Biocatalytic retrosynthesis approaches to D-(2,4,5-trifluorophenyl)alanine, key precursor of the antidiabetic sitagliptin

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ELECTRONIC SUPPLEMENTARY INFORMATION (ESI)

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Supplementary figures

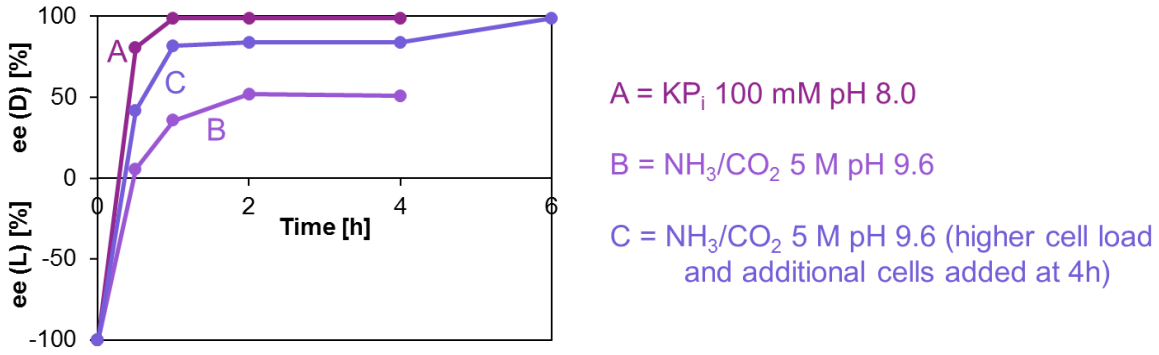


Figure S1. Preliminary test showing the feasibility of LAAD-DAAT mediated stereoinversion in the presence of 5 M ammonia (model substrate L-phenylalanine).

Supplementary tables

Table S1. Enantiomeric excess values for the PAL mediated hydroamination of **6**.

Buffer	AvPAL ee (L) [%][a]	RgPAL ee (L) [%][a]	PbPAL ee (L) [%][a]
NH_3/H_2SO_4 5 M, pH 9.6	97	97	80
NH_3/H_2SO_4 2.5 M, pH 9.6	93	98	58
NH_3/CO_2 5 M, pH 10.0	98	99	82
NH_3/CO_2 2.5 M, pH 10.0	96	99	63
$H_2NCOONH_4$ 4 M, pH 9.9	98	99	86
$H_2NCOONH_4$ 2 M, pH 9.9	61	98	84

Expt. cond.: 50 mM **6**, 50 mg mL^{-1} PAL whole cells, 37°C, 12 h.
[a] Determined by reverse-phase HPLC on a chiral phase.

Table S2. Preliminary screening of a panel of EREDs for the reduction of **7** (94:6 *Z*/*E* mixture).

ERED	Conv. [%][a]	*Z*/*E* ratio [–][b]	ee [%][c]
OYE1	11	21	90
OYE2	<1	24	–
OYE3	44	18	90
OYE2.6	48	6	79
YqjM	6	46	–
NemA	5	94	–
OPR1	<1	19	–
PETNR	<1	19	–
LeOPR	<1	24	–

Expt. cond.: 5 mM **7**, 0.1 mg mL^{-1} isol. ERED, 0.05 mg mL^{-1} isol. GDH, 4.0 equiv. D-Glc, 0.1 mM $NADP^+$, 5% *v*/*v* DMSO, 50 mM KP_i buffer, pH 7.0, 30°C, 24 h.
[a] Determined by GC-MS.
[b] *Z*/*E* ratio of the unconverted **7** after the reaction, determined by GC-MS.
[c] Determined by direct-phase HPLC on a chiral phase.

Table S3. Additional conditions tested for the reduction of **7** with raw lysates of OYE3 and GDH.

Conc. 7 [mM]	Biocatalysts	Conv. [%][a]
5	1 mg mL^{-1} OYE3 isol., 0.03 mg mL^{-1} GDH isol.	>99
10	1 mg mL^{-1} OYE3 isol., 0.03 mg mL^{-1} GDH isol.	>99
20	1 mg mL^{-1} OYE3 isol., 0.03 mg mL^{-1} GDH isol.	65
5	500 µL mL^{-1} OYE3 lysate[b], 150 µL mL^{-1} GDH lysate[c]	88
5	600 µL mL^{-1} OYE3 lysate[b], 200 µL mL^{-1} GDH lysate[c]	95
5	700 µL mL^{-1} OYE3 lysate[b], 200 µL mL^{-1} GDH lysate[c]	97

Expt. cond.: 5-20 mM subs. **7**, 4.0 equiv. D-Glc, 0.5 mM $NADP^+$, 5% *v*/*v* DMSO, 50 mM KP_i buffer, pH 7.0, 30°C, 24 h.
[a] Determined by GC-MS.
[b] Prepared from 6.75 g cell wet weight in 30 mL lysis buffer.
[c] Prepared from 8.82 g cell wet weight in 30 mL lysis buffer.

General experimental methods

Reagents and solvents

Analytical grade reagents and solvents were purchased from Sigma-Aldrich, Alfa Aesar or Fluorochem and used without further purification.

NMR spectroscopy

^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker Avance 400 spectrometer (400 MHz) at 298 K. Chemical shifts are reported as δ in parts per million (ppm) and are calibrated against residual solvent signal. A water suppression method was used to obtain the ^{1}H NMR spectra of amino acid derivatives in D_2O (basified with a small amount of NaOH), with HDO as the residual solvent peak (4.79 ppm). NMR data are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz) and proton integration.

HRMS

HRMS analyses were performed using an Agilent 1200 series LC system, coupled to an Agilent 6520 QTOF mass spectrometer, ESI positive mode. The sample (2 µL) was flow-injected into 0.3 mL min^{-1} MeCN/H_2O 1:1 + formic acid 0.1% v/v. The data was analyzed using Agilent MassHunter software.

HPLC

Reverse-phase HPLC analysis were performed on an Agilent 1200 series LC system. Conversions of **5** and **6** to **2** were determined on a non-chiral Zorbax Extend C18 column (50 mm × 4.6 mm × 3.5 µm, Agilent), according to the following method: flow rate 1.0 mL min^{-1}; temperature: 40°C; detection wavelength 250 nm; mobile phase aq. NH_4OH 0.1 M pH 10.0 / MeOH; gradient elution 90:10 (0-1 min), 90:10-10:90 (1-18 min), 10:90 (18-21 min), 10:90-90:10 (21-23 min), 90:10 (23-30 min). Enantiomeric excess values of **2** were determined on a chiral Crownpak CR(+) column (150 mm × 4 mm × 3.5 µm, Daicel), according to the following method: flow rate 1.0 mL min^{-1}; temperature: 25°C; detection wavelength 215 nm; mobile phase aq. $HClO_4$ 0.16% *w/v* / MeOH; isocratic elution 96:4. Enantiomeric excess values of **15** were determined on a LUX 5µm Cellulose-3 column (250 mm × 4.6 mm × 5.0 µm, Phenomenex), according to the following method: flow rate 0.6 mL min^{-1}; temperature: 25°C; detection wavelength 215 nm; mobile phase *n*-hexane / *i*-PrOH; isocratic elution 99:1.

GC-MS

GC-MS analyses were performed on an Agilent 7980B GC 5977B MSD system equipped with a HP-5-MS column (30 m × 0.25 mm × 0.25 µm, Agilent), according to the following temperature program: 60°C (1 min), 6°C/min, 150°C (1 min), 12°C/min, 280°C (5 min).

Strains and plasmids

Expression constructs were obtained as described previously, details and references are provided in the table below. *E. coli* DH5α was used as a cloning host for plasmid propagation, *E. coli* BL21(DE3) as an expression host for protein production.

Enzyme	Plasmid	Source	Sequence	Ref.
DAADH	pRSF-Duet-GDH-DAADH	*Corynebacterium glutamicum*	UniProt P04964	[S1]
GDH	pKTS-GDH	*Bacillus megaterium* DSM509	GenBank D90043	[S2]
DAAT	pET11a-DAAT-T242G	*Bacillus* sp. YM-1	GenBank J04460.1	[S3]
LAAD	pET28a-LAAD	*Proteus mirabilis*	UniProt B4EZ74	[S4]
DDO	pET11a-DDO	*Bos taurus*	GenBank CAA64622.1	[S3]
RgPAL	pET11b-RgPAL	*Rhodotorula glutinis*	GenPept XP_016272209	[S4]
AvPAL	pET11b-AvPAL	*Anabaena variabilis*	GenPept WP_011320679	[S4]
PbPAL	pET30a-PbPAL	*Planctomyces brasiliensis*	GenPept WP_013629471	[S5]
OYE1	pET30a-OYE1	*Saccharomyces pastorianus*	UniProt Q02899	[S6]
OYE2	pET30a-OYE2	*Saccharomyces cerevisiae*	UniProt Q03558	[S2]
OYE3	pET30a-OYE3	*Saccharomyces cerevisiae*	UniProt P41816	[S2]
OYE2.6	pDJBx-OYE2.6	*Scheffersomyces stipitis*	UniProt A3LT82	[S6]
YqjM	pET30a-OYE1	*Bacillus subtilis*	UniProt P54550	[S7]
NemA	pDJBx-NemA	*Escherichia coli*	UniProt P77258	[S6]
LeOPR1	pDJBx-LeOPR1	*Solanum lycopersicum*	UniProt Q9XG54	[S6]
PETNR	pDJBx-PETNR	*Enterobacter cloacae*	UniProt P71278	[S7]

Transformations of chemically competent cells were performed by incubating plasmid DNA (~20 ng) with the cells (50 µL aliquot) for 30 min on ice before heat shock (42°C, 20 s). SOC medium (1 mL) was immediately added, and the cells were incubated for 1 h at 37°C and 220 rpm. Colonies containing recombinant plasmids were selected on LB-agar plates containing the suitable antibiotic.
Cell concentrations are indicated as weight of the wet cell paste (CWW) per unit of volume of the biotransformation mixture.

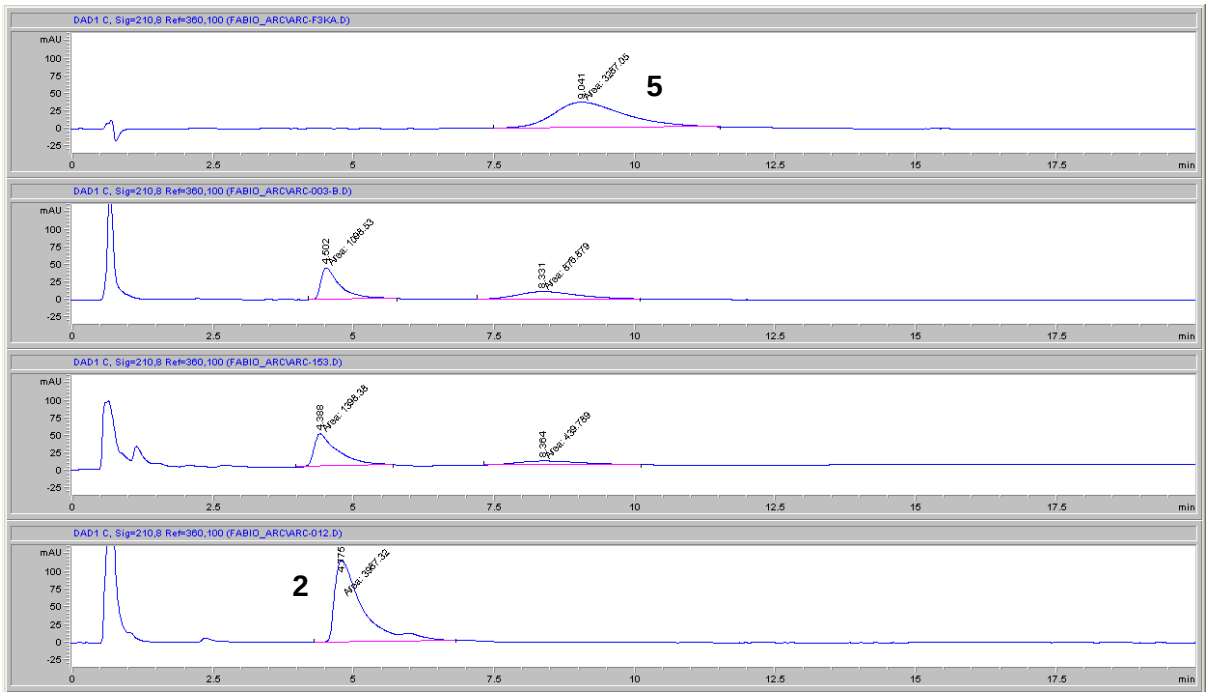
Biocatalyst preparation
A single colony of *E. coli* BL21(DE3) cells transformed with the suitable plasmid was used to inoculate LB medium (8 mL) supplemented with antibiotic. The culture was grown overnight at 37°C and 220 rpm, then used to inoculate the appropriate medium (800 mL) containing the same antibiotic. This culture was incubated according to the conditions listed in the table below for growth and protein production. After the specified time, the cells were harvested by centrifugation (1,700 x *g*, 20 min, 4°C), washed with KP_i buffer (100 mM, pH 7.4) and harvested again by centrifugation (1,700 x *g*, 20 min, 4°C). The cell pellet was aliquoted and stored at –20°C. Purification of the EREDs and of the GDH was performed according to previously published procedures.[S2,S7]

Enzyme	Plasmid	Growth conditions	Expression conditions	Ref.
DAADH+GDH	pRSF-Duet-GDH-DAADH	LB_{Kan}, 37°C, 180 rpm to OD_{600} ~0.6	50 µM IPTG 25°C, 180 rpm, 5 h,	[S1]
LAAD	pET28a-LAAD	LB_{Kan}, 37°C, 180 rpm to OD_{600} ~0.6	1 mM IPTG, 30°C, 180 rpm, 5 h,	[S4]
DAAT	pET11a-DAAT-T242G	LB_{Amp}, 37°C, 180 rpm to OD_{600} ~0.6	0.1 mM IPTG, 15°C, 180 rpm, o.n.	[S3]
DDO	pET11a-DDO	LB_{Amp}, 37°C, 180 rpm to OD_{600} ~0.6	0.1 mM IPTG, 15°C, 180 rpm, o.n.	[S3]
RgPAL AvPAL	pET11b-PAL	LB-AIM_{Amp}, 18°C, 180 rpm, 4 d		[S4
PbPAL	pET28b-PbPAL	LB-AIM_{Kan}, 18°C, 180 rpm, 4 d		[S5]
OYE1 OYE2 OYE3	pET30a-ERED	LB_{Kan}, 37°C, 220 rpm to OD_{600} ~0.6	0.1 mM IPTG, 30°C, 220 rpm, 5 h	[S2,S6]
YqjM	pMH-YqjM	TB_{Cam}, 37°C, 220 rpm to OD_{600} ~0.6	0.1 mM IPTG, 30°C, 220 rpm, 5 h	[S7]
OYE2.6 LeOPR1	pDJBx-ERED (GST-tag)	LB_{Amp}, 37°C, 220 rpm to OD_{600} ~0.6	0.1 mM IPTG, 30°C, 220 rpm, 5 h	[S6]
PETNR NemA	pDJBx-ERED	LB_{Amp}, 37°C, 220 rpm to OD_{600} ~0.6	0.1 mM IPTG, 30°C, 220 rpm, 5 h	[S6,S7]
GDH	pKTS-GDH	LB_{Amp}, 37°C, 220 rpm to OD_{600} ~0.6	0.1 mM IPTG, 50 ng mL^{-1} aTet, 37°C, 220 rpm, 5 h	[S2]

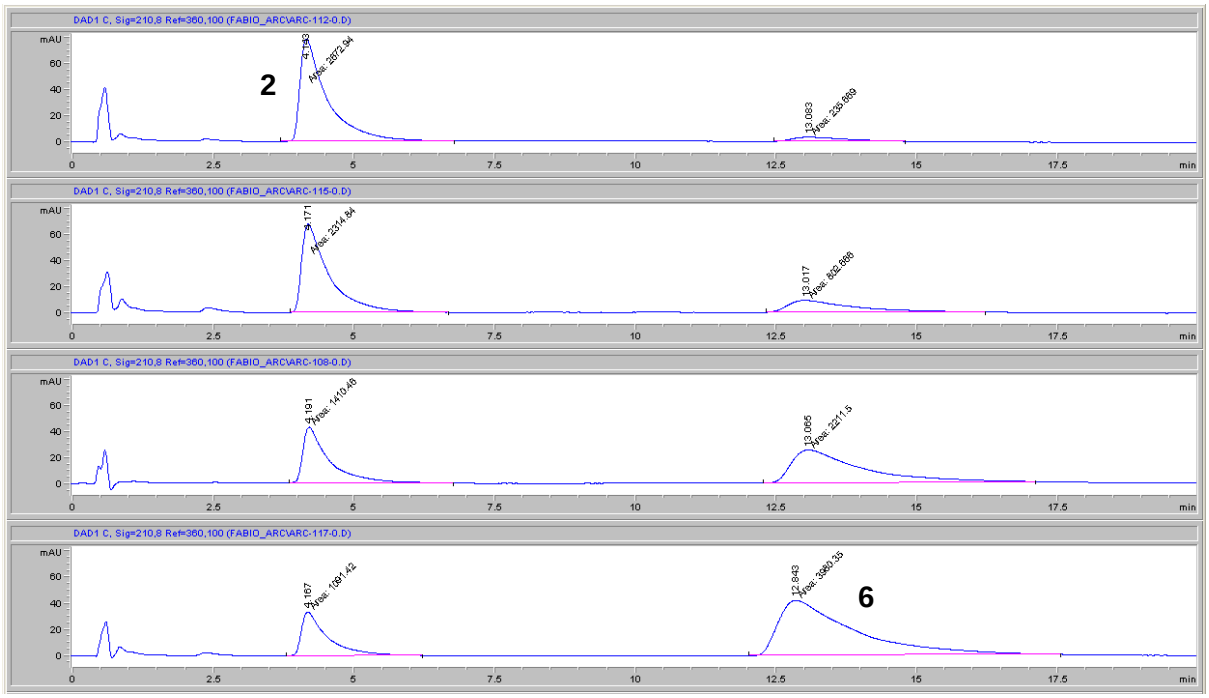
Abbreviations:
LB = Luria-Bertani medium
LB-AIM = LB-based autoinduction medium, including trace metals (Formedium Ltd.)
TB = terrific broth
Amp = ampicillin (100 µg mL^{-1})
Kan = kanamycin (60 µg mL^{-1})
Cam = chloramphenicol (30 µg mL^{-1})
IPTG = isopropyl β-D-1-thiogalactopyranoside
aTet = anhydrotetracyclin

