Supporting Information for

Stereodivergent Intramolecular Cyclopropanation Enabled by Engineered Carbene Transferases

Ajay L. Chandgude[†], Xinkun Ren[†], and Rudi Fasan*

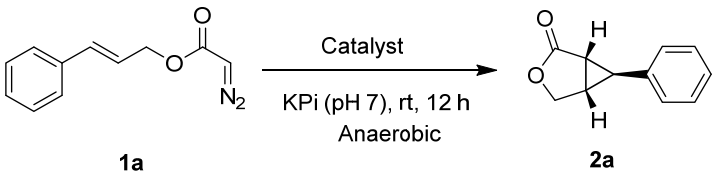
Department of Chemistry, University of Rochester, 14627 Rochester, New York, USA

† *These authors contributed equally to this work.*

Correspondence should be addressed to R.F. (rfasan@ur.rochester.edu)

Table of Contents

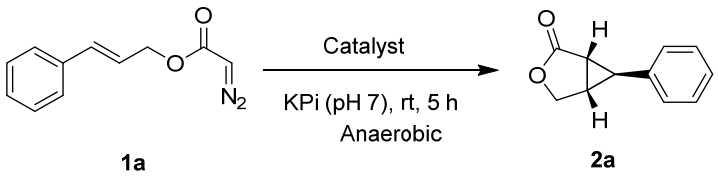
Table S1. Activity of hemin and hemoproteins in the intramolecular cyclopropanation reactions. Reaction conditions: 20 μM catalyst, 10 mM cinnamyl 2-diazoacetate (**1a**), 10 mM $Na_2S_2O_4$, in KPi buffer (50 mM, pH 7), room temperature, 12 hours, in anaerobic chamber.



1a **2a**

Entry	Catalyst	Yield (GC)	TON	% *ee* (1*R*,5*S*,6*S*)
1	Hemin	15%	75	0
2	Mb	9%	45	80
3	Catalase	2%	10	15
4	Cytochrome *c* (equine heart)	1%	6	-6
5	Cytochrome *c* (*Hydrogenobacter thermophilus*)	0.3%	1	-11
6	$P450_{BM3}$	0.6%	3	-22

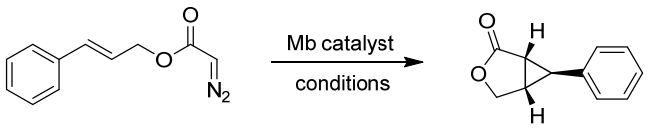
Table S2. Activity and selectivity of representative Mb variants for the intramolecular cyclopropanation of *trans*-cinnamyl-2-diazoacetate (**1a**). Reaction conditions: 20 μM catalyst, 5 mM cinnamyl 2-diazoacetate (**1a**), 10 mM $Na_2S_2O_4$, in KPi buffer (50 mM, pH 7), room temperature, 5 hours, in anaerobic chamber.



Entry	Mb variant	GC Yield %	TON	%ee (1R, 5S, 6S)
1	WT	13	32	80
2	L29A	65	163	93
3	F43A	29	73	79
4	F43G	13	32	67
5	H64V	15	38	40
6	H64V/V68A	33	82	81
7	H64A/V68A	23	58	72
8	H64G/V68A	80	200	71
9	F43V/V68L	22	55	-1
10	F43V/V68A	61	152	80
11	H64A/V68G	33	84	60
12	F43V/V68F	16	40	-53
13	F43V/H64F	17	42	67
14	H64G/V68G	15	39	66
15	F43V/H64W	42	104	86
16	L29T/H64V/V68F	20	50	-6
17	L29T/H64V/V68L	72	181	-32
18	L29F/F43S/H64V	17	43	81

19	F43Y/H64V/V68A	65	161	91
20	L29S/H64V/V68F	55	138	38
21	F43M/H64V/V68A	53	133	79
22	F43Y/H64V/V68A	88	219	91
23	L29F/F43V/V68F	22	54	51
24	L29T/F43W/H64V/V68F	14	35	-27
25	L29T/H64V/V68F/I107L	33	84	-33

Table S3. Optimization studies for Mb(L29A,H64V,V68A)- and Mb(H64V,I107S)-catalyzed intramolecular cyclopropanation of **1a** in reactions with purified protein and whole cell. Reaction conditions: 1-10 mM cinnamyl 2-diazoacetate (**1a**), 20 μM purified protein or Mb-expressing *E. coli* cells (C41(DE3)) at the indicated cell density (OD_{600}), 10 mM $Na_2S_2O_4$ (only for protein reactions) in 0.5 mL KPi buffer (50 mM, pH 7), room temperature, 5 hours in anaerobic chamber. Mb-free cells produce a background conversion of ~10% (0% *ee*) likely due to free hemin in the cell.



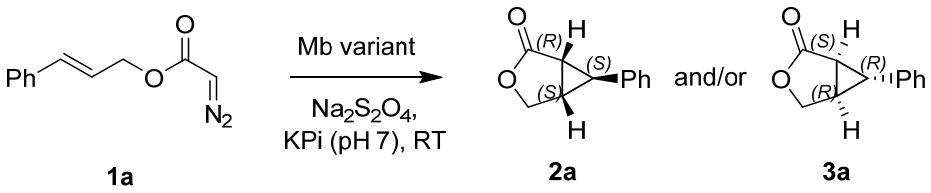
1a **2a**

Catalyst	Conditions	Protein/cell conc.	[1a] (mM)	Yield (GC)	TON	*e.e.* (1*R*,5*S*,6*S*)
Mb(L29A,H64V,V68A)	Protein	20 μM	2.5	>99%	125	96%
Mb(L29A,H64V,V68A)	Protein	20 μM	5	>99%	250	96%
Mb(L29A,H64V,V68A)	Protein	20 μM	10	65%	325	94%
Mb(L29A,H64V,V68A)	Whole cells	OD = 20	2.5	81%	163	95%
Mb(L29A,H64V,V68A)	Whole cells	OD = 40	2.5	>99%	90	96%
Mb(L29A,H64V,V68A)	Whole cells	OD = 60	2.5	>99%	60	97%
Mb(L29A,H64V,V68A)	Whole cells	OD = 20	5	51%	205	88%
Mb(L29A,H64V,V68A)	Whole cells	OD = 40	5	73%	131	96%
Mb(L29A,H64V,V68A)	Whole cells	OD = 60	5	98%	120	97%
Mb(H64V,I107S)	Protein	20 μM	2.5	>99%	125	>99%
Mb(H64V,I107S)	Protein	20 μM	5	78%	195	97%
Mb(H64V,I107S)	Protein	20 μM	10	56%	281	94%

Mb(H64V,I107S)	Whole cells	OD = 40	1	>99%	37	>99%
Mb(H64V,I107S)	Whole cells	OD = 60	1	>99%	24	>99%
Mb(H64V,I107S)	Whole cells	OD = 80	1	>99%	18	>99%
Mb(H64V,I107S)	Whole cells	OD = 20	2.5	64%	117	98%
Mb(H64V,I107S)	Whole cells	OD = 40	2.5	>99%	90	>99%
Mb(H64V,I107S)	Whole cells	OD = 60	2.5	>99%	61	>99%
Mb(H64V,I107S)	Whole cells	OD = 80	2.5	>99%	45	>99%
Mb(H64V,I107S)	Whole cells	OD = 20	5	32%	117	89%
Mb(H64V,I107S)	Whole cells	OD = 40	5	56%	102	91%
Mb(H64V,I107S)	Whole cells	OD = 60	5	81%	99	94%
Mb(H64V,I107S)	Whole cells	OD = 80	5	>99%	90	97%

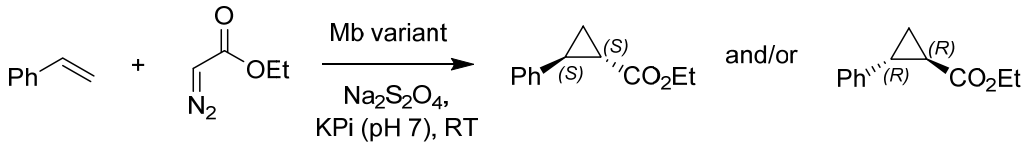
Table S4. Side-by-side comparison of the selectivity of engineered Mb variants optimized for stereodivergent intramolecular cyclopropanation ((1*R*,5*S*,6S)-selective = green; ((1*S*,5*R*,6R)-selective = orange) and for stereodivergent intermolecular cyclopropanation with ethyl α-diazoacetate (EDA) + styrene[ref] ((1*S*,2*S*)-selective = blue; (1*R*,2*R*)-selective = red) in intra- and intermolecular cyclopropanation reactions (see Scheme). These data highlight the distinct active site configurations associated with high enantioselectivity in the intra- vs. intermolecular cyclopropanation reactions.

Intramolecular cyclopropanation:



1a **2a** **3a**

Intermolecular cyclopropanation:



10a **10b** **10c** **10d**

Mb variant	*Intramolecular Cyclopropanation*[a]				*Intermolecular Cyclopropanation*[b]		
	GC yield (TON)	***de*$_{trans}$**	***ee*$_{(1R,5S,6S)}$**		**GC yield (TON)**	***de*$_{trans}$**	***ee*$_{(1S,2S)}$**
WT	13% (32)	>99%	80%		45% (225)	85%	7%
L29A	65% (163)	>99%	93%		38% (190)	82%	-1%
L29A/H64V/V68A	99% (250)	>99%	96%		55% (280)	95%	57%
H64V/I107S	78% (195)	>99%	97%		72% (360)	89%	35%
V68F	71%[c] (14)	>99%	-10%		36% (180)	75%	23%
F43A/V68F	81%[c] (16)	>99%	-80%		62% (310)	83%	-5%
F43A/H64W/V68F	99%[c] (20)	>99%	-89%		70% (350)	63%	-31%

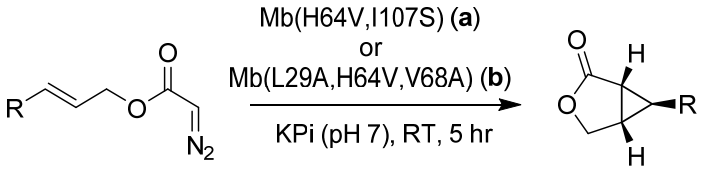
H64V/V68A	33% (82)	>99%	81%		99% (500)	>99%	>99%
H64V/V68G	48% (120)	>99%	60%		99% (500)	81%	>99%
L29S/H64V/V68F (RR1)	55% (140)	>99%	38%		27% (135)	90%	-91%
L29T/H64V/V68L (RR2)	72% (180)	>99%	-32%		61% (305)	>99%	-92%
L29T/H64V/V68F (RR3)	20% (50)	>99%	-6%		58% (290)	>99%	-92%
L29T/F43W/H64V/V68F (RR5)	14% (35)	>99%	-27%		53% (265)	99%	-95%

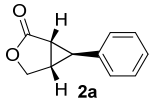
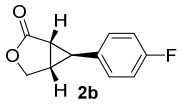
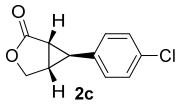
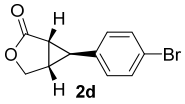
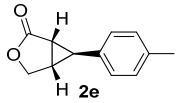
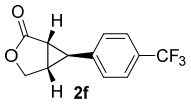
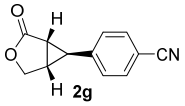
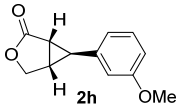
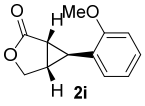
[a] Reactions conditions: 20 μM Mb variant, 5 mM cinnamyl 2-diazoacetate (**1a**), 10 mM $Na_2S_2O_4$, in KPi buffer (50 mM, pH 7), room temperature, 5 hours, in anaerobic chamber.

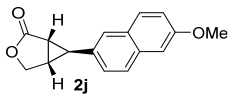
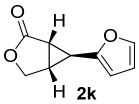
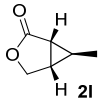
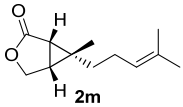
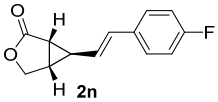
[b] Reactions conditions: 20 μM Mb variant, 10 mM styrene, 20 mM EDA, 10 mM $Na_2S_2O_4$, in KPi buffer (50 mM, pH 7.0), room temperature, 12 hours, anaerobic conditions.

[c] Reactions conditions: 50 μM Mb variant, 1 mM cinnamyl 2-diazoacetate (**1a**), 10 mM $Na_2S_2O_4$, in KPi buffer (50 mM, pH 7.0), room temperature, 5 hours, anaerobic conditions.

Table S5. Activity and selectivity of Mb(H64V,I107S) and Mb(L29A,H64V,V68A) for the conversion of substrates **1a-1n** from *in vitro* reactions with purified proteins. The higher yields obtained for the same reactions in whole cell systems (Table 2) indicates a beneficial effect of the intracellular environment on the performance of the biocatalyst in the context of this transformation.

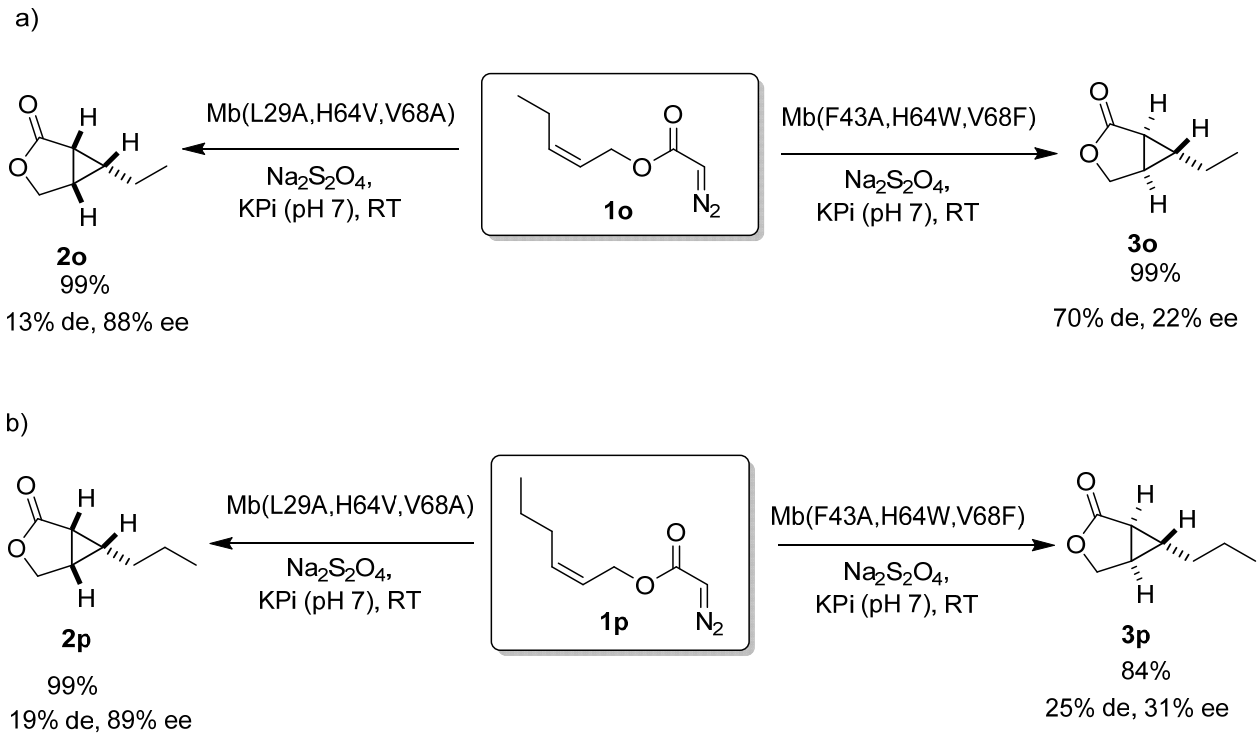


Entry	Product	Catalyst	TON	Yield[b]	*e.e.*
1		**a**	125	99%	99%
		b	125	99%	94%
2		**a**	125	99%	99%
		b	101	81%	95%
3		**a**	101	81%	97%
		b	41	33%	85%
4		**a**	96	77%	95%
		b	64	51%	80%
5		**a**	60	48%	95%
		b	44	35%	69%
6		**a**	90	72%	96%
		b	10	8%	62%
7		**a**	78	62%	90%
		b	76	61%	46%
8		**a**	79	63%	99%
		b	59	47%	70%
9		**a**	88	70%	99%
		b	55	44%	66%

10		**a**	21	17%	95%
		b	6	5%	78%
11		**a**	29	23%	72%
		b	89	71%	98%
12		**a**	94	75%	11%
		b	83	66%	52%
13		**a**	63	50%	6%
		b	59	47%	38%
14		**a**	26	21%	74%
		b	44	35%	51%

[a] Reaction conditions: 2.5 mM diazoacetate, purified Mb variant proteins (20 μM) in KPi buffer (50 mM, pH 7.0), 1 mL-scale, r.t., 5 hours. [b] GC or SFC yield.

Scheme S1. Mb(L29A,H64V,V68A)- and Mb(F43A,H64W,V68F)-catalyzed intramolecular cyclopropanation of (Z)-allylic diazoacetates. Reactions conditions: 20 μM Mb variant, 2.5 mM Z-allylic diazoacetate (**1o** and **1p**), 10 mM $Na_2S_2O_4$, in KPi buffer (50 mM, pH 7), room temperature, 5 hours, in anaerobic chamber.



Scheme S2. Activity tests with myoglobin variants Mb(H64V,I107S) or Mb(L29A,H64V,V68A) and methyl-substituted cinnamyl 2-diazoacetates and cis-/trans-homoallylic diazoacetates. Reactions conditions: 20 µM Mb variant (2.5 mM diazoacetate, 10 mM $Na_2S_2O_4$, in KPi buffer (50 mM, pH 7), room temperature, 12 hours, in anaerobic chamber.

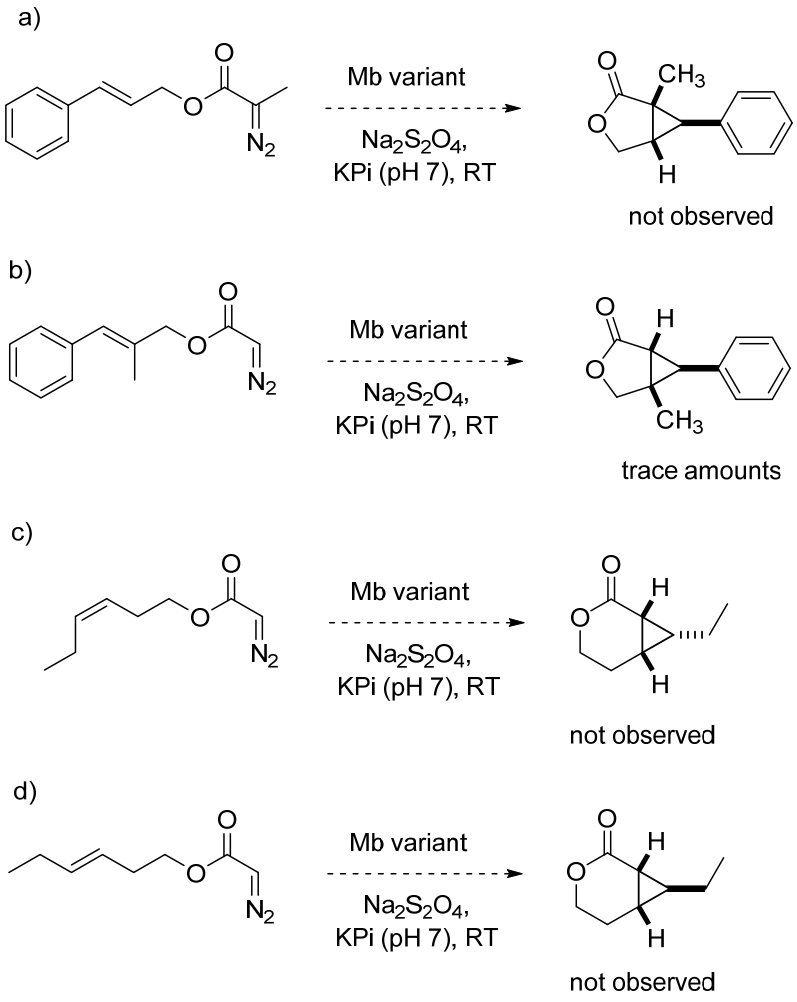


Figure S1. Crystal structure of sperm whale myoglobin (Mb). The amino acid residues lining the distal heme pocket are highlighted as stick models in light blue. The heme group (yellow) and the heme-coordinating proximal histidine (green) are shown as stick models.

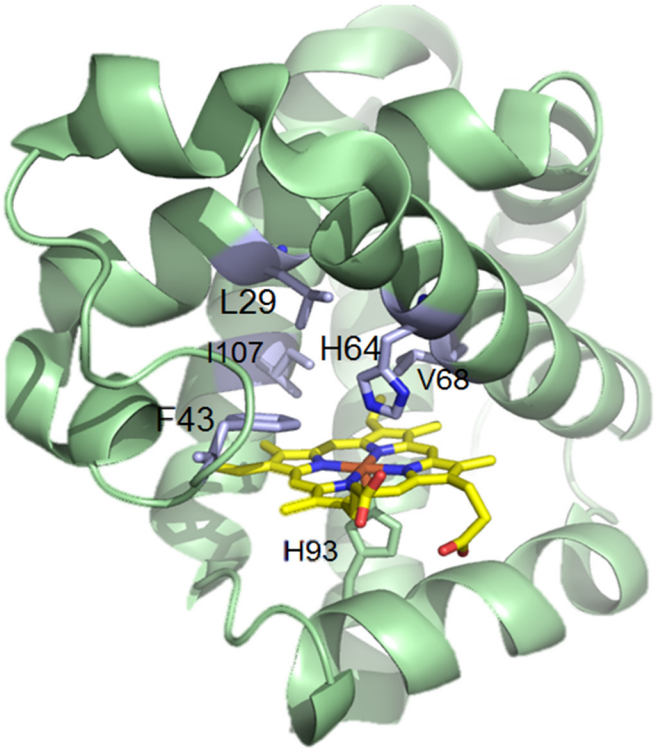


Figure S2 Time-course analysis of Mb(L29A,H64V,V68A)-catalyzed intramolecular cyclopropanation of cinnamyl 2-diazoacetate (**1a**) Conversion was determined by gas chromatography using calibration curves with isolated **2a**. Reaction conditions: Mb(L29A,H64V,V68A) expressing *E.coli.* C41(DE3) cells with cell density OD_{600} = 40, 5 mM **1a** in oxygenfree potassium phosphate buffer (50 mM, pH 7.0). The experiments were performed in duplicates with mean values being shown in the following figure.

