Supplementary Materials for

Catalyst-controlled site-selective methylene C–H lactonization of dicarboxylic acids

Hau Sun Sam Chan *et al*.

Corresponding author: Jin-Quan Yu, yu200@scripps.edu

The PDF file includes:

Table of Contents

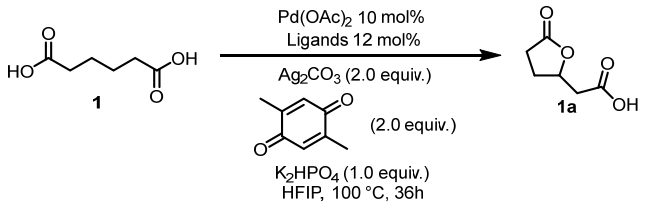
1. General Information

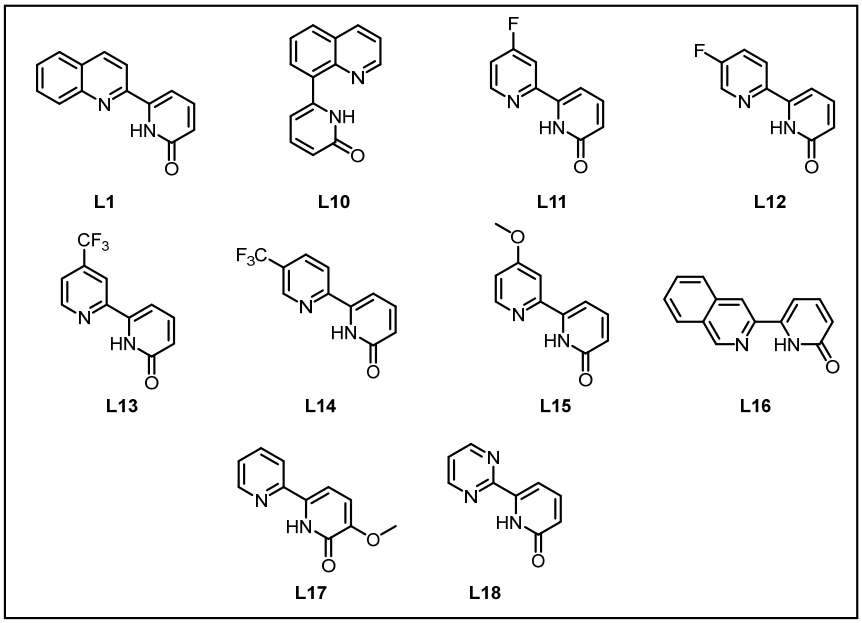
$Pd(OAc)_2$ was purchased from Strem. Solvents were obtained from Sigma-Aldrich, Alfa-Aeser, and Acros, and used directly without further purification. Other reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Analytical thin layer chromatography was performed on 0.25 mm silica gel 60F254 or Merck pre-coated aluminium-backed silica gel F254 plates. ^{1}H NMR spectra were recorded on Bruker AMX-400, Bruker AV-500, or Bruker DRX-600 instruments. 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 AMX-400, Bruker AV-500, or Bruker DRX-600 and were fully decoupled by broad band proton decoupling. Chemical shifts were referenced to the appropriate residual solvent peaks. Column chromatography was performed using E. Merck silica (60, particle size 0.043–0.063 mm), and pTLC was performed on Merck silica plates (60F254). High-resolution mass spectra (HRMS) were recorded on an Agilent Mass spectrometer using ESI-TOF (electrospray ionization-time of flight).

2. Experimental Section for the lactonization reaction

2.1 Optimization data for the lactonization reactions

1. Ligand investigation for β-directed, γ-lactonization:





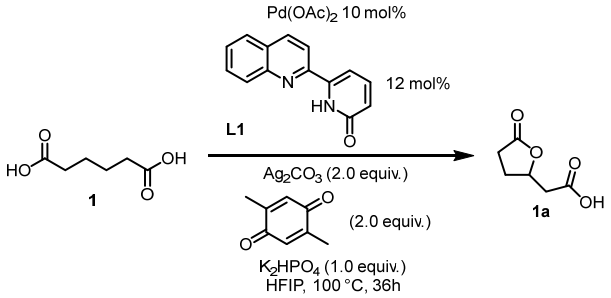
Ligand	Lactone NMR yield (%)	Ligand	Lactone NMR yield (%)
L1	45	**L16**	9
L11	16	**L17**	28
L12	6	**L18**	34
L13	19	**L1**	10
L14	19	**L10**	12
L15	6	**No L**	3

Table S1. Ligand investigation for β-directed, γ-lactonization.

Note: See below for the optimization data leading to the selection of Ag_2CO_3, *p*-xyloquinone, and K_2HPO_4 as the reagents. The optimization process for all the lactonization reactions were carried out simultaneously, with greater focus on the γ-directed, γ-lactonization reaction due to its novelty.

All ligands employed for the exploratory studies are prepared according to literature procedure.(*13*, *39*)

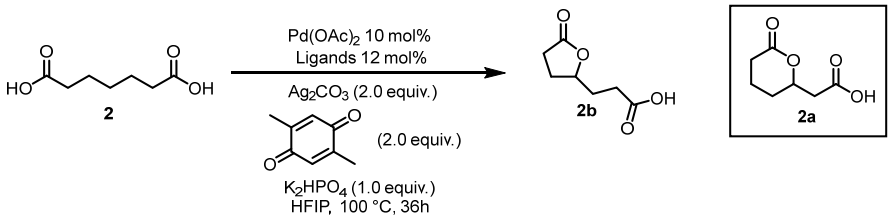
2. Fine-tuning of reaction conditions for β-directed, γ-lactonization:

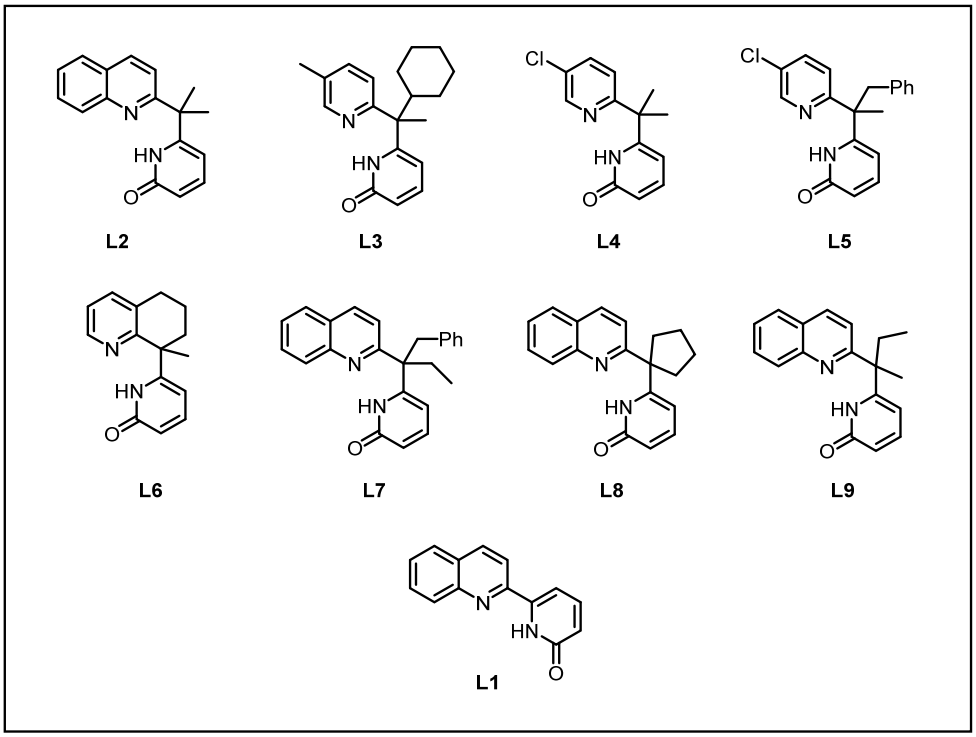


Deviations from reaction condition as shown	Lactone NMR yield (%)
No deviation (Reaction vessel: 10 mL vial)	45
Reaction vessel: 8 mL vial	65
0.75 equiv. K_2HPO_4 (Reaction vessel: 8 mL vial)	65
0.35. equiv. K_2HPO_4 + 0.4 equiv. CsOAc, (Reaction vessel: 8 mL vial)	72
Silver free condition: MnO_2 (4.0 equiv.) instead of Ag_2CO_3 (2.0 equiv.), K_2HPO_4:KH_2PO_4:CsOAc (1.0:1.5:1.0, 0.75 equiv. total)	46

Table S2. Fine-tuning of reaction conditions for β-directed, γ-lactonization.

3. Ligand investigation for γ-directed, γ-lactonization:

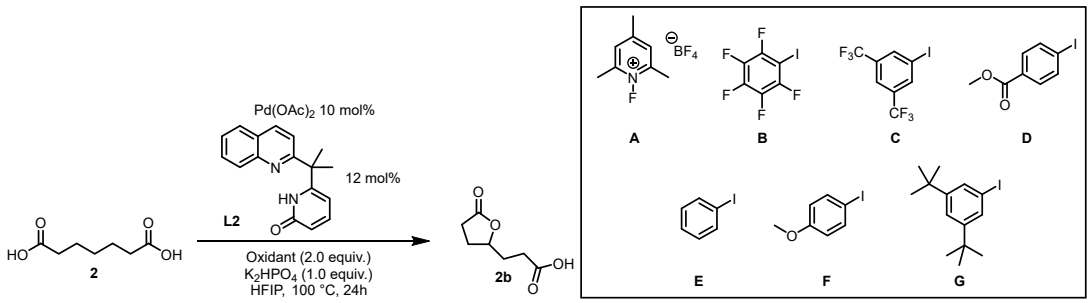




Ligand	Lactone NMR yield (%)	Ligand	Lactone NMR yield (%)
L2	52	**L7**	26
L3	0	**L8**	35
L4	20	**L9**	50
L5	21	**L1**	13 (**2a**)
L6	13	**No L**	0

Table S3. Ligand investigation for γ-directed, γ-lactonization.

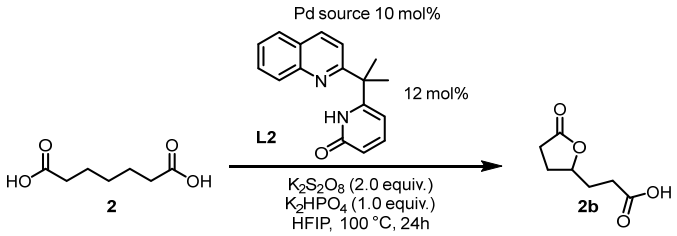
4. Investigation of oxidants for γ-directed, γ-lactonization:



Oxidant	NMR yield of 2b (%)	Oxidant	NMR yield of 2b (%)
TBHP in H_2O	2	$BzOO^tBu$	8
CMHP	5	BzOOBz	0
Na_2CO_3•1.5 H_2O_2	0	Lauroyl peroxide	0
H_2O_2 in H_2O	2	$^tBuOO^tBu$	5
H_2O_2•urea	0	*m*CPBA	0
$AcOO^tBu$	7	$Na_2S_2O_8$	12
$K_2S_2O_8$	11	DMP	0
$(TBA)_2S_2O_8$	0	**B**	4
Oxone	0	**C**	5
NFSI	0	**D**	5
A	0	**E**	0
Selectfluor	0	**F**	0
Selectfluor 2	0	**G**	0
PIDA	0	I_2	0
PIFA	0	$Ce(SO_4)_2$	6

Table S4. Investigation of oxidants for γ-directed, γ-lactonization.

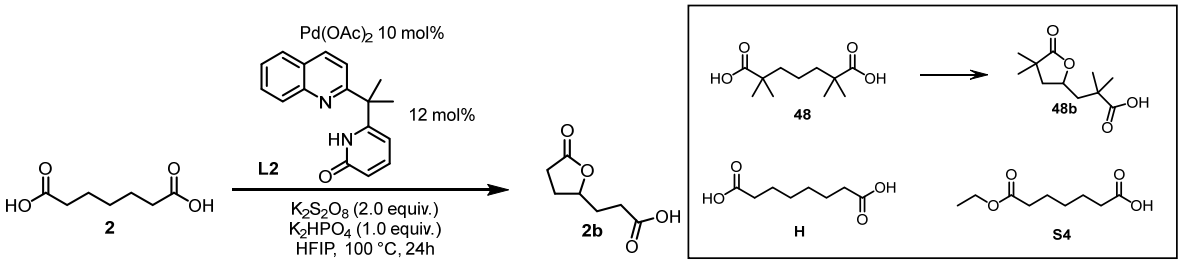
5. Investigation of palladium source for γ-directed, γ-lactonization:



Palladium source	NMR yield of 2b (%)
$Pd(OAc)_2$	11
$PdCl_2(MeCN)_2$	2
$Pd(MeCN)_4(BF_4)_2$	8
$PdCl_2(PhCN)_2$	3
$Pd(TFA)_2$	13
$Pd_2(dba)_3$	3
$PdCl_2$	4
$Pd(MeCN)_4(OTf)_2$	7

Table S5. Investigation of palladium source for γ-directed, γ-lactonization.

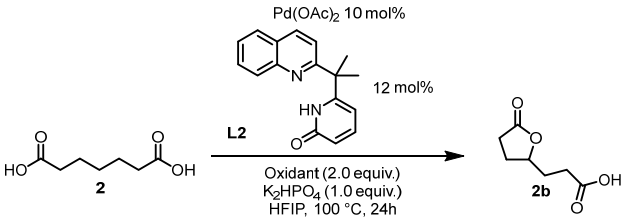
6. General control experiments for γ-directed, γ-lactonization:

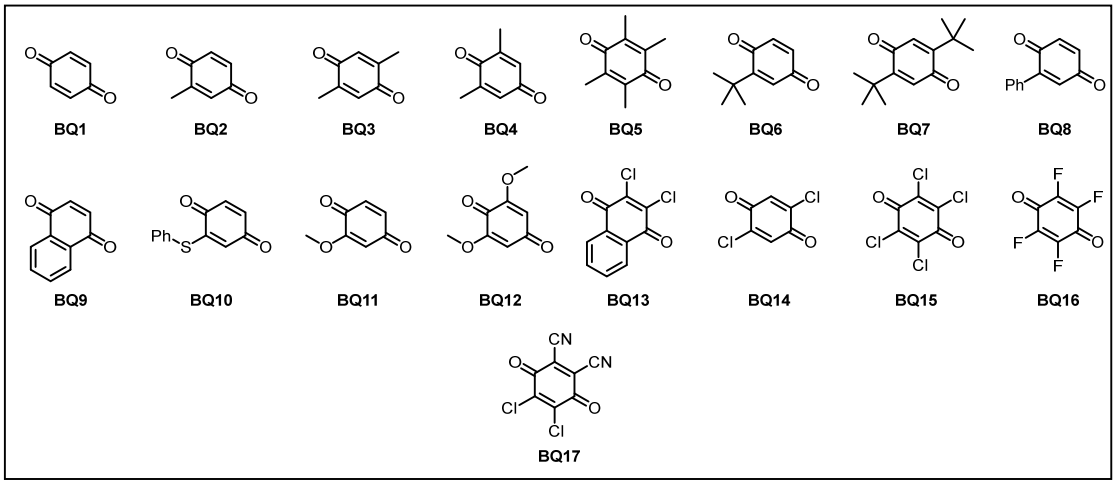


Deviations from reaction condition as shown	NMR yield of lactone (%)
No Palladium	0
No Ligand	0
No K_2HPO_4	0
2.0 equiv. K_2HPO_4	11
No $K_2S_2O_8$	4
30% Pd and Ligand	5
With **48** as substrate	21 (of **48b**)
With **H** as substrate	0
With **S4** as substrate	0

Table S6. General control experiments for γ-directed, γ-lactonization.

7. Investigation of other oxidants for γ-directed, γ-lactonization:

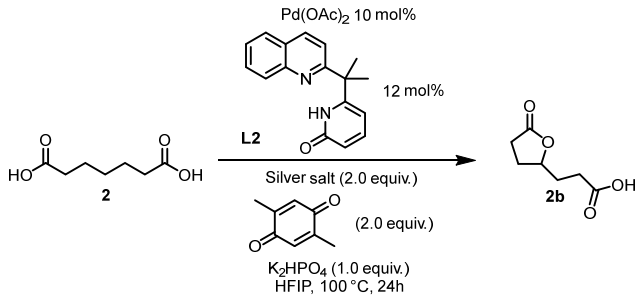




Oxidant	NMR yield of 2b (%)	Oxidant	NMR yield of 2b (%)
AgTFA	0	BQ1	9
$AgNO_3$	7	BQ2	7
Ag_2O	15	BQ3	19
AgF	14	BQ4	13
AgOAc	17	BQ5	16
Ag_3PO_4	7	BQ6	10
Ag_2CO_3	13	BQ7	4
$Cu(OAc)_2$	0	BQ8	20
$CuSO_4•5H_2O$	3	BQ9	5
CuF_2	2	BQ10	0
CuO	2	BQ11	4
$CuBr_2$	1	BQ12	9
$CuCl_2$	0	BQ13	3
$Cu(ClO_4)_2$	0	BQ14	0
$Cu_3(PO_4)_2$	2	BQ15	0
$CuCO_3$	1	BQ16	0
		BQ17	0

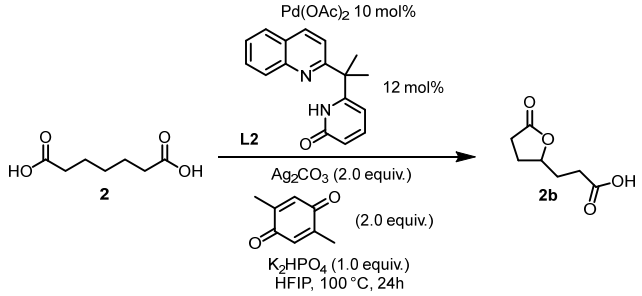
Table S7. Investigation of other oxidants for γ-directed, γ-lactonization.

8. Investigation of reaction conditions with silver salts and BQ3 for γ-directed, γ-lactonization:



Silver salts	NMR yield of 2b (%)
AgOAc	23
Ag_2O	27
AgF	29
Ag_3PO_4	41
Ag_2CO_3	52

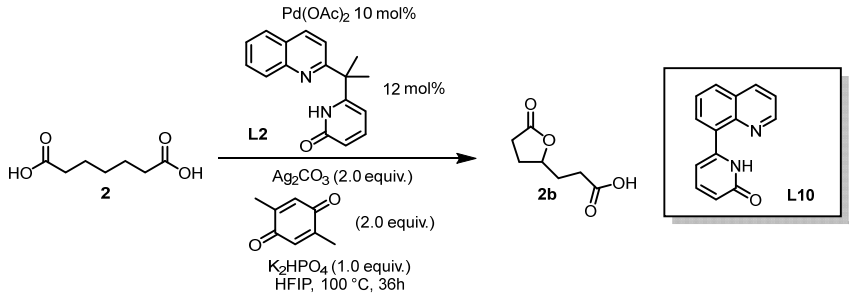
Table S8. Investigation of reaction conditions with silver salts for γ-directed, γ-lactonization.



Deviations from reaction condition as shown	NMR yield of 2b (%)
Replace Ag_2CO_3 with K_2CO_3	0
Replace Ag_2CO_3 with $K_2S_2O_8$	34
0.5 equiv. BQ3 + 0.5 equiv. Ag_2CO_3	26
1.0 equiv. BQ3 + 1.0 equiv. Ag_2CO_3	28
Reaction temperature at 80 °C	40
Reaction temperature at 120 °C	35
Reaction time: 12h	35
Reaction time: 36h	52
Reaction time: 72h	45

Table S9. Investigation of reaction conditions with **BQ3** for γ-directed, γ-lactonization.

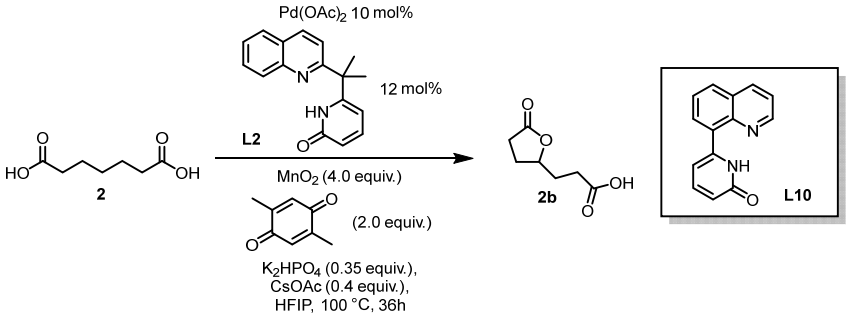
9. Further fine-tuning of reaction conditions for γ-directed, γ-lactonization:



Deviations from reaction condition as shown	Lactone NMR yield (%)
No deviation (Reaction vessel: 10 mL vial)	52
Reaction vessel: 8 mL vial	58
0.75 equiv. K_2HPO_4 (Reaction vessel: 8 mL vial)	60
0.35. equiv. K_2HPO_4 + 0.4 equiv. CsOAc, (Reaction vessel: 8 mL vial)	65
0.35. equiv. K_2HPO_4 + 0.4 equiv. CsOAc, **L10** instead of **L2,** (Reaction vessel: 8 mL vial)	69
0.35. equiv. K_2HPO_4 + 0.4 equiv. CsOAc, **L10** instead of **L2**, 48h reaction time, (Reaction vessel: 8 mL vial)	75

Table S10. Further fine-tuning of reaction conditions for γ-directed, γ-lactonization.

10. Optimization for silver-free reaction conditions using MnO_2 as oxidant for γ-directed, γ-lactonization:



Deviations from reaction condition as shown	Lactone NMR yield (%)
No deviation (Reaction vessel: 8 mL vial)	46
2.0 equiv. MnO_2	17
6.0 equiv. MnO_2	40
K_2HPO_4:KH_2PO_4:CsOAc (1:1.5:1, total 0.75 equiv.)	60
K_2HPO_4:KH_2PO_4:CsOAc (1:1.5:1, total 1.0 equiv.)	34
K_2HPO_4:KH_2PO_4:CsOAc (1:2:1, total 0.75 equiv.)	24
K_2HPO_4:KH_2PO_4:CsOAc (1:2:1, total 1.0 equiv.)	7
Reaction time 48h	38
L10 instead of **L2**, K_2HPO_4:KH_2PO_4:CsOAc (1:1.5:1, total 0.75 equiv.)	62
L10 instead of **L2**, K_2HPO_4:KH_2PO_4:CsOAc (1:1.5:1, total 0.75 equiv.), 48h reaction time	65

Table S11. Optimization for silver-free reaction conditions using MnO_2 as oxidant for γ-directed, γ-lactonization.

2.2 Reaction procedures of the β-directed, γ-C–H lactonization reaction

General procedure for the β-directed, γ-C–H lactonization reaction using Ag_2CO_3 as oxidant

A pictorial guide is also provided below to assist reaction set-up, work-up, and analysis.

To a 2-dram vial was added the substrate (0.1 mmol), $Pd(OAc)_2$ (10 mol%, 0.01 mmol), ligand (12 mol%, 0.012 mmol), *p*-xyloquinone (0.2 mmol), Ag_2CO_3 (0.2 mmol), K_2HPO_4 (0.035 mmol) and CsOAc (0.04 mmol, preferably added from a stock solution in HFIP as CsOAc is hygroscopic). HFIP (1.0 mL, or the volume needed to make up to 1.0 mL if a stock solution of CsOAc was used) and a stir-bar was then added, followed by sealing the reaction vessel with a PTFE septum inserted between the vial and its cap. **(Note: $Pd(OAc)_2$, ligand, *p*-xyloquinone, CsOAc, and the substrate could all be prepared as a stock solution in HFIP. The use of stock solution is recommended for setting up a series of reactions to maximize work efficiency).** The reaction mixture was sonicated for 30 seconds before stirring at 200 rpm and 100 °C (heating block temperature) for 36 hours. The reaction mixture was then cooled to room temperature and diluted with dichloromethane (1.0 mL), followed by addition of deionized water (2.0 mL), aq. 6M HCl (0.3 mL), brine (1.0 mL) and then shaken vigorously. The lower organic layer was carefully pipetted and filtered through a short plug of Celite®. The remaining aqueous layer was extracted with CH_2Cl_2 (1.0 mL) twice and the organic layer was pipetted and filtered as mentioned. The combined organic layer was then evaporated to dryness. The crude was then taken into $CDCl_3$ (0.6 mL) with CH_2Br_2 (10.0 μL) as the internal standard to determine the assay yield of the reaction by ^1H NMR spectroscopy. The isolation of the product was carried out with aqueous extractions of the organic layer (in 0.6 mL $CDCl_3$ diluted with 2.0 mL CH_2Cl_2) with sat. aq. $NaHCO_3$ solution (1.0 mL each, 3 times). The collected aqueous layer was then acidified by aq. 6M HCl to pH ~ 2 and extracted with EtOAc (1.0 mL, 3 times). The combined EtOAc layers was dried with anhydrous $MgSO_4$, filtered, and evaporated to dryness. The product was either further purified by column chromatography (General procedure for gradient elution unless stated otherwise: begin with 20% EtOAc/hexane + 1% AcOH, and increase the composition of EtOAc by 10% for every 8 mL of eluent used to 100% EtOAc + 1% AcOH, collecting 1.0-2.0 mL fractions. It was observed that the R_f values of carboxylic acids obtained by TLC analysis could not be directly used as a guide for column chromatography. Hence, the gradient elution method was employed for their purification.) or pTLC (exact eluent composition mentioned below for each example) or subject to further derivatization into benzyl esters for isolation if purification of the lactone acid was found to be not straightforward.

Procedure for the gram scale β-directed, γ-C–H lactonization reaction of adipic acid 1 using Ag_2CO_3 as oxidant

To a 150 mL heavy wall pressure vessel with an internal thread (see picture below) was added adipic acid (1.0 g, 6.84 mmol), $Pd(OAc)_2$ (153.0 mg, 0.68 mmol), ligand (151.0 mg, 0.68 mmol), *p*-xyloquinone (1.87 g, 13.7 mmol), Ag_2CO_3 (3.78 g, 13.7 mmol), K_2HPO_4 (416.0 mg, 2.39 mmol) and CsOAc (524.0 mg, 2.73 mmol, a stock solution is not required). HFIP (68.0 mL) and a stir-bar was then added, followed by sealing the reaction vessel with a screwed-on PTFE bushing. The reaction mixture was sonicated for **5 minutes** before stirring at **500 rpm** and 100 °C (oil bath temperature) for 36 hours. The reaction mixture was then cooled to room temperature and formic acid (5.0 mL) was added, followed by filtration through a short plug of Celite®. The filtrate was then concentrated under reduced pressure. The crude was dissolved in CH_2Cl_2 (20.0 mL) and extracted with sat. aq. $NaHCO_3$ (10.0 mL, 3 times). The aqueous layer was collected and combined, acidified by aq. 6M HCl to pH ~

2 (slow addition of acid with vigorous stirring is recommended) and extracted with EtOAc (10.0 mL, 3 times). The combined EtOAc layers was dried with anhydrous $MgSO_4$, filtered, and evaporated to dryness. The product was purified by column chromatography (Begin with 50% EtOAc/hexane + 1% AcOH (300 mL), then 75% EtOAc/hexane + 1% AcOH (300 mL), and finally 100% EtOAc + 1% AcOH (300 mL)). The desired product **1a** was isolated as a straw-coloured oil (607.3 mg, 4.21 mmol, 62%).

Experimental observation:

General procedure for the β-directed, γ-C–H lactonization reaction using MnO_2 as oxidant

To a 2-dram vial was added the substrate (0.1 mmol), $Pd(OAc)_2$ (10 mol%, 0.01 mmol), ligand (12 mol%, 0.012 mmol), *p*-xyloquinone (0.2 mmol), MnO_2 (0.4 mmol), K_2HPO_4 (0.021 mmol), KH_2PO_4 (0.032 mmol), CsOAc (0.021 mmol, preferably added from a stock solution in HFIP as CsOAc is hygroscopic). HFIP (1.0 mL, or the volume needed to make up to 1.0 mL if a stock solution of CsOAc was used) and a stir-bar was then added, followed by sealing the reaction vessel with a PTFE septum inserted between the vial and its cap. **(Note: $Pd(OAc)_2$, ligand, *p*-xyloquinone, CsOAc, and the substrate could all be prepared as a stock solution in HFIP. The use of stock solution is recommended for setting up a series of reactions to maximize work efficiency).** The reaction mixture was sonicated for 30 seconds before stirring at 200 rpm and 100 °C (heating block temperature) for 36-48 hours. The reaction mixture was then cooled to room temperature and diluted with dichloromethane (1.0 mL), followed by addition of deionized water (2.0 mL), aq. 6M HCl (0.3 mL), brine (1.0 mL) and then shaken vigorously. The lower organic layer was carefully pipetted and filtered through a short plug of Celite®. The remaining aqueous layer was extracted with CH_2Cl_2 (1.0 mL)

twice and the organic layer was pipetted and filtered as mentioned. The combined organic layer was then evaporated to dryness. The crude was then taken into $CDCl_3$ (0.6 mL) with CH_2Br_2 (10.0 µL) as the internal standard to determine the assay yield of the reaction by ^1H NMR spectroscopy. The isolation of the product was carried out with aqueous extractions of the organic layer (in 0.6 mL $CDCl_3$ diluted with 2.0 mL CH_2Cl_2) with sat. aq. $NaHCO_3$ solution (1.0 mL each, 3 times). The collected aqueous layer was then acidified by aq. 6M HCl to pH ~ 2 and extracted with EtOAc (1.0 mL, 3 times). The combined EtOAc layers was dried with anhydrous $MgSO_4$, filtered, and evaporated to dryness. The product was either further purified by column chromatography (General procedure for gradient elution unless stated otherwise: begin with 20% EtOAc/hexane + 1% AcOH, and increase the composition of EtOAc by 10% for every 8 mL of eluent used to 100% EtOAc + 1% AcOH, collecting 1.0-2.0 mL fractions. It was observed that the R_f values of carboxylic acids obtained by TLC analysis could not be directly used as a guide for column chromatography. Hence, the gradient elution method was employed for their purification.) or pTLC (exact eluent composition mentioned below for each example) or subject to further derivatization into benzyl esters for isolation if purification of the lactone acid was found to be not straightforward.

Note: Using the correct type of MnO_2 is crucial for reproducibility. MnO_2 (mesh, on the left) was found to be more active for this reaction than MnO_2 (powder, on the right).

General procedure for benzyl ester formation

To the product obtained after aqueous extraction with sat. $NaHCO_3$ solution as mentioned above was added dry CH_2Cl_2 (2.0 mL), BnOH (1.2 eq.), DMAP (1.2 eq.) and EDCI (1.2 eq.) sequentially at room temperature. The reaction mixture was stirred at room temperature overnight, and completion of the reaction was confirmed by TLC analysis of the reaction mixture. The reaction mixture was then

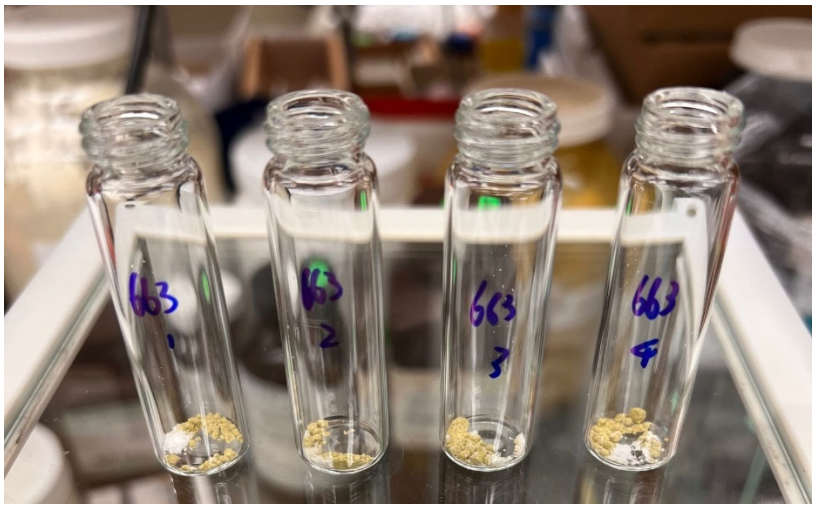
quenched by the addition of water and extracted with CH_2Cl_2 (3 times), and the desired product was purified by pTLC (exact eluent composition mentioned below for each example).

A pictorial guide for reaction set-up, work-up, and expected observations (Applicable to both β-directed and γ-directed lactonization reactions).

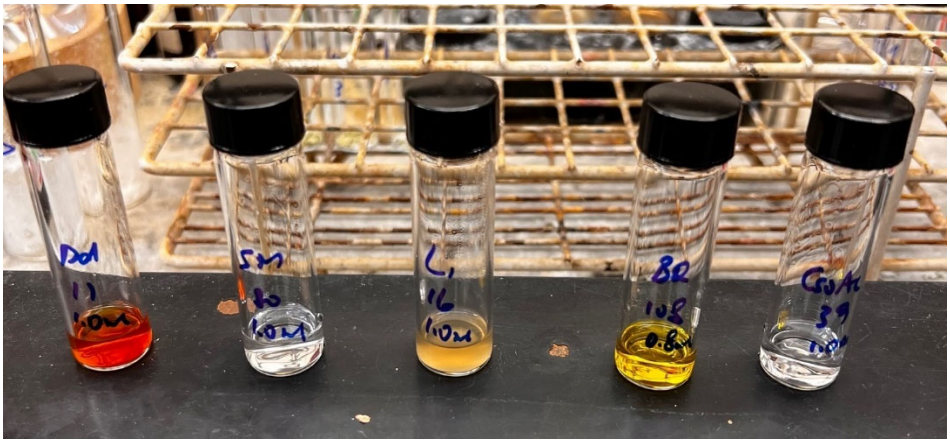
Scenario: Setting up 4 reactions for the conversion of pimelic acid **2** to lactone **2b**.

1. Weigh $Pd(OAc)_2$ (5.0 eq., to be dissolved in 1.0 mL HFIP), pimelic acid **2** (5.0 eq., to be dissolved in 1.0 mL HFIP), Ligand **L2** (5.0 eq., to be dissolved in 1.0 mL HFIP. Vial is labelled L1 in the picture, but it is ligand **L2** that was used), *p*-xyloquinone (4.0 eq., to be dissolved in 0.8 mL HFIP), and CsOAc (5.0 eq., to be dissolved into 1.0 mL HFIP) into 5 separate vials.

2. Weigh Ag_2CO_3 (2.0 eq. each), and K_2HPO_4 (0.35 eq. each) into 4 separate 2-dram vials, whereby each serves as the reaction vessel.

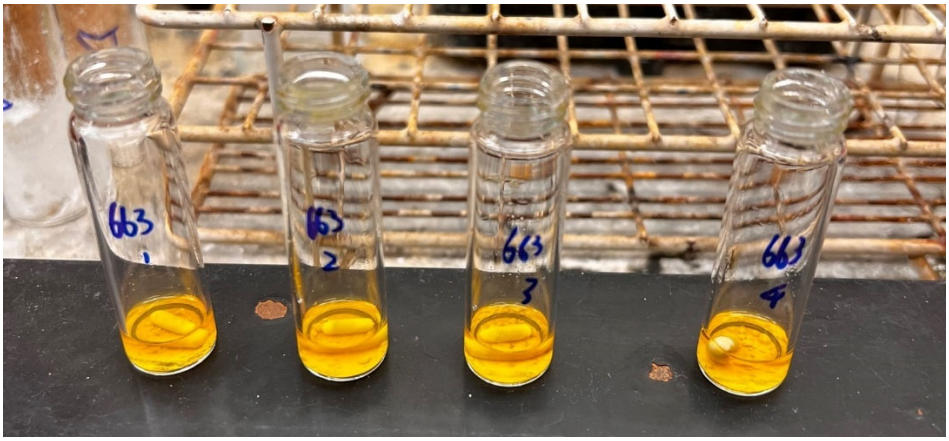


3. Add the required volume of HFIP into the vials containing $Pd(OAc)_2$ (1.0 mL), pimelic acid **2** (1.0 mL), ligand **L2** (1.0 mL), *p*-xyloquinone (0.8 mL), and CsOAc (1.0 mL). It is recommended to sonicate the mixture to facilitate dissolution of the solids to obtain homogenous solutions.



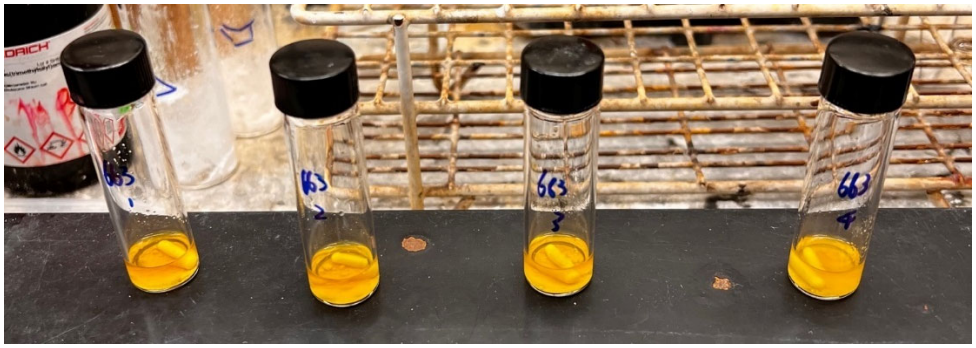
4. Use an autopipette or a syringe to add 0.2 mL each of the $Pd(OAc)_2$, pimelic acid **2**, ligand **L2**, *p*-xyloquinone, and CsOAc solutions into the 4 reaction vessels.

5. Add one stir bar to each of the reaction vessel.

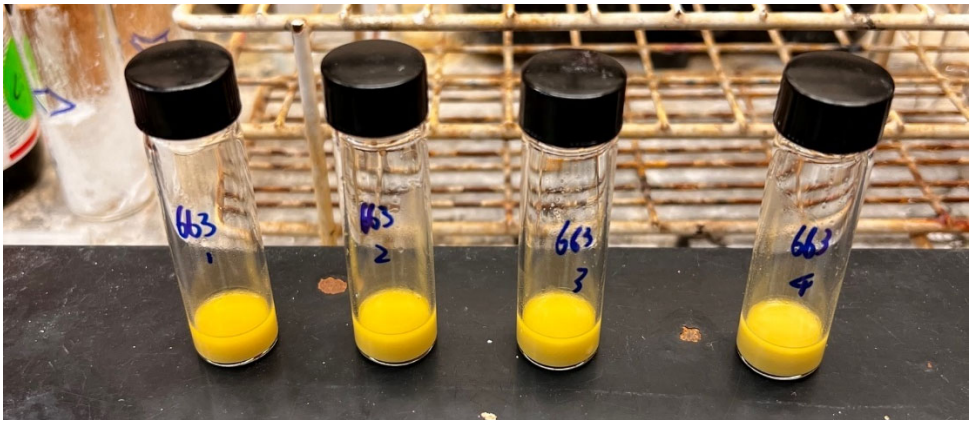


6. Prepare 4 vial caps with PTFE septum (glossy side of the septum should be in contact with the reaction vessel).

7. Put on the caps. Make sure the caps are tightly screwed to the vial and the reaction vessels should therefore be sealed. Tightening too much is not recommended as it would deform the PTFE septum and lead to solvent leakage.

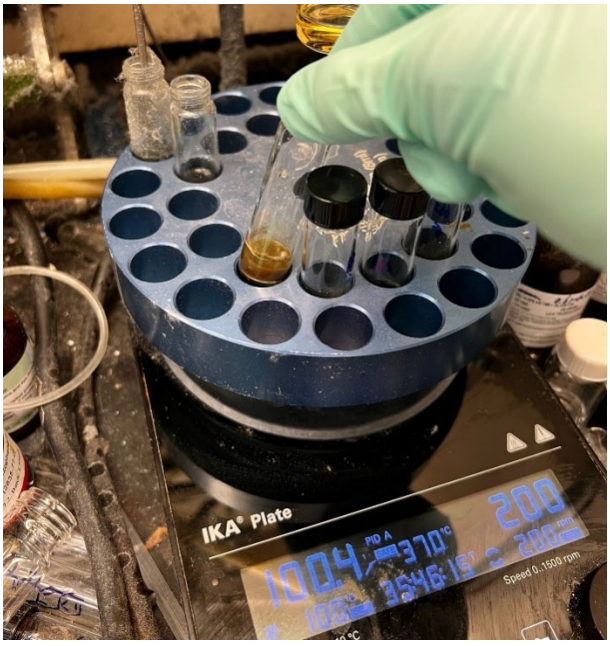


8. Sonicate the reaction mixture, whereby the reaction mixtures will then acquire a milky appearance. Make sure the caps are still tightly screwed to the vial afterwards.

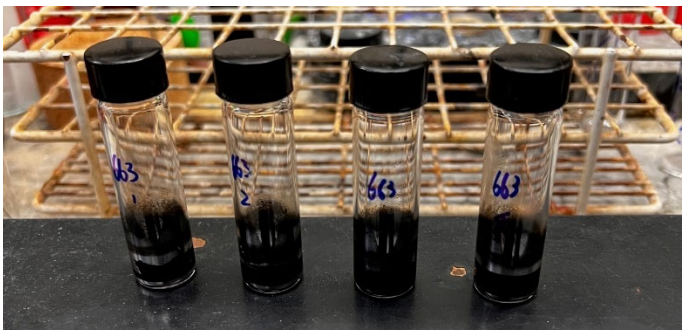


9. Load the reaction vessels onto the heating block, block temperature 100 °C, stirring rate 200 rpm, for 36 hours (Do not let the reactions run for longer than 36 hours, as yields were found to decrease with extended reaction time, please see optimization data above).

10. Colour of the reaction mixture changes from bright yellow before heating, to brown/crimson with ligand **L2** after ~15 minutes of heating at 100 °C (block temperature). With ligand **L1**, the colour changes from bright yellow to olive green (~5 minutes), and then to brown/crimson (~15-30 minutes) (not shown here). **Note:** colour changes of the reaction mixture occur faster with vials.

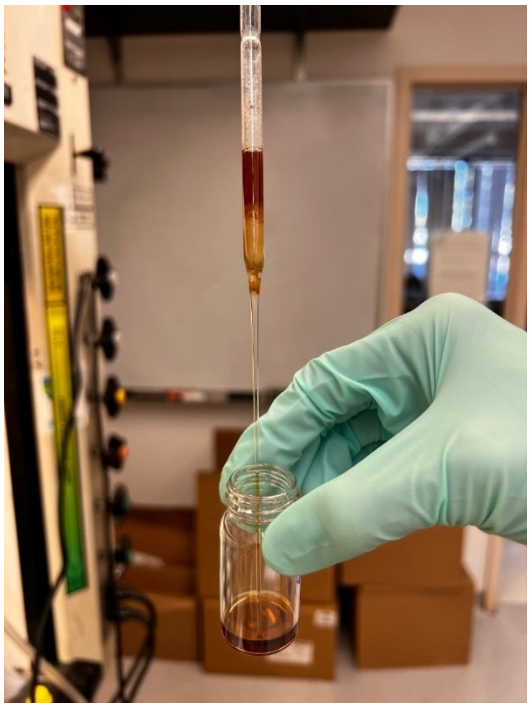


11. After 36 hours, cool the reaction mixture to room temperature, dilute with dichloromethane (1.0 mL), followed by addition of deionized water (2.0 mL), aq. 6M aq. HCl (0.3 mL), brine (1.0 mL) and then shaken vigorously. The lower organic layer was carefully pipetted and filtered through a short plug of Celite®.



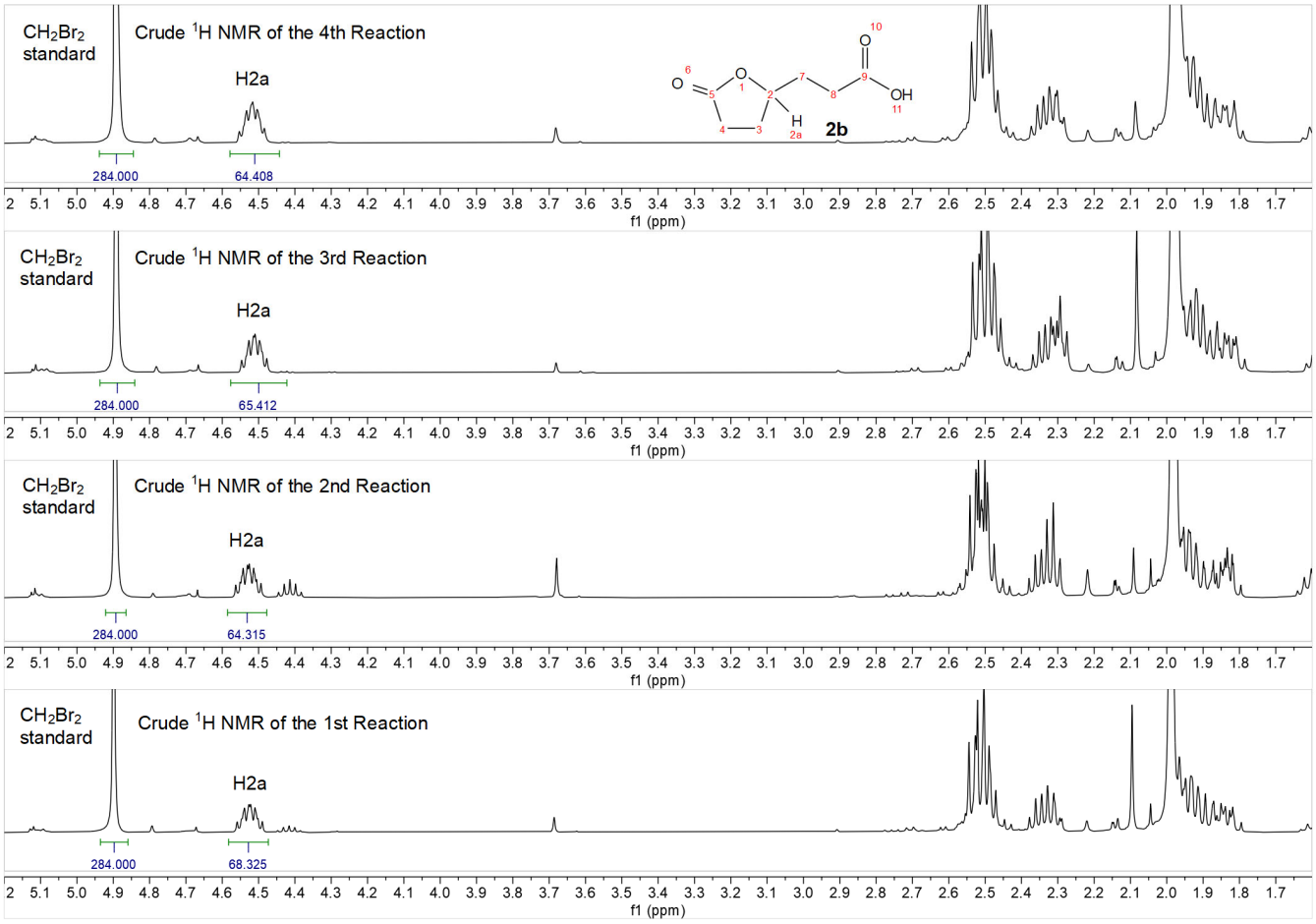
State of reaction mixture after 36 hours.

State of reaction mixture after aqueous workup.



Filtration set-up.

12. The combined organic layer was then evaporated to dryness. The crude was then taken into $CDCl_3$ (0.6 mL) with CH_2Br_2 (10.0 µL) as the internal standard to determine the assay yield of the reaction by ^1H NMR spectroscopy.



Determination of assay yield by ^1H NMR spectroscopy of the crude reaction mixture:

For 10.0 µL of CH_2Br_2, the no. of mmol of CH_2Br_2 is [(10.0*2.477)/173.83] = 0.142 mmol.

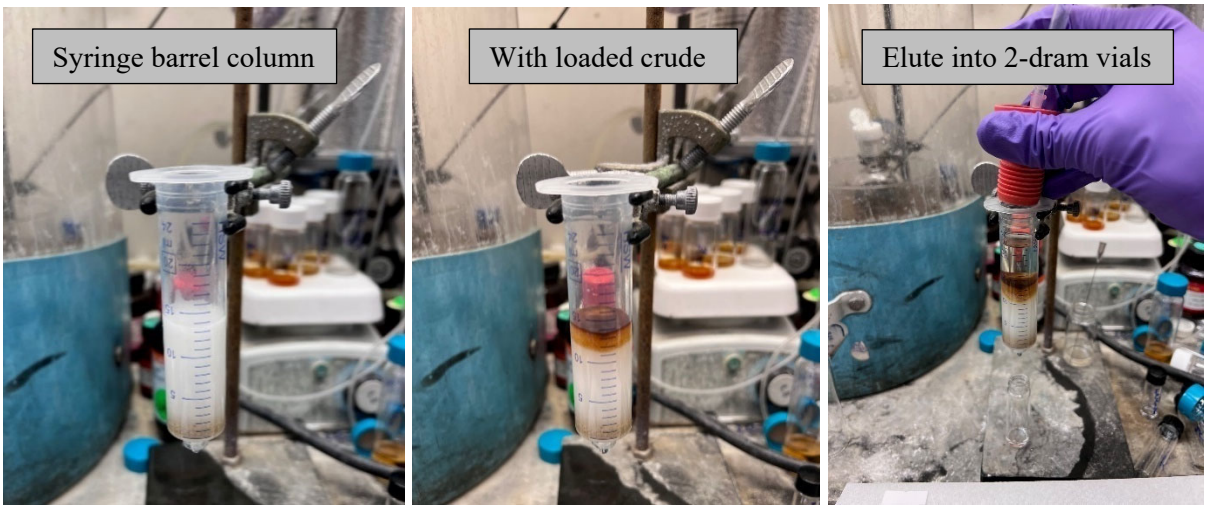
Since each mole of CH_2Br_2 contains 2 moles of H, the no. of mmol of H is 0.284 mmol.

Setting the integral of the resonance of the CH_2Br_2 standard to 0.284, the integral of each C–H resonance of any species on the crude ^1H NMR would reflect the no. of mmol of that species.

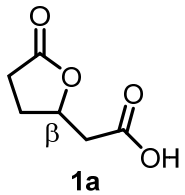
For the case of the lactone product **2b**, the resonance at ~ 4.5 ppm corresponds to H2a as shown on the structure of the product.

Setting the integral of the CH_2Br_2 standard to 284 would then reflect the percentage NMR yield of the product, because: [(Observed integral of the resonance of H2a when the integral of the standard is set to 0.284)/0.1]*100 = Percentage NMR yield of the product.

13. The purification of the lactone acids with column chromatography was performed using the following setup:



2.3 Characterization data of products obtained from β-directed, γ-C–H lactonization reaction



1a

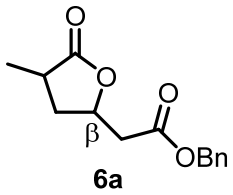
2-(5-Oxotetrahydrofuran-2-yl)acetic acid 1a

Following the general procedure for its synthesis, the compound was purified as the acid by column chromatography (General procedure for gradient elution: begin with 50% EtOAc/hexane + 1% AcOH, and increase the composition of EtOAc by 10% for every 8 mL of eluent used to 100% EtOAc + 1% AcOH). Isolated yield 65% (9.4 mg, 0.065 mmol, colorless oil).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90 (dddd, *J* = 9.1, 7.8, 6.9, 6.1 Hz, 1H), 2.85 (dd, *J* = 16.6, 6.9 Hz, 1H), 2.72 (dd, *J* = 16.6, 6.1 Hz, 1H), 2.67 – 2.55 (m, 2H), 2.49 (dt, *J* = 12.8, 7.8 Hz, 1H), 1.99 (dtd, *J* = 12.8, 9.1, 7.7 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 175.0, 76.1, 39.8, 28.6, 27.6.

HRMS (ESI-TOF) Calculated for $C_6H_6O_4$ [M-H]$^-$: 143.0350, found 143.0344.



6a

Benzyl 2-(4-methyl-5-oxotetrahydrofuran-2-yl)acetate 6a

Following the general procedure for its synthesis and benzyl ester formation, the compound was purified as the benzyl ester by pTLC (20% EA/hexanes, R_f = 0.30). Isolated yield 60% over 2 steps (14.9 mg, 0.60 mmol, colourless oil, d.r. = 1.5:1). Diastereomers were not separable by column chromatography, ^{1}H and ^{13}C NMR data reported as a mixture of diastereomers.

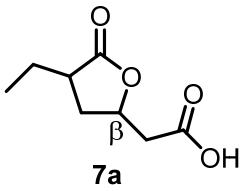
NMR for minor isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 – 7.32 (m, 5H), 5.15 (s, 2H), 4.97 – 4.88 (m, 1H), 2.83 (dd, *J* = 16.1, 6.7 Hz, 1H), 2.74 – 2.59 (m, 2H), 2.26 – 2.07 (m, 2H), 1.29 (d, *J* = 7.3 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 179.4, 169.5, 135.5, 128.8, 128.6, 128.5, 74.0, 67.0, 40.0, 35.1, 33.8, 15.9.

NMR for major isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 – 7.30 (m, 5H), 5.15 (s, 2H), 4.82 – 4.71 (m, 1H), 2.88 (dd, *J* = 16.3, 6.9 Hz, 1H), 2.74 – 2.59 (m, 2H), 1.65 – 1.55 (m, 2H), 1.27 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 178.8, 169.5, 135.5, 128.8, 128.6, 128.5, 74.1, 67.0, 40.2, 37.0, 35.8, 15.1.

HRMS (ESI-TOF) Calculated for $C_{14}H_{17}O_4$ $[M+H]^+$: 249.1127, found 249.1131.



7a

2-(4-Ethyl-5-oxotetrahydrofuran-2-yl)acetic acid 7a

Following the general procedure for its synthesis, the compound was purified as the acid by column chromatography (General procedure for gradient elution: begin with 20% EtOAc/hexane + 1% AcOH, and increase the composition of EtOAc by 10% for every 8 mL of eluent used to 100% EtOAc + 1% AcOH). Isolated yield 60% (10.3 mg, 0.060 mmol, colorless oil, d.r. = 1.4:1). Diastereomers were not separable by column chromatography, ^{1}H and ^{13}C NMR data reported as a mixture of diastereomers.

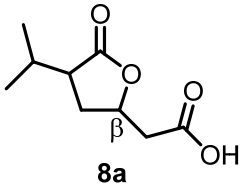
NMR for minor isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.98 – 4.86 (m, 1H), 2.90 – 2.77 (m, 1H), 2.74 – 2.64 (m, 1H), 2.64 – 2.54 (m, 1H), 2.24 – 2.13 (m, 2H), 1.89 – 1.82 (m, 1H), 1.59 – 1.53 (m, 1H), 1.01 (t, J = 7.5 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 178.9, 175.2, 74.2, 40.6, 39.9, 32.7, 24.0, 11.7.

NMR for major isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.78 – 4.72 (m, 1H), 2.89 – 2.78 (m, 1H), 2.74 – 2.64 (m, 1H), 2.64 – 2.55 (m, 2H), 1.97 – 1.89 (m, 1H), 1.68 – 1.60 (m, 1H), 1.53 – 1.46 (m, 1H), 0.99 (t, J = 7.5 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 178.3,175.2, 74.0, 42.2, 40.0, 34.3, 23.3, 11.7.

HRMS (ESI-TOF) Calculated for $C_8H_{11}O_4$, for $[M-H]^-$: 171.0657, found 171.0664.



8a

2-(4-Isopropyl-5-oxotetrahydrofuran-2-yl)acetic acid 8a

Following the general procedure for its synthesis, the compound was purified as the acid by column chromatography (General procedure for gradient elution: begin with 20% EtOAc/hexane + 1% AcOH, and increase the composition of EtOAc by 10% for every 8 mL of eluent used to 100% EtOAc + 1% AcOH). Isolated yield 55% (10.3 mg, 0.055 mmol, colorless oil, d.r. 1.3:1). Diastereomers were not separable by column chromatography, ^{1}H and ^{13}C NMR data reported as a mixture of diastereomers.

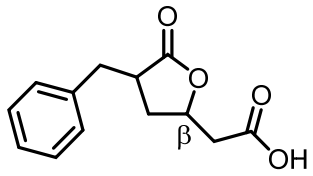
NMR for minor isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.85 (dt, *J* = 14.0, 6.6 Hz, 1H), 2.82 (dd, *J* = 16.5, 6.7 Hz, 1H), 2.75 – 2.65 (m, 1H), 2.65 – 2.57 (m, 1H), 2.34 – 2.25 (m, 1H), 2.23 – 2.14 (m, 1H), 2.05 (ddd, *J* = 14.0, 9.9, 5.4 Hz, 1H), 1.09 – 0.99 (m, 3H), 0.96 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 177.4, 175.0, 74.2, 45.3, 40.2, 29.3, 29.0, 20.8, 18.7.

NMR for major isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.73 (dq, *J* = 10.5, 6.3 Hz, 1H), 2.87 (dd, *J* = 16.5, 7.0 Hz, 1H), 2.75 – 2.65 (m, 1H), 2.65 – 2.57 (m, 1H), 2.43 (ddd, *J* = 13.1, 8.8, 5.8 Hz, 1H), 2.23 – 2.14 (m, 1H), 1.78 – 1.67 (m, 1H), 1.09 – 0.99 (m, 3H), 0.92 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 178.2, 175.0, 73.7, 46.9, 39.9, 30.3, 27.6, 20.6, 18.4.

HRMS (ESI-TOF) Calculated for $C_9H_{15}O_4$ $[M+H]^+$: 187.0970, Found: 187.0972.



9a

2-(4-Benzyl-5-oxotetrahydrofuran-2-yl)acetic acid 9a

Following the general procedure for its synthesis, the compound was purified as the acid by column chromatography (General procedure for gradient elution: begin with 20% EtOAc/hexane + 1% AcOH, and increase the composition of EtOAc by 10% for every 8 mL of eluent used to 100% EtOAc + 1% AcOH). Isolated yield 60% (14.0 mg, 0.060 mmol, colorless oil, d.r = 1.4:1). Diastereomers were not separable by column chromatography, ^{1}H and ^{13}C NMR data reported as a mixture of diastereomers.

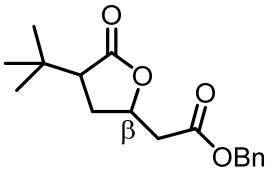
NMR for minor isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 – 7.15 (m, 5H), 4.79 – 4.65 (m, 1H), 3.18 (dd, *J* = 13.9, 4.5 Hz, 1H), 3.03 – 2.92 (m, 1H), 2.83 – 2.71 (m, 2H), 2.65 – 2.54 (m, 1H), 2.22 (dt, *J* = 13.1, 7.6 Hz, 1H), 2.03 (ddd, *J* = 13.8, 9.3, 5.1 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 178.3, 175.3, 138.0, 129.0, 128.9, 127.1, 74.2, 40.9, 39.9, 36.5, 32.2.

NMR for major isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 – 7.15 (m, 5H), 4.79 – 4.65 (m, 1H), 3.27 (dd, *J* = 14.1, 4.3 Hz, 1H), 3.03 – 2.92 (m, 1H), 2.83 – 2.71 (m, 2H), 2.64 – 2.54 (m, 1H), 2.49 – 2.40 (m, 1H), 1.71 – 1.61 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 178.3, 175.3, 138.3, 129.0, 128.9, 126.9, 74.2, 42.6, 39.8, 36.1, 34.3.

HRMS (ESI-TOF) Calculated for $C_{13}H_{15}O_4$ $[M+H]^+$: 235.0970, found 235.0967.



10a

Benzyl 2-(4-(*tert*-butyl)-5-oxotetrahydrofuran-2-yl)acetate 10a

Following the general procedure for its synthesis and benzyl ester formation, the compound was purified as the benzyl ester by pTLC (20% EA/hexanes, R_f = 0.30). Isolated yield 50% over 2 steps (14.5 mg, 0.050 mmol, colourless oil, d.r. = 1.5:1). Diastereomers were not separable by column chromatography, ^{1}H and ^{13}C NMR data reported as a mixture of diastereomers.

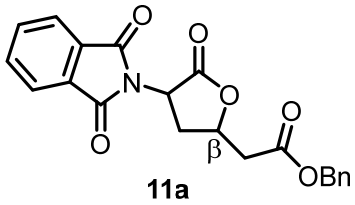
NMR for minor isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 – 7.28 (m, 5H), 5.30 – 5.07 (m, 2H), 4.83 (dtd, *J* = 8.1, 6.5, 5.0 Hz, 1H), 2.81 (dd, *J* = 16.1, 6.4 Hz, 1H), 2.64 – 2.58 (m, 1H), 2.45 (dd, *J* = 9.9, 7.6 Hz, 1H), 2.34 (dt, *J* = 13.5, 7.9 Hz, 1H), 2.03 (ddd, *J* = 13.5, 9.9, 5.0 Hz, 1H), 1.05 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 177.0, 169.6, 135.5, 128.8, 128.6, 128.5, 73.6, 67.0, 48.9, 40.5, 31.7, 30.2, 27.5.

NMR for major isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 – 7.28 (m, 5H), 5.30 – 5.07 (m, 2H), 4.67 (dtd, *J* = 10.4, 6.5, 5.6 Hz, 1H), 2.88 (dd, *J* = 16.3, 6.7 Hz, 1H), 2.70 – 2.64 (m, 1H), 2.50 (dd, *J* = 12.6, 8.6 Hz, 1H), 2.43 – 2.38 (m, 1H), 1.75 (td, *J* = 12.6, 10.5 Hz, 1H), 1.05 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 176.1, 169.6, 135.5, 128.8, 128.7, 128.5, 73.0, 67.0, 50.7, 40.2, 33.0, 31.7, 27.3.

HRMS (ESI-TOF) Calculated for $C_{17}H_{23}O_4$ $[M+H]^+$: 291.1596, Found: 291.1600.



11a

Benzyl 2-(4-(1,3-dioxoisoindolin-2-yl)-5-oxotetrahydrofuran-2-yl)acetate 11a

Following the general procedure for its synthesis and benzyl ester formation, the compound was purified as the benzyl ester by pTLC (30% EA/hexanes, R_f = 0.30). Isolated yield 25% over 2 steps (9.5 mg, 0.025 mmol, colourless oil, d.r. = 2:1). Diastereomers were not separable by column chromatography, ^{1}H and ^{13}C NMR data reported as a mixture of diastereomers.

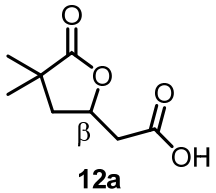
NMR for minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.82 (m, 2H), 7.82 – 7.72 (m, 2H), 7.46 – 7.31 (m, 5H), 5.36 – 5.11 (m, 4H), 2.96 – 2.85 (m, 2H), 2.85 – 2.73 (m, 1H), 2.61 – 2.44 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 169.2, 167.0, 135.4, 134.7, 131.8, 128.9, 128.7, 128.6, 124.0, 74.1, 67.2, 46.7, 39.6, 31.3.

NMR for major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.82 (m, 2H), 7.82 – 7.72 (m, 2H), 7.46 – 7.31 (m, 5H), 5.36 – 5.11 (m, 3H), 4.99 (tdd, *J* = 8.3, 6.9, 3.6 Hz, 1H), 3.12 (ddd, *J* = 16.5, 6.8, 1.7 Hz, 1H), 2.96 – 2.85 (m, 1H), 2.85 – 2.73 (m, 1H), 2.61 – 2.44 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 169.2, 167.0, 135.4, 134.7, 131.7, 128.8, 128.7, 128.6, 124.0, 73.7, 67.1, 48.2, 40.3, 32.4.

HRMS (ESI-TOF) Calculated for $C_{21}H_{18}NO_6$ $[M+H]^+$: 380.1134, Found: 380.1133.



12a

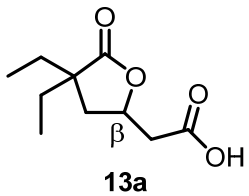
2-(4,4-Dimethyl-5-oxotetrahydrofuran-2-yl)acetic acid 12a

Following the general procedure for its synthesis, the compound was purified as the acid by column chromatography (General procedure for gradient elution: begin with 20% EtOAc/hexane + 1% AcOH, and increase the composition of EtOAc by 10% for every 8 mL of eluent used to 100% EtOAc + 1% AcOH). Isolated yield 84% (14.4 mg, 0.084 mmol, off white solid).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.83 (ddt, *J* = 10.0, 7.1, 6.0 Hz, 1H), 2.86 (dd, *J* = 16.6, 7.1 Hz, 1H), 2.68 (dd, *J* = 16.6, 6.0 Hz, 1H), 2.32 (dd, *J* = 12.8, 6.0 Hz, 1H), 1.85 (dd, *J* = 12.8, 9.9 Hz, 1H), 1.29 (s, 3H), 1.29 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 181.4, 175.0, 72.5, 43.1, 40.5, 40.0, 25.1, 24.5.

HRMS (ESI-TOF) Calculated for $C_8H_{13}O_4$ $[M+H]^+$: 173.0814, Found: 173.0809.



13a

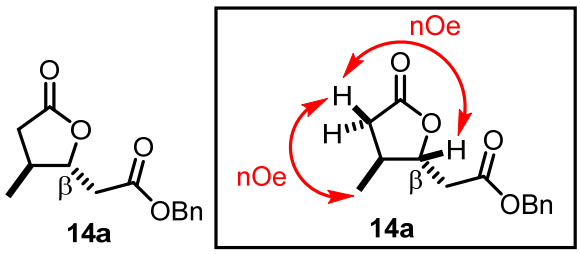
2-(4,4-Diethyl-5-oxotetrahydrofuran-2-yl)acetic acid 13a

Following the general procedure for its synthesis, the compound was purified as the acid by column chromatography (General procedure for gradient elution: begin with 20% EtOAc/hexane + 1% AcOH, and increase the composition of EtOAc by 10% for every 8 mL of eluent used to 100% EtOAc + 1% AcOH). Isolated yield 66% (13.2 mg, 0.066 mmol, off white solid).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.79 (dddd, *J* = 9.4, 7.0, 6.9, 6.1 Hz, 1H), 2.84 (dd, *J* = 16.5, 7.0 Hz, 1H), 2.66 (dd, *J* = 16.5, 6.1 Hz, 1H), 2.27 (dd, *J* = 13.2, 6.9 Hz, 1H), 1.88 (dd, *J* = 13.2, 9.4 Hz, 1H), 1.75 – 1.51 (m, 4H), 0.96 (t, *J* = 7.5 Hz, 3H), 0.90 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 180.4, 175.3, 72.7, 48.8, 40.6, 37.5, 29.3, 28.4, 8.9, 8.8.

HRMS (ESI-TOF) Calculated for $C_{10}H_{17}O_4$ $[M+H]^+$: 201.1127, Found: 201.1135.



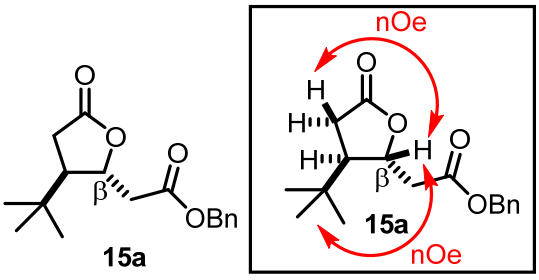
Benzyl 2-((2*R,3*S**)-3-methyl-5-oxotetrahydrofuran-2-yl)acetate 14a**

Following the general procedure for its synthesis and benzyl ester formation, the compound was purified as the benzyl ester by pTLC (10% EA/hexanes, R_f = 0.30). Isolated yield 70% over 2 steps (17.4 mg, 0.070 mmol, colourless oil, d.r. > 20:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 – 7.29 (m, 5H), 5.16 (s, 2H), 4.49 (td, *J* = 7.0, 5.7 Hz, 1H), 2.77 – 2.65 (m, 3H), 2.33 (ddd, *J* = 15.3, 8.5, 7.0 Hz, 1H), 2.22 (dd, *J* = 17.3, 9.1 Hz, 1H), 1.15 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 175.7, 169.7, 135.5, 128.8, 128.6, 128.6, 82.6, 67.1, 39.0, 36.7, 35.9, 17.5.

HRMS (ESI-TOF) Calculated for $C_{14}H_{17}O_4$ $[M+H]^+$: 249.1127, Found: 249.1131.



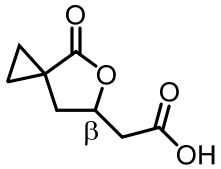
Benzyl 2-((2*R,3*R**)-3-(*tert*-butyl)-5-oxotetrahydrofuran-2-yl)acetate 15a**

Following the general procedure for its synthesis and benzyl ester formation, the compound was purified as the benzyl ester by pTLC (10% EA/hexanes, R_f = 0.50). Isolated yield 76% over 2 steps (22.0 mg, 0.076 mmol, colourless oil, d.r. > 20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.30 (m, 5H), 5.43 – 5.01 (m, 2H), 4.79 (ddd, *J* = 6.6, 5.5, 4.4 Hz, 1H), 2.78 – 2.68 (m, 2H), 2.63 (dd, *J* = 18.4, 10.0 Hz, 1H), 2.40 (dd, *J* = 18.4, 5.4 Hz, 1H), 2.09 (ddd, *J* = 10.0, 5.5, 5.4 Hz, 1H), 0.90 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 169.5, 135.4, 128.8, 128.6, 128.6, 77.8, 67.0, 49.5, 41.3, 32.5, 30.4, 26.8.

HRMS (ESI-TOF) Calculated for $C_{17}H_{23}O_4$ $[M+H]^+$: 291.1596, Found: 291.1602.



16a

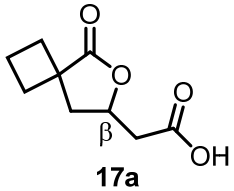
2-(4-Oxo-5-oxaspiro[2.4]heptan-6-yl)acetic acid 16a

Following the general procedure for its synthesis, the compound was purified as the acid by column chromatography (General procedure for gradient elution: begin with 20% EtOAc/hexane + 1% AcOH, and increase the composition of EtOAc by 10% for every 8 mL of eluent used to 100% EtOAc + 1% AcOH). Isolated yield 62% (10.5 mg, 0.062 mmol, off white solid).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.00 (dddd, *J* = 7.6, 7.0, 6.8, 6.5 Hz, 1H), 2.93 (dd, *J* = 16.5, 6.8 Hz, 1H), 2.76 (dd, *J* = 16.5, 6.5 Hz, 1H), 2.48 (dd, *J* = 12.9, 7.6 Hz, 1H), 2.14 (dd, *J* = 12.9, 7.0 Hz, 1H), 1.35 (ddd, *J* = 10.5, 6.5, 3.6 Hz, 1H), 1.26 (ddd, *J* = 10.5, 6.6, 3.7 Hz, 1H), 1.08 – 0.89 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 179.4, 175.0, 73.4, 40.3, 35.4, 20.3, 16.0, 14.9.

HRMS (ESI-TOF) Calculated for $C_8H_{11}O_4$ $[M+H]^+$: 171.0657, Found: 171.0661.



17a

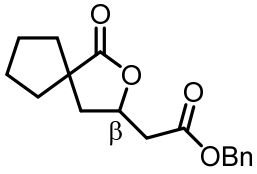
2-(5-Oxo-6-oxaspiro[3.4]octan-7-yl)acetic acid 17a

Following the general procedure for its synthesis, the compound was purified as the acid by column chromatography (General procedure for gradient elution: begin with 20% EtOAc/hexane + 1% AcOH, and increase the composition of EtOAc by 10% for every 8 mL of eluent used to 100% EtOAc + 1% AcOH). Isolated yield 65% (12.0 mg, 0.065 mmol, off white solid).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.74 (dq, *J* = 8.3, 6.4 Hz, 1H), 2.82 (dd, *J* = 16.5, 7.1 Hz, 1H), 2.68 – 2.64 (m, 2H), 2.64 – 2.60 (m, 1H), 2.60 – 2.53 (m, 1H), 2.46 (dtd, *J* = 11.5, 7.3, 2.6 Hz, 1H), 2.15 (dq, *J* = 11.4, 4.5 Hz, 1H), 2.13 – 2.08 (m, 1H), 2.08 – 2.04 (m, 1H), 2.04 – 2.02 (m, 1H), 2.02 – 1.98 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 180.5, 175.1, 72.9, 44.3, 41.6, 39.9, 31.8, 29.6, 16.6.

HRMS (ESI-TOF) Calculated for $C_9H_{13}O_4$ $[M+H]^+$: 185.0814 , Found: 185.0816.



18a

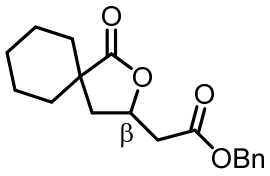
Benzyl 2-(1-Oxo-2-oxaspiro[4.4]nonan-3-yl)acetate 18a

Following the general procedure for its synthesis and benzyl ester formation, the compound was purified as the benzyl ester by pTLC (20% EA/hexanes, R_f = 0.30). Isolated yield 55% over 2 steps (15.9 mg, 0.055 mmol, colourless oil).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50 – 7.28 (m, 5H), 5.15 (s, 2H), 4.80 (dddd, *J* = 9.4, 6.9, 6.3, 6.0 Hz, 1H), 2.89 (dd, *J* = 16.2, 6.9 Hz, 1H), 2.65 (dd, *J* = 16.2, 6.3 Hz, 1H), 2.33 (dd, *J* = 12.7, 6.0 Hz, 1H), 2.17 (dtd, *J* = 12.9, 6.9, 1.8 Hz, 1H), 1.96 – 1.87 (m, 1H), 1.87 – 1.84 (m, 2H), 1.84 – 1.80 (m, 1H), 1.79 – 1.71 (m, 1H), 1.71 – 1.62 (m, 2H), 1.62 – 1.54 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 181.9, 169.7, 135.5, 128.8, 128.6, 128.5, 73.4, 67.0, 50.1, 42.9, 40.3, 37.6, 36.9, 25.6, 25.5.

HRMS (ESI-TOF) Calculated for $C_{17}H_{21}O_4$ $[M+H]^+$: 289.1440, Found: 289.1446.



19a

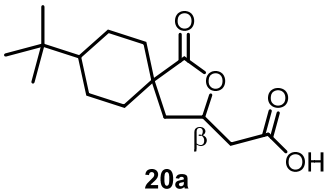
Benzyl 2-(1-oxo-2-oxaspiro[4.5]decan-3-yl)acetate 19a

Following the general procedure for its synthesis and benzyl ester formation, the compound was purified as the benzyl ester by pTLC (20% EA/hexanes, R_f = 0.35). Isolated yield 65% over 2 steps (20.0 mg, 0.065 mmol, colourless oil).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49 – 7.29 (m, 5H), 5.16 (s, 2H), 4.82 (dddd, *J* = 10.3, 6.8, 6.4, 6.3 Hz, 1H), 2.88 (dd, *J* = 16.2, 6.8 Hz, 1H), 2.66 (dd, *J* = 16.2, 6.4 Hz, 1H), 2.48 (dd, *J* = 13.0, 6.3 Hz, 1H), 1.88 – 1.80 (m, 1H), 1.80 – 1.75 (m, 1H), 1.73 (dd, *J* = 9.7, 4.1 Hz, 1H), 1.71 – 1.66 (m, 1H), 1.66 – 1.62 (m, 1H), 1.62 – 1.58 (m, 2H), 1.48 (dt, *J* = 13.9, 4.5 Hz, 1H), 1.42 – 1.36 (m, 1H), 1.36 – 1.30 (m, 1H), 1.28 – 1.18 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 181.0, 169.7, 135.5, 128.8, 128.6, 128.6, 73.1, 67.0, 45.0, 40.6, 39.3, 34.4, 31.7, 25.4, 22.3, 22.2.

HRMS (ESI-TOF) Calculated for $C_{18}H_{23}O_4$ $[M+H]^+$: 303.1596, Found: 303.1599.



20a

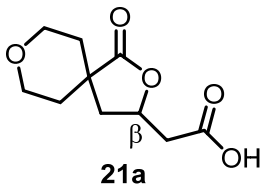
2-(8-(*tert*-Butyl)-1-oxo-2-oxaspiro[4.5]decan-3-yl)acetic acid 20a

Following the general procedure for its synthesis, the compound was purified as the acid by column chromatography (General procedure for gradient elution: begin with 20% EtOAc/hexane + 1% AcOH, and increase the composition of EtOAc by 10% for every 8 mL of eluent used to 100% EtOAc + 1% AcOH). Isolated yield 67% (18.0 mg, 0.067 mmol, off white solid, d.r. = 2.5:1). Diastereomers were not separable by column chromatography, ^{1}H and ^{13}C NMR data reported as a mixture of diastereomers.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.91 – 4.68 (m, 1H), 2.95 – 2.77 (m, 1H), 2.75 – 2.61 (m, 1H), 2.52 (dd, *J* = 13.0, 6.5 Hz, 0.4H), 2.20 – 2.13 (m, 1H), 1.98 – 1.92 (m, 1H), 1.92 – 1.87 (m, 1H), 1.87 – 1.81 (m, 1H), 1.81 – 1.73 (m, 1H), 1.72 – 1.65 (m, 0.5H), 1.65 – 1.57 (m, 2H), 1.57 – 1.50 (m, 0.4H), 1.46 – 1.33 (m, 2H), 1.15 – 1.04 (m, 1H), 0.99 – 0.92 (m, 1H), 0.89 – 0.83 (m, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 181.5, 179.1, 175.4, 175.3, 72.9, 72.1, 47.7, 47.2, 45.2, 44.6, 42.4, 40.4, 40.3, 38.4, 35.0, 34.9, 34.9, 32.6, 32.6, 32.0, 27.7, 27.5, 23.4, 23.3, 22.7, 22.7.

HRMS (ESI-TOF) Calculated for $C_{15}H_{25}O_4$ $[M+H]^+$: 269.1753, Found: 269.1758.



21a

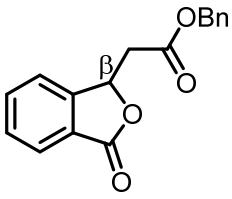
2-(1-Oxo-2,8-dioxaspiro[4.5]decan-3-yl)acetic acid 21a

Following the general procedure for its synthesis, the compound was purified as the acid by column chromatography (General procedure for gradient elution: begin with 20% EtOAc/hexane + 1% AcOH, and increase the composition of EtOAc by 10% for every 8 mL of eluent used to 100% EtOAc + 1% AcOH). Isolated yield 68% (14.5 mg, 0.068 mmol, off white solid).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.85 (dddd, *J* = 9.7, 6.8, 6.2, 6.0 Hz, 1H), 4.07 (dt, *J* = 11.7, 4.7 Hz, 1H), 3.93 (ddd, *J* = 12.0, 5.4, 4.0 Hz, 1H), 3.63 (ddd, *J* = 12.0, 9.2, 3.0 Hz, 1H), 3.52 (td, *J* = 11.7, 3.1 Hz, 1H), 2.88 (dd, *J* = 16.7, 6.8 Hz, 1H), 2.71 (dd, *J* = 16.6, 6.0 Hz, 1H), 2.58 (dd, *J* = 13.0, 6.2 Hz, 1H), 2.26 – 2.02 (m, 1H), 1.94 (ddd, *J* = 13.4, 9.2, 4.0 Hz, 1H), 1.85 (dd, *J* = 13.0, 9.7 Hz, 1H), 1.69 – 1.56 (m, 1H), 1.56 – 1.47 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 179.3, 174.5, 72.7, 64.1, 63.8, 42.2, 40.0, 39.9, 33.8, 32.1.

HRMS (ESI-TOF) Calculated for $C_{10}H_{13}O_5$ $[M-H]^-$: 213.0763, Found: 213.0767.



22a

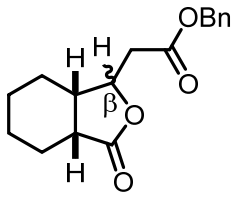
Benzyl 2-(3-oxo-1,3-dihydroisobenzofuran-1-yl)acetate 22a

Following the general procedure for its synthesis and benzyl ester formation, the compound was purified as the benzyl ester by pTLC (20% EA/hexanes, R_f = 0.40). Isolated yield 65% over 2 steps (18.3 mg, 0.065 mmol, colourless oil).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dt, *J* = 7.6, 1.0 Hz, 1H), 7.64 (td, *J* = 7.6, 1.0 Hz, 1H), 7.54 (tt, *J* = 7.6, 0.8 Hz, 1H), 7.42 (dt, *J* = 7.6, 0.8 Hz, 1H), 7.40 – 7.31 (m, 5H), 5.90 (dd, *J* = 7.1, 6.2 Hz, 1H), 5.31 – 5.12 (m, 2H), 3.00 (dd, *J* = 16.5, 7.1 Hz, 1H), 2.91 (dd, *J* = 16.5, 6.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 169.2, 148.8, 135.3, 134.4, 129.7, 128.8, 128.7, 128.7, 126.0, 126.0, 122.2, 77.0, 67.2, 39.7.

HRMS (ESI-TOF) Calculated for $C_{17}H_{15}O_4$ $[M+H]^+$: 283.0970, Found: 283.0973.



23a

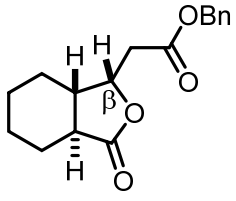
Benzyl 2-((3*aR,7*aS**)-3-oxooctahydroisobenzofuran-1-yl)acetate 23a**

Following the general procedure for its synthesis and benzyl ester formation, the compound was purified as the benzyl ester by pTLC (10% EA/hexanes, R_f = 0.30). Isolated yield 63% over 2 steps (18.2 mg, 0.063 mmol, colourless oil, d.r. = 2:1). Diastereomers were not separable by column chromatography, ^{1}H and ^{13}C NMR data reported as a mixture of diastereomers.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.30 (m, 8H), 4.75 (td, *J* = 7.1, 4.2 Hz, 0.5H), 4.59 (td, *J* = 7.0, 3.0 Hz, 1H), 2.86 (dd, *J* = 16.6, 7.6 Hz, 0.5H), 2.82 – 2.69 (m, 1.5H), 2.74 – 2.58 (m, 2.5H), 2.48 (dq, *J* = 11.6, 5.7 Hz, 0.5H), 2.31 – 2.20 (m, 1H), 1.99 (dt, *J* = 14.2, 4.6 Hz, 1H), 1.89 – 1.77 (m, 1H), 1.77 – 1.46 (m, 5.5H), 1.38 – 1.19 (m, 3H), 1.16 – 1.05 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8, 177.8, 170.0, 169.8, 135.5, 135.5, 128.8, 128.7, 128.7, 128.7, 128.6, 128.5, 79.0, 76.8, 67.0, 67.0, 41.7, 39.3, 38.6, 38.1, 38.1, 34.5, 27.2, 23.5, 23.1, 23.0, 23.0, 22.9, 22.8, 22.6.

HRMS (ESI-TOF) Calculated for $C_{17}H_{21}O_4$ $[M+H]^+$: 289.1440, Found: 289.1446.



24a

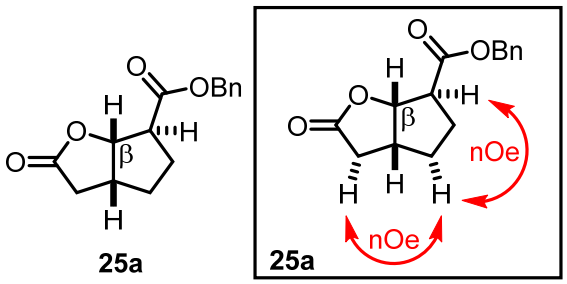
Benzyl 2-((1*S,3*aS**,7*aS**)-3-oxooctahydroisobenzofuran-1-yl)acetate 24a**

Following the general procedure for its synthesis and benzyl ester formation, the compound was purified as the benzyl ester by pTLC (10% EA/hexanes, R_f = 0.30). Isolated yield 60% over 2 steps (17.3 mg, 0.060 mmol, colourless oil, d.r. = 5:1). Diastereomers were not separable by column chromatography, ^{1}H and ^{13}C NMR data reported as a mixture of diastereomers.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 – 7.29 (m, 5H), 5.34 – 5.05 (m, 2H), 4.51 (ddd, *J* = 10.2, 7.5, 4.9 Hz, 1H), 2.76 (dd, *J* = 16.1, 7.5 Hz, 1H), 2.71 (dd, *J* = 16.1, 4.9 Hz, 1H), 2.26 – 2.09 (m, 1H), 2.02 (ddd, *J* = 13.3, 11.2, 3.3 Hz, 1H), 1.93 – 1.78 (m, 3H), 1.63 (dtd, *J* = 13.3, 10.2, 2.7 Hz, 1H), 1.31 – 1.16 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.3, 169.8, 135.5, 128.8, 128.6, 128.6, 80.0, 67.1, 48.9, 46.2, 38.4, 27.6, 25.3, 25.0, 25.0.

HRMS (ESI-TOF) Calculated for $C_{17}H_{21}O_4$ $[M+H]^+$: 289.1440, Found: 289.1452.



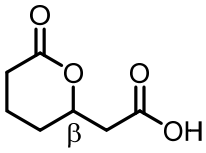
Benzyl (3*aR,6*S**,6*aS**)-2-oxohexahydro-2H-cyclopenta[b]furan-6-carboxylate 25a**

Following the general procedure for its synthesis and benzyl ester formation, the compound was purified as the benzyl ester by pTLC (30% EA/hexanes, R_f = 0.50). Isolated yield 20% over 2 steps (5.5 mg, 0.020 mmol, colourless oil).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.31 (m, 5H), 5.20 (dd, *J* = 6.6, 2.2 Hz, 1H), 5.15 (s, 2H), 3.14 (td, *J* = 7.1, 2.2 Hz, 1H), 2.97 (ddddd, *J* = 9.9, 9.4, 6.6, 6.5, 2.9 Hz, 1H), 2.81 (dd, *J* = 18.4, 9.9 Hz, 1H), 2.33 (dd, *J* = 18.4, 2.9 Hz, 1H), 2.18 – 2.11 (m, 1H), 2.11 – 2.03 (m, 1H), 1.96 (dt, *J* = 12.4, 6.3 Hz, 1H), 1.55 – 1.47 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.8, 172.7, 135.7, 128.8, 128.6, 128.3, 87.0, 67.0, 51.1, 38.5, 35.4, 32.6, 28.7.

HRMS (ESI-TOF) Calculated for $C_{15}H_{17}O_4$ $[M+H]^+$: 261.1127, Found: 261.1130.



2a

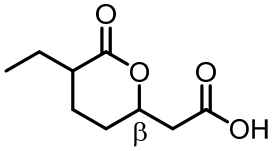
2-(6-Oxotetrahydro-2*H*-pyran-2-yl)acetic acid 2a

Following the general procedure for its synthesis, the compound was purified as the acid by column chromatography. Five parallel reactions were carried out to obtain enough material for effective purification, as purification at 0.1 mmol scale was found difficult. (General procedure for gradient elution: begin with 20% EtOAc/hexane + 1% AcOH, and increase the composition of EtOAc by 10% for every 8 mL of eluent used to 100% EtOAc + 1% AcOH). Isolated yield from the parallel reactions 25% (20.0 mg, 0.125 mmol, off white solid).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.76 (dddd, *J* = 10.7, 7.3, 5.7, 4.4 Hz, 1H), 2.81 (dd, *J* = 16.4, 7.3 Hz, 1H), 2.75 – 2.55 (m, 2H), 2.48 (ddd, *J* = 17.8, 9.0, 7.2 Hz, 1H), 2.05 (dq, *J* = 13.7, 4.4 Hz, 1H), 2.00 – 1.80 (m, 2H), 1.62 (dddd, *J* = 13.7, 10.9, 10.7, 5.8 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 175.0, 171.6, 76.4, 40.5, 29.4, 27.5, 18.4.

HRMS (ESI-TOF) Calculated for $C_7H_{11}O_4$ $[M-H]^-$: 157.0507, Found: 157.0501.



26a

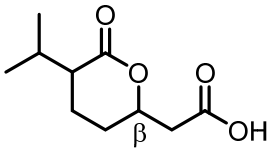
2-(5-Ethyl-6-oxotetrahydro-2*H*-pyran-2-yl)acetic acid 26a

Following the general procedure for its synthesis, the compound was purified as the acid by column chromatography (General procedure for gradient elution: begin with 20% EtOAc/hexane + 1% AcOH, and increase the composition of EtOAc by 10% for every 8 mL of eluent used to 100% EtOAc + 1% AcOH). Isolated yield 31% (5.8 mg, 0.031 mmol, colourless oil, d.r. = 1:1). Diastereomers were not separable by column chromatography, ^{1}H and ^{13}C NMR data reported as a mixture of diastereomers.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.79 – 4.66 (m, 1H), 2.93 – 2.72 (m, 1H), 2.69 – 2.58 (m, 0H), 2.45 – 2.32 (m, 1H), 2.20 – 2.13 (m, 0H), 2.09 – 2.01 (m, 1H), 2.00 – 1.80 (m, 1H), 1.75 – 1.61 (m, 1H), 1.61 – 1.53 (m, 0H), 1.53 – 1.44 (m, 0H), 1.05 – 0.94 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.9, 174.9, 173.2, 173.2, 77.0, 73.9, 42.1, 40.7, 39.8, 39.6, 28.6, 26.5, 24.9, 24.8, 23.9, 22.8, 11.7, 11.2.

HRMS (ESI-TOF) Calculated for $C_9H_{14}O_4Na$ $[M+Na]^+$: 209.0790, Found: 209.0797.



27a

2-(5-Isopropyl-6-oxotetrahydro-2*H*-pyran-2-yl)acetic acid 27a

Following the general procedure for its synthesis, the compound was purified as the acid by column chromatography (General procedure for gradient elution: begin with 20% EtOAc/hexane + 1% AcOH, and increase the composition of EtOAc by 10% for every 8 mL of eluent used to 100% EtOAc + 1% AcOH). Isolated yield 30% (6.0 mg, 0.030 mmol, colourless oil, d.r. : 2.2:1). Diastereomers were not separable by column chromatography, ^{1}H and ^{13}C NMR data reported as a mixture of diastereomers.

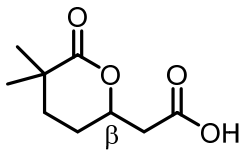
NMR for minor diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.79 – 4.71 (m, 1H), 2.84 – 2.74 (m, 1H), 2.68 – 2.56 (m, 1H), 2.41 – 2.33 (m, 1H), 2.26 (tt, *J* = 13.2, 6.8 Hz, 1H), 2.06 – 1.99 (m, 1H), 1.71 – 1.57 (m, 2H), 1.04 – 0.90 (m, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.4, 174.3, 73.7, 44.0, 39.9, 28.1, 26.9, 20.8, 18.6, 18.4.

NMR for major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.71 – 4.63 (m, 1H), 2.84 – 2.74 (m, 1H), 2.68 – 2.56 (m, 1H), 2.51 (dp, *J* = 11.0, 5.6 Hz, 1H), 2.43 (ddd, *J* = 11.0, 6.9, 3.6 Hz, 1H), 2.12 – 2.06 (m, 1H), 1.92 (ddd, *J* = 13.6, 7.0, 3.0 Hz, 1H), 1.71 – 1.57 (m, 4H), 1.04 – 0.90 (m, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.3, 172.9, 73.7, 46.7, 40.8, 29.2, 28.5, 20.0, 20.0, 18.1.

HRMS (ESI-TOF) Calculated for $C_{10}H_{17}O_4$ $[M+H]^+$: 201.1127, Found: 201.1134.



28a

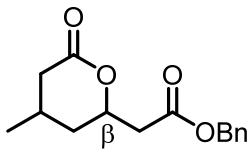
2-(5,5-Dimethyl-6-oxotetrahydro-2*H*-pyran-2-yl)acetic acid 28a

Following the general procedure for its synthesis, the compound was purified as the acid by column chromatography (General procedure for gradient elution: begin with 20% EtOAc/hexane + 1% AcOH, and increase the composition of EtOAc by 10% for every 8 mL of eluent used to 100% EtOAc + 1% AcOH). Isolated yield 31% (5.7 mg, 0.031 mmol, off white solid).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.82 – 4.68 (m, 1H), 2.79 (dd, *J* = 16.3, 7.1 Hz, 1H), 2.65 (dd, *J* = 16.3, 5.7 Hz, 1H), 2.02 – 1.90 (m, 1H), 1.87 – 1.78 (m, 2H), 1.78 – 1.70 (m, 1H), 1.31 (s, 3H), 1.29 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.2, 174.8, 77.4, 40.8, 38.1, 34.4, 27.9, 27.8, 25.8.

HRMS (ESI-TOF) Calculated for $C_9H_{13}O_4$ $[M-H]^-$: 185.0814, Found:185.0815.



29a

Benzyl 2-(4-methyl-6-oxotetrahydro-2*H*-pyran-2-yl)acetate 29a

Following the general procedure for its synthesis and benzyl ester formation, the compound was purified as the benzyl ester by pTLC (20% EA/hexanes, R_f = 0.30). Isolated yield 38% over 2 steps (10.4 mg, 0.040 mmol, colourless oil, d.r. : 1.9:1). Diastereomers were not separable by column chromatography, ^{1}H and ^{13}C NMR data reported as a mixture of diastereomers.

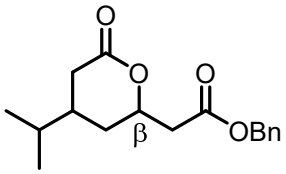
NMR for minor diastereomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 – 7.31 (m, 5H), 5.33 – 5.05 (m, 2H), 4.87 (ddd, *J* = 10.5, 6.7, 4.1 Hz, 1H), 2.93 – 2.78 (m, 1H), 2.66 – 2.56 (m, 2H), 2.24 – 2.15 (m, 2H), 1.83 (ddd, *J* = 14.9, 9.4, 6.2 Hz, 1H), 1.67 (dt, *J* = 14.2, 5.0 Hz, 1H), 1.10 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 171.7, 169.7, 135.6, 128.8, 128.6, 128.5, 73.4, 67.0, 40.4, 37.4, 34.7, 24.0, 21.4.

NMR for major diastereomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 – 7.31 (m, 5H), 5.33 – 5.05 (m, 2H), 4.74 (dtd, *J* = 12.2, 6.4, 3.0 Hz, 1H), 2.93 – 2.78 (m, 1H), 2.75 – 2.66 (m, 1H), 2.66 – 2.56 (m, 1H), 2.13 – 2.06 (m, 2H) , 2.05 – 1.97 (m, 1H), 1.27 (dt, *J* = 13.7, 11.5 Hz, 1H), 1.03 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 170.7, 169.7, 135.6, 128.8, 128.6, 128.5, 76.5, 66.9, 40.9, 38.0, 36.6, 26.7, 21.7.

HRMS (ESI-TOF) Calculated for $C_{15}H_{19}O_4$ $[M+H]^+$: 263.1283, Found: 263.1288.



30a

Benzyl 2-(4-isopropyl-6-oxotetrahydro-2*H*-pyran-2-yl)acetate 30a

Following the general procedure for its synthesis and benzyl ester formation, the compound was purified as the benzyl ester by pTLC (20% EA/hexanes, R_f = 0.35). Isolated yield 48% over 2 steps (14.0 mg, 0.048 mmol, colourless oil, d.r. : 3.2:1). Diastereomers were not separable by column chromatography, ^{1}H and ^{13}C NMR data reported as a mixture of diastereomers.

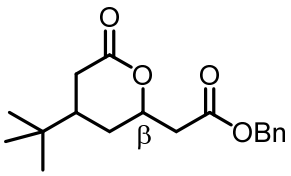
NMR for minor diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.29 (m, 5H), 5.16 (s, 2H), 4.79 – 4.74 (m, 1H), 2.90 – 2.79 (m, 1H), 2.70 – 2.57 (m, 1H), 2.53 (dd, *J* = 15.8, 5.4 Hz, 1H), 2.29 (dd, *J* = 15.8, 10.9 Hz, 1H), 1.83 – 1.71 (m, 3H), 1.59 (m, 1H), 0.93 – 0.86 (m, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.7, 169.7, 135.6, 128.8, 128.6, 128.5, 73.7, 67.0, 40.2, 35.3, 33.1, 32.3, 30.9, 19.5, 19.3.

NMR for major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.29 (m, 5H), 5.16 (s, 2H), 4.70 (dtd, *J* = 12.4, 6.4, 2.7 Hz, 1H), 2.90 – 2.79 (m, 1H), 2.70 – 2.57 (m, 2H), 2.16 (dd, *J* = 17.8, 10.5 Hz, 1H), 2.00 (ddt, *J* = 13.6, 4.2, 2.2 Hz, 1H), 1.83 – 1.71 (m, 1H), 1.51 (h, *J* = 6.7 Hz, 1H), 1.28 (dt, *J* = 14.1, 12.2 Hz, 1H), 0.93 – 0.86 (m, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.3, 169.7, 135.6, 128.8, 128.6, 128.5, 76.4, 66.9, 40.9, 37.8, 33.8, 32.4, 32.0, 19.3, 19.2.

HRMS (ESI-TOF) Calculated for $C_{17}H_{22}O_4Na$ $[M+Na]^+$: 313.1416, Found: 313.1429.



31a

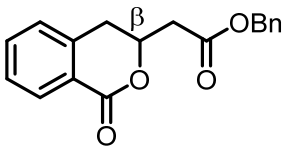
Benzyl 2-(4-(*tert*-butyl)-6-oxotetrahydro-2*H*-pyran-2-yl)acetate 31a

Following the general procedure for its synthesis and benzyl ester formation, the compound was purified as the benzyl ester by pTLC (20% EA/hexanes, R_f = 0.30). Isolated yield 50% over 2 steps (15.2 mg, 0.050 mmol, colourless oil, d.r. : 5:1). Diastereomers were not separable by column chromatography, ^{1}H and ^{13}C NMR data reported as a mixture of diastereomers.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 – 7.33 (m, 5H), 5.18 (s, 2H), 4.71 (ddt, *J* = 11.6, 6.4, 3.2 Hz, 1H), 2.86 (dd, *J* = 16.0, 6.6 Hz, 1H), 2.67 (dd, *J* = 15.9, 6.1 Hz, 1H), 2.68 – 2.61 (m, 1H), 2.26 (dd, *J* = 17.8, 10.4 Hz, 1H), 2.00 (ddt, *J* = 13.6, 4.3, 2.3 Hz, 1H), 1.87 – 1.74 (m, 1H), 1.31 (dt, *J* = 13.3, 11.8 Hz, 1H), 0.89 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.6, 169.6, 135.5, 128.7, 128.5, 128.4, 76.3, 66.8, 41.5, 40.8, 32.3, 31.7, 30.1, 26.5.

HRMS (ESI-TOF) Calculated for $C_{18}H_{25}O_4$ $[M+H]^+$: 305.1753, Found: 305.1754.



32a

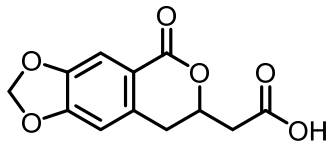
Benzyl 2-(1-oxoisochroman-3-yl)acetate 32a

Following the general procedure for its synthesis and benzyl ester formation, the compound was purified as the benzyl ester by pTLC (20% EA/hexanes, R_f = 0.30). Isolated yield 71% over 2 steps (21.0 mg, 0.071 mmol, off white solid).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.55 (td, *J* = 7.5, 1.4 Hz, 1H), 7.45 – 7.31 (m, 6H), 7.23 (d, *J* = 7.6 Hz, 1H), 5.18 (s, 2H), 5.00 (p, *J* = 6.9 Hz, 1H), 3.08 – 2.98 (m, 3H), 2.79 (dd, *J* = 16.2, 6.9 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 165.0, 138.5, 135.5, 134.1, 130.5, 128.8, 128.6, 128.5, 128.0, 127.6, 125.0, 74.7, 67.0, 39.9, 32.9.

HRMS (ESI-TOF) Calculated for $C_{18}H_{17}O_4$ $[M+H]^+$: 297.1127, Found: 297.1131.



33a

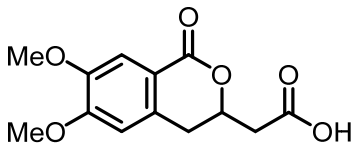
2-(5-Oxo-7,8-dihydro-5*H*-[1,3]dioxolo[4,5-*g*]isochromen-7-yl)acetic acid 33a

Following the general procedure for its synthesis, the compound was purified by pTLC (50% EA/hexanes, 2% AcOH). Isolated yield 75% (18.7 mg, 0.075 mmol, off white solid).

^{1}H NMR (600 MHz, CD_3OD) δ 7.36 (s, 1H), 6.81 (d, J = 0.9 Hz, 1H), 6.08 – 6.04 (m, 2H), 4.91 (dddd, J = 11.3, 7.4, 5.5, 4.0 Hz, 1H), 3.06 – 2.94 (m, 2H), 2.85 – 2.74 (m, 2H).

^{13}C NMR (151 MHz, CD_3OD) δ 173.4, 166.9, 154.3, 149.0, 137.5, 119.2, 109.6, 108.4, 103.6, 76.7, 40.4, 33.4.

HRMS (ESI-TOF) Calculated for $C_{12}H_{10}O_6Na$ $[M+Na]^+$: 273.0375, found 273.0384.



34a

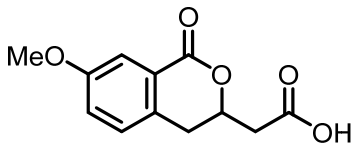
2-(6,7-Dimethoxy-1-oxoisochroman-3-yl)acetic acid 34a

Following the general procedure for its synthesis, the compound was purified by pTLC (50% EA/hexanes, 2% AcOH). Isolated yield 75% (19.9 mg, 0.075 mmol, off white solid).

^{1}H NMR (600 MHz, CD_3OD) δ 7.49 (s, 1H), 6.91 (s, 1H), 4.94 (dddd, J = 11.3, 7.4, 5.6, 4.0 Hz, 1H), 3.92 (s, 3H), 3.86 (s, 3H), 3.09 – 2.97 (m, 2H), 2.87 – 2.76 (m, 2H).

^{13}C NMR (151 MHz, CD_3OD) δ 173.4, 167.4, 155.9, 150.0, 135.6, 117.6, 112.7, 111.0, 77.0, 56.7, 56.5, 40.5, 33.0.

HRMS (ESI-TOF) Calculated for $C_{13}H_{15}O_6$ $[M+H]^+$: 267.0869, found 267.0875.



35a

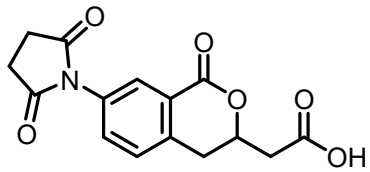
2-(7-Methoxy-1-oxoisochroman-3-yl)acetic acid 35a

Following the general procedure for its synthesis, the compound was purified by pTLC (50% EA/hexanes, 2% AcOH). Isolated yield 80% (18.9 mg, 0.08 mmol, off white solid).

^{1}H NMR (600 MHz, CD_3OD) δ 7.49 (d, *J* = 2.7 Hz, 1H), 7.26 (d, *J* = 8.3 Hz, 1H), 7.17 (dd, *J* = 8.4, 2.8 Hz, 1H), 4.93 (dddd, *J* = 11.1, 7.5, 5.6, 3.5 Hz, 1H), 3.83 (s, 3H), 3.07 – 2.93 (m, 2H), 2.86 – 2.74 (m, 2H).

^{13}C NMR (151 MHz, CD_3OD) δ 172.7, 165.8, 159.2, 131.5, 128.7, 125.2, 121.0, 112.8, 76.0, 54.6, 39.4, 31.2.

HRMS (ESI-TOF) Calculated for $C_{12}H_{13}O_5$ $[M+H]^+$: 237.0763, found 237.0762.



36a

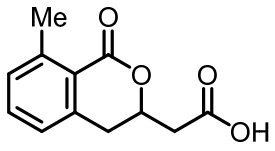
2-(7-(2,5-Dioxopyrrolidin-1-yl)-1-oxoisochroman-3-yl)acetic acid 36a

Following the general procedure for its synthesis, the compound was purified by pTLC (50% EA/hexanes, 2% AcOH). Isolated yield 80% (24.3 mg, 0.08 mmol, off white solid).

^{1}H NMR (600 MHz, DMSO) δ 7.88 – 7.84 (m, 1H), 7.55 – 7.51 (m, 2H), 4.93 (dddd, *J* = 9.4, 7.6, 4.7, 3.2 Hz, 1H), 3.17 – 3.07 (m, 2H), 2.86 – 2.72 (m, 6H).

^{13}C NMR (151 MHz, DMSO) δ 176.9, 171.1, 163.7, 139.2, 132.4, 132.0, 128.6, 127.8, 124.9, 75.2, 39.3, 31.4, 28.6.

HRMS (ESI-TOF) Calculated for $C_{15}H_{14}NO_6$ $[M+H]^+$: 304.0821, found 304.0820.



37a

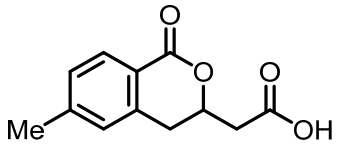
2-(8-Methyl-1-oxoisochroman-3-yl)acetic acid 37a

Following the general procedure for its synthesis, the compound was purified by pTLC (50% EA/hexanes, 2% AcOH). Isolated yield 85% (18.7 mg, 0.085 mmol, off white solid).

^{1}H NMR (600 MHz, CD_3OD) δ 7.44 (t, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 7.7 Hz, 1H), 7.18 (d, *J* = 7.5 Hz, 1H), 4.84 (dddd, *J* = 11.0, 7.4, 5.6, 3.3 Hz, 1H), 3.12 – 2.97 (m, 2H), 2.85 – 2.71 (m, 2H), 2.61 (s, 3H).

^{13}C NMR (151 MHz, CD_3OD) δ 173.6, 166.6, 143.8, 141.8, 134.3, 132.1, 126.7, 124.3, 76.2, 40.4, 34.6, 22.2.

HRMS (ESI-TOF) Calculated for $C_{12}H_{13}O_4$ $[M+H]^+$: 221.0814, found 221.0813.



38a

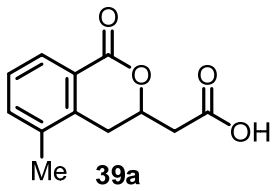
2-(6-Methyl-1-oxoisochroman-3-yl)acetic acid 38a

Following the general procedure for its synthesis, the compound was purified by pTLC (50% EA/hexanes, 2% AcOH). Isolated yield 80% (17.6mg, 0.08 mmol, off white solid).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.19 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.06 (s, 1H), (p, *J* = 6.9 Hz, 1H), 3.02 (d, *J* = 7.3 Hz, 2H), 2.97 (dd, *J* = 16.5, 6.7 Hz, 1H), 2.79 (dd, *J* = 16.5, 6.2 Hz, 1H), 2.40 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 174.8, 165.4, 145.3, 138.5, 130.6, 129.0, 128.2, 122.1, 74.5, 39.7, 32.8, 21.9.

HRMS (ESI-TOF) Calculated for $C_{12}H_{13}O_4$ $[M+H]^+$: 221.0814, found 221.0816.



39a

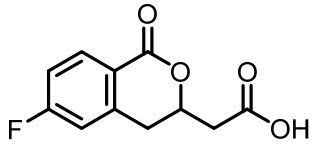
2-(5-Methyl-1-oxoisochroman-3-yl)acetic acid 39a

Following the general procedure for its synthesis, the compound was purified by pTLC (50% EA/hexanes, 2% AcOH). Isolated yield 80% (17.6 mg, 0.080 mmol, off white solid).

^{1}H NMR (600 MHz, CD_3OD) δ 7.87 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.48 (d, *J* = 7.5 Hz, 1H), 7.31 (t, *J* = 7.7 Hz, 1H), 4.93 (dddd, *J* = 11.5, 6.9, 5.9, 3.3 Hz, 1H), 3.17 (dd, *J* = 16.7, 3.3 Hz, 1H), 2.94 – 2.87 (m, 1H), 2.85 (dd, *J* = 16.7, 11.5 Hz, 2H), 2.34 (s, 3H).

^{13}C NMR (151 MHz, CD_3OD) δ 173.4, 167.6, 139.3, 137.0, 136.6, 128.7, 128.2, 125.7, 76.2, 40.5, 30.5, 18.8.

HRMS (ESI-TOF) Calculated for $C_{12}H_{13}O_4$ $[M+H]^+$: 221.0814, found 221.0824.



40a

2-(6-Fluoro-1-oxoisochroman-3-yl)acetic acid 40a

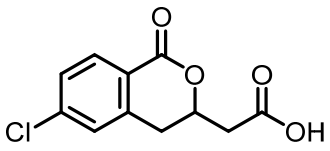
Following the general procedure for its synthesis, the compound was purified by pTLC (50% EA/hexanes, 2% AcOH). Isolated yield 68% (15.2mg, 0.068 mmol, off white solid).

^{1}H NMR (600 MHz, CD_3OD) δ 8.07 (dd, *J* = 8.6, 5.7 Hz, 1H), 7.20 – 7.09 (m, 2H), 4.98 (dddd, *J* = 10.0, 7.3, 5.6, 4.2 Hz, 1H), 3.17 – 3.03 (m, 2H), 2.90 – 2.75 (m, 2H).

^{13}C NMR (151 MHz, CD_3OD) δ 173.4, 167.5 (d, *J* = 254.8 Hz), 166.2, 144.3, 134.1 (d, *J* = 10.1 Hz), 122.4, 116.2 (d, *J* = 22.6 Hz), 115.8 (d, *J* = 22.6 Hz), 76.8, 40.5, 33.1.

^{19}F NMR (471 MHz, CD_3OD) δ -106.01.

HRMS (ESI-TOF) Calculated for $C_{11}H_{10}FO_4$ $[M+H]^+$: 225.0563, found 225.0560.



41a

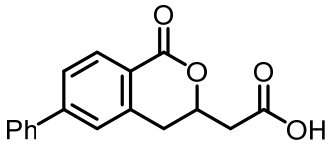
2-(6-Chloro-1-oxoisochroman-3-yl)acetic acid 41a

Following the general procedure for its synthesis, the compound was purified by pTLC (50% EA/hexanes, 2% AcOH). Isolated yield 78% (18.7 mg, 0.078 mmol, off white solid).

^{1}H NMR (600 MHz, CD_3OD) δ 7.98 (d, *J* = 8.2 Hz, 1H), 7.47 – 7.42 (m, 2H), 4.97 (dddd, *J* = 10.2, 7.3, 5.6, 4.5 Hz, 1H), 3.17 – 3.05 (m, 2H), 2.88 – 2.77 (m, 2H).

^{13}C NMR (151 MHz, CD_3OD) δ 173.2, 166.2, 142.8, 141.4, 132.6, 129.2, 128.9, 124.6, 76.8, 40.4, 33.1.

HRMS (ESI-TOF) Calculated for $C_{11}H_{10}ClO_4$ $[M+H]^+$: 241.0268, found 241.0264.



42a

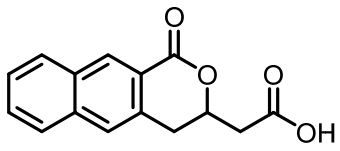
2-(1-Oxo-6-phenylisochroman-3-yl)acetic acid 42a

Following the general procedure for its synthesis, the compound was purified by pTLC (50% EA/hexanes, 2% AcOH). Isolated yield 75% (21.2 mg, 0.075 mmol, off white solid).

^{1}H NMR (600 MHz, CD_3OD) δ 8.07 (d, *J* = 8.1 Hz, 1H), 7.71 – 7.66 (m, 3H), 7.63 – 7.60 (m, 1H), 7.51 – 7.45 (m, 2H), 7.44 – 7.38 (m, 1H), 5.00 (dddd, *J* = 11.0, 7.3, 5.5, 3.6 Hz, 1H), 3.23 – 3.09 (m, 2H), 2.90 – 2.80 (m, 2H).

^{13}C NMR (151 MHz, CD_3OD) δ 173.4, 167.2, 148.3, 141.4, 140.8, 131.6, 130.1, 129.6, 128.3, 127.4, 127.2, 124.5, 76.9, 40.5, 33.5.

HRMS (ESI-TOF) Calculated for $C_{17}H_{15}O_4$ $[M+H]^+$: 283.0970, found 283.0966.



43a

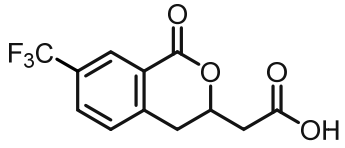
2-(1-Oxo-3,4-dihydro-1*H*-benzo[*g*]isochromen-3-yl)acetic acid 43a

Following the general procedure for its synthesis, the compound was purified by pTLC (50% EA/hexanes, 2% AcOH). Isolated yield 85% (21.8 mg, 0.085 mmol, off white solid).

^{1}H NMR (600 MHz, CD_3OD) δ 8.63 (s, 1H), 8.01 (d, *J* = 8.2 Hz, 1H), 7.90 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.80 (s, 1H), 7.64 (ddd, *J* = 8.3, 6.8, 1.2 Hz, 1H), 7.55 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 5.03 (dddd, *J* = 11.0, 7.2, 5.4, 3.3 Hz, 1H), 3.33 – 3.27 (m, 2H), 3.21 (ddd, *J* = 16.0, 11.0, 1.5 Hz, 1H), 2.93 – 2.76 (m, 2H).

^{13}C NMR (151 MHz, CD_3OD) δ 173.4, 167.5, 137.5, 135.2, 133.5, 133.0, 130.5, 130.3, 128.5, 127.7, 127.2, 123.7, 77.2, 40.6, 33.8.

HRMS (ESI-TOF) Calculated for $C_{15}H_{13}O_4$ $[M+H]^+$: 257.0814, found 257.0819.



44a

2-(1-Oxo-7-(trifluoromethyl)isochroman-3-yl)acetic acid 44a

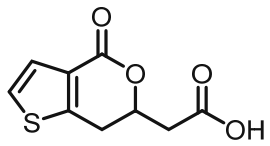
Following the general procedure for its synthesis, the compound was purified by pTLC (50% EA/hexanes, 2% AcOH). Isolated yield 85% (23.3 mg, 0.085 mmol, off white solid).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.81 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.44 (d, *J* = 9.5 Hz, 1H), 5.02 (dddd, *J* = 9.9, 7.0, 6.1, 4.7 Hz, 1H), 3.22 – 3.12 (m, 2H), 3.02 (dd, *J* = 16.6, 7.0 Hz, 1H), 2.85 (dd, *J* = 16.6, 6.1 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 174.9, 163.7, 142.1, 131.0(q, *J* = 33.0 Hz), 130.6 (q, *J* = 3.6 Hz), 128.5, 127.7 (q, *J* = 3.9 Hz), 125.5, 123.5 (q, *J* = 272.3 Hz), 74.4, 39.5, 32.7.

^{19}F NMR (376 MHz, $CDCl_3$) δ -65.56.

HRMS (ESI-TOF) Calculated for $C_{12}H_{10}O_4F_3$ $[M+H]^+$: 275.0531, found 275.0529.



45a

2-(4-Oxo-6,7-dihydro-4*H*-thieno[3,2-*c*]pyran-6-yl)acetic acid 45a

Following the general procedure for its synthesis, the compound was purified by pTLC (50% EA/hexanes, 2% AcOH). Isolated yield 30% (6.4 mg, 0.03 mmol, off white solid).

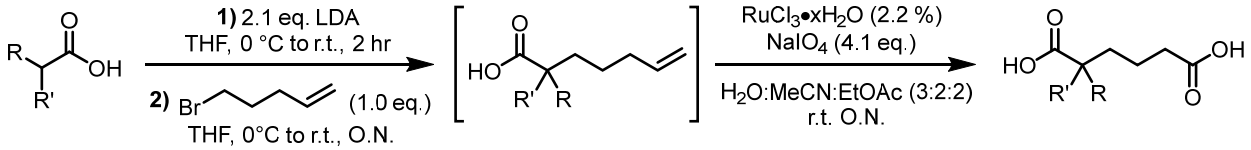
^{1}H NMR (600 MHz, CD_3OD) δ 7.40 – 7.34 (m, 2H), 5.04 (dddd, *J* = 11.3, 7.4, 5.6, 3.7 Hz, 1H), 3.34 (dd, *J* = 16.5, 3.7 Hz, 1H), 3.13 (dd, *J* = 17.0, 11.3 Hz, 1H), 2.85 (qd, *J* = 16.2, 6.5 Hz, 2H).

^{13}C NMR (151 MHz, CD_3OD) δ 173.7, 163.4, 151.4, 128.5, 127.1, 125.9, 78.0, 40.6, 29.9.

HRMS (ESI-TOF) Calculated for $C_9H_9O_4S$ $[M+H]^+$: 213.0222, found 213.0221.

2.4 Synthesis and characterization of substrates for β-directed, γ-C–H lactonization reaction

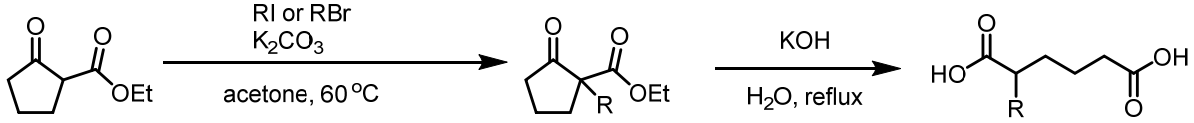
General procedure A for the preparation of α-substituted hexanedioic acids:



A solution of *n*BuLi (2.5M in hexanes, 2.1 eq.) was added to a solution of DIPA (2.0 eq.) in THF (0.1M) at 0 °C. The resultant solution was stirred at 0 °C for 30 minutes. A carboxylic acid (10.0 mmol, 1.0 eq.) was dissolved in THF (5.0 mL) and added dropwise to the LDA solution at 0 °C, in which the solution was warmed to r.t and stirred for 2 hours. The reaction mixture was then cooled to 0 °C and a solution of 5-bromo-1-pentene (10.0 mmol, 1.0 eq.) in THF (5.0 mL) was added. The reaction was warmed to room temperature and stirred overnight. The completion of the reaction was confirmed by TLC analysis of the reaction mixture. The reaction was then quenched with aq. HCl (1.0 M) and extracted three times with EtOAc. The combined organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The crude obtained was directly used for the next step without further purification.

To the crude carboxylic acid obtained in the previous step was added a 3:2:2 ratio of H_2O, MeCN, and EtOAc (0.3 M) at room temperature, followed by $RuCl_3•xH_2O$ (2.2 mol%). The reaction was stirred vigorously and $NaIO_4$ (4.1 eq.) was added in portions over 1 hour. The reaction mixture was then stirred at room temperature overnight. The reaction mixture was then diluted with water and extracted with EtOAc three times. The combined organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The desired α-substituted hexanedioic acids were obtained after purification by flash column chromatography on silica gel (specific elution conditions are described for each compound below).

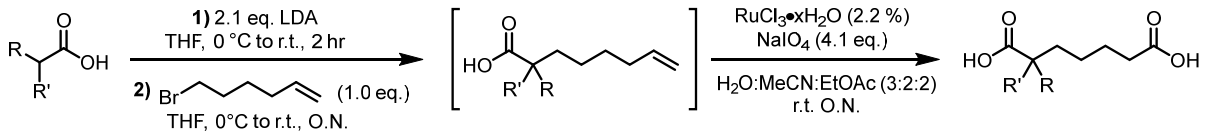
General procedure B for the preparation of α-substituted hexanedioic acids:



To a stirred suspension of dry potassium carbonate (16.0 mmol) in anhydrous acetone (45 mL) under N_2 was added ethyl 2-oxocyclopentane-1-carboxylate (8.0 mmol) followed by alkyl-iodide or alkyl-bromide (24 mmol). The reaction was heated to 60 °C and stirred overnight. The cooled reaction mixture was diluted with diethyl ether (200 mL) and then filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel to give the alkyl-keto ester.

20% aq. KOH (6 mL) was added to a solution 1-alkyl-keto ester (6 mmol) in methanol (6 mL), then the mixture was refluxed and stirred overnight. The cold mixture was extracted with ether. And the aqueous phase solution was acidified with 6M aq. HCl to pH ~ 2 followed by another extraction with EtOAc (three times). The combined organic layer obtained from extraction of the acidic aqueous layer was dried with anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The desired product was obtained after recrystallization by Et_2O and hexane.

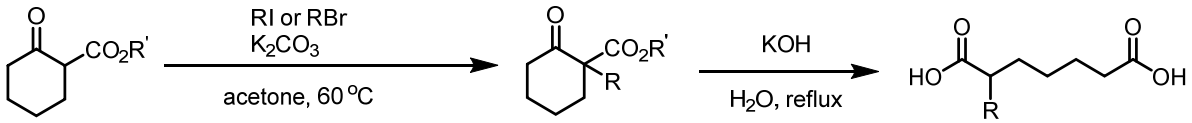
General procedure A for the preparation of α-substituted heptanedioic acids:



A solution of *n*BuLi (2.5M in hexanes, 2.1 eq.) was added to a solution of DIPA (2.0 eq.) in THF (0.1M) at 0 °C. The resultant solution was stirred at 0 °C for 30 minutes. A carboxylic acid (10.0 mmol, 1.0 eq.) was dissolved in THF (5.0 mL) and added dropwise to the LDA solution at 0 °C, in which the solution was warmed to r.t and stirred for 2 hours. The reaction mixture was then cooled to 0 °C and a solution of 6-bromo-1-hexene (10.0 mmol, 1.0 eq.) in THF (5.0 mL) was added. The reaction was warmed to room temperature and stirred overnight. The completion of the reaction was confirmed by TLC analysis of the reaction mixture. The reaction was then quenched with aq. HCl (1.0 M) and extracted three times with EtOAc. The combined organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The crude obtained was directly used for the next step without further purification.

To the crude carboxylic acid obtained in the previous step was added a 3:2:2 ratio of H_2O, MeCN, and EtOAc (0.3 M) at room temperature, followed by $RuCl_3•xH_2O$ (2.2 mol%). The reaction was stirred vigorously and $NaIO_4$ (4.1 eq.) was added in portions over 1 hour. The reaction mixture was then stirred at room temperature overnight. The reaction mixture was then diluted with water and extracted with EtOAc three times. The combined organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The desired α-substituted hexanedioic acids were obtained after purification by flash column chromatography on silica gel (specific elution conditions are described for each compound below).

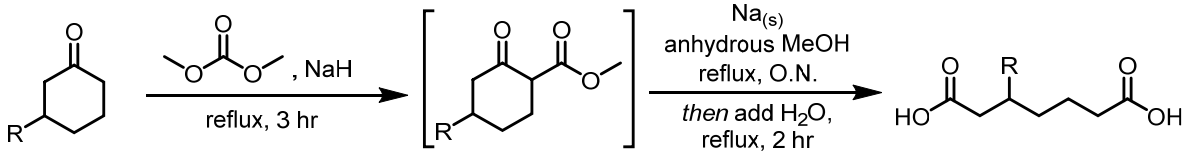
General procedure B for the preparation of α-substituted heptanedioic acids:



To a stirred suspension of dry potassium carbonate (16.0 mmol) in anhydrous acetone (45 mL) under N_2 was added methyl or ethyl 2-oxocyclohexanecarboxylate (8.0 mmol) followed by alkyl-iodide or alkyl-bromide (24 mmol). The reaction was heated to 60 °C and stirred overnight. The cooled reaction mixture was diluted with diethyl ether and then filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel to give the alkyl-keto ester.

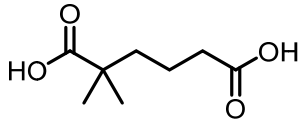
20% aq. KOH (6 mL) was added to a solution alkyl-keto ester (6 mmol) in methanol (6 mL), then the mixture was refluxed and stirred overnight. The cold mixture was extracted with ether. And the aqueous phase solution was acidified with 6M aq. HCl to pH ~ 2 followed by another extraction with EtOAc (three times). The combined organic layer obtained from extraction of the acidic aqueous layer was dried with anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The desired product was obtained after recrystallization by Et_2O and hexane.

General procedure A for the preparation of β-substituted heptanedioic acids:



3-Alkylcyclohexanone (8.0 mmol) was dissolved in dimethylcarbonate (15.0 mL) and NaH (0.5 g, 12.2 mmol, 60% dispersion in mineral oil) was added. The reaction mixture was heated to reflux and stirred at this temperature (90 °C) for 3 hours. The reaction was then quenched with sat. NH_4Cl and extracted with EtOAc. The combined organic layer was dried with anhydrous $MgSO_4$, filtered, and evaporated to dryness to provide the crude β-keto ester.

Sodium metal (1.0 g, 32.0 mmol) was divided into small pieces with a spatula and introduced portionwise to ice-cold anhydrous MeOH (30 mL) with vigorous stirring. After the complete addition of sodium metal, the crude β-keto ester obtained above was dissolved in anhydrous MeOH (5.0 mL) and added dropwise to the ice-cold reaction mixture. The reaction mixture was warmed to room temperature, then heated to reflux, and stirred at this temperature overnight. Water (5.0 mL) was then added to the refluxing reaction mixture and stirring was continued at reflux for 2 hours. The reaction mixture was cooled to room temperature and the MeOH was removed under vacuum. The aqueous residue was extracted with EtOAc three times, and then acidified to pH ~ 2 with 6M aq. HCl followed by another extraction with EtOAc (three times). The combined organic layer obtained from extraction of the acidic aqueous layer was dried with anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The desired product was obtained after purification by flash column chromatography on silica gel (specific elution conditions are described for each compound below).



12

2,2-Dimethylhexanedioic acid 12

This compound was prepared according to the general procedure A for the preparation of α-substituted hexanedioic acids.

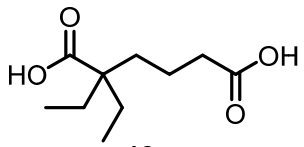
Elution condition: (20% EA/hexanes + 1% AcOH to 50% EA/hexanes + 1% AcOH, gradient elution)

Isolated yield: 52% over 2 steps (0.91 g, 5.2 mmol, white solid)

^{1}H NMR (500 MHz, DMSO) δ 12.03 (s, 2H), 2.32 – 2.04 (m, 2H), 1.75 – 1.37 (m, 4H), 1.07 (s, 6H).

^{13}C NMR (126 MHz, DMSO) δ 178.7, 174.3, 41.1, 39.5, 34.1, 25.0, 24.9, 20.2.

HRMS (ESI-TOF) Calculated for $C_8H_{13}O_4$ $[M-H]^-$: 173.0814, Found:173.0820.



13

2,2-Diethylhexanedioic acid 13

This compound was prepared according to the general procedure A for the preparation of α-substituted hexanedioic acids.

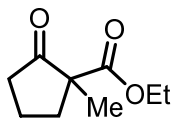
Elution condition: (20% EA/hexanes + 1% AcOH to 50% EA/hexanes + 1% AcOH, gradient elution)

Isolated yield: 60% over 2 steps (1.21 g, 6.0 mmol, white solid)

^{1}H NMR (500 MHz, DMSO) δ 12.04 (s, 2H), 2.19 (t, *J* = 7.0 Hz, 2H), 1.55 – 1.40 (m, 6H), 1.40 – 1.28 (m, 2H), 0.73 (t, *J* = 7.4 Hz, 6H).

^{13}C NMR (126 MHz, DMSO) δ 177.8, 174.3, 48.4, 34.1, 32.3, 26.2, 19.1, 8.2.

HRMS (ESI-TOF) Calculated for $C_{10}H_{17}O_4$ $[M-H]^-$: 201.1127, Found: 201.1128.



55

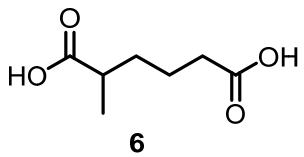
Ethyl 1-methyl-2-oxocyclopentane-1-carboxylate 55

This compound was prepared according to the general procedure B for the preparation of α-substituted hexanedioic acids by the reaction with MeI. Quantative yield, (1.36 g, 8.0 mmol, colorless oil).

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.20 – 4.07 (m, 2H), 2.54 – 2.50 (m, 1H), 2.50 – 2.39 (m, 1H), 2.35 – 2.26 (m, 1H), 2.10 – 2.00 (m, 1H), 1.97 – 1.81 (m, 2H), 1.30 (s, 3H), 1.24 (td, *J* = 7.1, 0.5 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 216.1, 172.5, 61.5, 56.0, 37.8, 36.3, 19.7, 19.5, 14.2.

The data is consistent with those reported in the literature.(*40*)



6

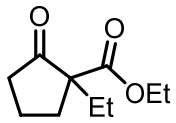
2-Methylhexanedioic acid 6

This compound was prepared according to the general procedure B for the preparation of α-substituted hexanedioic acids. 87% yield, (0.84 g, 5.22 mmol, white solid).

^{1}H NMR (600 MHz, $CDCl_3$) δ 2.52 – 2.45 (m, 1H), 2.44 – 2.33 (m, 2H), 1.79 – 1.65 (m, 3H), 1.55 – 1.46 (m, 1H), 1.20 (dd, *J* = 7.0, 1.0 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 182.5, 179.8, 47.0, 34.1, 31.1, 25.3, 22.7, 11.8.

HRMS (ESI-TOF) Calculated for $C_7H_{11}O_4$ $[M-H]^-$: 159.0657, found 159.0653.



SS1

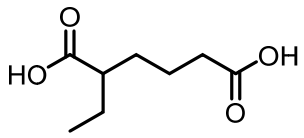
Ethyl 1-ethyl-2-oxocyclopentane-1-carboxylate SS1

This compound was prepared according to the general procedure B for the preparation of α-substituted hexanedioic acids by the reaction with EtI. 95% yield, (1.4 g, 7.6 mmol, colorless oil).

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.22 – 4.10 (m, 2H), 2.55 – 2.46 (m, 1H), 2.46 – 2.36 (m, 1H), 2.33 – 2.19 (m, 1H), 2.05 – 1.84 (m, 4H), 1.68 – 1.58 (m, 1H), 1.29 – 1.21 (m, 3H), 0.89 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 215.3, 171.3, 77.4, 77.2, 77.0, 61.4, 61.0, 38.2, 38.2, 32.4, 26.9, 19.7, 14.2, 9.3.

The data is consistent with those reported in the literature.(*40*)



7

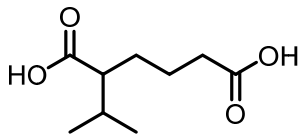
2-Ethylhexanedioic acid 7

This compound was prepared according to the general procedure B for the preparation of α-substituted hexanedioic acids. 85% yield, (0.89 g, 5.1 mmol, white solid).

^{1}H NMR (600 MHz, $CDCl_3$) δ 2.44 – 2.29 (m, 3H), 1.86 – 1.38 (m, 6H), 0.95 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 182.5, 179.8, 47.0, 34.1, 31.1, 25.3, 22.7, 11.8.

HRMS (ESI-TOF) Calculated for $C_8H_{13}O_4$ $[M-H]^-$: 173.0814, found 173.0810.



8

2-Isopropylhexanedioic acid 8

This compound was prepared according to the general procedure A for the preparation of α-substituted hexanedioic acids.

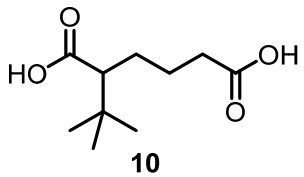
Elution condition: (20% EA/hexanes + 1% AcOH to 50% EA/hexanes + 1% AcOH, gradient elution)

Isolated yield: 42% over 2 steps (791 mg, 4.2 mmol, colourless oil)

^{1}H NMR (600 MHz, DMSO) δ 12.03 (s, 1H), 2.28 – 2.12 (m, 1H), 1.97 (td, *J* = 8.2, 4.8 Hz, 0H), 1.78 – 1.69 (m, *J* = 6.8 Hz, 1H), 1.52 – 1.33 (m, 2H), 0.87 (dd, *J* = 6.8, 4.2 Hz, 3H).

^{13}C NMR (151 MHz, DMSO) δ 176.3, 174.3, 51.9, 33.6, 29.9, 28.5, 22.9, 20.4, 19.9.

HRMS (ESI-TOF) Calculated for $C_9H_{15}O_4$ $[M-H]^-$: 187.0970, Found: 187.0978.



10

2-(*tert*-Butyl)hexanedioic acid 10

This compound was prepared according to the general procedure A for the preparation of α-substituted hexanedioic acids.

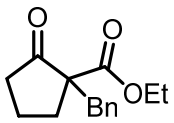
Elution condition: (20% EA/hexanes + 1% AcOH to 50% EA/hexanes + 1% AcOH, gradient elution)

Isolated yield: 35% over 2 steps (710 mg, 3.5 mmol, colourless oil)

^{1}H NMR (500 MHz, DMSO) δ 12.00 (s, 2H), 2.36 – 2.09 (m, 2H), 1.99 (dd, *J* = 11.3, 2.5 Hz, 1H), 1.53 – 1.39 (m, 3H), 1.36 (ddd, *J* = 13.1, 10.6, 5.0 Hz, 1H), 0.90 (s, 9H).

^{13}C NMR (126 MHz, DMSO) δ 176.1, 174.3, 55.5, 33.6, 32.1, 27.5, 26.6, 23.6.

HRMS (ESI-TOF) Calculated for $C_{10}H_{17}O_4$ $[M-H]^-$: 201.1127, Found: 201.1124.



SS2

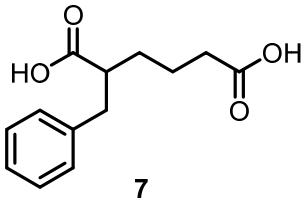
Ethyl 1-benzyl-2-oxocyclopentane-1-carboxylate SS2

This compound was prepared according to the general procedure B for the preparation of α-substituted hexanedioic acids by the reaction With BnBr. 95% yield, (2.34 g, 7.6 mmol, colorless oil).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 – 7.19 (m, 3H), 7.17 – 7.12 (m, 2H), 4.22 – 4.15 (m, 2H), 3.20 (dd, *J* = 13.8, 1.4 Hz, 1H), 3.13 (dd, *J* = 13.9, 1.5 Hz, 1H), 2.45 – 2.40 (m, 1H), 2.40 – 2.33 (m, 1H), 2.09 – 1.84 (m, 3H), 1.65 – 1.57 (m, 1H), 1.29 – 1.23 (m, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 215.1, 171.1, 136.8, 130.3, 128.5, 127.0, 77.4, 77.2, 76.9, 61.7, 61.6, 39.1, 38.5, 31.9, 19.6, 14.2.

The data is consistent with those reported in the literature.(*41*)



7

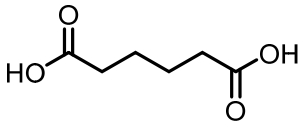
2-Benzylhexanedioic acid 9

This compound was prepared according to the general procedure B for the preparation of α-substituted hexanedioic acids. 90% yield, (1.28 g, 5.4 mmol, white solid).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30 – 7.16 (m, 5H), 3.01 (dd, *J* = 13.6, 7.4 Hz, 1H), 2.78 – 2.65 (m, 2H), 2.40 – 2.26 (m, 2H), 1.78 – 1.61 (m, 3H), 1.59 – 1.51 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 181.5, 179.5, 138.9, 129.0, 128.6, 126.7, 47.2, 38.1, 33.9, 31.0, 22.5.

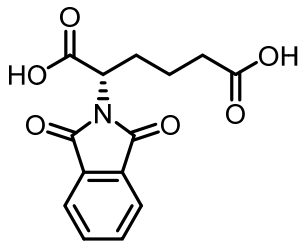
HRMS (ESI-TOF) Calculated for $C_{13}H_{16}O_4Na$ $[M+Na]^+$: 259.0946, Found: 259.0947.



1

Adipic acid/hexane-1,6-dioic acid 1

This compound is commercially available.



11

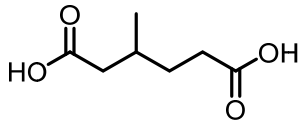
(*S*)-2-(1,3-dioxoisoindolin-2-yl)hexanedioic acid 11

This compound was synthesized from commercially available L-homoglutamic acid using the following general procedure(*42*). Amino acid (5.0 mmol, 1.0 equiv), phthalic anhydride (5.0 mmol, 1.0 equiv), and triethylamine (0.5 mmol, 0.1 equiv) were dissolved in toluene (30 mL) in a dried round bottom flask equipped with a stir bar and a reflux condenser. The reaction mixture was heated to reflux for 4 h. The reaction mixture was cooled to room temperature and concentrated under vacuum. The residue was dissolved in EtOAc, transferred to a separatory funnel, and washed with 1 M HCl. The organic layer was dried with $MgSO_4$, filtered through Celite, and concentrated to give the desired product quantitatively as a white powder (1.46 g, 5.0 mmol).

^{1}H NMR (500 MHz, DMSO) δ 8.14 – 7.74 (m, 4H), 4.74 (dd, J = 10.0, 5.4 Hz, 1H), 2.21 (hept, J = 8.0 Hz, 2H), 2.09 (ddt, J = 14.6, 12.6, 7.4 Hz, 2H), 1.46 (p, J = 7.5 Hz, 2H).

^{13}C NMR (126 MHz, DMSO) δ 174.1, 170.4, 167.4, 134.9, 131.1, 123.4, 51.4, 32.9, 27.5, 21.4.

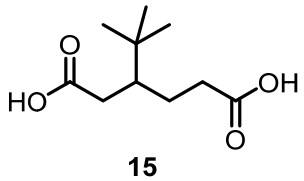
HRMS (ESI-TOF) Calculated for $C_{14}H_{14}NO_6$ $[M+H]^+$: 292.0821, Found: 292.0821.



14

3-Methylhexanedioic acid 14

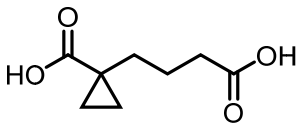
This compound is commercially available.



15

3-(*tert*-Butyl)hexanedioic acid 15

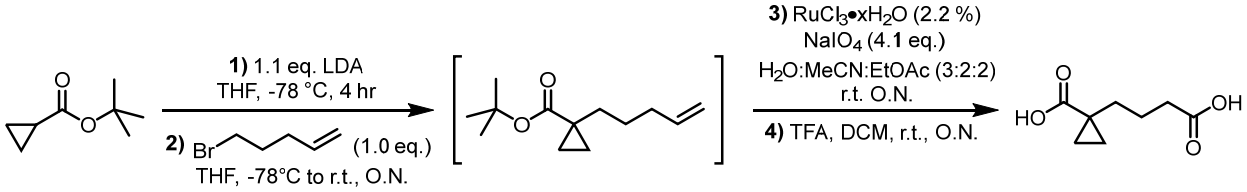
This compound is commercially available.



16

1-(3-Carboxypropyl)cyclopropane-1-carboxylic acid 16

This compound was synthesized using the following procedure:



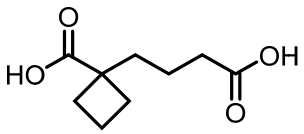
A solution of *n*BuLi (2.5M in hexanes, 1.4 mL, 3.6 mmol, 1.2 eq.) was added to a solution of DIPA (0.46 mL, 3.3 mmol, 1.1 eq.) in THF (30 mL) at 0 °C. The resultant solution was stirred at 0 °C for 30 minutes then cooled to -78 °C. *tert*-Butyl cyclopropanecarboxylate (427 mg, 3.0 mmol, 1.0 eq.) was dissolved in THF (2.0 mL) and added dropwise to the LDA solution at -78 °C, in which the solution was stirred at -78 °C for 4 hours. A solution of 5-bromo-1-pentene (0.36 mL, 3.0 mmol, 1.0 eq.) in THF (2.0 mL) was then added. The reaction was warmed to room temperature and stirred overnight. The completion of the reaction was confirmed by TLC analysis of the reaction mixture. The reaction was then quenched with aq. HCl (1.0 M) and extracted three times with EtOAc. The combined organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The crude product obtained was directly used for the next step without further purification.

To the crude product obtained in the previous step was added a 3:2:2 ratio of H_2O, MeCN, and EtOAc (0.3 M) at room temperature, followed by $RuCl_3•xH_2O$ (14 mg, 2.2 mol%). The reaction was stirred vigorously and $NaIO_4$ (2.7 g, 12.3 mmol, 4.1 eq.) was added in portions over 1 hour. The reaction mixture was then stirred at room temperature overnight. The reaction mixture was then diluted with water and extracted with EtOAc three times. The combined organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated under vacuum. To the crude product was added aq. NaOH (10.0 mL, 1.0 M) and quickly extracted with EtOAc three times. The aqueous layer was acidified with aq. HCl (6.0 M) to pH ~2 and extracted with EtOAc three times. The combined organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated. The residue was dissolved in DCM (10 mL) and trifluoroacetic acid (0.23 mL, 3.0 mmol, 1.0 eq.) was added and stirred at room temperature overnight. Evaporation of the volatiles provided the desired product as a white solid in 20% yield over 4 steps (103.0 mg, 0.6 mmol).

^{1}H NMR (500 MHz, DMSO) δ 2.17 (t, J = 7.5 Hz, 2H), 1.71 – 1.57 (m, 2H), 1.54 – 1.39 (m, 2H), 1.15 – 0.94 (m, 2H), 0.71 – 0.56 (m, 2H).

^{13}C NMR (126 MHz, DMSO) δ 176.2, 174.3, 33.7, 32.8, 22.9, 22.6, 14.7.

HRMS (ESI-TOF) Calculated for $C_8H_{11}O_4$ $[M-H]^-$: 171.0657, Found: 171.0661.



17

1-(3-Carboxypropyl)cyclobutane-1-carboxylic acid 17

This compound was prepared according to the general procedure A for the preparation of α-substituted hexanedioic acids.

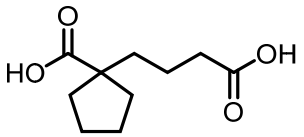
Elution condition: (20% EA/hexanes + 1% AcOH to 50% EA/hexanes + 1% AcOH, gradient elution)

Isolated yield: 41% over 2 steps (0.76 g, 4.1 mmol, white solid)

^{1}H NMR (500 MHz, DMSO) δ 12.05 (s, 2H), 2.32 – 2.23 (m, 2H), 2.19 (t, *J* = 7.4 Hz, 2H), 1.87 – 1.71 (m, 4H), 1.71 – 1.62 (m, 2H), 1.41 – 1.30 (m, 2H).

^{13}C NMR (126 MHz, DMSO) δ 177.8, 174.3, 46.8, 36.9, 33.7, 29.5, 20.2, 15.0.

HRMS (ESI-TOF) Calculated for $C_9H_{13}O_4$ $[M-H]^-$: 185.0814, Found: 185.0818.



18

1-(3-Carboxypropyl)cyclopentane-1-carboxylic acid 18

This compound was prepared according to the general procedure A for the preparation of α-substituted hexanedioic acids.

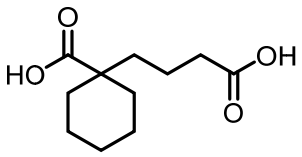
Elution condition: (20% EA/hexanes + 1% AcOH to 50% EA/hexanes + 1% AcOH, gradient elution)

Isolated yield: 55% over 2 steps (1.10 g, 5.5 mmol, white solid)

^{1}H NMR (500 MHz, DMSO) δ 12.02 (s, 2H), 2.17 (t, *J* = 7.3 Hz, 2H), 2.00 (dt, *J* = 12.0, 6.2 Hz, 2H), 1.69 – 1.45 (m, 6H), 1.45 – 1.20 (m, 4H).

^{13}C NMR (126 MHz, DMSO) δ 178.5, 174.2, 53.1, 38.1, 35.3, 34.0, 24.6, 21.3.

HRMS (ESI-TOF) Calculated for $C_{10}H_{15}O_4$ $[M-H]^-$: 199.0970, Found: 199.0978.



19

1-(3-Carboxypropyl)cyclohexane-1-carboxylic acid 19

This compound was prepared according to the general procedure A for the preparation of α-substituted hexanedioic acids.

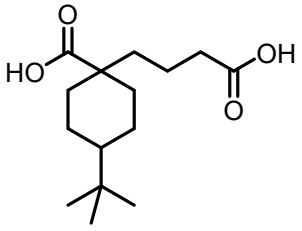
Elution condition: (20% EA/hexanes + 1% AcOH to 50% EA/hexanes + 1% AcOH, gradient elution)

Isolated yield: 56% over 2 steps (1.20 g, 5.6 mmol, white solid)

^{1}H NMR (500 MHz, DMSO) δ 12.04 (s, 2H), 2.15 (dq, *J* = 4.4, 2.3 Hz, 2H), 1.92 (d, *J* = 12.2 Hz, 2H), 1.61 – 1.47 (m, 3H), 1.40 (d, *J* = 3.7 Hz, 4H), 1.27 (dt, *J* = 14.5, 10.3 Hz, 2H), 1.20 (td, *J* = 9.5, 3.5 Hz, 1H), 1.13 (td, *J* = 12.1, 3.1 Hz, 2H).

^{13}C NMR (126 MHz, DMSO) δ 177.4, 174.2, 45.8, 39.3, 34.0, 33.6, 25.5, 22.9, 19.4.

HRMS (ESI-TOF) Calculated for $C_{11}H_{17}O_4$ $[M-H]^-$: 213.1127, Found: 213.1125.



20

4-(*tert*-Butyl)-1-(3-carboxypropyl)cyclohexane-1-carboxylic acid 20

This compound was prepared according to the general procedure A for the preparation of α-substituted hexanedioic acids.

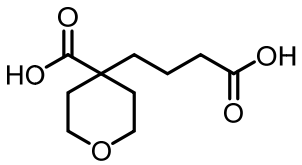
Elution condition: (10% EA/hexanes + 1% AcOH to 50% EA + 1% AcOH, gradient elution)

Isolated yield: 56% over 2 steps (1.51 g, 5.6 mmol, white solid, d.r. = 2.7:1)

^{1}H NMR (500 MHz, DMSO) δ 12.03 (s, 2H), 2.21 – 2.07 (m, 3.5H), 1.79 – 1.71 (m, 0.5H), 1.64 – 1.48 (m, 2.5H), 1.45 – 1.31 (m, 4H), 1.16 – 1.06 (m, 0.6H), 1.06 – 0.91 (m, 4H), 0.85 – 0.79 (m, 9H).

^{13}C NMR (126 MHz, DMSO) δ 178.8, 177.1, 174.3, 174.2, 47.2, 47.0, 45.9, 43.8, 40.9, 34.3, 34.0, 34.0, 32.1, 32.1, 30.9, 27.3, 24.2, 21.5, 19.8, 19.5.

HRMS (ESI-TOF) Calculated for $C_{15}H_{25}O_4$ $[M-H]^-$: 269.1753, Found: 269.1748.



21

4-(3-Carboxypropyl)tetrahydro-2*H*-pyran-4-carboxylic acid 21

This compound was prepared according to the general procedure A for the preparation of α-substituted hexanedioic acids.

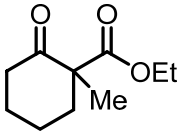
Elution condition: (40% EA/hexanes + 1% AcOH to 100% EA + 1% AcOH, gradient elution)

Isolated yield: 70% over 2 steps (1.51 g, 7.0 mmol, white solid)

^{1}H NMR (500 MHz, DMSO) δ 12.23 (s, 2H), 3.70 (dt, *J* = 11.8, 3.8 Hz, 2H), 3.29 (dd, *J* = 11.4, 2.3 Hz, 2H), 2.17 (t, *J* = 6.9 Hz, 2H), 1.90 (d, *J* = 13.2 Hz, 2H), 1.49 – 1.43 (m, 2H), 1.43 – 1.37 (m, 2H), 1.37 – 1.31 (m, 2H).

^{13}C NMR (126 MHz, DMSO) δ 176.7, 174.2, 64.6, 43.8, 39.2, 33.7, 19.1.

HRMS (ESI-TOF) Calculated for $C_{10}H_{15}O_5$ $[M-H]^-$: 215.0919, Found: 215.0914.



SS3

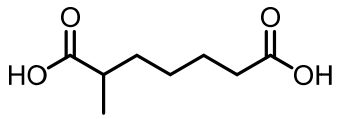
Ethyl 1-methyl-2-oxocyclohexane-1-carboxylate SS3

This compound was prepared according to the general procedure B for the preparation of α-substituted heptanedioic acids with the reaction of MeI and ethyl 2-oxocyclohexane-1-carboxylate. 73% yield, (1.1 g, 6.0 mmol, colorless oil).

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.22 – 4.14 (m, 2H), 2.54 – 2.41 (m, 3H), 2.06 – 1.97 (m, 1H), 1.78 – 1.57 (m, 4H), 1.50 – 1.41 (m, 1H), 1.28 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 208.5, 173.2, 61.4, 57.3, 40.8, 38.4, 27.7, 22.8, 21.4, 14.2.

The data is consistent with those reported in the literature.(*40*)



46

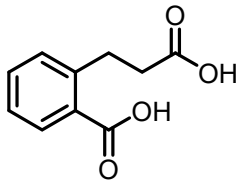
2-Methylheptanedioic acid 46

This compound was prepared according to the general procedure B for the preparation of α-substituted heptanedioic acids. 75% yield, (0.78 g, 4.5 mmol, white solid).

^{1}H NMR (500 MHz, DMSO) δ 2.29 (h, *J* = 6.9 Hz, 1H), 2.19 (t, *J* = 7.3 Hz, 2H), 1.57 – 1.50 (m, 1H), 1.50 – 1.41 (m, 2H), 1.33 (dq, *J* = 15.7, 6.8 Hz, 1H), 1.25 (qd, *J* = 7.6, 3.7 Hz, 2H), 1.03 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, DMSO) δ 177.4, 174.4, 38.6, 33.6, 33.0, 26.3, 24.4, 17.0.

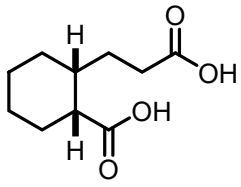
HRMS (ESI-TOF) Calculated for $C_8H_{13}O_4$, $[M-H]^-$: 173.0814, found: 173.0811.



22

2-(2-Carboxyethyl)benzoic acid 22

This compound is commercially available.



23

(1*R,2*R**)-2-(2-Carboxyethyl)cyclohexane-1-carboxylic acid 23**

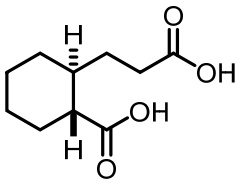
This compound was prepared according to the following procedure.(*43*)

The compound **20** (0.2 g, 1.03 mmol) was dissolved in glacial acetic acid (10.0 mL) and PtO_2 (40.0 mg) was added. The reaction vessel was purged with H_2 and the hydrogenation reaction was carried out at room temperature with a ballon of H_2 and stirred for 3 days. Analysis of an aliquot of the reaction mixture at this point suggested completion of reaction. The reaction mixture was filtered with a plug of Celite® and the filtrate was evaporated to dryness to give the desired compound as a white solid in 97% yield (0.2 g, 1.00 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.62 (dt, *J* = 8.1, 4.1 Hz, 1H), 2.41 (ddd, *J* = 15.8, 10.0, 5.8 Hz, 1H), 2.32 (ddd, *J* = 16.0, 9.7, 6.4 Hz, 1H), 1.98 – 1.85 (m, 1H), 1.83 – 1.73 (m, 2H), 1.73 – 1.61 (m, 4H), 1.60 – 1.43 (m, 2H), 1.41 – 1.30 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 181.6, 180.4, 45.2, 36.7, 32.6, 28.1, 25.3, 23.9, 22.4.

HRMS (ESI-TOF) Calculated for $C_{10}H_{15}O_4$ $[M-H]^-$: 199.0970, Found: 199.0968.



24

(1*R,2*S**)-2-(2-Carboxyethyl)cyclohexane-1-carboxylic acid 24**

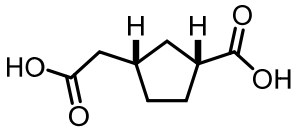
This compound was prepared according to the following procedure.(*43*)

The compound **21** (0.1g, 0.50 mmol) was suspended in conc. HCl (1.0 mL) in a sealed tube and stirred at 180 °C overnight. The reaction mixture was diluted with H2O and extracted with EtOAc three times. The combined organic layer was dried with anhydrous MgSO4, filtered, and evaporated to dryness to give the desired compound as an off-white solid in 76% yield (75.0 mg, 0.38 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.48 (ddd, *J* = 16.2, 10.8, 5.5 Hz, 1H), 2.28 (ddd, *J* = 16.1, 10.5, 5.7 Hz, 1H), 2.08 (td, *J* = 11.5, 3.5 Hz, 1H), 1.96 (d, *J* = 13.7 Hz, 1H), 1.89 – 1.79 (m, 2H), 1.79 – 1.72 (m, 2H), 1.66 – 1.56 (m, 1H), 1.53 – 1.41 (m, 2H), 1.30 – 1.19 (m, 2H), 0.92 (td, *J* = 12.3, 8.9 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 182.9, 180.6, 49.9, 38.3, 31.5, 30.4, 30.1, 29.8, 25.6, 25.4.

HRMS (ESI-TOF) Calculated for $C_{10}H_{15}O_4$ $[M-H]^-$: 199.0970, Found: 199.0974.



25

(1*R,3*S**)-3-(Carboxymethyl)cyclopentane-1-carboxylic acid 25**

This compound was prepared according to the following procedure.

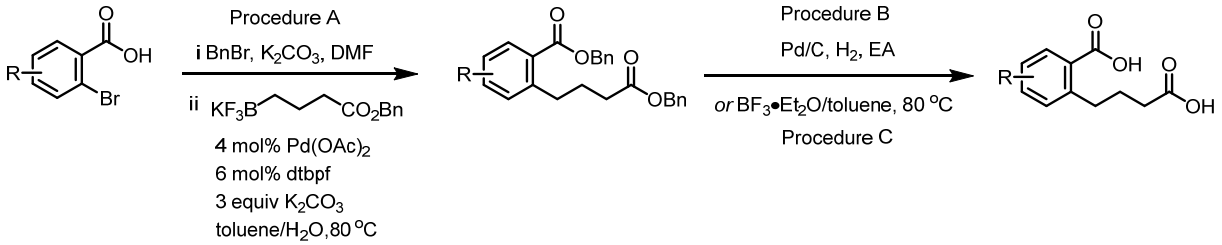
Bicyclo[3.2.1]oct-2-ene (1.0 g, 9.24 mmol) was dissolved in a 3:2:2 ratio of H_2O/MeCN/EtOAc (31 mL) at room temperature. $RuCl_3$•xH_2O (42.0 mg, 0.20 mmol) was added, followed by portionwise addition of $NaIO_4$ (8.1 g, 38.0 mmol) over 1 hour. The reaction mixture was stirred vigorously at room temperature overnight. The reaction mixture was diluted with H_2O and extracted with EtOAc three times. The combined organic layer was dried with anhydrous $MgSO_4$, filtered, and evaporated to dryness to give the desired compound as a pale grey solid in 83% yield (1.35 g, 7.6 mmol).

^{1}H NMR (600 MHz, DMSO) δ 12.01 (s, 2H), 2.69 (dt, *J* = 16.4, 8.1 Hz, 1H), 2.24 (dd, *J* = 7.3, 2.0 Hz, 2H), 2.19 – 2.10 (m, 1H), 2.03 (dt, *J* = 12.5, 7.5 Hz, 1H), 1.83 – 1.71 (m, 3H), 1.31 (dt, *J* = 12.5, 9.5 Hz, 1H), 1.24 – 1.18 (m, 1H).

^{13}C NMR (151 MHz, DMSO) δ 177.1, 173.9, 42.9, 39.4, 36.2, 36.0, 31.4, 28.3.

HRMS (ESI-TOF) Calculated for $C_8H_{11}O_4$ [M-H]$^-$: 171.0657, Found: 171.0657.

General method for the preparation of substituted benzoic acid substrates

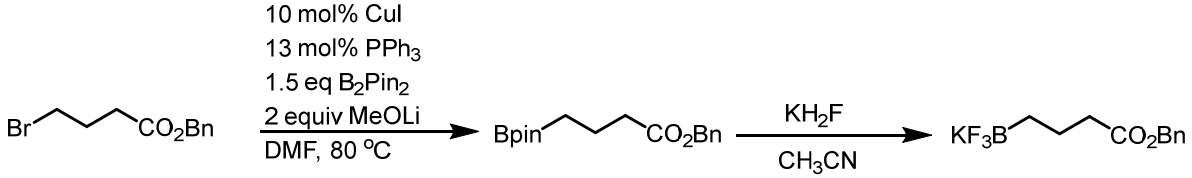


Procedure A

To a solution of 2-bromobenzoic acid (14.0 mmol) in DMF (30 mL) were added K_2CO_3 (21.0 mmol) and benzylbromide (14.3 mmol), and the mixture was stirred at room temperature for 12 h. The mixture was partitioned between EtOAc and H_2O, and extracted with EtOAc, and the organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give benzyl 2-bromobenzoate quantitatively.

A suspension of benzyl 2-bromobenzoate (2 mmol), benzyl 4-trifluoroboratebutanoate potassium salt (3 mmol), K_2CO_3 (829 mg, 6 mmol), $Pd(OAc)_2$ (18 mg, 0.08 mmol), 1,1'-bis(di-tert-butylphosphino)ferrocene (dtbpf, 56 mg, 0.12 mmol) in toluene (10 mL), was degassed with N_2 during 5 min and distilled water (2 mL) was added. The mixture was placed into a pre-heated oil bath at 80 °C during 18 h and controlled by TLC until the starting material was consumed. Then, the system was cooled to room temperature, diluted with H_2O (10 mL) and extracted with Et_2O (3 × 30 mL). The organic phase was washed with 1 M HCl (10 mL) and brine (20 mL), dried over $MgSO_4$ and filtered through a cotton pad. The volatiles were removed under vacuum and the crude material was purified by column chromatography affording benzyl 2-(4-(benzyloxy)-4-oxobutyl)benzoate.

Preparation of benzyl 4-trifluoroboratebutanoate potassium salt



In air, CuI (228 mg, 1.2 mmol), PPh_3 (409 mg, 1.56 mmol), LiOMe (912 mg, 24 mmol), and bis(pinacolato)diboron (4.57 g, 18 mmol) were added to a 50 ml round-bottom flask equipped with a stir bar. The vessel was evacuated and filled with N_2 (three cycles). DMF (15 mL), the benzyl 4-

bromobutanoate (12 mmol, 3.07 g) were added in turn by syringe. The resulting reaction mixture was stirred vigorously at room temperature for 18 h. The reaction mixture was then diluted with EtOAc, filtered through silica gel with copious washings (EtOAc), concentrated, and purified by column chromatography, affording benzyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate (2.9 g, 79% yield) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 5H), 5.11 (s, 2H), 2.41 – 2.35 (m, 2H), 1.81 – 1.73 (m, 2H), 1.23 (s, 12H), 0.82 (t, J = 7.9 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.6, 136.3, 128.6, 128.3, 128.2, 83.2, 66.1, 36.7, 24.9, 19.7. HRMS (ESI-TOF) Calculated for $C_{25}H_{25}O_4$ $[M+H]^+$: 304.1960, found: 304.1963.

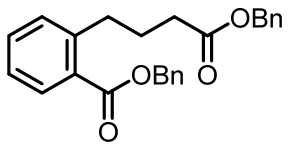
To a stirred solution of benzyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate (1.2 g, 4 mmol) in CH_3CN (10 mL) was added KHF_2 (936 mg, 12 mmol) Then the mixture was added with water (3 mL) dropwise at ambient temperature and the reaction mixture was stirred for 4 h. Then the solvent was removed under vacuum and dried. The resulting mixture was purified by dissolving in hot CH_3CN, and precipitation by adding Et_2O. Collect the white solid washed with Et_2O to afford benzyl 4-trifluoroboratebutanoate potassium salt (795 mg, 70% yield) as a white solid. ^{1}H NMR (600 MHz, DMSO) δ 7.60 – 7.16 (m, 5H), 5.04 (s, 2H), 2.33 – 2.03 (m, 2H), 1.83 – 1.32 (m, 2H), 0.40 – -0.18 (m, 2H). ^{13}C NMR (151 MHz, DMSO) δ 173.8, 136.6, 128.4, 127.9, 127.8, 73.6, 64.8, 37.3, 25.0, 21.7 (q, J = 2.7 Hz). HRMS (ESI-TOF) Calculated for $C_{11}H_{13}BF_3O_2$ $[M-H]^-$: 244.0997, found: 244.0992.

Procedure B

A solution of benzyl 2-(4-(benzyloxy)-4-oxobutyl)benzoate (1 mmol) in EtOAc (10 mL) was treated with 10% Pd/C (100 mg) and the mixture was stirred for overnight at room temperature under H_2. The mixture was passed through celite and the filtrate was concentrated under reduced pressure to give 2-(3-carboxypropyl)benzoic acid.

Procedure C

A solution of benzyl 2-(4-(benzyloxy)-4-oxobutyl)benzoate (1 mmol) in toluene (10 mL) was added with Boron trifluoride diethyl etherate (2.4 mmol) and the mixture was placed into a pre-heated oil bath at 80 °C for 2 h. The mixture was concentrated under reduced pressure and purified by column chromatography (EtOAc/Hexanes/3% AcOH) to give 2-(3-carboxypropyl)benzoic acid.



S32

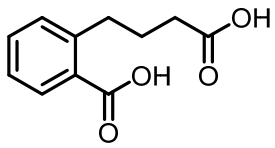
Benzyl 2-(4-(benzyloxy)-4-oxobutyl)benzoate S32

S32 was prepared by Procedure A, 97% yield for two steps, (0.75 g, 1.94 mmol, yellow oil).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.94 – 7.90 (m, 1H), 7.44 – 7.31 (m, 11H), 7.26 – 7.19 (m, 2H), 5.32 (s, 2H), 5.11 (s, 2H), 3.00 – 2.95 (m, 2H), 2.34 (t, J = 7.5 Hz, 2H), 1.97 – 1.89 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 173.4, 167.4, 143.6, 136.2, 136.1, 132.2, 131.3, 131.0, 129.5, 128.8, 128.7, 128.5, 128.4, 128.4, 128.3, 128.3, 126.3, 77.4, 77.2, 76.9, 66.8, 66.27, 34.02, 33.7, 26.8.

HRMS (ESI-TOF) Calculated for $C_{25}H_{25}O_4$ $[M+H]^+$: 389.1753, Found: 389.1749.



32

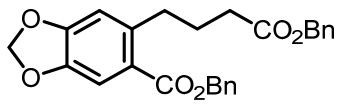
2-(3-Carboxypropyl)benzoic acid 32

32 was prepared by Procedure B, 99% yield, (0.21 g, 0.99 mmol, white solid).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.49 (td, *J* = 7.5, 1.5 Hz, 1H), 7.33 – 7.27 (m, 2H), 3.18 – 3.12 (m, 2H), 2.43 – 2.38 (m, 2H), 2.05 – 1.98 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 181.1, 174.3, 144.1, 133.0, 131.7, 131.3, 129.2, 126.4, 77.4, 77.2, 77.0, 33.4, 32.6, 27.7.

HRMS (ESI-TOF) Calculated for $C_{11}H_{12}O_4Na$ $[M+Na]^+$: 231.0633, Found: 231.0640.



S33

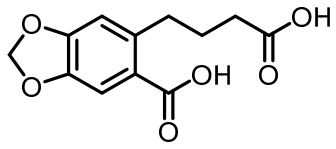
Benzyl 6-(4-(benzyloxy)-4-oxobutyl)benzo[*d*][1,3]dioxole-5-carboxylate S33

S33 was prepared by Procedure A, 95% yield for two steps, (0.82 g, 1.90 mmol, yellow oil).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 – 7.32 (m, 10H), 6.66 (s, 1H), 5.98 (s, 2H), 5.28 (s, 2H), 5.11 (s, 2H), 2.97 – 2.92 (m, 2H), 2.35 (t, 2H), 1.95 – 1.87 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 173.4, 166.3, 150.9, 146.0, 140.6, 136.2, 136.2, 128.7, 128.7, 128.4, 128.4, 128.3, 122.2, 111.0, 110.8, 101.8, 66.7, 66.3, 33.9, 33.9, 26.9.

HRMS (ESI-TOF) Calculated for $C_{26}H_{25}O_6$ $[M+H]^+$: 433.1651, Found: 433.1646.



33

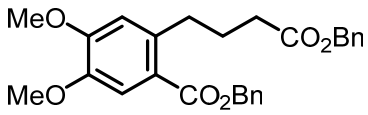
6-(3-Carboxypropyl)benzo[*d*][1,3]dioxole-5-carboxylic acid 33

33 was prepared by Procedure B, 99% yield, (0.25 g, 0.99 mmol, white solid).