Representative HPLC traces (non-chiral stationary phase)

Conversion of ketoacid **5** to amino acid D-**2**

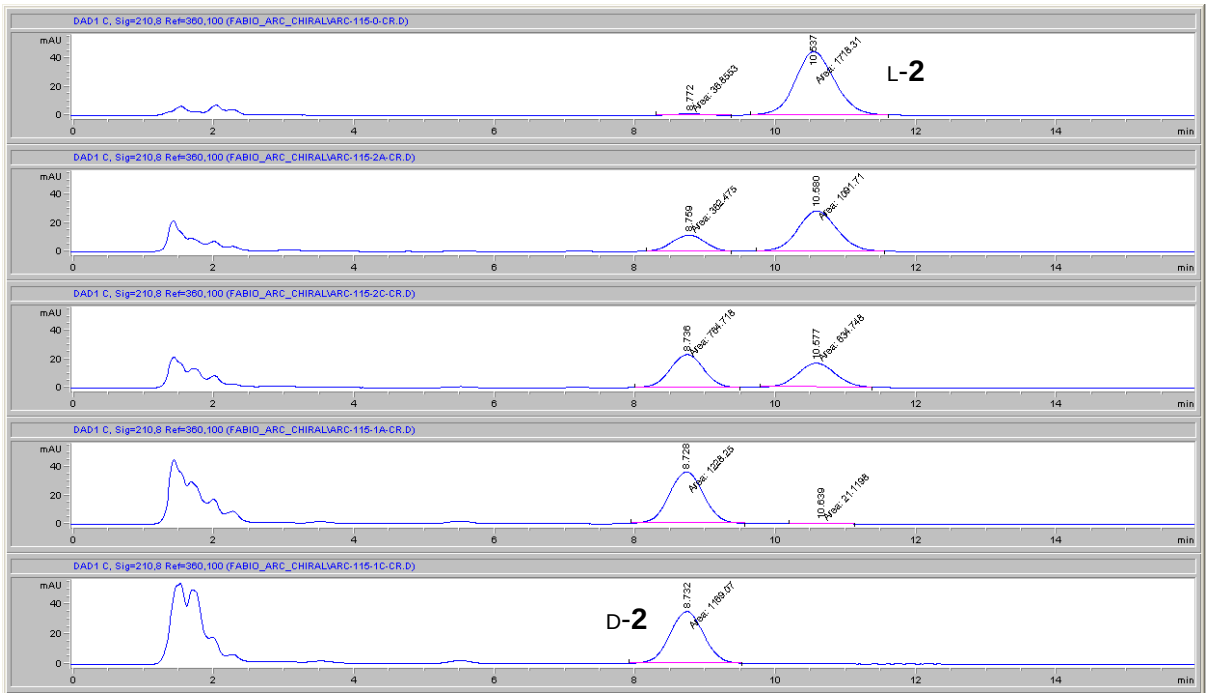


Conversion of cinnamic acid **6** to amino acid **2**

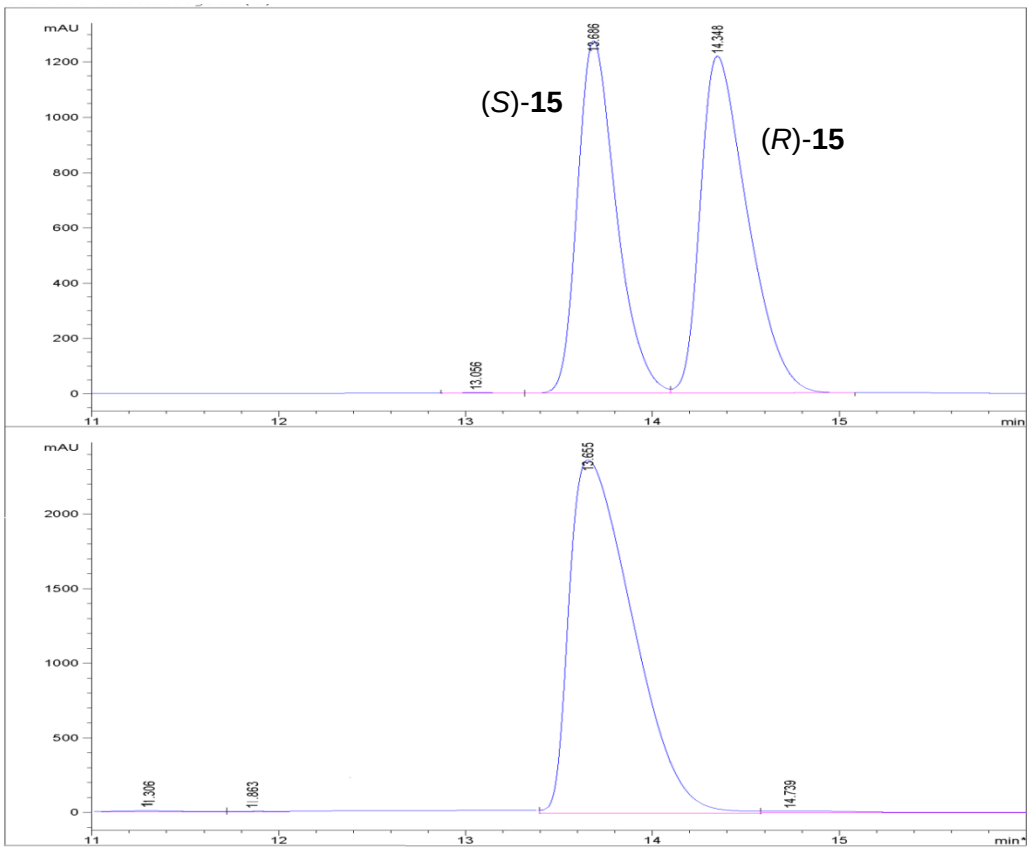


Representative HPLC traces (chiral stationary phase)

Enantiomeric excess of amino acid D-**2**

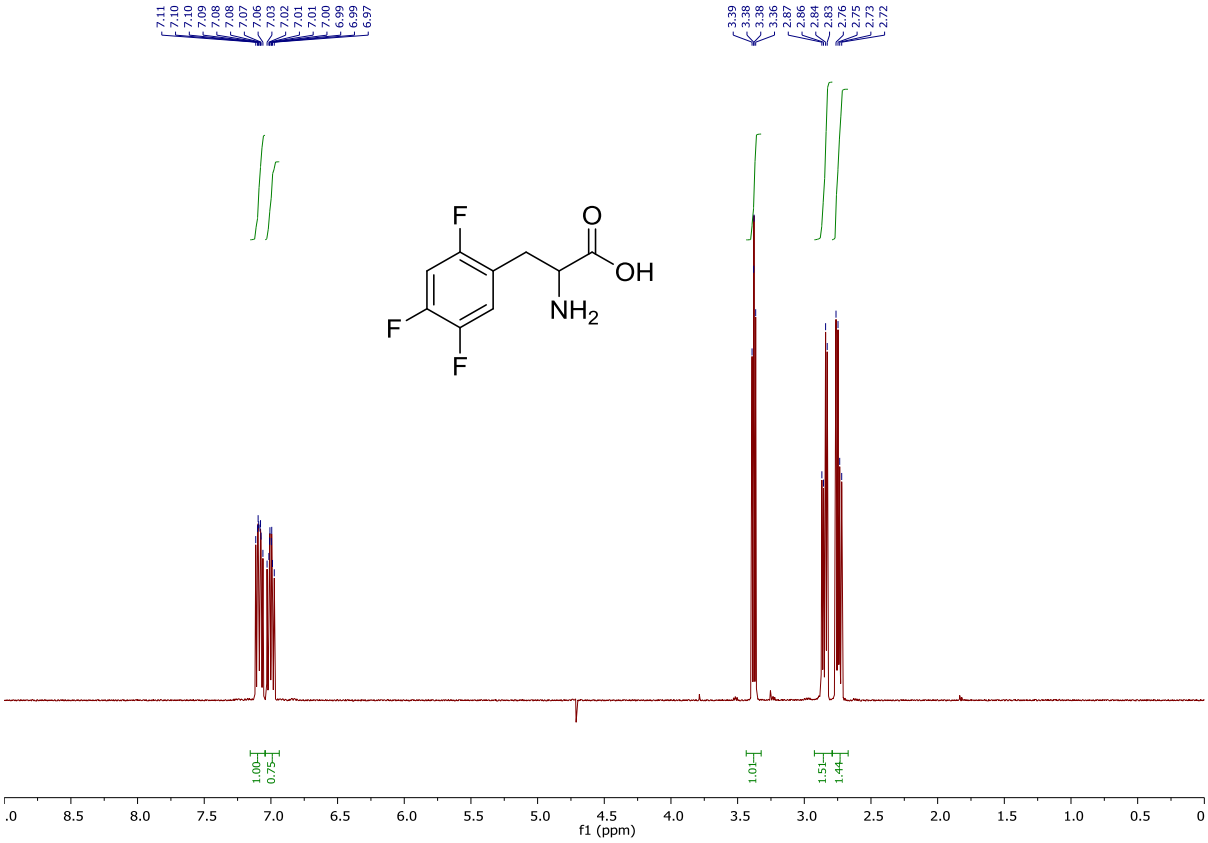


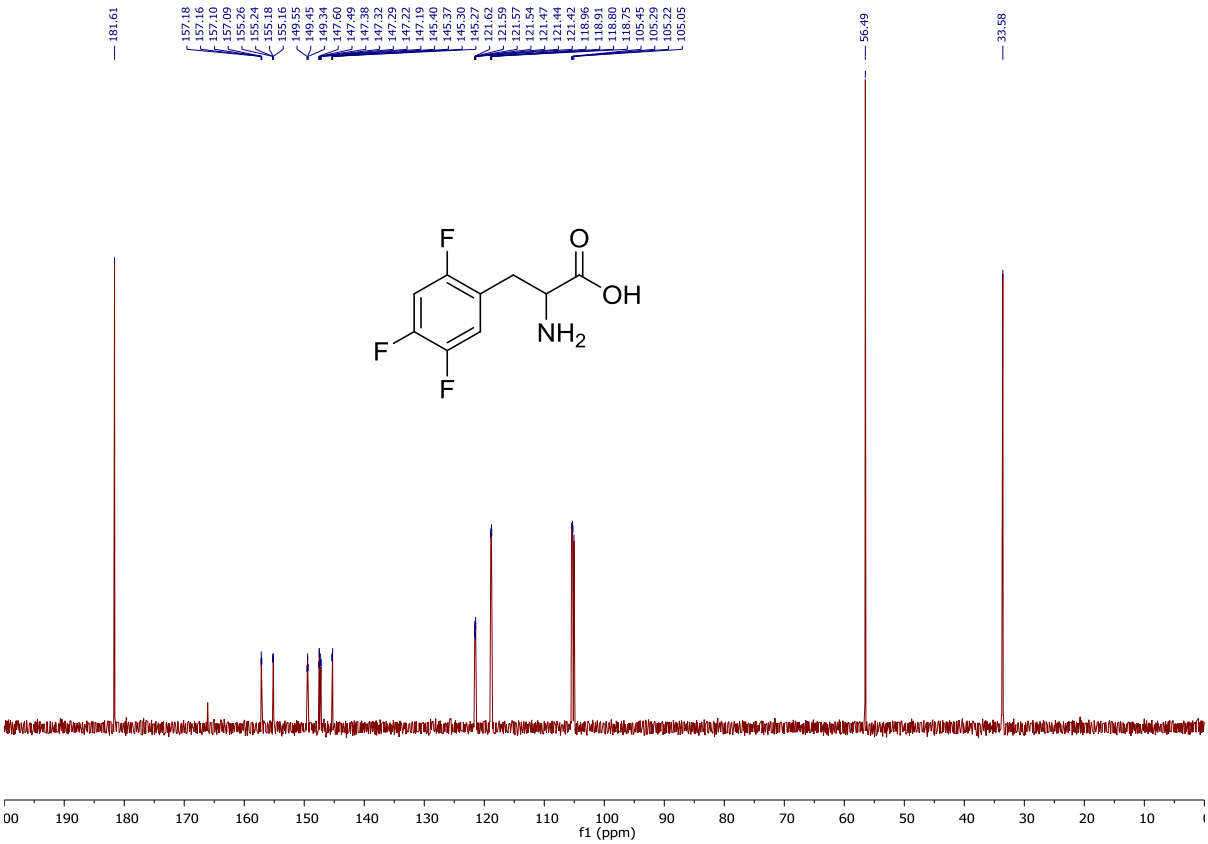
Enantiomeric excess of bromoester (*S*)-**15**

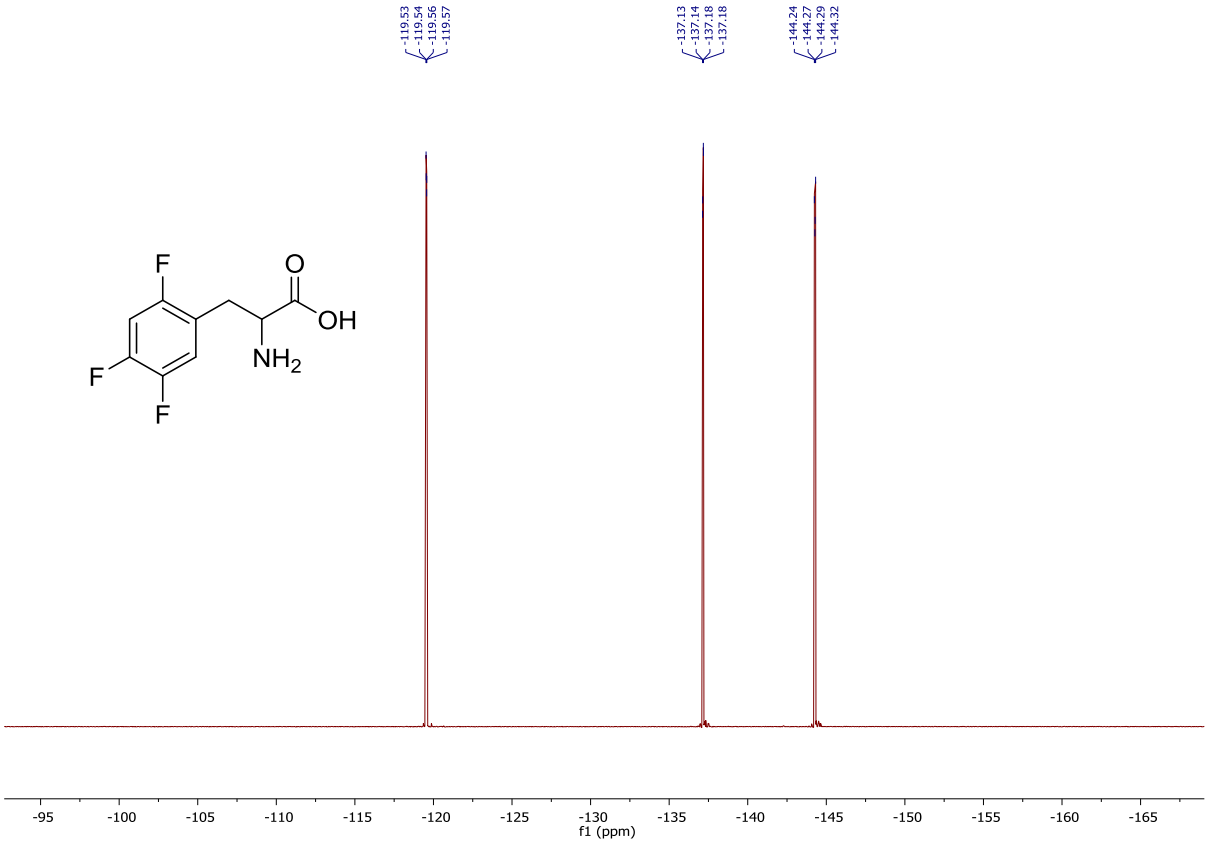


Copies of NMR spectra

2-Amino-3-(2,4,5-trifluorophenyl)propanoic acid (2)