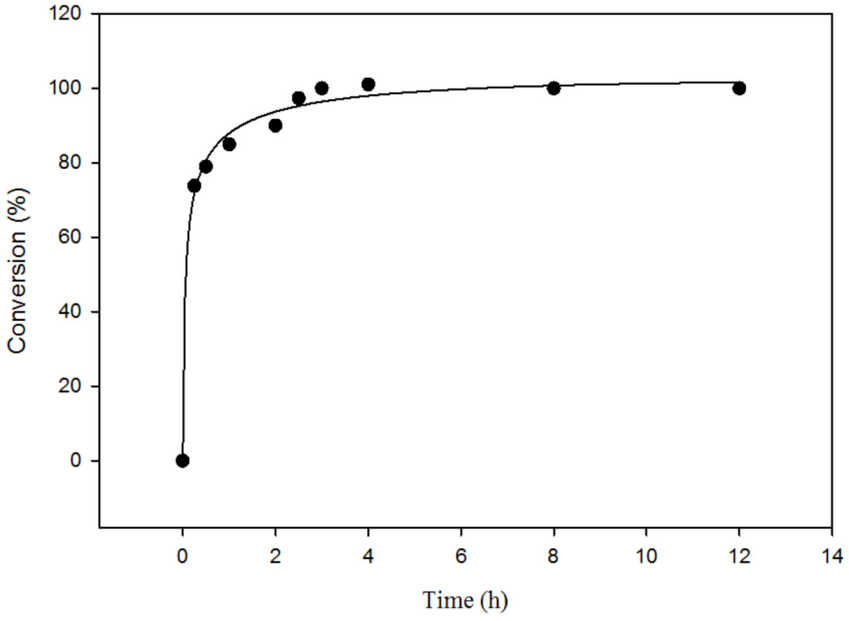
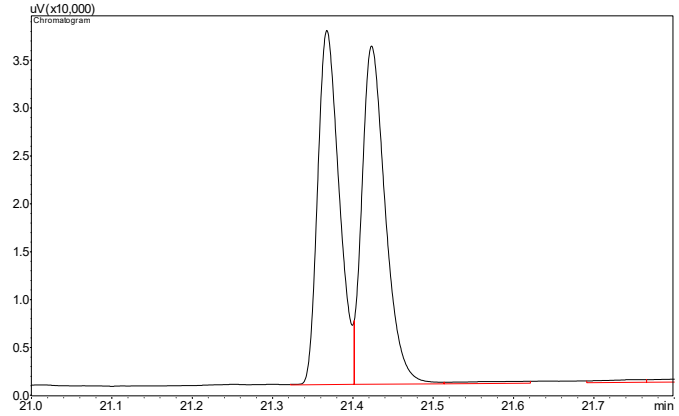
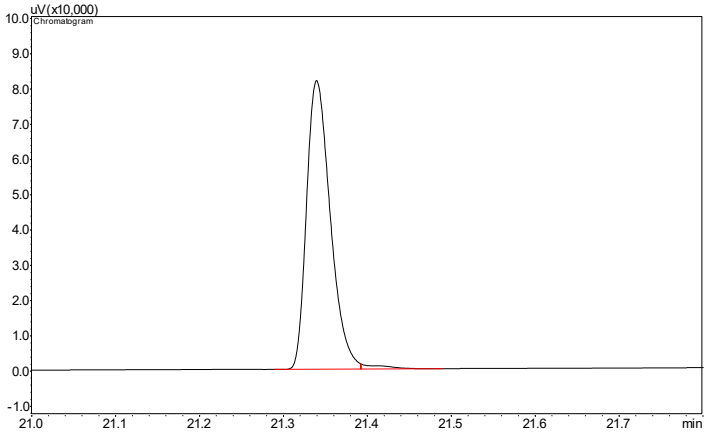


Figure S3. GC and SFC analysis for the determination of an enantiomeric excess in the Mb-catalyzed intramolecular cyclopropanation reactions. The reference racemic samples were prepared as described in the experimental procedures.

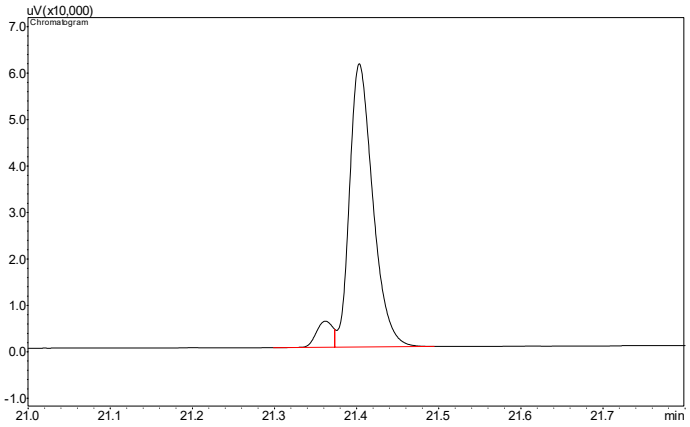
- Chiral GC analysis of racemic **2a** (*top*) and enzymatically produced **2a** (middle) and **3a** product (*bottom*):



Peak	tR (min)	Peak Area	Area%
1	21.38	68818.1	49.1%
2	21.43	71255.4	50.9%

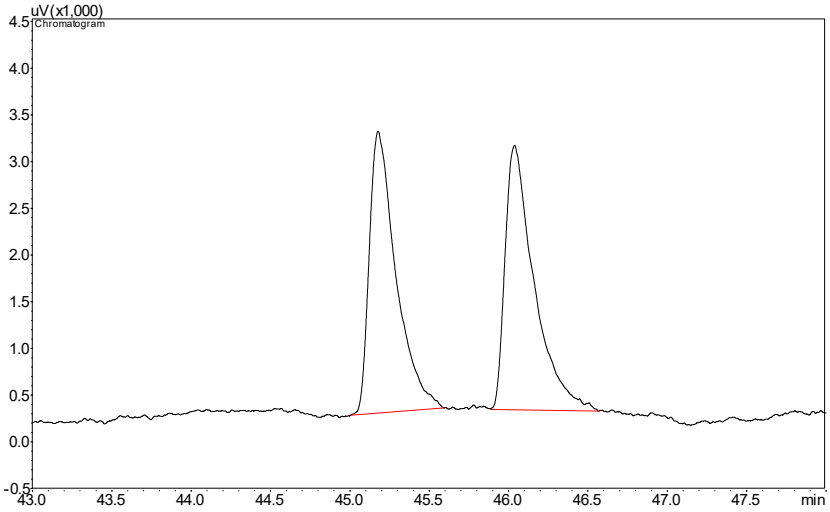


Peak	tR (min)	Peak Area	Area%
1	21.38	160633.3	99.7%
2	21.43	479.6	0.3%

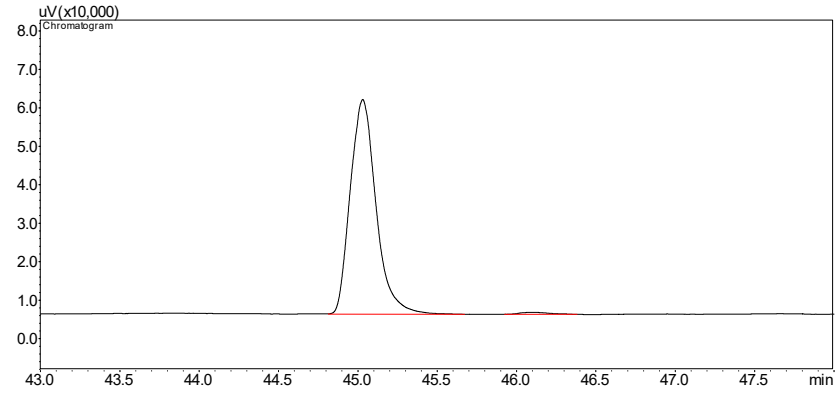


Peak	tR (min)	Peak Area	Area%
1	21.38	6718.6	5.3%
2	21.43	120204.8	94.7%

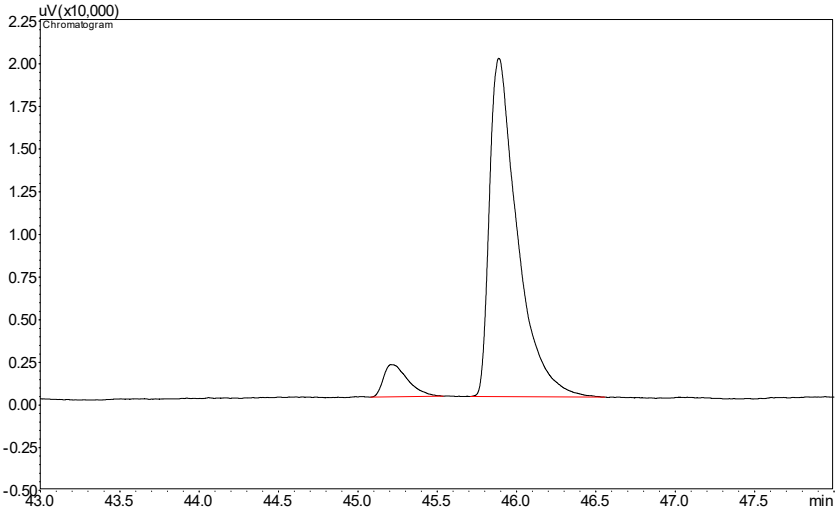
- Chiral GC analysis of racemic **2b** (*top*) and enzymatically produced **2b** (middle) and **3b** product (*bottom*):



Peak	tR (min)	Peak Area	Area%
1	45.18	35310.7	49.5%
2	46.15	36055.6	50.5%

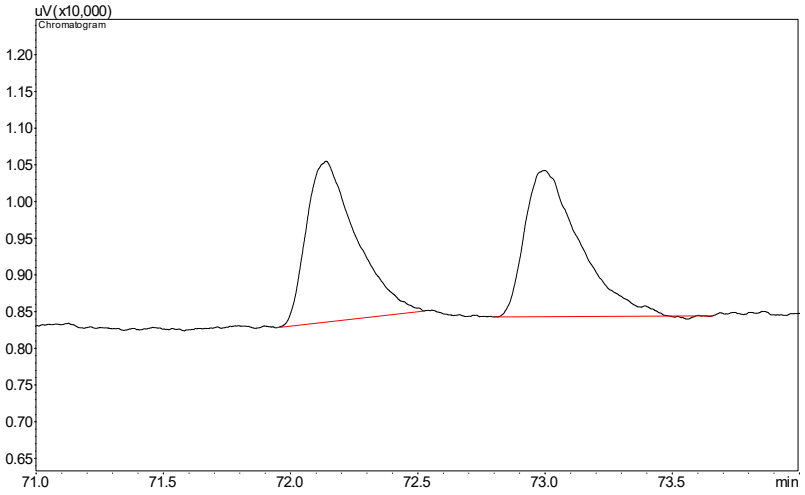


Peak	tR (min)	Peak Area	Area%
1	45.18	631421.1	99.5%
2	46.15	3591.7	0.5%

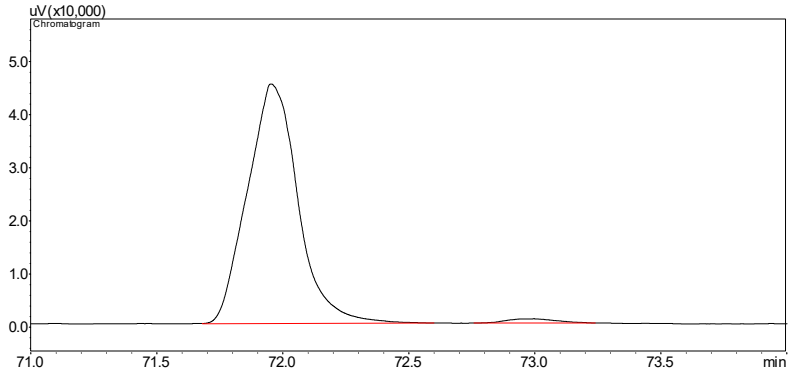


Peak	tR (min)	Peak Area	Area%
1	45.18	12261.9	4.8%
2	46.15	242274.4	95.2%

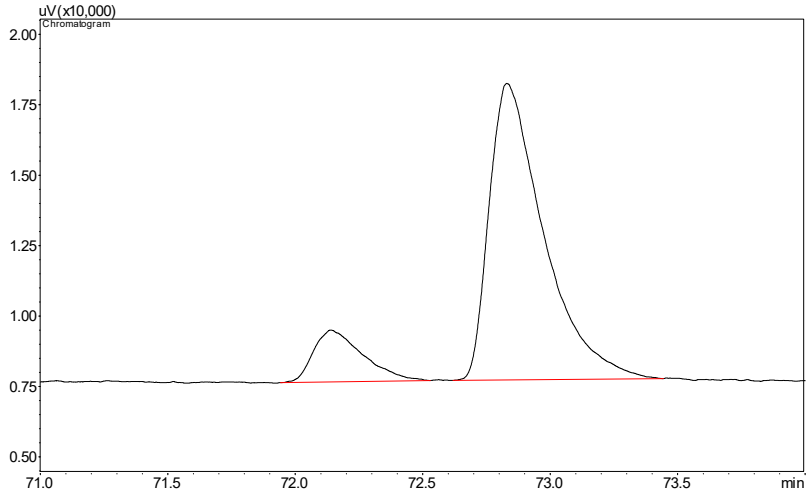
➢ Chiral GC analysis of racemic **2c** (*top*), enzymatically produced **2c** (middle) and **3c** product (*bottom*):



Peak	tR (min)	Peak Area	Area%
1	72.10	29999.9	50.0%
2	72.60	29970.2	50.0%

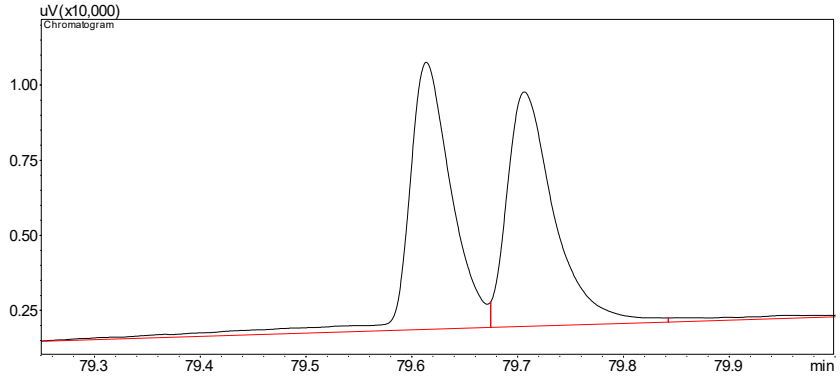


Peak	tR (min)	Peak Area	Area%
1	72.10	629878.7	98.3%
2	72.60	11151.8	1.7%

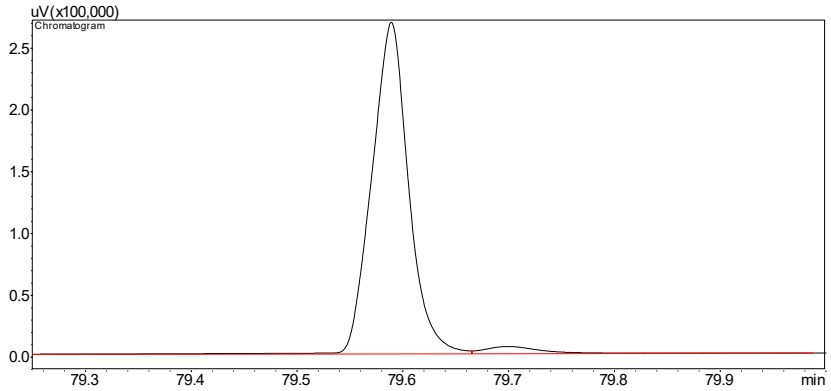


Peak	tR (min)	Peak Area	Area%
1	72.10	20651.3	10.5%
2	72.60	176651.9	89.5%

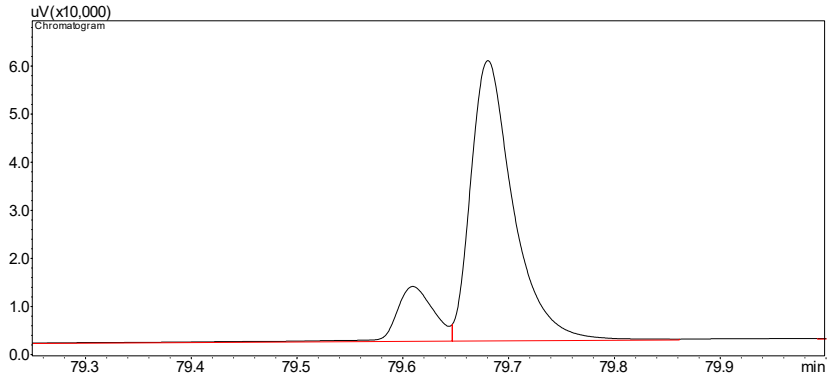
- Chiral GC analysis of racemic **2d** (*top*), enzymatically produced **2d** (middle) and **3d** product (*bottom*):



Peak	tR (min)	Peak Area	Area%
1	79.60	22349.4	49.6%
2	79.70	22736.2	50.4%

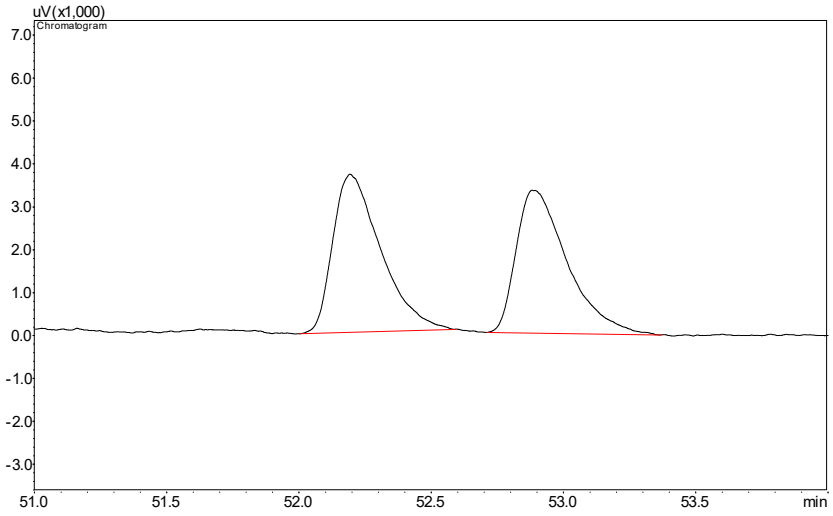


Peak	tR (min)	Peak Area	Area%
1	79.60	639909.2	97.4%
2	79.70	17376.7	2.7%

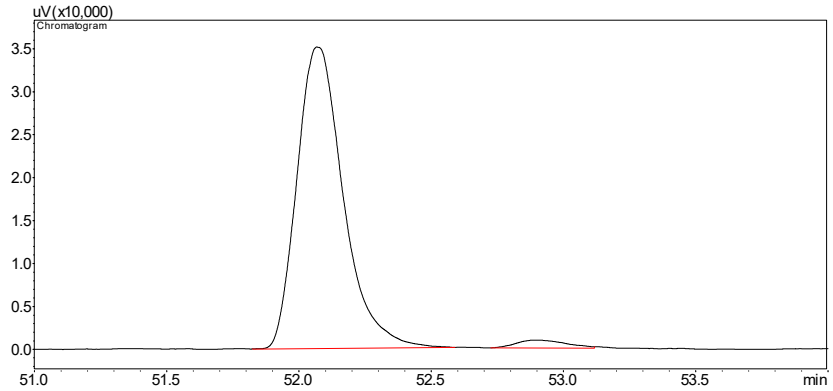


Peak	tR (min)	Peak Area	Area%
1	79.60	24302.9	11.8%
2	79.70	181870.1	88.2%

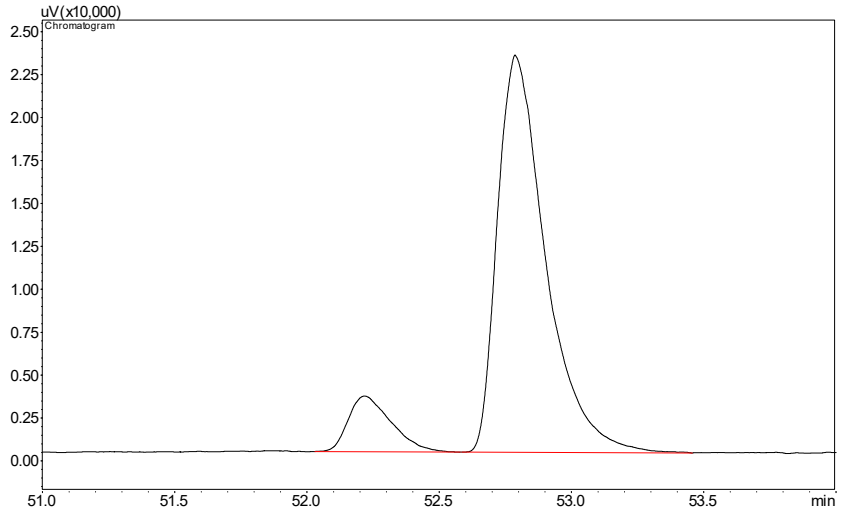
➢ Chiral GC analysis of racemic **2e** (*top*), enzymatically produced **2e** (middle) and **3e** product (*bottom*):



Peak	tR (min)	Peak Area	Area%
1	52.09	46400.6	50.9%
2	52.86	44767.9	49.1%

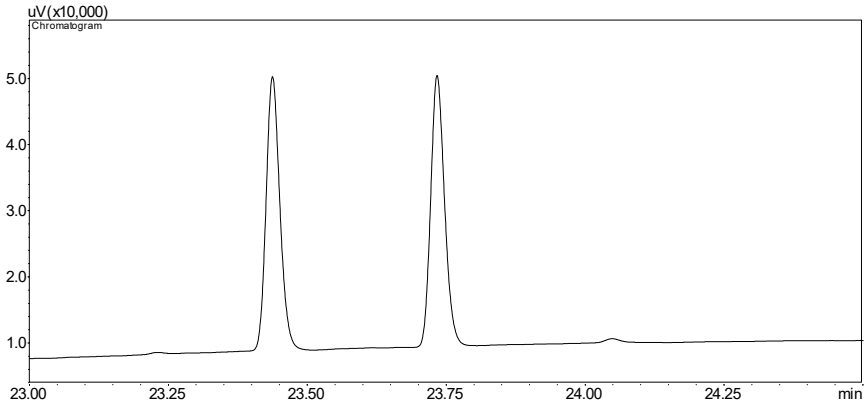


Peak	tR (min)	Peak Area	Area%
1	52.09	428496.2	97.3%
2	52.86	11917.1	2.7%

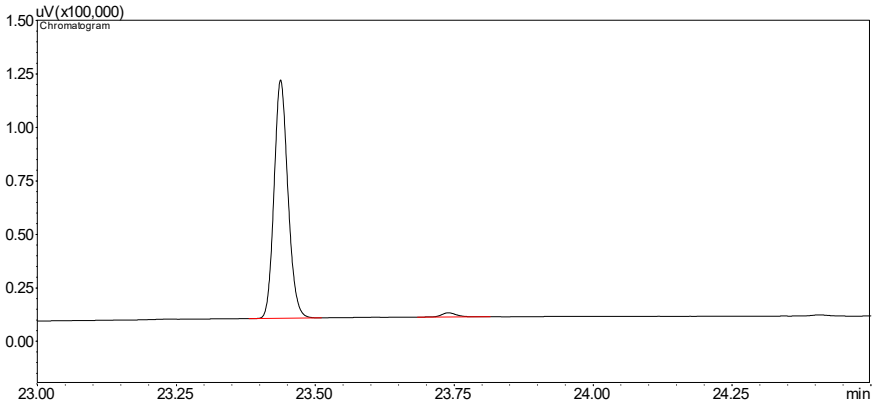


Peak	tR (min)	Peak Area	Area%
1	52.09	25620.1	8.0%
2	52.86	293025.7	92.0%

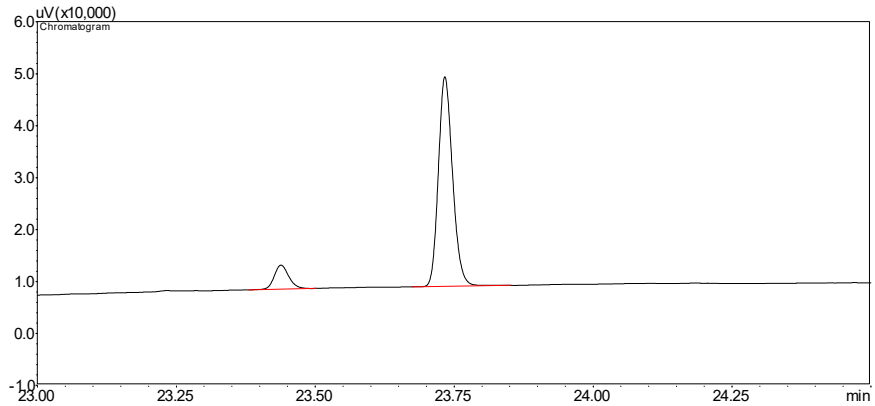
- Chiral GC analysis of racemic **2f** (*top*), enzymatically produced **2f** (middle) and **3f** product (*bottom*):



