



Access to unsaturated bicyclic lactones by overriding conventional C(sp^3)–H site selectivity

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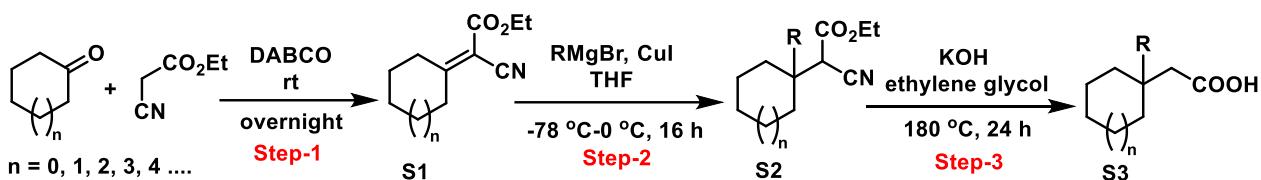
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1. General Consideration:

Reagent Information. Unless otherwise stated, all reactions were carried out in screw cap reaction tubes. All the solvents were bought from commercial sources and were used without further purification. Palladium salts and olefins were purchased from Aldrich and TCI-India. Silica gel (100–200 mesh) obtained from SRL Co. was used for column chromatography. Products and starting materials were visualized on TLC plate (Merck, TLC silica gel 60 F254) using UV-light or by staining with KMnO₄ solution, followed by heating. A gradient elution using petroleum ether and ethyl acetate was performed, based on Merck aluminium TLC sheets (silica gel 60F₂₅₄).

Analytical Information. All compounds are characterized by ¹H NMR, ¹³C NMR spectroscopy, and HR-MS. Copies of the ¹H NMR, ¹³C NMR and ¹⁹F can be found in the Supporting Information. Unless otherwise stated, all Nuclear Magnetic Resonance spectra were recorded on a Bruker 500 MHz / 400 MHz instrument. All ¹H NMR experiments are reported in units, parts per million (ppm), and were measured relative to the signals for residual chloroform (7.26 ppm) in the deuterated solvent, unless otherwise stated. All ¹³C NMR spectra were reported in ppm relative to deuteriochloroform (77.230 ppm), unless otherwise stated, and all were obtained with ¹H decoupling. High-resolution mass spectra (HRMS) were recorded on a micro-mass ESI TOF (time of flight) mass spectrometer.

2. Preparation of Cycloalkyl Acetic Acids



Step 1: Knoevenagel Condensation (S1)

To a round bottom flask with a magnetic stir bar, corresponding ketone (5.0 mmol), ethyl cyanoacetate (6.0 mmol), and 1,4-diazabicyclo[2.2.2]octane (DABCO, 10 mol%) were added. The resulting reaction mixture was stirred for overnight at room temperature. After completion of the reaction the mixture was diluted with EtOAc and washed with water and brine. Combined organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo. The crude product was purified through flash column chromatography using Hexane/EtOAc as the eluent to yield S1 in quantitatively.

Step 2: Grignard Reaction (S2)

To a round bottom flask with a magnetic stir bar was added copper iodide (1.0 equiv.) and THF solvent followed by the dropwise addition of alkyl magnesium bromide in THF or hexane (2.0 equiv.) at -25 °C. The resulting mixture was stirred for 2 h at the same temperature, then corresponding S1 in THF was added slowly. The reaction mixture was slowly warmed to room temperature and stirred for overnight. The reaction was quenched with sat. NH₄Cl (aq.) and filtered through a pad of celite. The resulting reaction mixture was diluted with EtOAc and washed with water and brine. The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo. The crude product was purified through flash column chromatography using Hexane/EtOAc as the eluent to provide corresponding S2 in the range of 40-95% yield.

Step 3: Base Mediated Decarboxylative Hydrolysis (S3)

A clean, oven-dried screw cap reaction tube with previously placed magnetic stir-bar was charged with S2 (2.0 mmol), KOH (10.0 equiv.), followed by addition of ethylene glycol (2 mL). The reaction mixture sealed tightly and was vigorously stirred for 24 h in a preheated oil bath at 180 °C. After stipulated time, the reaction mixture was cooled to room temperature and diluted with water. Diluted reaction mixture was acidified with 2N HCl up to pH 3.0 and then extracted with EtOAc three times. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuo. The crude product was purified through flash column chromatography using Hexane/EtOAc as the eluent to provide corresponding acid S3.

3. Optimization:

Yield and selectivity were determined by ^1H NMR analysis of the crude product using internal standard.

Table S1: Pd-catalyst optimization

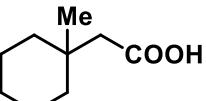
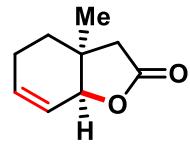
	Pd-catalyst (10 mol%) <i>N</i> -Ac-Leu (20 mol%) Ag_2CO_3 (2 equiv.) Na_2HPO_4 (2 equiv.) HFIP, 120 °C, 24 h	
Entry	Catalyst	Yield (%)
1	Pd(OAc)₂	24
2	$\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$	trace
3	$\text{Pd}(\text{PhCN})_2\text{Cl}_2$	8
4	$\text{Pd}(\text{allyl})_2\text{Cl}_2$	9
5	$\text{Pd}(\text{TFA})_2$	17
6	$\text{Pd}(\text{OPiv})_2$	20
7	$\text{Pd}(\text{COD})_2\text{Cl}_2$	16
8	$\text{Pd}(\text{PPh}_3)_4$	trace
9	$\text{Pd}(\text{acac})_2$	21
10	$\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$	11
11	$[\text{Pd}_2(\text{dba})_2]_3$	trace

Table S2: Temperature optimization

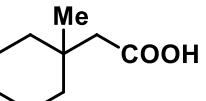
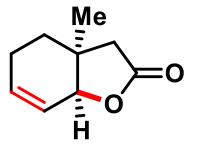
	Pd(OAc)₂ (10 mol%) <i>N</i> -Ac-Leu (20 mol%) Ag_2CO_3 (2 equiv.) Na_2HPO_4 (2 equiv.) HFIP, Temperature (°C) , 24 h	
Entry	Temp. (°C)	Yield (%)
1	80	Trace
2	90	<10
3	100	13
4	110	20
5	120	24
6	130	23
7	140	19

Table S3: Ligand optimization

Entry	Ligand	Yield (%)
1	<i>N</i> -Ac-Leu	24
2	<i>N</i> -Boc-Leu	NR
3	<i>N</i> -Ac-Ile	36
4	<i>N</i> -Boc-Ile	NR
5	<i>N</i> -Ac-Gly	13
6	<i>N</i> -Ac-Ala	19
7	<i>N</i> -Ac-Val	14
8	<i>N</i> -Ac-Nle	17
9	<i>N</i> -Ac- β -Ala	trace
10	<i>N</i> -Ac- β -Phe-Ala	trace
11	<i>N</i> -Ac-Anthranilic acid	trace
12	<i>N</i> -Ac-Ph-Ala	44
13	<i>N</i>-Ac-'Leu	66
14	<i>N</i> -Boc-'Leu	trace
15	<i>N</i> -Cbz-'Leu	NR
16	<i>N</i> -Bz-'Leu	NR
17	2-Pyridone	NR
18	pyridine	NR
19	phenanthroline	NR
20	8-nitroquinoline	NR
21	4-hydroxy pyridine	NR
22	2-hydroxy-5(trifluoromethyl) pyridine	NR

Table S4: Ligand amount optimization

Entry	Amount (mol%)	Yield (%)
1	10	45
2	15	51
3	20	66
4	25	67
5	30	64
6	35	56
7	40	48

Table S5: Oxidant optimization

Entry	Oxidant	Yield (%)
1	AgOAc	53
2	Ag2CO3	66
3	Ag2O	42
4	Ag2SO4	25
5	AgTFA	15
6	Ag3PO4	trace
7	Cu(OAc)2	26

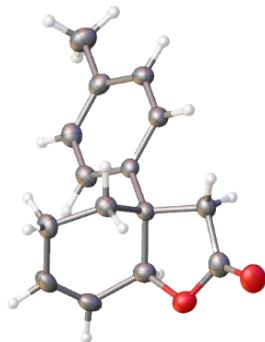
Table S6: Base optimization

Entry	Base	Yield (%)
1	CsCl	26
2	NaIO ₄	trace
3	K ₂ HPO ₄	42
4	Na ₂ CO ₃	66
5	K ₂ CO ₃	51
6	Na ₂ S ₂ O ₈	32
7	Na₃PO₄	73
8	Na ₃ PO ₄ (3 eq.)	69
9	Cs ₂ CO ₃	64
10	Na ₂ HPO ₄ (1 eq.)	56
11	Na ₂ HPO ₄ (1.5 eq.)	62
12	Na ₂ HPO ₄ (2 eq.)	66

Table S7: Time optimization

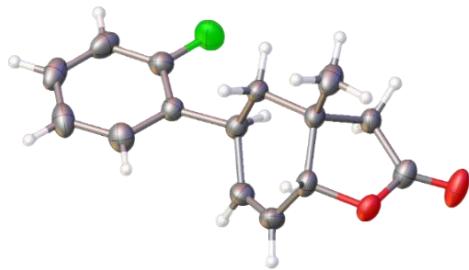
Entry	Time (h)	Yield (%)
1	12	42
2	16	53
3	24	73
4	30	68
5	48	57

4. X-ray Crystallographic Data:



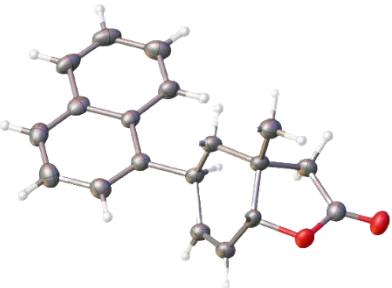
Crystal Data of 2k CCDC 2166862:

Crystal data and structure refinement for C ₁₅ H ₁₆ O ₂	
Identification code	2k
Formula	C ₁₅ H ₁₆ O ₂
Formula weight(g/mol)	228.28
Temperature/K	150 K
Crystal system	Monoclinic
Space group	P 1 21/c 1
a/Å	6.2421(4)
b/Å	19.2352(11)
c/Å	9.9231(8)
α/°	90
β/°	100.931(7)
γ/°	90
Volume/Å ³	1169.83(14)
Z	4
P _{calc} g/cm ³	1.296
μ/mm ⁻¹	0.085
F(000)	488.0
Crystal size/mm ³	0.115 x 0.098 x 0.092
Radiation	MoKα ($\lambda = 0.71073$)
2Θ range for data collection/°	3.1360 to 29.9700
Goodness-of-fit on F ²	1.025
R indices (all data)	R1 = 0.0542, wR2 = 0.1472
Largest diff. peak and hole/ e Å ⁻³	0.662 and -0.271



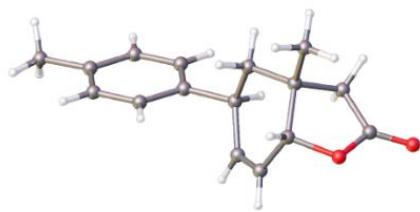
Crystal Data of 2w CCDC 2166863:

Crystal data and structure refinement for C ₁₅ H ₁₆ FO ₂	
Identification code	2w
Formula	C ₁₅ H ₁₆ FO ₂
Formula weight(g/mol)	246.27
Temperature/K	150 K
Crystal system	Orthorhombic
Space group	P 21 21 21
a/Å	6.6014(3)
b/Å	9.6883(5)
c/Å	19.9271(11)
α/°	90
β/°	90
γ/°	90
Volume/Å ³	1274.46(11)
Z	4
P _{calc} g/cm ³	1.283
μ/mm ⁻¹	0.094
F(000)	520.0
Crystal size/mm ³	0.112 x 0.098 x 0.095
Radiation	MoKα ($\lambda = 0.71073$)
2Θ range for data collection/°	3.1360 to 29.9700
Goodness-of-fit on F ²	1.056
R indices (all data)	R1 = 0.0373, wR2 = 0.0863
Largest diff. peak and hole/ e Å ⁻³	0.126 and -0.129



Crystal Data of 2x CCDC 2166865:

Crystal data and structure refinement for C ₁₉ H ₁₈ O ₂	
Identification code	2x
Formula	C ₁₉ H ₁₈ O ₂
Formula weight(g/mol)	278.33
Temperature/K	150 K
Crystal system	Monoclinic
Space group	P 1 21 1
a/Å	11.0225(9)
b/Å	6.4677(4)
c/Å	11.3616(10)
α/°	90
β/°	116.111(11)
γ/°	90
Volume/Å ³	727.31(12)
Z	2
P _{calc} g/cm ³	1.271
μ/mm ⁻¹	0.081
F(000)	296.0
Crystal size/mm ³	0.112 x 0.102 x 0.096
Radiation	MoKα ($\lambda = 0.71073$)
2Θ range for data collection/°	3.1360 to 29.9700
Goodness-of-fit on F ²	0.993
R indices (all data)	R1 = 0.0548, wR2 = 0.1359
Largest diff. peak and hole/ e Å ⁻³	0.172 and -0.272

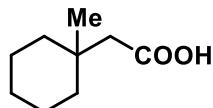


Crystal Data of 2u CCDC: 2236254

Crystal data and structure refinement for C ₁₉ H ₁₈ O ₂	
Identification code	2u
Formula	C ₁₆ H ₁₈ O ₂
Formula weight(g/mol)	242.30
Temperature/K	150 K
Crystal system	Monoclinic
Space group	P 1 21 1
a/Å	6.4447(2)
b/Å	99.350(3)
c/Å	10.0261(3)
α/°	90
β/°	116.111(11)
γ/°	90
Volume/Å ³	1340.83(7)
Z	4
P _{calc} g/cm ³	1.200
μ/mm ⁻¹	0.078
F(000)	520.0
Crystal size/mm ³	0.11 x 0.098 x 0.095
Radiation	MoKα ($\lambda = 0.71073$)
2Θ range for data collection/°	1.937 to 25.0000
Goodness-of-fit on F ²	0.993
R indices (all data)	R1 = 0.144, wR2 = 0.1273
Largest diff. peak and hole/ e Å ⁻³	0.336 and -0.170

5. Spectral Data of the Starting Material:

2-(1-Methylcyclohexyl)acetic acid (1)



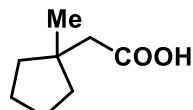
Eluent: ethyl acetate/ petroleum ether (90:10 v/v).

Appearance: colorless gummy

Isolated yield: 81% (254 mg, 1.61 mmol)

¹H NMR (400 MHz, CDCl₃) δ 2.27 (s, 2H), 1.63 – 1.22 (m, 10H), 1.05 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 179.38, 45.97, 38.02, 33.52, 26.29, 25.59, 22.18; **HRMS (ESI)**: calculated for C₉H₁₇O₂ [M+H]⁺: 157.1229; observed mass 157.1232.

2-(1-Methylcyclopentyl)acetic acid (2)



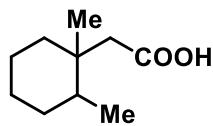
Eluent: ethyl acetate/ petroleum ether (90:10 v/v).

Appearance: colorless gummy.

Isolated yield: 72% (205 mg, 1.44 mmol)

¹H NMR (400 MHz, CDCl₃) δ 2.34 (s, 2H), 1.66 (qd, *J* = 5.1, 4.6, 1.9 Hz, 4H), 1.61 – 1.52 (m, 2H), 1.46 (dddd, *J* = 12.2, 6.7, 4.6, 3.0 Hz, 2H), 1.09 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 179.14, 45.98, 41.45, 39.64, 26.18, 24.31; **HRMS (ESI)**: Calculated mass for C₈H₁₅O₂ [M+H]⁺: 143.1072; observed mass: 143.1075.

2-(1,2-Dimethylcyclohexyl)acetic acid (3)



Eluent: ethyl acetate/ petroleum ether (10:90 v/v).

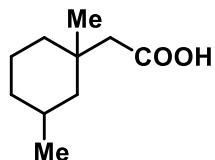
Appearance: colorless semisolid.

Isolated yield: 91% (310 mg, 1.82 mmol)

¹H NMR (400 MHz, CDCl₃) δ 2.60 – 2.02 (m, 2H), 1.72 (ddtd, *J* = 44.5, 12.6, 3.8, 1.5 Hz, 2H), 1.56 – 0.92 (m, 10H), 0.83 (d, *J* = 6.8 Hz, 3H); **¹³C NMR** (126 MHz, CDCl₃) δ 179.96, 46.90, 42.13, 39.14, 37.72, 37.23, 36.93, 36.70, 36.27, 30.89, 30.67, 27.24, 26.27, 26.13, 22.36,

22.28, 18.04, 16.42, 16.10; **HRMS (ESI)**: Calculated mass for C₁₀H₁₉O₂ [M+H]⁺: 171.1385; observed mass: 171.1390.

2-(1,3-Dimethylcyclohexyl)acetic acid (4)



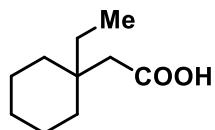
Eluent: ethyl acetate/ petroleum ether (10:90 v/v).

Appearance: colorless solid.

Isolated yield: 75% (205 mg, 1.21 mmol)

¹H NMR (400 MHz, CDCl₃) δ 2.34 (s, 2H), 1.75 – 1.33 (m, 6H), 1.16 – 0.97 (m, 4H), 0.85 (d, J = 6.4 Hz, 3H), 0.82 – 0.70 (m, 2H); **¹³C NMR** (101 MHz, CDCl₃) δ 179.13, 47.26, 41.31, 37.75, 35.04, 34.11, 30.10, 28.07, 23.07, 22.26; **HRMS (ESI)**: Calculated mass for C₁₀H₁₉O₂ [M+H]⁺: 171.1385; observed mass: 171.1387.

2-(1-Ethylcyclohexyl)acetic acid (5)



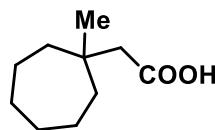
Eluent: ethyl acetate/ petroleum ether (12:88 v/v).

Appearance: colorless semisolid.

Isolated yield: 80% (272 mg, 1.6 mmol)

¹H NMR (400 MHz, CDCl₃) δ 2.29 (s, 2H), 1.64 – 1.18 (m, 12H), 0.85 (t, J = 7.5 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 179.24, 41.26, 36.21, 35.58, 30.15, 26.37, 21.85, 7.68; **HRMS (ESI)**: Calculated mass for C₁₀H₁₈NaO₂ [M+Na]⁺: 193.1204; observed mass: 193.1210.

2-(1-Methylcycloheptyl)acetic acid (6)



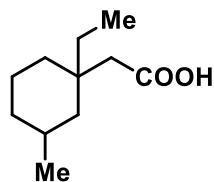
Eluent: ethyl acetate/ petroleum ether (10:90 v/v).

Appearance: white solid.

Isolated yield: 68% (231 mg, 1.36 mmol)

¹H NMR (500 MHz, CDCl₃) δ 2.23 (s, 2H), 1.87 – 1.34 (m, 12H), 1.04 (s, 3H); **¹³C NMR** (126 MHz, CDCl₃) δ 178.96, 46.99, 40.63, 37.74, 36.68, 30.72, 28.30, 27.83, 23.06, 22.80; **HRMS (ESI)**: Calculated mass for C₁₀H₁₉O₂ [M+H]⁺: 171.1385; observed mass: 171.1378.

2-(1-Ethyl-3-methylcyclohexyl)acetic acid (7)



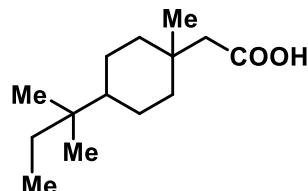
Eluent: ethyl acetate/ petroleum ether (8:92 v/v).

Appearance: colorless gummy.

Isolated yield: 73% (270 mg, 1.46 mmol)

¹H NMR (400 MHz, CDCl₃) δ 2.38 (s, 2H), 1.83 – 1.49 (m, 5H), 1.49 – 1.29 (m, 3H), 1.03 (td, J = 13.3, 4.1 Hz, 1H), 0.94 – 0.79 (m, 6H), 0.82 – 0.66 (m, 2H); **¹³C NMR** (101 MHz, CDCl₃) δ 179.08, 44.70, 37.92, 36.98, 35.36, 35.25, 34.69, 27.84, 23.21, 22.06, 7.66; **HRMS (ESI)**: Calculated mass for C₁₁H₂₁O₂ [M+H]⁺: 185.1542.; observed mass: 185.1550.

2-(1-Methyl-4-(*tert*-pentyl)cyclohexyl)acetic acid (8)



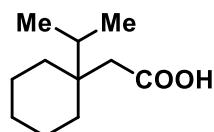
Eluent: ethyl acetate/ petroleum ether (12:88 v/v).

Appearance: white solid.

Isolated yield: 64% (290 mg, 0.64 mmol)

¹H NMR (500 MHz, CDCl₃) δ 2.31 (s, 2H), 1.85 – 1.67 (m, 2H), 1.64 – 1.45 (m, 2H), 1.25 (q, J = 7.5 Hz, 2H), 1.17 (t, J = 8.8 Hz, 4H), 1.03 (s, 4H), 0.78 (d, J = 6.5 Hz, 9H); **¹³C NMR** (101 MHz, CDCl₃) δ 179.44, 45.28, 40.72, 38.75, 34.88, 33.22, 32.86, 29.76, 24.52, 22.50, 8.31; **HRMS (ESI)**: Calculated mass for C₁₄H₂₇O₂ [M+H]⁺: 227.2011; observed mass: 227.2008.

2-(1-Isopropylcyclohexyl)acetic acid (9)



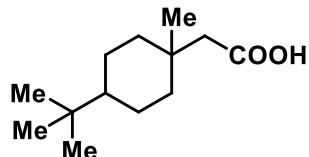
Eluent: ethyl acetate/ petroleum ether (10:90 v/v).

Appearance: colorless gummy.

Isolated yield: 71% (261 mg, 1.42 mmol)

¹H NMR (400 MHz, CDCl₃) δ 2.34 (s, 2H), 1.90 (hept, *J* = 6.9 Hz, 1H), 1.62 – 1.27 (m, 10H), 0.87 (d, *J* = 6.9 Hz, 6H); **¹³C NMR** (101 MHz, CDCl₃) δ 179.92, 38.86, 38.16, 32.54, 32.23, 26.29, 21.74, 16.92, 16.90; **HRMS (ESI)**: Calculated mass for C₁₁H₂₁O₂ [M+H]⁺: 185.1542; observed mass: 185.1550.

2-(4-(*tert*-Butyl)-1-methylcyclohexyl)acetic acid (10)



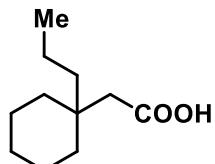
Eluent: ethyl acetate/ petroleum ether (10:90 v/v).

Appearance: white solid.

Isolated yield: 67% (299 mg, 1.34 mmol)

¹H NMR (400 MHz, CDCl₃) δ 2.32 (s, 2H), 1.78 – 1.68 (m, 2H), 1.64 – 1.51 (m, 2H), 1.22 – 1.11 (m, 4H), 1.04 (s, 3H), 0.96 (m, 1H), 0.85 (s, 9H); **¹³C NMR** (101 MHz, CDCl₃) δ 179.37, 48.14, 40.68, 38.68, 33.14, 32.62, 29.75, 27.78, 22.96; **HRMS (ESI)**: Calculated mass for C₁₃H₂₅O₂ [M+H]⁺: 213.1855; observed mass: 213.1860.

2-(1-Propylcyclohexyl)acetic acid (11)



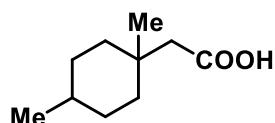
Eluent: ethyl acetate/ petroleum ether (10:90 v/v).

Appearance: colorless gummy.

Isolated yield: 75% (276 mg, 1.5 mmol)

¹H NMR (500 MHz, CDCl₃) δ 2.30 (s, 2H), 1.62 – 1.32 (m, 12H), 1.32 – 1.21 (m, 2H), 0.90 (t, *J* = 7.1 Hz, 3H); **¹³C NMR** (126 MHz, CDCl₃) δ 179.28, 41.95, 36.23, 36.02, 26.35, 21.85, 16.42, 15.10; **HRMS (ESI)**: Calculated mass for C₁₁H₂₁O₂ [M+H]⁺: 185.1542; observed mass: 185.1540.

2-(1,4-Dimethylcyclohexyl)acetic acid (12)



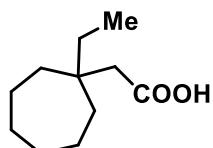
Eluent: ethyl acetate/ petroleum ether (10:90 v/v).

Appearance: whitish solid.

Isolated yield: 63% (215 mg, 1.26 mmol)

¹H NMR (400 MHz, CDCl₃) δ 2.33 (s, 2H), 1.77 – 1.59 (m, 2H), 1.58 – 1.47 (m, 2H), 1.40 – 1.07 (m, 5H), 1.05 (s, 3H), 0.90 (d, *J* = 6.5 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 179.48, 41.22, 37.89, 33.06, 32.41, 30.80, 29.43, 22.44; **HRMS (ESI):** Calculated mass for C₁₀H₁₉O₂ [M+H]⁺: 171.1385; observed mass: 171.1379.

2-(1-Ethylcycloheptyl)acetic acid (13)



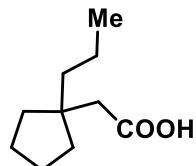
Eluent: ethyl acetate/ petroleum ether (12:88 v/v).

Appearance: colorless gummy.

Isolated yield: 61% (225 mg, 1.22 mmol)

¹H NMR (400 MHz, CDCl₃) δ 2.23 (s, 2H), 1.49 (dqd, *J* = 22.3, 7.7, 4.1 Hz, 14H), 0.86 (t, *J* = 7.5 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 179.66, 43.20, 39.44, 38.49, 32.20, 30.90, 23.00, 8.35; **HRMS (ESI):** Calculated mass for C₁₁H₂₀NaO₂ [M+Na]⁺: 207.1361; observed mass: 207.1365.

2-(1-Propylcyclopentyl)acetic acid (14)



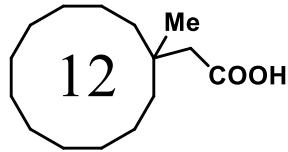
Eluent: ethyl acetate/ petroleum ether (10:90 v/v).

Appearance: colorless gummy.

Isolated yield: 64% (219 mg, 1.28 mmol)

¹H NMR (400 MHz, CDCl₃) δ 2.33 (s, 2H), 1.70 – 1.53 (m, 5H), 1.48 (tdd, *J* = 7.0, 4.8, 2.7 Hz, 2H), 1.44 – 1.37 (m, 2H), 1.36 – 1.23 (m, 3H), 0.90 (t, *J* = 7.0 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 179.05, 44.90, 42.58, 41.70, 37.88, 24.56, 18.33, 15.09; **HRMS (ESI):** Calculated mass for C₁₀H₁₈NaO₂ [M+Na]⁺: 193.1204; observed mass: 193.1210.

2-(1-Methylcyclododecyl)acetic acid (15)



Eluent: ethyl acetate/ petroleum ether (12:88 v/v).

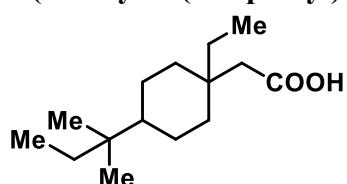
Appearance: colorless semisolid.

Isolated yield: 52% (250 mg, 1.04 mmol)

¹H NMR (400 MHz, CDCl₃) δ 2.19 (s, 2H), 1.34 (d, *J* = 13.3 Hz, 2H), 1.00 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 178.88, 45.34, 36.11, 34.51, 26.91, 26.40, 25.46, 22.90, 22.37, 19.35;

HRMS (ESI): Calculated mass for C₁₅H₂₉O₂ [M+H]⁺: 241.2168; observed mass: 241.2170.

2-(1-Ethyl-4-(*tert*-pentyl)cyclohexyl)acetic acid (16)



Eluent: ethyl acetate/ petroleum ether (10:90 v/v).

Appearance: white solid.

Isolated yield: 50% (240 mg, 1.0 mmol)

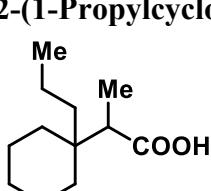
¹H NMR (400 MHz, CDCl₃) δ 2.35 (s, 2H), 1.75 – 1.64 (m, 2H), 1.58 – 1.50 (m, 2H), 1.38 (q, *J* = 7.5 Hz, 2H), 1.26 (q, *J* = 7.5 Hz, 2H), 1.21 – 1.02 (m, 5H), 0.87 (t, *J* = 7.5 Hz, 3H), 0.79

(d, *J* = 5.3 Hz, 9H); **¹³C NMR** (101 MHz, CDCl₃) δ 178.35, 45.61, 37.15, 36.21, 36.01, 34.91,

34.47, 32.85, 24.51, 22.29, 8.31, 7.80; **HRMS (ESI):** Calculated mass for C₁₅H₂₈NaO₂

[M+Na]⁺: 263.1987; observed mass: 263.1990.

2-(1-Propylcyclohexyl)propanoic acid (17)



Eluent: ethyl acetate/ petroleum ether (10:90 v/v).

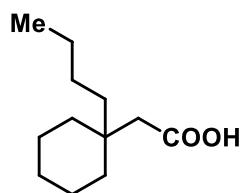
Appearance: colorless gummy.

Isolated yield: 51% (201 mg, 1.02 mmol)

¹H NMR (400 MHz, CDCl₃) δ 2.62 (q, *J* = 7.1 Hz, 1H), 1.63 – 1.23 (m, 14H), 1.08 (d, *J* = 7.1 Hz, 3H), 0.90 (t, *J* = 7.1 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 182.50, 45.15, 37.78, 35.48,

32.12, 31.95, 29.92, 26.25, 21.73, 21.62, 16.29, 15.23, 11.60; **HRMS (ESI):** Calculated mass for C₁₂H₂₃O₂ [M+H]⁺: 199.1698; observed mass: 199.1700.

2-(1-Butylcyclohexyl)acetic acid (18)



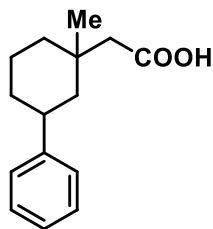
Eluent: ethyl acetate/ petroleum ether (10:90 v/v).

Appearance: colorless gummy.

Isolated yield: 82% (325 mg, 1.64 mmol)

¹H NMR (400 MHz, CDCl₃) δ 2.30 (s, 2H), 1.51 – 1.33 (m, 10H), 1.31 – 1.16 (m, 6H), 0.90 (t, *J* = 6.9 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 179.49, 42.00, 37.53, 36.08, 36.03, 26.35, 25.39, 23.67, 21.86, 14.32; **HRMS (ESI):** Calculated mass for C₁₂H₂₃O₂ [M+H]⁺: 199.1698; observed mass: 199.1690.

2-(1-Methyl-3-phenylcyclohexyl)acetic acid (19)



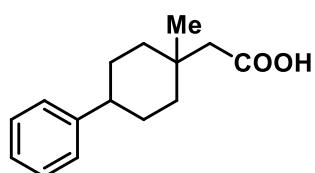
Eluent: ethyl acetate/ petroleum ether (15:85 v/v).

Appearance: white solid.

Isolated yield: 78% (361 mg, 1.56 mmol)

¹H NMR (500 MHz, CDCl₃) δ 7.29 (t, *J* = 7.5 Hz, 2H), 7.20 (dd, *J* = 17.0, 7.7 Hz, 3H), 2.76 (ddd, *J* = 12.6, 9.1, 3.5 Hz, 1H), 2.54 (d, *J* = 13.1 Hz, 1H), 2.44 (d, *J* = 13.0 Hz, 2H), 1.96 – 1.81 (m, 1H), 1.79 – 1.71 (m, 1H), 1.62 (dd, *J* = 14.0, 3.5 Hz, 1H), 1.49 – 1.18 (m, 4H), 1.12 (s, 3H); **¹³C NMR** (126 MHz, CDCl₃) δ 179.02, 147.26, 128.59, 128.57, 127.08, 127.06, 126.19, 46.10, 46.08, 41.23, 39.61, 39.58, 37.83, 37.81, 34.45, 34.43, 33.58, 33.55, 30.17, 30.14, 22.49, 22.47; **HRMS (ESI):** Calculated mass for C₁₅H₂₁O₂ [M+H]⁺: 233.1542; observed mass: 233.1545.

2-(1-Methyl-4-phenylcyclohexyl)acetic acid (20)



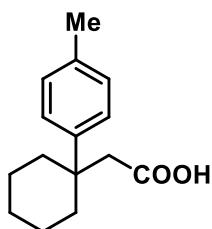
Eluent: ethyl acetate/ petroleum ether (15:85 v/v).

Appearance: white solid.

Isolated yield: 76% (354 mg, 1.52 mmol)

¹H NMR (400 MHz, CDCl₃) δ 7.30 (t, *J* = 7.5 Hz, 2H), 7.23 (d, *J* = 7.6 Hz, 2H), 7.21 – 7.16 (m, 1H), 2.65 – 2.34 (m, 3H), 1.85 – 1.71 (m, 4H), 1.65 (qd, *J* = 13.2, 3.1 Hz, 2H), 1.38 (td, *J* = 13.3, 3.8 Hz, 2H), 1.13 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 178.38, 147.31, 128.56, 127.03, 126.19, 44.24, 40.69, 38.39, 32.97, 29.84, 29.77; **HRMS (ESI):** Calculated mass for C₁₅H₂₁O₂ [M+H]⁺: 233.1542; observed mass: 233.1540.

2-(1-(*p*-Tolyl)cyclohexyl)acetic acid (21)



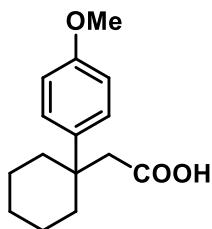
Eluent: ethyl acetate/ petroleum ether (15:85 v/v).

Appearance: colorless liquid.

Isolated yield: 61% (283 mg, 1.22 mmol)

¹H NMR (400 MHz, CDCl₃) δ 7.24 (d, *J* = 8.1 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 2.51 (s, 2H), 2.33 (s, 3H), 2.28 – 2.10 (m, 2H), 1.87 – 1.68 (m, 2H), 1.55 (dt, *J* = 8.7, 4.8 Hz, 2H), 1.52 – 1.35 (m, 4H); **¹³C NMR** (101 MHz, CDCl₃) δ 177.45, 142.09, 135.54, 129.24, 126.68, 48.35, 40.55, 36.14, 26.36, 22.48, 21.13; **HRMS (ESI):** Calculated mass for C₁₅H₂₁O₂ [M+H]⁺: 233.1542; observed mass: 233.1539.

2-(1-(4-Methoxyphenyl)cyclohexyl)acetic acid (22)



Eluent: ethyl acetate/ petroleum ether (20:80 v/v).

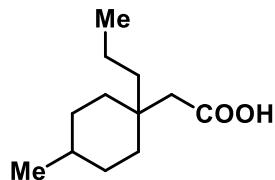
Appearance: white solid.

Isolated yield: 60% (300 mg, 1.2 mmol)

¹H NMR (500 MHz, CDCl₃) δ 7.26 (dd, *J* = 6.0, 3.9 Hz, 2H), 7.05 – 6.74 (m, 2H), 3.79 (d, *J* = 1.9 Hz, 3H), 2.50 (s, 2H), 2.17 (dd, *J* = 14.0, 6.4 Hz, 2H), 1.76 (t, *J* = 10.8 Hz, 2H), 1.54 (d, *J* = 6.8 Hz, 2H), 1.48 – 1.29 (m, 4H); **¹³C NMR** (126 MHz, CDCl₃) δ 157.77, 127.88, 113.80,

55.33, 40.27, 36.34, 26.39, 22.45; **HRMS (ESI)**: Calculated mass for C₁₅H₂₁O₃ [M+H]⁺: 249.1491; observed mass: 249.1495.

2-(4-Methyl-1-propylcyclohexyl)acetic acid (23)



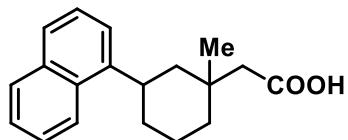
Eluent: ethyl acetate/ petroleum ether (10:90 v/v).

Appearance: colorless gummy.

Isolated yield: 75% (298 mg, 1.5 mmol)

¹H NMR (400 MHz, CDCl₃) δ 2.37 (s, 2H), 1.73 – 1.58 (m, 2H), 1.57 – 1.47 (m, 2H), 1.37 – 1.25 (m, 5H), 1.25 – 1.05 (m, 4H), 0.89 (dd, *J* = 5.7, 2.9 Hz, 6H); **¹³C NMR** (101 MHz, CDCl₃) δ 179.43, 44.46, 38.12, 35.91, 35.87, 32.77, 30.64, 22.58, 16.48, 15.11; **HRMS (ESI)**: Calculated mass for C₁₂H₂₃O₂ [M+H]⁺: 199.1698; observed mass: 199.1695.

2-(1-Methyl-3-(naphthalen-1-yl)cyclohexyl)acetic acid (24)



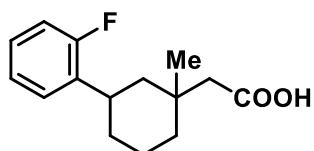
Eluent: ethyl acetate/ petroleum ether (15:85 v/v).

Appearance: white solid.

Isolated yield: 79% (449 mg, 1.58 mmol)

¹H NMR (400 MHz, CDCl₃) δ 8.18 (d, *J* = 8.4 Hz, 1H), 7.84 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.70 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.57 – 7.33 (m, 4H), 3.81 – 3.44 (m, 1H), 2.88 – 2.49 (m, 2H), 2.03 (ddt, *J* = 11.0, 5.3, 2.5 Hz, 2H), 1.80 (dddd, *J* = 23.3, 12.9, 6.9, 2.8 Hz, 3H), 1.59 (td, *J* = 12.3, 4.1 Hz, 1H), 1.43 (dd, *J* = 13.8, 12.5 Hz, 1H), 1.39 – 1.21 (m, 1H), 1.14 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 178.71, 143.00, 134.13, 131.58, 129.10, 126.69, 125.94, 125.78, 125.54, 123.37, 122.51, 45.82, 41.32, 38.26, 34.80, 34.11, 33.34, 30.18, 22.86; **HRMS (ESI)**: Calculated mass for C₁₉H₂₃O₂ [M+H]⁺: 283.1698; observed mass: 283.1690.

2-(3-(2-Fluorophenyl)-1-methylcyclohexyl)acetic acid (25)



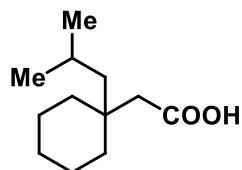
Eluent: ethyl acetate/ petroleum ether (15:85 v/v).

Appearance: white solid.

Isolated yield: 73% (365 mg, 1.46 mmol)

¹H NMR (400 MHz, CDCl₃) δ 7.22 (td, *J* = 7.6, 1.9 Hz, 1H), 7.15 (tdd, *J* = 7.3, 5.1, 1.9 Hz, 1H), 7.07 (td, *J* = 7.5, 1.4 Hz, 1H), 6.99 (ddd, *J* = 9.6, 8.1, 1.4 Hz, 1H), 3.22 – 2.98 (m, 1H), 2.61 – 2.40 (m, 2H), 1.94 – 1.56 (m, 5H), 1.47 – 1.32 (m, 2H), 1.29 – 1.15 (m, 1H), 1.12 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 178.88, 162.12, 159.68, 133.78, 133.63, 127.82, 127.77, 127.49, 127.41, 124.25, 124.22, 115.63, 115.40, 44.56, 41.03, 37.48, 34.35, 32.54, 32.52, 32.42, 30.11, 22.44; **¹⁹F NMR** (376 MHz, CDCl₃) δ -119.01, -119.03, -119.04, -119.06, -119.07; **HRMS (ESI):** Calculated mass for C₁₅H₂₀FO₂ [M+H]⁺: 251.1447; observed mass: 251.1450.

2-(1-Isobutylcyclohexyl)acetic acid (26)



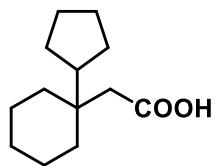
Eluent: ethyl acetate/ petroleum ether (10:90 v/v).

Appearance: colorless gummy.

Isolated yield: 79% (313 mg, 1.58 mmol)

¹H NMR (400 MHz, CDCl₃) δ 2.36 (s, 2H), 1.80 – 1.64 (m, 1H), 1.57 – 1.37 (m, 9H), 1.36 (d, *J* = 5.2 Hz, 3H), 0.93 (d, *J* = 6.7 Hz, 6H); **¹³C NMR** (101 MHz, CDCl₃) δ 179.50, 46.94, 42.13, 36.95, 36.32, 29.92, 26.30, 25.75, 25.69, 23.78, 22.00; **HRMS (ESI):** Calculated mass for C₁₂H₂₂NaO₂ [M+Na]⁺: 221.1517; observed mass: 221.1520.

2-(1-Cyclopentylcyclohexyl)acetic acid (27)



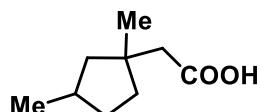
Eluent: ethyl acetate/ petroleum ether (10:90 v/v).

Appearance: colorless gummy.

Isolated yield: 76% (320 mg, 1.52 mmol)

¹H NMR (400 MHz, CDCl₃) δ 2.38 (s, 2H), 2.23 – 2.00 (m, 1H), 1.75 – 1.43 (m, 12H), 1.41 – 1.19 (m, 6H); **¹³C NMR** (101 MHz, CDCl₃) δ 180.32, 46.73, 39.50, 39.46, 38.36, 32.70, 26.19, 25.93, 21.82; **HRMS (ESI)**: Calculated mass for C₁₃H₂₃O₂ [M+H]⁺: 211.1698; observed mass: 211.1695.

2-(1,3-Dimethylcyclopentyl)acetic acid (28)



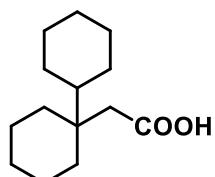
Eluent: ethyl acetate/ petroleum ether (10:90 v/v).

Appearance: colorless liquid.

Isolated yield: 71% (111 mg, 0.71 mmol)

¹H NMR (400 MHz, CDCl₃) δ 2.33 (dd, *J* = 17.0, 3.6 Hz, 2H), 2.06 (dq, *J* = 16.9, 8.2 Hz, 1H), 1.96 – 1.40 (m, 4H), 1.34 – 1.16 (m, 2H), 1.11 (dd, *J* = 24.4, 3.6 Hz, 3H), 0.98 (dt, *J* = 6.4, 2.9 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 179.19, 48.93, 48.43, 47.42, 46.22, 41.66, 41.53, 40.02, 39.43, 34.05, 33.94, 33.65, 33.32, 28.17, 27.04, 21.31, 21.15; **HRMS (ESI)**: Calculated mass for C₉H₁₇O₂ [M+H]⁺: 157.1229; observed mass: 157.1232.

2-([1,1'-Bi(cyclohexan)]-1-yl)acetic acid (29)



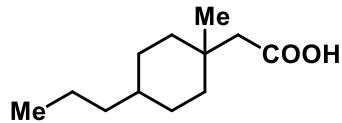
Eluent: ethyl acetate/ petroleum ether (10:90 v/v).

Appearance: white solid.

Isolated yield: 66% (148 mg, 0.66 mmol)

¹H NMR (400 MHz, CDCl₃) δ 2.34 (s, 2H), 1.87 – 1.72 (m, 4H), 1.65 (dt, *J* = 13.8, 3.1 Hz, 1H), 1.60 – 1.40 (m, 9H), 1.38 – 1.05 (m, 4H), 1.05 – 0.91 (m, 2H), 0.92 – 0.83 (m, 1H); **¹³C NMR** (101 MHz, CDCl₃) δ 180.23, 43.26, 38.98, 38.84, 32.59, 31.80, 27.53, 26.97, 26.73, 26.30, 22.86, 21.73, 14.31; **HRMS (ESI)**: Calculated mass for C₁₄H₂₅O₂ [M+H]⁺: 225.1855; observed mass: 225.1860.

2-(1-Methyl-4-propylcyclohexyl)acetic acid (30)



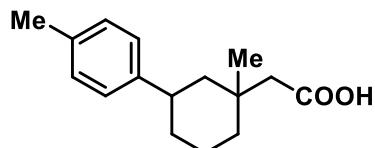
Eluent: ethyl acetate/ petroleum ether (10:90 v/v).

Appearance: colorless oil.

Isolated yield: 82% (162 mg, 0.82 mmol)

¹H NMR (400 MHz, CDCl₃) δ 2.32 (s, 2H), 1.70 – 1.50 (m, 4H), 1.35 – 1.24 (m, 3H), 1.23 – 1.14 (m, 5H), 1.13 – 1.07 (m, 1H), 1.04 (s, 3H), 0.87 (t, *J* = 7.2 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 179.70, 41.22, 39.42, 37.89, 37.05, 33.45, 29.47, 28.77, 20.24, 14.57; **HRMS (ESI):** Calculated mass for C₁₂H₂₃O₂ [M+H]⁺: 199.1698; observed mass: 199.1690.

2-(1-Methyl-3-(*p*-tolyl)cyclohexyl)acetic acid (31)



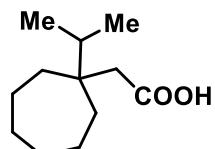
Eluent: ethyl acetate/ petroleum ether (15:85 v/v).

Appearance: white solid.

Isolated yield: 77% (190 mg, 0.77 mmol)

¹H NMR (400 MHz, CDCl₃) δ 7.11 (s, 4H), 2.73 (tt, *J* = 12.6, 3.4 Hz, 1H), 2.53 (d, *J* = 13.2 Hz, 1H), 2.44 (d, *J* = 13.2 Hz, 1H), 2.33 (s, 3H), 1.96 – 1.79 (m, 2H), 1.78 – 1.71 (m, 1H), 1.67 – 1.54 (m, 1H), 1.46 – 1.17 (m, 4H), 1.12 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 179.12, 144.30, 135.63, 129.26, 126.92, 46.24, 41.23, 39.16, 37.79, 34.44, 33.70, 30.15, 22.50, 21.17; **HRMS (ESI):** Calculated mass for C₁₆H₂₃O₂ [M+H]⁺: 247.1698; observed mass: 247.1690.

2-(1-Isopropylcycloheptyl)acetic acid (32)



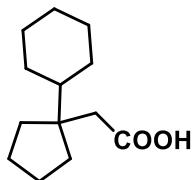
Eluent: ethyl acetate/ petroleum ether (10:90 v/v).

Appearance: colorless gummy.

Isolated yield: 69% (137 mg, 0.69 mmol)

¹H NMR (500 MHz, CDCl₃) δ 2.24 (s, 2H), 1.84 (p, *J* = 6.9 Hz, 1H), 1.61 (dd, *J* = 6.2, 3.7 Hz, 4H), 1.53 – 1.46 (m, 8H), 0.88 (d, *J* = 6.9 Hz, 6H); **¹³C NMR** (126 MHz, CDCl₃) δ 180.11, 42.06, 41.70, 36.00, 35.32, 30.87, 23.85, 17.70; **HRMS (ESI):** Calculated mass for C₁₂H₂₂NaO₂ [M+H]⁺: 221.1517; observed mass: 221.1520.

2-(1-Cyclohexylcyclopentyl)acetic acid (33)



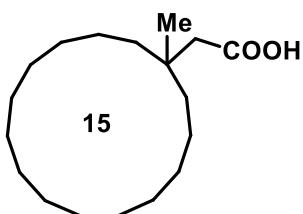
Eluent: ethyl acetate/ petroleum ether (10:90 v/v).

Appearance: colorless gummy.

Isolated yield: 71% (149 mg, 0.71 mmol)

¹H NMR (400 MHz, CDCl₃) δ 2.31 (s, 2H), 1.75 (dq, *J* = 9.7, 2.8, 2.3 Hz, 4H), 1.69 – 1.51 (m, 9H), 1.40 – 1.28 (m, 1H), 1.27 – 1.07 (m, 3H), 1.00 (qd, *J* = 12.6, 11.8, 3.5 Hz, 2H); **¹³C NMR** (101 MHz, CDCl₃) δ 180.34, 48.31, 46.60, 41.44, 41.38, 41.32, 35.44, 28.52, 27.29, 26.91, 25.48; **HRMS (ESI):** Calculated mass for C₁₃H₂₃O₂ [M+H]⁺: 211.1698; observed mass: 211.1690.

2-(1-Methylcyclopentadecyl)acetic acid (34)



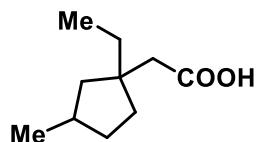
Eluent: ethyl acetate/ petroleum ether (15:85 v/v).

Appearance: white solid.

Isolated yield: 43% (121 mg, 0.43 mmol)

¹H NMR (400 MHz, CDCl₃) δ 2.22 (s, 2H), 1.60 – 1.21 (m, 28H), 1.02 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 178.59, 45.50, 38.28, 36.01, 29.92, 28.13, 27.23, 27.13, 26.93, 26.37, 25.88, 21.88; **HRMS (ESI):** Calculated mass for C₁₈H₃₅O₂ [M+H]⁺: 283.2637; observed mass: 283.2640.

2-(1-Ethyl-3-methylcyclopentyl)acetic acid (35)



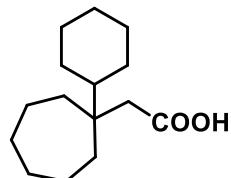
Eluent: ethyl acetate/ petroleum ether (10:90 v/v).

Appearance: colorless liquid.

Isolated yield: 68% (115 mg, 0.68 mmol)

¹H NMR (500 MHz, CDCl₃) δ 2.47 – 2.13 (m, 2H), 2.15 – 1.93 (m, 1H), 1.79 (dtd, *J* = 25.6, 13.1, 7.5 Hz, 2H), 1.69 – 1.44 (m, 4H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.87 (dtd, *J* = 14.7, 7.1, 2.7 Hz, 5H); **¹³C NMR** (126 MHz, CDCl₃) δ 178.75, 46.59, 46.53, 45.48, 45.02, 43.66, 42.54, 37.52, 37.46, 34.89, 34.05, 33.92, 33.81, 33.12, 32.15, 31.91, 31.81, 29.93, 29.88, 29.59, 27.14, 22.92, 22.88, 22.84, 20.96, 20.95, 14.34, 11.65, 9.49, 9.23; **HRMS (ESI)**: Calculated mass for C₁₀H₁₉O₂ [M+H]⁺: 171.1385; observed mass: 171.1390.

2-(1-Cyclohexylcycloheptyl)acetic acid (36)



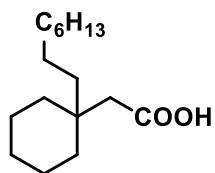
Eluent: ethyl acetate/ petroleum ether (15:85 v/v).

Appearance: white solid.

Isolated yield: 71% (170 mg, 0.71 mmol)

¹H NMR (400 MHz, CDCl₃) δ 2.26 (s, 2H), 1.86 – 1.73 (m, 4H), 1.70 – 1.35 (m, 14H), 1.32 – 1.06 (m, 3H), 0.98 (qd, *J* = 12.4, 11.8, 3.3 Hz, 2H); **¹³C NMR** (101 MHz, CDCl₃) δ 179.85, 46.28, 42.39, 42.15, 36.27, 31.01, 27.63, 27.50, 26.99, 23.93; **HRMS (ESI)**: Calculated mass for C₁₅H₂₇O₂ [M+H]⁺: 239.2011; observed mass: 239.2015.

2-(1-Octylcyclohexyl)acetic acid (37)



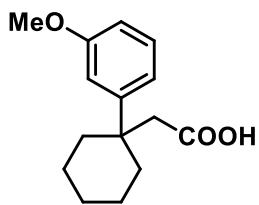
Eluent: ethyl acetate/ petroleum ether (10:90 v/v).

Appearance: colorless gummy.

Isolated yield: 72% (183 mg, 0.72 mmol)

¹H NMR (400 MHz, CDCl₃) δ 9.66 (s, 1H), 2.29 (s, 2H), 1.51 – 1.33 (m, 12H), 1.26 (s, 12H), 0.88 (t, *J* = 6.7 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 179.48, 41.98, 37.84, 36.13, 36.02, 32.14, 30.66, 29.82, 29.56, 26.35, 23.14, 22.91, 21.87, 14.34; **HRMS (ESI)**: Calculated mass for C₁₆H₃₁O₂ [M+H]⁺: 255.2324; observed mass: 255.2330.

2-(1-(3-Methoxyphenyl)cyclohexyl)acetic acid (38)



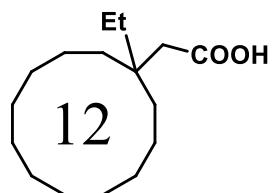
Eluent: ethyl acetate/ petroleum ether (20:80 v/v).

Appearance: white solid.

Isolated yield: 71% (177 mg, 0.71 mmol)

¹H NMR (400 MHz, CDCl₃) δ 7.29 (d, *J* = 8.1 Hz, 1H), 6.99 (ddd, *J* = 7.8, 1.9, 0.9 Hz, 1H), 6.95 (t, *J* = 2.2 Hz, 1H), 6.78 (ddd, *J* = 8.2, 2.5, 0.9 Hz, 1H), 3.83 (s, 3H), 2.56 (s, 2H), 2.29 – 2.15 (m, 2H), 1.81 (ddd, *J* = 12.9, 8.8, 3.5 Hz, 2H), 1.59 (qd, *J* = 8.8, 4.4 Hz, 2H), 1.47 (ddd, *J* = 13.5, 9.1, 6.3 Hz, 4H); **¹³C NMR** (101 MHz, CDCl₃) δ 177.01, 159.80, 147.10, 129.40, 119.29, 113.56, 110.77, 55.34, 48.04, 40.94, 36.14, 26.30, 22.51; **HRMS (ESI):** Calculated mass for C₁₅H₂₀NaO₃ [M+Na]⁺: 271.1310; observed mass: 271.1315.

2-(1-Ethylcyclododecyl)acetic acid (39)



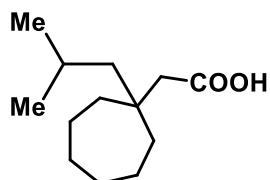
Eluent: ethyl acetate/ petroleum ether (10:90 v/v).

Appearance: colorless gummy.

Isolated yield: 52% (133 mg, 0.52 mmol)

¹H NMR (400 MHz, CDCl₃) δ 2.19 (s, 2H), 1.41 – 1.16 (m, 24H), 0.86 (t, *J* = 7.4 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 178.42, 40.34, 39.02, 32.63, 29.16, 26.95, 26.39, 22.88, 22.28, 18.81, 8.01; **HRMS (ESI):** Calculated mass for C₁₆H₃₁O₂ [M+H]⁺: 255.2324; observed mass: 255.2322.

2-(1-Isobutylcycloheptyl)acetic acid (40)



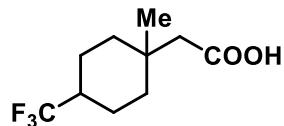
Eluent: ethyl acetate/ petroleum ether (15:85 v/v).

Appearance: colorless gummy.

Isolated yield: 62% (132 mg, 0.62 mmol)

¹H NMR (400 MHz, CDCl₃) δ 2.29 (s, 2H), 1.78 – 1.65 (m, 1H), 1.61 (ddd, *J* = 14.3, 7.5, 2.9 Hz, 2H), 1.56 – 1.39 (m, 10H), 1.36 (d, *J* = 5.2 Hz, 2H), 0.93 (d, *J* = 6.7 Hz, 6H); **¹³C NMR** (101 MHz, CDCl₃) δ 179.55, 48.82, 44.24, 40.10, 39.13, 30.93, 25.76, 24.03, 22.98; **HRMS (ESI)**: Calculated mass for C₁₃H₂₅O₂ [M+H]⁺: 213.1855; observed mass: 213.1860.

2-(1-Methyl-4-(trifluoromethyl)cyclohexyl)acetic acid (41)



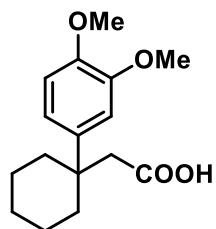
Eluent: ethyl acetate/ petroleum ether (15:85 v/v).

Appearance: white solid.

Isolated yield: 70% (157 mg, 0.59 mmol)

¹H NMR (400 MHz, CDCl₃) δ 2.36 (s, 2H), 1.98 (ddt, *J* = 16.5, 8.5, 4.0 Hz, 1H), 1.85 – 1.70 (m, 4H), 1.60 – 1.38 (m, 2H), 1.21 (td, *J* = 14.6, 13.9, 4.1 Hz, 2H), 1.08 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 178.92, 129.36, 126.59, 41.86, 41.59, 40.47, 36.36, 32.74, 29.24, 20.82, 20.80, 20.77, 20.75; **¹⁹F NMR** (376 MHz, CDCl₃) δ -73.60; **HRMS (ESI)**: Calculated mass for C₁₀H₁₆F₃O₂ [M+H]⁺: 225.1102; observed mass: 225.1105.

2-(1-(3,4-Dimethoxyphenyl)cyclohexyl)acetic acid (42)



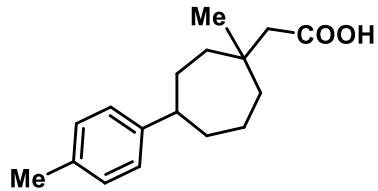
Eluent: ethyl acetate/ petroleum ether (30:70 v/v).

Appearance: white solid.

Isolated yield: 72% (200 mg, 0.72 mmol)

¹H NMR (500 MHz, CDCl₃) δ 6.88 (d, *J* = 8.3 Hz, 2H), 6.80 (d, *J* = 8.2 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 2.49 (s, 2H), 2.21 – 2.10 (m, 2H), 1.76 (ddd, *J* = 13.0, 9.1, 3.4 Hz, 2H), 1.60 – 1.50 (m, 2H), 1.42 (ddd, *J* = 14.5, 10.6, 7.5 Hz, 4H); **¹³C NMR** (126 MHz, CDCl₃) δ 177.75, 148.69, 147.21, 137.72, 119.04, 111.02, 110.46, 56.00, 55.83, 48.22, 40.50, 36.28, 26.24, 22.40; **HRMS (ESI)**: Calculated mass for C₁₆H₂₃O₄ [M+H]⁺: 279.1596; observed mass: 279.1600.

2-(1-Methyl-4-(*p*-tolyl)cycloheptyl)acetic acid (43)



Eluent: ethyl acetate/ petroleum ether (15:85 v/v).

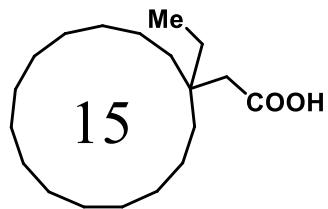
Appearance: white solid.

Isolated yield: 69% (180 mg, 0.69 mmol)

¹H NMR (400 MHz, CDCl₃) δ 7.14 – 7.02 (m, 4H), 2.66 (ddt, *J* = 11.3, 8.9, 2.4 Hz, 1H), 2.42 (d, *J* = 13.2 Hz, 1H), 2.32 (s, 3H), 2.30 – 2.21 (m, 1H), 1.97 – 1.83 (m, 2H), 1.83 – 1.72 (m, 2H), 1.65 (dtdd, *J* = 18.2, 14.2, 7.1, 4.7 Hz, 4H), 1.54 – 1.42 (m, 2H), 1.09 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 178.92, 147.19, 135.19, 129.29, 126.46, 49.91, 49.15, 47.98, 46.14, 40.78, 40.27, 40.23, 39.41, 39.30, 36.42, 30.52, 30.39, 29.92, 28.98, 27.14, 22.85, 22.75, 21.16, 14.34;

HRMS (ESI): Calculated mass for C₁₇H₂₅O₂ [M+H]⁺: 261.1855; observed mass: 261.1860.

2-(1-Ethylcyclopentadecyl)acetic acid (44)



Eluent: ethyl acetate/ petroleum ether (12:88 v/v).

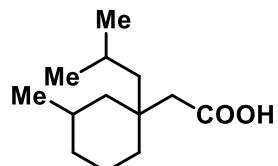
Appearance: white solid.

Isolated yield: 47% (140 mg, 0.47 mmol)

¹H NMR (400 MHz, CDCl₃) δ 2.21 (s, 2H), 1.49 – 1.15 (m, 30H), 0.85 (t, *J* = 7.4 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 178.93, 40.90, 38.91, 36.09, 29.93, 29.58, 28.16, 27.21, 27.16, 26.90, 26.31, 21.42, 8.02; **HRMS (ESI):** Calculated mass for C₁₉H₃₇O₂ [M+H]⁺: 297.2794;

observed mass: 297.2790.

2-(1-Isobutyl-3-methylcyclohexyl)acetic acid (45)



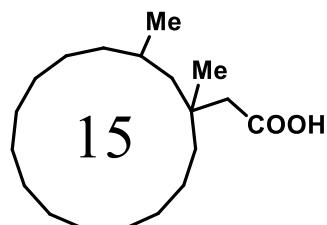
Eluent: ethyl acetate/ petroleum ether (12:88 v/v).

Appearance: colorless liquid.

Isolated yield: 61% (129 mg, 0.61 mmol)

¹H NMR (400 MHz, CDCl₃) δ 2.42 (s, 2H), 1.83 – 1.37 (m, 7H), 1.30 (d, *J* = 5.2 Hz, 2H), 1.12 (td, *J* = 13.3, 4.2 Hz, 1H), 0.93 (d, *J* = 6.6 Hz, 6H), 0.85 (d, *J* = 6.3 Hz, 3H), 0.83 – 0.69 (m, 2H); **¹³C NMR** (101 MHz, CDCl₃) δ 179.28, 51.11, 45.31, 39.17, 37.81, 35.82, 35.18, 27.88, 25.87, 25.84, 23.55, 23.25, 22.11; **HRMS (ESI)**: Calculated mass for C₁₃H₂₅O₂ [M+H]⁺: 213.1855; observed mass: 213.1860.

2-(1,3-Dimethylcyclopentadecyl)acetic acid (46)



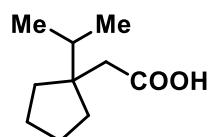
Eluent: ethyl acetate/ petroleum ether (12:88 v/v).

Appearance: colorless liquid.

Isolated yield: 71% (210 mg, 0.71 mmol)

¹H NMR (400 MHz, CDCl₃) δ 2.30 (s, 1H), 2.25 – 2.13 (m, 1H), 1.47 – 1.26 (m, 21H), 1.03 (d, *J* = 14.2 Hz, 3H), 0.88 (ddt, *J* = 13.6, 10.2, 5.1 Hz, 9H); **¹³C NMR** (101 MHz, CDCl₃) δ 178.87, 178.66, 46.94, 46.10, 44.98, 38.70, 38.29, 37.99, 37.75, 36.85, 36.65, 32.15, 29.93, 29.89, 29.59, 28.13, 27.83, 27.78, 27.71, 27.48, 27.45, 27.24, 27.14, 27.07, 27.04, 26.66, 26.34, 26.24, 26.15, 25.95, 25.89, 25.80, 25.73, 25.58, 25.39, 25.07, 22.92, 22.87, 22.48, 22.31, 22.22, 14.35; **HRMS (ESI)**: Calculated mass for C₁₉H₃₇O₂ [M+H]⁺: 297.2794; observed mass: 297.2791.

2-(1-Isopropylcyclopentyl)acetic acid (47)



Eluent: ethyl acetate/ petroleum ether (10:90 v/v).

Appearance: colorless liquid.

Isolated yield: 79% (135 mg, 0.79 mmol)

¹H NMR (400 MHz, CDCl₃) δ 2.32 (s, 2H), 1.79 (p, *J* = 6.8 Hz, 1H), 1.66 – 1.52 (m, 8H), 0.89 (d, *J* = 6.8 Hz, 6H); **¹³C NMR** (101 MHz, CDCl₃) δ 179.87, 48.45, 41.33, 35.29, 35.08, 25.69, 18.45; **HRMS (ESI)**: Calculated mass for C₁₀H₁₉O₂ [M+H]⁺: 171.1385; observed mass: 171.1382.

6. General Procedure for Dehydrogenative Lactonization:

In an oven-dried screw capped reaction tube was charged with magnetic stir-bar, corresponding acid (0.2 mmol), Pd(OAc)₂ (10 mol%), *N*-Ac-'Leu (20 mol%), Ag₂CO₃ (2 equiv.), and Na₃PO₄ (2 equiv.) in 1.5 mL of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) were added. The reaction tube was capped and placed in a preheated bath at 120 °C with stirring (800 rpm) for 24 h. Upon completion the mixture was diluted with EtOAc and filtered through a celite pad. The filtrate was evaporated under reduced pressure and the crude mixture was purified by column chromatography using silica (100-200 mesh size) and petroleum ether/ ethyl acetate as the eluent.

General Procedure for Intermolecular Dehydrogenative Lactonization with Olefins:

In an oven-dried screw capped reaction tube was charged with magnetic stir-bar, corresponding acid (0.2 mmol), Pd(OAc)₂ (10 mol%), *N*-Ac-'Leu (20 mol%), Ag₂CO₃ (2 equiv.), Na₂HPO₄ (2 equiv.) and olefin or allyl alcohol (2 equiv.) in 2 mL of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) were added. The reaction tube was capped and placed in a heating bath at 110 °C with stirring (800 rpm) for 24 h. Upon completion the mixture was diluted with EtOAc and filtered through a celite pad. The filtrate was evaporated under reduced pressure and the crude mixture was purified by column chromatography using silica (100-200 mesh size) and petroleum ether/ ethyl acetate as the eluent.

7. Analysis of the Crude Reaction Mixture

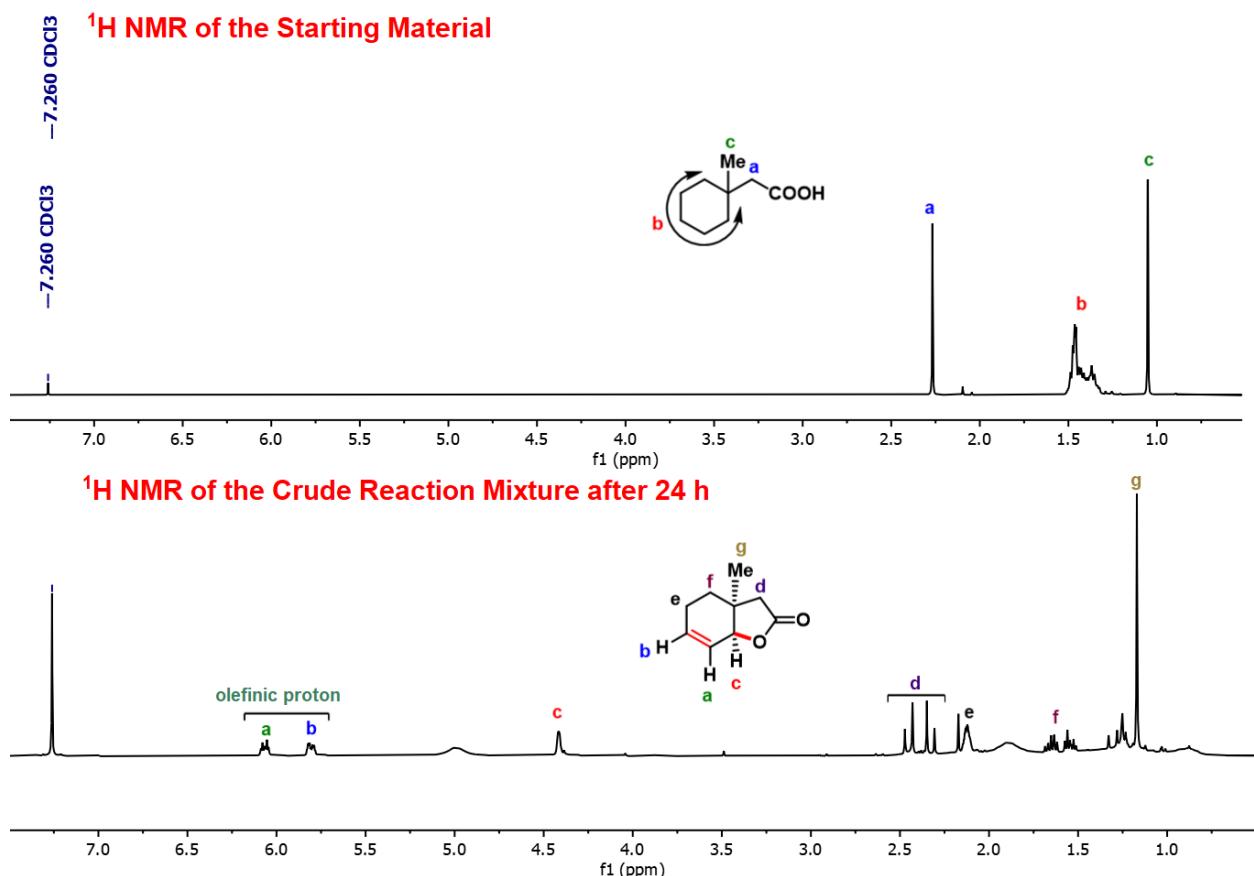
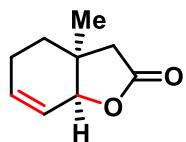


Figure S1: Comparison of ¹H NMR of starting material and reaction mixture after 24 h.

8. Spectral Data of the Unsaturated Bicyclic Lactones:

(3a*S*,7a*S*)-3a-Methyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one (2a)



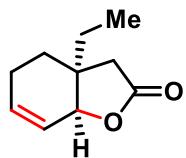
Eluent: ethyl acetate/ petroleum ether (6:94 v/v).

Appearance: colorless liquid.

Isolated yield: 70% (21.5 mg, 0.14 mmol)

¹H NMR (400 MHz, CDCl₃) δ 6.13 – 5.95 (m, 1H), 5.78 (dq, *J* = 10.2, 1.9 Hz, 1H), 4.44 – 4.28 (m, 1H), 2.51 – 2.37 (m, 1H), 2.34 – 2.24 (m, 1H), 2.17 – 2.03 (m, 2H), 1.69 – 1.58 (m, 1H), 1.52 (dt, *J* = 13.7, 5.6 Hz, 1H), 1.15 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 176.45, 133.22, 123.03, 81.24, 42.13, 37.26, 29.53, 23.50, 21.85; **HRMS (ESI):** Calculated mass for C₉H₁₃O₂ [M+H]⁺: 153.0916; observed mass: 153.0920.

(3a*S*,7a*S*)-3a-Ethyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one (2b)



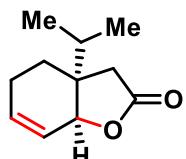
Eluent: ethyl acetate/ petroleum ether (6:94 v/v).

Appearance: colorless gummy.

Isolated yield: 74% (24.5 mg, 0.15 mmol)

¹H NMR (400 MHz, CDCl₃) δ 6.23 – 5.92 (m, 1H), 5.81 (ddt, *J* = 10.0, 4.1, 2.1 Hz, 1H), 4.42 (dd, *J* = 4.2, 1.6 Hz, 1H), 2.37 (s, 2H), 2.08 (dtt, *J* = 7.3, 3.5, 1.9 Hz, 2H), 1.61 – 1.50 (m, 3H), 1.41 (dq, *J* = 14.7, 7.5 Hz, 1H), 0.93 (t, *J* = 7.5 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 176.62, 133.45, 123.22, 80.54, 80.52, 40.89, 39.77, 39.74, 28.70, 26.15, 21.63, 8.93; **HRMS (ESI):** Calculated mass for C₁₀H₁₅O₂ [M+H]⁺: 167.1072; observed mass: 167.1077.

(3a*S*,7a*S*)-3a-Isopropyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one (2c)



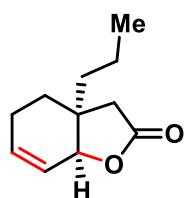
Eluent: ethyl acetate/ petroleum ether (6:96 v/v).

Appearance: colorless liquid.

Isolated yield: 75% (27 mg, 0.15 mmol)

¹H NMR (400 MHz, CDCl₃) δ 6.05 (dtd, *J* = 10.0, 3.8, 1.0 Hz, 1H), 5.79 (ddt, *J* = 10.1, 4.2, 2.2 Hz, 1H), 4.68 (dq, *J* = 4.1, 1.4 Hz, 1H), 2.41 (d, *J* = 17.4 Hz, 1H), 2.27 (d, *J* = 17.5 Hz, 1H), 2.18 – 2.03 (m, 2H), 1.90 – 1.71 (m, 1H), 1.71 – 1.55 (m, 2H), 0.94 (dd, *J* = 8.5, 6.8 Hz, 6H); **¹³C NMR** (101 MHz, CDCl₃) δ 176.86, 133.16, 124.07, 78.58, 43.48, 35.61, 31.70, 25.80, 21.62, 18.16, 18.13, 17.78, 17.76; **HRMS (ESI)**: Calculated mass for C₁₁H₁₇O₂ [M+H]⁺: 181.1229; observed mass: 181.1235.

(3a*S*,7a*S*)-3a-Propyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one (2d)



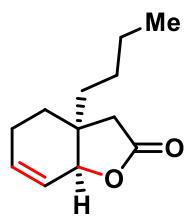
Eluent: ethyl acetate/ petroleum ether (6:94 v/v).

Appearance: colorless liquid.

Isolated yield: 82% (29.5 mg, 0.16 mmol)

¹H NMR (400 MHz, CDCl₃) δ 6.28 – 5.97 (m, 1H), 5.81 (ddt, *J* = 10.1, 4.2, 2.1 Hz, 1H), 4.40 (dd, *J* = 4.1, 1.4 Hz, 1H), 2.38 (s, 2H), 2.19 – 1.98 (m, 2H), 1.59 – 1.46 (m, 2H), 1.43 – 1.21 (m, 4H), 0.94 (t, *J* = 7.0 Hz, 3H); **¹³C NMR** (126 MHz, CDCl₃) δ 176.65, 133.56, 123.11, 80.67, 40.66, 40.44, 38.42, 26.66, 21.70, 17.99, 14.83; **HRMS (ESI)**: Calculated mass for C₁₁H₁₆NaO₂ [M+Na]⁺: 203.1048; observed mass: 203.1055.

(3a*S*,7a*S*)-3a-Butyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one (2e)



Eluent: ethyl acetate/ petroleum ether (6:94 v/v).

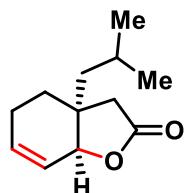
Appearance: colorless liquid.

Isolated yield: 68% (26.5 mg, 0.136 mmol) (dr = 5:1)

¹H NMR (400 MHz, CDCl₃) δ 6.14 – 6.00 (m, 1H), 5.84 – 5.74 (m, 1H), 4.40 (dd, *J* = 4.0, 1.4 Hz, 1H), 2.38 (s, 2H), 2.08 (ddq, *J* = 7.5, 3.7, 1.8 Hz, 2H), 1.71 – 1.51 (m, 4H), 1.38 – 1.29 (m, 4H), 0.92 (t, *J* = 7.0 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 176.63, 133.55, 123.17, 80.72,

40.61, 40.44, 35.84, 29.91, 26.86, 26.69, 23.43, 21.71, 14.18; **HRMS (ESI)**: Calculated mass for C₁₂H₁₉O₂ [M+H]⁺: 195.1385; observed mass: 195.1390.

(3a*R*,7a*S*)-3a-Isobutyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one (2f)



Eluent: ethyl acetate/ petroleum ether (7:93 v/v).

Appearance: colorless gummy.

Isolated yield: 79% (30.5 mg, 0.16 mmol)

¹H NMR (400 MHz, CDCl₃) δ 6.19 – 6.01 (m, 1H), 5.83 (ddt, *J* = 10.1, 4.3, 2.1 Hz, 1H), 4.29 (d, *J* = 4.4 Hz, 1H), 2.50 (d, *J* = 17.1 Hz, 1H), 2.42 (d, *J* = 17.1 Hz, 1H), 2.17 – 1.99 (m, 2H), 1.79 – 1.64 (m, 2H), 1.62 – 1.48 (m, 2H), 1.11 (ddd, *J* = 14.3, 8.8, 1.1 Hz, 1H), 0.93 (dd, *J* = 11.7, 6.6 Hz, 6H); **¹³C NMR** (101 MHz, CDCl₃) δ 176.66, 134.11, 122.31, 80.83, 80.80, 43.81, 42.89, 40.50, 26.30, 25.16, 25.02, 23.55, 21.91; **HRMS (ESI)**: Calculated mass for C₁₂H₁₉O₂ [M+H]⁺: 195.1385; observed mass: 195.1382.

(3a*S*,7a*S*)-3a-Octyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one (2g)



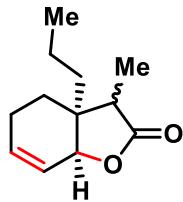
Eluent: ethyl acetate/ petroleum ether (8:92 v/v).

Appearance: colorless gummy.

Isolated yield: 78% (39 mg, 0.156 mmol) (d.r. = 4:1)

¹H NMR (500 MHz, CDCl₃) δ 6.06 (dt, *J* = 10.1, 3.8 Hz, 1H), 5.85 – 5.76 (m, 1H), 4.42 (dd, *J* = 33.3, 6.0 Hz, 1H), 2.64 – 2.21 (m, 2H), 2.07 (ddd, *J* = 8.1, 4.9, 2.8 Hz, 2H), 1.66 – 1.37 (m, 6H), 1.28 (tdq, *J* = 13.6, 9.7, 5.8, 4.1 Hz, 10H), 0.98 – 0.79 (m, 3H); **¹³C NMR** (126 MHz, CDCl₃) δ 176.60, 136.92, 133.53, 123.60, 123.12, 80.67, 43.96, 40.60, 40.41, 39.86, 36.06, 35.25, 32.45, 32.01, 31.47, 30.85, 30.31, 29.88, 29.63, 29.41, 28.72, 26.63, 25.93, 24.65, 23.27, 22.82, 22.62, 22.52, 21.68, 14.27, 14.22; **HRMS (ESI)**: Calculated mass for C₁₆H₂₇O₂ [M+H]⁺: 251.2011; observed mass: 251.2004.

(3a*S*,7a*S*)-3-Methyl-3a-propyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one (2h)



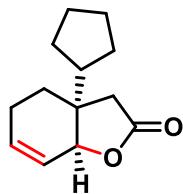
Eluent: ethyl acetate/ petroleum ether (6:94 v/v).

Appearance: colorless gummy.

Isolated yield: 65% (25.3 mg, 0.13 mmol) (d.r. = 1.5:1)

¹H NMR (400 MHz, CDCl₃) δ 6.11 (ddd, *J* = 10.2, 5.0, 2.4 Hz, 1H), 5.97 (ddt, *J* = 10.2, 3.7, 1.1 Hz, 1H), 5.87 (dddd, *J* = 10.0, 4.5, 2.6, 1.6 Hz, 1H), 5.74 (ddt, *J* = 10.1, 3.9, 2.2 Hz, 1H), 4.58 (dd, *J* = 3.3, 1.6 Hz, 1H), 4.25 (d, *J* = 4.8 Hz, 1H), 2.66 (q, *J* = 7.2 Hz, 1H), 2.53 (q, *J* = 7.4 Hz, 1H), 2.09 (dddt, *J* = 7.2, 5.6, 3.8, 2.0 Hz, 2H), 1.69 (dt, *J* = 14.2, 7.1 Hz, 1H), 1.53 (dt, *J* = 14.2, 5.2 Hz, 1H), 1.44 – 1.26 (m, 4H), 1.14 (dd, *J* = 10.9, 7.3 Hz, 3H), 0.93 (td, *J* = 6.8, 5.4 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 179.85, 134.64, 132.17, 124.16, 121.82, 78.45, 45.18, 42.81, 42.62, 40.58, 35.84, 35.66, 32.13, 29.91, 29.86, 29.57, 26.94, 22.90, 22.87, 21.70, 21.59, 17.80, 17.69, 15.05, 14.95, 14.33, 9.15, 9.07; **HRMS (ESI):** Calculated mass for C₁₂H₁₉O₂ [M+H]⁺: 195.1385; observed mass: 195.1384.

(3a*S*,7a*S*)-3a-Cyclopentyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one (2i)



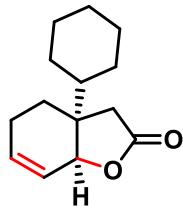
Eluent: ethyl acetate/ petroleum ether (6:94 v/v).

Appearance: colorless gummy.

Isolated yield: 80% (33 mg, 0.16 mmol) (d.r. = 5:1)

¹H NMR (500 MHz, CDCl₃) δ 6.05 (dt, *J* = 10.1, 3.8 Hz, 1H), 5.79 (ddt, *J* = 10.1, 4.2, 2.2 Hz, 1H), 4.59 (d, *J* = 4.0 Hz, 1H), 2.43 (d, *J* = 17.4 Hz, 1H), 2.29 (d, *J* = 17.4 Hz, 1H), 2.11 (ddt, *J* = 5.8, 3.8, 1.9 Hz, 2H), 1.98 (tt, *J* = 10.3, 7.7 Hz, 1H), 1.84 – 1.50 (m, 8H), 1.29 (ddd, *J* = 10.1, 7.9, 3.7 Hz, 1H), 1.16 (ddd, *J* = 14.2, 6.4, 2.8 Hz, 1H); **¹³C NMR** (101 MHz, CDCl₃) δ 176.85, 133.28, 123.79, 79.40, 79.37, 44.01, 42.84, 36.36, 36.33, 28.26, 27.47, 27.35, 25.63, 25.43, 21.55; **HRMS (ESI):** Calculated mass for C₁₃H₁₉O₂ [M+H]⁺: 207.1385; observed mass: 207.1392.

(3a*S*,7a*S*)-3a-Cyclohexyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one (2j)



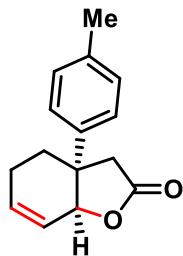
Eluent: ethyl acetate/ petroleum ether (8:92 v/v).

Appearance: colorless gummy.

Isolated yield: 82% (36 mg, 0.16 mmol) (d.r. = 6:1)

¹H NMR (400 MHz, CDCl₃) δ 6.04 (dt, *J* = 10.0, 3.8 Hz, 1H), 5.78 (ddt, *J* = 10.0, 4.1, 2.1 Hz, 1H), 4.70 (d, *J* = 4.0 Hz, 1H), 2.44 (d, *J* = 17.4 Hz, 1H), 2.27 (d, *J* = 17.4 Hz, 1H), 2.10 (td, *J* = 3.8, 1.9 Hz, 2H), 1.88 – 1.76 (m, 3H), 1.70 – 1.55 (m, 3H), 1.35 (ddd, *J* = 12.0, 9.0, 2.9 Hz, 1H), 1.28 – 1.15 (m, 3H), 1.15 – 0.88 (m, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 176.95, 133.23, 124.05, 78.28, 43.28, 42.42, 36.44, 28.05, 27.79, 26.93, 26.83, 26.54, 25.83, 21.71; **HRMS (ESI)**: Calculated mass for C₁₄H₂₀NaO₂ [M+Na]⁺: 243.1361; observed mass: 243.1355.

(3a*S*,7a*S*)-3a-(*p*-Tolyl)-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one (2k)



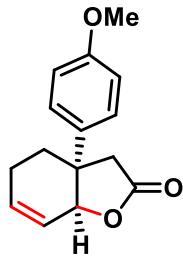
Eluent: ethyl acetate/ petroleum ether (10:90 v/v).

Appearance: white solid.

Isolated yield: 67% (30.5 mg, 0.13 mmol)

¹H NMR (400 MHz, CDCl₃) δ 7.14 (d, *J* = 8.0 Hz, 2H), 7.03 (d, *J* = 8.2 Hz, 2H), 6.25 (ddd, *J* = 10.7, 5.9, 2.1 Hz, 1H), 6.20 – 6.10 (m, 1H), 4.94 (d, *J* = 4.4 Hz, 1H), 2.99 – 2.78 (m, 2H), 2.33 (s, 3H), 2.14 – 2.00 (m, 1H), 1.93 – 1.80 (m, 1H), 1.79 – 1.65 (m, 2H); **¹³C NMR** (101 MHz, CDCl₃) δ 175.36, 139.69, 137.07, 136.11, 129.70, 129.57, 125.86, 123.00, 78.36, 44.86, 44.38, 31.83, 29.92, 22.12, 21.16; **HRMS (ESI)**: Calculated mass for C₁₅H₁₆NaO₂ [M+Na]⁺: 251.1048; observed mass: 251.1050.

(3a*S*,7a*S*)-3a-(4-Methoxyphenyl)-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one (2l)



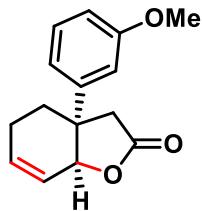
Eluent: ethyl acetate/ petroleum ether (12:88 v/v).

Appearance: white gummy.

Isolated yield: 61% (30 mg, 0.12 mmol) (d.r. = 5:1)

¹H NMR (400 MHz, CDCl₃) δ 7.06 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.30 – 6.20 (m, 1H), 6.19 – 6.10 (m, 1H), 4.92 (dd, *J* = 4.3, 1.3 Hz, 1H), 3.80 (s, 3H), 2.87 (d, *J* = 6.2 Hz, 2H), 2.11 – 1.98 (m, 2H), 1.87 – 1.79 (m, 1H), 1.72 (tt, *J* = 2.8, 1.5 Hz, 1H); **¹³C NMR** (101 MHz, CDCl₃) δ 175.34, 158.73, 136.11, 134.73, 128.20, 127.06, 122.97, 114.33, 114.24, 78.44, 55.49, 44.56, 44.46, 31.83, 22.12; **HRMS (ESI):** Calculated mass for C₁₅H₁₇O₃ [M+H]⁺: 245.1178; observed mass: 245.1180.

(3a*S*,7a*S*)-3a-(3-Methoxyphenyl)-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one (2m)



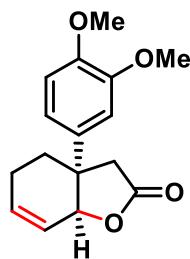
Eluent: ethyl acetate/ petroleum ether (15:85 v/v).

Appearance: white gummy.

Isolated yield: 57% (28 mg, 0.114 mmol)

¹H NMR (400 MHz, CDCl₃) δ 7.30 – 7.19 (m, 1H), 6.78 (ddd, *J* = 8.2, 2.5, 0.9 Hz, 1H), 6.70 (ddd, *J* = 7.7, 1.9, 0.9 Hz, 1H), 6.65 (t, *J* = 2.2 Hz, 1H), 6.30 – 6.18 (m, 1H), 6.11 (dq, *J* = 9.8, 2.3 Hz, 1H), 4.95 – 4.87 (m, 1H), 3.77 (s, 3H), 2.90 (d, *J* = 17.0 Hz, 1H), 2.82 (d, *J* = 17.0 Hz, 1H), 2.11 – 1.97 (m, 1H), 1.90 – 1.64 (m, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 175.10, 159.99, 144.32, 136.18, 129.98, 122.96, 118.41, 112.89, 111.76, 78.18, 55.47, 45.19, 44.30, 31.82, 22.17; **HRMS (ESI):** Calculated mass for C₁₅H₁₆NaO₃ [M+Na]⁺: 267.0997; observed mass: 267.0995.

(3a*S*,7a*S*)-3a-(3,4-Dimethoxyphenyl)-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one (2n)



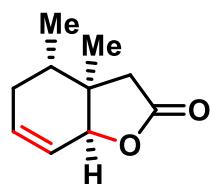
Eluent: ethyl acetate/ petroleum ether (20:80 v/v).

Appearance: white gummy.

Isolated yield: 52% (28.5 mg, 0.104 mmol)

¹H NMR (500 MHz, CDCl₃) δ 6.81 (d, *J* = 8.1 Hz, 1H), 6.71 – 6.63 (m, 2H), 6.26 (dd, *J* = 10.3, 5.5 Hz, 1H), 6.18 – 6.10 (m, 1H), 4.94 (d, *J* = 4.4 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 2.92 (d, *J* = 16.8 Hz, 1H), 2.85 (d, *J* = 17.0 Hz, 1H), 2.12 – 2.02 (m, 1H), 1.88 – 1.80 (m, 1H), 1.80 – 1.72 (m, 2H); **¹³C NMR** (126 MHz, CDCl₃) δ 175.22, 149.29, 148.37, 136.10, 135.25, 123.03, 118.24, 111.38, 109.64, 78.44, 56.23, 56.13, 44.85, 44.41, 31.85, 22.22; **HRMS (ESI):** Calculated mass for C₁₆H₁₉O₄ [M+H]⁺: 275.1283; observed mass: 275.1287.

(3a*R*,7a*S*)-3a,4-Dimethyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one (2o)



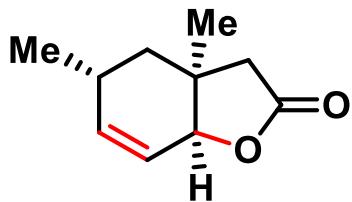
Eluent: ethyl acetate/ petroleum ether (6:94 v/v).

Appearance: colorless liquid.

Isolated yield: 85% (28 mg, 0.17 mmol)

¹H NMR (400 MHz, CDCl₃) δ 5.91 (ddt, *J* = 10.2, 5.3, 1.6 Hz, 1H), 5.66 (dtd, *J* = 10.2, 2.7, 1.3 Hz, 1H), 4.54 (td, *J* = 2.7, 1.3 Hz, 1H), 2.47 (dd, *J* = 17.0, 0.8 Hz, 1H), 2.25 – 2.06 (m, 1H), 1.98 (d, *J* = 16.9 Hz, 1H), 1.91 – 1.75 (m, 2H), 1.24 (d, *J* = 0.8 Hz, 3H), 0.96 (d, *J* = 6.5 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 176.84, 131.05, 125.26, 83.87, 41.74, 34.84, 34.46, 30.41, 25.23, 16.84; **HRMS (ESI):** Calculated mass for C₁₀H₁₅O₂ [M+H]⁺: 167.1072; observed mass: 167.1075.

(3a*S*,7a*S*)-3a,5-Dimethyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one (2p)



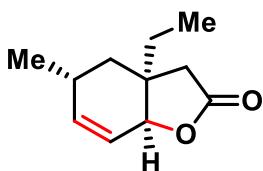
Eluent: ethyl acetate/ petroleum ether (6:94 v/v).

Appearance: colorless gummy.

Isolated yield: 78% (26 mg, 0.16 mmol)

¹H NMR (400 MHz, CDCl₃) δ 5.82 – 5.73 (m, 1H), 5.63 (dt, *J* = 10.1, 2.7 Hz, 1H), 4.54 (dt, *J* = 2.7, 1.3 Hz, 1H), 2.60 (d, *J* = 17.1 Hz, 1H), 2.36 – 2.24 (m, 1H), 2.02 (d, *J* = 17.0 Hz, 1H), 1.86 (ddd, *J* = 14.2, 5.1, 1.3 Hz, 1H), 1.37 – 1.24 (m, 1H), 1.22 (d, *J* = 0.7 Hz, 3H), 1.04 (d, *J* = 7.0 Hz, 3H); **¹³C NMR** (126 MHz, CDCl₃) δ 176.91, 137.35, 124.31, 82.90, 39.43, 38.28, 38.04, 27.92, 27.25, 21.29; **HRMS (ESI):** Calculated mass for C₁₀H₁₄NaO₂ [M+Na]⁺: 189.0891; observed mass: 189.0895.

(3a*S*,7a*S*)-3a-Ethyl-5-methyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one (2q)



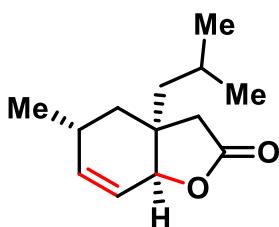
Eluent: ethyl acetate/ petroleum ether (6:94 v/v).

Appearance: colorless liquid.

Isolated yield: 75% (27 mg, 0.15 mmol)

¹H NMR (400 MHz, CDCl₃) δ 5.78 (dq, *J* = 10.1, 1.5 Hz, 1H), 5.69 – 5.56 (m, 1H), 4.61 (td, *J* = 2.6, 1.1 Hz, 1H), 2.55 (d, *J* = 17.3 Hz, 1H), 2.30 (dddd, *J* = 12.3, 6.9, 4.7, 2.3 Hz, 1H), 2.13 (d, *J* = 17.2 Hz, 1H), 1.83 (ddd, *J* = 14.2, 5.1, 1.3 Hz, 1H), 1.58 – 1.48 (m, 2H), 1.18 (dd, *J* = 14.1, 10.6 Hz, 1H), 1.05 (d, *J* = 7.1 Hz, 3H), 0.94 (t, *J* = 7.5 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 177.09, 137.50, 124.55, 81.30, 41.33, 36.47, 35.82, 33.12, 27.01, 21.42, 8.22; **HRMS (ESI):** Calculated mass for C₁₁H₁₇O₂ [M+H]⁺: 181.1229; observed mass: 181.1235.

(3a*S*,7a*S*)-3a-Isobutyl-5-methyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one (2r)



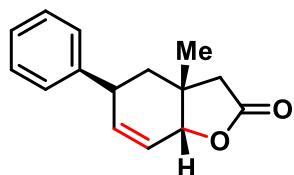
Eluent: ethyl acetate/ petroleum ether (6:94 v/v).

Appearance: colorless gummy.

Isolated yield: 78% (32.5 mg, 0.156 mmol)

¹H NMR (400 MHz, CDCl₃) δ 5.82 – 5.73 (m, 1H), 5.63 (dt, *J* = 10.1, 2.8 Hz, 1H), 4.59 (td, *J* = 2.7, 1.2 Hz, 1H), 2.55 (d, *J* = 17.2 Hz, 1H), 2.29 (ddt, *J* = 9.7, 7.2, 4.9, 2.4 Hz, 1H), 2.16 (d, *J* = 17.2 Hz, 1H), 1.87 (ddd, *J* = 14.0, 5.1, 1.3 Hz, 1H), 1.79 – 1.68 (m, 1H), 1.43 (d, *J* = 5.7 Hz, 2H), 1.26 (dd, *J* = 14.1, 10.3 Hz, 1H), 1.04 (d, *J* = 7.1 Hz, 3H), 0.96 (d, *J* = 6.6 Hz, 6H); **¹³C NMR** (101 MHz, CDCl₃) δ 177.01, 137.44, 124.31, 81.81, 48.83, 41.83, 36.95, 36.91, 27.07, 25.34, 25.15, 24.51, 21.41; **HRMS (ESI):** Calculated mass for C₁₃H₂₁O₂ [M+H]⁺: 209.1542; observed mass: 209.1550.

(3a*S*,7a*S*)-3a-Methyl-5-phenyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one (2s)



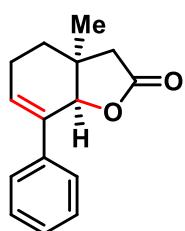
Eluent: ethyl acetate/ petroleum ether (8:92 v/v).

Appearance: colorless gummy.

Isolated yield: 64% (29.5 mg, 0.13 mmol)

¹H NMR (400 MHz, CDCl₃) δ 7.45 – 7.35 (m, 1H), 7.34 – 7.28 (m, 1H), 7.29 – 7.21 (m, 1H), 7.20 – 7.13 (m, 2H), 6.08 – 5.93 (m, 1H), 5.87 (dt, *J* = 10.2, 2.7 Hz, 1H), 4.68 (q, *J* = 1.4 Hz, 1H), 3.48 (ddd, *J* = 10.8, 5.2, 2.6 Hz, 1H), 2.77 (d, *J* = 17.1 Hz, 1H), 2.28 – 1.96 (m, 2H), 1.63 (d, *J* = 3.3 Hz, 1H), 1.24 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 176.55, 144.17, 134.58, 129.07, 129.00, 127.96, 127.64, 127.06, 126.07, 82.52, 40.86, 39.21, 38.61, 37.94, 27.68; **HRMS (ESI):** Calculated mass for C₁₅H₁₇O₂ [M+H]⁺: 229.1229; observed mass: 229.1235.

(3a*S*,7a*R*)-3a-Methyl-7-phenyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one (2t)



Eluent: ethyl acetate/ petroleum ether (10:90 v/v).

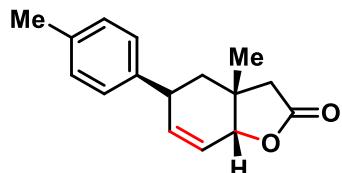
Appearance: colorless gummy.

Isolated yield: 10% (5 mg, 0.02 mmol)

¹H NMR (400 MHz, CDCl₃) δ 7.54 – 7.45 (m, 2H), 7.34 (t, *J* = 7.4 Hz, 2H), 7.30 – 7.26 (m, 1H), 6.45 (dd, *J* = 4.8, 3.4 Hz, 1H), 4.78 (d, *J* = 1.2 Hz, 1H), 2.60 – 2.46 (m, 2H), 2.39 – 2.28

(m, 2H), 1.72 (ddd, $J = 13.4, 9.4, 6.5$ Hz, 1H), 1.56 (dd, $J = 9.2, 4.7$ Hz, 1H), 1.21 (s, 3H); ^{13}C NMR (101 MHz, CDCl₃) δ 176.20, 139.54, 132.93, 130.39, 128.70, 128.47, 127.74, 126.06, 82.28, 43.92, 38.14, 28.99, 22.95, 21.71; HRMS (ESI): Calculated mass for C₁₅H₁₇O₂ [M+H]⁺: 229.1229; observed mass: 229.1231.

(3a*S*,7a*S*)-3a-Methyl-5-(*p*-tolyl)-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one (2u)



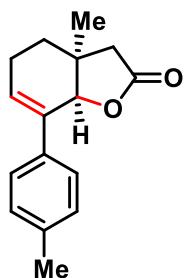
Eluent: ethyl acetate/ petroleum ether (6:94 v/v).

Appearance: colorless gummy.

Isolated yield: 66% (32 mg, 0.13 mmol)

^1H NMR (400 MHz, CDCl₃) δ 7.15 (d, $J = 7.9$ Hz, 2H), 7.06 (d, $J = 8.1$ Hz, 2H), 6.02 – 5.94 (m, 1H), 5.85 (dt, $J = 10.2, 2.8$ Hz, 1H), 4.67 (td, $J = 2.6, 1.3$ Hz, 1H), 3.44 (ddd, $J = 10.8, 5.2,$ 2.6 Hz, 1H), 2.77 (d, $J = 17.0$ Hz, 1H), 2.34 (s, 3H), 2.12 (d, $J = 17.0$ Hz, 1H), 2.07 (ddd, $J = 14.3, 5.3, 1.3$ Hz, 1H), 1.61 (dd, $J = 14.4, 11.0$ Hz, 1H), 1.23 (s, 3H); ^{13}C NMR (101 MHz, CDCl₃) δ 176.60, 141.15, 136.66, 134.84, 129.65, 127.49, 125.86, 82.55, 40.91, 38.76, 38.61, 37.90, 27.66, 21.19; HRMS (ESI): Calculated mass for C₁₆H₁₉O₂ [M+H]⁺: 243.1385.; observed mass: 243.1387.

(3a*S*,7a*R*)-3a-Methyl-7-(*p*-tolyl)-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one (2v)



Eluent: ethyl acetate/ petroleum ether (8:92 v/v).

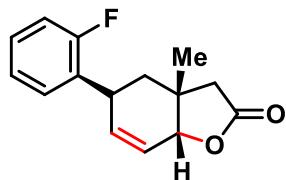
Appearance: colorless gummy.

Isolated yield: 10% (5 mg, 0.02 mmol)

^1H NMR (400 MHz, CDCl₃) δ 7.38 (d, $J = 8.3$ Hz, 2H), 7.15 (d, $J = 8.1$ Hz, 2H), 6.41 (dd, $J = 4.7, 3.4$ Hz, 1H), 4.77 (s, 1H), 2.49 (d, $J = 11.2$ Hz, 2H), 2.33 (d, $J = 7.9$ Hz, 5H), 1.70 (ddd, $J = 13.4, 9.3, 6.7$ Hz, 1H), 1.59 – 1.50 (m, 1H), 1.20 (s, 3H); ^{13}C NMR (101 MHz, CDCl₃) δ 176.26, 137.48, 136.68, 132.66, 129.49, 129.36, 125.89, 82.36, 43.93, 38.10, 29.00, 22.89,

21.69, 21.27; **HRMS (ESI)**: Calculated mass for C₁₆H₁₉O₂ [M+H]⁺: 243.1385.; observed mass: 243.1390.

(3a*S*,7a*S*)-5-(2-Fluorophenyl)-3a-methyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one (2w)



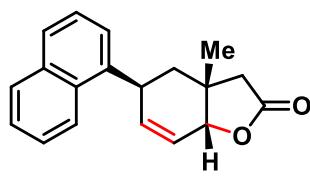
Eluent: ethyl acetate/ petroleum ether (10:90 v/v).

Appearance: white solid.

Isolated yield: 72% (35.5 mg, 0.14 mmol)

¹H NMR (400 MHz, CDCl₃) δ 7.25 – 7.19 (m, 1H), 7.17 – 7.09 (m, 2H), 7.04 (ddd, *J* = 10.4, 8.0, 1.1 Hz, 1H), 5.98 – 5.92 (m, 1H), 5.90 (dt, *J* = 10.2, 2.6 Hz, 1H), 4.67 (td, *J* = 2.6, 1.1 Hz, 1H), 3.84 (ddt, *J* = 10.1, 5.2, 2.4 Hz, 1H), 2.79 (d, *J* = 17.0 Hz, 1H), 2.21 – 2.06 (m, 2H), 1.64 – 1.56 (m, 1H), 1.24 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 176.42, 161.97, 159.53, 133.48, 130.81, 130.67, 128.97, 128.92, 128.68, 128.60, 126.56, 124.77, 124.73, 115.86, 115.64, 82.35, 38.79, 38.54, 37.88, 32.21, 32.18, 27.64; **¹⁹F NMR** (376 MHz, CDCl₃) δ -119.841; **HRMS (ESI)**: Calculated mass for C₁₅H₁₆FO₂ [M+H]⁺: 247.1134; observed mass: 247.1140.

(3a*S*,7a*S*)-3a-Methyl-5-(naphthalen-1-yl)-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one (2x)



Eluent: ethyl acetate/ petroleum ether (10:90 v/v).

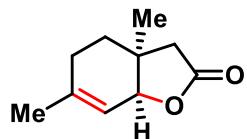
Appearance: colorless gummy.

Isolated yield: 68% (38 mg, 0.14 mmol)

¹H NMR (400 MHz, CDCl₃) δ 8.04 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.94 – 7.86 (m, 1H), 7.81 – 7.74 (m, 1H), 7.60 – 7.47 (m, 2H), 7.46 (dd, *J* = 8.2, 7.2 Hz, 1H), 7.31 (dd, *J* = 7.2, 1.2 Hz, 1H), 6.26 – 6.12 (m, 1H), 5.99 (dt, *J* = 10.2, 2.8 Hz, 1H), 4.76 (td, *J* = 2.6, 1.3 Hz, 1H), 4.32 (ddd, *J* = 10.6, 5.1, 2.5 Hz, 1H), 2.94 (d, *J* = 16.9 Hz, 1H), 2.31 (ddd, *J* = 14.4, 5.3, 1.4 Hz, 1H), 2.24 (d, *J* = 16.9 Hz, 1H), 1.76 (dd, *J* = 14.5, 10.9 Hz, 1H), 1.24 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 176.49, 140.00, 135.02, 134.21, 131.22, 129.42, 127.68, 126.47, 126.26, 125.92,

124.86, 122.77, 82.72, 39.83, 38.75, 38.19, 27.60; **HRMS (ESI)**: Calculated mass for C₁₉H₁₉O₂ [M+H]⁺: 279.1385; observed mass: 279.1390.

(3a*S*,7a*S*)-3a,6-Dimethyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one (2y)



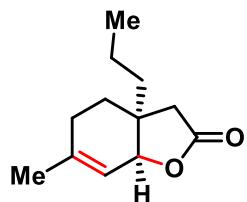
Eluent: ethyl acetate/ petroleum ether (8:92 v/v).

Appearance: colorless gummy.

Isolated yield: 65% (21.5 mg, 0.13 mmol)

¹**H NMR** (400 MHz, CDCl₃) δ 5.54 (dq, *J* = 4.5, 1.6 Hz, 1H), 4.67 – 4.14 (m, 1H), 2.42 (d, *J* = 17.1 Hz, 1H), 2.33 (d, *J* = 17.0 Hz, 1H), 2.16 – 1.90 (m, 2H), 1.76 (t, *J* = 1.2 Hz, 3H), 1.73 – 1.61 (m, 1H), 1.56 – 1.48 (m, 1H), 1.14 (s, 3H); ¹³**C NMR** (101 MHz, CDCl₃) δ 176.53, 141.83, 117.61, 82.47, 42.58, 36.75, 30.11, 26.95, 23.72, 23.18; **HRMS (ESI)**: Calculated mass for C₁₀H₁₅O₂ [M+H]⁺: 167.1072; observed mass: 167.1075.

(3a*S*,7a*S*)-6-Methyl-3a-propyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one (2z)



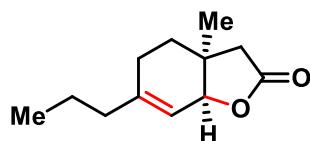
Eluent: ethyl acetate/ petroleum ether (8:92 v/v).

Appearance: colorless gummy.

Isolated yield: 56% (22 mg, 0.112 mmol)

¹**H NMR** (400 MHz, CDCl₃) δ 5.63 – 5.48 (m, 1H), 4.61 – 4.26 (m, 1H), 2.48 – 2.27 (m, 2H), 1.98 (tdd, *J* = 5.1, 1.8, 0.9 Hz, 2H), 1.76 (t, *J* = 1.2 Hz, 3H), 1.69 – 1.61 (m, 1H), 1.51 – 1.44 (m, 1H), 1.43 – 1.32 (m, 1H), 1.32 – 1.17 (m, 3H), 0.94 (t, *J* = 7.1 Hz, 3H); ¹³**C NMR** (126 MHz, CDCl₃) δ 176.76, 142.22, 117.56, 81.91, 40.80, 40.13, 38.01, 27.09, 26.73, 23.75, 18.08, 14.84; **HRMS (ESI)**: Calculated mass for C₁₂H₁₈NaO₂ [M+Na]⁺: 217.1204; observed mass: 217.1208.

(3a*S*,7a*S*)-3a-Methyl-6-propyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one (2aa)



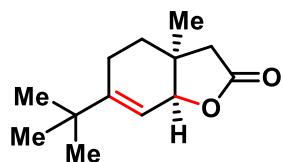
Eluent: ethyl acetate/ petroleum ether (7:93 v/v).

Appearance: colorless gummy.

Isolated yield: 64% (25 mg, 0.13 mmol) (d.r. = 6:1)

¹H NMR (500 MHz, CDCl₃) δ 5.54 (dt, *J* = 4.4, 1.6 Hz, 1H), 4.43 (d, *J* = 4.1 Hz, 1H), 2.42 (d, *J* = 17.1 Hz, 1H), 2.34 (d, *J* = 17.1 Hz, 1H), 2.02 (t, *J* = 7.6 Hz, 4H), 1.71 – 1.62 (m, 1H), 1.46 (qd, *J* = 7.4, 2.3 Hz, 1H), 1.25 (d, *J* = 2.3 Hz, 2H), 1.14 (s, 3H), 0.89 (t, *J* = 7.4 Hz, 3H); **¹³C NMR** (126 MHz, CDCl₃) δ 176.61, 145.51, 117.05, 82.51, 42.61, 39.64, 36.97, 30.13, 29.91, 25.27, 23.15, 20.67, 13.91; **HRMS (ESI):** Calculated mass for C₁₂H₁₉O₂ [M+H]⁺: 195.1385; observed mass: 195.1387.

(3a*S*,7a*S*)-6-(*tert*-Butyl)-3a-methyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one (2ab)



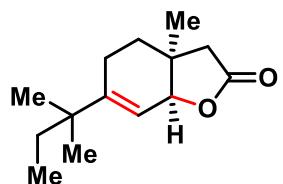
Eluent: ethyl acetate/ petroleum ether (8:92 v/v).

Appearance: colorless gummy.

Isolated yield: 55% (23 mg, 0.11 mmol)

¹H NMR (400 MHz, CDCl₃) δ 5.61 (d, *J* = 4.2 Hz, 1H), 4.46 (d, *J* = 4.2 Hz, 1H), 2.43 (d, *J* = 17.1 Hz, 1H), 2.34 (d, *J* = 17.1 Hz, 1H), 2.21 – 1.98 (m, 2H), 1.73 – 1.60 (m, 1H), 1.56 – 1.48 (m, 1H), 1.14 (s, 3H), 1.06 (s, 9H); **¹³C NMR** (126 MHz, CDCl₃) δ 176.59, 153.09, 114.22, 82.95, 42.53, 36.67, 35.90, 30.73, 28.91, 23.25, 21.34; **HRMS (ESI):** Calculated mass for C₁₃H₂₁O₂ [M+H]⁺: 209.1542; observed mass: 209.1540.

(3a*S*,7a*S*)-3a-Methyl-6-(*tert*-pentyl)-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one (2ac)



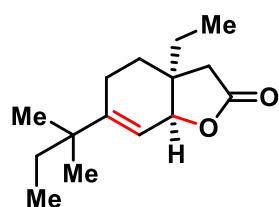
Eluent: ethyl acetate/ petroleum ether (8:92 v/v).

Appearance: colorless gummy.

Isolated yield: 57% (25.5 mg, 0.114 mmol)

¹H NMR (500 MHz, CDCl₃) δ 5.57 (dt, *J* = 4.2, 1.6 Hz, 1H), 4.47 (d, *J* = 4.2 Hz, 1H), 2.42 (d, *J* = 17.1 Hz, 1H), 2.35 (d, *J* = 17.1 Hz, 1H), 2.17 – 2.05 (m, 1H), 1.99 (ddt, *J* = 17.7, 8.6, 5.2, 1.6 Hz, 1H), 1.62 (td, *J* = 8.8, 4.4 Hz, 1H), 1.53 (dt, *J* = 13.5, 5.3 Hz, 1H), 1.38 (qd, *J* = 7.5, 2.1 Hz, 2H), 1.14 (s, 3H), 1.02 (s, 6H), 0.68 (t, *J* = 7.5 Hz, 3H); **¹³C NMR** (126 MHz, CDCl₃) δ 176.63, 151.19, 116.17, 82.91, 42.61, 39.15, 36.67, 33.31, 30.64, 26.81, 26.60, 23.17, 21.16, 9.21; **HRMS (ESI)**: Calculated mass for C₁₄H₂₃O₂ [M+H]⁺: 223.1698; observed mass: 223.1695.

(3a*S*,7a*S*)-3a-Ethyl-6-(*tert*-pentyl)-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one (2ad)



Eluent: ethyl acetate/ petroleum ether (8:92 v/v).

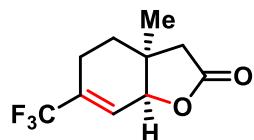
Appearance: colorless gummy.

Isolated yield: 60% (28.5 mg, 0.12 mmol)

¹H NMR (400 MHz, CDCl₃) δ 5.57 (d, *J* = 4.4 Hz, 1H), 4.47 (d, *J* = 4.3 Hz, 1H), 2.37 (d, *J* = 5.0 Hz, 2H), 2.14 – 1.99 (m, 1H), 1.99 – 1.88 (m, 1H), 1.65 (dd, *J* = 13.7, 5.1 Hz, 1H), 1.58 – 1.46 (m, 2H), 1.45 – 1.31 (m, 3H), 1.01 (d, *J* = 1.4 Hz, 6H), 0.92 (t, *J* = 7.5 Hz, 3H), 0.68 (t, *J* = 7.5 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 176.72, 151.40, 116.29, 82.24, 40.29, 40.19, 39.16, 33.32, 28.39, 27.17, 26.79, 26.59, 20.88, 9.23, 9.04; **HRMS (ESI)**: Calculated mass for C₁₅H₂₅O₂ [M+H]⁺: 237.1855; observed mass: 237.1860.

(3a*S*,7a*S*)-3a-Methyl-6-(trifluoromethyl)-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one

(2ae)



Eluent: ethyl acetate/ petroleum ether (10:90 v/v).

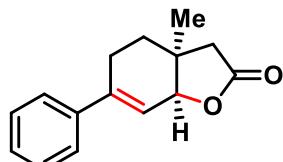
Appearance: colorless gummy.

Isolated yield: 85% (37.5 mg, 0.17 mmol)

¹H NMR (400 MHz, CDCl₃) δ 6.43 – 6.34 (m, 1H), 4.56 – 4.42 (m, 1H), 2.48 (d, *J* = 17.3 Hz, 1H), 2.39 (dd, *J* = 17.3, 0.8 Hz, 1H), 2.33 – 2.22 (m, 2H), 1.80 – 1.65 (m, 2H), 1.21 (s, 3H);

¹³C NMR (101 MHz, CDCl₃) δ 175.15, 133.91, 133.60, 133.29, 125.14, 125.09, 125.03, 124.98, 124.47, 121.76, 79.46, 41.38, 37.02, 29.15, 23.46, 19.21; **¹⁹F NMR** (376 MHz, CDCl₃) δ -70.12; **HRMS (ESI)**: Calculated mass for C₁₀H₁₂F₃O₂ [M+H]⁺: 221.0789; observed mass: 221.0795.

(3a*S*,7a*S*)-3a-Methyl-6-phenyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one (2af)



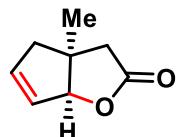
Eluent: ethyl acetate/ petroleum ether (10:90 v/v).

Appearance: colorless gummy.

Isolated yield: 60% (28 mg, 0.12 mmol)

¹H NMR (400 MHz, CDCl₃) δ 7.44 – 7.40 (m, 2H), 7.38 – 7.28 (m, 3H), 6.15 (dd, *J* = 4.2, 1.8 Hz, 1H), 5.06 – 4.50 (m, 1H), 2.57 – 2.51 (m, 2H), 2.50 (s, 1H), 2.41 (d, *J* = 17.1 Hz, 1H), 1.83 (ddd, *J* = 13.8, 7.6, 6.2 Hz, 1H), 1.72 (dt, *J* = 13.7, 5.4 Hz, 1H), 1.24 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 176.28, 142.93, 140.34, 128.70, 128.44, 125.77, 119.22, 82.30, 42.35, 36.89, 30.33, 24.39, 23.32; **HRMS (ESI)**: Calculated mass for C₁₅H₁₇O₂ [M+H]⁺: 229.1229; observed mass: 229.1219.

(3a*S*,6a*S*)-3a-Methyl-3,3a,4,6a-tetrahydro-2H-cyclopenta[b]furan-2-one (3a)



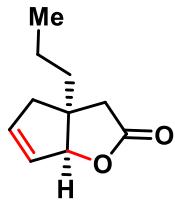
Eluent: ethyl acetate/ petroleum ether (6:94 v/v).

Appearance: colorless liquid.

Isolated yield: 62% (17 mg, 0.123 mmol) (d.r. = 7:1)

¹H NMR (400 MHz, CDCl₃) δ 6.04 (dt, *J* = 5.2, 2.4 Hz, 1H), 5.88 – 5.76 (m, 1H), 5.03 (dt, *J* = 2.1, 1.1 Hz, 1H), 2.66 – 2.30 (m, 4H), 1.35 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 176.83, 136.92, 136.64, 129.12, 128.00, 95.40, 88.78, 46.58, 44.40, 43.38, 40.53, 38.51, 32.14, 29.91, 25.61, 23.39; **HRMS (ESI)**: Calculated mass for C₈H₁₁O₂ [M+H]⁺: 139.0759; observed mass: 139.0765.

(3a*S*,6a*S*)-3a-Propyl-3,3a,4,6a-tetrahydro-2H-cyclopenta[b]furan-2-one (3b)



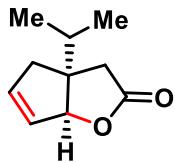
Eluent: ethyl acetate / petroleum ether (6:94 v/v)

Appearance: colorless liquid.

Isolated yield: 59% (19.5 mg, 0.117 mmol) (d.r. = 5:1)

¹H NMR (400 MHz, CDCl₃) δ 6.03 (dt, *J* = 5.2, 2.4 Hz, 1H), 5.82 (dq, *J* = 6.1, 2.1 Hz, 1H), 5.11 (d, *J* = 2.1 Hz, 1H), 2.63 – 2.53 (m, 1H), 2.51 – 2.40 (m, 3H), 1.59 – 1.51 (m, 2H), 1.40 – 1.29 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 177.04, 136.55, 135.14, 132.52, 129.29, 128.94, 94.14, 87.87, 48.42, 44.56, 41.94, 41.33, 41.10, 40.23, 39.34, 39.12, 18.53, 14.74; **HRMS (ESI):** Calculated mass for C₁₀H₁₄NaO₂ [M+Na]⁺: 189.0891; observed mass: 189.0895.

(3a*S*,6a*S*)-3a-Isopropyl-3,3a,4,6a-tetrahydro-2H-cyclopenta[b]furan-2-one (3c)



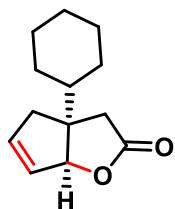
Eluent: ethyl acetate/ petroleum ether (6:94 v/v).

Appearance: colorless gummy.

Isolated yield: 57% (19 mg, 0.114 mmol) (d.r. = 4:1)

¹H NMR (400 MHz, CDCl₃) δ 6.02 (dtd, *J* = 5.8, 2.3, 0.9 Hz, 1H), 5.82 (dq, *J* = 6.1, 2.0 Hz, 1H), 5.21 (dq, *J* = 2.6, 1.3 Hz, 1H), 2.62 (d, *J* = 18.3 Hz, 1H), 2.47 (dq, *J* = 17.5, 2.1 Hz, 1H), 2.40 – 2.30 (m, 2H), 1.84 (p, *J* = 6.8 Hz, 1H), 0.93 (dd, *J* = 17.2, 6.8 Hz, 6H); **¹³C NMR** (101 MHz, CDCl₃) δ 177.24, 136.22, 132.50, 130.25, 129.65, 93.09, 86.98, 52.49, 43.14, 39.84, 38.69, 38.56, 35.43, 34.89, 19.04, 18.05, 17.87; **HRMS (ESI):** Calculated mass for C₁₀H₁₅O₂ [M+H]⁺: 167.1072; observed mass: 167.1064.

(3a*S*,6a*S*)-3a-Cyclohexyl-3,3a,4,6a-tetrahydro-2H-cyclopenta[b]furan-2-one (3d)



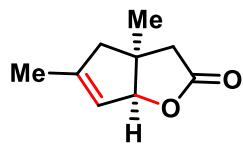
Eluent: ethyl acetate/ petroleum ether (6:94 v/v).

Appearance: colorless gummy.

Isolated yield: 70% (29 mg, 0.14 mmol) (d.r. = 8:1)

¹H NMR (400 MHz, CDCl₃) δ 6.01 (dt, *J* = 5.7, 2.5 Hz, 1H), 5.81 (dq, *J* = 6.0, 2.0 Hz, 1H), 5.24 (q, *J* = 2.3 Hz, 1H), 2.63 (d, *J* = 18.1 Hz, 1H), 2.47 (dq, *J* = 17.2, 2.1 Hz, 1H), 2.37 – 2.28 (m, 2H), 1.79 – 1.57 (m, 5H), 1.45 (tt, *J* = 12.0, 3.1 Hz, 1H), 1.28 – 1.09 (m, 3H), 1.07 – 0.97 (m, 2H); **¹³C NMR** (101 MHz, CDCl₃) δ 177.26, 136.05, 133.14, 129.86, 129.57, 92.85, 86.98, 52.35, 45.88, 45.41, 43.17, 39.88, 38.94, 38.58, 29.14, 28.29, 28.21, 28.06, 26.63, 26.51, 26.48, 26.46, 26.36, 26.26; **HRMS (ESI):** Calculated mass for C₁₃H₁₉O₂ [M+H]⁺: 207.1385; observed mass: 207.1380.

(3a*S*,6a*S*)-3a,5-Dimethyl-3,3a,4,6a-tetrahydro-2H-cyclopenta[b]furan-2-one (3e)



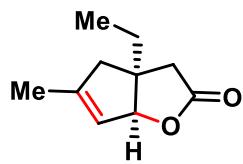
Eluent: ethyl acetate/ petroleum ether (6:94 v/v).

Appearance: colorless gummy.

Isolated yield: 53% (16 mg, 0.105 mmol)

¹H NMR (400 MHz, CDCl₃) δ 6.04 (s, 1H), 4.99 (d, *J* = 2.0 Hz, 1H), 4.53 – 4.34 (m, 2H), 4.10 (p, *J* = 5.9 Hz, 1H), 2.59 (d, *J* = 18.1 Hz, 1H), 2.55 – 2.41 (m, 3H), 1.38 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 176.48, 136.90, 135.33, 93.36, 70.78, 45.92, 44.73, 43.31, 29.91, 25.74; **HRMS (ESI):** Calculated mass for C₉H₁₃O₂ [M+H]⁺: 153.0916; observed mass: 153.0920.

(3a*S*,6a*S*)-3a-Ethyl-5-methyl-3,3a,4,6a-tetrahydro-2H-cyclopenta[b]furan-2-one (3f)



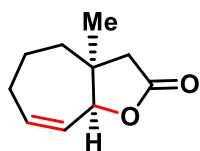
Eluent: ethyl acetate/ petroleum ether (7:93 v/v).

Appearance: colorless gummy.

Isolated yield: 51% (17 mg, 0.10 mmol)

¹H NMR (400 MHz, CDCl₃) δ 6.03 (s, 1H), 5.07 (s, 1H), 4.50 – 4.31 (m, 2H), 4.10 (p, *J* = 5.9 Hz, 1H), 2.61 (d, *J* = 18.2 Hz, 1H), 2.57 – 2.36 (m, 3H), 1.67 (q, *J* = 7.4 Hz, 2H), 0.97 (t, *J* = 7.4 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 176.61, 137.07, 134.95, 91.77, 70.75, 49.16, 43.54, 40.84, 31.34, 9.29; **HRMS (ESI):** Calculated mass for C₁₀H₁₅O₂ [M+H]⁺: 167.1072; observed mass: 167.1075.

(3a*S*,8a*S*)-3a-Methyl-3,3a,4,5,6,8a-hexahydro-2H-cyclohepta[b]furan-2-one (3g)



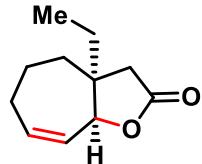
Eluent: ethyl acetate/ petroleum ether (7:93 v/v).

Appearance: colorless gummy.

Isolated yield: 70% (23.2 mg, 0.139 mmol)

¹H NMR (400 MHz, CDCl₃) δ 5.71 (dtd, *J* = 11.6, 5.3, 2.2 Hz, 1H), 5.57 (ddt, *J* = 11.7, 3.4, 1.6 Hz, 1H), 4.85 (dq, *J* = 4.0, 2.1 Hz, 1H), 2.43 (d, *J* = 17.2 Hz, 1H), 2.29 (d, *J* = 17.1 Hz, 1H), 2.21 (dtt, *J* = 6.8, 5.0, 1.8 Hz, 2H), 1.76 – 1.55 (m, 4H), 1.22 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 176.53, 130.80, 127.29, 127.25, 86.34, 86.28, 43.88, 43.79, 43.76, 43.73, 42.52, 35.73, 28.94, 25.89, 25.83, 25.69, 19.06; **HRMS (ESI):** Calculated mass for C₁₀H₁₅O₂ [M+H]⁺: 167.1072; observed mass: 167.1080.

(3a*S*,8a*S*)-3a-Ethyl-3,3a,4,5,6,8a-hexahydro-2H-cyclohepta[b]furan-2-one (3h)



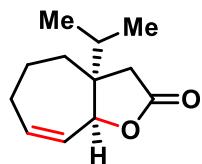
Eluent: ethyl acetate/ petroleum ether (8:92 v/v).

Appearance: colorless gummy.

Isolated yield: 66% (24 mg, 0.133 mmol) (d.r. = 7:1)

¹H NMR (400 MHz, CDCl₃) δ 5.75 (dtd, *J* = 11.3, 5.6, 2.0 Hz, 1H), 5.62 (ddd, *J* = 11.5, 4.1, 1.6 Hz, 1H), 4.84 (dd, *J* = 3.9, 1.9 Hz, 1H), 2.44 (d, *J* = 17.6 Hz, 1H), 2.29 (d, *J* = 17.5 Hz, 1H), 2.19 (d, *J* = 14.2 Hz, 2H), 1.85 – 1.69 (m, 1H), 1.69 – 1.49 (m, 5H), 0.92 (t, *J* = 7.5 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 176.84, 131.11, 127.71, 86.04, 45.42, 41.32, 32.84, 30.55, 28.63, 18.90, 8.67; **HRMS (ESI):** Calculated mass for C₁₁H₁₆NaO₂ [M+Na]⁺: 203.1048; observed mass: 203.1050.

(3a*S*,8a*S*)-3a-Isopropyl-3,3a,4,5,6,8a-hexahydro-2H-cyclohepta[b]furan-2-one (3i)



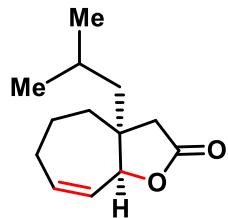
Eluent: ethyl acetate/ petroleum ether (10:90 v/v).

Appearance: colorless gummy.

Isolated yield: 71% (27.5 mg, 0.14 mmol) (d.r. = 8:1)

¹H NMR (400 MHz, CDCl₃) δ 5.80 (dtd, *J* = 11.2, 5.7, 1.3 Hz, 1H), 5.72 (ddd, *J* = 11.1, 4.8, 1.8 Hz, 1H), 4.94 – 4.80 (m, 1H), 2.51 (d, *J* = 18.0 Hz, 1H), 2.37 – 2.25 (m, 1H), 2.20 (d, *J* = 17.9 Hz, 1H), 2.16 – 2.01 (m, 1H), 1.90 – 1.80 (m, 1H), 1.79 – 1.70 (m, 1H), 1.57 – 1.45 (m, 3H), 0.92 (dt, *J* = 6.8, 4.9 Hz, 6H); **¹³C NMR** (101 MHz, CDCl₃) δ 177.10, 131.92, 127.86, 85.56, 85.52, 47.85, 40.05, 34.69, 28.21, 18.37, 18.01, 17.70; **HRMS (ESI)**: Calculated mass for C₁₂H₁₉O₂ [M+H]⁺: 195.1385; observed mass: 195.1392.

(3a*R*,8a*S*)-3a-Isobutyl-3,3a,4,5,6,8a-hexahydro-2H-cyclohepta[b]furan-2-one (3j)



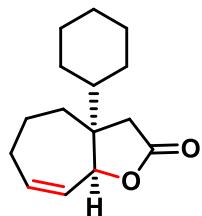
Eluent: ethyl acetate/ petroleum ether (8:92 v/v).

Appearance: colorless gummy.

Isolated yield: 64% (26.5 mg, 0.127 mmol) (d.r. = 7:1)

¹H NMR (400 MHz, CDCl₃) δ 5.83 (dddd, *J* = 11.8, 6.1, 4.9, 1.3 Hz, 1H), 5.62 (ddt, *J* = 11.7, 5.1, 1.7 Hz, 1H), 4.69 (dd, *J* = 5.1, 1.3 Hz, 1H), 2.54 (d, *J* = 17.3 Hz, 1H), 2.36 (d, *J* = 17.4 Hz, 1H), 2.24 (ddt, *J* = 8.0, 4.5, 1.5 Hz, 2H), 1.82 – 1.67 (m, 2H), 1.67 – 1.57 (m, 4H), 1.30 (dd, *J* = 14.2, 7.3 Hz, 1H), 0.95 (t, *J* = 6.8 Hz, 6H); **¹³C NMR** (101 MHz, CDCl₃) δ 176.95, 133.84, 125.53, 86.34, 46.65, 46.19, 43.16, 33.71, 29.54, 25.29, 24.70, 24.38, 19.48; **HRMS (ESI)**: Calculated mass for C₁₃H₂₁O₂ [M+H]⁺: 209.1542.; observed mass: 209.1548.