^{1}H NMR (600 MHz, CD_3OD) δ 7.37 (s, 1H), 6.76 (s, 1H), 6.00 (s, 2H), 3.00 – 2.95 (m, 2H), 2.31 (t, *J* = 7.6 Hz, 2H), 1.90 – 1.82 (m, 2H).

^{13}C NMR (151 MHz, CD_3OD) δ 177.4, 170.0, 152.2, 147.3, 141.6, 124.0, 111.8, 111.5, 103.1, 34.7, 34.6, 28.2.

HRMS (ESI-TOF) Calculated for $C_{12}H_{12}O_6Na$ $[M+Na]^+$: 275.0532, Found: 275.0530.



S34

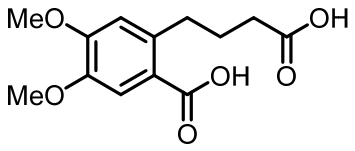
Benzyl 2-(4-(benzyloxy)-4-oxobutyl)-4,5-dimethoxybenzoate S34

S34 was prepared by Procedure A, 95% yield for two steps, (0.85 g, 1.90 mmol, yellow oil).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.44 – 7.41 (m, 2H), 7.40 – 7.30 (m, 9H), 6.66 (s, 1H), 5.31 (s, 2H), 5.11 (s, 2H), 3.87 (s, 3H), 3.87 (s, 3H), 2.98 – 2.92 (m, 2H), 2.31 (t, *J* = 7.4 Hz, 2H), 1.95 – 1.87 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 173.5, 166.8, 152.1, 146.9, 138.5, 136.3, 136.2, 128.7, 128.7, 128.4, 128.4, 128.4, 128.3, 120.8, 113.9, 113.8, 66.7, 66.3, 56.2, 56.0, 33.9, 33.8, 27.0.

HRMS (ESI-TOF) Calculated for $C_{27}H_{29}O_6$ $[M+H]^+$: 449.1964, Found: 449.1956.



34

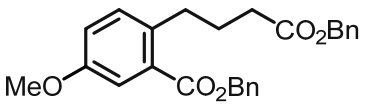
2-(3-Carboxypropyl)-4,5-dimethoxybenzoic acid 34

34 was prepared by Procedure B, 99% yield, (0.27 g, 0.99 mmol, white solid).

^{1}H NMR (600 MHz, CD_3OD) δ 7.52 (s, 1H), 6.84 (s, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 3.04 – 2.98 (m, 2H), 2.32 (t, *J* = 7.4 Hz, 2H), 1.93 – 1.85 (m, 2H).

^{13}C NMR (151 MHz, CD_3OD) δ 177.8, 170.7, 153.5, 148.1, 139.9, 122.7, 115.7, 115.2, 34.75, 34.2, 28.2.

HRMS (ESI-TOF) Calculated for $C_{13}H_{15}O_6$ $[M-H]^-$: 267.0869, Found: 267.0858.



S35

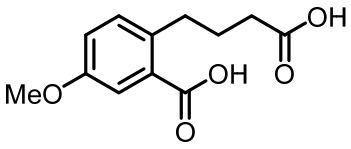
Benzyl 2-(4-(benzyloxy)-4-oxobutyl)-4-methoxybenzoate S35

S35 was prepared by Procedure A, 74% yield for two steps, (0.62 g, 1.48 mmol, yellow oil).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 – 7.41 (m, 3H), 7.40 – 7.30 (m, 8H), 7.12 (d, *J* = 8.5 Hz, 1H), 6.97 (dd, *J* = 8.4, 2.9 Hz, 1H), 5.33 (s, 2H), 5.11 (s, 2H), 3.80 (s, 3H), 2.93 – 2.87 (m, 2H), 2.34 – 2.28 (m, 2H), 1.94 – 1.86 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 173.5, 167.2, 157.7, 136.2, 136.0, 135.6, 132.4, 130.3, 128.8, 128.7, 128.5, 128.4, 128.4, 128.3, 118.3, 115.8, 115.8, 66.9, 66.2, 55.6, 33.9, 33.0, 27.0.

HRMS (ESI-TOF) Calculated for $C_{26}H_{27}O_5$ $[M+H]^+$: 419.1858, Found: 419.1860.



35

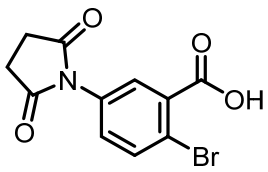
2-(3-Carboxypropyl)-5-methoxybenzoic acid 35

35 was prepared by Procedure B, 99% yield, (0.24 g, 0.99 mmol, white solid).

^{1}H NMR (600 MHz, CD_3OD) δ 7.41 (d, *J* = 3.0 Hz, 1H), 7.20 (d, *J* = 8.5 Hz, 1H), 7.03 (dd, *J* = 8.5, 3.0 Hz, 1H), 3.80 (s, 3H), 2.97 – 2.91 (m, 2H), 2.32 – 2.27 (m, 2H), 1.90 – 1.82 (m, 2H).

^{13}C NMR (151 MHz, CD_3OD) δ 177.5, 170.9, 159.2, 136.5, 133.3, 132.3, 118.8, 116.6, 55.82, 34.7, 33.8, 28.3.

HRMS (ESI-TOF) Calculated for $C_{12}H_{13}O_5$ $[M-H]^-$: 237.0763, found: 237.0766.



SS4

2-Bromo-4-(2,5-dioxopyrrolidin-1-yl)benzoic acid SS4

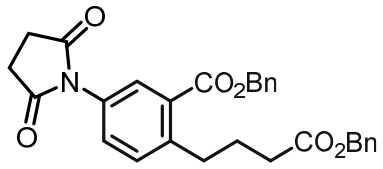
The synthesis of 2-bromo-4-(2,5-dioxopyrrolidin-1-yl)benzoic acid **SS4**: A mixture of 864 mg (4 mmol) of 4-amino-2-bromobenzoic acid, 1 g (4 mmol) of succinic anhydride, 0.6 ml of $ClSiMe_3$, and 1.5 ml DMF was heated for 1.5 h on a bath at 160 – 165 °C cooled to room temperature, and diluted

with water. The precipitate was separated by filtration, washed with water, and dried in air to obtain 2-bromo-4-(2,5-dioxopyrrolidin-1-yl)benzoic acid (90% yield, 1.07 g, 3.6 mmol) as yellow solid.

^{1}H NMR (600 MHz, CD_3OD) δ 7.85 – 7.80 (m, 2H), 7.40 (dd, *J* = 8.5, 2.6 Hz, 1H), 2.88 (s, 4H).

^{13}C NMR (151 MHz, CD_3OD) δ 178.4, 168.5, 135.8, 135.1, 131.8, 130.6, 121.6, 29.4.

HRMS (ESI-TOF) Calculated for $C_{11}H_9BrNO_4$ $[M+H]^+$: 297.9715, Found: 297.9716.



S36

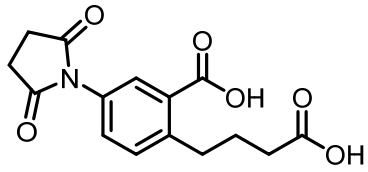
Benzyl 2-(4-(benzyloxy)-4-oxobutyl)-4-(2,5-dioxopyrrolidin-1-yl)benzoate S36

S36 was prepared by Procedure A, 77% yield for two steps, (0.75 g, 1.54 mmol, yellow oil).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 2.0, 0.8 Hz, 1H), 7.44 – 7.30 (m, 12H), 5.31 (s, 2H), 5.12 (s, 2H), 3.03 – 2.99 (m, 2H), 2.88 (s, 4H), 2.36 (t, *J* = 7.4 Hz, 2H), 1.98 – 1.90 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 176.1, 173.3, 166.1, 144.5, 136.2, 135.8, 132.3, 130.3, 130.1, 130.1, 129.2, 128.8, 128.8, 128.6, 128.6, 128.5, 128.4, 67.1, 66.3, 34.0, 33.5, 28.5, 26.7.

HRMS (ESI-TOF) Calculated for $C_{29}H_{28}NO_6$ $[M+H]^+$: 486.1917, Found: 486.1910.



36

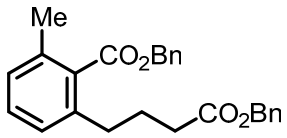
2-(3-Carboxypropyl)-4-(2,5-dioxopyrrolidin-1-yl)benzoic acid 36

36 was prepared by Method B, 98% yield, (0.3 g, 0.98 mmol, white solid).

^{1}H NMR (600 MHz, CD_3OD) δ 7.86 (d, *J* = 2.2 Hz, 1H), 7.44 – 7.37 (m, 2H), 3.10 – 3.04 (m, 2H), 2.85 (s, 4H), 2.35 (t, *J* = 7.5 Hz, 2H), 1.97 – 1.89 (m, 2H).

^{13}C NMR (151 MHz, CD_3OD) δ 177.6, 175.9, 168.5, 143.7, 131.5, 130.7, 130.5, 129.9, 129.1, 33.2, 32.9, 28.0, 26.6.

HRMS (ESI-TOF) Calculated for $C_{15}H_{16}NO_6$ $[M+H]^+$: 306.0978, Found: 306.0965.



S37

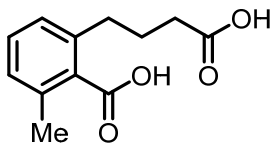
Benzyl 2-(4-(benzyloxy)-4-oxobutyl)-3-methylbenzoate S37

S37 was prepared by Procedure A, 83% yield for two steps, (0.67 g, 1.66 mmol, yellow oil).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 – 7.41 (m, 2H), 7.40 – 7.30 (m, 8H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.05 – 6.98 (m, 2H), 5.35 (s, 2H), 5.10 (s, 2H), 2.58 – 2.53 (m, 2H), 2.27 (s, 3H), 2.24 (t, *J* = 7.5 Hz, 2H), 1.90 – 1.82 (m, 2H)

^{13}C NMR (151 MHz, $CDCl_3$) δ 173.2, 169.8, 138.5, 136.2, 135.6, 135.1, 133.7, 129.6, 129.1, 128.7, 128.7, 128.6, 128.4, 128.3, 128.1, 127.0, 67.1, 66.3, 33.8, 33.0, 26.5, 19.8.

HRMS (ESI-TOF) Calculated for $C_{26}H_{27}O_4$ $[M+H]^+$: 403.1909, Found: 403.1906.



37

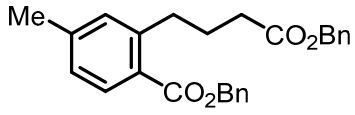
2-(3-Carboxypropyl)-6-methylbenzoic acid 37

37 was prepared by Procedure B, 99% yield, (0.22 g, 0.99 mmol, white solid).

^{1}H NMR (600 MHz, CD_3OD) δ 7.23 (t, *J* = 7.6 Hz, 1H), 7.12 – 7.06 (m, 2H), 2.71 – 2.66 (m, 2H), 2.33 (s, 3H), 2.30 (t, *J* = 7.4 Hz, 2H), 1.95 – 1.87 (m, 2H).

^{13}C NMR (151 MHz, CD_3OD) δ 177.2, 173.8, 139.1, 136.3, 135.3, 130.1, 128.9, 127.9, 34.5, 33.9, 27.8, 19.8.

HRMS (ESI-TOF) Calculated for $C_{12}H_{14}O_4Na$ $[M+Na]^+$: 245.0790, Found: 245.0795.



S38

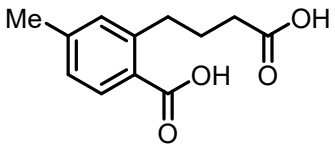
Benzyl 2-(4-(benzyloxy)-4-oxobutyl)-4-methylbenzoate S38

S38 was prepared by Procedure A, 95% yield for two steps, (0.77 g, 1.90 mmol, yellow oil).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.0 Hz, 1H), 7.45 – 7.40 (m, 2H), 7.37 (dd, *J* = 7.3, 1.0 Hz, 2H), 7.37 – 7.29 (m, 6H), 7.07 – 7.00 (m, 2H), 5.30 (s, 2H), 5.11 (s, 2H), 2.98 – 2.93 (m, 2H), 2.37 – 2.31 (m, 5H), 1.97 – 1.88 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 173.5, 167.3, 143.9, 142.8, 136.3, 132.1, 131.3, 128.7, 128.7, 128.4, 128.4, 128.3, 128.3, 127.0, 126.5, 66.6, 66.3, 34.1, 33.8, 26.9, 21.6.

HRMS (ESI-TOF) Calculated for $C_{26}H_{27}O_4$ $[M+H]^+$: 403.1909, Found: 403.1914.



38

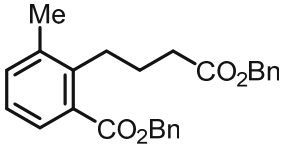
2-(3-Carboxypropyl)-4-methylbenzoic acid 38

38 was prepared by Procedure B, 99% yield, (0.22 g, 0.99 mmol, white solid).

^{1}H NMR (600 MHz, CD_3OD) δ 7.83 – 7.78 (m, 1H), 7.13 – 7.07 (m, 2H), 3.02 – 2.96 (m, 2H), 2.37 – 2.29 (m, 5H), 1.92 – 1.84 (m, 2H).

^{13}C NMR (151 MHz, CD_3OD) δ 177.4, 170.9, 145.0, 143.8, 132.9, 132.3, 128.2, 127.8, 34.7, 34.7, 28.1, 25.0, 21.4.

HRMS (ESI-TOF) Calculated for $C_{12}H_{14}O_4Na$ $[M+Na]^+$: 245.0790, Found: 245.0789.



S39

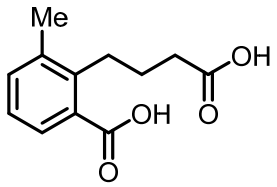
Benzyl 2-(4-(benzyloxy)-4-oxobutyl)-3-methylbenzoate S39

S39 was prepared by Procedure A, 98% yield for two steps, (0.79 g, 1.96 mmol, yellow oil).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 – 7.65 (m, 1H), 7.45 – 7.40 (m, 2H), 7.38 – 7.30 (m, 8H), 7.29 – 7.26 (m, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 5.31 (s, 2H), 5.12 (s, 2H), 2.93 – 2.87 (m, 2H), 2.37 (t, *J* = 7.3 Hz, 2H), 2.33 (s, 3H), 1.90 – 1.81 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 173.4, 168.2, 141.3, 137.7, 136.2, 136.1, 134.1, 130.7, 128.7, 128.7, 128.5, 128.4, 128.4, 128.3, 127.9, 125.9, 125.9, 66.9, 66.3, 34.4, 29.4, 25.4, 19.8.

HRMS (ESI-TOF) Calculated for $C_{26}H_{26}O_4Na$ $[M+Na]^+$: 425.1729, Found: 425.1721.



39

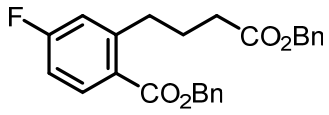
2-(3-Carboxypropyl)-3-methylbenzoic acid 39

39 was prepared by Procedure B, 99% yield, (0.22 g, 0.99 mmol, white solid).

^{1}H NMR (600 MHz, CD_3OD) δ 7.62 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.31 (dt, *J* = 7.6, 1.4 Hz, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 2.99 – 2.94 (m, 2H), 2.41 – 2.35 (m, 5H), 1.88 – 1.79 (m, 2H).

^{13}C NMR (151 MHz, CD_3OD) δ 177.4, 172.2, 142.0, 138.7, 134.6, 132.8, 129.1, 126.7, 35.1, 30.5, 30.4, 26.8, 19.8.

HRMS (ESI-TOF) Calculated for $C_{12}H_{14}O_4Na$ $[M+Na]^+$: 245.0790, Found: 245.0798.



S40

Benzyl 2-(4-(benzyloxy)-4-oxobutyl)-4-fluorobenzoate S40

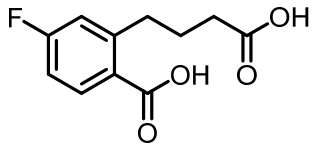
S40 was prepared by Procedure A, 98% yield for two steps, (0.80 g, 1.96 mmol, yellow oil).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.01 – 7.95 (m, 1H), 7.45 – 7.40 (m, 2H), 7.40 – 7.37 (m, 3H), 7.37 – 7.30 (m, 5H), 6.96 – 6.90 (m, 2H), 5.31 (s, 2H), 5.12 (s, 2H), 3.02 – 2.97 (m, 2H), 2.35 (t, *J* = 7.4 Hz, 2H), 1.98 – 1.90 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 173.2, 166.3, 164.9 (d, *J* = 253.6 Hz), 147.4 (d, *J* = 8.8 Hz), 136.1 (d, *J* = 29.7 Hz), 133.8 (d, *J* = 9.3 Hz), 128.8, 128.7, 128.5, 128.4, 128.4, 125.5 (d, *J* = 2.8 Hz), 117.9 (d, *J* = 21.4 Hz), 113.4 (d, *J* = 21.4 Hz), 66.9, 66.3, 33.9, 33.8, 26.5.

^{19}F NMR (376 MHz, $CDCl_3$) δ -109.70.

HRMS (ESI-TOF) Calculated for $C_{25}H_{24}O_4F$ $[M+H]^+$: 407.1659, Found: 407.1653.



40

2-(3-Carboxypropyl)-4-fluorobenzoic acid 40

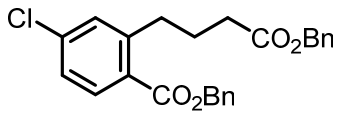
40 was prepared by Procedure B, 98% yield, (0.22 g, 0.98 mmol, white solid).

^{1}H NMR (600 MHz, CD_3OD) δ 7.98 (dd, *J* = 8.7, 6.0 Hz, 1H), 7.08 – 6.98 (m, 2H), 3.07 – 3.01 (m, 2H), 2.33 (t, *J* = 7.5 Hz, 2H), 1.94 – 1.86 (m, 2H).

^{13}C NMR (151 MHz, CD_3OD) δ 177.2, 169.8, 166.0 (d, *J* = 251.4 Hz), 148.7 (d, *J* = 8.6 Hz), 134.9 (d, *J* = 9.3 Hz), 127.5 (d, *J* = 3.0 Hz), 118.6 (d, *J* = 21.6 Hz), 114.0 (d, *J* = 21.8 Hz), 34.6, 34.6, 27.8.

^{19}F NMR (376 MHz, CD_3OD) δ -108.88.

HRMS (ESI-TOF) Calculated for $C_{11}H_{11}O_4FNa$ $[M+Na]^+$: 249.0539, Found: 249.0537.



S41

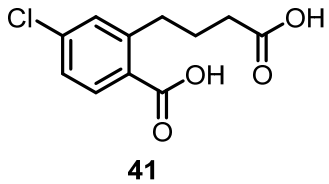
Benzyl 2-(4-(benzyloxy)-4-oxobutyl)-4-chlorobenzoate S41

S41 was prepared by Procedure A by using 2-bromo-4-chlorobenzoic acid (3 mmol) with other condition no change, 75% yield, (0.63 g, 1.50 mmol, yellow oil).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90 – 7.84 (m, 1H), 7.44 – 7.30 (m, 10H), 7.24 – 7.19 (m, 2H), 5.31 (s, 2H), 5.12 (s, 2H), 2.98 – 2.93 (m, 2H), 2.34 (t, *J* = 7.4 Hz, 2H), 1.96 – 1.88 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 173.2, 166.5, 145.8, 138.4, 136.2, 131.2, 128.8, 128.7, 128.6, 128.5, 128.4, 127.8, 126.5, 67.0, 66.4, 33.9, 33.6, 26.6.

HRMS (ESI-TOF) Calculated for $C_{25}H_{24}ClO_4$ $[M+H]^+$: 423.1363, Found: 423.1356.



41

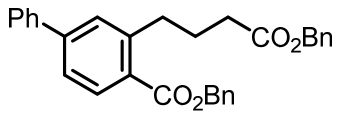
2-(3-Carboxypropyl)-4-chlorobenzoic acid 41

41 was prepared by Procedure C, 75% yield, (0.18 g, 0.75 mmol, white solid).

^{1}H NMR (600 MHz, CD_3OD) δ 7.88 (d, *J* = 8.3 Hz, 1H), 7.33 (d, *J* = 2.2 Hz, 1H), 7.29 (dd, *J* = 8.4, 2.2 Hz, 1H), 3.04 – 2.98 (m, 2H), 2.33 (t, *J* = 7.4 Hz, 2H), 1.93 – 1.85 (m, 2H).

^{13}C NMR (151 MHz, CD_3OD) δ 177.2, 169.9, 147.1, 138.8, 133.7, 131.9, 127.3, 34.6, 34.4, 27.9.

HRMS (ESI-TOF) Calculated for $C_{11}H_{12}ClO_4$ $[M+H]^+$: 243.0424, Found: 243.0424.



S42

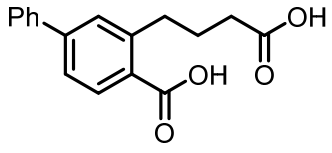
Benzyl 3-(4-(benzyloxy)-4-oxobutyl)-[1,1'-biphenyl]-4-carboxylate S42

To a solution of $Pd_2(dba)_3$ (183 mg, 0.2 mmol), SPhos (164 mg, 0.4 mmol) in dioxane (8 mL) was added a solution of **S41** (844 mg, 2 mmol) in dioxane (8 mL) and stirred for 10 minutes. K_3PO_4 (1.27 g, 6 mmol) and $PhB(OH)_2$ were added. The resulting mixture was heated to 100 °C and stirred for 15 hours. The reaction was cooled to room temperature and diluted with ethyl acetate. Then washed with brine and the organic phase was concentrated under reduced pressure and purified by column chromatography to give the product **S42** (85% yield, 0.79 g, 1.7 mmol) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.1 Hz, 1H), 7.61 – 7.56 (m, 2H), 7.49 – 7.42 (m, 6H), 7.41 – 7.29 (m, 10H), 5.35 (s, 2H), 5.11 (s, 2H), 3.09 – 3.04 (m, 2H), 2.38 (t, *J* = 7.5 Hz, 2H), 2.03 – 1.95 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 173.4, 167.1, 145.0, 144.3, 140.0, 136.2, 136.1, 131.8, 130.0, 129.0, 128.8, 128.7, 128.5, 128.4, 128.4, 128.3, 128.2, 128.1, 128.0, 127.4, 124.9, 66.8, 66.3, 34.0, 34.0, 26.9.

HRMS (ESI-TOF) Calculated for $C_{31}H_{29}O_4$ $[M+H]^+$: 465.2066, Found: 465.2062.



42

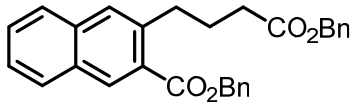
3-(3-Carboxypropyl)-[1,1'-biphenyl]-4-carboxylic acid 42

42 was prepared by Procedure B, 99% yield, (0.28 g, 0.99 mmol, white solid).

^{1}H NMR (600 MHz, CD_3OD) δ 8.01 (d, *J* = 8.1 Hz, 1H), 7.71 – 7.66 (m, 2H), 7.58 – 7.53 (m, 2H), 7.51 – 7.45 (m, 2H), 7.42 – 7.36 (m, 1H), 3.13 (t, *J* = 7.7 Hz, 2H), 2.38 (t, *J* = 7.4 Hz, 2H), 2.02 – 1.94 (m, 2H).

^{13}C NMR (151 MHz, CD_3OD) δ 177.6, 171.1, 145.8, 145.4, 141.3, 132.8, 130.7, 130.0, 129.1, 128.16, 125.6, 34.8, 34.7, 28.2.

HRMS (ESI-TOF) Calculated for $C_{17}H_{15}O_4$ $[M-H]^-$: 283.0970, Found: 283.0966.



S43

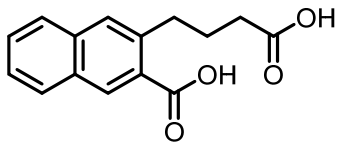
Benzyl 3-(4-(benzyloxy)-4-oxobutyl)-2-naphthoate S43

S43 was prepared by Procedure A, 91% yield for two steps, (0.80 g, 1.82 mmol, yellow oil).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.86 (ddq, *J* = 8.2, 1.3, 0.6 Hz, 1H), 7.78 – 7.73 (m, 1H), 7.64 (d, *J* = 0.8 Hz, 1H), 7.57 – 7.51 (m, 1H), 7.51 – 7.44 (m, 3H), 7.43 – 7.38 (m, 2H), 7.38 – 7.30 (m, 6H), 5.39 (s, 2H), 5.11 (s, 2H), 3.16 – 3.11 (m, 2H), 2.38 (t, *J* = 7.5 Hz, 2H), 2.01 (tt, *J* = 9.5, 6.7 Hz, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 173.5, 167.5, 138.9, 136.2, 136.1, 135.1, 132.5, 131.3, 129.6, 128.8, 128.7, 128.6, 128.5, 128.4, 127.9, 127.2, 126.2, 67.0, 66.3, 34.0, 33.9, 26.8.

HRMS (ESI-TOF) Calculated for $C_{29}H_{27}O_4$ $[M+H]^+$: 439.1909, Found: 439.1908.



43

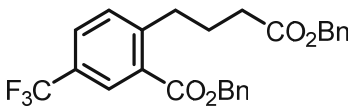
3-(3-Carboxypropyl)-2-naphthoic acid 43

43 was prepared by Procedure B, 99% yield, (0.26 g, 0.99 mmol, white solid).

^{1}H NMR (600 MHz, CD_3OD) δ 8.48 (s, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.82 (d, *J* = 8.3 Hz, 1H), 7.72 (s, 1H), 7.55 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.48 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 3.19 – 3.14 (m, 2H), 2.36 (t, *J* = 7.5 Hz, 2H), 2.01 – 1.93 (m, 2H).

^{13}C NMR (151 MHz, CD_3OD) δ 177.5, 171.0, 140.1, 136.4, 133.2, 132.7, 130.4, 129.7, 129.6, 129.2, 128.2, 127.2, 34.8, 34.7, 28.1.

HRMS (ESI-TOF) Calculated for $C_{29}H_{27}O_4$ $[M+H]^+$: 439.1909, found: 439.1908.



S44

Benzyl 2-(4-(benzyloxy)-4-oxobutyl)-5-(trifluoromethyl)benzoate S44

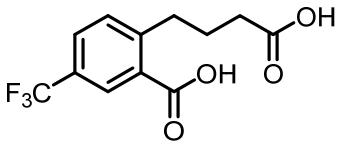
S44 was prepared by Procedure A, 88% yield for two steps, (0.80 g, 1.76 mmol, yellow oil).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.18 – 8.15 (m, 1H), 7.64 (ddd, *J* = 8.1, 2.2, 0.7 Hz, 1H), 7.46 – 7.30 (m, 11H), 5.35 (s, 2H), 5.11 (s, 2H), 3.05 – 2.99 (m, 2H), 2.34 (t, *J* = 7.4 Hz, 2H), 1.97 – 1.89 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 173.1, 166.2, 147.6 (q, *J* = 2.2 Hz), 136.1, 135.6, 131.9, 130.2, 128.9 (q, *J* = 33.0 Hz), 128.7, 128.7, 128.6, 128.6, 128.5, 128.4, 128.4, 128.0 (q, *J* = 4.1 Hz), 123.8 (q, *J* = 272.3 Hz), 67.4, 66.4, 33.9, 33.6, 26.6.

^{19}F NMR (376 MHz, $CDCl_3$) δ -65.26.

HRMS (ESI-TOF) Calculated for $C_{26}H_{24}F_3O_4$ $[M+H]^+$: 457.1627, Found: 457.1624.



44

2-(3-Carboxypropyl)-5-(trifluoromethyl)benzoic acid 44

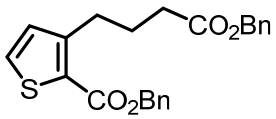
44 was prepared by Procedure B, 99% yield, (0.27 g, 0.99 mmol, white solid).

^{1}H NMR (600 MHz, CD_3OD) δ 8.15 (d, *J* = 2.0 Hz, 1H), 7.74 (ddd, *J* = 8.0, 2.1, 0.8 Hz, 1H), 7.52 (d, *J* = 8.1 Hz, 1H), 3.13 – 3.08 (m, 2H), 2.35 (t, *J* = 7.4 Hz, 2H), 1.97 – 1.89 (m, 2H).

^{13}C NMR (151 MHz, CD_3OD) δ 177.1, 169.3, 149.2, 133.2, 129.5 (q, *J* = 33.0 Hz), 129.2 (q, *J* = 3.6 Hz), 128.7 (q, *J* = 3.9 Hz), 125.4 (q, *J* = 271.3 Hz), 34.60, 34.5, 27.8.

^{19}F NMR (376 MHz, CD_3OD) δ -62.91.

HRMS (ESI-TOF) Calculated for $C_{12}H_{12}F_3O_4$ $[M+H]^+$: 277.0688, Found: 277.0681.



S45

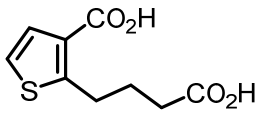
Benzyl 3-(4-(benzyloxy)-4-oxobutyl)thiophene-2-carboxylate S45

S45 was prepared by Procedure A, 85% yield for two steps, (0.67 g, 1.70 mmol, yellow oil).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 (d, *J* = 5.4 Hz, 1H), 7.42 – 7.27 (m, 10H), 7.03 (d, *J* = 5.4 Hz, 1H), 5.28 (s, 2H), 5.11 (s, 2H), 3.26 – 3.20 (m, 2H), 2.39 (t, *J* = 8.5 Hz, 2H), 2.07 – 1.99 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 173.1, 163.2, 154.1, 136.2, 136.1, 129.6, 128.7, 128.7, 128.4, 128.4, 128.4, 128.0, 121.8, 66.3, 33.7, 28.7, 26.7.

HRMS (ESI-TOF) Calculated for $C_{23}H_{23}O_4S$ $[M+H]^+$: 395.1317, found: 395.1309.



45

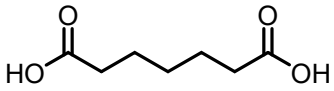
2-(3-carboxypropyl)thiophene-3-carboxylic acid **45**

45 was prepared by Procedure C, 85% yield (182 mg, 0.85 mmol, white solid).

^{1}H NMR (600 MHz, CD_3OD) δ 7.38 (d, *J* = 5.4 Hz, 1H), 7.18 (dd, *J* = 5.3, 0.8 Hz, 1H), 3.27 – 3.22 (m, 2H), 2.36 (t, *J* = 7.4 Hz, 2H), 2.02 – 1.94 (m, 2H).

^{13}C NMR (151 MHz, CD_3OD) δ 177.0, 166.5, 155.0, 130.7, 129.8, 129.6, 122.8, 34.2, 29.4, 28.0.

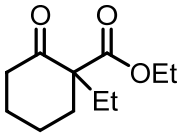
HRMS (ESI-TOF) Calculated for $C_9H_9O_4S$ $[M-H]^-$: 213.0222, found: 213.0218.



2

Pimelic acid/heptane-1,7-dioic acid 2

This compound is commercially available.



SS5

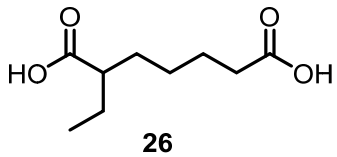
Ethyl 1-ethyl-2-oxocyclohexane-1-carboxylate SS5

This compound was prepared according to the general procedure B for the preparation of β-substituted heptanedioic acids with the reaction of EtI and methyl 2-oxocyclohexane-1-carboxylate. 75% yield, (1.19 g, 6.0 mmol, colorless oil).

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.20 (q, *J* = 7.3 Hz, 2H), 2.53 – 2.40 (m, 3H), 2.06 – 1.89 (m, 1H), 1.77 – 1.56 (m, 2H), 1. 44 – 1.41 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.84 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 208.4, 172.1, 61.3, 61.2, 41.3, 35.7, 27.8, 27.7, 22.7, 14.3, 8.9.

The data is consistent with those reported in the literature.(*40*)



26

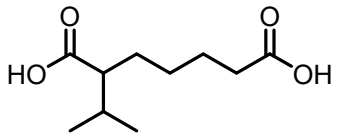
2-Ethylheptanedioic acid 26

This compound was prepared according to the general procedure B for the preparation of β-substituted heptanedioic acids. 75% yield, (0.85 g, 4.5 mmol, white solid).

^{1}H NMR (500 MHz, DMSO) δ 12.00 (s, 2H), 2.18 (t, *J* = 7.3 Hz, 2H), 2.12 (tt, *J* = 8.4, 5.4 Hz, 1H), 1.55 – 1.40 (m, 5H), 1.40 – 1.33 (m, 1H), 1.23 (p, *J* = 7.7 Hz, 2H), 0.90 – 0.74 (m, 3H).

^{13}C NMR (126 MHz, DMSO) δ 176.8, 174.4, 46.4, 33.5, 31.2, 26.5, 26.5, 24.8, 24.5, 11.7, 11.6.

HRMS (ESI-TOF) Calculated for $C_9H_{15}O_4$ $[M-H]^-$: 187.0970, found: 187.0973.



27

2-Isopropylheptanedioic acid 27

This compound was prepared according to the general procedure for the preparation of α-substituted heptanedioic acids.

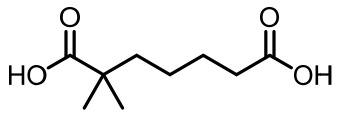
Elution condition: (20% EA/hexanes + 1% AcOH to 50% EA + 1% AcOH, gradient elution)

Isolated yield: 61% over 2 steps (1.23 g, 6.1 mmol, colourless oil)

^{1}H NMR (500 MHz, DMSO) δ 11.98 (s, 2H), 2.18 (t, *J* = 7.3 Hz, 2H), 1.95 (ddd, *J* = 9.5, 7.4, 4.8 Hz, 1H), 1.73 (h, *J* = 6.8 Hz, 1H), 1.56 – 1.44 (m, 2H), 1.42 (ddd, *J* = 9.7, 6.0, 4.0 Hz, 2H), 1.29 – 1.13 (m, 2H), 0.91 – 0.82 (m, 6H).

^{13}C NMR (126 MHz, DMSO) δ 176.4, 174.4, 174.3, 52.1, 33.6, 30.0, 28.8, 27.0, 24.6, 20.4, 20.0, 19.8.

HRMS (ESI-TOF) Calculated for $C_{10}H_{17}O_4$ $[M-H]^-$: 201.1127, Found: 201.1125.



28

2,2-Dimethylheptanedioic acid 28

This compound was prepared according to the general procedure for the preparation of α-substituted heptanedioic acids.

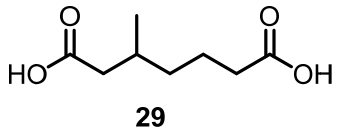
Elution condition: (20% EA/hexanes + 1% AcOH to 50% EA + 1% AcOH, gradient elution)

Isolated yield: 57% over 2 steps (1.07 g, 5.7 mmol, white solid)

^{1}H NMR (500 MHz, DMSO) δ 3.33 (s, 2H), 2.19 (t, *J* = 7.3 Hz, 2H), 1.54 – 1.37 (m, 4H), 1.19 (tq, *J* = 12.4, 6.0 Hz, 2H), 1.06 (s, 6H).

^{13}C NMR (126 MHz, DMSO) δ 178.8, 174.4, 41.2, 39.9, 33.6, 25.0, 25.0, 24.1.

HRMS (ESI-TOF) Calculated for $C_9H_{15}O_4$ $[M-H]^-$: 187.0970, Found: 187.0972.



29

3-Methylheptanedioic acid 29

This compound was prepared according to the general procedure for the preparation of β-substituted heptanedioic acids:

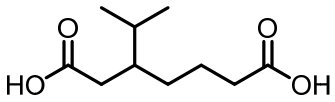
Elution condition: (20% EA/hexanes + 1% AcOH to 50% EA + 1% AcOH, gradient elution)

Isolated yield: 20% over 2 steps (0.28 g, 1.6 mmol, pale yellow oil)

^{1}H NMR (500 MHz, DMSO) δ 11.99 (s, 2H), 2.23 – 2.12 (m, 3H), 1.99 (dd, *J* = 15.0, 8.0 Hz, 1H), 1.80 (dq, *J* = 13.8, 6.9 Hz, 1H), 1.59 – 1.39 (m, 2H), 1.28 (ddt, *J* = 13.2, 10.9, 5.6 Hz, 1H), 1.14 (dddd, *J* = 13.2, 10.5, 7.7, 5.4 Hz, 1H), 0.88 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (126 MHz, DMSO) δ 174.4, 173.9, 41.3, 35.5, 33.8, 29.5, 22.0, 19.5.

HRMS (ESI-TOF) Calculated for $C_8H_{13}O_4$ $[M-H]^-$: 173.0814, Found: 173.0815.



30

3-Isopropylheptanedioic acid 30

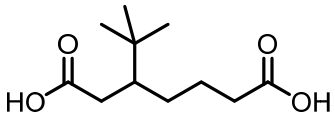
This compound was prepared according to the general procedure for the preparation of β-substituted heptanedioic acids:

Elution condition: (20% EA/hexanes + 1% AcOH to 50% EA + 1% AcOH, gradient elution) Isolated yield: 50% over 2 steps (0.81 g, 4 mmol, pale yellow oil).

^{1}H NMR (500 MHz, DMSO) δ 11.97 (s, 2H), 2.25 – 2.09 (m, 3H), 2.01 (dd, *J* = 15.3, 7.1 Hz, 1H), 1.71 – 1.60 (m, 2H), 1.53 – 1.39 (m, 2H), 1.28 (ddt, *J* = 13.2, 11.0, 5.7 Hz, 1H), 1.14 (ddt, *J* = 13.0, 9.9, 6.8 Hz, 1H), 0.80 (dd, *J* = 13.6, 6.5 Hz, 6H).

^{13}C NMR (126 MHz, DMSO) δ 174.7, 174.4, 40.0, 35.7, 33.9, 30.2, 29.4, 22.3, 19.2, 18.5.

HRMS (ESI-TOF) Calculated for $C_{10}H_{17}O_4$ $[M-H]^-$: 201.1127, Found: 201.1127.



31

3-(*tert*-Butyl)heptanedioic acid 31

This compound was prepared according to the general procedure for the preparation of β-substituted heptanedioic acids:

Elution condition: (20% EA/hexanes + 1% AcOH to 50% EA + 1% AcOH, gradient elution) Isolated yield: 52% over 2 steps (0.9 g, 4.16 mmol, white solid).

^{1}H NMR (500 MHz, DMSO) δ 11.97 (s, 2H), 2.29 (dd, *J* = 16.2, 5.1 Hz, 1H), 2.25 – 2.10 (m, 2H), 1.94 (dd, *J* = 16.2, 6.3 Hz, 1H), 1.62 – 1.51 (m, 2H), 1.51 – 1.42 (m, 1H), 1.42 – 1.33 (m, 1H), 0.98 (tdd, *J* = 11.9, 8.1, 3.6 Hz, 1H), 0.82 (s, 9H).

^{13}C NMR (126 MHz, DMSO) δ 175.3, 174.4, 44.0, 35.6, 33.9, 33.2, 33.1, 30.2, 27.3, 23.6.

HRMS (ESI-TOF) Calculated for $C_{11}H_{19}O_4$ $[M-H]^-$: 215.1283 Found: 215.1284.

2.5 Reaction procedures of the γ-directed, γ-C–H lactonization reaction

General procedure for the γ-directed, γ-C–H lactonization reaction using Ag_2CO_3 as oxidant

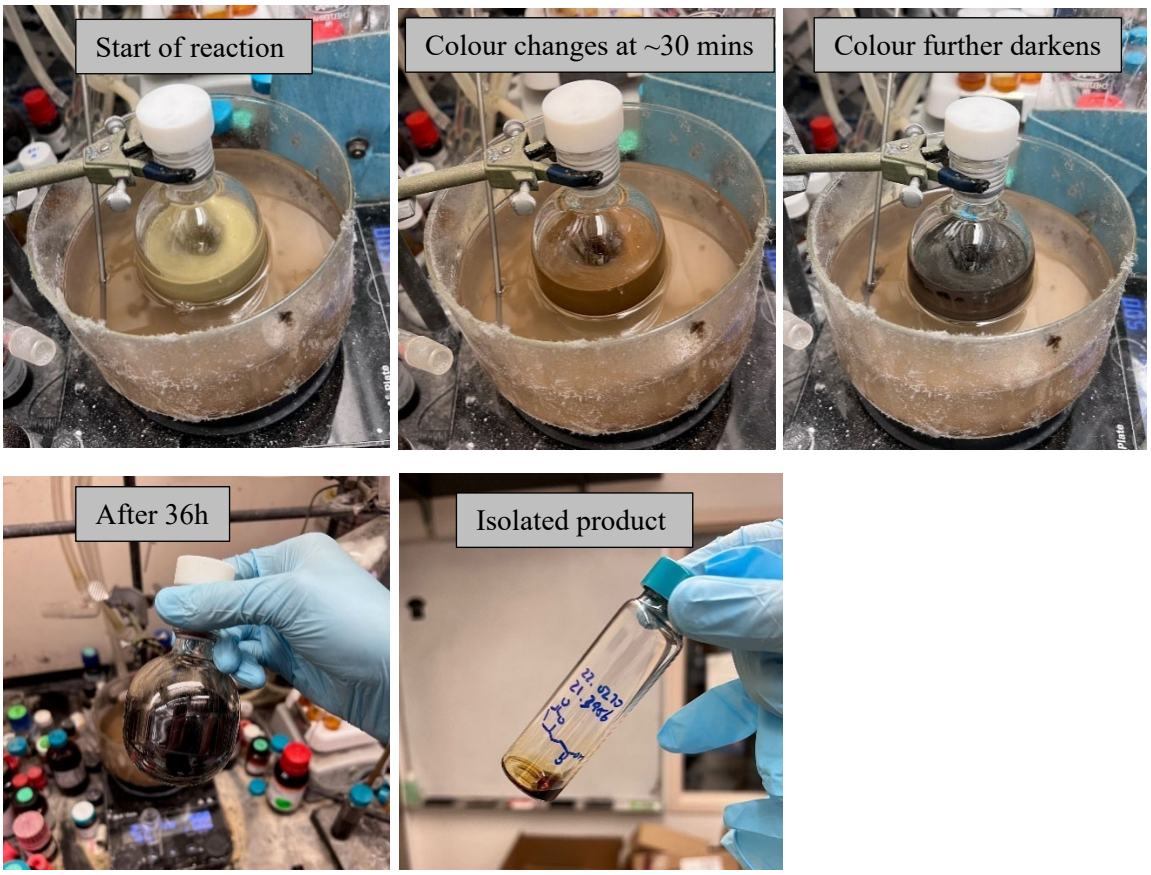
To a 2-dram vial was added the substrate (0.1 mmol), $Pd(OAc)_2$ (10 mol%, 0.01 mmol), ligand (12 mol%, 0.012 mmol), *p*-xyloquinone (0.2 mmol), Ag_2CO_3 (0.2 mmol), K_2HPO_4 (0.035 mmol) and CsOAc (0.04 mmol, preferably added from a stock solution in HFIP as CsOAc is hygroscopic). HFIP (1.0 mL, or the volume needed to make up to 1.0 mL if a stock solution of CsOAc was used) and a stir-bar was then added, followed by sealing the reaction vessel with a PTFE septum inserted between the vial and its cap. **(Note: $Pd(OAc)_2$, ligand, *p*-xyloquinone, CsOAc, and the substrate could all be prepared as a stock solution in HFIP. The use of stock solution is recommended for setting up a series of reactions to maximize work efficiency).** The reaction mixture was sonicated for 30 seconds before stirring at 200 rpm and 100 °C (heating block temperature) for 36 hours. The reaction mixture was then cooled to room temperature and diluted with dichloromethane (1.0 mL), followed by addition of deionized water (2.0 mL), aq. 6M HCl (0.3 mL), brine (1.0 mL) and then shaken vigorously. The lower organic layer was carefully pipetted and filtered through a short plug of Celite®. The remaining aqueous layer was extracted with CH_2Cl_2 (1.0 mL) twice and the organic layer was pipetted and filtered as mentioned. The combined organic layer was then evaporated to dryness. The crude was then taken into $CDCl_3$ (0.6 mL) with CH_2Br_2 (10.0 μL) as the internal standard to determine the assay yield of the reaction by ^1H NMR spectroscopy. The isolation of the product was carried out with aqueous extractions of the organic layer (in 0.6 mL $CDCl_3$ diluted with 2.0 mL CH_2Cl_2) with sat. aq. $NaHCO_3$ solution (1.0 mL each, 3 times). The collected aqueous layer was then acidified by aq. 6M HCl to pH ~ 2 and extracted with EtOAc (1.0 mL, 3 times). The combined EtOAc layers was dried with anhydrous $MgSO_4$, filtered, and evaporated to dryness. The product was either further purified by column chromatography (General procedure for gradient elution unless stated otherwise: begin with 20% EtOAc/hexane + 1% AcOH, and increase the composition of EtOAc by 10% for every 8 mL of eluent used to 100% EtOAc + 1% AcOH, collecting 1.0-2.0 mL fractions. It was observed that the R_f values of carboxylic acids obtained by TLC analysis could not be directly used as a guide for column chromatography. Hence, the gradient elution method was employed for their purification.) or pTLC (exact eluent composition mentioned below for each example) or subject to further derivatization into benzyl esters for isolation if purification of the lactone acid was found to be not straightforward.

Procedure for the gram scale γ-directed, γ-C–H lactonization reaction of pimelic acid 2 using Ag_2CO_3 as oxidant

To a 150 mL heavy wall pressure vessel with an internal thread (see picture below) was added pimelic acid (1.0 g, 6.24 mmol), $Pd(OAc)_2$ (140.0 mg, 0.62 mmol), ligand (164.0 mg, 0.62 mmol), *p*-xyloquinone (1.70 g, 12.5 mmol), Ag_2CO_3 (3.45 g, 12.5 mmol), K_2HPO_4 (380.0 mg, 2.18 mmol) and CsOAc (480.0 mg, 2.50 mmol, a stock solution is not required). HFIP (62.0 mL) and a stir-bar was then added, followed by sealing the reaction vessel with a screwed-on PTFE bushing. The reaction mixture was sonicated for **5 minutes** before stirring at **500 rpm** and 100 °C (oil bath temperature) for 36 hours. The reaction mixture was then cooled to room temperature and formic acid (5.0 mL) was added, followed by filtration through a short plug of Celite®. The filtrate was then concentrated under reduced pressure. The crude was dissolved in CH_2Cl_2 (20.0 mL) and extracted with sat. aq. $NaHCO_3$ (10.0 mL, 3 times). The aqueous layer was collected and combined, acidified by aq. 6M HCl to pH ~ 2 (slow addition of acid with vigorous stirring is recommended) and extracted with EtOAc (10.0 mL,

3 times). The combined EtOAc layers was dried with anhydrous $MgSO_4$, filtered, and evaporated to dryness. The product was purified by column chromatography (Begin with 50% EtOAc/hexane + 1% AcOH (300 mL), then 75% EtOAc/hexane + 1% AcOH (300 mL), and finally 100% EtOAc + 1% AcOH (300 mL)). The desired product **2b** was isolated as a brown oil (631 mg, 3.99 mmol, 63%).

Experimental observations:



General procedure for the γ-directed, γ-C–H lactonization reaction using MnO_2 as oxidant

To a 2-dram vial was added the substrate (0.1 mmol), $Pd(OAc)_2$ (10 mol%, 0.01 mmol), ligand (12 mol%, 0.012 mmol), *p*-xyloquinone (0.2 mmol), MnO_2 (0.4 mmol), K_2HPO_4 (0.021 mmol), KH_2PO_4 (0.032 mmol), CsOAc (0.021 mmol, preferably added from a stock solution in HFIP as CsOAc is hygroscopic). HFIP (1.0 mL, or the volume needed to make up to 1.0 mL if a stock solution of CsOAc was used) and a stir-bar was then added, followed by sealing the reaction vessel with a PTFE septum inserted between the vial and its cap. **(Note: $Pd(OAc)_2$, ligand, *p*-xyloquinone, CsOAc, and the substrate could all be prepared as a stock solution in HFIP. The use of stock solution is recommended for setting up a series of reactions to maximize work efficiency).** The reaction mixture was sonicated for 30 seconds before stirring at 200 rpm and 100 °C (heating block temperature) for 36-48 hours. The reaction mixture was then cooled to room temperature and diluted with dichloromethane (1.0 mL), followed by addition of deionized water (2.0 mL), aq. 6M HCl (0.3 mL), brine (1.0 mL) and then shaken vigorously. The lower organic layer was carefully pipetted and filtered through a short plug of Celite®. The remaining aqueous layer was extracted with CH_2Cl_2 (1.0 mL) twice and the organic layer was pipetted and filtered as mentioned. The combined organic layer was

then evaporated to dryness. The crude was then taken into $CDCl_3$ (0.6 mL) with CH_2Br_2 (10.0 µL) as the internal standard to determine the assay yield of the reaction by ^1H NMR spectroscopy. The isolation of the product was carried out with aqueous extractions of the organic layer (in 0.6 mL $CDCl_3$ diluted with 2.0 mL CH_2Cl_2) with sat. aq. $NaHCO_3$ solution (1.0 mL each, 3 times). The collected aqueous layer was then acidified by aq. 6M HCl to pH ~ 2 and extracted with EtOAc (1.0 mL, 3 times). The combined EtOAc layers was dried with anhydrous $MgSO_4$, filtered, and evaporated to dryness. The product was either further purified by column chromatography (General procedure for gradient elution unless stated otherwise: begin with 20% EtOAc/hexane + 1% AcOH, and increase the composition of EtOAc by 10% for every 8 mL of eluent used to 100% EtOAc + 1% AcOH, collecting 1.0-2.0 mL fractions. It was observed that the R_f values of carboxylic acids obtained by TLC analysis could not be directly used as a guide for column chromatography. Hence, the gradient elution method was employed for their purification.) or pTLC (exact eluent composition mentioned below for each example) or subject to further derivatization into benzyl esters for isolation if purification of the lactone acid was found to be not straightforward.

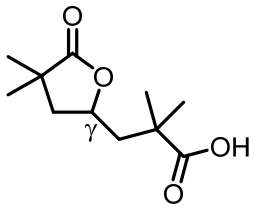
Note: Using the correct type of MnO_2 is crucial for reproducibility. MnO_2 (mesh, on the left) was found to be more active for this reaction than MnO_2 (powder, on the right).

General procedure for benzyl ester formation

To the product obtained after aqueous extraction with sat. $NaHCO_3$ solution as mentioned above was added dry CH_2Cl_2 (2.0 mL), BnOH (1.2 eq.), DMAP (1.2 eq.) and EDCI (1.2 eq.) sequentially at room temperature. The reaction mixture was stirred at room temperature overnight, and completion of the reaction was confirmed by TLC analysis of the reaction mixture. The reaction mixture was then

quenched by the addition of water and extracted with CH_2Cl_2 (3 times), and the desired product was purified by pTLC (exact eluent composition mentioned below for each example).

2.6 Characterization data of products obtained from γ-directed, γ-C–H lactonization reaction



50b

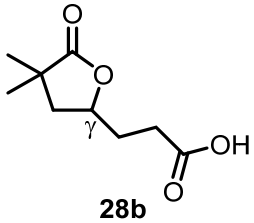
3-(4,4-Dimethyl-5-oxotetrahydrofuran-2-yl)-2,2-dimethylpropanoic acid 50b

Following the general procedure for its synthesis, the compound was purified as the acid by column chromatography (General procedure for gradient elution: begin with 20% EtOAc/hexane + 1% AcOH, and increase the composition of EtOAc by 10% for every 8 mL of eluent used to 100% EtOAc + 1% AcOH). Isolated yield >99% (21.4 mg, 0.1 mmol, off white solid).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.53 (dq, *J* = 9.9, 5.9 Hz, 1H), 2.19 (dd, *J* = 12.7, 5.9 Hz, 1H), 1.93 (d, *J* = 5.9 Hz, 2H), 1.73 (dd, *J* = 12.7, 9.9 Hz, 1H), 1.31 (s, 3H), 1.29 (s, 3H), 1.25 (s, 3H), 1.24 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 183.8, 182.0, 74.5, 45.9, 44.5, 41.4, 40.1, 26.1, 25.1, 25.1, 24.4.

HRMS (ESI-TOF) Calculated for $C_{11}H_{17}O_4$ $[M-H]^-$: 213.1127, Found: 213.1128



28b

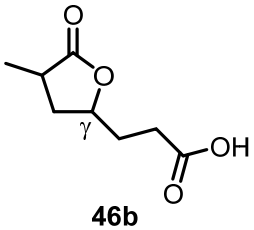
3-(4,4-Dimethyl-5-oxotetrahydrofuran-2-yl)propanoic acid 28b

Following the general procedure for its synthesis, the compound was purified as the acid by column chromatography (General procedure for gradient elution: begin with 20% EtOAc/hexane + 1% AcOH, and increase the composition of EtOAc by 10% for every 8 mL of eluent used to 100% EtOAc + 1% AcOH). Isolated yield 62% (11.4 mg, 0.062 mmol, off white solid).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.48 (dddd, *J* = 9.9, 8.9, 5.9, 4.1 Hz, 1H), 2.76 – 2.49 (m, 2H), 2.20 (dd, *J* = 12.7, 5.9 Hz, 1H), 2.02 (dtd, *J* = 15.3, 7.7, 4.1 Hz, 1H), 1.98 – 1.89 (m, 1H), 1.75 (dd, *J* = 12.7, 9.9 Hz, 1H), 1.28 (s, 3H), 1.26 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 181.8, 178.2, 75.9, 43.4, 40.6, 30.7, 30.1, 25.2, 24.6.

HRMS (ESI-TOF) Calculated for $C_9H_{13}O_4$ $[M-H]^-$: 185.0814, Found: 185.0815.



46b

3-(4-Methyl-5-oxotetrahydrofuran-2-yl)propanoic acid 46b

Following the general procedure for its synthesis, the compound was purified as the acid by column chromatography (General procedure for gradient elution: begin with 20% EtOAc/hexane + 1% AcOH, and increase the composition of EtOAc by 10% for every 8 mL of eluent used to 100% EtOAc + 1% AcOH). Isolated yield 61% (10.5 mg, 0.061 mmol, colorless oil, d.r = 1.3:1). Diastereomers were not separable by column chromatography, ^{1}H and ^{13}C NMR data reported as a mixture of diastereomers.

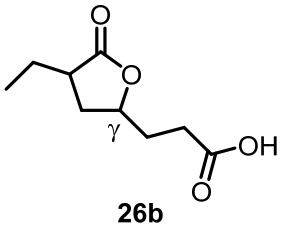
NMR for minor isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.61 – 4.54 (m, 1H), 2.61 – 2.48 (m, 3H), 2.18 – 2.09 (m, 1H), 1.98 – 1.90 (m, 3H), 1.28 (d, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 179.9, 178.5, 77.2, 35.5, 34.0, 30.4, 30.1, 15.9.

NMR for major isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.41 (dddd, *J* = 10.1, 8.8, 5.5, 4.1 Hz, 1H), 2.77 – 2.64 (m, 2H), 2.61 – 2.48 (m, 2H), 2.08 – 1.98 (m, 2H), 1.52 (td, *J* = 12.3, 10.4 Hz, 1H), 1.27 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 179.4, 178.5, 77.2, 37.2, 36.0, 30.5, 30.1, 15.2.

HRMS (ESI-TOF) Calculated for $C_8H_{11}O_4$ for $[M-H]^-$: 171.0657, found 171.0657.



26b

3-(4-Ethyl-5-oxotetrahydrofuran-2-yl)propanoic acid 26b

Following the general procedure for its synthesis, the compound was purified as the acid by column chromatography (General procedure for gradient elution: begin with 20% EtOAc/hexane + 1% AcOH, and increase the composition of EtOAc by 10% for every 8 mL of eluent used to 100% EtOAc + 1% AcOH). Isolated yield 54% (10.0 mg, 0.054 mmol, colorless oil, d.r. = 1.2:1). Diastereomers were not separable by column chromatography, ^{1}H and ^{13}C NMR data reported as a mixture of diastereomers.

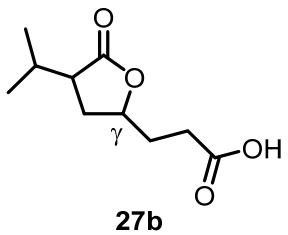
NMR for minor isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.59 – 4.50 (m, 1H), 2.66 – 2.51 (m, 3H), 2.15 – 2.06 (m, 2H), 2.07 – 2.00 (m, 2H), 1.88 – 1.82 (m, 1H), 1.58 – 1.42 (m, 1H), 1.01 (t, *J* = 6.6 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 179.2, 178.3, 77.5, 40.7, 33.1, 30.7, 30.1, 24.1, 11.8.

NMR for major isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.42 (dddd, *J* = 9.9, 8.6, 5.7, 4.1 Hz, 1H), 2.66 – 2.51 (m, 3H), 1.98 – 1.89 (m, 4H), 1.58 – 1.44 (m, 2H), 1.01 (t, *J* = 6.6 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 178.6, 178.3, 77.5, 42.5, 34.5, 30.6, 30.1, 23.4, 11.7.

HRMS (ESI-TOF) Calculated $C_9H_{13}O_4$ for $[M-H]^-$: 185.0814, found 185.0812.



27b

3-(4-Isopropyl-5-oxotetrahydrofuran-2-yl)propanoic acid 27b

Following the general procedure for its synthesis, the compound was purified as the acid by column chromatography (General procedure for gradient elution: begin with 20% EtOAc/hexane + 1% AcOH, and increase the composition of EtOAc by 10% for every 8 mL of eluent used to 100% EtOAc + 1% AcOH). Isolated yield 74% (14.8 mg, 0.074 mmol, colorless oil, d.r = 1.1:1). Diastereomers were not separable by column chromatography, ^{1}H and ^{13}C NMR data reported as a mixture of diastereomers.

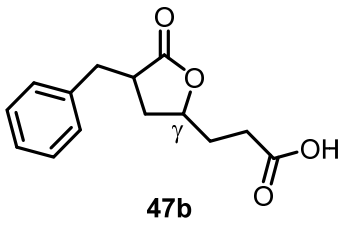
NMR for minor diastereomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.51 (tt, *J* = 9.0, 4.9 Hz, 1H), 2.64 – 2.58 (m, 1H), 2.58 – 2.48 (m, 2H), 2.25 – 2.21 (m, 1H), 2.16 – 2.12 (m, 1H), 2.00 – 1.88 (m, 3H), 1.07 – 0.98 (m, 3H), 0.91 (dd, *J* = 6.8, 1.1 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 178.5, 178.2, 77.6, 47.2, 31.1, 30.1, 29.6, 28.9, 20.6, 18.3.

NMR for major diastereomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.39 (tdd, *J* = 9.8, 5.6, 4.2 Hz, 1H), 2.64 – 2.58 (m, 1H), 2.58 – 2.48 (m, 2H), 2.30 (ddd, *J* = 12.8, 8.8, 5.7 Hz, 1H), 2.21 – 2.16 (m, 1H), 2.04 (dtd, *J* = 15.2, 7.7, 4.1 Hz, 1H), 2.00 – 1.88 (m, 1H), 1.64 (td, *J* = 12.4, 10.2 Hz, 1H), 1.07 – 0.98 (m, 3H), 0.94 (dd, *J* = 6.8, 1.1 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 178.2, 177.9, 77.1, 45.4, 30.6, 30.3, 30.1, 27.6, 20.8, 18.7.

HRMS (ESI-TOF) Calculated for $C_{10}H_{15}O_4$ $[M-H]^-$: 199.0970, Found: 199.0972.



47b

3-(4-Benzyl-5-oxotetrahydrofuran-2-yl)propanoic acid 47b

Following the general procedure for its synthesis, the compound was purified as the acid by column chromatography (General procedure for gradient elution: begin with 20% EtOAc/hexane + 1% AcOH, and increase the composition of EtOAc by 10% for every 8 mL of eluent used to 100% EtOAc + 1% AcOH). Isolated yield 57% (14.1 mg, 0.057 mmol, colorless oil, d.r. = 1.2:1). Diastereomers were not separable by column chromatography, ^{1}H and ^{13}C NMR data reported as a mixture of diastereomers.

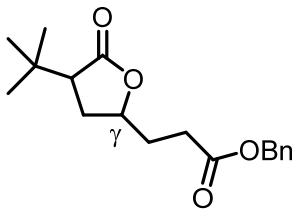
NMR for minor isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 – 7.13 (m, 5H), 4.44 – 4.33 (m, 1H), 3.18 (dd, *J* = 13.9, 4.5 Hz, 1H), 3.00 – 2.89 (m, 1H), 2.78 (dd, *J* = 13.8, 9.4 Hz, 1H), 2.59 – 2.41 (m, 2H), 2.14 (dt, *J* = 13.2, 7.5 Hz, 1H), 1.91 – 1.81 (m, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 178.1, 177.9, 138.5, 128.9, 128.9, 126.9, 77.6, 42.9, 36.2, 34.6, 30.4, 29.9.

NMR for major isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 – 7.13 (m, 5H), 4.44 – 4.33 (m, 1H), 3.28 (dd, *J* = 14.0, 4.3 Hz, 1H), 3.00 – 2.89 (m, 1H), 2.73 (dd, *J* = 14.1, 9.5 Hz, 1H), 2.59 – 2.41 (m, 2H), 2.32 (ddd, *J* = 12.7, 8.5, 5.6 Hz, 1H), 1.99 – 1.91 (m, 2H), 1.58 (td, *J* = 12.3, 10.2 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 178.1, 177.9, 138.5, 128.9, 128.9, 127.0, 77.6, 42.9, 36.2, 34.6, 30.4, 29.9.

HRMS (ESI-TOF) Calculated for $C_{14}H_{17}O_4$ $[M+H]^+$: 249.1127, Found: 249.1134.



48b

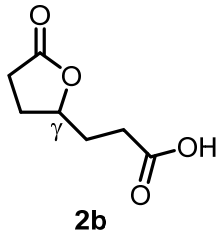
Benzyl 3-(4-(*tert*-butyl)-5-oxotetrahydrofuran-2-yl)propanoate 48b

Following the general procedure for its synthesis and benzyl ester formation, the compound was purified as the benzyl ester by pTLC (10% EA/hexanes, R_f = 0.30). Isolated yield 57% over 2 steps (17.3 mg, 0.057 mmol, colourless oil, d.r. = 1:1). Diastereomers were not separable by column chromatography, ^{1}H and ^{13}C NMR data reported as a mixture of diastereomers.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 – 7.29 (m, 10H), 5.26 – 4.97 (m, 4H), 4.43 (ddt, *J* = 8.9, 8.0, 4.8 Hz, 1H), 4.29 (dddd, *J* = 10.1, 8.4, 5.6, 4.3 Hz, 1H), 2.62 – 2.49 (m, 4H), 2.49 – 2.45 (m, 1H), 2.45 – 2.41 (m, 1H), 2.35 – 2.27 (m, 1H), 2.27 – 2.21 (m, 1H), 2.04 (dddd, *J* = 14.3, 8.3, 7.3, 4.3 Hz, 1H), 1.98 – 1.88 (m, 4H), 1.66 (td, *J* = 12.6, 10.5 Hz, 1H), 1.04 (s, 18H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 177.2, 176.6, 172.7, 172.7, 135.9, 135.9, 128.7, 128.7, 128.5, 128.5, 128.4, 128.4, 76.7, 76.1, 66.6, 66.6, 50.9, 49.0, 32.9, 31.8, 31.7, 31.3, 30.7, 30.4, 30.4, 30.3, 27.5, 27.3.

HRMS (ESI-TOF) Calculated for $C_{18}H_{25}O_4$ $[M+H]^+$: 305.1753, Found: 305.1754.



2b

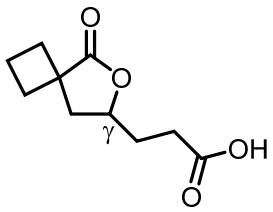
3-(5-Oxotetrahydrofuran-2-yl)propanoic acid 2b

Following the general procedure for its synthesis, the compound was purified as the acid by column chromatography (General procedure for gradient elution: begin with 50% EtOAc/hexane + 1% AcOH, and increase the composition of EtOAc by 10% for every 8 mL of eluent used to 100% EtOAc + 1% AcOH). Isolated yield 62% (9.8 mg, 0.062 mmol, colorless oil).

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.57 (dddd, *J* = 9.1, 7.4, 6.8, 4.7 Hz, 1H), 2.74 – 2.45 (m, 4H), 2.38 (dq, *J* = 12.7, 6.9 Hz, 1H), 2.03 (dq, *J* = 14.6, 7.8 Hz, 1H), 1.96 (dt, *J* = 14.6, 7.4 Hz, 1H), 1.89 (dq, *J* = 12.7, 9.1 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 176.9, 176.4, 79.6, 30.6, 29.7, 28.8, 28.1.

HRMS (ESI-TOF) Calculated for $C_7H_9O_4$ $[M-H]^-$: 157.0501, found: 157.0501.



49b

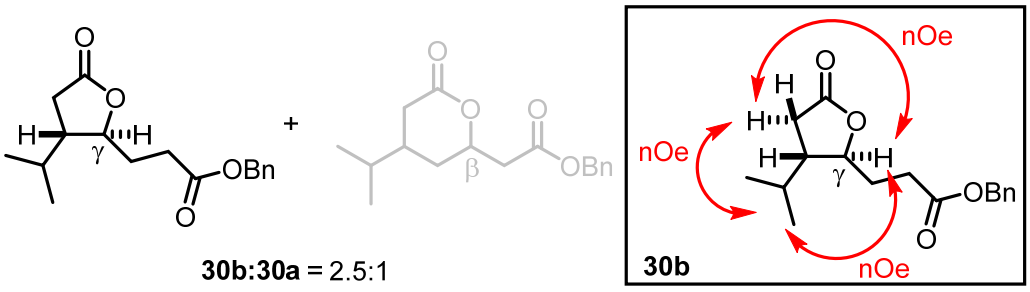
3-(5-Oxo-6-oxaspiro[3.4]octan-7-yl)propanoic acid 49b

Following the general procedure for its synthesis, the compound was purified as the acid by column chromatography (General procedure for gradient elution: begin with 20% EtOAc/hexane + 1% AcOH, and increase the composition of EtOAc by 10% for every 8 mL of eluent used to 100% EtOAc + 1% AcOH). Isolated yield 60% (11.9 mg, 0.060 mmol, off white solid).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.39 (tdd, *J* = 8.7, 6.1, 4.1 Hz, 1H), 2.62 – 2.54 (m, 2H), 2.54 – 2.47 (m, 2H), 2.47 – 2.39 (m, 1H), 2.17 – 2.11 (m, 1H), 2.11 – 2.05 (m, 1H), 2.02 – 1.96 (m, 3H), 1.95 – 1.91 (m, 1H), 1.91 – 1.85 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 180.9, 178.2, 76.3, 44.5, 41.9, 31.8, 30.6, 30.1, 29.7, 16.6.

HRMS (ESI-TOF) Calculated for $C_{10}H_{13}O_4$ $[M-H]^-$: 197.0814, Found: 197.0813.



30b:30a = 2.5:1

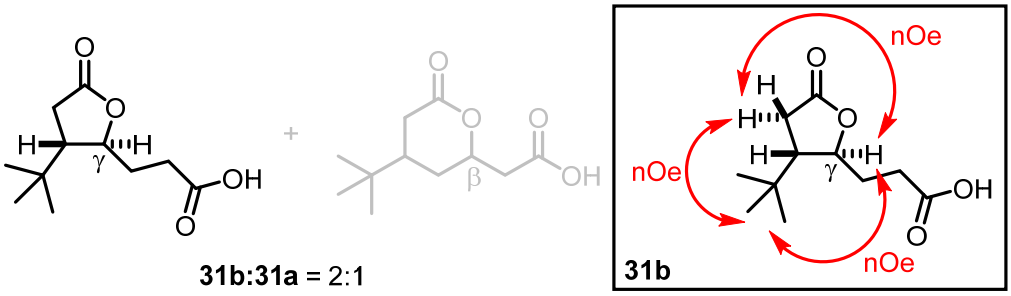
Benzyl 3-((2*S,3*S**)-3-isopropyl-5-oxotetrahydrofuran-2-yl)propanoate 30b**

Following the general procedure for its synthesis and benzyl ester formation, the mixture of compound **30b** and **30a** was obtained as the benzyl ester by pTLC (20% EA/hexanes, R_f = 0.30). Total isolated yield 50% over 2 steps, (14.5 mg, 0.050 mmol, colourless oil, **30b**:**30a** = 2.5:1). A sample of the lactone **30b** (7.0 mg, 0.024 mmol, colourless oil) was obtained by further purification (pTLC, 10% EA/hexanes, R_f = 0.17) for unambiguous characterization.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 – 7.29 (m, 5H), 5.24 – 5.02 (m, 2H), 4.29 (ddd, *J* = 9.8, 6.5, 3.1 Hz, 1H), 2.76 – 2.47 (m, 3H), 2.31 (dd, *J* = 18.0, 9.0 Hz, 1H), 2.10 (dtd, *J* = 14.5, 7.9, 3.1 Hz, 1H), 1.98 (dddd, *J* = 9.0, 7.9, 6.5, 6.5 Hz, 1H), 1.85 (dddd, *J* = 14.5, 9.8, 7.5, 5.8 Hz, 1H), 1.71 (h, *J* = 6.8 Hz, 1H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.90 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.5, 172.8, 135.9, 128.7, 128.5, 128.4, 82.8, 66.6, 47.1, 32.3, 31.2, 30.8, 30.5, 20.6, 19.5.

HRMS (ESI-TOF) Calculated for $C_{17}H_{23}O_4$ $[M+H]^+$: 291.1596, Found: 291.1597.



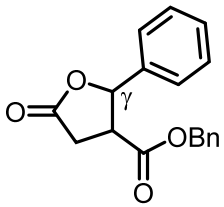
3-((2*S,3*S**)-3-(tert-butyl)-5-oxotetrahydrofuran-2-yl)propanoic acid 31b**

Following the general procedure for its synthesis, the mixture of compounds **31b** and **31a** was obtained as the acid by column chromatography (Gradient elution: begin with 20% EtOAc/hexane + 1% AcOH, and increase the composition of EtOAc by 10% for every 8 mL of eluent used to 70% EtOAc + 1% AcOH). Total isolated yield 70% (15.0 mg, 0.070 mmol, colourless oil, **31b**:**31a** = 2:1). A sample of the lactone **31b** (3.0 mg, 0.014 mmol, white solid) was obtained by further purification (Gradient elution: begin with 20% EtOAc/hexane + 1% AcOH, and increase the composition of EtOAc by 10% for every 8 mL of eluent used to 50% EtOAc + 1% AcOH, then continue elution using this eluant for the separation of the two lactones) for unambiguous characterization.

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.44 (ddd, *J* = 11.3, 4.5, 3.3 Hz, 1H), 2.72 – 2.52 (m, 3H), 2.42 (dd, *J* = 18.6, 5.5 Hz, 1H), 2.03 (ddd, *J* = 14.5, 7.4, 3.3 Hz, 1H), 1.98 (ddd, *J* = 10.1, 5.5, 4.5 Hz, 1H), 1.87 (ddd, *J* = 14.5, 11.3, 6.5 Hz, 1H), 0.92 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 177.5, 176.9, 81.0, 50.4, 32.4, 32.1, 30.5, 30.0, 26.9.

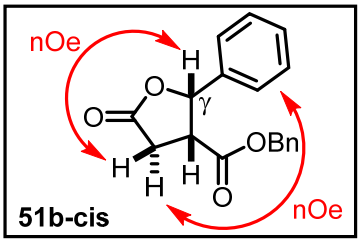
HRMS (ESI-TOF) Calculated for $C_{11}H_{17}O_4$ $[M-H]^-$: 213.1127, Found: 213.1130.



51b

Benzyl 5-oxo-2-phenyltetrahydrofuran-3-carboxylate 51b

Following the general procedure for its synthesis and benzyl ester formation, the compound was purified as the benzyl ester by pTLC (30% EA/hexanes, R_f = 0.20). Isolated yield 36% over 2 steps (Total yield 71% for both diastereomers), (10.7 mg, 0.036 mmol, off white solid).

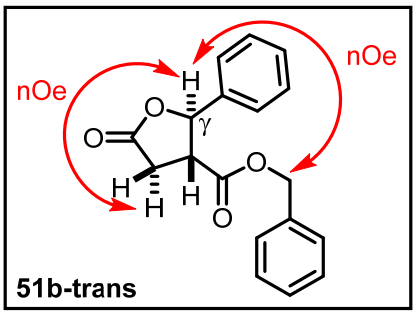


Cis-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 6H), 7.25 – 7.21 (m, 2H), 7.10 – 7.00 (m, 2H), 5.75 (d, *J* = 7.8 Hz, 1H), 4.79 (d, *J* = 12.1 Hz, 1H), 4.52 (d, *J* = 12.1 Hz, 1H), 3.76 (ddd, *J* = 8.7, 7.8, 5.3 Hz, 1H), 3.11 (dd, *J* = 17.7, 5.3 Hz, 1H), 2.82 (dd, *J* = 17.7, 8.7 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 169.7, 135.2, 134.7, 129.1, 128.7, 128.7, 128.7, 128.7, 125.8, 81.3, 67.4, 46.8, 31.7.

HRMS (ESI-TOF) Calculated for $C_{18}H_{17}O_4$ $[M+H]^+$: 297.1127, Found: 297.1118.

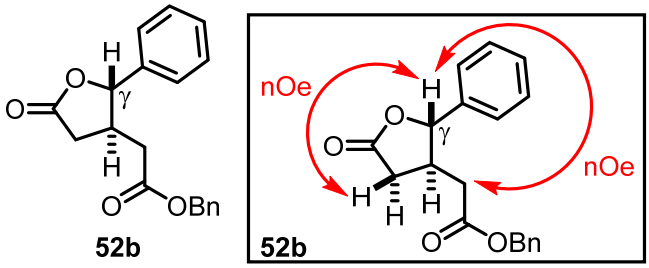
Following the general procedure for its synthesis and benzyl ester formation, the compound was purified as the benzyl ester by pTLC (30% EA/hexanes, R_f = 0.45). Isolated yield 35% over 2 steps (Total yield 71% for both diastereomers), (10.5 mg, 0.035 mmol, off white solid).



Trans-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.33 (m, 6H), 7.33 – 7.27 (m, 4H), 5.63 (d, *J* = 7.3 Hz, 1H), 5.23 (d, *J* = 12.1 Hz, 1H), 5.17 (d, *J* = 12.2 Hz, 1H), 3.37 (ddd, *J* = 9.4, 8.9, 7.3 Hz, 1H), 3.02 (dd, *J* = 17.7, 8.9 Hz, 1H), 2.91 (dd, *J* = 17.8, 9.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 170.7, 138.0, 135.0, 129.1, 129.0, 128.9, 128.9 128.6, 125.6, 82.4, 67.7, 48.9, 32.4.

HRMS (ESI-TOF) Calculated for $C_{18}H_{17}O_4$ $[M+H]^+$: 297.1127, Found: 297.1127.



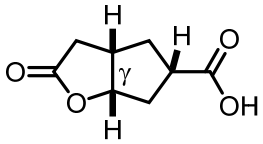
Benzyl 2-((2*S,3*S**)-5-oxo-2-phenyltetrahydrofuran-3-yl)acetate 52b**

Following the general procedure for its synthesis and benzyl ester formation, the compound was purified as the benzyl ester by pTLC (20% EA/hexanes, $R_f = 0.25$). Isolated yield 25% over 2 steps, (7.8 mg, 0.025 mmol, off white solid).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.30 (m, 10H), 5.12 (d, J = 7.0 Hz, 1H), 5.12 – 5.05 (m, 2H), 2.91 (dd, J = 16.7, 8.2 Hz, 1H), 2.84 (ddddd, J = 8.2, 8.2, 8.1, 7.0, 5.6 Hz, 1H), 2.67 (dd, J = 16.3, 5.6 Hz, 1H), 2.52 (dd, J = 16.3, 8.1 Hz, 1H), 2.42 (dd, J = 16.7, 8.2 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 175.6, 170.8, 137.6, 135.4, 129.1, 129.0, 128.9, 128.8, 128.6, 126.1, 85.5, 67.1, 41.2, 36.4, 34.9.

HRMS (ESI-TOF) Calculated for $C_{19}H_{19}O_4$ $[M+H]^+$: 311.1283, Found: 311.1278.



25b

(3*aS,5*S**,6*aS**)-2-Oxohexahydro-2*H*-cyclopenta[*b*]furan-5-carboxylic acid 25b**

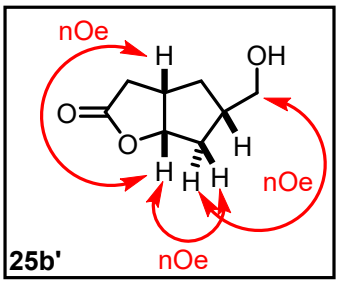
Following the general procedure for its synthesis, the compound was purified as the acid by column chromatography (General procedure for gradient elution: begin with 20% EtOAc/hexane + 1% AcOH, and increase the composition of EtOAc by 10% for every 8 mL of eluent used to 100% EtOAc + 1% AcOH). Isolated yield 66% (11.2 mg, 0.066 mmol, off white solid).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.97 (td, J = 6.2, 2.4 Hz, 1H), 2.95 (dddd, J = 8.8, 8.1, 6.5, 6.3 Hz, 1H), 2.91 (dddd, J = 10.0, 8.1, 6.9, 6.2 Hz, 1H), 2.78 (dd, J = 17.7, 10.0 Hz, 1H), 2.51 (d, J = 17.7 Hz, 1H), 2.42 (ddd, J = 15.0, 6.3, 2.4 Hz, 1H), 2.32 (ddd, J = 15.1, 8.8, 6.2 Hz, 1H), 2.23 (dt, J = 13.4, 8.1 Hz, 1H), 1.94 (dt, J = 13.7, 6.9 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 179.6, 177.3, 85.5, 43.5, 38.8, 36.9, 35.9, 35.1.

HRMS (ESI-TOF) Calculated for $C_8H_9O_4$ $[M-H]^-$: 169.0501, Found: 169.0499.

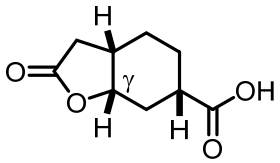
The relative configuration of **25b** was determined from its reduced analogue **25b'** through treatment with BH_3•THF.



Compound **25b** (50.0 mg, 0.30 mmol) was dissolved in anhydrous THF (2.0 mL), the reaction mixture was cooled to 0 °C and a solution of BH_3•THF (0.9 mL, 0.9 mmol, 1.0 M in THF) was added. The reaction was gradually warmed to room temperature and stirred overnight. TLC analysis at this stage suggested completion of reaction. The reaction was quenched by addition of MeOH and all the volatiles were removed under reduced pressure. The desired compound was then purified by flash column chromatography (100% EA, $R_f = 0.4$) and obtained as a colourless liquid (45.0 mg, 0.29 mmol, 97%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.93 (td, J = 6.8, 3.5 Hz, 1H), 3.68 – 3.48 (m, 2H), 2.84 – 2.77 (m, 1H), 2.73 (dd, J = 17.6, 9.1 Hz, 1H), 2.36 (dd, J = 17.6, 1.5 Hz, 1H), 2.32 – 2.21 (m, 1H), 2.22 – 2.12 (m, 3H), 1.67 (ddd, J = 14.1, 8.6, 3.5 Hz, 1H), 1.27 – 1.14 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.5, 86.2, 65.8, 42.3, 39.4, 35.8, 35.7, 35.7.



53b

(3*aS,6*S**,7*aS**)-2-Oxooctahydrobenzofuran-6-carboxylic acid 53b**

Following the general procedure for its synthesis, the compound was purified as the acid by column chromatography (General procedure for gradient elution: begin with 20% EtOAc/hexane + 1% AcOH, and increase the composition of EtOAc by 10% for every 8 mL of eluent used to 100% EtOAc + 1% AcOH). Isolated yield 60% based on reactive diastereomers* (7.6 mg, 0.042 mmol, off white solid).

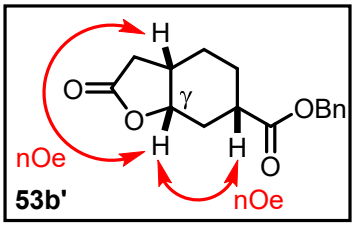
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.57 (dt, J = 8.9, 6.0 Hz, 1H), 2.75 – 2.59 (m, 1H), 2.47 (dd, J = 17.2, 7.8 Hz, 1H), 2.44 – 2.37 (m, 2H), 2.29 (dddd, J = 13.9, 5.5, 4.0, 1.4 Hz, 1H), 1.90 – 1.85 (m, 1H), 1.85 – 1.78 (m, 2H), 1.75 – 1.66 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 179.3, 176.6, 78.0, 38.3, 34.0, 32.8, 30.2, 24.1, 22.9.

HRMS (ESI-TOF) Calculated for $C_9H_{11}O_4$ $[M-H]^-$: 183.0657, Found: 183.0660.

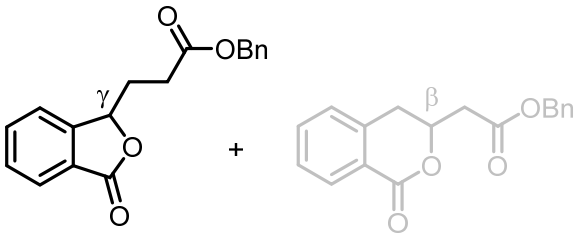
*It was observed that only the *syn*-diacid of **53** provided the lactone **53b**, whereas the *anti*-diacid of **53** was not reactive.

The relative configuration of **53b** was determined from its benzyl ester analogue **53b'**, the synthesis of benzyl ester 51b' was carried out according to the general procedure as described above.



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 5H), 5.13 (s, 2H), 4.55 (ddd, *J* = 9.3, 6.2, 5.0 Hz, 1H), 2.70 – 2.62 (m, 1H), 2.46 – 2.39 (m, 2H), 2.41 – 2.36 (m, 1H), 2.30 (dt, *J* = 13.8, 5.0 Hz, 1H), 1.91 – 1.84 (m, 1H), 1.84 – 1.79 (m, 1H), 1.79 – 1.74 (m, 1H), 1.74 – 1.63 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.5, 173.8, 135.9, 128.8, 128.5, 128.4, 78.1, 66.8, 38.8, 34.1, 32.5, 30.6, 24.2, 23.1.



32b:32a = 10:1

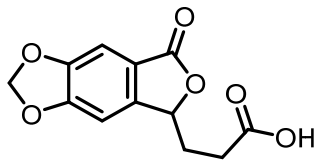
Benzyl 3-(3-oxo-1,3-dihydroisobenzofuran-1-yl)propanoate 32b

Following the general procedure for its synthesis and benzyl ester formation, the compound was purified as the benzyl ester by pTLC (20% EA/hexanes, R_f = 0.30). Isolated yield 57% over 2 steps, (16.9 mg, 0.057 mmol, off white solid, **32b**:**32a** = 10:1 by ^{1}H NMR).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.5 Hz, 1H), 7.68 (td, *J* = 7.5, 1.0 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.46 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.39 – 7.30 (m, 5H), 5.55 (dd, *J* = 8.7, 2.8 Hz, 1H), 5.12 (s, 2H), 2.70 – 2.57 (m, 1H), 2.57 – 2.44 (m, 2H), 2.08 – 1.91 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6, 170.3, 149.3, 135.8, 134.3, 129.5, 128.8, 128.5, 128.4, 126.2, 126.0, 122.0, 80.1, 66.7, 30.0, 29.6.

HRMS (ESI-TOF) Calculated for $C_{18}H_{17}O_4$ $[M+H]^+$: 297.1127, Found: 297.1129.



33b

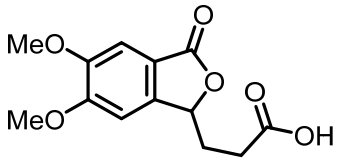
3-(7-Oxo-5,7-dihydro-[1,3]dioxolo[4,5-*f*]isobenzofuran-5-yl)propanoic acid 33b

Following the general procedure for its synthesis, the compound was purified by pTLC (50% EA/hexanes, 2% AcOH). Isolated yield 75% (18.7 mg, 0.075 mmol, off white solid).

^{1}H NMR (600 MHz, DMSO-*d*$_6$) δ 7.24 – 7.21 (m, 2H), 6.21 (dd, *J* = 3.5, 1.0 Hz, 2H), 5.49 (dd, *J* = 7.5, 3.9 Hz, 1H), 2.37 – 2.27 (m, 2H), 2.27 – 2.18 (m, 1H), 1.89 – 1.80 (m, 1H).

^{13}C NMR (151 MHz, DMSO-*d*$_6$) δ 173.6, 169.2, 153.5, 149.1, 146.4, 118.7, 103.3, 102.9, 102.4, 79.4, 29.3, 29.1.

HRMS (ESI-TOF) Calculated for $C_{12}H_{10}O_6Na$ $[M+Na]^+$: 273.0375, Found: 273.0384.



34b

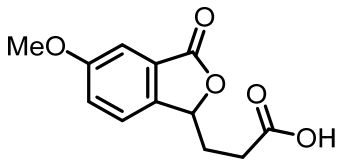
3-(5,6-Dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)propanoic acid 34b

Following the general procedure for its synthesis, the compound was purified by pTLC (50% EA/hexanes, 2% AcOH). Isolated yield 61% (16.2 mg, 0.061 mmol, off white solid).

^{1}H NMR (600 MHz, CD_3OD) δ 7.29 (s, 1H), 7.14 (d, *J* = 0.8 Hz, 1H), 5.54 – 5.49 (m, 1H), 3.96 (s, 3H), 3.90 (s, 3H), 2.53 – 2.35 (m, 3H), 2.03 – 1.94 (m, 1H).

^{13}C NMR (151 MHz, CD_3OD) δ 174.9, 172.8, 156.9, 152.3, 145.8, 118.6, 106.9, 105.2, 81.5, 56.9, 56.7, 30.8, 30.0.

HRMS (ESI-TOF) Calculated for $C_{13}H_{15}O_6$ $[M+H]^+$: 267.0869, Found: 267.0865.



35b

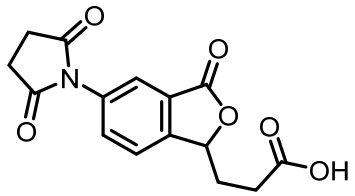
3-(5-Methoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)propanoic acid 35b

Following the general procedure for its synthesis, the compound was purified by pTLC (50% EA/hexanes, 2% AcOH). Isolated yield 70% (16.5 mg, 0.07 mmol, off white solid).

^{1}H NMR (600 MHz, CD_3OD) δ 7.53 – 7.48 (m, 1H), 7.35 – 7.30 (m, 2H), 5.57 (dd, *J* = 8.0, 3.3 Hz, 1H), 3.88 (s, 3H), 2.50 – 2.34 (m, 3H), 2.00 – 1.90 (m, 1H).

^{13}C NMR (151 MHz, CD_3OD) δ 176.9, 172.4, 162.4, 143.5, 128.4, 124.4, 124.0, 108.5, 82.1, 56.3, 31.3, 30.6.

HRMS (ESI-TOF) Calculated for $C_{12}H_{13}O_5$ $[M+H]^+$: 237.0763, Found: 237.0762.



36b

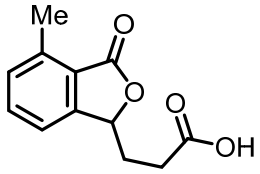
3-(6-(2,5-Dioxopyrrolidin-1-yl)-3-oxo-1,3-dihydroisobenzofuran-1-yl)propanoic acid 36b

Following the general procedure for its synthesis, the compound was purified by pTLC (70% EA/hexanes, 2% AcOH). Isolated yield 50% (15.1 mg, 0.050 mmol, off white solid, **36b**:**36a** = 5:1 by ^{1}H NMR).

^{1}H NMR (600 MHz, CD_3OD) δ 7.83 (dd, *J* = 1.8, 0.7 Hz, 1H), 7.76 – 7.68 (m, 2H), 5.69 (dd, *J* = 8.4, 3.0 Hz, 1H), 2.89 (s, 4H), 2.56 – 2.39 (m, 3H), 2.02 – 1.98 (m, 1H).

^{13}C NMR (151 MHz, CD_3OD) δ 178.6, 176.2, 171.3, 150.7, 135.2, 134.2, 127.9, 124.9, 124.2, 82.2, 30.9, 30.3, 29.5.

HRMS (ESI-TOF) Calculated for $C_{15}H_{14}NO_6$ $[M+H]^+$: 304.0821, Found: 304.0824.



37b

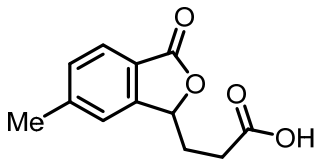
3-(4-Methyl-3-oxo-1,3-dihydroisobenzofuran-1-yl)propanoic acid 37b

Following the general procedure for its synthesis, the compound was purified by pTLC (50% EA/hexanes, 2% AcOH). Isolated yield 73% (16.0 mg, 0.073 mmol, off white solid, **37b**:**37a** = 8:1 by ^{1}H NMR).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (t, *J* = 7.6 Hz, 1H), 7.30 – 7.24 (m, 2H), 5.48 (dd, *J* = 8.5, 3.2 Hz, 1H), 2.68 (s, 3H), 2.67 – 2.58 (m, 1H), 2.54 – 2.41 (m, 2H), 2.00 – 1.92 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 178.1, 170.6, 149.7, 140.1, 134.1, 131.2, 123.6, 119.2, 79.0, 29.9, 29.3, 17.5.

HRMS (ESI-TOF) Calculated for $C_{12}H_{13}O_4$ $[M+H]^+$: 221.0814, Found: 221.0814.



38b

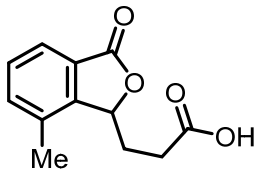
3-(6-Methyl-3-oxo-1,3-dihydroisobenzofuran-1-yl)propanoic acid 38b

Following the general procedure for its synthesis, the compound was purified by pTLC (50% EA/hexanes, 2% AcOH). Isolated yield 55% (12.1 mg, 0.055 mmol, off white solid, **38b**:**38a** = 9:1 by ^{1}H NMR).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.25 (s, 2H), 5.50 (dd, *J* = 8.6, 3.1 Hz, 1H), 2.64 – 2.57 (m, 1H), 2.53 – 2.41 (m, 5H), 2.01 – 1.92 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 177.4, 170.5, 149.8, 145.7, 130.7, 125.8, 123.6, 122.3, 79.8, 29.9, 29.4, 22.2.

HRMS (ESI-TOF) Calculated for $C_{12}H_{13}O_4$ $[M+H]^+$: 221.0814, Found: 221.0813.



39b

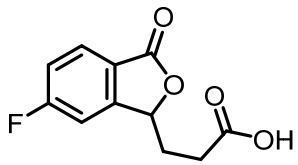
3-(7-Methyl-3-oxo-1,3-dihydroisobenzofuran-1-yl)propanoic acid 39b

Following the general procedure for its synthesis, the compound was purified by pTLC (50% EA/hexanes, 2% AcOH). Isolated yield 60% (13.2 mg, 0.055 mmol, off white solid, **39b**:**39a** = 1.6:1 by 1H NMR).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 6.5, 2.3 Hz, 1H), 7.47 – 7.41 (m, 2H), 5.59 (dd, *J* = 8.6, 2.5 Hz, 1H), 2.67 – 2.57 (m, 2H), 2.51 – 2.44 (m, 1H), 2.43 (s, 3H), 1.96 – 1.87 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 177.5, 170.7, 147.5, 135.8, 132.7, 129.8, 126.1, 123.5, 79.9, 29.3, 28.4, 18.2.

HRMS (ESI-TOF) Calculated for $C_{12}H_{13}O_4$ $[M+H]^+$: 221.0814, Found: 221.0816.



40b

3-(6-Fluoro-3-oxo-1,3-dihydroisobenzofuran-1-yl)propanoic acid 40b

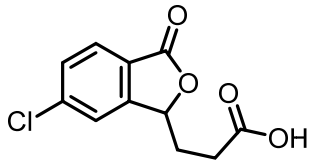
Following the general procedure for its synthesis, the compound was purified by pTLC (50% EA/hexanes, 2% AcOH). Isolated yield 68% (15.2 mg, 0.068 mmol, off white solid, **40b**:**40a** = 10:1 by ^{1}H NMR).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 8.5, 4.8 Hz, 1H), 7.24 (td, *J* = 8.5, 2.1 Hz, 1H), 7.16 (dd, *J* = 7.6, 2.4 Hz, 1H), 5.54 (dd, *J* = 8.6, 3.5 Hz, 1H), 2.69 – 2.61 (m, 1H), 2.55 –2.50 (m, 1H), 2.50 – 2.42 (m, 1H), 2.03 – 1.94 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 177.5, 169.1, 167.6, 165.9, 152.0 (d, *J* = 10.4 Hz), 128.5 (d, *J* = 10.1 Hz), 117.9 (d, *J* = 23.8 Hz), 109.4 (d, *J* = 24.3 Hz), 79.3 (d, *J* = 2.8 Hz), 29.7, 29.2.

^{19}F NMR (471 MHz, $CDCl_3$) δ -105.19.

HRMS (ESI-TOF) Calculated for $C_{11}H_{10}FO_4$ $[M+H]^+$: 225.0563, Found: 225.0559.



41b

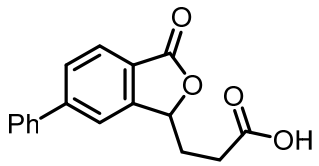
3-(6-Chloro-3-oxo-1,3-dihydroisobenzofuran-1-yl)propanoic acid 41b

Following the general procedure for its synthesis, the compound was purified by pTLC (50% EA/hexanes, 2% AcOH). Isolated yield 42% (10.1 mg, 0.042 mmol, off white solid, **41b**:**41a** = 5:1 by ^{1}H NMR).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.1 Hz, 1H), 7.53 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.49 – 7.47 (m, 1H), 5.54 (dd, *J* = 8.8, 3.4 Hz, 1H), 2.70 – 2.61 (m, 1H), 2.58 – 2.43 (m, 2H), 2.03 – 1.94 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 174.8, 169.2, 150.8, 141.2, 130.4, 127.3, 124.7, 122.5, 79.4, 29.7, 29.2.

HRMS (ESI-TOF) Calculated for $C_{11}H_{10}ClO_4$ $[M+H]^+$: 241.0268, Found: 241.0268.



42b

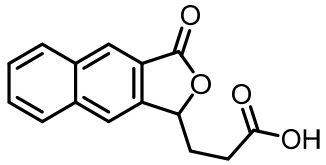
3-(3-Oxo-6-phenyl-1,3-dihydroisobenzofuran-1-yl)propanoic acid 42b

Following the general procedure for its synthesis, the compound was purified by pTLC (50% EA/hexanes, 2% AcOH). Isolated yield 50% (14.1 mg, 0.05 mmol, off white solid, **42b**:**42a** = 16:1 by ^{1}H NMR).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.9 Hz, 1H), 7.75 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.65 – 7.59 (m, 3H), 7.52 – 7.49 (m, 2H), 7.49 – 7.41 (m, 2H), 5.60 (dd, *J* = 8.0, 2.1 Hz, 1H), 2.69 – 2.61 (m, 1H), 2.58 – 2.50 (m, 2H), 2.09 – 1.99 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 177.1, 170.3, 150.1, 147.9, 139.7, 129.3, 128.9, 128.9, 127.69, 126.4, 124.9, 120.5, 80.0, 29.9, 29.3.

HRMS (ESI-TOF) Calculated for $C_{17}H_{15}O_4$ $[M+H]^+$: 283.0970, Found: 283.0964.



43b

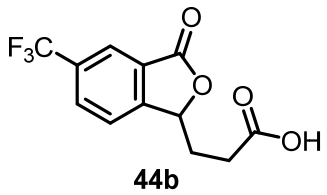
3-(3-Oxo-1,3-dihydronaphtho[2,3-*c*]furan-1-yl)propanoic acid 43b

Following the general procedure for its synthesis, the compound was purified by pTLC (50% EA/hexanes, 2% AcOH). Isolated yield 60% (15.4 mg, 0.06 mmol, off white solid, **43b**:**43a** = 10:1 by ^{1}H NMR).

^{1}H NMR (600 MHz, CD_3OD) δ 8.43 (s, 1H), 8.08 (dd, *J* = 8.3, 1.2 Hz, 1H), 8.07 – 8.00 (m, 2H), 7.67 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.60 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1H), 5.76 (dd, *J* = 8.4, 3.4 Hz, 1H), 2.60 – 2.48 (m, 2H), 2.48 – 2.37 (m, 1H), 2.13 – 1.96 (m, 1H).

^{13}C NMR (151 MHz, CD_3OD) δ 176.6, 172.2, 144.6, 137.9, 134.7, 130.9, 130.2, 129.5, 128.2, 127.7, 124.8, 122.3, 82.2, 31.7, 30.5.

HRMS (ESI-TOF) Calculated for $C_{15}H_{13}O_4$ $[M+H]^+$: 257.0814, Found: 257.0814.



44b

3-(3-Oxo-5-(trifluoromethyl)-1,3-dihydroisobenzofuran-1-yl)propanoic acid 44b

Following the general procedure for its synthesis, the compound was purified by pTLC (50% EA/hexanes, 2% AcOH). Isolated yield 40% (10.1 mg, 0.04 mmol, off white solid).

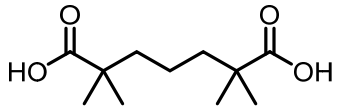
^{1}H NMR (600 MHz, CD_3OD) δ 8.15 (s, 1H), 8.07 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.89 – 7.84 (m, 1H), 5.75 (dd, *J* = 8.4, 3.1 Hz, 1H), 2.57 – 2.48 (m, 2H), 2.48 – 2.40 (m, 1H), 2.07 – 1.97 (m, 1H).

^{13}C NMR (151 MHz, CD_3OD) δ 176.4, 170.6, 154.7, 133.1 (q, *J* = 33.0 Hz), 132.3 (q, *J* = 3.3 Hz), 128.2, 125.1 (d, *J* = 271.8 Hz), 123.5 (q, *J* = 4.1 Hz), 125.0, 82.3, 30.8, 30.5.

^{19}F NMR (376 MHz, CD_3OD) δ -66.59.

HRMS (ESI-TOF) Calculated for $C_{12}H_{10}F_3O_4$ $[M+H]^+$: 275.0531, Found: 275.0531.

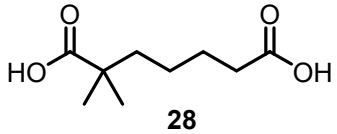
2.7 Synthesis and characterization of substrates for the γ-directed, γ-C–H lactonization reaction



50

2,2,6,6-Tetramethylheptanedioic acid 50

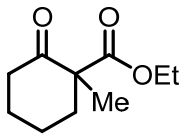
This compound is commercially available.



28

2,2-Dimethylheptanedioic acid 28

Please see Section 2.4



SS6

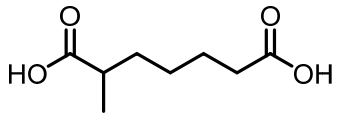
Ethyl 1-methyl-2-oxocyclohexane-1-carboxylate SS6

This compound was prepared according to the general procedure B for the preparation of β-substituted heptanedioic acids with the reaction of MeI and ethyl 2-oxocyclohexane-1-carboxylate. 73% yield, (1.08 g, 5.86 mmol, colorless oil).

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.22 – 4.14 (m, 2H), 2.54 – 2.41 (m, 3H), 2.06 – 1.97 (m, 1H), 1.78 – 1.57 (m, 4H), 1.50 – 1.41 (m, 1H), 1.28 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 208.5, 173.2, 61.4, 57.3, 40.8, 38.4, 27.7, 22.8, 21.4, 14.2.

The data is consistent with those reported in the literature.(*40*)



46

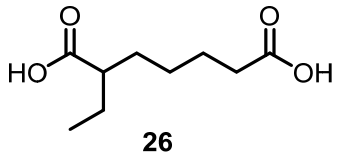
2-Methylheptanedioic acid 46

This compound was prepared according to the general procedure B for the preparation of β-substituted heptanedioic acids. 75% yield, (0.78 g, 4.5 mmol, white solid).

^{1}H NMR (500 MHz, DMSO) δ 2.29 (h, *J* = 6.9 Hz, 1H), 2.19 (t, *J* = 7.3 Hz, 2H), 1.57 – 1.50 (m, 1H), 1.50 – 1.41 (m, 2H), 1.33 (dq, *J* = 15.7, 6.8 Hz, 1H), 1.25 (qd, *J* = 7.6, 3.7 Hz, 2H), 1.03 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, DMSO) δ 177.4, 174.4, 38.6, 33.6, 33.0, 26.3, 24.4, 17.0.

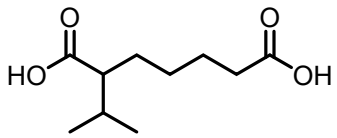
HRMS (ESI-TOF) Calculated for $C_8H_{13}O_4$, $[M-H]^-$: 173.0814, found: 173.0811.



26

2-Ethylheptanedioic acid 26

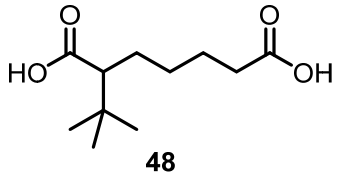
Please see Section 2.4



27

2-Isopropylheptanedioic acid 27

Please see Section 2.4



48

2-(*tert*-Butyl)heptanedioic acid 48

This compound was prepared according to the general procedure for the preparation of α-substituted heptanedioic acids.

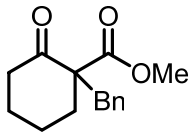
Elution condition: (20% EA/hexanes + 1% AcOH to 50% EA + 1% AcOH, gradient elution)

Isolated yield: 44% over 2 steps (0.95 g, 4.4 mmol, colourless oil)

^{1}H NMR (500 MHz, DMSO) δ 11.97 (s, 2H), 2.18 (t, *J* = 7.4 Hz, 2H), 1.97 (dd, *J* = 11.8, 2.9 Hz, 1H), 1.55 – 1.43 (m, 3H), 1.39 (dddd, *J* = 12.8, 9.4, 6.3, 2.8 Hz, 1H), 1.26 – 1.11 (m, 2H), 0.91 (s, 9H).

^{13}C NMR (126 MHz, DMSO) δ 176.1, 174.4, 55.6, 33.6, 32.1, 27.7, 27.6, 26.9, 24.5.

HRMS (ESI-TOF) Calculated for $C_{11}H_{19}O_4$ $[M-H]^-$: 215.1283, Found: 215.1281.



SS7

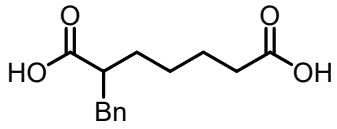
Methyl 1-benzyl-2-oxocyclohexane-1-carboxylate SS7

This compound was prepared according to the general procedure B for the preparation of α-substituted heptanedioic acids with the reaction of BnBr and methyl 2-oxocyclohexane-1-carboxylate. 95% yield, (1.87g, 7.6 mmol, white solid).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27 – 7.22 (m, 2H), 7.22 – 7.17 (m, 1H), 7.11 – 7.07 (m, 2H), 3.64 (s, 3H), 3.32 (d, *J* = 13.8 Hz, 1H), 2.87 (d, *J* = 13.8 Hz, 1H), 2.52 – 2.35 (m, 3H), 2.05 – 1.97 (m, 1H), 1.78 – 1.57 (m, 3H), 1.46 (ddd, *J* = 13.8, 12.1, 4.5 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 207.3, 171.6, 136.7, 130.4, 128.2, 126.8, 62.4, 52.3, 41.5, 40.6, 36.0, 27.7, 22.6.

The data is consistent with those reported in the literature.(*44*)



47

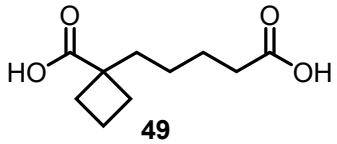
2-Benzylheptanedioic acid 47

This compound was prepared according to the general procedure B for the preparation of α-substituted heptanedioic acids. 85% yield, (1.28 g, 5.1 mmol, white solid).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 7.24 – 7.20 (m, 1H), 7.19 – 7.15 (m, 2H), 3.06 – 2.98 (m, 1H), 2.74 – 2.65 (m, 2H), 2.40 (ddd, *J* = 15.2, 8.1, 4.4 Hz, 1H), 2.32 (ddd, *J* = 15.3, 8.6, 4.4 Hz, 1H), 1.72 – 1.48 (m, 4H), 1.44 – 1.25 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 182.5, 180.7, 139.0, 129.0, 128.6, 126.6, 47.6, 38.4, 33.9, 31.5, 26.2, 24.7.

HRMS (ESI-TOF) Calculated for $C_{14}H_{18}O_4Na$ $[M+Na]^+$: 273.1103, Found: 273.1095.



49

1-(4-Carboxybutyl)cyclobutane-1-carboxylic acid 49

This compound was prepared according to the general procedure for the preparation of α-substituted heptanedioic acids.

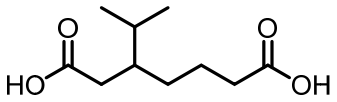
Elution condition: (20% EA/hexanes + 1% AcOH to 50% EA/hexanes + 1% AcOH, gradient elution)

Isolated yield: 30% over 2 steps (0.60 g, 3.0 mmol, off-white solid)

^{1}H NMR (500 MHz, DMSO) δ 12.01 (s, 2H), 2.27 (qd, *J* = 8.0, 4.4 Hz, 2H), 2.19 (t, *J* = 7.3 Hz, 2H), 1.89 – 1.71 (m, 4H), 1.71 – 1.63 (m, 2H), 1.47 (p, *J* = 7.5 Hz, 2H), 1.20 – 1.07 (m, 2H).

^{13}C NMR (126 MHz, DMSO) δ 177.9, 174.4, 46.9, 37.3, 33.6, 33.5, 29.5, 24.8, 24.1, 15.0.

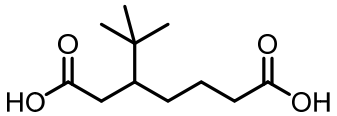
HRMS (ESI-TOF) Calculated for $C_{10}H_{15}O_4$ $[M-H]^-$: 199.0970, Found: 199.0971.



30

3-Isopropylheptanedioic acid 30

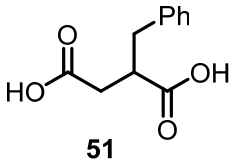
Please see Section 2.4



31

3-(*tert*-Butyl)heptanedioic acid 31

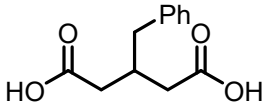
Please see Section 2.4



51

2-Benzylsuccinic acid 51

This compound is commercially available.



52

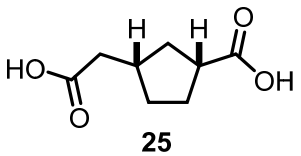
3-Benzylpentanedioic acid 52

This compound was prepared exactly according to the procedures published by Bonati and co-workers.(*45*)

^{1}H NMR (500 MHz, DMSO) δ 12.15 (s, 2H), 7.36 – 7.26 (m, 2H), 7.24 – 7.18 (m, 1H), 7.18 – 7.12 (m, 2H), 2.60 (d, *J* = 6.9 Hz, 2H), 2.38 (p, *J* = 6.7 Hz, 1H), 2.26 – 2.14 (m, 4H).

^{13}C NMR (126 MHz, DMSO) δ 173.5, 139.6, 129.1, 128.3, 126.1, 39.0, 37.2, 33.5.

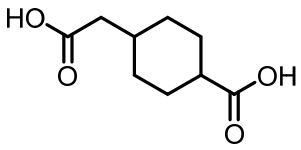
HRMS (ESI-TOF) Calculated for $C_{12}H_{13}O_4$ $[M-H]^-$: 221.0814, Found: 221.0815.



25

(1*R,3*S**)-3-(Carboxymethyl)cyclopentane-1-carboxylic acid 25**

Please see Section 2.4



53

cis:*trans* = 2.3:1

4-(Carboxymethyl)cyclohexane-1-carboxylic acid 53

This compound was prepared according to the following procedure.(*43*)

4-(Carboxymethyl)benzoic acid (0.3 g, 1.67 mmol) was dissolved in glacial acetic acid (15.0 mL) and PtO_2 (60.0 mg) was added. The reaction vessel was purged with H_2 and the hydrogenation reaction was carried out at room temperature with a ballon of H_2 and stirred for 3 days. Analysis of an aliquot of the reaction mixture at this point suggested completion of reaction. The reaction mixture was filtered with a plug of Celite® and the filtrate was evaporated to dryness to give the titled compound as a white solid in 93% yield (0.29 g, 1.56 mmol).

NMR for minor diastereomer: ^{1}H NMR (500 MHz, DMSO) δ 2.09 – 2.05 (m, 3H), 1.89 – 1.79 (m, 2H), 1.79 – 1.69 (m, 2H), 1.59 (ddt, *J* = 11.4, 7.7, 3.9 Hz, 1H), 1.28 (qd, *J* = 13.1, 3.4 Hz, 2H), 0.96 (qd, *J* = 13.0, 3.5 Hz, 2H).

^{13}C NMR (126 MHz, DMSO) δ 176.7, 173.7, 42.3, 41.4, 33.7, 31.4, 28.5.

NMR for major diastereomer: ^{1}H NMR (500 MHz, DMSO) δ 2.43 (q, *J* = 4.9 Hz, 1H), 2.10 (d, *J* = 7.3 Hz, 2H), 1.89 – 1.79 (m, 2H), 1.79 – 1.69 (m, 1H), 1.55 – 1.50 (m, 2H), 1.47 (ddd, *J* = 13.9, 8.7, 4.5 Hz, 2H), 1.18 (dtd, *J* = 15.2, 11.0, 4.7 Hz, 2H).

^{13}C NMR (126 MHz, DMSO) δ 176.1, 173.8, 39.9, 39.3, 32.4, 28.9, 25.7.

HRMS (ESI-TOF) Calculated for $C_9H_{13}O_4$ $[M-H]^-$: 185.0814, Found: 185.0813.

2.8 Preliminary mechanistic studies

1. H/D exchange experiments – investigations of carboxylic acid directed γ-methylene C–H activation

With Ligand L2:

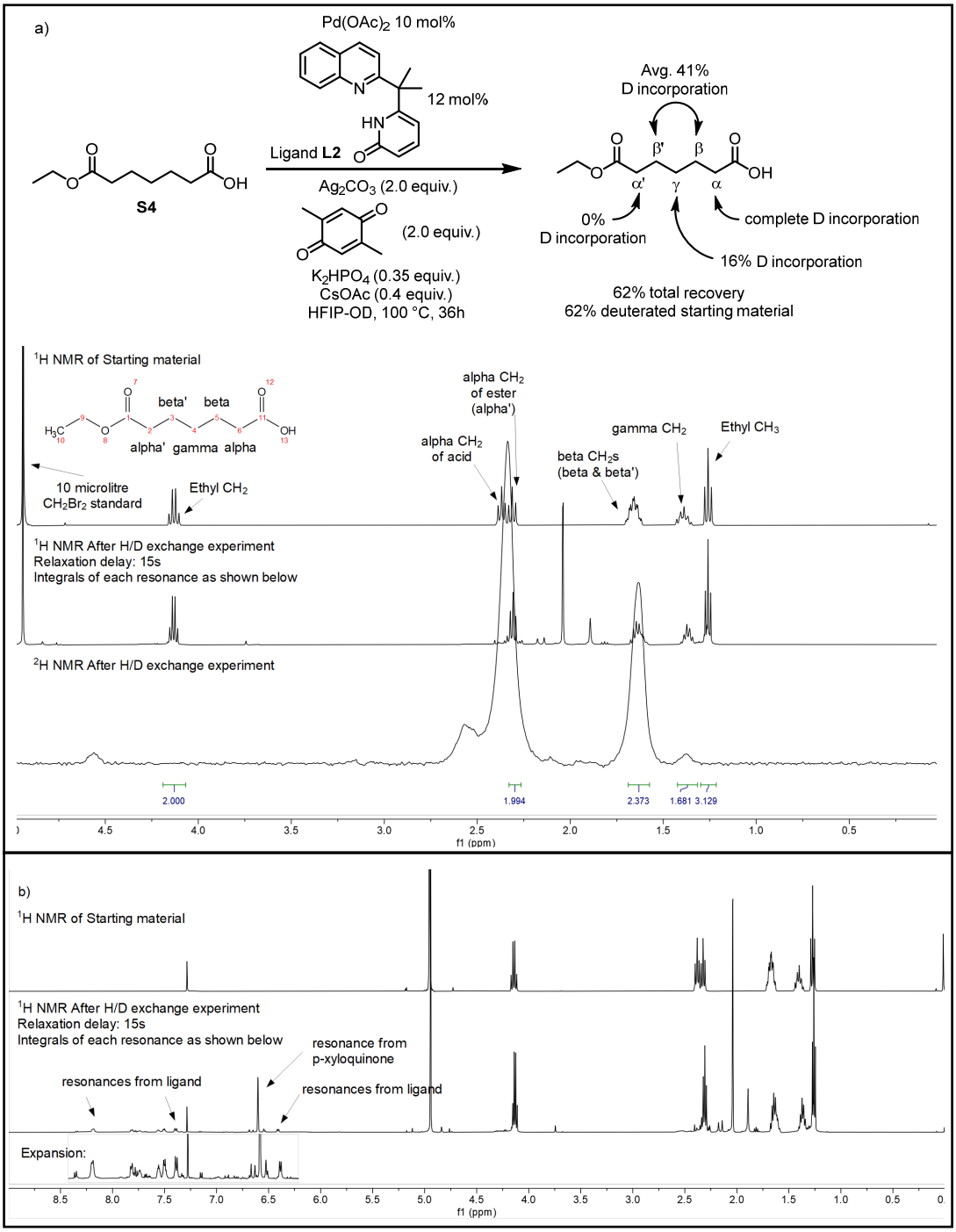


Figure S1. a) H/D exchange experiments – investigations of carboxylic acid directed γ-methylene C–H activation. **b)** ^{1}H NMR spectra of monoethyl pimelate **S4** and the crude ^{1}H NMR spectrum of the H/D exchange experiment, displayed from 0.0 ppm to 9.0 ppm, suggesting the absence of dehydrogenation products and the major recovered species is deuterated **S4**.

H/D exchange experiment with monoethyl pimelate **S4** under the stated reaction condition using ligand **L2** suggested that γ-methylene C–H activation is feasible. H/D exchange at the α, β, and γ-positions were all observed.

% Deuteration at γ-methylene CH_2 : [|(1.681-2.000)|/2.000] x 100% = 16%

The presence of deuterium at γ-methylene CH_2 is further supported by ^2H NMR spectroscopy.

% Deuteration at β-methylene CH_2s (indistinguishable due to overlap of resonances) :

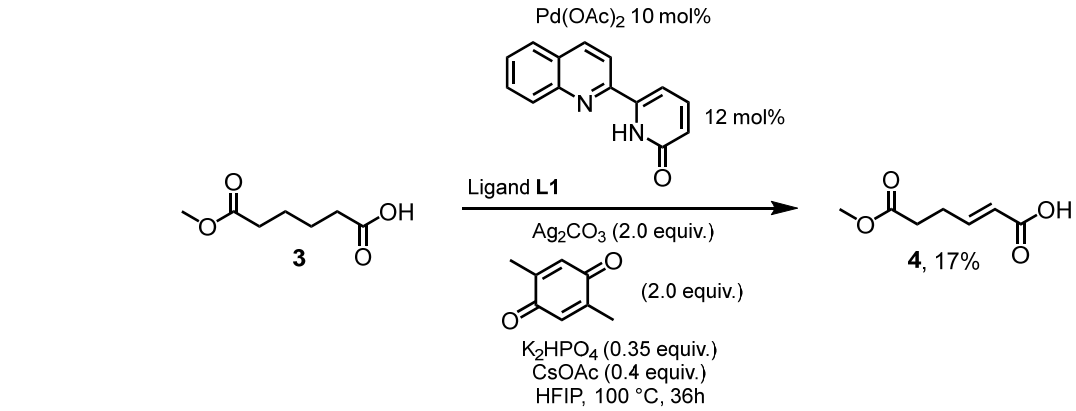
[|(2.373-4.000)|/4.000] x 100% = 41%

% Deuteration at α-methylene CH_2 of acid: NMR analysis suggests complete deuteration.

% Deuteration at α-methylene CH_2 of ester: NMR analysis suggests no deuteration.

Note: Compound **S4** is commercially available.

2. Outcome of using monomethyl adipate 3 as substrate for γ-lactonization via β-C–H activation



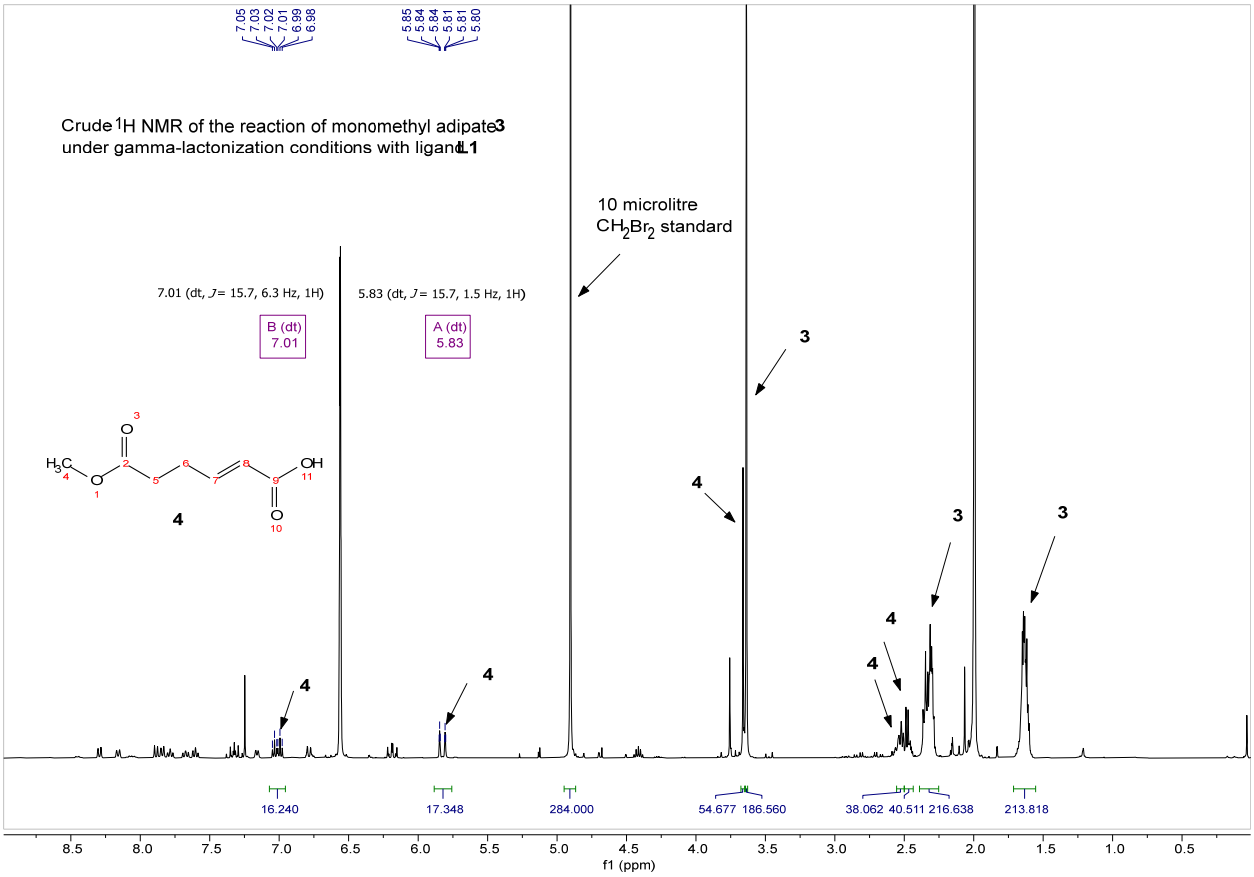


Figure S2. Reaction of monomethyl adipate **3** under γ-lactonization conditions with ligand **L1.**

2. Investigations on the mechanism of C–O bond formation. Are (*E*)-hex-2-enedioic acid 5 and (*E*)-hept-2-enedioic acid S5 viable reaction intermediates?

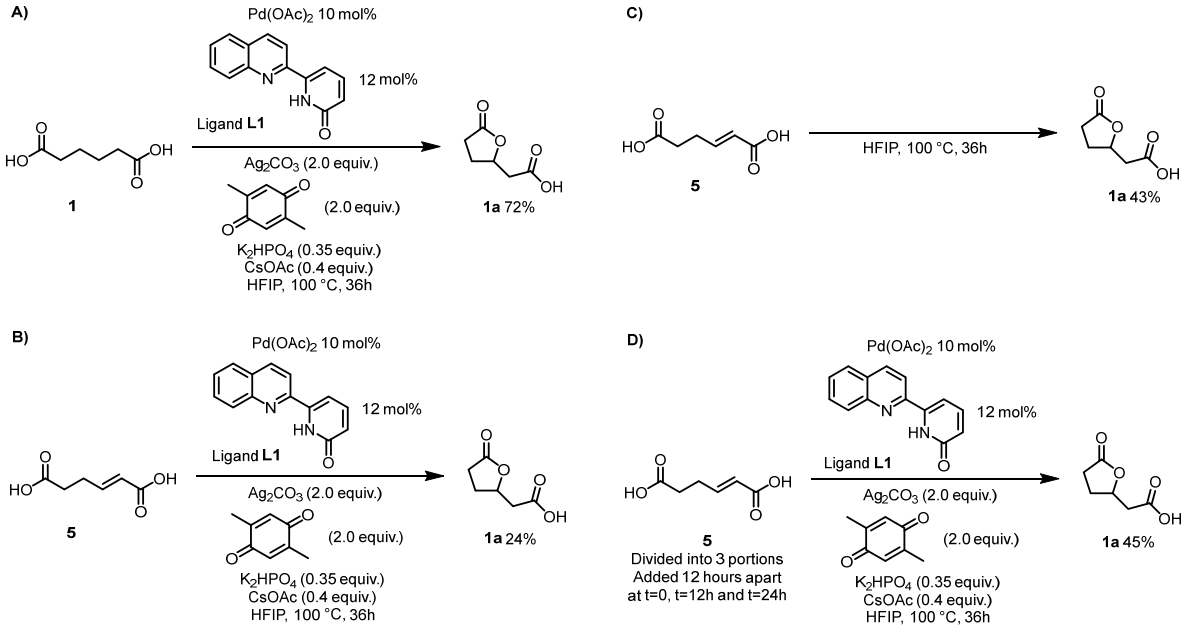


Figure S3. Investigations on the mechanism of C–O bond formation. Is (*E*)-hex-2-enedioic acid S5 a viable reaction intermediate?

Employing (*E*)-hex-2-enedioic acid **5** as the substrate under the lactonization reaction condition developed for adipic acid **1** gave only 24% yield of the expected lactone **1a**, as opposed to a 72% yield observed when adipic acid **1** was used as the substrate. Simply heating (*E*)-hex-2-enedioic acid **5** in HFIP at 100 °C for 36h gave the lactone product **1a** in 43% yield. Gradual addition of (*E*)-hex-2-enedioic acid **5** as the substrate in 3 portions, 12 hours apart, to the reaction mixture using the condition optimized for adipic acid **1** gave 45% yield of the lactone **1a**. These experiments suggest (*E*)-hex-2-enedioic acid **5** could be a viable intermediate for the lactonization reaction, and the C–O bond forming step could be an intramolecular conjugation addition process. However, the discrepancy in reaction yields also suggests that this intramolecular conjugation addition pathway may not be the only pathway possible for lactone formation. The existence of two simultaneous pathways for lactone formation is possible, one arising from intramolecular conjugate addition of (*E*)-hex-2-enedioic acid **5**, and another pathway for C–O bond formation arising from reductive elimination at palladium.

Compound **5** was synthesized according to the procedure below:

3-Oxohexanedicarboxylic acid dimethyl ester (1.0 g, 5.3 mmol) was dissolved in MeOH (10.0 mL) and $NaBH_4$ (200 mg, 5.3 mmol) was added. The reaction mixture was then stirred at room temperature for 1 hour. Aqueous NaOH solution (5.0 mL, 15% w/w) was added and the reaction mixture was stirred for 2 hours. The pH of the reaction mixture was then adjusted to 1 with aq. HCl (6.0 M), and the reaction mixture was concentrated under reduced pressure. Recrystallization of the crude with water gave the desired diacid 5 as a white solid (640 mg, 4.4 mmol, 83%).

^{1}H NMR (500 MHz, DMSO) δ 12.18 (s, 2H), 6.81 (ddd, J = 15.6, 9.5, 3.6 Hz, 1H), 5.77 (d, J = 15.6 Hz, 1H), 2.39 (m, 4H).

^{13}C NMR (126 MHz, DMSO) δ 173.6, 167.0, 147.4, 122.3, 32.0, 26.7.

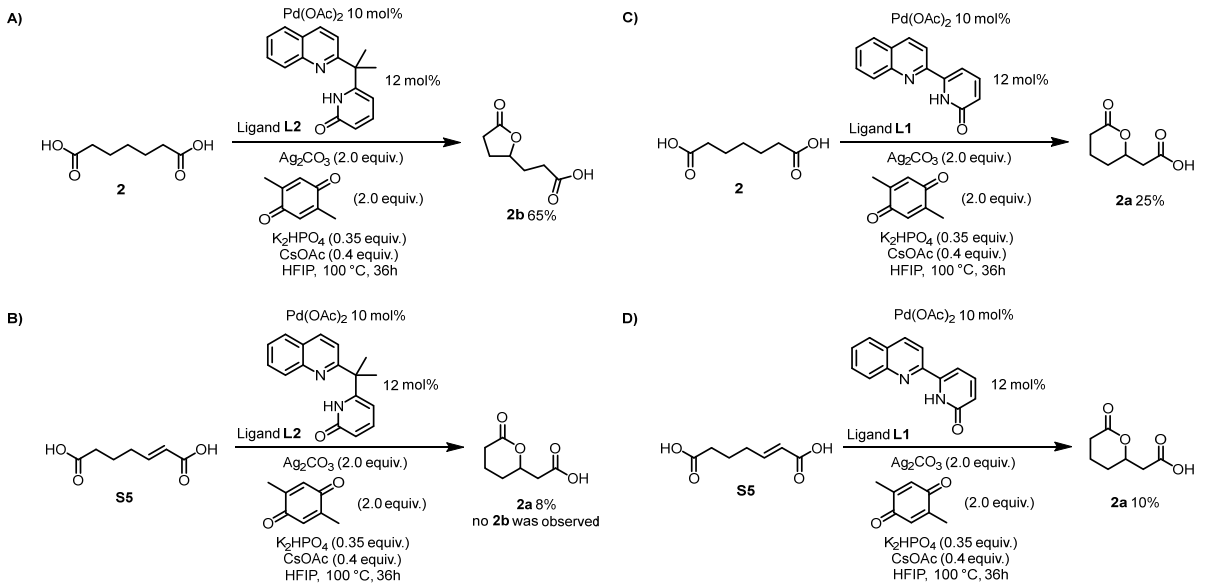


Figure S4. Investigations on the mechanism of C–O bond formation. Is (*E*)-hept-2-enedioic acid **S5** a viable reaction intermediate?

The use of (*E*)-hept-2-enedioic acid **S5** as the substrate with **L2** did not provide any of the γ-lactone **2b**, thus suggesting that (*E*)-hept-2-enedioic acid **S5** is not a viable intermediate for the formation of γ-lactone **2b**. Using (*E*)-hept-2-enedioic acid **S5** as the substrate with **L1** did provide the δ-lactone **2a** in 10% yield, as opposed to the 25% yield obtained with pimelic acid **2** as the substrate. These results suggest that the most likely mechanism for the C–O bond formation in the generation of γ-lactone **2b** with **L2** does not involve (*E*)-hept-2-enedioic acid **S5** as an intermediate. Taking into account the results obtained from the H/D exchange experiments, the absence of other olefinic products suggests the most likely mechanism for C–O bond formation using ligand **L2** with pimelic acid is *via* reductive elimination at palladium. As for δ-lactone formation using pimelic acid and ligand **L1**, the most likely mechanistic scenario would be similar to that described above for the formation of γ-lactone **1a** using adipic acid **1** and ligand **L1**, in which simultaneous existence of two reaction pathways is possible.

Compound **S5** was synthesized according to the procedure below:

3-Oxoheptanedicarboxylic acid diethyl ester (1.0 g, 4.3 mmol) was dissolved in MeOH (10.0 mL) and $NaBH_4$ (163 mg, 4.3 mmol) was added. The reaction mixture was then stirred at room temperature for 1 hour. Aqueous NaOH solution (5.0 mL, 15% w/w) was added and the reaction mixture was stirred for 2 hours. The pH of the reaction mixture was then adjusted to 1 with aq. HCl (6.0 M), and the reaction mixture was concentrated under reduced pressure. Purification of the crude by flash column chromatography (30% EtOAc/hexane + 1% AcOH, then 50% EtOAc/hexane + 1% AcOH) gave the desired diacid **S5** as a white solid (241 mg, 1.52 mmol, 35%).

^{1}H NMR (600 MHz, DMSO) δ 12.11 (s, 1H), 6.79 (dt, *J* = 15.6, 6.9 Hz, 1H), 5.76 (dt, *J* = 15.6, 1.6 Hz, 1H), 2.33 – 2.11 (m, 4H), 1.63 (p, *J* = 7.4 Hz, 2H).

^{13}C NMR (151 MHz, DMSO) δ 174.1, 167.0, 148.1, 122.3, 32.9, 30.7, 22.9.

3. Derivatization of lactone products

Total synthesis of myrotheciumone A

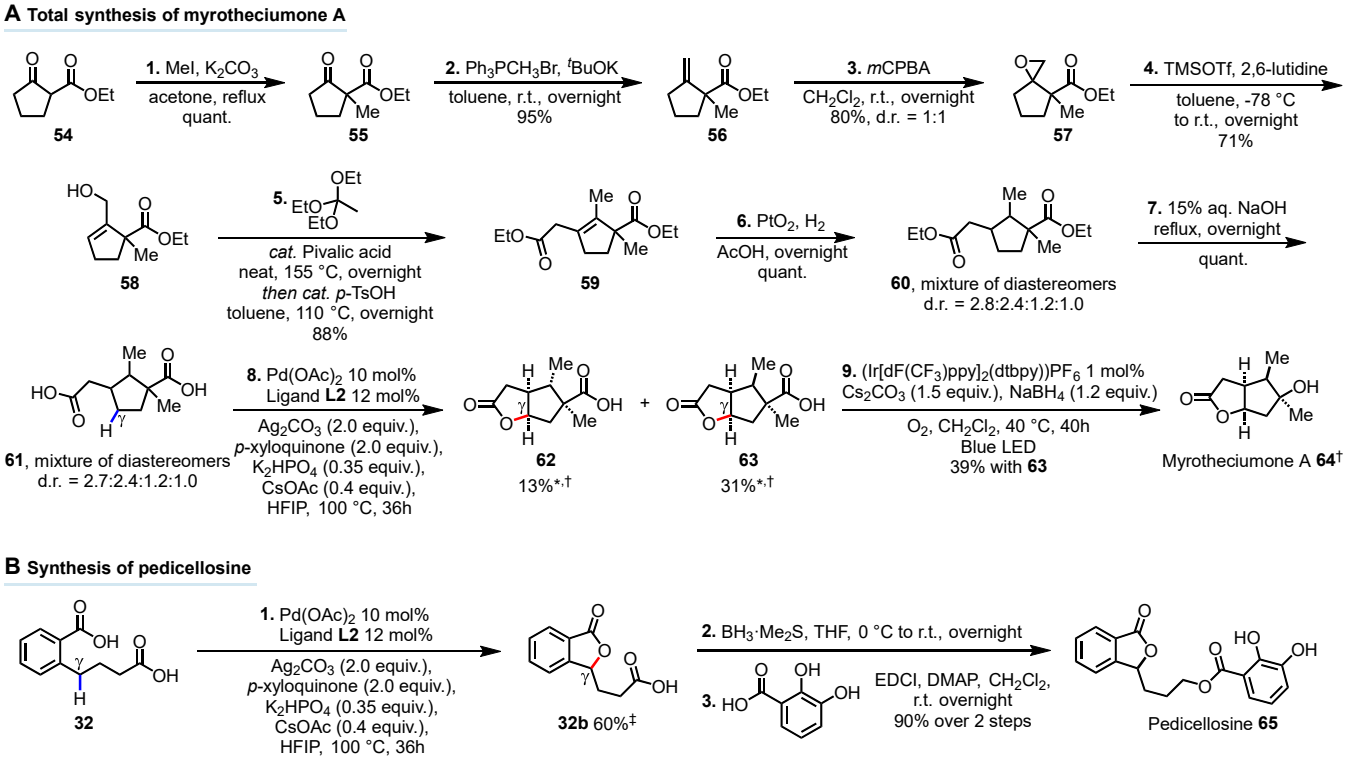
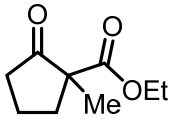


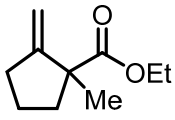
Figure S5. Total synthesis of myrotheciumone A and pedicellosine.



55

Ethyl 1-methyl-2-oxocyclopentane-1-carboxylate 55

Please see Section 2.4 for the synthesis of **55**.



54

Ethyl 1-methyl-2-methylenecyclopentane-1-carboxylate 56

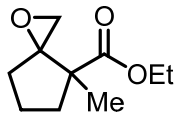
Ph_3PCH_3Br (9.2 g, 25.8 mmol) was suspended with *t*BuOK (2.4 g, 21.3 mmol) in dry toluene (44.0 mL) at room temperature. The reaction was stirred for 1 hour at this temperature followed by addition of a solution of compound **55** (1.5 g, 8.8 mmol) in dry toluene (5.0 mL). The reaction mixture was stirred overnight at room temperature. TLC analysis at this stage suggested completion of reaction. The reaction mixture was quenched with sat. aq. NH_4Cl followed by extraction with EtOAc (three

times). The combined organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude was purified by flash column chromatography on silica gel (3% EtOAc/hexane to 5% EtOAc/hexane) to give the desired product in 95% yield as a colourless oil (1.4 g, 8.4 mmol, R_f = 0.5 (5% EtOAc/hexane)).

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.06 – 4.88 (m, 2H), 4.31 – 3.92 (m, 2H), 2.51 – 2.37 (m, 2H), 2.34 (dt, *J* = 13.2, 7.0 Hz, 1H), 1.80 (dq, *J* = 13.5, 6.5 Hz, 1H), 1.67 (td, *J* = 13.5, 7.3 Hz, 1H), 1.58 (dd, *J* = 12.8, 6.5 Hz, 1H), 1.32 (s, 3H), 1.28 – 1.16 (m, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 176.5, 156.7, 106.9, 60.7, 52.4, 39.0, 33.8, 25.2, 24.0, 14.2.

HRMS (ESI-TOF) : Expected mass not observed.



57

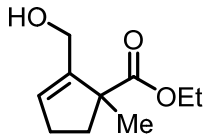
Ethyl 4-methyl-1-oxaspiro[2.4]heptane-4-carboxylate 57

The compound **56** (1.0 g, 6.0 mmol) was dissolved in dry CH_2Cl_2 and *m*CPBA (1.7 g, 75% purity, 7.4 mmol) was added. The reaction was stirred at room temperature overnight. TLC analysis at this stage suggested completion of reaction. The reaction mixture was quenched with sat. aq. $NaHCO_3$ and sat. aq. $Na_2S_2O_3$, followed by extraction with EtOAc (three times). The combined organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude was purified by flash column chromatography on silica gel (10% EtOAc/hexane to 20% EtOAc/hexane) to give the desired product in 80% yield as a colourless oil (0.88 g, 4.8 mmol, d.r. 1:1, R_f = 0.4 (20% EtOAc/hexane)).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.35 – 3.99 (m, 4H), 2.94 (d, *J* = 4.7 Hz, 1H), 2.88 (d, *J* = 4.5 Hz, 1H), 2.78 (d, *J* = 4.5 Hz, 1H), 2.73 (d, *J* = 4.7 Hz, 1H), 2.57 (dt, *J* = 12.6, 7.9 Hz, 1H), 2.35 – 2.27 (m, 1H), 2.24 – 2.15 (m, 1H), 2.11 (tt, *J* = 11.2, 6.1 Hz, 1H), 2.01 – 1.92 (m, 1H), 1.85 – 1.79 (m, 1H), 1.79 – 1.73 (m, 3H), 1.73 – 1.66 (m, 2H), 1.63 – 1.56 (m, 1H), 1.27 – 1.19 (m, 9H), 1.06 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.3, 173.5, 69.1, 67.6, 60.8, 60.8, 50.8, 50.6, 49.8, 49.7, 38.4, 36.4, 33.1, 32.1, 22.2, 22.0, 21.8, 18.1, 14.3.

HRMS (ESI-TOF) Calculated for $C_{10}H_{17}O_3$, $[M+H]^+$: 185.1178, Found: 185.1175.



58

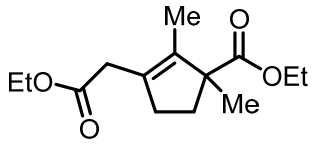
Ethyl 2-(hydroxymethyl)-1-methylcyclopent-2-ene-1-carboxylate 58

The compound **57** (0.65 g, 3.5 mmol) was dissolved in dry toluene (34.0 mL) and 2,6-lutidine (0.83 mL, 7.0 mmol) was added. The reaction mixture was then cooled to -78 °C. TMSOTf (1.28 mL, 7.0 mmol) was then added dropwise to the reaction mixture. The reaction mixture was gradually warmed to r.t. and stirred overnight. TLC analysis at this stage suggested completion of reaction. MeOH (10.0 mL) was added to the reaction mixture followed by aq. HCl (6.0 M, 3.0 mL) and stirred for 1 hour. TLC analysis at this stage suggested completion of reaction. The reaction mixture was neutralized with sat. aq. $NaHCO_3$ and extracted with EtOAc (three times). The combined organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude was purified by flash column chromatography on silica gel (30% EtOAc/hexane to 50% EtOAc/hexane) to give the desired product in 71% yield as a colourless oil (0.46 g, 2.5 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (d, J = 2.6 Hz, 1H), 4.26 – 4.19 (m, 2H), 4.15 (q, J = 7.1 Hz, 2H), 2.48 – 2.42 (m, 1H), 2.42 – 2.36 (m, 1H), 2.36 – 2.30 (m, 1H), 2.27 (t, J = 5.9 Hz, 1H), 1.85 – 1.78 (m, 1H), 1.36 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.8, 145.9, 130.2, 61.1, 59.8, 55.9, 38.0, 30.0, 23.0, 14.3.

HRMS (ESI-TOF) Calculated for $C_{10}H_{16}O_3Na$, $[M+Na]^+$: 207.0997, Found: 207.0998.



59

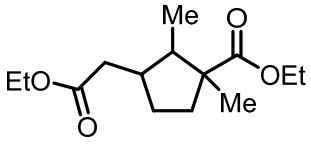
Ethyl 3-(2-ethoxy-2-oxoethyl)-1,2-dimethylcyclopent-2-ene-1-carboxylate 59

The compound **58** (0.34 g, 1.85 mmol) was dissolved in triethyl orthoacetate (5.0 mL) and pivalic acid (20.0 mg, 0.2 mmol) was added. The reaction mixture was heated to reflux and stirred overnight. TLC analysis at this stage suggested completion of reaction. All volatiles were removed under reduced pressure and the crude was washed with sat. aq. $NaHCO_3$ and extracted with EtOAc (three times). The combined organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was dissolved in toluene (15.0 mL) and *p*-TsOH (34.4 mg, 0.2 mmol) was added. The reaction mixture was heated to reflux and stirred overnight. TLC analysis at this stage suggested completion of reaction. The reaction mixture was neutralized with sat. aq. $NaHCO_3$ and extracted with EtOAc (three times). The combined organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude was purified by flash column chromatography on silica gel (5% EtOAc/hexane to 10% EtOAc/hexane) to give the desired product in 88% yield as a pale yellow oil (0.41g, 1.63 mmol).

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.32 – 3.90 (m, 4H), 3.12 (d, *J* = 15.1 Hz, 1H), 3.03 (d, *J* = 15.1 Hz, 1H), 2.50 – 2.38 (m, 2H), 2.35 (ddd, *J* = 14.3, 8.5, 3.8 Hz, 1H), 1.78 – 1.63 (m, 1H), 1.63 – 1.51 (m, 3H), 1.26 (s, 3H), 1.26 – 1.20 (m, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 176.7, 171.3, 138.0, 130.8, 60.6, 60.5, 35.6, 35.1, 34.3, 22.1, 14.4, 14.4, 10.8.

HRMS (ESI-TOF) Calculated for $C_{14}H_{23}O_4$, $[M+H]^+$: 255.1596, Found: 255.1590.



mixture of
diastereomers
Ratio: 2.8:2.4:1.2:1.0

60

Ethyl 3-(2-ethoxy-2-oxoethyl)-1,2-dimethylcyclopentane-1-carboxylate 60

The compound **59** (0.41 g, 1.63 mmol) was dissolved in AcOH (44.0 mL) and PtO_2 (41.0 mg) was added. The reaction mixture was purged with H_2 and the H_2 atmosphere in the reaction vessel was secured with an inflated H_2 balloon (4 layers). The reaction mixture was stirred at room temperature overnight. Analysis of the reaction mixture by ^{1}H NMR spectroscopy suggested the completion of reaction. The reaction mixture was filtered through a plug of Celite ®, and the volatiles were evaporated to provide the desired compound as a pale yellow oil in quantitative yield (0.42 g, 1.63 mmol, d.r. 2.8:2.4:1.2:1.0).

HRMS (ESI-TOF) Calculated for $C_{14}H_{24}O_4Na$, $[M+Na]^+$: 279.1572, Found: 279.1581.

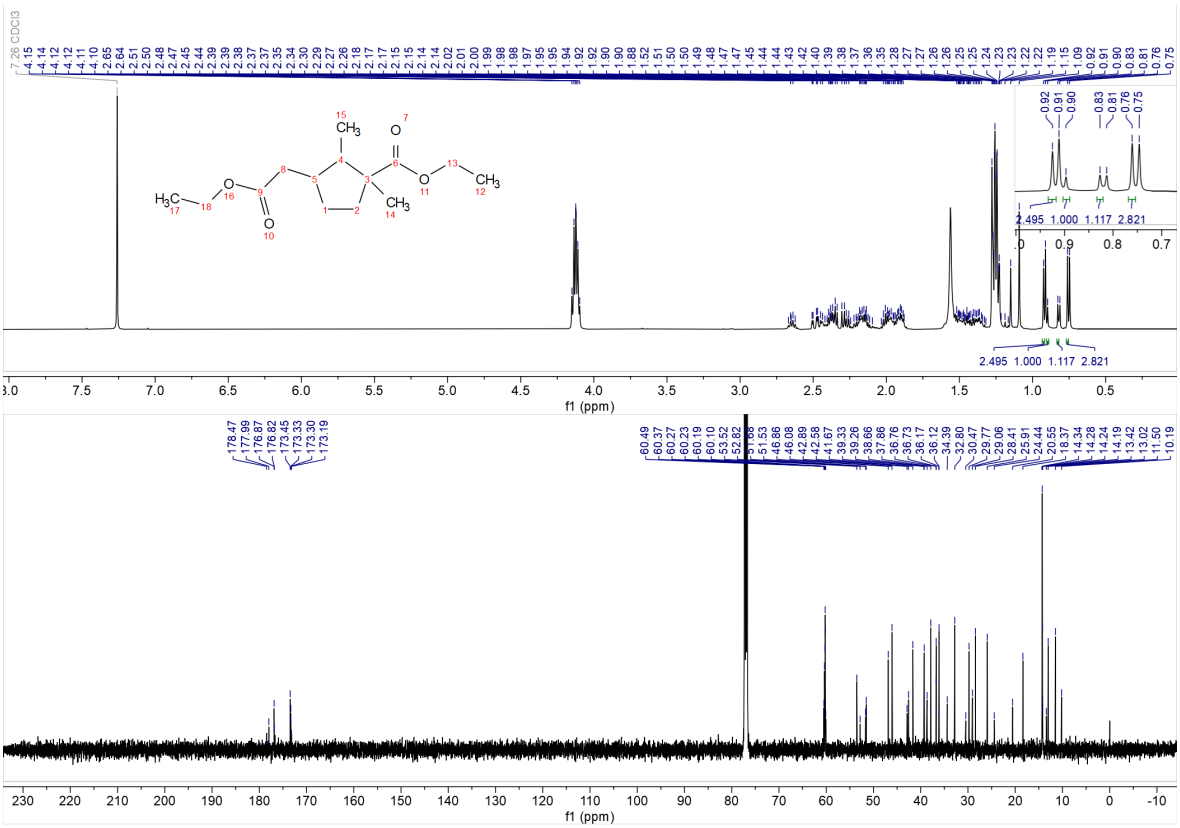
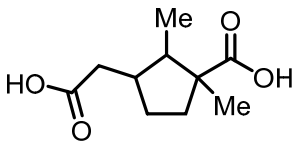


Figure S6. ^{1}H and ^{13}C NMR of compound **60.**



mixture of diastereomers
Ratio: 2.7:2.4:1.2:1.0
61

3-(Carboxymethyl)-1,2-dimethylcyclopentane-1-carboxylic acid 61

The compound **60** (0.42 g, 1.63 mmol) was suspended in 15% aq. NaOH and heated to reflux. The reaction mixture was stirred overnight. The reaction mixture was acidified to pH ~2 by addition of aq. HCl (6.0 M) and extracted with EtOAc (three times). The combined organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the titled dicarboxylic acid in quantitative yield as a white solid (0.33 g, 1.63 mmol, d.r. 2.7:2.4:1.2:1.0).

HRMS (ESI-TOF) Calculated for $C_{10}H_{15}O_4$, $[M-H]^-$: 199.0970, Found: 199.0969.

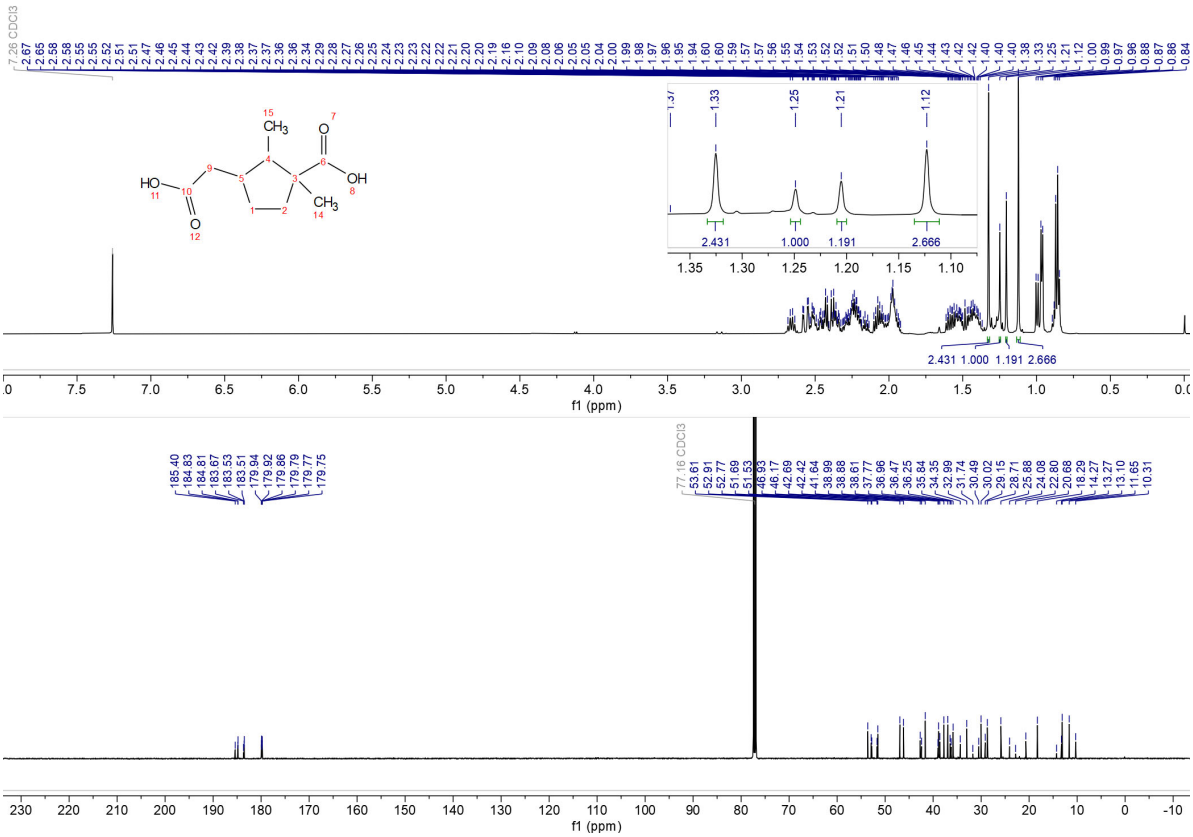
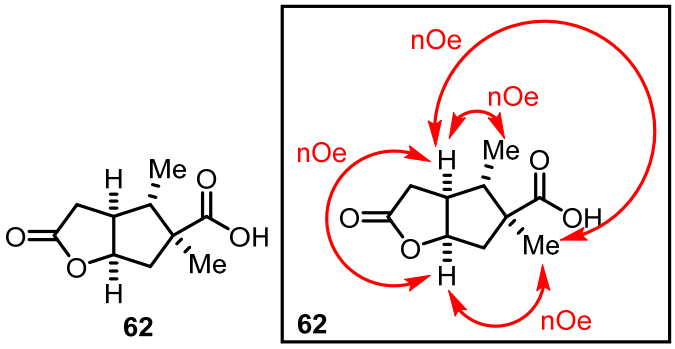


Figure S7. ^{1}H and ^{13}C NMR of compound **61.**



(3*aS,4*S**,5*S**,6*aR**)-4,5-dimethyl-2-oxohexahydro-2*H*-cyclopenta[*b*]furan-5-carboxylic acid 62**

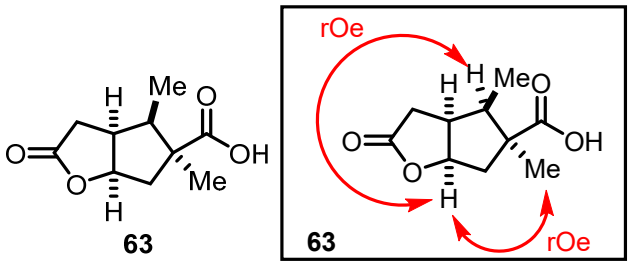
This compound was prepared according to the general procedure for the γ-directed, γ-C–H lactonization reaction using Ag_2CO_3 as oxidant (0.1 mmol of substrate per reaction, 4 reactions set up at a time).

Following the general procedure for its synthesis, the compound was purified as the acid by column chromatography (General procedure for gradient elution: begin with 20% EtOAc/hexane + 1% AcOH, and increase the composition of EtOAc by 10% for every 8 mL of eluent used to 50% EtOAc + 1% AcOH). Isolated yield 13% based on reactive diastereomers (7.2 mg, 0.036 mmol, white solid, R_f (TLC) 40% EtOAc/hexane + 1% AcOH = 0.27).

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.95 (ddd, *J* = 7.6, 7.3, 4.2 Hz, 1H), 2.77 (dd, *J* = 18.2, 9.3 Hz, 1H), 2.51 (dddd, *J* = 10.9, 9.3, 7.6, 2.0 Hz, 1H), 2.46 (dd, *J* = 14.7, 4.2 Hz, 1H), 2.40 (dd, *J* = 18.2, 2.0 Hz, 1H), 2.28 (dd, *J* = 14.7, 7.3 Hz, 1H), 2.23 (dq, *J* = 10.9, 6.8 Hz, 1H), 1.14 (s, 3H), 1.04 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 181.8, 176.8, 83.7, 52.1, 46.3, 45.1, 44.8, 34.1, 18.0, 13.2.

HRMS (ESI-TOF) Calculated for $C_{10}H_{15}O_4$, $[M+H]^+$: 199.0970, Found: 199.0969.



(3*aS,4*R**,5*S**,6*aR**)-4,5-dimethyl-2-oxohexahydro-2*H*-cyclopenta[*b*]furan-5-carboxylic acid 63**

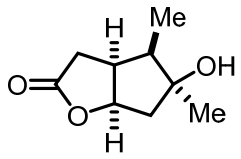
This compound was prepared according to the general procedure for the γ-directed, γ-C–H lactonization reaction using Ag_2CO_3 as oxidant (0.1 mmol of substrate per reaction, 4 reactions set up at a time).

Following the general procedure for its synthesis, the compound was purified as the acid by column chromatography (General procedure for gradient elution: begin with 20% EtOAc/hexane + 1% AcOH, and increase the composition of EtOAc by 10% for every 8 mL of eluent used to 50% EtOAc + 1% AcOH). Isolated yield 31% based on reactive diastereomers (17.0 mg, 0.086 mmol, white solid, R_f (TLC) 40% EtOAc/hexane + 1% AcOH = 0.34).

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.04 (ddd, *J* = 8.2, 6.9, 1.9 Hz, 1H), 3.13 (dtd, *J* = 11.6, 8.2, 3.7 Hz, 1H), 2.74 – 2.61 (m, 2H), 2.48 (dd, *J* = 18.6, 11.6 Hz, 1H), 2.07 (dq, *J* = 8.2, 7.5 Hz, 1H), 1.89 (dd, *J* = 15.1, 6.9 Hz, 1H), 1.32 (s, 3H), 1.10 (d, *J* = 7.5 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 181.0, 178.4, 84.4, 52.3, 46.2, 44.1, 42.3, 30.2, 24.6, 11.3.

HRMS (ESI-TOF) Calculated for $C_{10}H_{15}O_4$, $[M+H]^+$: 199.0970, Found: 199.0974.



Myrotheciumone A **64**

(3*aS,4*R**,5*S**,6*aR**)-5-hydroxy-4,5-dimethylhexahydro-2H-cyclopenta[b]furan-2-one, myrotheciumone A 64**

This compound was prepared according to a modification of the procedure published by Khan and co-workers.(*35*)

The compound **63** (5.0 mg, 0.025 mmol) was dissolved in CH_2Cl_2 (0.5 mL). Cs_2CO_3 (12.3 mg, 0.038 mmol), $NaBH_4$ (1.1 mg, 0.030 mmol) and $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ (0.3 mg, 2.5 x 10^{-4} mmol) was added. The reaction mixture was purged with O_2 and kept under an atmosphere of O_2 in a sealed 2-dram reaction vial. The reaction mixture was stirred for 40 hours under irradiation with four 100W blue LED lamps 5 cm away from the reaction vessel. The reaction mixture was diluted with H_2O, followed by extraction with EtOAc (three times). The combined organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude was purified by flash column chromatography on silica gel (20% EtOAc/hexane to 50% EtOAc/hexane) to give the desired product in 39% yield (1.7 mg, 9.8 x 10^{-3} mmol). The NMR spectroscopic data of our synthetic myrotheciumone A is in accordance with the NMR spectroscopic data in literature.(21, 22)

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.03 (t, *J* = 7.6 Hz, 1H), 3.05 (dtd, *J* = 12.2, 8.3, 4.5 Hz, 1H), 2.77 (dd, *J* = 18.7, 4.5 Hz, 1H), 2.45 (dd, *J* = 18.7, 12.2 Hz, 1H), 2.18 (d, *J* = 15.1 Hz, 1H), 1.87 (dd, *J* = 15.1, 7.1 Hz, 1H), 1.87 – 1.82 (m, 1H), 1.27 (s, 3H), 1.03 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 178.5, 83.6, 79.7, 48.0, 45.2, 42.3, 30.2, 25.6, 8.8.

HRMS (ESI-TOF) Calculated for $C_9H_{14}O_3Na$, $[M+Na]^+$: 193.0841, Found: 193.0848.

Determination of yields for 62 and 63:

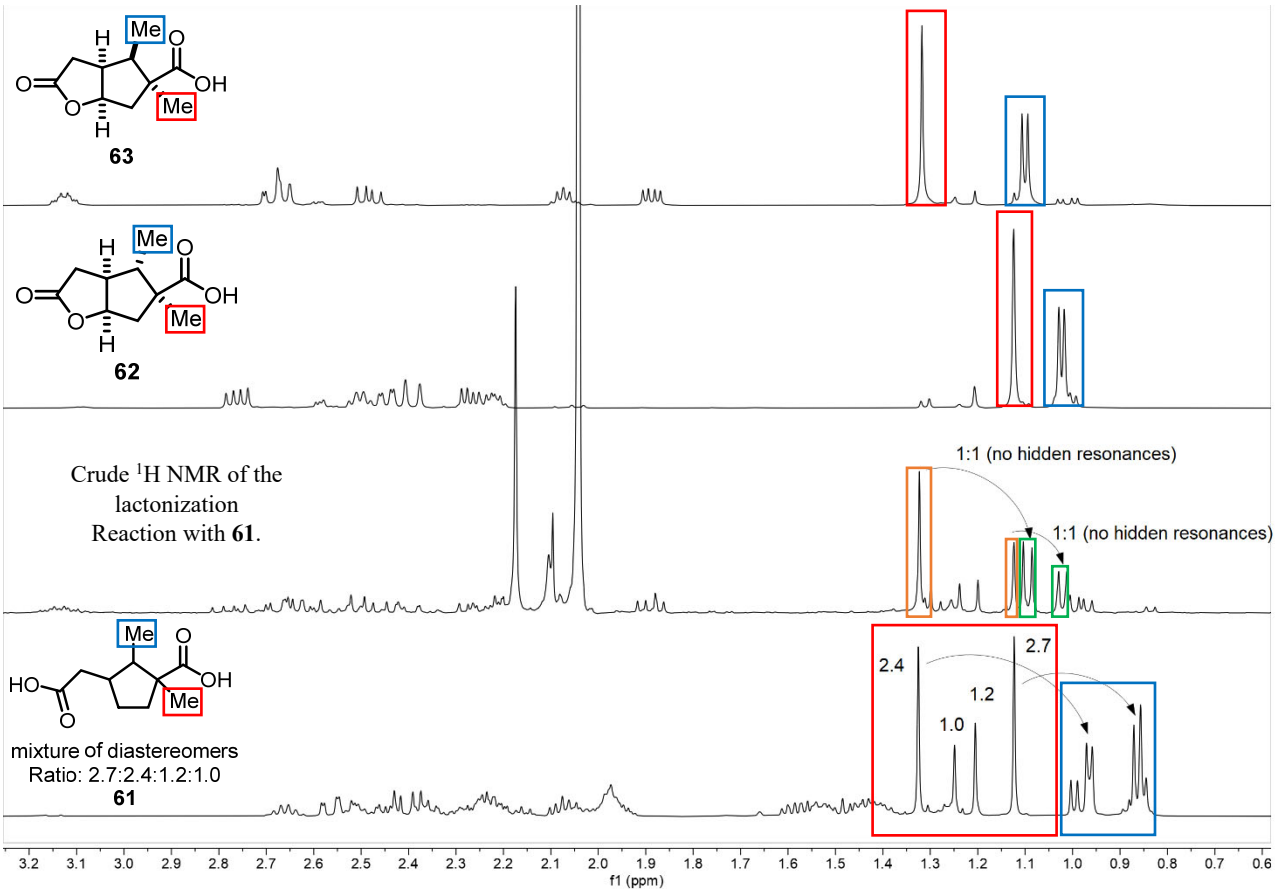


Figure S8. ^{1}H NMRs of **62**, **63**, crude ^{1}H NMR of the lactonization reaction with **61**, and **61** for the determination of yield of **62** and **63** based on reactive diastereomers.

As previously observed with the lactonization of **53** to give lactone **53b**, only the *syn*-diacids were found to be reactive whereas the *anti*-diacids were not. The same phenomenon was observed in the case for **61**.

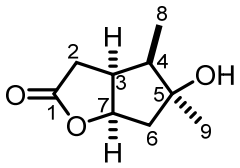
In the lowest panel, the 4 singlet resonances around 1.1-1.3 ppm with a ratio of 2.4, 1.0, 1.2, and 2.7 correspond to the methyl groups bonded to the quaternary centers of the 4 diastereomers of **61** (highlighted in red). The cluster of doublet resonances around 0.8-1.0 ppm correspond to the methyl groups bonded to the methine carbons of the 4 diastereomers of **61** (highlighted in blue).

In the second lowest panel displaying the crude ^{1}H NMR of the lactonization reaction with **61**, the doublet resonances corresponding to the diastereomers of **61** having the ratio 2.4 and 2.7 were found to be consumed, whereas the other two doublets remain. The two new doublets that emerged around 1.0-1.1 ppm (highlighted in green) each has a 1:1 integration ratio with the two singlets (highlighted in orange). These resonances correspond to **62** and **63**. This suggests that the consumed diastereomers are the reactive diastereomers. The no. of mmol of reactive diastereomers of **61** is therefore: [(2.4+2.7)/(2.4+2.7+1.0+1.2)]*0.4 = 0.28 mmol, for 4 reactions each at 0.1 mmol scale.

The yield of **62** based on the reactive diastereomers of **61** is therefore: (0.036/0.28)*100% = 13%

The yield of **63** based on the reactive diastereomers of **61** is therefore: (0.086/0.28)*100% = 31%

Comparison of synthetic and literature NMR data of myrotheciumone A:



myrotheciumone A

Atom Number	δ^1H/ppm (synthetic) 600 MHz, $CDCl_3$	δ^1H/ppm (literature)(21) 600 MHz, $CDCl_3$	δ^1H/ppm (literature)(*36*) 400 MHz, $CDCl_3$
1	-	-	-
2	2.77, dd (18.7, 4.5)	2.82, dd (18.5, 4.1)	2.76, dd (18.5, 4.3)
	2.45, dd (18.7, 12.2)	2.51, dd (18.5, 12.1)	2.44, dd (18.5, 11.9)
3	3.05, dtd (12.2, 8.3, 4.5)	3.09, m	3.09-3.00, m
4	1.84, m	1.89, m	1.87-1.80, m
5	-	-	-
6	2.18, d (15.1)	2.22, d (15.2)	2.18, dd (15.1)
	1.87, dd (15.1, 7.1)	1.92, dd (14.9, 6.6)	1.86, dd (15.3, 6.6)
7	5.03, t (7.6)	5.07, t (7.1)	5.03, t (7.1)
8	1.03, d (7.1)	1.06, d (7.0)	1.02, d (7.0)
9	1.27, s	1.28, s	1.26, s

Table S12. Comparison of synthetic and literature ^{1}H NMR data of myrotheciumone A.

Atom Number	δ^{13}C/ppm (synthetic) 151 MHz, $CDCl_3$	δ^{13}C /ppm (literature)(*34*) 100 MHz, $CDCl_3$	δ^{13}C /ppm (literature)(*36*) 100 MHz, $CDCl_3$
1	178.5	178.3	178.4
2	30.2	30.1	30.0
3	42.3	42.1	42.1
4	45.2	45.1	45.0
5	79.8	79.6	79.5
6	48.0	47.8	47.7
7	83.6	83.4	83.4
8	8.8	8.7	8.6
9	25.6	25.5	25.3

Table S13. Comparison of synthetic and literature ^{13}C NMR data of myrotheciumone A.