Peak	tR (min)	Peak Area	Area%
1	23.37	71702.6	50.2%
2	23.68	71242.9	49.8%

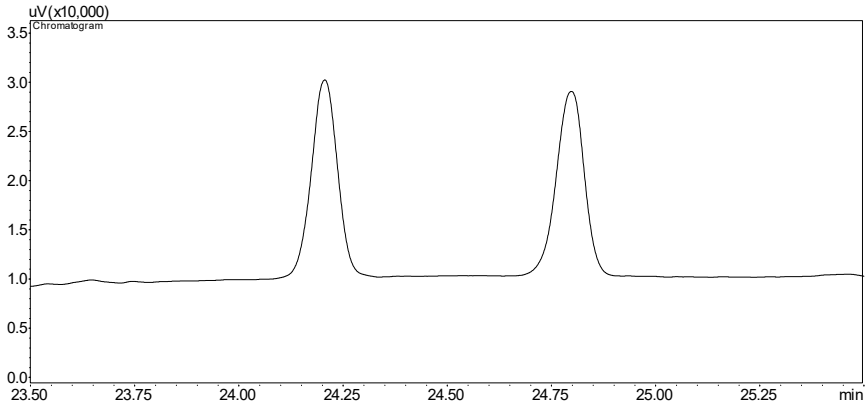


Peak	tR (min)	Peak Area	Area%
1	23.37	193157.7	98.1%
2	23.68	3662.3	1.8%

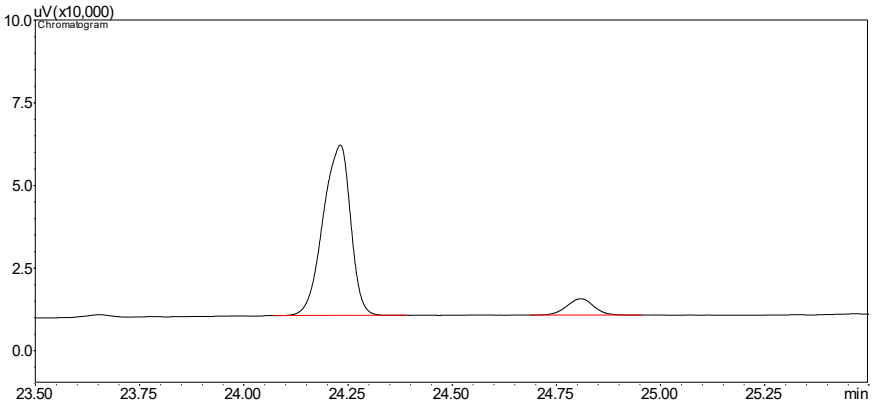


Peak	tR (min)	Peak Area	Area%
1	23.37	8429.7	10.5%
2	23.68	71855.5	89.5%

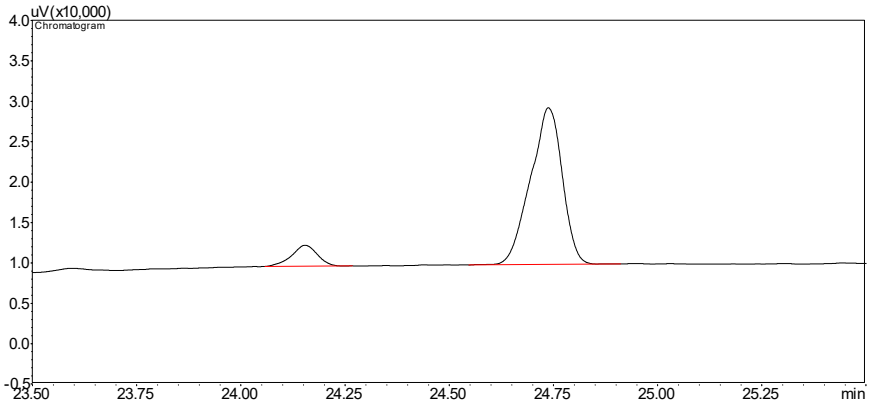
- Chiral GC analysis of racemic **2g** (*top*), enzymatically produced **2g** (middle) and **3g** product (*bottom*):



Peak	tR (min)	Peak Area	Area%
1	24.23	88438.2	50.4%
2	24.81	87074.8	49.6%

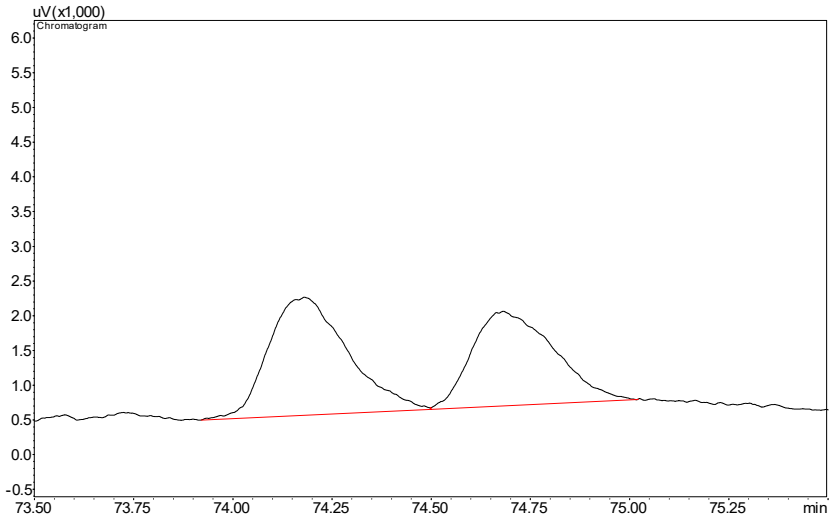


Peak	tR (min)	Peak Area	Area%
1	24.23	72870.7	94.8%
2	24.81	3957.5	5.2%

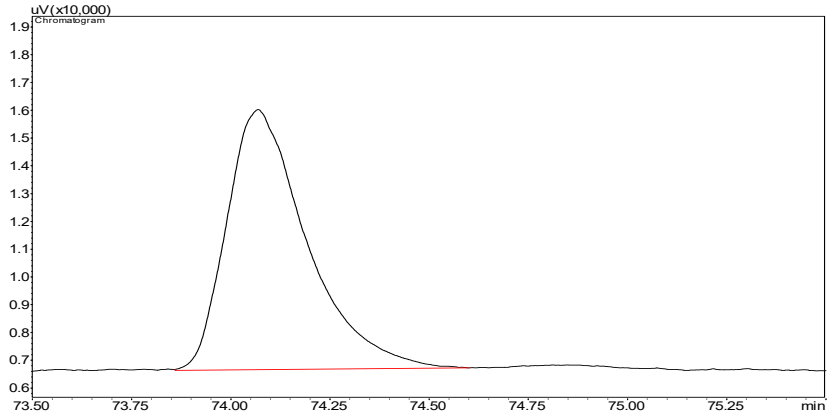


Peak	tR (min)	Peak Area	Area%
1	24.23	11100.0	9.7%
2	24.81	103028.9	90.3%

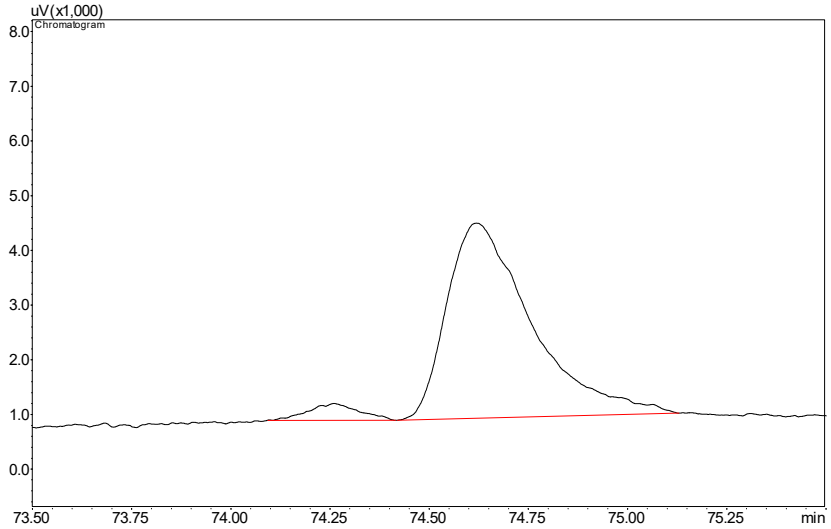
- Chiral GC analysis of racemic **2h** (*top*), enzymatically produced **2h** (middle) and **3h** product (*bottom*):



Peak	tR (min)	Peak Area	Area%
1	74.15	23686.0	50.1%
2	74.69	23576.3	49.9%

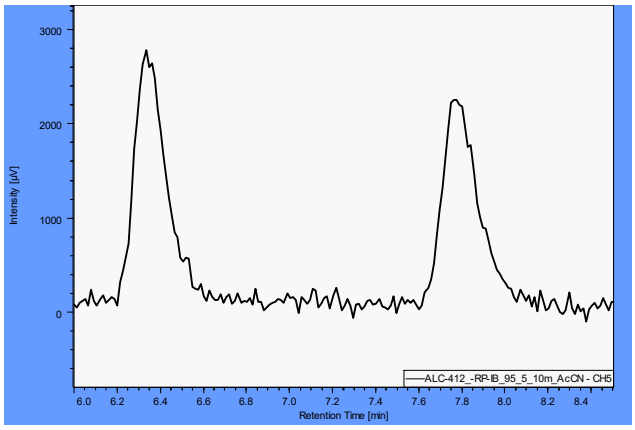


Peak	tR (min)	Peak Area	Area%
1	74.15	131326.5	99.7%
2	74.69	437.4	0.3%

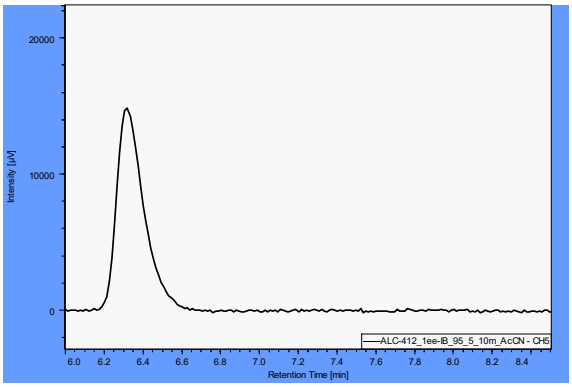


Peak	tR (min)	Peak Area	Area%
1	74.15	2761.2	4.9%
2	74.69	52921.9	95.1%

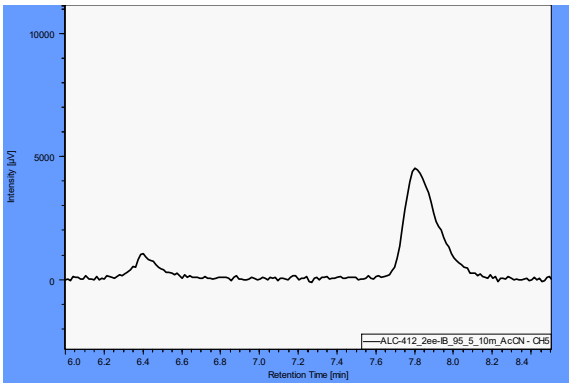
- Chiral GC analysis of racemic **2i** (*top*), enzymatically produced **2i** (middle) and **3i** product (*bottom*):



Peak	tR (min)	Peak Area	Area%
1	6.38	39205	50.0%
2	7.82	39165	50.0%

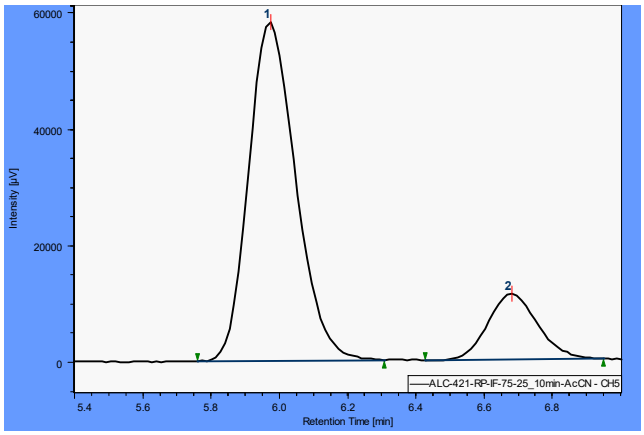


Peak	tR (min)	Peak Area	Area%
1	6.38	143429	100.0%
2	7.82	0	0.0%

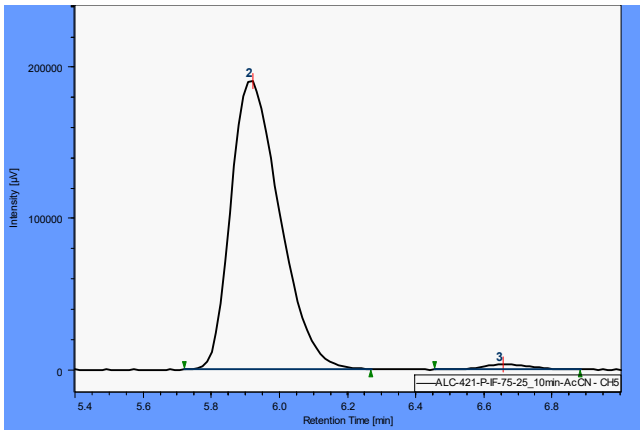


Peak	tR (min)	Peak Area	Area%
1	6.38	4724	8.4%
2	7.82	51735	91.6%

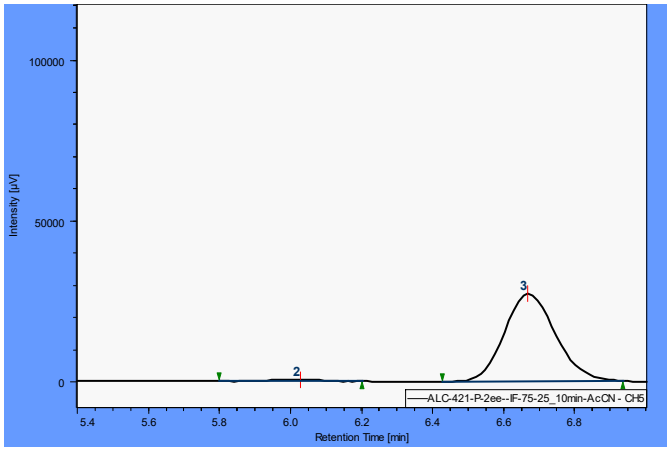
- Chiral GC analysis of racemic (Mb-WT catalyzed reaction) **2j** (*top*), enzymatically produced **2j** (middle) and **3j** product (*bottom*):



Peak	tR (min)	Peak Area	Area%
1	5.85	556957	83.1%
2	6.70	113508	16.9%

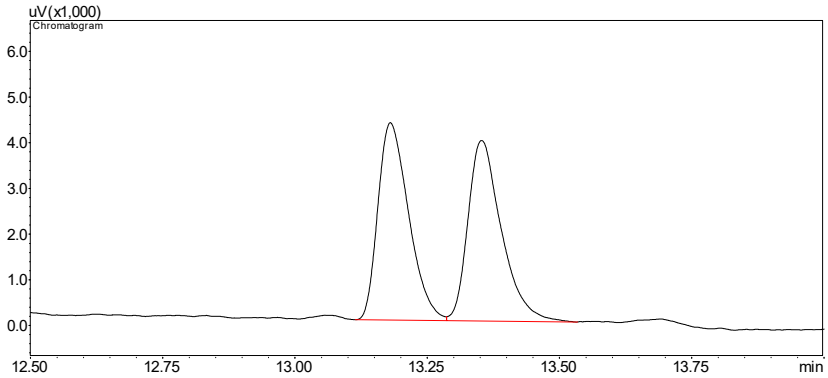


Peak	tR (min)	Peak Area	Area%
1	5.85	1899125	98.3%
2	6.70	32011	1.7%

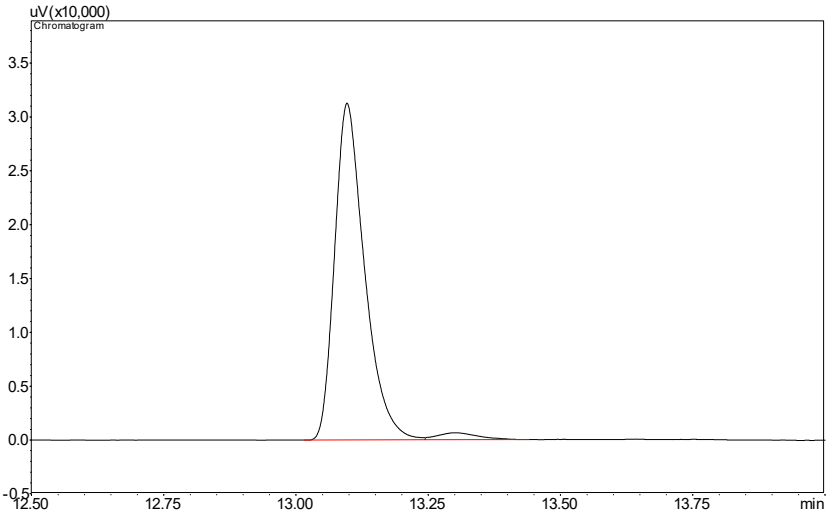


Peak	tR (min)	Peak Area	Area%
1	5.85	5508	2.0%
2	6.70	272157	98.0%

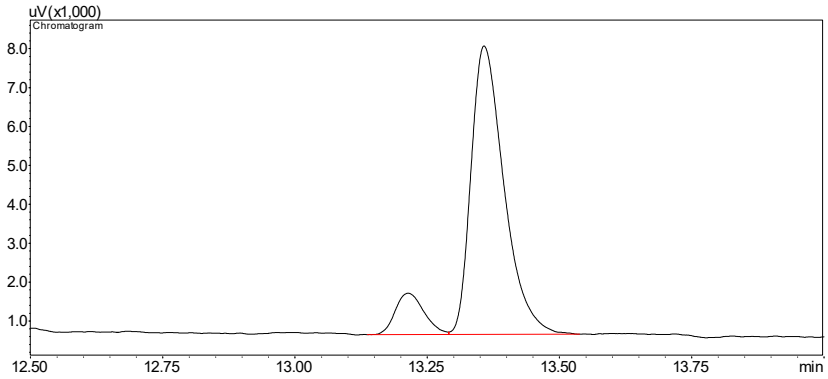
- Chiral GC analysis of racemic **2k** (*top*), enzymatically produced **2k** (middle) and **3k** product (*bottom*):



Peak	tR (min)	Peak Area	Area%
1	13.20	17426.3	50.0%
2	13.31	17396.5	50.0%

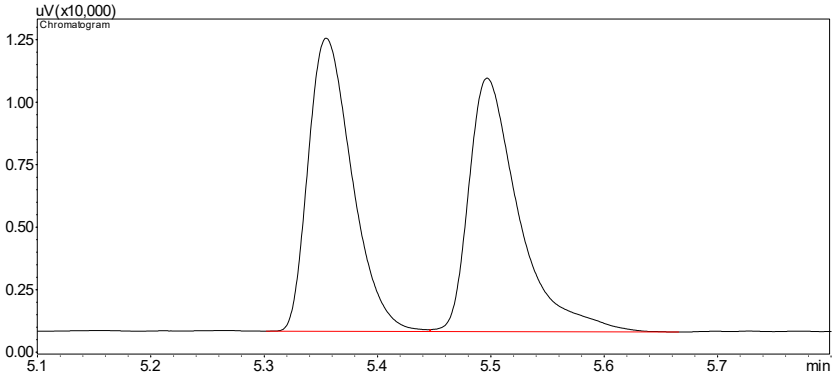


Peak	tR (min)	Peak Area	Area%
1	13.20	122974.3	98.8%
2	13.31	1427.1	1.2%

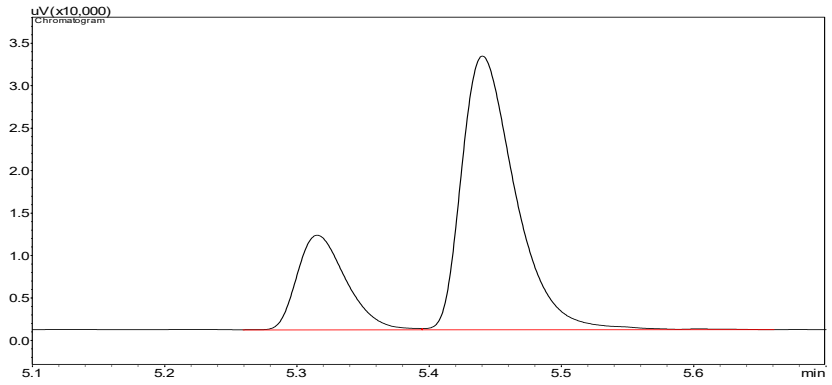


Peak	tR (min)	Peak Area	Area%
1	13.20	3983	10.7%
2	13.31	33158.1	89.2%

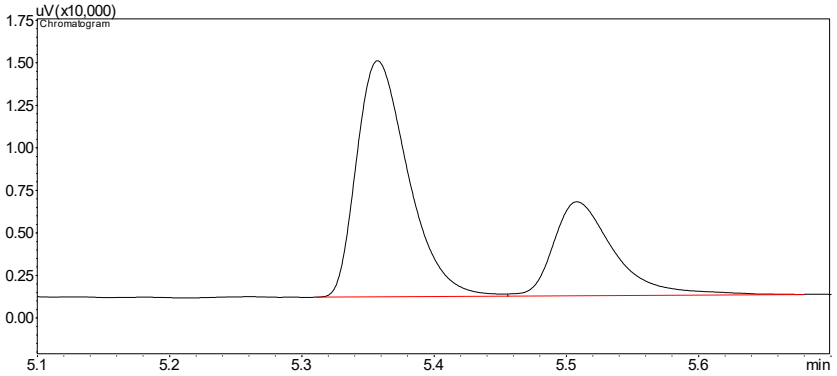
- Chiral GC analysis of racemic **2l** (*top*), enzymatically produced **2l** (middle) and **3l** product (*bottom*):



Peak	tR (min)	Peak Area	Area%
1	5.35	37558.2	50.5%
2	5.55	36777.6	49.5%

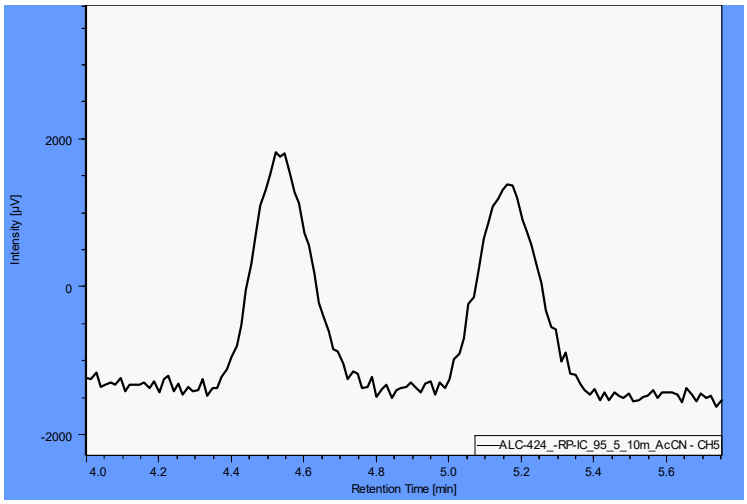


Peak	tR (min)	Peak Area	Area%
1	5.35	28649.7	24.0%
2	5.55	90946.9	76.0%

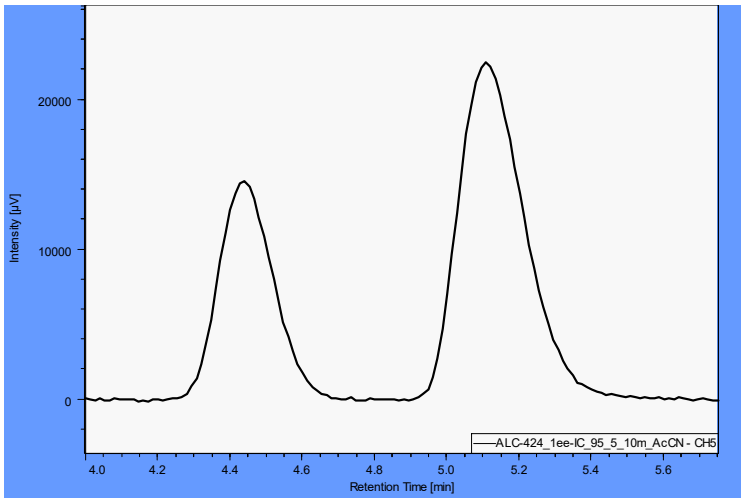


Peak	tR (min)	Peak Area	Area%
1	5.35	34648.2	77.8%
2	5.55	9894.2	22.2%

➢ Chiral GC analysis of racemic **2m** (*top*), enzymatically produced **2m** (*bottom*):

