Ligand-Enabled *β*-C(sp3)–H Olefination of Free Carboxylic Acids

Zhe Zhuang,[†,⊥] Chang-Bin Yu,[†,⊥] Gang Chen,[†] Qing-Feng Wu,[†] Yi Hsiao,[‡] Candice L. Joe,[‡] Jennifer X. Qiao,[§] Michael. A. Poss,[§] and Jin-Quan Yu*[,†]

[†]Department of Chemistry, The Scripps Research Institute, 10550 N. Torrey Pines Road, La Jolla, California 92037, United States

[‡]Chemical and Synthetic Development, Bristol-Myers Squibb, 1 Squibb Drive, New Brunswick, New Jersey 08903, United States

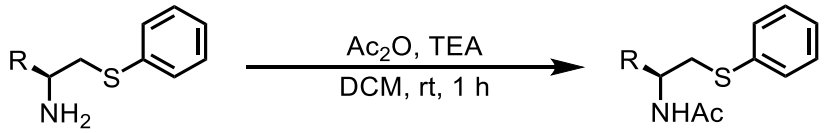
[§]Discovery Chemistry, Bristol-Myers Squibb Company, PO Box 4000, Princeton, New Jersey 08543, United States

Table of Contents

General Information: HFIP was obtained from Oakwood and other solvents were obtained from Sigma-Aldrich, Alfa-Aesar, and Acros and used directly without further purification. $Pd(TFA)_2$ and $Pd(OAc)_2$ was obtained from Strem. Ag_2CO_3 was purchased from Sigma-Aldrich. Carboxylic acids were obtained from the commercial sources or synthesized following literature procedures. Other reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Analytical thin layer chromatography was performed on 0.25 mm silica gel 60-F254. Visualization was carried out with short-wave UV light or $KMnO_4$ and heat as developing agents. ^1H NMR spectra were recorded on Bruker DRX-600, DRX-500, and AMX-400 instruments. Chemical shifts were quoted in parts per million (ppm) referenced to 0.0 ppm for TMS. The following abbreviations (or combinations thereof) were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Coupling constants, *J*, were reported in Hertz unit (Hz). ^{13}C NMR spectra were recorded on Bruker DRX-600 and DRX-500 and were fully decoupled by broad band proton decoupling. Chemical shifts were reported in ppm referenced to the center line of a triplet at 77.0 ppm of $CDCl_3$. Column chromatography was performed using E. Merck silica (60, particle size 0.043–0.063 mm), and pTLC was performed on Merck silica plates (60F-254). High-resolution mass spectra (HRMS) were recorded on an Agilent Mass spectrometer using ESI-TOF (electrospray ionization-time of flight).

Experimental Section

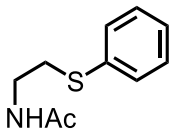
Preparation of Acetyl-Protected Aminoethyl Phenyl Thioether and Related Ligands



R = H or *i*-Pr

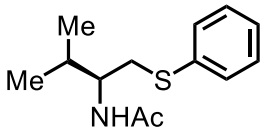
R = H or *i*-Pr
L14 or **L15**

TEA (1.2 eq) and Ac_2O (1.2 eq) were added to the solution of the amine[1, 2] (5.0 mmol) in DCM (25 mL). The reaction was stirred at room temperature for 1 h. After completion, the reaction mixture was concentrated *in vacuo*, and the resulting mixture purified by column chromatography afforded the desired thioether ligand.



***N*-(2-(Phenylthio)ethyl)acetamide (L14)**

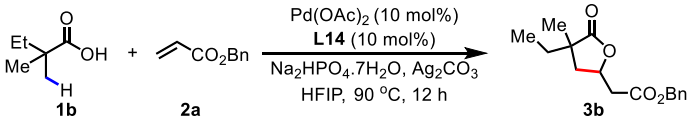
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 – 7.35 (m, 2H), 7.35 – 7.25 (m, 2H), 7.25 – 7.17 (m, 1H), 5.83 (s, 1H), 3.47 (q, *J* = 6.1 Hz, 2H), 3.12 – 3.03 (m, 2H), 1.94 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.11, 134.94, 129.76, 129.12, 126.57, 38.63, 33.65, 23.22; HRMS (ESI-TOF) Calcd for $C_{10}H_{14}NOS$ $[M+H]^+$: 196.0796; found: 196.0801.



(*S*)-*N*-(3-Methyl-1-(phenylthio)butan-2-yl)acetamide (L15)

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 – 7.36 (m, 2H), 7.32 – 7.26 (m, 2H), 7.22 – 7.15 (m, 1H), 5.41 (d, *J* = 9.1 Hz, 1H), 4.05 – 3.95 (m, 1H), 3.19 – 3.04 (m, 2H), 2.01 – 1.90 (m, 1H), 1.89 (s, 3H), 0.99 – 0.85 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.89, 136.31, 129.61, 129.05, 126.34, 54.10, 36.84, 30.48, 23.30, 19.37, 18.32; HRMS (ESI-TOF) Calcd for $C_{13}H_{20}NOS$ $[M+H]^+$: 238.1266; found: 238.1274.

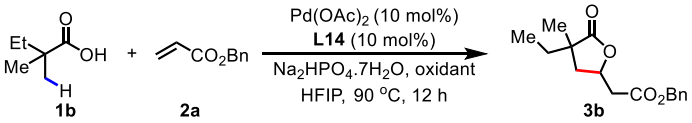
Table S1. Control Experiments for *β*-C(sp^3)–H Olefination[a,b]



entry	variation from standard conditions	yield (%)
1	none	90
2	no $Pd(OAc)_2$	0
3	no **L14**	16
4	no $Na_2HPO_4.7H_2O$	0
5	no Ag_2CO_3	0

[a]Conditions: **1b** (0.1 mmol), **2a** (2.0 eq), $Pd(OAc)_2$ (10 mol%), **L14** (10 mol%), $Na_2HPO_4.7H_2O$ (1.0 eq), Ag_2CO_3 (1.0 eq), HFIP (1.0 mL), 90 ^{O}C, 12 h. [b]The yields were determined by ^{1}H NMR analysis of the crude product using CH_2Br_2 as the internal standard.

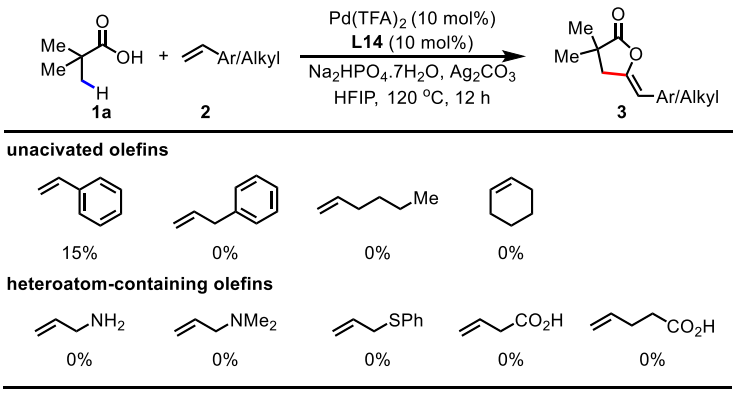
Table S2. Oxidant Investigation for *β*-C(sp^3)–H Olefination[a,b]



entry	oxidant	yield (%)	entry	oxidant	yield (%)
1	w/o oxidant	0	7	BQ + 1 atm O_2	8
2	Ag_2CO_3	90	8	$Cu(OAc)_2$	24
3	AgOAc	36	9	$Cu(TFA)_2.xH_2O$	10
4	AgTFA	0	10	CuF_2	8
5	BQ	6	11	$CuCl_2$	0
6	1 atm O2	8	12	$CuCO_3$	10

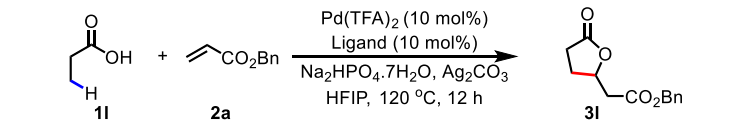
[a]Conditions: **1b** (0.1 mmol), **2a** (2.0 eq), $Pd(OAc)_2$ (10 mol%), **L14** (10 mol%), $Na_2HPO_4.7H_2O$ (1.0 eq), oxidant (1.0 eq), HFIP (1.0 mL), 90 ^{O}C, 12 h. [b]The yields were determined by ^{1}H NMR analysis of the crude product using CH_2Br_2 as the internal standard.

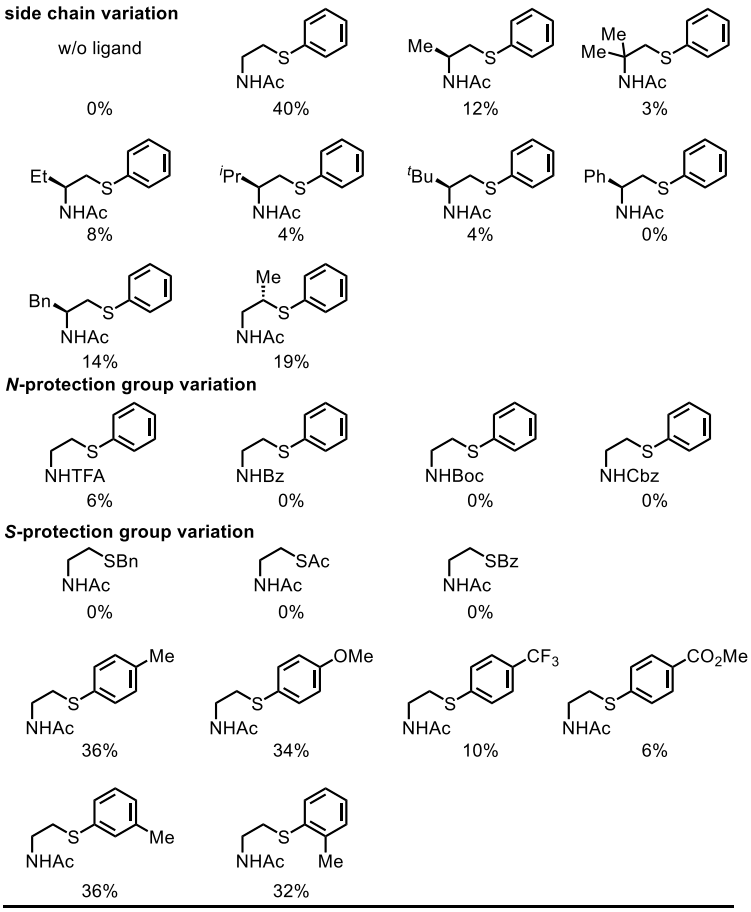
Table S3. Unactivated Olefin Scope for *β*-C(sp^3)–H Olefination[a,b]



[a]Conditions: **1a** (0.1 mmol), **2** (2.0 eq), Pd(TFA)$_2$ (10 mol%), **L14** (10 mol%), $Na_2HPO_4.7H_2O$ (1.0 eq), Ag_2CO_3 (1.0 eq), HFIP (1.0 mL), 120 ^{O}C, 12 h. [b]The yields were determined by ^{1}H NMR analysis of the crude product using CH_2Br_2 as the internal standard.

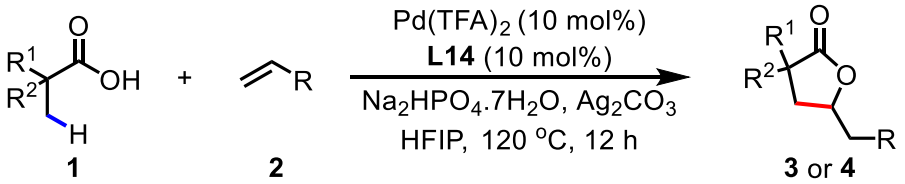
Table S4. Ligand Development for *β*-C(sp^3)–H Olefination of Propionic Acid[a,b]



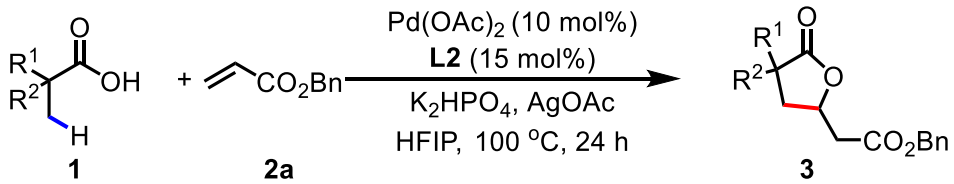


[a]Conditions: **1l** (0.1 mmol), **2** (2.0 eq), $Pd(TFA)_2$ (10 mol%), ligand (10 mol%), $Na_2HPO_4.7H_2O$ (1.0 eq), Ag_2CO_3 (1.0 eq), HFIP (1.0 mL), 120 °C, 12 h. [b]The yields were determined by ^1H NMR analysis of the crude product using CH_2Br_2 as the internal standard.

General Procedure for *β*-C(sp^3)–H Olefination

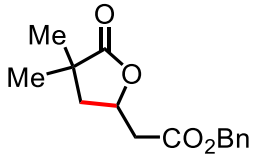


General Procedure A: In the control tube, $Pd(TFA)_2$ (10 mol%), ligand **L14** (10 mol%), $Na_2HPO_4.7H_2O$ (1.0 eq), Ag_2CO_3 (1.0 eq), and carboxylic acid **1** (0.1 mmol) in order were weighed in air and placed with a magnetic stir bar. Then HFIP (1.0 mL) and olefin **2** (2.0 eq) were added. The reaction mixture was stirred at rt for 10 min, and then heated to 120 °C for 12 h (300 rpm). After being allowed to cool to room temperature, the mixture was diluted with DCM, and filtered through a pad of celite. The filtrate was concentrated *in vacuo*, and the resulting mixture purified by column chromatography (**4a**-**4k**) or pTLC (**3a**-**3x**) using hexane/EA (2/1) as the eluent.



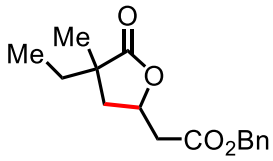
General Procedure B: In the control tube, $Pd(OAc)_2$ (10 mol%), K_2HPO_4 (2.0 eq), AgOAc (2.0 eq), and carboxylic acid **1** (0.1 mmol) in order were weighed in air and placed with a magnetic stir bar. Then HFIP (1.0 mL), **L2** (15 mol%), and olefin **2** (2.0 eq) in order were added. The reaction mixture was stirred at room temperature for 10 min, and then heated to 100 °C for 24 h (300 rpm). After being allowed to cool to room temperature, the mixture was diluted with DCM, and filtered through a pad of celite. The filtrate was concentrated *in vacuo*, and the resulting mixture purified by pTLC using hexane/EA (2/1) as the eluent.

Substrate and Olefin Scope for *β*-C(sp^3)–H Olefination



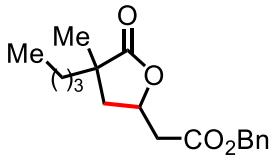
Benzyl 2-(4,4-dimethyl-5-oxotetrahydrofuran-2-yl)acetate (3a)

Following **General Procedure A** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 25 mg, 95%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 – 7.30 (m, 5H), 5.16 (s, 2H), 4.85 (ddt, *J* = 9.9, 6.9, 6.1 Hz, 1H), 2.87 (dd, *J* = 16.3, 6.9 Hz, 1H), 2.66 (dd, *J* = 16.3, 6.1 Hz, 1H), 2.28 (dd, *J* = 12.8, 6.0 Hz, 1H), 1.82 (dd, *J* = 12.8, 9.9 Hz, 1H), 1.27 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 181.14, 169.42, 135.35, 128.63, 128.46, 128.36, 72.56, 66.83, 43.04, 40.31, 40.22, 24.93, 24.38; HRMS (ESI-TOF) Calcd for $C_{15}H_{19}O_4$ $[M+H]^+$: 263.1278; found: 263.1277.



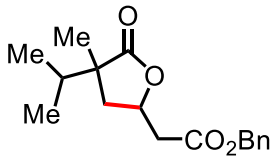
Benzyl 2-(4-ethyl-4-methyl-5-oxotetrahydrofuran-2-yl)acetate (3b)

Following **General Procedure A** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 26.5 mg, 96%, dr = 1.0/1.0). Data for inseparable isomers: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 – 7.29 (m, 10H), 5.16 (s, 4H), 4.89 – 4.74 (m, 2H), 2.92 – 2.81 (m, 2H), 2.71 – 2.57 (m, 2H), 2.39 (dd, *J* = 13.1, 6.6 Hz, 1H), 2.13 (dd, *J* = 12.8, 6.2 Hz, 1H), 1.87 (dd, *J* = 12.9, 10.0 Hz, 1H), 1.76 (dd, *J* = 13.1, 9.5 Hz, 1H), 1.70 – 1.53 (m, 4H), 1.25 (s, 3H), 1.23 (s, 3H), 0.96 (t, *J* = 7.5 Hz, 3H), 0.91 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 180.79, 180.71, 169.43, 169.41, 135.35, 128.61, 128.43, 128.34, 72.66, 72.65, 66.80, 66.78, 44.40, 44.17, 40.60, 40.56, 40.25, 39.53, 30.37, 30.16, 22.83, 22.22, 8.73, 8.64; HRMS (ESI-TOF) Calcd for $C_{16}H_{21}O_4$ $[M+H]^+$: 277.1434; found: 277.1432.



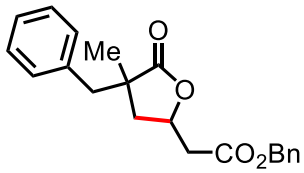
Benzyl 2-(4-butyl-4-methyl-5-oxotetrahydrofuran-2-yl)acetate (3c)

Following **General Procedure A** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 29.0 mg, 95%, dr = 1.0/1.0). Data for inseparable isomers: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49 – 7.31 (m, 10H), 5.16 (s, 4H), 4.88 – 4.76 (m, 2H), 2.91 – 2.81 (m, 2H), 2.70 – 2.59 (m, 2H), 2.39 (dd, *J* = 13.1, 6.6 Hz, 1H), 2.15 (dd, *J* = 12.8, 6.1 Hz, 1H), 1.87 (dd, *J* = 12.8, 10.0 Hz, 1H), 1.76 (dd, *J* = 13.1, 9.5 Hz, 1H), 1.64 – 1.50 (m, 4H), 1.40 – 1.28 (m, 7H), 1.25 (s, 3H), 1.24 (s, 3H), 1.19 – 1.10 (m, 1H), 0.95 – 0.85 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 180.93, 180.85, 169.44, 135.35, 128.61, 128.44, 128.34, 72.70, 66.81, 66.79, 43.98, 43.84, 40.97, 40.59, 40.29, 40.12, 37.45, 37.18, 26.52, 26.51, 23.48, 22.95, 22.58, 13.92, 13.88; HRMS (ESI-TOF) Calcd for $C_{18}H_{25}O_4$ $[M+H]^+$: 305.1747; found: 305.1748.



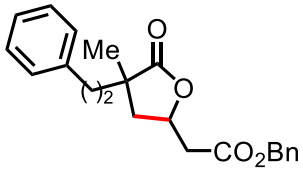
Benzyl 2-(4-isopropyl-4-methyl-5-oxotetrahydrofuran-2-yl)acetate (3d)

Following **General Procedure A** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 21.5 mg, 74%, dr = 1.0/1.0). Data for inseparable isomers: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 – 7.31 (m, 10H), 5.20 – 5.08 (m, 4H), 4.86 – 4.82 (m, 1H), 4.80 – 4.72 (m, 1H), 2.91 – 2.82 (m, 2H), 2.69 – 2.61 (m, 2H), 2.49 (dd, *J* = 13.6, 7.4 Hz, 1H), 2.02 – 1.95 (m, 2H), 1.95 – 1.91 (m, 1H), 1.91 – 1.83 (m, 1H), 1.64 (dd, *J* = 13.5, 8.5 Hz, 1H), 1.27 (s, 3H), 1.22 (s, 3H), 0.99 – 0.84 (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 181.07, 180.51, 169.44, 169.42, 135.35, 135.34, 128.60, 128.43, 128.34, 128.33, 72.91, 72.55, 66.80, 66.76, 48.04, 47.57, 41.10, 40.28, 37.54, 36.02, 33.67, 32.82, 22.61, 21.68, 18.29, 18.22, 17.04, 16.90; HRMS (ESI-TOF) Calcd for $C_{17}H_{23}O_4$ $[M+H]^+$: 291.1591; found: 291.1591.



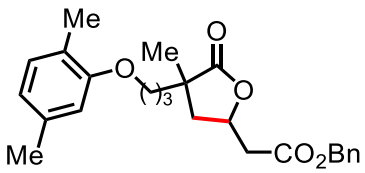
Benzyl 2-(4-benzyl-4-methyl-5-oxotetrahydrofuran-2-yl)acetate (3e)

Following **General Procedure A** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 31.0 mg, 91%, dr = 1.0/1.0). Data for inseparable isomers: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 – 7.22 (m, 16H), 7.21 – 7.10 (m, 4H), 5.14 – 5.06 (m, 4H), 4.84 – 4.74 (m, 1H), 4.05 – 3.96 (m, 1H), 3.08 (d, *J* = 13.7 Hz, 1H), 3.00 (d, *J* = 13.4 Hz, 1H), 2.79 – 2.70 (m, 2H), 2.68 (d, *J* = 13.3 Hz, 1H), 2.59 (dd, *J* = 16.3, 6.9 Hz, 1H), 2.56 – 2.47 (m, 2H), 2.31 (dd, *J* = 16.3, 6.3 Hz, 1H), 2.05 (dd, *J* = 12.9, 6.4 Hz, 1H), 1.93 (dd, *J* = 12.9, 9.5 Hz, 1H), 1.72 (dd, *J* = 13.3, 9.5 Hz, 1H), 1.32 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 180.80, 180.46, 169.37, 169.15, 136.77, 136.18, 135.35, 135.31, 130.12, 129.80, 128.60, 128.56, 128.47, 128.43, 128.42, 128.32, 128.29, 127.25, 126.95, 72.77, 72.62, 66.72, 66.71, 45.74, 45.51, 44.03, 43.34, 40.41, 40.00, 39.62, 38.95, 24.96, 23.62; HRMS (ESI-TOF) Calcd for $C_{21}H_{23}O_4$ $[M+H]^+$: 339.1591; found: 339.1596.



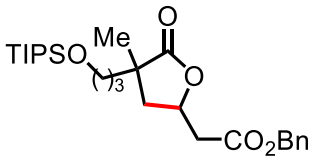
Benzyl 2-(4-methyl-5-oxo-4-phenethyltetrahydrofuran-2-yl)acetate (3f)

Following **General Procedure A** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 33.5 mg, 95%, dr = 1.0/1.0). Data for inseparable isomers: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 – 7.31 (m, 9H), 7.31 – 7.23 (m, 5H), 7.22 – 7.11 (m, 6H), 5.16 (s, 4H), 4.92 – 4.82 (m, 2H), 2.95 – 2.83 (m, 2H), 2.80 – 2.57 (m, 5H), 2.55 – 2.41 (m, 2H), 2.20 (dd, *J* = 12.8, 6.1 Hz, 1H), 2.01 – 1.77 (m, 6H), 1.33 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 180.46, 180.44, 169.41, 169.38, 141.24, 140.99, 135.32, 130.01, 129.08, 128.64, 128.54, 128.49, 128.48, 128.39, 128.38, 128.29, 128.24, 126.17, 126.08, 125.88, 72.80, 72.76, 66.88, 66.87, 44.06, 43.93, 41.20, 40.54, 40.20, 40.17, 39.57, 39.31, 30.79, 30.78, 23.33, 22.60; HRMS (ESI-TOF) Calcd for $C_{22}H_{25}O_4$ $[M+H]^+$: 353.1747; found: 353.1746.



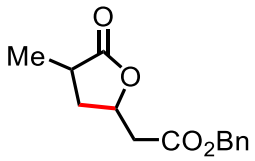
Benzyl 2-(4-(3-(2,5-dimethylphenoxy)propyl)-4-methyl-5-oxotetrahydrofuran-2-yl)acetate (3g)

Following **General Procedure A** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 33.0 mg, 81%, dr = 1.0/1.0). Data for inseparable isomers: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 – 7.30 (m, 10H), 7.00 (d, *J* = 7.5 Hz, 2H), 6.66 (d, *J* = 7.5 Hz, 2H), 6.60 (s, 2H), 5.21 – 5.11 (m, 4H), 4.91 – 4.80 (m, 2H), 4.00 – 3.89 (m, 4H), 2.92 – 2.84 (m, 2H), 2.71 – 2.63 (m, 2H), 2.43 (dd, *J* = 13.1, 6.6 Hz, 1H), 2.30 (s, 6H), 2.21 (dd, *J* = 12.8, 6.1 Hz, 1H), 2.16 (s, 6H), 1.97 – 1.86 (m, 3H), 1.86 – 1.64 (m, 7H), 1.31 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 180.47, 180.43, 169.37, 169.33, 156.73, 156.70, 136.50, 136.48, 135.33, 130.33, 130.31, 128.62, 128.45, 128.35, 123.49, 120.88, 120.83, 111.94, 111.93, 72.73, 72.68, 67.49, 67.33, 66.83, 66.81, 43.78, 43.56, 41.16, 40.52, 40.23, 40.18, 34.19, 34.08, 24.61, 24.58, 23.22, 22.51, 21.37, 15.77, 15.75; HRMS (ESI-TOF) Calcd for $C_{25}H_{31}O_5$ $[M+H]^+$: 411.2166; found: 411.2167.



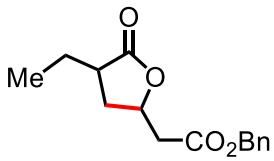
Benzyl 2-(4-methyl-5-oxo-4-(3-((triisopropylsilyl)oxy)propyl)tetrahydrofuran-2-yl)acetate (3h)

Following **General Procedure A** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 41.5 mg, 90%, dr = 1.0/1.0). Data for inseparable isomers: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 – 7.30 (m, 10H), 5.15 (s, 4H), 4.91 – 4.76 (m, 2H), 3.73 – 3.63 (m, 4H), 2.92 – 2.81 (m, 2H), 2.65 (dd, *J* = 16.3, 6.1 Hz, 2H), 2.40 (dd, *J* = 13.1, 6.5 Hz, 1H), 2.17 (dd, *J* = 12.8, 6.1 Hz, 1H), 1.88 (dd, *J* = 12.9, 10.0 Hz, 1H), 1.78 (dd, *J* = 13.1, 9.5 Hz, 1H), 1.74 – 1.57 (m, 6H), 1.57 – 1.48 (m, 1H), 1.48 – 1.39 (m, 1H), 1.27 (s, 3H), 1.25 (s, 3H), 1.13 – 0.97 (m, 21H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 180.75, 180.67, 169.43, 169.37, 135.36, 135.36, 128.62, 128.44, 128.35, 72.70, 72.66, 66.81, 66.79, 63.17, 62.97, 43.75, 43.57, 41.06, 40.58, 40.28, 33.87, 33.82, 27.94, 27.89, 23.23, 22.51, 18.00, 11.93, 11.92; HRMS (ESI-TOF) Calcd for $C_{26}H_{43}O_5Si$ $[M+H]^+$: 463.2874; found: 463.2870.



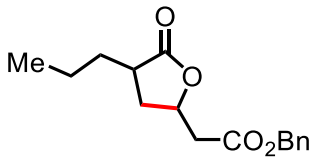
Benzyl 2-(4-methyl-5-oxotetrahydrofuran-2-yl)acetate (3i)

Following **General Procedure A** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 17.5 mg, 71%, dr = 1.8/1.0). Data for inseparable isomers: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 – 7.30 (m, 14H), 5.16 (s, 5.6H), 4.99 – 4.90 (m, 1H), 4.82 – 4.73 (m, 1.8H), 2.88 (dd, *J* = 16.3, 6.9 Hz, 1.8H), 2.83 (dd, *J* = 16.1, 6.7 Hz, 1H), 2.76 – 2.57 (m, 7.4H), 2.25 – 2.17 (m, 1H), 2.11 (dt, *J* = 13.1, 7.7 Hz, 1H), 1.64 – 1.57 (m, 1.8H), 1.29 (d, *J* = 7.3 Hz, 3H), 1.27 (d, *J* = 7.0 Hz, 5.4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.22, 178.67, 169.34, 169.33, 135.33, 135.30, 128.64, 128.63, 128.48, 128.46, 128.37, 128.35, 73.91, 73.84, 66.85, 66.83, 40.05, 39.83, 36.89, 35.66, 34.99, 33.65, 15.79, 14.98; HRMS (ESI-TOF) Calcd for $C_{14}H_{17}O_4$ $[M+H]^+$: 249.1127; found: 249.1128.



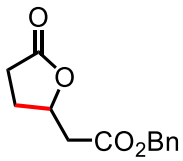
Benzyl 2-(4-ethyl-5-oxotetrahydrofuran-2-yl)acetate (3j)

Following **General Procedure A** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 16.0 mg, 62%, dr = 1.2/1.0). Data for inseparable isomers: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 – 7.30 (m, 11H), 5.16 (s, 4.4H), 4.95 – 4.86 (m, 1H), 4.81 – 4.73 (m, 1.2H), 2.89 (dd, *J* = 16.3, 6.8 Hz, 1.2H), 2.83 (dd, *J* = 16.1, 6.6 Hz, 1H), 2.72 – 2.61 (m, 2.2H), 2.62 – 2.53 (m, 3.2H), 2.21 – 2.10 (m, 1.2H), 1.98 – 1.89 (m, 1.2H), 1.90 – 1.81 (m, 1H), 1.65 – 1.53 (m, 3.2H), 1.54 – 1.44 (m, 1.2H), 1.04 – 0.94 (m, 6.6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.49, 177.92, 169.38, 169.36, 135.34, 135.31, 128.63, 128.63, 128.48, 128.46, 128.37, 128.36, 74.14, 74.07, 66.84, 66.83, 42.11, 40.34, 40.12, 40.04, 34.27, 32.61, 23.91, 23.21, 11.60, 11.56; HRMS (ESI-TOF) Calcd for $C_{15}H_{19}O_4$ $[M+H]^+$: 263.1283; found: 263.1286.



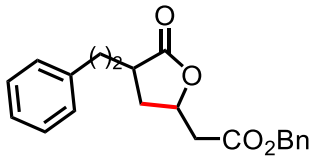
Benzyl 2-(5-oxo-4-propyltetrahydrofuran-2-yl)acetate (3k)

Following **General Procedure A** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 12.0 mg, 44%, dr = 1.8/1.0). Data for inseparable isomers: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 – 7.30 (m, 14H), 5.16 (s, 5.6H), 4.96 – 4.88 (m, 1H), 4.81 – 4.72 (m, 1.8H), 2.89 (dd, *J* = 16.3, 6.8 Hz, 1.8H), 2.83 (dd, *J* = 16.1, 6.5 Hz, 1H), 2.70 – 2.53 (m, 7.4H), 2.18 – 2.10 (m, 1.8H), 1.93 – 1.84 (m, 1.8H), 1.84 – 1.77 (m, 1H), 1.65 – 1.57 (m, 1.8H), 1.51 – 1.34 (m, 8.6H), 1.00 – 0.89 (m, 8.4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.73, 178.19, 169.39, 169.37, 135.34, 135.31, 128.64, 128.63, 128.48, 128.47, 128.37, 128.37, 74.15, 74.12, 66.85, 66.83, 40.51, 40.11, 40.01, 38.73, 34.86, 33.08, 32.82, 32.28, 20.50, 20.47, 13.76, 13.73; HRMS (ESI-TOF) Calcd for $C_{16}H_{21}O_4$ $[M+H]^+$: 277.1440; found: 277.1445.



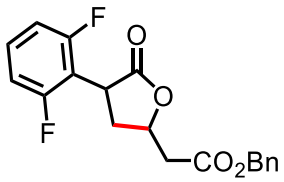
Benzyl 2-(5-oxotetrahydrofuran-2-yl)acetate (3l)

Following **General Procedure A** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 9.0 mg, 40%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 – 7.30 (m, 5H), 5.16 (s, 2H), 4.96 – 4.87 (m, 1H), 2.87 (dd, *J* = 16.3, 6.5 Hz, 1H), 2.69 (dd, *J* = 16.3, 6.4 Hz, 1H), 2.60 – 2.52 (m, 2H), 2.50 – 2.41 (m, 1H), 2.02 – 1.91 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.33, 169.27, 135.31, 128.65, 128.50, 128.38, 76.13, 66.87, 40.00, 28.44, 27.60; HRMS (ESI-TOF) Calcd for $C_{13}H_{15}O_4$ $[M+H]^+$: 235.0970; found: 235.0972.



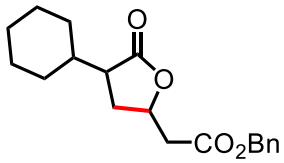
Benzyl 2-(5-oxo-4-phenethyltetrahydrofuran-2-yl)acetate (3m)

Following **General Procedure A** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 17.5 mg, 52%, dr = 2.0/1.0). Data for inseparable isomers: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 – 7.34 (m, 15H), 7.34 – 7.29 (m, 6H), 7.27 – 7.15 (m, 9H), 5.18 (s, 4H), 5.18 (s, 2H), 4.99 – 4.93 (m, 1H), 4.79 – 4.72 (m, 2H), 2.91 (dd, *J* = 16.3, 6.7 Hz, 2H), 2.87 – 2.55 (m, 16H), 2.34 – 2.24 (m, 2H), 2.24 – 2.14 (m, 3H), 1.86 – 1.79 (m, 1H), 1.79 – 1.71 (m, 2H), 1.68 – 1.61 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.33, 177.90, 169.32, 169.29, 140.58, 140.54, 135.32, 135.29, 129.90, 128.64, 128.63, 128.53, 128.52, 128.48, 128.42, 128.39, 128.38, 128.37, 126.25, 126.24, 74.09, 66.85, 66.84, 40.03, 39.95, 39.83, 38.07, 34.95, 33.24, 33.21, 33.17, 32.46, 31.82, 28.29; HRMS (ESI-TOF) Calcd for $C_{21}H_{23}O_4$ $[M+H]^+$: 339.1596; found: 339.1598.



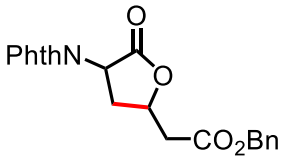
Benzyl 2-(4-(2,6-difluorophenyl)-5-oxotetrahydrofuran-2-yl)acetate (3n)

Following **General Procedure A** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 16.5 mg, 48%, dr = 2.0/1.0). Data for inseparable isomers: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.31 (m, 15H), 7.31 – 7.20 (m, 3H), 6.97 – 6.86 (m, 6H), 5.15 – 5.10 (m, 7H), 5.04 – 4.92 (m, 2H), 4.36 – 4.20 (m, 3H), 3.02 (dd, *J* = 16.4, 6.9 Hz, 2H), 2.91 (dd, *J* = 16.3, 6.1 Hz, 1H), 2.87 – 2.73 (m, 5H), 2.65 – 2.55 (m, 1H), 2.55 – 2.45 (m, 1H), 2.24 – 2.11 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.26, 174.46, 169.15, 161.09 (dd, *J* = 249.0, 7.2 Hz), 160.96 (dd, *J* = 248.9, 7.6 Hz), 135.27, 135.22, 129.77 (t, *J* = 10.8 Hz), 129.66 (t, *J* = 10.7 Hz), 128.64, 128.62, 128.49, 128.45, 128.37, 128.34, 113.90 (t, *J* = 18.3 Hz), 113.03 (t, *J* = 18.0 Hz), 111.74 (d, *J* = 3.3 Hz), 111.57 (d, *J* = 3.3 Hz), 74.56, 74.36, 66.91, 66.89, 40.14, 39.66, 36.41, 35.43, 34.15, 33.71; HRMS (ESI-TOF) Calcd for $C_{19}H_{17}F_2O_4$ $[M+H]^+$: 347.1095; found: 347.1092.