^{1}H NMR spectra (Synthetic: 600 MHz, $CDCl_3$; Literature(*36*): 400 MHz, $CDCl_3$):

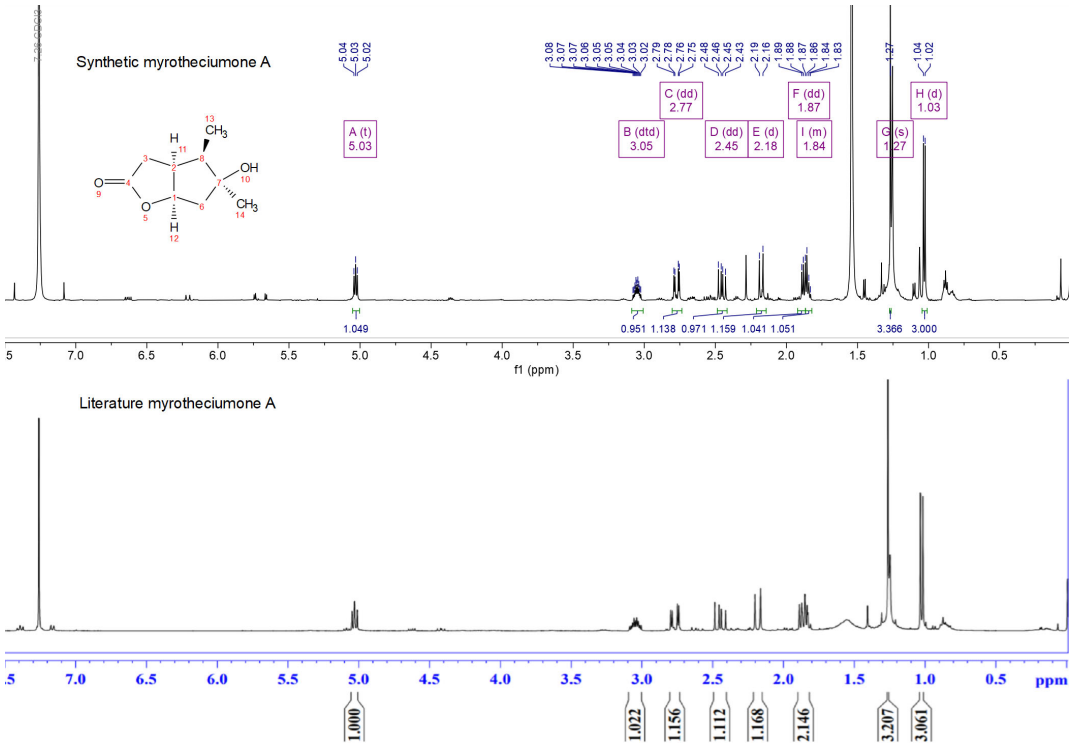


Figure S9. Comparison of synthetic and literature ^{1}H NMR spectra of myrotheciumone A.

^{13}C NMR spectra (Synthetic: 151 MHz, $CDCl_3$; Literature(*36*): 100 MHz, $CDCl_3$):

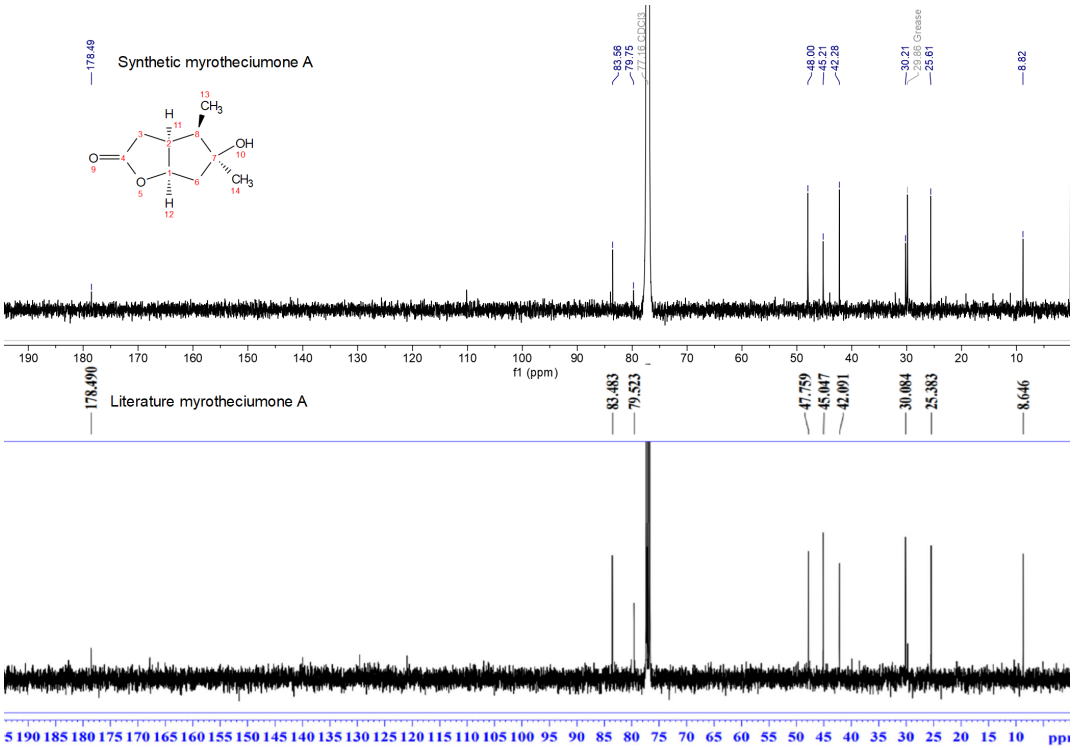
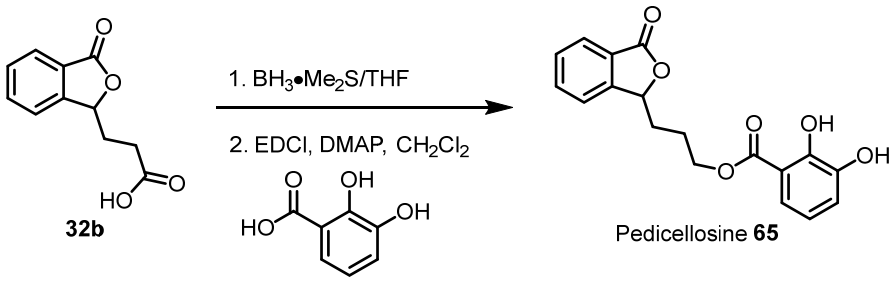


Figure S10. Comparison of synthetic and literature ^{13}C NMR spectra of myrotheciumone A.

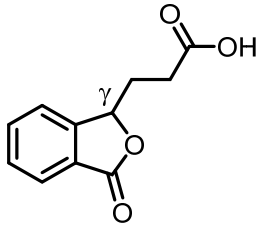
Total synthesis of pedicellosine



To an ice-cold solution of acid **32b** (10.3 mg, 0.05 mmol) in THF (1 mL), a borane dimethyl sulfide complex (0.4 mL, 0.08 mmol) was added dropwise. The solution was warmed at room temperature and stirred for overnight. Then the reaction was cooled at 0 °C and quenched with MeOH (0.5 mL) and stirred for 10 min. The residue was dissolved in EtOAc, washed with brine, dried over Na_2SO_4 and concentrated in vacuo to obtain the alcohol, which was used in the next step without further purification.

To a solution of the alcohol (0.05 mmol), 2,3-dihydroxybenzoic acid (11.6 mg, 0.075 mmol) in CH_2Cl_2 (1 mL). EDCI (14.4 mg, 0.075 mmol), DMAP (1.2 mg, 0.01 mmol) was added. The mixture was stirred at room temperature for 24 h. After the addition of water, the solution was extracted with CH_2Cl_2. The solvent was removed under reduced pressure, and the crude product was further purified by flash chromatography (hexane/EA 3:1) to obtain the desired product in 90% yield for two steps (14.8 mg, 0.045 mmol, colorless oil).

Please refer to Section 2.5 for the synthesis of **32b**.



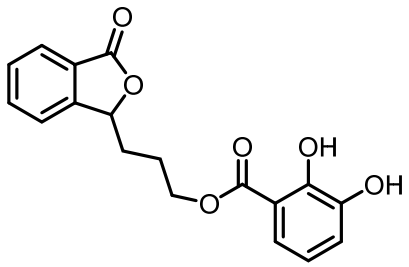
32b

3-(3-Oxo-1,3-dihydroisobenzofuran-1-yl)propanoic acid 32b (as free carboxylic acid)

^{1}H NMR (600 MHz, CD_3OD) δ 7.86 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.77 (td, *J* = 7.5, 1.1 Hz, 1H), 7.66 – 7.57 (m, 2H), 5.65 (dd, *J* = 8.3, 3.3 Hz, 1H), 2.54 – 2.43 (m, 2H), 2.43 – 2.36 (m, 1H), 2.02 – 1.92 (m, 1H).

^{13}C NMR (151 MHz, CD_3OD) δ 176.2, 172.4, 151.2, 135.7, 130.5, 127.0, 126.3, 123.5, 82.2, 31.0, 30.3.

HRMS (ESI-TOF) Calculated for $C_{11}H_9O_4$, $[M-H]^-$, 205.0506, found: 205.0510.



Pedicellosine **65**

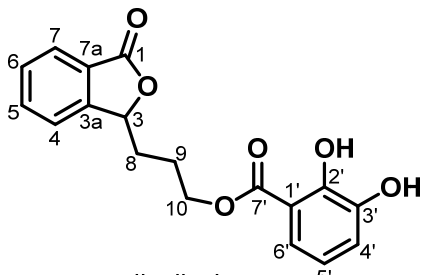
3-(3-Oxo-1,3-dihydroisobenzofuran-1-yl)propyl 2,3-dihydroxybenzoate, pedicellosine 65

^{1}H NMR (600 MHz, CD_3OD) δ 7.88 (d, *J* = 7.5 Hz, 1H), 7.78 (td, *J* = 7.5, 1.1 Hz, 1H), 7.64 (d, *J* = 7.6 Hz, 1H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.36 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.03 (dd, *J* = 7.9, 1.5 Hz, 1H), 6.77 (t, *J* = 7.9 Hz, 1H), 5.71 (dd, *J* = 7.6, 3.9 Hz, 1H), 4.58 – 4.17 (m, 2H), 2.34 (ddt, *J* = 13.7, 8.7, 3.6 Hz, 1H), 2.02 – 1.95 (m, 1H), 1.95 – 1.84 (m, 2H).

^{13}C NMR (151 MHz, CD_3OD) δ 172.5, 171.7, 151.5, 151.4, 147.2, 135.7, 130.5, 127.0, 126.3, 123.4, 121.8, 121.2, 120.1, 113.9, 82.7, 65.9, 32.2, 25.2.

HRMS (ESI-TOF) Calculated for $C_{18}H_{17}O_6$, $[M+H]^+$, 329.1020, found: 329.1032.

Comparison of synthetic and literature NMR data of pedicellosine:



pedicellosine

Atom Number	δ^1H/ppm (synthetic) 600 MHz, CD_3OD	δ^1H/ppm (literature)(*37*) 300 MHz, CD_3OD
1	-	-
3	5.71, dd (7.6, 3.9)	5.68, dd (7.5, 3.5)
4	7.64, d (7.6)	7.62, d (7.5)
5	7.78, td (7.5, 1.1)	7.75, td (7.5, 7.5, 1)
6	7.62, t (7.5)	7.59 td (7.5, 7.5, 1)
7	7.89, d (7.5)	7.86 d (7.5)
8	2.34, ddt (13.7, 8.7, 3.6)	2.29, m
	1.92, m	1.88, m
9	1.99, m	1.95, m
10	4.43, m	4.41, m
1'	-	-
2'	-	-
3'	-	-
4'	7.03, dd (7.9, 1.5)	7.01, dd (8, 1.5)
5'	6.77, t (7.9)	6.75, t (8)
6'	7.36, dd (8.1, 1.5)	7.33, dd (8, 1.5)
7'	-	-

Table S14. Comparison of synthetic and literature ^{1}H NMR data of pedicellosine.

The slight difference in ^{1}H NMR chemical shifts is due to different calibration.

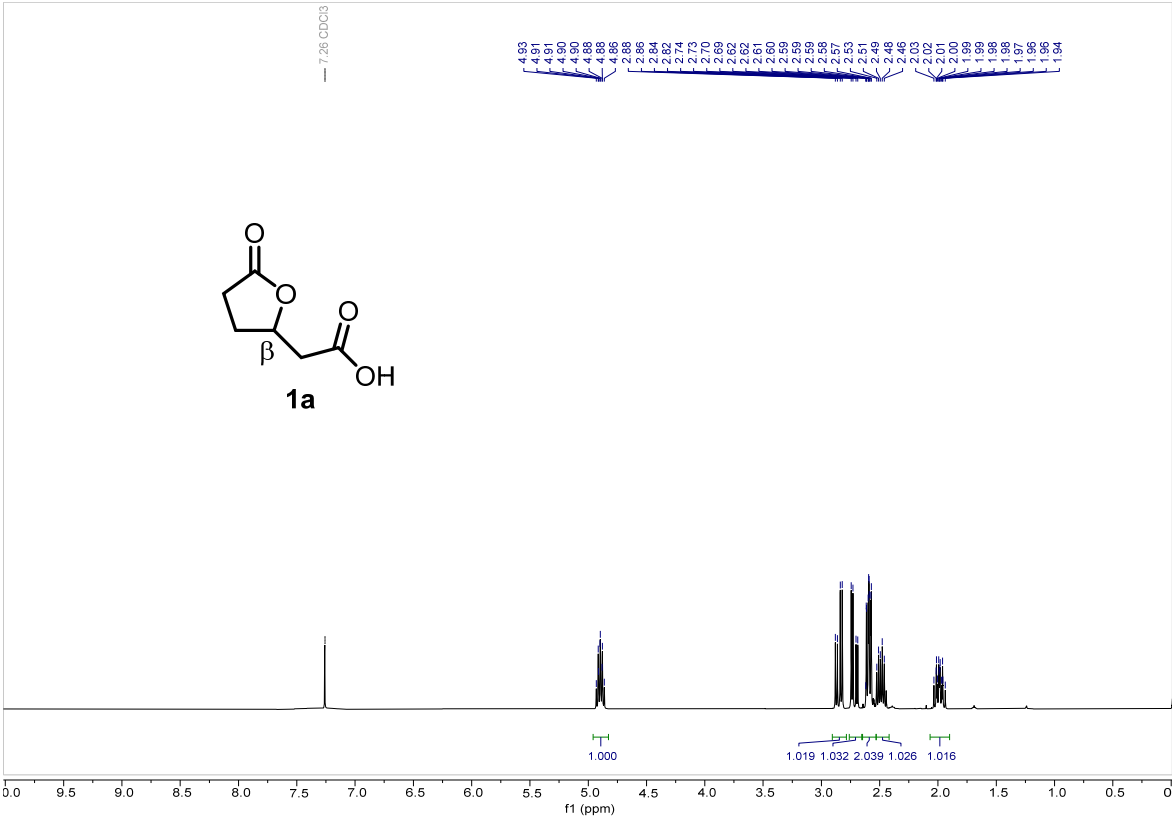
Atom Number	δ^{13}C/ppm (synthetic) 151 MHz, CD_3OD	δ^{13}C/ppm (literature)(*37*) 76 MHz, CD_3OD
1	172.5	171.7
3	82.7	82.7
3a	151.5	151.5
4	123.4	123.4
5	135.7	135.7
6	130.5	130.5
7	126.3	126.3
7a	127.0	127.0
8	25.2	25.2
9	32.2	32.2
10	65.9	66.0
1'	113.9	115.0
2'	151.4	151.5
3'	147.2	147.2
4'	121.8	121.8
5'	120.1	120.1
6'	121.2	121.3
7'	171.7	171.7

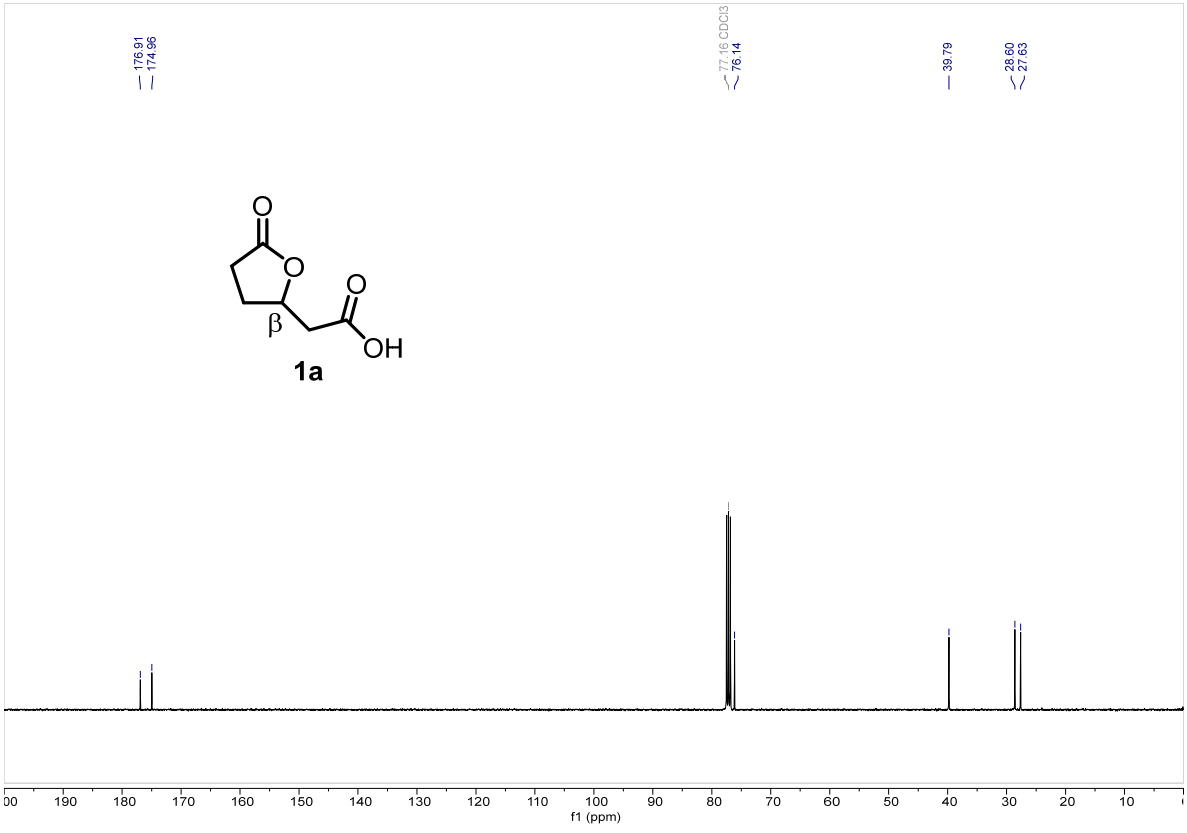
Table S15. Comparison of synthetic and literature ^{13}C NMR data of pedicellosine.

The slight difference in ^{13}C NMR chemical shifts is due to different calibration.

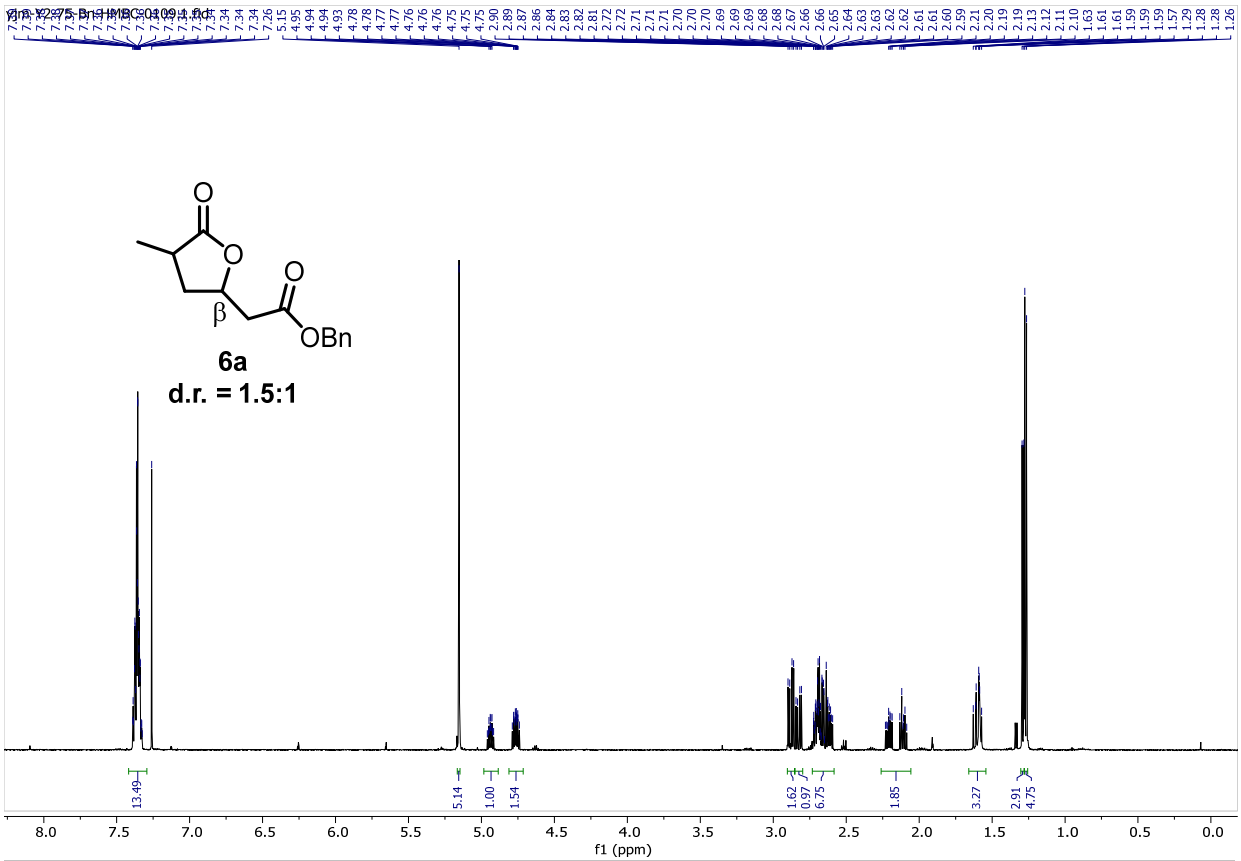
4. NMR Spectra

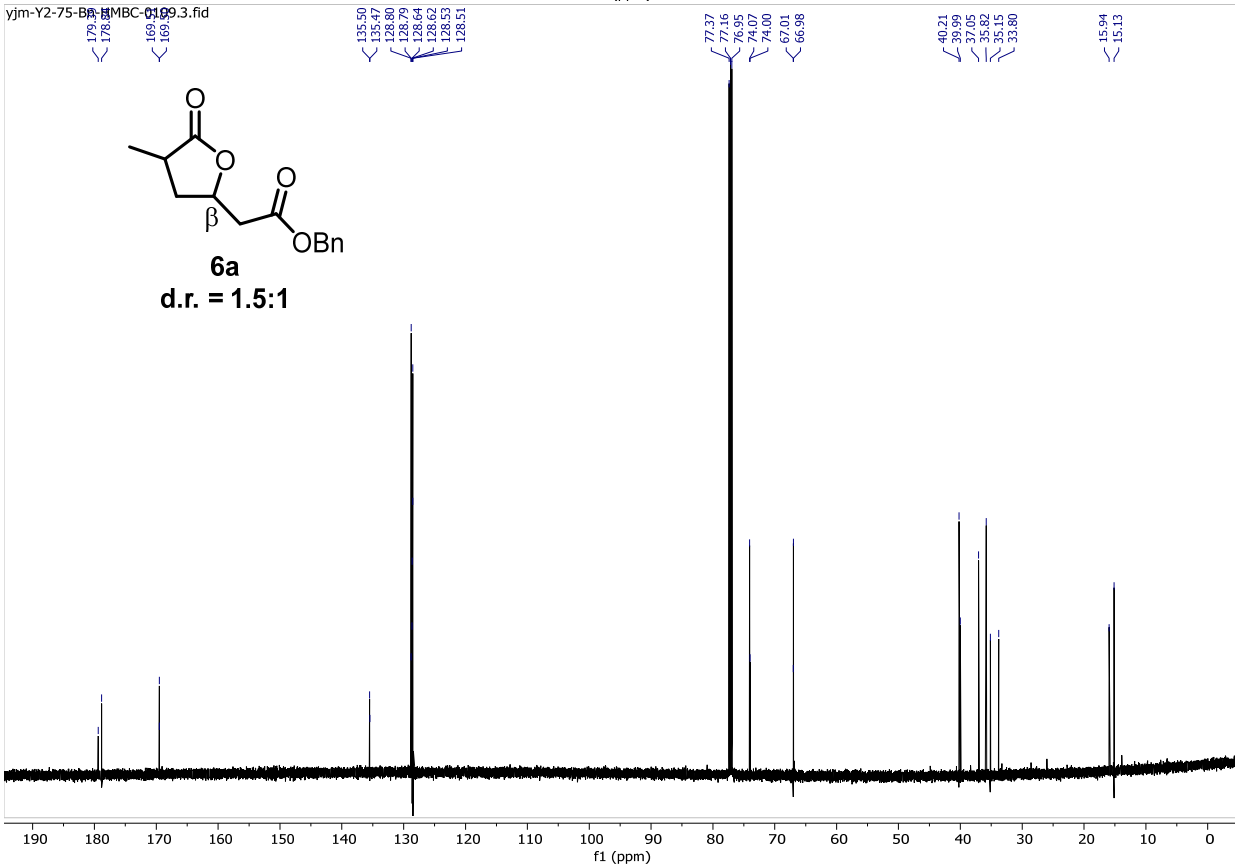
2-(5-Oxotetrahydrofuran-2-yl)acetic acid 1a



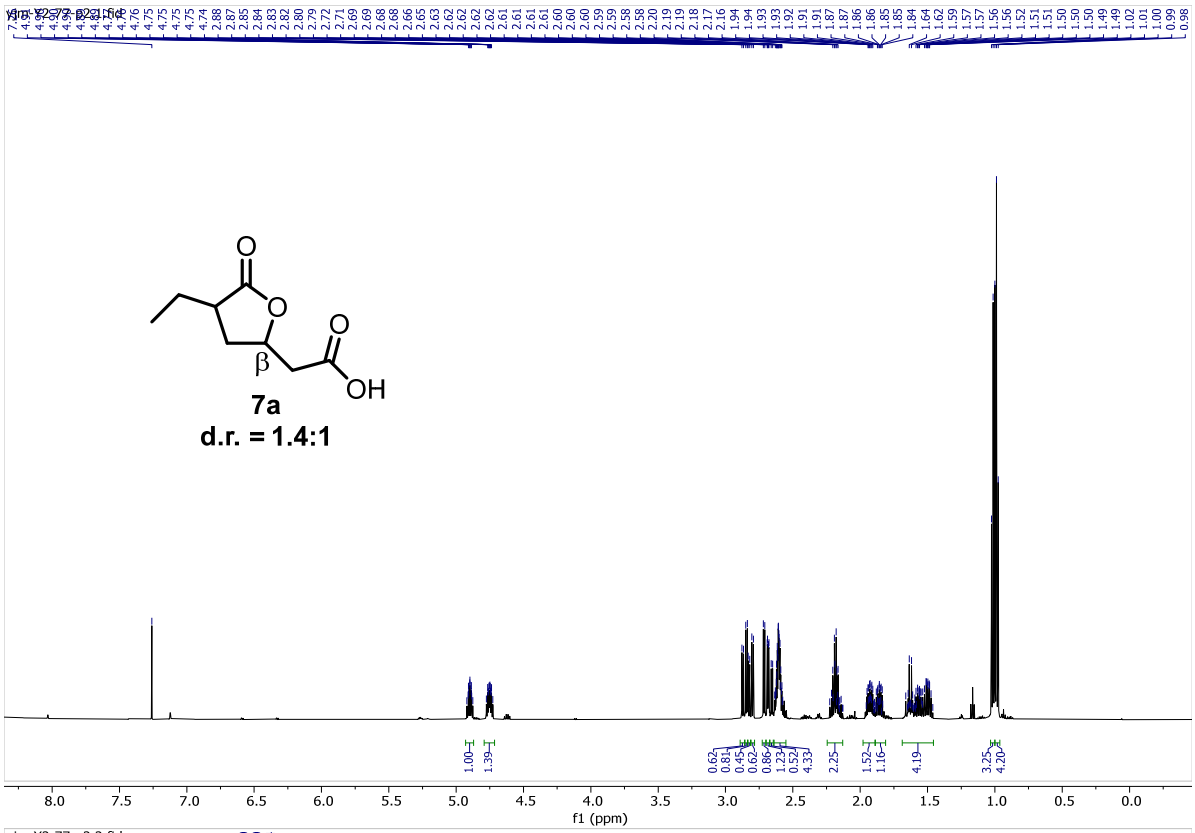


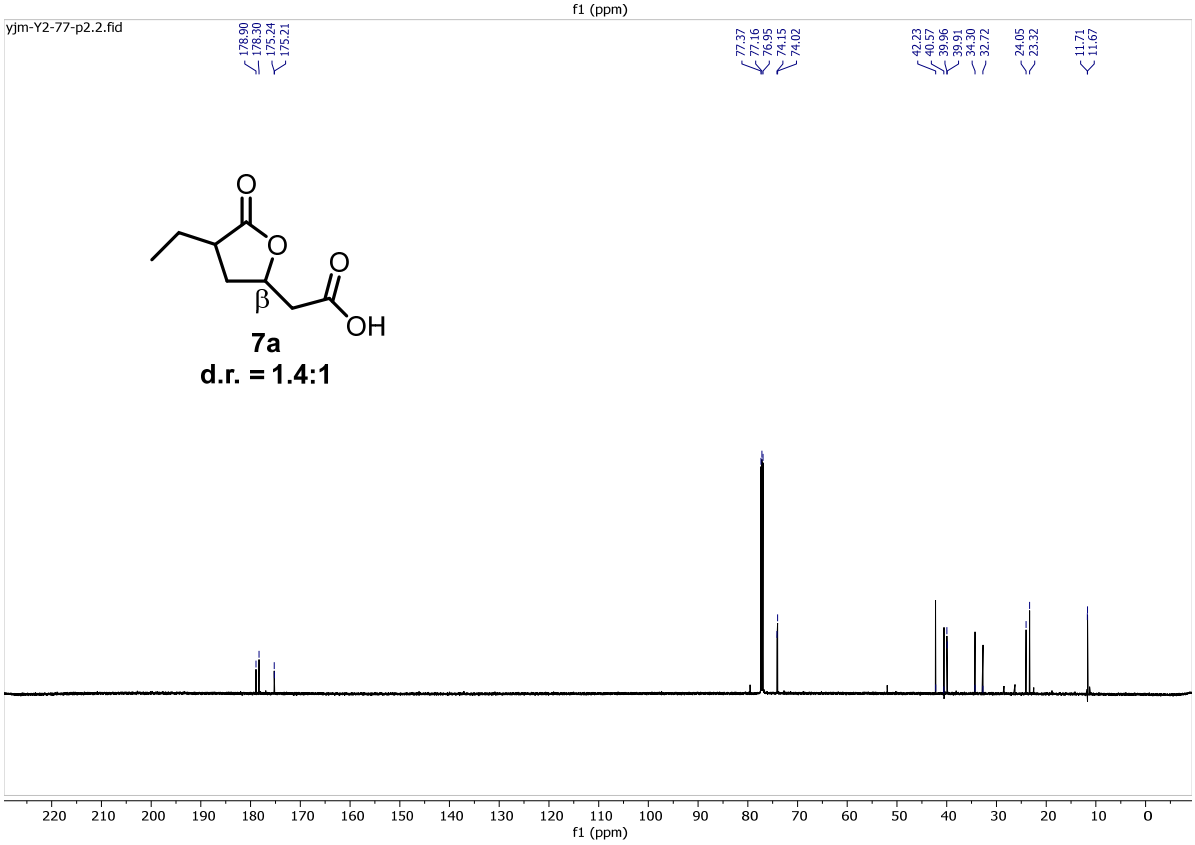
Benzyl 2-(4-methyl-5-oxotetrahydrofuran-2-yl)acetate 6a



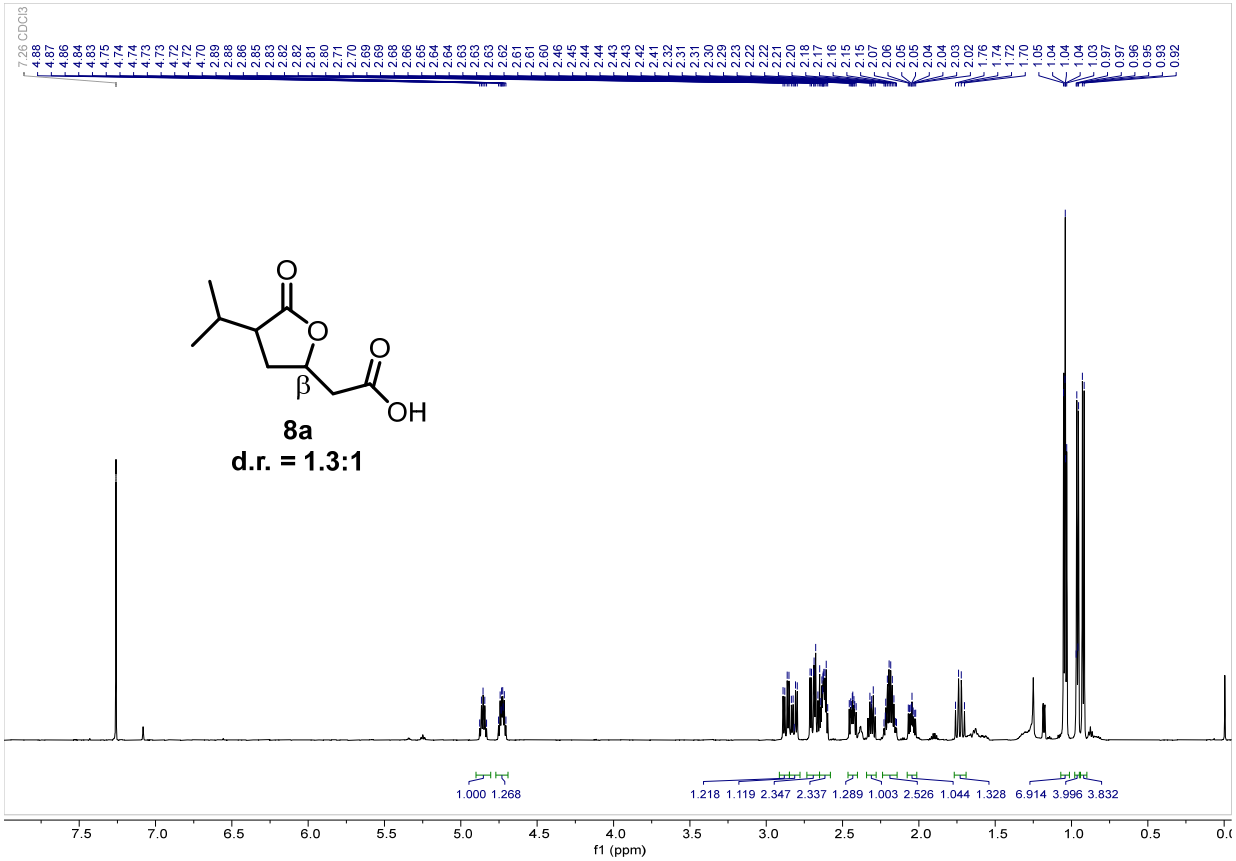


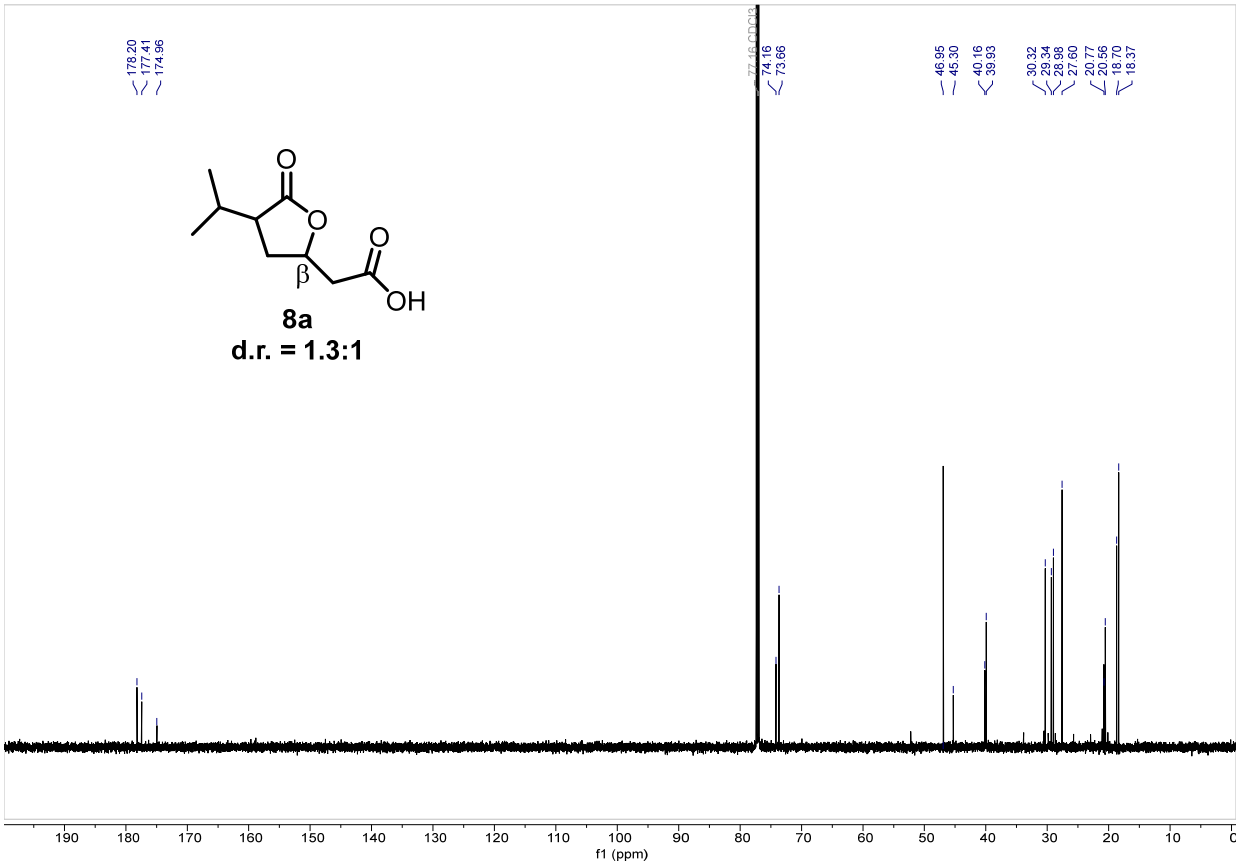
2-(4-Ethyl-5-oxotetrahydrofuran-2-yl)acetic acid 7a



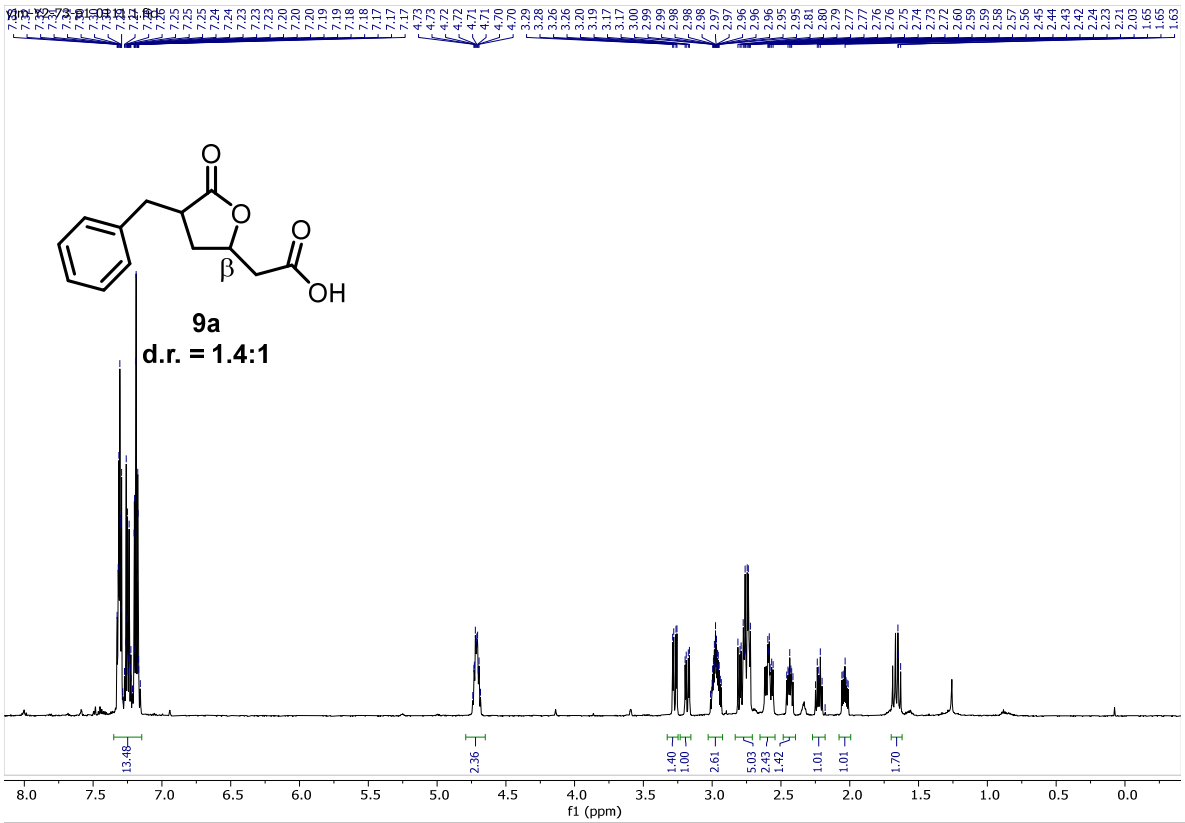


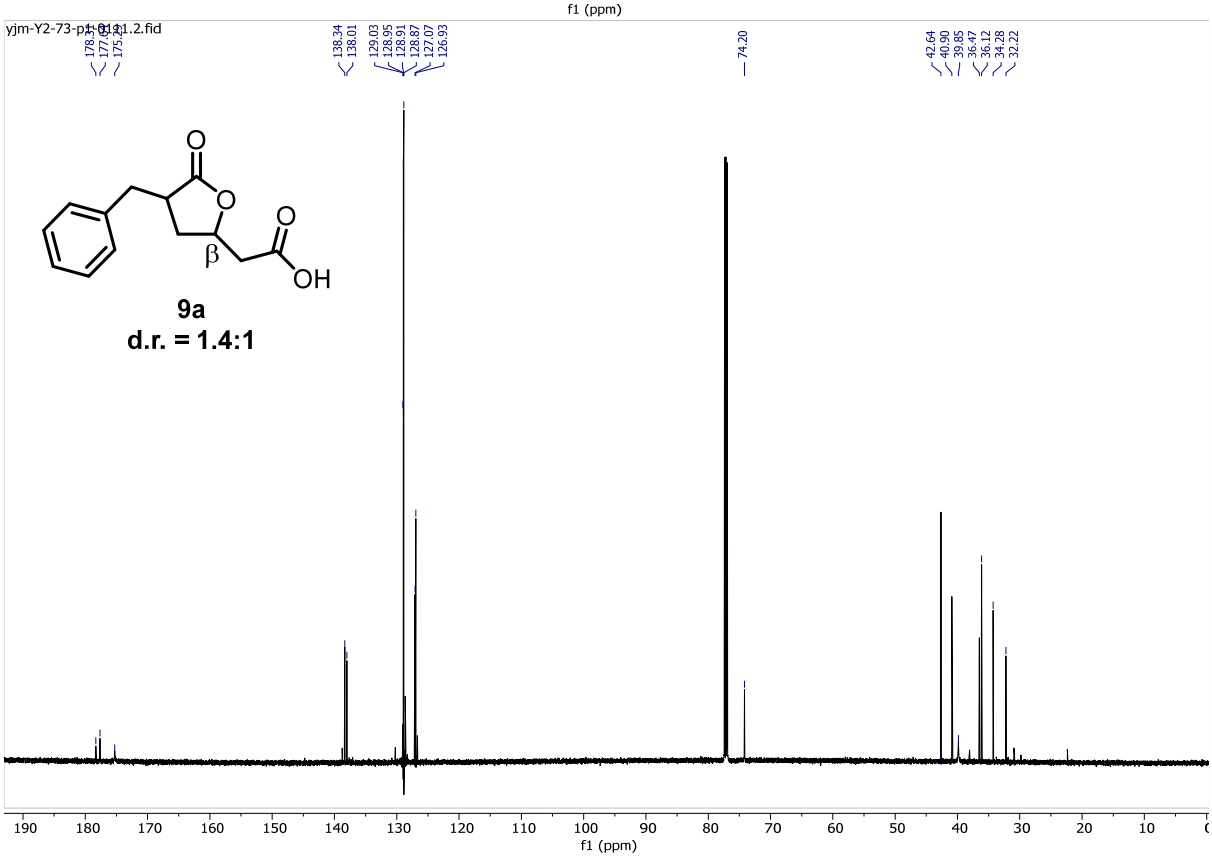
2-(4-Isopropyl-5-oxotetrahydrofuran-2-yl)acetic acid 8a



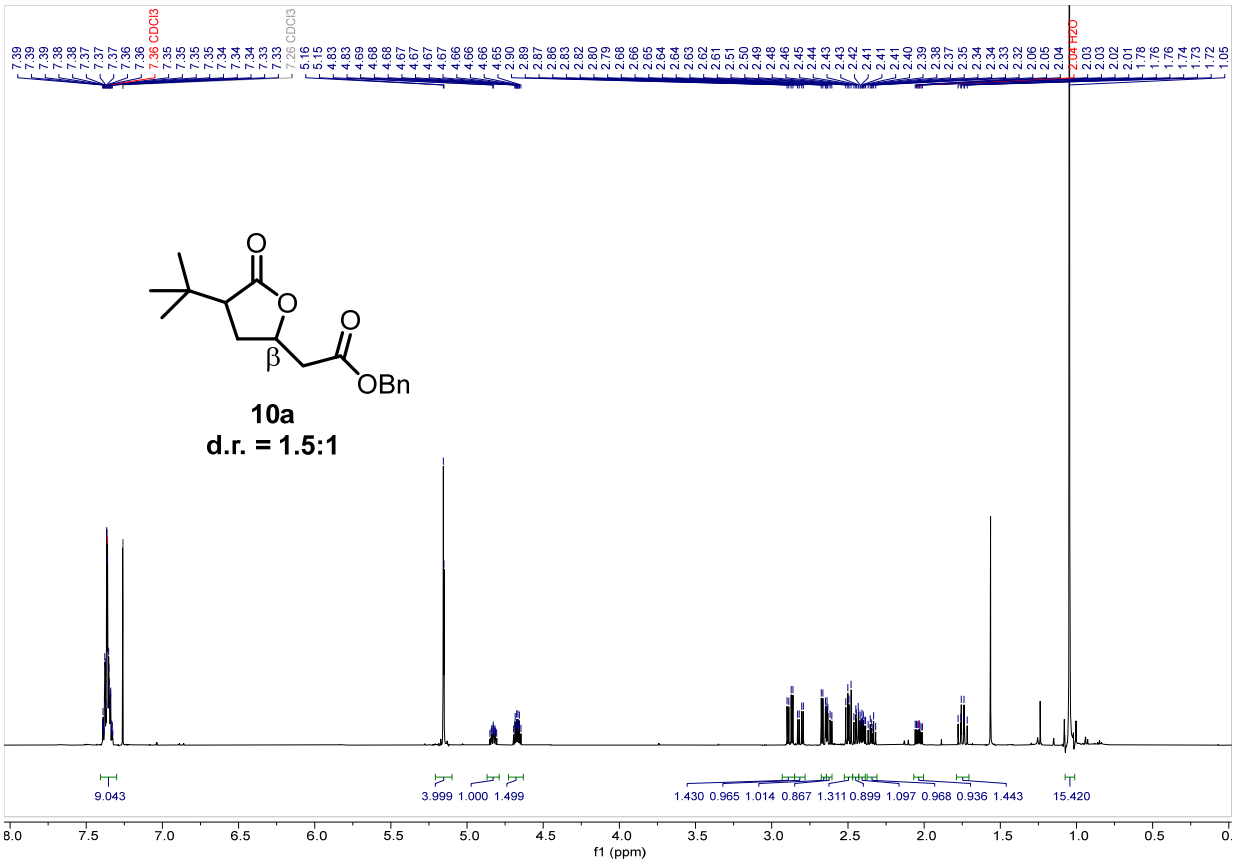


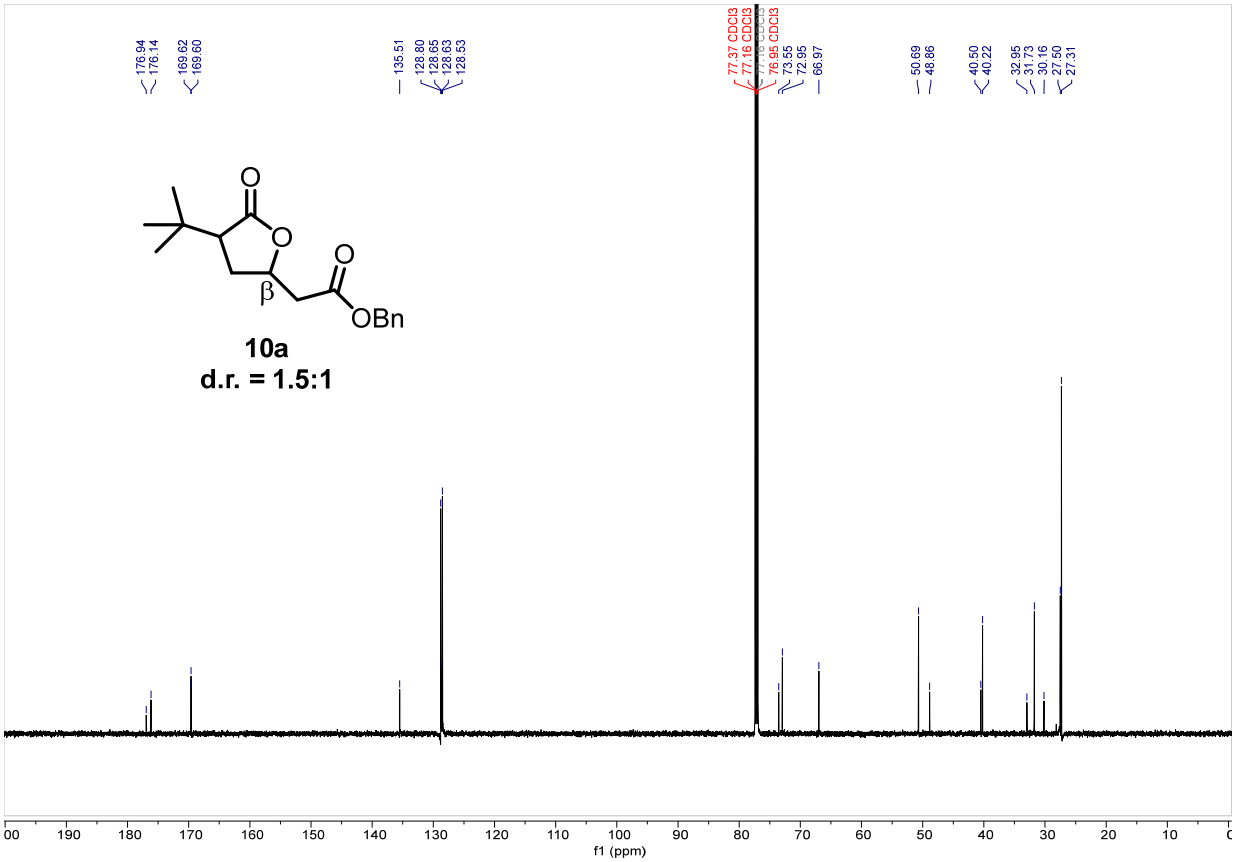
2-(4-Benzyl-5-oxotetrahydrofuran-2-yl)acetic acid 9a



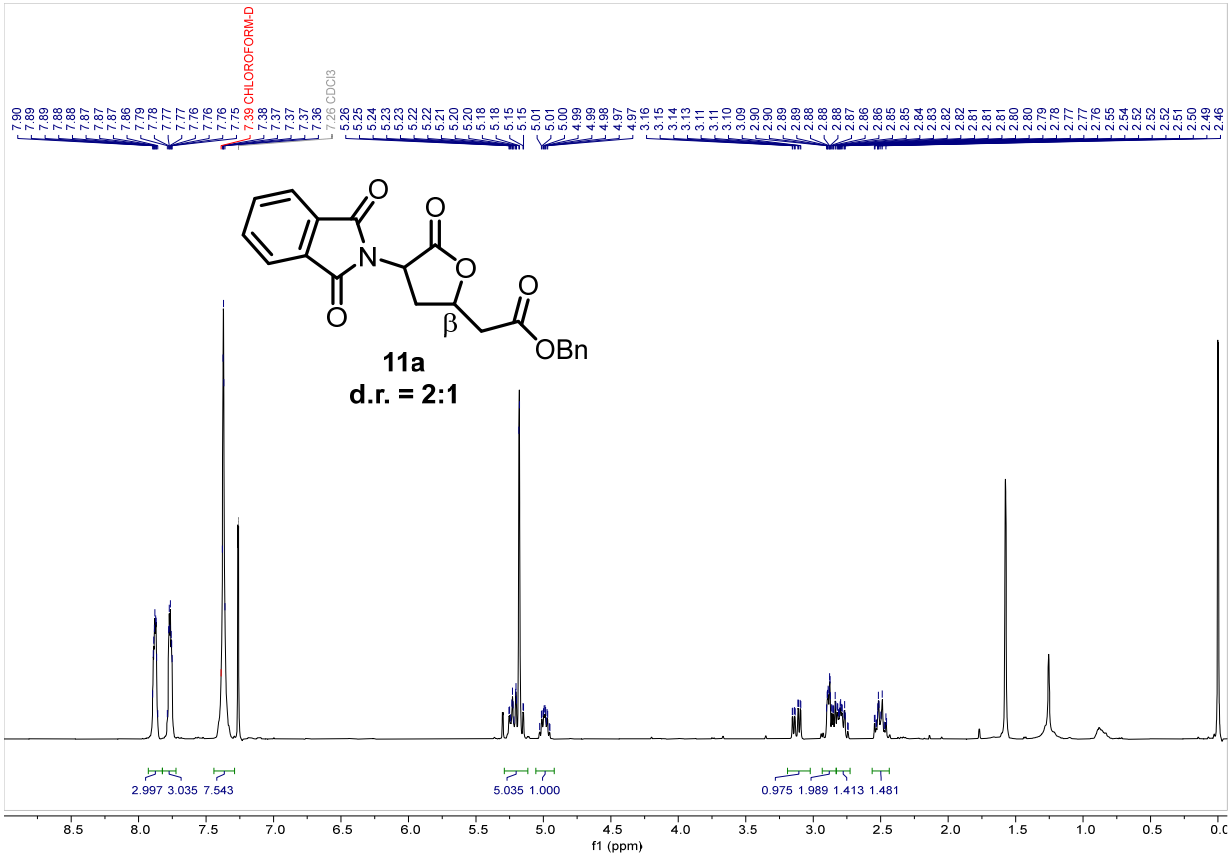


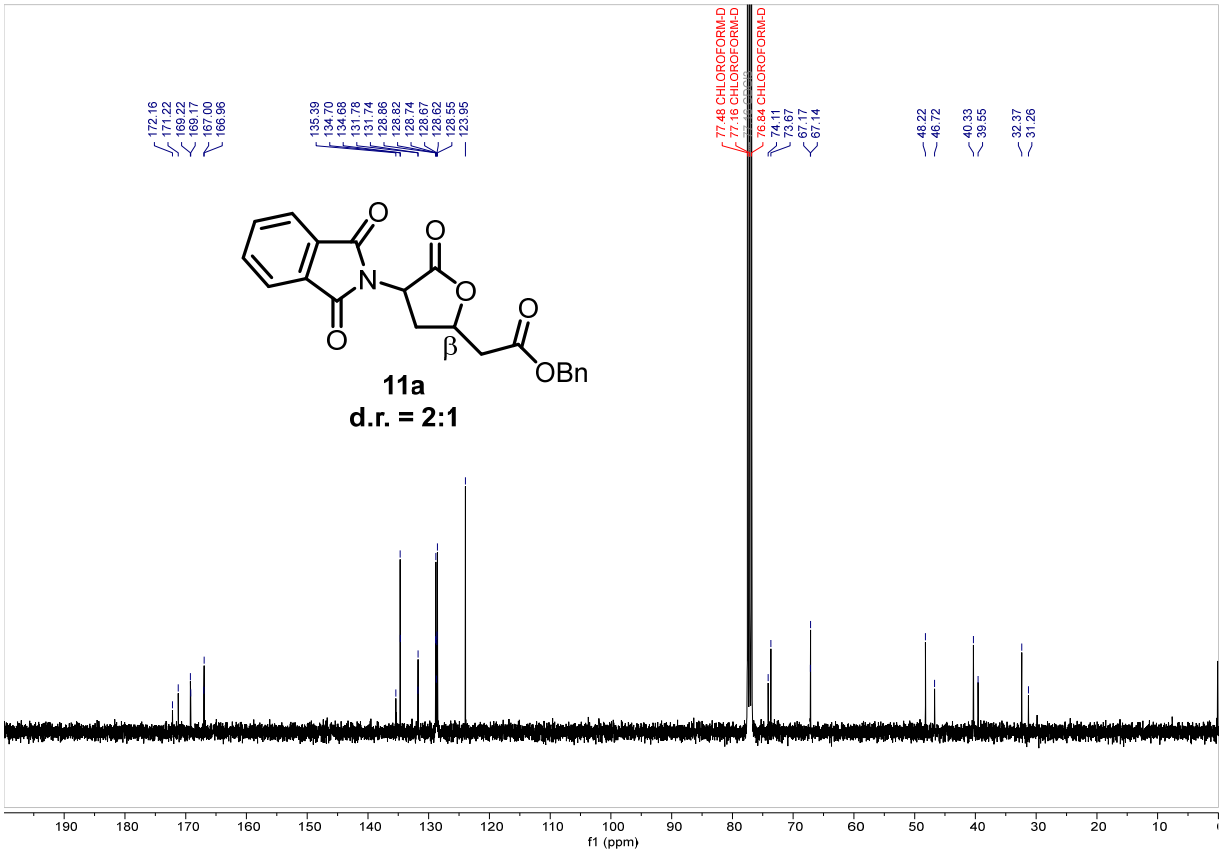
Benzyl 2-(4-(*tert*-butyl)-5-oxotetrahydrofuran-2-yl)acetate 10a



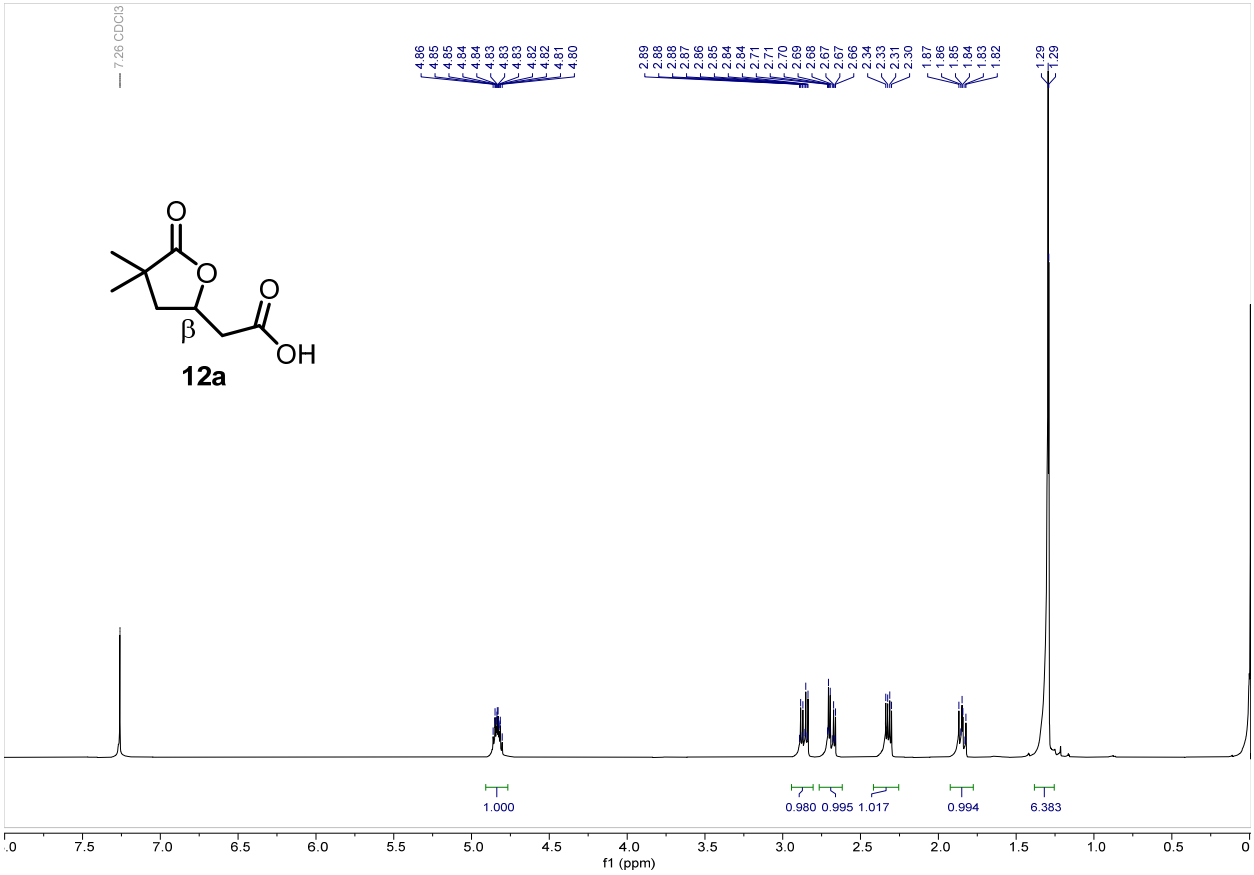


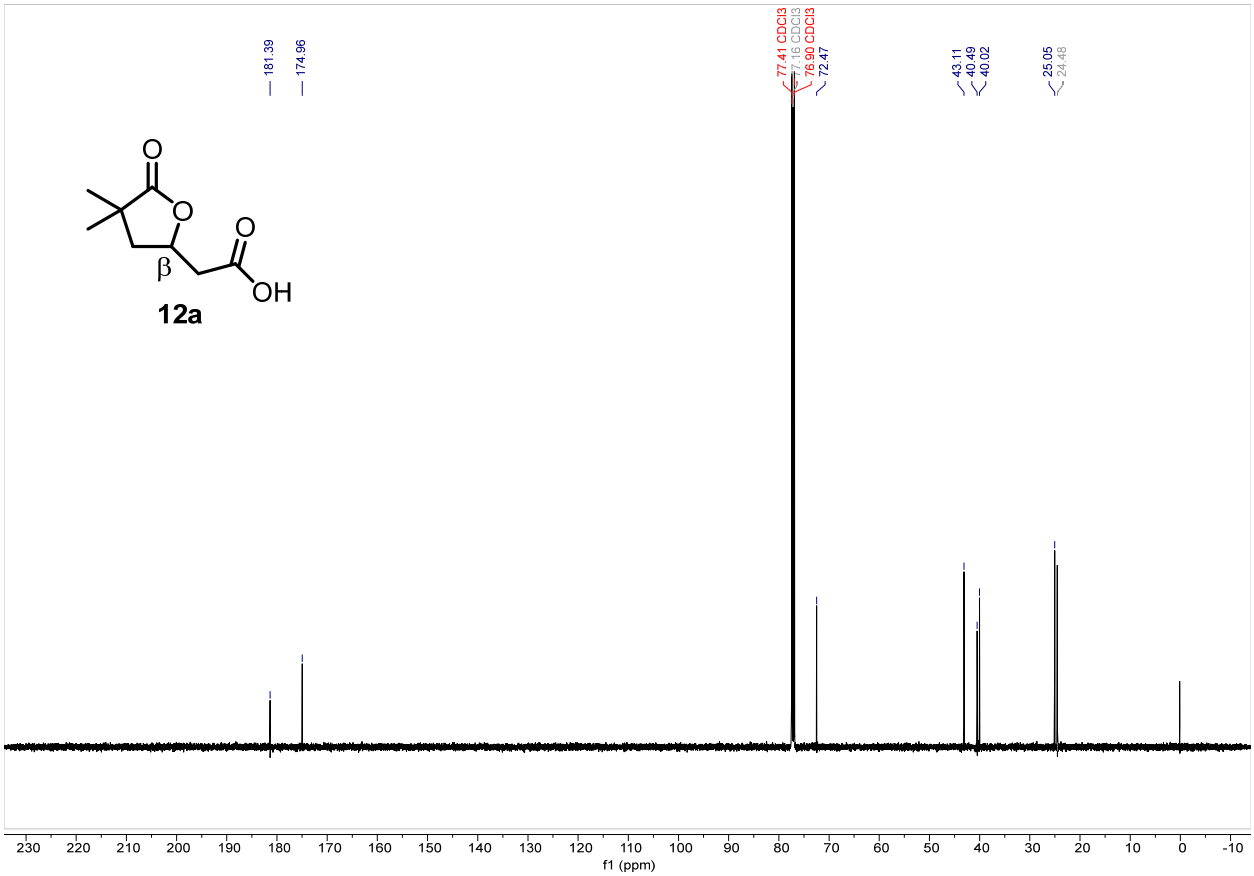
Benzyl 2-(4-(1,3-dioxoisoindolin-2-yl)-5-oxotetrahydrofuran-2-yl)acetate 11a



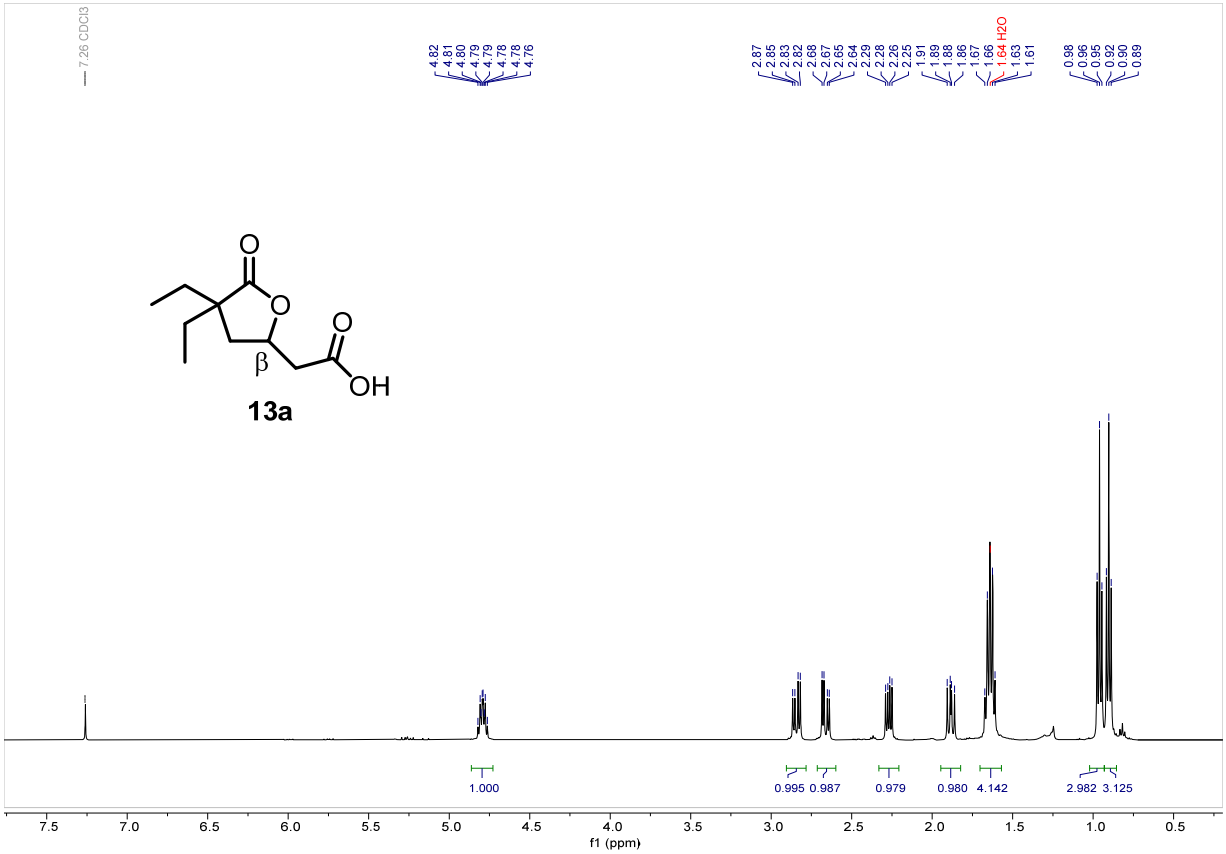


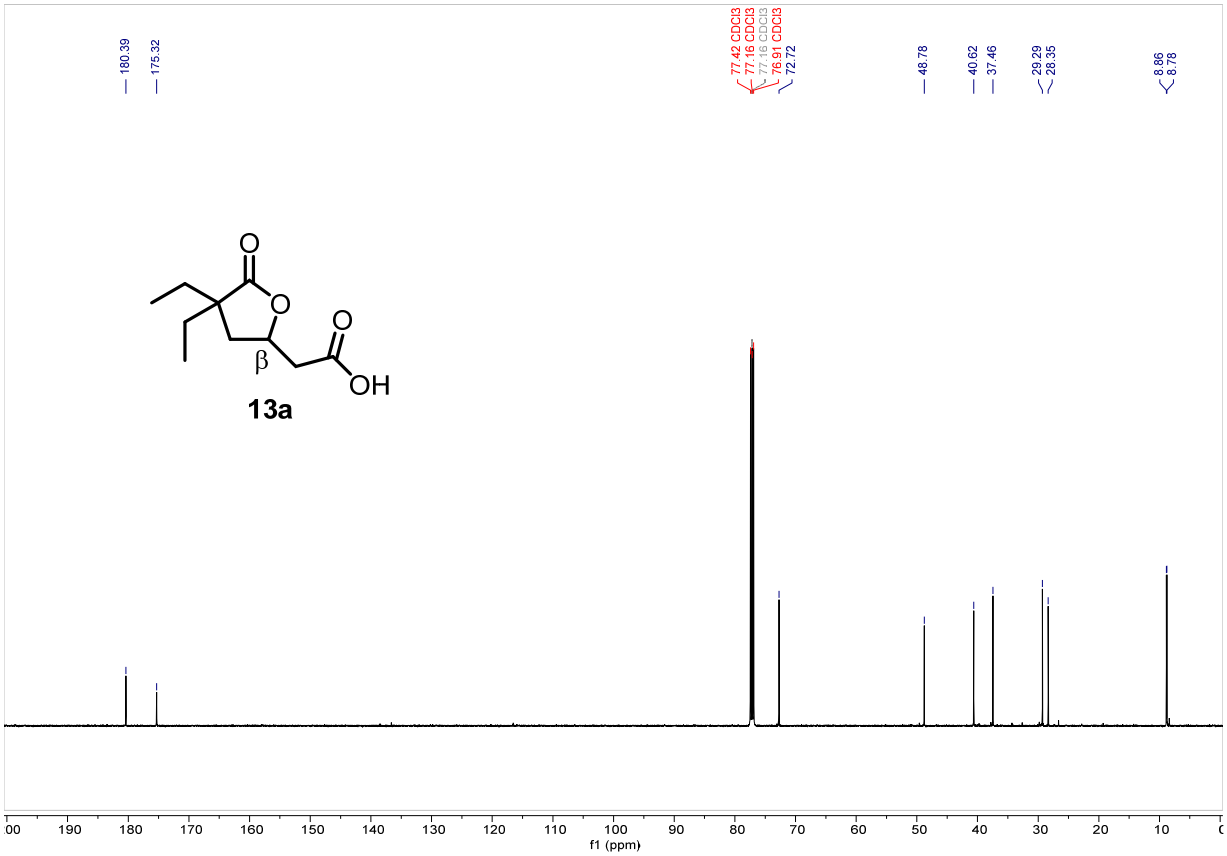
2-(4,4-Dimethyl-5-oxotetrahydrofuran-2-yl)acetic acid 12a



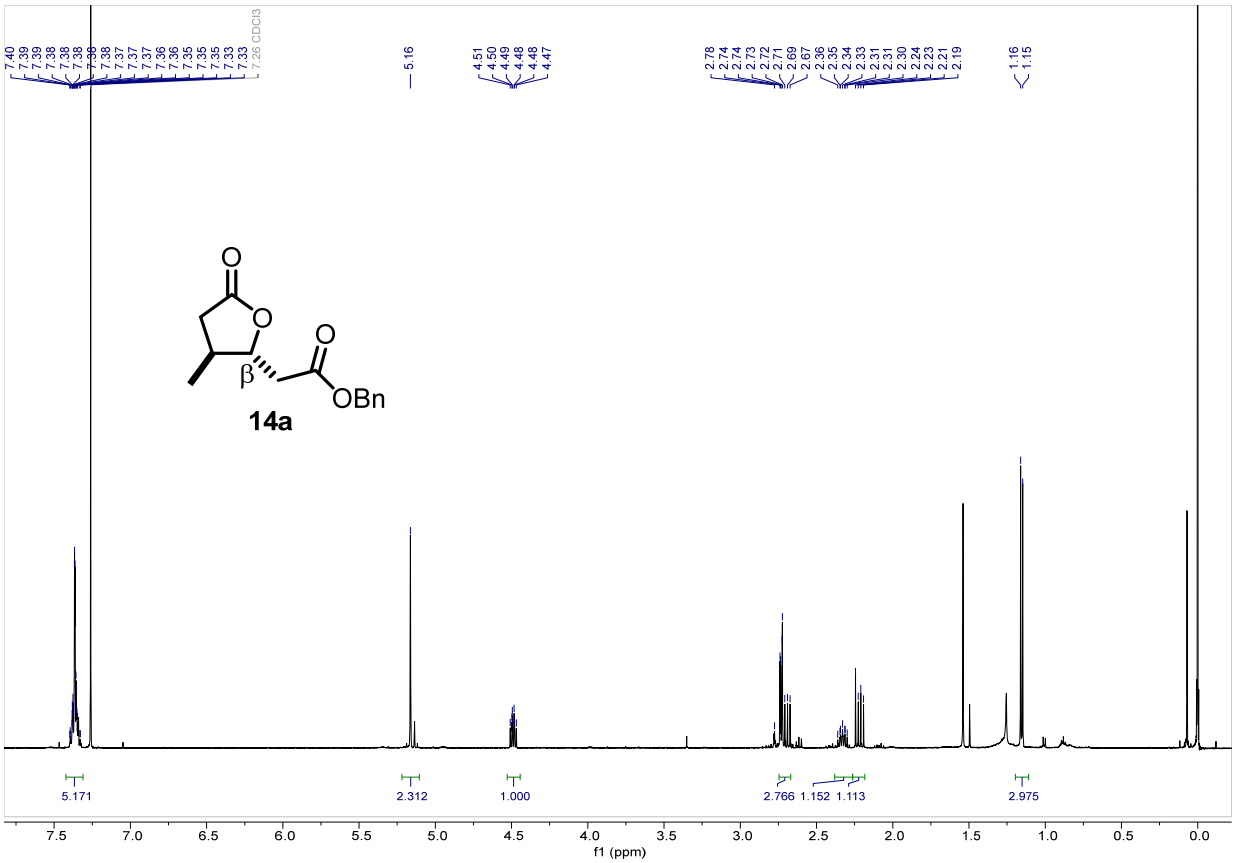


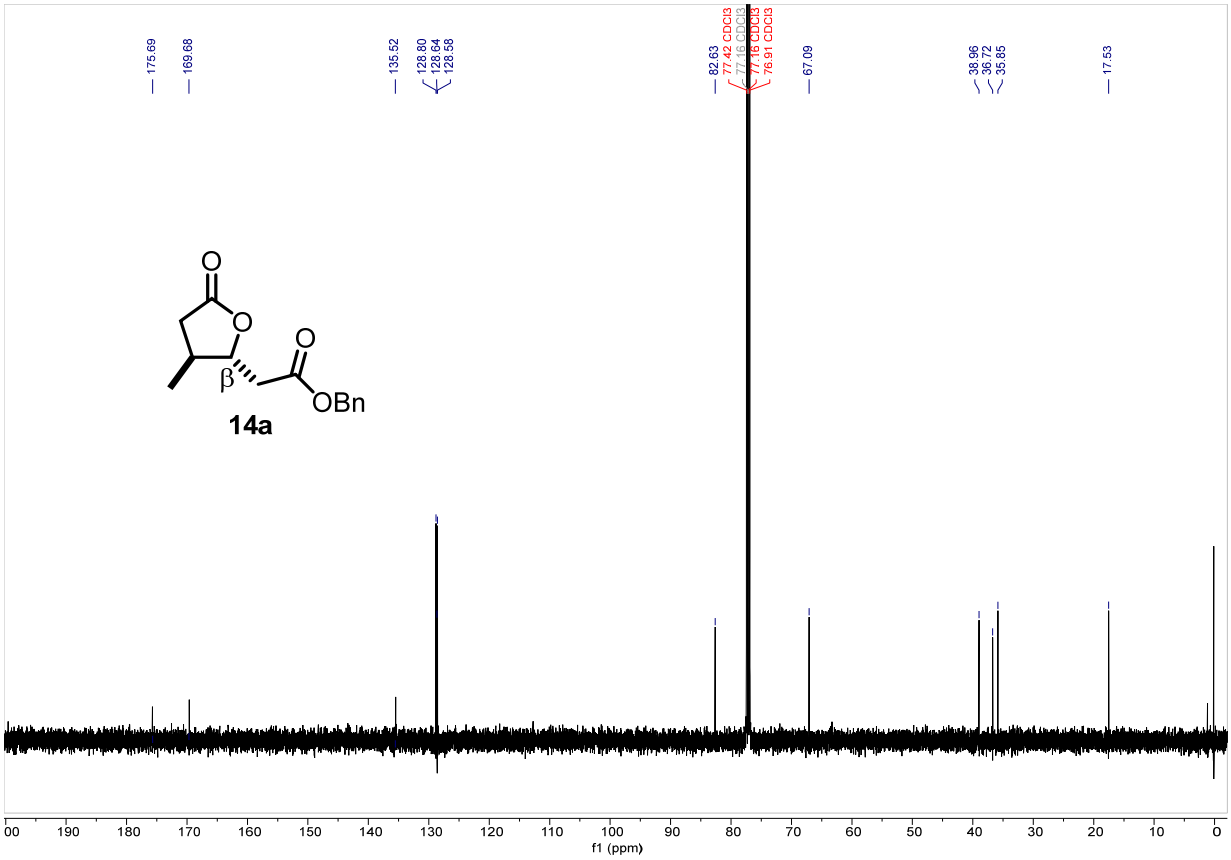
2-(4,4-Diethyl-5-oxotetrahydrofuran-2-yl)acetic acid 13a



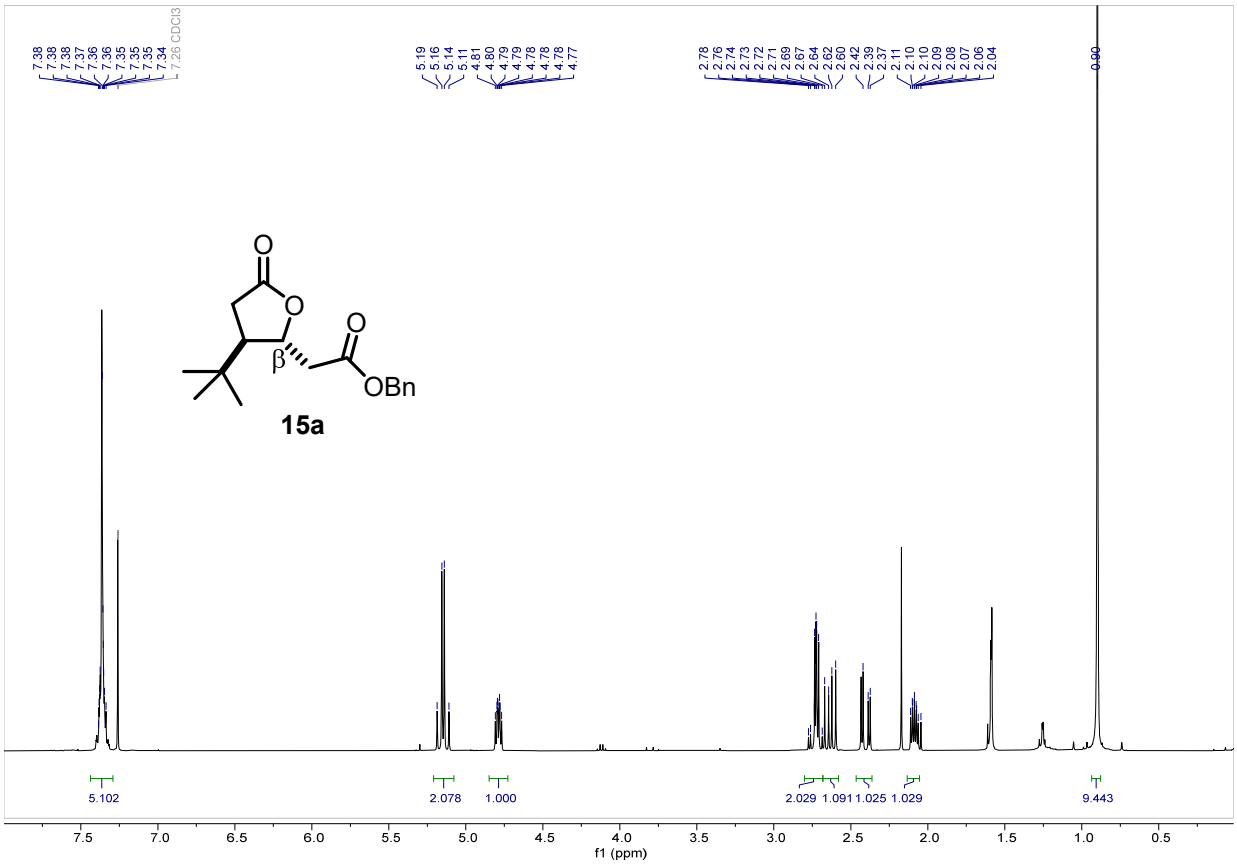


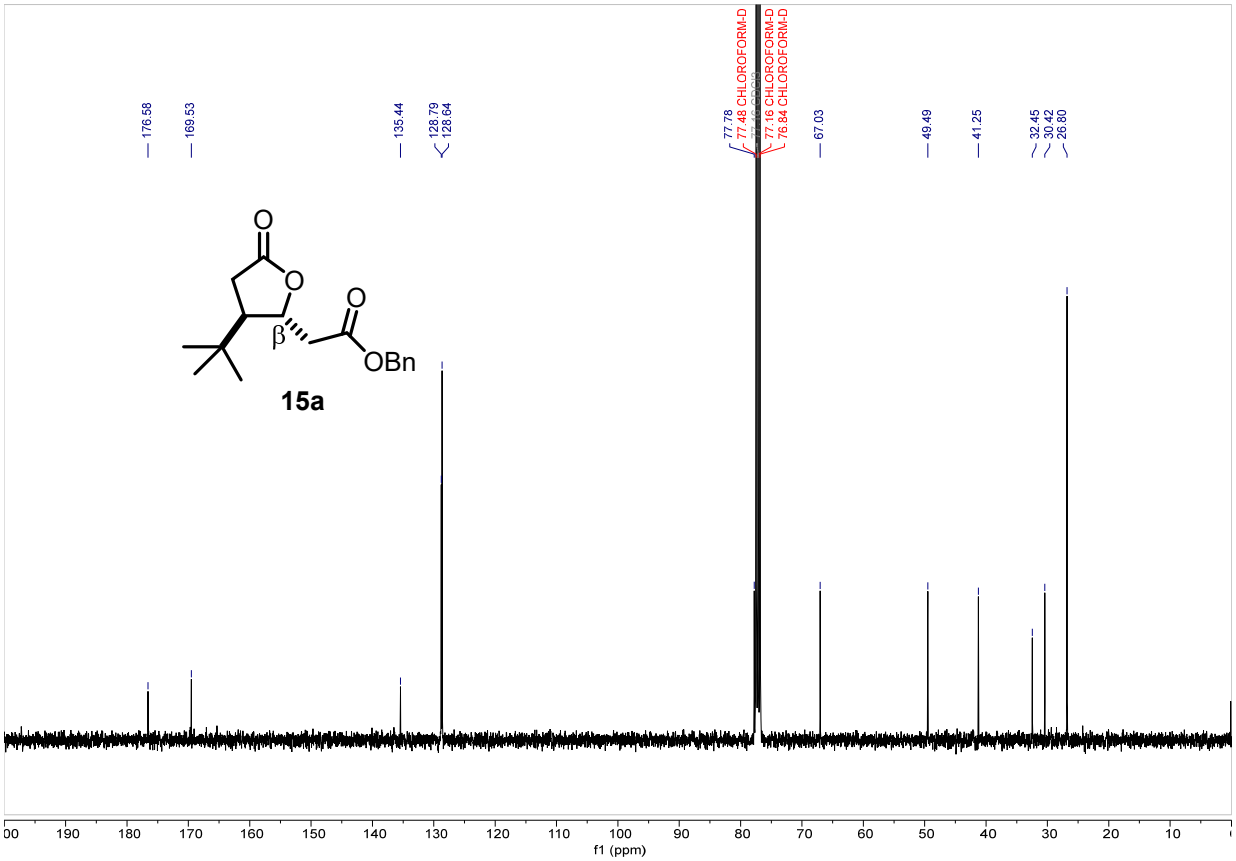
Benzyl 2-((2*R,3*S**)-3-methyl-5-oxotetrahydrofuran-2-yl)acetate 14a**



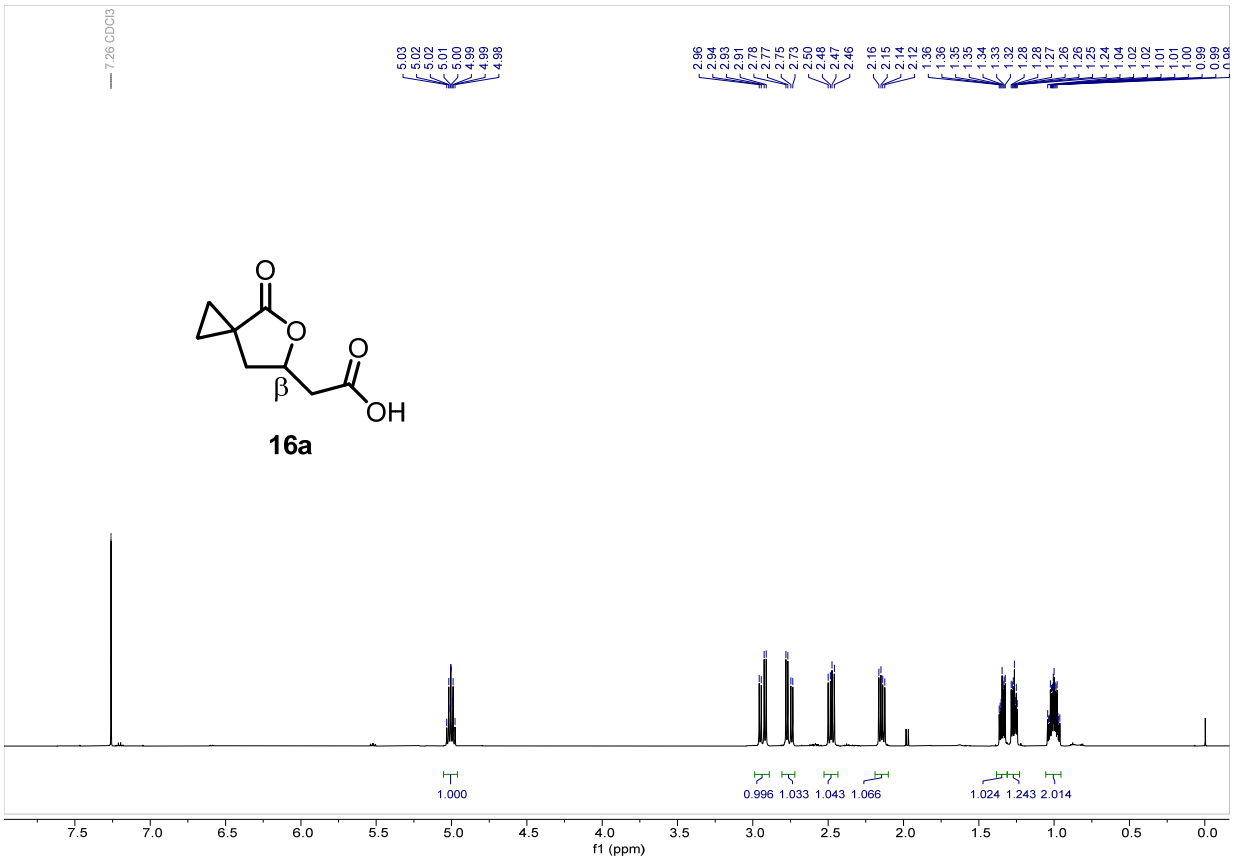


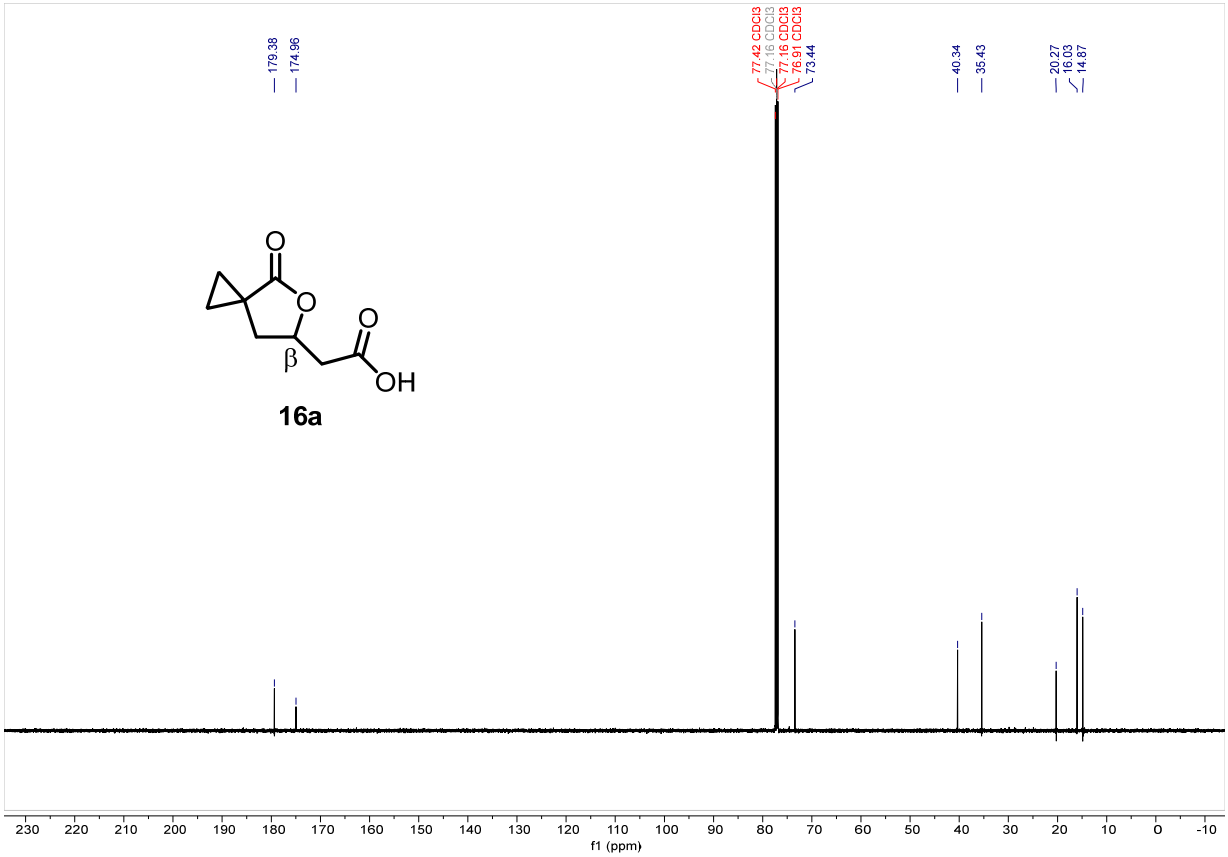
Benzyl 2-((2*R,3*R**)-3-(*tert*-butyl)-5-oxotetrahydrofuran-2-yl)acetate 15a**



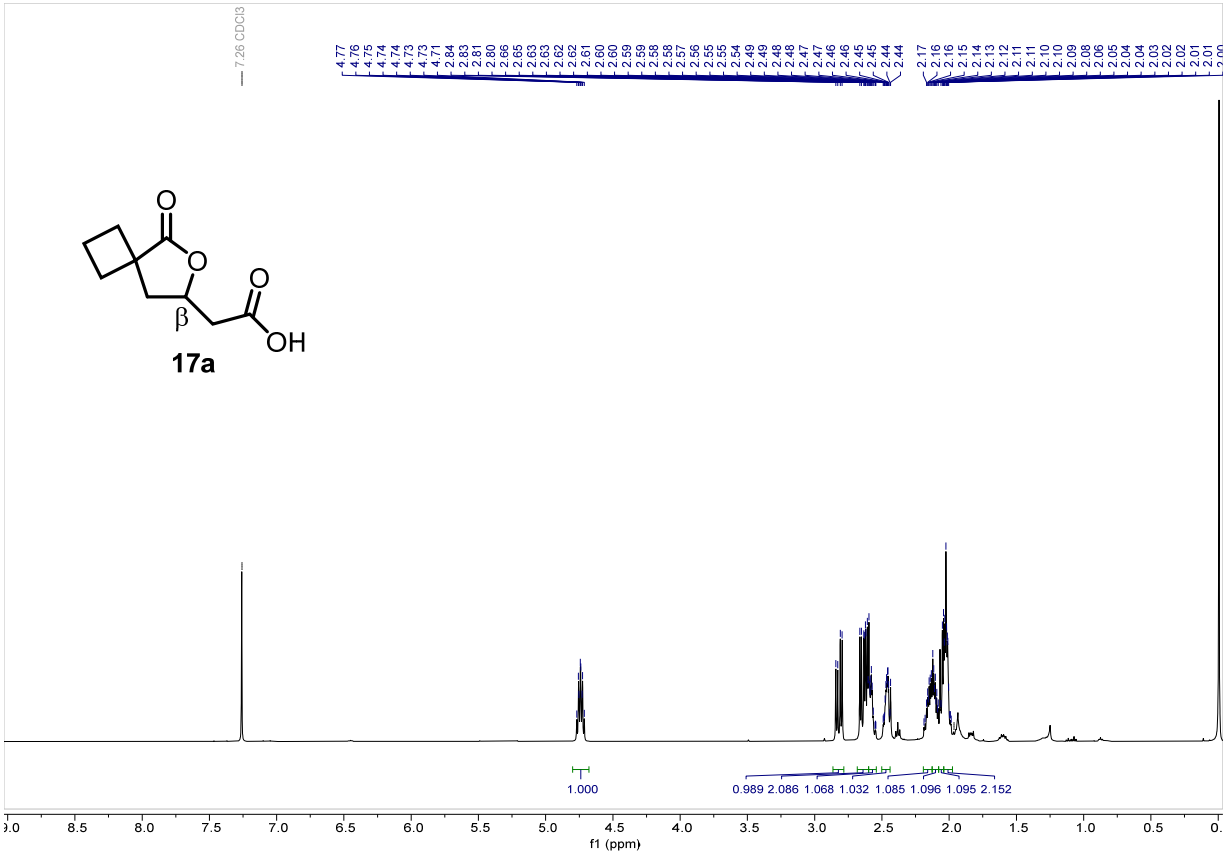


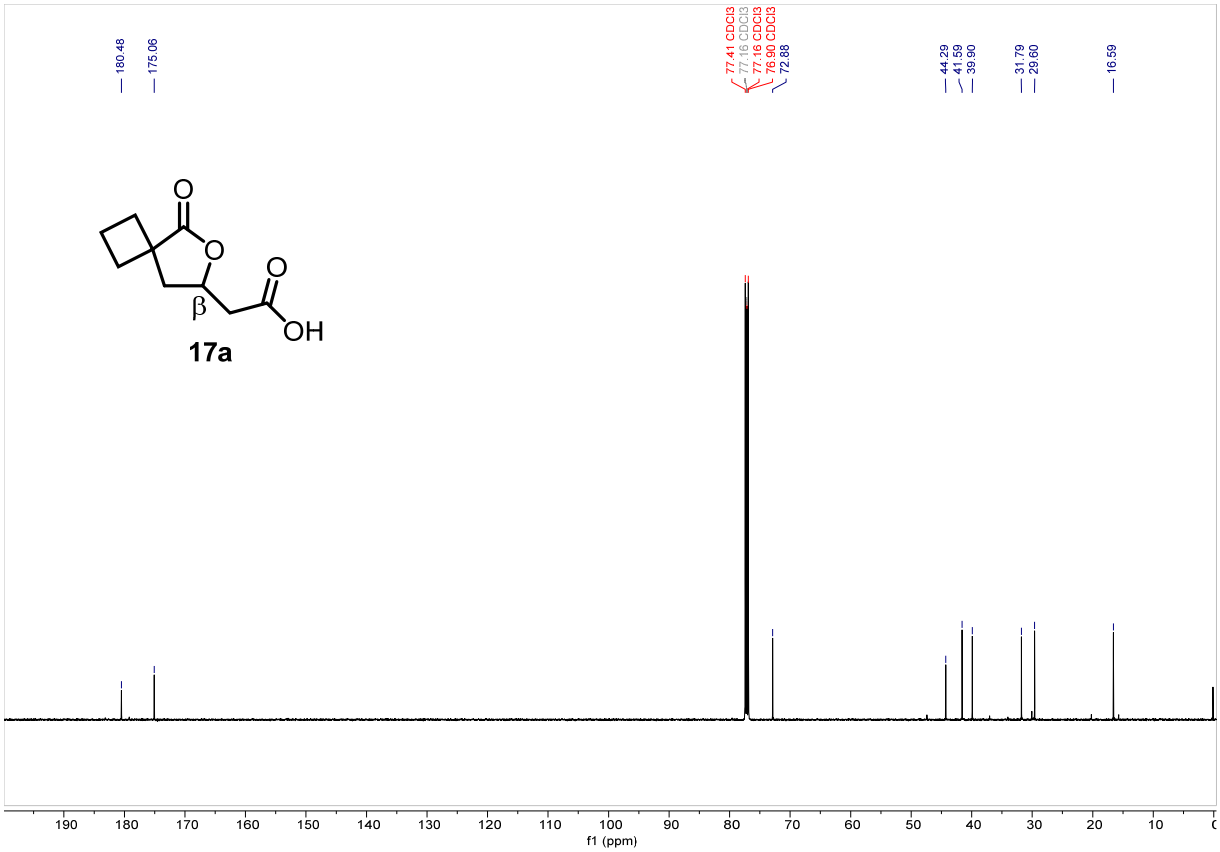
2-(4-Oxo-5-oxaspiro[2.4]heptan-6-yl)acetic acid 16a



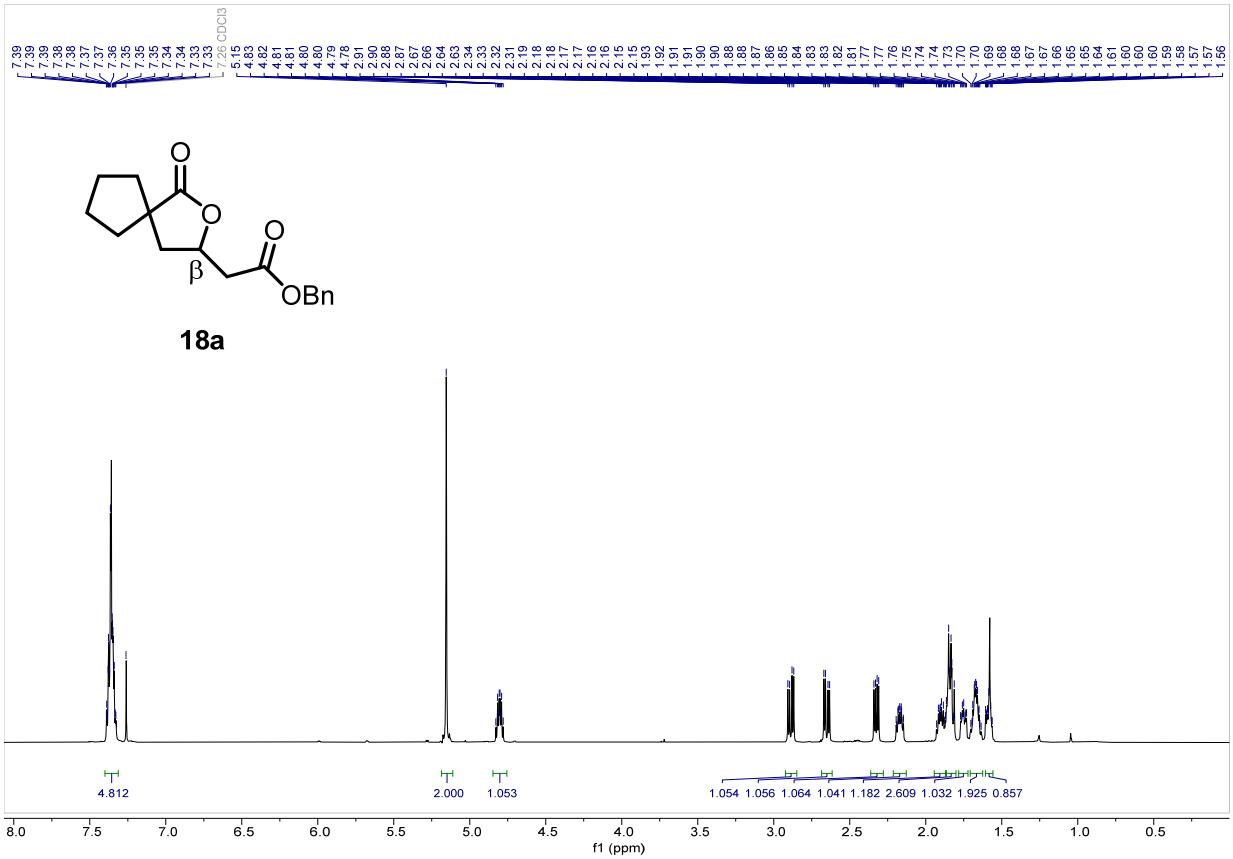


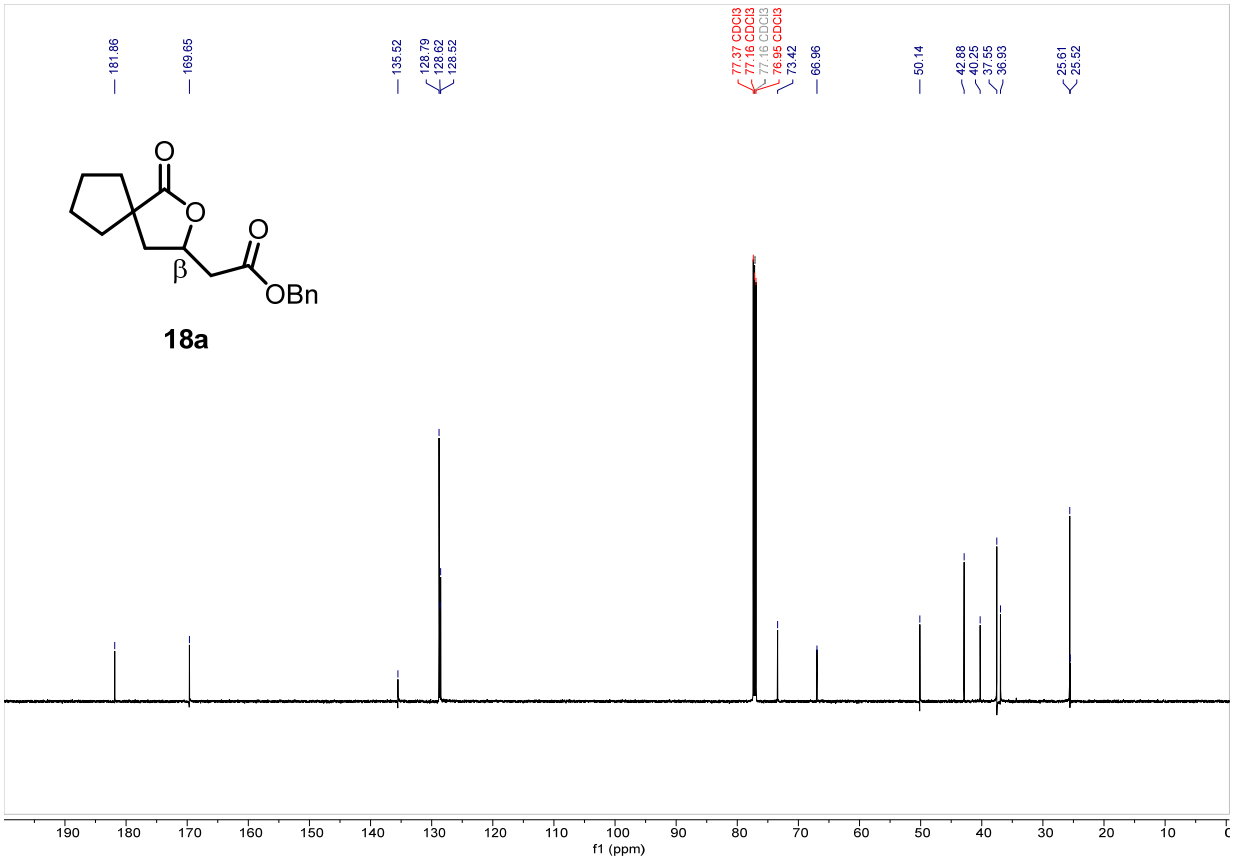
2-(5-Oxo-6-oxaspiro[3.4]octan-7-yl)acetic acid 17a



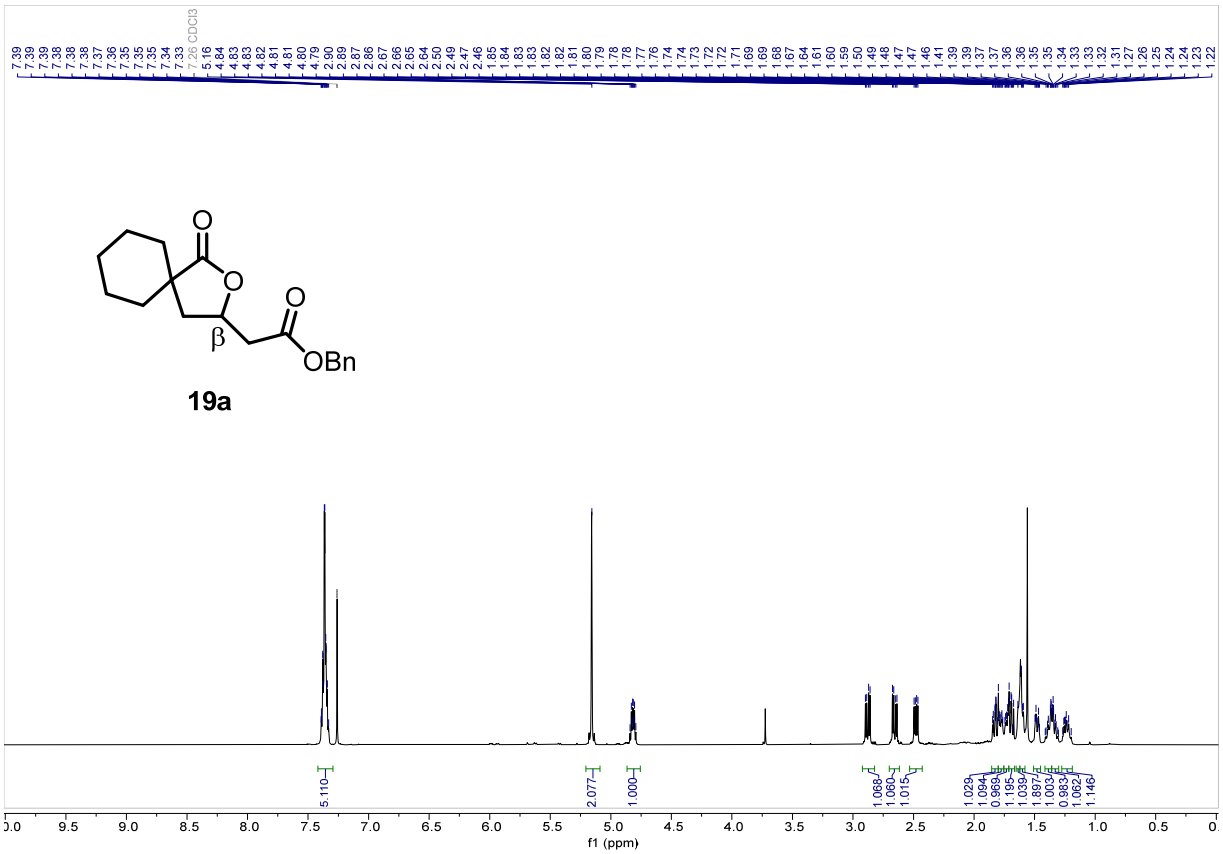


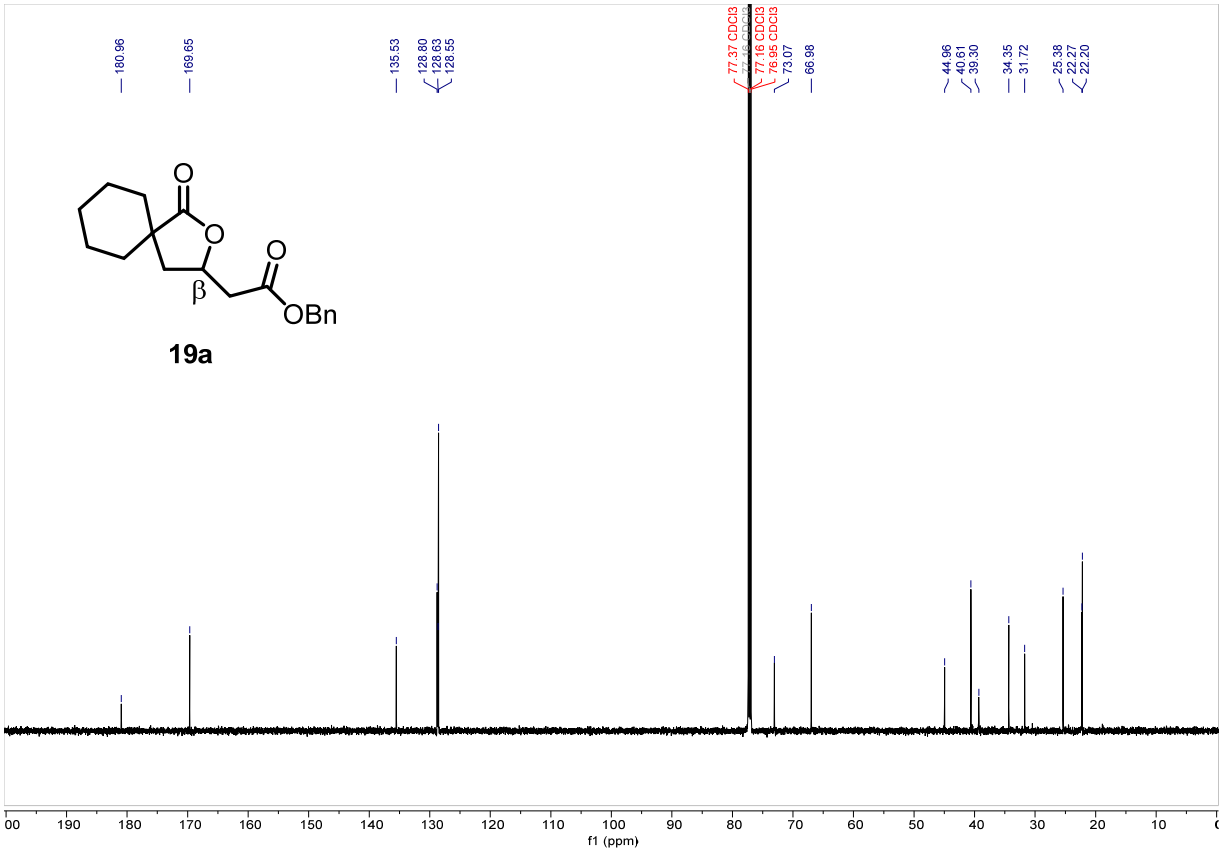
Benzyl 2-(1-Oxo-2-oxaspiro[4.4]nonan-3-yl)acetate 18a



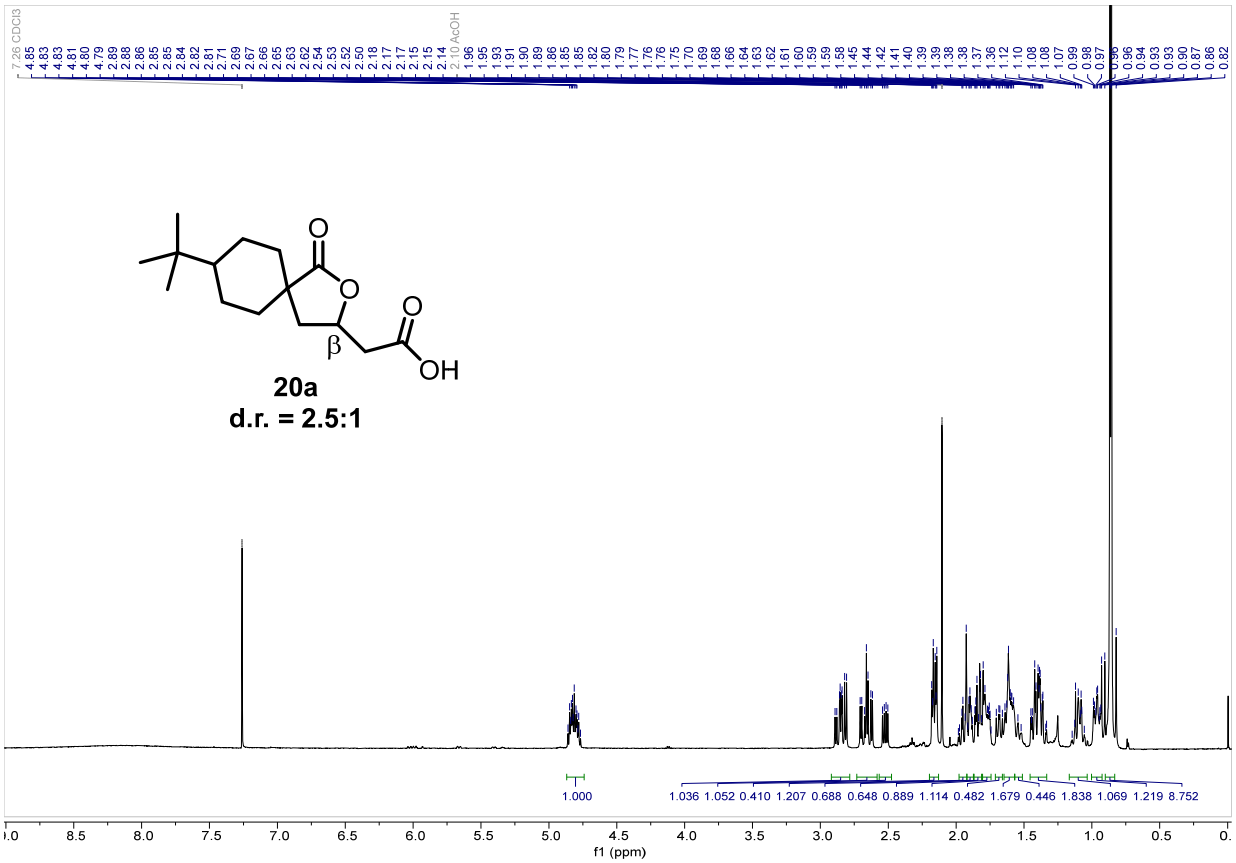


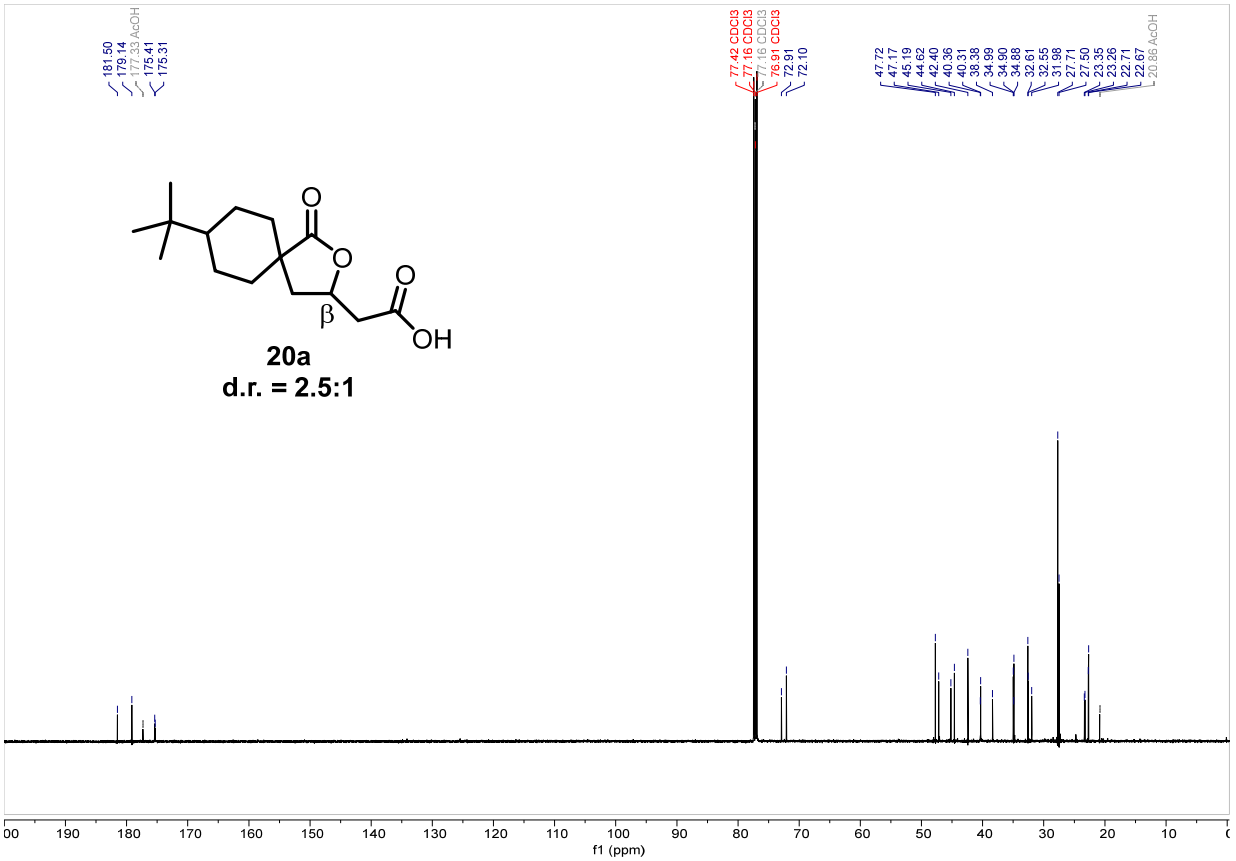
Benzyl 2-(1-oxo-2-oxaspiro[4.5]decan-3-yl)acetate 19a



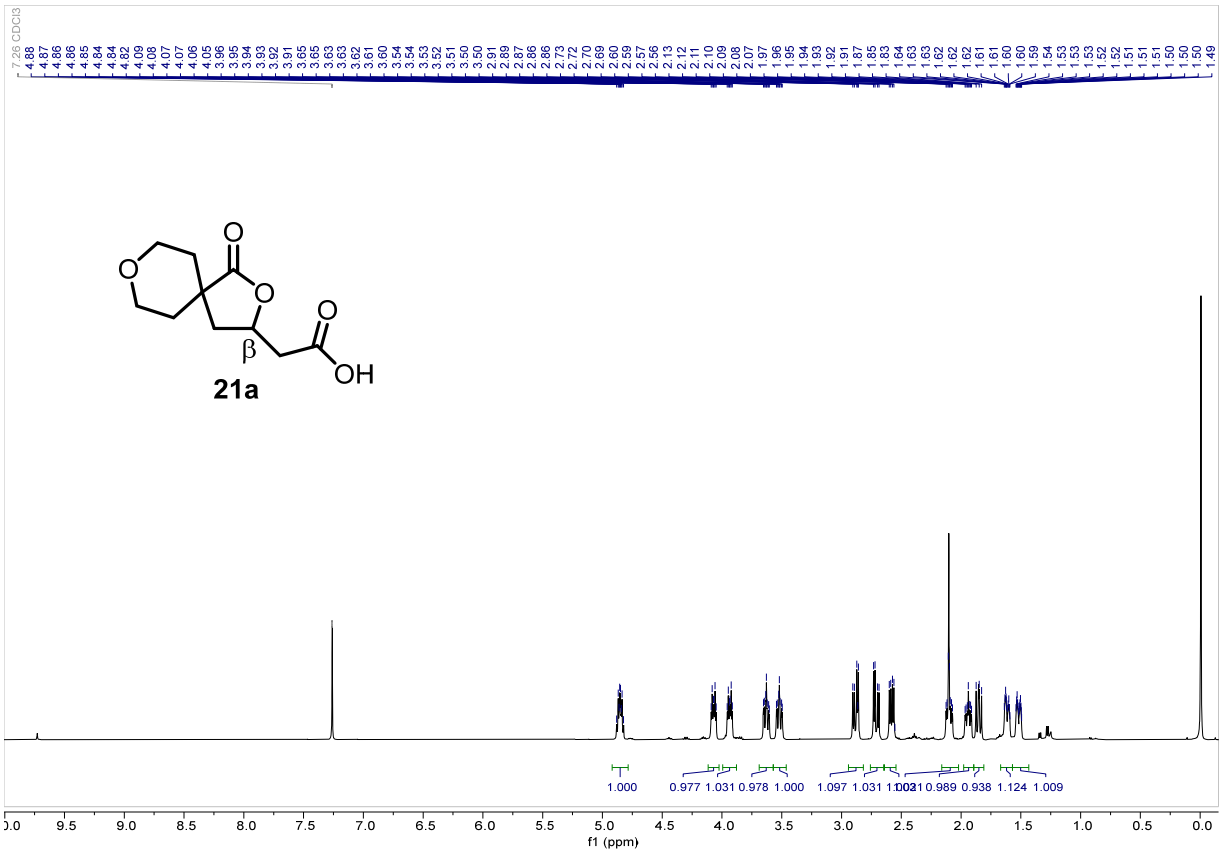


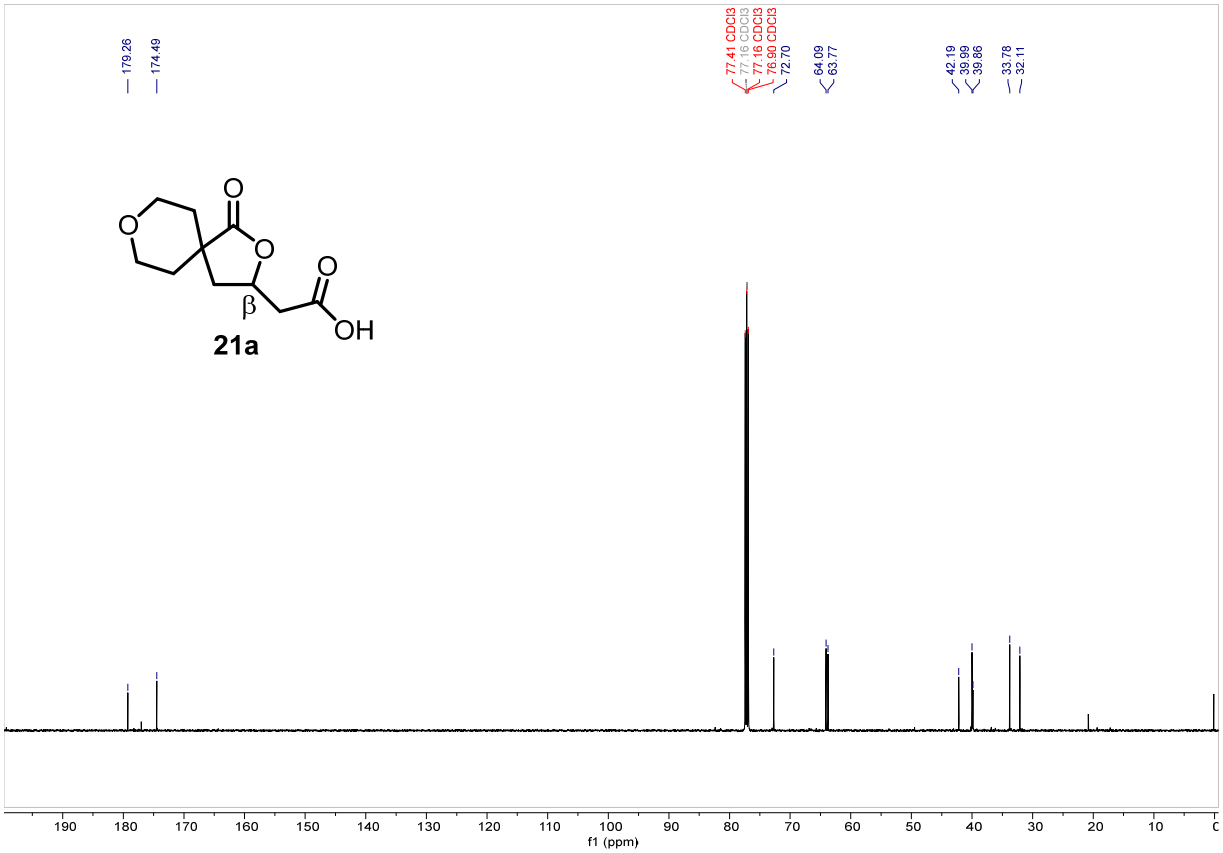
2-(8-(*tert*-Butyl)-1-oxo-2-oxaspiro[4.5]decan-3-yl)acetic acid 20a



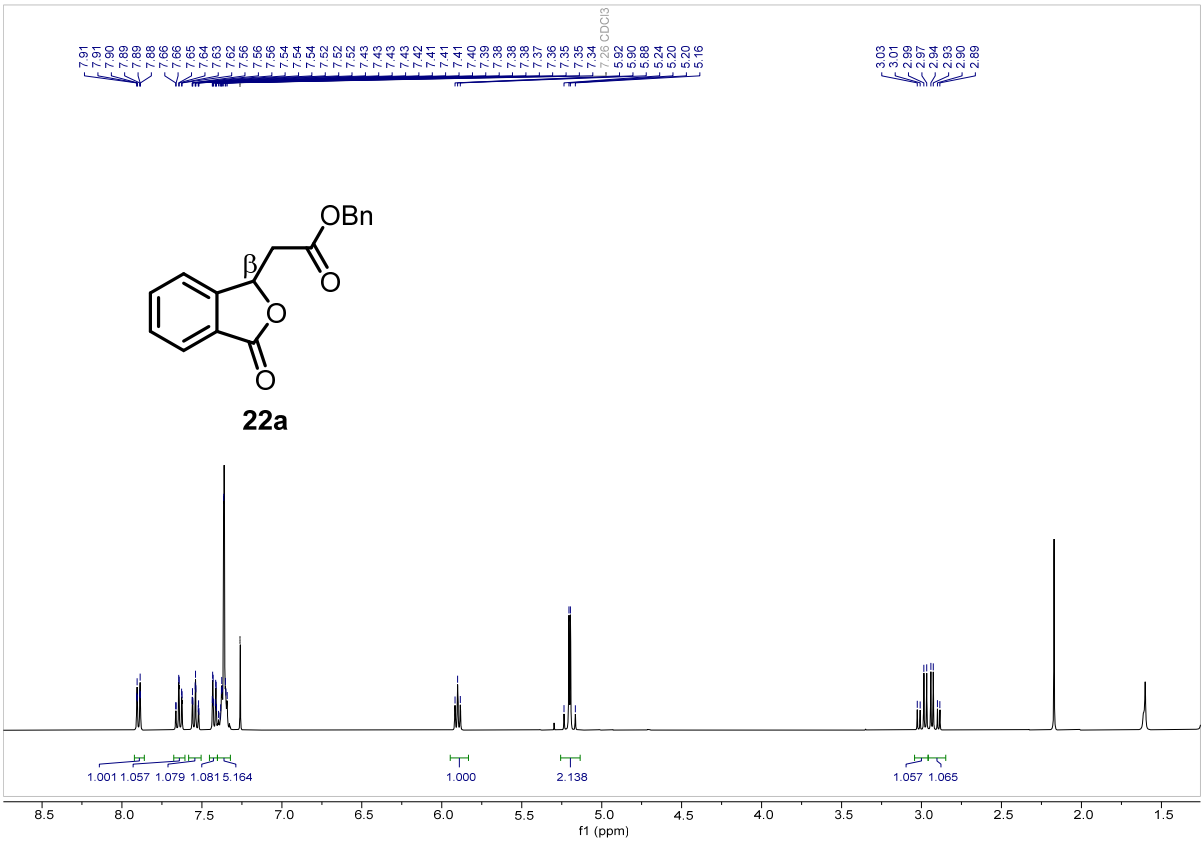


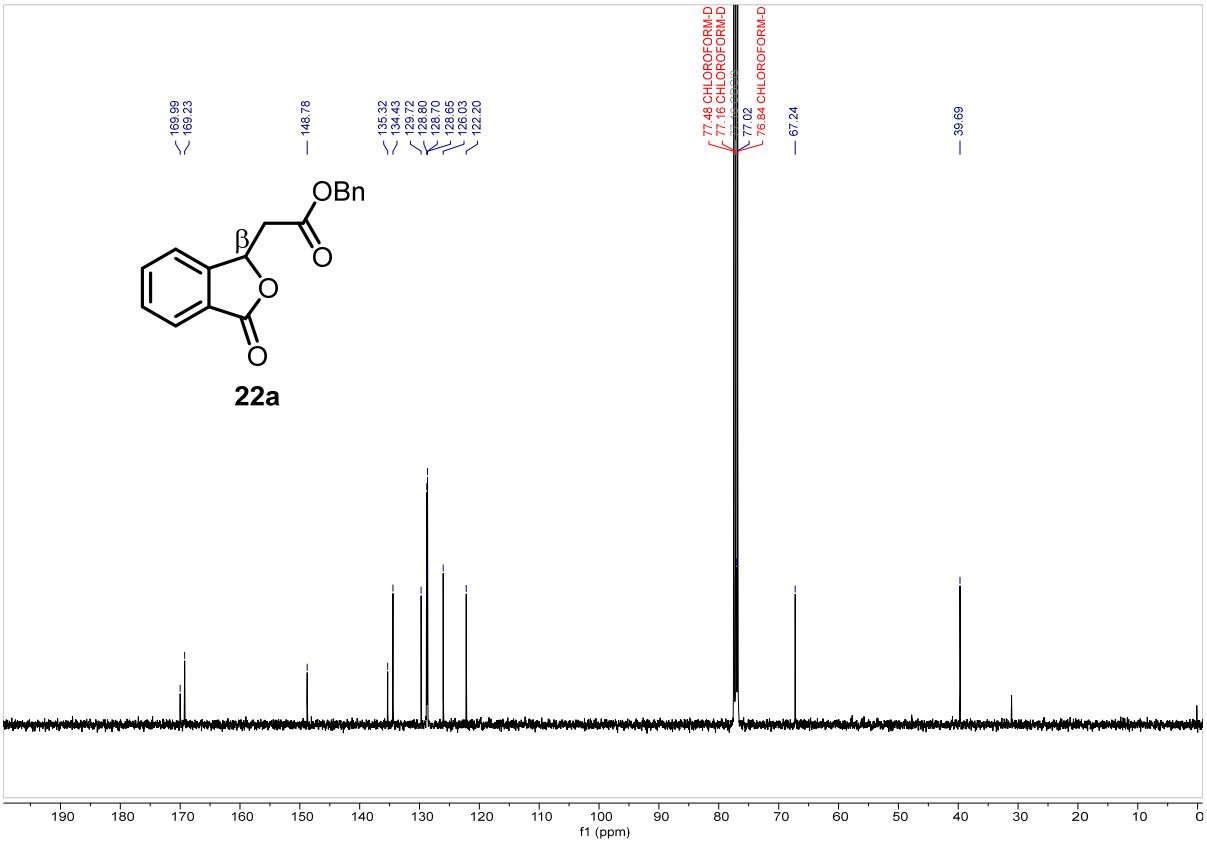
2-(1-Oxo-2,8-dioxaspiro[4.5]decan-3-yl)acetic acid 21a



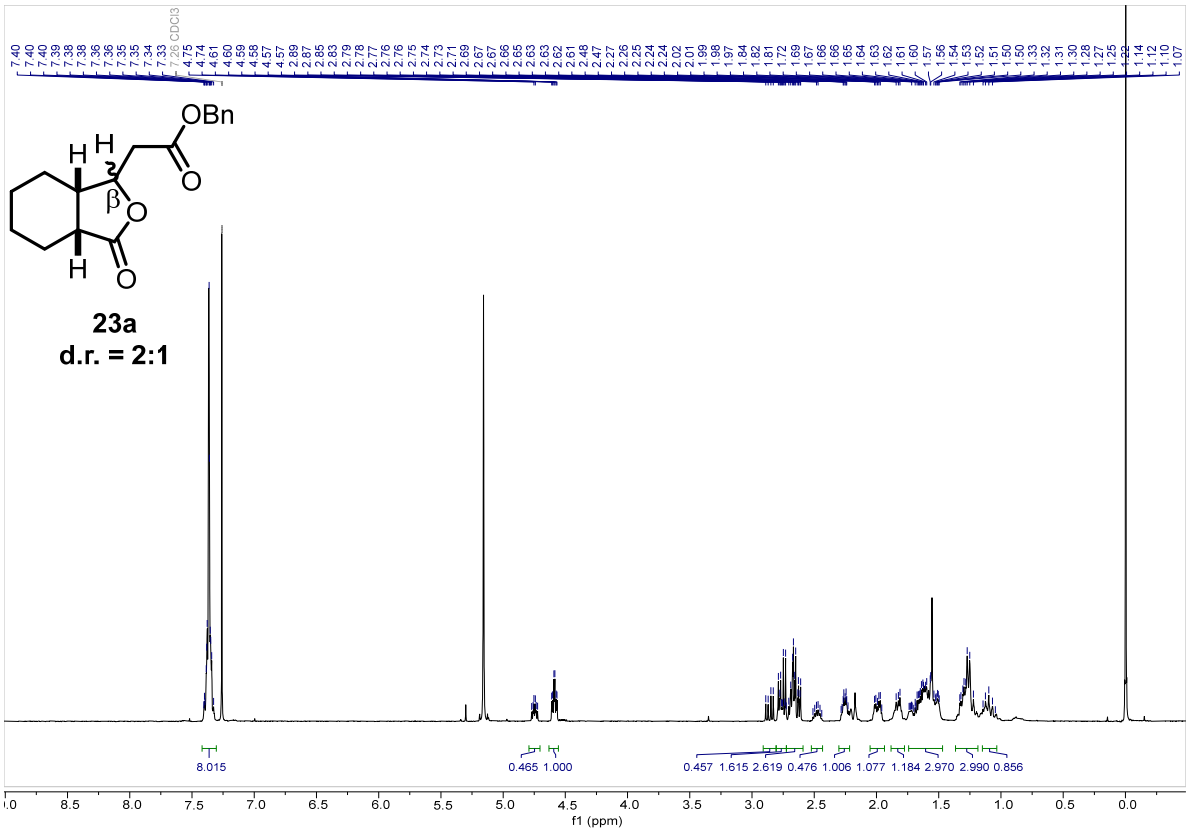


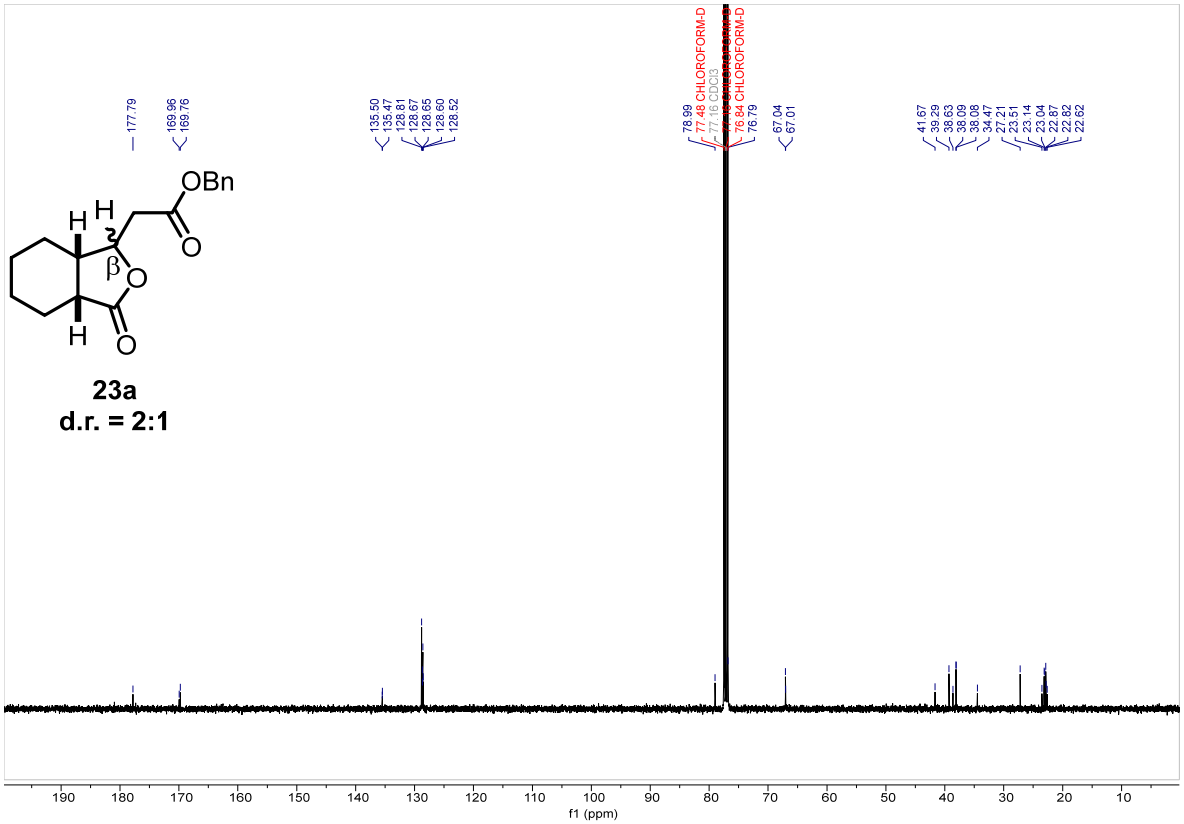
Benzyl 2-(3-oxo-1,3-dihydroisobenzofuran-1-yl)acetate 22a



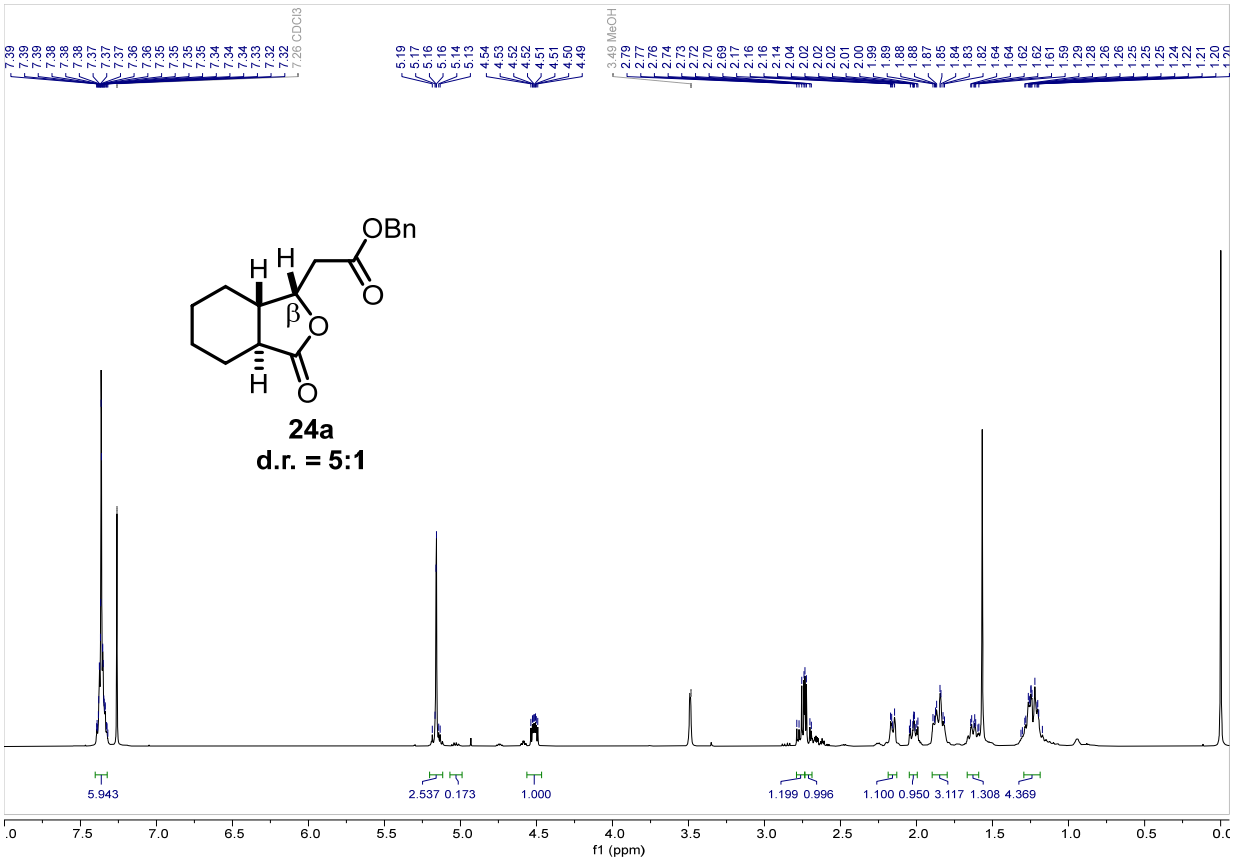


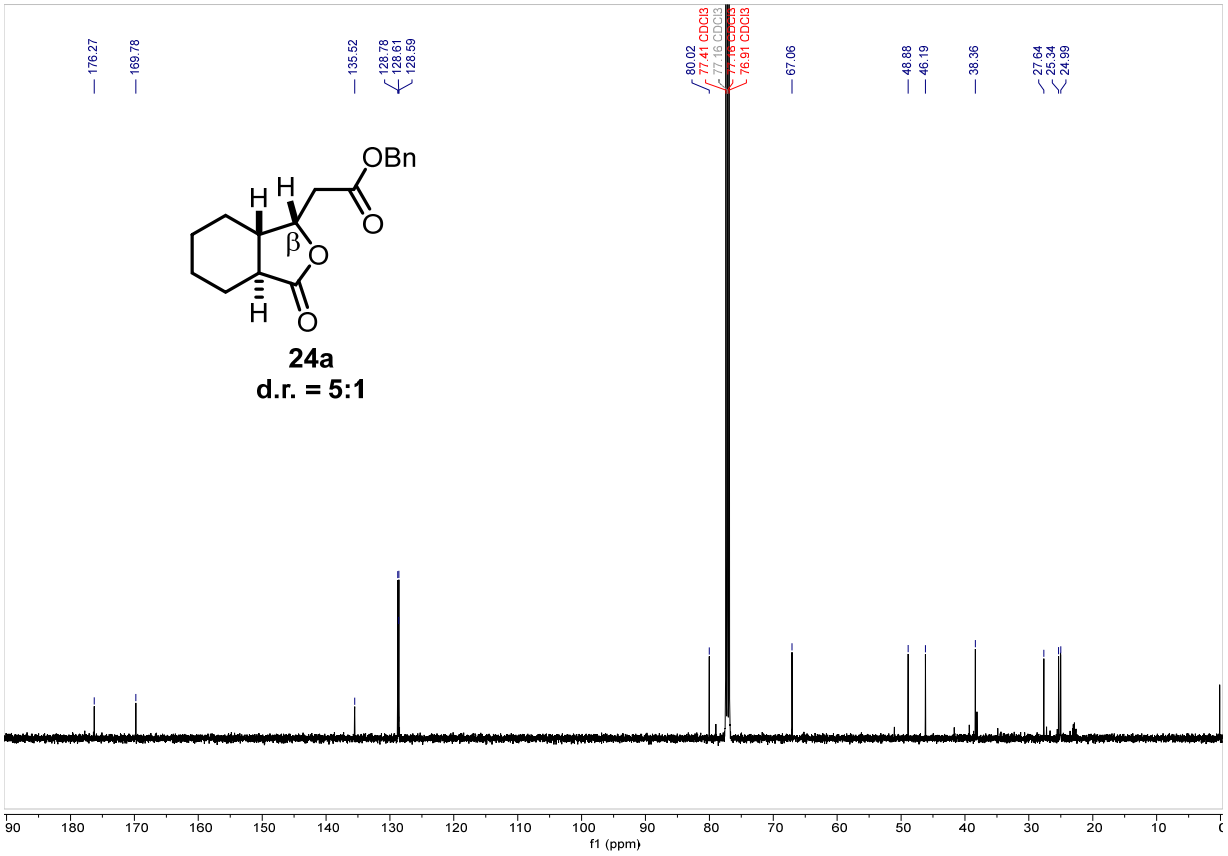
Benzyl 2-((3*aR,7*aS**)-3-oxooctahydroisobenzofuran-1-yl)acetate 23a**



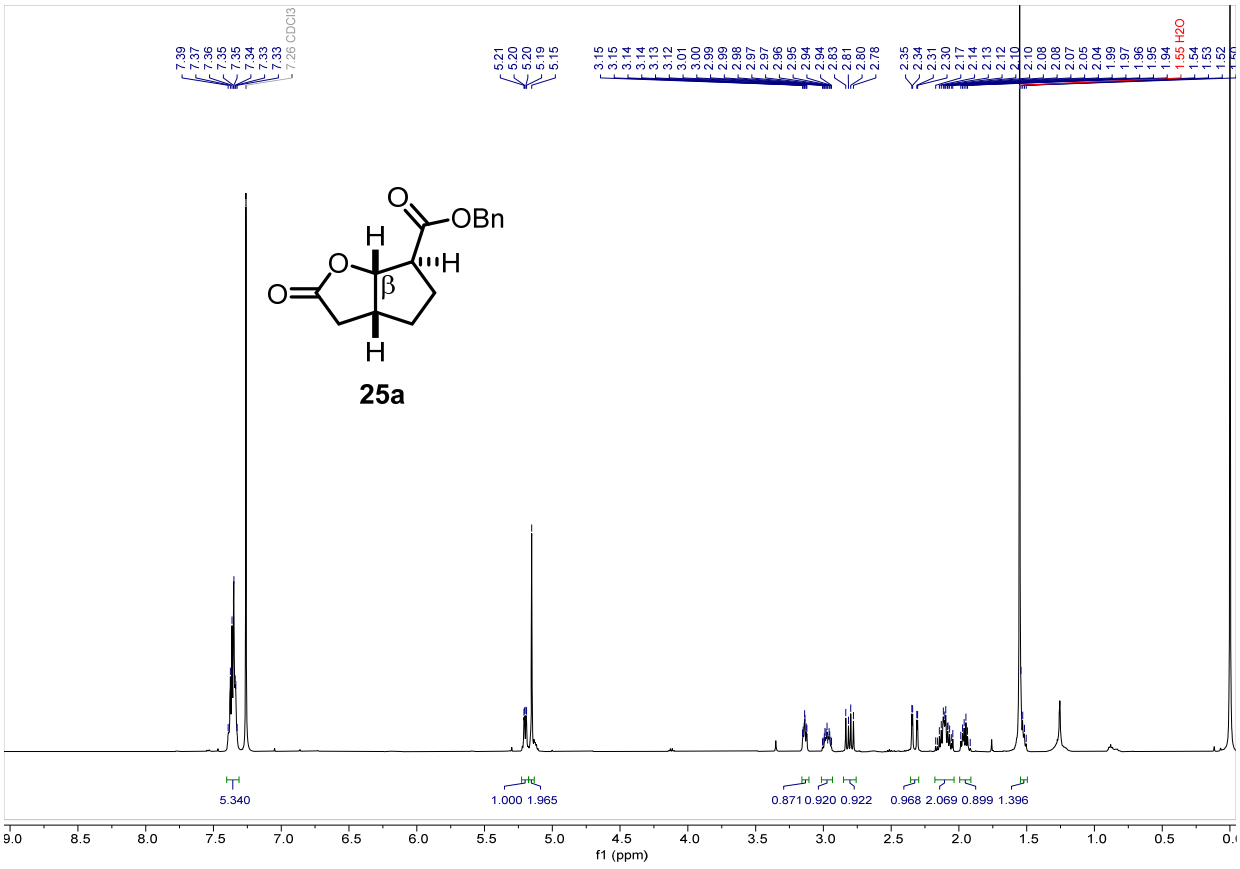


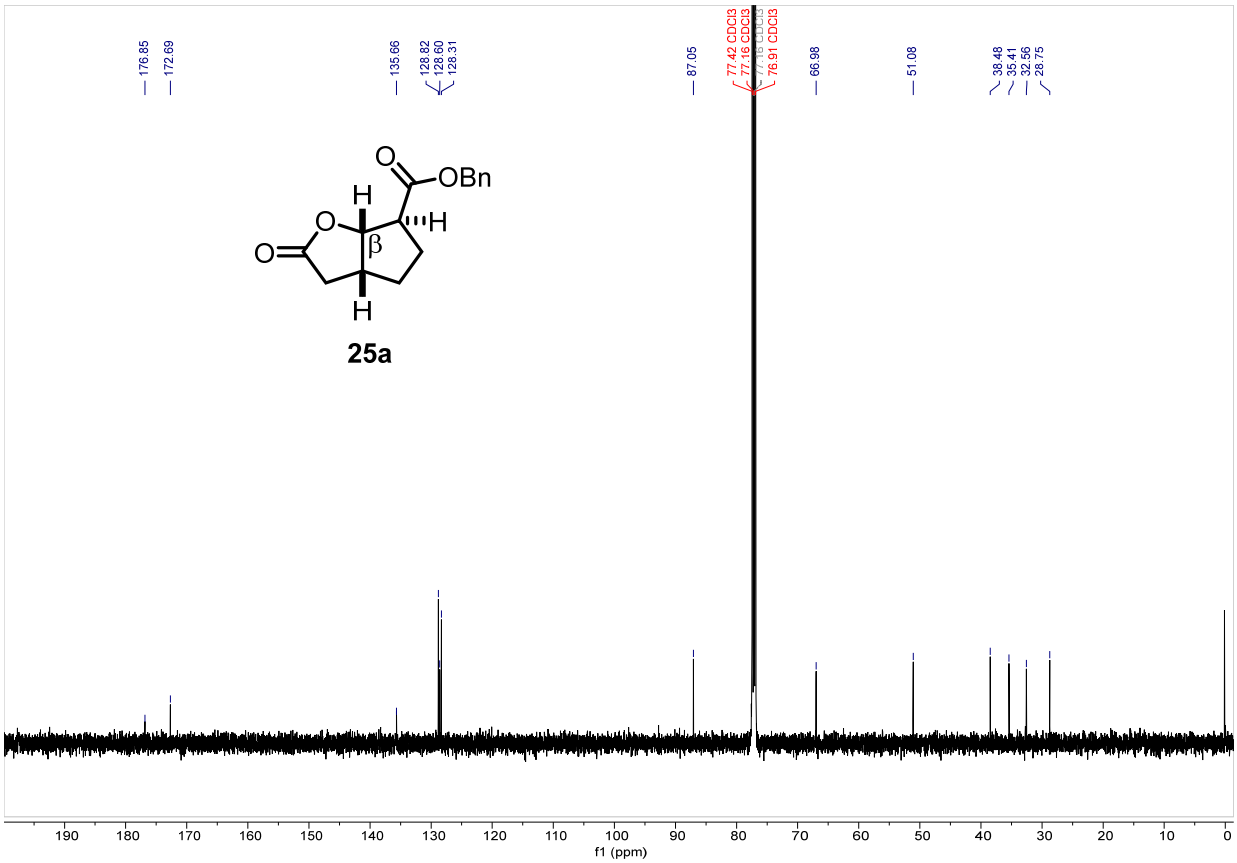
Benzyl 2-((1*S,3*aS**,7*aS**)-3-oxooctahydroisobenzofuran-1-yl)acetate 24a**



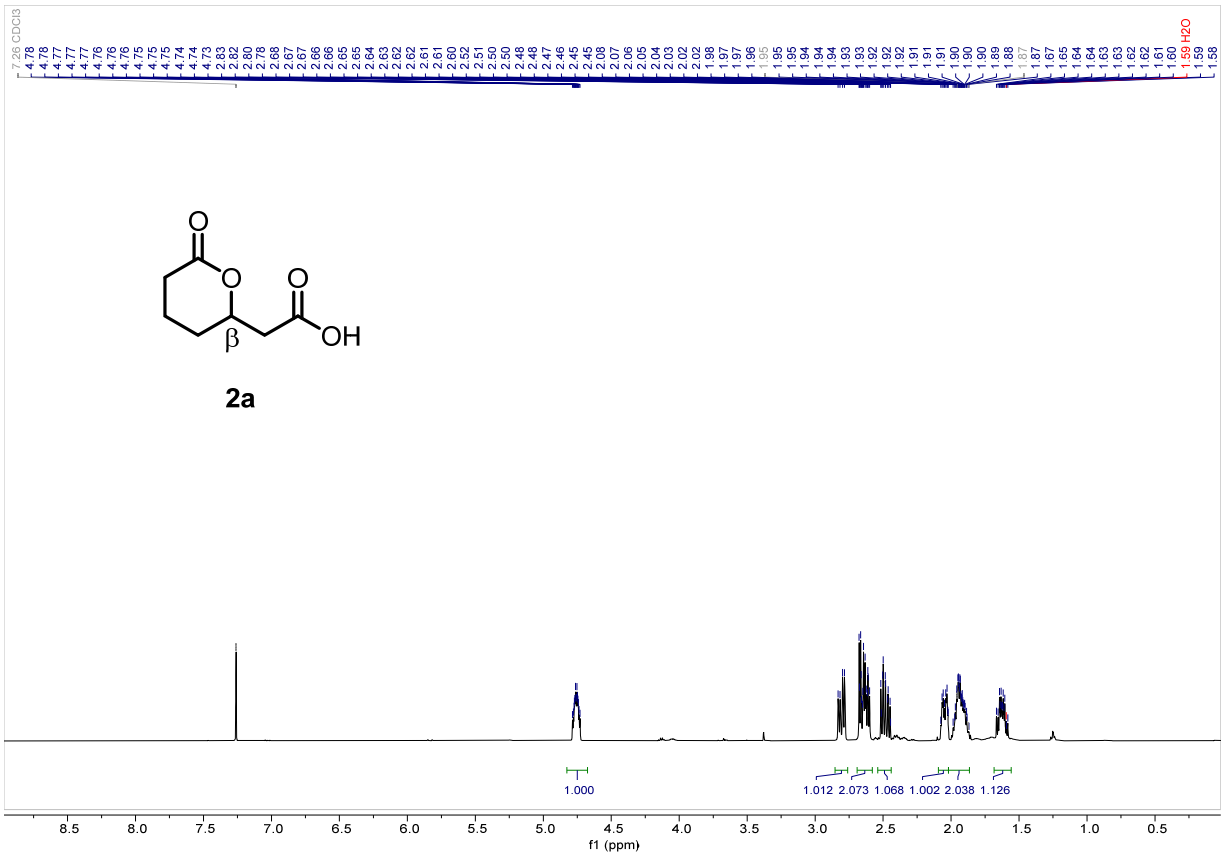


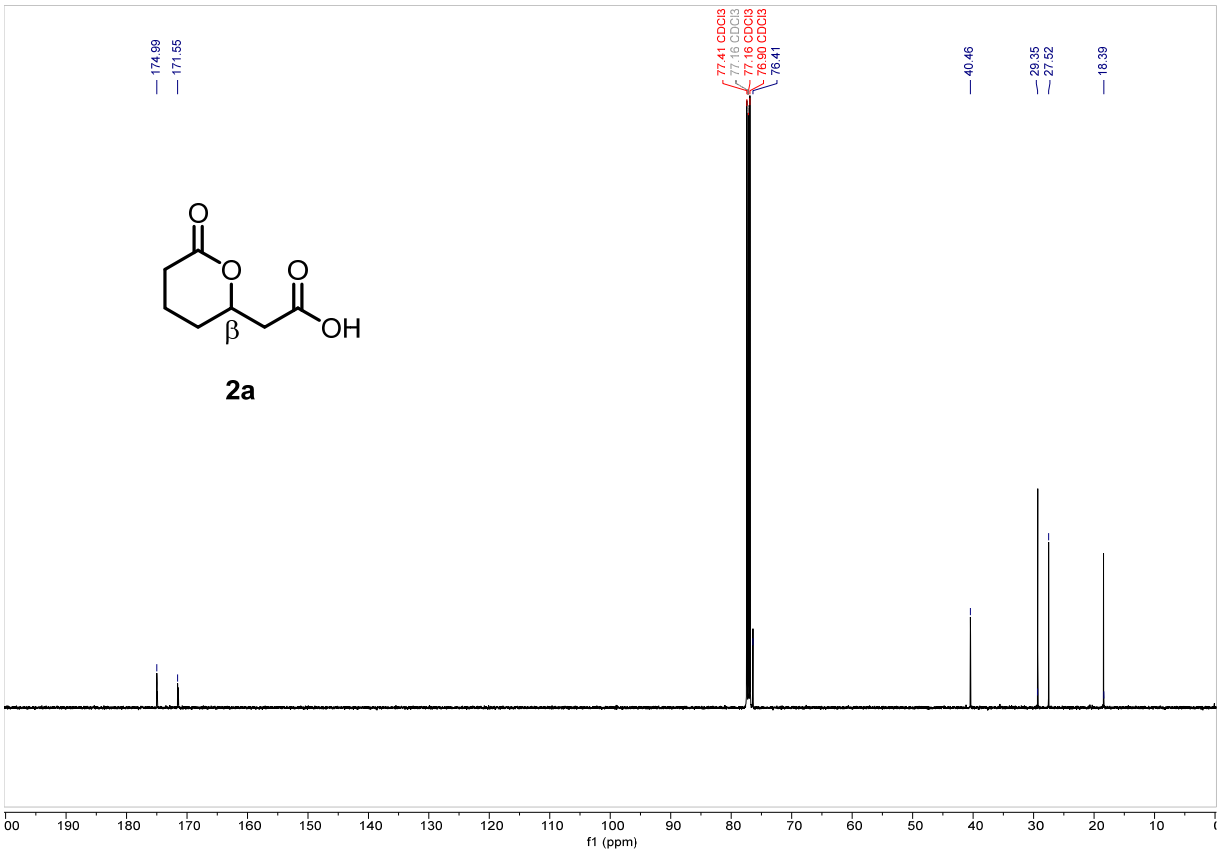
Benzyl (3*aR,6*S**,6*aS**)-2-oxohexahydro-2H-cyclopenta[b]furan-6-carboxylate 25a**



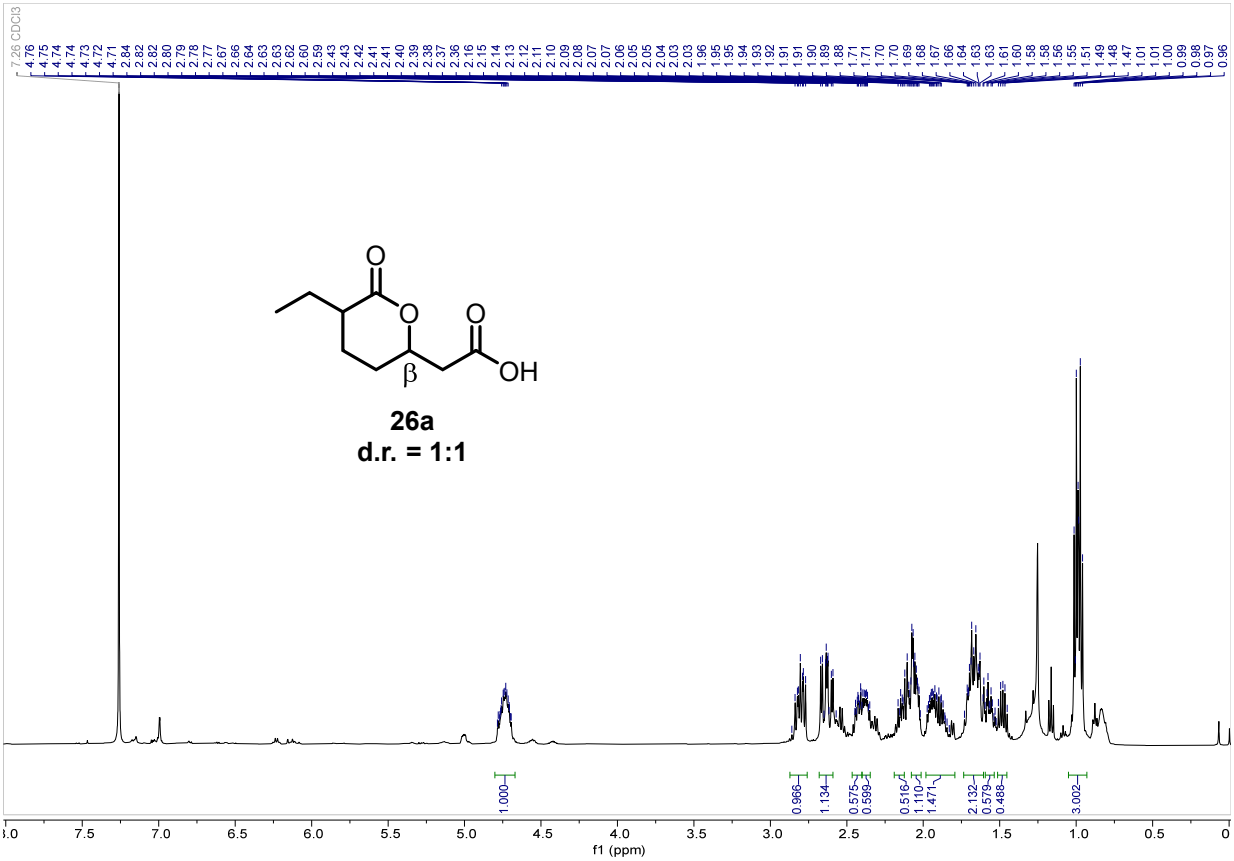


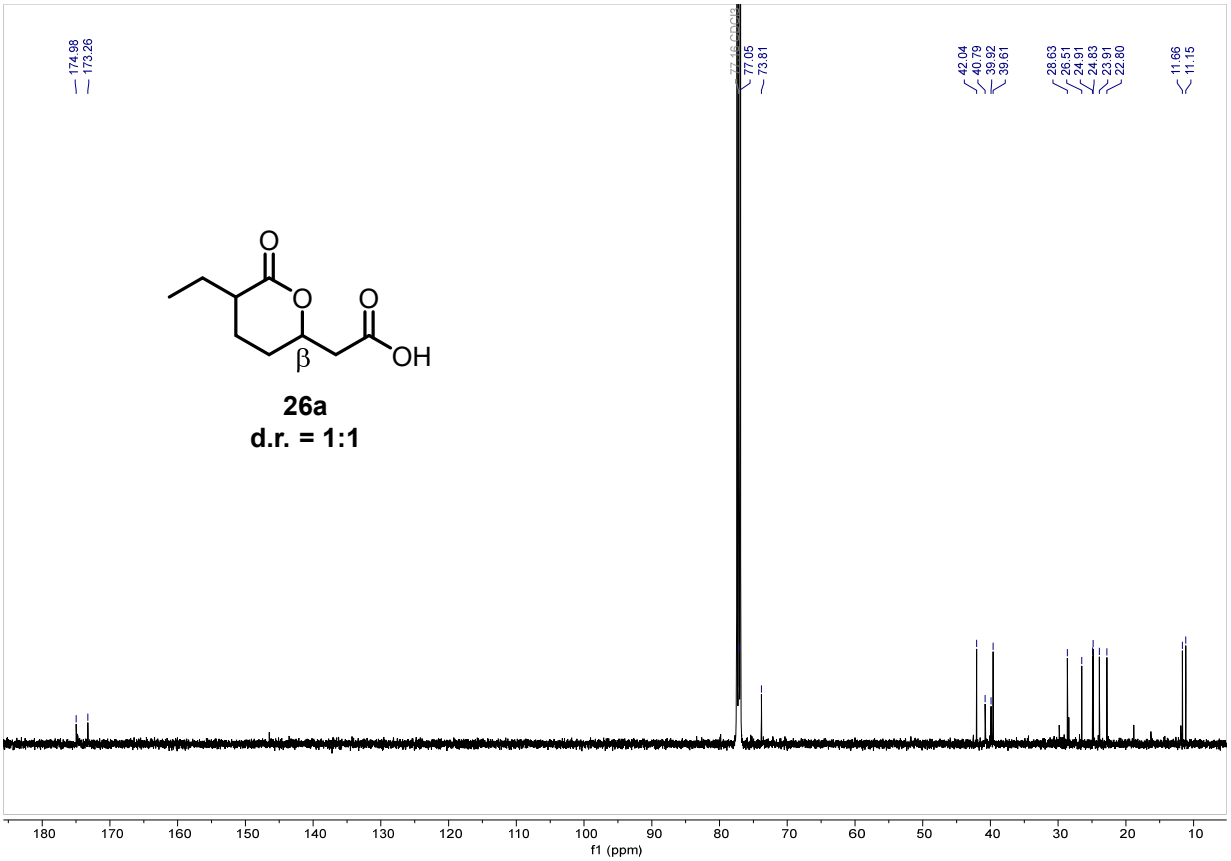
2-(6-Oxotetrahydro-2*H*-pyran-2-yl)acetic acid 2a