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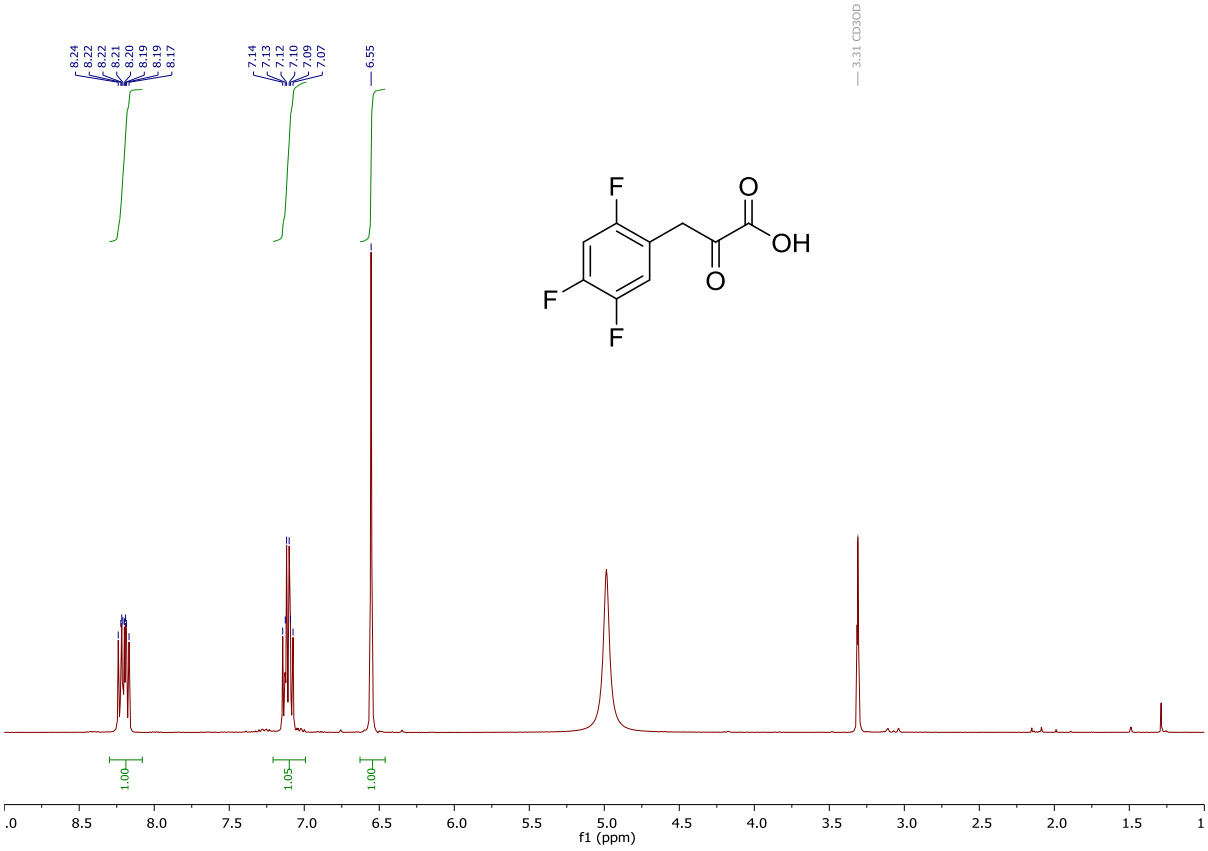
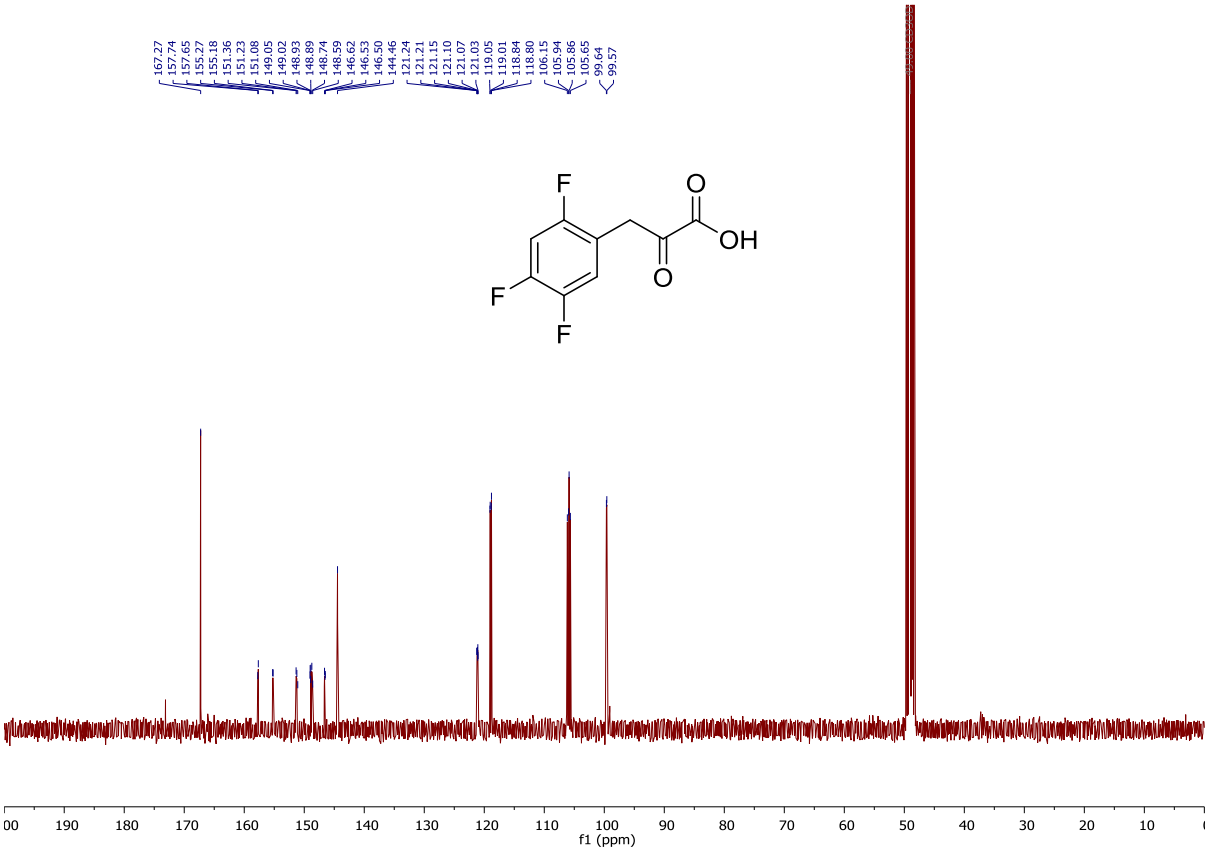
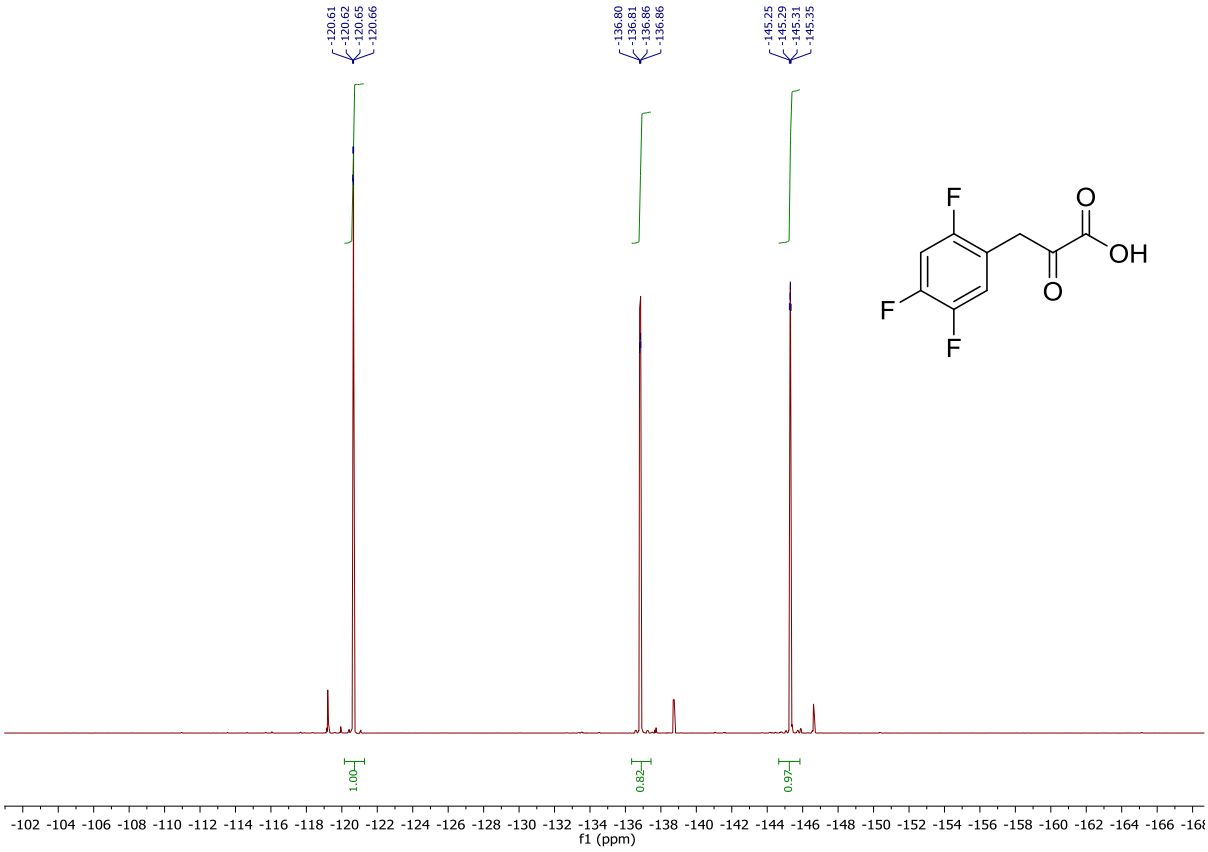
-137.18
-144.24
-144.27
-144.29
-144.32
F
O
OH
NH2
F
F
-95
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
-150
-155
-160
-165
f1 (ppm)

2-Oxo-3-(2,4,5-trifluorophenyl)propanoic acid (5)



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-145.35
F
O
OH
O
F
F
1.00
0.82
0.97
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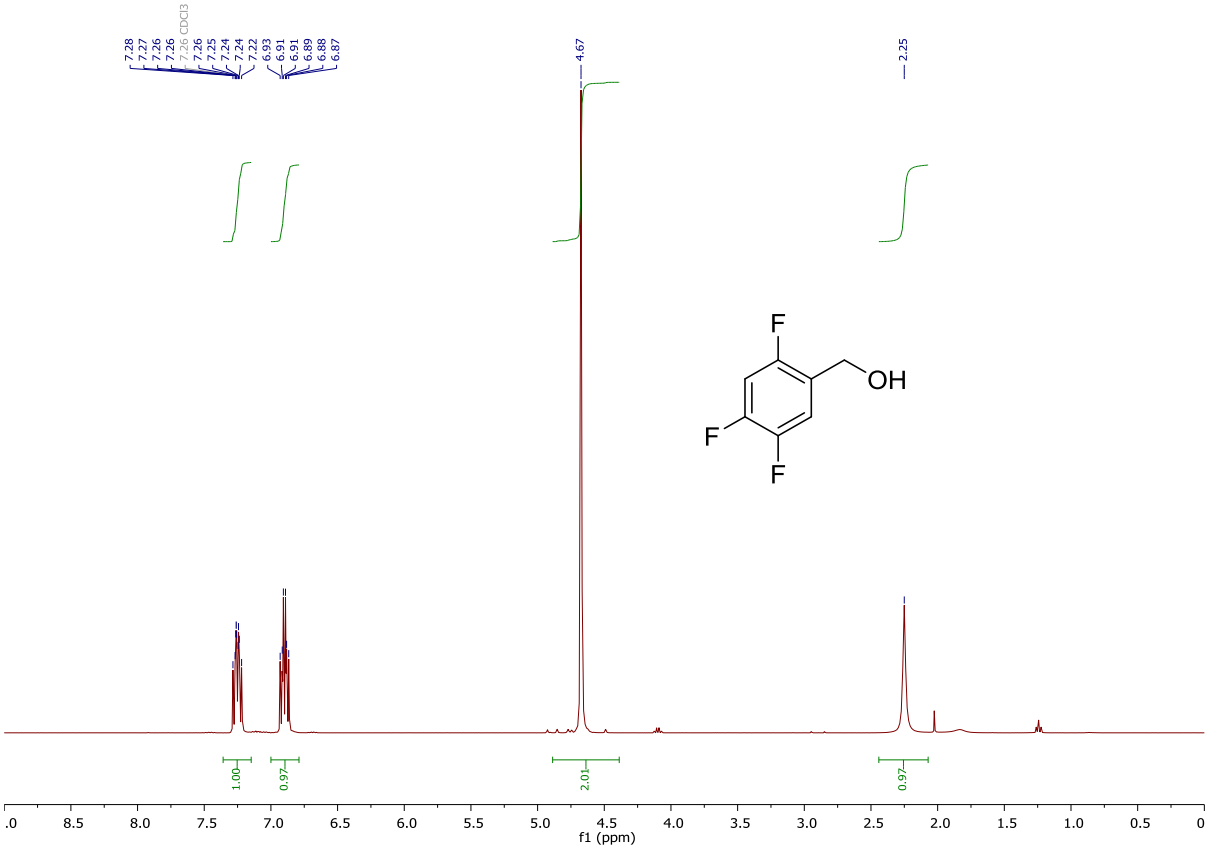
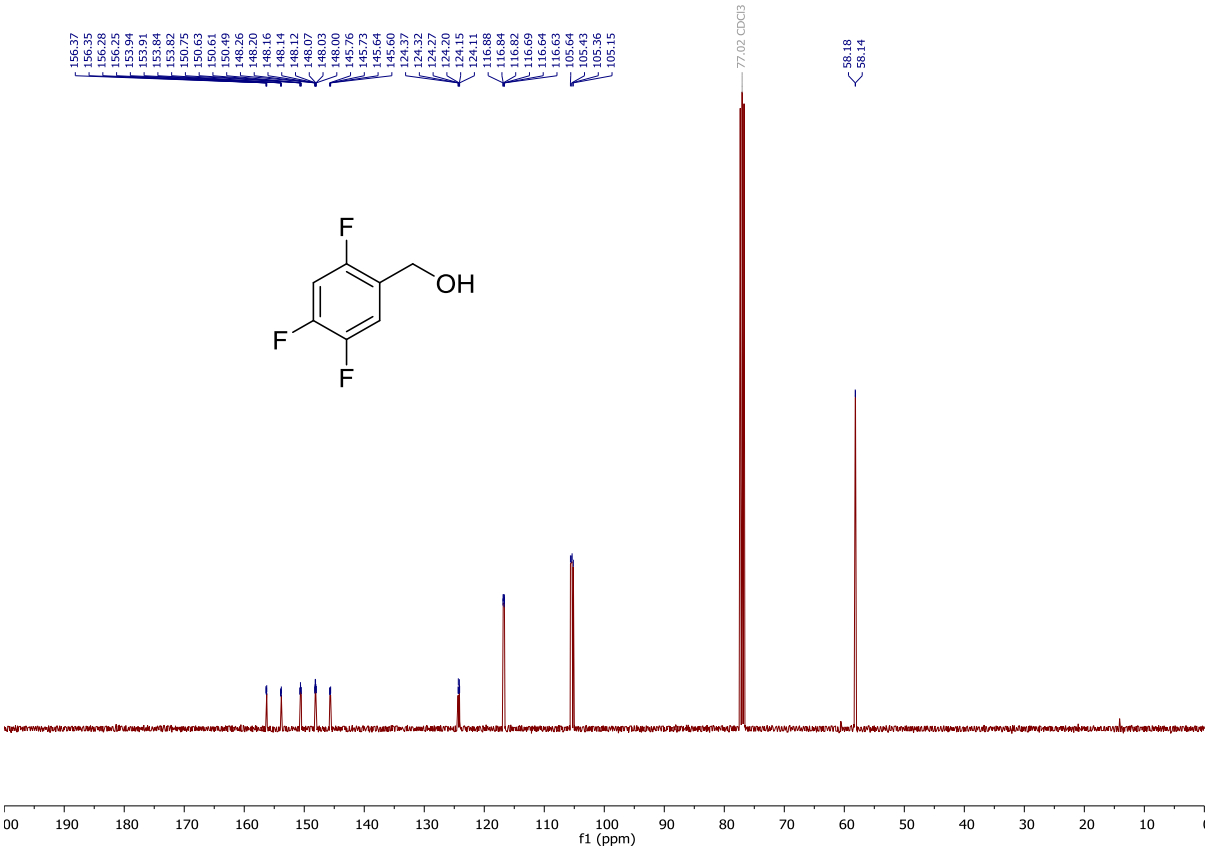
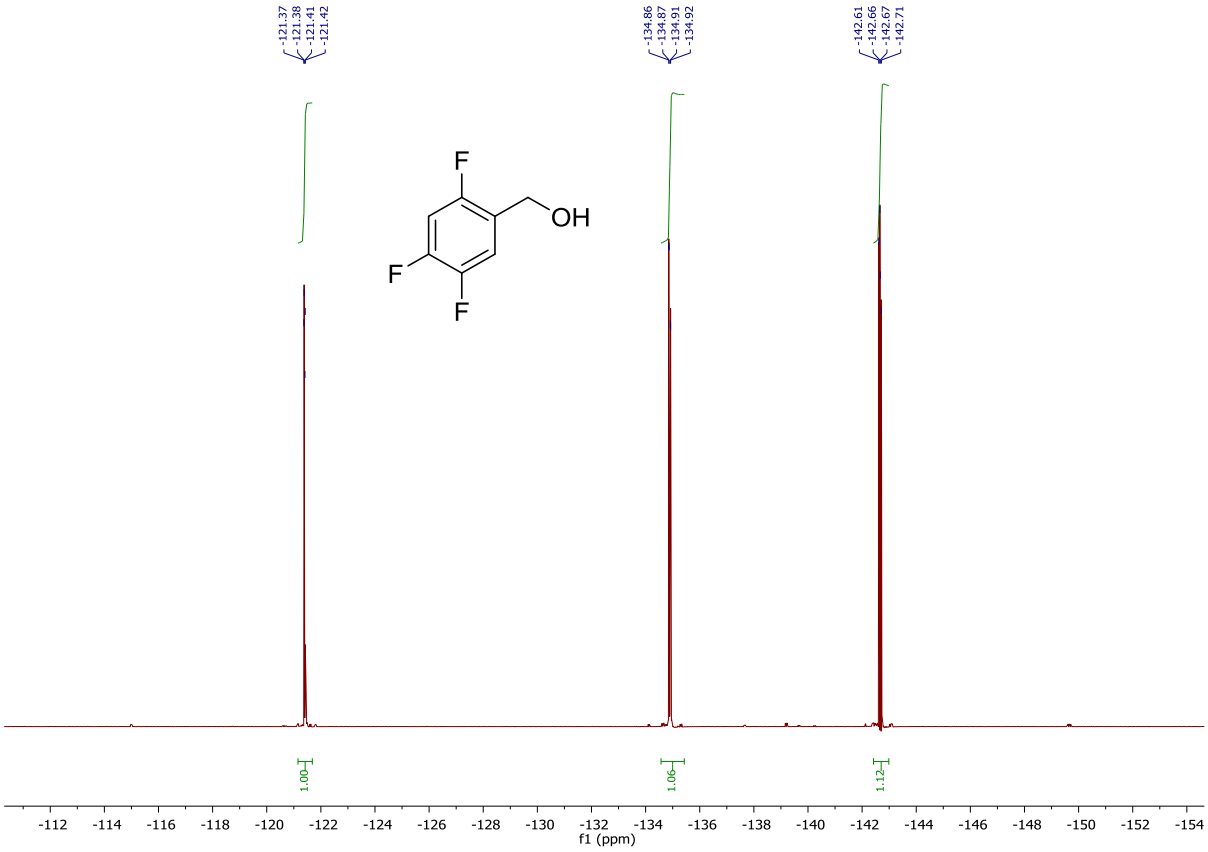
f1 (ppm)