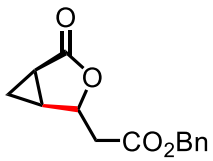
Benzyl 2-(4-cyclohexyl-5-oxotetrahydrofuran-2-yl)acetate (3o)

Following **General Procedure A** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 14.0 mg, 44%, dr = 1.0/1.0). Data for inseparable isomers: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 – 7.29 (m, 10H), 5.15 (s, 2H), 5.15 (s, 2H), 4.89 – 4.81 (m, 1H), 4.77 – 4.69 (m, 1H), 2.88 (dd, *J* = 16.2, 6.7 Hz, 1H), 2.82 (dd, *J* = 16.1, 6.5 Hz, 1H), 2.69 – 2.60 (m, 2H), 2.60 – 2.51 (m, 2H), 2.42 – 2.34 (m, 1H), 2.32 – 2.26 (m, 1H), 2.04 – 1.96 (m, 1H), 1.92 – 1.85 (m, 1H), 1.82 – 1.71 (m, 8H), 1.71 – 1.63 (m, 3H), 1.63 – 1.51 (m, 3H), 1.33 – 1.23 (m, 4H), 1.12 – 0.98 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.01, 177.24, 169.43, 169.40, 135.36, 135.35, 128.64, 128.63, 128.47, 128.46, 128.37, 74.45, 73.89, 66.82, 66.81, 46.13, 44.76, 40.30, 40.11, 38.66, 37.27, 31.21, 30.90, 30.85, 29.91, 28.90, 28.49, 26.22, 26.17, 26.11, 26.01, 25.99; HRMS (ESI-TOF) Calcd for $C_{19}H_{25}O_4$ $[M+H]^+$: 317.1753; found: 317.1754.



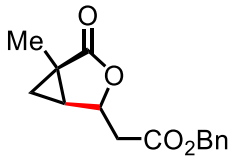
Benzyl 2-(4-(1,3-dioxoisoindolin-2-yl)-5-oxotetrahydrofuran-2-yl)acetate (3p)

Following **General Procedure A** on 0.1 mmol scale with the following modification: $Pd(OAc)_2$ (10 mol%), **L12** (10 mol%), CsOAc (1.0 eq), and Ag_2CO_3 (1.0 eq). Purification by pTLC afforded the title compound (colorless oil, 15.0 mg, 40%, dr = 2.1/1.0). Data for inseparable isomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.83 (m, 6.2H), 7.83 – 7.71 (m, 6.2H), 7.44 – 7.29 (m, 15.5H), 5.28 – 5.11 (m, 10.3H), 4.99 (dq, *J* = 10.0, 6.4 Hz, 2.1H), 3.12 (dd, *J* = 16.5, 6.8 Hz, 2.1H), 2.97 – 2.71 (m, 7.2H), 2.59 – 2.43 (m, 3.1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.95, 171.02, 169.03, 168.98, 166.81, 166.77, 135.26, 135.17, 134.51, 134.49, 131.63, 131.60, 128.68, 128.64, 128.55, 128.48, 128.43, 128.35, 123.77, 73.96, 73.51, 66.99, 66.96, 48.08, 46.58, 40.19, 39.43, 32.21, 31.12; HRMS (ESI-TOF) Calcd for $C_{21}H_{18}NO_6$ $[M+H]^+$: 380.1129; found: 380.1131.



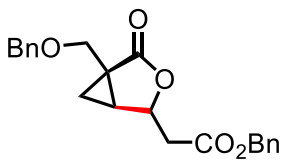
Benzyl 2-(4-oxo-3-oxabicyclo[3.1.0]hexan-2-yl)acetate (3q)

Following **General Procedure A** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 13.0 mg, 52%, dr = 1.6/1.0). Data for inseparable isomers: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 – 7.32 (m, 13H), 5.17 (s, 3.2H), 5.17 (s, 2H), 5.08 – 4.98 (m, 1H), 4.74 (t, *J* = 6.5 Hz, 1.6H), 2.90 – 2.80 (m, 2.6H), 2.73 (dd, *J* = 16.2, 6.9 Hz, 1.6H), 2.64 (dd, *J* = 16.4, 7.5 Hz, 1H), 2.40 – 2.32 (m, 1H), 2.20 – 2.10 (m, 2.6H), 2.12 – 2.04 (m, 1.6H), 1.34 – 1.23 (m, 1.6H), 1.19 – 1.11 (m, 1H), 0.98 – 0.91 (m, 1.6H), 0.93 – 0.86 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.19, 175.15, 169.35, 169.02, 135.29, 135.27, 128.64, 128.63, 128.49, 128.43, 128.34, 76.54, 74.87, 66.89, 66.86, 40.41, 37.27, 22.18, 20.86, 18.47, 17.61, 12.55, 9.02; HRMS (ESI-TOF) Calcd for $C_{14}H_{15}O_4$ $[M+H]^+$: 247.0970; found: 247.0972.



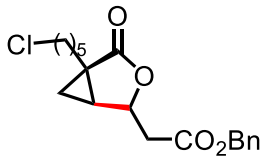
Benzyl 2-(5-methyl-4-oxo-3-oxabicyclo[3.1.0]hexan-2-yl)acetate (3r)

Following **General Procedure A** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 12.5 mg, 48%, dr = 1.3/1.0). Data for inseparable isomers: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 – 7.31 (m, 11.5H), 5.16 (s, 4.6H), 4.97 (td, *J* = 6.9, 4.3 Hz, 1H), 4.62 (t, *J* = 6.2 Hz, 1.3H), 2.85 – 2.75 (m, 2.3H), 2.72 (dd, *J* = 16.2, 6.5 Hz, 1.3H), 2.59 (dd, *J* = 16.4, 7.4 Hz, 1H), 2.17 (dt, *J* = 7.4, 4.5 Hz, 1H), 1.97 (dd, *J* = 7.6, 4.2 Hz, 1.3H), 1.41 (s, 3H), 1.40 (s, 3.9H), 1.10 (dd, *J* = 7.6, 4.9 Hz, 1.3H), 1.00 (t, *J* = 4.5 Hz, 1.3H), 0.99 – 0.92 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.30, 177.16, 169.43, 169.03, 135.33, 135.30, 128.62, 128.61, 128.45, 128.37, 128.32, 75.42, 73.71, 66.82, 66.80, 40.49, 37.14, 27.90, 26.68, 24.61, 24.03, 19.30, 15.56, 14.31, 14.06; HRMS (ESI-TOF) Calcd for $C_{15}H_{17}O_4$ $[M+H]^+$: 261.1127; found: 261.1131.



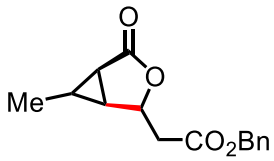
Benzyl 2-(5-((benzyloxy)methyl)-4-oxo-3-oxabicyclo[3.1.0]hexan-2-yl)acetate (3s)

Following **General Procedure A** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 23.0 mg, 62%, dr = 1.3/1.0). Data for inseparable isomers: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 – 7.29 (m, 23H), 5.18 (s, 4.6H), 5.00 (td, *J* = 7.0, 4.5 Hz, 1H), 4.73 (t, *J* = 6.5 Hz, 1.3H), 4.61 (d, *J* = 12.1 Hz, 2.3H), 4.55 (d, *J* = 12.1 Hz, 2.3H), 4.13 (d, *J* = 10.8 Hz, 1H), 4.11 (d, *J* = 10.6 Hz, 1.3H), 3.48 (d, *J* = 10.8 Hz, 1H), 3.45 (d, *J* = 10.7 Hz, 1.3H), 2.90 – 2.80 (m, 2.3H), 2.75 (dd, *J* = 16.3, 6.8 Hz, 1.3H), 2.63 (dd, *J* = 16.4, 7.4 Hz, 1H), 2.43 (dt, *J* = 8.4, 4.5 Hz, 1H), 2.21 (dd, *J* = 7.8, 4.5 Hz, 1.3H), 1.38 (dd, *J* = 7.8, 5.0 Hz, 1.3H), 1.23 (dd, *J* = 7.7, 5.2 Hz, 1H), 1.06 (t, *J* = 4.8 Hz, 1.3H), 1.01 (t, *J* = 4.9 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.24, 175.19, 169.27, 169.09, 137.85, 137.78, 135.33, 135.29, 128.63, 128.61, 128.48, 128.44, 128.42, 128.39, 128.35, 128.33, 127.77, 127.69, 127.64, 127.54, 75.47, 73.94, 73.24, 73.17, 66.95, 66.87, 66.85, 66.83, 40.45, 37.23, 29.93, 29.25, 26.21, 25.04, 16.40, 12.90; HRMS (ESI-TOF) Calcd for $C_{22}H_{23}O_5$ $[M+H]^+$: 367.1545; found: 367.1543.



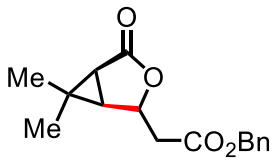
Benzyl 2-(5-(5-chloropentyl)-4-oxo-3-oxabicyclo[3.1.0]hexan-2-yl)acetate (3t)

Following **General Procedure A** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 16.5 mg, 47%, dr = 1.2/1.0). Data for inseparable isomers: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 – 7.30 (m, 11H), 5.26 – 5.09 (m, 4.4H), 4.95 (td, *J* = 7.0, 4.3 Hz, 1H), 4.65 (t, *J* = 6.6 Hz, 1.2H), 3.56 – 3.50 (m, 4.4H), 2.80 (dd, *J* = 15.9, 6.4 Hz, 2.2H), 2.66 (dd, *J* = 16.1, 6.8 Hz, 1.2H), 2.60 (dd, *J* = 16.4, 7.4 Hz, 1H), 2.22 – 2.16 (m, 1H), 2.01 – 1.90 (m, 3.4H), 1.82 – 1.73 (m, 4.4H), 1.52 – 1.37 (m, 11H), 1.14 (dd, *J* = 7.7, 5.0 Hz, 1.2H), 1.03 – 0.96 (m, 2.2H), 0.94 (t, *J* = 4.7 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.68, 176.51, 169.45, 169.00, 135.31, 135.28, 128.63, 128.49, 128.48, 128.37, 128.34, 75.35, 73.81, 66.89, 66.83, 44.89, 44.87, 40.71, 37.17, 32.25, 32.24, 29.19, 28.53, 28.41, 28.36, 26.88, 26.67, 26.55, 26.42, 26.31, 25.62, 18.11, 14.35; HRMS (ESI-TOF) Calcd for $C_{19}H_{24}ClO_4$ $[M+H]^+$: 351.1363; found: 351.1359.



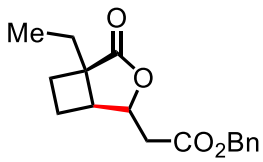
Benzyl 2-(6-methyl-4-oxo-3-oxabicyclo[3.1.0]hexan-2-yl)acetate (3u)

Following **General Procedure A** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 11.0 mg, 42%, dr = 1.4/1.0). Data for inseparable isomers: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 – 7.31 (m, 12H), 5.16 (s, 4.8H), 4.99 – 4.92 (m, 1H), 4.73 (t, *J* = 6.5 Hz, 1.4H), 2.89 – 2.78 (m, 2.4H), 2.68 (dd, *J* = 16.1, 7.0 Hz, 1.4H), 2.63 (dd, *J* = 16.2, 7.5 Hz, 1H), 2.14 – 2.07 (m, 1H), 1.91 (dd, *J* = 5.7, 3.7 Hz, 1.4H), 1.87 (dd, *J* = 5.8, 2.7 Hz, 1H), 1.82 (ddd, *J* = 5.7, 2.8, 1.0 Hz, 1.4H), 1.33 – 1.22 (m, 2.4H), 1.14 (d, *J* = 6.0 Hz, 4.2H), 1.12 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.73, 174.68, 169.37, 169.07, 135.33, 135.30, 128.64, 128.62, 128.48, 128.42, 128.35, 76.48, 75.16, 66.85, 66.82, 40.29, 37.30, 29.69, 28.33, 26.06, 25.22, 21.26, 17.52, 15.98, 15.92; HRMS (ESI-TOF) Calcd for $C_{15}H_{17}O_4$ $[M+H]^+$: 261.1127; found: 261.1132.



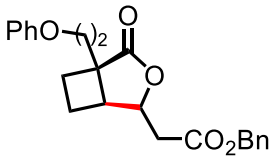
Benzyl 2-(6,6-dimethyl-4-oxo-3-oxabicyclo[3.1.0]hexan-2-yl)acetate (3v)

Following **General Procedure A** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 26.0 mg, 95%, dr > 20.0/1.0). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 – 7.29 (m, 5H), 5.17 (s, 2H), 4.64 (t, *J* = 6.5 Hz, 1H), 2.85 (dd, *J* = 16.0, 6.1 Hz, 1H), 2.72 (dd, *J* = 16.0, 6.9 Hz, 1H), 1.95 (d, *J* = 6.0 Hz, 1H), 1.90 (d, *J* = 6.1 Hz, 1H), 1.21 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.61, 169.15, 135.32, 128.62, 128.47, 128.40, 73.73, 66.84, 40.06, 34.63, 30.82, 25.24, 23.88, 14.85; HRMS (ESI-TOF) Calcd for $C_{16}H_{19}O_4$ $[M+H]^+$: 275.1278; found: 275.1277.



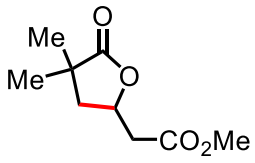
Benzyl 2-(5-ethyl-4-oxo-3-oxabicyclo[3.2.0]heptan-2-yl)acetate (3w)

Following **General Procedure A** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 15.0 mg, 52%, dr = 1.1/1.0). Data for inseparable isomers: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 – 7.30 (m, 10.5H), 5.15 (s, 4.2H), 4.86 – 4.79 (m, 1.1H), 4.78 (td, *J* = 7.1, 1.9 Hz, 1H), 3.01 – 2.94 (m, 1.1H), 2.93 (dd, *J* = 16.3, 7.2 Hz, 1.1H), 2.77 (dd, *J* = 16.0, 6.8 Hz, 1H), 2.63 (dd, *J* = 16.3, 6.9 Hz, 1H), 2.59 – 2.54 (m, 1H), 2.53 (dd, *J* = 16.0, 7.3 Hz, 1.1H), 2.36 – 2.24 (m, 2.1H), 2.19 – 2.05 (m, 2.1H), 2.05 – 1.86 (m, 4.2H), 1.86 – 1.74 (m, 2.1H), 1.76 – 1.64 (m, 2.1H), 0.95 (t, *J* = 7.3 Hz, 3H), 0.94 (t, *J* = 7.3 Hz, 3.3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 181.43, 180.92, 169.57, 169.24, 135.37, 135.34, 128.63, 128.46, 128.34, 128.32, 80.75, 76.34, 66.81, 51.42, 49.20, 41.44, 41.41, 40.68, 35.36, 28.16, 27.72, 27.55, 27.18, 22.05, 15.74, 9.33, 9.22; HRMS (ESI-TOF) Calcd for $C_{17}H_{21}O_4$ $[M+H]^+$: 289.1440; found: 289.1442.



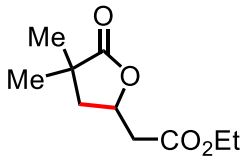
Benzyl 2-(4-oxo-5-(2-phenoxyethyl)-3-oxabicyclo[3.2.0]heptan-2-yl)acetate (3x)

Following **General Procedure A** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 16.0 mg, 43%, dr = 1.6/1.0). Data for inseparable isomers: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 – 7.29 (m, 13H), 7.28 – 7.21 (m, 5.2H), 6.98 – 6.89 (m, 2.6H), 6.88 – 6.81 (m, 5.2H), 5.17 – 5.05 (m, 5.2H), 4.90 – 4.83 (m, 1.6H), 4.83 – 4.77 (m, 1H), 4.09 (t, *J* = 5.9 Hz, 2H), 4.09 – 4.02 (m, 1.6H), 4.02 – 3.95 (m, 1.6H), 3.26 – 3.19 (m, 1.6H), 2.95 – 2.86 (m, 2.6H), 2.74 (dd, *J* = 16.2, 6.5 Hz, 1H), 2.63 (dd, *J* = 16.3, 7.4 Hz, 1.6H), 2.54 (dd, *J* = 16.2, 7.5 Hz, 1H), 2.47 – 2.32 (m, 2.6H), 2.32 – 2.13 (m, 7.8H), 2.11 – 1.92 (m, 5.2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 181.15, 180.69, 169.37, 169.36, 158.19, 158.09, 135.37, 135.36, 129.53, 129.51, 128.60, 128.58, 128.42, 128.38, 128.27, 128.25, 121.06, 121.01, 114.26, 114.23, 81.41, 76.34, 66.73, 66.66, 64.26, 64.21, 49.01, 46.92, 42.05, 42.02, 40.16, 35.12, 33.92, 33.42, 29.29, 28.93, 22.42, 16.14; HRMS (ESI-TOF) Calcd for $C_{23}H_{25}O_5$ $[M+H]^+$: 381.1702; found: 381.1707.



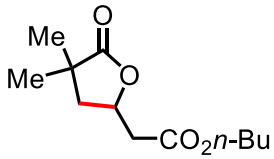
Methyl 2-(4,4-dimethyl-5-oxotetrahydrofuran-2-yl)acetate (4a)

Following **General Procedure A** on 0.1 mmol scale. Purification by column chromatography afforded the title compound (colorless oil, 17.0 mg, 92%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.84 (ddt, *J* = 9.9, 6.9, 6.1 Hz, 1H), 3.72 (s, 3H), 2.83 (dd, *J* = 16.2, 7.0 Hz, 1H), 2.62 (dd, *J* = 16.2, 6.2 Hz, 1H), 2.30 (dd, *J* = 12.8, 6.0 Hz, 1H), 1.83 (dd, *J* = 12.8, 9.9 Hz, 1H), 1.29 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.14, 170.01, 72.60, 52.00, 43.09, 40.33, 40.04, 24.95, 24.39; HRMS (ESI-TOF) Calcd for $C_9H_{15}O_4$ $[M+H]^+$: 187.0965; found: 187.0962.



Ethyl 2-(4,4-dimethyl-5-oxotetrahydrofuran-2-yl)acetate (4b)

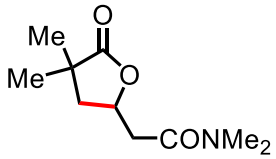
Following **General Procedure A** on 0.1 mmol scale. Purification by column chromatography afforded the title compound (colorless oil, 18.0 mg, 90%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.84 (dq, *J* = 9.9, 6.4 Hz, 1H), 4.24 – 4.10 (m, 2H), 2.82 (dd, *J* = 16.2, 6.9 Hz, 1H), 2.60 (dd, *J* = 16.2, 6.2 Hz, 1H), 2.30 (dd, *J* = 12.8, 6.0 Hz, 1H), 1.83 (dd, *J* = 12.8, 9.9 Hz, 1H), 1.35 – 1.21 (m, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 181.21, 169.57, 72.68, 60.99, 43.07, 40.31, 40.28, 24.94, 24.39, 14.13; HRMS (ESI-TOF) Calcd for $C_{10}H_{17}O_4$ $[M+H]^+$: 201.1121; found: 201.1120.



Butyl 2-(4,4-dimethyl-5-oxotetrahydrofuran-2-yl)acetate (4c)

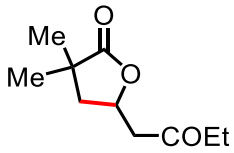
Following **General Procedure A** on 0.1 mmol scale. Purification by column chromatography afforded the title compound (colorless oil, 21.0 mg, 91%). ^{1}H NMR (600

MHz, $CDCl_3$) δ 4.83 (dq, *J* = 9.9, 6.3 Hz, 1H), 4.12 (tt, *J* = 7.0, 3.5 Hz, 2H), 2.82 (dd, *J* = 16.2, 6.9 Hz, 1H), 2.60 (dd, *J* = 16.1, 6.3 Hz, 1H), 2.30 (dd, *J* = 12.8, 6.0 Hz, 1H), 1.83 (dd, *J* = 12.8, 9.9 Hz, 1H), 1.67 – 1.58 (m, 2H), 1.43 – 1.35 (m, 2H), 1.29 (s, 3H), 1.29 (s, 3H), 0.94 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 181.20, 169.66, 72.68, 64.90, 43.09, 40.31, 40.26, 30.52, 24.95, 24.38, 19.06, 13.65; HRMS (ESI-TOF) Calcd for $C_{12}H_{21}O_4$ $[M+H]^+$: 229.1434; found: 229.1438.



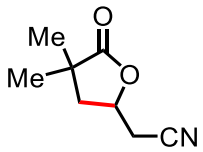
2-(4,4-Dimethyl-5-oxotetrahydrofuran-2-yl)-N,N-dimethylacetamide (4d)

Following **General Procedure A** on 0.1 mmol scale. Purification by column chromatography afforded the title compound (colorless oil, 19.0 mg, 95%). ^1H NMR (600 MHz, $CDCl_3$) δ 4.92 (ddt, *J* = 10.0, 7.1, 5.8 Hz, 1H), 3.03 (s, 3H), 3.00 – 2.93 (m, 4H), 2.52 (dd, *J* = 15.8, 7.1 Hz, 1H), 2.44 (dd, *J* = 12.9, 5.9 Hz, 1H), 1.80 (dd, *J* = 12.9, 9.9 Hz, 1H), 1.28 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 181.53, 168.89, 74.02, 43.90, 40.28, 39.15, 37.30, 35.25, 24.96, 24.33; HRMS (ESI-TOF) Calcd for $C_{10}H_{18}NO_3$ $[M+H]^+$: 200.1287; found: 200.1292.



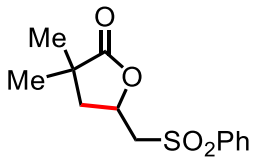
3,3-Dimethyl-5-(2-oxobutyl)dihydrofuran-2(3H)-one (4e)

Following **General Procedure A** on 0.1 mmol scale. Purification by column chromatography afforded the title compound (colorless oil, 17.0 mg, 94%). ^1H NMR (400 MHz, $CDCl_3$) δ 4.92 – 4.80 (m, 1H), 2.98 (dd, *J* = 16.9, 6.6 Hz, 1H), 2.64 (dd, *J* = 16.9, 6.1 Hz, 1H), 2.49 (qd, *J* = 7.3, 4.5 Hz, 2H), 2.32 (dd, *J* = 12.8, 5.9 Hz, 1H), 1.74 (dd, *J* = 12.8, 10.1 Hz, 1H), 1.28 (s, 6H), 1.07 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.67, 181.34, 72.64, 47.60, 43.53, 40.24, 36.89, 24.95, 24.30, 7.46; HRMS (ESI-TOF) Calcd for $C_{10}H_{17}O_3$ $[M+H]^+$: 185.1172; found: 185.1176.



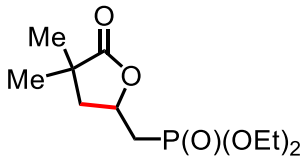
2-(4,4-Dimethyl-5-oxotetrahydrofuran-2-yl)acetonitrile (4f)

Following **General Procedure A** on 0.1 mmol scale. Purification by column chromatography afforded the title compound (colorless oil, 12.0 mg, 78%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.72 – 4.60 (m, 1H), 2.87 – 2.75 (m, 2H), 2.34 (dd, *J* = 12.9, 6.1 Hz, 1H), 1.98 (dd, *J* = 12.9, 9.8 Hz, 1H), 1.34 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.07, 115.20, 70.83, 42.24, 40.47, 24.80, 24.45, 23.99; HRMS (ESI-TOF) Calcd for $C_8H_{12}NO_2$ $[M+H]^+$: 154.0863; found: 154.0863.



3,3-Dimethyl-5-((phenylsulfonyl)methyl)dihydrofuran-2(3H)-one (4g)

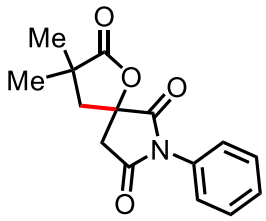
Following **General Procedure A** on 0.1 mmol scale. Purification by column chromatography afforded the title compound (colorless oil, 24.0 mg, 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 – 7.90 (m, 2H), 7.76 – 7.65 (m, 1H), 7.65 – 7.54 (m, 2H), 4.89 (dq, *J* = 10.0, 6.1 Hz, 1H), 3.62 (dd, *J* = 14.3, 6.1 Hz, 1H), 3.34 (dd, *J* = 14.4, 6.2 Hz, 1H), 2.40 (dd, *J* = 13.0, 6.1 Hz, 1H), 1.94 (dd, *J* = 13.0, 10.0 Hz, 1H), 1.26 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.16, 139.24, 134.28, 129.45, 128.05, 70.36, 60.82, 43.25, 39.78, 24.73, 24.11; HRMS (ESI-TOF) Calcd for $C_{13}H_{17}O_4S$ $[M+H]^+$: 269.0842; found: 269.0842.



Diethyl ((4,4-dimethyl-5-oxotetrahydrofuran-2-yl)methyl)phosphonate (4h)

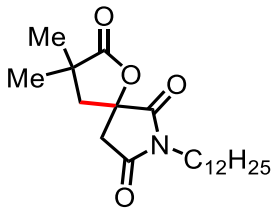
Following **General Procedure A** on 0.1 mmol scale. Purification by column chromatography afforded the title compound (colorless oil, 23.0 mg, 88%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.81 – 4.67 (m, 1H), 4.21 – 4.07 (m, 4H), 2.44 – 2.39 (m, 1H), 2.39 – 2.32 (m, 1H), 2.12 – 2.00 (m, 1H), 1.90 (dd, *J* = 13.0, 10.0 Hz, 1H), 1.39 – 1.31 (m, 6H), 1.29 (s,

3H), 1.27 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 181.05, 71.89, 62.18 (d, *J* = 6.5 Hz), 61.95 (d, *J* = 6.4 Hz), 44.39 (d, *J* = 5.8 Hz), 40.44, 32.59 (d, *J* = 139.8 Hz), 24.88, 24.19, 16.40 (d, *J* = 6.1 Hz), 16.39 (d, *J* = 6.1 Hz); HRMS (ESI-TOF) Calcd for $C_{11}H_{22}O_5P$ $[M+H]^+$: 265.1199; found: 265.1197.



3,3-Dimethyl-7-phenyl-1-oxa-7-azaspiro[4.4]nonane-2,6,8-trione (4i)

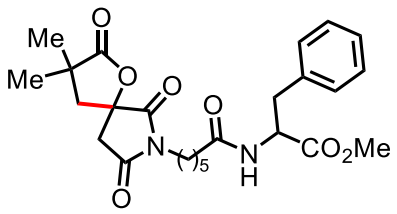
Following **General Procedure A** on 0.1 mmol scale with the following modification: $Pd(OAc)_2$ (10 mol%) without $Na_2HPO_4.7H_2O$. Purification by column chromatography afforded the title compound (colorless oil, 27.0 mg, 99%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.55 – 7.48 (m, 2H), 7.47 – 7.41 (m, 1H), 7.35 – 7.29 (m, 2H), 3.33 (d, *J* = 18.4 Hz, 1H), 3.08 (d, *J* = 18.5 Hz, 1H), 2.79 (d, *J* = 13.5 Hz, 1H), 2.24 (d, *J* = 13.5 Hz, 1H), 1.51 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.80, 174.16, 171.27, 131.04, 129.31, 129.15, 126.14, 78.69, 44.86, 42.87, 40.40, 27.01, 25.78; HRMS (ESI-TOF) Calcd for $C_{15}H_{16}NO_4$ $[M+H]^+$: 274.1074; found: 274.1071.



7-Dodecyl-3,3-dimethyl-1-oxa-7-azaspiro[4.4]nonane-2,6,8-trione (4j)

Following **General Procedure A** on 0.1 mmol scale with the following modification: $Pd(OAc)_2$ (10 mol%) without $Na_2HPO_4.7H_2O$. Purification by column chromatography afforded the title compound (colorless oil, 26.0 mg, 71%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.60 – 3.48 (m, 2H), 3.14 (d, *J* = 18.3 Hz, 1H), 2.89 (d, *J* = 18.3 Hz, 1H), 2.66 (d, *J* = 13.4 Hz, 1H), 2.13 (d, *J* = 13.4 Hz, 1H), 1.64 – 1.53 (m, 2H), 1.48 (s, 3H), 1.37 (s, 3H), 1.35 – 1.20 (m, 18H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.89, 175.06, 172.27, 78.64, 44.74, 42.77, 40.33, 39.50, 31.88, 29.58, 29.50, 29.39, 29.31, 29.03, 27.48,

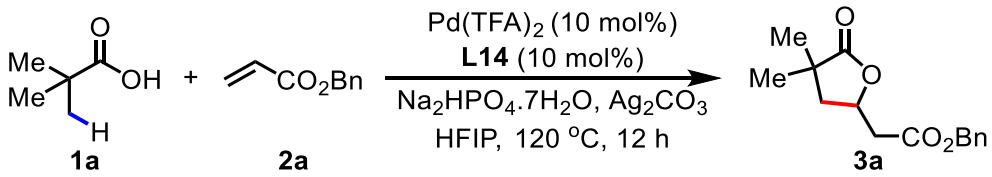
26.85, 26.68, 25.72, 22.65, 14.09; HRMS (ESI-TOF) Calcd for $C_{21}H_{36}NO_4$ $[M+H]^+$: 366.2644; found: 366.2647.



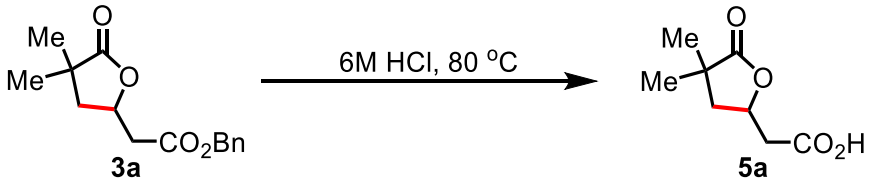
Methyl (6-(3,3-dimethyl-2,6,8-trioxo-1-oxa-7-azaspiro[4.4]nonan-7-yl)hexanoyl)phenylalaninate (4k)

Following **General Procedure A** on 0.1 mmol scale with the following modification: $Pd(OAc)_2$ (10 mol%) without $Na_2HPO_4.7H_2O$. Purification by column chromatography afforded the title compound (colorless oil, 25.0 mg, 53%, dr = 1.0/1.0). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 7.27 – 7.20 (m, 1H), 7.12 – 7.05 (m, 2H), 5.87 (d, *J* = 7.9 Hz, 1H), 4.91 – 4.84 (m, 1H), 3.73 (s, 3H), 3.53 (td, *J* = 7.1, 6.2, 3.3 Hz, 2H), 3.19 – 3.11 (m, 2H), 3.10 – 3.04 (m, 1H), 2.90 (dd, *J* = 18.3, 2.0 Hz, 1H), 2.66 (d, *J* = 13.4 Hz, 1H), 2.20 – 2.10 (m, 3H), 1.65 – 1.52 (m, 4H), 1.48 (s, 3H), 1.36 (s, 3H), 1.33 – 1.21 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.88, 175.05, 172.30, 172.26, 172.09, 172.08, 172.06, 172.04, 135.82, 129.72, 129.18, 129.10, 128.56, 127.11, 126.54, 78.66, 52.91, 52.90, 52.30, 44.66, 44.65, 42.74, 42.73, 40.30, 39.13, 37.86, 37.84, 36.00, 27.09, 26.84, 26.08, 26.05, 25.71, 24.76; HRMS (ESI-TOF) Calcd for $C_{25}H_{32}N_2O_7$ $[M+H]^+$: 473.2288; found: 473.2289.

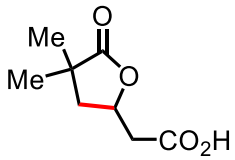
Gram-Scale Experiment and Synthetic Application



In the sealed tube, $Pd(TFA)_2$ (10 mol%, 0.40 g), ligand **L14** (10 mol%, 0.23 g), $Na_2HPO_4.7H_2O$ (1.0 eq, 3.22 g), Ag_2CO_3 (1.0 eq, 3.30 g), and pivalic acid **1a** (12.0 mmol, 1.22 g) in order were weighed in air and placed with a magnetic stir bar. Then HFIP (24.0 mL) and benzyl acrylate **2a** (2.0 eq, 3.60 mL) was added. The reaction mixture was stirred at rt for 10 min, and then heated to 120 °C for 12 h (300 rpm). After being allowed to cool to room temperature, the mixture was diluted with DCM, and filtered through a pad of celite. The filtrate was concentrated *in vacuo*, and the resulting mixture purified by column chromatography to afford **3a** (2.92 g, 93%).



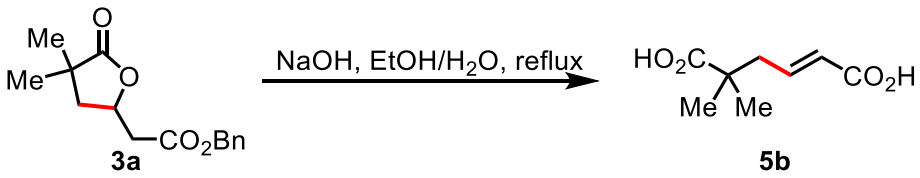
To a solution of 6M HCl (2 mL) was added **3a** (0.2 mmol) then the mixture was heated to 80 °C until TLC showed that the **3a** was fully consumed. The reaction mixture was cooled down to room temperature, then extracted with DCM. The organic phase was dried with anhydrous Na_2SO_4, and the solvent was removed under vacuum. The residue was purified by column chromatography to afford **5a** (31.6 mg, 92%).



2-(4,4-Dimethyl-5-oxotetrahydrofuran-2-yl)acetic acid (5a)

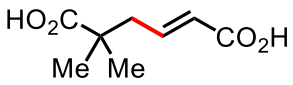
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.67 (br s, 1H), 4.82 (ddt, *J* = 10.0, 7.2, 5.9 Hz, 1H), 2.84 (ddd, *J* = 16.6, 7.2, 1.4 Hz, 1H), 2.68 (dd, *J* = 16.6, 5.8 Hz, 1H), 2.31 (dd, *J* = 12.8, 6.0 Hz, 1H), 1.84 (dd, *J* = 12.8, 10.0 Hz, 1H), 1.28 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ

181.39, 175.00, 72.41, 42.87, 40.33, 39.88, 24.84, 24.32; HRMS (ESI-TOF) Calcd for $C_8H_{12}O_4$ $[M+H]^+$: 173.0808; found: 173.0807.



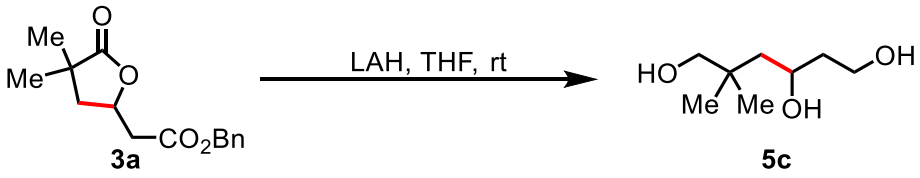
3a **5b**

To a solution of **3a** (1.0 mmol) in EtOH/H_2O (5.0/5.0 mL) was added NaOH (4.0 eq), then the mixture was heated to reflux until TLC showed that the **3a** was fully consumed. The reaction mixture was cooled down to room temperature, and 1M HCl was added until the pH value to about 3, followed by filtration through a pad of celite, and the solvent was removed under vacuum. The residue was purified by column chromatography to afford **5b** (135 mg, 78%).



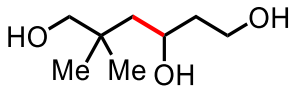
(*E*)-5,5-Dimethylhex-2-enedioic acid (5b)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04 (dt, *J* = 15.5, 7.7 Hz, 1H), 5.88 (dt, *J* = 15.5, 1.4 Hz, 1H), 2.48 (dd, *J* = 7.7, 1.4 Hz, 2H), 1.26 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.39, 171.57, 147.38, 123.70, 42.51, 42.24, 25.07; HRMS (ESI-TOF) Calcd for $C_8H_{12}O_4$ $[M+H]^+$: 173.0808; found: 173.0807.



3a **5c**

To a solution of **3a** (0.2 mmol) in THF (2.0 mL) was added 0.4 mL of LAH solution (1.0 M in THF), then the mixture was stirred at room temperature until TLC showed that the **3a** was fully consumed (around 1h). The reaction mixture was added $Na_2SO_4{\cdot}10H_2O$ (10 mg) followed by water (2 mL), then extracted with DCM. The organic phase was dried with anhydrous Na_2SO_4, and the solvent was removed under vacuum. The residue was purified by column chromatography to afford **5c** (27.0 mg, 83%).

