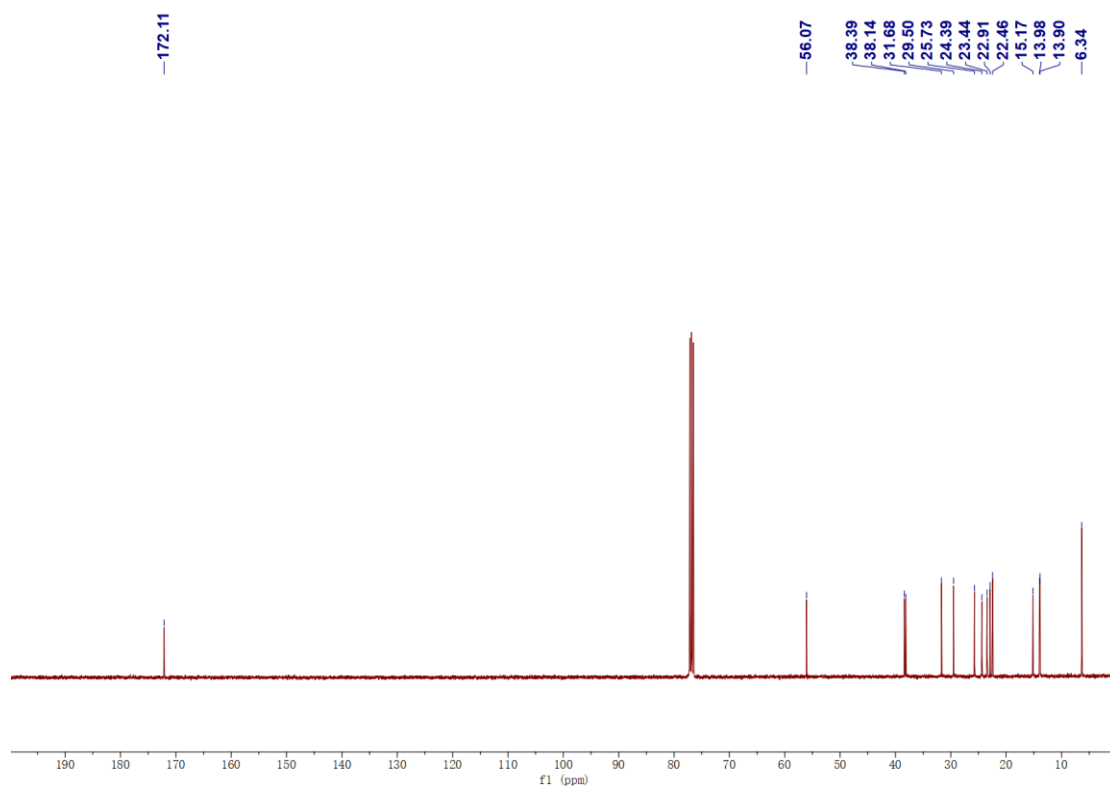
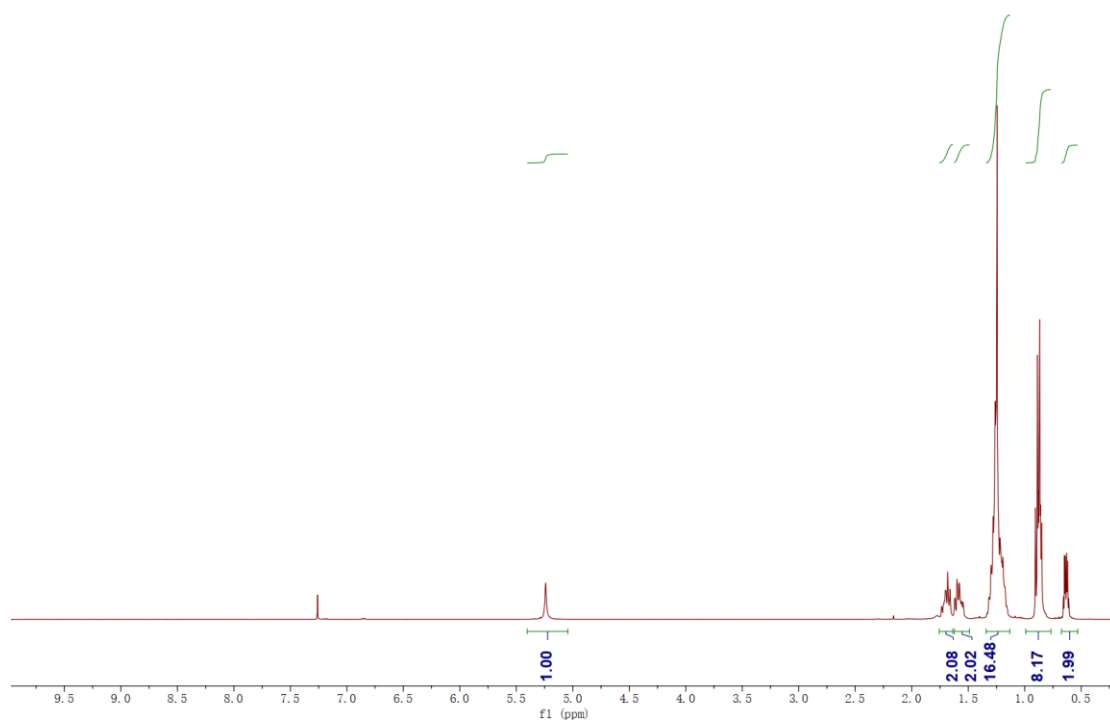
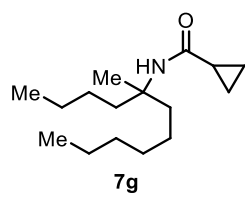


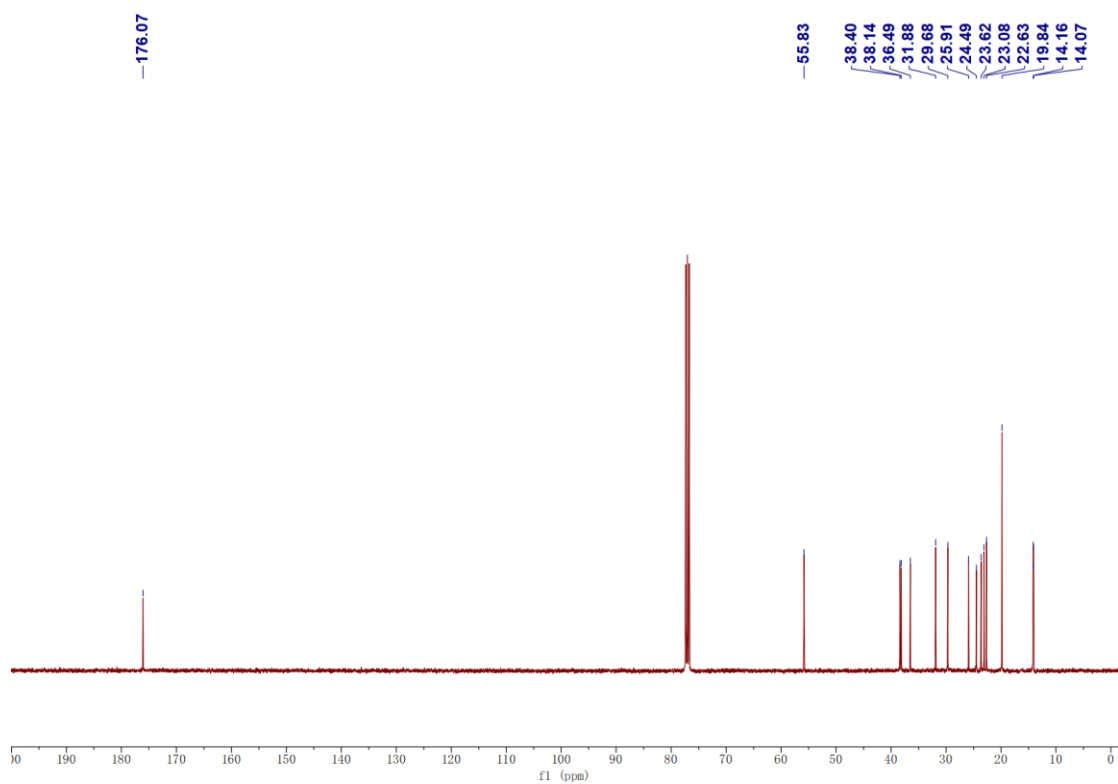