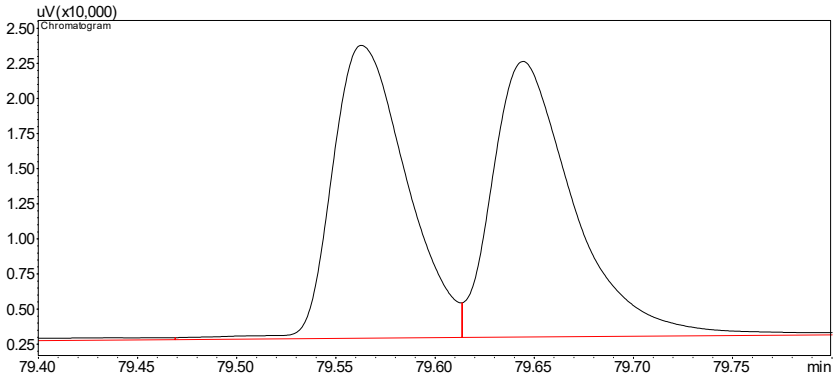


Peak	tR (min)	Peak Area	Area%
1	4.57	37106	52.0%
2	5.15	34216	48.0%

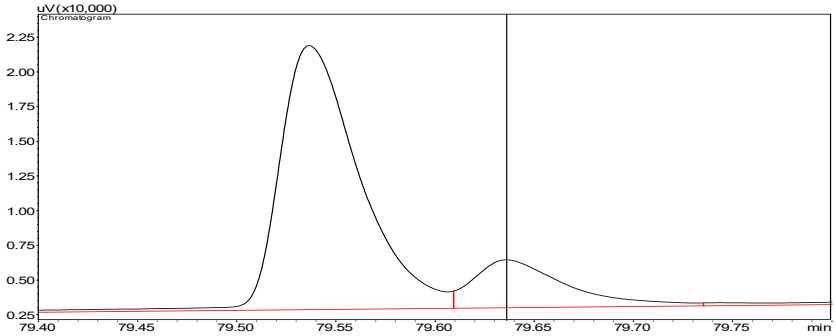


Peak	tR (min)	Peak Area	Area%
1	4.57	131415	30.9%
2	5.15	294043	69.1%

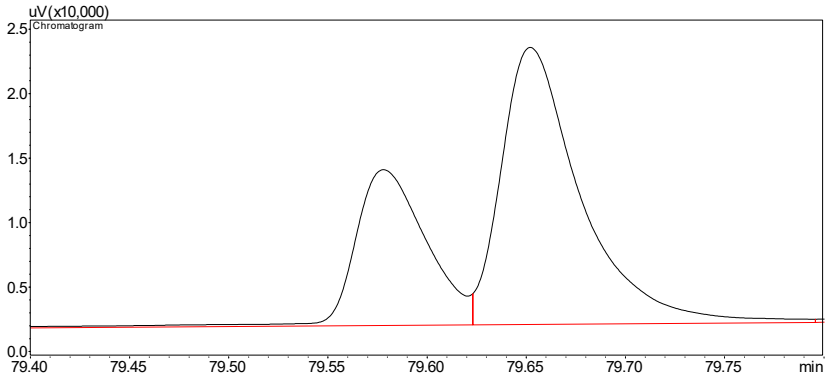
➢ Chiral GC analysis of racemic **2n** (*top*), enzymatically produced **2n** (*middle*) and **3n** product (*bottom*):



Peak	tR (min)	Peak Area	Area%
1	79.55	52442.0	49.3%
2	79.68	53946.0	50.7%

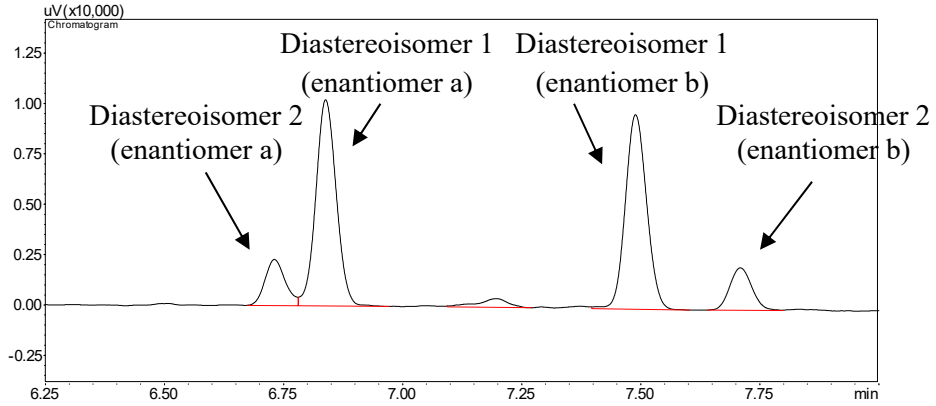


Peak	tR (min)	Peak Area	Area%
1	79.55	50792.8	86.8%
2	79.68	7774.8	13.2%



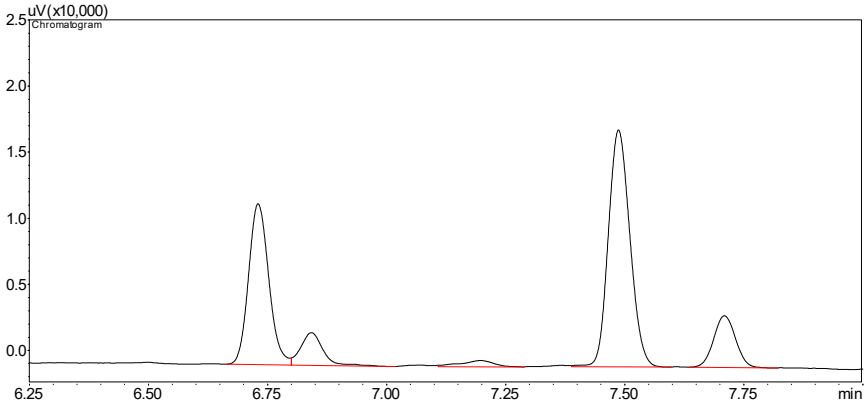
Peak	tR (min)	Peak Area	Area%
1	79.55	30582.2	34.0%
2	79.68	59927.2	66.0%

- Chiral GC analysis of racemic **2o** (*top*), enzymatically produced **2o** product (*bottom;* enzyme is indicated)



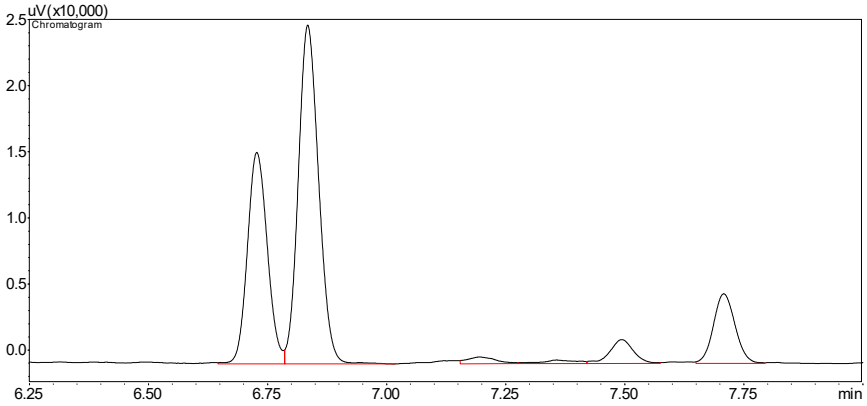
Peak	tR (min)	Peak Area	Area%
1	6.73	6835.2	9.2%
2	6.84	30631.3	41.2%
3	7.49	30099.8	40.4%
4	7.71	6847.1	9.2%

Mb(H64V/I107S)



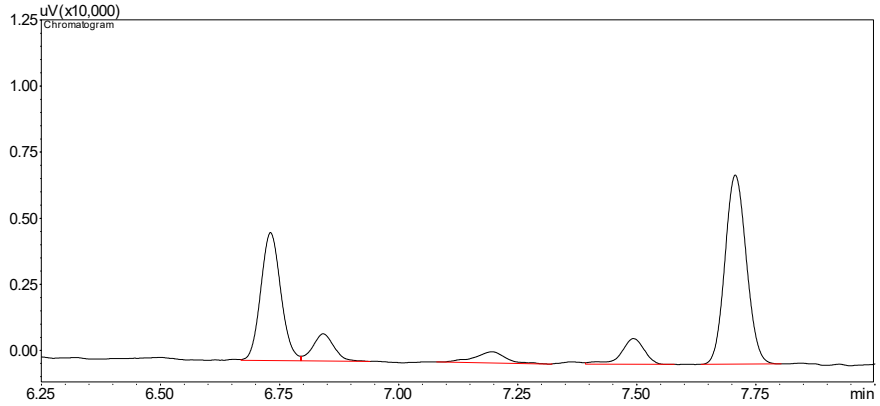
Peak	tR (min)	Peak Area	Area%
1	6.73	35338.2	31.9%
2	6.84	7439.2	6.7%
3	7.49	55226.4	49.8%
4	7.71	12889.1	11.6%

Mb(L29A/H64V/V68A)



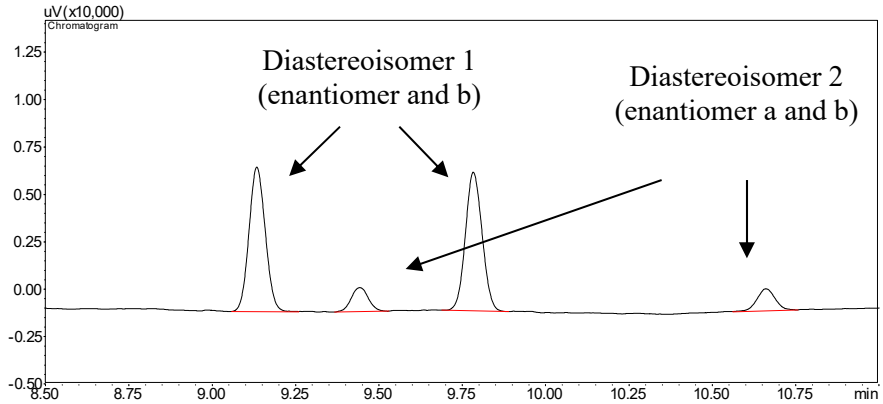
Peak	tR (min)	Peak Area	Area%
1	6.73	44746.3	32.0%
2	6.84	74207	53.1%
3	7.49	4944	3.5%
4	7.71	15758.6	11.3%

Mb(F43A/H64W/V68F)



Peak	tR (min)	Peak Area	Area%
1	6.73	14198.3	32.9%
2	6.84	3200.4	7.4%
3	7.49	3317.8	7.7%
4	7.71	22459.1	52.0%

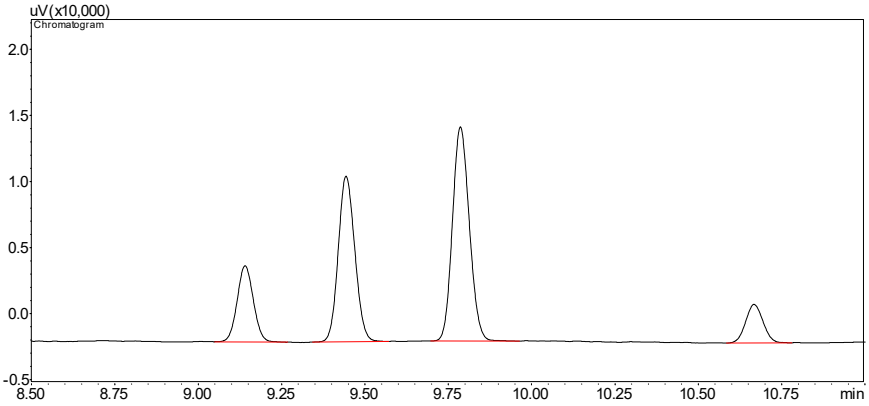
- Chiral GC analysis of racemic **2p** (*top*), enzymatically produced **2p** product (*bottom*; enzyme is indicated):



Peak	tR (min)	Peak Area	Area%
1	9.14	27713.1	43.1%
2	9.44	5112.0	7.9%
3	9.79	27056.2	42.1%

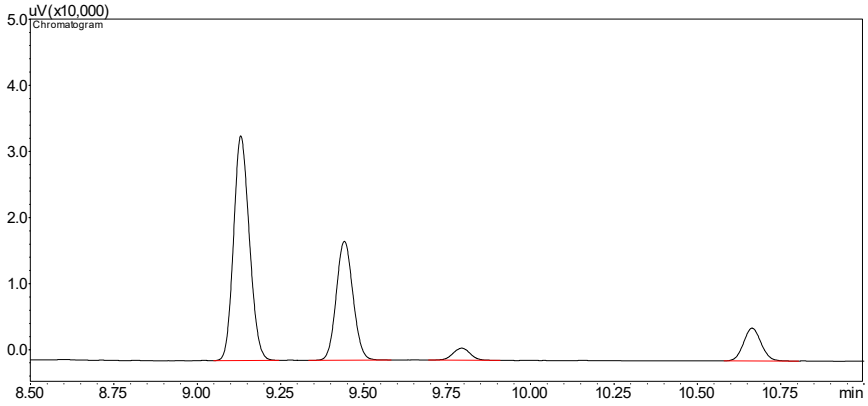
4	10.67	4460.8	6.9%

Mb(H64V/I107S)



Peak	tR (min)	Peak Area	Area%
1	9.14	16782.4	14.1%
2	9.44	40149.8	33.8%
3	9.79	53145.8	44.7%
4	10.67	8852.8	7.4%

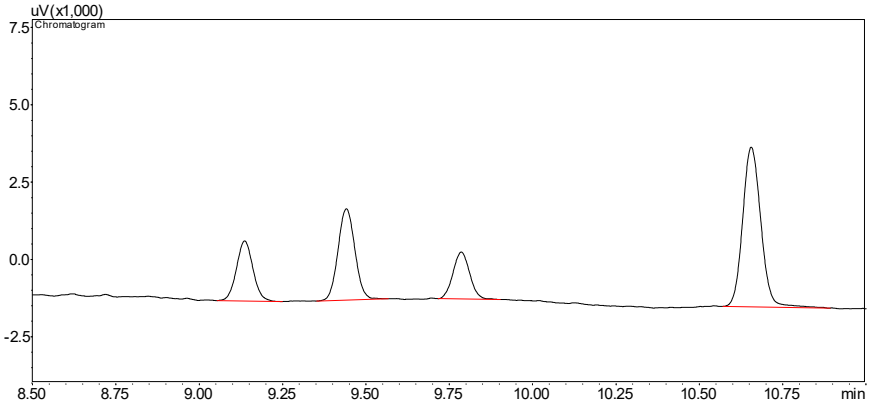
Mb(L29A/H64V/V68A)



Peak	tR (min)	Peak Area	Area%
1	9.14	112324.4	56.1%
2	9.44	63027.7	31.5%
3	9.79	6664.9	3.3%

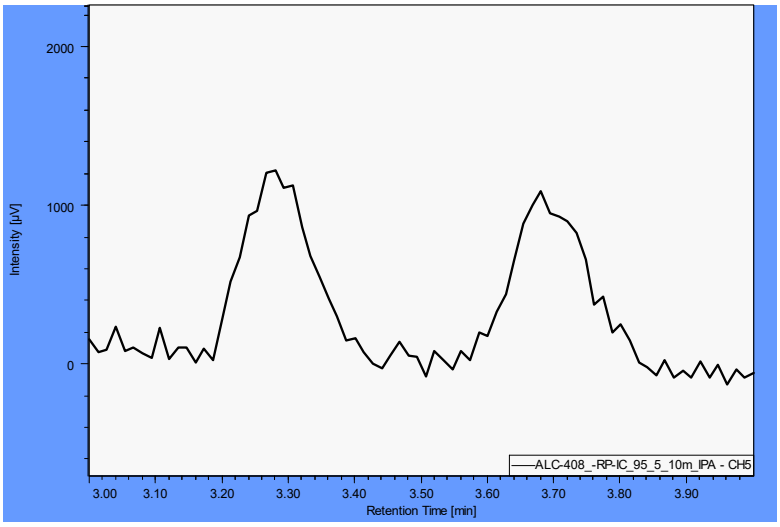
4	10.67	18341.3	9.2%

Mb(F43A/H64W/V68F

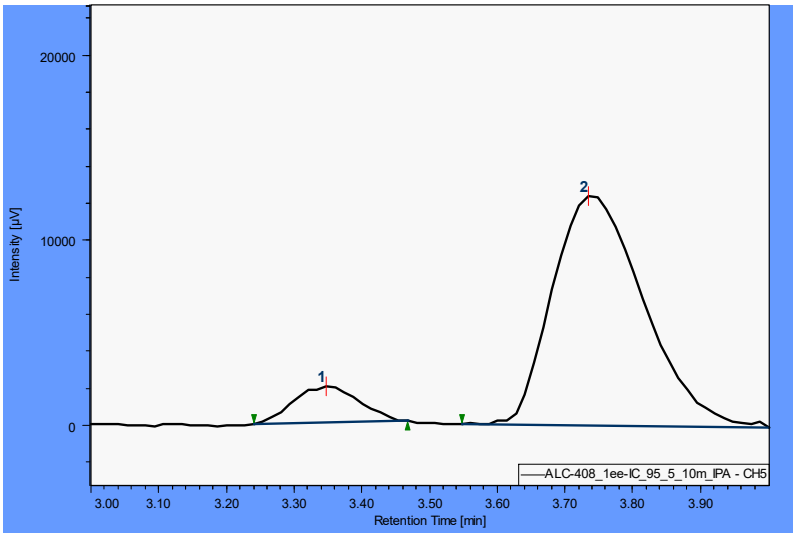


Peak	tR (min)	Peak Area	Area%
1	9.14	7598.3	15.5%
2	9.44	12060.6	24.7%
3	9.79	6312.6	12.9%
4	10.67	22934.6	46.9%

➢ Chiral GC analysis of racemic **5** (*top*), enzymatically produced **5** product (*bottom*):

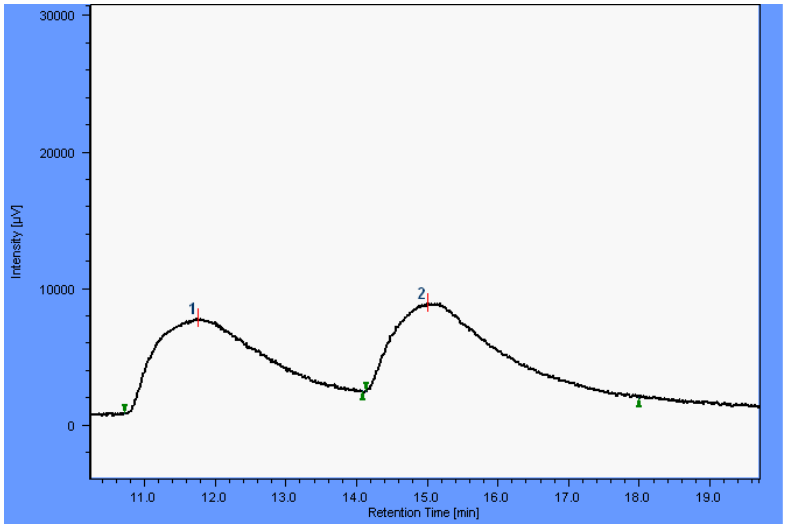


Peak	tR (min)	Peak Area	Area%
1	3.35	8970	49.0%
2	3.76	9331	51.0%

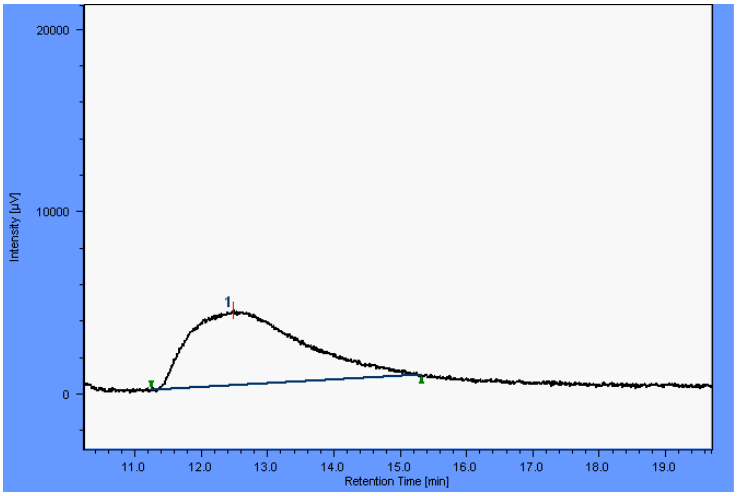


Peak	tR (min)	Peak Area	Area%
1	3.35	12022	9.4%
2	3.76	115470	90.6%

- Chiral GC analysis of racemic **7** (*top*), enzymatically produced **7** product (*bottom*):

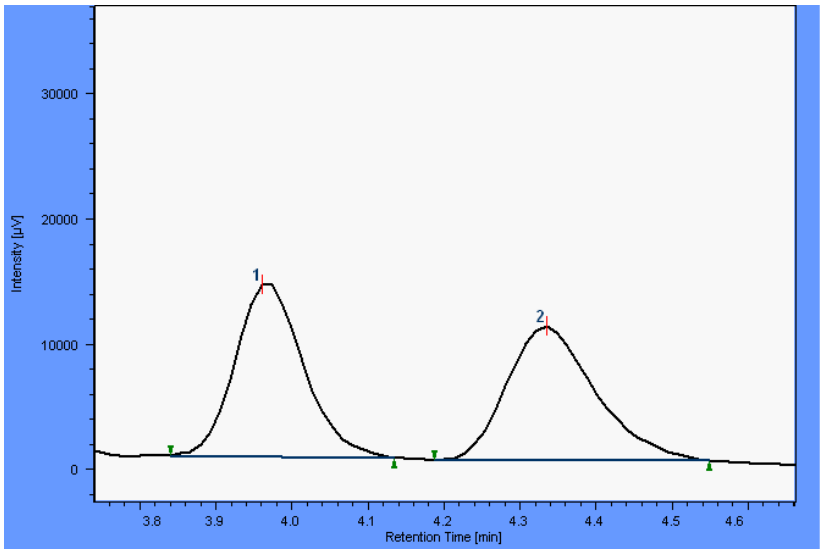


Peak	tR (min)	Peak Area	Area%
1	11.76	652487	49.913
2	15.00	654749	50.087

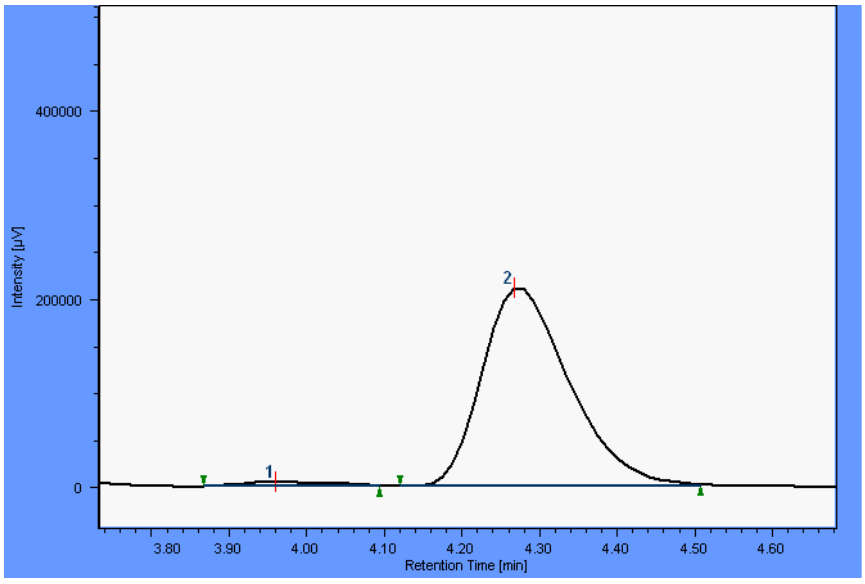


Peak	tR (min)	Peak Area	Area%
1	12.48	474452	100
2	15.00	0	0

➢ Chiral GC analysis of racemic **8** (*top*), enzymatically produced **8** product (*bottom*):