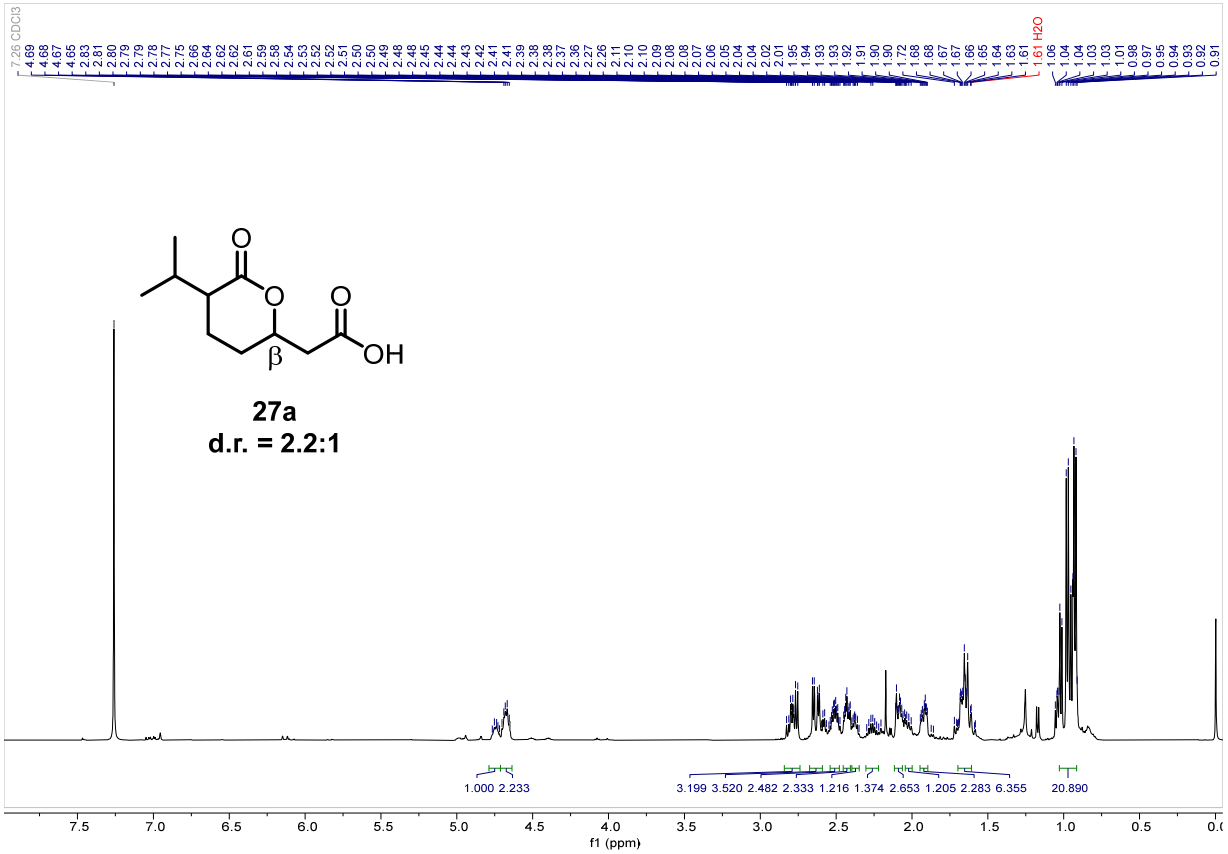


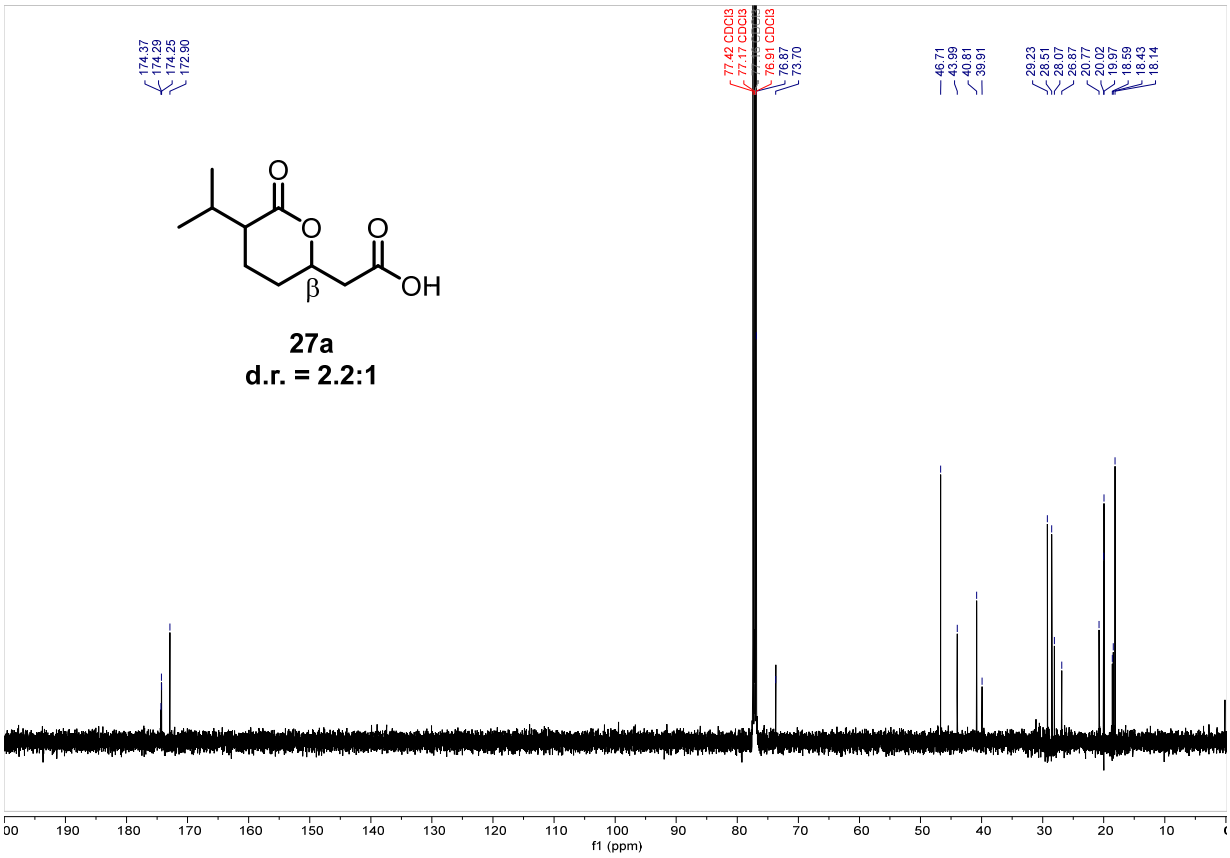
2-(5-Ethyl-6-oxotetrahydro-2*H*-pyran-2-yl)acetic acid 26a



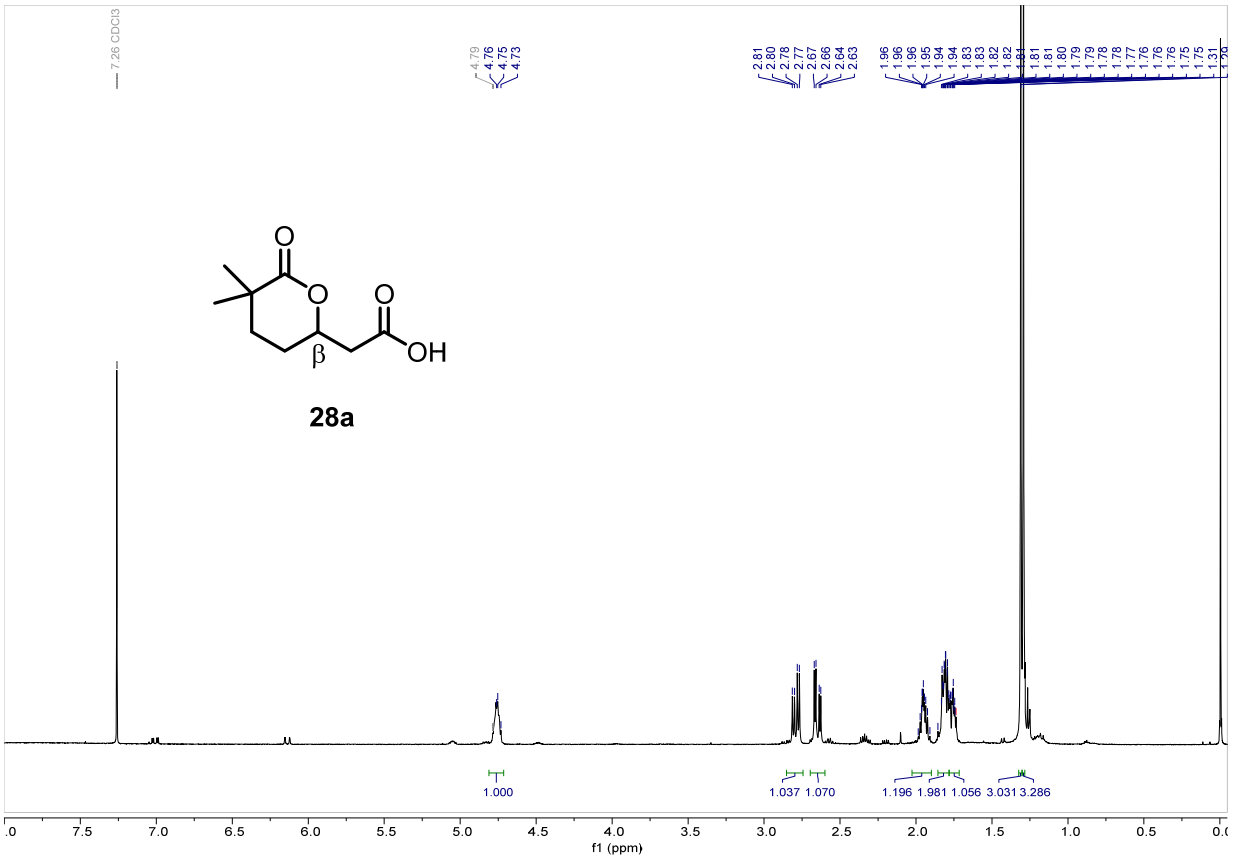


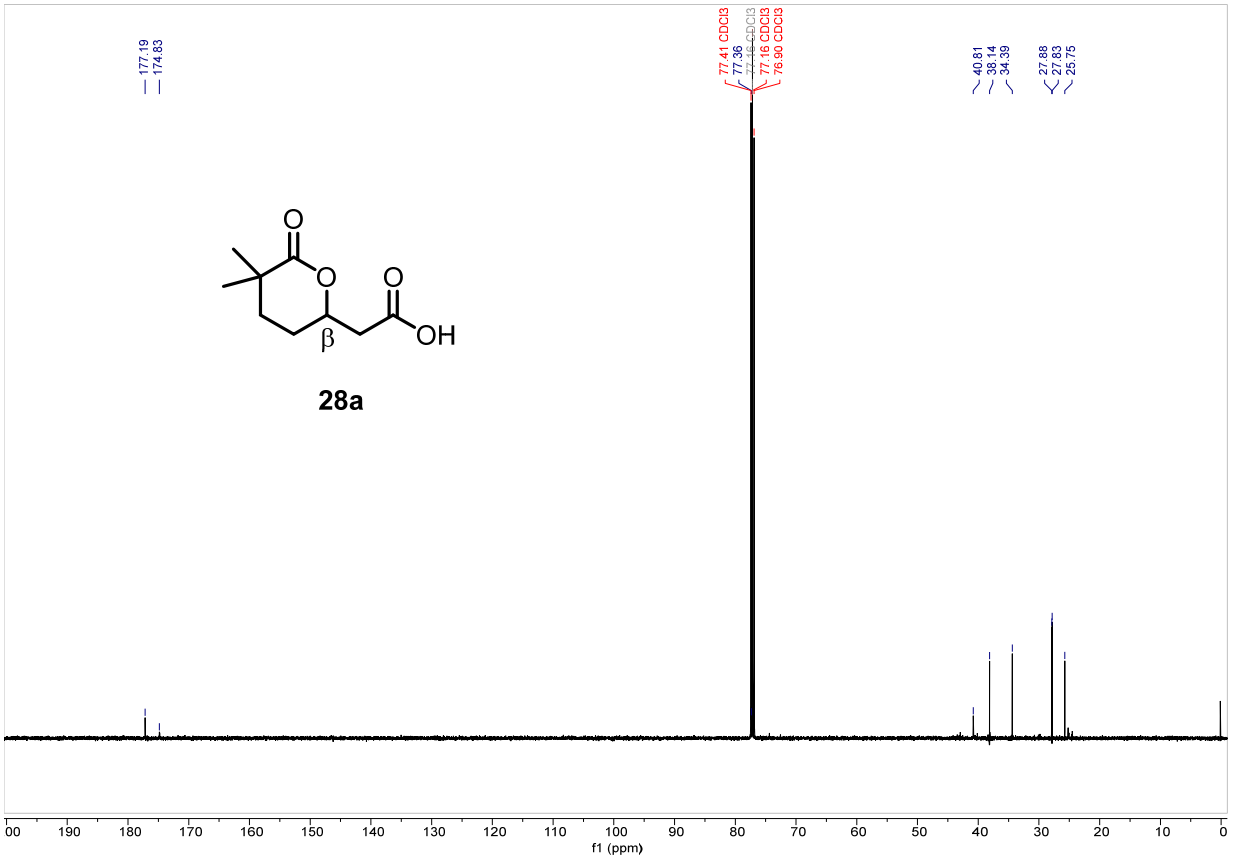
2-(5-Isopropyl-6-oxotetrahydro-2*H*-pyran-2-yl)acetic acid 27a



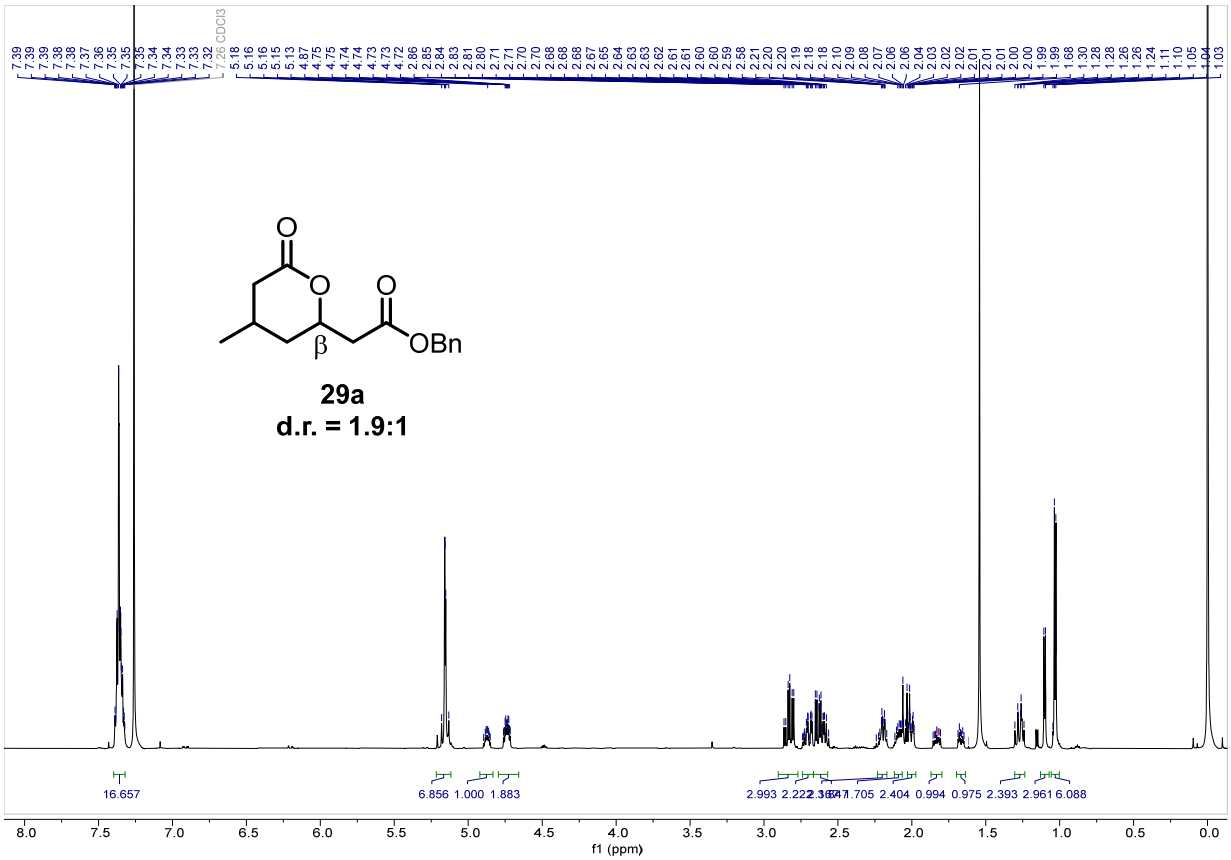


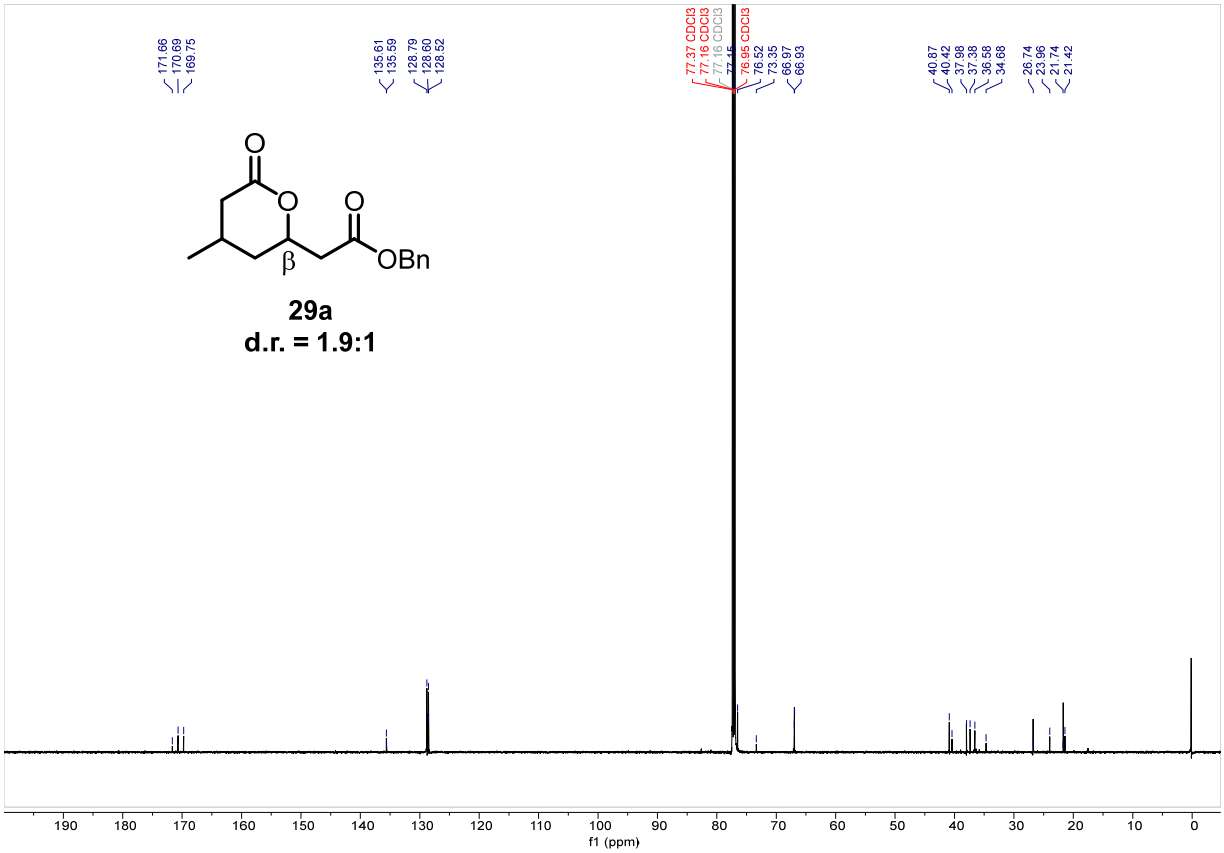
2-(5,5-Dimethyl-6-oxotetrahydro-2*H*-pyran-2-yl)acetic acid 28a



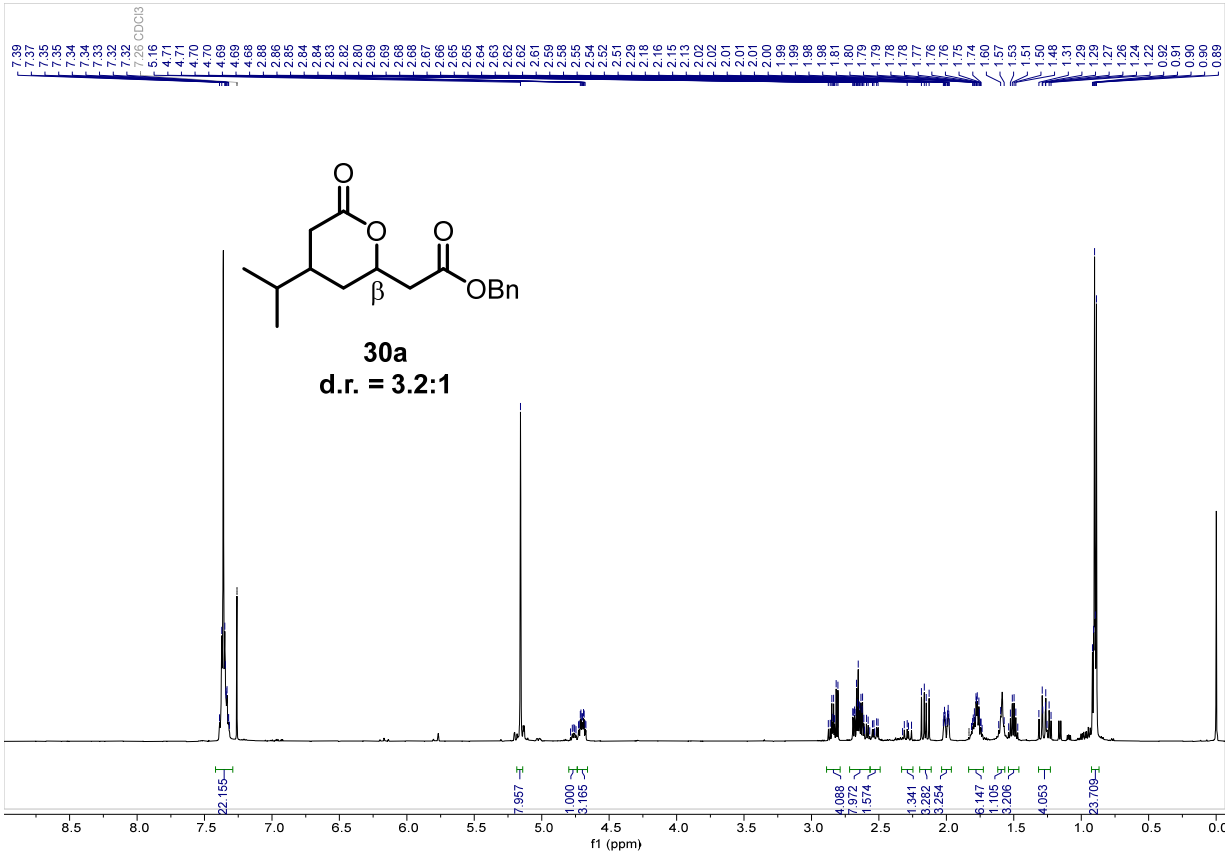


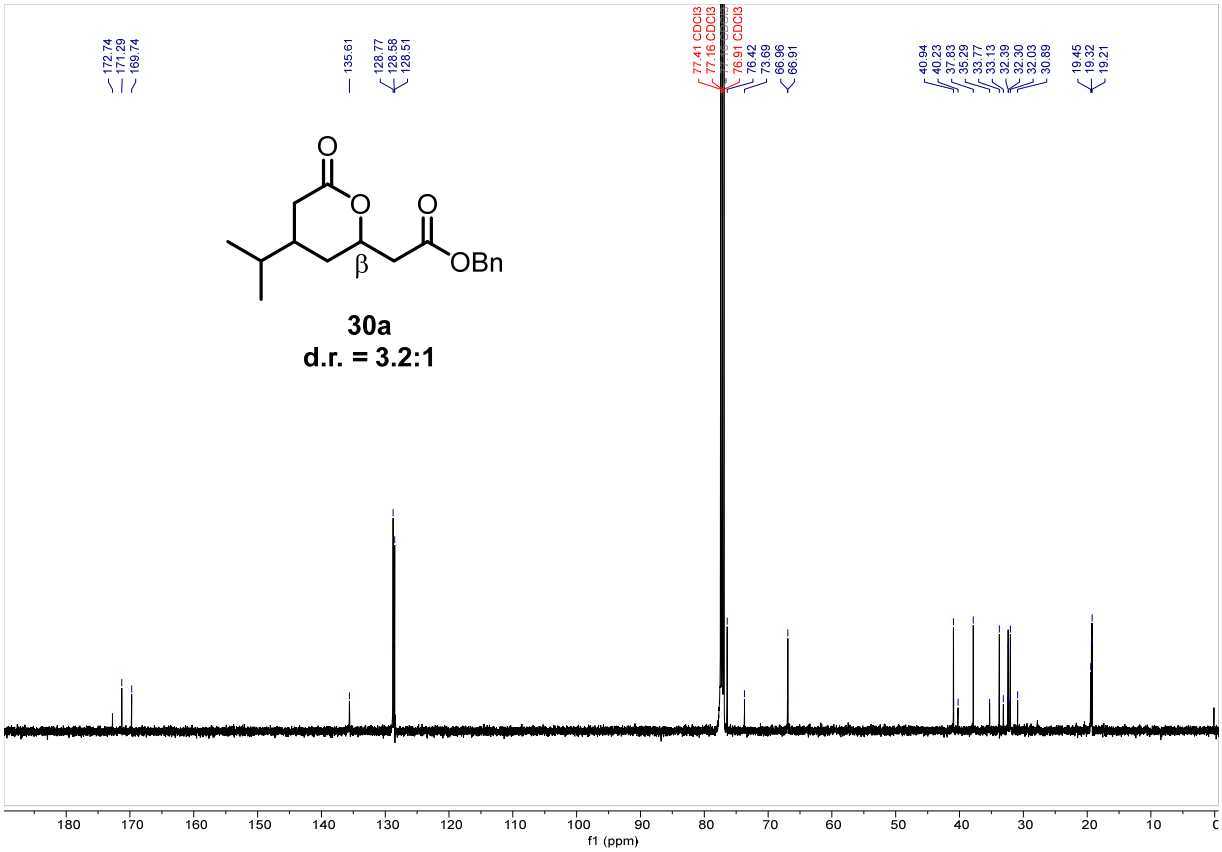
Benzyl 2-(4-methyl-6-oxotetrahydro-2*H*-pyran-2-yl)acetate 29a



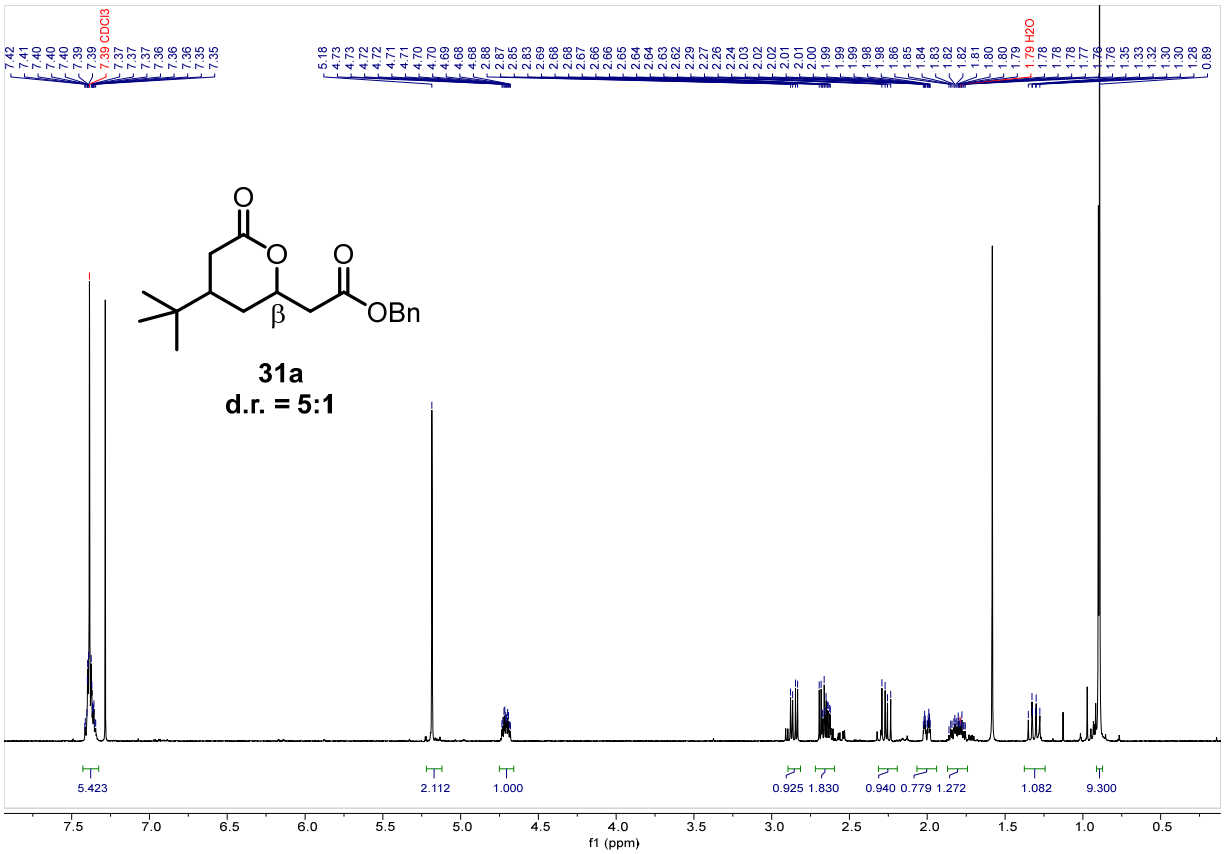


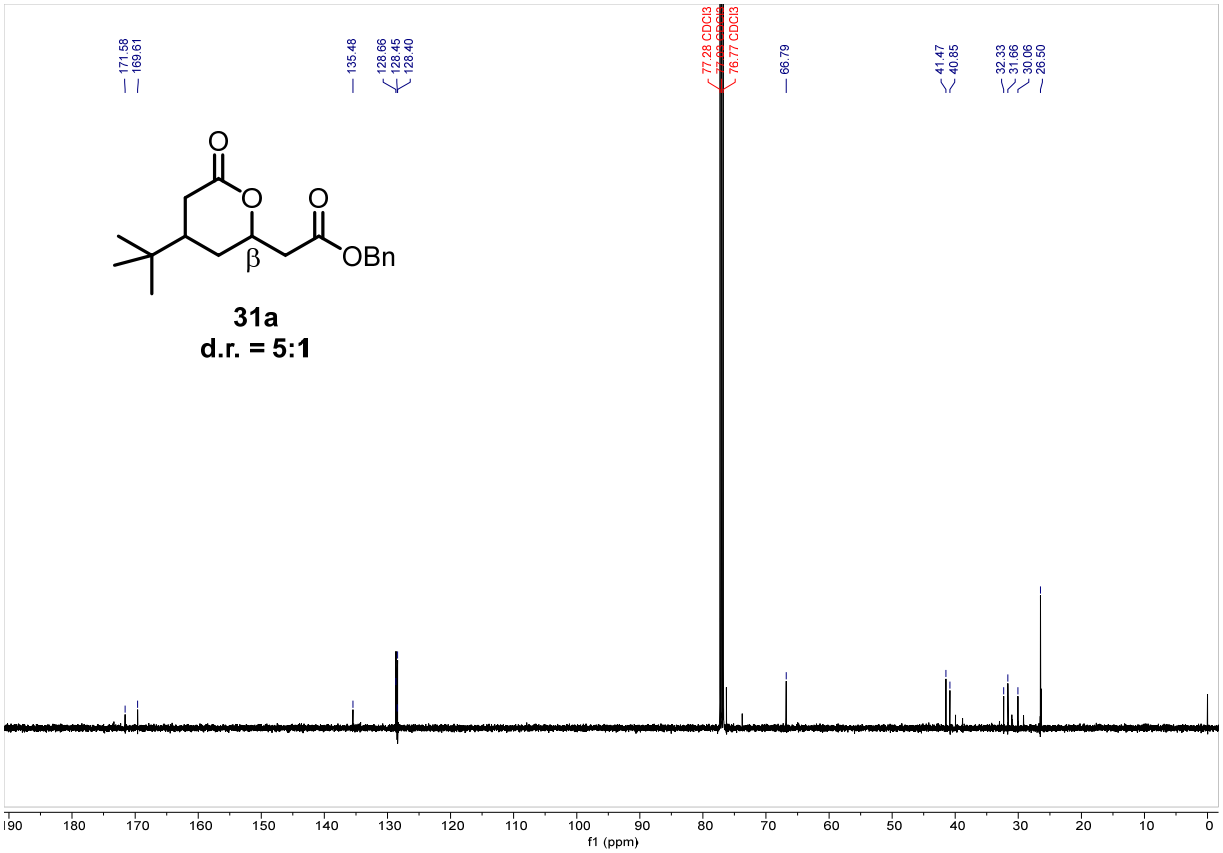
Benzyl 2-(4-isopropyl-6-oxotetrahydro-2*H*-pyran-2-yl)acetate 30a



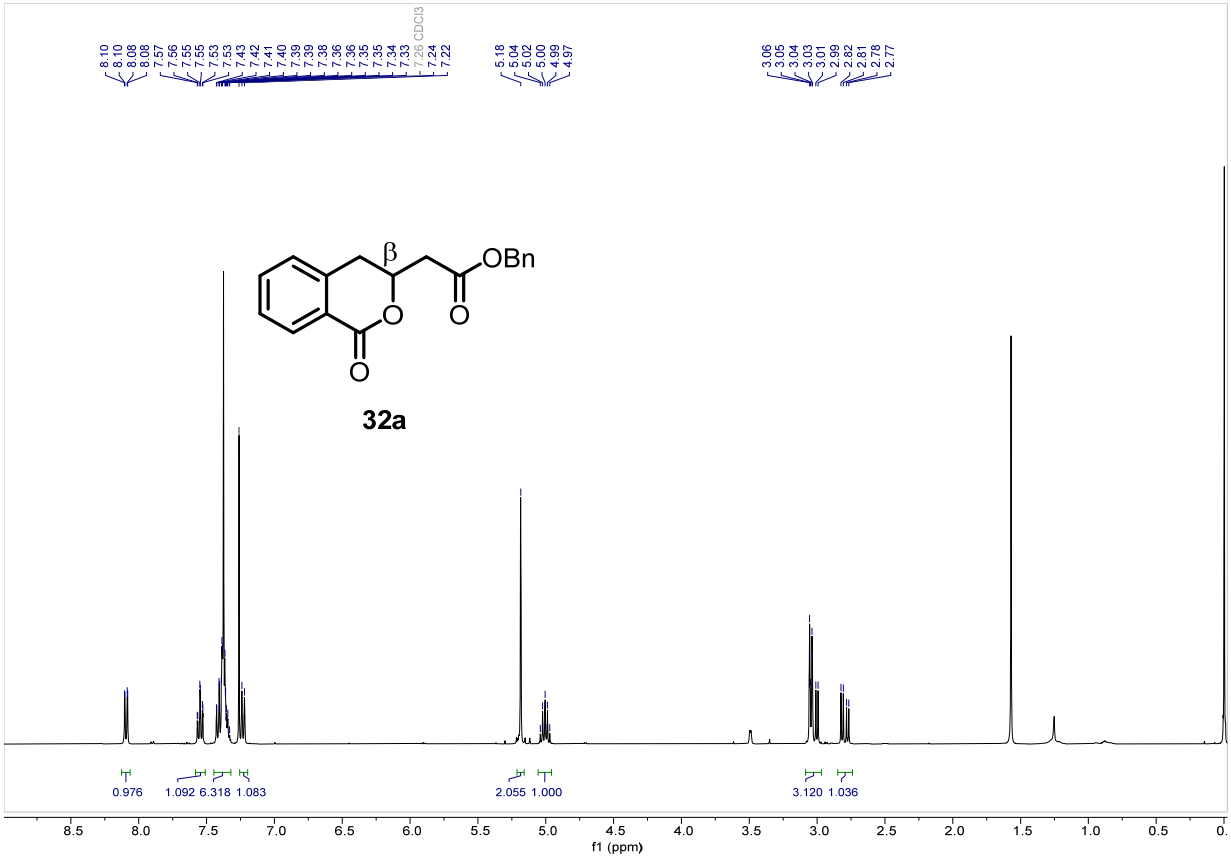


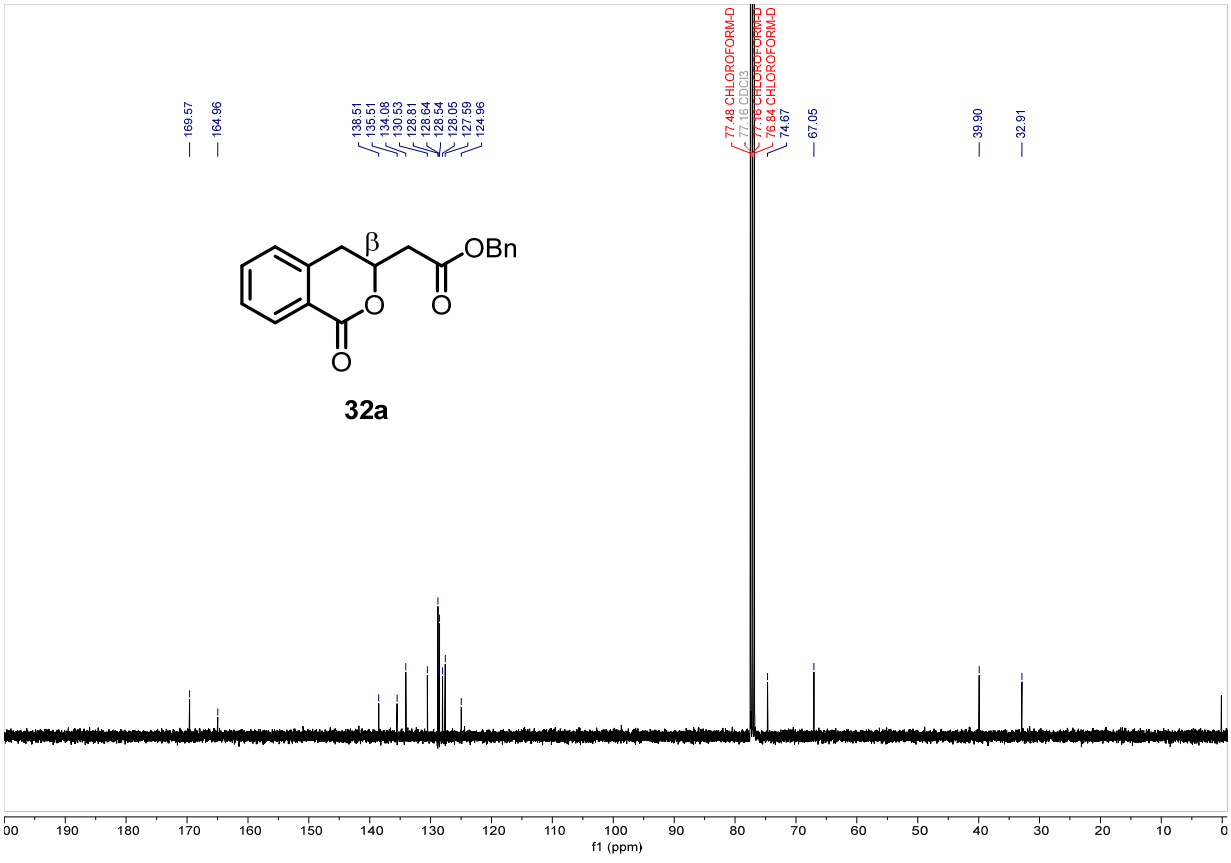
Benzyl 2-(4-(*tert*-butyl)-6-oxotetrahydro-2*H*-pyran-2-yl)acetate 31a



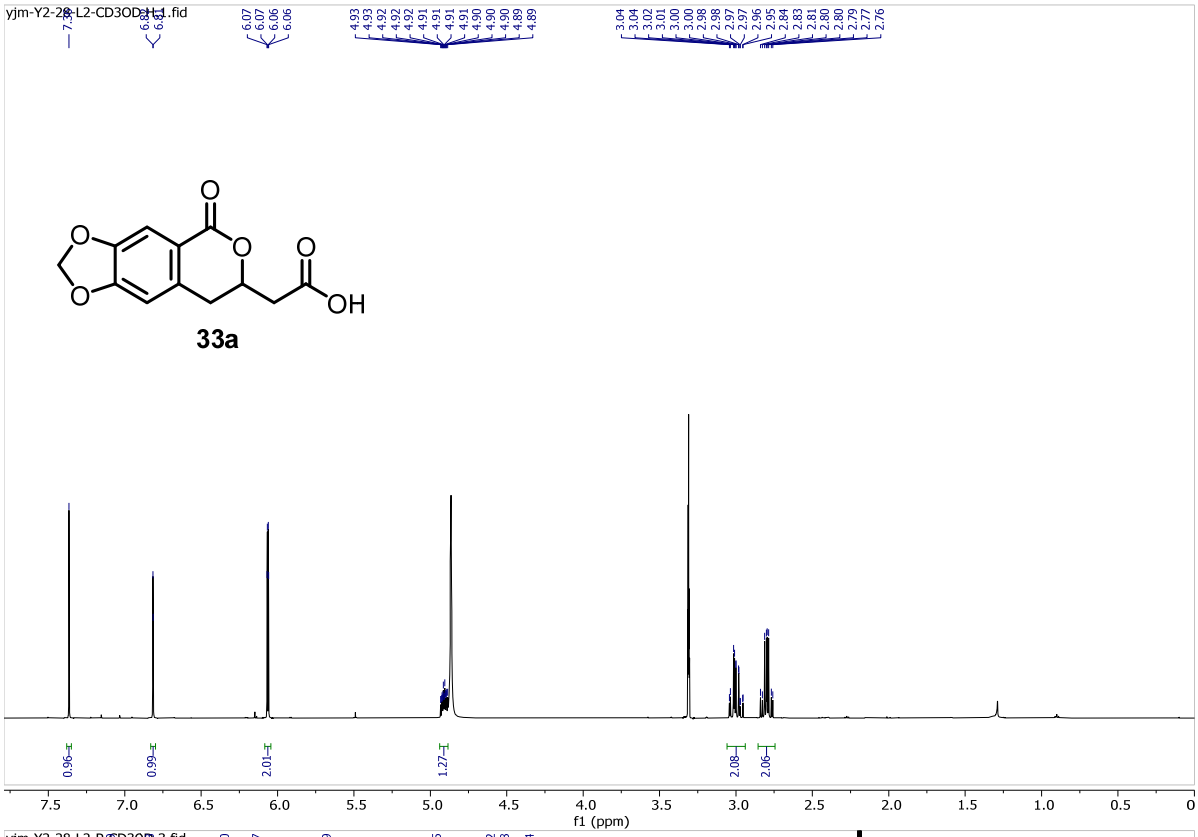


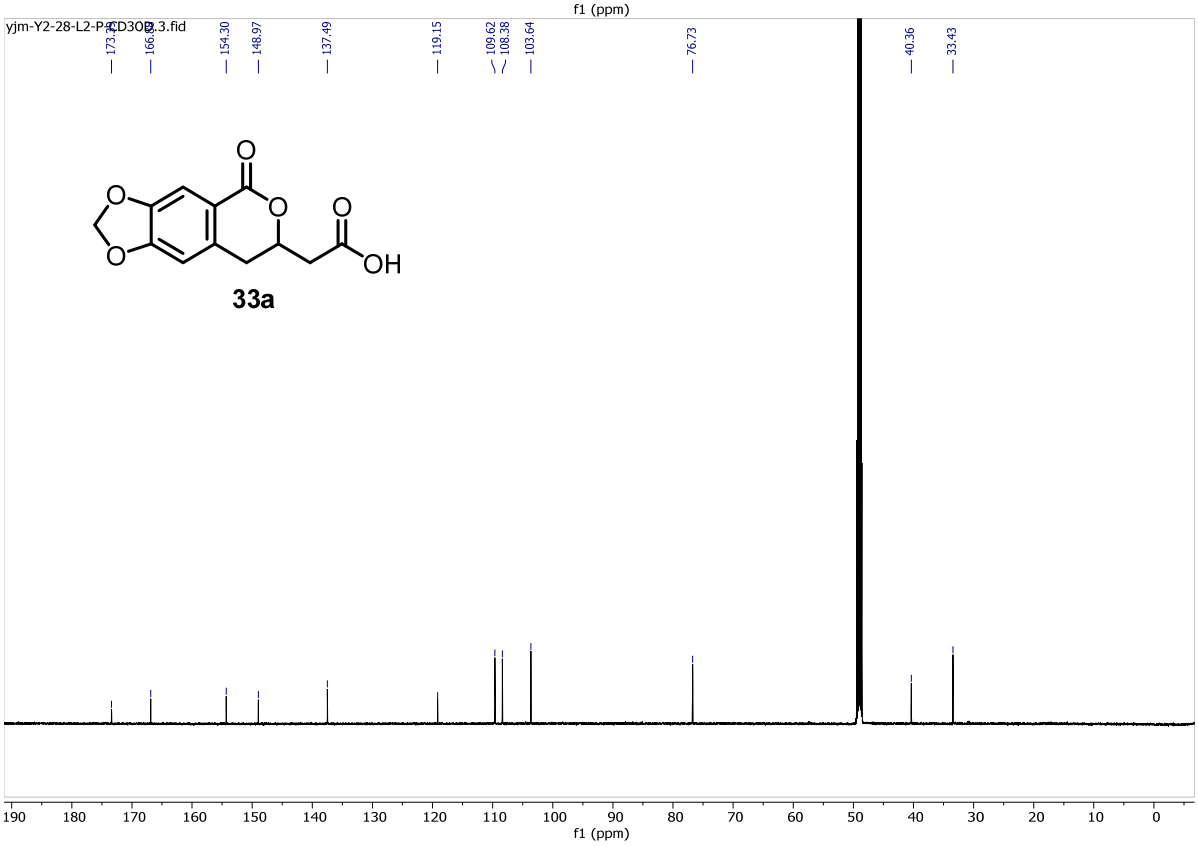
Benzyl 2-(1-oxoisochroman-3-yl)acetate 32a



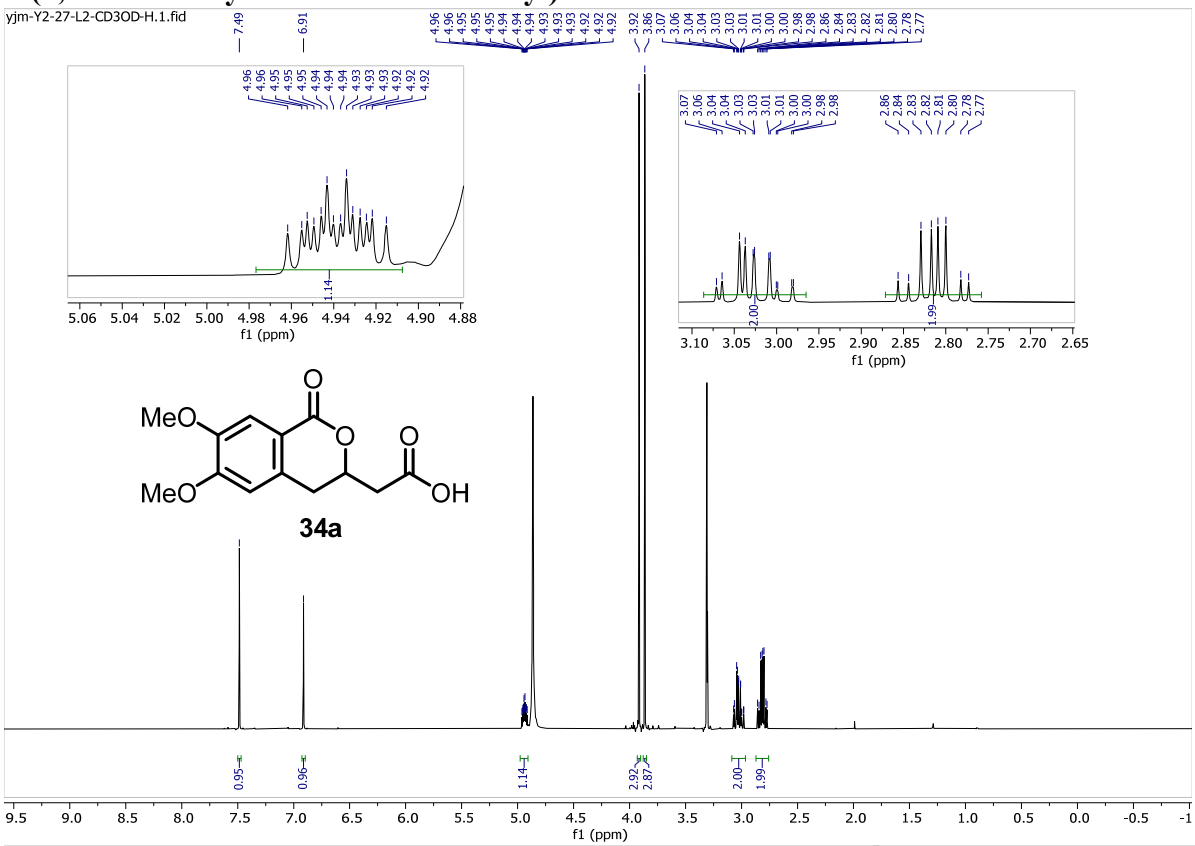


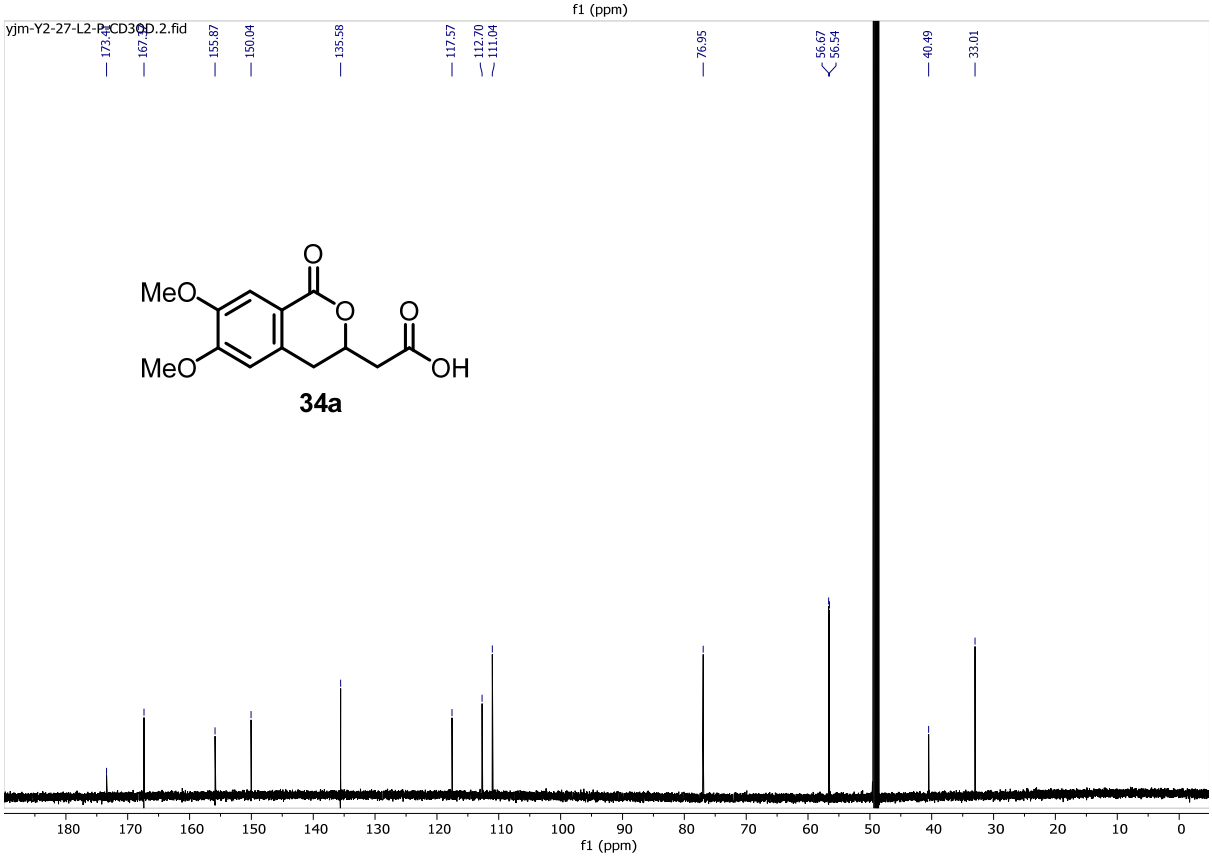
2-(5-Oxo-7,8-dihydro-5*H*-[1,3]dioxolo[4,5-*g*]isochromen-7-yl)acetic acid 33a



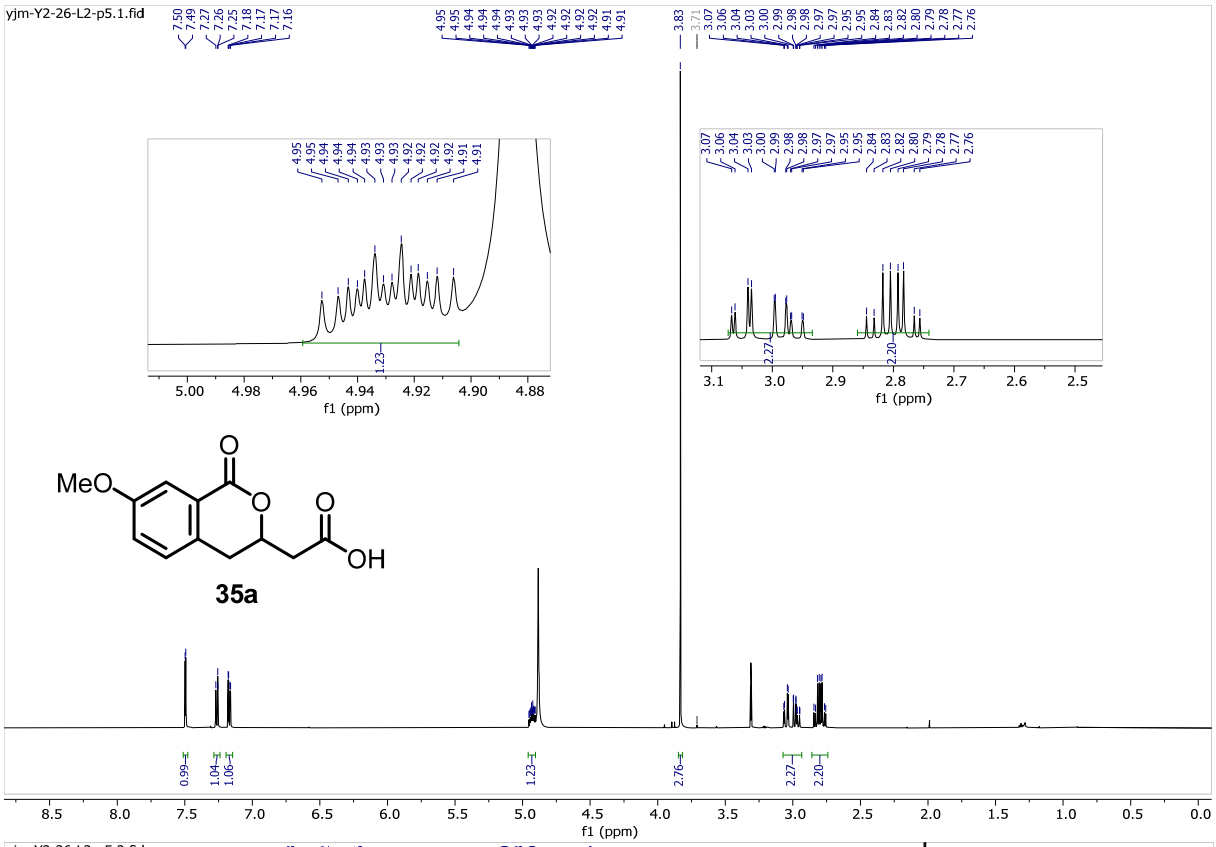


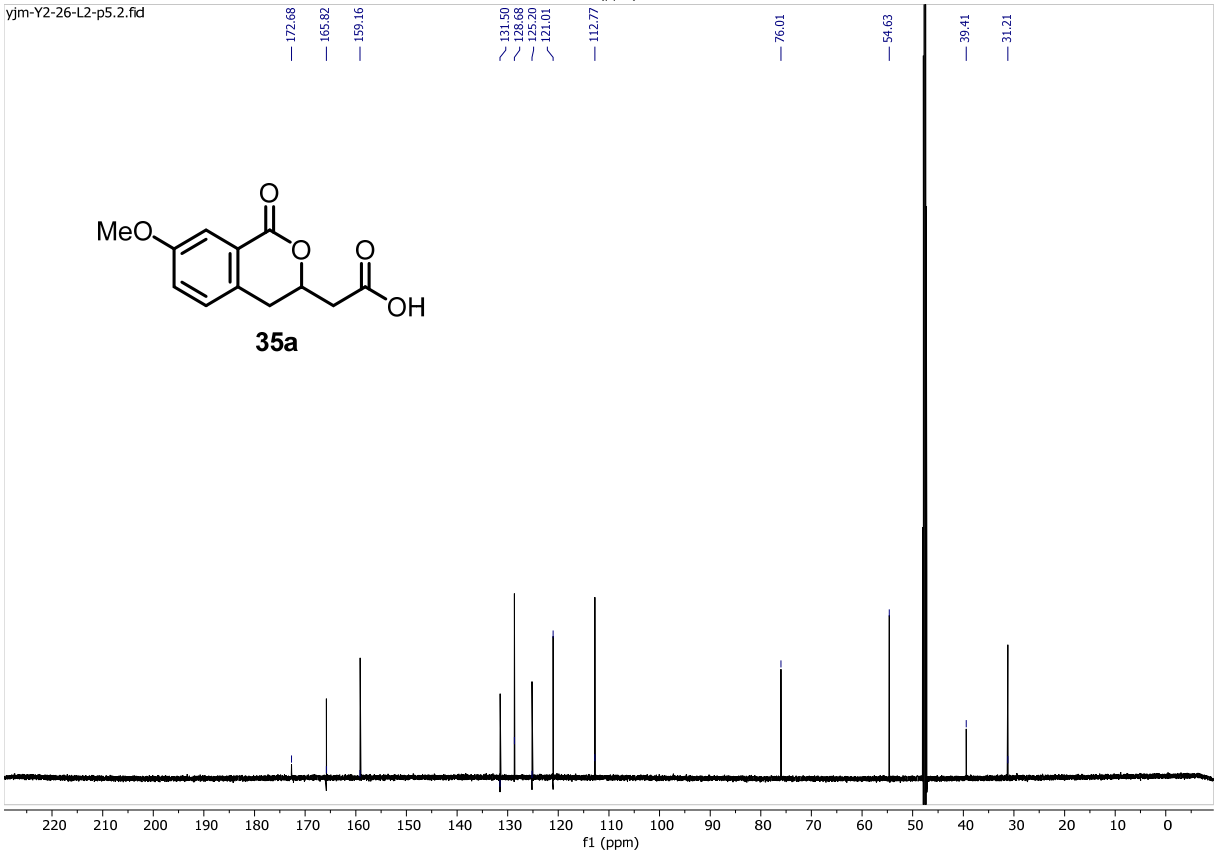
2-(6,7-Dimethoxy-1-oxoisochroman-3-yl)acetic acid 34a



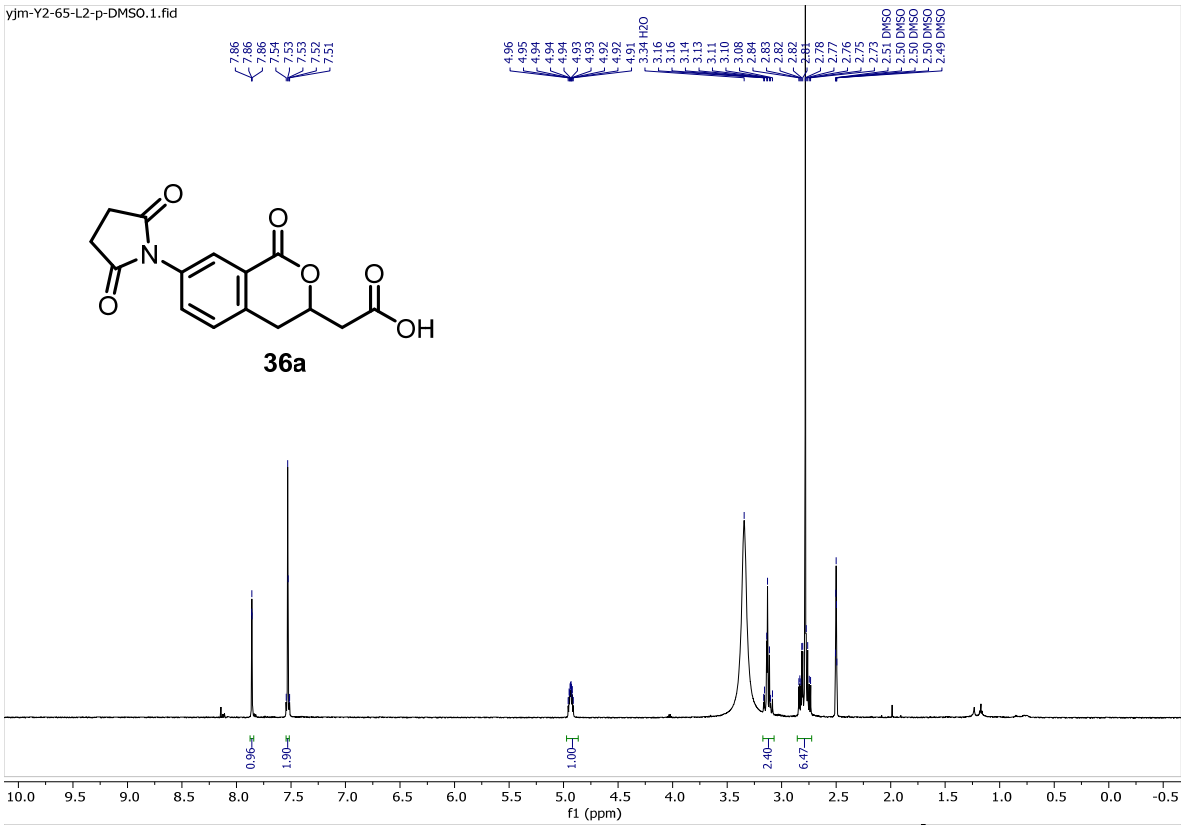


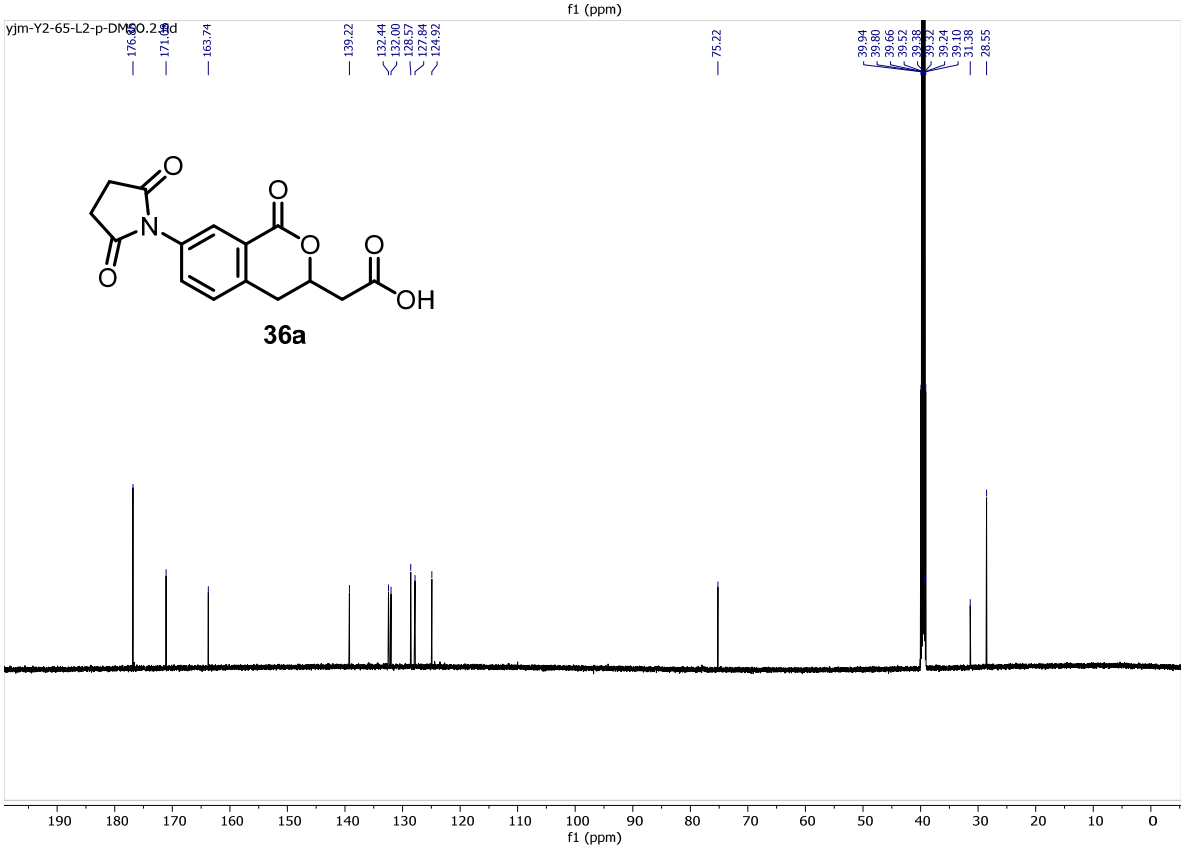
2-(7-Methoxy-1-oxoisochroman-3-yl)acetic acid 35a



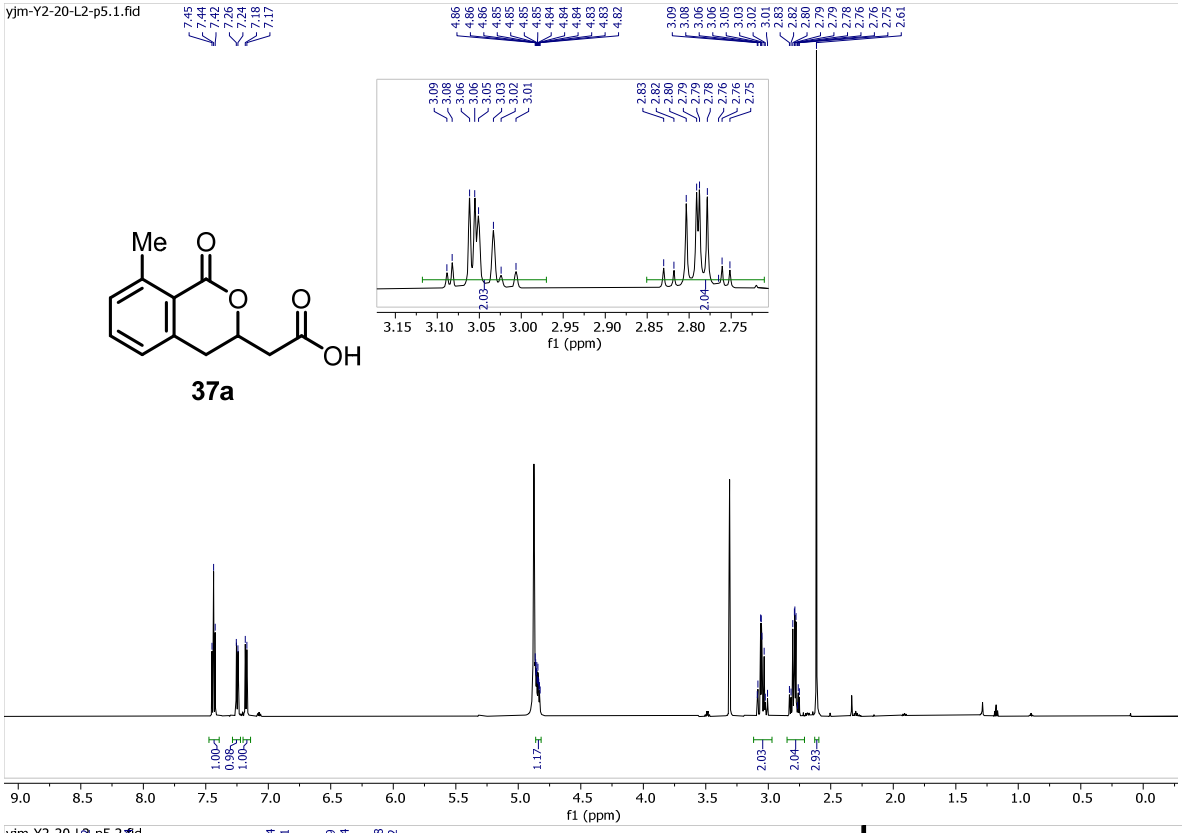


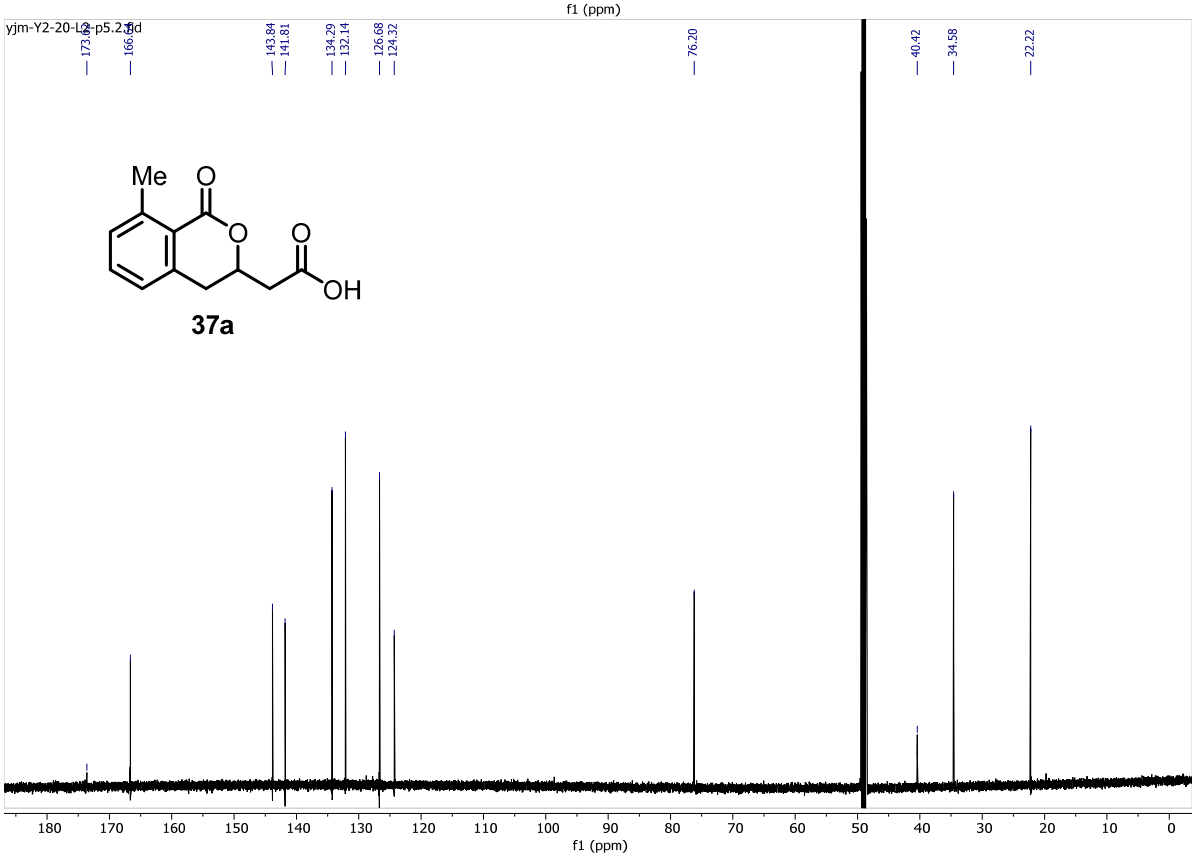
2-(7-(2,5-Dioxopyrrolidin-1-yl)-1-oxoisochroman-3-yl)acetic acid 36a



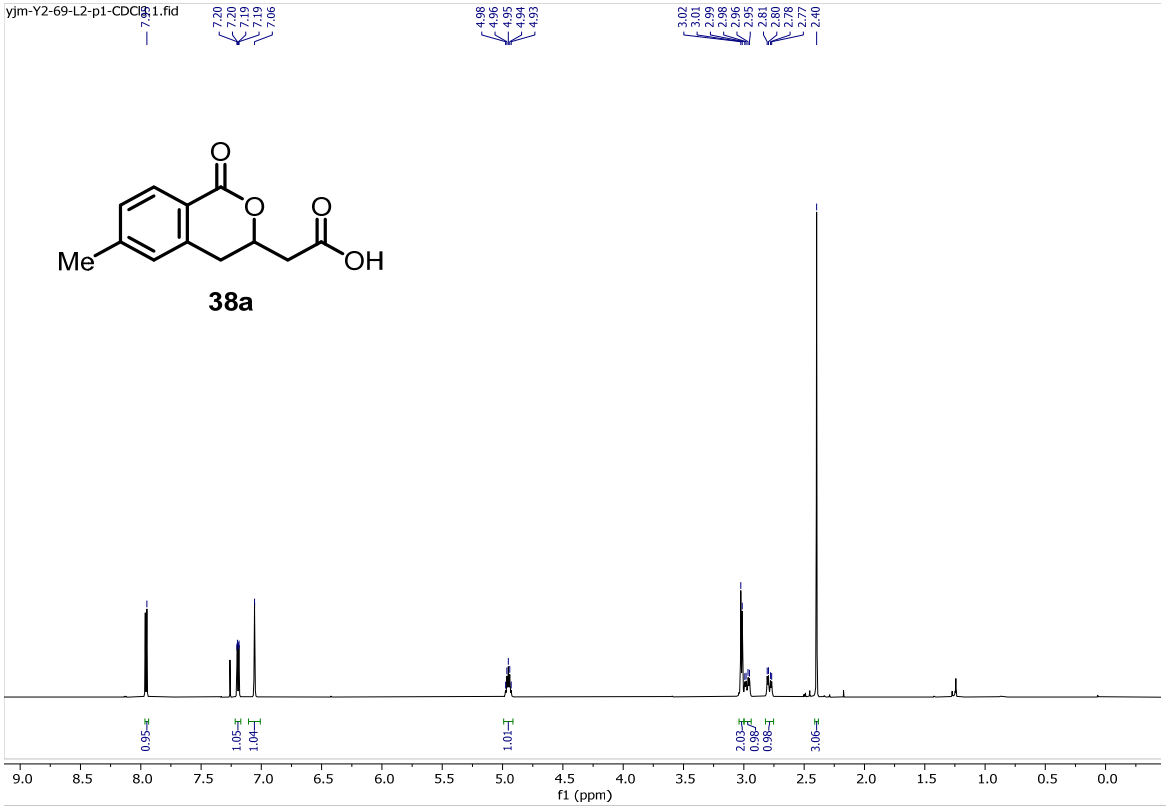


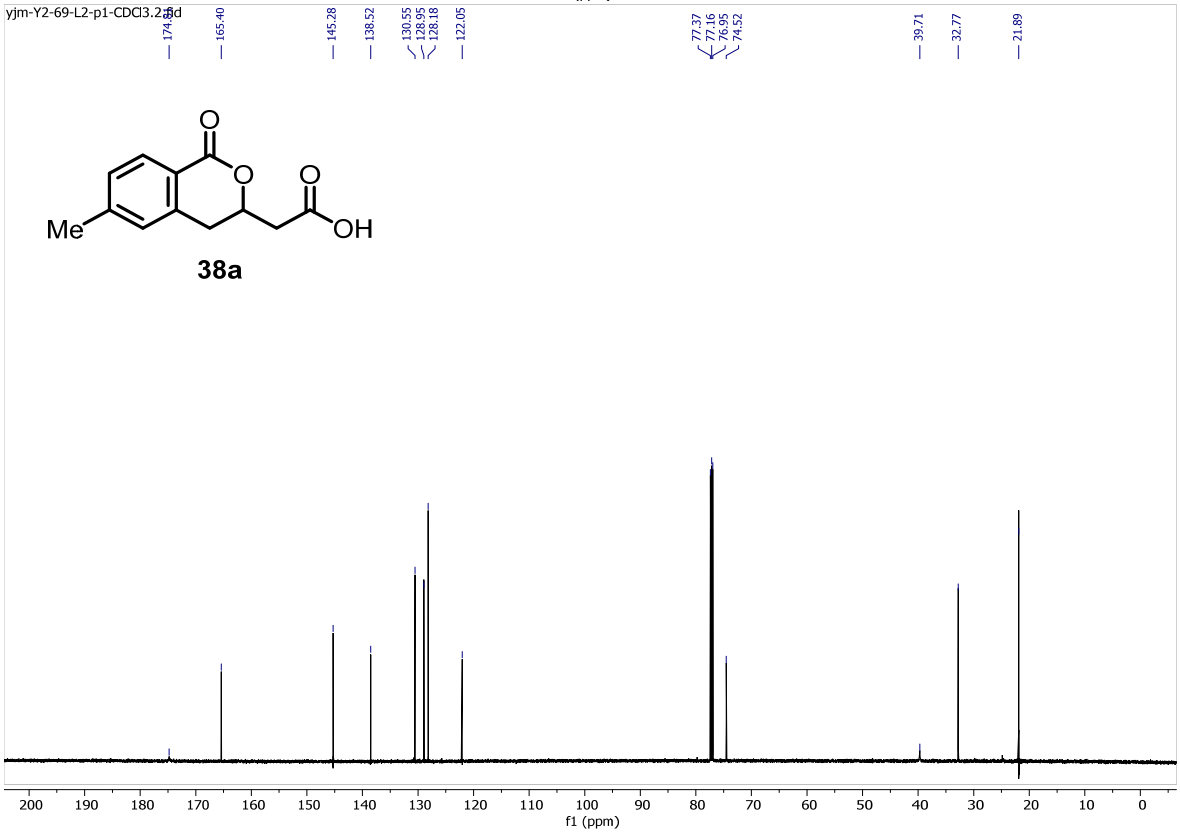
2-(8-Methyl-1-oxoisochroman-3-yl)acetic acid 37a



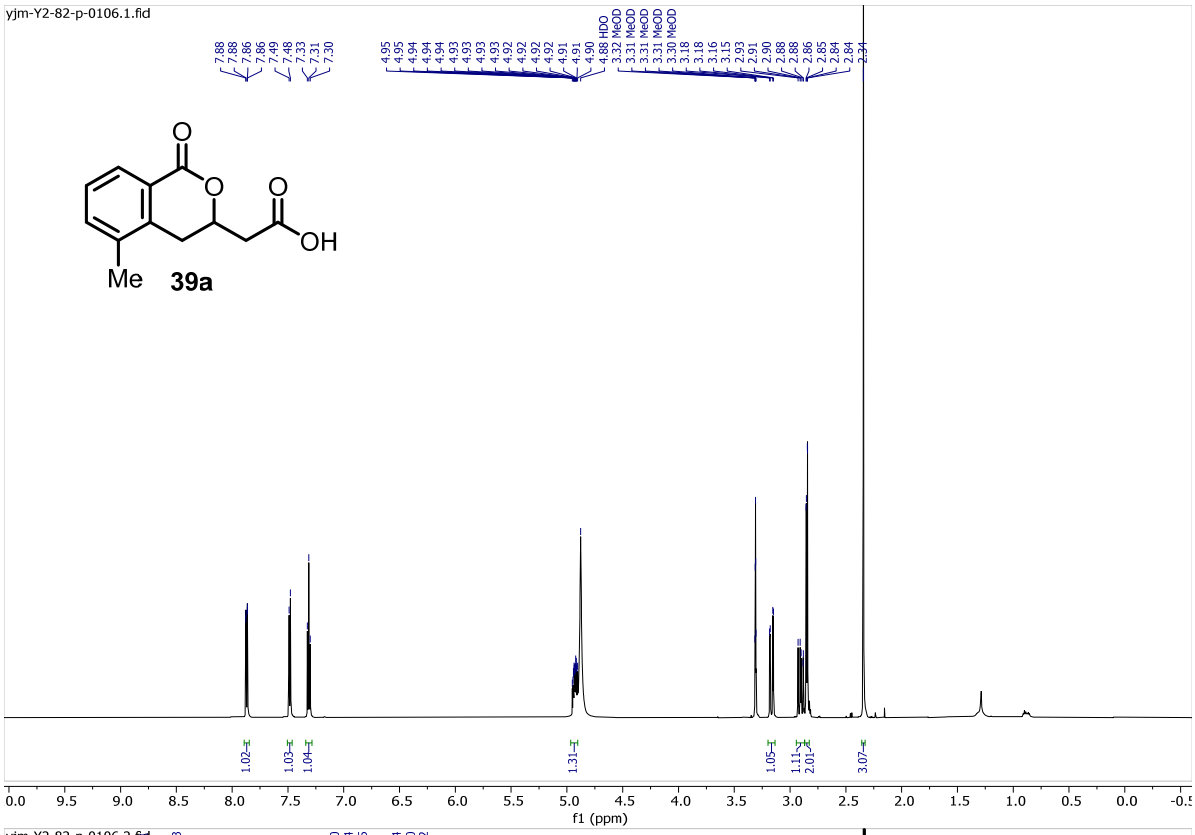


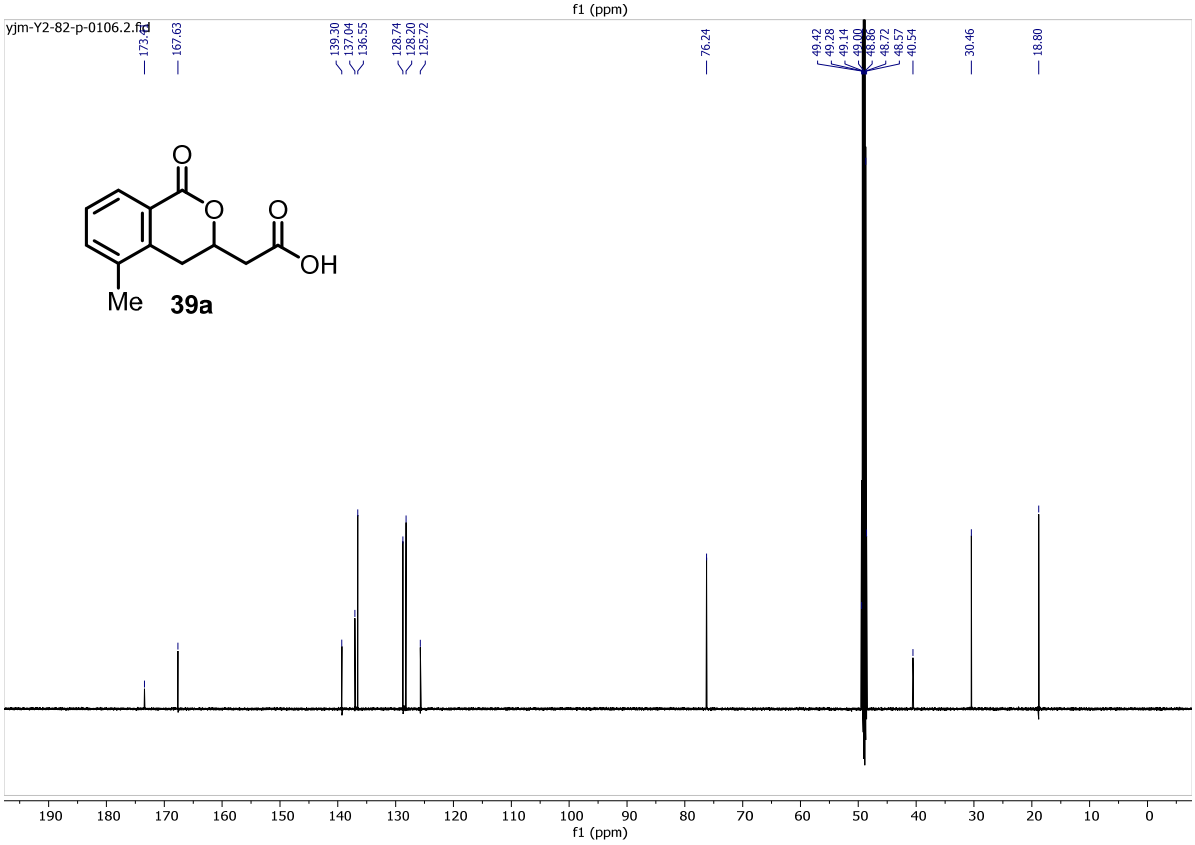
2-(6-Methyl-1-oxoisochroman-3-yl)acetic acid 38a



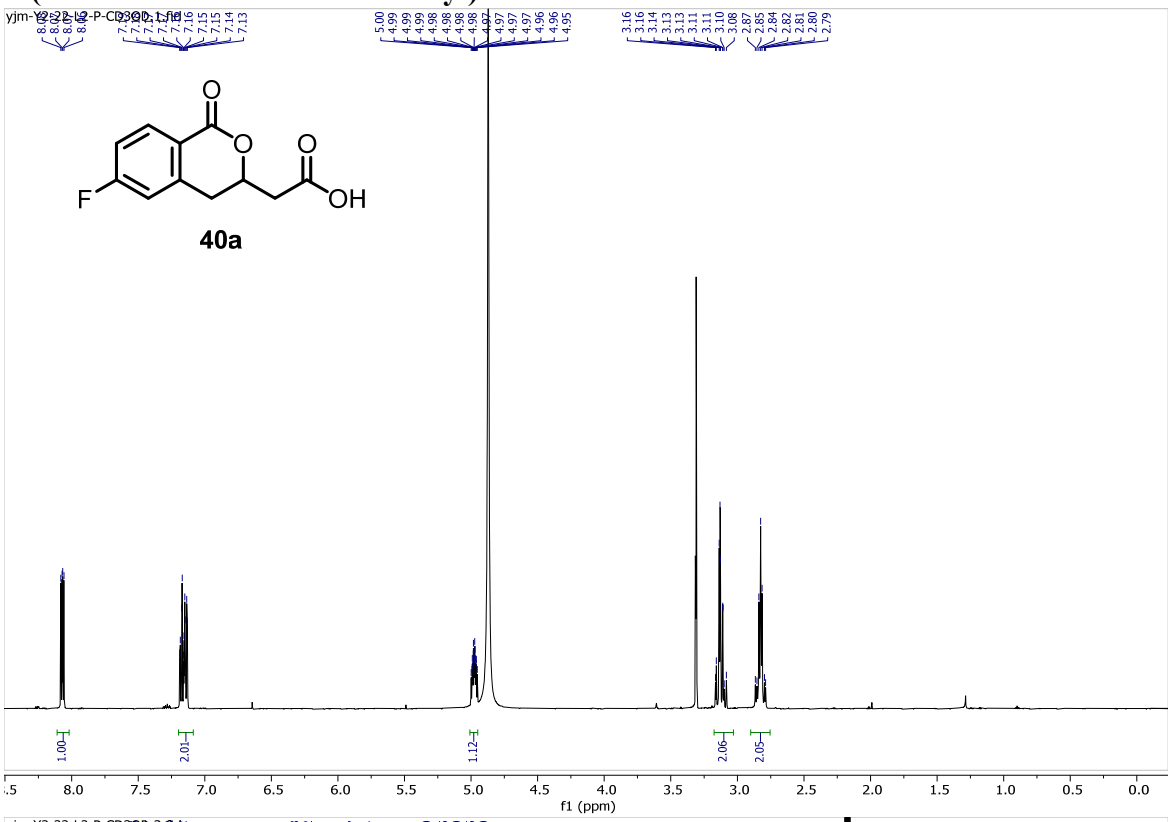


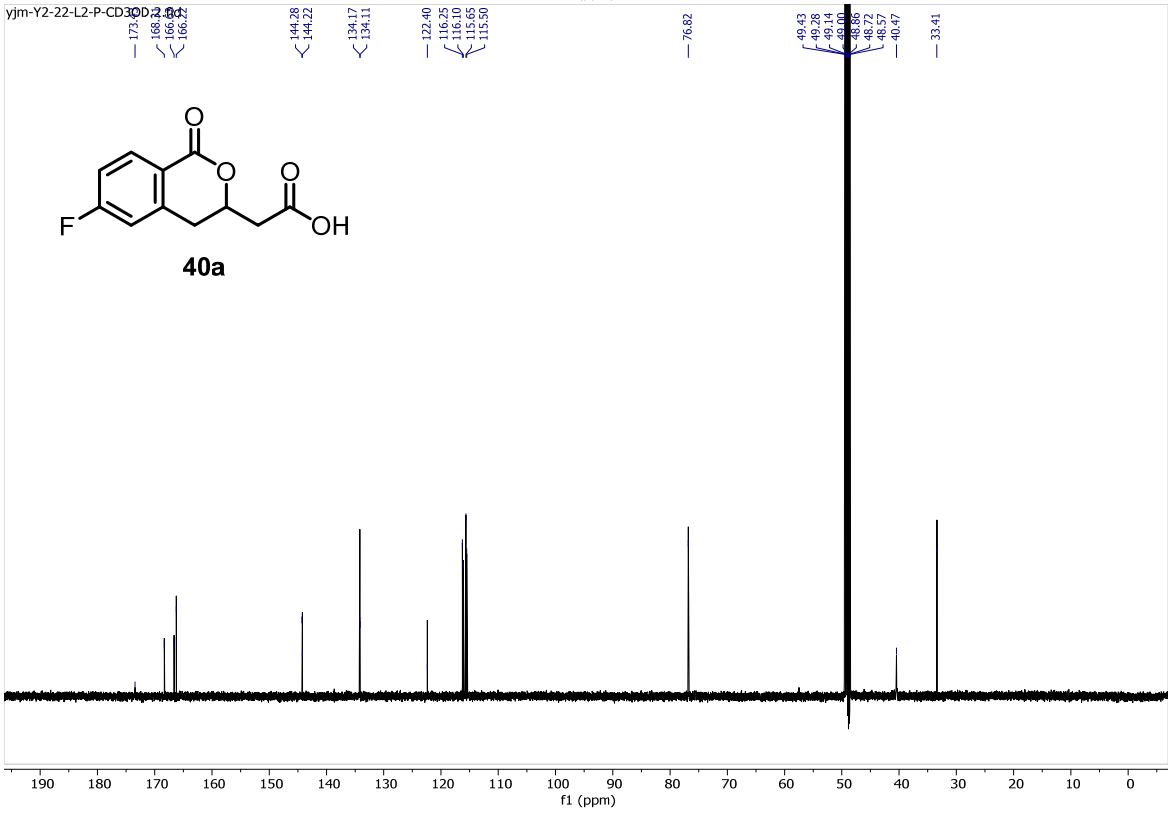
2-(5-Methyl-1-oxoisochroman-3-yl)acetic acid 39a

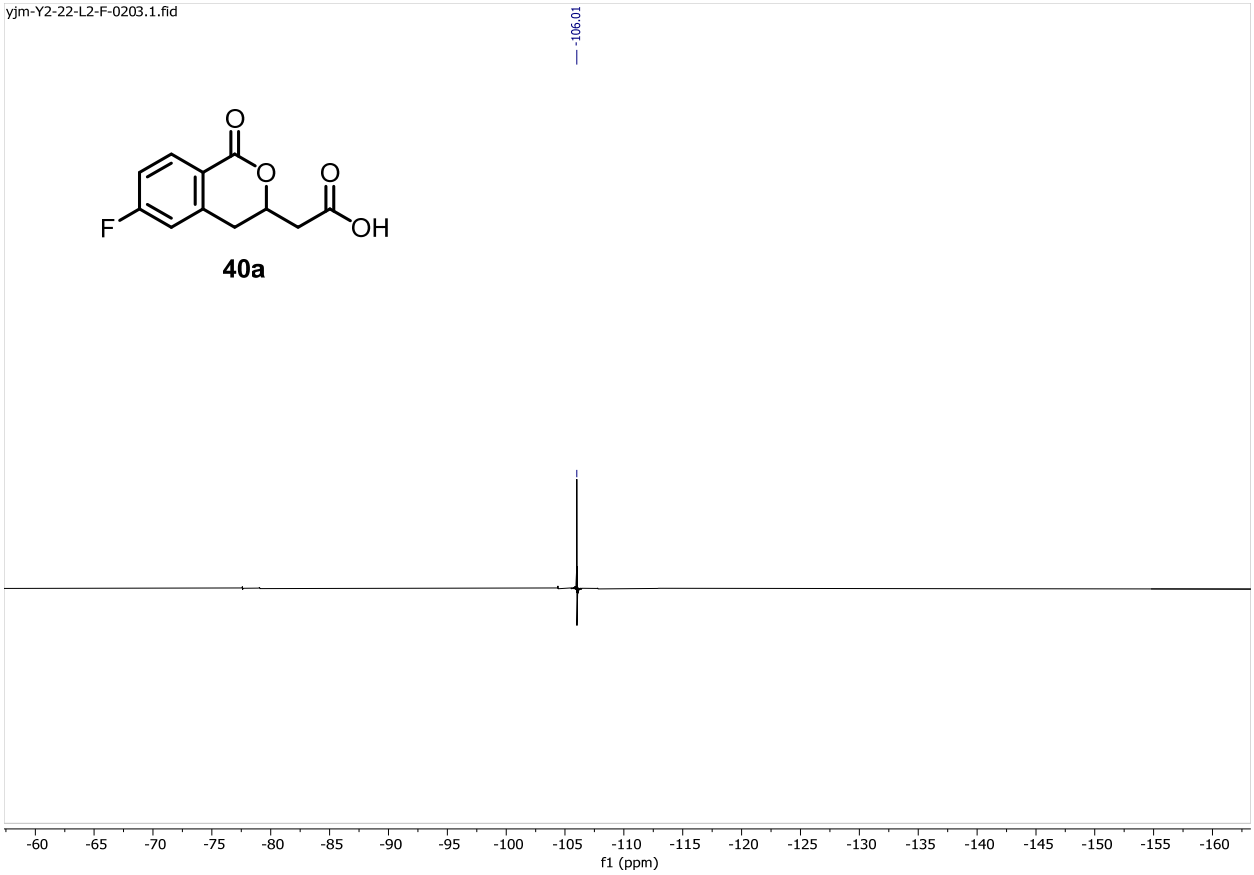




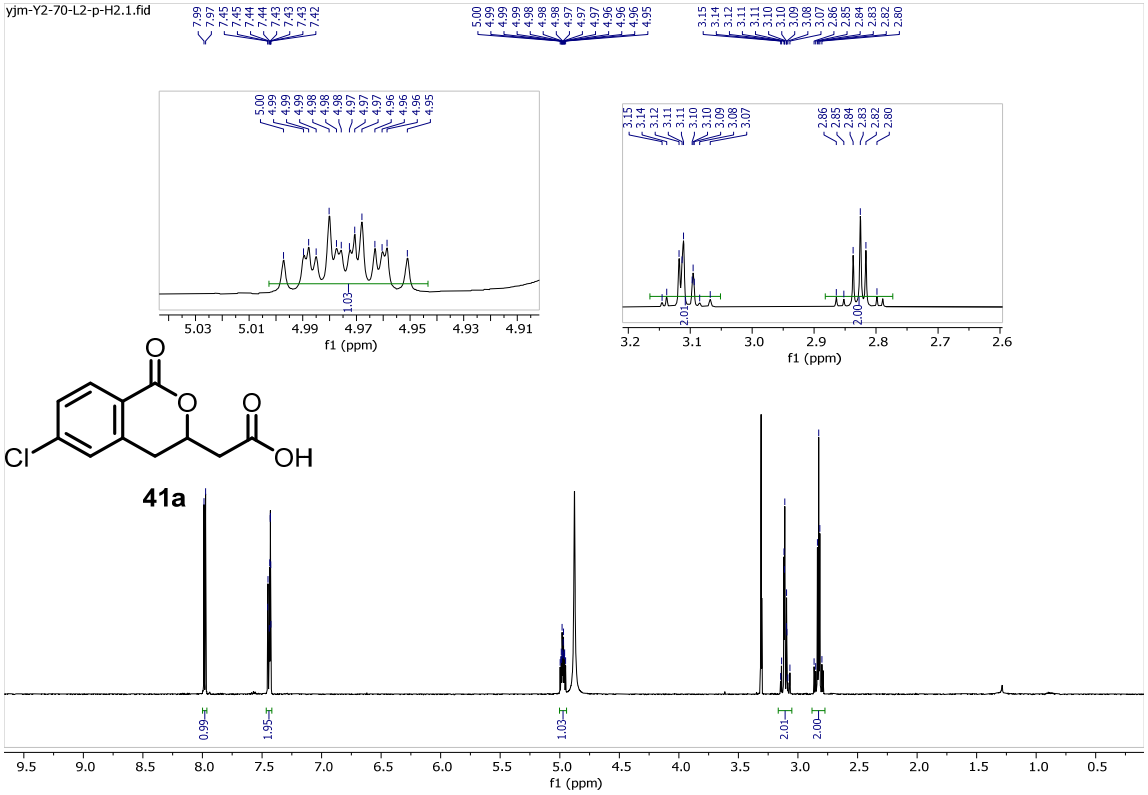
2-(6-Fluoro-1-oxoisochroman-3-yl)acetic acid 40a

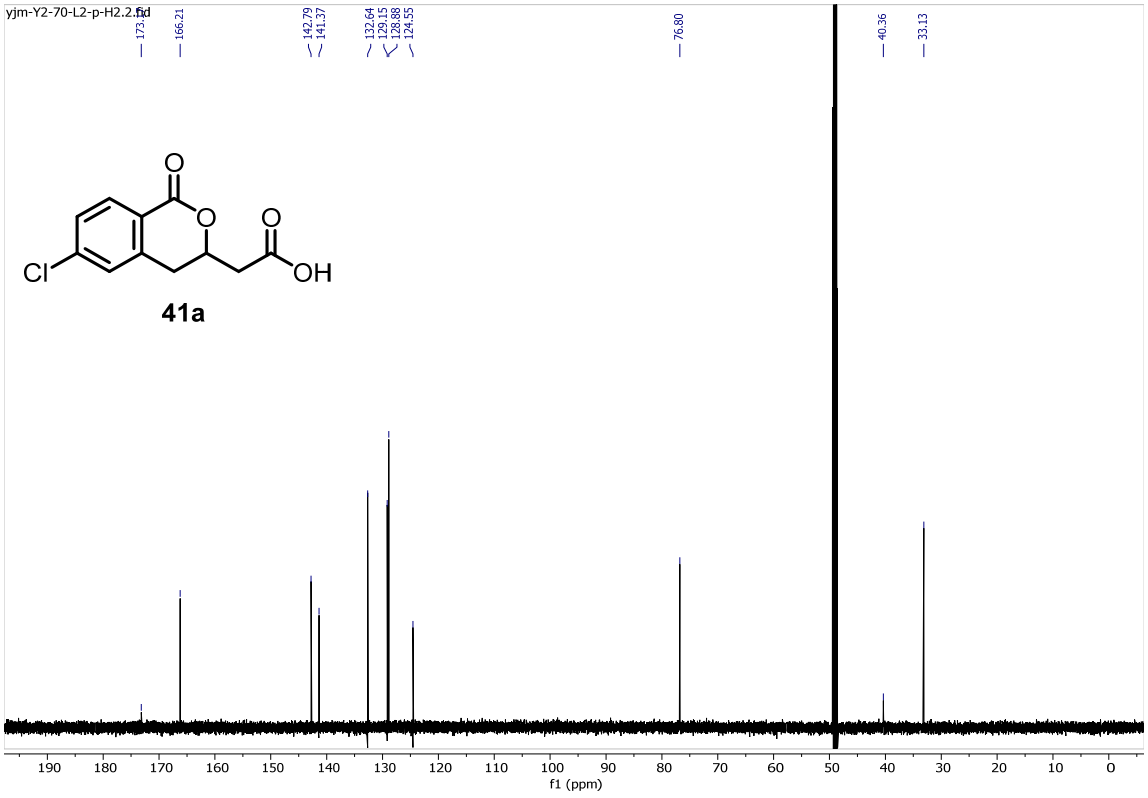




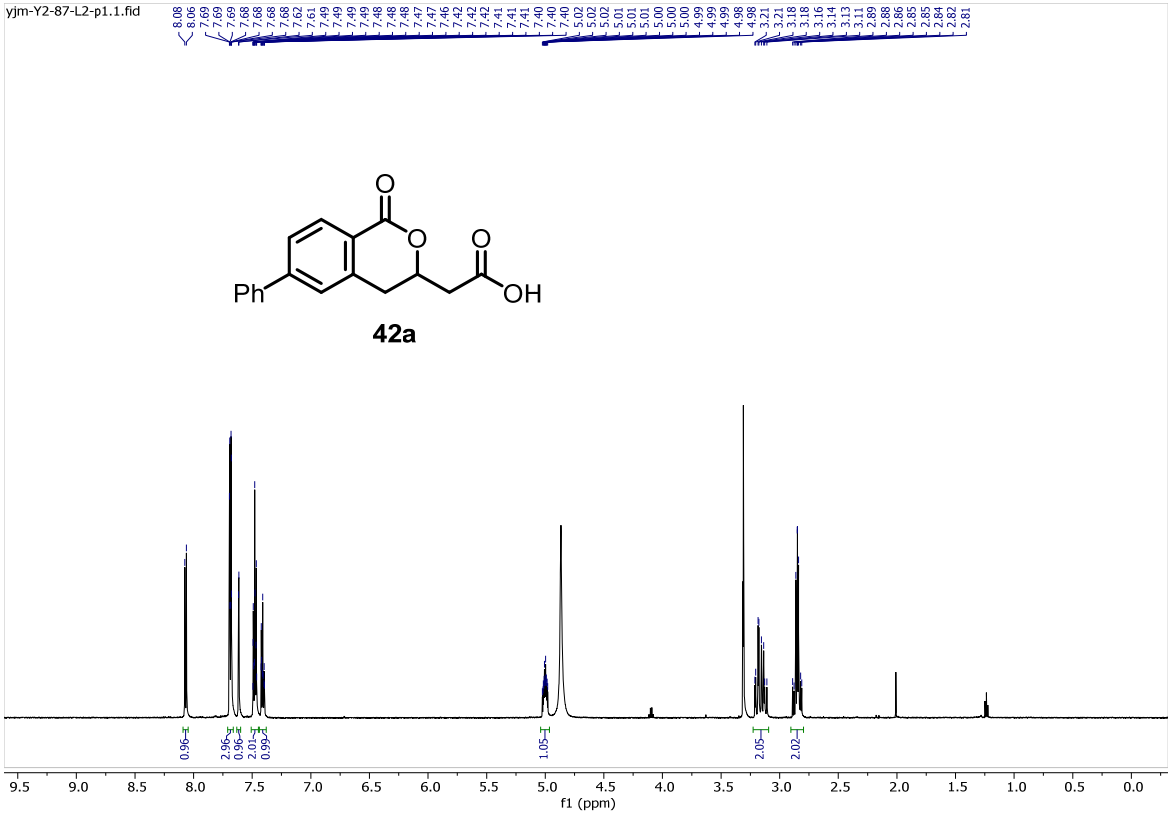

yjm-Y2-22-L2-F-0203.1.fid
-106.01
O
O
O
F
OH
40a
-60
-65
-70
-75
-80
-85
-90
-95
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
-150
-155
-160
f1 (ppm)

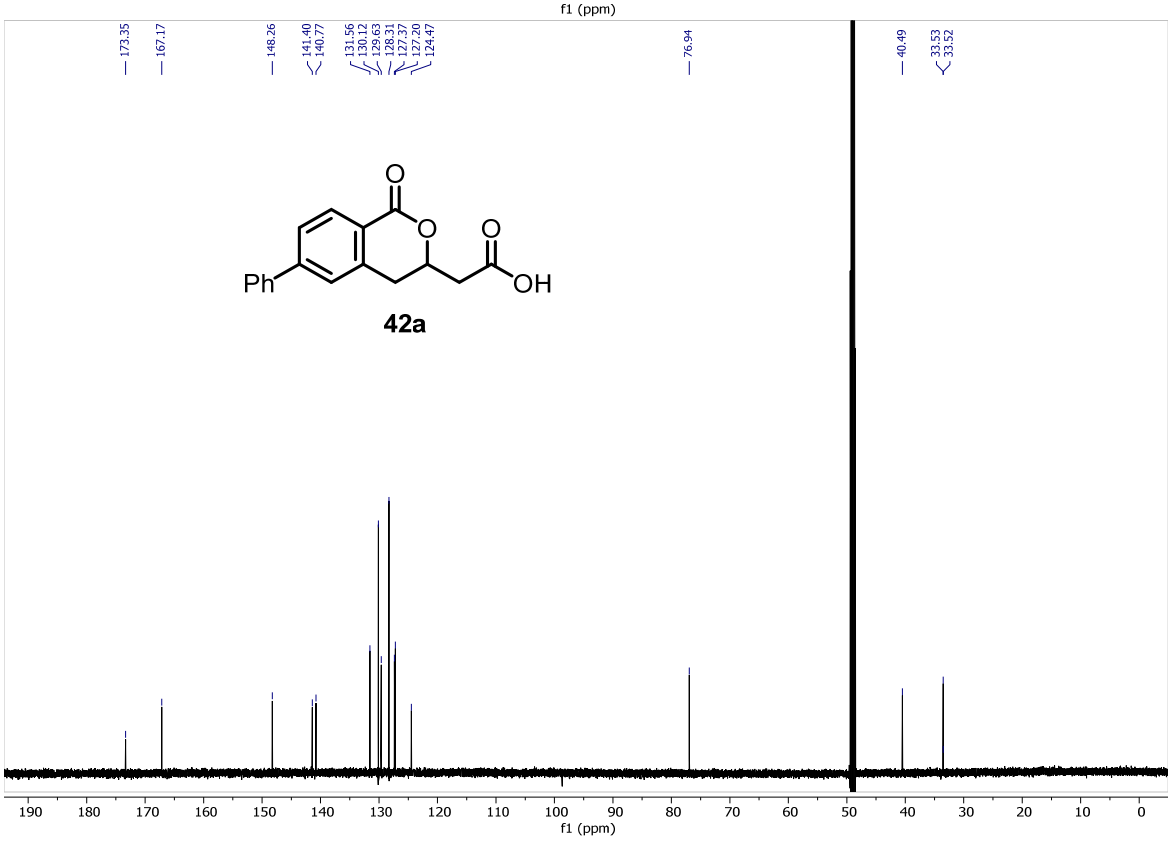
2-(6-Chloro-1-oxoisochroman-3-yl)acetic acid 41a



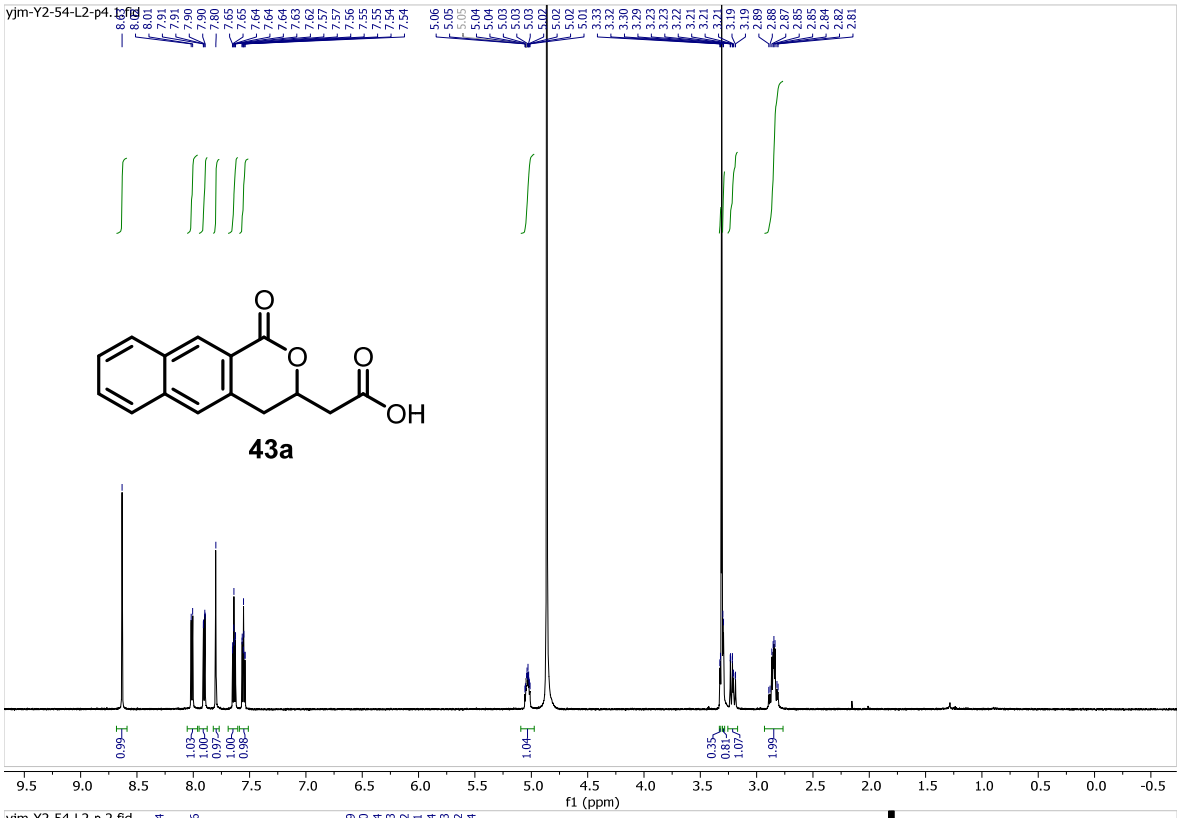


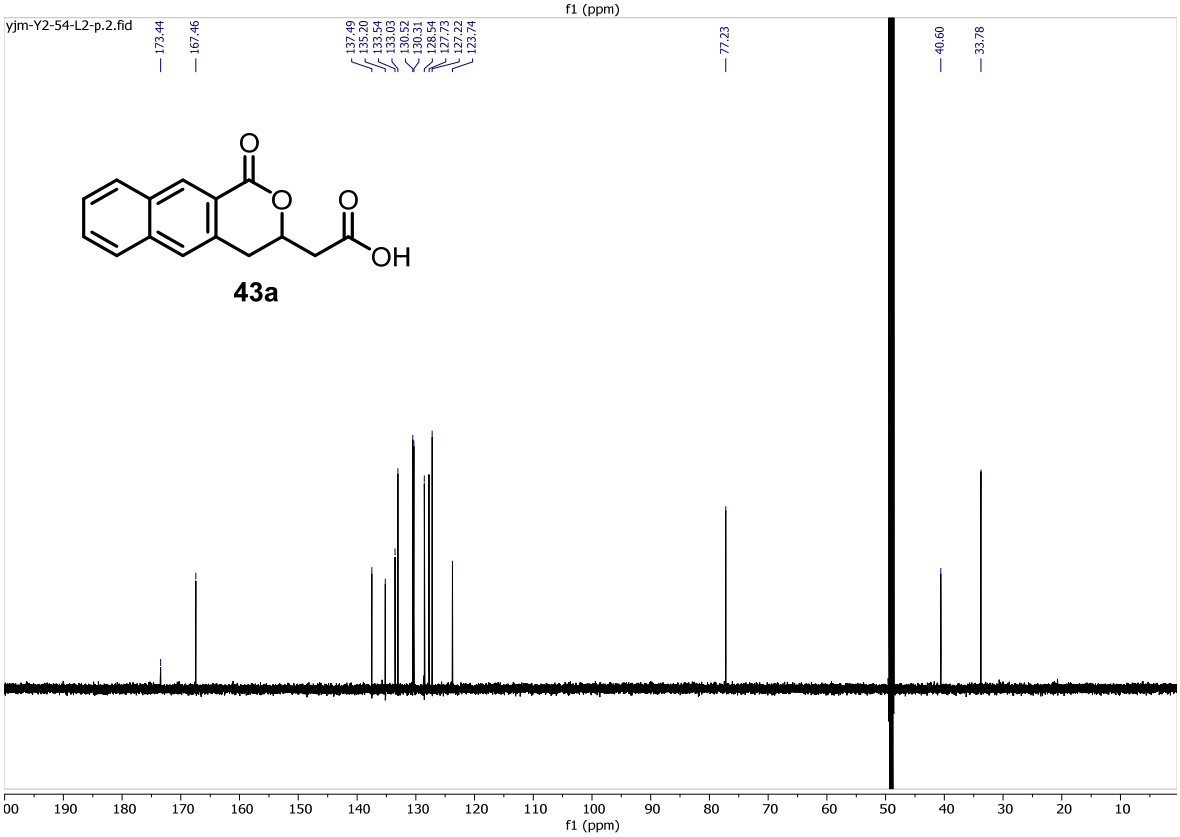
2-(1-Oxo-6-phenylisochroman-3-yl)acetic acid 42a



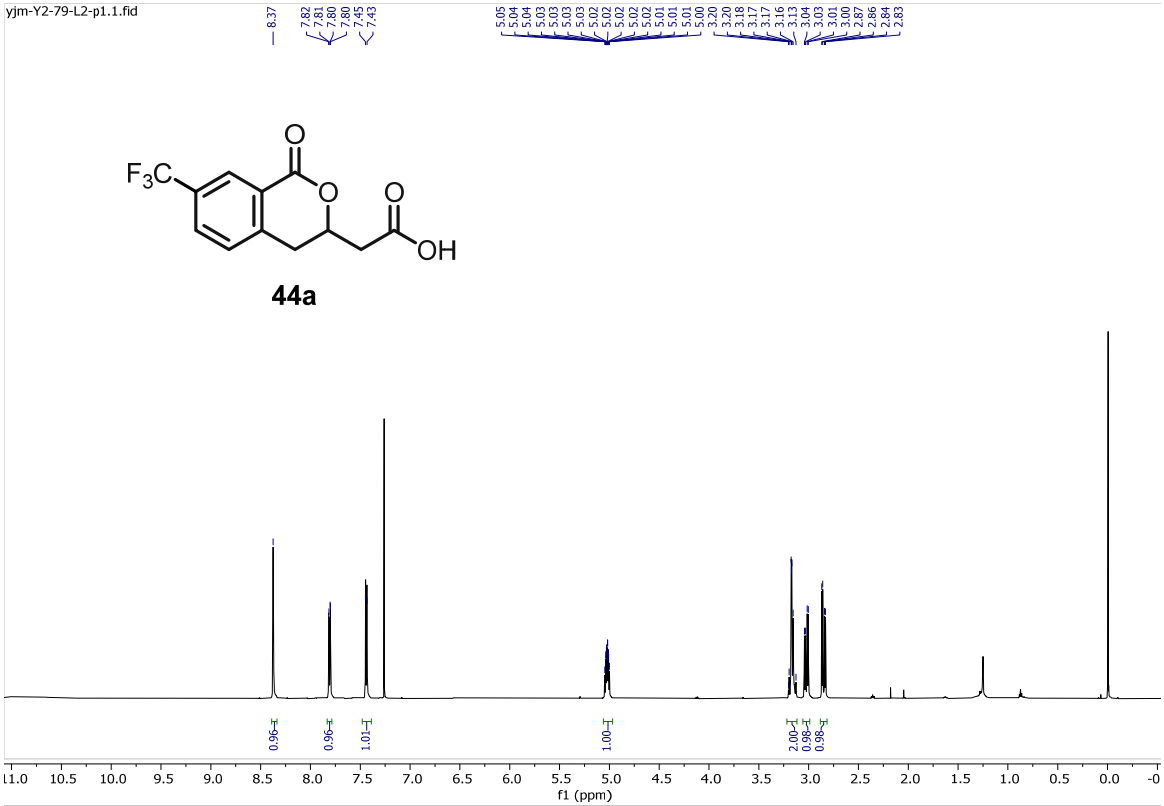


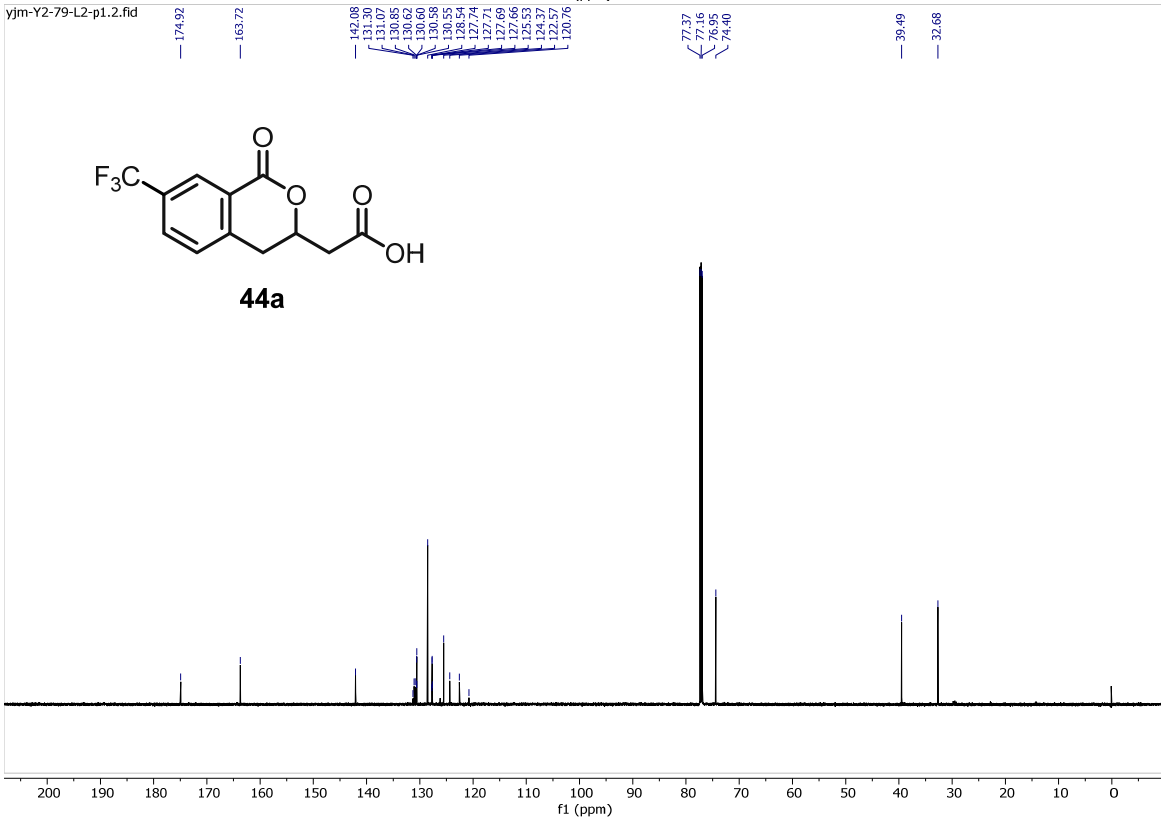
2-(1-Oxo-3,4-dihydro-1*H*-benzo[*g*]isochromen-3-yl)acetic acid 43a

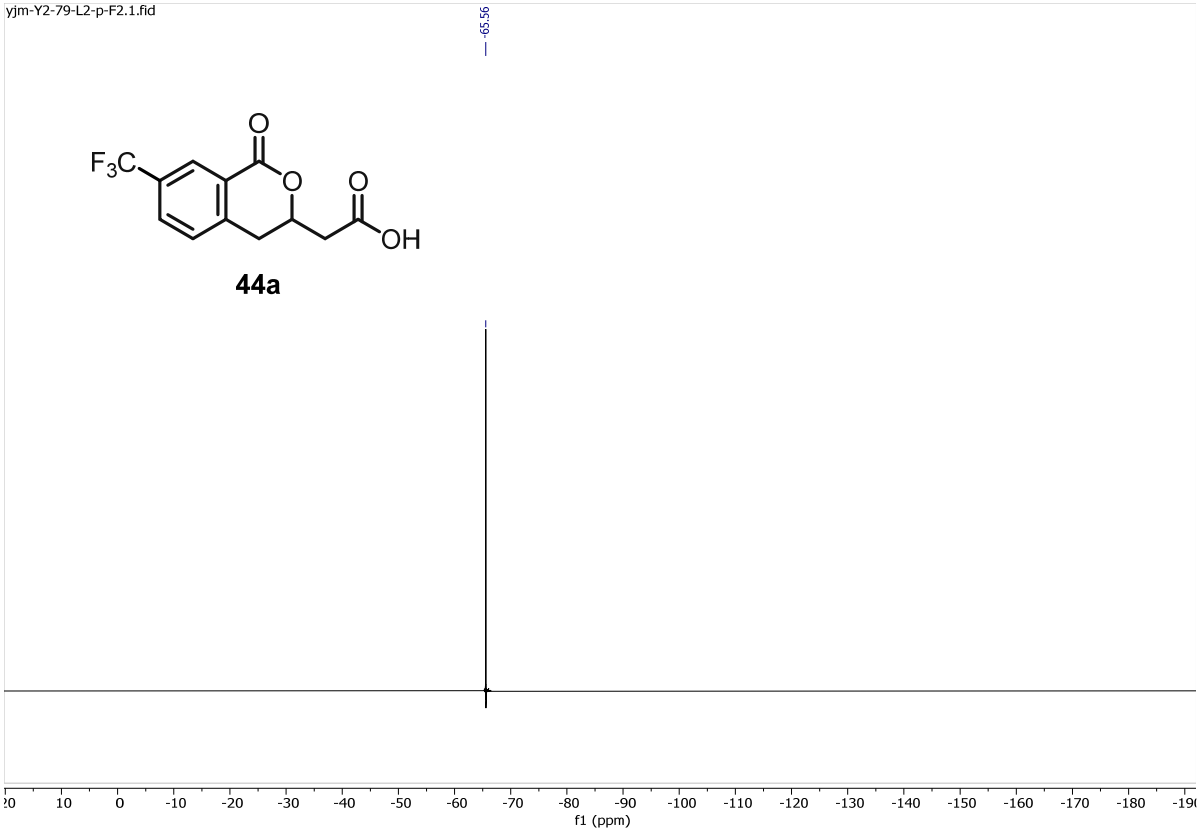




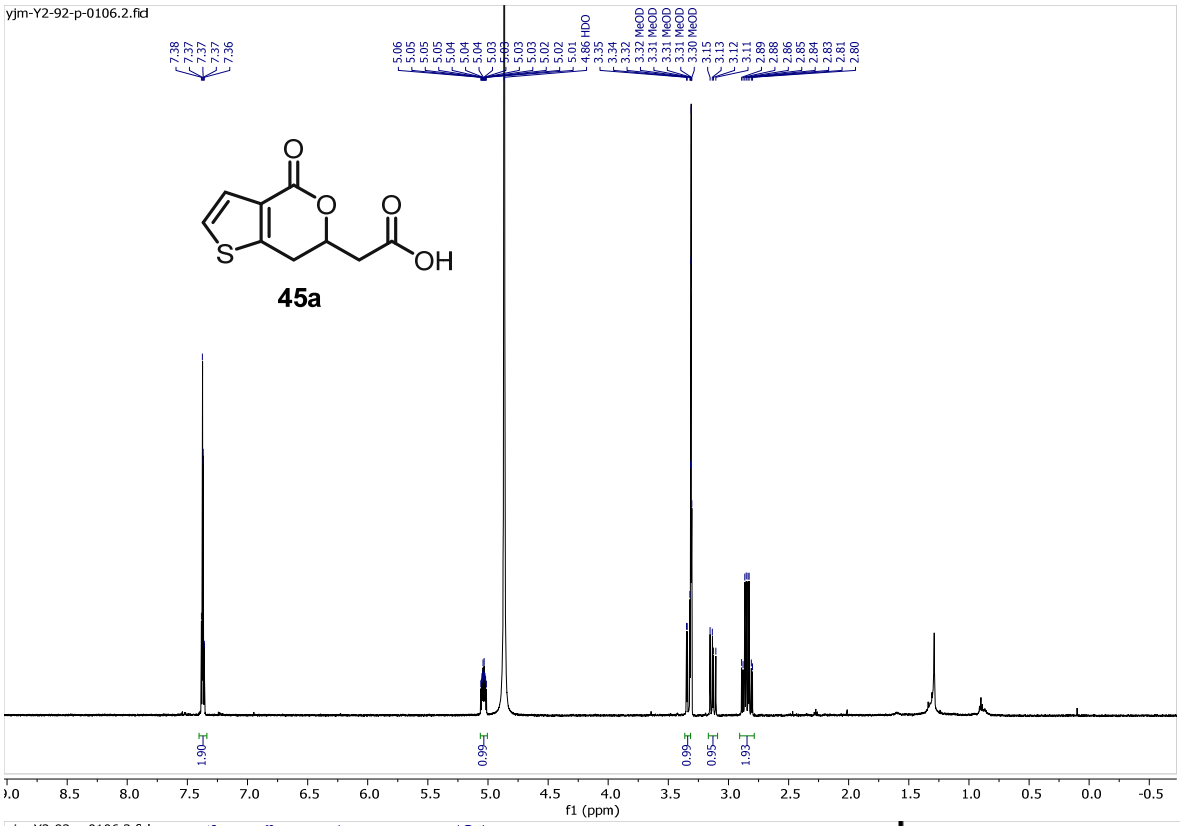
2-(1-Oxo-7-(trifluoromethyl)isochroman-3-yl)acetic acid 44a

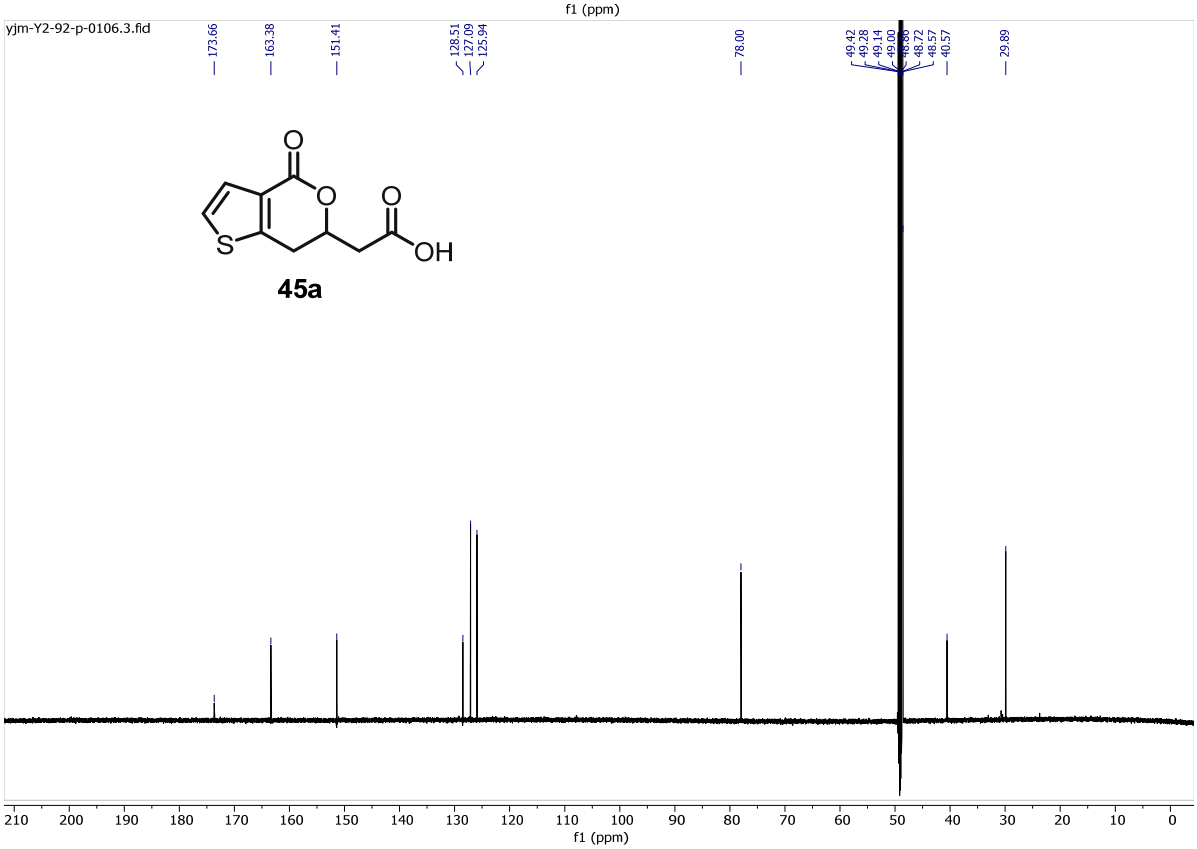




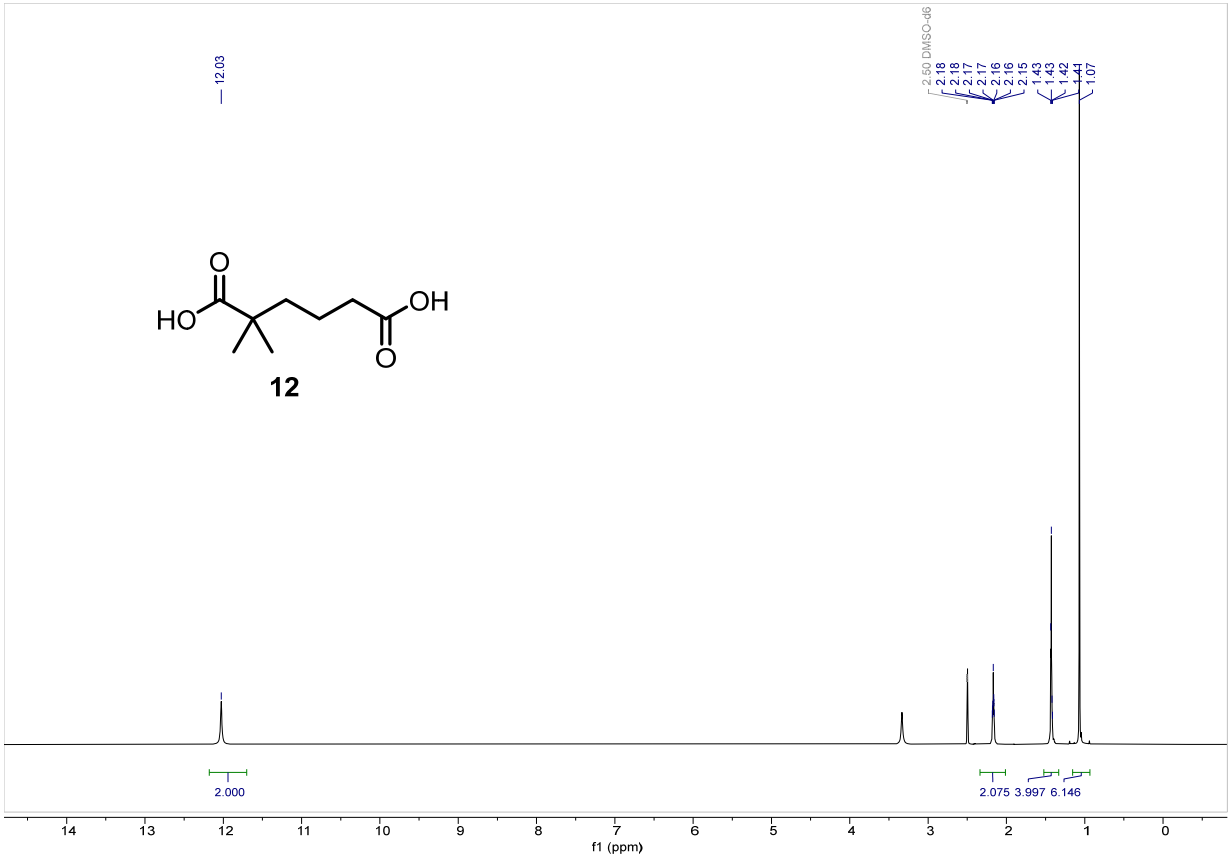

yjm-Y2-79-L2-p-F2.1.fid
-65.56
O
F3C
O
O
OH
44a
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
f1 (ppm)

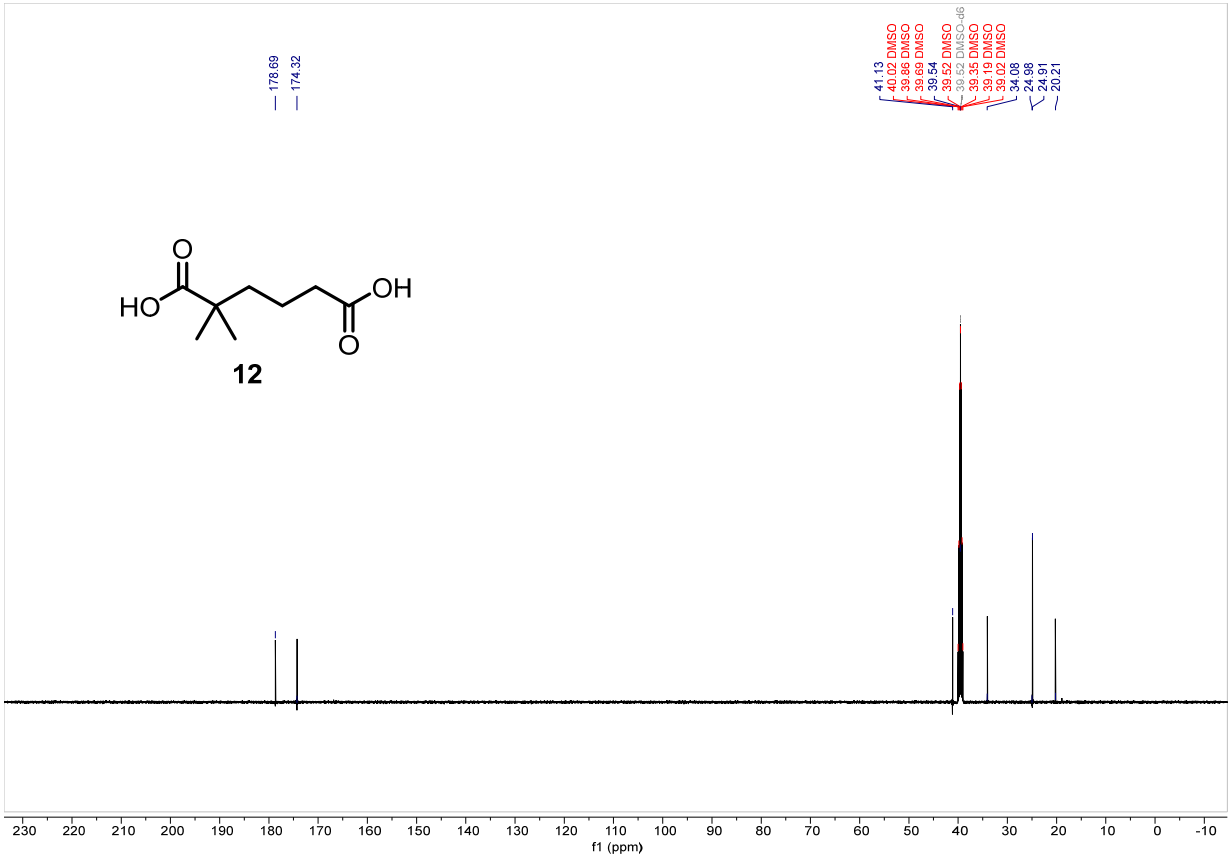
2-(4-Oxo-6,7-dihydro-4*H*-thieno[3,2-*c*]pyran-6-yl)acetic acid 45a