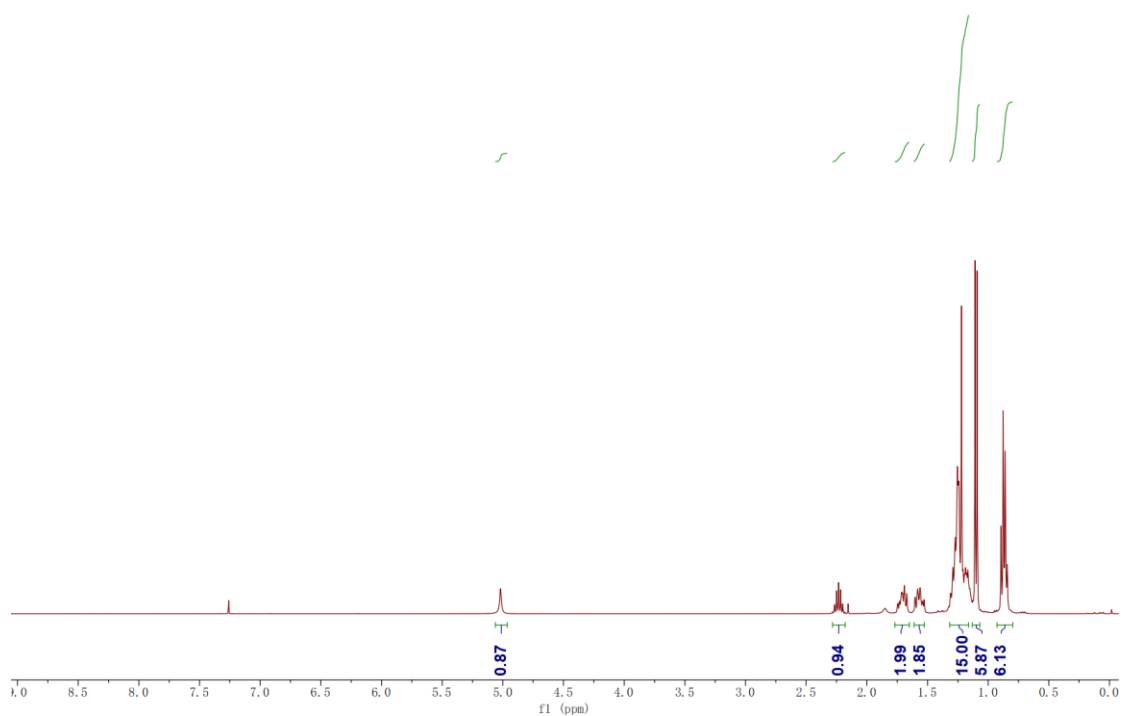
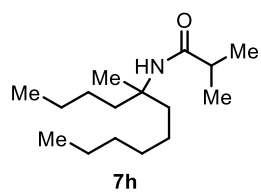


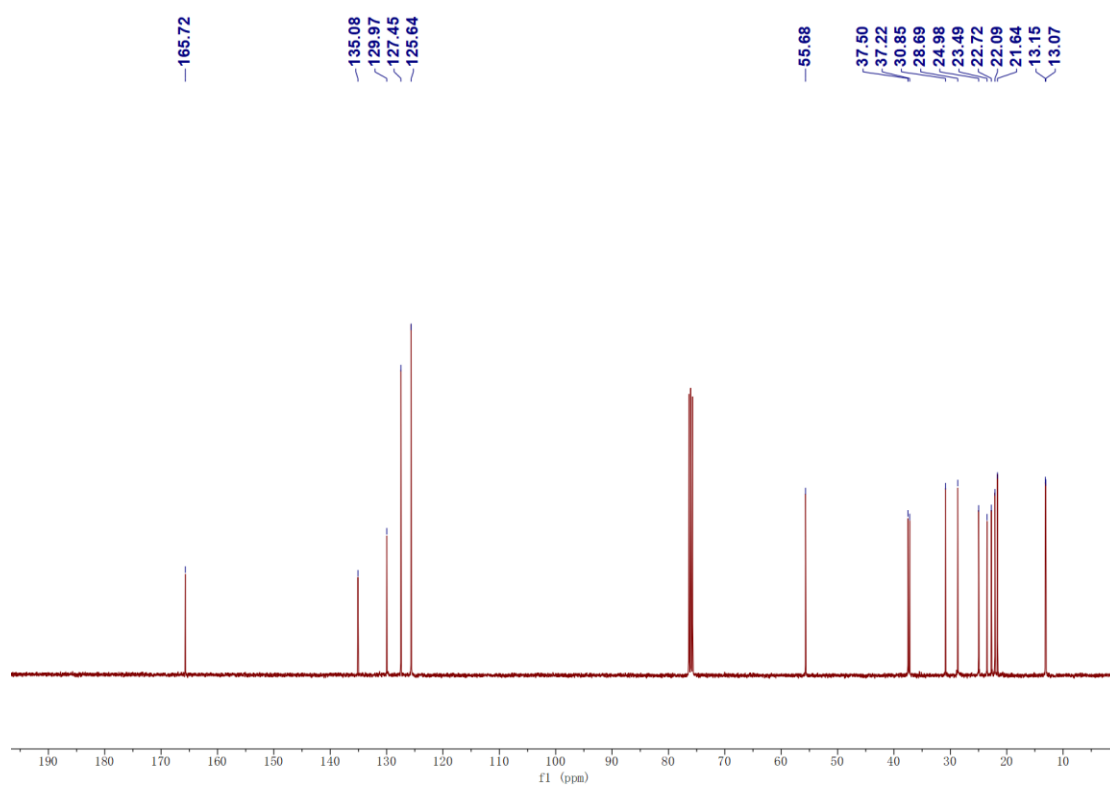
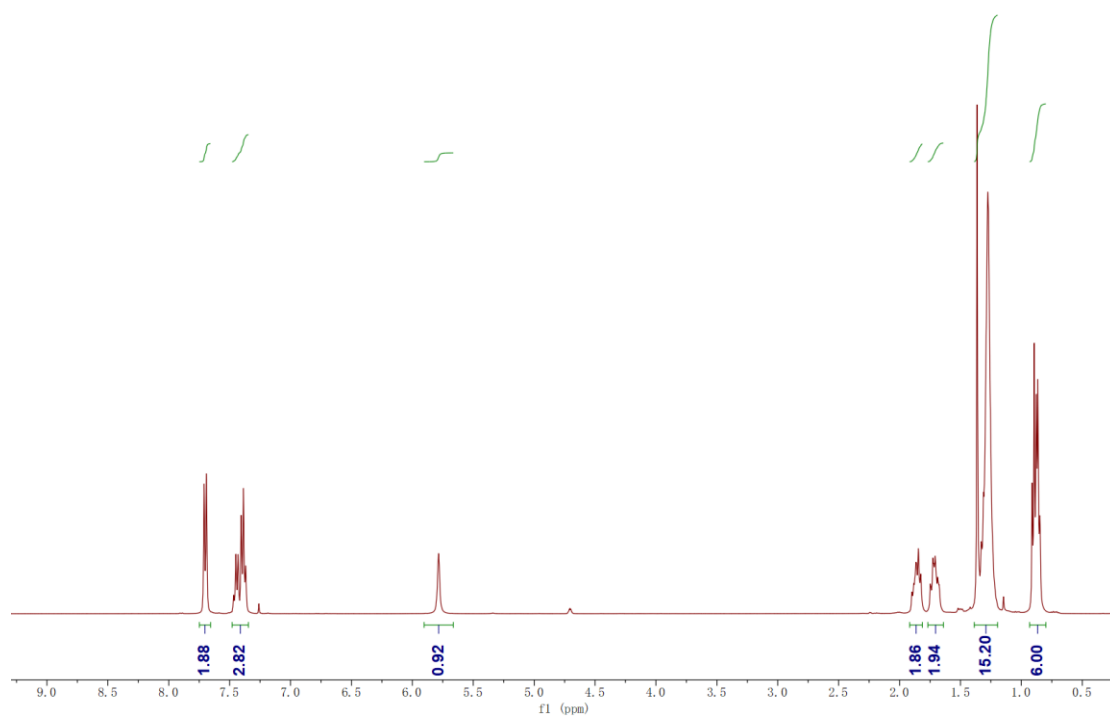