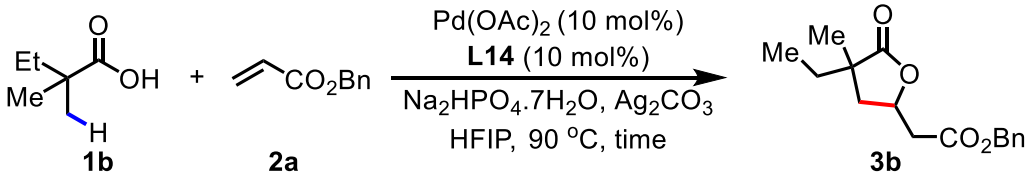


5,5-Dimethylhexane-1,3,6-triol (5c)

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.09 – 4.01 (m, 1H), 3.95 – 3.88 (m, 1H), 3.90 – 3.82 (m, 1H), 3.42 (d, *J* = 11.0 Hz, 1H), 3.37 (d, *J* = 11.0 Hz, 1H), 1.79 – 1.68 (m, 1H), 1.66 – 1.58 (m, 2H), 1.31 (d, *J* = 14.8 Hz, 1H), 0.97 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 71.54, 69.03, 62.12, 48.93, 39.28, 35.08, 28.19, 22.90; HRMS (ESI-TOF) Calcd for $C_8H_{18}O_3$ $[M+H]^+$: 163.1329; found: 163.1333.

Kinetic Experiments

Kinetic data with **L14**



General Procedure: In the control tube, $Pd(OAc)_2$ (10 mol%), ligand **L14** (10 mol%), $Na_2HPO_4.7H_2O$ (1.0 eq), and Ag_2CO_3 (1.0 eq) in order were weighed in air and placed with a magnetic stir bar. Then HFIP (1.0 mL), **1b** (0.1 mmol), and **2a** (2.0 eq) were added. The reaction mixture was stirred at rt for 10 min, and then heated to 90 ^oC for the appropriate time (300 rpm). After being allowed to cool in a dry ice bath, the mixture was diluted with DCM, and filtered through a pad of celite. The filtrate was concentrated *in vacuo*, and the yield was determined by ^1H NMR analysis of the crude product using CH_2Br_2 as the internal standard. The obtained average yields for three trials were plotted as concentration [**3b**] vs. time t (Figure S1). Kinetic data under the standard conditions are shown below:

3b (10^{-3} M)

entry	t(min)	trial 1	trial 2	trial 3	average	std. dev.
1	0	0.0	0.0	0.0	0.0	0.0
2	10	16.0	20.6	21.0	19.2	2.8
3	20	20.2	22.4	25.0	22.5	2.4
4	30	31.8	37.4	39.4	36.2	3.9
5	40	39.4	38.4	42.6	40.1	2.2
6	50	42.4	42.4	44.2	43.0	1.0
7	60	44.6	44.4	47.0	45.3	1.4

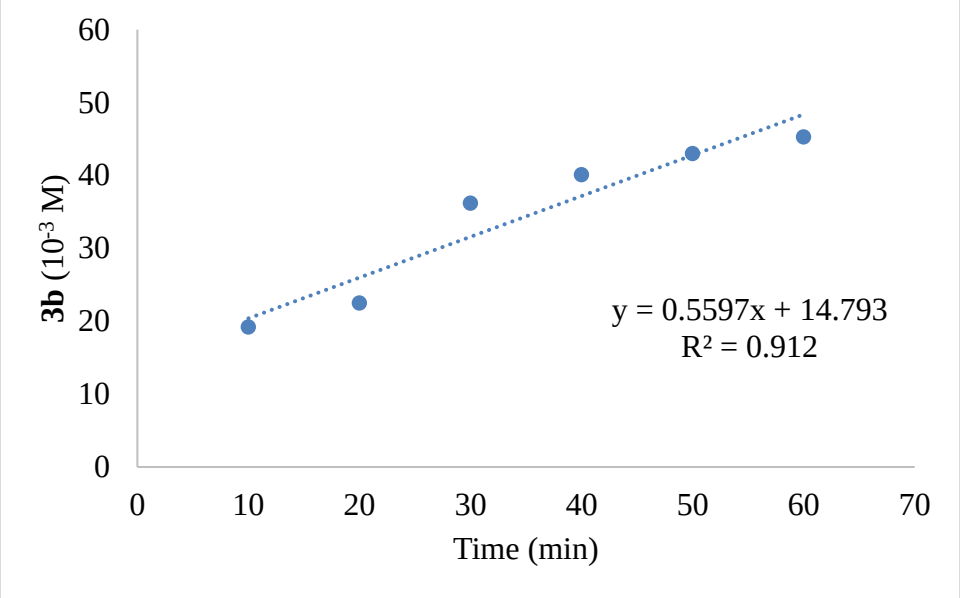
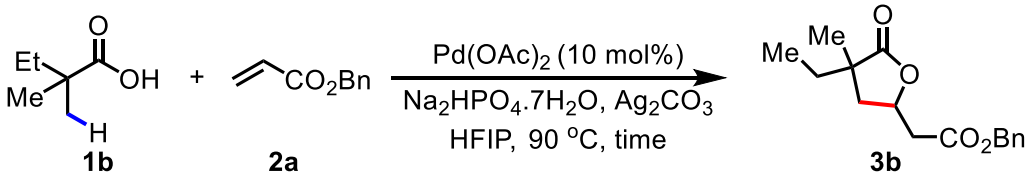


Figure S1. Representative initial data for *β*-C(sp^3)–H olefination of **1b** with **L14**

Kinetic data in the absence of **L14**



General Procedure: In the control tube, $Pd(OAc)_2$ (10 mol%), $Na_2HPO_4.7H_2O$ (1.0 eq), and Ag_2CO_3 (1.0 eq) in order were weighed in air and placed with a magnetic stir bar. Then HFIP (1.0 mL), **1b** (0.1 mmol), and **2a** (2.0 eq) were added. The reaction mixture was stirred at rt for 10 min, and then heated to 90 °C for the appropriate time (300 rpm). After being allowed to cool in a dry ice bath, the mixture was diluted with DCM, and filtered through a pad of celite. The filtrate was concentrated *in vacuo*, and the yield was determined by ^1H NMR analysis of the crude product using CH_2Br_2 as the internal standard. The obtained average yields for three trials were plotted as concentration [**3b**] vs. time t (Figure S2). Kinetic data under the standard conditions are shown below:

3b (10^{-3} M)

entry	t(min)	trial 1	trial 2	trial 3	average	std. dev.
1	0	0.0	0.0	0.0	0.0	0.0
2	60	9.8	8.8	8.4	9.0	0.7
3	120	10.4	10.2	9.6	10.1	0.4
4	180	11.0	10.8	11.4	11.1	0.3
5	240	11.4	11.4	12.0	11.6	0.3
6	300	13.2	13.8	16.8	14.6	1.9
7	360	19.6	15.8	18.4	17.9	1.9

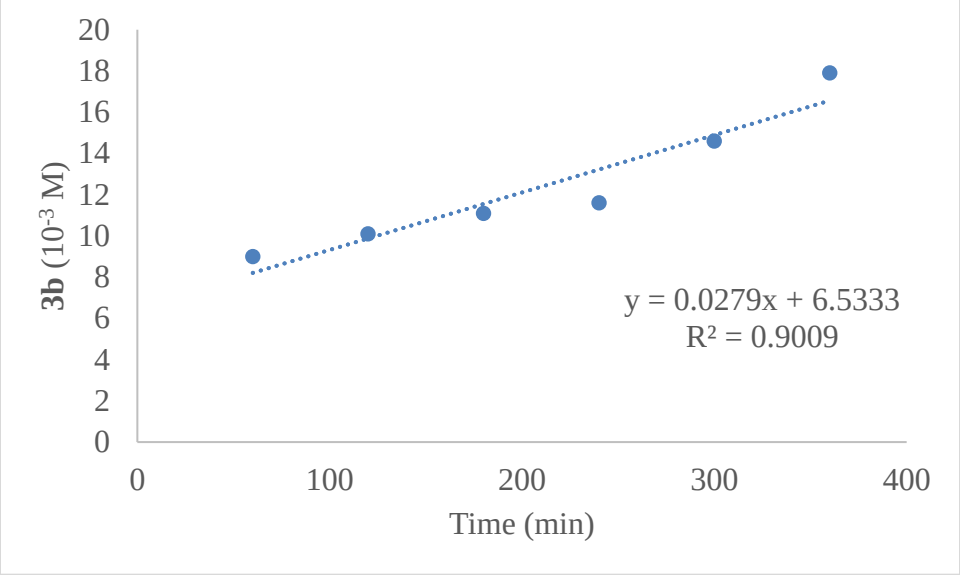


Figure S2. Representative data for *β*-C(sp^3)–H olefination of **1b** in the absence of **L14**

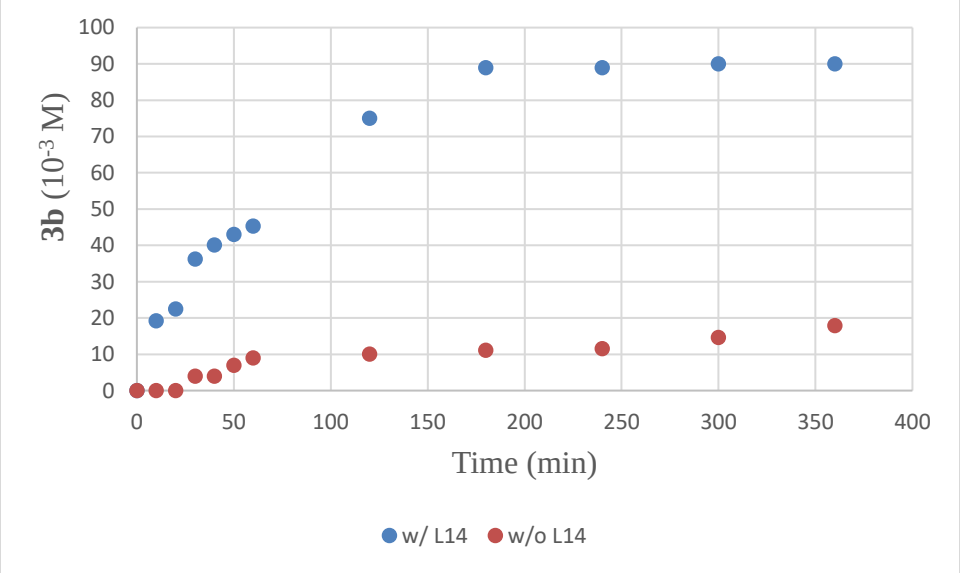
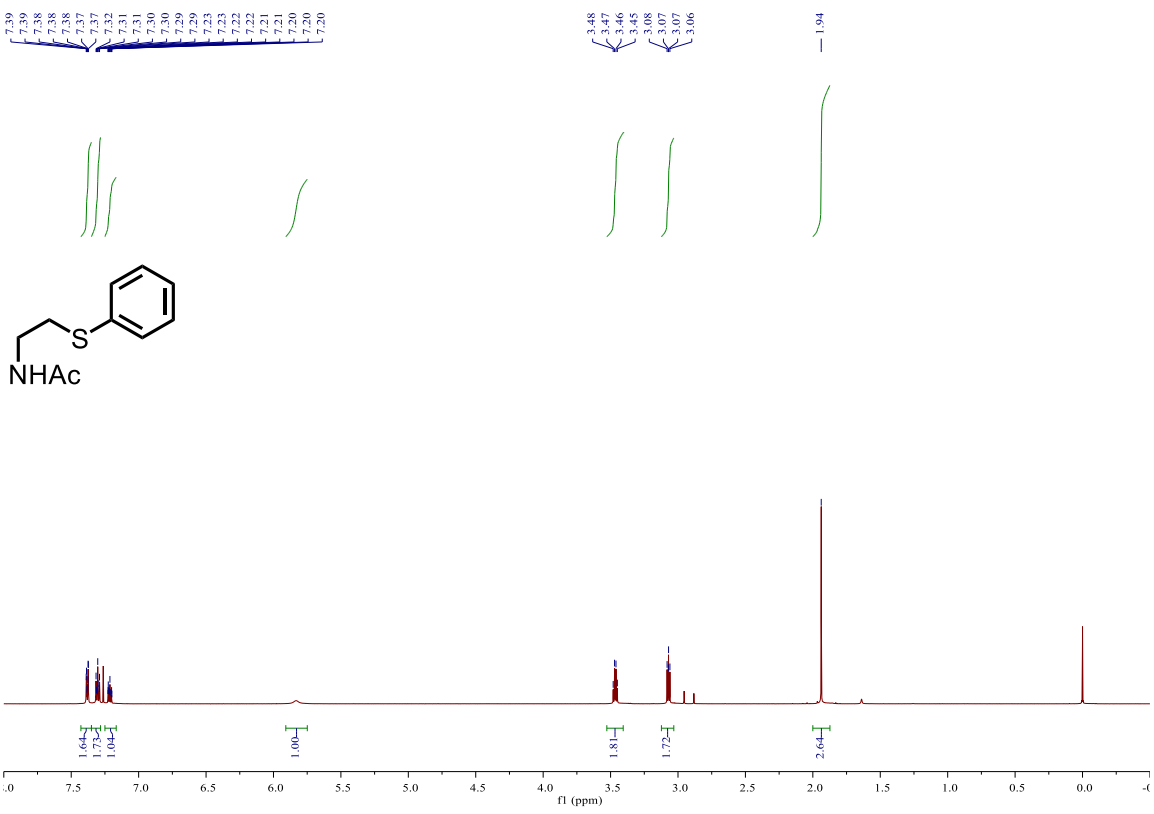
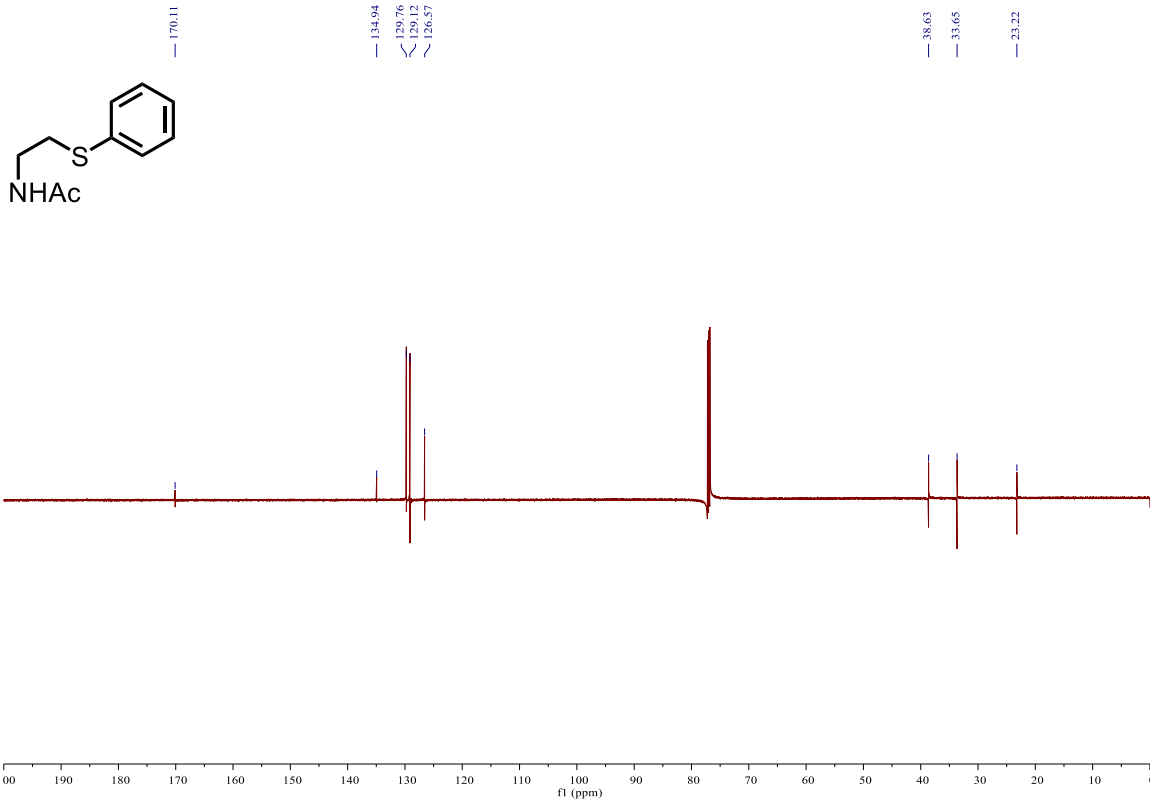


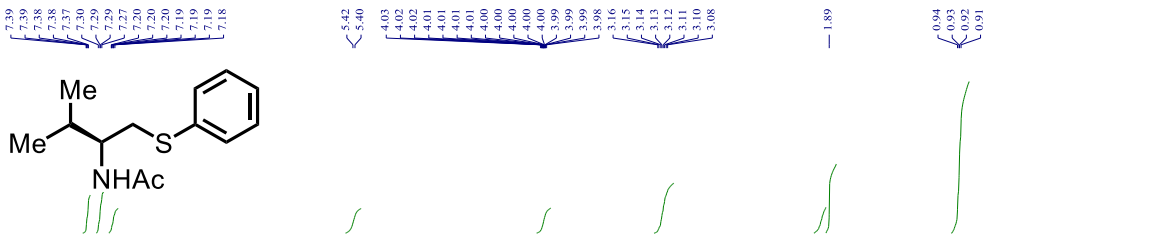
Figure S3. Representative data for *β*-C(sp^3)–H olefination of **1b**

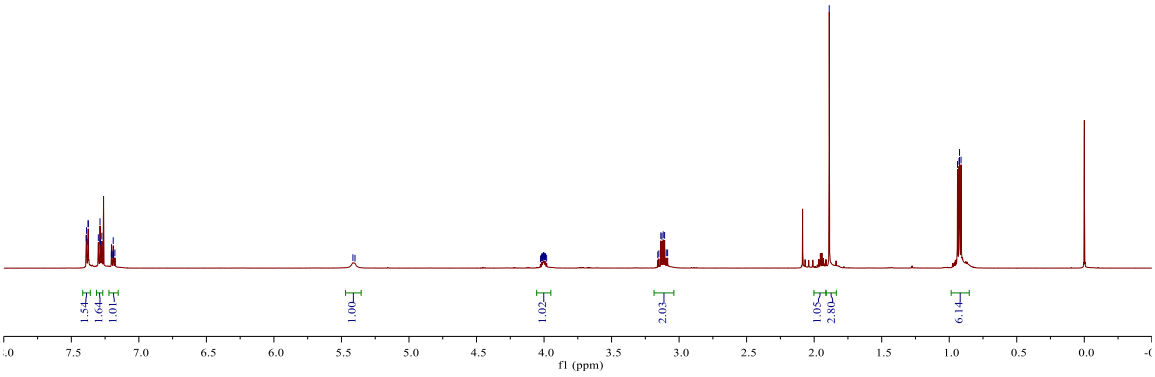
Reference:

1. Katritzky, A. R.; Xu, Y. J.; He, H. Y.; Mehta, S. *J. Org. Chem.* **2001**, *66*, 5590.
2. Adams, H.; Anderson, J. C.; Cubbon, R.; James, D. S.; Mathias, J. P. *J. Org. Chem.* **1999**, *64*, 8256.

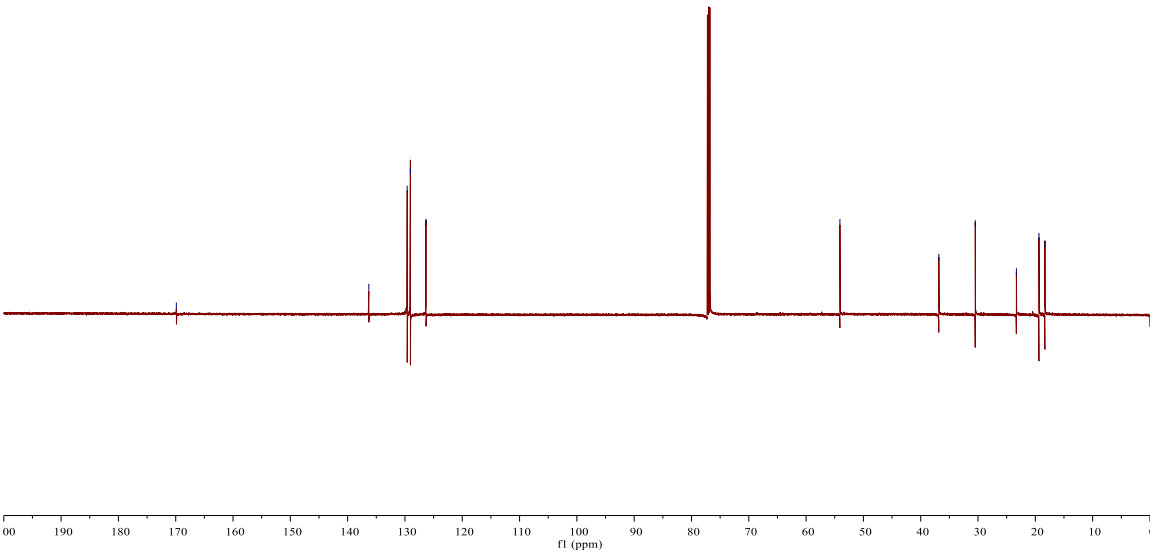

7.39
7.39
7.38
7.38
7.38
7.37
7.37
7.32
7.31
7.31
7.30
7.30
7.29
7.29
7.23
7.23
7.22
7.22
7.21
7.21
7.20
7.20
7.20
3.48
3.47
3.46
3.45
3.08
3.07
3.07
3.06
1.94
S
NHAc
1.64
1.73
1.04
1.00
1.81
1.72
2.64
f1 (ppm)

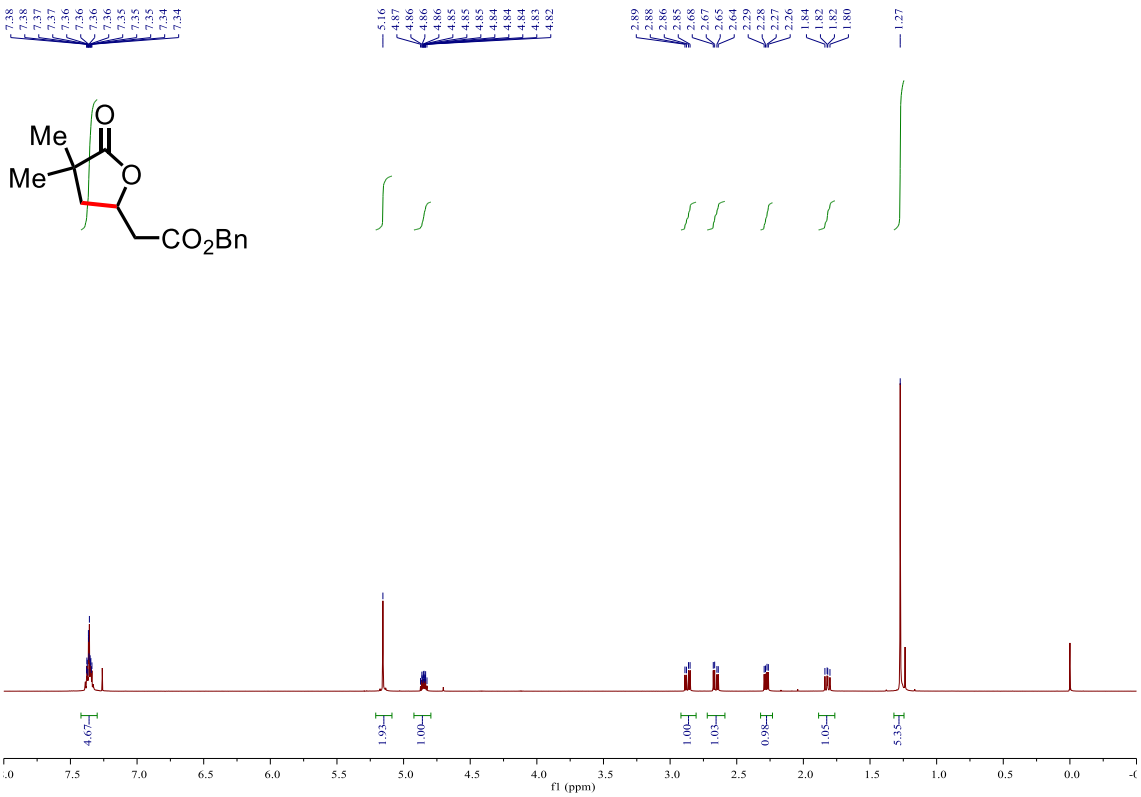

170.11
134.94
129.76
129.12
126.57
38.63
33.65
23.22
S
NHAc
f1 (ppm)

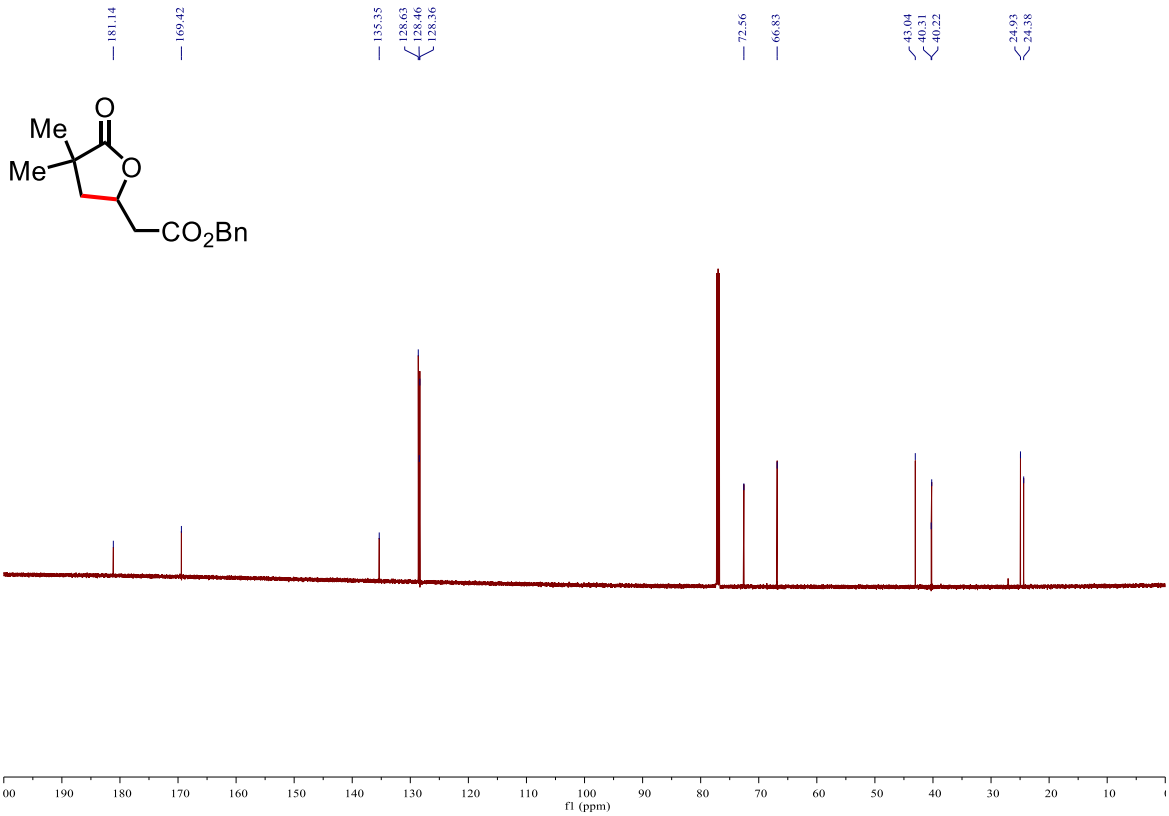

Me
Me
S
NHAc

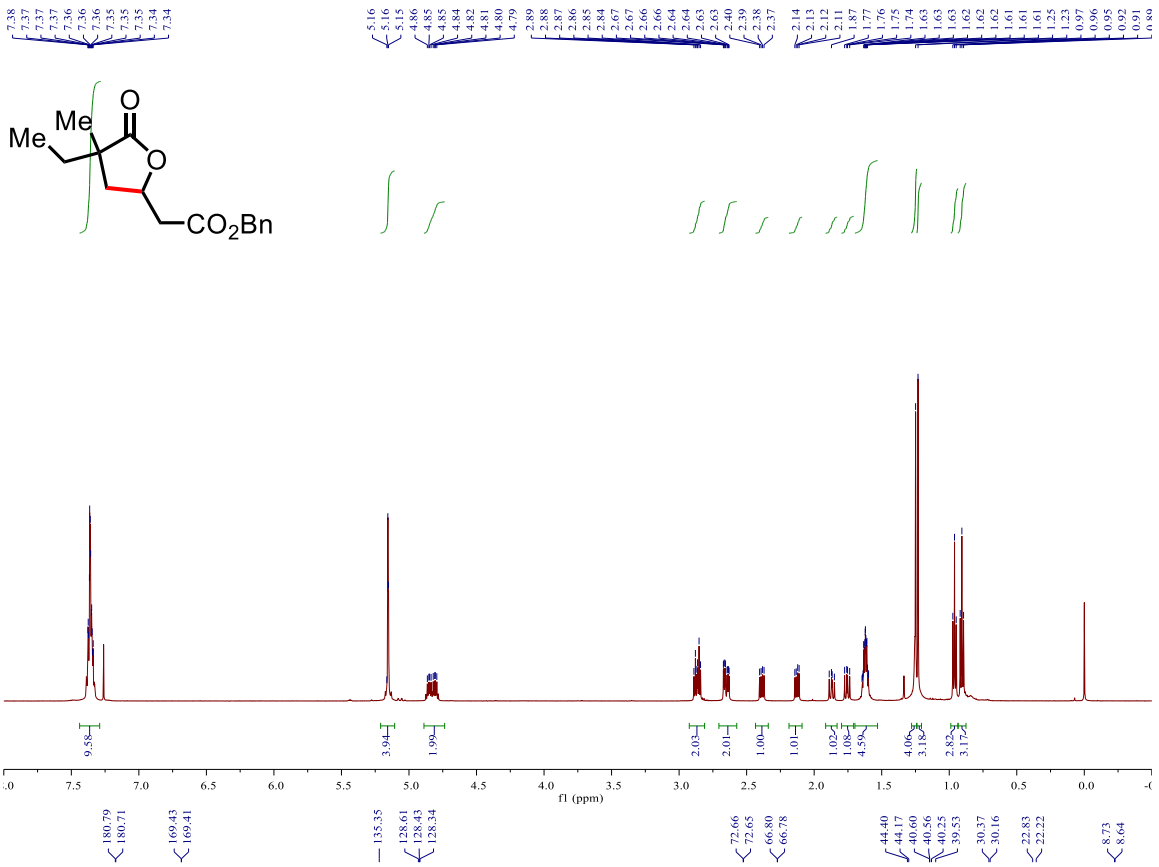

f1 (ppm)

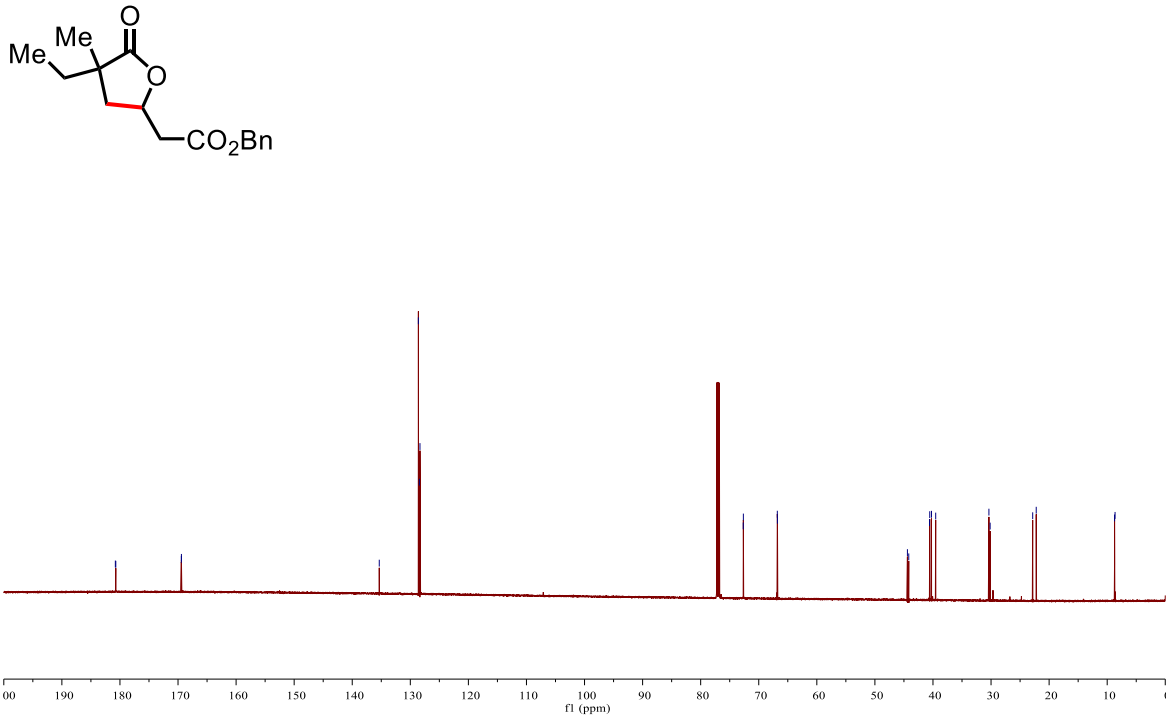

Me
Me
S
NHAc

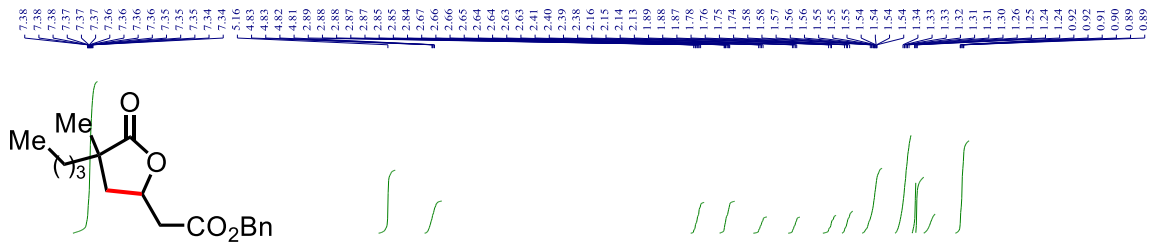

f1 (ppm)

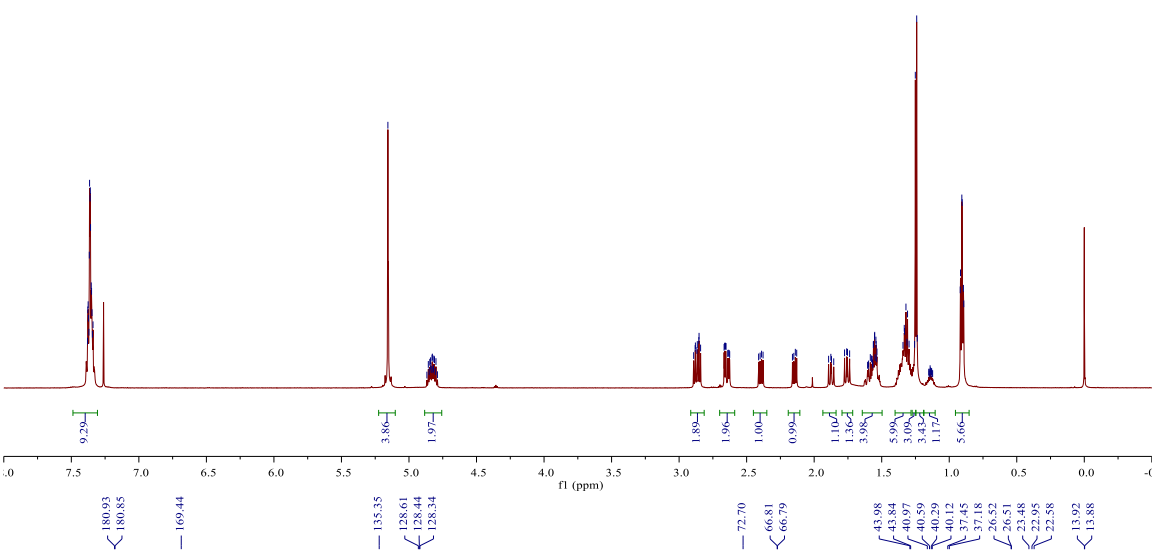

Me
Me
O
O
CO2Bn
f1 (ppm)


Me
Me
O
O
CO2Bn
f1 (ppm)


Me
Me
O
O
CO2Bn
f1 (ppm)

