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Supplementary information

Lactonization as a general route to β-C(sp^3)–H functionalization

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Lactonization as a general route to β-C(sp^3)–H functionalization

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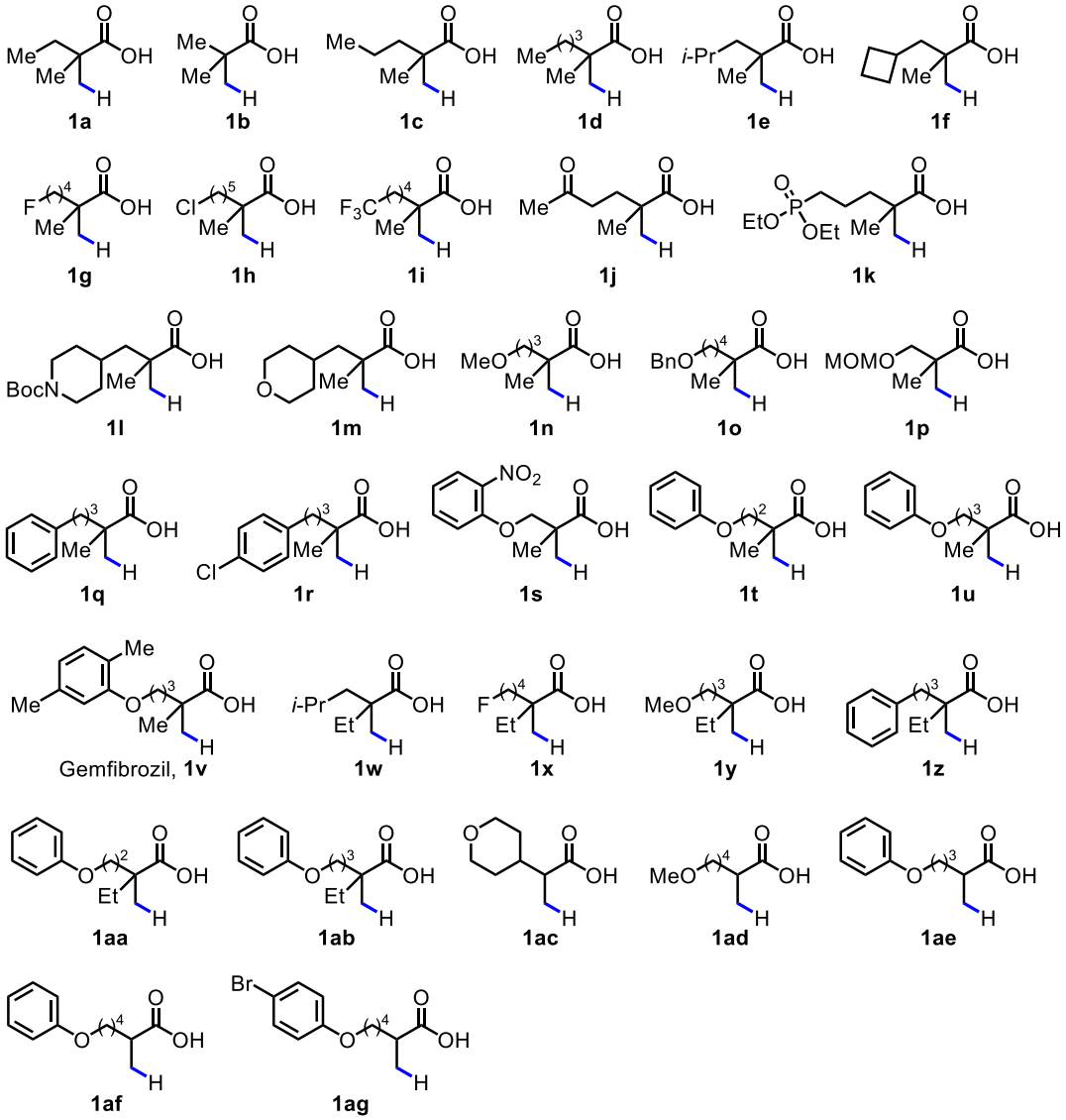
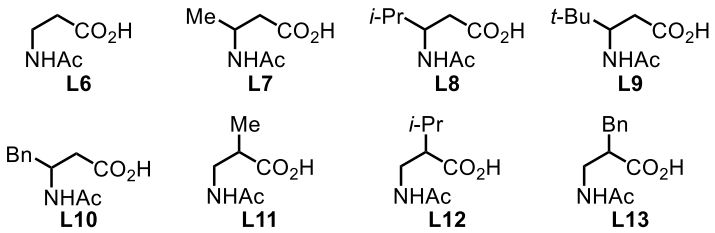
General Information: HFIP was obtained from Oakwood and other solvents were obtained from Sigma-Aldrich, Alfa-Aesar, and Acros and used directly without further purification. $Pd(CH_3CN)_2Cl_2$ and $Pd(OAc)_2$ were obtained from Strem. TBHP (70% in water or ca. 5.5 M in decane), $CsHCO_3$, and NaOAc were purchased from Sigma-Aldrich. 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).

Preparation of Aliphatic Carboxylic Acids



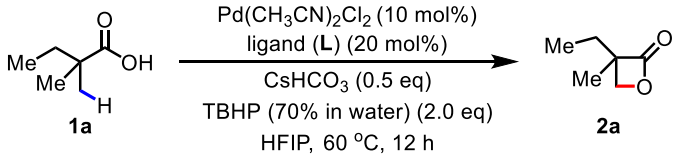
Aliphatic carboxylic acids were obtained from the commercial sources or synthesized following literature procedures (*1*-*2*).

Preparation of Mono-*N*-Protected β-Amino Acid Ligands



Mono-*N*-protected β-amino acid ligands were obtained from the commercial sources or synthesized following literature procedures (*3*-*4*).

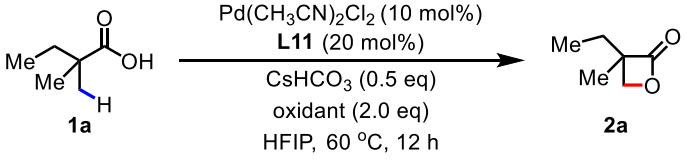
Table S1. Ligand Investigation for β-C(sp^3)–H Lactonization[a,b]



w/o ligand 15%	**L1**, 36%	**L2**, 42%	**L3**, 44%	**L4**, 43%
L5, 40%	**L6**, 48%	**L7**, 45%	**L8**, 40%	**L9**, 10%
L10, 46%	**L11**, 65%	**L12**, 57%	**L13**, 63%	**L14**, 17%

[a]Conditions: **1a** (0.1 mmol), $Pd(CH_3CN)_2Cl_2$ (10 mol%), **L** (20 mol%), $CsHCO_3$ (0.5 eq), TBHP (70% in water) (2.0 eq), HFIP (1.0 mL), 60 °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.

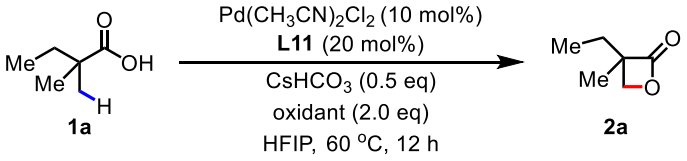
Table S2. Peroxide Oxidant Investigation for β-C(sp^3)–H Lactonization[a,b]



entry	oxidant	yield (%)	entry	oxidant	yield (%)
1	w/o	0	7	Lauroyl peroxide	0
2	H_2O_2	0	8	mCPBA	0
3	AcOO*t*-Bu	34[d]	9	CMHP	0
4	BzOO*t*-Bu	0	10	TBHP (70% in water)	65
5	*t*-BuOO*t*-Bu	0	11	TBHP (ca. 5.5 M in decane)	73[c]
6	BzOOBz	0			

[a]Conditions: **1a** (0.1 mmol), $Pd(CH_3CN)_2Cl_2$ (10 mol%), **L11** (20 mol%), $CsHCO_3$ (0.5 eq), oxidant (2.0 eq), HFIP (1.0 mL), 60 °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. [c]Isolated yield. [d]With 5% acetoxylation product.

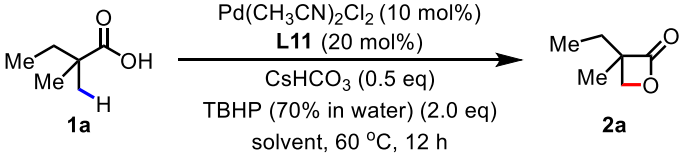
Table S3. Other Oxidants Investigation for β-C(sp^3)–H Lactonization[a,b]



entry	oxidant	yield (%)	entry	oxidant	yield (%)
1	$PhI(OAc)_2$	0[c]	7	Oxone	0
2	$PhI(OTFA)_2$	0	8	Selectfluor	0[e]
3	$PhI(OPiv)_2$	0	9	NFSI	0
4	$(NH_4)_2S_2O_8$	0	10	FP	0
5	$Na_2S_2O_8$	0	11	FTMP	0
6	$K_2S_2O_8$	0[d]			

[a]Conditions: **1a** (0.1 mmol), $Pd(CH_3CN)_2Cl_2$ (10 mol%), **L11** (20 mol%), $CsHCO_3$ (0.5 eq), oxidant (2.0 eq), HFIP (1.0 mL), 60 °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. [c]With 8% acetoxylation product. [d]With 9% self-acyloxylation product. [e]With 5% self-acyloxylation product.

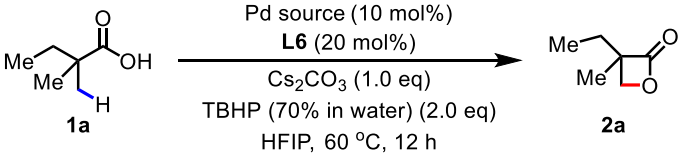
Table S4. Solvent Investigation for β-C(sp^3)–H Lactonization[a,b]



entry	solvent	yield (%)	entry	solvent	yield (%)
1	DCM	0	6	toluene	0
2	DCE	0	7	ACN	0
3	THF	0	8	MeOH	0
4	dioxane	0	9	IPA	0
5	ether	0	10	HFIP	65

[a]Conditions: **1a** (0.1 mmol), $Pd(CH_3CN)_2Cl_2$ (10 mol%), **L11** (20 mol%), $CsHCO_3$ (0.5 eq), TBHP (70% in water) (2.0 eq), HFIP (1.0 mL), 60 °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.

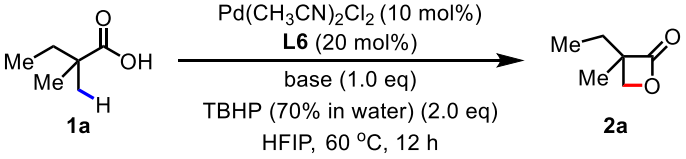
Table S5. Pd Source Investigation for β-C(sp^3)–H Lactonization[a,b]



entry	Pd source	yield (%)	entry	Pd source	yield (%)
1	w/o	0	6	$Pd(acac)_2$	0
2	$Pd(OAc)_2$	0	7	$Pd(CH_3CN)_2Cl_2$	31
3	$Pd(TFA)_2$	0	8	$Pd(PhCN)_2Cl_2$	23
4	$PdCl_2$	23	9	$[PdCl(allyl)]_2$	18
5	PdI_2	0	10	$Pd(CH_3CN)_4(BF_4)_2$	0

[a]Conditions: **1a** (0.1 mmol), Pd source (10 mol%), **L6** (20 mol%), Cs_2CO_3 (1.0 eq), TBHP (70% in water) (2.0 eq), HFIP (1.0 mL), 60 °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.

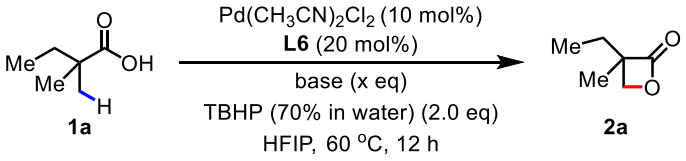
Table S6. Base Investigation for β-C(sp^3)–H Lactonization[a,b]



entry	base	yield (%)	entry	base	yield (%)
1	w/o	0	9	NaTFA	0
2	$NaHCO_3$	0	10	Li_2CO_3	31
3	Na_2CO_3	8	11	K_2CO_3	23
4	NaH_2PO_4	0	12	Cs_2CO_3	31
5	Na_2HPO_4	12	13	$CsHCO_3$	42
6	$Na_2HPO_4{\cdot}7H_2O$	20	14	CsOAc	43
7	Na_3PO_4	31	15	$CsOH{\cdot}H_2O$	44
8	NaOAc	18	16	CsF	13

[a]Conditions: **1a** (0.1 mmol), $Pd(CH_3CN)_2Cl_2$ (10 mol%), **L6** (20 mol%), base (1.0 eq), TBHP (70% in water) (2.0 eq), HFIP (1.0 mL), 60 °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.

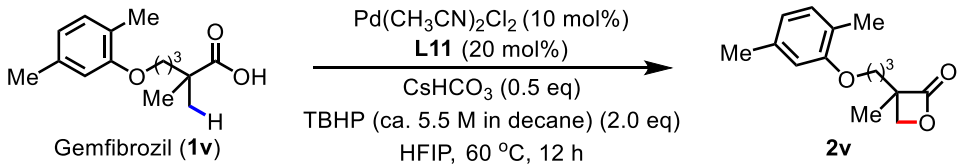
Table S7. Base Equivalent Investigation for β-C(sp^3)–H Lactonization[a,b]



entry	base	x eq	yield (%)
1	Cs_2CO_3	1	31
2	Cs_2CO_3	0.5	36
3	Cs_2CO_3	0.25	47
4	$CsHCO_3$	1	42
5	$CsHCO_3$	0.5	48
6	$CsHCO_3$	0.25	25
7	CsOAc	1	43
8	CsOAc	0.5	16
9	$CsOH{\cdot}H_2O$	1	44
10	$CsOH{\cdot}H_2O$	0.5	40

[a]Conditions: **1a** (0.1 mmol), $Pd(CH_3CN)_2Cl_2$ (10 mol%), **L6** (20 mol%), base (x eq), TBHP (70% in water) (2.0 eq), HFIP (1.0 mL), 60 °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.

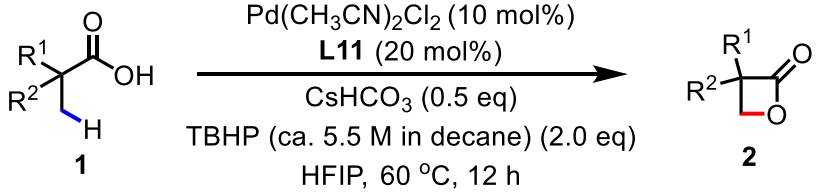
Table S8. Conditions Investigation for β-C(sp^3)–H Lactonization of Gemfibrozil 1v[a,b]



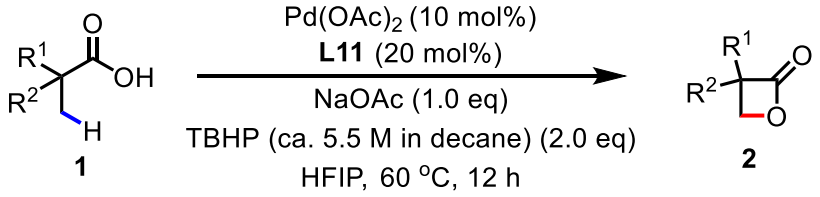
entry	variation from standard conditions	yield (%)
1	none	56
2	$Pd(OAc)_2$ replaced $Pd(CH_3CN)_2Cl_2$, NaOAc (1.0 eq) replaced CsHCO3 (0.5 eq)	93[c]

[a]Conditions: **1a** (0.1 mmol), $Pd(CH_3CN)_2Cl_2$ (10 mol%), **L6** (20 mol%), $CsHCO_3$ (0.5 eq), TBHP (ca. 5.5M in decane) (2.0 eq), HFIP (1.0 mL), 60 °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. [c]Isolated yield.

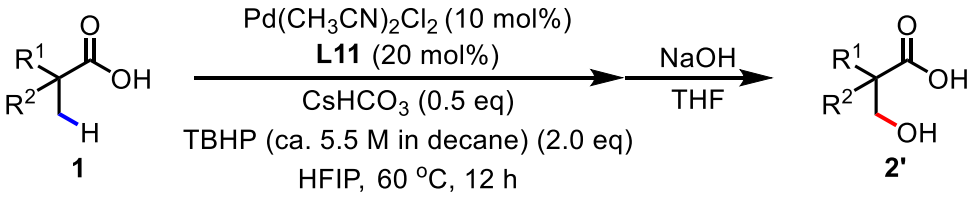
General Procedure for β-C(sp^3)–H Lactonization



General Procedure A: In the culture tube, $Pd(CH_3CN)_2Cl_2$ (10 mol%, 2.6 mg), ligand **L11** (20 mol%, 2.9 mg), $CsHCO_3$ (0.5 eq, 9.7 mg), 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 TBHP (ca. 5.5 M in decane) (2.0 eq, 36 μL) were added. The reaction mixture was stirred at rt for 3 min, and then heated to 60 °C for 12 h (600 rpm). After being allowed to cool to room temperature, the mixture was concentrated *in vacuo*, and the resulting mixture was either purified by pTLC or diluted with EA, washed with saturated $NaHCO_3$ solution, and concentrated *in vacuo* to afford the title compound (If the impurities from the lactone opening was significant, the mixture was filtered through silica gel plug prior to recording the NMR).

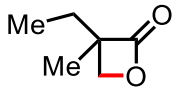


General Procedure B: In the culture tube, $Pd(OAc)_2$ (10 mol%, 2.2 mg), ligand **L11** (20 mol%, 2.9 mg), NaOAc (1.0 eq, 8.2 mg), and carboxylic acid **1** (0.1 mmol) in order were weighed in air and placed with a magnetic stir bar. Then HFIP (1.0 mL) and TBHP (ca. 5.5 M in decane) (2.0 eq, 36 μL) were added. The reaction mixture was stirred at rt for 3 min, and then heated to 60 °C for 12 h (600 rpm). After being allowed to cool to room temperature, the mixture was concentrated *in vacuo*, and the resulting mixture was either purified by pTLC or diluted with EA, washed with saturated $NaHCO_3$ solution, and concentrated *in vacuo* to afford the title compound (If the impurities from the lactone opening was significant, the mixture was filtered through silica gel plug prior to recording the NMR).



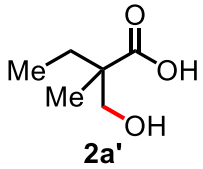
General Procedure C: In the culture tube, $Pd(CH_3CN)_2Cl_2$ (10 mol%, 2.6 mg), ligand **L11** (20 mol%, 2.9 mg), $CsHCO_3$ (0.5 eq, 9.7 mg), and carboxylic acid **1** (0.1 mmol) in order were weighed in air and placed with a magnetic stir bar. Then HFIP (1.0 mL) and TBHP (ca. 5.5 M in decane) (2.0 eq, 36 μL) were added. The reaction mixture was stirred at rt for 3 min, and then heated to 60 °C for 12 h (600 rpm). After being allowed to cool to room temperature, the mixture was concentrated *in vacuo* carefully to remove solvent HFIP. The resulting mixture was dissolved in THF (1.0 mL), treated with 2M NaOH (1.0 mL), and stirred at 60 °C for 1 h. After being allowed to cool to room temperature, the mixture was acidified by 2M HCl (5.0 mL) and extracted with EA. After being concentrated *in vacuo*, the resulting mixture was purified by column chromatography to afford the title compound.

Substrate Scope for β-C(sp^3)–H Lactonization



3-Ethyl-3-methyloxetan-2-one (2a)

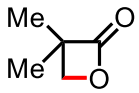
Following **General Procedure A** on 0.1 mmol scale. Purification by diluting with EA and washing with saturated $NaHCO_3$ solution afforded the title compound (colorless oil, 8.3 mg, 73% yield). Due to the volatility of the product, the yield was determined by ^1H NMR analysis of the crude product using CH_2Br_2 (0.1 mmol, 7 μL) as the internal standard (72% yield). Following **General Procedure A** on 3.0 mmol scale. Further purification by diluting with EA, washing with saturated $NaHCO_3$ solution, and filtering through silica gel using hexane/EA (5/1) as eluent afforded the title compound. ^1H NMR (600 MHz, $CDCl_3$) δ 4.16 (d, *J* = 5.0 Hz, 1H), 4.03 (d, *J* = 5.0 Hz, 1H), 1.81 – 1.68 (m, 2H), 1.42 (s, 3H), 1.03 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.04, 71.02, 58.00, 27.38, 18.97, 8.98. The NMR data matches the reported data (*5*).



2a'

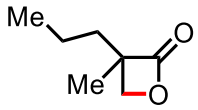
2-(Hydroxymethyl)-2-methylbutanoic acid (2a')

Following **General Procedure C** on 0.1 mmol scale. Purification by column chromatography afforded the title compound (colorless oil, 10.5 mg, 80% yield). ^1H NMR (600 MHz, $CDCl_3$) δ 3.75 (br s, 1H), 3.54 (d, *J* = 10.7 Hz, 1H), 1.76 – 1.64 (m, 1H), 1.66 – 1.56 (m, 1H), 1.20 (s, 3H), 0.92 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 182.26, 67.16, 47.48, 27.88, 18.40, 8.06.



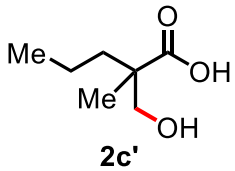
3,3-Dimethyloxetan-2-one (2b)

Following **General Procedure A** on 0.1 mmol scale. Due to the volatility of the product, the yield was determined by ^1H NMR analysis of the crude product using CH_2Br_2 (0.1 mmol, 7 μL) as the internal standard (50% yield). The NMR data matches the reported data (*6*).



3-Methyl-3-propyloxetan-2-one (2c)

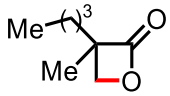
Following **General Procedure A** on 0.1 mmol scale. Purification by diluting with EA and washing with saturated $NaHCO_3$ solution afforded the title compound (colorless oil, 9.1 mg, 71% yield) (S40). Due to the volatility of the product, the yield was determined by ^1H NMR analysis of the crude product using CH_2Br_2 (0.1 mmol, 7 μL) as the internal standard (70% yield). Further purification by filtering through silica gel plug afforded the title compound. ^1H NMR (600 MHz, $CDCl_3$) δ 4.16 (d, *J* = 5.0 Hz, 1H), 4.02 (d, *J* = 5.0 Hz, 1H), 1.71 – 1.65 (m, 2H), 1.59 – 1.48 (m, 2H), 1.42 (s, 3H), 0.97 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.15, 71.55, 57.48, 36.57, 19.33, 18.05, 14.31. The NMR data matches the reported data (*5*).



2c'

2-(Hydroxymethyl)-2-methylpentanoic acid (2c')

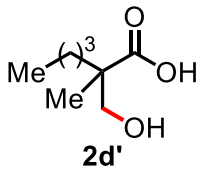
Following **General Procedure C** on 0.1 mmol scale. Purification by column chromatography afforded the title compound (colorless oil, 12.0 mg, 82% yield). ^1H NMR (600 MHz, $CDCl_3$) δ 3.75 (d, *J* = 11.2 Hz, 1H), 3.52 (d, *J* = 11.2 Hz, 1H), 1.64 – 1.56 (m, 1H), 1.57 – 1.49 (m, 1H), 1.40 – 1.28 (m, 2H), 1.21 (s, 3H), 0.92 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 182.37, 68.15, 47.82, 38.15, 19.57, 17.63, 14.70.



3-Butyl-3-methyloxetan-2-one (2d)

Following **General Procedure A** on 0.1 mmol scale. Purification by diluting with EA and washing with saturated $NaHCO_3$ solution afforded the title compound (colorless oil, 10.5 mg, 74% yield). Further purification by filtering through silica gel plug afforded the title compound. ^1H NMR (600 MHz, $CDCl_3$) δ 4.16 (d, *J* = 5.0 Hz, 1H), 4.02 (d, *J* = 5.0 Hz, 1H),

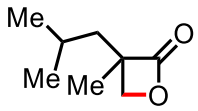
1.76 – 1.64 (m, 2H), 1.51 – 1.44 (m, 1H), 1.42 (s, 3H), 1.39 – 1.27 (m, 3H), 0.93 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.20, 71.53, 57.44, 34.16, 26.80, 22.94, 19.35, 13.99.



2d'

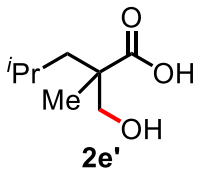
2-(Hydroxymethyl)-2-methylhexanoic acid (2d')

Following **General Procedure C** on 0.1 mmol scale. Purification by column chromatography afforded the title compound (colorless oil, 14.0 mg, 87% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.75 (d, *J* = 11.1 Hz, 1H), 3.53 (d, *J* = 11.1 Hz, 1H), 1.67 – 1.58 (m, 1H), 1.58 – 1.51 (m, 1H), 1.36 – 1.25 (m, 4H), 1.21 (s, 3H), 0.91 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 183.05, 68.12, 47.79, 35.62, 26.41, 23.33, 19.52, 14.06.



3-Isobutyl-3-methyloxetan-2-one (2e)

Following **General Procedure A** on 0.1 mmol scale. Purification by diluting with EA and washing with saturated $NaHCO_3$ solution afforded the title compound (colorless oil, 10.4 mg, 73% yield). Further purification by filtering through silica gel plug afforded the title compound. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.21 (d, *J* = 5.0 Hz, 1H), 4.06 (dd, *J* = 5.0, 0.8 Hz, 1H), 1.87 – 1.78 (m, 1H), 1.78 – 1.71 (m, 1H), 1.61 – 1.55 (m, 1H), 1.42 (s, 3H), 0.99 (d, *J* = 6.6 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.54, 72.80, 56.75, 42.64, 24.80, 23.97, 22.35, 18.92.

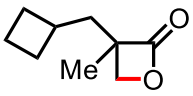


2e'

2-(Hydroxymethyl)-2,4-dimethylpentanoic acid (2e')

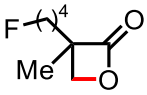
Following **General Procedure C** on 0.1 mmol scale. Purification by column chromatography afforded the title compound (colorless oil, 13.3 mg, 83% yield). ^{1}H NMR

(600 MHz, $CDCl_3$) δ 3.80 (d, *J* = 10.7 Hz, 1H), 3.48 (d, *J* = 10.7 Hz, 1H), 1.81 – 1.70 (m, 1H), 1.60 (dd, *J* = 14.1, 6.7 Hz, 1H), 1.48 (dd, *J* = 14.1, 6.1 Hz, 1H), 1.24 (s, 3H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 183.42, 68.95, 47.58, 44.86, 24.65, 24.22, 23.83, 20.01.



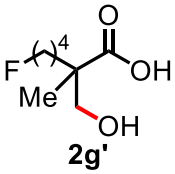
3-(Cyclobutylmethyl)-3-methyloxetan-2-one (2f)

Following **General Procedure A** on 0.1 mmol scale. Purification by diluting with EA and washing with saturated $NaHCO_3$ solution afforded the title compound (colorless oil, 7.0 mg, 45% yield). ^1H NMR (600 MHz, $CDCl_3$) δ 4.16 (d, *J* = 5.0 Hz, 1H), 3.98 (d, *J* = 5.0 Hz, 1H), 2.52 – 2.41 (m, 1H), 2.16 – 2.01 (m, 2H), 1.95 – 1.87 (m, 1H), 1.87 – 1.75 (m, 3H), 1.75 – 1.66 (m, 2H), 1.38 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.14, 71.48, 57.19, 41.37, 32.64, 30.00, 29.41, 19.72, 19.15; HRMS (ESI-TOF) Calcd for $C_9H_{13}O_2$ $[M-H]^-$: 153.0916; found: 153.0912.



3-(4-Fluorobutyl)-3-methyloxetan-2-one (2g)

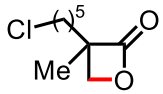
Following **General Procedure A** on 0.1 mmol scale. Purification by diluting with EA and washing with saturated $NaHCO_3$ solution afforded the title compound (colorless oil, 11.5 mg, 72% yield). ^1H NMR (600 MHz, $CDCl_3$) δ 4.48 (dt, *J* = 47.2, 5.9 Hz, 2H), 4.18 (d, *J* = 5.1 Hz, 1H), 4.06 (d, *J* = 5.1 Hz, 1H), 1.82 – 1.70 (m, 4H), 1.70 – 1.60 (m, 1H), 1.55 – 1.47 (m, 1H), 1.45 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.91, 83.67 (d, *J* = 165.0 Hz), 71.45, 57.31, 34.04, 30.50 (d, *J* = 19.9 Hz), 20.69 (d, *J* = 4.9 Hz), 19.25; HRMS (ESI-TOF) Calcd for $C_8H_{14}FO_3$ $[M+H]^+$: 161.0978; found: 161.0975.



2g'

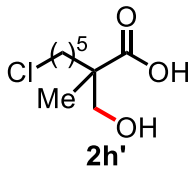
6-Fluoro-2-(hydroxymethyl)-2-methylhexanoic acid (2g')

Following **General Procedure C** on 0.1 mmol scale. Purification by column chromatography afforded the title compound (colorless oil, 14.5 mg, 81% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.45 (dt, *J* = 47.3, 5.9 Hz, 2H), 3.74 (d, *J* = 11.4 Hz, 1H), 3.58 (d, *J* = 11.4 Hz, 1H), 1.75 – 1.65 (m, 3H), 1.65 – 1.57 (m, 1H), 1.49 – 1.40 (m, 2H), 1.23 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 182.36, 83.91 (d, *J* = 164.6 Hz), 68.00, 47.74, 35.34, 30.96 (d, *J* = 19.8 Hz), 20.24 (d, *J* = 5.3 Hz), 19.50.



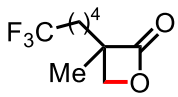
3-(5-Chloropentyl)-3-methyloxetan-2-one (2h)

Following **General Procedure A** on 0.1 mmol scale. Purification by diluting with EA and washing with saturated $NaHCO_3$ solution afforded the title compound (colorless oil, 9.0 mg, 47% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.15 (d, *J* = 5.0 Hz, 1H), 4.04 (d, *J* = 5.0 Hz, 1H), 3.54 (t, *J* = 6.6 Hz, 2H), 1.86 – 1.75 (m, 2H), 1.75 – 1.66 (m, 2H), 1.55 – 1.46 (m, 2H), 1.43 (s, 3H), 1.40 – 1.29 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.90, 71.48, 57.36, 44.93, 34.34, 32.39, 27.05, 24.04, 19.38; HRMS (ESI-TOF) Calcd for $C_9H_{16}ClO_2$ $[M+H]^+$: 191.0839; found: 191.0827.



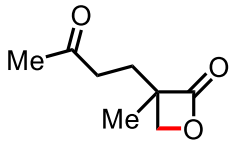
7-Chloro-2-(hydroxymethyl)-2-methylheptanoic acid (2h')

Following **General Procedure C** on 0.1 mmol scale. Purification by column chromatography afforded the title compound (colorless oil, 13.5 mg, 65% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.74 (d, *J* = 12.9 Hz, 1H), 3.63 – 3.43 (m, 3H), 1.84 – 1.72 (m, 2H), 1.70 – 1.61 (m, 1H), 1.60 – 1.52 (m, 1H), 1.50 – 1.40 (m, 2H), 1.39 – 1.29 (m, 2H), 1.22 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 182.18, 68.07, 47.72, 45.09, 35.61, 32.47, 27.46, 23.63, 19.56.



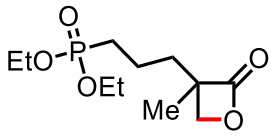
3-Methyl-3-(5,5,5-trifluoropentyl)oxetan-2-one (2i)

Following **General Procedure A** on 0.1 mmol scale. Purification by diluting with EA and washing with saturated $NaHCO_3$ solution afforded the title compound (colorless oil, 14.0 mg, 67% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.15 (d, *J* = 5.1 Hz, 1H), 4.05 (d, *J* = 5.1 Hz, 1H), 2.18 – 2.00 (m, 2H), 1.77 – 1.68 (m, 2H), 1.67 – 1.50 (m, 4H), 1.43 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.70, 127.10 (q, *J* = 276.4 Hz), 71.45, 57.20, 34.14, 33.60 (q, *J* = 28.6 Hz), 23.84, 22.18 (q, *J* = 2.9 Hz), 19.31; HRMS (ESI-TOF) Calcd for $C_9H_{14}F_3O_2$ $[M+H]^+$: 211.0946; found: 211.0949.



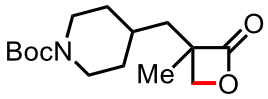
3-Methyl-3-(3-oxobutyl)oxetan-2-one (2j)

Following **General Procedure A** on 0.1 mmol scale. Purification by diluting with EA and washing with saturated $NaHCO_3$ solution afforded the title compound (colorless oil, 11.6 mg, 74% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.84 (d, *J* = 8.7 Hz, 1H), 3.80 (dd, *J* = 8.7, 2.9 Hz, 1H), 2.19 – 2.08 (m, 1H), 2.08 – 1.99 (m, 1H), 1.88 – 1.79 (m, 2H), 1.56 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.49, 175.48, 72.09, 38.26, 31.38, 28.95, 24.30, 16.40; HRMS (ESI-TOF) Calcd for $C_8H_{13}O_3$ $[M+H]^+$: 157.0865; found: 157.0863.



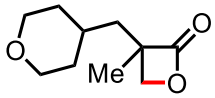
Diethyl (3-(3-methyl-2-oxooxetan-3-yl)propyl)phosphonate (2k)

Following **General Procedure A** on 0.1 mmol scale. Purification by diluting with EA and washing with saturated $NaHCO_3$ solution afforded the title compound (colorless oil, 10.0 mg, 38% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.17 (d, *J* = 5.2 Hz, 1H), 4.15 – 4.05 (m, 4H), 4.04 (d, *J* = 5.2 Hz, 1H), 1.87 – 1.68 (m, 6H), 1.44 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.53, 71.37, 61.94 (d, *J* = 6.7 Hz), 61.93 (d, *J* = 6.8 Hz), 57.17 (d, *J* = 1.7 Hz), 35.09 (d, *J* = 16.0 Hz), 25.70 (d, *J* = 142.3 Hz), 19.16, 18.03 (d, *J* = 4.9 Hz), 16.57 (d, *J* = 5.9 Hz); HRMS (ESI-TOF) Calcd for $C_{11}H_{22}O_5P$ $[M+H]^+$: 265.1205; found: 265.1208.



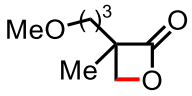
***tert*-Butyl 4-((3-methyl-2-oxooxetan-3-yl)methyl)piperidine-1-carboxylate (2l)**

Following **General Procedure A** on 0.1 mmol scale. Purification by diluting with EA and washing with saturated $NaHCO_3$ solution afforded the title compound (colorless oil, 14.5 mg, 51% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.16 (d, *J* = 5.1 Hz, 1H), 4.11 (br s, 2H), 4.06 (d, *J* = 5.0 Hz, 1H), 2.68 (br s, 2H), 1.79 – 1.57 (m, 7H), 1.45 (s, 9H), 1.21 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.00, 154.90, 79.69, 56.31, 40.73, 33.24, 33.06, 32.66, 28.59, 28.57; HRMS (ESI-TOF) Calcd for $C_{15}H_{25}NNaO_4$ $[M+Na]^+$: 306.1676; found: 306.1677.



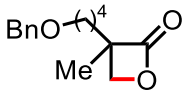
3-Methyl-3-((tetrahydro-2*H*-pyran-4-yl)methyl)oxetan-2-one (2m)

Following **General Procedure A** on 0.1 mmol scale. Purification by diluting with EA and washing with saturated $NaHCO_3$ solution afforded the title compound (colorless oil, 13.0 mg, 71% yield). Further purification by filtering through silica gel plug afforded the title compound. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.18 (d, *J* = 5.1 Hz, 1H), 4.06 (d, *J* = 5.1 Hz, 1H), 4.00 – 3.91 (m, 2H), 3.45 – 3.33 (m, 2H), 1.79 – 1.70 (m, 2H), 1.70 – 1.62 (m, 2H), 1.54 – 1.47 (m, 1H), 1.44 (s, 3H), 1.42 – 1.34 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.03, 72.48, 67.96, 67.72, 56.28, 41.11, 33.86, 33.21, 31.68, 19.32; HRMS (ESI-TOF) Calcd for $C_{10}H_{17}O_3$ $[M+H]^+$: 185.1178; found: 185.1172.



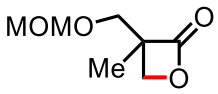
3-(3-Methoxypropyl)-3-methyloxetan-2-one (2n)

Following **General Procedure A** on 0.1 mmol scale. Purification by diluting with EA and washing with saturated $NaHCO_3$ solution afforded the title compound (colorless oil, 12.8 mg, 81% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.17 (d, *J* = 5.0 Hz, 1H), 4.04 (d, *J* = 5.0 Hz, 1H), 3.41 (t, *J* = 5.8 Hz, 2H), 3.33 (s, 3H), 1.83 – 1.70 (m, 3H), 1.67 – 1.57 (m, 1H), 1.43 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.08, 72.21, 71.62, 58.70, 57.08, 31.16, 24.82, 19.20; HRMS (ESI-TOF) Calcd for $C_8H_{15}O_3$ $[M+H]^+$: 159.1021; found: 159.1022.



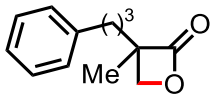
3-(4-(Benzyloxy)butyl)-3-methyloxetan-2-one (2o)

Following **General Procedure A** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 11.5 mg, 46% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 – 7.31 (m, 3H), 7.31 – 7.26 (m, 2H), 4.50 (s, 2H), 4.15 (d, *J* = 5.0 Hz, 1H), 4.01 (d, *J* = 5.0 Hz, 1H), 3.48 (t, *J* = 6.2 Hz, 2H), 1.78 – 1.56 (m, 6H), 1.41 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.02, 138.56, 128.55, 127.84, 127.76, 73.17, 71.49, 69.87, 57.42, 34.23, 29.92, 21.52, 19.30; HRMS (ESI-TOF) Calcd for $C_{15}H_{21}O_3$ $[M+H]^+$: 249.1491; found: 249.1494.



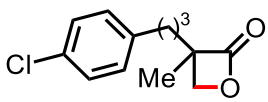
3-((Methoxymethoxy)methyl)-3-methyloxetan-2-one (2p)

Following **General Procedure A** on 0.1 mmol scale. Purification by diluting with EA and washing with saturated $NaHCO_3$ solution afforded the title compound (colorless oil, 9.0 mg, 56% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.42 – 5.33 (m, 2H), 4.16 (d, *J* = 11.3 Hz, 1H), 3.77 – 3.72 (m, 2H), 3.35 (s, 3H), 3.23 (d, *J* = 9.2 Hz, 1H), 1.31 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.68, 95.10, 75.53, 72.35, 59.53, 45.96, 20.89; HRMS (ESI-TOF) Calcd for $C_7H_{13}O_4$ $[M+H]^+$: 161.0814; found: 161.0821.



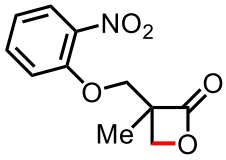
3-Methyl-3-(3-phenylpropyl)oxetan-2-one (2q)

Following **General Procedure A** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 12.3 mg, 60% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.23 (m, 2H), 7.23 – 7.14 (m, 3H), 4.12 (d, *J* = 5.0 Hz, 1H), 4.01 (d, *J* = 5.0 Hz, 1H), 2.66 (t, *J* = 7.2 Hz, 2H), 1.88 – 1.77 (m, 1H), 1.77 – 1.61 (m, 3H), 1.41 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.92, 141.46, 128.60, 128.50, 126.21, 71.45, 57.33, 35.89, 33.93, 26.41, 19.36; HRMS (ESI-TOF) Calcd for $C_{13}H_{17}O_2$ $[M+H]^+$: 205.1229; found: 205.1232.



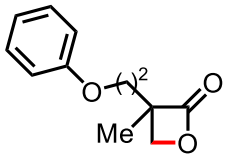
3-(3-(4-Chlorophenyl)propyl)-3-methyloxetan-2-one (2r)

Following **General Procedure A** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 11.0 mg, 46% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 4.11 (d, *J* = 5.0 Hz, 1H), 4.01 (d, *J* = 5.0 Hz, 1H), 2.67 – 2.58 (m, 2H), 1.84 – 1.75 (m, 1H), 1.75 – 1.66 (m, 2H), 1.68 – 1.59 (m, 1H), 1.41 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.77, 139.86, 131.97, 129.84, 128.71, 71.42, 57.27, 35.21, 33.85, 26.30, 19.38; HRMS (ESI-TOF) Calcd for $C_{13}H_{16}ClO_2$ $[M+H]^+$: 239.0839; found: 239.0843.



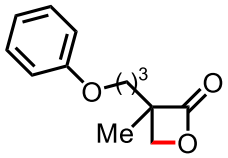
3-Methyl-3-((2-nitrophenoxy)methyl)oxetan-2-one (2s)

Following **General Procedure A** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 9.7 mg, 41% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.56 (ddd, *J* = 8.6, 7.5, 1.7 Hz, 1H), 7.17 – 7.07 (m, 2H), 4.69 (d, *J* = 5.1 Hz, 1H), 4.36 (d, *J* = 9.5 Hz, 1H), 4.19 (d, *J* = 5.1 Hz, 1H), 4.11 (d, *J* = 9.5 Hz, 1H), 1.58 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 185.74, 172.18, 151.43, 134.50, 126.11, 122.01, 115.63, 69.93, 69.49, 57.76, 16.45; HRMS (ESI-TOF) Calcd for $C_{11}H_{12}NO_5$ $[M+H]^+$: 238.0715; found: 238.0716.



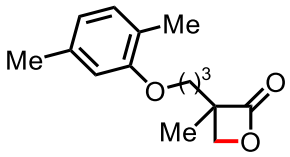
3-Methyl-3-(2-phenoxyethyl)oxetan-2-one (2t)

Following **General Procedure B** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 17.8 mg, 86% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 2H), 7.01 – 6.94 (m, 1H), 6.90 – 6.85 (m, 2H), 4.47 (d, *J* = 5.1 Hz, 1H), 4.20 – 4.13 (m, 1H), 4.14 – 4.08 (m, 2H), 2.39 – 2.30 (m, 1H), 2.16 – 2.08 (m, 1H), 1.50 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.77, 158.38, 129.73, 121.40, 114.49, 72.45, 63.66, 55.63, 33.25, 19.03; HRMS (ESI-TOF) Calcd for $C_{12}H_{15}O_3$ $[M+H]^+$: 207.1021; found: 207.1029.



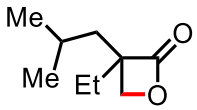
3-Methyl-3-(3-phenoxypropyl)oxetan-2-one (2u)

Following **General Procedure B** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 20.7 mg, 94% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 2H), 6.98 – 6.92 (m, 1H), 6.90 – 6.86 (m, 2H), 4.18 (d, *J* = 5.1 Hz, 1H), 4.06 (d, *J* = 5.1 Hz, 1H), 3.99 (t, *J* = 5.8 Hz, 2H), 2.04 – 1.94 (m, 1H), 1.94 – 1.89 (m, 2H), 1.88 – 1.77 (m, 1H), 1.47 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.81, 158.80, 129.63, 120.99, 114.52, 71.65, 67.24, 57.08, 31.23, 24.65, 19.23; HRMS (ESI-TOF) Calcd for $C_{13}H_{17}O_3$ $[M+H]^+$: 221.1178; found: 221.1181.



3-(3-(2,5-Dimethylphenoxy)propyl)-3-methyloxetan-2-one (2v)

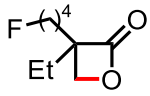
Following **General Procedure B** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 23.0 mg, 93% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.01 (d, *J* = 7.5 Hz, 1H), 6.68 (d, *J* = 7.5 Hz, 1H), 6.61 (s, 1H), 4.19 (d, *J* = 5.1 Hz, 1H), 4.07 (d, *J* = 5.1 Hz, 1H), 4.03 – 3.92 (m, 2H), 2.31 (s, 3H), 2.17 (s, 3H), 2.04 – 1.98 (m, 1H), 1.98 – 1.90 (m, 2H), 1.90 – 1.78 (m, 1H), 1.48 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.82, 156.78, 136.72, 130.55, 123.62, 121.13, 112.03, 71.66, 67.24, 57.14, 31.33, 24.86, 21.54, 19.26, 15.94; HRMS (ESI-TOF) Calcd for $C_{15}H_{21}O_3$ $[M+H]^+$: 249.1491; found: 249.1492.



3-Ethyl-3-isobutyloxetan-2-one (2w)

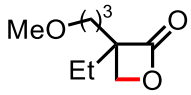
Following **General Procedure A** on 0.1 mmol scale. Purification by diluting with EA and washing with saturated $NaHCO_3$ solution afforded the title compound (colorless oil, 9.7 mg, 62% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.16 (d, *J* = 5.2 Hz, 1H), 4.11 (d, *J* = 5.2 Hz, 1H), 1.84 – 1.74 (m, 4H), 1.62 – 1.55 (m, 1H), 1.04 (t, *J* = 7.5 Hz, 3H), 0.99 (d, *J* = 6.4 Hz, 3H),

0.88 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.86, 70.11, 61.45, 40.97, 25.20, 24.68, 24.13, 22.54, 8.88; HRMS (ESI-TOF) Calcd for $C_9H_{17}O_2$ $[M+H]^+$: 157.1229; found: 157.1226.



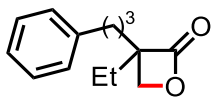
3-Ethyl-3-(4-fluorobutyl)oxetan-2-one (2x)

Following **General Procedure A** on 0.1 mmol scale. Purification by diluting with EA and washing with saturated $NaHCO_3$ solution afforded the title compound (colorless oil, 9.0 mg, 52% yield). Further purification by filtering through silica gel plug afforded the title compound. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.47 (dt, *J* = 46.9, 5.6 Hz, 2H), 4.12 (d, *J* = 5.7 Hz, 1H), 4.11 (d, *J* = 5.7 Hz, 1H), 1.85 – 1.67 (m, 5H), 1.67 – 1.59 (m, 1H), 1.53 – 1.39 (m, 2H), 1.03 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.28, 83.69 (d, *J* = 165.1 Hz), 68.72, 62.13, 31.93, 30.61 (d, *J* = 19.9 Hz), 25.43, 20.55 (d, *J* = 4.8 Hz), 8.85; HRMS (ESI-TOF) Calcd for $C_9H_{16}FO_2$ $[M+H]^+$: 175.1134; found: 175.1135.



3-Ethyl-3-(3-methoxypropyl)oxetan-2-one (2y)

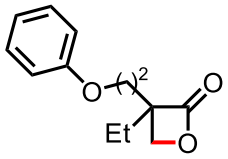
Following **General Procedure A** on 0.1 mmol scale. Purification by diluting with EA and washing with saturated $NaHCO_3$ solution afforded the title compound (colorless oil, 10.7 mg, 62% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.11 (s, 2H), 3.44 – 3.39 (m, 2H), 3.33 (s, 3H), 1.86 – 1.71 (m, 5H), 1.66 – 1.54 (m, 1H), 1.03 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.85, 71.68, 68.28, 61.29, 58.13, 28.44, 24.81, 24.09, 8.23; HRMS (ESI-TOF) Calcd for $C_9H_{17}O_3$ $[M+H]^+$: 173.1178; found: 173.1189.



3-Ethyl-3-(3-phenylpropyl)oxetan-2-one (2z)

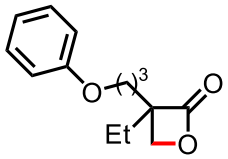
Following **General Procedure A** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 12.8 mg, 59% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 2H), 7.23 – 7.18 (m, 1H), 7.18 – 7.13 (m, 2H), 4.08 (d, *J* = 5.2 Hz, 1H), 4.06 (d, *J* = 5.2 Hz,

1H), 2.72 – 2.62 (m, 2H), 1.86 – 1.69 (m, 5H), 1.69 – 1.61 (m, 1H), 0.99 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.37, 141.49, 128.59, 128.49, 126.20, 68.76, 62.11, 35.97, 31.80, 26.24, 25.47, 8.84; HRMS (ESI-TOF) Calcd for $C_{14}H_{19}O_2$ $[M+H]^+$: 219.1385; found: 219.1387.



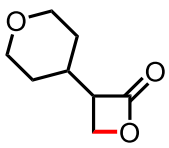
3-Ethyl-3-(2-phenoxyethyl)oxetan-2-one (2aa)

Following **General Procedure B** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 15.0 mg, 68% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 2H), 7.03 – 6.96 (m, 1H), 6.93 – 6.85 (m, 2H), 4.45 (d, *J* = 5.3 Hz, 1H), 4.20 (d, *J* = 5.3 Hz, 1H), 4.19 – 4.16 (m, 1H), 4.16 – 4.08 (m, 1H), 2.42 – 2.32 (m, 1H), 2.26 – 2.16 (m, 1H), 1.91 – 1.82 (m, 2H), 1.11 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.10, 158.39, 129.71, 121.36, 114.49, 69.72, 63.74, 60.35, 31.49, 25.37, 8.87; HRMS (ESI-TOF) Calcd for $C_{13}H_{17}O_3$ $[M+H]^+$: 221.1172; found: 221.1176.



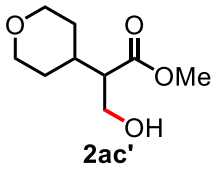
3-Ethyl-3-(4-phenoxybutyl)oxetan-2-one (2ab)

Following **General Procedure B** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 21.0 mg, 90% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.24 (m, 2H), 6.98 – 6.91 (m, 1H), 6.91 – 6.84 (m, 2H), 4.13 (s, 2H), 4.02 – 3.96 (m, 2H), 2.05 – 1.89 (m, 3H), 1.89 – 1.75 (m, 3H), 1.05 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.25, 158.82, 129.63, 120.98, 114.54, 68.92, 67.31, 61.86, 29.08, 25.38, 24.50, 8.83; HRMS (ESI-TOF) Calcd for $C_{14}H_{19}O_3$ $[M+H]^+$: 235.1334; found: 235.1336.



3-(Tetrahydro-2*H*-pyran-4-yl)oxetan-2-one (2ac)

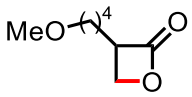
Following **General Procedure B** on 0.1 mmol scale. Purification by diluting with EA and washing with saturated $NaHCO_3$ solution afforded the title compound (colorless oil, 8.0 mg, 51%). Further purification by filtering through silica gel plug afforded the title compound. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.33 (dd, *J* = 6.4, 5.4 Hz, 1H), 4.11 (dd, *J* = 5.4, 4.6 Hz, 1H), 4.04 – 3.98 (m, 2H), 3.62 (ddd, *J* = 8.5, 6.4, 4.6 Hz, 1H), 3.46 – 3.38 (m, 2H), 2.12 – 2.00 (m, 1H), 1.93 – 1.85 (m, 1H), 1.55 – 1.46 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.40, 67.47, 67.42, 62.77, 57.36, 34.55, 30.29, 30.22; HRMS (ESI-TOF) Calcd for $C_8H_{13}O_3$ $[M+H]^+$: 157.0865; found: 157.0852.



2ac'

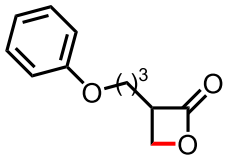
Methyl 3-hydroxy-2-(tetrahydro-*2H*-pyran-4-yl)propanoate (2ac')

Following **General Procedure C** on 0.1 mmol scale. The crude acid was methyl esterification by $TMSCHN_2$ for isolation purpose. Purification by column chromatography afforded the title compound (colorless oil, 10.3 mg, 55% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.04 – 3.92 (m, 2H), 3.91 – 3.78 (m, 2H), 3.74 (s, 3H), 3.44 – 3.32 (m, 2H), 2.44 (td, *J* = 7.6, 3.7 Hz, 1H), 2.14 – 2.06 (m, 1H), 2.04 – 1.94 (m, 1H), 1.70 – 1.62 (m, 1H), 1.51 – 1.38 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.24, 67.99, 67.97, 61.04, 52.99, 51.88, 34.56, 31.13, 30.67.