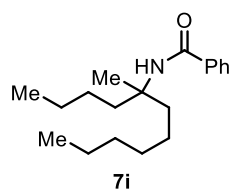
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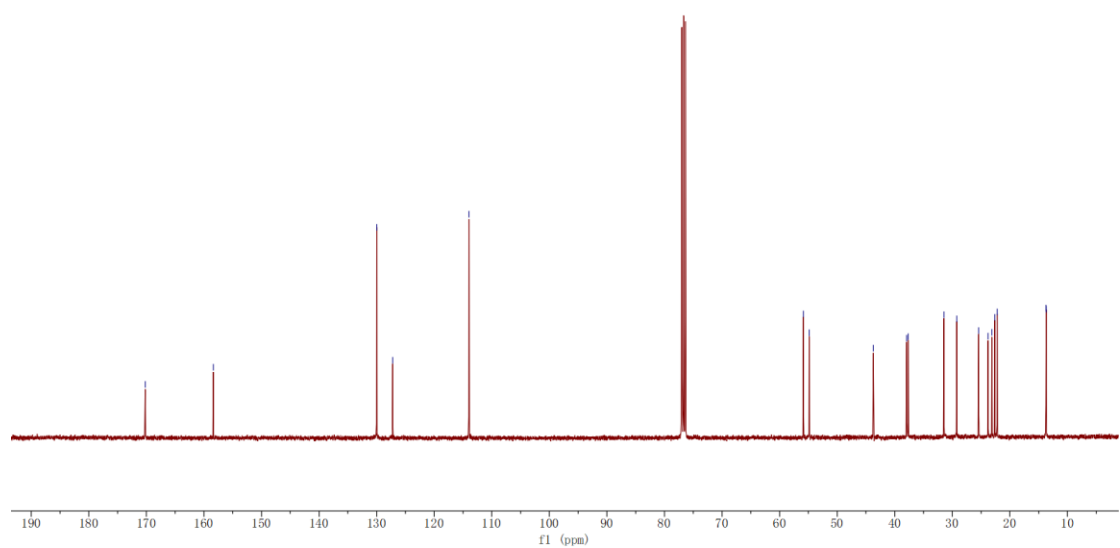