(3a*S*,8a*S*)-3a-Cyclohexyl-3,3a,4,5,6,8a-hexahydro-2H-cyclohepta[b]furan-2-one (3k)



Eluent: ethyl acetate/ petroleum ether (8:92 v/v).

Appearance: colorless gummy.

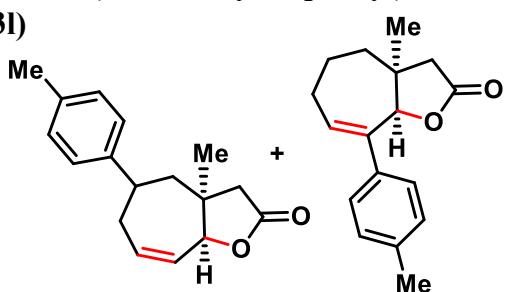
Isolated yield: 68% (32 mg, 0.136 mmol) (d.r. = 4:1)

¹H NMR (400 MHz, CDCl₃) δ 6.14 – 5.60 (m, 2H), 4.84 (d, *J* = 4.9 Hz, 1H), 2.84 – 2.44 (m, 1H), 2.31 (dtd, *J* = 15.5, 6.2, 2.7 Hz, 1H), 2.20 (d, *J* = 17.9 Hz, 1H), 2.07 (ddt, *J* = 16.9, 7.6, 5.3 Hz, 1H), 1.89 – 1.36 (m, 10H), 1.31 – 0.91 (m, 5H); **¹³C NMR** (101 MHz, CDCl₃) δ 177.20,

135.51, 131.95, 129.76, 127.76, 126.69, 125.66, 86.36, 85.47, 52.65, 47.94, 46.69, 45.57, 40.94, 39.66, 32.08, 31.39, 28.27, 28.04, 27.84, 27.69, 27.59, 26.93, 26.80, 26.77, 26.74, 26.54, 26.51, 18.35; **HRMS (ESI)**: Calculated mass for C₁₅H₂₂NaO₂ [M+H]⁺: 257.1517; observed mass: 257.1520.

(3a*S*,8a*S*)-3a-Methyl-6-(*p*-tolyl)-3,3a,4,5,6,8a-hexahydro-2*H*-cyclohepta[b]furan-2-one

(3l)



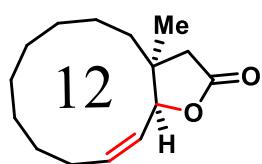
Eluent: ethyl acetate/ petroleum ether (8:92 v/v).

Appearance: colorless gummy.

Isolated yield: 59% (30.2 mg, 0.117 mmol) (r.r. = 2:1)

¹H NMR (400 MHz, CDCl₃) δ 7.23 – 7.02 (m, 12H), 6.05 (dd, *J* = 7.6, 5.1 Hz, 1H), 5.95 (dt, *J* = 12.3, 5.0 Hz, 2H), 5.72 (dd, *J* = 12.2, 5.5, 2.4, 1.5 Hz, 2H), 5.04 (s, 1H), 4.73 (d, *J* = 5.5 Hz, 2H), 3.04 (tdd, *J* = 10.8, 4.6, 1.6 Hz, 2H), 2.71 (d, *J* = 17.4 Hz, 2H), 2.66 – 2.56 (m, 2H), 2.54 – 2.39 (m, 3H), 2.36 – 2.24 (m, 14H), 2.10 (dd, *J* = 14.5, 10.6 Hz, 2H), 1.95 – 1.85 (m, 3H), 1.71 (dd, *J* = 4.0, 1.7 Hz, 3H), 1.21 (d, *J* = 1.2 Hz, 9H); **¹³C NMR** (101 MHz, CDCl₃) δ 176.69, 176.66, 144.58, 139.88, 137.01, 136.82, 136.18, 134.60, 132.46, 129.55, 129.49, 129.17, 127.26, 126.60, 124.20, 89.06, 85.98, 46.02, 44.46, 42.90, 42.07, 41.68, 39.09, 38.01, 36.89, 28.90, 27.29, 25.41, 21.24, 21.15, 19.37; **HRMS (ESI)**: Calculated mass for C₁₇H₂₁O₂ [M+H]⁺: 257.1542; observed mass: 257.1550.

(3a*S*,13a*S*,*Z*)-3a-Methyl-3a,4,5,6,7,8,9,10,11,13a-decahydrocyclododeca[b]furan-2(3*H*)-one (3m)



Eluent: ethyl acetate/ petroleum ether (10:90 v/v).

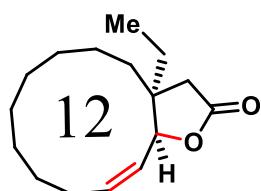
Appearance: colorless gummy.

Isolated yield: 55% (26 mg, 0.11 mmol) (d.r. = 4:1)

¹H NMR (400 MHz, CDCl₃) δ 5.93 (ddd, *J* = 14.9, 8.4, 6.1 Hz, 1H), 5.53 – 5.40 (m, 1H), 4.53 (d, *J* = 8.5 Hz, 1H), 2.45 (d, *J* = 17.1 Hz, 1H), 2.28 (d, *J* = 19.5 Hz, 1H), 2.23 – 2.07 (m, 2H),

1.55 – 1.23 (m, 14H), 1.19 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 176.48, 138.02, 137.89, 124.28, 122.98, 90.17, 80.40, 43.10, 42.50, 41.05, 34.99, 32.88, 32.84, 31.36, 27.90, 26.82, 26.56, 26.50, 26.34, 26.28, 25.43, 25.39, 25.23, 25.05, 24.65, 24.37, 22.64, 22.50, 22.14, 22.04, 21.77, 20.05, 19.94, 19.56; HRMS (ESI): Calculated mass for $\text{C}_{15}\text{H}_{24}\text{NaO}_2$ $[\text{M}+\text{Na}]^+$: 259.1674; observed mass: 259.1678.

(3a*S*,13a*S*,*Z*)-3a-Ethyl-3a,4,5,6,7,8,9,10,11,13a-decahydrocyclododeca[b]furan-2(3H)-one (3n)



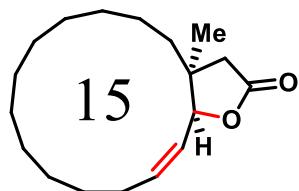
Eluent: ethyl acetate/ petroleum ether (10:90 v/v).

Appearance: colorless gummy.

Isolated yield: 58% (29 mg, 0.116 mmol)

^1H NMR (400 MHz, CDCl_3) δ 5.72 – 5.61 (m, 1H), 5.54 – 5.44 (m, 1H), 4.25 (dd, $J = 9.9, 2.4$ Hz, 1H), 2.65 – 2.54 (m, 2H), 2.44 – 2.31 (m, 2H), 2.27 – 2.17 (m, 2H), 1.93 – 1.79 (m, 2H), 1.69 (ddd, $J = 13.3, 6.7, 4.9$ Hz, 2H), 1.52 – 1.42 (m, 2H), 1.38 (dd, $J = 14.4, 6.9$ Hz, 2H), 0.94 (ddd, $J = 11.3, 6.6, 2.7$ Hz, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 176.60, 137.34, 124.40, 90.17, 45.92, 39.71, 32.81, 31.86, 29.53, 27.67, 26.73, 26.68, 25.38, 24.69, 19.53, 8.51; HRMS (ESI): Calculated mass for $\text{C}_{16}\text{H}_{27}\text{O}_2$ $[\text{M}+\text{H}]^+$: 251.2011; observed mass: 251.2015.

(3a*R*,16a*S*,*E*)-3a-Methyl-3,3a,4,5,6,7,8,9,10,11,12,13,14,16a-tetradecahydro-2H-cyclopentadeca[b]furan-2-one (3o)



Eluent: ethyl acetate/ petroleum ether (8:92 v/v).

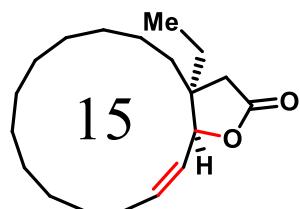
Appearance: colorless gummy.

Isolated yield: 50% (27.8 mg, 0.1 mmol) (d.r. = 3:1)

^1H NMR (400 MHz, CDCl_3) δ 5.84 (ddd, $J = 14.8, 10.1, 4.2$ Hz, 1H), 5.58 – 5.40 (m, 1H), 4.48 (d, $J = 9.1$ Hz, 1H), 2.44 (dd, $J = 16.9, 5.0$ Hz, 1H), 2.33 – 2.25 (m, 1H), 2.21 – 1.97 (m, 2H), 1.52 – 1.21 (m, 20H), 1.04 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 176.36, 140.00, 124.97, 90.05, 44.55, 43.67, 38.49, 31.98, 28.74, 27.80, 27.60, 27.38, 26.70, 26.59, 26.51, 25.72, 22.89,

19.43; **HRMS (ESI)**: Calculated mass for $C_{18}H_{31}O_2$ $[M+H]^+$: 279.2324; observed mass: 279.2328.

(3a*S*,16a*S*,*E*)-3a-Ethyl-3,3a,4,5,6,7,8,9,10,11,12,13,14,16a-tetradecahydro-2H-cyclopentadeca[b]furan-2-one (3p)



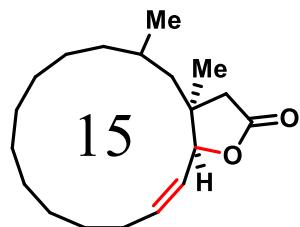
Eluent: ethyl acetate/ petroleum ether (8:92 v/v).

Appearance: colorless gummy.

Isolated yield: 54% (31.5 mg, 0.107 mmol)

1H NMR (400 MHz, $CDCl_3$) δ 5.88 (ddd, $J = 14.7, 10.1, 4.1$ Hz, 1H), 5.60 (ddd, $J = 15.2, 9.3, 1.9$ Hz, 1H), 4.58 (d, $J = 9.4$ Hz, 1H), 2.49 (d, $J = 17.1$ Hz, 1H), 2.35 – 2.22 (m, 2H), 2.14 – 2.02 (m, 1H), 1.51 – 1.16 (m, 22H), 0.91 (t, $J = 7.5$ Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.34, 140.78, 125.01, 91.22, 46.39, 41.68, 41.06, 37.21, 32.97, 31.98, 28.39, 28.31, 28.02, 27.74, 27.18, 27.14, 26.98, 26.87, 26.67, 26.50, 26.21, 26.10, 26.06, 25.72, 23.70, 22.92, 21.92, 8.34; **HRMS (ESI)**: Calculated mass for $C_{19}H_{33}O_2$ $[M+H]^+$: 293.2481; observed mass: 293.2490.

(3a*S*,16a*S*,*E*)-3a,5-Dimethyl-3,3a,4,5,6,7,8,9,10,11,12,13,14,16a-tetradecahydro-2H-cyclopentadeca[b]furan-2-one (3q)



Eluent: ethyl acetate/ petroleum ether (9:91 v/v).

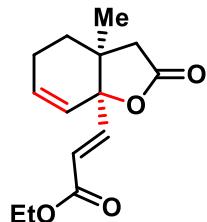
Appearance: colorless gummy.

Isolated yield: 37% (21.5 mg, 0.074 mmol)

1H NMR (400 MHz, $CDCl_3$) δ 5.96 – 5.62 (m, 1H), 5.58 – 5.35 (m, 1H), 4.76 – 4.25 (m, 1H), 2.60 – 2.41 (m, 1H), 2.34 – 2.00 (m, 3H), 1.46 – 1.20 (m, 16H), 1.18 – 1.05 (m, 3H), 1.02 – 0.85 (m, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 176.79, 138.97, 137.39, 125.11, 124.62, 124.46, 91.81, 90.60, 88.04, 45.02, 43.87, 43.62, 43.47, 42.53, 41.25, 37.54, 36.98, 35.49, 32.26, 31.65, 29.91, 29.26, 28.68, 27.88, 27.78, 27.67, 27.57, 27.50, 27.28, 26.90, 26.84, 26.79, 26.72, 26.61, 26.44, 26.32, 26.23, 26.20, 26.10, 25.99, 25.87, 25.44, 25.06, 24.01, 23.57, 22.45, 22.27, 21.14,

18.52; **HRMS (ESI)**: Calculated mass for C₁₉H₃₃O₂ [M+H]⁺: 293.2481; observed mass: 293.2484.

Ethyl (E)-3-((3a*S*,7a*R*)-3a-methyl-2-oxo-3,3a,4,5-tetrahydrobenzofuran-7a(2H)-yl)acrylate (4a)



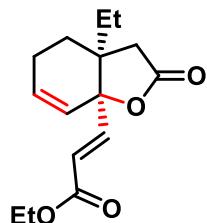
Eluent: ethyl acetate/ petroleum ether (10:90 v/v).

Appearance: colorless liquid.

Isolated yield: 68% (34 mg, 0.136 mmol)

¹H NMR (400 MHz, CDCl₃) δ 6.88 (d, *J* = 15.7 Hz, 1H), 6.10 (d, *J* = 15.7 Hz, 1H), 6.07 – 5.95 (m, 1H), 5.48 (dt, *J* = 10.1, 2.2 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 2.64 (d, *J* = 16.9 Hz, 1H), 2.26 (s, 1H), 2.22 – 2.13 (m, 2H), 1.80 – 1.60 (m, 2H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.07 (s, 3H); **¹³C NMR** (126 MHz, CDCl₃) δ 175.22, 166.02, 144.48, 131.49, 126.19, 122.47, 86.21, 61.00, 41.31, 40.01, 37.99, 29.09, 26.28, 23.71, 22.16, 21.74, 14.39; **HRMS (ESI)**: Calculated mass for C₁₄H₁₉O₄ [M+H]⁺: 251.1283; observed mass: 251.1285.

Ethyl (E)-3-((3a*S*,7a*R*)-3a-ethyl-2-oxo-3,3a,4,5-tetrahydrobenzofuran-7a(2H)-yl)acrylate (4b)



Eluent: ethyl acetate/ petroleum ether (10:90 v/v).

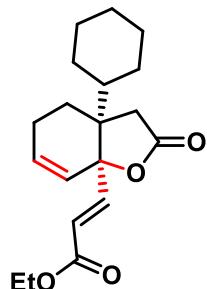
Appearance: colorless liquid.

Isolated yield: 73% (38.5 mg, 0.146 mmol)

¹H NMR (400 MHz, CDCl₃) δ 6.89 (d, *J* = 15.7 Hz, 1H), 6.10 (d, *J* = 15.8 Hz, 1H), 6.04 (dt, *J* = 10.1, 3.7 Hz, 1H), 5.47 (dt, *J* = 10.0, 2.2 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 2.50 (dd, *J* = 17.1, 0.9 Hz, 1H), 2.35 (d, *J* = 17.1 Hz, 1H), 2.16 (dd, *J* = 8.2, 5.5, 2.7, 1.5 Hz, 2H), 1.77 (dt, *J* = 14.3, 5.2 Hz, 1H), 1.68 – 1.61 (m, 1H), 1.52 – 1.38 (m, 2H), 1.30 (t, *J* = 7.1 Hz, 3H), 0.89 (t, *J* = 7.5 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 175.25, 166.02, 144.65, 131.59, 126.39, 122.29,

86.57, 60.98, 44.76, 36.83, 27.93, 25.64, 21.59, 14.41, 8.64; **HRMS (ESI)**: Calculated mass for C₁₅H₂₁O₄ [M+H]⁺: 265.1440; observed mass: 265.1447.

Ethyl (E)-3-((3a*S*,7a*R*)-3a-cyclohexyl-2-oxo-3,3a,4,5-tetrahydrobenzofuran-7a(2H)-yl)acrylate (4c)



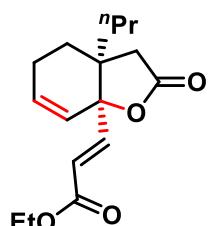
Eluent: ethyl acetate/ petroleum ether (12:88 v/v).

Appearance: colorless gummy.

Isolated yield: 75% (48 mg, 0.15 mmol)

¹H NMR (400 MHz, CDCl₃) δ 7.03 (d, *J* = 15.8 Hz, 1H), 6.14 (d, *J* = 15.7 Hz, 1H), 5.95 (ddd, *J* = 10.0, 4.5, 2.8 Hz, 1H), 5.37 (ddd, *J* = 10.0, 2.6, 1.7 Hz, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 2.45 (d, *J* = 17.3 Hz, 1H), 2.33 (d, *J* = 17.3 Hz, 1H), 2.28 – 2.08 (m, 2H), 1.95 (ddd, *J* = 14.6, 5.9, 3.3 Hz, 1H), 1.83 – 1.68 (m, 3H), 1.64 – 1.50 (m, 4H), 1.39 (td, *J* = 8.8, 4.3 Hz, 1H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.17 – 0.91 (m, 4H); **¹³C NMR** (101 MHz, CDCl₃) δ 175.79, 166.14, 143.97, 129.96, 127.92, 121.80, 87.24, 60.95, 47.11, 44.46, 34.63, 29.90, 28.67, 27.08, 26.84, 26.57, 26.42, 25.11, 22.03, 14.41; **HRMS (ESI)**: Calculated mass for C₁₉H₂₇O₄ [M+H]⁺: 319.1909; observed mass: 319.1914.

Ethyl (E)-3-((3a*S*,7a*R*)-2-oxo-3a-propyl-3,3a,4,5-tetrahydrobenzofuran-7a(2H)-yl)acrylate (4d)



Eluent: ethyl acetate/ petroleum ether (10:90 v/v).

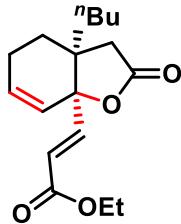
Appearance: colorless gummy.

Isolated yield: 74% (41 mg, 0.148 mmol)

¹H NMR (400 MHz, CDCl₃) δ 6.89 (d, *J* = 15.7 Hz, 1H), 6.09 (d, *J* = 15.7 Hz, 1H), 6.03 (dt, *J* = 10.0, 3.7 Hz, 1H), 5.46 (dt, *J* = 10.0, 2.1 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 2.50 (d, *J* = 17.0 Hz, 1H), 2.36 (d, *J* = 17.1 Hz, 1H), 2.15 (td, *J* = 5.4, 2.1 Hz, 2H), 1.75 (dt, *J* = 14.3, 5.3 Hz,

1H), 1.69 – 1.58 (m, 1H), 1.38 – 1.20 (m, 7H), 0.91 (t, J = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 175.37, 166.04, 144.71, 131.73, 126.17, 122.20, 86.51, 60.98, 44.56, 37.53, 37.47, 26.21, 21.60, 17.67, 14.84, 14.40; HRMS (ESI): Calculated mass for $\text{C}_{16}\text{H}_{23}\text{O}_4$ [M+H] $^+$: 279.1526; observed mass: 279.1530.

Ethyl (E)-3-((3a*S*,7a*R*)-3a-butyl-2-oxo-3,3a,4,5-tetrahydrobenzofuran-7a(2H)-yl)acrylate (4e)



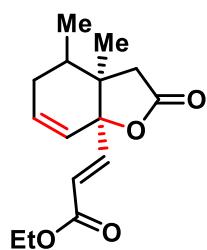
Eluent: ethyl acetate/ petroleum ether (10:90 v/v).

Appearance: colorless gummy.

Isolated yield: 71% (41.5 mg, 0.142 mmol)

^1H NMR (400 MHz, CDCl_3) δ 6.89 (d, J = 15.7 Hz, 1H), 6.08 (d, J = 15.7 Hz, 1H), 6.03 (dt, J = 10.0, 3.7 Hz, 1H), 5.46 (dt, J = 10.1, 2.2 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 2.49 (d, J = 17.1 Hz, 1H), 2.35 (d, J = 17.1 Hz, 1H), 2.15 (tt, J = 6.0, 2.1 Hz, 2H), 1.75 (dt, J = 14.3, 5.3 Hz, 1H), 1.62 (ddd, J = 14.2, 7.8, 6.3 Hz, 1H), 1.46 – 1.19 (m, 9H), 0.88 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 175.37, 166.01, 144.72, 131.72, 126.15, 122.20, 86.52, 60.96, 44.47, 37.47, 26.54, 26.20, 23.41, 21.58, 14.43, 14.33, 14.18; HRMS (ESI): Calculated mass for $\text{C}_{17}\text{H}_{25}\text{O}_4$ [M+H] $^+$: 293.1753; observed mass: 293.1760.

Ethyl (E)-3-((3a*R*,7a*R*)-3a,4-dimethyl-2-oxo-3,3a,4,5-tetrahydrobenzofuran-7a(2H)-yl)acrylate (4f)



Eluent: ethyl acetate/ petroleum ether (10:90 v/v).

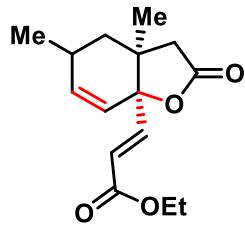
Appearance: colorless liquid.

Isolated yield: 64% (34 mg, 0.128 mmol) (d.r. = 6:1)

^1H NMR (500 MHz, CDCl_3) δ 6.87 (d, J = 15.7 Hz, 1H), 6.10 (d, J = 15.8 Hz, 1H), 5.94 (ddd, J = 10.2, 5.1, 1.8 Hz, 1H), 5.51 – 5.38 (m, 1H), 4.20 (q, J = 7.2 Hz, 2H), 2.61 (d, J = 16.7 Hz, 1H), 2.27 – 2.17 (m, 1H), 2.08 (d, J = 16.8 Hz, 1H), 1.96 – 1.80 (m, 2H), 1.29 (t, J = 7.1 Hz,

3H), 1.07 (s, 3H), 0.96 (d, J = 6.4 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 175.20, 166.06, 144.09, 141.72, 130.34, 126.87, 122.98, 122.38, 87.55, 60.95, 45.50, 36.47, 32.47, 30.74, 21.91, 16.93, 14.40; HRMS (ESI): Calculated mass for $\text{C}_{15}\text{H}_{21}\text{O}_4$ [$\text{M}+\text{H}]^+$: 265.1440; observed mass: 265.1445.

Ethyl (E)-3-((3a*S*,7a*R*)-3*a*,5-dimethyl-2-oxo-3,3*a*,4,5-tetrahydrobenzofuran-7*a*(2*H*)-yl)acrylate (4g)



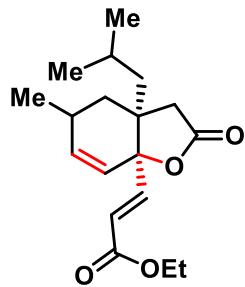
Eluent: ethyl acetate/ petroleum ether (10:90 v/v).

Appearance: colorless gummy.

Isolated yield: 67% (35.5 mg, 0.134 mmol) (d.r. = 5:1)

^1H NMR (400 MHz, CDCl_3) δ 6.85 (d, J = 15.7 Hz, 1H), 6.07 (d, J = 15.7 Hz, 1H), 5.82 (dt, J = 10.2, 1.7 Hz, 1H), 5.40 (dd, J = 10.0, 2.7 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 2.75 (d, J = 16.9 Hz, 1H), 2.36 (ddd, J = 10.3, 5.3, 2.6 Hz, 1H), 2.11 (d, J = 16.9 Hz, 1H), 1.82 (ddd, J = 14.6, 5.5, 1.3 Hz, 1H), 1.36 – 1.25 (m, 4H), 1.07 (d, J = 7.0 Hz, 3H), 1.04 – 1.01 (m, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 175.15, 166.01, 143.97, 136.75, 125.77, 122.51, 86.70, 60.97, 42.09, 39.63, 37.66, 27.49, 24.77, 21.07, 14.38; HRMS (ESI): Calculated mass for $\text{C}_{15}\text{H}_{21}\text{O}_4$ [$\text{M}+\text{H}]^+$: 265.1440; observed mass: 265.1442.

Ethyl (E)-3-((3a*S*,7a*R*)-3*a*-isobutyl-5-methyl-2-oxo-3,3*a*,4,5-tetrahydrobenzofuran-7*a*(2*H*)-yl)acrylate (4h)



Eluent: ethyl acetate/ petroleum ether (10:90 v/v).

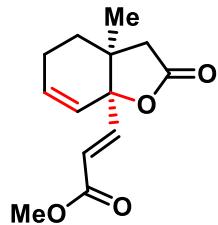
Appearance: colorless gummy.

Isolated yield: 79% (48.5 mg, 0.158 mmol)

^1H NMR (400 MHz, CDCl_3) δ 6.84 (d, J = 15.7 Hz, 1H), 6.07 (d, J = 15.7 Hz, 1H), 5.81 (dt, J = 10.0, 1.6 Hz, 1H), 5.35 (dd, J = 10.0, 2.6 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 2.62 (dd, J =

17.1, 1.9 Hz, 1H), 2.39 (d, J = 17.1 Hz, 1H), 2.32 (td, J = 9.9, 6.1, 5.2, 2.5 Hz, 1H), 2.02 (ddd, J = 14.5, 5.4, 1.3 Hz, 1H), 1.66 – 1.52 (m, 1H), 1.40 – 1.32 (m, 1H), 1.30 (d, J = 7.2 Hz, 3H), 1.20 – 1.11 (m, 2H), 1.08 (d, J = 7.0 Hz, 3H), 0.94 (dd, J = 6.7, 4.8 Hz, 6H); ^{13}C NMR (101 MHz, CDCl_3) δ 175.24, 166.12, 143.95, 136.40, 126.03, 122.26, 87.34, 60.98, 46.15, 44.28, 36.11, 35.05, 27.36, 25.74, 25.54, 24.48, 21.22, 14.41; HRMS (ESI): Calculated mass for $\text{C}_{18}\text{H}_{26}\text{NaO}_4$ [M+Na] $^+$: 329.1729; observed mass: 329.1725.

Methyl (E)-3-((3a*S*,7a*R*)-3a-methyl-2-oxo-3,3a,4,5-tetrahydrobenzofuran-7a(2H)-yl)acrylate (4i)



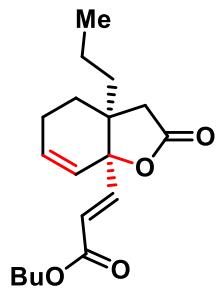
Eluent: ethyl acetate/ petroleum ether (10:90 v/v).

Appearance: colorless gummy.

Isolated yield: 62% (29.5 mg, 0.124 mmol)

^1H NMR (400 MHz, CDCl_3) δ 6.88 (d, J = 15.8 Hz, 1H), 6.11 (d, J = 15.8 Hz, 1H), 6.06 – 5.99 (m, 1H), 5.47 (dt, J = 10.1, 2.2 Hz, 1H), 3.75 (s, 3H), 2.64 (d, J = 16.9 Hz, 1H), 2.22 – 2.13 (m, 3H), 1.87 – 1.55 (m, 2H), 1.06 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 175.17, 166.46, 144.74, 131.53, 126.13, 121.93, 86.17, 52.07, 41.28, 39.96, 37.98, 33.44, 29.06, 26.27, 23.73, 22.15, 21.73; HRMS (ESI): Calculated mass for $\text{C}_{13}\text{H}_{16}\text{NaO}_4$ [M+Na] $^+$: 259.0946; observed mass: 259.0950.

Butyl (E)-3-((3a*S*,7a*R*)-2-oxo-3a-propyl-3,3a,4,5-tetrahydrobenzofuran-7a(2H)-yl)acrylate (4j)



Eluent: ethyl acetate/ petroleum ether (10:90 v/v).

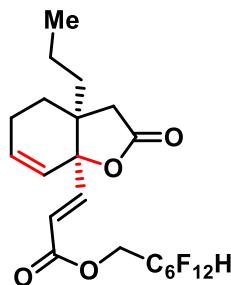
Appearance: colorless gummy.

Isolated yield: 78% (48 mg, 0.156 mmol)

^1H NMR (400 MHz, CDCl_3) δ 6.89 (d, J = 15.7 Hz, 1H), 6.10 (d, J = 15.7 Hz, 1H), 6.04 (dt, J = 10.0, 3.7 Hz, 1H), 5.47 (dt, J = 10.0, 2.2 Hz, 1H), 4.16 (t, J = 6.7 Hz, 2H), 2.50 (d, J = 17.1

Hz, 1H), 2.36 (d, J = 17.0 Hz, 1H), 2.15 (ddt, J = 5.6, 3.8, 2.0 Hz, 2H), 1.82 – 1.71 (m, 1H), 1.69 – 1.59 (m, 3H), 1.48 – 1.31 (m, 5H), 1.33 – 1.18 (m, 1H), 1.00 – 0.85 (m, 6H); ^{13}C NMR (101 MHz, CDCl_3) δ 175.40, 166.15, 144.71, 131.75, 126.18, 122.22, 86.52, 64.91, 44.57, 37.56, 37.50, 30.82, 26.24, 21.61, 19.36, 17.69, 14.84, 13.92; HRMS (ESI): Calculated mass for $\text{C}_{18}\text{H}_{27}\text{O}_4$ [$\text{M}+\text{H}]^+$: 307.1909; observed mass: 307.1912.

7-(1*I*-Fluoraneyl)-7,7,7,7,7,7,7,7,7-undecafluoro-7*I*15-hepta-2,4,6-triyn-1-yl (*E*)-3-((3a*S*,7a*R*)-2-oxo-3a-propyl-3,3a,4,5-tetrahydrobenzofuran-7a(2H)-yl)acrylate (4k)



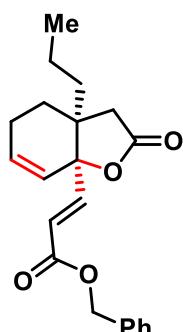
Eluent: ethyl acetate/ petroleum ether (12:88 v/v).

Appearance: colorless gummy.

Isolated yield: 60% (68 mg, 0.12 mmol)

^1H NMR (400 MHz, CDCl_3) δ 7.00 (d, J = 15.7 Hz, 1H), 6.17 (d, J = 15.7 Hz, 1H), 6.07 (ddd, J = 10.1, 4.5, 2.7 Hz, 2H), 5.45 (dt, J = 10.0, 2.2 Hz, 1H), 4.67 (td, J = 13.4, 2.1 Hz, 2H), 2.52 (d, J = 17.1 Hz, 1H), 2.36 (d, J = 17.1 Hz, 1H), 2.17 (ddd, J = 9.0, 4.0, 1.9 Hz, 2H), 1.78 (dt, J = 14.4, 5.2 Hz, 1H), 1.68 – 1.56 (m, 1H), 1.42 – 1.14 (m, 4H), 0.93 – 0.83 (m, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 175.05, 164.17, 147.59, 132.15, 125.75, 119.98, 110.30, 108.08, 107.77, 105.23, 86.34, 60.25, 59.98, 59.71, 44.61, 37.75, 37.28, 26.23, 21.58, 17.60, 14.69; ^{19}F NMR (376 MHz, CDCl_3) δ -119.37, -119.42, -119.46, -122.10, -122.14, -122.19, -122.23, -122.28, -123.32, -123.37, -123.42, -123.52, -129.45, -129.45, -129.51, -137.07, -137.07; HRMS (ESI): Calculated mass for $\text{C}_{21}\text{H}_{21}\text{F}_{12}\text{O}_4$ [$\text{M}+\text{H}]^+$: 565.1248; observed mass: 565.1250.

Benzyl (*E*)-3-((3a*S*,7a*R*)-2-oxo-3a-propyl-3,3a,4,5-tetrahydrobenzofuran-7a(2H)-yl)acrylate (4l)



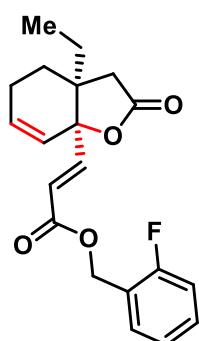
Eluent: ethyl acetate/ petroleum ether (15:85 v/v).

Appearance: colorless gummy.

Isolated yield: 67% (45.5 mg, 0.134 mmol)

¹H NMR (400 MHz, CDCl₃) δ 7.51 – 7.30 (m, 5H), 6.95 (d, *J* = 15.7 Hz, 1H), 6.15 (d, *J* = 15.7 Hz, 1H), 6.03 (dt, *J* = 10.0, 3.7 Hz, 1H), 5.56 – 5.41 (m, 1H), 5.21 (s, 2H), 2.50 (d, *J* = 17.0 Hz, 1H), 2.36 (d, *J* = 17.0 Hz, 1H), 2.15 (ddd, *J* = 5.8, 4.5, 2.3 Hz, 2H), 1.75 (dt, *J* = 14.3, 5.3 Hz, 1H), 1.62 (ddd, *J* = 14.2, 7.8, 6.3 Hz, 1H), 1.43 – 1.29 (m, 2H), 1.27 – 1.15 (m, 2H), 1.03 – 0.86 (m, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 175.30, 165.81, 145.40, 135.87, 131.80, 128.81, 128.55, 128.45, 126.10, 121.90, 86.49, 66.78, 44.59, 37.51, 37.49, 26.20, 21.59, 17.67, 14.84; **HRMS (ESI)**: Calculated mass for C₂₁H₂₅O₄ [M+H]⁺: 341.1753; observed mass: 341.1760.

2-Fluorobenzyl (*E*)-3-((3a*S*,7a*R*)-3a-ethyl-2-oxo-3,3a,4,5-tetrahydrobenzofuran-7a(2H)-yl)acrylate (4m)



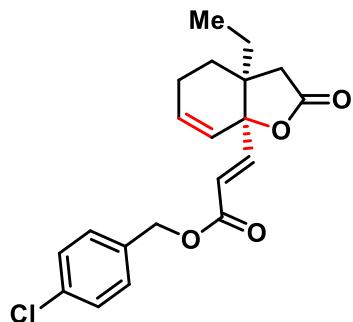
Eluent: ethyl acetate/ petroleum ether (15:85 v/v).

Appearance: colorless gummy.

Isolated yield: 69% (47.5 mg, 0.138 mmol)

¹H NMR (400 MHz, CDCl₃) δ 7.40 (td, *J* = 7.5, 1.9 Hz, 1H), 7.33 (tdd, *J* = 7.5, 5.3, 1.8 Hz, 1H), 7.15 (td, *J* = 7.5, 1.2 Hz, 1H), 7.08 (ddd, *J* = 9.7, 8.3, 1.2 Hz, 1H), 6.94 (d, *J* = 15.7 Hz, 1H), 6.14 (d, *J* = 15.7 Hz, 1H), 6.03 (dt, *J* = 10.0, 3.7 Hz, 1H), 5.46 (dt, *J* = 10.0, 2.1 Hz, 1H), 5.26 (d, *J* = 1.2 Hz, 2H), 2.50 (dd, *J* = 17.1, 0.8 Hz, 1H), 2.34 (d, *J* = 17.1 Hz, 1H), 2.16 (tt, *J* = 5.6, 2.1 Hz, 2H), 1.77 (dt, *J* = 14.4, 5.2 Hz, 1H), 1.66 – 1.54 (m, 1H), 1.54 – 1.34 (m, 2H), 0.88 (t, *J* = 7.5 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 175.22, 165.67, 162.17, 159.97, 145.53, 131.71, 130.87, 130.83, 130.59, 130.51, 126.19, 124.42, 124.38, 123.12, 122.98, 121.70, 115.83, 115.62, 86.55, 60.72, 60.67, 44.77, 36.73, 27.91, 25.55, 21.54, 8.62; **¹⁹F NMR** (376 MHz, CDCl₃) δ -117.90; **HRMS (ESI)**: Calculated mass for C₂₀H₂₁FNaO₄ [M+Na]⁺: 367.1322; observed mass: 367.1325.

4-Chlorobenzyl (*E*)-3-((3a*S*,7a*R*)-3a-ethyl-2-oxo-3,3a,4,5-tetrahydrobenzofuran-7a(2H)-yl)acrylate (4n)



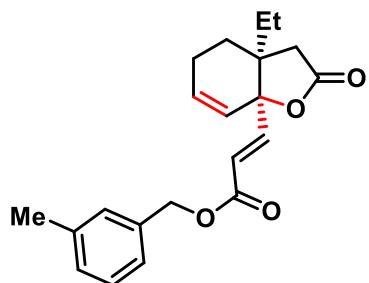
Eluent: ethyl acetate/ petroleum ether (15:85 v/v).

Appearance: colorless gummy.

Isolated yield: 66% (48 mg, 0.132 mmol)

¹H NMR (400 MHz, CDCl₃) δ 7.39 – 7.28 (m, 4H), 6.93 (d, *J* = 15.7 Hz, 1H), 6.14 (d, *J* = 15.7 Hz, 1H), 6.04 (d, *J* = 10.0 Hz, 1H), 5.46 (d, *J* = 10.0 Hz, 1H), 5.15 (s, 2H), 2.50 (dd, *J* = 17.1, 0.9 Hz, 1H), 2.34 (d, *J* = 17.1 Hz, 1H), 2.16 (ddd, *J* = 7.7, 4.2, 2.1 Hz, 2H), 1.77 (dt, *J* = 14.4, 5.1 Hz, 1H), 1.61 – 1.53 (m, 1H), 1.53 – 1.33 (m, 2H), 0.88 (t, *J* = 7.4 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 175.12, 165.68, 145.58, 134.50, 134.44, 131.73, 129.87, 129.02, 128.89, 126.24, 121.69, 86.52, 65.94, 44.77, 36.76, 27.96, 25.62, 21.57, 8.62; **HRMS (ESI)**: Calculated mass for C₂₀H₂₂ClO₄ [M+H]⁺: 361.1207; observed mass: 361.1210.

3-Methylbenzyl (*E*)-3-((3a*S*,7a*R*)-3a-ethyl-2-oxo-3,3a,4,5-tetrahydrobenzofuran-7a(2H)-yl)acrylate (4o)



Eluent: ethyl acetate/ petroleum ether (9:91 v/v).

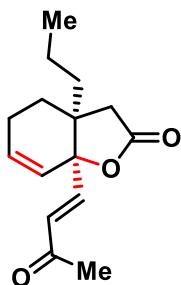
Appearance: colorless gummy.

Isolated yield: 68% (46.2 mg, 0.136 mmol)

¹H NMR (500 MHz, CDCl₃) δ 7.37 – 7.21 (m, 1H), 7.22 – 7.10 (m, 3H), 6.94 (d, *J* = 15.7 Hz, 1H), 6.15 (d, *J* = 15.7 Hz, 1H), 6.03 (dt, *J* = 10.0, 3.7 Hz, 1H), 5.46 (dt, *J* = 10.1, 2.2 Hz, 1H), 5.16 (s, 2H), 2.50 (d, *J* = 17.1 Hz, 1H), 2.37 (s, 3H), 2.34 (d, *J* = 10.8 Hz, 1H), 2.16 (ddt, *J* = 8.5, 6.0, 2.7 Hz, 2H), 1.76 (dt, *J* = 14.4, 5.2 Hz, 1H), 1.62 – 1.55 (m, 1H), 1.44 (dp, *J* = 29.2, 7.1 Hz, 2H), 0.88 (t, *J* = 7.5 Hz, 3H); **¹³C NMR** (126 MHz, CDCl₃) δ 175.25, 165.83, 145.26,

138.54, 135.77, 131.67, 129.31, 129.23, 128.72, 126.25, 125.55, 121.99, 86.58, 66.85, 44.78, 36.77, 27.91, 25.57, 21.55, 8.63; **HRMS (ESI)**: Calculated mass for $C_{21}H_{25}O_4$ $[M+H]^+$: 341.1753; observed mass: 341.1760.

(3a*S*,7a*R*)-7a-((*E*)-3-Oxobut-1-en-1-yl)-3a-propyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one (4p)



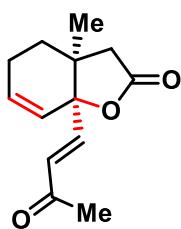
Eluent: ethyl acetate/ petroleum ether (20:80 v/v).

Appearance: colorless gummy.

Isolated yield: 67% (33.5 mg, 0.135 mmol)

1H NMR (400 MHz, $CDCl_3$) δ 6.74 (d, $J = 15.9$ Hz, 1H), 6.37 (d, $J = 15.9$ Hz, 1H), 6.04 (dt, $J = 10.0, 3.7$ Hz, 1H), 5.45 (dt, $J = 10.0, 2.2$ Hz, 1H), 2.52 (d, $J = 17.1$ Hz, 1H), 2.36 (d, $J = 17.1$ Hz, 1H), 2.29 (s, 3H), 2.16 (ddd, $J = 8.5, 4.3, 2.3$ Hz, 2H), 1.77 (dt, $J = 14.4, 5.2$ Hz, 1H), 1.68 – 1.55 (m, 1H), 1.38 – 1.30 (m, 4H), 0.96 – 0.87 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 197.46, 175.33, 142.96, 131.74, 129.80, 126.17, 86.56, 44.67, 37.70, 37.36, 28.87, 26.18, 21.59, 17.63, 14.85; **HRMS (ESI)**: Calculated mass for $C_{15}H_{21}O_3$ $[M+H]^+$: 249.1491; observed mass: 249.1495.

(3a*S*,7a*R*)-3a-Methyl-7a-((*E*)-3-oxobut-1-en-1-yl)-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one (4q)



Eluent: ethyl acetate/ petroleum ether (15:85 v/v).

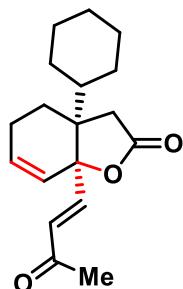
Appearance: colorless gummy.

Isolated yield: 65% (28.5 mg, 0.130 mmol)

1H NMR (400 MHz, $CDCl_3$) δ 6.72 (d, $J = 15.9$ Hz, 1H), 6.36 (d, $J = 15.9$ Hz, 1H), 6.04 (dt, $J = 10.0, 3.7$ Hz, 1H), 5.61 – 5.40 (m, 1H), 2.67 (d, $J = 16.9$ Hz, 1H), 2.29 (s, 3H), 2.23 – 2.11 (m, 3H), 1.78 – 1.64 (m, 2H), 1.07 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 197.53, 175.11,

142.82, 131.56, 130.21, 126.16, 86.24, 41.43, 39.91, 29.01, 28.65, 23.82, 21.74; **HRMS (ESI)**: Calculated mass for C₁₃H₁₇O₃ [M+H]⁺: 221.1178; observed mass: 221.1185.

(3a*S*,7a*R*)-3a-Cyclohexyl-7a-((*E*)-3-oxobut-1-en-1-yl)-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one (4r)



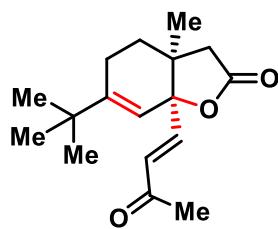
Eluent: ethyl acetate/ petroleum ether (10:90 v/v).

Appearance: colorless gummy.

Isolated yield: 68% (39.5 mg, 0.136 mmol)

¹H NMR (400 MHz, CDCl₃) δ 6.88 (d, *J* = 15.8 Hz, 1H), 6.42 (d, *J* = 15.9 Hz, 1H), 5.96 (ddd, *J* = 10.0, 4.6, 2.8 Hz, 1H), 5.36 (dt, *J* = 10.1, 2.1 Hz, 1H), 2.47 (d, *J* = 17.4 Hz, 1H), 2.34 (d, *J* = 17.4 Hz, 1H), 2.30 (s, 3H), 2.25 – 2.09 (m, 2H), 1.98 (ddd, *J* = 14.5, 5.8, 3.1 Hz, 1H), 1.79 (d, *J* = 11.0 Hz, 2H), 1.56 – 1.31 (m, 5H), 1.14 – 0.80 (m, 5H); **¹³C NMR** (101 MHz, CDCl₃) δ 197.50, 175.78, 142.30, 130.01, 129.46, 127.84, 87.31, 53.64, 47.23, 44.58, 34.37, 28.80, 28.72, 27.01, 26.83, 26.61, 26.39, 25.12, 21.95; **HRMS (ESI)**: Calculated mass for C₁₈H₂₅O₃ [M+H]⁺: 289.1804; observed mass: 289.1810.

(3a*S*,7a*S*)-6-(*tert*-Butyl)-3a-methyl-7a-((*E*)-3-oxobut-1-en-1-yl)-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one (4s)



Eluent: ethyl acetate/ petroleum ether (15:85 v/v).

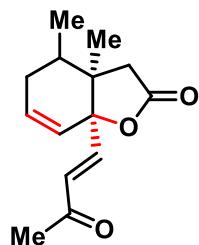
Appearance: colorless liquid.

Isolated yield: 35% (19.5 mg, 0.07 mmol)

¹H NMR (400 MHz, CDCl₃) δ 6.62 (d, *J* = 15.9 Hz, 1H), 6.32 (d, *J* = 15.9 Hz, 1H), 5.43 (s, 1H), 2.29 (s, 3H), 2.28 – 2.10 (m, 3H), 1.98 (dd, *J* = 15.2, 2.4 Hz, 1H), 1.78 (dd, *J* = 15.2, 4.5 Hz, 2H), 1.18 (s, 9H), 1.02 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 197.65, 175.60, 150.27,

142.25, 129.83, 121.69, 87.14, 63.70, 41.61, 39.33, 39.05, 35.83, 30.44, 28.79, 24.94; **HRMS (ESI)**: Calculated mass for C₁₇H₂₅O₃ [M+H]⁺: 277.1804; observed mass: 277.1810.

(3a*R*,7a*R*)-3a,4-Dimethyl-7a-((*E*)-3-oxobut-1-en-1-yl)-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one (4t)



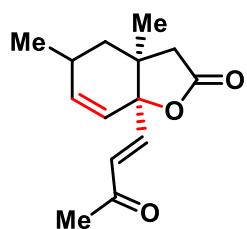
Eluent: ethyl acetate/ petroleum ether (8:92 v/v).

Appearance: colorless gummy.

Isolated yield: 57% (26.5 mg, 0.114 mmol)

¹H NMR (500 MHz, CDCl₃) δ 6.72 (d, *J* = 15.9 Hz, 1H), 6.37 (d, *J* = 15.9 Hz, 1H), 5.96 (ddd, *J* = 10.1, 5.1, 1.9 Hz, 1H), 5.43 (dt, *J* = 10.2, 2.2 Hz, 1H), 2.62 (d, *J* = 16.8 Hz, 1H), 2.28 (s, 3H), 2.26 – 2.19 (m, 1H), 2.10 (d, *J* = 16.8 Hz, 1H), 1.97 – 1.83 (m, 2H), 1.07 (s, 3H), 0.96 (d, *J* = 6.1 Hz, 3H); **¹³C NMR** (126 MHz, CDCl₃) δ 197.63, 175.14, 142.52, 130.52, 130.21, 126.79, 87.56, 45.64, 36.48, 32.52, 30.76, 28.59, 21.92, 16.92; **HRMS (ESI)**: Calculated mass for C₁₄H₁₉O₃ [M+H]⁺: 235.1334; observed mass: 235.1339.

(3a*S*,7a*R*)-3a,5-Dimethyl-7a-((*E*)-3-oxobut-1-en-1-yl)-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one (4u)



Eluent: ethyl acetate/ petroleum ether (10:90 v/v).

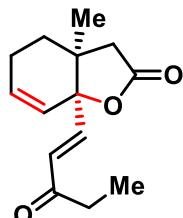
Appearance: colorless gummy.

Isolated yield: 49% (23 mg, 0.098 mmol)

¹H NMR (400 MHz, CDCl₃) δ 6.71 (d, *J* = 15.9 Hz, 1H), 6.35 (d, *J* = 15.9 Hz, 1H), 5.91 – 5.80 (m, 1H), 5.41 (dd, *J* = 10.1, 2.7 Hz, 1H), 2.77 (d, *J* = 16.9 Hz, 1H), 2.43 – 2.33 (m, 1H), 2.30 (s, 3H), 2.13 (d, *J* = 16.8 Hz, 1H), 1.84 (ddd, *J* = 14.5, 5.5, 1.3 Hz, 1H), 1.36 – 1.26 (m, 1H), 1.09 (d, *J* = 7.0 Hz, 3H), 1.04 (s, 3H); **¹³C NMR** (126 MHz, CDCl₃) δ 197.63, 175.11, 142.44,

136.94, 130.35, 125.73, 86.75, 42.24, 39.68, 37.72, 29.92, 28.61, 27.54, 24.80, 21.09; **HRMS (ESI)**: Calculated mass for C₁₄H₁₉O₃ [M+H]⁺: 235.1334; observed mass: 235.1330.

(3a*S*,7a*R*)-3a-Methyl-7a-((*E*)-3-oxopent-1-en-1-yl)-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one (4v)



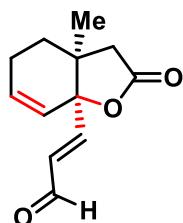
Eluent: ethyl acetate/ petroleum ether (16:84 v/v).

Appearance: colorless gummy.

Isolated yield: 66% (31 mg, 0.132 mmol)

¹H NMR (500 MHz, CDCl₃) δ 6.75 (d, *J* = 15.8 Hz, 1H), 6.40 (d, *J* = 15.8 Hz, 1H), 6.03 (dt, *J* = 10.1, 3.7 Hz, 1H), 5.47 (dt, *J* = 10.0, 2.3 Hz, 1H), 2.66 (d, *J* = 16.9 Hz, 1H), 2.59 (q, *J* = 7.3 Hz, 2H), 2.19 (dt, *J* = 14.2, 5.6 Hz, 3H), 1.80 – 1.58 (m, 2H), 1.12 (d, *J* = 7.3 Hz, 3H), 1.06 (s, 3H); **¹³C NMR** (126 MHz, CDCl₃) δ 200.18, 175.23, 141.63, 131.44, 129.00, 126.26, 86.37, 41.36, 39.98, 37.99, 35.24, 29.07, 23.80, 22.16, 21.75, 8.04; **HRMS (ESI)**: Calculated mass for C₁₄H₁₉O₃ [M+H]⁺: 235.1334; observed mass: 235.1340.

(*E*)-3-((3a*S*,7a*R*)-3a-Methyl-2-oxo-3,3a,4,5-tetrahydrobenzofuran-7a(2H)-yl)acrylaldehyde (4w)



Eluent: ethyl acetate/ petroleum ether (15:85 v/v).

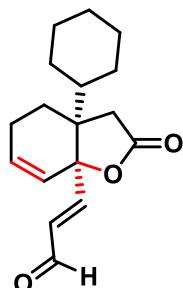
Appearance: colorless gummy.

Isolated yield: 47% (19.5 mg, 0.094 mmol) (d.r. = 3:1)

¹H NMR (400 MHz, CDCl₃) δ 9.62 (dd, *J* = 7.6, 1.0 Hz, 1H), 6.75 (dd, *J* = 15.8, 1.0 Hz, 1H), 6.35 (ddd, *J* = 15.8, 7.5, 1.2 Hz, 1H), 6.08 (dt, *J* = 10.1, 3.7 Hz, 1H), 5.52 (ddd, *J* = 10.1, 2.8, 1.6 Hz, 1H), 2.69 (d, *J* = 16.8 Hz, 1H), 2.28 – 2.13 (m, 3H), 1.82 – 1.73 (m, 2H), 1.10 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 192.45, 174.71, 152.40, 132.72, 131.94, 131.19, 126.58, 125.83, 86.07, 77.43, 41.57, 40.92, 40.81, 39.83, 38.99, 31.79, 29.91, 29.71, 29.03, 27.09,

23.89, 22.69, 21.80, 21.75, 14.30; **HRMS (ESI)**: Calculated mass for C₁₂H₁₅O₃ [M+H]⁺: 207.1021; observed mass: 207.1025.

(E)-3-((3a*S*,7a*R*)-3a-Cyclohexyl-2-oxo-3,3a,4,5-tetrahydrobenzofuran-7a(2H)-yl)acrylaldehyde (4x)



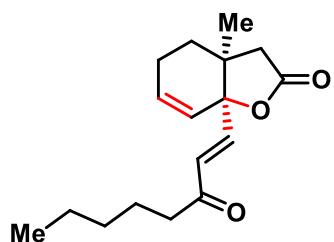
Eluent: ethyl acetate/ petroleum ether (15:85 v/v).

Appearance: colorless gummy.

Isolated yield: 40% (22 mg, 0.08 mmol)

¹H NMR (400 MHz, CDCl₃) δ 9.63 (d, *J* = 7.6 Hz, 1H), 6.90 (d, *J* = 15.8 Hz, 1H), 6.41 (dd, *J* = 15.8, 7.6 Hz, 1H), 6.05 – 5.94 (m, 1H), 5.47 – 5.33 (m, 1H), 2.49 (d, *J* = 17.4 Hz, 1H), 2.41 – 2.27 (m, 3H), 2.03 (ddd, *J* = 15.2, 5.8, 3.2 Hz, 2H), 1.81 (d, *J* = 11.4 Hz, 4H), 1.15 – 0.94 (m, 7H); **¹³C NMR** (126 MHz, CDCl₃) δ 192.58, 151.98, 132.06, 130.36, 127.45, 87.19, 47.40, 44.65, 34.10, 32.15, 29.92, 29.88, 29.58, 28.70, 26.93, 26.81, 26.54, 26.32, 25.18, 22.91, 21.91, 14.34; **HRMS (ESI)**: Calculated mass for C₁₇H₂₂NaO₃ [M+Na]⁺: 297.1467; observed mass: 297.1470.

(3a*S*,7a*R*)-3a-Methyl-7a-((*E*)-3-oxooct-1-en-1-yl)-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one (4y)



Eluent: ethyl acetate/ petroleum ether (15:85 v/v).

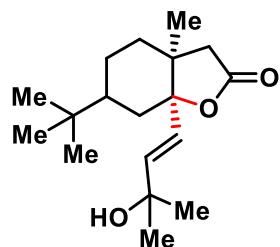
Appearance: colorless gummy.

Isolated yield: 64% (35.5 mg, 0.128 mmol) (d.r. = 10:1)

¹H NMR (400 MHz, CDCl₃) δ 6.73 (d, *J* = 15.8 Hz, 1H), 6.39 (d, *J* = 15.8 Hz, 1H), 6.03 (dt, *J* = 10.1, 3.7 Hz, 1H), 5.47 (dt, *J* = 10.1, 2.2 Hz, 1H), 2.66 (d, *J* = 16.9 Hz, 1H), 2.61 – 2.50 (m,

2H), 2.24 – 2.08 (m, 3H), 1.76 – 1.64 (m, 2H), 1.30 (ddd, J = 7.3, 5.5, 3.5 Hz, 6H), 1.06 (s, 3H), 0.99 – 0.83 (m, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 199.95, 175.19, 141.72, 131.42, 129.29, 126.30, 86.38, 42.03, 41.37, 40.00, 31.60, 29.10, 23.88, 23.80, 22.65, 21.77, 14.12; HRMS (ESI): Calculated mass for $\text{C}_{17}\text{H}_{25}\text{O}_3$ $[\text{M}+\text{H}]^+$: 277.1804; observed mass: 277.1807.

(3a*S*,7a*S*)-6-(*tert*-Butyl)-7a-((*E*)-3-hydroxy-3-methylbut-1-en-1-yl)-3a-methyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one (4z)



Eluent: ethyl acetate/ petroleum ether (15:85 v/v).

Appearance: colorless gummy.

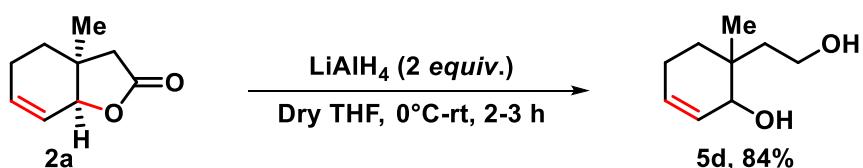
Isolated yield: 55% (32.2 mg, 0.110 mmol) (d.r. = 3:1)

^1H NMR (400 MHz, CDCl_3) δ 6.02 (d, J = 15.6 Hz, 1H), 5.83 (d, J = 15.7 Hz, 1H), 2.84 (d, J = 17.1 Hz, 1H), 2.13 – 1.91 (m, 2H), 1.77 – 1.58 (m, 6H), 1.33 (dd, J = 8.1, 1.9 Hz, 6H), 0.94 (s, 3H), 0.86 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 176.18, 142.87, 138.22, 122.73, 120.51, 89.18, 71.09, 47.97, 44.54, 41.36, 40.49, 39.17, 38.02, 35.61, 33.40, 32.58, 32.45, 30.40, 30.29, 30.04, 27.63, 27.61, 27.50, 25.83, 24.26, 23.38, 22.60; HRMS (ESI): Calculated mass for $\text{C}_{18}\text{H}_{31}\text{O}_3$ $[\text{M}+\text{H}]^+$: 295.2273; observed mass: 295.2276.

Procedure for the Hydrogenation of Unsaturated Bicyclic Lactones:

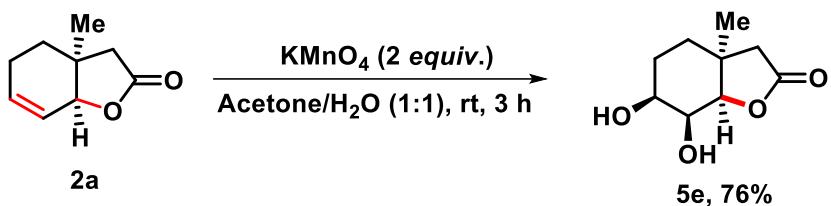
In an oven-dried round bottom flask was charged with magnetic stir-bar, corresponding unsaturated bicyclic lactone (1.0 equiv.), Pd/C (10 mol%), in MeOH and then H₂ balloon was purged through the reaction. The reaction mixture was stirred for 2-3 h at room temperature. Upon completion the mixture was diluted with EtOAc and filtered through a celite pad. The filtrate was evaporated under reduced pressure and dried under high vacuum yielding saturated lactones in almost quantitative yield. The resulting saturated lactone was characterized by NMR and HRMS analysis.

Procedure for the Reduction of Unsaturated Bicyclic Lactone **2a with LiAlH₄:**



In an oven-dried screw capped reaction tube was charged with magnetic stir-bar, unsaturated bicyclic lactone **2a** (1.0 equiv.) and then dry THF (2 mL) was added. Then LiAlH₄ (2.0 equiv.) was added to it under ice cold condition and the reaction was stirred for 2 h at room temperature. Upon completion the reaction was quenched with NH₄Cl solution and then was diluted with EtOAc and filtered through a celite pad. The filtrate was evaporated under reduced pressure and the crude mixture was purified by column chromatography using silica (100-200 mesh size) and petroleum ether/ ethyl acetate as the eluent to yield diol product in 84% (**5c**).

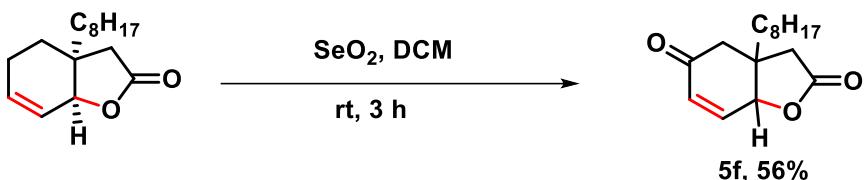
Procedure for the Dihydroxylation of Unsaturated Bicyclic Lactone **2a with KMnO₄:**



In an oven-dried screw capped reaction tube was charged with magnetic stir-bar, unsaturated bicyclic lactone **2a** (1.0 equiv.), KMnO₄ (2.0 equiv.) then acetone and water (2 mL, 1:1) was added to it and the reaction was stirred for 3 h at room temperature. Upon completion the solvent was removed under reduce pressure and diluted with EtOAc. The organic layer was washed with brine solution two times and dried on anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the crude mixture was purified by column

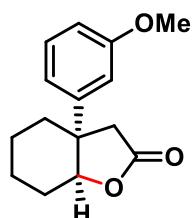
chromatography using silica (100-200 mesh size) and petroleum ether/ ethyl acetate as the eluent to yield dihydroxylated product in 76% (**5d**).

Procedure for the Allylic Oxidation of Unsaturated Bicyclic Lactone:



In an oven-dried screw capped reaction tube was charged with magnetic stir-bar, unsaturated bicyclic lactone **2g** (1.0 equiv.), SeO_2 (1.2 equiv.) then dichloromethane (2 mL) was added to it and the reaction was stirred for 3 h at room temperature. Upon completion the solvent was removed under reduced pressure and diluted with EtOAc. The organic layer was washed with brine solution two times and dried on anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the crude mixture was purified by column chromatography using silica (100-200 mesh size) and petroleum ether/ ethyl acetate as the eluent to yield allylic oxidation product in 56% (**5e**).

(3a*S*,7a*S*)-3a-(3-Methoxyphenyl)hexahydrobenzofuran-2(3H)-one (5a**)**



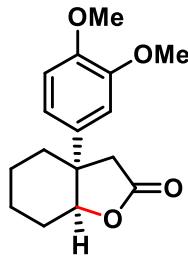
Eluent: ethyl acetate/ petroleum ether (13:87 v/v).

Appearance: colorless gummy.

Isolated yield: 87% (10.7 mg, 0.0435 mmol) (d.r. = 1:1)

$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.26 (ddd, $J = 23.5, 15.9, 8.0$ Hz, 2H), 7.03 – 6.67 (m, 6H), 4.89 (d, $J = 3.4$ Hz, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.46 (s, 1H), 2.86 – 2.60 (m, 2H), 2.50 (s, 2H), 2.31 – 2.01 (m, 4H), 1.95 – 1.65 (m, 4H), 1.68 – 1.50 (m, 4H), 1.42 (dq, $J = 20.7, 12.3, 10.6$ Hz, 4H); **$^{13}\text{C NMR}$** (126 MHz, CDCl_3) δ 175.90, 160.00, 159.77, 144.06, 129.98, 129.36, 119.33, 118.92, 113.69, 113.64, 111.38, 110.66, 81.92, 55.48, 55.33, 47.11, 45.75, 40.93, 36.15, 34.57, 26.44, 26.32, 22.53, 21.03, 19.82; **HRMS (ESI)**: Calculated mass for $\text{C}_{15}\text{H}_{19}\text{O}_3$ $[\text{M}+\text{H}]^+$: 247.1334; observed mass: 247.1340.

(3a*S*,7a*S*)-3a-(3,4-Dimethoxyphenyl)hexahydrobenzofuran-2(3H)-one (5b**)**



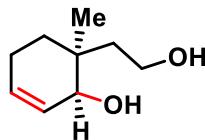
Eluent: ethyl acetate/ petroleum ether (18:82 v/v).

Appearance: colorless gummy.

Isolated yield: 85% (11.7 mg, 0.0425 mmol) (d.r. = 3:1)

¹H NMR (500 MHz, CDCl₃) δ 6.91 (d, *J* = 10.4 Hz, 1H), 6.87 – 6.70 (m, 2H), 4.94 – 4.84 (m, 1H), 3.95 – 3.80 (m, 6H), 3.63 (s, 1H), 2.72 (dd, *J* = 20.0, 9.8 Hz, 1H), 2.53 (s, 1H), 2.24 – 2.13 (m, 2H), 2.12 – 1.74 (m, 2H), 1.65 – 1.53 (m, 2H), 1.48 – 1.40 (m, 2H); **¹³C NMR** (126 MHz, CDCl₃) δ 175.64, 148.84, 147.35, 119.19, 118.83, 111.34, 111.11, 110.60, 82.15, 56.29, 56.16, 55.95, 47.32, 40.55, 36.42, 34.46, 32.15, 29.58, 26.34, 22.91, 22.51; **HRMS (ESI):** Calculated mass for C₁₆H₂₁O₄ [M+H]⁺: 277.1440; observed mass: 277.1446.

(1*S*,6*S*)-6-(2-Hydroxyethyl)-6-methylcyclohex-2-en-1-ol (5c)



Eluent: ethyl acetate/ petroleum ether (35:65 v/v).

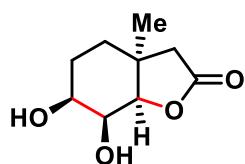
Appearance: colorless gummy.

Isolated yield: 84% (26.3 mg, 0.168 mmol)

¹H NMR (400 MHz, CDCl₃) δ 5.79 (dtd, *J* = 10.0, 3.5, 1.1 Hz, 1H), 5.74 – 5.65 (m, 1H), 3.93 – 3.76 (m, 2H), 3.71 (ddd, *J* = 10.8, 5.2, 4.3 Hz, 1H), 3.01 (s, 2H), 2.09 – 1.99 (m, 2H), 1.88 (ddd, *J* = 14.3, 9.6, 4.4 Hz, 1H), 1.57 (dt, *J* = 13.4, 7.3 Hz, 1H), 1.42 – 1.26 (m, 2H), 0.91 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 129.74, 129.71, 129.66, 128.45, 128.41, 128.36, 71.62, 71.59, 71.51, 71.47, 58.77, 39.95, 39.85, 36.10, 31.63, 29.88, 23.02, 22.98, 21.96, 21.82, 21.67;

HRMS (ESI): Calculated mass for C₉H₁₇O₂ [M+H]⁺: 157.1229; observed mass: 157.1235.

(3a*S*,6*S*,7*S*,7a*R*)-6,7-Dihydroxy-3a-methylhexahydrobenzofuran-2(3H)-one (5d)



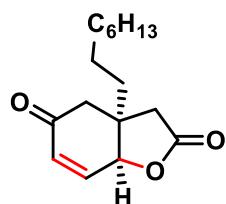
Eluent: ethyl acetate/ petroleum ether (35:65 v/v).

Appearance: white solid.

Isolated yield: 76% (28.3 mg, 0.152 mmol)

¹H NMR (400 MHz, CDCl₃) δ 4.24 (d, *J* = 5.6 Hz, 1H), 3.96 (dt, *J* = 8.0, 3.1 Hz, 1H), 3.85 (dd, *J* = 5.6, 3.0 Hz, 1H), 2.42 (d, *J* = 17.0 Hz, 1H), 2.24 (d, *J* = 17.0 Hz, 1H), 2.19 – 2.04 (m, 2H), 2.02 – 1.81 (m, 1H), 1.81 – 1.70 (m, 1H), 1.57 (tdd, *J* = 13.5, 7.5, 3.8 Hz, 2H), 1.26 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 176.45, 87.73, 71.60, 68.74, 42.21, 38.90, 29.43, 25.39, 24.77; **HRMS (ESI):** Calculated mass for C₉H₁₄NaO₄ [M+Na]⁺: 209.0790; observed mass: 209.0795.

(3a*S*,7*aS*)-3a-Octyl-3a,7a-dihydrobenzofuran-2,5(3H,4H)-dione (5e)



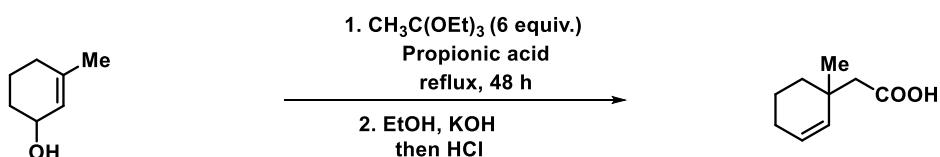
Eluent: ethyl acetate / petroleum ether (15:85 v/v)

Appearance: colorless gummy.

Isolated yield: 56% (15 mg, 0.056 mmol)

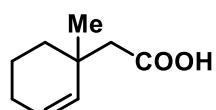
¹H NMR (500 MHz, CDCl₃) δ 6.89 (ddd, *J* = 9.2, 5.7, 2.4 Hz, 1H), 5.96 (dq, *J* = 10.1, 1.2 Hz, 1H), 5.72 (p, *J* = 6.1 Hz, 1H), 2.94 (d, *J* = 16.3 Hz, 1H), 2.63 (s, 1H), 2.46 (dddd, *J* = 19.0, 10.8, 5.3, 2.7 Hz, 1H), 2.40 – 2.33 (m, 1H), 2.24 (ddd, *J* = 13.7, 11.0, 5.4 Hz, 1H), 2.07 – 1.89 (m, 1H), 1.65 – 1.52 (m, 2H), 1.37 – 1.20 (m, 10H), 0.87 (t, *J* = 7.0 Hz, 3H); **¹³C NMR** (126 MHz, CDCl₃) δ 201.04, 168.82, 148.99, 128.24, 66.69, 66.42, 66.14, 47.25, 38.39, 34.00, 32.02, 30.71, 30.19, 29.92, 29.57, 29.41, 24.05, 23.05, 22.83, 14.28; **HRMS (ESI):** Calculated mass for C₁₆H₂₅O₃ [M+H]⁺: 265.1804; observed mass: 265.1810.

Procedure for the formation of alkenoic acid intermediate:



To a solution of 3-methylcyclohex-2-en-1-ol (2 mmol) in triethyl orthoacetate (6 *equiv.*) was added 0.5 mL propionic acid. The reaction mixture was heated to reflux and stirred for 2 days, then cooled to room temperature. Then it was diluted by 30 mL ethanol, and KOH (4 *equiv.*) was added. The mixture was stirred at room temperature for 8 hours. The solvent was removed under reduced pressure and 30 mL water was added. Then it was extracted with EtOAc (20 mL × 3). The organic layer was discarded and the aqueous layer was acidified with 12 M HCl and extracted with EtOAc (20 mL × 3). The combined organic layers were dried with anhydrous MgSO₄, concentrated under reduced pressure and purified by column chromatography on silica gel (petroleum ether/EtOH = 10 : 1) to give the alkenoic acid.

2-(1-methylcyclohex-2-en-1-yl)acetic acid (5f)



Eluent: ethyl acetate / petroleum ether (10:90 v/v)

Appearance: yellow

Isolated yield: 81% (25 mg)

¹H NMR (400 MHz, CDCl₃) δ 5.68 – 5.61 (m, 1H), 5.57 – 5.48 (m, 1H), 2.32 (d, *J* = 2.5 Hz, 2H), 1.96 (dd, *J* = 3.7, 1.8 Hz, 2H), 1.73 – 1.59 (m, 3H), 1.55 – 1.47 (m, 1H), 1.13 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 178.34, 134.94, 126.71, 46.63, 35.37, 34.21, 27.42, 25.10, 19.17.;

HRMS (ESI): Calculated mass for C₉H₁₅O₂ [M+H]⁺: 155.1072; observed mass: 155.1073.

9. DFT Calculation:

Computational Methods.

Density functional theory (DFT) calculations were performed with *Gaussian 16* rev. B.01.¹ Geometry optimizations were initially performed using the global-hybrid meta-NGA (nonseparable gradient approximation) MN15 functional² with the def2-SVP^{3,4} Karlsruhe-family basis set and the optimized structures further refined with a mix of larger basis set consisting of triple- ζ valence def2-TZVPPD (where ‘D’ indicates diffuse basis functions) for Pd^{5,6} atom and def2-SVP^{3,4} for all other atoms (BS1). Minima and transition structures on the potential energy surface (PES) were confirmed using harmonic frequency analysis at the same level of theory, showing respectively zero and one imaginary frequency. Where appropriate for cases where visual inspection of TS imaginary frequency is not obvious, intrinsic reaction coordinate (IRC) analyses^{7,8} were performed to confirm that the found TSs connect to the right reactants and products.

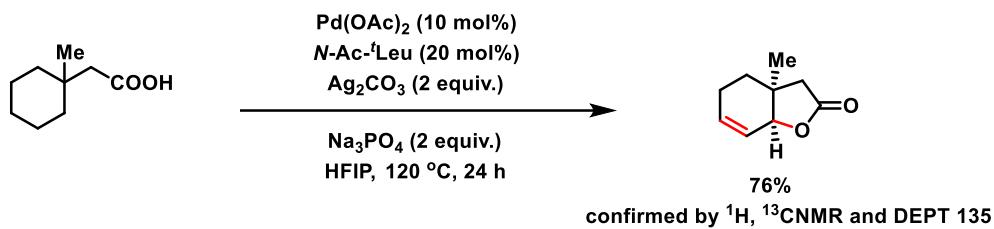
Single point (SP) corrections were performed using MN15 functional and def2-QZVP³ basis set for all atoms. The SMD implicit continuum solvation model⁹ was used to account for the effect of hexafluoroisopropanol (HFIP) solvent on the computed Gibbs energy profile. Since HFIP solvent is not available in the list of default/pre-defined solvents in the *Gaussian 16* software, it is herein parametrised using a set of *seven* parameters.⁹ These include 1) the static dielectric constant of the solvent at 25°C (*Eps* = 16.7);^{10–12} 2) dynamic (optical) dielectric constant – the square of the refractive index value of 1.275 at 20°C was used¹³ (*EpsInf* = 1.625625); 3) hydrogen bond acidity (*HBondAcidity* = 0.77)¹⁴ and 4) hydrogen bond basicity (*HBondBasicity* = 0.10)¹⁴, which are Abraham’s *A* and *B* values respectively; 5) the surface tension of the solvent at interface (*SurfaceTensionAtInterface* = 23.23)¹⁵ – this value is obtained from the conversion of the surface tension of HFIP at 16.14 mN/m at 25°C¹⁶ to cal mol⁻¹ Å⁻² used in the SMD model by the conversion factor of 1 dyne/cm = 1 mN/m = 1.43932 cal mol⁻¹ Å⁻² as outlined in the Truhlar’s Minnesota Solvent Descriptor Database¹⁷; 6) carbon aromaticity – the fraction of aromatic carbons (*CarbonAromaticity* = 0.00) and 7) electronegative halogenicity – the fraction of halogens (*Electronegative Halogenicity* = 0.60). These parameters were specified using the keyword “SCRF = (SMD, Solvent= Generic, Read)” in *Gaussian 16*.

Gibbs energies were evaluated at the reaction temperature of 393.15 K (120°C), using a quasi-RRHO treatment of vibrational entropies.^{18,19} Vibrational entropies of frequencies below 100

cm^{-1} were obtained according to a free rotor description, using a smooth damping function to interpolate between the two limiting descriptions. The free energies were further corrected using standard concentration of 1 mol/L, which were used in solvation calculations. Unless otherwise stated, the final SMD (dichloroethane)-MN15/def2-QZVP//MN15/BS1 Gibbs energies are used for discussion throughout. All Gibbs energy values in the text and figures are quoted in kcal mol^{-1} . All molecular structures and molecular orbitals were visualized using PyMOL software.²⁰

9.1. Model reaction

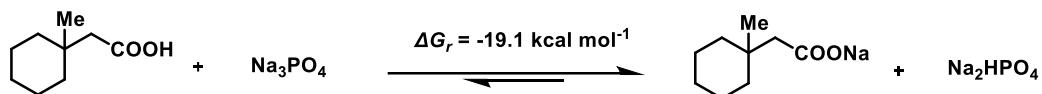
For computational modelling, we have chosen the following reaction (Scheme S1) for mechanistic studies.



Scheme S1. Model reaction used for computational mechanistic studies.

9.2. Actual substrate for the reaction

The acid substrate in the reaction will get deprotonated by sodium phosphate, so that the actual substrate involved in the transformation will be its corresponding sodium salt. We calculated the thermodynamics for this reaction and found that the formation of sodium salt of the acid is indeed favoured, by 19.1 kcal mol^{-1} (Scheme S2).



Scheme S2. Thermodynamics for the deprotonation of the acid substrate.

9.3. C–H activation transition states (TSs) – methylene vs methyl activation

The Gibbs energy profiles for the C–H activation of different H atoms are shown in Figure S2. In these transition states for the concerted metalation deprotonation (CMD) using the mono-protected amino acid (MPAA), N-acetyl *tert*-leucine, as an internal base, C–H activation can occur at either methylene carbon or methyl carbon. MPAA has been shown to lower the C–H

activation barrier over acetate ligands innate in $\text{Pd}(\text{OAc})_2$ by forming favourable [5,6]-palladacyclic ring^{21–26} conducive for C–H bond cleavage.

For the C–H activation at the methylene site, two different, prochiral H-atoms can be deprotonated, giving activated Pd–C bond either *cis* or *trans* to the methyl group. The pathway **INT1** → **TS1** → **INT2** via **TS1** forms **INT2** with Pd–C bond *cis* to the methyl group, whereas the pathway **INT1'** → **TS1'** → **INT2'** via **TS1'** forms **INT2'** with Pd–C bond *trans* to the methyl group. The pathway **INT1''** → **TS1''** → **INT2''** carries out C–H activation of the methyl C–H bond via **TS1''** (Figure S2).

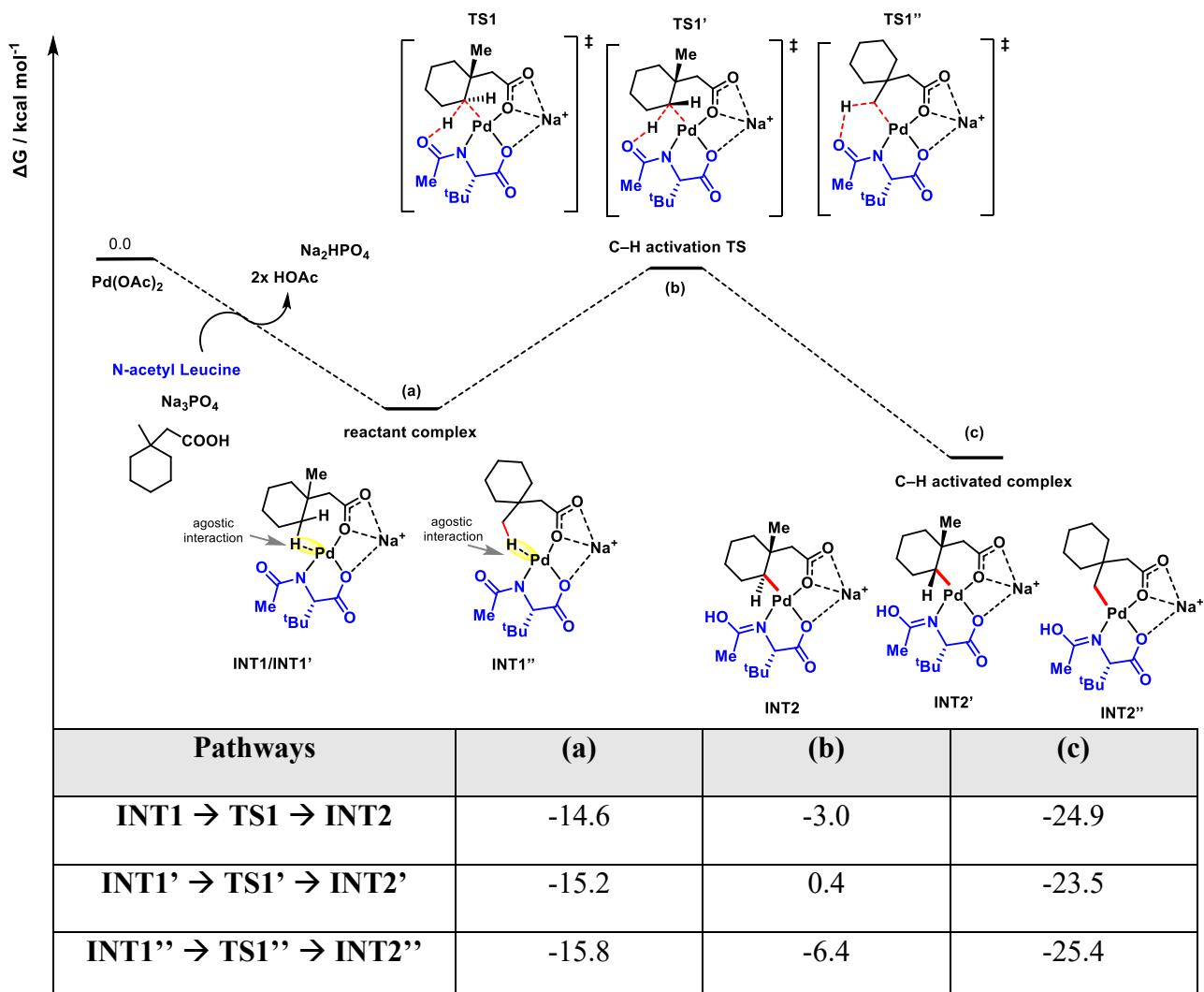
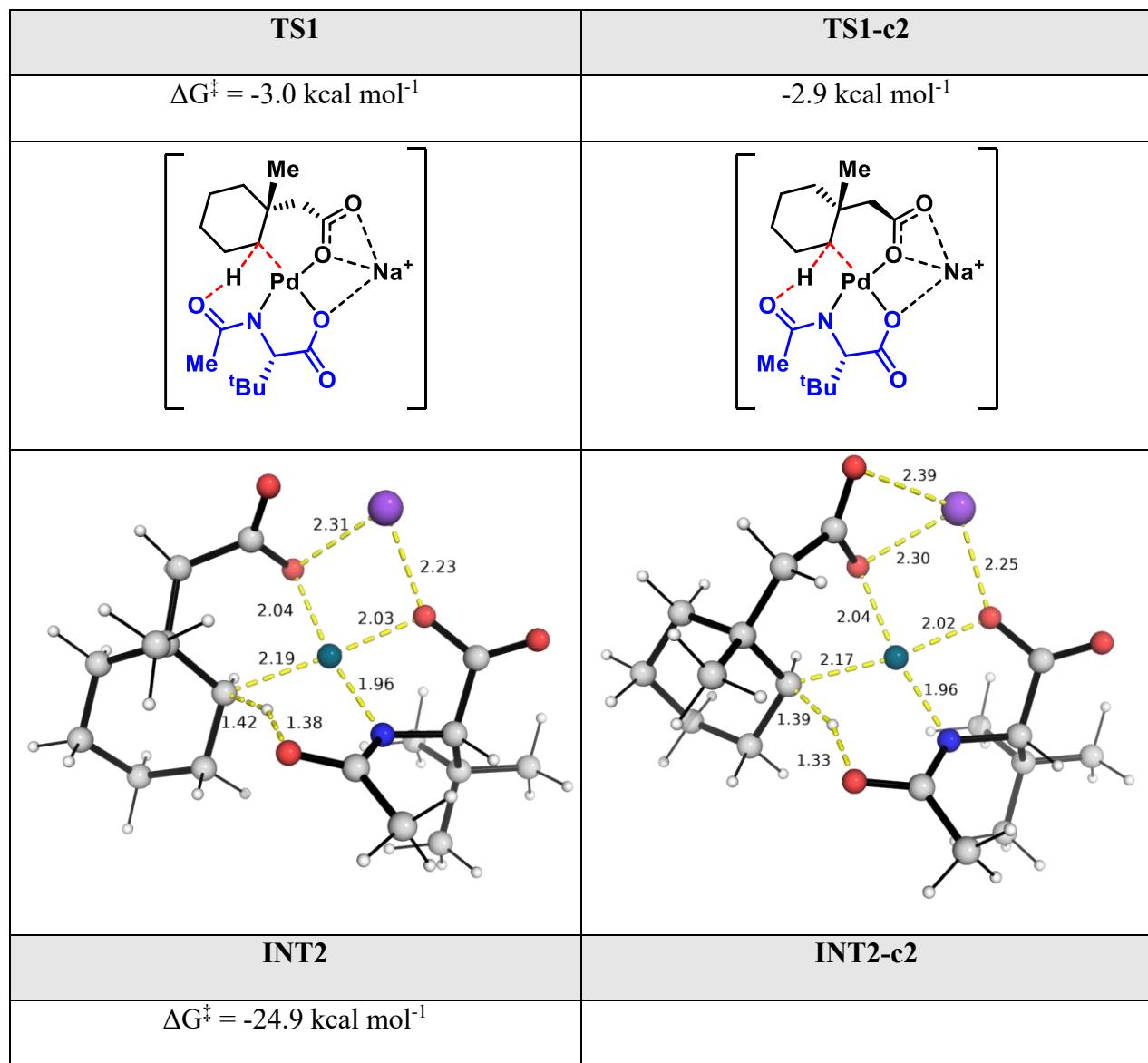
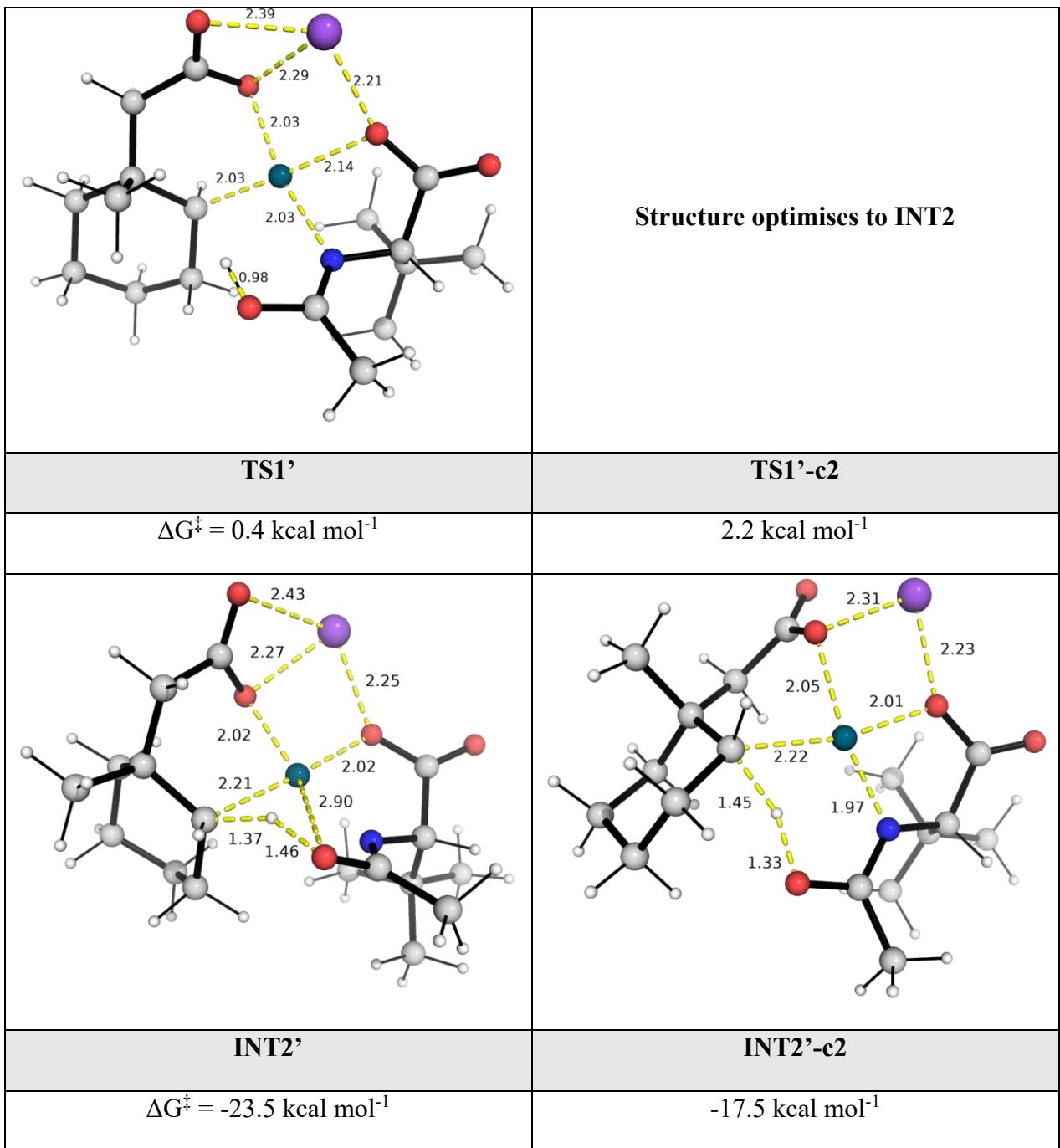


Figure S1. Gibbs energy profiles for the C–H activation step at different sites. Values are quoted in kcal mol^{-1} .

The DFT optimised structures for these TSs and their reactant and product states are shown in Figure S3. Conformational flexibility in how the acetate coordinates to the Pd-centre to form differently ring-puckered orientations (TSs with different conformations) have been considered. For methylene activation, **TS1** (at -3.0 kcal mol^{-1}) has a lower barrier than **TS1'**

(at 0.4 kcal mol⁻¹), by 3.4 kcal mol⁻¹. The activation of C(methyl)–H bond via **TS1''** has the lowest barrier, at -6.4 kcal mol⁻¹, which is lower than the C(methylene)–H activation, **TS1** by 3.4 kcal mol⁻¹. This suggests that the C(methyl)–H activation is kinetically favoured by about 78 times than C(methylene)–H at the reaction temperature of 120°C. However, the subsequent reductive elimination of **INT2''** occurs via **TS2''** at 19.9 kcal mol⁻¹ (*vide infra*), giving a barrier of 45.3 kcal mol⁻¹ from the activated complex **INT2''**. Thus, the reductive elimination step could not occur at the reaction condition and that the C(methyl)–H activation leads to catalytic off-cycle. It is likely that **INT2''** reverts back to the reactant complex, via **TS1''**, with a backwards barrier from **INT2''** to **INT1''** of 21.1 kcal mol⁻¹ than going forward with a barrier of 45.3 kcal mol⁻¹ to undergo reductive elimination.





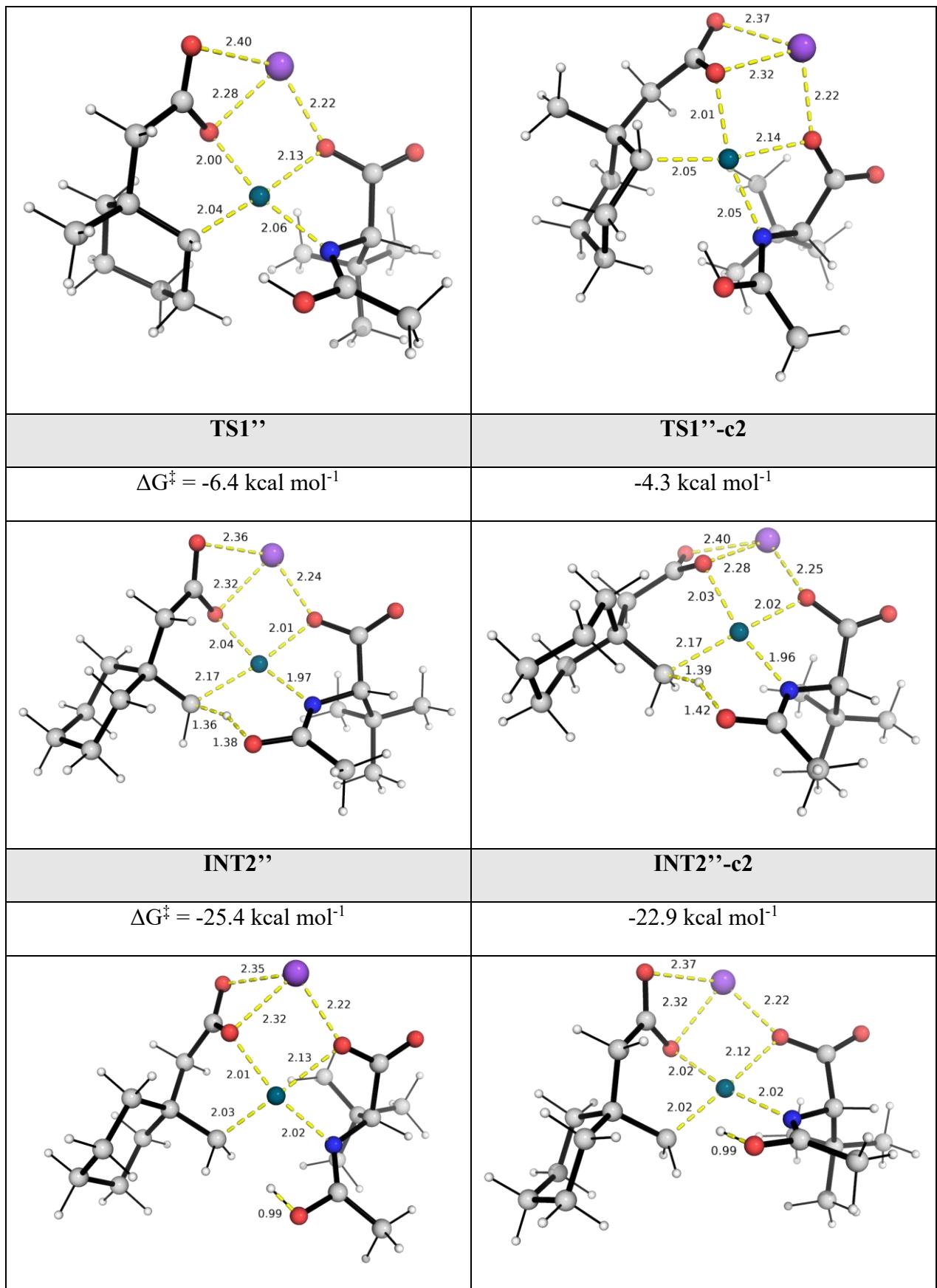
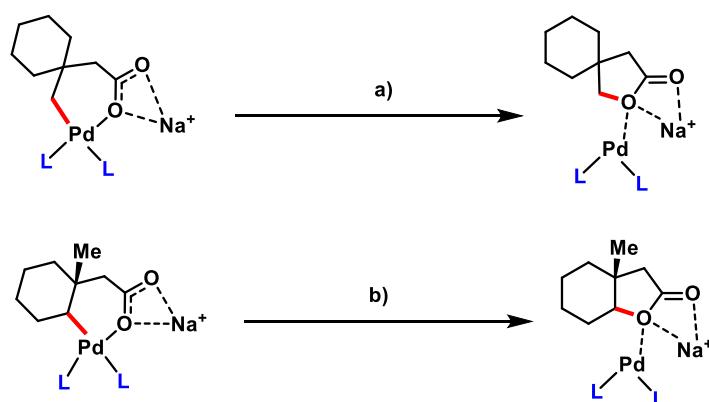


Figure S2. DFT optimised transition state structures for the C–H activation of substrate at different sites. Activation barriers are taken relative to the sum of starting materials.

9.4. Reductive C–O bond coupling in C–H activated complexes

For the C(methyl)–H activation pathway **INT1”** → **TS1”** → **INT2”**, no β-H is available on the quaternary carbon in the C–H activated intermediate **INT2”** for elimination. We considered the alternative C–O bond formation following reductive elimination in **INT2”** to give the spirocyclic lactone product (Scheme S3a)). For the C(methylene)–H activation pathway **INT1”** → **TS1”** → **INT2”**, in addition to β-H elimination that was considered, we also considered the alternative pathway of C–O reductive coupling to give the bicyclic lactone side product (Scheme S3b)).

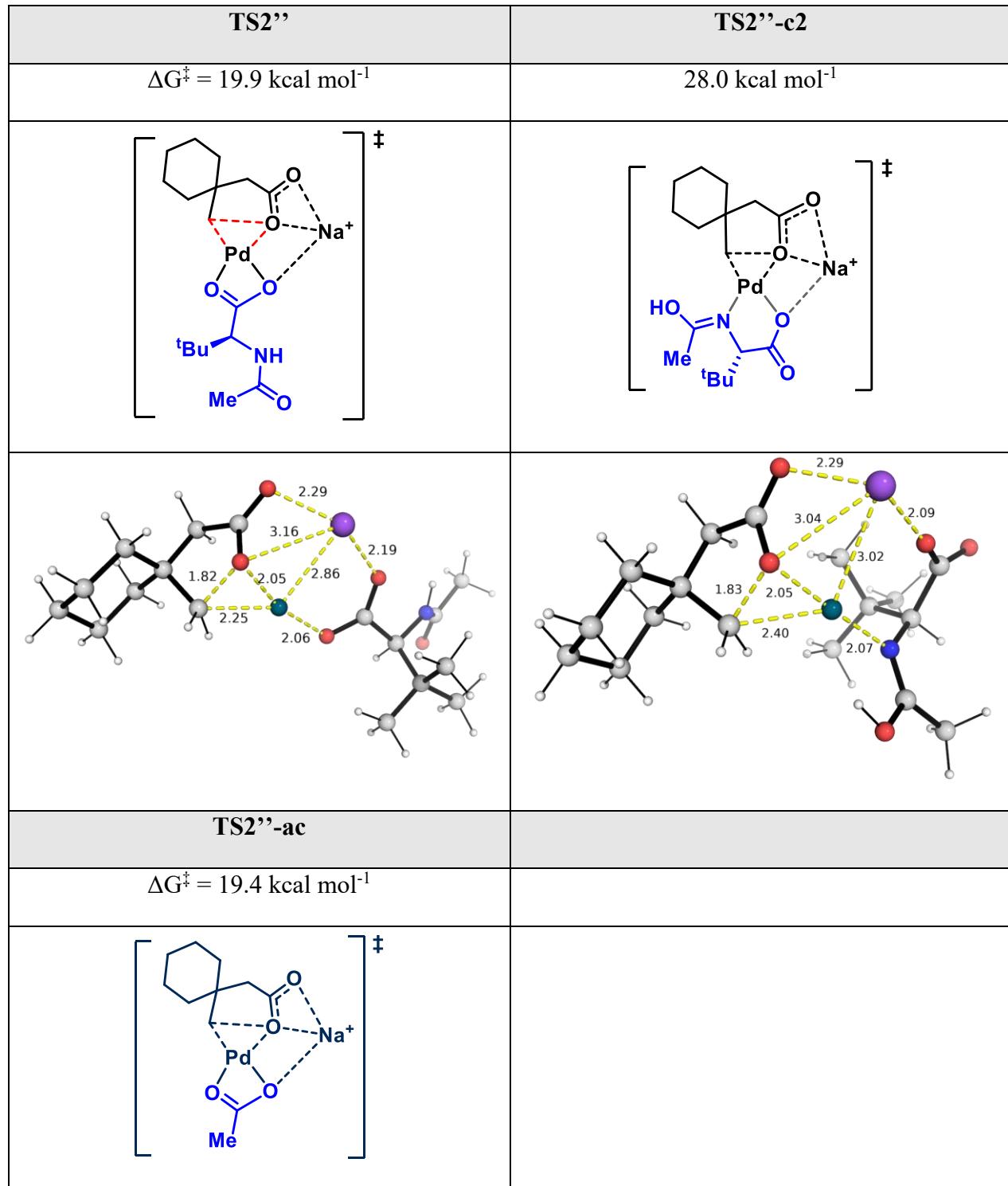


Scheme S3. Reductive C–O bond formation in a) C(methyl)–H activated complex and b) C(methylene)–H activated complex.

The optimized DFT TS structures with different ligands and conformations are shown in Figure S4 and the Gibbs energy profile for the reaction pathway following from C(methyl)–H activation is shown in Figure S5. We see that the reductive elimination with MPAA ligand coordinating in its imidic acid form (**TS2”-c2**, at 28.0 kcal mol⁻¹) has a much higher barrier than with MPAA coordinating via bidentate acetate moiety (**TS2”**, at 19.9 kcal mol⁻¹). We further note that the replacement of MPAA in **TS2”** by acetate ligand gives the C–O reductive coupling transition structure **TS2”-ac** at 19.4 kcal mol⁻¹, which is very similar to **TS2”**. This is likely because both MPAA and acetate ligands, in **TS2”** and **TS2”-ac** respectively, coordinate in a bidentate fashion (Figure S4), where both species have two Pd–O interactions; the Pd–O interactions are similar in both cases and are dominant over possible non-covalent interactions (NCIs) in the side chains of the MPAA ligand in **TS2”**.

From the Gibbs energy profile in Figure S5, we see that the activation barriers for the reductive C–O coupling is 44.8 kcal mol⁻¹ (from **INT2”** to **TS2”-ac**) and 45.3 kcal mol⁻¹ (from **INT2”** to **TS2”**), which are thermodynamically inaccessible at the reaction temperature of 120°C. On the other hand, the reaction from **INT2”** back to **INT1”** though **TS1”** has a barrier of 19.0

kcal mol^{-1} , which is much lower than the forward reaction from **INT2''** to **INT4''**. Thus, the C(methyl)-H activation step is reversible.



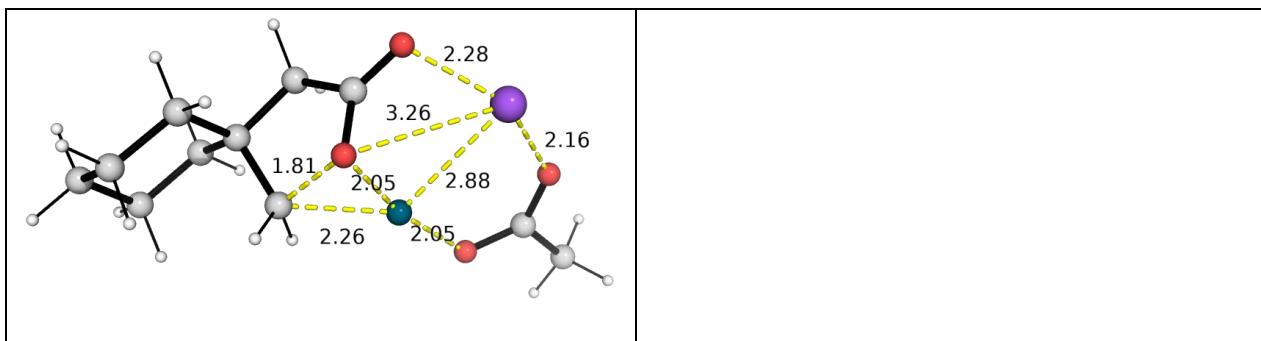


Figure S4. DFT optimised transition state structures for the reductive elimination to form C–O bond from the C(methyl)–H activated intermediate. Activation barriers are taken relative to the sum of starting materials.

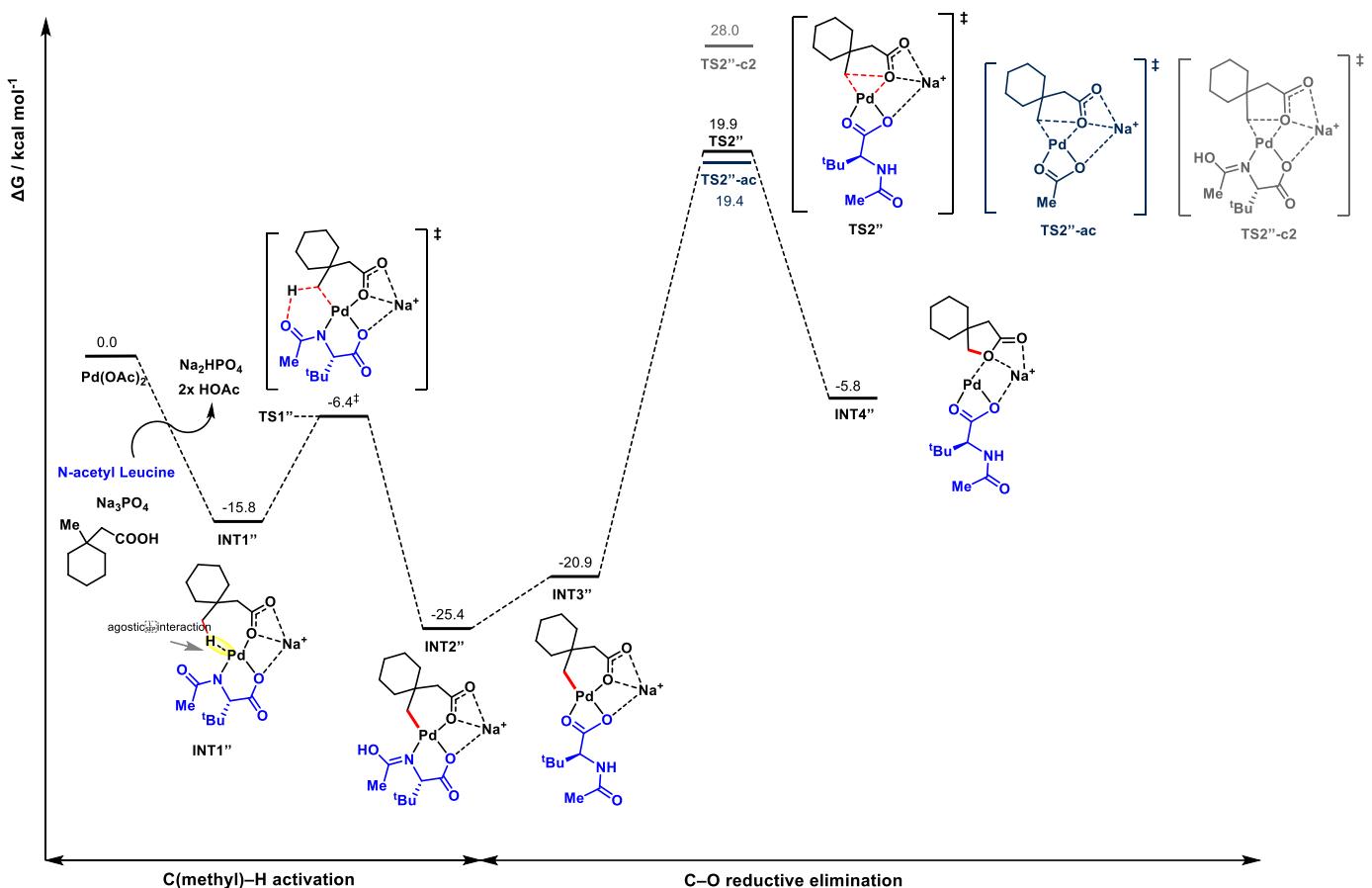


Figure S5. Gibbs energy profile for the reaction pathway following from C(methyl)–H activation.

To consider the C–O reductive coupling in the C(methylene)–H activated complex **INT2**, to give the bicyclic lactone side product (Scheme S3b)), we separately performed relaxed PES scans along the prospective C–O bond starting from optimised structure **INT2** and **INT3**. Using the highest energy structures on these PESs as initial guess, we successfully located the TSs for the C–O reductive elimination. The DFT optimised TS structures are shown in Figure S6 and the Gibbs energy profile for the reaction pathways following from C(methylene)–H

activation, comparing β -H elimination vs C–O reductive elimination, is shown in Figure S7. We note that the barriers for the C–O reductive elimination are similar to those identified C(methyl)–H activation pathway (**TS2''**, **TS2''-c2**, and **TS2''-ac**, Figure S4). In addition, these barriers (**TS3a** and **TS3b**) are much higher than the barrier for β -H elimination (**TS3**), by more than 35 kcal mol⁻¹, suggesting C–O reductive elimination is much energetically less favourable than β -H elimination.

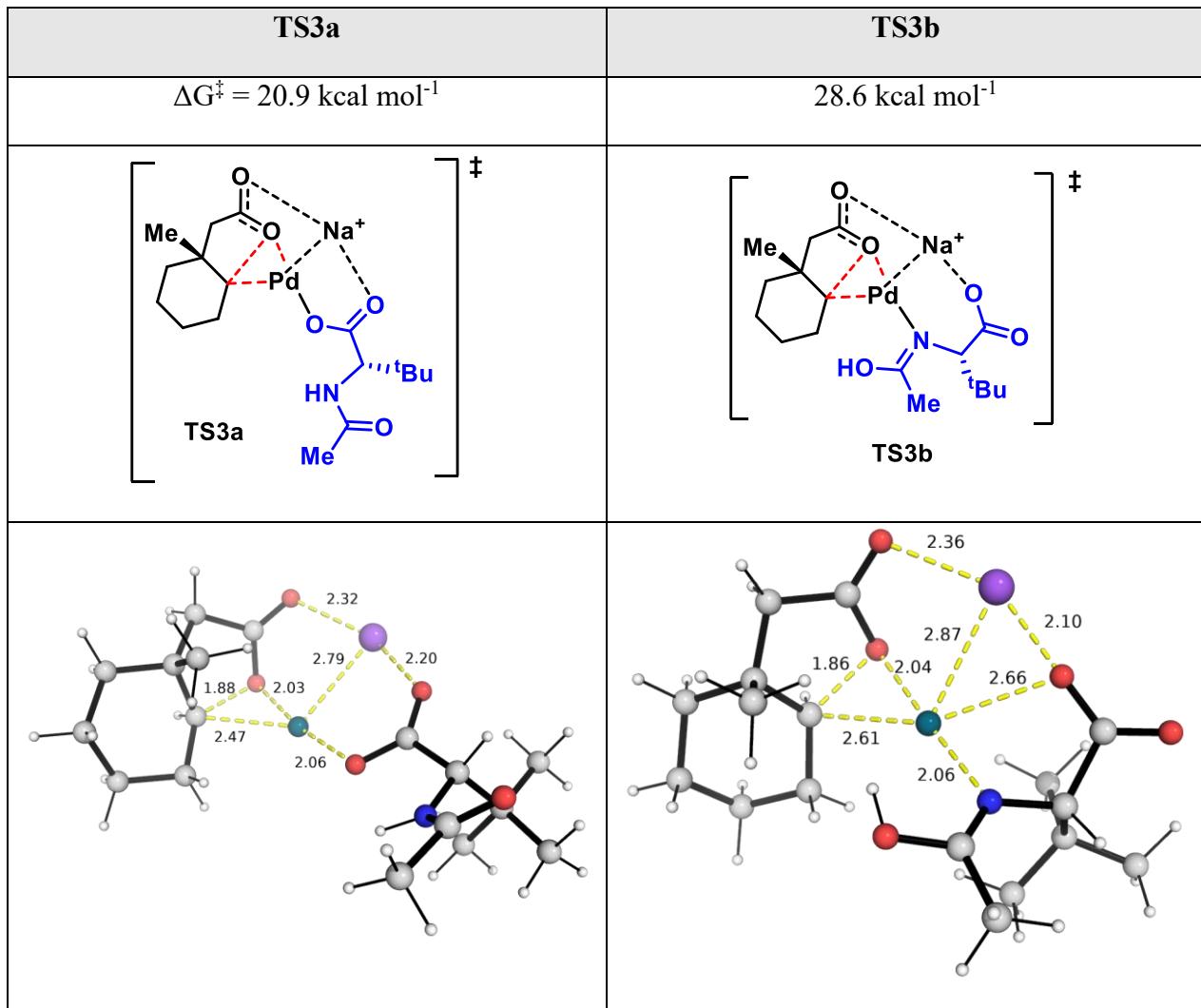


Figure S6. DFT optimised transition state structures for the reductive elimination to form C–O bond from the C(methylene)–H activated intermediate **INT2** and **INT3**. Activation barriers are taken relative to the sum of starting materials.

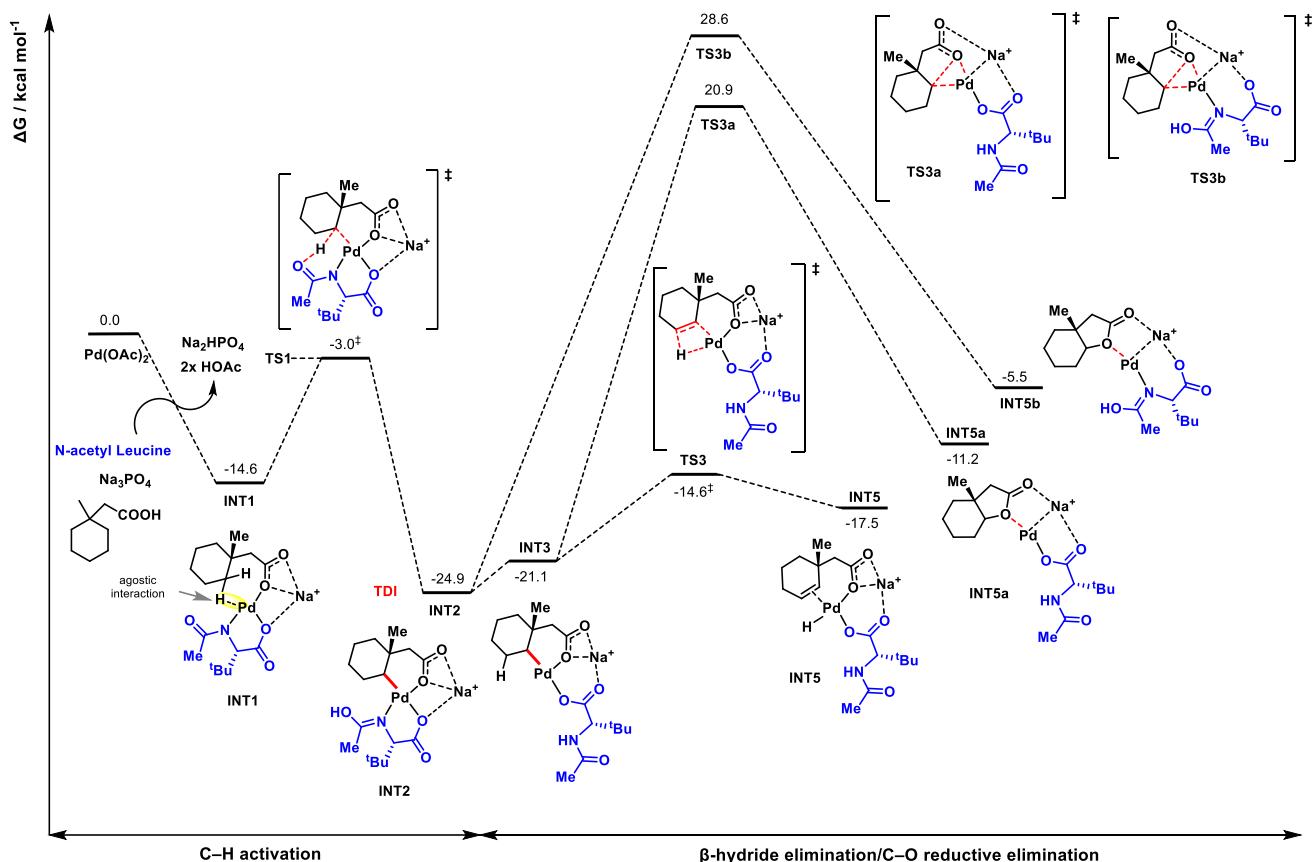


Figure S7. Gibbs energy profile for the reaction pathways (β -H elimination vs C–O reductive elimination) following from C(methylene)–H activation.

9.5. Rotational transition state for coordinating β -H to vacant Pd-site for elimination

From the C(methylene)–H activated **INT2**, a stable intermediate resulting from both **TS1** and **TS1-c2** (Figure S3), we found that the structure undergoes a rotation along the H(1)–C–C–Pd dihedral angle (**TS2**) to position one of the adjacent methylene H atoms to coordinate to the Pd-centre via agostic interaction. The DFT optimised structure **TS2** and the resulting intermediate **INT4** are shown in Figure S8.

TS2	INT4
$\Delta G^\ddagger = -16.8 \text{ kcal mol}^{-1}$	$-18.8 \text{ kcal mol}^{-1}$
<p>TS2</p>	<p>INT4</p>

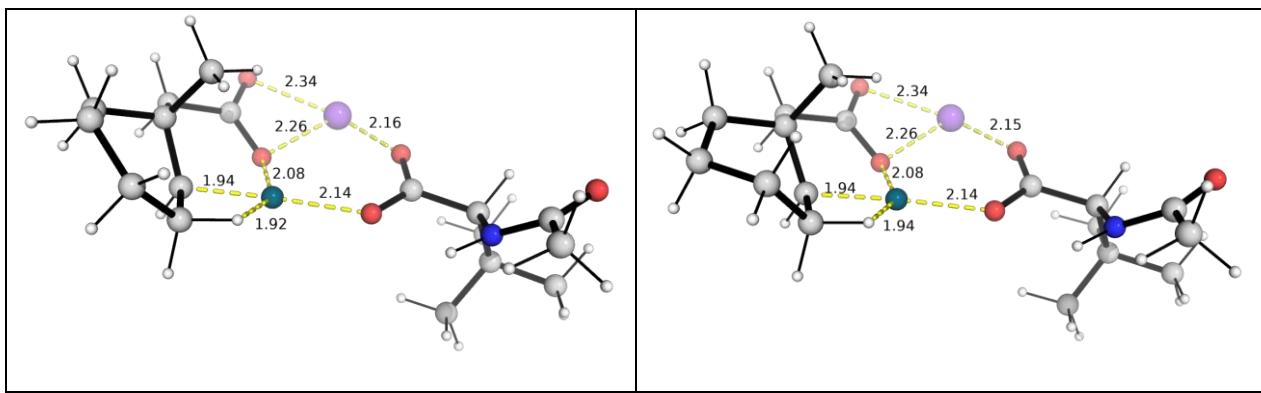


Figure S8. DFT optimised structures for the dihedral angle rotation in intermediate **INT2** to give **INT4** with CH–Pd agostic interaction. Activation barriers are taken relative to the sum of starting materials.

We note that, however, there is no such a rotational barrier to position the other H atom to coordinate to the Pd centre, as shown by the relaxed PES scan along the H(2)–C–C–Pd dihedral angle which shows no maximum point as the dihedral angle sweeps from negative value to positive value (Figure S9). This indicates that may not be a rotational barrier to bring the H(2) atom to coordinate to Pd-centre to give CH–Pd agostic interaction.

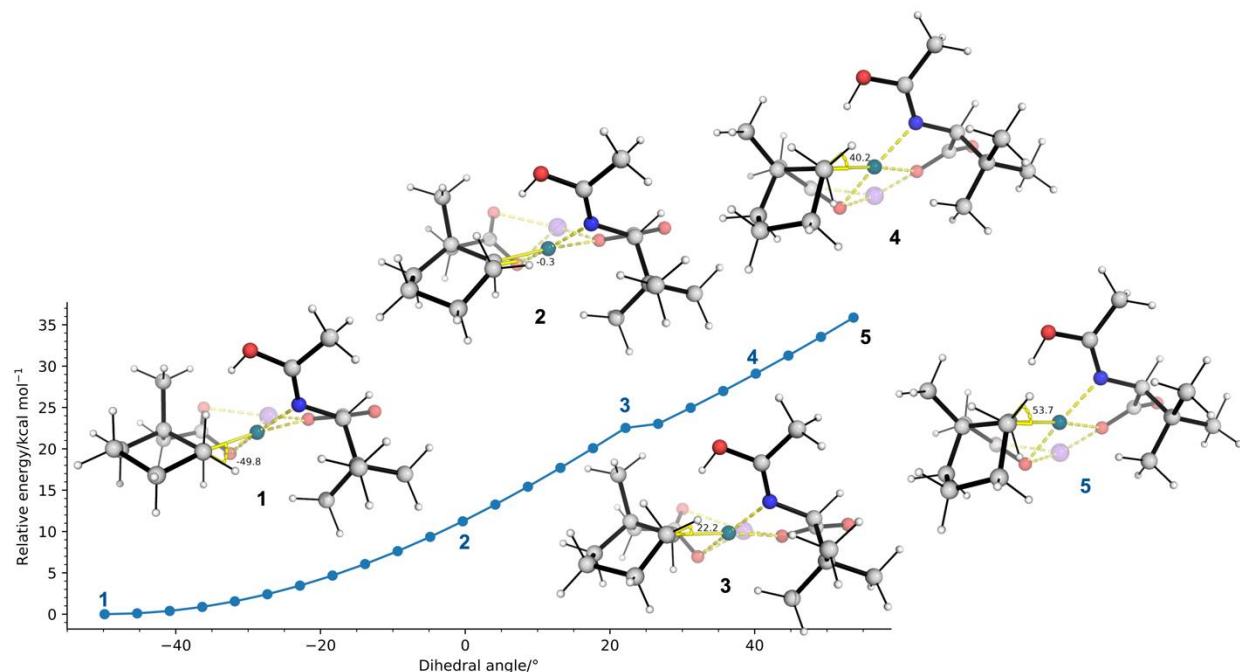


Figure S9. Relaxed PES scan in the gas-phase along H(2)–C–C–Pd dihedral angle. Gas-phase energies are used without further corrections.

9.6. Stereo determining migratory insertion TSs

Figure S10 shows the DFT optimised TS structures for the migratory insertion of the cyclohexene olefin C=C double bond into the Pd–O bond. This step is stereodetermining as the formation of new C–O bond resulting from the attack of O-atom from either side of the C=C

bond generates different stereochemistry at the fused carbons. The reaction pathway proceeding via transition state **TS4**, at 3.8 kcal mol⁻¹, gives the product with observed stereochemistry at the fused ring (*cis*-isomer). On the other hand, the reaction pathway proceeding via transition state **TS4'**, at 12.6 kcal mol⁻¹, would give the *trans*-isomer. The barrier difference of 8.8 kcal mol⁻¹ suggests that **TS4** will be favoured kinetically by around 78,000 times, indicating that the *cis*-isomer will be formed predominantly, consistent with experimental observation of stereochemistry of the lactone product at the fused rings.

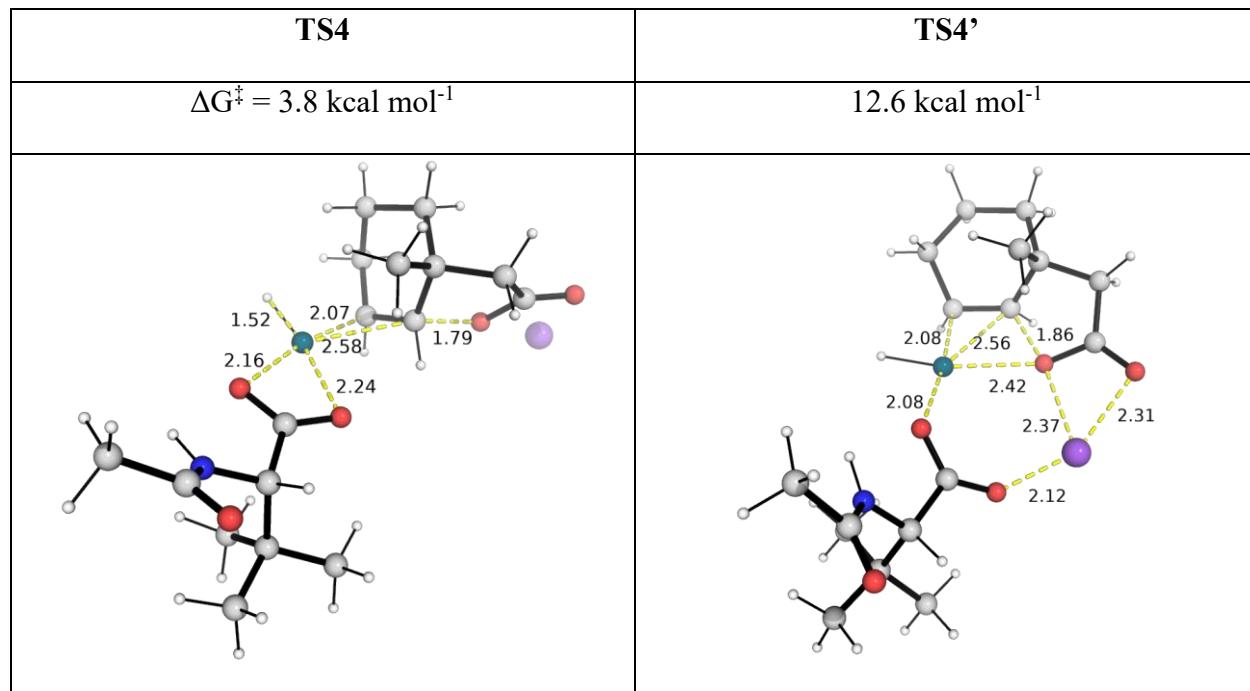


Figure S10. DFT optimised transition state structures for the stereodetermining migratory insertion step. Activation barriers are taken relative to the sum of starting materials.

9.7. β -H elimination TSs

β -H elimination occurs firstly after the C–H activation step to give the cyclohexene and secondly after the migratory insertion of cyclohexene C=C bond into Pd–O bond to regenerate the cyclohexene C=C bond, as the lactone ring closes. The DFT optimised TS structures for these steps are given in Figure S11.



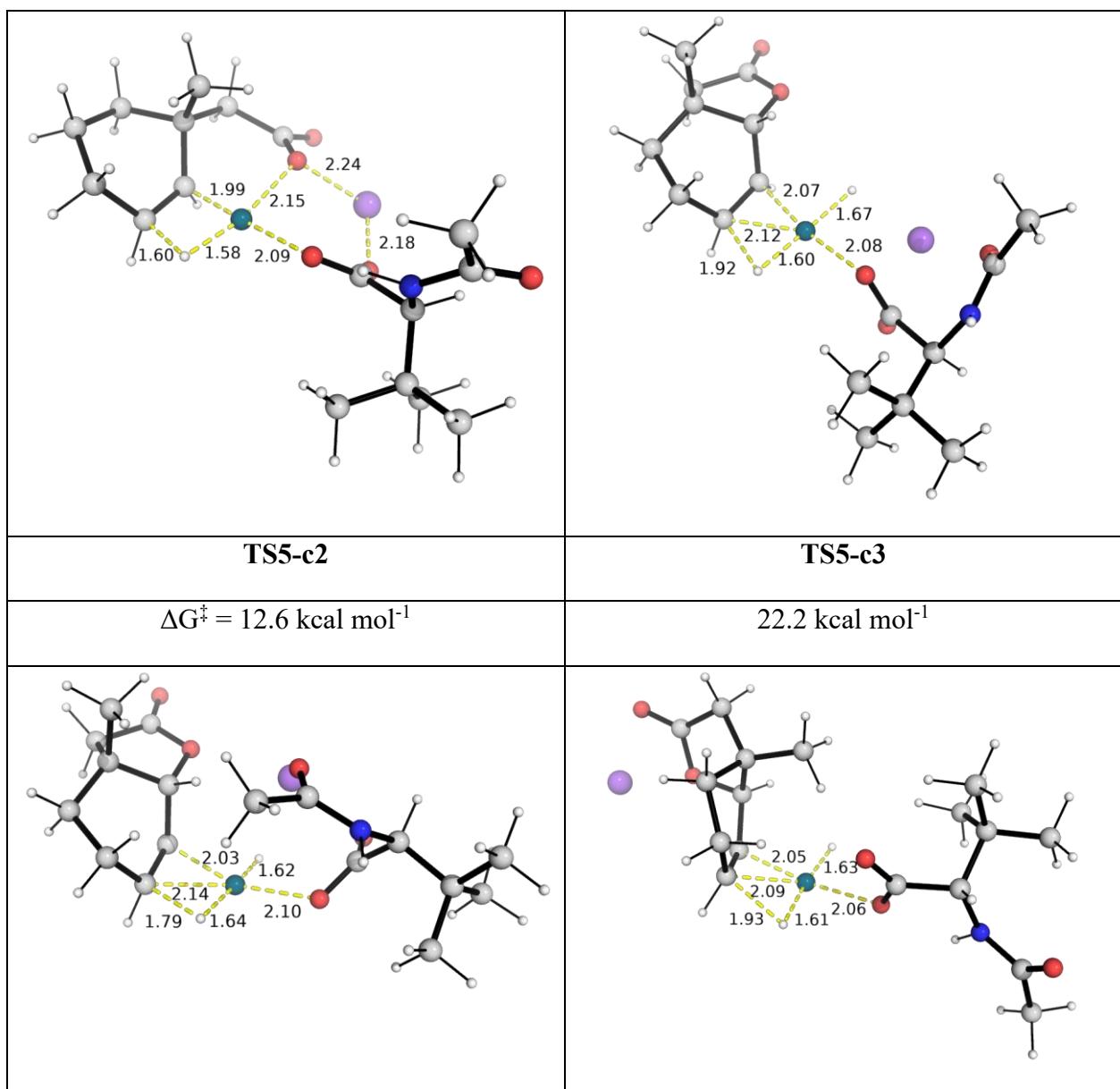


Figure S11. DFT optimised transition state structures for the β -H elimination step. Activation barriers are taken relative to the sum of starting materials. Conformers are denoted c2, c3 etc.

9.8. Product release

The formation of palladium-bound lactone product, **INT9**, is endergonic and uphill by 6.9 kcal mol⁻¹ and is thus thermodynamically disfavoured. We investigated the release of the lactone product from the catalyst centre (Figure S12).

The release of the lactone product from **INT9** in the absence of another species gives **INT10'**, with Pd centre having a vacant site (Figure S12a). This process is uphill by 16.7 kcal mol⁻¹ and is unfavourable. When one HFIP solvent molecule is used to displace the product from **INT9** (Figure 12b), the resulting Pd-species formed, **INT11'**, is uphill by 14.1 kcal mol⁻¹. This is still thermodynamically unfavourable. When the silver carbonate salt is used to displace the lactone

product (Figure S12c), the resulting Pd–Ag species is thermodynamically downhill and is thus favourable.