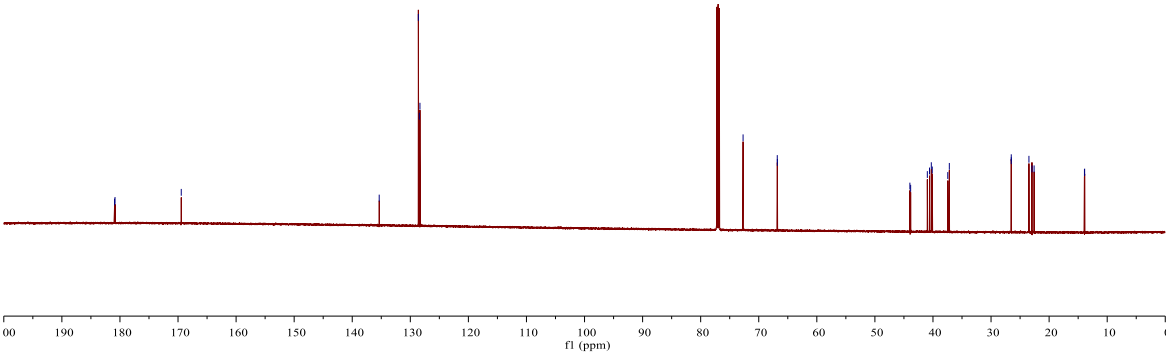

Me
Me
O
O
CO2Bn
f1 (ppm)

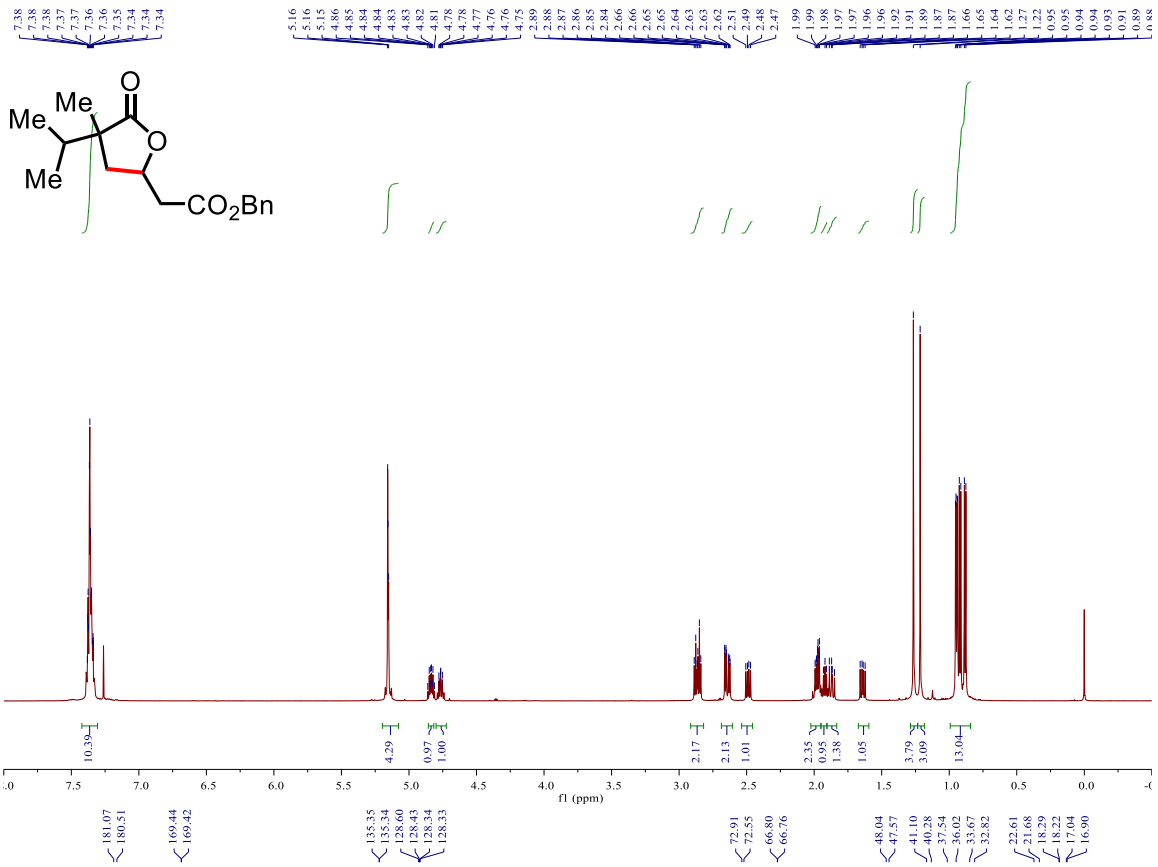

Me
Me
3
O
O
CO2Bn

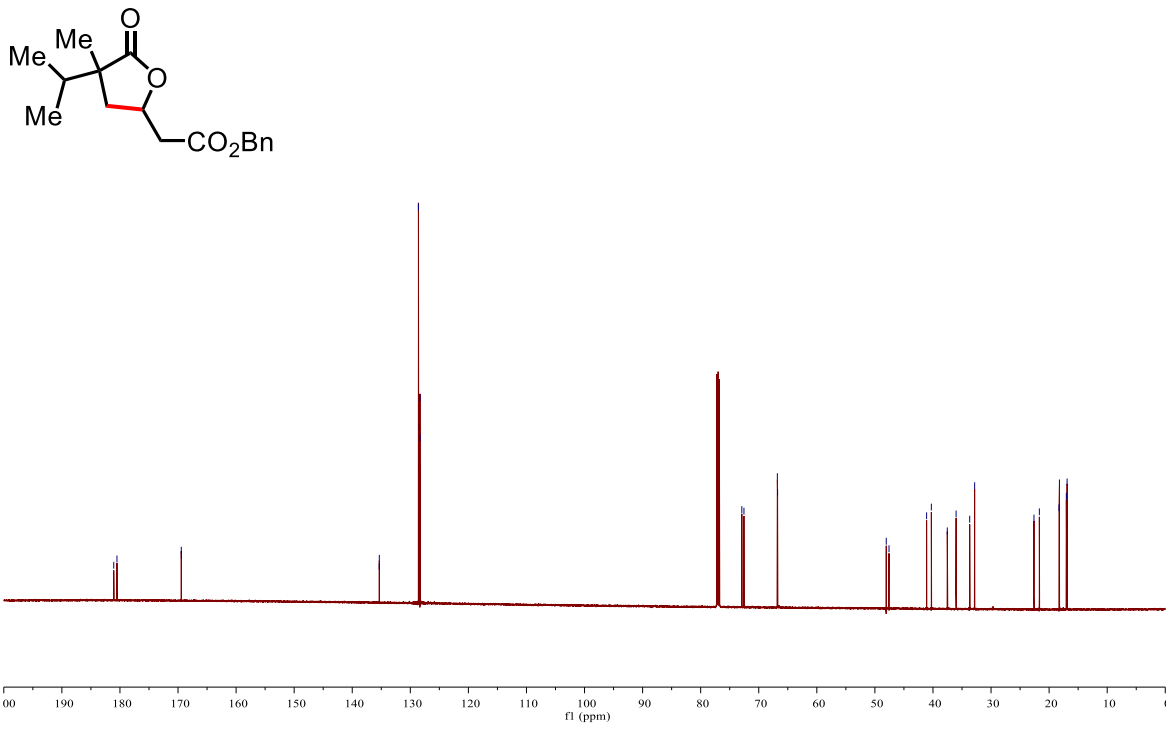

9.29
3.86
1.97
1.89
1.96
1.00
0.99
1.10
1.36
3.98
5.99
3.09
3.43
1.17
5.66
f1 (ppm)

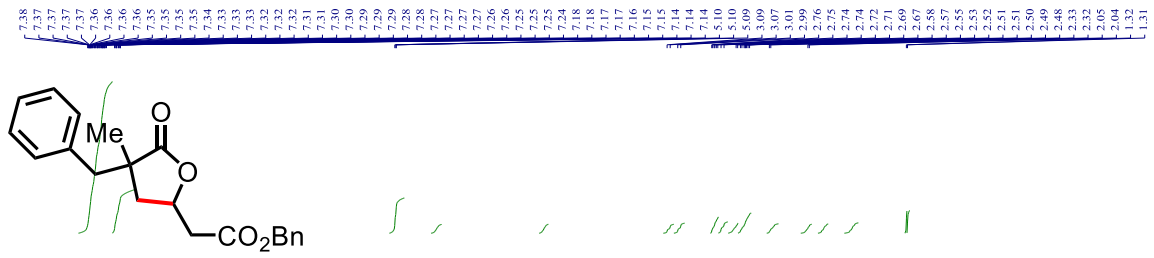
180.93
180.85
169.44
135.35
128.61
128.44
128.34
72.70
66.81
66.79
43.98
43.84
40.97
40.59
40.29
40.12
37.45
37.18
26.52
26.51
23.48
22.95
22.58
13.92
13.88

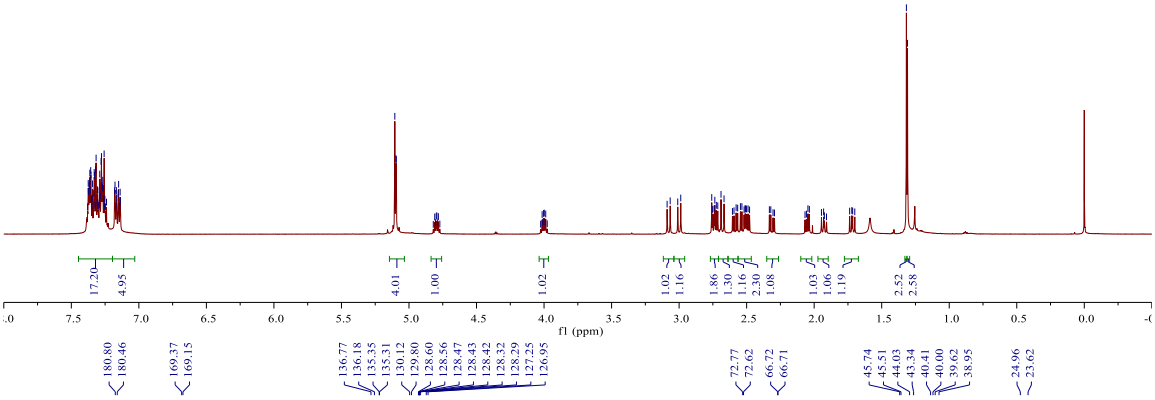

Me
Me
3
O
O
CO2Bn


f1 (ppm)

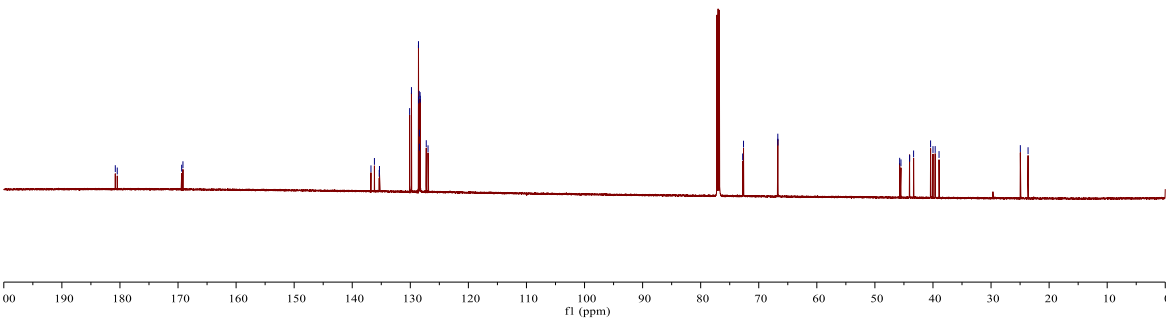

Me
Me
Me
O
O
CO2Bn
f1 (ppm)

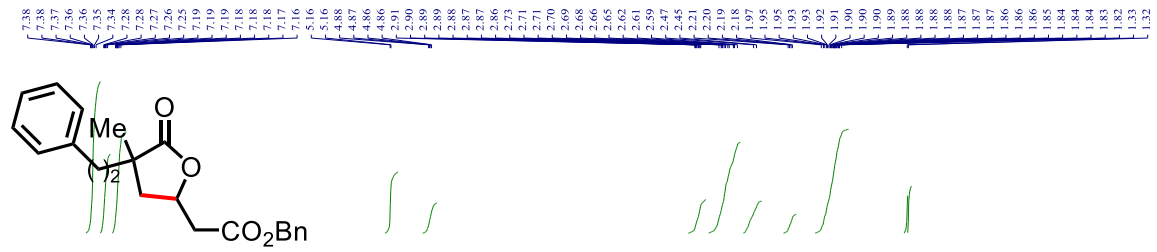

Me
Me
Me
O
O
CO2Bn
f1 (ppm)

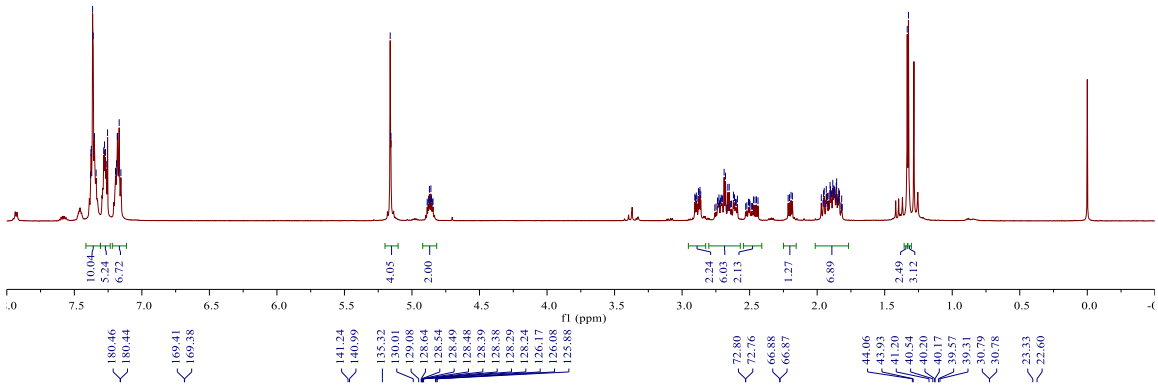

Me
O
O
CO2Bn


f1 (ppm)


Me
O
O
CO2Bn

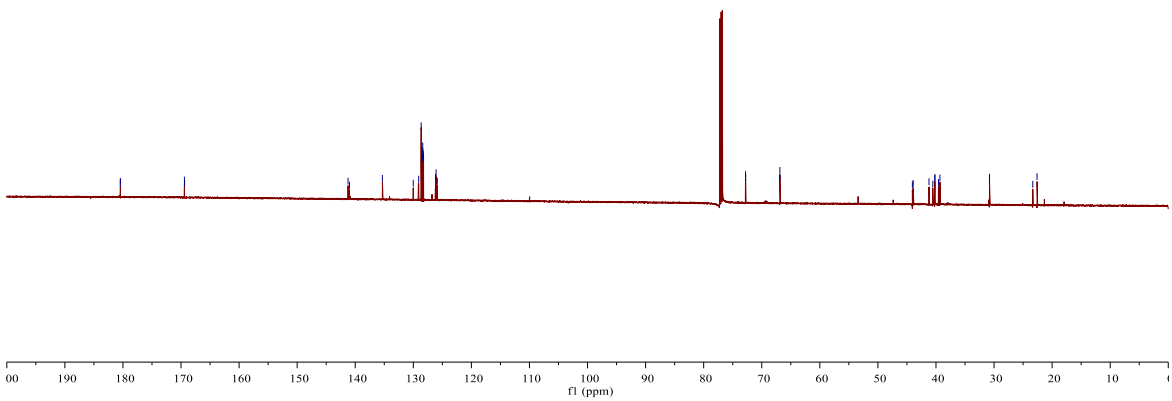

f1 (ppm)

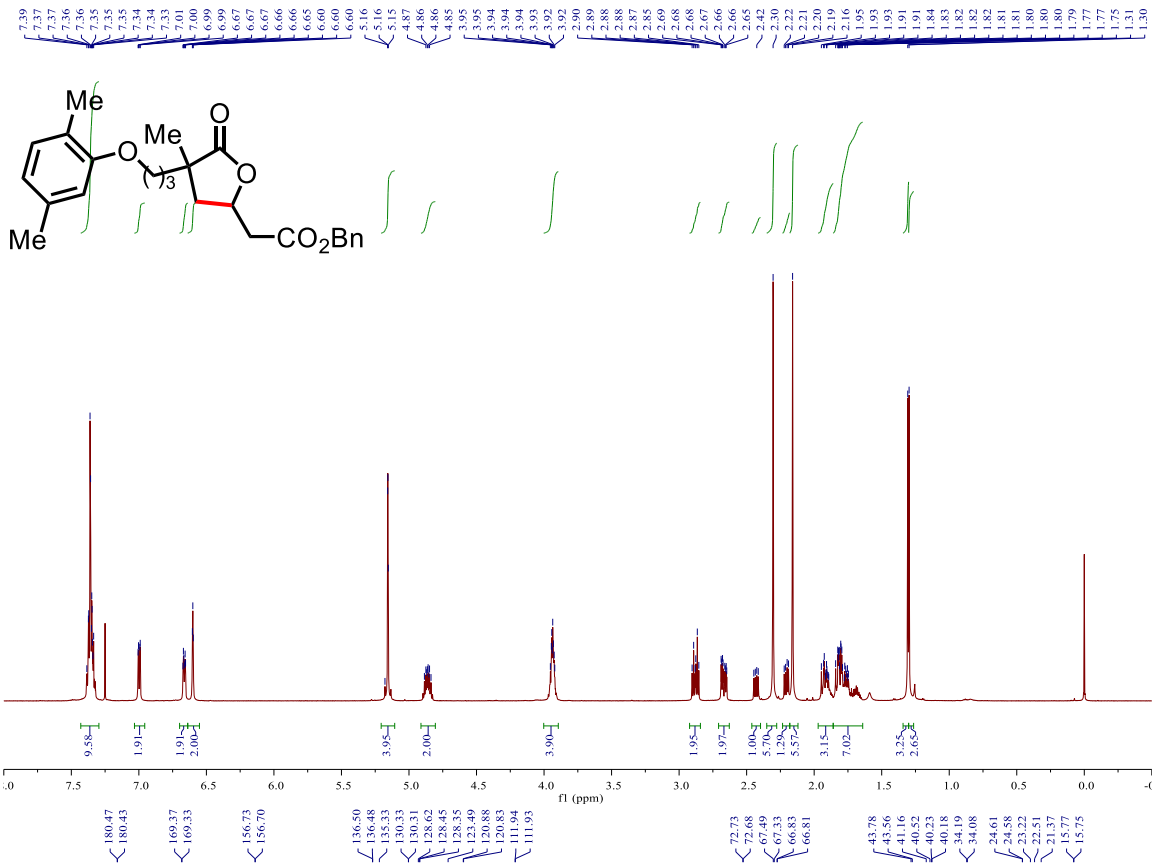

Me
O
O
2
CO2Bn

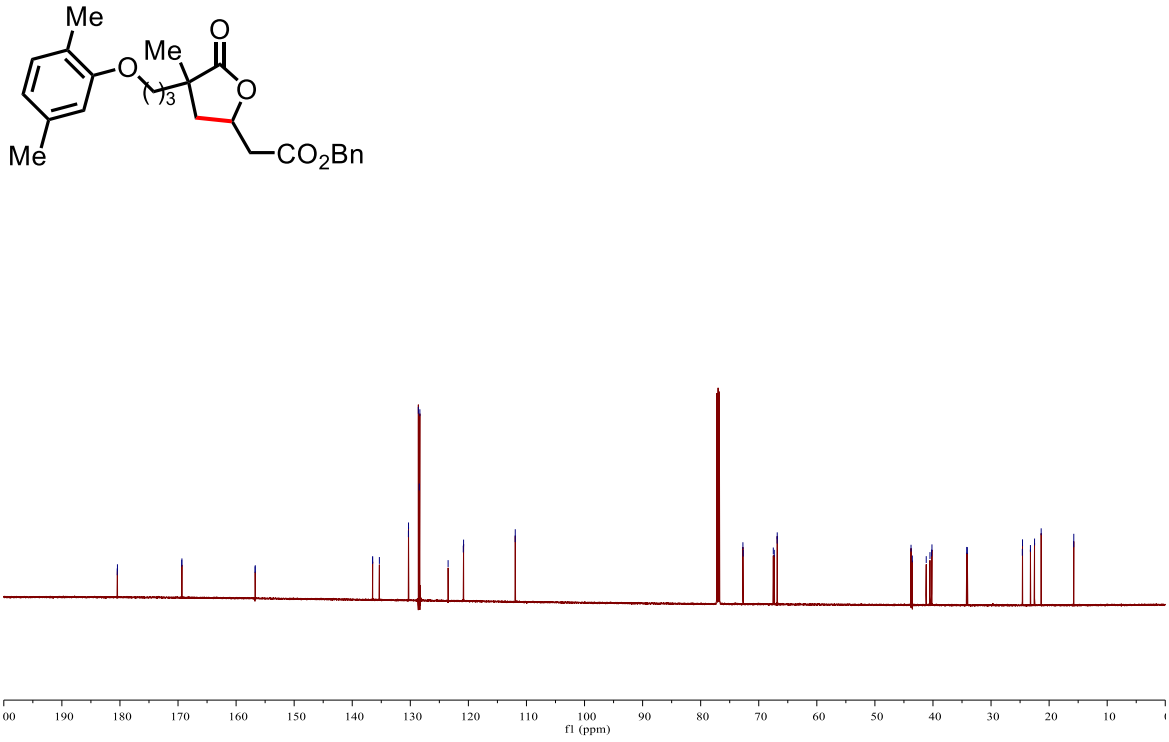

10.04
5.24
6.72
4.05
2.00
2.24
6.03
2.13
1.27
6.89
2.49
3.12
f1 (ppm)

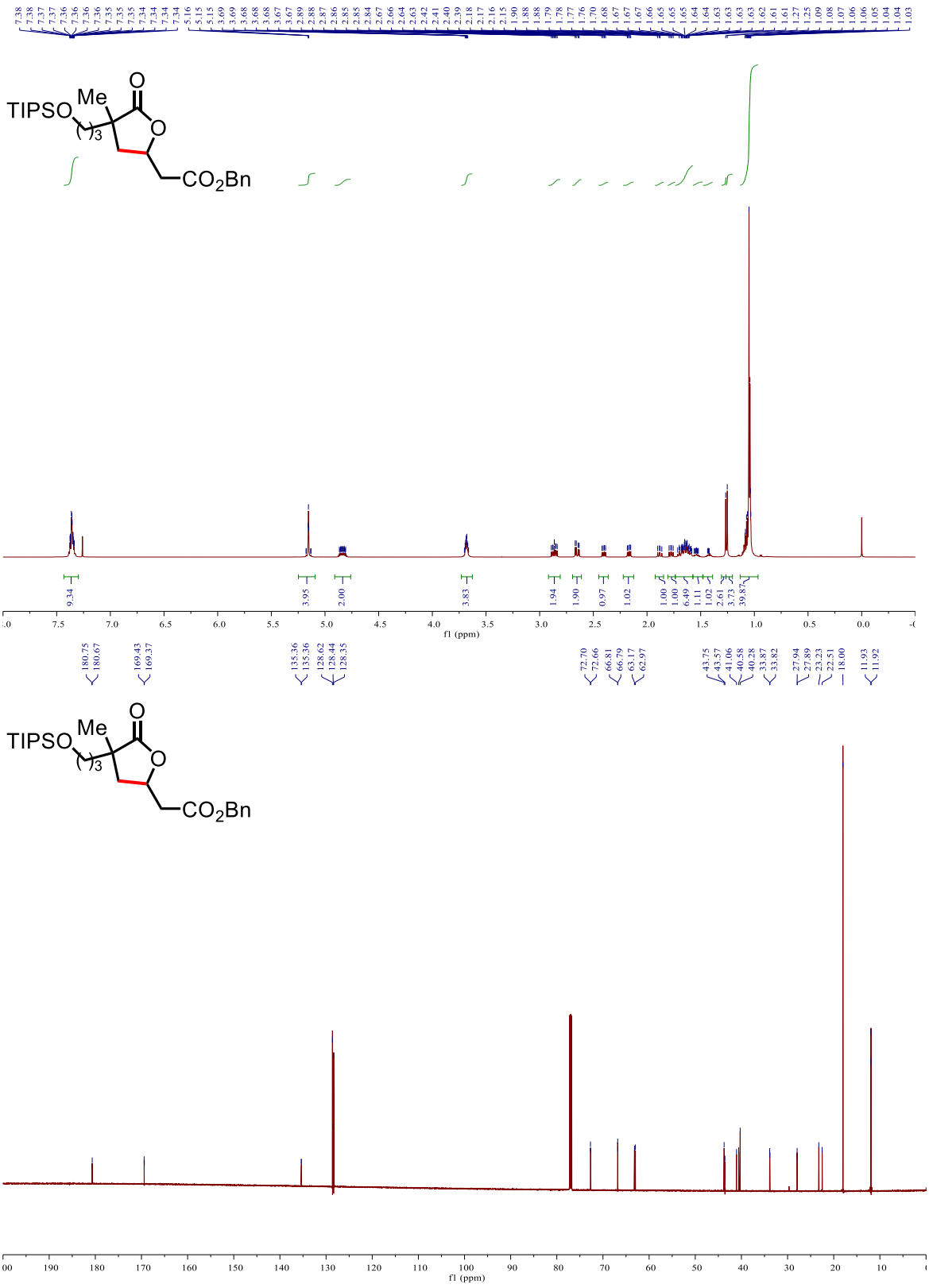
180.46
180.44
169.41
169.38
141.24
140.99
135.32
130.01
129.08
128.64
128.54
128.49
128.48
128.39
128.38
128.29
128.24
126.17
126.08
125.88
72.80
72.76
66.88
66.87
44.06
43.93
41.20
40.54
40.20
40.17
39.57
39.31
30.79
30.78
23.33
22.60

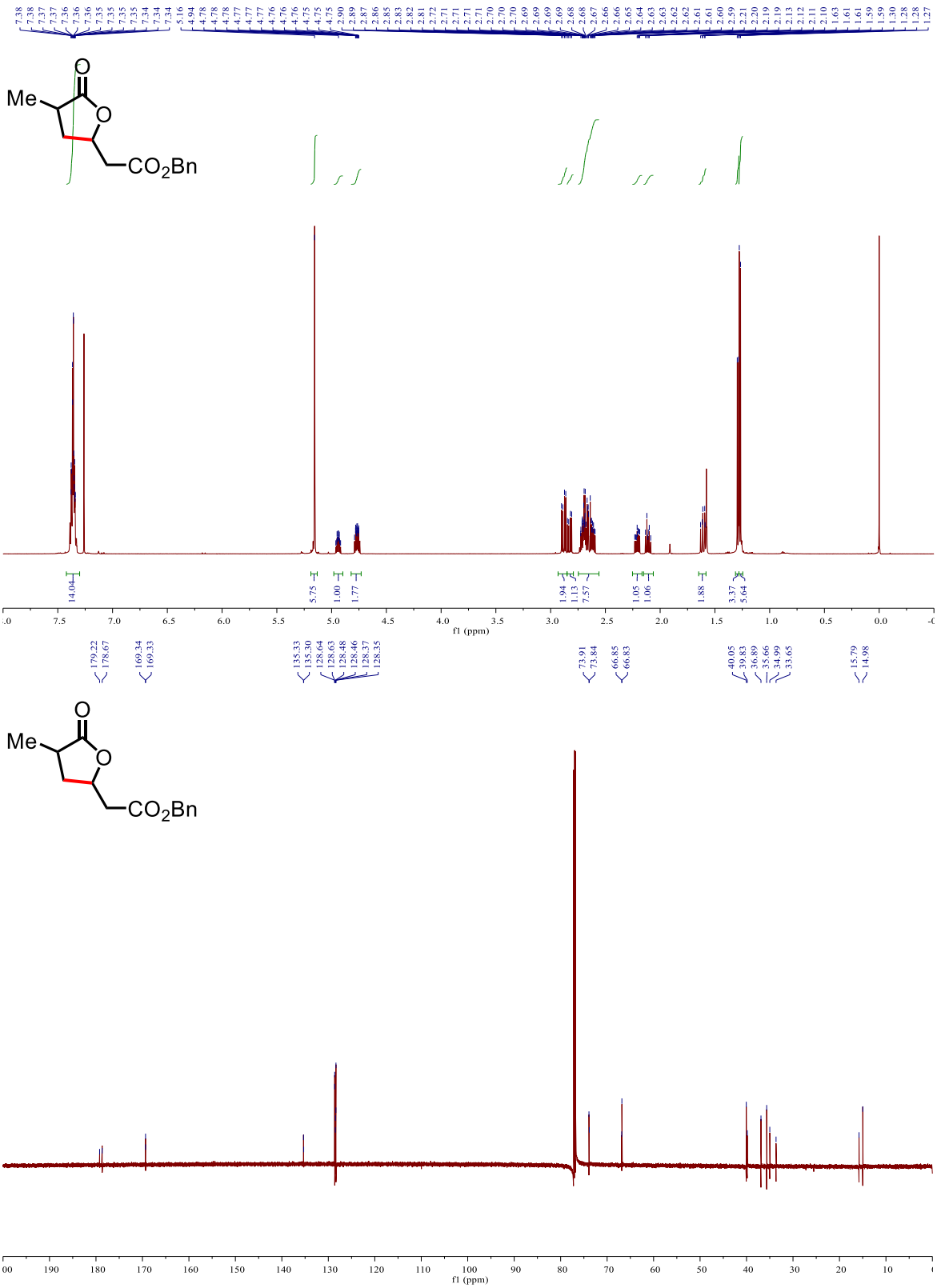

Me
O
O
2
CO2Bn

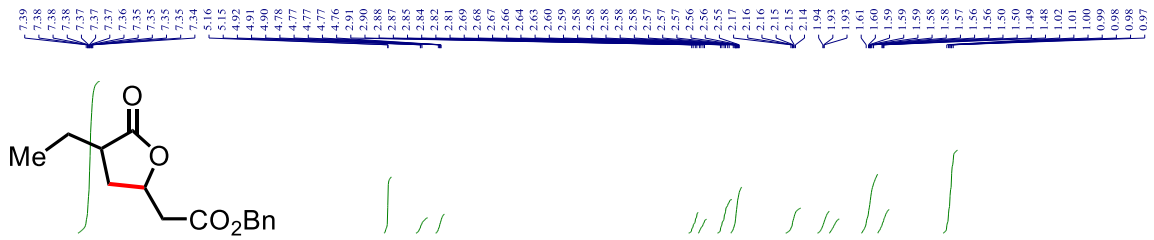

f1 (ppm)


Me
Me
O
O
O
Me
CO2Bn
f1 (ppm)

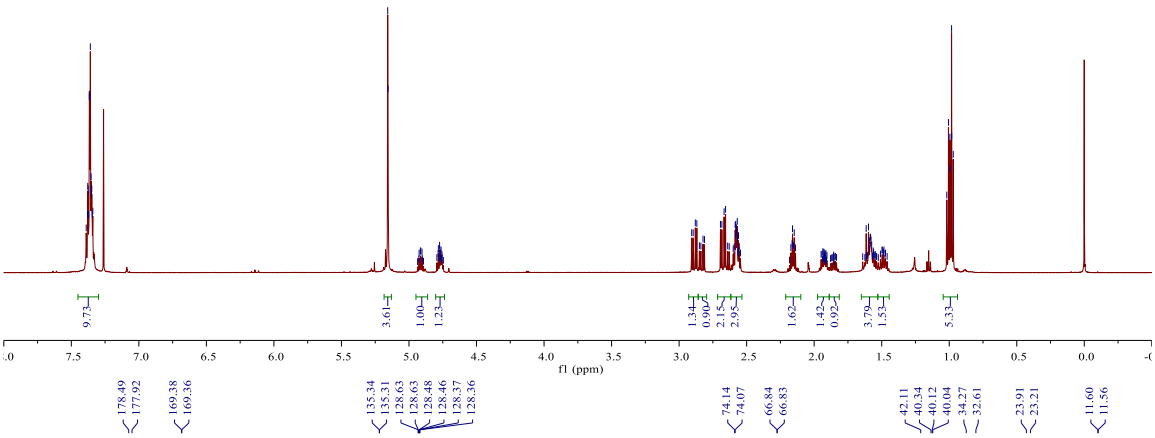

f1 (ppm)


TIPSO
Me
3
O
O
CO2Bn
f1 (ppm)

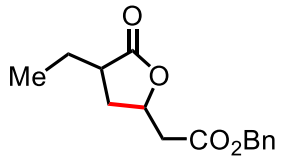

Me
O
O
CO2Bn
f1 (ppm)

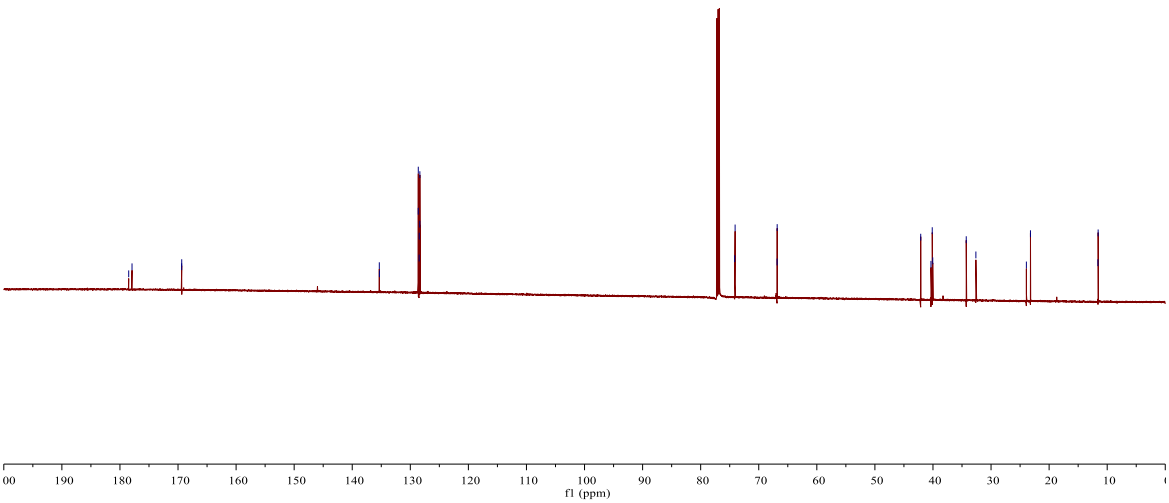


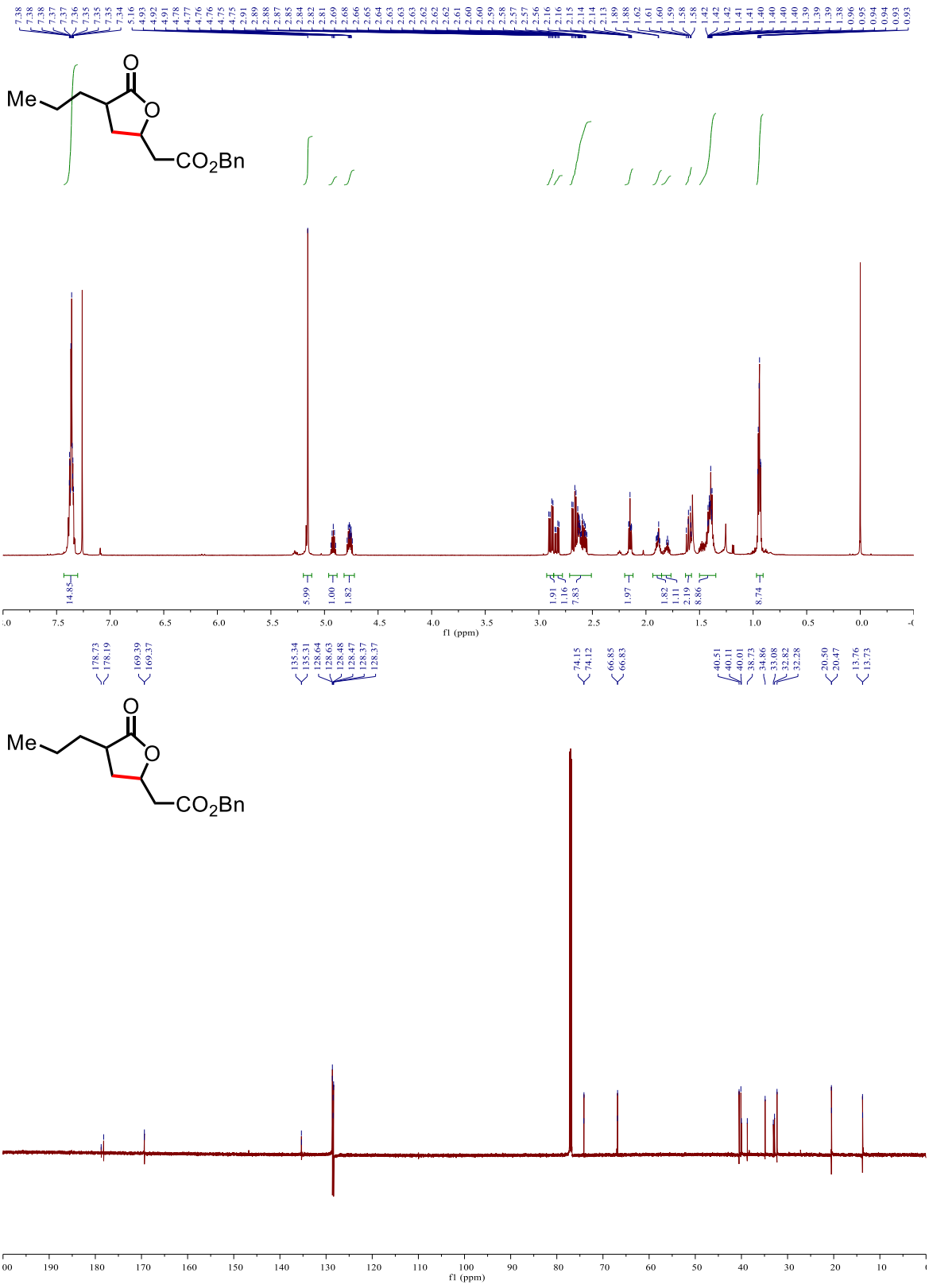
O
Me
O
CO2Bn

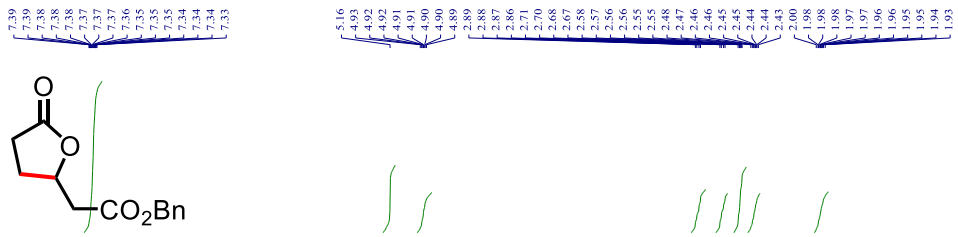

9.73
3.61
1.00
1.23
1.34
0.90
2.15
2.95
1.62
1.42
0.92
3.79
1.53
5.33
f1 (ppm)