(2,4,5-Trifluorophenyl)methanol (10)



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-122
-124
-126
-128
-130
-132
-134
-136
-138
-140
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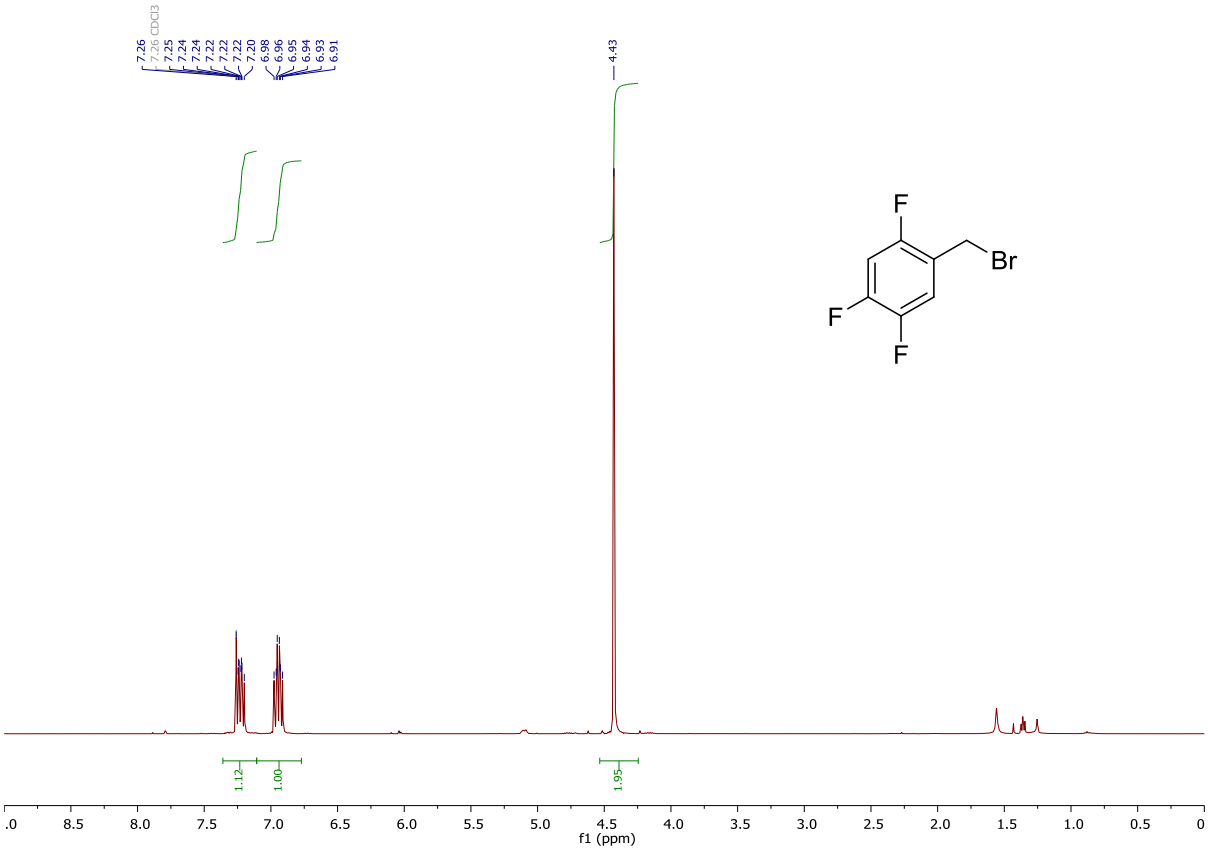
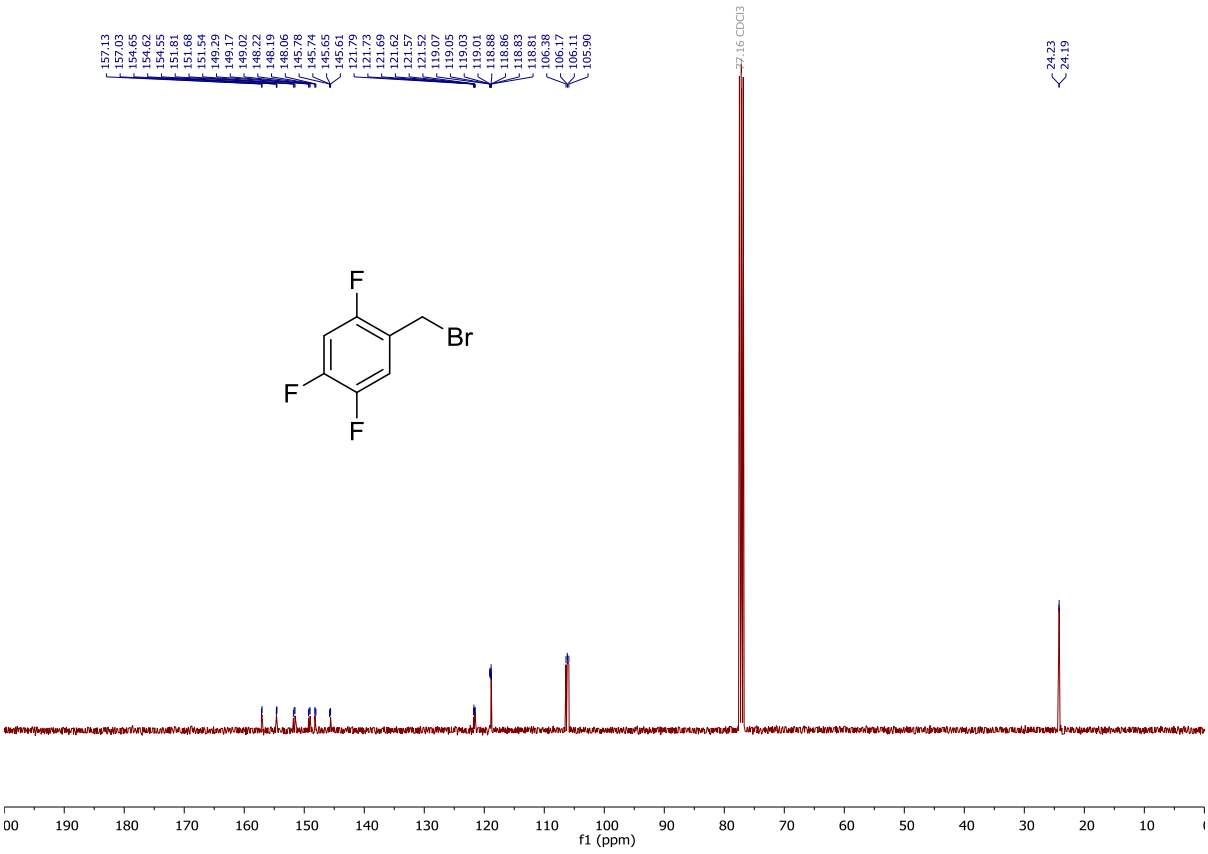
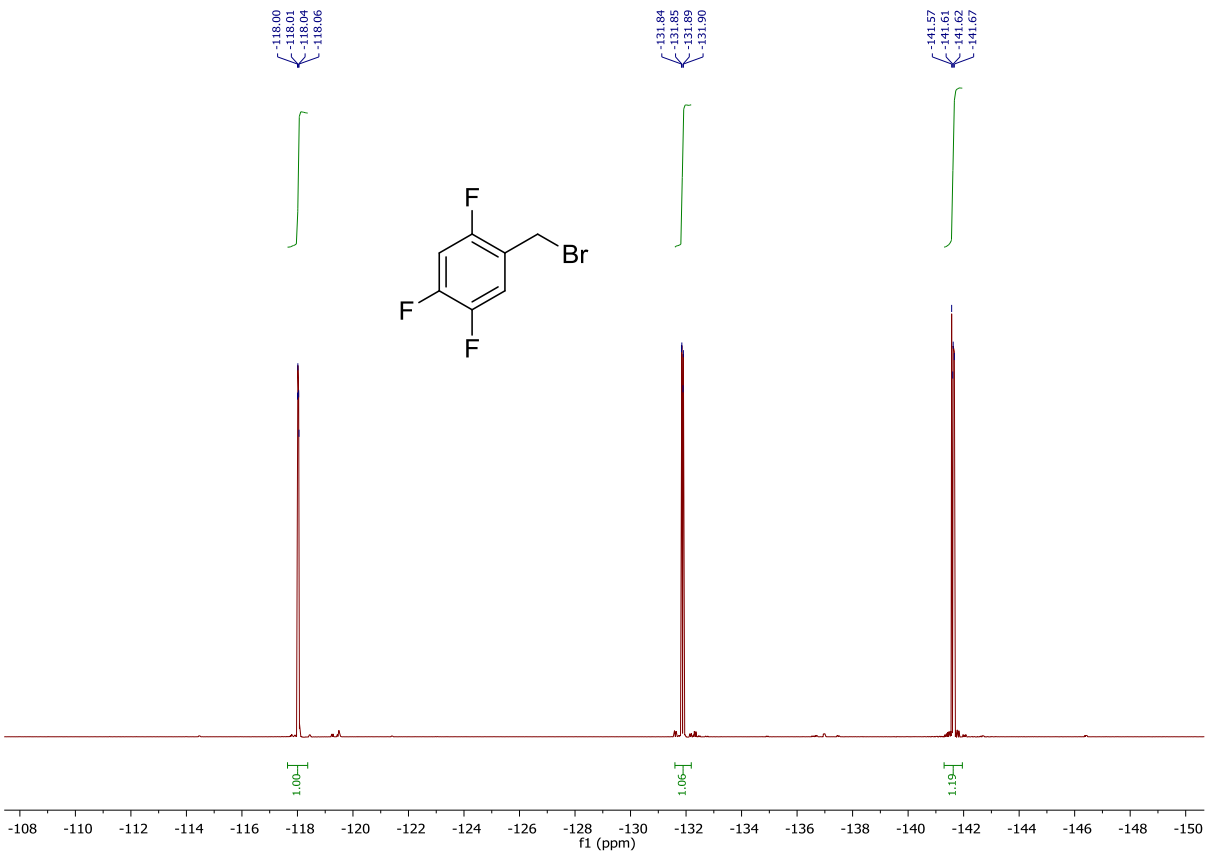
-152
-154
f1 (ppm)

1-(Bromomethyl)-2,4,5-trifluorobenzene (11)



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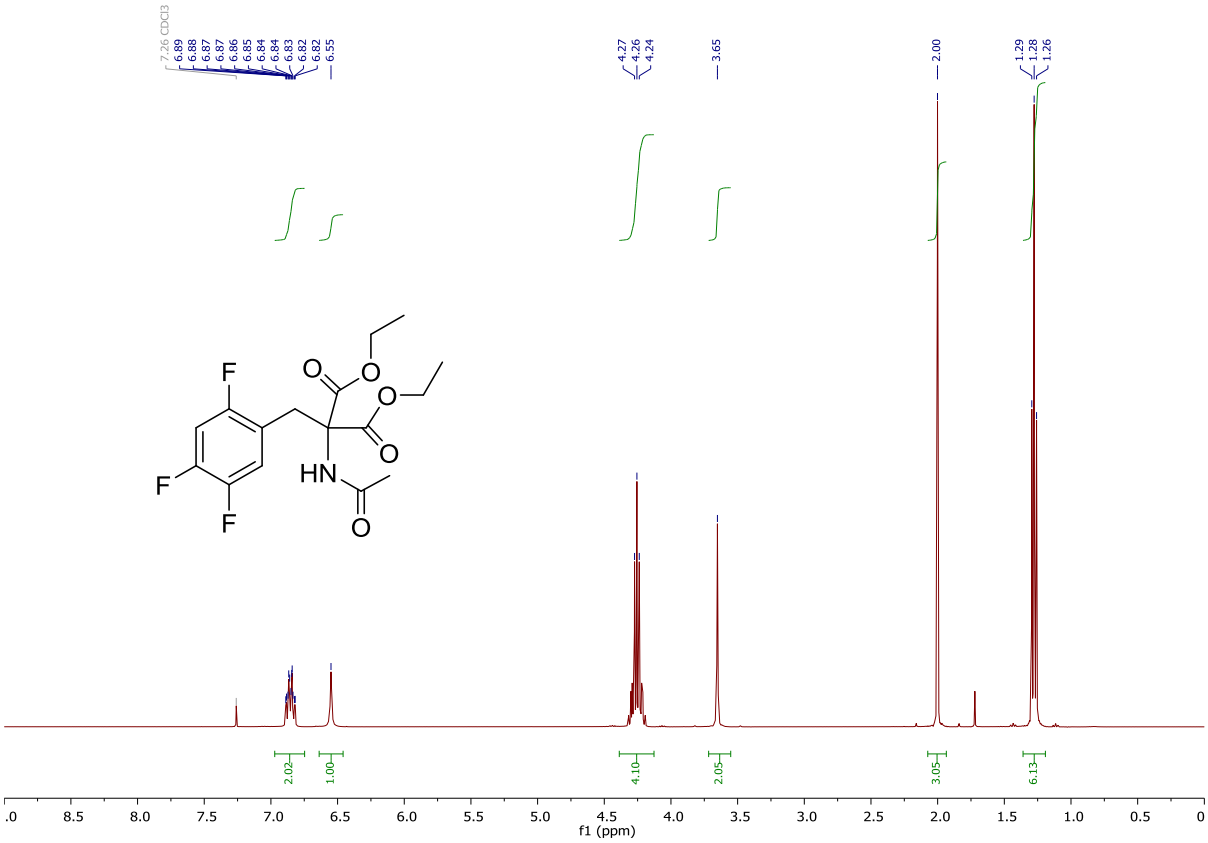
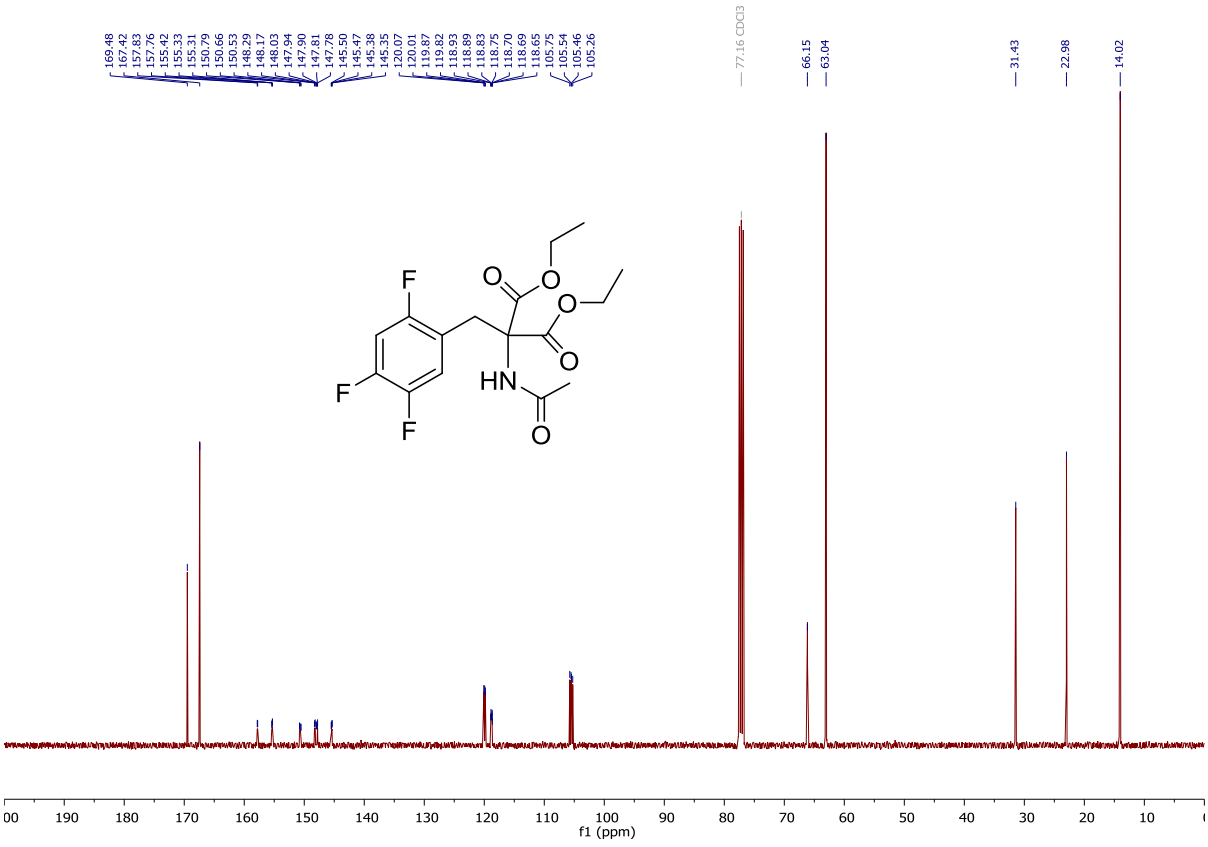
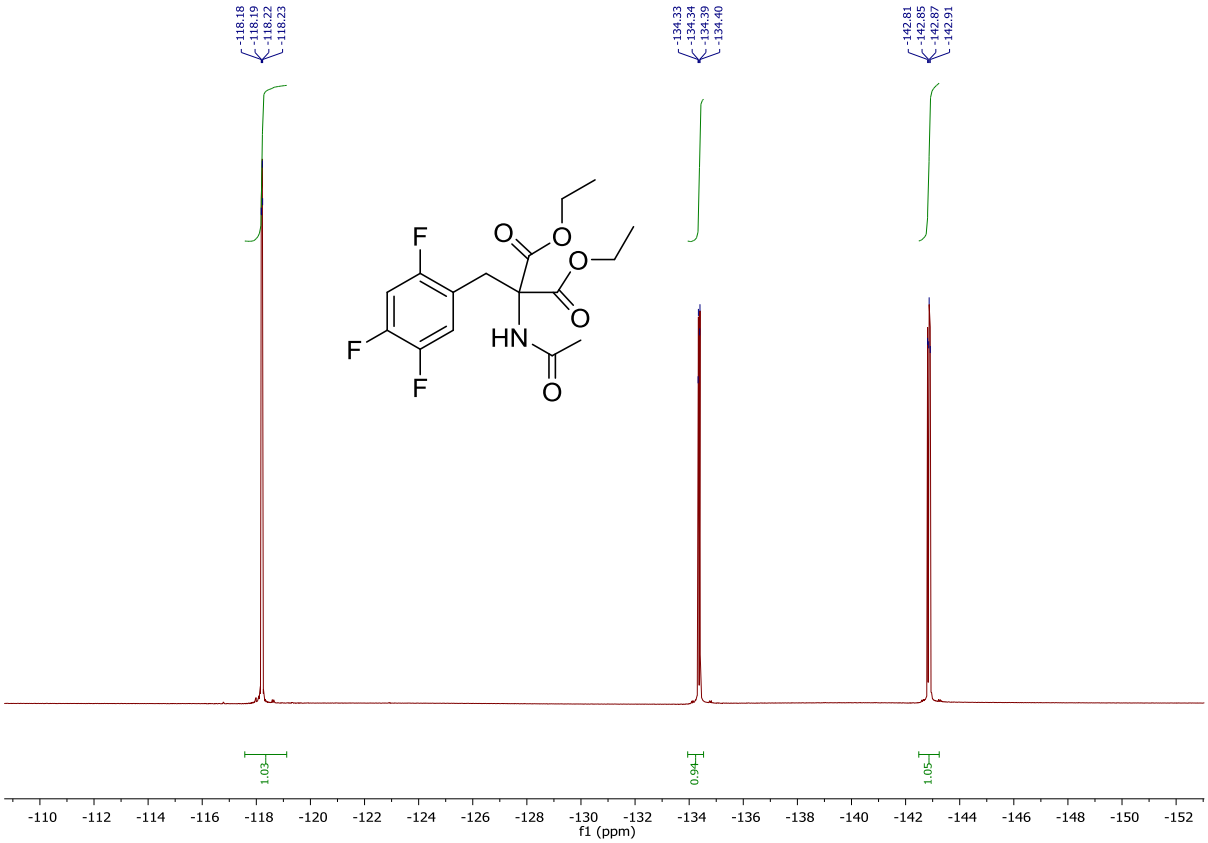
-141.67
F
Br
F
F
1.00
1.06
1.19
-108
-110
-112
-114
-116
-118
-120
-122
-124
-126
-128
-130
-132
-134
-136
-138
-140
-142
-144
-146
-148
-150
f1 (ppm)