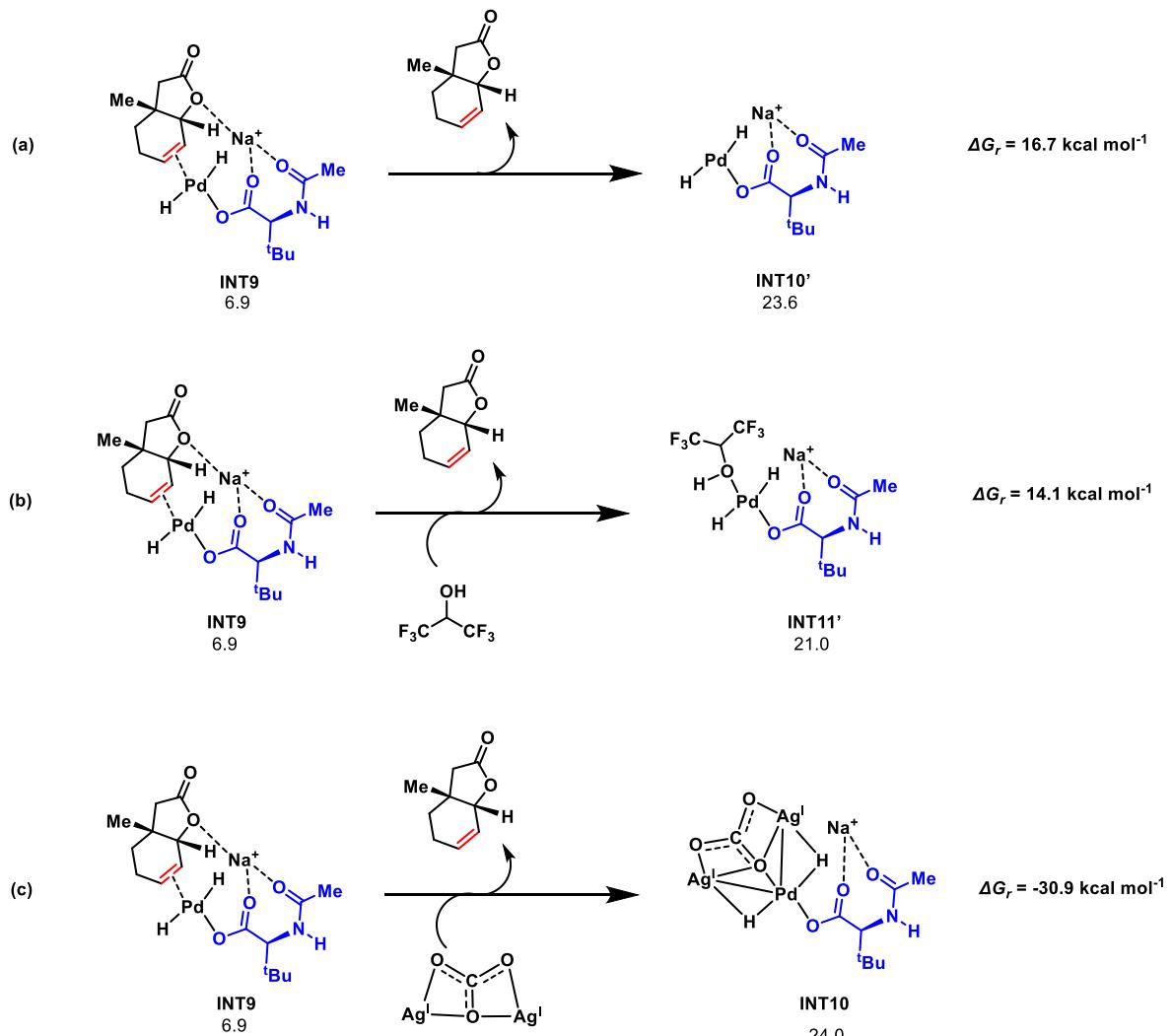


Figure S12. Thermodynamics for the release of bicyclic lactone product from Pd-catalyst.

9.9. Regioselectivity studies for 3-substituted substrate

3-Phenyl substituted substrate, where Ph and Me groups are syn to each other (relative stereochemistry), was used as a representative to study the regioselectivity outcomes for 3-substituted substrates using DFT. Herein, only a single enantiomer was used for DFT calculations as minor images of all structures are isoenergetic (the syn relation between Me and Aryl has been established through NOESY experiment). As the reaction outcomes depend on the turnover frequency-determining intermediate (TDI) and transition state (TDTS)²⁷, we study the energetics for these two states for the competing pathways. Figure S13 shows the associated Gibbs energy profile. Different conformations where the Me and Ph groups can be either axial or equatorial, were considered for both the TDI and the TDTS (lowest energy

conformers **INT2** and **TS5** from the study of unsubstituted substrate were used as guess structures) and the DFT-optimised structures were shown in Figure S14. For the competing pathways for the formation of regioisomeric products shown in Figure S13, the overall TDI for the reaction is **INT2Ph-equatorial**, as the C–H activation step leading to the activated complex **INT2-regio-equatorial** is reversible, such that **INT2-regio-equatorial** will revert back to the starting materials and form **INT2Ph-equatorial**, which is more thermodynamically stable (competing pathways with shared states need to take the lowest/most stable state into account)²⁷. As such, the selectivity outcomes for the formation of the major vs minor product depends on the difference in the activation barriers for the TDTSs. **TS5Ph-equatorial** (at 4.3 kcal mol⁻¹) leading to the major product has a barrier that is 3.9 kcal mol⁻¹ lower than **TS5Ph-regio** (at 8.2 kcal mol⁻¹) leading to the minor product. This predicts the right major product which was experimentally observed.

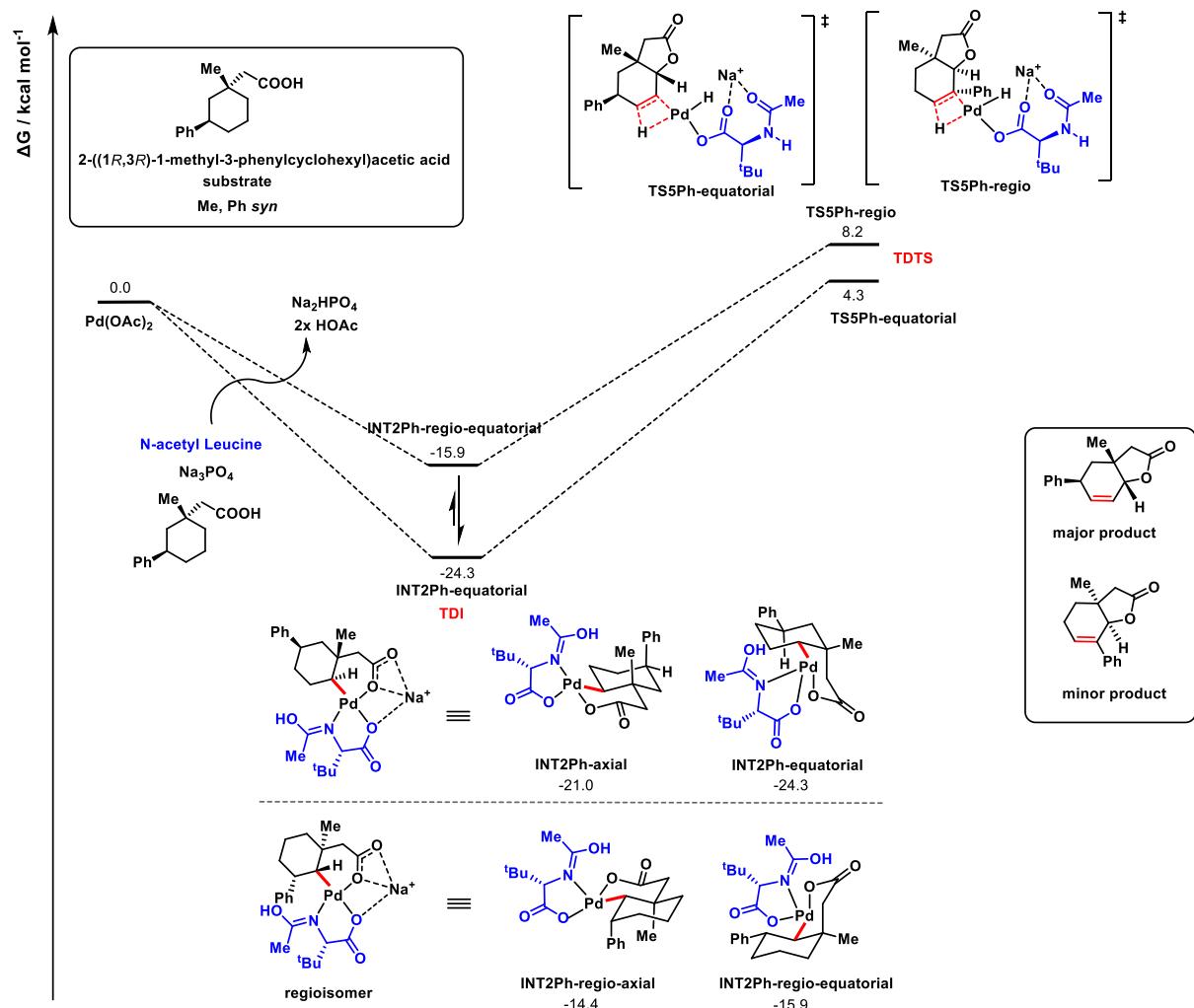
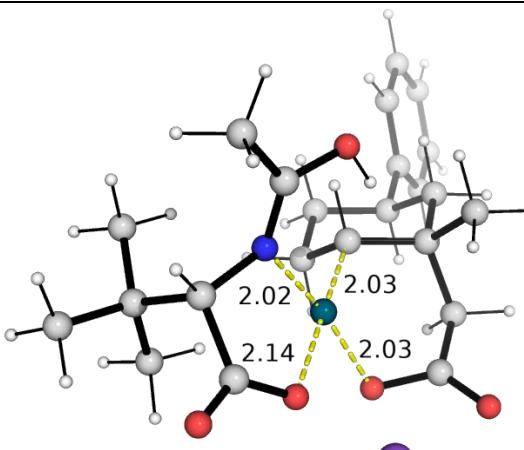
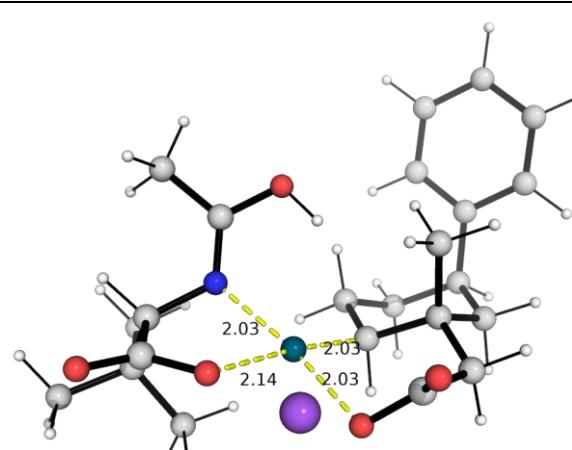
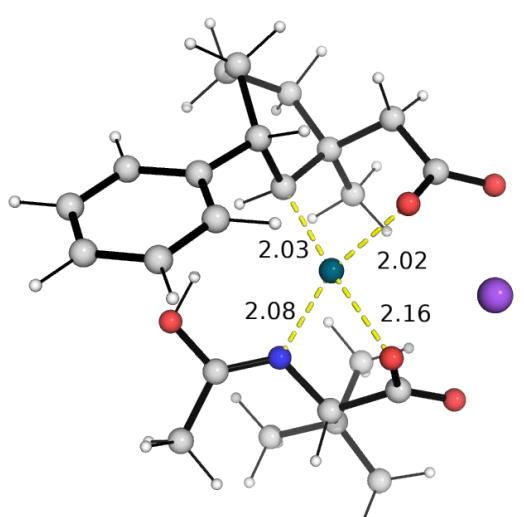
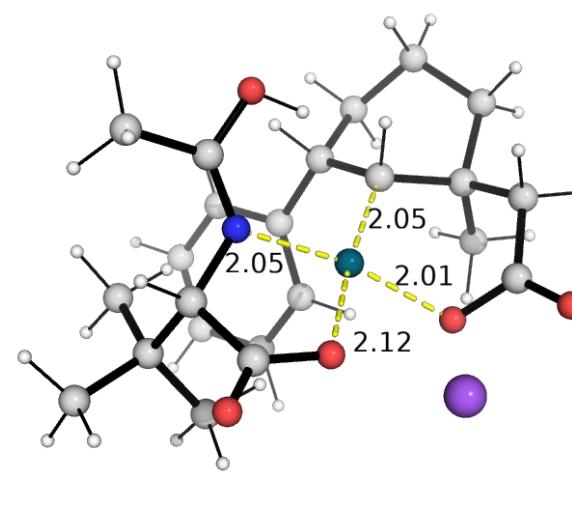
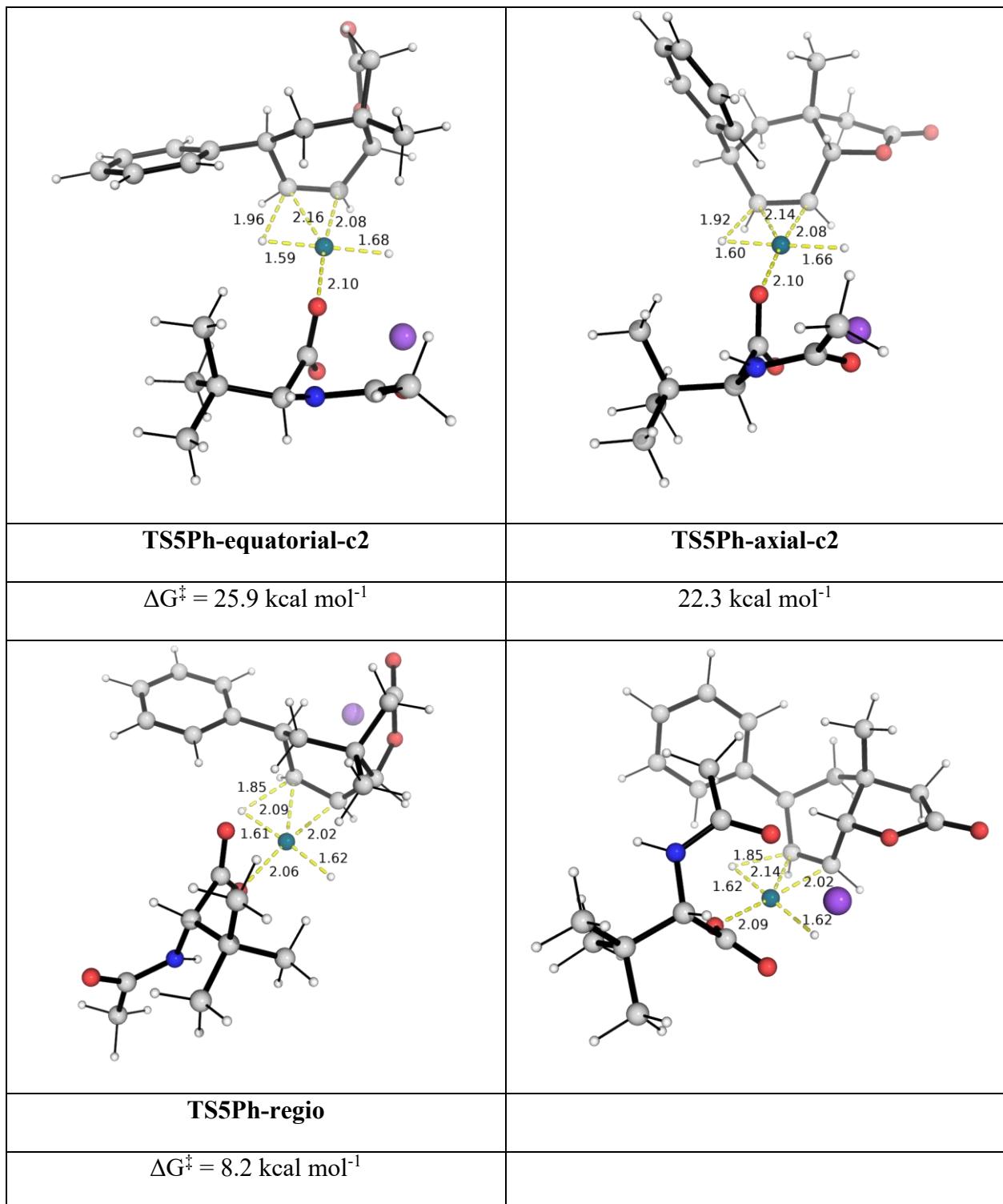


Figure S13. Gibbs energy profile for the turnover-frequency determining intermediate (TDI) and transition state (TDTS) for the functionalisation of 3-substituted substrate.

INT2Ph-equatorial	INT2Ph-axial
$\Delta G = -24.3 \text{ kcal mol}^{-1}$	-21.0 kcal mol ⁻¹
	
INT2Ph-regio-equatorial	INT2Ph-regio-axial
$\Delta G = -15.9 \text{ kcal mol}^{-1}$	-14.4 kcal mol ⁻¹
	
TS5Ph-equatorial	TS5Ph-axial
$\Delta G^\ddagger = 4.3 \text{ kcal mol}^{-1}$	12.3 kcal mol ⁻¹



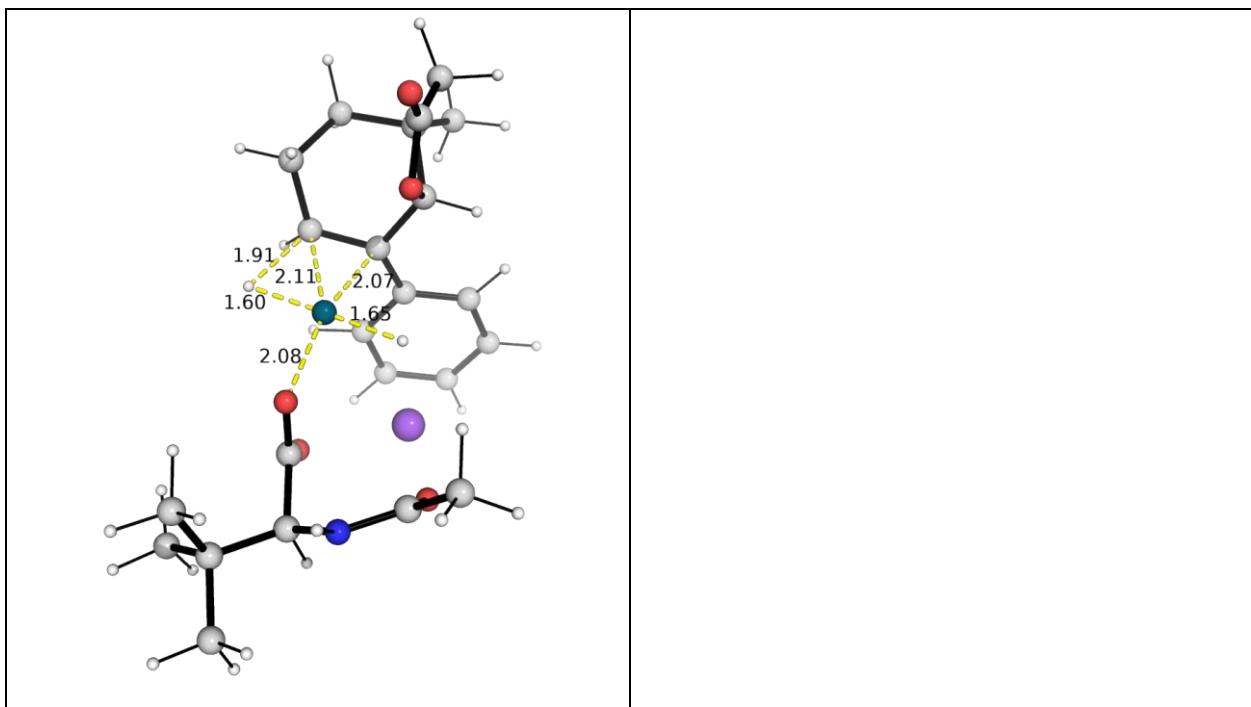


Figure S14. DFT optimised turnover frequency-determining intermediate (TDI) and transition state (TDTs) structures for the 3-substituted substrate. Gibbs energy values are taken relative to the sum of starting materials. Different transition state conformers are included and are denoted by c2, c3 etc, in increasing energy.

9.10. Optimized structures and absolute energies, zero-point energies

Geometries of all optimized structures (in .xyz format with their associated energy in Hartrees) are included in a separate folder named *final_xyz* with an associated *readme.txt* file. All these data have been deposited and uploaded to zenodo.org (<https://zenodo.org/record/7516355>; DOI: 10.5281/zenodo.7516355).

Absolute values (in Hartrees) for SCF energy, zero-point vibrational energy (ZPE), enthalpy and quasi-harmonic Gibbs free energy (at 120°C/393.15 K) for optimized structures are given below. Single point corrections in SMD hexafluoroisopropanol using MN15/def2-QZVP level of theory are also included.

Structure	E/au	ZPE/a u	H/au	T.S/au	qh-G/au	SP SMD MN15/def2- QZVP
HOAc	-228.644533	0.0621 97	228.5741 1	0.0417 23	-228.61541	-229.06457600

		0.0482	-	0.0422	-	228.04417	
acetate	-228.059294	19	2	8	9	-	-228.592055
PdOAc2_monomer		0.1043	583.6880	0.0683	583.75309	-	
	-583.809931	26	9	64	6	-	-584.634037
Na_substrate_2_salt		0.2304	663.3855	0.0760	663.45844	-	
	-663.638026	12	2	65	1	-	-664.677056
substrate_2		0.2418	501.7783	0.0691	501.84583	-	
	-502.040305	76	6	48	1	-	-502.967425
Na2HPO4		0.0294	966.5361	0.0577	966.59249	-	
	-966.579407	98	4	07	5	-	-967.610931
Na3PO4		-	-	-	-	-	
	1128.16117	0.0191	1128.126	0.0618	1128.1873	-	
	6	46	6	21	68	-	-1129.292047
Nacetyltert leucine		0.2300	592.9075	0.0800	592.98437	-	
	-593.162022	84	6	11	9	-	-594.257468
hfip		0.0644	788.4202	0.0617	788.48022	-	
	-788.500116	58	8	98	3	-	-789.866397
Ag2CO3		0.0172	-	0.0552	556.75378	-	
	-556.727692	56	556.6994	06	8	-	-557.239514
Pd_leucine_2_hfip		-	-	-	-	-	
	2296.72285	0.3411	2296.325	0.1554	2296.4688	-	
	2	01	5	23	8	-	-2300.5114
lactone_prd		0.1960	499.4000	0.0627	499.46198	-	
	-499.613569	67	7	79	6	-	-500.529069
lactone_prd-c2		0.1964	499.4072	0.0620	499.46884	-	
	-499.620948	17	3	24	5	-	-500.536485
INT1'		-	-	-	-	-	
	1383.33564	0.4388	1382.849	0.1298	1382.9727	-	
	8	2	5	97	13	-	-1385.432754

	-	1383.32315	0.4353	1382.841	0.1260	1382.9620	-
TS1'	5	8		5	11	16	-1385.413749
	-	1383.36438	0.4410	1382.876	0.1276	1382.9983	-
INT2'	1	78		4	74	63	-1385.456831
	-	1383.34274	0.4395	-	0.1311	1382.9796	-
INT1'-c2	8	02		1382.856	74	85	-1385.440655
	-	1383.32092	0.4360	-	0.1253	1382.9588	-
TS1'-c2	1	12		1382.839	91	15	-1385.411889
	-	1383.35452	0.4411	1382.866	0.1268	1382.9881	-
INT2'-c2	6	79		5	31	31	-1385.447502
	-	1383.34315	0.4392	1382.856	0.1305	1382.9798	-
INT1''	1	78		7	2	11	-1385.441807
	-	1383.32904	0.4352	1382.847	0.1274	1382.9684	-
TS1''-c2	2	38		7	81	55	-1385.420691
	-	1383.36598	0.4408	1382.878	0.1297	1383.0006	-
INT2''	4	23		3	08	75	-1385.459128
	-	1383.27990	0.4384	1382.793	0.1367	1382.9198	-
TS2''	8	68		9	25	5	-1385.381637
	-	1383.26416	0.4384	1382.778	0.1329	1382.9027	-
TS2''-c2	4	2		6	98	05	-1385.370122
	-	1383.34295	0.4398	1382.856	0.1303	1382.9789	-
INT1''-c2	7	03		2	16	13	-1385.440542
	-	1383.33305	0.4357	1382.851	0.1264	1382.9715	-
TS1''	3	9		4	71	42	-1385.425058
	-	1383.36139	0.4410	1382.873	0.1296	1382.9958	-
INT2''-c2	6	1		6	36	93	-1385.455347

	-	1383.34332	0.4399	1382.856	0.1294	1382.9791	-
INT1	5	16	3	38	85	-	-1385.440646
	-	1383.32785	0.4356	-	0.1265	1382.9666	-
TS1	1	23	1382.846	01	69	-	-1385.41921
	-	1383.32272	0.4360	1382.840	0.1252	1382.9604	-
TS1-c2	6	62	8	48	93	-	-1385.414883
	-	1383.36611	0.4412	1382.878	0.1268	1382.9996	-
INT2	5	26	2	19	07	-	-1385.4595
	-	1383.36611	0.4412	-	0.1268	1382.9996	-
INT2-c2	5	28	2	15	06	-	-1385.459521
	-	1383.32058	0.4389	1382.834	0.1305	1382.9579	-
INT3a	9	74	1	58	34	-	-1385.431006
	-	1383.34446	0.4388	1382.856	0.1390	1382.9851	-
INT3	4	8	9	31	78	-	-1385.446155
	-	1383.33847	0.4379	-	0.1355	1382.9785	-
TS2	7	74	1382.853	94	8	-	-1385.439945
	-	1383.34049	0.4379	1382.853	0.1387	1382.9821	-
INT4	3	25	9	73	76	-	-1385.441536
	-	1383.33219	0.4351	-	0.1361	1382.9754	-
TS3	5	3	1382.849	64	25	-	-1385.433272
	-	1383.33832	0.4368	1382.852	0.1371	1382.9802	-
INT5	8	55	9	79	74	-	-1385.439261
	-	1383.33657	0.4371	-	0.1362	1382.9778	-
INT5-c2	9	38	1382.851	32	23	-	-1385.437325
	-	1383.30662	0.4360	1382.821	0.1402	1382.9502	-
INT6	-1383.30662	92	6	35	05	-	-1385.42623

	-	1383.28268	0.4354	1382.799	0.1364	1382.9256	-
TS4	2	16		5	58	85	-1385.40426
	-			-		-	
	1383.27881	0.4345			0.1362	1382.9227	
TS4-c2	1	36		1382.796	82	53	-1385.381705
	-			-		-	
	1383.28894	0.4351		1382.805	0.1383	1382.9328	
TS4'	8	96		4	42	89	-1385.389267
	-			-		-	
	1383.24968	0.4363		1382.765	0.1343	1382.8907	
INT7	1	33		6	17	37	-1385.411514
	-			-		-	
	1383.28699	0.4363		1382.802	0.1360	1382.9286	
INT7-c2	7	92		7	92	5	-1385.409455
	-			-		-	
	1383.29048	0.4324		1382.810	0.1347	1382.9358	
TS5	7	71		6	7	67	-1385.396015
	-			-		-	
	1383.29071	0.4323		1382.811	0.1295	1382.9340	
TS5-c2	4	82		3	01	9	-1385.389864
	-			-		-	
	1383.23118	0.4317		1382.752		1382.8762	
TS5-c3	2	33		2	0.1333	81	-1385.372786
	-			-		-	
	1383.24800	0.4317		1382.768		1382.8926	
TS5-c4	7	87		9	0.1314	72	-1385.348645
	-			-		-	
	1383.33745	0.4373		1382.852	0.1338	1382.9775	
INT8	5	43		3	59	75	-1385.432126
	-			-		-	
	1383.32952	0.4364		1382.844	0.1340	1382.9709	
INT8-c2	5	05		7	37	05	-1385.426338
	-			-		-	
	1383.31570	0.4360		1382.831	0.1375	1382.9588	
INT8-c3	4	02		5	18	2	-1385.422172
	-			-		-	
	1383.29049	0.4328		1382.809	0.1375	1382.9366	
INT9	8	57		2	26	34	-1385.39617

	-	1383.29360	0.4334	1382.812	0.1310	1382.9365	-
INT9-c2	9	47		5	29	39	-1385.393111
			0.2537	1440.193	0.1233	1440.3097	
INT10	-1440.48886	4		6	22	22	-1442.151878
			0.2342	883.3376	0.0963	883.42946	
INT10'	-883.602395	6		9	14	8	-884.804197
	-			-		-	
	1439.30780	0.2390	1439.027	0.1243	1439.1439		
INT11	3	55	9	09	45	-	-1440.970405
	-			-		-	
	1672.15006	0.3009	1671.802	0.1350	1671.9274		
INT11'	5	31	8	5	64	-	-1674.704568
	-			-		-	
	1672.13861	0.3003	1671.791	0.1344	1671.9164		
INT11'-c2	1	8	6	21	67	-	-1674.687228
	-			-		-	
	1018.75577	0.2704	1018.453	0.1003	1018.5479		
TS2''-ac	7	25	9	56	66	-	-1020.185855
	-			-		-	
	1383.34994	0.4399	1382.862	0.1353	1382.9878		
INT3''	7	82	2	25	26	-	-1385.448716
	-			-		-	
	1383.27990	0.4384	1382.793	0.1367	1382.9198		
TS2''	8	68	9	25	5	-	-1385.381637
	-			-		-	
	1383.32591	0.4416	1382.836	0.1378	1382.9632		
INT4''	2	11	6	26	34	-	-1385.425169
	-			-		-	
	1383.27690	0.4387	1382.790	0.1374	1382.9170		
TS3a	9	12	3	02	9	-	-1385.379846
	-			-		-	
	0.4419	1382.802	0.1390	1382.9302			
INT5a	-1383.2926	24	6	08	7	-	-1385.433396
	-			-		-	
	1383.26246	0.4386	1382.776	0.1314	1382.9001		
TS3b	5	85	6	14	03	-	-1385.370109

	-	1383.31642	0.4410	-	1382.827	0.1341	-	1382.9530	
INT5b	9	99		8	85	82		-1385.425482	

9.11. References:

Full reference Gaussian 16:

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10. Deuterium Exchange Experiment:

In an oven-dried screw capped reaction tube was charged with magnetic stir-bar, corresponding acid (0.1 mmol), Pd(OAc)₂ (10 mol%), *N*-Ac-³'Leu (20 mol%), Ag₂CO₃ (2 equiv.), and Na₃PO₄ (2 equiv.) in 1 mL of deuterated version of 1,1,1,3,3,3-hexafluoro-2-propanol (d²-HFIP) were added. The reaction tube was capped and placed in a preheated bath at 120 °C with stirring (800 rpm) for 24 h. Upon completion the mixture was diluted with EtOAc and filtered through a celite pad. The filtrate was evaporated under reduced pressure and NMR of the crude mixture was taken. γ -Methyl group was found to be 59% deuterated and γ -methylene 45% deuterated.

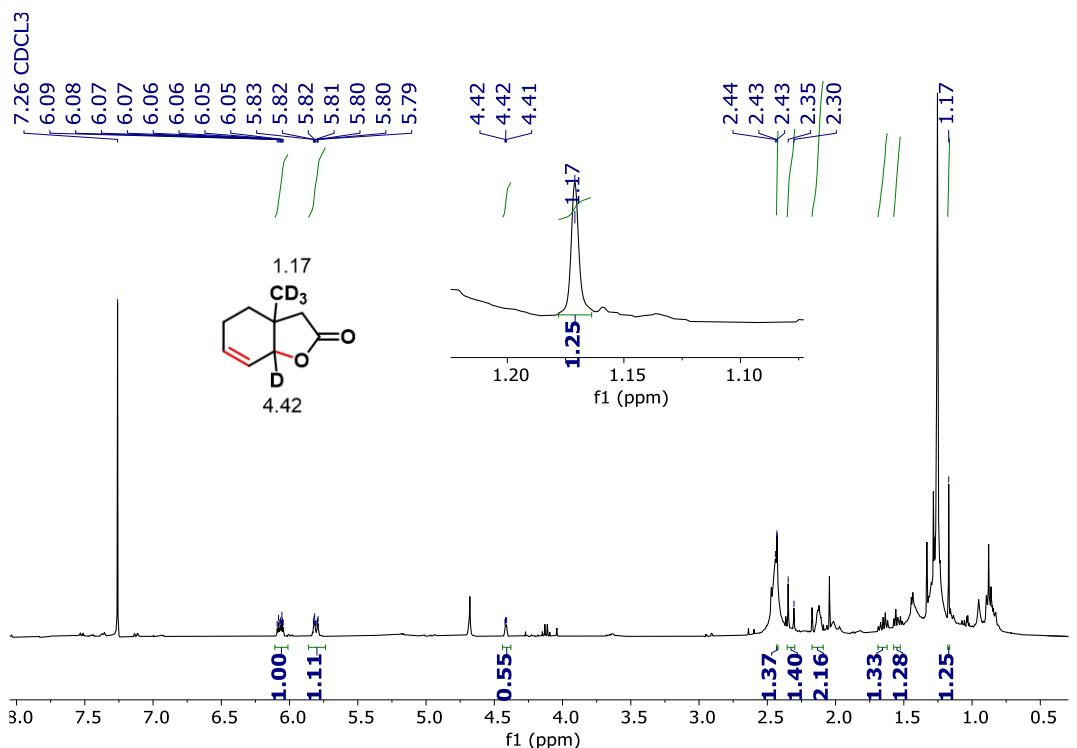
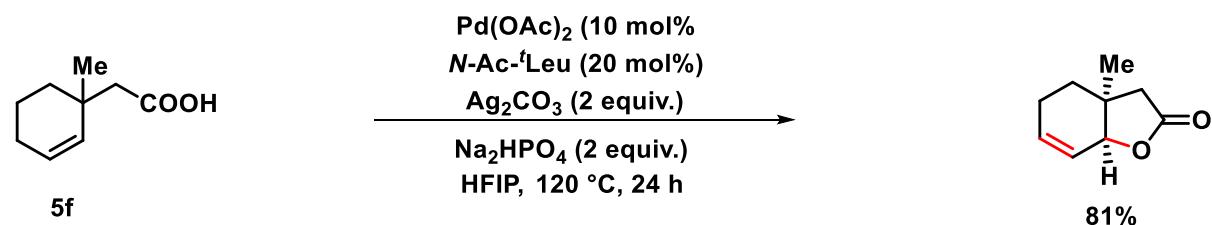


Figure S15. ^1H NMR spectra of product performed in $\text{d}^2\text{-HFIP}$.

Chemical competence of the alkenoic acid 5f.



In an oven-dried screw capped reaction tube was charged with magnetic stir-bar, corresponding alkenoic acid (0.2 mmol), Pd(OAc)₂ (10 mol%), N-Ac'-Leu (20 mol%), Ag₂CO₃ (2 equiv.), and Na₃PO₄ (2 equiv.) in 1.5 mL of 1,1,1,3,3-hexafluoro-2-propanol (HFIP) were added. The reaction tube was capped and placed in a preheated bath at 120 °C with stirring (800 rpm) for 24 h. Upon completion the mixture was diluted with EtOAc and filtered through a celite pad. The filtrate was evaporated under reduced pressure and the crude mixture was purified by column chromatography using silica (100-200 mesh size) and petroleum ether/ ethyl acetate as the eluent.

11. Headspace Analysis:

Following the general procedure, after 24 h, the gas phase over the reaction mixture was analysed by headspace GC analysis using an Nucon 5700 gas chromatography. Argon used as carrier gas (pressure 15 psi) and the sample was analysed by a temperature conductivity detector at 40 °C (injected temperature 40 °C, detector temperature 40 °C, oven temperature 40 °C, current 120 mA). For comparison a blank sample of the carrier gas was conducted.

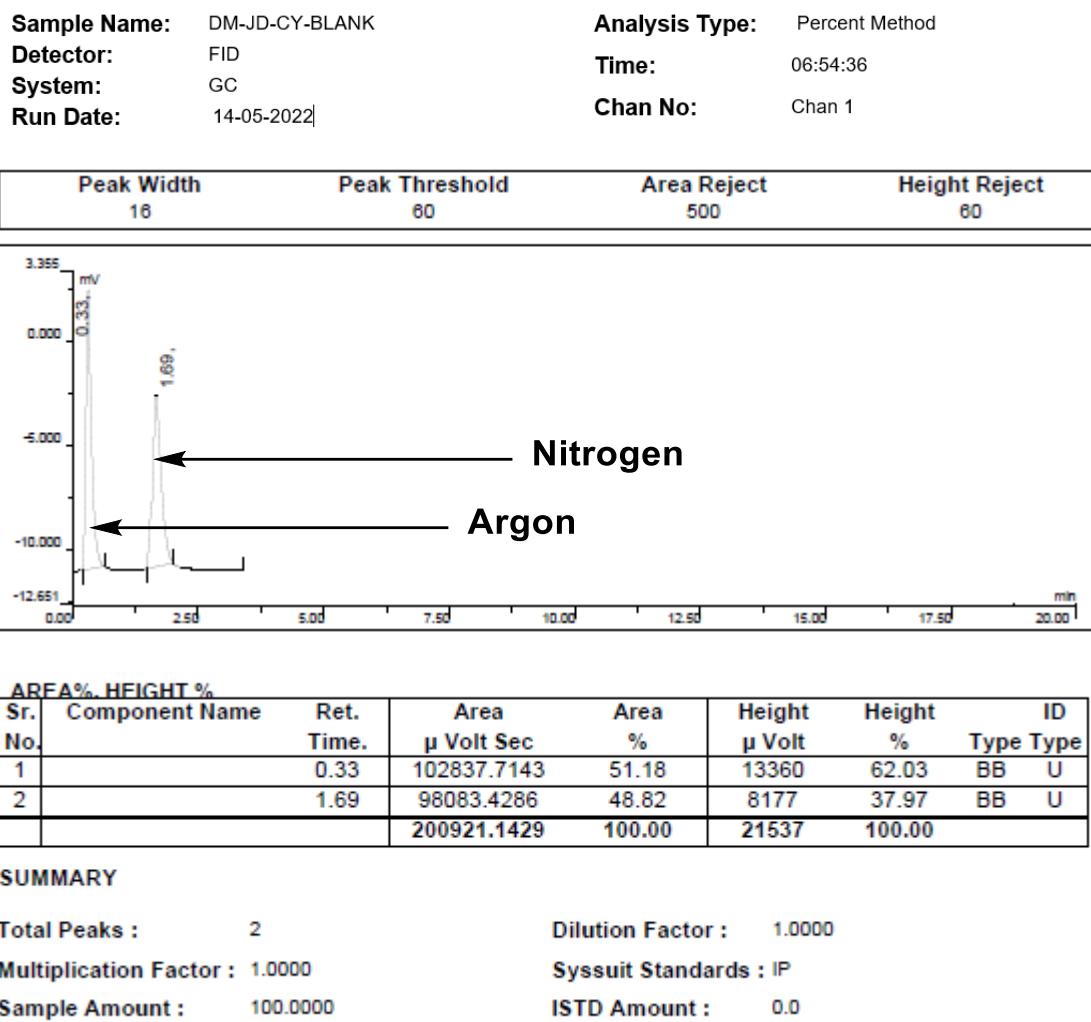
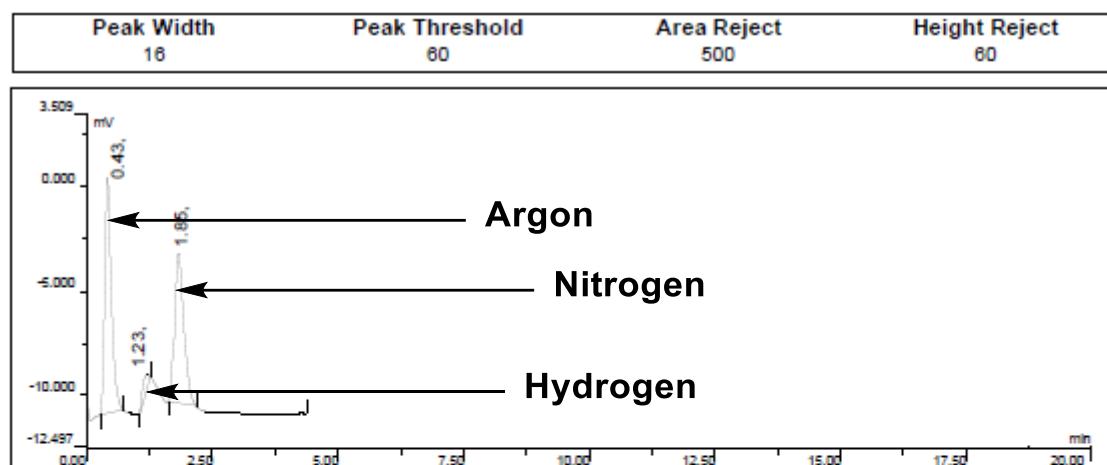


Figure S16. Headspace analysis of the blank.

Sample Name: DM-JD-CY-REACTION
Detector: FID
System: GC
Run Date: 14-05-2022

Analysis Type: Percent Method
Time: 04:55:25
Chan No: Chan 1



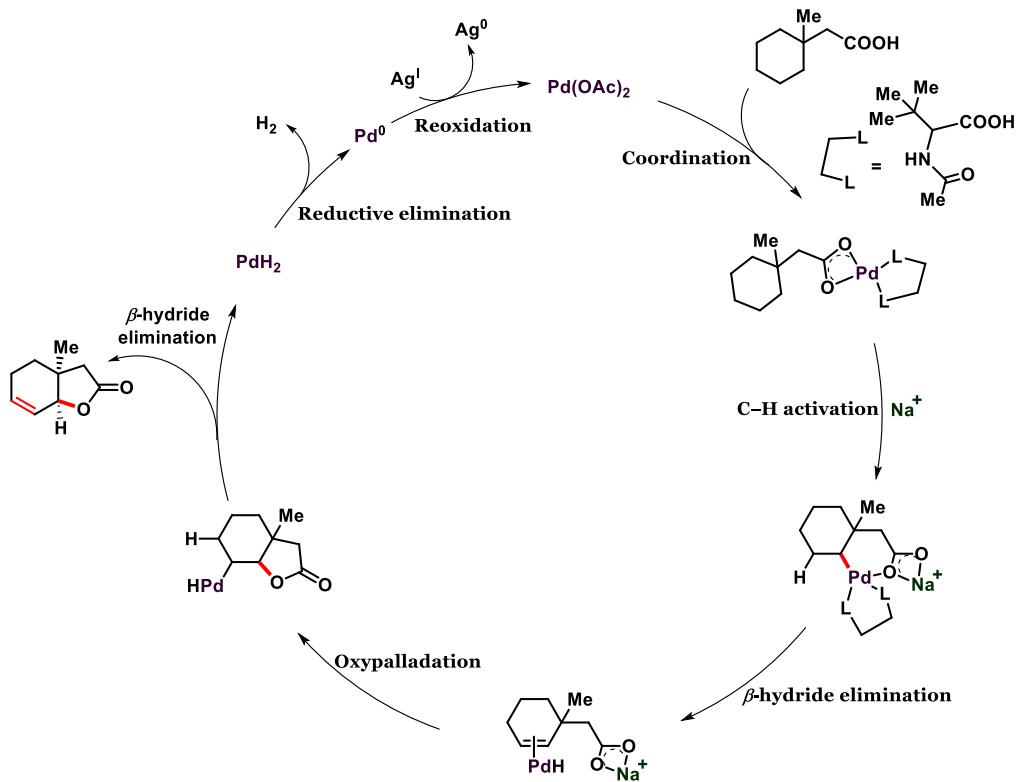
ARFA %, HFIGHT %						
Sr. No.	Component Name	Ret. Time.	Area μ Volt Sec	Area %	Height μ Volt	Height %
ID	Type	Type				
1		0.43	101479.6000	51.13	11302	59.81
2		1.23	5409.2571	2.73	422	2.24
3		1.85	91572.7429	46.14	7171	37.95
			198461.6000	100.00	18897	100.00

SUMMARY

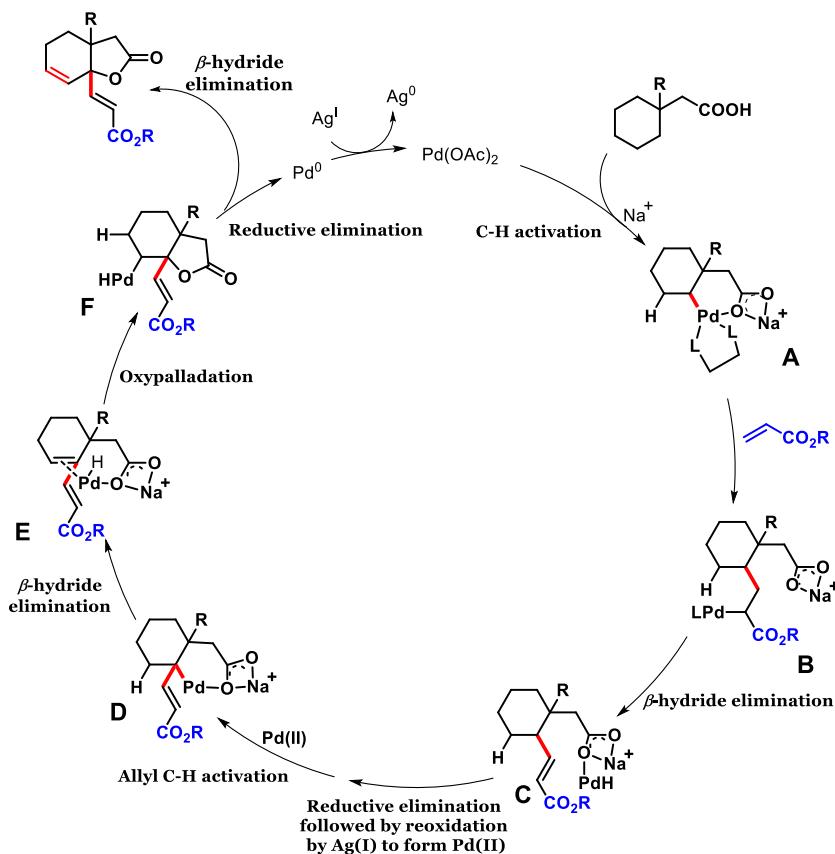
Total Peaks : 3 Dilution Factor : 1.0000
Multiplication Factor : 1.0000 Syssuit Standards : IP
Sample Amount : 100.0000 ISTD Amount : 0.0

Figure S17. Headspace analysis of the reaction mixture.

12.1. Proposed catalytic cycle for the unsaturated bicyclic lactone formation



12.2. Proposed catalytic cycle for the unsaturated olefin containing bicyclic lactone formation

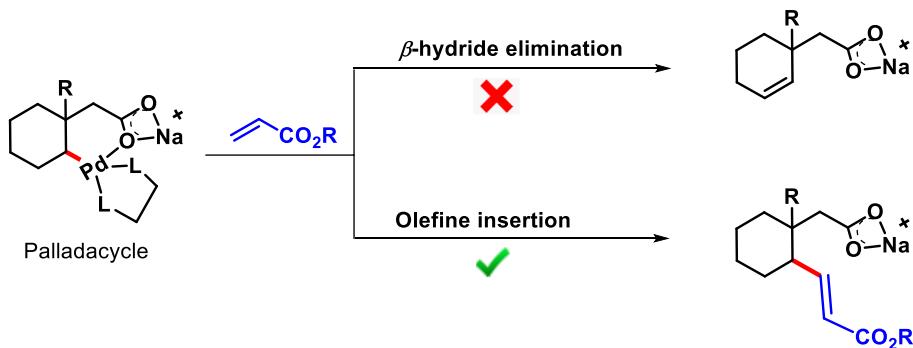


Control experiment:

In an oven-dried screw capped reaction tube was charged with magnetic stir-bar, corresponding alkenoic acid (**5f**, 0.2 mmol), Pd(OAc)₂ (10 mol%), *N*-Ac-*t*Leu (20 mol%), Ag₂CO₃ (2 equiv.), and Na₃PO₄ (2 equiv.) in 1.5 mL of 1,1,1,3,3-hexafluoro-2-propanol (HFIP) were added. The reaction tube was capped and placed in a preheated bath at 110 °C with stirring (800 rpm) for 24 h. Upon completion the mixture was diluted with EtOAc and filtered through a celite pad. The filtrate was evaporated under reduced pressure and the crude mixture was purified by column chromatography using silica (100-200 mesh size) and petroleum ether/ ethyl acetate as the eluent.



This control experiment implies that in presence of an olefin, the activated intermediate **A** undergo olefin insertion not β -hydride elimination as shown in abovementioned mechanism. Had β -hydride elimination occurs before olefin insertion; above experiment should have provided the intermolecular product and not intramolecular product. Thus, alkenoic acid **5f** most likely is not an intermediate for the intermolecular product formation mechanism and allyl activation is likely occurring in this case.



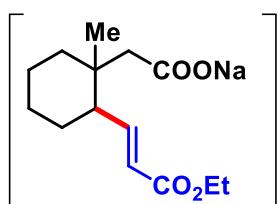
A similar report involving allyl activation of acid has been recently reported in literature.²⁷

Mass spectral analysis of intermediate

A Clean, oven-dried screw cap reaction tube was charged with a magnetic stir-bar, 2-(1-methylcyclohexyl)acetic acid (15 mg, 0.1 mmol) Pd(OAc)₂ (1.2 mg, 10 mol%), *N*-Ac-Gly-OH (2.3 mg, 20 mol%), Ag₂CO₃ (55 mg, 2 equiv.), Na₂HPO₄ (28 mg, 2 equiv.) and ethyl acrylate (32 μ L, 2 equiv.) Then 1 mL of 1,1,1,3,3-hexafluoro-2-propanol (HFIP) was added. The reaction tube was screwed by a cap fitted with a rubber septum. The reaction mixture was

stirred vigorously on a preheated oil bath at 110 °C for 8 h. The crude reaction mixture was subjected to mass analysis.

ESI-MS of the reaction mixture



Calculated Mass = 277.1410

Observed Mass = 277.1414

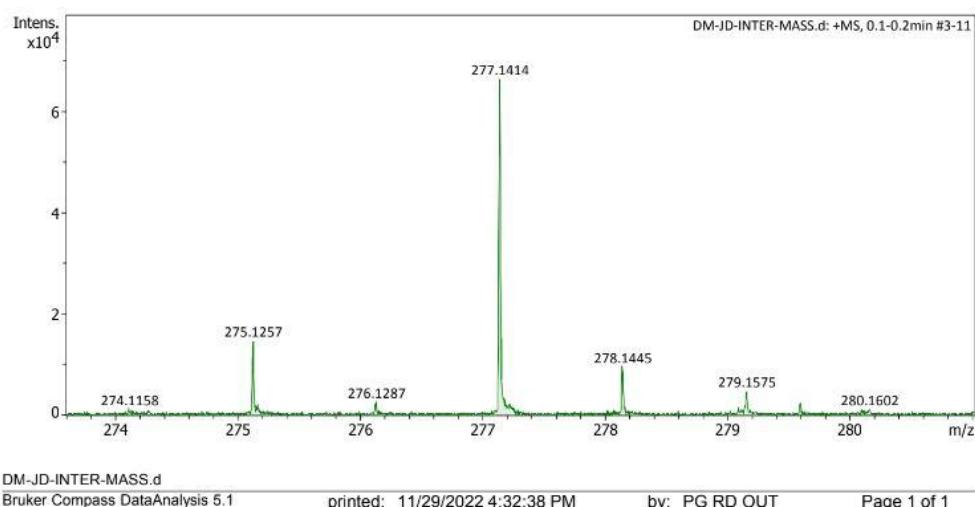


Figure S18. ESI-MS spectra of the reaction mixture showing γ -olefinated intermediate mass.

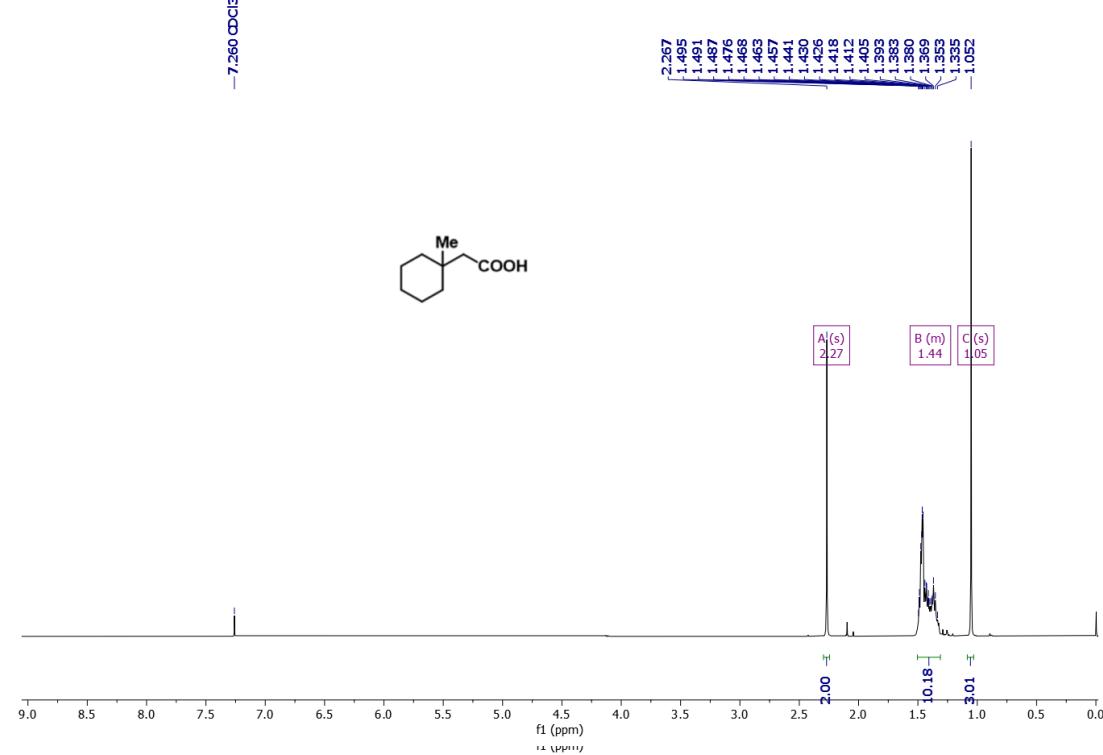
Reference:

27. Das, J.; Pal, T.; Ali, W.; Sahoo, S. K.; Maiti. D. Pd-Catalyzed Dual- γ -1,1-C(sp^3)-H Activation of Free Aliphatic Acids with Allyl-O Moieties. *ACS. Catal.* **2022**, *12*, 11169-11176.

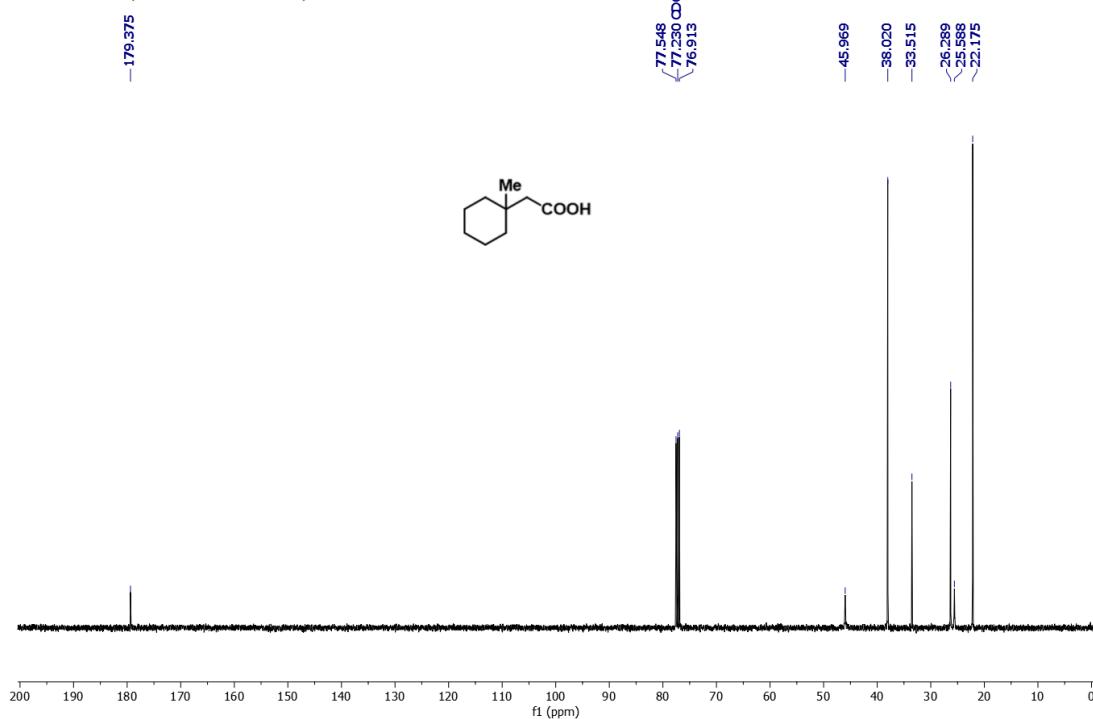
14. NMR Spectra of the Starting Material:

2-(1-Methylcyclohexyl)acetic acid (1)

¹H NMR (400 MHz, CDCl₃)

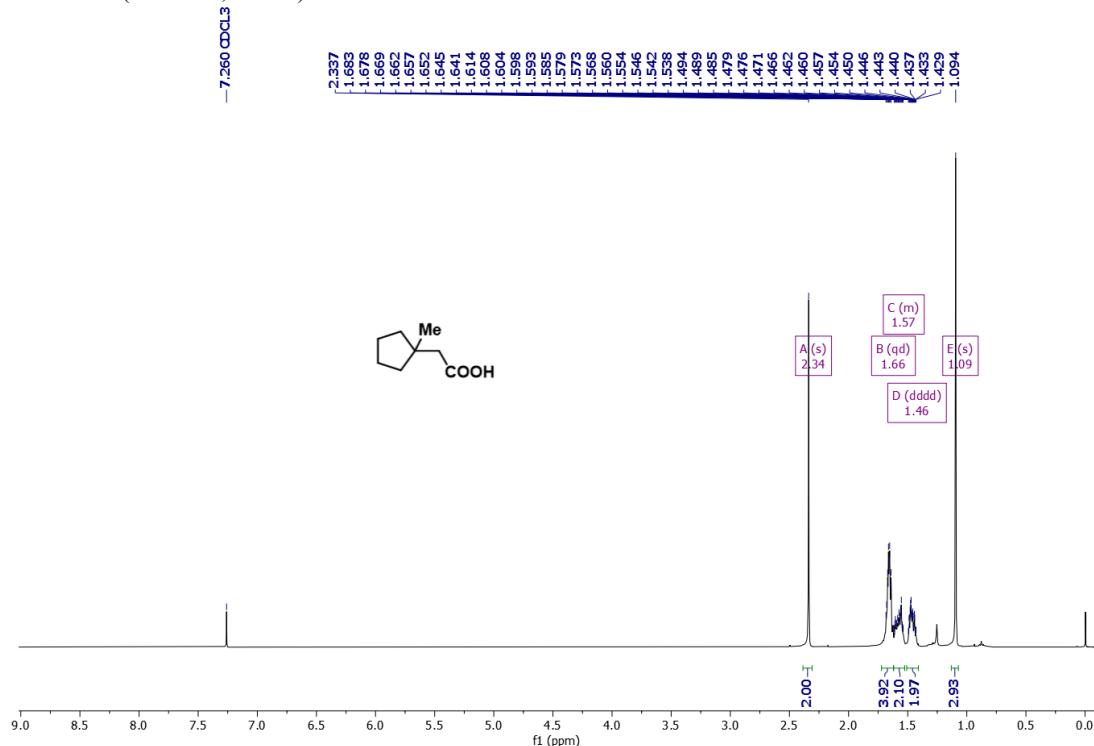


¹³C NMR (101 MHz, CDCl₃)

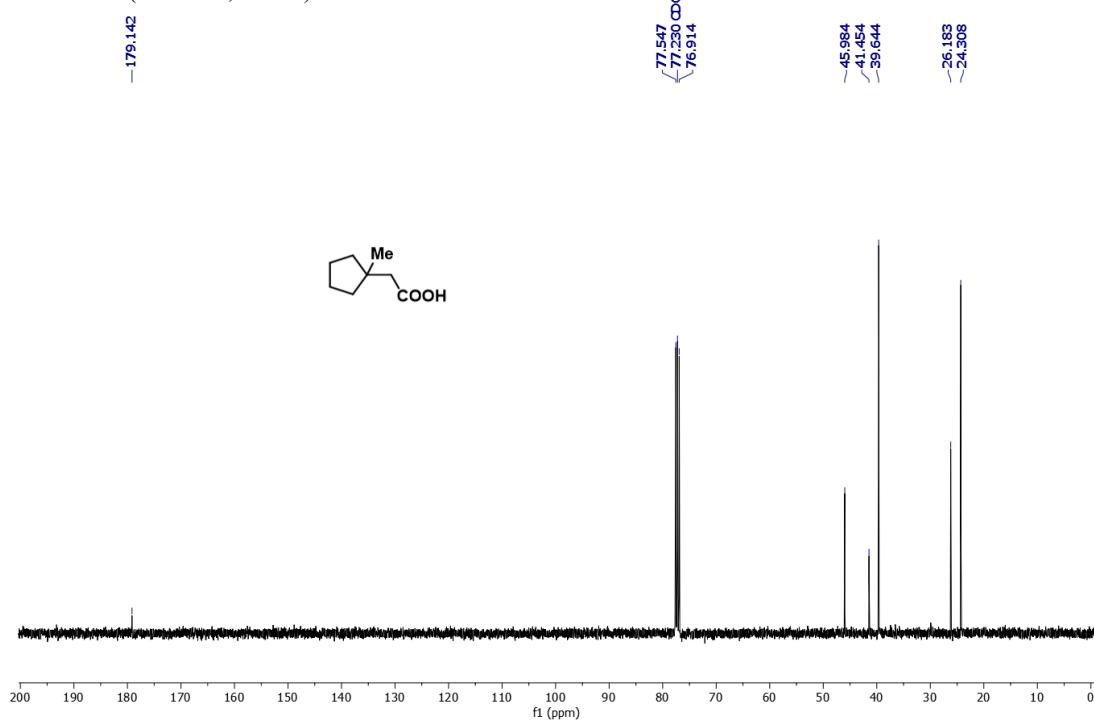


2-(1-Methylcyclopentyl)acetic acid (2)

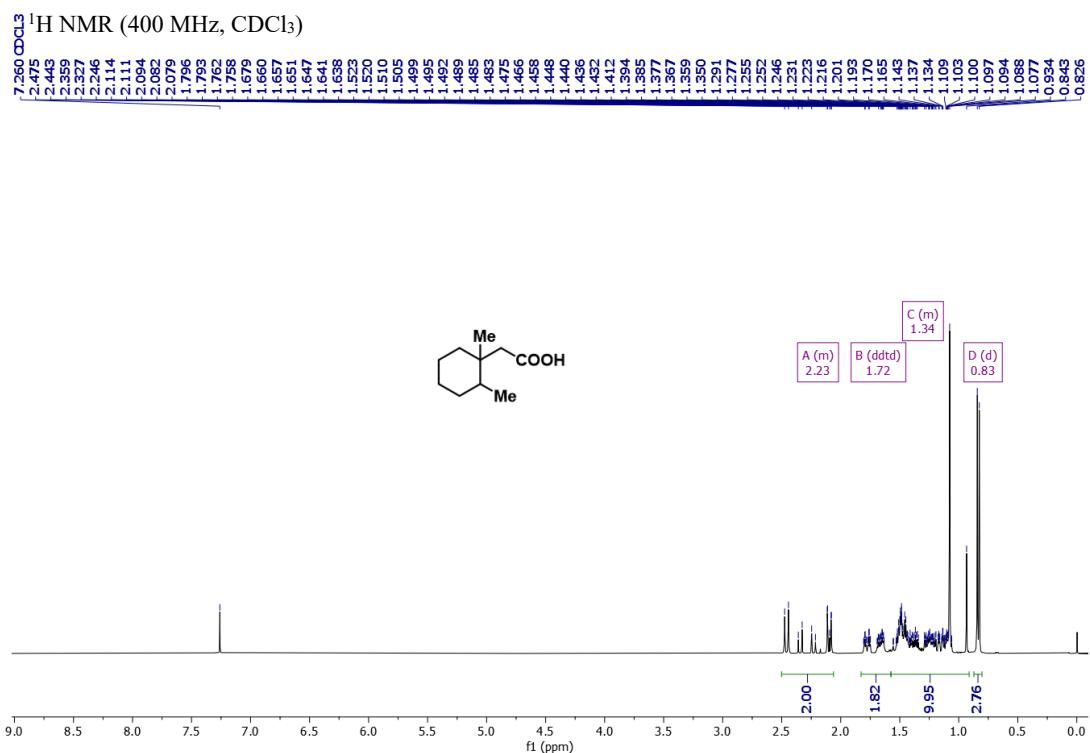
¹H NMR (400 MHz, CDCl₃)



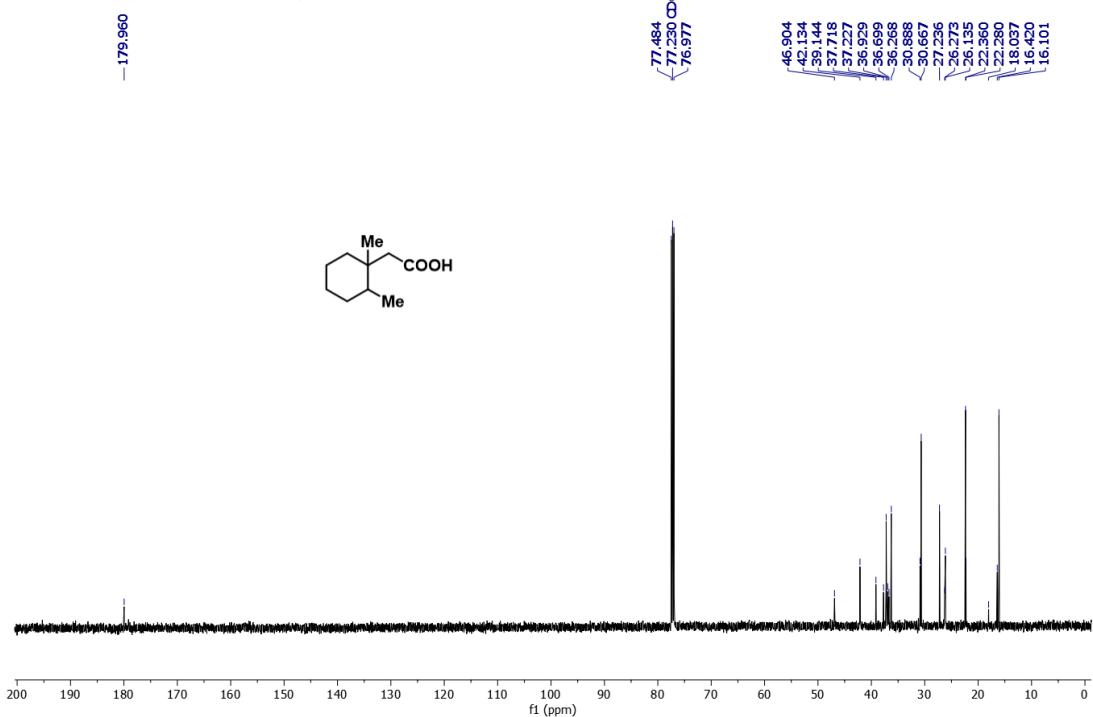
¹³C NMR (101 MHz, CDCl₃)



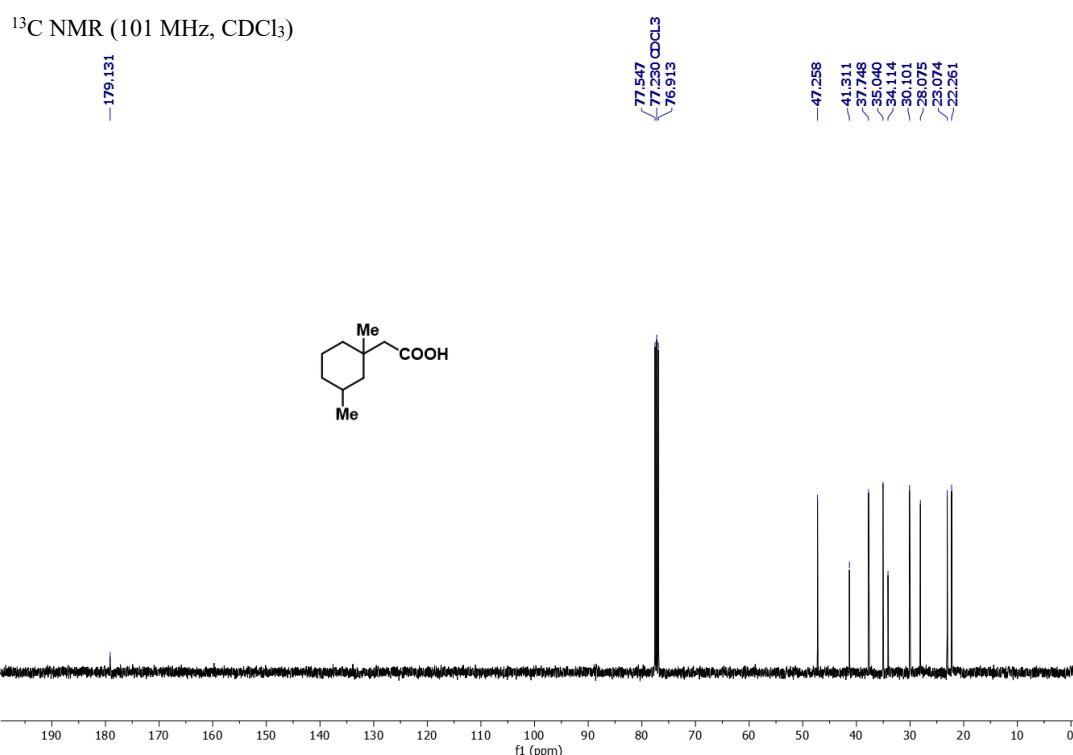
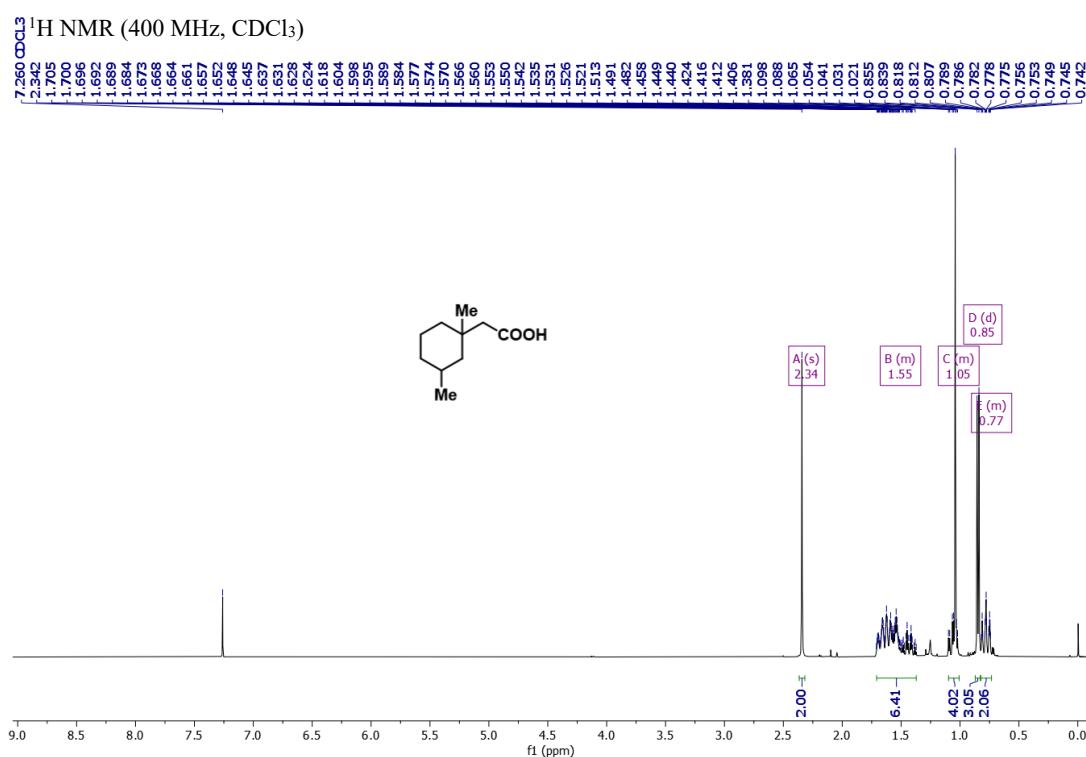
2-(1,2-Dimethylcyclohexyl)acetic acid (3)



¹³C NMR (126 MHz, CDCl₃)

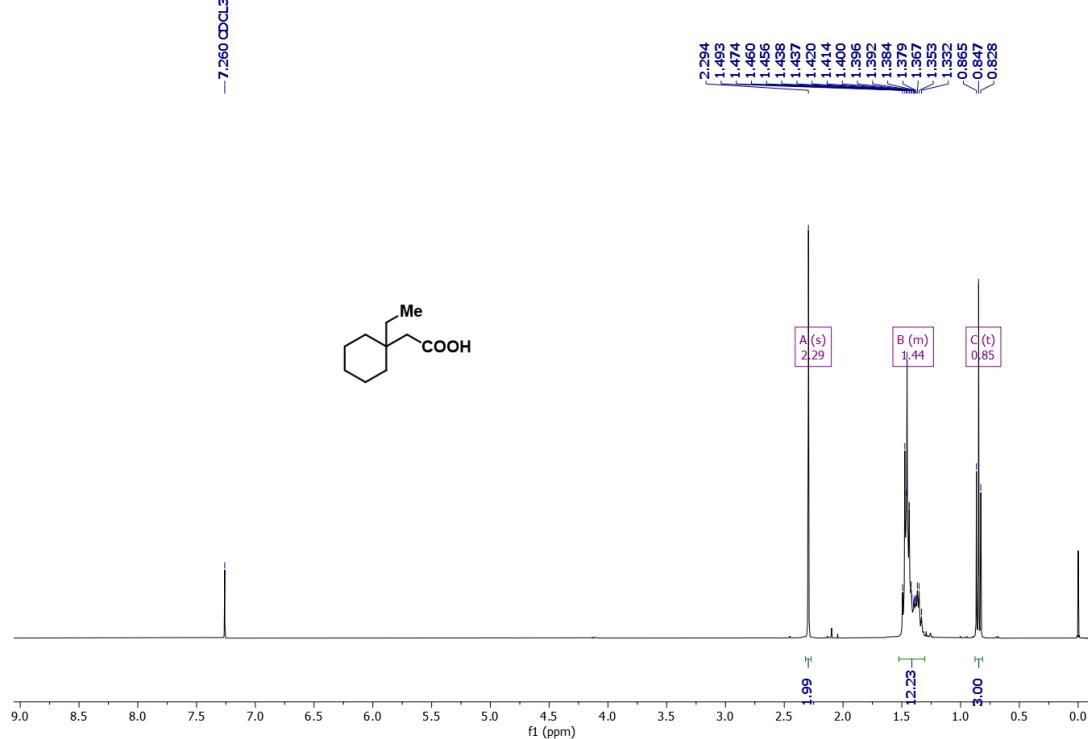


2-(1,3-Dimethylcyclohexyl)acetic acid (4)

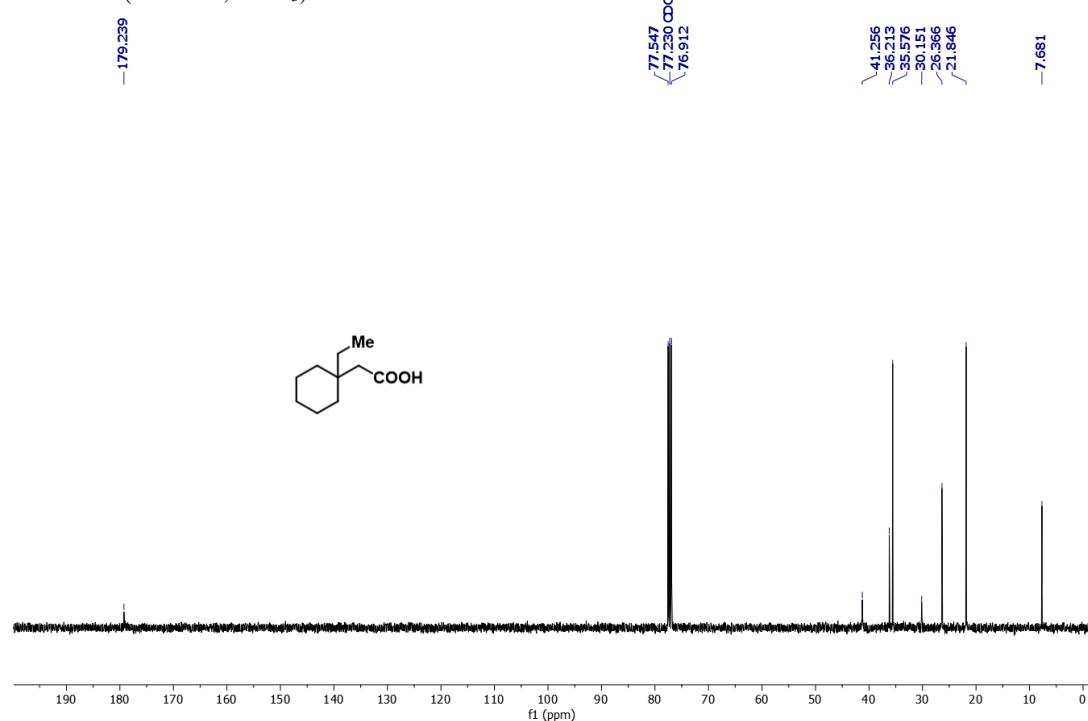


2-(1-Ethylcyclohexyl)acetic acid (5)

¹H NMR (400 MHz, CDCl₃)

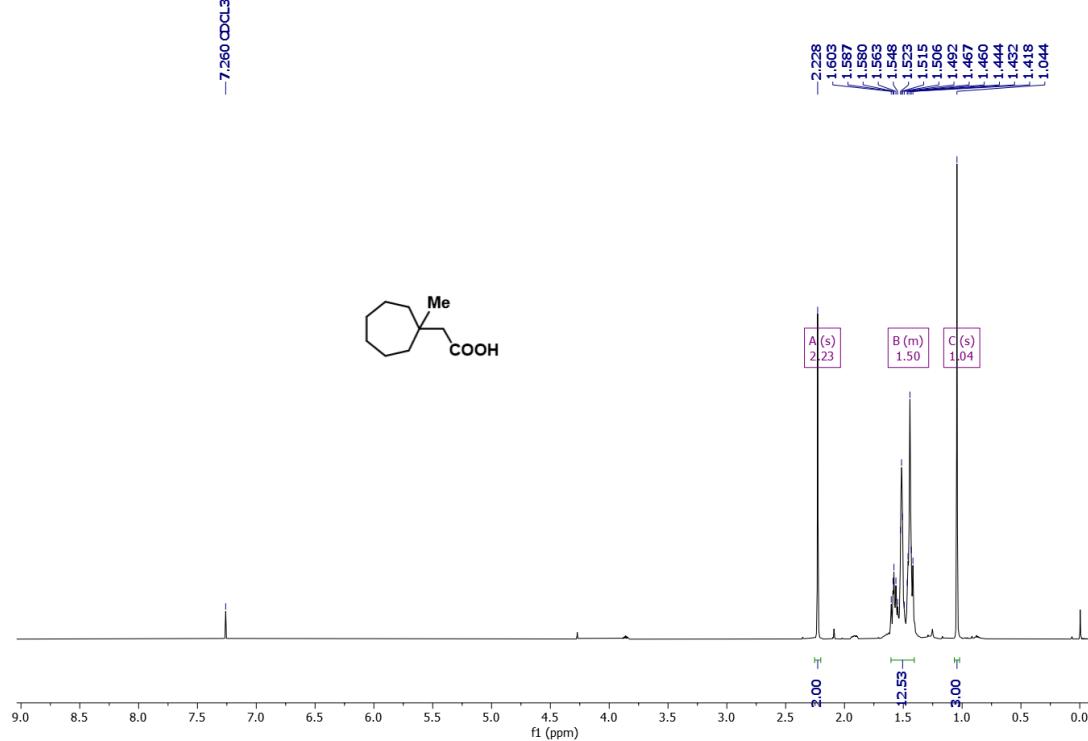


¹³C NMR (101 MHz, CDCl₃)

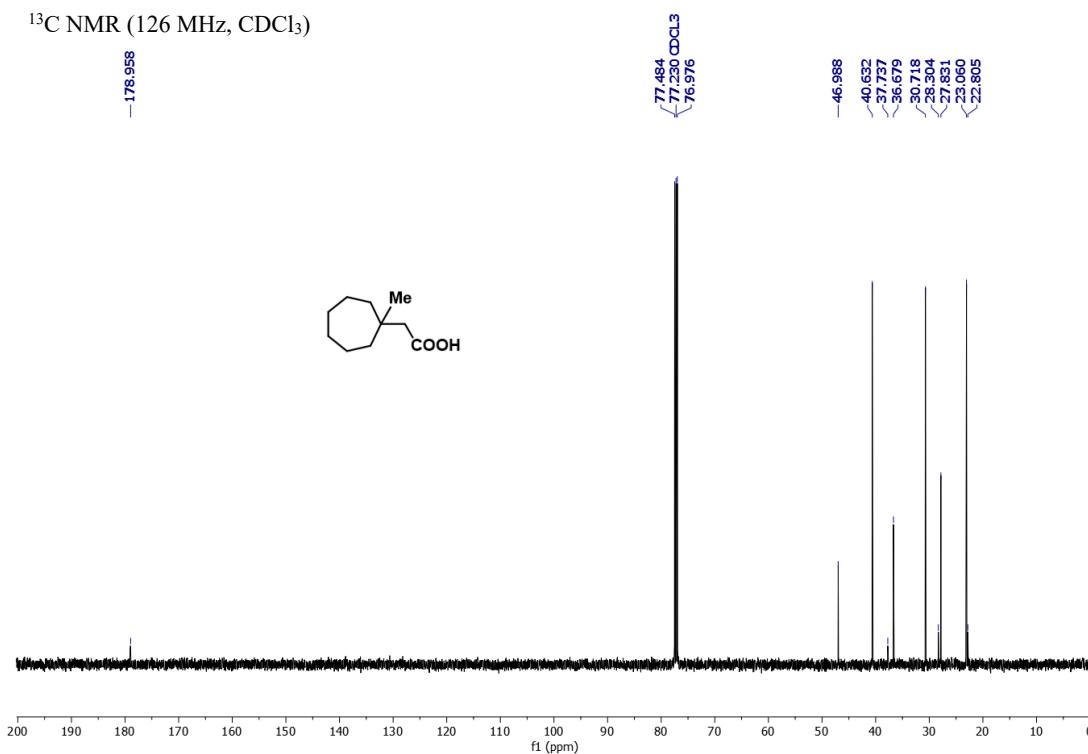


2-(1-Methylcycloheptyl)acetic acid (6)

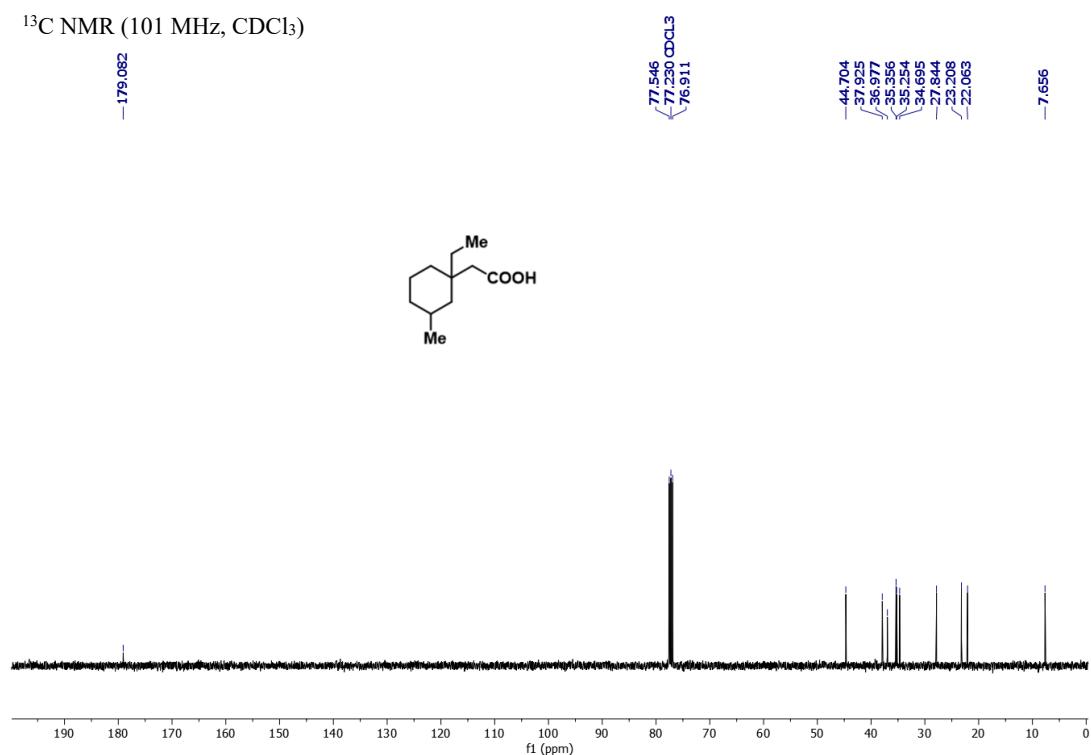
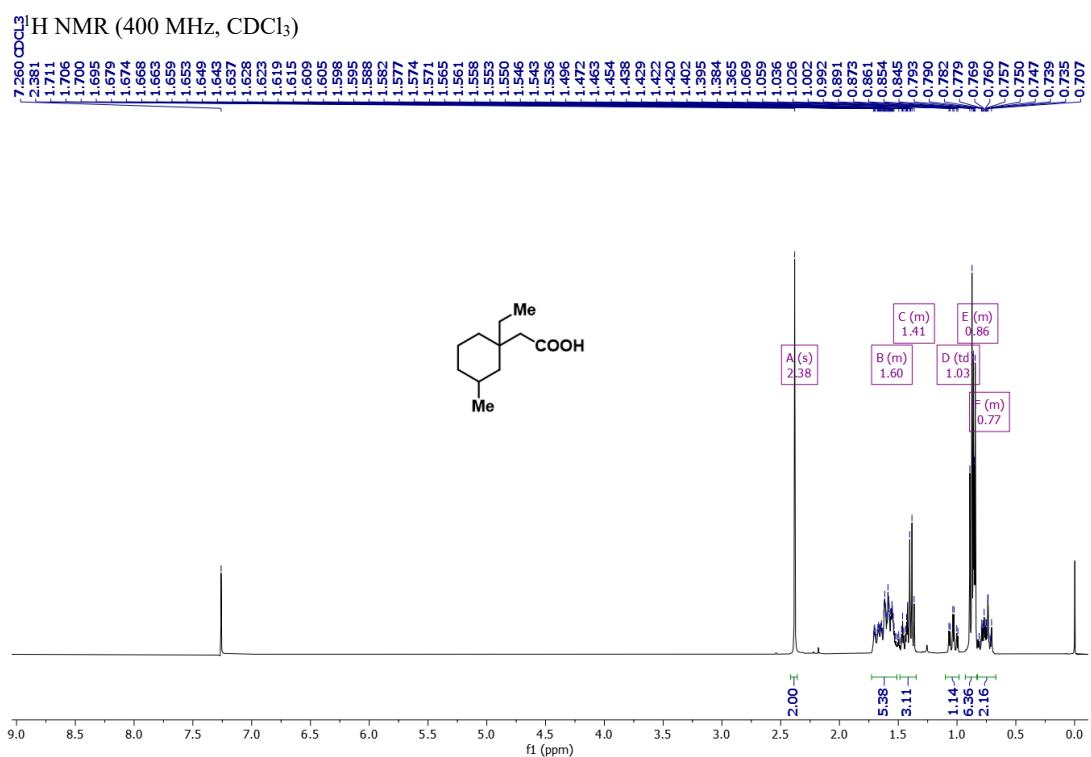
¹H NMR (500 MHz, CDCl₃)



¹³C NMR (126 MHz, CDCl₃)

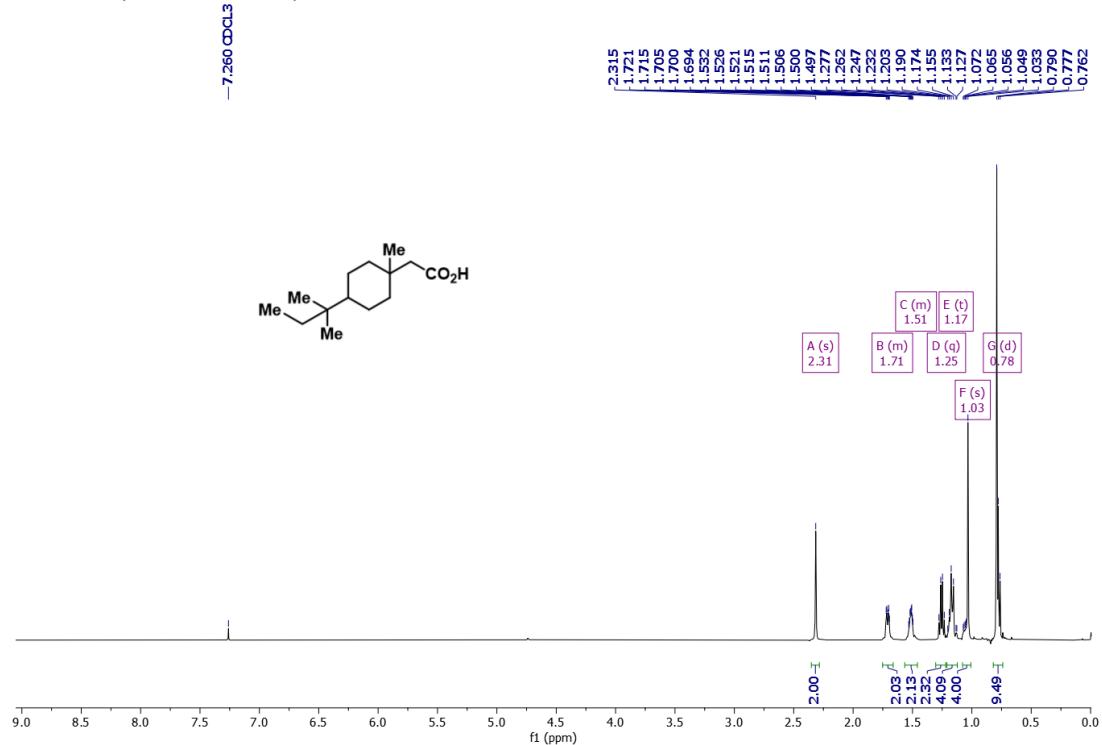


2-(1-Ethyl-3-methylcyclohexyl)acetic acid (7)

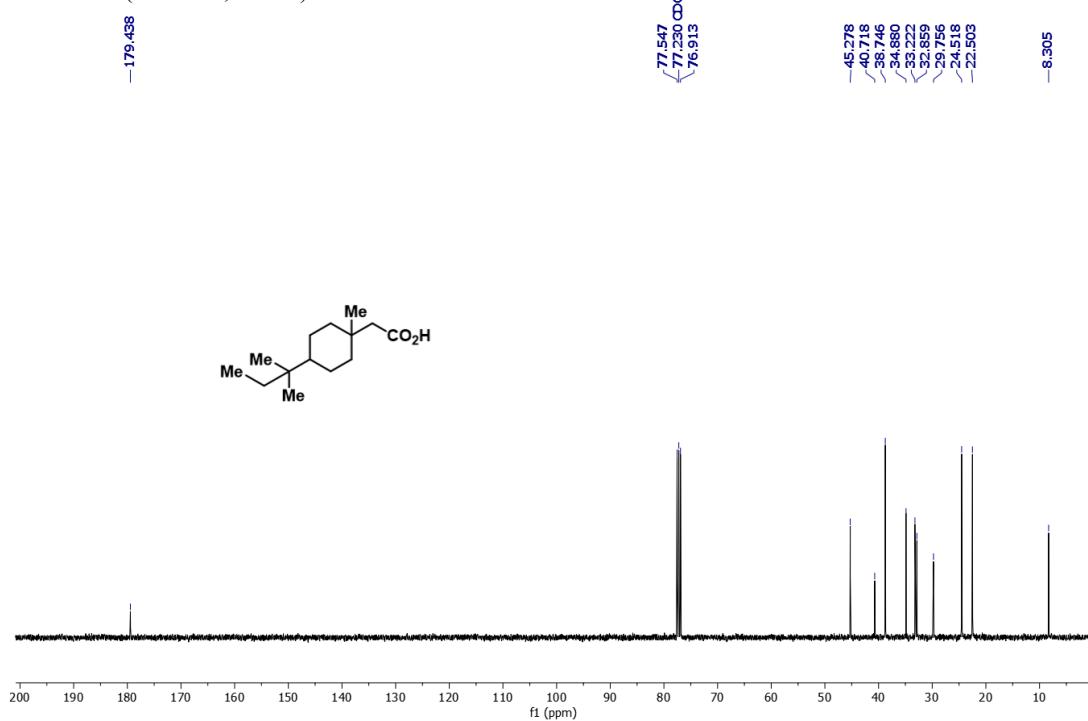


2-(1-Methyl-4-(*tert*-pentyl)cyclohexyl)acetic acid (8)

¹H NMR (500 MHz, CDCl₃)

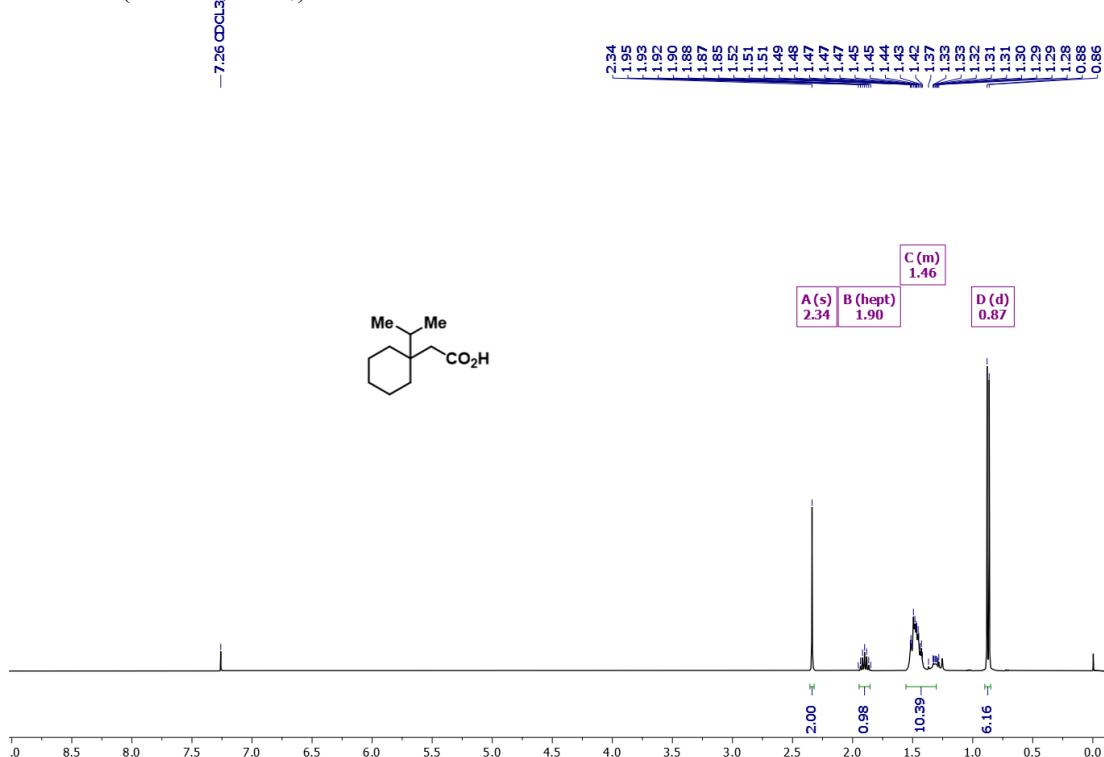


¹³C NMR (101 MHz, CDCl₃)

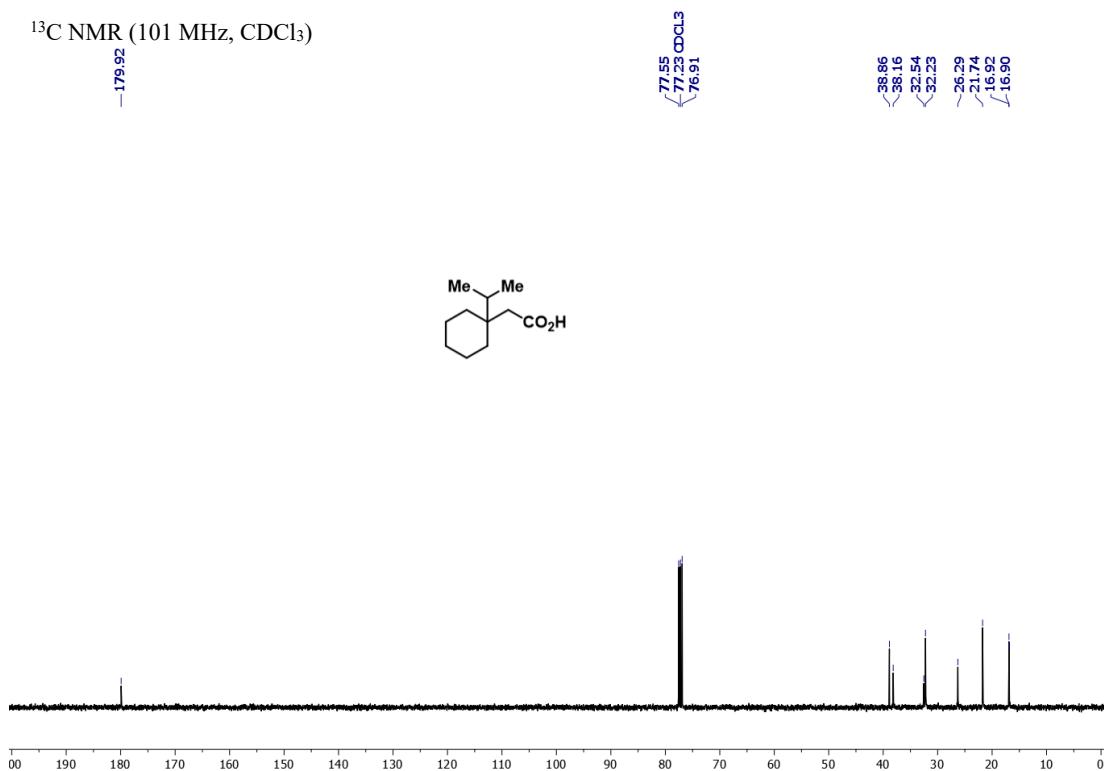


2-(1-Isopropylcyclohexyl)acetic acid (9)

¹H NMR (400 MHz, CDCl₃)

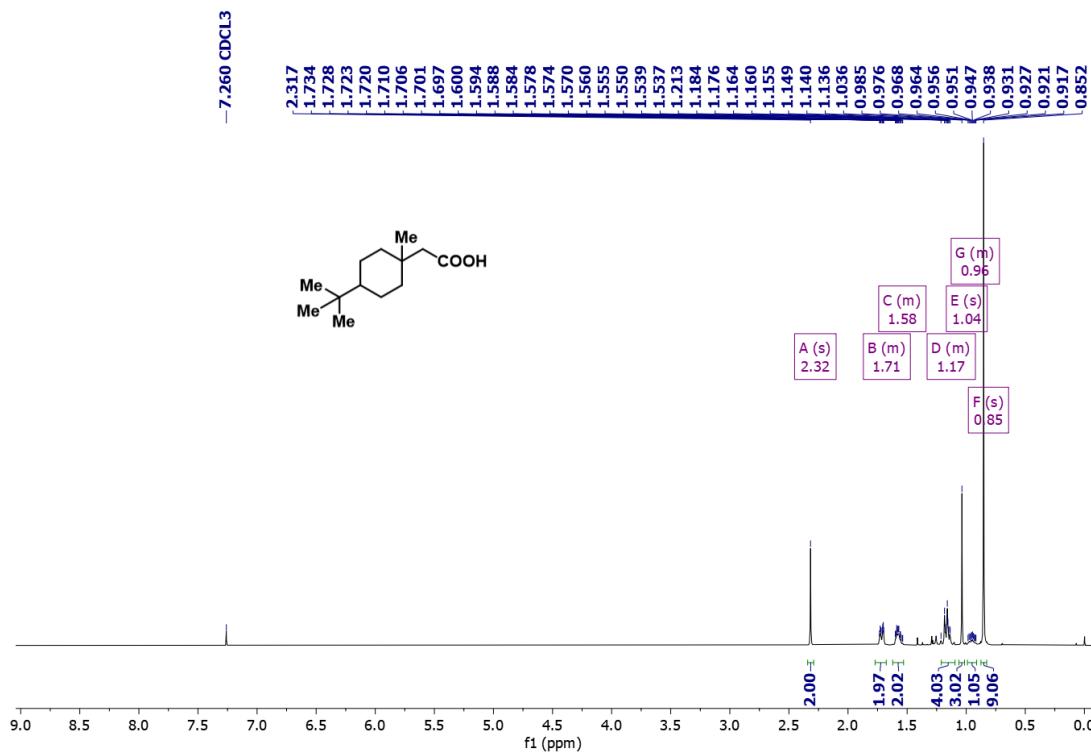


¹³C NMR (101 MHz, CDCl₃)

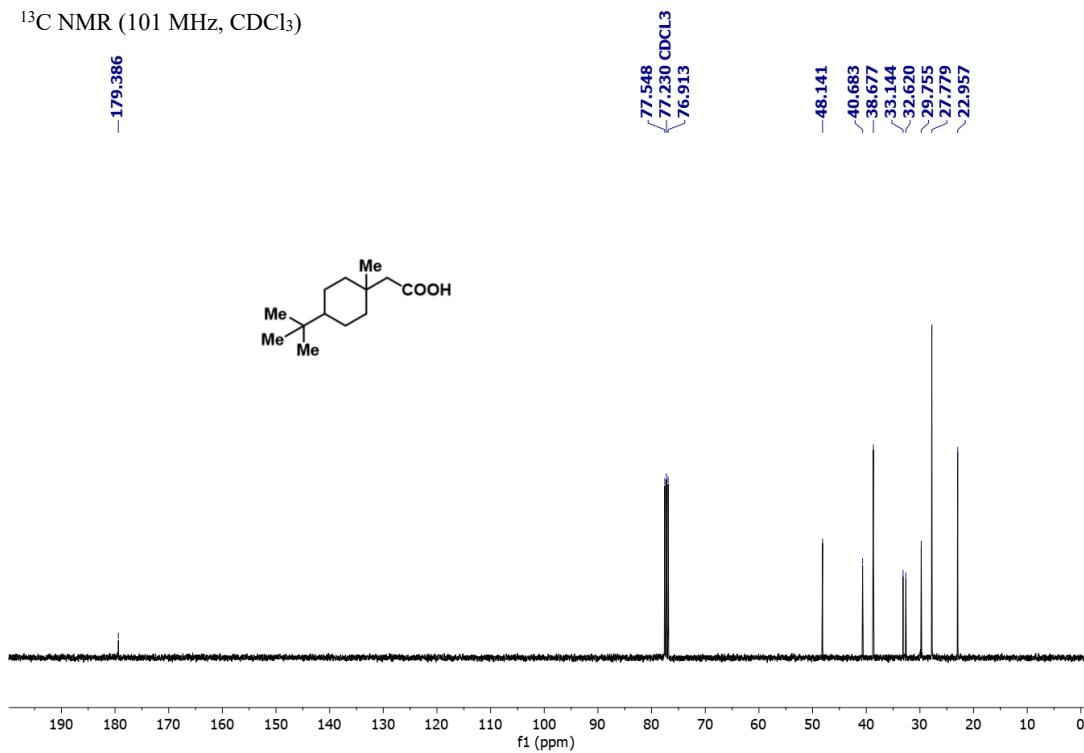


2-(4-(*tert*-Butyl)-1-methylcyclohexyl)acetic acid (10)

¹H NMR (400 MHz, CDCl₃)

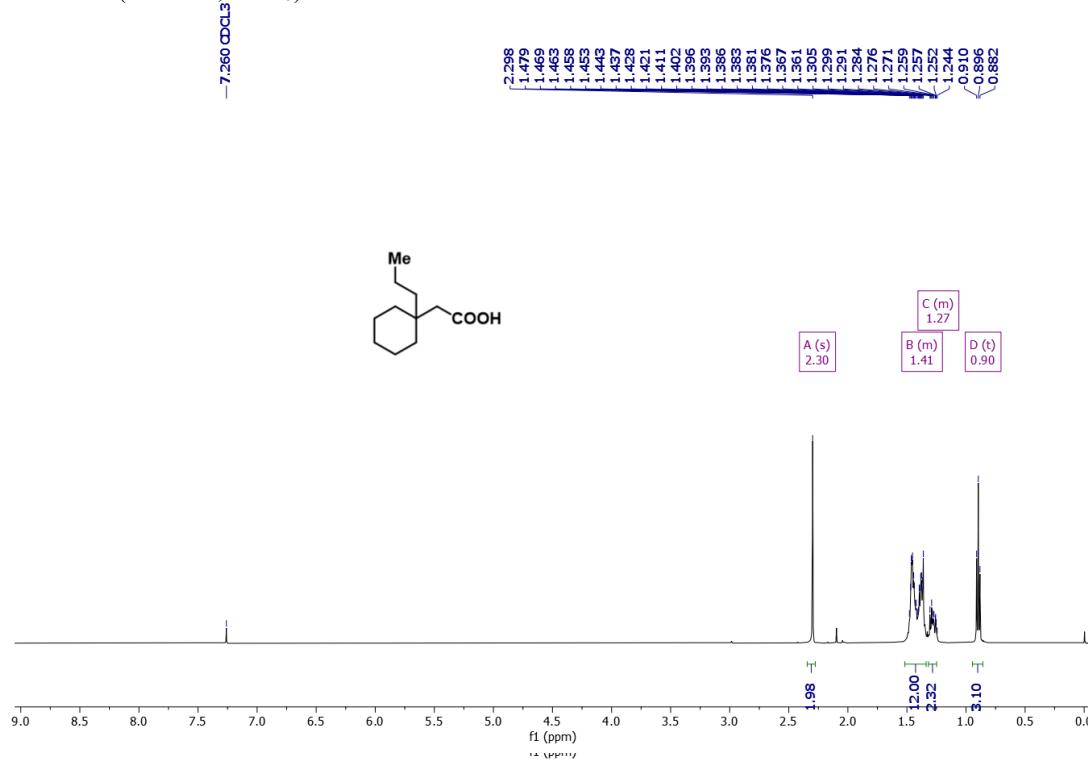


¹³C NMR (101 MHz, CDCl₃)

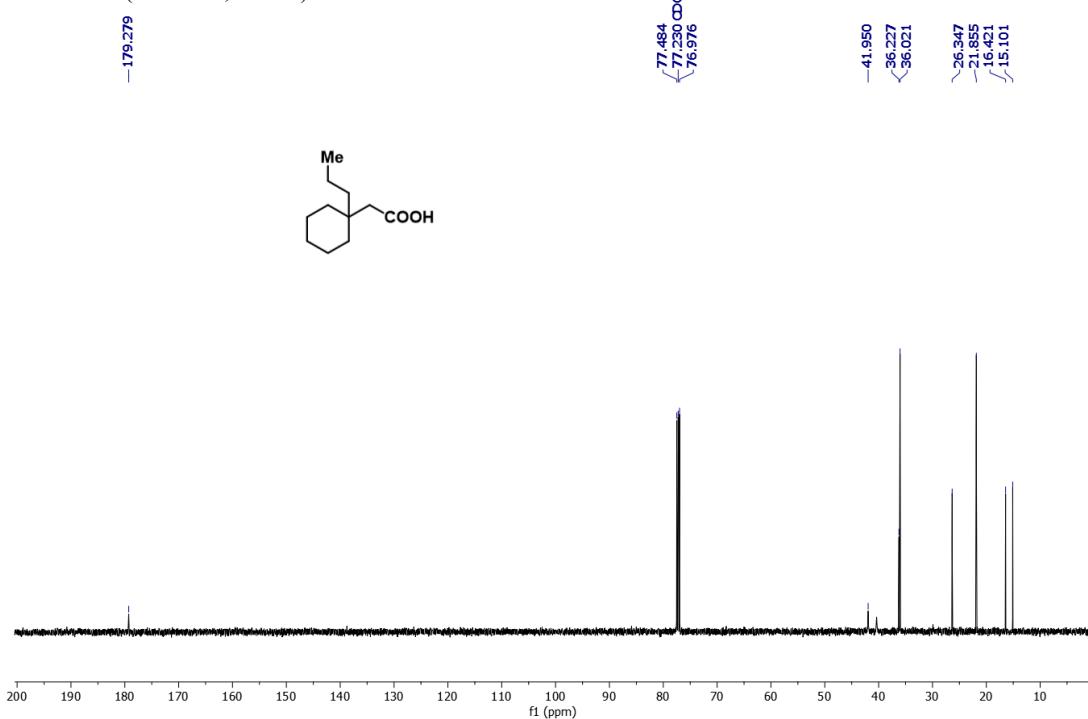


2-(1-Propylcyclohexyl)acetic acid (11)

¹H NMR (500 MHz, CDCl₃)

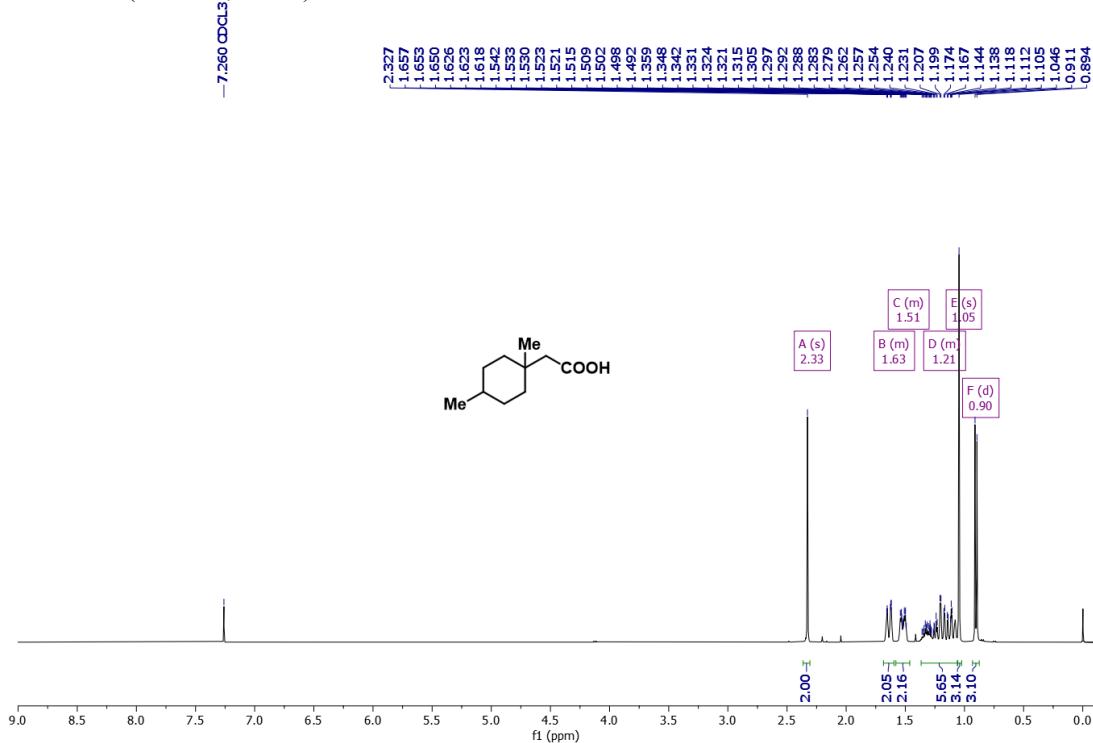


¹³C NMR (126 MHz, CDCl₃)

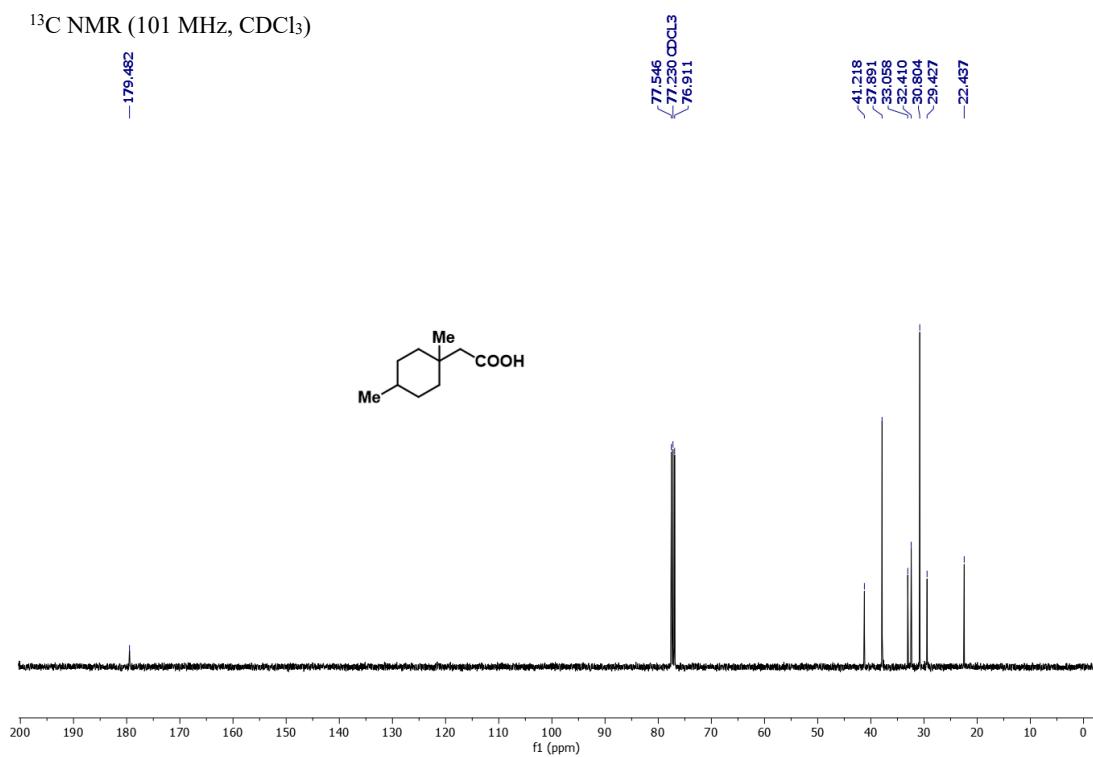


2-(1,4-Dimethylcyclohexyl)acetic acid (12)

¹H NMR (400 MHz, CDCl₃)

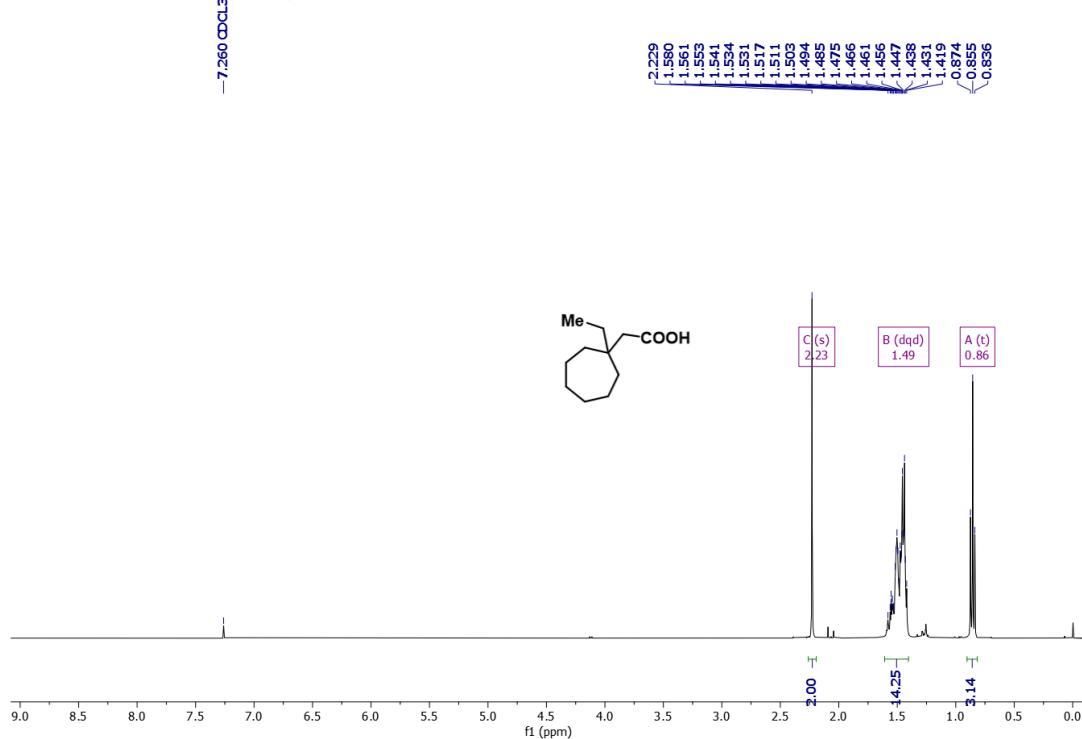


¹³C NMR (101 MHz, CDCl₃)

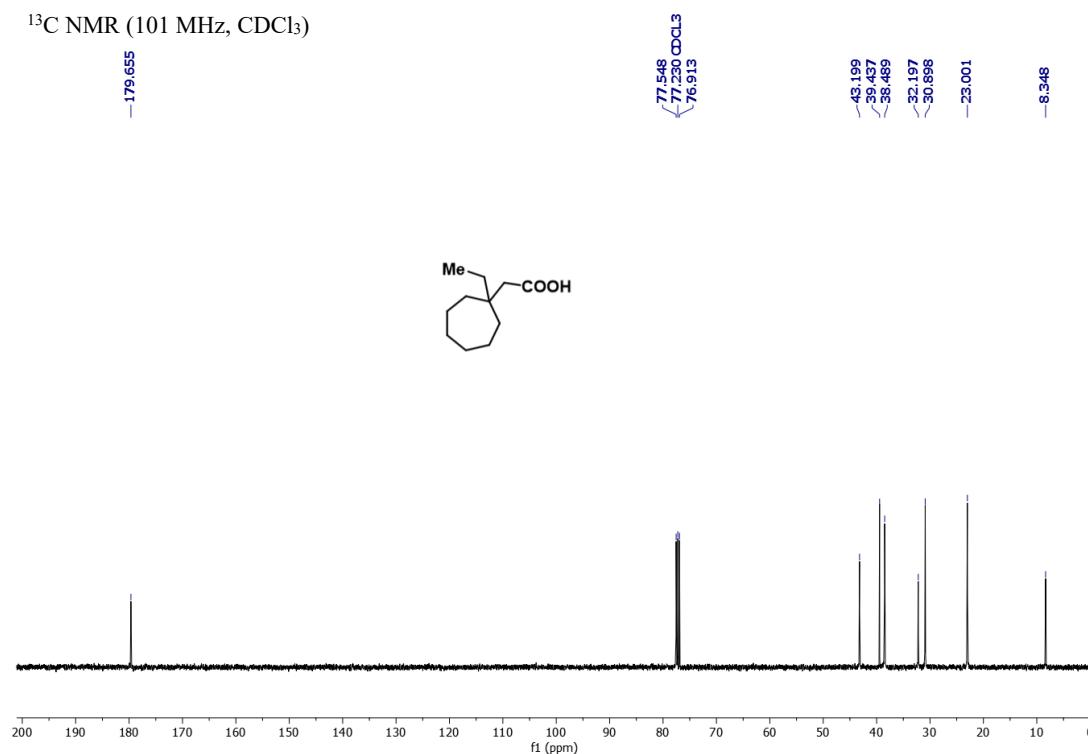


2-(1-Ethylcycloheptyl)acetic acid (13)

¹H NMR (400 MHz, CDCl₃)

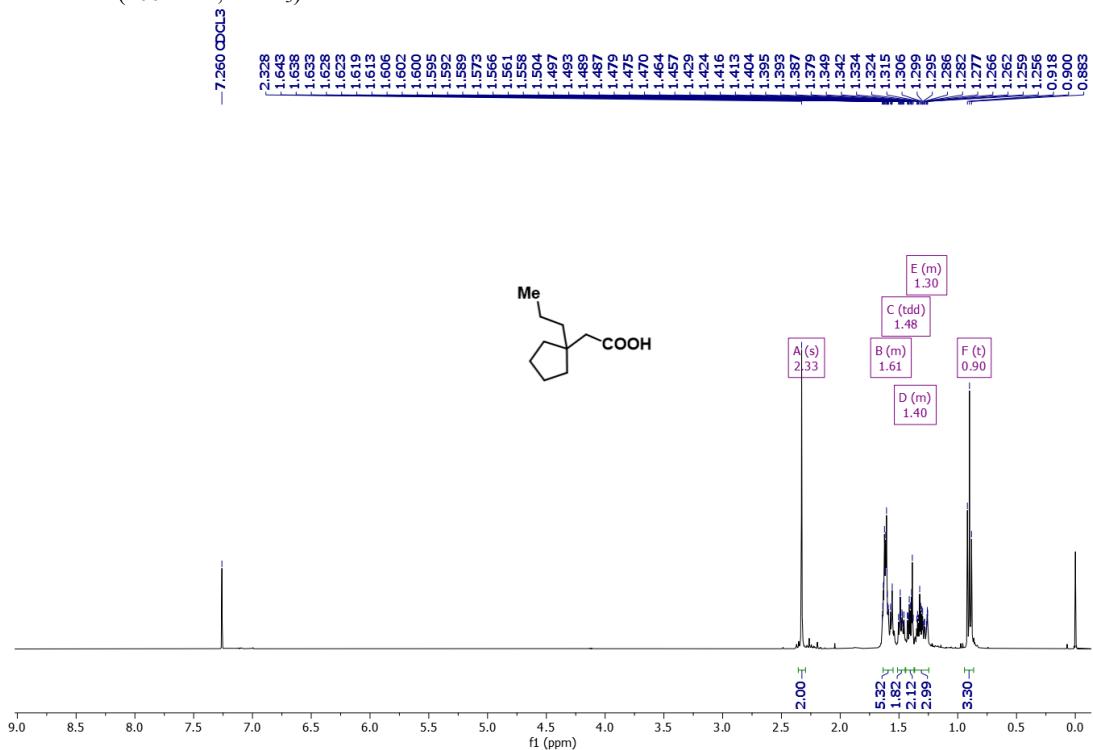


¹³C NMR (101 MHz, CDCl₃)

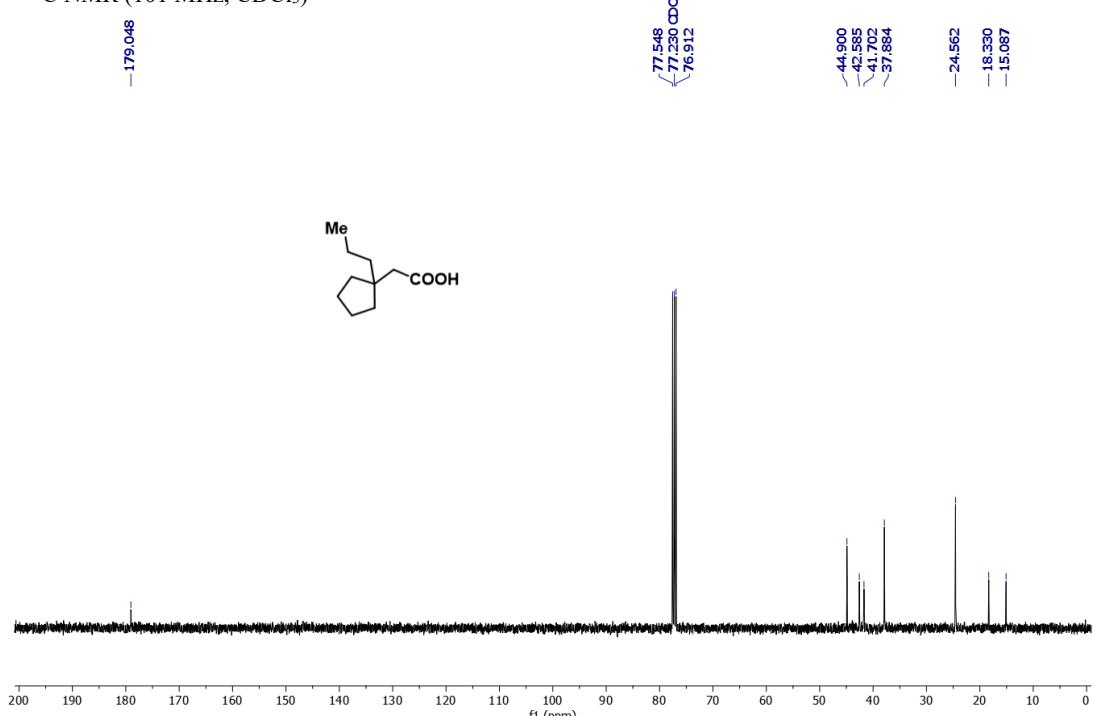


2-(1-Propylcyclopentyl)acetic acid (14)

¹H NMR (400 MHz, CDCl₃)

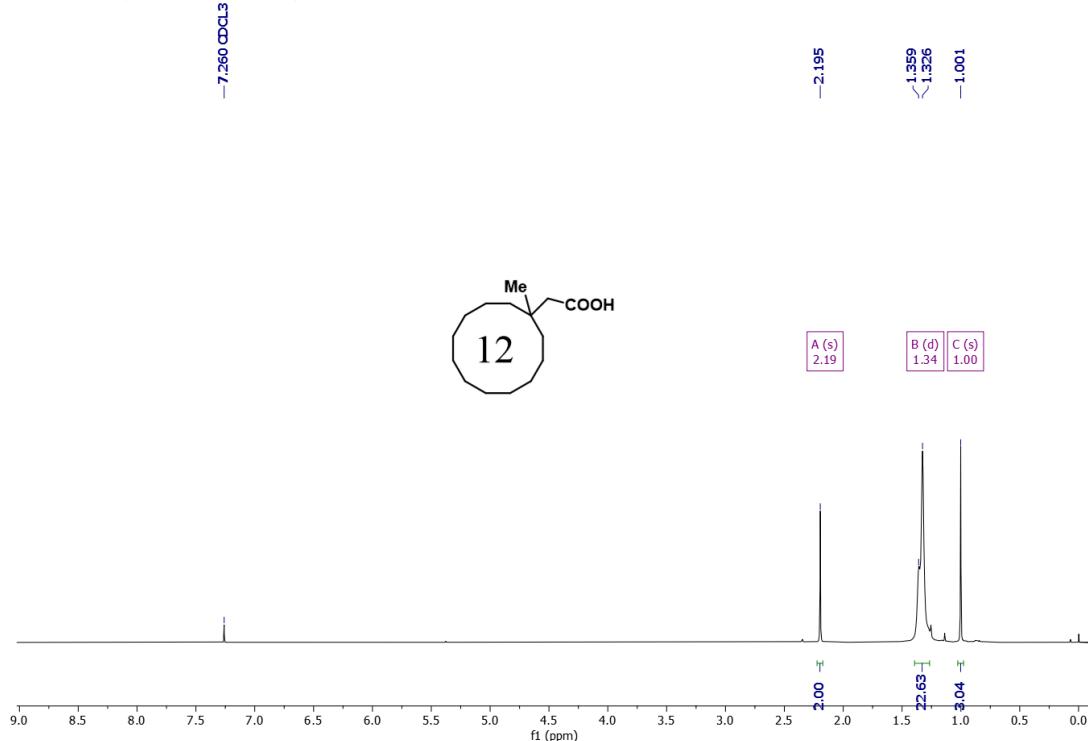


¹³C NMR (101 MHz, CDCl₃)