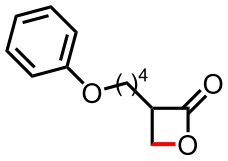
3-(4-Methoxybutyl)oxetan-2-one (2ad)

Following **General Procedure B** on 0.1 mmol scale. Purification by diluting with EA and washing with saturated $NaHCO_3$ solution afforded the title compound (colorless oil, 13.0 mg, 82%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.37 (dd, *J* = 6.3, 5.2 Hz, 1H), 4.05 – 4.00 (m, 1H), 3.75 – 3.68 (m, 1H), 3.39 (t, *J* = 6.1 Hz, 2H), 3.33 (s, 3H), 1.95 – 1.85 (m, 1H), 1.83 – 1.76 (m, 1H), 1.65 – 1.52 (m, 3H), 1.51 – 1.43 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.85, 72.36, 65.11, 58.75, 52.17, 29.36, 28.09, 23.76; HRMS (ESI-TOF) Calcd for $C_8H_{14}NaO_3$ $[M+Na]^+$: 181.0835; found: 181.0835.



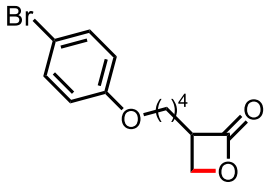
3-(3-Phenoxypropyl)oxetan-2-one (2ae)

Following **General Procedure B** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 14.5 mg, 69%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 – 7.26 (m, 2H), 6.99 – 6.92 (m, 1H), 6.92 – 6.85 (m, 2H), 4.40 (dd, *J* = 6.3, 5.3 Hz, 1H), 4.05 (dd, *J* = 5.3, 4.5 Hz, 1H), 4.03 – 3.97 (m, 2H), 3.85 – 3.77 (m, 1H), 2.40 – 2.30 (m, 1H), 2.13 – 2.04 (m, 1H), 2.04 – 1.97 (m, 1H), 1.94 – 1.85 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.64, 158.78, 129.68, 121.06, 114.52, 66.92, 65.28, 51.96, 26.77, 25.38; HRMS (ESI-TOF) Calcd for $C_{12}H_{15}O_3$ $[M+H]^+$: 207.1021; found: 207.1023.



3-(4-Phenoxybutyl)oxetan-2-one (2af)

Following **General Procedure B** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 7.0 mg, 32%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30 – 7.26 (m, 2H), 6.97 – 6.91 (m, 1H), 6.91 – 6.86 (m, 2H), 4.38 (dd, *J* = 6.3, 5.2 Hz, 1H), 4.06 – 4.01 (m, 1H), 3.98 (t, *J* = 6.2 Hz, 2H), 3.78 – 3.70 (m, 1H), 1.99 – 1.89 (m, 1H), 1.89 – 1.80 (m, 2H), 1.74 – 1.65 (m, 1H), 1.65 – 1.55 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.69, 158.99, 129.62, 120.87, 114.58, 67.32, 65.07, 52.18, 29.06, 28.06, 23.76; HRMS (ESI-TOF) Calcd for $C_{13}H_{17}O_3$ $[M+H]^+$: 221.1178; found: 221.1183.

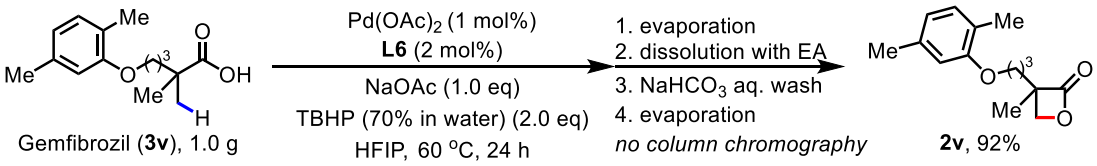


3-(4-(4-Bromophenoxy)butyl)oxetan-2-one (2ag)

Following **General Procedure B** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 12.0 mg, 40%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 – 7.34 (m, 2H),

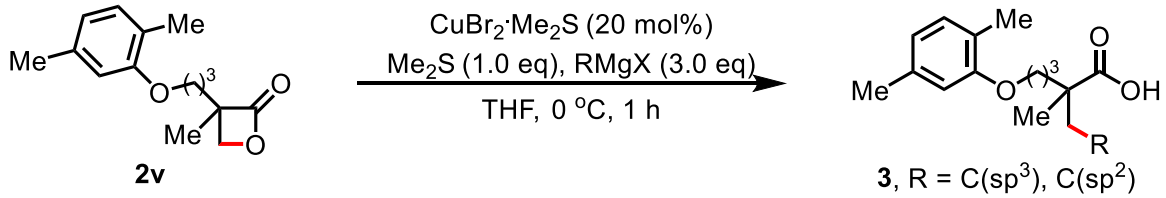
6.80 – 6.73 (m, 2H), 4.38 (dd, *J* = 6.3, 5.2 Hz, 1H), 4.03 (dd, *J* = 5.2, 4.5 Hz, 1H), 3.94 (t, *J* = 6.2 Hz, 2H), 3.78 – 3.70 (m, 1H), 2.00 – 1.90 (m, 1H), 1.90 – 1.76 (m, 3H), 1.73 – 1.63 (m, 1H), 1.63 – 1.57 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.63, 158.12, 132.42, 116.38, 113.01, 67.71, 65.02, 52.14, 28.96, 28.04, 23.67; HRMS (ESI-TOF) Calcd for $C_{13}H_{16}BrO_3$ $[M+H]^+$: 299.0283; found: 299.0284.

General Procedure for Gram-Scale β-C(sp^3)–H Lactonization with 1 mol% Pd

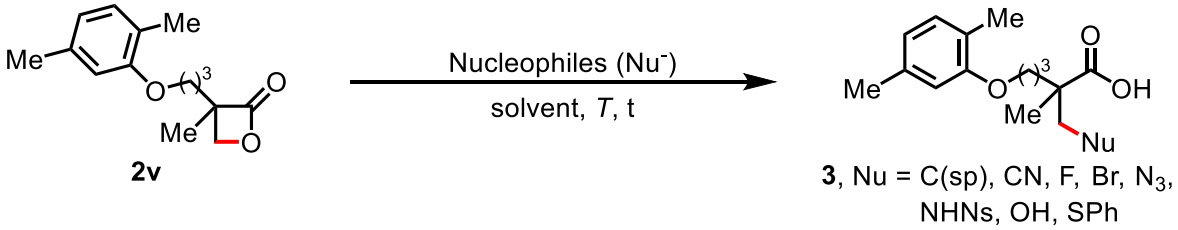


In the sealed tube, $Pd(OAc)_2$ (1.0 mol%, 9.0 mg), ligand **L6** (2.0 mol%, 10.5 mg), NaOAc (1.0 eq, 328 mg), and Gemfibrozil **3v** (4.0 mmol, 1.0 g) in order were weighed in air and placed with a magnetic stir bar. Then HFIP (40.0 mL) and TBHP (70% in water) (2.0 eq, 1.44 mL) were added. The reaction mixture was stirred at rt for 3 min, and then heated to 60 ^oC for 24 h (600 rpm). After being allowed to cool to room temperature, the mixture was concentrated *in vacuo*, and the resulting mixture was diluted with EA and washed with saturated $NaHCO_3$ solution. The resulting solution was dried with $MgSO_4$ and concentrated *in vacuo* to afford the title product **2v** (915 mg, 92% yield).

General Procedure for Formal β-C(sp^3)–H Functionalizations

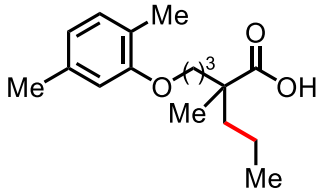


General Procedure A: In the culture tube, $CuBr_2 \cdot Me_2S$ (20 mol%, 4.1 mg), β-lactone **2v** (0.1 mmol, 24.8 mg), and Me_2S (1.0 eq, 7 μL) in order were added and placed with a magnetic stir bar. Then THF (1.0 mL) was added. The reaction mixture was stirred at rt for 3 min, and then Grignard reagent (3.0 eq) was added dropwise at 0 °C. After being allowed to stir at 0 °C in 1 h, the mixture was quenched with saturated NH_4Cl solution. The resulting mixture was diluted with EA, washed with saturated NH_4Cl solution, and dried with $MgSO_4$. After being concentrated *in vacuo*, the resulting mixture was purified by pTLC using hexane/EA with AcOH (1% v/v) if necessary as eluent. (*7-9*)



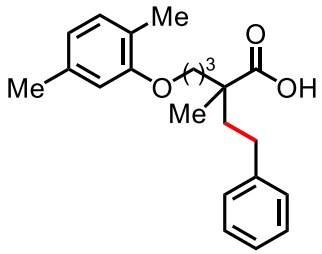
General Procedure B: In the culture tube, Nu^- was added and placed with a magnetic stir bar. Then **2v** in the corresponding solvent (1.0 mL) was added. The reaction mixture was stirred at indicated temperature, and then quenched with saturated NH_4Cl solution. The resulting mixture was diluted with EA, washed with saturated NH_4Cl solution, and dried with $MgSO_4$. After being concentrated *in vacuo*, the resulting mixture was purified by pTLC using hexane/EA with AcOH (1% v/v) if necessary as eluent. (*10-12*)

Diversification of Gemfibrozil 1v



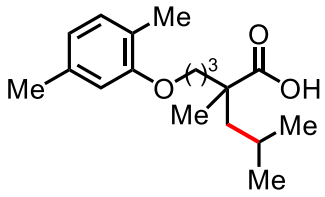
5-(2,5-Dimethylphenoxy)-2-methyl-2-propylpentanoic acid (3a)

Following **General Procedure A** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 26.0 mg, 93%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.99 (d, *J* = 7.5 Hz, 1H), 6.65 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.60 (d, *J* = 1.5 Hz, 1H), 3.97 – 3.86 (m, 2H), 2.30 (s, 3H), 2.17 (s, 3H), 1.87 – 1.78 (m, 2H), 1.78 – 1.69 (m, 1H), 1.69 – 1.61 (m, 2H), 1.49 (ddd, *J* = 13.4, 12.3, 4.6 Hz, 1H), 1.40 – 1.26 (m, 2H), 1.20 (s, 3H), 0.92 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 184.00, 157.07, 136.59, 130.43, 123.72, 120.82, 112.06, 68.06, 45.72, 41.45, 35.39, 24.88, 21.55, 21.38, 17.88, 15.90, 14.71; HRMS (ESI-TOF) Calcd for $C_{17}H_{26}NaO_3$ $[M+Na]^+$: 301.1780; found: 301.1771.



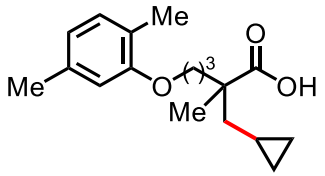
5-(2,5-Dimethylphenoxy)-2-methyl-2-phenethylpentanoic acid (3b)

Following **General Procedure A** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 28.0 mg, 82%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 – 7.21 (m, 2H), 7.21 – 7.13 (m, 3H), 6.99 (d, *J* = 7.5 Hz, 1H), 6.65 (d, *J* = 7.5 Hz, 1H), 6.61 (s, 1H), 4.02 – 3.87 (m, 2H), 2.71 – 2.53 (m, 2H), 2.30 (s, 3H), 2.17 (s, 3H), 2.10 – 1.95 (m, 1H), 1.95 – 1.71 (m, 5H), 1.31 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 183.85, 157.02, 142.15, 136.59, 130.46, 128.54, 128.49, 126.04, 123.71, 120.87, 112.04, 67.92, 45.74, 40.99, 35.42, 31.19, 24.85, 21.55, 15.94 (1 carbon signal was not assigned due to overlaps); HRMS (ESI-TOF) Calcd for $C_{22}H_{27}O_3$ $[M-H]^-$: 339.1960; found: 339.1967.



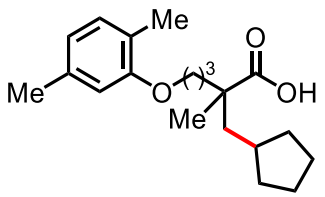
5-(2,5-Dimethylphenoxy)-2-isobutyl-2-methylpentanoic acid (3c)

Following **General Procedure A** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 23.0 mg, 79%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.99 (d, *J* = 7.5 Hz, 1H), 6.65 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.60 (d, *J* = 1.5 Hz, 1H), 4.00 – 3.85 (m, 2H), 2.30 (s, 3H), 2.17 (s, 3H), 1.90 – 1.79 (m, 2H), 1.79 – 1.58 (m, 4H), 1.46 (dd, *J* = 13.9, 5.4 Hz, 1H), 1.20 (s, 3H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 184.66, 157.08, 136.58, 130.43, 123.73, 120.82, 112.05, 68.04, 48.29, 45.25, 36.65, 24.98, 24.72, 24.55, 23.34, 21.54, 21.15, 15.90; HRMS (ESI-TOF) Calcd for $C_{18}H_{29}O_3$ $[M+H]^+$: 293.2117; found: 293.2115.



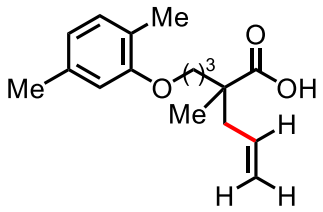
2-(Cyclopropylmethyl)-5-(2,5-dimethylphenoxy)-2-methylpentanoic acid (3d)

Following **General Procedure A** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 22.0 mg, 76%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.99 (d, *J* = 7.5 Hz, 1H), 6.70 – 6.64 (m, 1H), 6.61 (d, *J* = 1.5 Hz, 1H), 4.00 – 3.87 (m, 2H), 2.30 (s, 3H), 2.17 (s, 3H), 1.96 – 1.87 (m, 1H), 1.88 – 1.79 (m, 1H), 1.79 – 1.70 (m, 1H), 1.72 – 1.64 (m, 1H), 1.62 (dd, *J* = 14.0, 6.9 Hz, 1H), 1.53 – 1.45 (m, 1H), 1.28 (s, 3H), 0.75 – 0.67 (m, 1H), 0.53 – 0.39 (m, 2H), 0.14 – 0.04 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 184.13, 157.08, 136.58, 130.42, 123.73, 120.82, 112.08, 68.09, 46.52, 44.22, 35.51, 24.97, 21.55, 21.42, 15.90, 6.77, 4.78, 4.36; HRMS (ESI-TOF) Calcd for $C_{18}H_{27}O_3$ $[M+H]^+$: 291.1960; found: 291.1953.



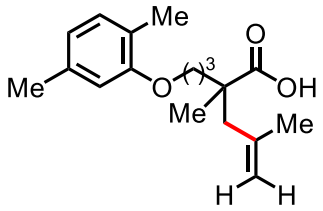
2-(Cyclopentylmethyl)-5-(2,5-dimethylphenoxy)-2-methylpentanoic acid (3e)

Following **General Procedure A** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 21.0 mg, 66%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.99 (d, *J* = 7.5 Hz, 1H), 6.65 (d, *J* = 7.5 Hz, 1H), 6.60 (s, 1H), 3.99 – 3.86 (m, 2H), 2.30 (s, 3H), 2.17 (s, 3H), 1.91 – 1.68 (m, 7H), 1.68 – 1.53 (m, 4H), 1.52 – 1.40 (m, 2H), 1.22 (s, 3H), 1.14 – 1.02 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 184.53, 157.08, 136.58, 130.42, 123.72, 120.81, 112.05, 68.07, 45.86, 45.76, 36.99, 36.23, 34.37, 33.65, 25.19, 24.98, 24.87, 21.55, 21.47, 15.91; HRMS (ESI-TOF) Calcd for $C_{20}H_{29}O_3$ [M-H]$^-$: 317.2117; found: 317.2121.



2-(3-(2,5-Dimethylphenoxy)propyl)-2-methylpent-4-enoic acid (3f)

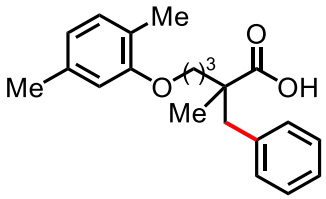
Following **General Procedure A** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 25.0 mg, 91%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.00 (d, *J* = 7.4 Hz, 1H), 6.65 (d, *J* = 7.4 Hz, 1H), 6.60 (s, 1H), 5.83 – 5.72 (m, 1H), 5.15 – 5.10 (m, 1H), 5.09 (s, 1H), 3.96 – 3.88 (m, 2H), 2.44 (dd, *J* = 13.8, 7.1 Hz, 1H), 2.34 – 2.25 (m, 4H), 2.17 (s, 3H), 1.88 – 1.71 (m, 3H), 1.71 – 1.63 (m, 1H), 1.21 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 183.29, 157.05, 136.59, 133.65, 130.44, 123.73, 120.85, 118.59, 112.04, 67.94, 43.03, 35.05, 24.88, 21.55, 21.49, 15.91 (1 carbon signal was not assigned due to overlaps); HRMS (ESI-TOF) Calcd for $C_{17}H_{24}NaO_3$ [M+Na]$^+$: 299.1623; found: 299.1613.



2-(3-(2,5-Dimethylphenoxy)propyl)-2,4-dimethylpent-4-enoic acid (3g)

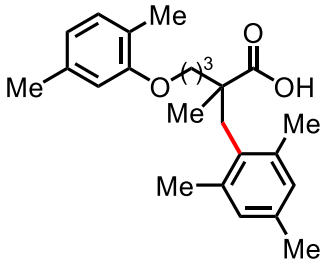
Following **General Procedure A** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 23.5 mg, 81%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.00 (d, *J* = 7.4 Hz, 1H), 6.65 (d, *J* = 7.4 Hz, 1H), 6.60 (s, 1H), 4.85 (s, 1H), 4.72 (s, 1H), 3.98 – 3.87 (m, 2H),

2.54 (d, *J* = 13.7 Hz, 1H), 2.30 (s, 3H), 2.23 (d, *J* = 13.7 Hz, 1H), 2.17 (s, 3H), 1.96 – 1.81 (m, 2H), 1.77 – 1.74 (m, 1H), 1.72 (s, 3H), 1.67 – 1.58 (m, 1H), 1.20 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 183.81, 157.05, 141.99, 136.59, 130.44, 123.73, 120.85, 114.97, 112.05, 67.96, 47.58, 45.58, 36.40, 24.90, 23.83, 21.55, 21.01, 15.91; HRMS (ESI-TOF) Calcd for $C_{18}H_{27}O_3$ $[M+H]^+$: 291.1960; found: 291.1961.



2-Benzyl-5-(2,5-dimethylphenoxy)-2-methylpentanoic acid (3h)

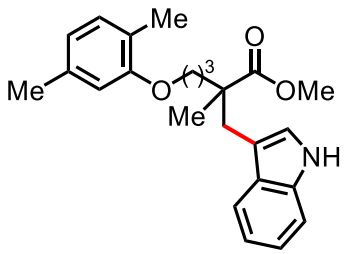
Following **General Procedure A** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 20.0 mg, 61%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 2H), 7.26 – 7.20 (m, 1H), 7.19 – 7.14 (m, 2H), 7.00 (d, *J* = 7.5 Hz, 1H), 6.66 (d, *J* = 7.5 Hz, 1H), 6.61 (s, 1H), 4.03 – 3.83 (m, 2H), 3.06 (d, *J* = 13.4 Hz, 1H), 2.82 (d, *J* = 13.4 Hz, 1H), 2.31 (s, 3H), 2.17 (s, 3H), 1.99 – 1.76 (m, 3H), 1.65 (td, *J* = 12.3, 4.1 Hz, 1H), 1.17 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 182.32, 157.04, 137.31, 136.62, 130.46, 130.40, 128.25, 126.78, 123.75, 120.88, 112.06, 67.94, 45.18, 35.49, 25.13, 21.56, 21.01, 15.94 (1 carbon signal was not assigned due to overlaps); HRMS (ESI-TOF) Calcd for $C_{21}H_{25}O_3$ $[M-H]^-$: 325.1804; found: 325.1812.



5-(2,5-Dimethylphenoxy)-2-methyl-2-(2,4,6-trimethylbenzyl)pentanoic acid (3i)

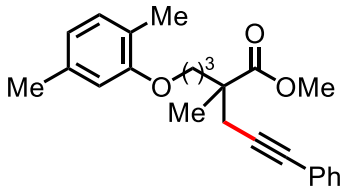
Following **General Procedure A** on 0.1 mmol scale. Purification by pTLC afforded the title compound (colorless oil, 25.0 mg, 68%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.00 (d, *J* = 7.5 Hz, 1H), 6.82 (s, 2H), 6.66 (d, *J* = 7.5 Hz, 1H), 6.61 (s, 1H), 4.02 – 3.85 (m, 2H), 3.20 (d, *J* = 14.8 Hz, 1H), 2.99 (d, *J* = 14.8 Hz, 1H), 2.30 (s, 3H), 2.28 (s, 6H), 2.23 (s, 3H), 2.17 (s, 3H),

2.15 – 2.06 (m, 1H), 1.91 – 1.81 (m, 1H), 1.78 – 1.61 (m, 2H), 1.11 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 183.67, 157.07, 137.86, 136.62, 135.75, 131.87, 130.46, 129.37, 123.75, 120.87, 112.10, 68.02, 47.32, 38.50, 37.07, 25.49, 21.55, 21.38, 20.90, 20.26, 15.91; HRMS (ESI-TOF) Calcd for $C_{24}H_{32}NaO_3$ $[M+Na]^+$: 391.2249; found: 391.2247.



Methyl 2-((1*H*-indol-3-yl)methyl)-5-(2,5-dimethylphenoxy)-2-methylpentanoate (3j)

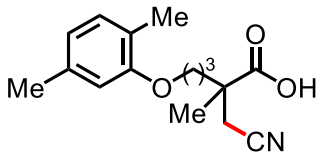
Following **General Procedure A** on 0.1 mmol scale with Grignard reagent (6.0 eq); the crude acid was methyl esterification by $TMSCHN_2$ for isolation purpose. Purification by pTLC afforded the title compound (colorless oil, 12.0 mg, 32%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.02 (br s, 1H), 7.58 (d, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.19 – 7.14 (m, 1H), 7.14 – 7.07 (m, 1H), 7.00 (d, *J* = 7.5 Hz, 1H), 6.96 (d, *J* = 2.3 Hz, 1H), 6.66 (d, *J* = 7.5 Hz, 1H), 6.61 (s, 1H), 3.99 – 3.87 (m, 2H), 3.62 (s, 3H), 3.18 (d, *J* = 14.4 Hz, 1H), 2.94 (d, *J* = 14.4 Hz, 1H), 2.30 (s, 3H), 2.17 (s, 3H), 2.07 – 1.97 (m, 1H), 1.89 – 1.81 (m, 1H), 1.78 – 1.65 (m, 2H), 1.22 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 177.74, 157.07, 136.61, 135.95, 130.44, 128.64, 123.75, 123.20, 121.94, 120.83, 119.52, 119.34, 112.13, 111.11, 68.07, 51.78, 47.83, 35.95, 34.89, 25.33, 21.58, 21.57, 15.95 (1 carbon signal was not assigned due to overlaps); HRMS (ESI-TOF) Calcd for $C_{24}H_{30}NO_3$ $[M+H]^+$: 380.2226; found: 380.2224.



Methyl 2-(3-(2,5-dimethylphenoxy)propyl)-2-methyl-5-phenylpent-4-ynoate (3k)

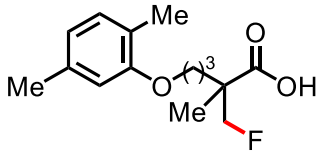
Following **General Procedure B** on 0.1 mmol scale with alkynylaluminum reagent (3.0 eq) in toluene at 0 °C for 1 h; the crude acid was methyl esterification by $TMSCHN_2$ for isolation purpose. (*11*) Purification by pTLC afforded the title compound (colorless oil, 25.5 mg, 70%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 – 7.35 (m, 2H), 7.30 – 7.25 (m, 3H), 6.99 (d, *J* = 7.4 Hz, 1H), 6.67 (d, *J* = 7.4 Hz, 1H), 6.65 – 6.61 (m, 1H), 4.04 (d, *J* = 8.7 Hz, 1H), 3.95 (d, *J* = 8.7 Hz, 1H), 3.70 (s, 3H), 2.42 (t, *J* = 7.0 Hz, 2H), 2.31 (s, 3H), 2.13 (s, 3H), 1.95 (td, *J* = 12.8, 4.9 Hz, 1H), 1.80 (td, *J* = 12.8, 4.6 Hz, 1H), 1.67 – 1.55 (m, 2H), 1.37 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.04, 156.79, 136.71, 131.69, 130.44, 128.33, 127.73, 124.01, 123.84, 121.12, 112.03, 89.67, 81.18, 72.60, 52.09, 47.13, 35.25, 24.04, 21.51, 20.40, 20.01, 15.82; HRMS (ESI-TOF) Calcd for $C_{24}H_{29}O_3$ $[M+H]^+$: 365.2117; found: 365.2112.



2-(Cyanomethyl)-5-(2,5-dimethylphenoxy)-2-methylpentanoic acid (3l)

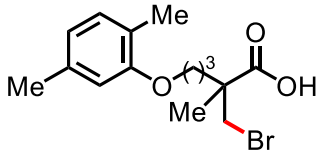
Following **General Procedure B** on 0.1 mmol scale with TBACN (2.0 eq) in DMF at 60 ºC for 12 h. Purification by pTLC afforded the title compound (colorless oil, 27.0 mg, 98%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.04 – 6.97 (m, 1H), 6.67 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.59 (d, *J* = 1.5 Hz, 1H), 3.95 (t, *J* = 6.0 Hz, 2H), 2.72 (d, *J* = 16.8 Hz, 1H), 2.64 (d, *J* = 16.8 Hz, 1H), 2.30 (s, 3H), 2.17 (s, 3H), 2.04 – 1.86 (m, 2H), 1.86 – 1.72 (m, 2H), 1.45 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.56, 156.76, 136.67, 130.56, 123.71, 121.13, 117.21, 112.01, 67.15, 44.30, 34.90, 25.87, 24.93, 23.20, 21.54, 15.90; HRMS (ESI-TOF) Calcd for $C_{16}H_{22}NO_3$ $[M+H]^+$: 276.1600; found: 276.1603.



5-(2,5-Dimethylphenoxy)-2-(fluoromethyl)-2-methylpentanoic acid (3m)

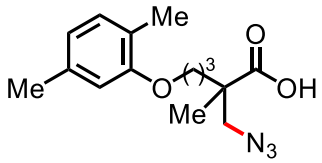
Following **General Procedure B** on 0.1 mmol scale with TBAF (2.0 eq) in THF at rt for 12 h. Purification by pTLC afforded the title compound (colorless oil, 13.5 mg, 50%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.00 (d, *J* = 7.3 Hz, 1H), 6.66 (d, *J* = 7.3 Hz, 1H), 6.60 (s, 1H), 4.55 (dd, *J* = 47.1, 9.0 Hz, 1H), 4.44 (dd, *J* = 47.1, 9.0 Hz, 1H), 3.93 (t, *J* = 5.5 Hz, 2H), 2.30 (s, 3H), 2.17 (s, 3H), 1.91 – 1.71 (m, 4H), 1.32 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 180.72, 156.93, 136.63, 130.49, 123.73, 120.99, 112.07, 87.11 (d, *J* = 175.0 Hz), 67.66, 47.04 (d, *J*

= 18.3 Hz), 31.42 (d, *J* = 4.8 Hz), 24.54, 21.52, 19.11 (d, *J* = 4.8 Hz), 15.87; HRMS (ESI-TOF) Calcd for $C_{15}H_{21}FNaO_3$ $[M+Na]^+$: 291.1372; found: 291.1363.



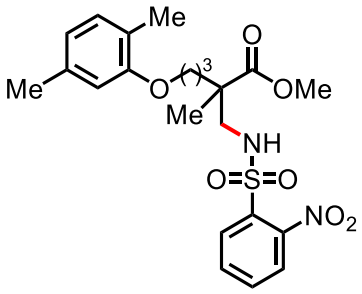
2-(Bromomethyl)-5-(2,5-dimethylphenoxy)-2-methylpentanoic acid (3n)

Following **General Procedure B** on 0.1 mmol scale with $MgBr_2$ (2.0 eq) in THF at rt for 1 h. Purification by pTLC afforded the title compound (colorless oil, 30.0 mg, 92%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.00 (d, *J* = 7.4 Hz, 1H), 6.72 – 6.64 (m, 1H), 6.60 (d, *J* = 1.6 Hz, 1H), 3.94 (t, *J* = 5.8 Hz, 2H), 3.65 (d, *J* = 10.2 Hz, 1H), 3.53 (d, *J* = 10.2 Hz, 1H), 2.30 (s, 3H), 2.17 (s, 3H), 2.02 – 1.90 (m, 1H), 1.90 – 1.72 (m, 3H), 1.39 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.34, 156.31, 136.03, 129.89, 123.11, 120.38, 111.43, 66.91, 38.82, 33.46, 24.27, 20.96, 20.94, 15.30 (1 carbon signal was not assigned due to overlaps); HRMS (ESI-TOF) Calcd for $C_{15}H_{21}BrNaO_3$ $[M+Na]^+$: 351.0572; found: 351.0565.



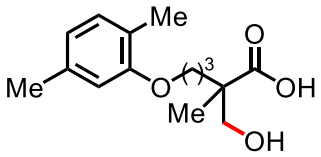
2-(Azidomethyl)-5-(2,5-dimethylphenoxy)-2-methylpentanoic acid (3o)

Following **General Procedure B** on 0.1 mmol scale with NaN_3 (2.0 eq) in DMF at 60 °C for 1 h. Purification by pTLC afforded the title compound (colorless oil, 25.0 mg, 86%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.00 (d, *J* = 7.5 Hz, 1H), 6.66 (d, *J* = 7.5 Hz, 1H), 6.63 – 6.53 (m, 1H), 3.93 (t, *J* = 5.5 Hz, 2H), 3.60 (d, *J* = 12.1 Hz, 1H), 3.43 (d, *J* = 12.1 Hz, 1H), 2.30 (s, 3H), 2.17 (s, 3H), 1.88 – 1.72 (m, 4H), 1.29 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 181.17, 156.90, 136.64, 130.50, 123.72, 121.00, 112.06, 67.59, 57.85, 46.89, 33.16, 24.63, 21.54, 20.50, 15.88; HRMS (ESI-TOF) Calcd for $C_{15}H_{21}N_3NaO_3$ $[M+Na]^+$: 314.1481; found: 314.1477.



Methyl 5-(2,5-dimethylphenoxy)-2-methyl-2-(((2-nitrophenyl)sulfonamido)methyl)-pentanoate (3p)

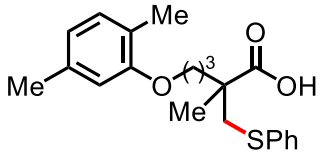
Following **General Procedure B** on 0.1 mmol scale with NaNHNs (2.0 eq) in DMF at rt for 1 h; the crude acid was methyl esterification by $TMSCHN_2$ for isolation purpose. (*12*) Purification by pTLC afforded the title compound (colorless oil, 34.0 mg, 73%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.16 – 8.04 (m, 1H), 7.90 – 7.79 (m, 1H), 7.79 – 7.66 (m, 2H), 6.99 (d, *J* = 7.5 Hz, 1H), 6.66 (d, *J* = 7.5 Hz, 1H), 6.57 (s, 1H), 5.98 (t, *J* = 6.7 Hz, 1H), 3.95 – 3.82 (m, 2H), 3.70 (s, 3H), 3.27 (dd, *J* = 12.6, 6.5 Hz, 1H), 3.10 (dd, *J* = 12.6, 7.1 Hz, 1H), 2.30 (s, 3H), 2.15 (s, 3H), 1.85 – 1.69 (m, 4H), 1.28 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.34, 156.82, 148.26, 136.61, 133.70, 132.89, 131.02, 130.43, 125.53, 123.58, 120.94, 111.99, 67.47, 52.44, 49.66, 46.34, 33.45, 24.40, 21.50, 20.99, 15.86 (1 carbon signal was not assigned due to overlaps); HRMS (ESI-TOF) Calcd for $C_{22}H_{29}N_2O_7S$ $[M+H]^+$: 465.1695; found: 465.1695.



5-(2,5-Dimethylphenoxy)-2-(hydroxymethyl)-2-methylpentanoic acid (3q)

Following **General Procedure B** on 0.1 mmol scale with KOH (2.0 eq) in THF at 60 °C for 1 h. Purification by pTLC afforded the title compound (colorless oil, 25.5 mg, 95%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.00 (d, *J* = 7.5 Hz, 1H), 6.66 (dd, *J* = 7.5, 1.4 Hz, 1H), 6.60 (d, *J* = 1.4 Hz, 1H), 3.99 – 3.87 (m, 2H), 3.78 (d, *J* = 11.3 Hz, 1H), 3.61 (d, *J* = 11.3 Hz, 1H), 2.30 (s, 3H), 2.17 (s, 3H), 1.89 – 1.71 (m, 4H), 1.26 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 182.50, 156.96, 136.63, 130.48, 123.72, 120.98, 112.14, 68.04, 67.89, 32.30, 24.55, 21.54,

19.60, 15.90 (1 carbon signal was not assigned due to overlaps); HRMS (ESI-TOF) Calcd for $C_{15}H_{23}O_4$ $[M+H]^+$: 267.1596; found: 267.1596.



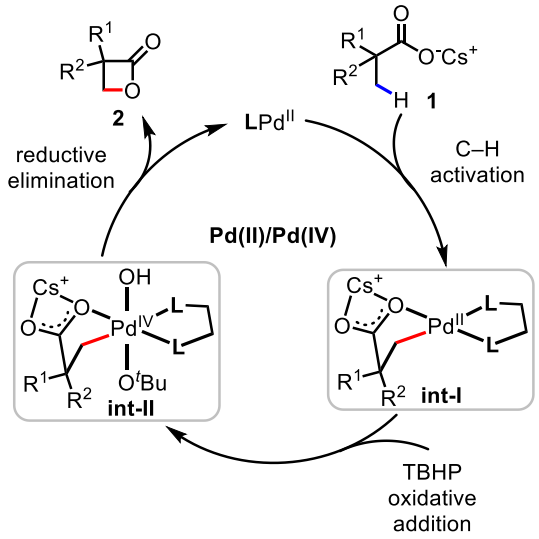
5-(2,5-Dimethylphenoxy)-2-methyl-2-((phenylthio)methyl)pentanoic acid (3r)

Following **General Procedure B** on 0.1 mmol scale with PhSNa (2.0 eq) in DMF at 60 ^oC for 1 h. Purification by pTLC afforded the title compound (colorless oil, 33.0 mg, 92%). ^1H NMR (600 MHz, $CDCl_3$) δ 7.42 – 7.37 (m, 2H), 7.26 – 7.22 (m, 2H), 7.17 (t, *J* = 7.3 Hz, 1H), 6.99 (d, *J* = 7.4 Hz, 1H), 6.65 (d, *J* = 7.4 Hz, 1H), 6.58 (s, 1H), 3.94 – 3.84 (m, 2H), 3.30 (d, *J* = 12.7 Hz, 1H), 3.19 (d, *J* = 12.7 Hz, 1H), 2.29 (s, 3H), 2.17 (s, 3H), 1.93 (dt, *J* = 11.4, 6.6 Hz, 1H), 1.88 – 1.70 (m, 3H), 1.33 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 182.00, 156.97, 136.89, 136.58, 130.45, 130.36, 129.05, 126.57, 123.72, 120.90, 112.05, 67.71, 47.21, 43.06, 34.75, 24.88, 21.82, 21.54, 15.93; HRMS (ESI-TOF) Calcd for $C_{21}H_{26}NaO_3S$ $[M+Na]^+$: 381.1500; found: 381.1494.

Mechanistic Studies of β-C(sp^3)–H Lactonization

Since peroxides have been shown by Canty to oxidize Pd(II) to Pd(IV) in organometallic studies, TBHP is likely to oxidize our C–H activation intermediate as a Pd(II) complex to Pd(IV) species[13-15]. We have therefore proposed a Pd(II)/Pd(IV) catalytic cycle (Scheme S1). In this catalytic cycle the selective reductive elimination to form β-lactone is realized only when TBHP is used as the oxidant.

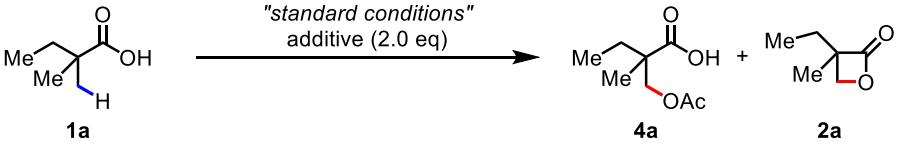
Scheme S1. Proposed Pd(II)/Pd(IV) Catalytic Cycle for β-C(sp^3)–H Lactonization



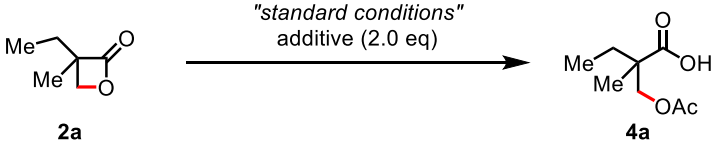
To support this mechanistic hypothesis that TBHP promotes the desired selective reductive elimination, we have performed intermolecular competition experiments (Scheme S2) and investigated other oxidants that were used in Pd(II)/Pd(IV) chemistry (Scheme S3).

First, model substrate **1a** and two equivalents NaOAc were subjected to the standard conditions. Only β-acetoxylation product **4a** was detected in 22% yield without any β-lactone product **2a**. Additionally, adding two equivalents Ac_2O to the standard conditions with **1a** resulted in the formation of β-acetoxylation product **4a** in 14% yield combined with β-lactone product **2a** in 12% yield. To rule out the possibility of the formation of acetoxylation product by lactone opening, β-lactone **2a** was subjected to the aforementioned conditions; however, no β-acetoxylation product was observed after the reaction.

Scheme S2. Intermolecular Competition Experiments



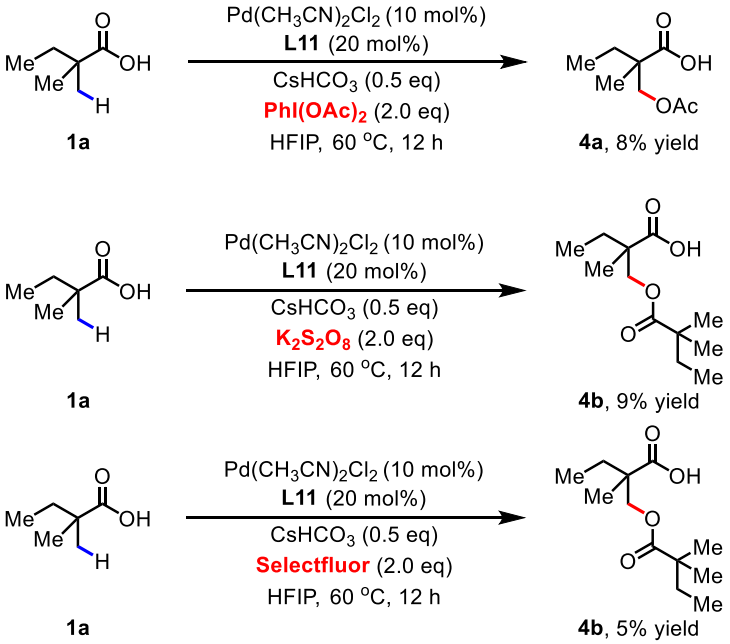
entry	additive	yield of **4a** (%)	yield of **2a** (%)
1	*"standard conditions"*	0%	73%
2	NaOAc (2.0 eq)	22%	0%
3	Ac_2O (2.0 eq)	14%	12%



entry	additive	yield of **4a** (%)	recovery of **2a** (%)
1	NaOAc (2.0 eq)	0%	83%
2	Ac_2O (2.0 eq)	0%	75%

Next, several oxidants that traditionally effect oxidation Pd(II) to Pd(IV) have been investigated. For example, when $PhI(OAc)_2$ was used as the oxidant, 8% β-acetoylation product **4a** can be obtained with trace amount of β-lactone from ^1H NMR. When $K_2S_2O_8$ was used as the oxidant, 9% β-acyloxylation product **4b** was formed but no β-lactone product was observed. Similarly, using selectfluor as the oxidant, 5% β-acyloxylation product **4b** was formed.

Scheme S3. Effects of Other Oxidants



These experiments suggest presence of any acetate from additives or other oxidants will lead to the undesired reductive elimination/acetoxylation products.

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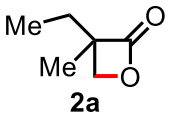

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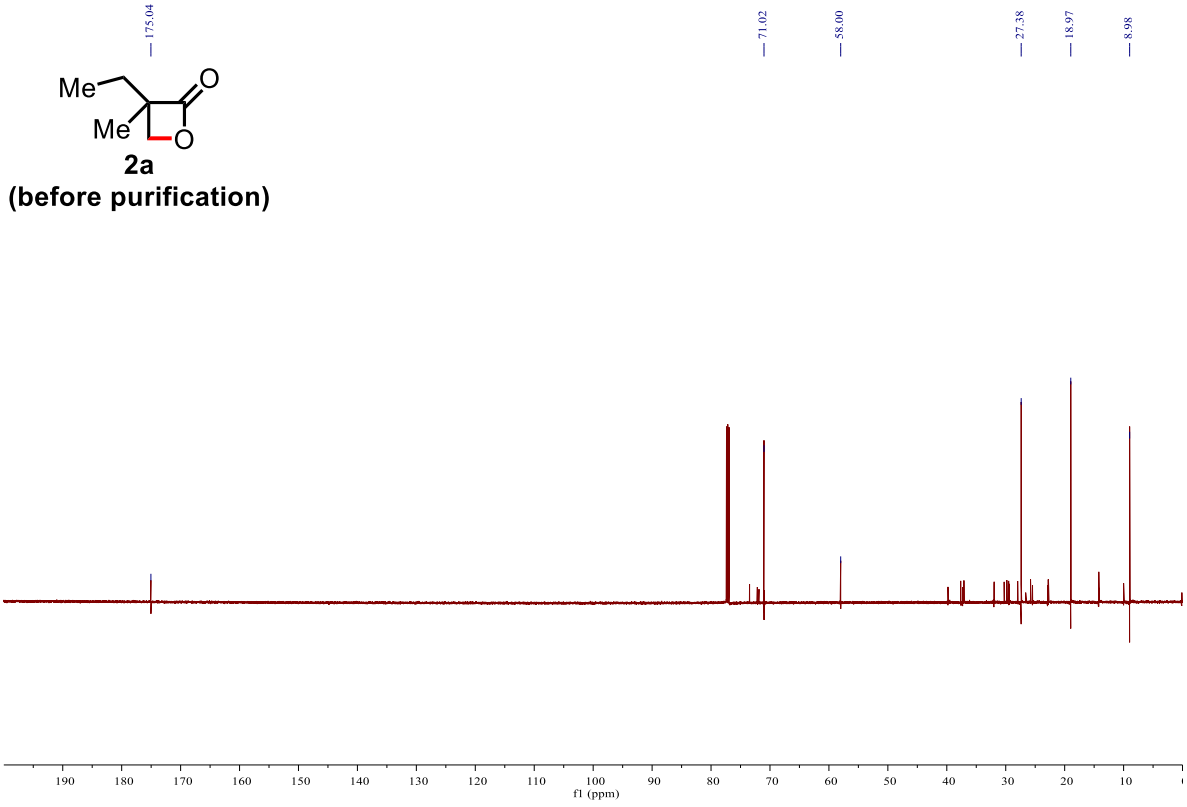
(before purification)



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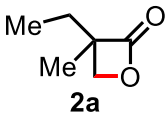
(before purification)



2a

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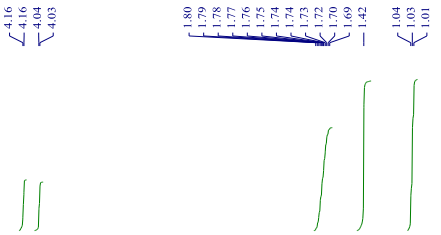

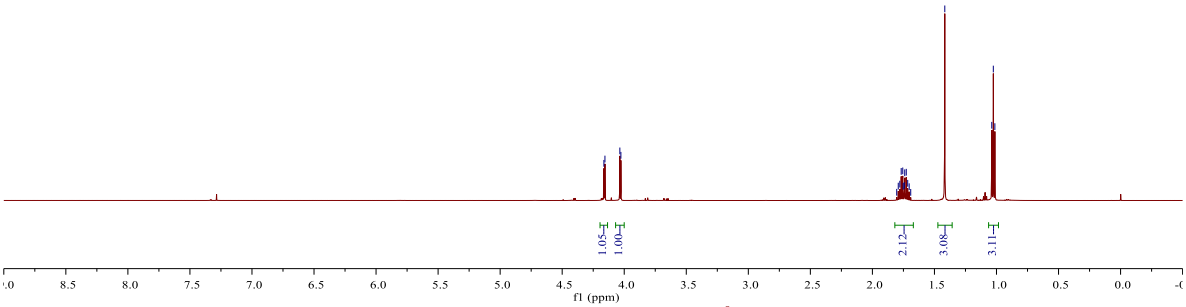

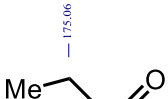

2a

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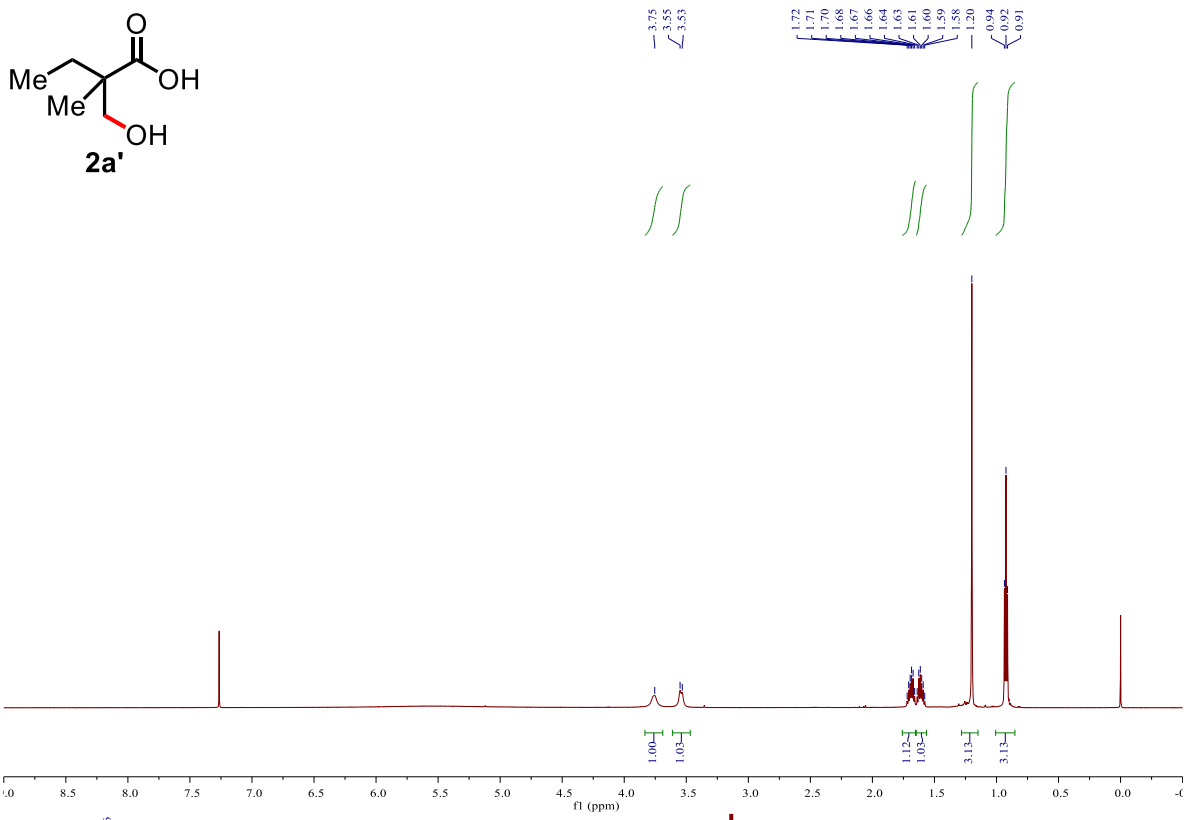
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OH
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3.53
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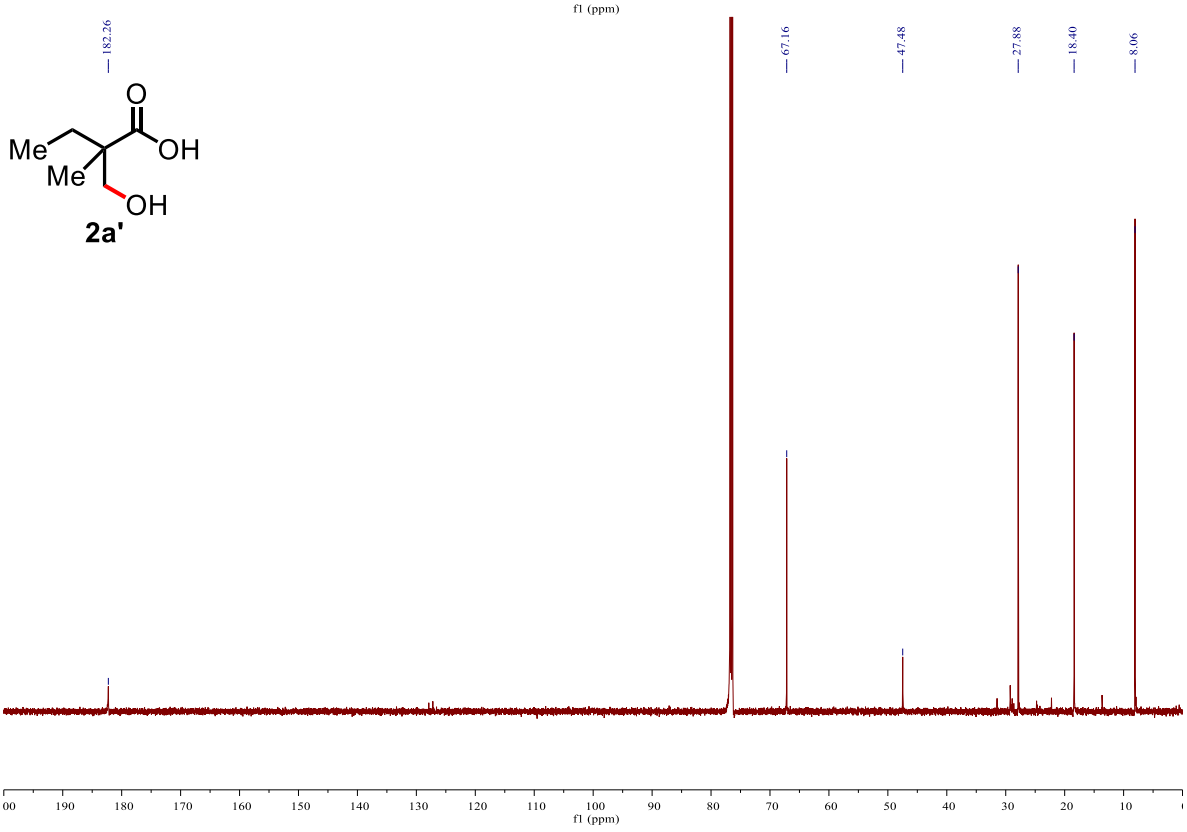
1.66
1.64
1.63
1.61
1.60
1.59
1.58
1.20
0.94
0.92
0.91
1.00
1.03
1.12
1.03
3.13
3.13
f1 (ppm)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OH
OH
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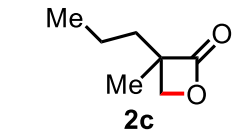
8.06
f1 (ppm)