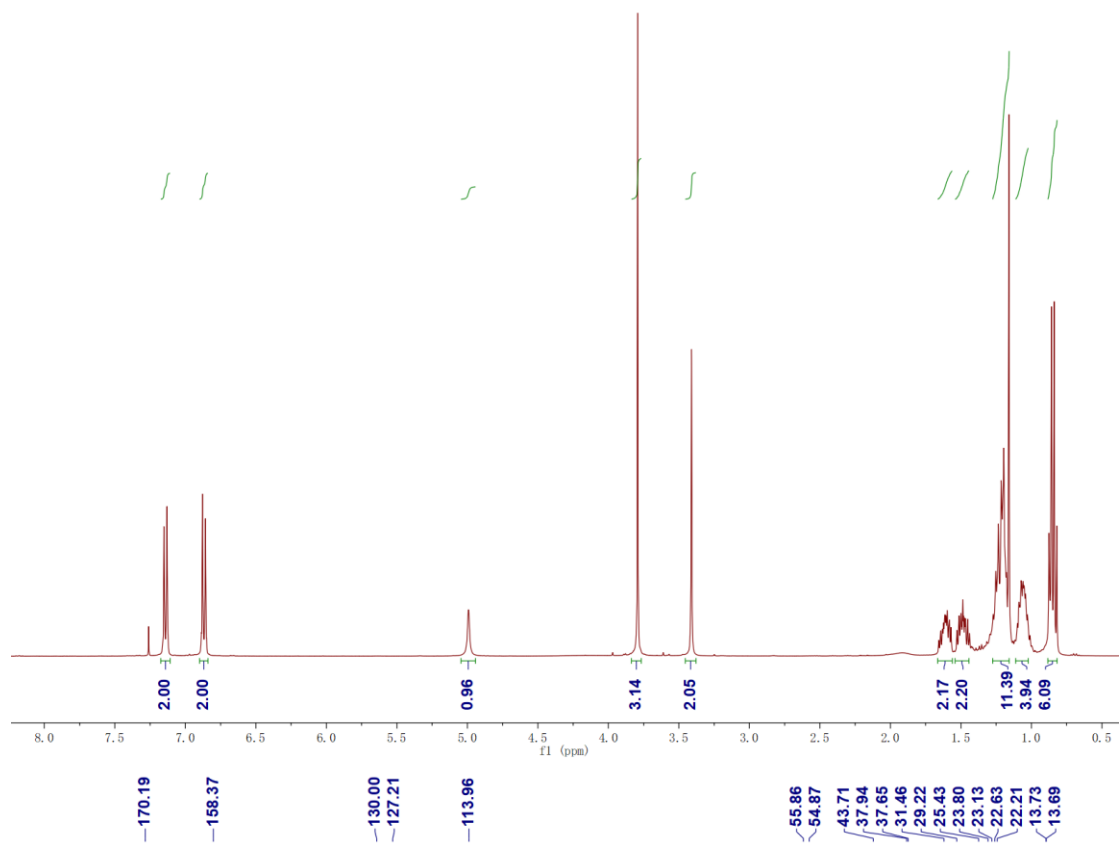
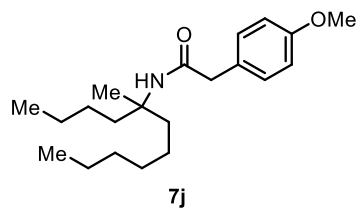


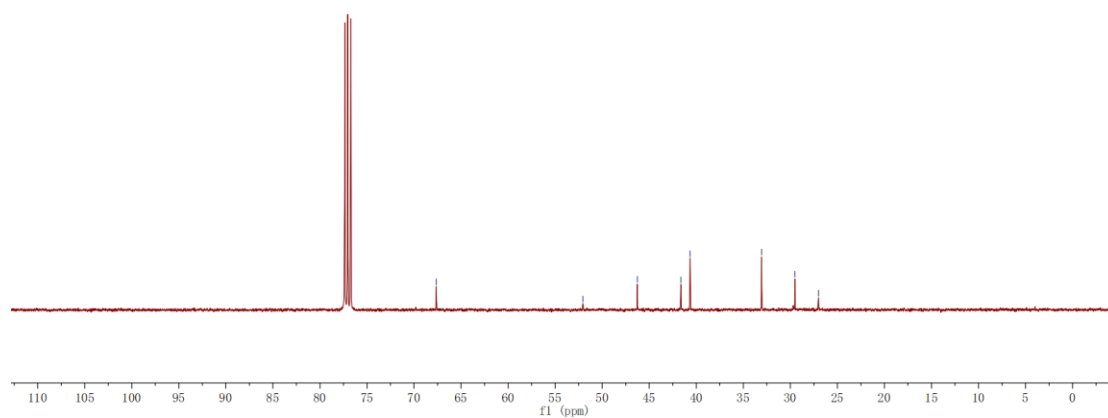
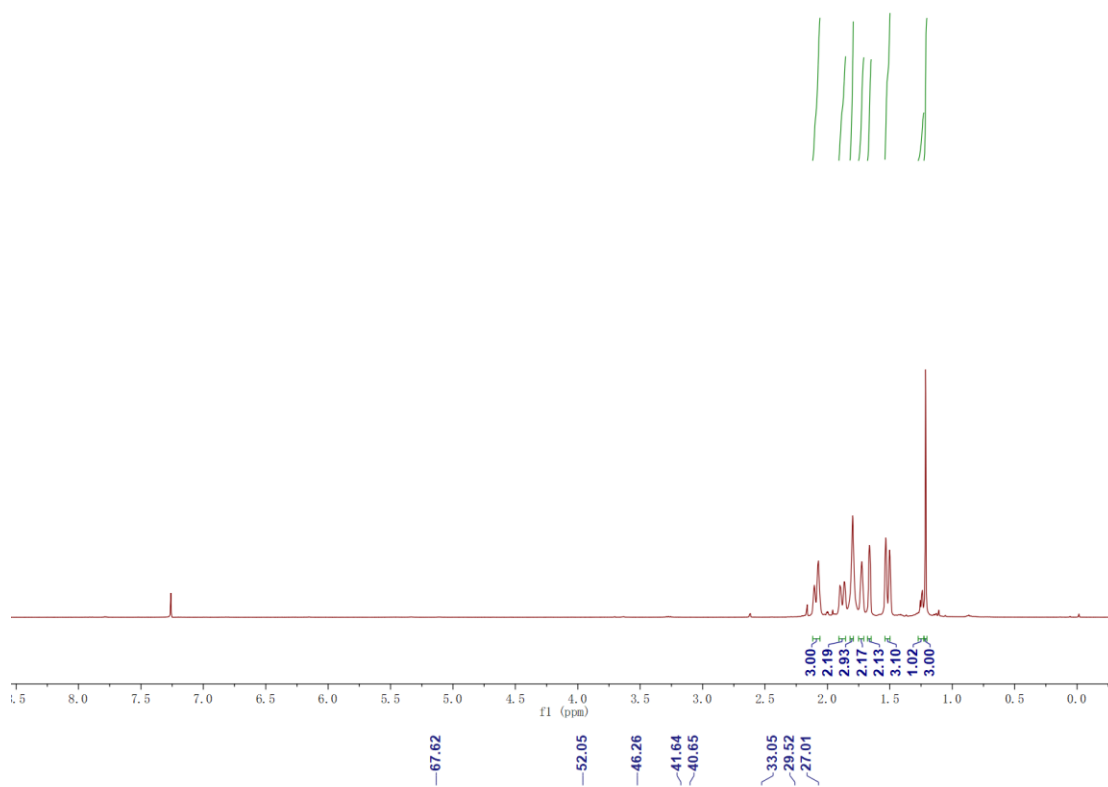