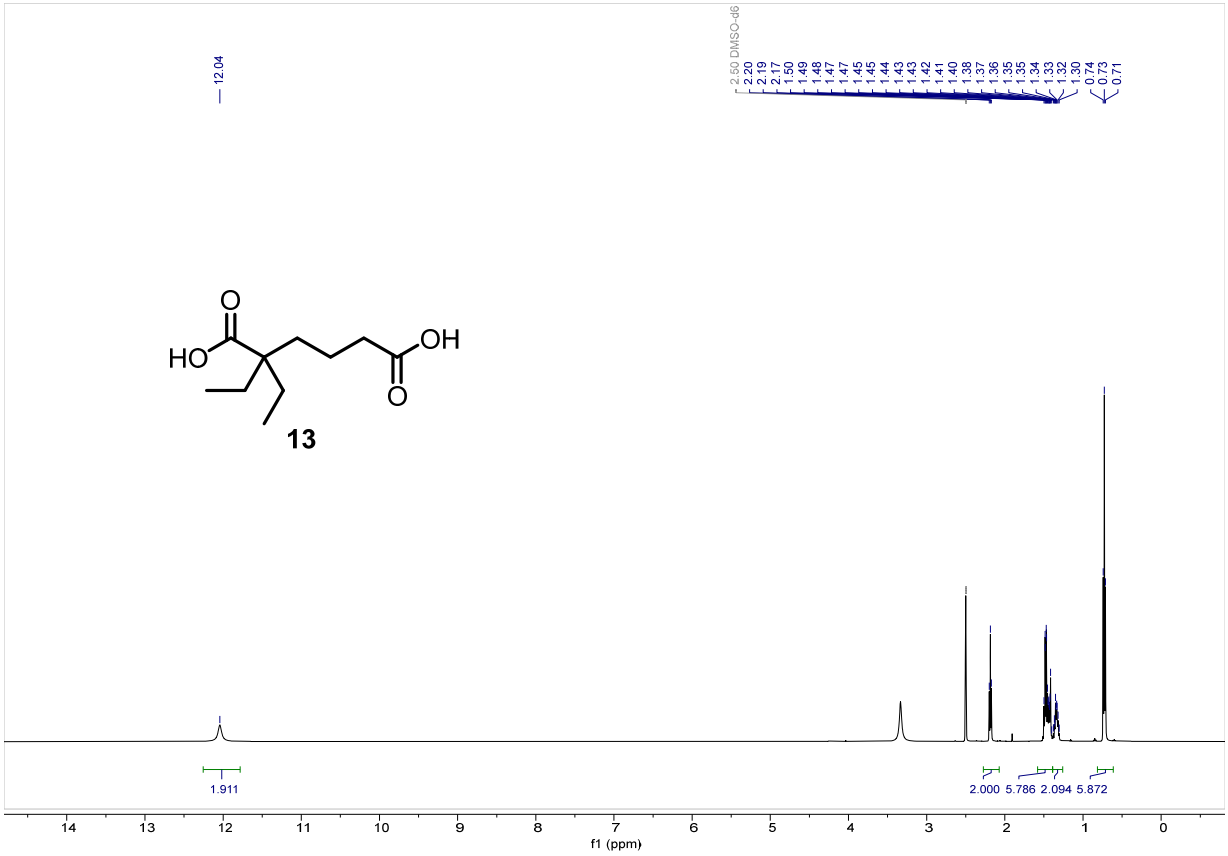


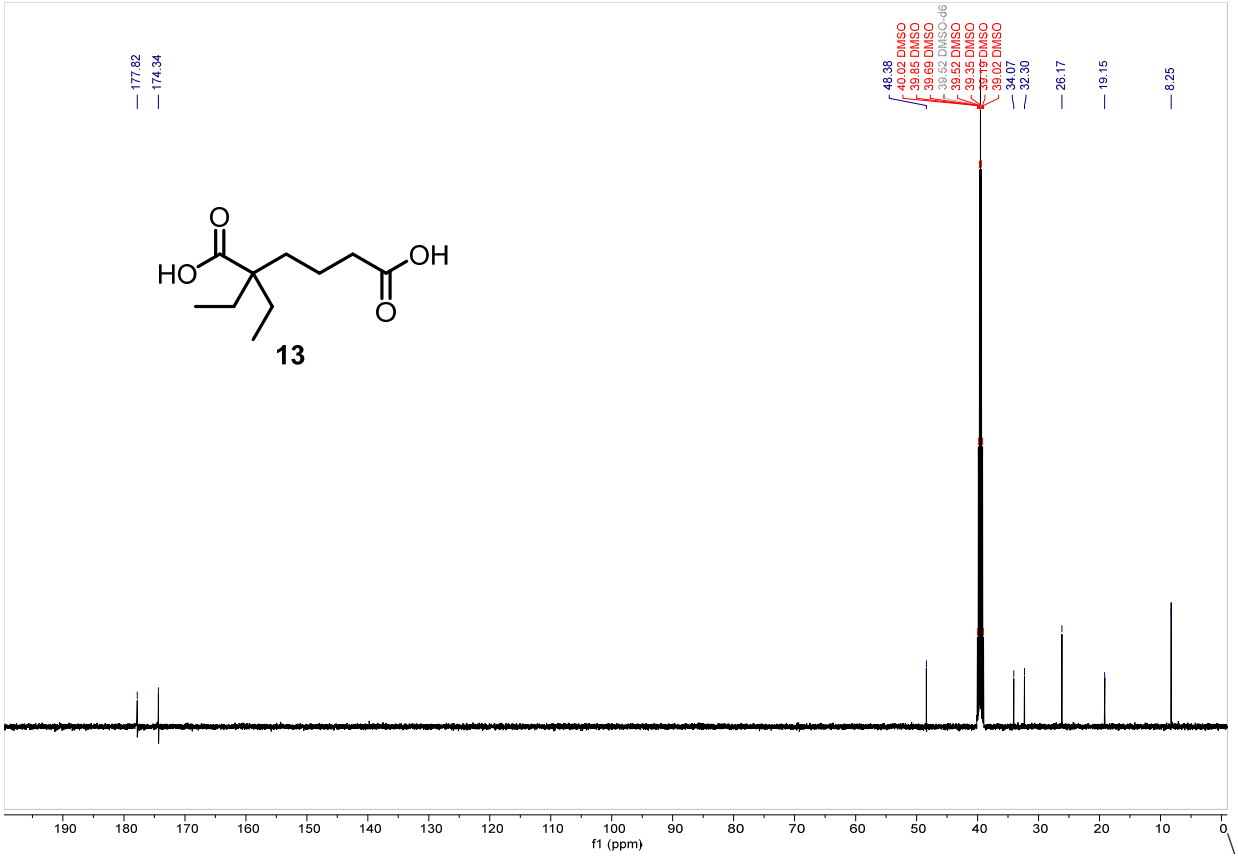
2,2-Dimethylhexanedioic acid 12



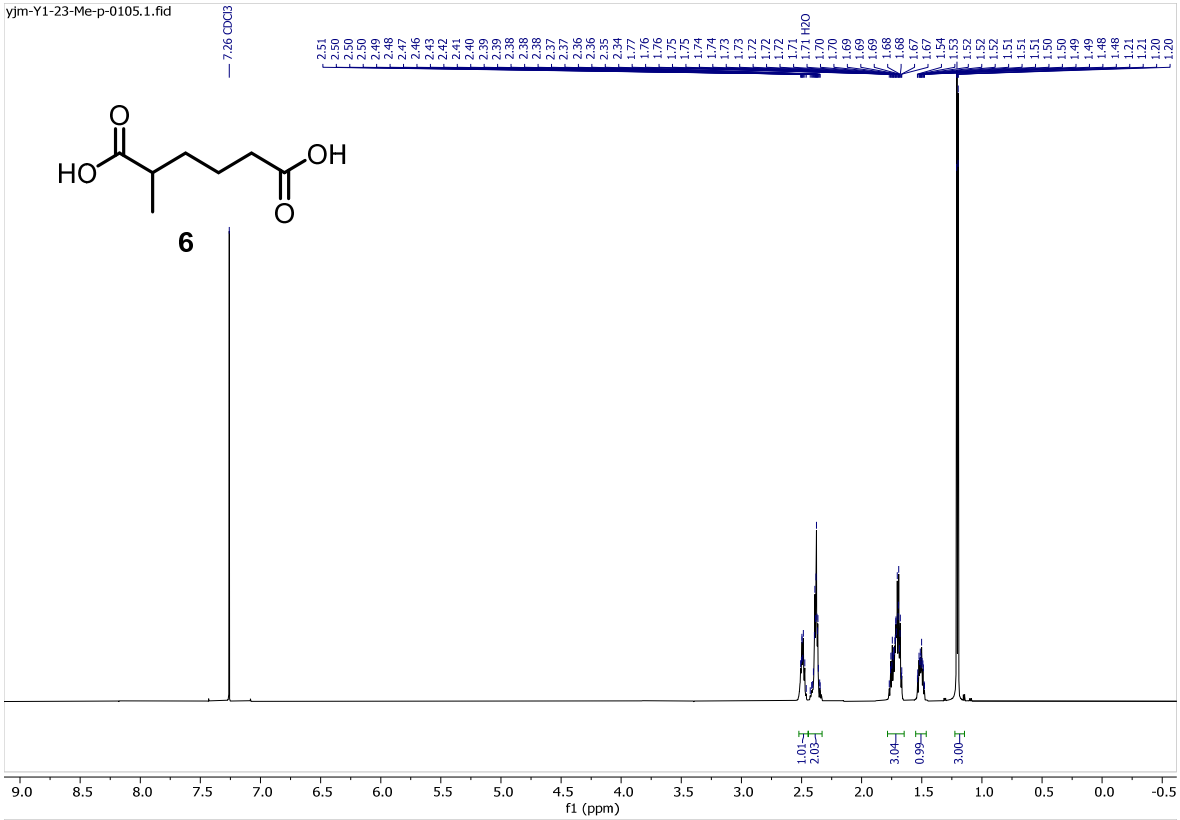


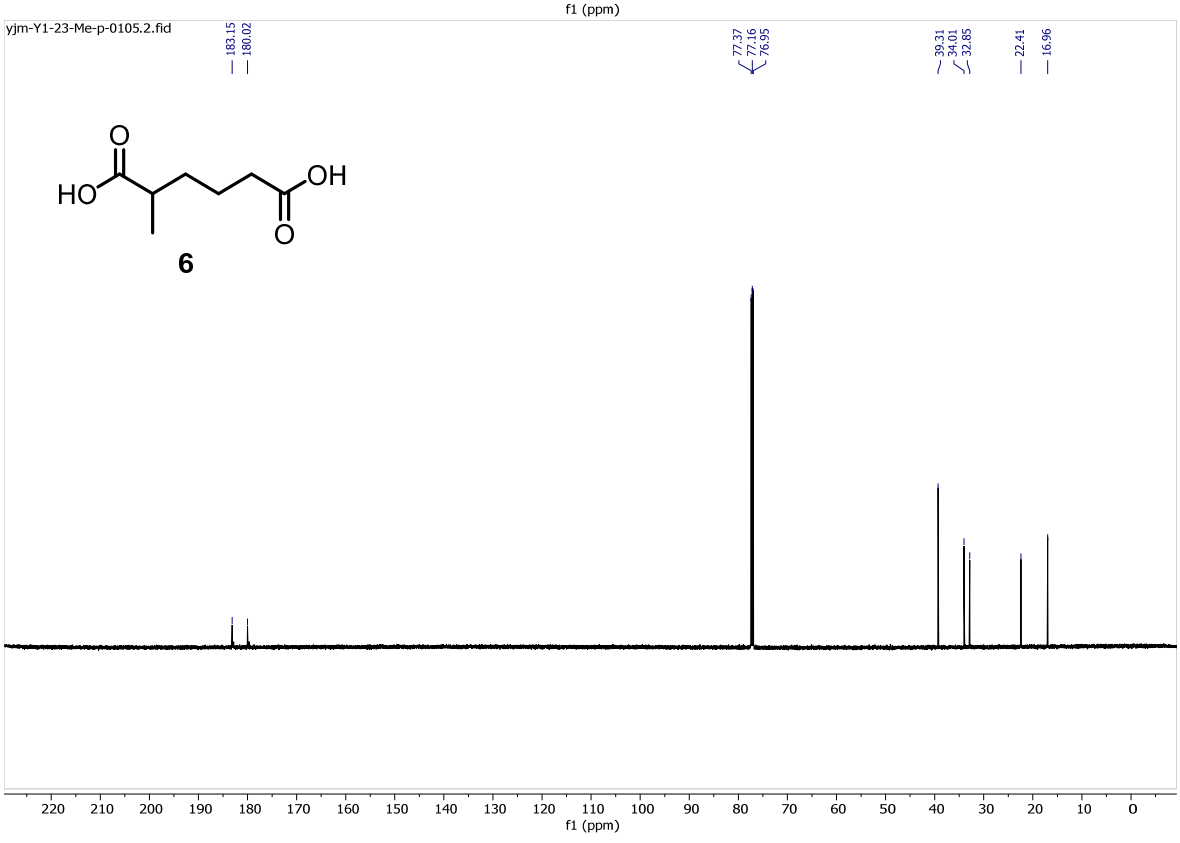
2,2-Diethylhexanedioic acid 13



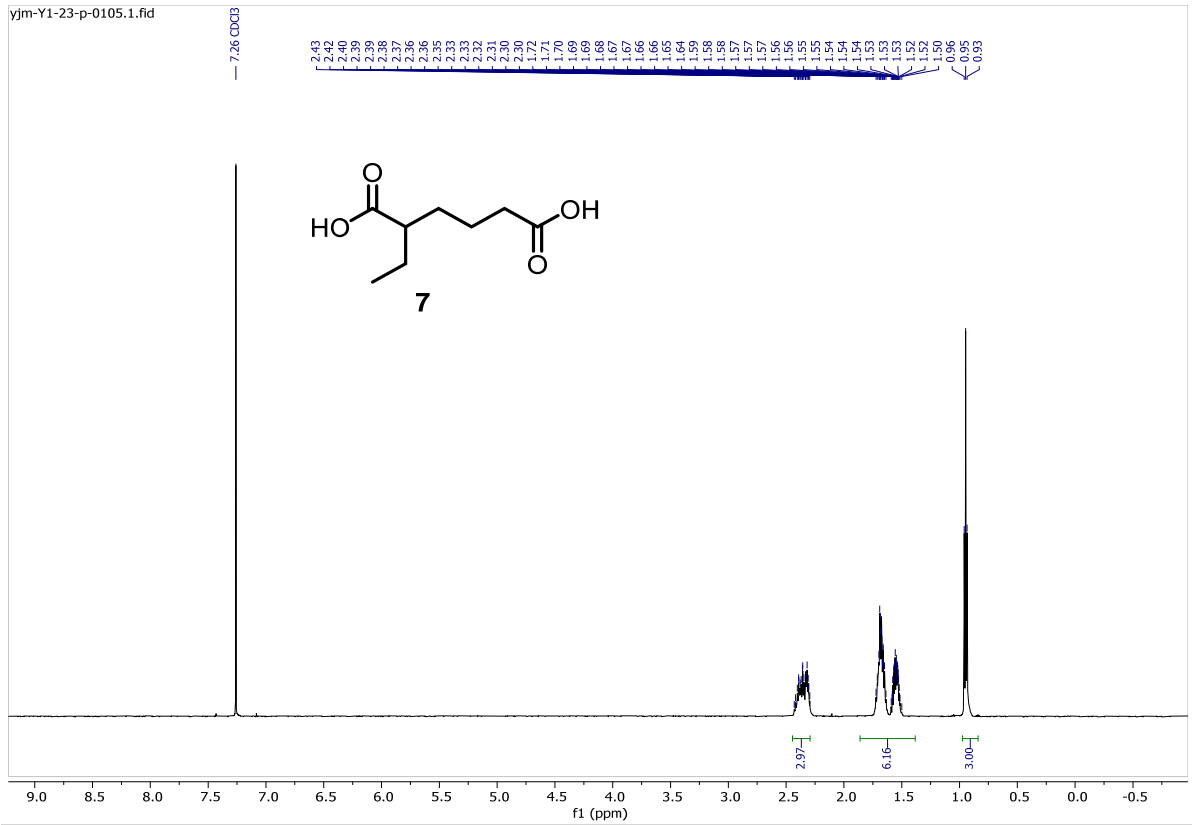


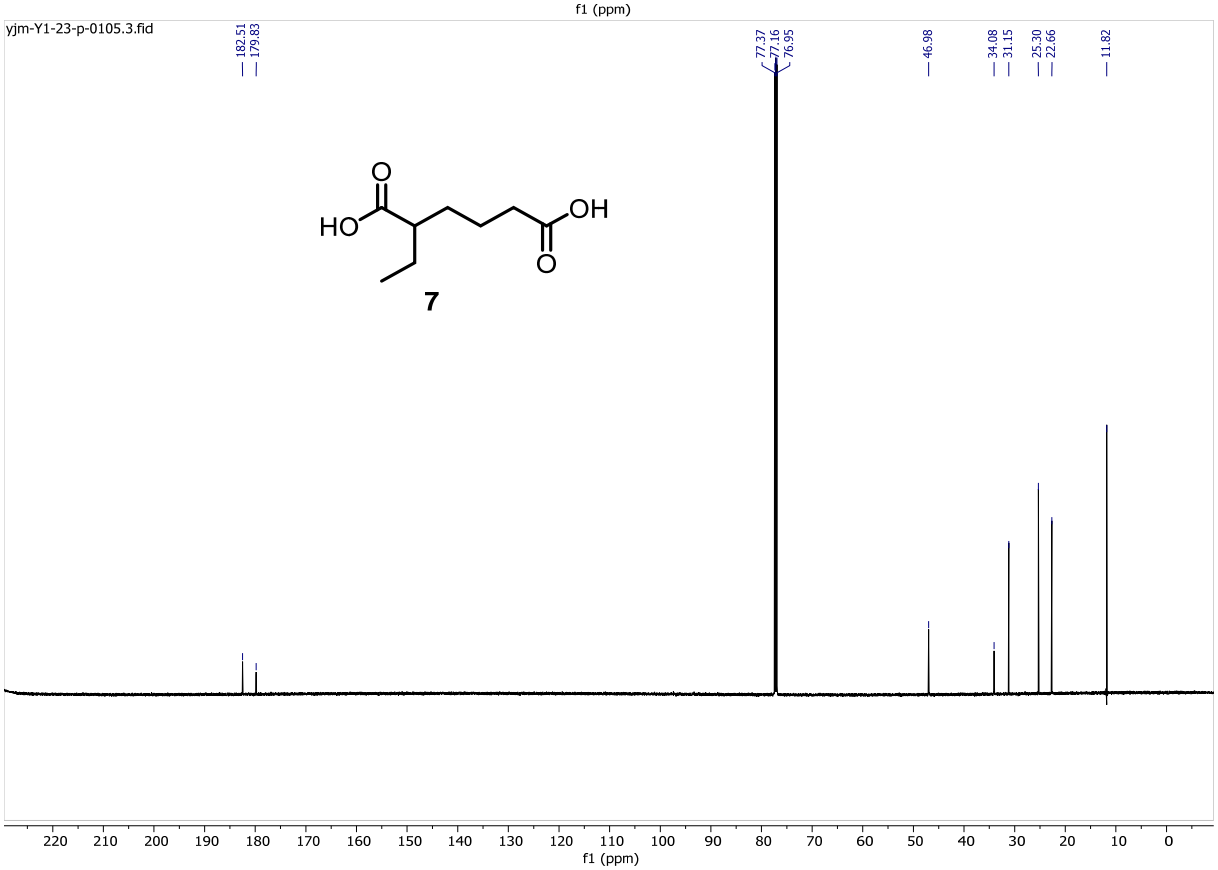
2-Methylhexanedioic acid 6



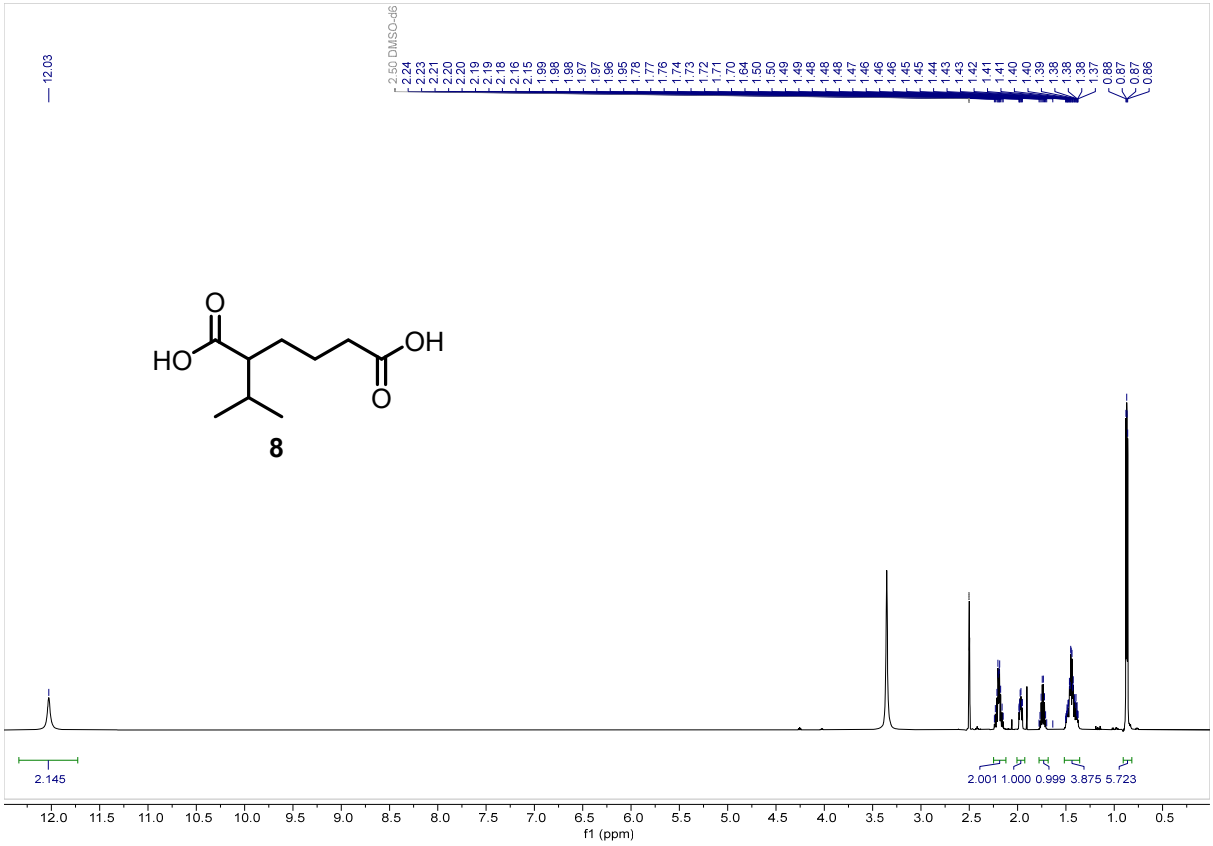


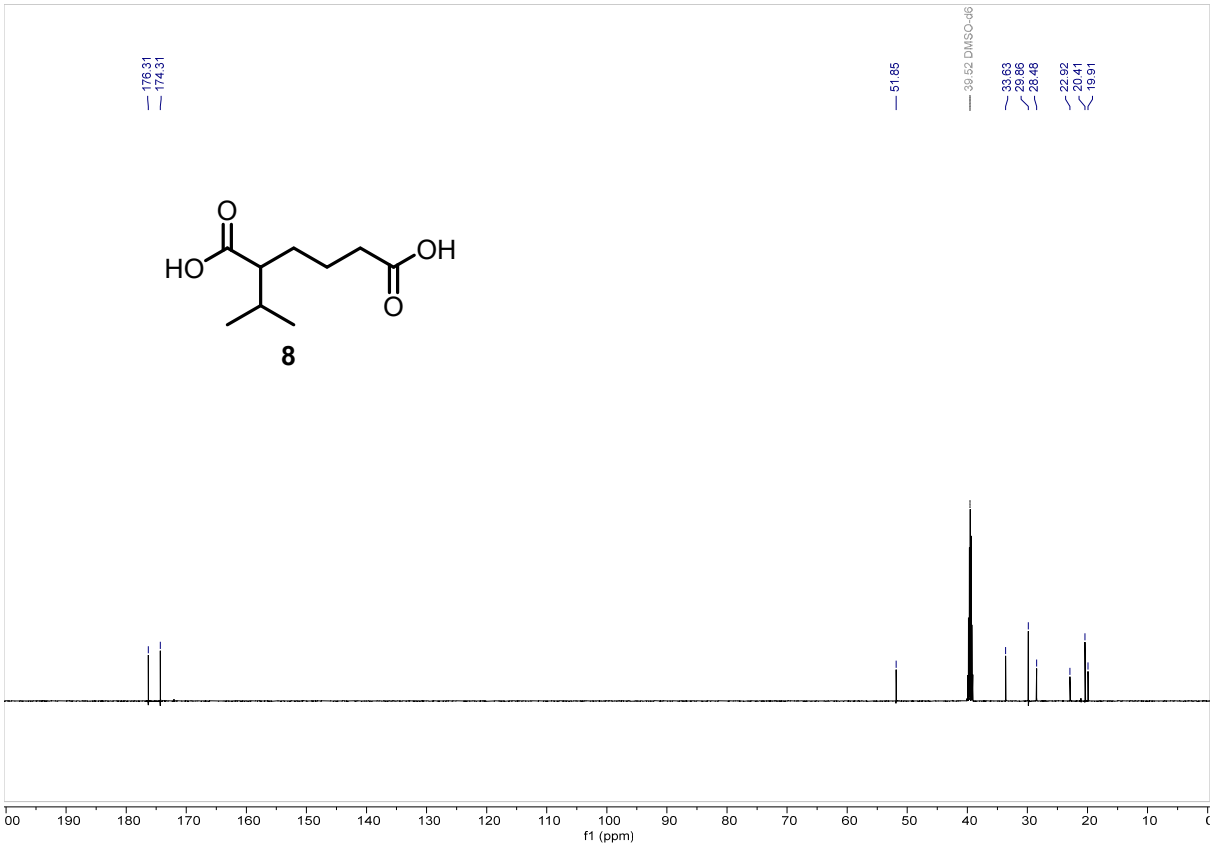
2-Ethylhexanedioic acid 7



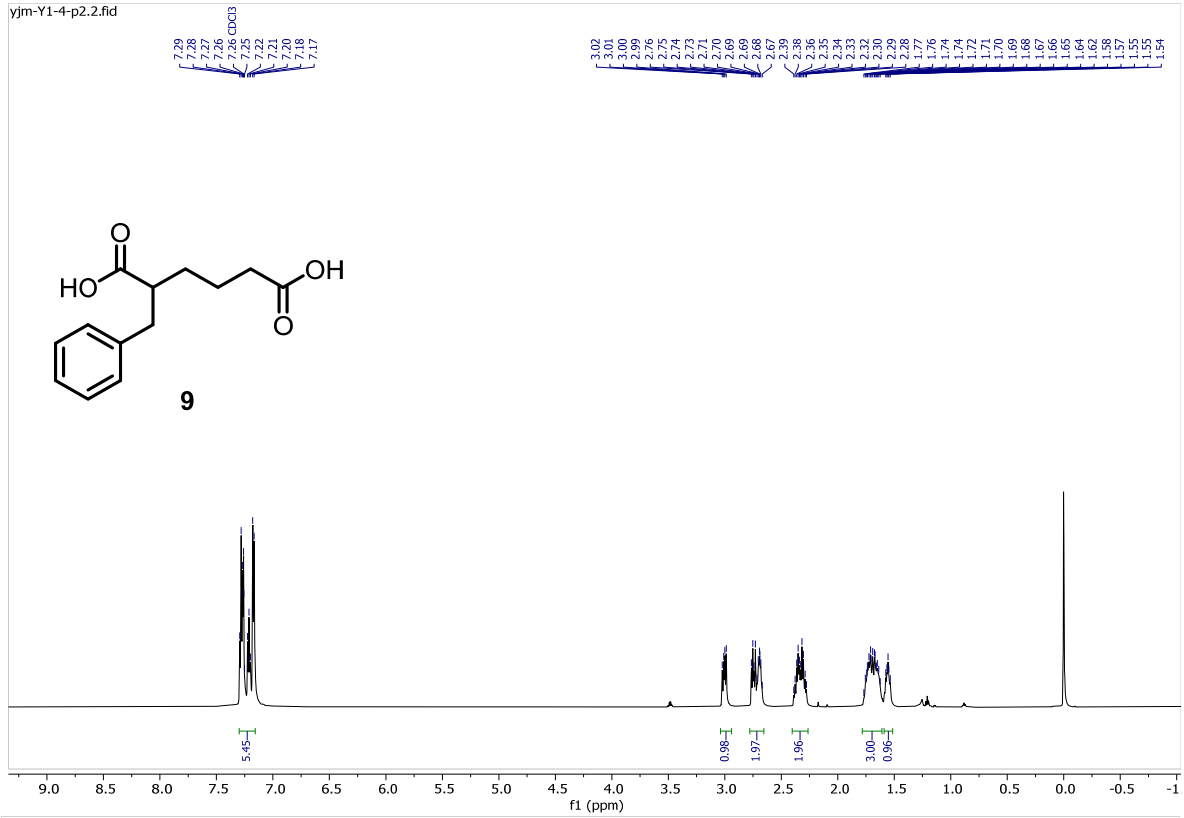


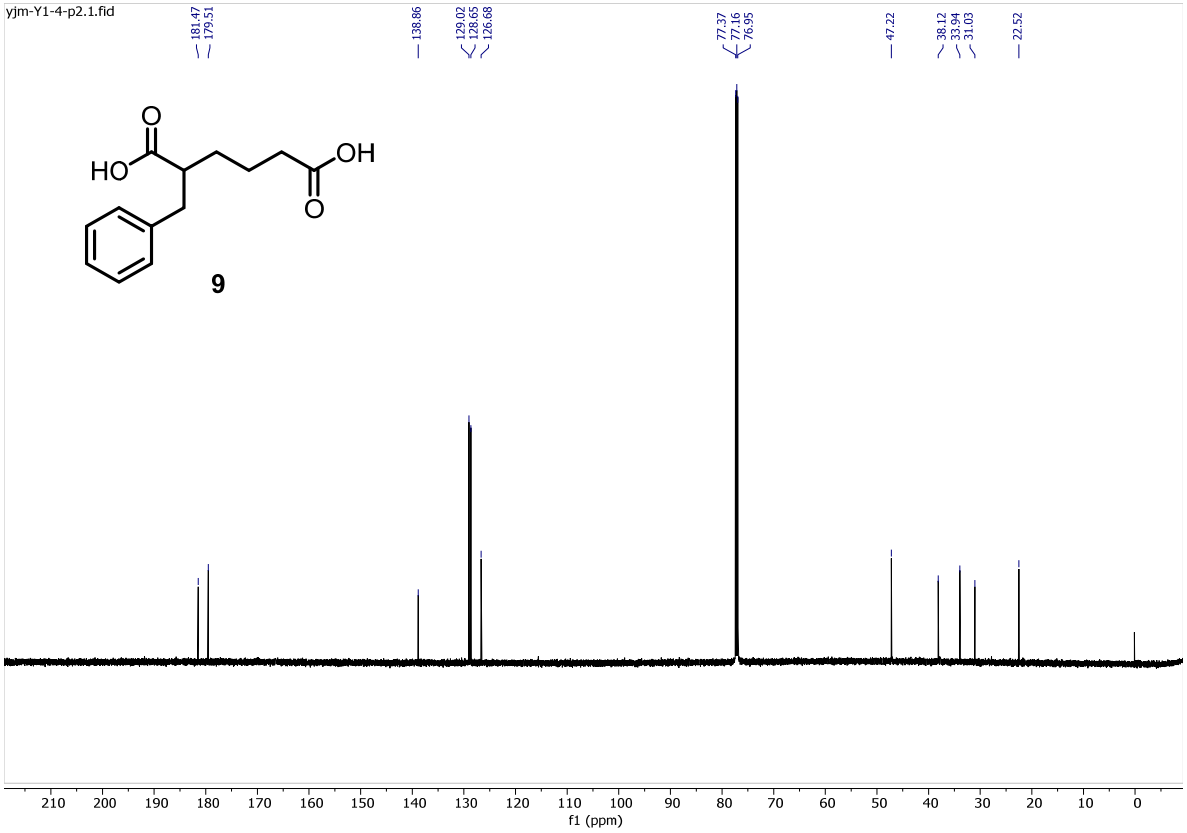
2-Isopropylhexanedioic acid 8



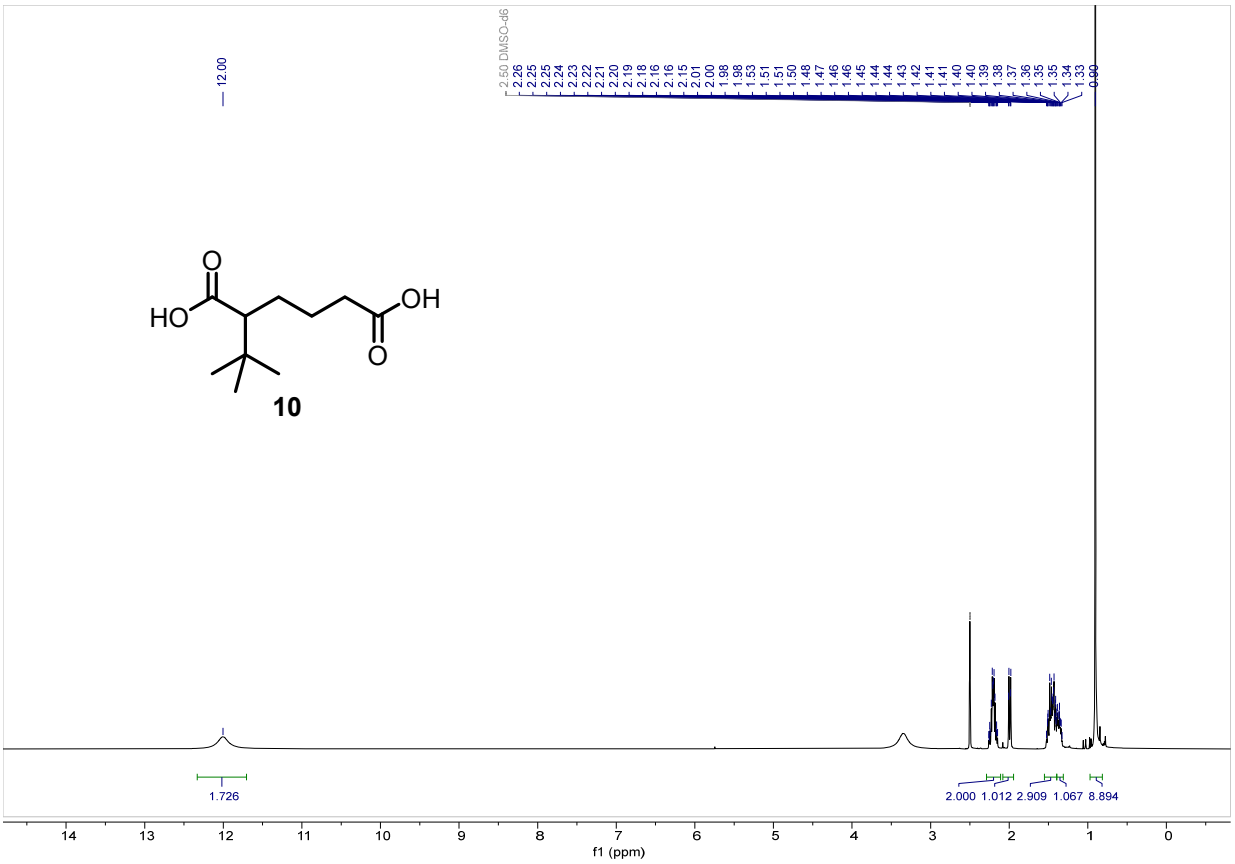


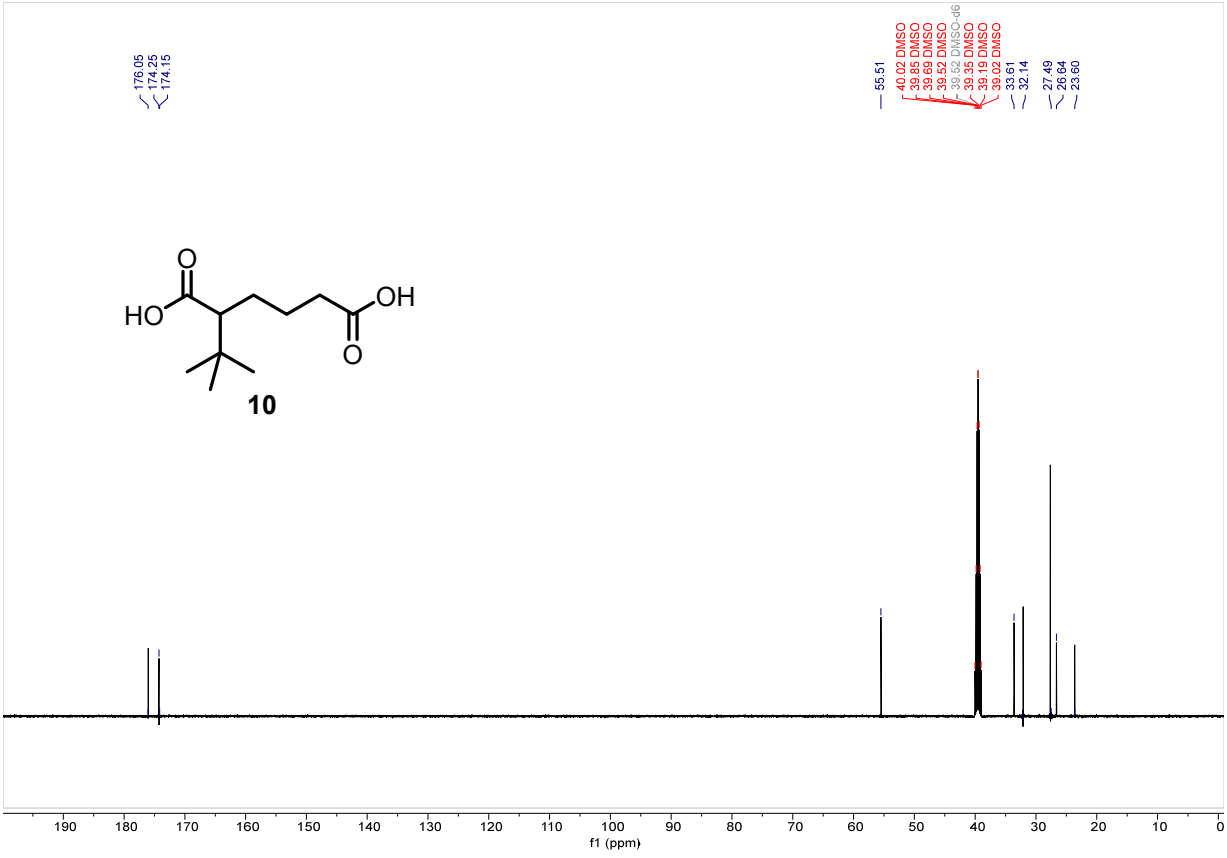
2-Benzylhexanedioic acid 9



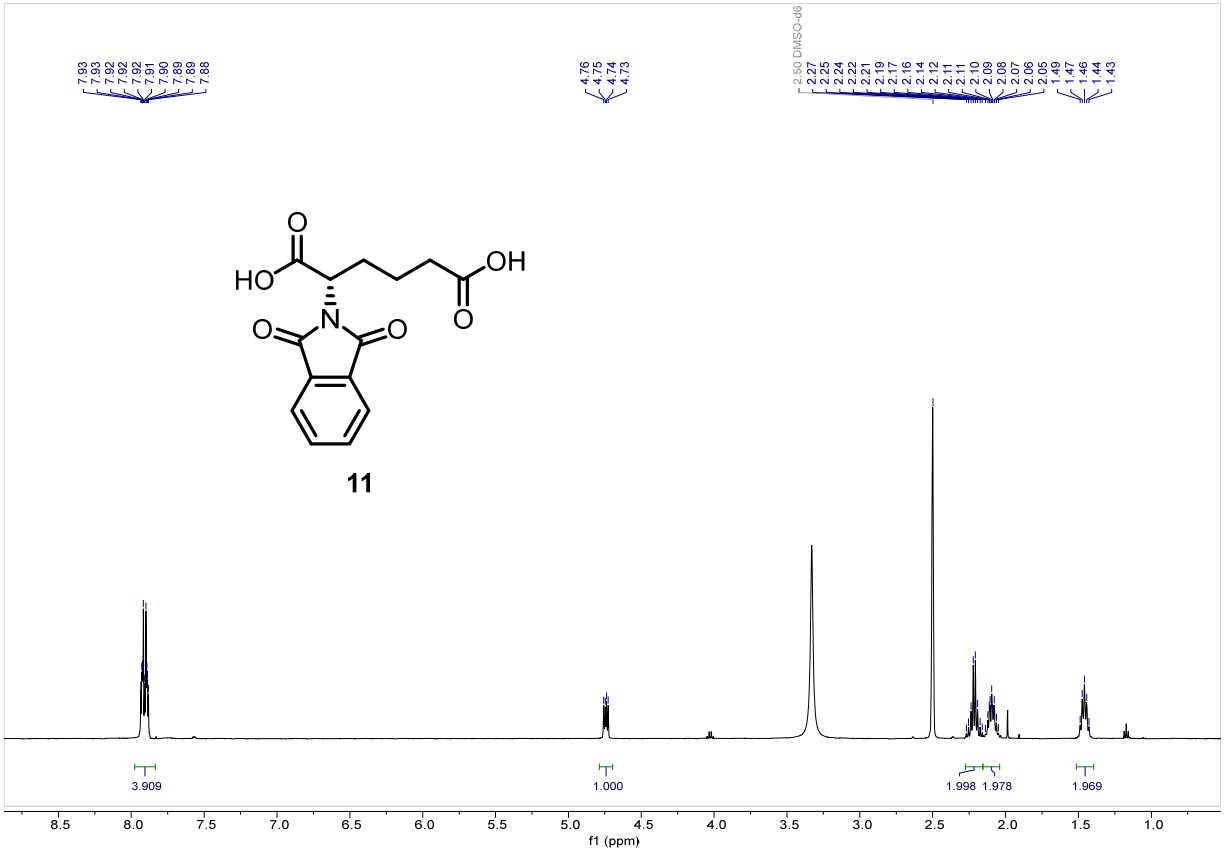


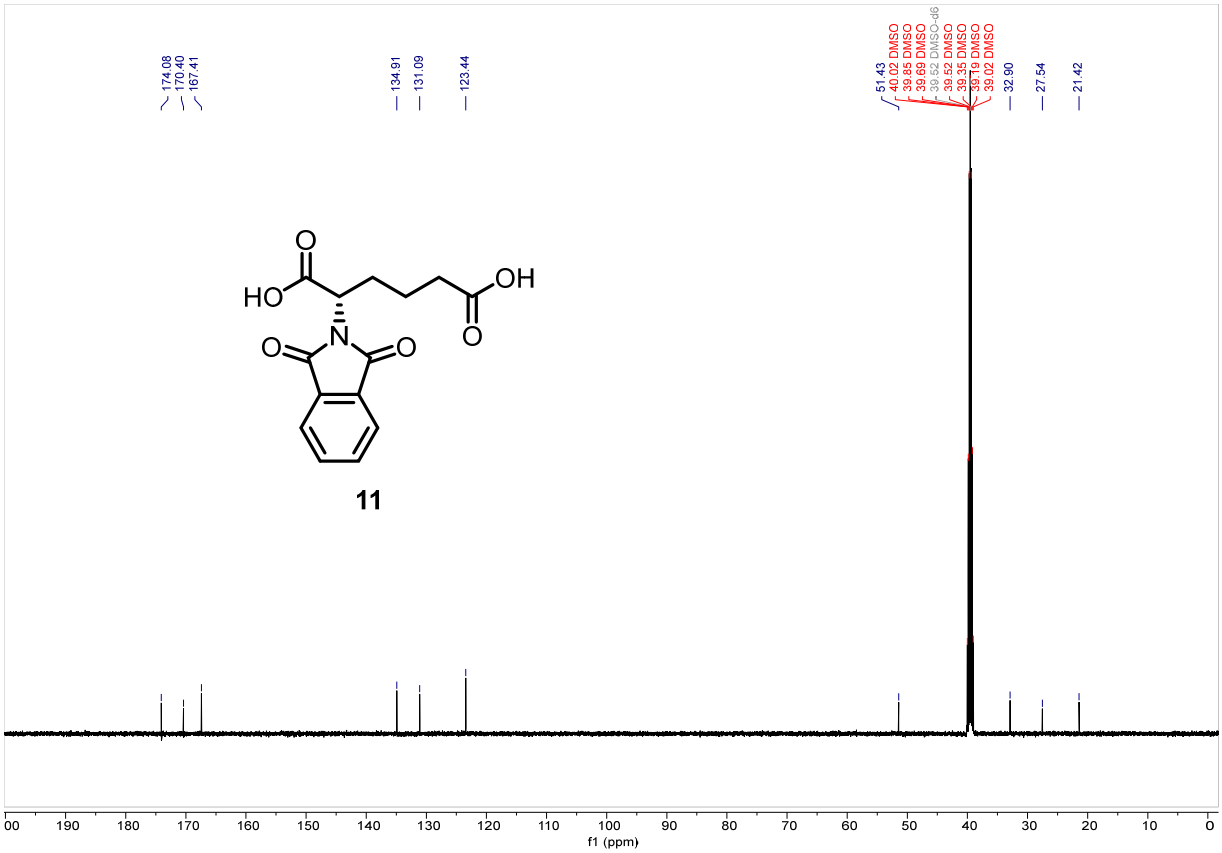
2-(*tert*-Butyl)hexanedioic acid 10



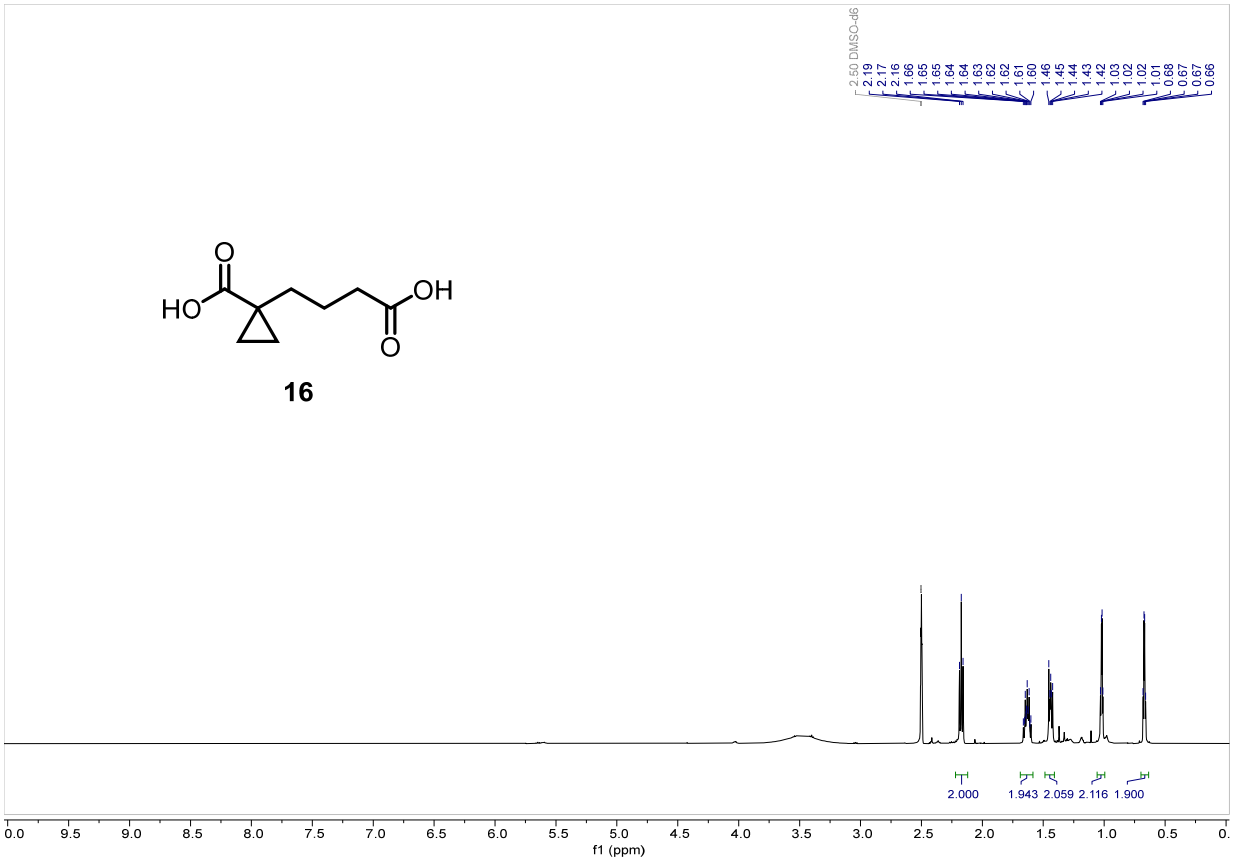


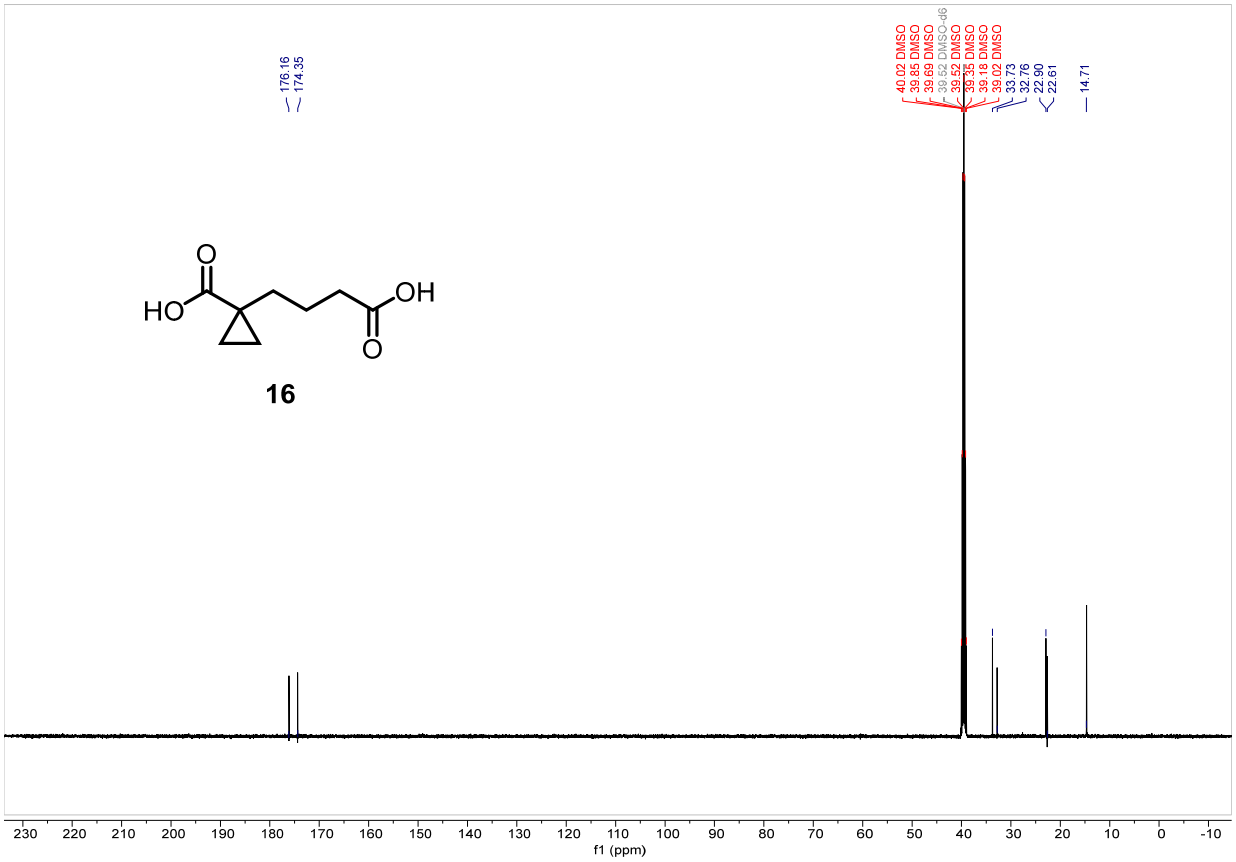
(*S*)-2-(1,3-dioxoisoindolin-2-yl)hexanedioic acid 11



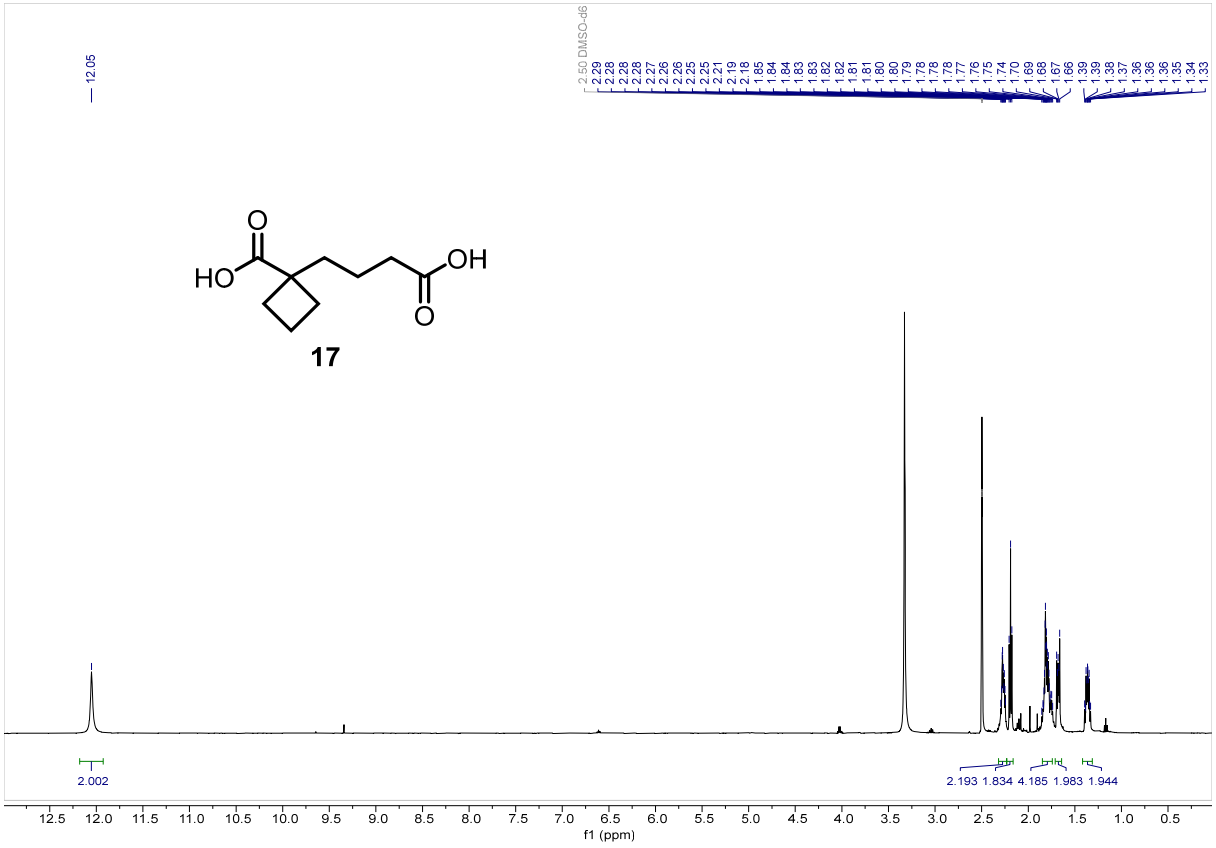


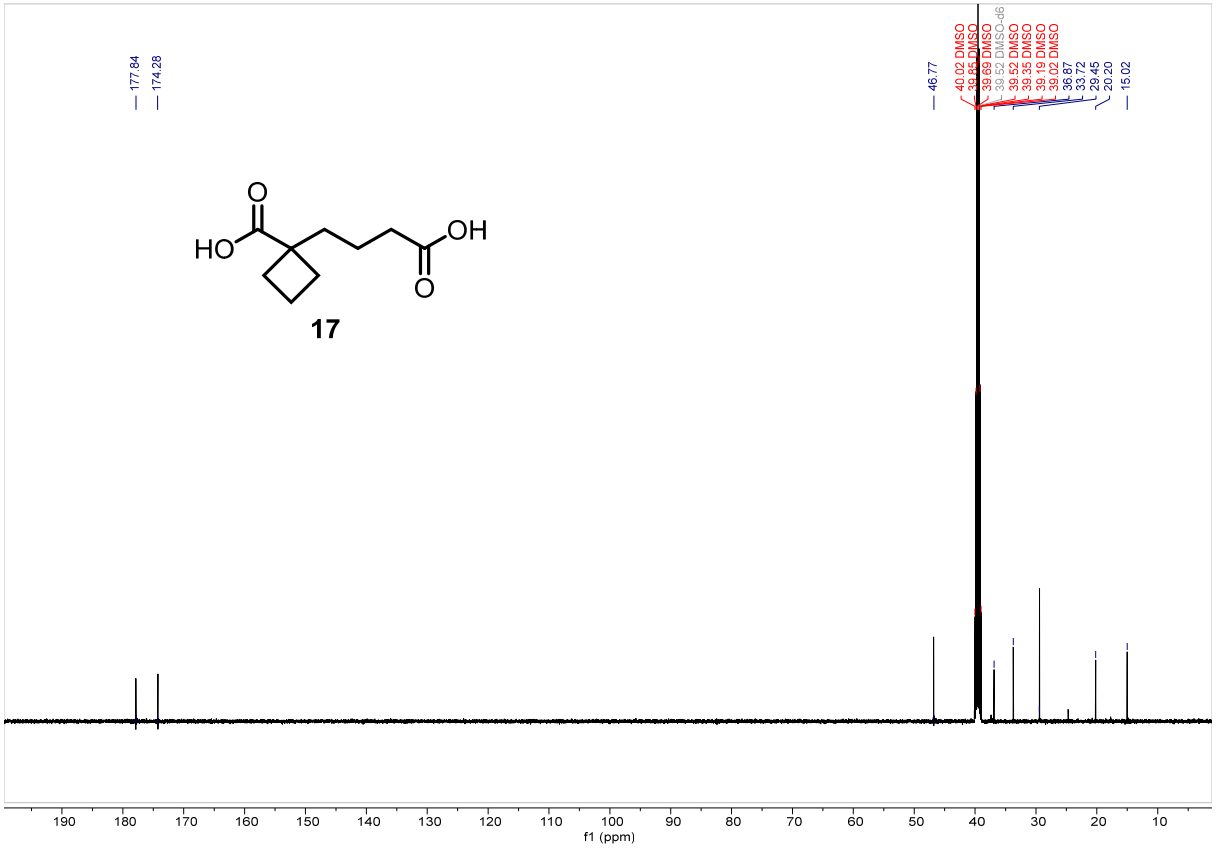
1-(3-Carboxypropyl)cyclopropane-1-carboxylic acid 16



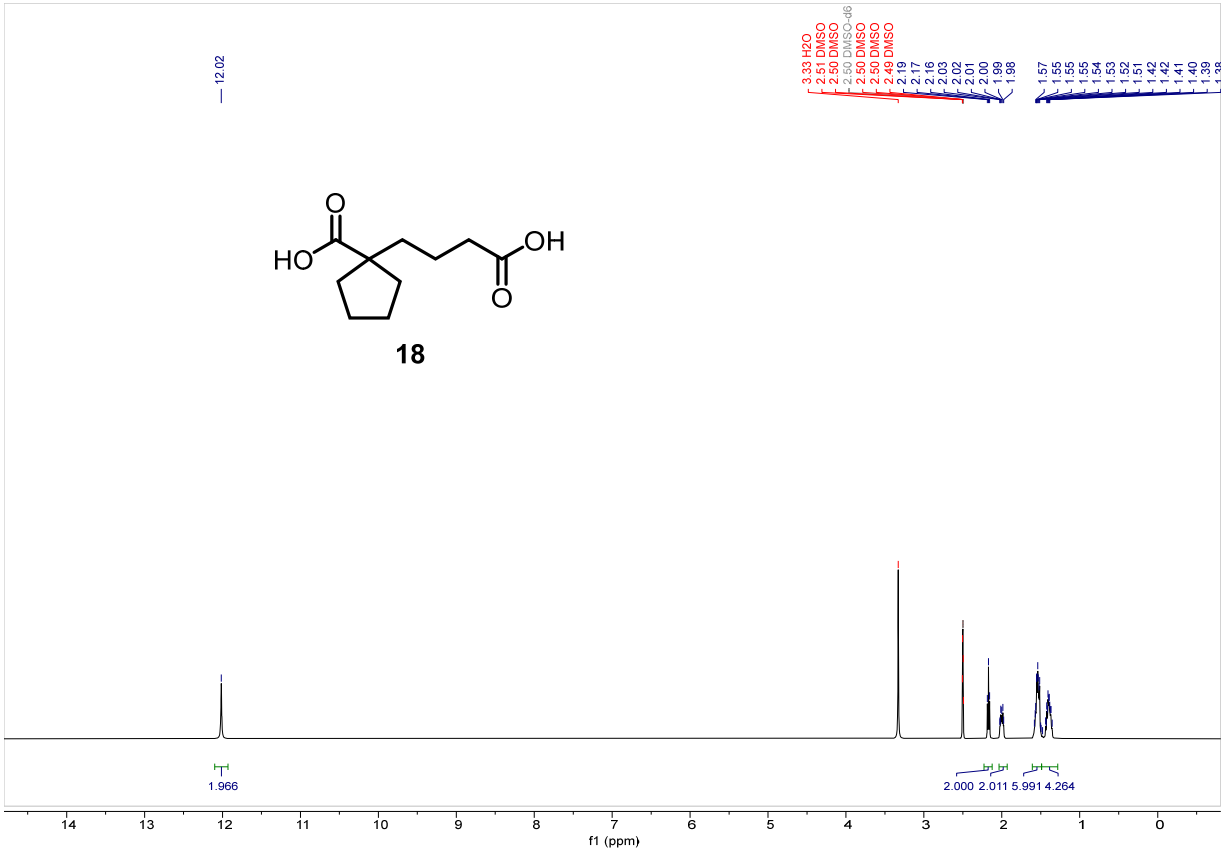


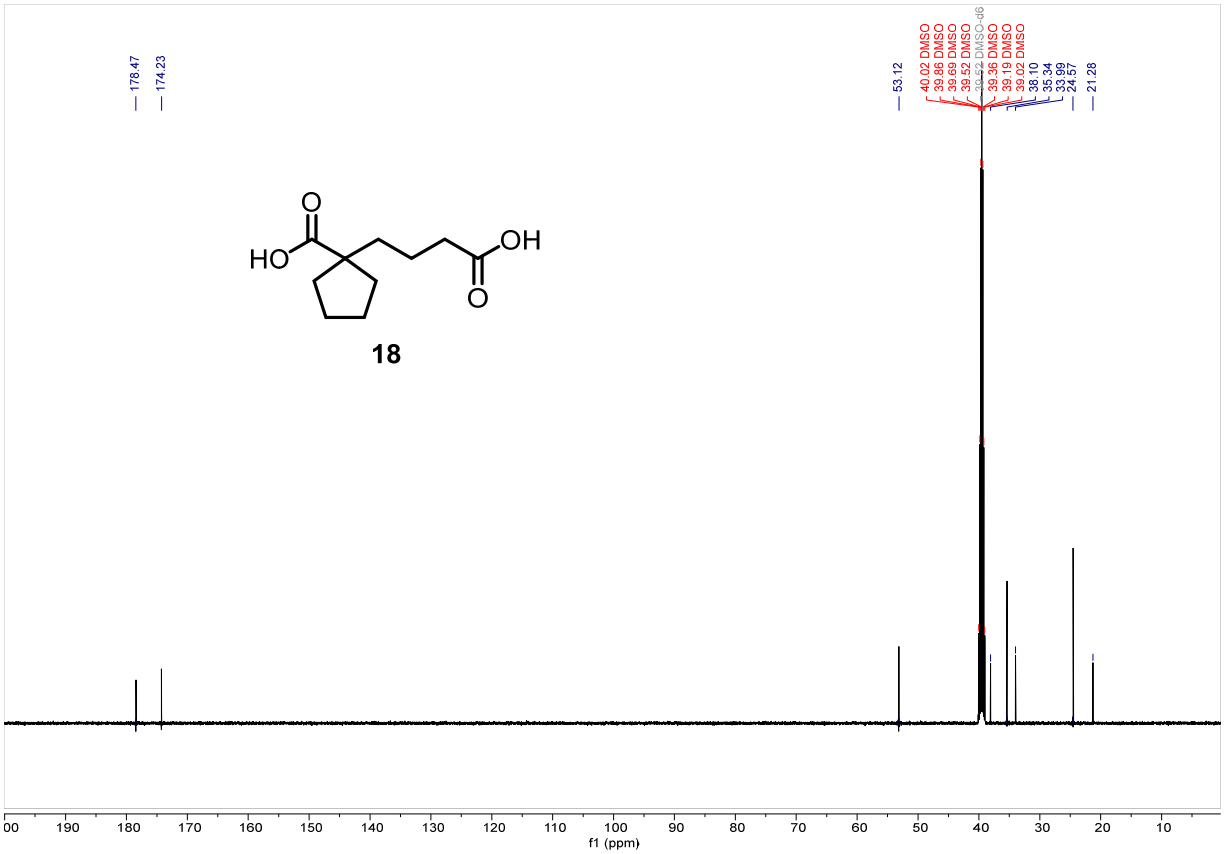
1-(3-Carboxypropyl)cyclobutane-1-carboxylic acid 17



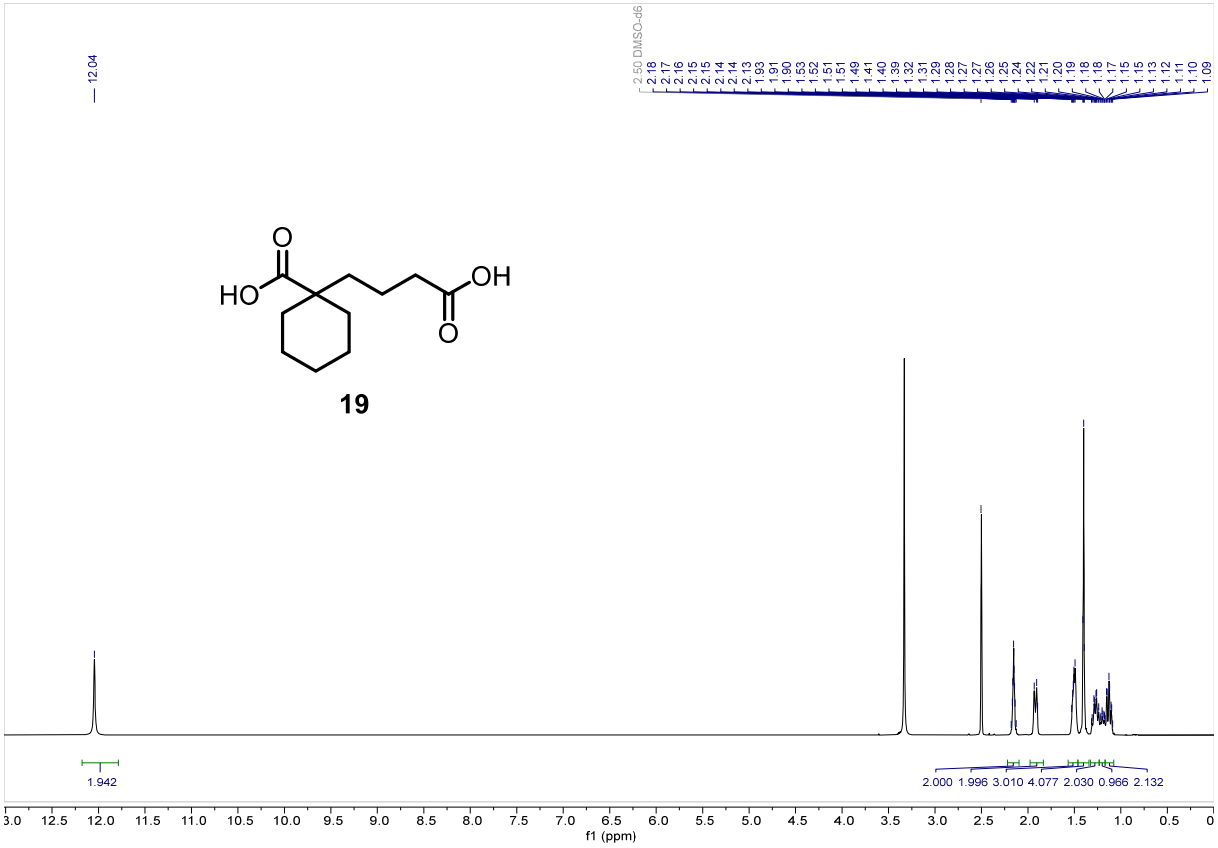


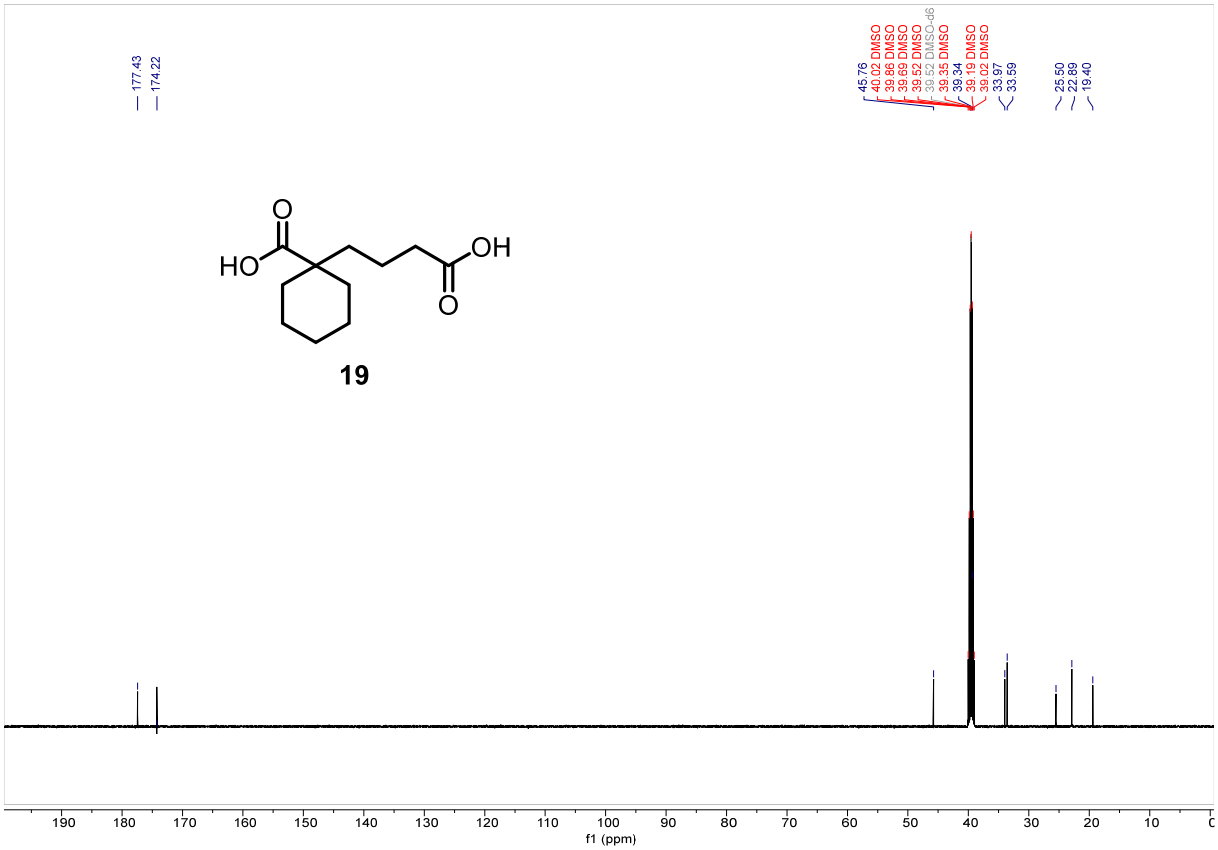
1-(3-Carboxypropyl)cyclopentane-1-carboxylic acid 18



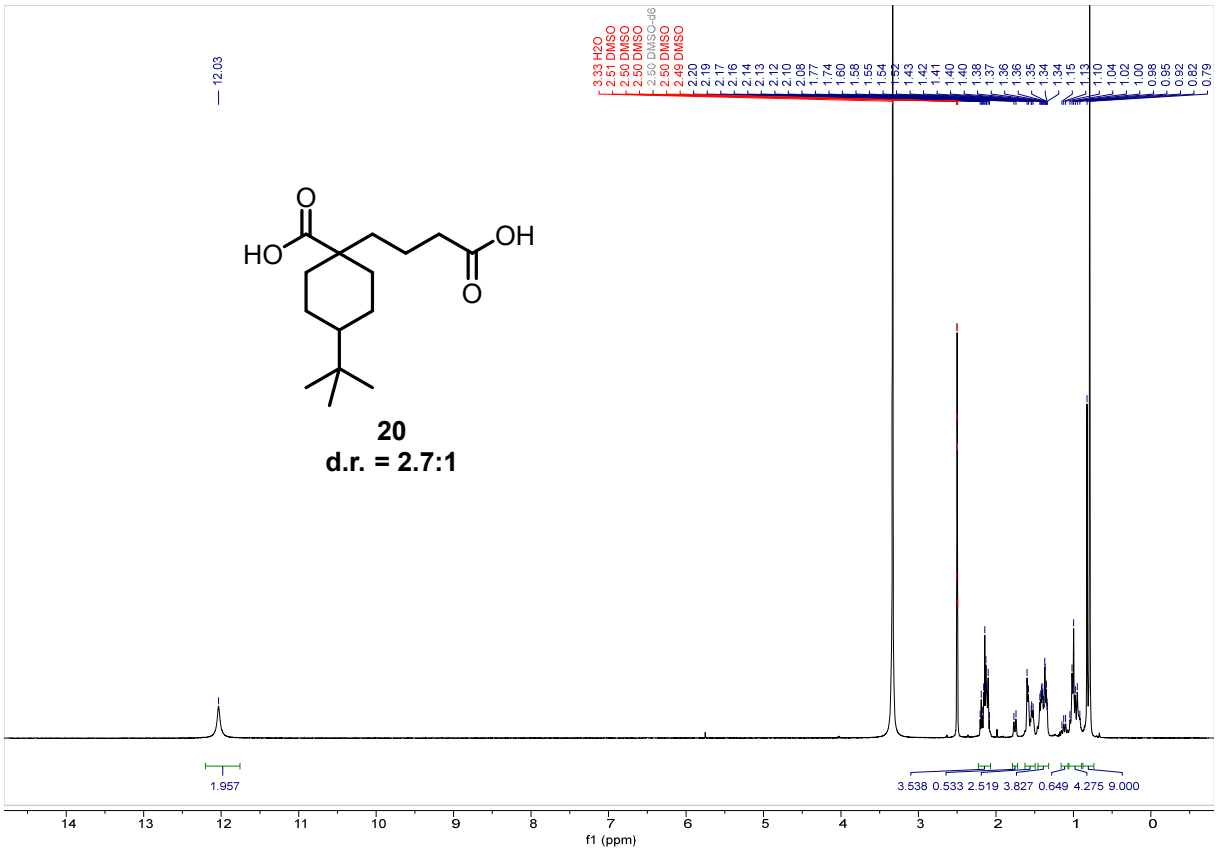


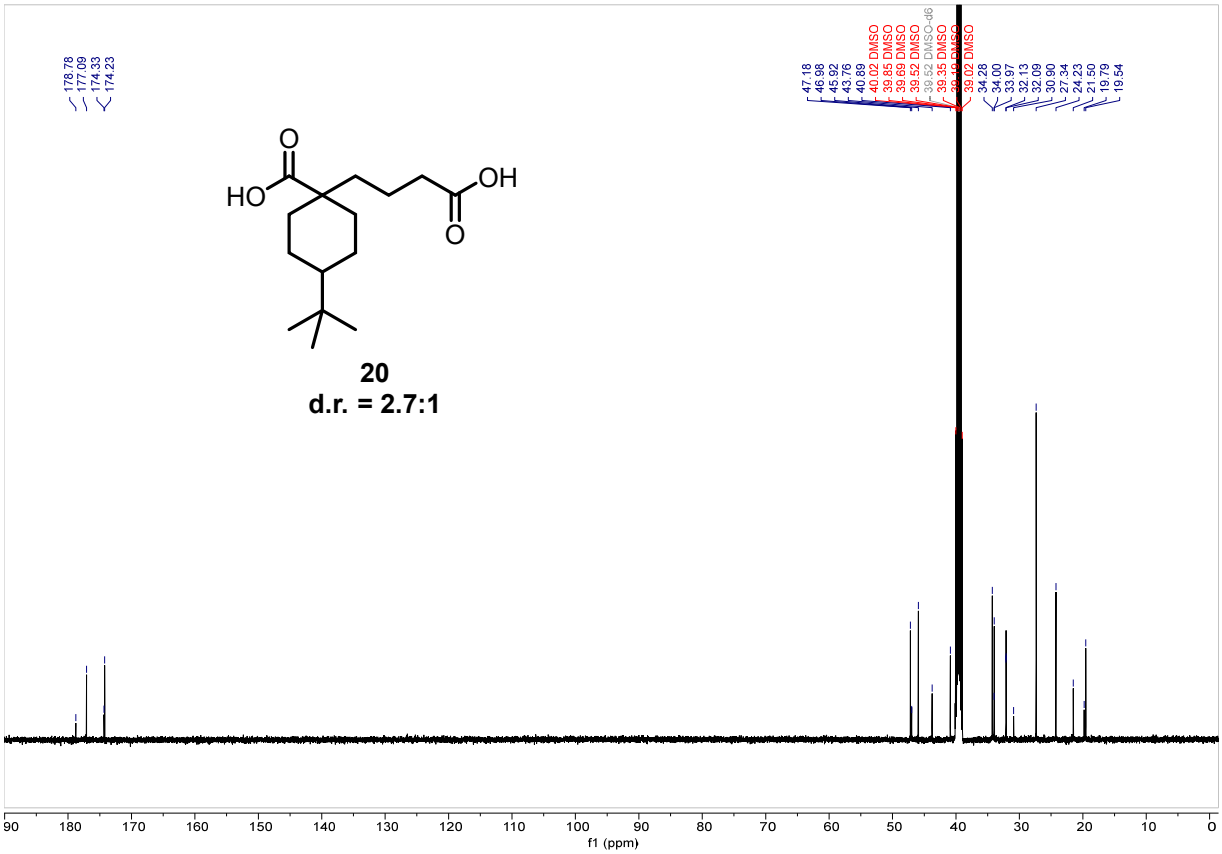
1-(3-Carboxypropyl)cyclohexane-1-carboxylic acid 19



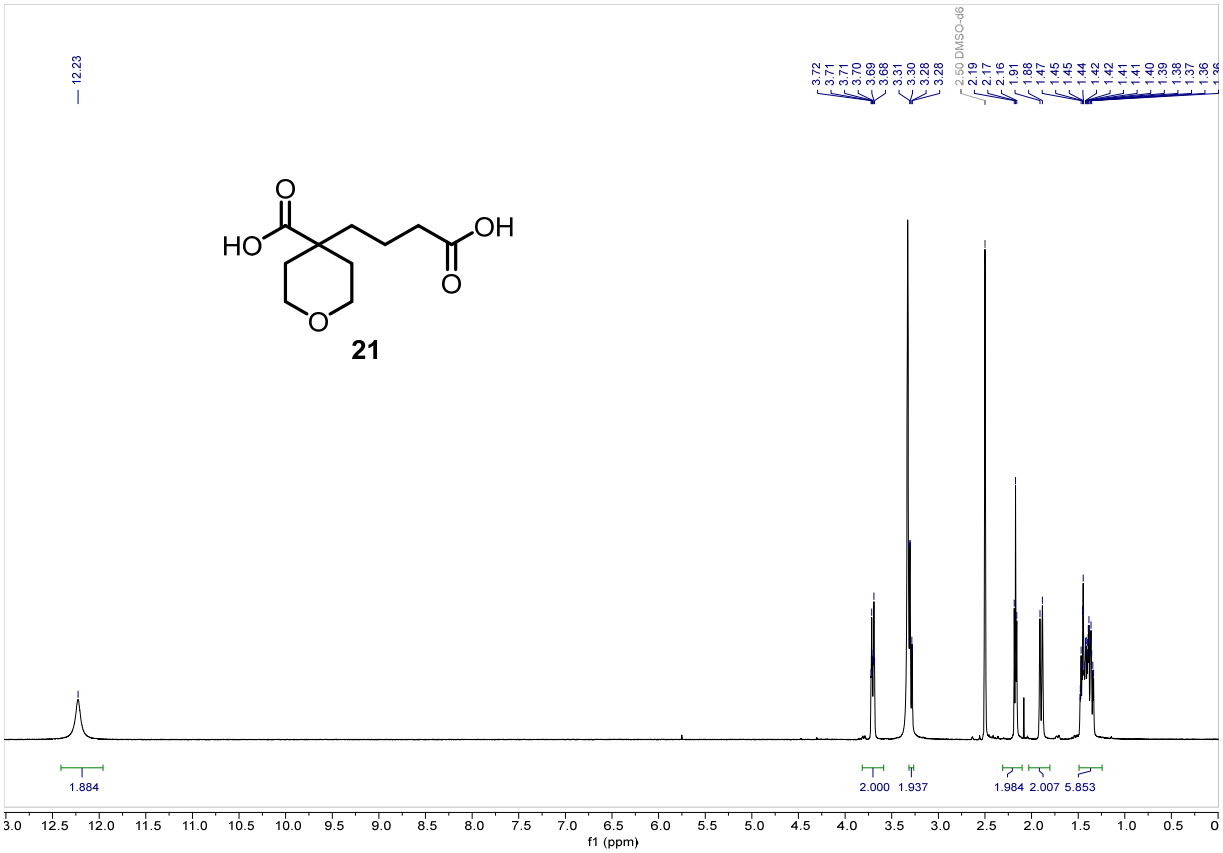


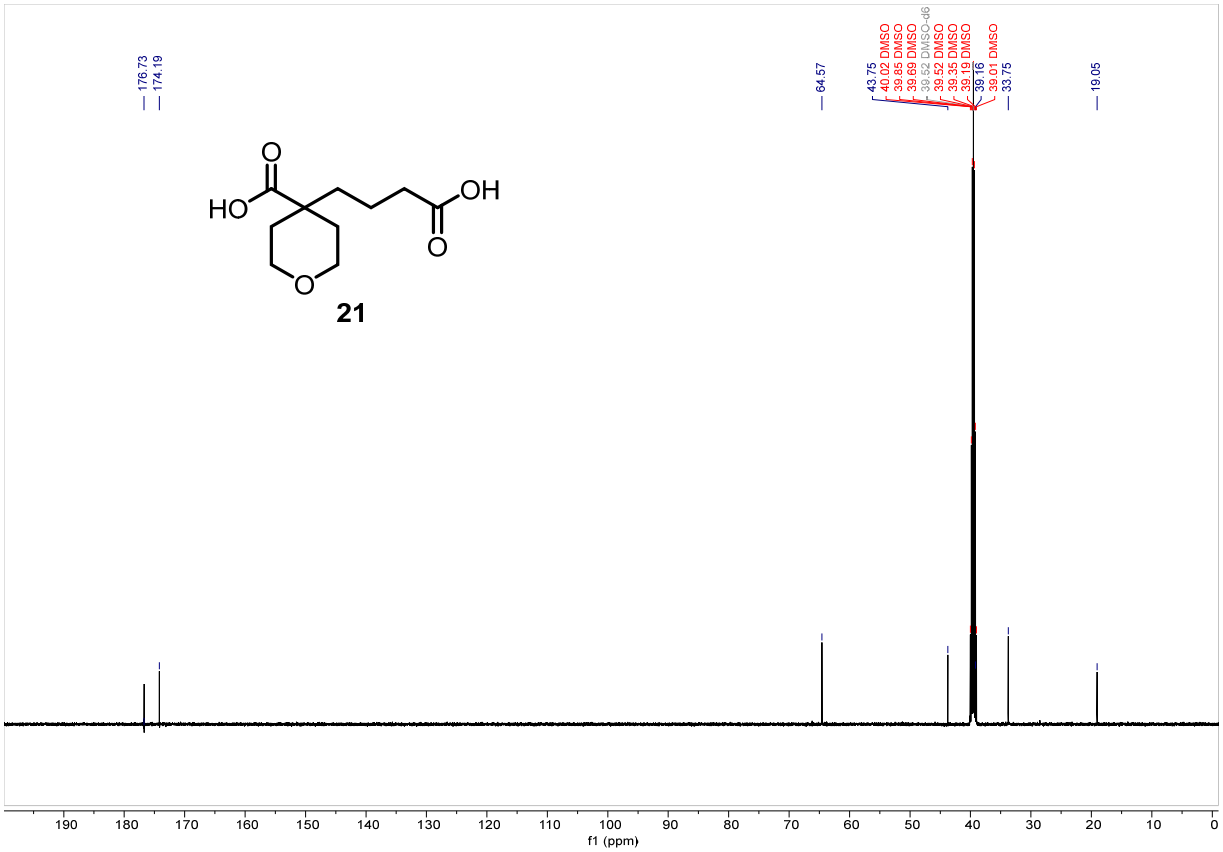
4-(*tert*-Butyl)-1-(3-carboxypropyl)cyclohexane-1-carboxylic acid 20



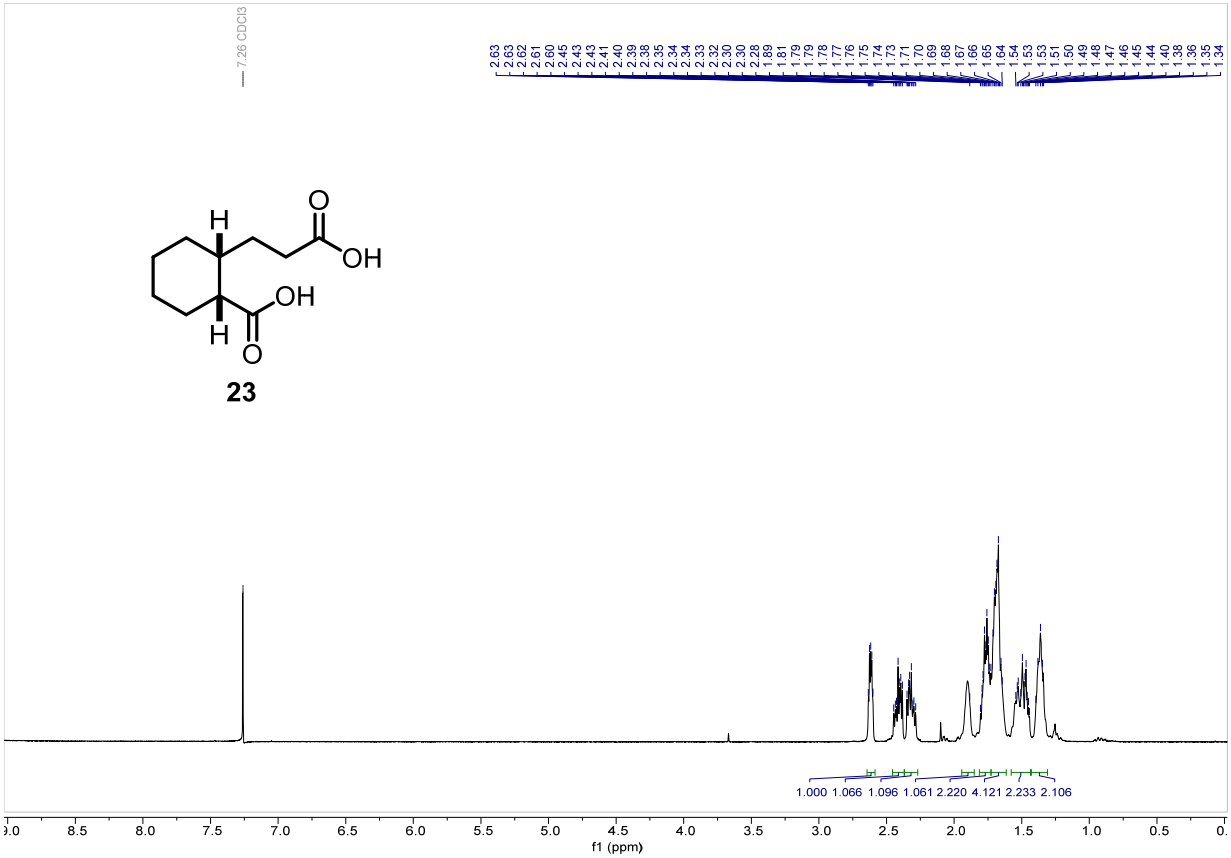


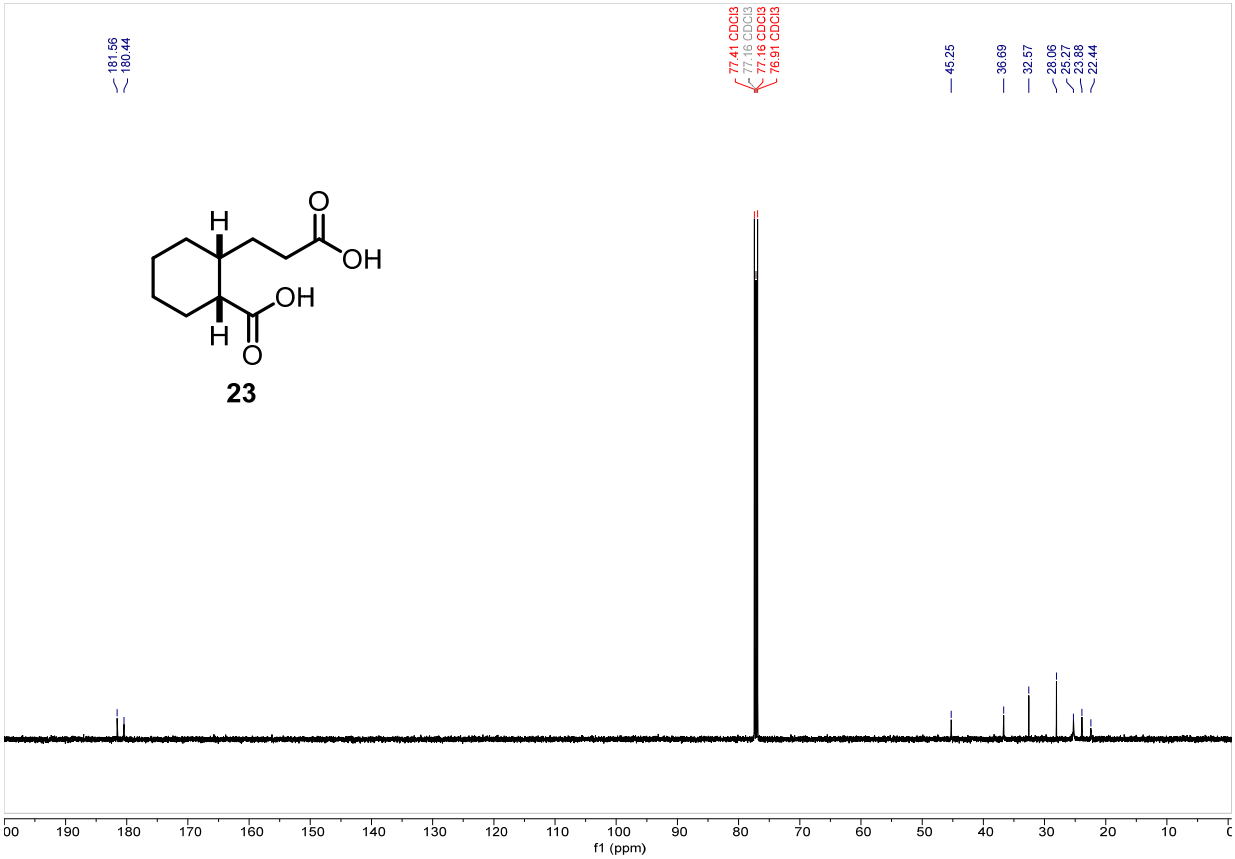
4-(3-Carboxypropyl)tetrahydro-2*H*-pyran-4-carboxylic acid 21



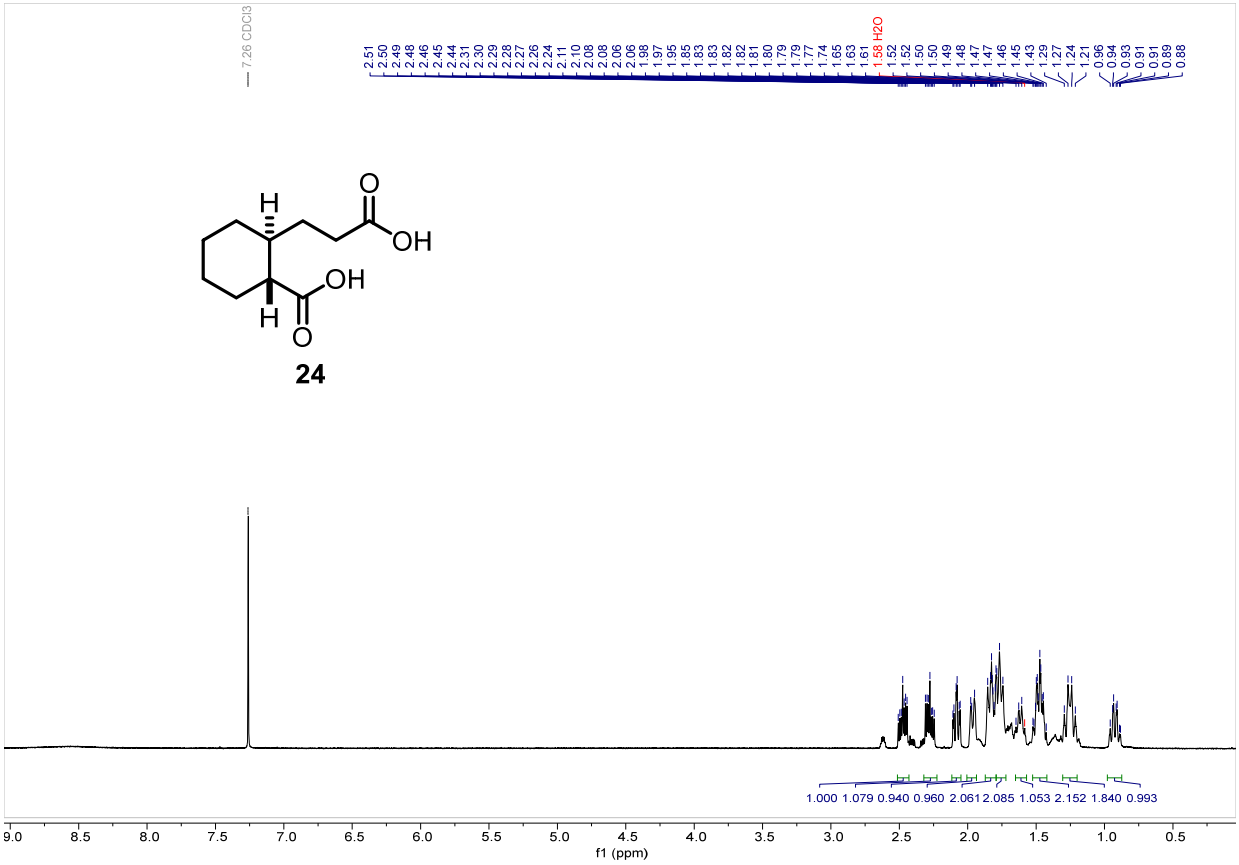


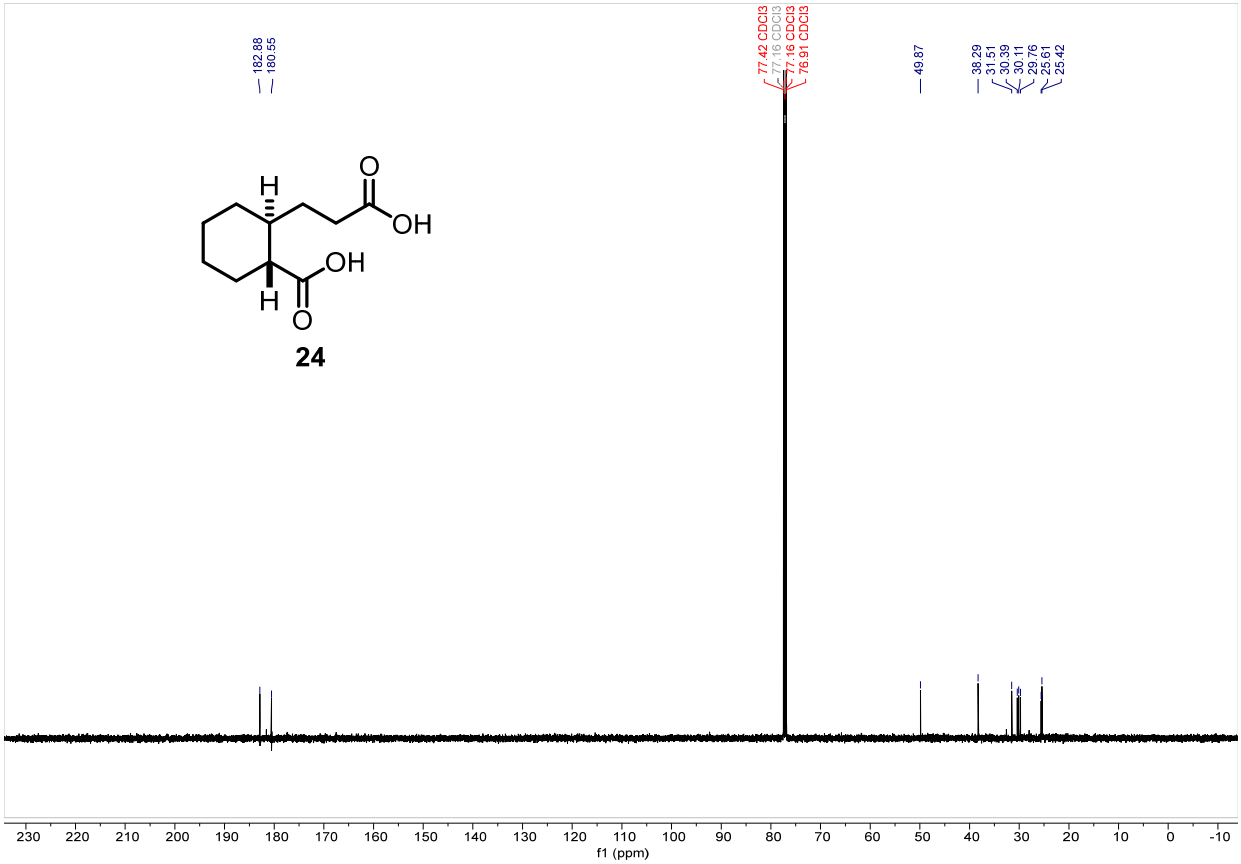
(1*R**,2*R**)-2-(2-Carboxyethyl)cyclohexane-1-carboxylic acid 23



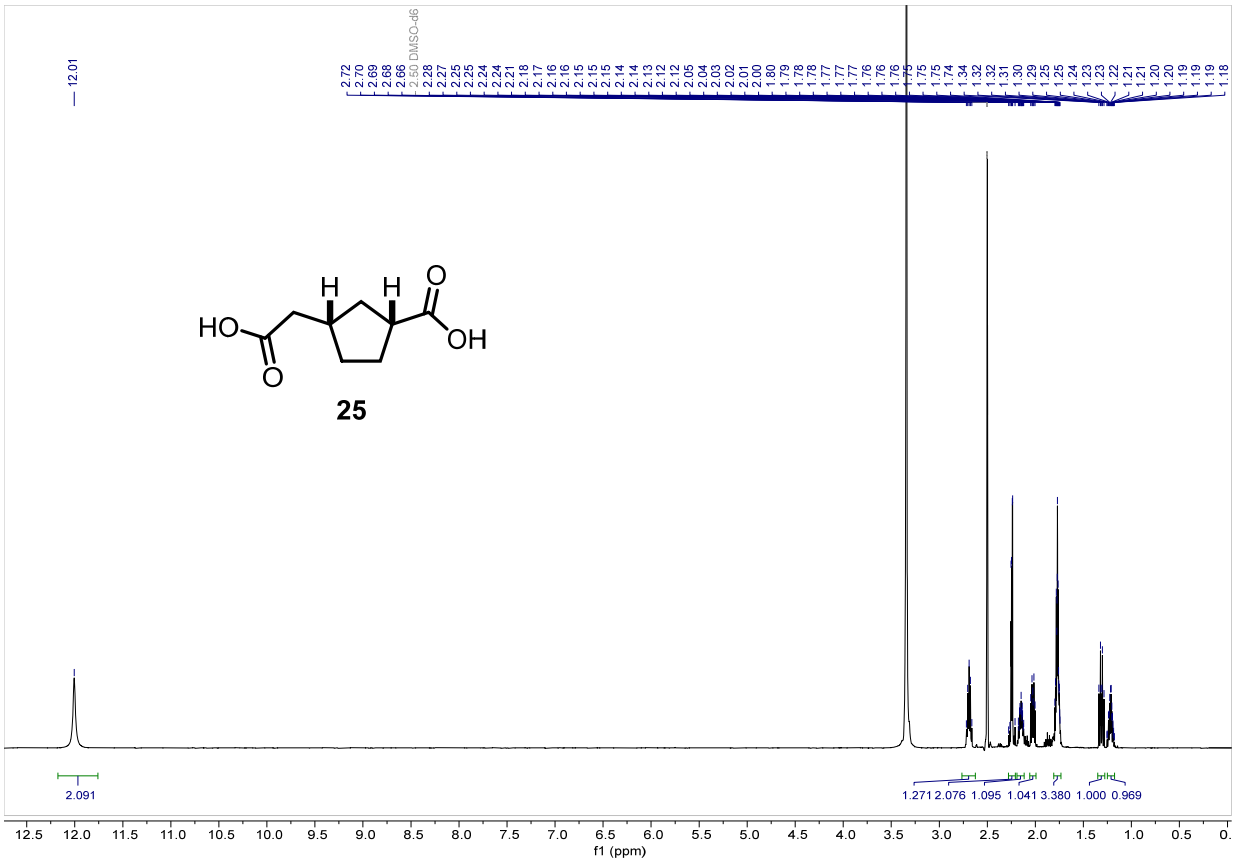


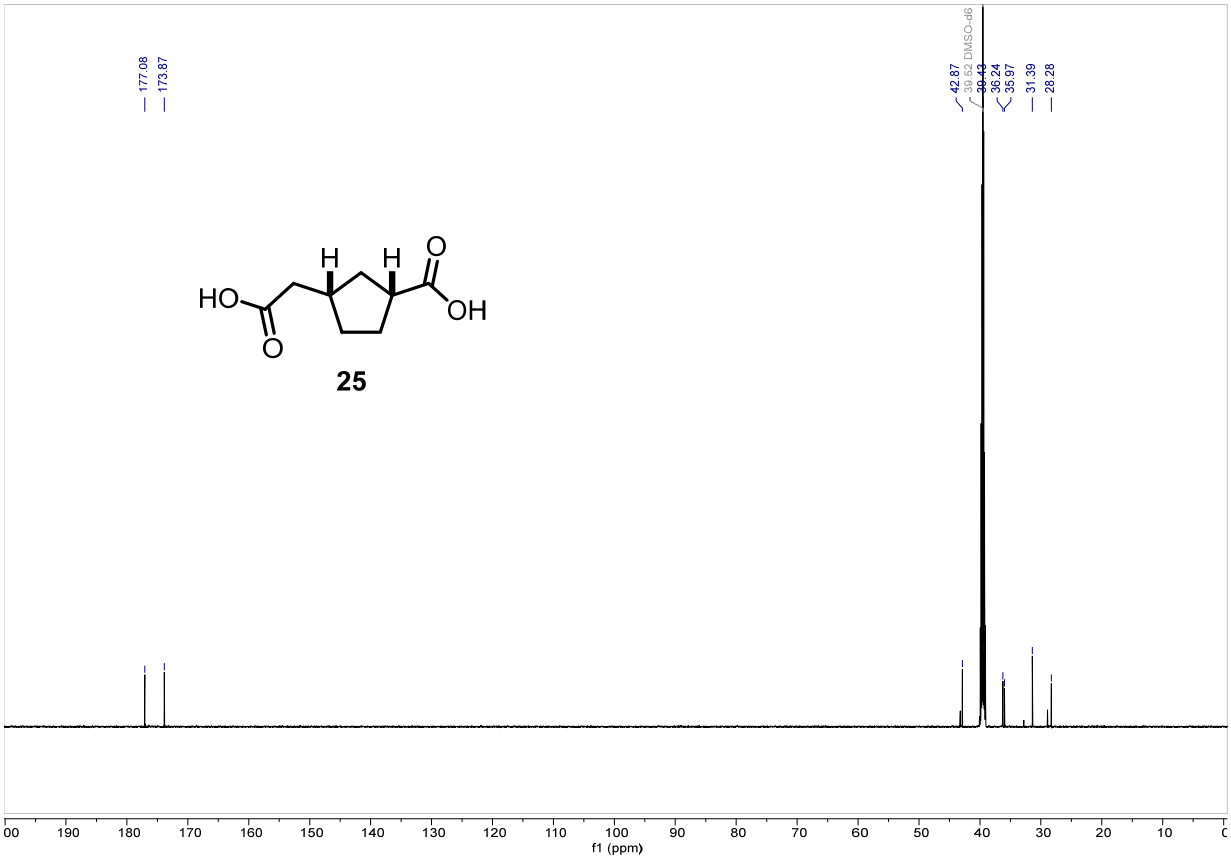
(1*R**,2*S**)-2-(2-Carboxyethyl)cyclohexane-1-carboxylic acid 24



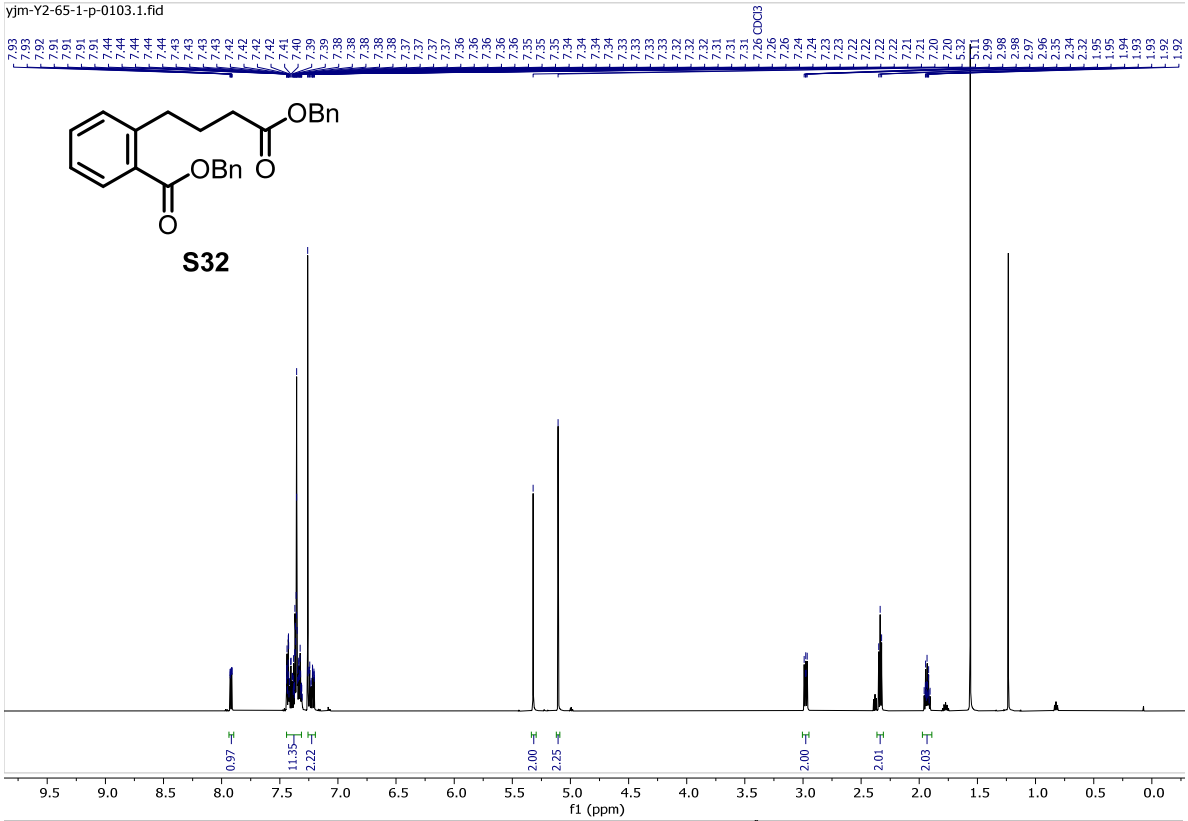


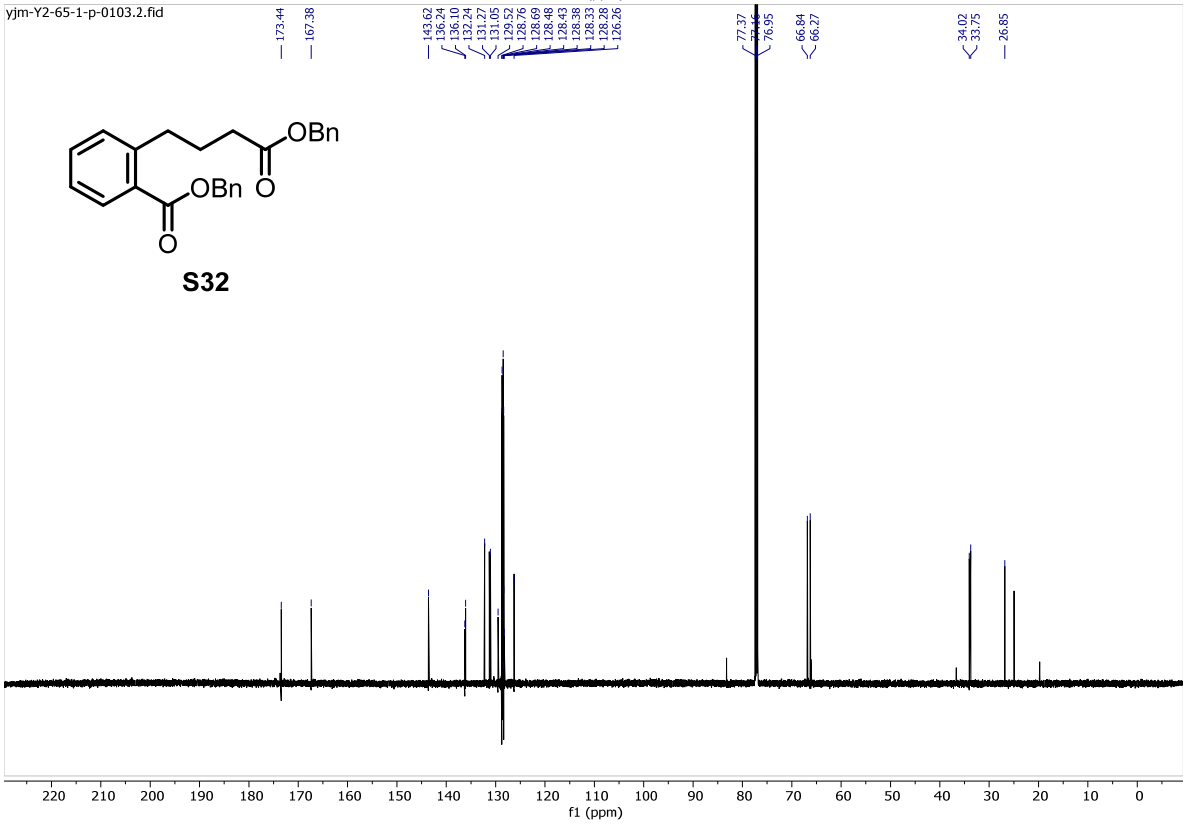
(1*R**,3*S**)-3-(Carboxymethyl)cyclopentane-1-carboxylic acid 25



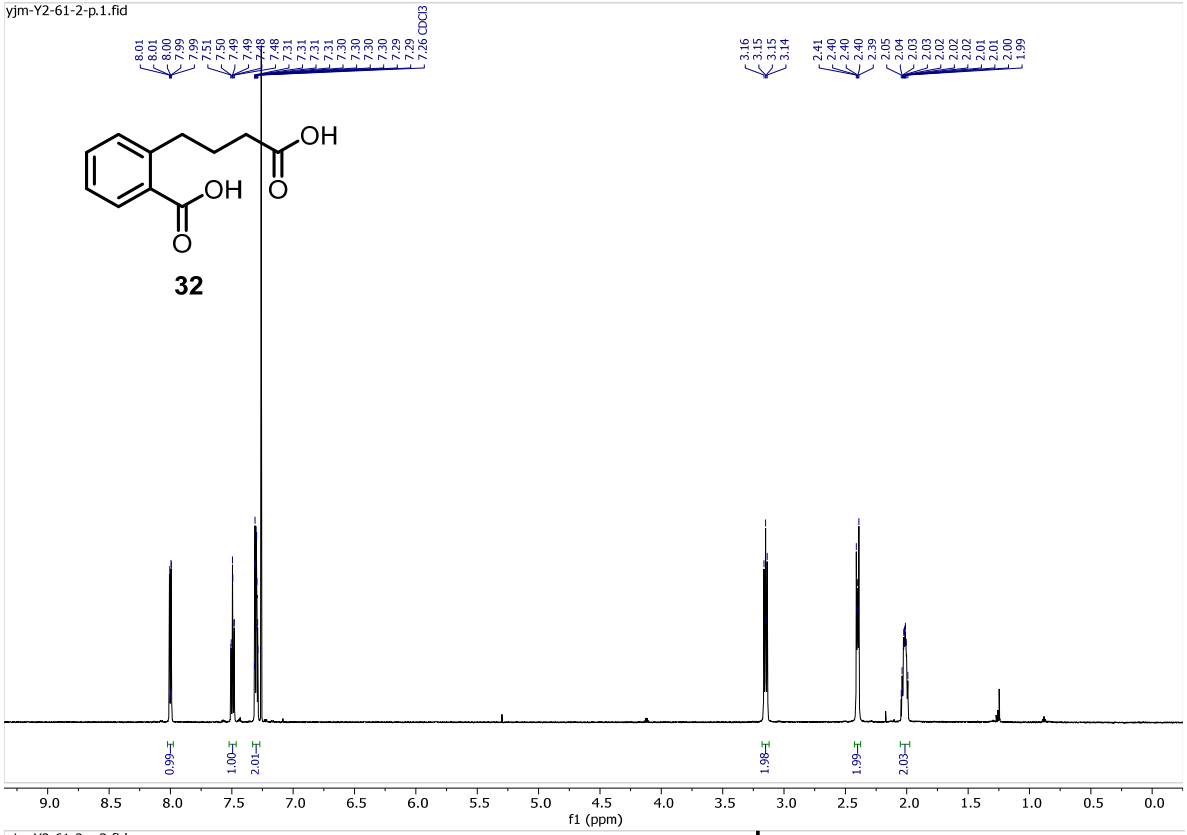


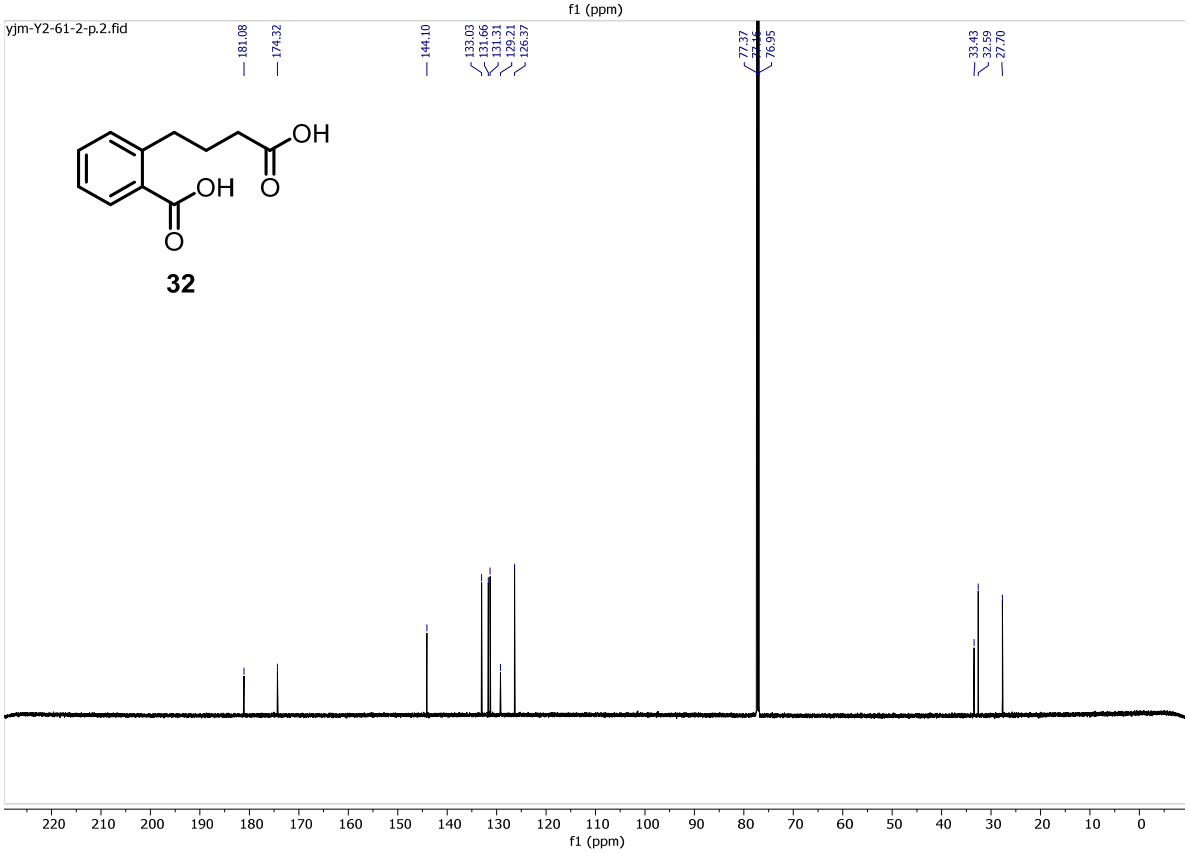
Benzyl 2-(4-(benzyloxy)-4-oxobutyl)benzoate S32



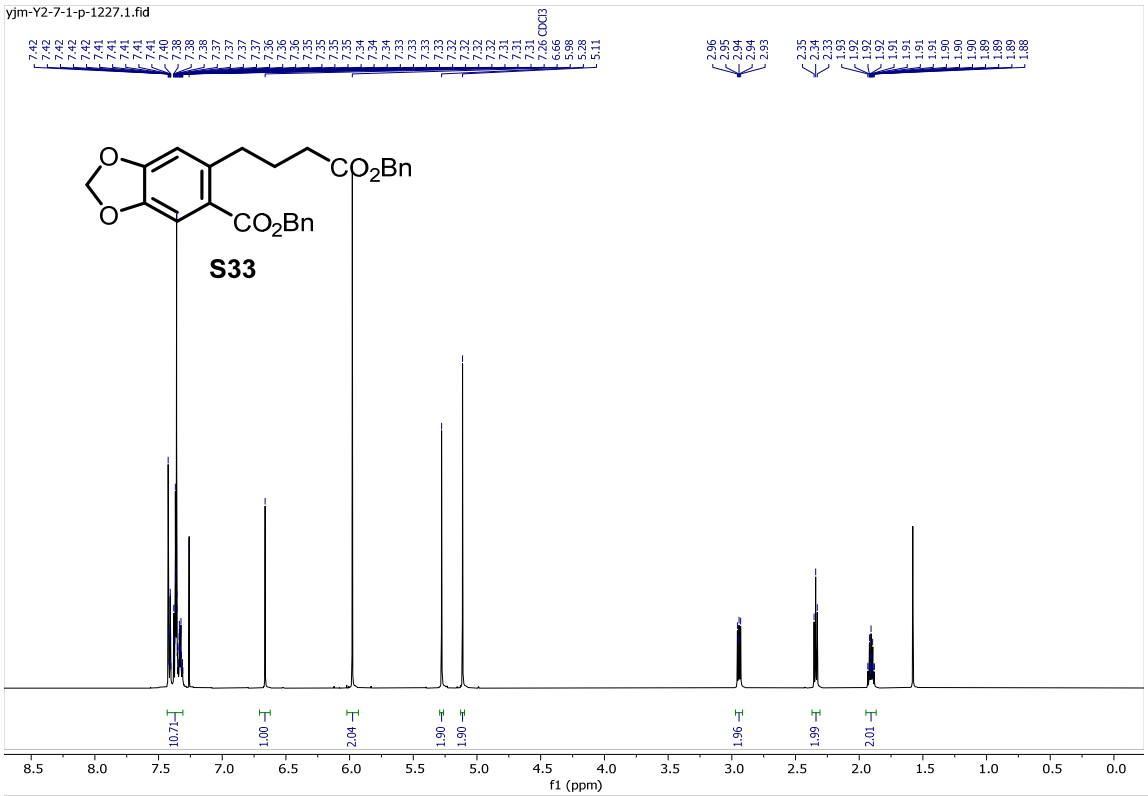


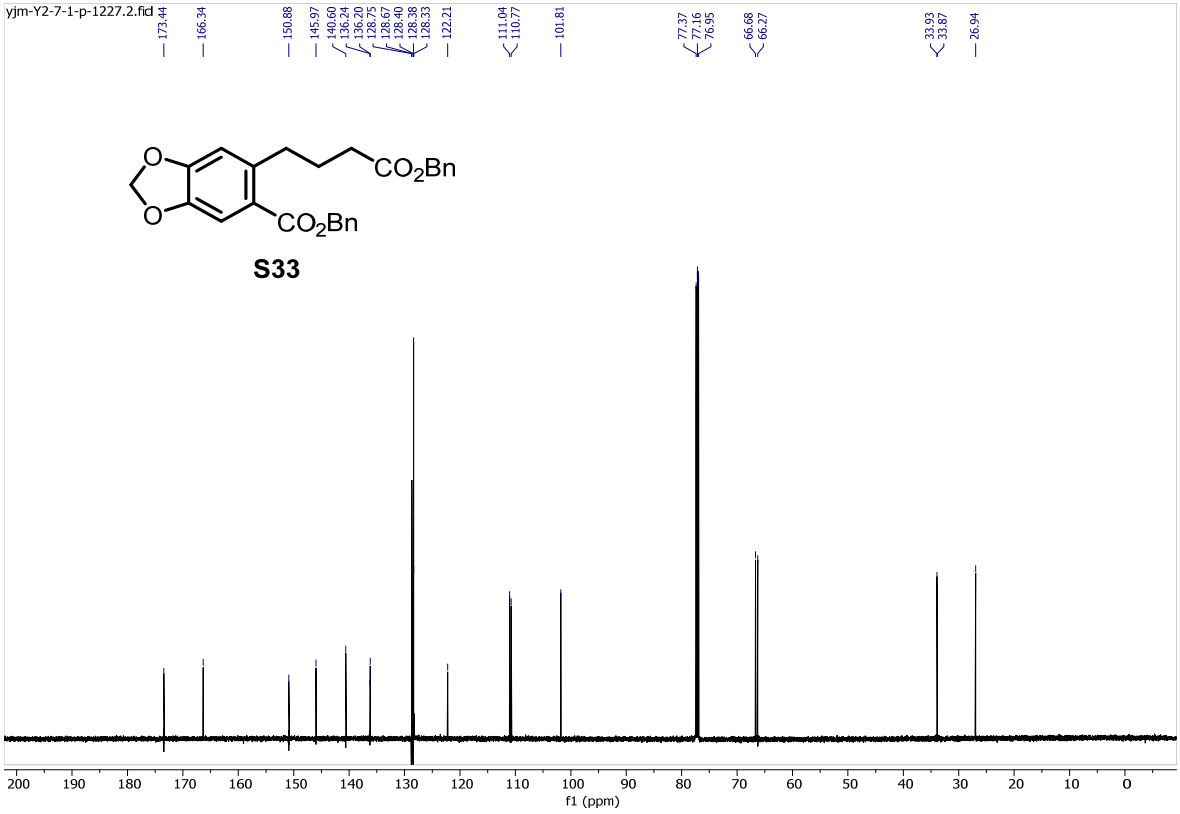
2-(3-Carboxypropyl)benzoic acid 32



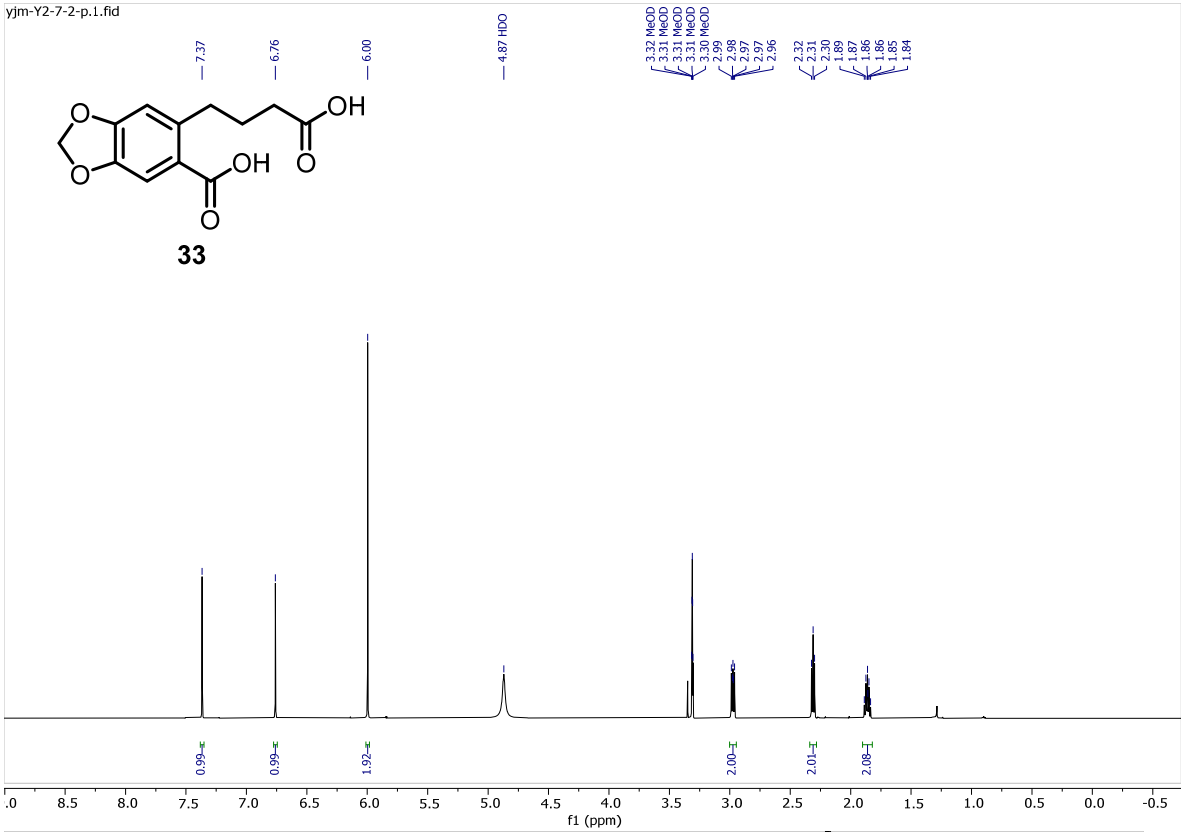


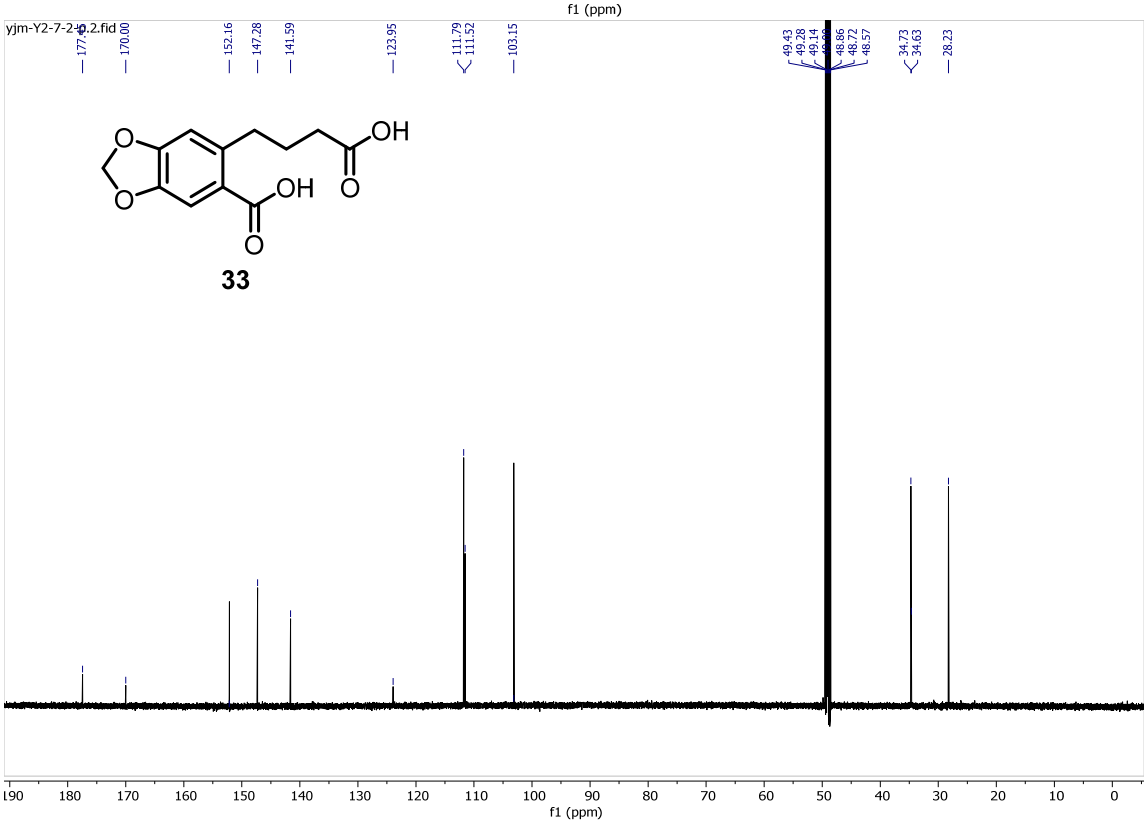
Benzyl 6-(4-(benzyloxy)-4-oxobutyl)benzo[*d*][1,3]dioxole-5-carboxylate S33



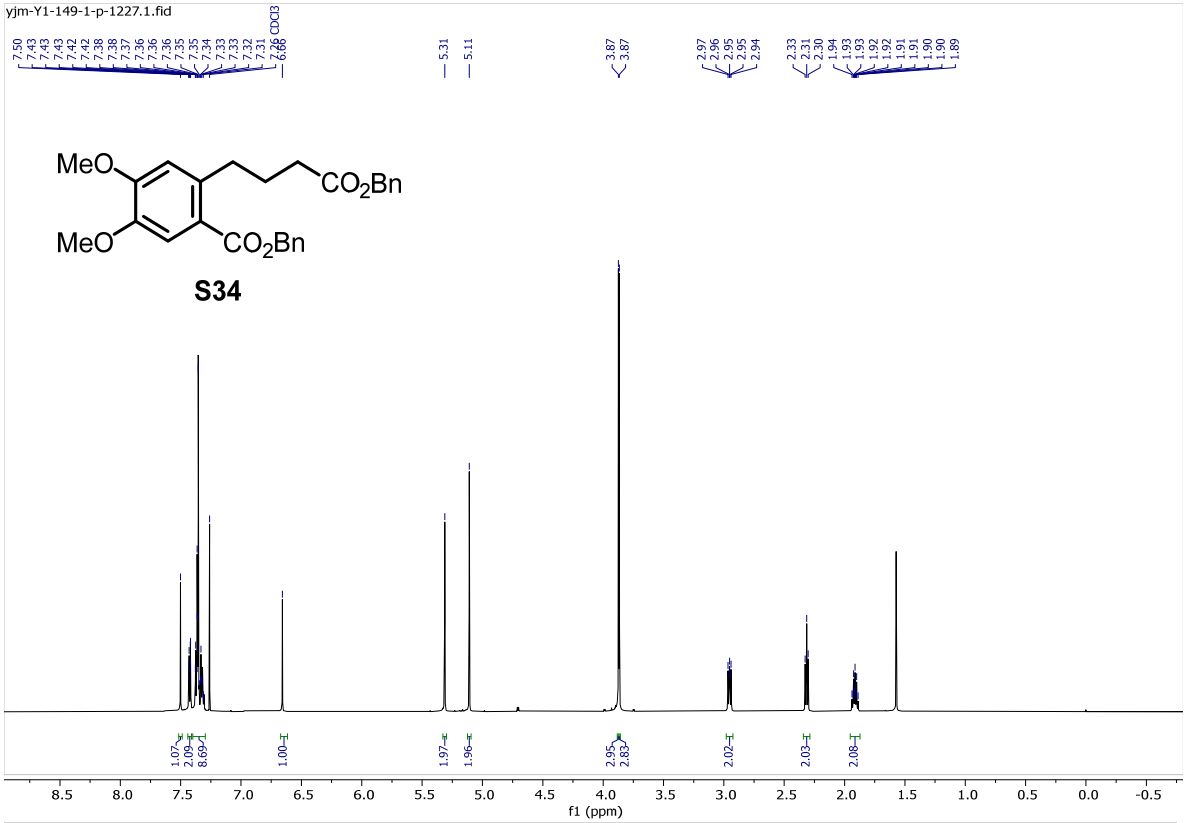


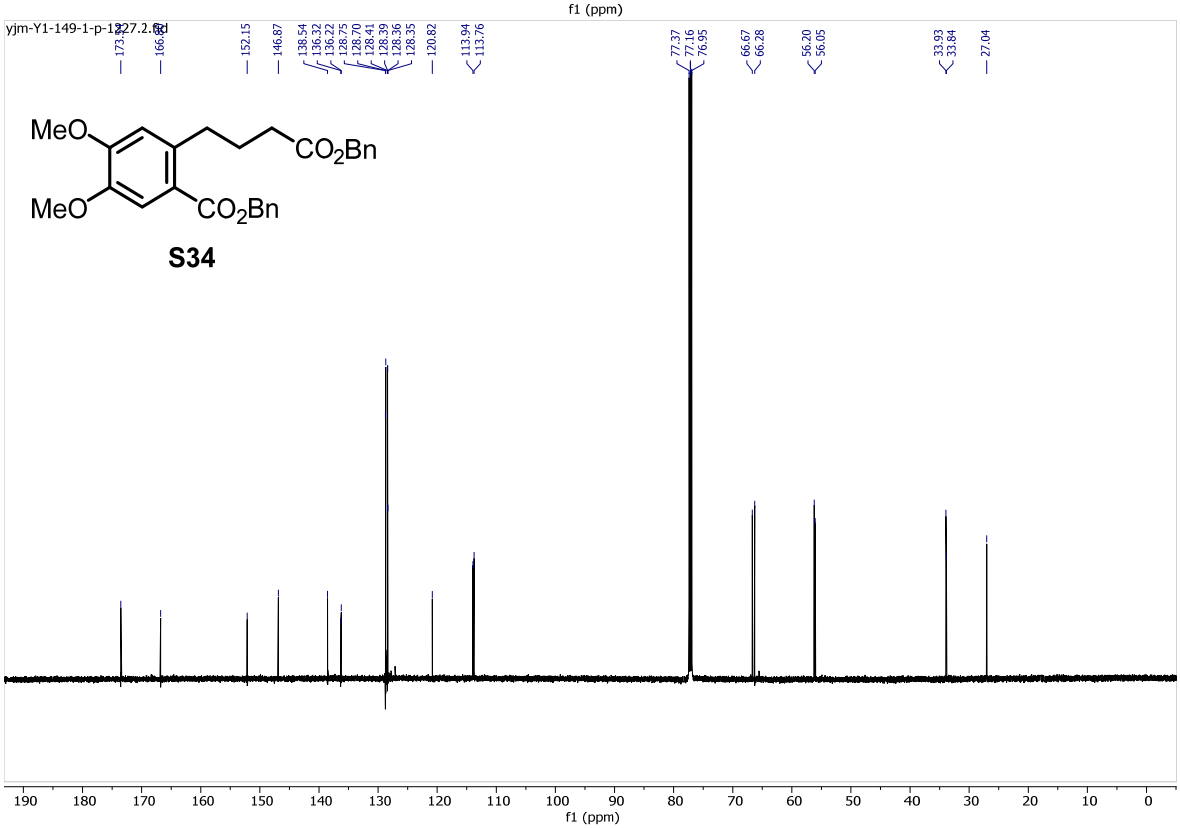
6-(3-Carboxypropyl)benzo[*d*][1,3]dioxole-5-carboxylic acid 33



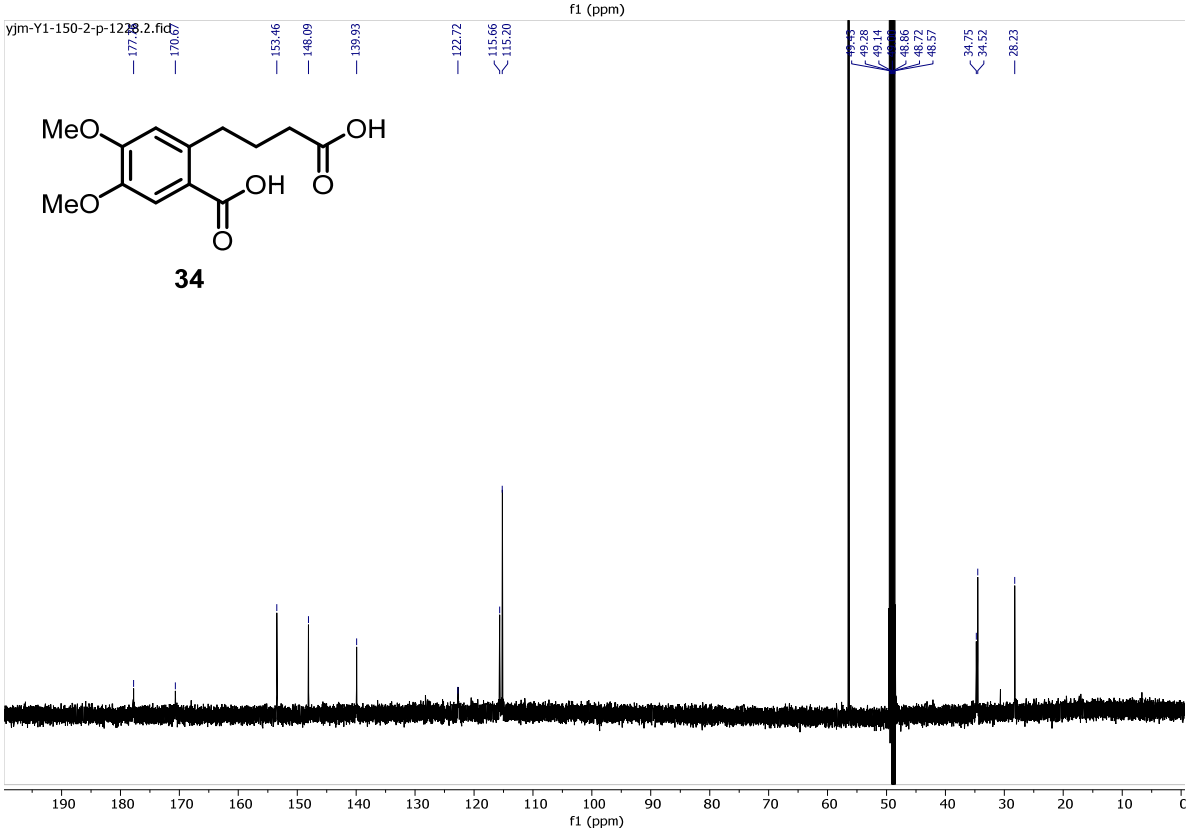


Benzyl 2-(4-(benzyloxy)-4-oxobutyl)-4,5-dimethoxybenzoate S34

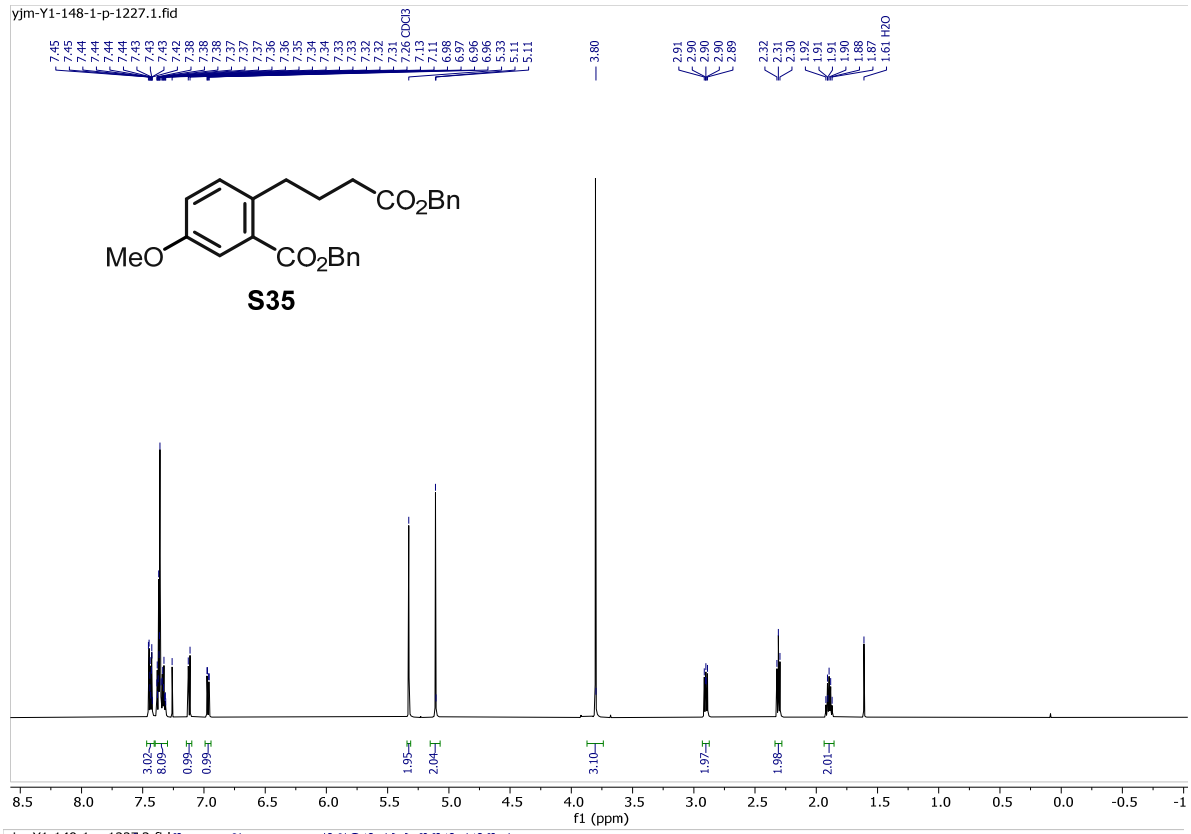


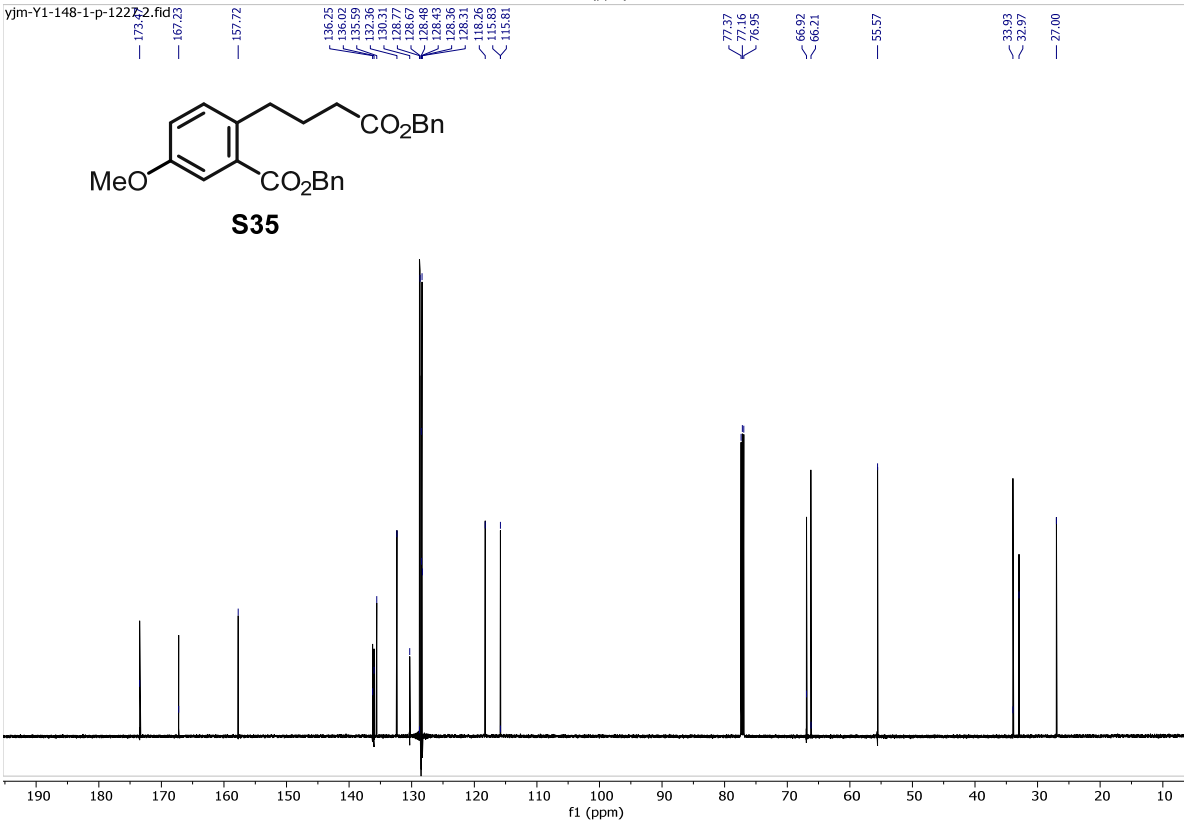


2-(3-Carboxypropyl)-4,5-dimethoxybenzoic acid 34

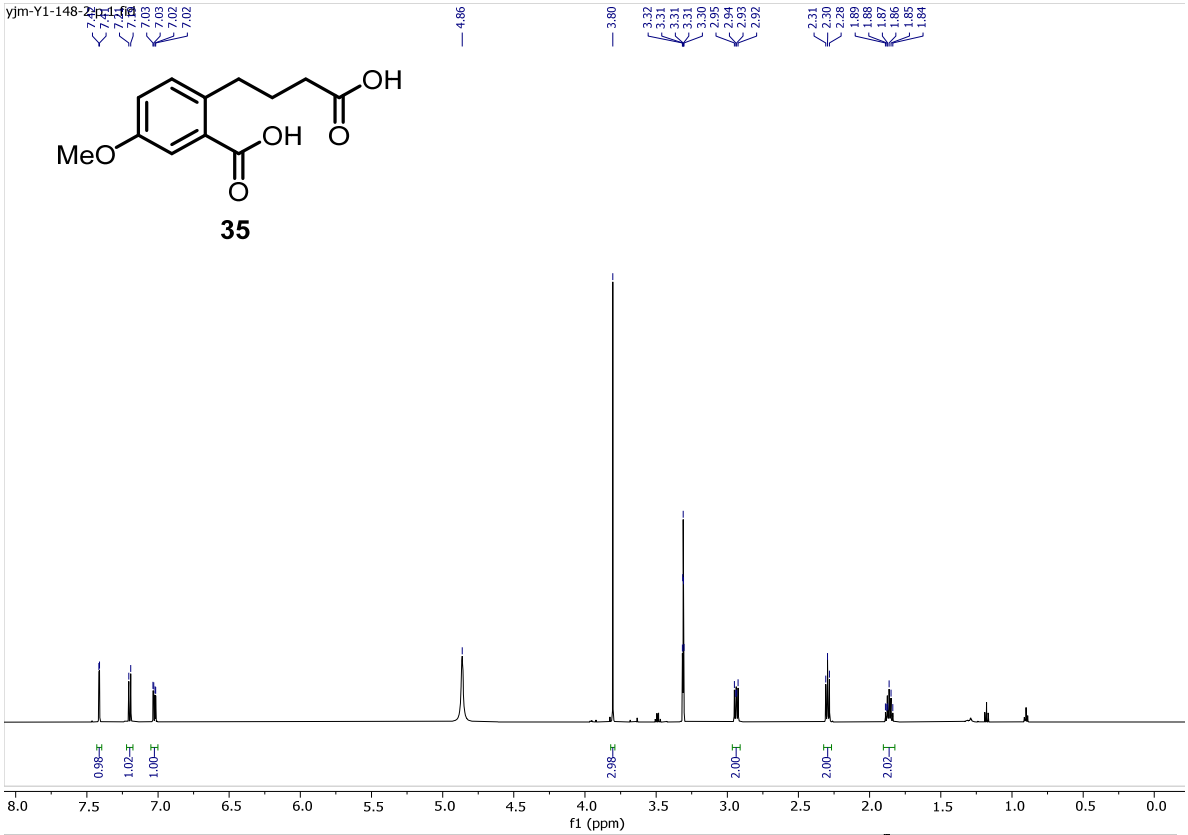


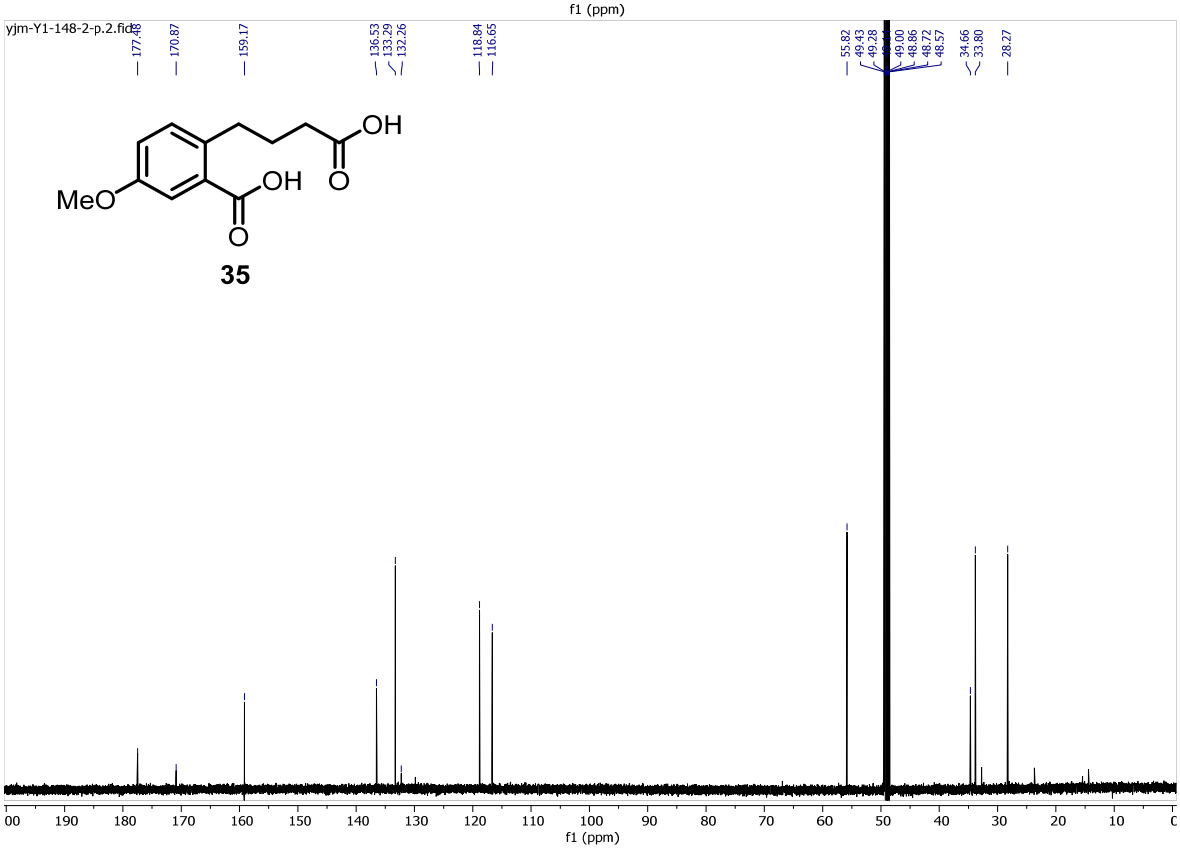
Benzyl 2-(4-(benzyloxy)-4-oxobutyl)-4-methoxybenzoate S35



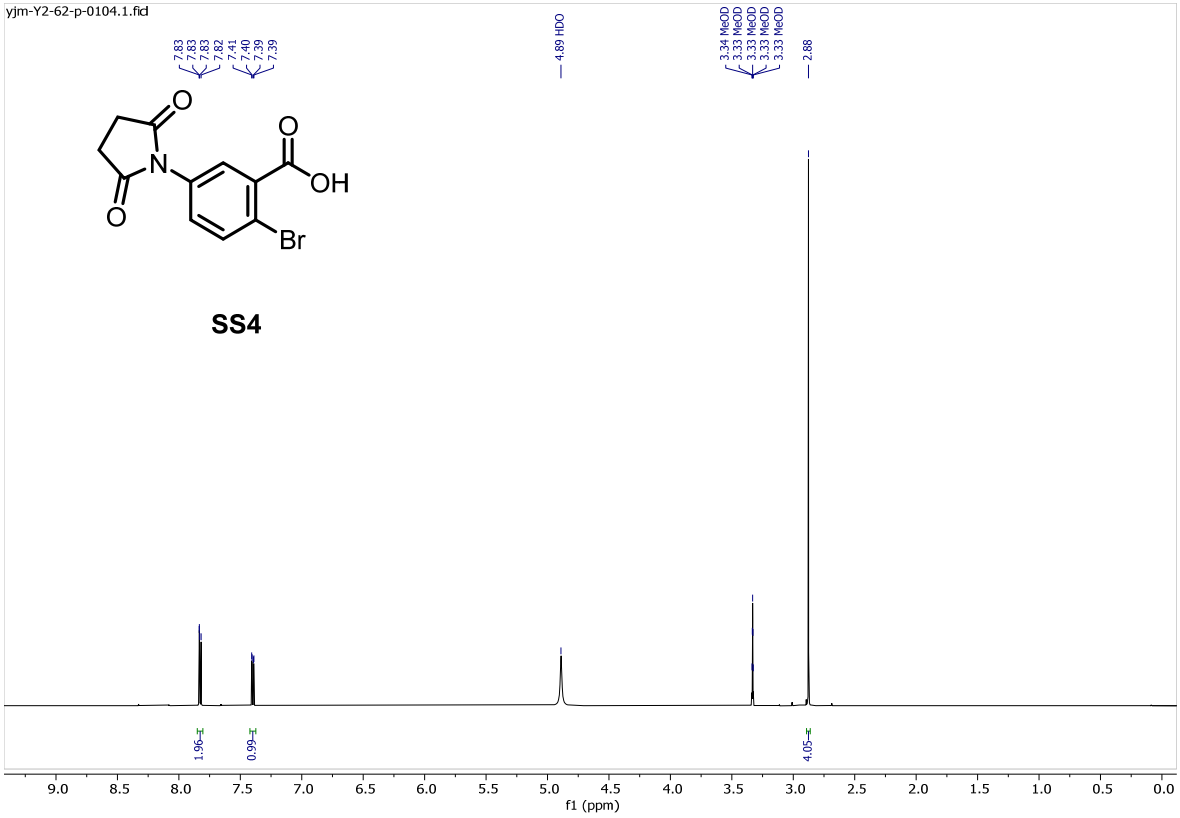


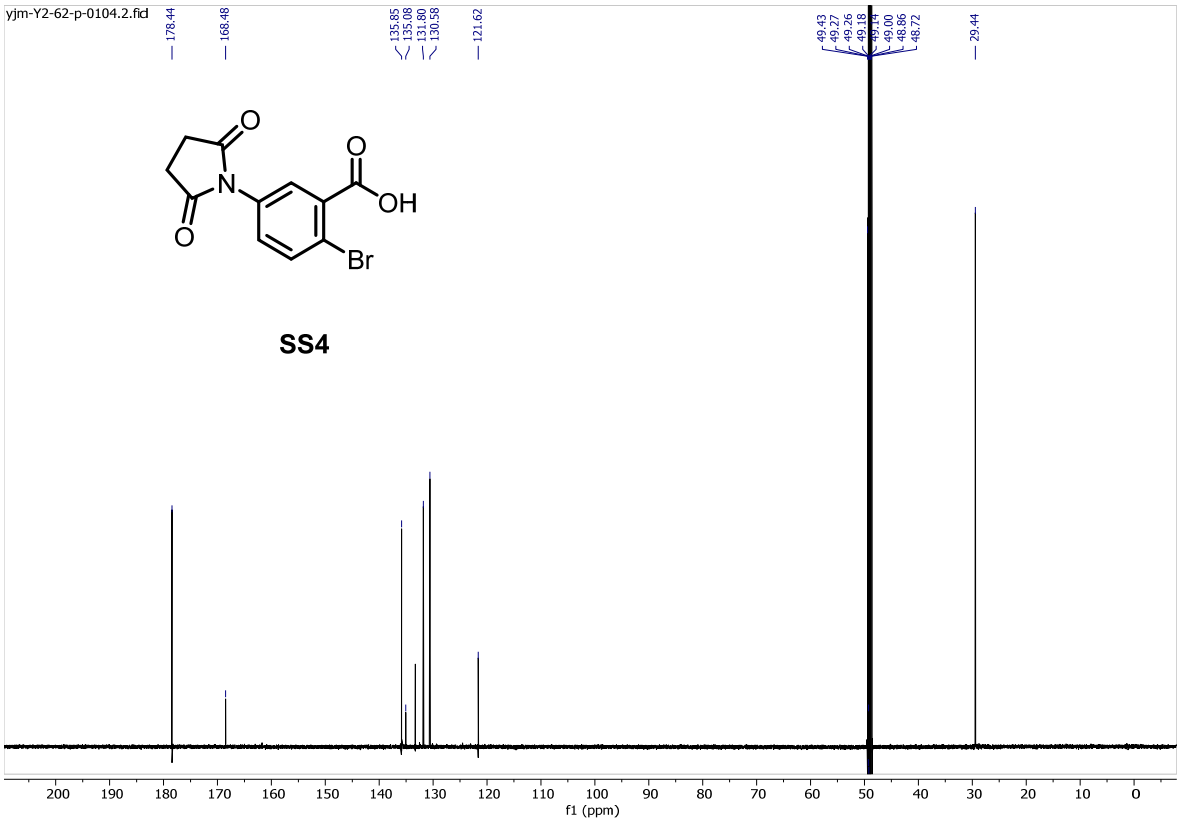
2-(3-Carboxypropyl)-5-methoxybenzoic acid 35



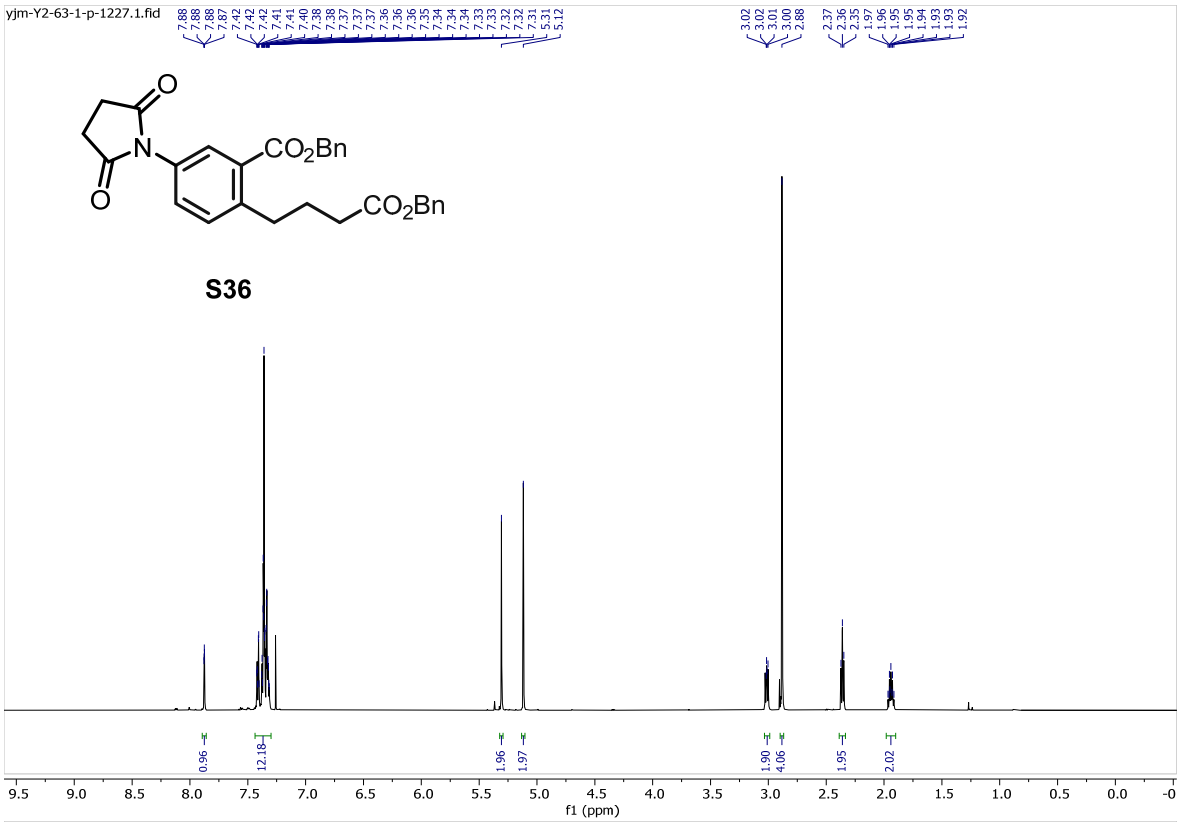


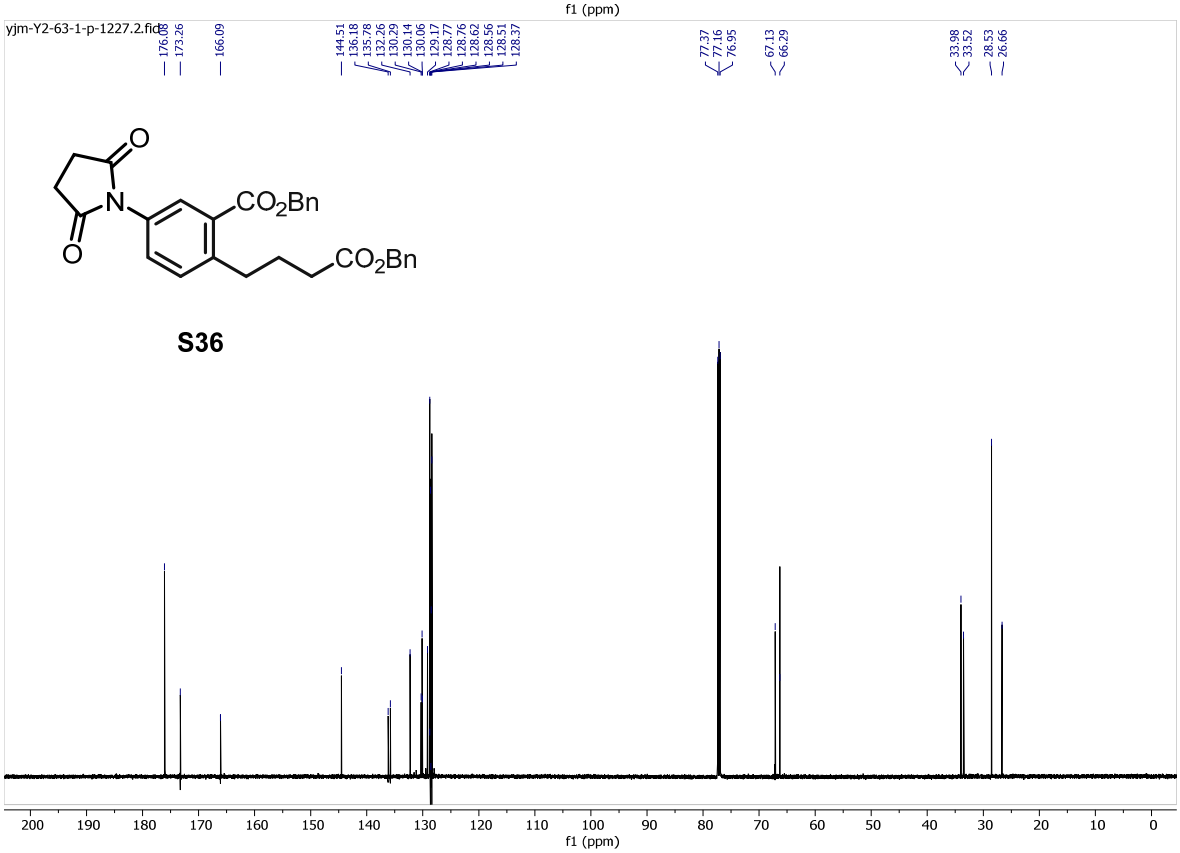
2-Bromo-4-(2,5-dioxopyrrolidin-1-yl)benzoic acid SS4



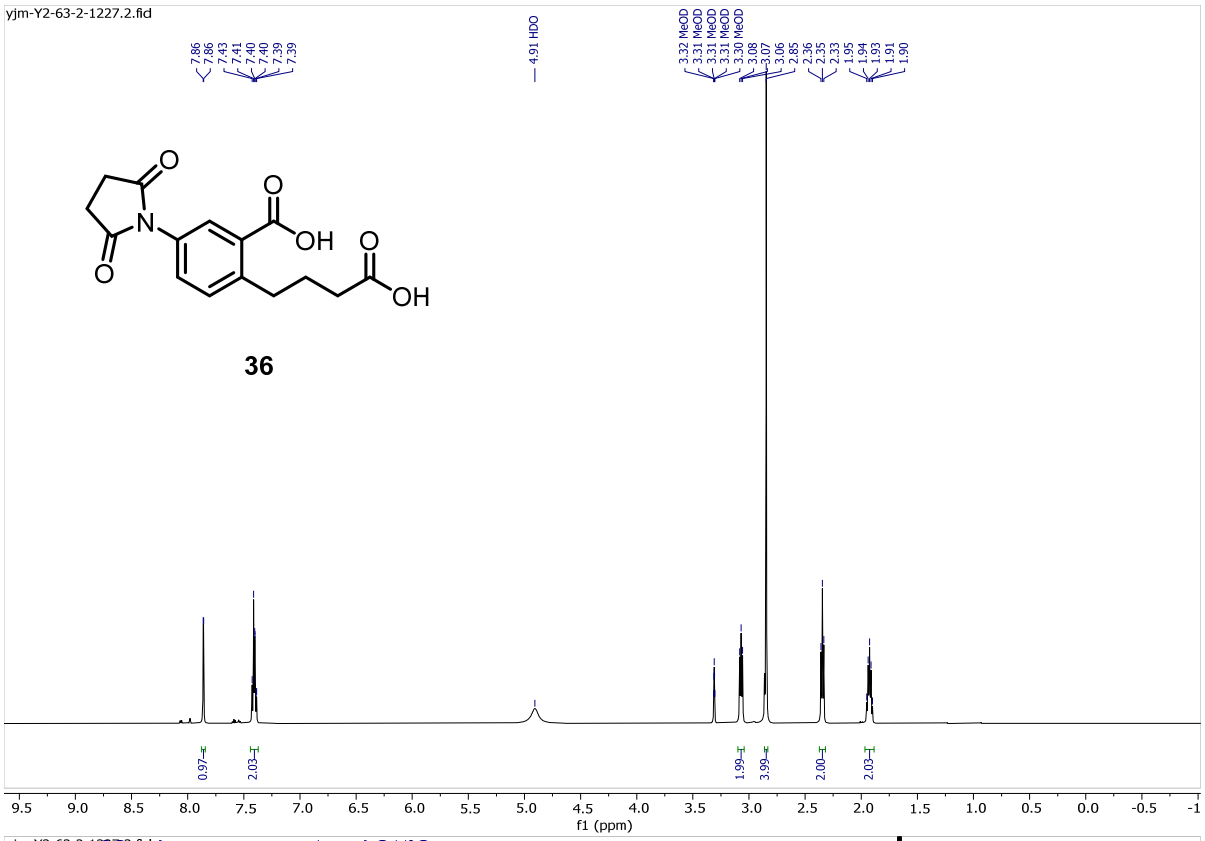


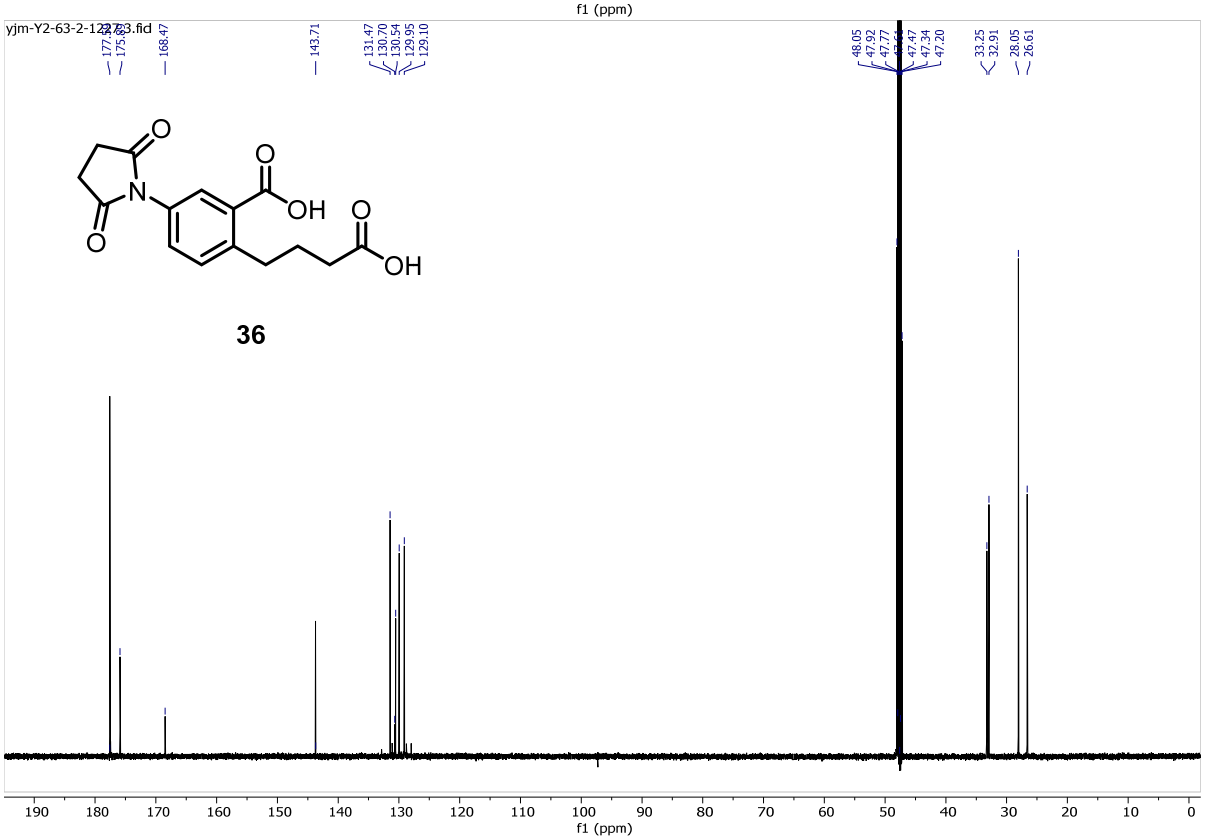
Benzyl 2-(4-(benzyloxy)-4-oxobutyl)-4-(2,5-dioxopyrrolidin-1-yl)benzoate S36



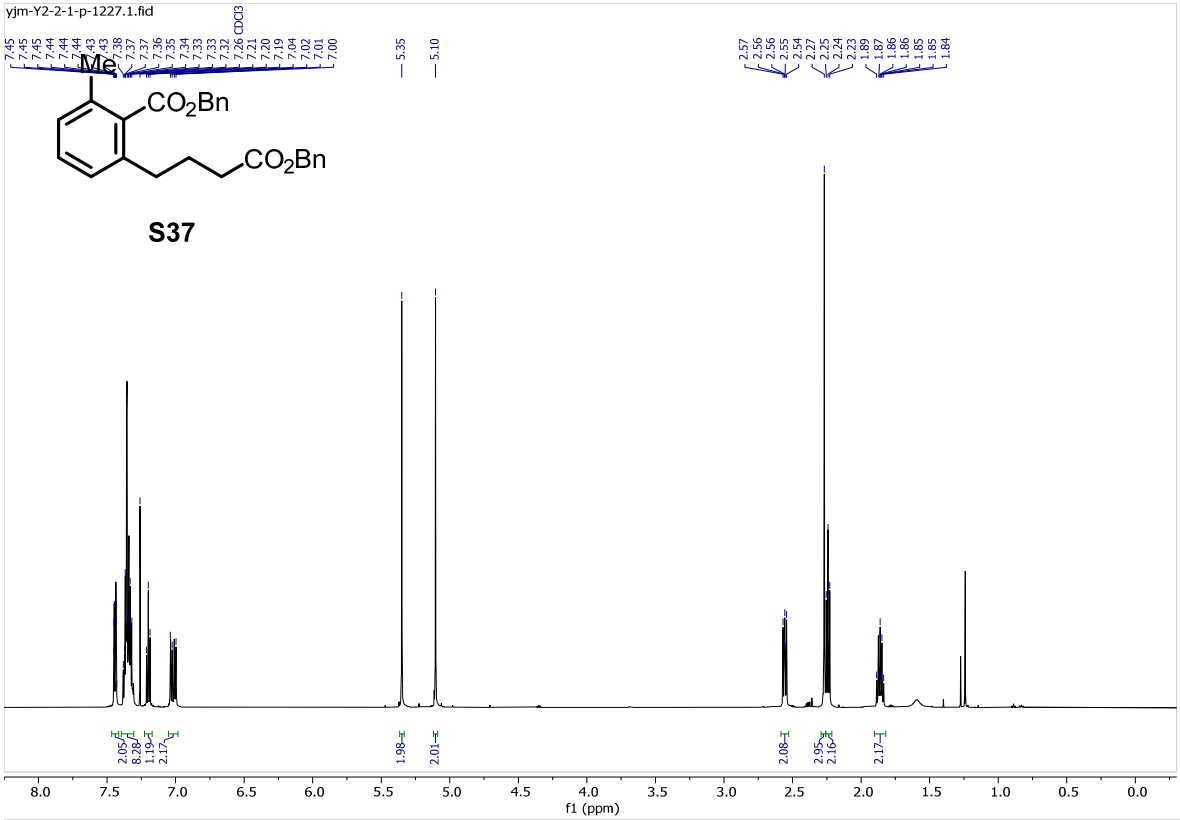


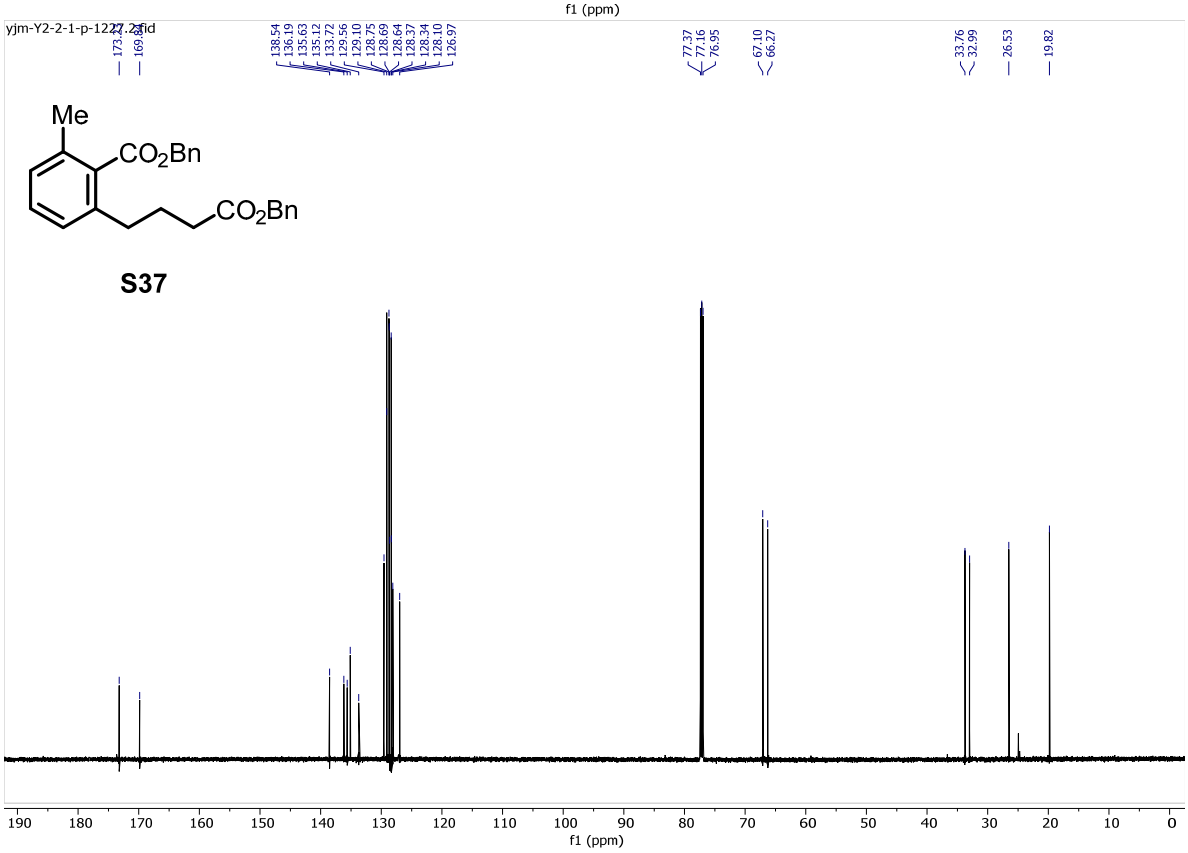
2-(3-Carboxypropyl)-4-(2,5-dioxopyrrolidin-1-yl)benzoic acid 36



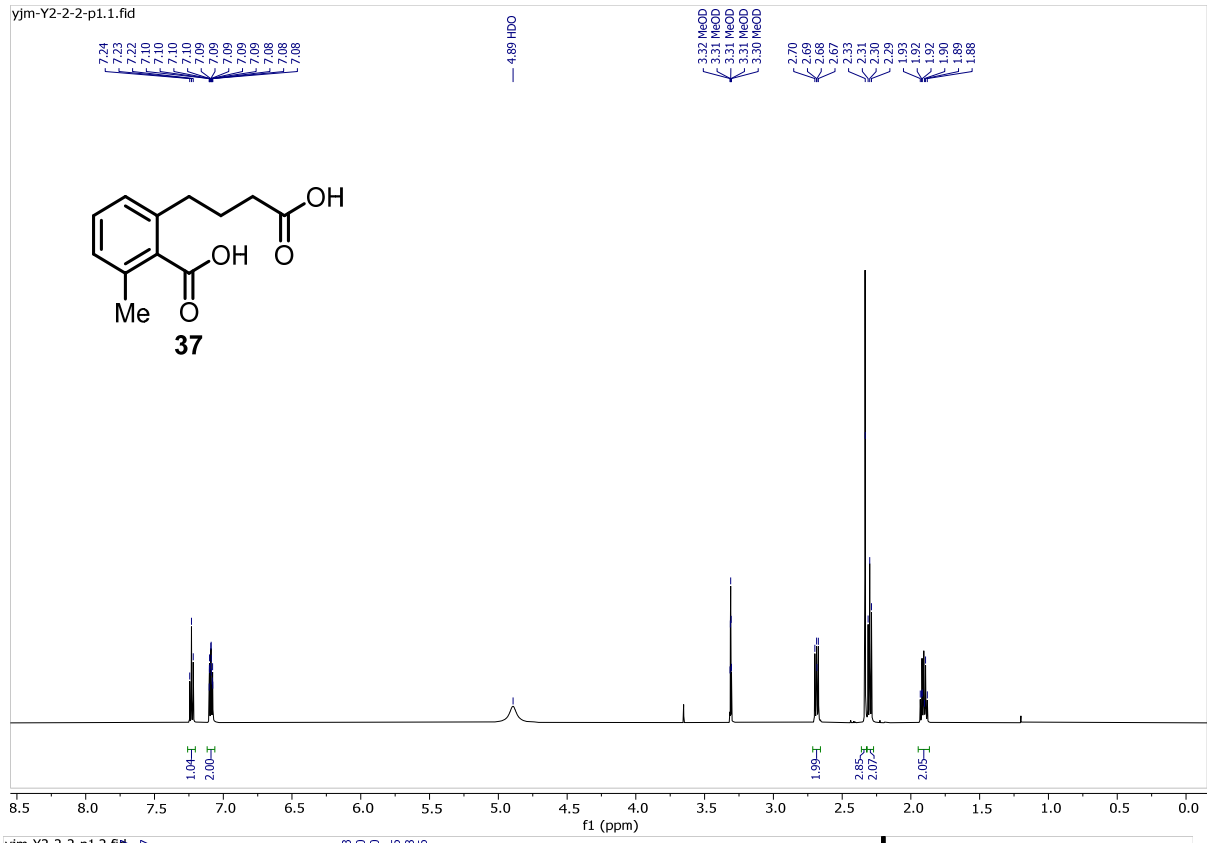


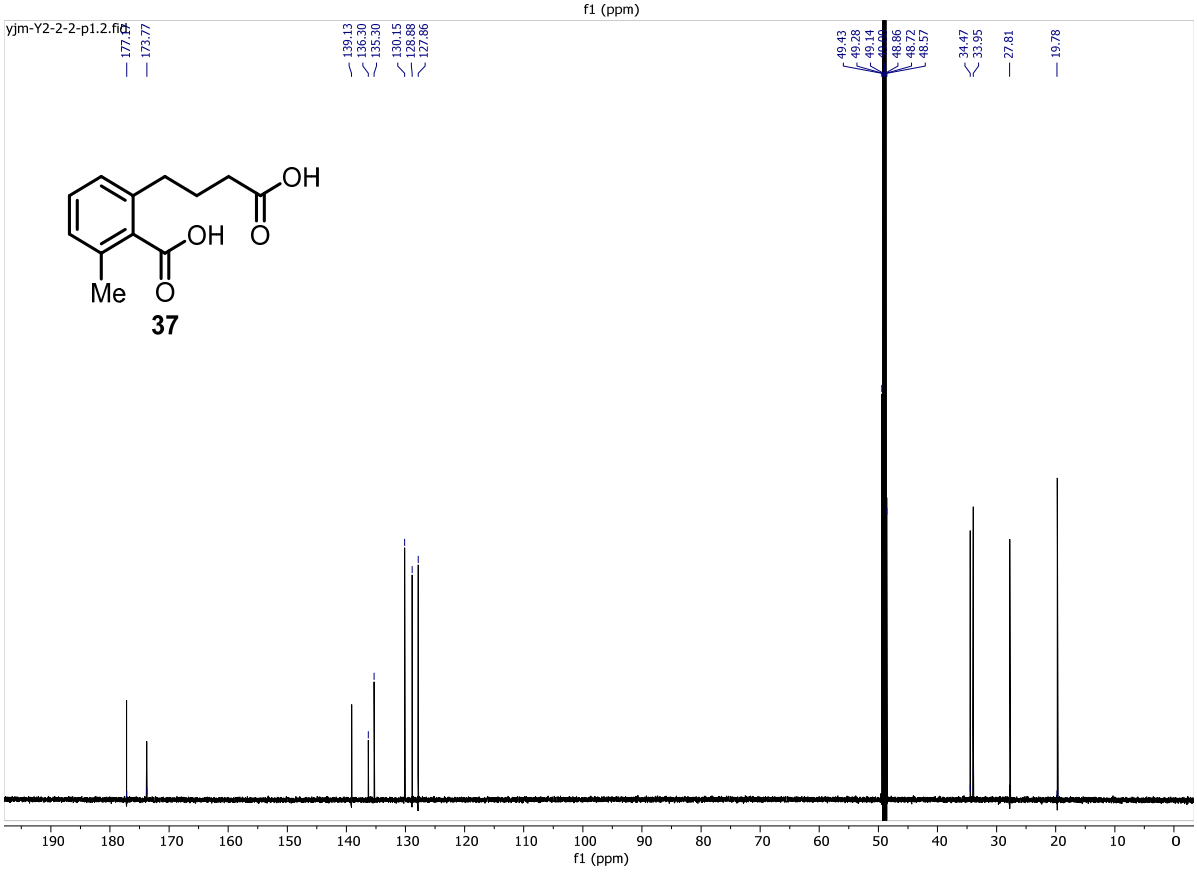
Benzyl 2-(4-(benzyloxy)-4-oxobutyl)-3-methylbenzoate S37



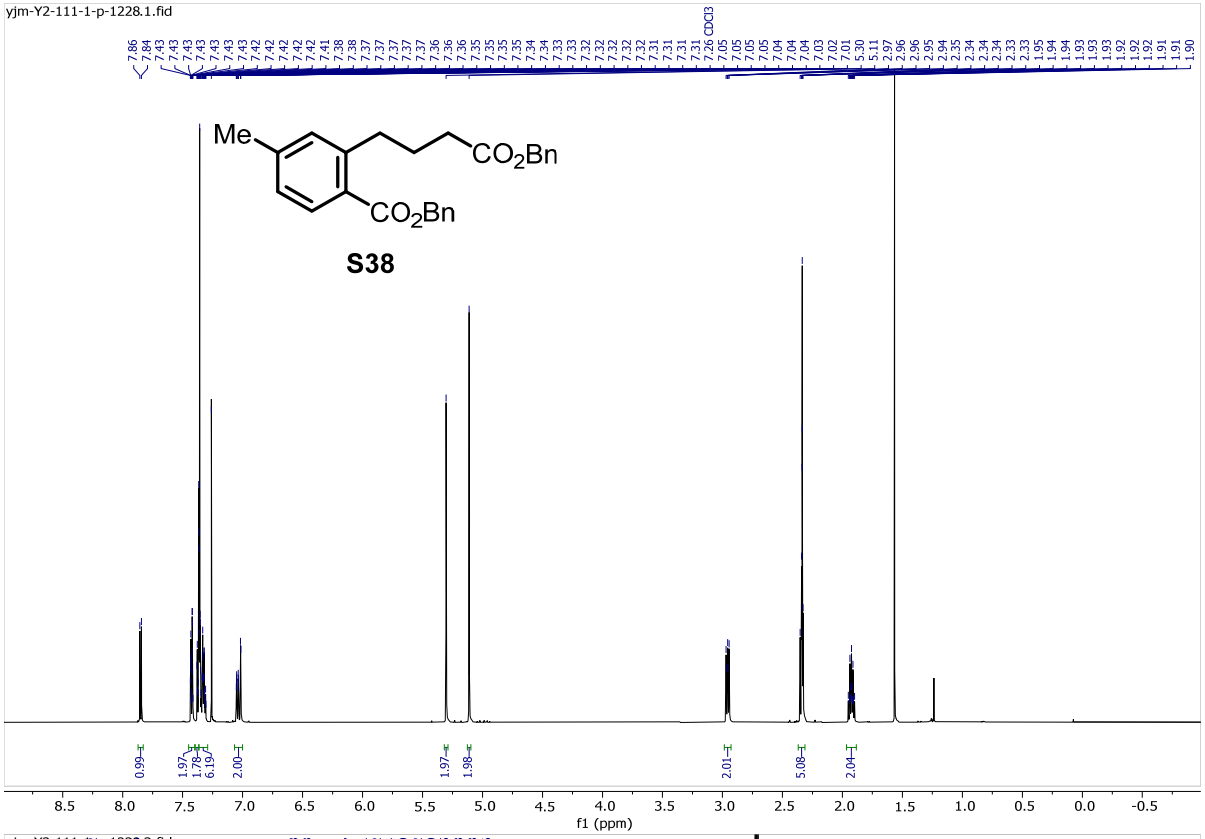


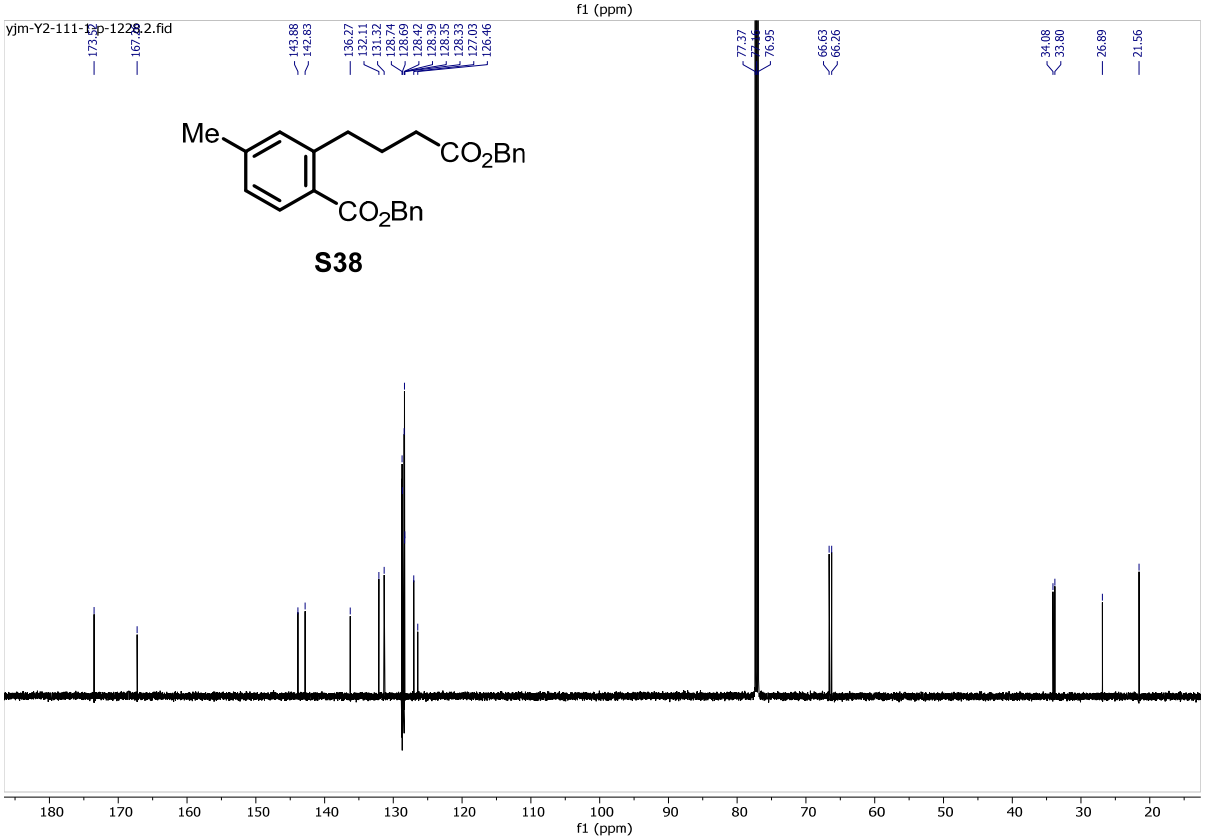
2-(3-Carboxypropyl)-6-methylbenzoic acid 37