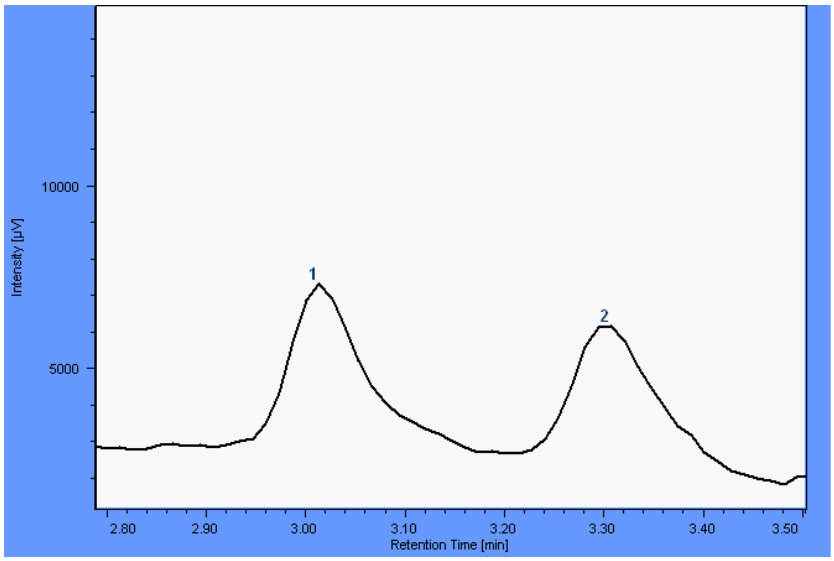


Peak	tR (min)	Peak Area	Area%
1	3.96	85651	49.884
2	4.33	86051	50.116

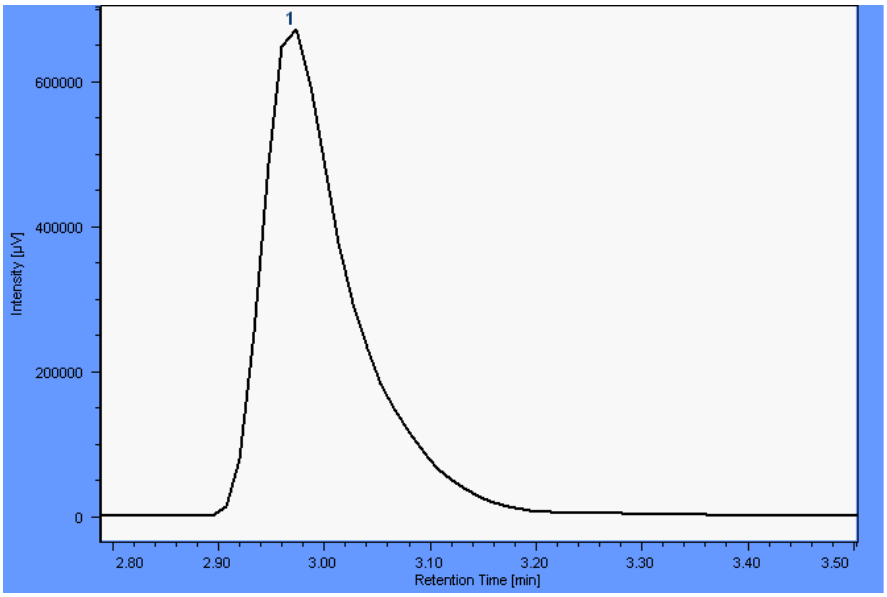


Peak	tR (min)	Peak Area	Area%
1	3.96	17864	1.07
2	4.27	1651188	98.93

➢ Chiral GC analysis of racemic **9** (*top*), enzymatically produced **9** product (*bottom*):



Peak	tR (min)	Peak Area	Area%
1	3.01	21957	51.125
2	3.31	20991	48.875



Peak	tR (min)	Peak Area	Area%
1	2.973	3837237	100
2	3.31	0	0

Figure S4. ORTEP of (1R,5S,6S)-6-phenyl-3-oxabicyclo[3.1.0]hexan-2-one **(2a)** with ellipsoids drawn at the 50% probability level. Hydrogen atoms were located in the difference Fourier map and refined freely. They are represented here as spheres of arbitrary radius for clarity.

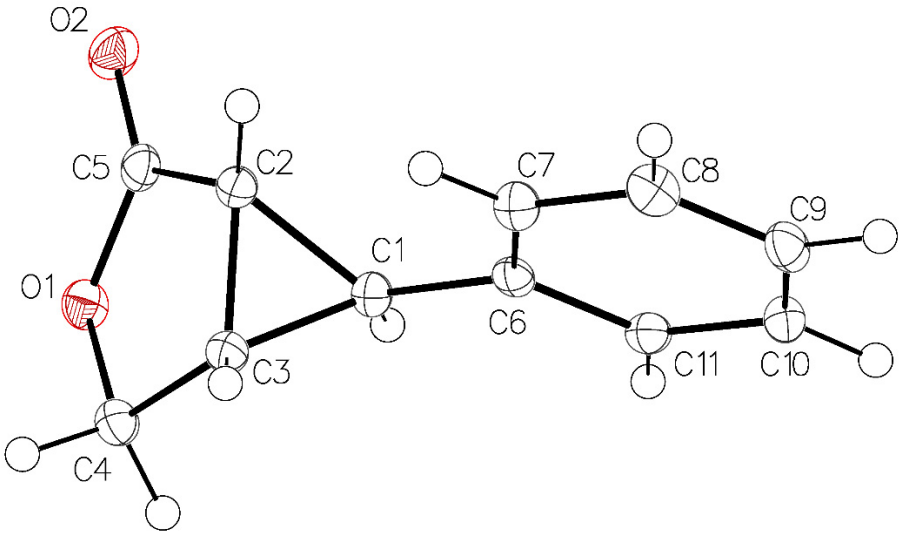


Figure S5. ORTEP of (1R,5S,6S)-6-(4-chlorophenyl)-3-oxabicyclo[3.1.0]hexan-2-one **(2c)** with ellipsoids drawn at the 50% probability level. Hydrogen atoms were located in the difference Fourier map and refined freely. They are represented here as spheres of arbitrary radius for clarity.

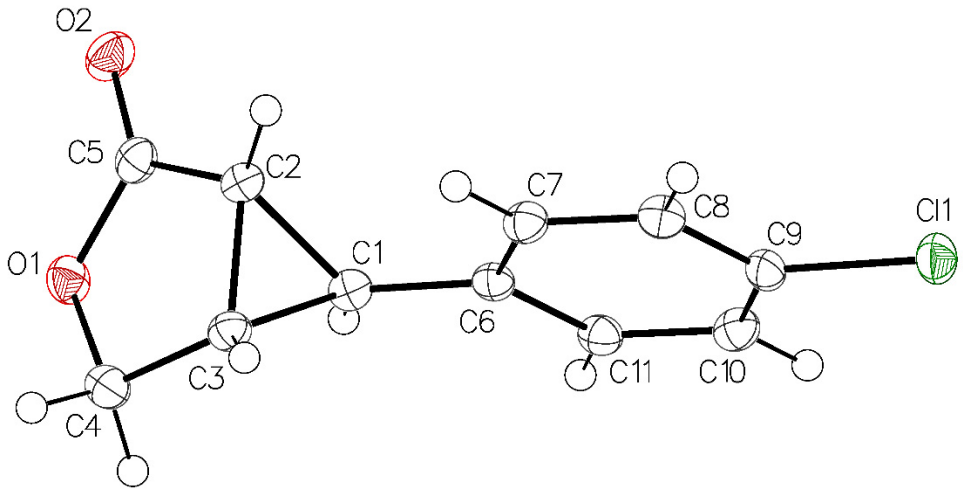
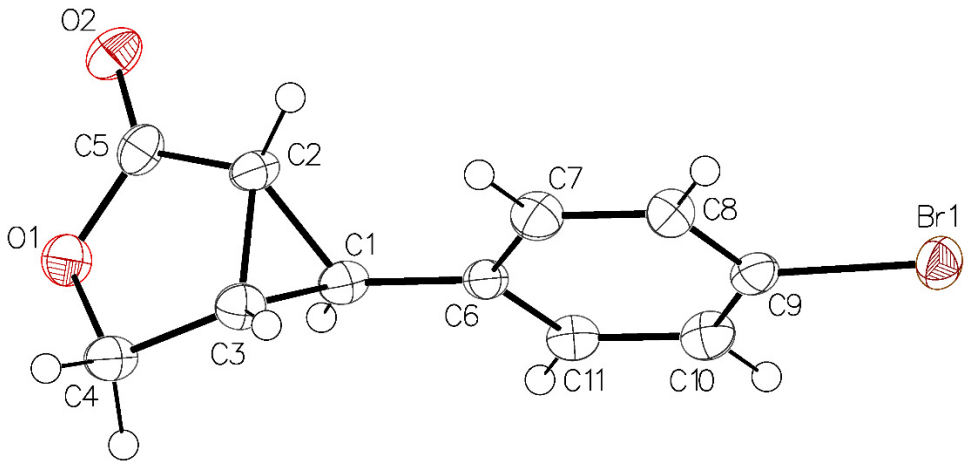


Figure S6. ORTEP of (1R,5S,6S)-6-(4-bromophenyl)-3-oxabicyclo[3.1.0]hexan-2-one **(2d)** with ellipsoids drawn at the 50% probability level. Hydrogen atoms were located in the difference Fourier map and refined freely. They are represented here as spheres of arbitrary radius for clarity.



Experimental Procedures

General Information

All chemicals and reagents were purchased from commercial suppliers (Sigma-Aldrich, AK Scientific, Alfa Aesar, TCI, Acros) and used without any further purification, unless otherwise stated. ^{1}H, and ^{13}C NMR spectra were measured on a Bruker DPX-500 instrument (operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C). Tetramethylsilane (TMS) served as the internal standard (0 ppm) for ^{1}H NMR and $CDCl_3$ was used as the internal standard (77.0 ppm) for ^{13}C NMR. Flash column chromatography purification was carried out using AMD Silica Gel 60 Å 230-400 mesh or Alumina, (Fisher adsorption) 80-200 mesh. Thin Layer Chromatography (TLC) was carried out using Merck Millipore TLC silica gel 60 F254 glass plates.

Protein Expression

Cloning procedures of the Mb variants investigated in this work were described previously.[1, 2] The oligonucleotides used for site saturation mutagenesis are shown in **Table S6**. The Mb variants were expressed in *E. coli* BL21(DE3) cells as follows. After transformation, cells were grown in TB medium (ampicillin, 100 mg L^{-1}) at 37 °C (200 rpm) until OD_{600} reached 0.6. Cells were then induced with 0.25 mM isopropyl-β-D-1-thiogalactopyranoside (IPTG) and 0.3 mM δ-aminolevulinic acid (ALA). After induction, cultures were shaken at 180 rpm and 27 °C and harvested after 20 h by centrifugation at 4,000 rpm at 4 °C. Myoglobin concentration was determined after cell lysis by sonication, followed by CO-binding assay using an extinction coefficient ε_{424} = 187 $mM^{-1}cm^{-1}$.

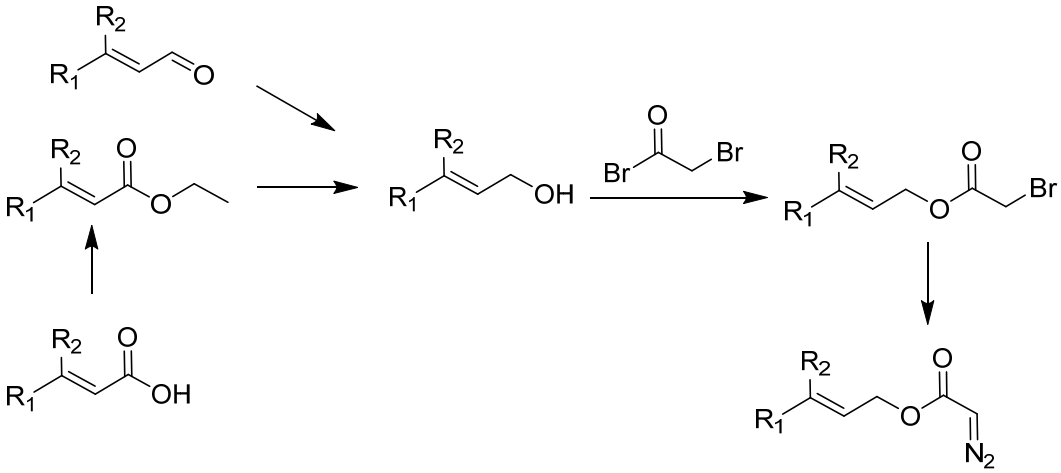
Table S6. Oligonucleotide used for site saturation mutagenesis

Oligonucleotide	**sequence (5' – 3')**
XhoI Rev	GGCTTTGTTAGCAGCCGGAT
L29NNK Fwd	GTCACGGTCAGGACATCNNKATCCGTCTGTTC
F43NNK Fwd	CAC CCG GAAACCCTG GAAAAANNKGACCGTTTC
H64NNK Fwd	GAAGGCTTCTGAAGACCTGAAAAAANNKGGTGTTACCG
V68NNK Fwd	CCTGAAAAAACACGGTGTTACCNNKCTGACCGCT
I107NNK Fwd	CCCGATCAAATACCTGGAGTTCNNKTCTGAAGCTATC
H64NNK on V68F Fwd	GAAGGCTTCTGAAGACCTGAAAAAANNKGGTGTTACCTTTC

Synthetic Procedures:

Synthesis of allylic diazoacetate:

All diazo-compounds were synthesized by following reported procedures.[3, 4] First, commercially available aldehyde, acid or esters were converted to allylic alcohol and then allylic alcohol used for the synthesis of diazoacetate.



General Procedure A: Synthesis of allylic esters from allylic acids:

To a solution of the allylic acid (1.0 equiv) in ethanol was added conc. H_2SO_4 (0.1 mL/g acid). The reaction was heated at reflux for 5 h, then allowed to cool, and concentrated *in vacuo*. The residue was neutralised with saturated aqueous $NaHCO_3$, extracted with EtOAc and the combined organic layers were washed with brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to obtain the pure allylic esters which was used in next step without any further purification.

General Procedure B: Synthesis of allylic alcohols from allylic esters:

To a solution of the allylic ester (1.0 equiv) in dry DCM (0.2 M) at −78 °C under argon was added DIBAL-H (1.0 M in hexane, 2.3 equiv) in dropwise. The reaction was stirred for 2 hours at −78 °C. The reaction mixture was diluted with 1 M HCl and then allowed to warm to room temperature and stirred for overnight. The layers were separated, and the aqueous layer was extracted with DCM. The combined organic layers were washed with 1 M HCl, sat. $NaHCO_3$ and brine, dried over $MgSO_4$ and filtered. Organic layer was concentrated *in vacuo* to afford pure allylic alcohols which was used in the next step.

General Procedure C: Synthesis of allylic alcohols from allylic aldehydes:

A solution of allylic aldehyde (1.0 equiv.) in MeOH was added $NaBH_4$ (1.2 equiv.) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h, subsequently quenched by the addition of saturated aqueous NH_4Cl solution and diluted with DCM. The aqueous phase was separated and extracted with DCM. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Filtration through a plug of silica gel yielded the desired allylic alcohols which was used in the next step without any further purification.

General Procedure D: Synthesis of allylic esters from allylic aldehydes (for the synthesis of 1l):

To a stirred solution of the allylic aldehyde (1.0 equiv) in THF was added ethyl 2-(triphenylphosphoranylidene)acetate (1.05 equiv). The reaction was refluxed for 4 h and allowed to reach room temperature. The reaction mixture was concentrated in vacuo, the residue triturated with pet. ether / Et_2O (9:1), and the solids removed by filtration. The solvent was removed in vacuo and the crude residue purified by flash chromatography on silica gel to afford pure allylic ester.

General Procedure E: Synthesis of allylic diazoacetate from allylic alcohols:

To a solution of allylic alcohol (3 mmol) and K_2CO_3 (2.08 g, 15 mmol) in DCM (15.0 mL), bromoacetyl bromide (780 µl, 9 mmol) was added slowly at 0 °C and stirred for 30 min. The

reaction mixture was quenched with H_2O and extracted with DCM three times. The organic phase was washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo and the obtained bromoacetate residue was used in the next step without any future purification. To the solution of the resulting bromoacetate and N',N-ditosylhydrazine (2.04 g, 6.0 mmol) in THF (15.0 mL), DBU (2.28 mL, 15 mmol) was added dropwise at 0 °C and stirred for 30 min. Reaction was quenched by aqueous saturated solution of $NaHCO_3$. Reaction mixture was extracted with Et_2O three times. The organic phase was washed with brine, dried over $MgSO_4$ and evaporated to give crude diazoacetate. The crude product was purified by column chromatography on silica gel with ethyl acetate/hexanes to afford the desired allylic diazoacetate product.

General procedure F: Biocatalytic intramolecular cyclopropanation reactions using whole cells expressing myoglobin on preparative scale:

These reactions were carried out on a 40 mL-scale using 39 mL of Mb(L29A,H64V,V68A) (otherwise mentioned) expressing *E. coli* cells, 2.5 mM of allylic diazoacete. In a typical procedure, the allylic diazoacetate (0.1 mmol in 1 mL of ethanol) was added slowly to a 125 mL Erlenmeyer flask containing a suspension of Mb-expressing cells (OD_{600} = 40 in KPi, pH 7) (19 mL) under argon pressure, equipped with a magnetic stir bar and sealed with a rubber septum. Reaction mixture stirred at room temperature for 3-5 hours. The reaction mixtures were extracted with diethyl ether (20 mL x 3) and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The TON for the whole-cell reactions were calculated based on Mb concentration in the reaction mixture as measured via UV-vis spectroscopy using the CO-binding assay (ε_{424} = 187 $mM^{-1}cm^{-1}$) after cell lysis. The crude product was purified by flash column chromatography using silica gel and ethyl acetate/hexanes as the eluent to isolate the intramolecular cyclopropanation product. The purified product was characterized by NMR, GC-MS, and chiral SFC or GC for stereoselectivity determination and they were used as authentic standards for the construction of the calibration curves (TON and % conversion determination).

General Procedure G: Synthesis of racemic standards using hemin

Under standard reaction conditions, 500 μL scale reactions were carried out using 20 μM Hemin (except 20 μM Mb-WT variant for **2j**), 10 mM allylic diazoacetate, and 10 mM sodium dithionite. In a typical procedure, a solution containing Hemin in potassium phosphate buffer (50 mM, pH 7.0) with sodium dithionite was prepared in an anaerobic chamber. Reactions were initiated by addition of 10 μL of diazoacetate from 0.5 M stock solutions, and the reaction mixtures were stirred in the chamber for 12 h at room temperature. Reaction mixtures were extracted by using DCM and used for analysis.

General Procedure H: General procedure for Mb(F43A,H64W,V68F)-catalyzed intramolecular cyclopropanation with purified protein.

Under standard reaction conditions, 500 μL scale reactions were carried out using 50 μM Mb, 1 mM allylic diazoacetate, and 10 mM sodium dithionite. In a typical procedure, a solution containing Mb in potassium phosphate buffer (50 mM, pH 7.0) with sodium dithionite was prepared in an anaerobic chamber. Reactions were initiated by addition of 10 μL of diazoacetate from 0.5 M stock solutions, and the reaction mixtures were stirred in the chamber for 3-5 h at room temperature. Reaction mixtures were extracted by using DCM and used for analysis.

Reaction Analysis

The reactions were analyzed by adding 25 μL of internal standard (benzodioxole, 100 mM in methanol) to a 500 μL aliquot of the reaction mixture, followed by extraction with 500 μL dichloromethane (DCM) and centrifugation at 14,000 rpm. The organic layer was collected and analyzed by SFC or GC-FID. The TON for the whole-cell reactions were calculated based on Mb concentration in the reaction mixture as measured via UV-vis using the CO-binding assay (ε_{424} = 187 $mM^{-1}cm^{-1}$) after cell lysis. Calibration curves of the different intramolecular cyclopropane products were constructed using authentic standards from the whole cell reactions (procedure F). Enantioselectivity was determined by using SFC or GC-FID using a chiral column as described below. No traces of the dimerization and/or intermolecular cyclopropanation byproducts were observed by GCMS, HPLC and/or SFC for any of the biocatalytic reactions.

Analytical Methods

Gas chromatography (GC) analyses were carried out using a Shimadzu GC-2010 gas chromatograph equipped with a FID detector, and a Cyclosil-B column (30 m x 0.25 mm x 0.25 μm film). The following GC methods were used for TON analysis and stereoisomer separation (% *ee* analysis)**,** 1 μL injection, injector temp.: 200 ºC, detector temp: 300 ºC.

Gradient for method A: column temperature set at 140 ºC for 3 min, then to 160 ºC at 1.8 ºC/min, then to 165 ºC at 1.0 ºC/min, then to 245 at 25 ºC/min, then 245 ºC for 6 min. Total run time was 28 min.

Gradient for method B: column temperature set at 130ºC for 2 min, then to 150 ºC at 0.8 ºC/min, then to 180 ºC at 0.6 ºC/min, then 245 °C at 25 ºC/min, 245 ºC hold for 3 min. Total run time was 82 min.

Gradient for method C: column temperature set at 120ºC for 3 min, then to 150 ºC at 0.8 ºC/min, then to 245 °C at 25 ºC/min, 245 ºC hold for 2 min. Total run time was 46 min.

Table S7. Enantiomer resolution via chiral GC analysis.

Product	**Method**	**t_R for 1st isomer (min)**	**t_R for 2nd isomer (min)**
2a/3a	A	21.38	21.43
2b/3b	B	45.18	46.15
2c/3c	B	72.10	73.06
2d/3d	B	79.60	79.70
2e/3e	B	52.09	52.86
2f/3f	A	23.37	23.68
2g/3g	A	24.23	24.81
2h/3h	B	74.15	74.69
2k/3k	A	13.20	13.31
2l/3l	C	5.35	5.55
2n/3n	B	79.55	79.68
2o/3o	A	6.73	7.49
2p/3p	A	9.14	9.79

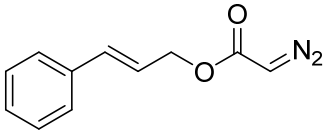
Enantiomer resolution for compounds **2i, 2j, 2l**, **5, 7, 8** and **9** were performed by Supercritical Fluid Chromatography (SFC) using a JASCO Analytical and Semi-Preparative SFC instrument equipped with a column oven (35 °C), photodiode array detector, a backpressure regulator (12.0 MPa), a carbon dioxide pump and a sample injection volume of 3 μL. Daicel Chiralpak IA, IB IC or IF column (0.46 cm ID × 25 cm L) were used for separation of the enantiomers and % *ee* determination. All samples were eluted using an isocratic solvent system with the indicated modifier in liquid CO_2 at an elution rate of 4 mL/min and detected at λ = 220 nm. Total run time was 10.2 min.

Table S8. Enantiomer resolution via chiral SFC analysis.

Product	**Column**	**Modifier Solvent**	**t_R for 1st enantiomer (min)**	**t_R for 2nd enantiomer (min)**
2i/3i	IB	AcCN (5%)	6.38	7.82
2j/3j	IF	AcCN (25%)	5.85	6.70
2m	IC	AcCN (5%)	4.57	5.15
5	IC	IPA (10%)	3.35	3.76
7	IA	IPA (8%)	11.76	15.00
8	IF	IPA (25%)	3.96	4.33
9	IA	IPA (25%)	3.01	3.31

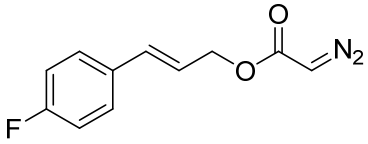
Compound Characterization Data

Cinnamyl 2-diazoacetate (1a):



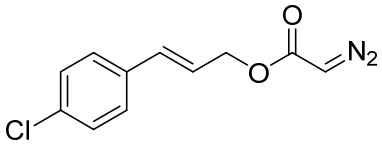
Cinnamyl 2-diazoacetate (**1a**) was prepared according to the general procedure for the synthesis of allylic diazoacetate. Reaction mixture was purified by silica gel column chromatography with EtOAc/hexanes as an eluent to give the desired product as pale-yellow liquid in 69% yield (yield of step E). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 2H), 7.25 (m, 1H), 6.64 (d, *J* = 15.5 Hz, 1H), 6.28 (dt, *J* = 15.8, 6.4 Hz, 1H), 4.80 (d, *J* = 6.4 Hz, 2H), 4.79 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.4, 136.9, 135.1, 129.4, 128.9, 127.4, 123.9, 66.1, 47.0.