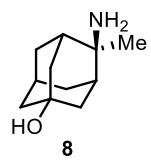


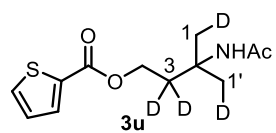






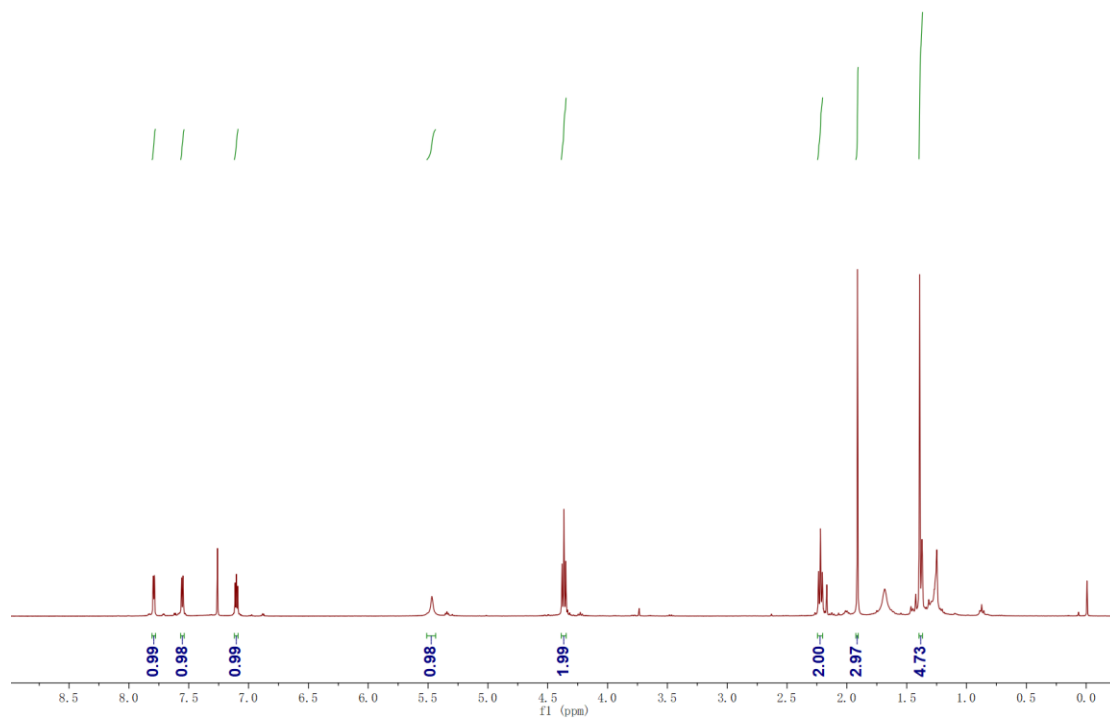


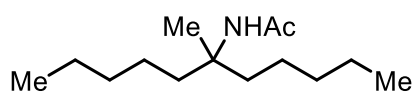