Diethyl 2-acetamido-2-(2,4,5-trifluorobenzyl)malonate (12)



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-142.91
F
F
F
O
O
O
O
HN
O
1.03
0.94
1.05
-110
-112
-114
-116
-118
-120
-122
-124
-126
-128
-130
-132
-134
-136
-138
-140
-142
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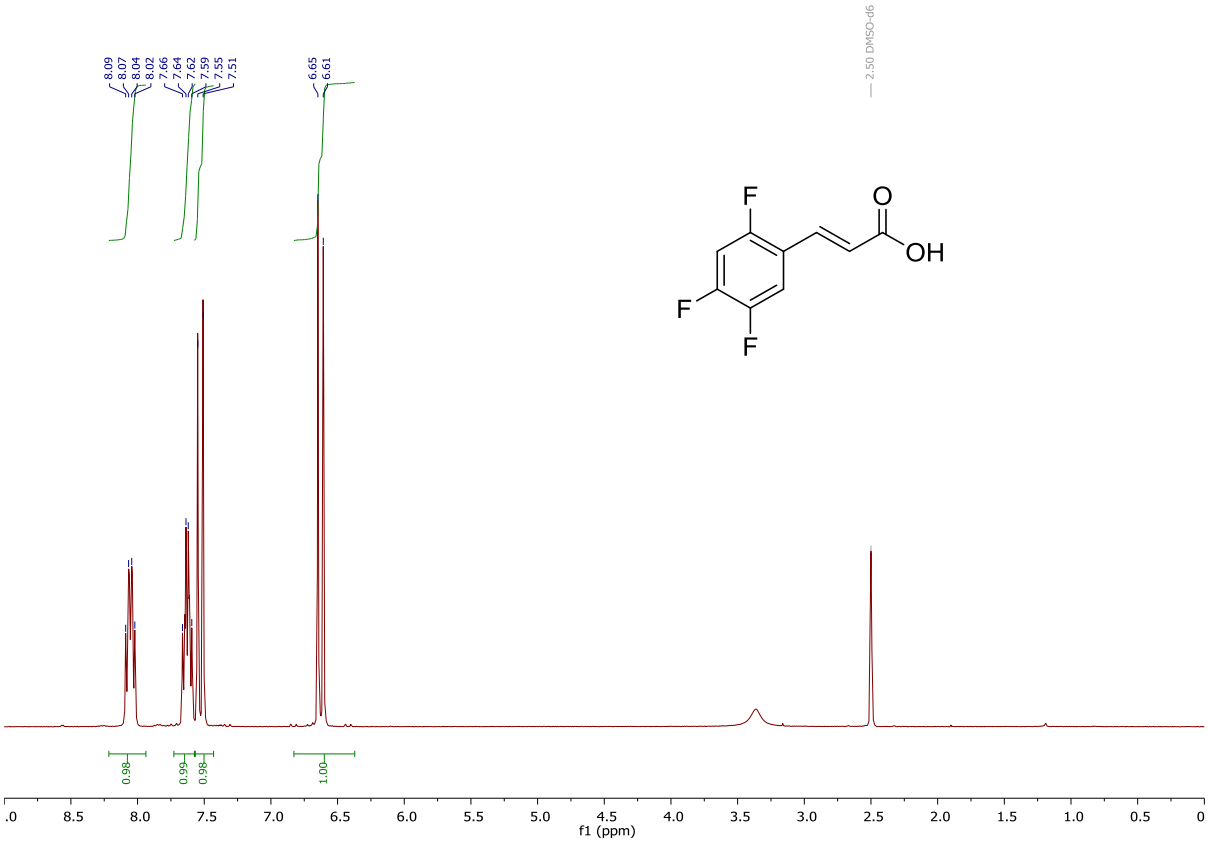
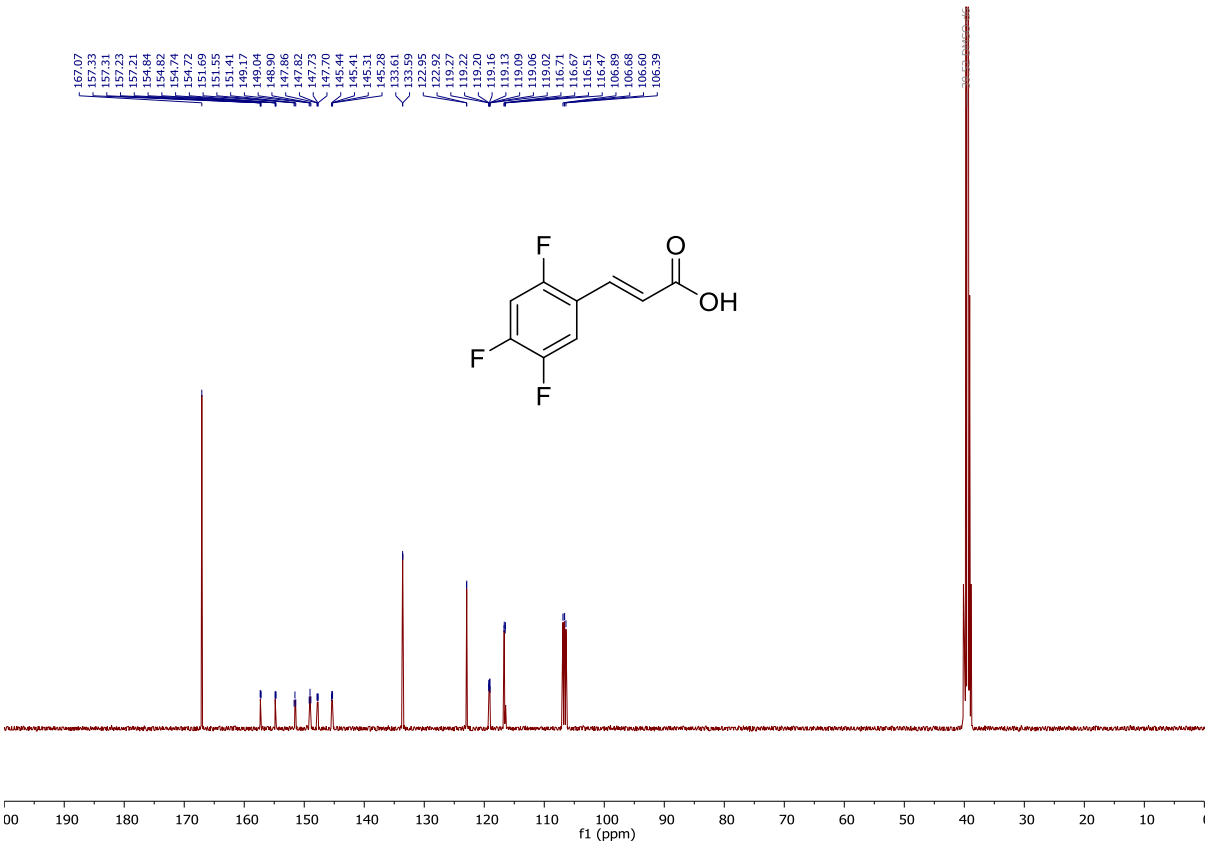
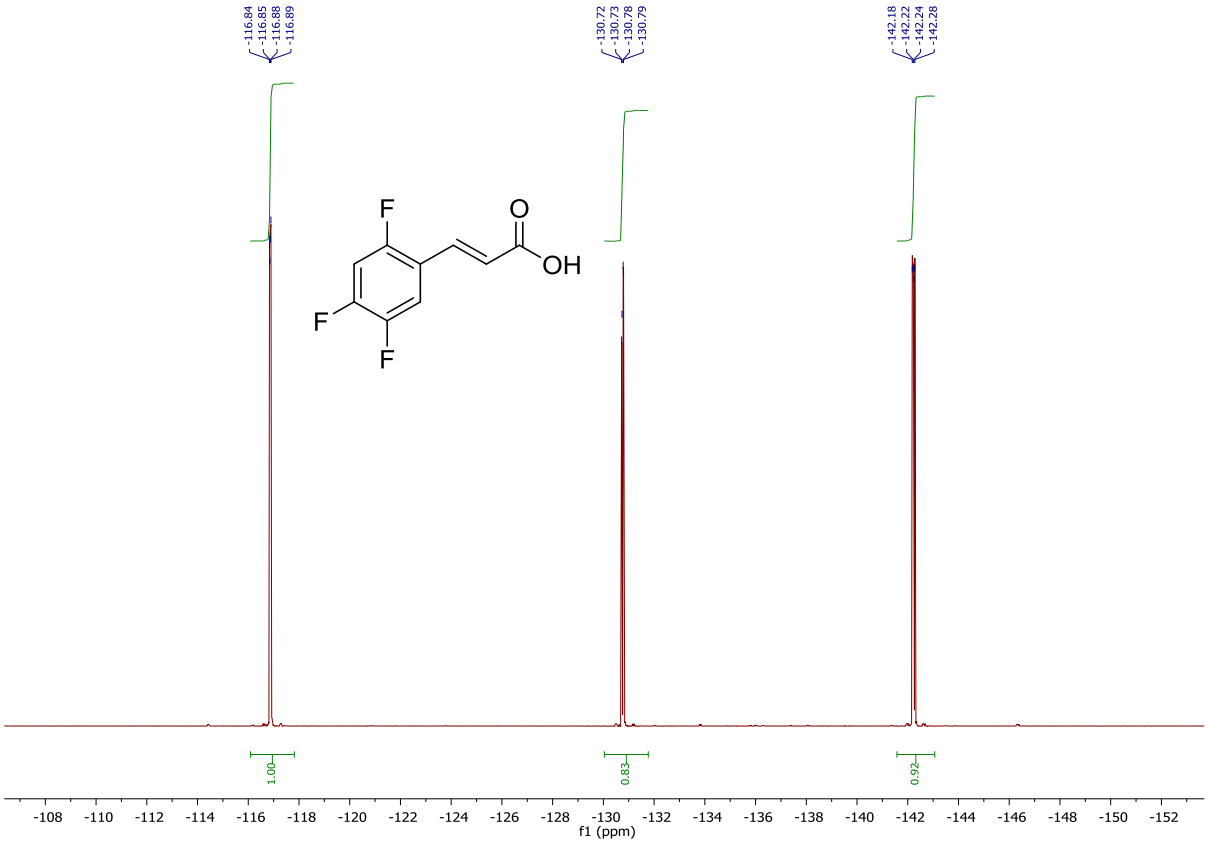
-146
-148
-150
-152
f1 (ppm)

(*E*)-3-(2,4,5-Trifluorophenyl)acrylic acid (6)