(*E*)-3-(4-fluorophenyl)allyl 2-diazoacetate (1b):



(*E*)-3-(4-fluorophenyl)allyl 2-diazoacetate (**1b**) was prepared according to the general procedure for the synthesis of allylic diazoacetate. Reaction mixture was purified by silica gel column chromatography with EtOAc/hexanes as an eluent to give the desired product as pale-yellow liquid in 75% yield (yield of step E). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.40 – 7.30 (m, 2H), 7.01 (t, *J* = 8.6 Hz, 2H), 6.61 (d, *J* = 15.9 Hz, 1H), 6.20 (dt, *J* = 15.8, 6.4 Hz, 1H), 4.80 (d, *J* = 6.4 Hz, 2H + merged 1H, -CH=N_2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.4, 162.4, 133.9, 133.1, 129.0, 128.9, 123.7, 116.4, 116.2, 66.0, 47.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ -113.76.

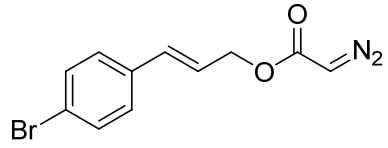
(*E*)-3-(4-chlorophenyl)allyl 2-diazoacetate (1c):



(*E*)-3-(4-chlorophenyl)allyl 2-diazoacetate (**1c**) was prepared according to the general procedure for the synthesis of allylic diazoacetate. Reaction mixture was purified by silica gel column chromatography with EtOAc/hexanes as an eluent to give the desired product as pale-yellow solid in 48% yield (yield of step E). ^{1}H NMR (500 MHz, $CDCl_3$)

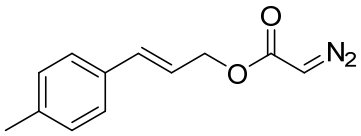
δ 7.44 – 7.18 (m, 4H), 6.60 (d, *J* = 15.8 Hz, 1H), 6.38 – 6.14 (m, 1H), 4.80 (br s, 3H). ; ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.2, 135.40, 134.55, 133.70, 129.55, 128.60, 124.64, 65.86, 47.04.

(*E*)-3-(4-bromophenyl)allyl 2-diazoacetate (1d):



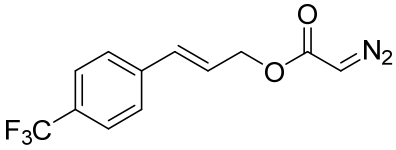
(*E*)-3-(4-bromophenyl)allyl 2-diazoacetate (**1d**) was prepared according to the general procedure for the synthesis of allylic diazoacetate. Reaction mixture was purified by silica gel column chromatography with EtOAc/hexanes as an eluent to give the desired product as pale-yellow liquid in 69% yield (yield of step E). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.4 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 6.58 (d, *J* = 16.4 Hz, 1H), 6.37 – 6.18 (m, 1H), 4.80 (d, *J* = 6.6 Hz, 2H + merged 1H, -CH=N_2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.6, 135.8, 133.7, 132.5, 128.9, 124.8, 122.7, 65.8, 47.0.

(*E*)-3-(p-tolyl)allyl 2-diazoacetate (1e):



(*E*)-3-(p-tolyl)allyl 2-diazoacetate **(1e)** was prepared according to the general procedure for the synthesis of allylic diazoacetate. Reaction mixture was purified by silica gel column chromatography with EtOAc/hexanes as an eluent to give the desired product as pale-yellow liquid in 45% yield (yield of step E). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 7.8 Hz, 2H), 7.14 (d, *J* = 7.8 Hz, 2H), 6.63 (d, *J* = 15.8 Hz, 1H), 6.25 (dt, *J* = 15.8, 6.5 Hz, 1H), 4.81 (d, *J* = 6.5 Hz, 2H), 4.79 (br s, 1H), 2.35 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.7, 138.8, 135.2, 134.1, 130.1, 127.3, 122.8, 66.3, 47.2, 22.0.

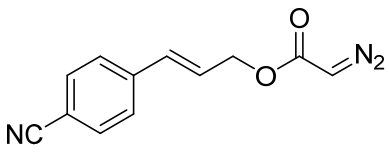
(*E*)-3-(4-(trifluoromethyl)phenyl)allyl 2-diazoacetate (1f):



(*E*)-3-(4-(trifluoromethyl)phenyl)allyl 2-diazoacetate **(1f)** was prepared according to the general procedure for the synthesis of allylic diazoacetate. Reaction mixture was purified by silica gel

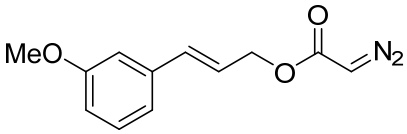
column chromatography with EtOAc/hexanes as an eluent to give the desired product as pale-yellow liquid in 67% yield (yield of step E). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 6.65 (d, *J* = 15.9 Hz, 1H), 6.36 (dt, *J* = 15.9, 6.1 Hz, 1H), 4.82 (d, *J* = 6.0 Hz, 2H), 4.79 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.3, 140.4, 133.2, 130.8, 130.5, 127.5, 126.8, 126.3, 123.7, 65.5, 47.4; ^{19}F NMR (370 MHz, $CDCl_3$): δ -62.76.

(*E*)-3-(4-cyanophenyl)allyl 2-diazoacetate (1g):



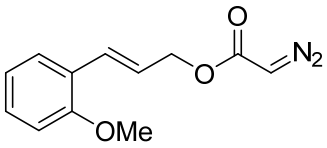
(*E*)-3-(4-cyanophenyl)allyl 2-diazoacetate **(1g)** was prepared according to the general procedure for the synthesis of allylic diazoacetate. Reaction mixture was purified by silica gel column chromatography with EtOAc/hexanes as an eluent to give the desired product as pale-yellow liquid in 67% yield (yield of step E). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.3 Hz, 6H), 7.44 (d, *J* = 8.3 Hz, 7H), 6.62 (d, *J* = 16.0 Hz, 3H), 6.38 (dt, *J* = 15.9, 6.0 Hz, 3H), 4.82 (d, *J* = 6.0 Hz, 7H), 4.79 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.1, 141.3, 133.2, 132.6, 128.1, 127.9, 119.5, 112.1, 65.3, 47.0.

(*E*)-3-(3-methoxyphenyl)allyl 2-diazoacetate (1h):



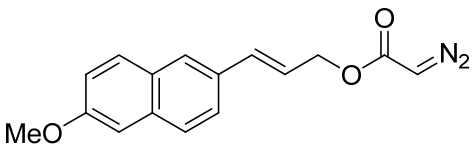
(*E*)-3-(3-methoxyphenyl)allyl 2-diazoacetate **(1h)** was prepared according to the general procedure for the synthesis of allylic diazoacetate. Reaction mixture was purified by silica gel column chromatography with EtOAc/hexanes as an eluent to give the desired product as pale-yellow liquid in 46% yield (yield of step E). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (t, *J* = 8.7 Hz, 1H), 6.99 (d, *J* = 7.4 Hz, 1H), 6.92 (d, *J* = 7.9 Hz, 1H), 6.82 (s, 1H), 6.62 (dd, *J* = 15.5, 9.2 Hz, 1H), 6.36 – 6.21 (m, 1H), 4.82 (d, *J* = 6.3 Hz, 2H), 4.80 (br s, 1H), 3.82 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.3, 160.6, 138.3, 135.0, 130.4, 124.2, 120.1, 114.6, 112.6, 66.0, 56.0, 47.0.

(*E*)-3-(2-methoxyphenyl)allyl 2-diazoacetate (1i):



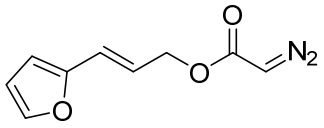
(*E*)-3-(2-methoxyphenyl)allyl 2-diazoacetate **(1i)** was prepared according to the general procedure for the synthesis of allylic diazoacetate. Reaction mixture was purified by silica gel column chromatography with EtOAc/hexanes as an eluent to give the desired product as pale-yellow liquid in 28% yield (yield of step E). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.1 Hz, 1H), 7.25 (t, *J* = 6.6 Hz, 1H), 6.99 (d, *J* = 16.0 Hz, 1H), 6.93 (t, *J* = 7.2 Hz, 1H), 6.87 (d, *J* = 8.1 Hz, 1H), 6.32 (dt, *J* = 15.8, 6.4 Hz, 1H), 4.83 (d, *J* = 6.0 Hz, 2H), 4.78 (br s, 1H), 3.85 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.2, 157.7, 130.2, 130.0, 128.0, 125.9, 124.5, 121.4, 111.6, 66.7, 56.2, 47.0.

(*E*)-3-(6-methoxynaphthalen-2-yl)allyl 2-diazoacetate (1j):



(*E*)-3-(6-methoxynaphthalen-2-yl)allyl 2-diazoacetate **(1j)** was prepared according to the general procedure for the synthesis of allylic diazoacetate. Reaction mixture was purified by silica gel column chromatography with EtOAc/hexanes as an eluent to give the desired product as green solid in 48% yield (yield of step E). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 – 7.64 (m, 3H), 7.54 (d, *J* = 8.6 Hz, 1H), 7.12 (dd, *J* = 8.9, 2.1 Hz, 1H), 7.09 (s, 1H), 6.76 (d, *J* = 15.8 Hz, 1H), 6.34 (dt, *J* = 15.6, 6.5 Hz, 1H), 4.84 (d, *J* = 6.4 Hz, 2H), 4.78 (br s, 1H), 3.89 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.4, 158.7, 135.4, 135.2, 132.2, 130.3, 129.6, 127.9, 127.5, 124.8, 123.1, 119.8, 106.6, 66.3, 56.1, 47.1.

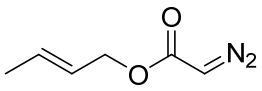
(*E*)-3-(furan-2-yl)allyl 2-diazoacetate (1k):



(*E*)-3-(furan-2-yl)allyl 2-diazoacetate **(1k)** was prepared according to the general procedure for the synthesis of allylic diazoacetate. Reaction mixture was purified by silica gel column chromatography with EtOAc/hexanes as an eluent to give the desired product as pale-yellow liquid in 31% yield (yield of step E). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.32 (m, 1H), 6.46 (d, *J* = 15.9 Hz, 1H),

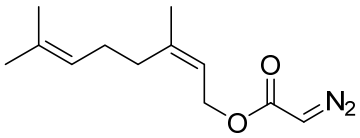
6.41 – 6.34 (m, 1H), 6.29 (d, *J* = 3.4 Hz, 1H), 6.21 (dt, *J* = 15.8, 6.4 Hz, 1H), 4.79 (d, *J* = 6.5 Hz, 2H + merged 1H, -CH=N_2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.5, 152.6, 143.2, 123.0, 122.4, 112.1, 109.7, 65.7, 50.3.

(*E*)-but-2-en-1-yl 2-diazoacetate (1l):



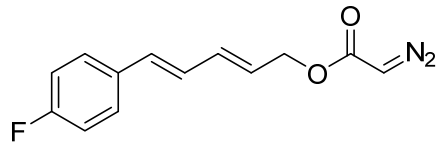
(*E*)-but-2-en-1-yl 2-diazoacetate **(1l)** was prepared according to the general procedure for the synthesis of allylic diazoacetate. Reaction mixture was purified by silica gel column chromatography with EtOAc/hexanes as an eluent to give the desired product as pale-yellow liquid in 38% yield (yield of step E). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.92 – 5.70 (m, 1H), 5.66 – 5.47 (m, 1H), 4.74 (s, 1H), 4.57 (d, *J* = 6.8 Hz, 2H), 1.72 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.5, 132.4, 125.8, 66.3, 46.9, 18.5.

(*Z*)-3,7-dimethylocta-2,6-dien-1-yl 2-diazoacetate (1m):



(*Z*)-3,7-dimethylocta-2,6-dien-1-yl 2-diazoacetate **(1m)** was prepared according to the general procedure for the synthesis of allylic diazoacetate. Reaction mixture was purified by silica gel column chromatography with EtOAc/hexanes as an eluent to give the desired product as pale-yellow liquid in 24% yield (yield of step E). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.36 (t, *J* = 7.1 Hz, 1H), 5.08 (t, *J* = 6.7 Hz, 1H), 4.73 (s, 1H), 4.64 (d, *J* = 7.3 Hz, 2H), 2.14 – 2.04 (m, 4H), 1.76 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.8, 143.6, 133.0, 124.3, 119.9, 62.2, 46.9, 32.9, 27.4, 26.4, 24.3, 18.4.

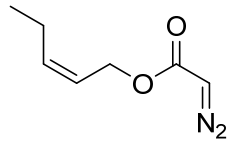
(2*E*,4*E*)-5-(4-fluorophenyl)penta-2,4-dien-1-yl 2-diazoacetate (1n):



(2*E*,4*E*)-5-(4-fluorophenyl)penta-2,4-dien-1-yl 2-diazoacetate **(1n)** was prepared according to the general procedure for the synthesis of allylic diazoacetate. Reaction mixture was purified by silica gel column chromatography with EtOAc/hexanes as an eluent to give the desired product as pale-yellow liquid in 37% yield

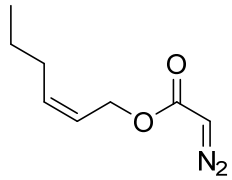
(yield of step E). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 8.4, 5.4 Hz, 2H), 7.01 (t, *J* = 8.6 Hz, 2H), 6.68 (dd, *J* = 15.5, 10.5 Hz, 1H), 6.55 (d, *J* = 15.7 Hz, 1H), 6.43 (dd, *J* = 15.3, 10.5 Hz, 1H), 5.94 – 5.78 (m, *J* = 12.9, 6.5 Hz, 1H), 4.74 (d, *J* = 6.3 Hz, 2H + merged 1H, -CH=N_2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.4, 158.7, 135.4, 132.3, 130.3, 127.9, 127.5, 124.8, 123.1, 119.9, 106.6, 66.3, 56.1;^{19}F NMR (375 MHz, $CDCl_3$): δ -113.93.

(*Z*)-pent-2-en-1-yl 2-diazoacetate (1o):



(*Z*)-pent-2-en-1-yl 2-diazoacetate **(1o)** was prepared according to the general procedure for the synthesis of allylic diazoacetate. Reaction mixture was purified by silica gel column chromatography with EtOAc/hexanes as an eluent to give the desired product as pale-yellow liquid in 64% yield (yield of step E). ^{1}H NMR δ 5.72 – 5.56 (m, 1H), 5.55 – 5.40 (m, 1H), 4.72 (s, 1H), 4.68 (d, *J* = 6.8 Hz, 2H), 2.09 (p, *J* = 7.1 Hz, 2H), 0.96 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9, 135.4, 120.7, 58.7, 44.4, 19.0, 12.2.

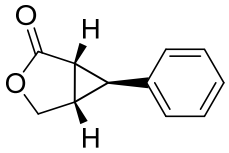
(*Z*)-hex-2-en-1-yl 2-diazoacetate (1p):



(*Z*)-hex-2-en-1-yl 2-diazoacetate **(1p)** was prepared according to the general procedure for the synthesis of allylic diazoacetate. Reaction mixture was purified by silica gel column chromatography with EtOAc/hexanes as an eluent to give the desired product as pale-yellow liquid in 49% yield (yield of step E). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.70 – 5.62 (m, 1H), 5.55 (m, 1H), 4.76 (s, 1H), 4.71 (d, *J* = 6.8 Hz, 2H), 2.09 (q, *J* = 7.2 Hz, 2H), 1.46 – 1.35 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.6, 136.2, 124.1, 61.4, 46.9, 30.3, 23.3, 14.4.

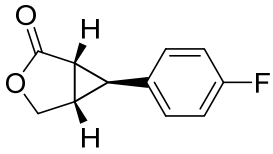
Characterization data for intramolecular cyclopropanation products from Mb-catalyzed reactions on preparative scale.

(1R,5S,6S)-6-phenyl-3-oxabicyclo[3.1.0]hexan-2-one (2a):



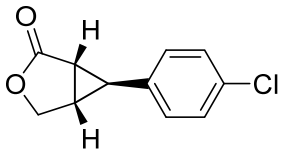
(1R,5S,6S)-6-phenyl-3-oxabicyclo[3.1.0]hexan-2-one **(2a)** was prepared according to the general **Procedure F** with *E. coli* cells expressing Mb(H64V,I107S) on 12.5 mmol scale to afford the product as a white solid, 180 mg, 83% yield. GC-MS m/z (% relative intensity): 174(29.8), 173(12.9), 131(10.3), 130(66.4), 129(100), 115(72.1), 91(12.1), 77(10.6); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (t, *J* = 7.3 Hz, 2H), 7.28 – 7.24 (m, 1H), 7.07 (d, *J* = 7.2 Hz, 2H), 4.47 (dd, *J* = 9.5, 4.7 Hz, 1H), 4.42 (d, *J* = 9.5 Hz, 1H), 2.54 (dd, *J* = 9.9, 4.8 Hz, 1H), 2.39 – 2.30 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.8, 137.9, 129.7, 128.0, 126.7, 70.5, 30.2, 28.2, 26.9.

(1R,5S,6S)-6-(4-fluorophenyl)-3-oxabicyclo[3.1.0]hexan-2-one (2b):



(1R,5S,6S)-6-(4-fluorophenyl)-3-oxabicyclo[3.1.0]hexan-2-one **(2b)** was prepared according to the general **Procedure F** with *E. coli* cells expressing Mb(L29A,H64V,V68A) on 0.1 mmol scale to afford the product as a white solid, 17 mg, 89% yield. GC-MS m/z (% relative intensity): 193(5.4), 192(41.2), 191(13.4), 148(78.7), 147(96.6), 133(100), 115(17.0), 109(17.6), 75(11.1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 – 6.89 (m, 4H), 4.45 (dd, *J* = 9.5, 4.7 Hz, 1H), 4.39 (d, *J* = 9.5 Hz, 1H), 2.48 (dd, *J* = 9.8, 4.8 Hz, 1H), 2.35 – 2.24 (m, *J* = 5.1 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.5, 163.7, 161.7, 133.6, 128.4, 128.4, 116.5, 116.4, 70.4, 29.4, 28.1, 26.7; ^{19}F NMR (376 MHz, $CDCl_3$): δ -115.22.

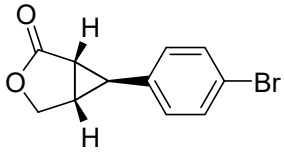
(1R,5S,6S)-6-(4-chlorophenyl)-3-oxabicyclo[3.1.0]hexan-2-one (2c):



(1R,5S,6S)-6-(4-chlorophenyl)-3-oxabicyclo[3.1.0]hexan-2-one **(2c)** was prepared according to the general **Procedure F** with *E. coli* cells expressing Mb(L29A,H64V,V68A) on a 0.1 mmol scale to afford the product as a white solid, 13 mg, 62% yield. GC-MS m/z (% relative intensity): 210(8.6), 209(4.6), 208(27.0), 164(19.5), 163(12.6), 129(100), 128(35.5), 115(45.0),

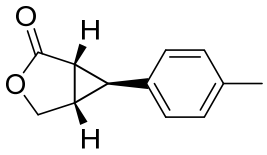
89(9.2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.4 Hz, 2H), 7.00 (d, *J* = 8.4 Hz, 2H), 4.47 (dd, *J* = 9.5, 4.7 Hz, 1H), 4.41 (d, *J* = 9.5 Hz, 1H), 2.51 (dd, *J* = 10.0, 4.4 Hz, 1H), 2.37 – 2.26 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.4, 136.4, 133.8, 129.7, 128.1, 70.4, 29.5, 28.2, 26.9.

(1R,5S,6S)-6-(4-bromophenyl)-3-oxabicyclo[3.1.0]hexan-2-one (2d):



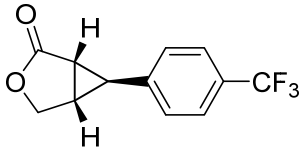
(1R,5S,6S)-6-(4-bromophenyl)-3-oxabicyclo[3.1.0]hexan-2-one **(2d)** was prepared according to the general **Procedure F** with *E. coli* cells expressing Mb(L29A,H64V,V68A) on a 0.1 mmol scale to afford the product as a white solid, 19 mg, 75% yield. GC-MS m/z (% relative intensity): 254(15.5), 253(4.2), 252(15.9), 208(14.4), 129(100), 128(56.0), 115(46.4), 89(10.1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 2H), 4.45 (dd, *J* = 9.5, 4.7 Hz, 1H), 4.39 (d, *J* = 9.5 Hz, 1H), 2.49 (dd, *J* = 9.6, 4.6 Hz, 1H), 2.30 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.3, 137.0, 132.6, 128.4, 121.8, 70.4, 29.5, 28.1, 26.9.

(1R,5S,6S)-6-(p-tolyl)-3-oxabicyclo[3.1.0]hexan-2-one (2e):



(1R,5S,6S)-6-(p-tolyl)-3-oxabicyclo[3.1.0]hexan-2-one **(2e)** was prepared according to the general **Procedure F** with *E. coli* cells expressing Mb(L29A,H64V,V68A) on a 0.1 mmol scale to afford the product as a white solid, 7.5 mg, 40% yield. GC-MS m/z (% relative intensity): 189(6.1), 188(47.2), 187(7.7), 173(14.0), 144(36.4), 143(57.8), 129(100), 128(51.1), 115(44.8), 77(12.1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (d, *J* = 7.7 Hz, 2H), 6.96 (d, *J* = 8.0 Hz, 2H), 4.46 (dd, *J* = 9.5, 4.7 Hz, 1H), 4.41 (d, *J* = 9.4 Hz, 1H), 2.50 (dd, *J* = 9.8, 4.9 Hz, 1H), 2.33 (s, 3H), 2.31 – 2.30 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.9, 137.7, 134.9, 130.2, 126.6, 70.5, 30.0, 28.1, 26.7, 21.8.

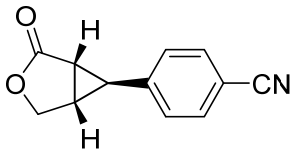
(1R,5S,6S)-6-(4-(trifluoromethyl)phenyl)-3-oxabicyclo[3.1.0]hexan-2-one (2f):



(1R,5S,6S)-6-(4-(trifluoromethyl)phenyl)-3-oxabicyclo[3.1.0]hexan-2-one **(2f)** was prepared according to the general **Procedure F** with *E. coli* cells expressing Mb(L29A,H64V,V68A) on 0.1 mmol scale to

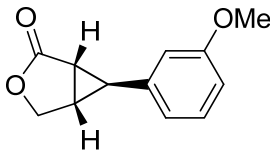
afford the product as a white solid, 20 mg, 84% yield. GC-MS m/z (% relative intensity): 242(8.5), 241(6.8), 223(13.2), 198(59.8), 184(10.6), 177(22.8), 129(100), 128(26.5), 115(40.4); ^{1}H NMR (500 MHz, $CDCl_3$) ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.57 (d, *J* = 7.9 Hz, 2H), 7.18 (d, *J* = 7.8 Hz, 2H), 4.50 (dd, *J* = 9.4, 4.6 Hz, 1H), 4.44 (d, *J* = 9.5 Hz, 1H), 2.64 – 2.52 (m, 1H), 2.44 – 2.31 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.1, 142.1, 130.1, 127.0, 126.4, 125.8, 123.6, 70.3, 29.6, 28.4, 27.3; ^{19}F NMR (376 MHz, $CDCl_3$): δ -62.72.

4-((1R,5S,6S)-2-oxo-3-oxabicyclo[3.1.0]hexan-6-yl)benzonitrile (2g):



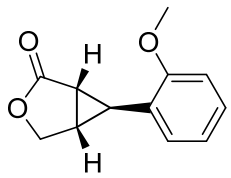
4-((1R,5S,6S)-2-oxo-3-oxabicyclo[3.1.0]hexan-6-yl)benzonitrile **(2g)** was prepared according to the general **Procedure F** with *E. coli* cells expressing Mb(L29A,H64V,V68A) on 0.1 mmol scale to afford the product as a white solid, 14 mg, 71% yield. GC-MS m/z (% relative intensity): 200(4.1), 199(31.5), 198(17.5), 155(100), 154(84.1), 141(34.7), 127(31.1), 115(55.8); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.9 Hz, 2H), 7.14 (d, *J* = 7.9 Hz, 2H), 4.48 (dd, *J* = 9.7, 4.8 Hz, 1H), 4.42 (d, *J* = 9.7 Hz, 1H), 2.63 – 2.53 (m, 1H), 2.44 – 2.36 (m, 1H), 2.35 – 2.28 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.7, 143.5, 133.3, 127.3, 119.2, 111.8, 70.3, 29.6, 28.7, 27.6.