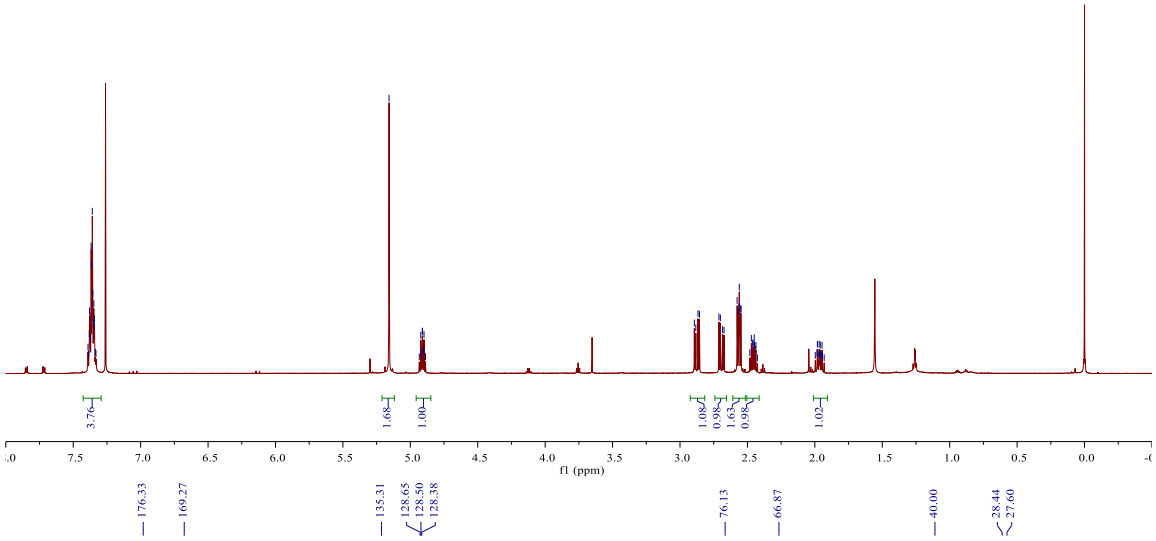
178.49
177.92
169.38
169.36
135.34
135.31
128.63
128.63
128.48
128.46
128.37
128.36
74.14
74.07
66.84
66.83
42.11
40.34
40.12
40.04
34.27
32.61
23.91
23.21
11.60
11.56

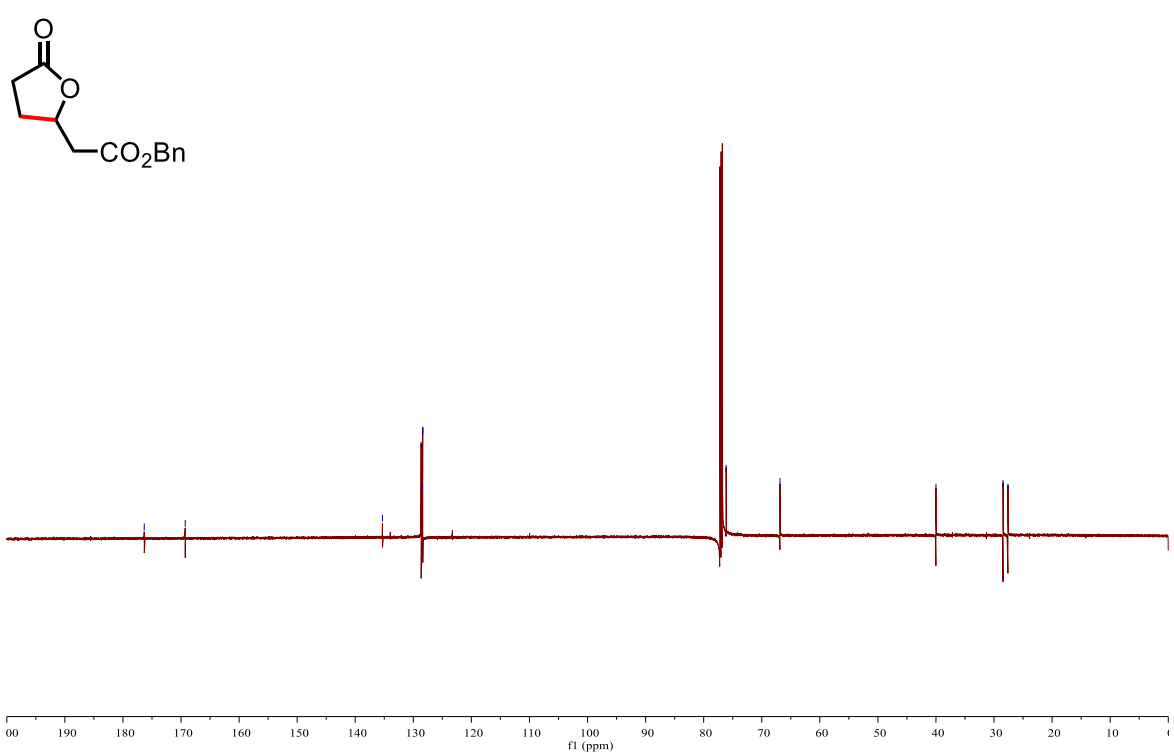

O
Me
O
CO2Bn

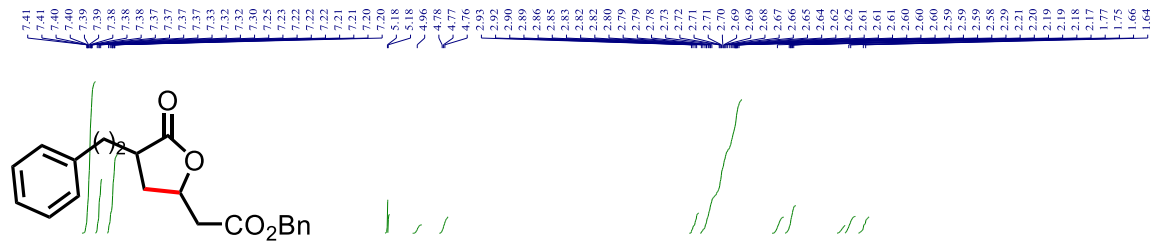

f1 (ppm)

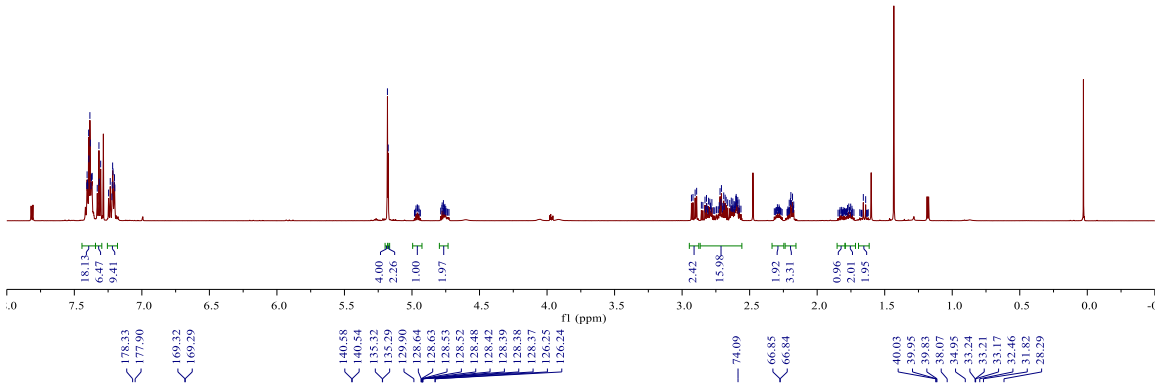

Me
O
O
CO2Bn
f1 (ppm)


7.39
7.39
7.38
7.38
7.38
7.37
7.37
7.37
7.36
7.35
7.35
7.35
7.34
7.34
7.34
7.33
5.16
4.93
4.92
4.92
4.91
4.91
4.90
4.90
4.89
2.89
2.88
2.87
2.86
2.71
2.70
2.68
2.67
2.58
2.57
2.56
2.56
2.55
2.55
2.48
2.47
2.46
2.46
2.45
2.45
2.44
2.44
2.43
2.00
1.98
1.98
1.98
1.97
1.97
1.96
1.96
1.95
1.95
1.94
1.93
O
O
CO2Bn

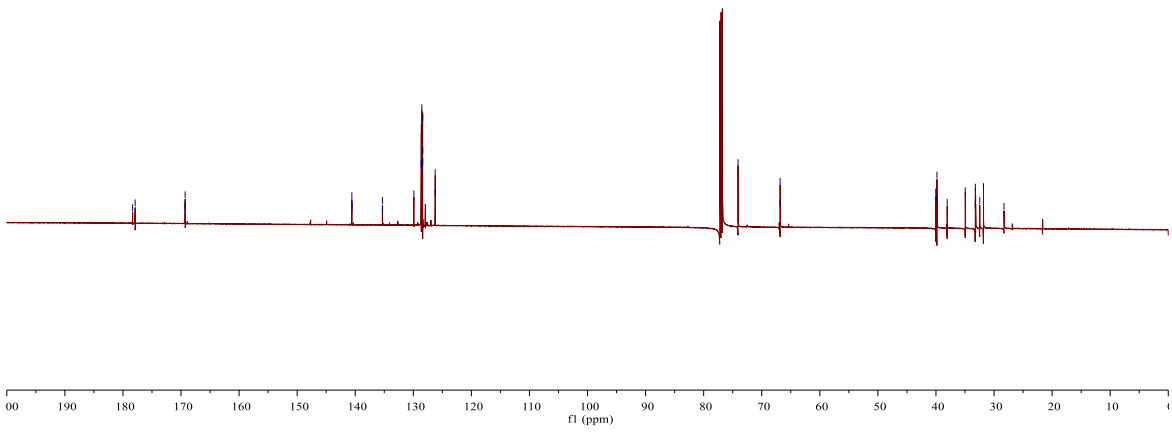

3.76
1.68
1.00
1.08
0.98
1.63
0.98
1.02
f1 (ppm)

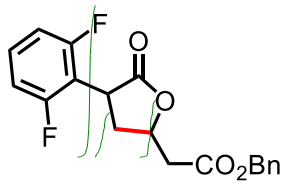

176.33
169.27
135.31
128.65
128.50
128.38
76.13
66.87
40.00
28.44
27.60
O
O
CO2Bn
f1 (ppm)

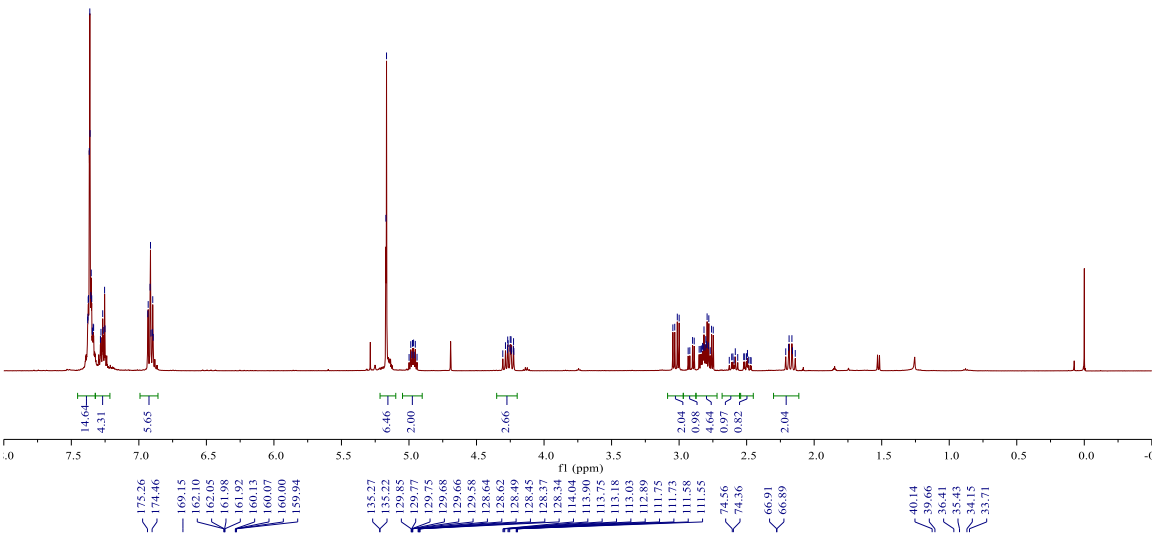

O
O
CO2Bn

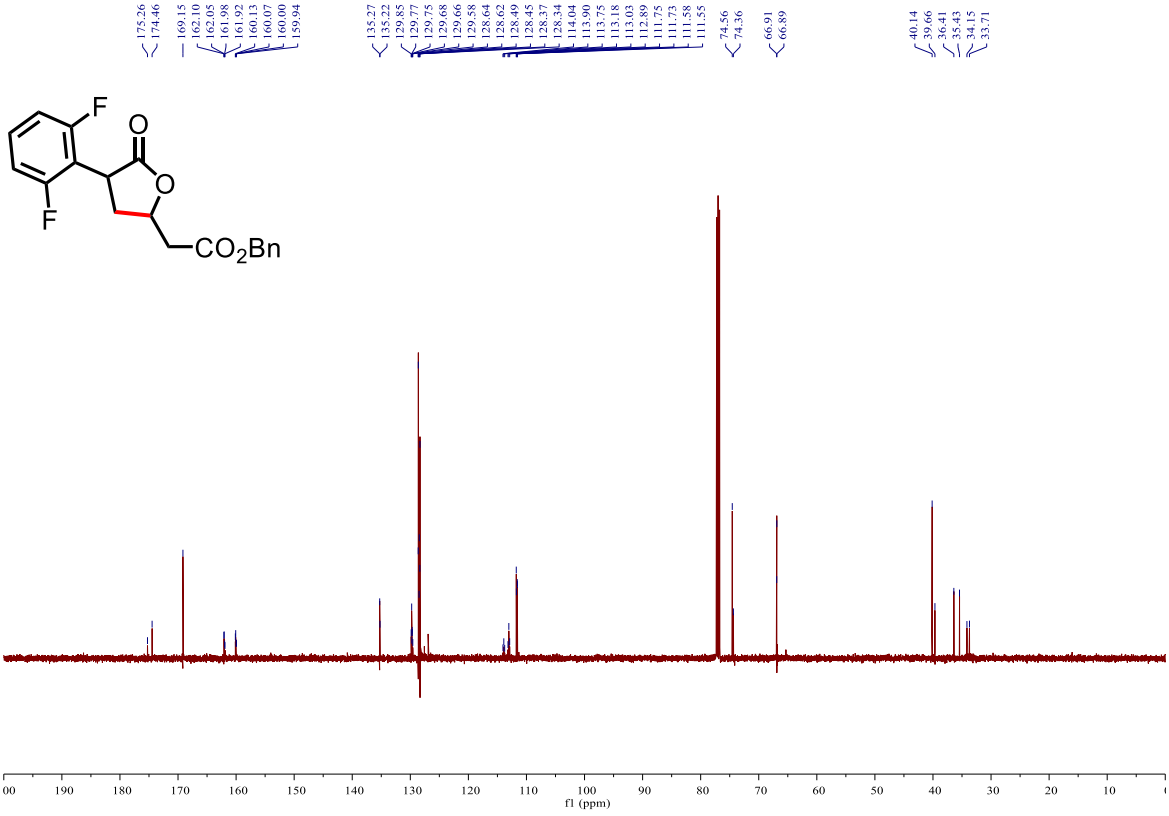

f1 (ppm)

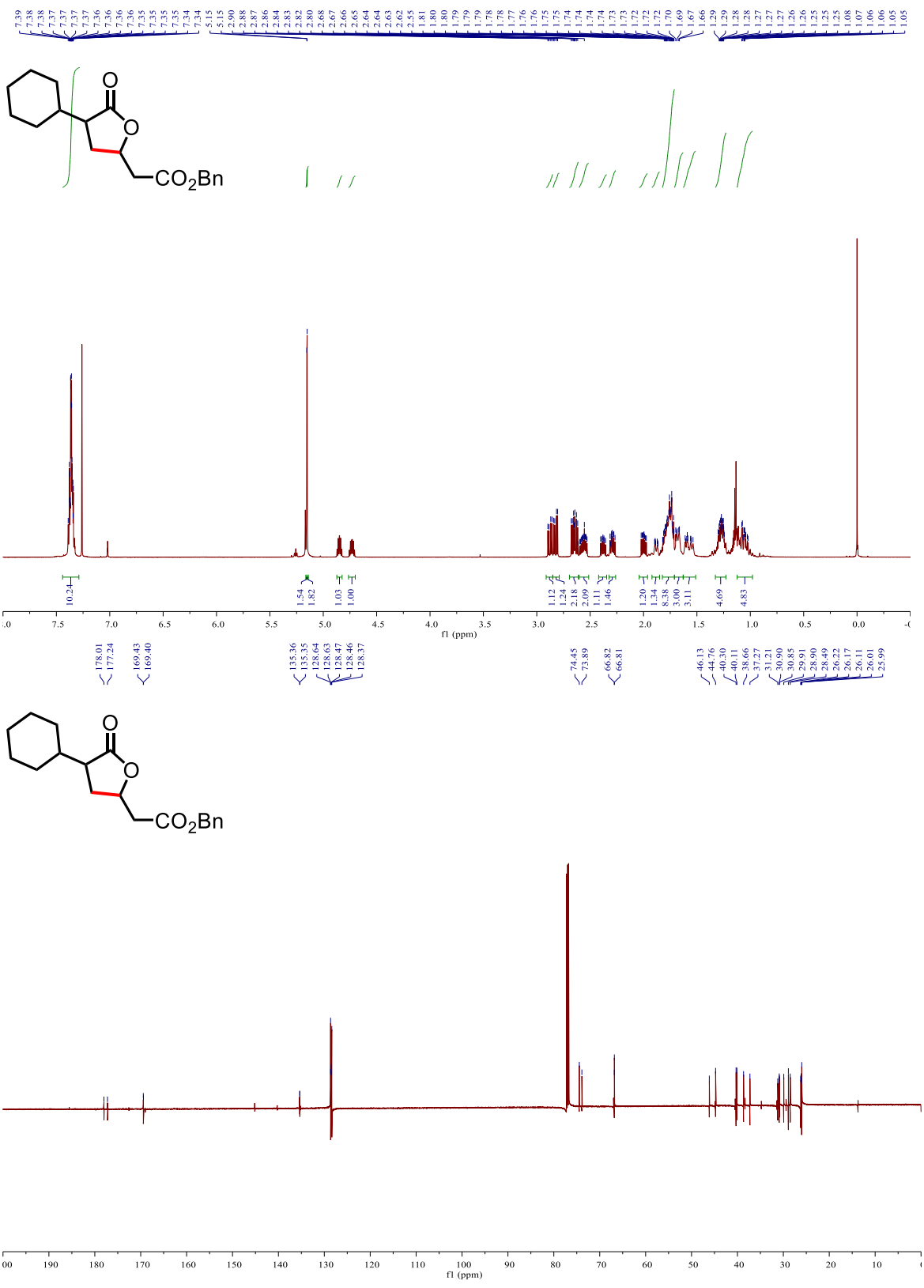

O
O
CO2Bn

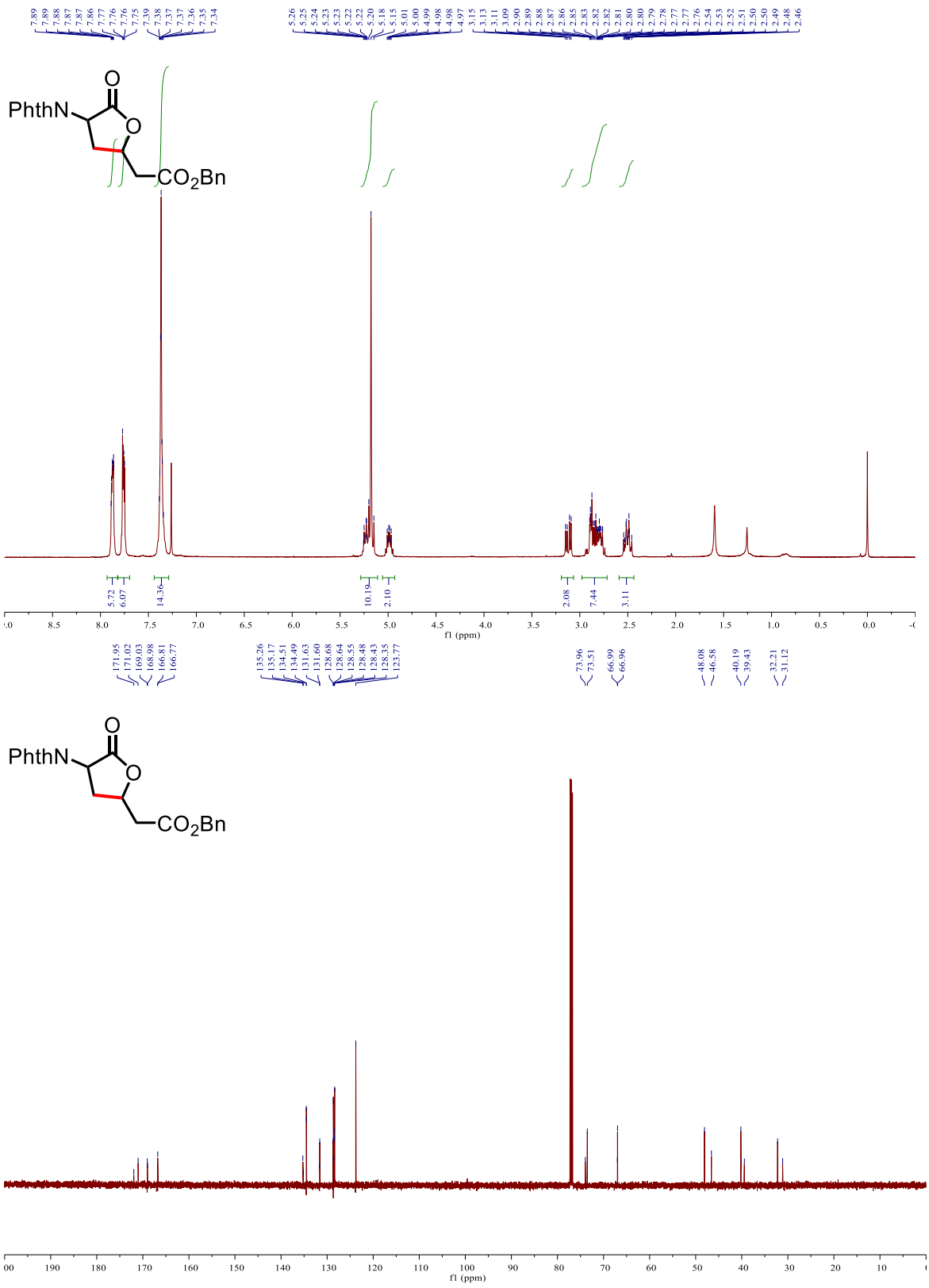

f1 (ppm)

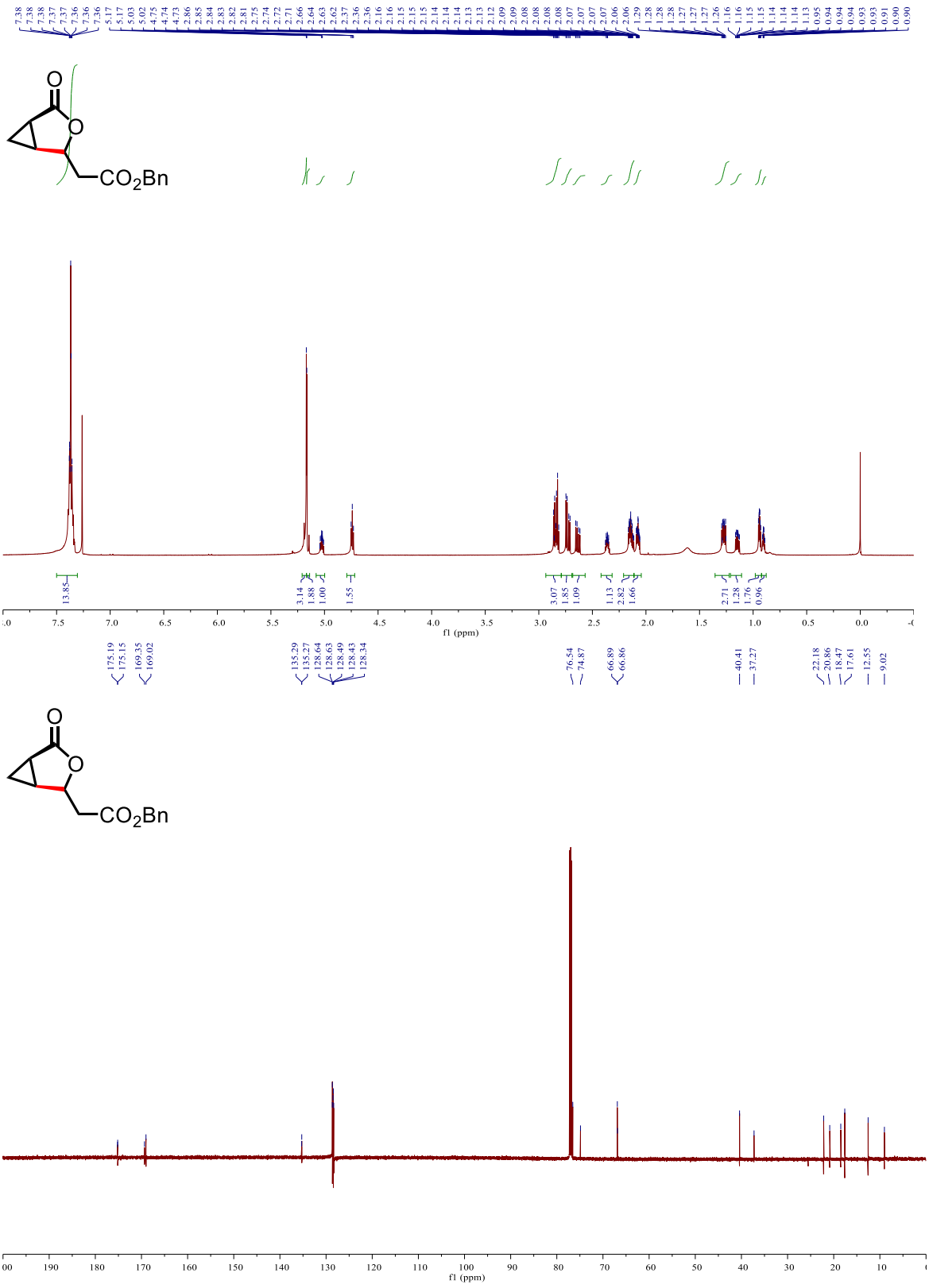

F
O
O
F
CO2Bn

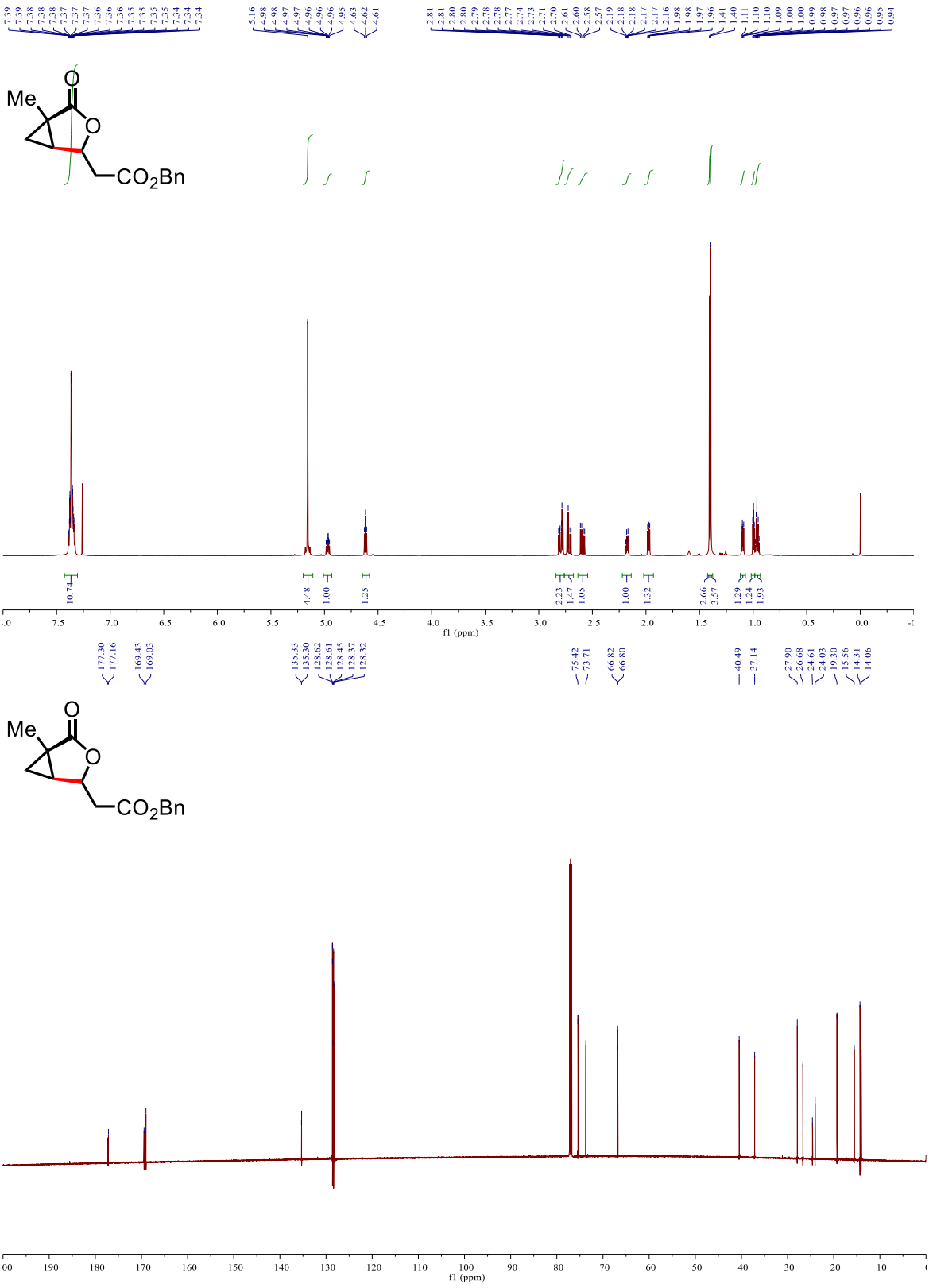

14.64
4.31
5.65
6.46
2.00
2.66
2.04
0.98
4.64
0.97
0.82
2.04
f1 (ppm)

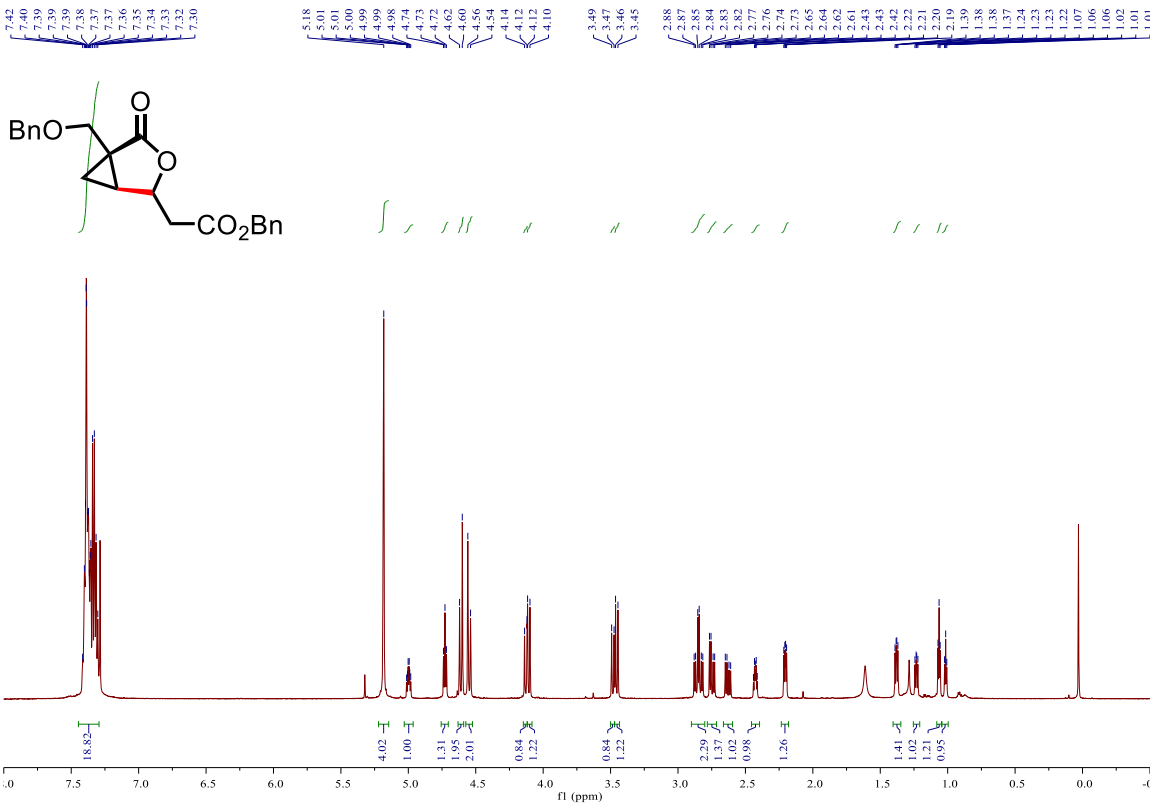

F
O
O
F
CO2Bn
f1 (ppm)