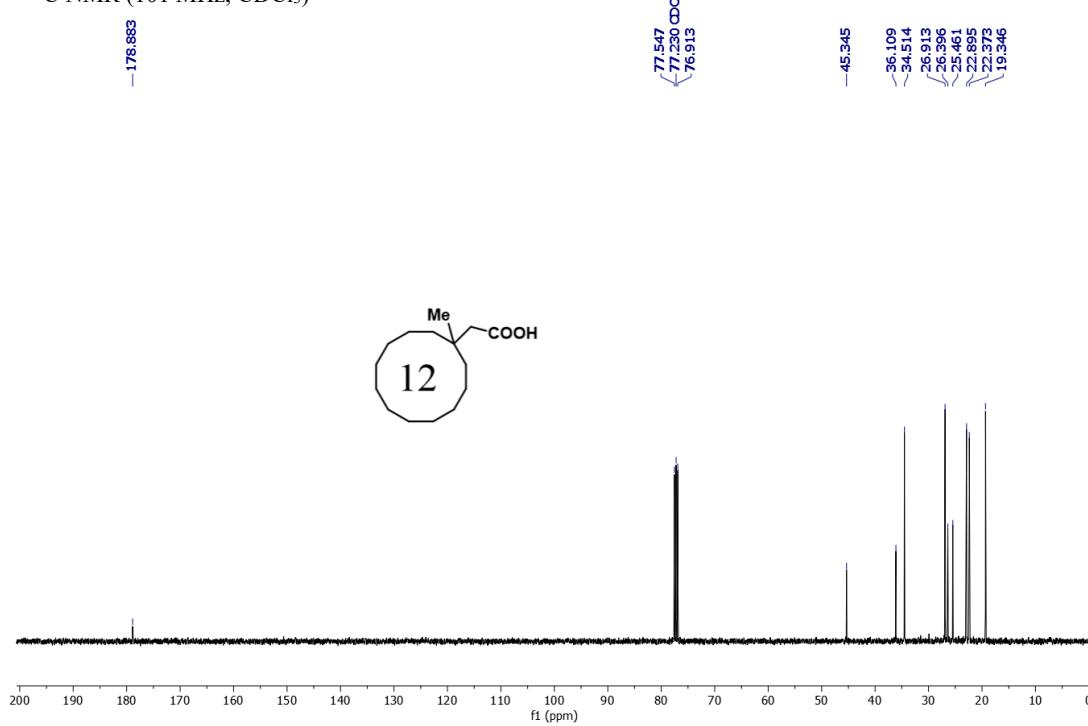


2-(1-Methylcyclododecyl)acetic acid (15)

¹H NMR (400 MHz, CDCl₃)

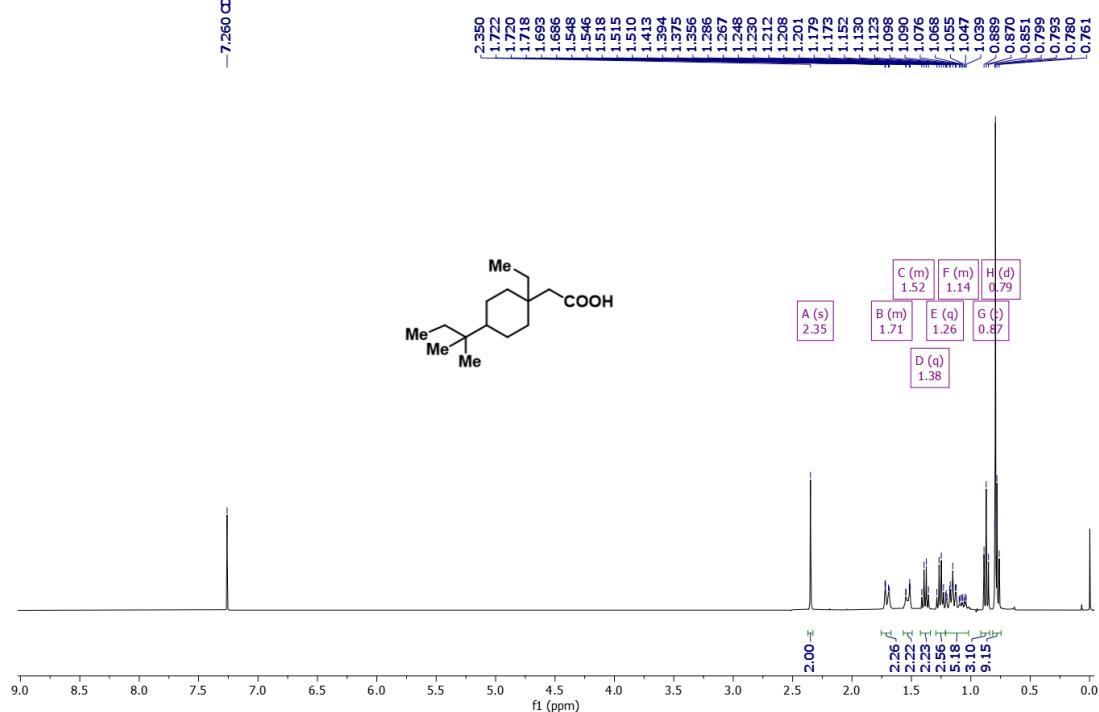


¹³C NMR (101 MHz, CDCl₃)

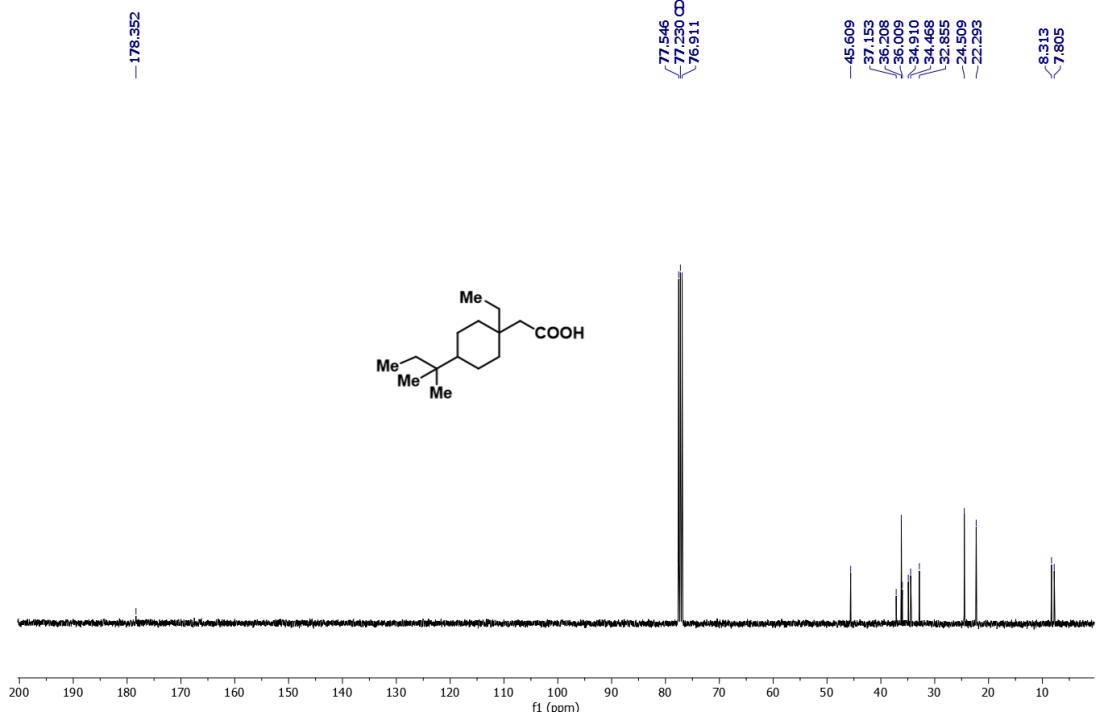


2-(1-Ethyl-4-(*tert*-pentyl)cyclohexyl)acetic acid (16)

^1H NMR (400 MHz, CDCl_3)

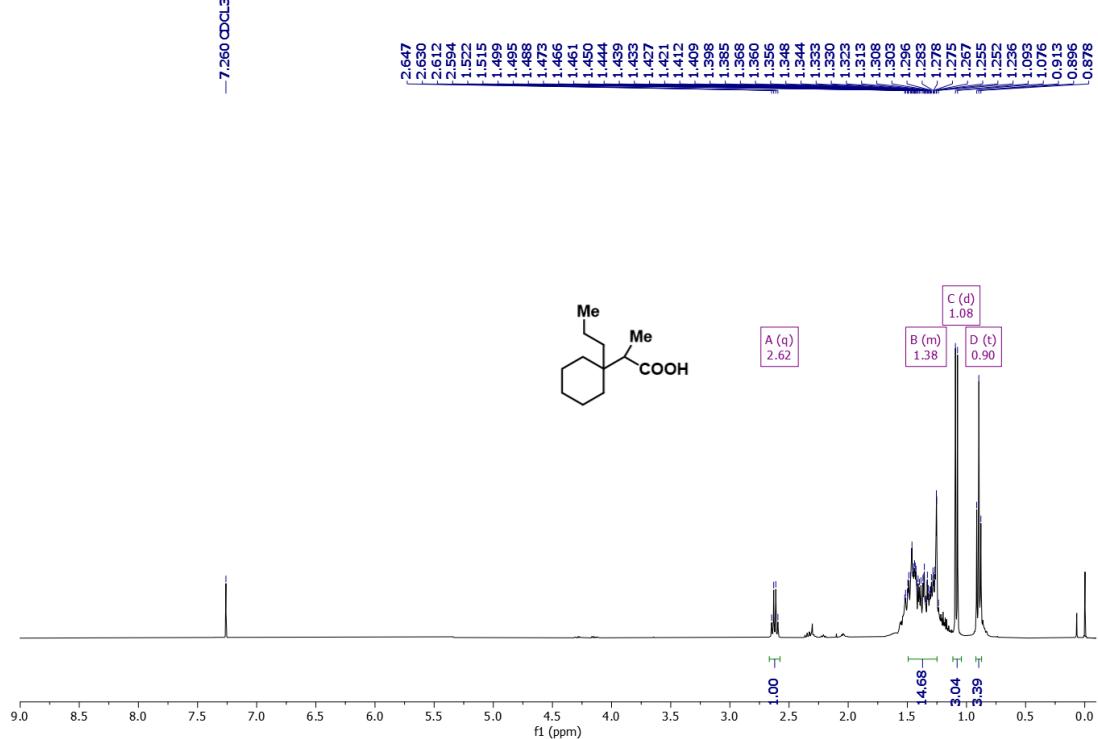


^{13}C NMR (101 MHz, CDCl_3)

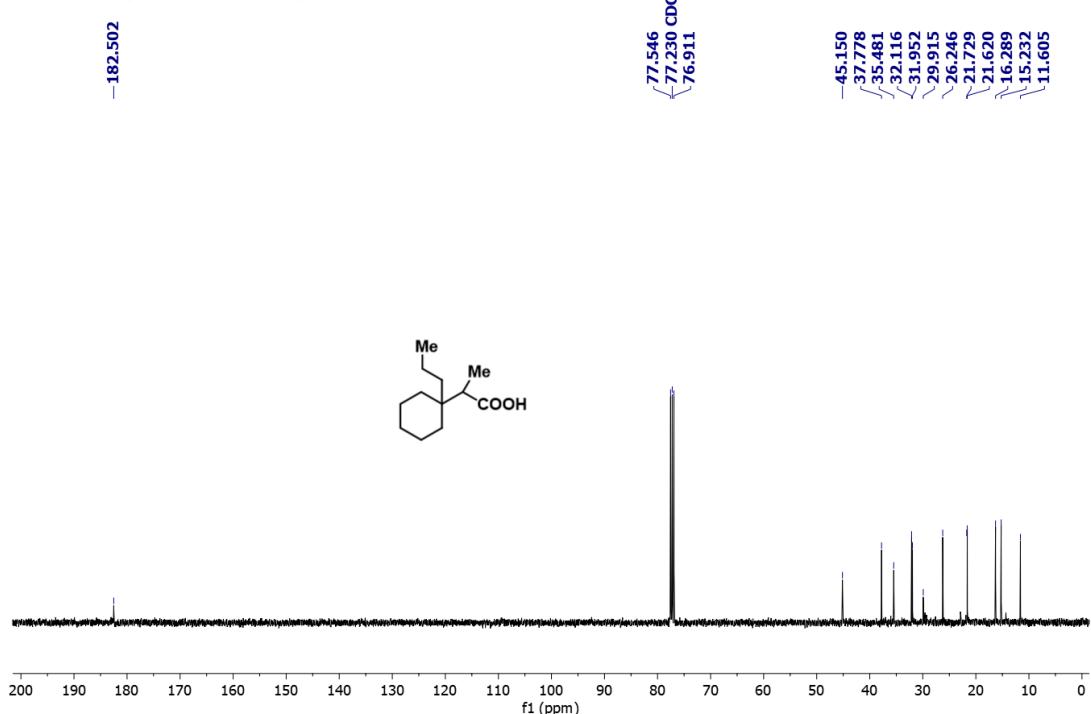


2-(1-Propylcyclohexyl)propanoic acid (17)

¹H NMR (400 MHz, CDCl₃)

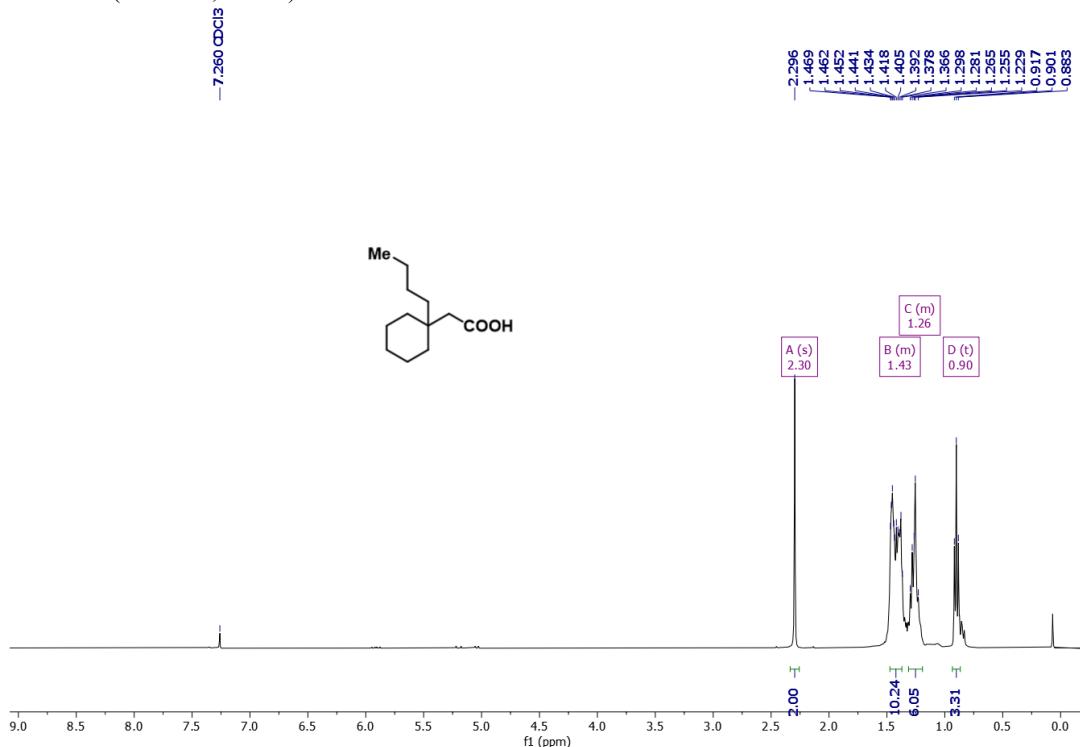


¹³C NMR (101 MHz, CDCl₃)

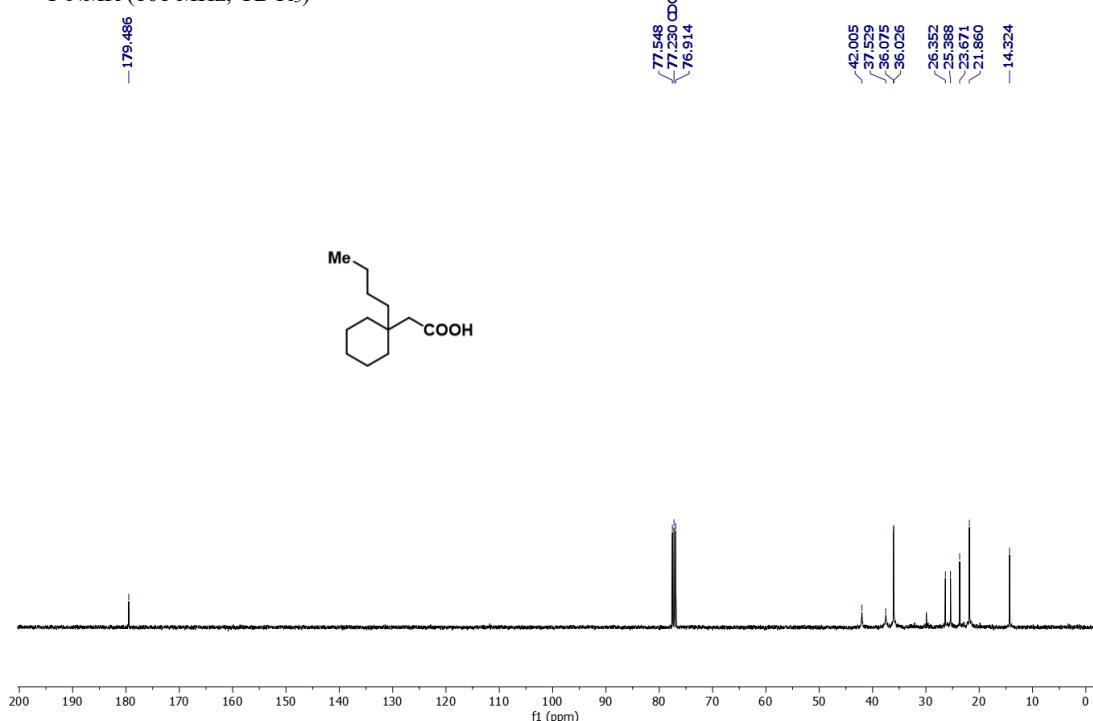


2-(1-Butylcyclohexyl)acetic acid (18)

¹H NMR (400 MHz, CDCl₃)

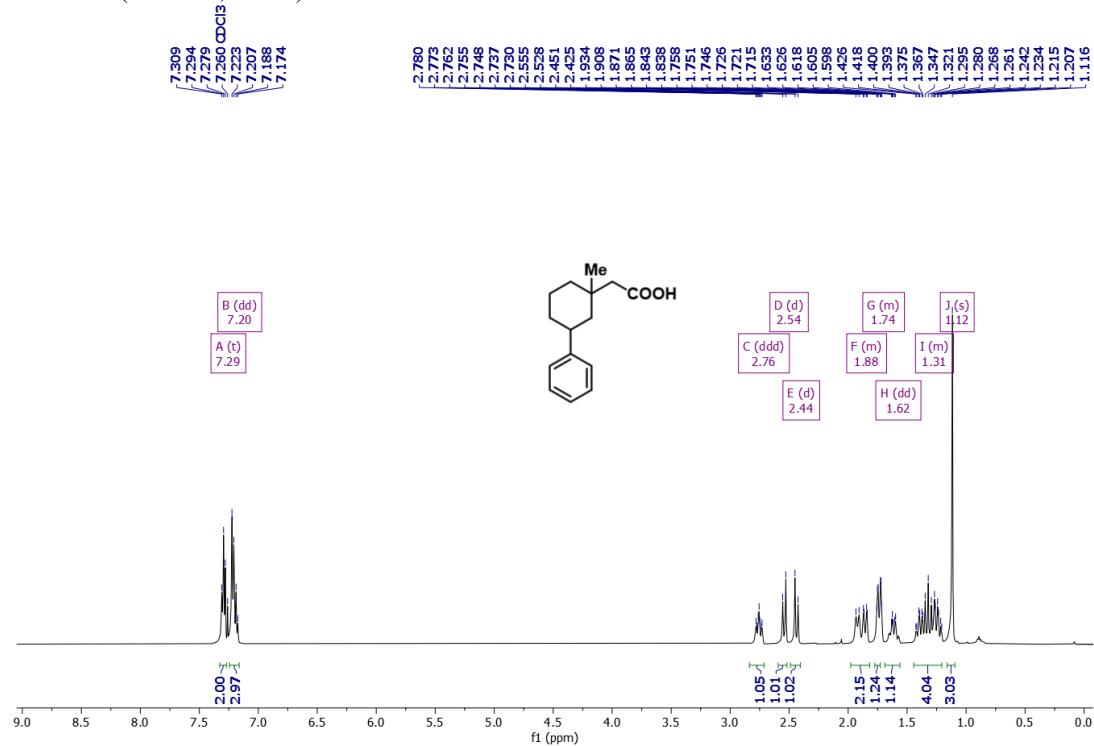


¹³C NMR (101 MHz, CDCl₃)

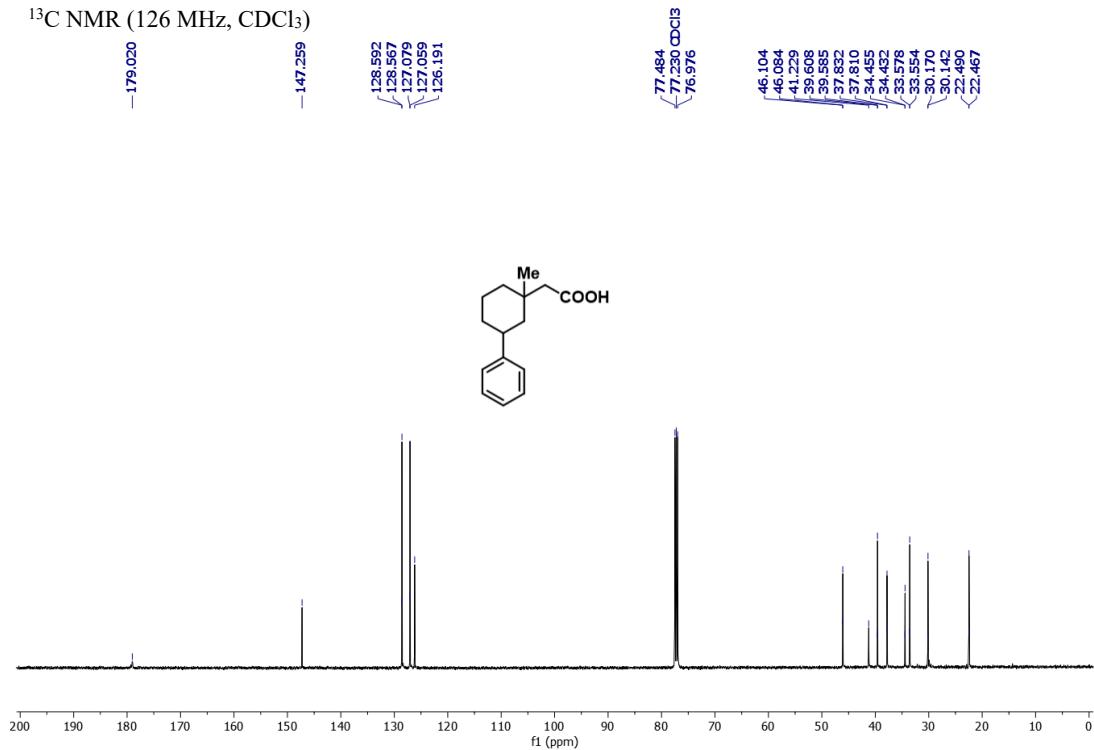


2-(1-Methyl-3-phenylcyclohexyl)acetic acid (19)

¹H NMR (500 MHz, CDCl₃)

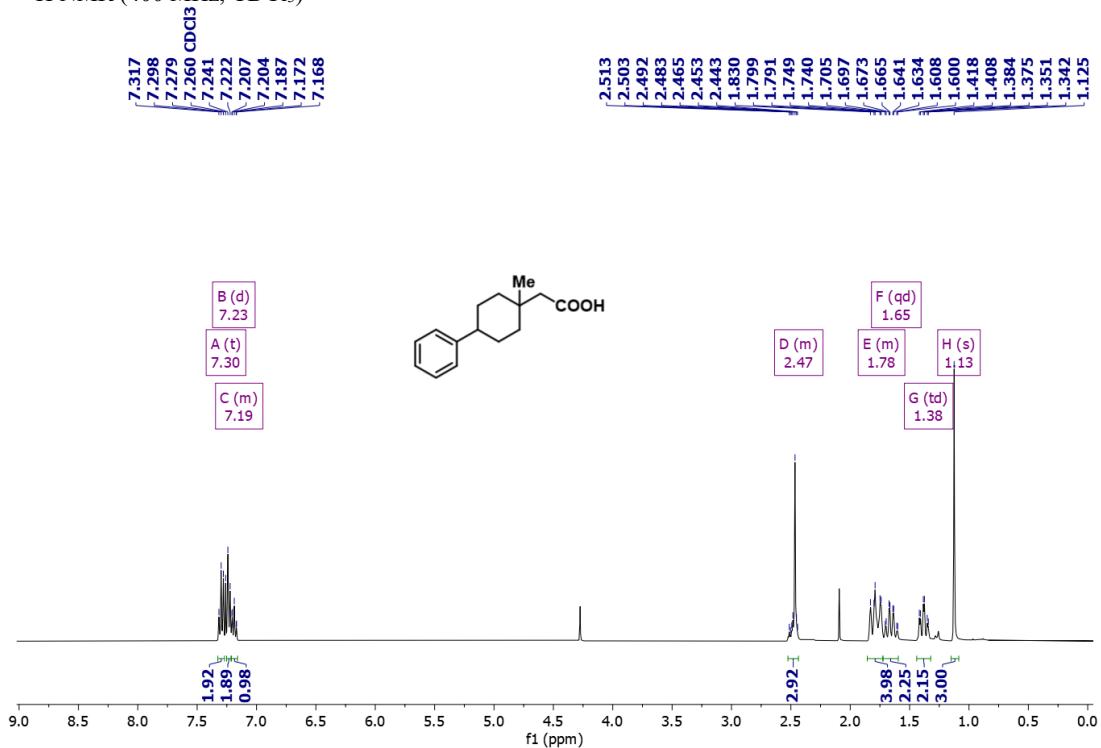


¹³C NMR (126 MHz, CDCl₃)

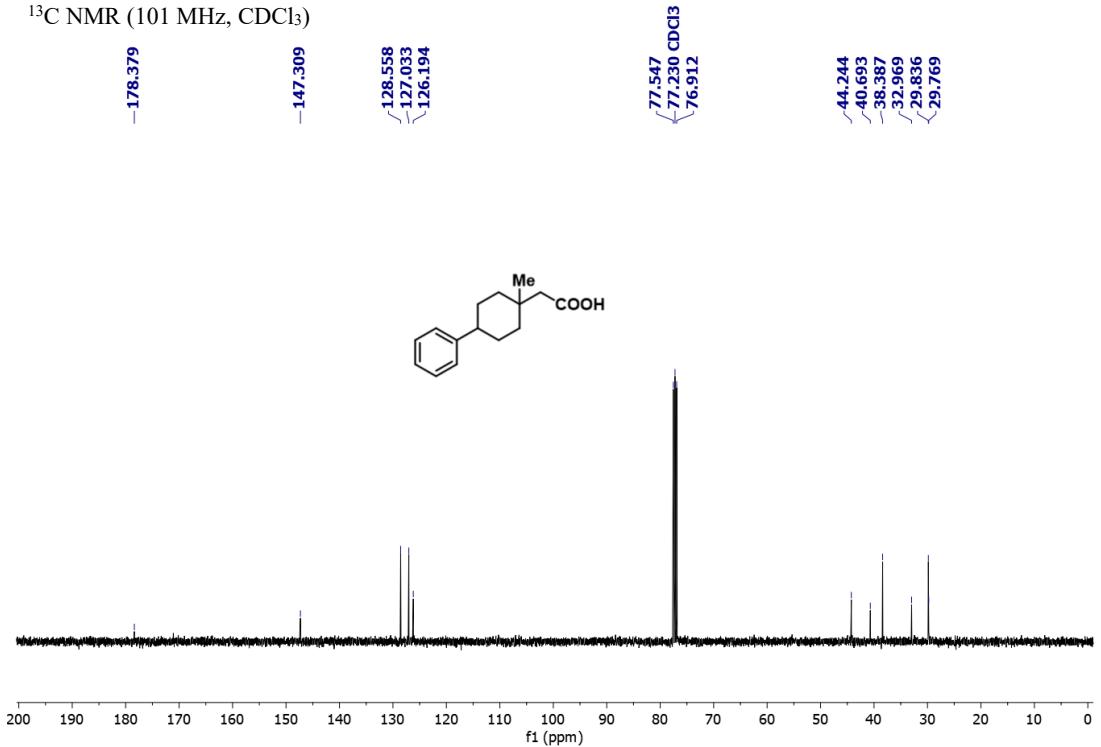


2-(1-Methyl-4-phenylcyclohexyl)acetic acid (20)

¹H NMR (400 MHz, CDCl₃)

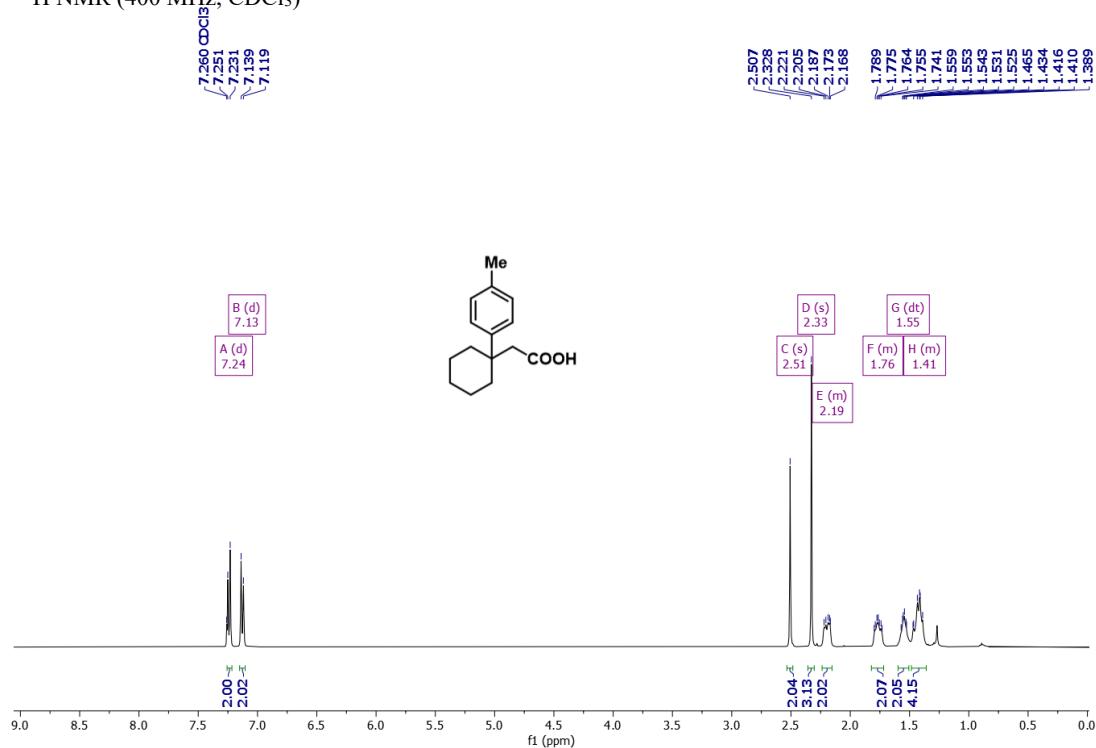


¹³C NMR (101 MHz, CDCl₃)

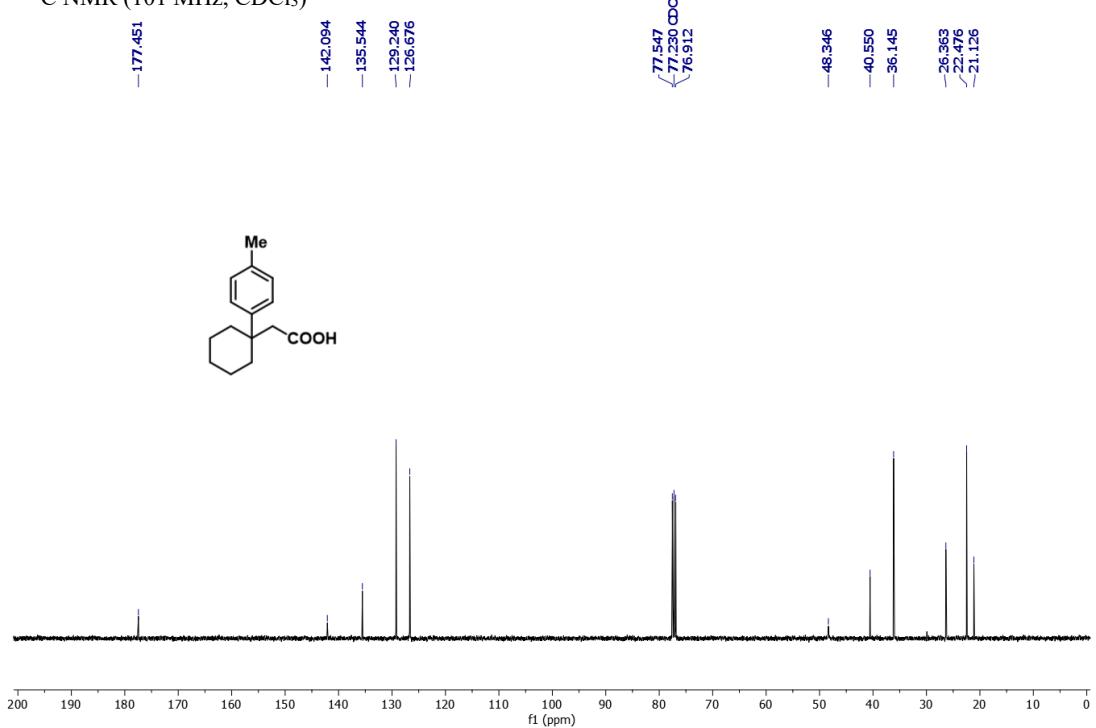


2-(1-(*p*-Tolyl)cyclohexyl)acetic acid (21)

¹H NMR (400 MHz, CDCl₃)

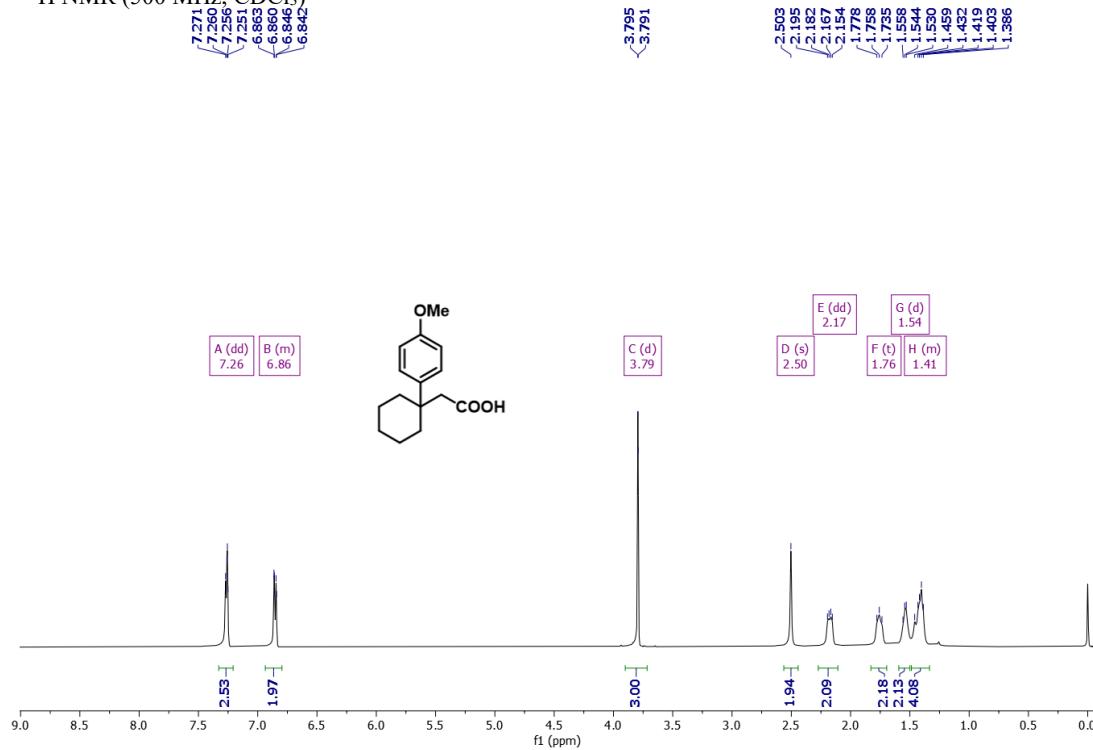


¹³C NMR (101 MHz, CDCl₃)

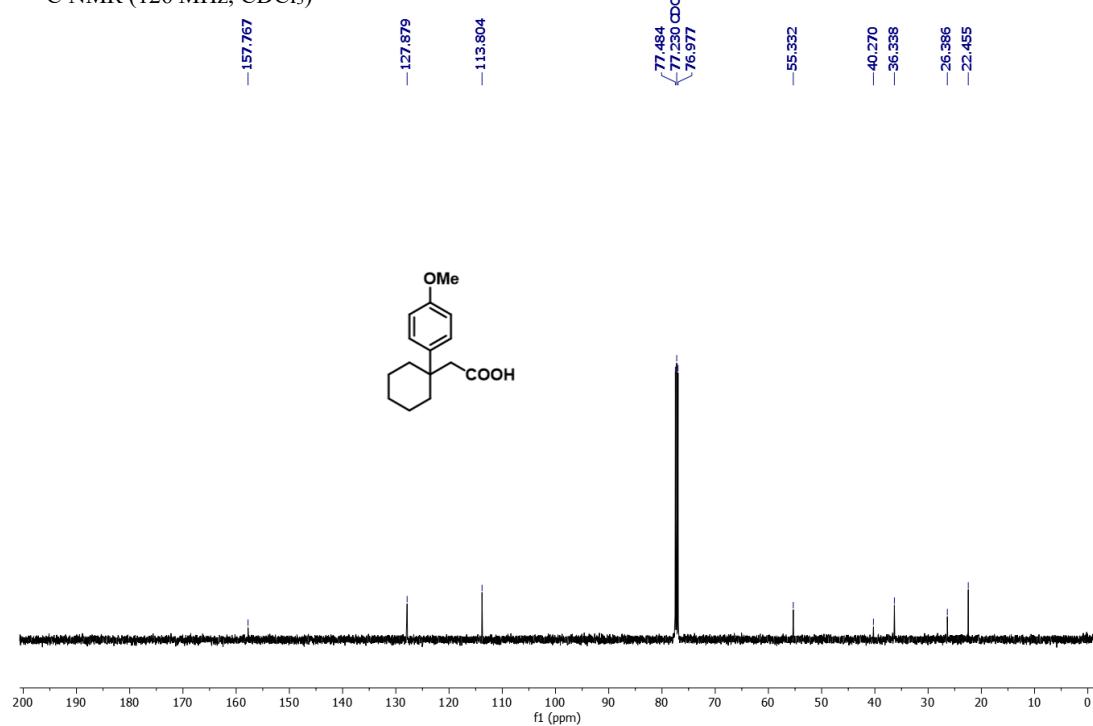


2-(1-(4-Methoxyphenyl)cyclohexyl)acetic acid (22)

¹H NMR (500 MHz, CDCl₃)

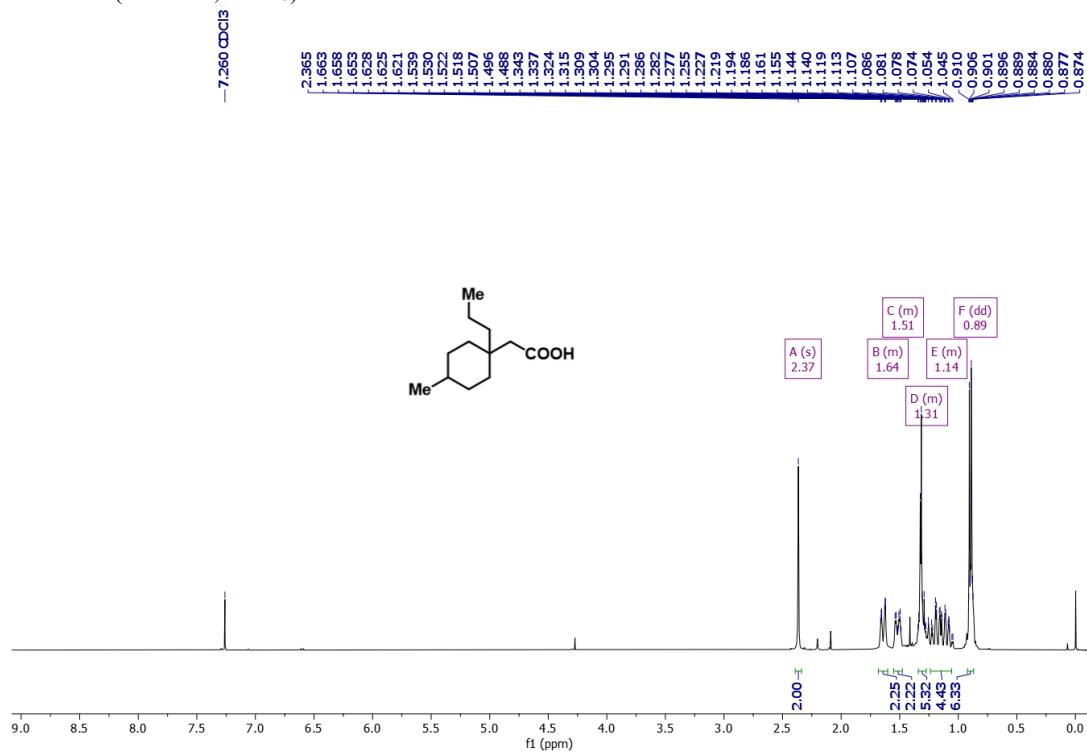


¹³C NMR (126 MHz, CDCl₃)

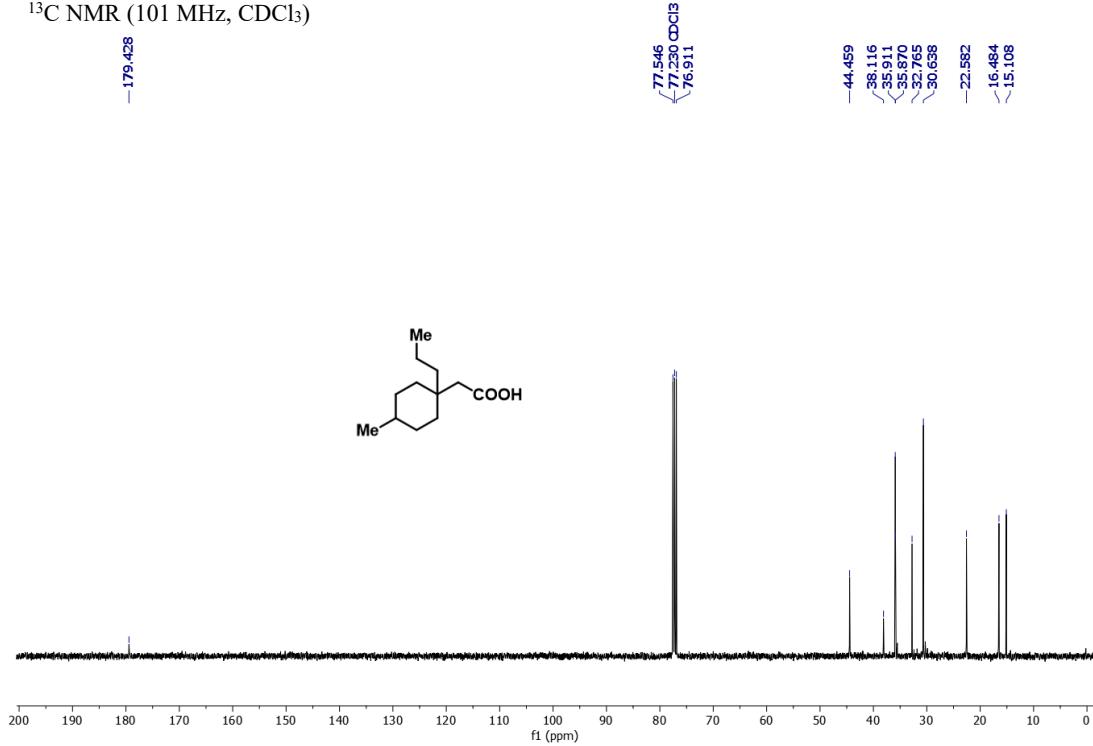


2-(4-Methyl-1-propylcyclohexyl)acetic acid (23)

¹H NMR (400 MHz, CDCl₃)

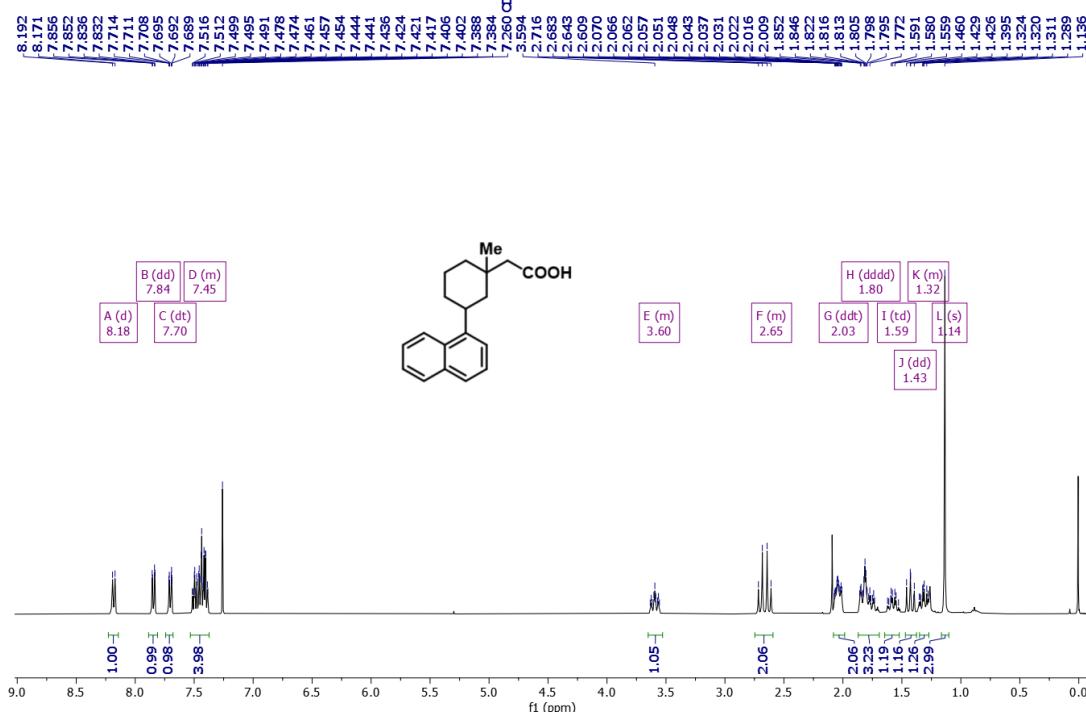


¹³C NMR (101 MHz, CDCl₃)

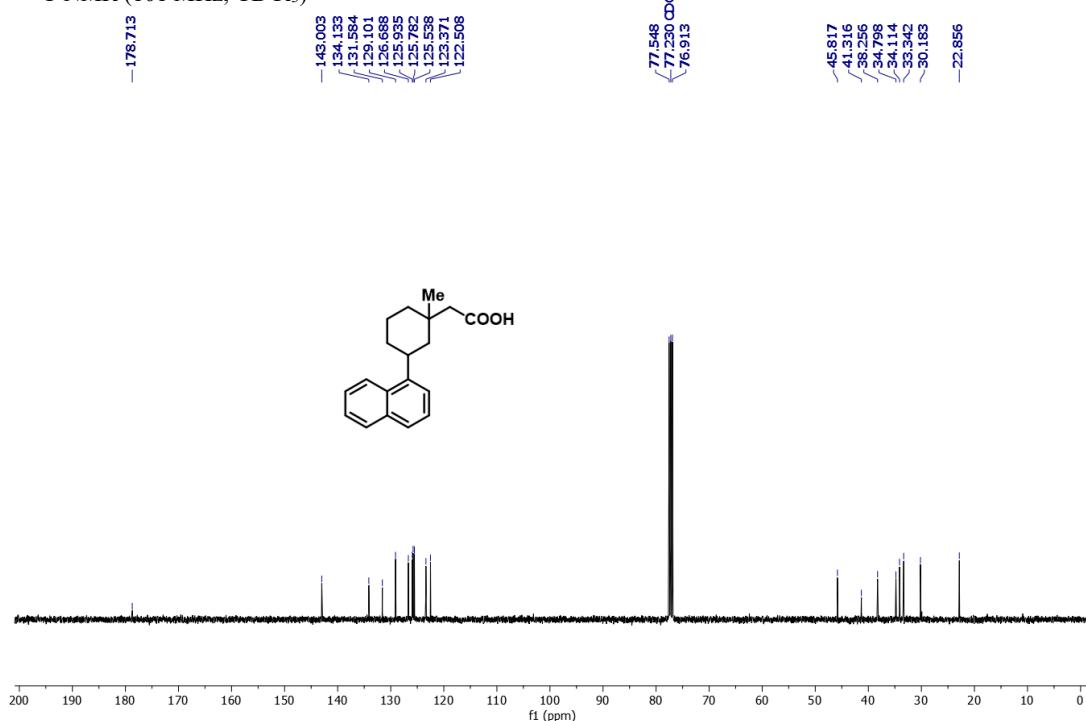


2-(1-Methyl-3-(naphthalen-1-yl)cyclohexyl)acetic acid (24)

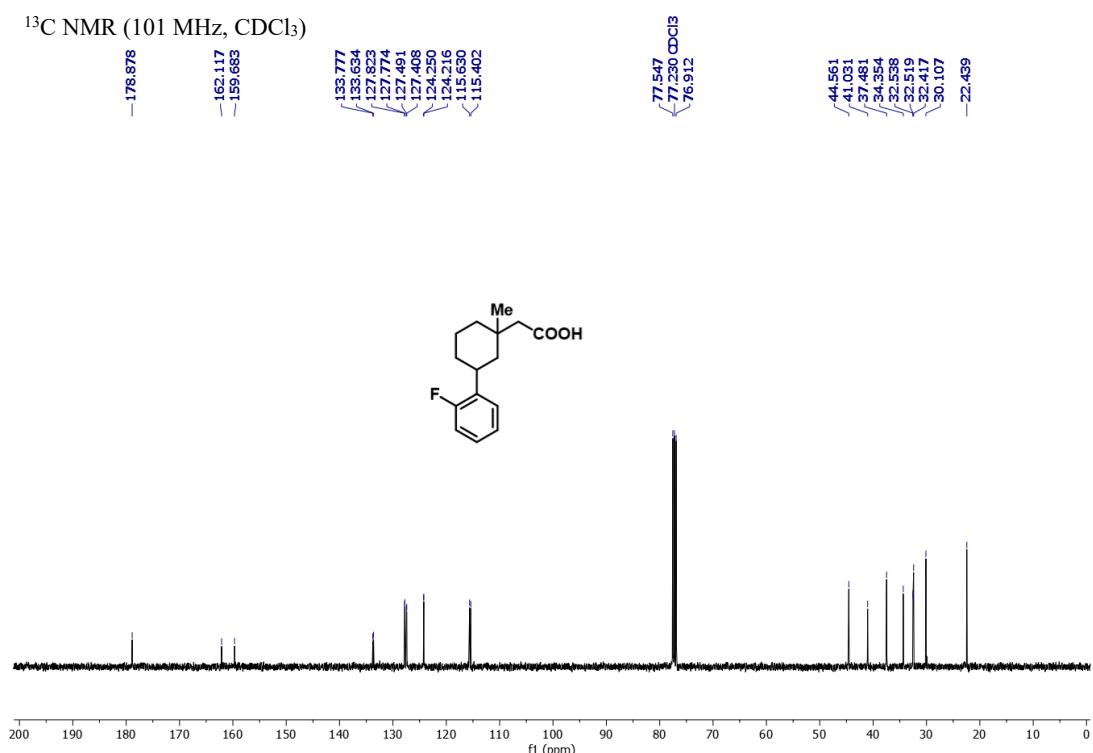
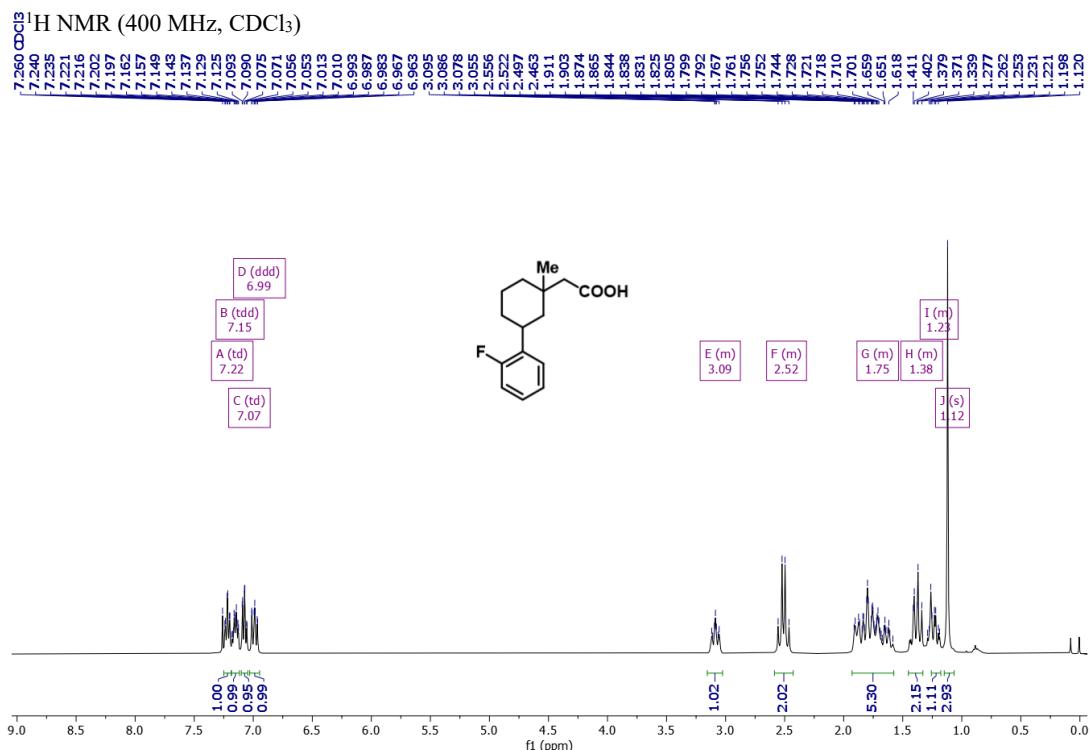
¹H NMR (400 MHz, CDCl₃)



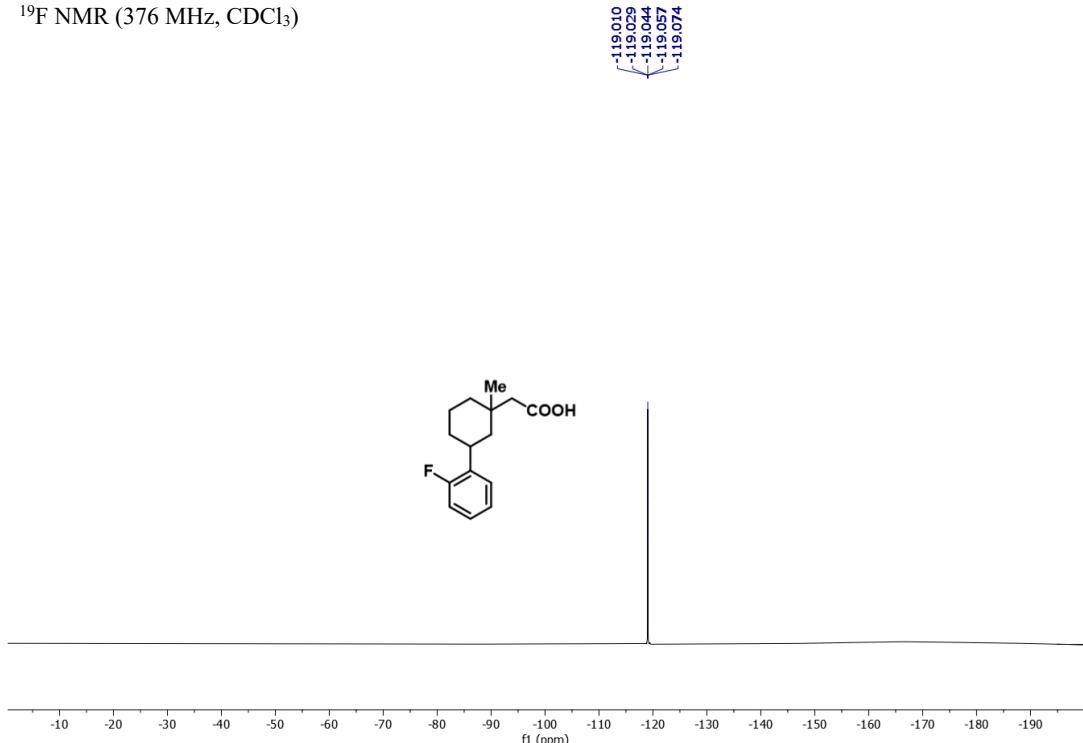
¹³C NMR (101 MHz, CDCl₃)



2-(3-(2-Fluorophenyl)-1-methylcyclohexyl)acetic acid (25)

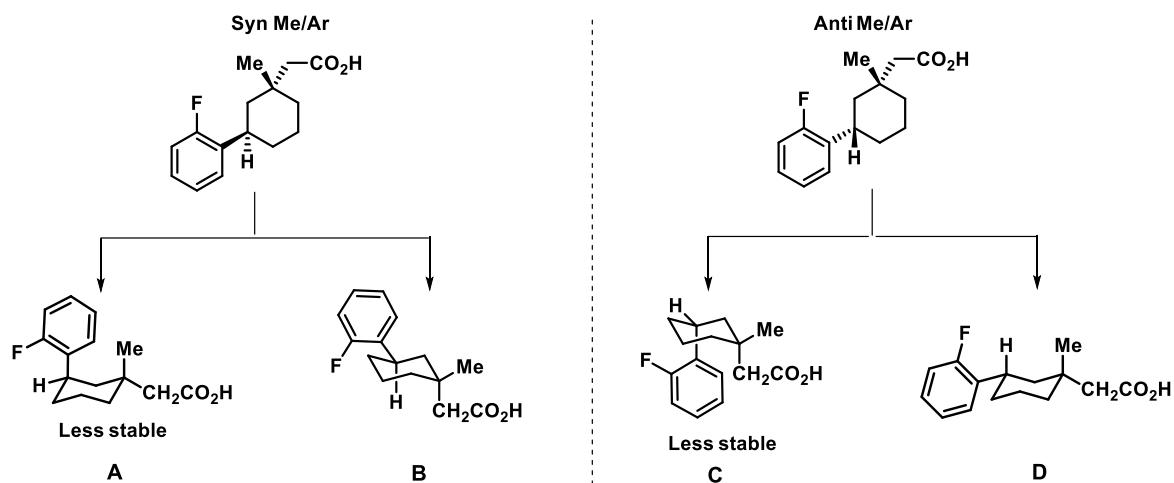


¹⁹F NMR (376 MHz, CDCl₃)

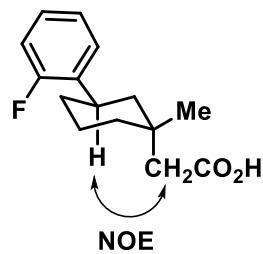
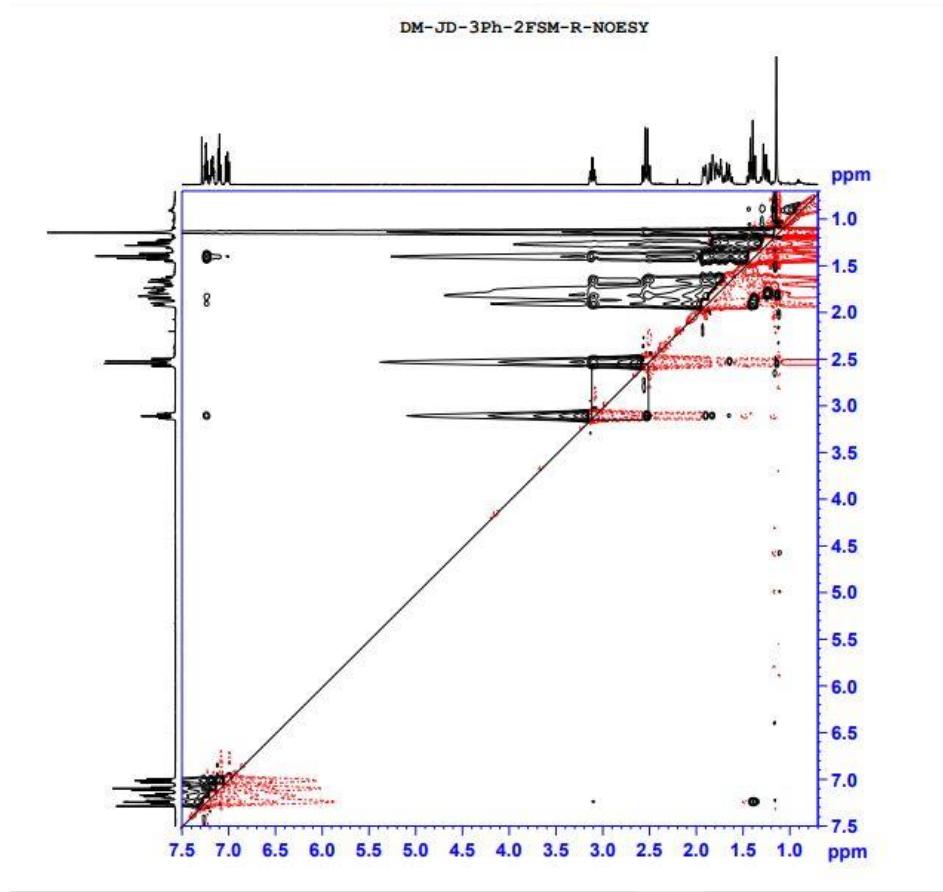


NOESY data to establish the stereochemistry of 3-aryl-1-(methylcyclohexyl)acetic acids. 2-(3-(2-fluorophenyl)-1-methylcyclohexyl)acetic acid has taken here as an representative example.

There could be total four conformations based on syn and anti-relationship between Me and 3-substituted Aryl group as shown below. Conformations where Aryl ring is in axial position would be less stable due to 1,3-diaxial interaction (A and C). Thus B and D are more stable conformations for syn and anti-diastereomers. Our aim here to identify the relative stereochemistry (syn or anti) though NOESY.



Following is the NOESY data for 2-(3-(2-fluorophenyl)-1-methylcyclohexyl)acetic acid.

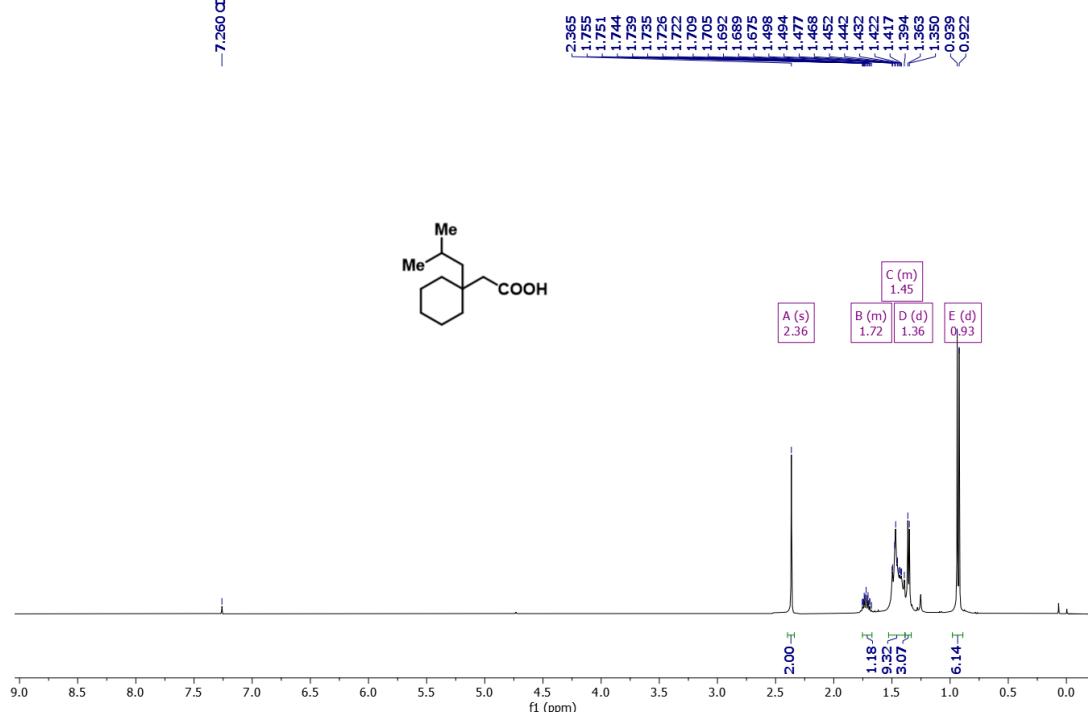


B
Established via NOESY
experiment

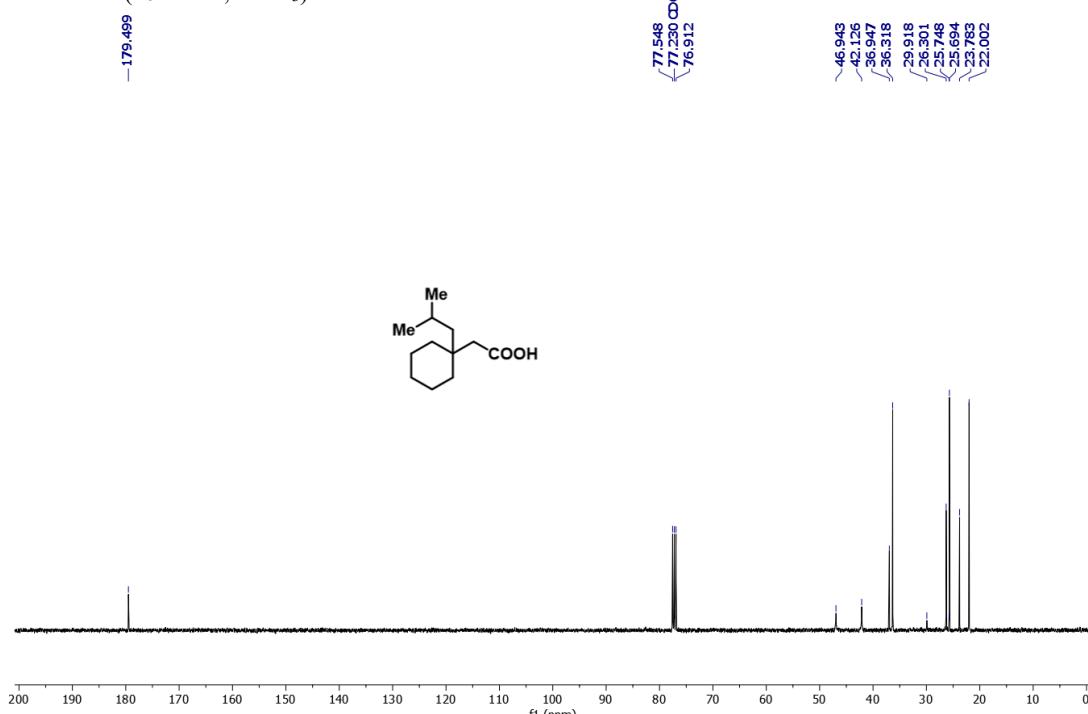
Thus NOE interaction between H and methylene group as shown in the abovementioned structure indicates the syn Me/Aryl relationship.

2-(1-Isobutylcyclohexyl)acetic acid (26)

¹H NMR (400 MHz, CDCl₃)

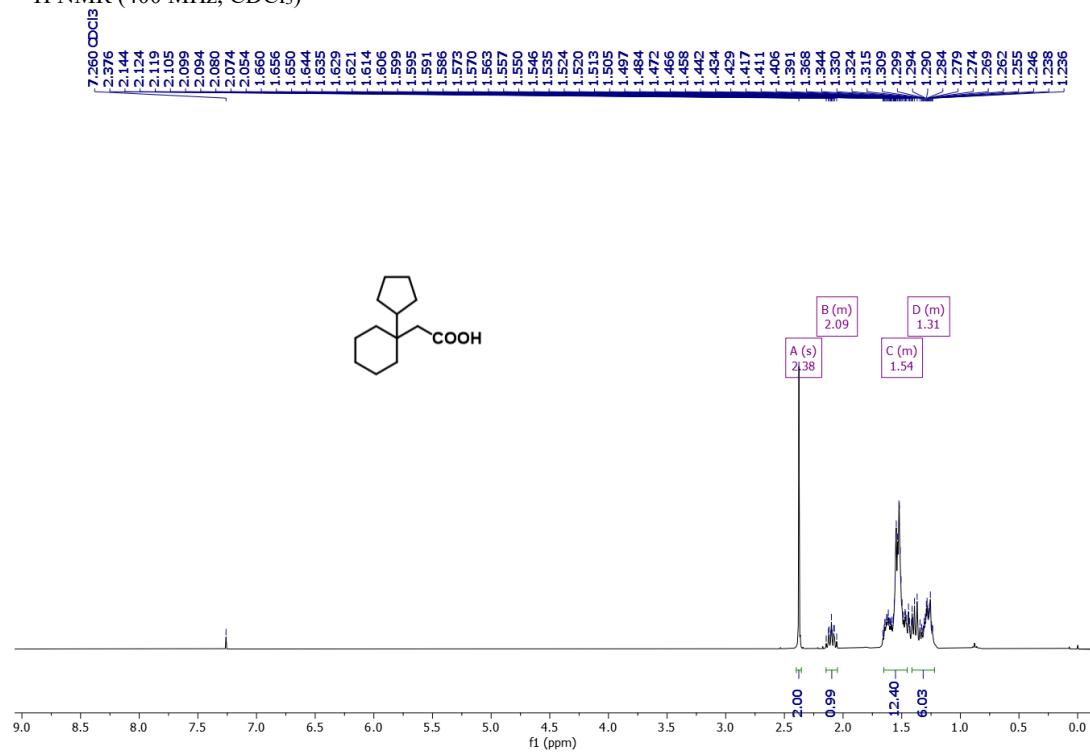


¹³C NMR (101 MHz, CDCl₃)

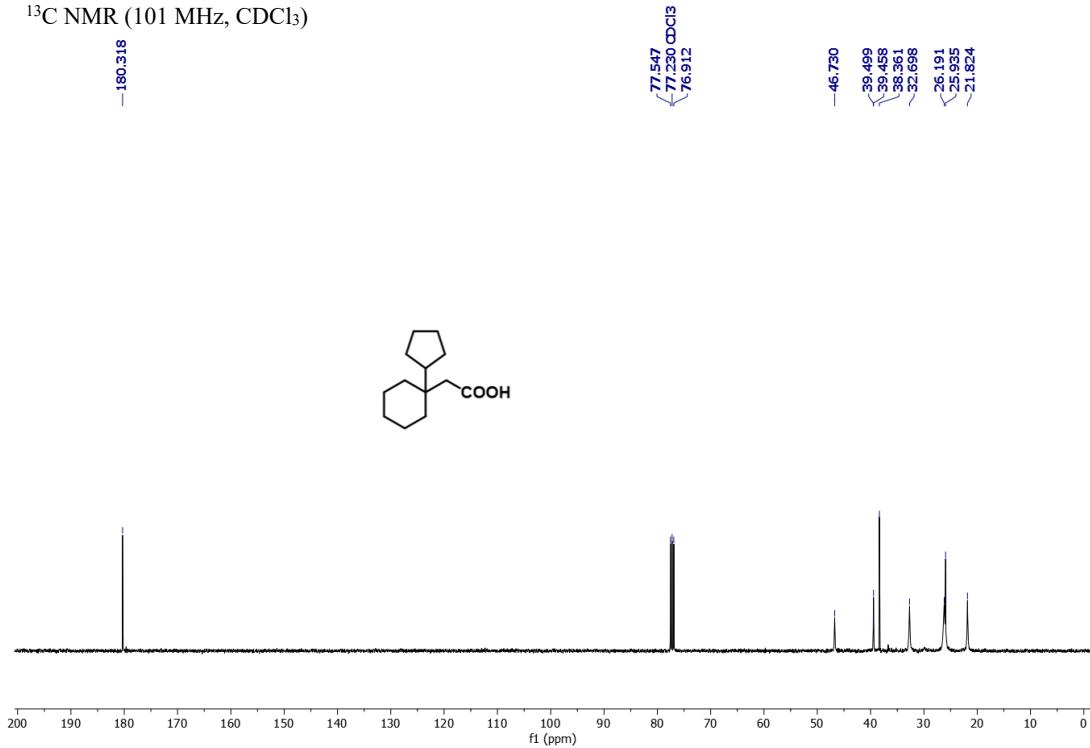


2-(1-Cyclopentylcyclohexyl)acetic acid (27)

¹H NMR (400 MHz, CDCl₃)

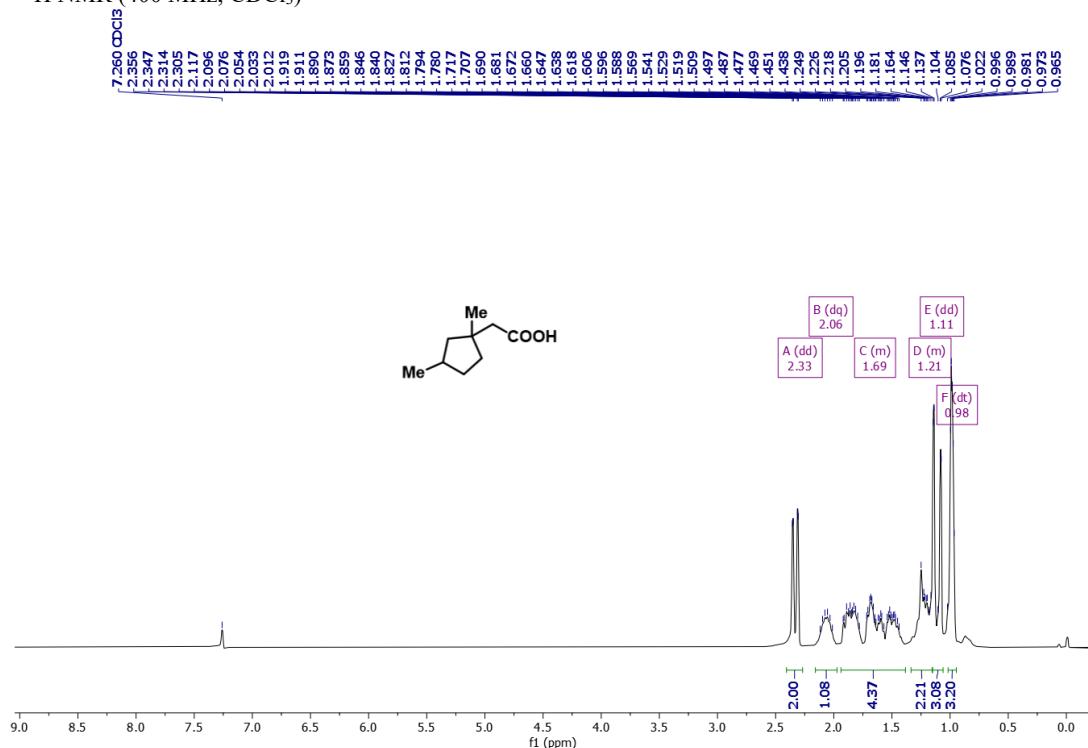


¹³C NMR (101 MHz, CDCl₃)

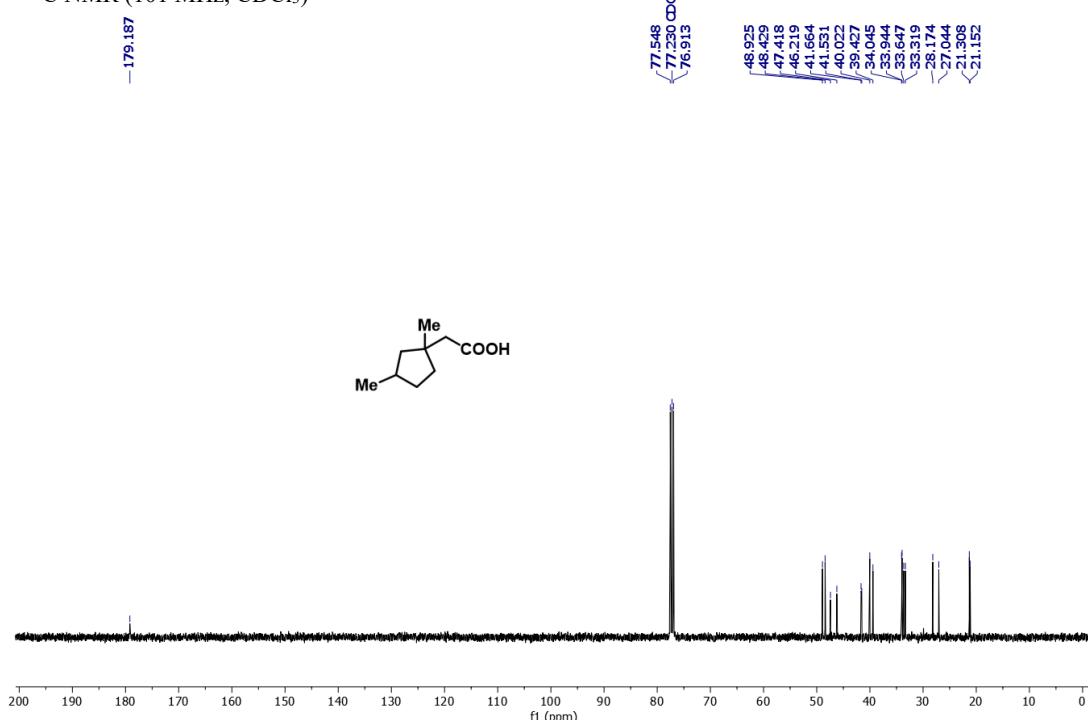


2-(1,3-Dimethylcyclopentyl)acetic acid (28)

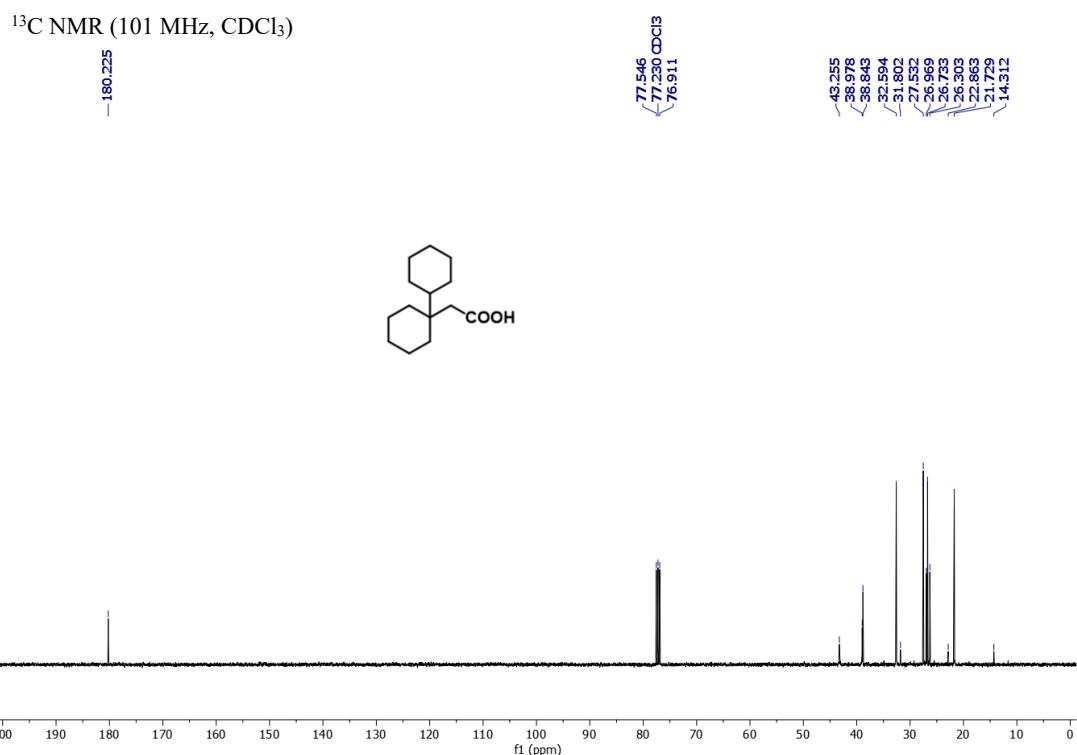
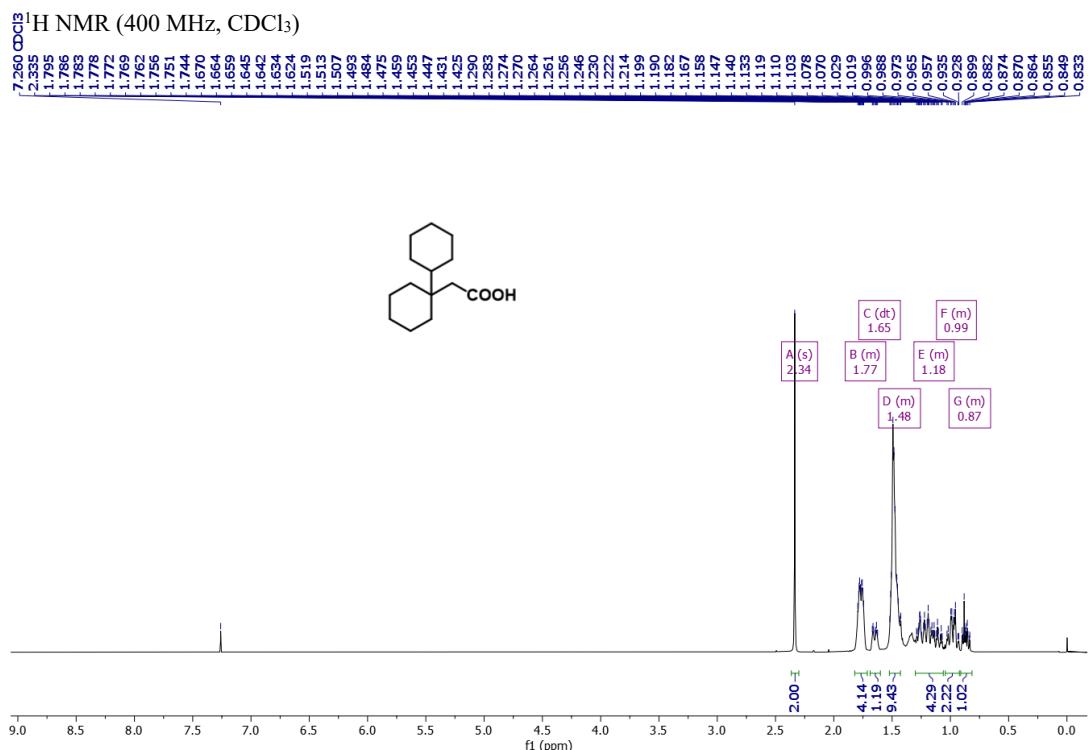
¹H NMR (400 MHz, CDCl₃)



¹³C NMR (101 MHz, CDCl₃)

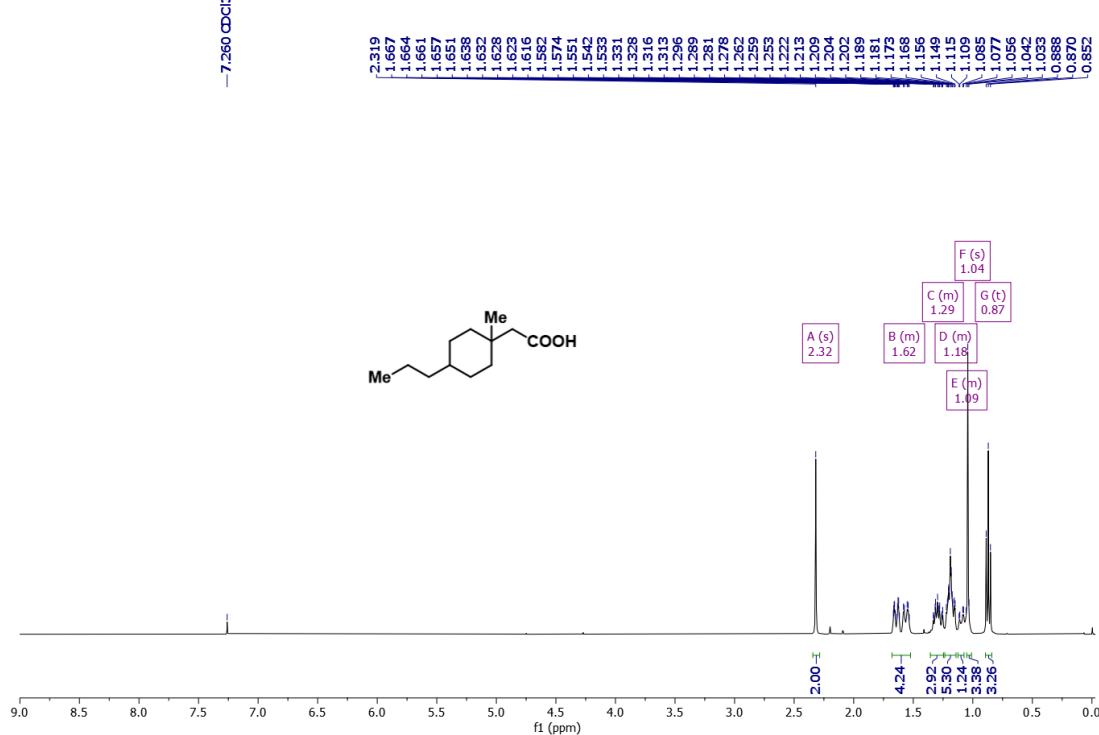


2-([1,1'-Bi(cyclohexan)]-1-yl)acetic acid (29)

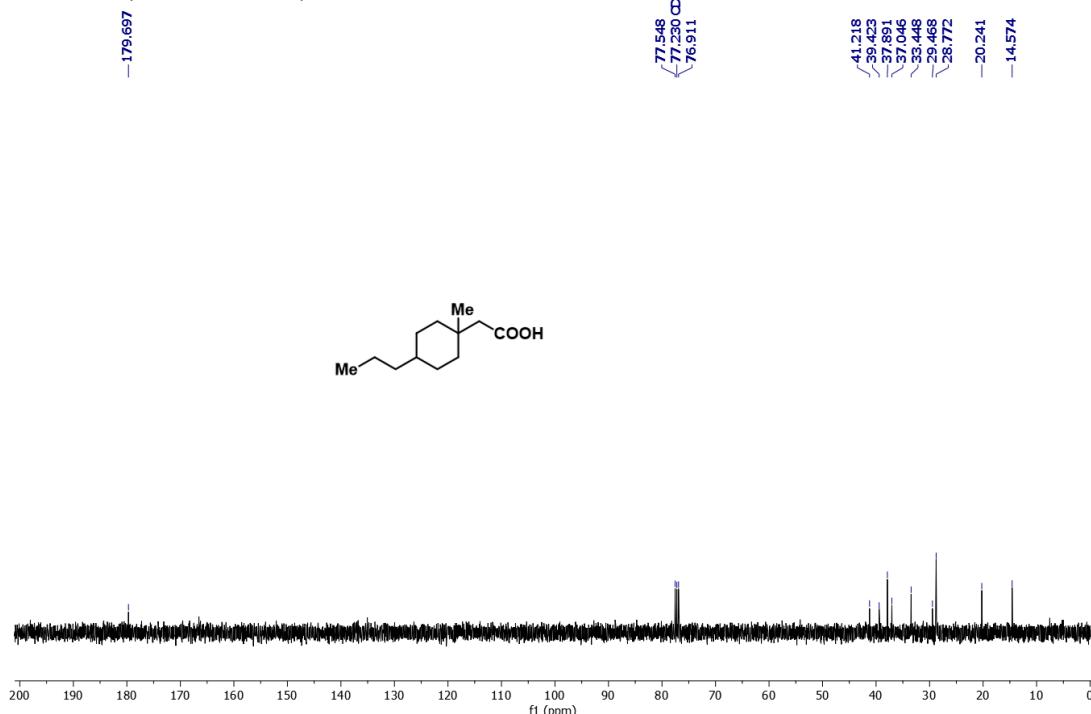


2-(1-Methyl-4-propylcyclohexyl)acetic acid (30)

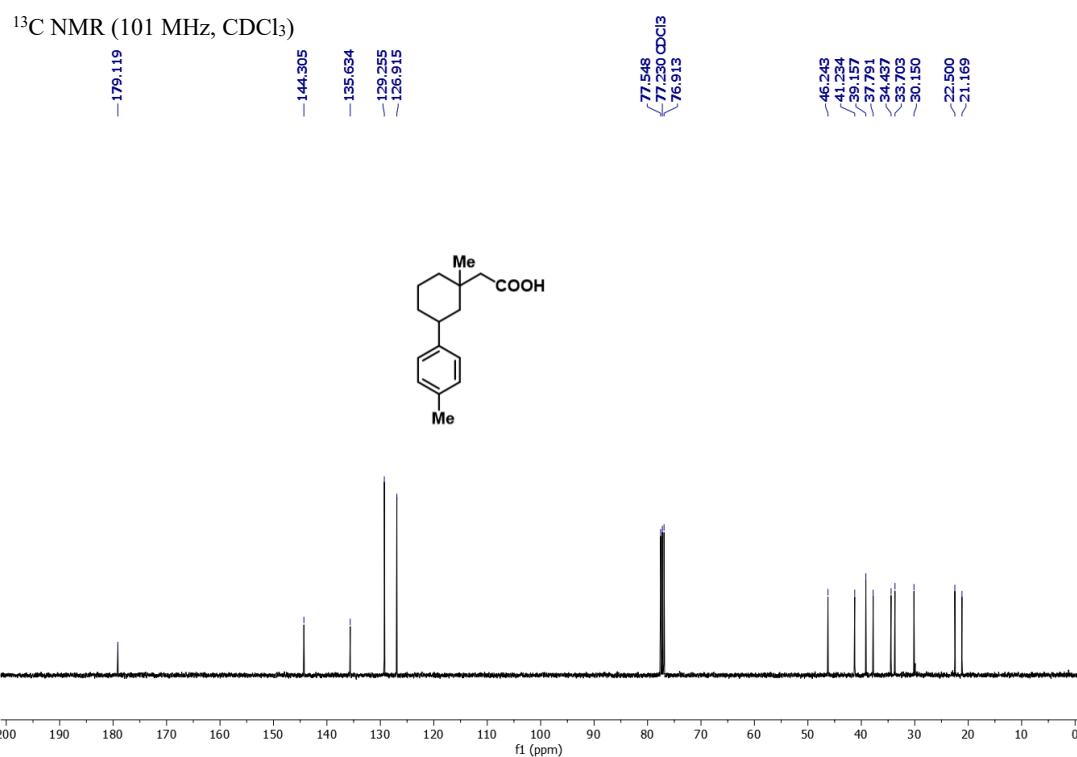
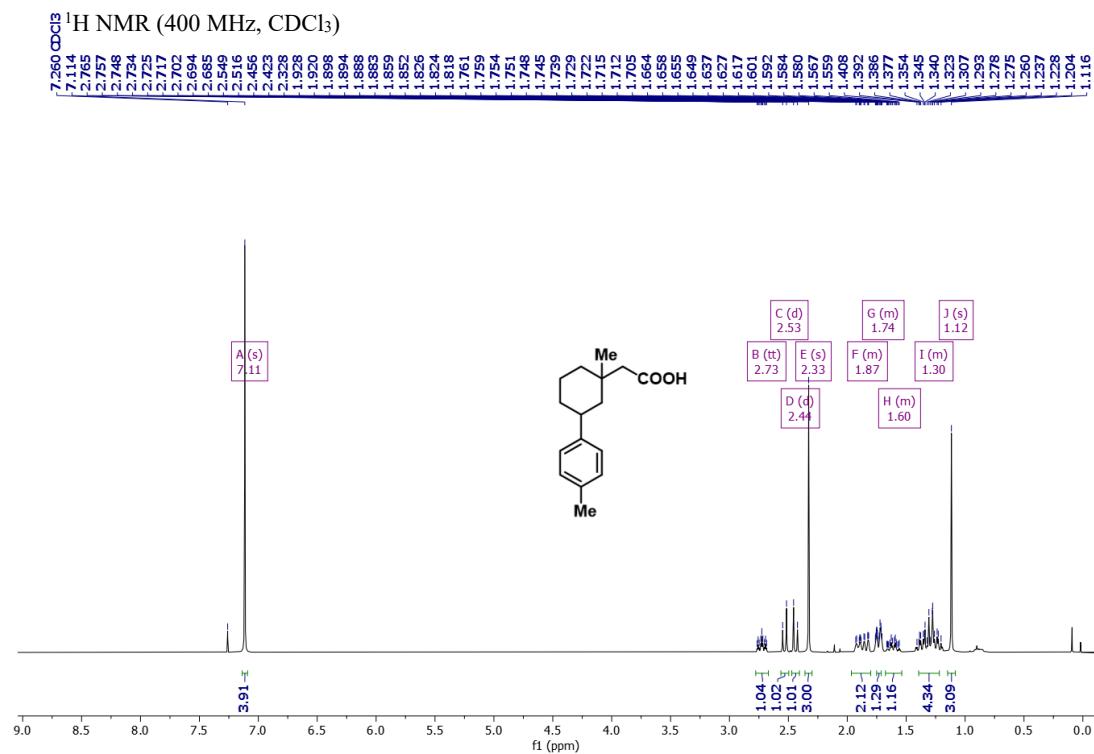
¹H NMR (400 MHz, CDCl₃)



¹³C NMR (101 MHz, CDCl₃)

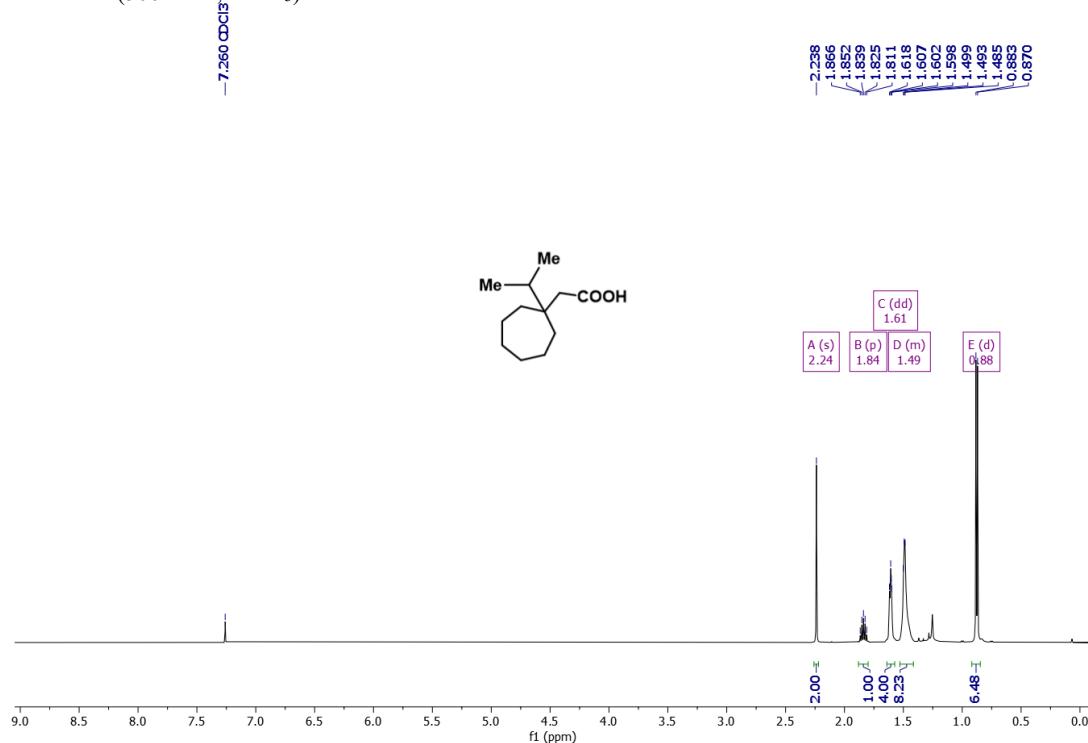


2-(1-Methyl-3-(*p*-tolyl)cyclohexyl)acetic acid (31)

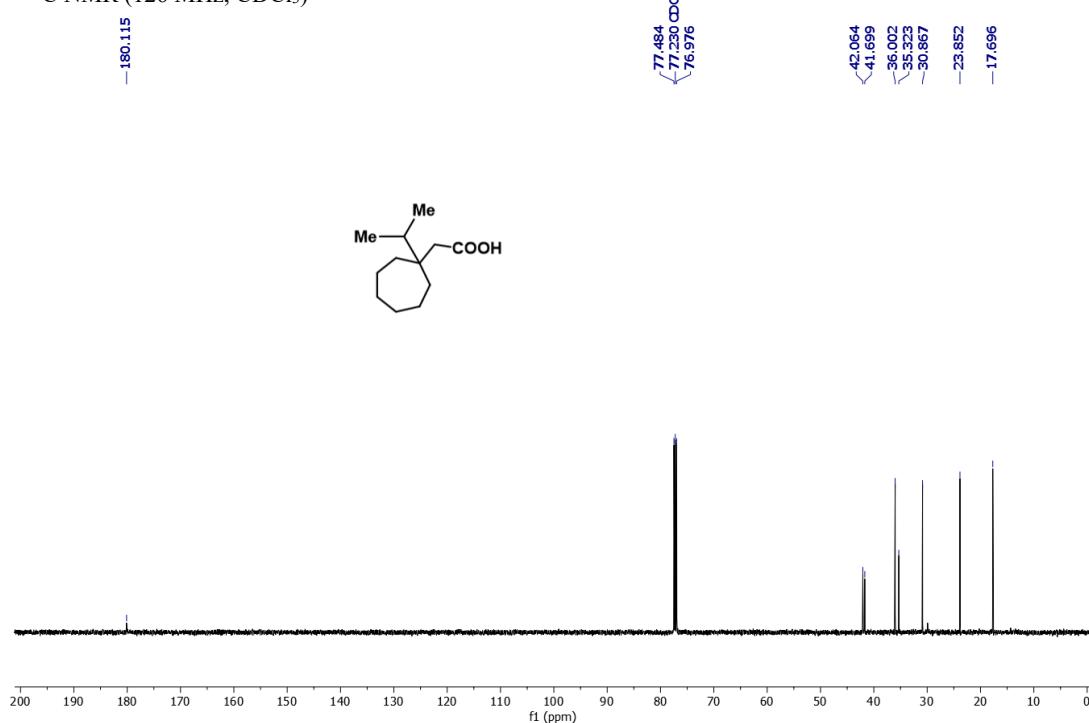


2-(1-Isopropylcycloheptyl)acetic acid (32)

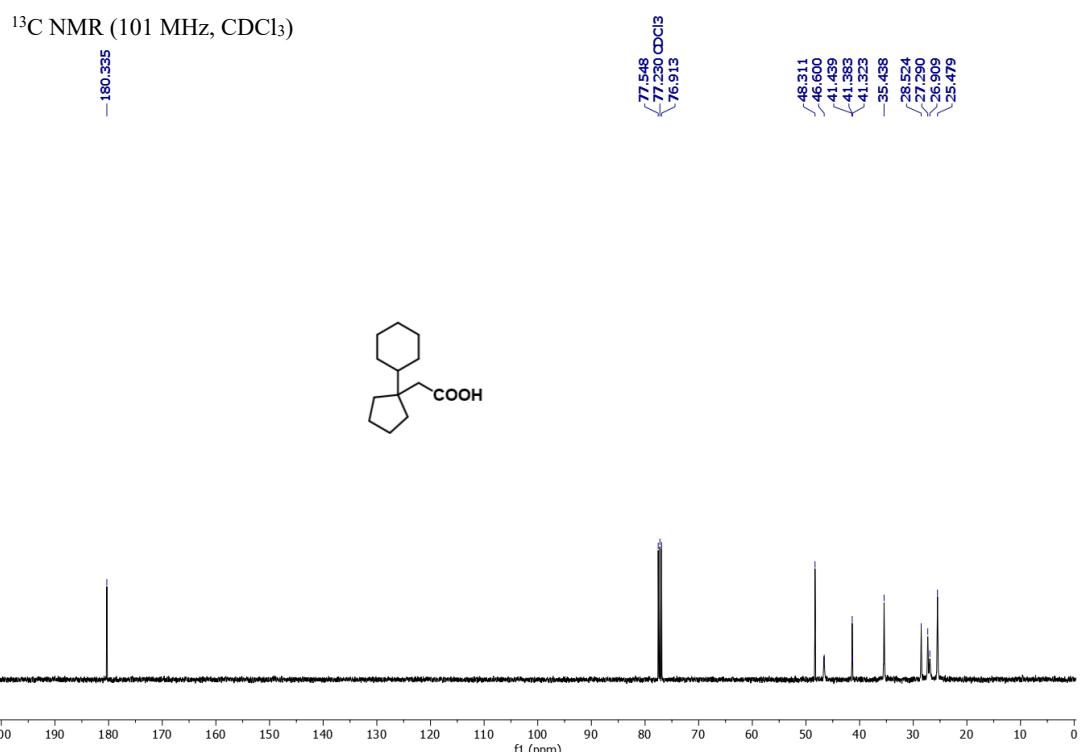
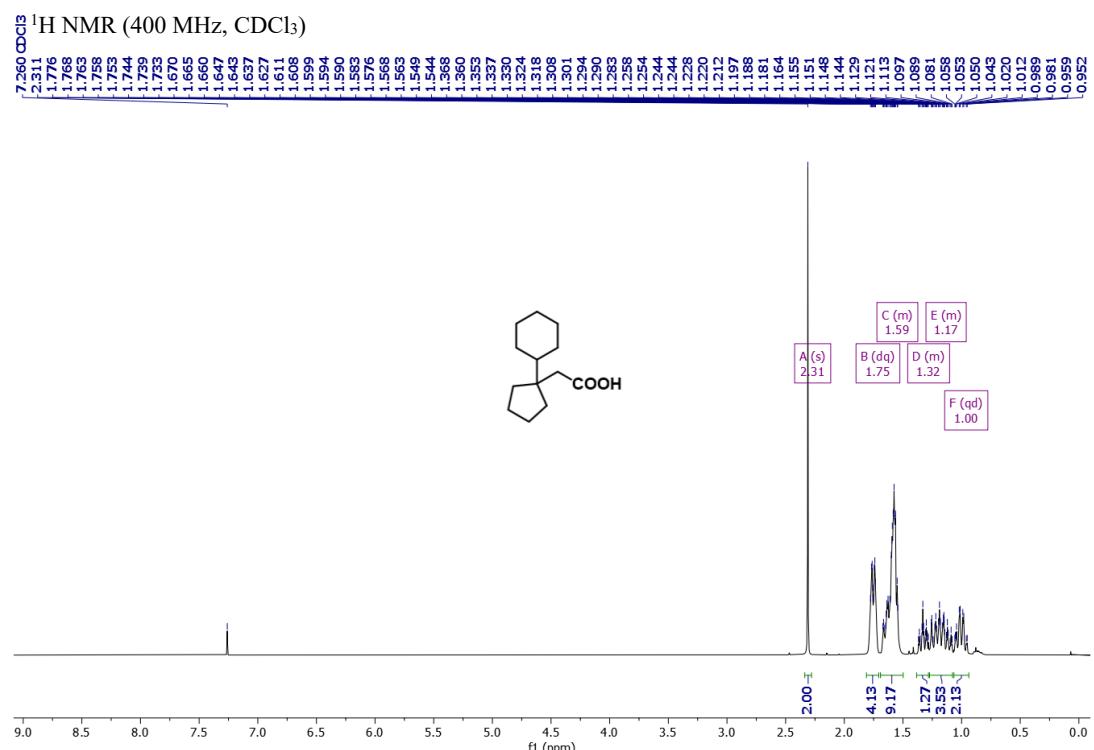
¹H NMR (500 MHz, CDCl₃)



¹³C NMR (126 MHz, CDCl₃)

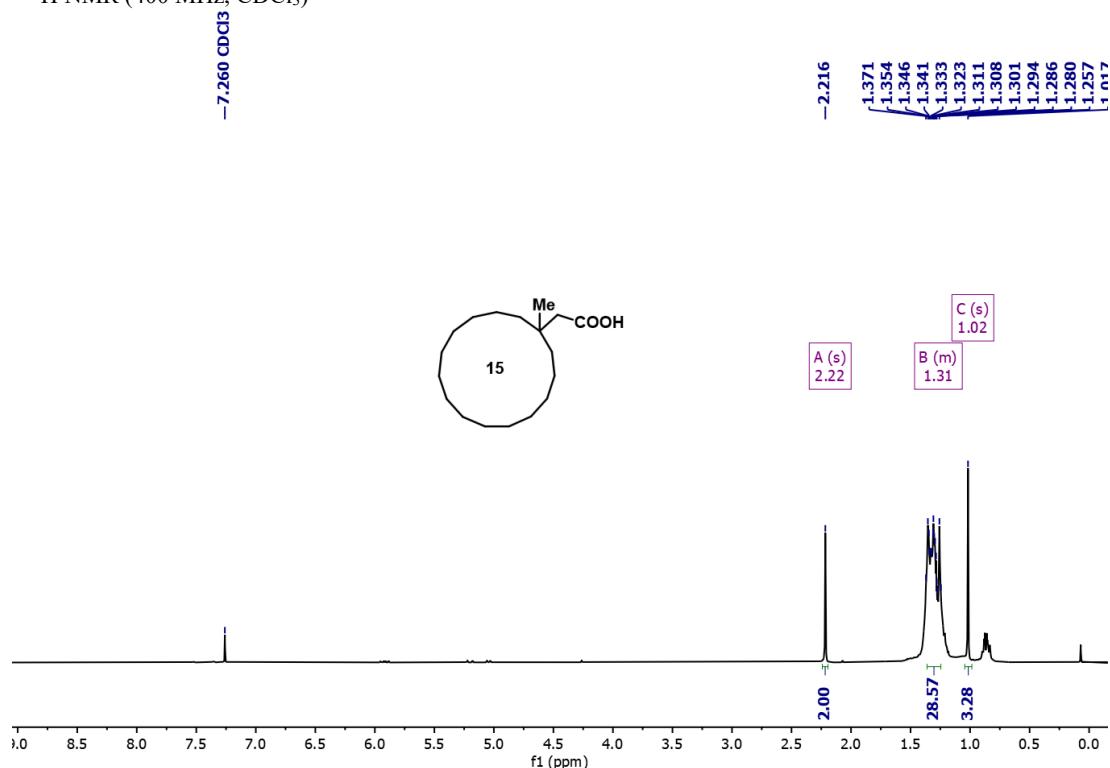


2-(1-Cyclohexylcyclopentyl)acetic acid (33)

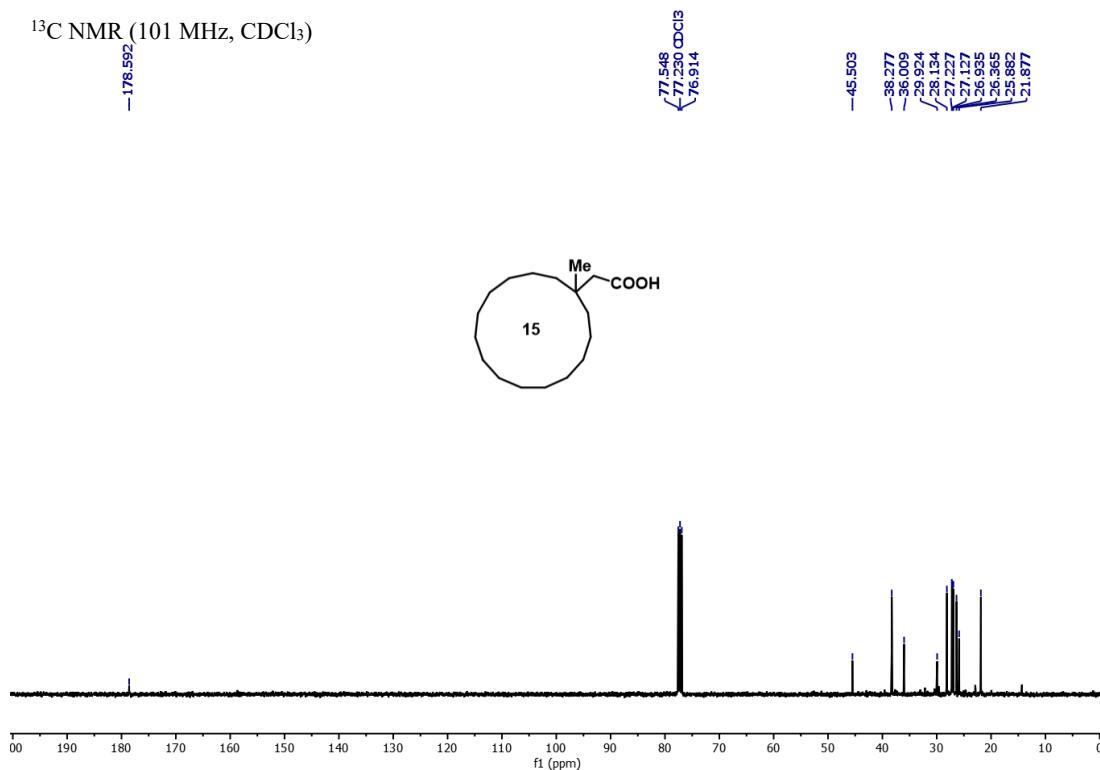


2-(1-Methylcyclopentadecyl)acetic acid (34)

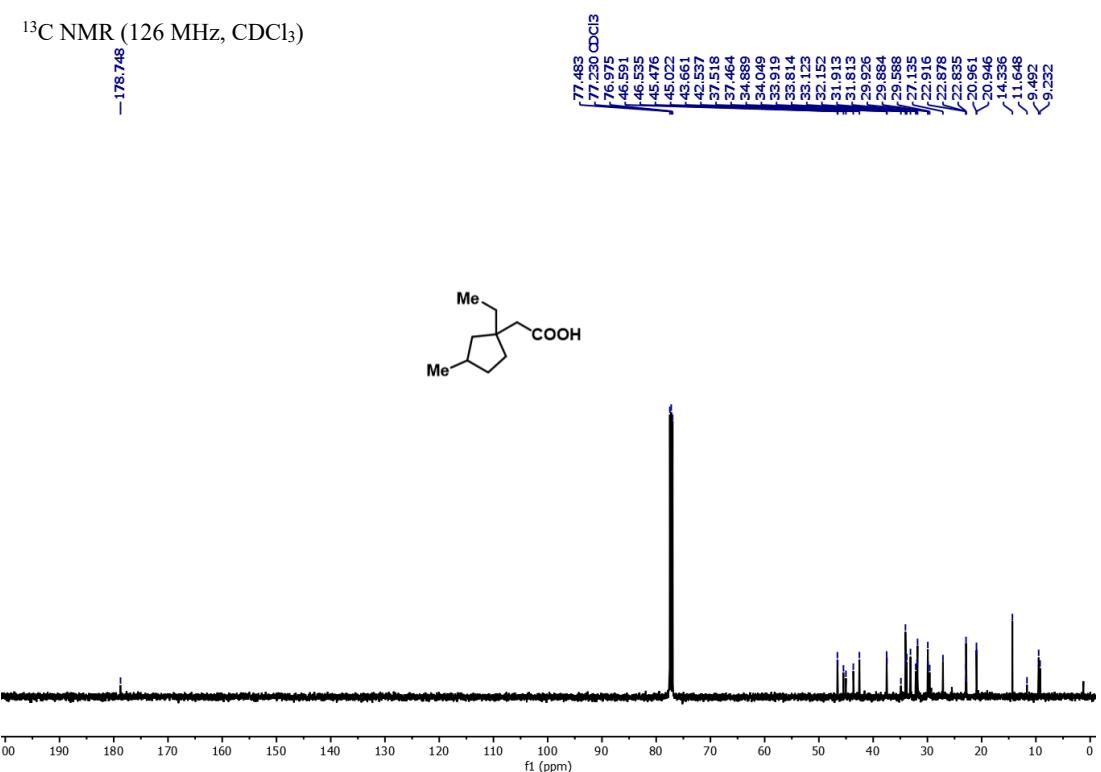
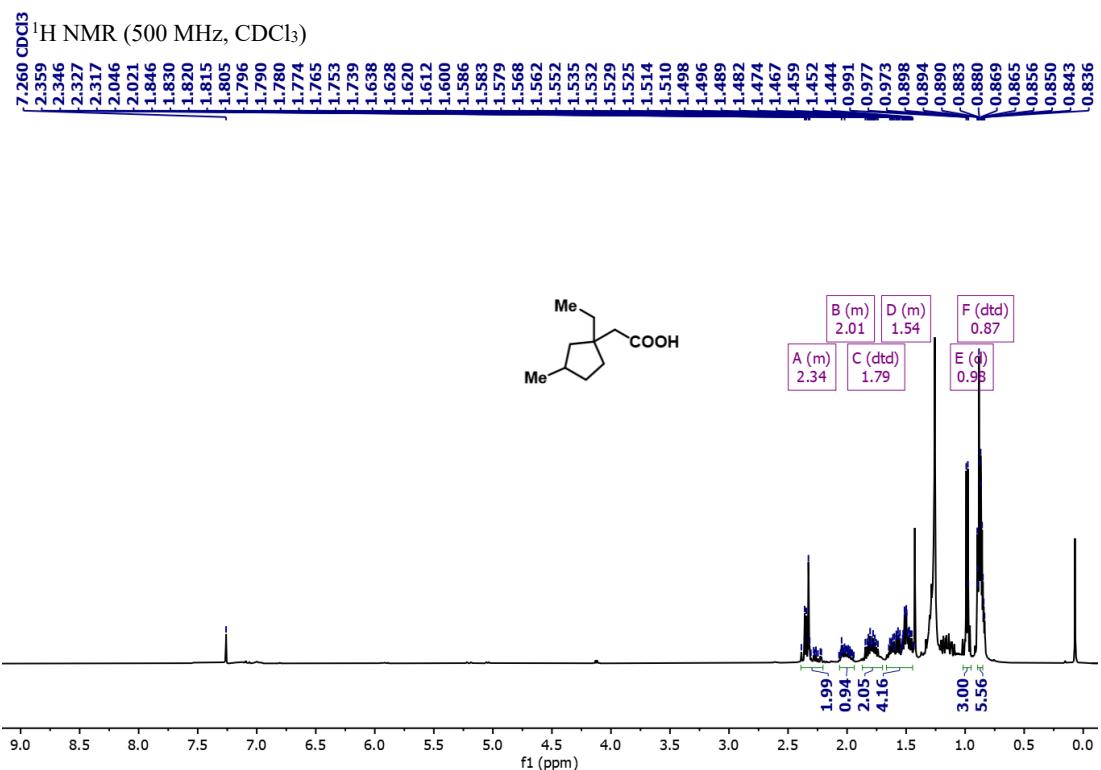
¹H NMR (400 MHz, CDCl₃)



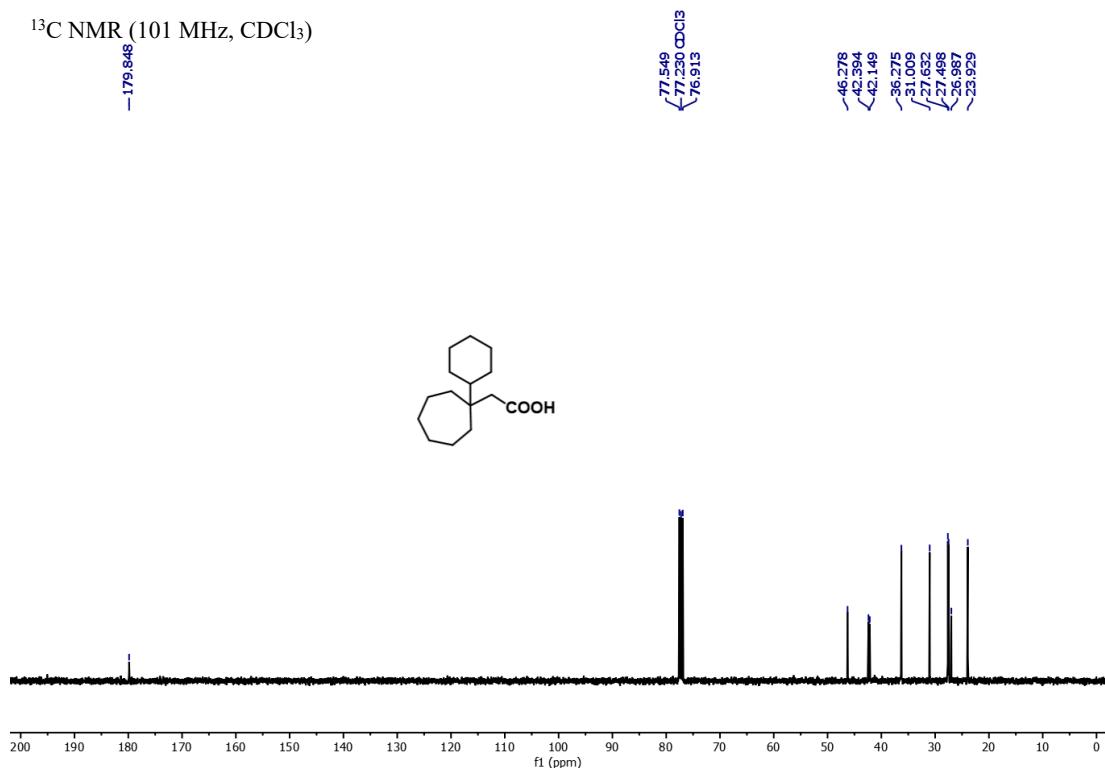
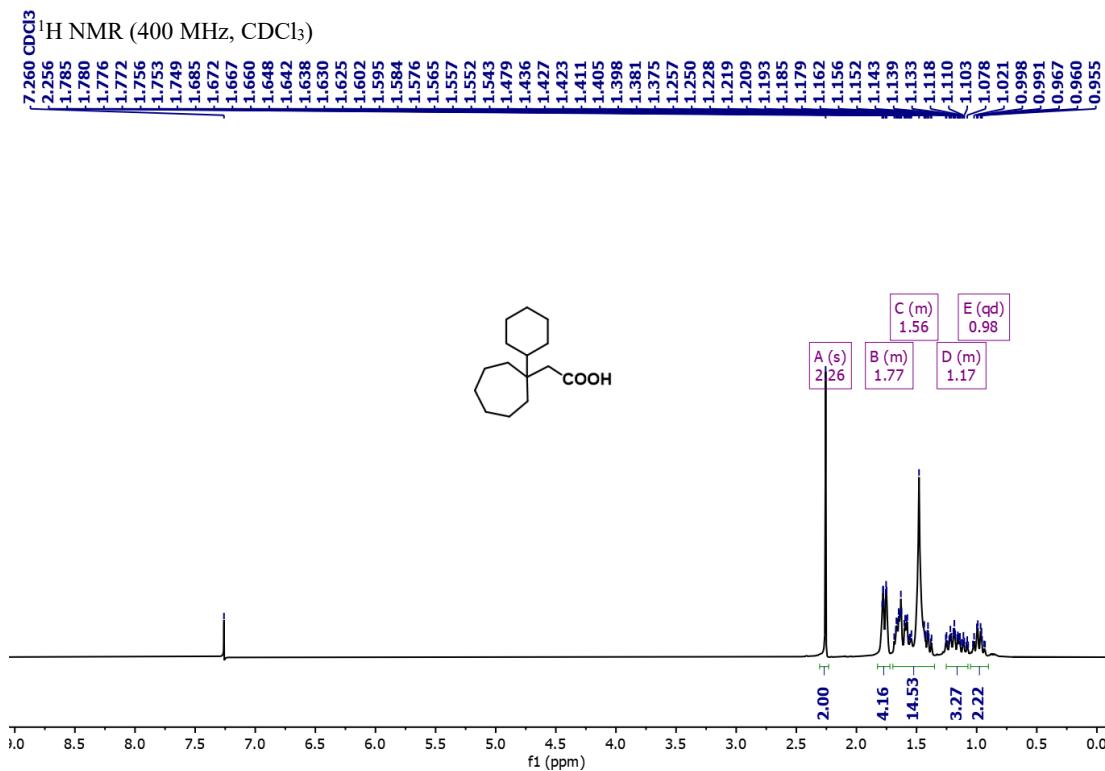
¹³C NMR (101 MHz, CDCl₃)



2-(1-Ethyl-3-methylcyclopentyl)acetic acid (35)

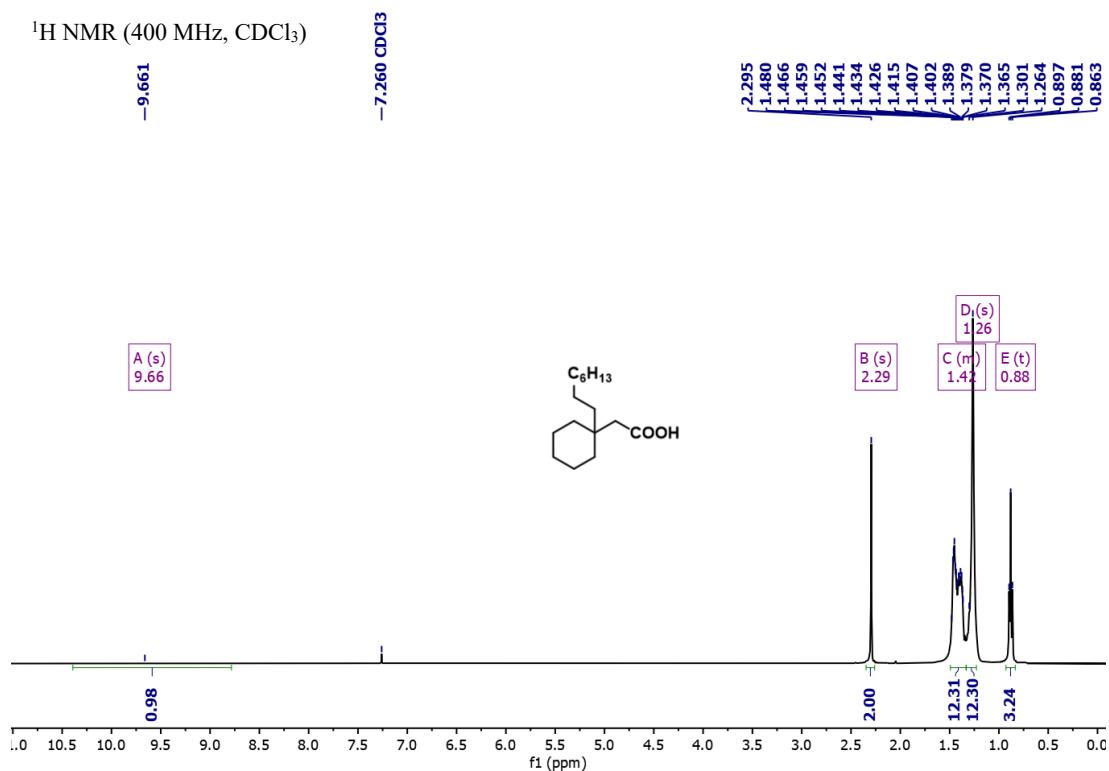


2-(1-Cyclohexylcycloheptyl)acetic acid (36)

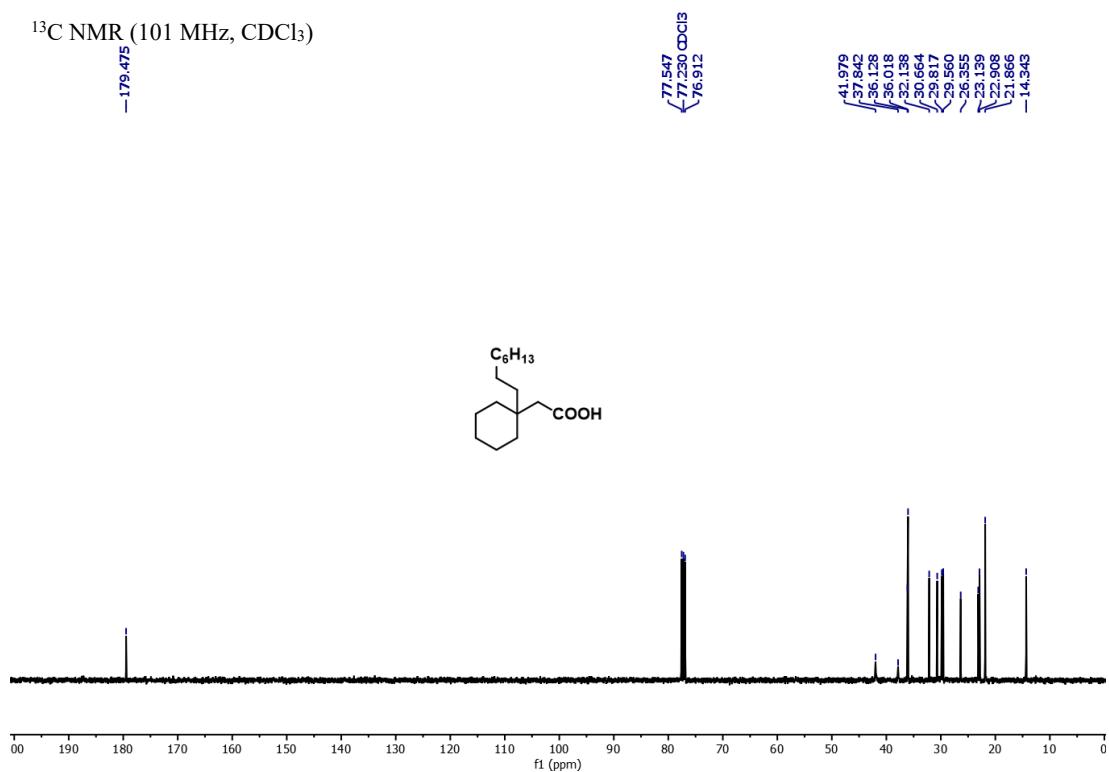


2-(1-Octylcyclohexyl)acetic acid (37)