(1R,5S,6S)-6-(3-methoxyphenyl)-3-oxabicyclo[3.1.0]hexan-2-one (2h):



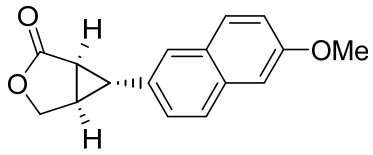
(1R,5S,6S)-6-(3-methoxyphenyl)-3-oxabicyclo[3.1.0]hexan-2-one **(2h)** was prepared according to the general **Procedure F** with *E. coli* cells expressing Mb(H64V,I107S) on a 0.1 mmol scale to afford the product as a white solid, 18 mg, 88% yield. GC-MS m/z (% relative intensity): 205(13.4), 204(100), 175(21.2), 160(16.2), 159(49.9), 144(27.4), 129(19.6), 115(27.9), 103(14.9), 77(17.9); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (t, *J* = 7.9 Hz, 1H), 6.77 (d, *J* = 8.2 Hz, 1H), 6.63 (d, *J* = 7.6 Hz, 1H), 6.59 (s, 1H), 4.44 (dd, *J* = 9.4, 4.7 Hz, 1H), 4.39 (d, *J* = 9.4 Hz, 1H), 3.78 (s, 3H), 2.51 (dd, *J* = 8.9, 4.3 Hz, 1H), 2.40 – 2.22 (m, 2H); ^{13}C NMR NMR (126 MHz, $CDCl_3$) δ 175.7, 160.6, 139.6, 130.5, 118.9, 113.1, 112.9, 70.4, 56.0, 30.1, 28.1, 26.9.

(1R,5S,6S)-6-(2-methoxyphenyl)-3-oxabicyclo[3.1.0]hexan-2-one (2i):



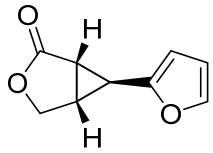
(1R,5S,6S)-6-(2-methoxyphenyl)-3-oxabicyclo[3.1.0]hexan-2-one **(2i)** was prepared according to the general **Procedure F** with *E. coli* cells expressing Mb(H64V,I107S) on 0.1 mmol scale to afford the product as a white solid, 18.5 mg, 91% yield. GC-MS m/z (% relative intensity): 205(10.3), 204(77.9), 160(37.5), 159(100), 145(21.0), 144(31.5), 129(34.6), 115(38.7), 91(27.4), 77(23.9); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (t, *J* = 7.8 Hz, 1H), 6.85 (m, 3H), 4.49 – 4.37 (m, 2H), 3.83 (s, 3H), 2.61 – 2.55 (m, 1H), 2.50 (dd, *J* = 9.3, 4.5 Hz, 1H), 2.36 – 2.29 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.4, 158.6, 129.0, 126.5, 126.0, 121.3, 111.2, 70.6, 56.2, 26.8, 25.9, 25.1.

(1S,5R,6R)-6-(6-methoxynaphthalen-2-yl)-3-oxabicyclo[3.1.0]hexan-2-one (3j):



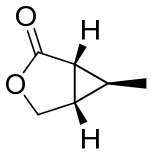
(1S,5R,6R)-6-(6-methoxynaphthalen-2-yl)-3-oxabicyclo[3.1.0]hexan-2-one **(3j)** was prepared according to the general **Procedure F** with *E. coli* cells expressing Mb(F43A,H64W,V68F) on a 0.1 mmol scale to afford the product as a green solid, 20 mg, 79% yield. GC-MS m/z (% relative intensity): 255(14.4), 254(79.4), 210(28.6), 209(100), 194(33.1), 179(20.3), 165(28.4), 153(20.9), 152(31.3); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 – 7.62 (m, 2H), 7.45 (s, 1H), 7.18 – 7.05 (m, 3H), 4.48 (dd, *J* = 9.4, 4.7 Hz, 1H), 4.44 (d, *J* = 9.4 Hz, 1H), 3.90 (s, 3H), 2.61 (dd, *J* = 9.5, 4.6 Hz, 1H), 2.50 – 2.43 (m, 1H), 2.41 – 2.39 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.8, 158.5, 134.4, 132.8, 129.7, 129.5, 128.1, 125.4, 125.3, 120.2, 106.4, 70.5, 56.1, 30.3, 28.1, 26.7.

(1S,5S,6S)-6-(furan-2-yl)-3-oxabicyclo[3.1.0]hexan-2-one (2k):



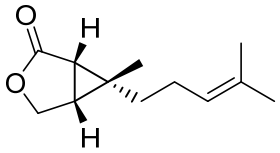
(1S,5S,6S)-6-(furan-2-yl)-3-oxabicyclo[3.1.0]hexan-2-one **(2k)** was prepared according to the general **Procedure F** with *E. coli* cells expressing Mb(L29A,H64V,V68A) on a 0.1 mmol scale to afford the product as a white liquid, 14 mg, 85% yield. GC-MS m/z (% relative intensity): 166(2.5), 165(11.0), 164(100), 120(44.4), 119(13.9), 106(16.2), 91(64.1), 78(38.6), 115(27.2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 10.0 Hz, 1H), 6.29 (dd, *J* = 3.3, 1.9 Hz, 1H), 6.13 (d, *J* = 3.1 Hz, 1H), 4.43 (dd, *J* = 9.5, 4.7 Hz, 1H), 4.37 (d, *J* = 9.6 Hz, 1H), 2.62 (dd, *J* = 10.1, 4.6 Hz, 1H), 2.42 (dd, *J* = 6.0, 2.7 Hz, 1H), 2.38 – 2.30 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.2, 150.7, 142.5, 111.4, 107.1, 70.1, 26.0, 24.8, 23.6.

(1R,5S,6S)-6-methyl-3-oxabicyclo[3.1.0]hexan-2-one (2l):



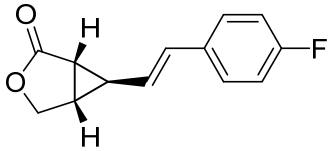
(1R,5S,6S)-6-methyl-3-oxabicyclo[3.1.0]hexan-2-one **(2l)** was prepared according to the general **Procedure F** with *E. coli* cells expressing Mb(L29A,H64V,V68A) on a 0.2 mmol scale to afford the product as a white solid, 21 mg, 94% yield. GC-MS m/z (% relative intensity): 113(1.3), 112(29.3), 86(60.9), 84(100), 83(24.8), 68(76.7), 67(43.8), 55(42.5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.27 (dd, *J* = 9.2, 4.9 Hz, 1H), 4.20 (d, *J* = 9.2 Hz, 1H), 1.97 (dd, *J* = 9.5, 5.0 Hz, 1H), 1.79 (dd, *J* = 5.8, 2.4 Hz, 1H), 1.24 – 1.19 (m, 1H), 1.13 (d, *J* = 5.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.8, 70.2, 25.9, 25.8, 21.7, 16.8.

(1S,5R,6R)-6-methyl-6-(4-methylpent-3-en-1-yl)-3-oxabicyclo[3.1.0]hexan-2-one (2m):



(1S,5R,6R)-6-methyl-6-(4-methylpent-3-en-1-yl)-3-oxabicyclo[3.1.0]hexan-2-one **(2m)** was prepared according to the general **Procedure F** with *E. coli* cells expressing Mb(L29A,H64V,V68A) on a 0.2 mmol scale to afford the product as a white solid, 26 mg, 67% yield. GC-MS m/z (% relative intensity): 195(1.1), 194(4.7), 163(6.6), 126(10.9), 111(24.3), 85(25.9), 82(11.3), 81(18.5), 69(100), 67(27.2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.11 (t, *J* = 7.2 Hz, 1H), 4.34 (dd, *J* = 10.0, 5.7 Hz, 1H), 4.15 (d, *J* = 10.0 Hz, 1H), 2.13 (m, 2H), 2.05 (dd, *J* = 11.4, 5.5 Hz, 1H), 1.95 (d, J = 6.3 Hz, 1H), 1.67 (s, 3H), 1.60 (s, 3H), 1.51 – 1.38 (m, 2H), 1.15 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.6, 133.1, 124.0, 67.3, 31.6, 31.5, 29.1, 27.7, 26.4, 25.7, 23.3, 18.3.

(1R,5S,6S)-6-((E)-4-fluorostyryl)-3-oxabicyclo[3.1.0]hexan-2-one (2n):



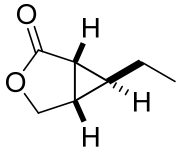
(1R,5S,6S)-6-((E)-4-fluorostyryl)-3-oxabicyclo[3.1.0]hexan-2-one **(2n)** was prepared according to the general **Procedure F** with *E. coli* cells expressing Mb(L29A,H64V,V68A) on 0.4 mmol scale to afford the product as a white solid, 46 mg, 53% yield. GC-MS m/z (% relative intensity): 219(4.1), 218(28.4), 174(33.8), 173(100), 159(60.3), 153(28.4), 146(27.2), 133(53.3), 109(66.5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.20 (m, 2H), 7.02 – 6.92 (m, 2H), 6.50 (d, *J* = 15.8 Hz, 1H), 5.60 (dd, *J* = 15.8, 8.5 Hz, 1H), 4.39 (dd, *J* = 9.5, 4.8 Hz, 1H), 4.32 (d,

J = 9.5 Hz, 1H), 2.34 (dd, *J* = 9.6, 4.6 Hz, 1H), 2.19 (dd, *J* = 5.8, 2.3 Hz, 1H), 2.03 – 1.94 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.6, 162.1, 133.3, 131.3, 128.3, 128.3, 126.3, 116.4, 116.3, 70.1, 29.4, 26.2, 25.8; ^{19}F NMR (375 MHz, $CDCl_3$): δ -114.26.

6-ethyl-3-oxabicyclo[3.1.0]hexan-2-one (2o):

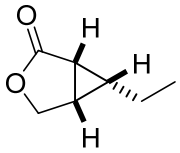
Partially seperable diastereomeric mixture of 6-ethyl-3-oxabicyclo[3.1.0]hexan-2-one **(2o)** was prepared according to the general **Procedure F** with *E. coli* cells expressing Mb(L29A,H64V,V68A) on 0.2 mmol scale to afford the product as a colorless liquid, 18 mg, 72% yield. GC-MS m/z (% relative intensity): 126(2.6), 111(6.36), 97(8.7), 85(100), 81(47.3), 67(68.4), 55(18).

(1R,5S,6S)-6-ethyl-3-oxabicyclo[3.1.0]hexan-2-one (2o) – Diastereomer 1:



^{1}H NMR (500 MHz, Chloroform-d) δ 4.31 (dd, *J* = 9.2, 4.9 Hz, 1H), 4.23 (d, *J* = 9.2 Hz, 1H), 2.02 (dd, *J* = 4.9, 4.9 Hz, 1H), 1.86 (dd, *J* = 5.8, 2.5 Hz, 1H), 1.45-1.37 (m, 2H), 1.21-1.17 (m, 1H), 1.03 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.2, 69.6, 28.1, 24.5, 23.9, 23.9, 13.0.

(1R,5S,6R)-6-ethyl-3-oxabicyclo[3.1.0]hexan-2-one (2o) – Diastereomer 2:

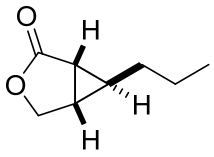


^{1}H NMR (500 MHz, Chloroform-d) δ 4.41 (dd, *J* = 9.8, 5.5 Hz, 1H), 4.15 (d, *J* = 9.8 Hz, 1H), 2.27 (ddd, *J* = 5.9, 5.9, 5.9 Hz, 1H), 2.20 (dd, *J* = 7.0, 7.0 Hz, 1H), 1.50 – 1.35 (m, 3H), 1.07 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.2, 66.1, 24.0, 22.8, 22.6, 16.4, 13.4.

6-propyl-3-oxabicyclo[3.1.0]hexan-2-one (2p):

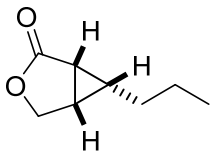
Partially seperable diastereomeric mixture of 6-propyl-3-oxabicyclo[3.1.0]hexan-2-one **(2p)** was prepared according to the general **Procedure F** with *E. coli* cells expressing Mb(L29A,H64V,V68A) on 0.2 mmol scale to afford the product as a colorless liquid, 21 mg, 75% yield. GC-MS m/z (% relative intensity): 141(0.3), 140(0.2), 125(2.8), 111(4.7), 85(100), 81(44.0), 67(22.1), 55(30.9).

(1R,5S,6S)-6-propyl-3-oxabicyclo[3.1.0]hexan-2-one (2p) – Diastereomer 1:



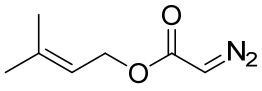
^{1}H NMR (500 MHz, Chloroform-d) ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.31 (dd, *J* = 9.1, 4.9 Hz, 1H), 4.23 (d, *J* = 9.1 Hz, 1H), 2.02 (dd, *J* = 8.9, 4.6 Hz, 1H), 1.91 – 1.82 (m, 1H), 1.54 – 1.42 (m, 2H), 1.41 – 1.30 (m, 2H), 1.25 – 1.17 (m, 1H), 0.95 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.8, 70.3, 33.9, 27.0, 24.8, 24.6, 22.7, 14.5.

(1R,5S,6R)-6-propyl-3-oxabicyclo[3.1.0]hexan-2-one (2p) – Diastereomer 2:



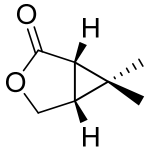
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.41 (dd, *J* = 9.8, 5.4 Hz, 1H), 4.15 (d, *J* = 9.8 Hz, 1H), 2.31 – 2.23 (m, 1H), 2.23 – 2.16 (m, 1H), 1.56 – 1.44 (m, 2H), 1.43 – 1.31 (m, 2H), 0.97 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.9, 66.9, 25.6, 23.4, 23.2, 22.9, 22.8, 14.5.

3-methylbut-2-en-1-yl 2-diazoacetate (4):



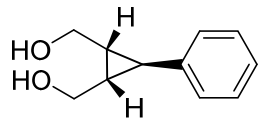
3-methylbut-2-en-1-yl 2-diazoacetate **(4)** was prepared according to the general procedure for the synthesis of allylic diazoacetate. Reaction mixture was purified by silica gel column chromatography with EtOAc/hexanes as an eluent to give the desired product as pale-yellow liquid in 47% yield (yield of step E). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.34 (t, *J* = 7.2 Hz, 1H), 4.74 (s, 1H), 4.65 (d, *J* = 7.2 Hz, 3H), 1.76 (s, 3H), 1.71 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.1, 140.1, 119.3, 62.5, 46.9, 26.5, 18.8.

(1S,5R)-6,6-dimethyl-3-oxabicyclo[3.1.0]hexan-2-one (5):



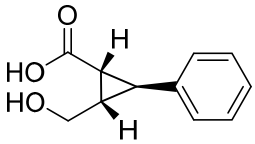
(1S,5R)-6,6-dimethyl-3-oxabicyclo[3.1.0]hexan-2-one **(5)** was prepared according to the general **Procedure F** with *E. coli* cells expressing Mb(L29A,H64V,V68A) on a 10 mmol scale to afford the product as a white solid, 1.02 gm, 83% yield. GC-MS m/z (% relative intensity): 127(1.2), 126(10.5), 111(61.0), 97(22.6), 82(37.8), 81(59.2), 67(100), 53(28.2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.33 (dd, *J* = 9.9, 5.6 Hz, 1H), 4.12 (d, *J* = 9.9 Hz, 1H), 2.02 (dd, *J* = 5.9, 5.9 Hz, 1H), 1.92 (d, *J* = 6.3 Hz, 1H), 1.15 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.8, 67.3, 31.2, 30.8, 26.0, 23.8, 15.2.

((1R,2S,3s)-3-phenylcyclopropane-1,2-diyl)dimethanol (6):



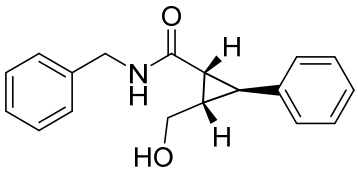
((1R,2S,3s)-3-phenylcyclopropane-1,2-diyl)dimethanol **(6)** was prepared according to a modified version of a reported procedure.[5] (1R,5S,6S)-6-phenyl-3-oxabicyclo[3.1.0]hexan-2-one **(2a)** (30 mg, 0.17 mmol, 1 equiv) in dry THF was added dropwise to a suspension of $LiAlH_4$ (1 equiv) in dry THF at 0 °C. The resulting mixture was stirred for 2 h at room temperature and then quenched with aqueous diethyl ether and stirred for 1 h at room temperature. After filtration through a pad of Celite, the filtrate was dried over $MgSO_4$ and concentrated to give a residue, which was further purified by silica-gel chromatography using 80% EtOAc/hexanes as eluent to afford the product as a white solid, 27 mg, 89% yield. GC-MS m/z (% relative intensity): 178(4.6), 147(13.4), 134(16.4), 130(100), 129(91.5), 115(33.8), 91(68.0), 77(17.6); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 – 7.25 (m, 2H), 7.15 (t, *J* = 7.3 Hz, 1H), 7.02 (d, *J* = 7.9 Hz, 2H), 4.21 (d, *J* = 11.6 Hz, 2H), 3.63 – 3.40 (m, 2H), 3.06 (s, 2H), 2.05 – 1.64 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.8, 129.2, 126.7, 126.7, 63.0, 29.4, 28.1.

(1R,2S,3S)-2-(hydroxymethyl)-3-phenylcyclopropane-1-carboxylic acid (7):



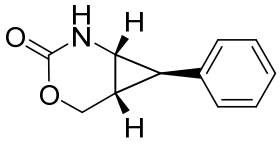
(1R,2S,3S)-2-(hydroxymethyl)-3-phenylcyclopropane-1-carboxylic acid **(7)** was prepared according to a modified version of a reported procedure.[6] To a solution of LiOH (5 equiv) in water:THF (1:5) at RT was slowly added the (1R,5S,6S)-6-phenyl-3-oxabicyclo[3.1.0]hexan-2-one **(2a)** (30 mg, 0.17 mmol, 1 equiv). The mixture was stirred at room temperature for overnight. Solvent was removed under reduced pressure. The residue was dissolved in water and acidified with 2M HCl to pH 1 followed by extraction with DCM. The crude product was purified by column chromatography on silica gel with Ethyl acetate/Hexanes to afford the product as a white solid, 31 mg, 94% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 7.34 – 7.20 (m, 2H), 7.20 – 7.04 (m, 3H), 4.08 – 3.94 (m, 1H), 3.89 (d, *J* = 6.8 Hz, 1H), 3.73 (s, 1H), 2.54 (d, *J* = 3.8 Hz, 1H), 2.16 – 1.93 (m, 1H), 1.92 – 1.77 (m, 1H); ^{13}C NMR (126 MHz, CD_3OD) δ 183.4, 142.1, 129.4, 127.2, 127.2, 67.1, 60.7, 32.9, 30.3.

(1R,2S,3S)-*N*-benzyl-2-(hydroxymethyl)-3-phenylcyclopropane-1-carboxamide (8):



(1R,2S,3S)-*N*-benzyl-2-(hydroxymethyl)-3-phenylcyclopropane-1-carboxamide **(8)** was prepared according to a modified version of a reported procedure.[7] To a stirred solution of (1R,5S,6S)-6-phenyl-3-oxabicyclo[3.1.0]hexan-2-one **(2a)** (30 mg, 0.17 mmol, 1 equiv) and a benzylamine (1.2 equiv) in ethanol at 25 °C were added Et_3N (0.20 equiv) and LiCl (1 equiv). The reaction mixture was stirred at 25 °C for 12 h. Reaction mixture was quenched with 0.1 M HCl and diluted with EtOAc, then the organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with 60% Ethyl acetate/Hexanes to afford the expected product as a white solid, 38 mg, 81% yield. GC-MS m/z (% relative intensity): 281(5.9), 195(20.9), 194(20.1), 189(78.0), 130(53.1), 129(92.7), 116(30.2), 115(100), 91(68.9), 77(21.1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.30 (m, 2H), 7.30 – 7.22 (m, 5H), 7.18 (t, *J* = 7.3 Hz, 1H), 7.07 (m, 2H), 6.11 (s, 1H), 4.49 (dd, *J* = 14.6, 5.8 Hz, 1H), 4.43 (dd, *J* = 17.4, 8.3 Hz, 1H), 4.12 (d, *J* = 11.8 Hz, 1H), 3.95 (dt, *J* = 12.8, 6.3 Hz, 1H), 3.44 (s, 1H), 2.78 (t, *J* = 5.8 Hz, 1H), 2.02 – 1.89 (m, 1H), 1.77 (dd, *J* = 8.7, 5.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3, 140.8, 138.6, 129.6, 129.3, 128.6, 128.4, 127.3, 126.9, 60.5, 44.8, 32.6, 31.7, 28.9.

(1S,6R,7S)-7-phenyl-4-oxa-2-azabicyclo[4.1.0]heptan-3-one (9):



2-(4-Chlorophenyl)cyclopropane-1-carbaldehyde (**9**) was prepared according to a modified version of a reported procedure.[8] To a solution of (1R,5S,6S)-6-phenyl-3-oxabicyclo[3.1.0]hexan-2-one **(2a)** (40 mg, 0.23 mmol) in MeOH (5 mL) at room temperature was added hydrazine monohydrate (10 equiv) over 15 min. The mixture was stirred at room temperature for 12 h and was concentrated under reduced pressure to get the crude hydrazide as an off-white solid which was used in next step without any further purification. To a suspension of the crude acyl hydrazide in H_2O/Et_2O (1:1) at 0 °C was slowly added $NaNO_2$ (2.5 equiv). A solution of 6 N HCl (2.5 equiv) was then added dropwise. Upon completion of the addition, the mixture was stirred for 30 min at 0 °C, and cold $CHCl_3$ was added. The layers were separated, and the aqueous layer was extracted with $CHCl_3$. The organic layers were combined and washed with

aqueous $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to half volume, whereupon a volume of toluene (5 mL) was added. The remaining chloroform was removed under reduced pressure, and an additional portion of toluene (5 mL) was added. The reaction mixture was heated at 80 °C for 16 h, whereupon the reaction mixture was concentrated under reduced pressure, and the crude yellow solid was purified by column chromatography on silica gel with 40% Ethyl acetate/Hexanes to afford the expected product as a white solid, 34 mg, 78% yield. GC-MS m/z (% relative intensity): 190(2.3), 189(16.7), 146(27.0), 145(21.6), 144(100), 130(26.2), 128(19.6), 117(61.9), 115(47.0), 91(22.1), 77(13.4) ; ^{1}H NMR NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.23 (m, 2H), 7.19 (t, *J* = 7.4 Hz, 1H), 6.99 (d, *J* = 7.0 Hz, 2H), 6.41 (s, 1H), 4.76 (dd, *J* = 12.0, 6.3 Hz, 1H), 4.27 (dd, *J* = 12.0, 4.7 Hz, 1H), 3.03 (dt, *J* = 8.9, 2.8 Hz, 1H), 2.18 (dd, *J* = 5.0, 3.0 Hz, 1H), 1.96 – 1.87 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.3, 138.8, 129.4, 127.4, 126.4, 69.1, 37.2, 33.5, 18.9.

X-ray crystallographic analyses

X-ray crystal diffraction data were collected using a XtaLab Synergy-S Dualflex diffractometer equipped with a HyPix-6000HE HPC area detector for data collection at 100.00(10) K. A preliminary set of cell constants and an orientation matrix were calculated from reflections harvested from a sampling of reciprocal space. The full data collection was carried out using a PhotonJet (Cu) X-ray Source with frame times of 0.05 and 0.06 seconds and a detector distance of 31.2 mm. Series of frames were collected in 0.50º steps in ω at different 2θ, κ, and ϕ settings. The intensity data were scaled and corrected for absorption, and final cell constants were calculated from the xyz centroids of strong reflections from the actual data collections after integration. Space groups were determined based on systematic absences and intensity statistics.