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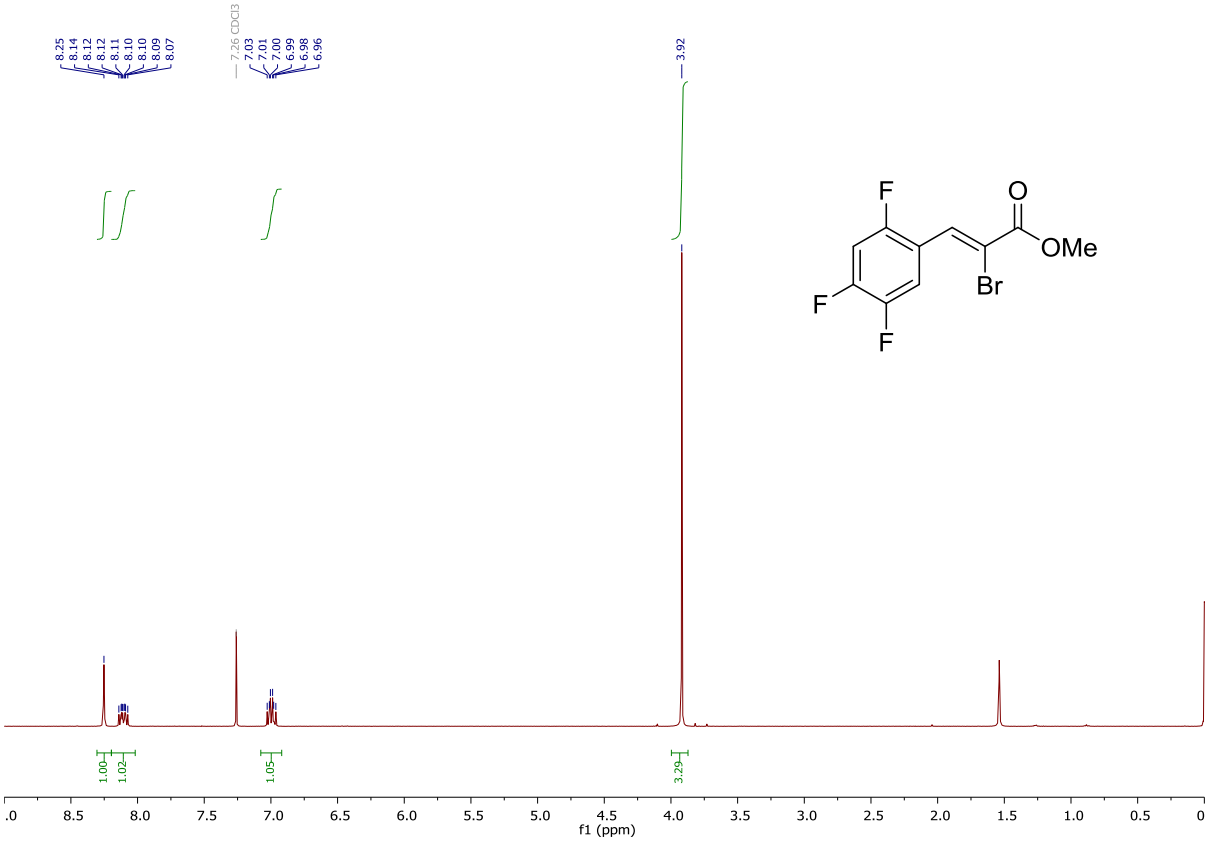
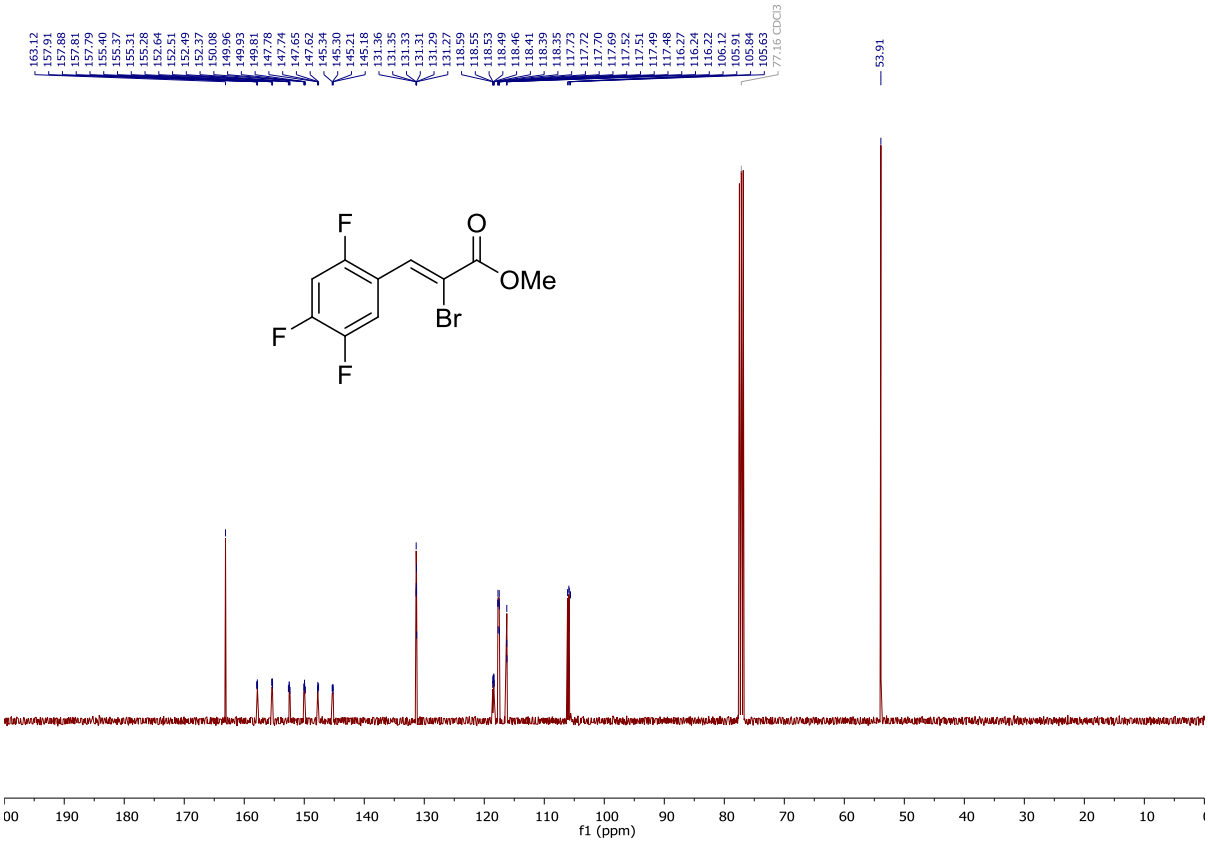
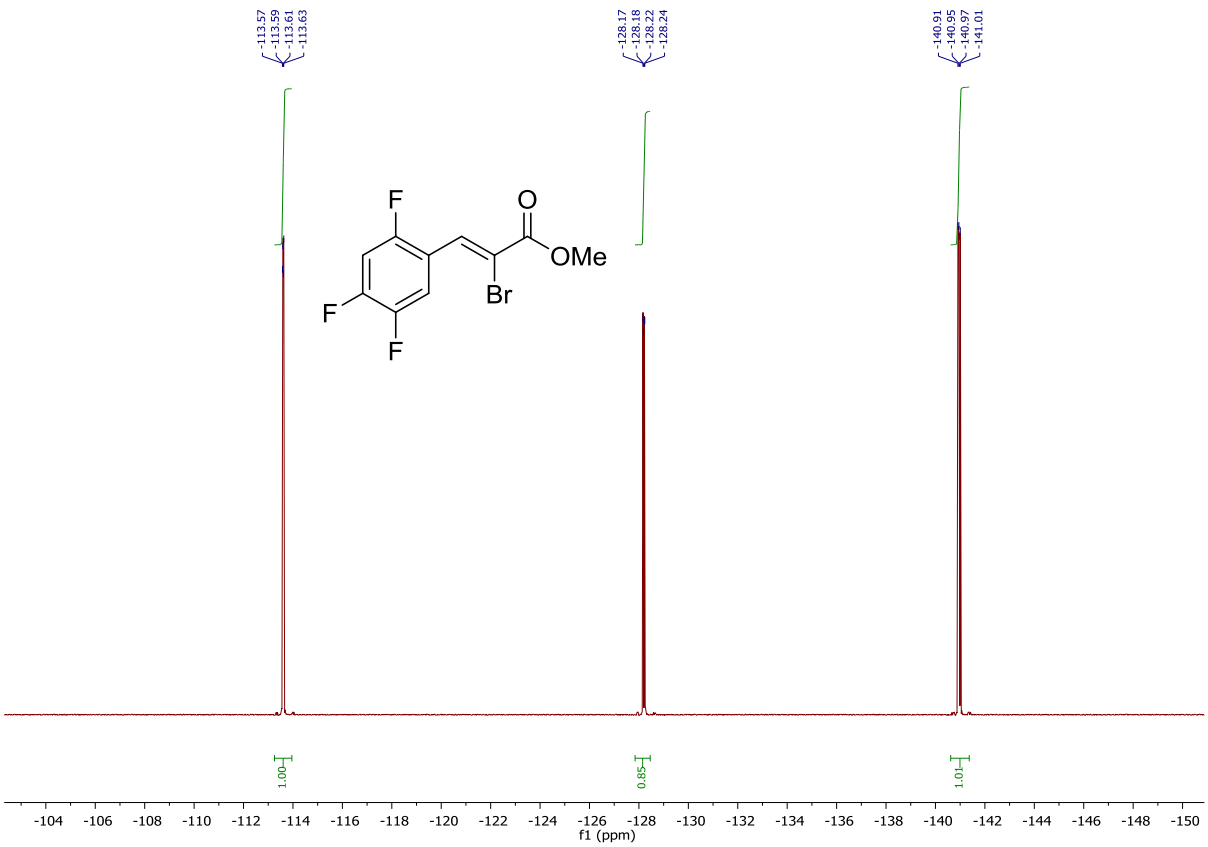
-142.28
F
O
OH
F
F
1.00
0.83
0.92
-108 -110 -112 -114 -116 -118 -120 -122 -124 -126 -128 -130 -132 -134 -136 -138 -140 -142 -144 -146 -148 -150 -152
f1 (ppm)

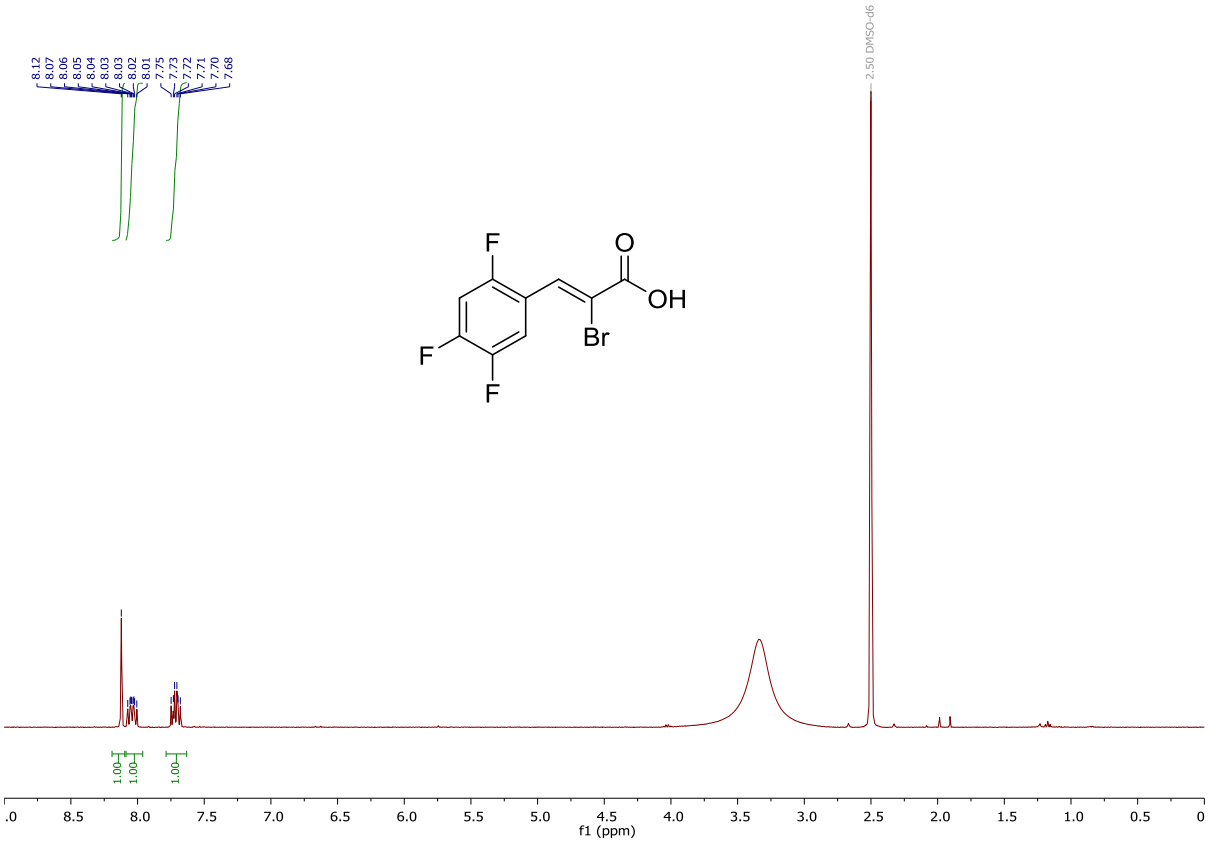
Methyl (*Z*)-2-bromo-3-(2,4,5-trifluorophenyl)acrylate (7)

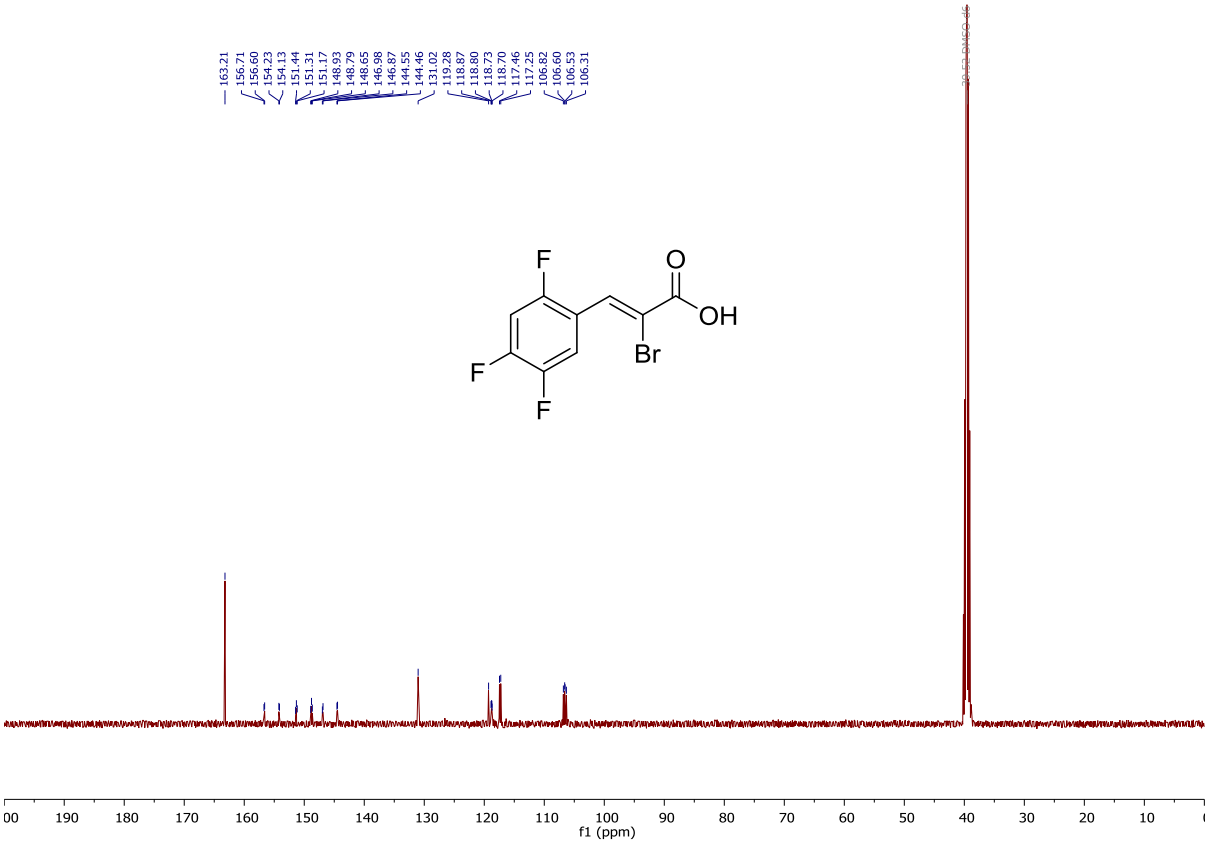


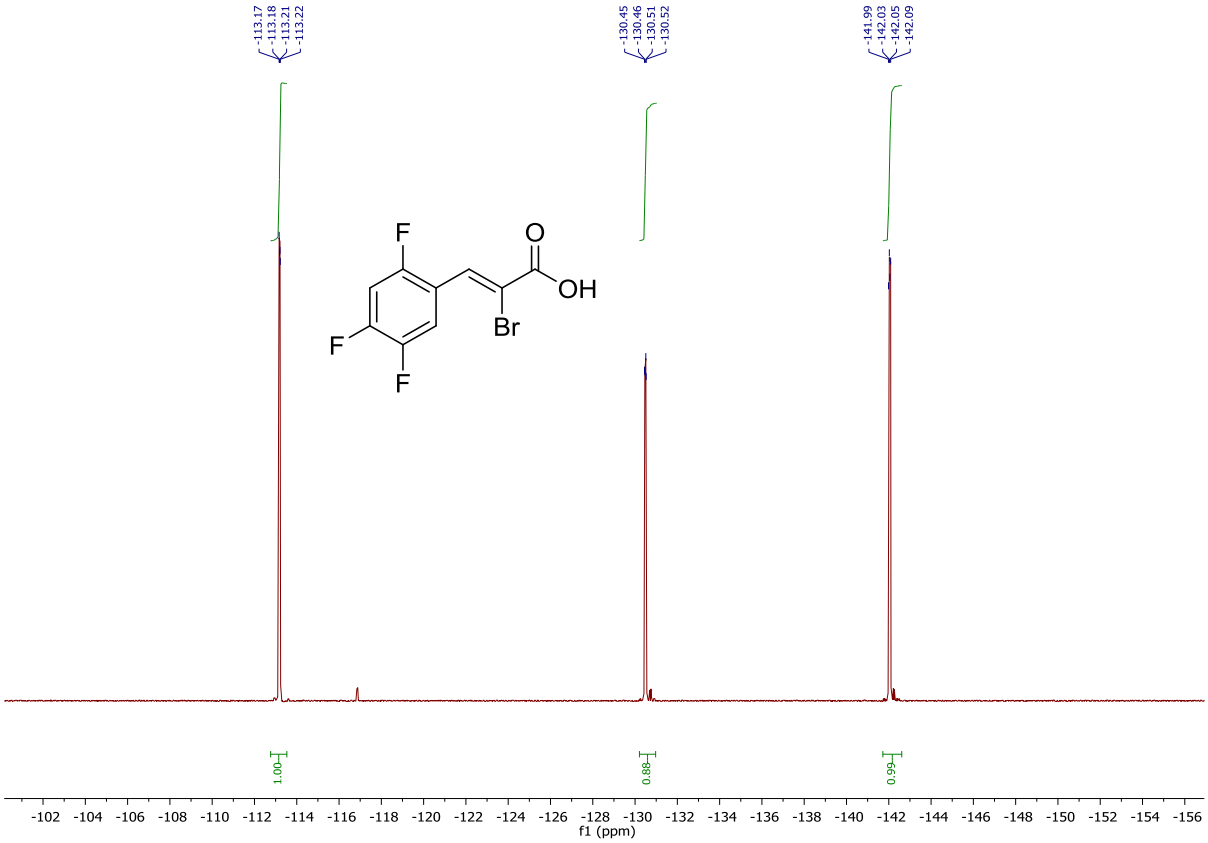



-113.57
-113.59
-113.61
-113.63
-128.17
-128.18
-128.22
-128.24
-140.91
-140.95
-140.97
-141.01
F
O
OMe
Br
F
F
1.00
0.85
1.01
-104 -106 -108 -110 -112 -114 -116 -118 -120 -122 -124 -126 -128 -130 -132 -134 -136 -138 -140 -142 -144 -146 -148 -150
f1 (ppm)

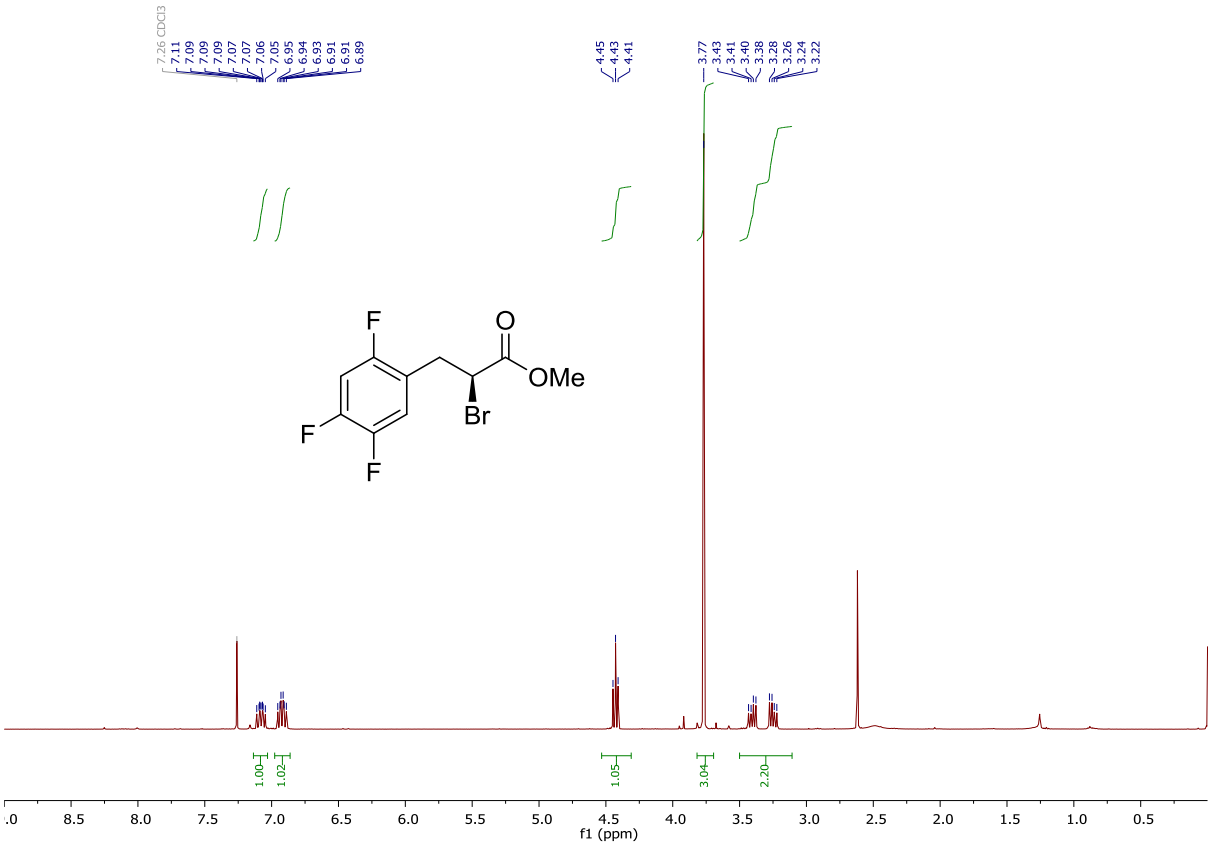
(*Z*)-2-Bromo-3-(2,4,5-trifluorophenyl)acrylic acid (18)