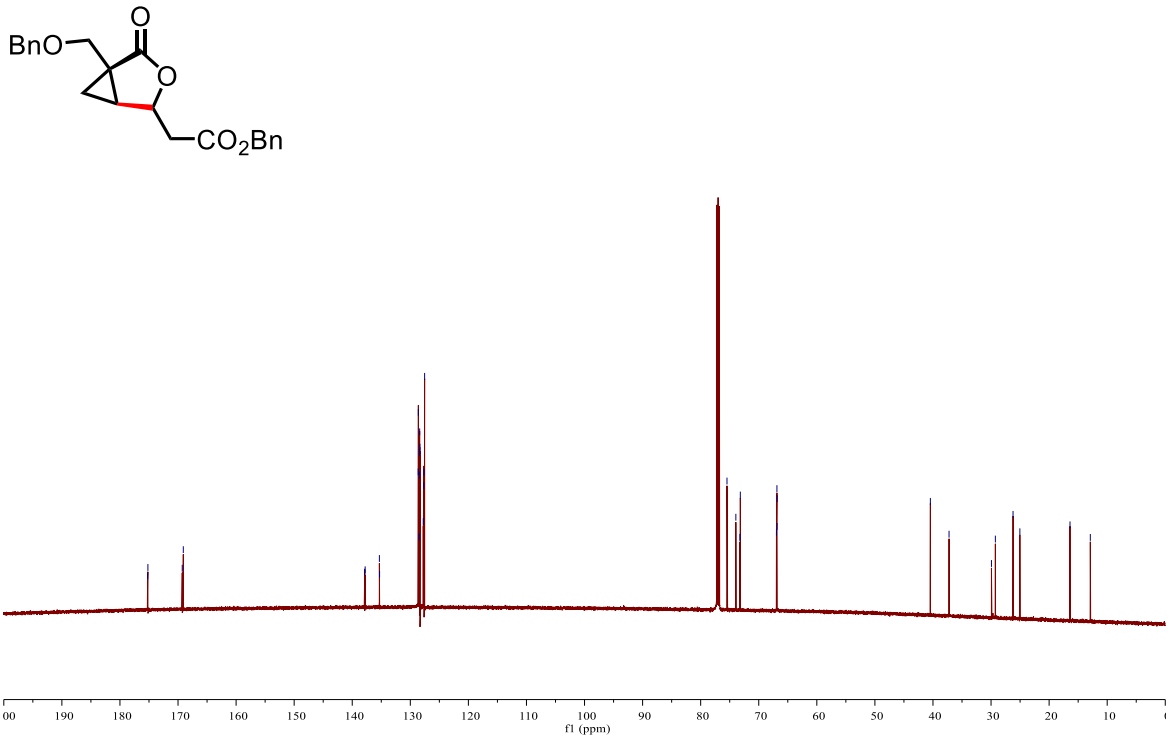

CO2Bn
f1 (ppm)
CO2Bn
f1 (ppm)

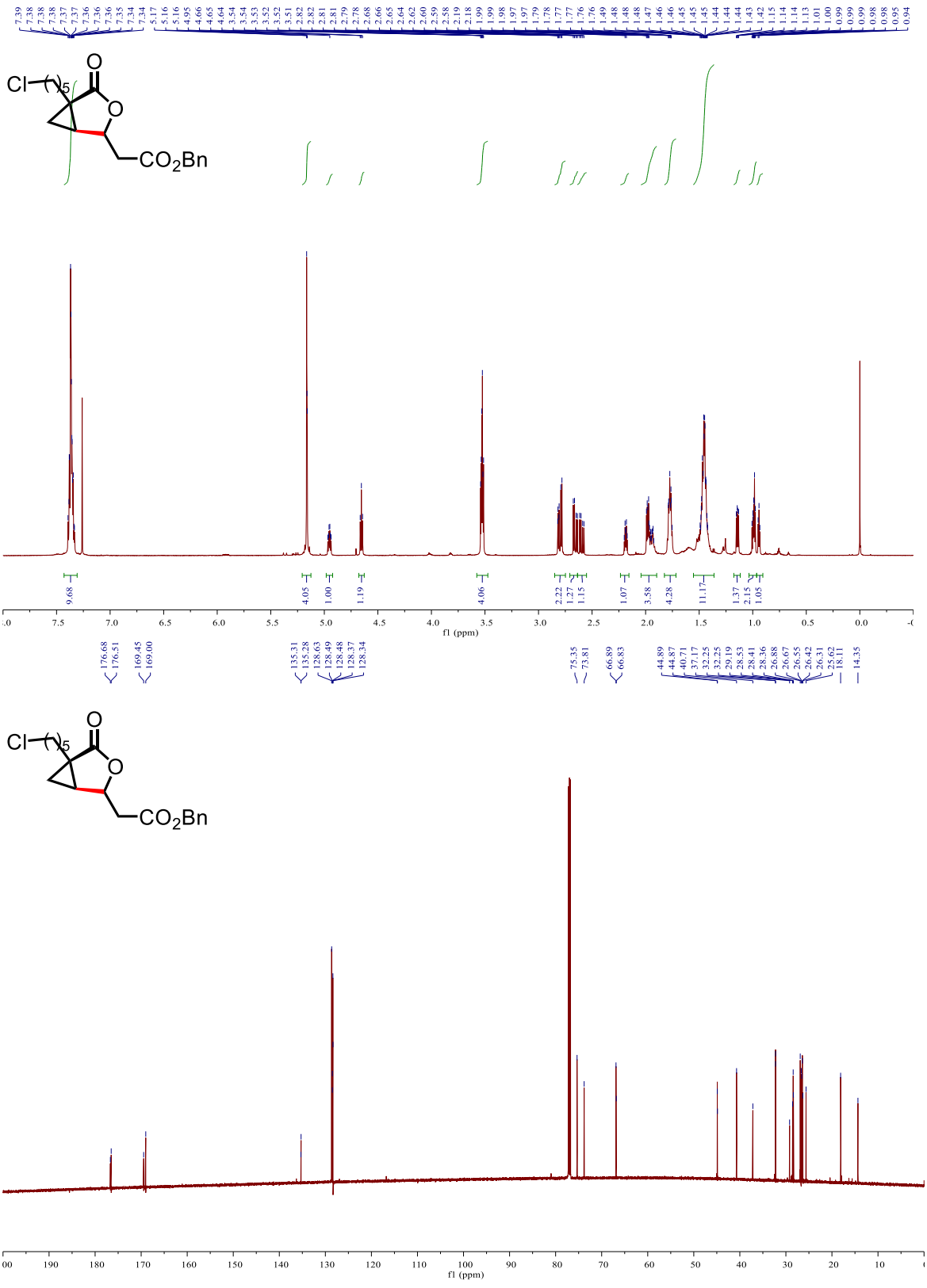

PhthN
O
O
CO2Bn
f1 (ppm)

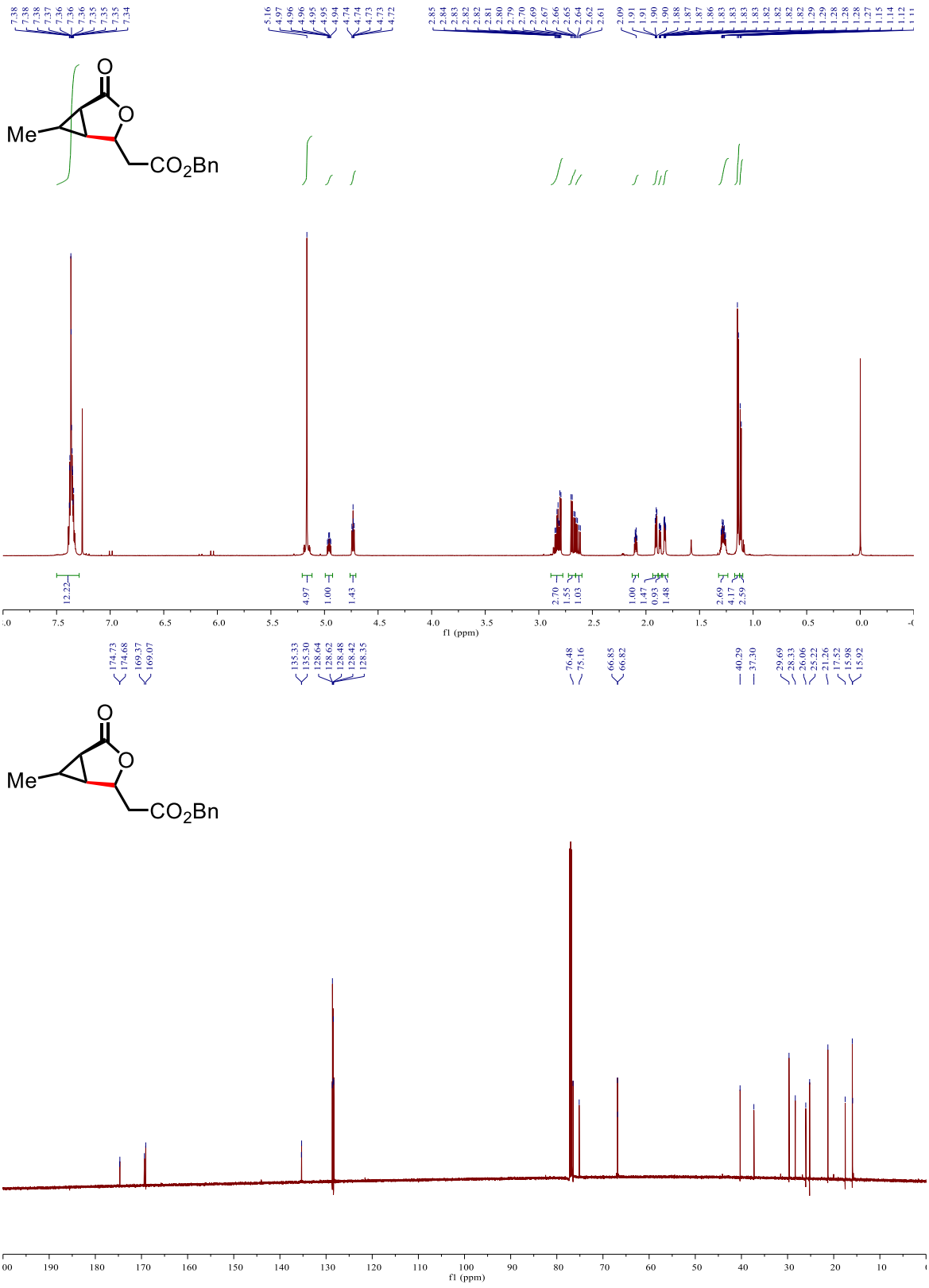

CO2Bn
fl (ppm)
CO2Bn
fl (ppm)

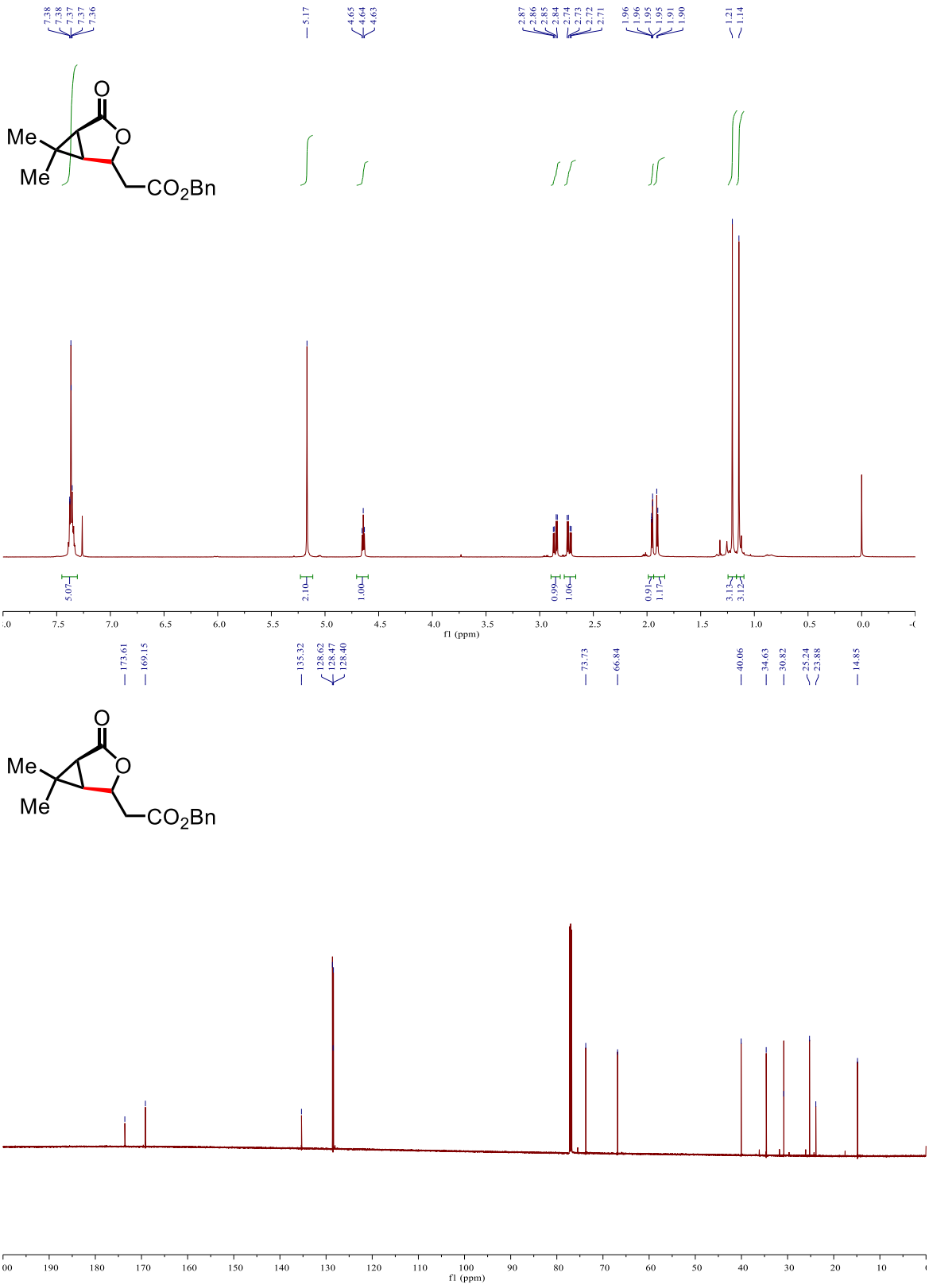

Me
O
O
CO2Bn
fl (ppm)

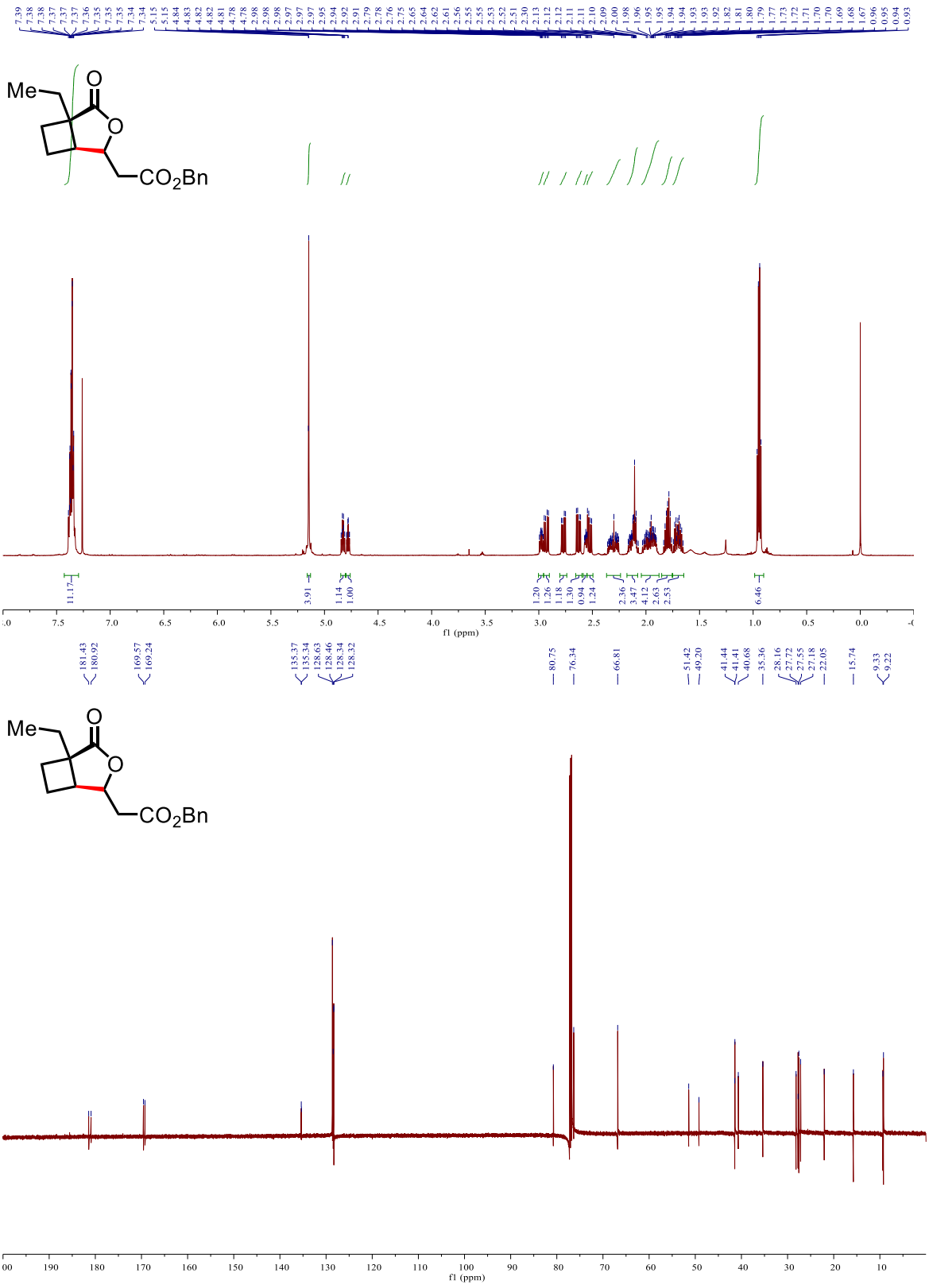

BnO
O
O
CO2Bn
fl (ppm)

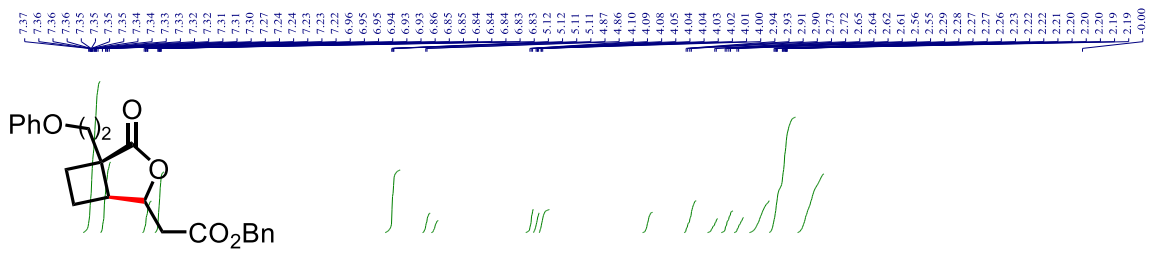

BnO
O
O
CO2Bn
fl (ppm)

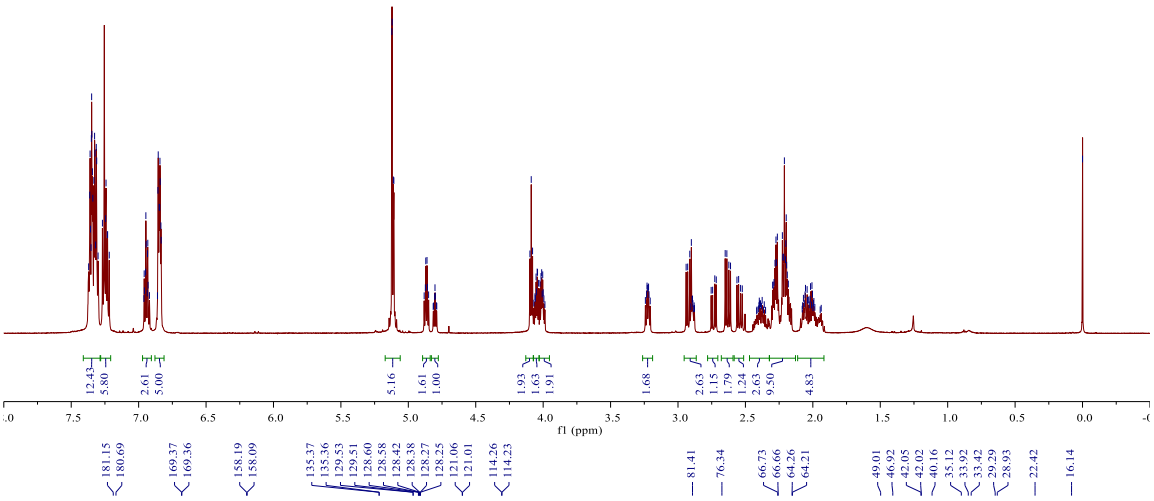

Cl
5
O
O
CO2Bn
f1 (ppm)


Me
CO2Bn
f1 (ppm)
Me
CO2Bn
f1 (ppm)


7.38
7.38
7.37
7.37
7.36
5.17
4.65
4.64
4.63
2.87
2.86
2.85
2.84
2.74
2.73
2.72
2.71
1.96
1.96
1.95
1.95
1.91
1.90
1.21
1.14
Me
Me
O
O
CO2Bn
5.07
2.10
1.00
0.99
1.06
0.91
1.17
3.13
3.12
f1 (ppm)
173.61
169.15
135.32
128.62
128.47
128.40
73.73
66.84
40.06
34.63
30.82
25.24
23.88
14.85
f1 (ppm)

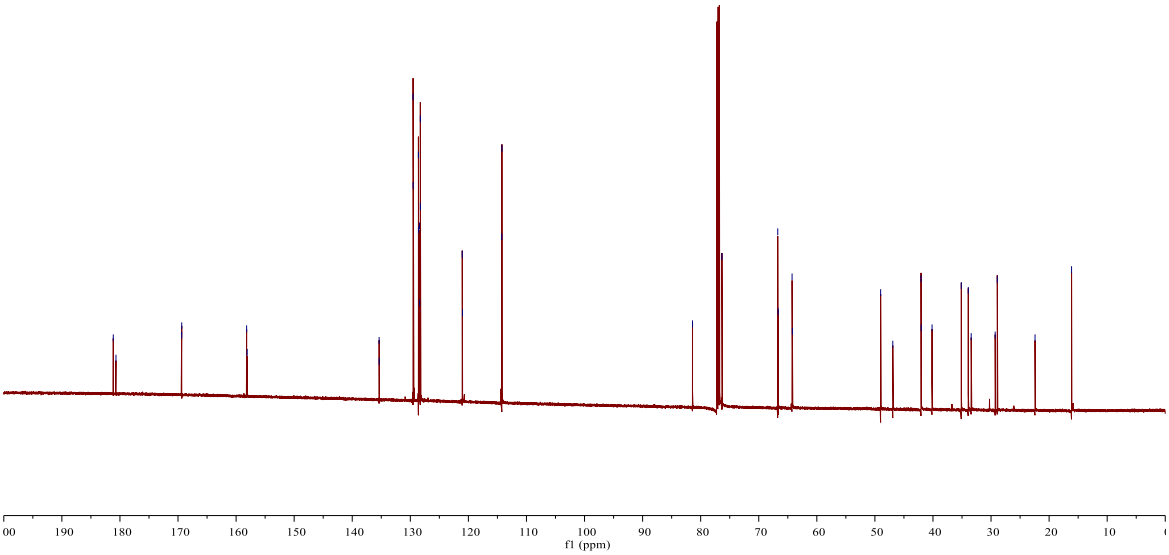

Me
O
O
CO2Bn
f1 (ppm)

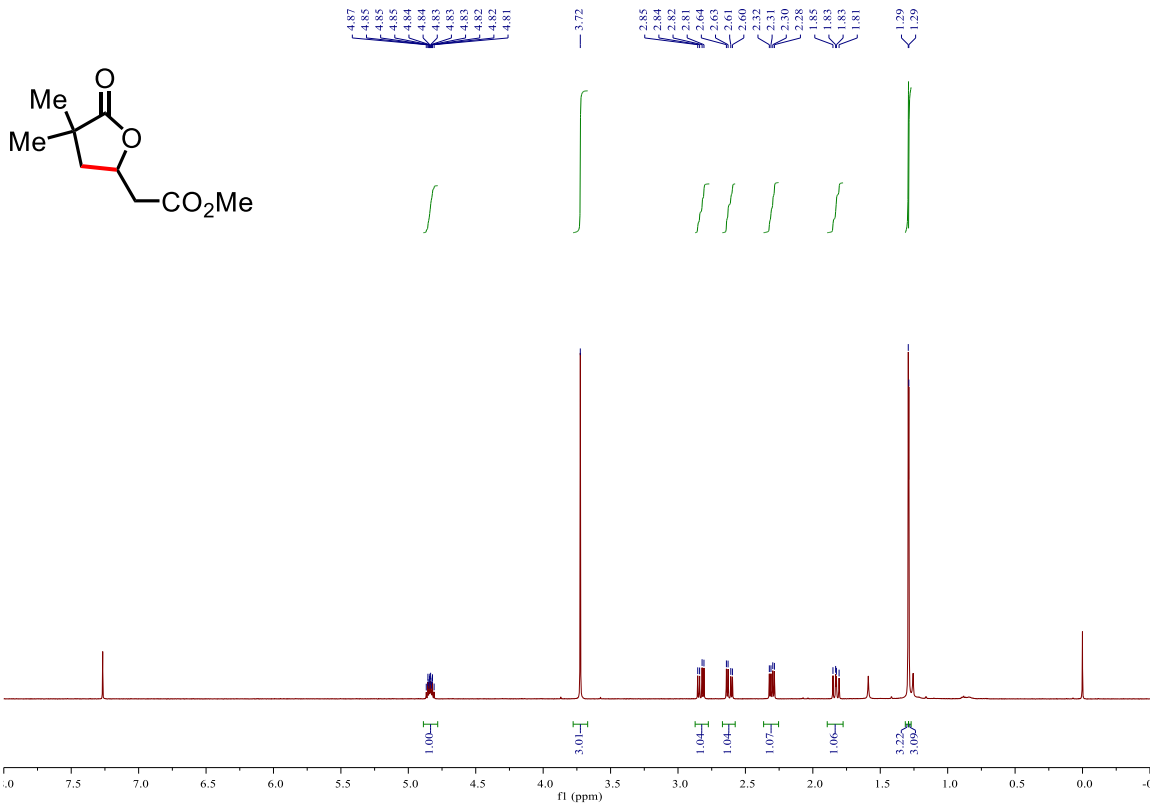

PhO
2
O
O
CO2Bn

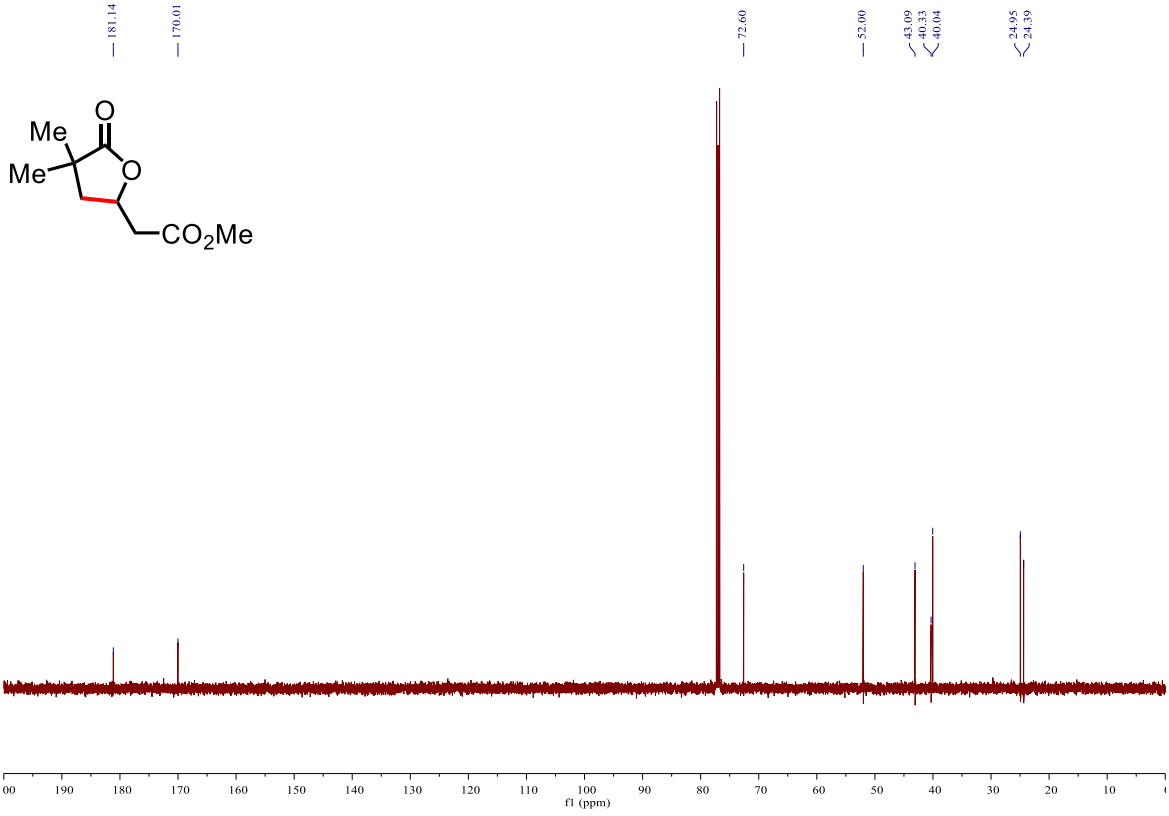

12.43
5.80
2.61
5.00
5.16
1.61
1.00
1.93
1.63
1.91
1.68
2.63
1.15
1.79
1.24
2.63
9.50
4.83
f1 (ppm)

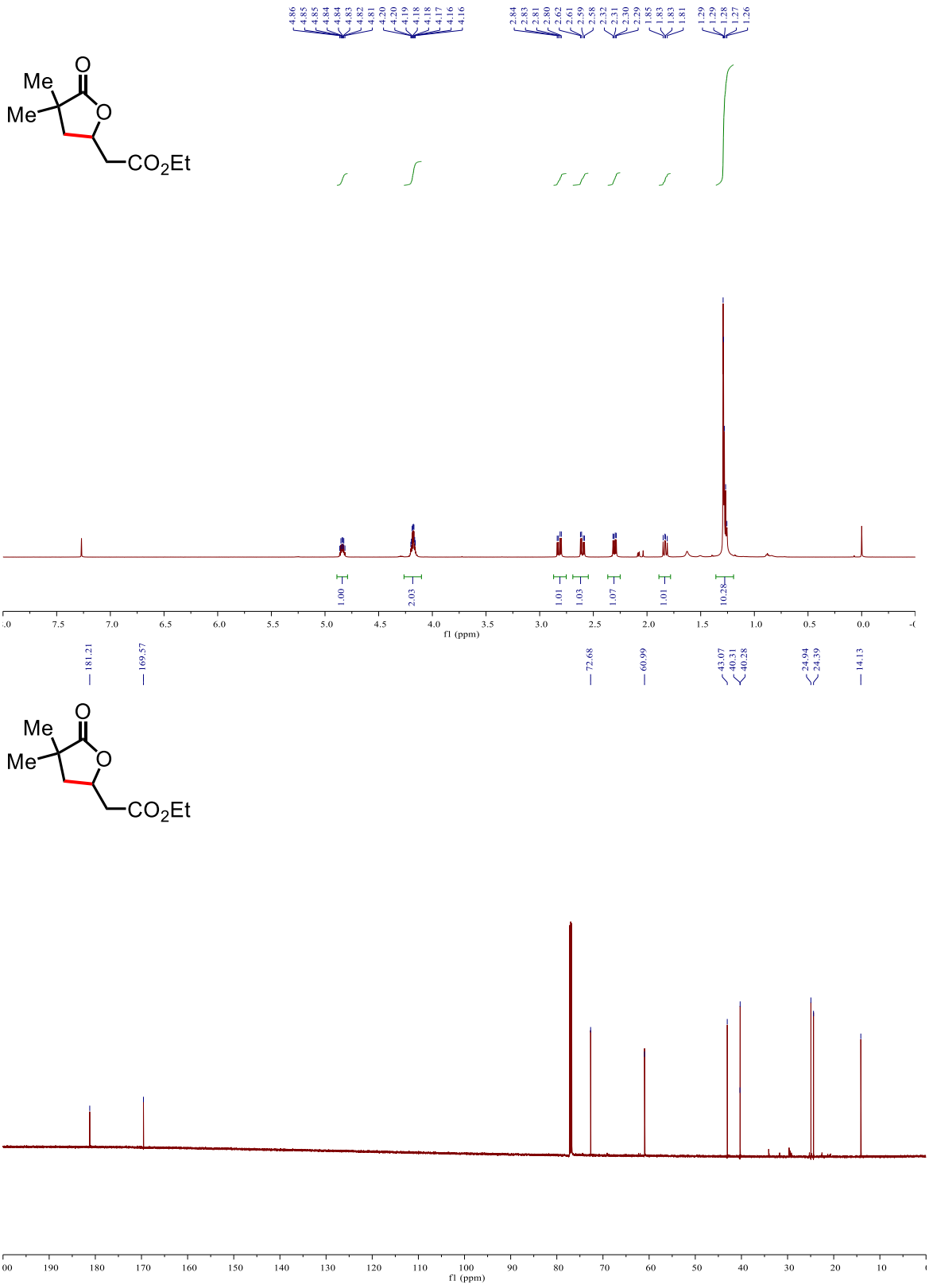
181.15
180.69
169.37
169.36
158.19
158.09
135.37
135.36
129.53
129.51
128.60
128.58
128.42
128.38
128.27
128.25
121.06
121.01
114.26
114.23
81.41
76.34
66.73
66.66
64.26
64.21
49.01
46.92
42.05
42.02
40.16
35.12
33.92
33.42
29.29
28.93
22.42
16.14