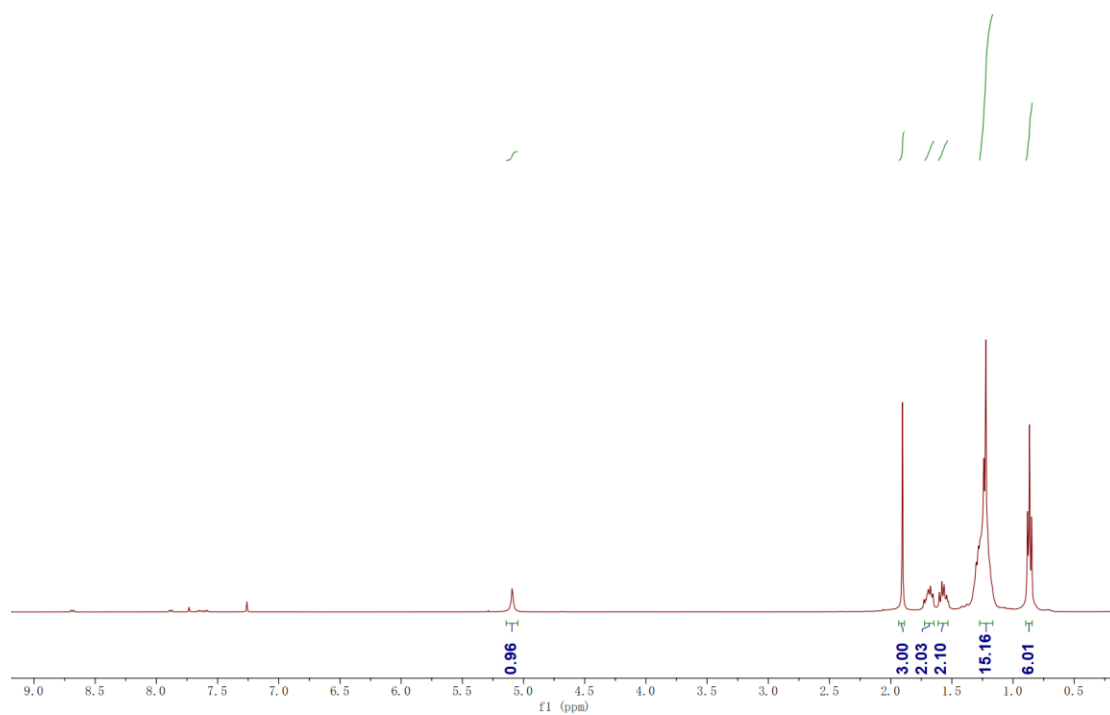
C_{1/1'}: 127%

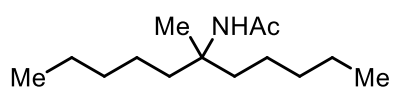
C₃: 0%



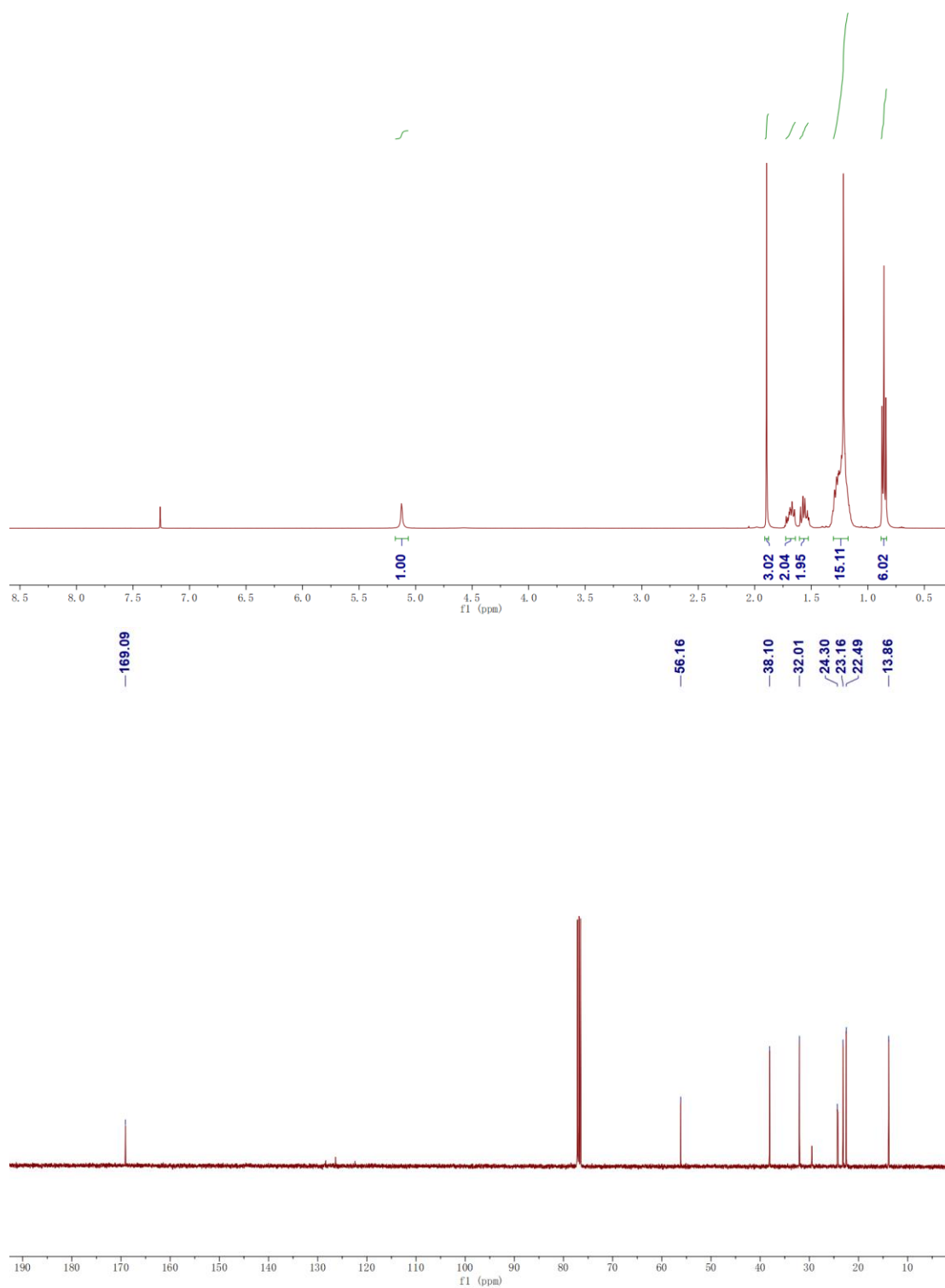