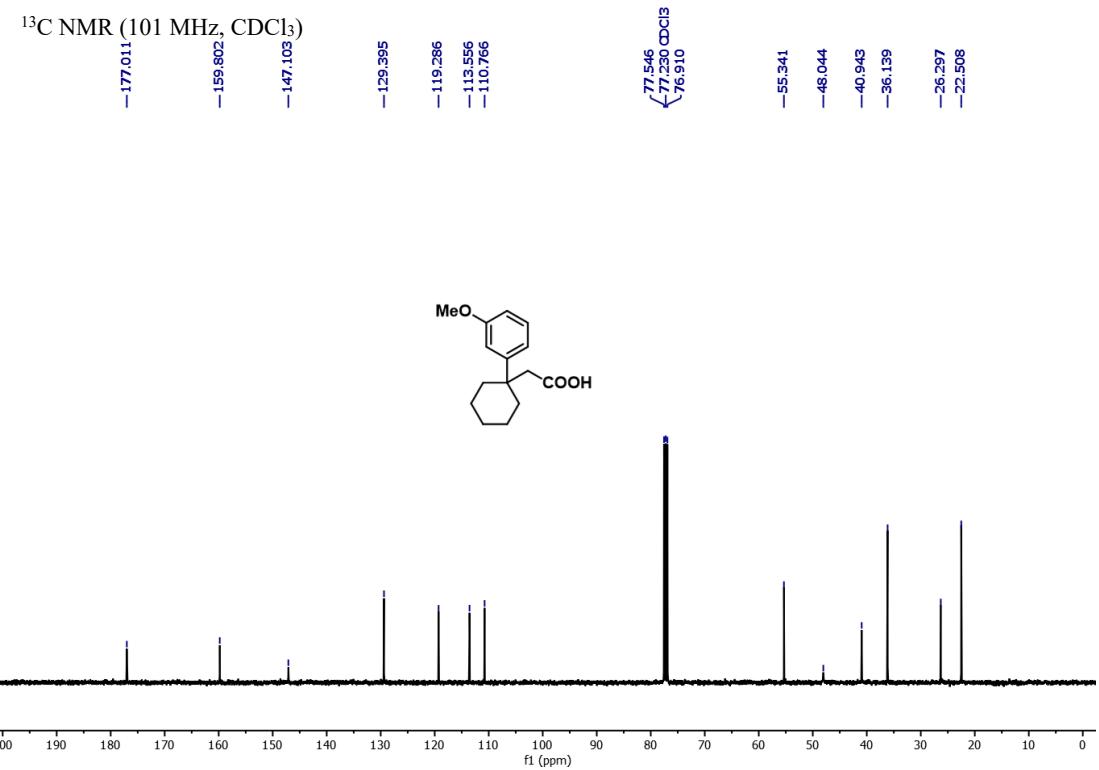
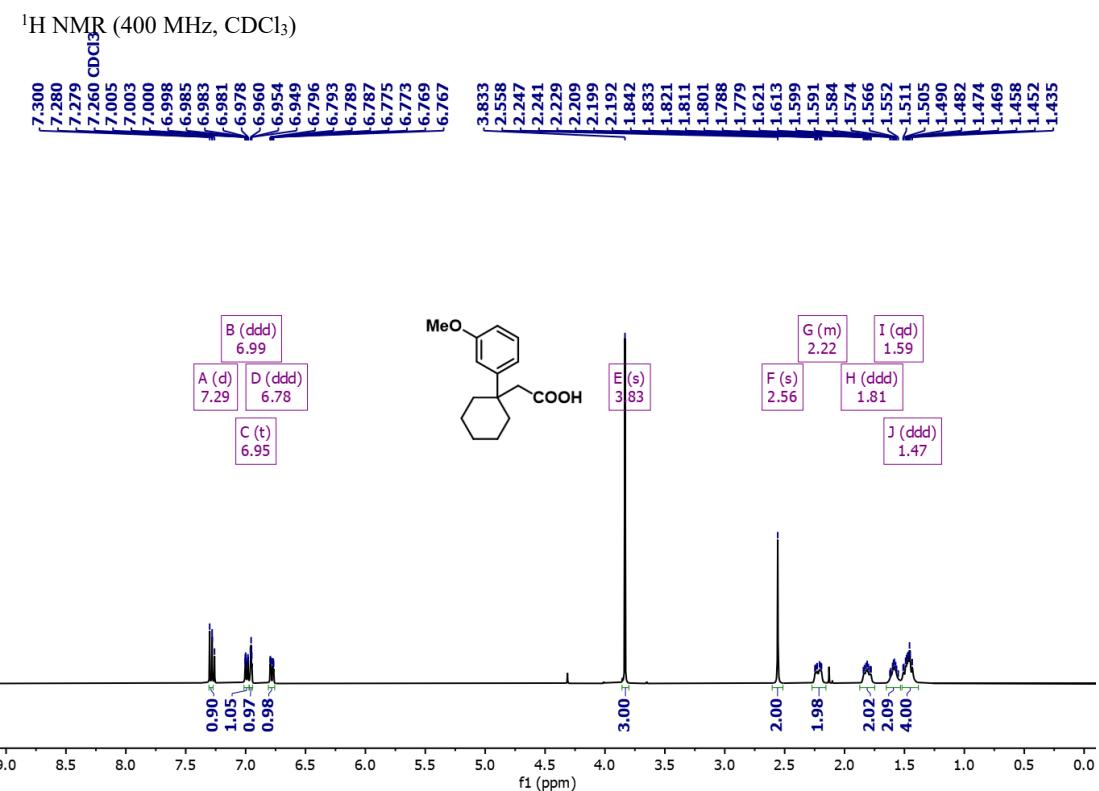
¹H NMR (400 MHz, CDCl₃)



¹³C NMR (101 MHz, CDCl₃)

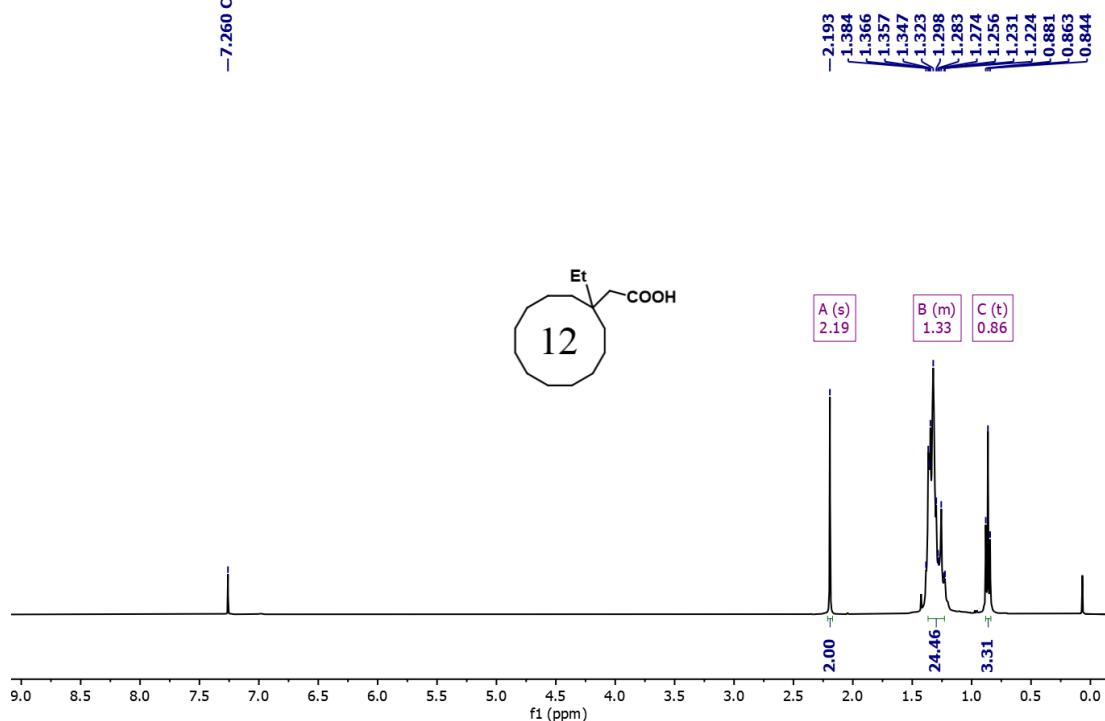


2-(1-(3-Methoxyphenyl)cyclohexyl)acetic acid (38)

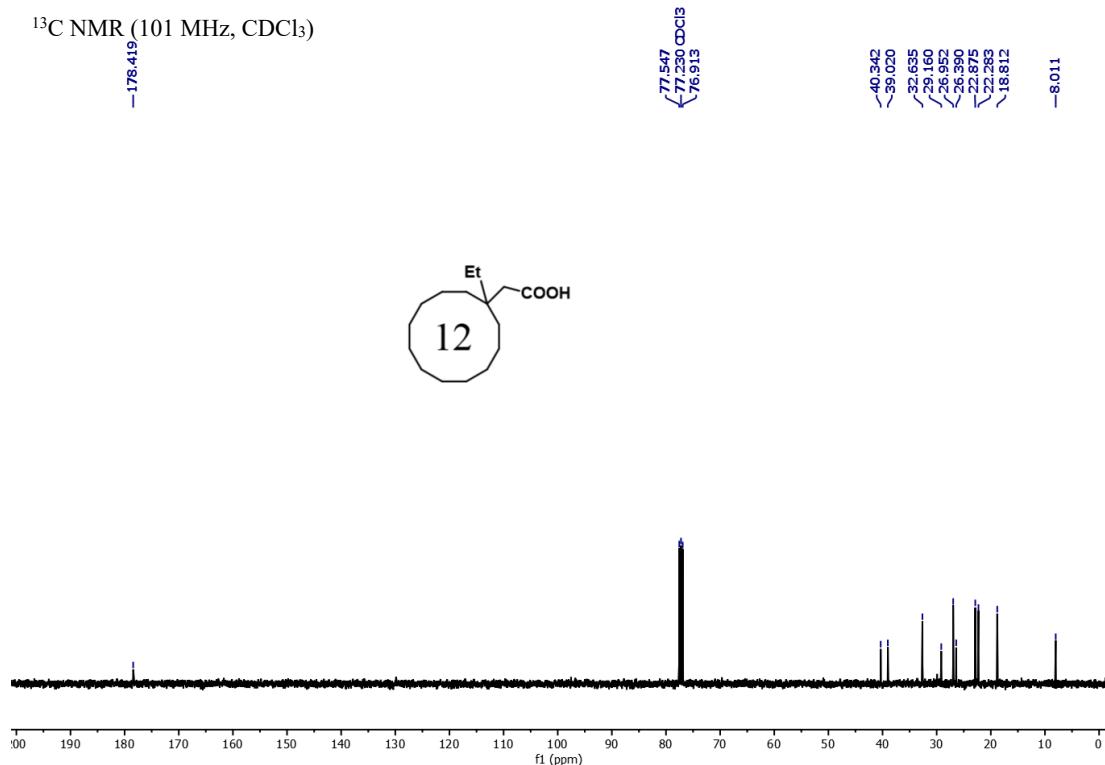


2-(1-Ethylcyclododecyl)acetic acid (39)

¹H NMR (400 MHz, CDCl₃)

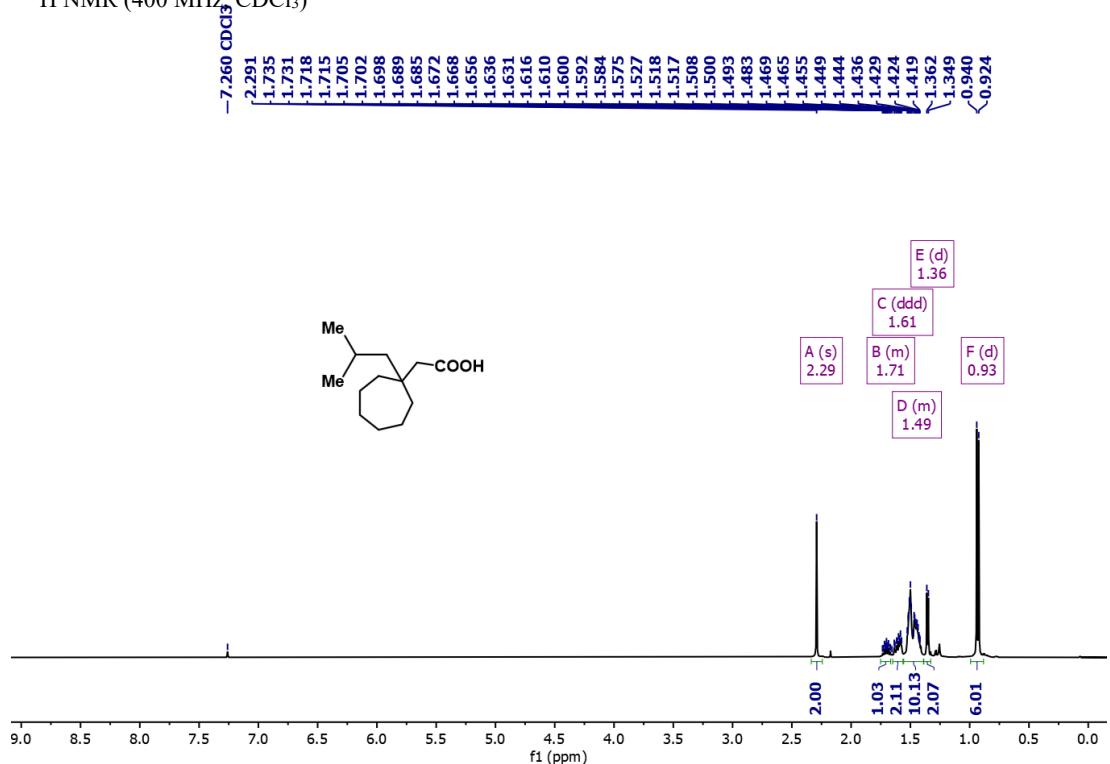


^{13}C NMR (101 MHz, CDCl_3)

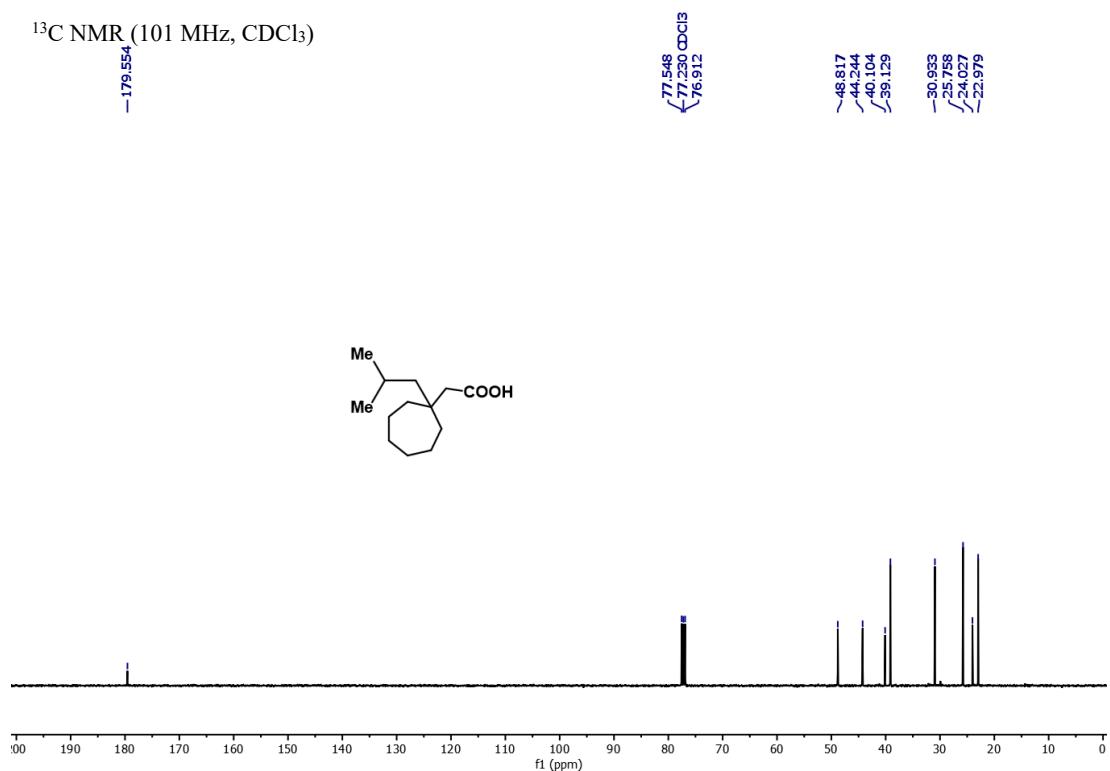


2-(1-Isobutylcycloheptyl)acetic acid (40)

¹H NMR (400 MHz, CDCl₃)

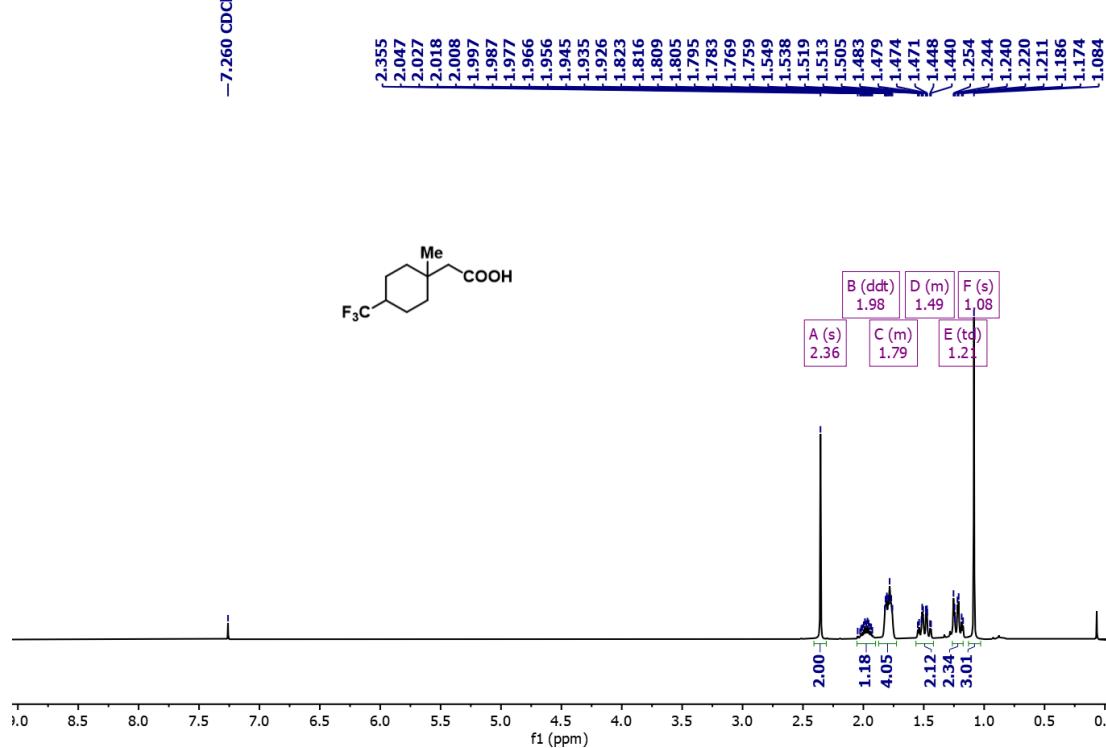


¹³C NMR (101 MHz, CDCl₃)

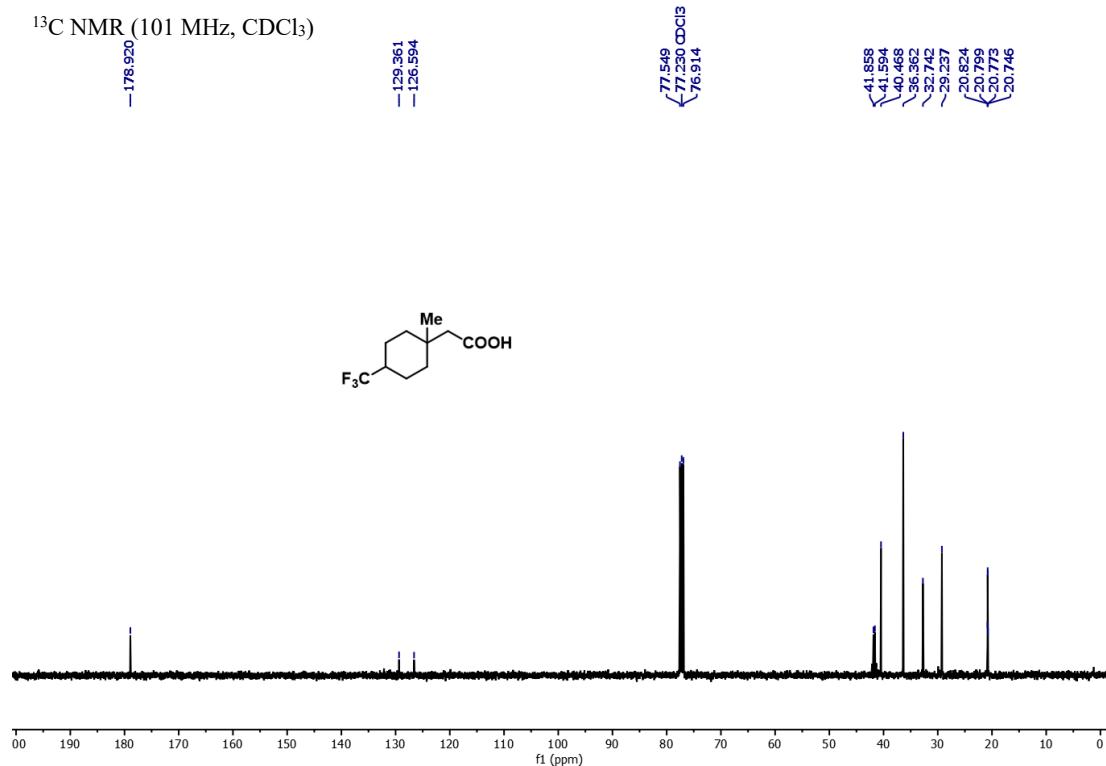


2-(1-Methyl-4-(trifluoromethyl)cyclohexyl)acetic acid (41)

¹H NMR (400 MHz, CDCl₃)

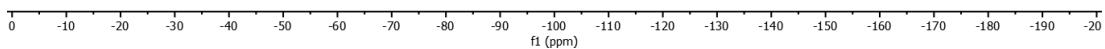
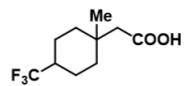


¹³C NMR (101 MHz, CDCl₃)



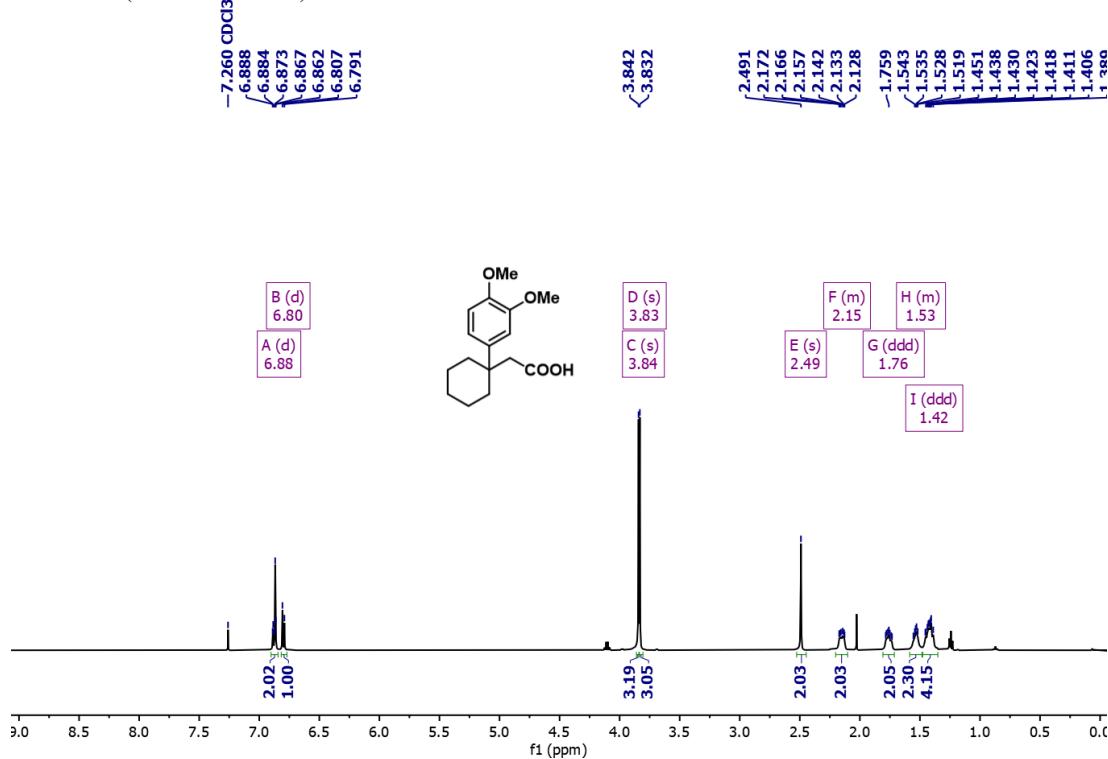
¹⁹F NMR 376 MHz, CDCl₃)

—73.601

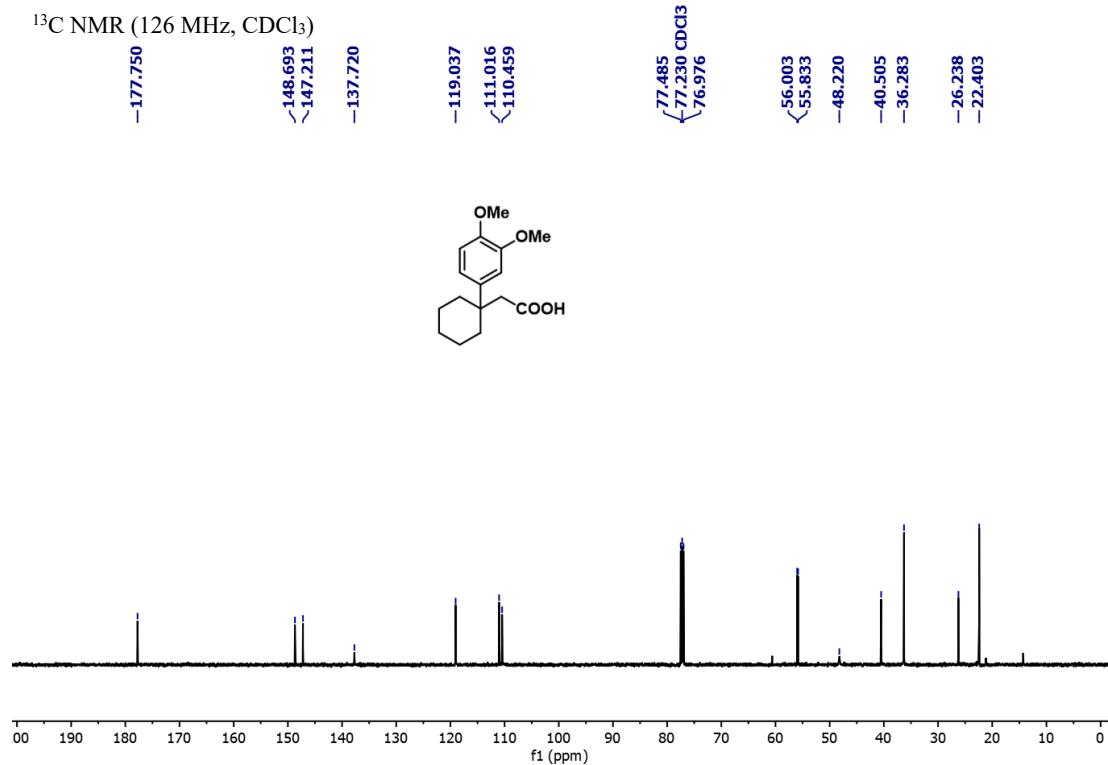


2-(1-(3,4-Dimethoxyphenyl)cyclohexyl)acetic acid (42)

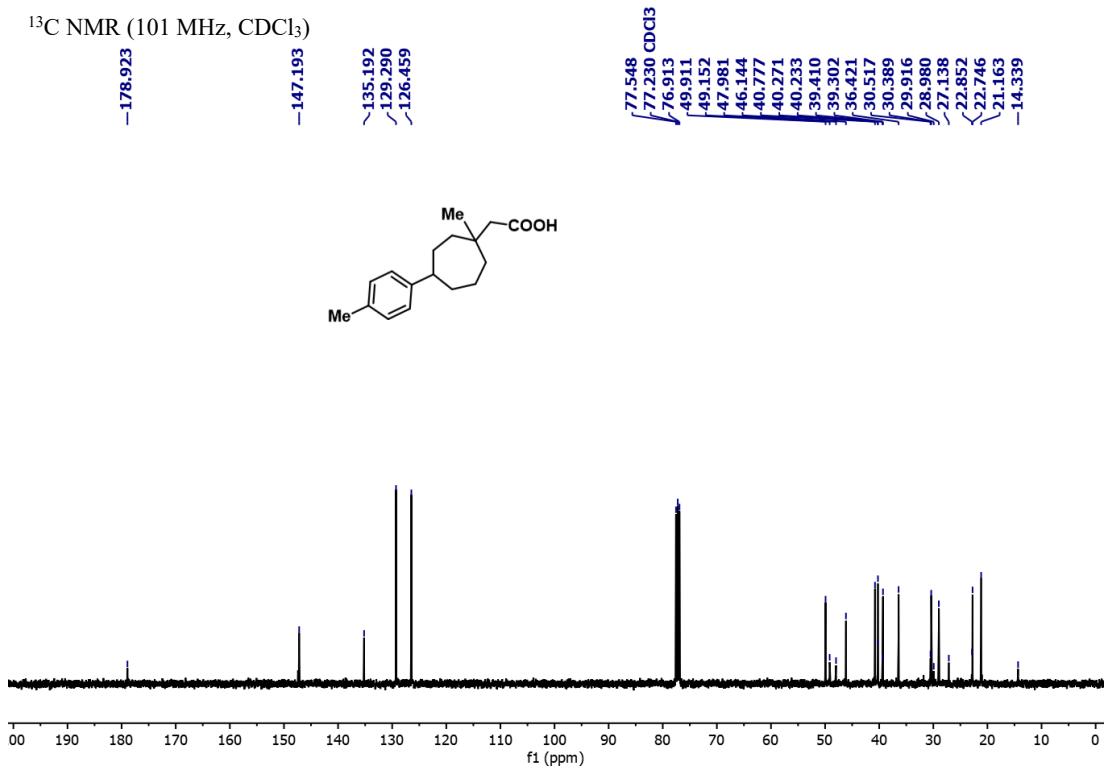
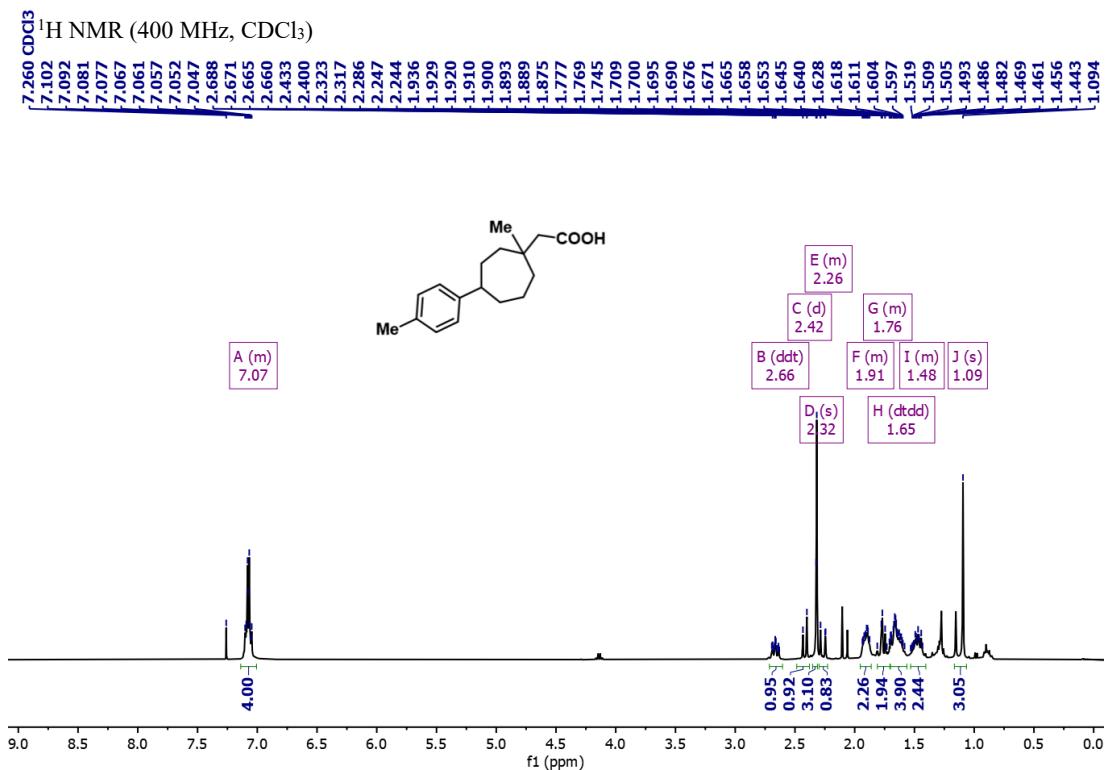
¹H NMR (500 MHz, CDCl₃)



¹³C NMR (126 MHz, CDCl₃)

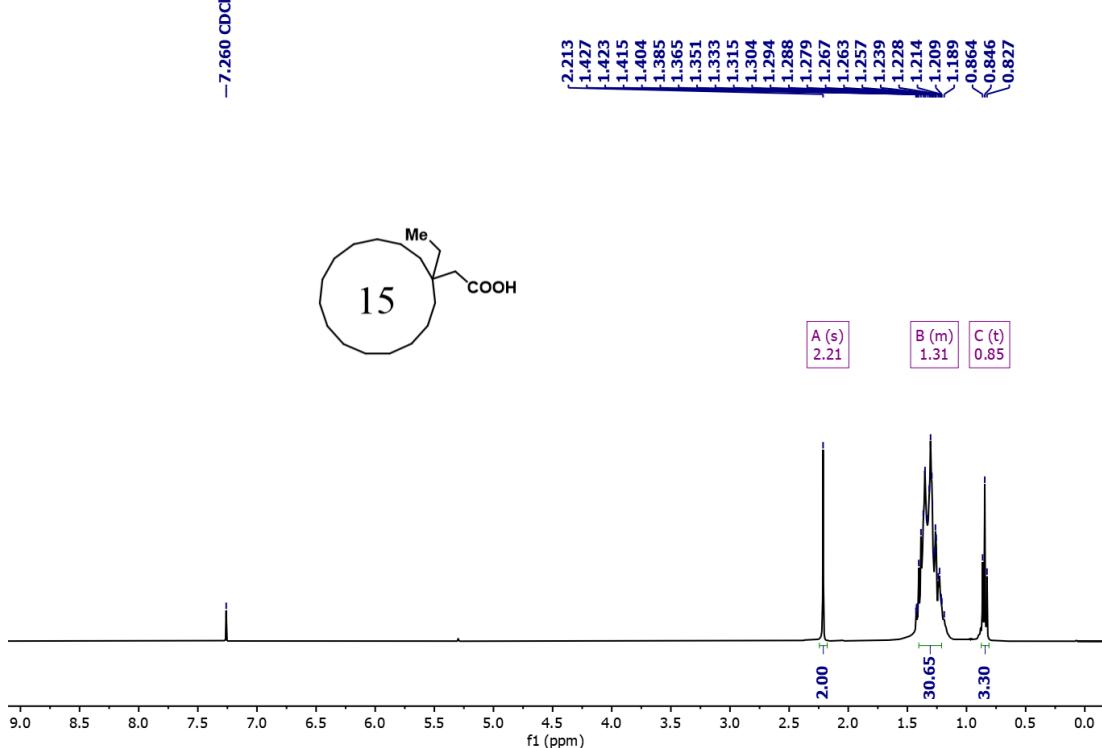


2-(1-Methyl-4-(*p*-tolyl)cycloheptyl)acetic acid (43)

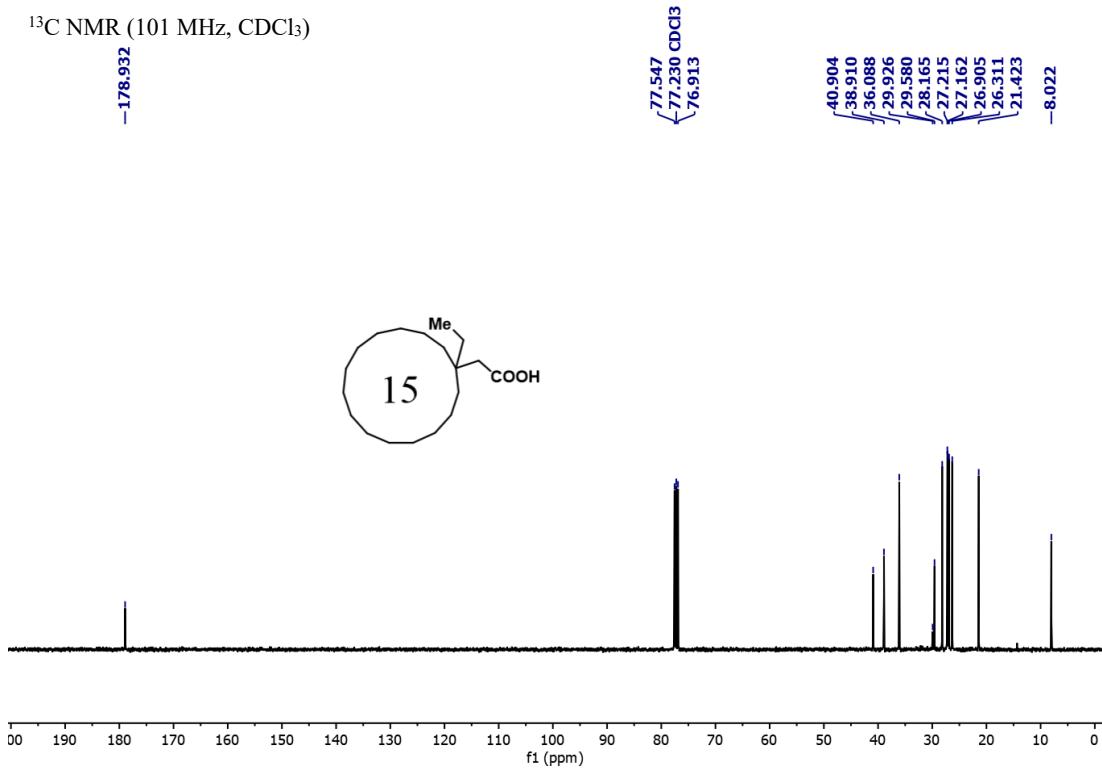


2-(1-Ethylcyclopentadecyl)acetic acid (44)

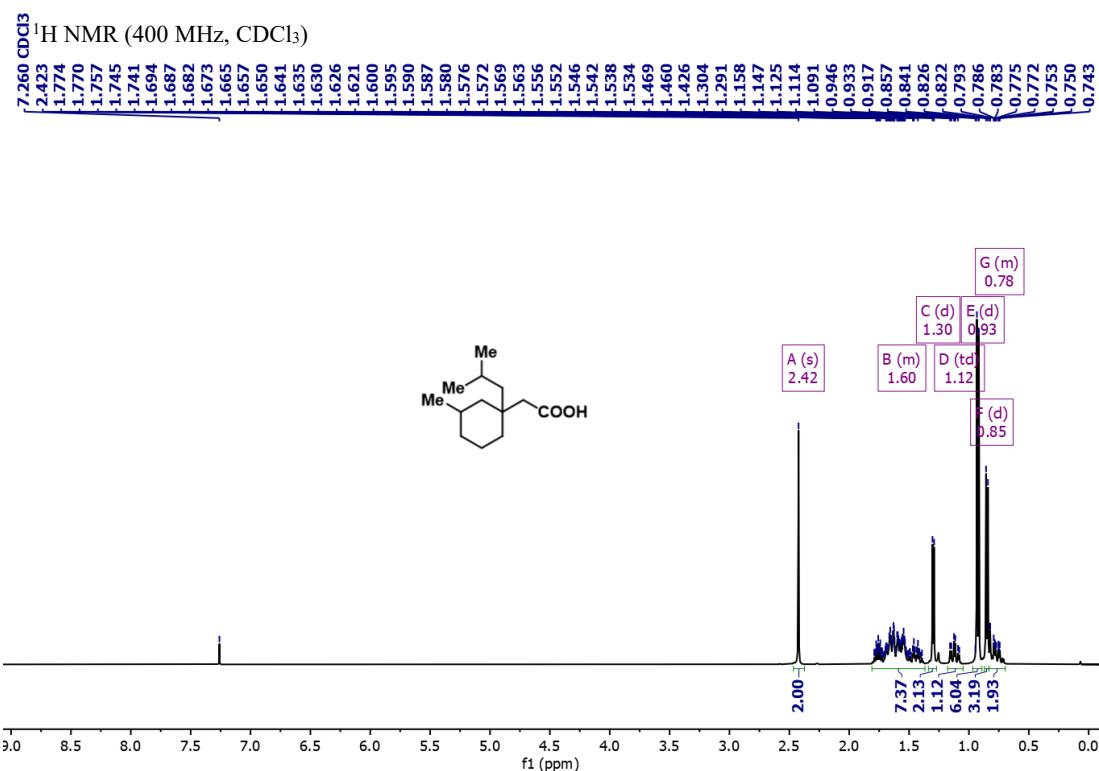
¹H NMR (400 MHz, CDCl₃)



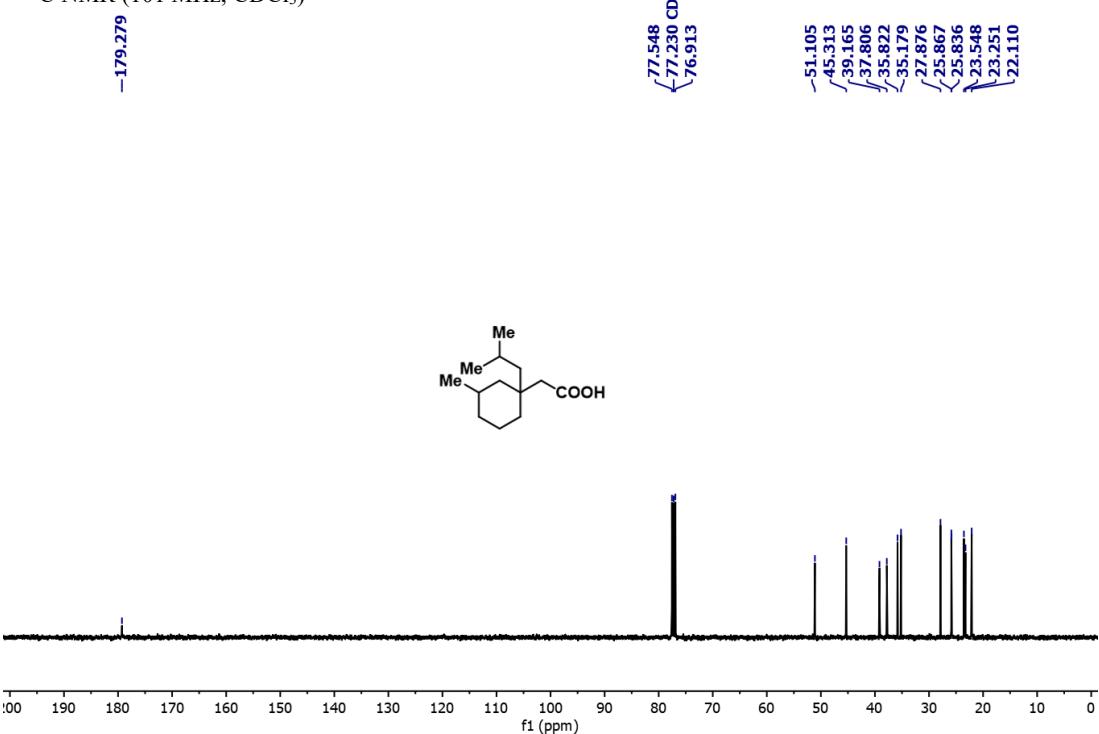
¹³C NMR (101 MHz, CDCl₃)



2-(1-Isobutyl-3-methylcyclohexyl)acetic acid (45)

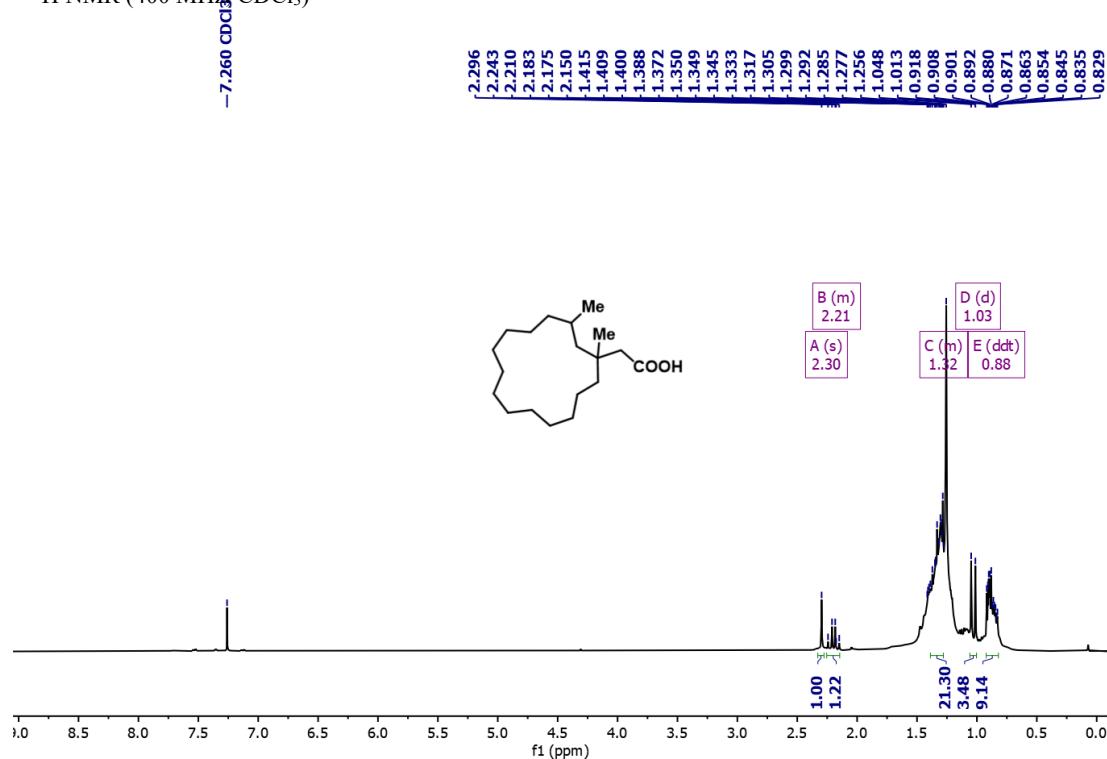


¹³C NMR (101 MHz, CDCl₃)

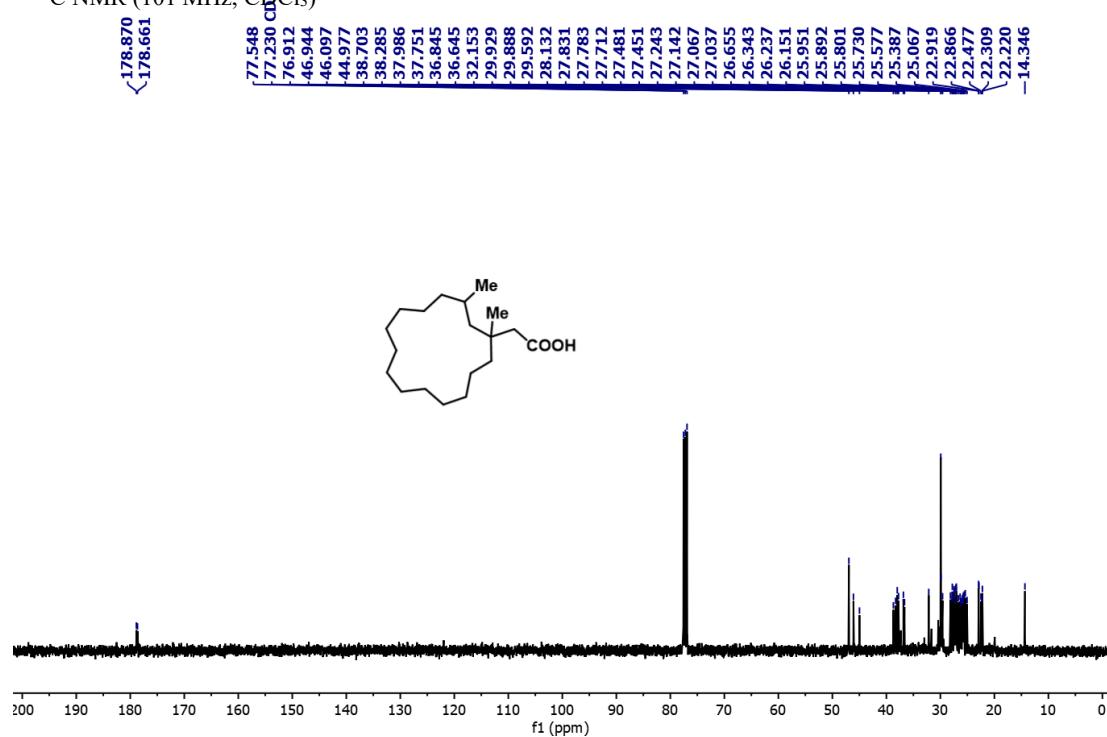


2-(1,3-Dimethylcyclopentadecyl)acetic acid (46)

¹H NMR (400 MHz, CDCl₃)

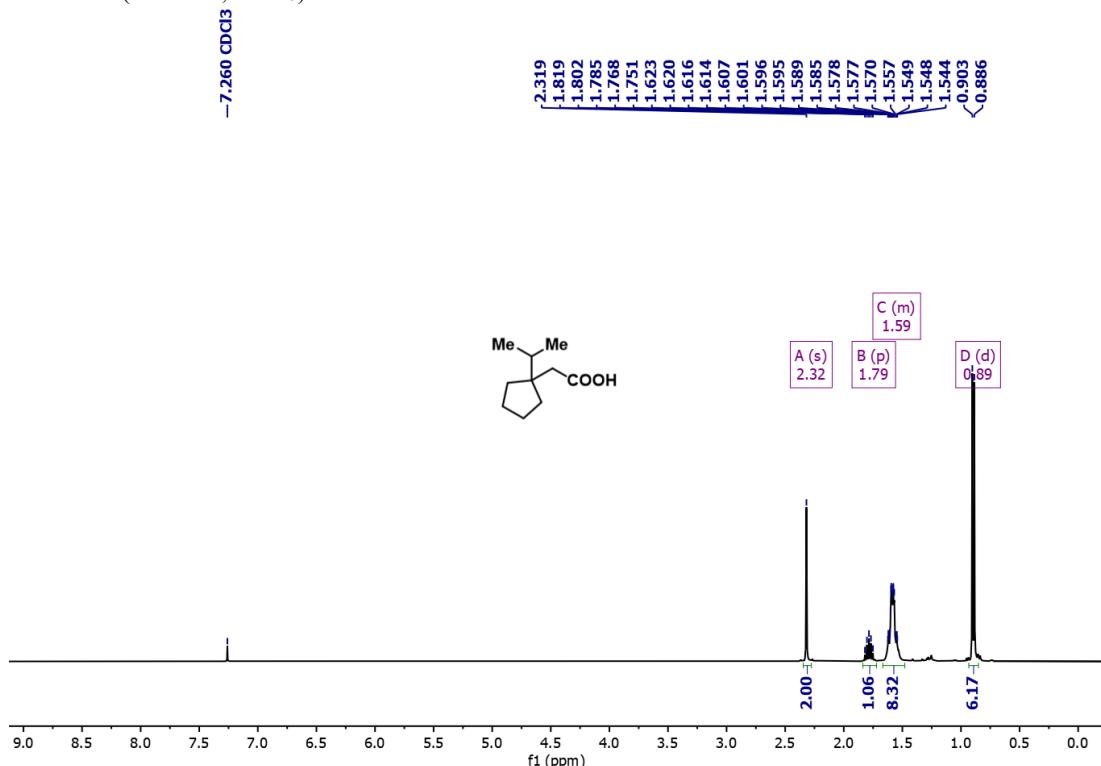


¹³C NMR (101 MHz, CDCl₃)

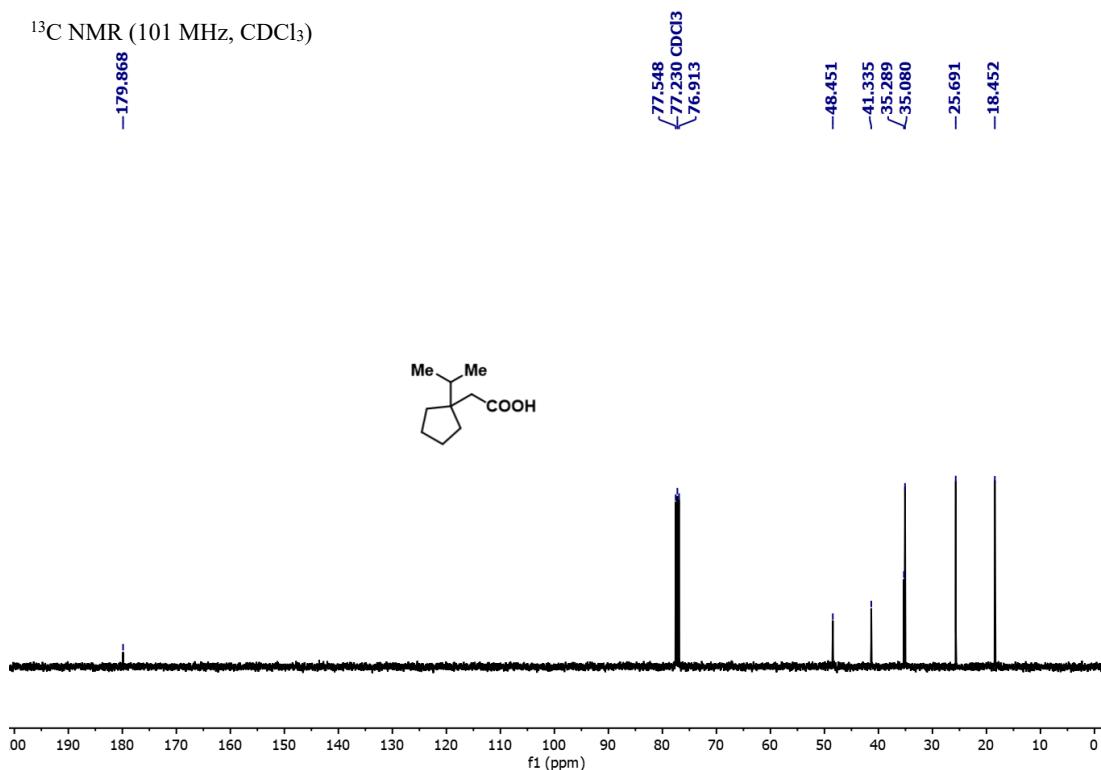


2-(1-Isopropylcyclopentyl)acetic acid (47)

¹H NMR (400 MHz, CDCl₃)



¹³C NMR (101 MHz, CDCl₃)

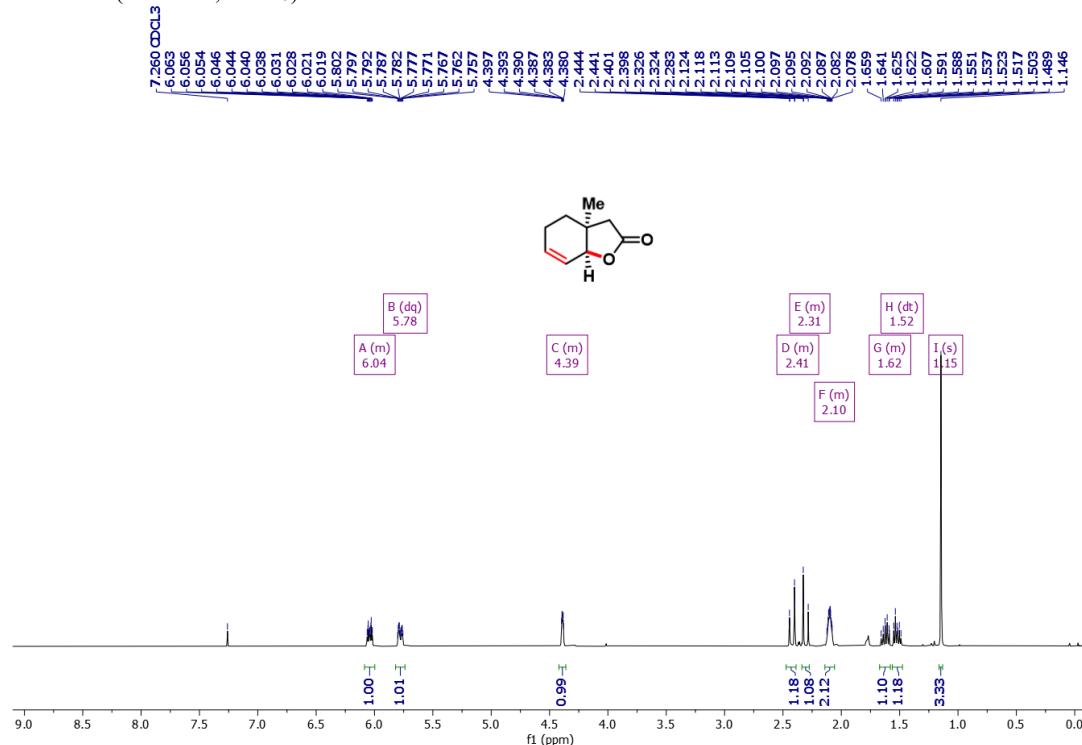


15. NMR Spectra of the Unsaturated Bicyclic Lactones:

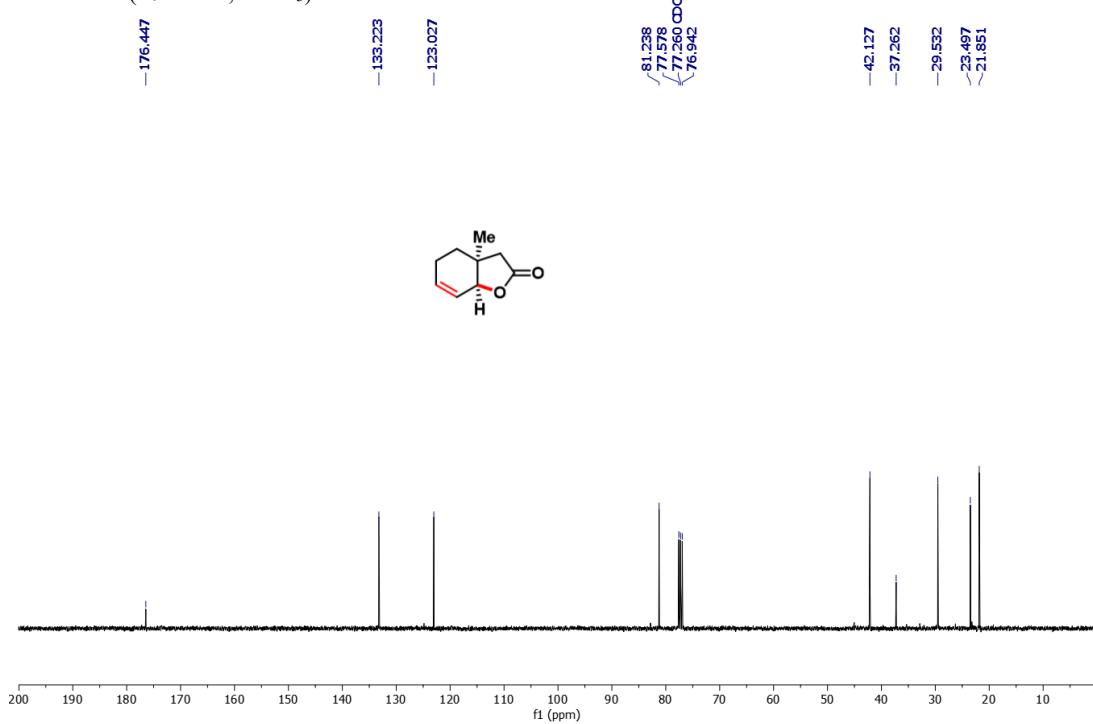
Compound 2a

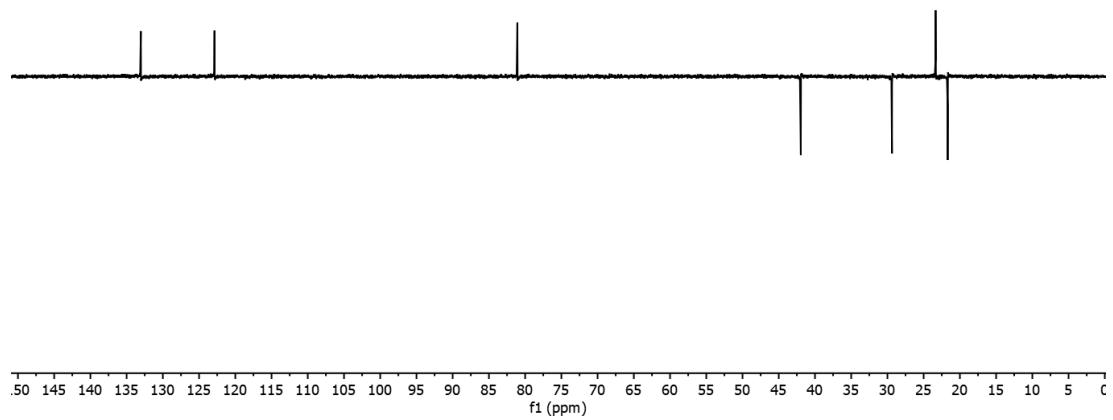
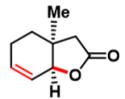
(3a*S*,7a*S*)-3a-Methyl-3a,4,5,7a-tetrahydrobenzofuran-2(3*H*)-one

¹H NMR (400 MHz, CDCl₃)



¹³C NMR (101 MHz, CDCl₃)

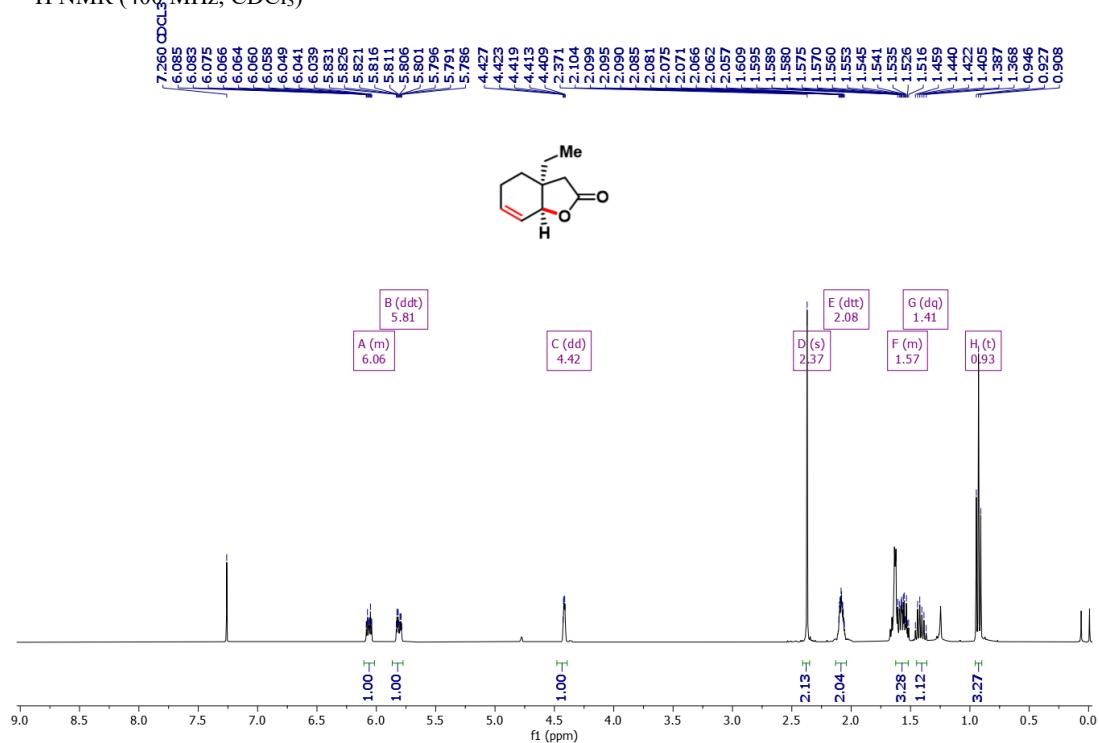




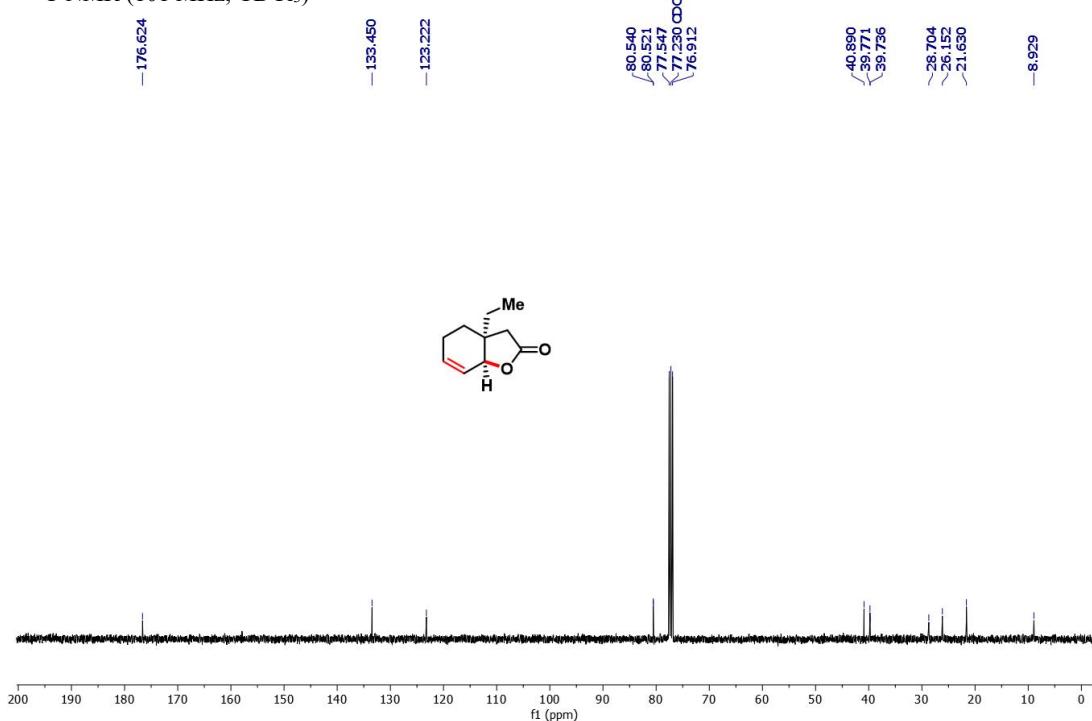
Compound 2b

(3a*S*,7a*S*)-3a-Ethyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one

¹H NMR (400 MHz, CDCl₃)



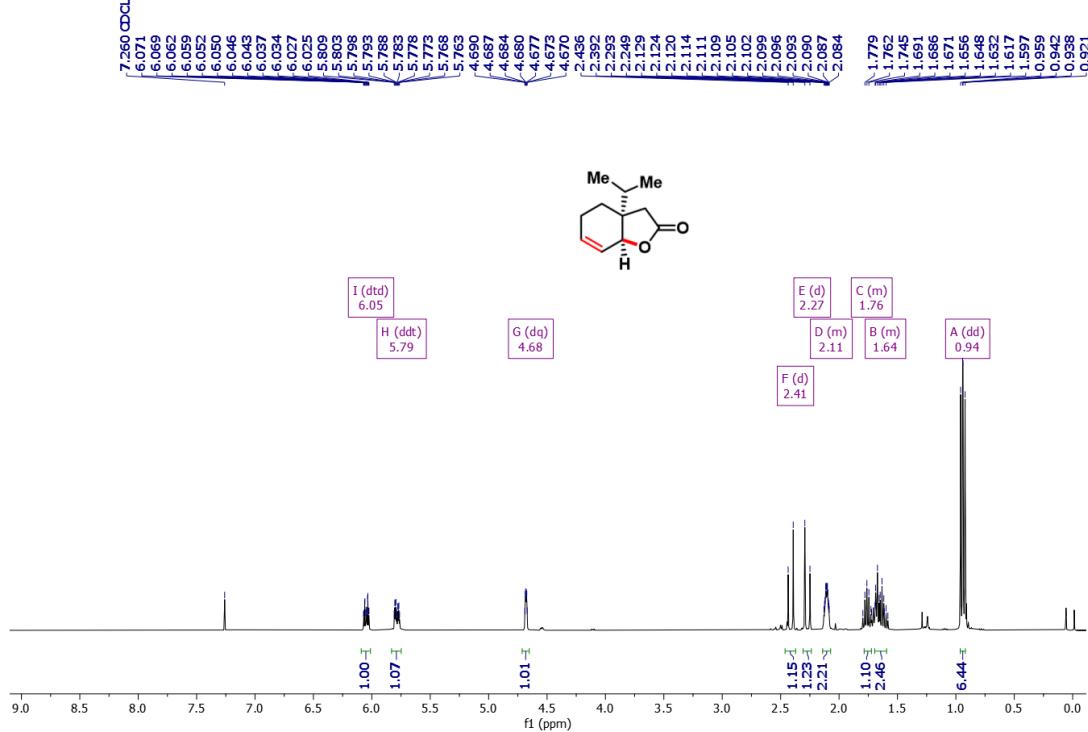
¹³C NMR (101 MHz, CDCl₃)



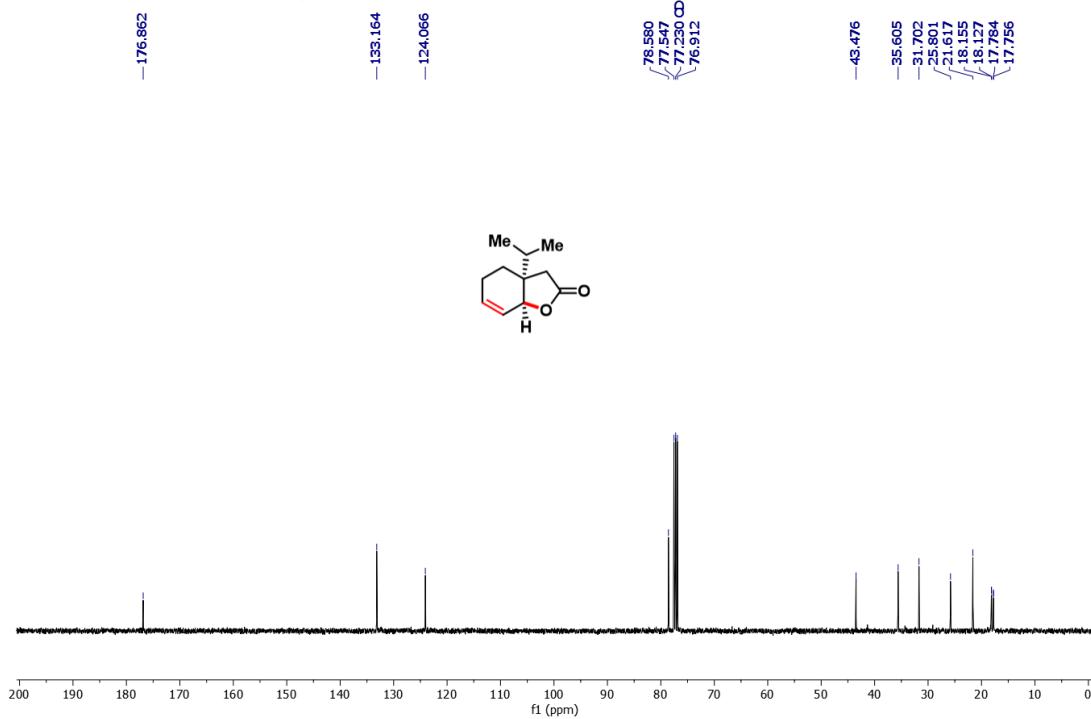
Compound 2c

(3a*S*,7a*S*)-3a-Isopropyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one

¹H NMR (400 MHz, CDCl₃)

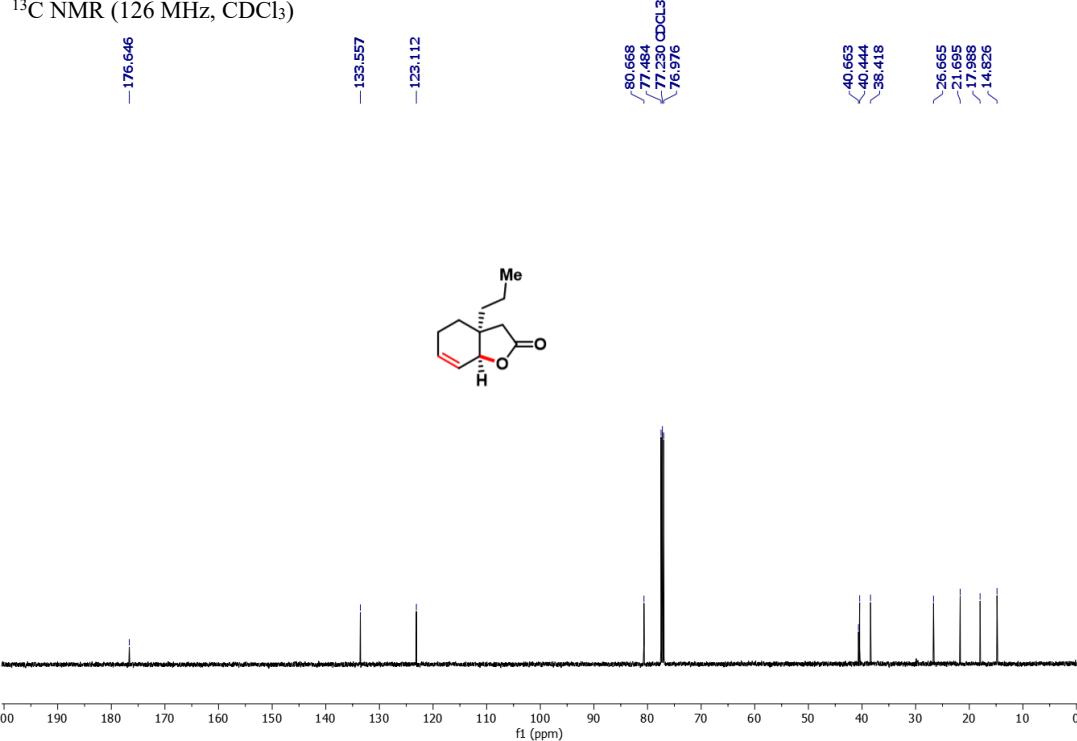
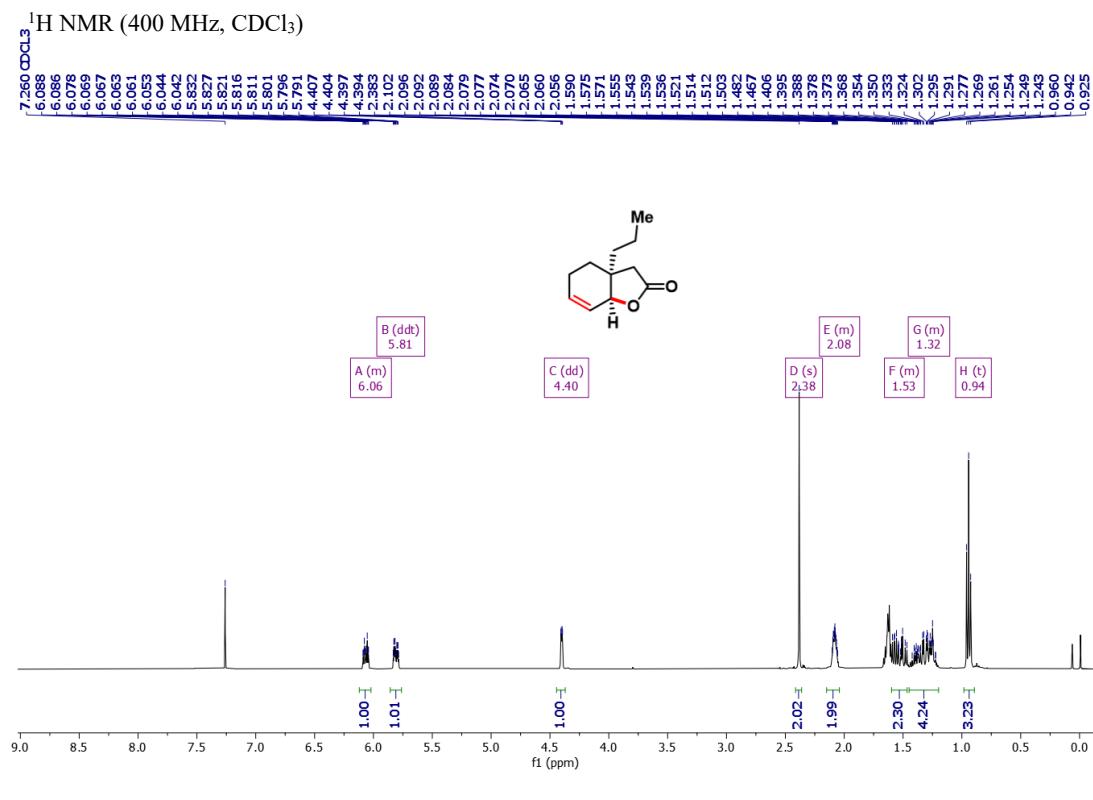


¹³C NMR (101 MHz, CDCl₃)



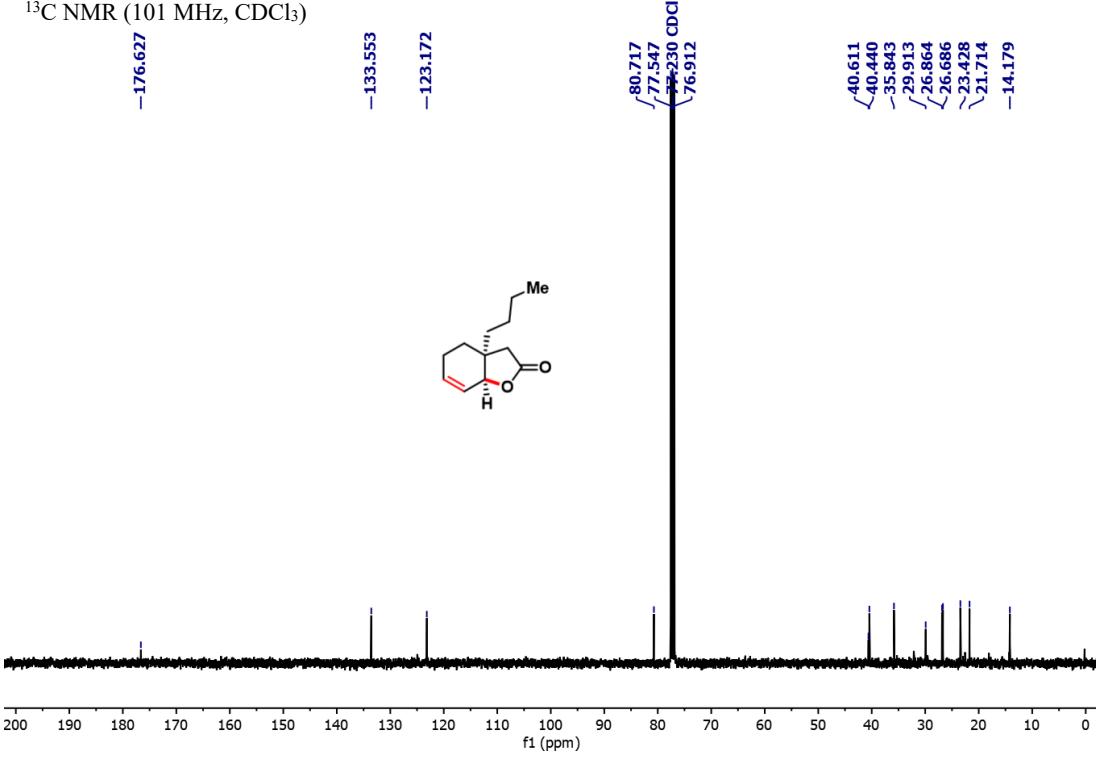
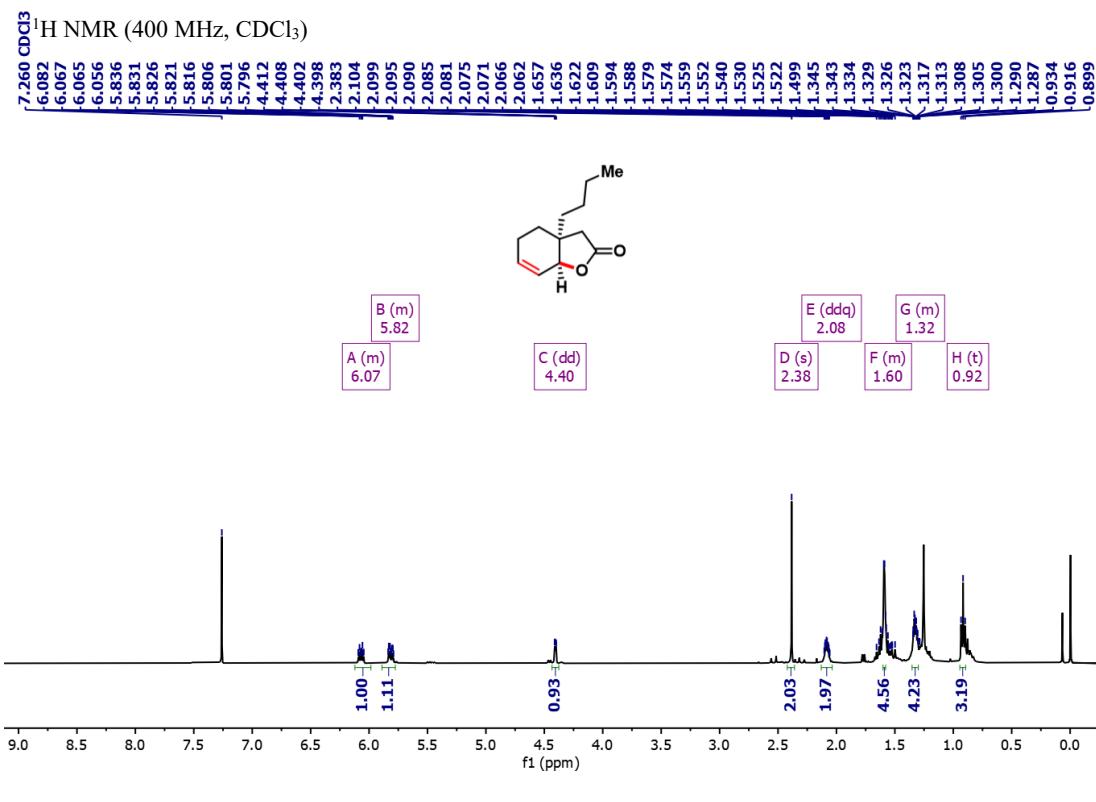
Compound 2d

(3a*S*,7a*S*)-3a-Propyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one



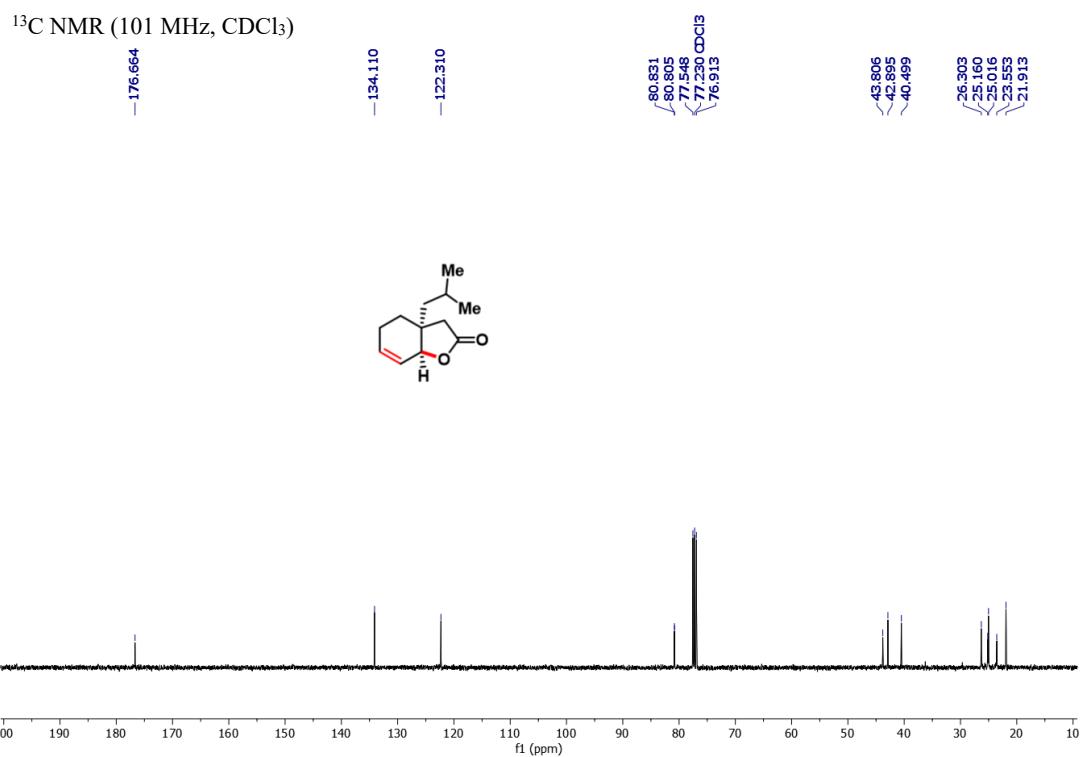
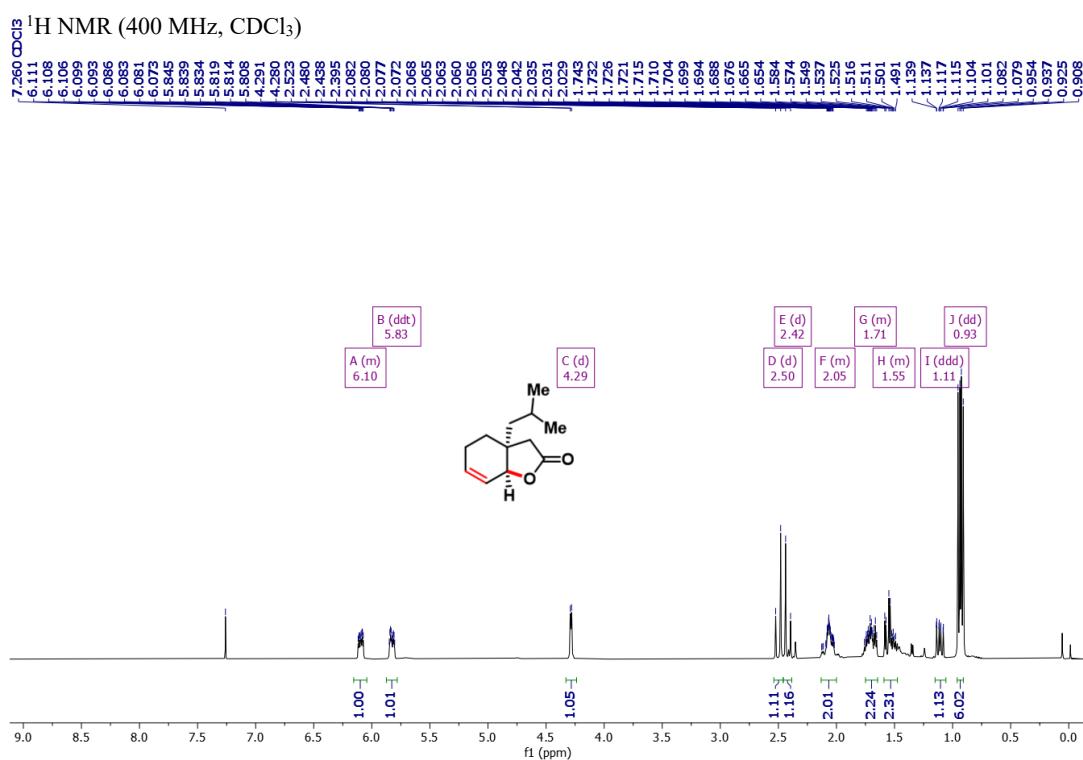
Compound 2e

(3a*S*,7a*S*)-3a-Butyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one



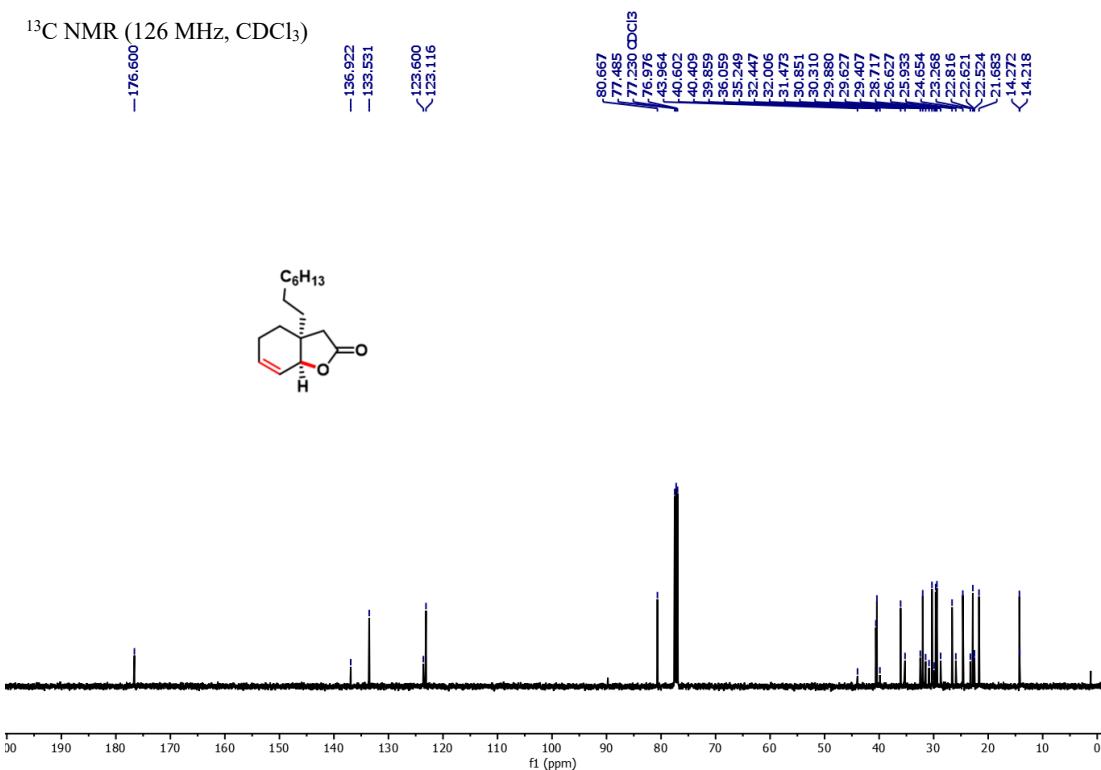
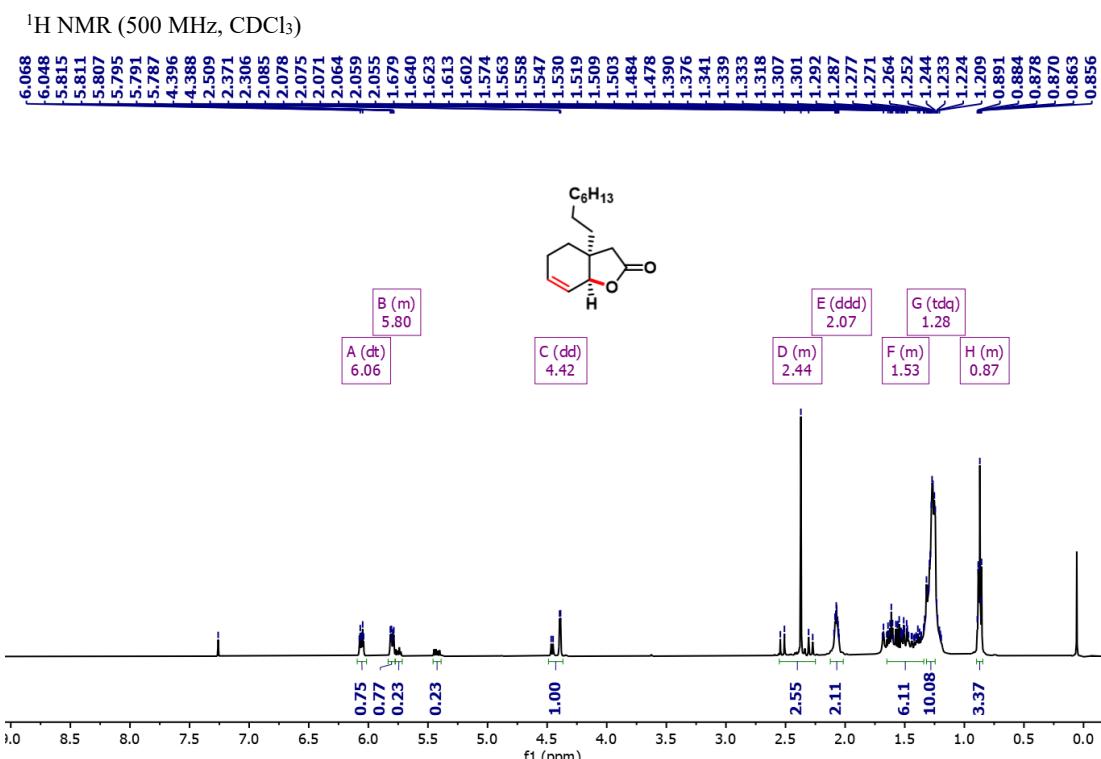
Compound 2f

(3a*R*,7a*S*)-3a-Isobutyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one



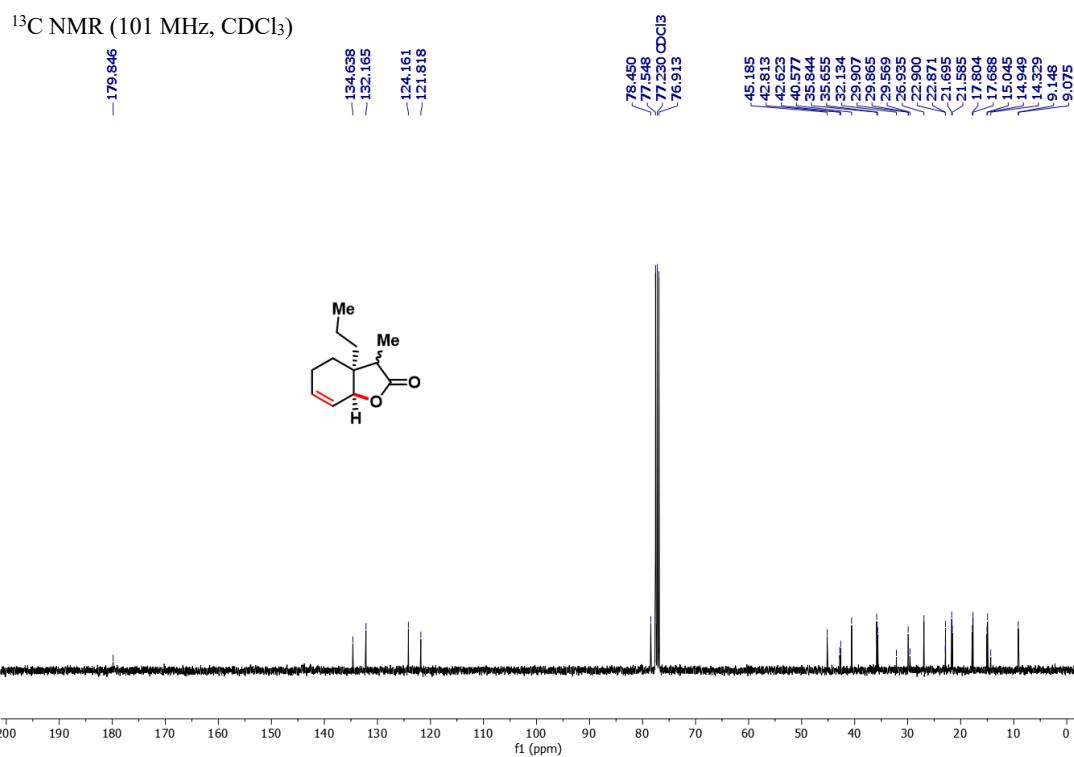
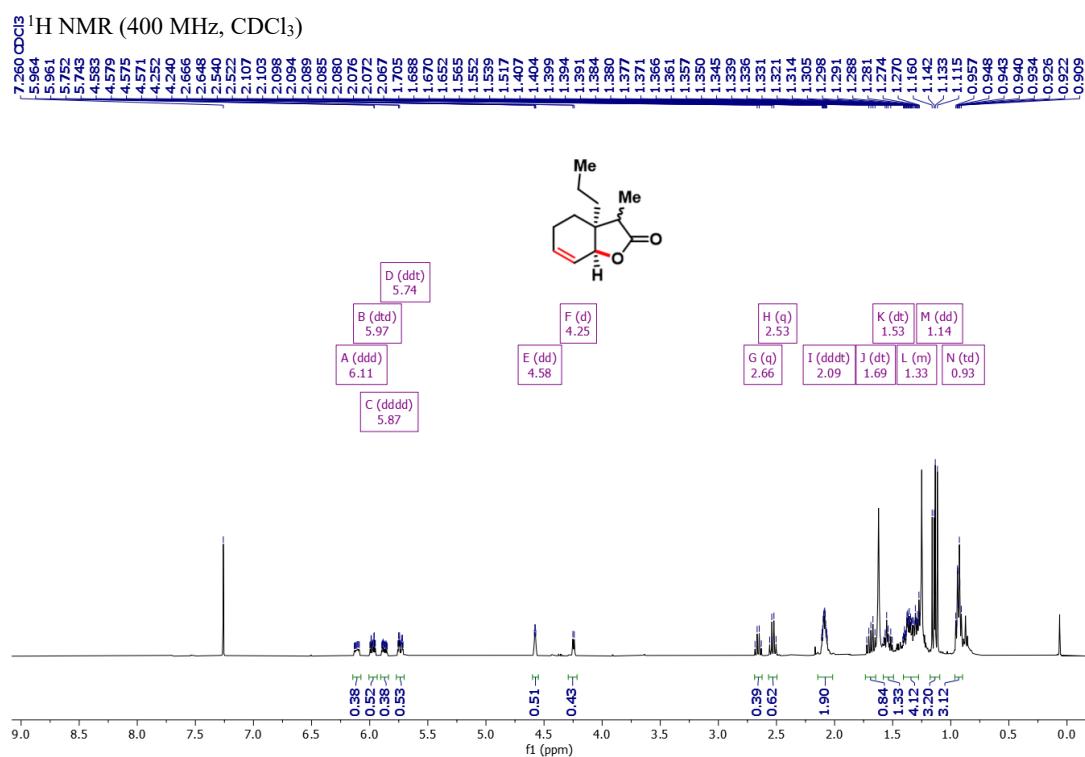
Compound 2g

(3a*S*,7a*S*)-3a-Octyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one



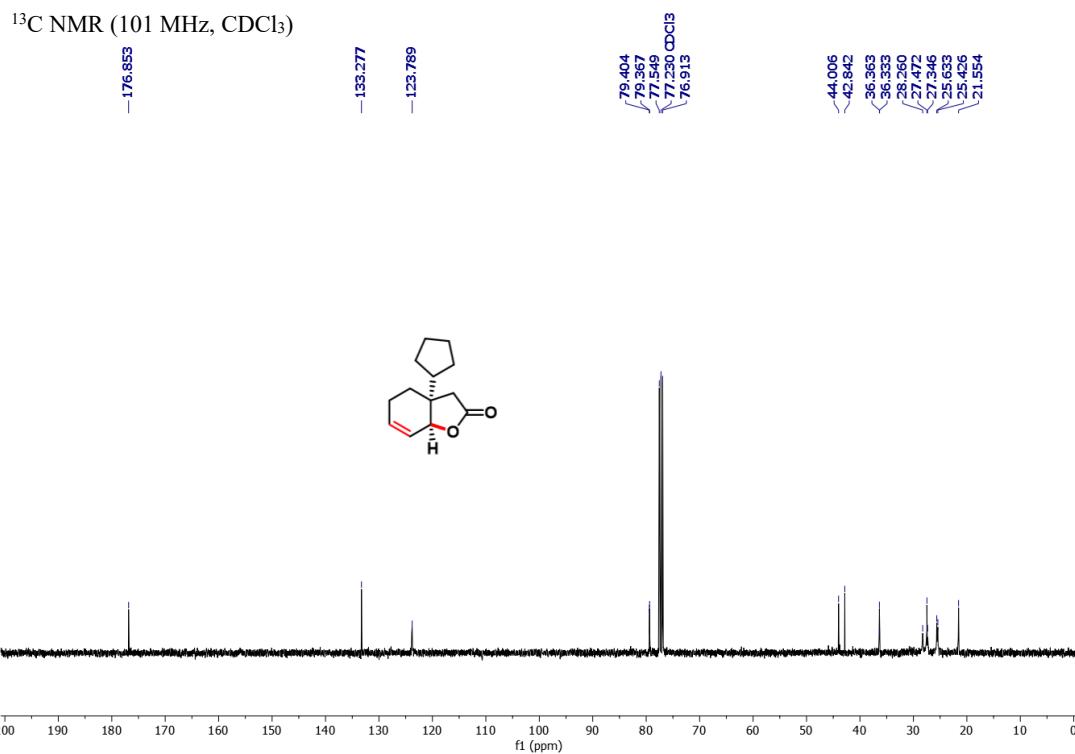
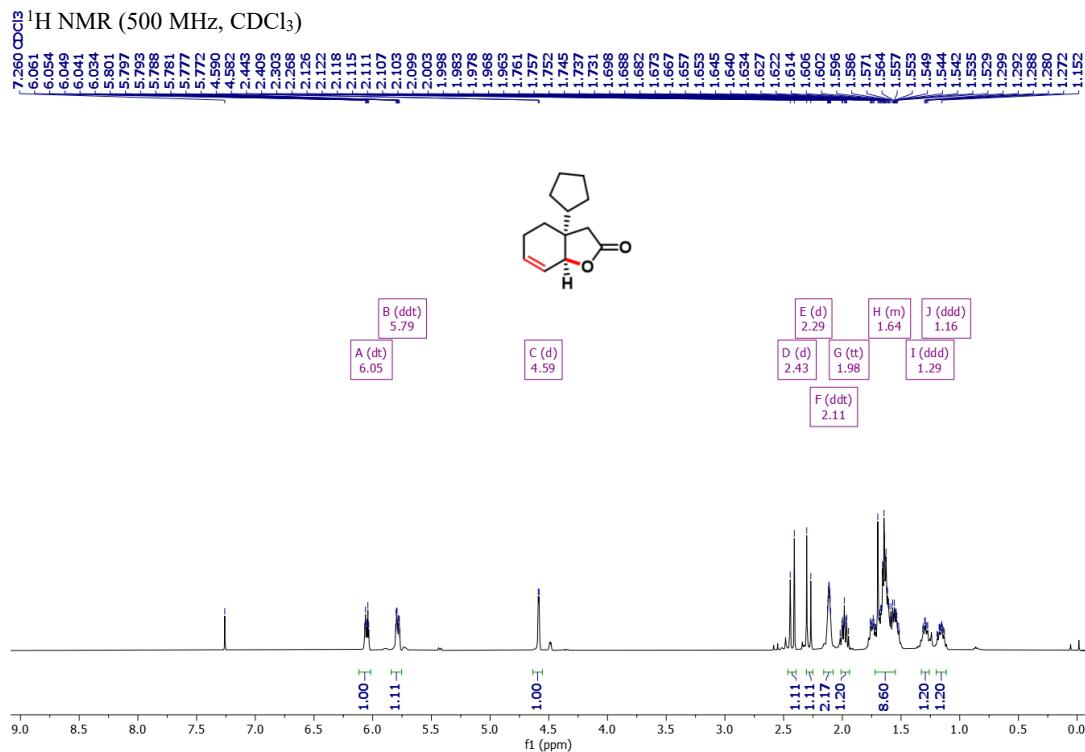
Compound 2h

(3a*S*,7a*S*)-3-Methyl-3a-propyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one



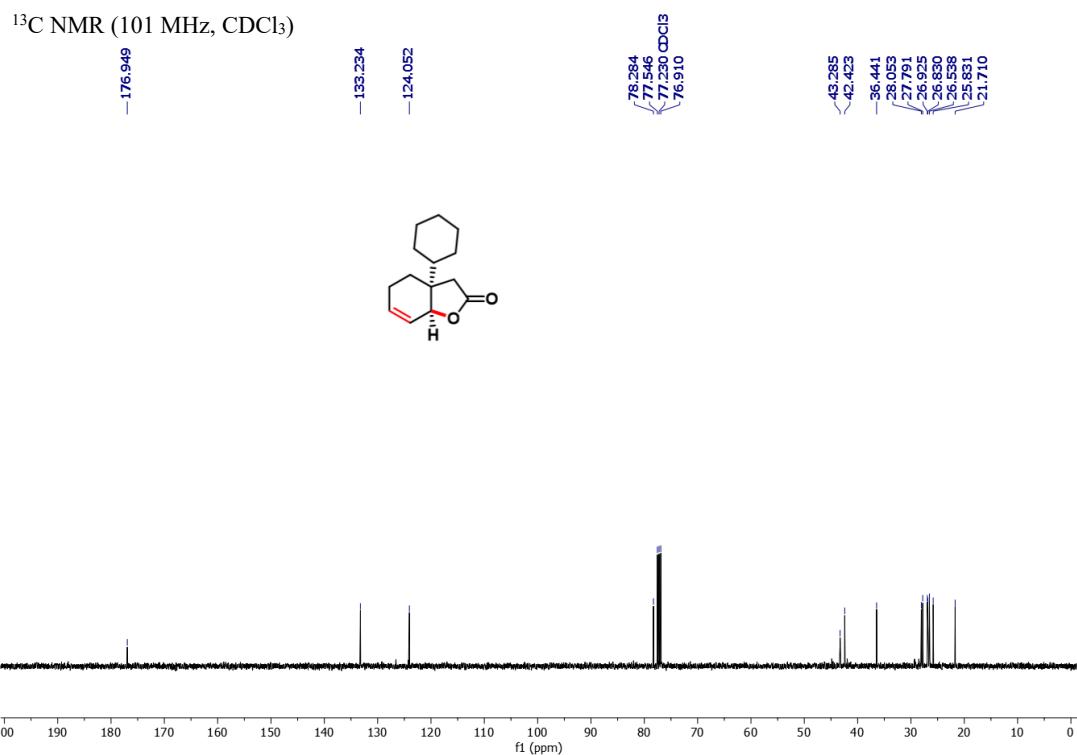
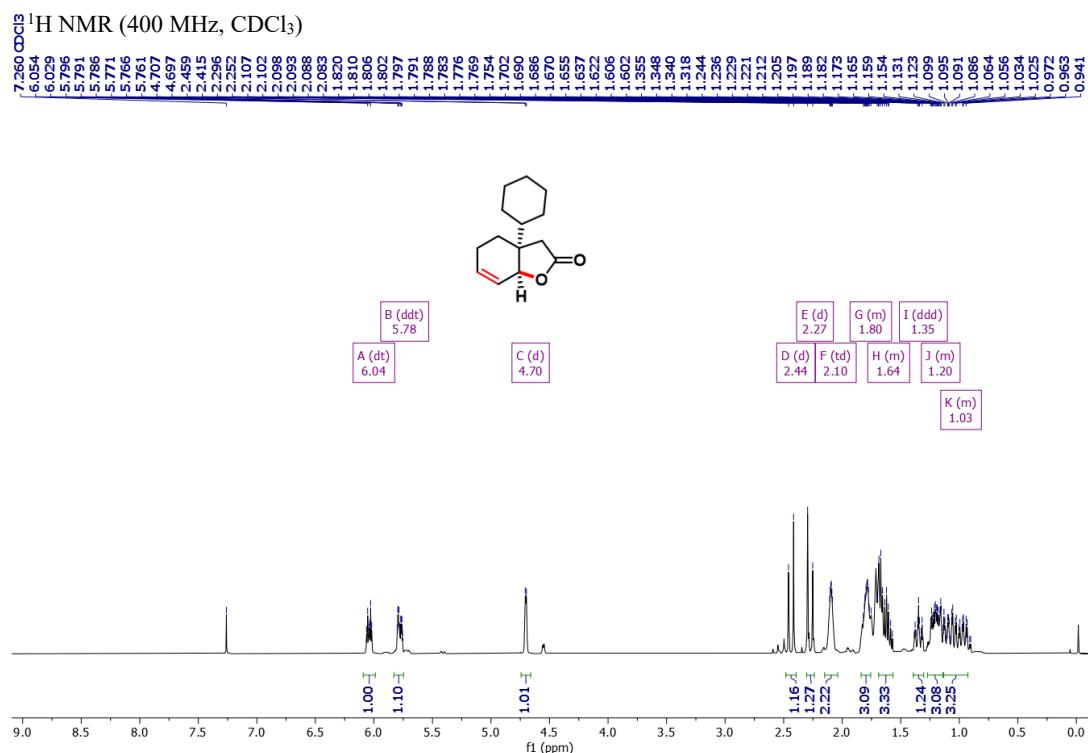
Compound 2i

(3a*S*,7a*S*)-3a-Cyclopentyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one



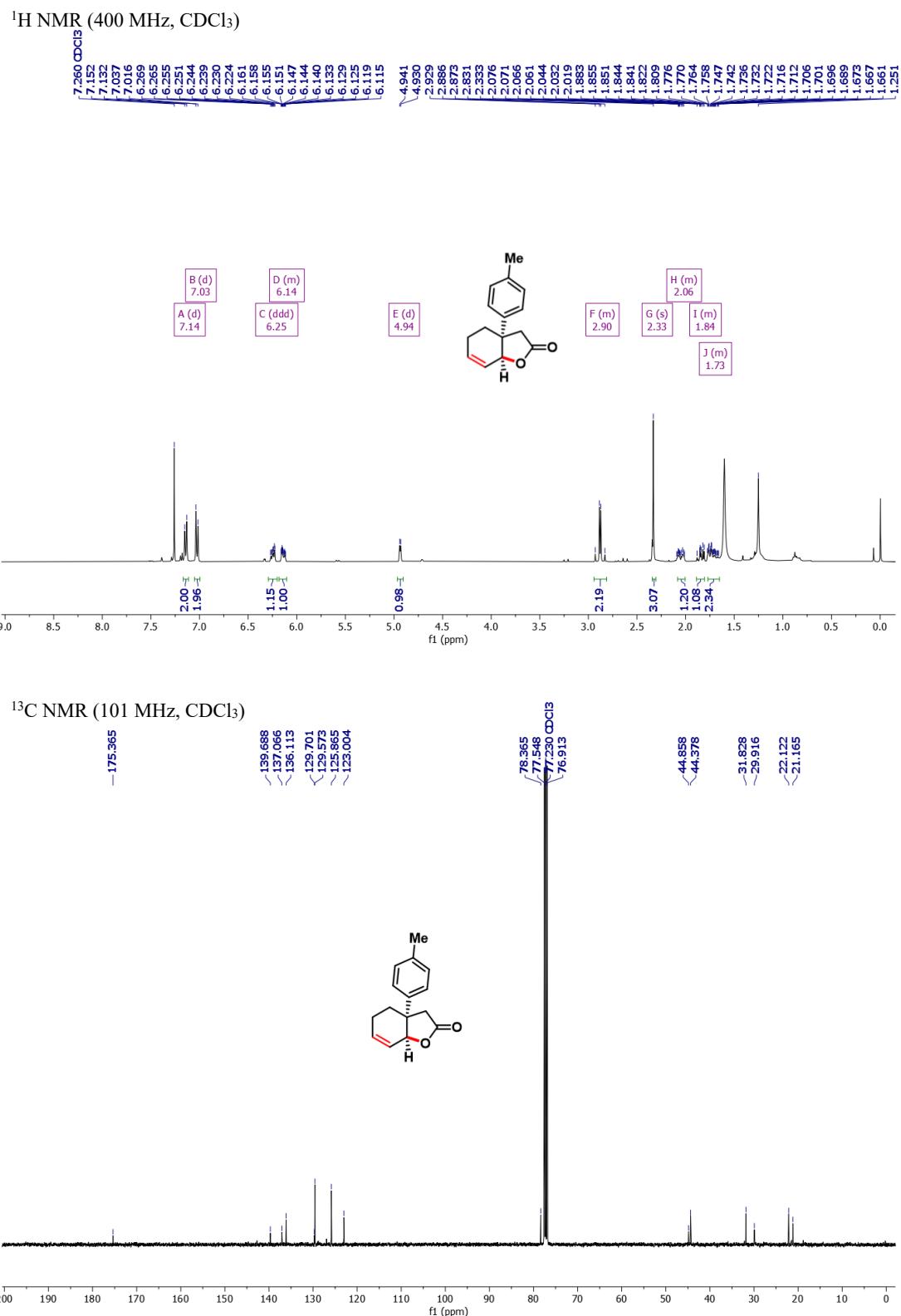
Compound 2j

(3a*S*,7a*S*)-3a-Cyclohexyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one



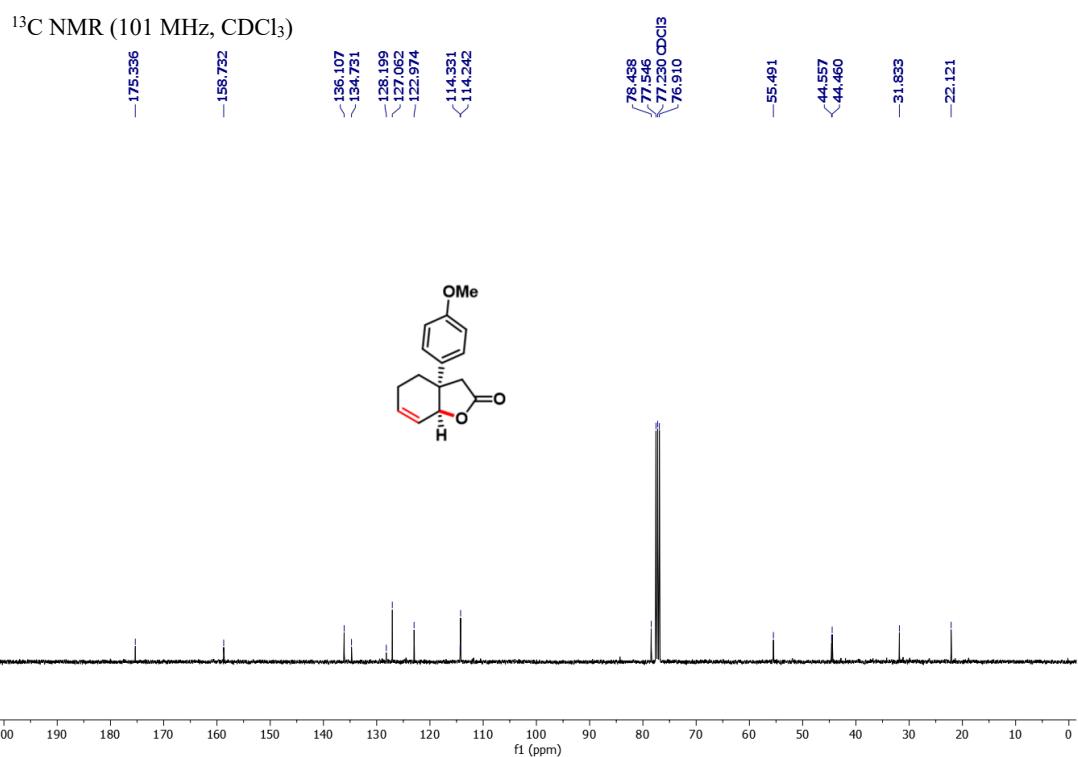
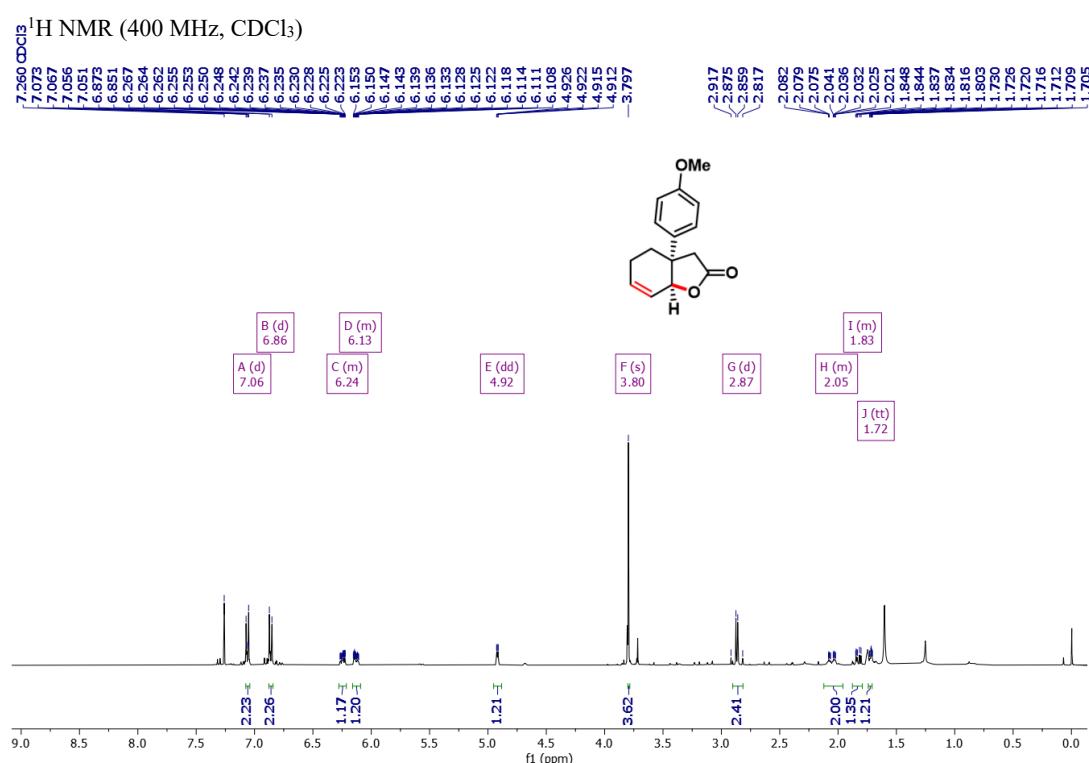
Compound 2k

(3a*S*,7a*S*)-3a-(*p*-Tolyl)-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one



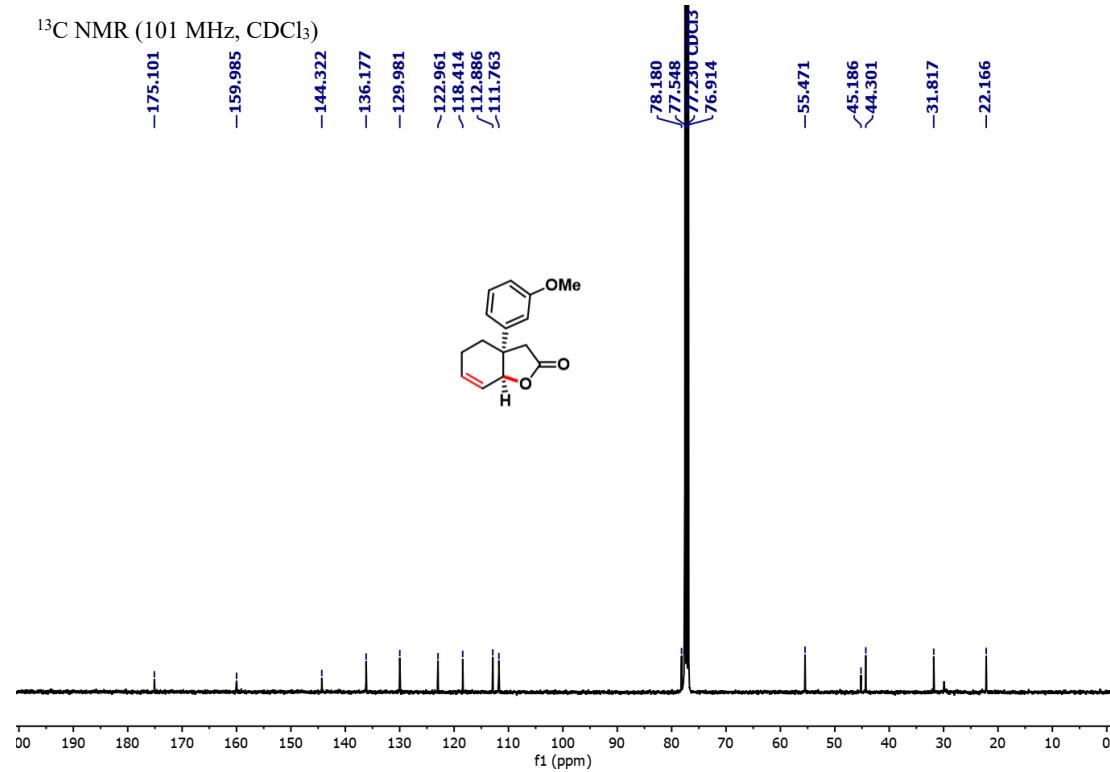
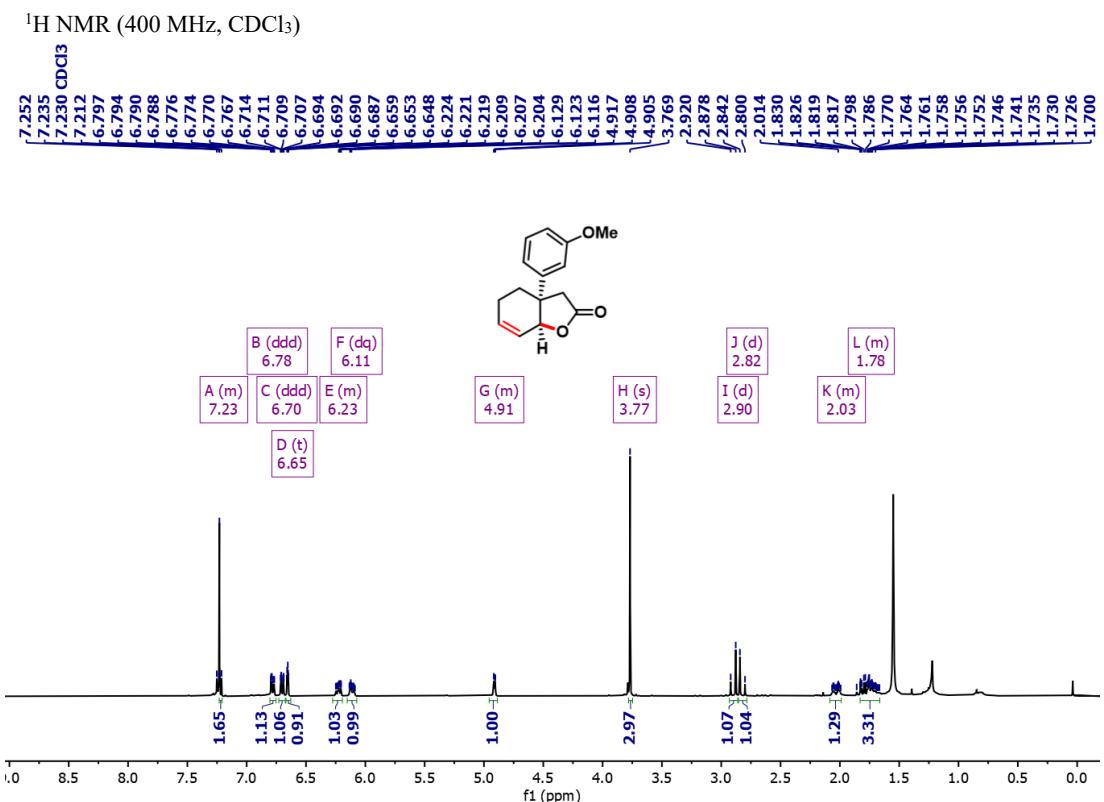
Compound 2l

(3a*S*,7a*S*)-3a-(4-Methoxyphenyl)-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one



Compound 2m

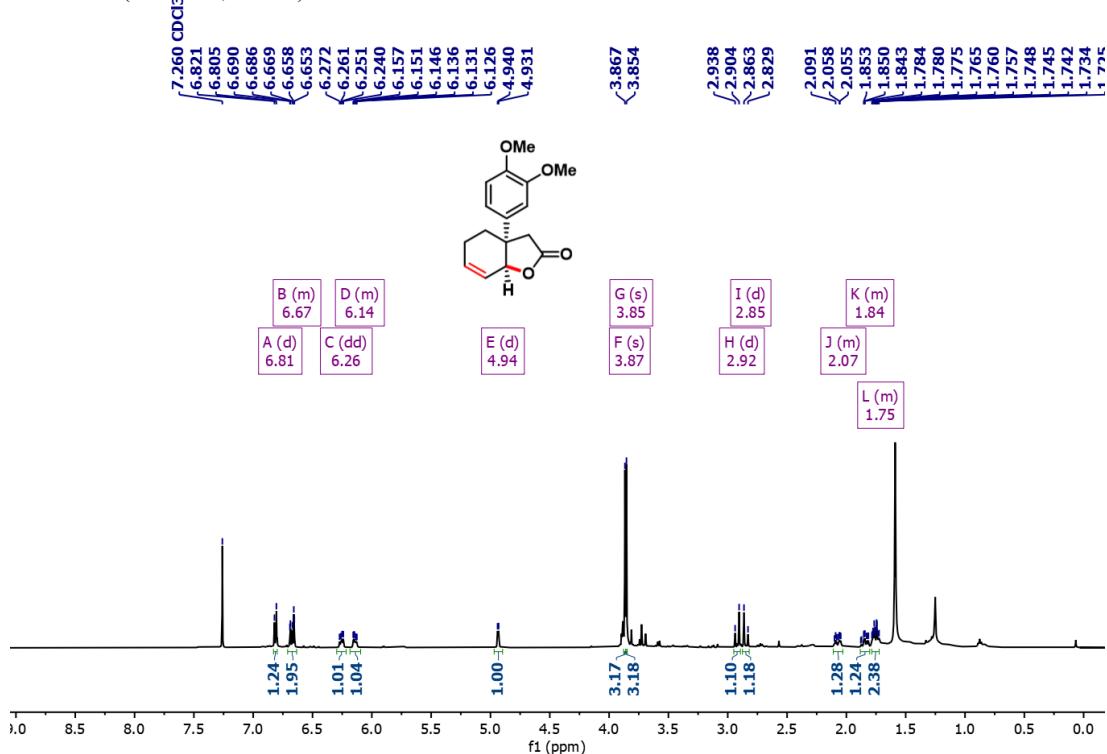
(3a*S*,7a*S*)-3a-(3-Methoxyphenyl)-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one



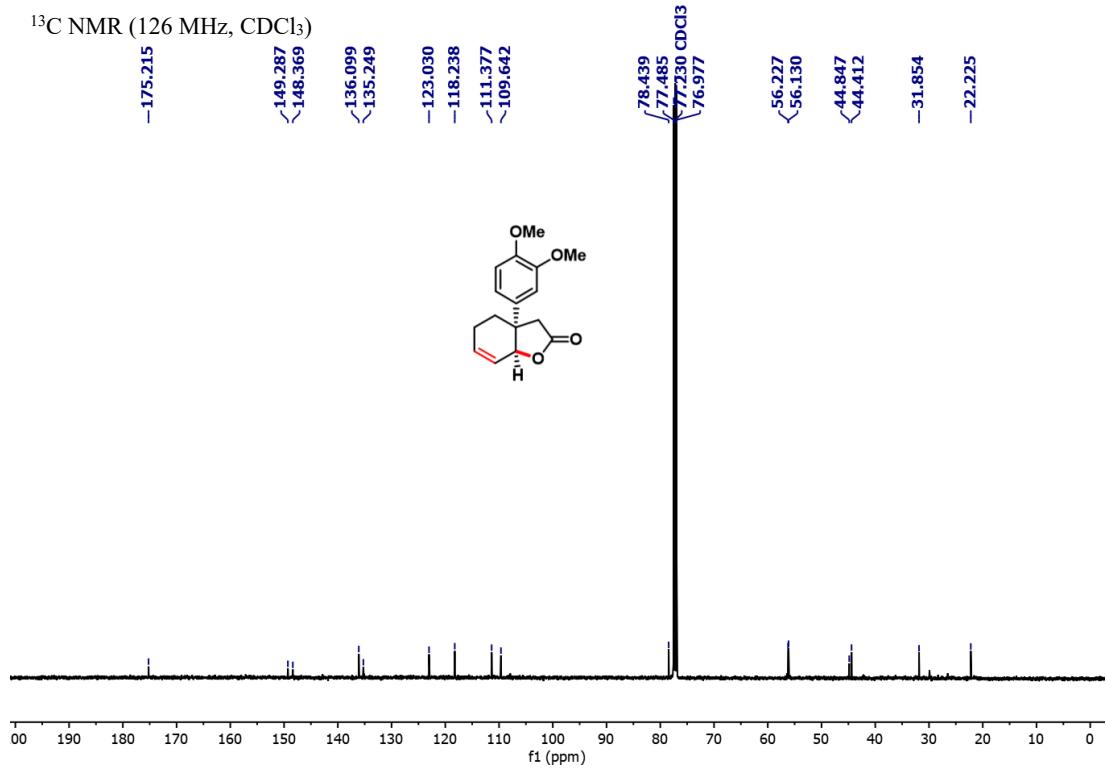
Compound 2n

(3a*S*,7a*S*)-3a-(3,4-Dimethoxyphenyl)-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one