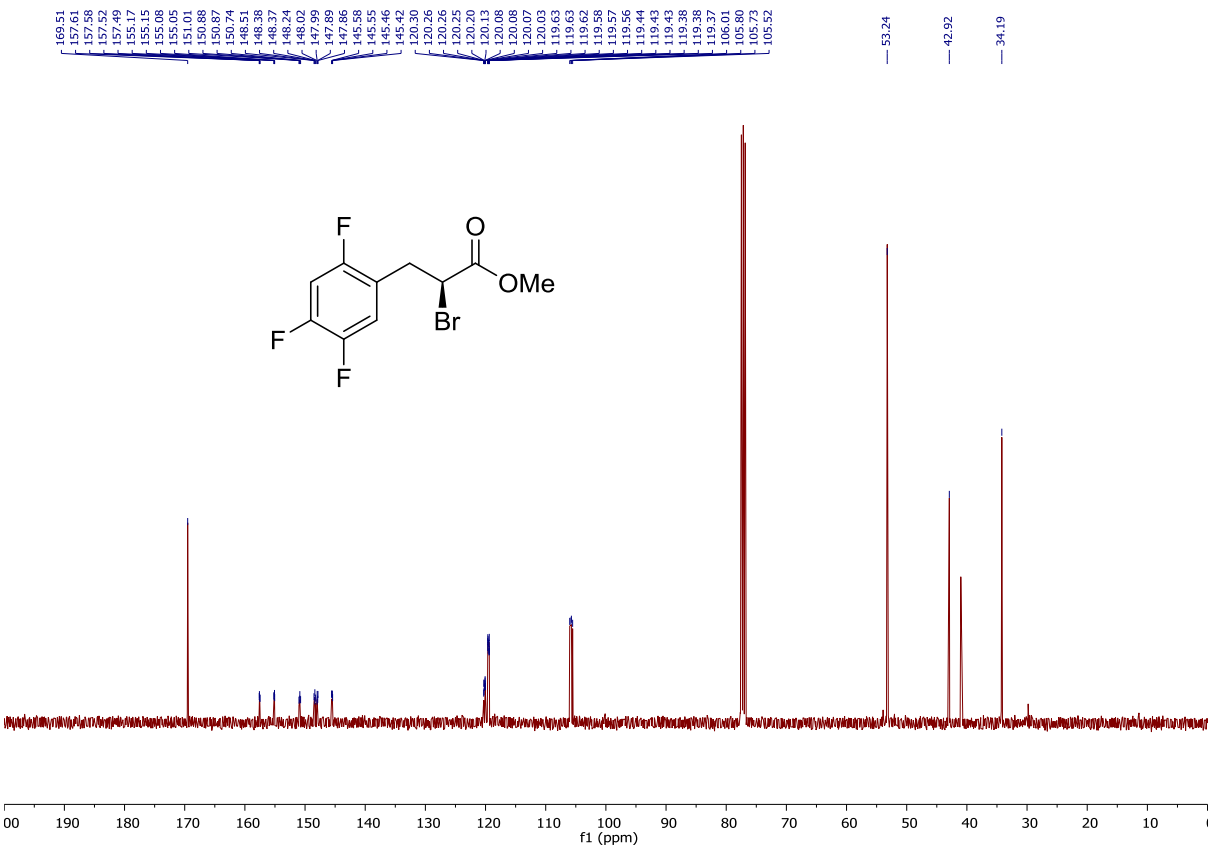




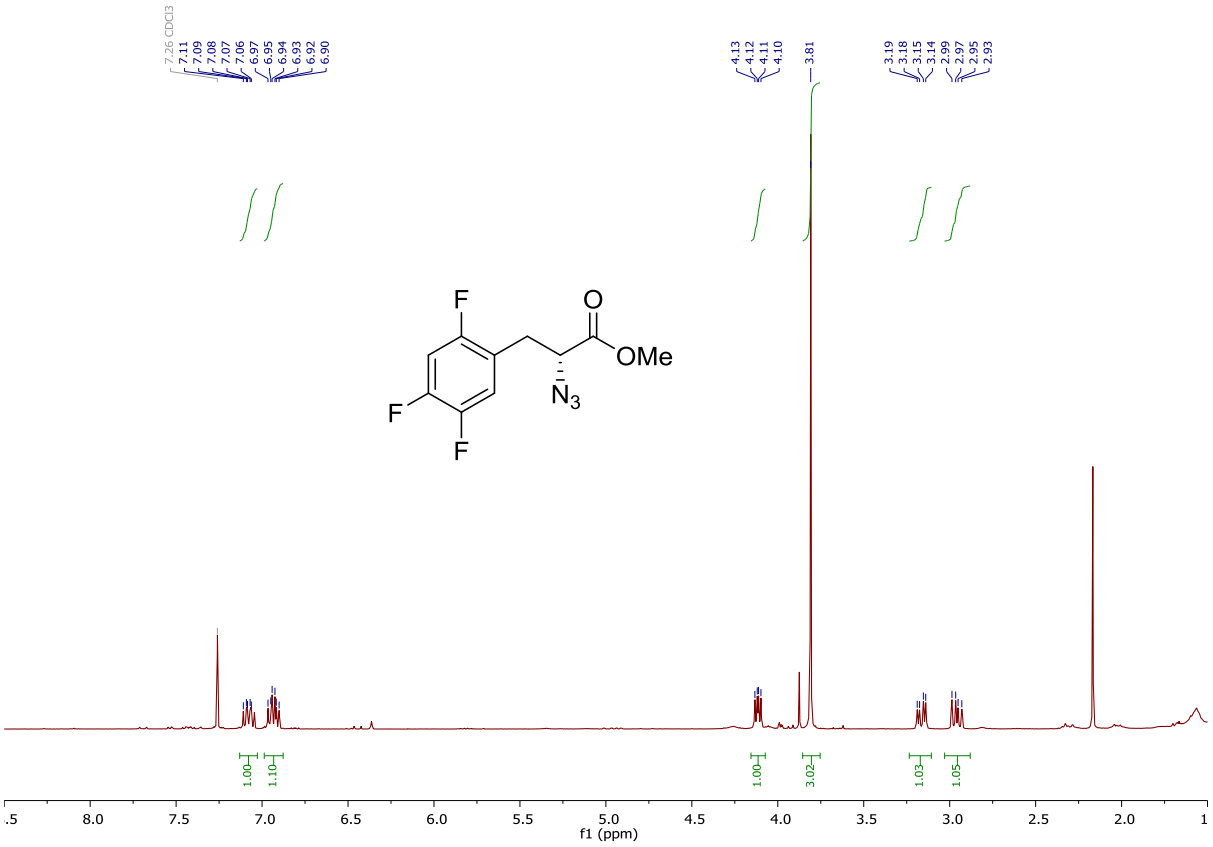

-113.17
-113.18
-113.21
-113.22
-130.45
-130.46
-130.51
-130.52
-141.99
-142.03
-142.05
-142.09
F
O
OH
Br
F
F
1.00
0.88
0.99
-102 -104 -106 -108 -110 -112 -114 -116 -118 -120 -122 -124 -126 -128 -130 -132 -134 -136 -138 -140 -142 -144 -146 -148 -150 -152 -154 -156
f1 (ppm)

Methyl (*S*)-2-bromo-3-(2,4,5-trifluorophenyl)propanoate ((*S*)-15)

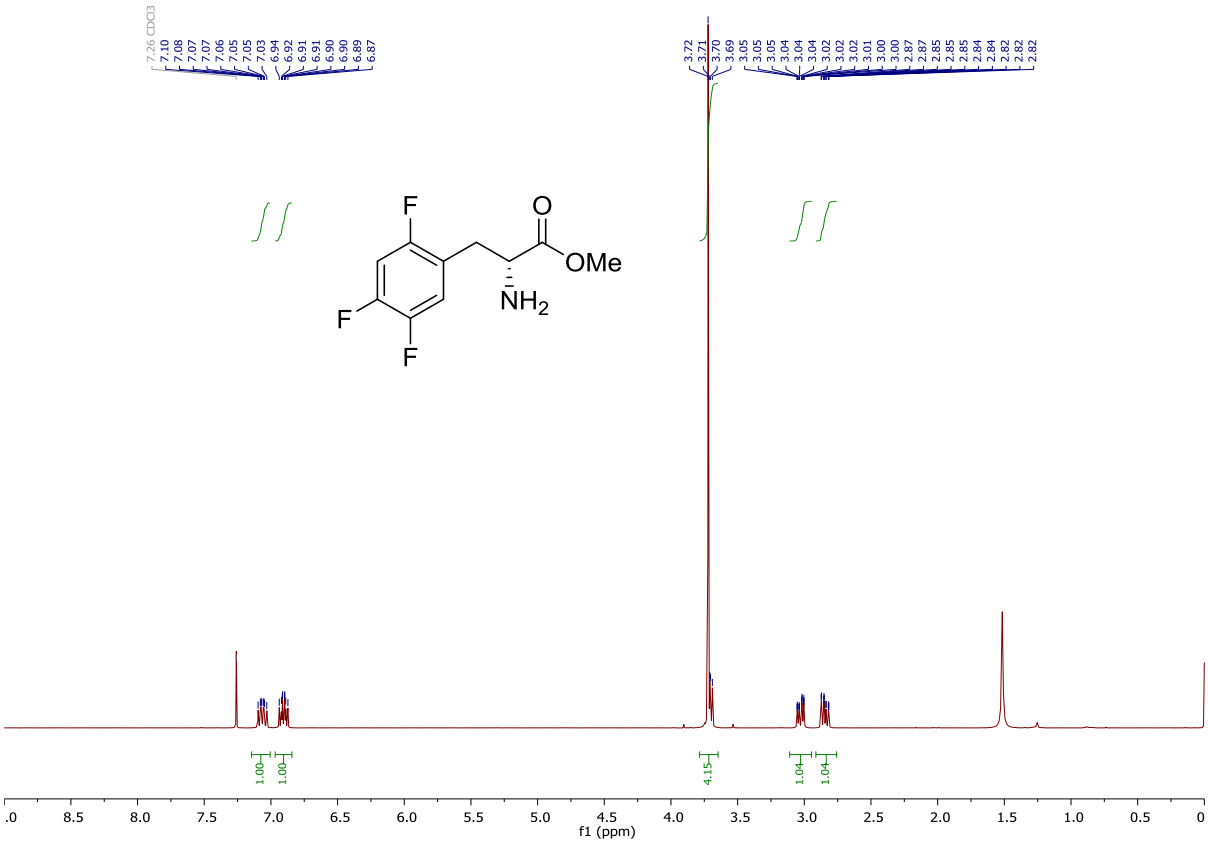


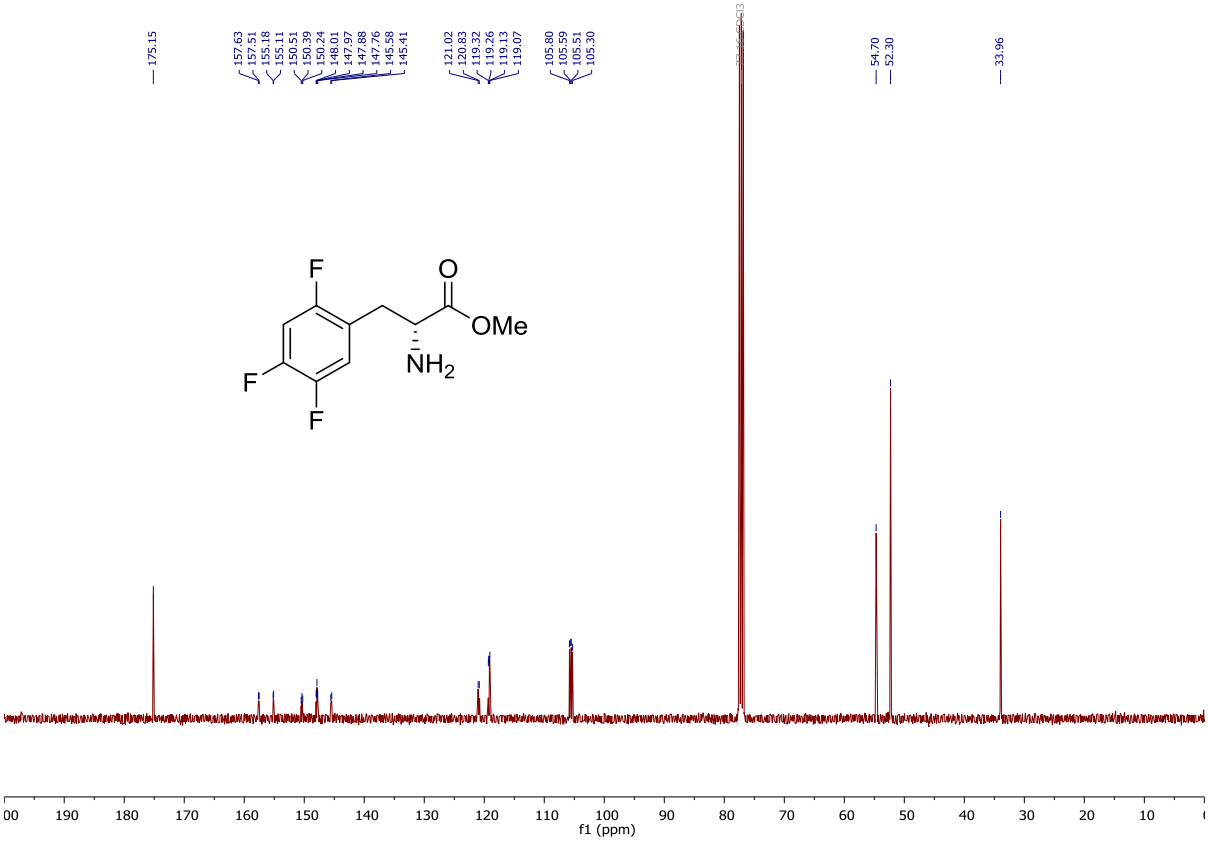


Methyl (*R*)-2-azido-3-(2,4,5-trifluorophenyl)propanoate ((*R*)-16)



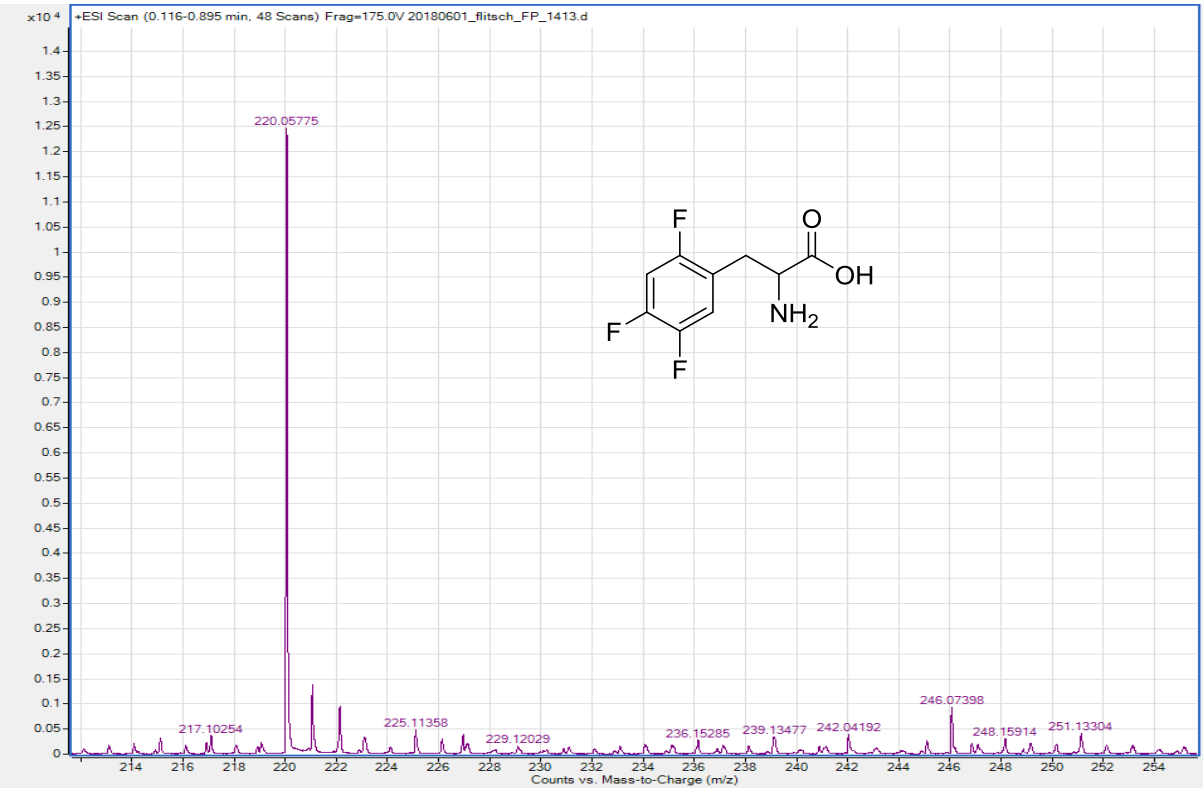
Methyl (*R*)-2-amino-3-(2,4,5-trifluorophenyl)propanoate ((*R*)-17)