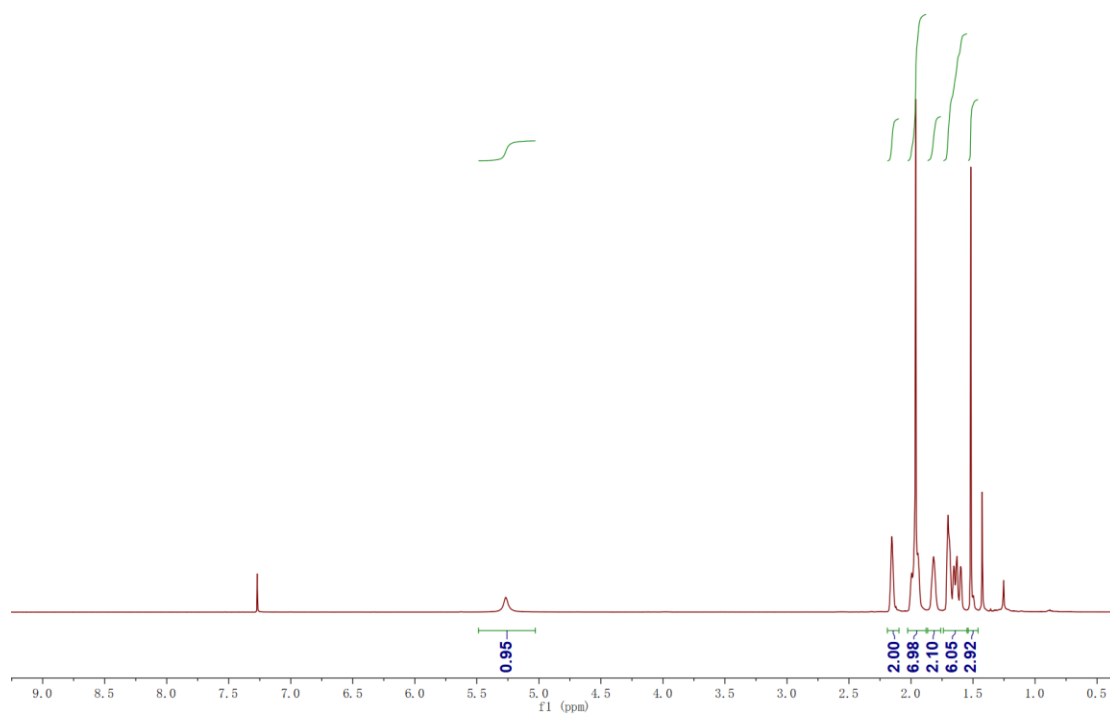
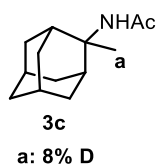
YYN-2-65-2, 3w, in the presence of D₂O

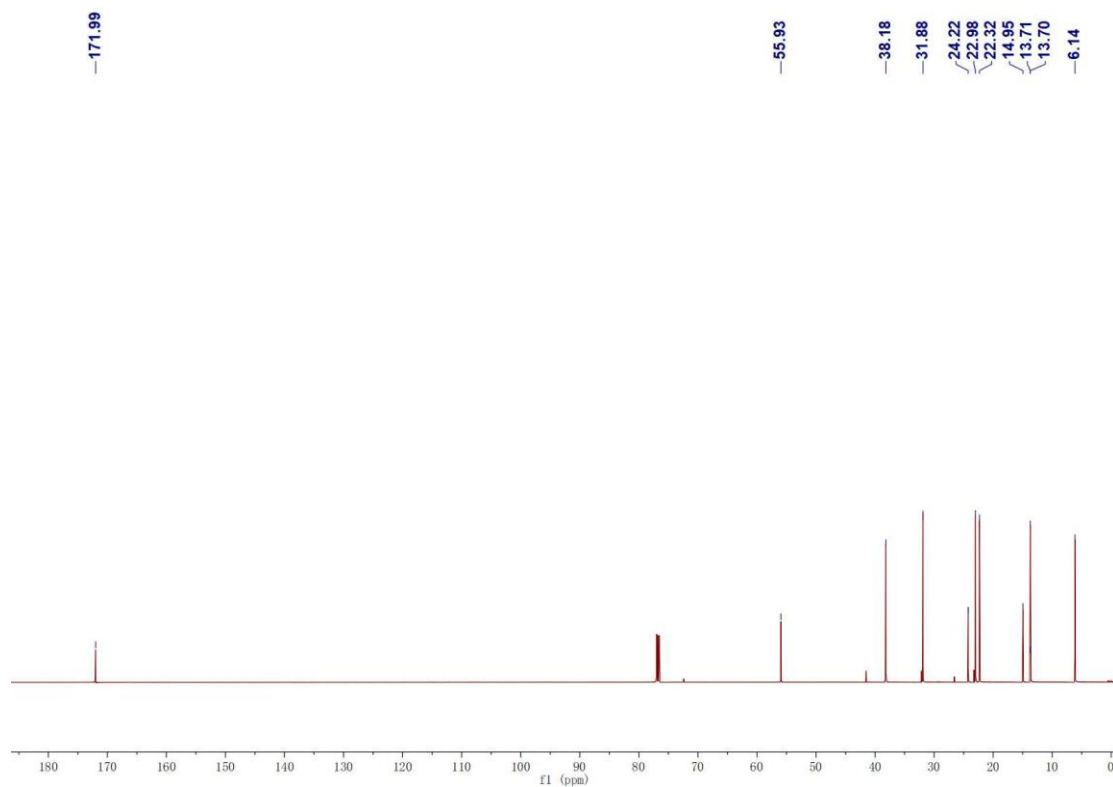