2c
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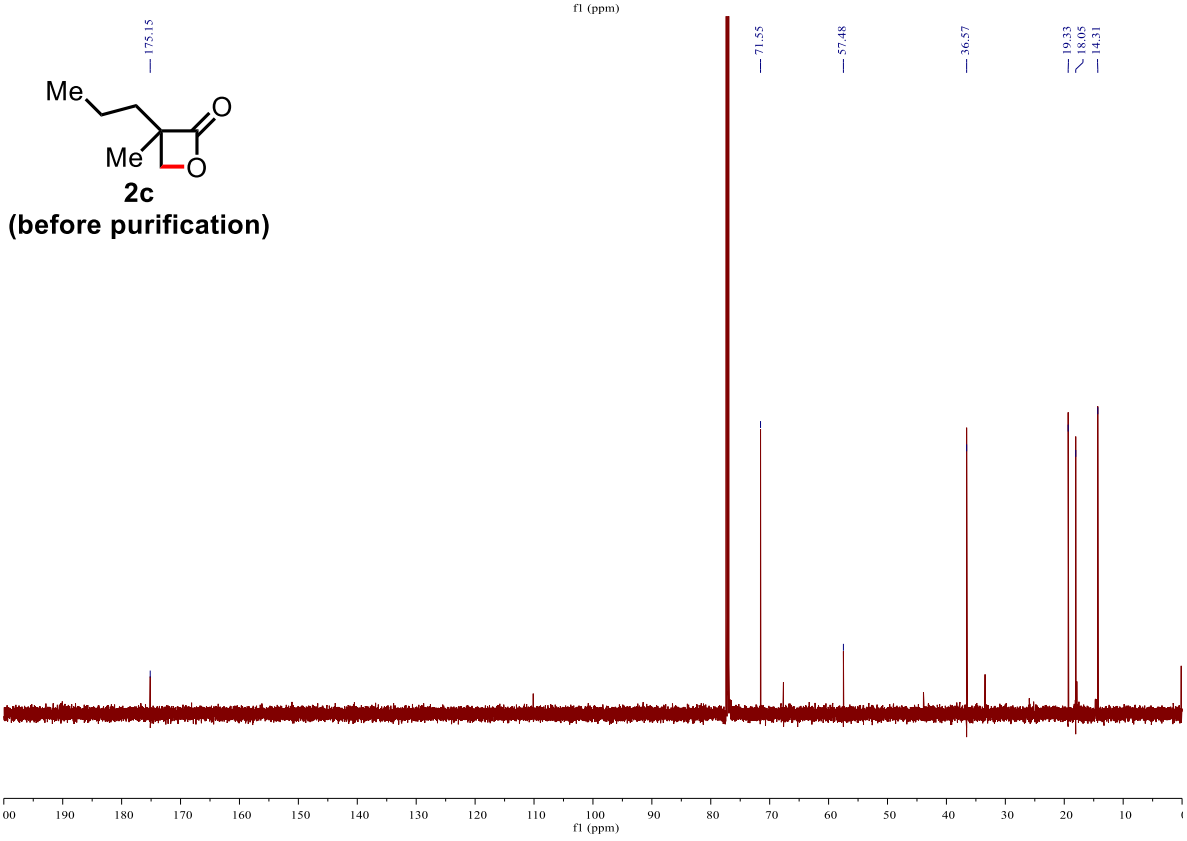

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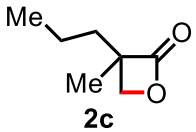

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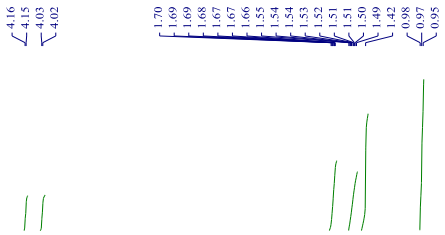

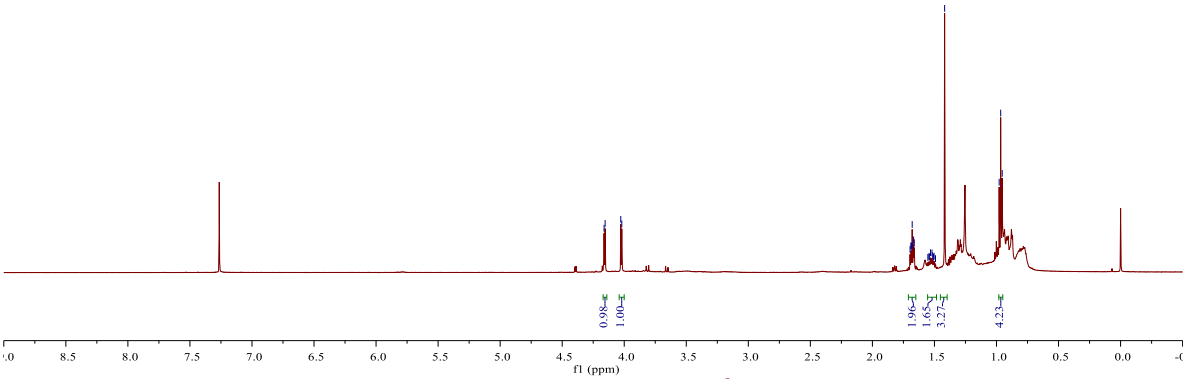

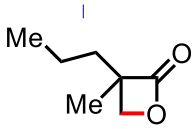

2c

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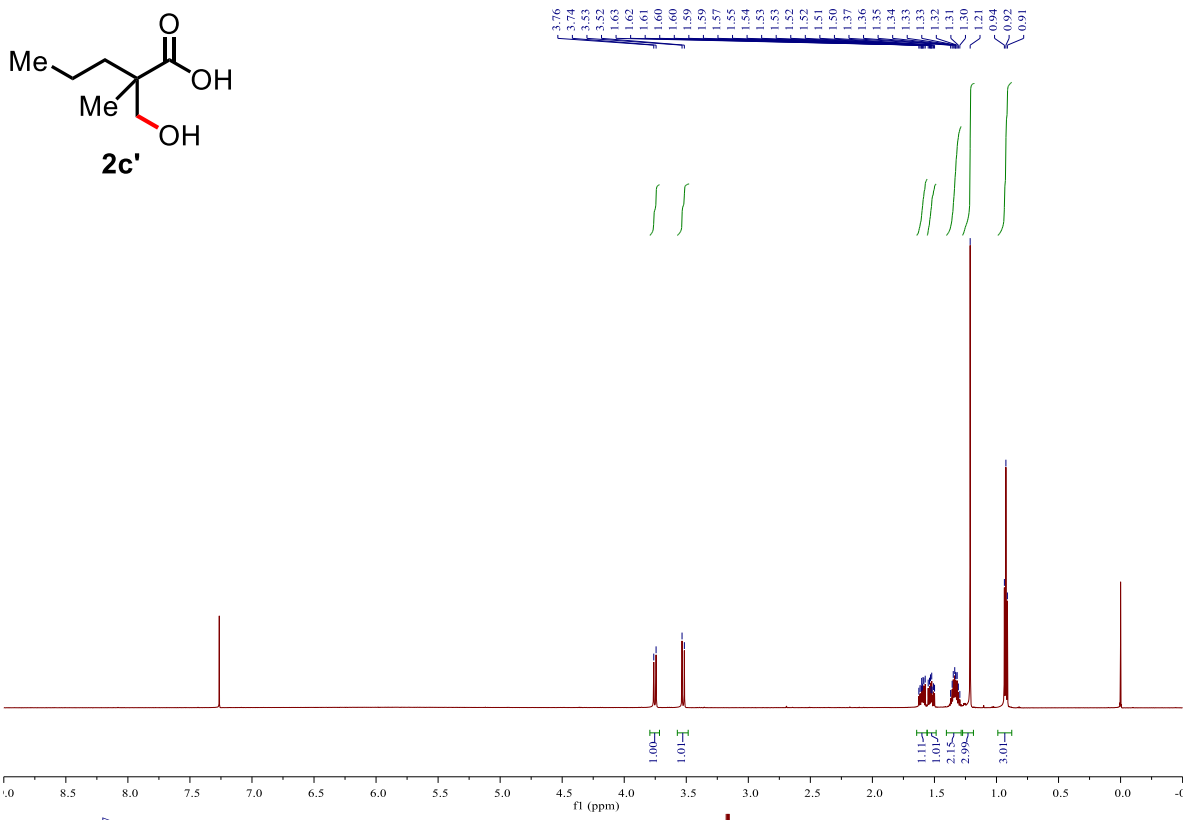
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1.35
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1.33
1.32
1.31
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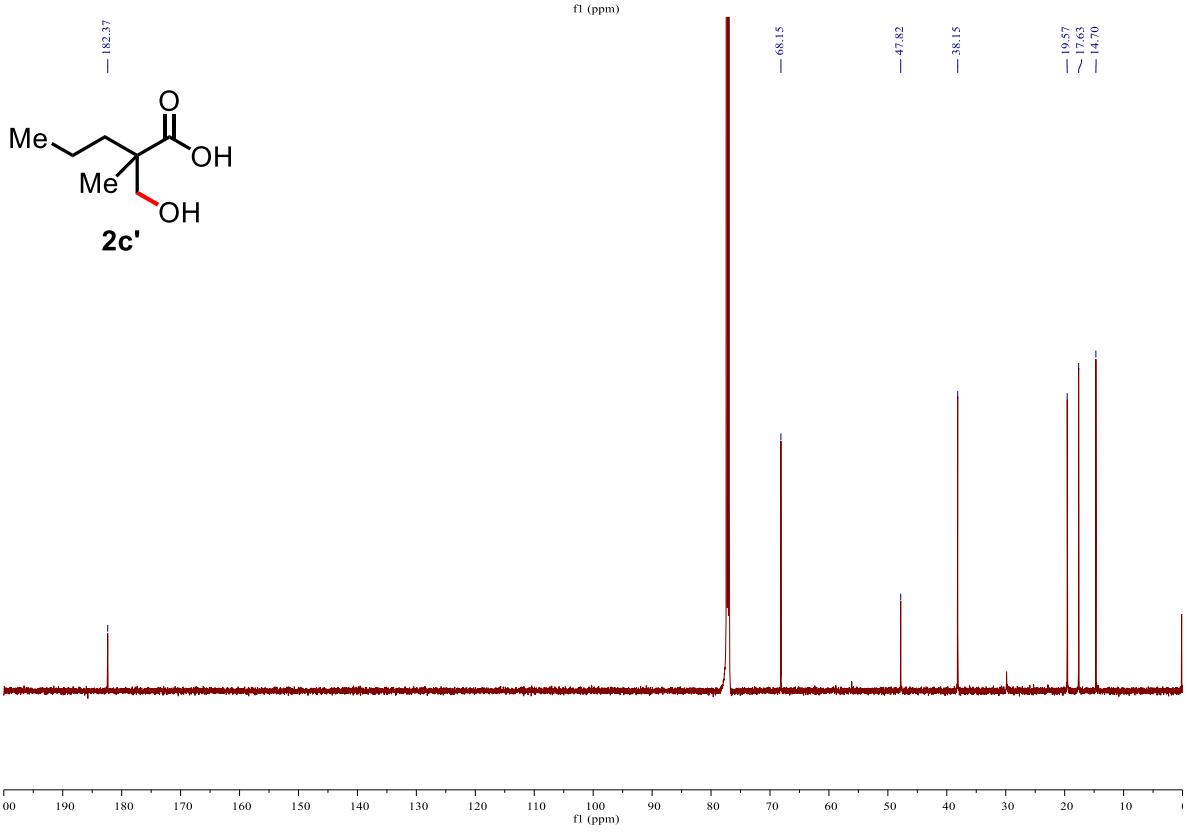
f1 (ppm)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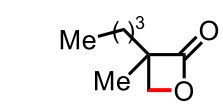
OH
Me
OH
2c'
f1 (ppm)



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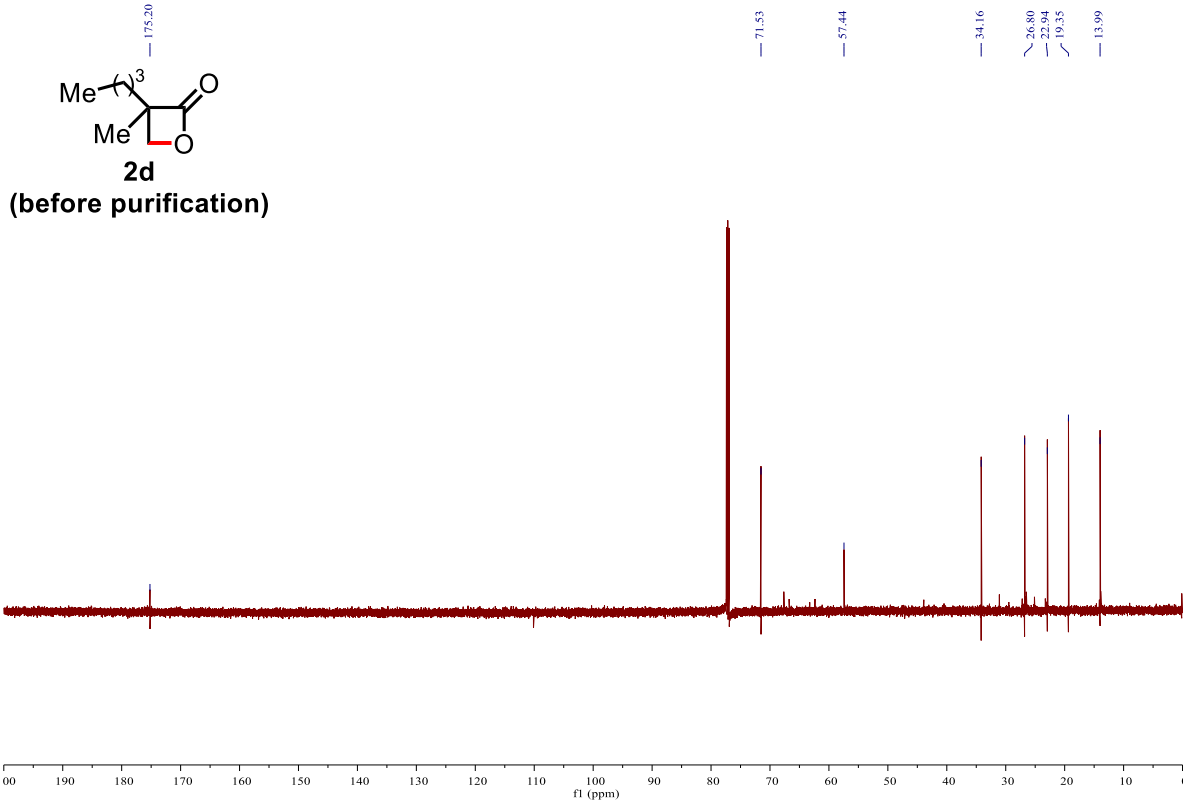

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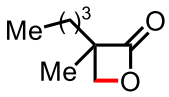

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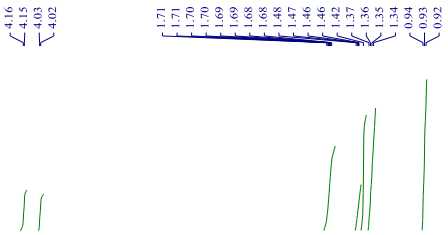
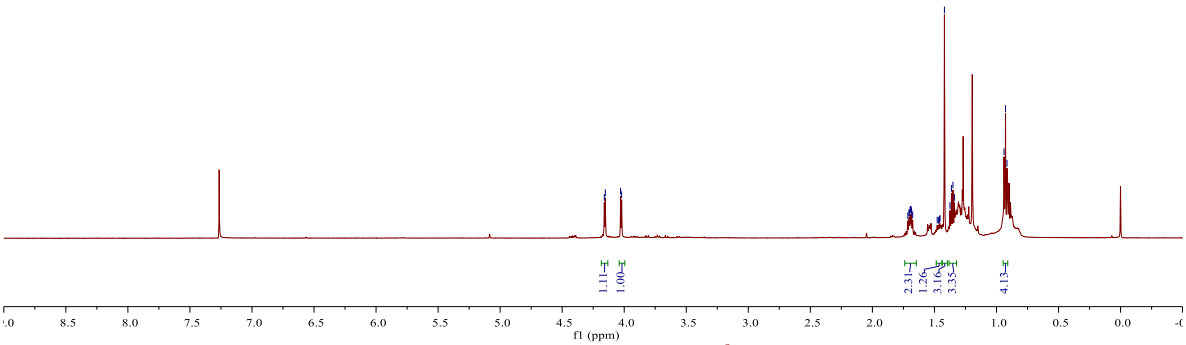
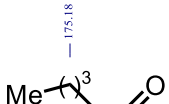
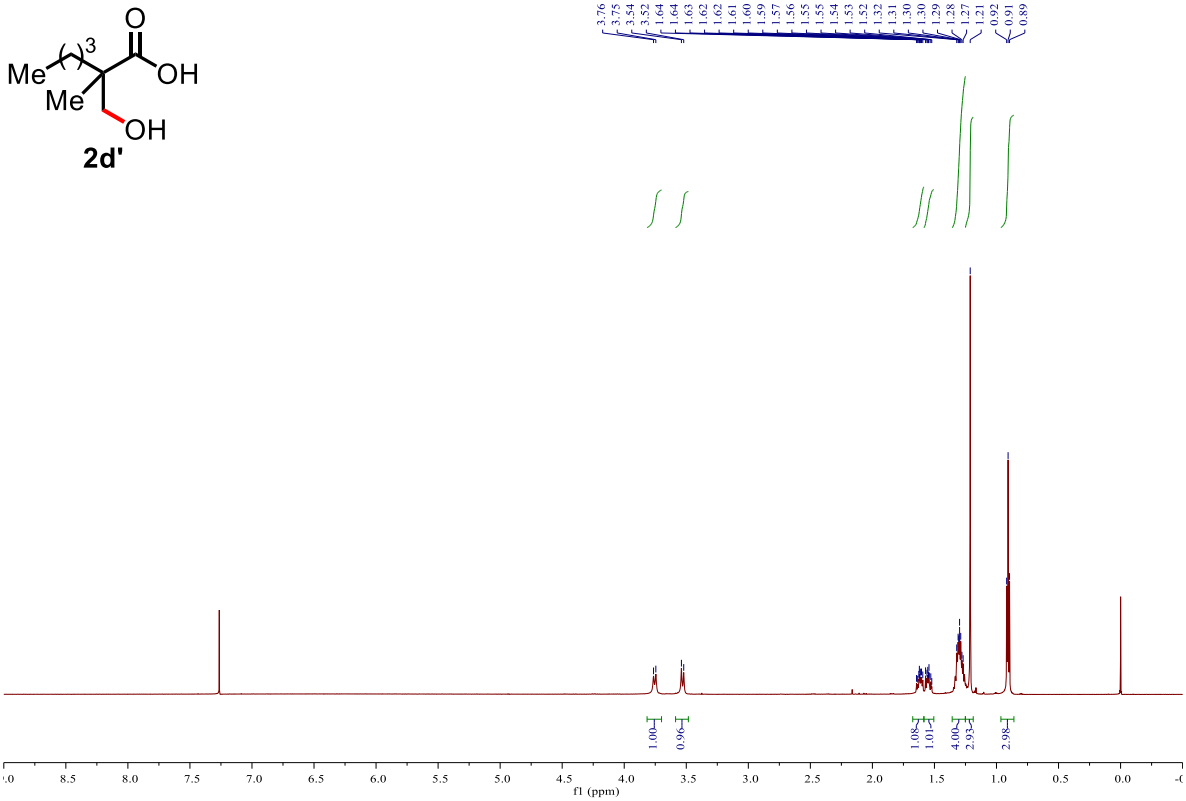


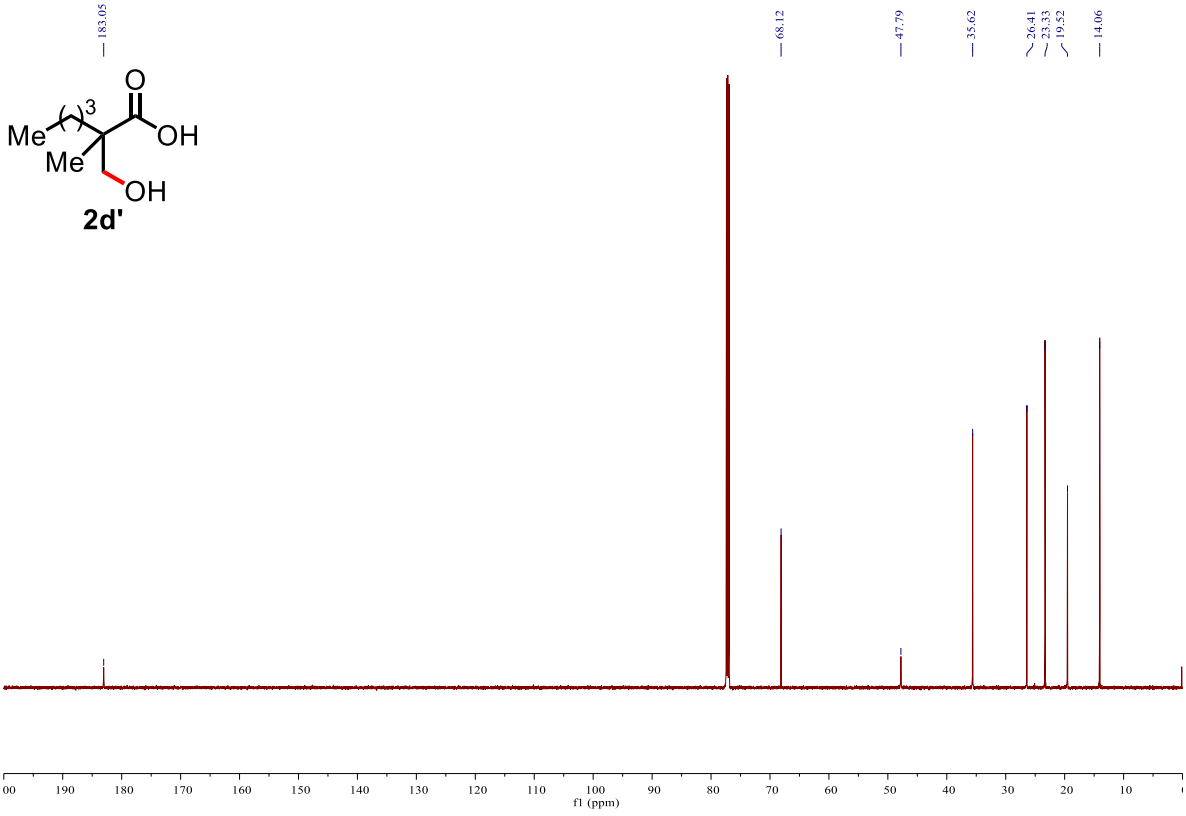


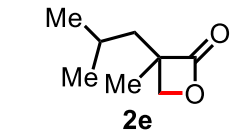


2d

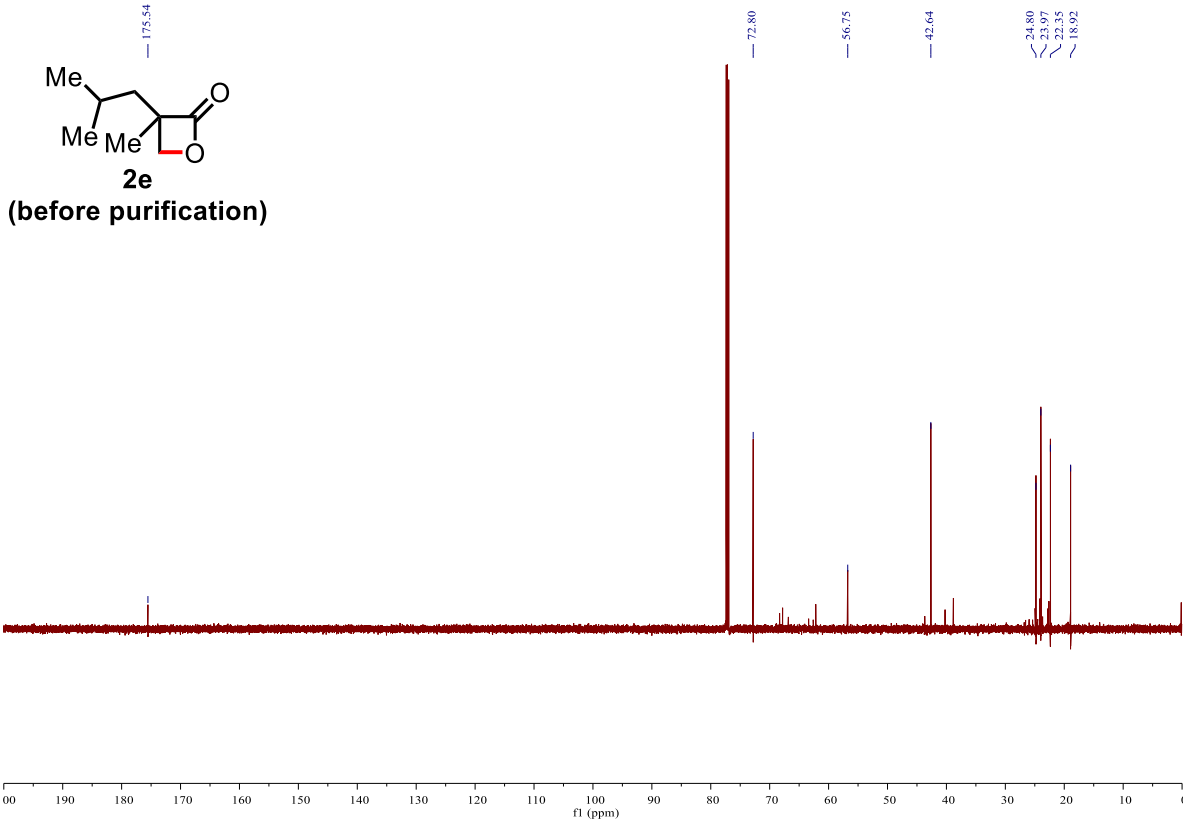
(filter through silica gel)


Me
Me
OH
OH
O
3
2d'
3.76
3.75
3.54
3.52
1.64
1.64
1.63
1.62
1.62
1.61
1.60
1.59
1.57
1.56
1.55
1.55
1.54
1.53
1.52
1.32
1.31
1.30
1.30
1.29
1.28
1.27
1.21
0.92
0.91
0.89
1.00
0.96
1.08
1.01
4.00
2.93
2.98
f1 (ppm)

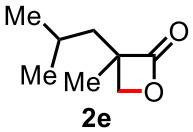

183.05
68.12
47.79
35.62
26.41
23.33
19.52
14.06
Me
Me
OH
OH
O
3
2d'
f1 (ppm)



2e
(before purification)

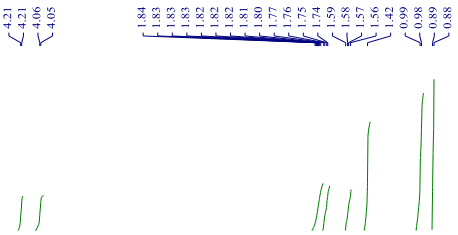


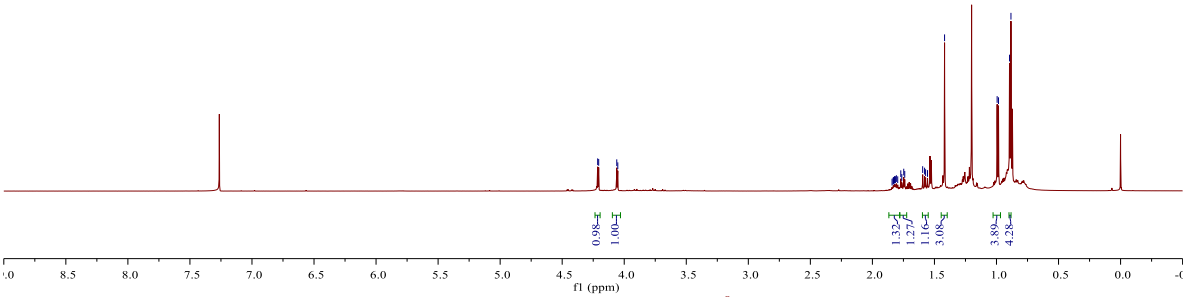
2e
(before purification)

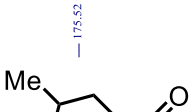


2e

(filter through silica gel)

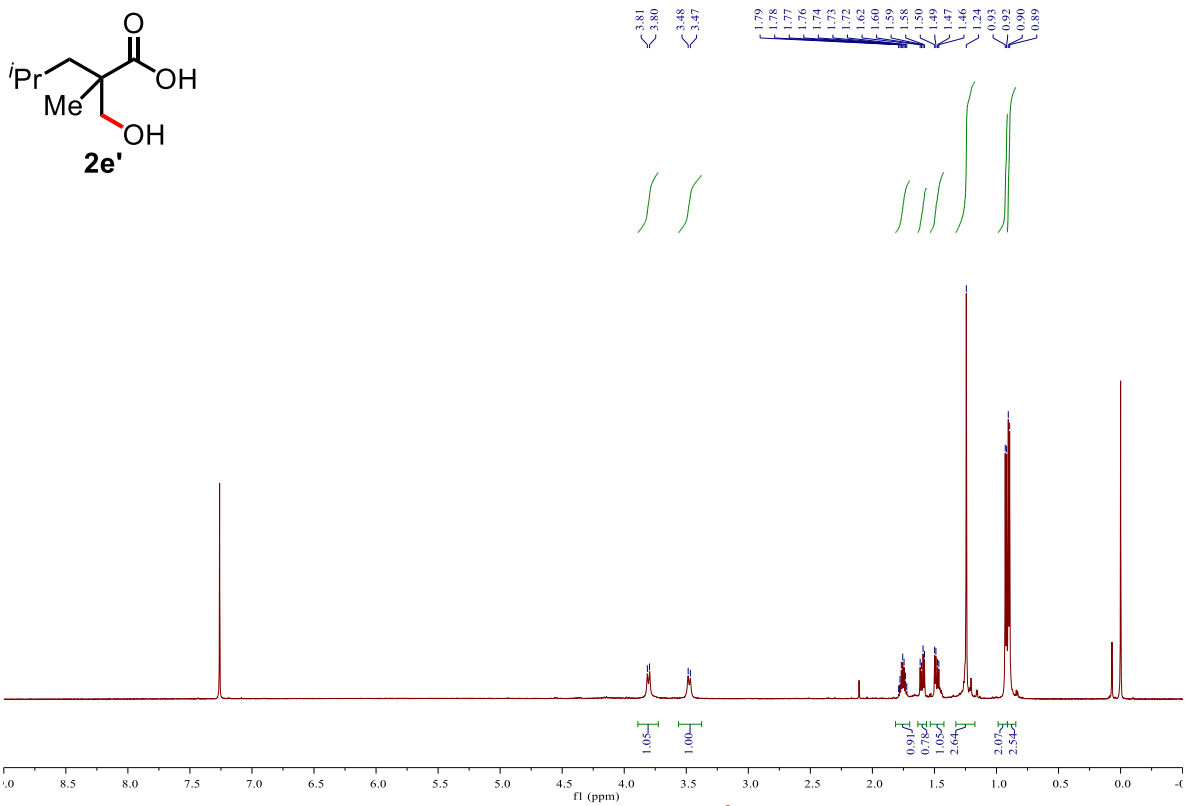


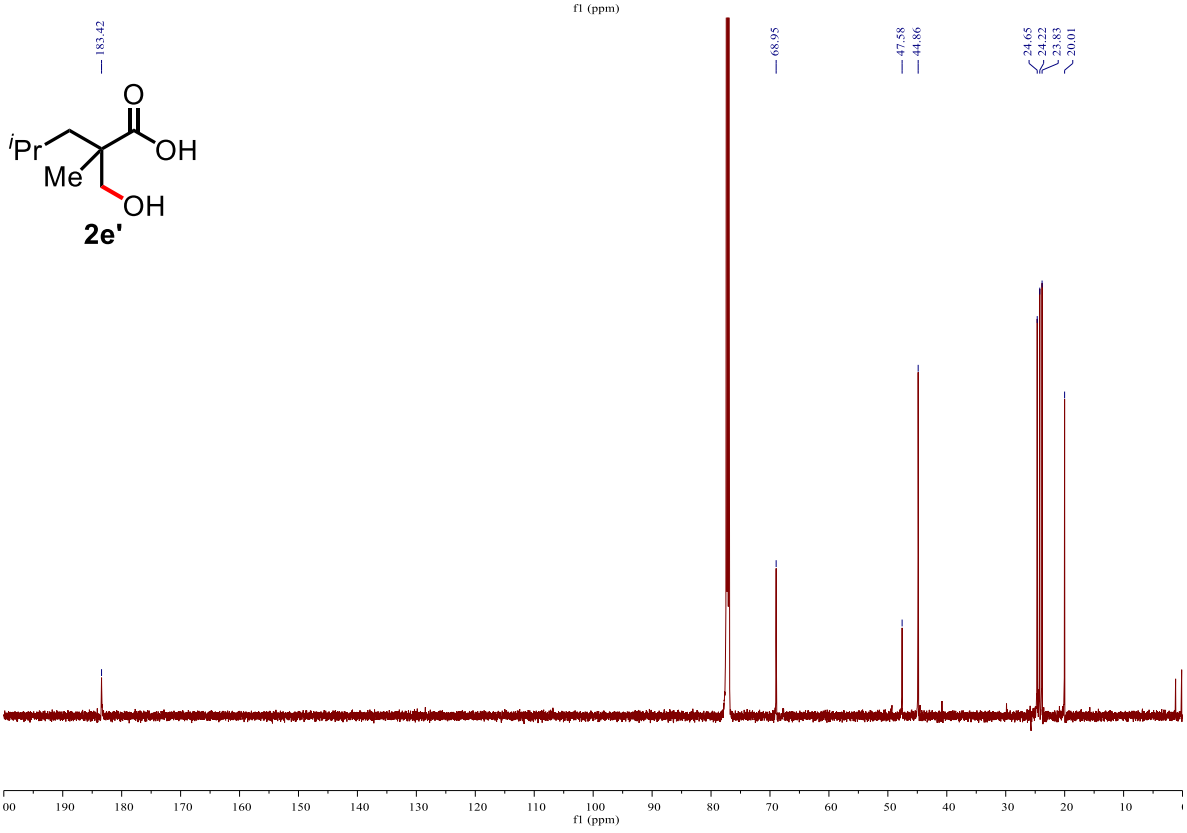


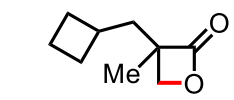


2e

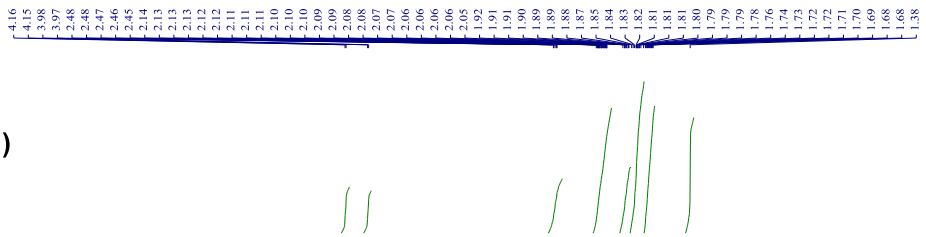
(filter through silica gel)

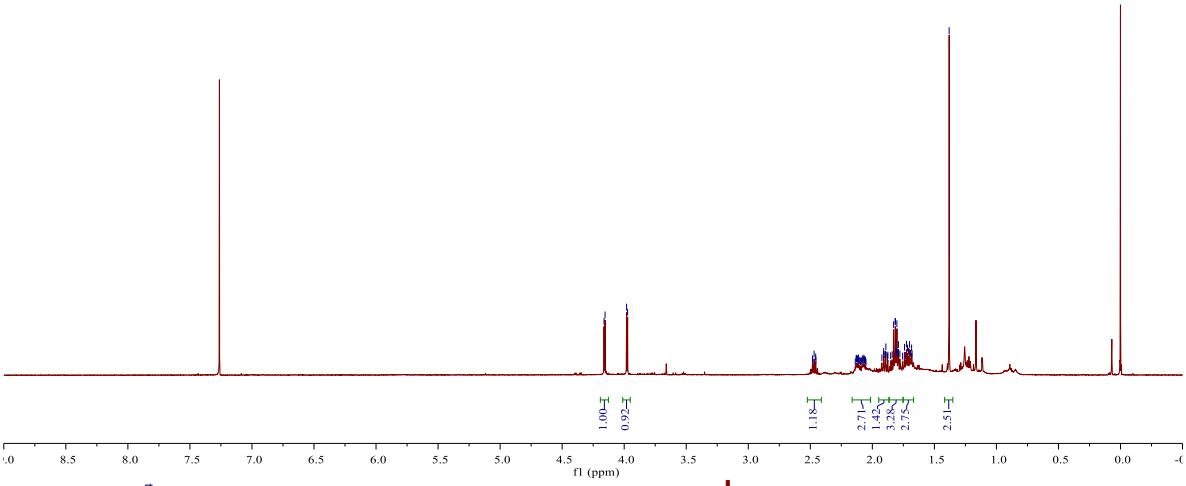

O
OH
iPr
Me
OH
2e'
3.81
3.80
3.48
3.47
1.79
1.78
1.77
1.76
1.74
1.73
1.72
1.62
1.60
1.59
1.58
1.50
1.49
1.47
1.46
1.24
0.93
0.92
0.90
0.89
1.05
1.00
0.91
0.78
1.05
2.64
2.07
2.54
f1 (ppm)

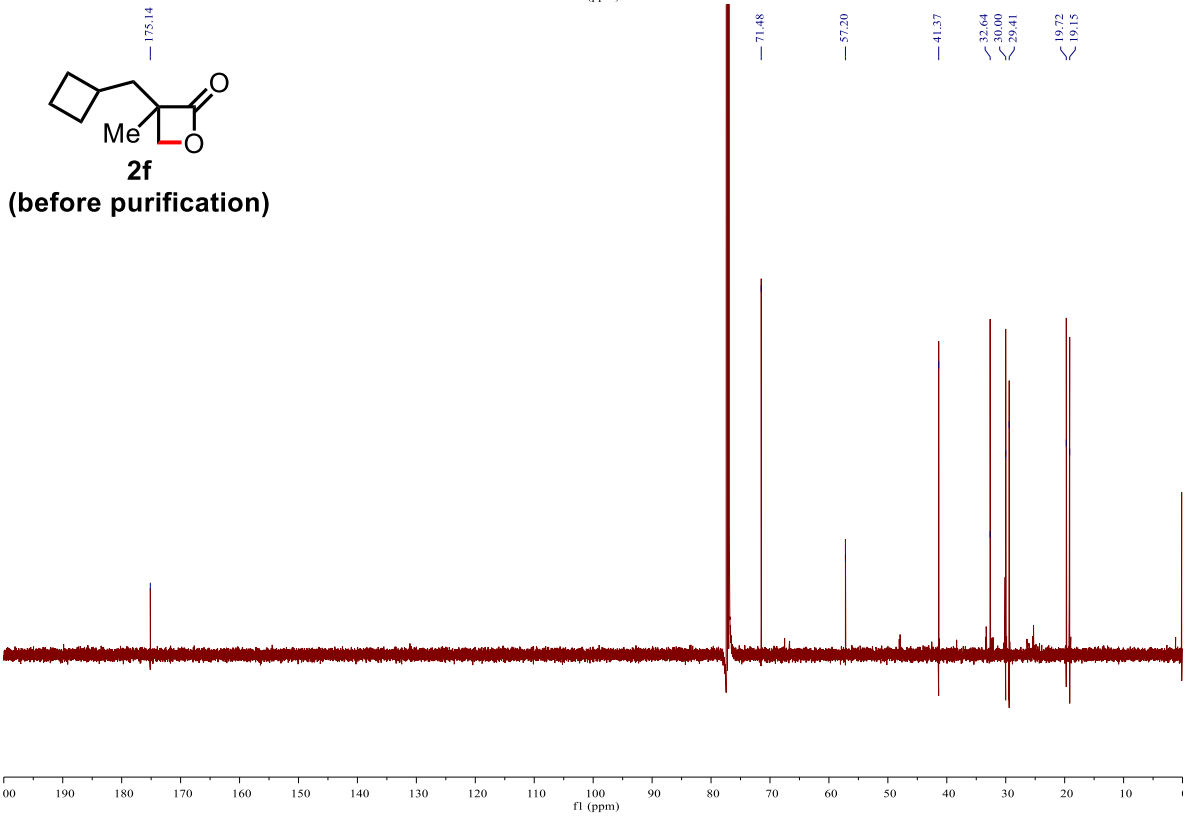

183.42
68.95
47.58
44.86
24.65
24.22
23.83
20.01
O
OH
iPr
Me
OH
2e'
f1 (ppm)



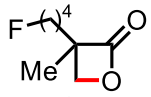
2f
(before purification)



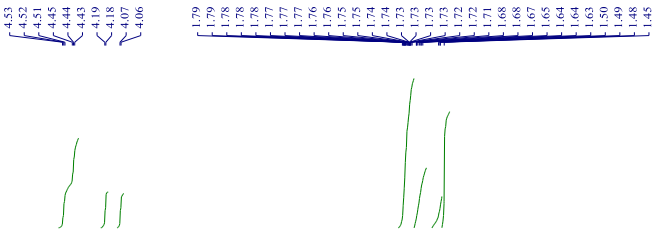


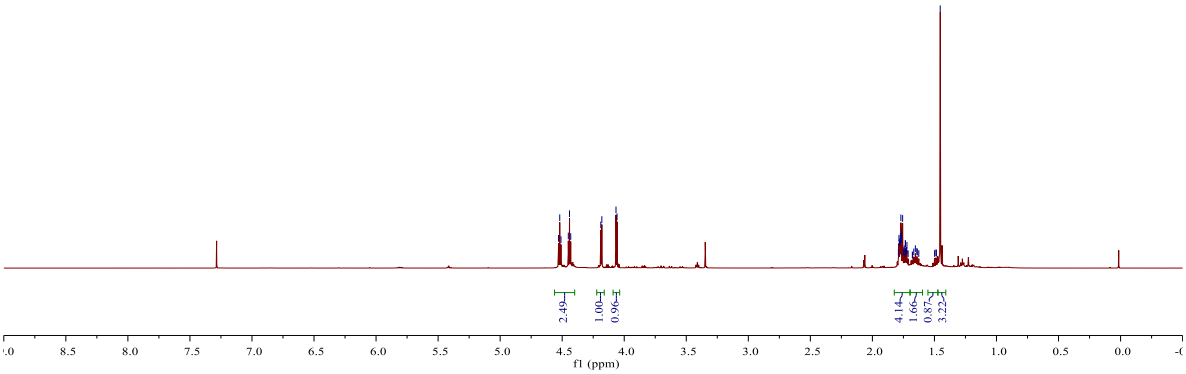


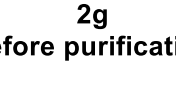
2f
(before purification)



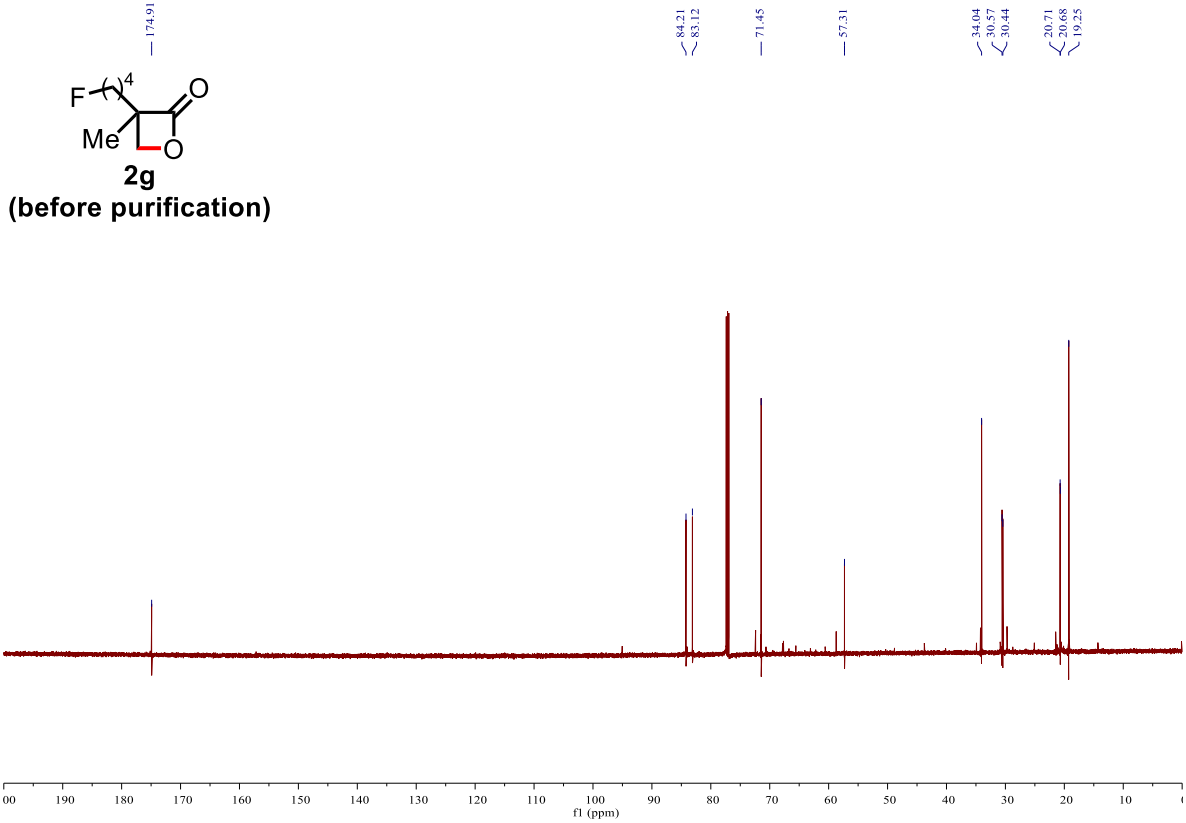
2g
(before purification)

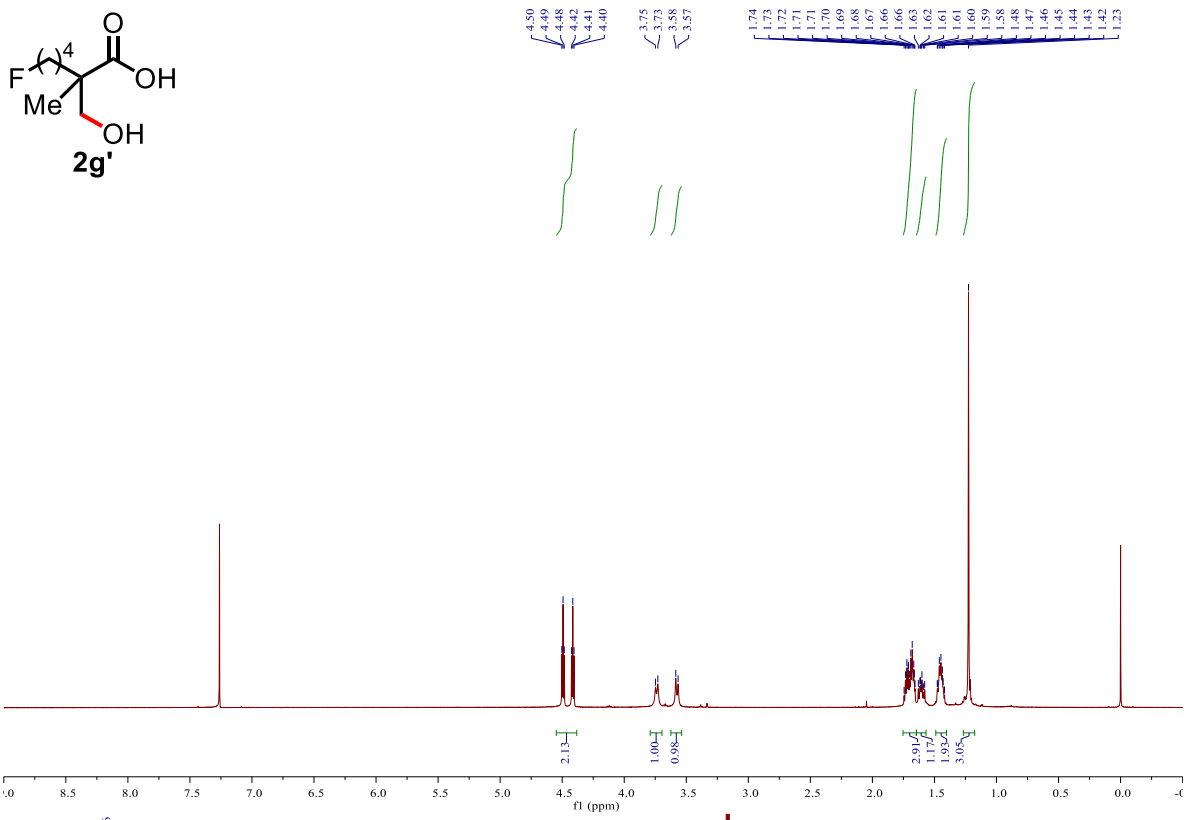


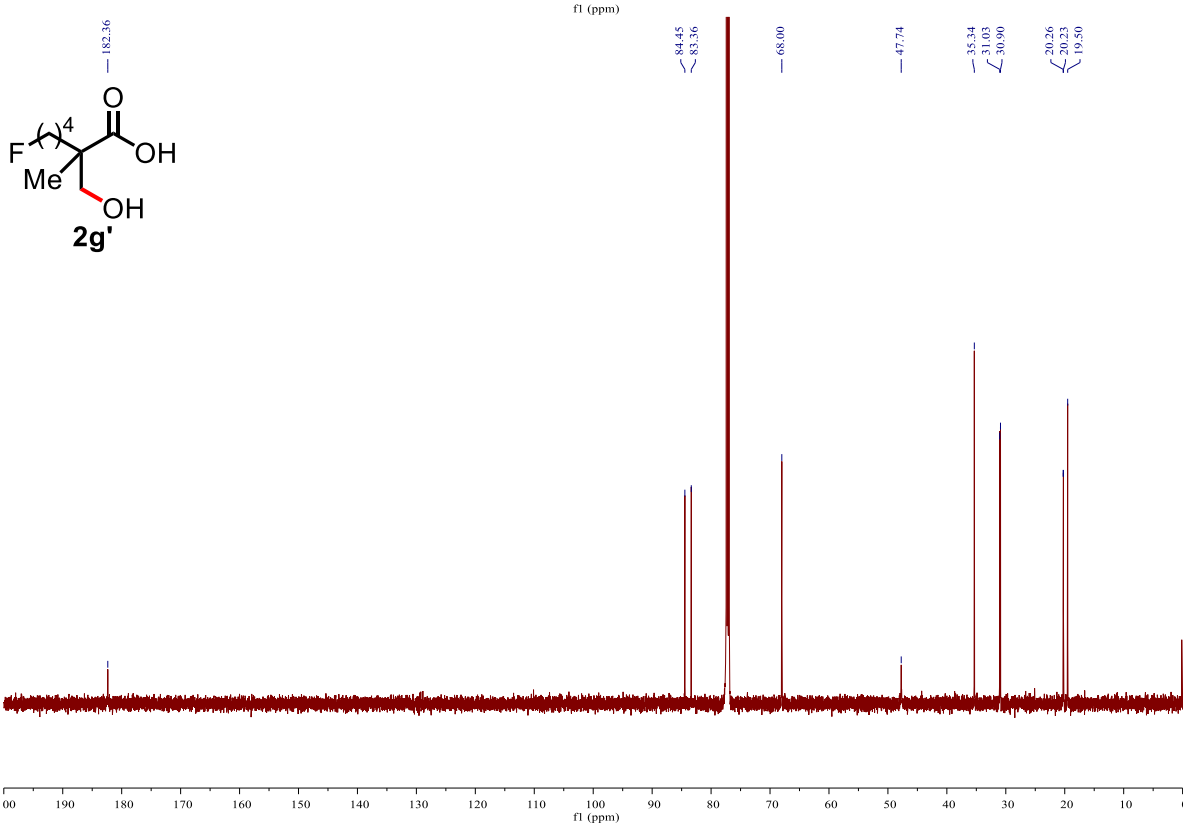


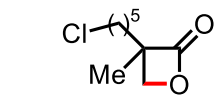


2g
(before purification)

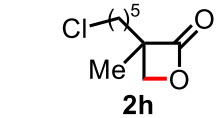



F
4
Me
O
OH
OH
2g'
4.50
4.49
4.48
4.42
4.41
4.40
3.75
3.73
3.58
3.57
1.74
1.73
1.72
1.71
1.71
1.70
1.69
1.68
1.67
1.66
1.66
1.63
1.62
1.61
1.61
1.60
1.59
1.58
1.48
1.47
1.46
1.45
1.44
1.43
1.42
1.23
2.13
1.00
0.98
2.91
1.17
1.93
3.05
f1 (ppm)