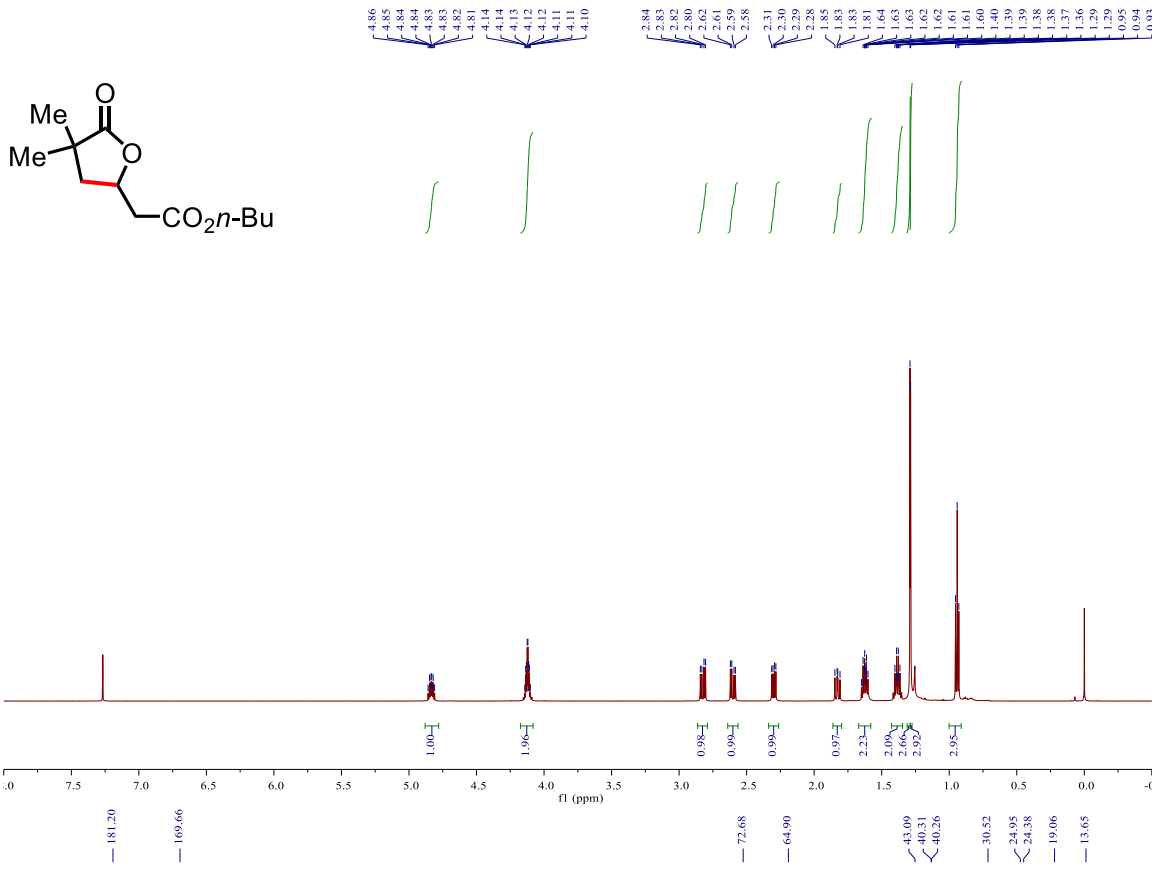

PhO
2
O
O
CO2Bn

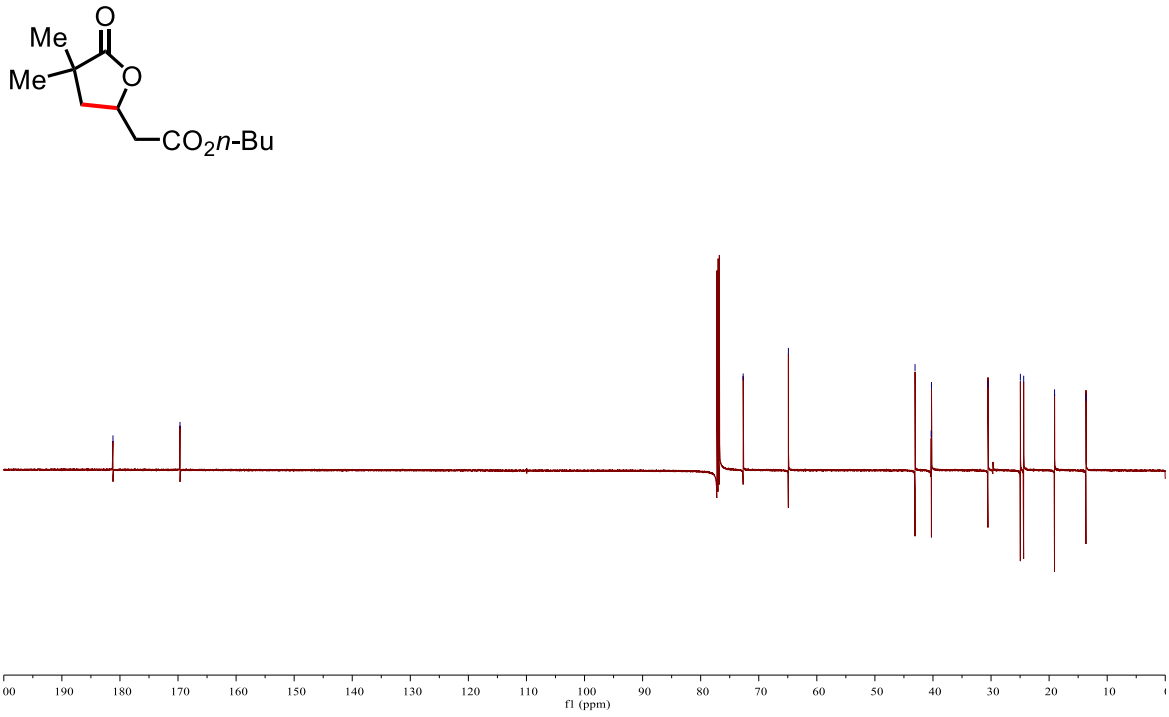

f1 (ppm)

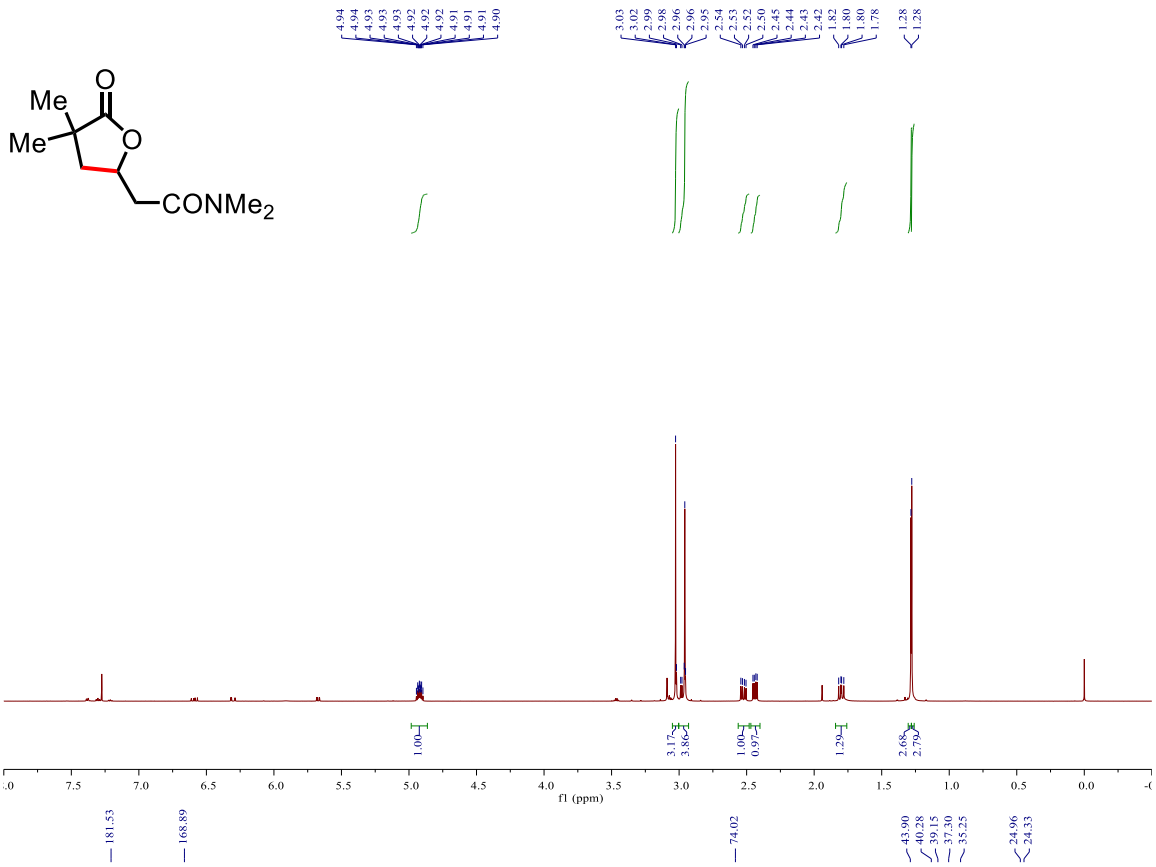

Me
Me
O
O
CO2Me
4.87
4.85
4.85
4.85
4.84
4.84
4.83
4.83
4.83
4.82
4.82
4.81
3.72
2.85
2.84
2.82
2.81
2.64
2.63
2.61
2.60
2.32
2.31
2.30
2.28
1.85
1.83
1.83
1.81
1.29
1.29
1.00
3.01
1.04
1.04
1.07
1.06
3.22
3.09
f1 (ppm)

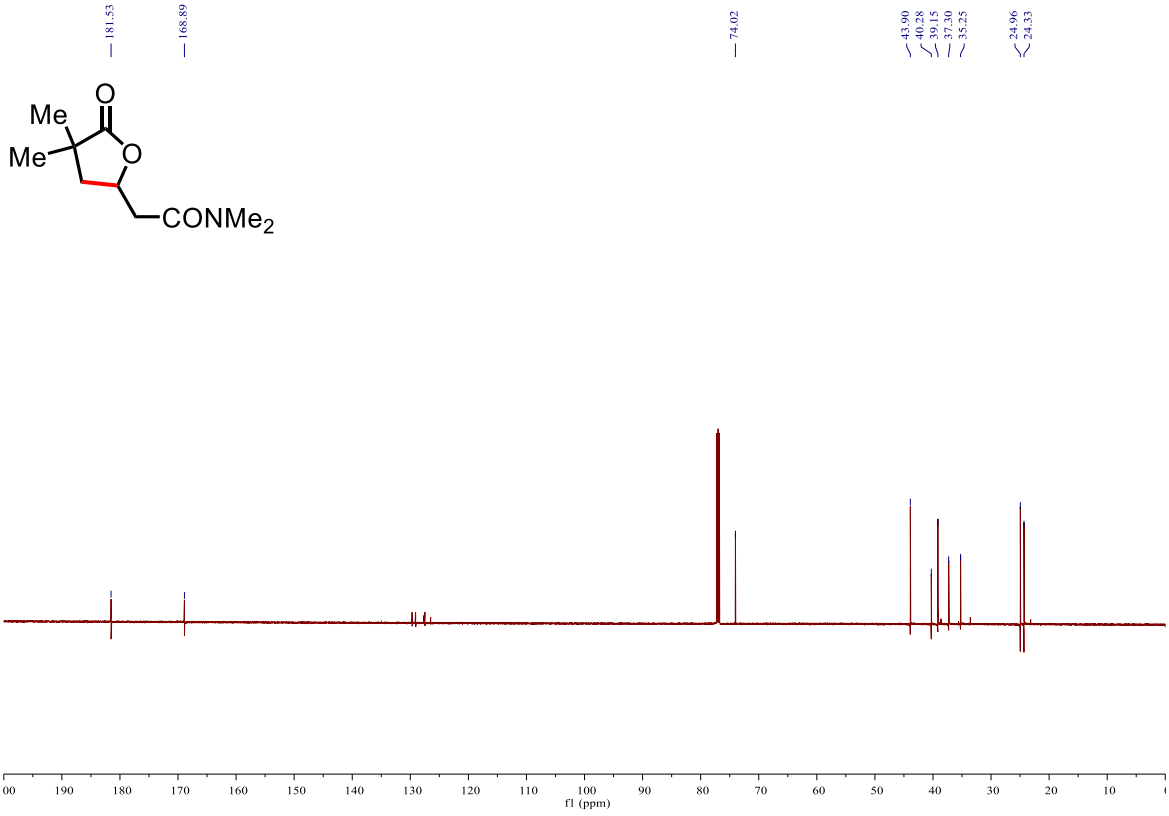

Me
Me
O
O
CO2Me
181.14
170.01
72.60
52.00
43.09
40.33
40.04
24.95
24.39
f1 (ppm)

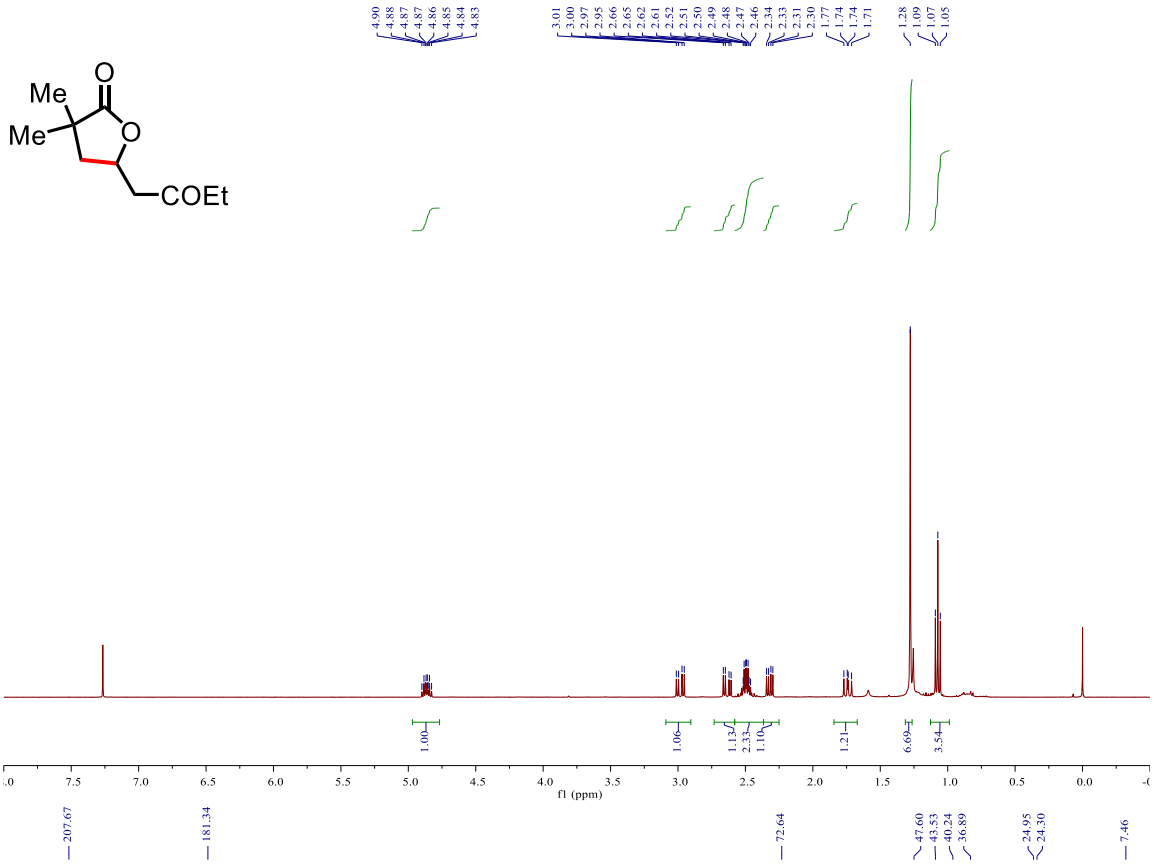

Me
Me
O
O
CO2Et
4.86
4.85
4.85
4.84
4.84
4.84
4.83
4.82
4.81
4.20
4.20
4.19
4.18
4.18
4.17
4.16
4.16
2.84
2.83
2.81
2.80
2.62
2.61
2.59
2.58
2.32
2.31
2.30
2.29
1.85
1.83
1.83
1.81
1.29
1.29
1.28
1.27
1.26
1.00
2.03
1.01
1.03
1.07
1.01
10.28
f1 (ppm)
181.21
169.57
72.68
60.99
43.07
40.31
40.28
24.94
24.39
14.13
f1 (ppm)

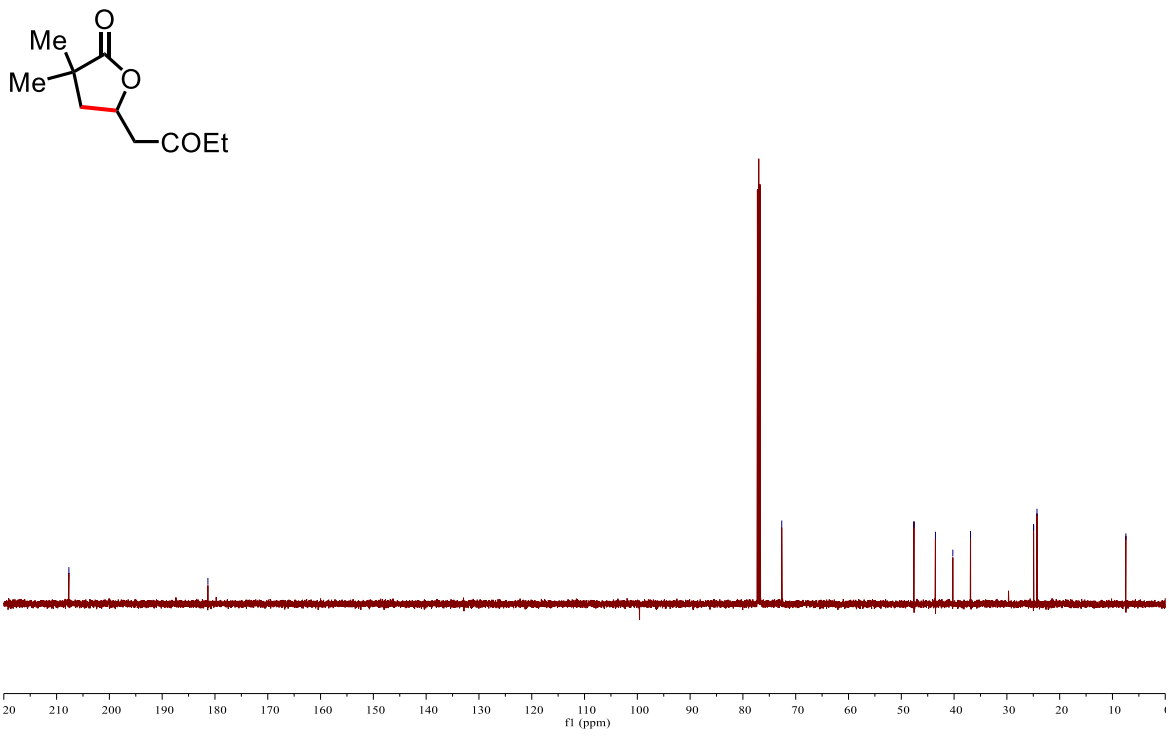

Me
Me
O
O
CO2n-Bu
f1 (ppm)

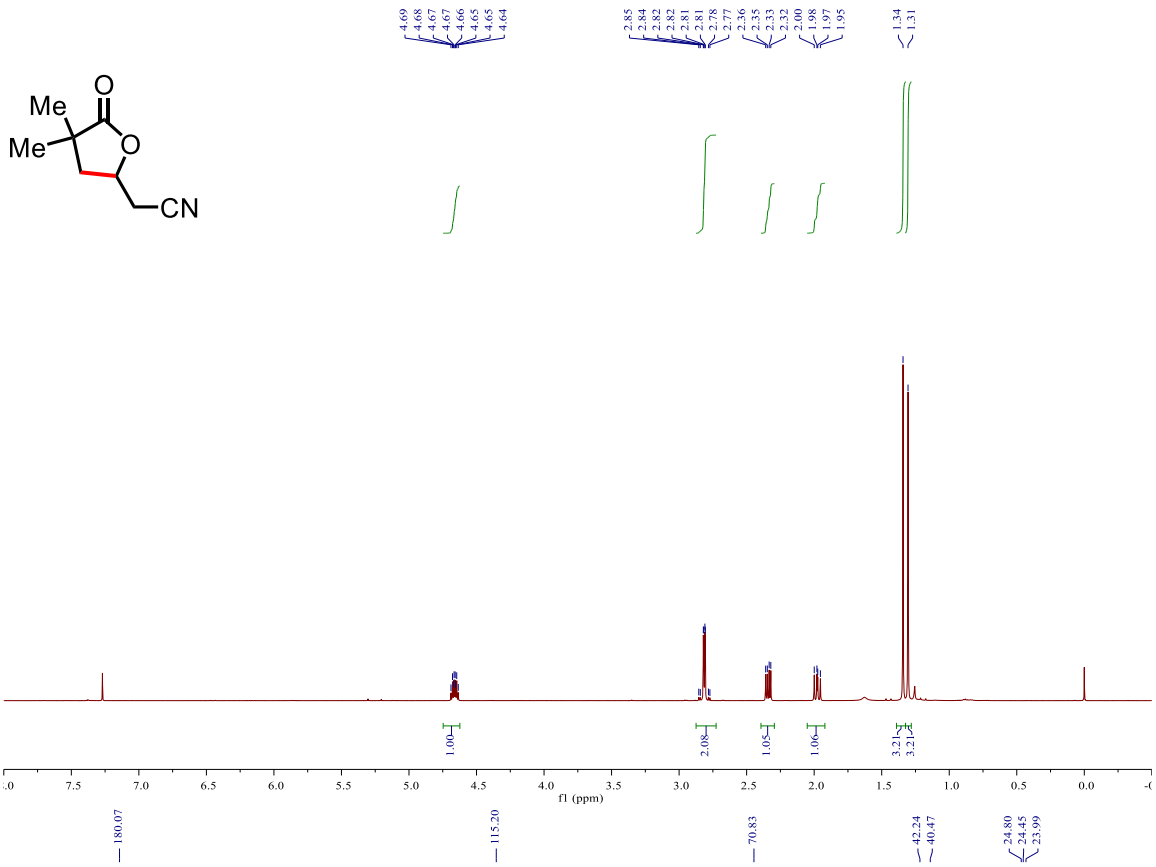

Me
Me
O
O
CO2n-Bu
f1 (ppm)

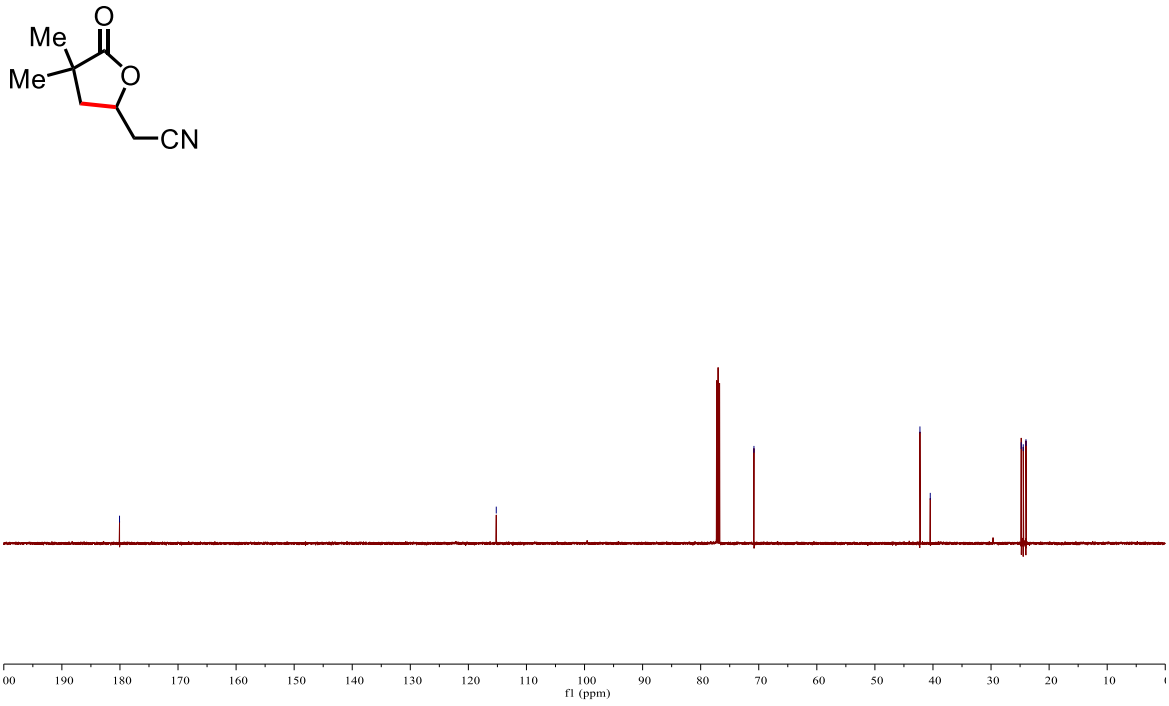

Me
Me
O
O
CONMe2
4.94
4.94
4.93
4.93
4.93
4.92
4.92
4.92
4.91
4.91
4.91
4.90
3.03
3.02
2.99
2.98
2.96
2.96
2.95
2.54
2.53
2.52
2.50
2.45
2.44
2.43
2.42
1.82
1.80
1.80
1.78
1.28
1.28
1.00
3.17
3.86
1.00
0.97
1.29
2.68
2.79
f1 (ppm)

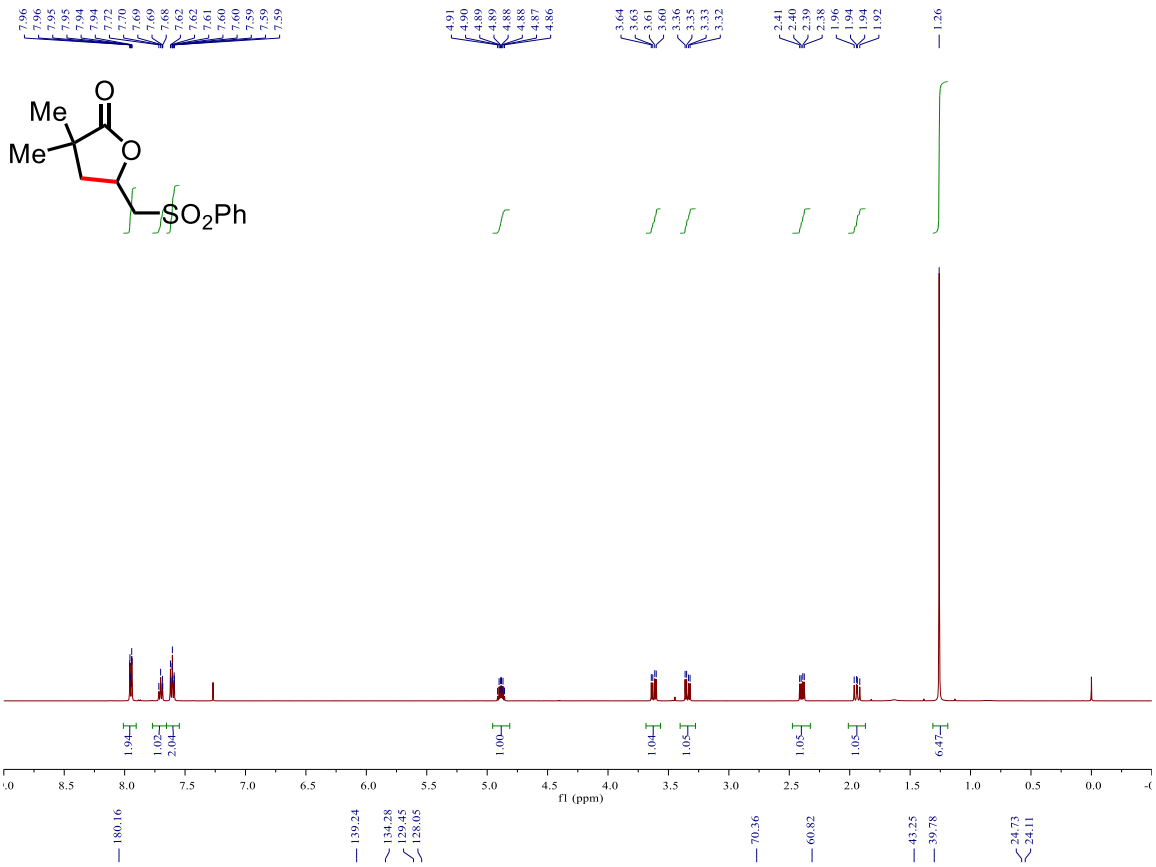

Me
Me
O
O
CONMe2
181.53
168.89
74.02
43.90
40.28
39.15
37.30
35.25
24.96
24.33
f1 (ppm)

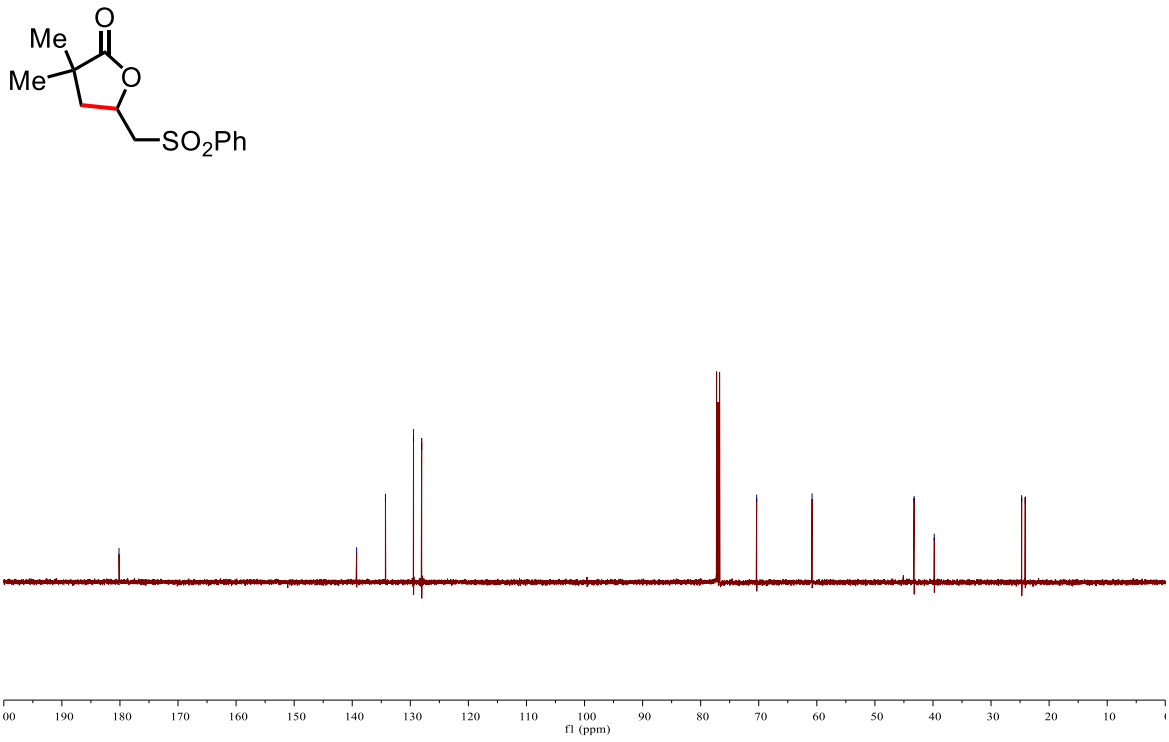

Me
Me
O
O
COEt
4.90
4.88
4.87
4.87
4.86
4.85
4.84
4.83
3.01
3.00
2.97
2.95
2.66
2.65
2.62
2.61
2.52
2.51
2.50
2.49
2.48
2.47
2.46
2.34
2.33
2.31
2.30
1.77
1.74
1.74
1.71
1.28
1.09
1.07
1.05
1.00
1.06
1.13
2.33
1.10
1.21
6.69
3.54
f1 (ppm)

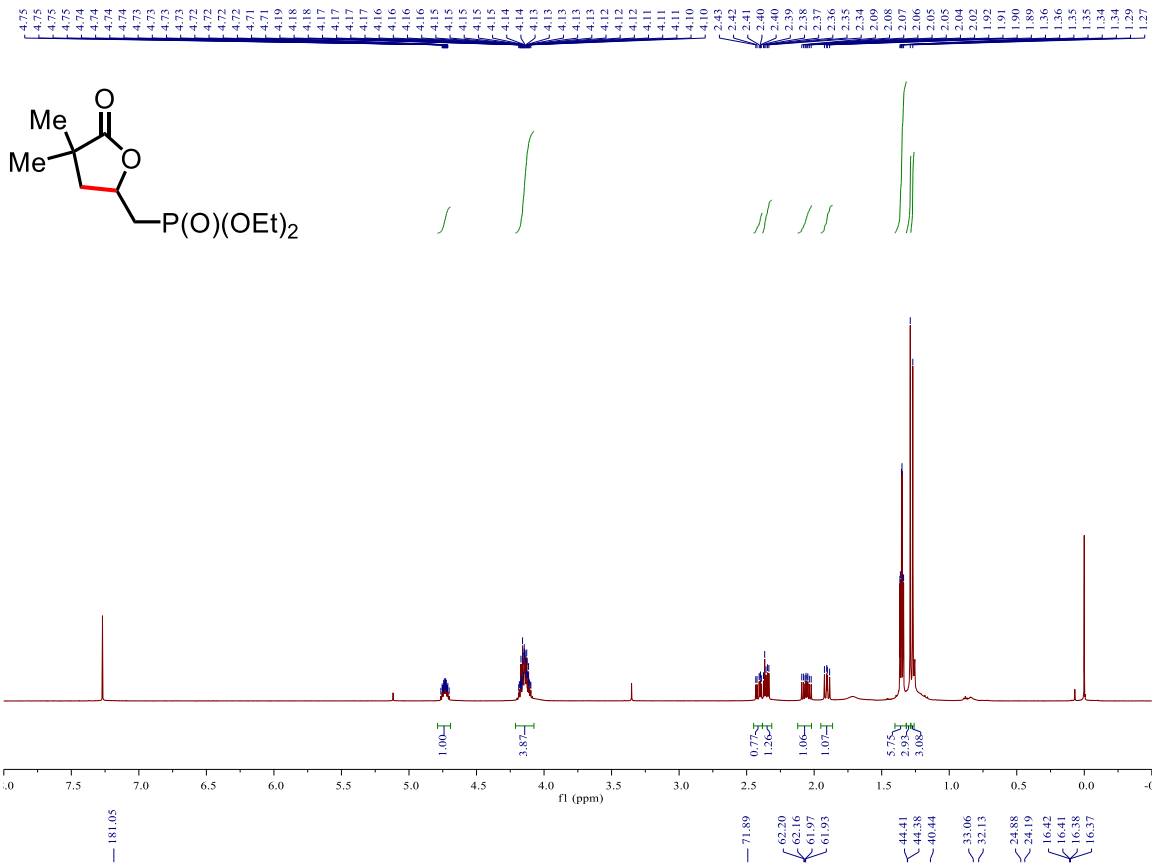

Me
Me
O
O
COEt
207.67
181.34
72.64
47.60
43.53
40.24
36.89
24.95
24.30
7.46
f1 (ppm)

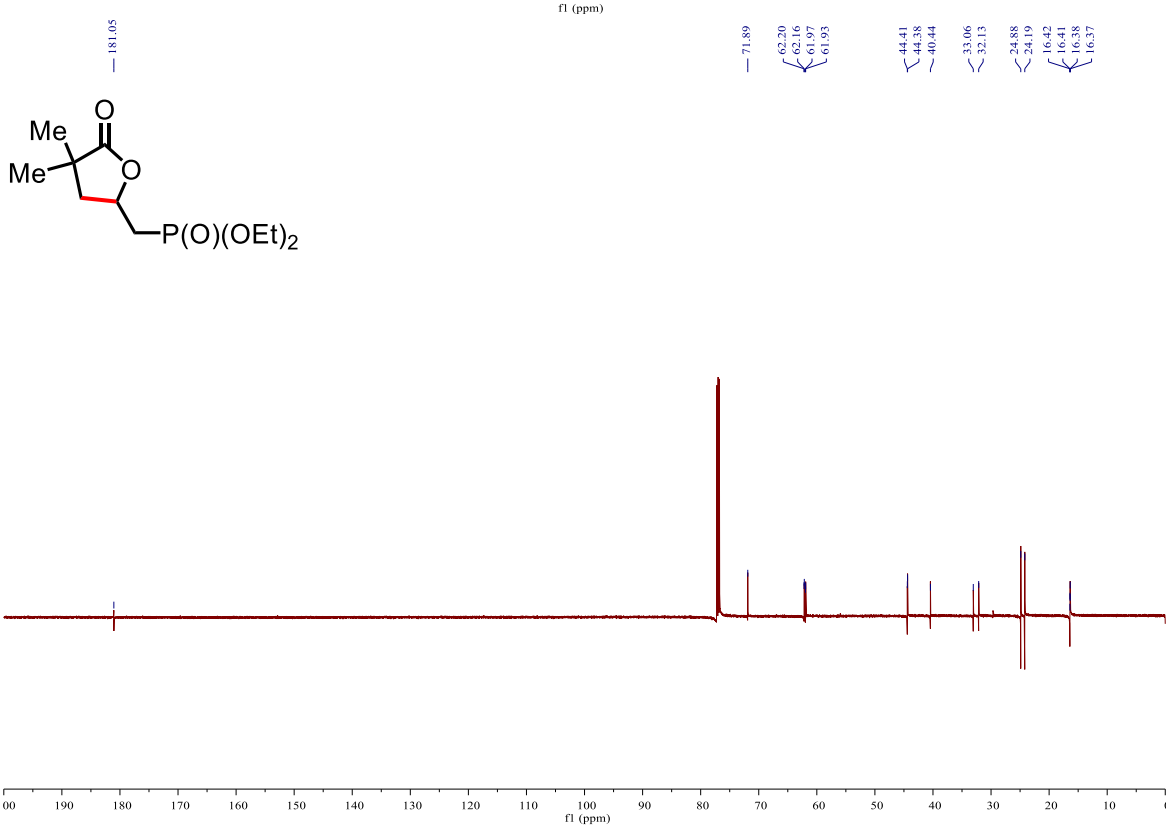

Me
Me
O
O
CN
4.69
4.68
4.67
4.67
4.66
4.65
4.65
4.64
2.85
2.84
2.82
2.82
2.81
2.81
2.78
2.77
2.36
2.35
2.33
2.32
2.00
1.98
1.97
1.95
1.34
1.31
1.00
2.08
1.05
1.06
3.21
3.21
f1 (ppm)