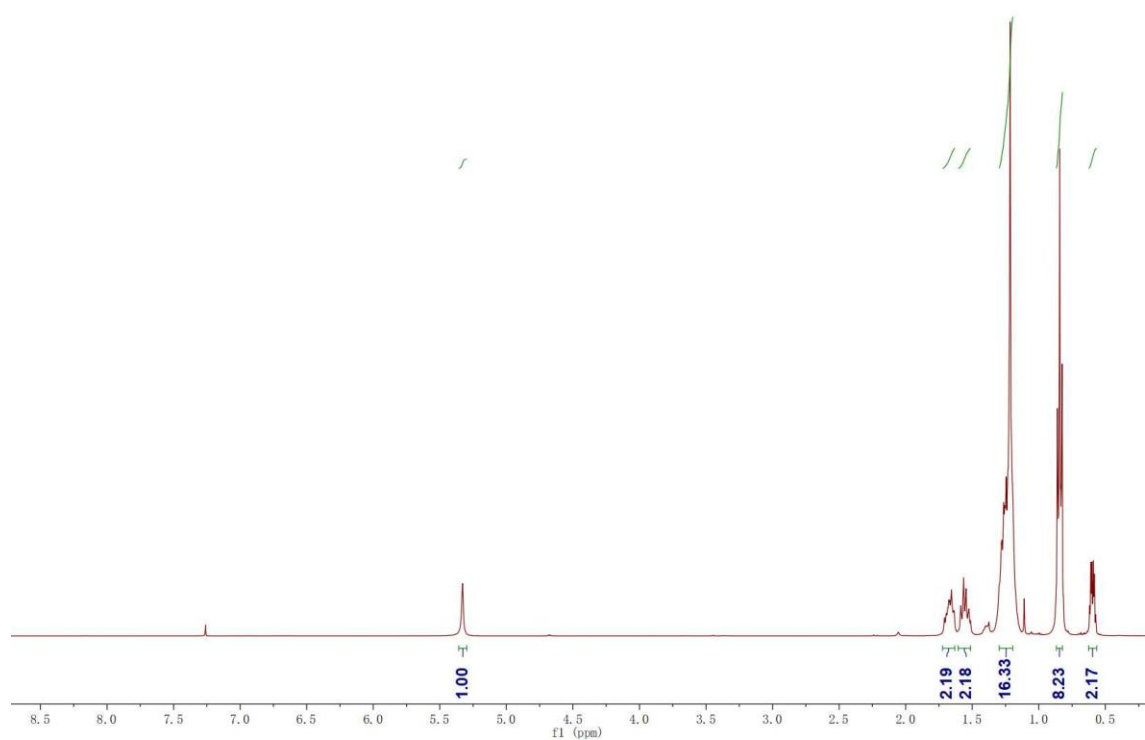




YYN-2-65-1, 3w, in the presence of H₂O







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