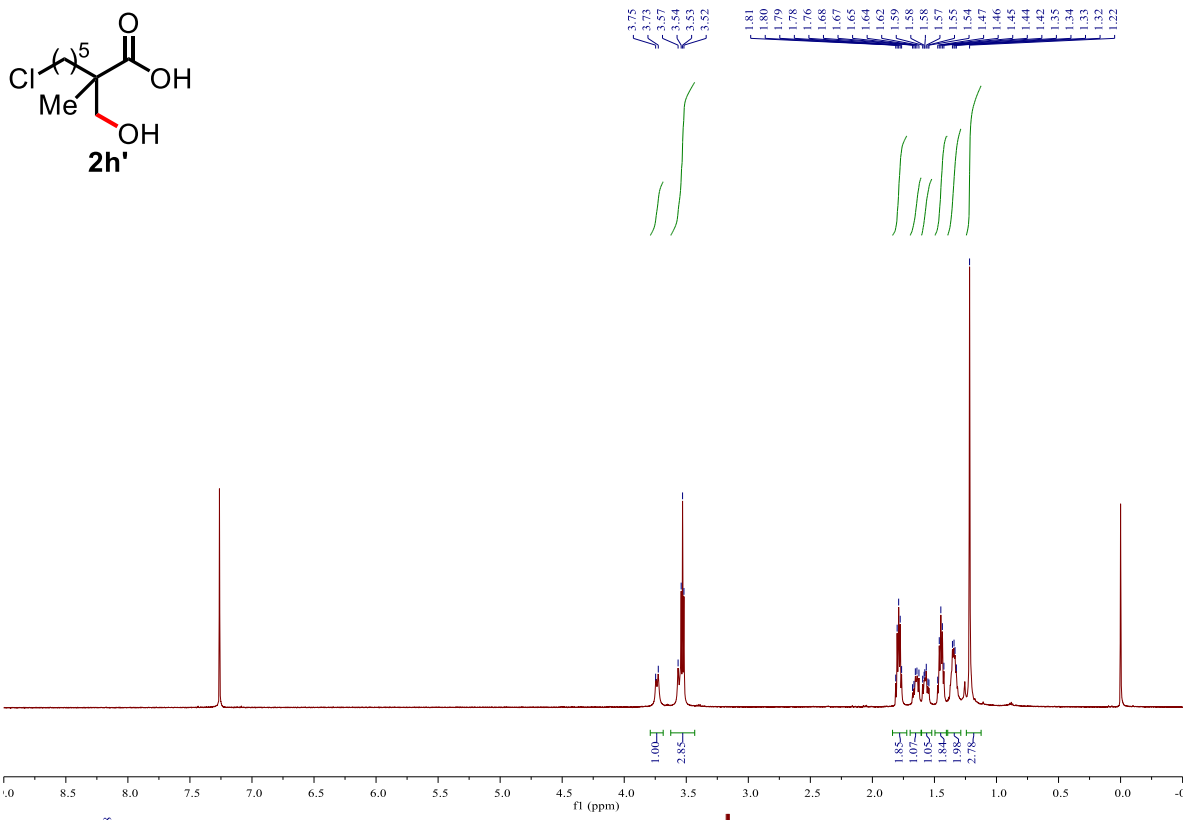

182.36
84.45
83.36
68.00
47.74
35.34
31.03
30.90
20.26
20.23
19.50
F
4
Me
O
OH
OH
2g'
f1 (ppm)

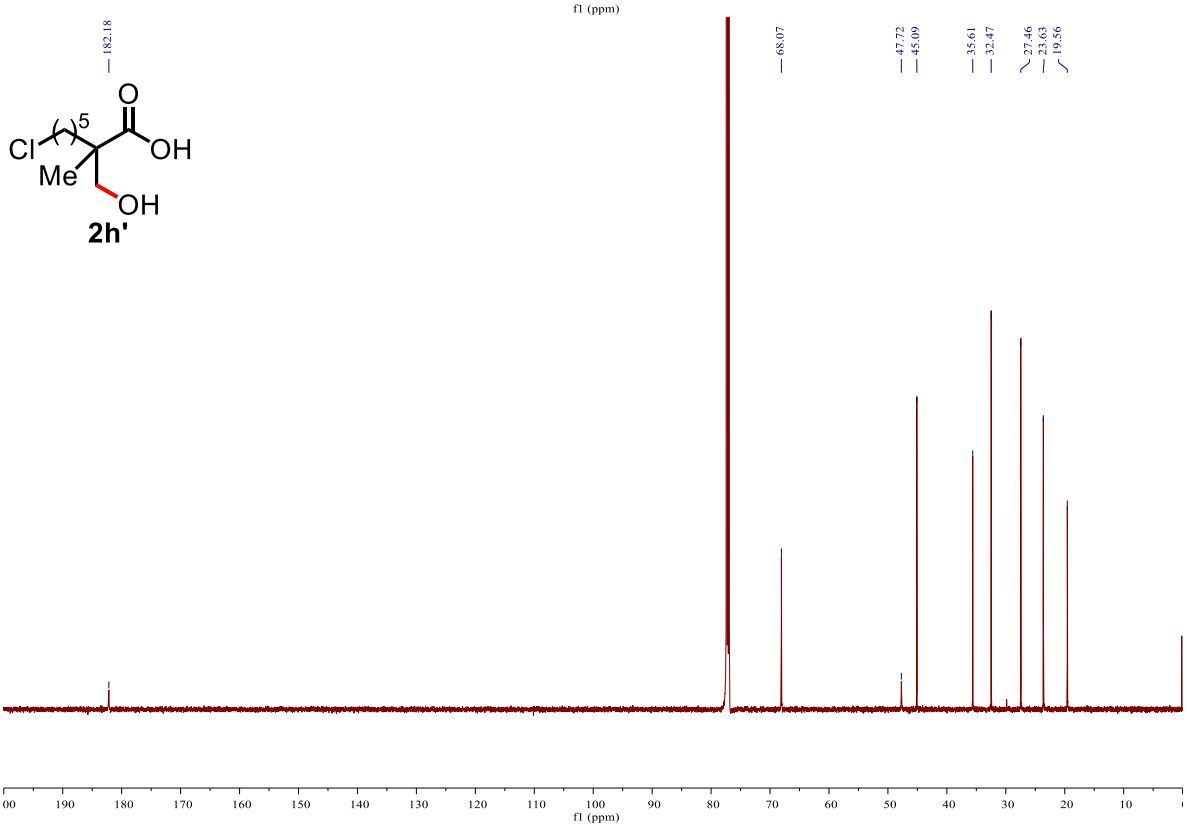


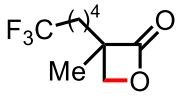
2h
(before purification)



2h
(before purification)

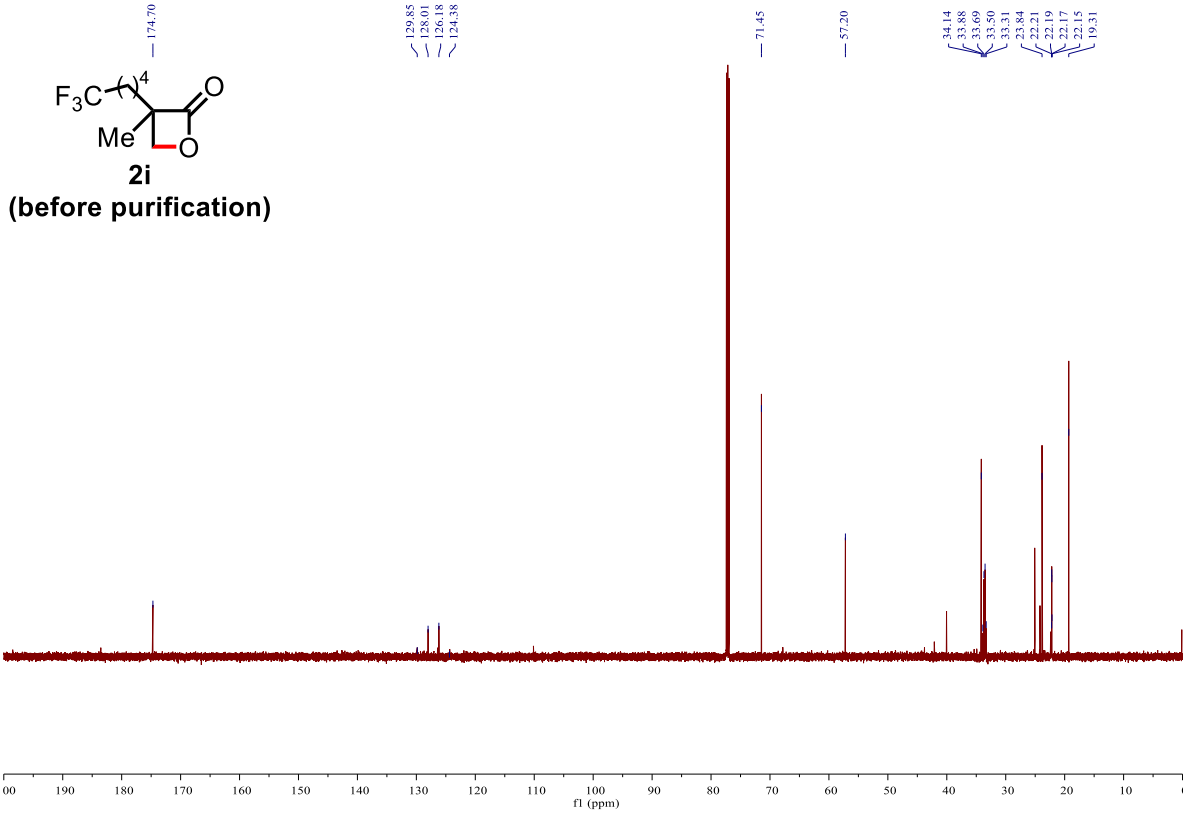

Cl
5
Me
O
OH
OH
2h'
3.75
3.73
3.57
3.54
3.53
3.52
1.81
1.80
1.79
1.78
1.76
1.68
1.67
1.65
1.64
1.62
1.59
1.58
1.58
1.57
1.55
1.54
1.47
1.46
1.45
1.44
1.42
1.35
1.34
1.33
1.32
1.22
1.00
2.85
1.85
1.07
1.05
1.84
1.98
2.78
f1 (ppm)

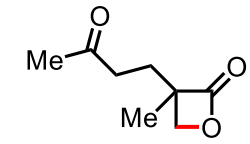

182.18
68.07
47.72
45.09
35.61
32.47
27.46
23.63
19.56
Cl
5
Me
O
OH
OH
2h'
f1 (ppm)



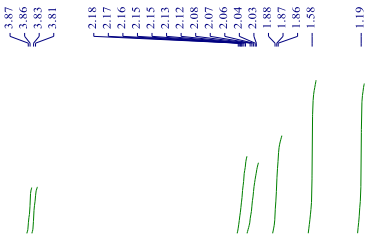
2i
(before purification)

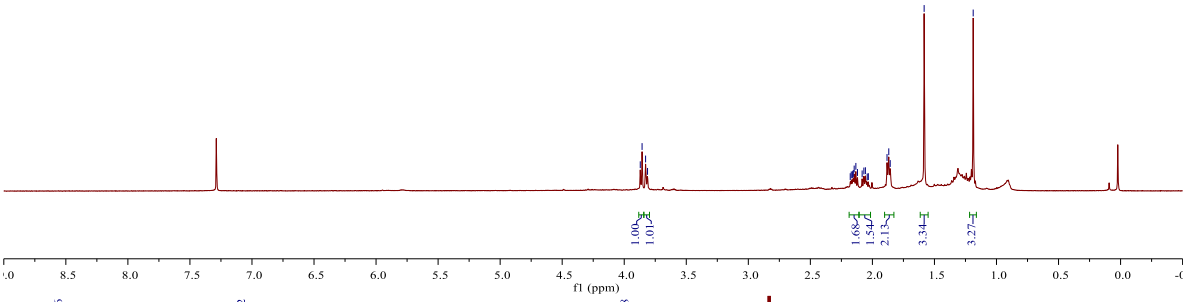
2i
(before purification)

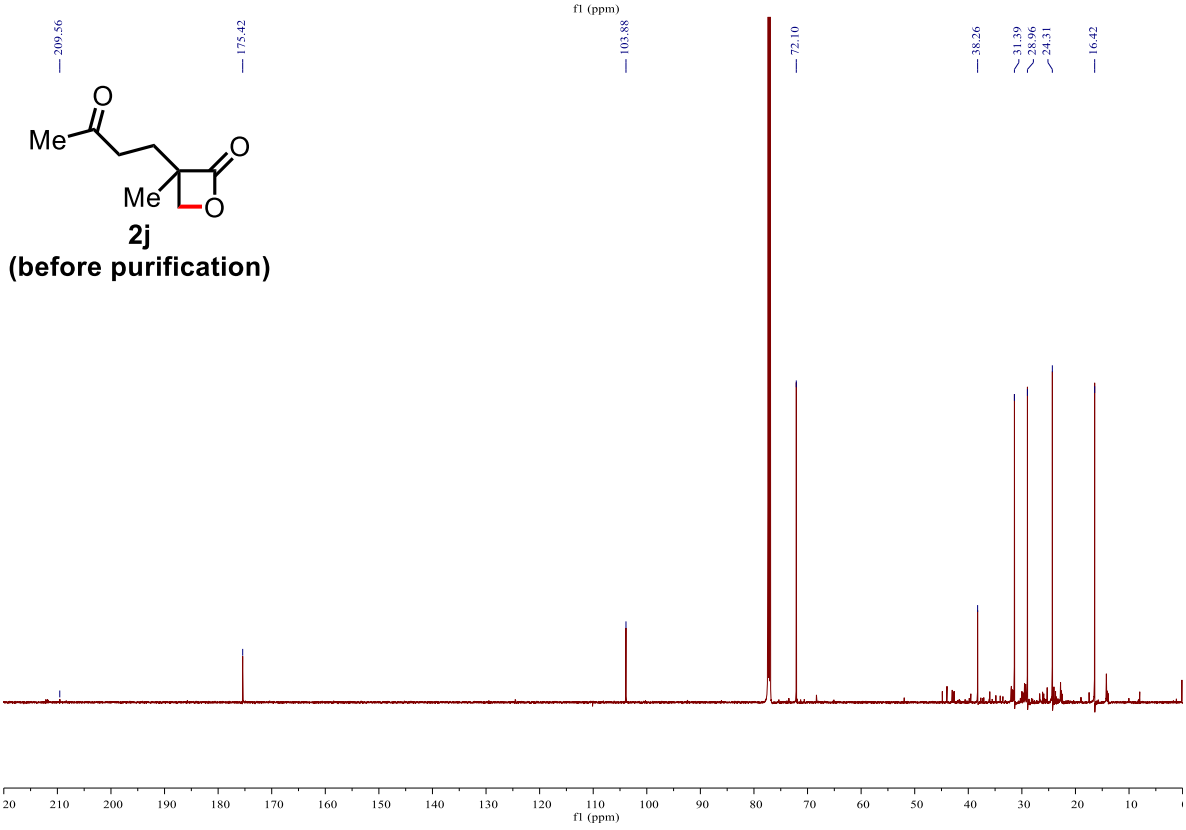




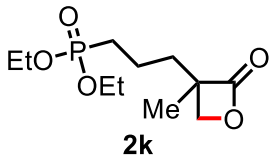
2j
(before purification)



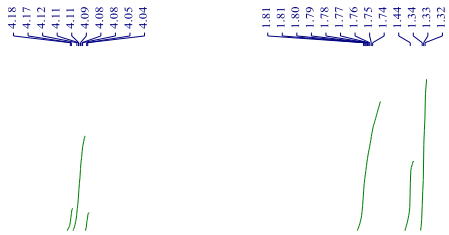


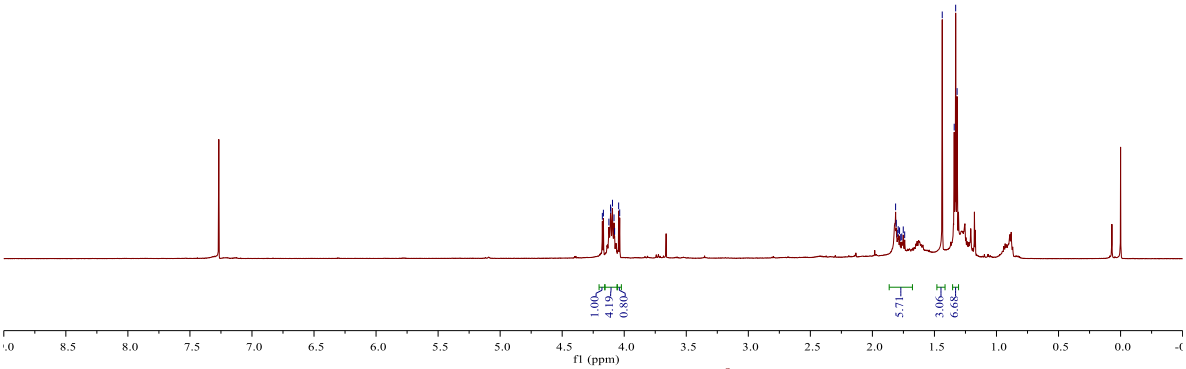


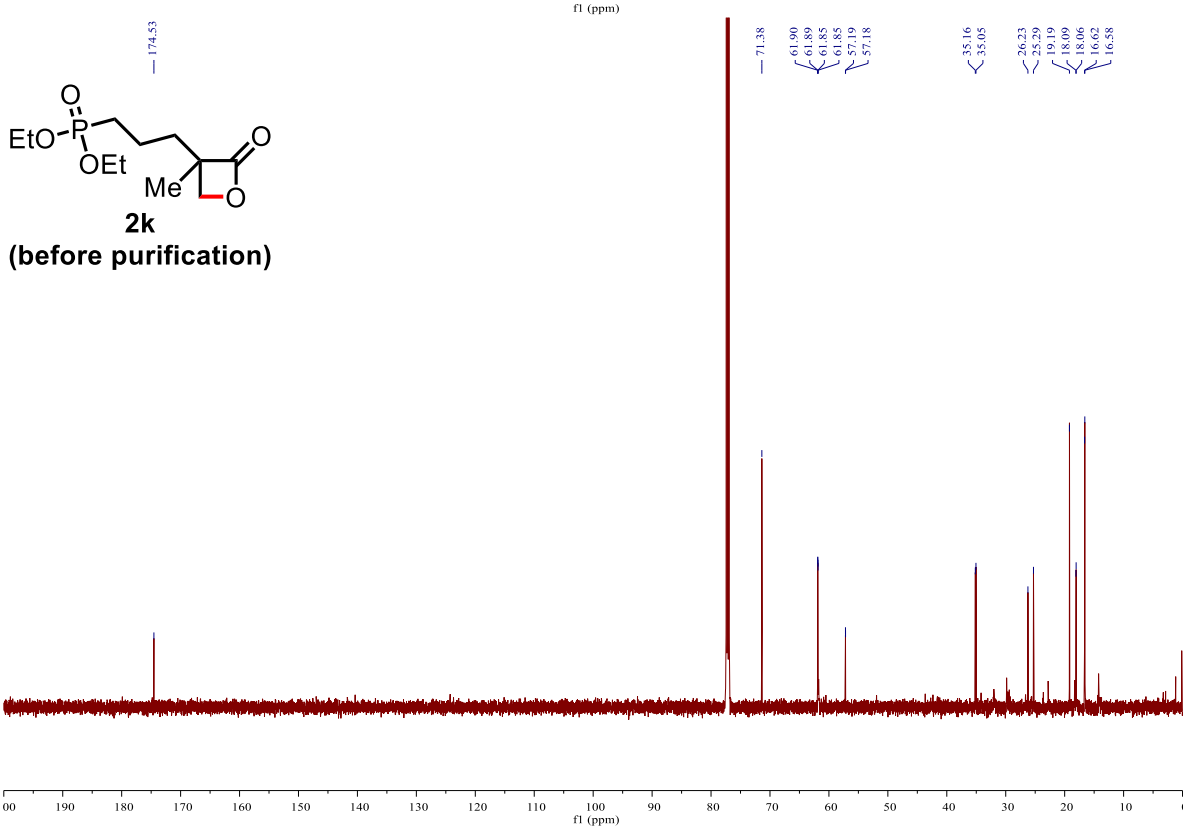
2j
(before purification)



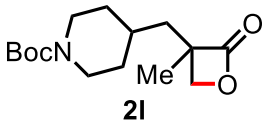
2k
(before purification)



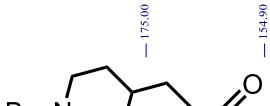




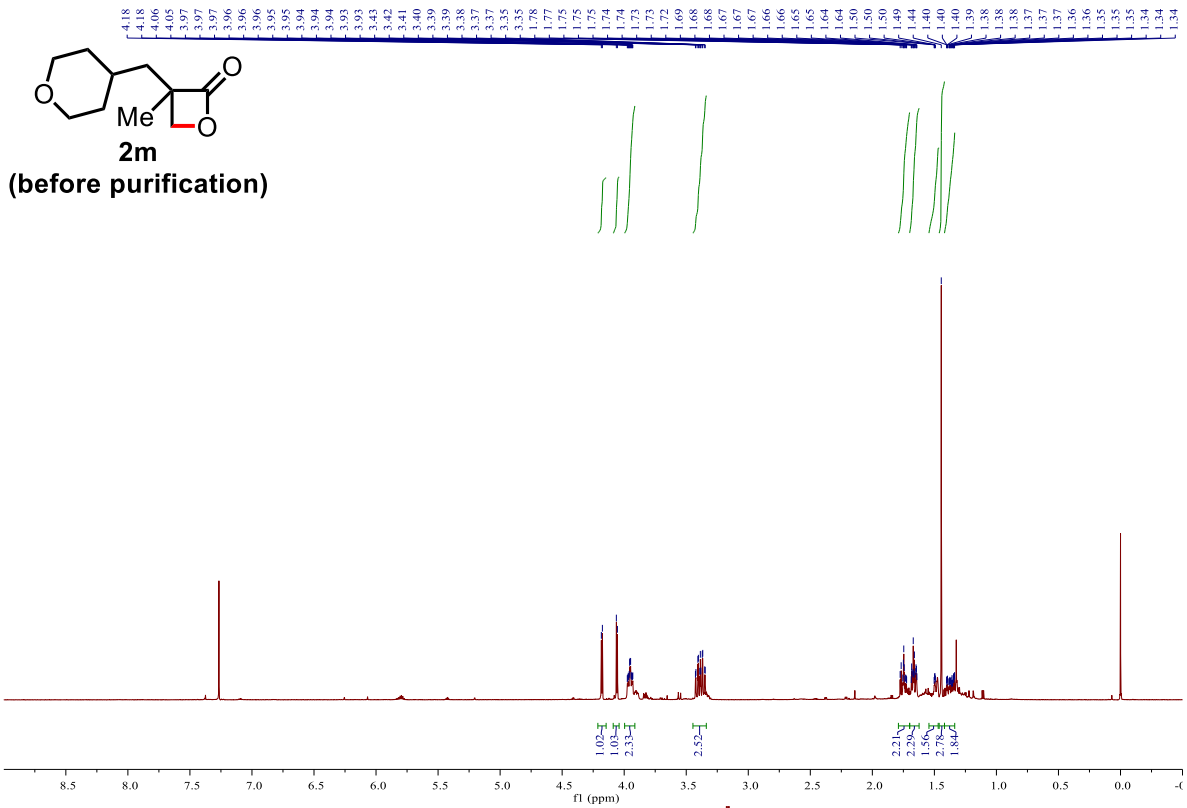
2k
(before purification)

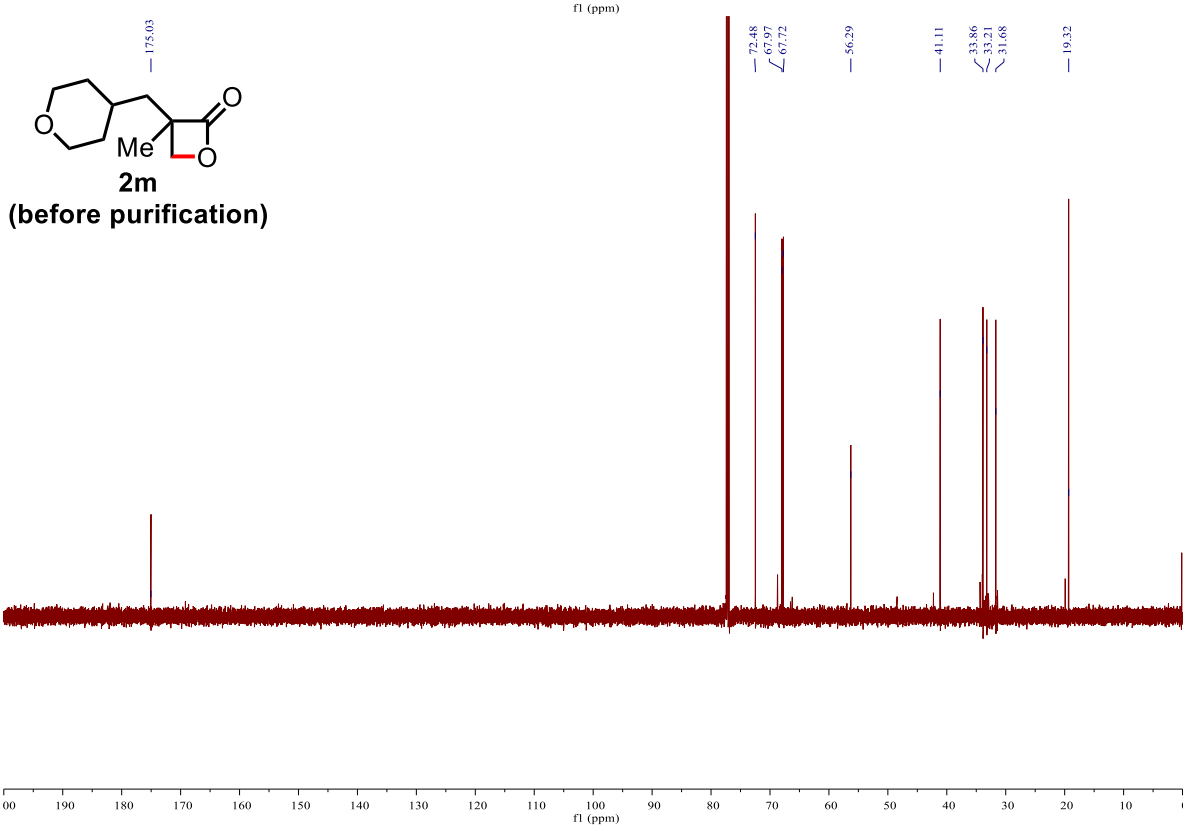


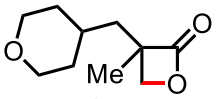
2l
(before purification)



2l
(before purification)

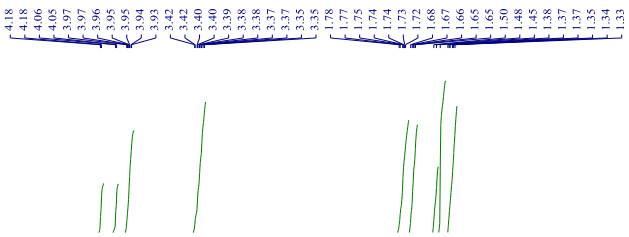

Me
2m
(before purification)
1.02
1.03
2.33
2.52
2.21
2.29
1.56
2.78
1.84
f1 (ppm)

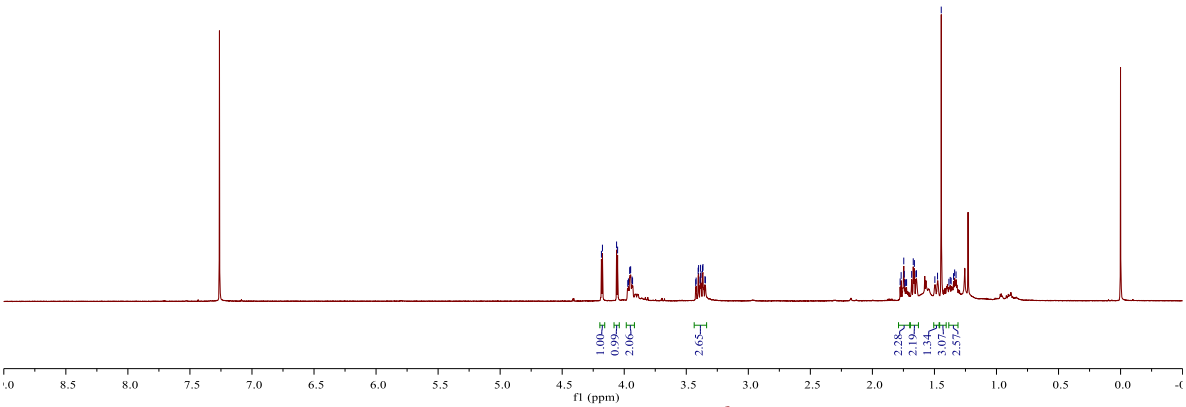

175.03
72.48
67.97
67.72
56.29
41.11
33.86
33.21
31.68
19.32
Me
2m
(before purification)
f1 (ppm)

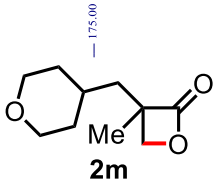


2m

(filter through silica gel)

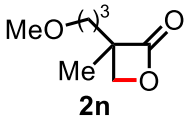




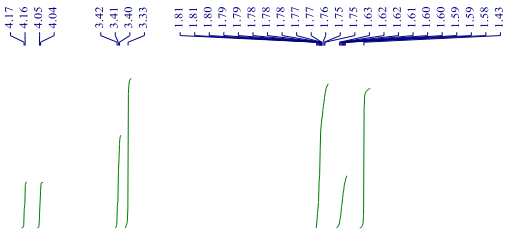


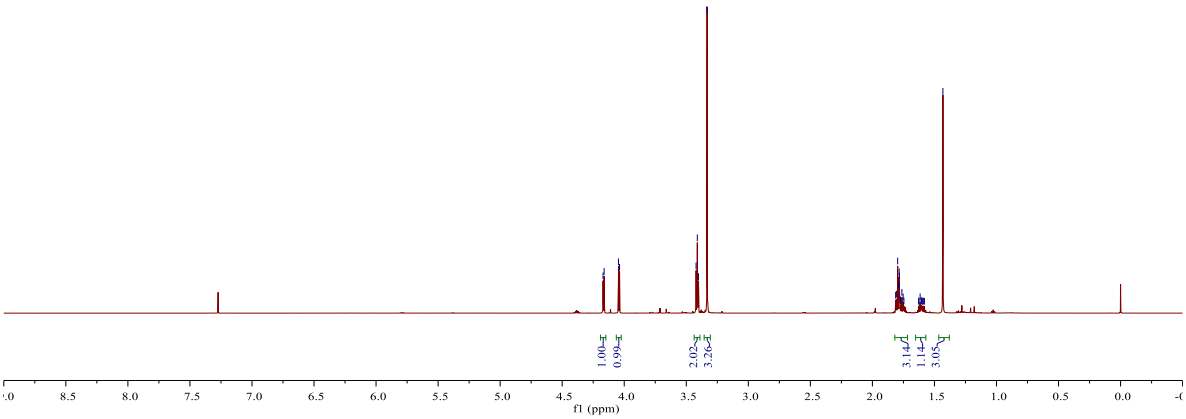
2m

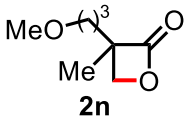
(filter through silica gel)



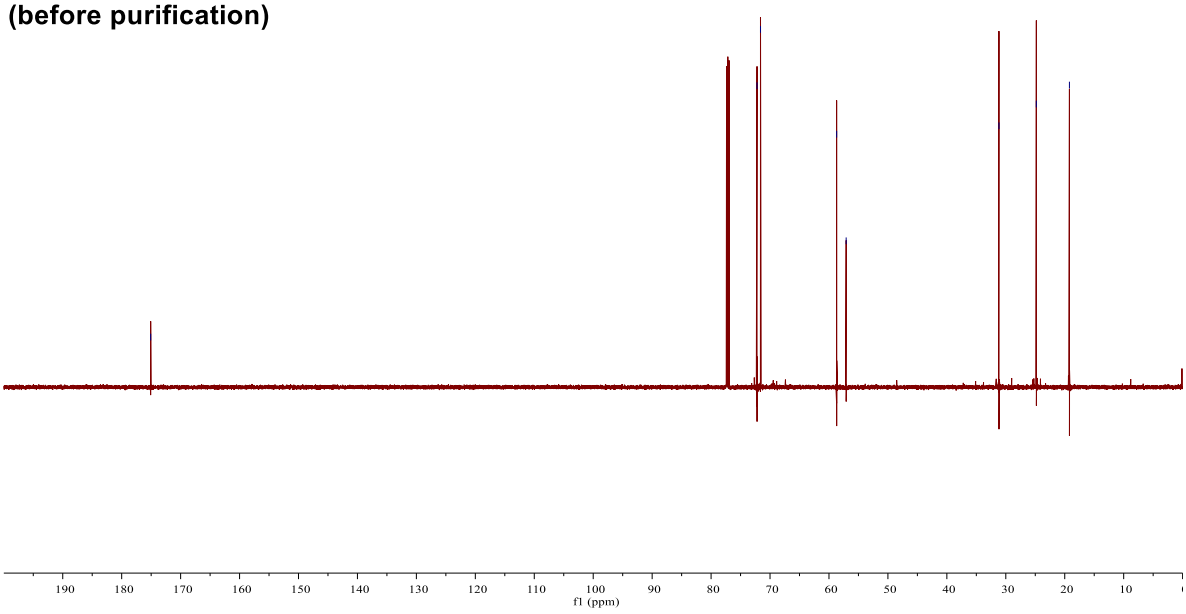
2n
(before purification)

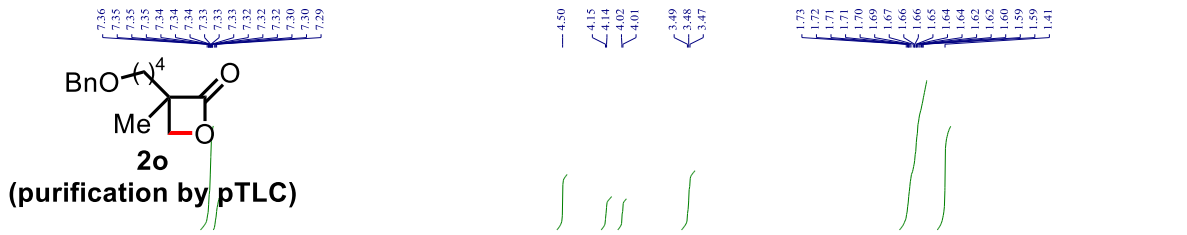


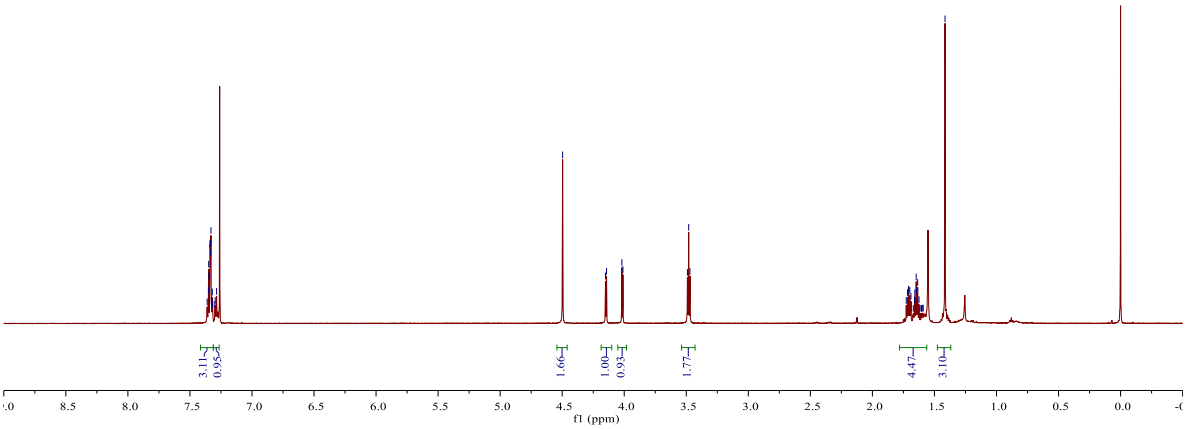


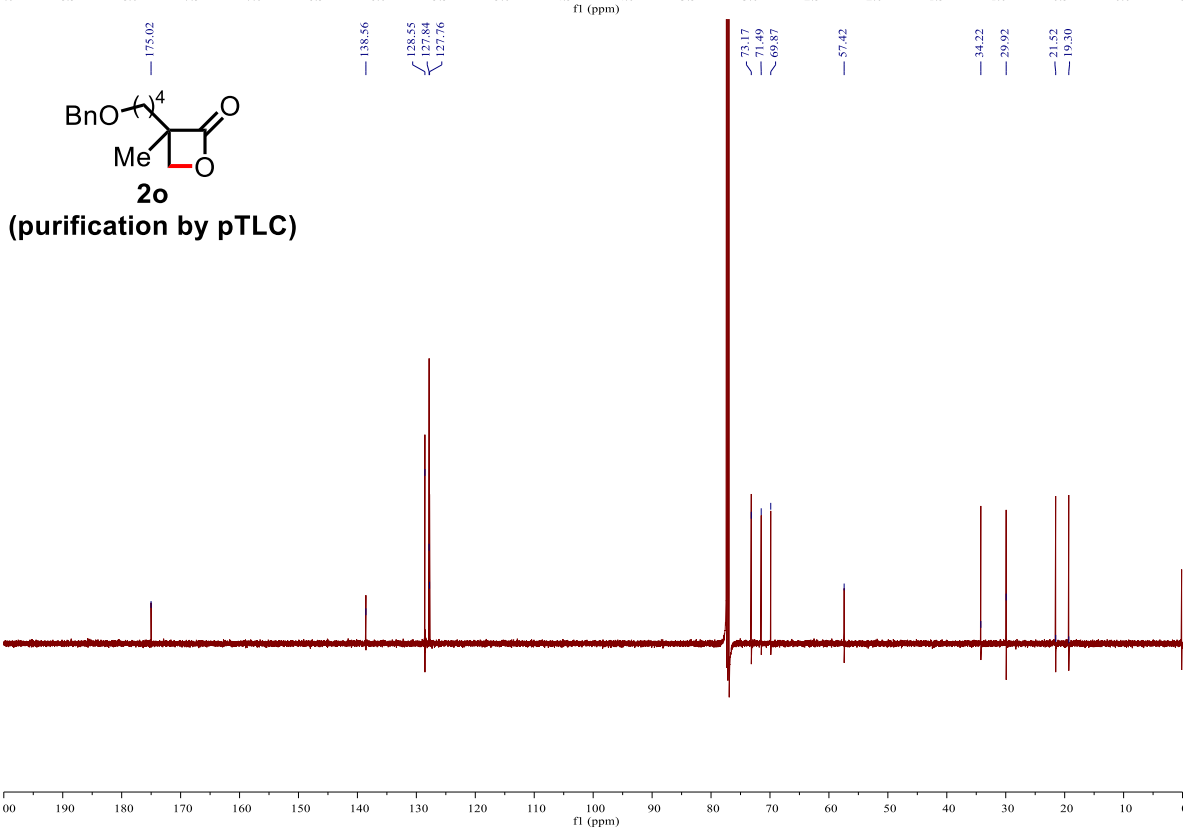


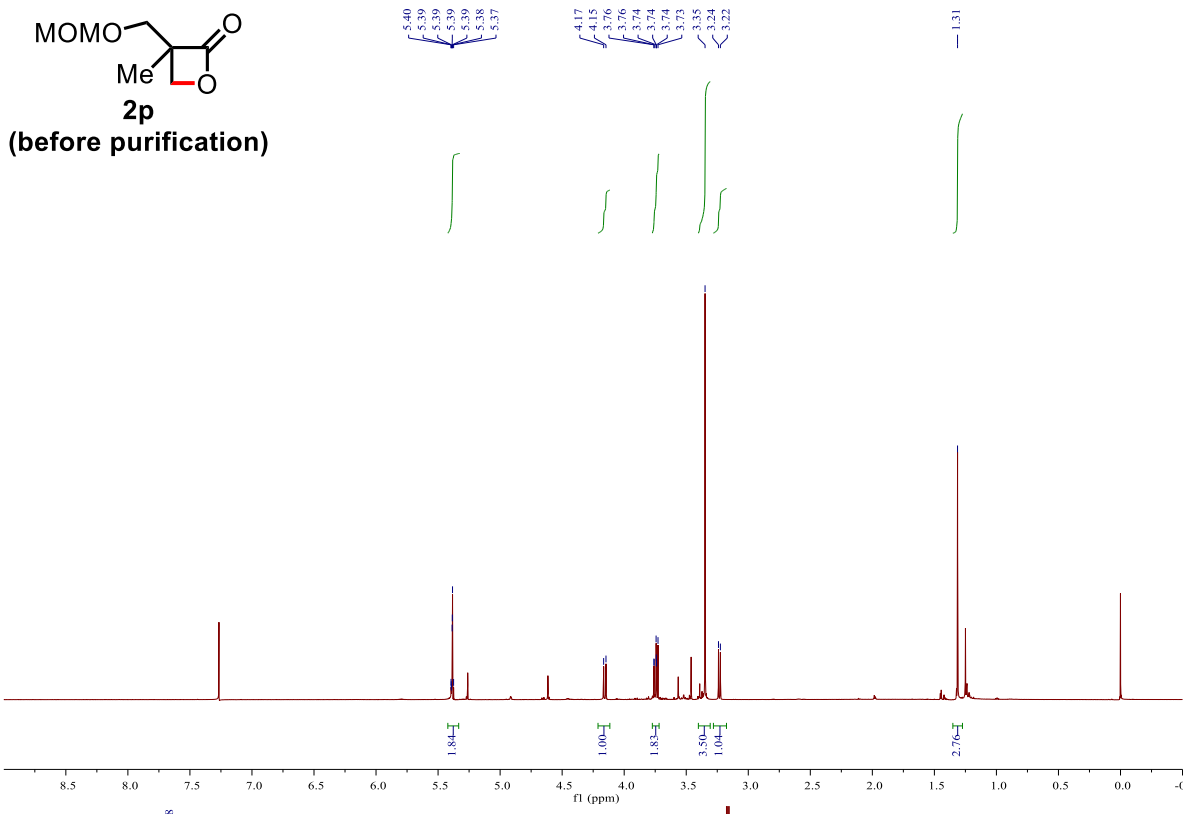
2n
(before purification)

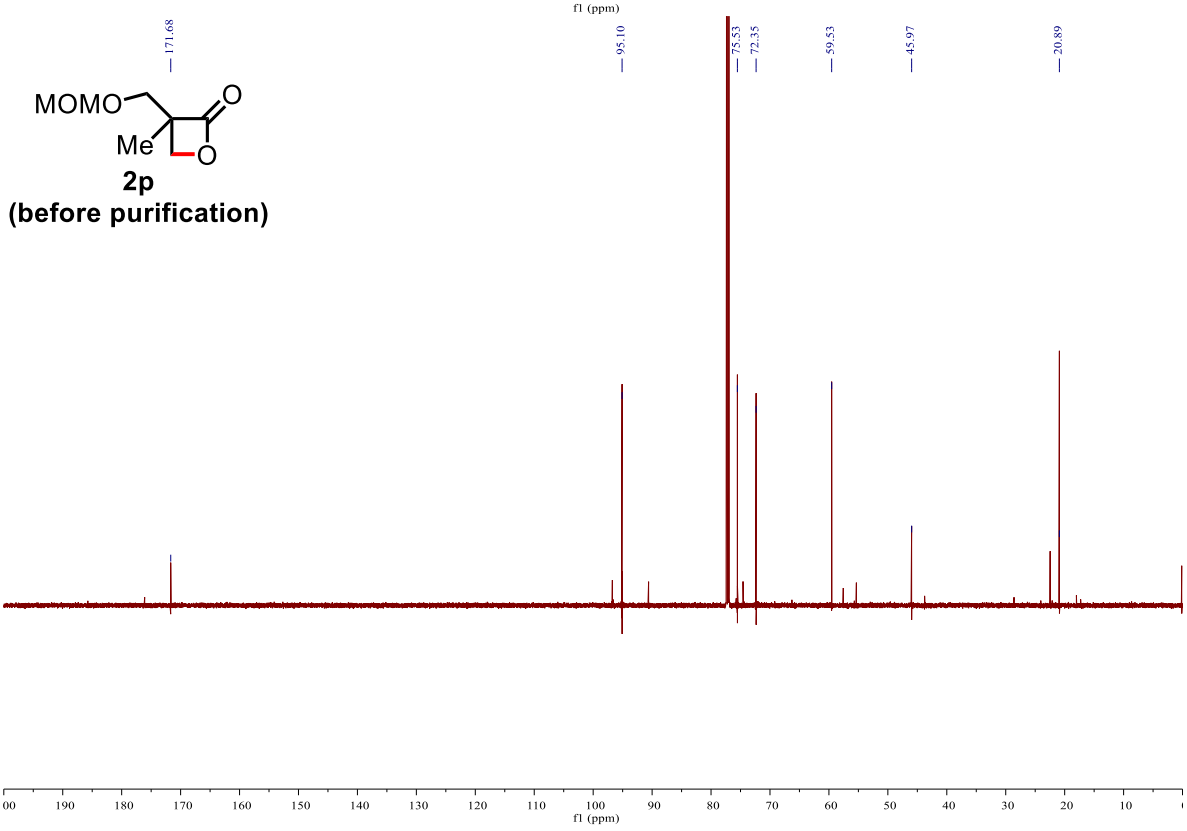


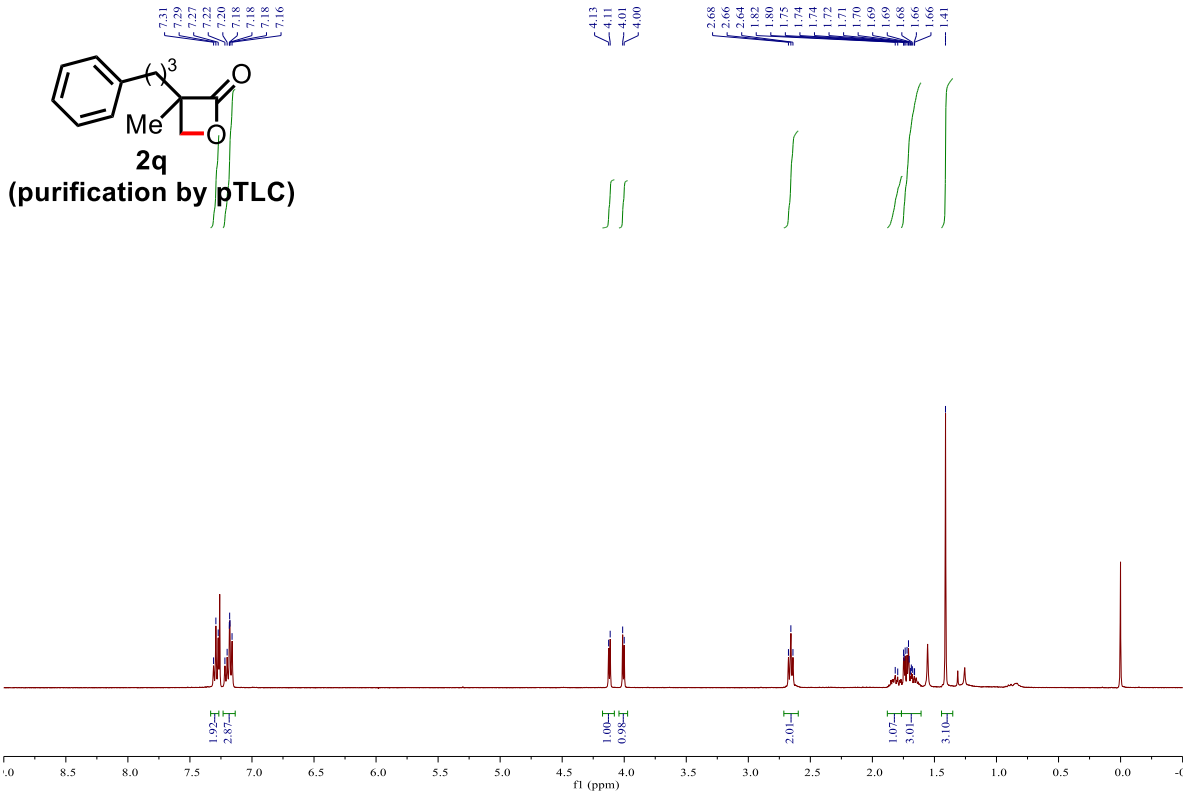

BnO
4
O
Me
O
2o
(purification by pTLC)

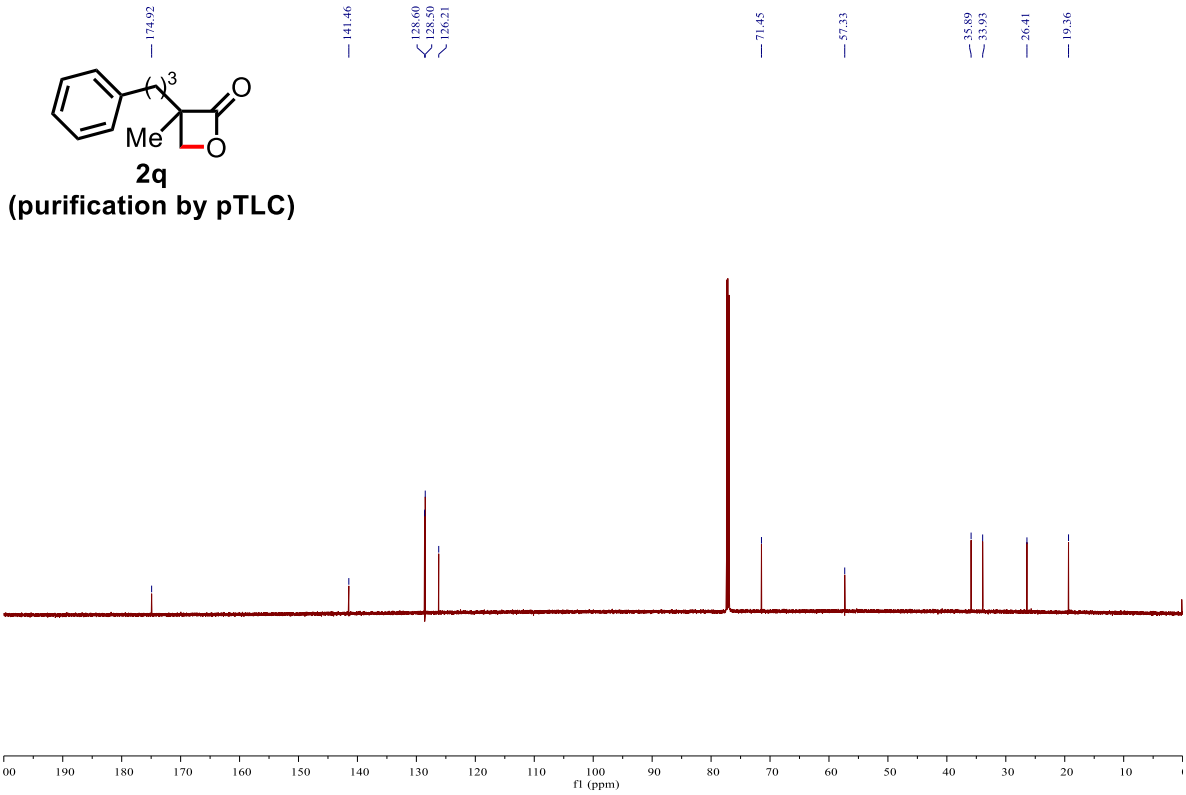

f1 (ppm)