¹H NMR (500 MHz, CDCl₃)

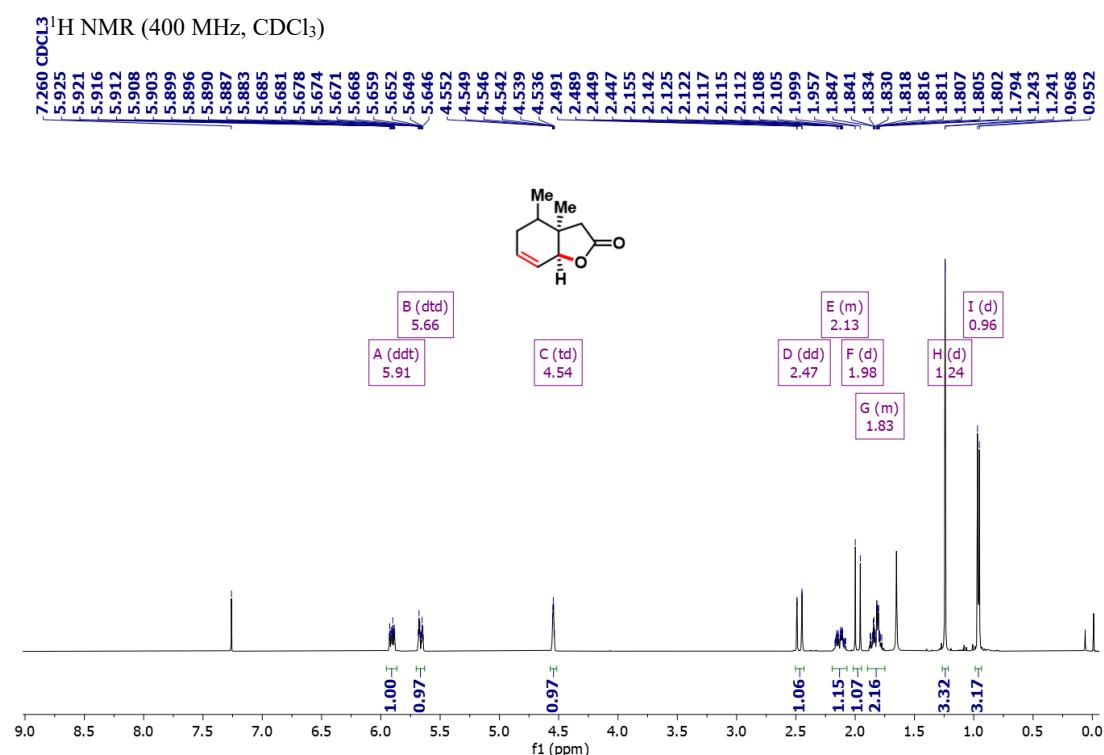


¹³C NMR (126 MHz, CDCl₃)

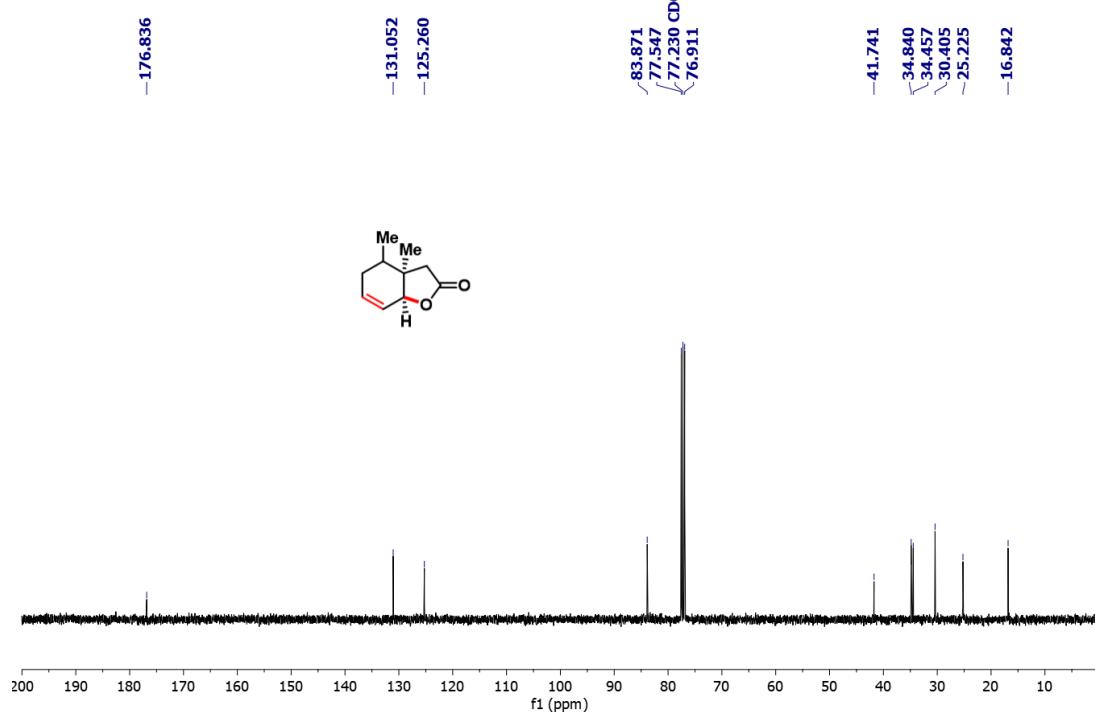


Compound 2o

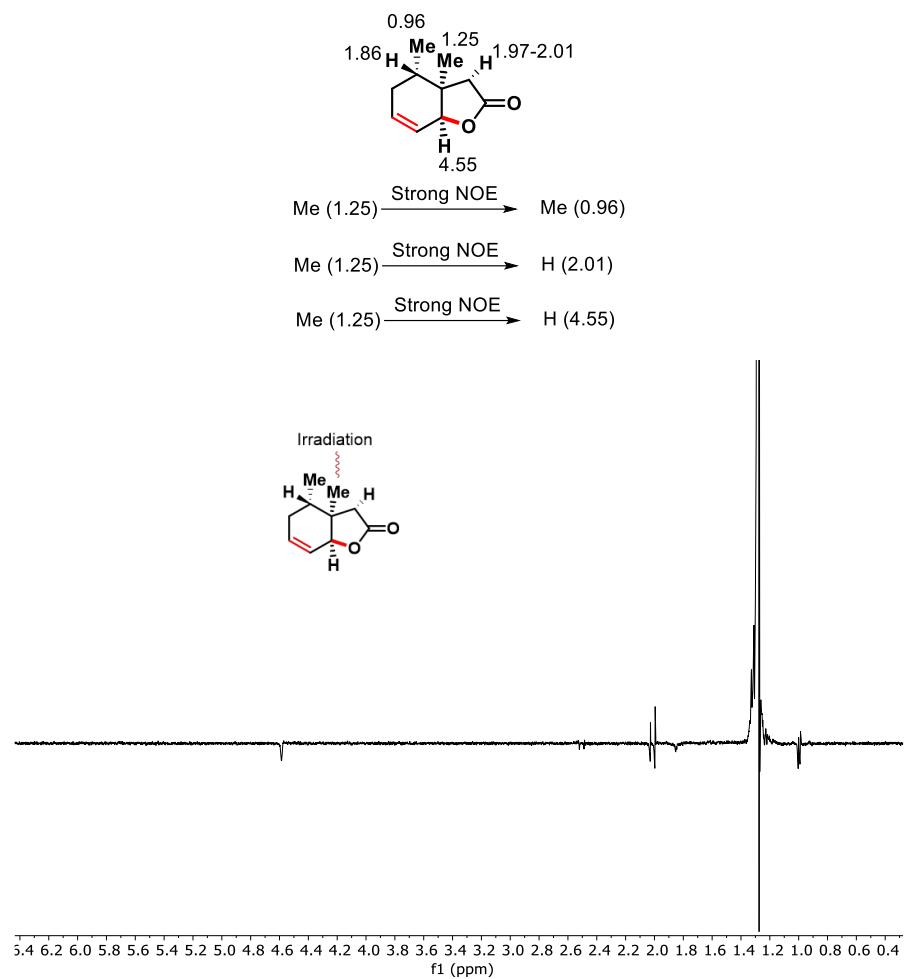
(3a*R*,7a*S*)-3a,4-Dimethyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one

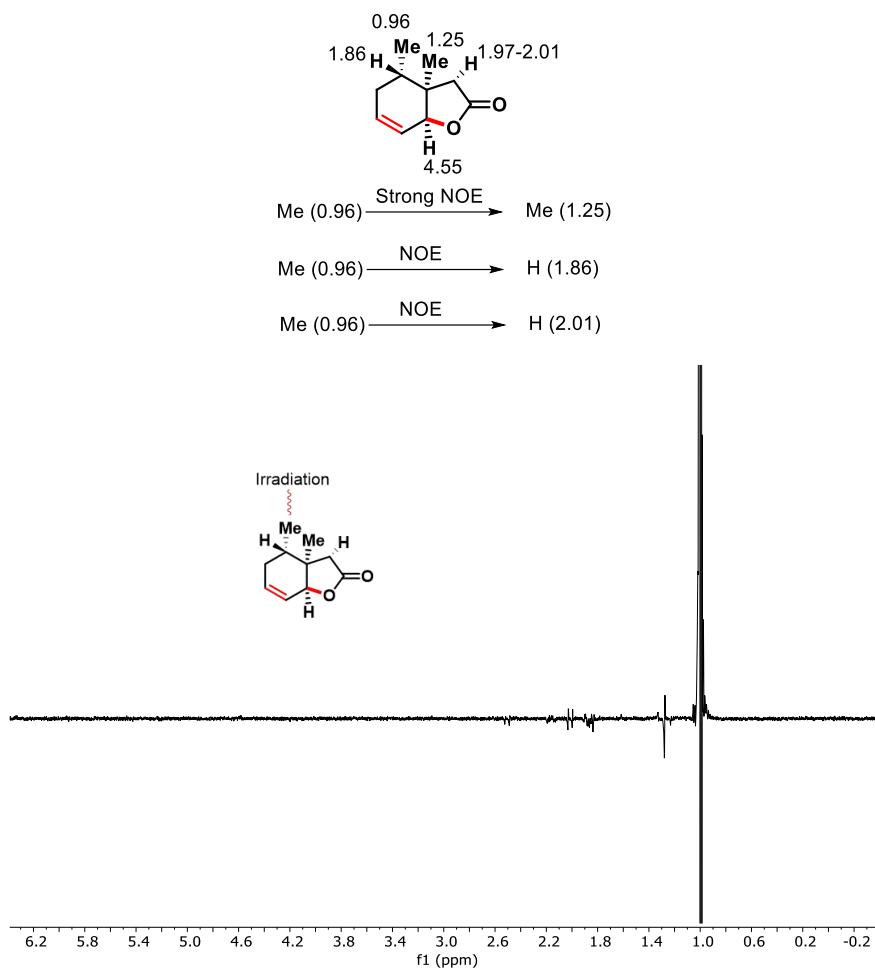


¹³C NMR (101 MHz, CDCl₃)



NOE Experiment:

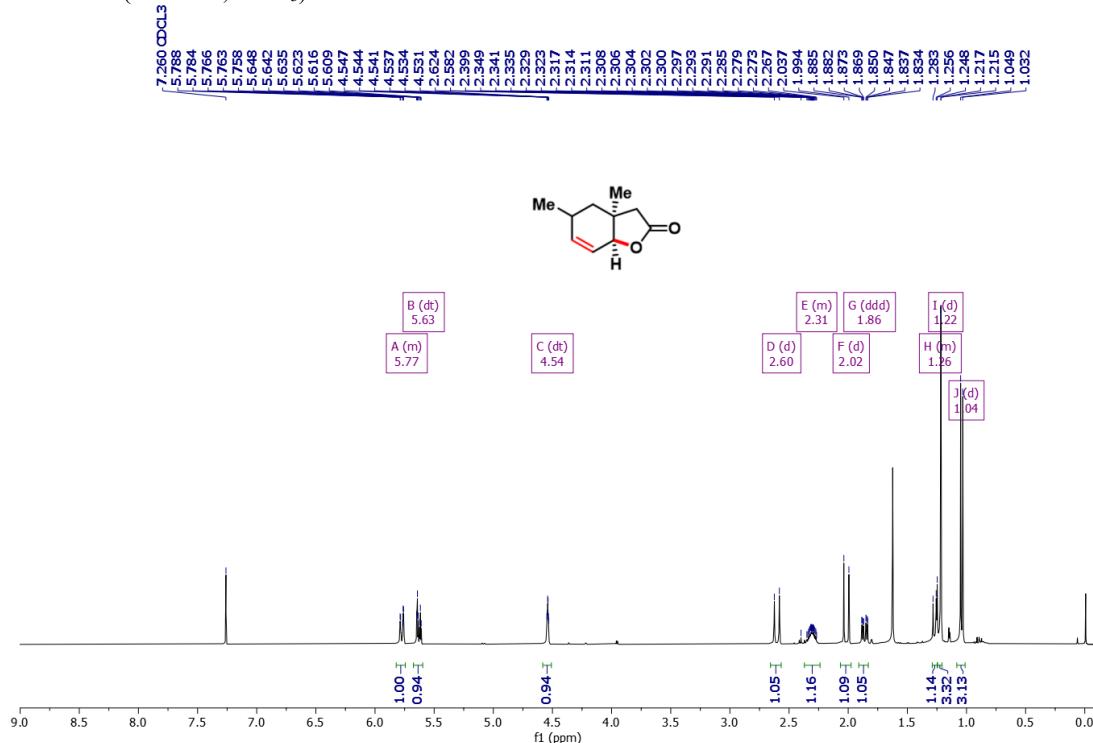




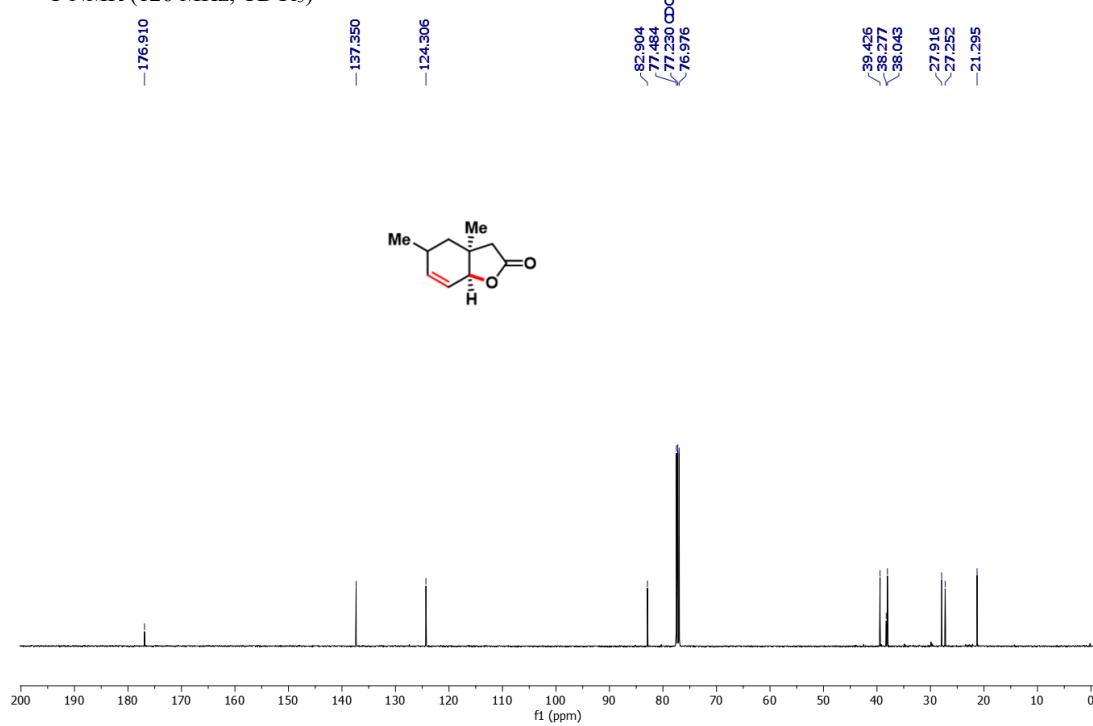
Compound 2p

(3a*S*,7a*S*)-3a,5-Dimethyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one

¹H NMR (400 MHz, CDCl₃)



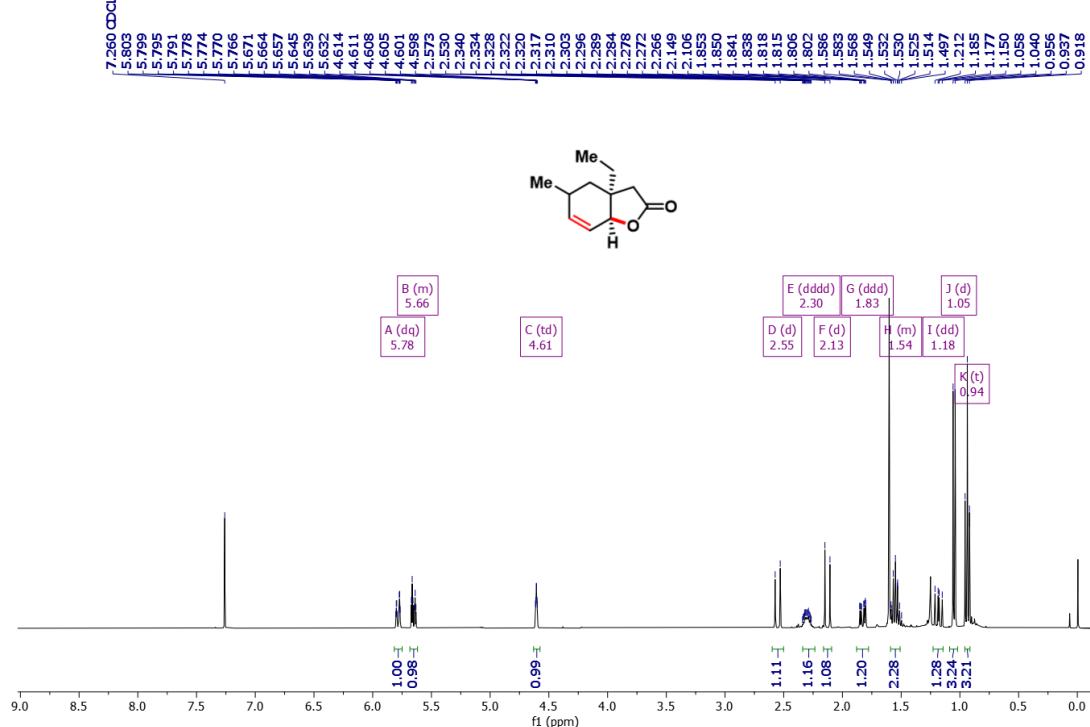
¹³C NMR (126 MHz, CDCl₃)



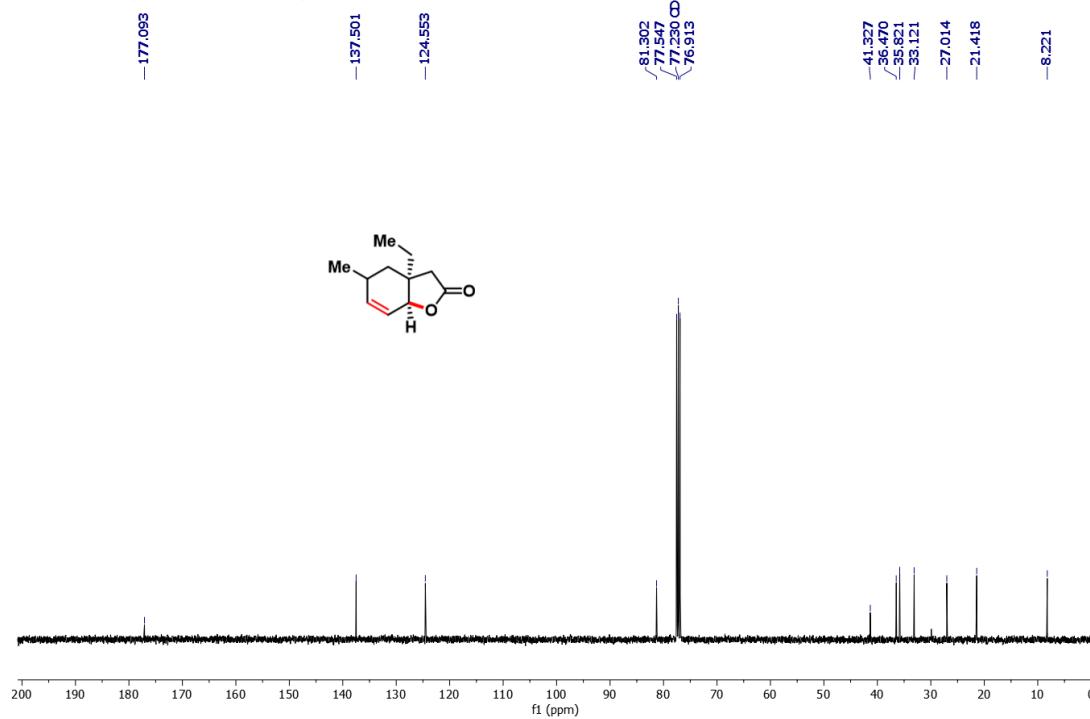
Compound 2q

(3a*S*,7a*S*)-3a-Ethyl-5-methyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one

¹H NMR (400 MHz, CDCl₃)

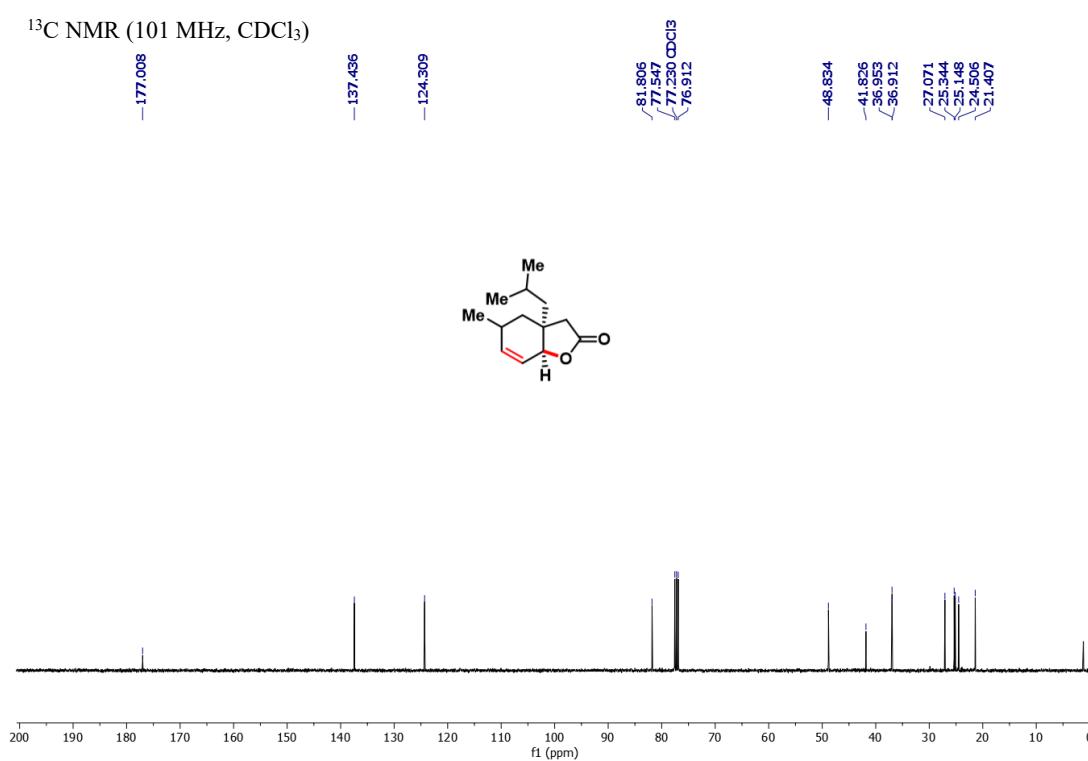
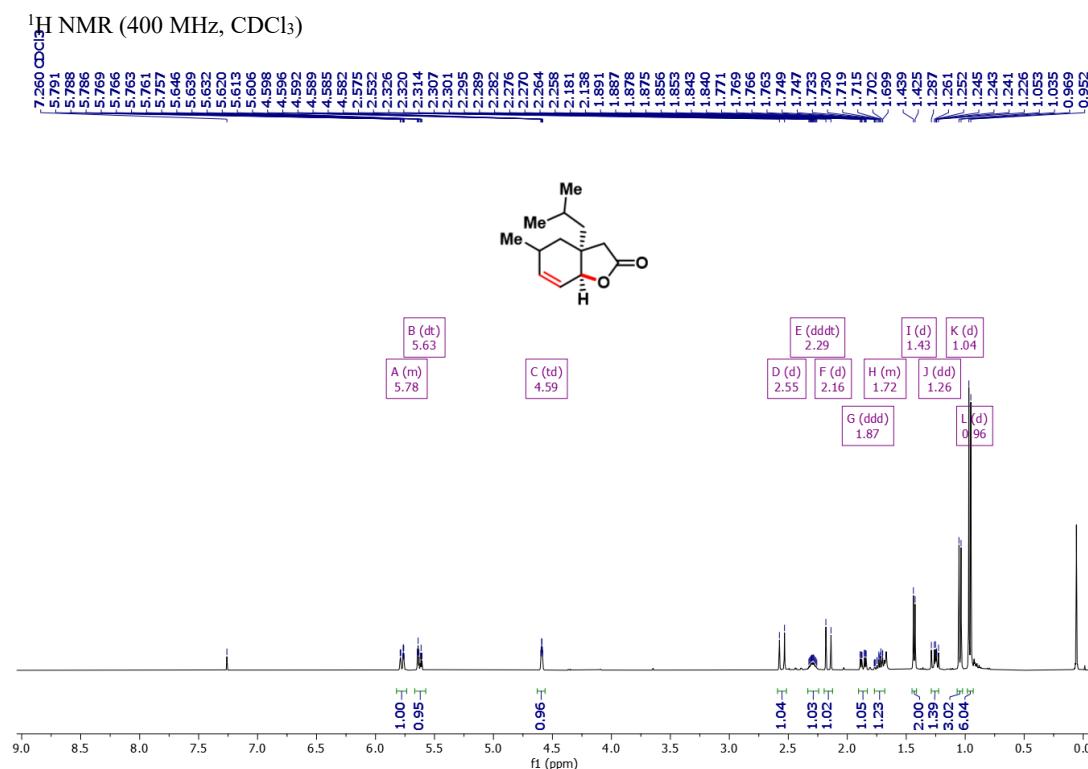


¹³C NMR (101 MHz, CDCl₃)



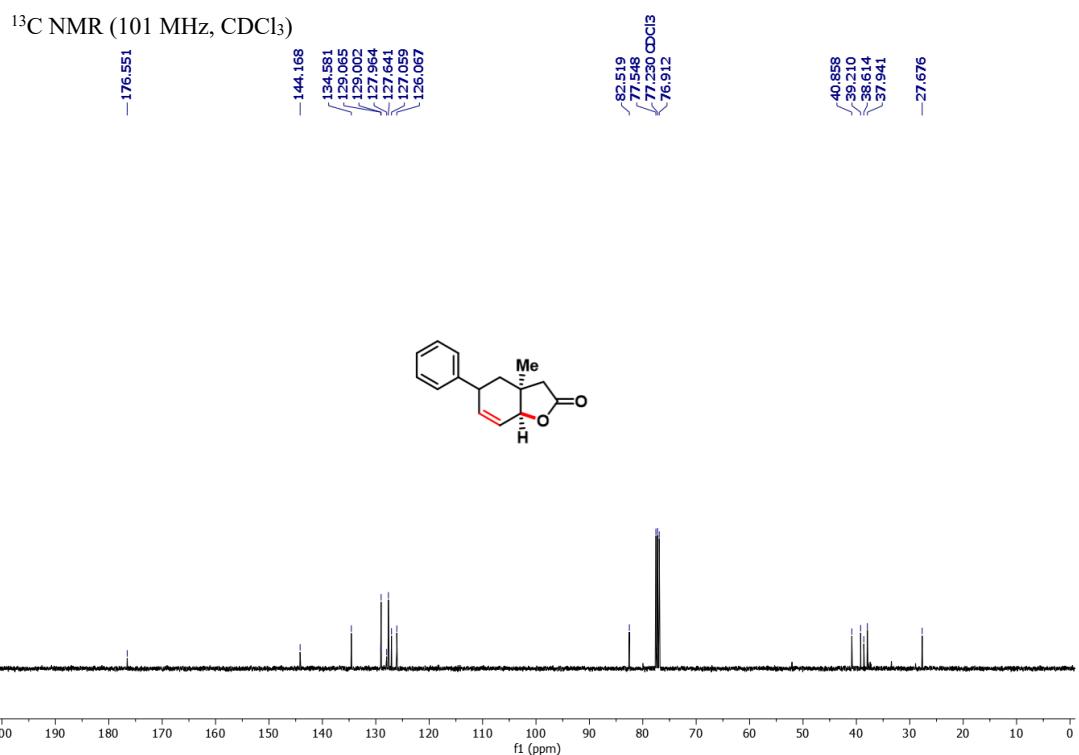
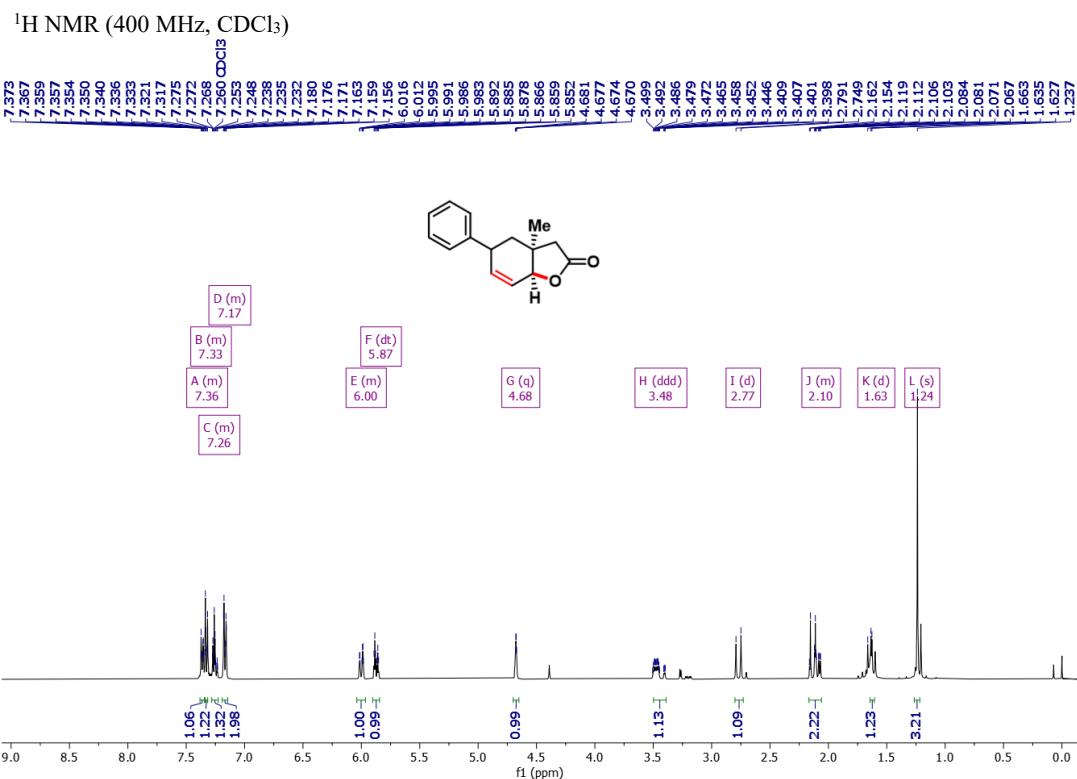
Compound 2r

(3a*S*,7a*S*)-3a-Isobutyl-5-methyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one



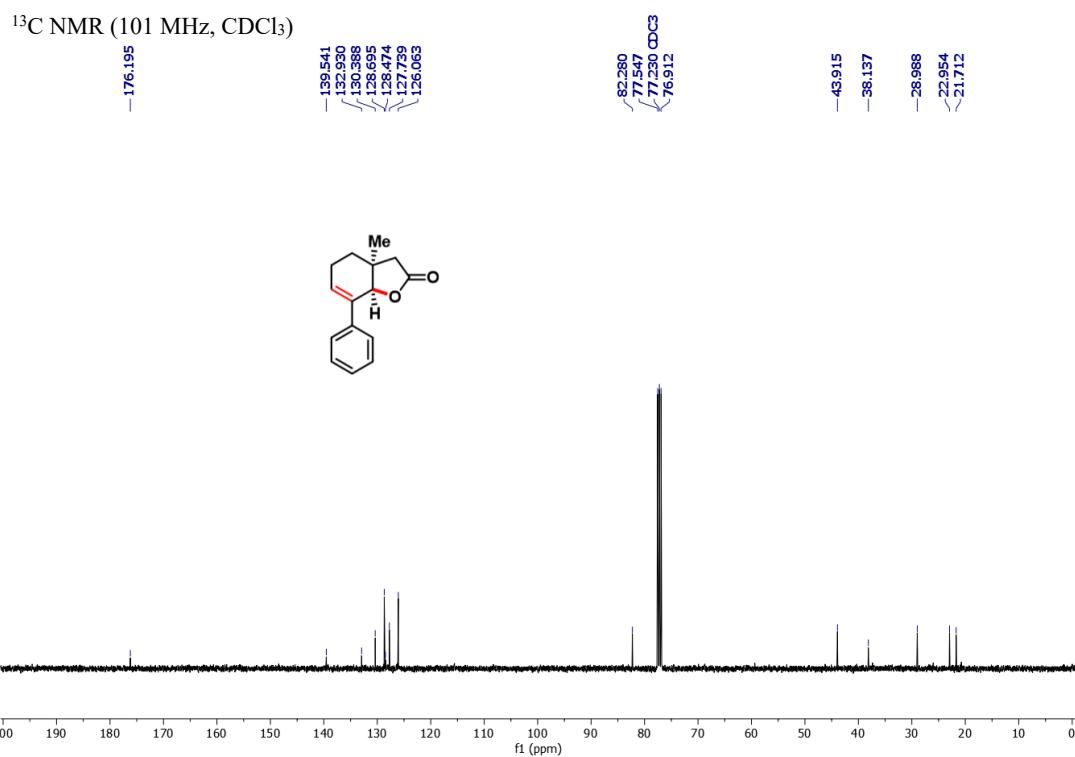
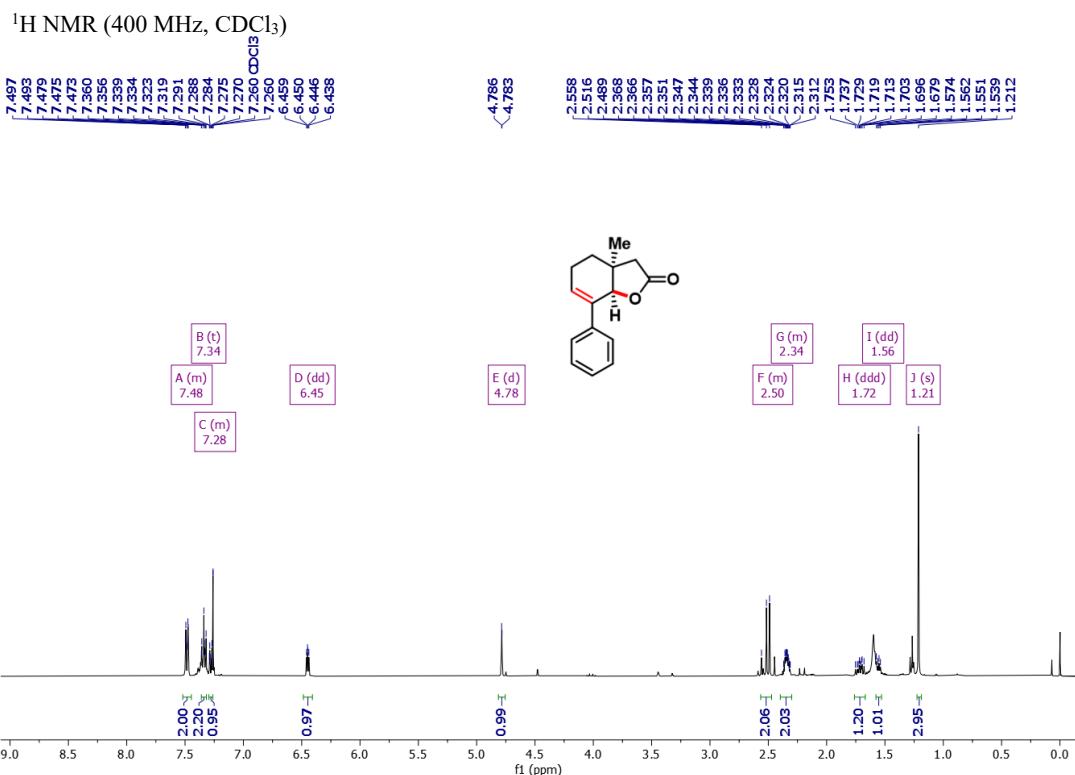
Compound 2s

(3a*S*,7a*S*)-3a-Methyl-5-phenyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one



Compound 2t

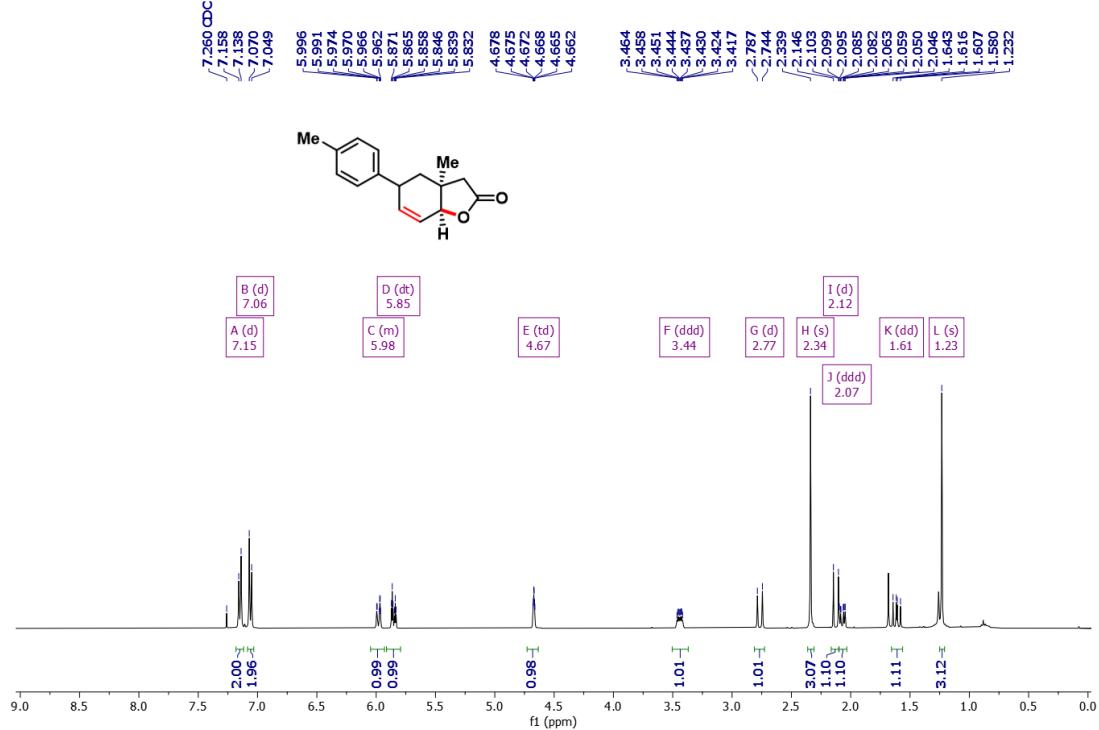
(3a*S*,7a*R*)-3a-Methyl-7-phenyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one



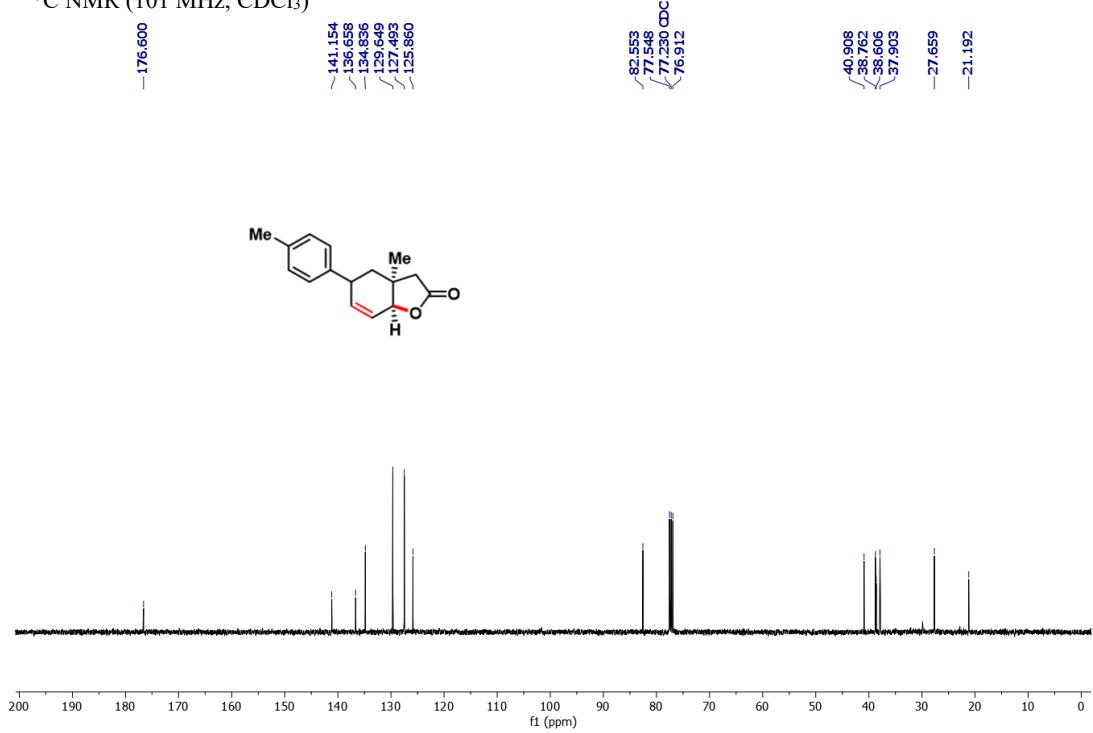
Compound 2u

(3a*S*,7a*S*)-3a-Methyl-5-(*p*-tolyl)-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one

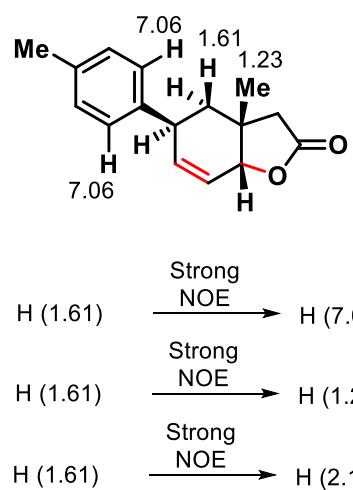
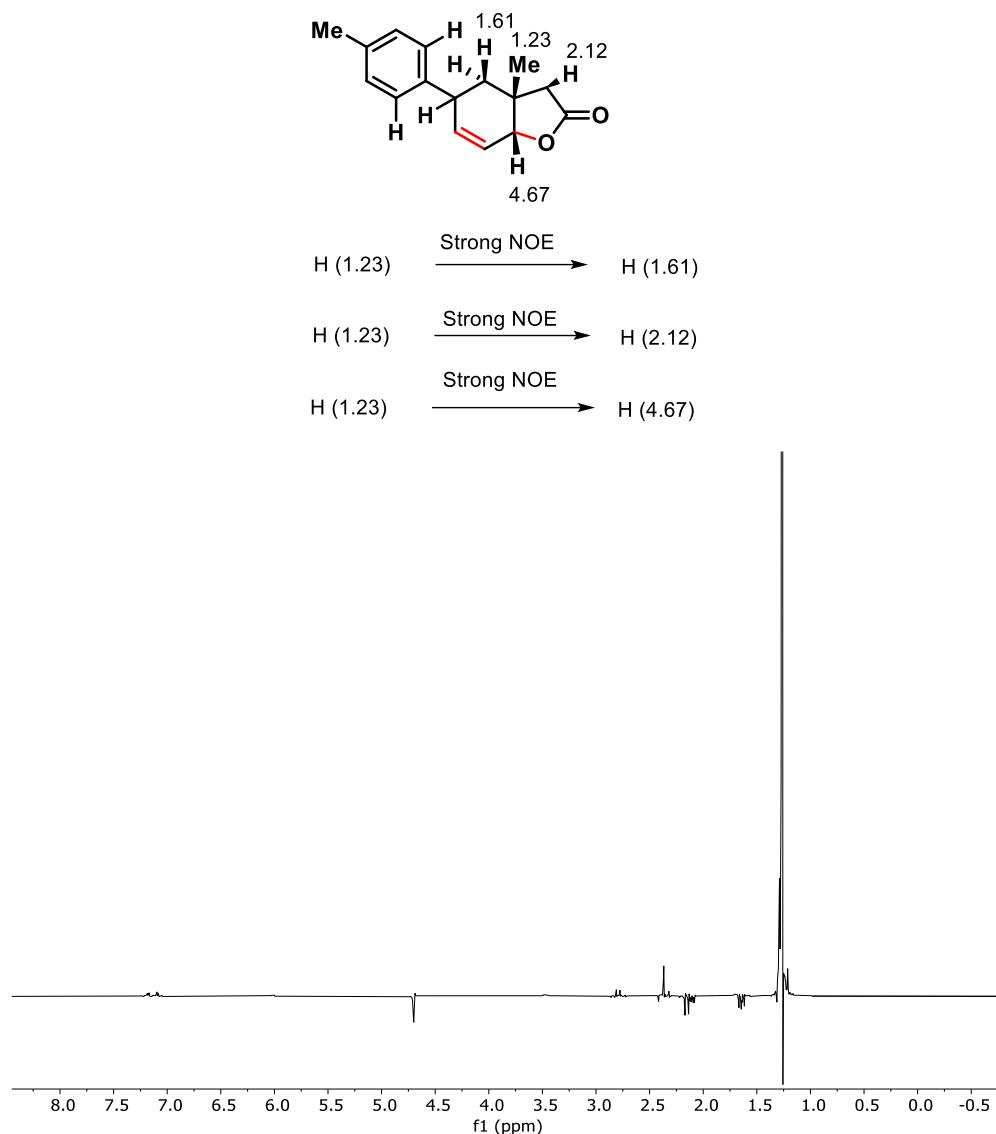
¹H NMR (400 MHz, CDCl₃)

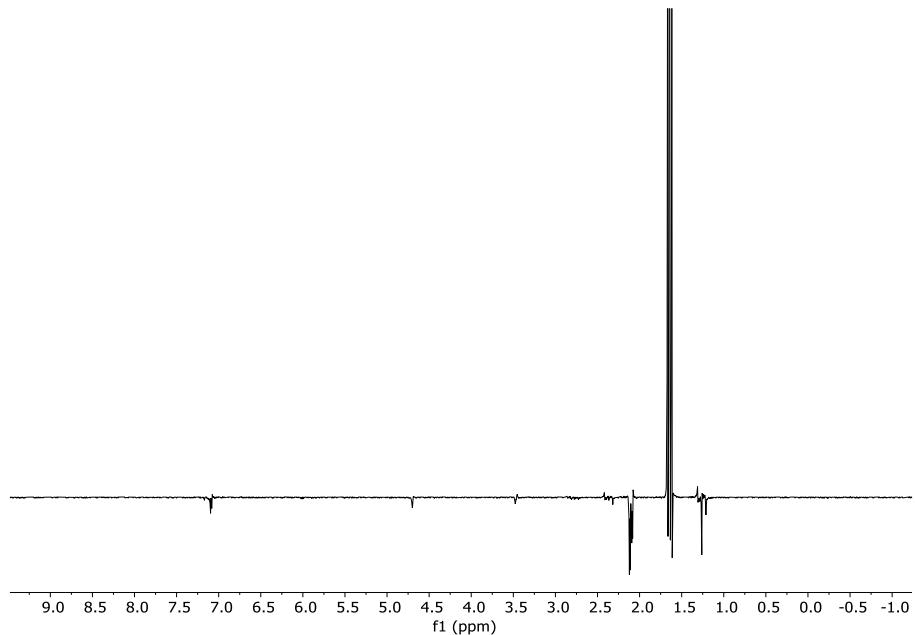


¹³C NMR (101 MHz, CDCl₃)

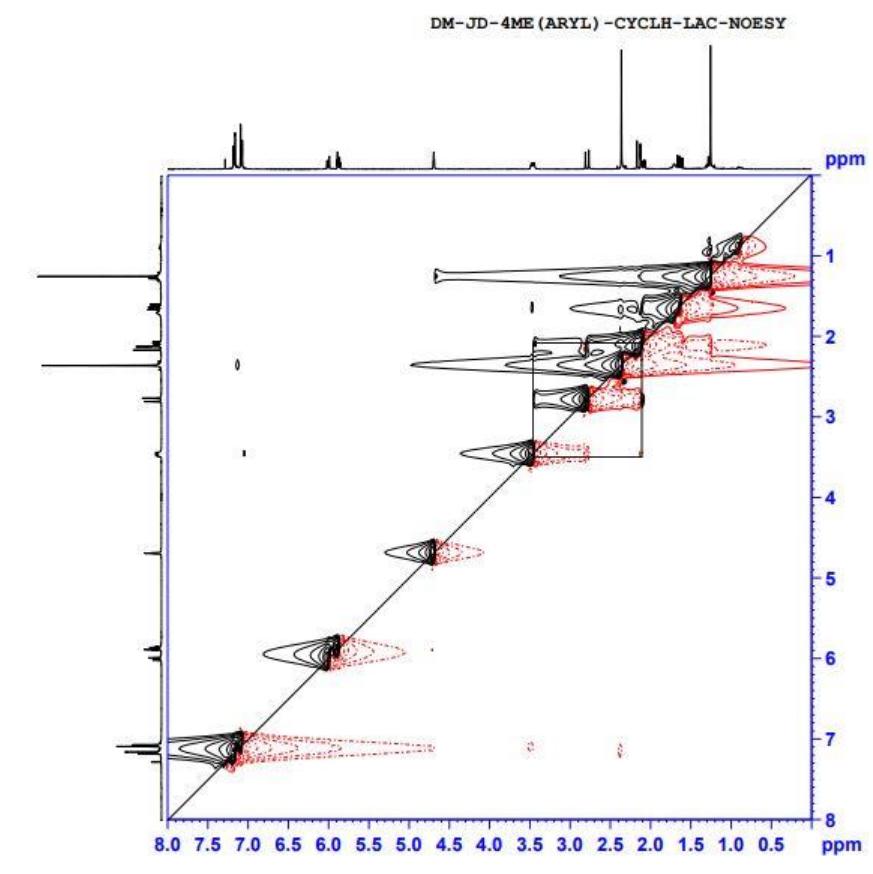
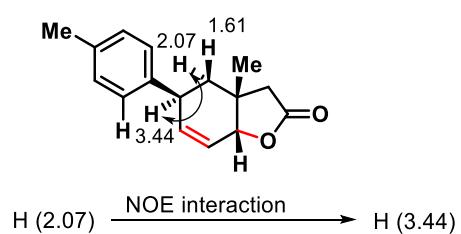


NOE experiment:





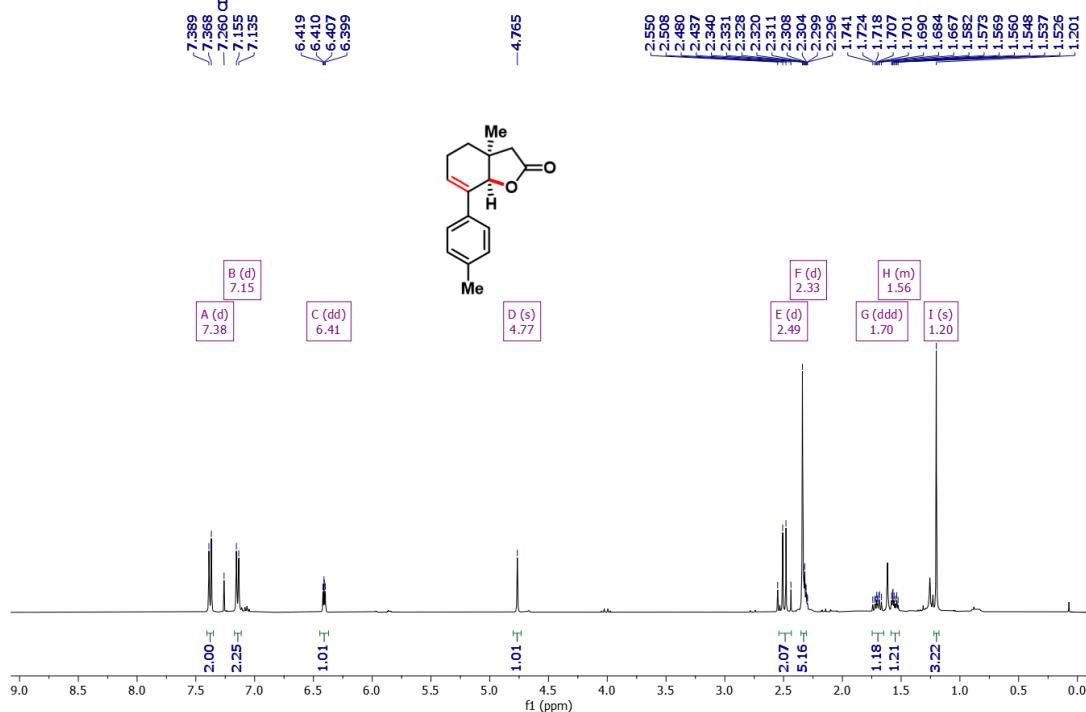
NOESY Experiment:



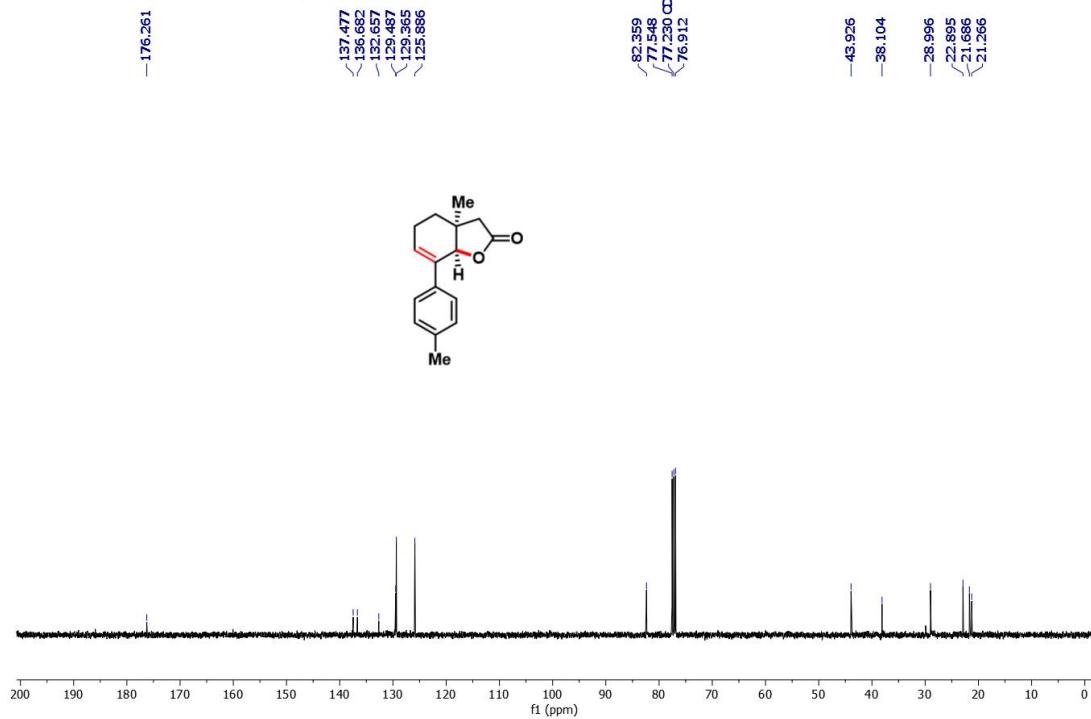
Compound 2v

(3a*S*,7a*R*)-3a-Methyl-7-(*p*-tolyl)-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one

¹H NMR (400 MHz, CDCl₃)

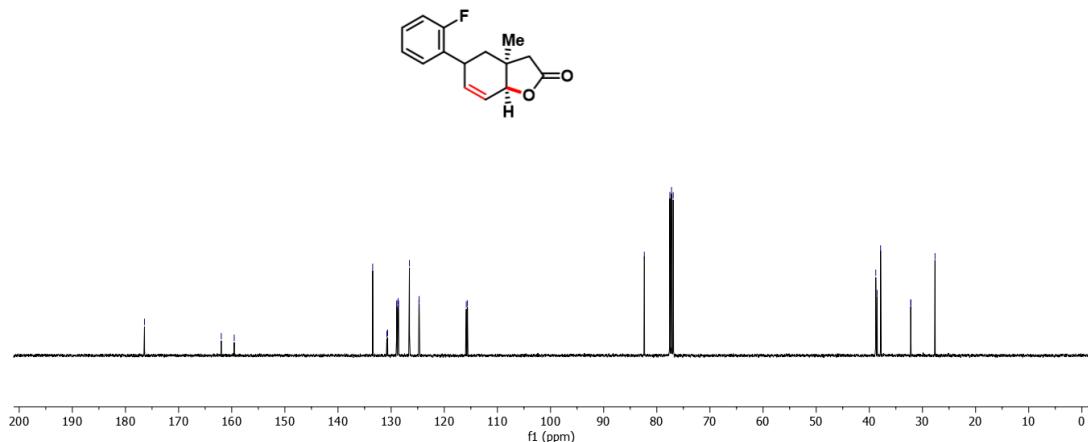
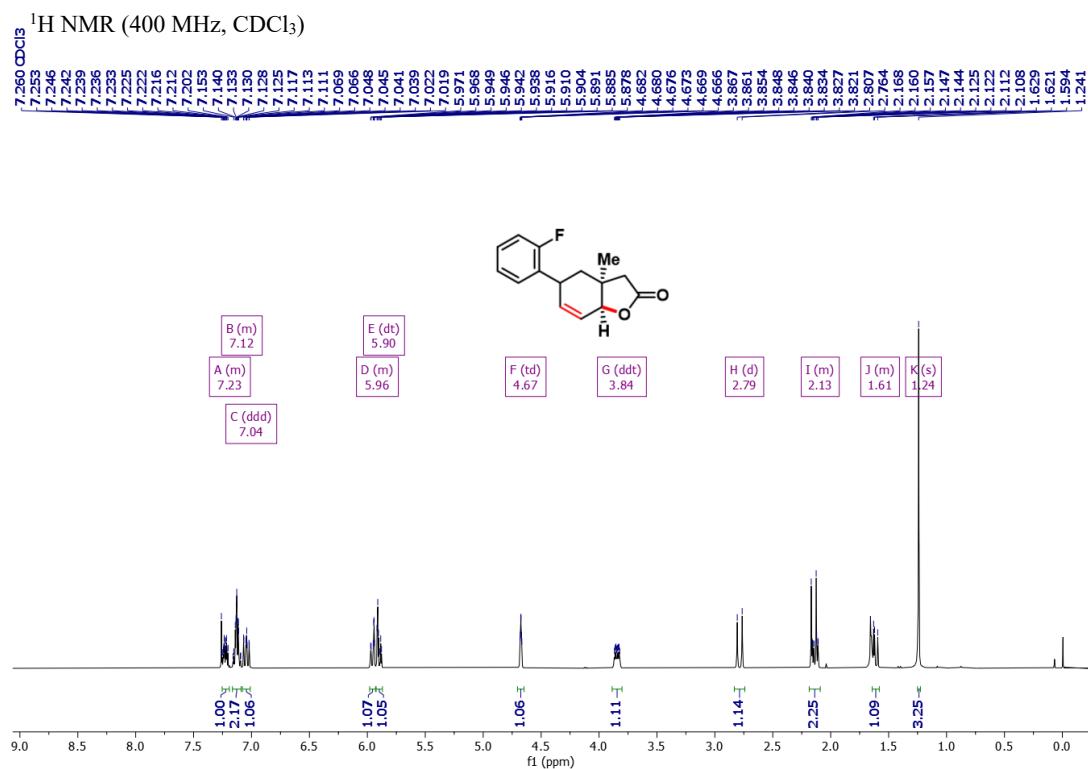


¹³C NMR (101 MHz, CDCl₃)



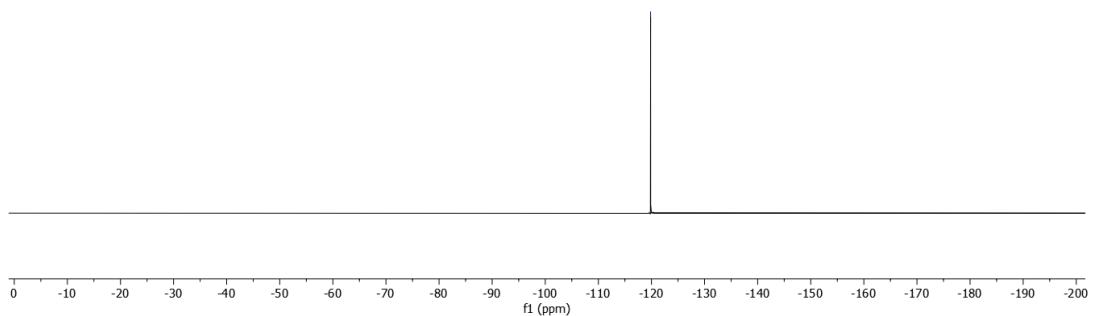
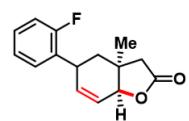
Compound 2w

(3a*S*,7a*S*)-5-(2-Fluorophenyl)-3a-methyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one



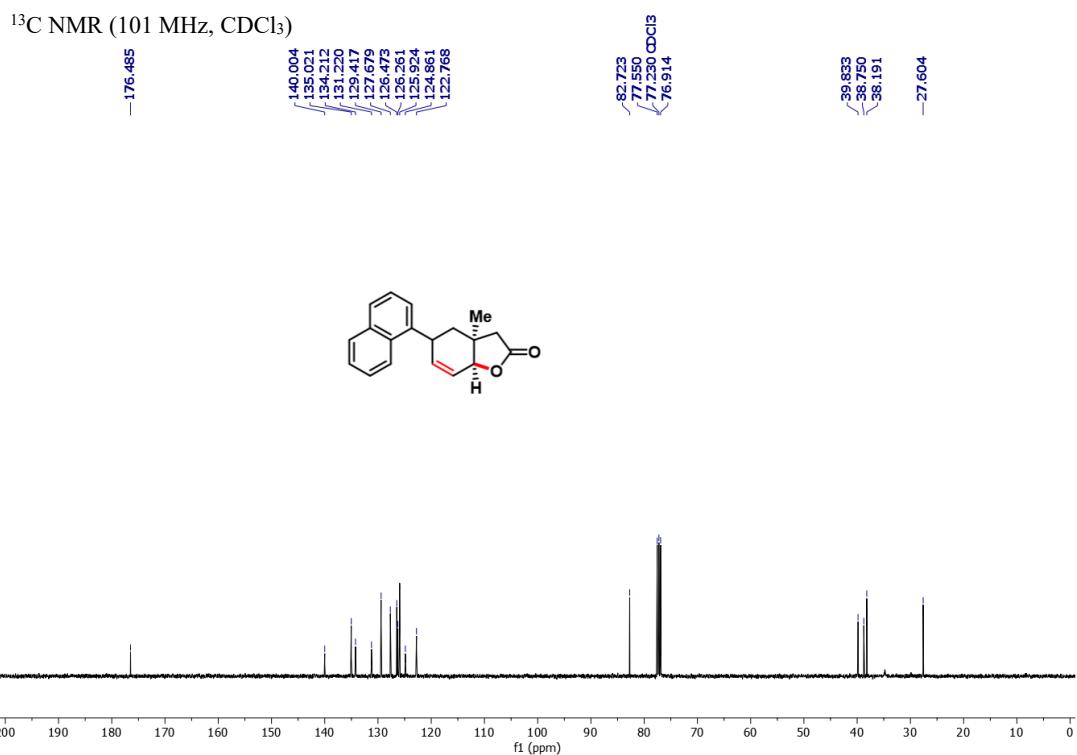
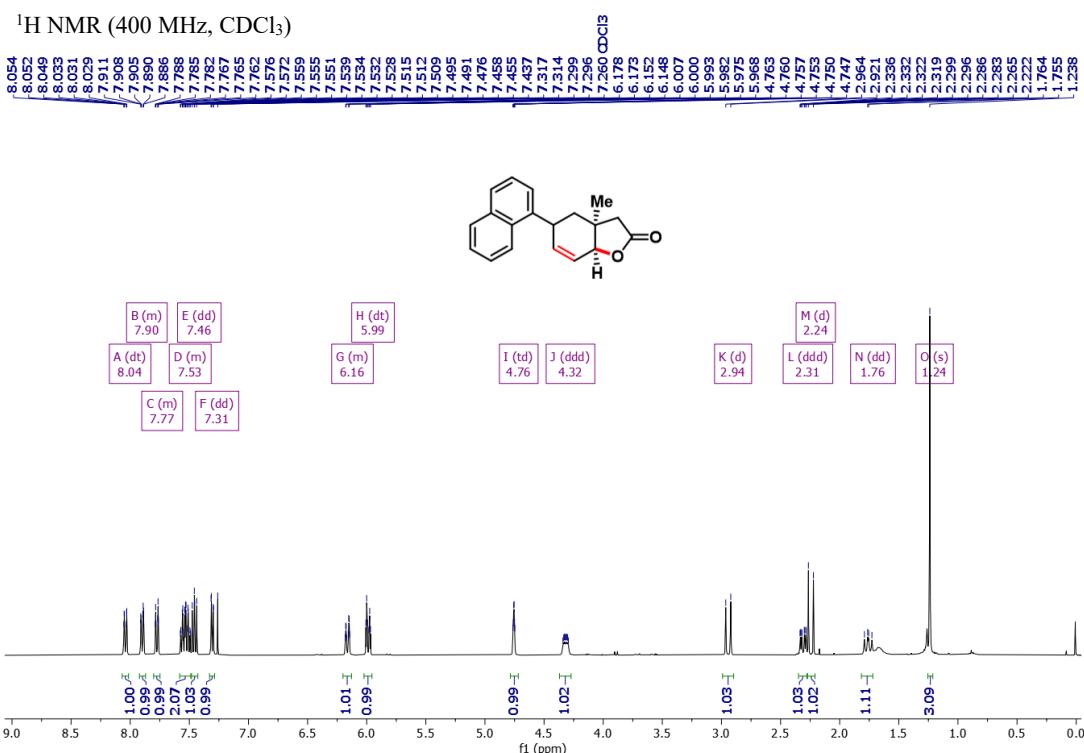
¹⁹F NMR (376 MHz, CDCl₃)

-119.841



Compound 2x

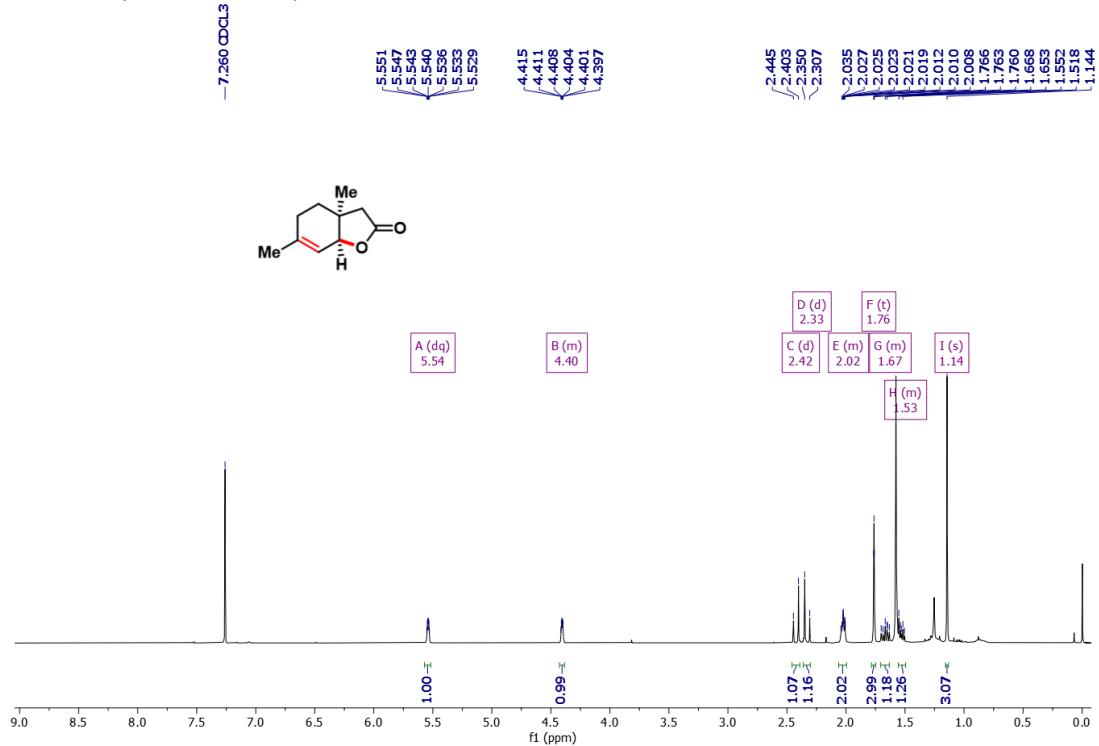
(3a*S*,7a*S*)-3a-Methyl-5-(naphthalen-1-yl)-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one



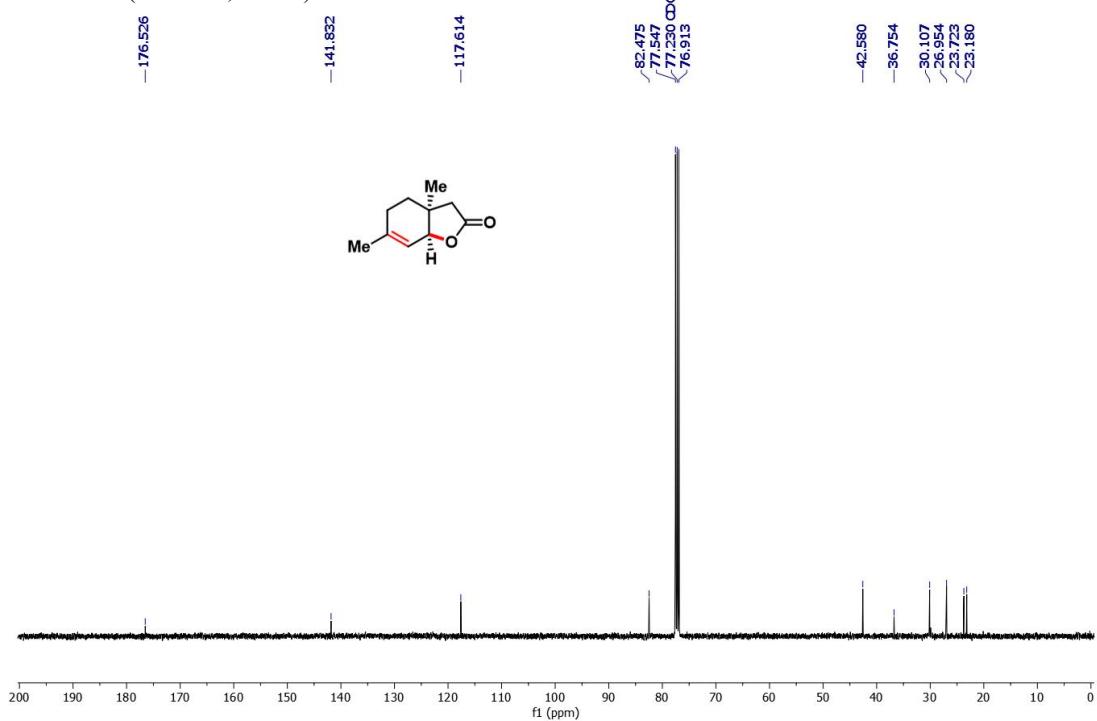
Compound 2y

(3a*S*,7a*S*)-3a,6-Dimethyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one

¹H NMR (400 MHz, CDCl₃)

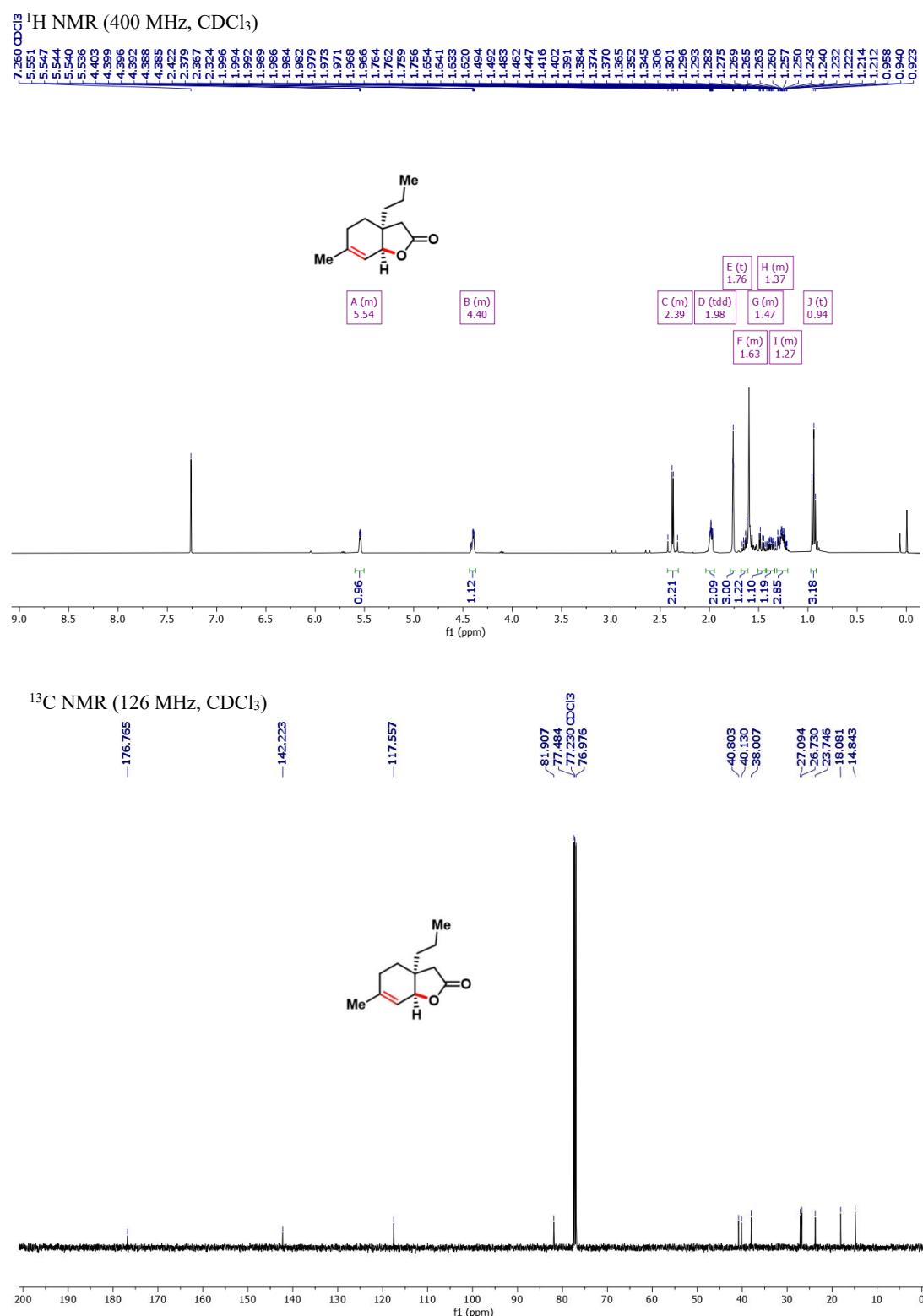


¹³C NMR (101 MHz, CDCl₃)



Compound 2z

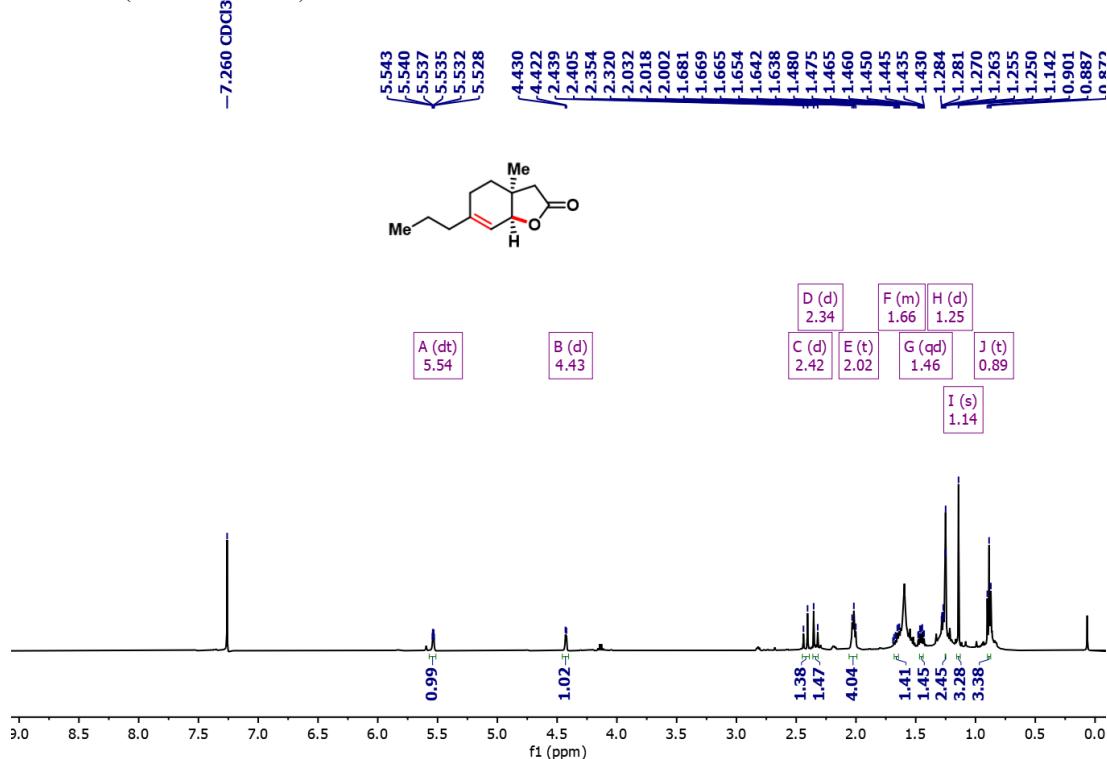
(3a*S*,7a*S*)-6-Methyl-3a-propyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one



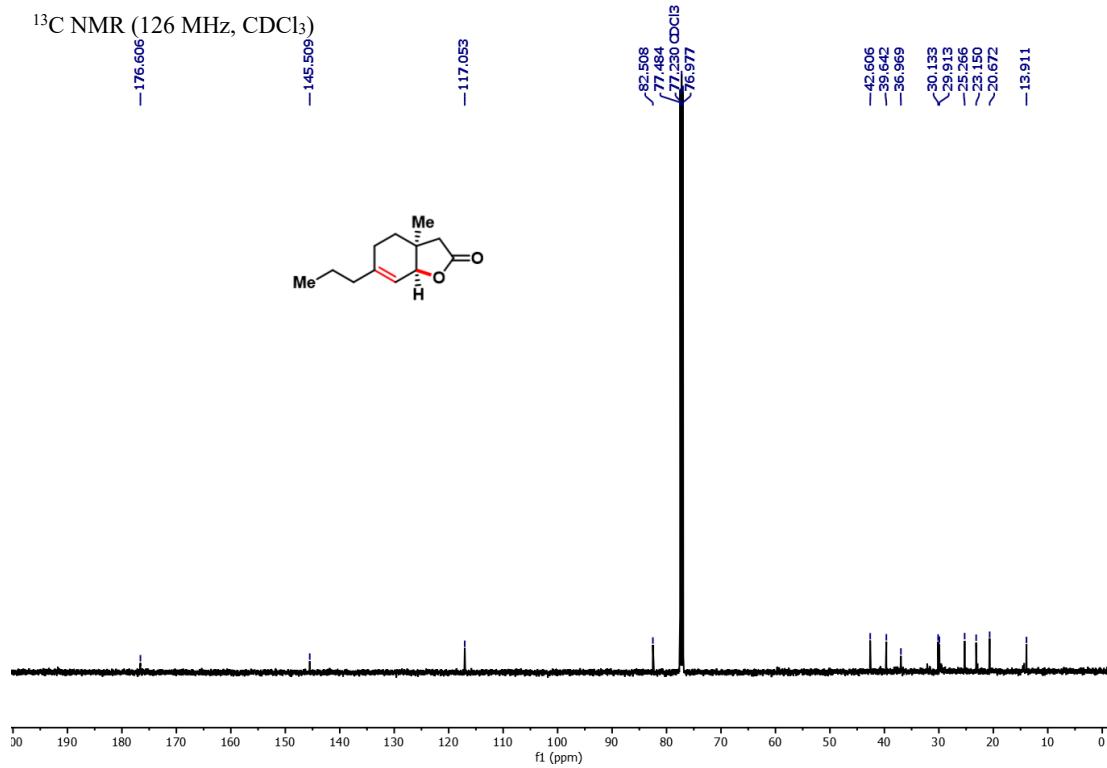
Compound 2aa

(3a*S*,7a*S*)-3a-Methyl-6-propyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one

¹H NMR (500 MHz, CDCl₃)



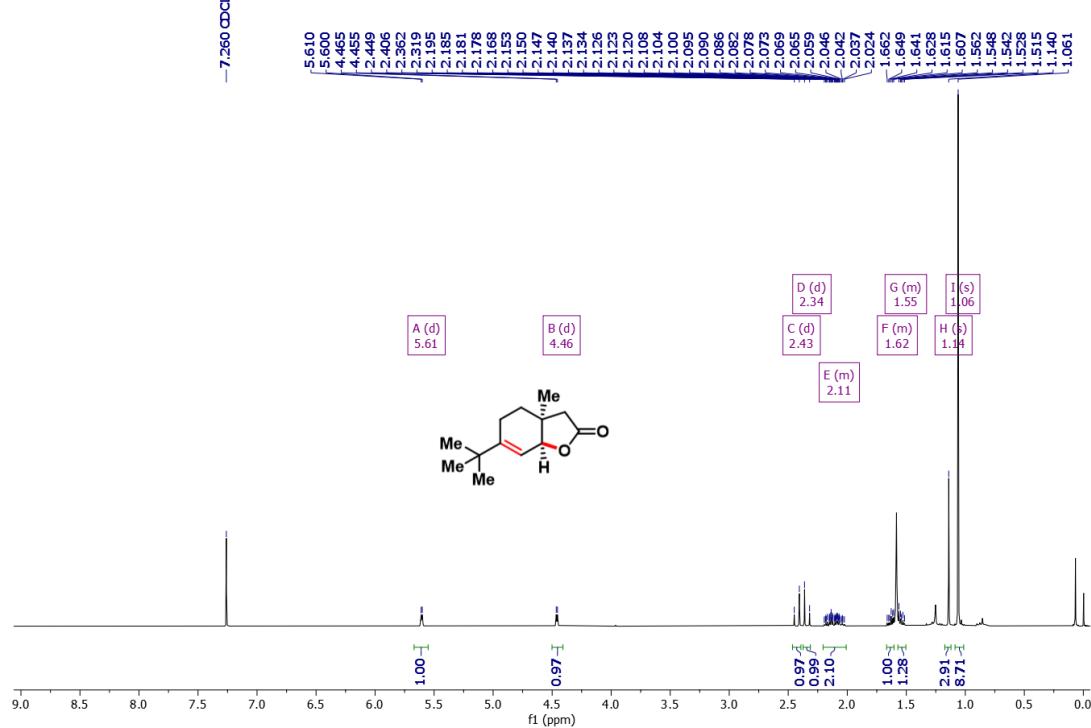
¹³C NMR (126 MHz, CDCl₃)



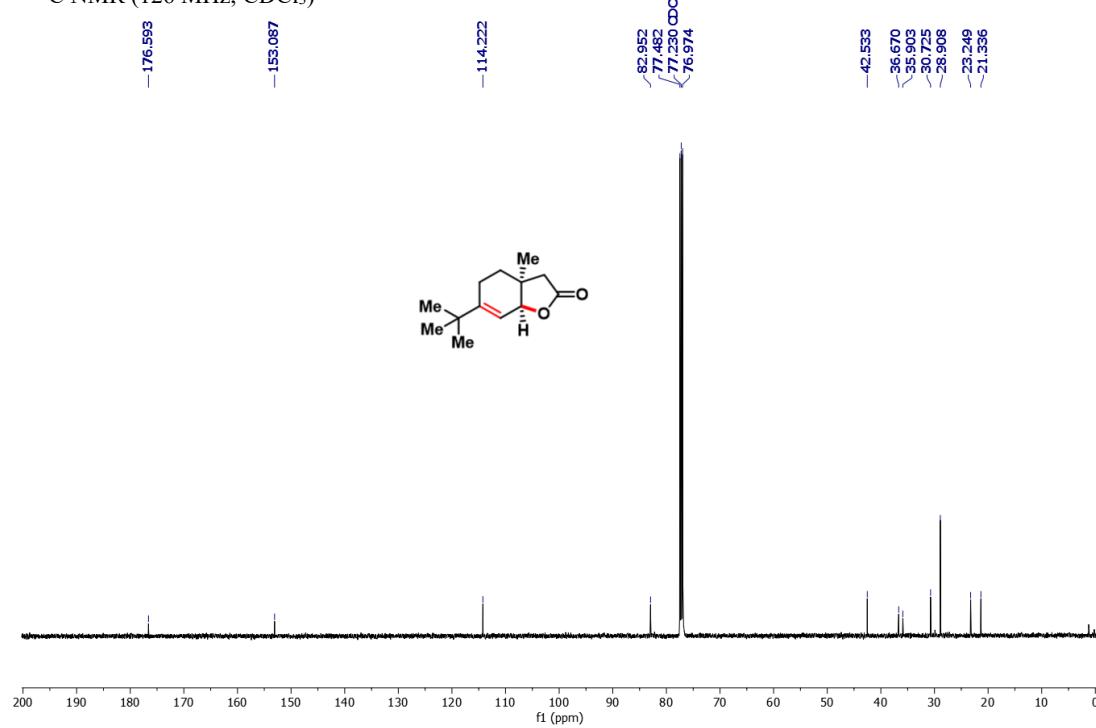
Compound 2ab

(3a*S*,7a*S*)-6-(*tert*-Butyl)-3a-methyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one

¹H NMR (400 MHz, CDCl₃)

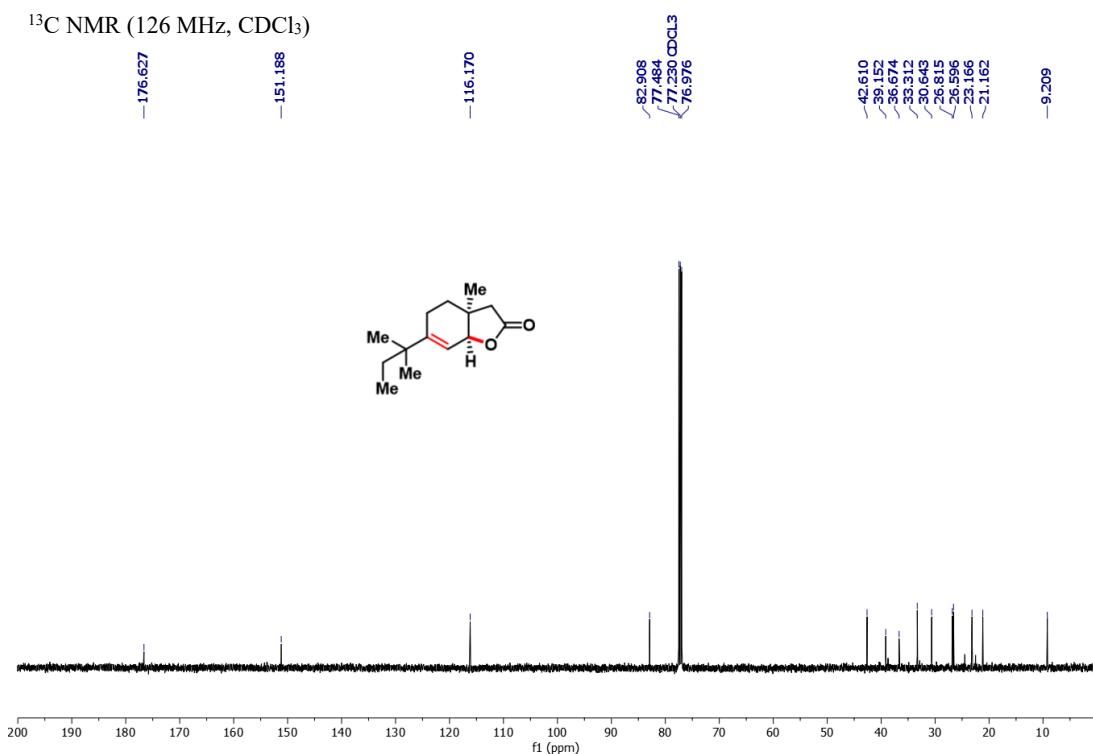
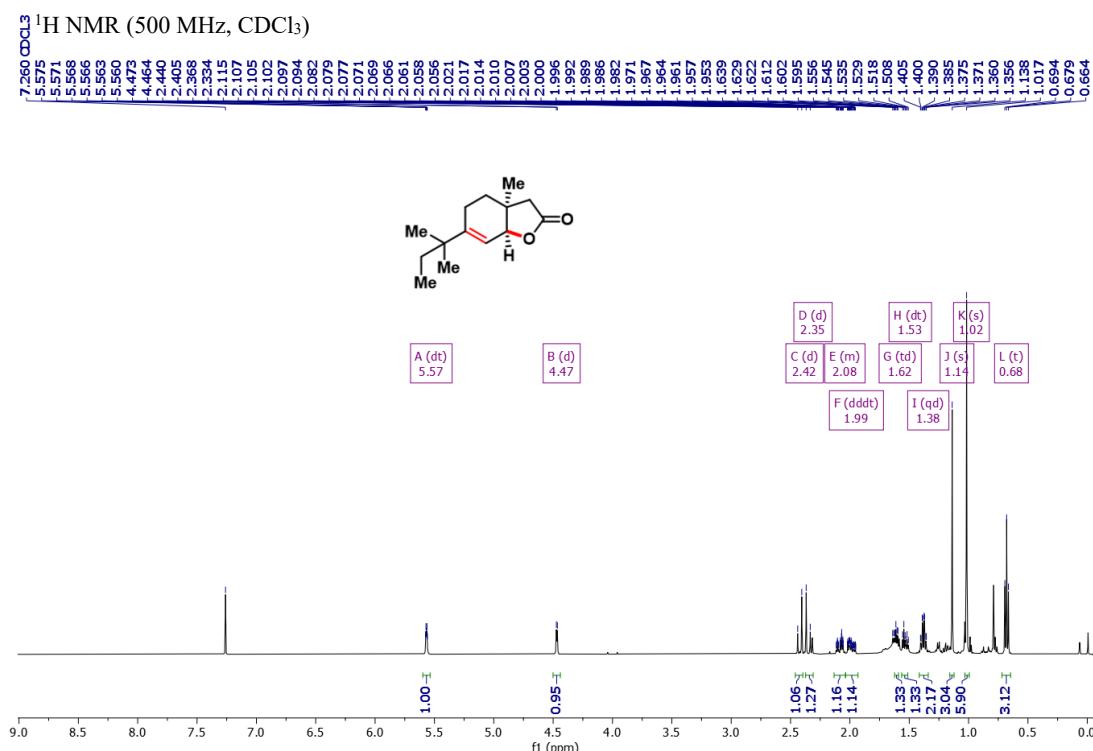


¹³C NMR (126 MHz, CDCl₃)



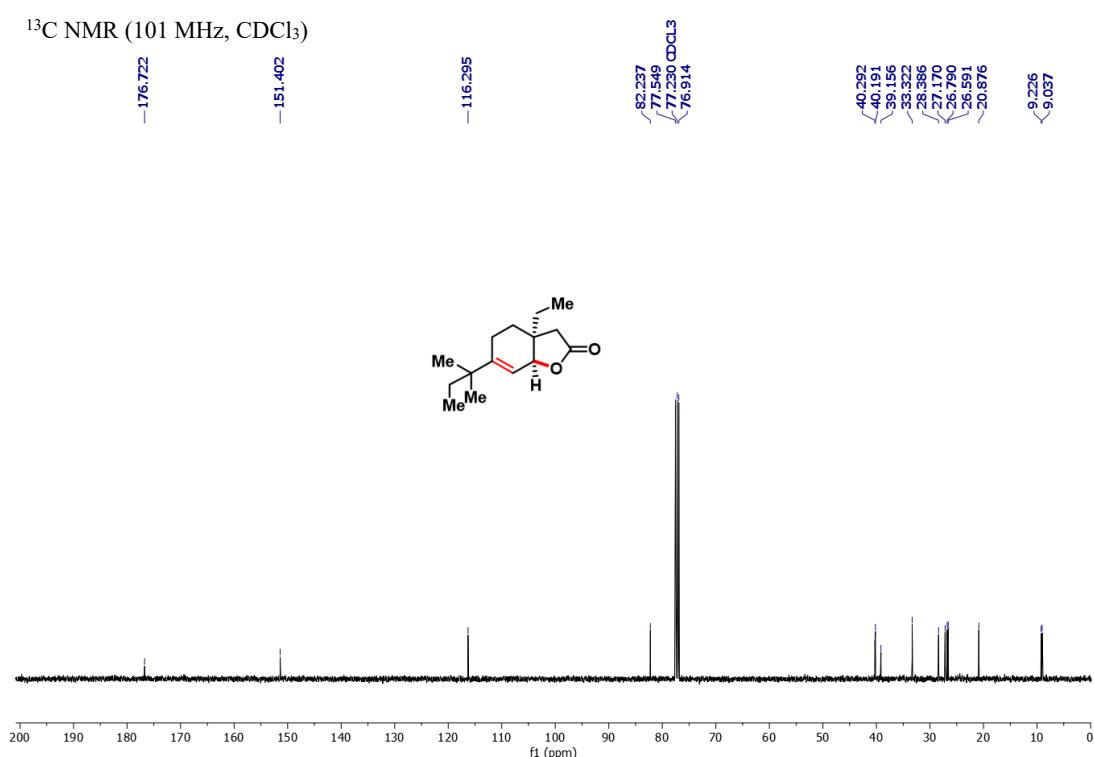
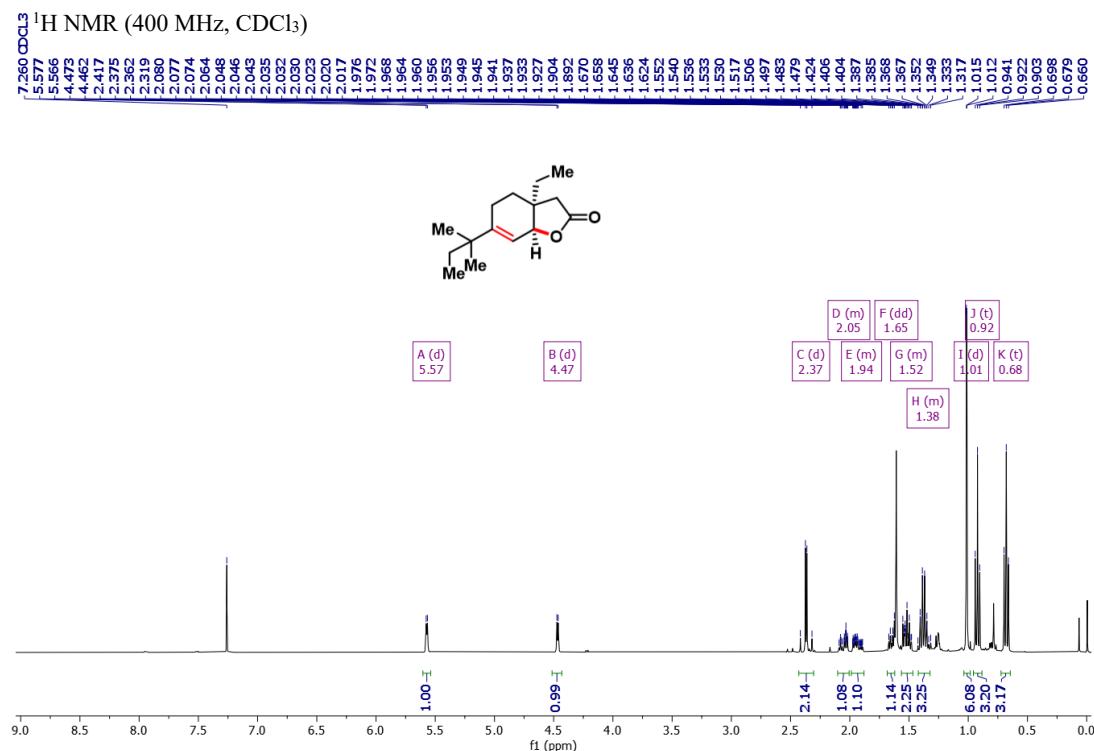
Compound 2ac

(3a*S*,7a*S*)-3a-Methyl-6-(*tert*-pentyl)-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one



Compound 2ad

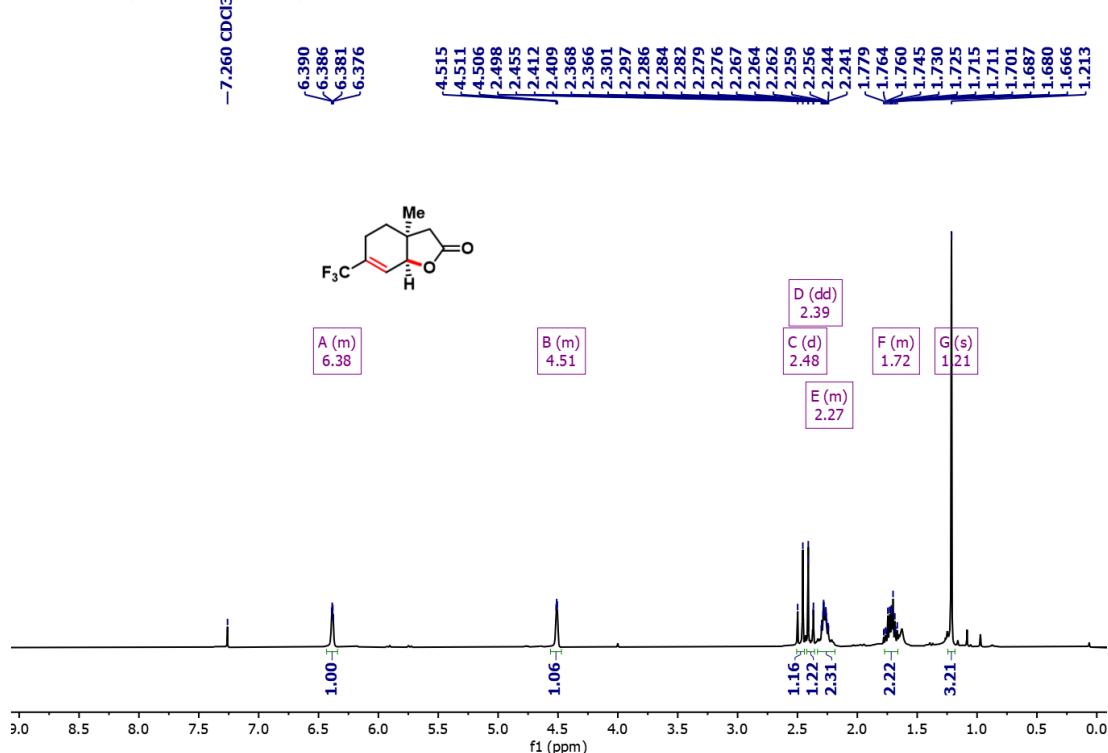
(3a*S*,7a*S*)-3a-Ethyl-6-(*tert*-pentyl)-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one



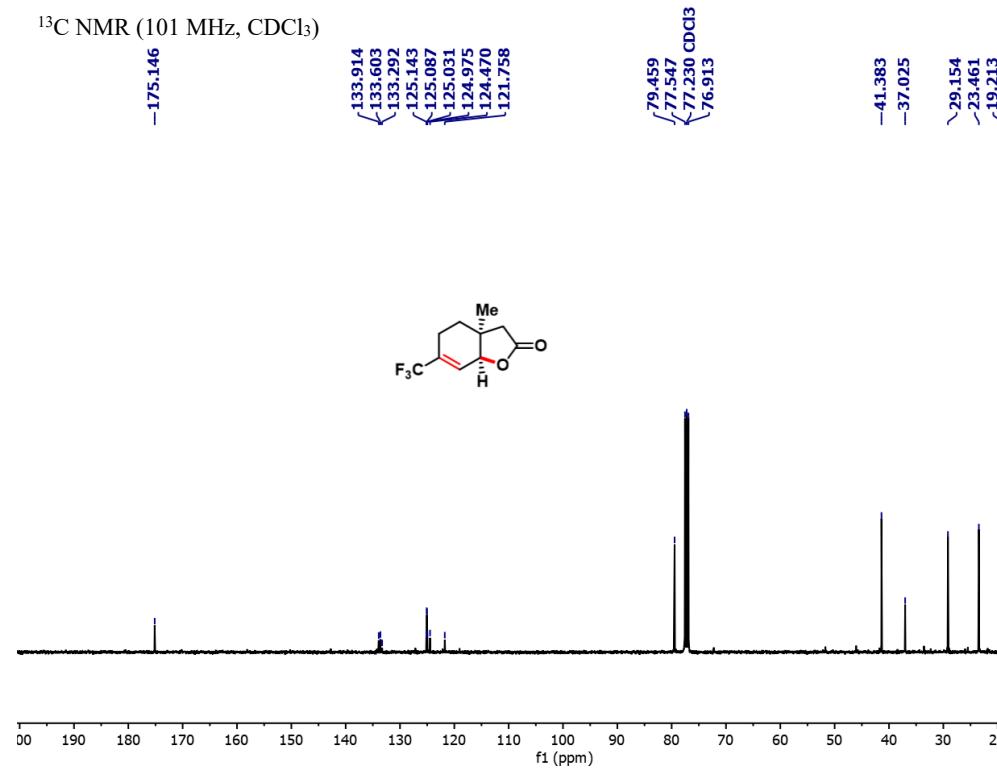
Compound 2ae

(3a*S*,7a*S*)-3a-Methyl-6-(trifluoromethyl)-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one

¹H NMR (400 MHz, CDCl₃)

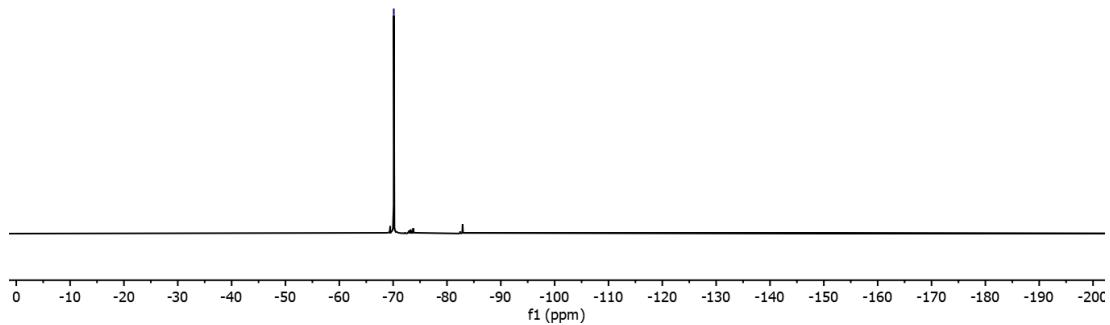
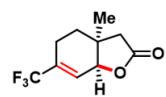


¹³C NMR (101 MHz, CDCl₃)



¹⁹F NMR (376 MHz, CDCl₃)

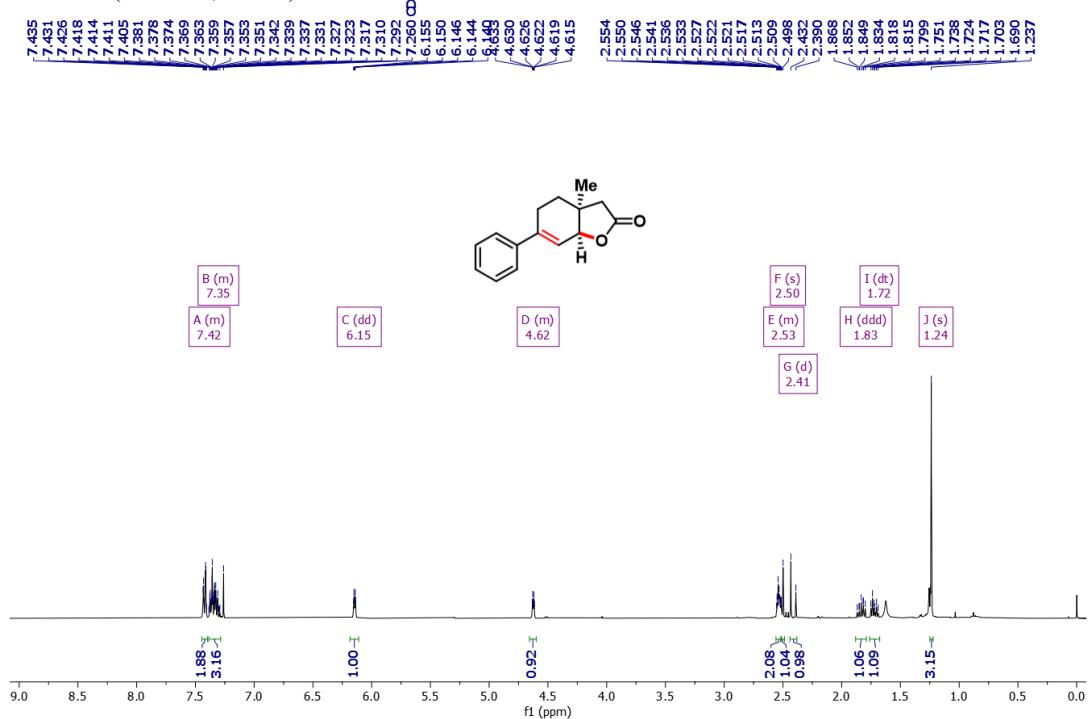
-70.119



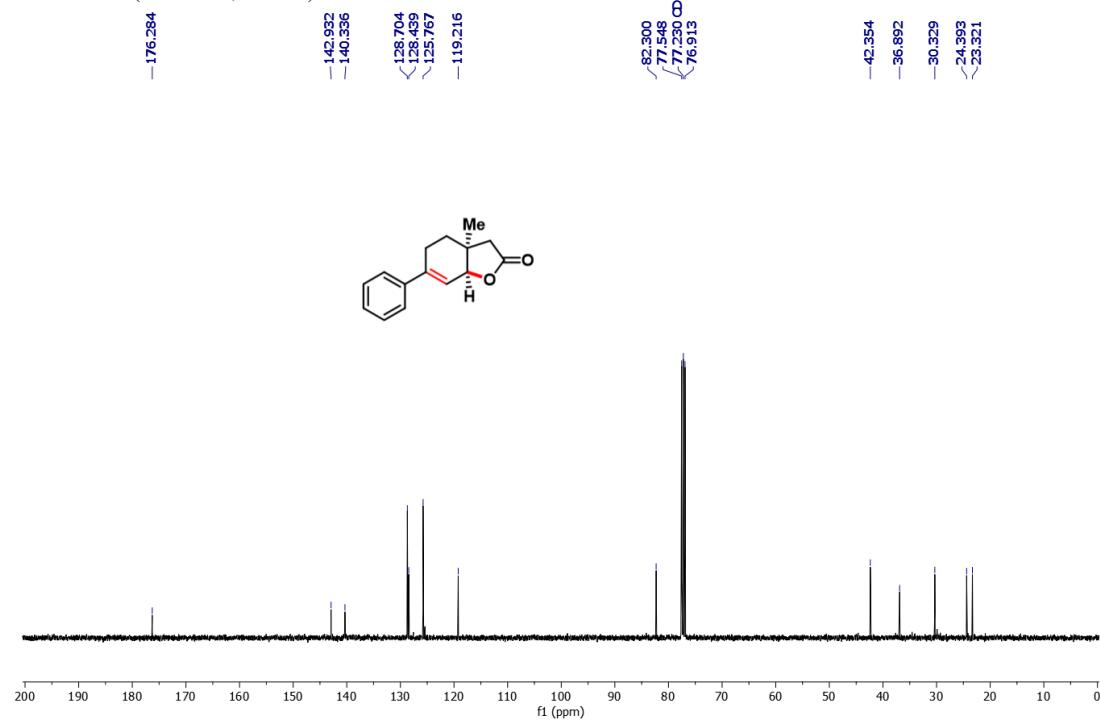
Compound 2af

(3a*S*,7a*S*)-3a-Methyl-6-phenyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one

¹H NMR (400 MHz, CDCl₃)



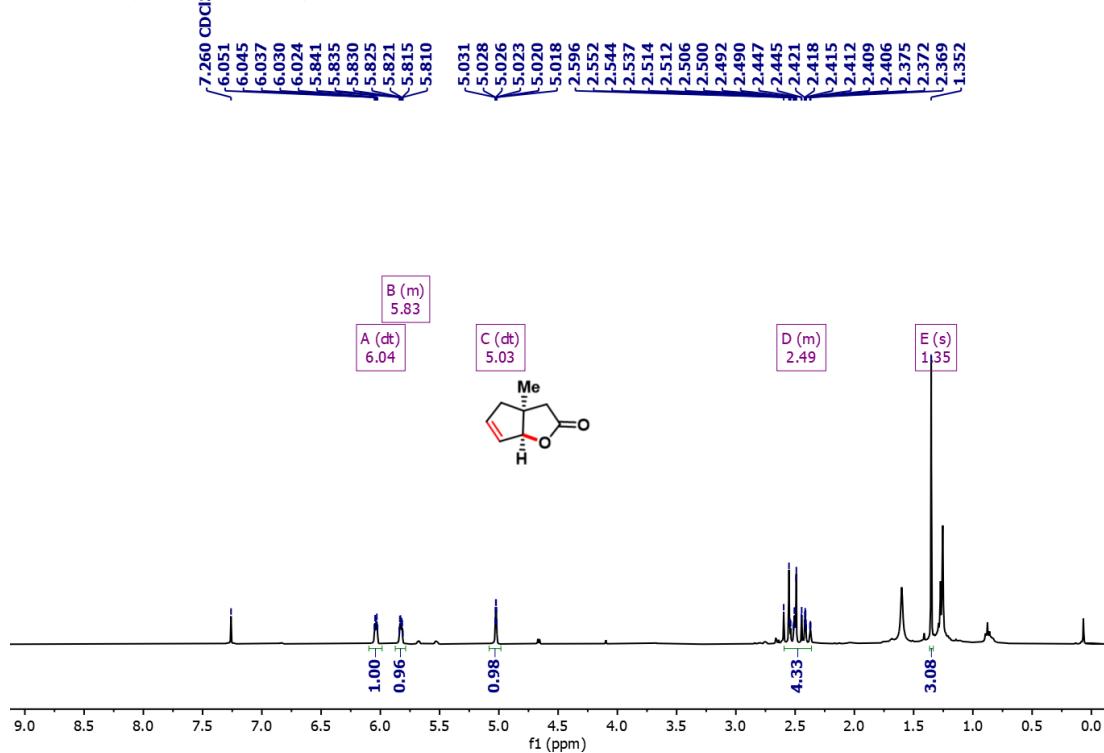
¹³C NMR (101 MHz, CDCl₃)



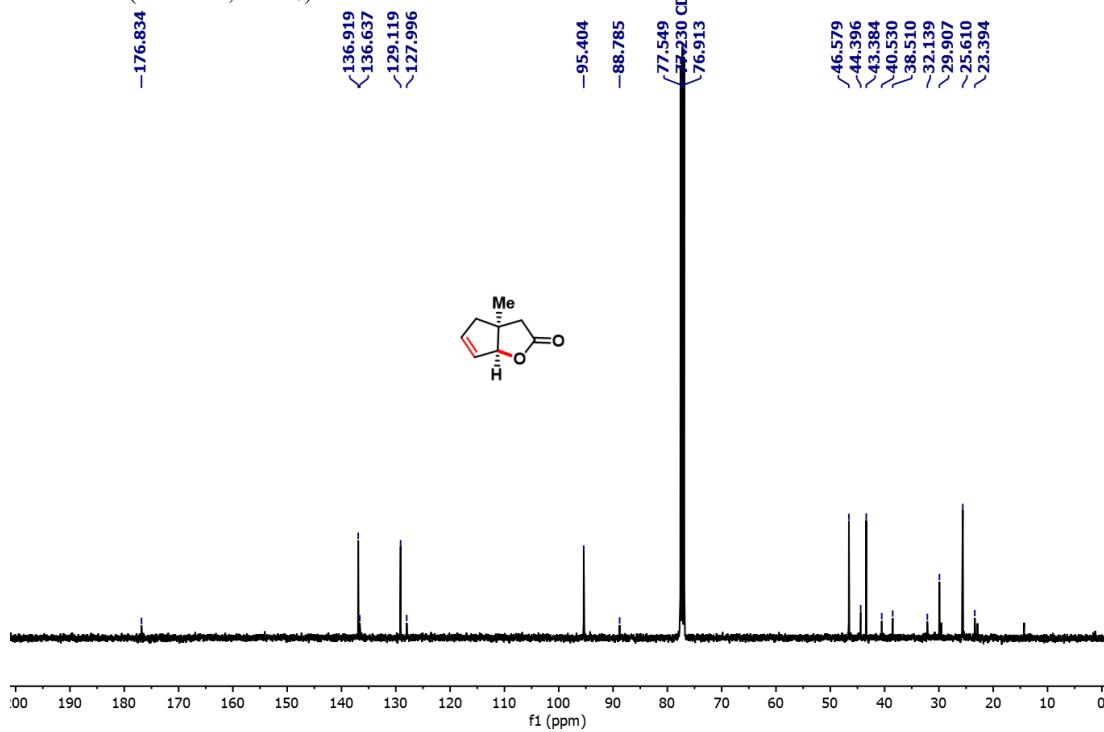
Compound 3a

(3a*S*,6a*S*)-3a-Methyl-3,3a,4,6a-tetrahydro-2H-cyclopenta[b]furan-2-one

¹H NMR (400 MHz, CDCl₃)

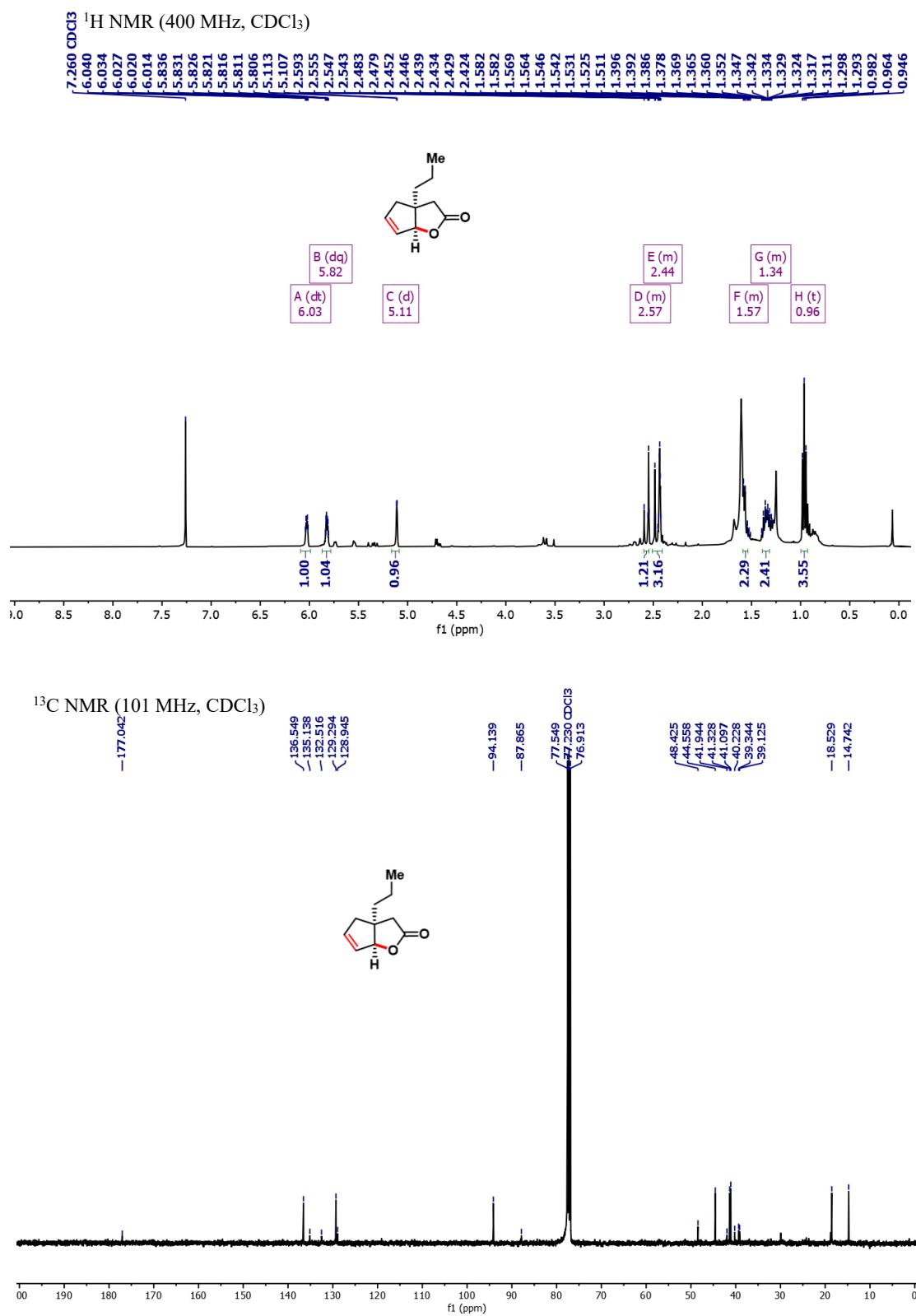


¹³C NMR (101 MHz, CDCl₃)



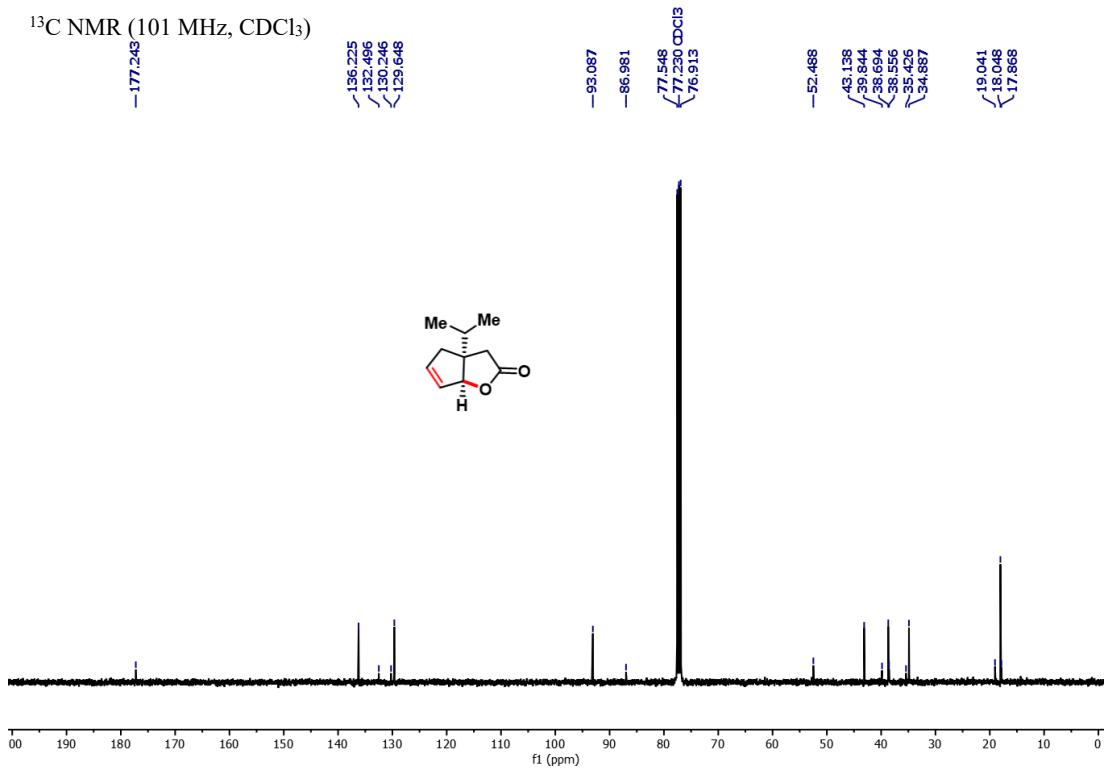
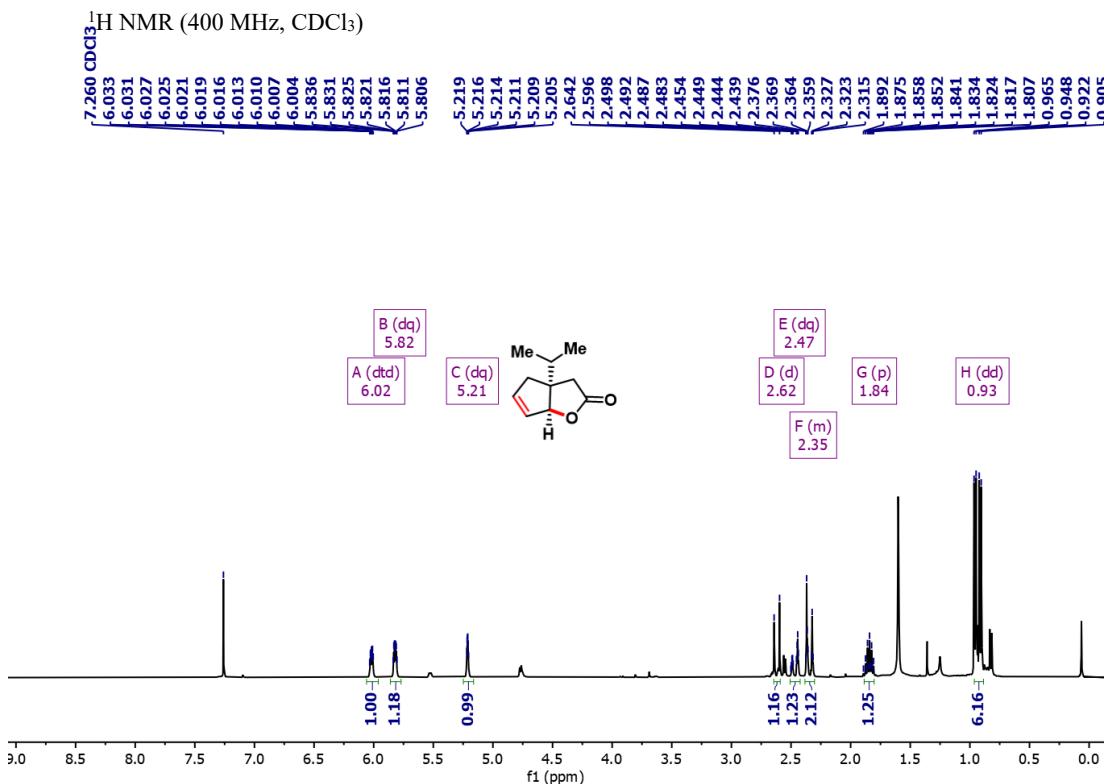
Compound 3b