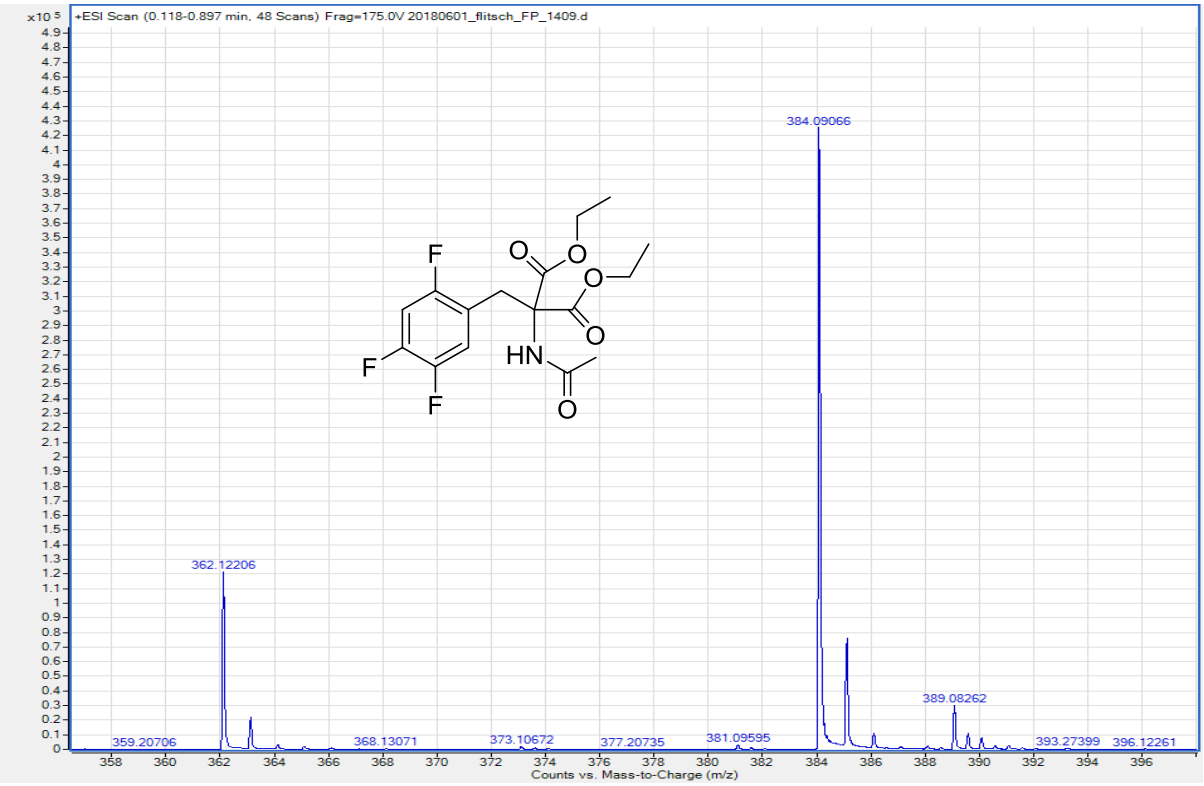


Copies of the HRMS spectra

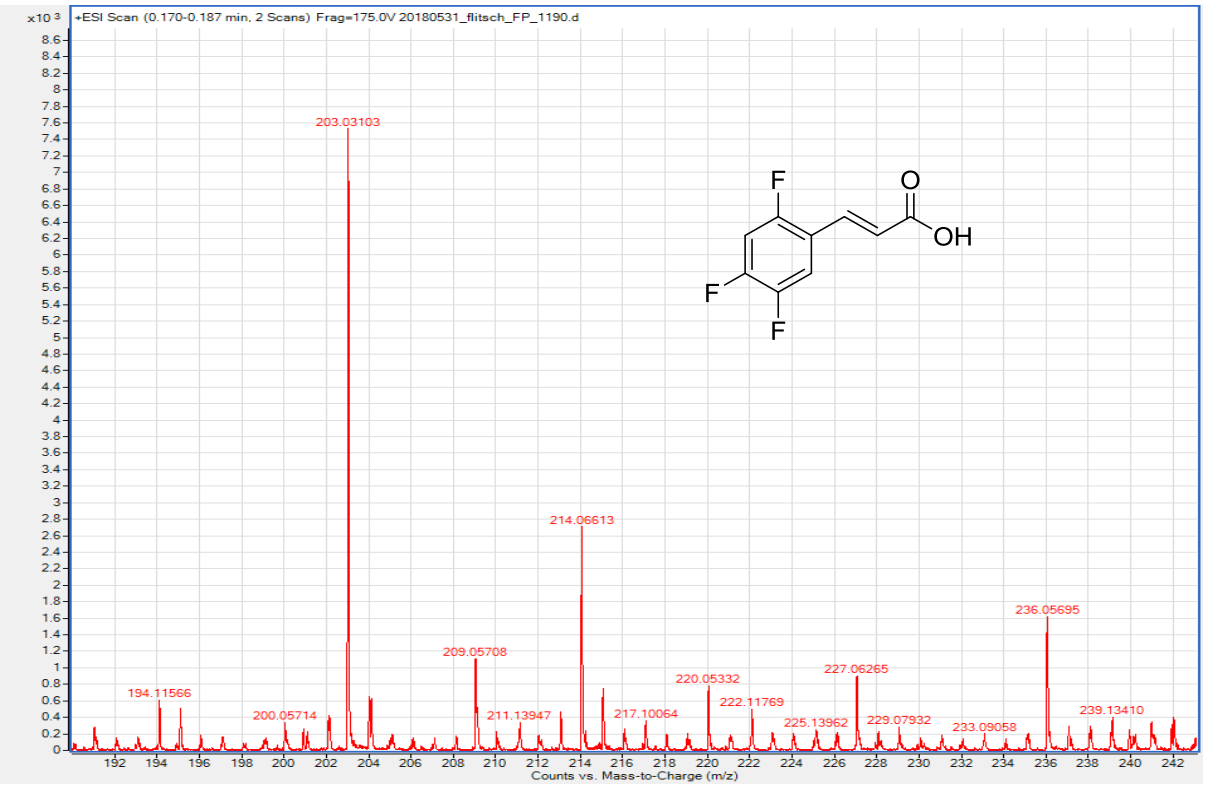
2-Amino-3-(2,4,5-trifluorophenyl)propanoic acid (2)



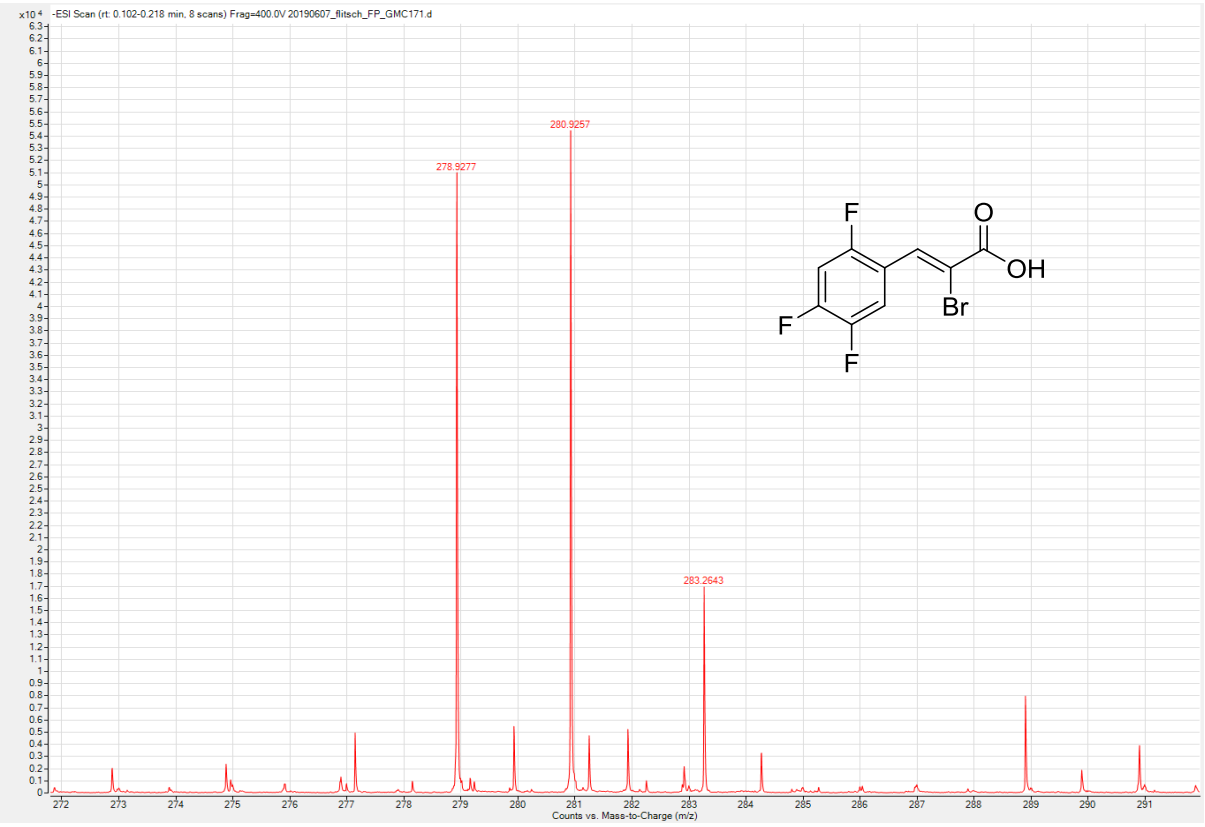
Diethyl 2-acetamido-2-(2,4,5-trifluorobenzyl)malonate (12)



(*E*)-3-(2,4,5-Trifluorophenyl)acrylic acid (6)

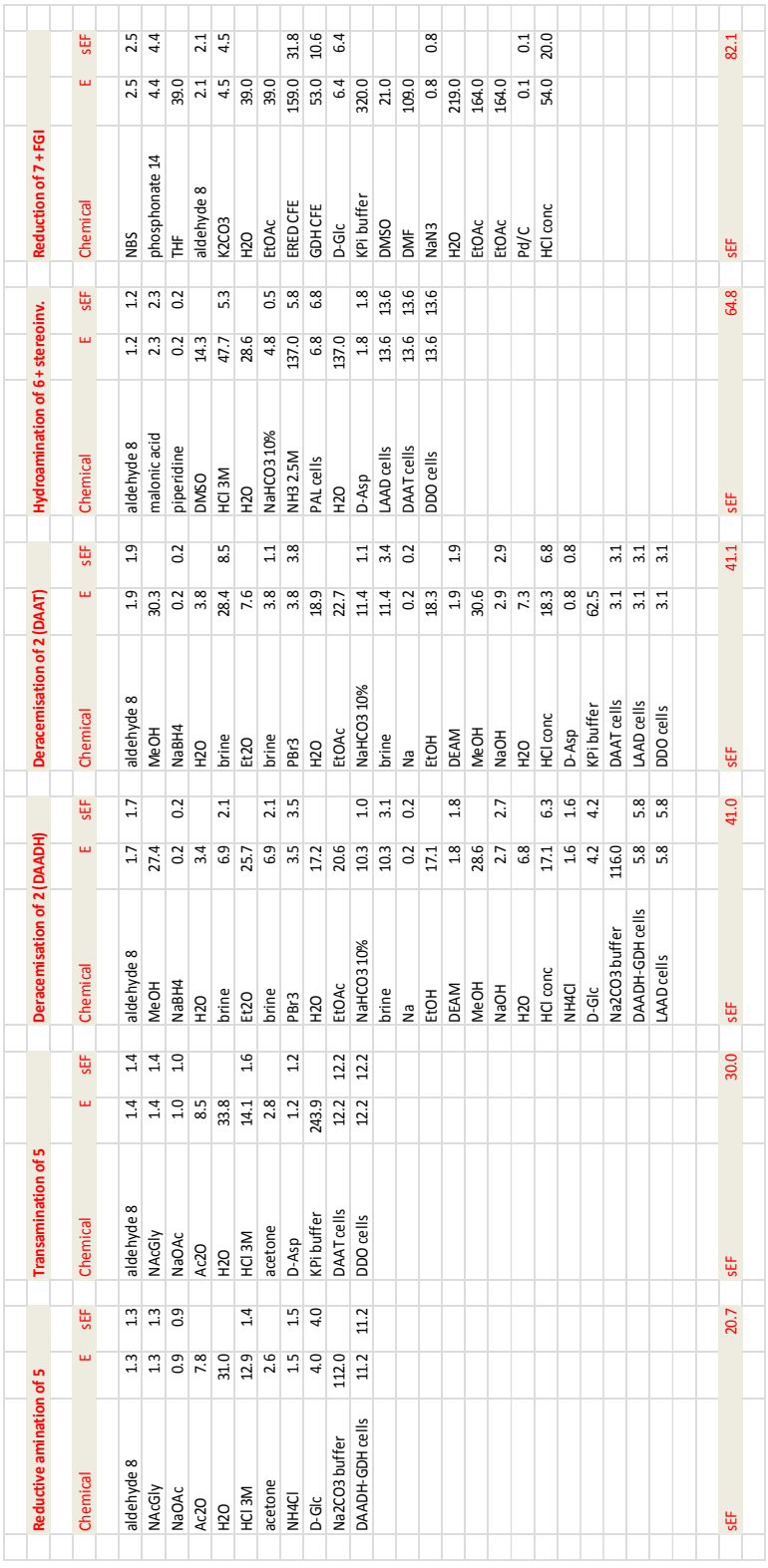


(*Z*)-2-Bromo-3-(2,4,5-trifluorophenyl)acrylic acid (18)



Calculation of the simplified E-factors (sEF)

The simplified E-factors have been calculated (according to ref. S8) not taking into account water and solvents. Due to its definition, this metric should only be used for the purpose of comparison, and not to draw conclusions on the actual amount of waste produced.
In the spreadsheet below, the quantities of each chemical involved have been normalised for the isolation of 1 kg of D-**2** for each route. In column "E" all the components used in each process are listed. In column "sEF" only those that contribute to the simplified E-factor are listed.



Reductive amination of 5			Transamination of 5			Deracemisation of 2 (DAADH)			Deracemisation of 2 (DAAT)			Hydroamination of 6 + stereoinv.			Reduction of 7 + FGI		
Chemical	E	sEF	Chemical	E	sEF	Chemical	E	sEF	Chemical	E	sEF	Chemical	E	sEF	Chemical	E	sEF
aldehyde 8	1.3	1.3	aldehyde 8	1.4	1.4	aldehyde 8	1.7	1.7	aldehyde 8	1.9	1.9	aldehyde 8	1.2	1.2	NBS	2.5	2.5
NAcGly	1.3	1.3	NAcGly	1.4	1.4	MeOH	27.4		MeOH	30.3		malonic acid	2.3	2.3	phosphonate 14	4.4	4.4
NaOAc	0.9	0.9	NaOAc	1.0	1.0	NaBH4	0.2	0.2	NaBH4	0.2	0.2	piperidine	0.2	0.2	THF	39.0	
Ac2O	7.8		Ac2O	8.5		H2O	3.4		H2O	3.8		DMSO	14.3		aldehyde 8	2.1	2.1
H2O	31.0		H2O	33.8		brine	6.9	2.1	brine	28.4	8.5	HCl 3M	47.7	5.3	K2CO3	4.5	4.5
HCl 3M	12.9	1.4	HCl 3M	14.1	1.6	Et2O	25.7		Et2O	7.6		H2O	28.6		H2O	39.0	
acetone	2.6		acetone	2.8		brine	6.9	2.1	brine	3.8	1.1	NaHCO3 10%	4.8	0.5	EtOAc	39.0	
NH4Cl	1.5	1.5	D-Asp	1.2	1.2	PBr3	3.5	3.5	PBr3	3.8	3.8	NH3 2.5M	137.0	5.8	ERED CFE	159.0	31.8
D-Glc	4.0	4.0	KPi buffer	243.9		H2O	17.2		H2O	18.9		PAL cells	6.8	6.8	GDH CFE	53.0	10.6
Na2CO3 buffer	112.0		DAAT cells	12.2	12.2	EtOAc	20.6		EtOAc	22.7		H2O	137.0		D-Glc	6.4	6.4
DAADH-GDH cells	11.2	11.2	DDO cells	12.2	12.2	NaHCO3 10%	10.3	1.0	NaHCO3 10%	11.4	1.1	D-Asp	1.8	1.8	KPi buffer	320.0	
						brine	10.3	3.1	brine	11.4	3.4	LAAD cells	13.6	13.6	DMSO	21.0	
						Na	0.2	0.2	Na	0.2	0.2	DAAT cells	13.6	13.6	DMF	109.0	
						EtOH	17.1		EtOH	18.3		DDO cells	13.6	13.6	NaN3	0.8	0.8
						DEAM	1.8	1.8	DEAM	1.9	1.9				H2O	219.0	
						MeOH	28.6		MeOH	30.6					EtOAc	164.0	
						NaOH	2.7	2.7	NaOH	2.9	2.9				EtOAc	164.0	
						H2O	6.8		H2O	7.3					Pd/C	0.1	0.1
						HCl conc	17.1	6.3	HCl conc	18.3	6.8				HCl conc	54.0	20.0
						NH4Cl	1.6	1.6	D-Asp	0.8	0.8						
						D-Glc	4.2	4.2	KPi buffer	62.5							
						Na2CO3 buffer	116.0		DAAT cells	3.1	3.1						
						DAADH-GDH cells	5.8	5.8	LAAD cells	3.1	3.1						
						LAAD cells	5.8	5.8	DDO cells	3.1	3.1						
sEF		20.7	sEF		30.0	sEF		41.0	sEF		41.1	sEF		64.8	sEF		82.1

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