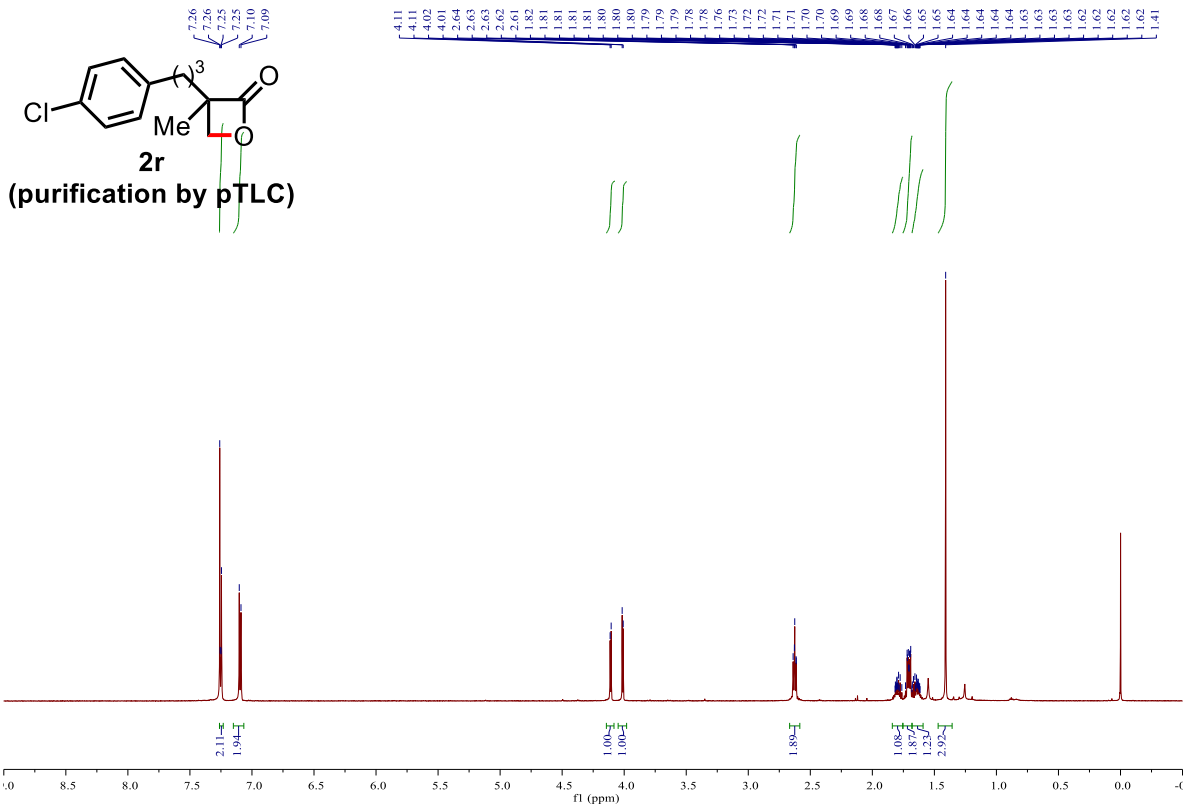

BnO
4
O
Me
O
2o
(purification by pTLC)
f1 (ppm)

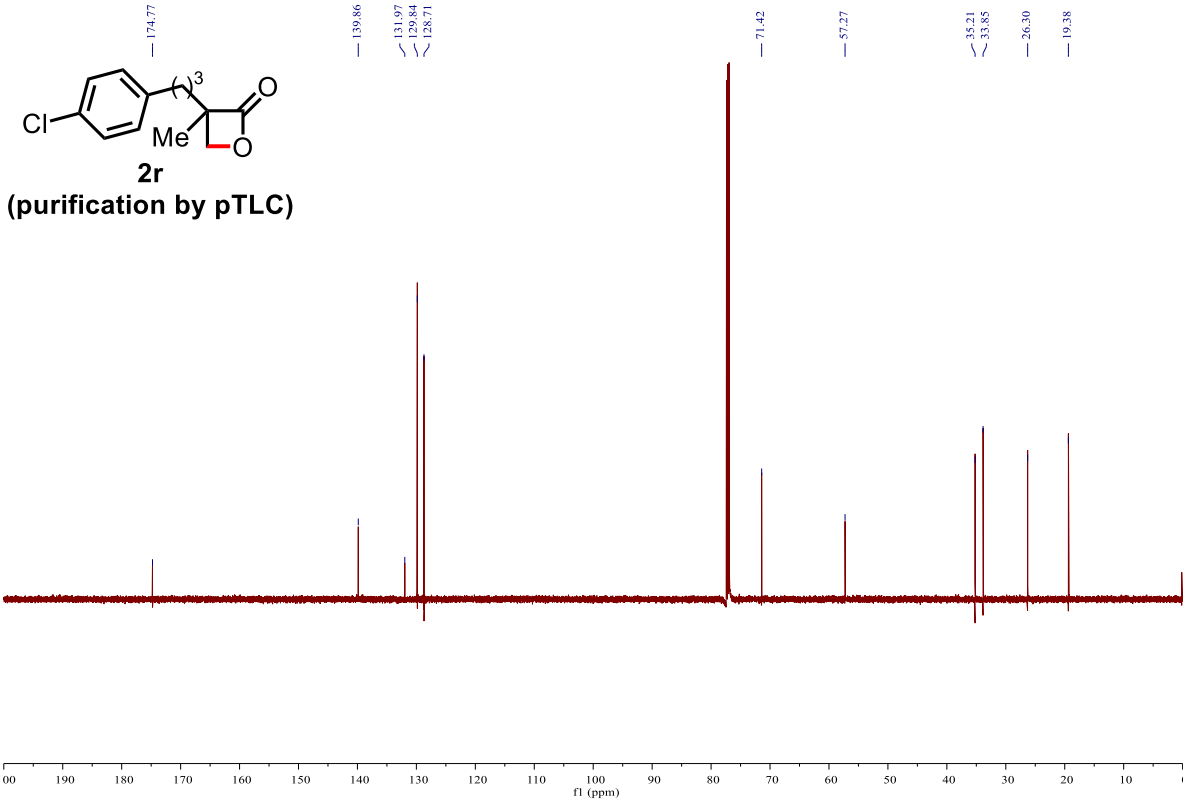

MOMO
Me
O
O
2p
(before purification)
5.40
5.39
5.39
5.39
5.39
5.38
5.37
4.17
4.15
3.76
3.76
3.74
3.74
3.74
3.73
3.35
3.24
3.22
1.31
1.84
1.00
1.83
3.50
1.04
2.76
f1 (ppm)

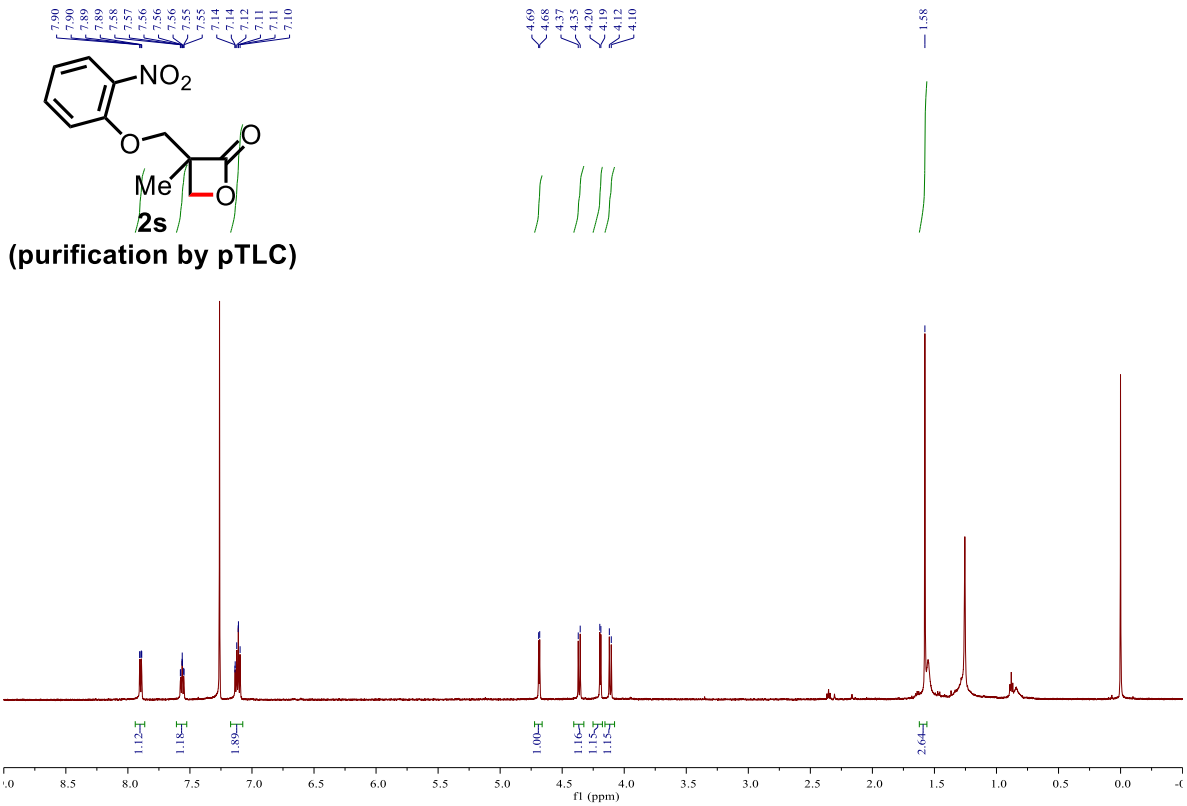

MOMO
Me
O
O
2p
(before purification)
171.68
95.10
75.53
72.35
59.53
45.97
20.89
f1 (ppm)

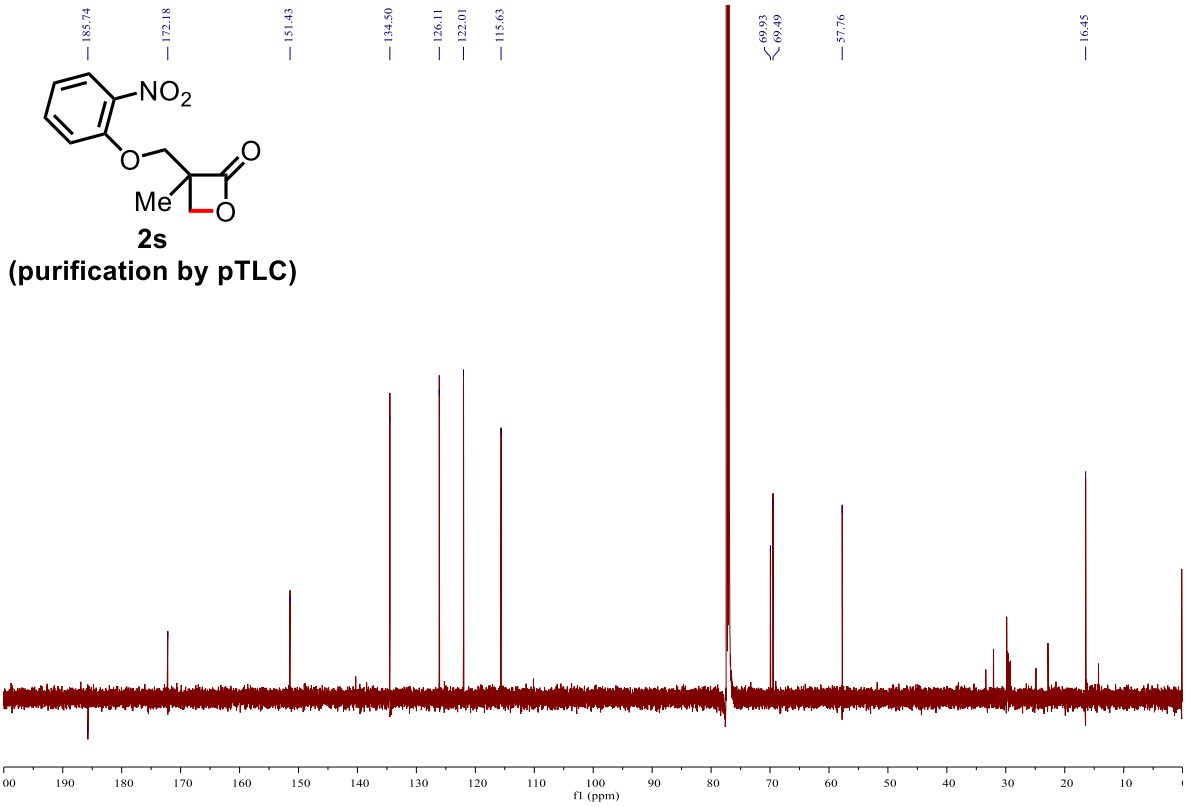

7.31
7.29
7.27
7.22
7.20
7.18
7.18
7.18
7.16
4.13
4.11
4.01
4.00
2.68
2.66
2.64
1.82
1.80
1.75
1.74
1.74
1.72
1.71
1.70
1.69
1.69
1.68
1.66
1.66
1.41
Me
2q
(purification by pTLC)
1.92
2.87
1.00
0.98
2.01
1.07
3.01
3.10
f1 (ppm)

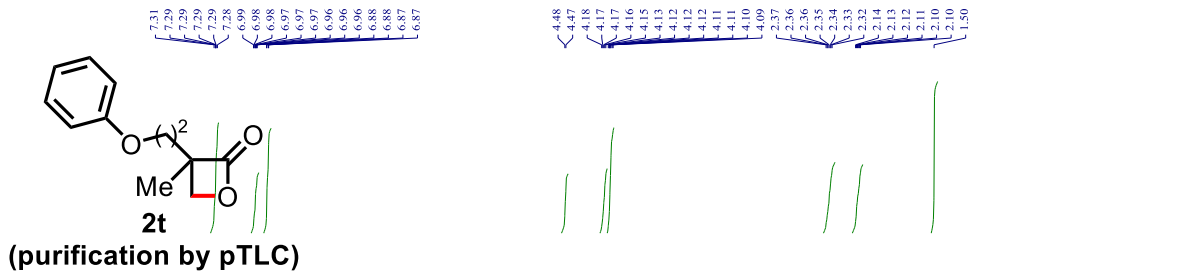

174.92
141.46
128.60
128.50
126.21
71.45
57.33
35.89
33.93
26.41
19.36
Me
2q
(purification by pTLC)
f1 (ppm)

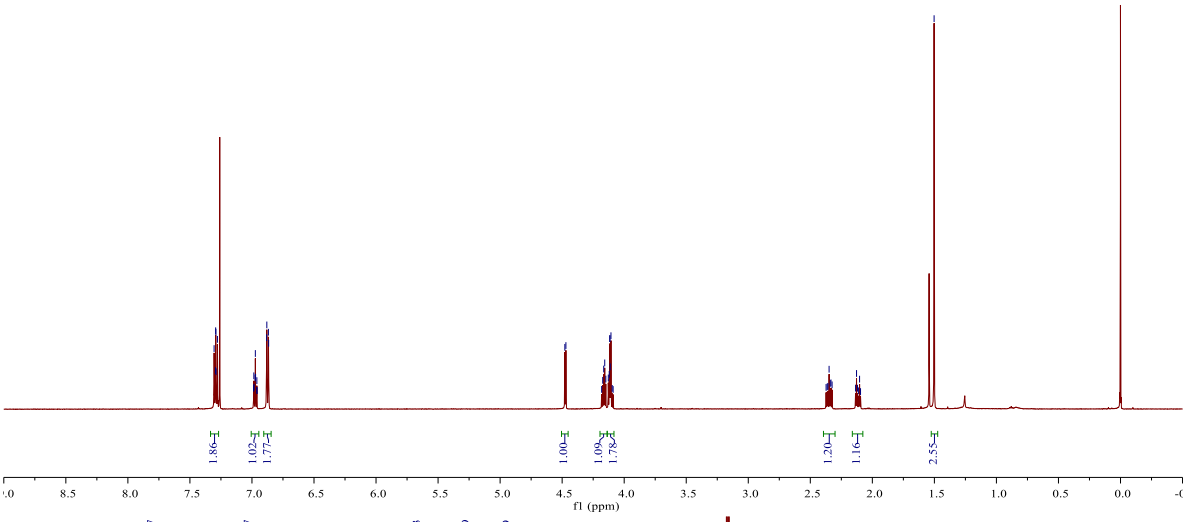

Cl
Me
O
O
3
2r
(purification by pTLC)
f1 (ppm)

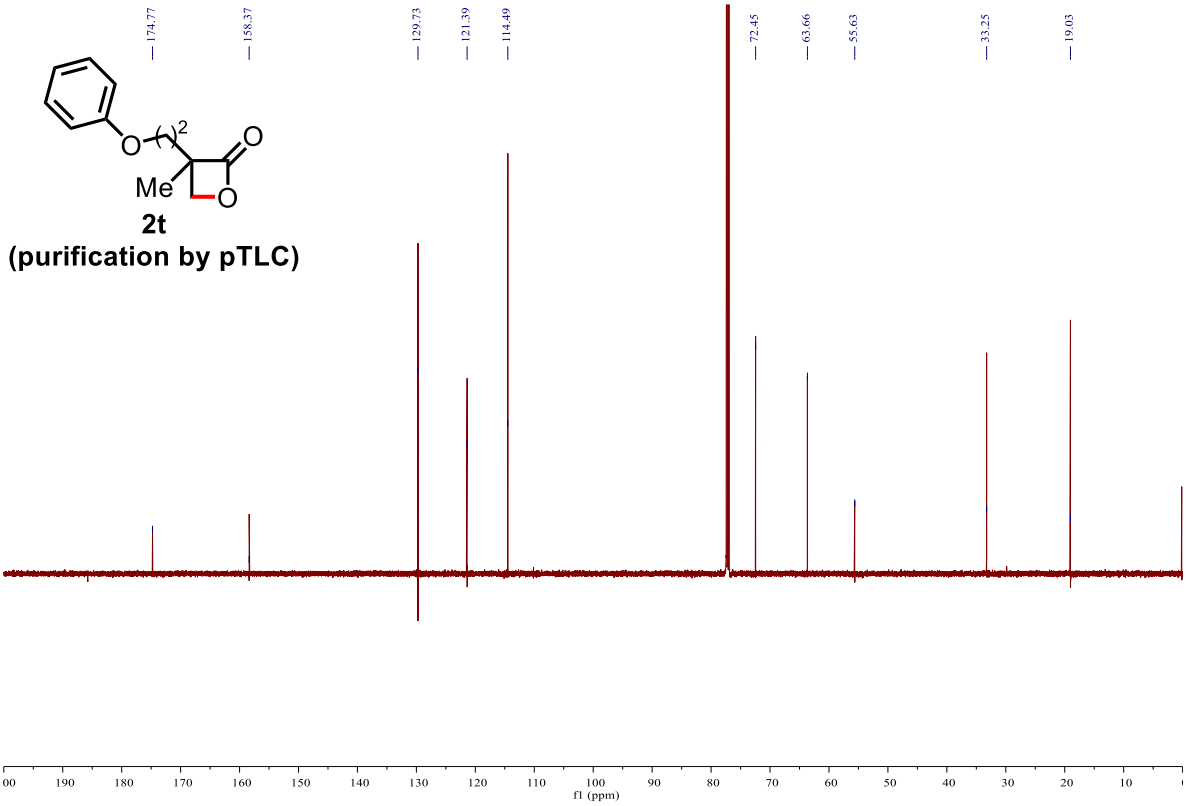

Cl
Me
O
O
3
2r
(purification by pTLC)
f1 (ppm)

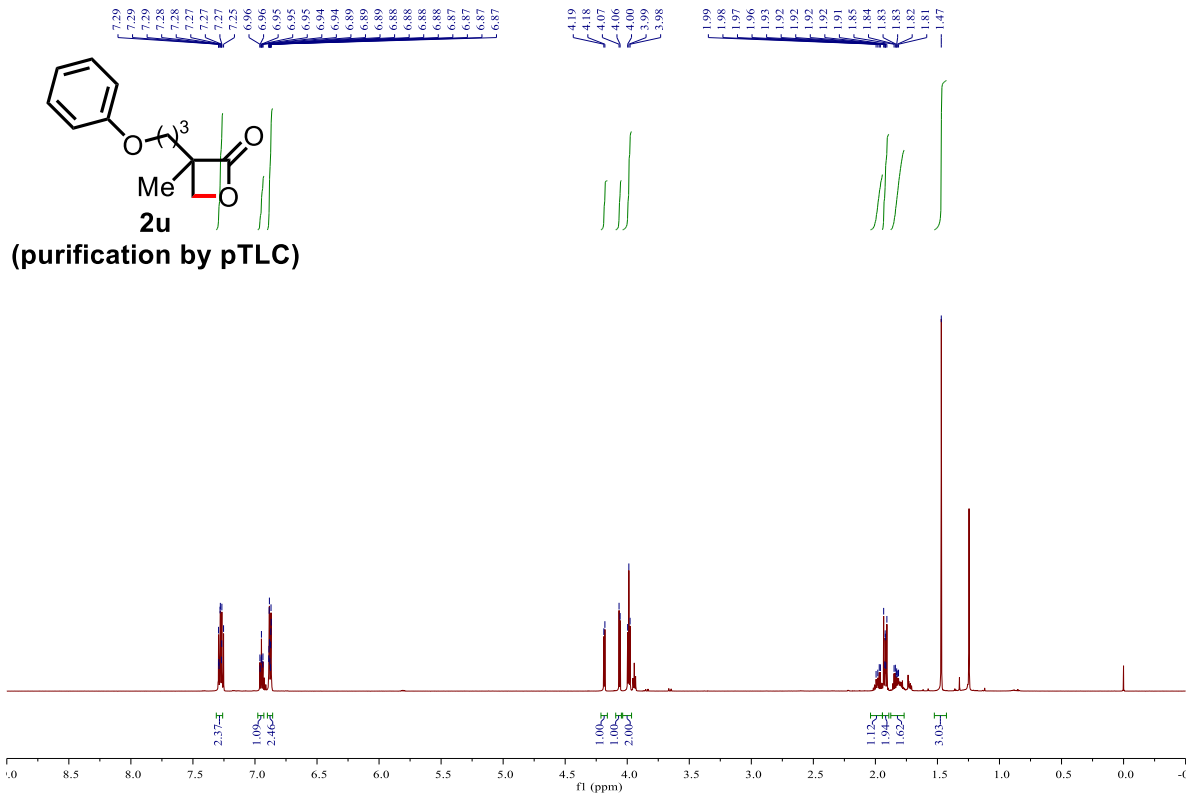

7.90
7.90
7.89
7.89
7.58
7.57
7.56
7.56
7.56
7.55
7.55
7.14
7.14
7.12
7.11
7.11
7.10
4.69
4.68
4.37
4.35
4.20
4.19
4.12
4.10
1.58
NO2
O
O
Me
O
2s
(purification by pTLC)
1.12
1.18
1.89
1.00
1.16
1.15
1.15
2.64
f1 (ppm)

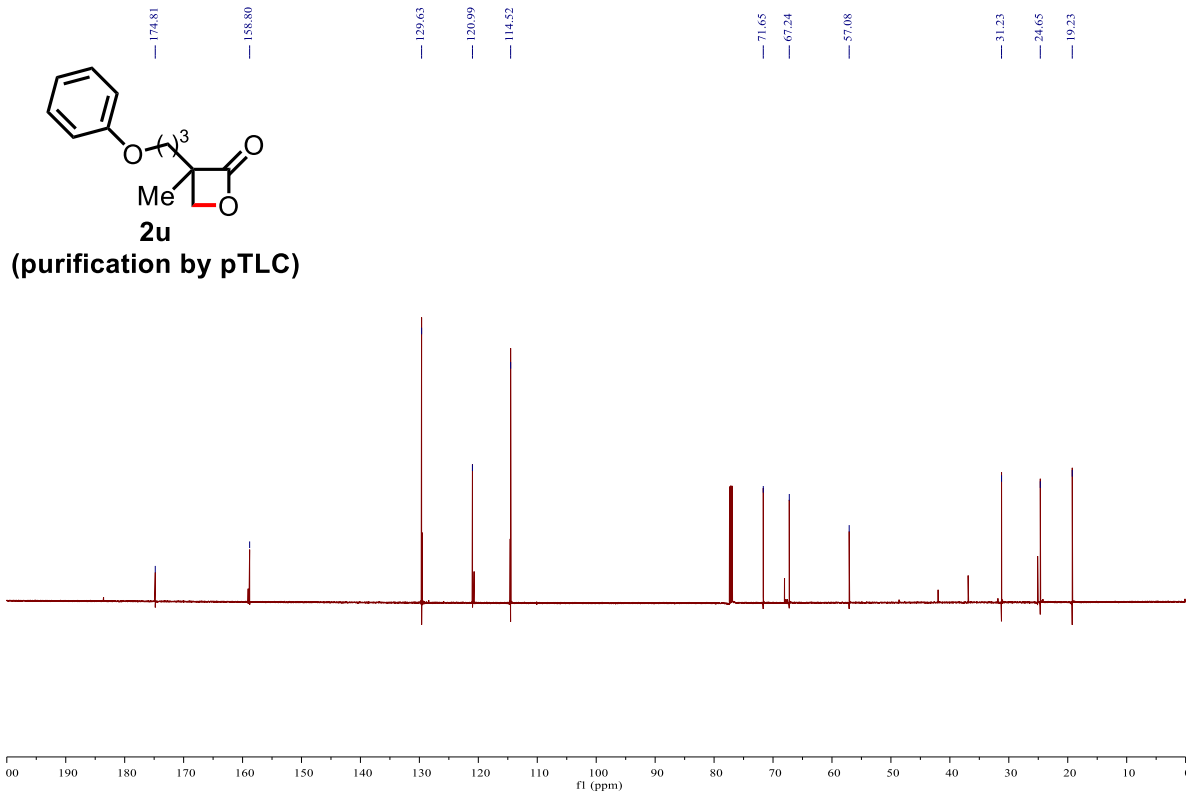

185.74
172.18
151.43
134.50
126.11
122.01
115.63
69.93
69.49
57.76
16.45
NO2
O
O
Me
O
2s
(purification by pTLC)
f1 (ppm)

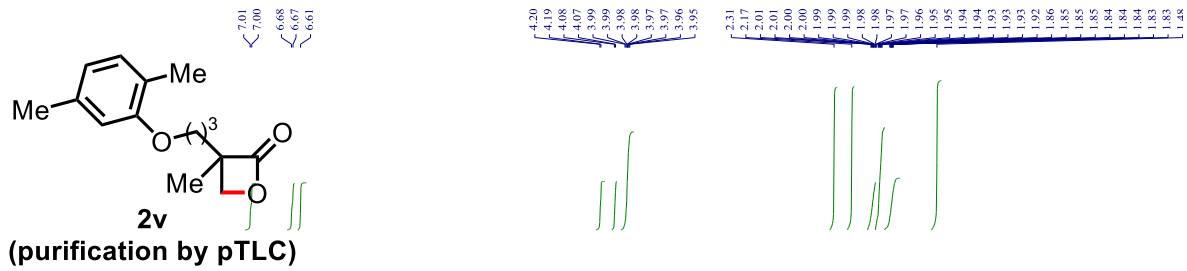

Me
2t
(purification by pTLC)


f1 (ppm)

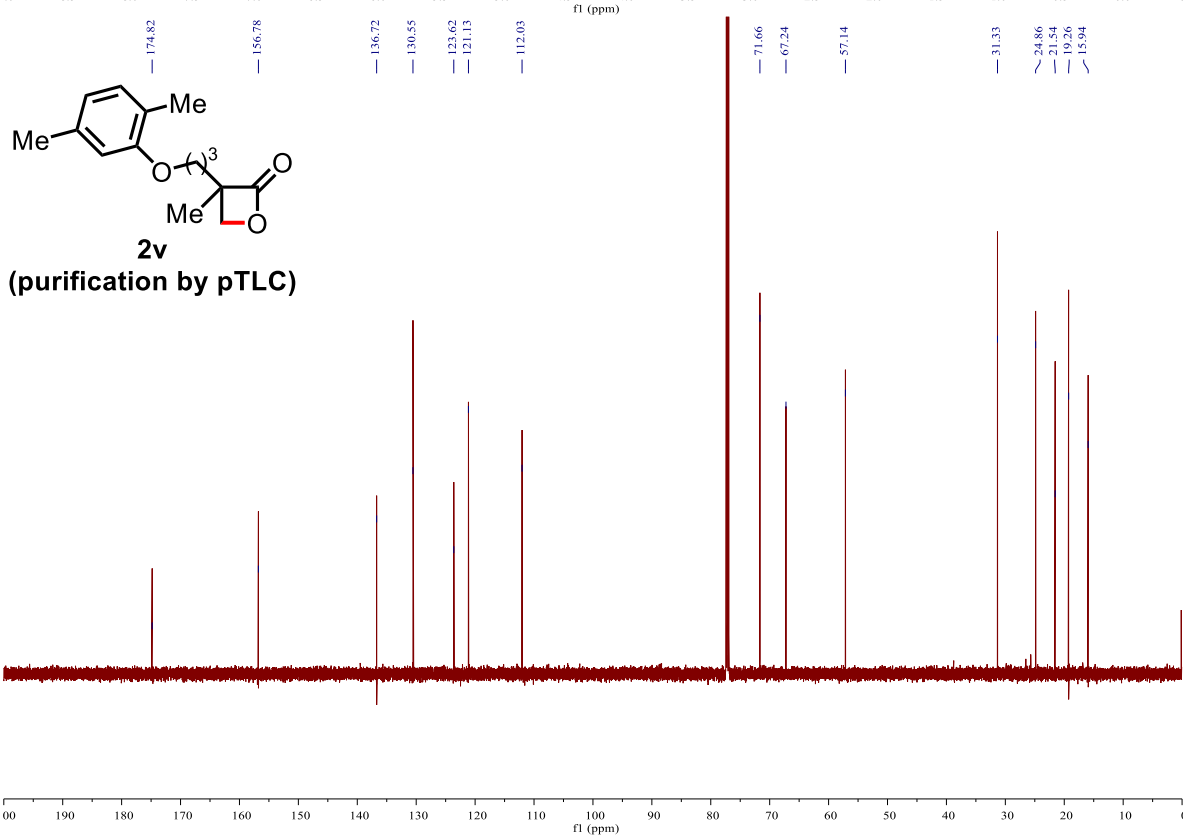

Me
2t
(purification by pTLC)
f1 (ppm)


7.29 7.29 7.29 7.28 7.28 7.27 7.27 7.27 7.25 6.96 6.96 6.95 6.95 6.95 6.94 6.94 6.89 6.89 6.89 6.88 6.88 6.88 6.88 6.87 6.87 6.87 6.87
4.19 4.18 4.07 4.06 4.00 3.99 3.98
1.99 1.98 1.97 1.96 1.93 1.92 1.92 1.92 1.91 1.85 1.84 1.83 1.83 1.82 1.81 1.47
O
3
O
Me
O
2u
(purification by pTLC)
2.37 1.09 2.46 1.00 1.00 2.00 1.12 1.94 1.62 3.03
f1 (ppm)

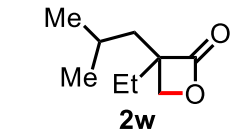

174.81 158.80 129.63 120.99 114.52 71.65 67.24 57.08 31.23 24.65 19.23
O
3
O
Me
O
2u
(purification by pTLC)
f1 (ppm)



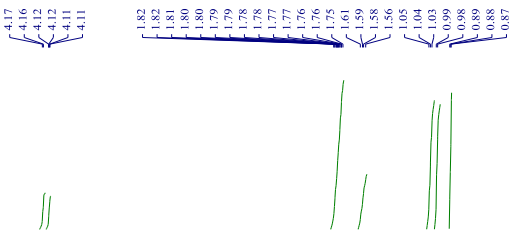
2v
(purification by pTLC)

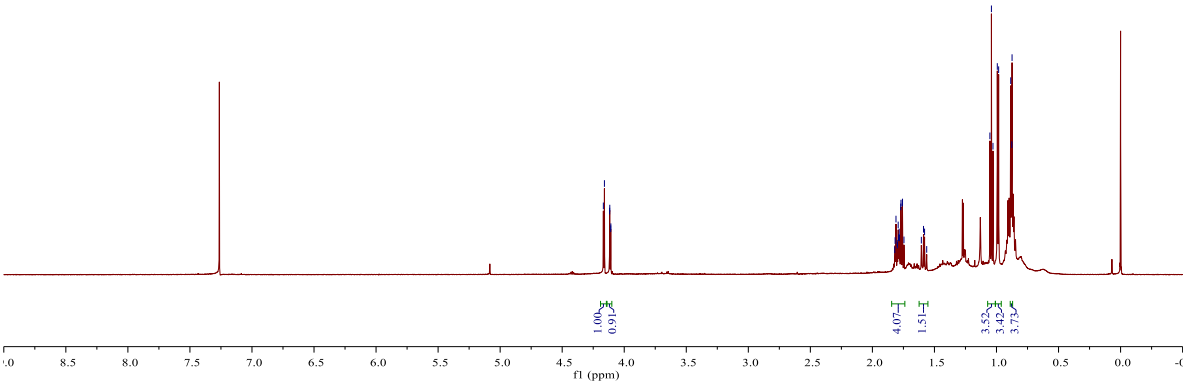


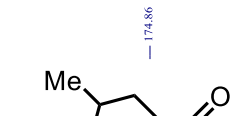
2v
(purification by pTLC)



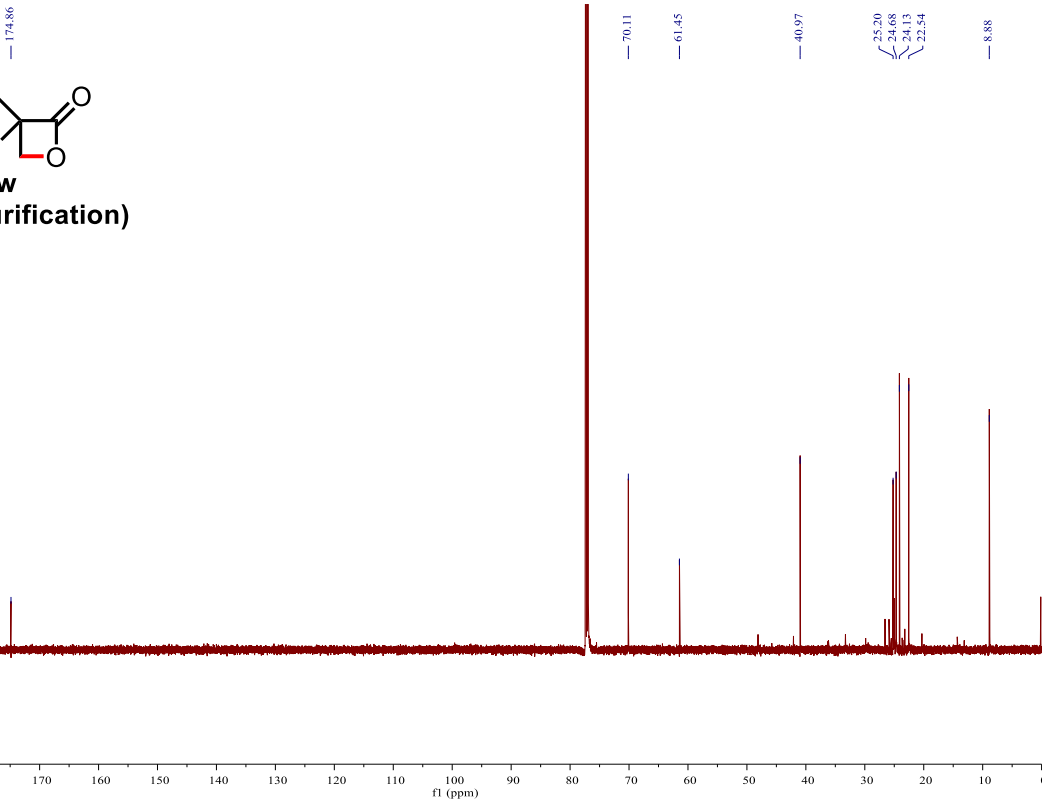
2w
(before purification)

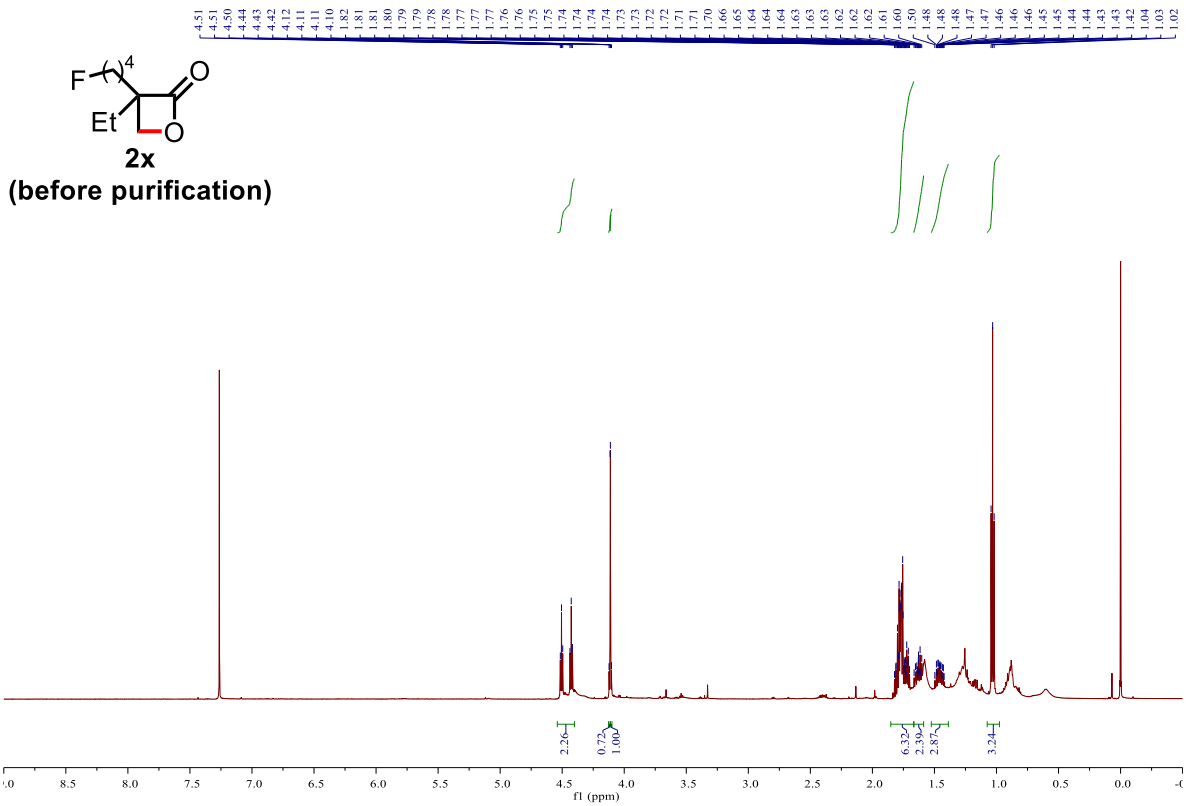


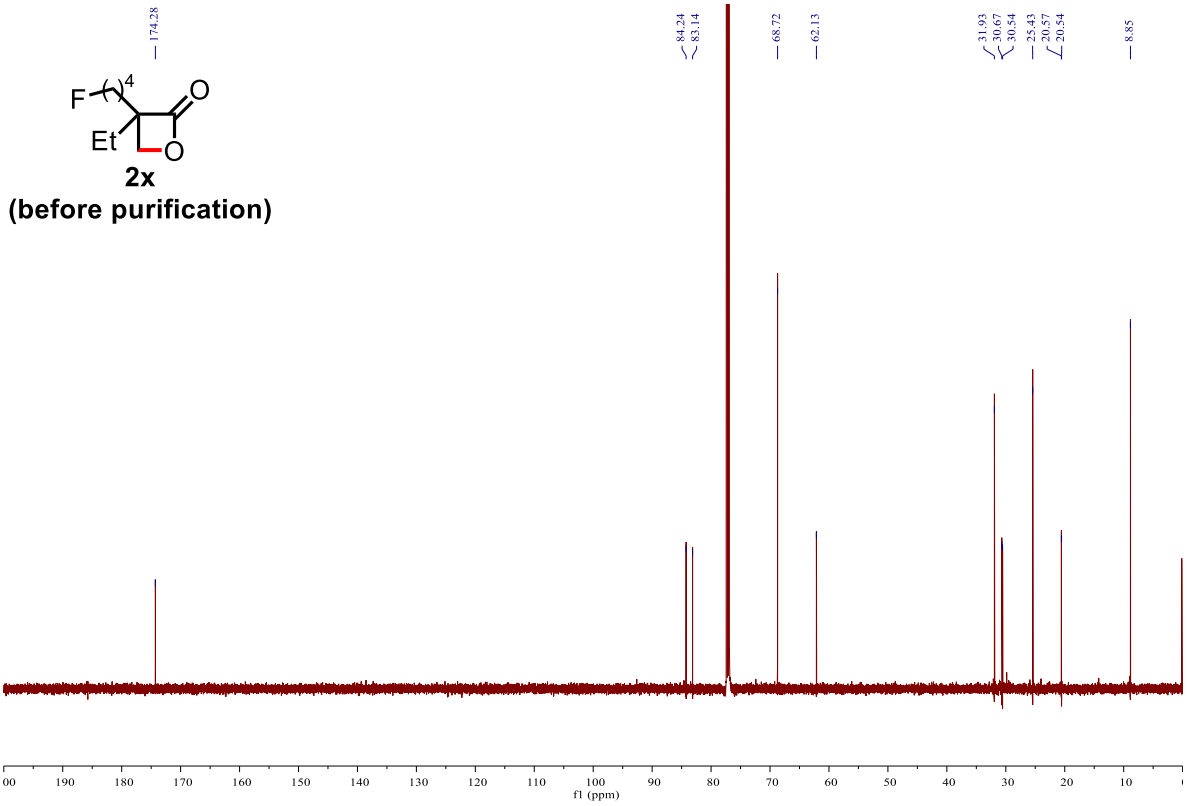


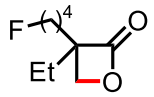


2w
(before purification)



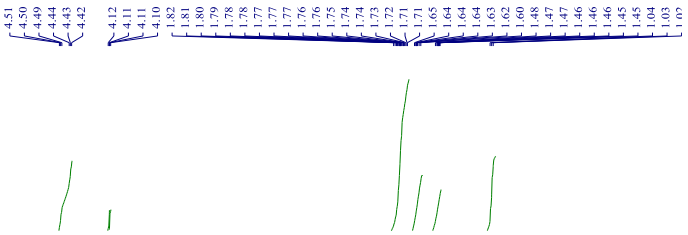

F
4
O
Et
O
2x
(before purification)
f1 (ppm)

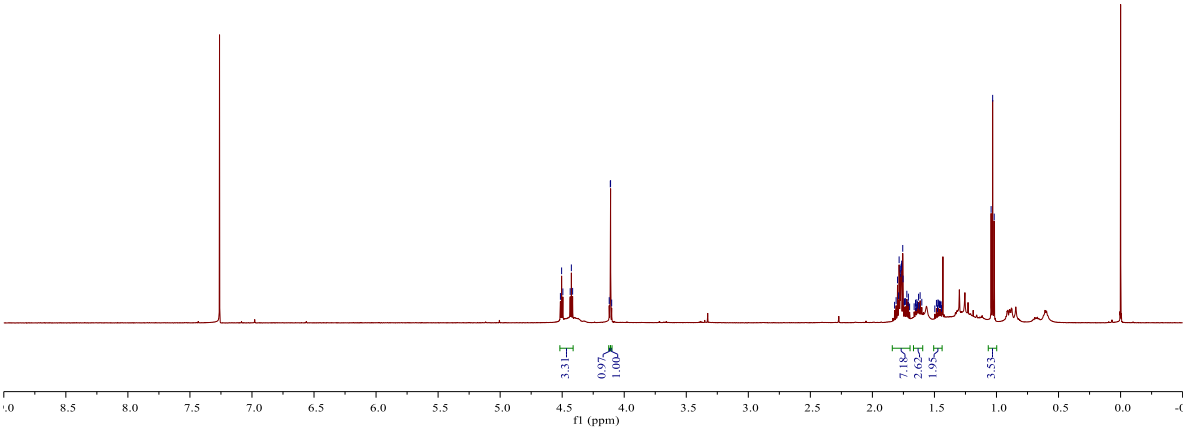

174.28
84.24
83.14
68.72
62.13
31.93
30.67
30.54
25.43
20.57
20.54
8.85
F
4
O
Et
O
2x
(before purification)
f1 (ppm)

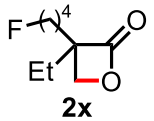


2x

(filter through silica gel)

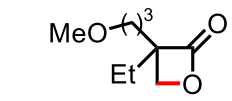




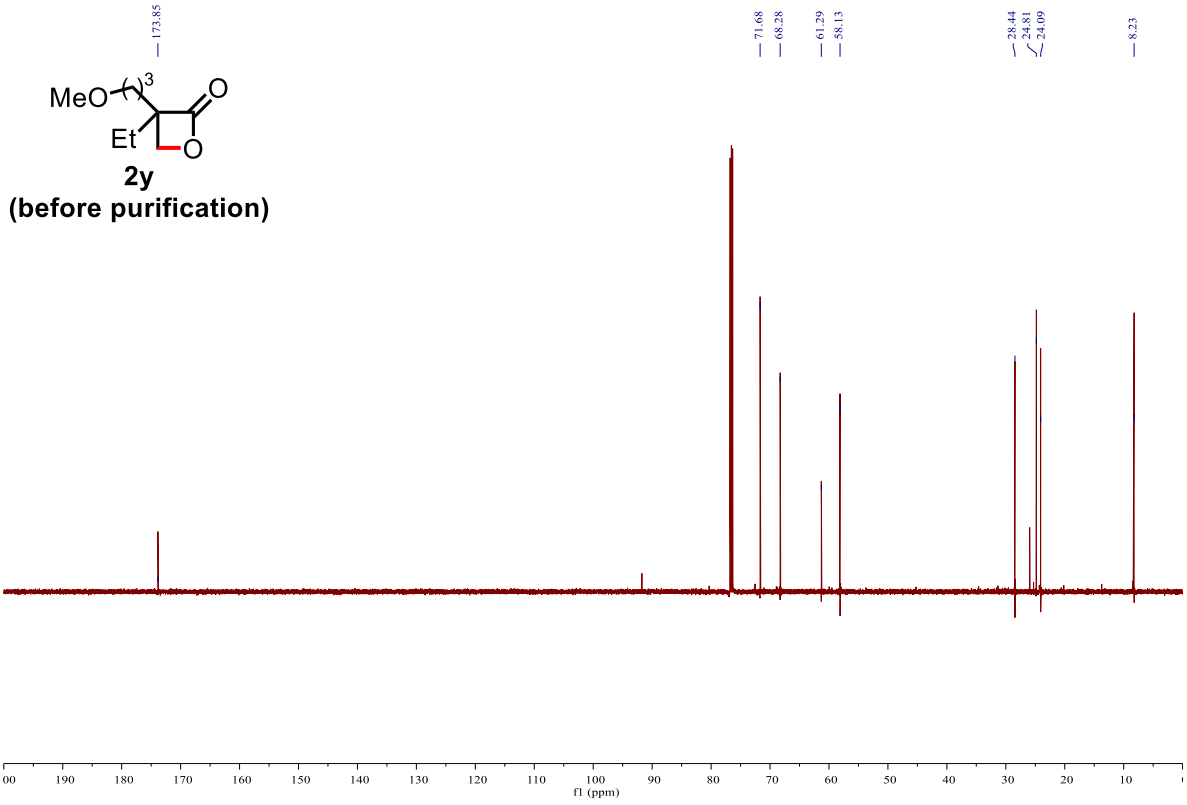


2x

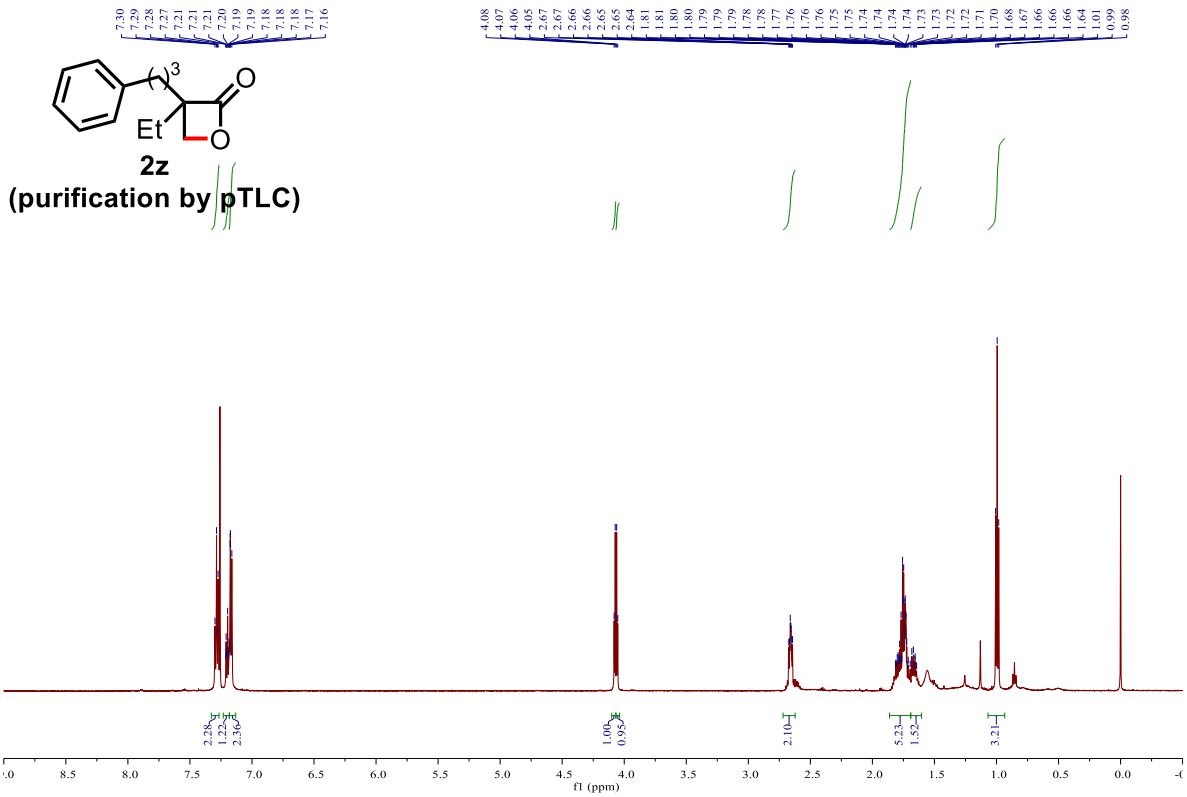
(filter through silica gel)

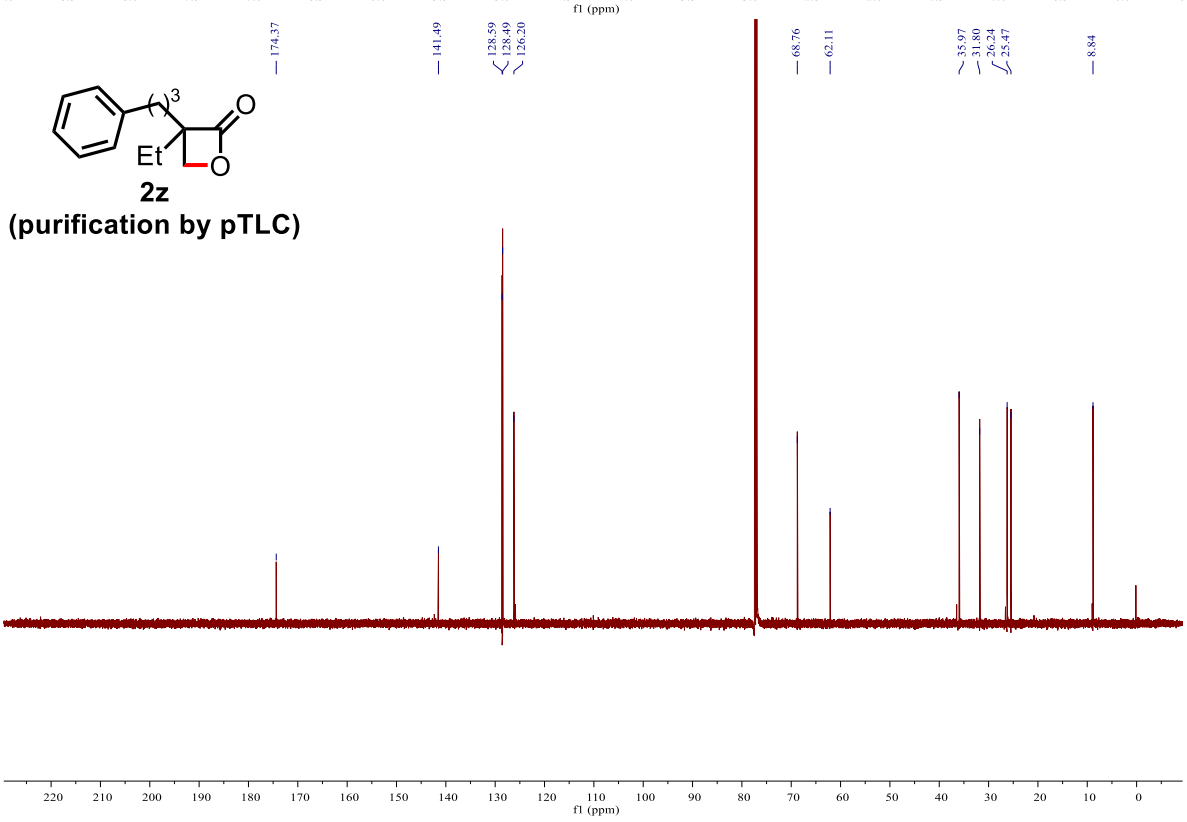


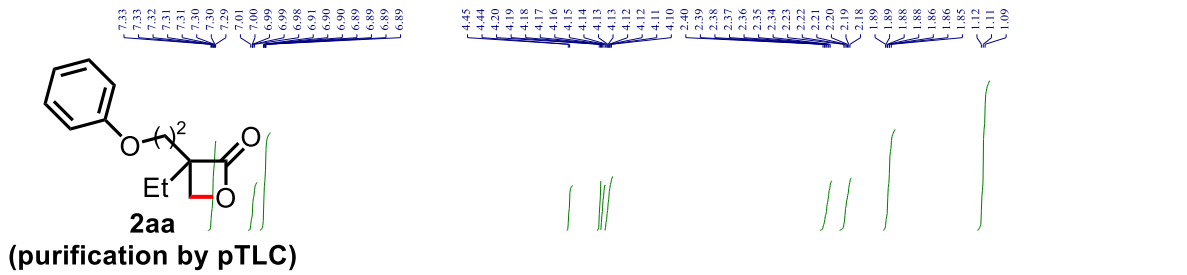
2y
(before purification)