(3a*S*,6a*S*)-3a-Propyl-3a,4,6a-tetrahydro-2H-cyclopenta[b]furan-2-one



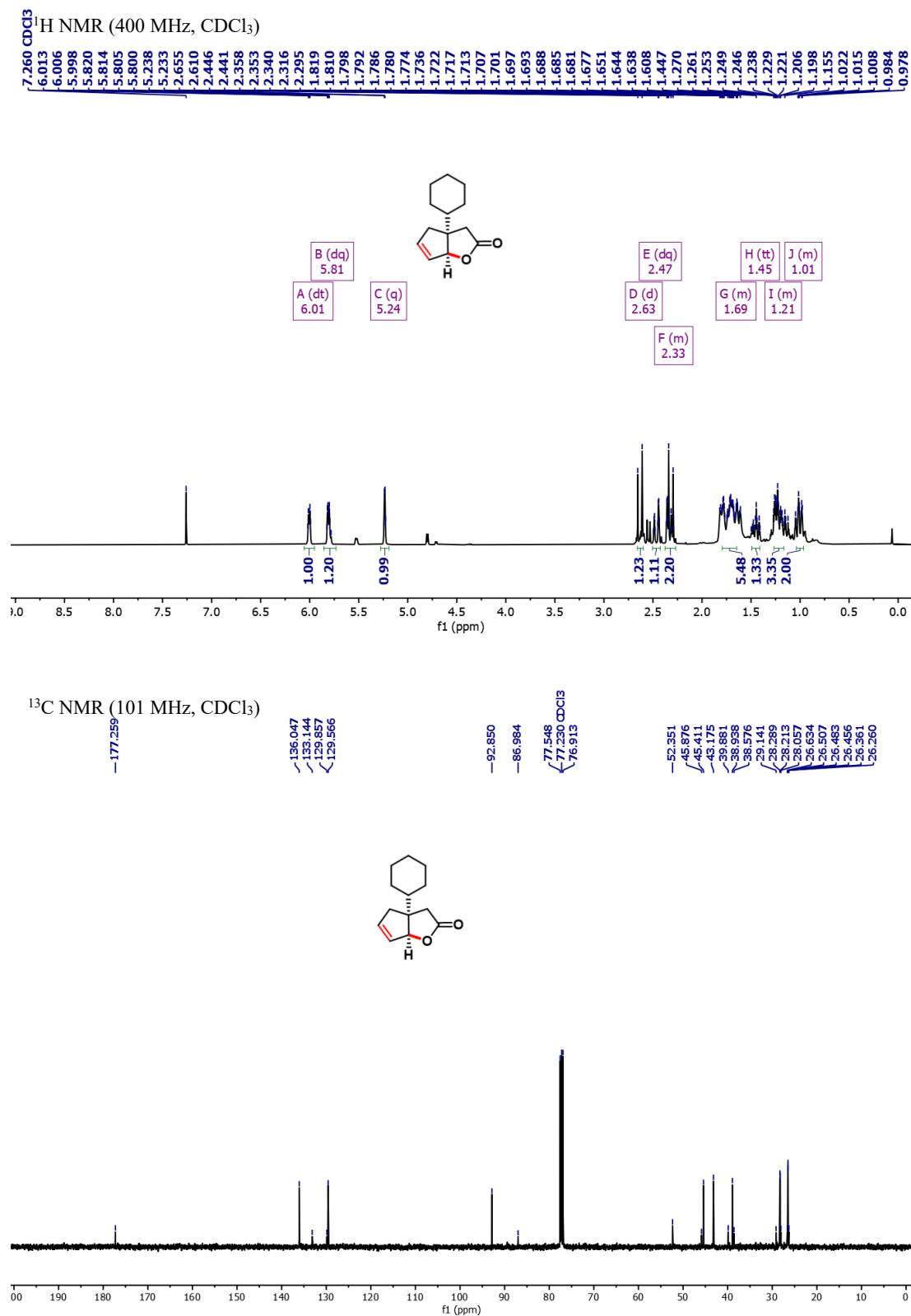
Compound 3c

(3a*S*,6a*S*)-3a-Isopropyl-3a,4,6a-tetrahydro-2H-cyclopenta[b]furan-2-one



Compound 3d

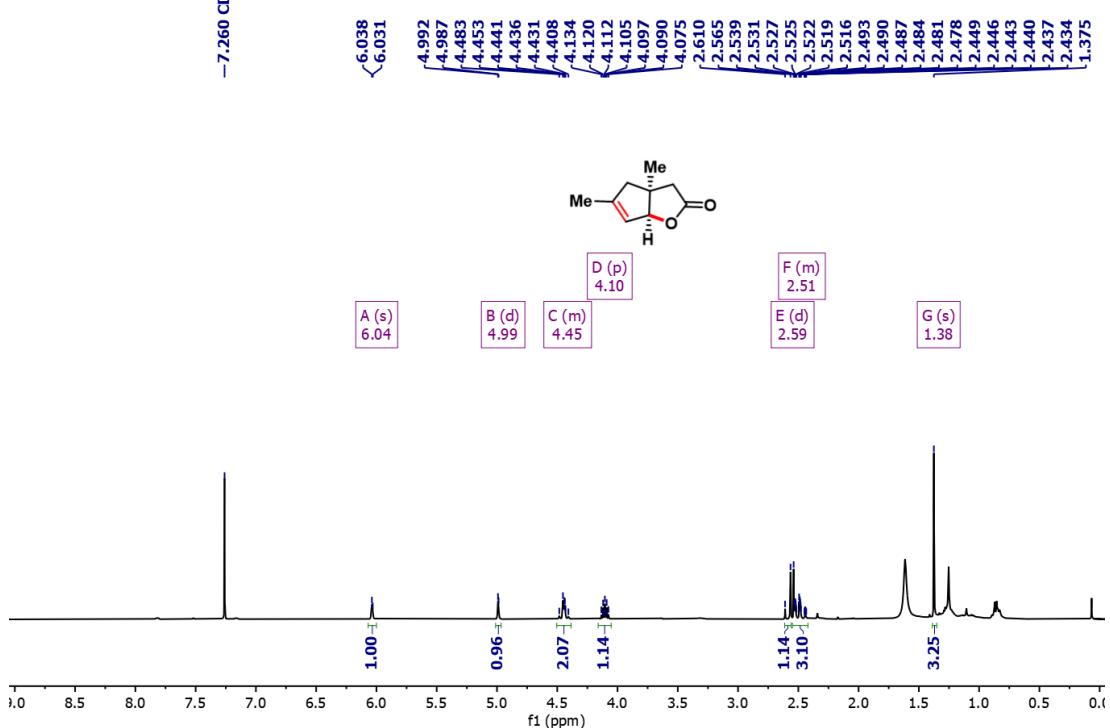
(3a*S*,6a*S*)-3a-Cyclohexyl-3,3a,4,6a-tetrahydro-2H-cyclopenta[b]furan-2-one



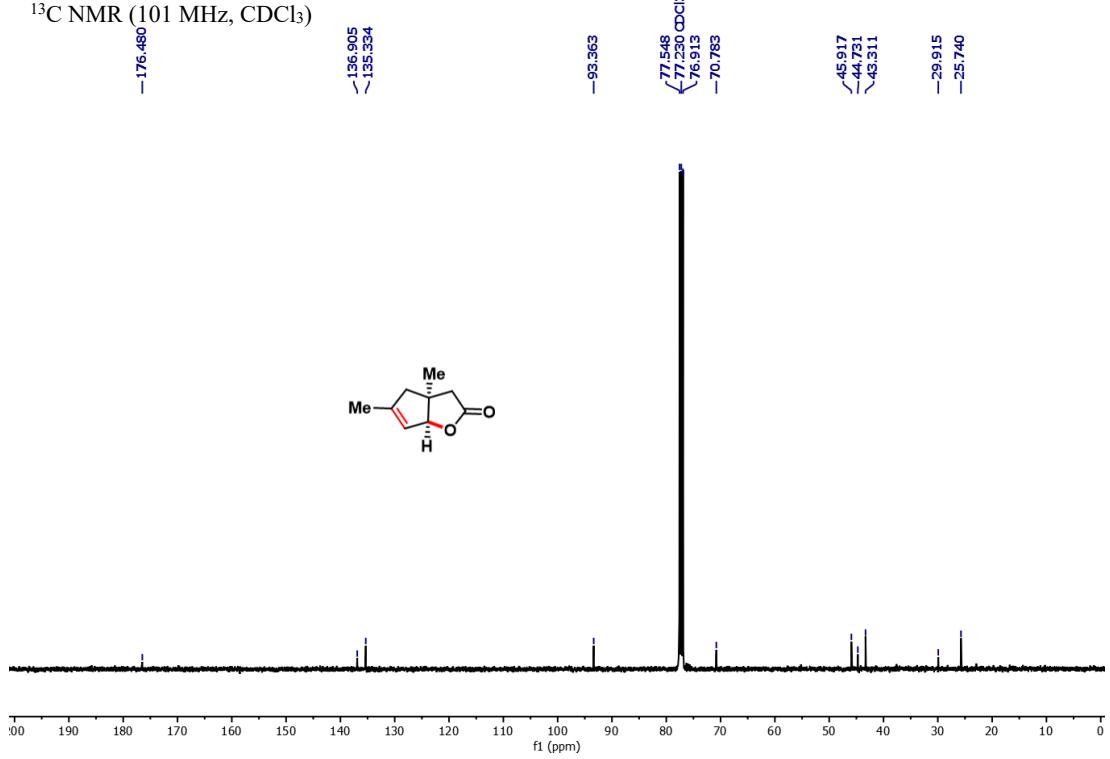
Compound 3e

(3a*S*,6a*S*)-3a,5-Dimethyl-3,3a,4,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-2-one

¹H NMR (400 MHz, CDCl₃)



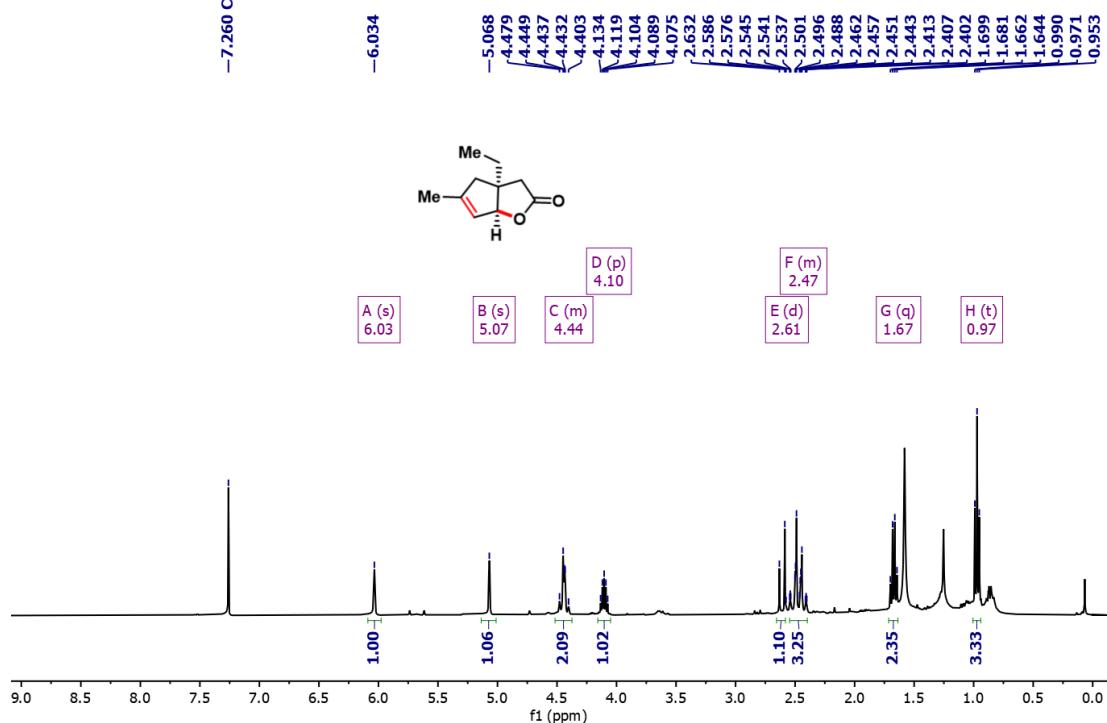
¹³C NMR (101 MHz, CDCl₃)



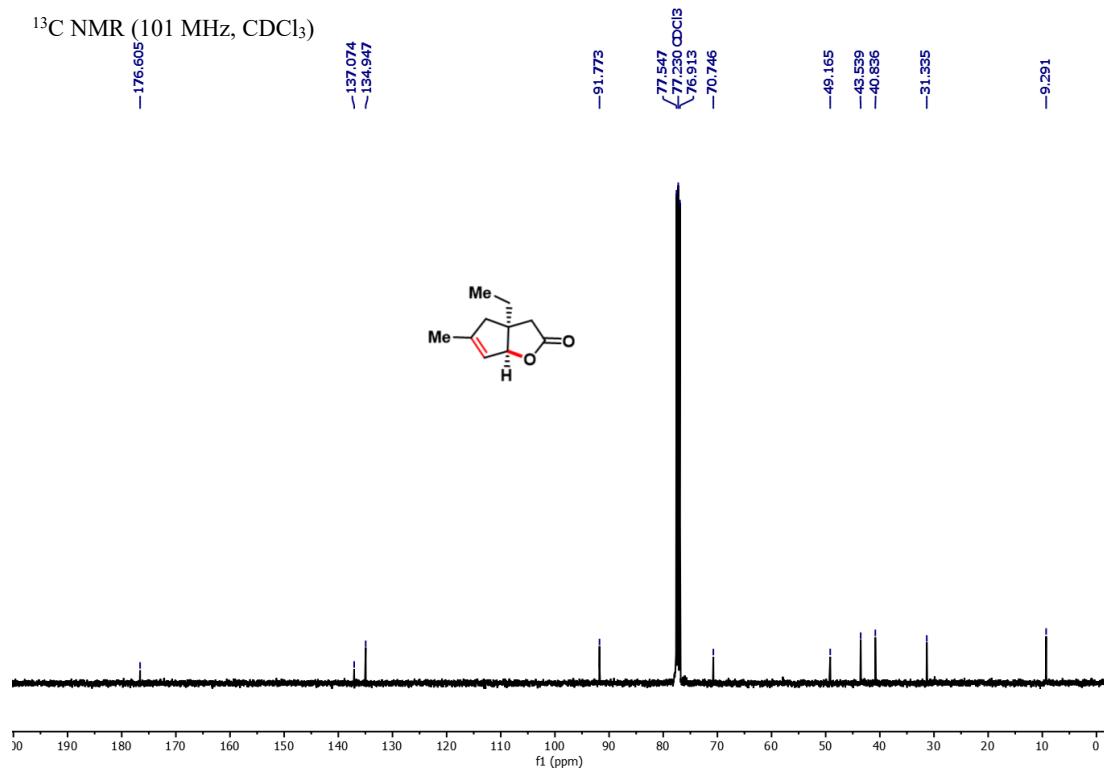
Compound 3f

(3a*S*,6a*S*)-3a-Ethyl-5-methyl-3,3a,4,6a-tetrahydro-2H-cyclopenta[b]furan-2-one

¹H NMR (400 MHz, CDCl₃)

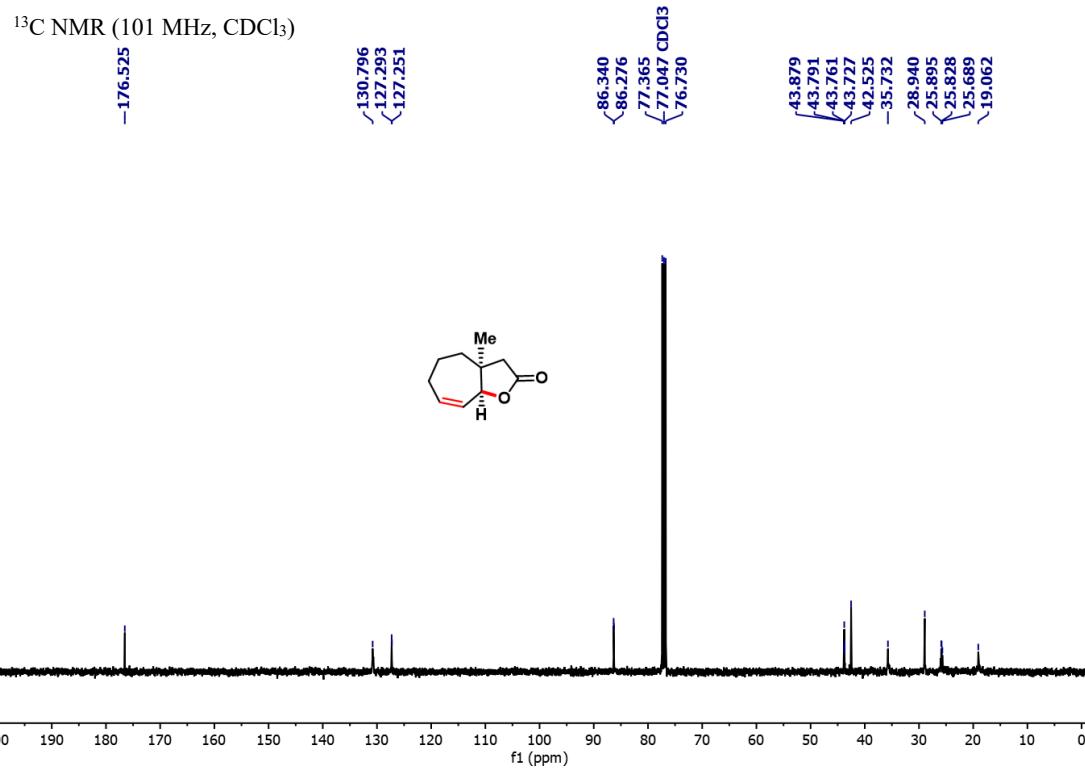
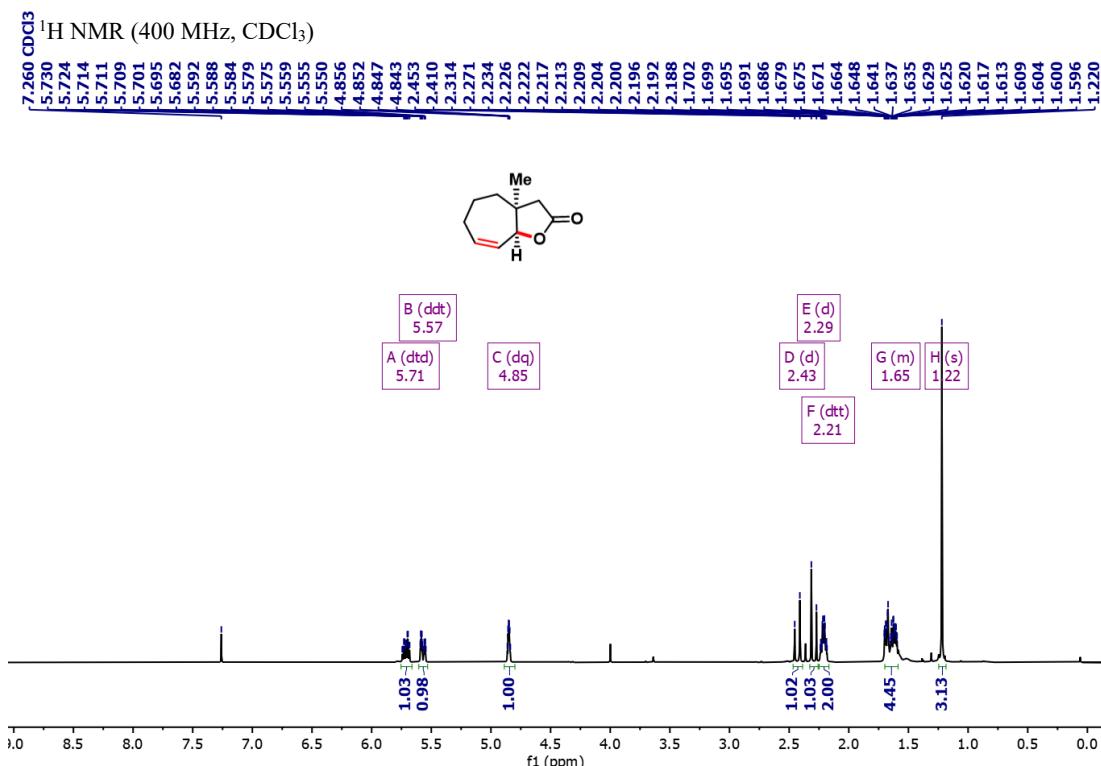


¹³C NMR (101 MHz, CDCl₃)



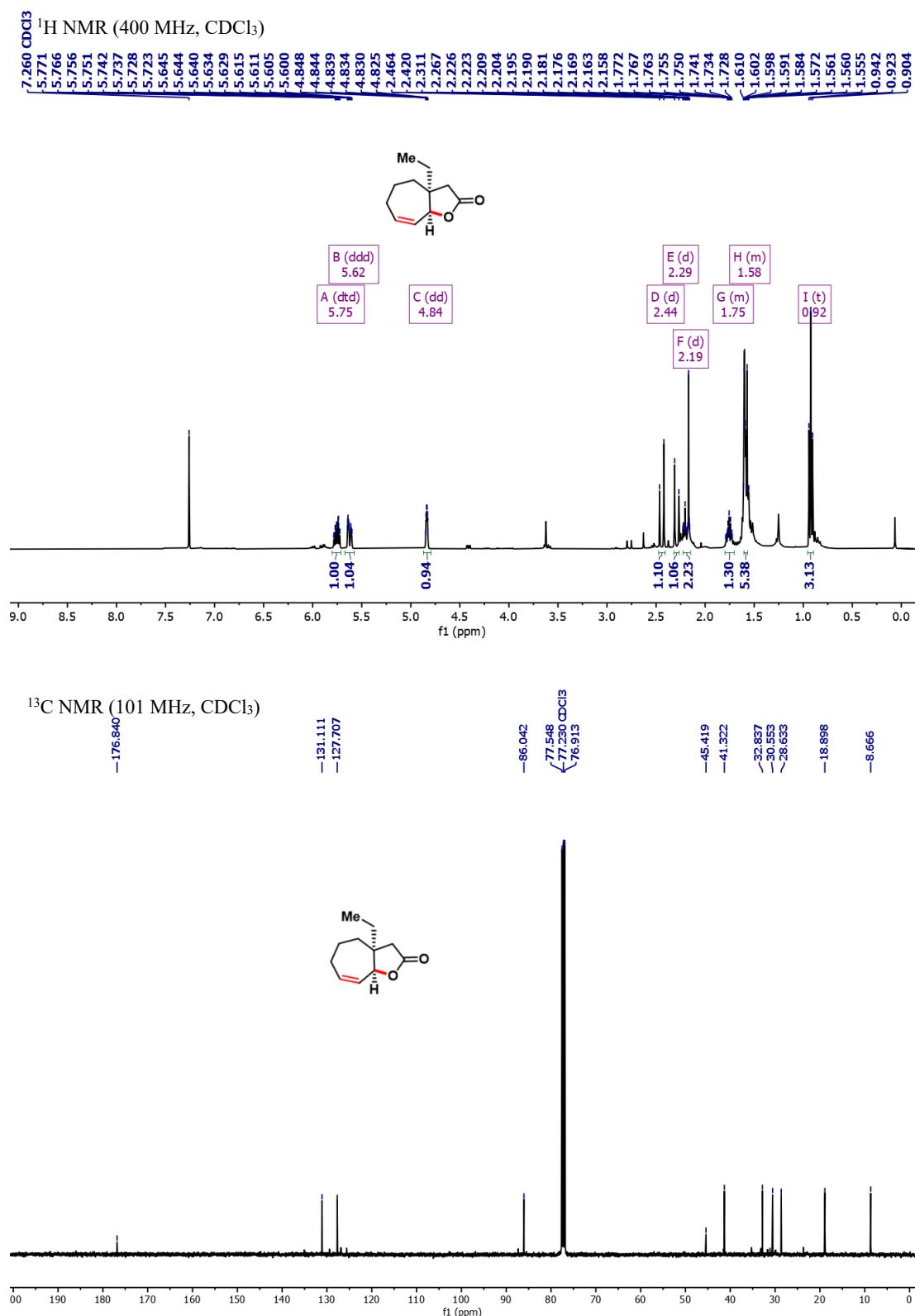
Compound 3g

(3a*S*,8a*S*)-3a-Methyl-3,3a,4,5,6,8a-hexahydro-2H-cyclohepta[b]furan-2-one



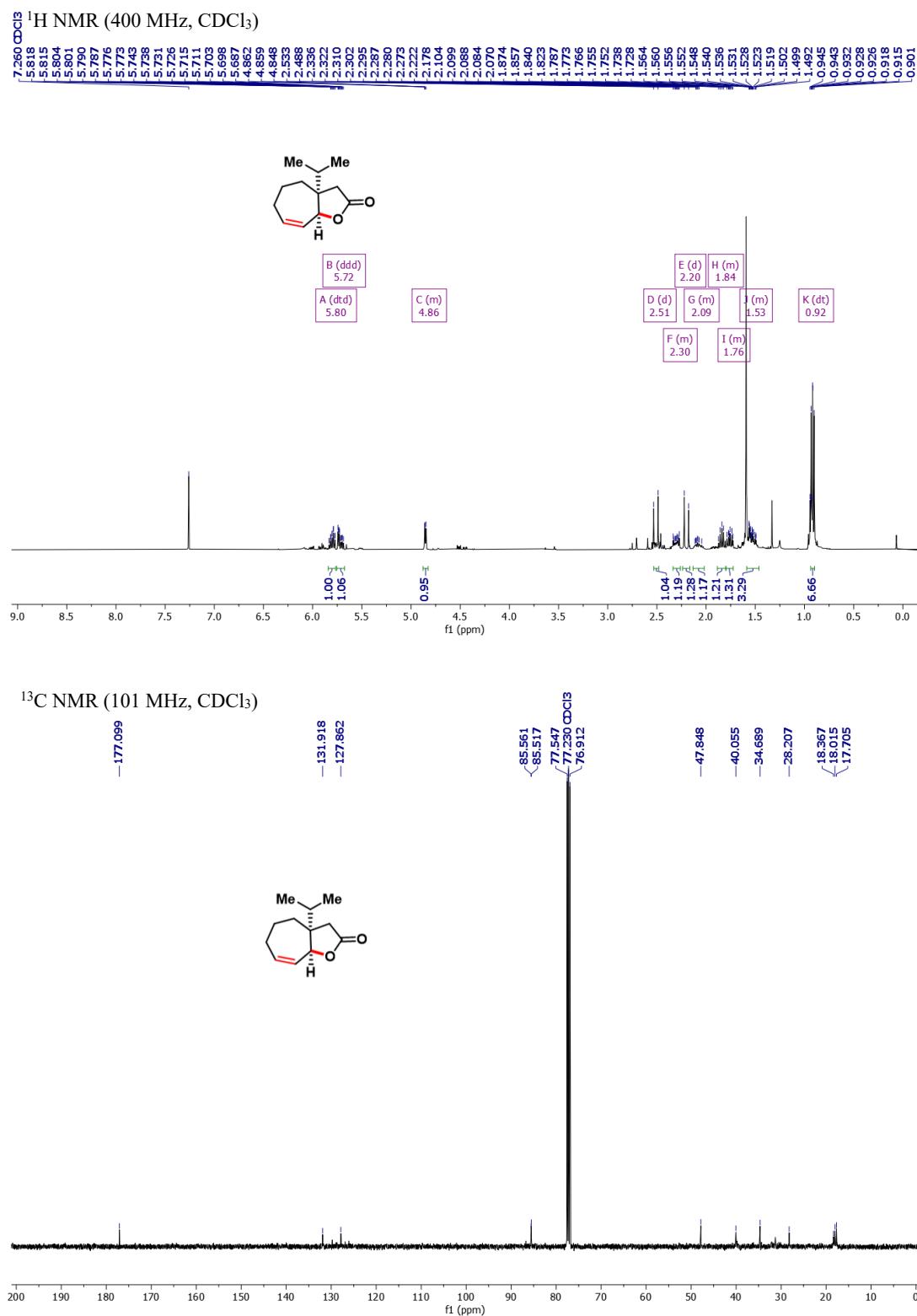
Compound 3h

(3a*S*,8a*S*)-3a-Ethyl-3,3a,4,5,6,8a-hexahydro-2*H*-cyclohepta[*b*]furan-2-one



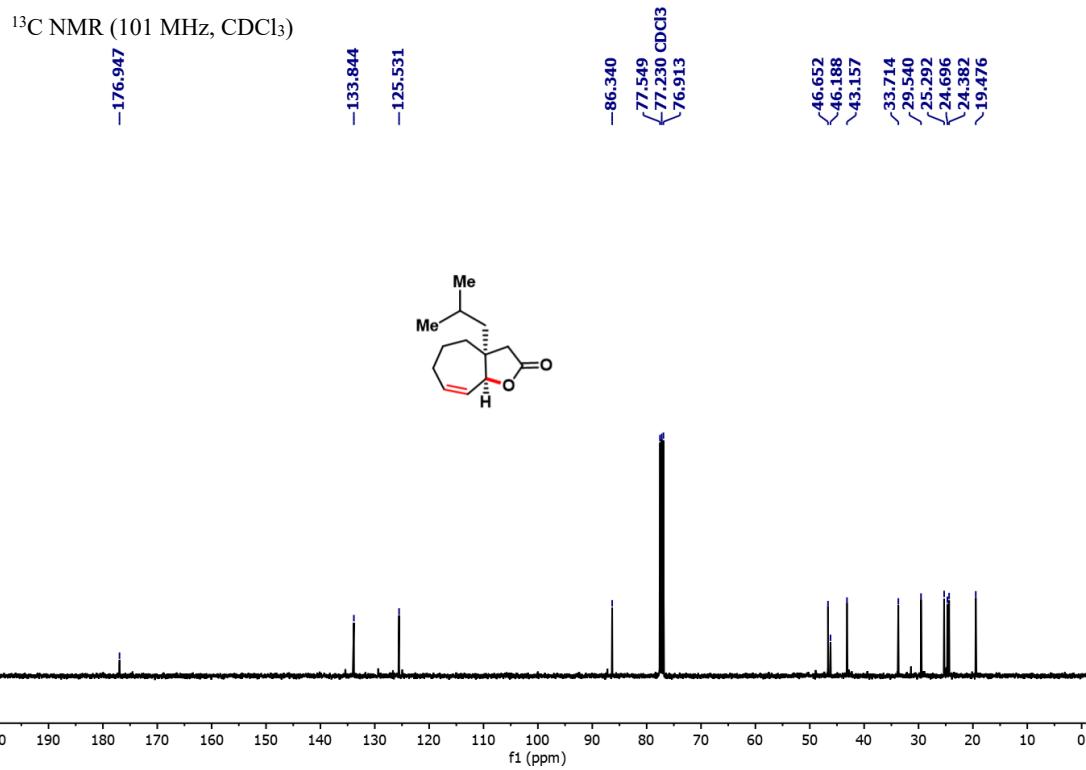
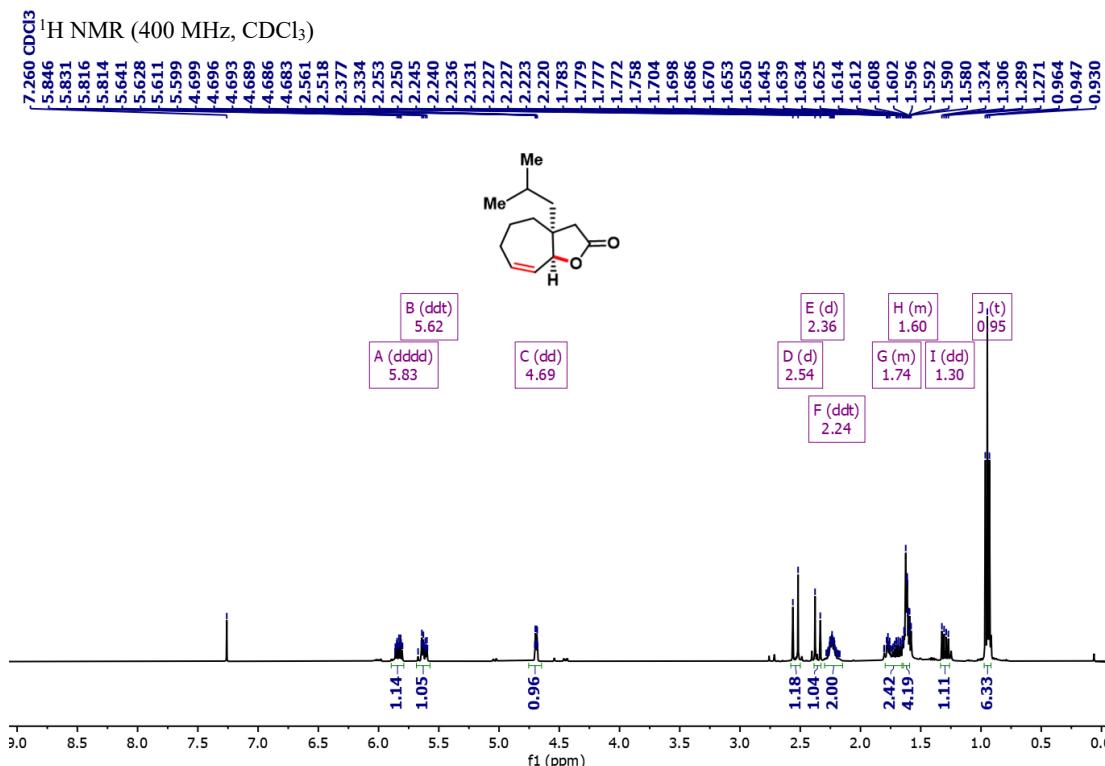
Compound 3i

(3a*S*,8a*S*)-3a-Isopropyl-3,3a,4,5,6,8a-hexahydro-2H-cyclohepta[b]furan-2-one



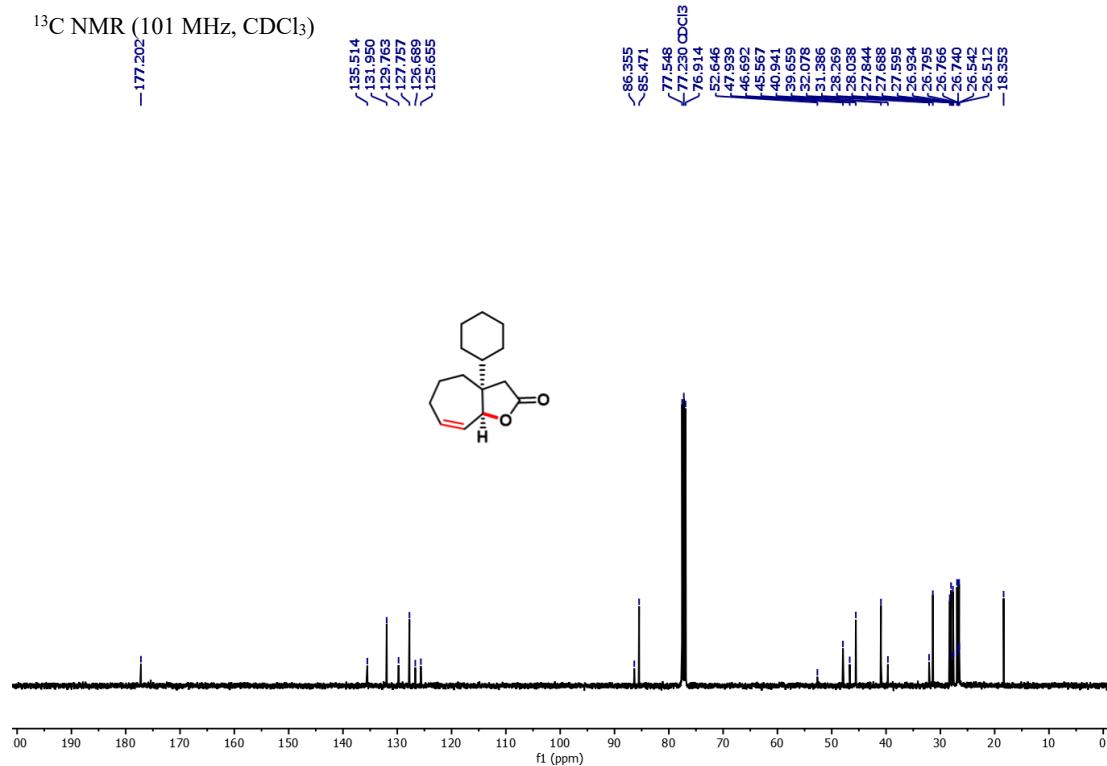
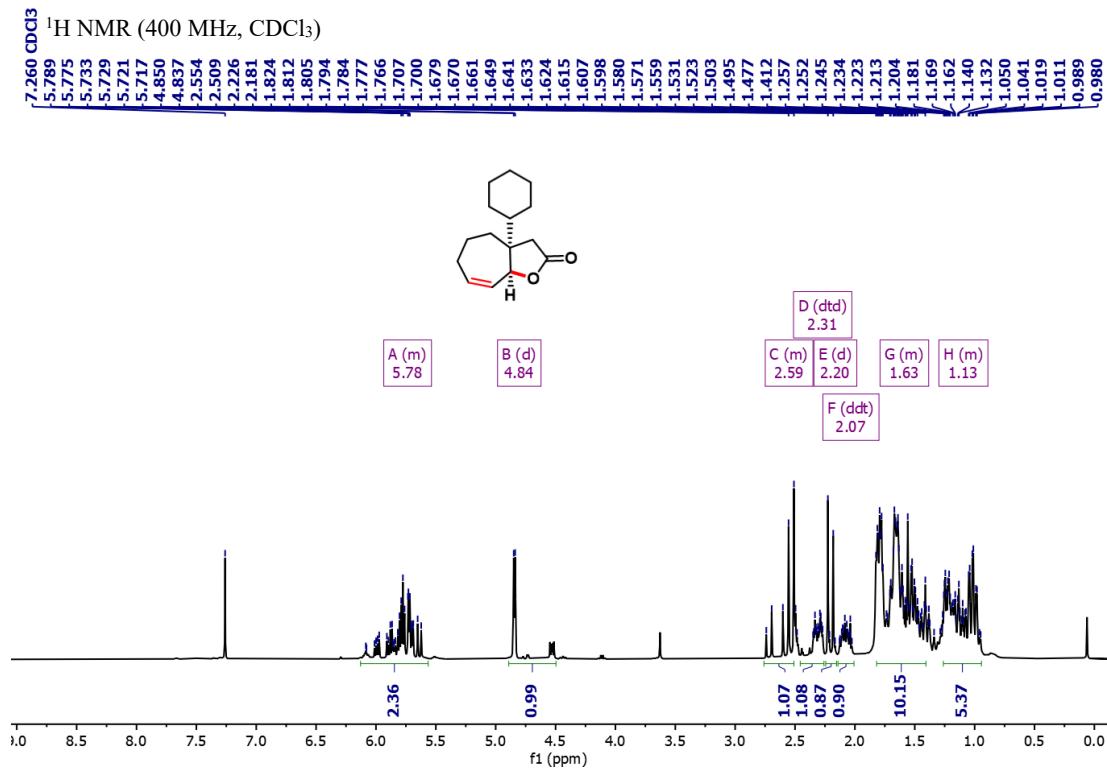
Compound 3j

(3a*R*,8a*S*)-3a-Isobutyl-3,3a,4,5,6,8a-hexahydro-2H-cyclohepta[b]furan-2-one



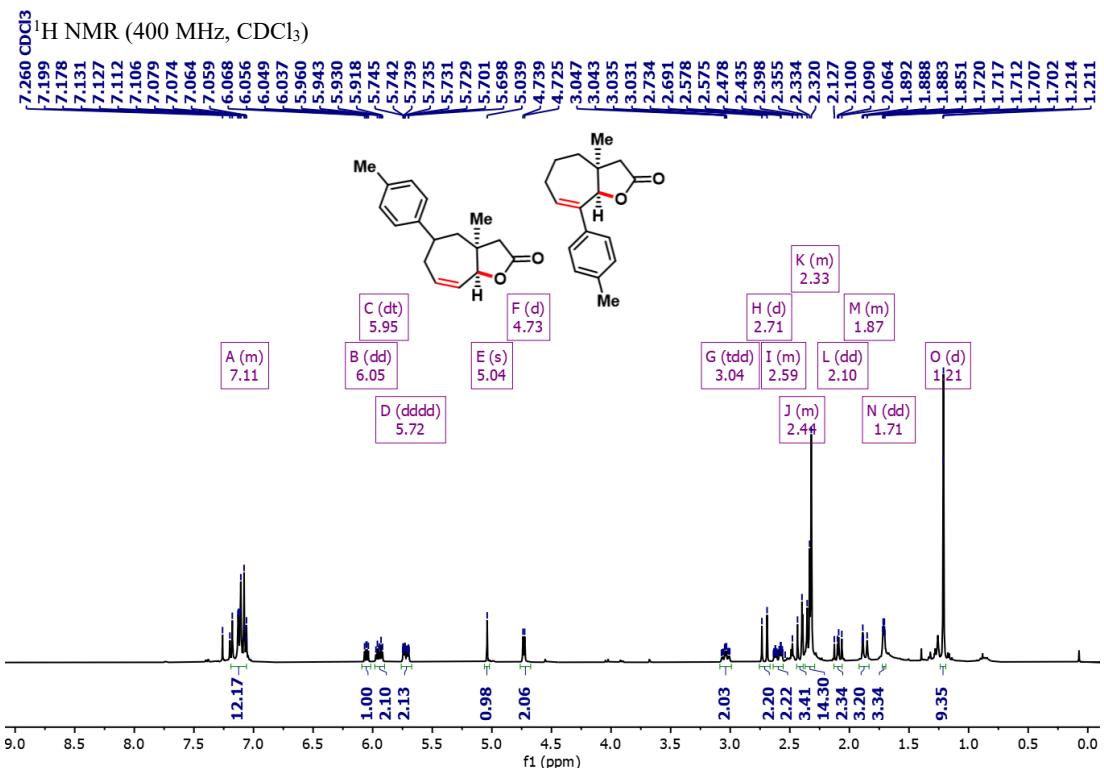
Compound 3k

(3a*S*,8a*S*)-3a-Cyclohexyl-3,3a,4,5,6,8a-hexahydro-2H-cyclohepta[b]furan-2-one

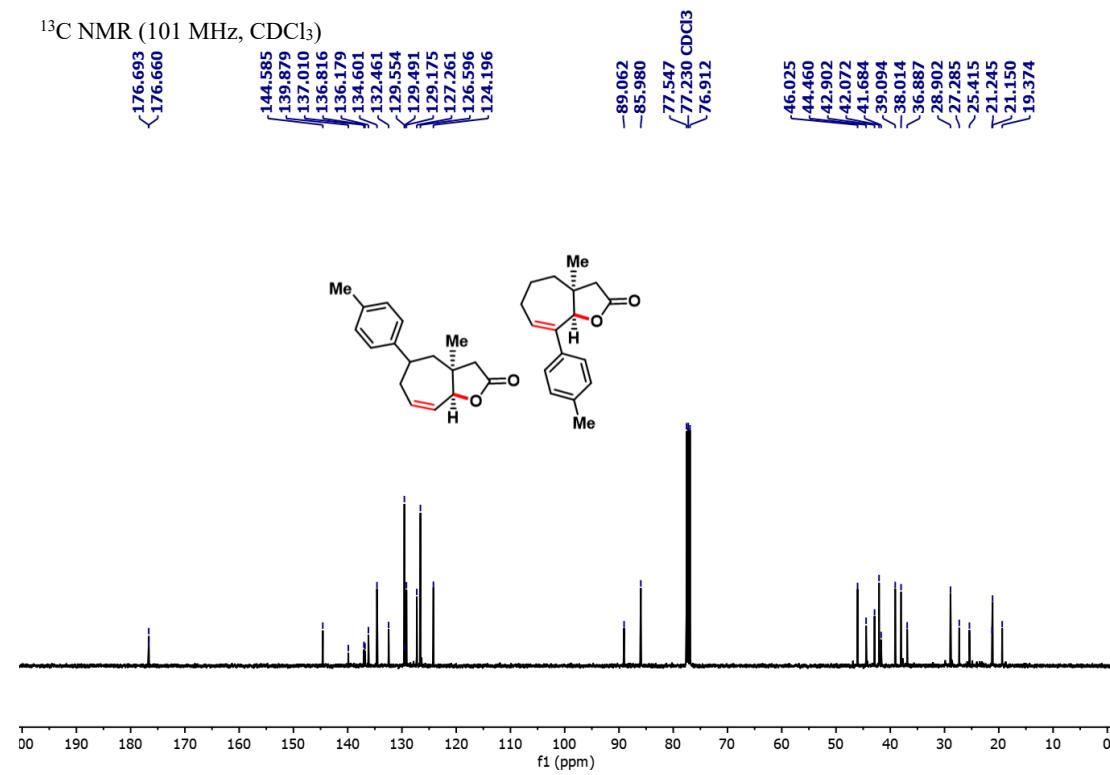


Compound 3l

(3a*S*,8a*S*)-3a-Methyl-6-(*p*-tolyl)-3,3a,4,5,6,8a-hexahydro-2H-cyclohepta[b]furan-2-one

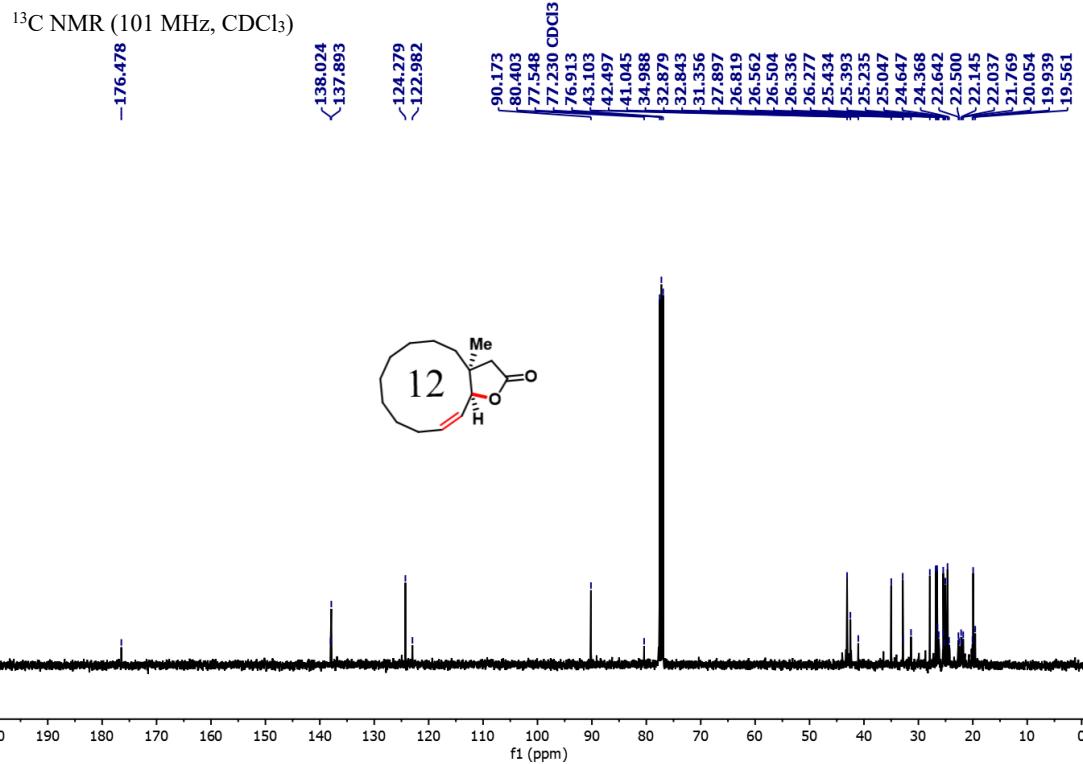
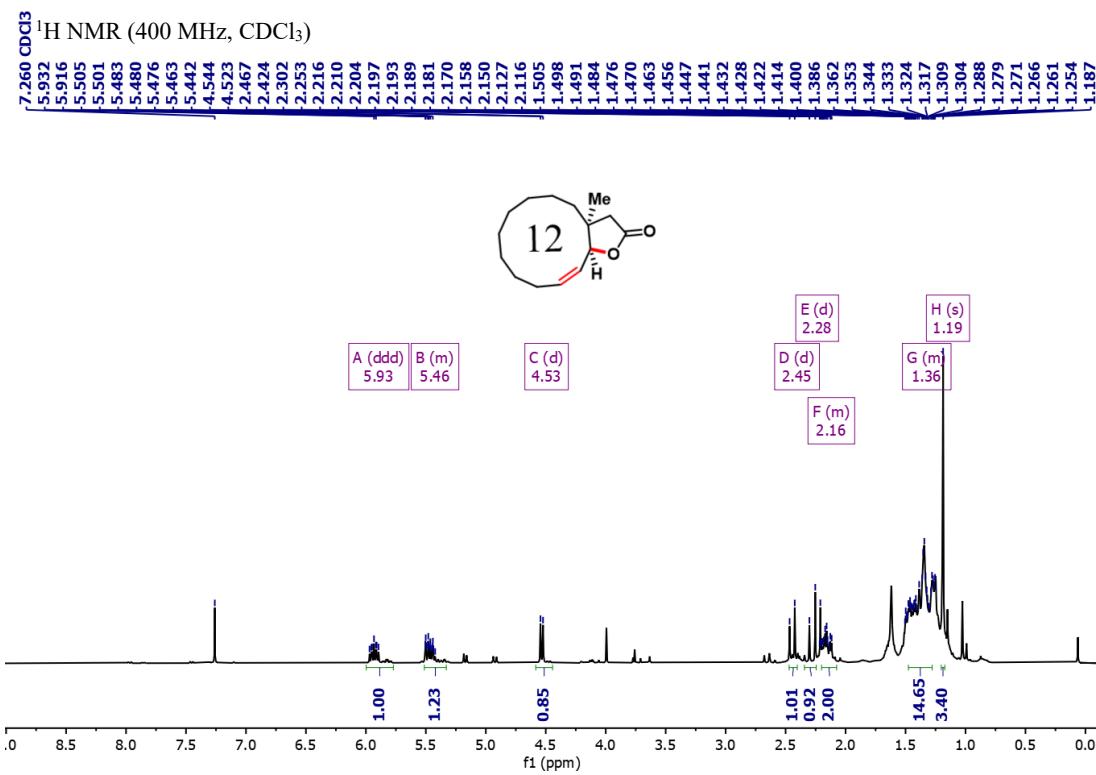


¹³C NMR (101 MHz, CDCl₃)



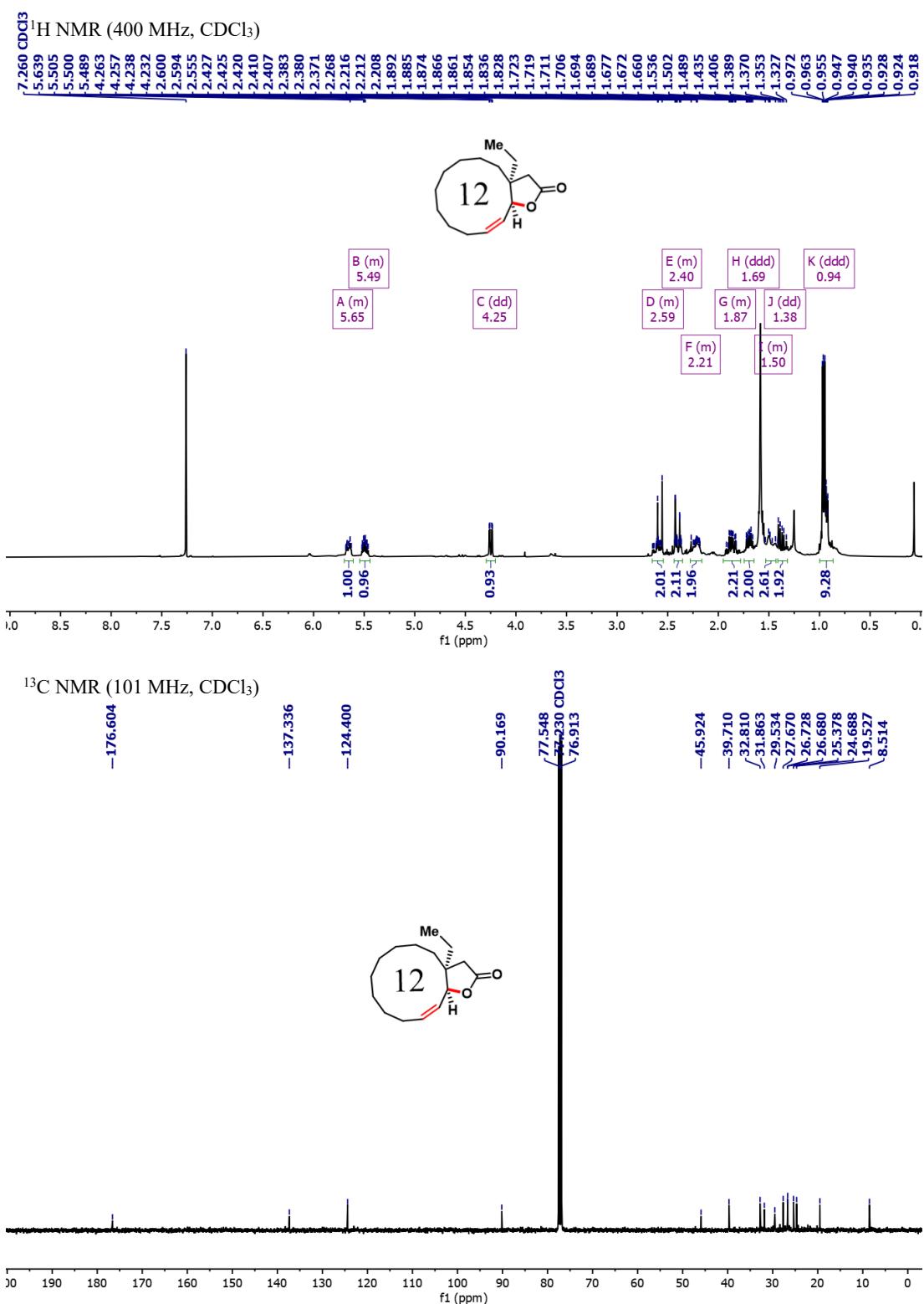
Compound 3m

(3a*S*,13a*S*,*Z*)-3a-Methyl-3a,4,5,6,7,8,9,10,11,13a-deahydrocyclododeca[b]furan-2(3H)-one



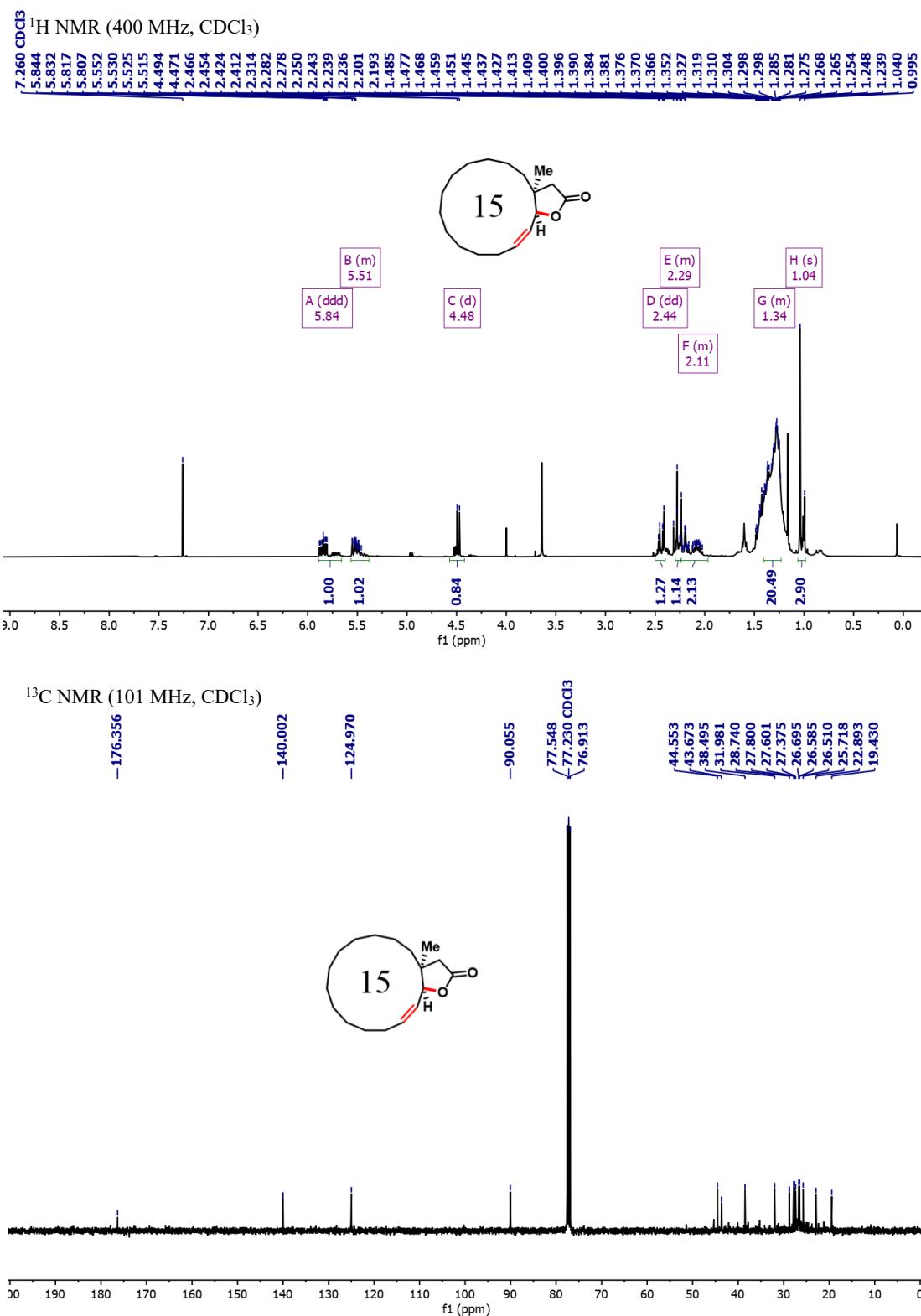
Compound 3n

(3a*S*,13a*S*,*Z*)-3a-Ethyl-3a,4,5,6,7,8,9,10,11,13a-decahydrocyclododeca[**b**]furan-2(3H)-one



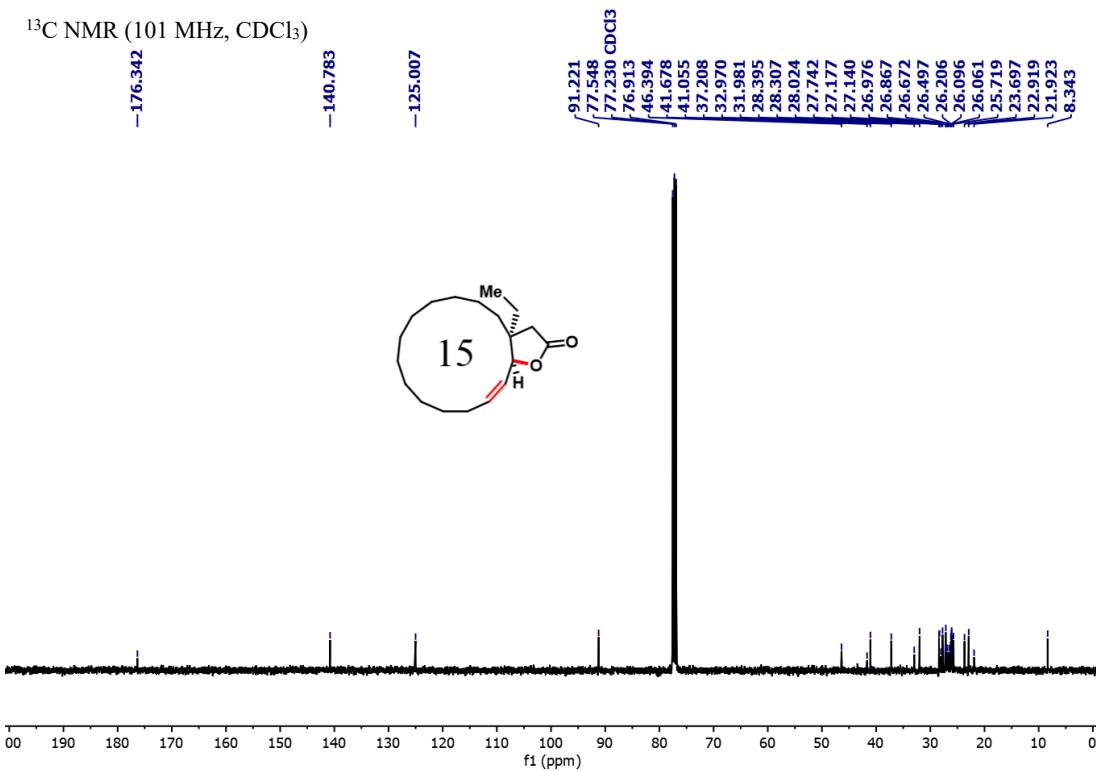
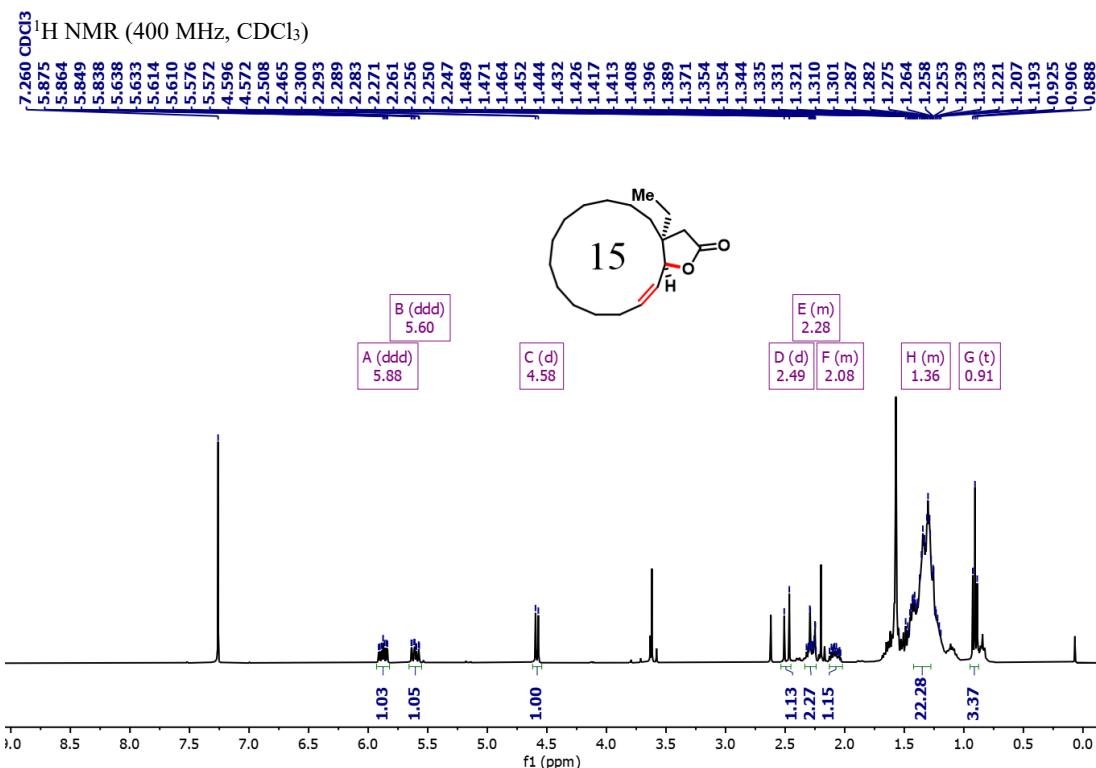
Compound 3o

(3a*R*,16a*S,E*)-3a-Methyl-3,3a,4,5,6,7,8,9,10,11,12,13,14,16a-tetradecahydro-2H-cyclopentadeca[b]furan-2-one



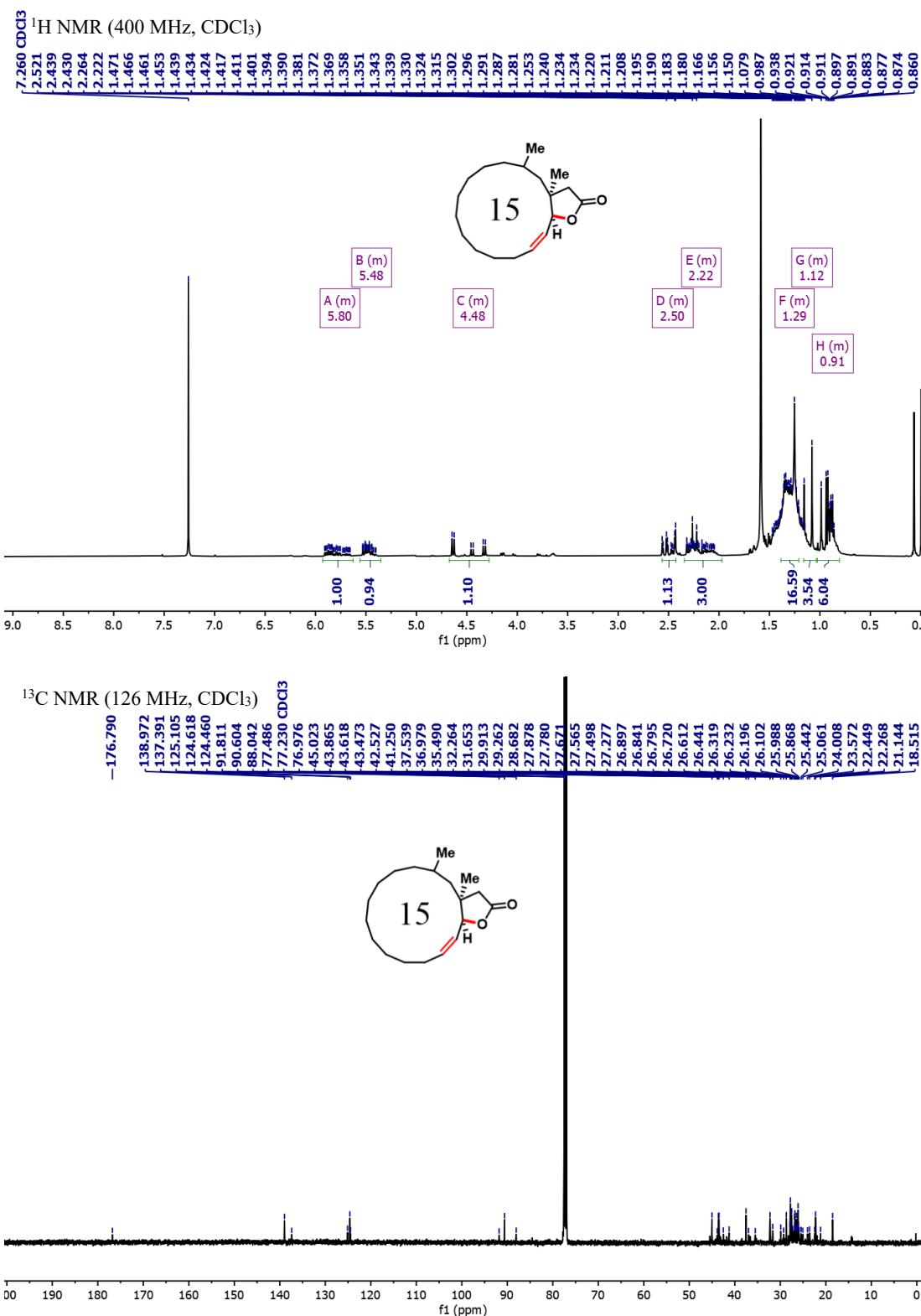
Compound 3p

(3a*S*,16a*S*,*E*)-3a-Ethyl-3,3a,4,5,6,7,8,9,10,11,12,13,14,16a-tetradecahydro-2*H*-cyclopentadeca[b]furan-2-one



Compound 3q

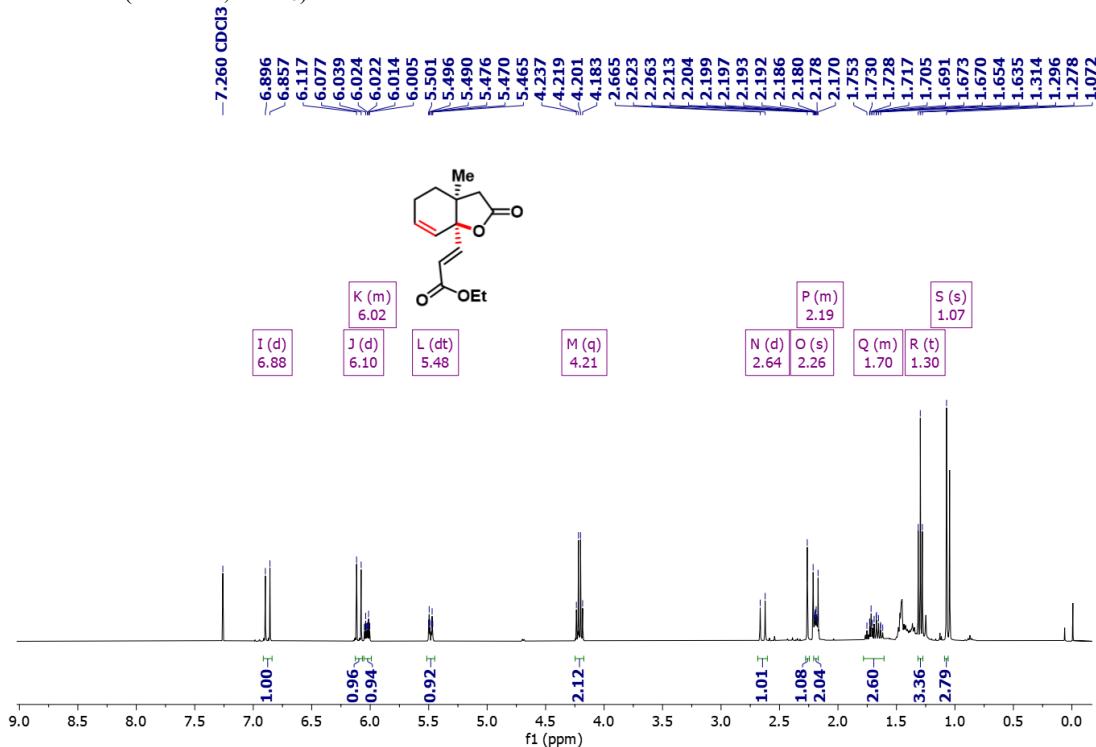
(3a*S*,16a*S*,*E*)-3a,5-Dimethyl-3,3a,4,5,6,7,8,9,10,11,12,13,14,16a-tetradecahydro-2H-cyclopentadeca[b]furan-2-one



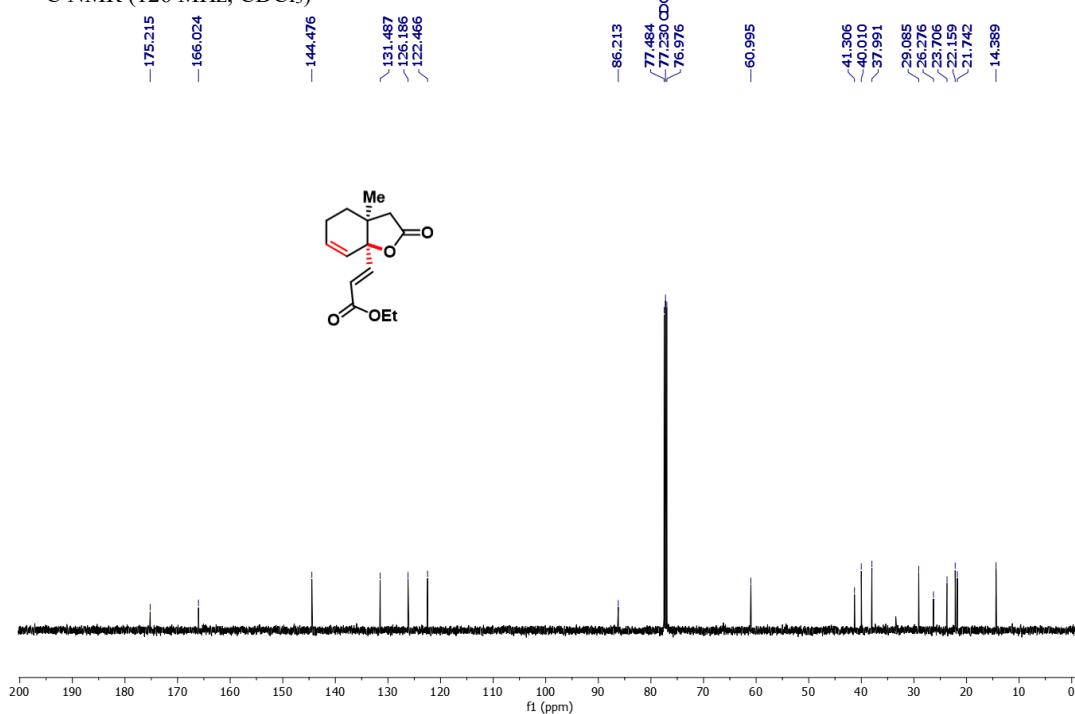
Compound 4a

Ethyl (E)-3-((3a*S*,7a*R*)-3a-methyl-2-oxo-3,3a,4,5-tetrahydrobenzofuran-7a(2H)-yl)acrylate

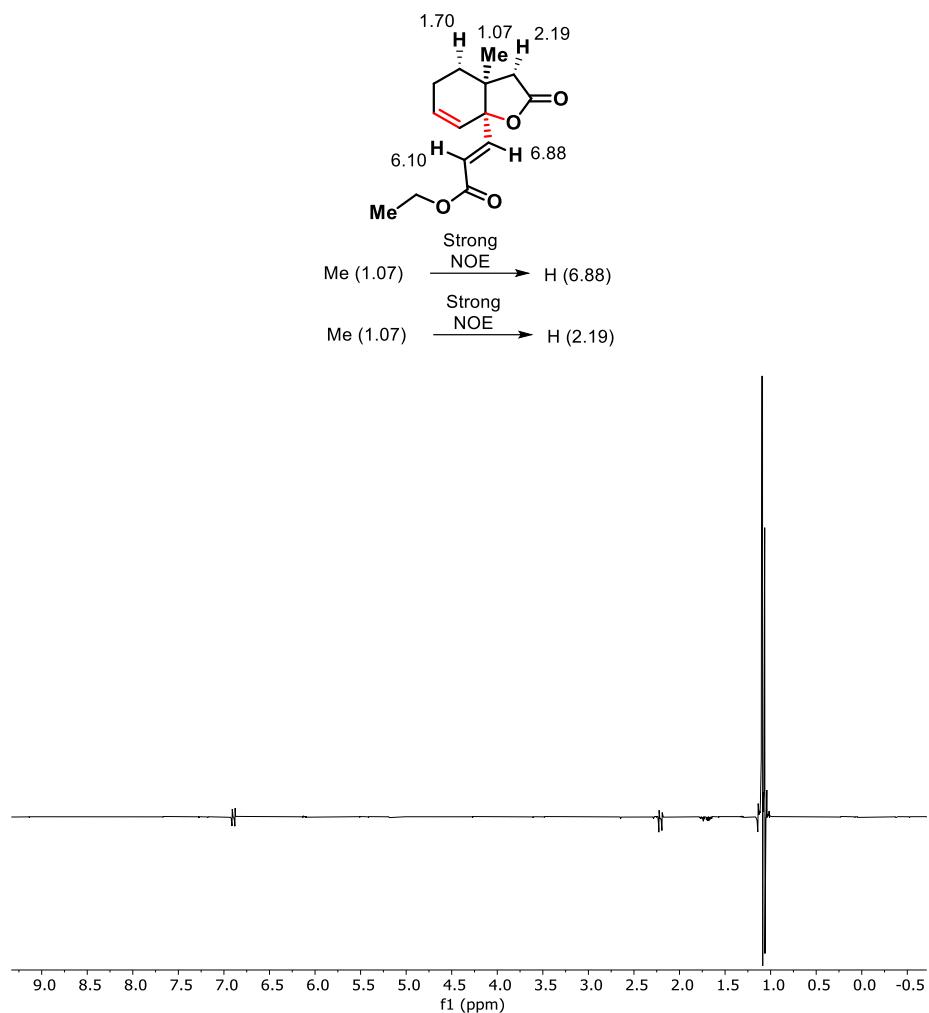
¹H NMR (400 MHz, CDCl₃)



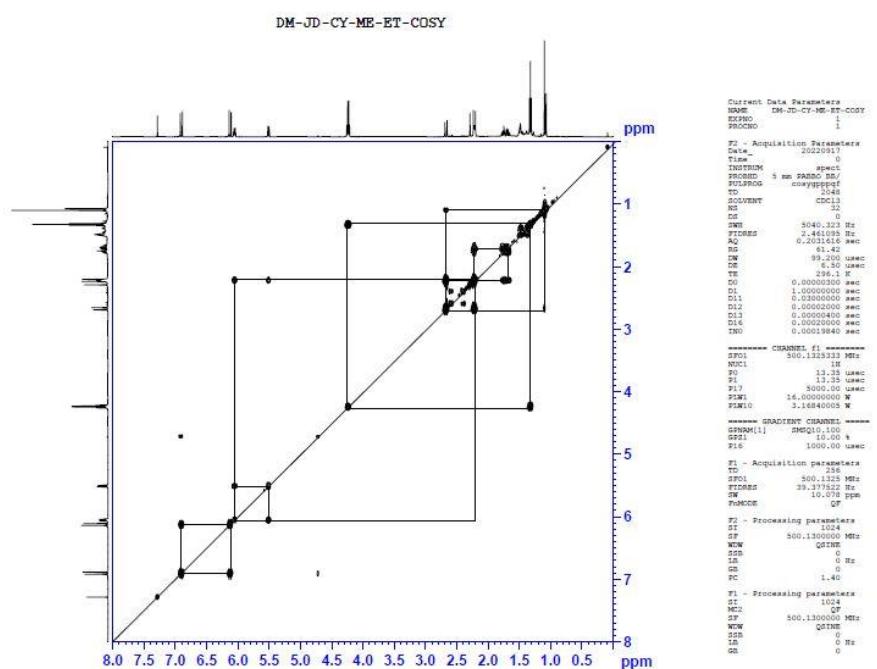
¹³C NMR (126 MHz, CDCl₃)



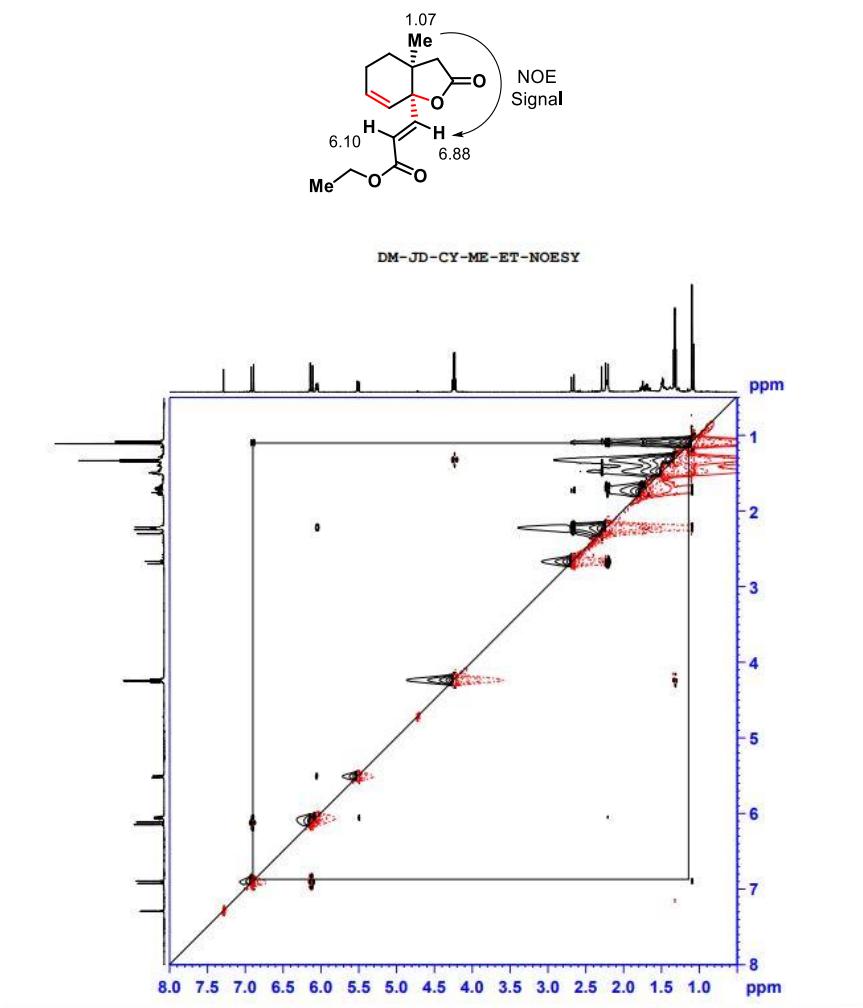
NOE experiment:



COSY Experiment:

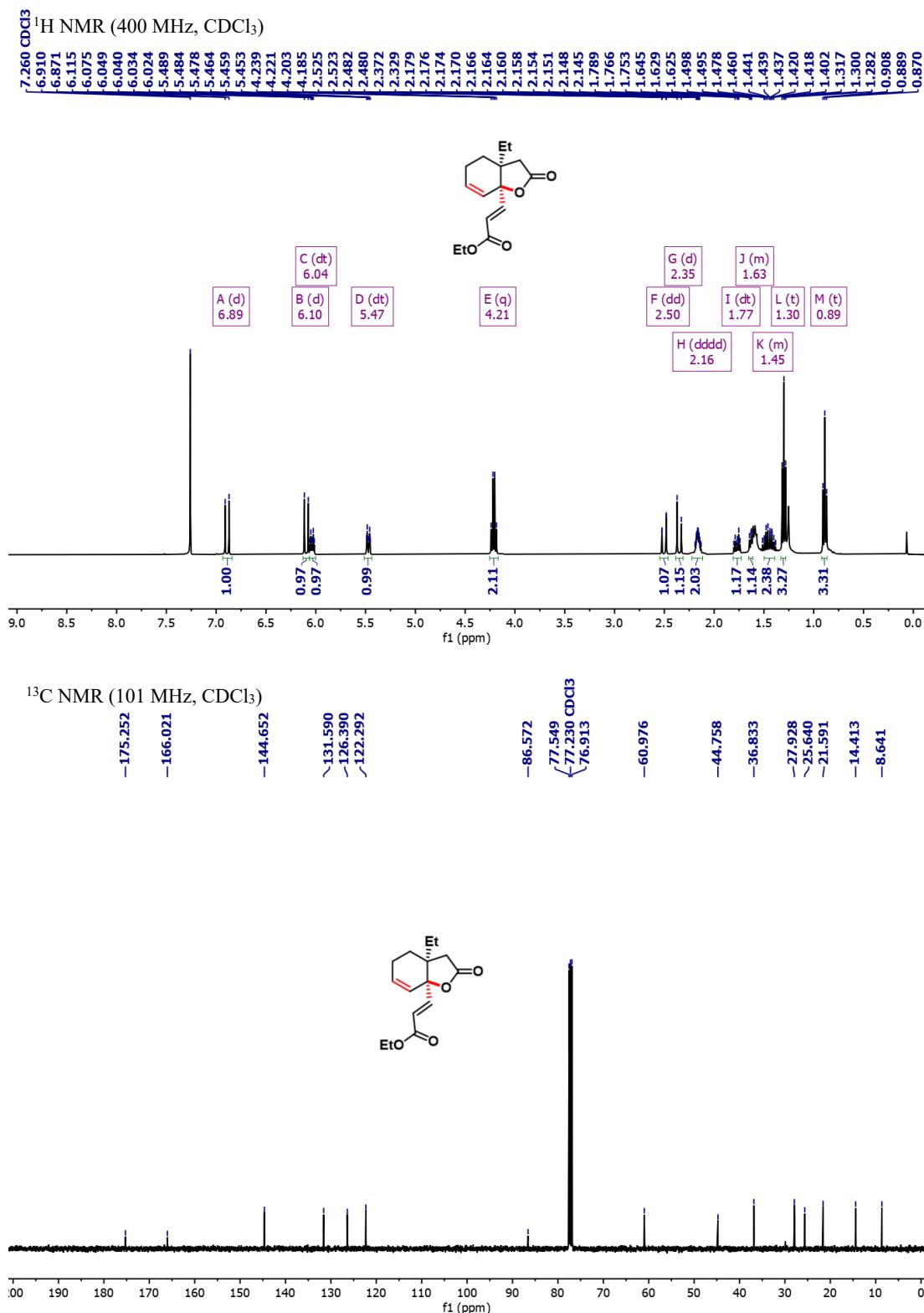


NOESY Experiment:



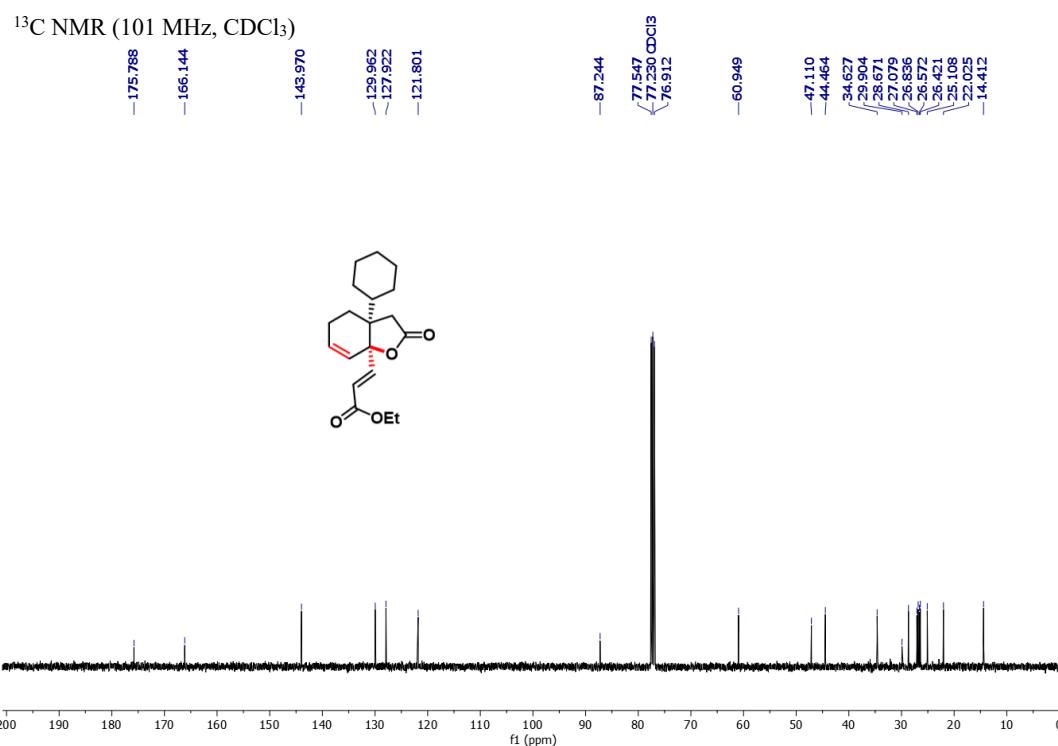
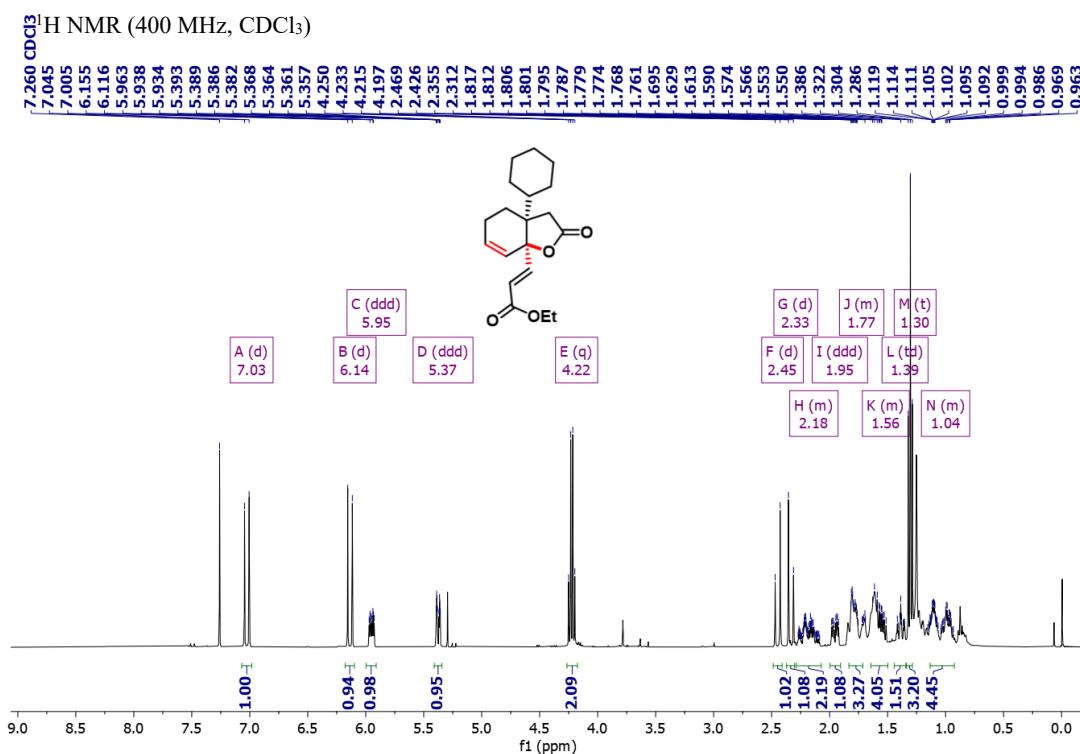
Compound 4b

Ethyl (*E*)-3-((3a*S*,7a*R*)-3a-ethyl-2-oxo-3,3a,4,5-tetrahydrobenzofuran-7a(2H)-yl)acrylate



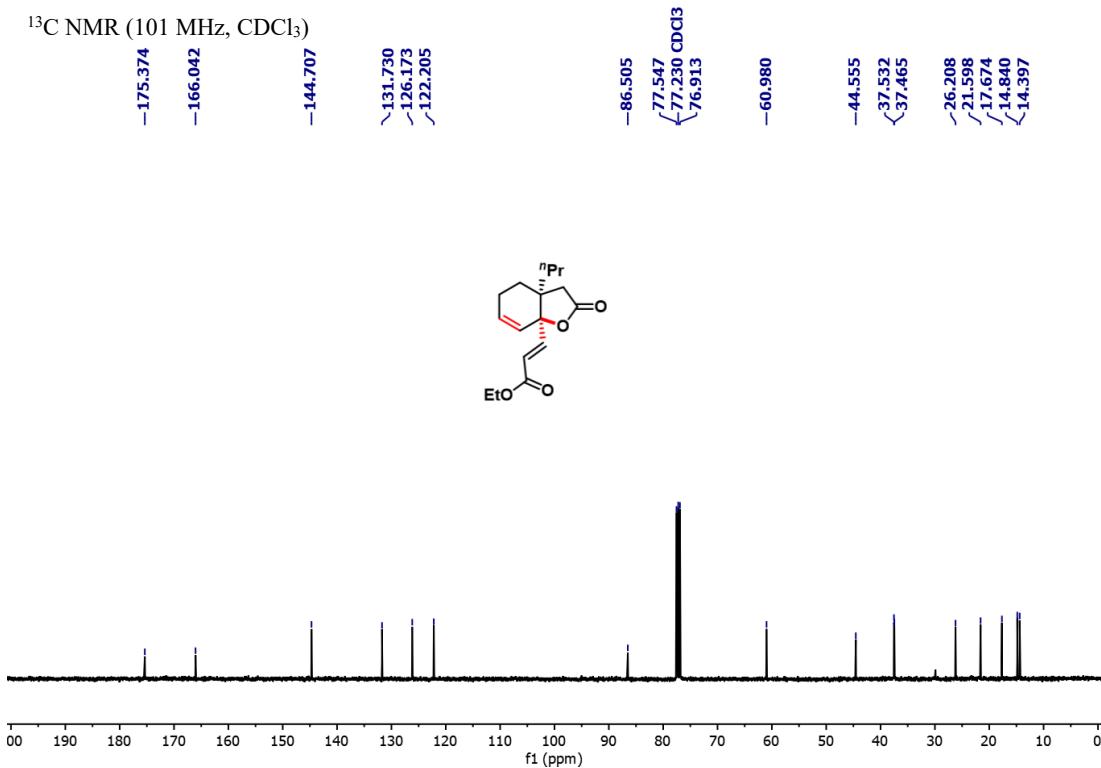
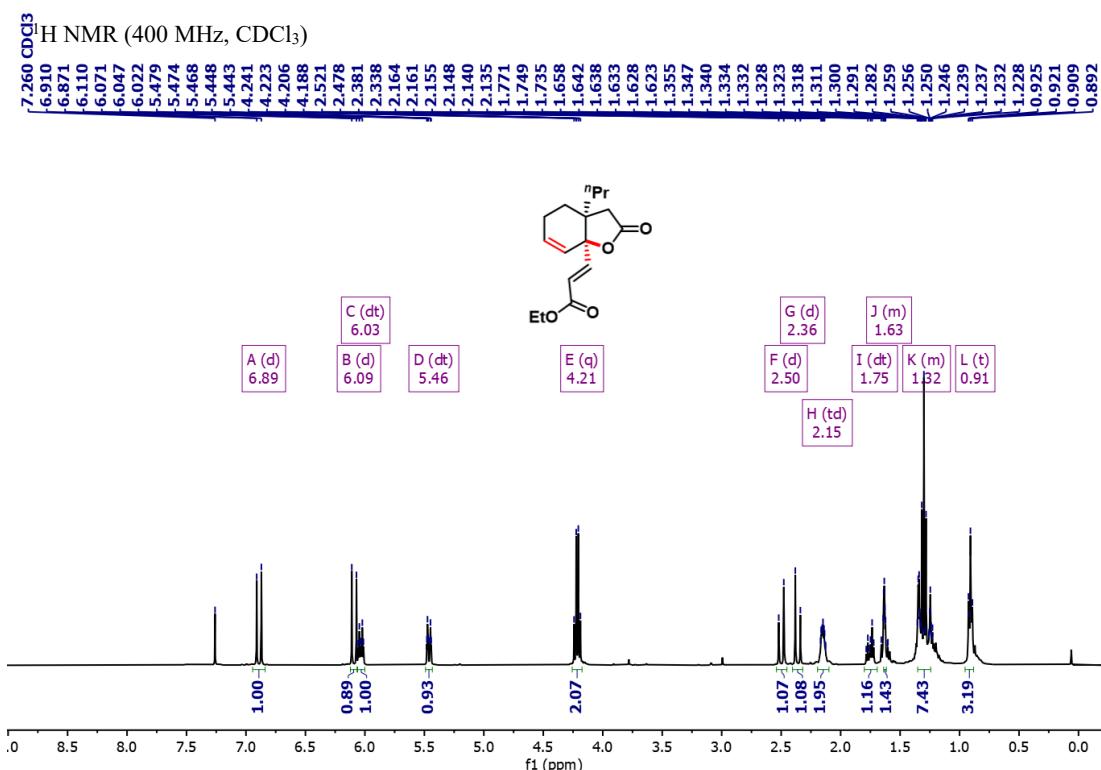
Compound 4c

Ethyl (E)-3-((3a*S*,7a*R*)-3a-cyclohexyl-2-oxo-3,3a,4,5-tetrahydrobenzofuran-7a(2H)-yl)acrylate



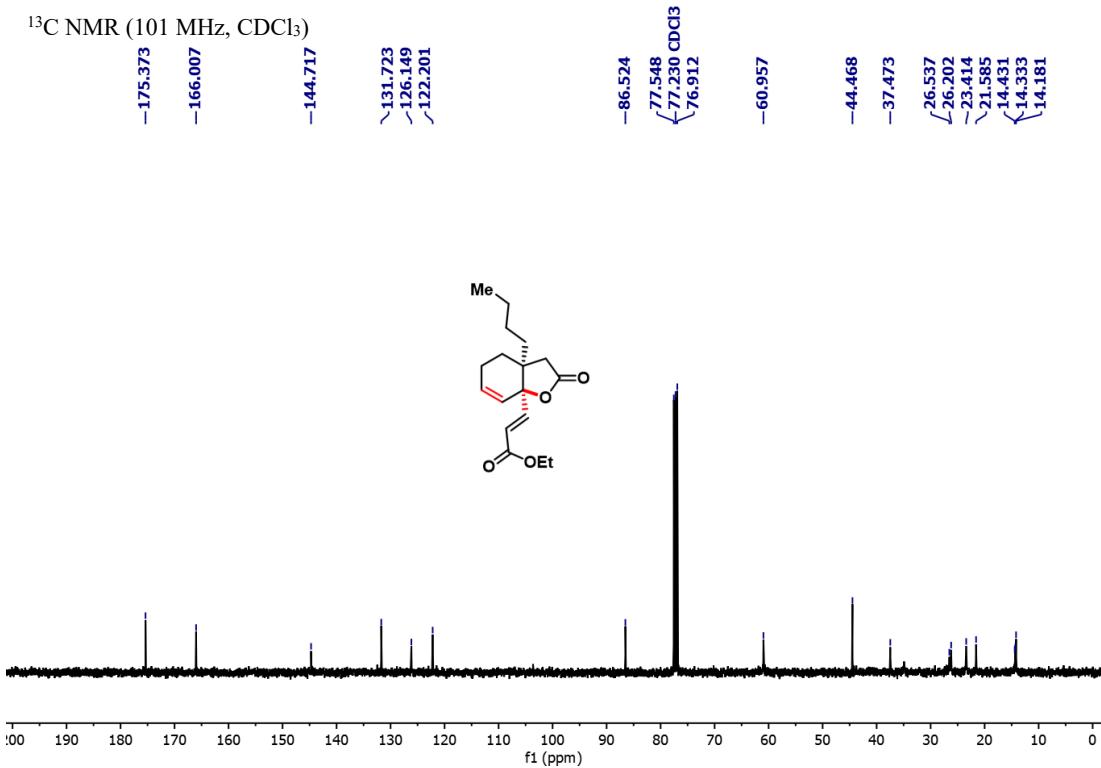
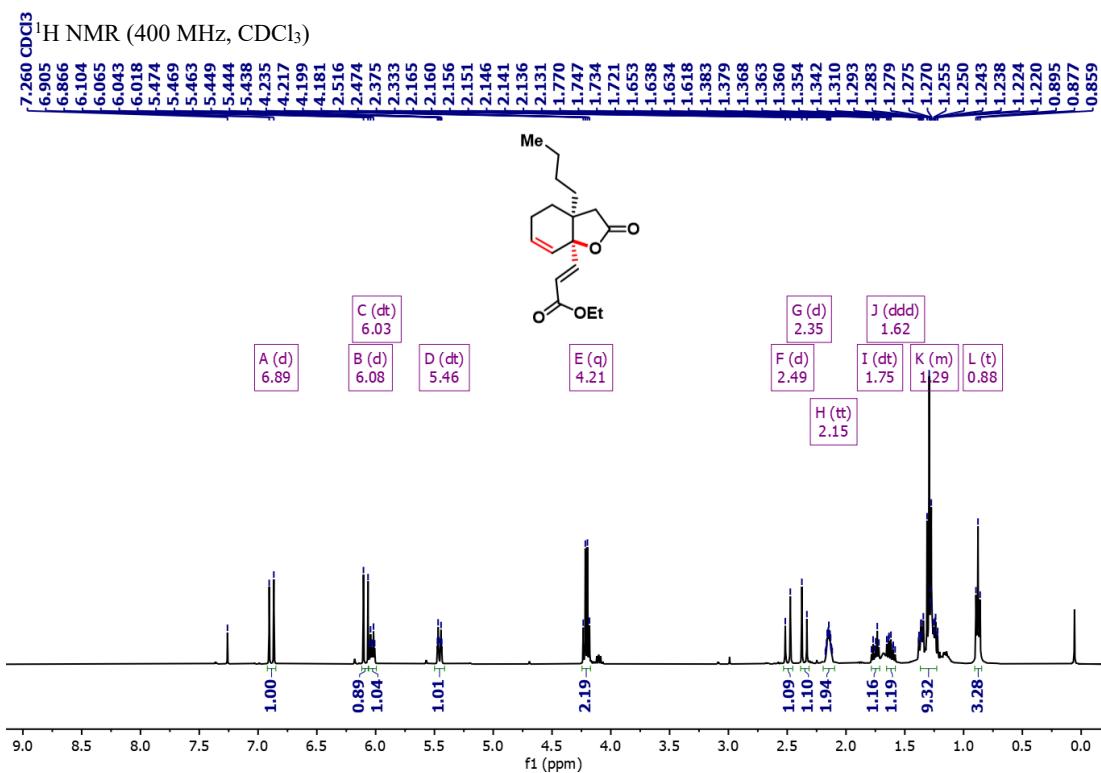
Compound 4d

Ethyl (E)-3-((3a*S*,7a*R*)-2-oxo-3*a*-propyl-3,3*a*,4,5-tetrahydrobenzofuran-7*a*(2*H*)-yl)acrylate



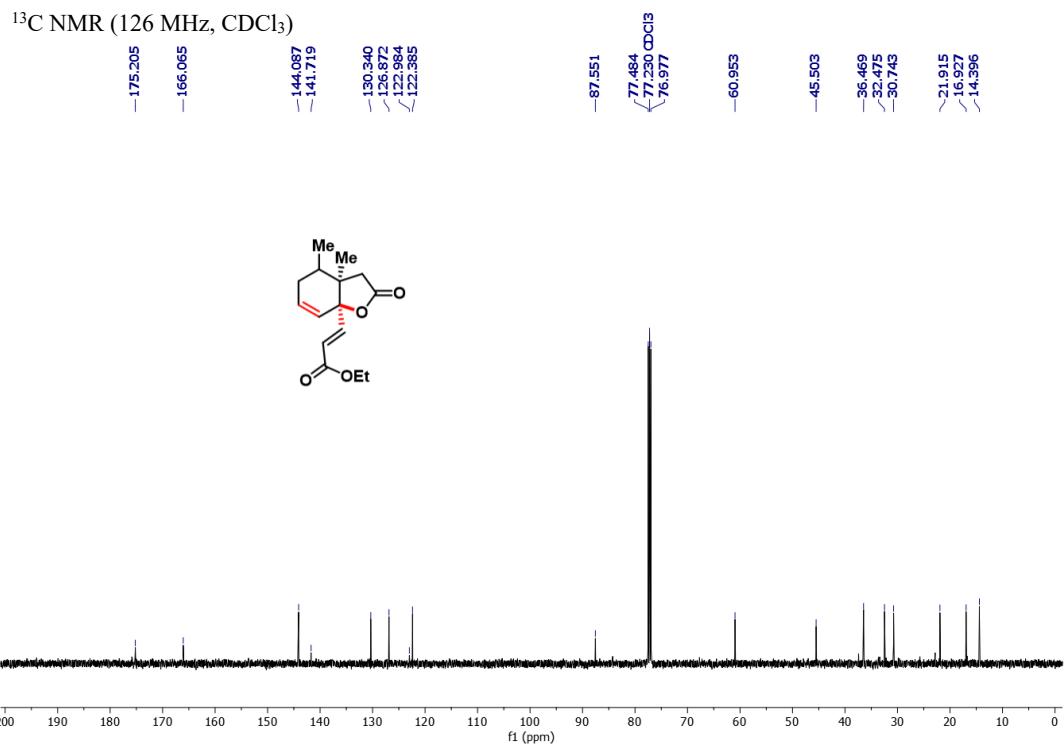
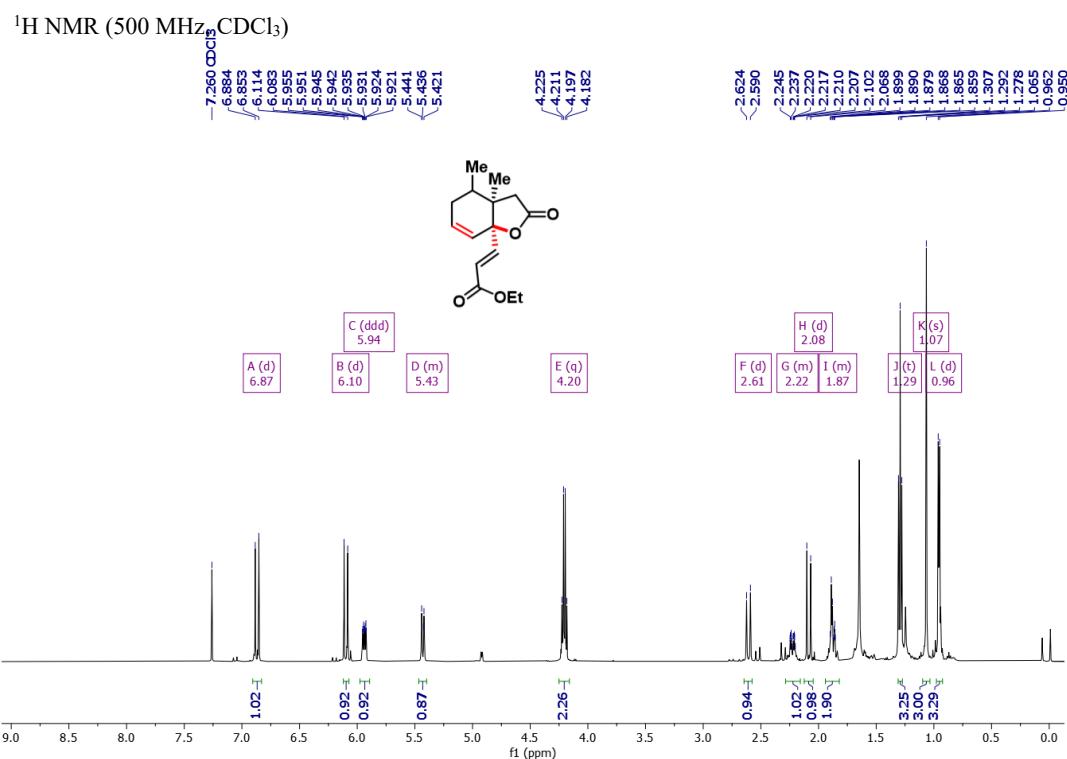
Compound 4e

Ethyl (E)-3-((3a*S*,7a*R*)-3a-butyl-2-oxo-3,3a,4,5-tetrahydrobenzofuran-7a(2H)-yl)acrylate

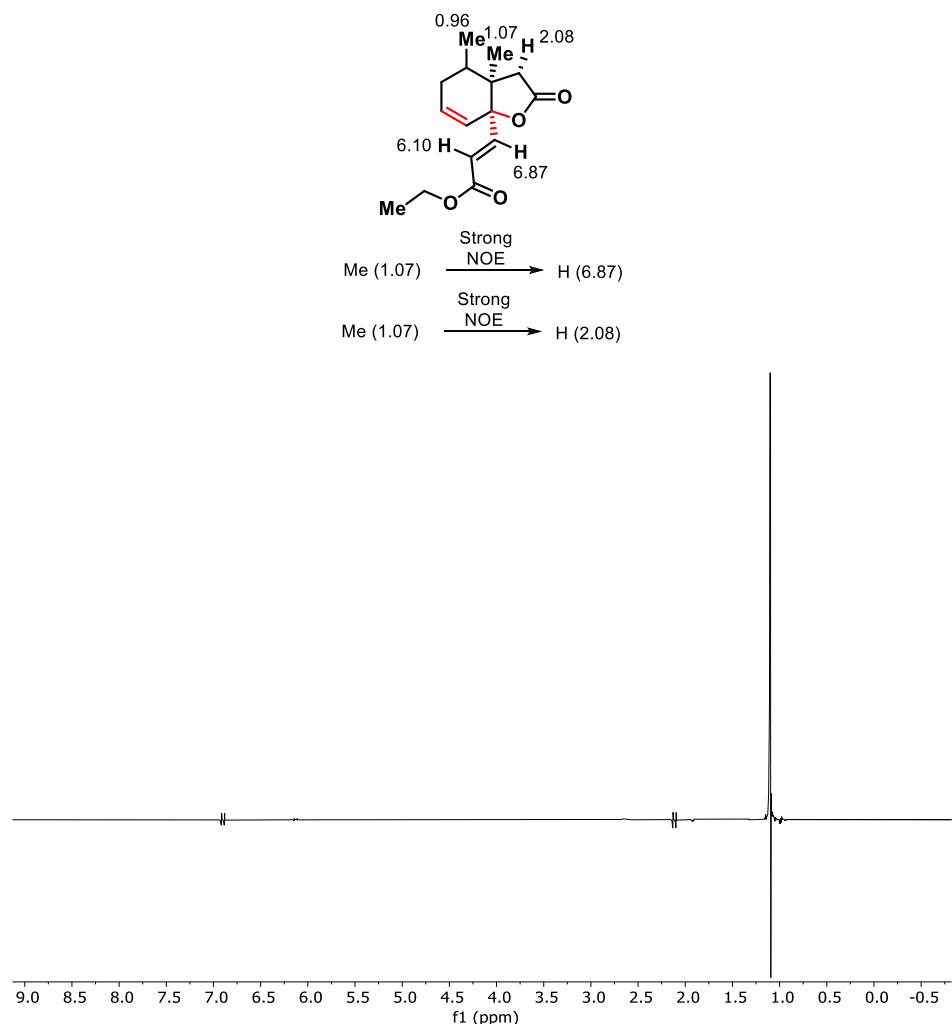


Compound 4f

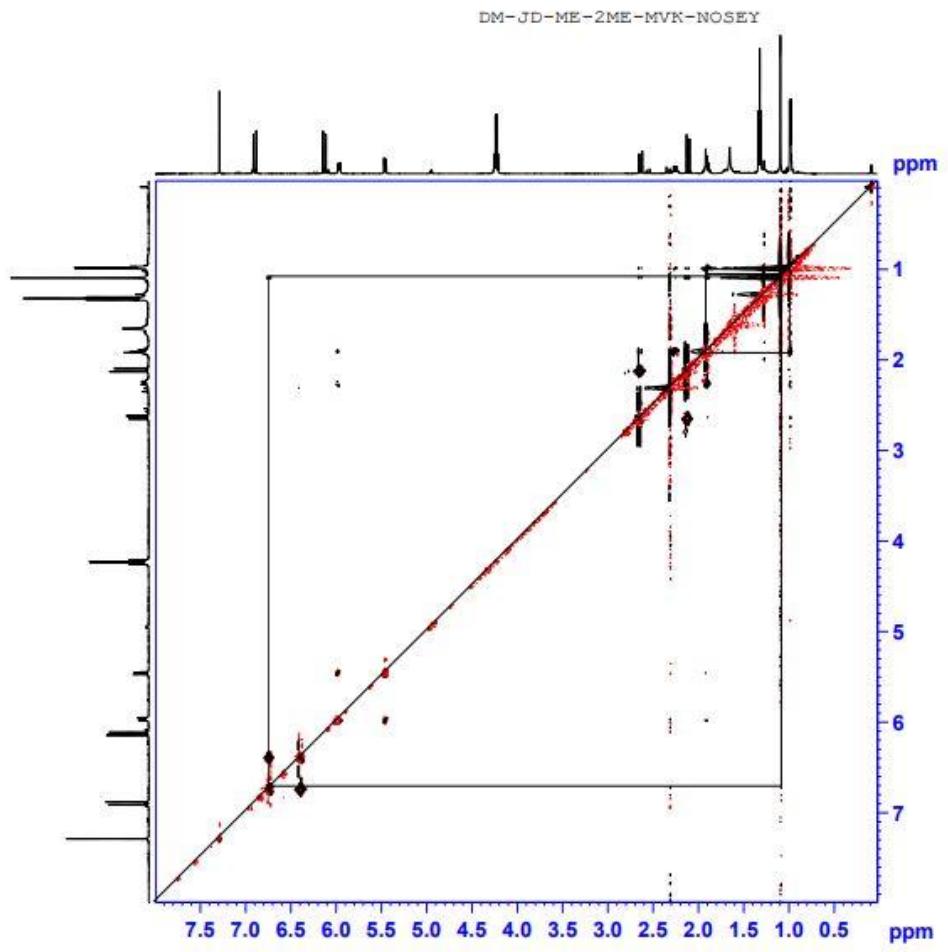
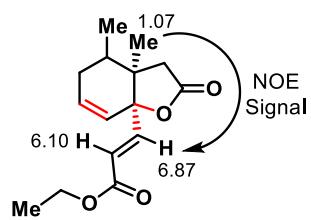
Ethyl (E)-3-((3a*R*,7a*R*)-3*a*,4-dimethyl-2-oxo-3,3*a*,4,5-tetrahydrobenzofuran-7*a*(2*H*)-yl)acrylate



NOE Experiment:

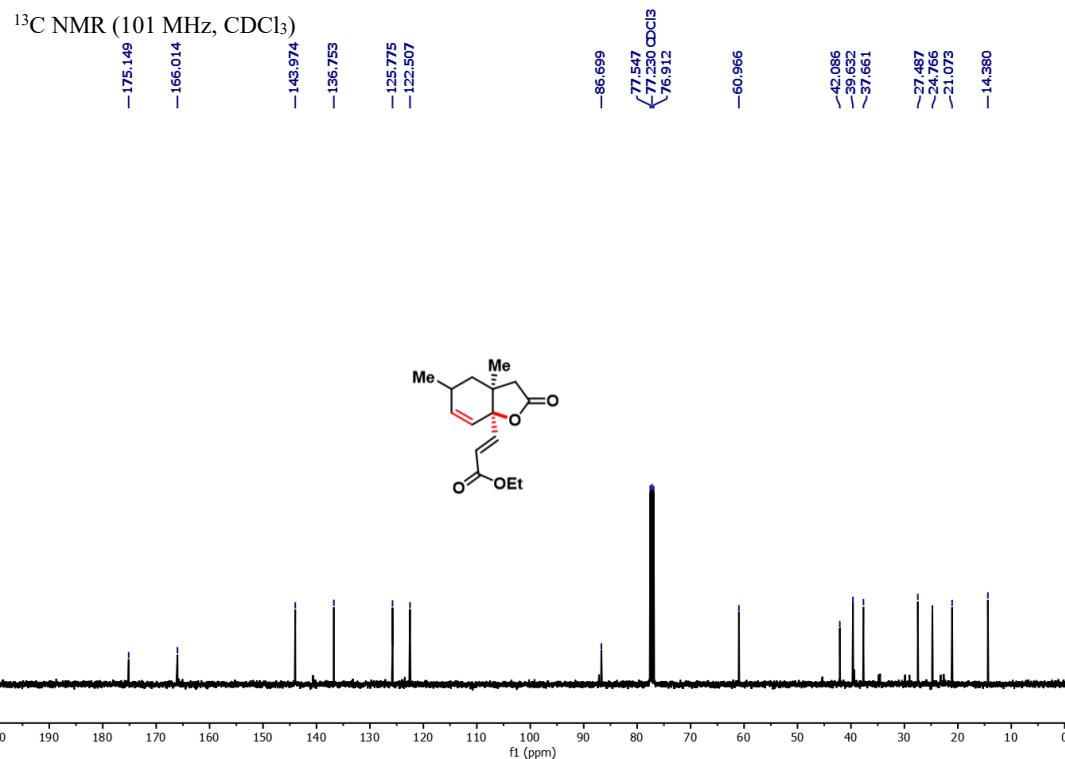
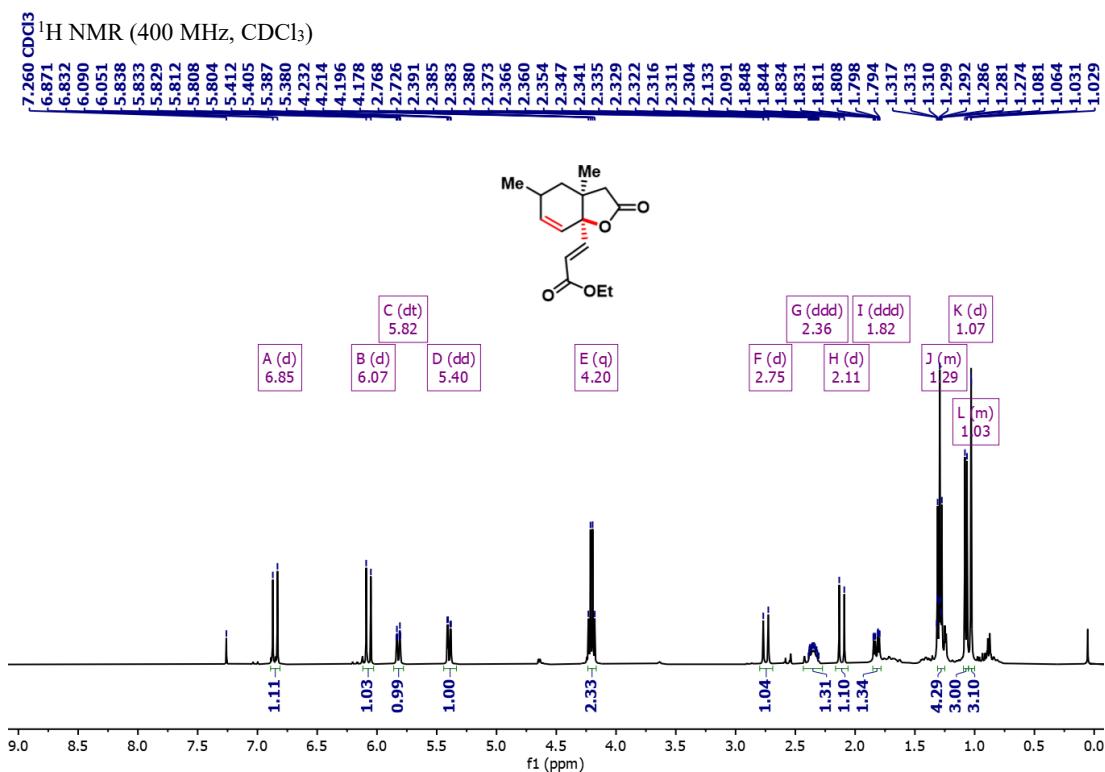


NOESY Experiment:



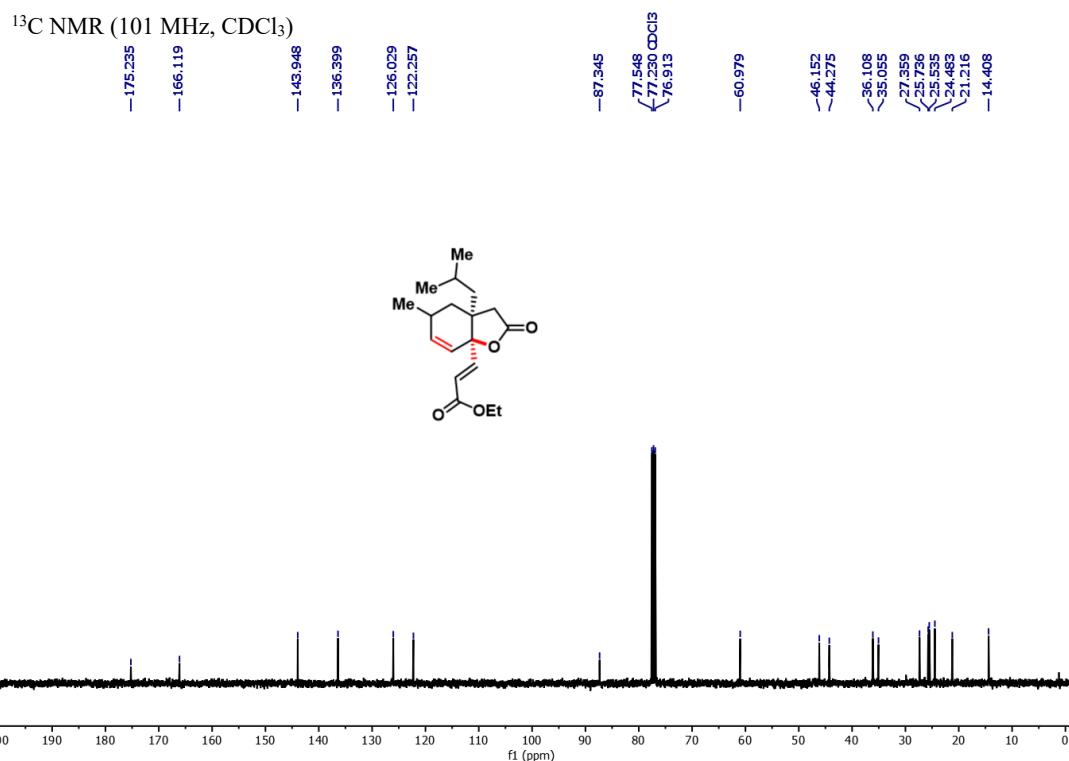
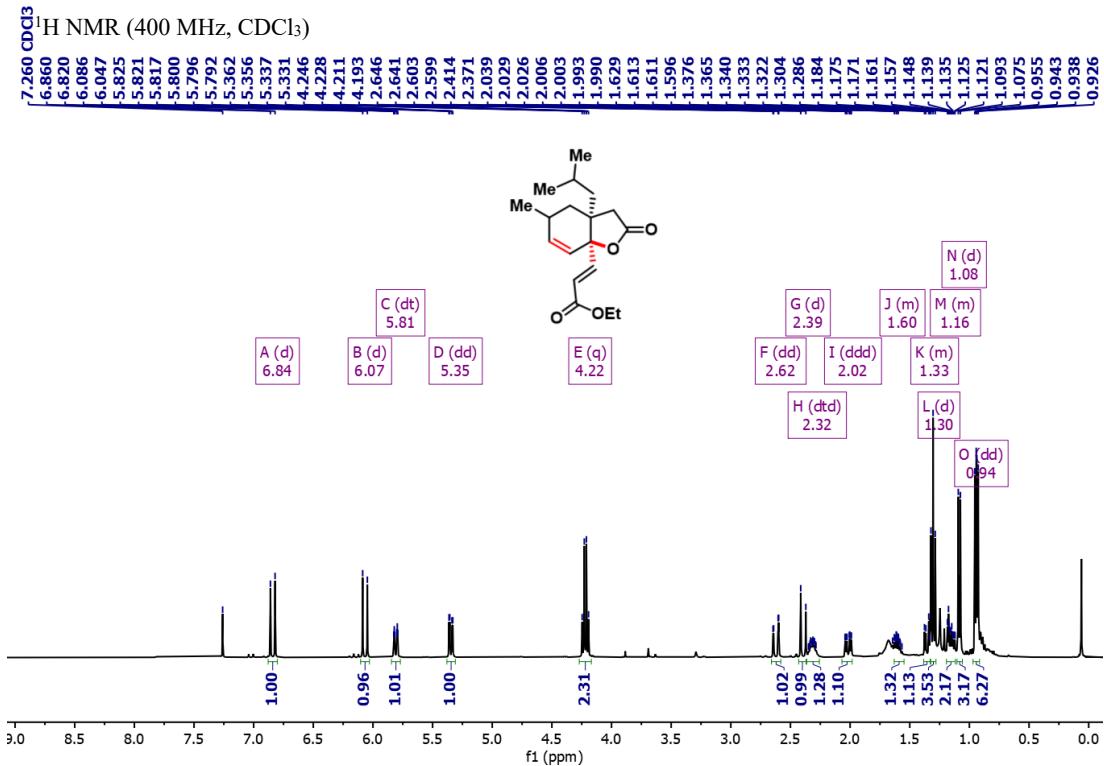
Compound 4g

Ethyl (E)-3-((3a*S*,7a*R*)-3*a*,5-dimethyl-2-oxo-3,3*a*,4,5-tetrahydrobenzofuran-7*a*(2*H*)-yl)acrylate



Compound 4h

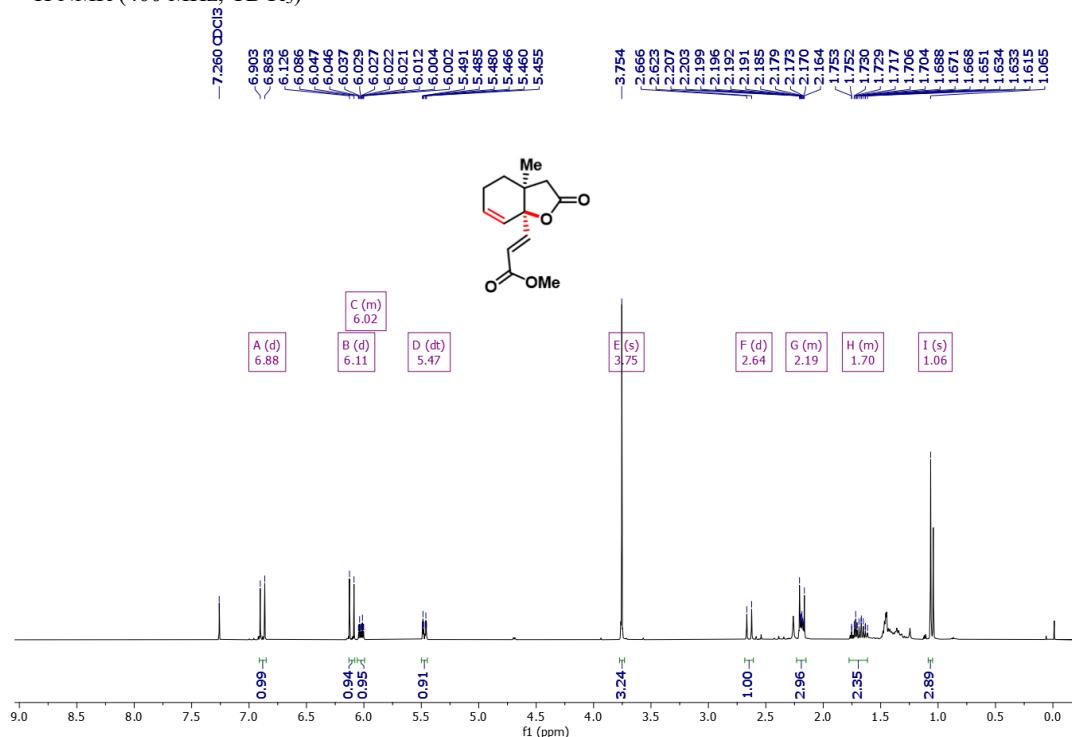
Ethyl (E)-3-((3a*S*,7a*R*)-3a-isobutyl-5-methyl-2-oxo-3,3a,4,5-tetrahydrobenzofuran-7a(2H-yl)acrylate



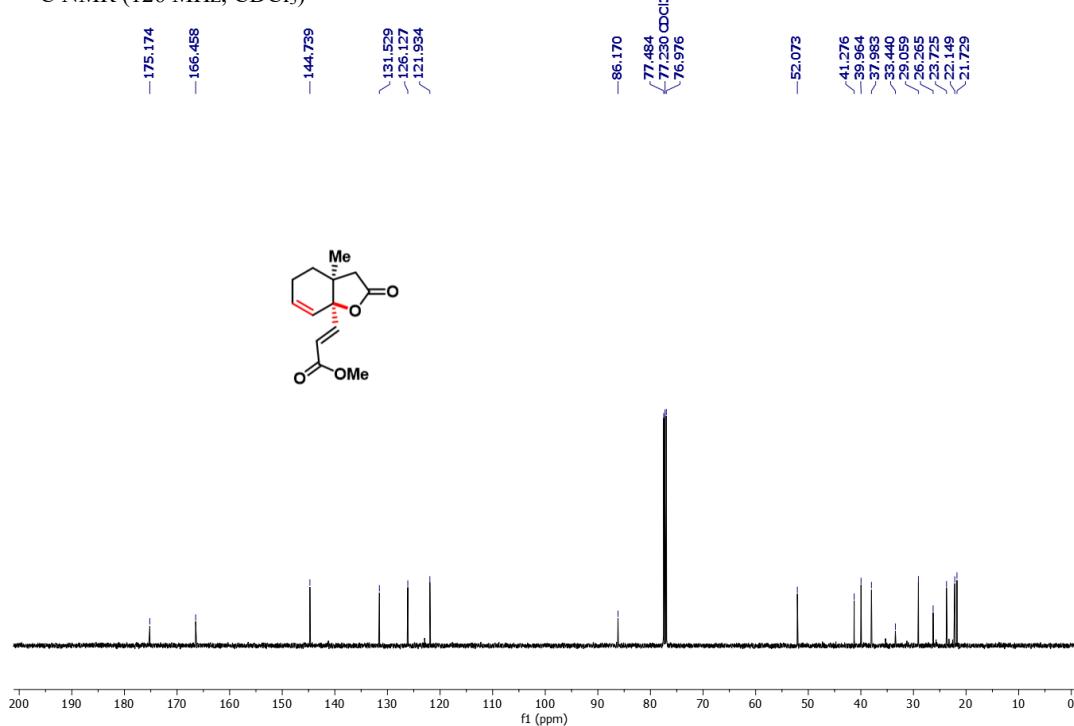
Compound 4i

Methyl (E)-3-((3a*S*,7a*R*)-3a-methyl-2-oxo-3,3a,4,5-tetrahydrobenzofuran-7a(2H)-yl)acrylate

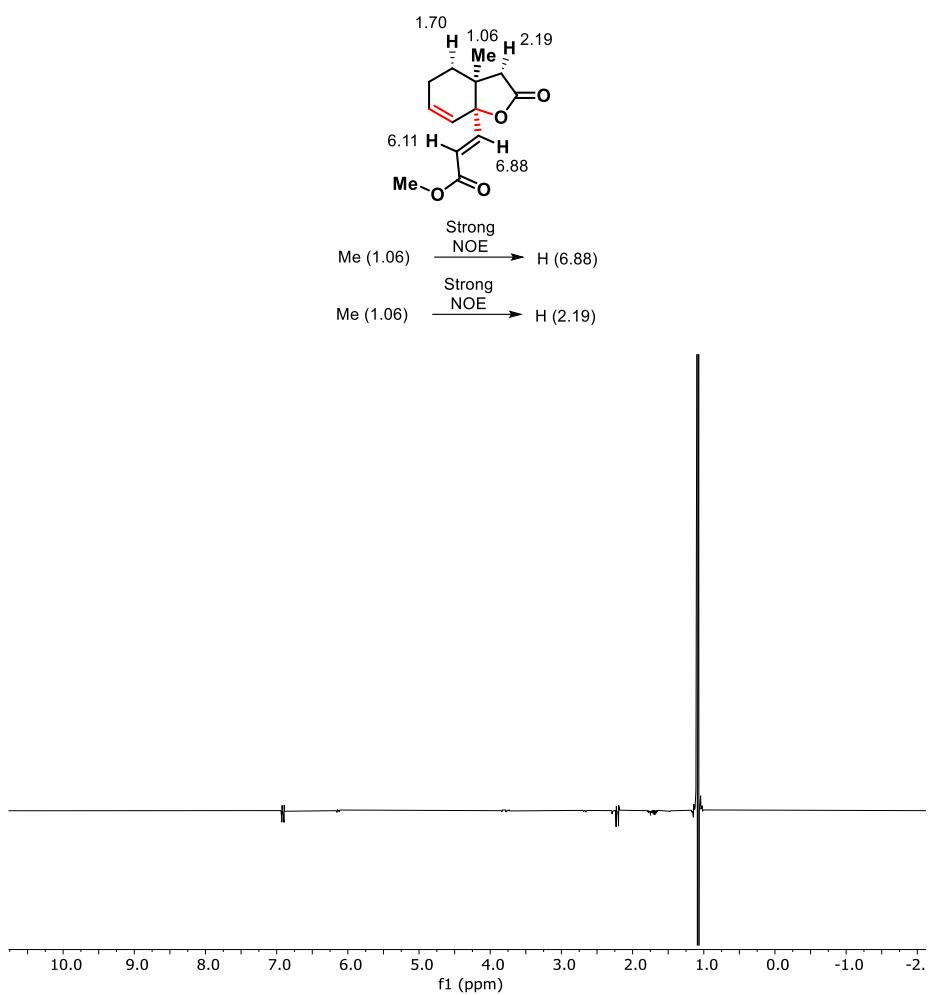
¹H NMR (400 MHz, CDCl₃)