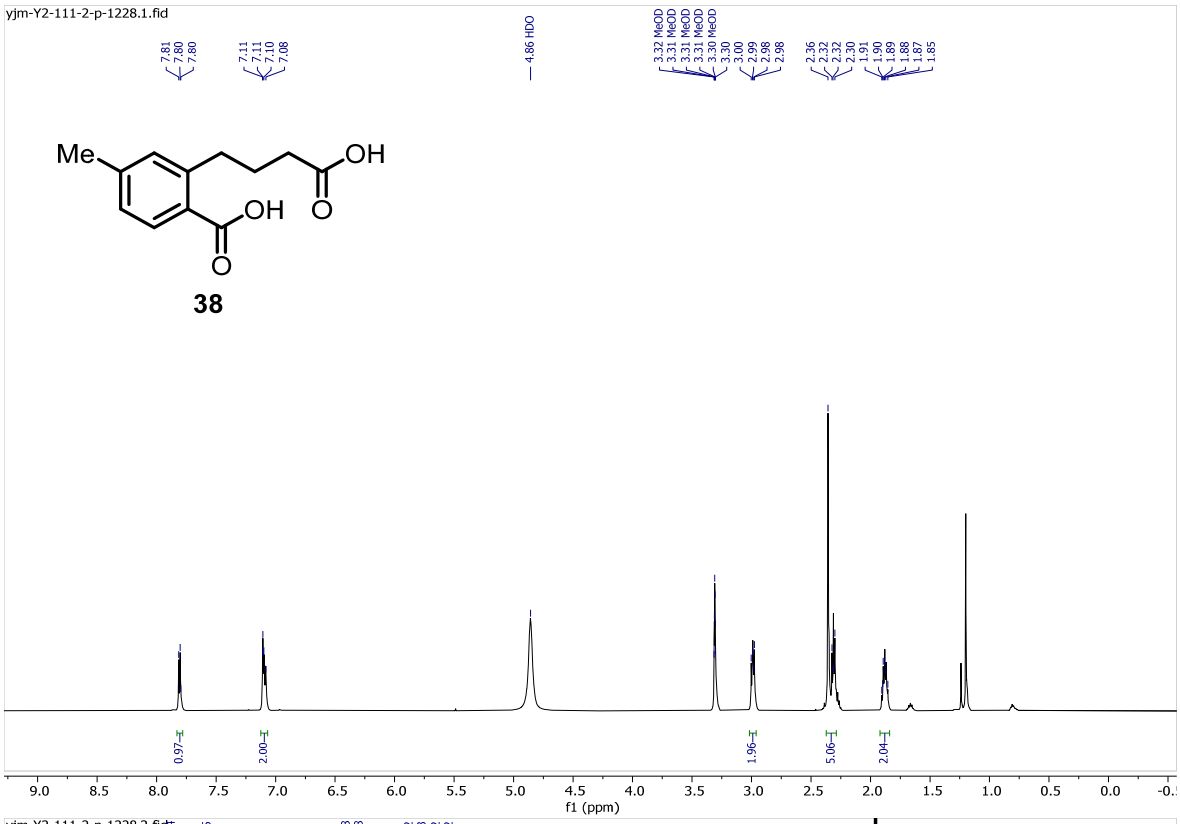


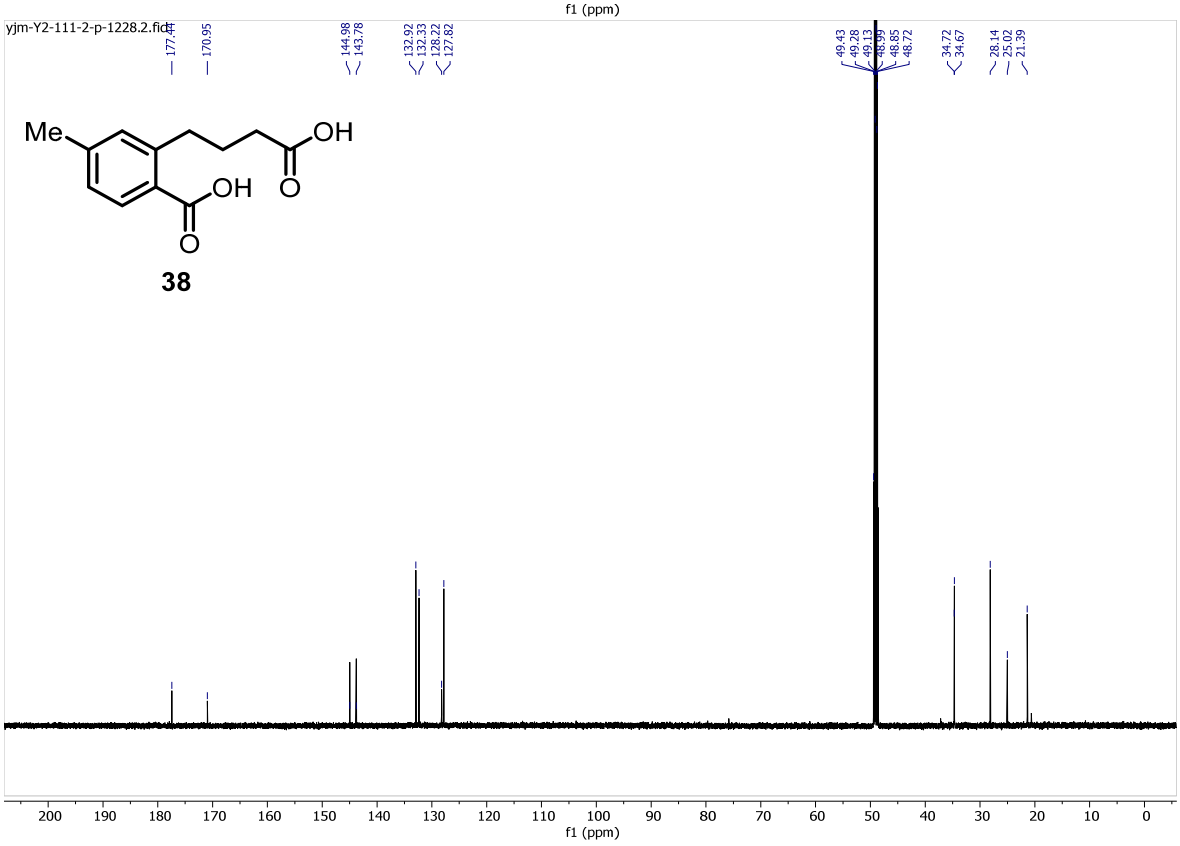
Benzyl 2-(4-(benzyloxy)-4-oxobutyl)-4-methylbenzoate S38



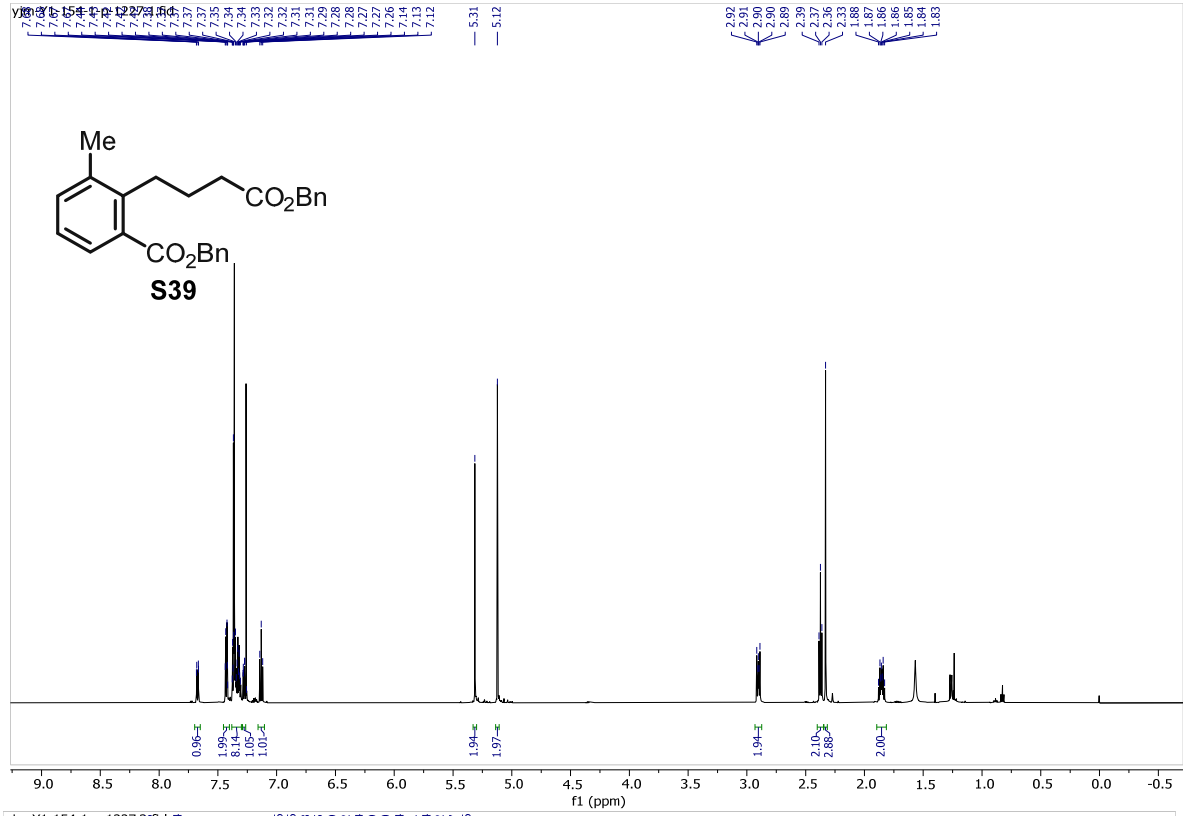


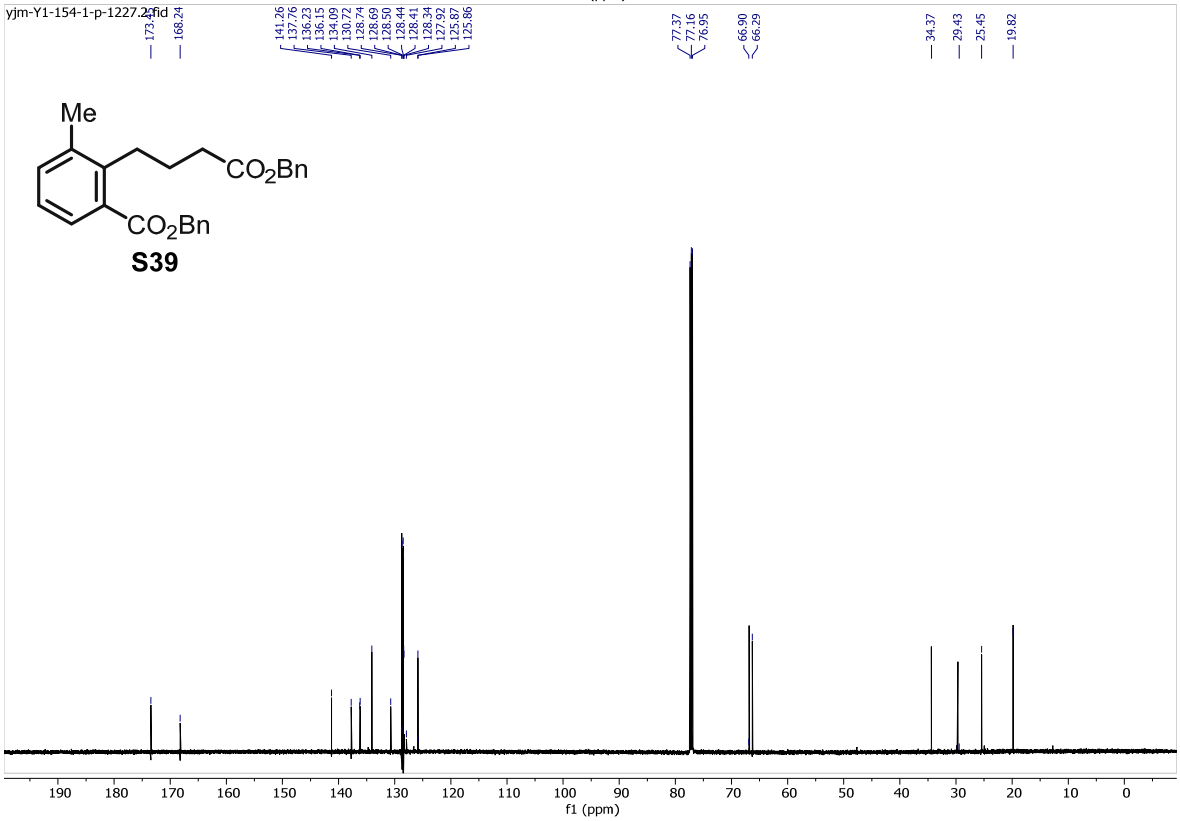
2-(3-Carboxypropyl)-4-methylbenzoic acid 38



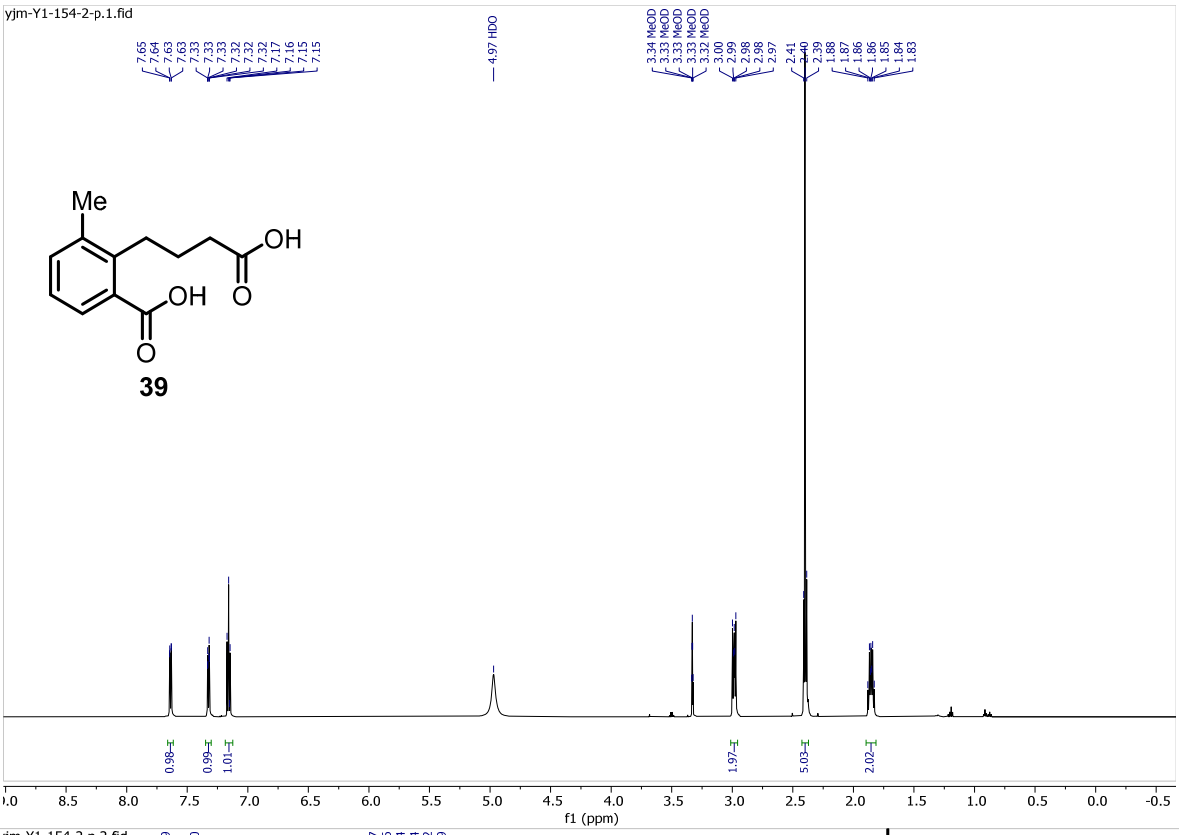


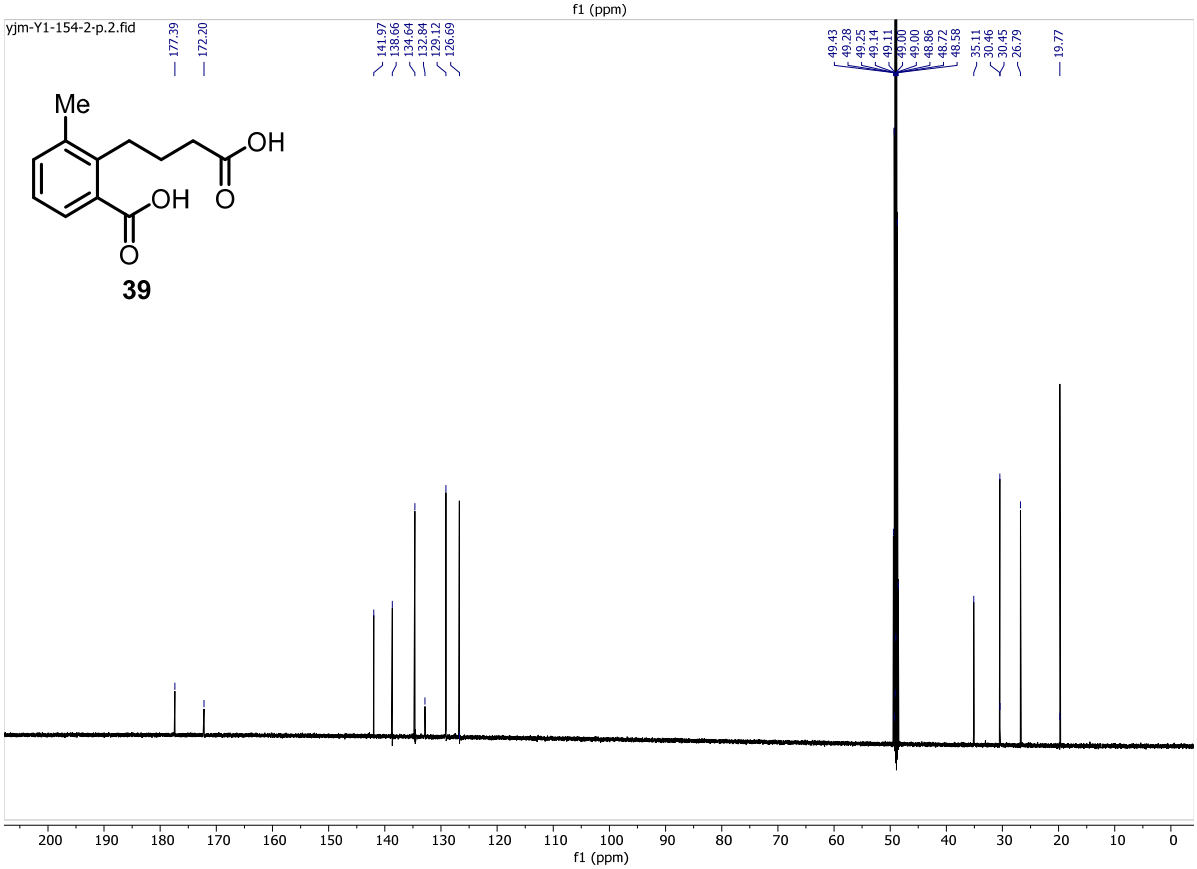
Benzyl 2-(4-(benzyloxy)-4-oxobutyl)-3-methylbenzoate S39



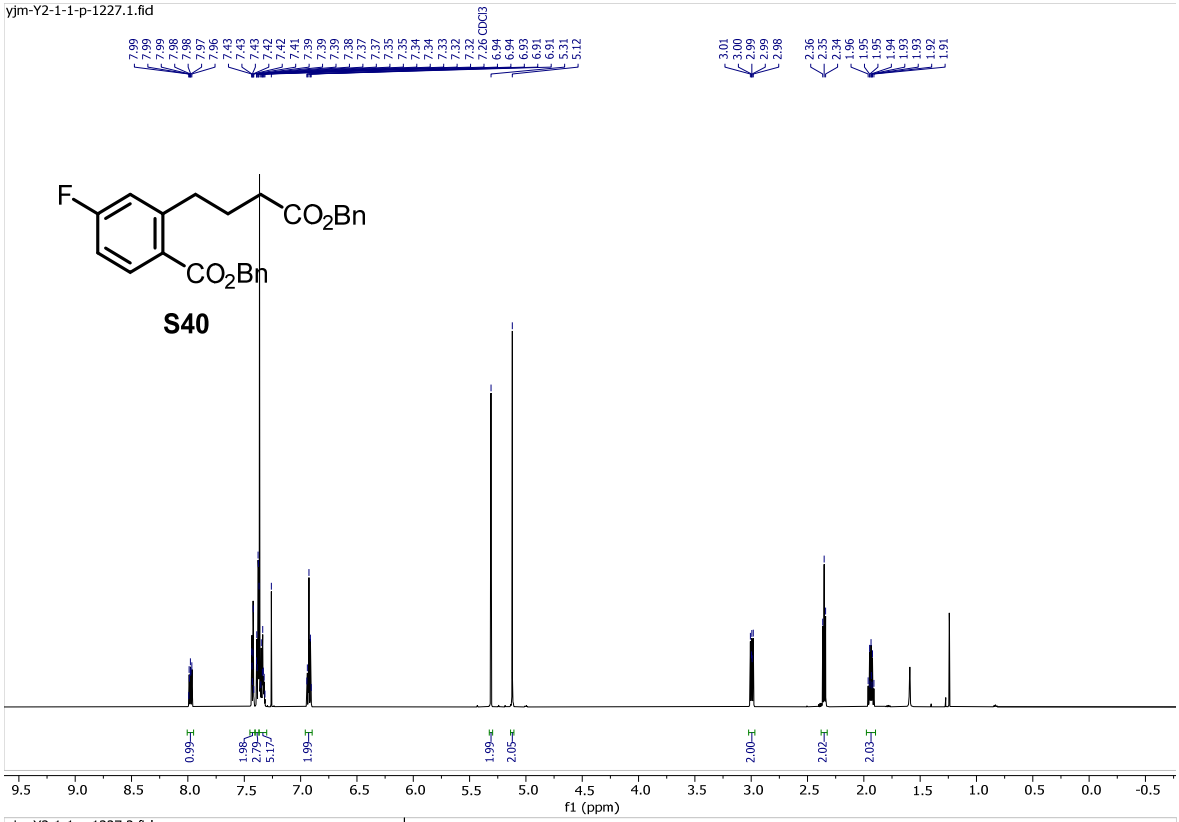


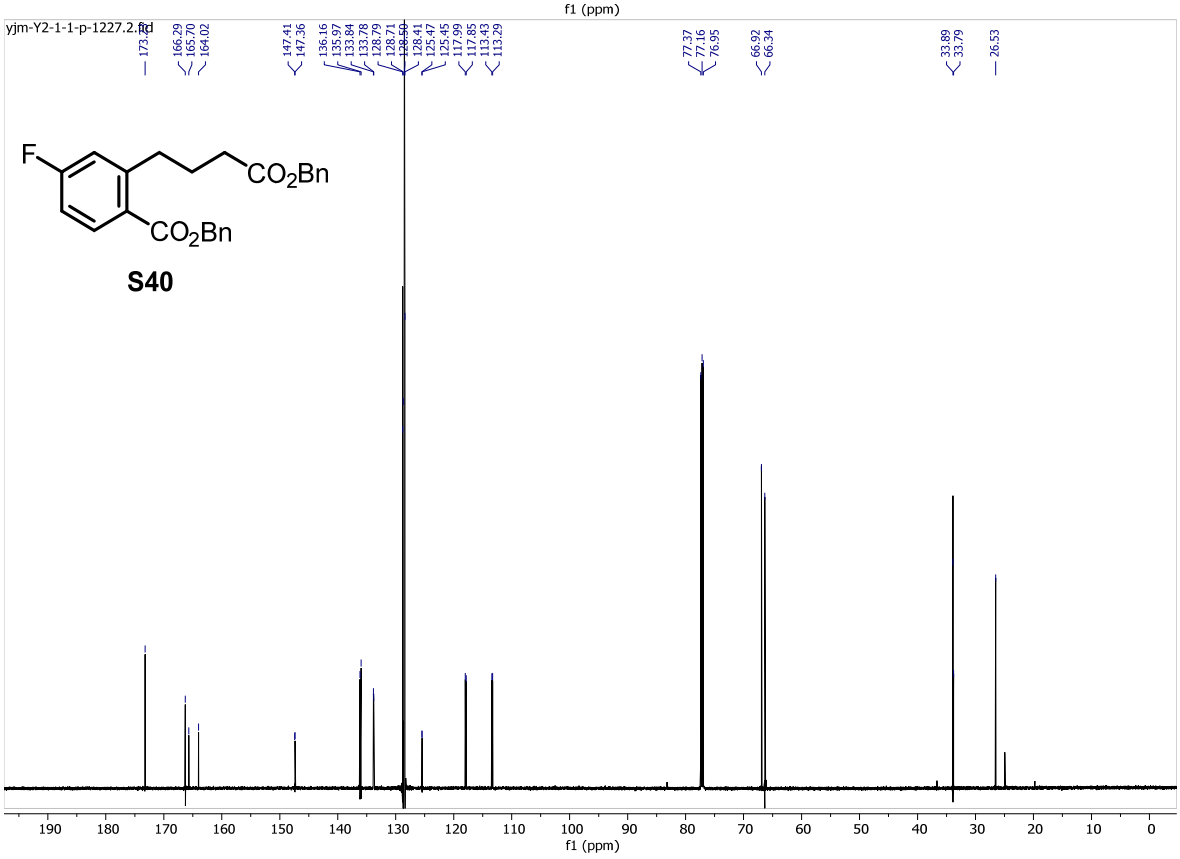
2-(3-Carboxypropyl)-3-methylbenzoic acid 39

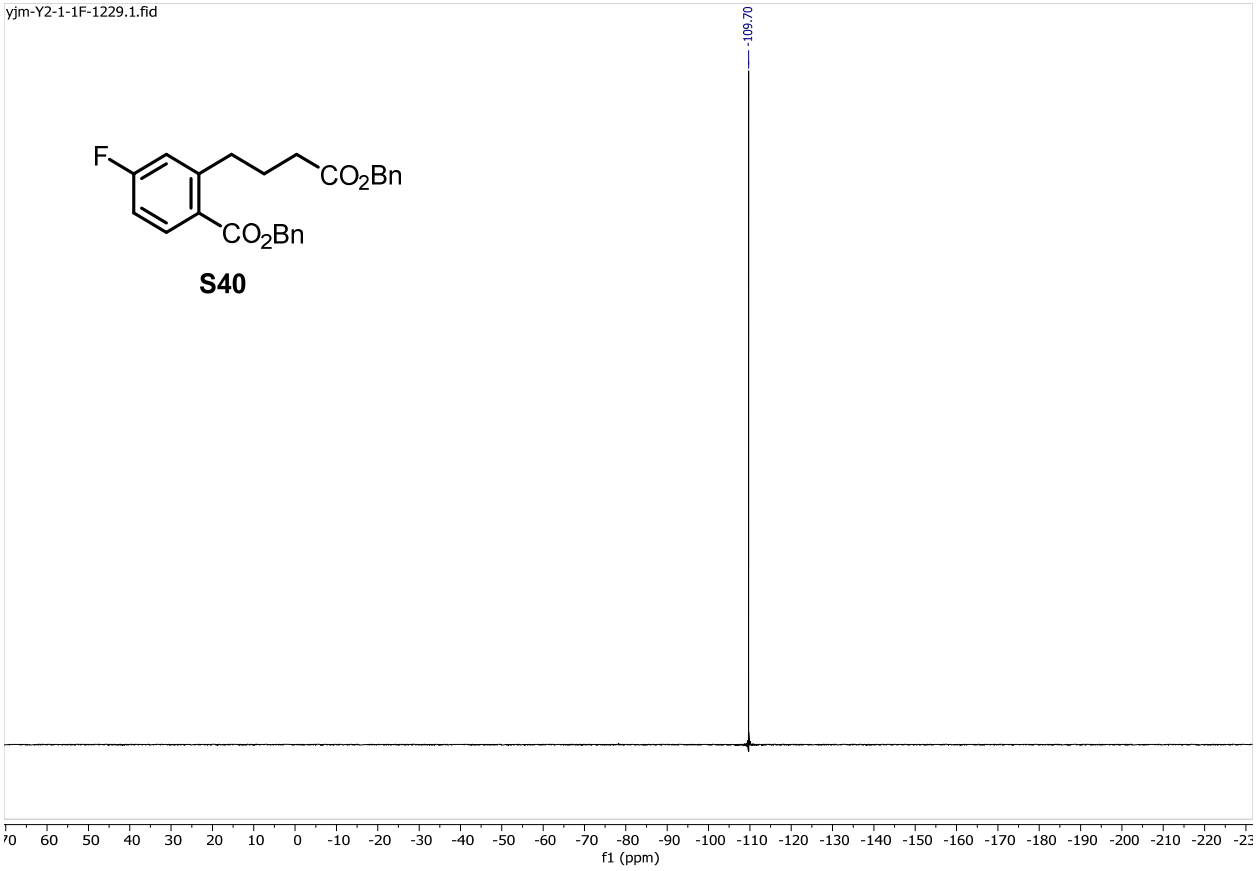




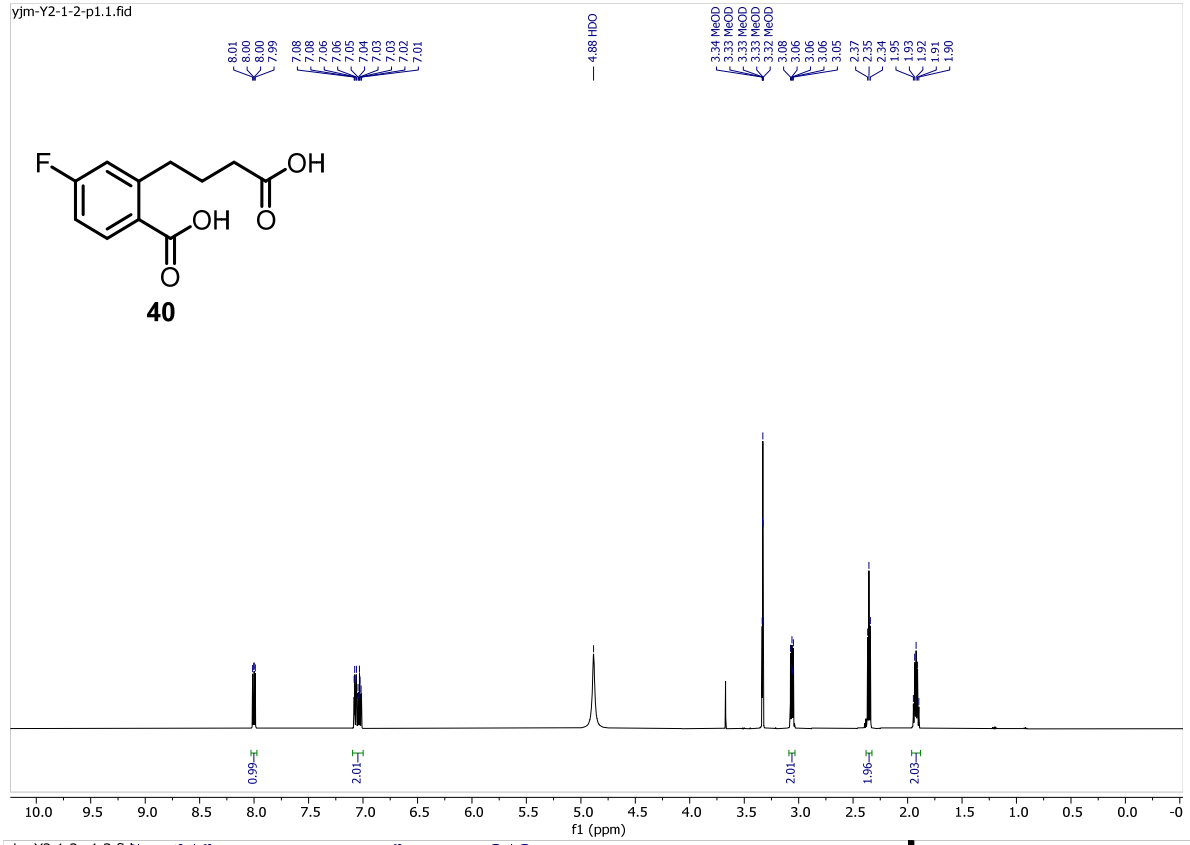
Benzyl 2-(4-(benzyloxy)-4-oxobutyl)-4-fluorobenzoate S40

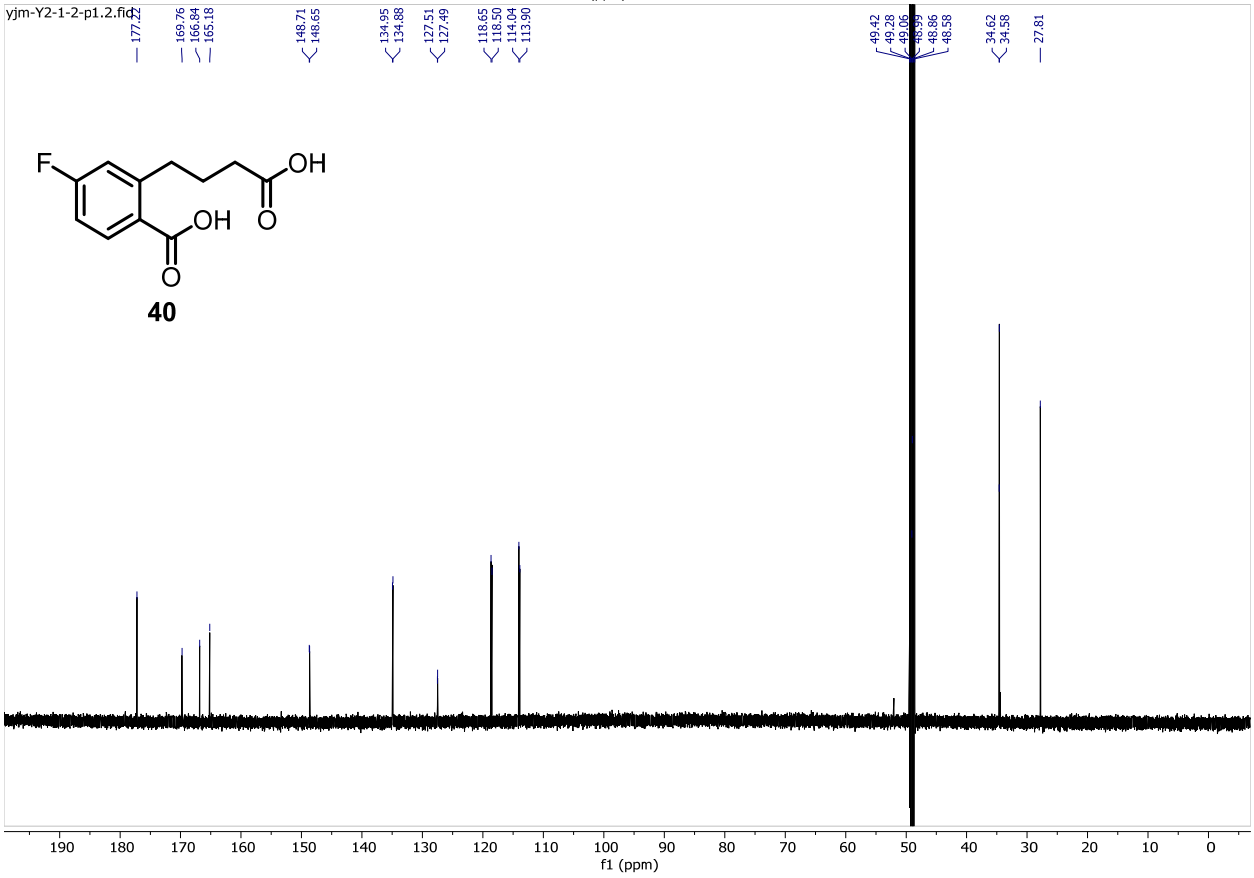


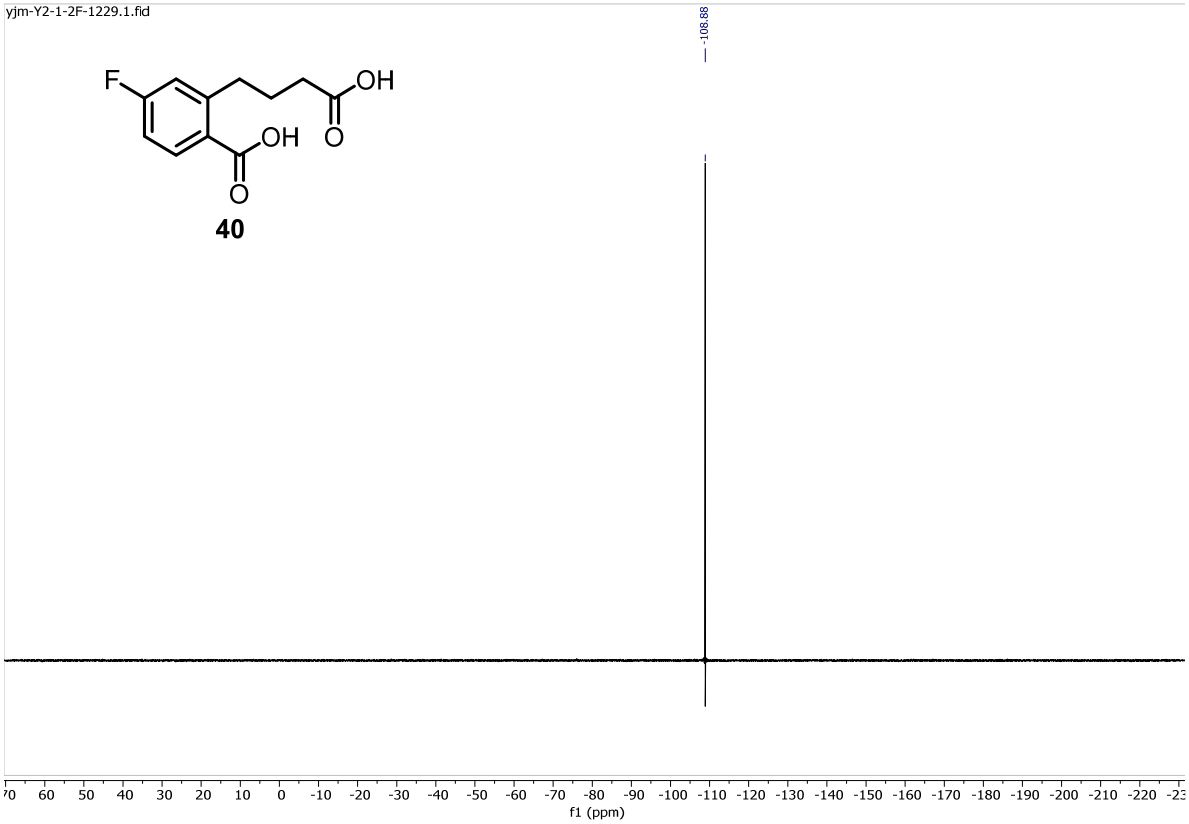



yjm-Y2-1-1F-1229.1.fid
-109.70
F
CO2Bn
CO2Bn
S40
70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -23
f1 (ppm)

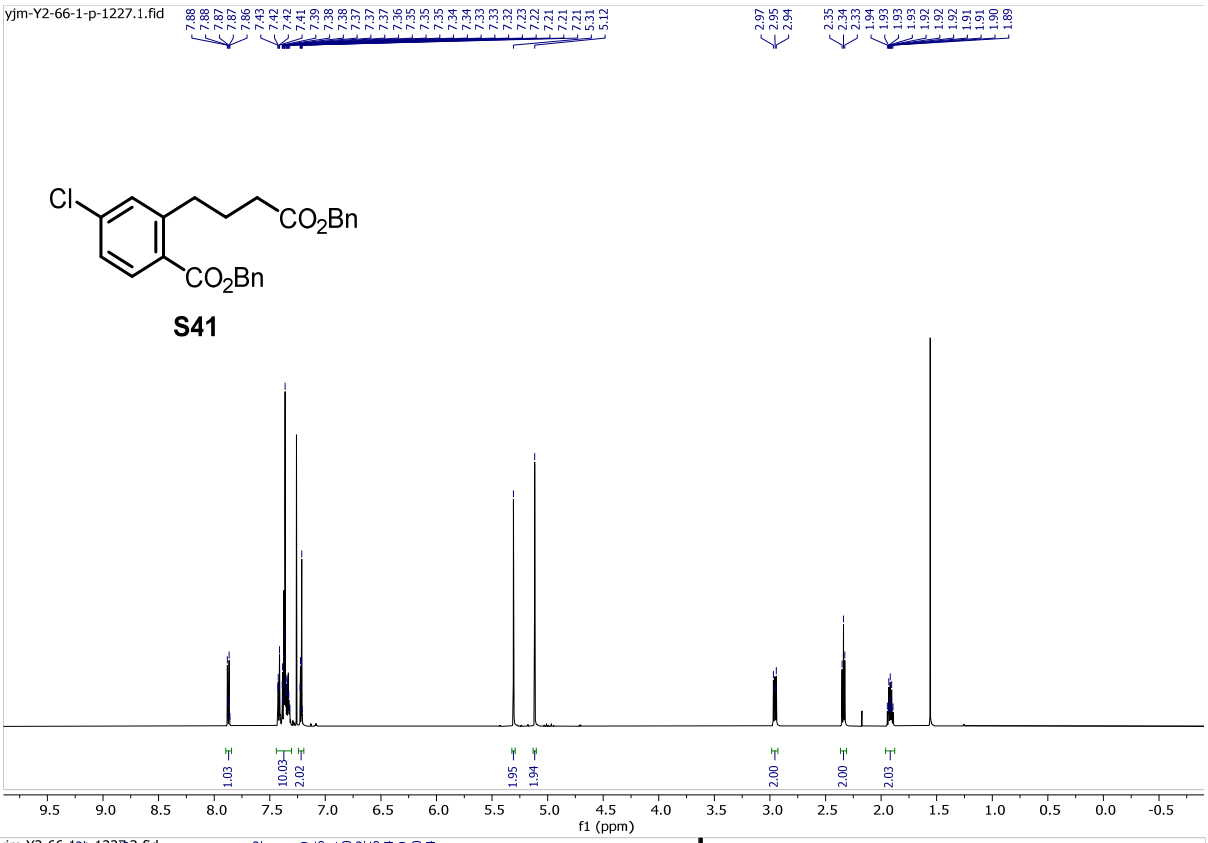
2-(3-Carboxypropyl)-4-fluorobenzoic acid 40

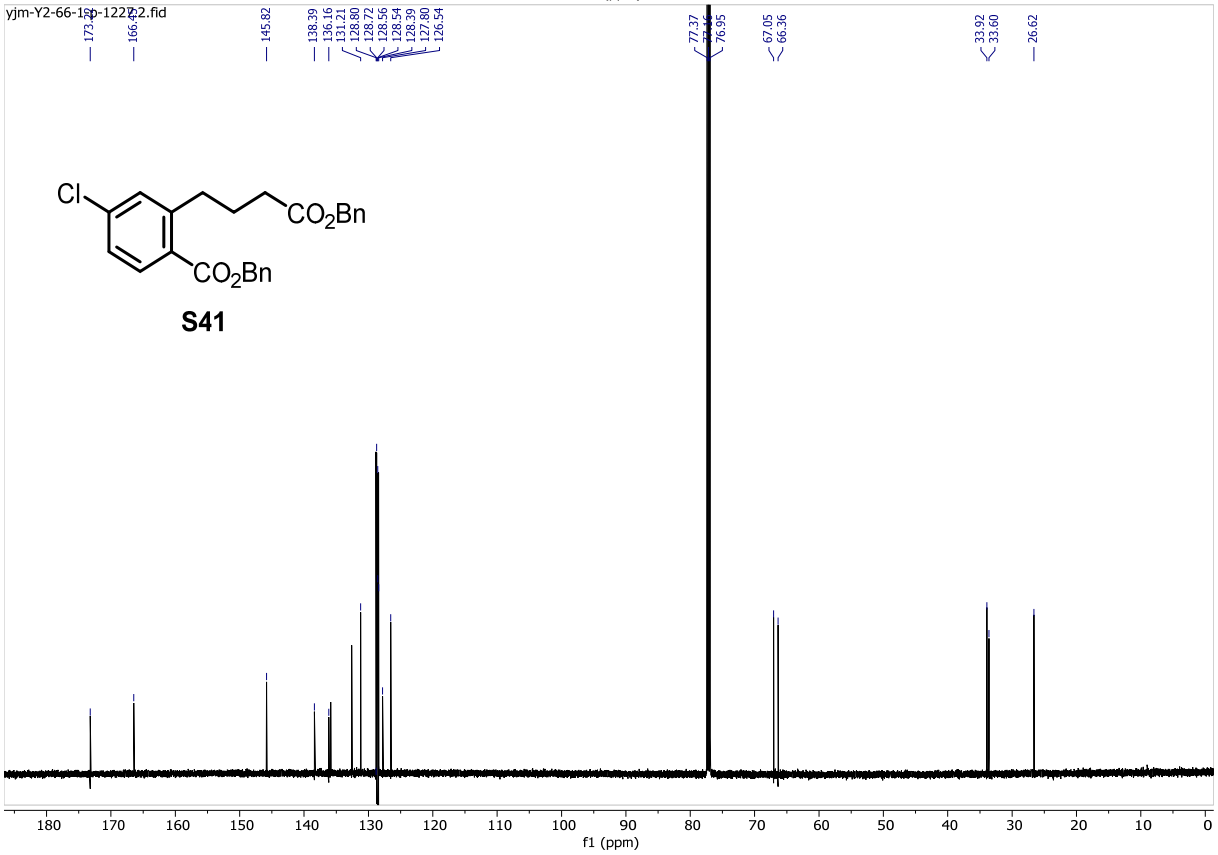




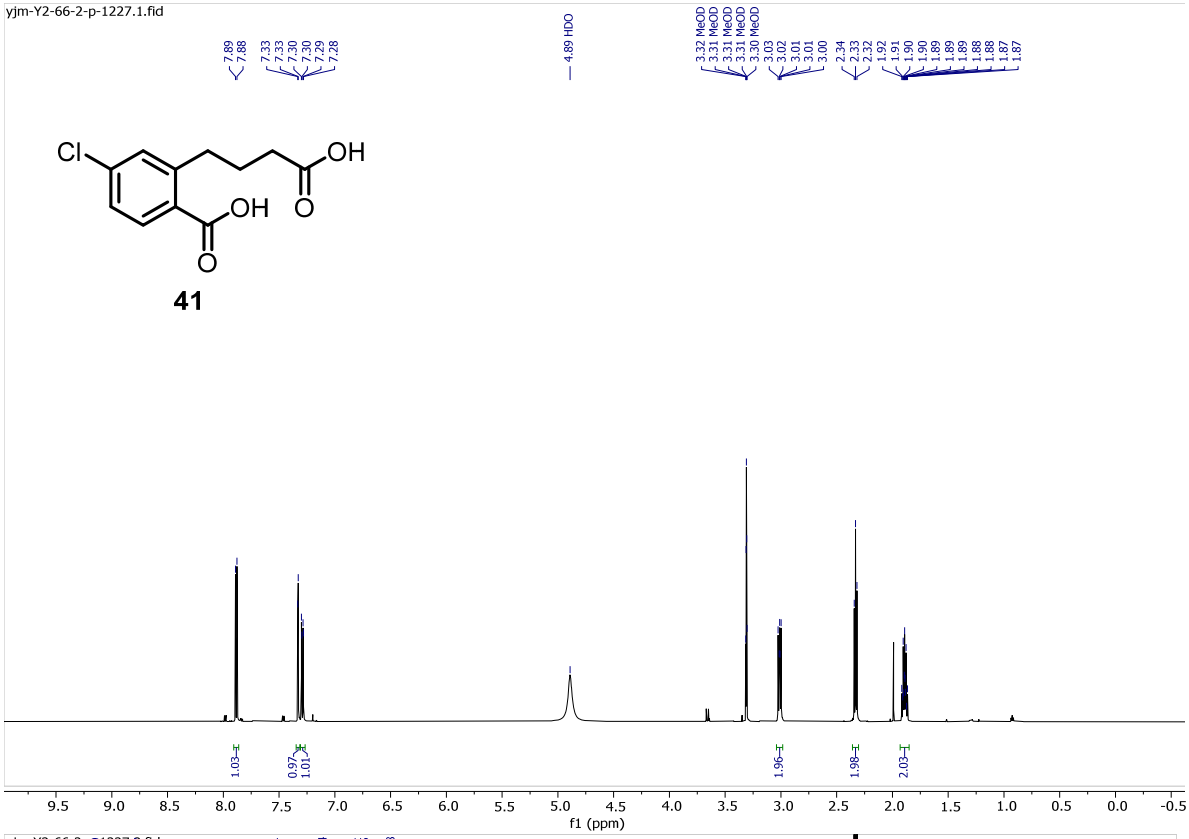

yjm-Y2-1-2F-1229.1.fid
-108.88
F
OH
OH
O
O
40
70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)

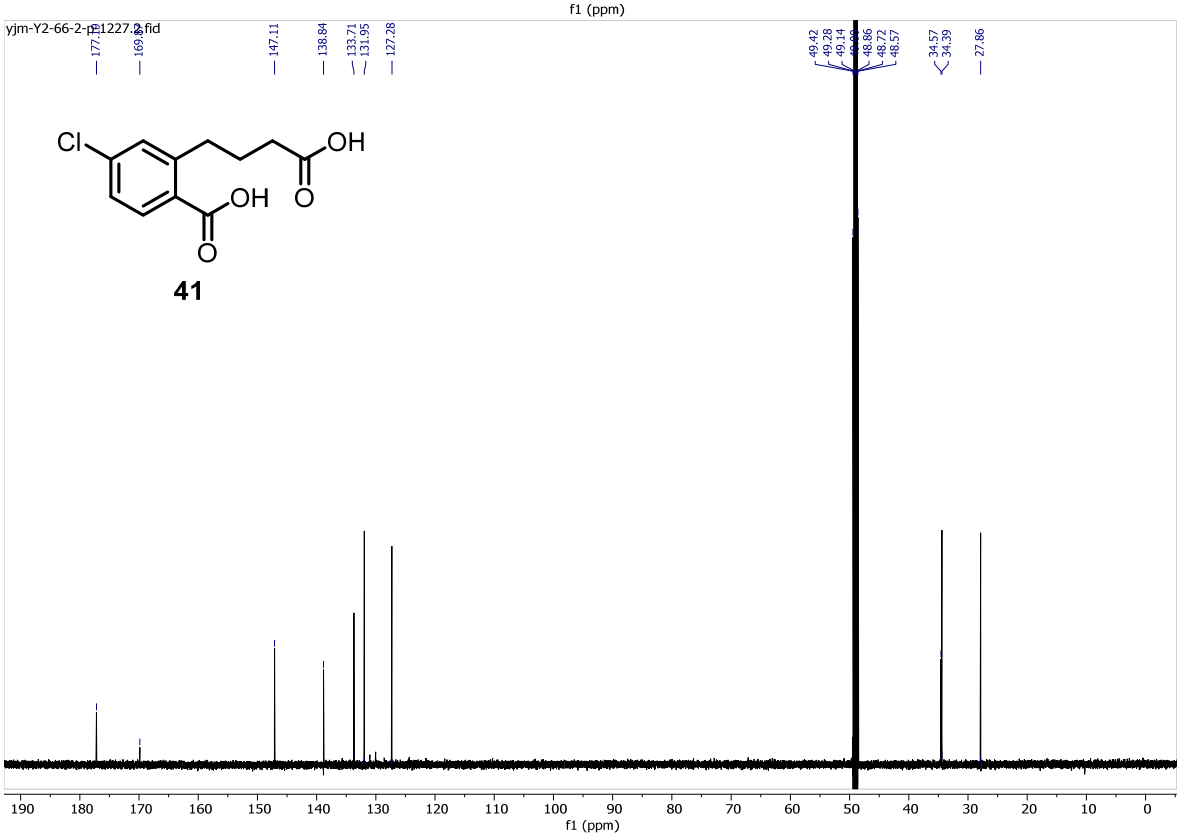
Benzyl 2-(4-(benzyloxy)-4-oxobutyl)-4-chlorobenzoate S41



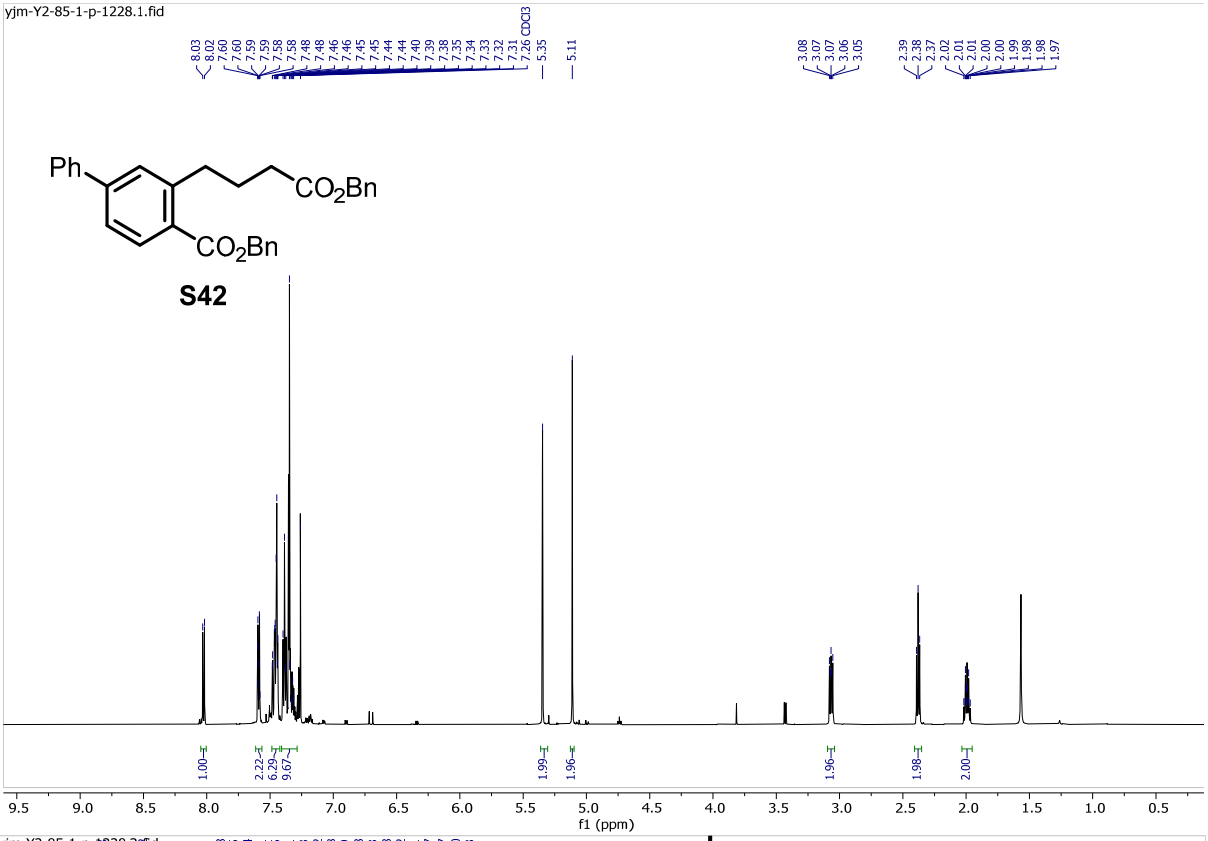


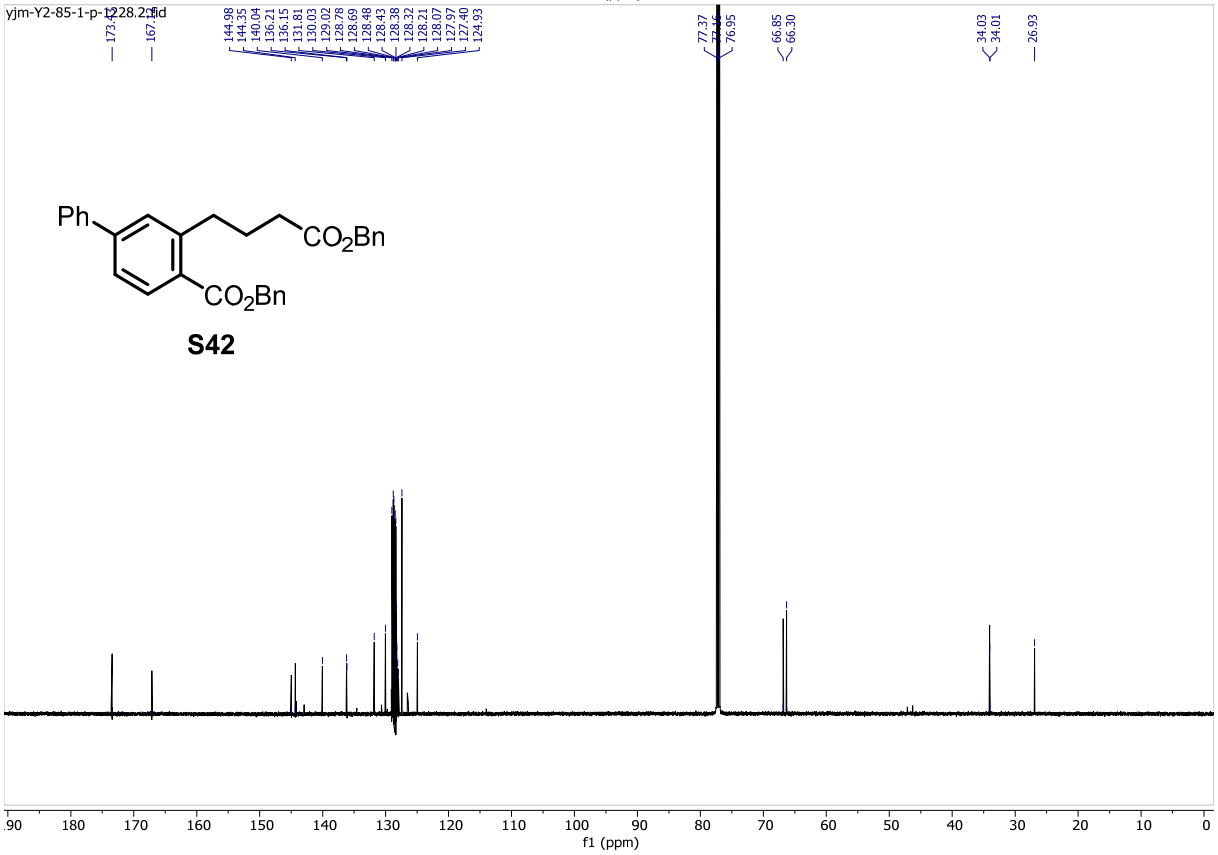
2-(3-Carboxypropyl)-4-chlorobenzoic acid 41



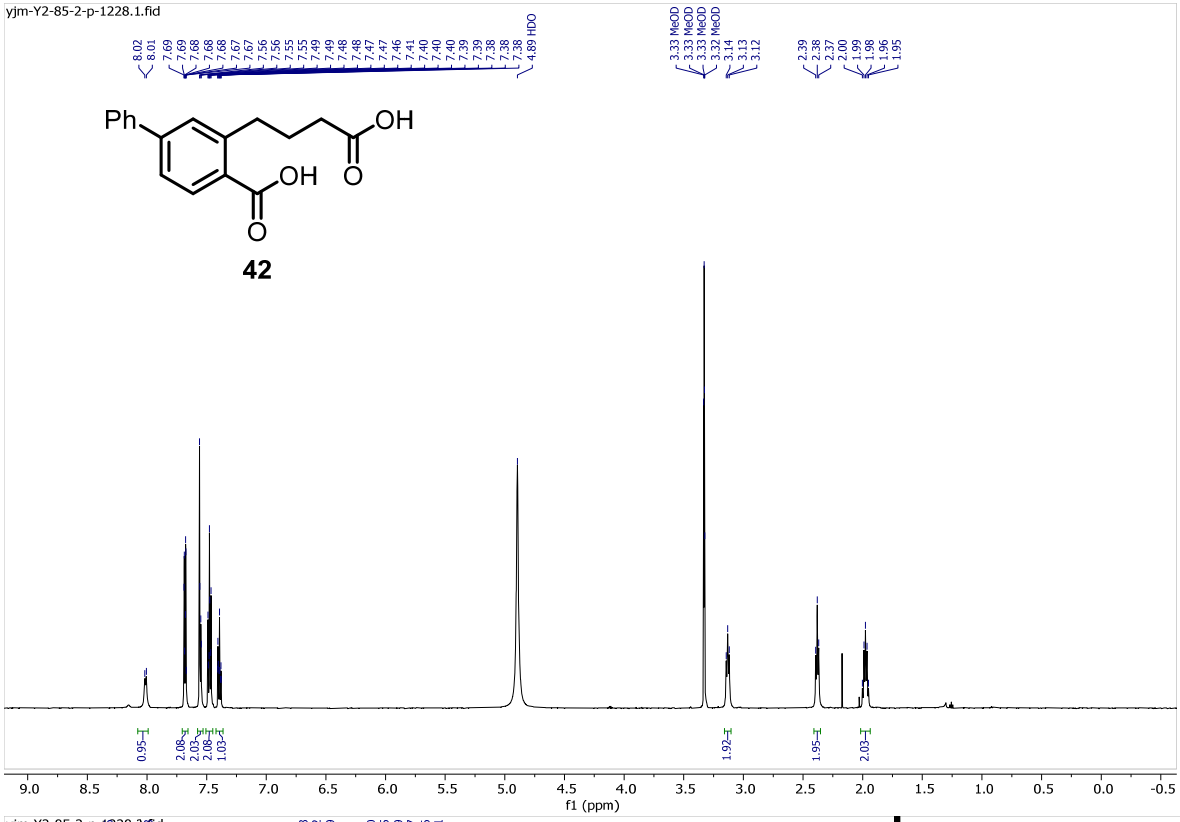


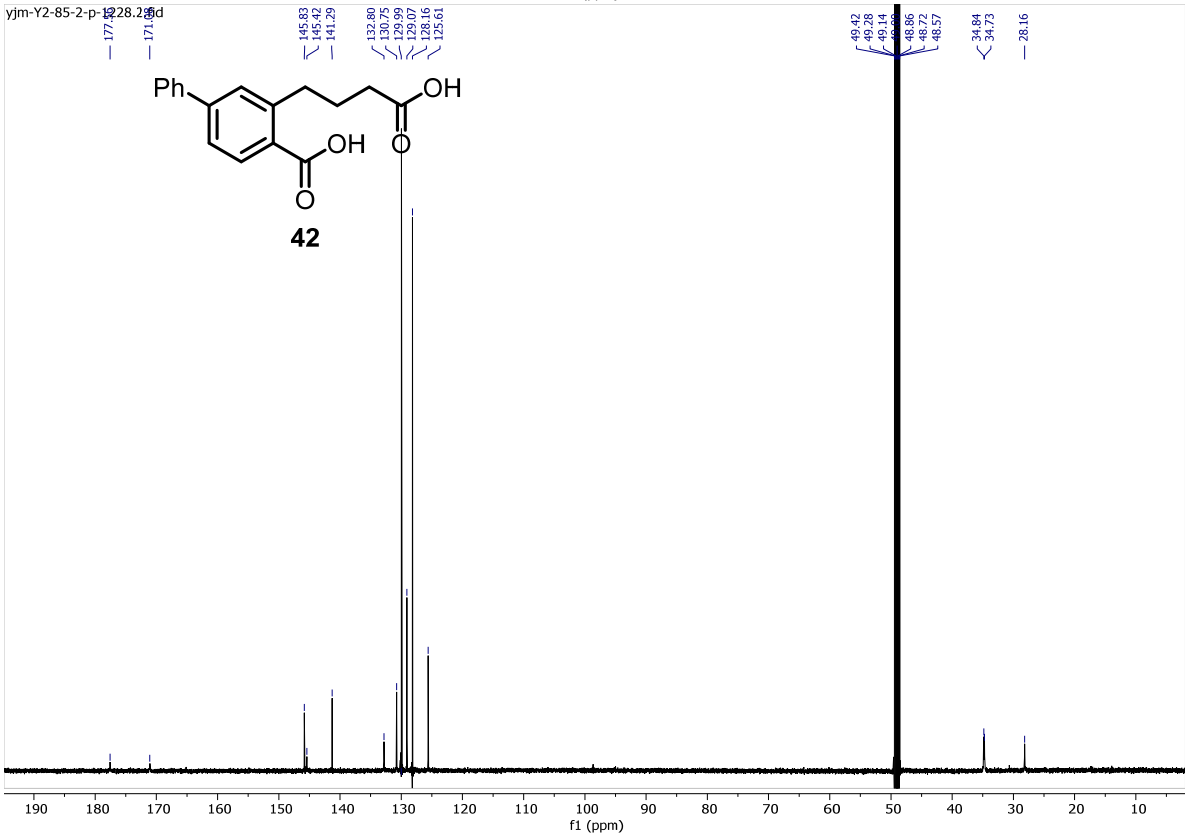
Benzyl 3-(4-(benzyloxy)-4-oxobutyl)-[1,1'-biphenyl]-4-carboxylate S42



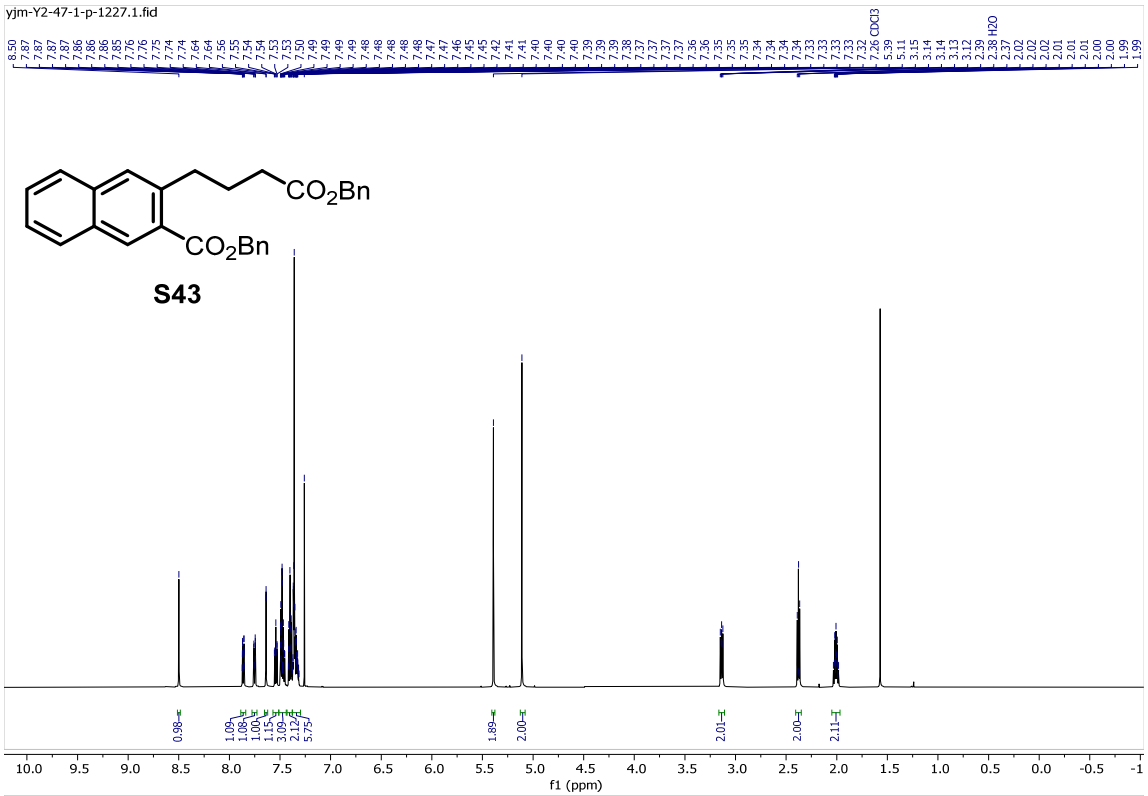


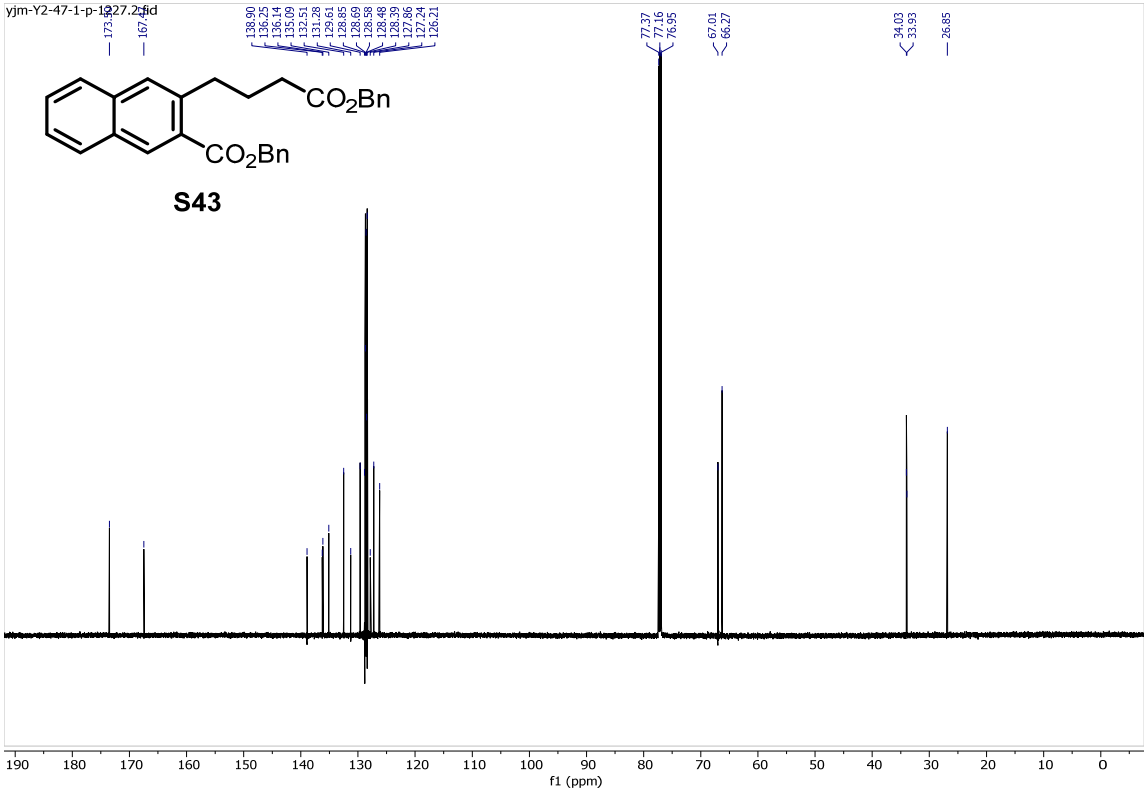
3-(3-Carboxypropyl)-[1,1'-biphenyl]-4-carboxylic acid 42



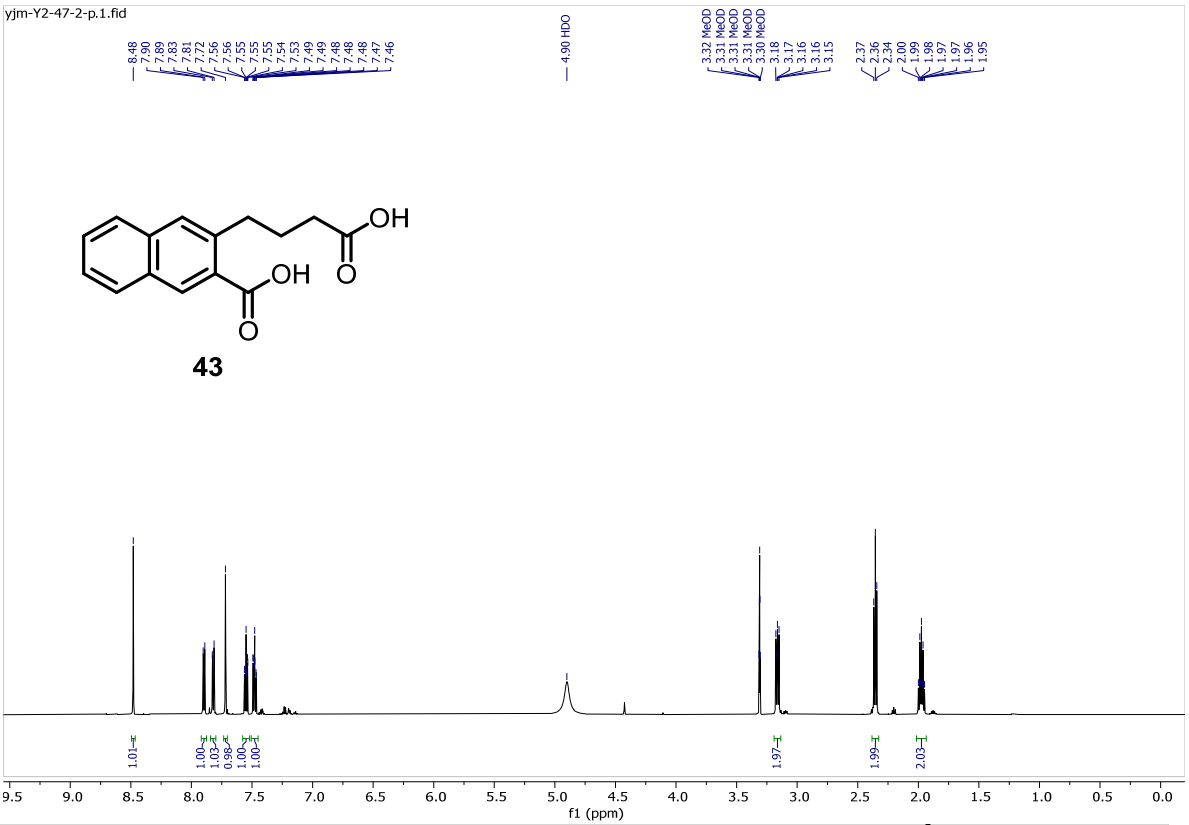


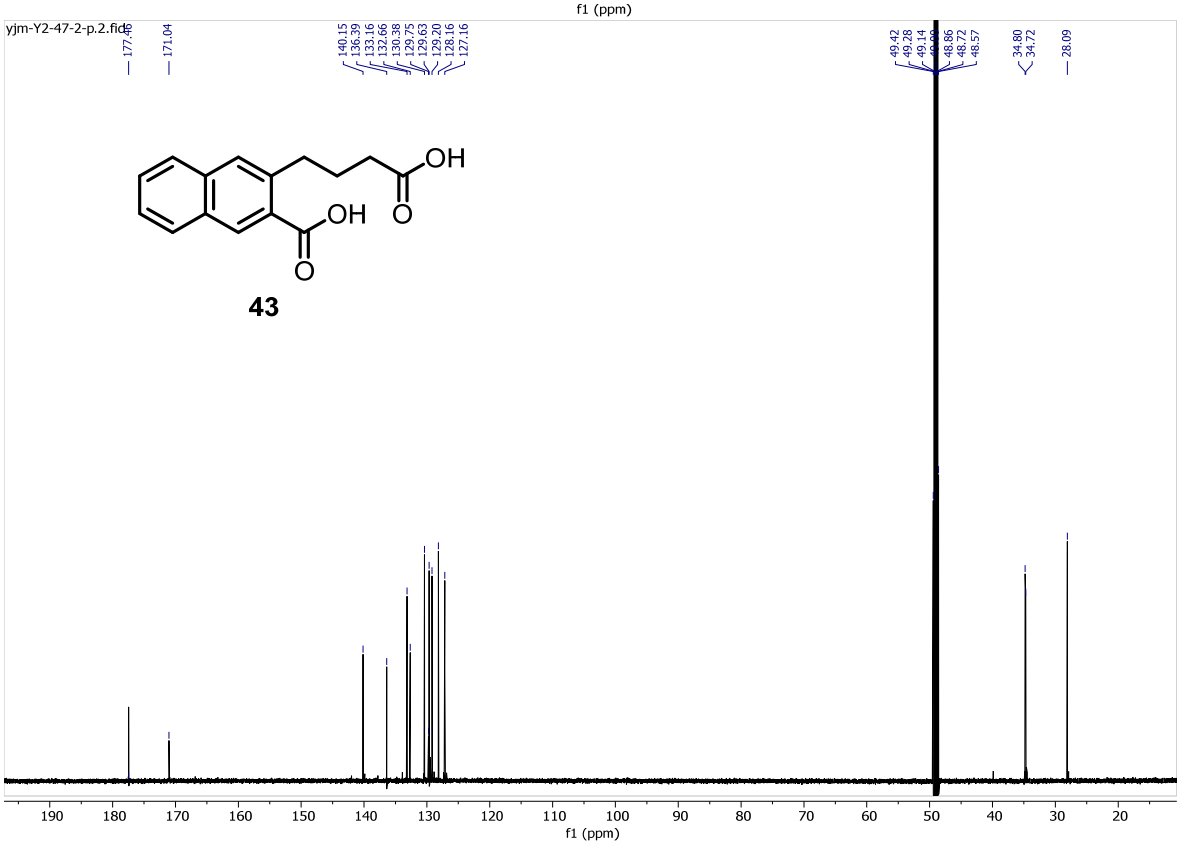
Benzyl 3-(4-(benzyloxy)-4-oxobutyl)-2-naphthoate S43



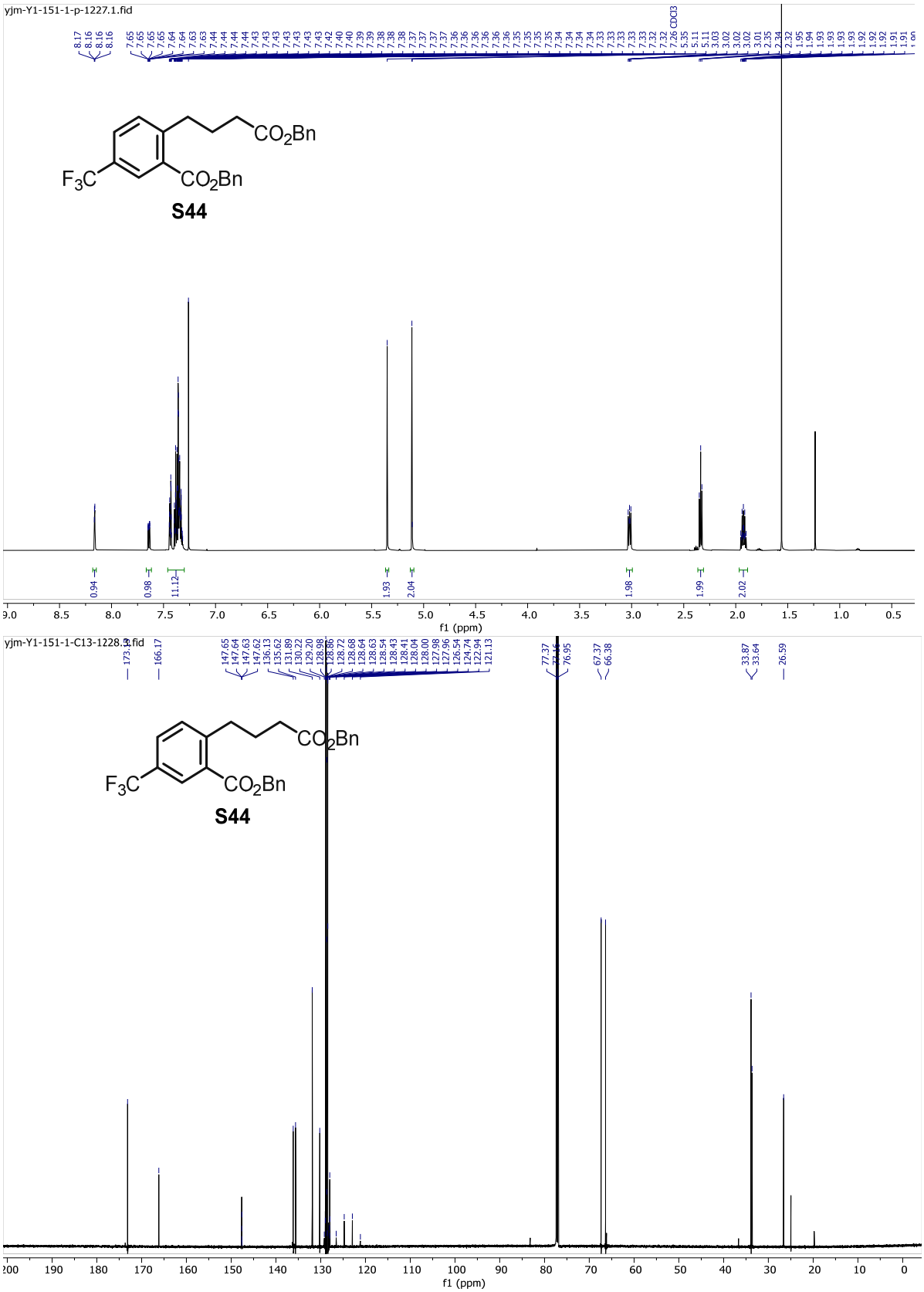


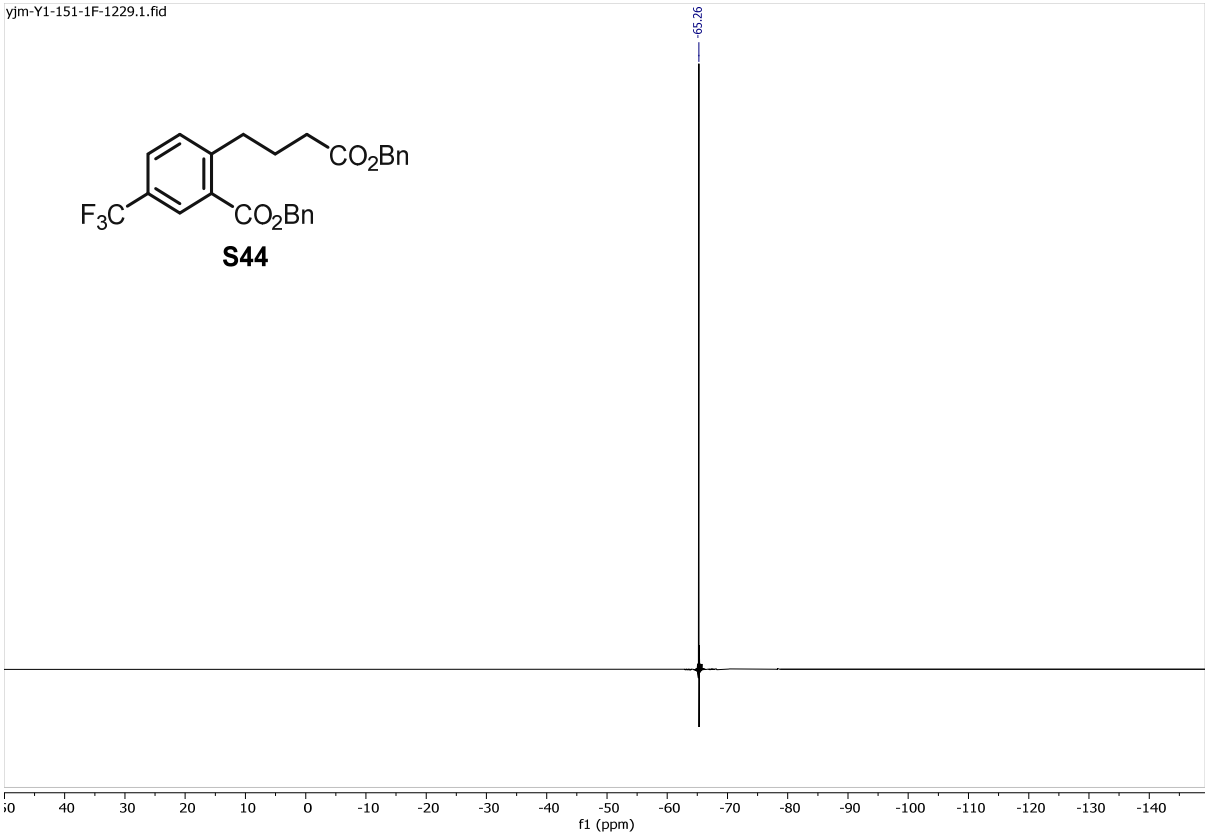
3-(3-Carboxypropyl)-2-naphthoic acid 43



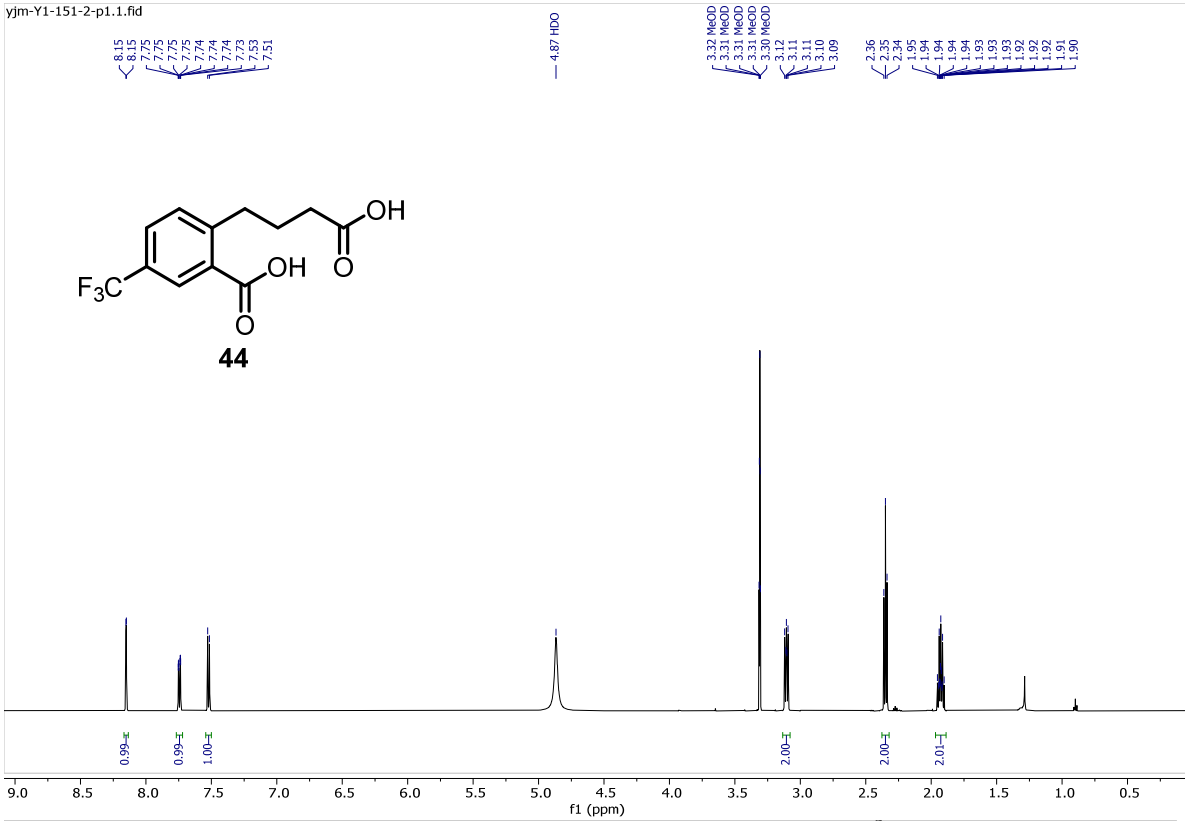


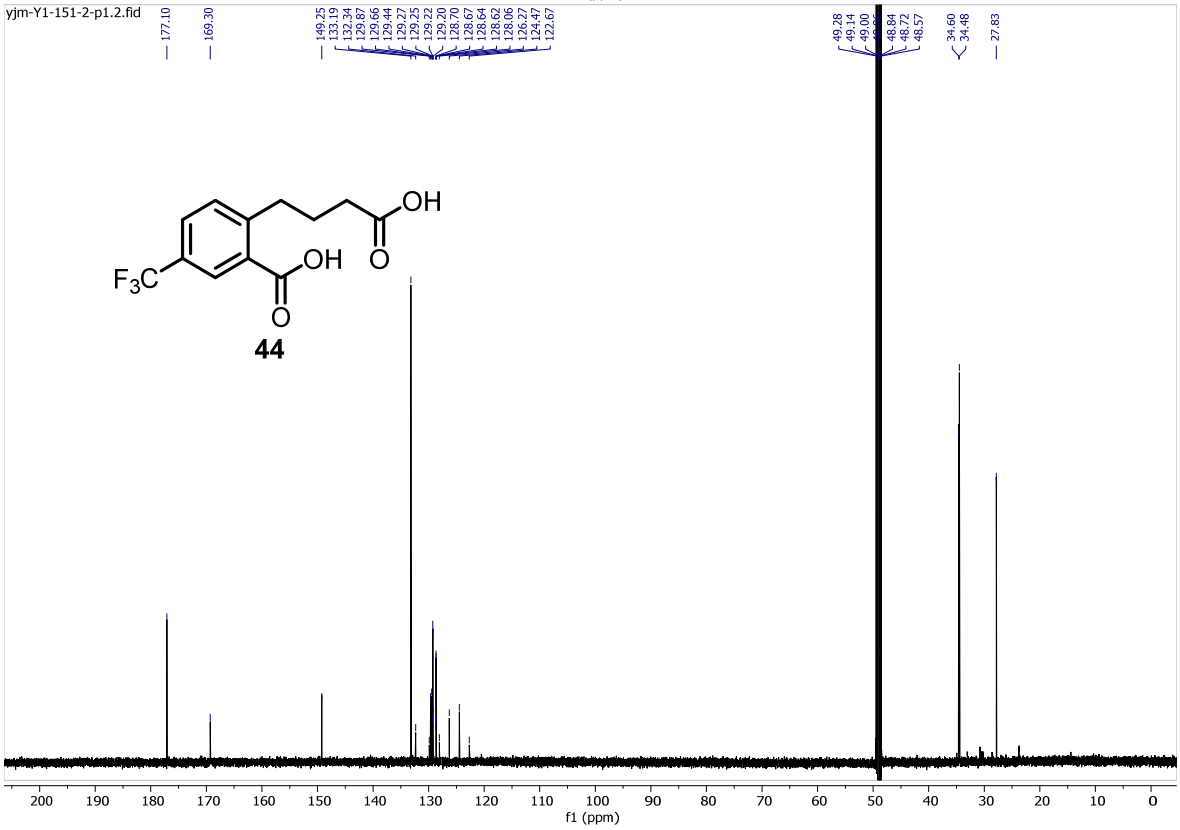
Benzyl 2-(4-(benzyloxy)-4-oxobutyl)-5-(trifluoromethyl)benzoate S44

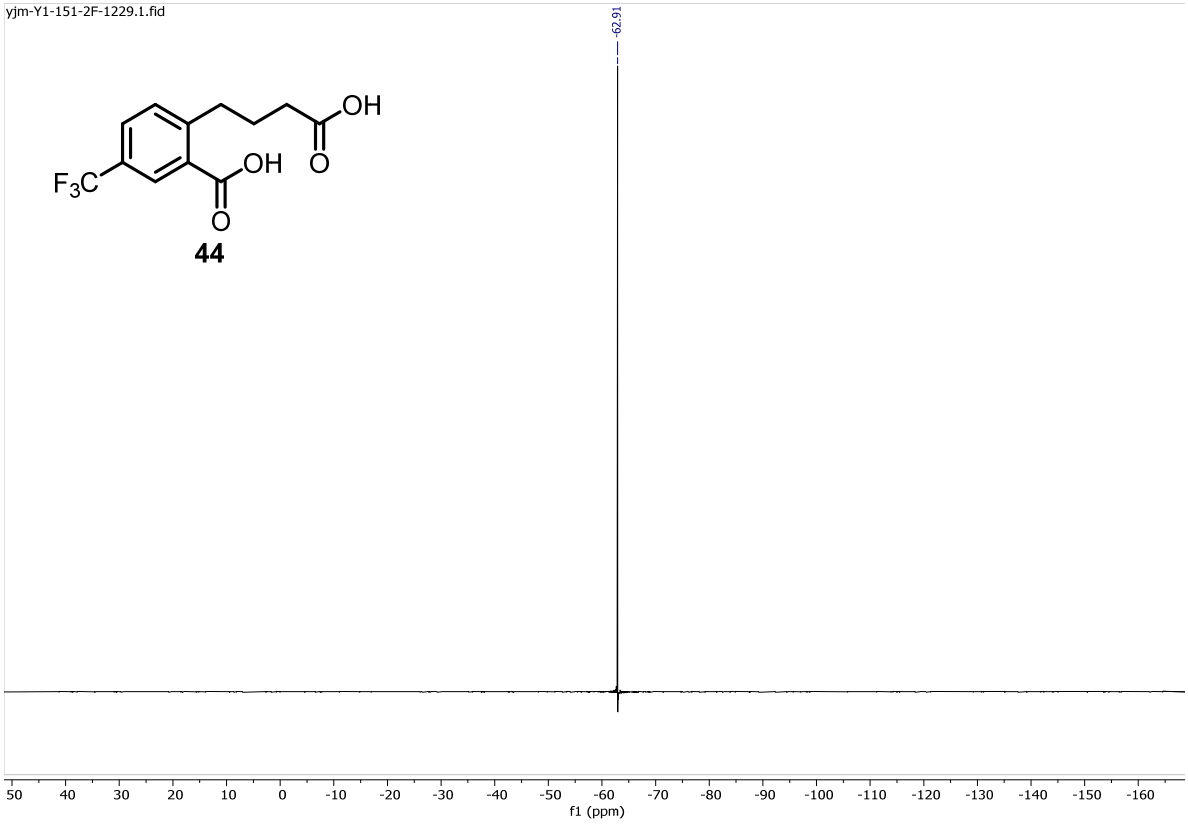



yjm-Y1-151-1F-1229.1.fid
-65.26
CO2Bn
F3C
CO2Bn
S44
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
f1 (ppm)

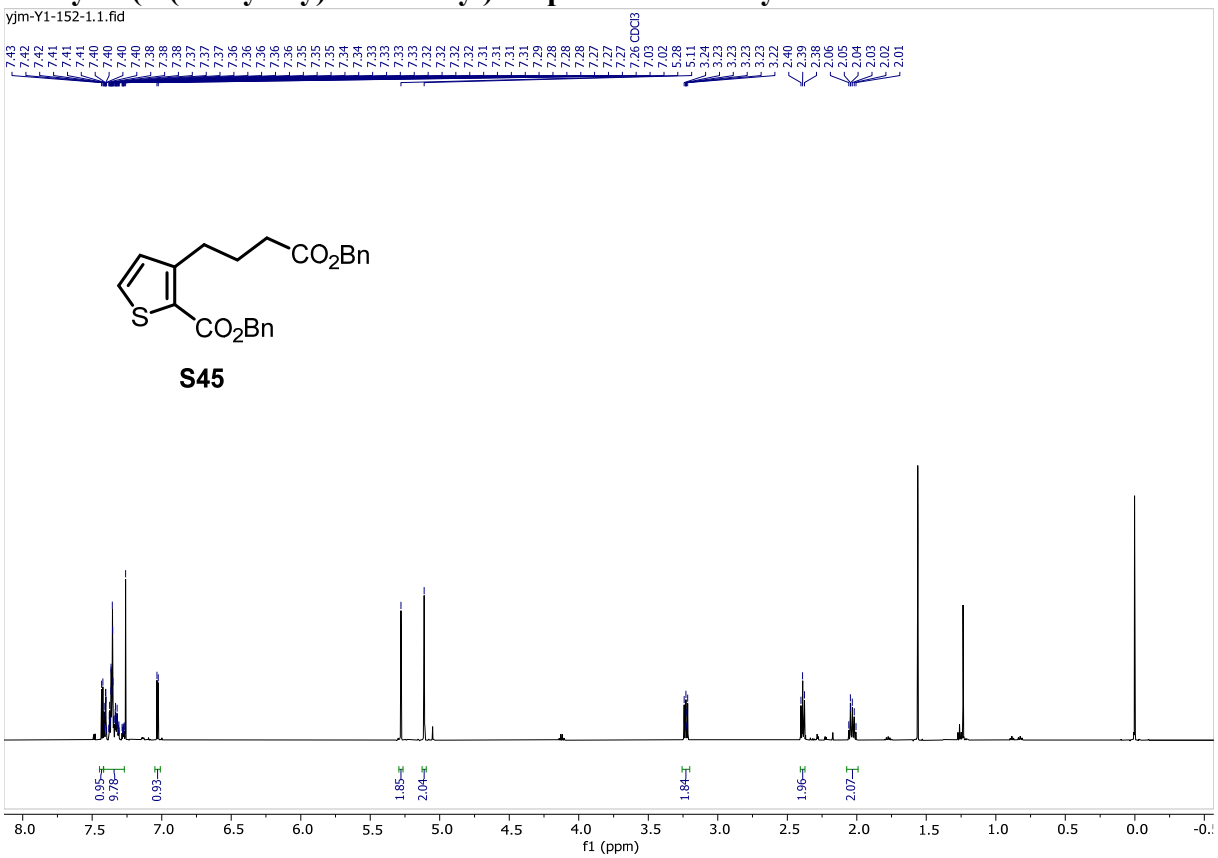
2-(3-Carboxypropyl)-5-(trifluoromethyl)benzoic acid 44

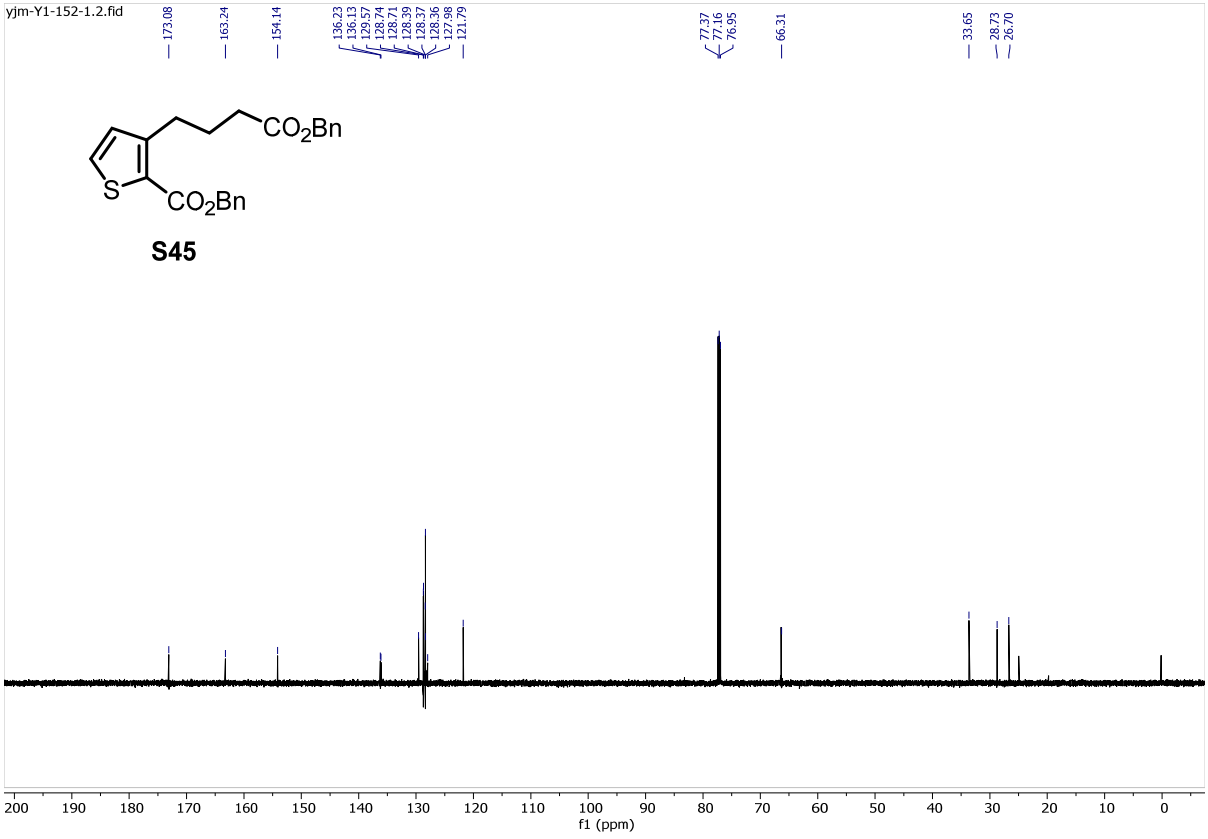




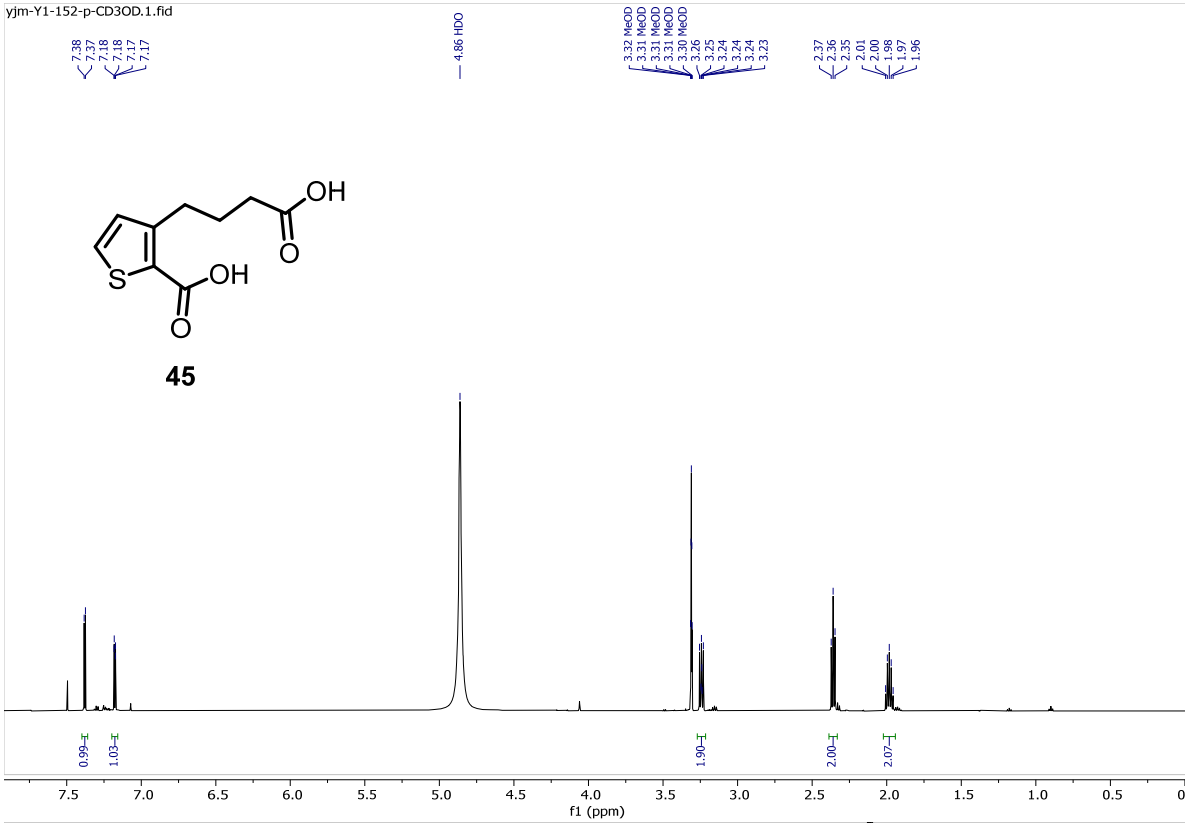

yjm-Y1-151-2F-1229.1.fid
-62.91
OH
O
OH
O
F3C
44
50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160
f1 (ppm)

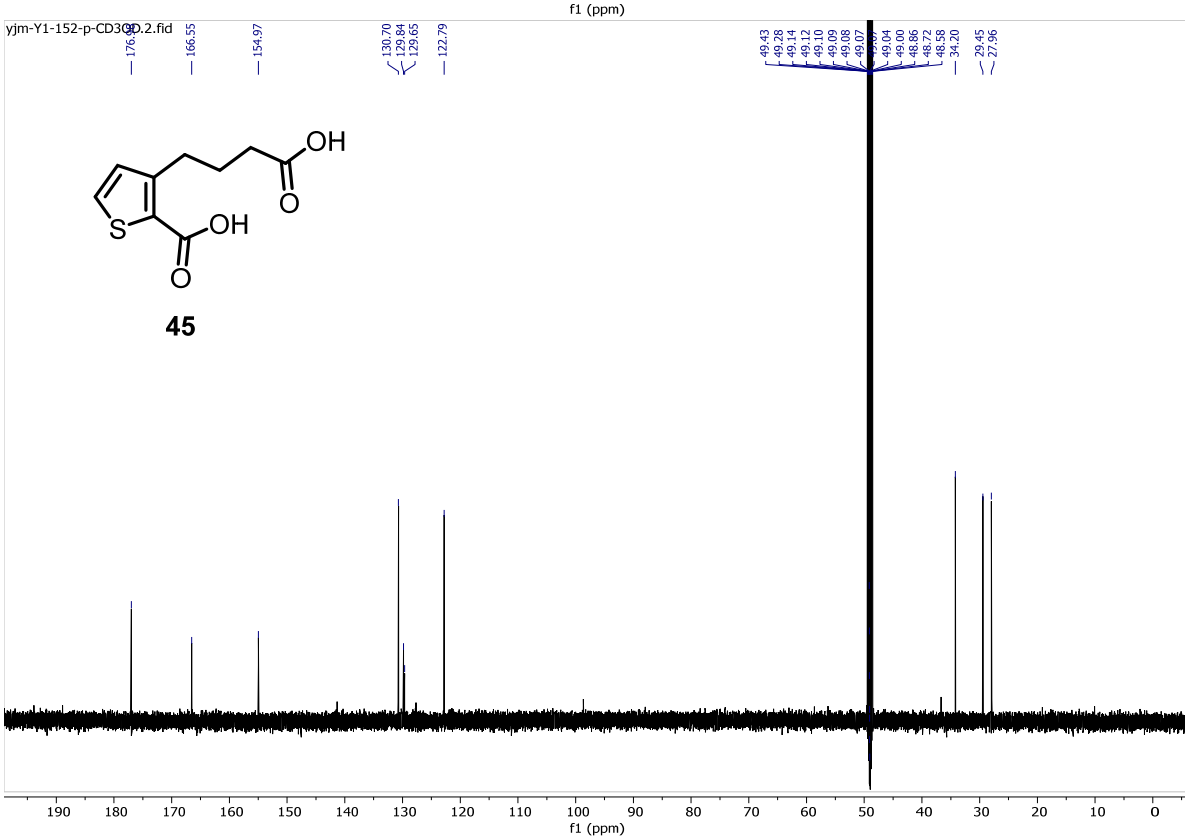
Benzyl 3-(4-(benzyloxy)-4-oxobutyl)thiophene-2-carboxylate S45



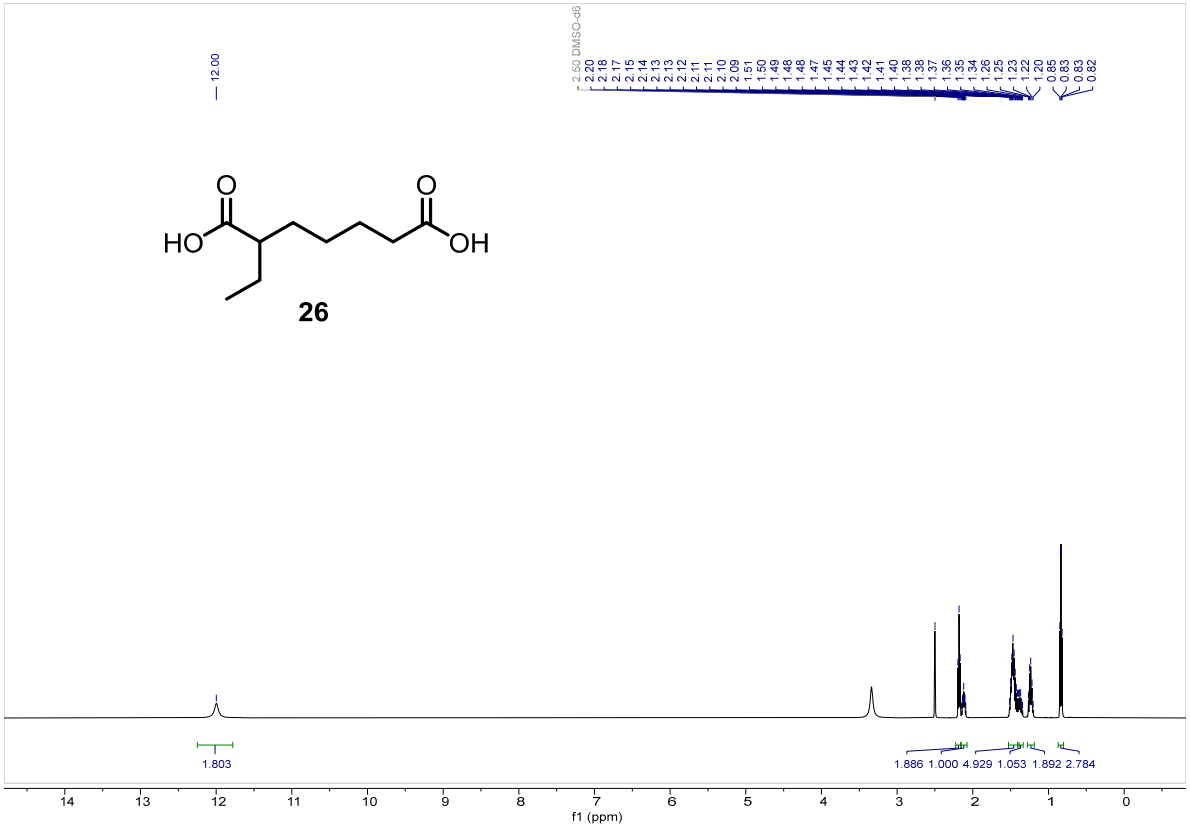


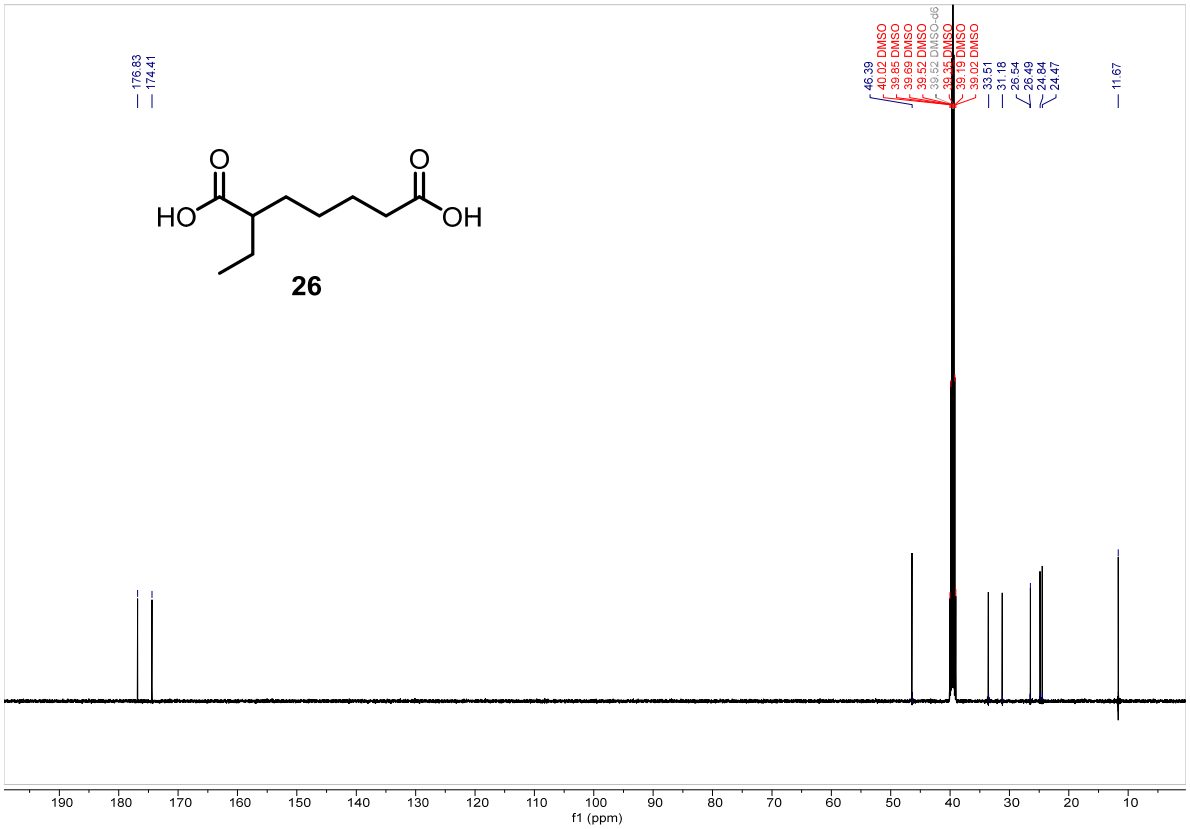
3-(3-Carboxypropyl)thiophene-2-carboxylic acid 45



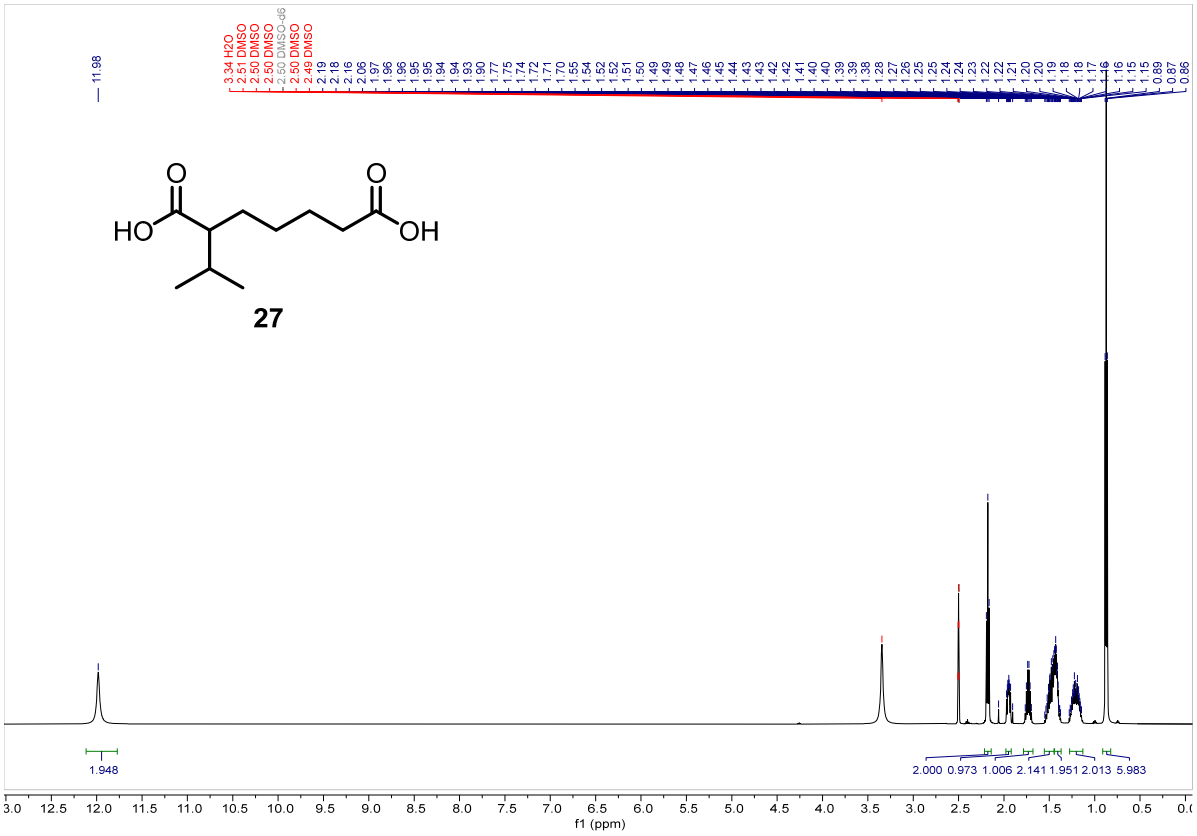


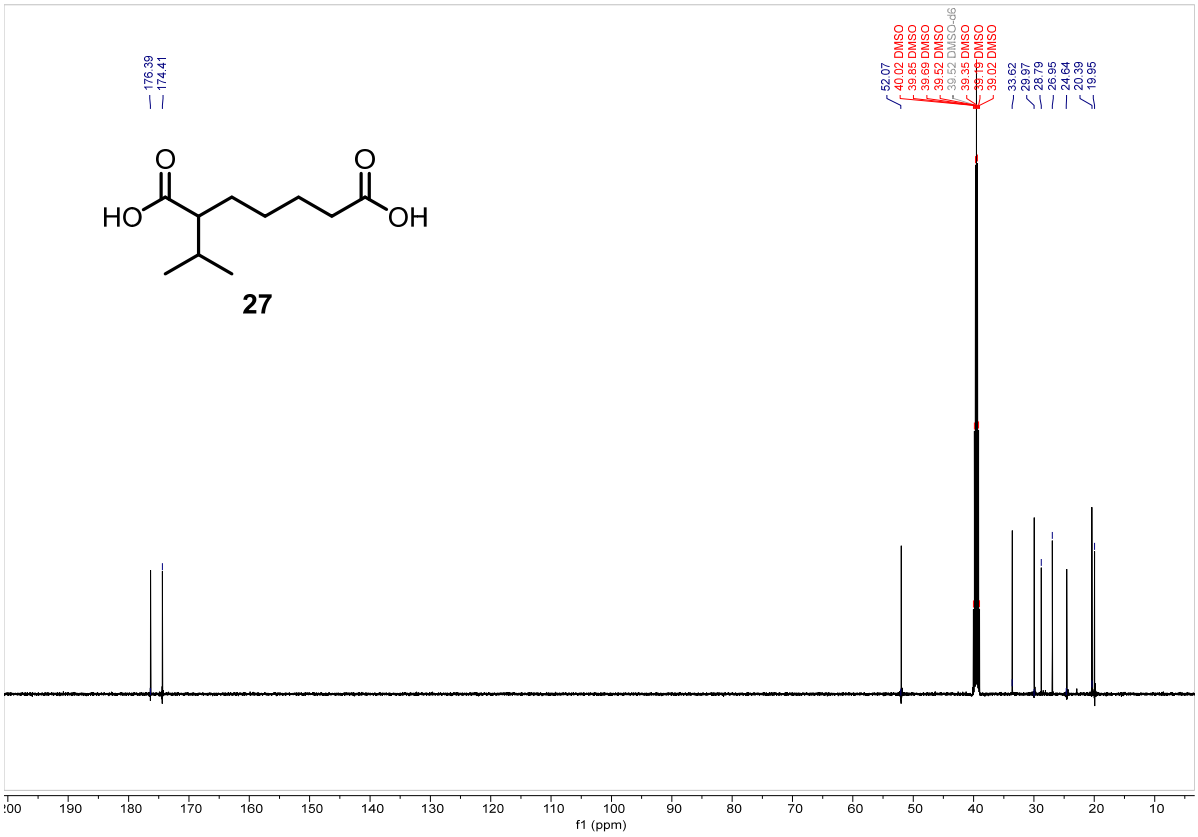
2-Ethylheptanedioic acid 26



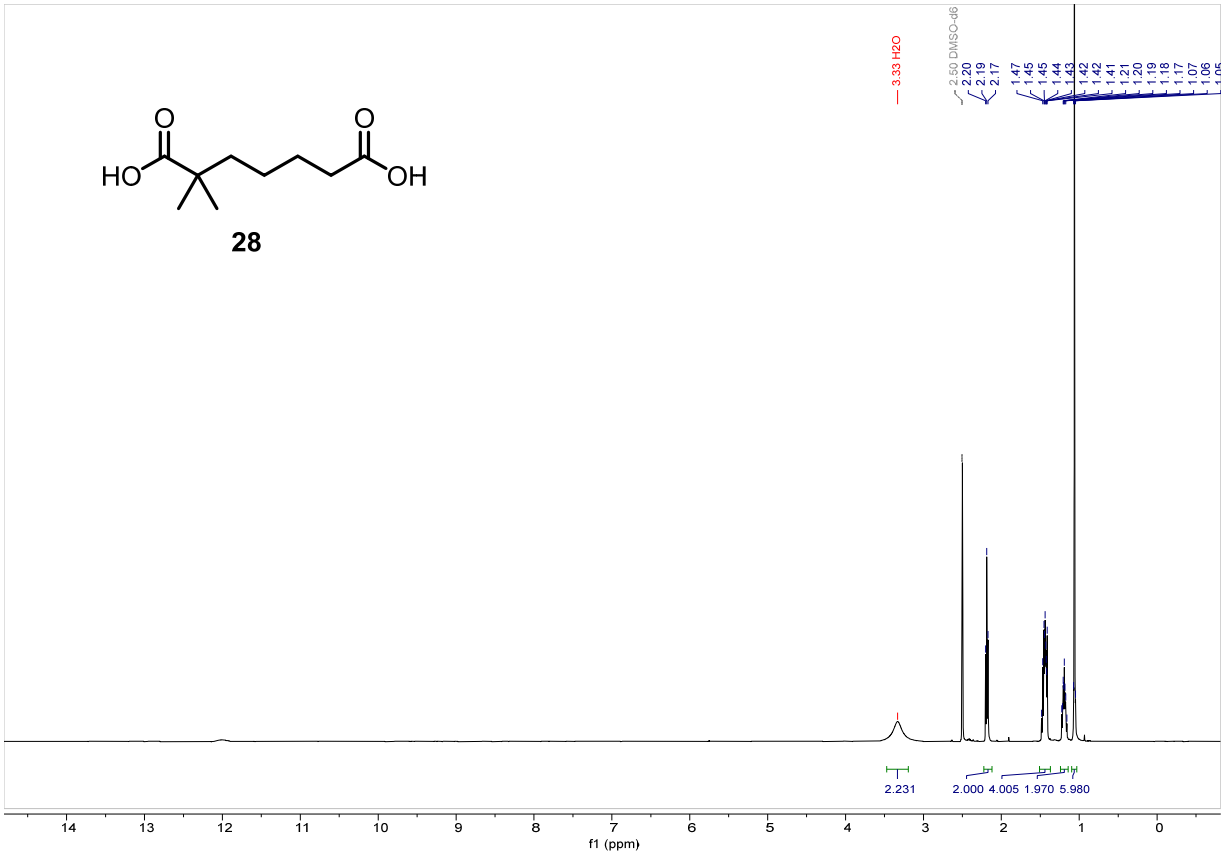


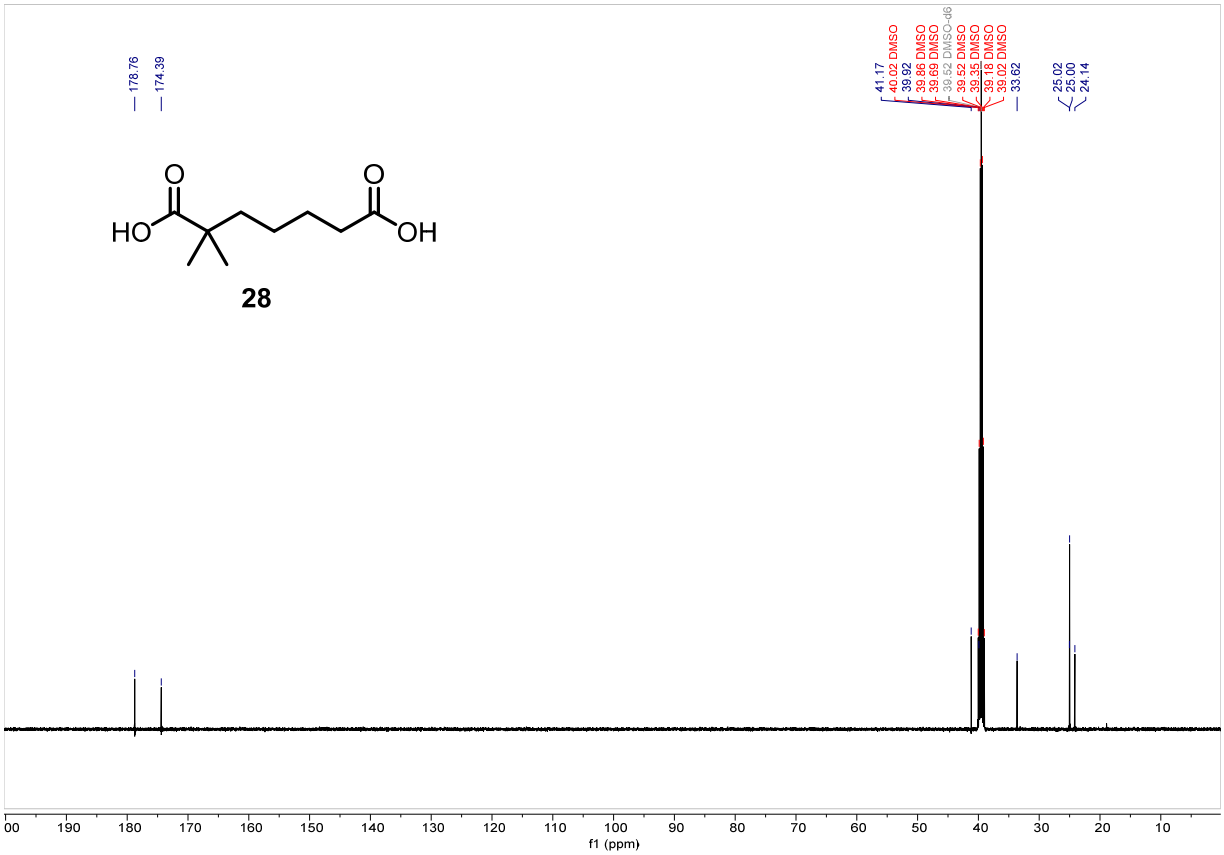
2-Isopropylheptanedioic acid 27



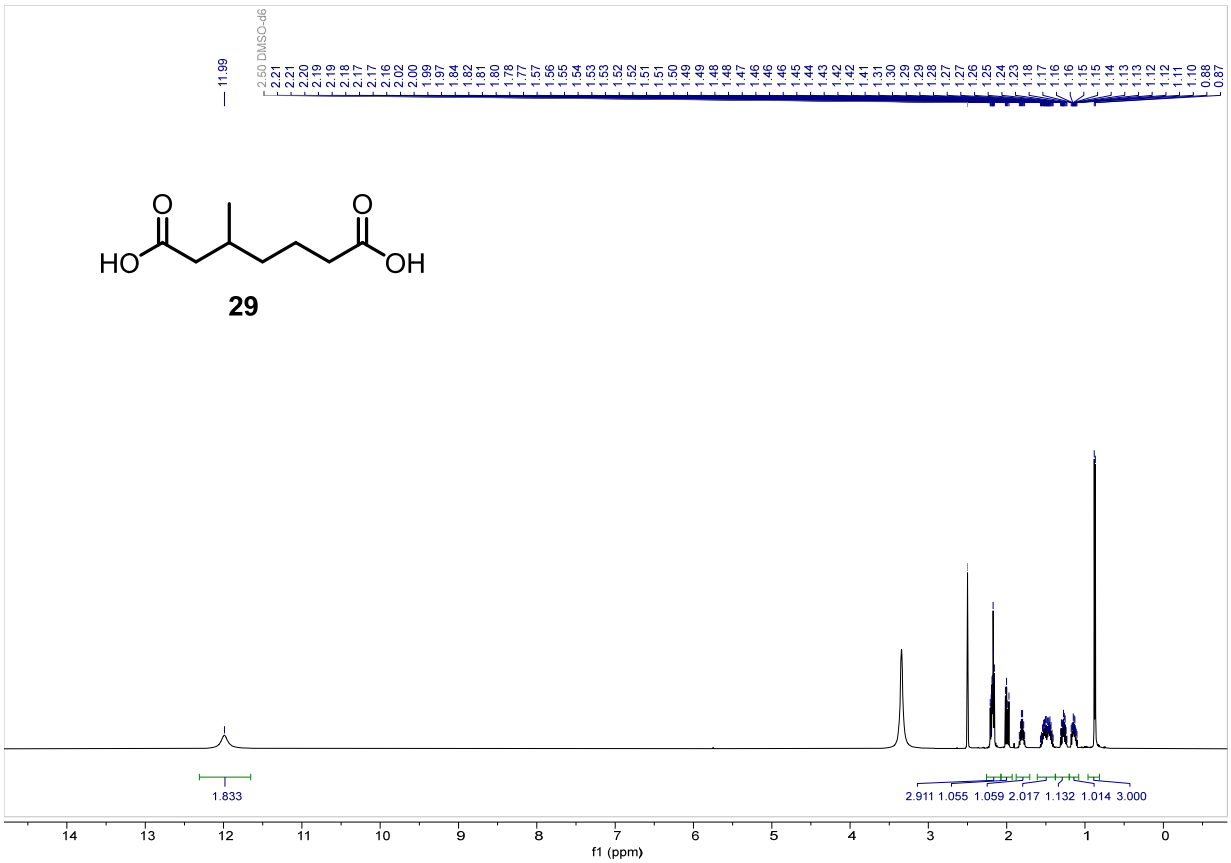


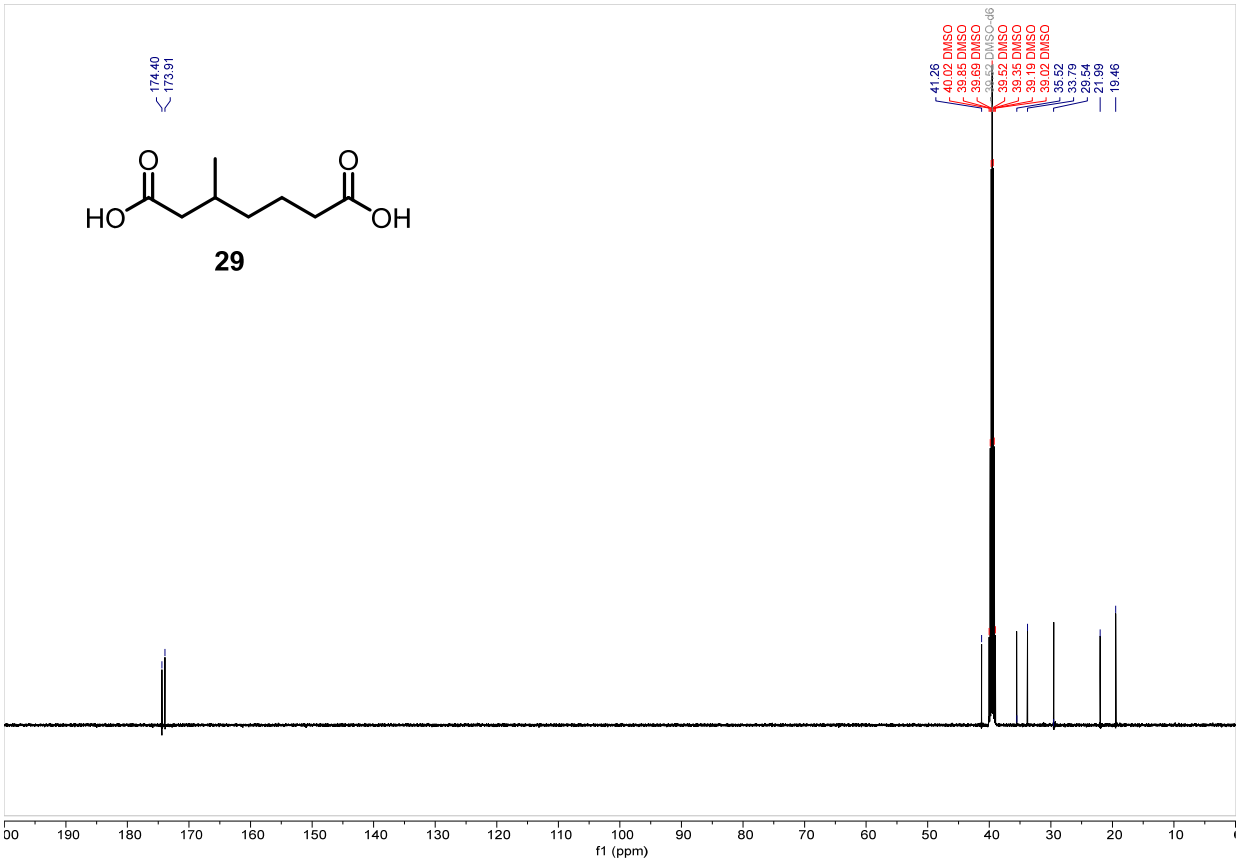
2,2-Dimethylheptanedioic acid 28



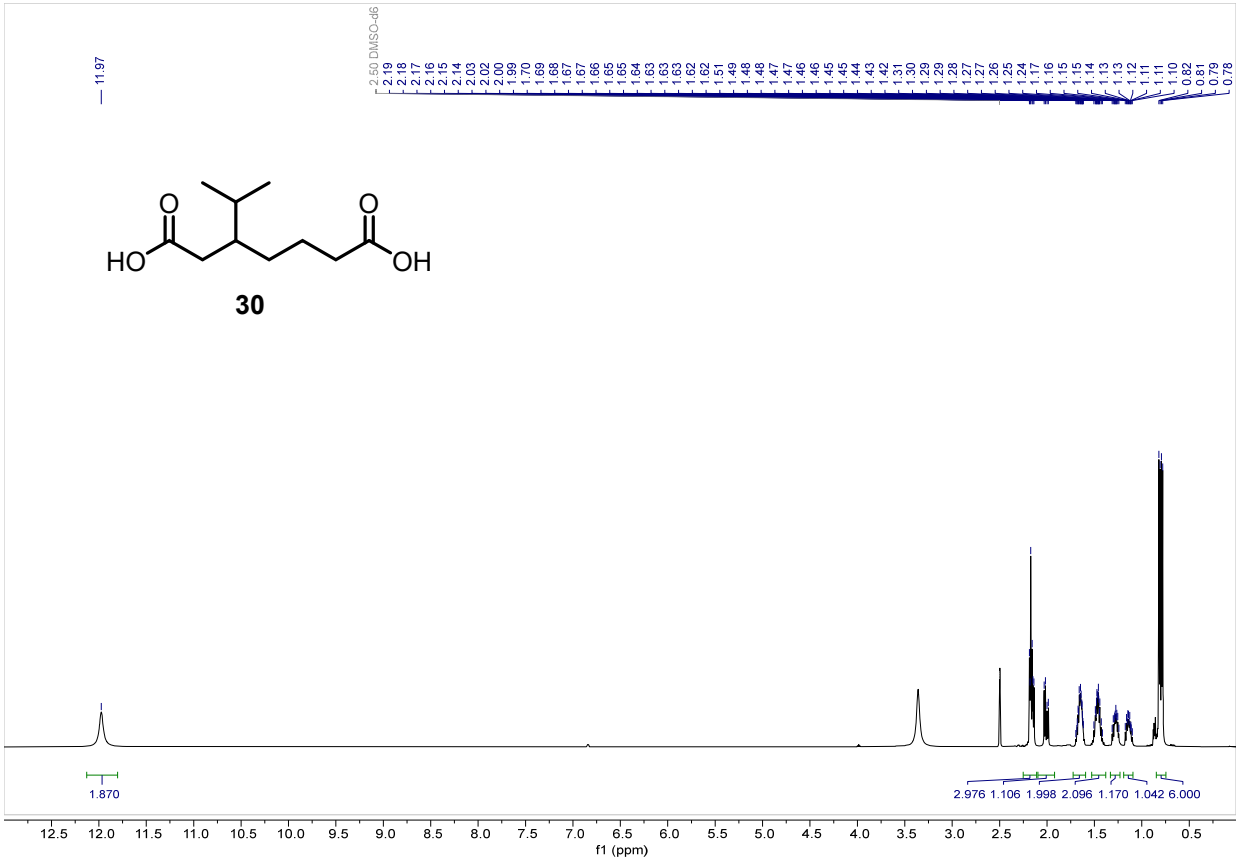


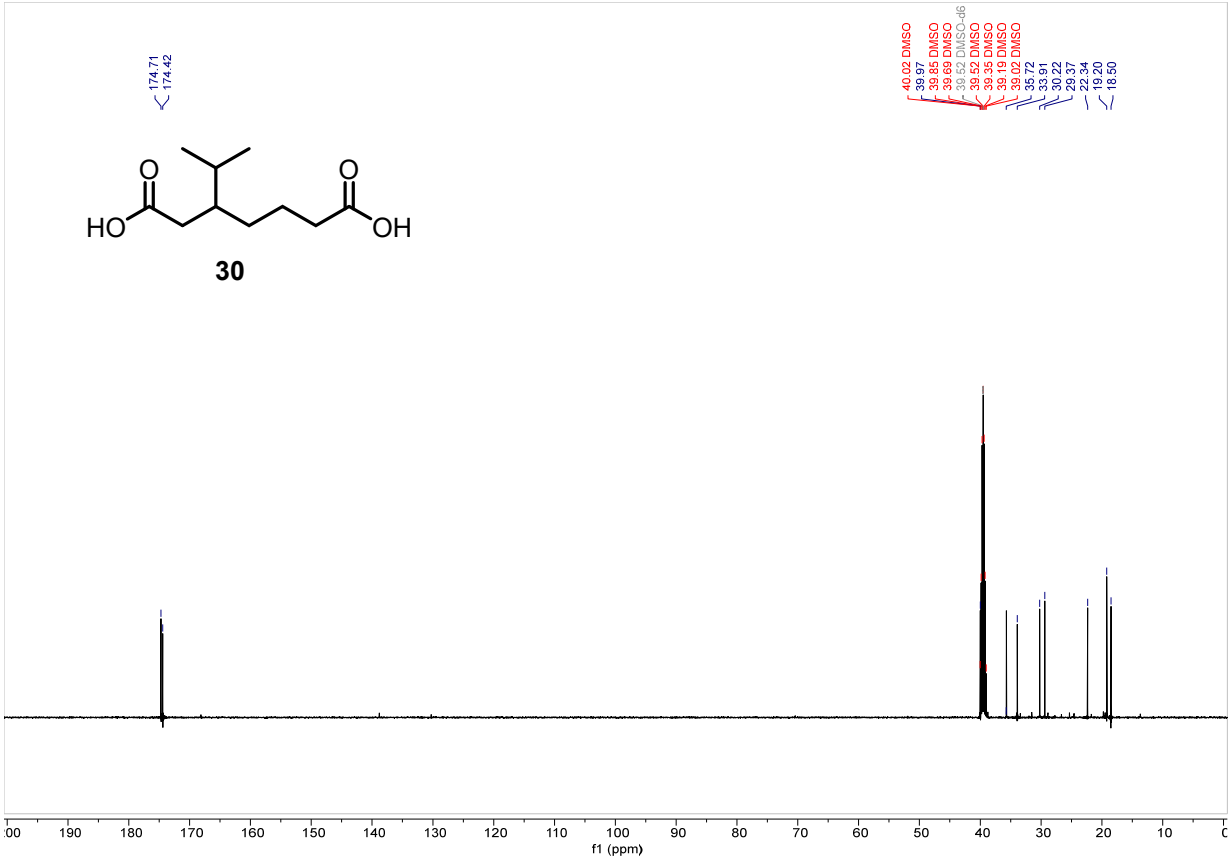
3-Methylheptanedioic acid 29



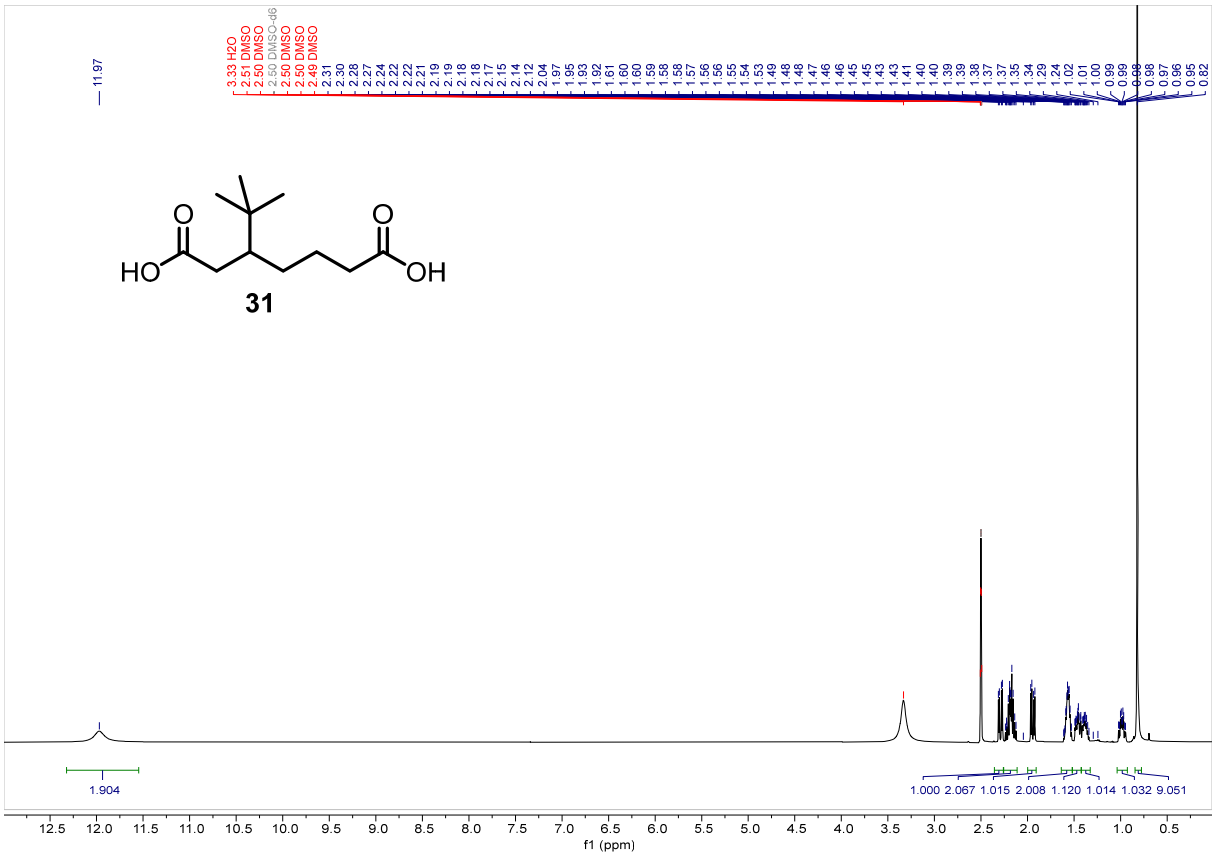


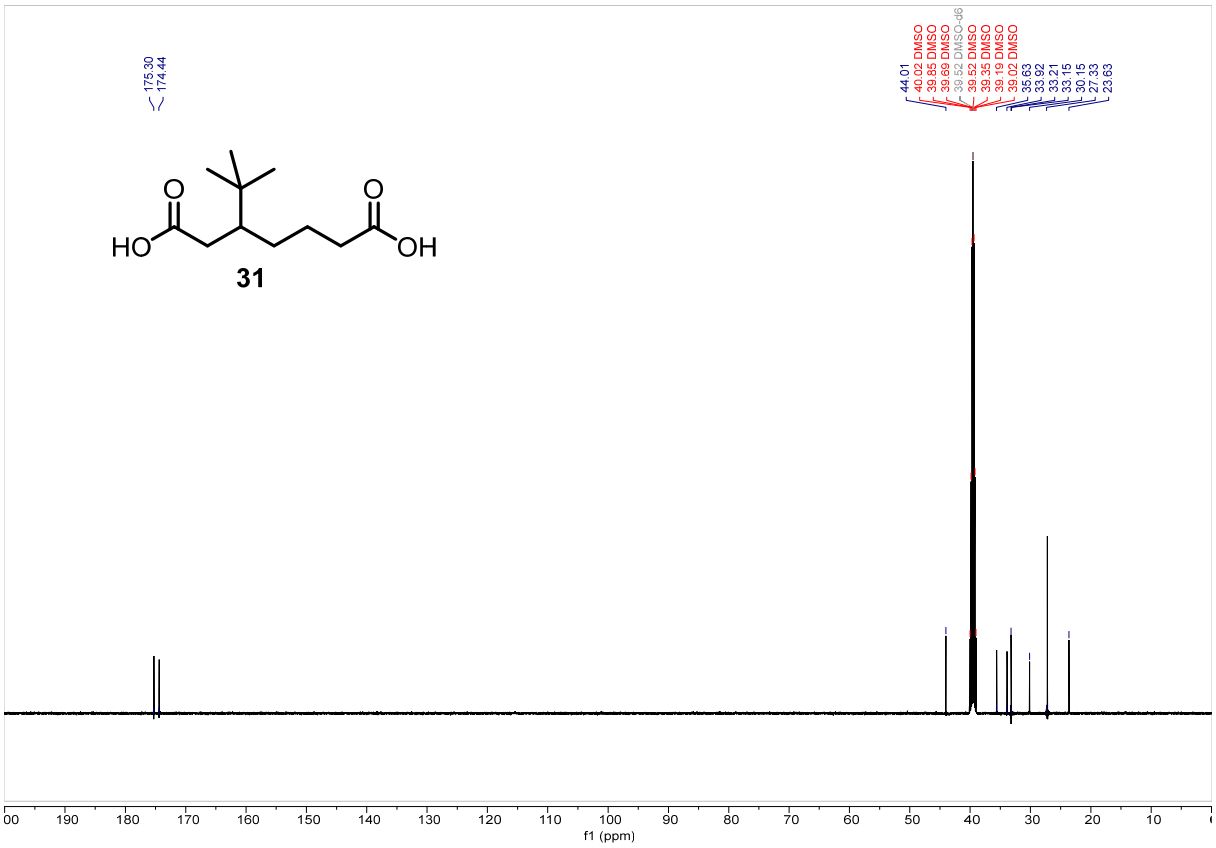
3-Isopropylheptanedioic acid 30



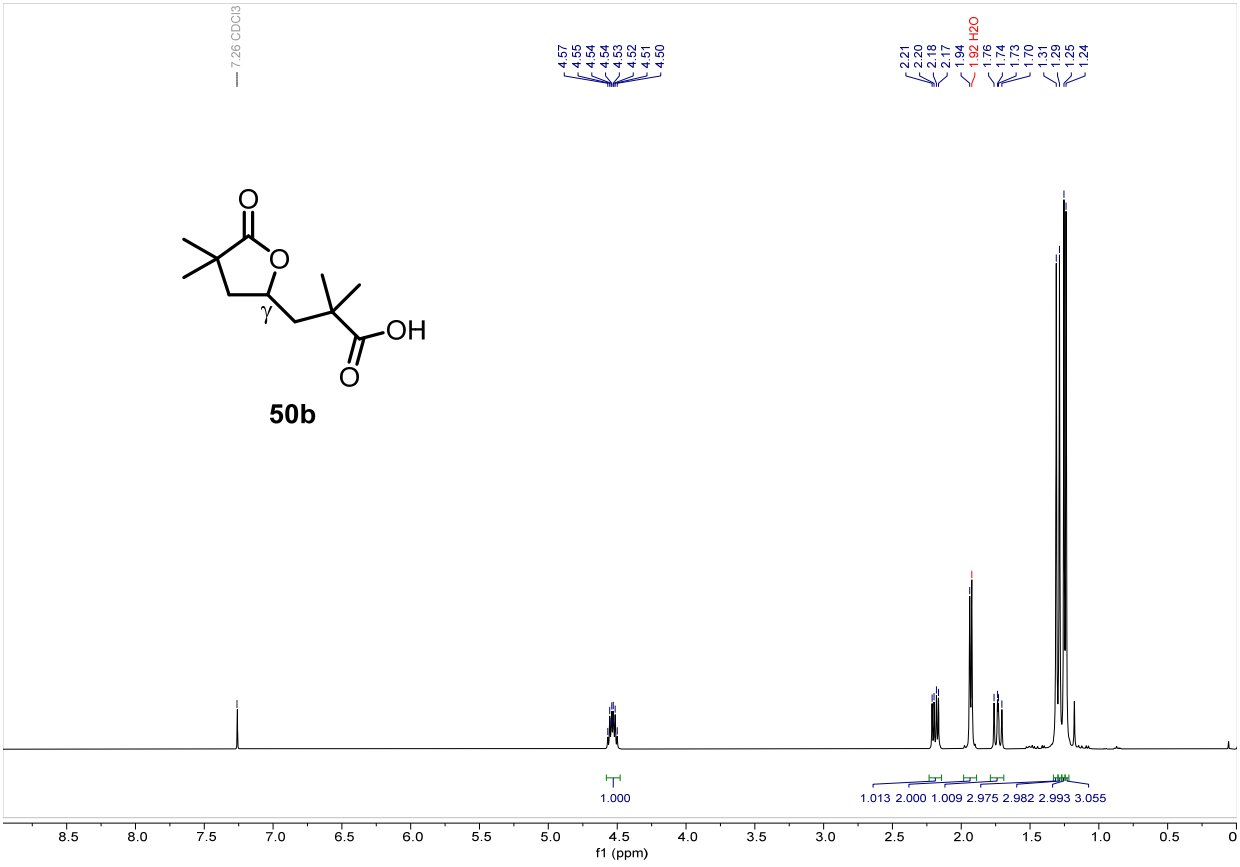


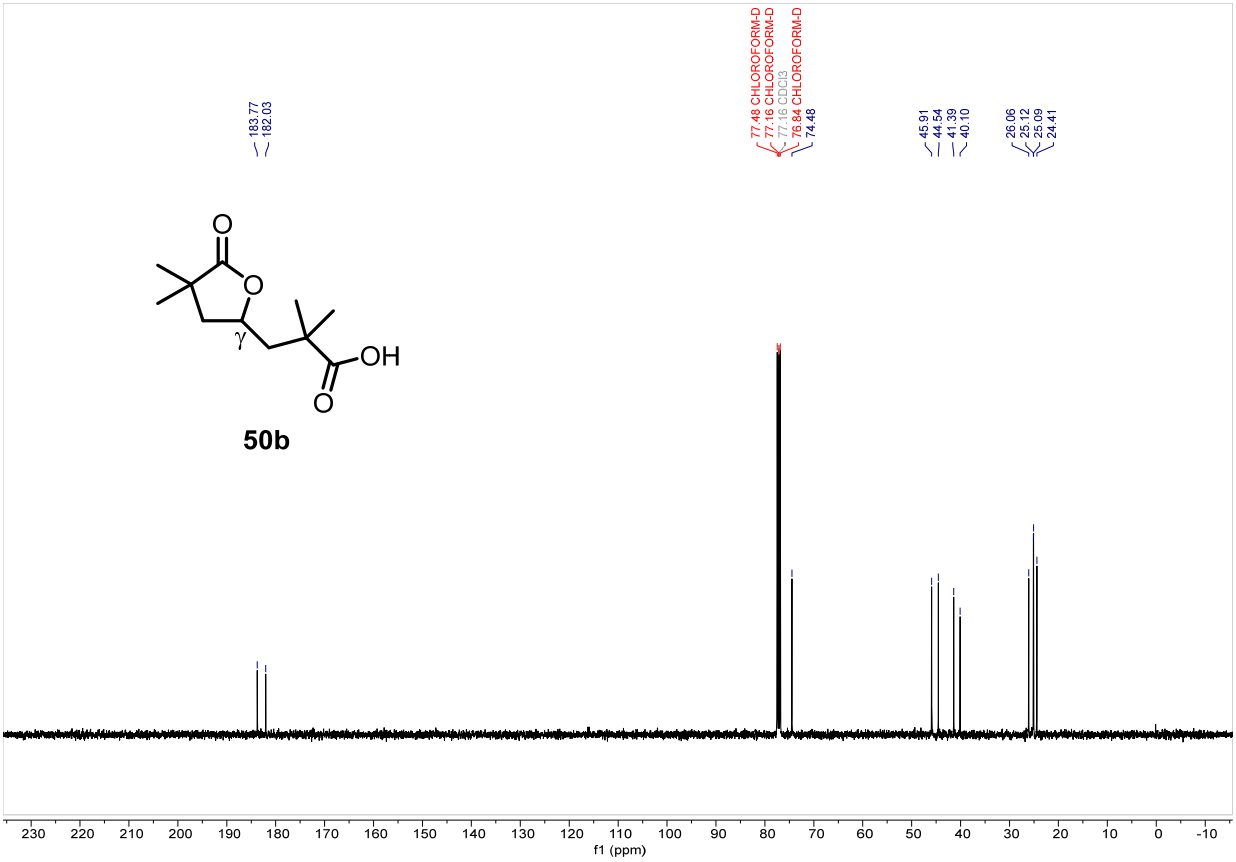
3-(*tert*-Butyl)heptanedioic acid 31



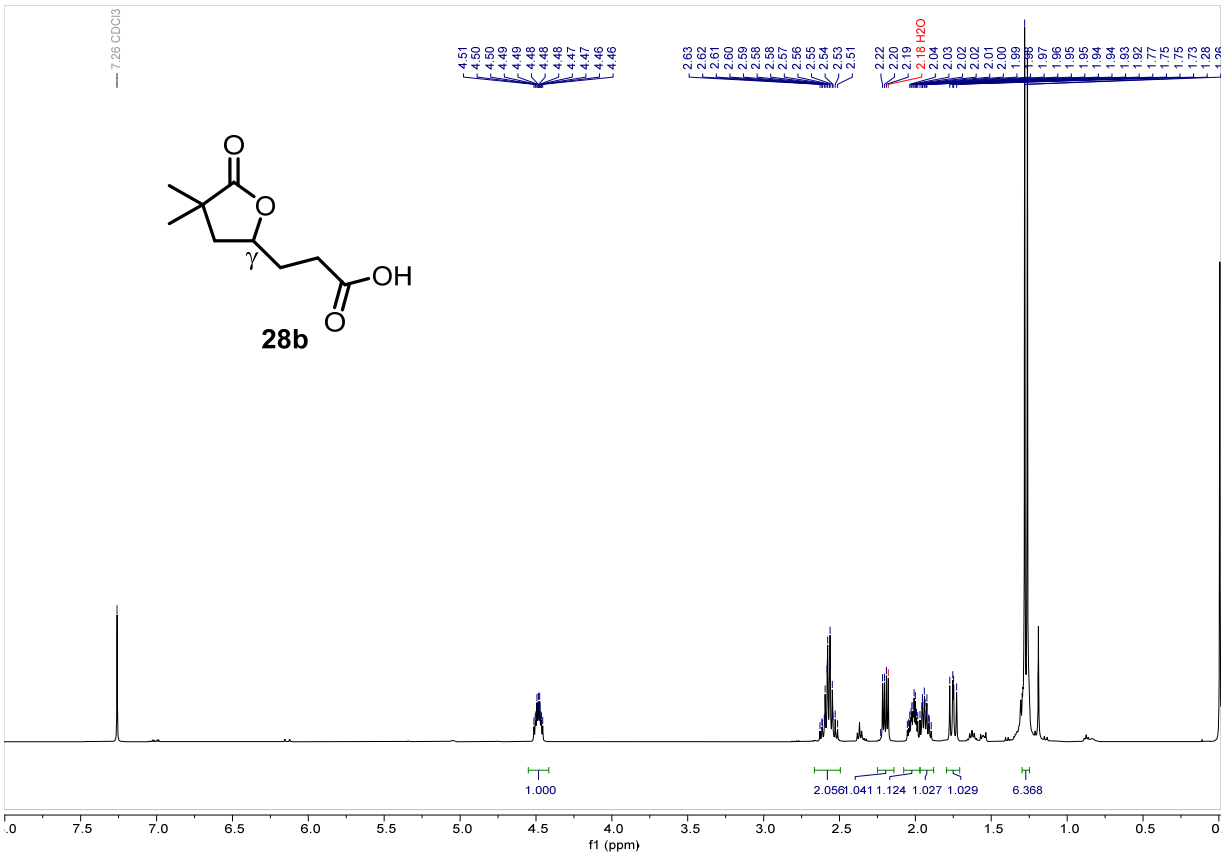


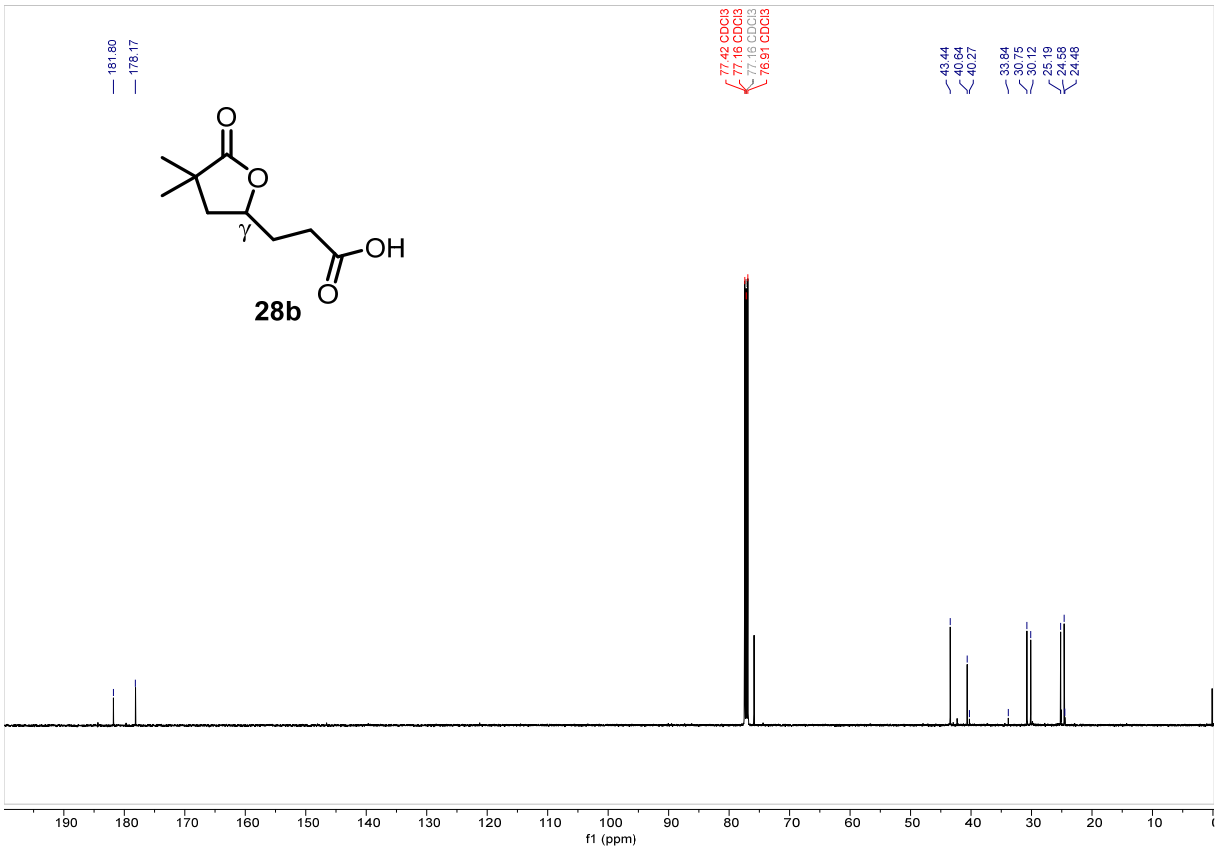
3-(4,4-Dimethyl-5-oxotetrahydrofuran-2-yl)-2,2-dimethylpropanoic acid 50b



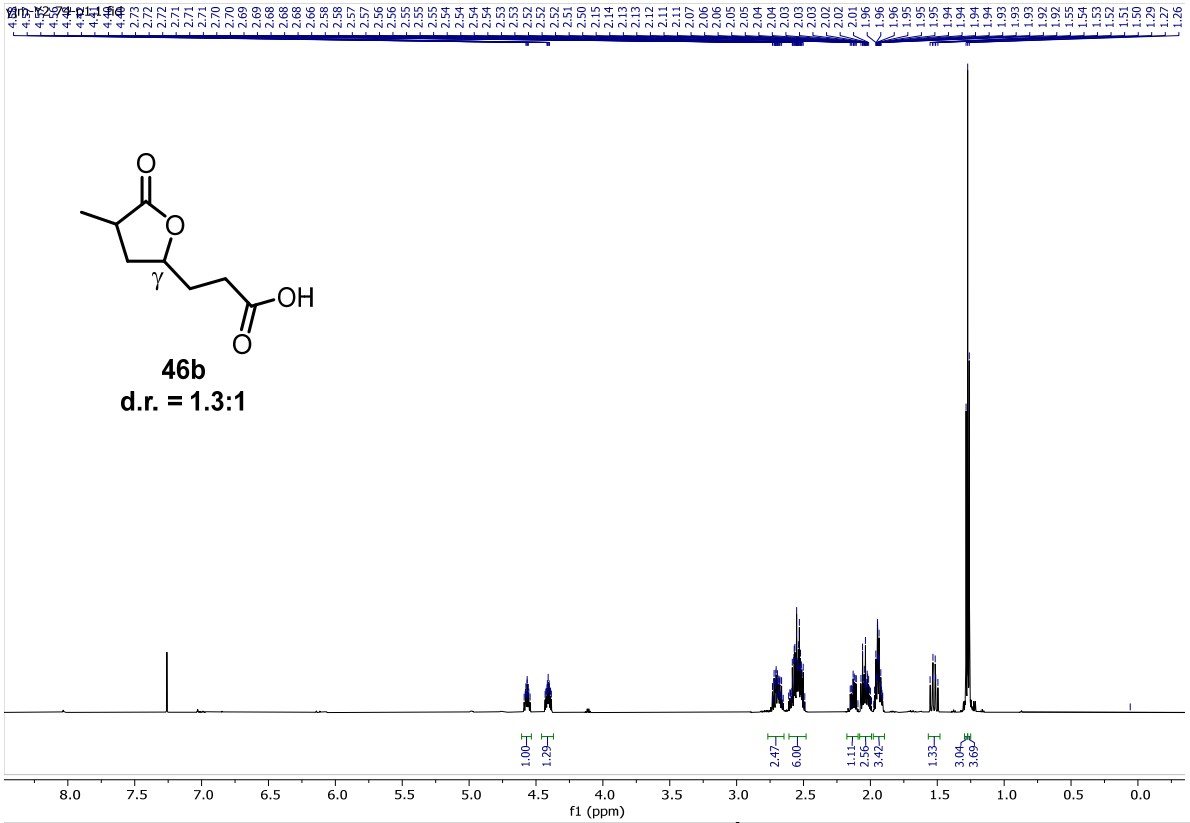


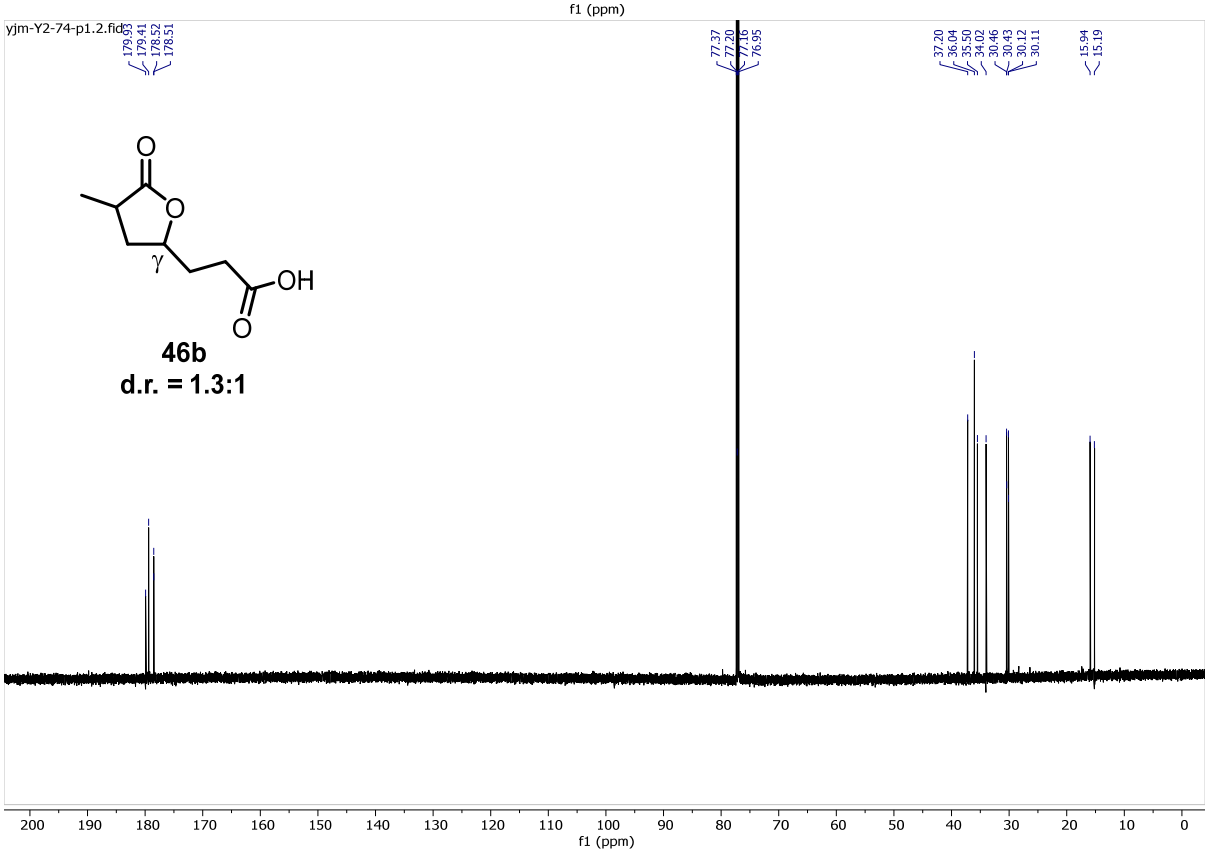
3-(4,4-Dimethyl-5-oxotetrahydrofuran-2-yl)propanoic acid 28b