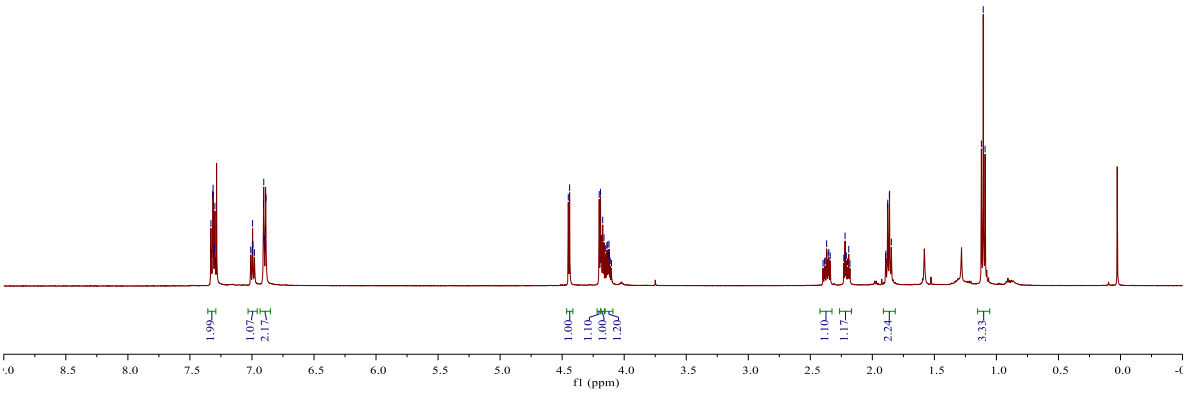
2y
(before purification)

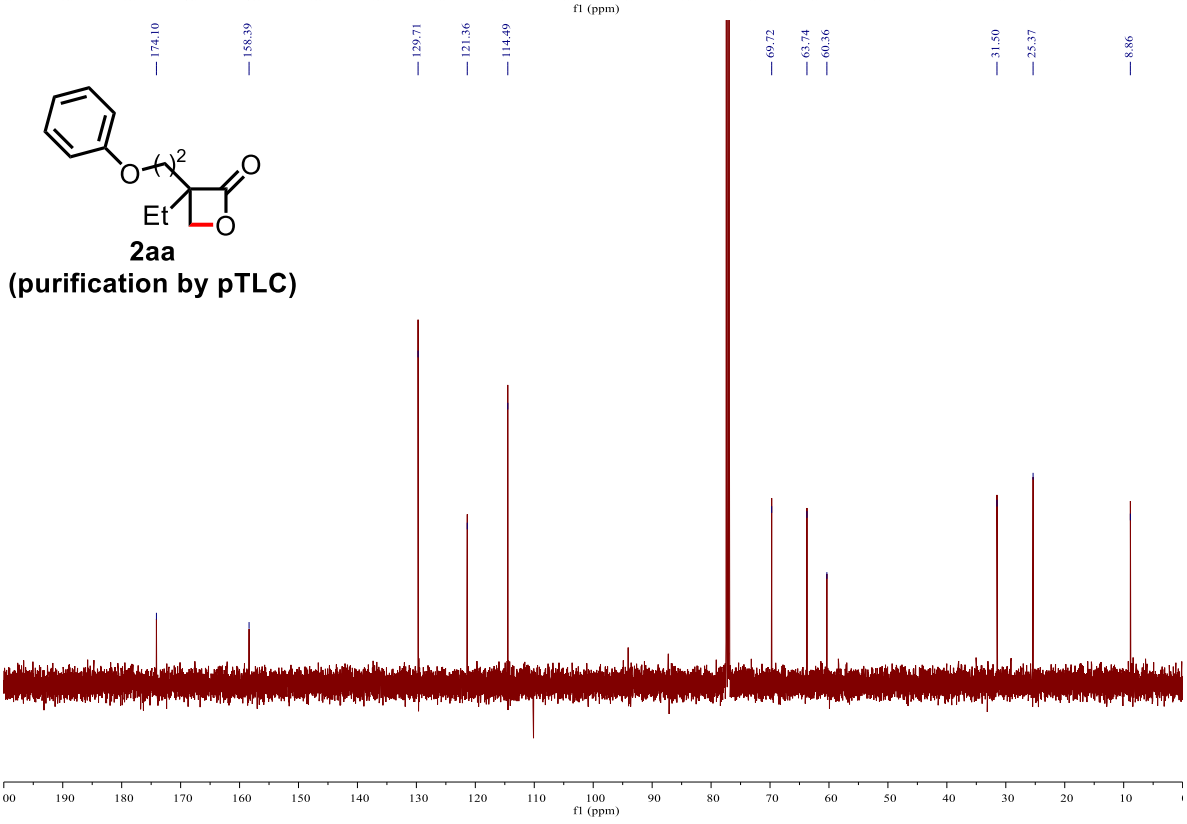

Et
O
O
2z
(purification by pTLC)
fl (ppm)


Et
O
O
2z
(purification by pTLC)
fl (ppm)

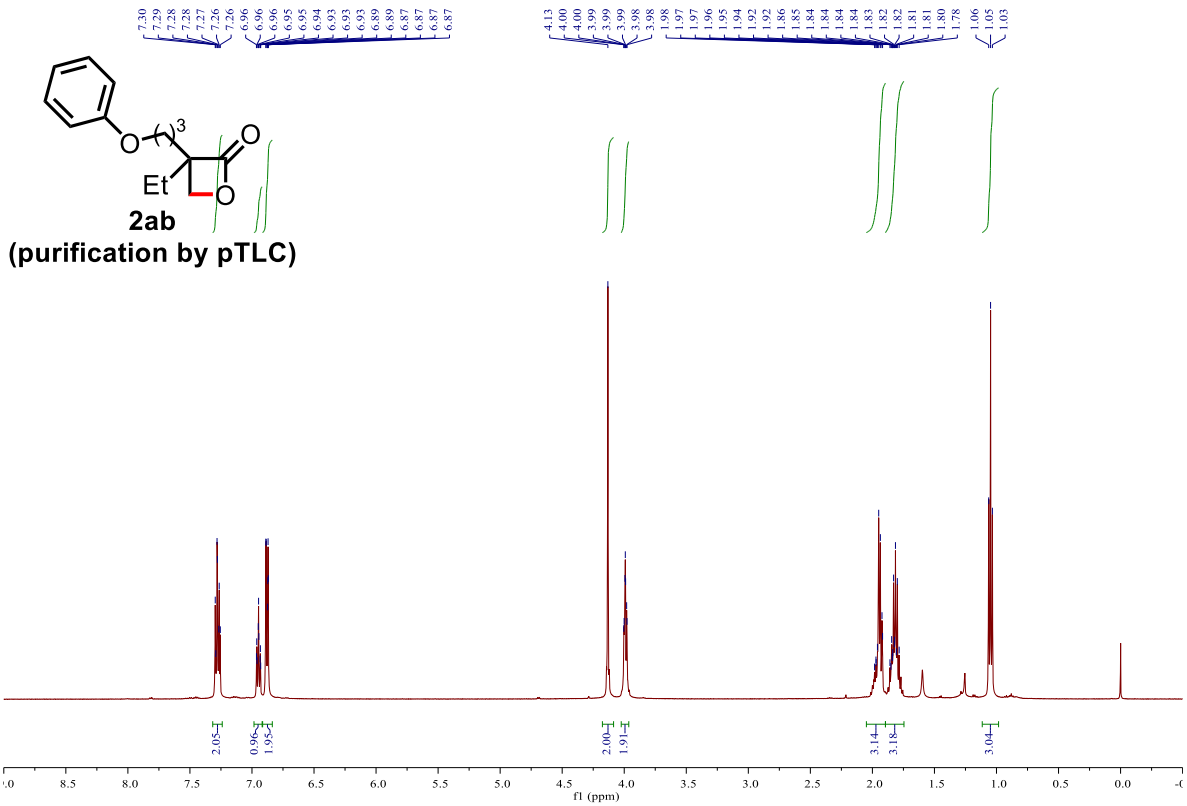


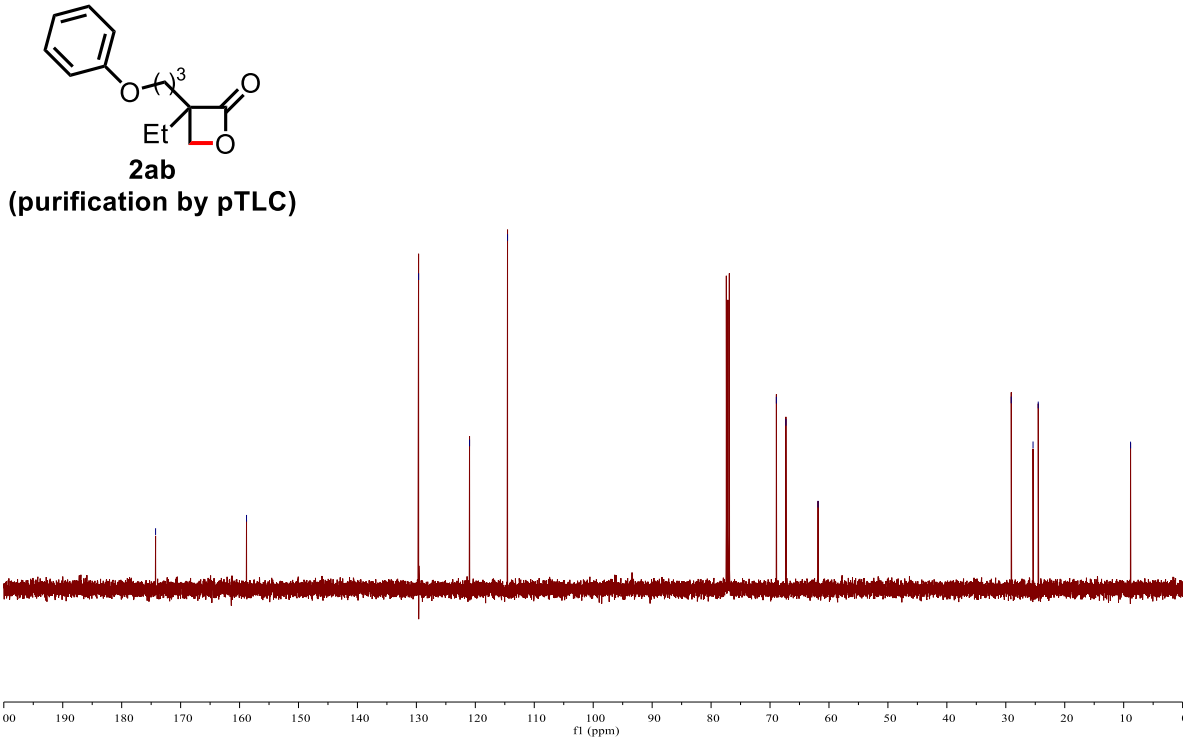
2aa
(purification by pTLC)

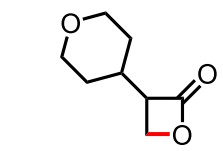




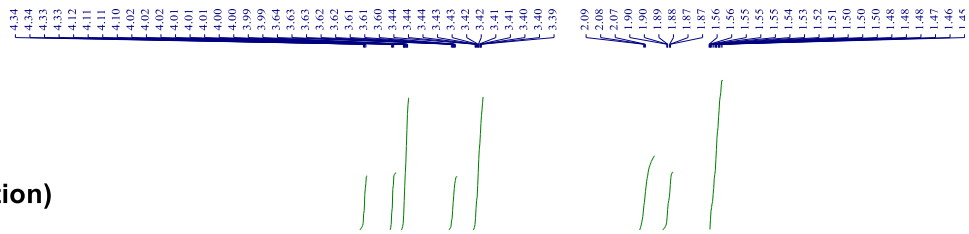
2aa
(purification by pTLC)

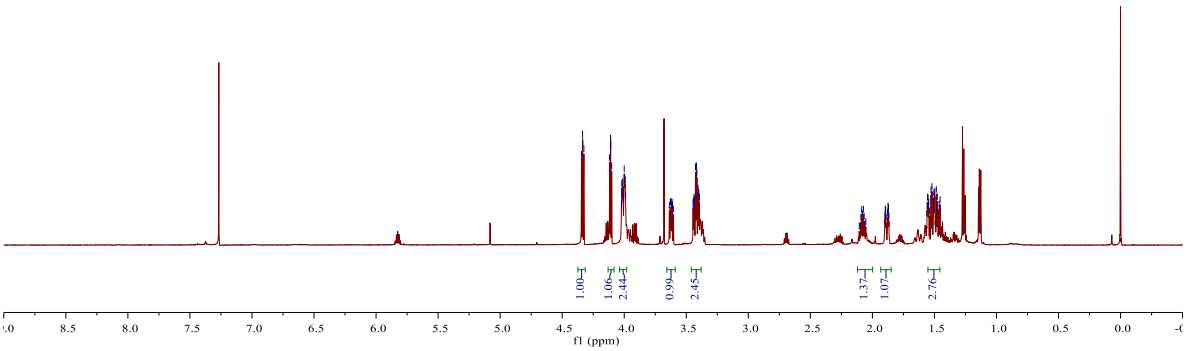

7.30 7.29 7.28 7.28 7.27 7.26 7.26 6.96 6.96 6.96 6.95 6.95 6.94 6.93 6.93 6.93 6.89 6.89 6.87 6.87 6.87 6.87
4.13 4.00 4.00 3.99 3.99 3.99 3.98 3.98 1.98 1.97 1.97 1.96 1.95 1.94 1.92 1.92 1.86 1.85 1.84 1.84 1.84 1.84 1.83 1.82 1.82 1.81 1.81 1.80 1.78 1.06 1.05 1.03
O
3
O
Et
O
2ab
(purification by pTLC)
2.05 0.96 1.95 2.00 1.91 3.14 3.18 3.04
f1 (ppm)

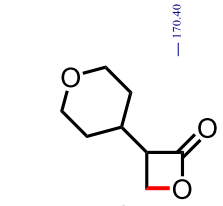

174.25 158.82 129.63 120.98 114.54 68.92 67.30 61.86 29.08 25.38 24.49 8.83
O
3
O
Et
O
2ab
(purification by pTLC)
f1 (ppm)



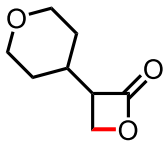
2ac
(before purification)



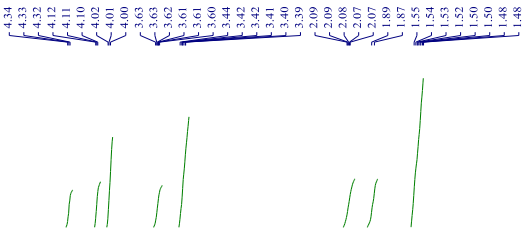


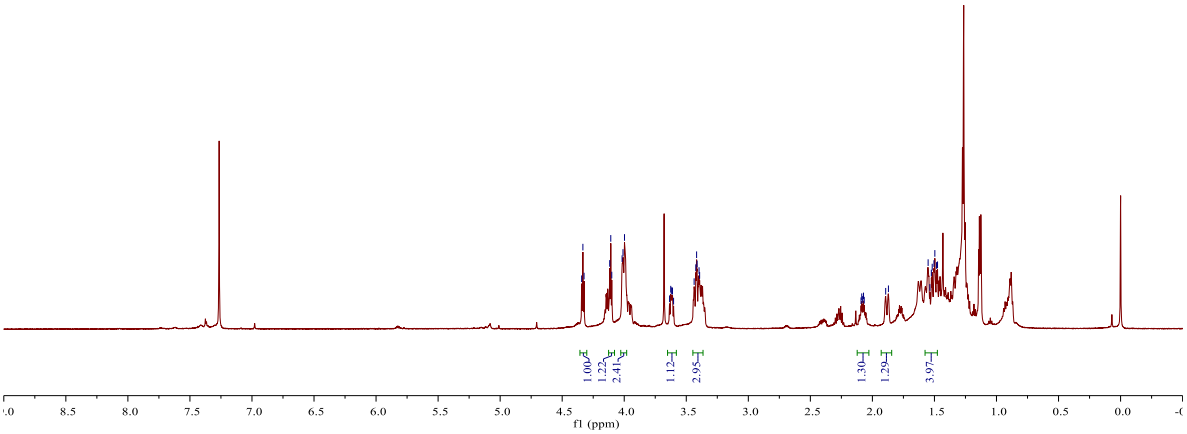


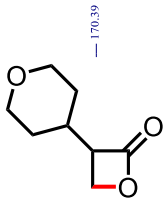
2ac
(before purification)



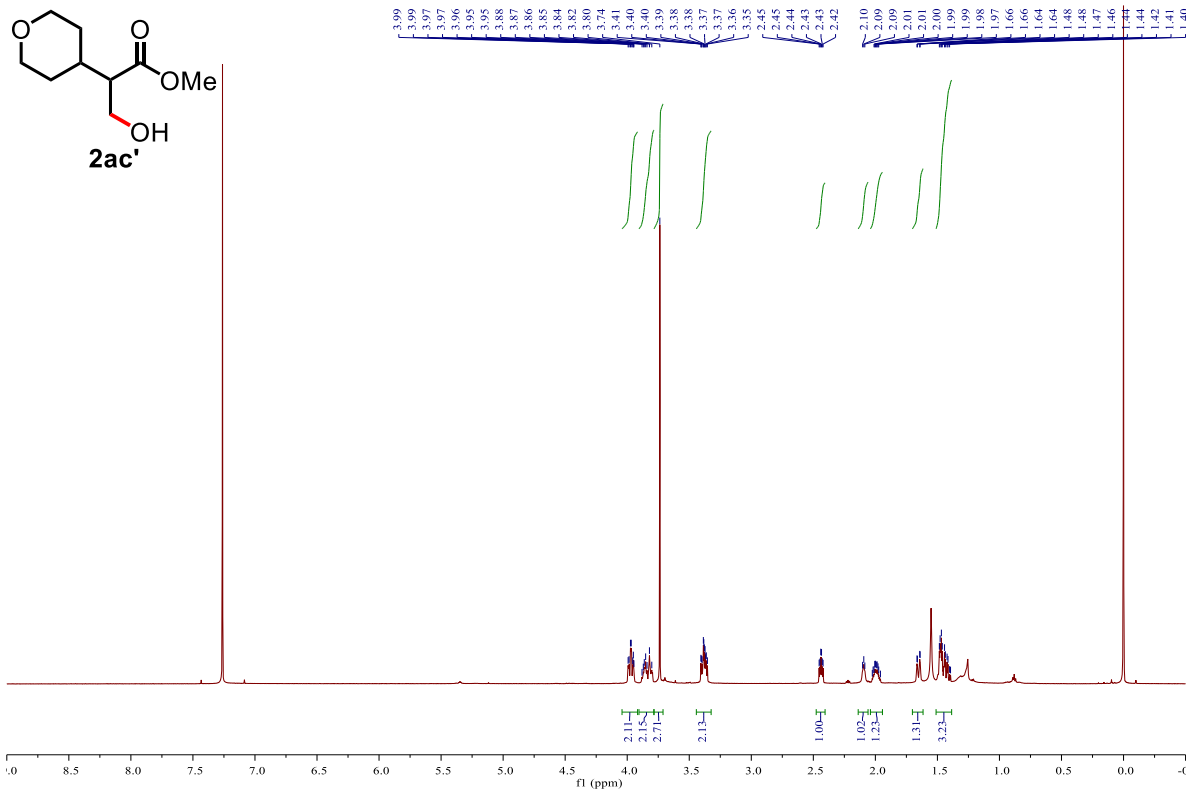
2ac
(filter through silica gel)

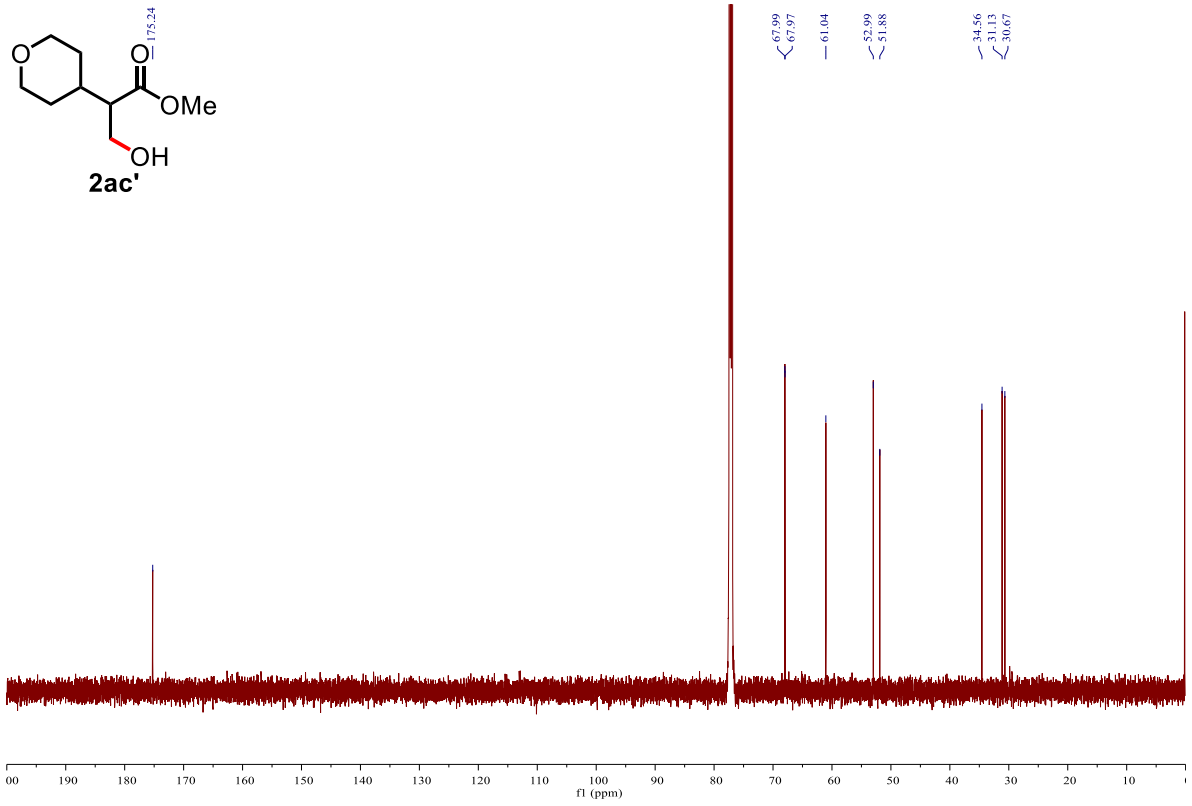


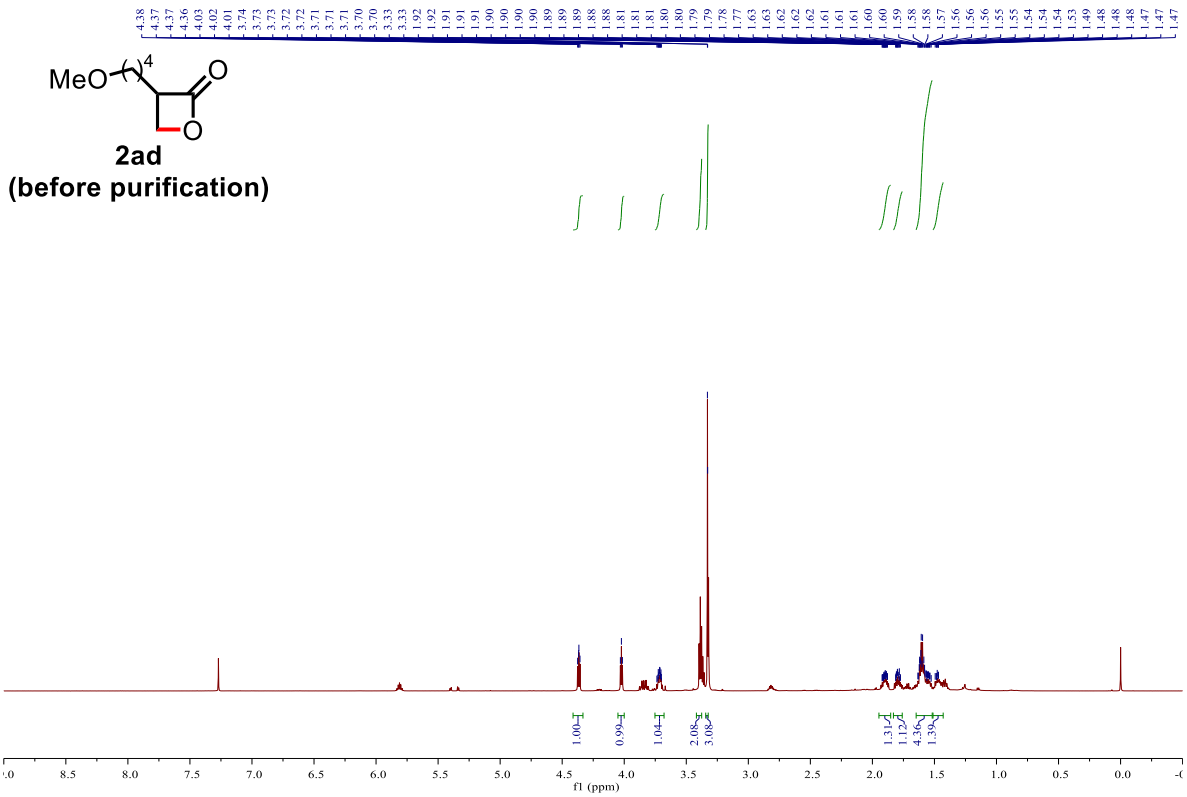


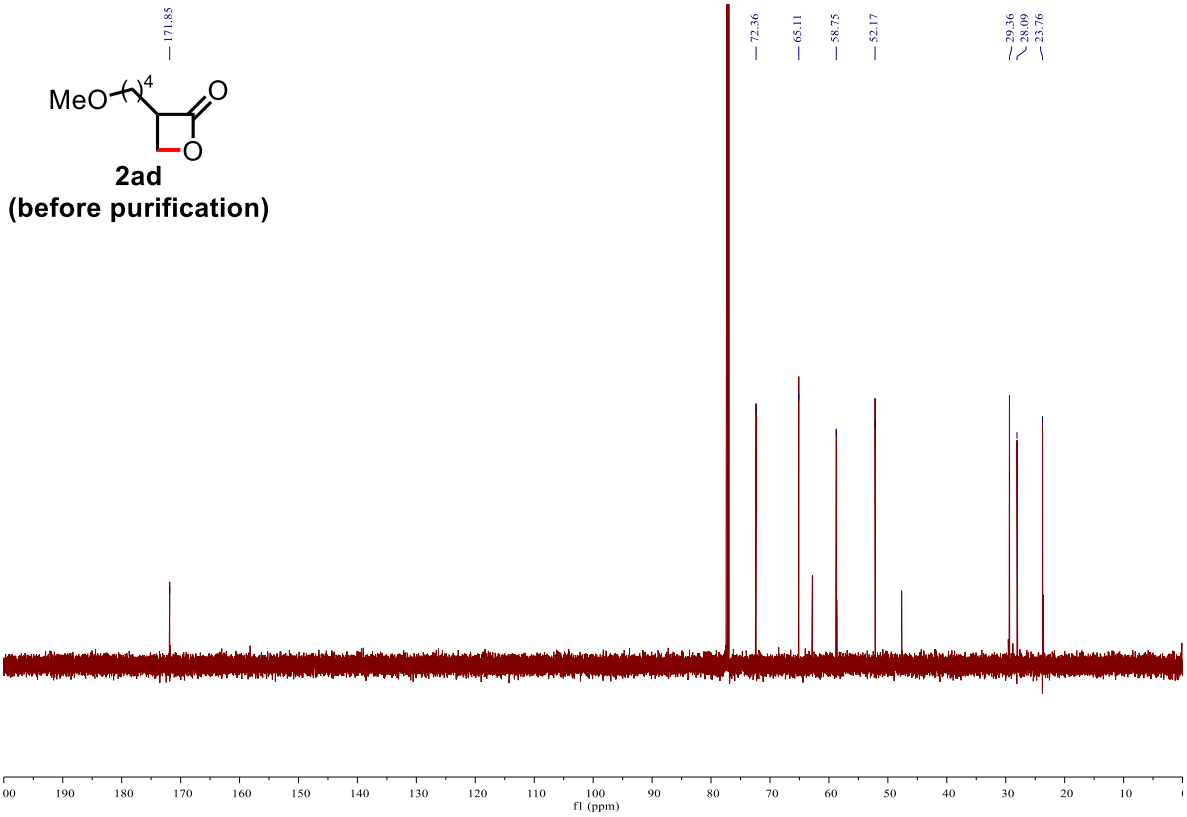


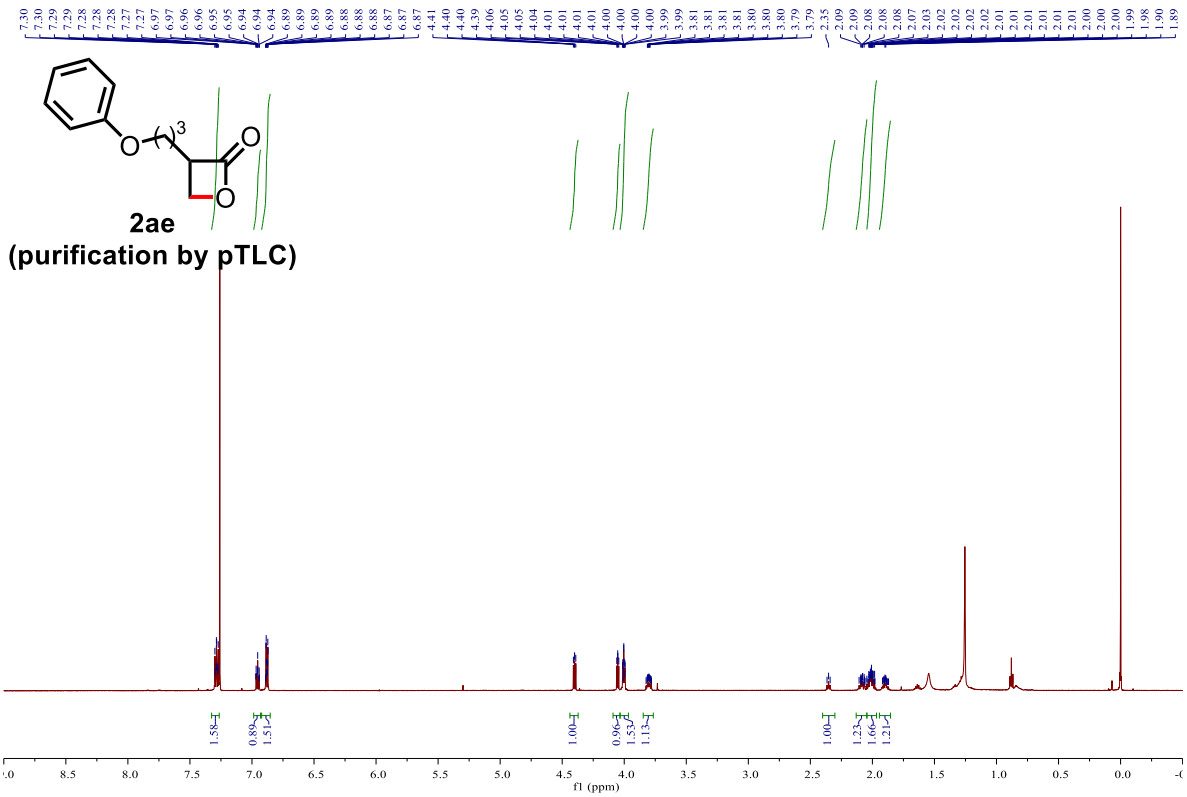
2ac
(filter through silica gel)

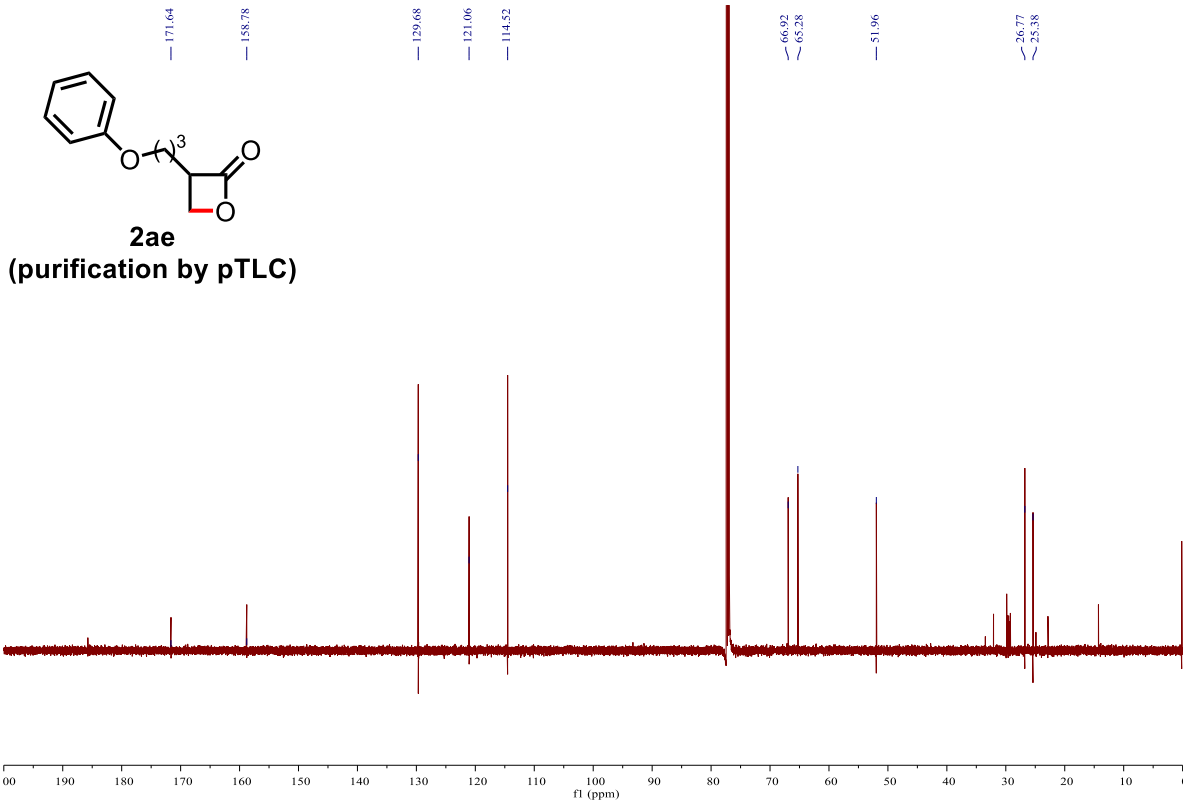

O
O
OMe
OH
2ac'
f1 (ppm)

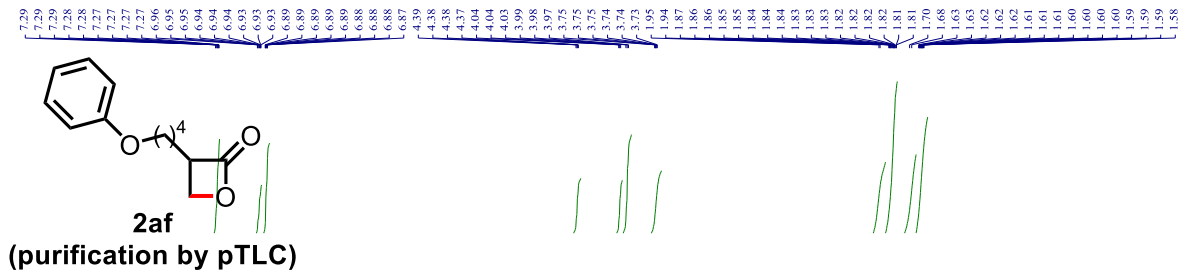

175.24
O
O
OMe
OH
2ac'
67.99
67.97
61.04
52.99
51.88
34.56
31.13
30.67
f1 (ppm)


MeO
4
O
O
2ad
(before purification)
fl (ppm)

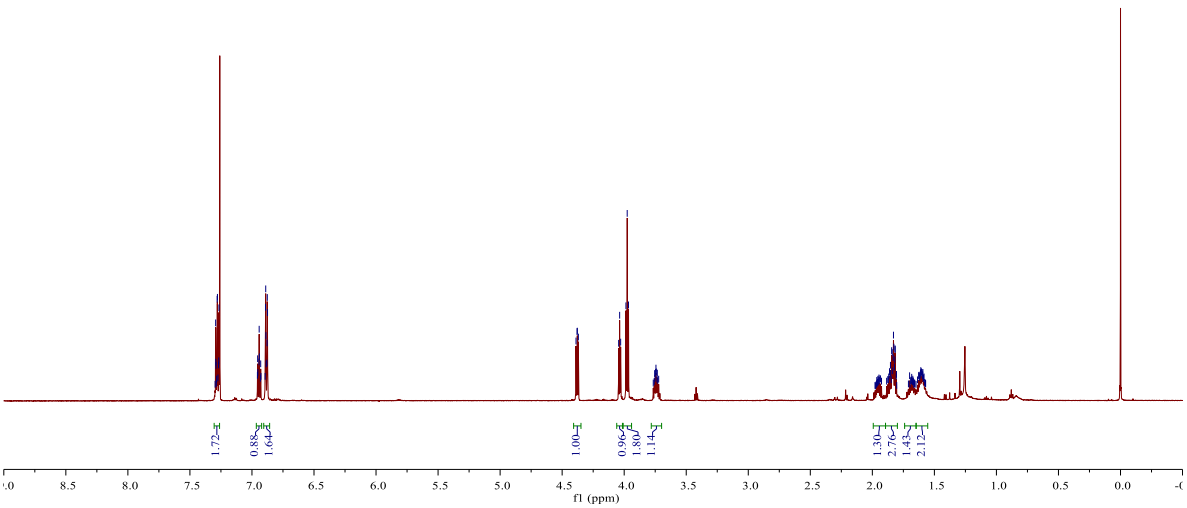

171.85
72.36
65.11
58.75
52.17
29.36
28.09
23.76
MeO
4
O
O
2ad
(before purification)
fl (ppm)

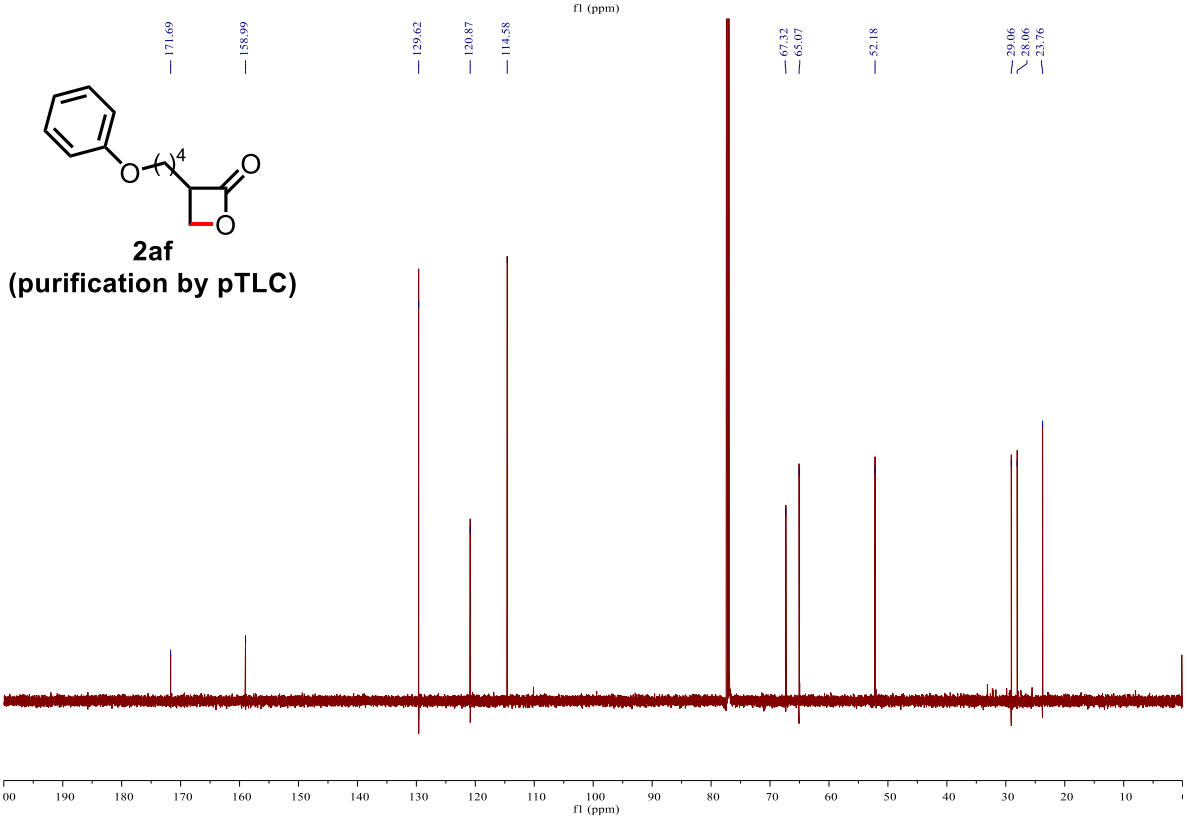

2ae
(purification by pTLC)
f1 (ppm)


2ae
(purification by pTLC)
f1 (ppm)

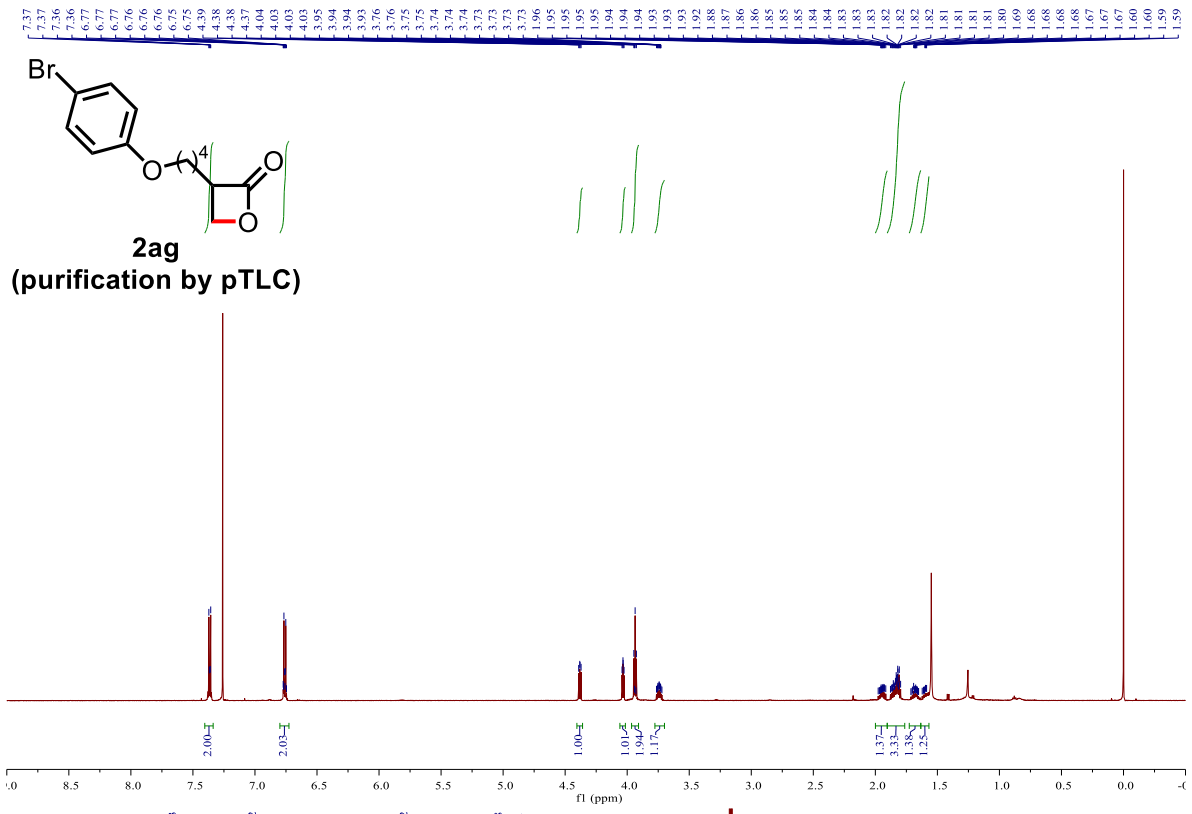


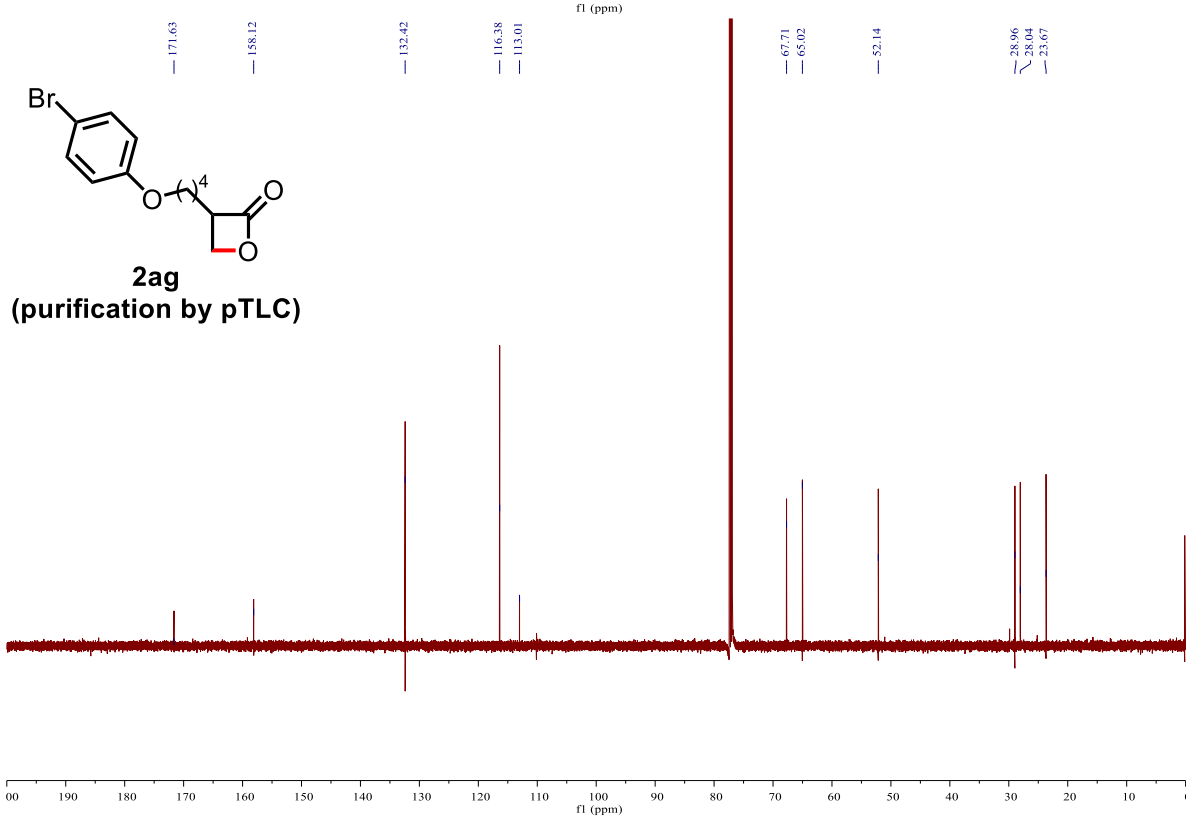
2af
(purification by pTLC)

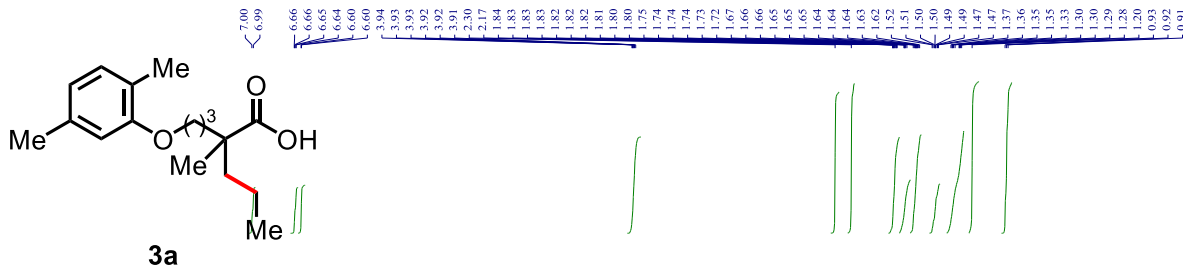


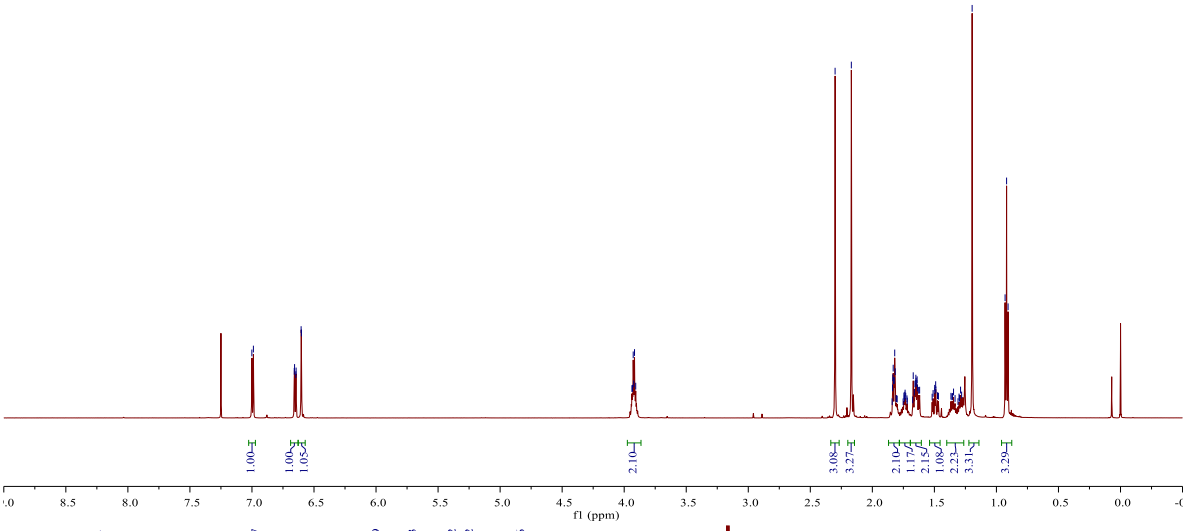


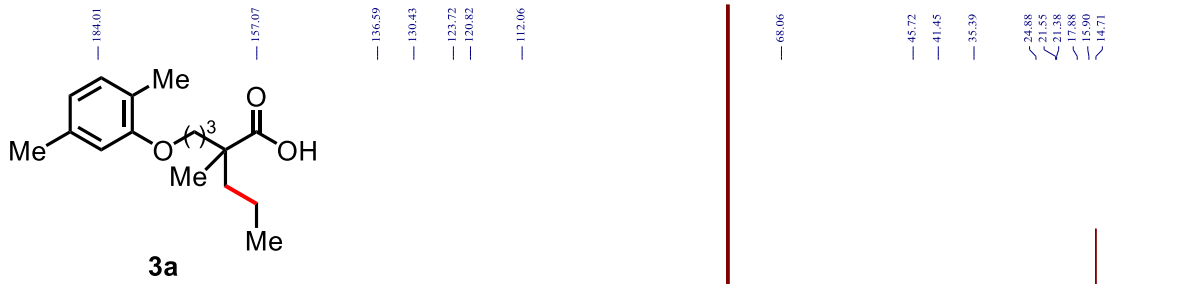
2af
(purification by pTLC)