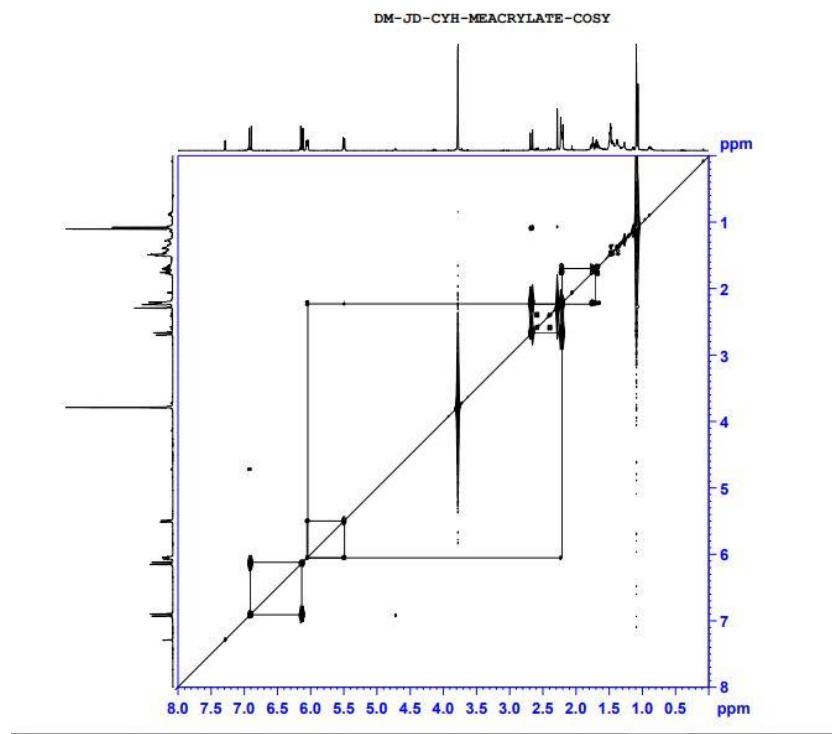
¹³C NMR (126 MHz, CDCl₃)



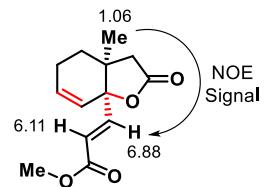
NOE Experiment:

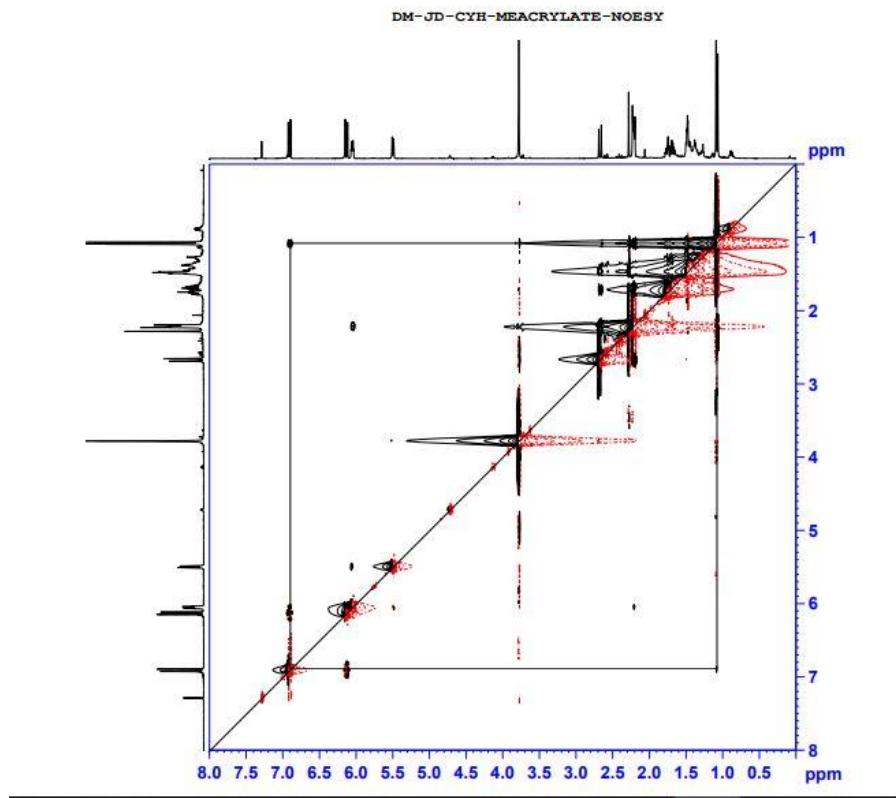


COSY Experiment:



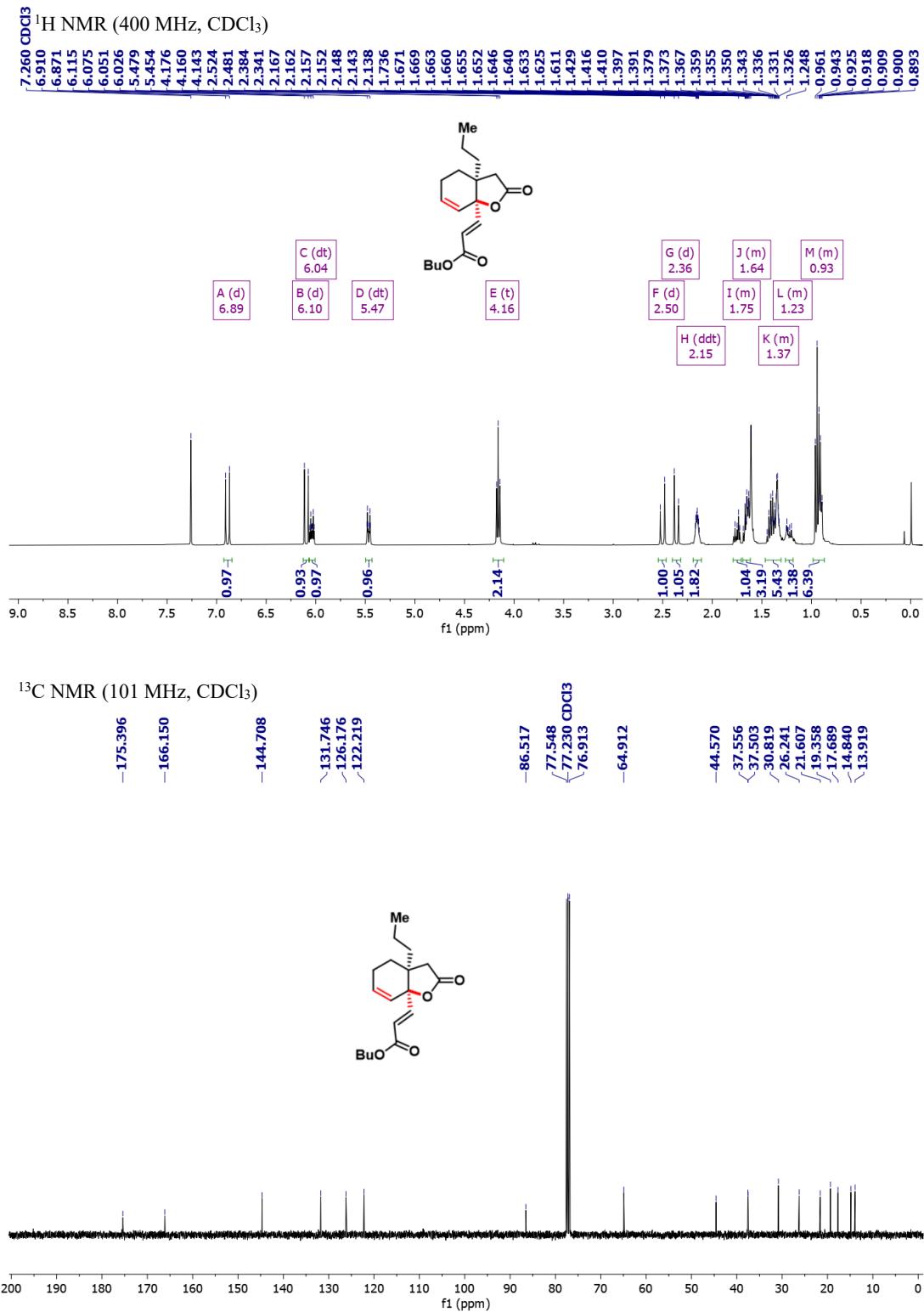
NOESY Experiment:





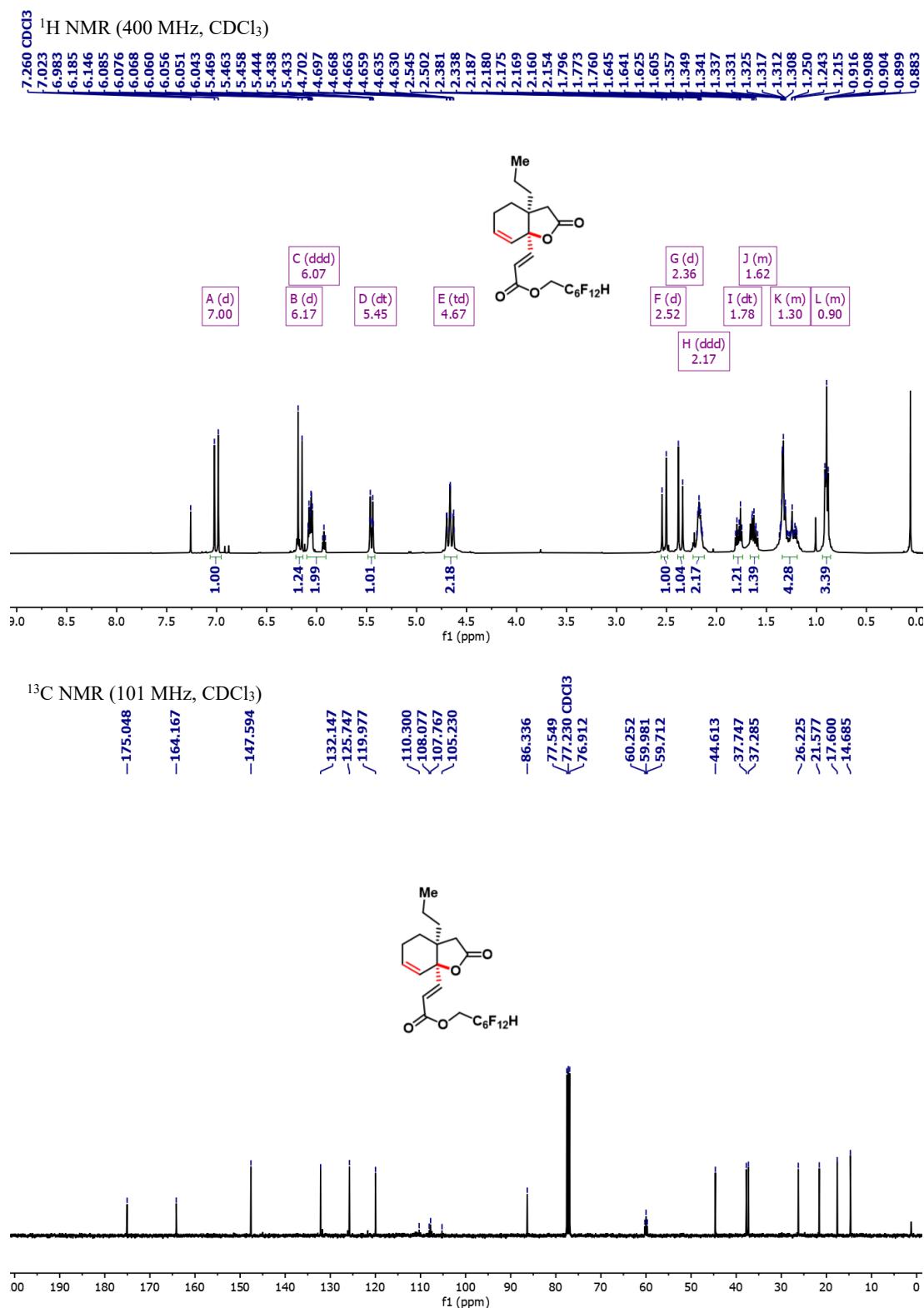
Compound 4j

Butyl (E)-3-((3a*S*,7a*R*)-2-oxo-3*a*-propyl-3,3*a*,4,5-tetrahydrobenzofuran-7*a*(2*H*)-yl)acrylate

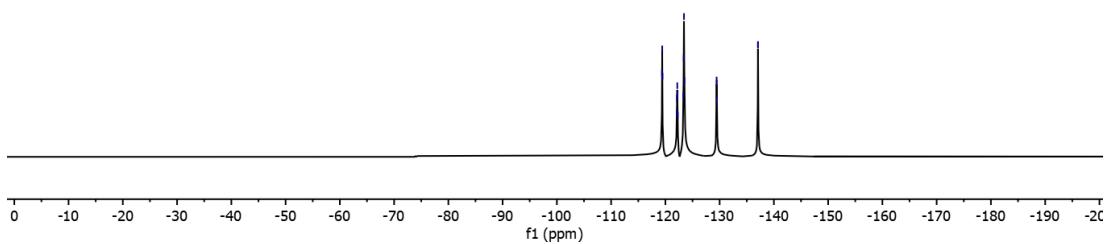


Compound 4k

7-(12-Fluoranyl)-7,7,7,7,7,7,7,7,7,7-undecafluoro-7l15-hepta-2,4,6-triyn-1-yl (*E*)-3-((3a*S*,7a*R*)-2-oxo-3a-propyl-3,3a,4,5-tetrahydrobenzofuran-7a(2H)-yl)acrylate



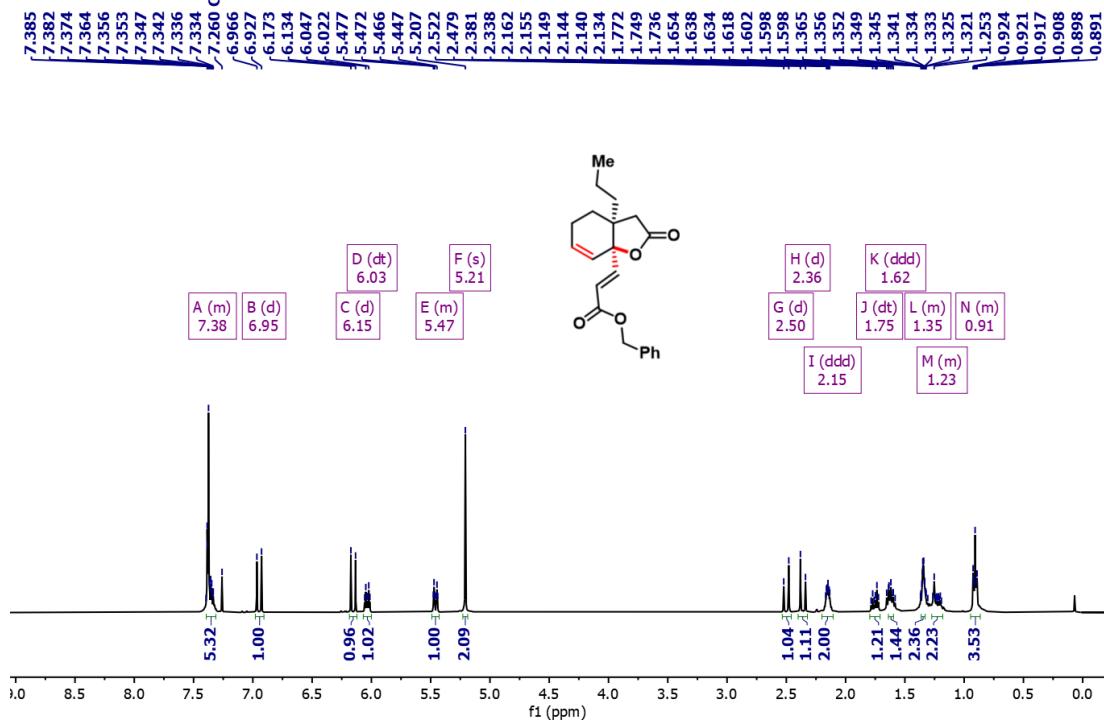
¹⁹F NMR (376 MHz, CDCl₃)



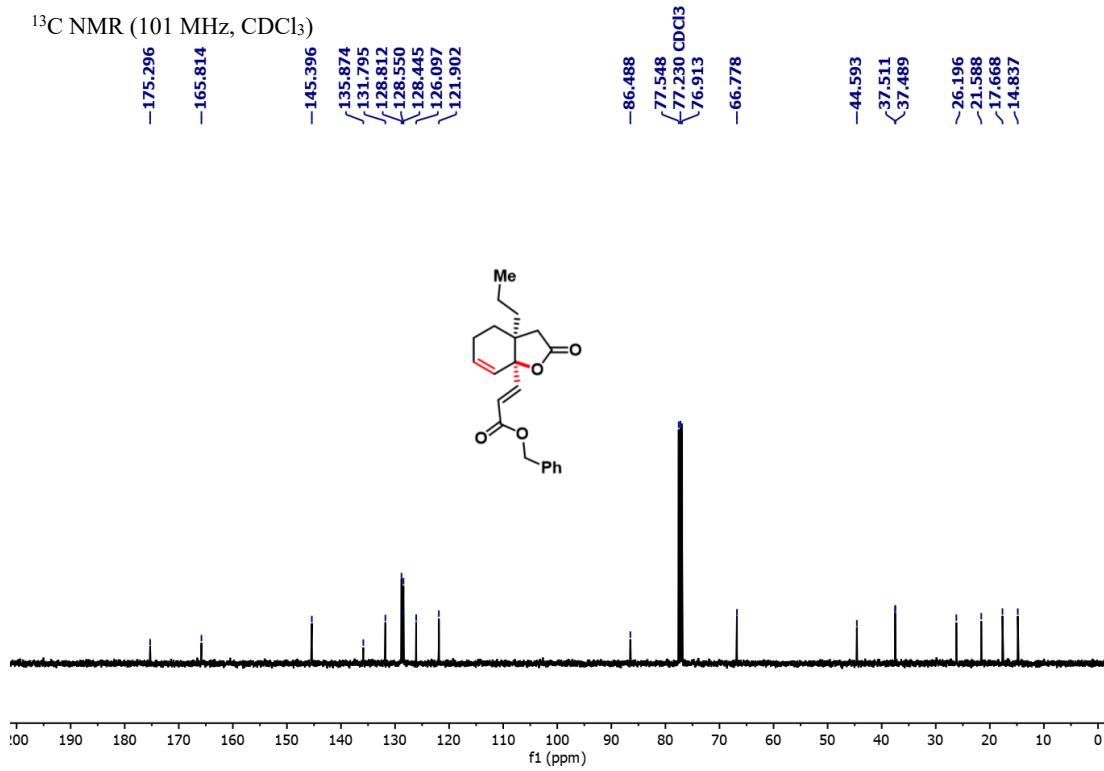
Compound 4l

Benzyl (E)-3-((3a*S*,7a*R*)-2-oxo-3*a*-propyl-3,3*a*,4,5-tetrahydrobenzofuran-7*a*(2*H*)-yl)acrylate

¹H NMR (400 MHz, CDCl₃)



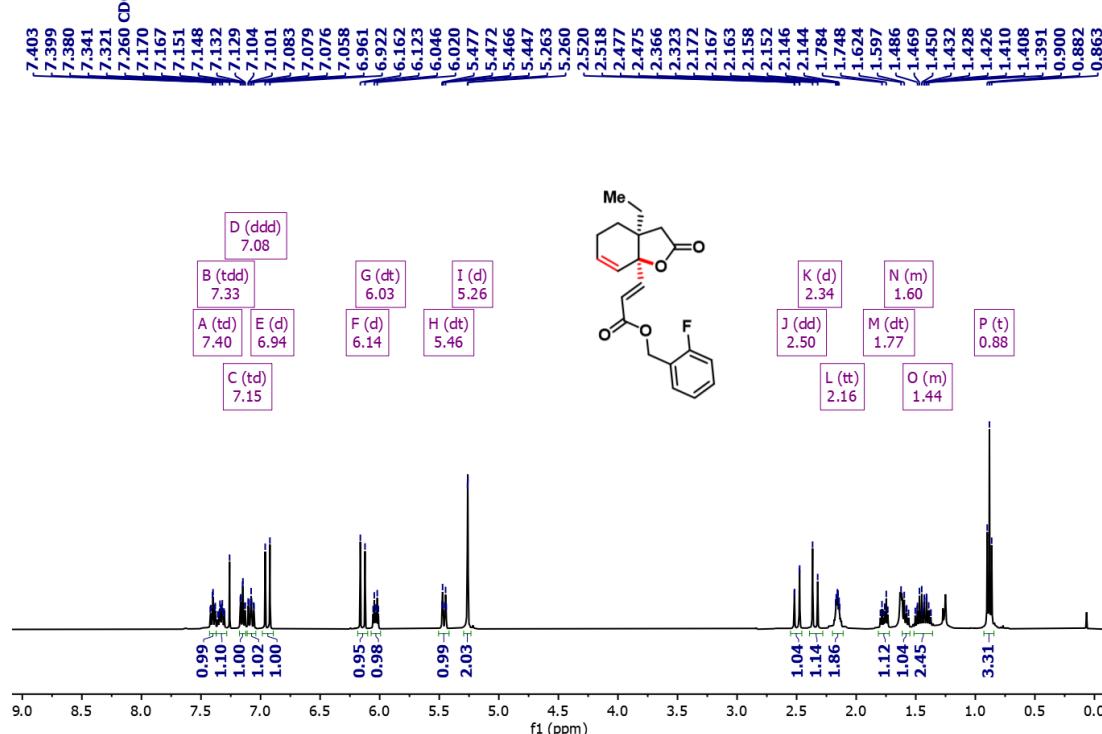
¹³C NMR (101 MHz, CDCl₃)



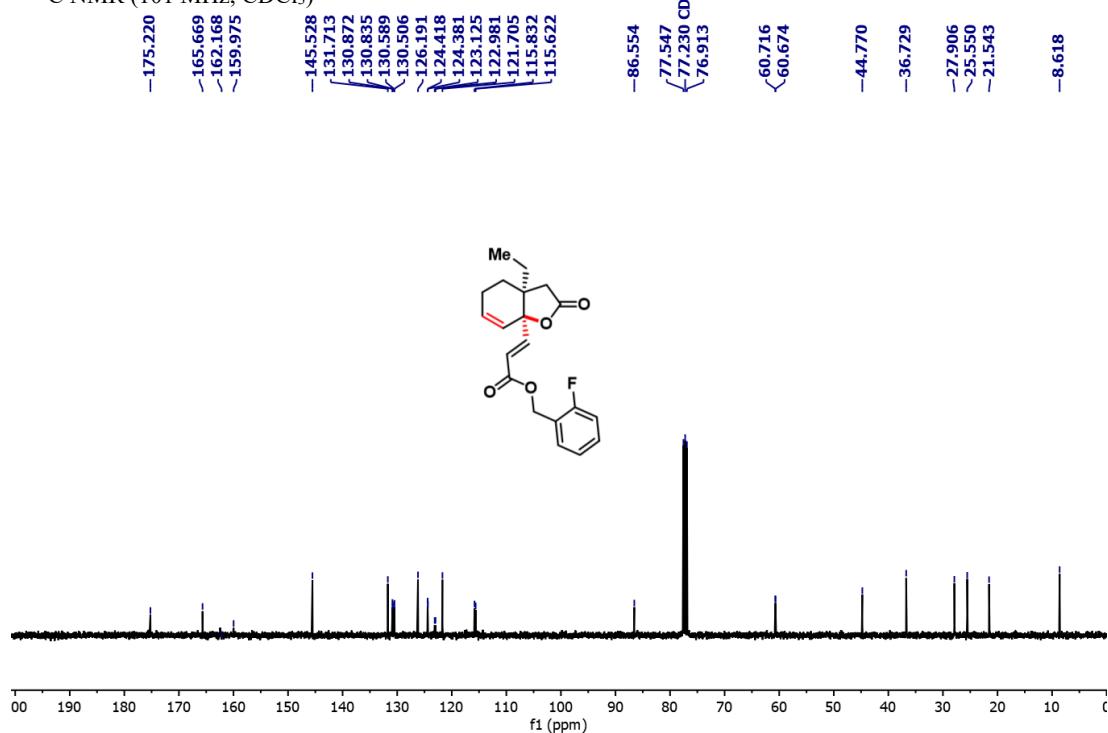
Compound 4m

2-Fluorobenzyl (*E*)-3-((3a*S*,7a*R*)-3a-ethyl-2-oxo-3,3a,4,5-tetrahydrobenzofuran-7a(2H)-yl)acrylate

¹H NMR (400 MHz, CDCl₃)

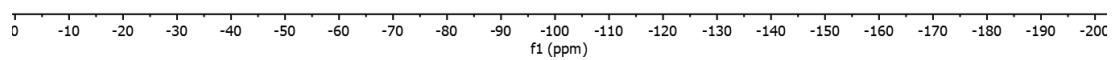
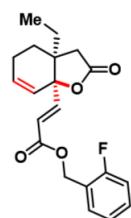


¹³C NMR (101 MHz, CDCl₃)



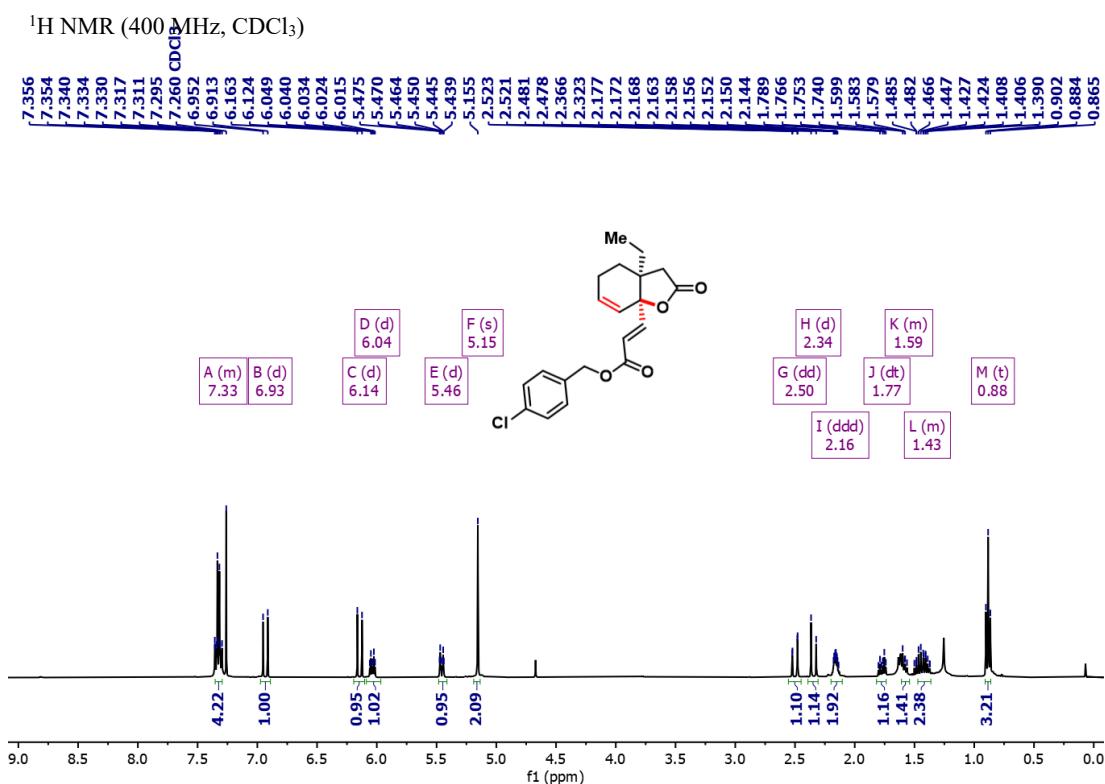
¹⁹F NMR (376 MHz, CDCl₃)

—117.898

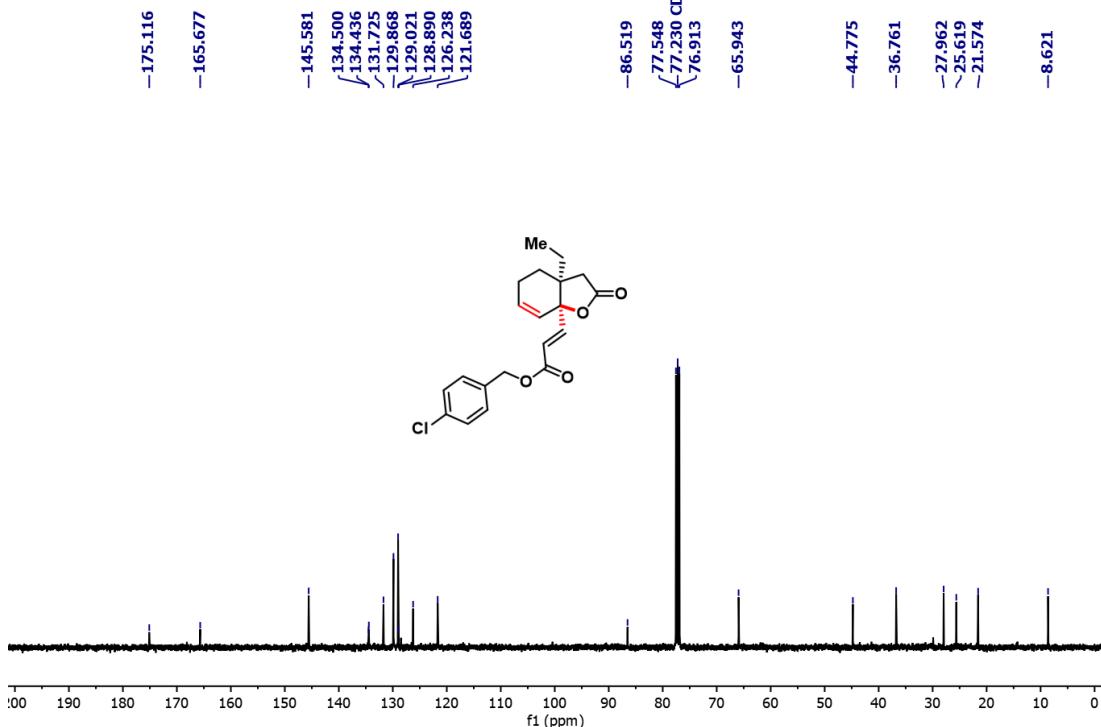


Compound 4n

4-Chlorobenzyl (*E*)-3-((3a*S*,7a*R*)-3a-ethyl-2-oxo-3,3a,4,5-tetrahydrobenzofuran-7a(2H)-yl)acrylate

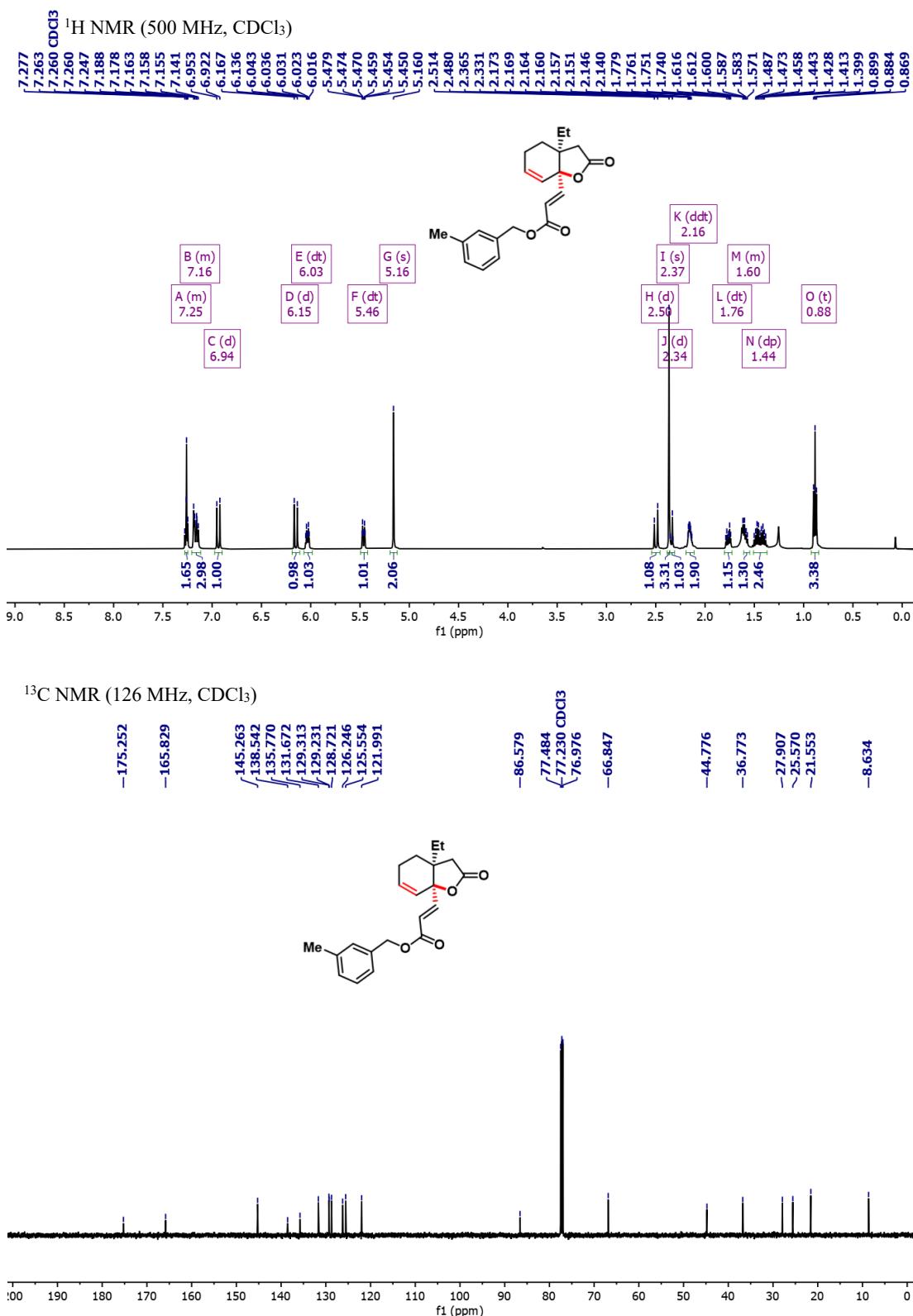


¹³C NMR (101 MHz, CDCl₃)

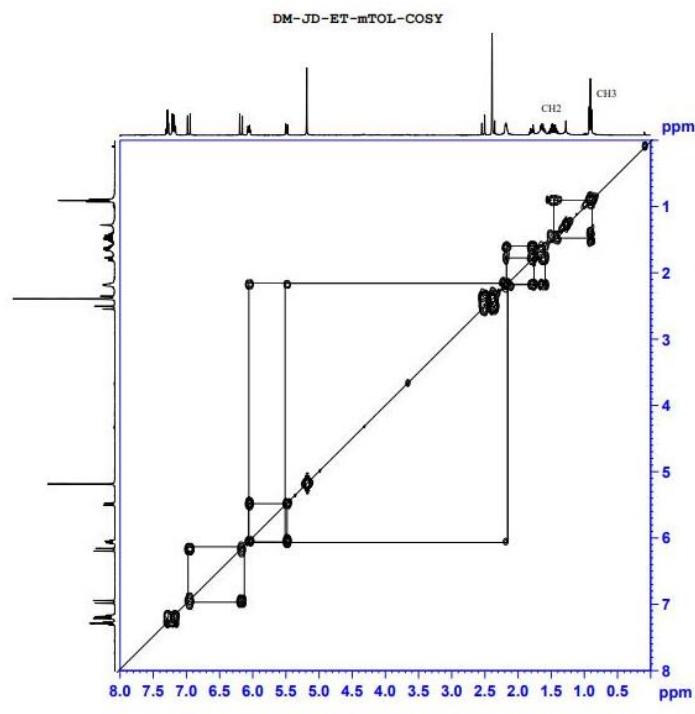


Compound 4o

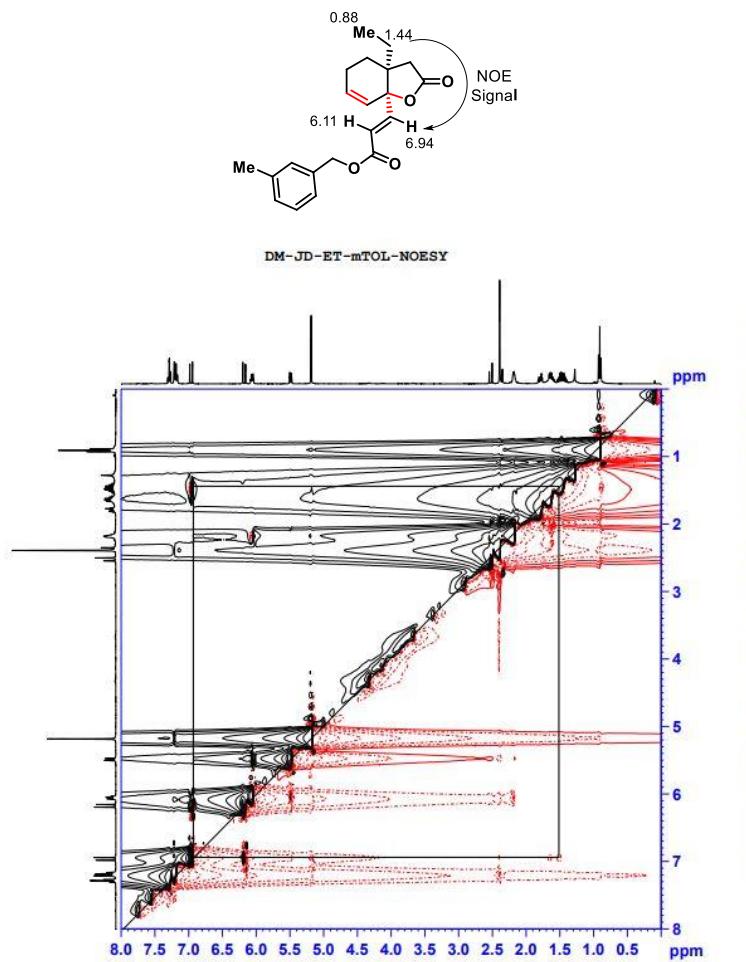
3-Methylbenzyl (*E*)-3-((3a*S*,7a*R*)-3a-ethyl-2-oxo-3,3a,4,5-tetrahydrobenzofuran-7a(2H)-yl)acrylate



COSY Experiment:

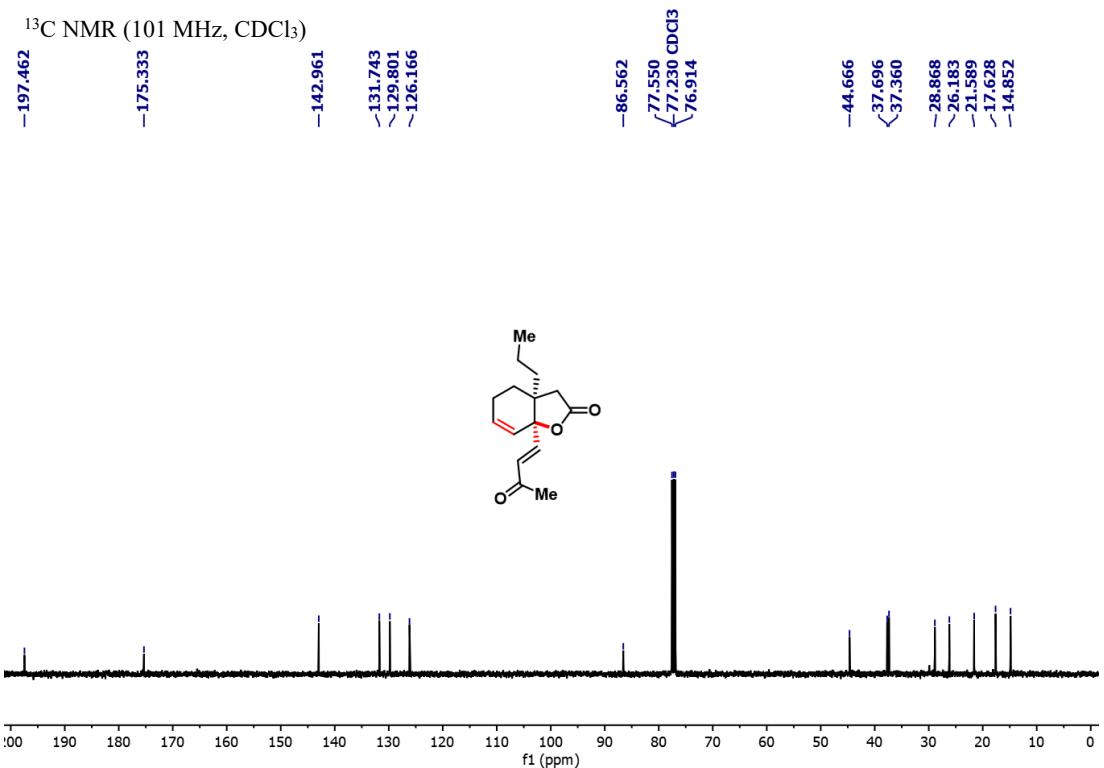
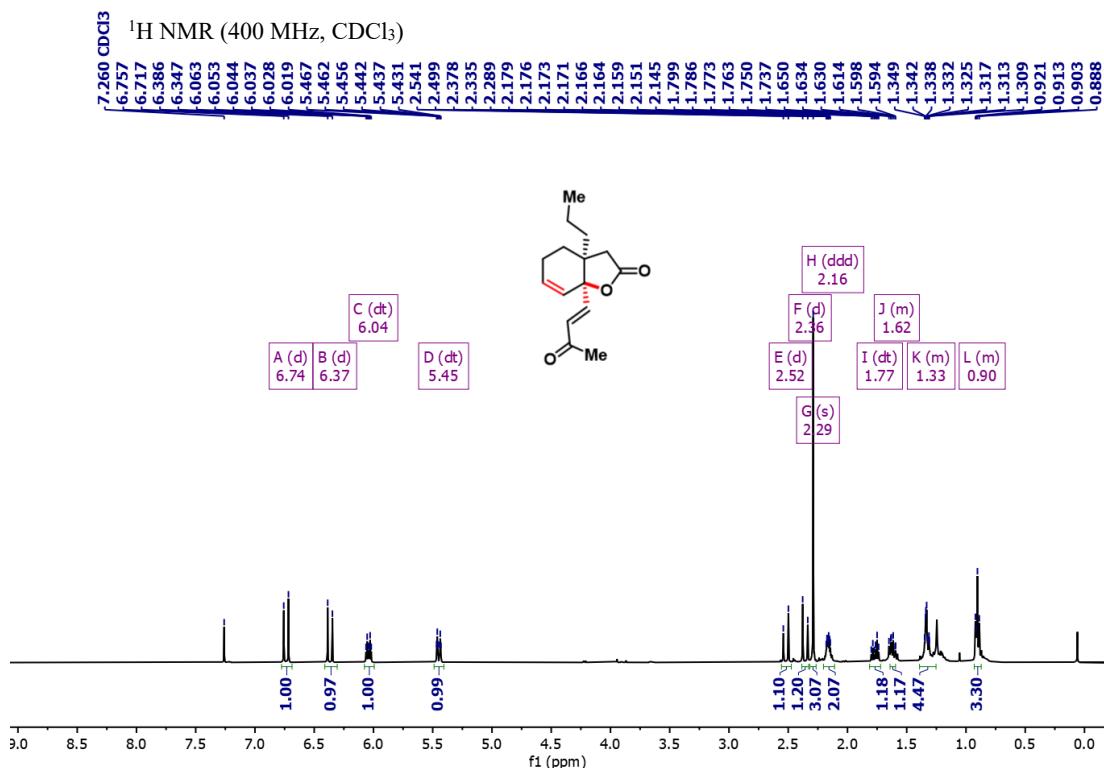


NOESY Experiment:



Compound 4p

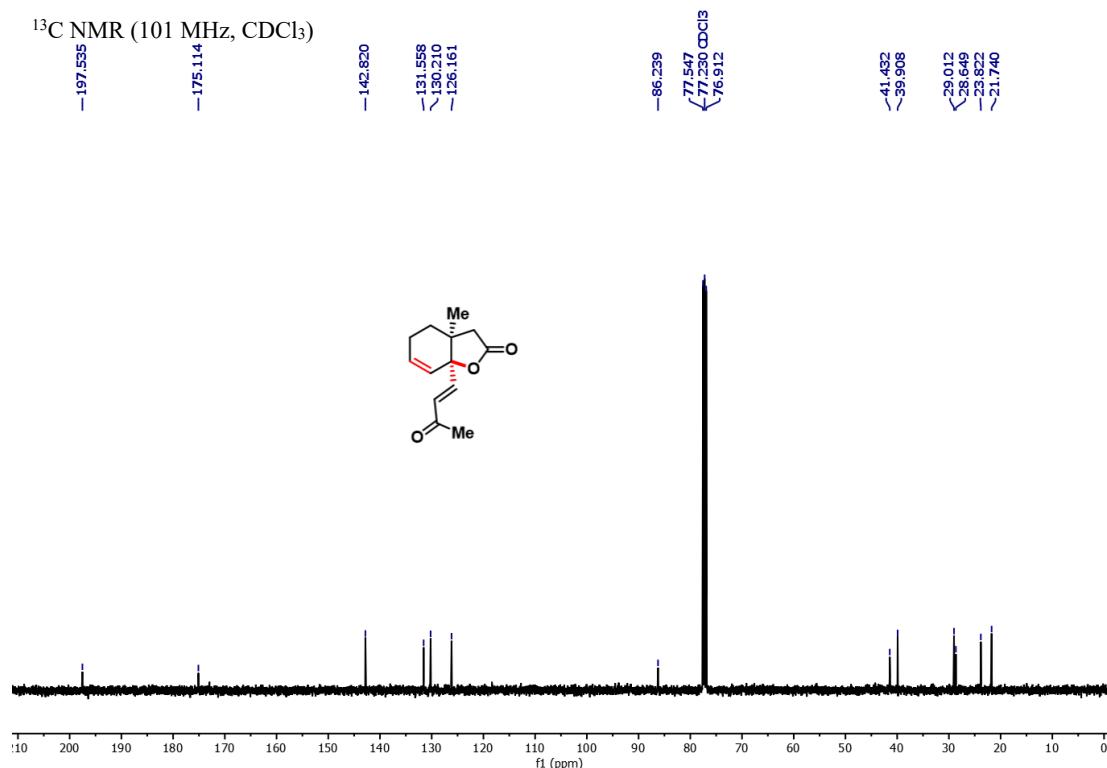
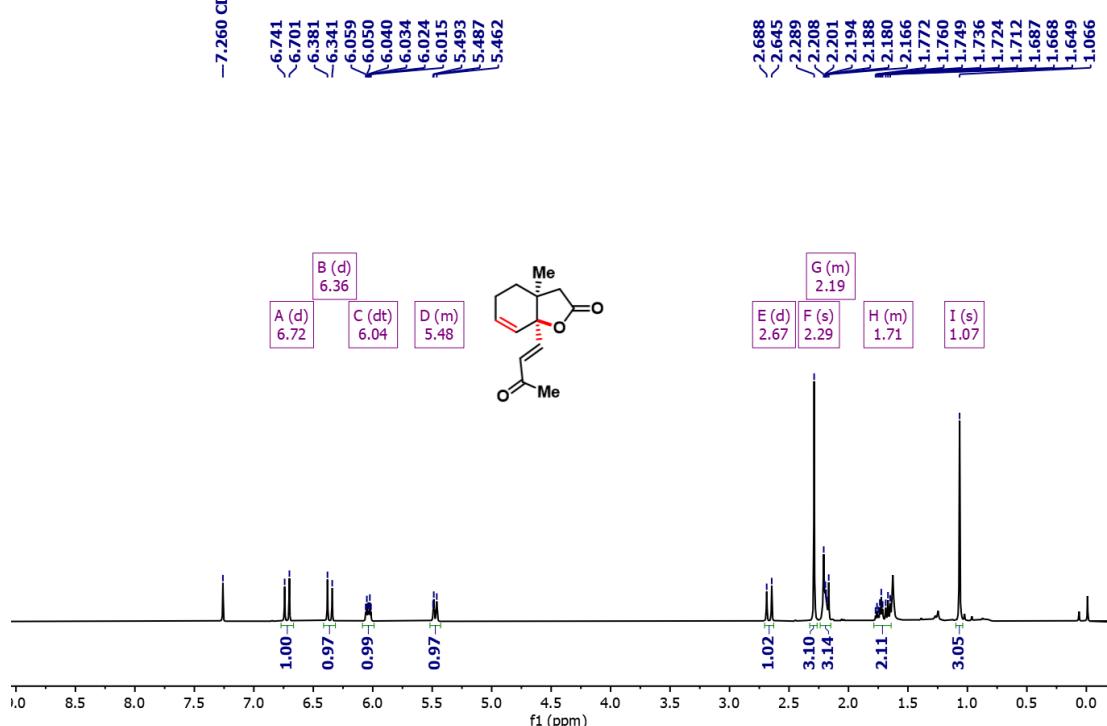
(3a*S*,7a*R*)-7a-((*E*)-3-Oxobut-1-en-1-yl)-3a-propyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one

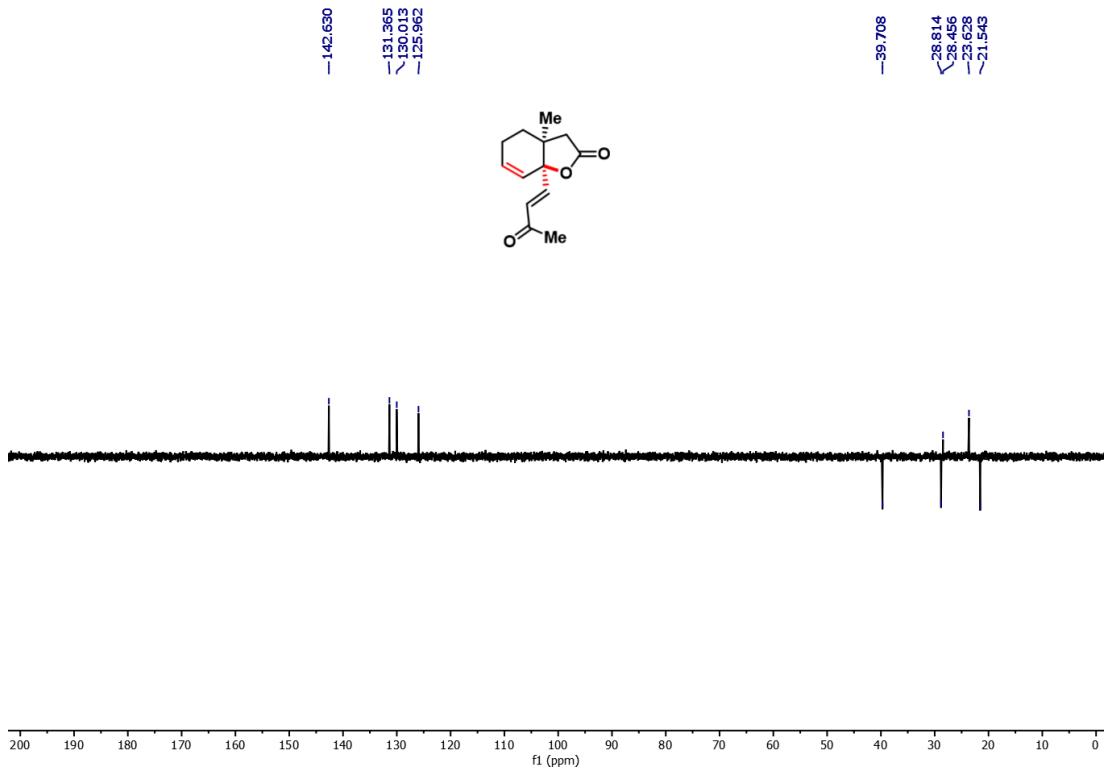


Compound 4q

(3a*S*,7a*R*)-3a-Methyl-7a-((*E*)-3-oxobut-1-en-1-yl)-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one

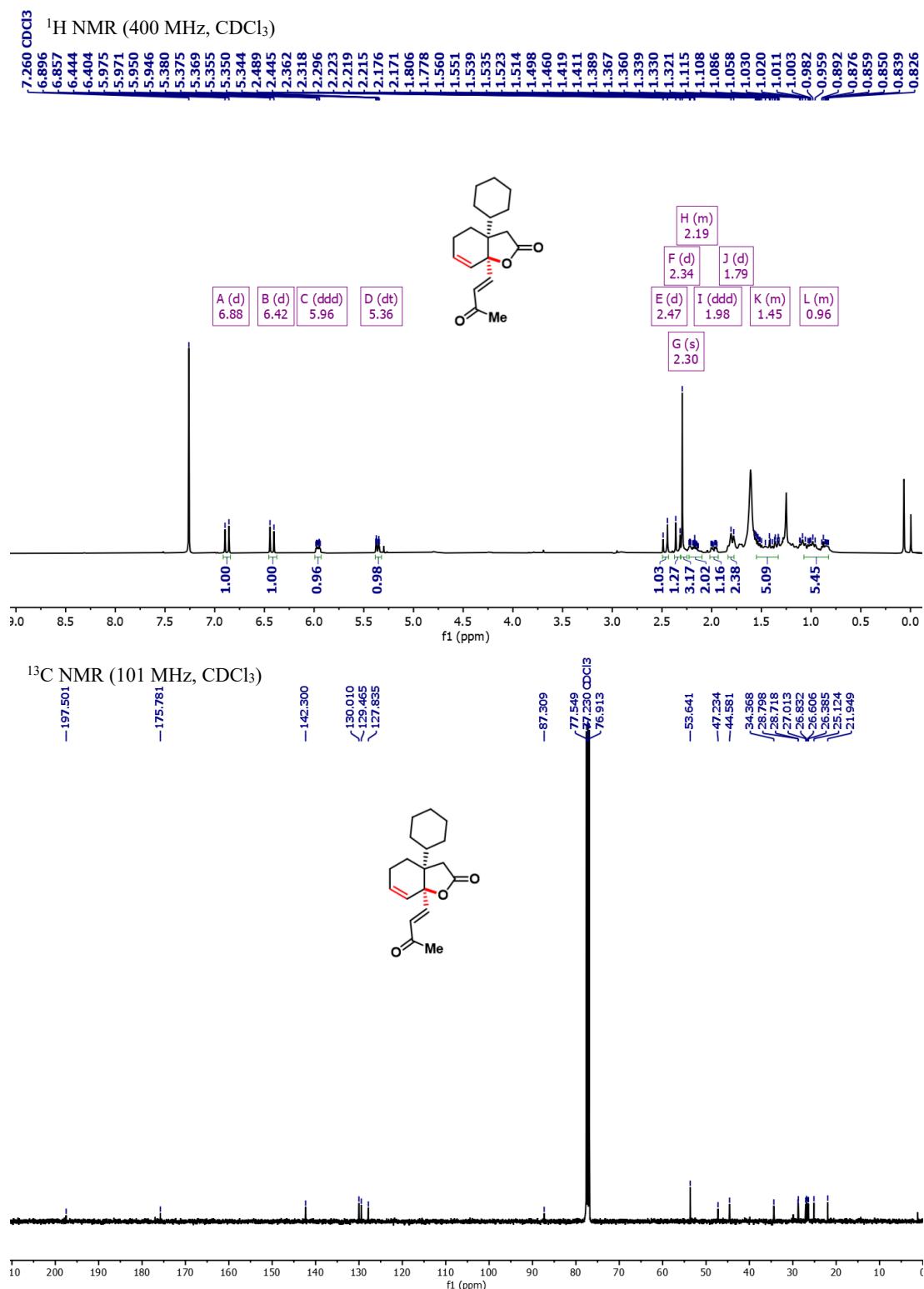
¹H NMR (400 MHz, CDCl₃)





Compound 4r

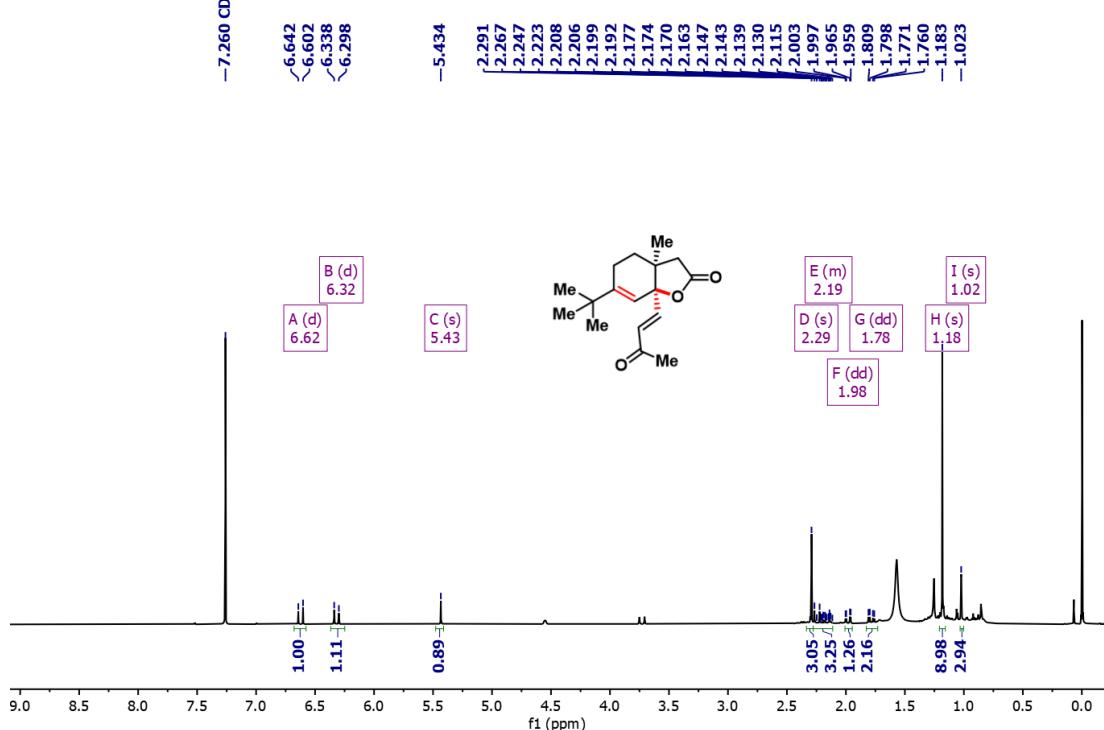
(3a*S*,7a*R*)-3a-Cyclohexyl-7a-((*E*)-3-oxobut-1-en-1-yl)-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one



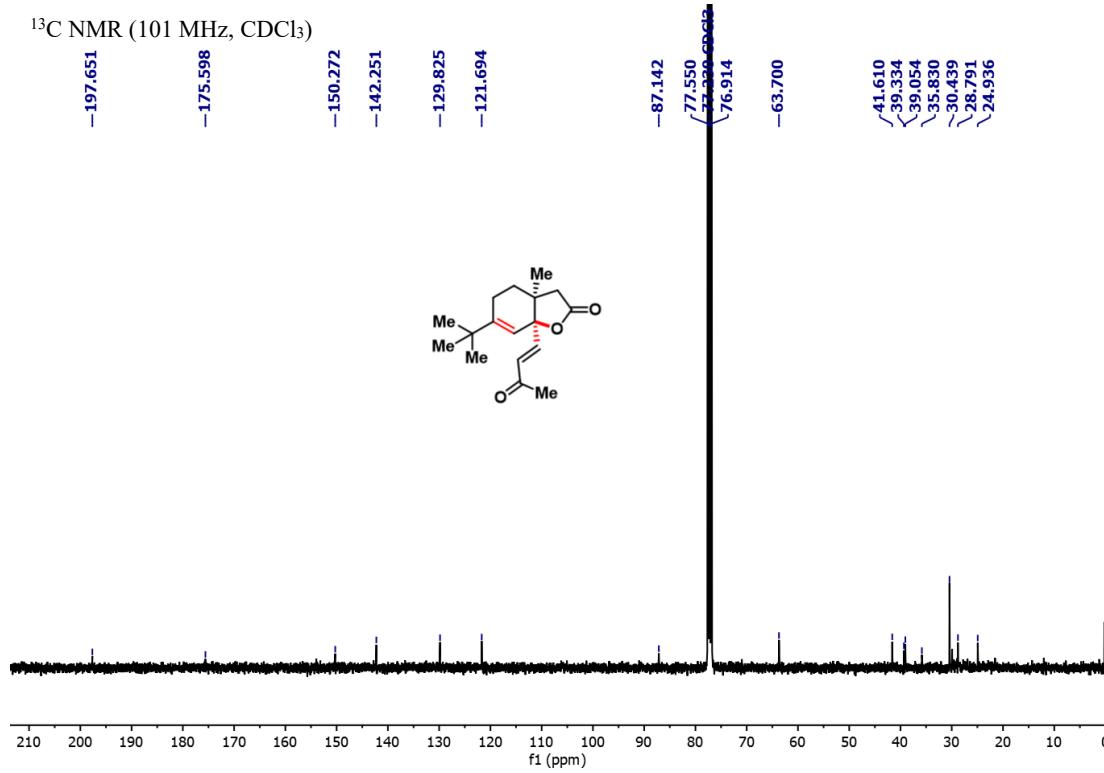
Compound 4s

(3a*S*,7a*S*)-6-(*tert*-Butyl)-3a-methyl-7a-((*E*)-3-oxobut-1-en-1-yl)-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one

¹H NMR (400 MHz, CDCl₃)

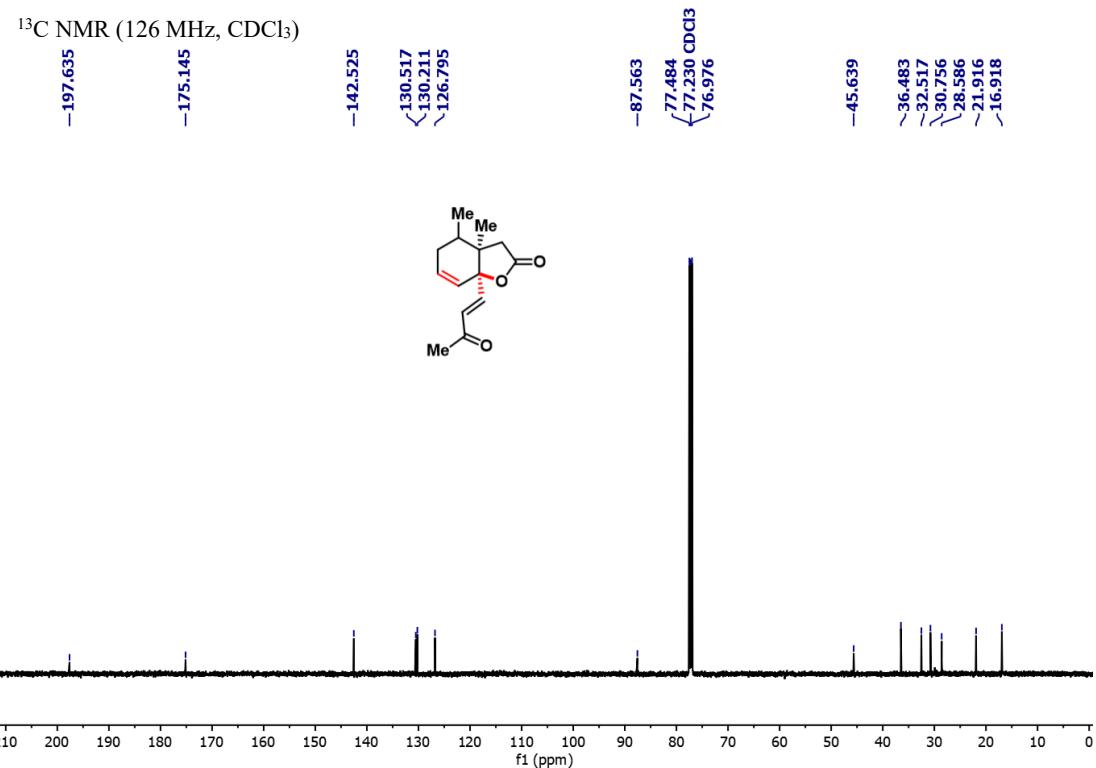
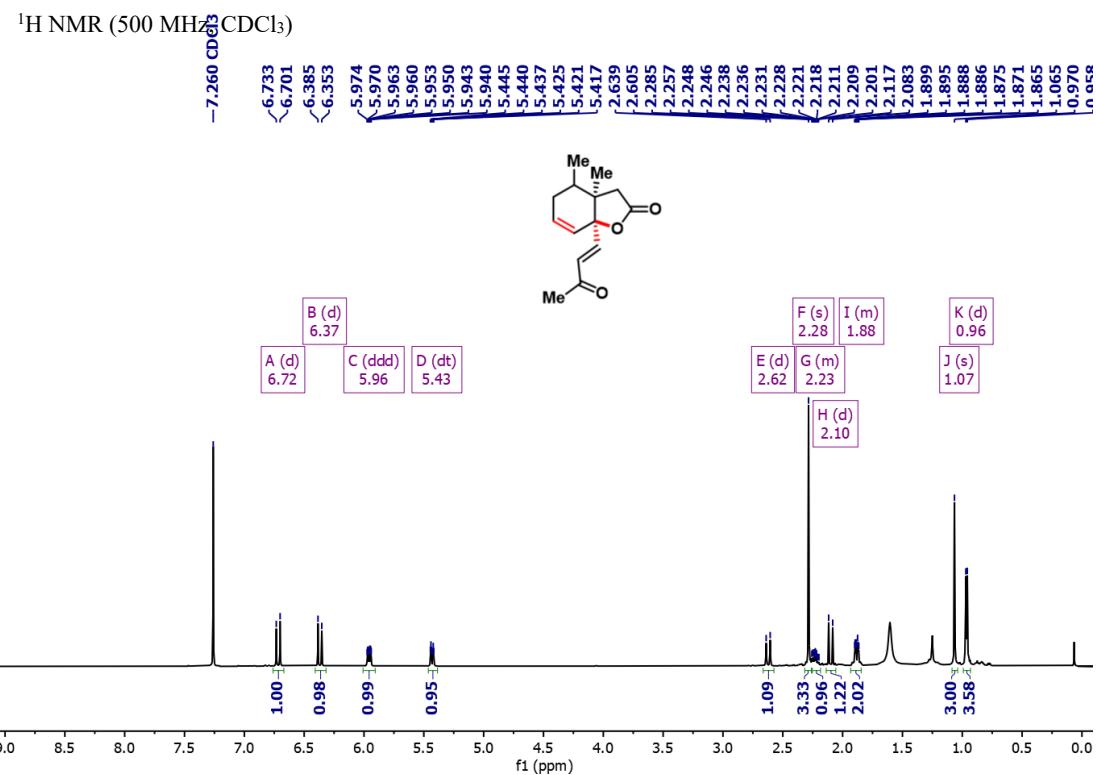


¹³C NMR (101 MHz, CDCl₃)

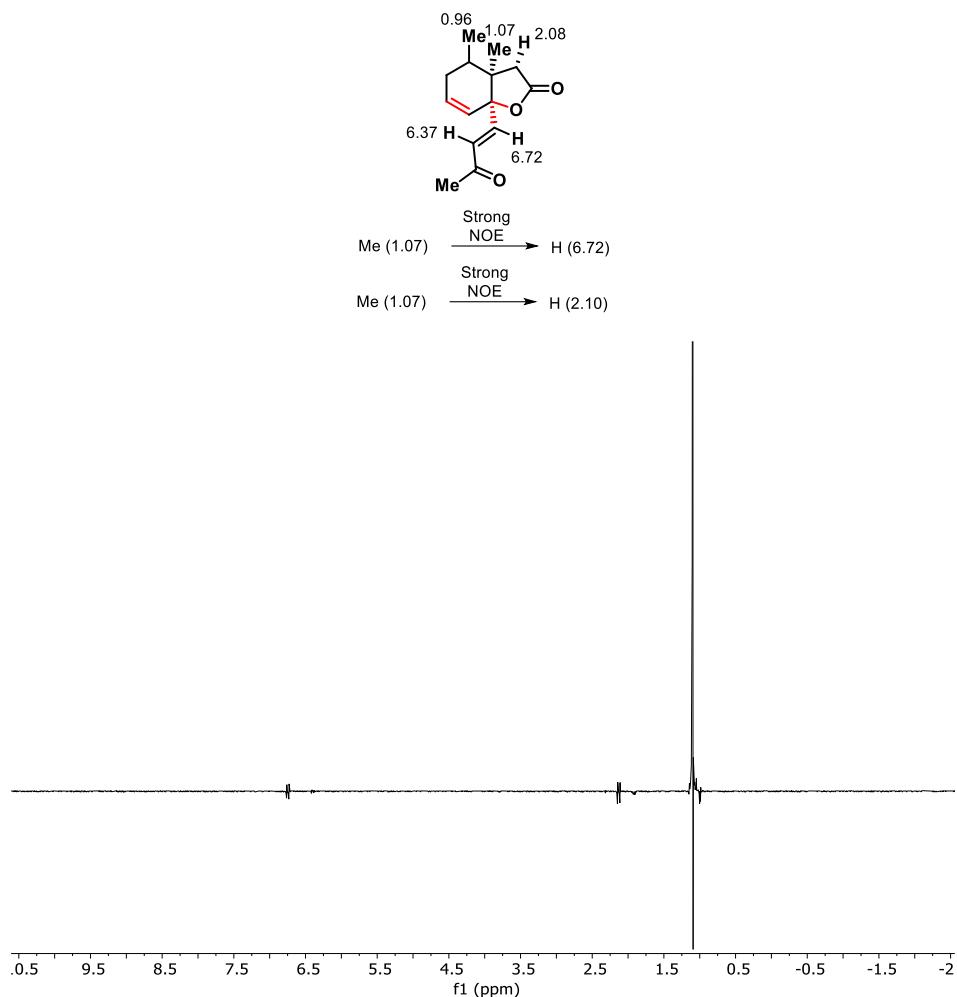


Compound 4t

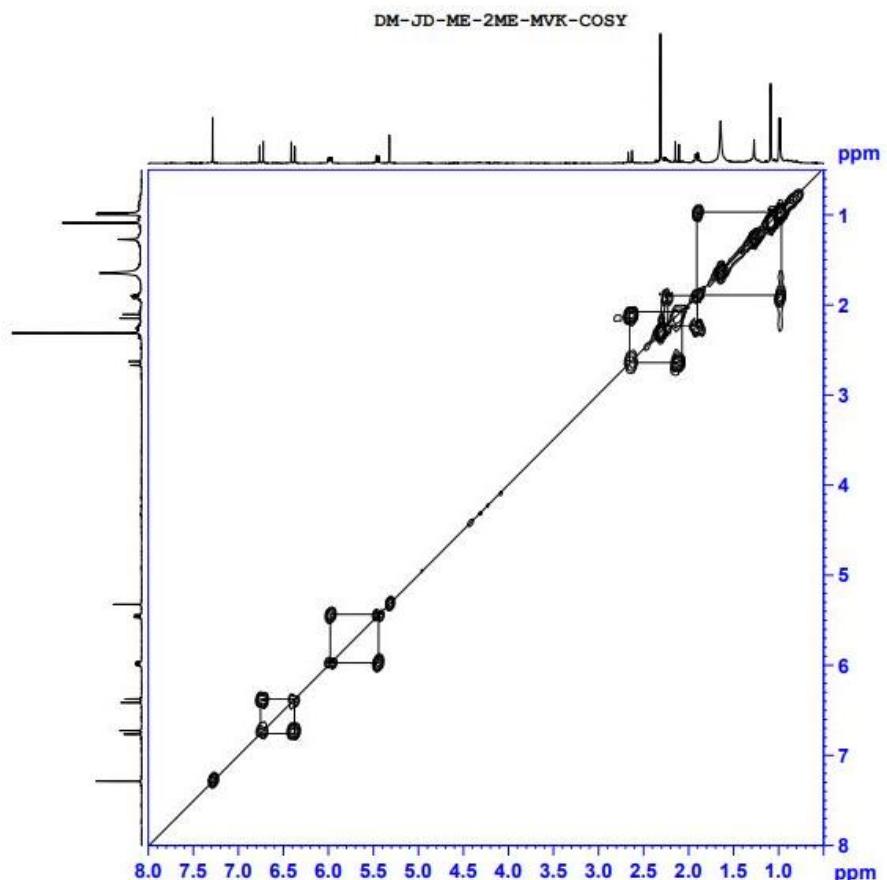
(3a*R*,7a*R*)-3a,4-Dimethyl-7a-((*E*)-3-oxobut-1-en-1-yl)-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one



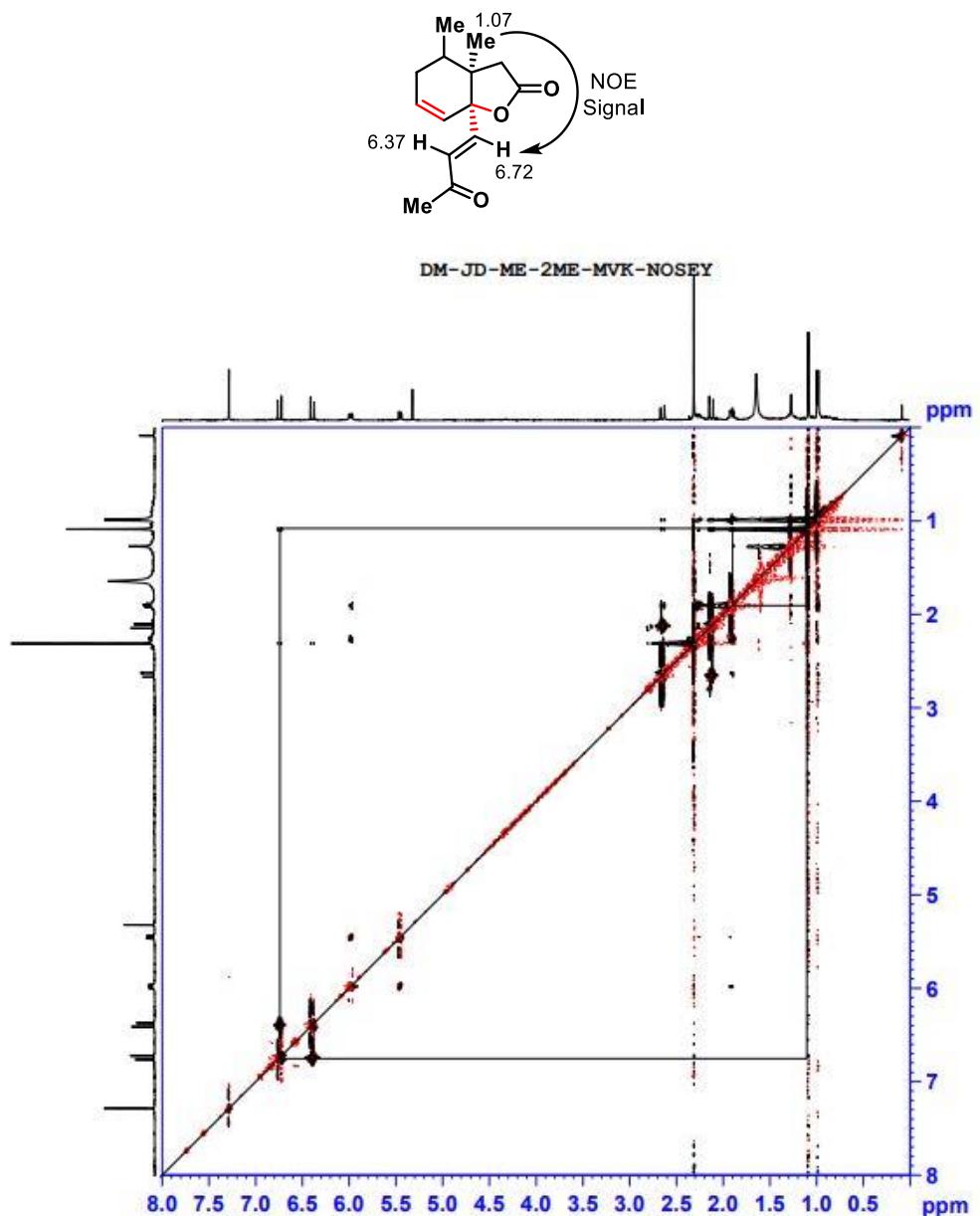
NOE Experiment:



COSY Experiment:

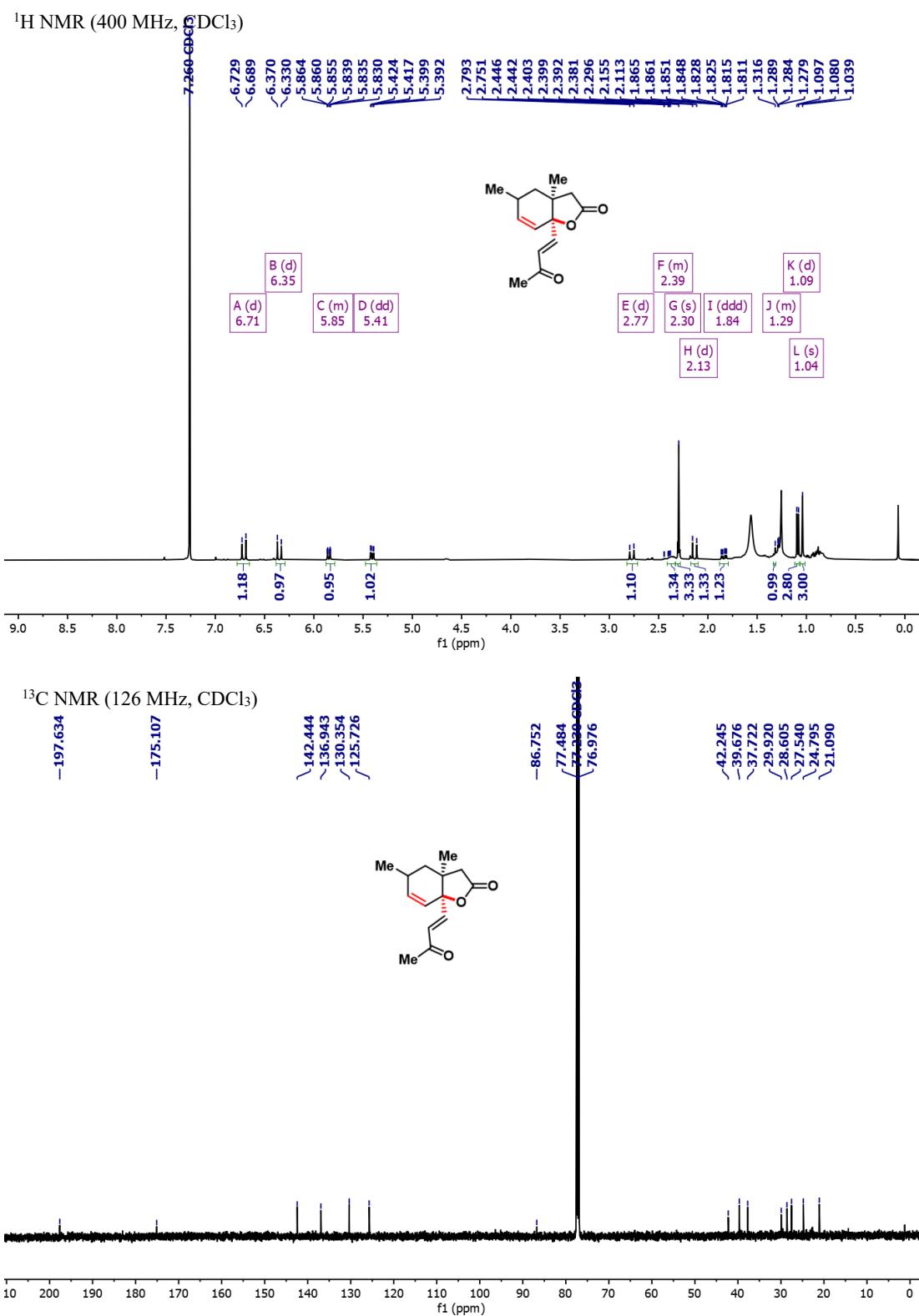


NOESY Experiment:



Compound 4u

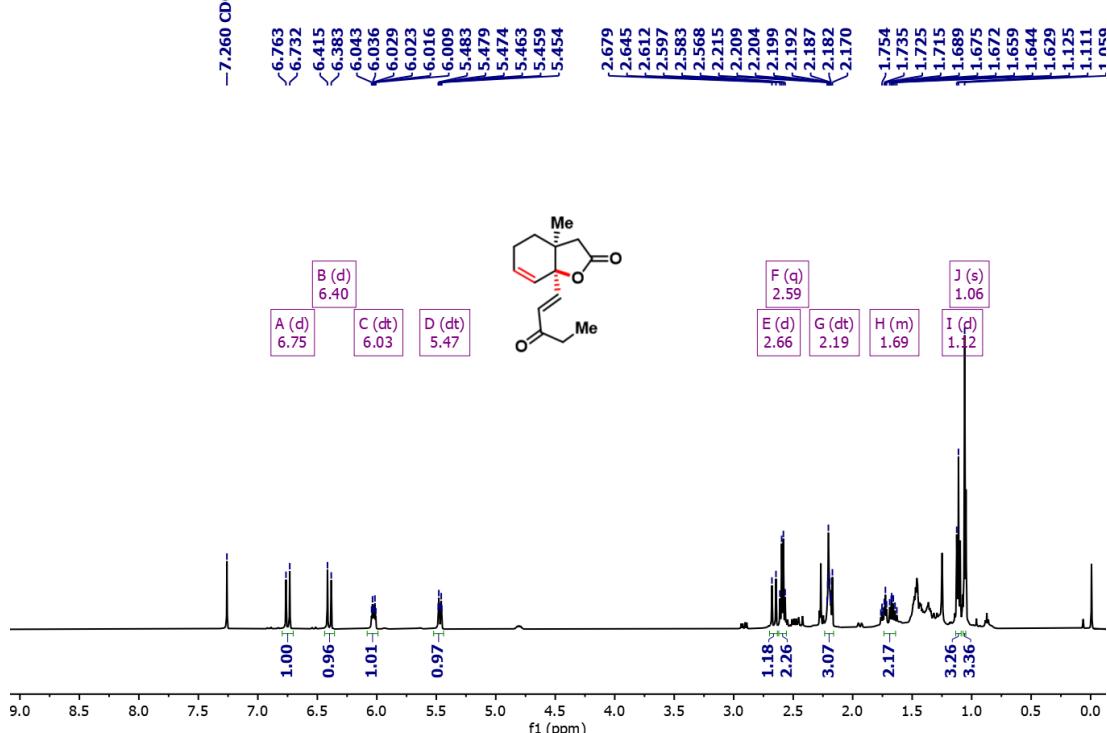
(3a*S*,7a*R*)-3a,5-Dimethyl-7a-((*E*)-3-oxobut-1-en-1-yl)-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one



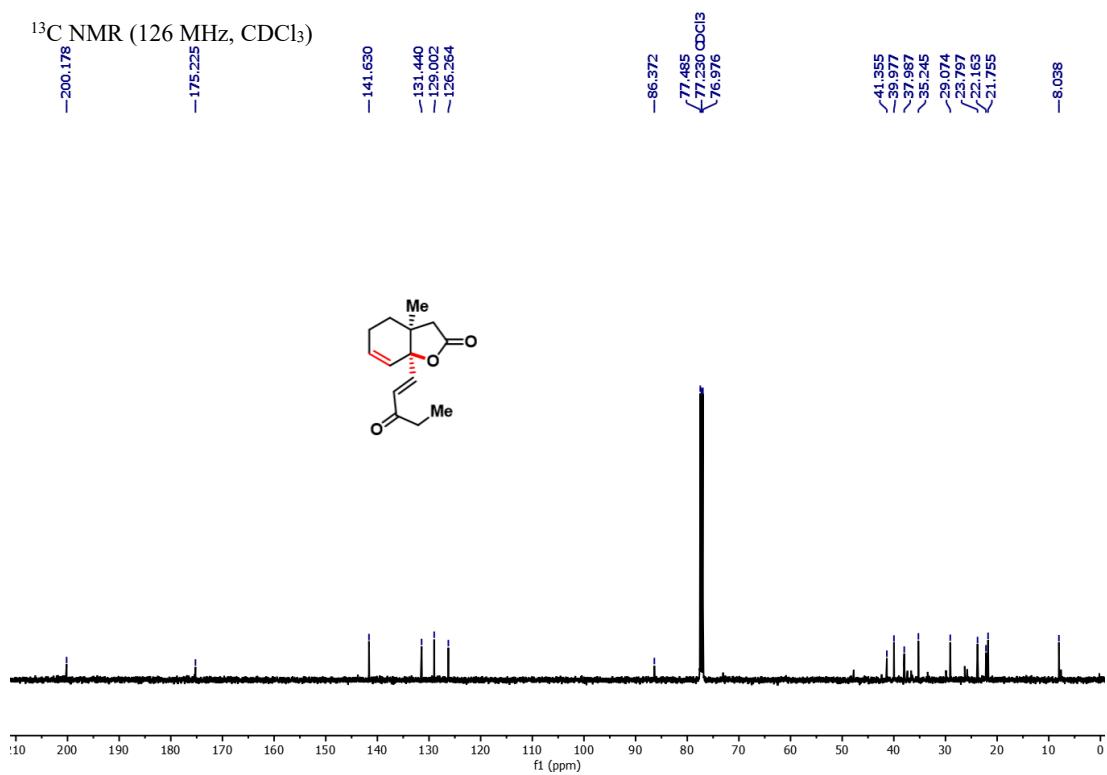
Compound 4v

(3a*S*,7a*R*)-3a-Methyl-7a-((*E*)-3-oxopent-1-en-1-yl)-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one

¹H NMR (500 MHz, CDCl₃)

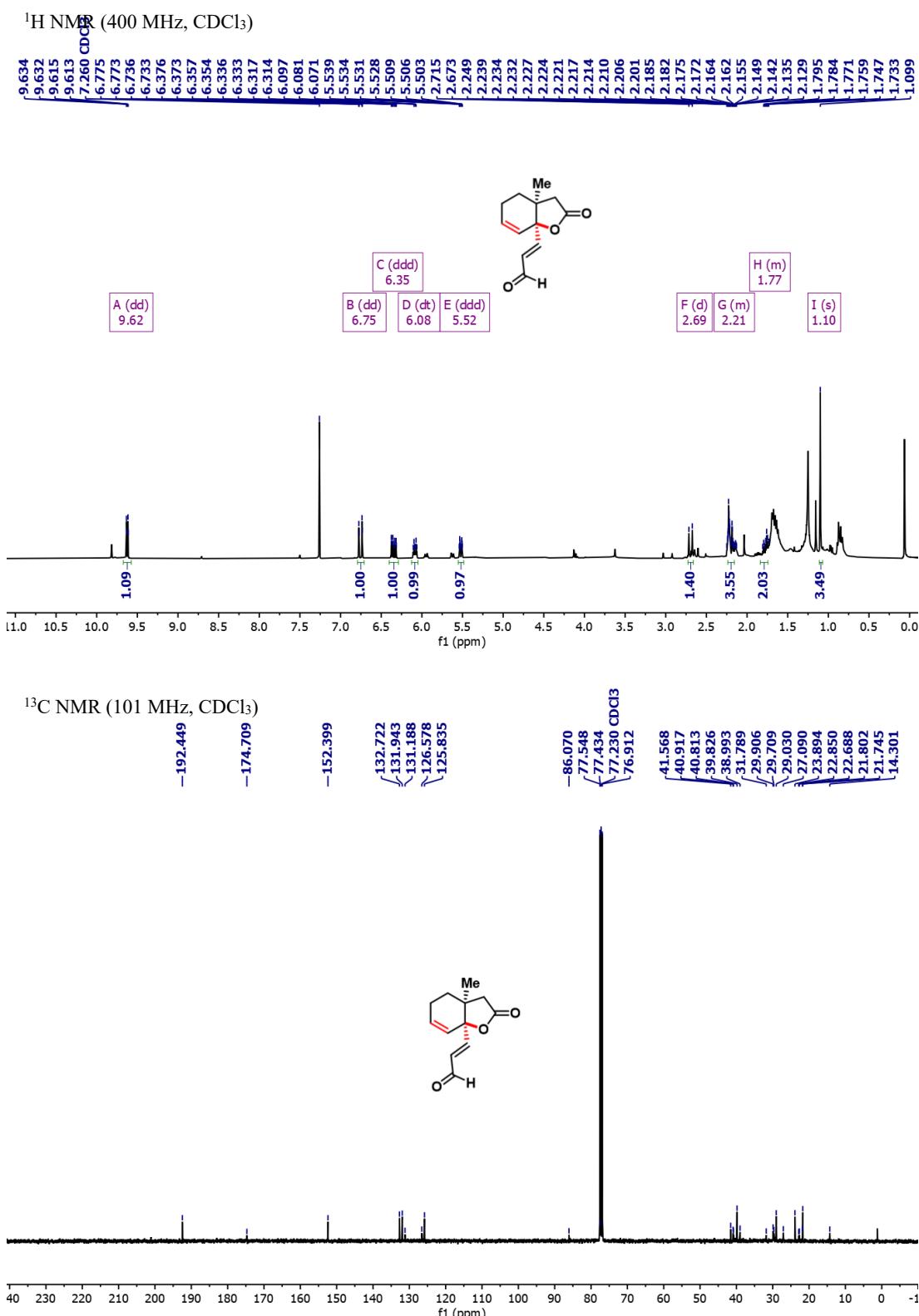


¹³C NMR (126 MHz, CDCl₃)



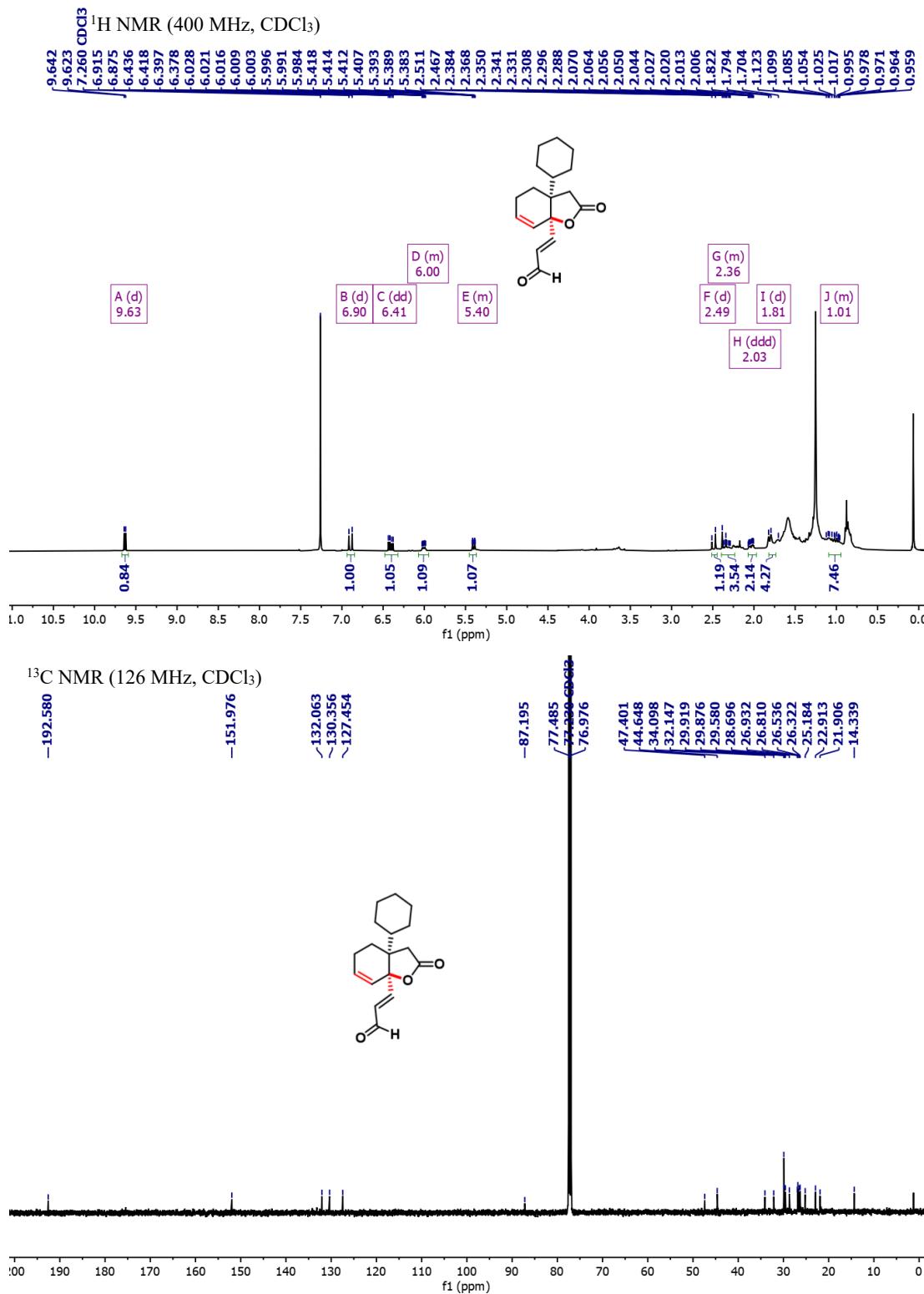
Compound 4w

*(E)-3-((3a*S*,7a*R*)-3a-Methyl-2-oxo-3,3a,4,5-tetrahydrobenzofuran-7a(2H)-yl)acrylaldehyde*



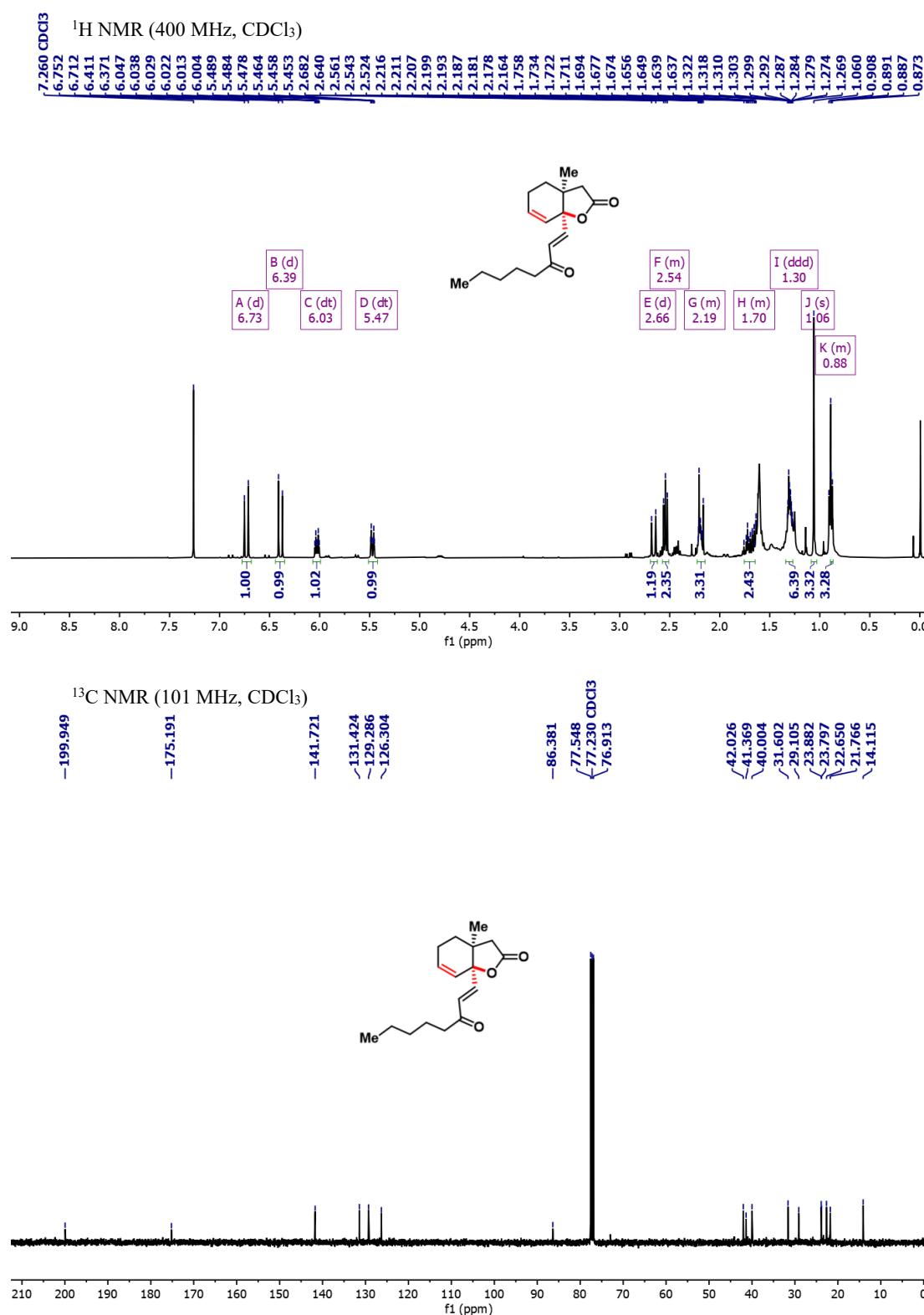
Compound 4x

(E)-3-((3a*S*,7a*R*)-3*a*-Cyclohexyl-2-oxo-3,3*a*,4,5-tetrahydrobenzofuran-7*a*(2*H*)-yl)acrylaldehyde



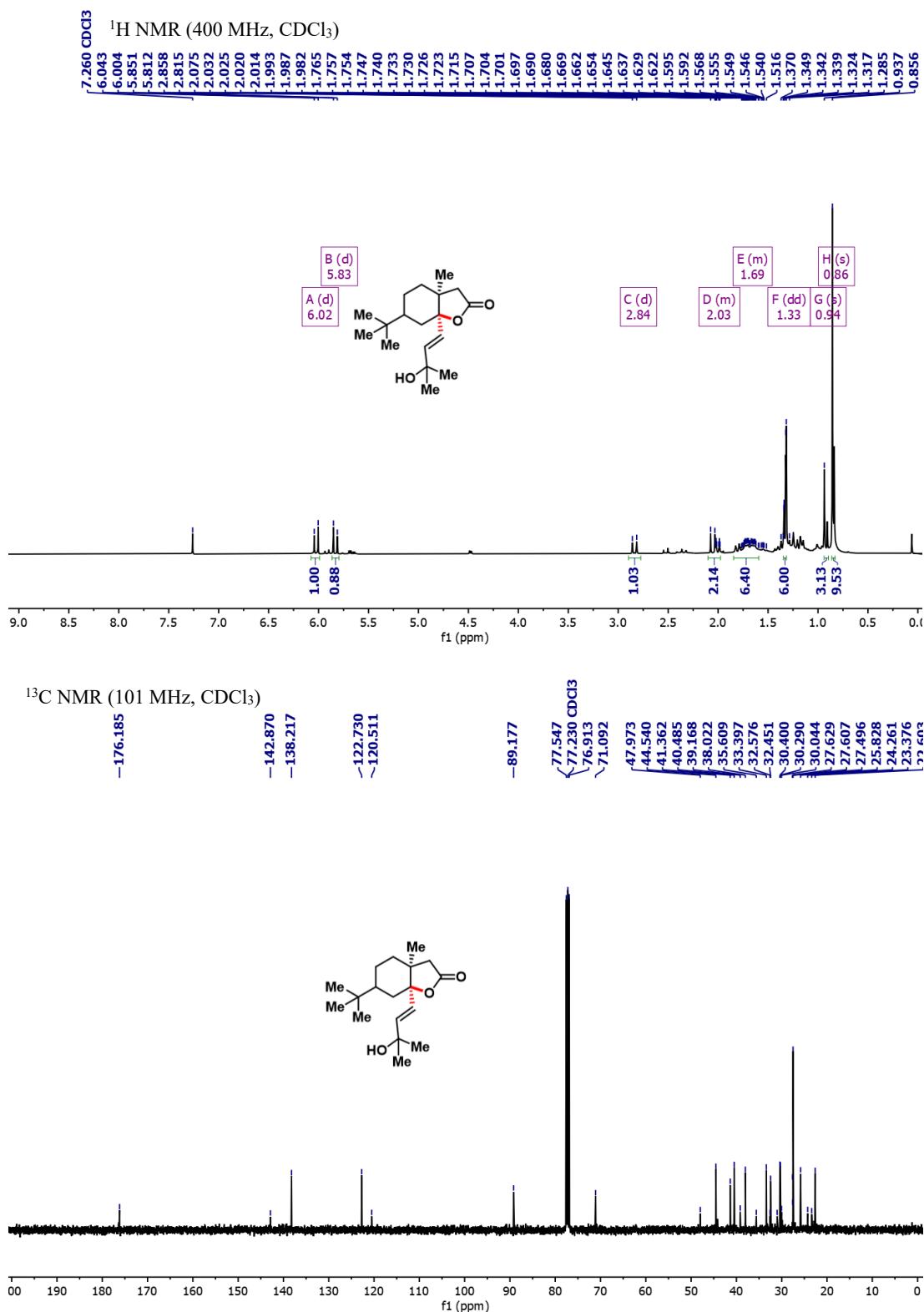
Compound 4y

(3a*S*,7a*R*)-3a-Methyl-7a-((*E*)-3-oxooct-1-en-1-yl)-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one



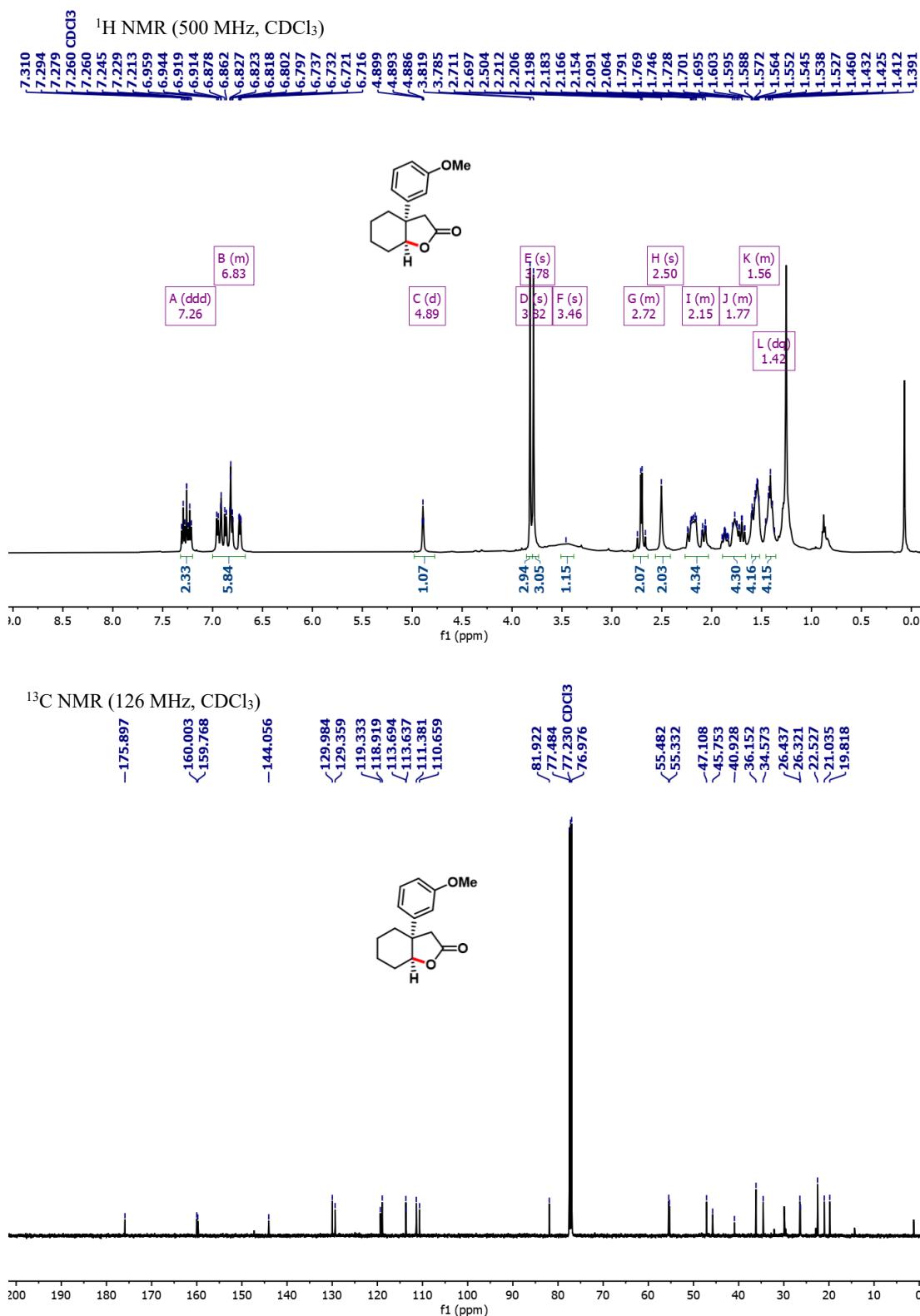
Compound 4z

(3a*S*,7a*S*)-6-(*tert*-Butyl)-7a-((*E*)-3-hydroxy-3-methylbut-1-en-1-yl)-3a-methyl-3a,4,5,7a-tetrahydrobenzofuran-2(3H)-one



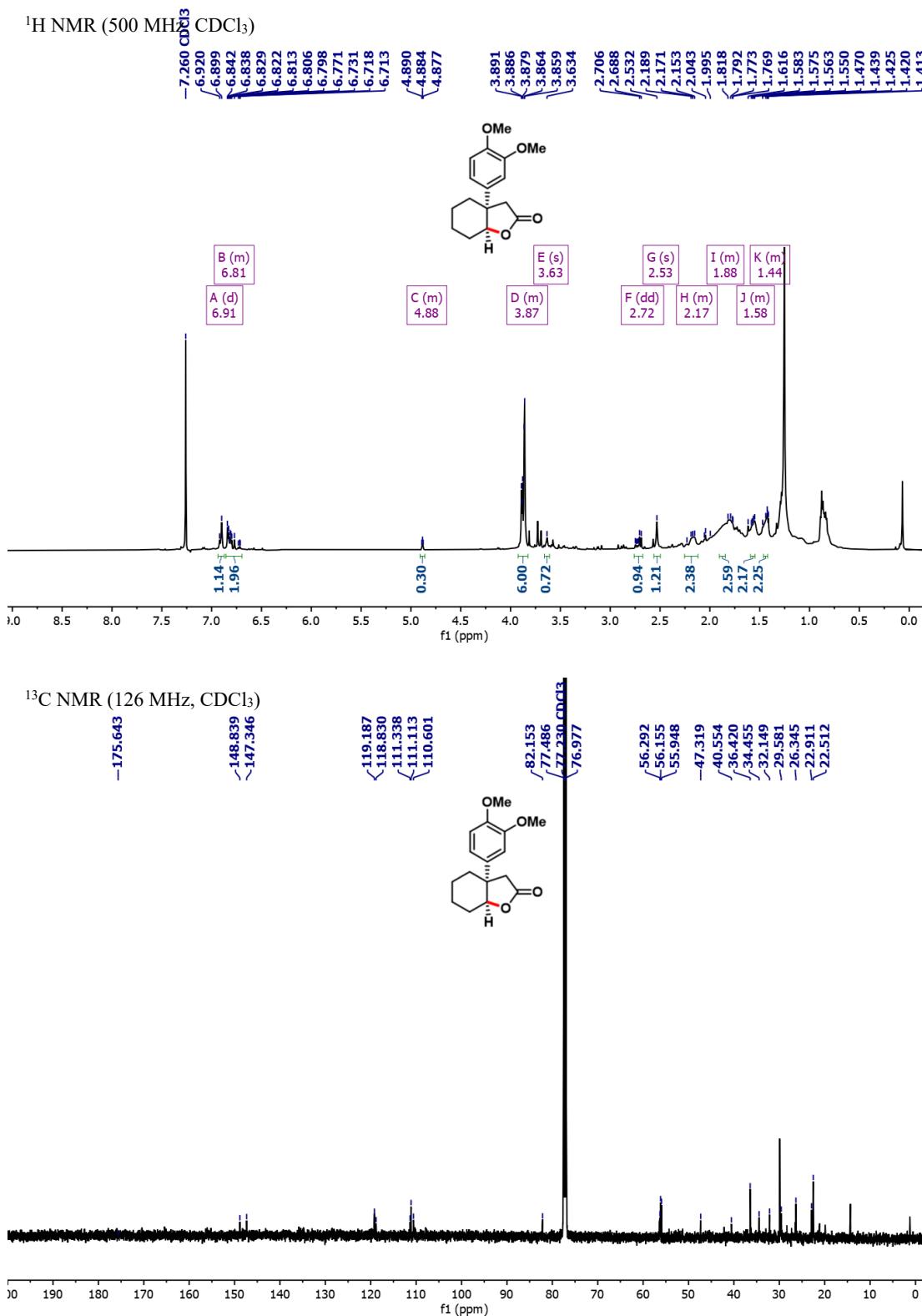
Compound 5a

(3a*S*,7a*S*)-3a-(3-Methoxyphenyl)hexahydrobenzofuran-2(3H)-one



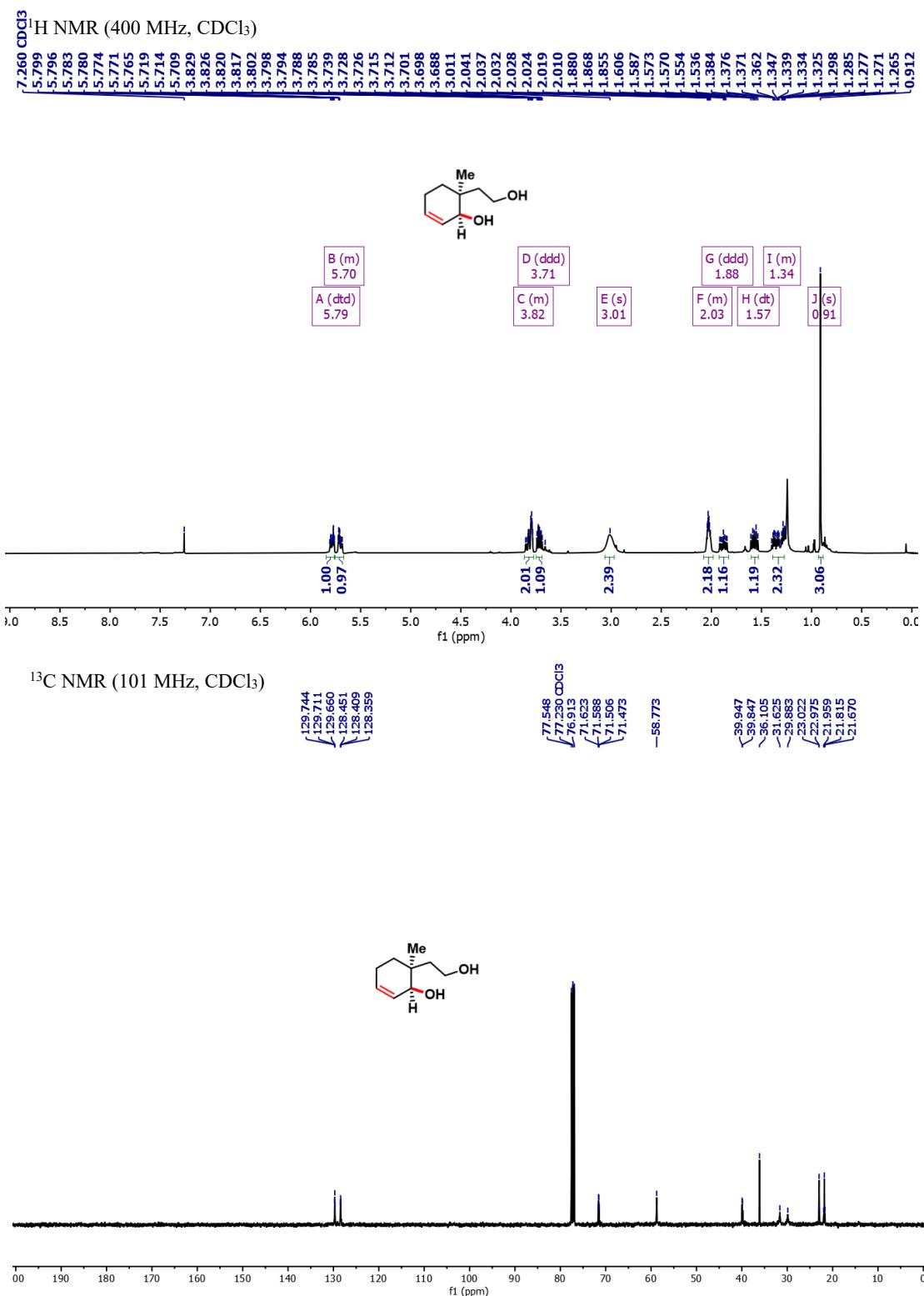
Compound 5b

(3a*S*,7a*S*)-3a-(3,4-Dimethoxyphenyl)hexahydrobenzofuran-2(3H)-one



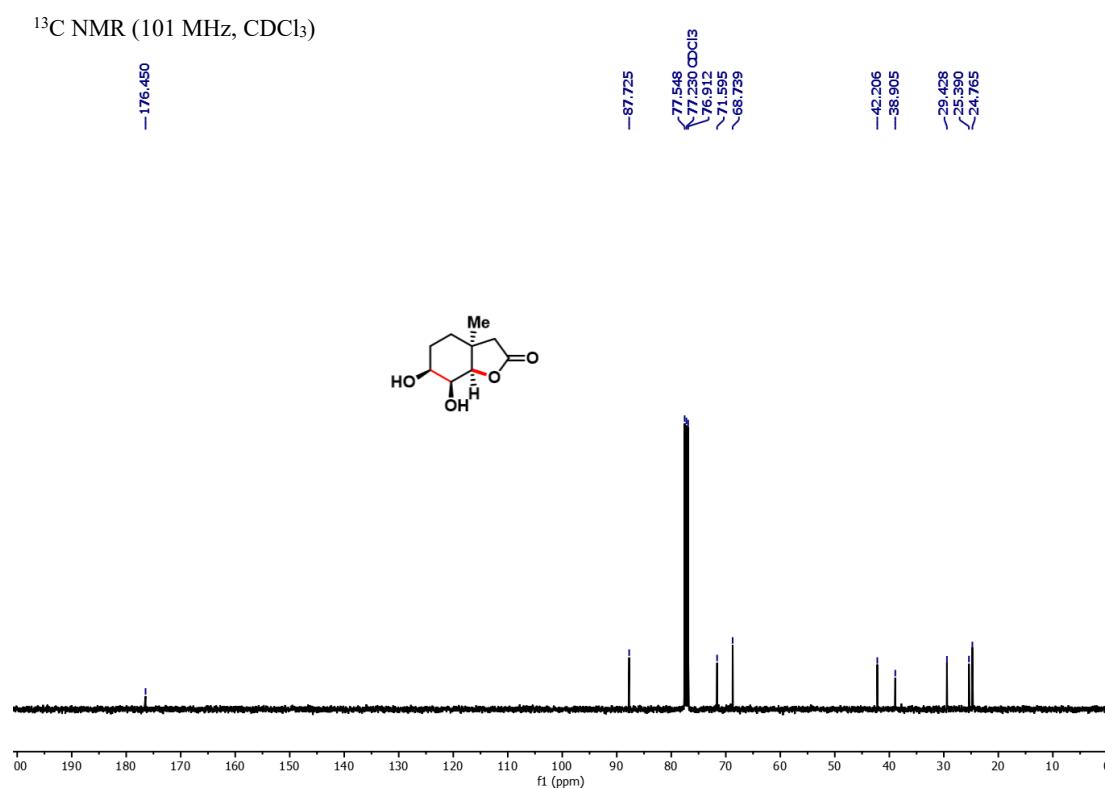
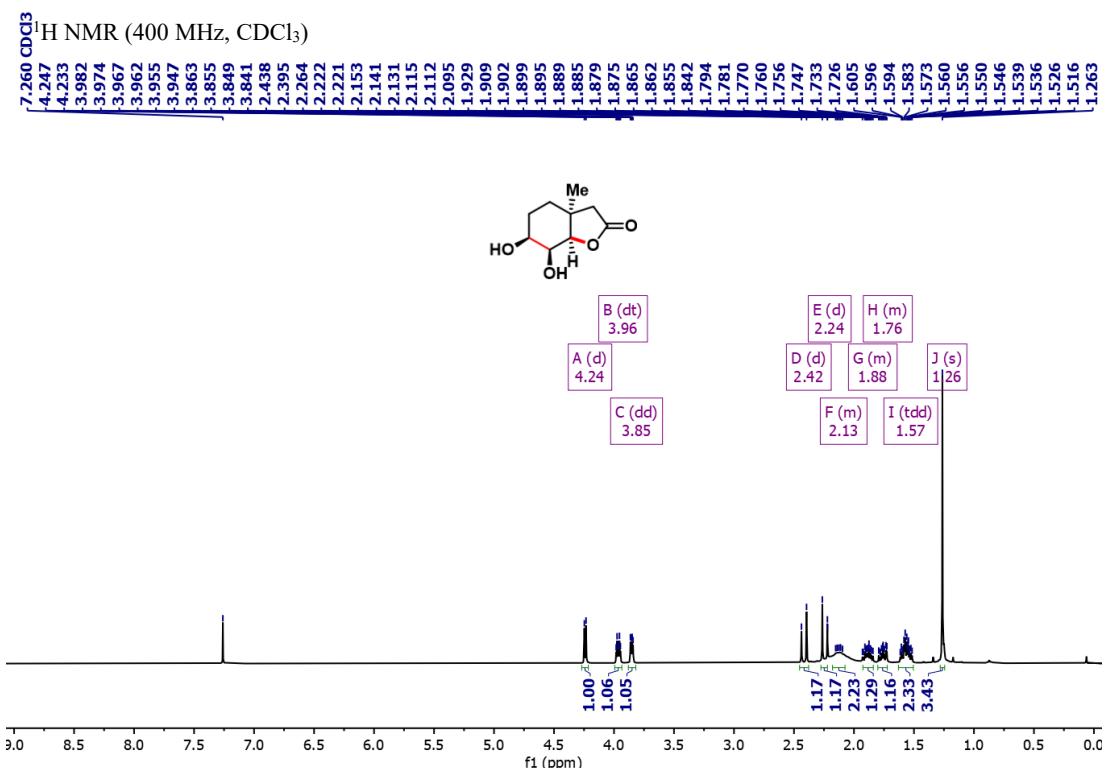
Compound 5c

(1*S*,6*S*)-6-(2-Hydroxyethyl)-6-methylcyclohex-2-en-1-ol



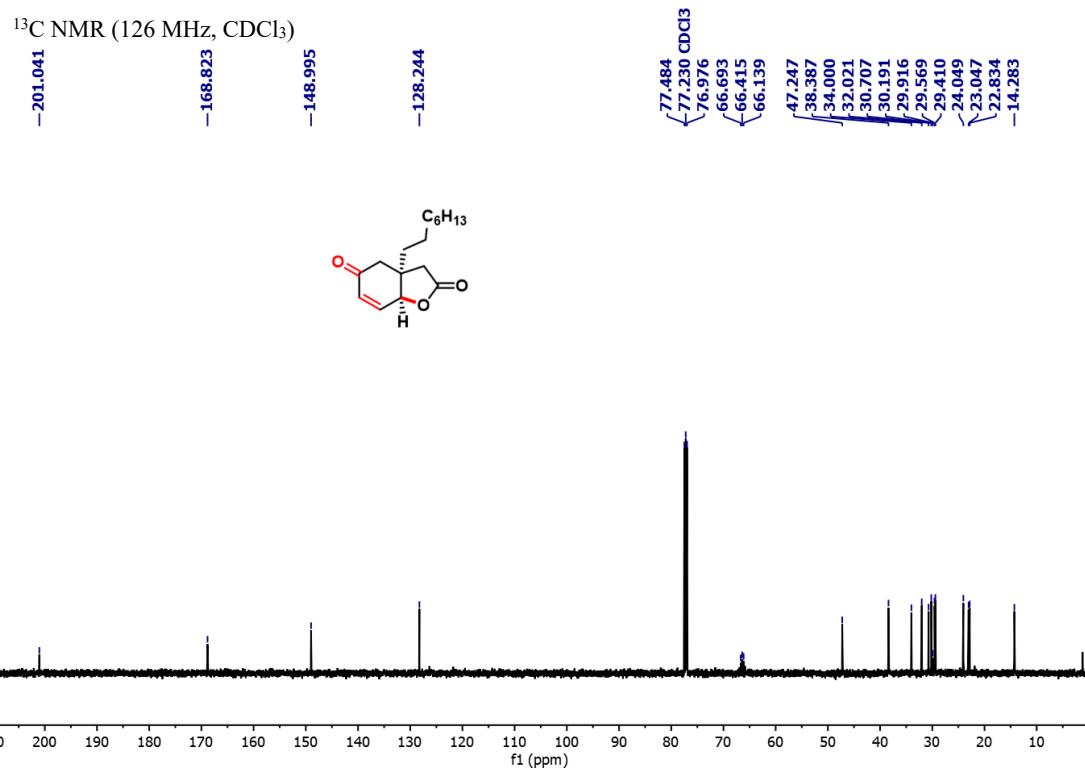
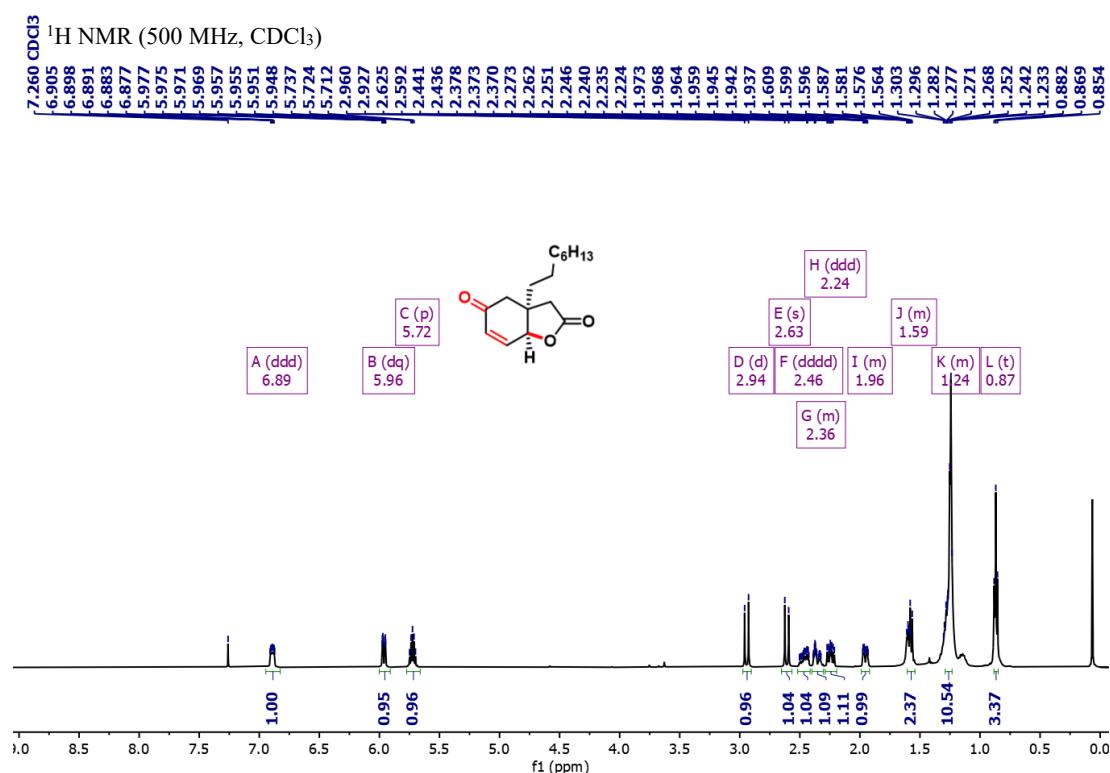
Compound 5d

(3a*S*,6*S*,7*S*,7a*R*)-6,7-Dihydroxy-3a-methylhexahydrobenzofuran-2(3H)-one



Compound 5e

(3a*S*,7a*S*)-3a-Octyl-3a,7a-dihydrobenzofuran-2,5(3H,4H)-dione

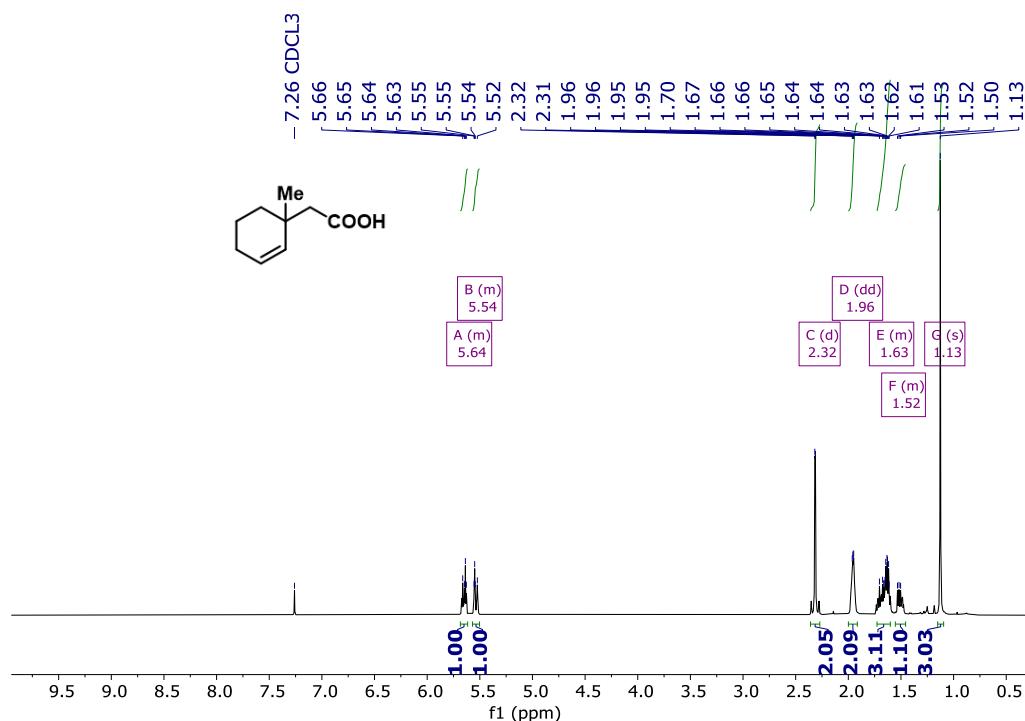


16. NMR Spectra of Alkenoic Acid

Compound 5f

2-(1-methylcyclohex-2-en-1-yl)acetic acid

¹H NMR (400 MHz, CDCl₃)



¹³C NMR (101 MHz, CDCl₃)