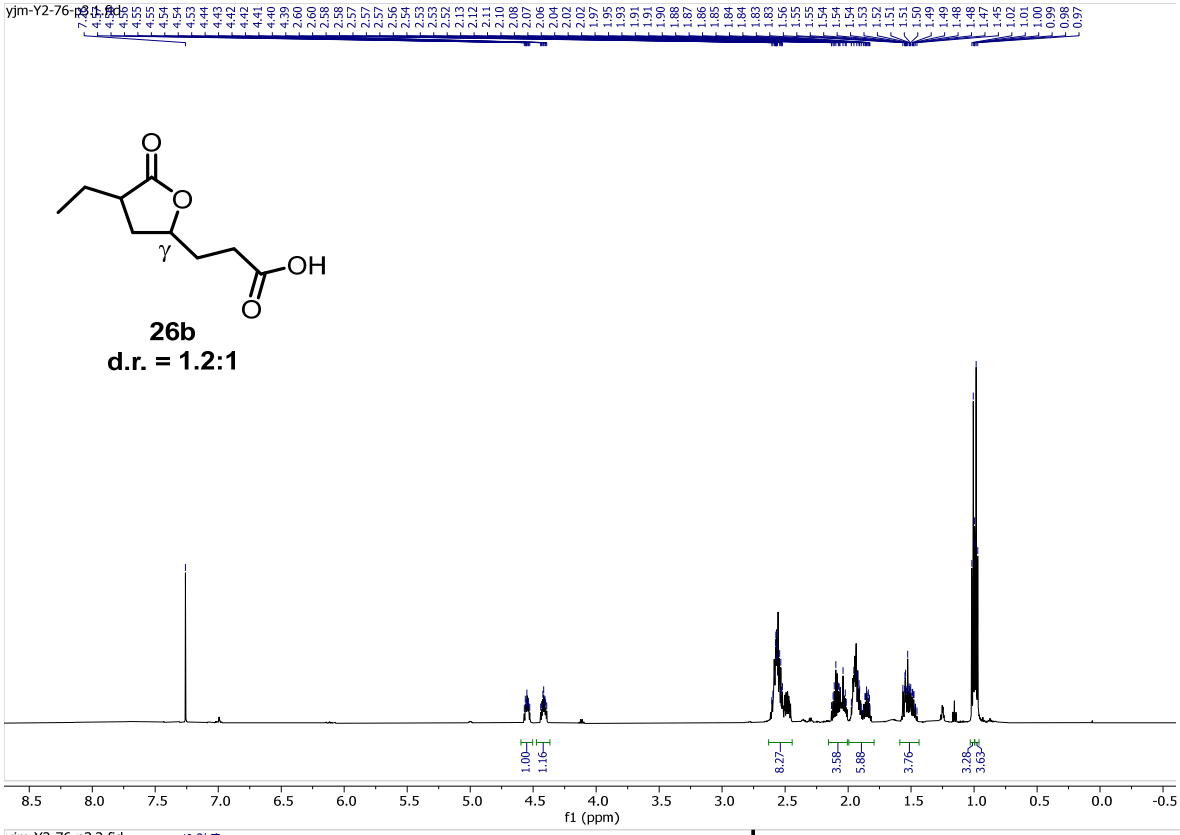


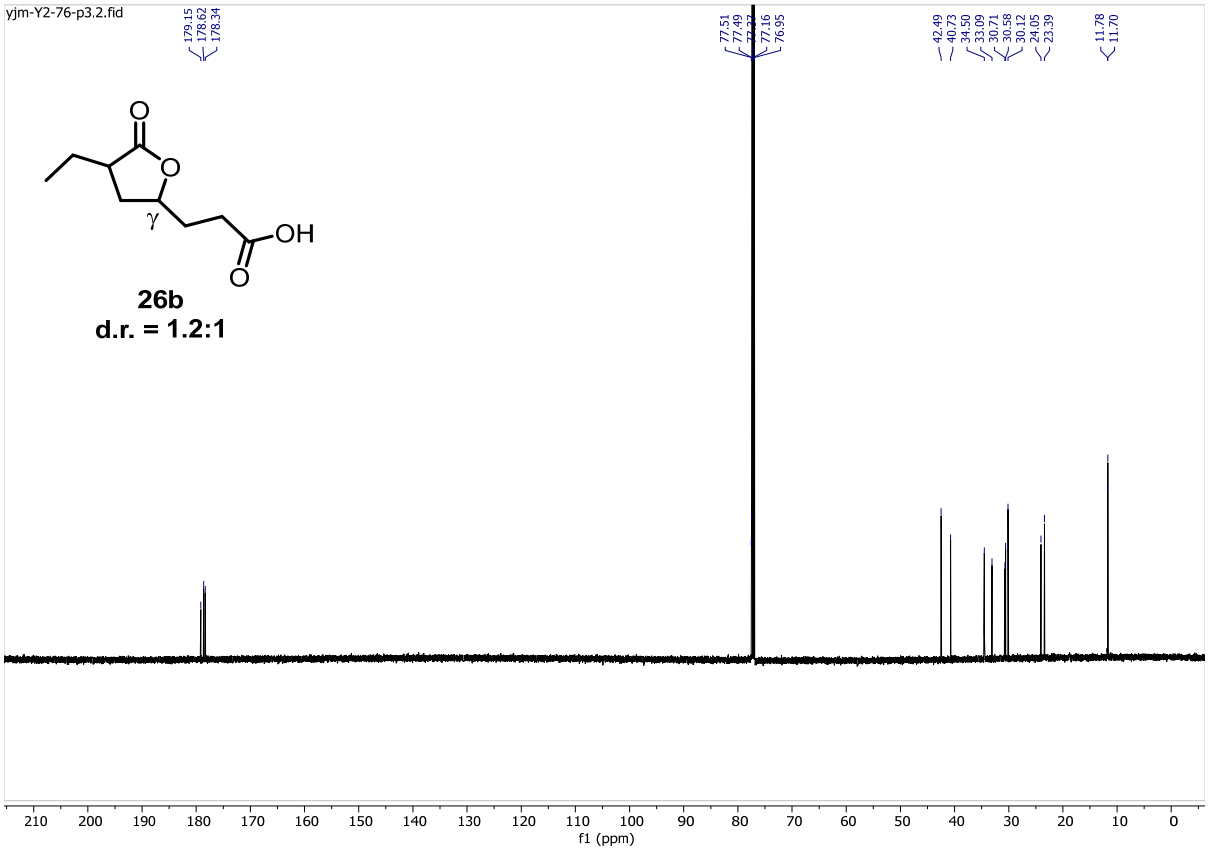
3-(4-Methyl-5-oxotetrahydrofuran-2-yl)propanoic acid 46b



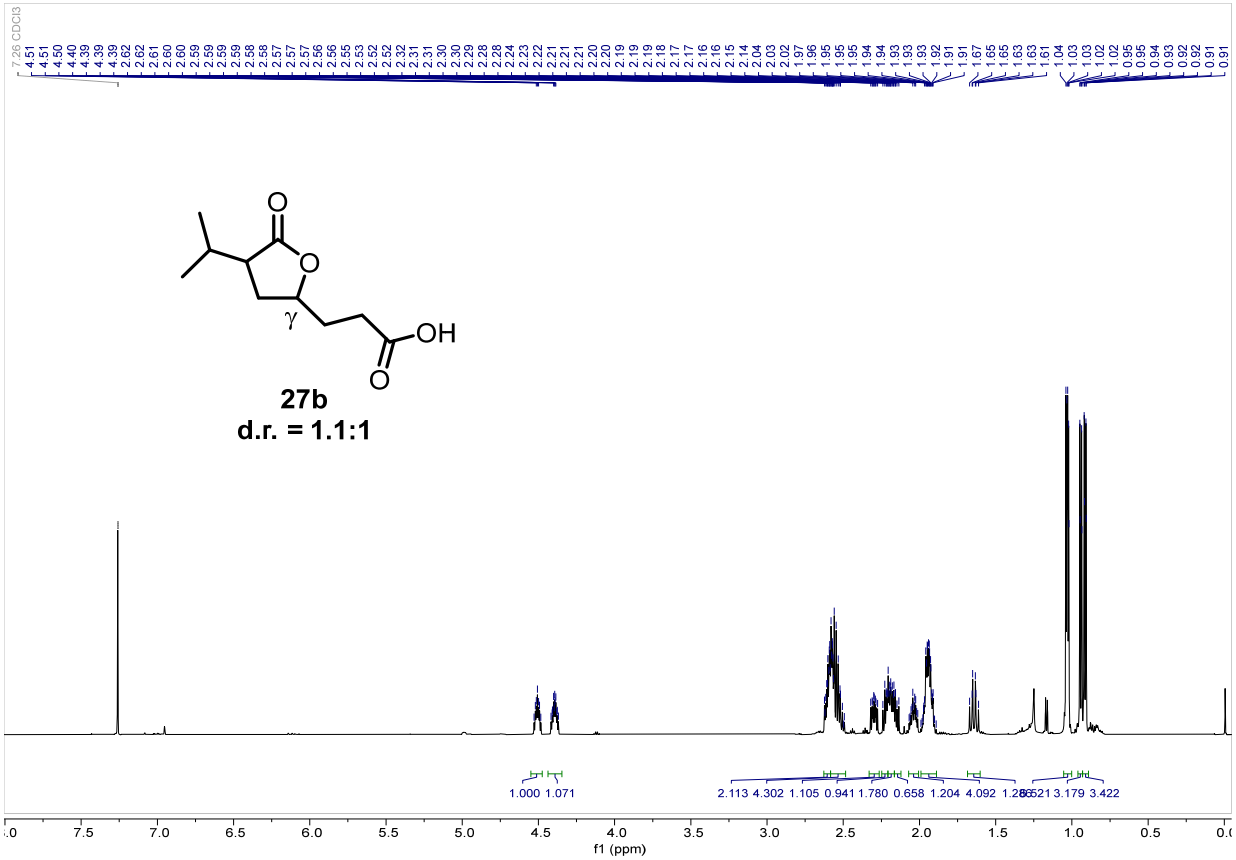


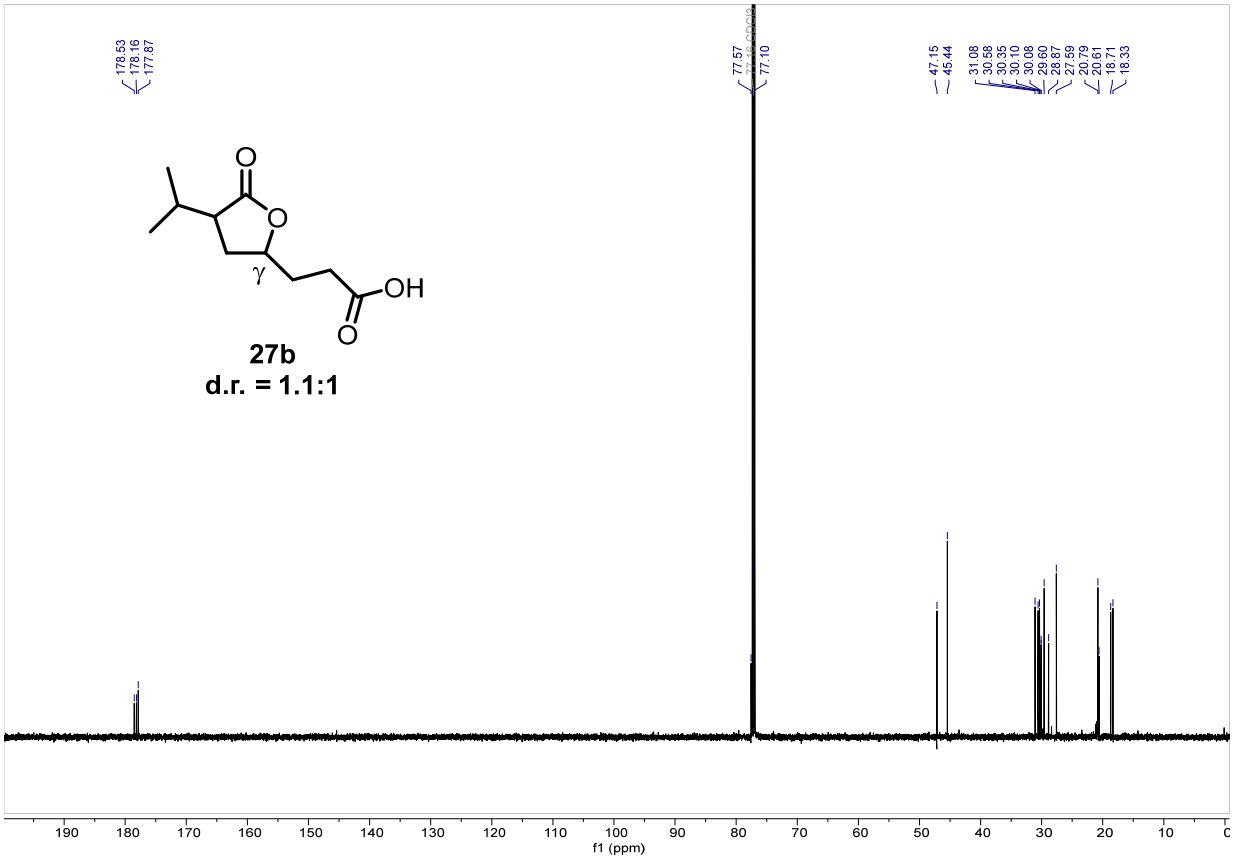
3-(4-Ethyl-5-oxotetrahydrofuran-2-yl)propanoic acid 26b



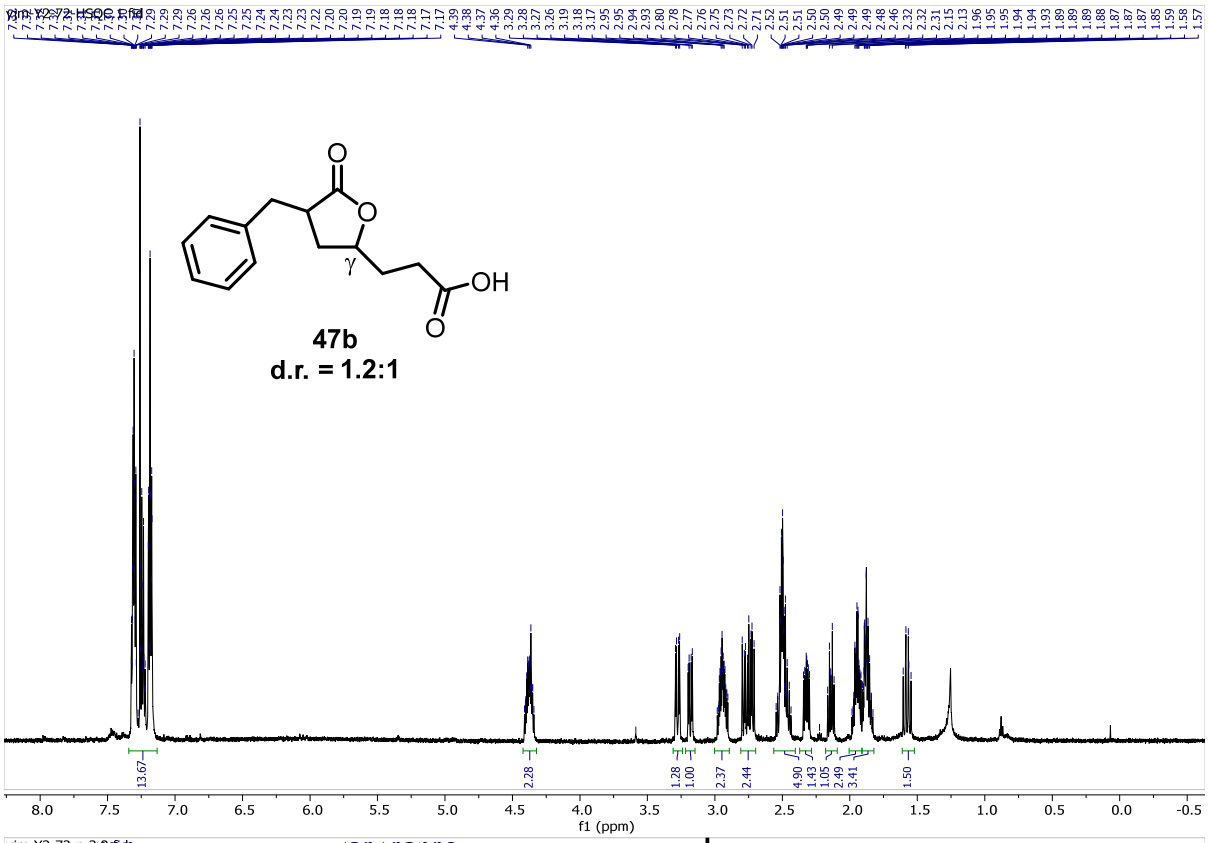


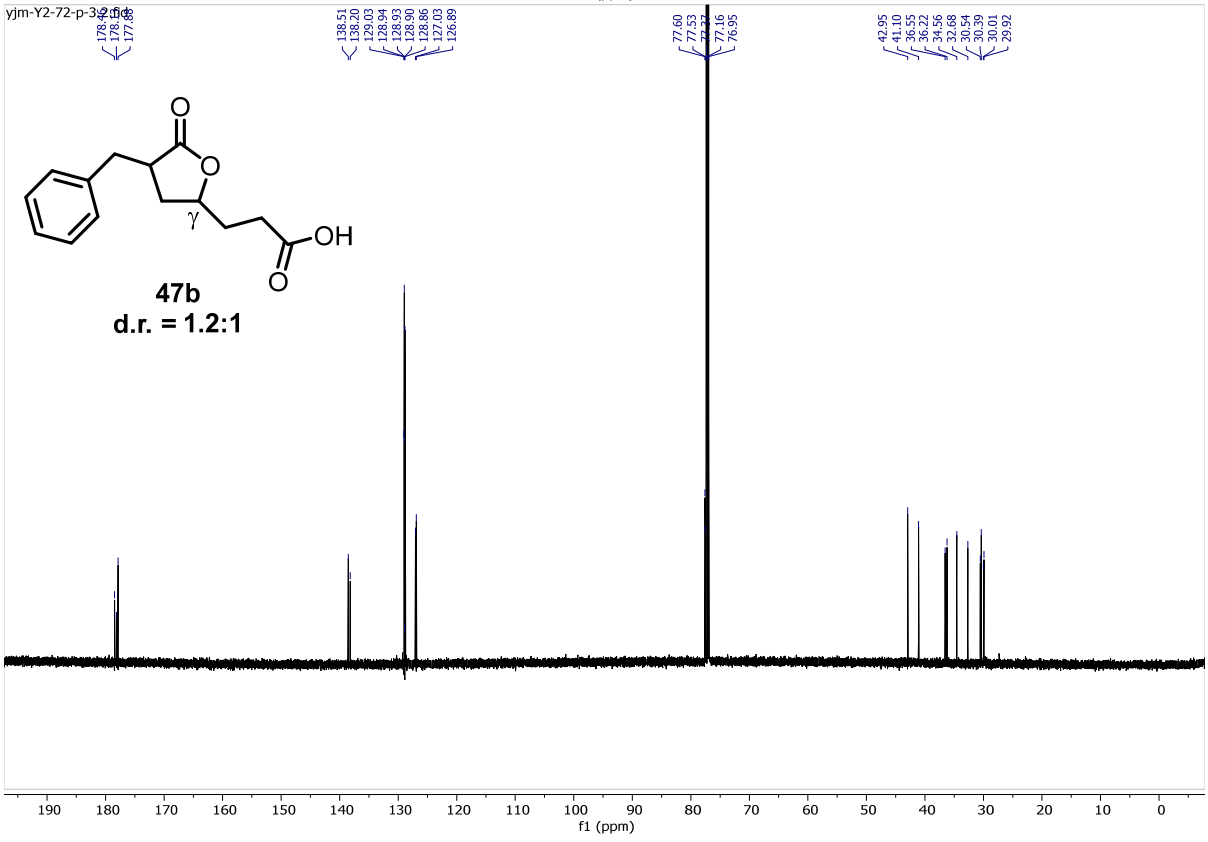
3-(4-Isopropyl-5-oxotetrahydrofuran-2-yl)propanoic acid 27b



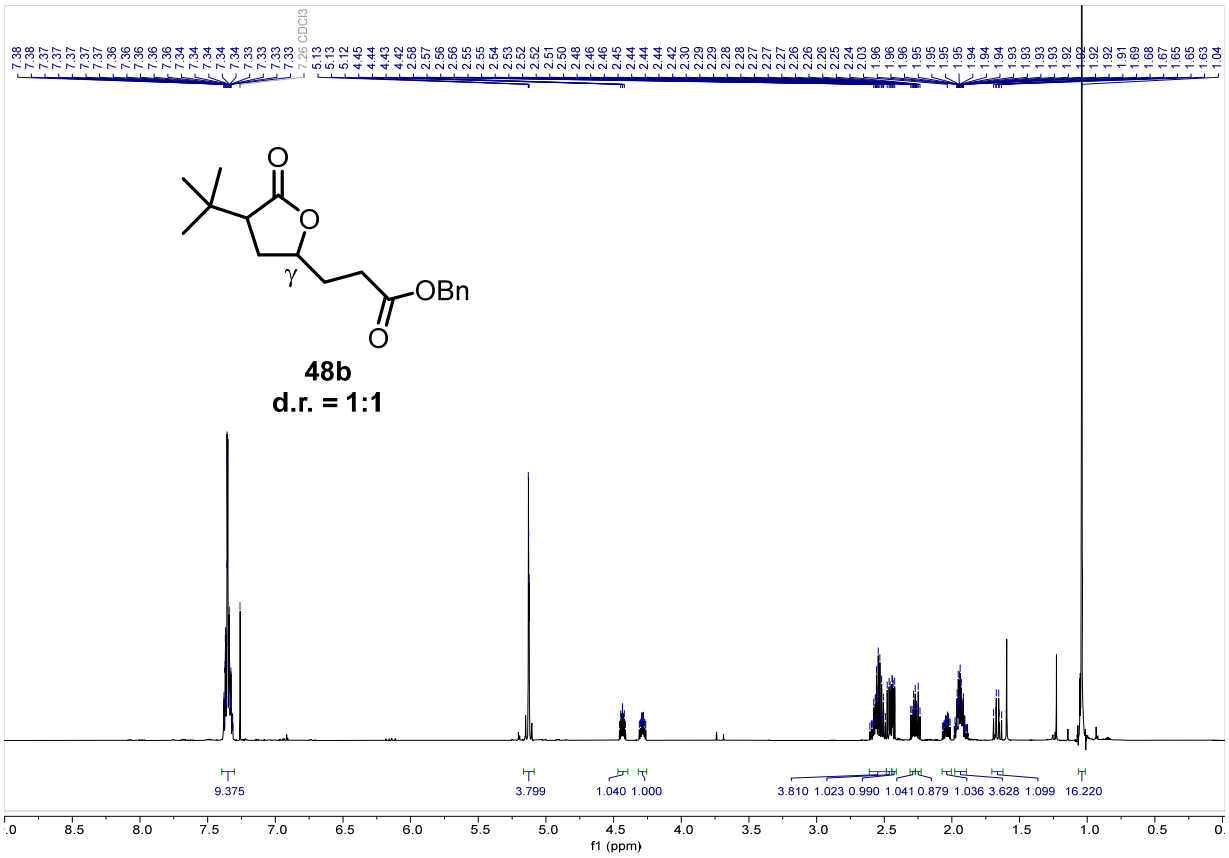


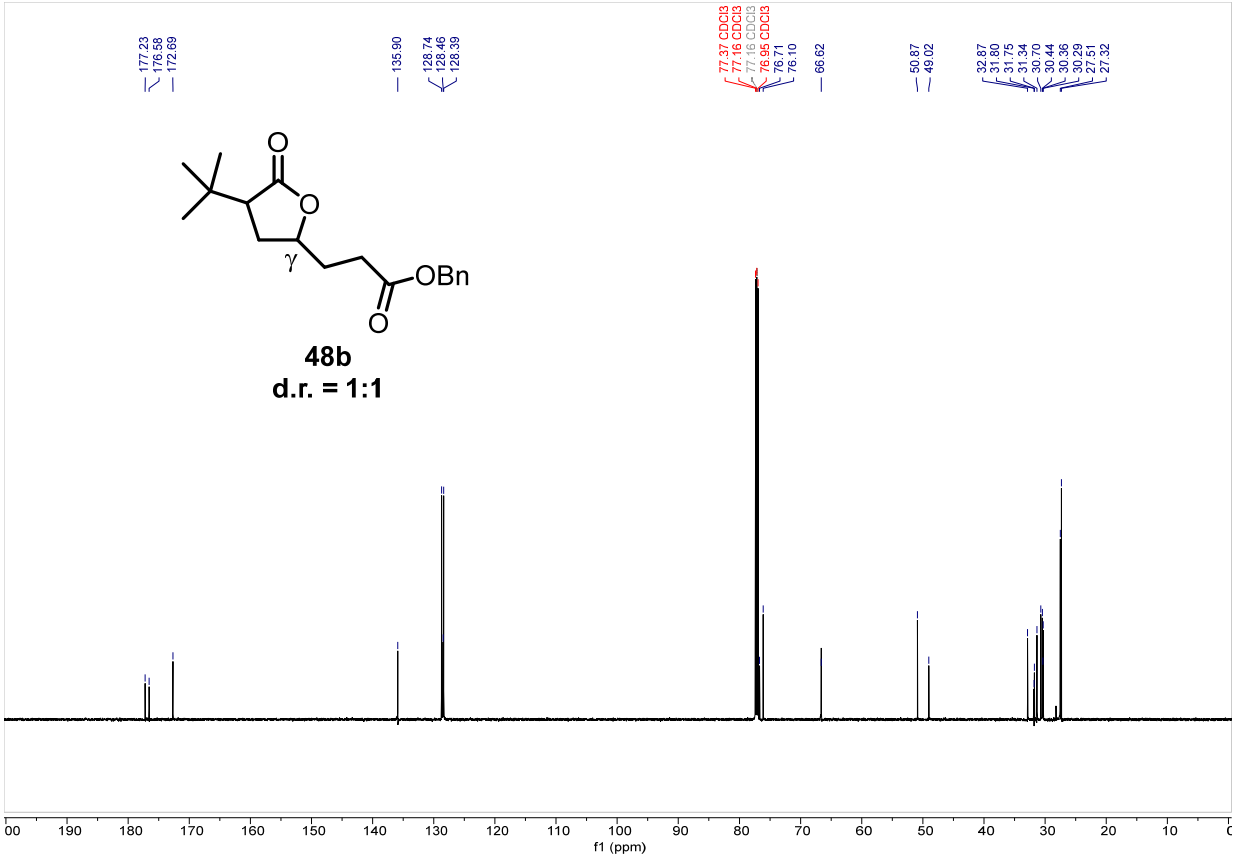
3-(4-Benzyl-5-oxotetrahydrofuran-2-yl)propanoic acid 47b



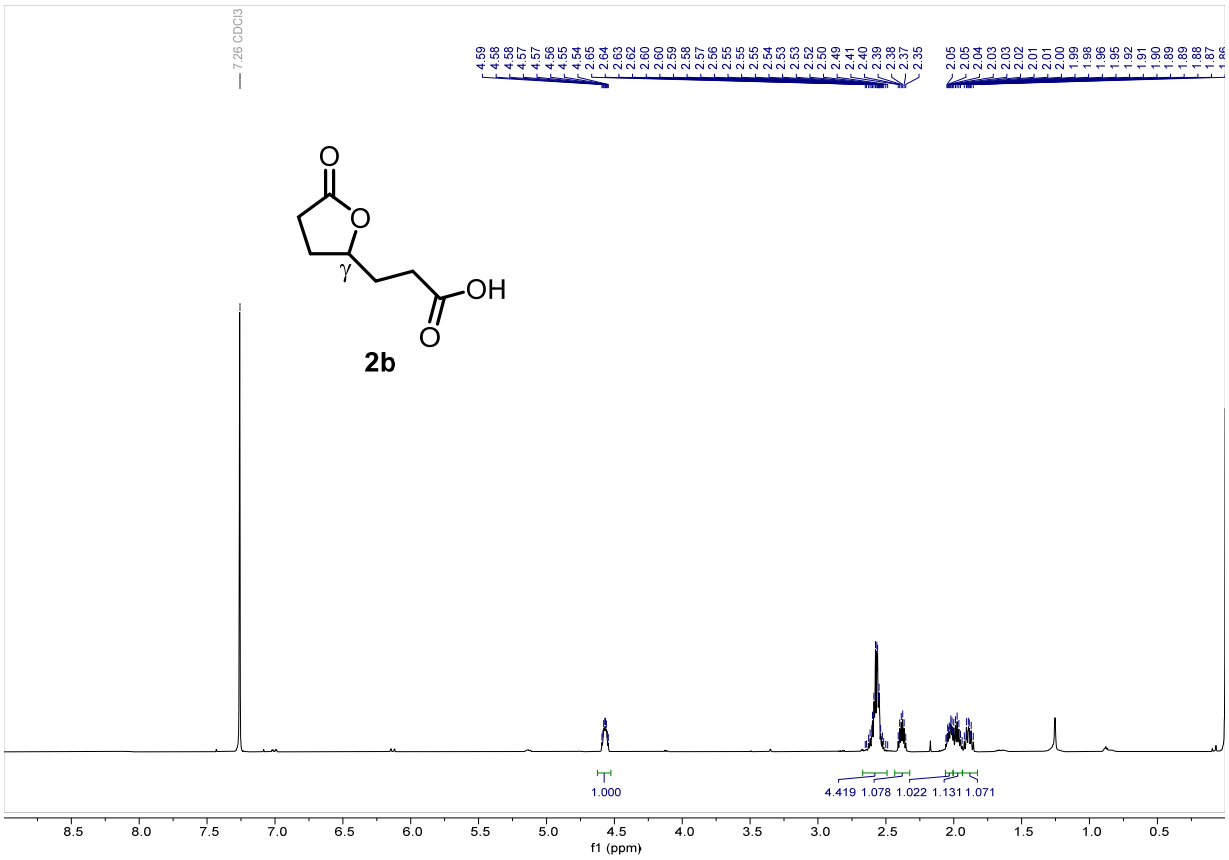


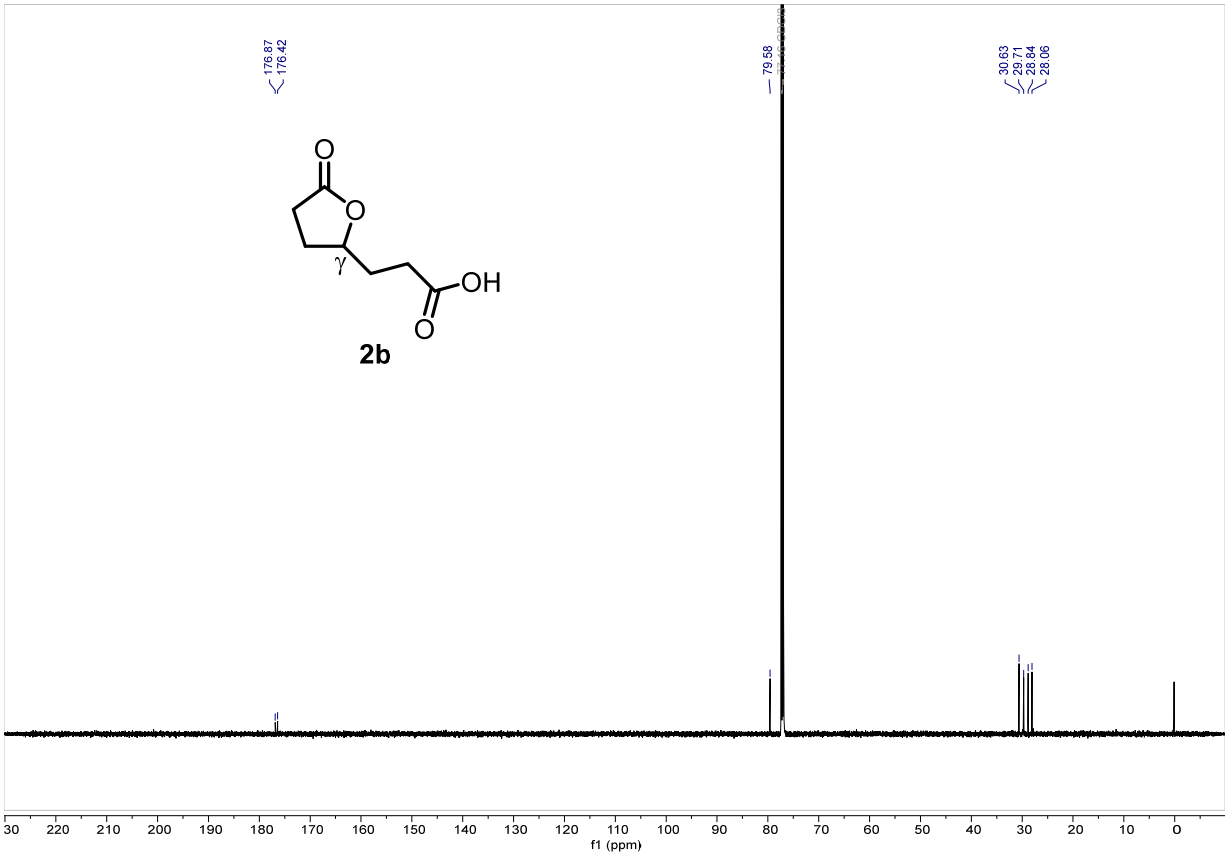
Benzyl 3-(4-(*tert*-butyl)-5-oxotetrahydrofuran-2-yl)propanoate 48b



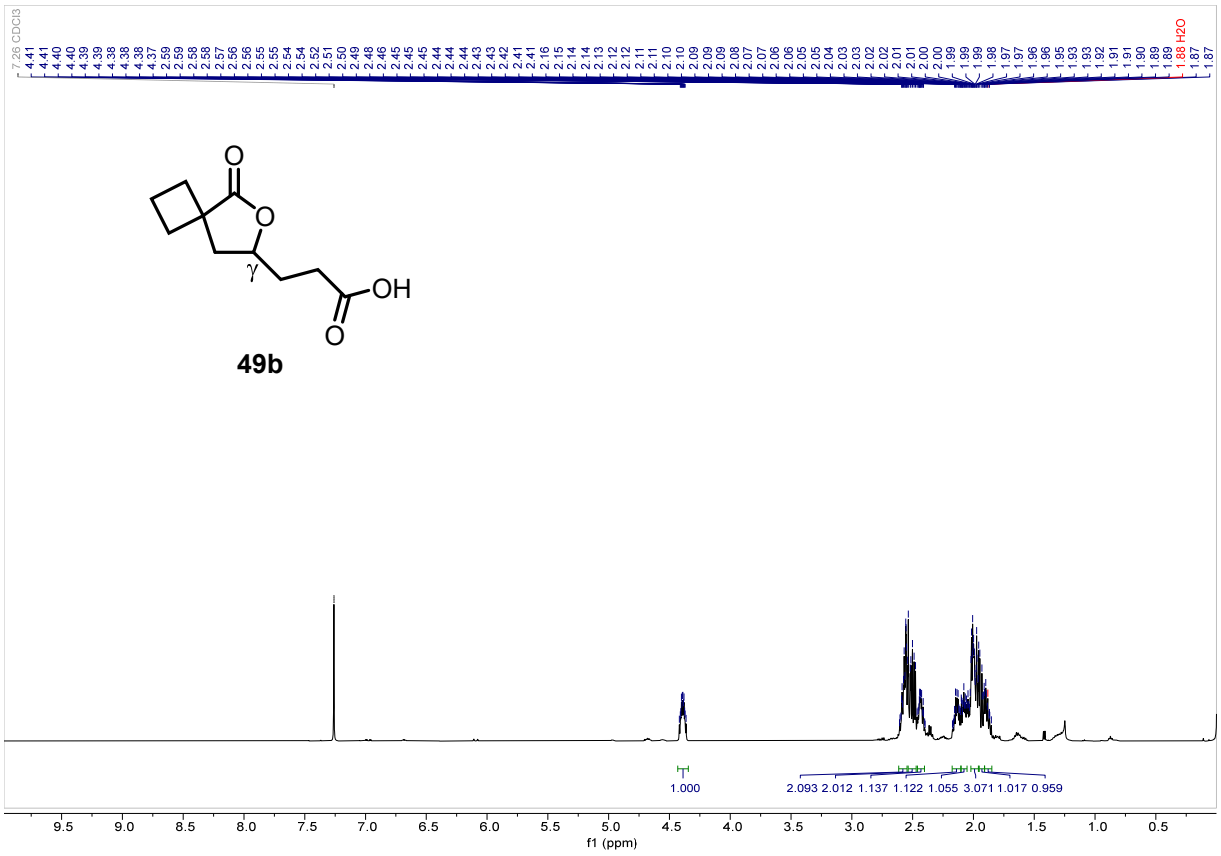


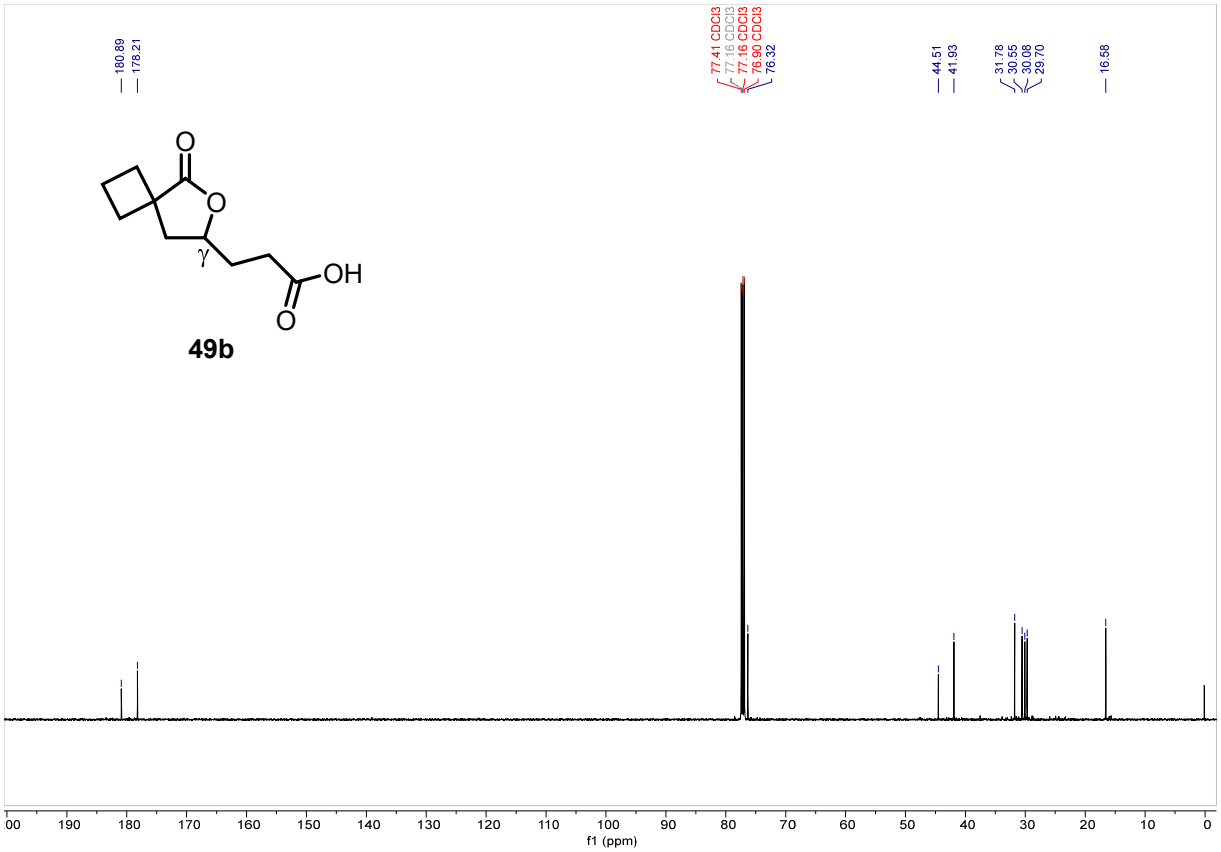
3-(5-Oxotetrahydrofuran-2-yl)propanoic acid 2b



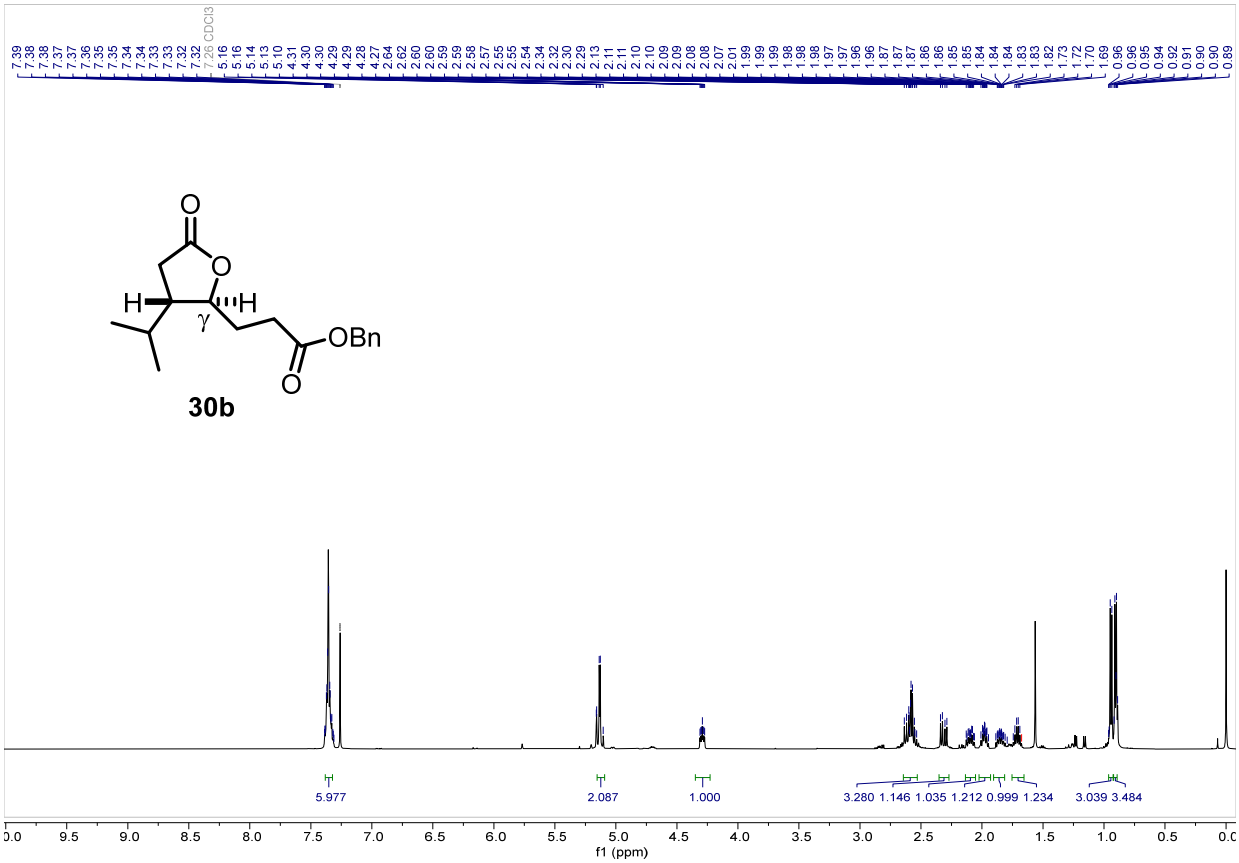


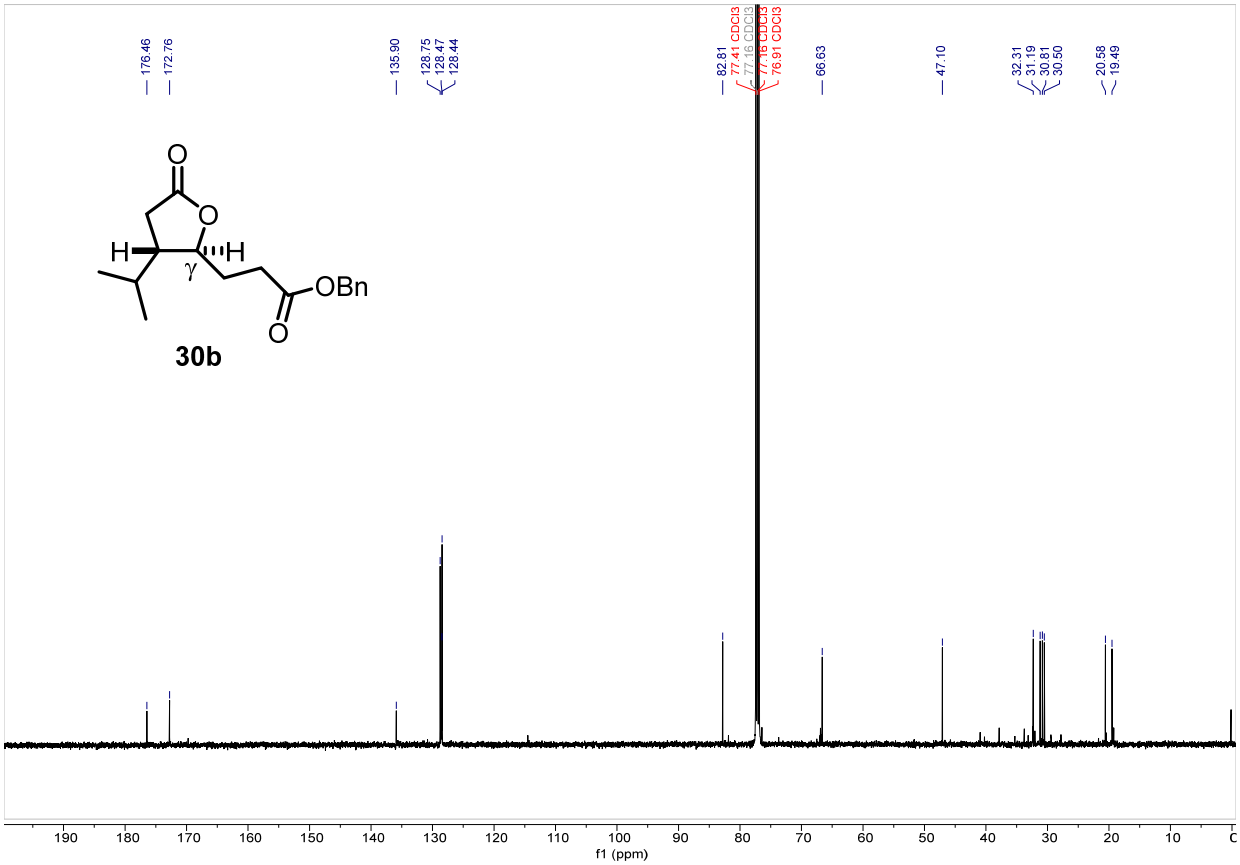
3-(5-Oxo-6-oxaspiro[3.4]octan-7-yl)propanoic acid 49b



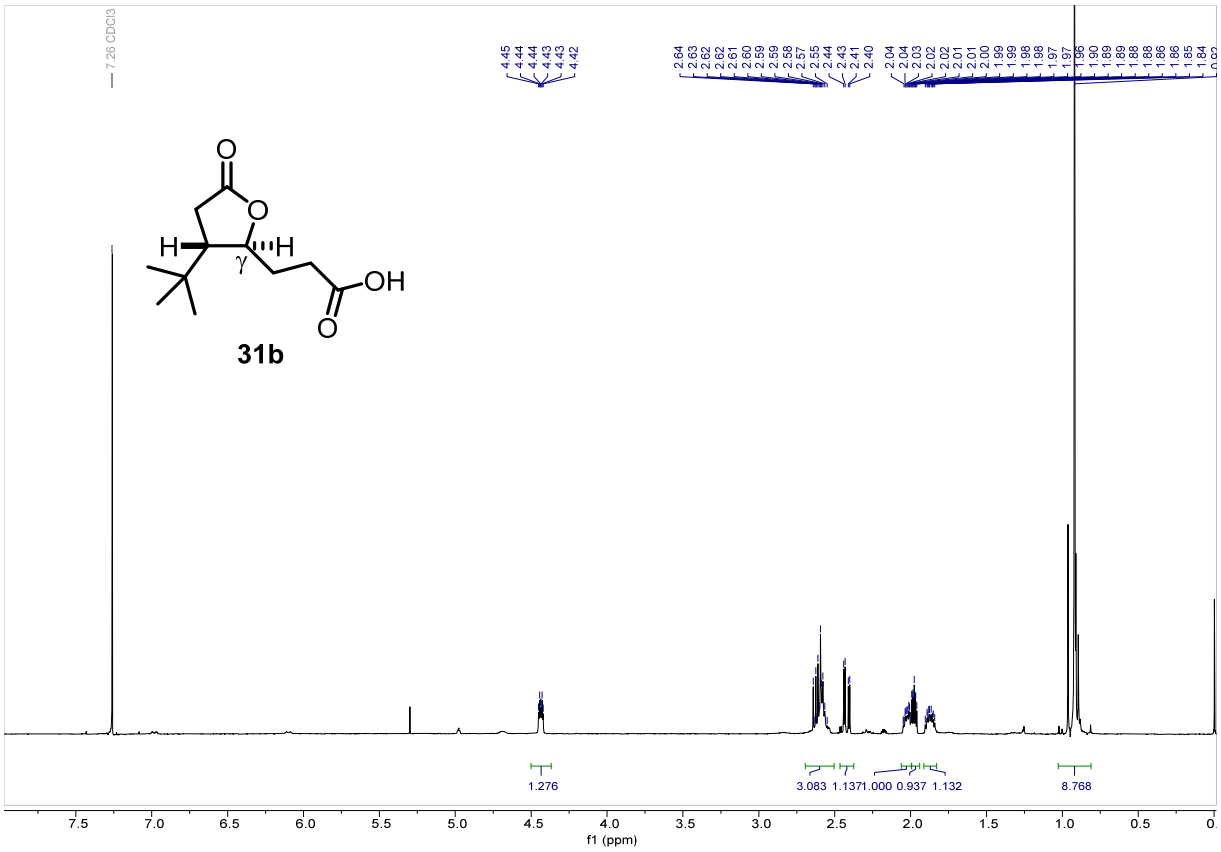


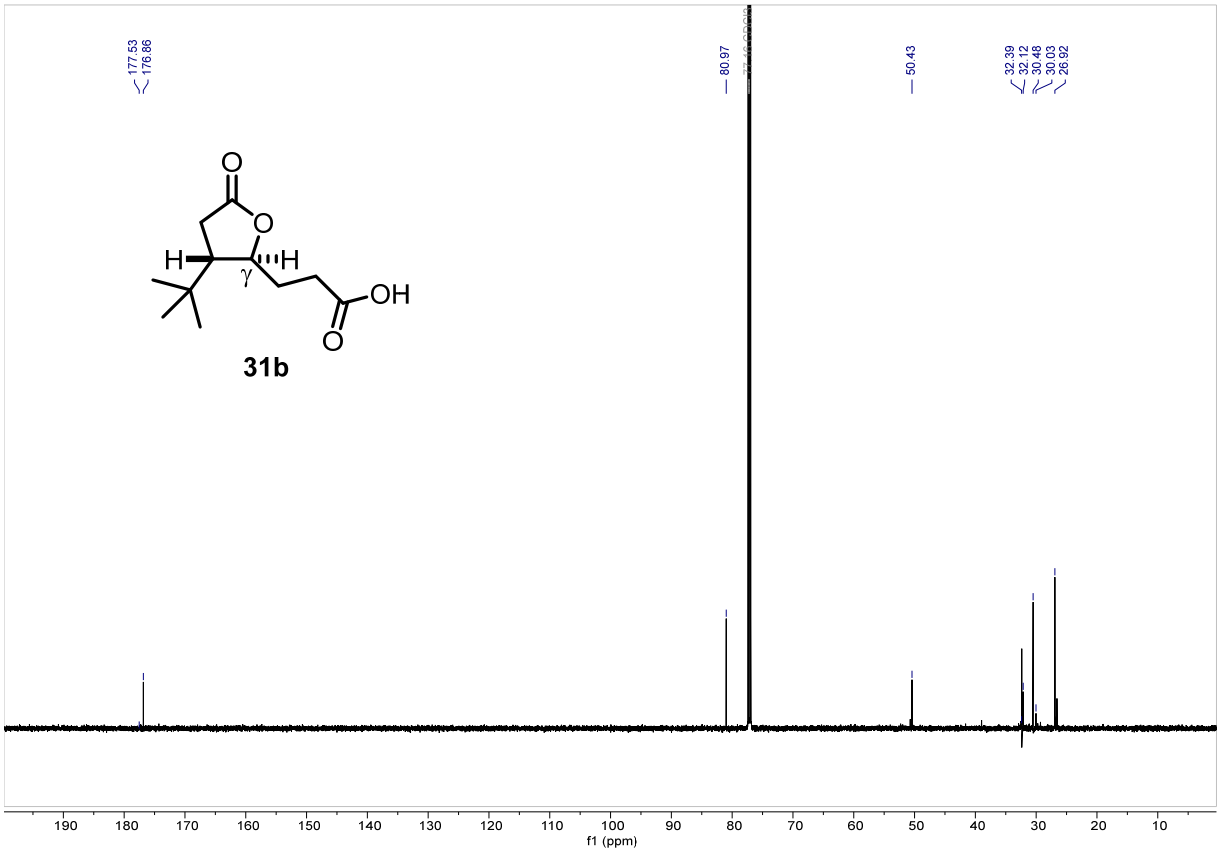
Benzyl 3-((2*S,3*S**)-3-isopropyl-5-oxotetrahydrofuran-2-yl)propanoate 30b**



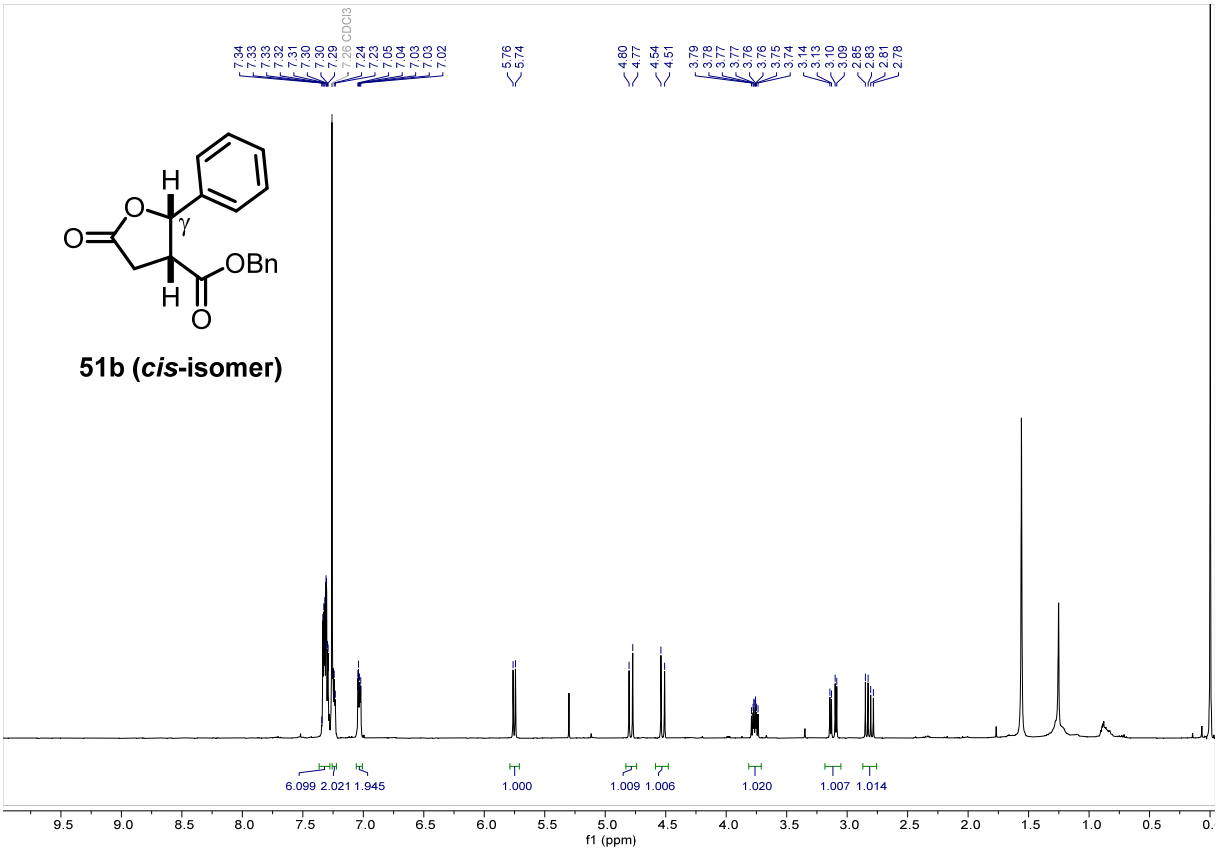


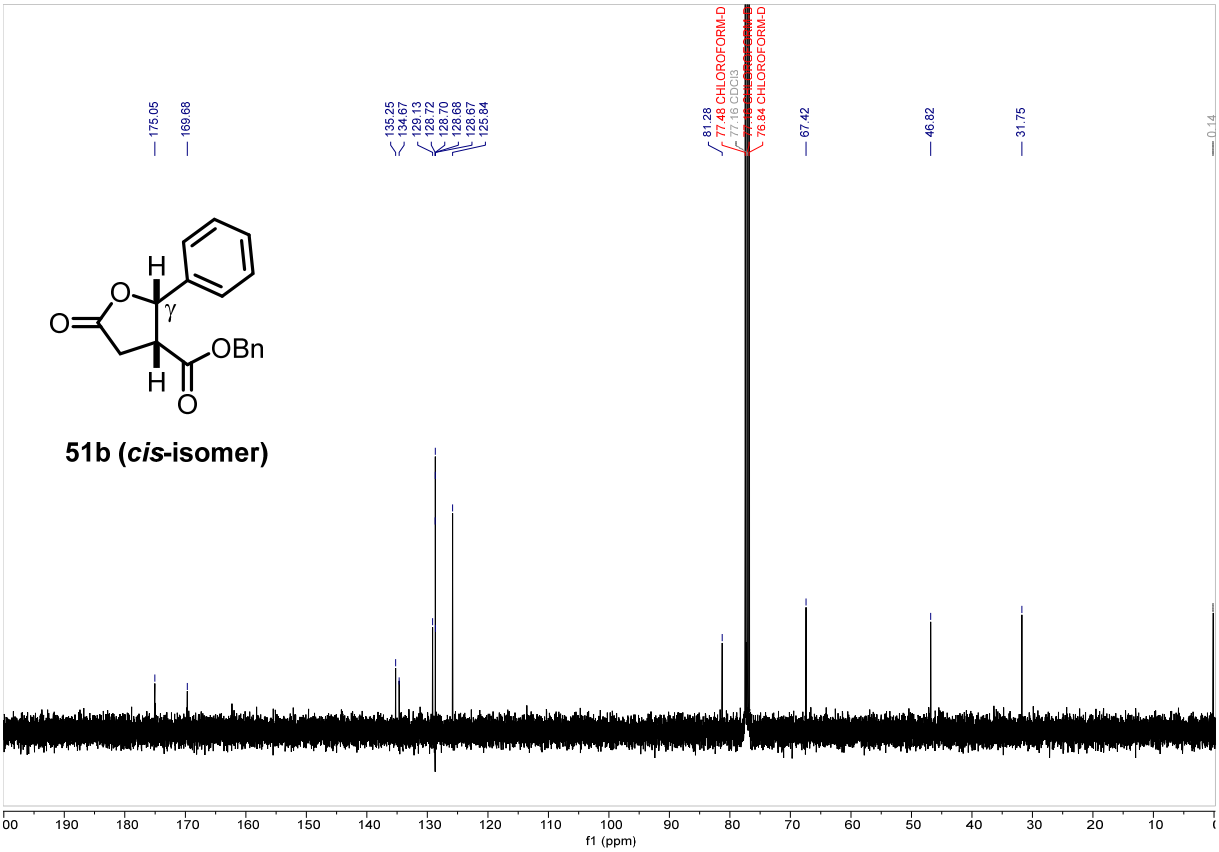
3-((2*S,3*S**)-3-(tert-butyl)-5-oxotetrahydrofuran-2-yl)propanoic acid 31b**

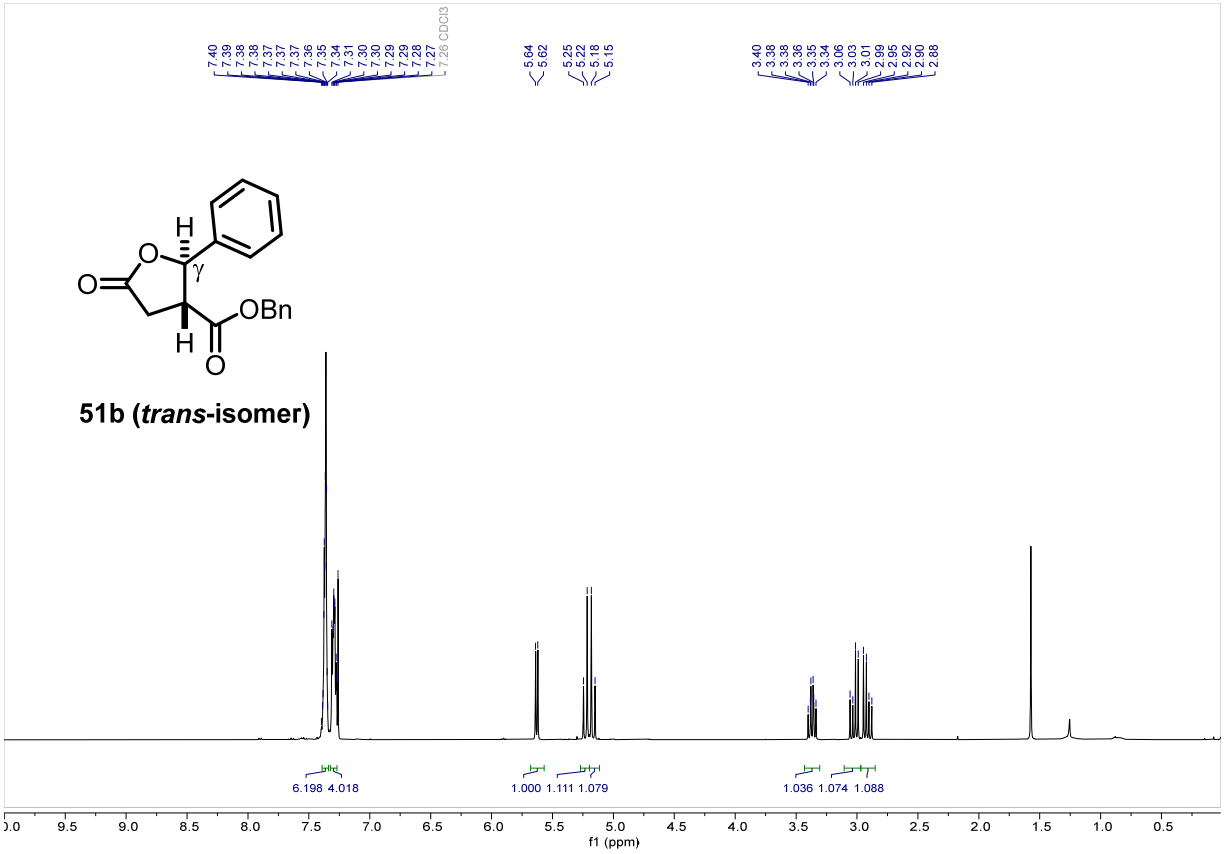


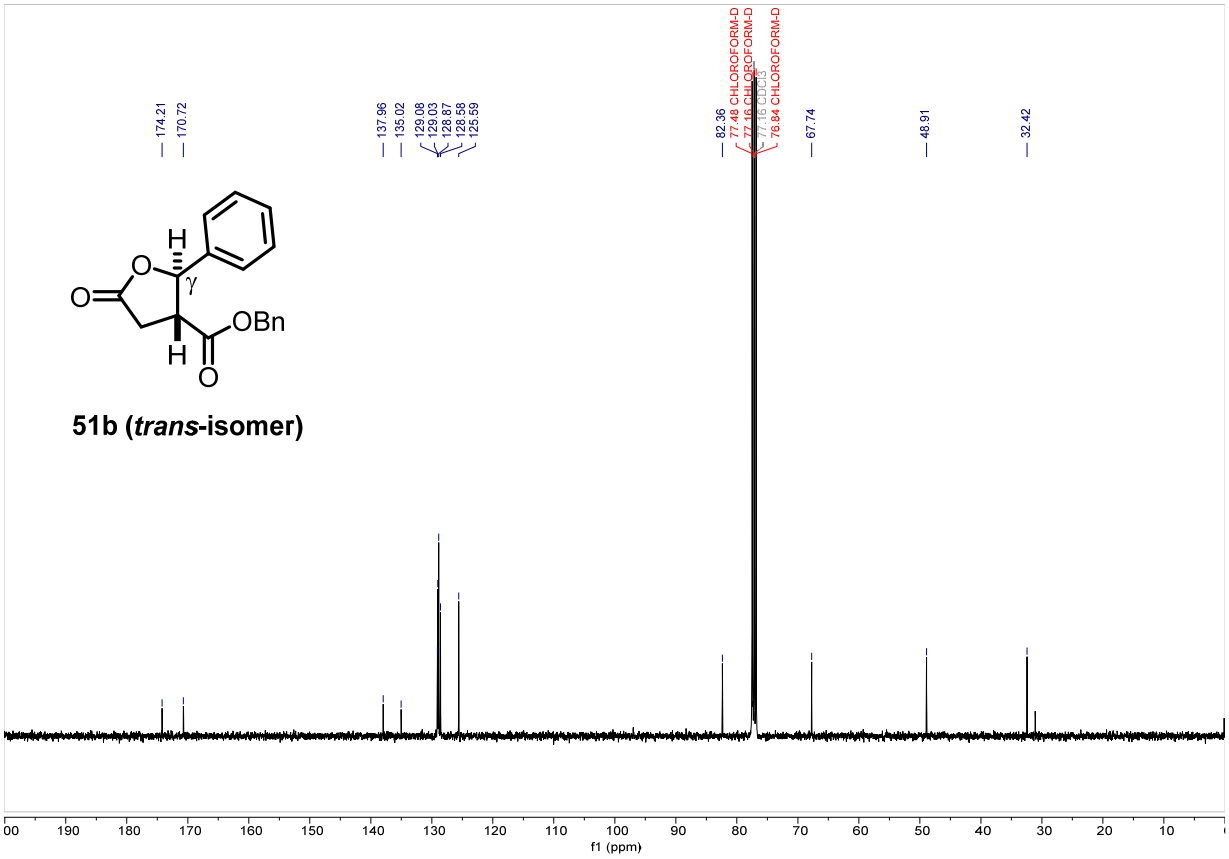


Benzyl 5-oxo-2-phenyltetrahydrofuran-3-carboxylate 51b

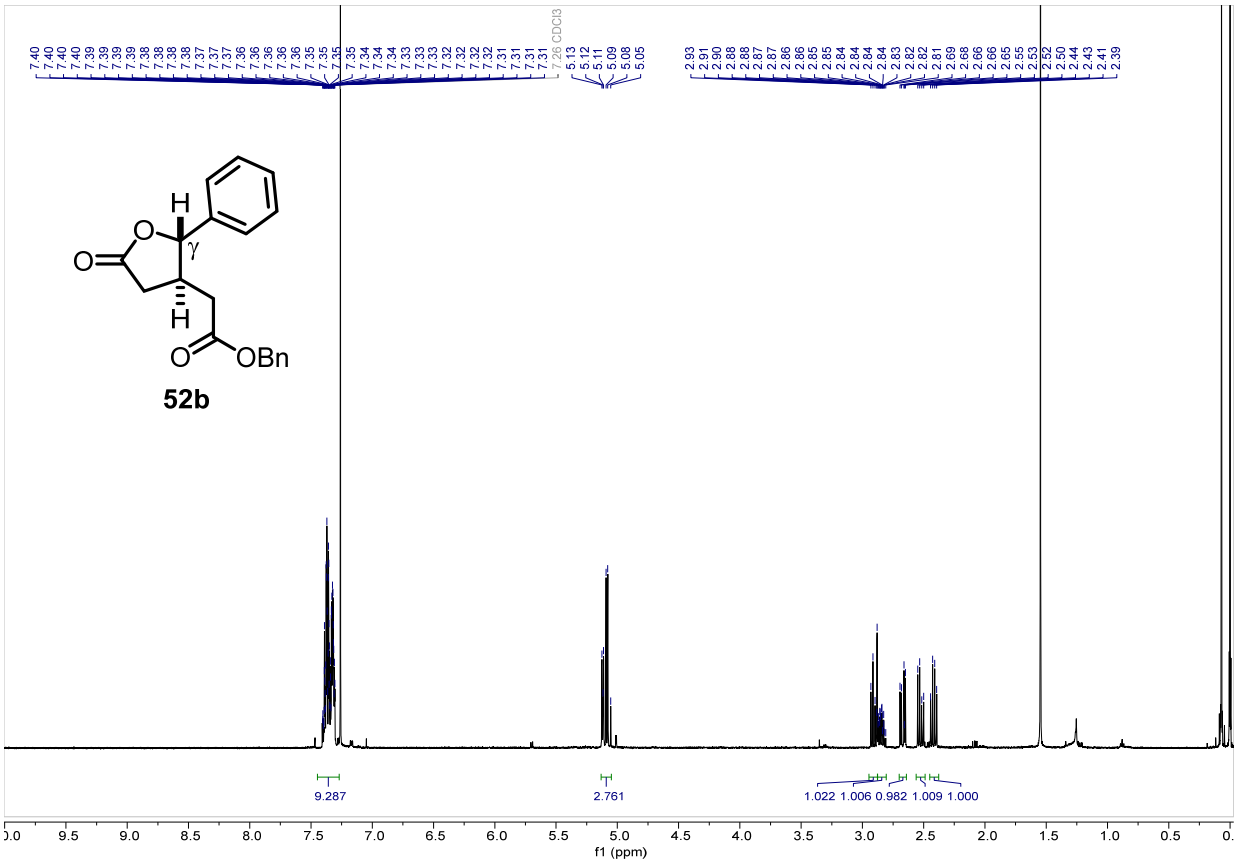


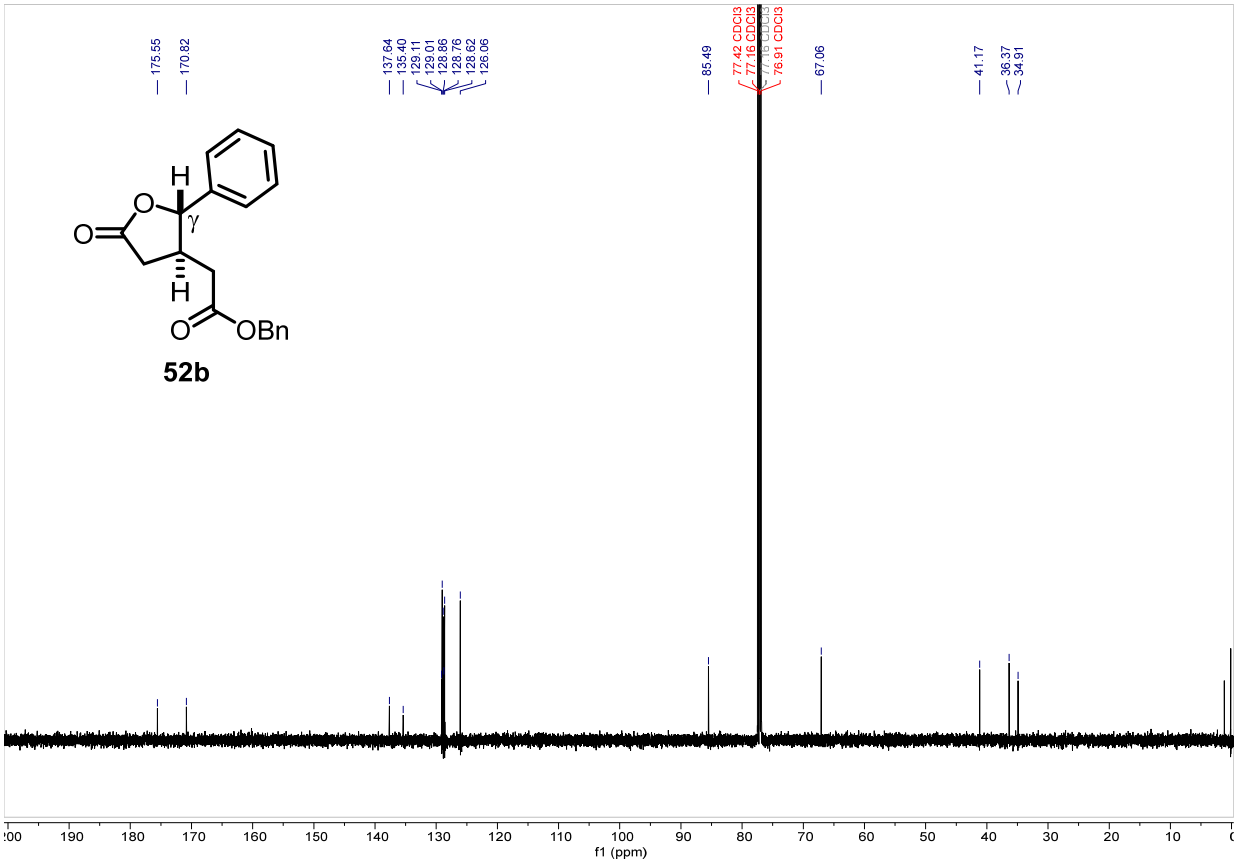



7.40
7.39
7.38
7.38
7.37
7.37
7.37
7.36
7.35
7.34
7.31
7.30
7.30
7.29
7.29
7.28
7.27
7.26 CDCl3
5.64
5.62
5.25
5.22
5.18
5.15
3.40
3.38
3.38
3.36
3.35
3.34
3.06
3.03
3.01
2.99
2.95
2.92
2.90
2.88
H
O
γ
OBn
H
O
O
51b (*trans*-isomer)
6.198 4.018
1.000 1.111 1.079
1.036 1.074 1.088
f1 (ppm)

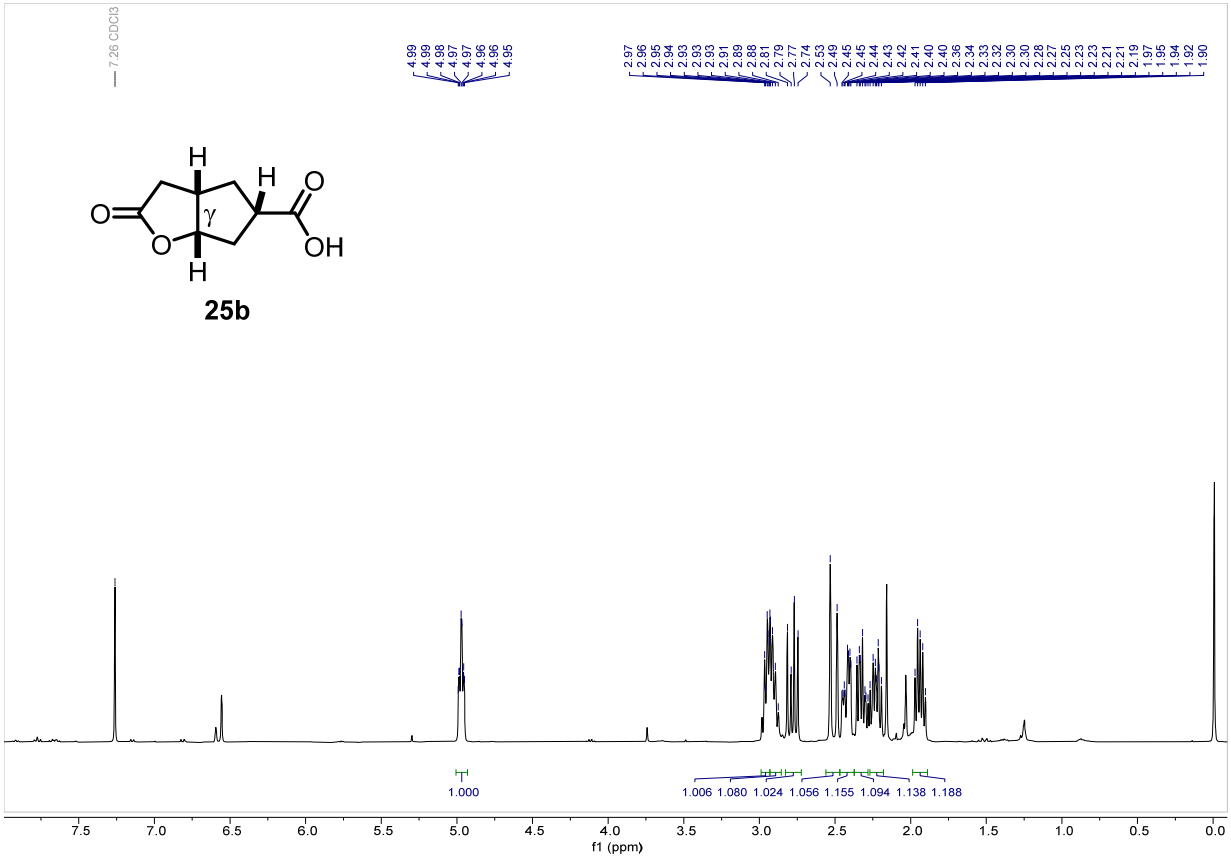

174.21
170.72
137.96
135.02
129.08
129.03
128.87
128.58
125.59
82.36
77.48 CHLOROFORM-D
77.16 CHLOROFORM-D
76.84 CHLOROFORM-D
77.16 CDCl3
67.74
48.91
32.42
H
O
γ
O
OBn
H
O
51b (*trans*-isomer)
f1 (ppm)

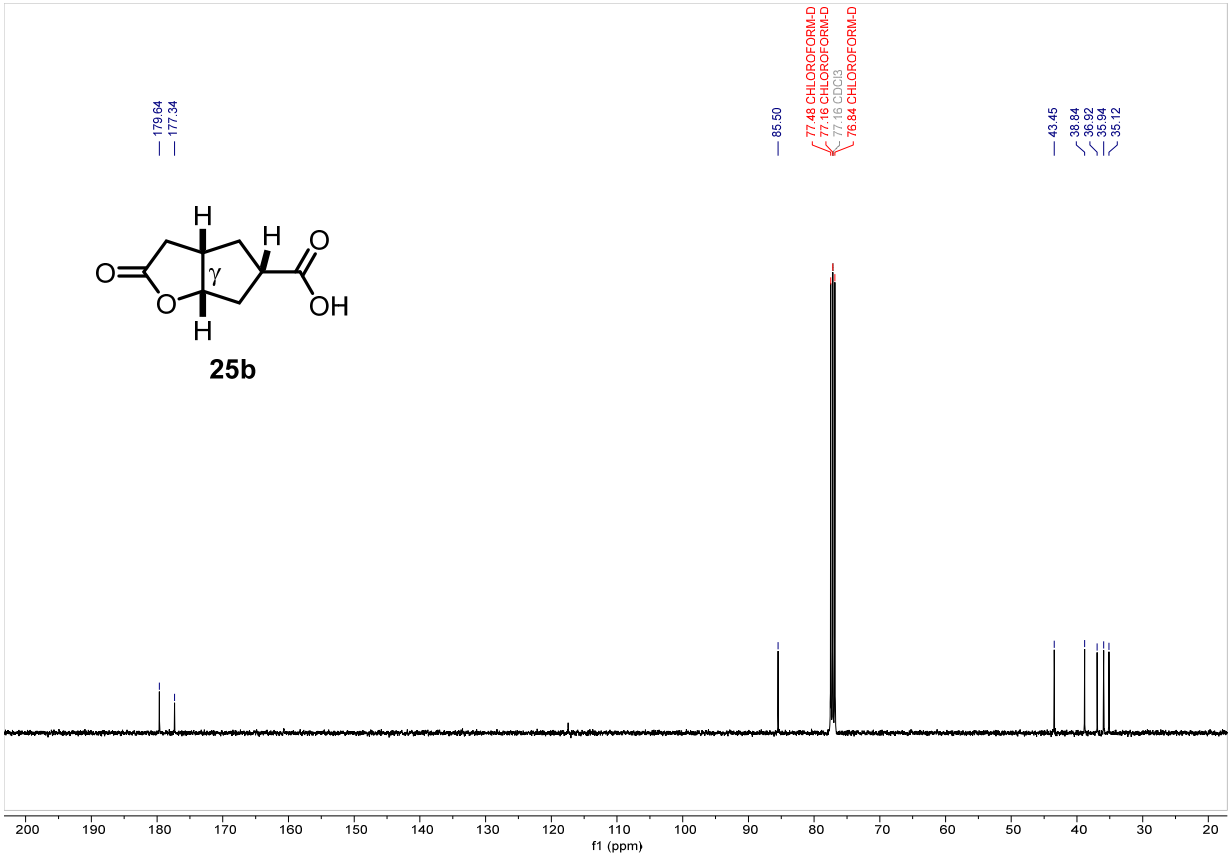
Benzyl 2-((2*S,3*S**)-5-oxo-2-phenyltetrahydrofuran-3-yl)acetate 52b**



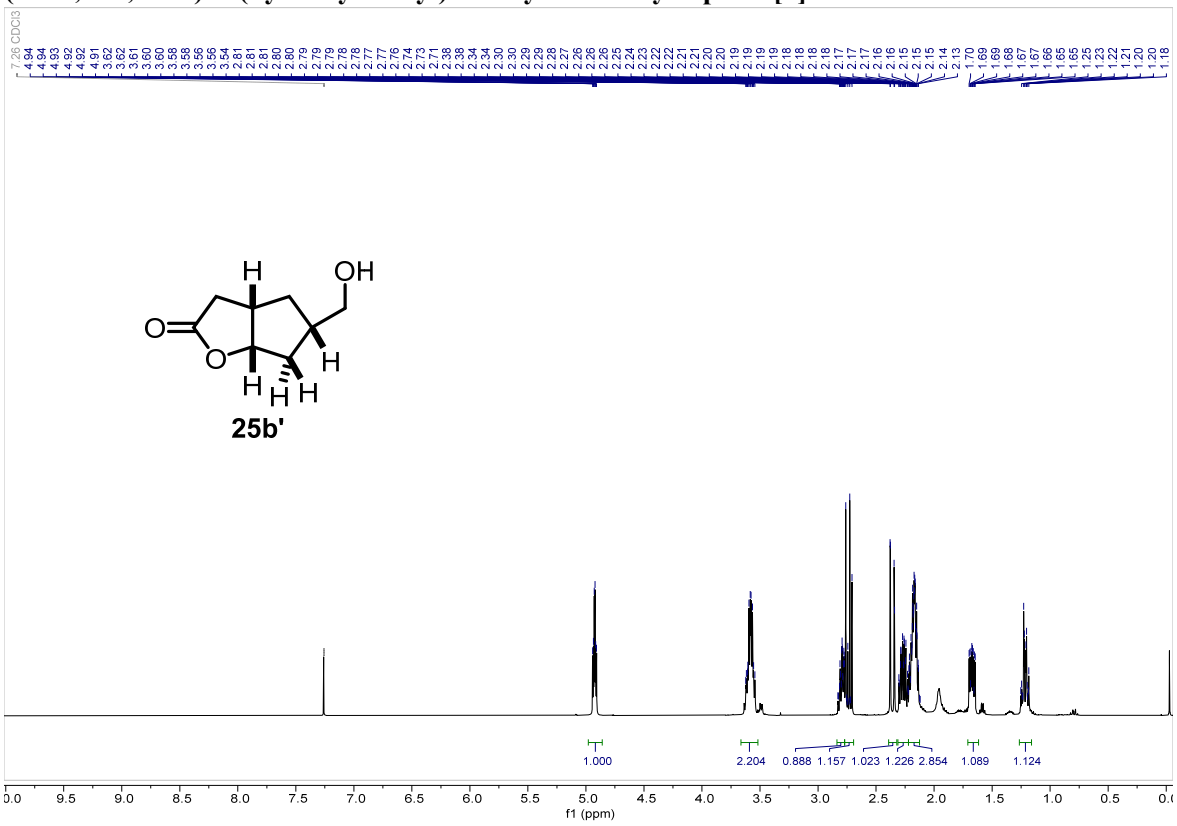


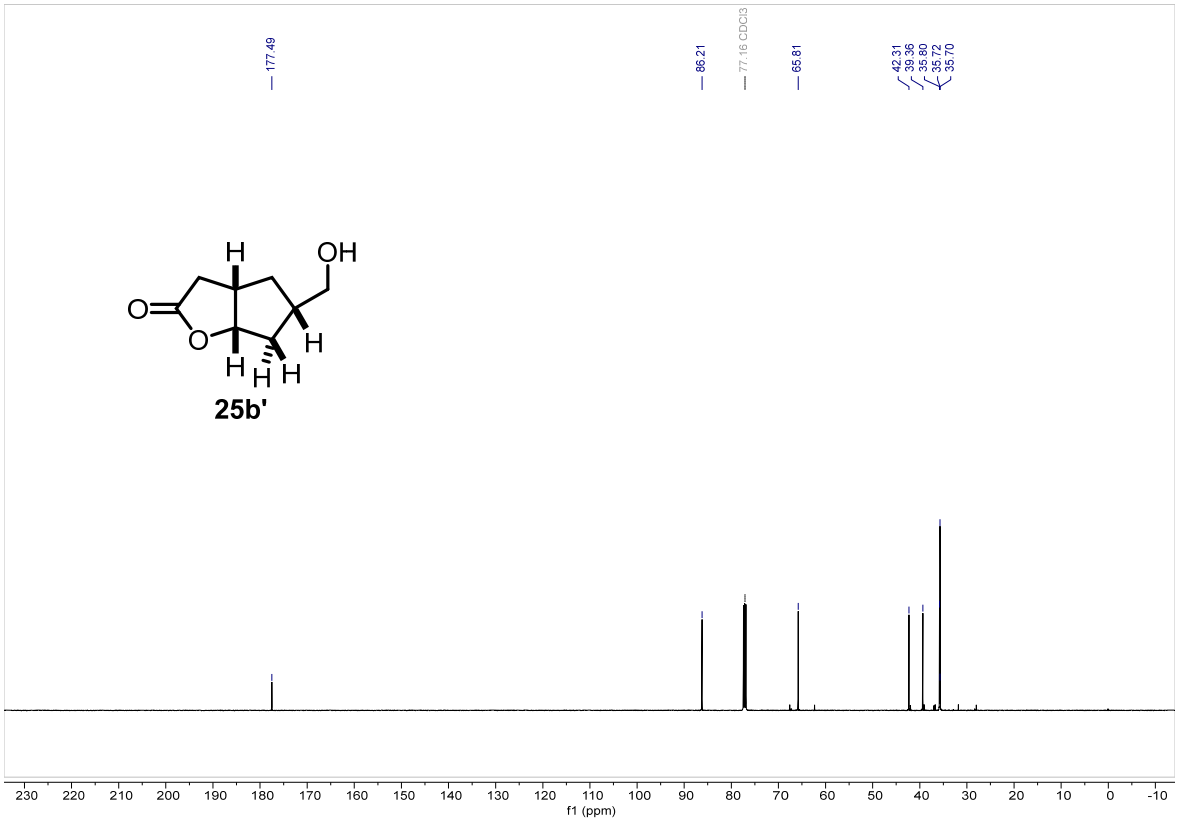
(3*aS,5*S**,6*aS**)-2-Oxohexahydro-2*H*-cyclopenta[*b*]furan-5-carboxylic acid 25b**



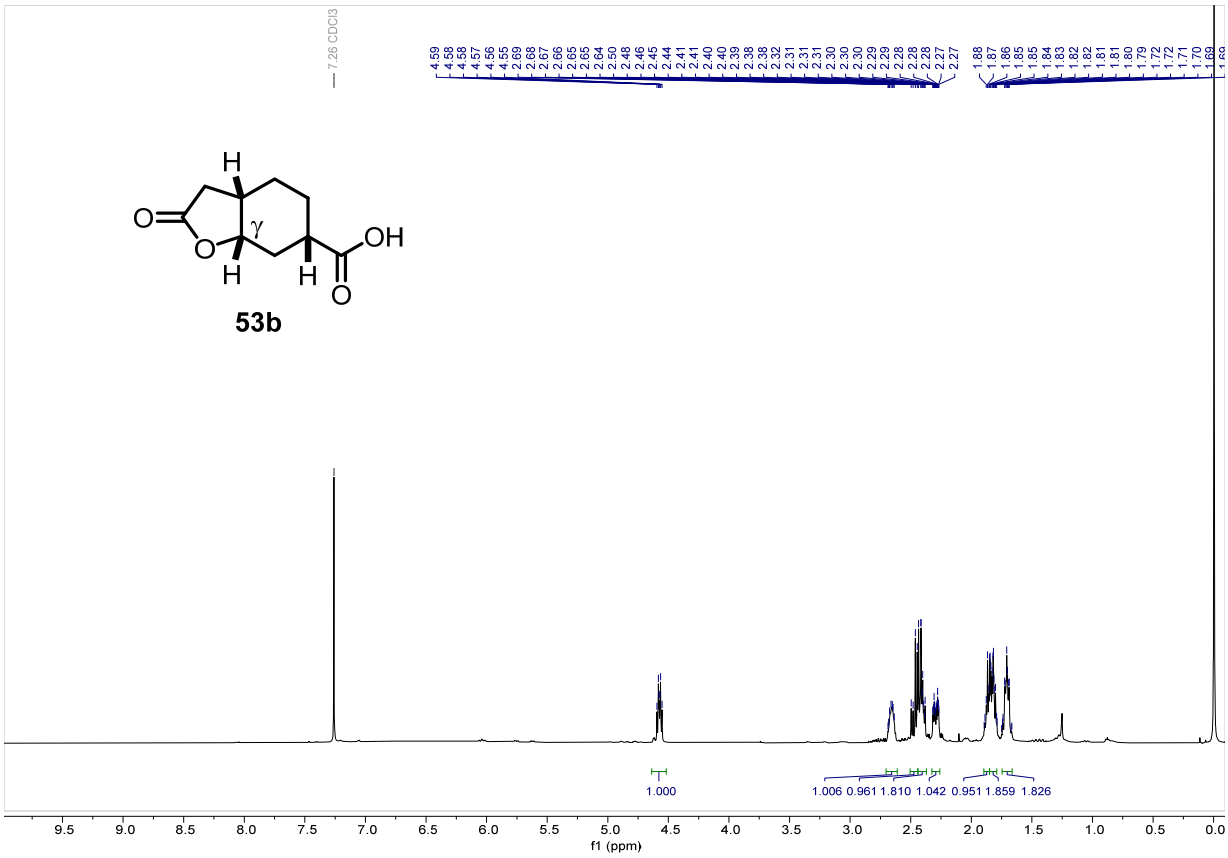


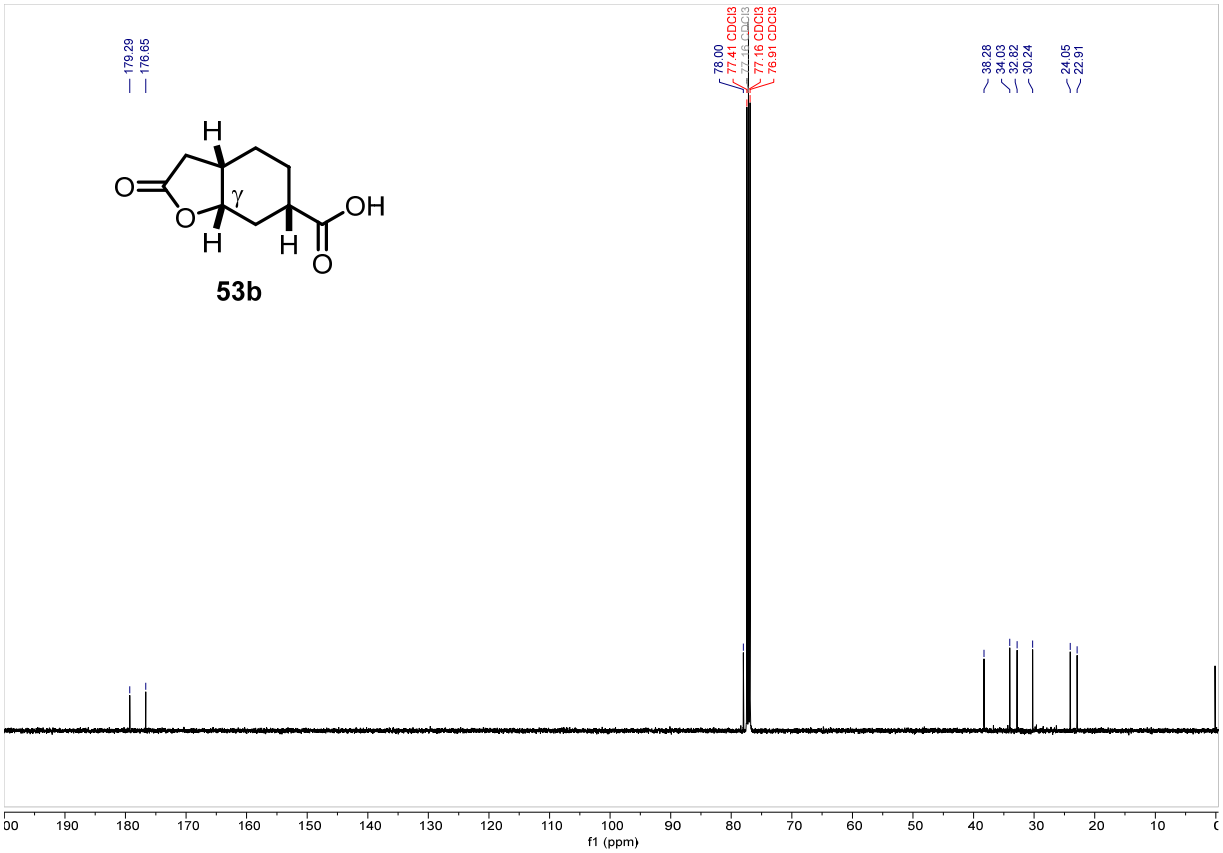
(3*aS,5*S**,6*aS**)-5-(hydroxymethyl)hexahydro-2*H*-cyclopenta[*b*]furan-2-one 25b'**



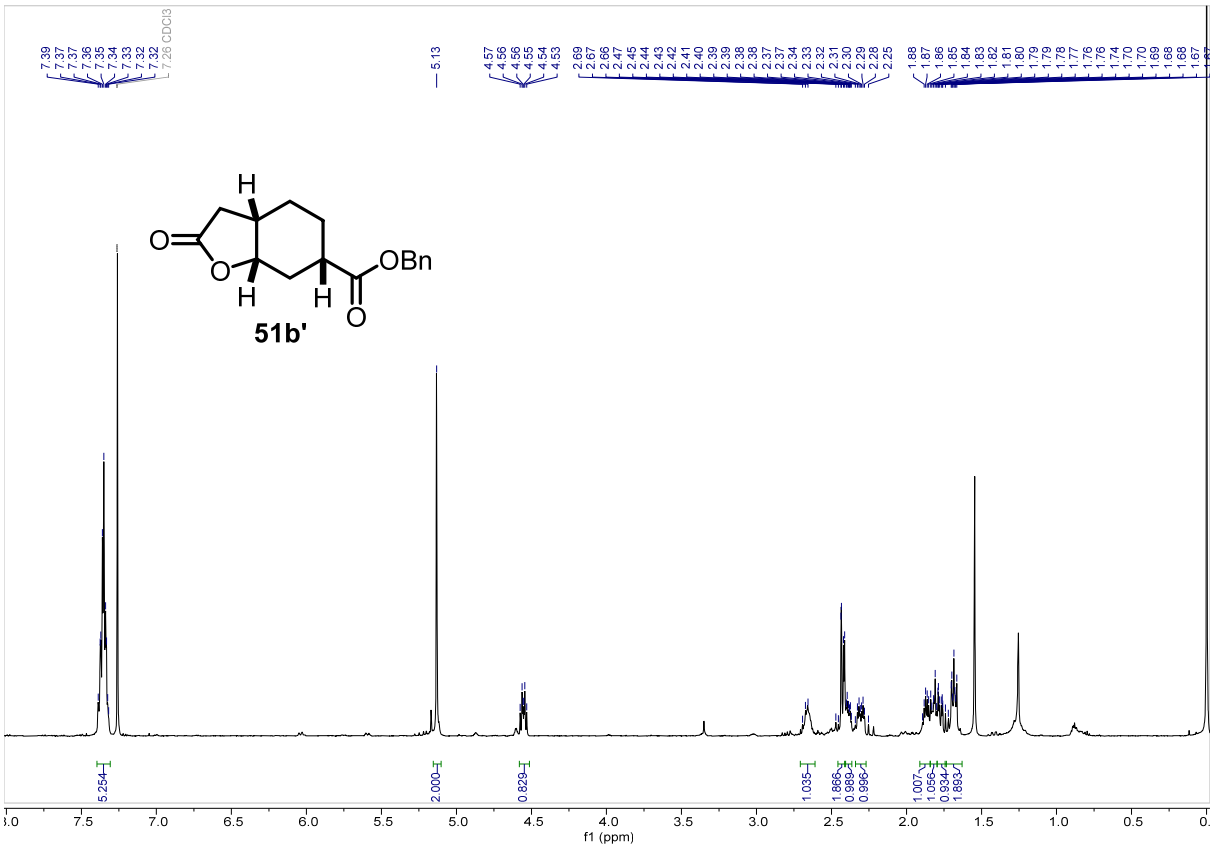


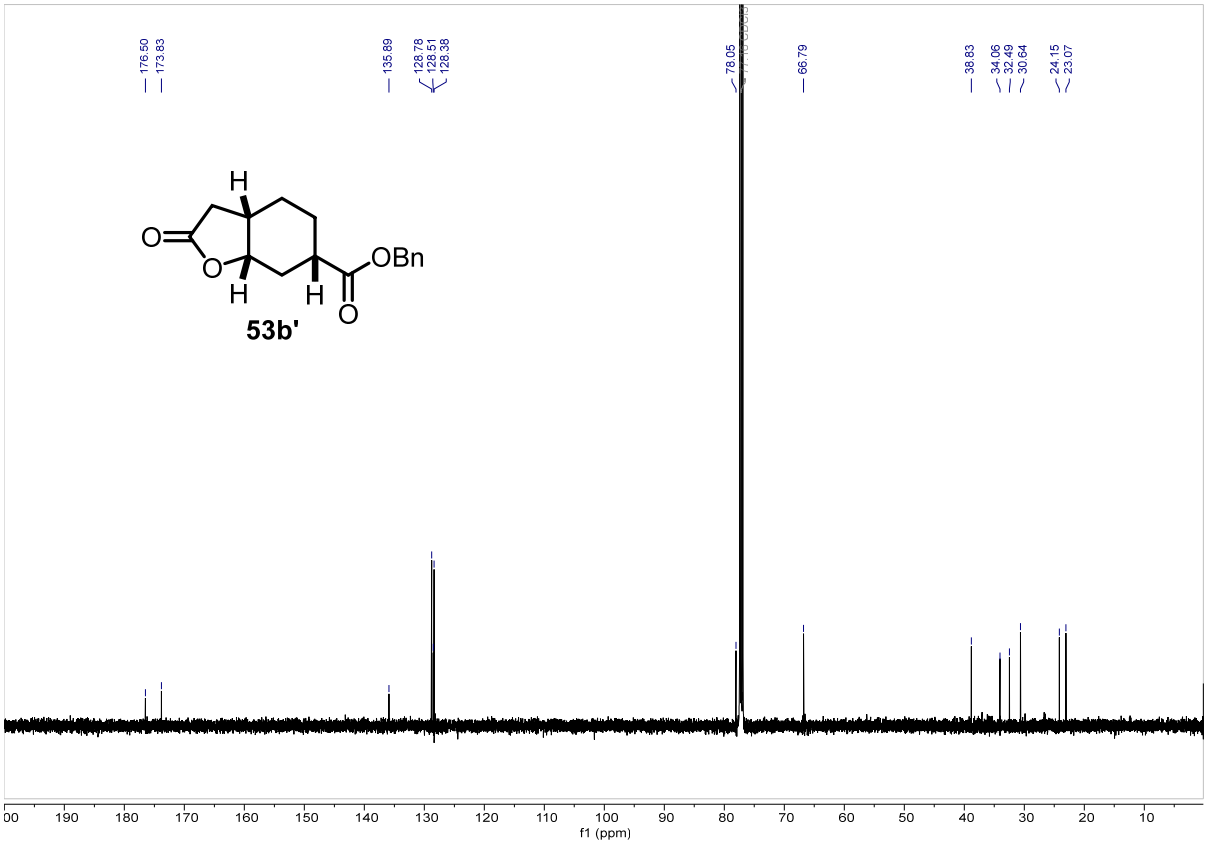
(3*aS,6*S**,7*aS**)-2-Oxooctahydrobenzofuran-6-carboxylic acid 53b**



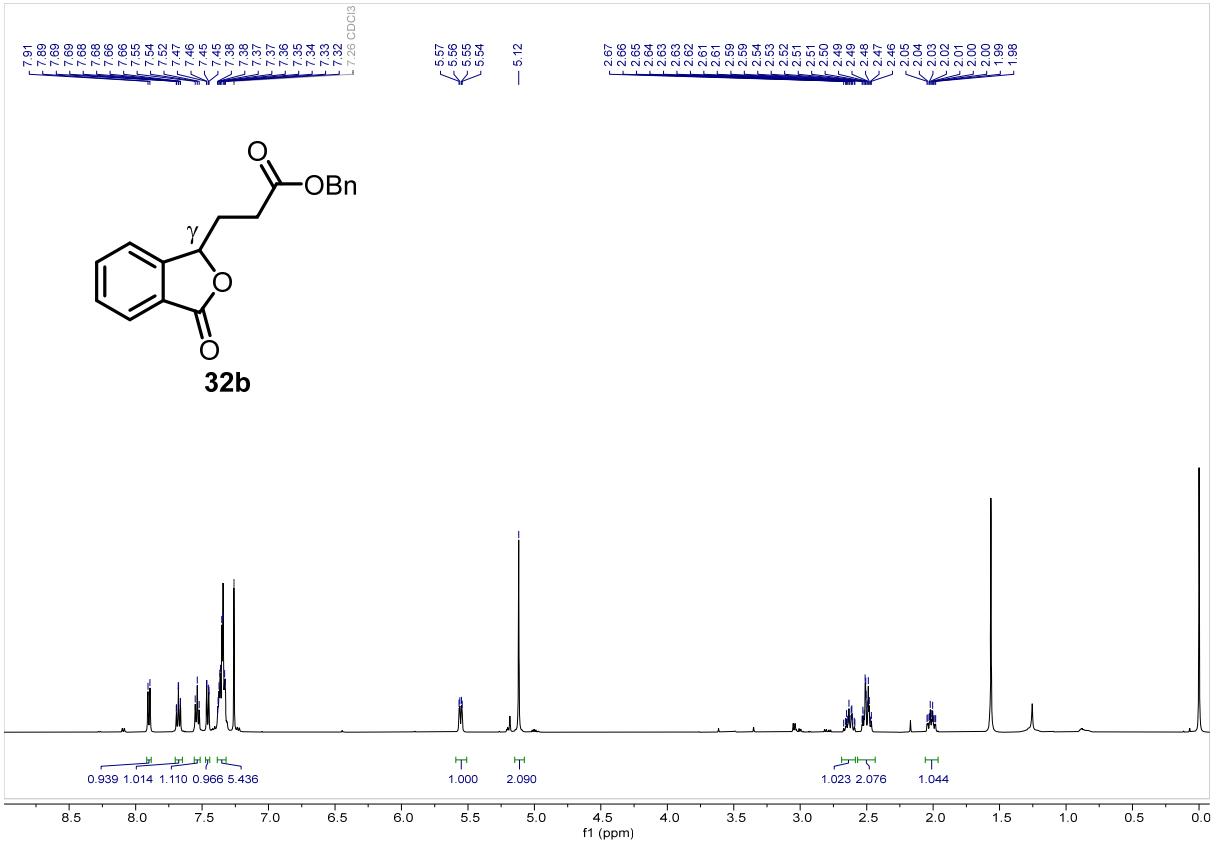


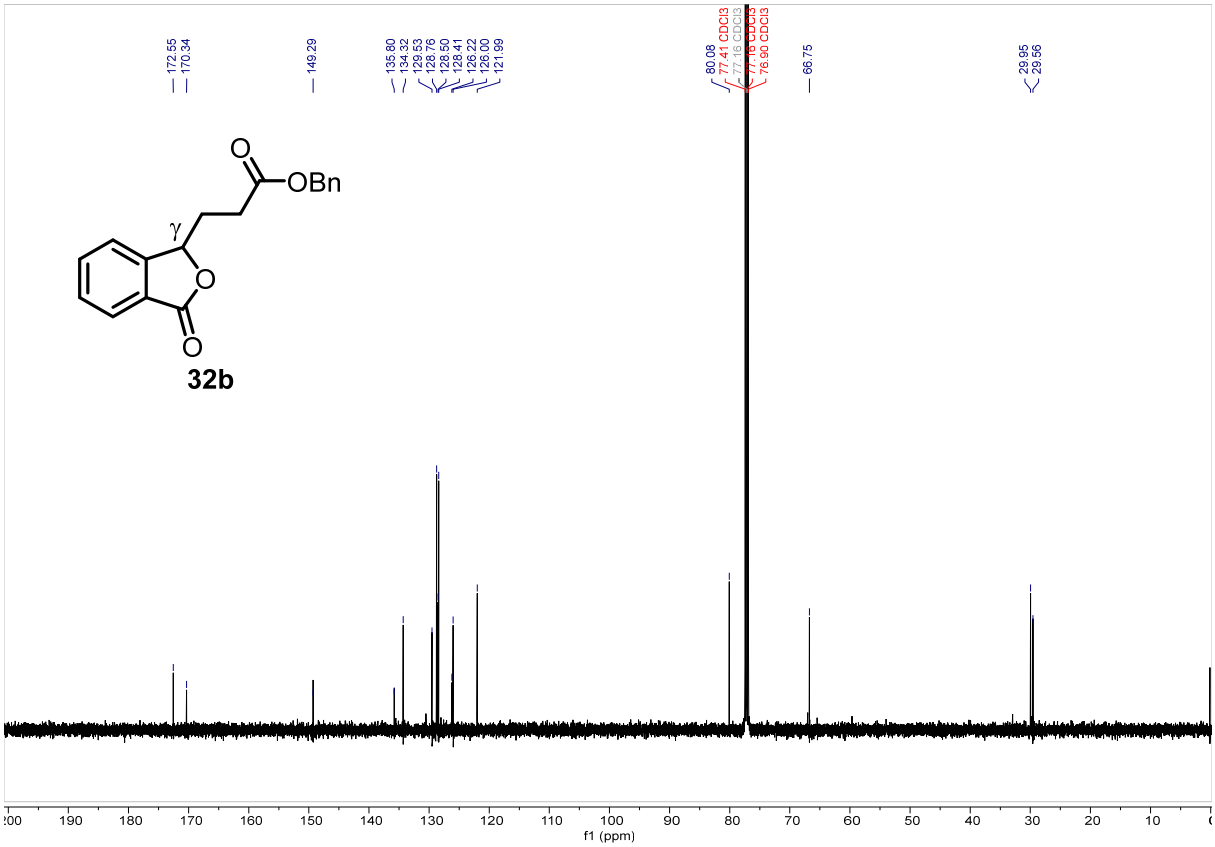
Benzyl (3*aS,6*S**,7a*S**)-2-oxooctahydrobenzofuran-6-carboxylate 53b'**



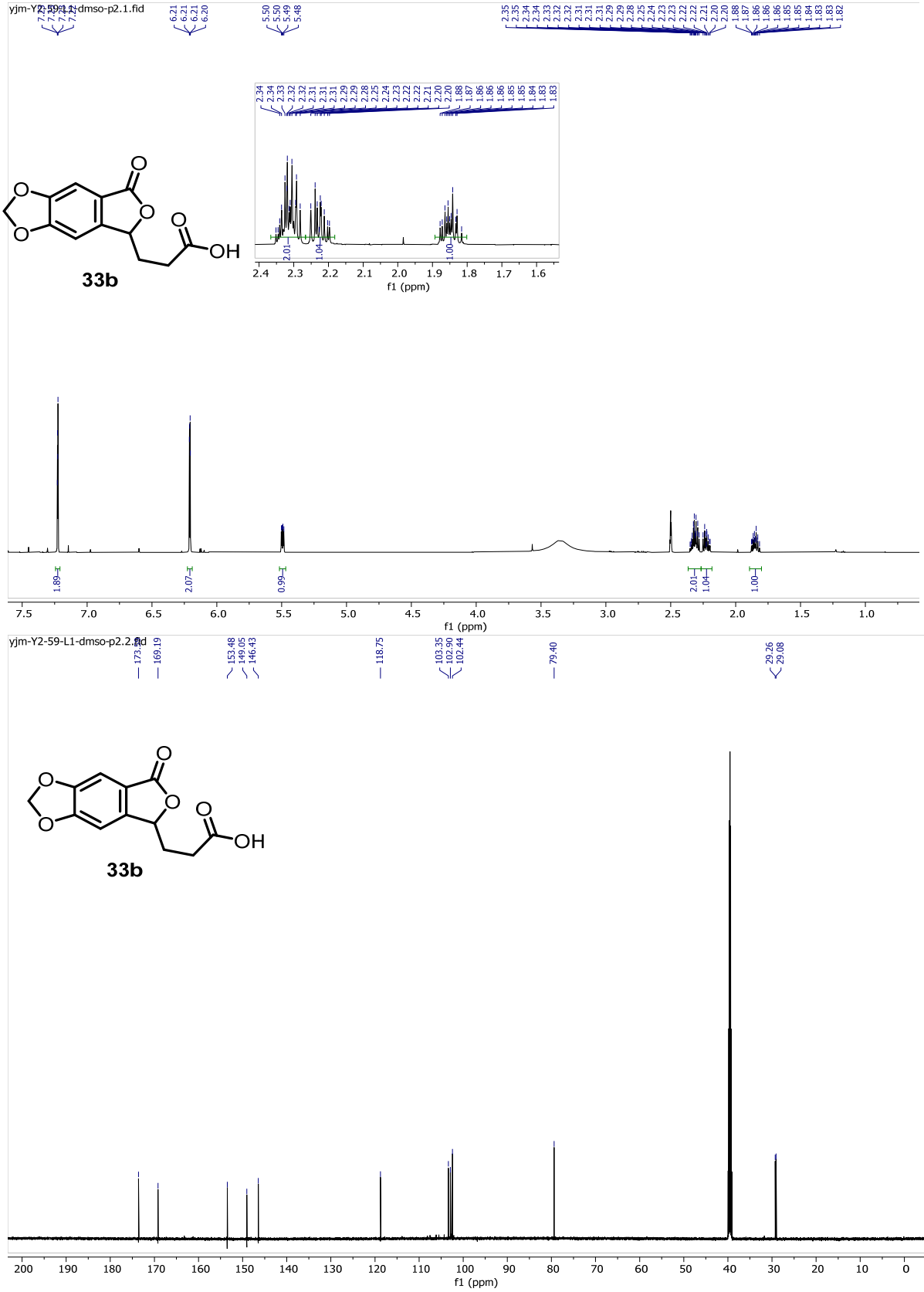


Benzyl 3-(3-oxo-1,3-dihydroisobenzofuran-1-yl)propanoate 32b

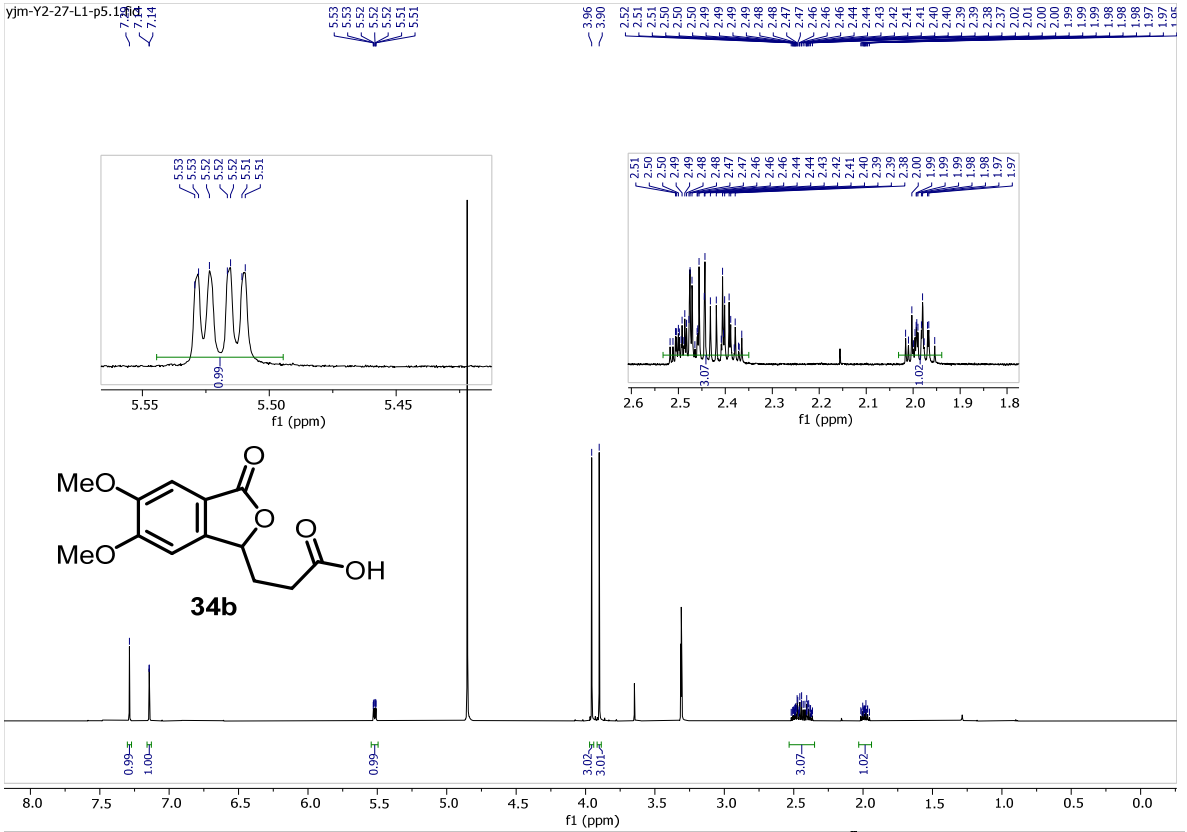


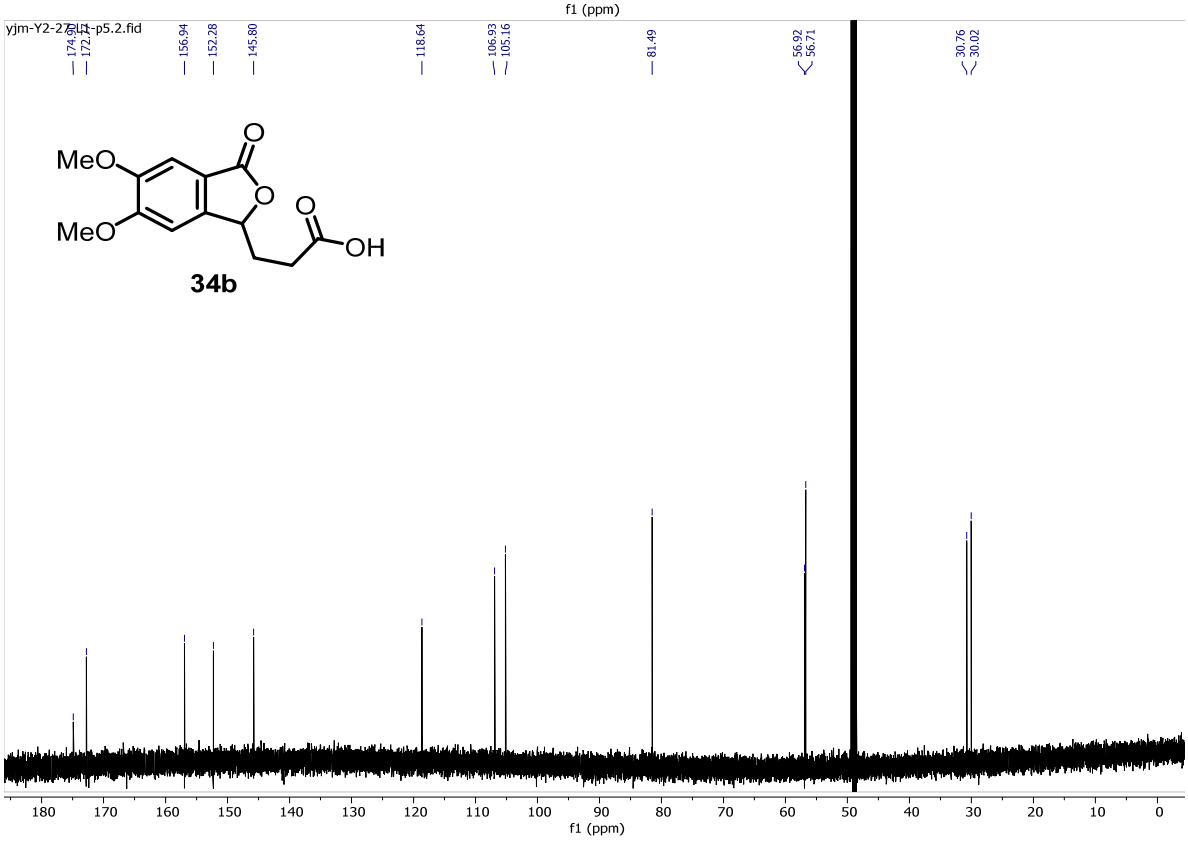


3-(7-Oxo-5,7-dihydro-[1,3]dioxolo[4,5-*f*]isobenzofuran-5-yl)propanoic acid 33b

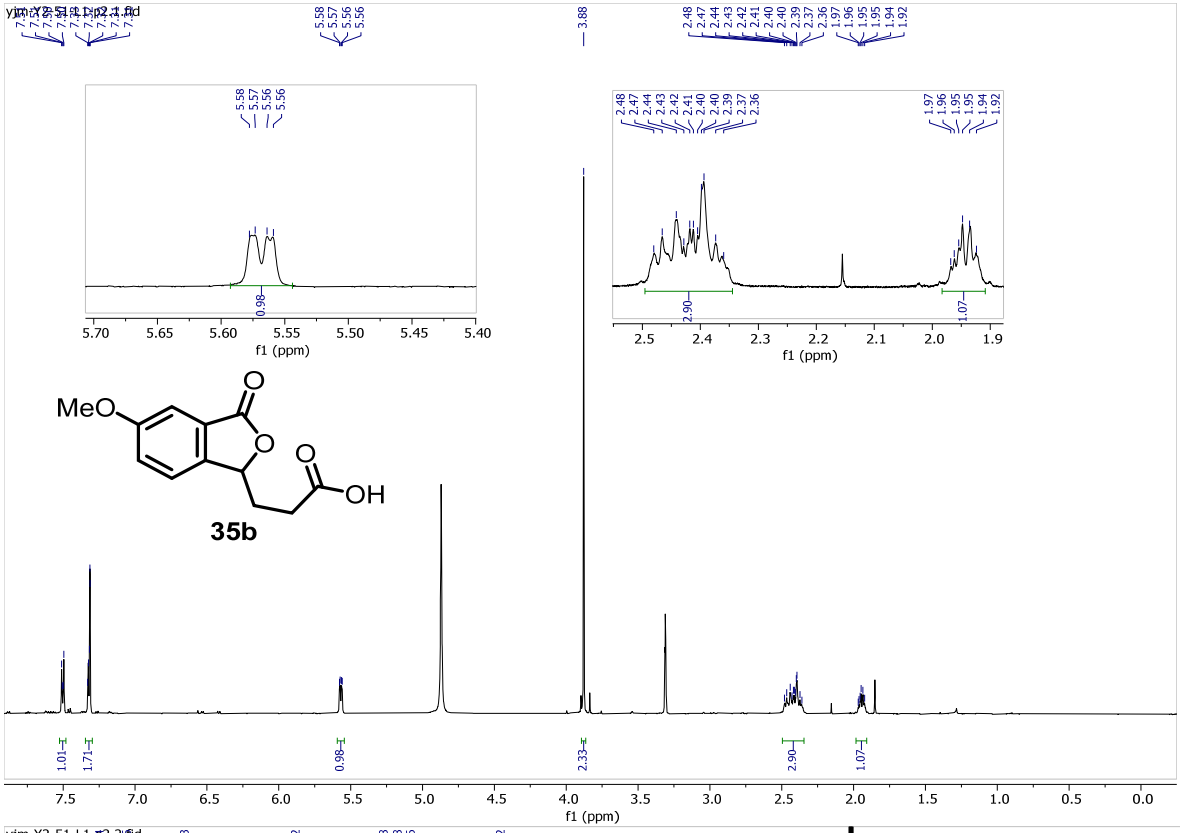


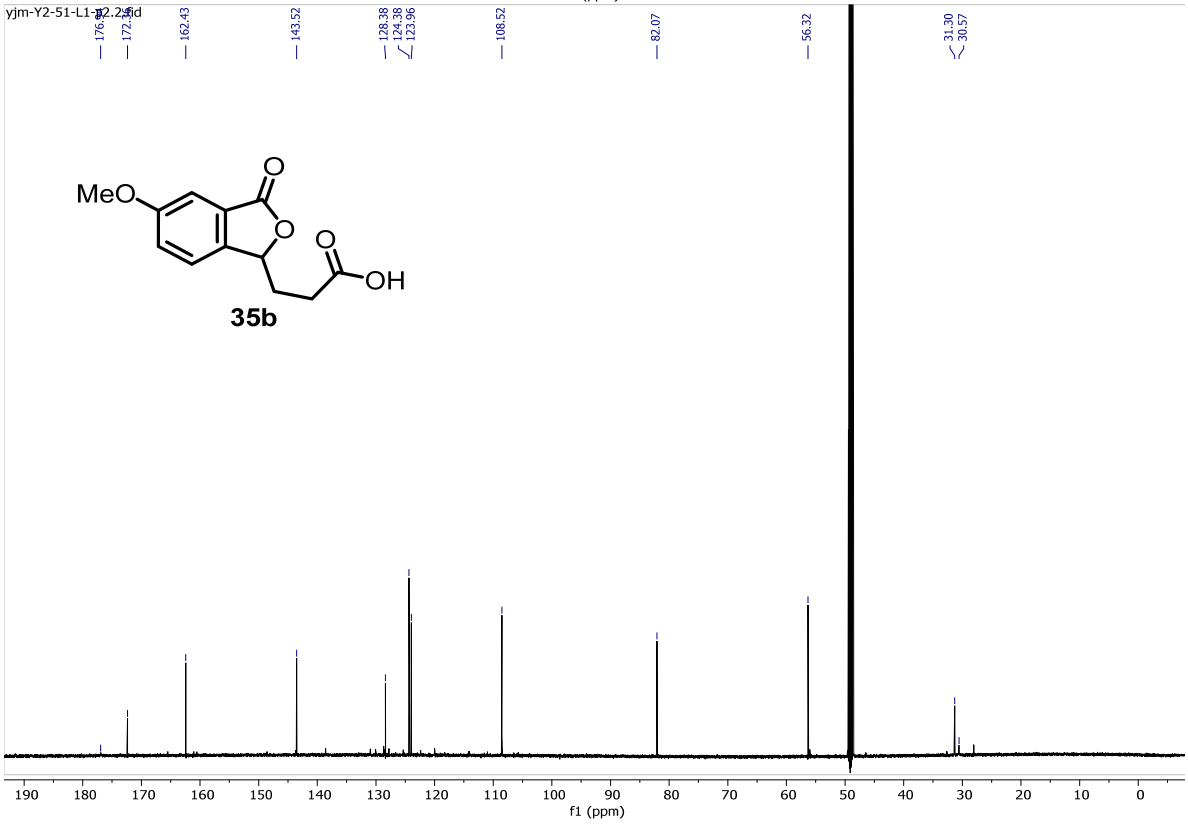
3-(5,6-Dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)propanoic acid 34b



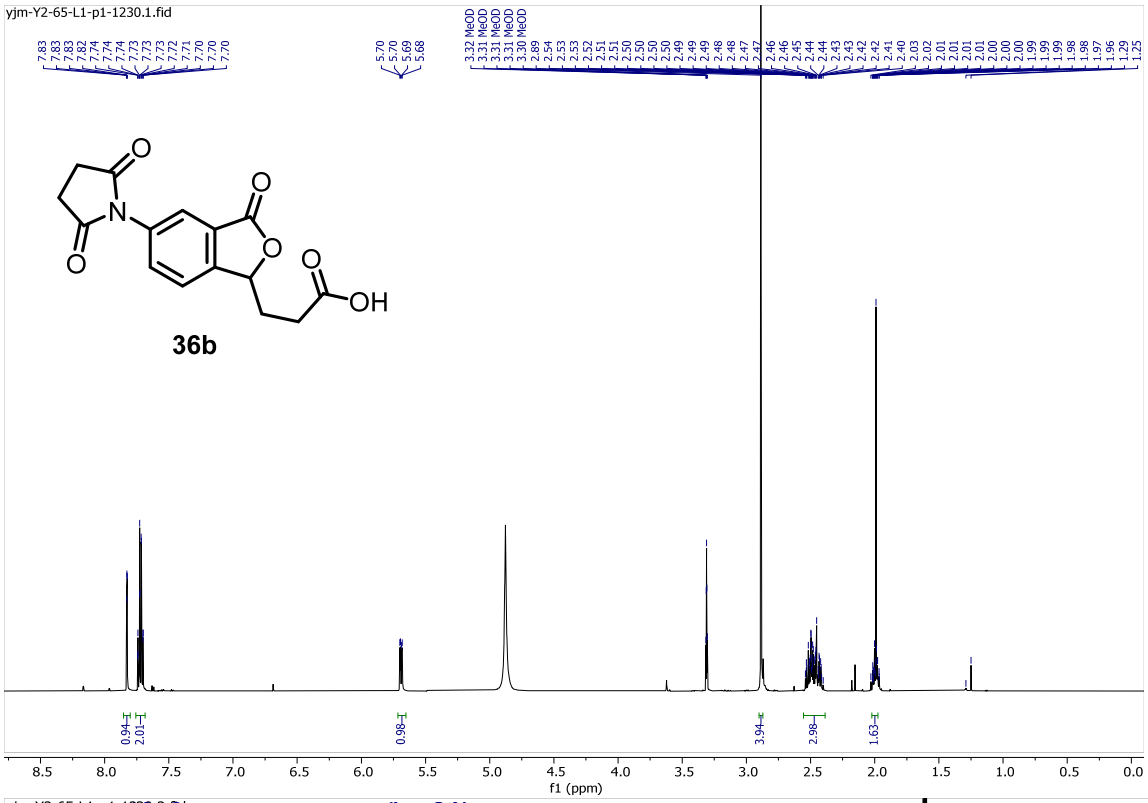


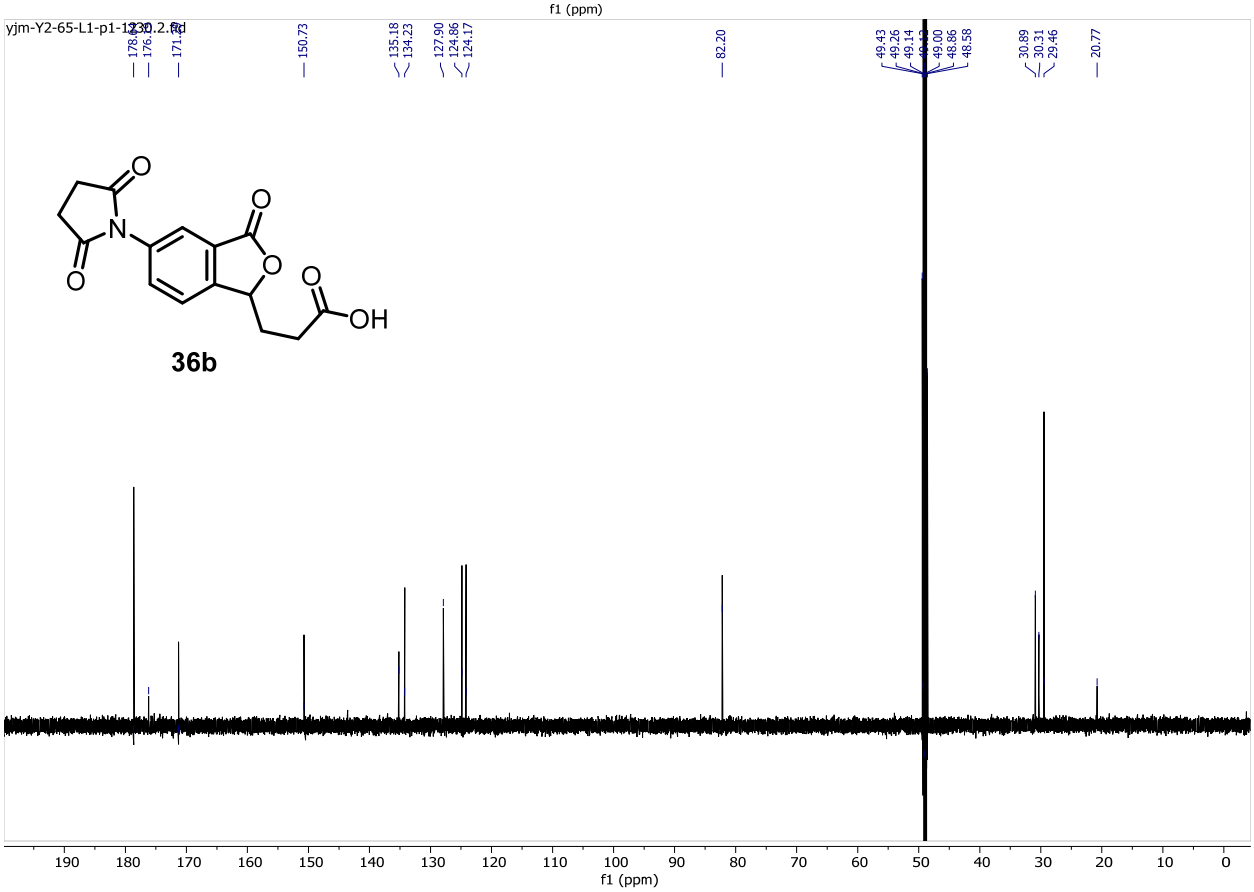
3-(5-Methoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)propanoic acid 35b



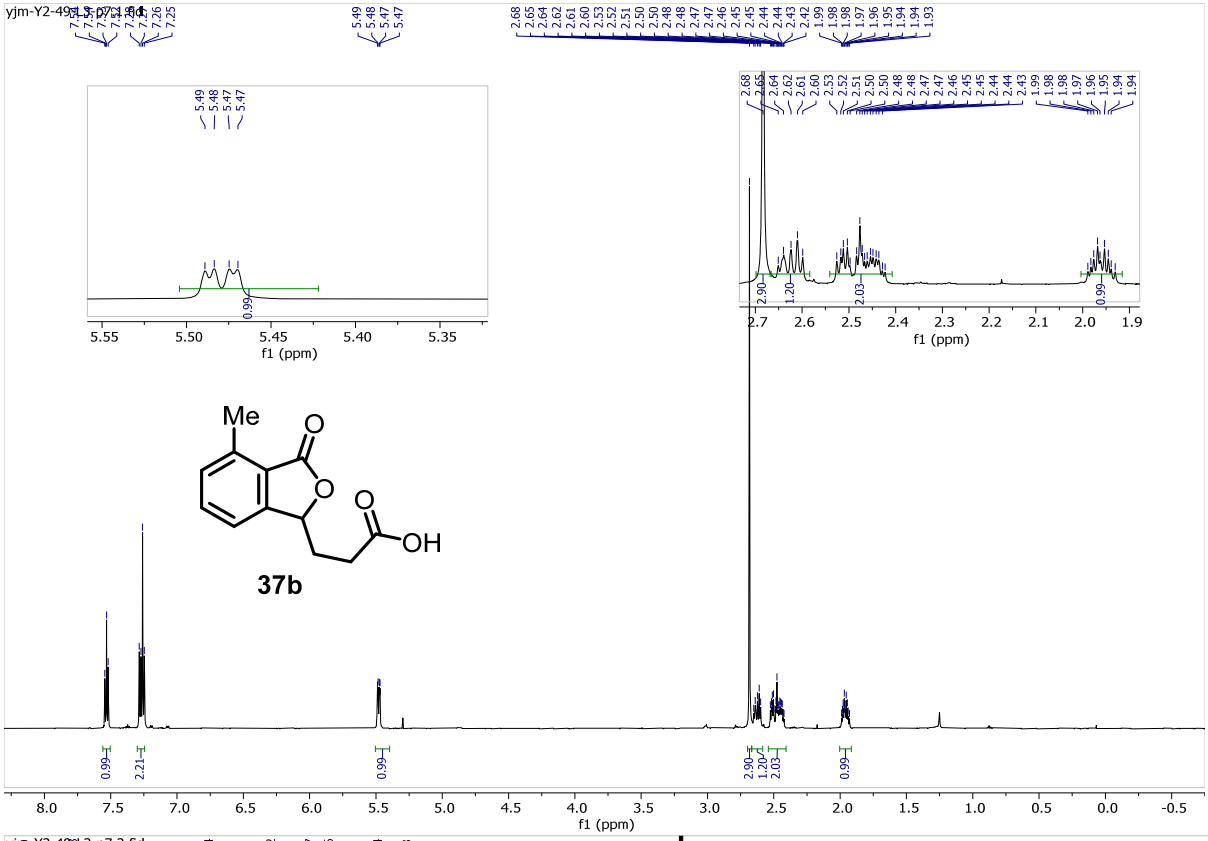


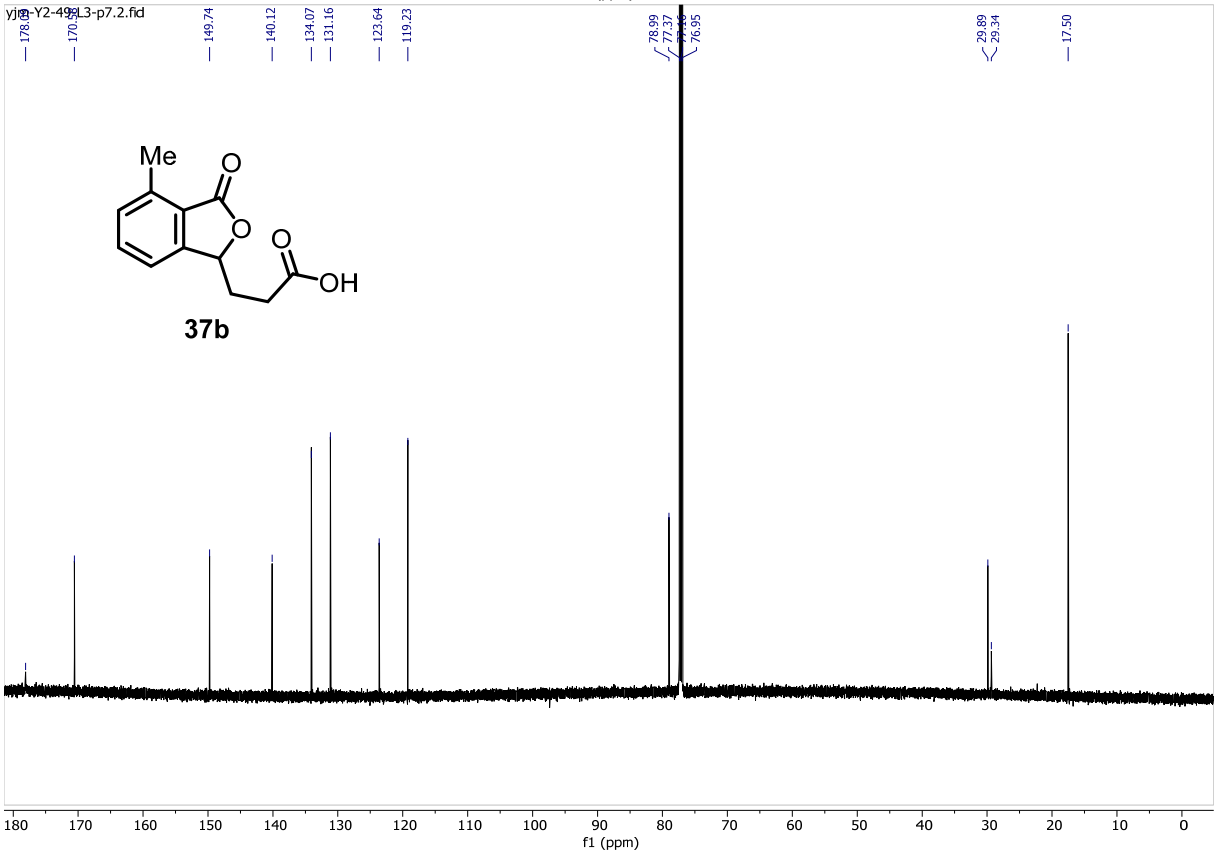
3-(6-(2,5-Dioxopyrrolidin-1-yl)-3-oxo-1,3-dihydroisobenzofuran-1-yl)propanoic acid 36b



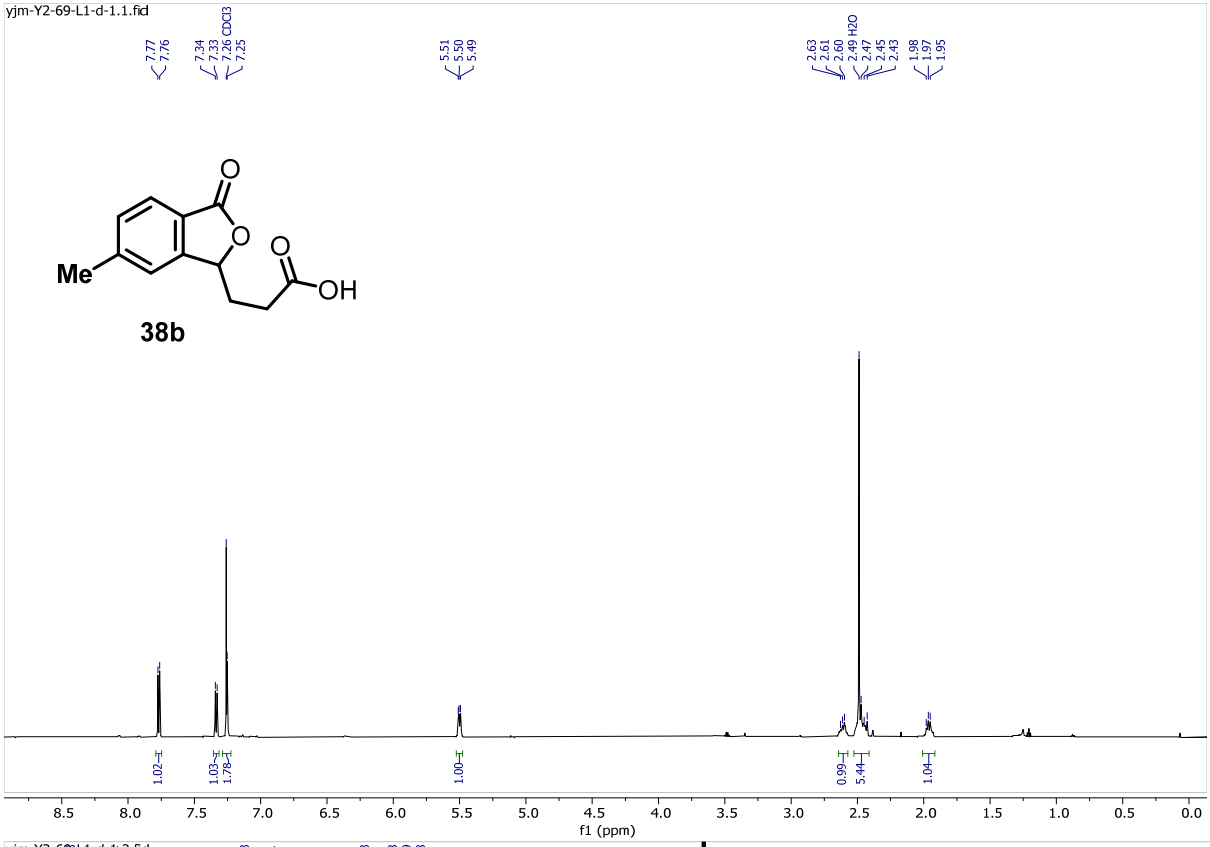


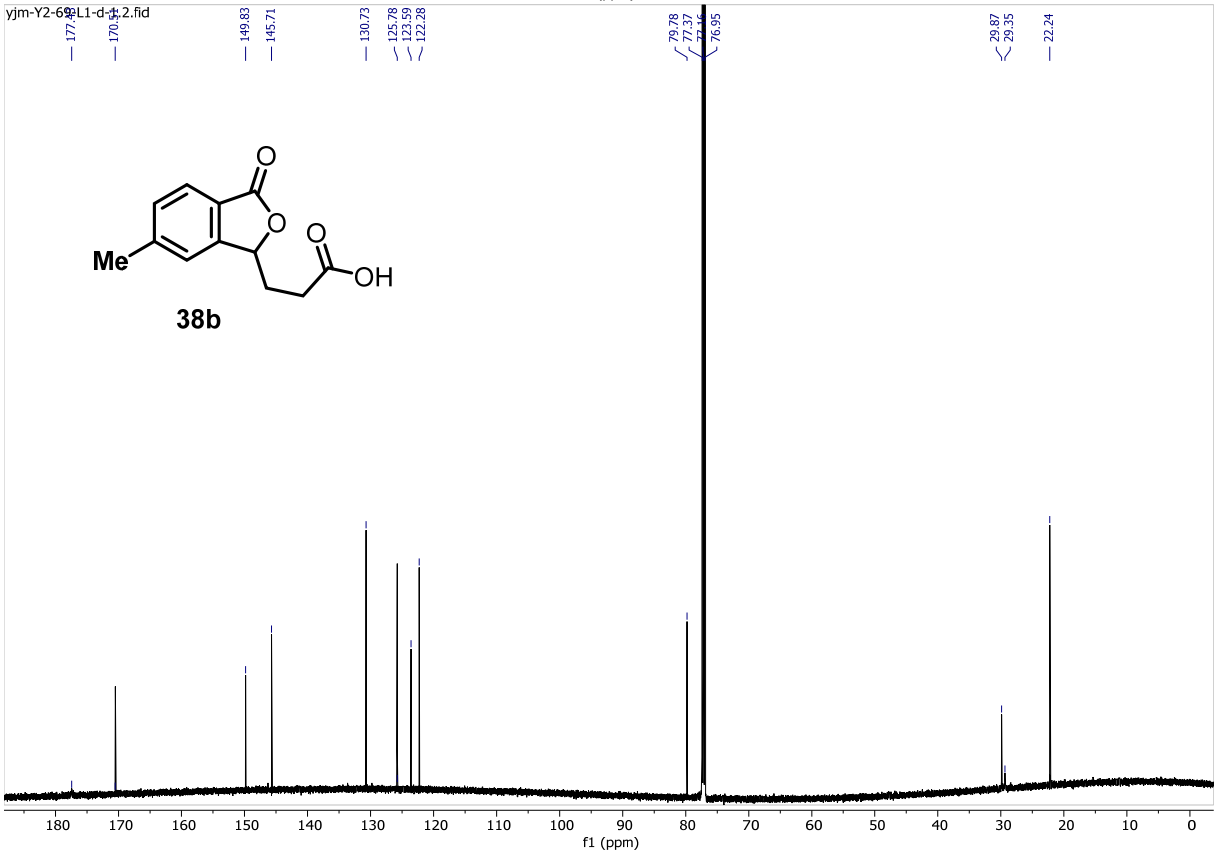
3-(4-Methyl-3-oxo-1,3-dihydroisobenzofuran-1-yl)propanoic acid 37b



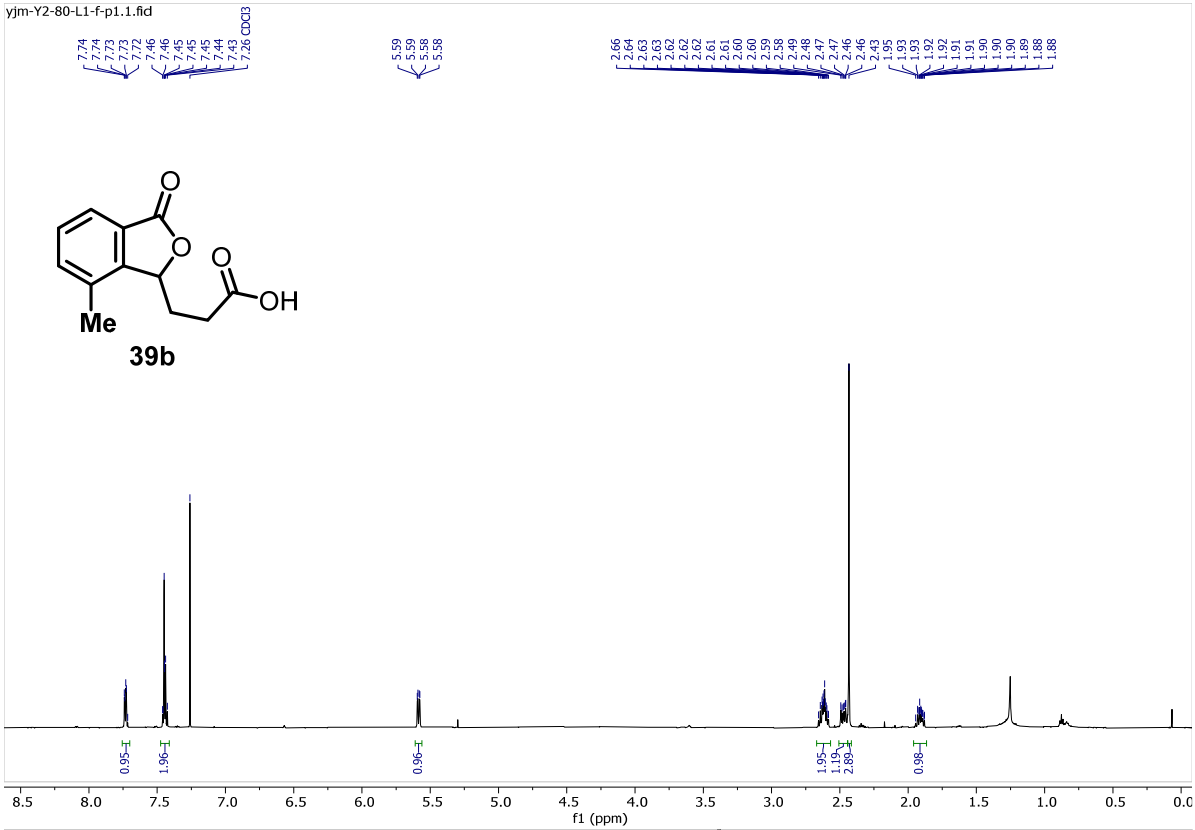


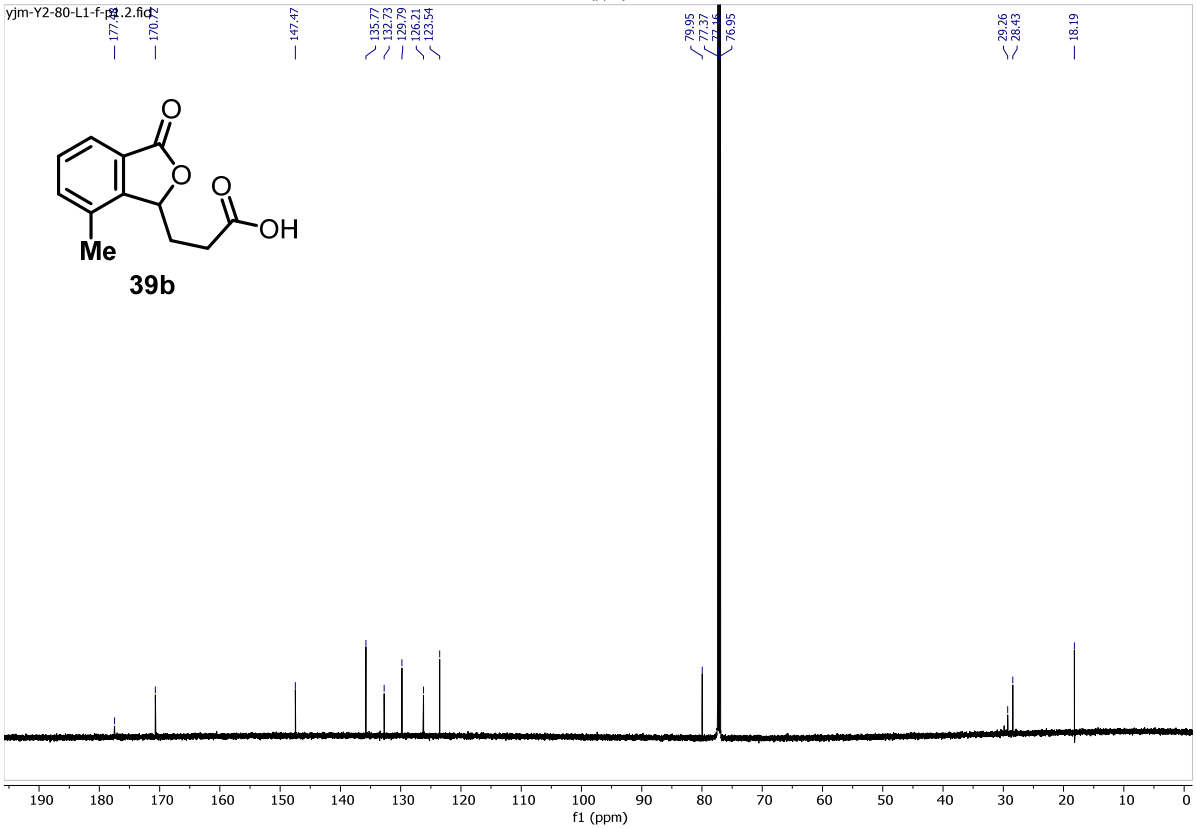
3-(6-Methyl-3-oxo-1,3-dihydroisobenzofuran-1-yl)propanoic acid 38b



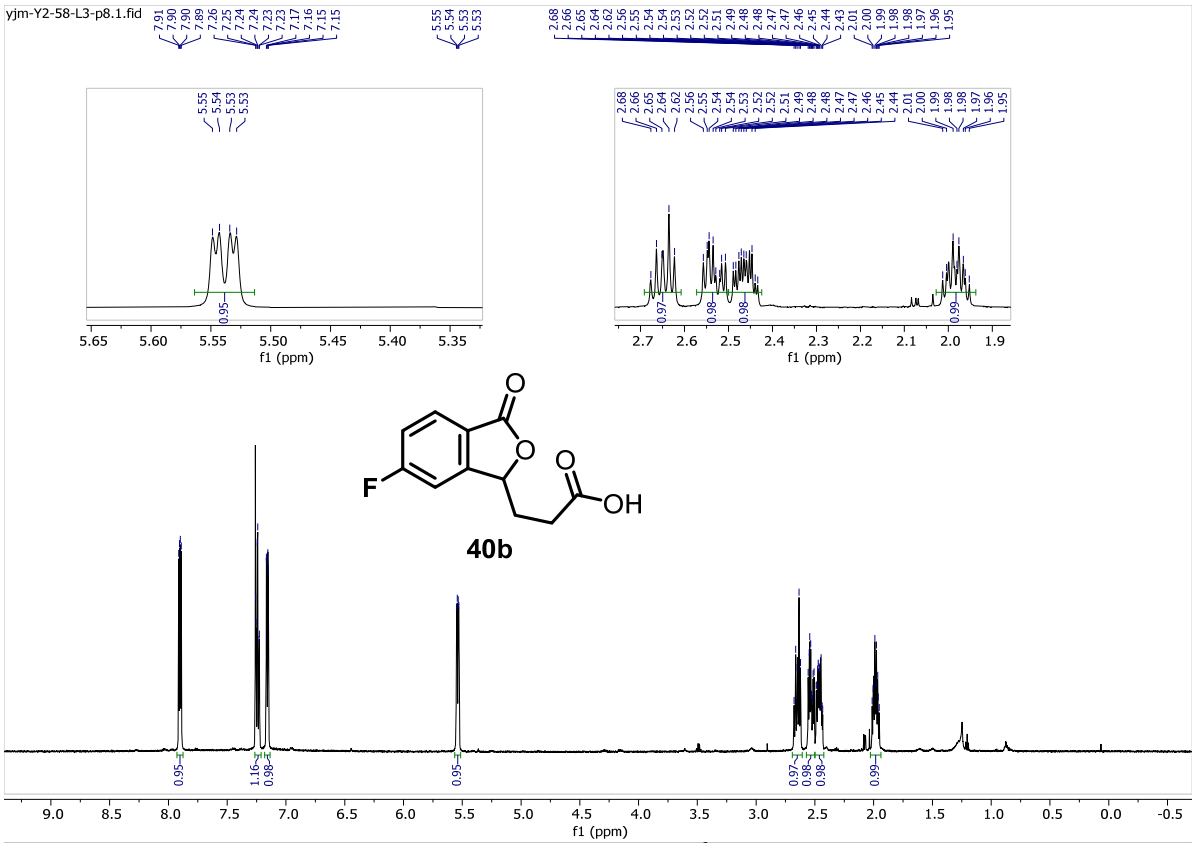


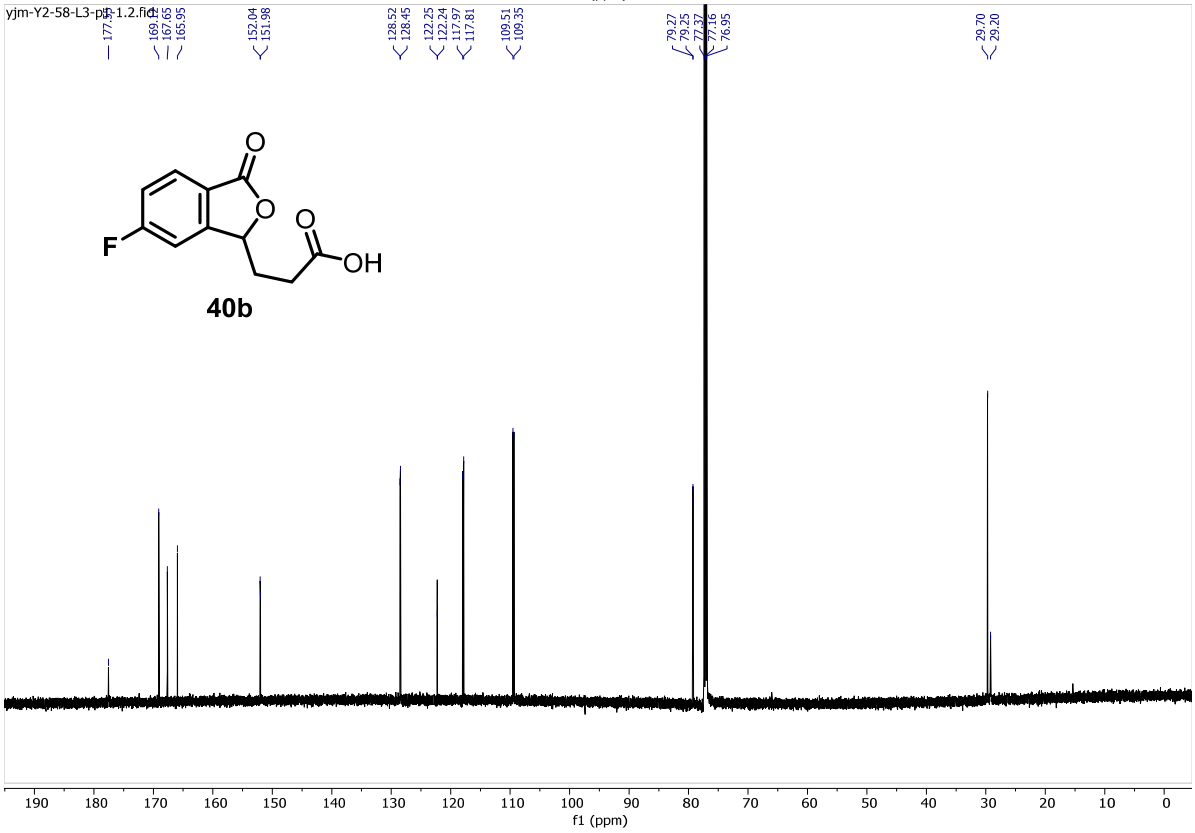
3-(7-Methyl-3-oxo-1,3-dihydroisobenzofuran-1-yl)propanoic acid 39b

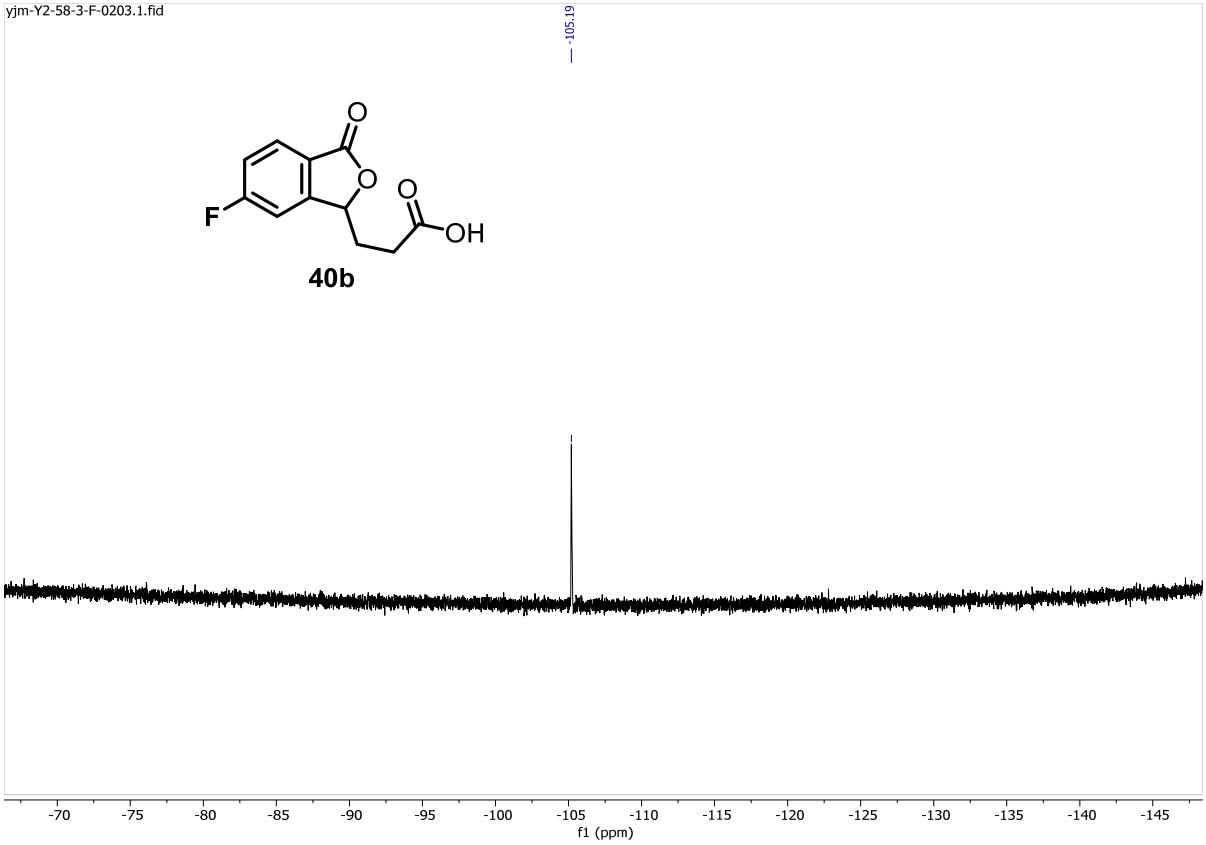




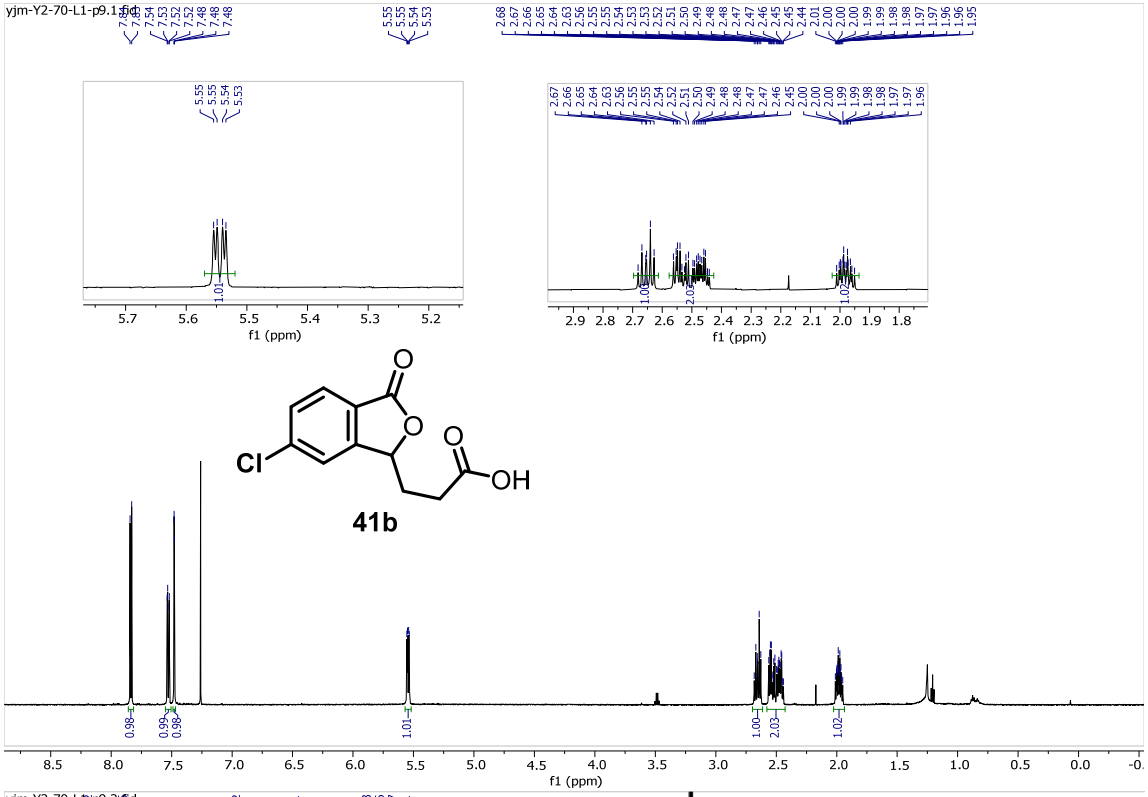
3-(6-Fluoro-3-oxo-1,3-dihydroisobenzofuran-1-yl)propanoic acid 40b