Br
O
4
O
O
2ag
(purification by pTLC)
2.00
2.03
1.00
1.01
1.94
1.17
1.37
3.33
1.38
1.25
f1 (ppm)

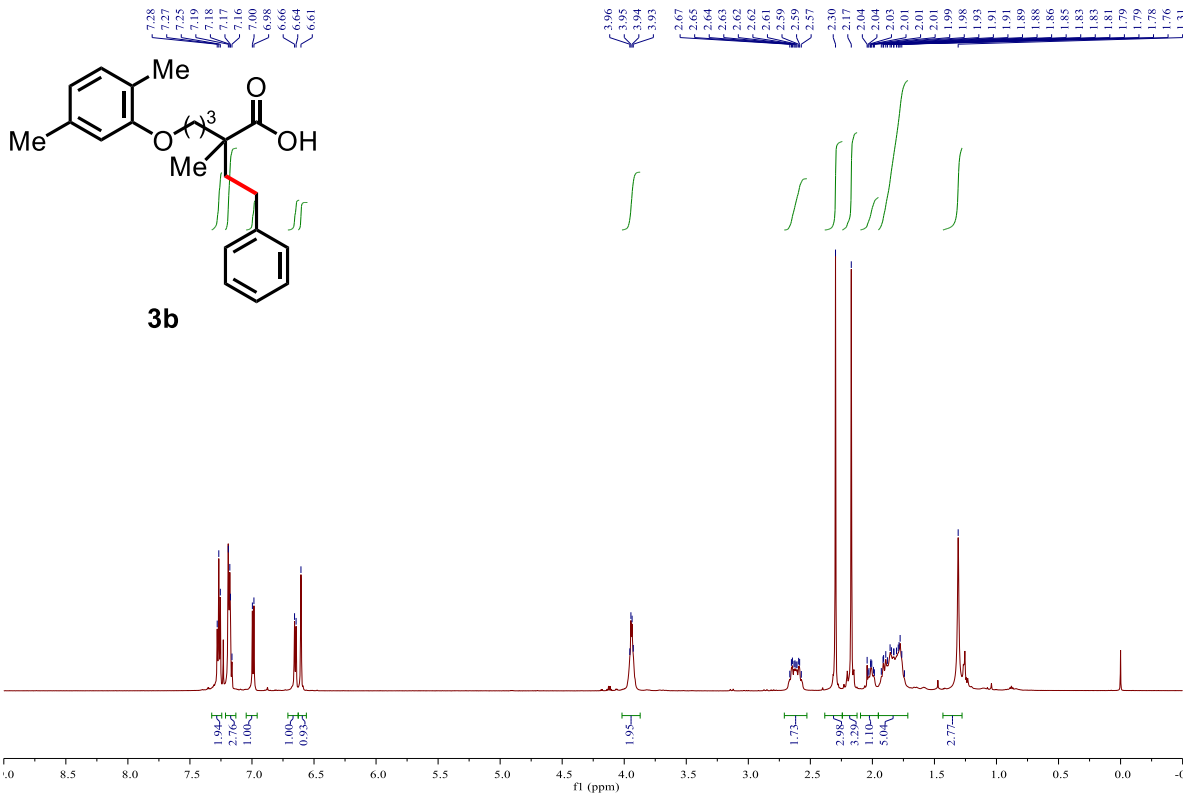

171.63
158.12
132.42
116.38
113.01
67.71
65.02
52.14
28.96
28.04
23.67
Br
O
4
O
O
2ag
(purification by pTLC)
f1 (ppm)

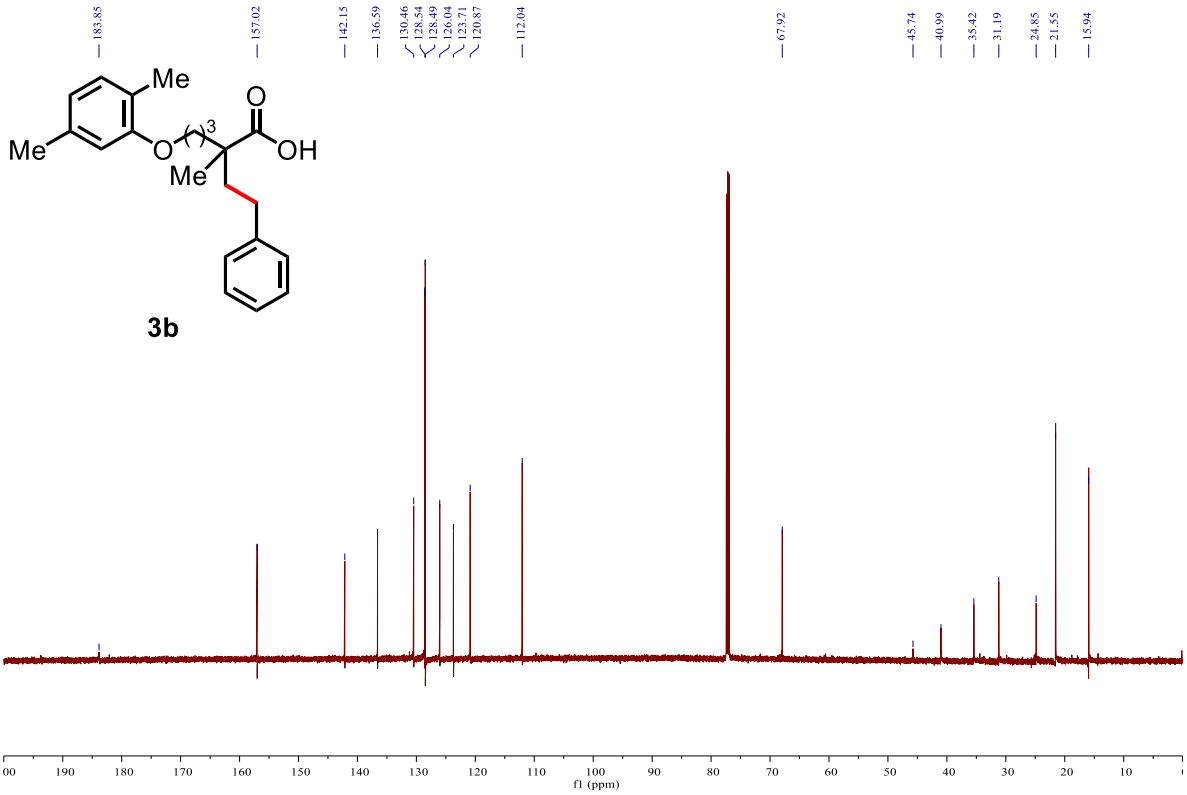

Me
Me
O
OH
Me
Me
3
3a

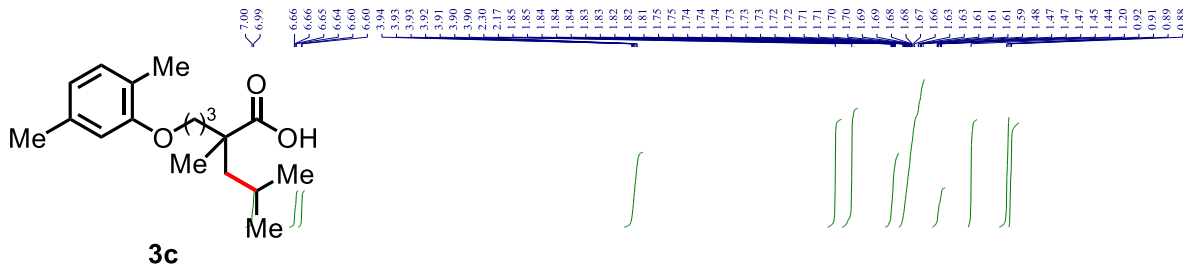

f1 (ppm)


Me
Me
O
OH
Me
Me
3
3a

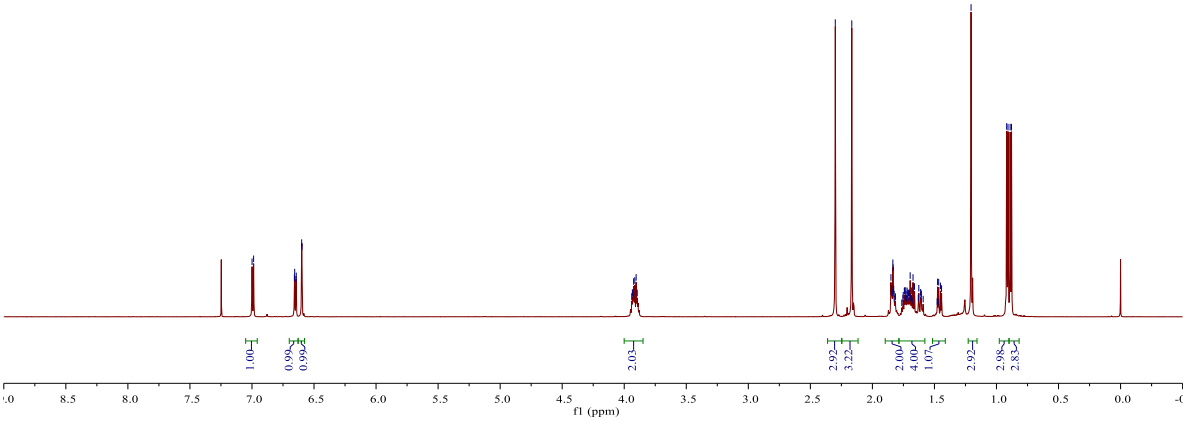
f1 (ppm)

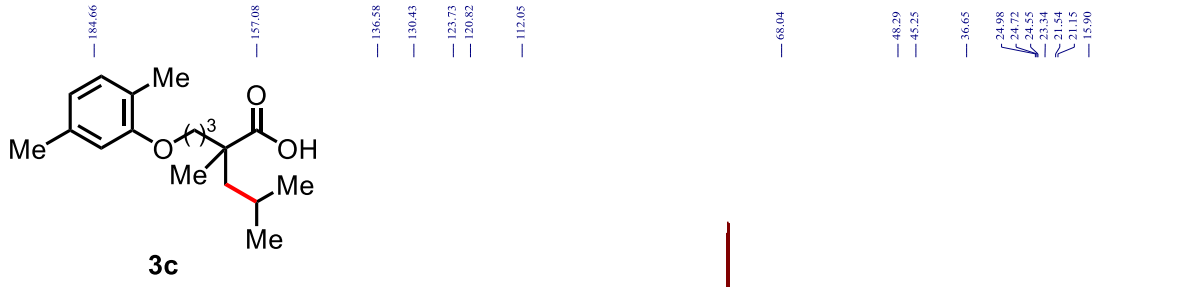

Me
Me
O
OH
Me
3
3b
f1 (ppm)


Me
Me
O
OH
Me
3
3b
f1 (ppm)

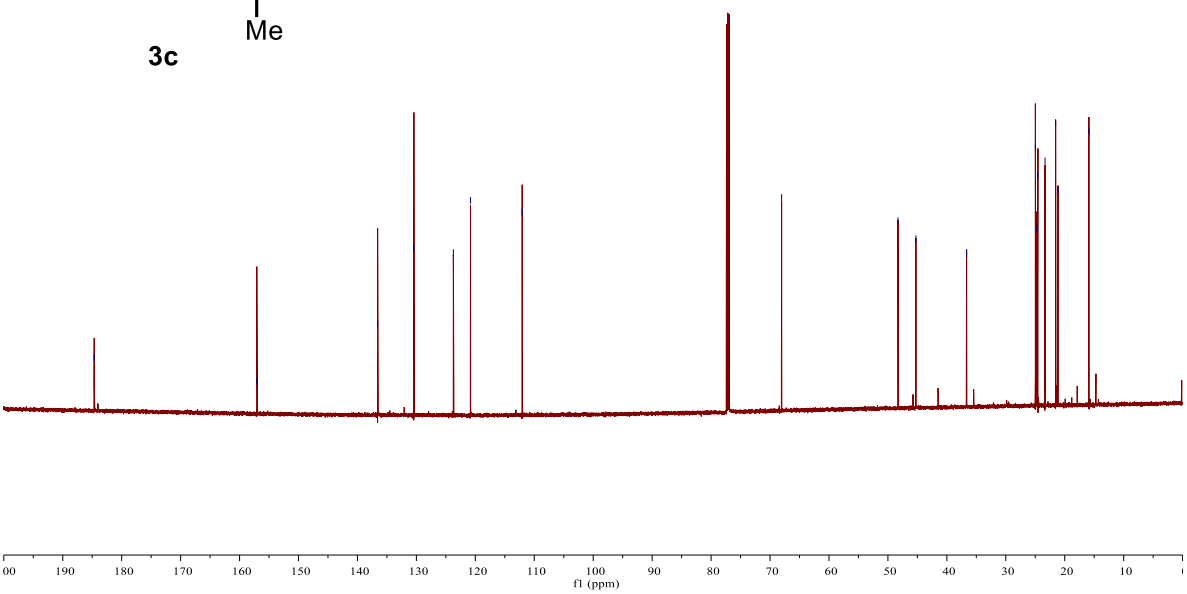


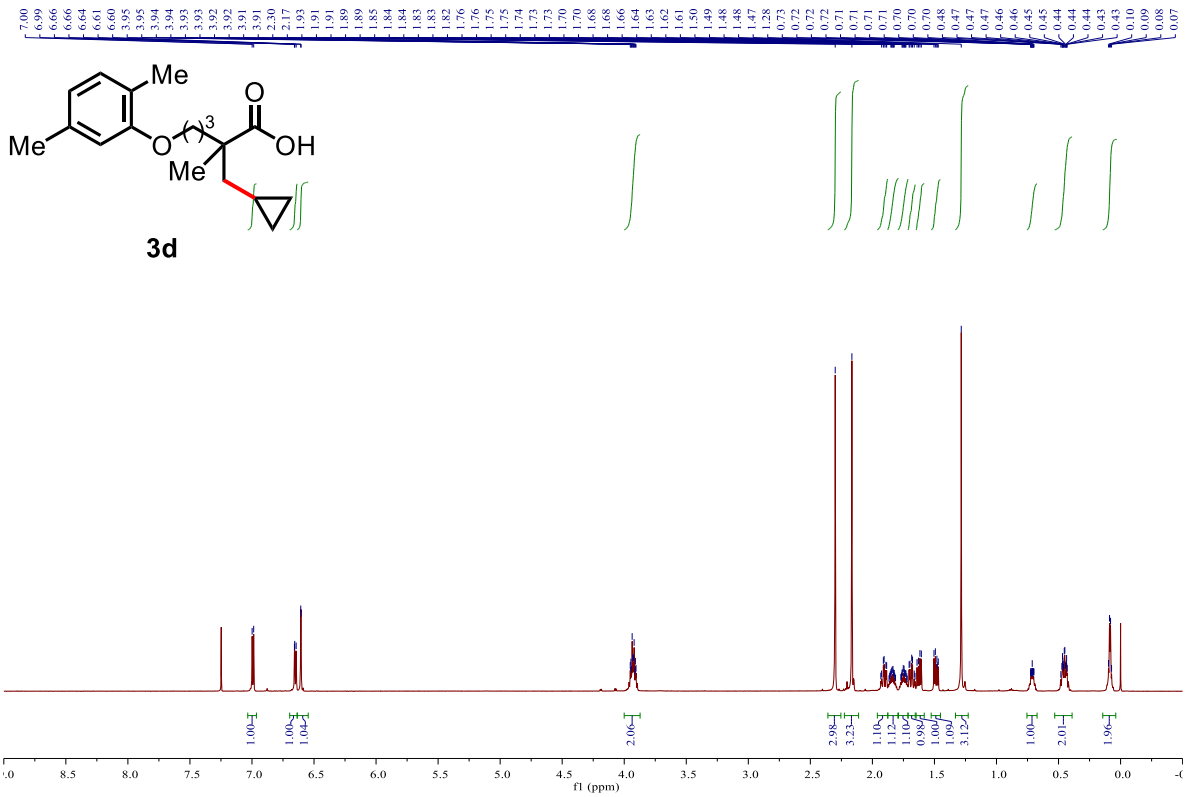
3c

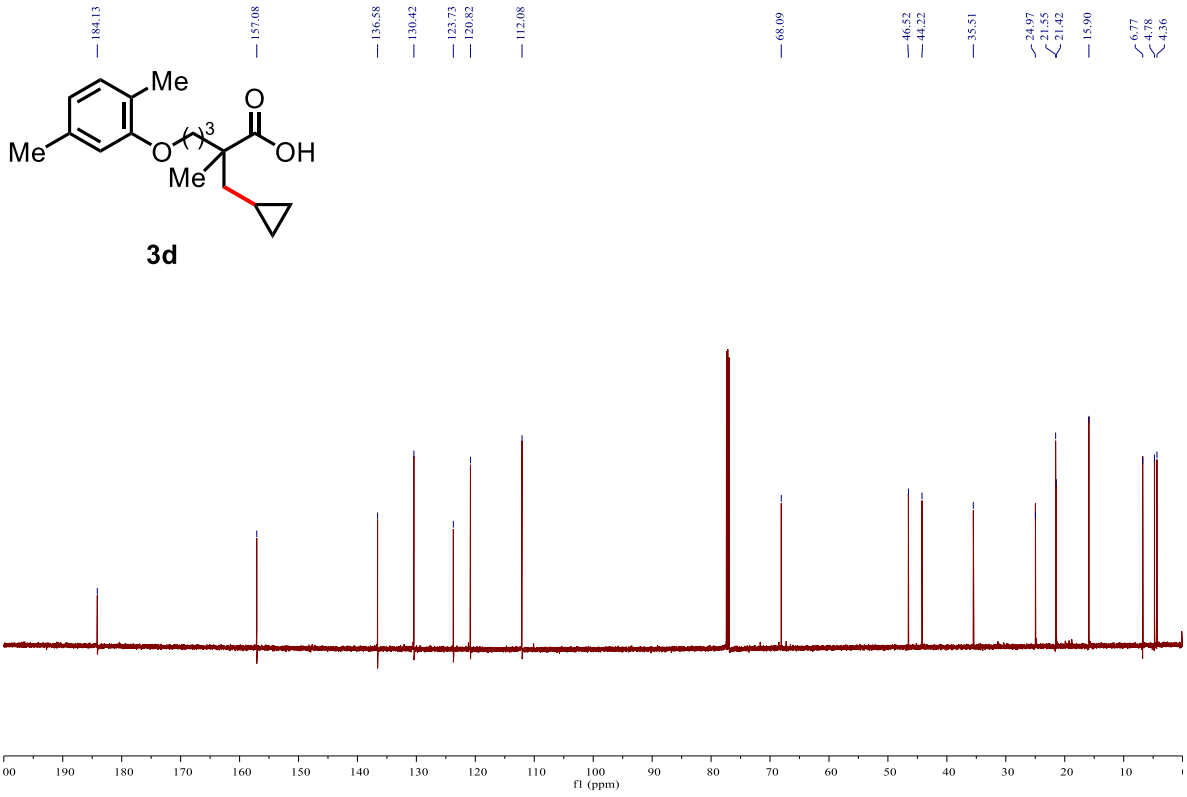


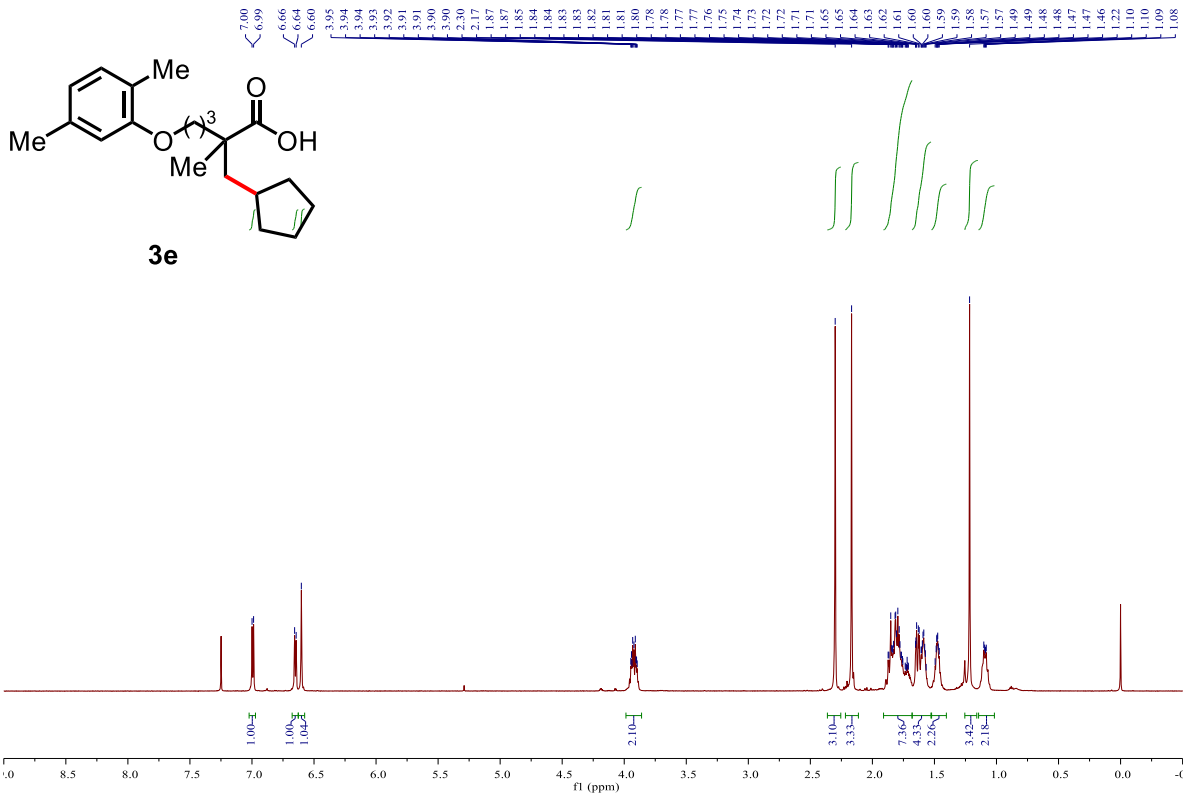


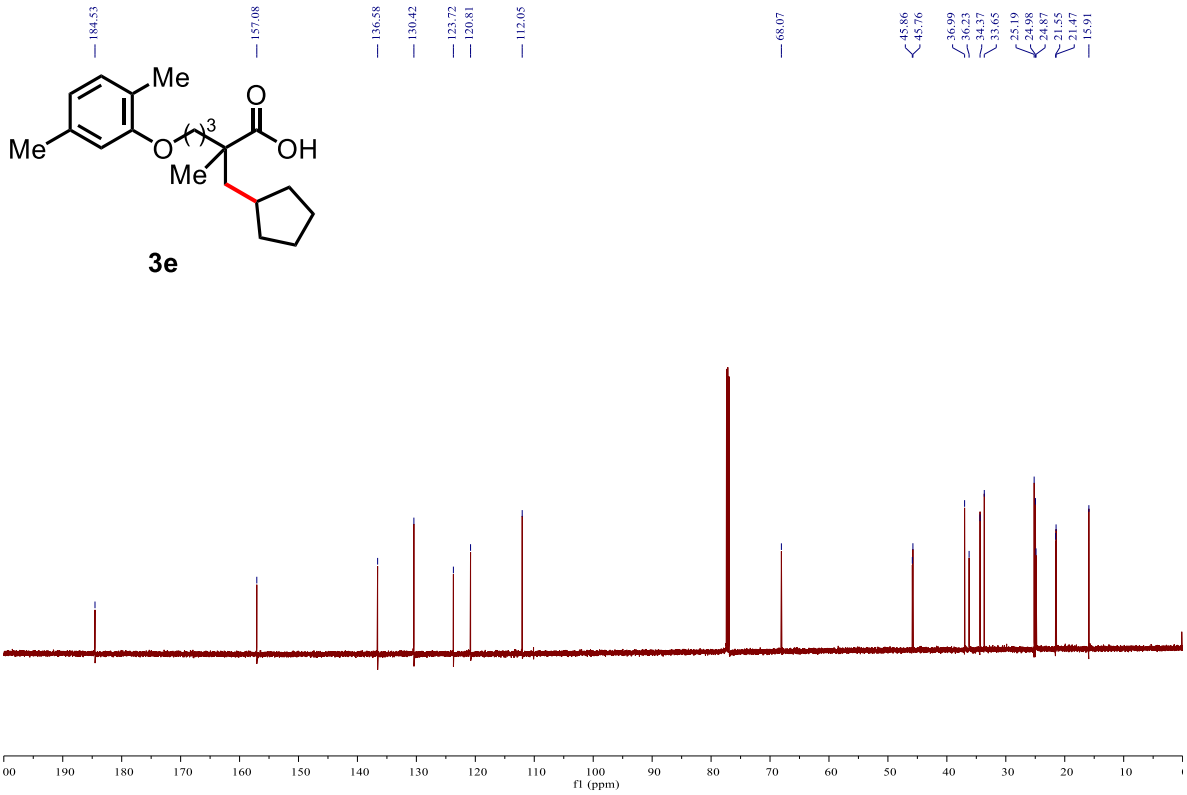
3c

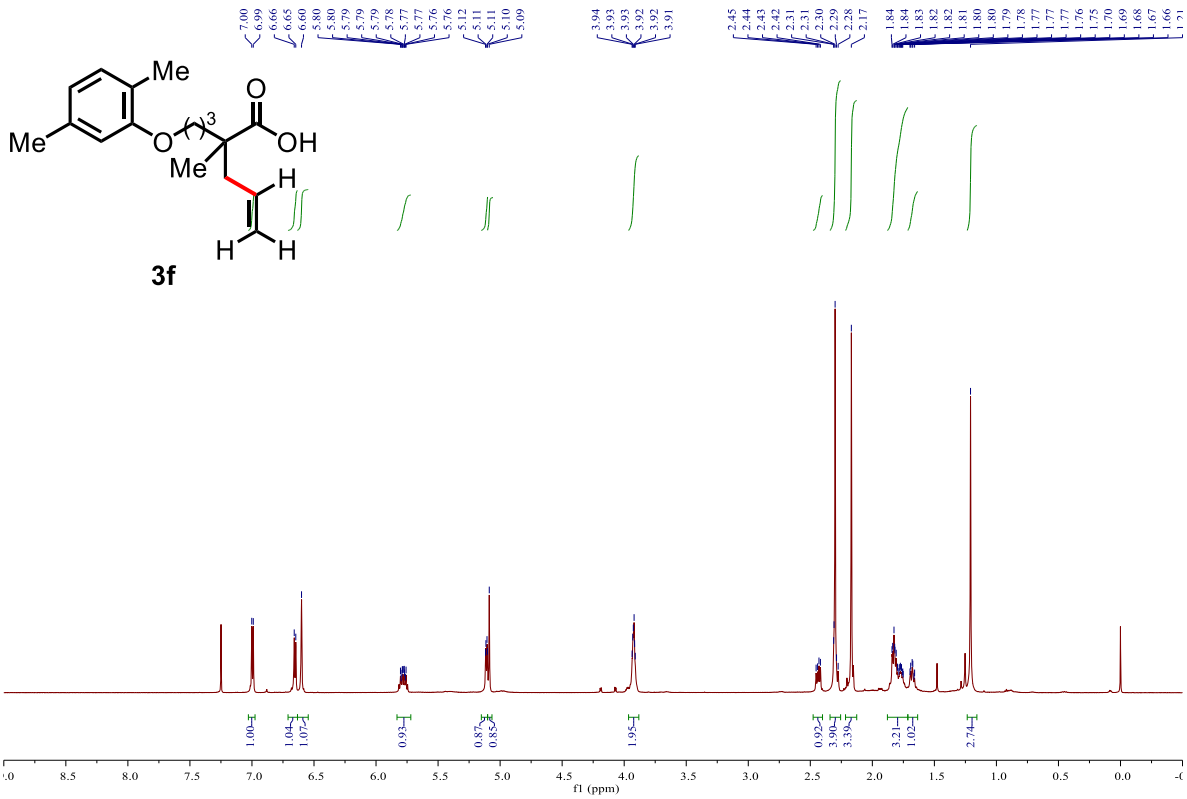


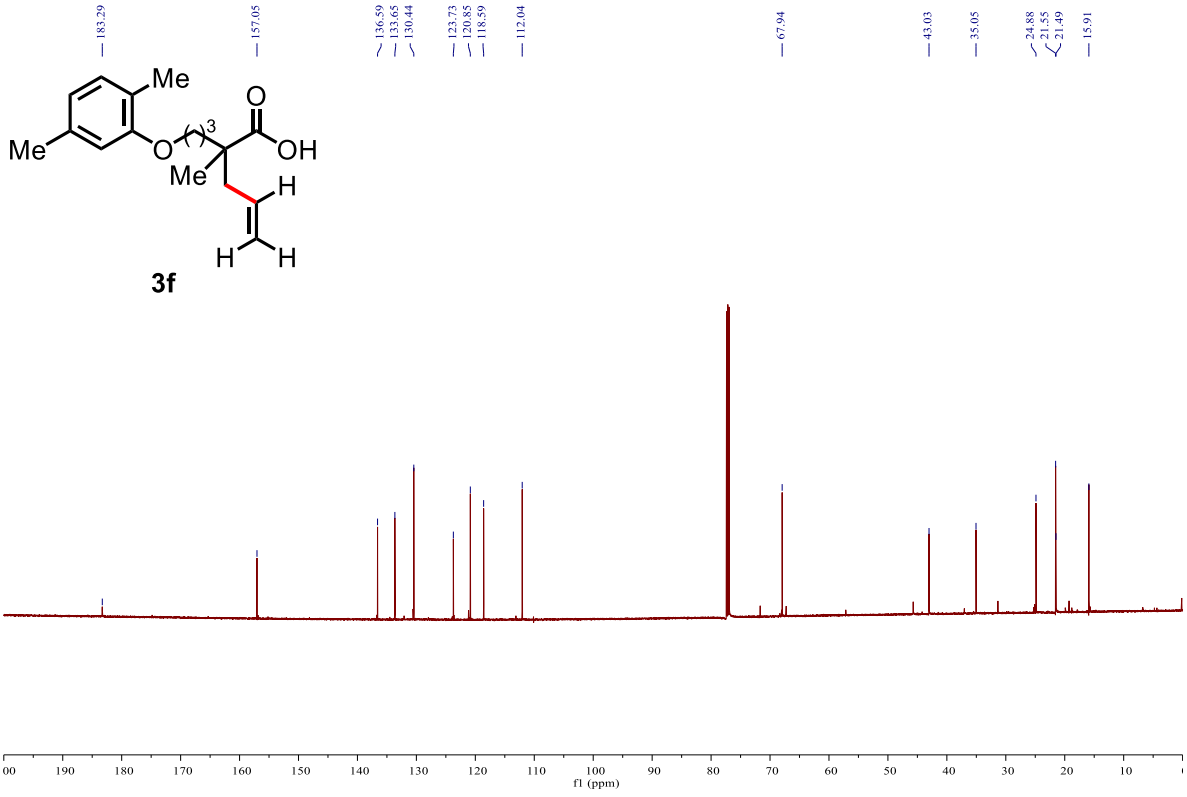

Me
Me
O
3
Me
OH
3d
f1 (ppm)

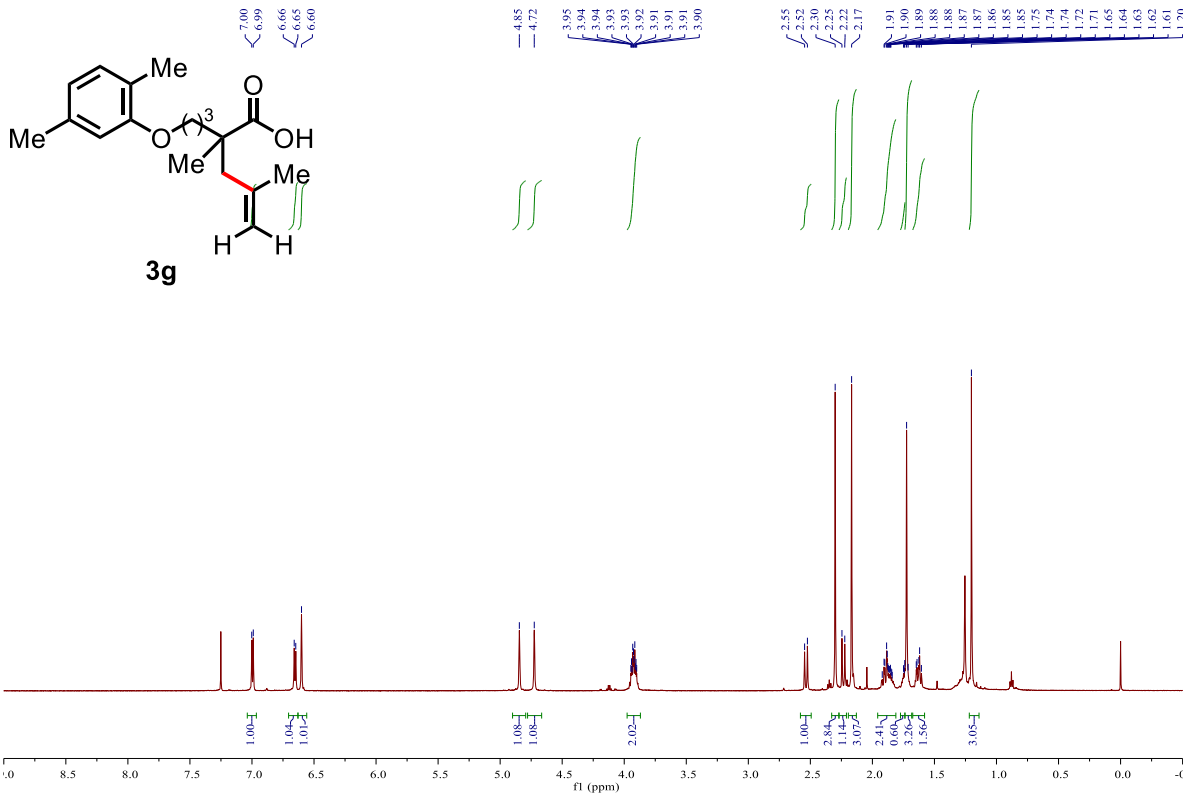

184.13
157.08
136.58
130.42
123.73
120.82
112.08
68.09
46.52
44.22
35.51
24.97
21.55
21.42
15.90
6.77
4.78
4.36
Me
Me
O
3
Me
OH
3d
f1 (ppm)

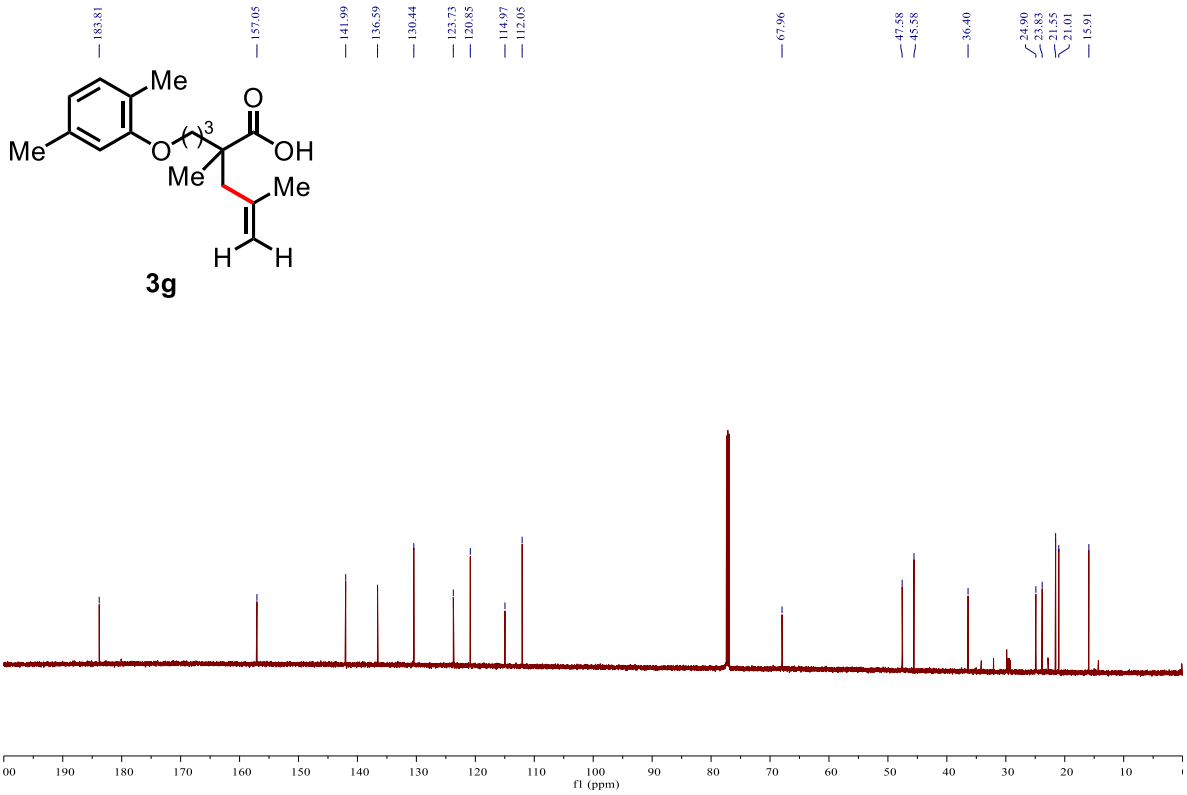

Me
Me
O
3
O
OH
Me
3e
fl (ppm)

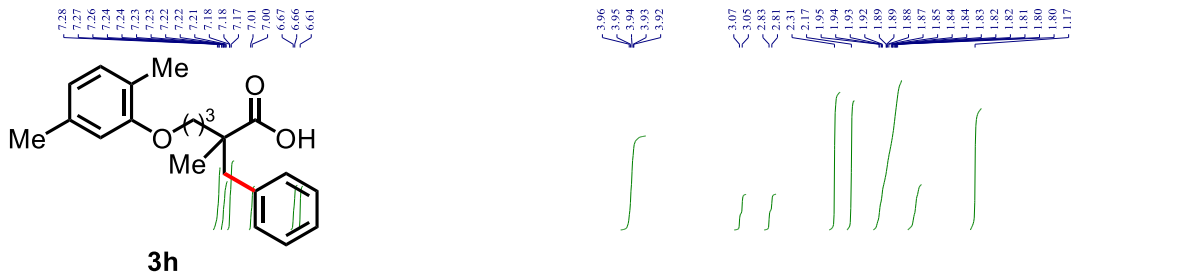

Me
Me
O
3
O
OH
Me
3e
fl (ppm)

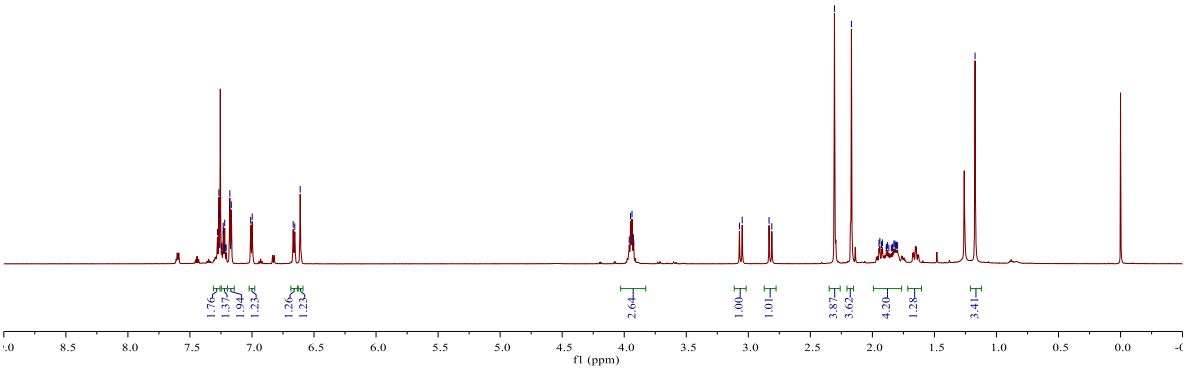

Me
Me
O
3
O
OH
Me
H
H
H
3f
f1 (ppm)

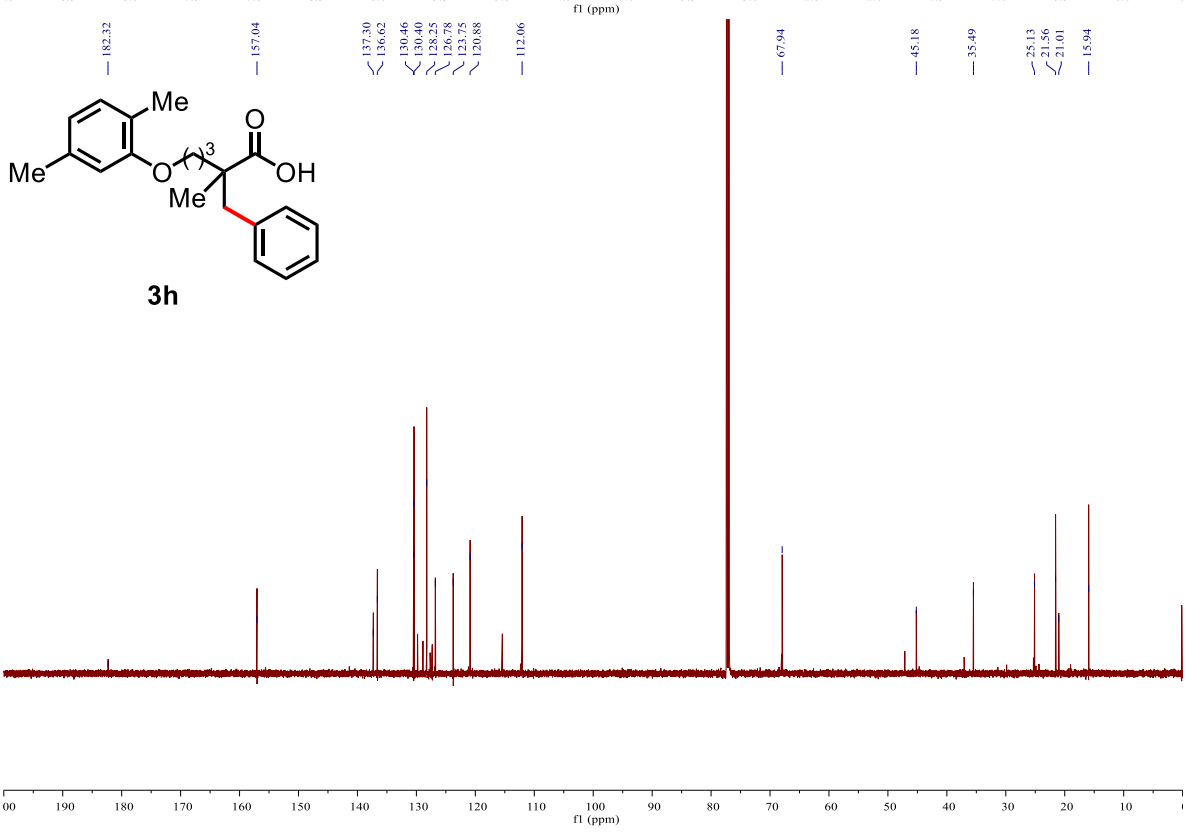

Me
Me
O
3
O
OH
Me
H
H
H
3f
f1 (ppm)

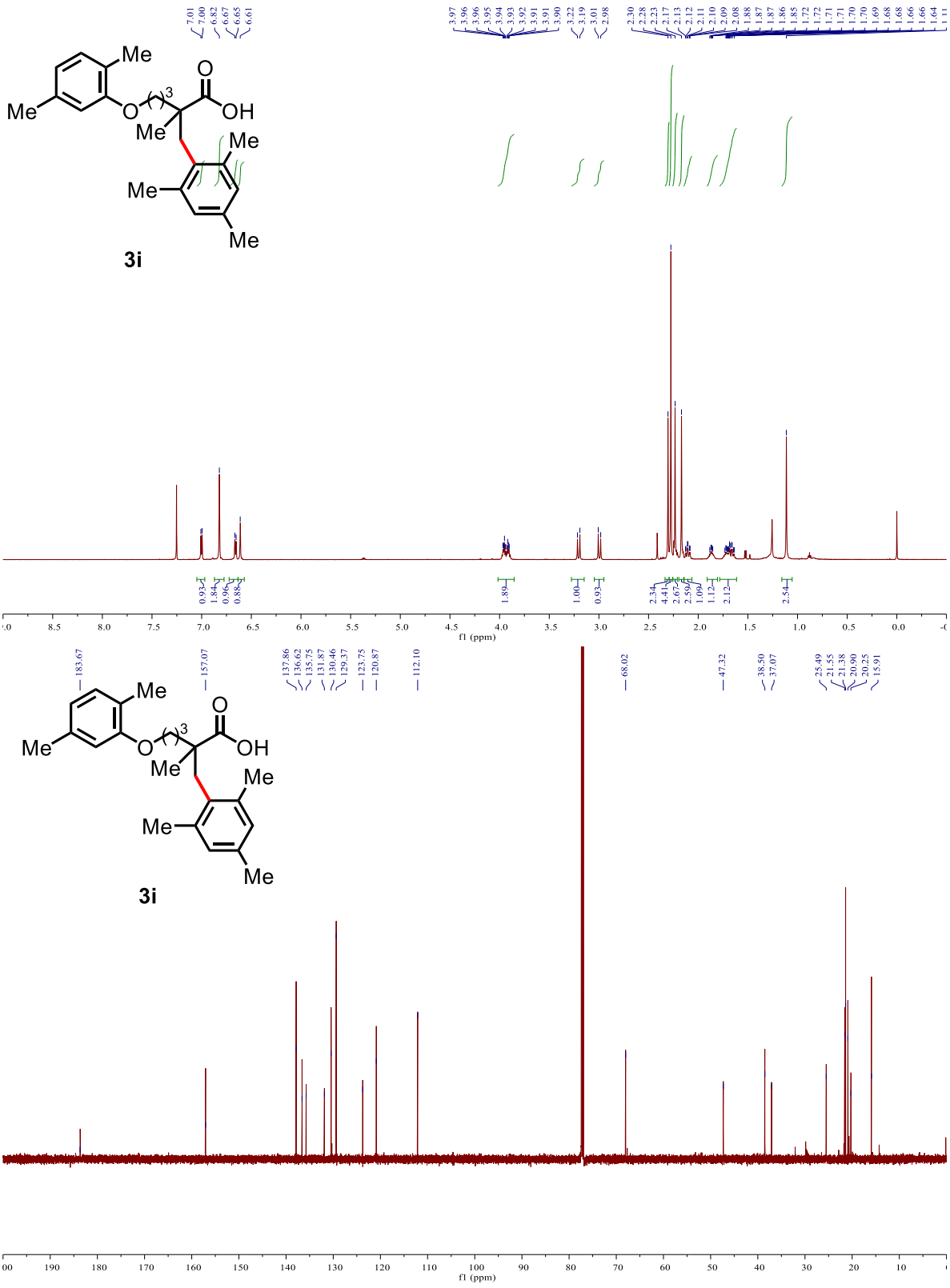

Me
Me
O
3
OH
Me
Me
H
H
3g
f1 (ppm)

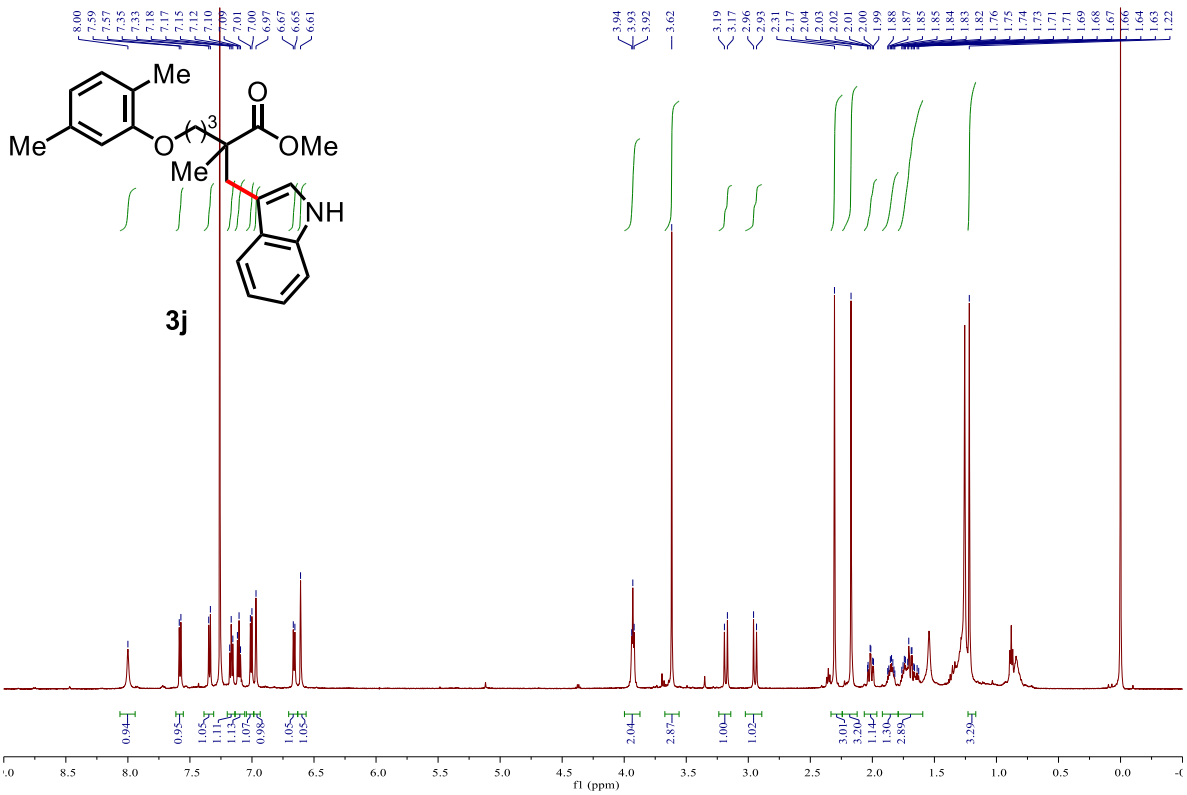

Me
Me
O
3
OH
Me
Me
H
H
3g
f1 (ppm)