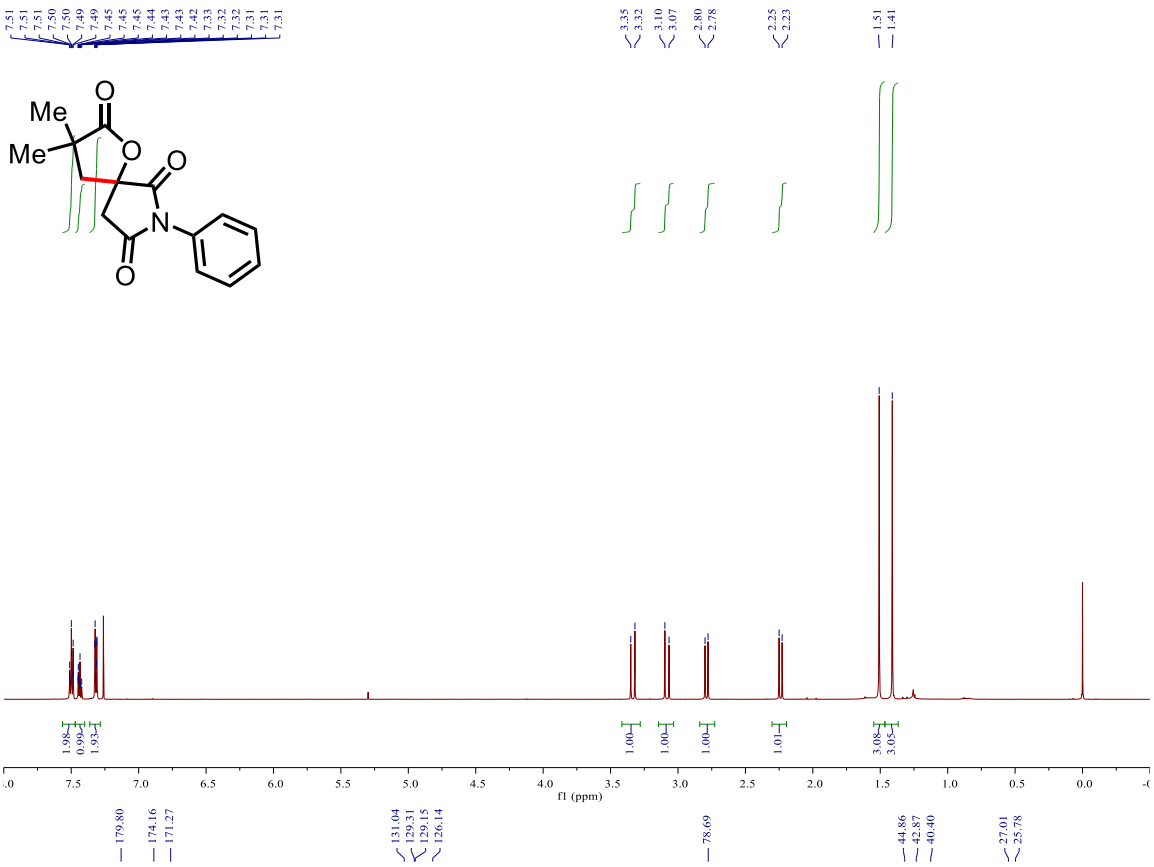

Me
Me
O
O
CN
180.07
115.20
70.83
42.24
40.47
24.80
24.45
23.99
f1 (ppm)

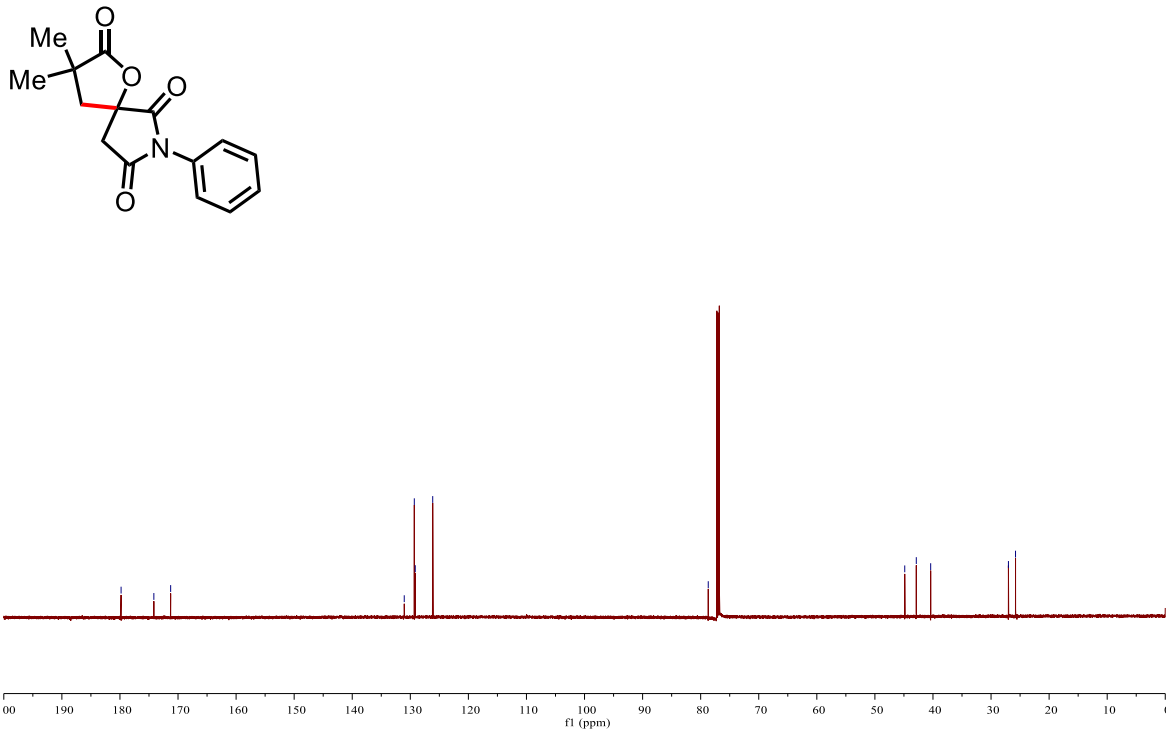

Me
Me
O
O
SO2Ph
f1 (ppm)

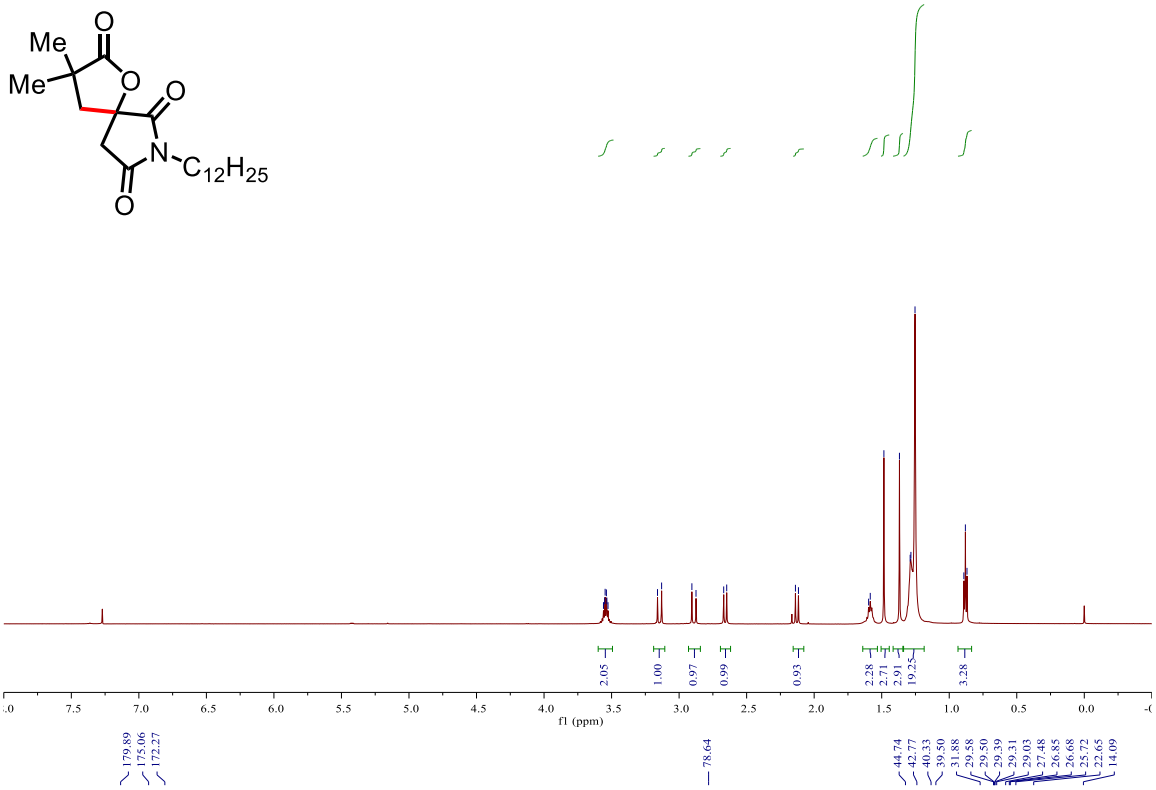

Me
Me
O
O
SO2Ph
f1 (ppm)

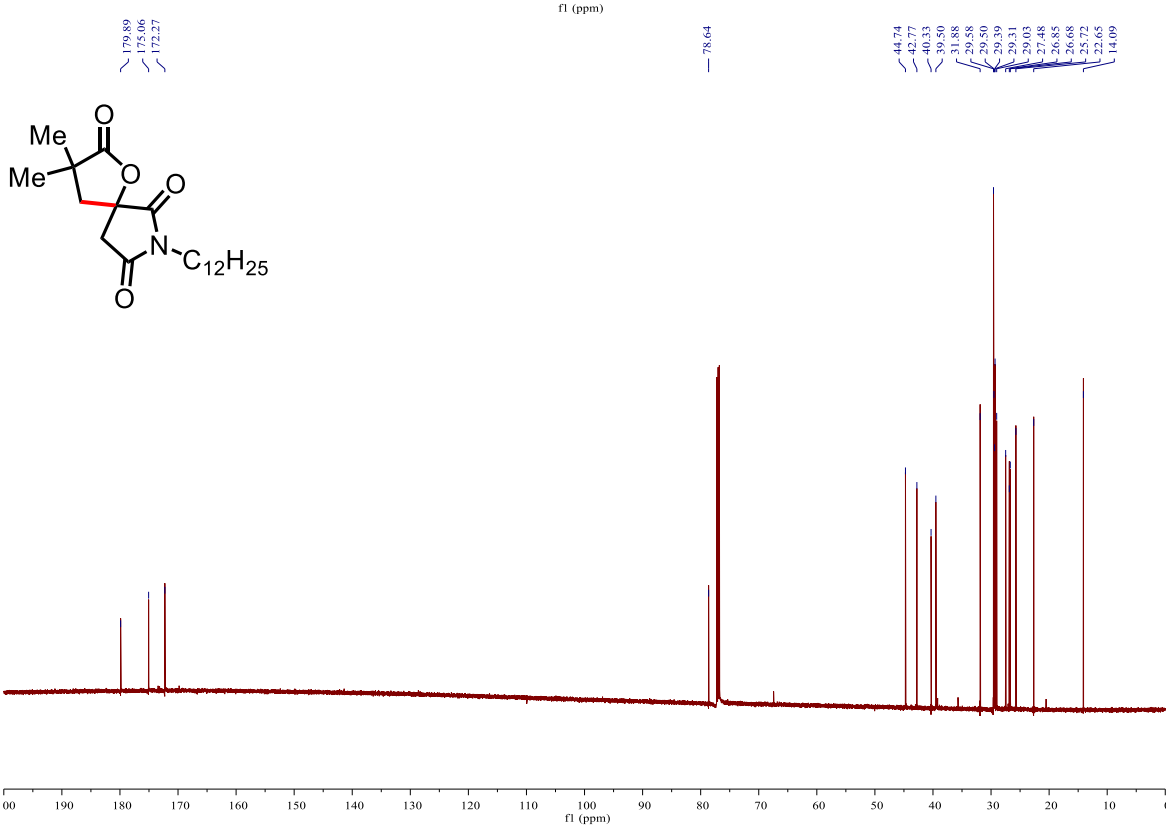

Me
Me
O
O
P(O)(OEt)2
1.00
3.87
0.77
1.26
1.06
1.07
5.75
2.93
3.08
f1 (ppm)

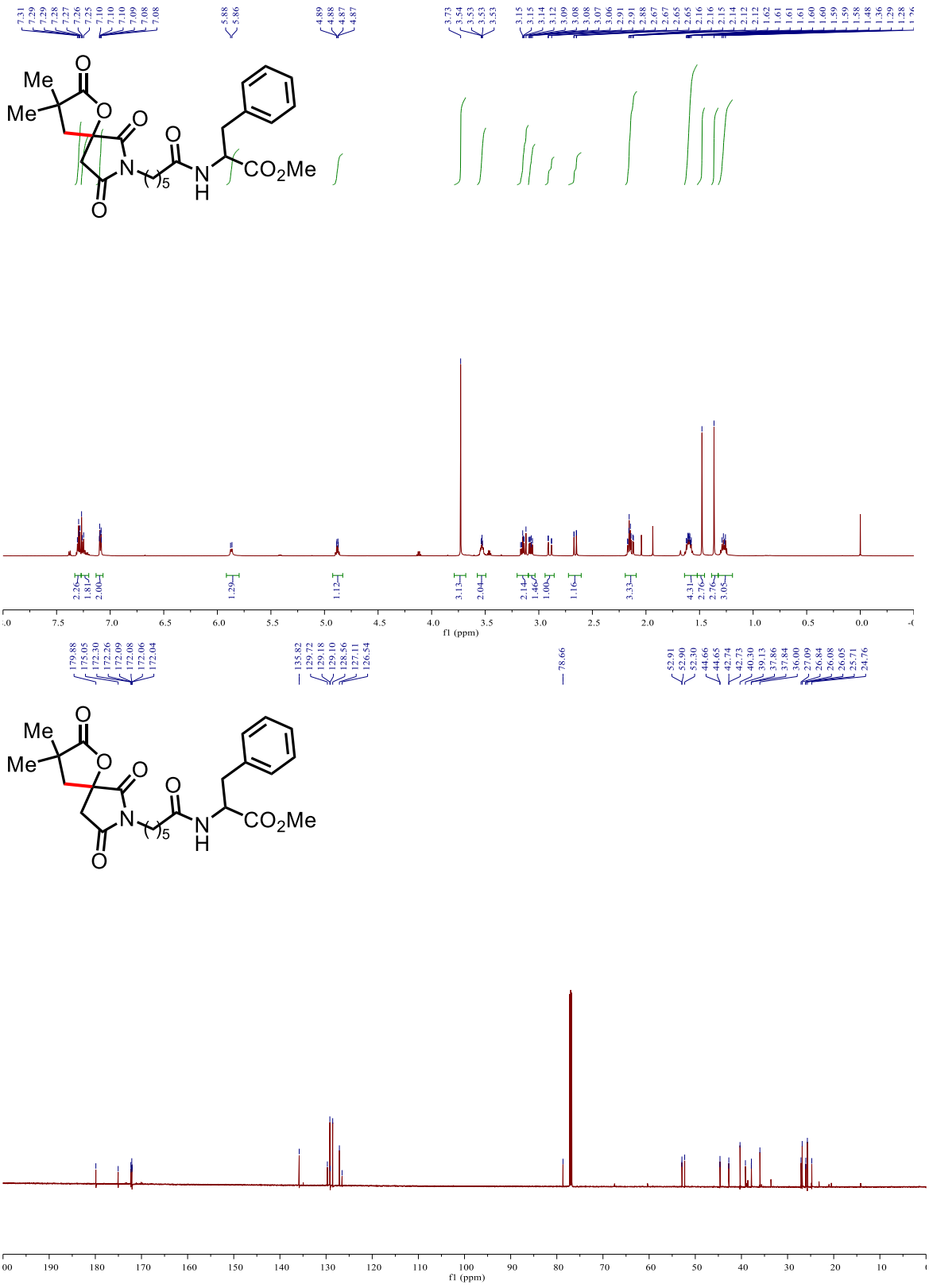

181.05
71.89
62.20
62.16
61.97
61.93
44.41
44.38
40.44
33.06
32.13
24.88
24.19
16.42
16.41
16.38
16.37
Me
Me
O
O
P(O)(OEt)2
f1 (ppm)

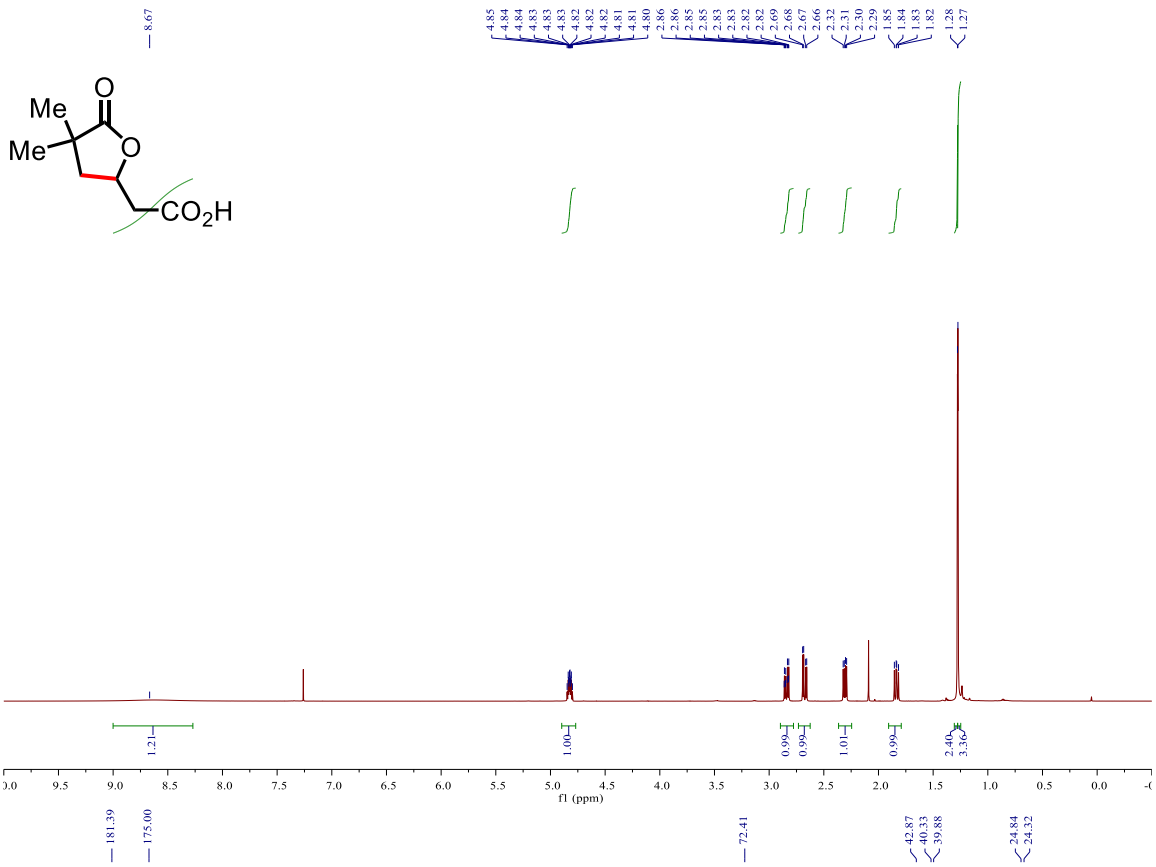

7.51
7.51
7.51
7.50
7.50
7.49
7.49
7.45
7.45
7.45
7.44
7.43
7.43
7.42
7.33
7.32
7.32
7.31
7.31
7.31
3.35
3.32
3.10
3.07
2.80
2.78
2.25
2.23
1.51
1.41
Me
Me
O
O
O
O
N
O
1.98
0.99
1.93
1.00
1.00
1.00
1.01
3.08
3.05
f1 (ppm)

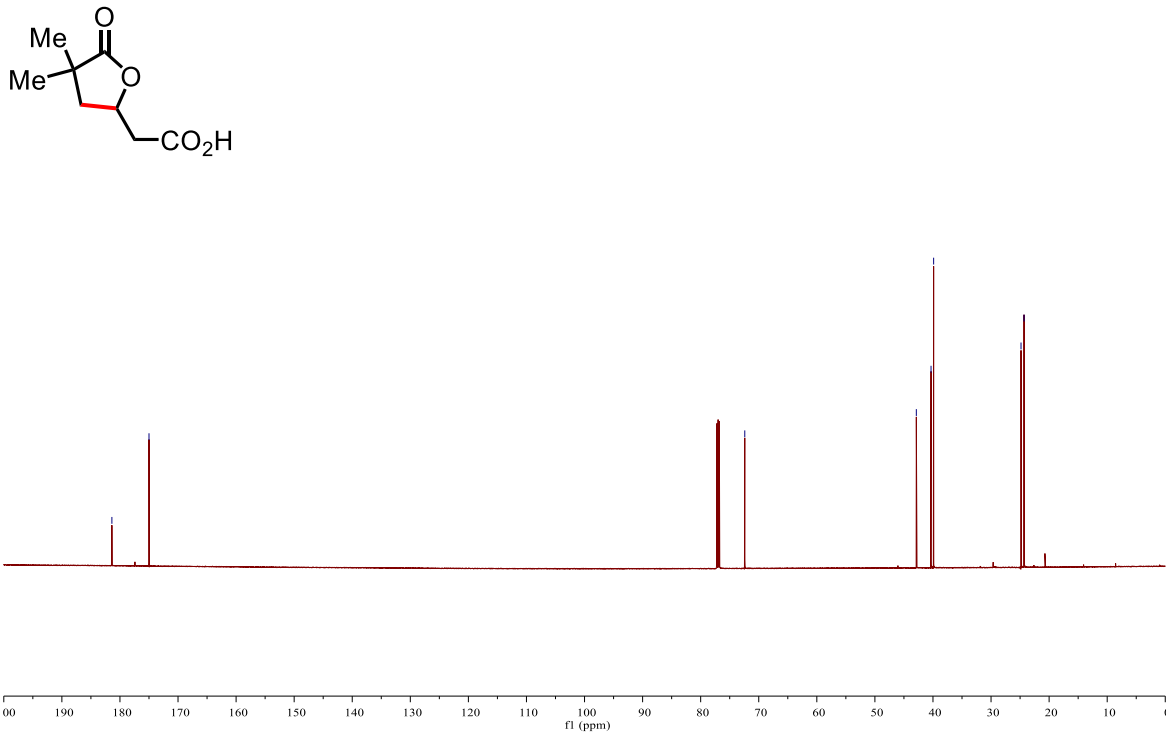

179.80
174.16
171.27
131.04
129.31
129.15
126.14
78.69
44.86
42.87
40.40
27.01
25.78
Me
Me
O
O
O
O
N
O
f1 (ppm)

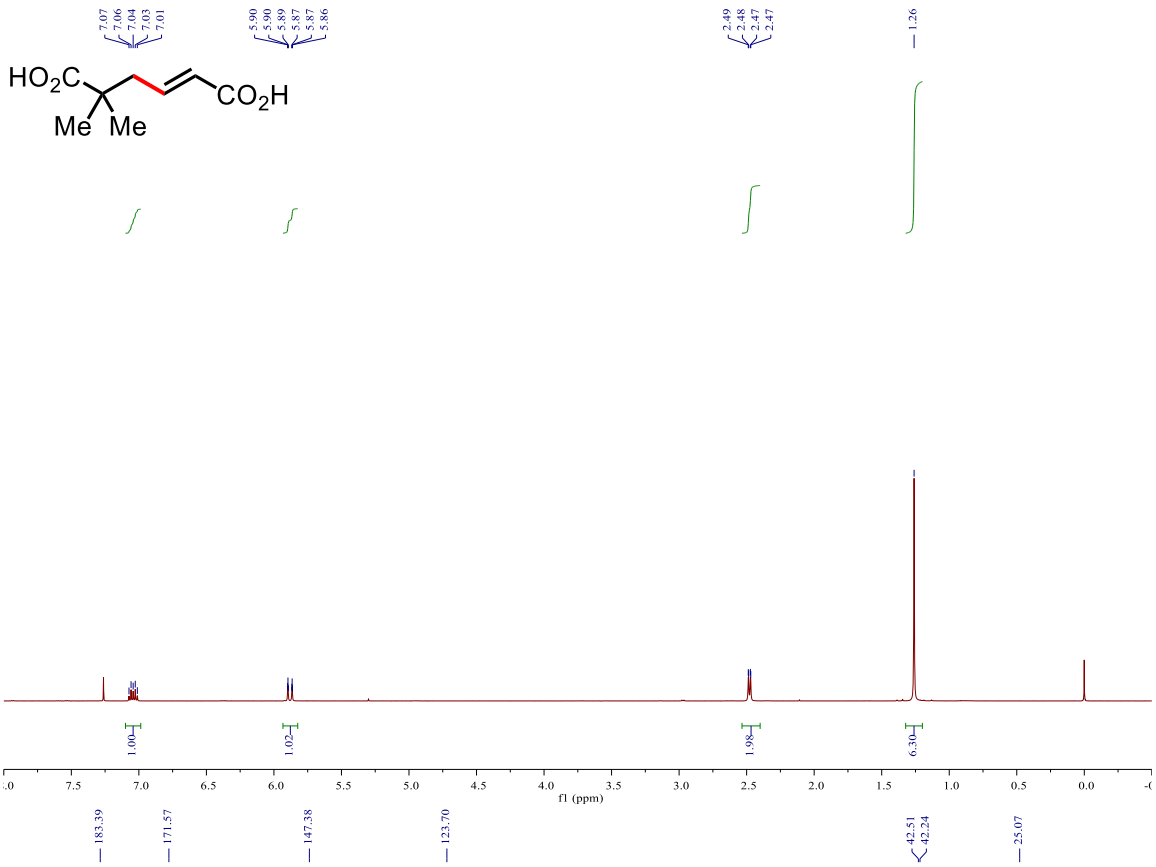

Me
Me
O
O
O
N
$C_{12}H_{25}$
O
3.56
3.55
3.55
3.54
3.53
3.53
3.16
3.13
2.91
2.87
2.67
2.65
2.14
2.12
1.60
1.58
1.48
1.37
1.29
1.28
1.25
0.89
0.88
0.87
2.05
1.00
0.97
0.99
0.93
2.28
2.71
2.91
19.25
3.28
f1 (ppm)

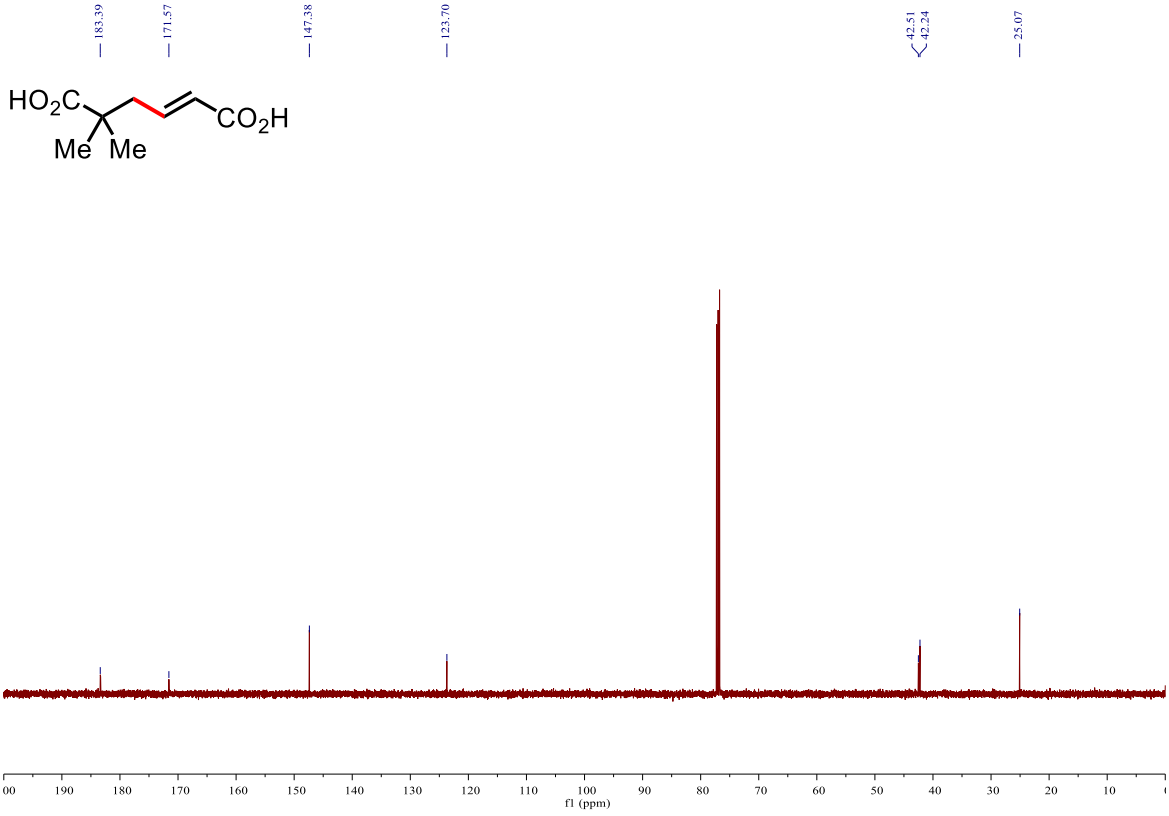

179.89
175.06
172.27
78.64
44.74
42.77
40.33
39.50
31.88
29.58
29.50
29.39
29.31
29.03
27.48
26.85
26.68
25.72
22.65
14.09
Me
Me
O
O
O
N
$C_{12}H_{25}$
O
f1 (ppm)

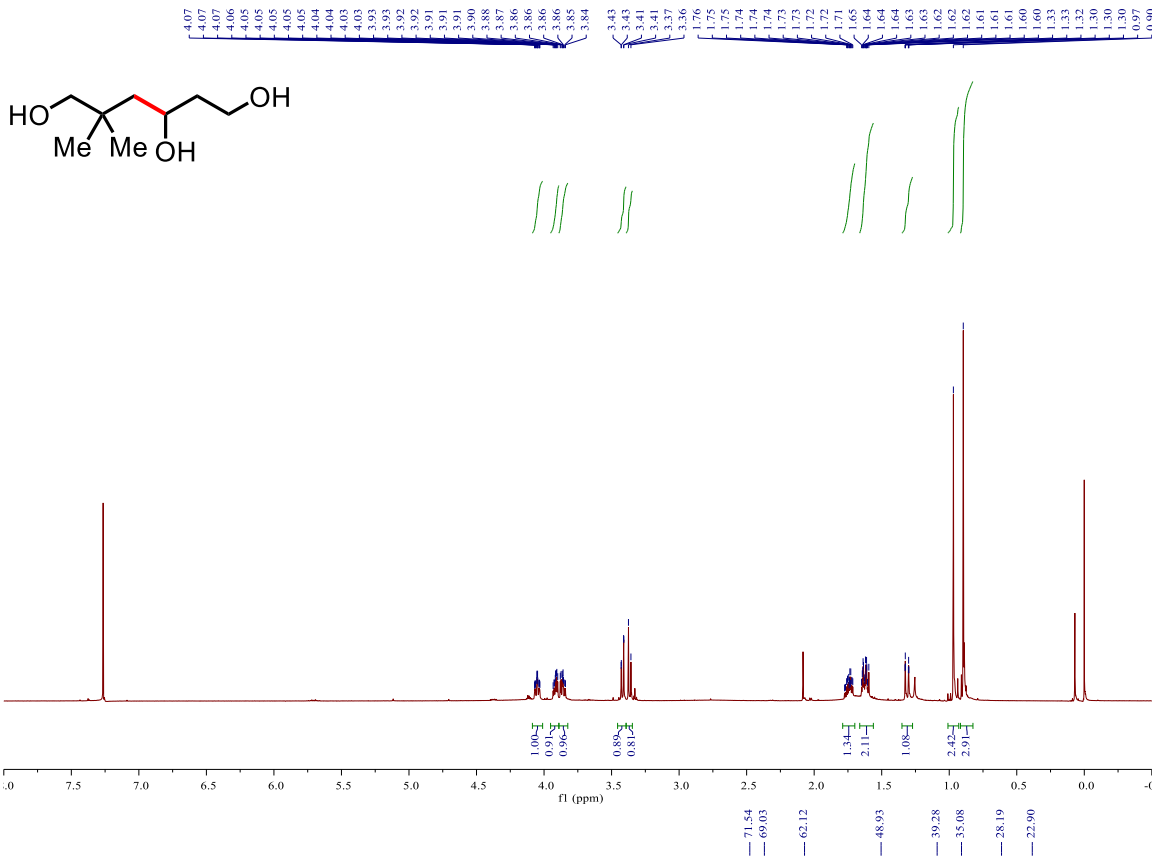

Me
Me
O
O
O
O
N
5
N
H
CO2Me
f1 (ppm)

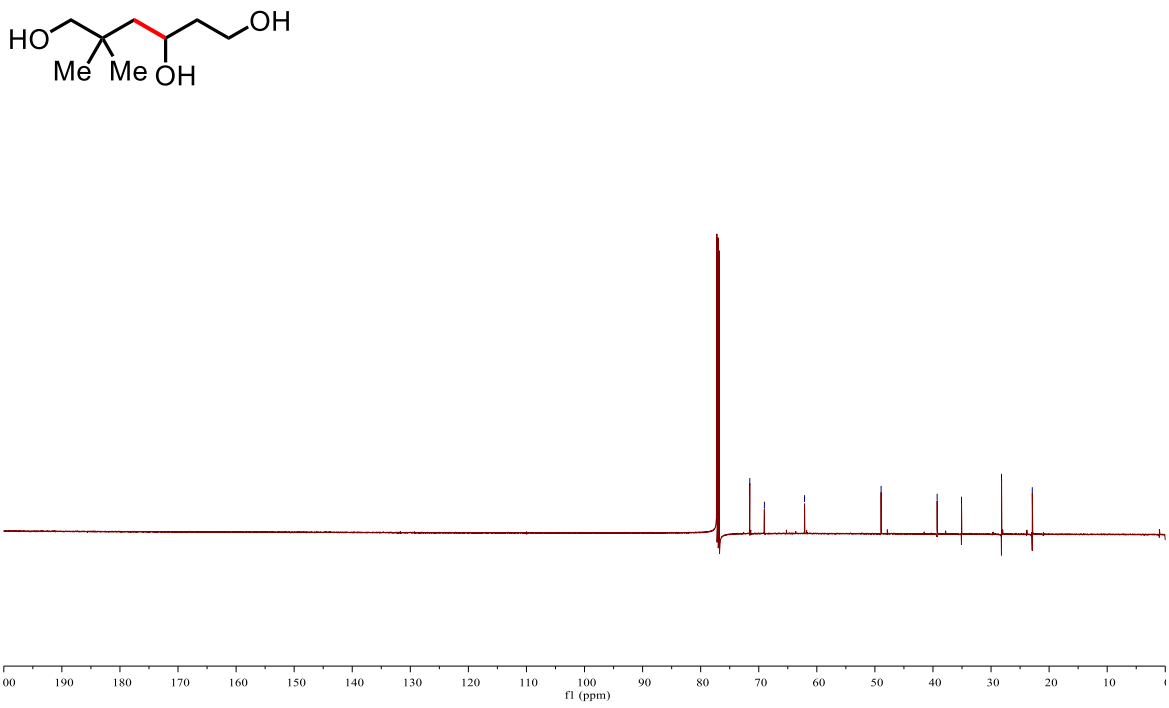

Me
Me
O
O
CO2H
8.67
4.85
4.84
4.84
4.83
4.83
4.83
4.82
4.82
4.82
4.81
4.81
4.80
2.86
2.86
2.85
2.85
2.83
2.82
2.82
2.69
2.68
2.67
2.66
2.32
2.31
2.30
2.29
1.85
1.84
1.83
1.82
1.28
1.27
1.21
1.00
0.99
0.99
1.01
0.99
2.40
3.36
f1 (ppm)


Me
Me
O
O
CO2H
181.39
175.00
72.41
42.87
40.33
39.88
24.84
24.32
f1 (ppm)


7.07
7.06
7.04
7.03
7.01
5.90
5.90
5.89
5.87
5.87
5.86
2.49
2.48
2.47
2.47
1.26
HO2C
CO2H
Me Me
1.00
1.02
1.98
6.30
f1 (ppm)


183.39
171.57
147.38
123.70
42.51
42.24
25.07
HO2C
CO2H
Me Me
f1 (ppm)


HO
Me
Me
OH
OH
f1 (ppm)


HO
Me
Me
OH
OH
f1 (ppm)