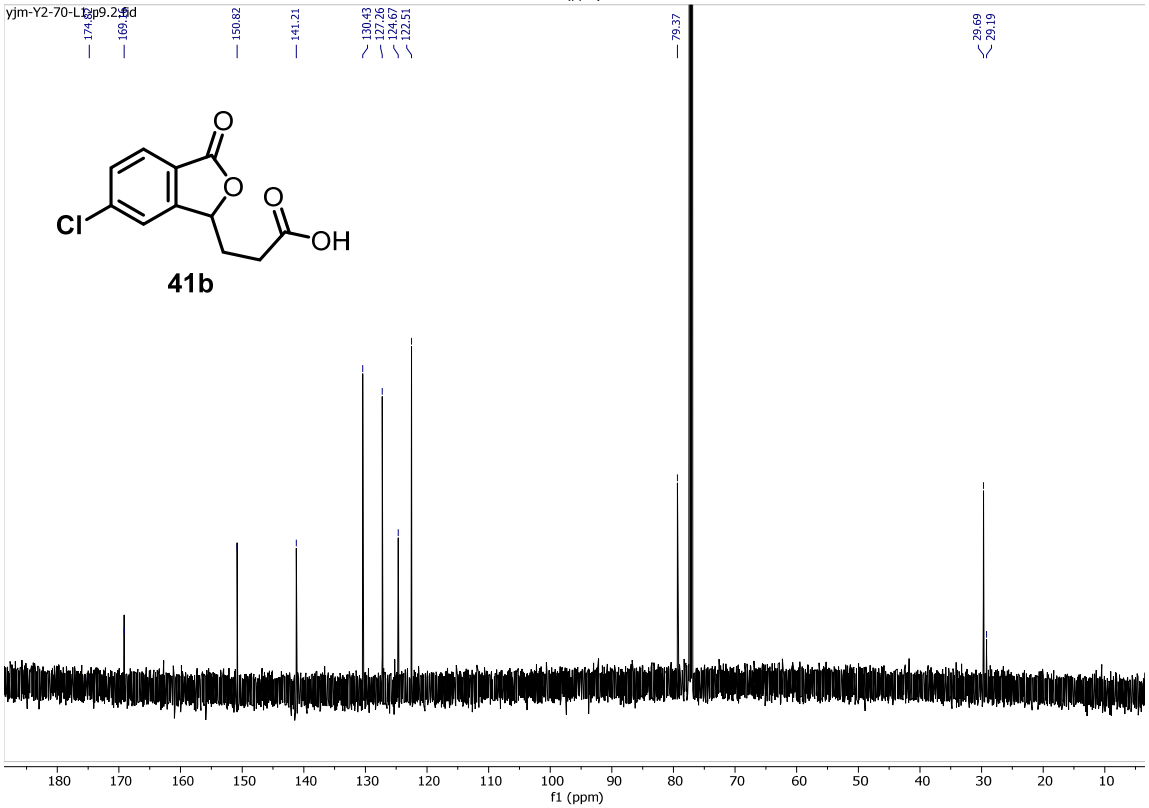




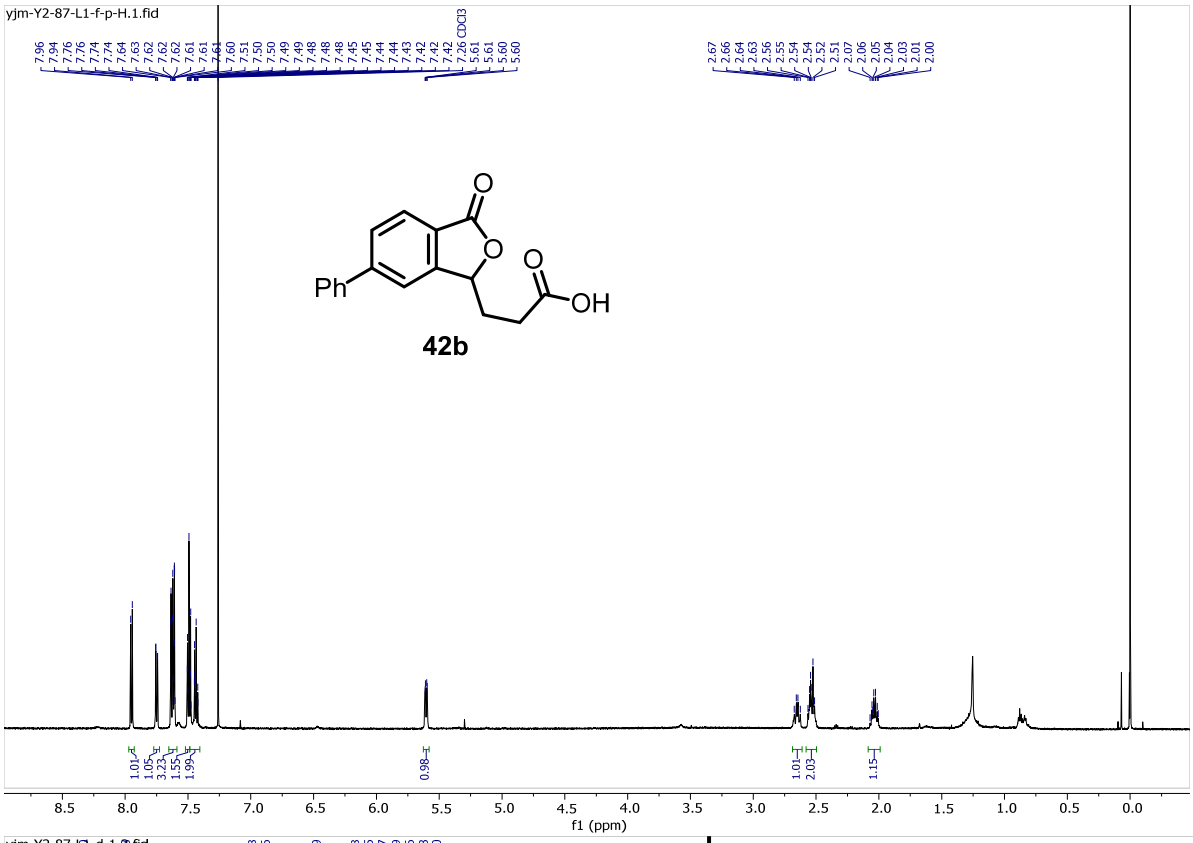

yjm-Y2-58-3-F-0203.1.fid
-105.19
O
O
O
OH
F
40b
-70
-75
-80
-85
-90
-95
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
f1 (ppm)

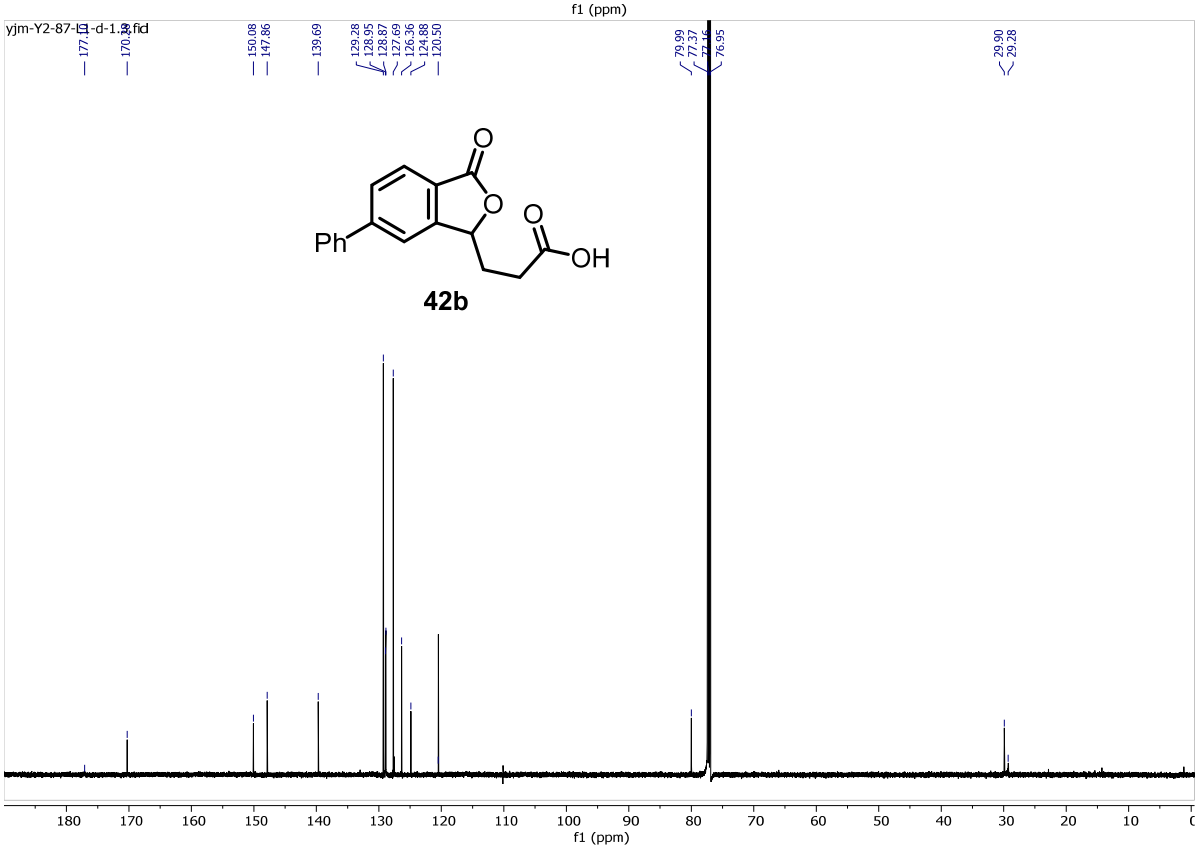
3-(6-Chloro-3-oxo-1,3-dihydroisobenzofuran-1-yl)propanoic acid 41b



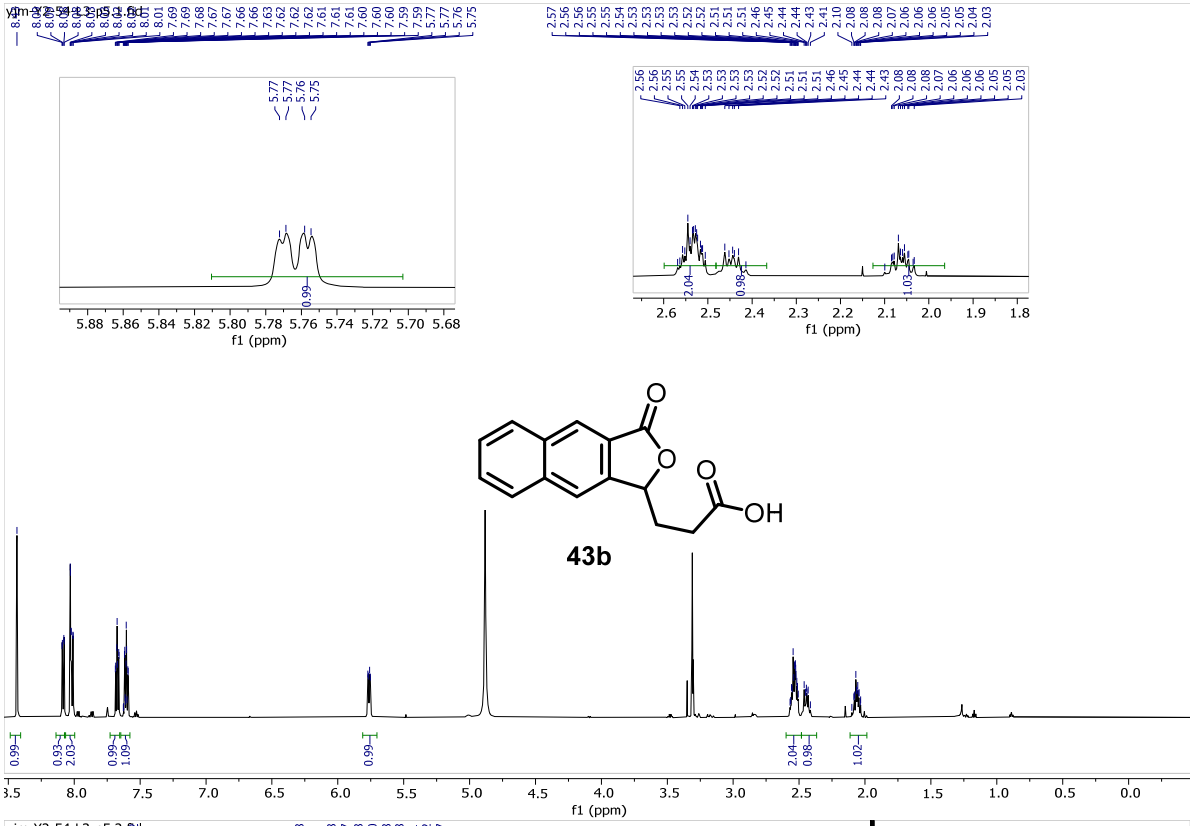


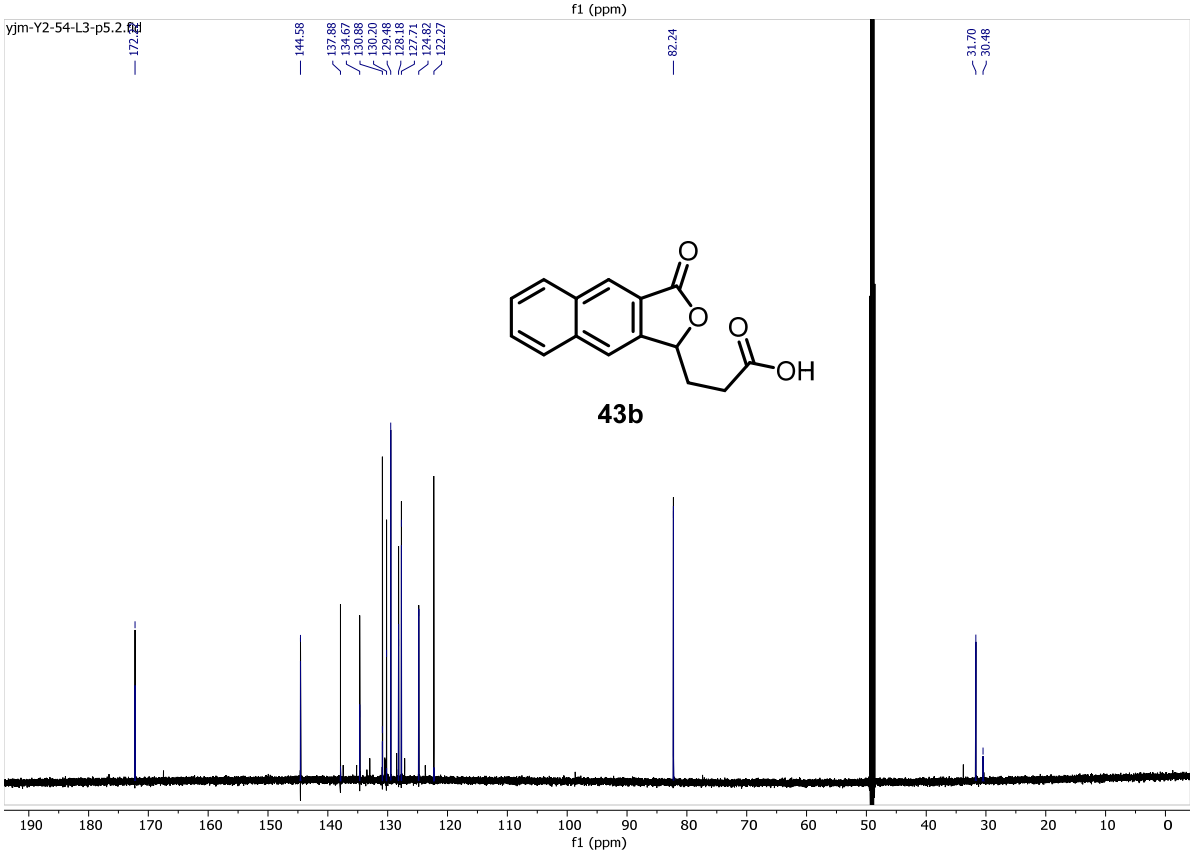
3-(3-Oxo-6-phenyl-1,3-dihydroisobenzofuran-1-yl)propanoic acid 42b



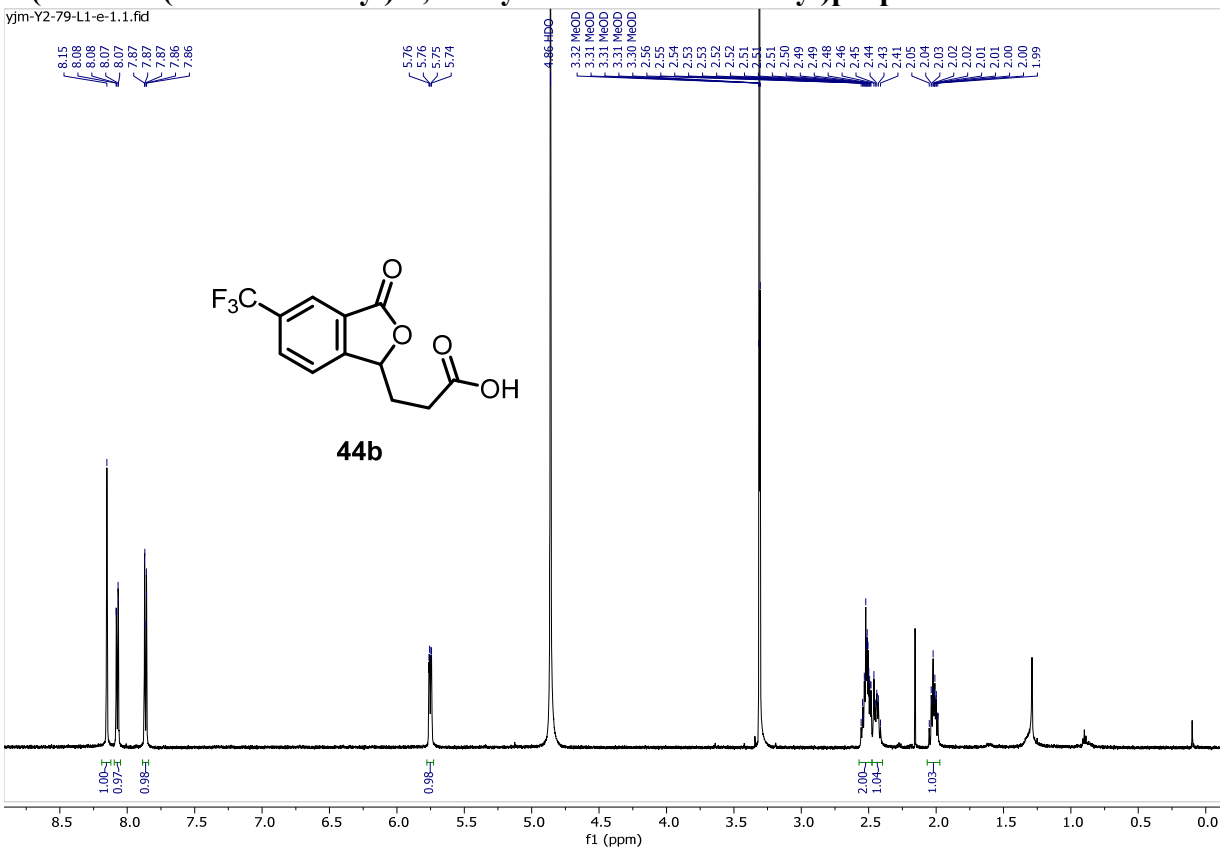


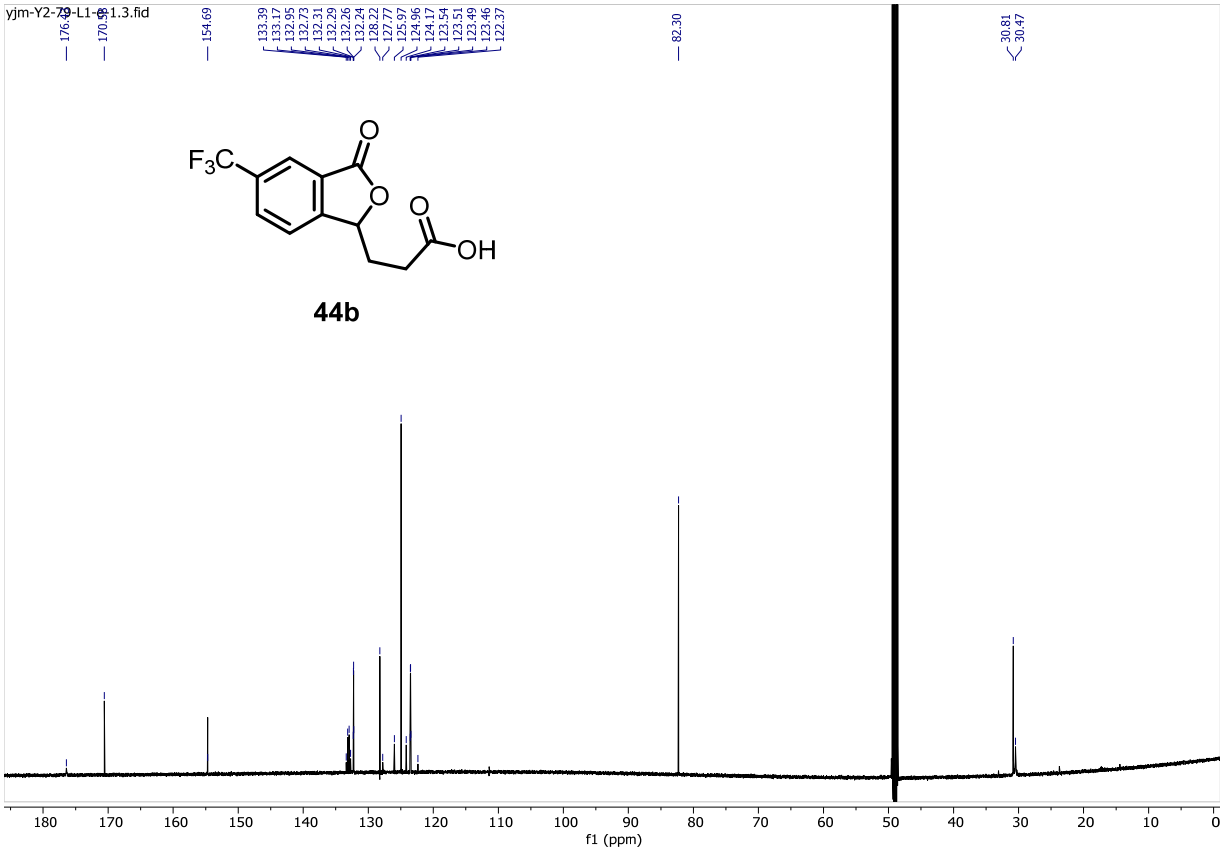
3-(3-Oxo-1,3-dihydronaphtho[2,3-*c*]furan-1-yl)propanoic acid 43b

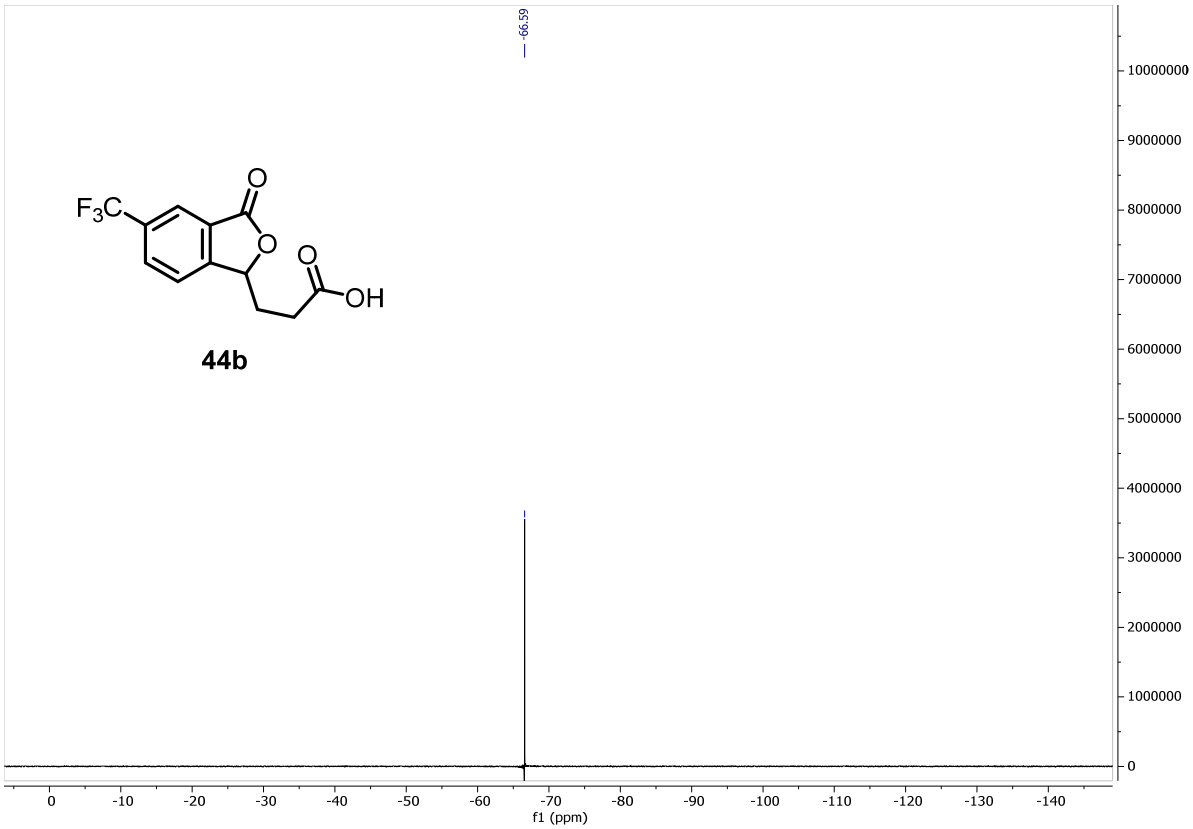




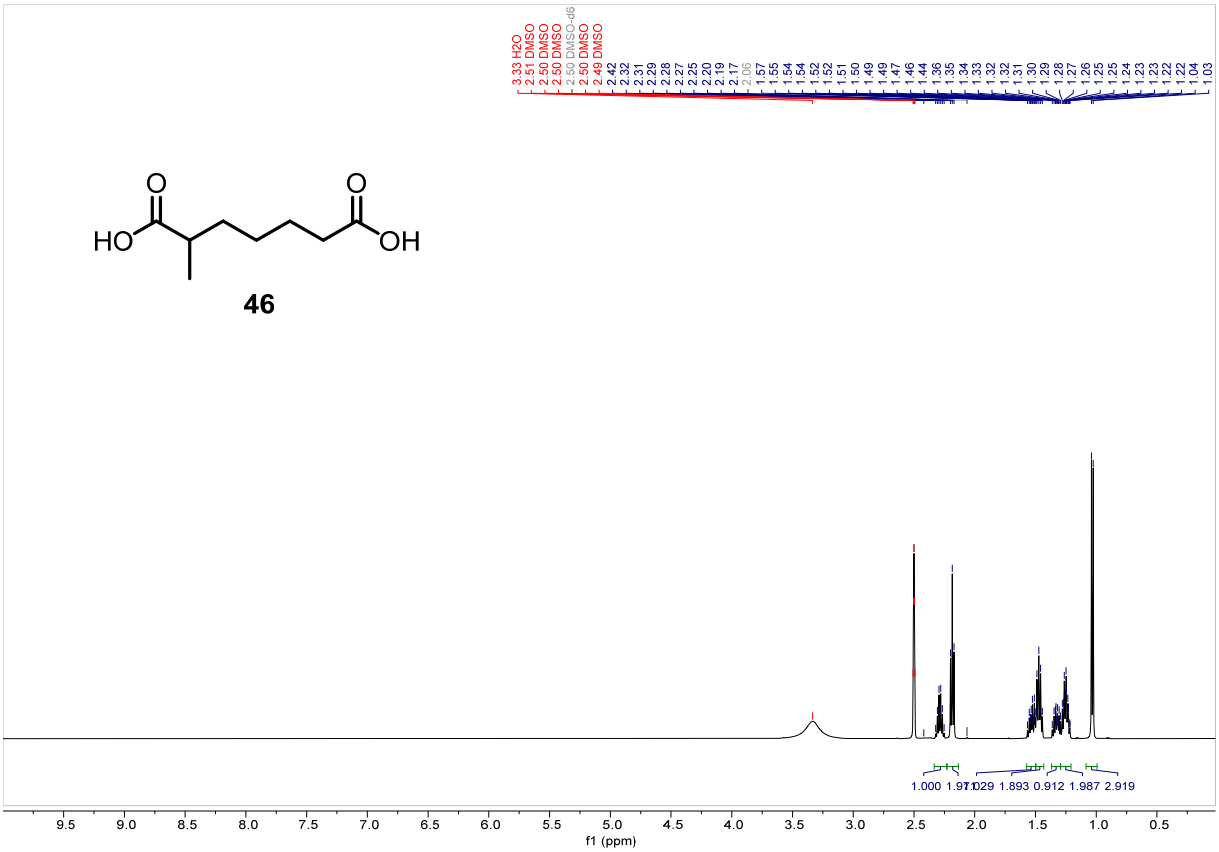
3-(3-Oxo-5-(trifluoromethyl)-1,3-dihydroisobenzofuran-1-yl)propanoic acid 44b

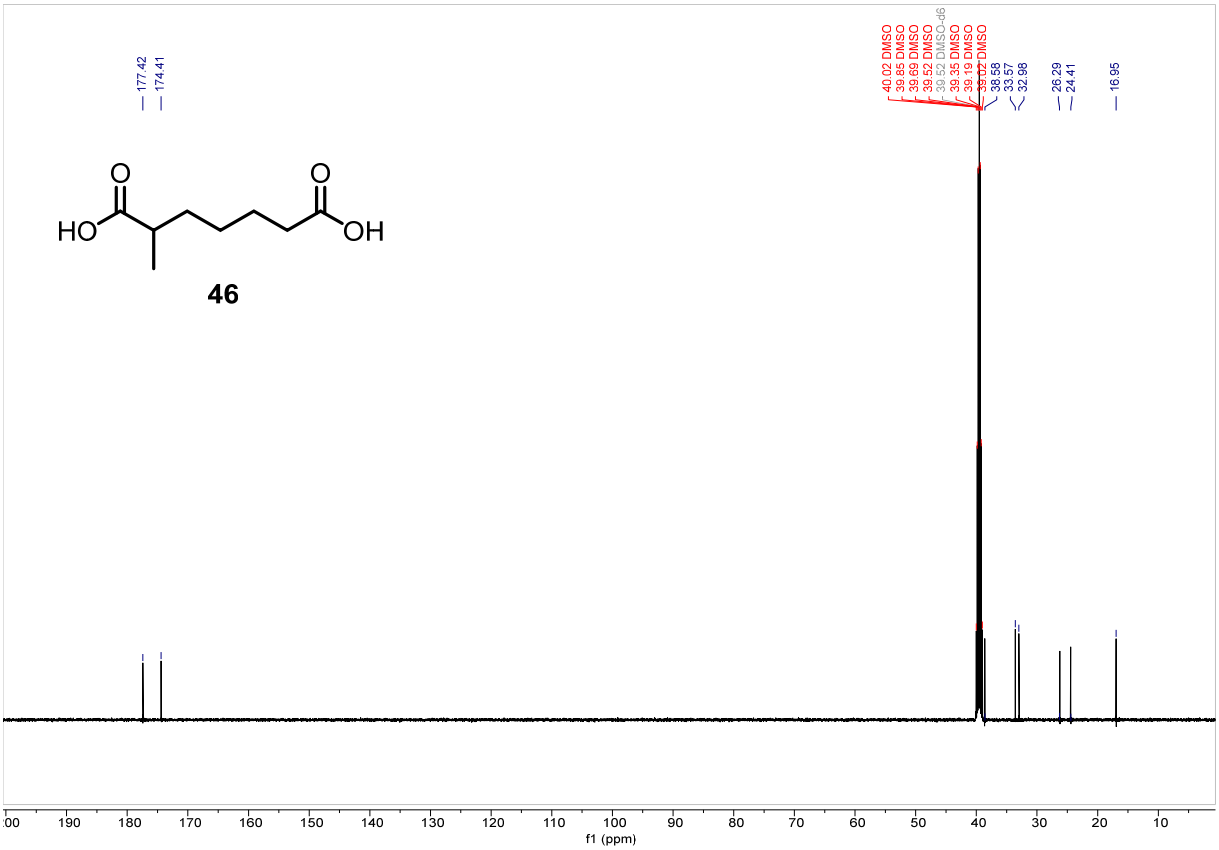




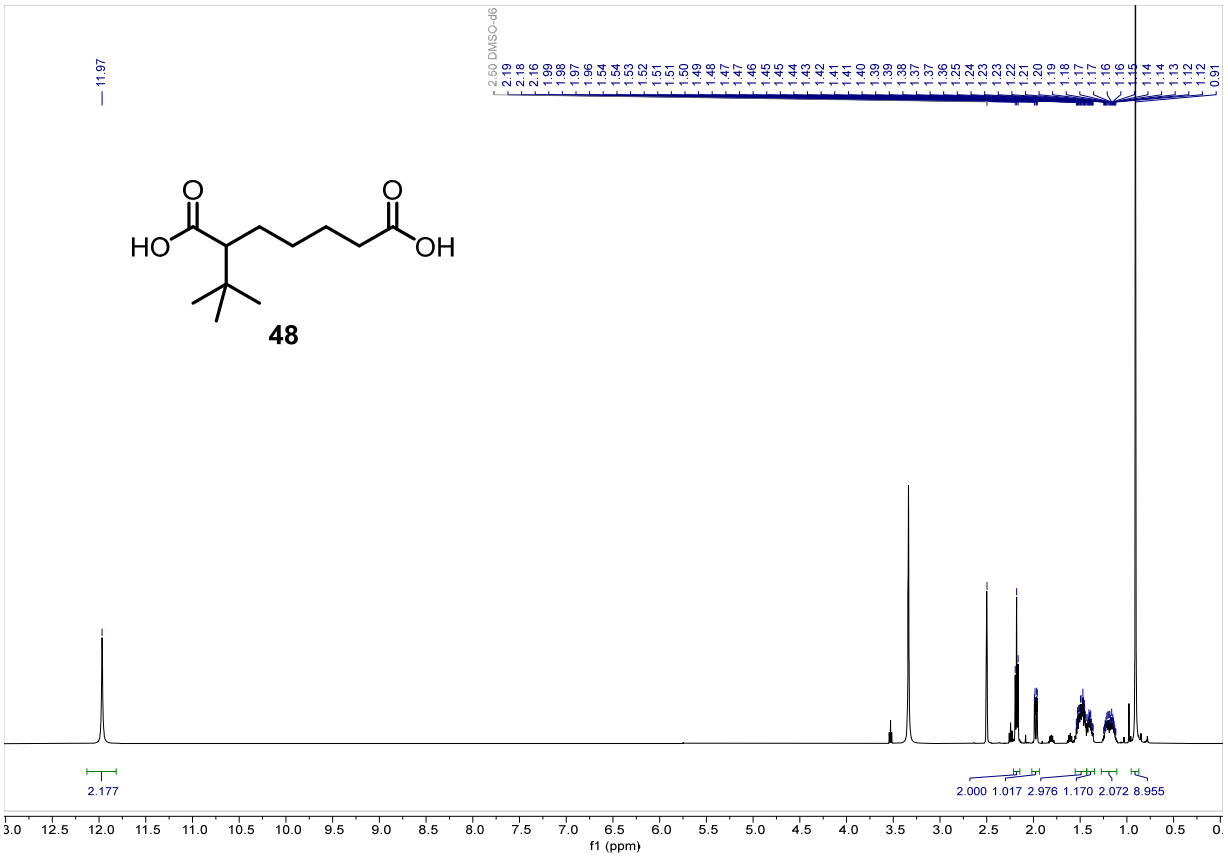

-66.59
F3C
O
O
O
OH
44b
10000000
9000000
8000000
7000000
6000000
5000000
4000000
3000000
2000000
1000000
0
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
f1 (ppm)

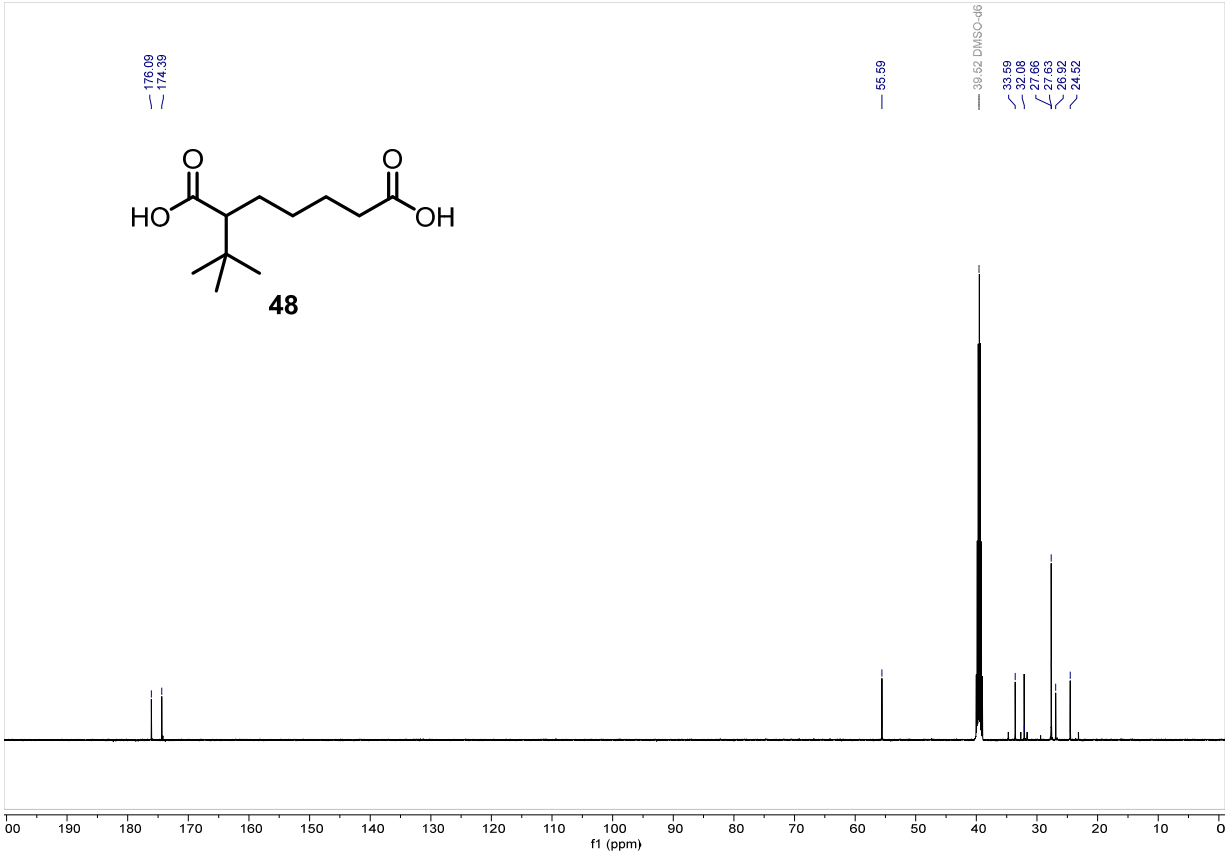
2-Methylheptanedioic acid 46



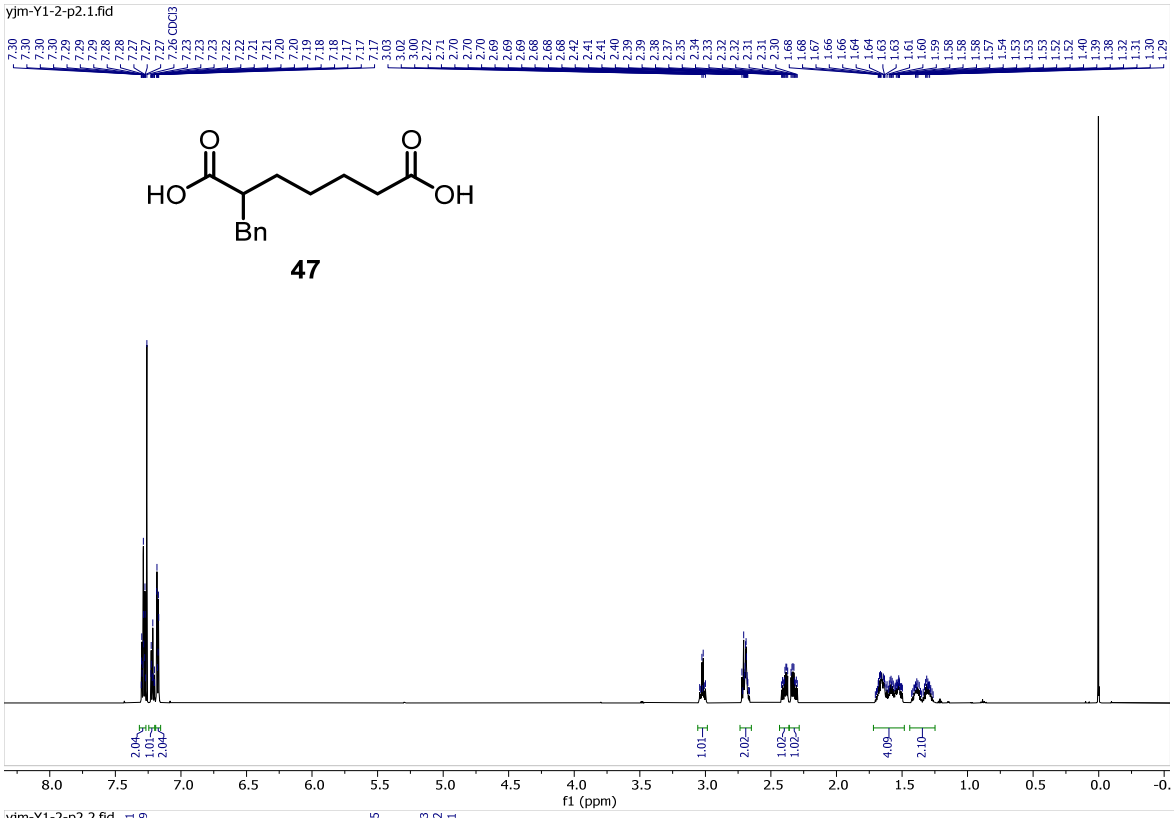


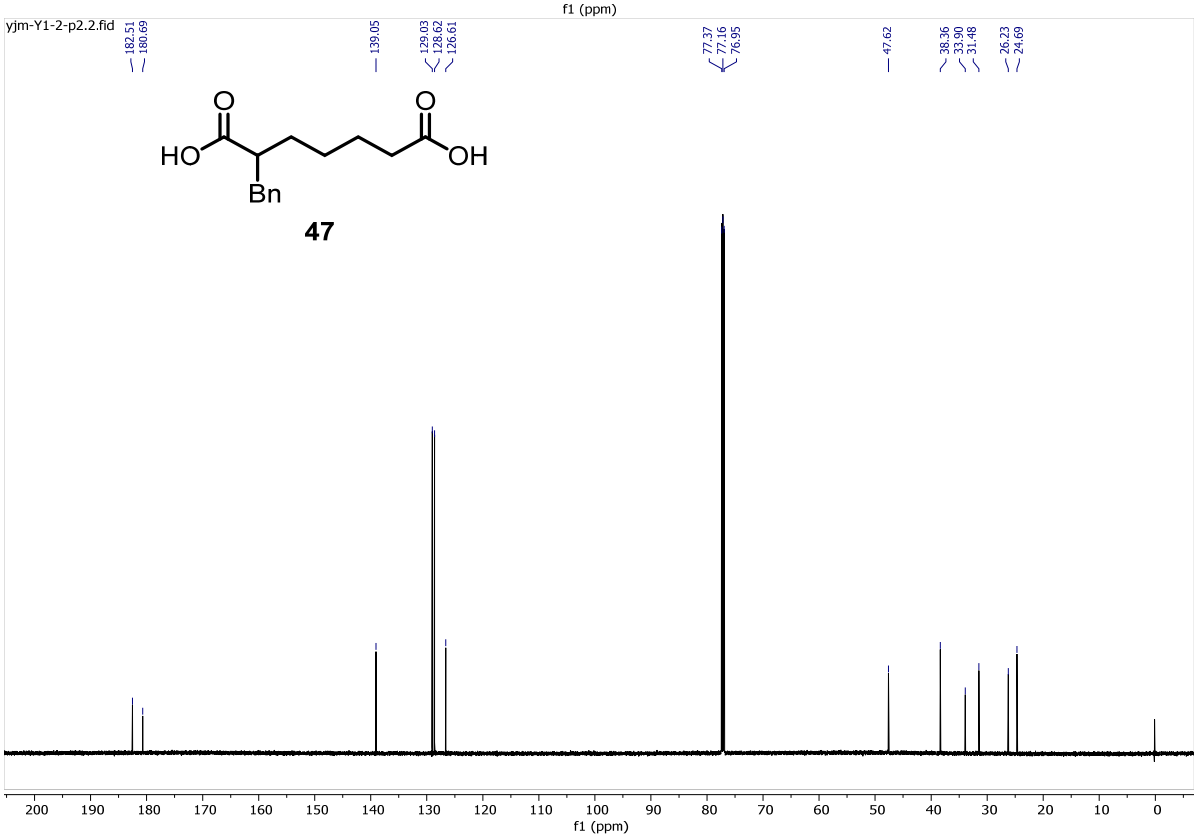
2-(*tert*-Butyl)heptanedioic acid 48



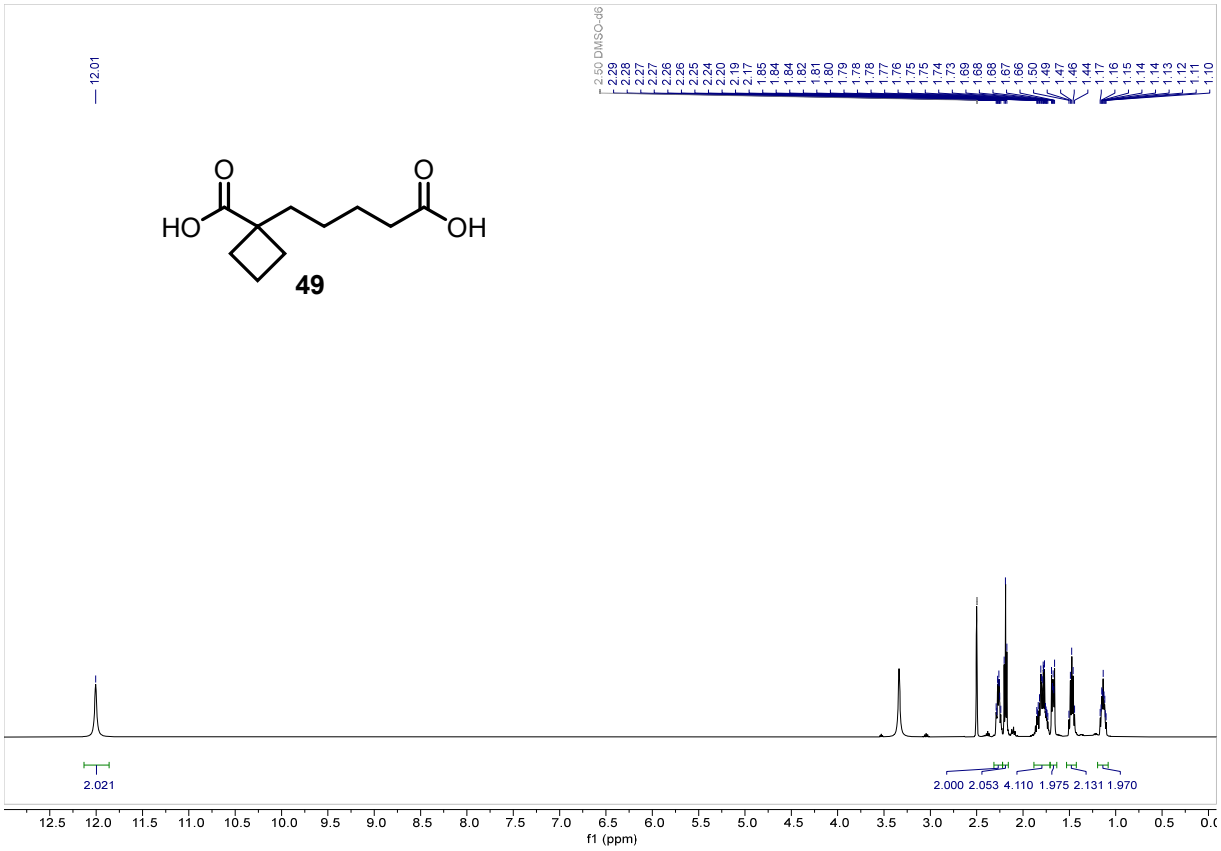


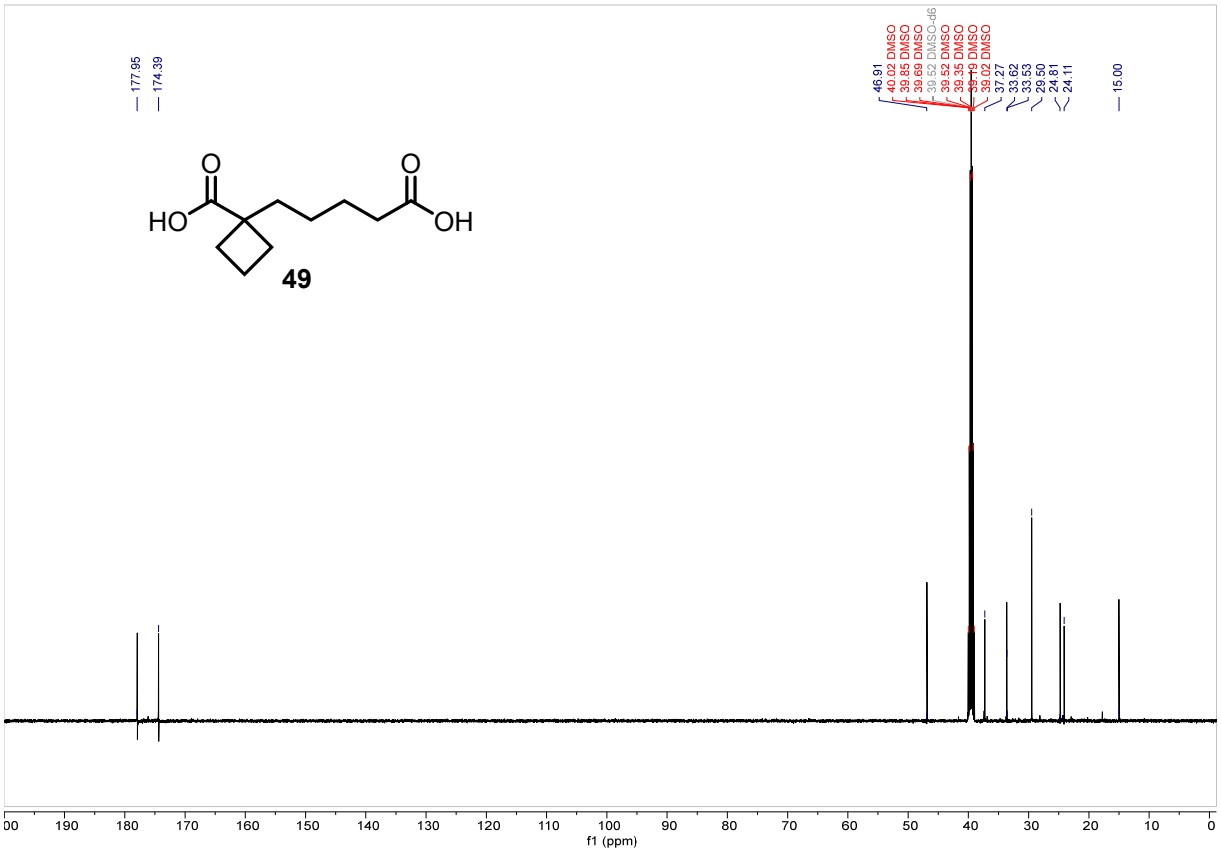
2-Benzylheptanedioic acid 47



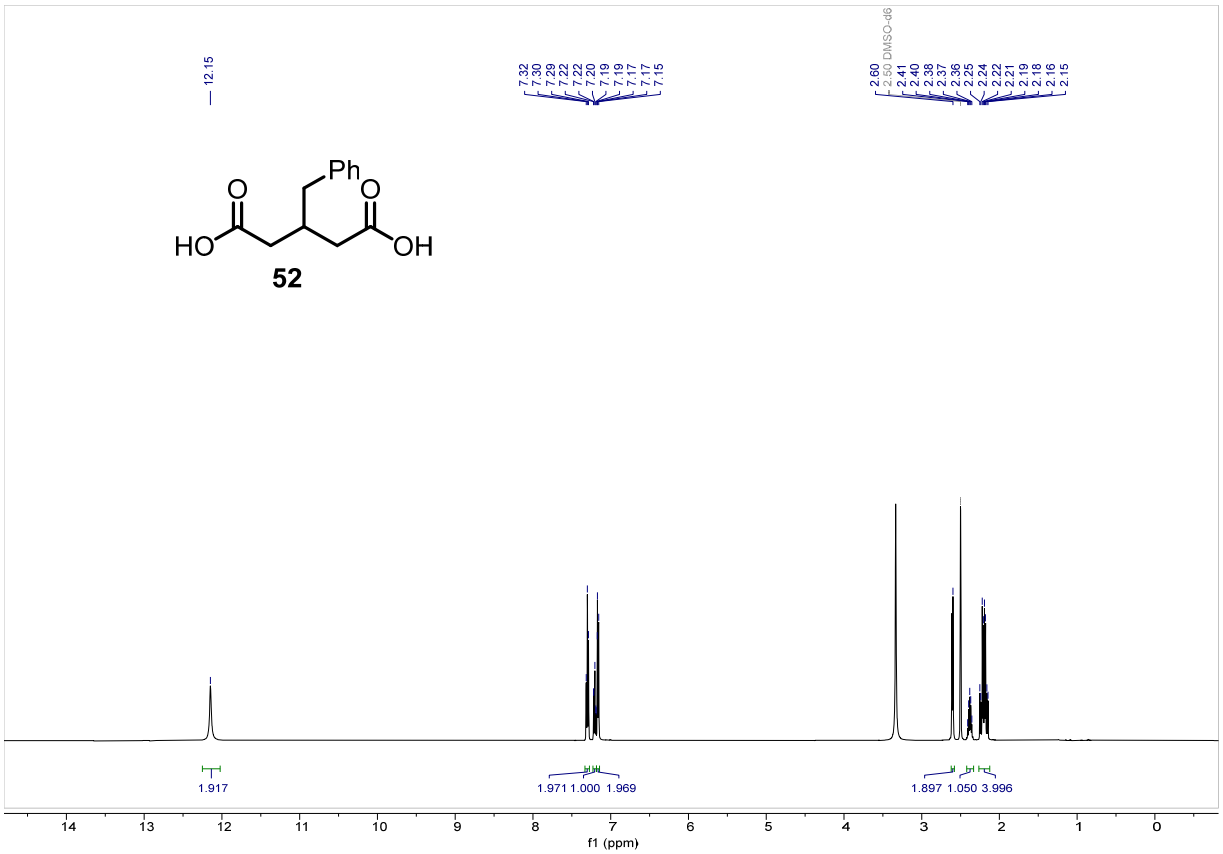


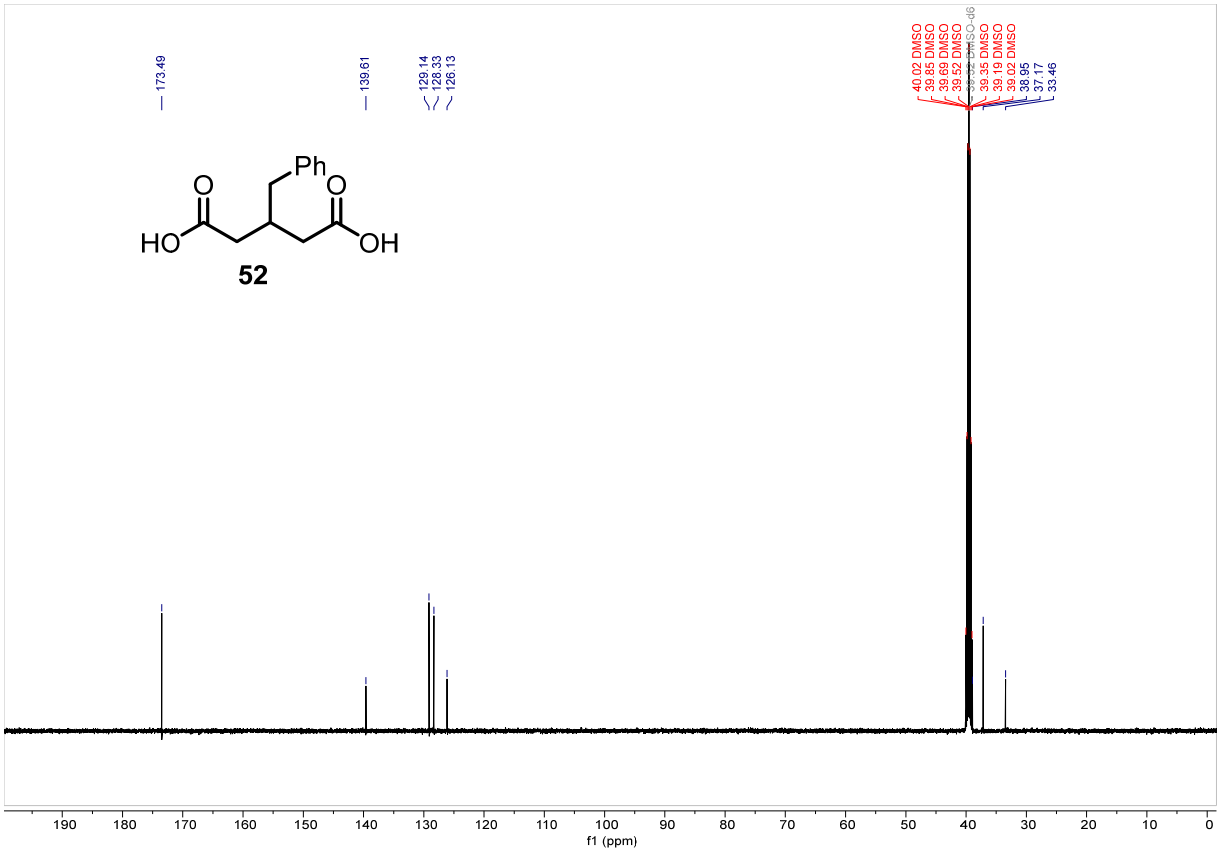
1-(4-Carboxybutyl)cyclobutane-1-carboxylic acid 49



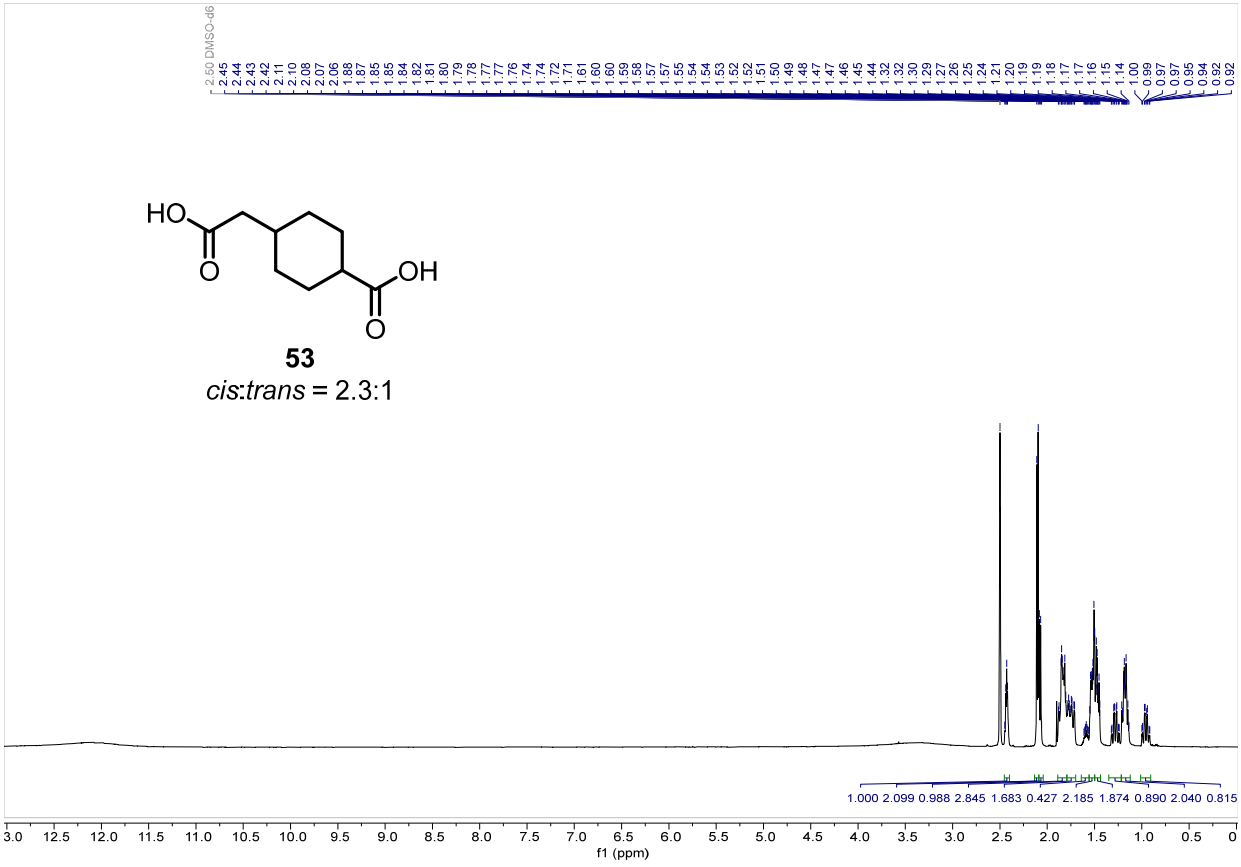


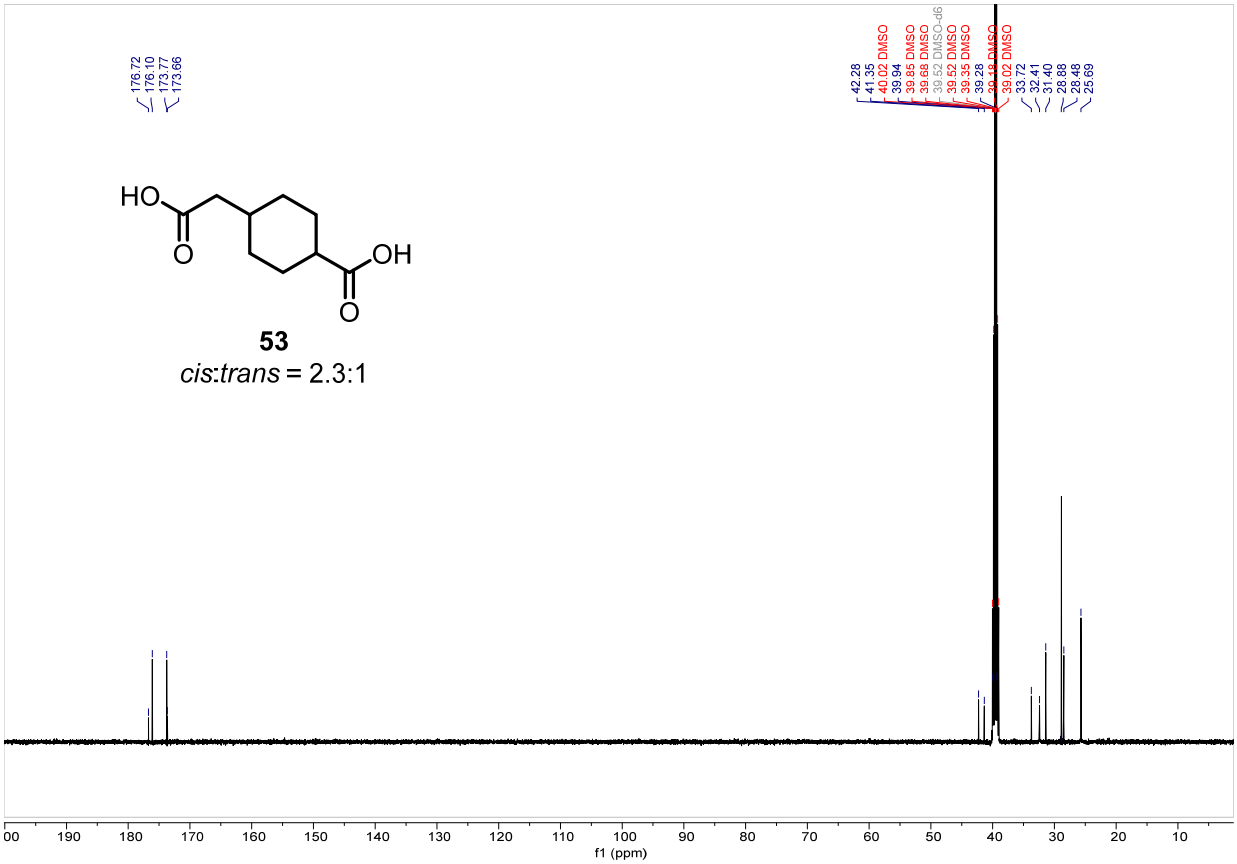
3-Benzylpentanedioic acid 52



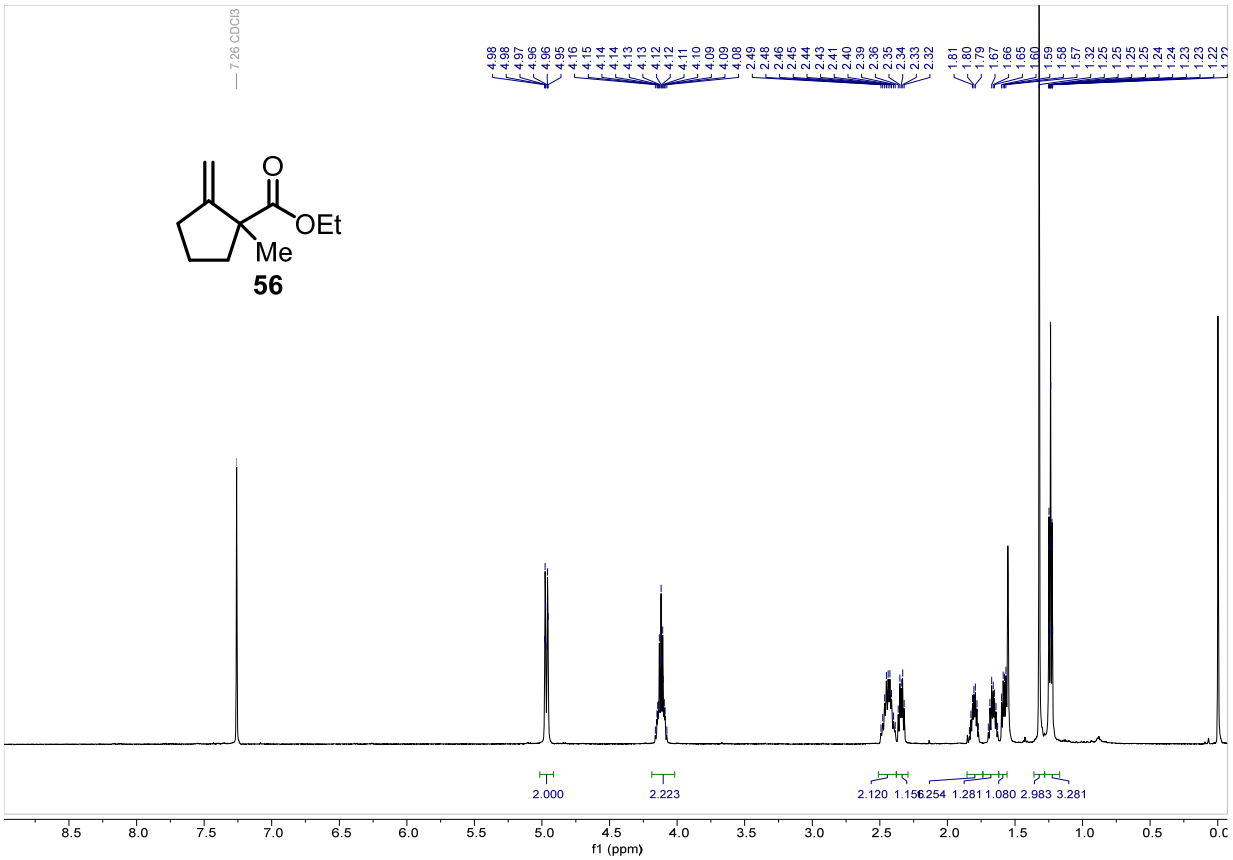


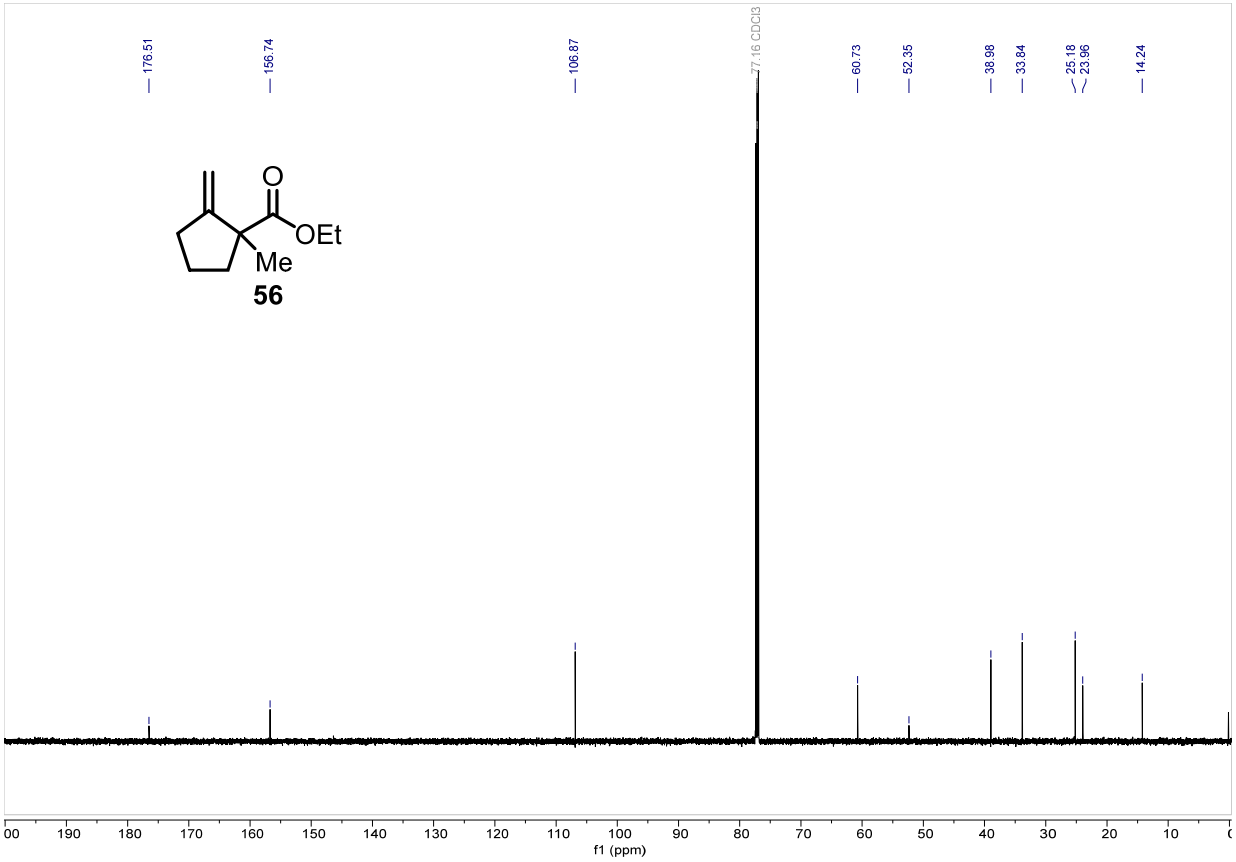
4-(Carboxymethyl)cyclohexane-1-carboxylic acid 53



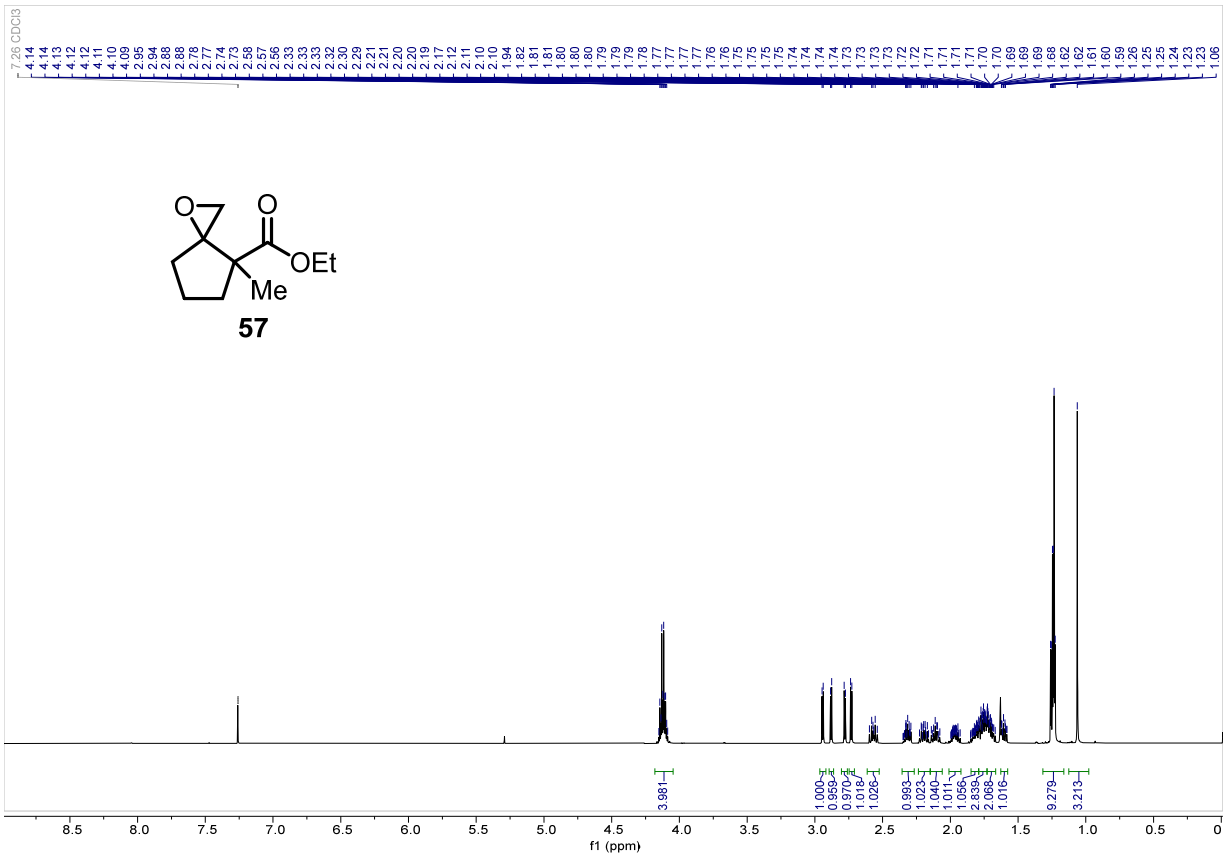


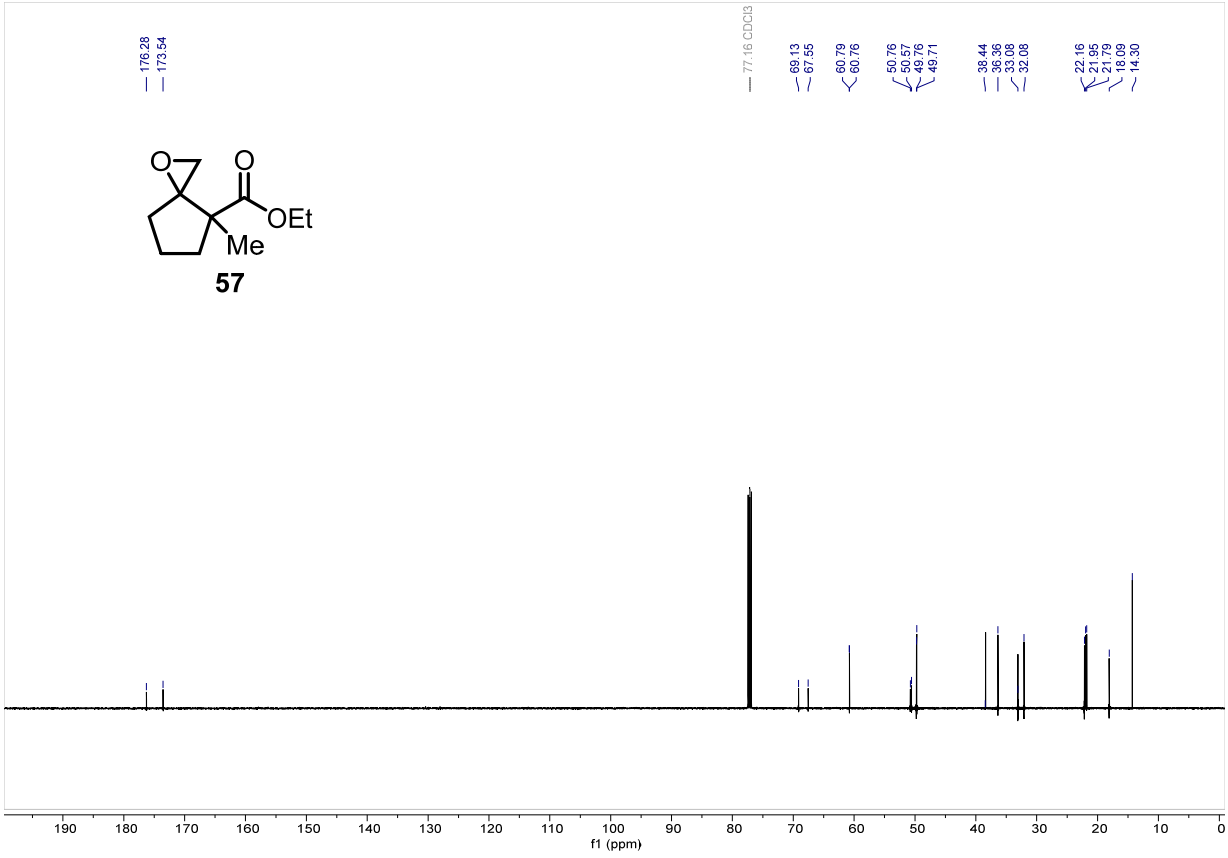
Ethyl 1-methyl-2-methylenecyclopentane-1-carboxylate 56



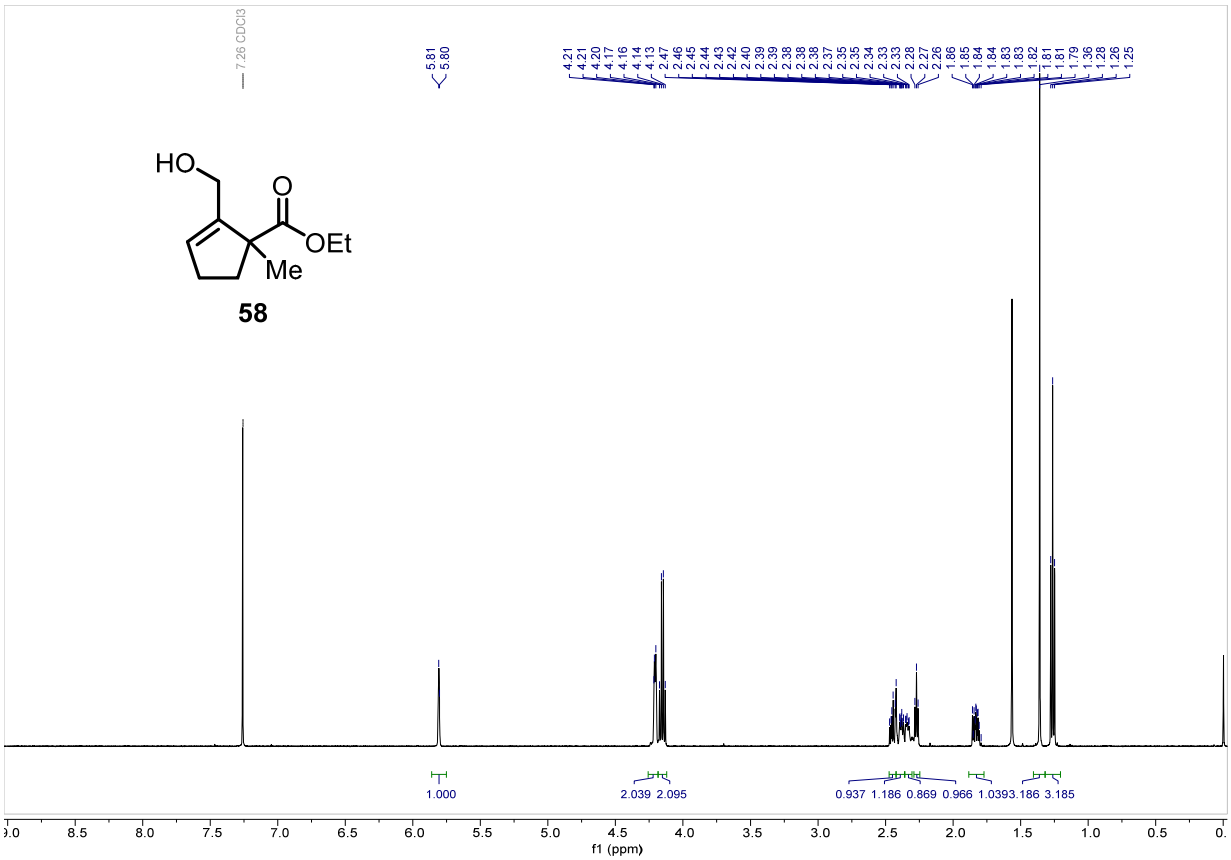


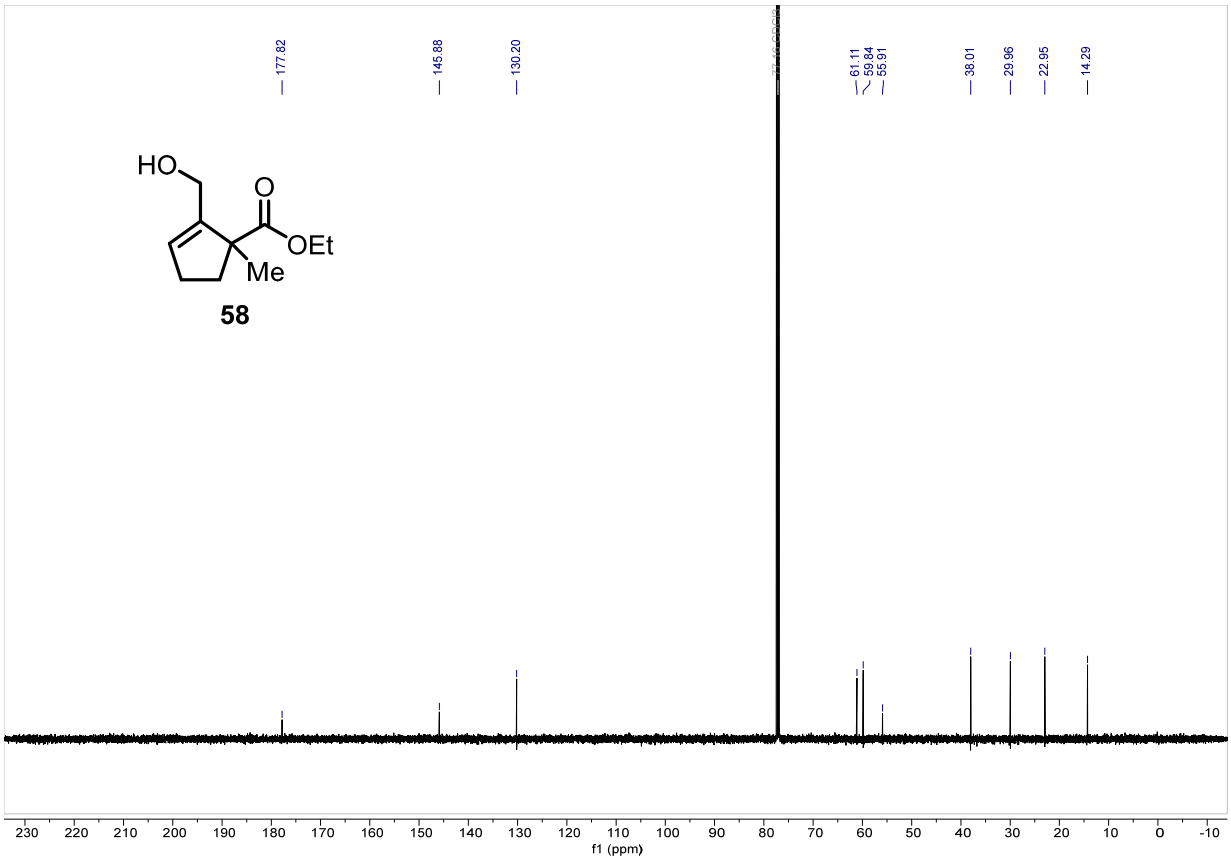
Ethyl 4-methyl-1-oxaspiro[2.4]heptane-4-carboxylate 57



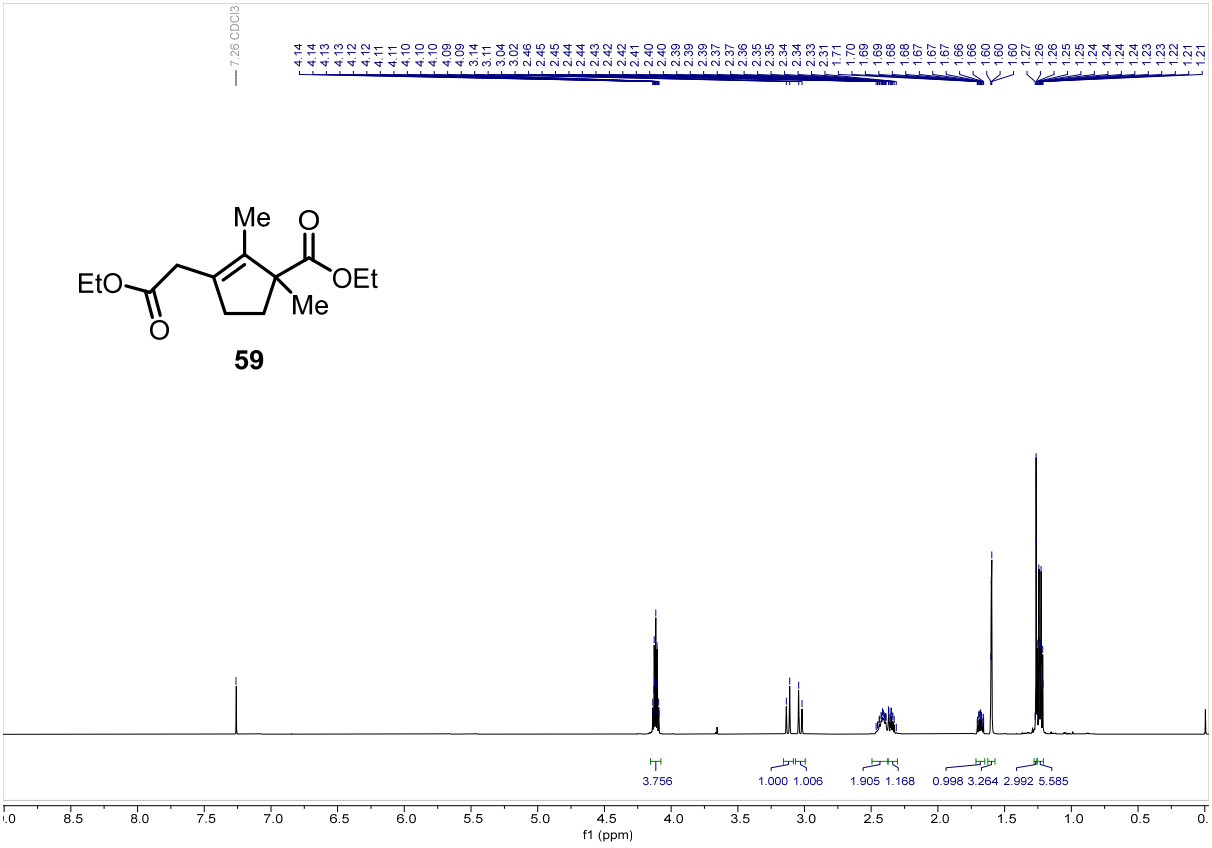


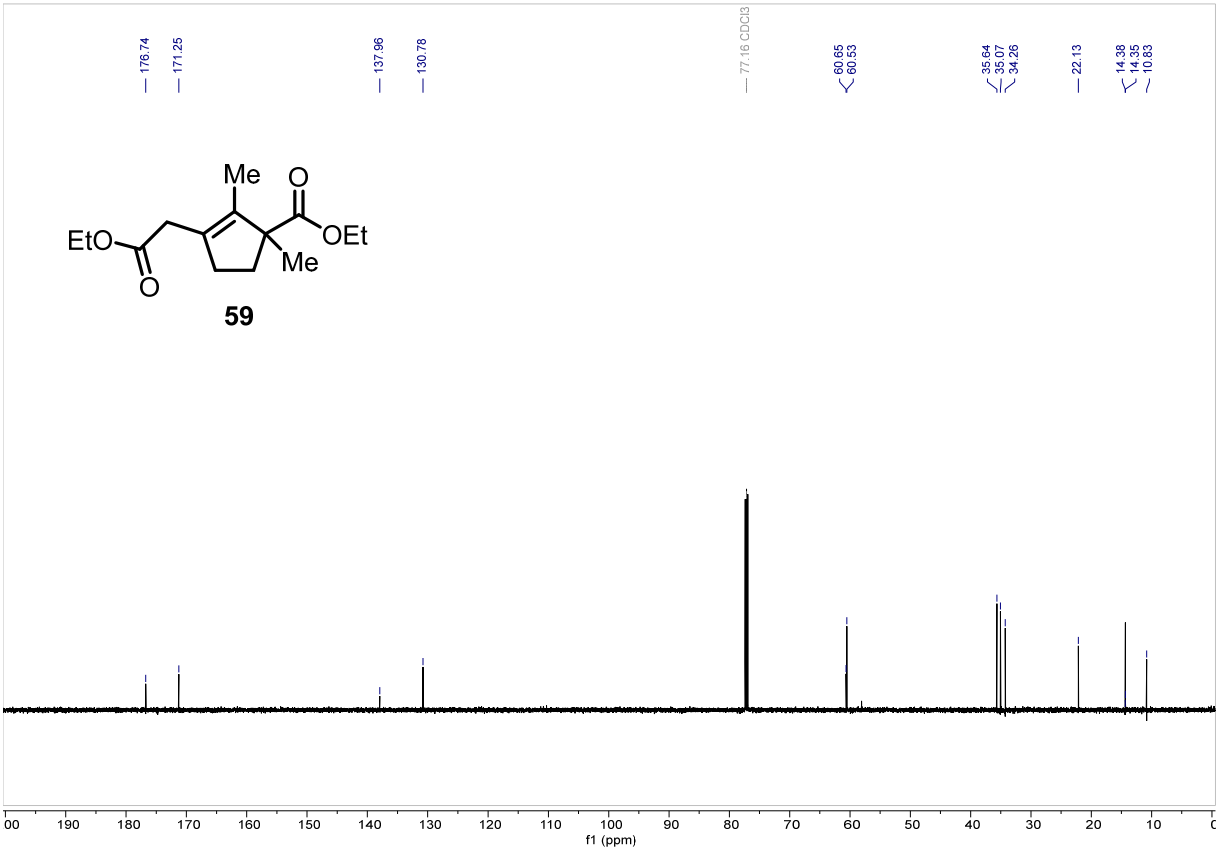
Ethyl 2-(hydroxymethyl)-1-methylcyclopent-2-ene-1-carboxylate 58



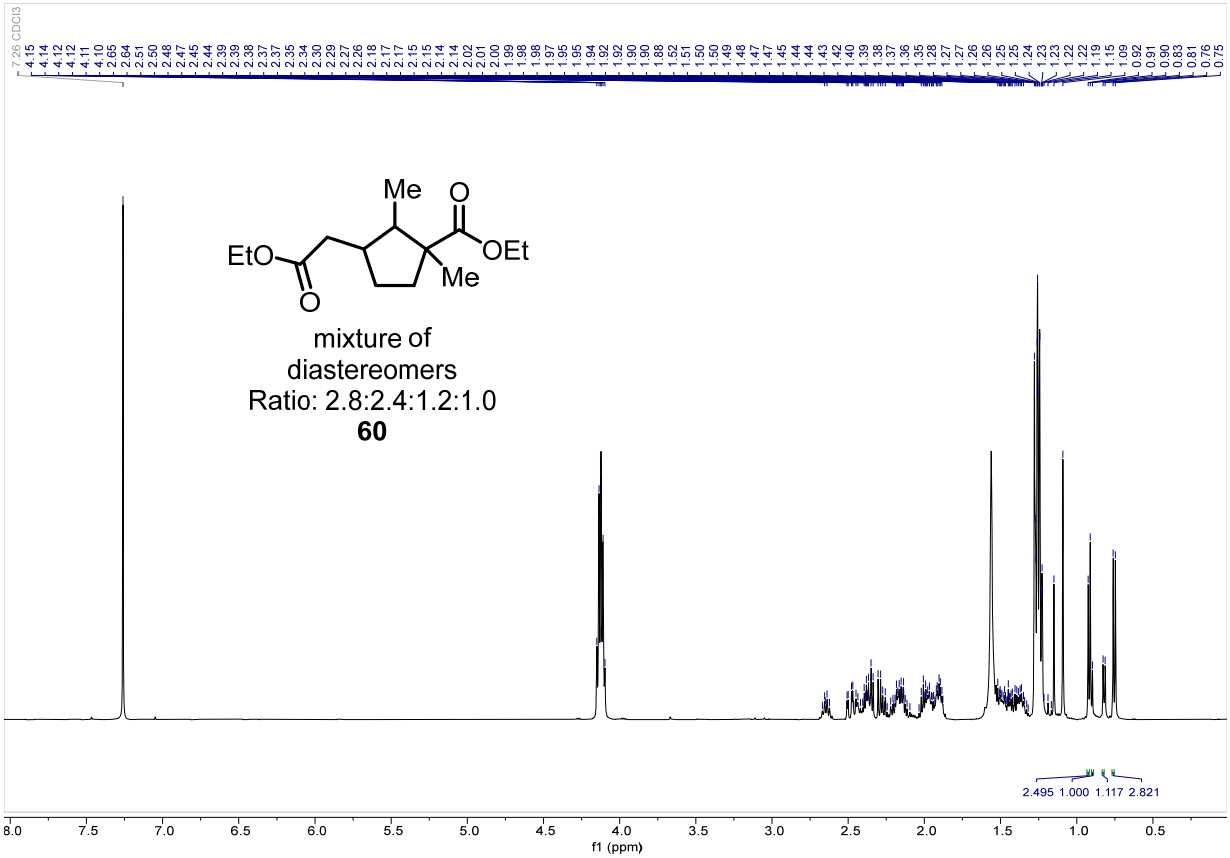


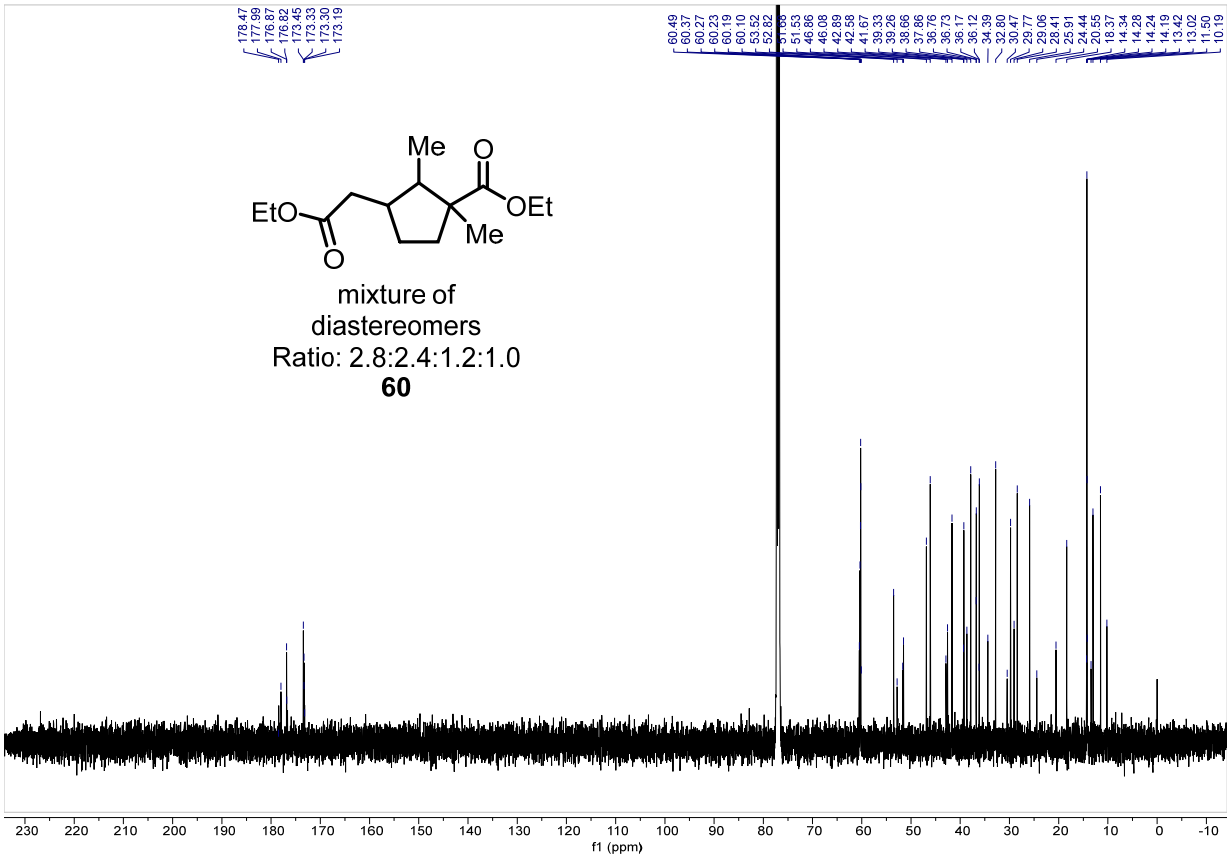
Ethyl 3-(2-ethoxy-2-oxoethyl)-1,2-dimethylcyclopent-2-ene-1-carboxylate 59



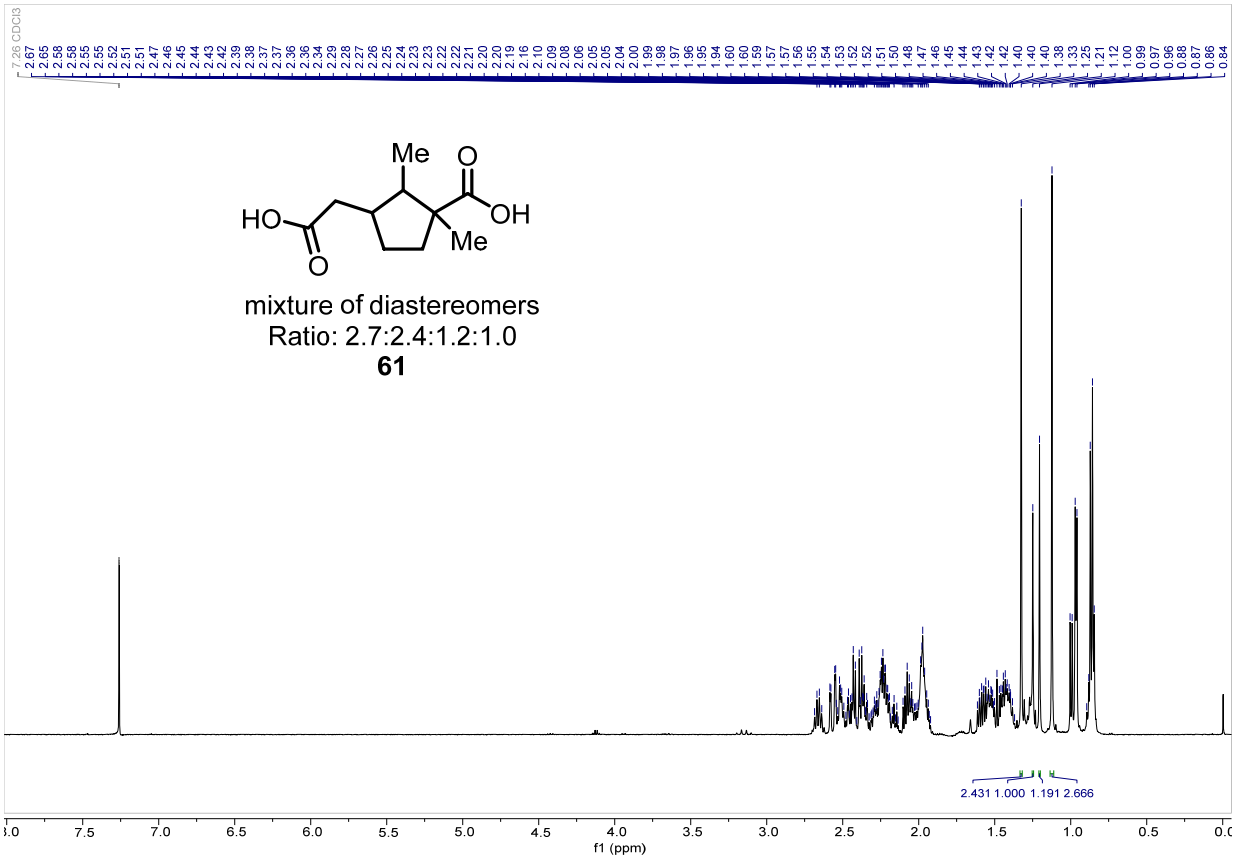


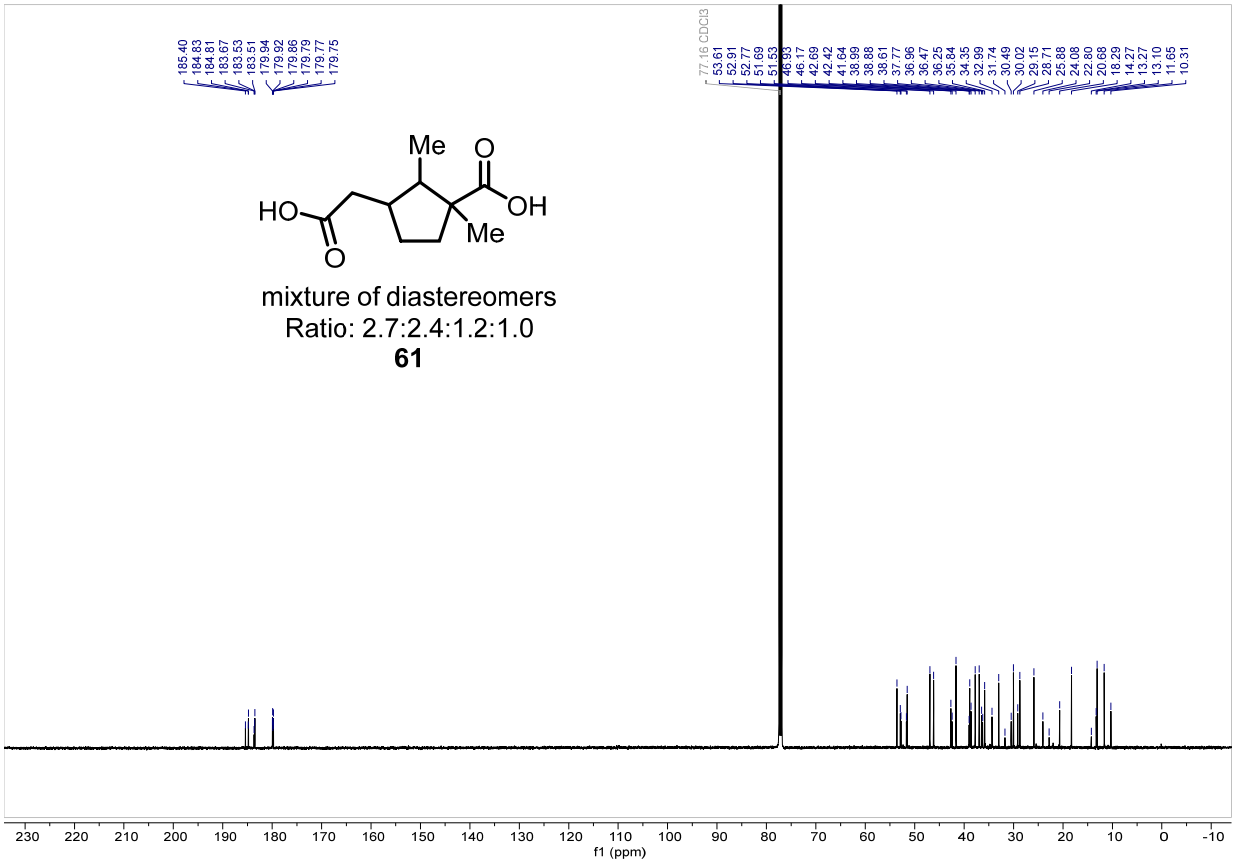
Ethyl 3-(2-ethoxy-2-oxoethyl)-1,2-dimethylcyclopentane-1-carboxylate 60



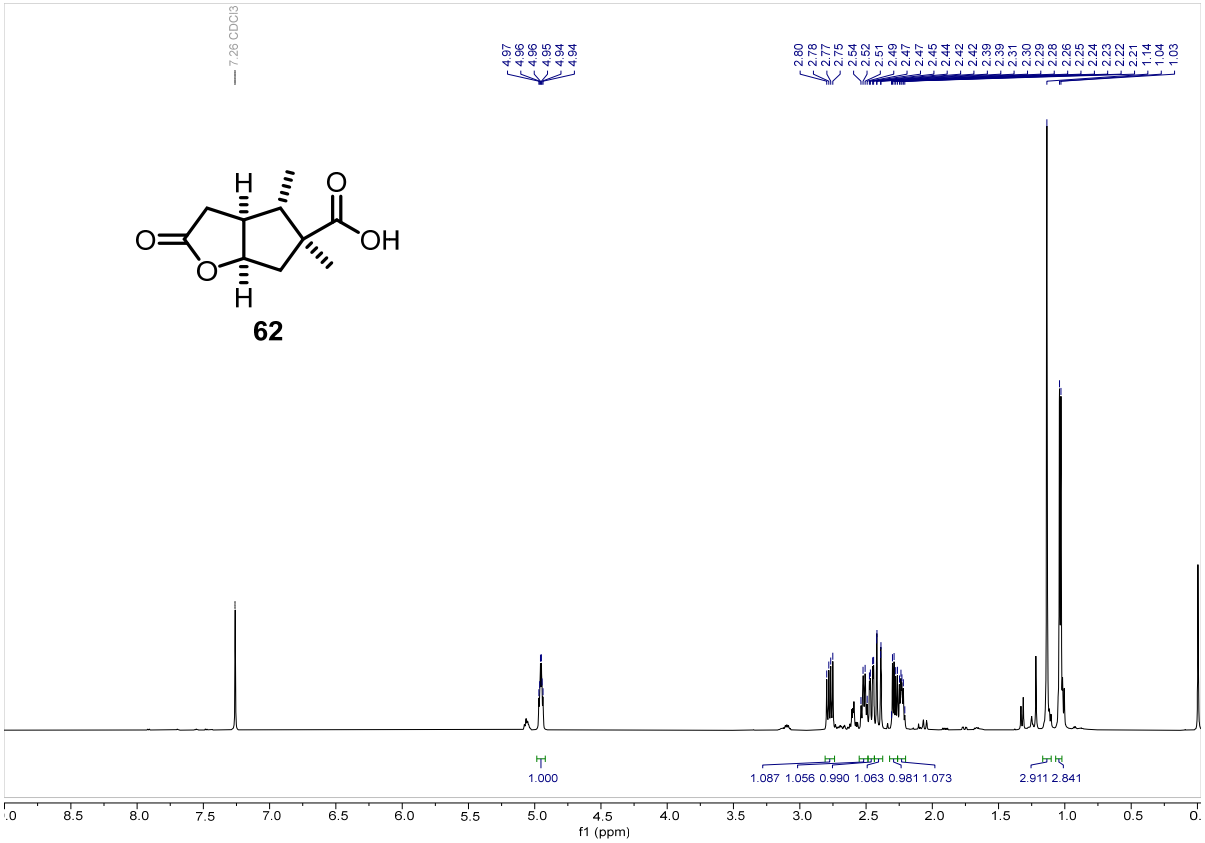


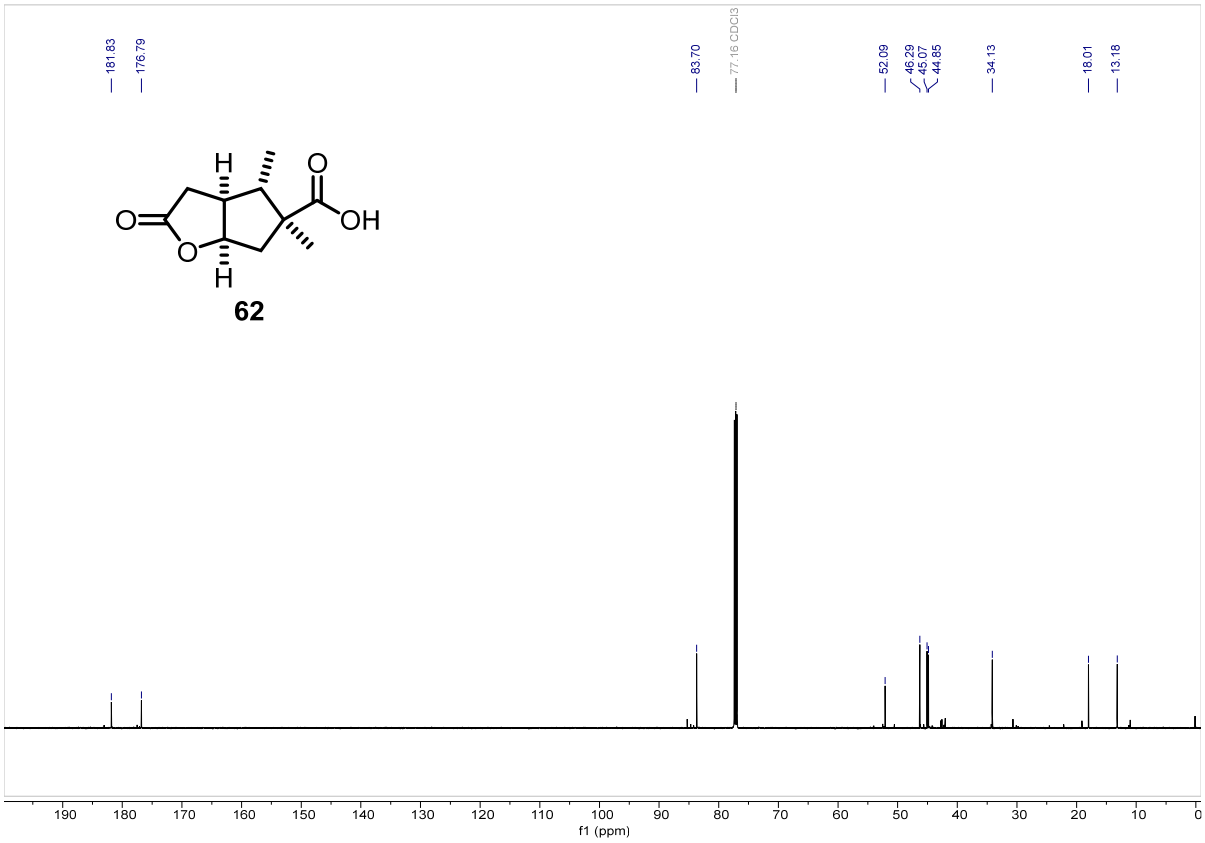
3-(Carboxymethyl)-1,2-dimethylcyclopentane-1-carboxylic acid 61



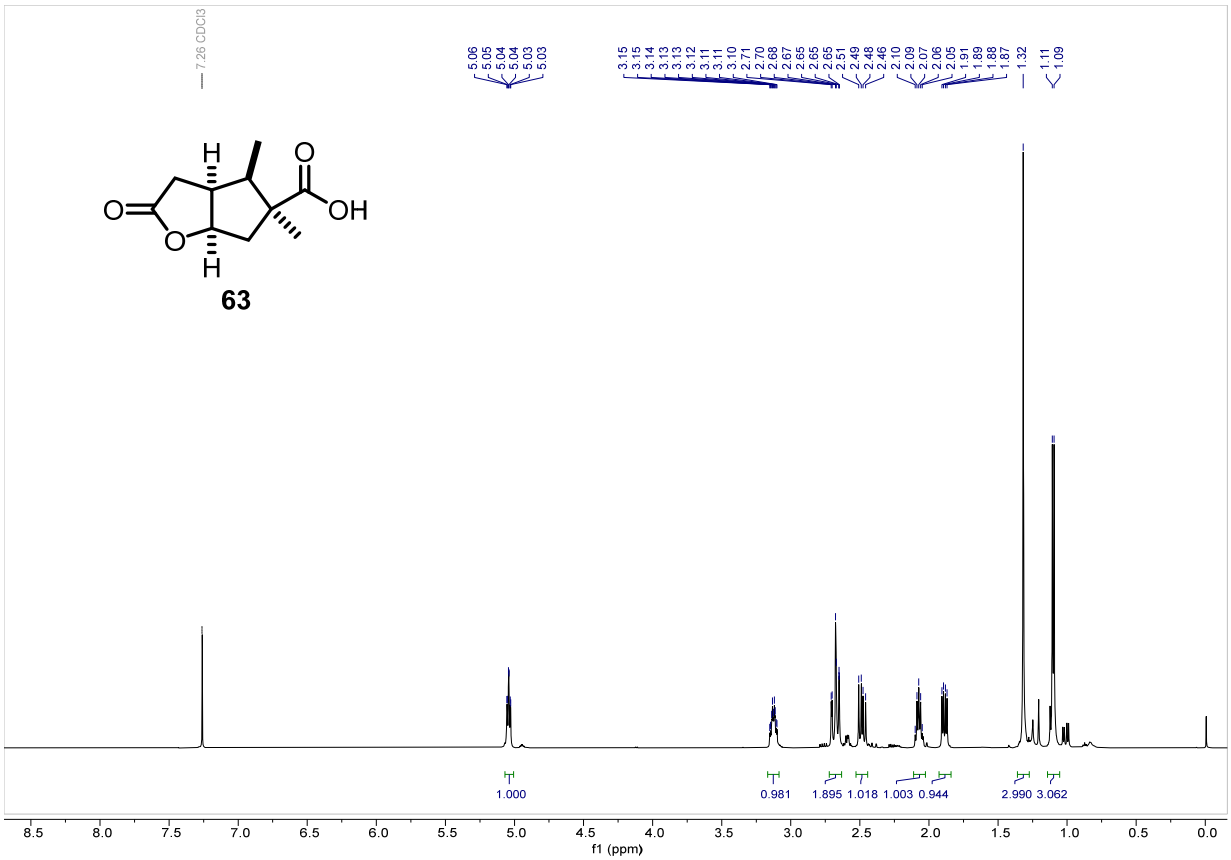


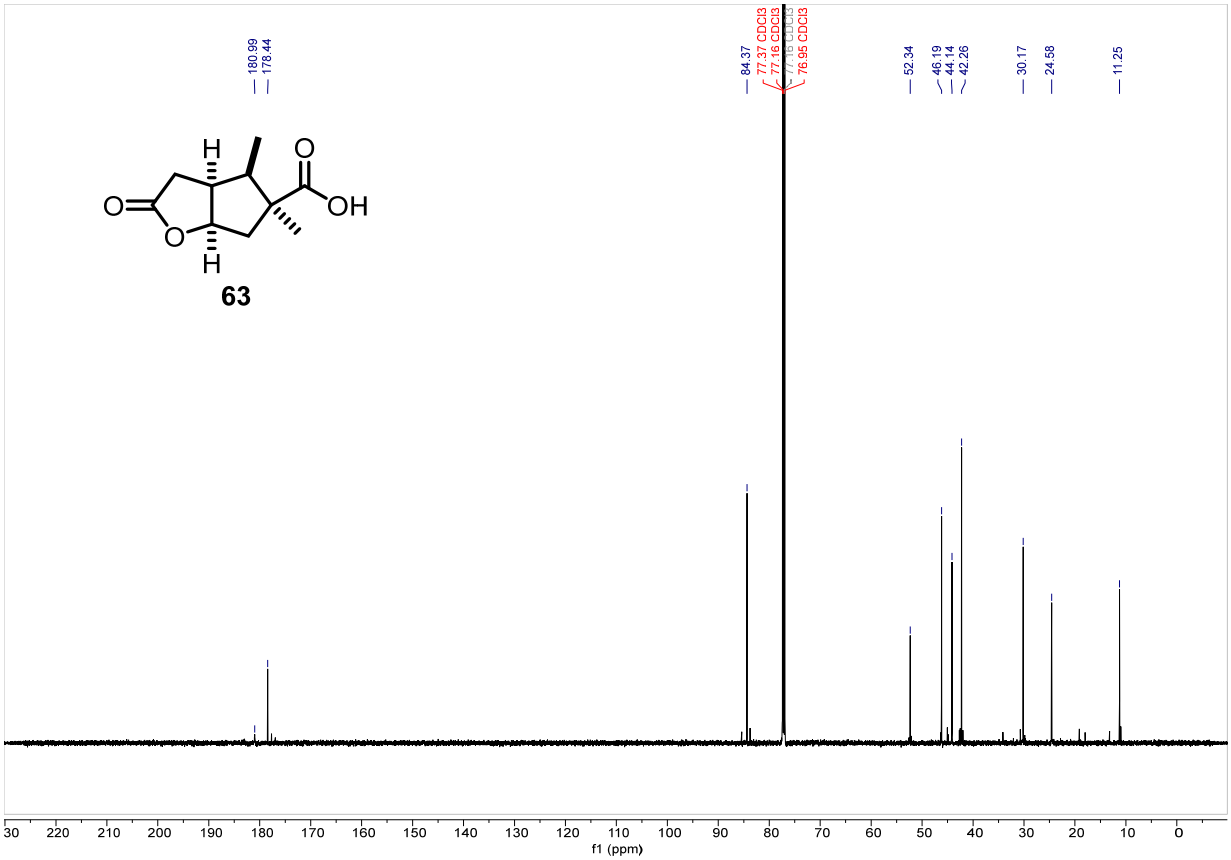
(3*aS,4*S**,5*S**,6*aR**)-4,5-dimethyl-2-oxohexahydro-2*H*-cyclopenta[*b*]furan-5-carboxylic acid 62**



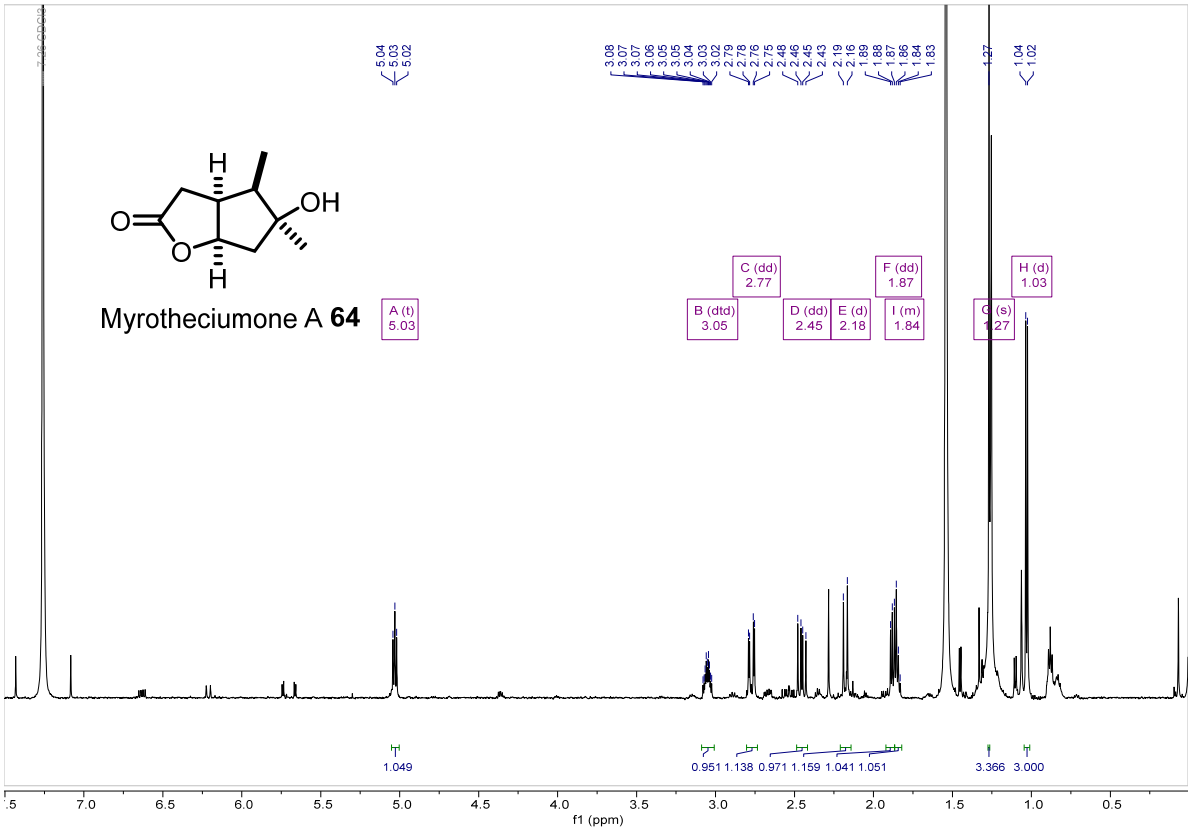


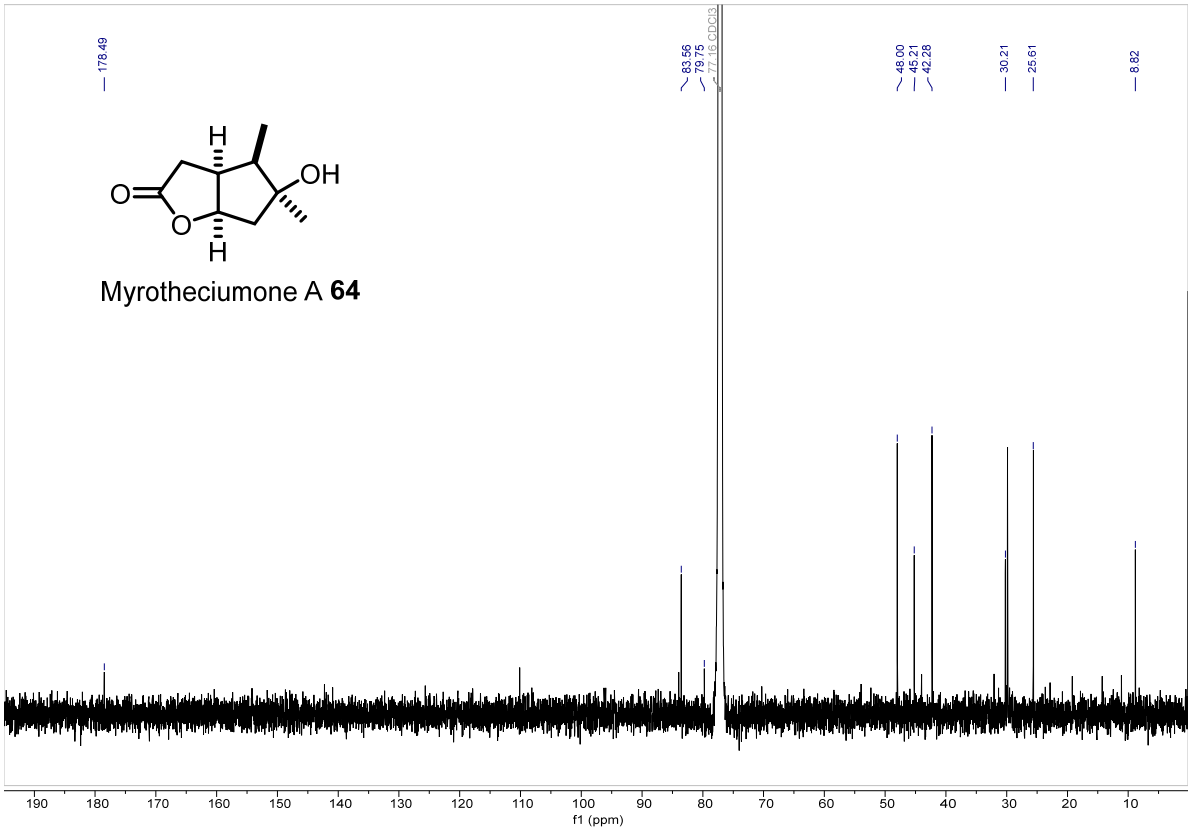
(3*aS,4*R**,5*S**,6*aR**)-4,5-dimethyl-2-oxohexahydro-2*H*-cyclopenta[*b*]furan-5-carboxylic acid 63**



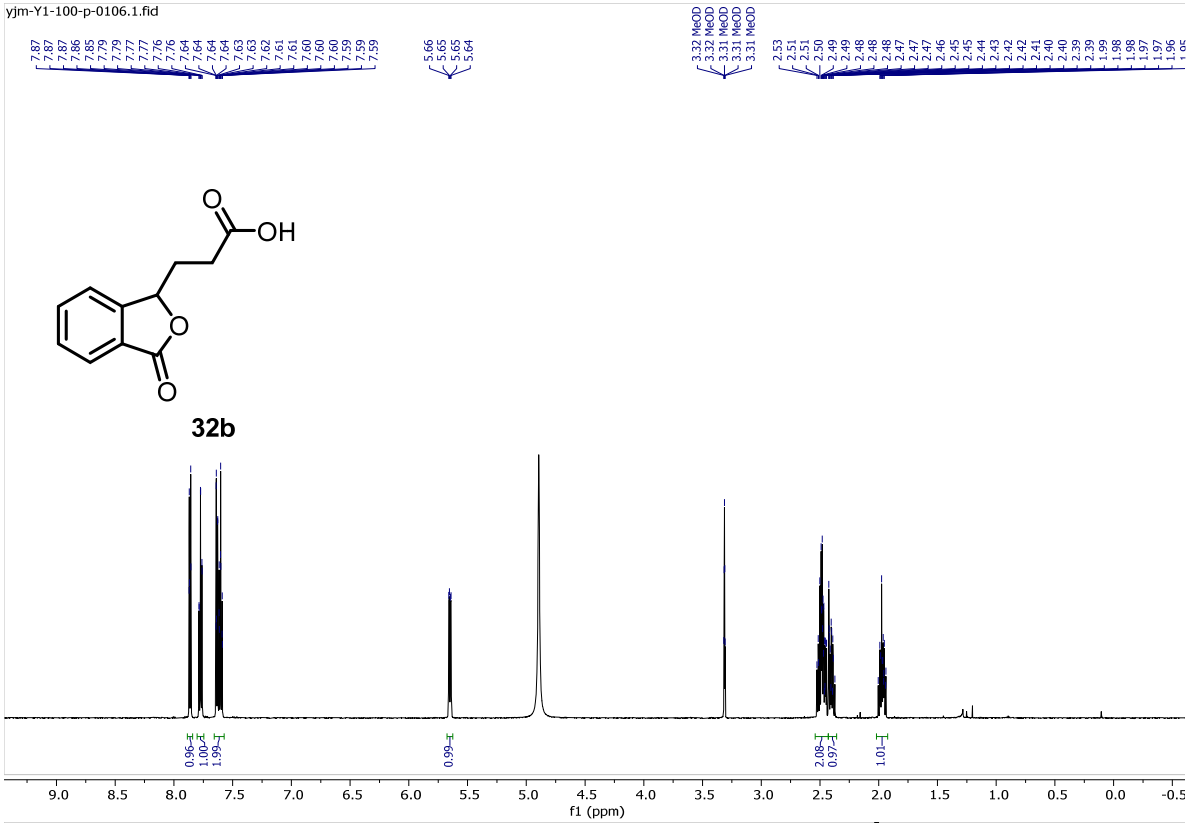


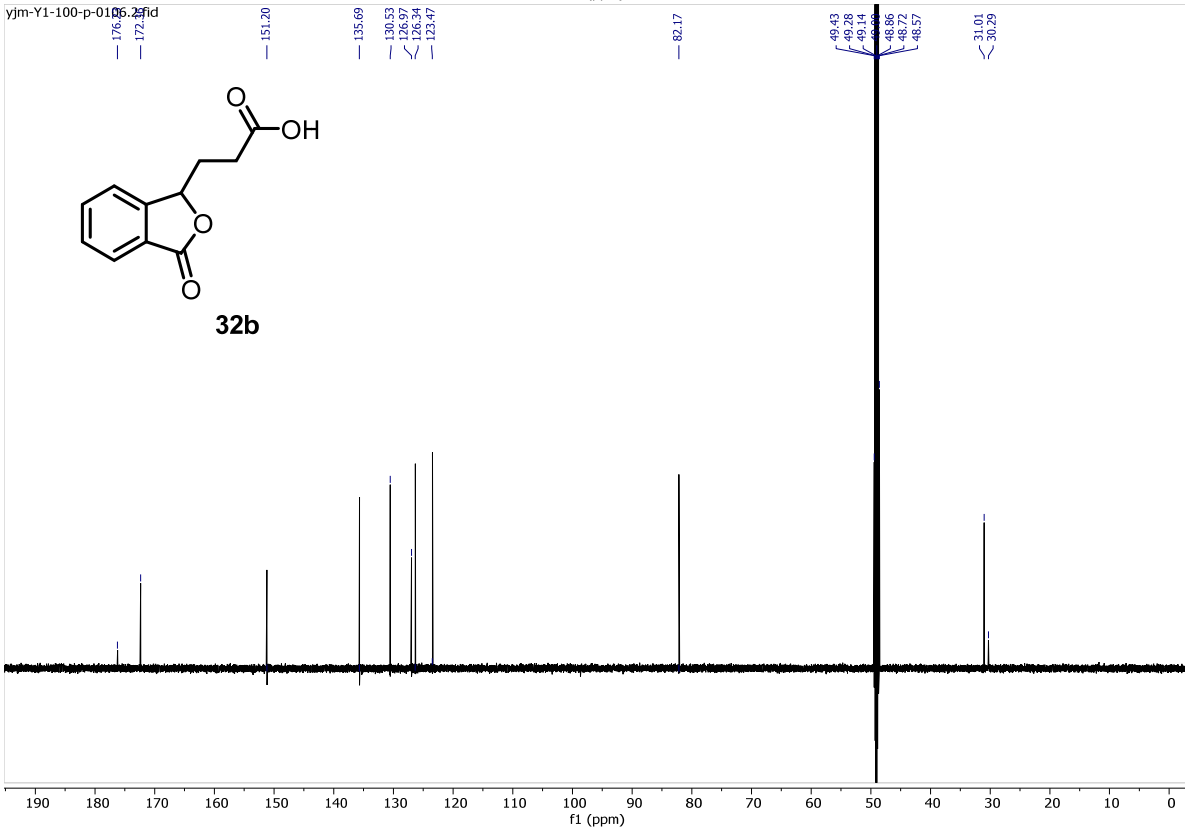
(3*aS,4*R**,5*S**,6*aR**)-5-hydroxy-4,5-dimethylhexahydro-2H-cyclopenta[b]furan-2-one, myrotheciumone A 64**



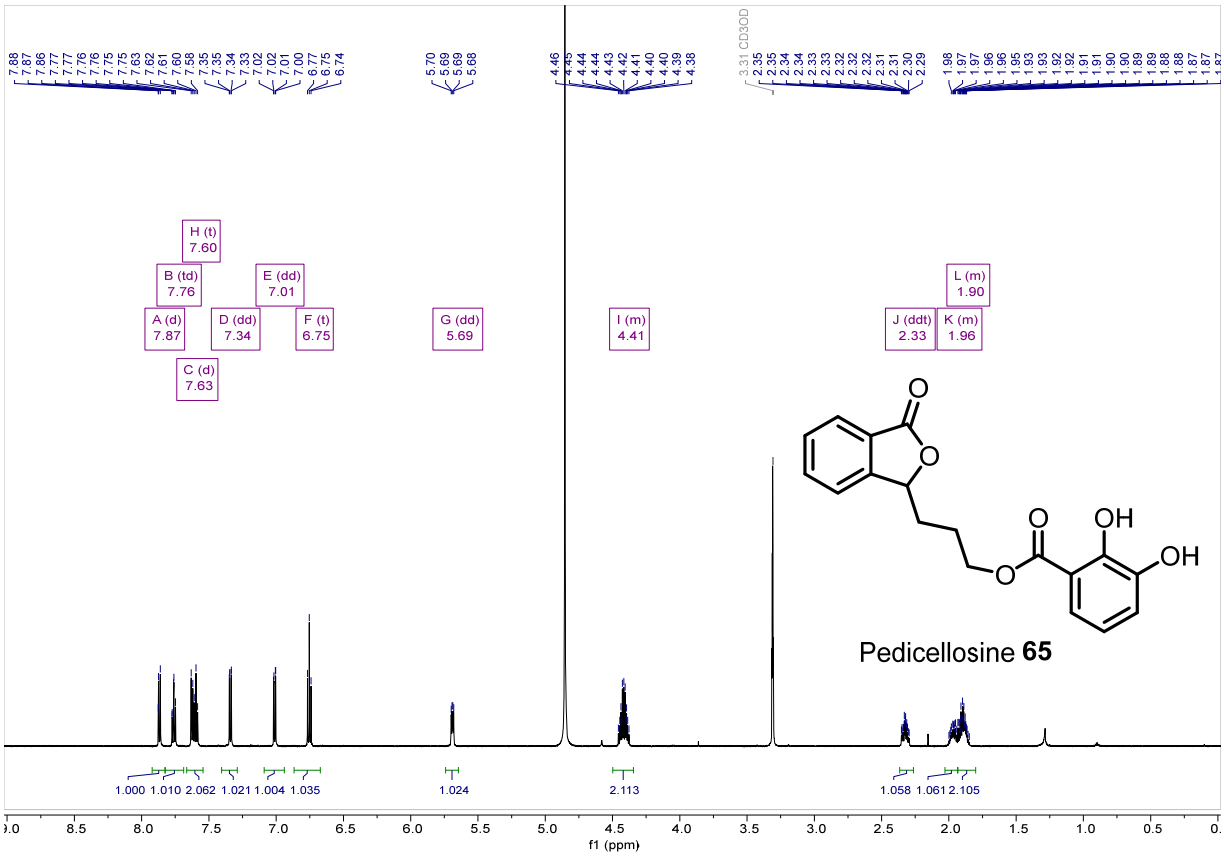


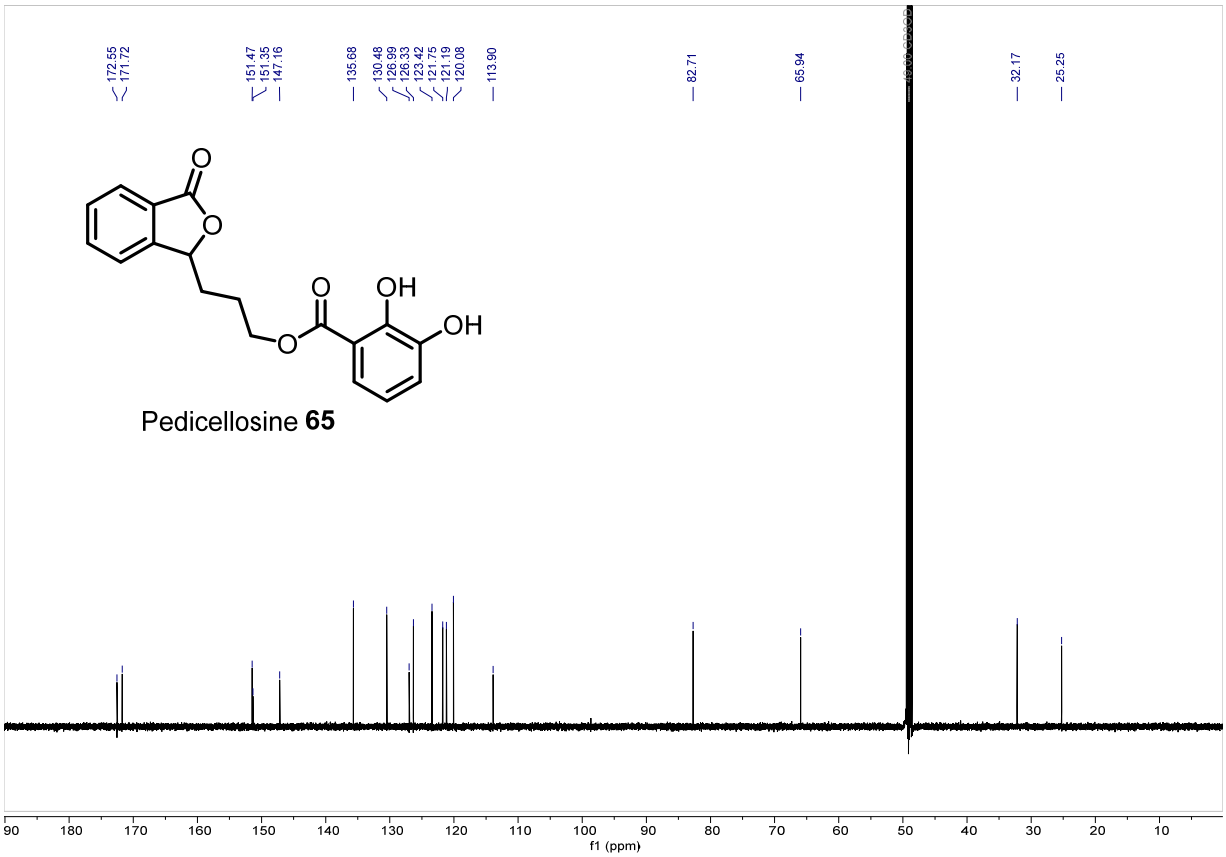
3-(3-Oxo-1,3-dihydroisobenzofuran-1-yl)propanoic acid 32b



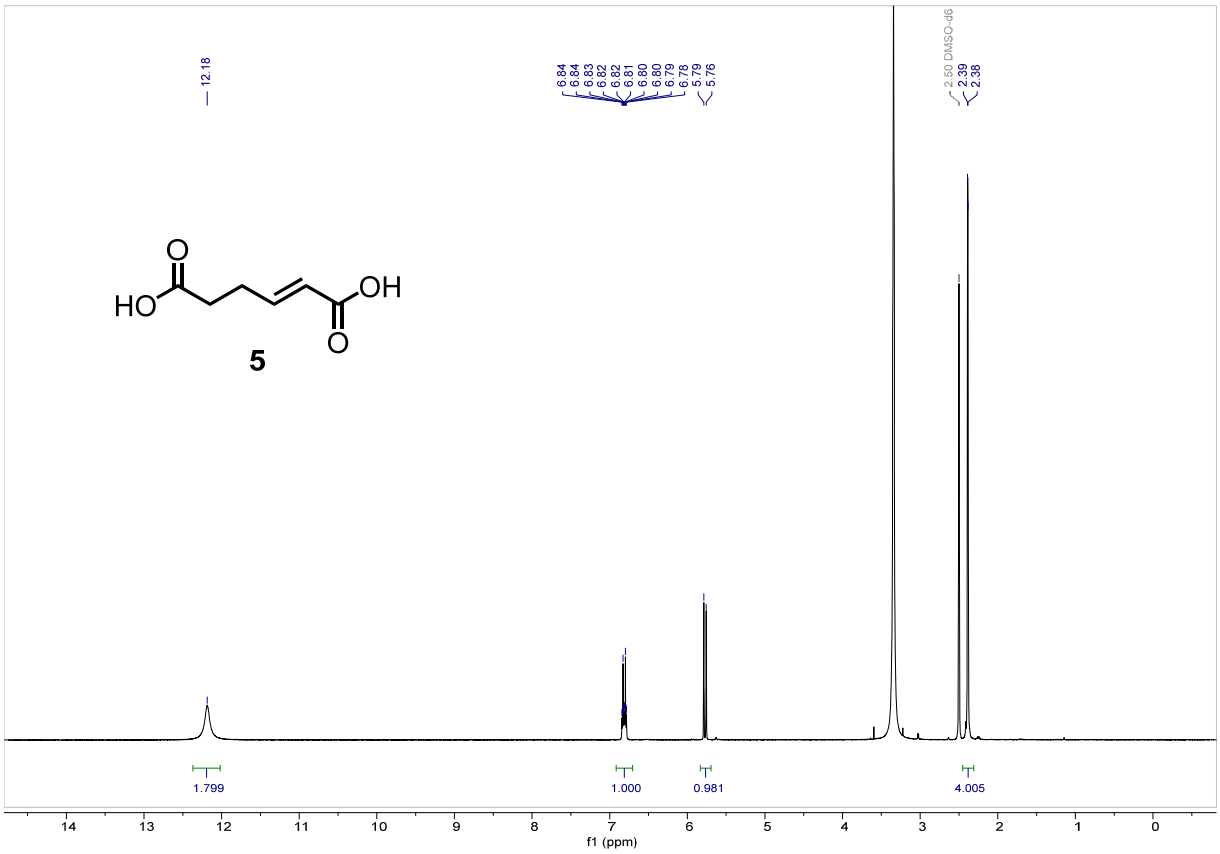


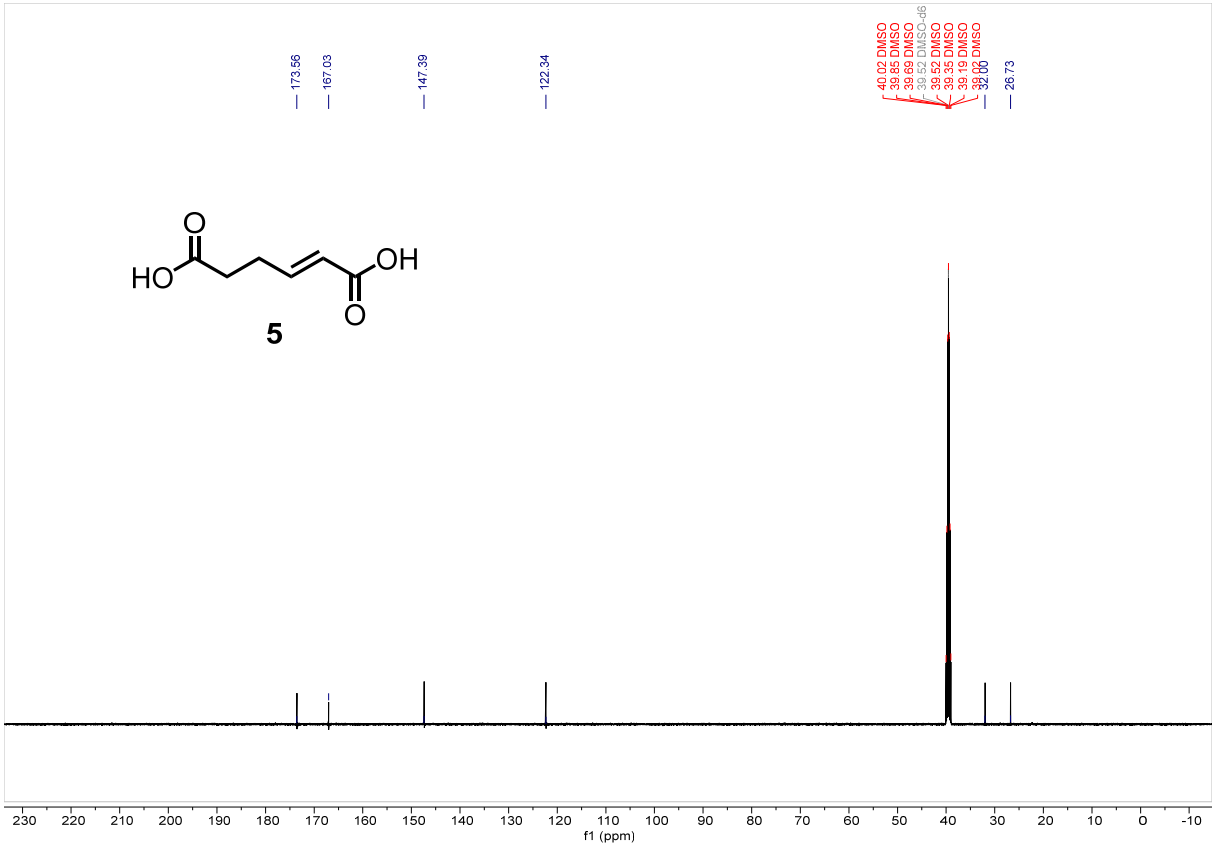
3-(3-Oxo-1,3-dihydroisobenzofuran-1-yl)propyl 2,3-dihydroxybenzoate, pedicellosine 65



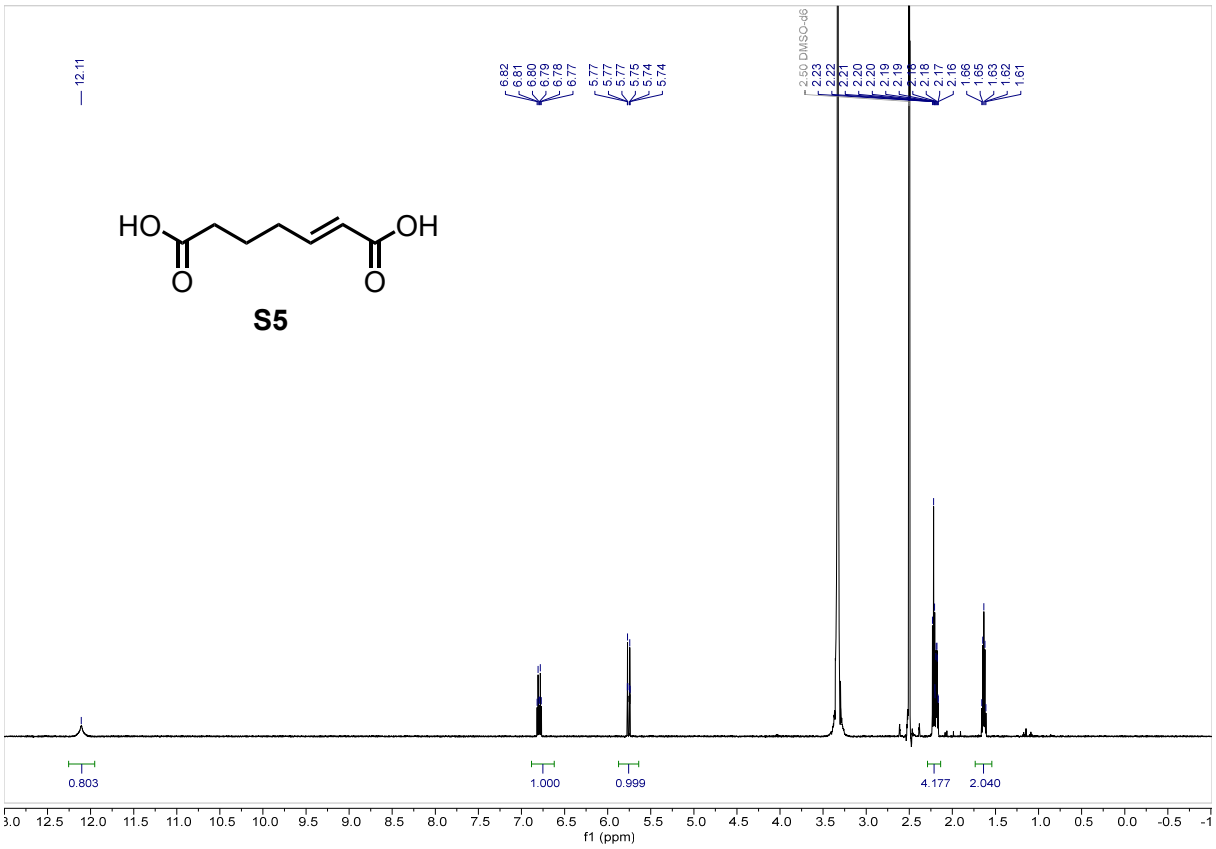


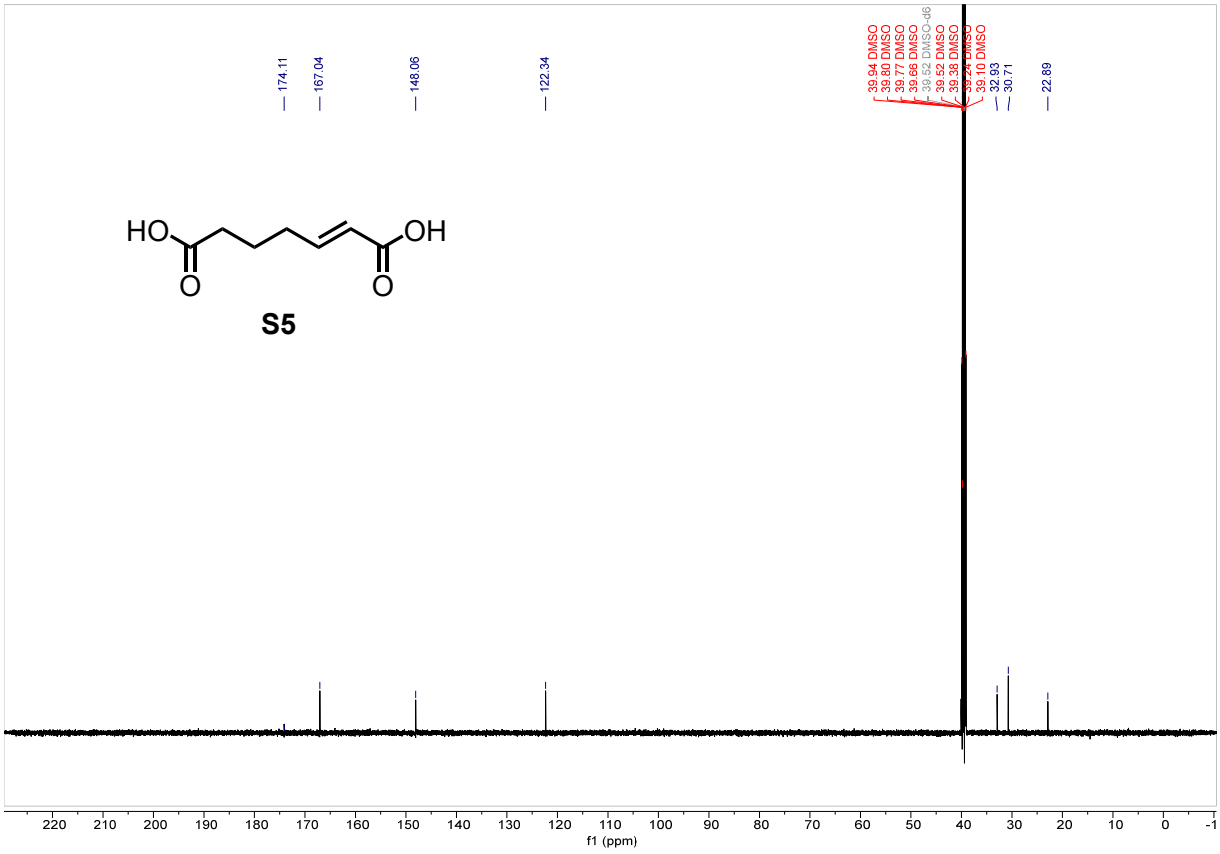
(*E*)-hex-2-enedioic acid 5





(*E*)-hept-2-enedioic acid S5





5. References

1. L. C. Kao, A. Sen, Platinum(II) Catalysed Selective Remote Oxidation of Unactivated C−H Bonds in Aliphatic Carboxylic Acids. *J. Chem. Soc., Chem. Commun.* 1242–1243 (1991).

2. B. D. Dangel, J. A. Johnson, D. Sames, Selective functionalization of amino acids in water: A synthetic method via catalytic C−H bond activation. *J. Am. Chem. Soc*. **123**, 8149–8150 (2001).

3. R. Giri, N. Maugel, J. J. Li, D. H. Wang, S. P. Breazzano, L. B. Saunders, J. Q. Yu, Palladium-catalyzed methylation and arylation of sp^2 and sp^3 C−H bonds in simple carboxylic acids. *J. Am. Chem. Soc*. **129**, 3510–3511 (2007).

4. Z. Zhuang, C. B. Yu, G. Chen, Q. F. Wu, Y. Hsiao, C. L. Joe, J. X. Qiao, M. A. Poss, J. Q. Yu, Ligand-Enabled β-C(sp^3)−H Olefination of Free Carboxylic Acids. *J. Am. Chem. Soc*. **140**, 10363–10367 (2018).

5. Z. Zhuang, A. N. Herron, Z. Fan, J. Q. Yu, Ligand-Enabled Monoselective β-C(sp^3)−H Acyloxylation of Free Carboxylic Acids Using a Practical Oxidant. *J. Am. Chem. Soc*. **142**, 6769–6776 (2020).

6. Z. Zhuang, J. Q. Yu, Lactonization as a general route to β-C(sp^3)–H functionalization. *Nature*. **577**, 656–659 (2020).

7. Z. Zhuang, A. N. Herron, J. Q. Yu, Synthesis of Cyclic Anhydrides via Ligand-Enabled C–H Carbonylation of Simple Aliphatic Acids. *Angew. Chem. Int. Ed*. **60**, 16382–16387 (2021).

8. K. K. Ghosh, M. van Gemmeren, Pd-Catalyzed β-C(sp^3)−H Arylation of Propionic Acid and Related Aliphatic Acids. *Chemistry - A European Journal*. **23**, 17697–17700 (2017).

9. K. K. Ghosh, A. Uttry, A. Koldemir, M. Ong, M. van Gemmeren, Direct β-C(sp^3)−H acetoxylation of aliphatic carboxylic acids. *Org. Lett*. **21**, 7154–7157 (2019).

10. K. K. Ghosh, A. Uttry, F. Ghiringhelli, A. Mondal, M. van Gemmeren, Ligand-Enabled γ-C(sp^3)–H Olefination of Free Carboxylic Acids. *Angew. Chem. Int. Ed*. **59**, 12848–12852 (2020).

11. F. Ghiringhelli, A. Uttry, K. K. Ghosh, M. van Gemmeren, Direct β-and γ-C(sp^3)−H Alkynylation of Free Carboxylic Acids. *Angew. Chem. Int. Ed*. **59**, 23127–23131 (2020).

12. A. Uttry, S. Mal, M. van Gemmeren, Late-Stage β-C(sp^3)−H Deuteration of Carboxylic Acids. *J. Am. Chem. Soc*. **143**, 10895–10901 (2021).

13. Z. Wang, L. Hu, N. Chekshin, Z. Zhuang, S. Qian, J. X. Qiao, J.-Q. Yu, Ligand-controlled divergent dehydrogenative reactions of carboxylic acids via C−H activation. *Science*. **374**, 1281–1285 (2021).

14. M. S. Chen, M. C. White, A Predictably Selective Aliphatic C–H Oxidation Reaction for Complex Molecule Synthesis. *Science*. **318**, 783–787 (2007).

15. L. Vicens, M. Bietti, M. Costas, General Access to Modified α-Amino Acids by Bioinspired Stereoselective γ-C−H Bond Lactonization. *Angew. Chem. Int. Ed*. **60**, 4740–4746 (2021).

16. J. Schwarz, B. König, Decarboxylative reactions with and without light-a comparison. *Green Chemistry*. **20**, 323–361 (2018).

17. S. K. Sartori, M. A. N. Diaz, G. Diaz-Muñoz, Lactones: Classification, synthesis, biological activities, and industrial applications. *Tetrahedron*. **84**, 132001–132039 (2021).

18. M. Seitz, O. Reiser, Synthetic approaches towards structurally diverse γ-butyrolactone natural-product-like compounds. *Current Opinion in Chemical Biology*. **9** (2005), pp. 285–292.

19. E. J. Corey, M. C. Kang, M. C. Desai, A. K. Ghosh, I. N. Houpis, Total synthesis of (.+-.)-ginkgolide B. *J. Am. Chem. Soc.* **110**, 649–651 (1988).

20. M. T. Crimmins, J. M. Pace, P. G. Nantermet, A. S. Kim-Meade, J. B. Thomas, S. H. Watterson, A. S. Wagman, The total synthesis of (±)-ginkgolide B. *J. Am. Chem. Soc*. **122**, 8453–8463 (2000).

21. E. J. Corey, W. G. Su, Total synthesis of a C15 ginkgolide, (.+-.)-bilobalide. *J. Am. Chem. Soc.* **109**, 7534–7536 (1987).

22. M. A. Baker, R. M. Demoret, M. Ohtawa, R. A. Shenvi, Concise asymmetric synthesis of (−)-bilobalide. *Nature*. **575**, 643–646 (2019).

23. E. J. Corey, H. L. Pearce, Total synthesis of picrotoxinin. *J. Am. Chem. Soc.* **101**, 5841–5843 (1979).

24. B. M. Trost, M. J. Krische, General Strategy for the Asymmetric Synthesis of the Picrotoxanes. *J. Am. Chem. Soc.* **118**, 233–234 (1996).

25. S. W. M. Crossley, G. Tong, M. J. Lambrecht, H. E. Burdge, R. A. Shenvi, Synthesis of (-)-Picrotoxinin by Late-Stage Strong Bond Activation. *J. Am. Chem. Soc*. **142**, 11376–11381 (2020).

26. E. Lee, C. H. Yoon, Y. Sung, Y. K. Kim, M. Yun, S. Kim, Total Synthesis of (+)-Cladantholide and (−)-Estafiatin: 5-Exo, 7-Endo Radical Cyclization Strategy for the Construction of Guaianolide Skeleton. *J. Am. Chem. Soc.* **119**, 8391–8392 (1997).

27. G. Shabir, A. Saeed, H. R. El-Seedi, Natural isocoumarins: Structural styles and biological activities, the revelations carry on. *Phytochemistry*. **181**, 112568–112787 (2021).

28. A. D. Kinghorn, H. Falk, S. Gibbons, J. Kobayashi, Eds., *Progress in the Chemistry of Organic Natural Products* (Springer Nature, 2017), vol. 104.

29. F. Zaragoza Dörwald, *Side Reactions in Organic Synthesis: A Guide to Successful Synthesis Design* (Wiley, 2004).

30. X. Chen, J. J. Li, X. S. Hao, C. E. Goodhue, J. Q. Yu, Palladium-catalyzed alkylation of aryl C-H bonds with sp^3 organotin reagents using benzoquinone as a crucial promoter. *J. Am. Chem. Soc*. **128**, 78–79 (2006).

31. G. Xia, J. Weng, L. Liu, P. Verma, Z. Li, J. Q. Yu, Reversing conventional site-selectivity in C(sp^3)–H bond activation. *Nature Chemistry*. **11**, 571–577 (2019).

32. P. Novák, A. Correa, J. Gallardo-Donaire, R. Martin, Synergistic palladium-catalyzed C(sp^3)−H Activation/C(sp^3)−O bond formation: A direct, step-economical route to benzolactones. *Angew. Chem. Int. Ed*. **50**, 12236–12239 (2011).

33. J. M. Lee, S. Chang, Pt-Catalyzed sp^3 C−H bond activation of *o*-alkyl substituted aromatic carboxylic acid derivatives for the formation of aryl lactones. *Tetrahedron Letters*. **47**, 1375–1379 (2006).

34. T. Lin, G. Wang, W. Shan, D. Zeng, R. Ding, X. Jiang, D. Zhu, X. Liu, S. Yang, H. Chen, Myrotheciumones: Bicyclic cytotoxic lactones isolated from an endophytic fungus of Ajuga decumbens. *Bioorganic and Medicinal Chemistry Letters*. **24**, 2504–2507 (2014).

35. S. Begum, T. K. Chakraborty, Cp_2TiCl-Mediated Reductive Cyclization: Total Synthesis of Pestalotiolactone A, Myrotheciumone A, and Scabrol A. *J. Org. Chem*. **86**, 11812–11821 (2021).

36. S. N. Khan, M. K. Zaman, R. Li, Z. Sun, A General Method for Photocatalytic Decarboxylative Hydroxylation of Carboxylic Acids. *J. Org. Chem*. **85**, 5019–5026 (2020).

37. E. M. Mpondo, J. Garcia, A. J. Chulia, New Phthalides from Gentiana pedicellata. *Planta Medica*. **53**, 297–298 (1987).

38. Q. Gao, S. B. Li, Synthesis of 3-(3-Hydroxypropyl)-phthalide and Pedicellosine. *Chinese Chemical Letters*. **10**, 109–110 (1999).

39. Z. Li, Z. Wang, N. Chekshin, S. Qian, J. X. Qiao, P. T. Cheng, K.-S. Yeung, W. R. Ewing, J.-Q. Yu, A tautomeric ligand enables directed C−H hydroxylation with molecular oxygen. *Science*. **372**, 1452–1457 (2021).

40. O. S. Shneider, E. Pisarevsky, P. Fristrup, A. M. Szpilman, Oxidative umpolung α-alkylation of ketones. *Org. Lett*. **17**, 282–285 (2015).

41. M. Azimioara, P. Alper, C. Cow, D. Mutnick, V. Nikulin, G. Lelais, J. Mecom, M. McNeill, P. Y. Michellys, Z. Wang, E. Reding, M. Paliotti, J. Li, D. Bao, J. Zoll, Y. Kim, M. Zimmerman, T. Groessl, T. Tuntland, S. B. Joseph, P. McNamara, H. M. Seidel, R. Epple, Novel tricyclic pyrazolopyrimidines as potent and selective GPR119 agonists. *Bioorganic and Medicinal Chemistry Letters*. **24**, 5478–5483 (2014).

42. D. D. Bume, C. R. Pitts, R. T. Jokhai, T. Lectka, Direct, visible light-sensitized benzylic C−H fluorination of peptides using dibenzosuberenone: selectivity for phenylalanine-like residues. *Tetrahedron*. **72**, 6031–6036 (2016).

43. J. T. Pinhey, E. Ritchie, W. C. Taylor, The Chemical Constituents Of Himantandra (Galbulimima) Species. *Australian Journal of Chemistry*. **14**, 106–134 (1961).

44. J. le Nôtre, D. van Mele, C. G. Frost, A new method for constructing quaternary carbon centres: Tandem rhodium-catalysed 1,4-addition/intramolecular cyclisation. *Advanced Synthesis and Catalysis*. **349**, 432–440 (2007).

45. F. Bonati, G. Minghetti, Mercury(II) Derivatives Of Acetylacetone. *Journal of Organometallic Chemistry*. **22**, 5–10 (1970).