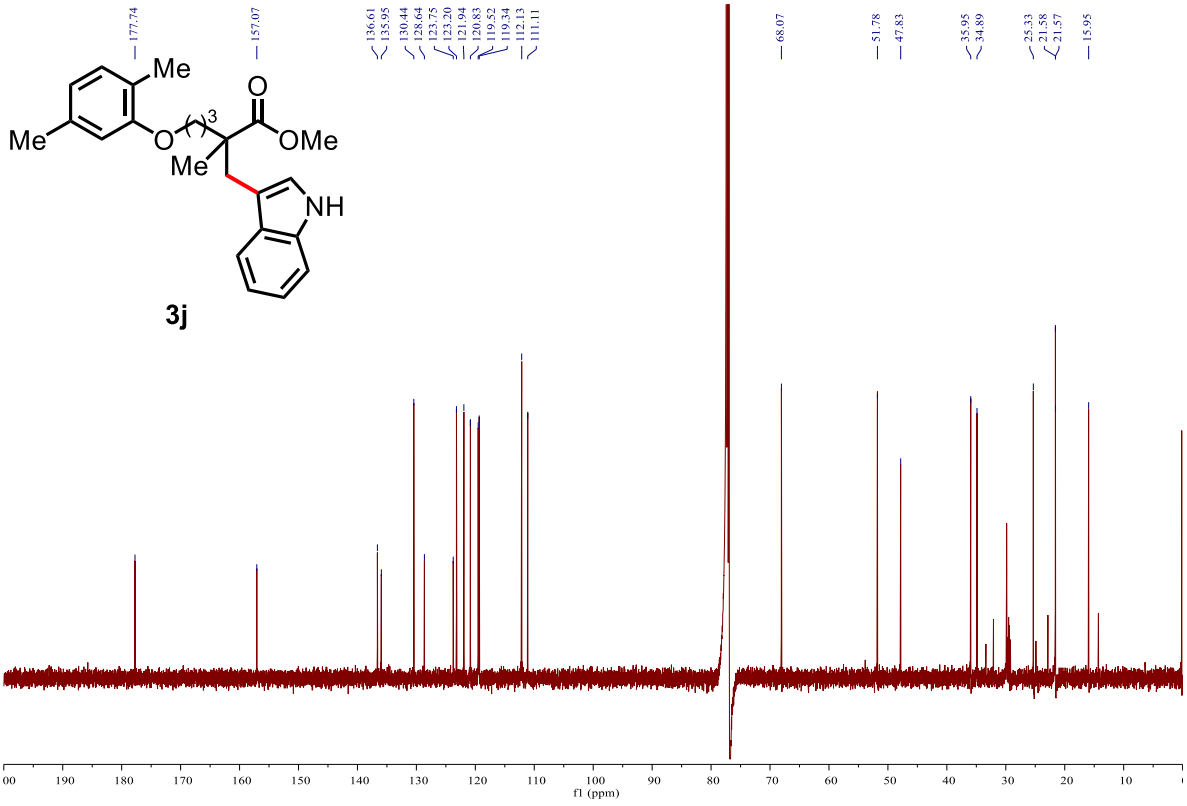

Me
Me
O
OH
Me
3
3h

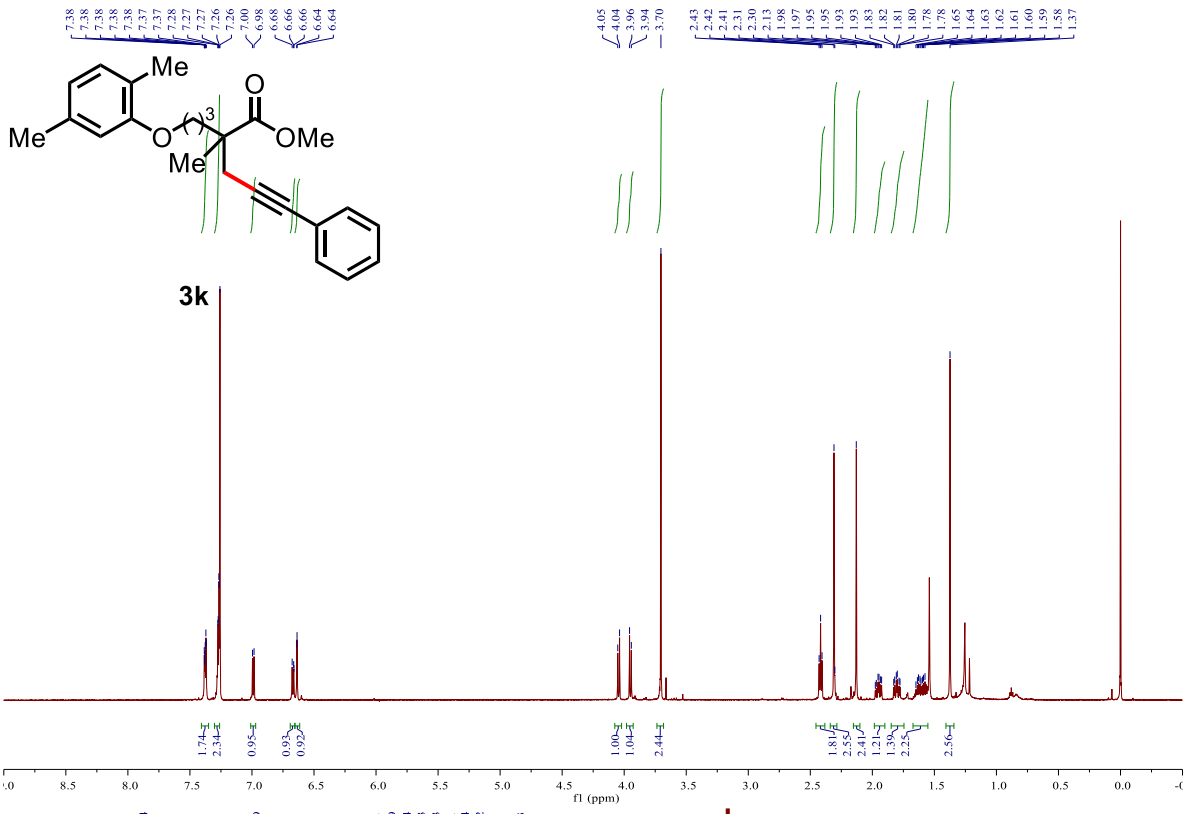

f1 (ppm)

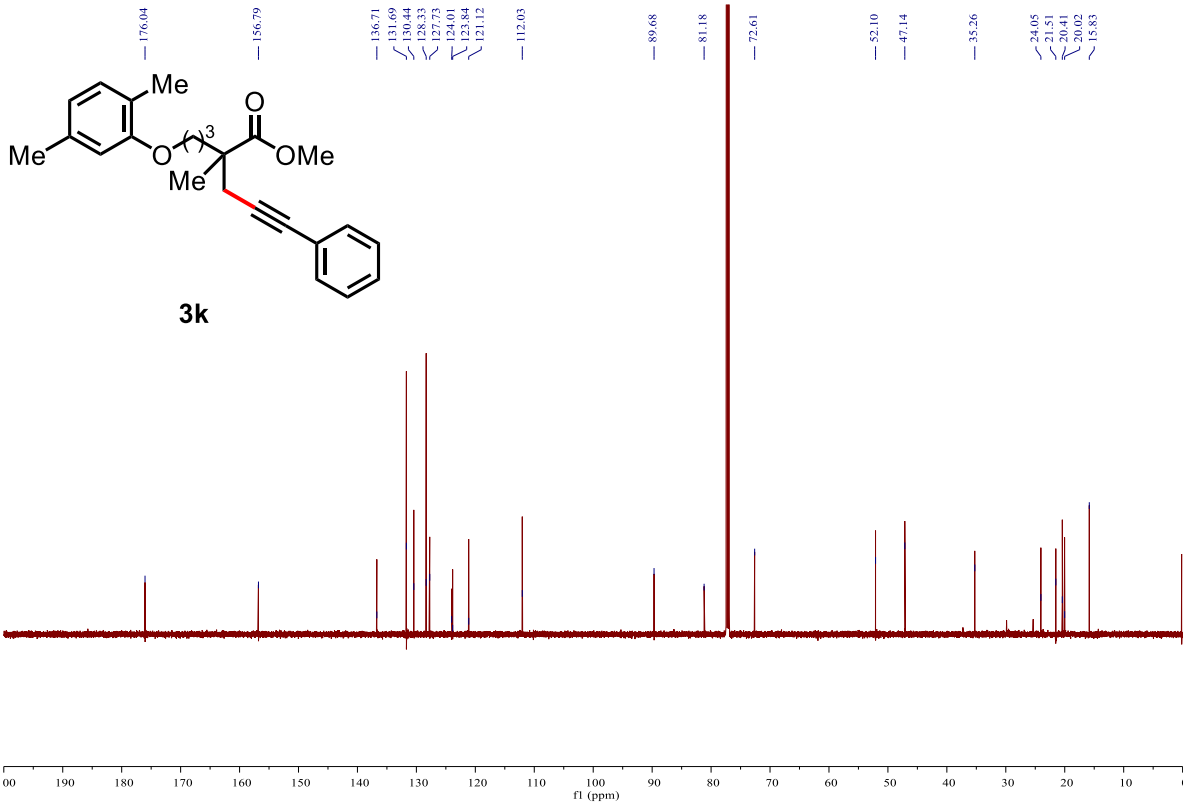

Me
Me
O
OH
Me
3
3h
f1 (ppm)

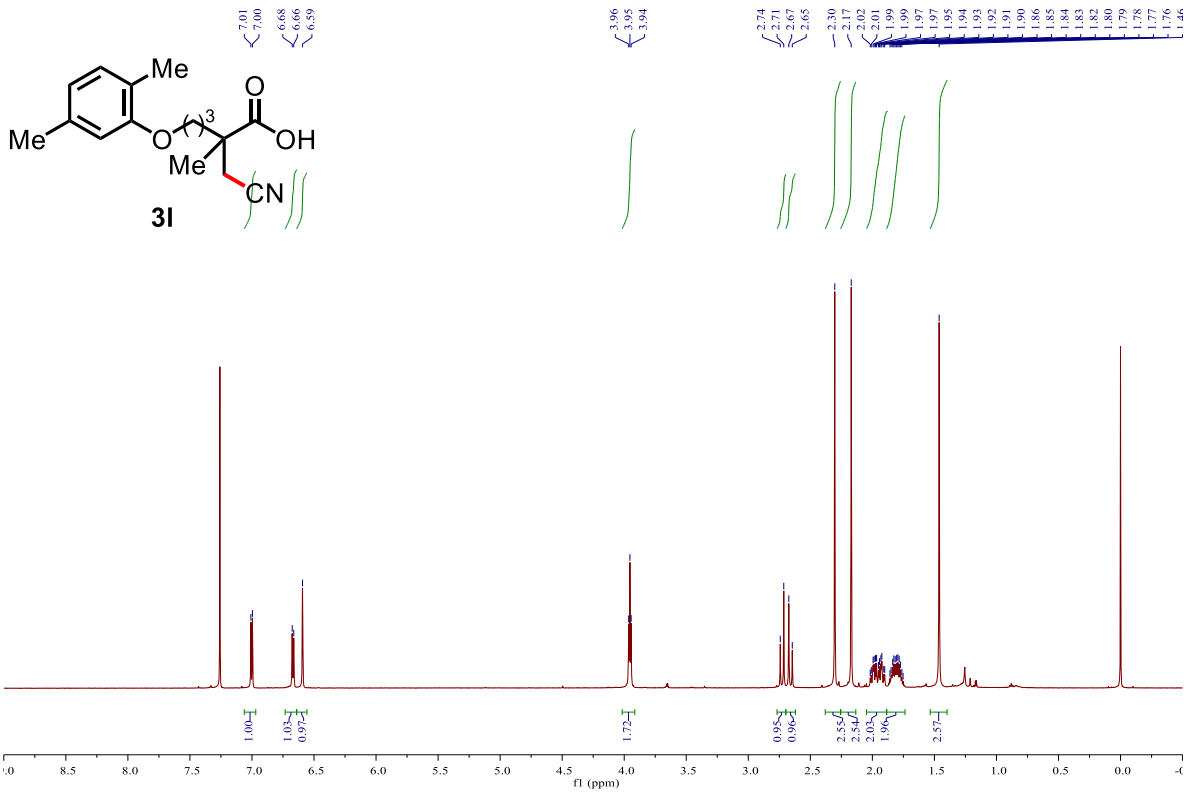

Me
Me
O
3
OH
Me
Me
Me
Me
3i
f1 (ppm)
f1 (ppm)

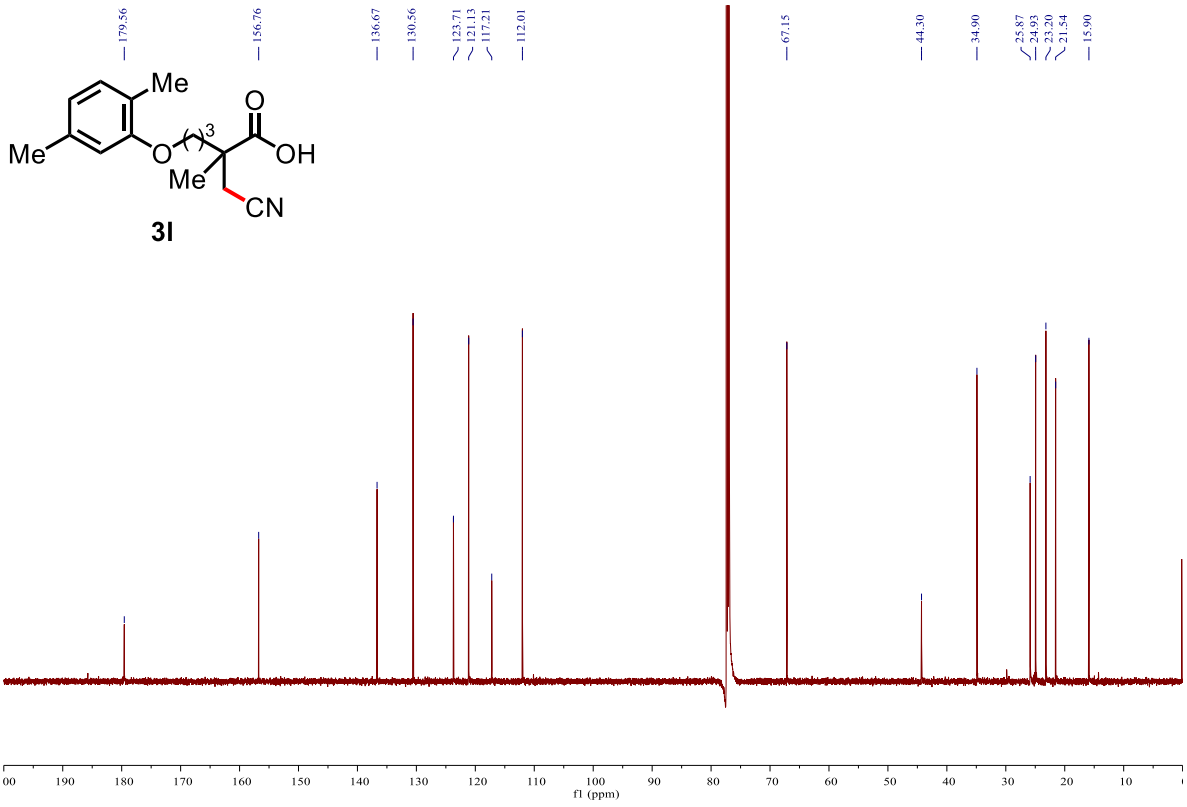

Me
Me
O
OMe
Me
NH
3j
fl (ppm)

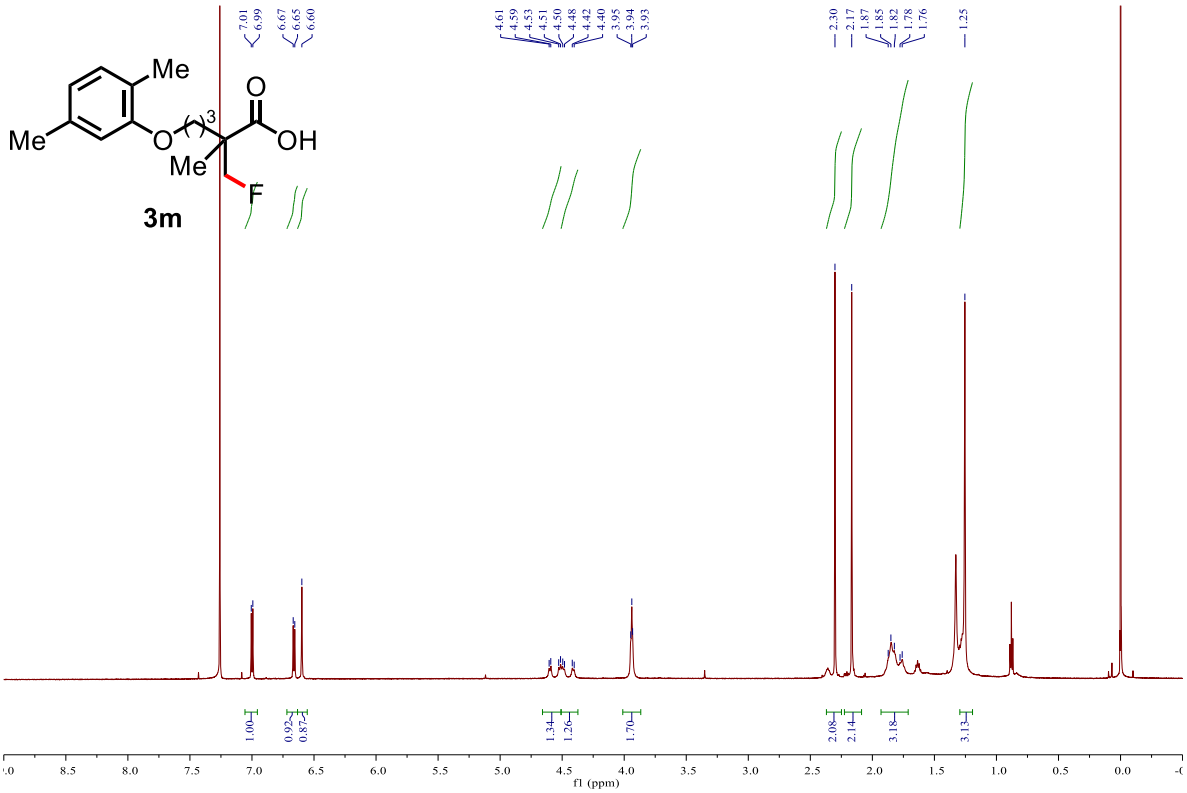

Me
Me
O
OMe
Me
NH
3j
fl (ppm)

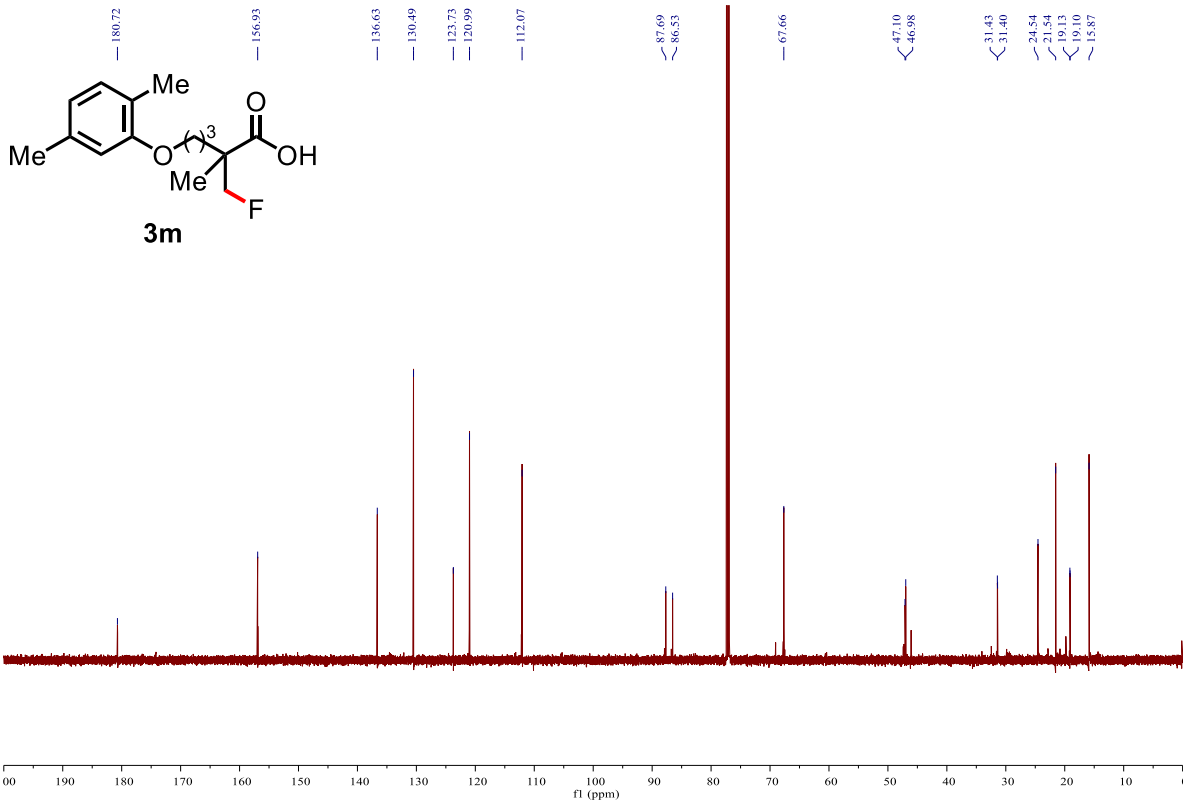

Me
Me
O
3
O
OMe
Me
3k
fl (ppm)

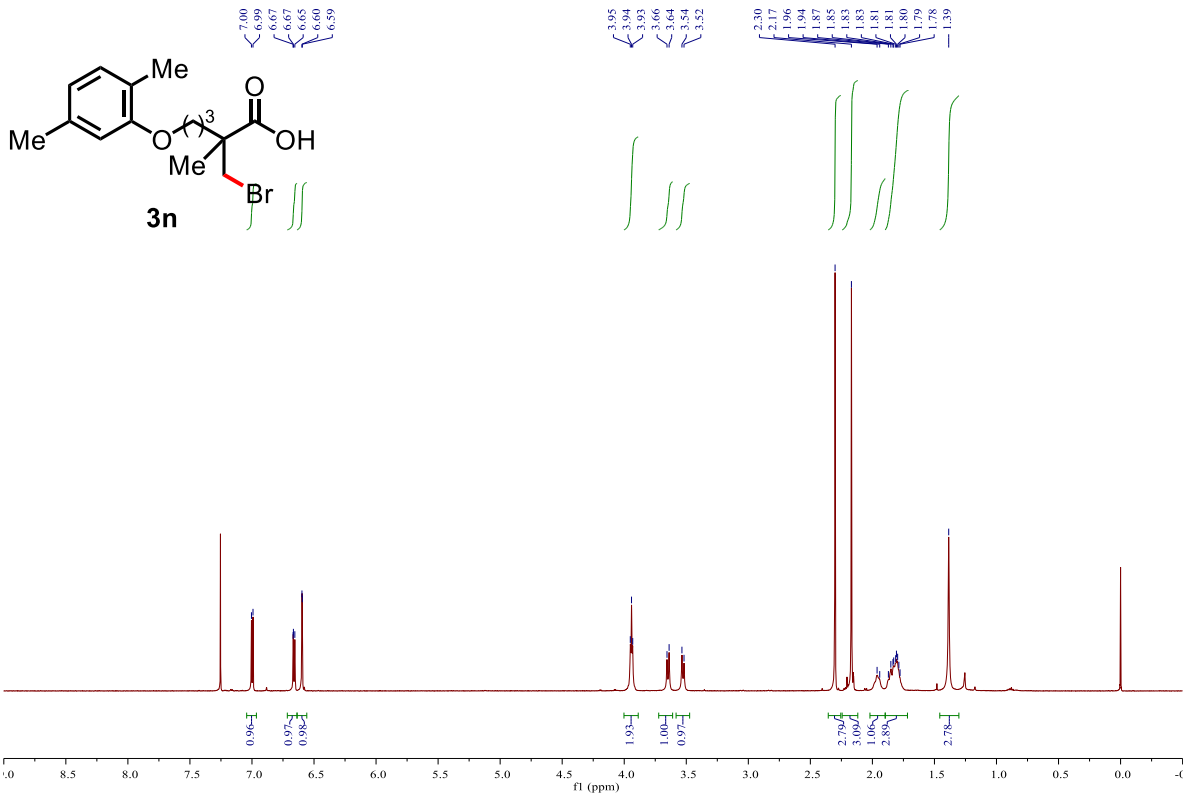

Me
Me
O
3
O
OMe
Me
3k
fl (ppm)

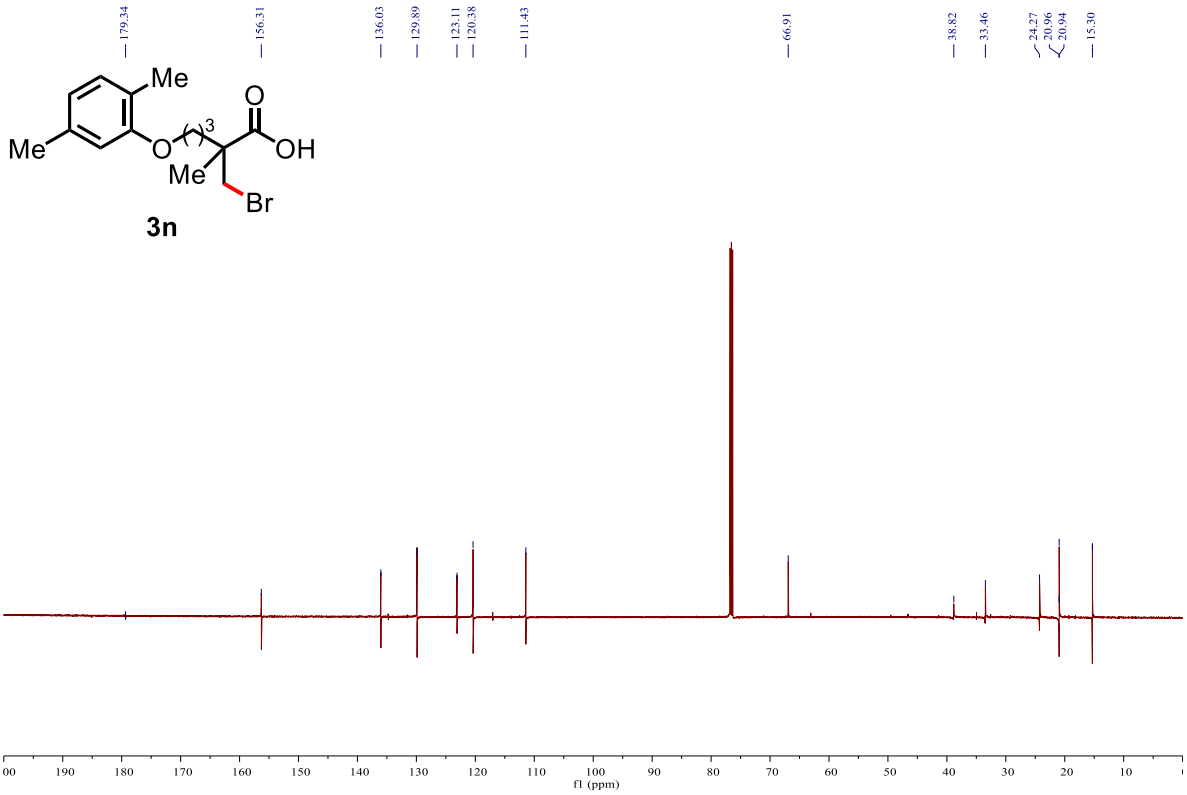

Me
Me
O
OH
Me
CN
3
3l
7.01
7.00
6.68
6.66
6.59
3.96
3.95
3.94
2.74
2.71
2.67
2.65
2.30
2.17
2.02
2.01
1.99
1.99
1.97
1.97
1.95
1.94
1.93
1.92
1.91
1.90
1.86
1.85
1.84
1.83
1.82
1.80
1.79
1.78
1.77
1.76
1.00
1.03
0.97
1.72
0.95
0.96
2.55
2.54
2.03
1.96
2.57
f1 (ppm)

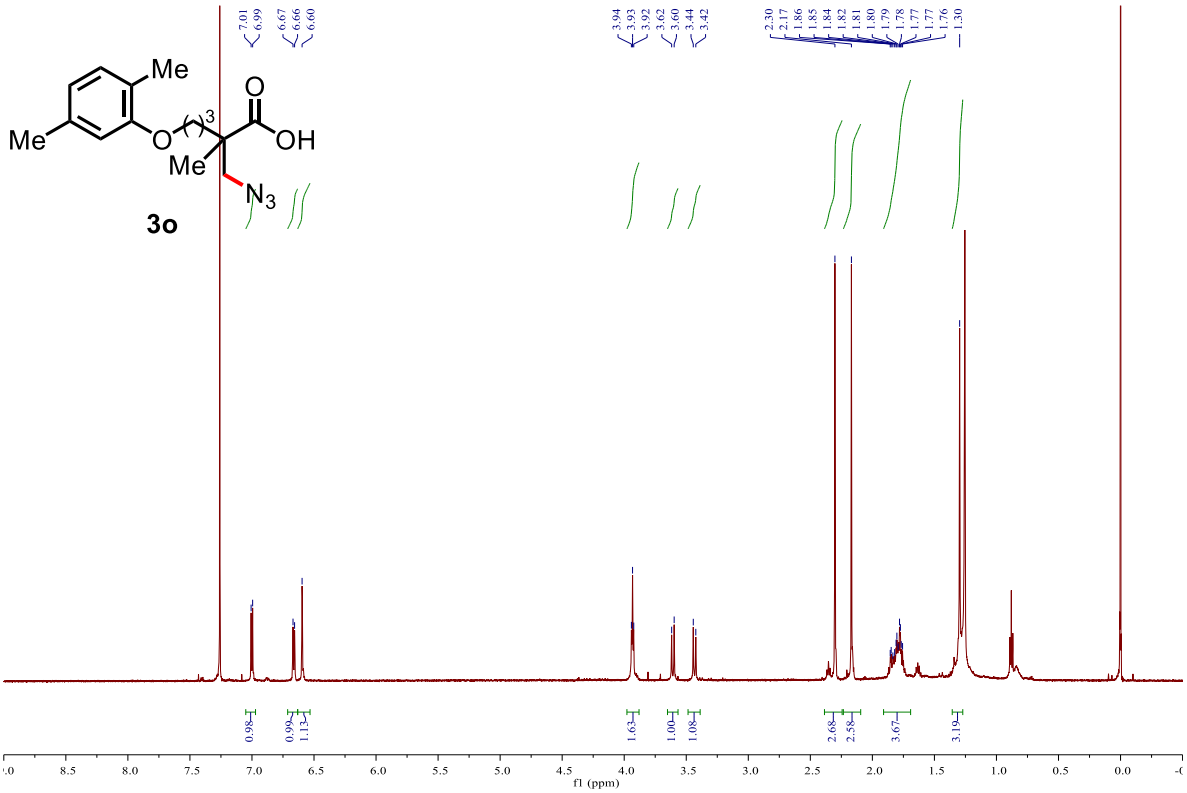

179.56
156.76
136.67
130.56
123.71
121.13
117.21
112.01
67.15
44.30
34.90
25.87
24.93
23.20
21.54
15.90
Me
Me
O
OH
Me
CN
3
3l
f1 (ppm)

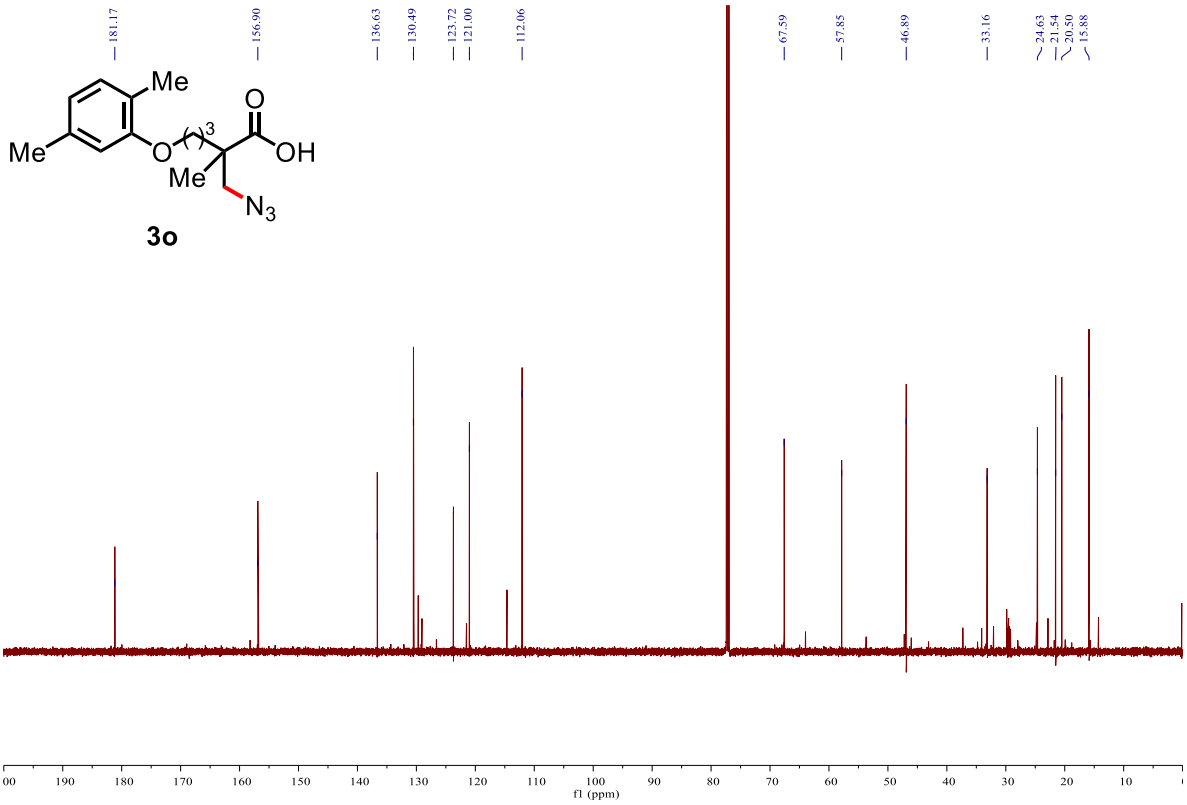

Me
Me
O
OH
Me
F
3m
7.01
6.99
6.67
6.65
6.60
4.61
4.59
4.53
4.51
4.50
4.48
4.42
4.40
3.95
3.94
3.93
2.30
2.17
1.87
1.85
1.82
1.78
1.76
1.25
1.00
0.92
0.87
1.34
1.26
1.70
2.08
2.14
3.18
3.13
f1 (ppm)

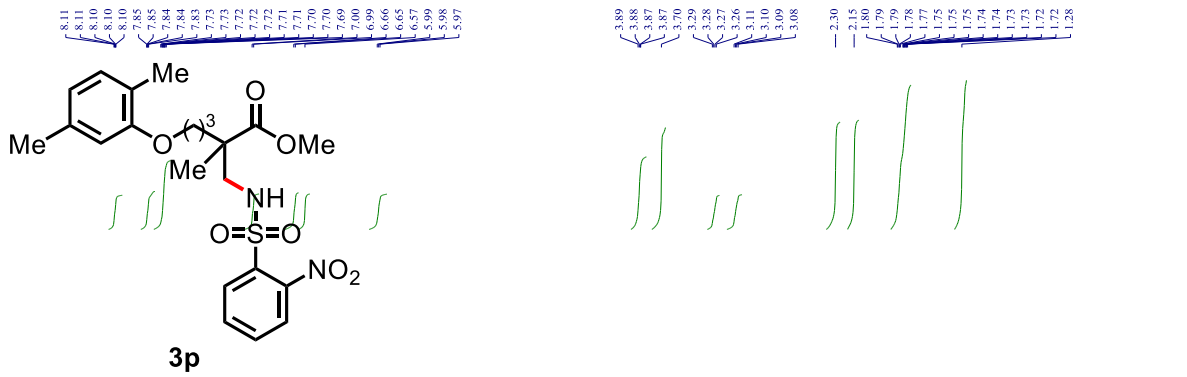

Me
Me
O
OH
Me
F
3m
180.72
156.93
136.63
130.49
123.73
120.99
112.07
87.69
86.53
67.66
47.10
46.98
31.43
31.40
24.54
21.54
19.13
19.10
15.87
f1 (ppm)


Me
Me
O
OH
Me
Br
3n
7.00
6.99
6.67
6.67
6.65
6.60
6.59
3.95
3.94
3.93
3.66
3.64
3.54
3.52
2.30
2.17
1.96
1.94
1.87
1.85
1.83
1.83
1.81
1.81
1.80
1.79
1.78
1.39
0.96
0.97
0.98
1.93
1.00
0.97
2.79
3.09
1.06
2.89
2.78
f1 (ppm)

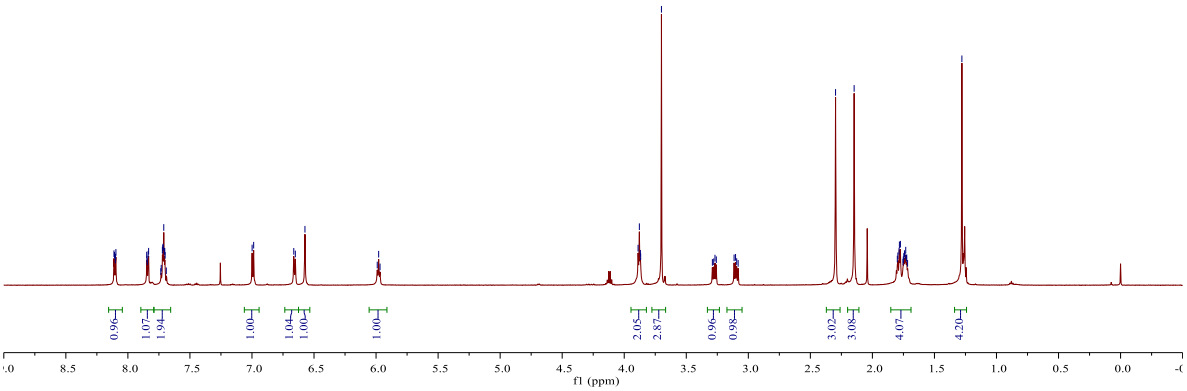

Me
Me
O
OH
Me
Br
3n
179.34
156.31
136.03
129.89
123.11
120.38
111.43
66.91
38.82
33.46
24.27
20.96
20.94
15.30
f1 (ppm)

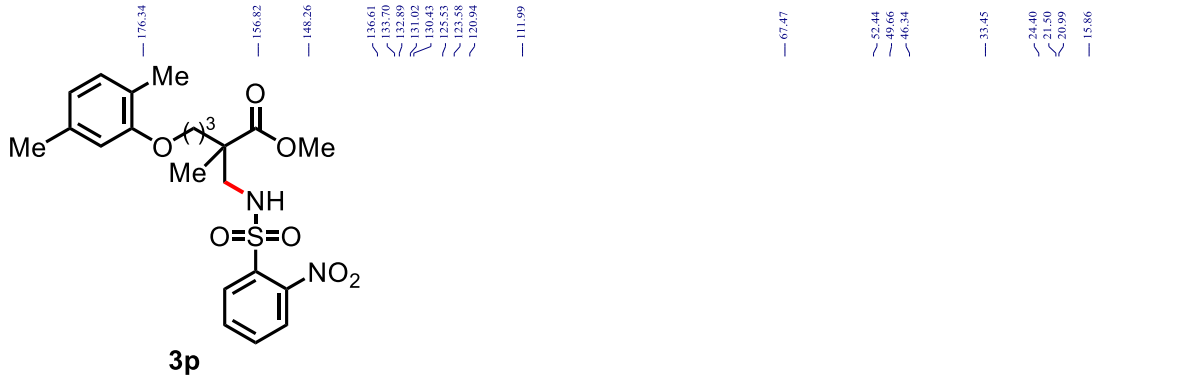

Me
Me
O
OH
Me
N3
3
3o
7.01
6.99
6.67
6.66
6.60
3.94
3.93
3.92
3.62
3.60
3.44
3.42
2.30
2.17
1.86
1.85
1.84
1.82
1.81
1.80
1.79
1.78
1.77
1.77
1.76
1.30
0.98
0.99
1.13
1.63
1.00
1.08
2.68
2.58
3.67
3.19
f1 (ppm)


Me
Me
O
OH
Me
N3
3
3o
181.17
156.90
136.63
130.49
123.72
121.00
112.06
67.59
57.85
46.89
33.16
24.63
21.54
20.50
15.88
f1 (ppm)

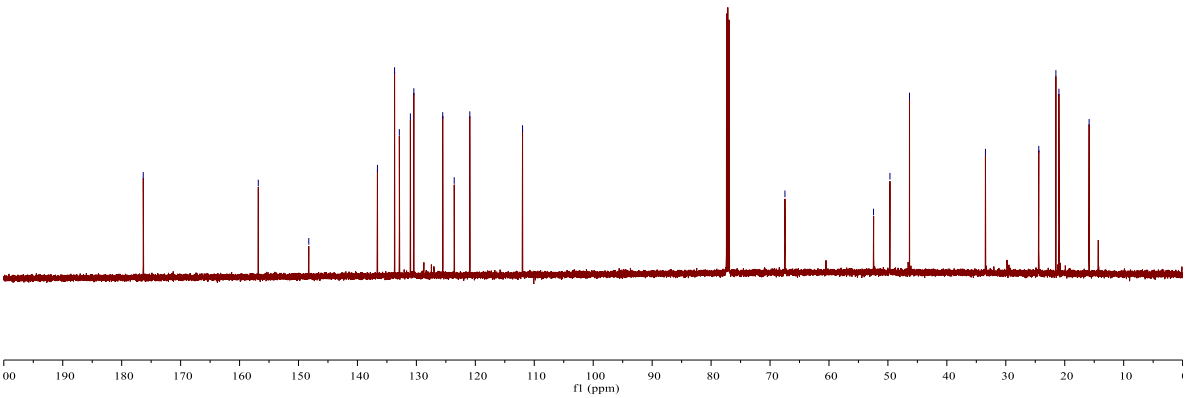


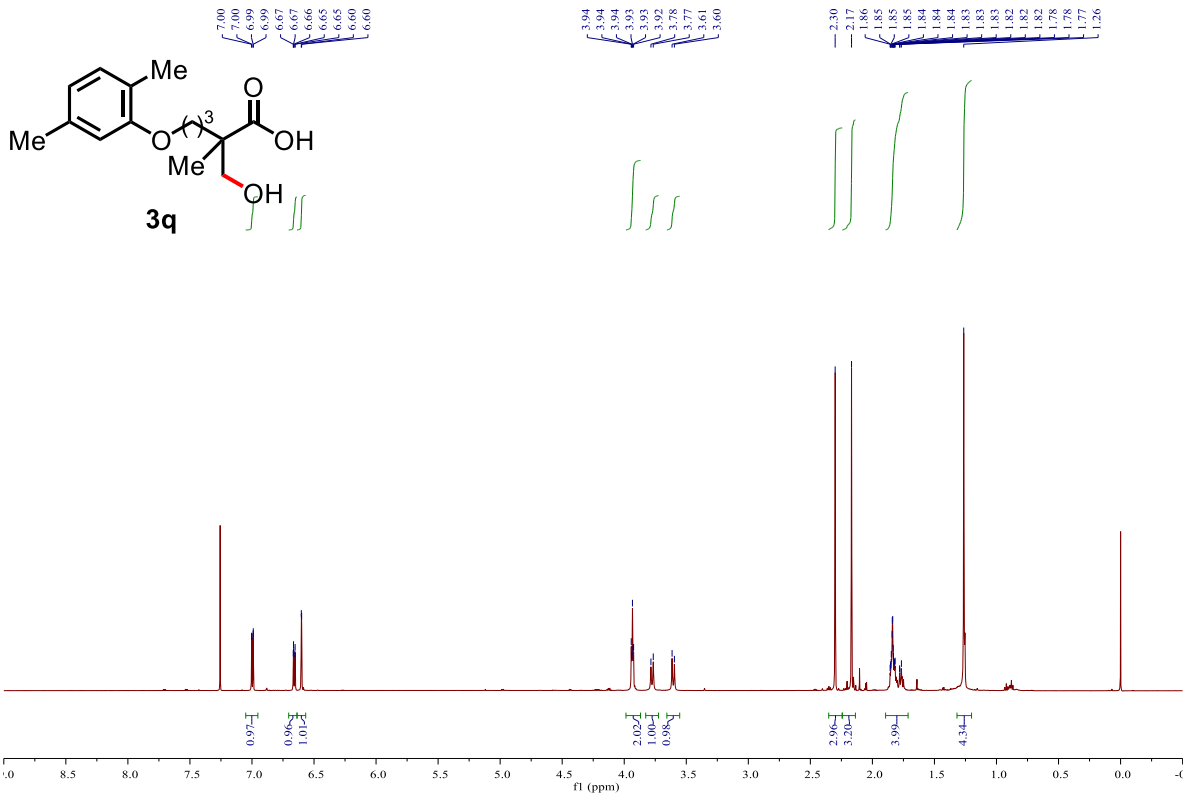
3p

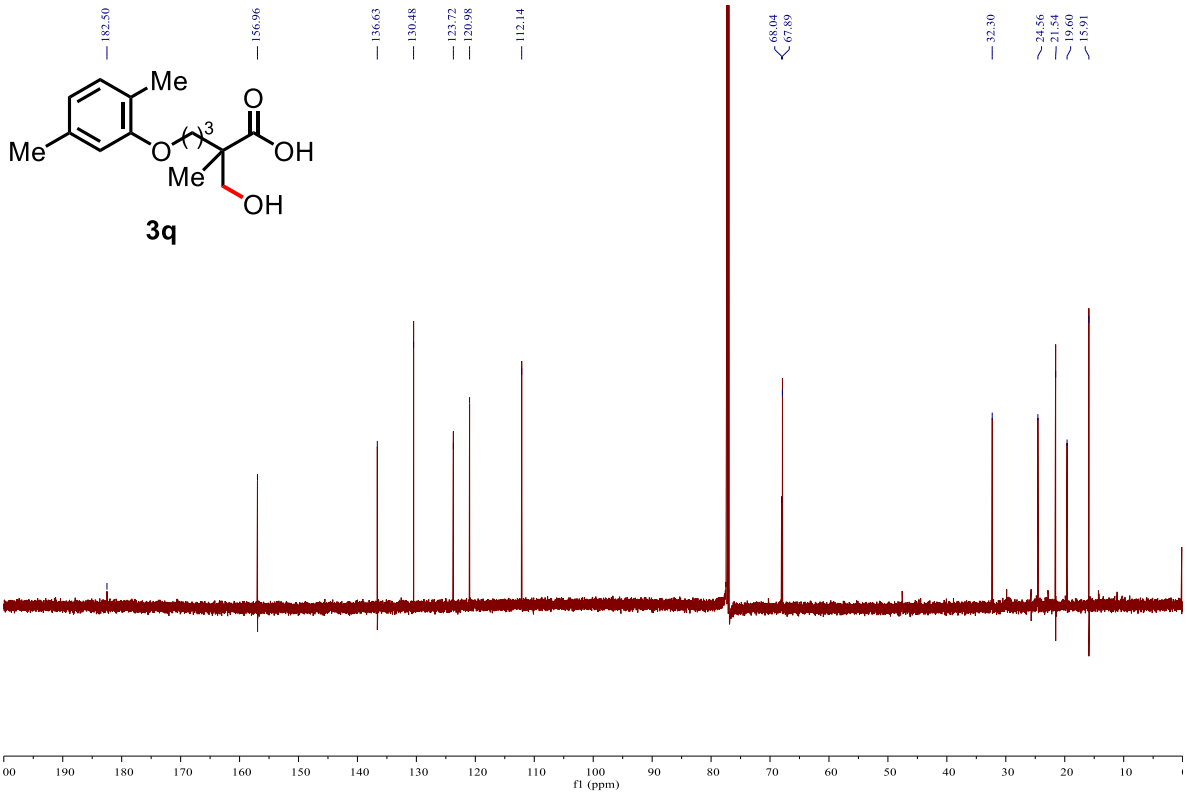


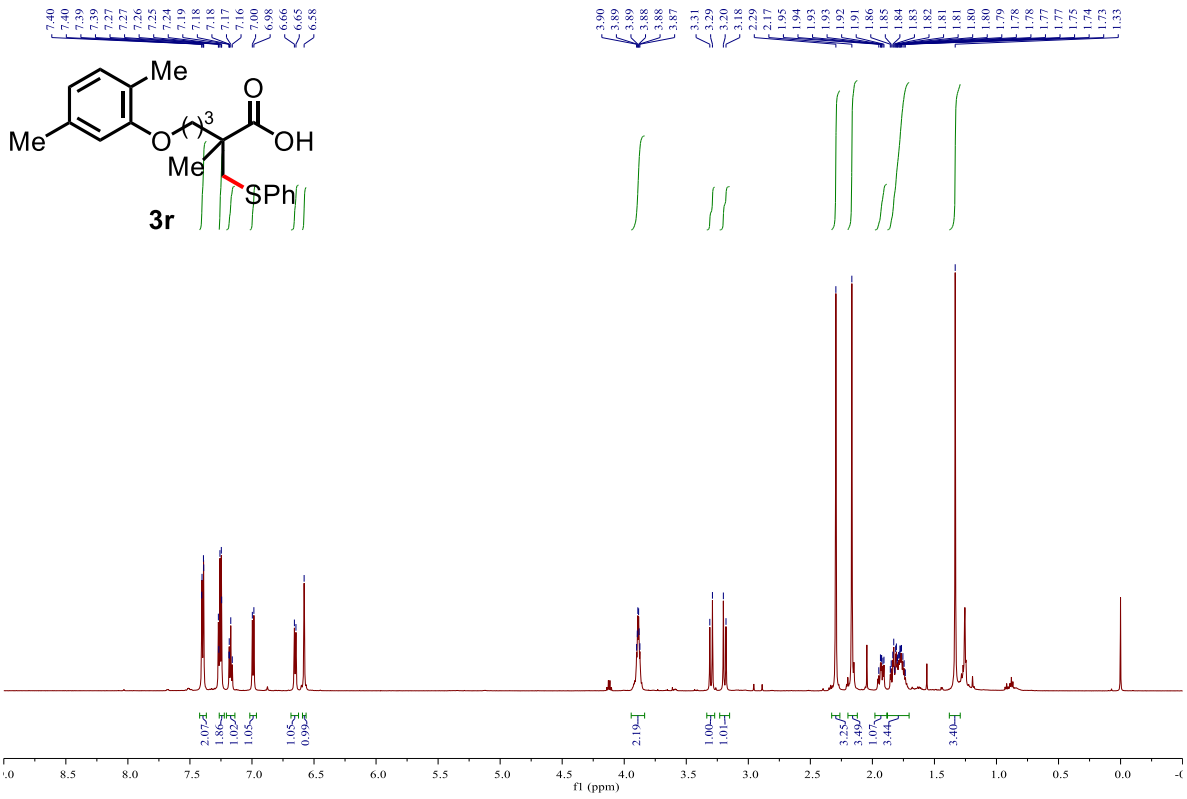


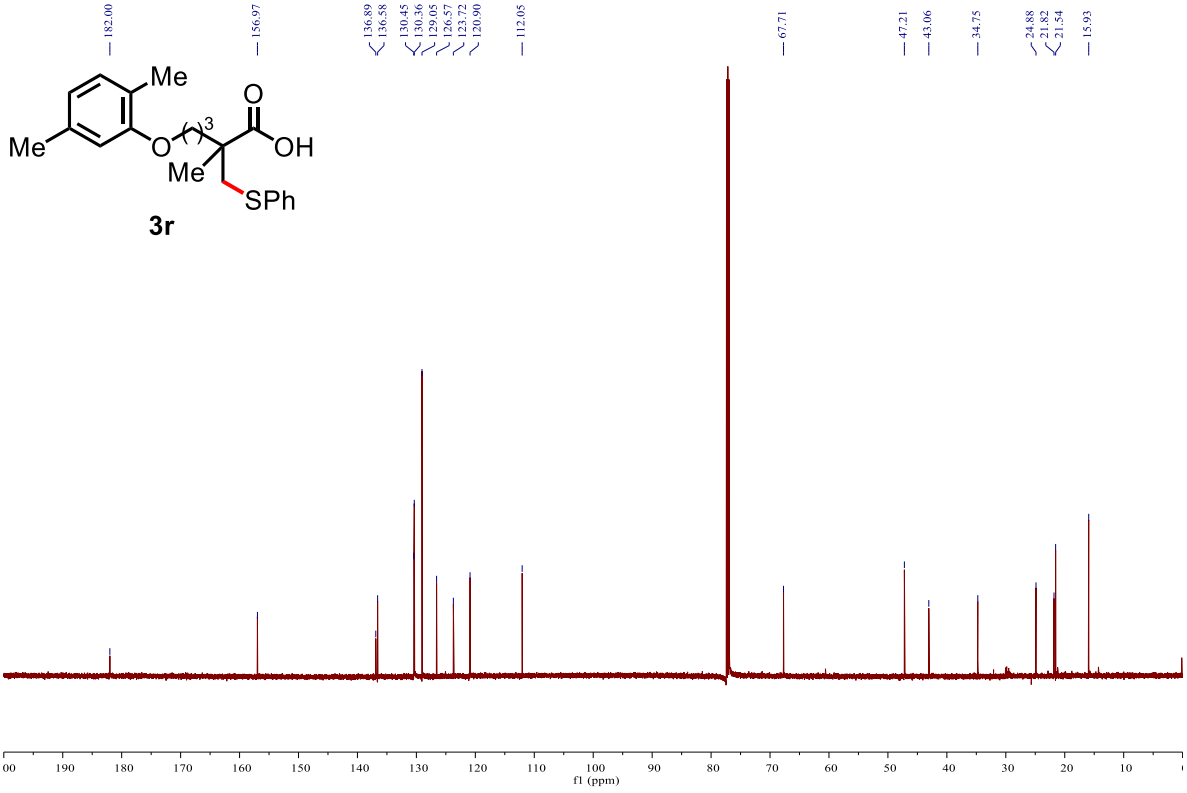
3p




Me
Me
O
3
O
OH
Me
OH
3q
f1 (ppm)


Me
Me
O
3
O
OH
Me
OH
3q
f1 (ppm)


Me
Me
O
OH
Me
SPh
3r
f1 (ppm)


Me
Me
O
OH
Me
SPh
3r
f1 (ppm)