Structures were solved using SHELXT(Sheldrick, G. M. *SHELXT*, version 2014/5; University of Göttingen: Göttingen, Germany)and refined using SHELXL (against F^2) (Sheldrick, G. M. *SHELXL-2016/6*;*Acta Crystallogr.* **2015**, *C71*, 3-8.).All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were placed in ideal positions and refined as riding atoms with relative isotropic displacement parameters. Absolute configurations for **2a**, **2c**, and **2d** were determined by anomalous dispersion effects (Parsons, S; Flack, H. D.; Wagner, T. *Acta Crystallogr.* **2013**, *B69*, 249-259). See **Figure S4-S6** and **Table S8-S10** for additional crystal data and structure refinement information. The crystallographic data and coordinates for compounds **2a**, **2c**, and **2d**, were deposited in the Cambridge Crystallographic Data Centre (CCDC) under entries 1902135- through 1902137.

Table S9. Crystal data and structure refinement for (1R,5S,6S)-6-phenyl-3-oxabicyclo [3.1.0]hexan -2-one **(2a)**. Cambridge Crystallographic Data Centre (CCDC) entry: 1902135.

Identification code	**2a**	
Empirical formula	C11 H10 O2	
Formula weight	174.19	
Temperature	100.00(10) K	
Wavelength	1.54184 Å	
Crystal system	monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 5.56590(10) Å	$\alpha = 90°$
	b = 9.7305(2) Å	$\beta = 92.8530(10)°$
	c = 7.66930(10) Å	$\gamma = 90°$
Volume	414.847(13) Å^3	
Z	2	
Density (calculated)	1.394 Mg/m^3	
Absorption coefficient	0.773 mm^{-1}	
F(000)	184	
Crystal color, morphology	colourless, needle	
Crystal size	0.305 x 0.236 x 0.144 mm^3	
Theta range for data collection	5.776 to 77.899°	
Index ranges	$-6 \le h \le 7$, $-11 \le k \le 12$, $-9 \le l \le 9$	
Reflections collected	15070	
Independent reflections	1701 [R(int) = 0.0348]	
Observed reflections	1691	
Completeness to theta = 74.504°	99.9%	
Absorption correction	Multi-scan	
Max. and min. transmission	1.00000 and 0.01562	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1701 / 1 / 118	
Goodness-of-fit on F^2	1.081	
Final R indices [I>2sigma(I)]	$R1$ = 0.0280, $wR2$ = 0.0690	
R indices (all data)	$R1$ = 0.0284, $wR2$ = 0.0691	
Absolute structure parameter	0.03(7)	
Largest diff. peak and hole	0.184 and -0.191 e.Å^{-3}	

Table S10. Crystal data and structure refinement for (1R,5S,6S)-6-(4-chlorophenyl)-3oxabicyclo [3.1.0]hexan-2-one (**2c**). Cambridge Crystallographic Data Centre (CCDC) entry: 1902137.

Identification code	**2c**	
Empirical formula	C11 H9 Cl O2	
Formula weight	208.63	
Temperature	99.98(10) K	
Wavelength	1.54184 Å	
Crystal system	monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 5.51150(10) Å	α = 90°
	b = 9.7152(2) Å	β = 96.864(2)°
	c = 8.7681(2) Å	γ = 90°
Volume	466.126(17) Å^3	
Z	2	
Density (calculated)	1.486 Mg/m^3	
Absorption coefficient	3.365 mm^{-1}	
F(000)	216	
Crystal color, morphology	colourless, needle	
Crystal size	0.494 x 0.077 x 0.064 mm^3	
Theta range for data collection	5.081 to 77.720°	
Index ranges	$-5 \le h \le 6$, $-12 \le k \le 12$, $-11 \le l \le 11$	
Reflections collected	11264	
Independent reflections	1947 [R(int) = 0.0582]	
Observed reflections	1930	
Completeness to theta = 74.504°	99.9%	
Absorption correction	Multi-scan	
Max. and min. transmission	1.00000 and 0.43353	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1947 / 1 / 127	
Goodness-of-fit on F^2	1.106	
Final R indices [I>2sigma(I)]	$R1$ = 0.0310, $wR2$ = 0.0804	
R indices (all data)	$R1$ = 0.0312, $wR2$ = 0.0806	
Absolute structure parameter	0.005(8)	
Largest diff. peak and hole	0.276 and -0.247 e.Å^{-3}	

Table S11. Crystal data and structure refinement for (1R,5S,6S)-6-(4-bromophenyl) 3oxabicyclo [3.1.0]hexan-2-one (**2d**). Cambridge Crystallographic Data Centre (CCDC) entry: 1902136.

Identification code	**2d**	
Empirical formula	C11 H9 Br O2	
Formula weight	253.09	
Temperature	100.00(10) K	
Wavelength	1.54184 Å	
Crystal system	monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 5.61190(10) Å	$\alpha = 90°$
	b = 9.6719(2) Å	$\beta = 97.545(2)°$
	c = 8.9813(2) Å	$\gamma = 90°$
Volume	483.264(17) $Å^3$	
Z	2	
Density (calculated)	1.739 Mg/m^3	
Absorption coefficient	5.547 mm^{-1}	
$F(000)$	252	
Crystal color, morphology	colourless, plate	
Crystal size	0.334 x 0.194 x 0.026 mm^3	
Theta range for data collection	4.967 to 77.000°	
Index ranges	$-6 \le h \le 7$, $-12 \le k \le 12$, $-11 \le l \le 11$	
Reflections collected	19153	
Independent reflections	2023 [R(int) = 0.0941]	
Observed reflections	1978	
Completeness to theta = 74.504°	100.0%	
Absorption correction	Multi-scan	
Max. and min. transmission	1.00000 and 0.46972	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2023 / 1 / 127	
Goodness-of-fit on F^2	1.126	
Final R indices [I>2sigma(I)]	$R1$ = 0.0405, $wR2$ = 0.1097	
R indices (all data)	$R1$ = 0.0412, $wR2$ = 0.1105	
Absolute structure parameter	-0.06(2)	
Largest diff. peak and hole	1.194 and -0.917 $e.Å^{-3}$	

References:

(1) Bordeaux, M., Tyagi, V., and Fasan, R. Highly Diastereoselective and Enantioselective Olefin Cyclopropanation Using Engineered Myoglobin-Based Catalysts, *Angew. Chem. Int. Ed.* **2015**, *54*, 1744–1748.

(2) Bajaj, P., Sreenilayam, G., Tyagi, V., and Fasan, R. Gram-Scale Synthesis of Chiral Cyclopropane-Containing Drugs and Drug Precursors with Engineered Myoglobin Catalysts Featuring Complementary Stereoselectivity, *Angew. Chem. Int. Ed.* **2016**, *55*, 16110–16114.

(3) Abu-Elfotoh, A. M., Diem, P. T. N., Chanthamath, S., Phomkeona, K., Shibatomi, K., and Iwasa, S. Water-Soluble Chiral Ruthenium(II) Phenyloxazoline Complex: Reusable and Highly Enantioselective Catalyst for Intramolecular Cyclopropanation Reactions, *Adv. Synth. Catal.* **2012**, *354*, 3435-3439.

(4) West, T. H., Daniels, D. S. B., Slawin, A. M. Z., and Smith, A. D. An Isothiourea-Catalyzed Asymmetric [2,3]-Rearrangement of Allylic Ammonium Ylides, *J. Am. Chem. Soc.* **2014**, *136*, 4476-4479.

(5) Takekawa, Y., and Shishido, K. Fragmentation reactions of optically active trisubstituted cyclopropylcarbinyl radicals, *J. Org. Chem.* **2001**, *66*, 8490-8503.

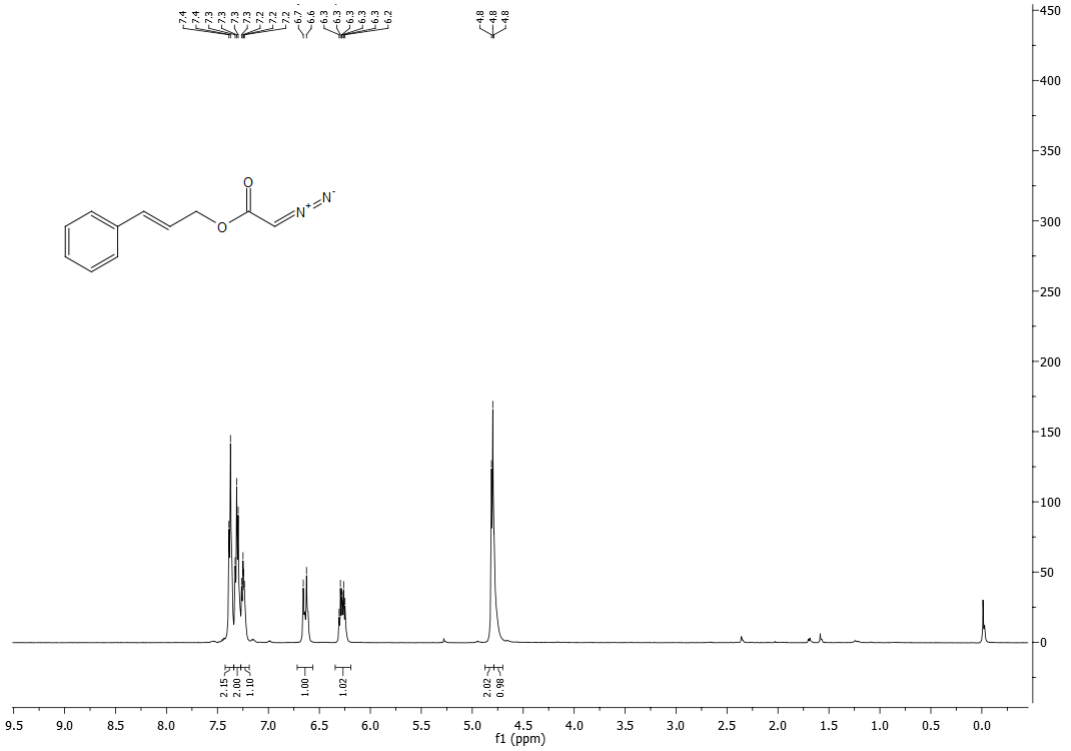
(6) Brana, M. F., Guisado, C., Alguacil, L. F., Garrido, E., Perez-Garcia, C., and Ruiz-Gayo, M. Synthesis and biological evaluation of novel 2-(1H-imidazol-4-yl)cyclopropane carboxylic acids: Key intermediates for H-3 histamine receptor ligands, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3561-3563.

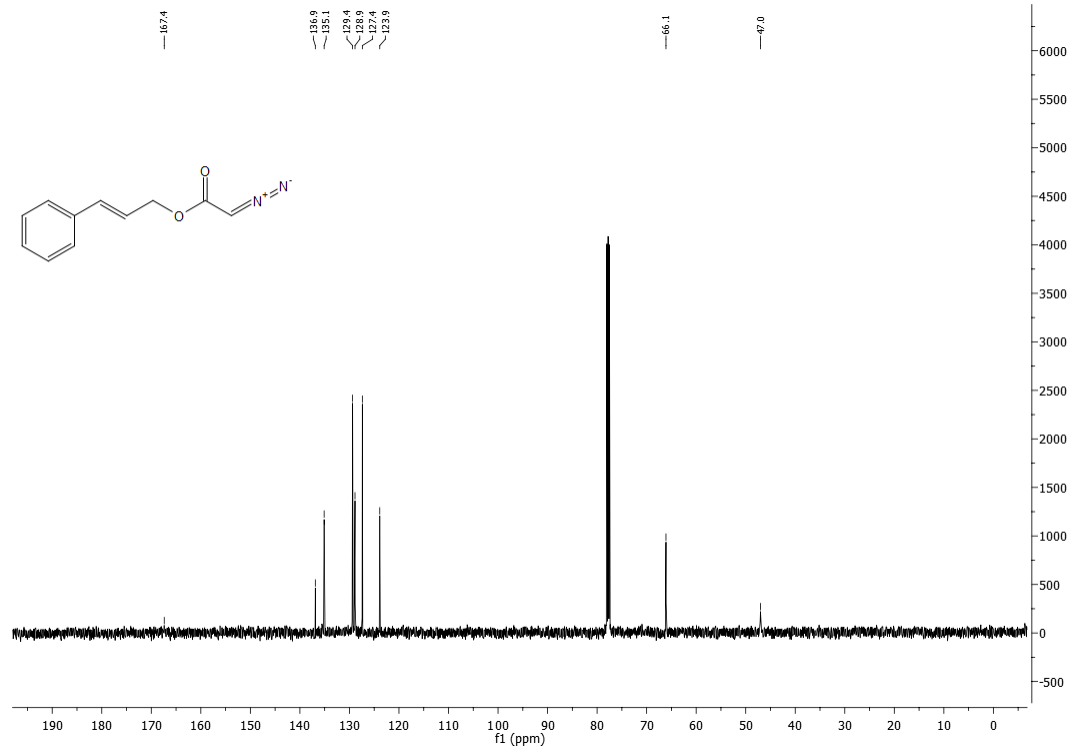
(7) Marques, M. V., and Sa, M. M. Lithium Chloride-Mediated Stereoselective Synthesis of Cyclopropanecarboxamides from gamma,delta-Epoxy Malonates through a Domino Cyclopropanation/Lactonization/Aminolysis Process, *J. Org. Chem.* **2014**, *79*, 4650-4658.

(8) Martin, S. F., Dwyer, M. P., Hartmann, B., and Knight, K. S. Cyclopropane-derived peptidomimetics. Design, synthesis, and evaluation of novel enkephalin analogues, *J. Org. Chem.* **2000**, *65*, 1305-1318.

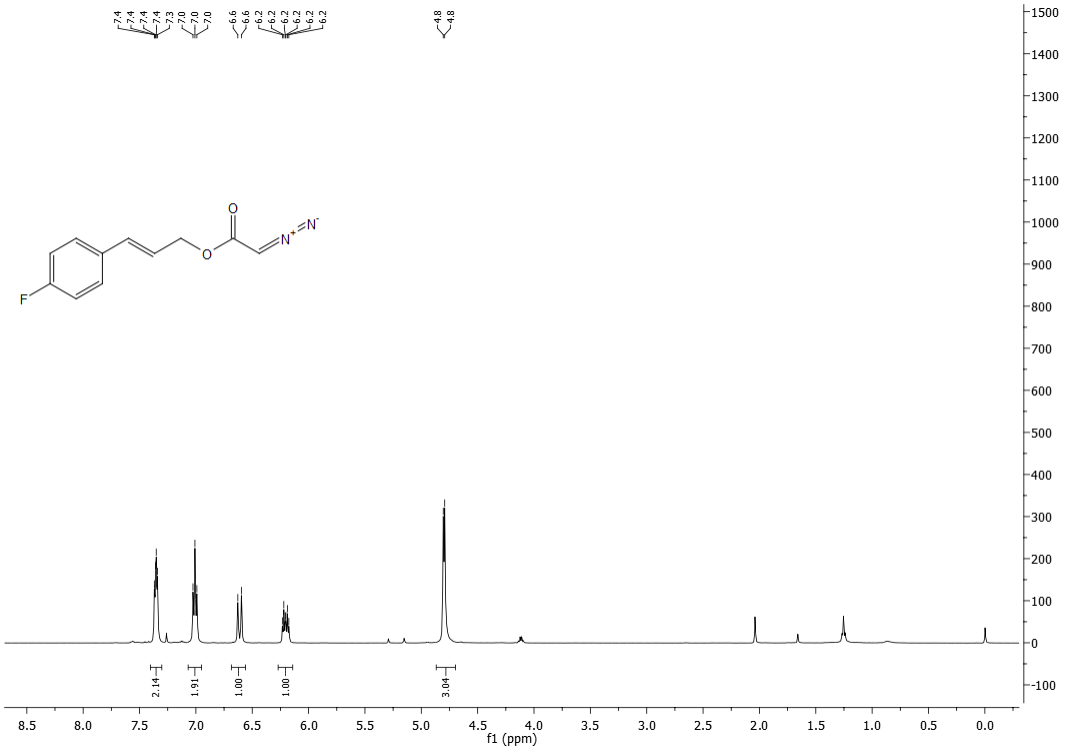
NMR Spectra

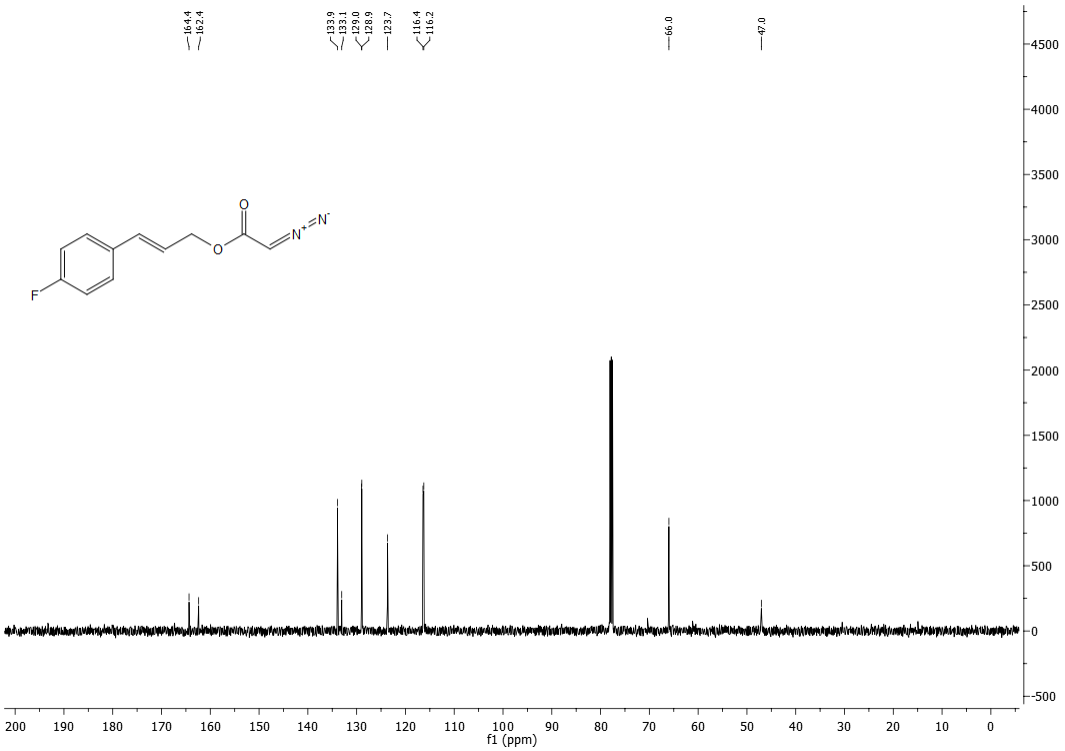
Cinnamyl 2-diazoacetate (1a): 500 MHz ^{1}H spectrum and 126 MHz ^{13}C spectrum in $CDCl_3$ solvent





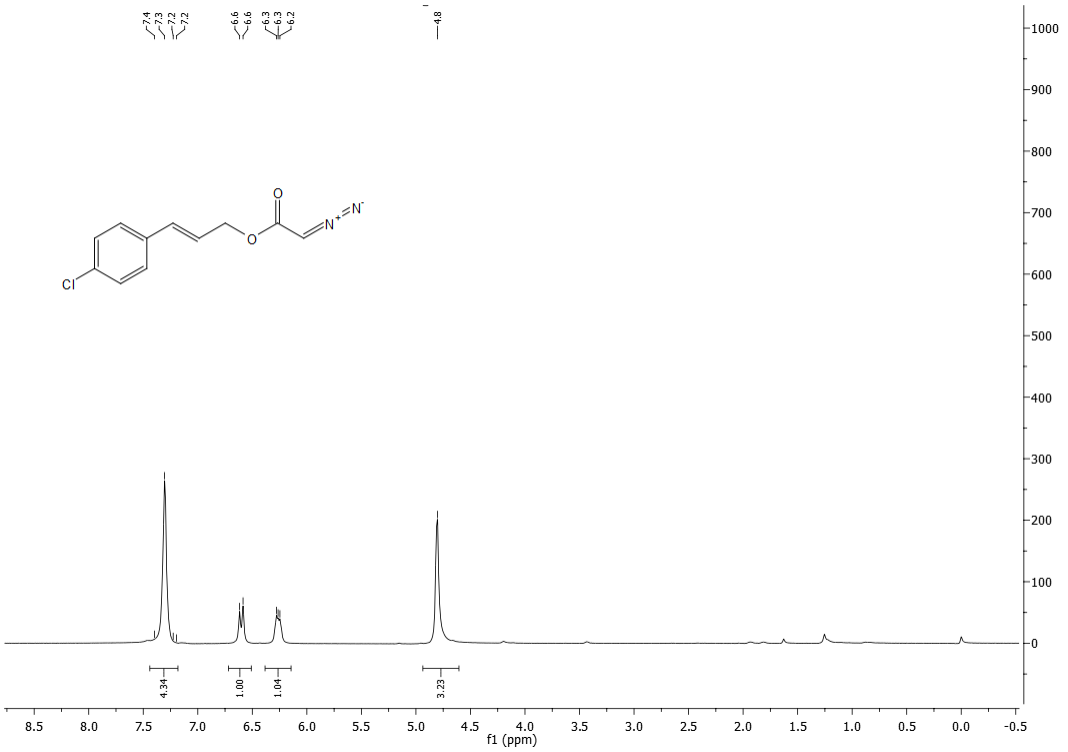
(E)-3-(4-fluorophenyl)allyl 2-diazoacetate (1b): 500 MHz ^{1}H spectrum, 126 MHz ^{13}C spectrum and 376 MHz ^{19}F spectrum in $CDCl_3$ solvent

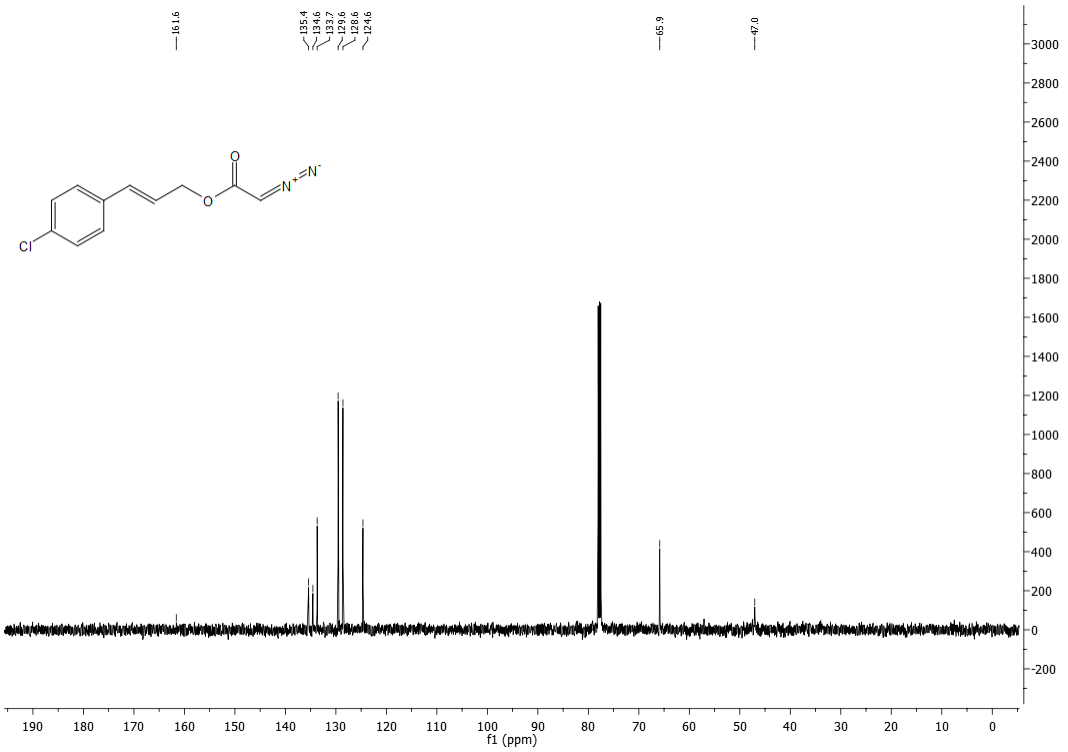




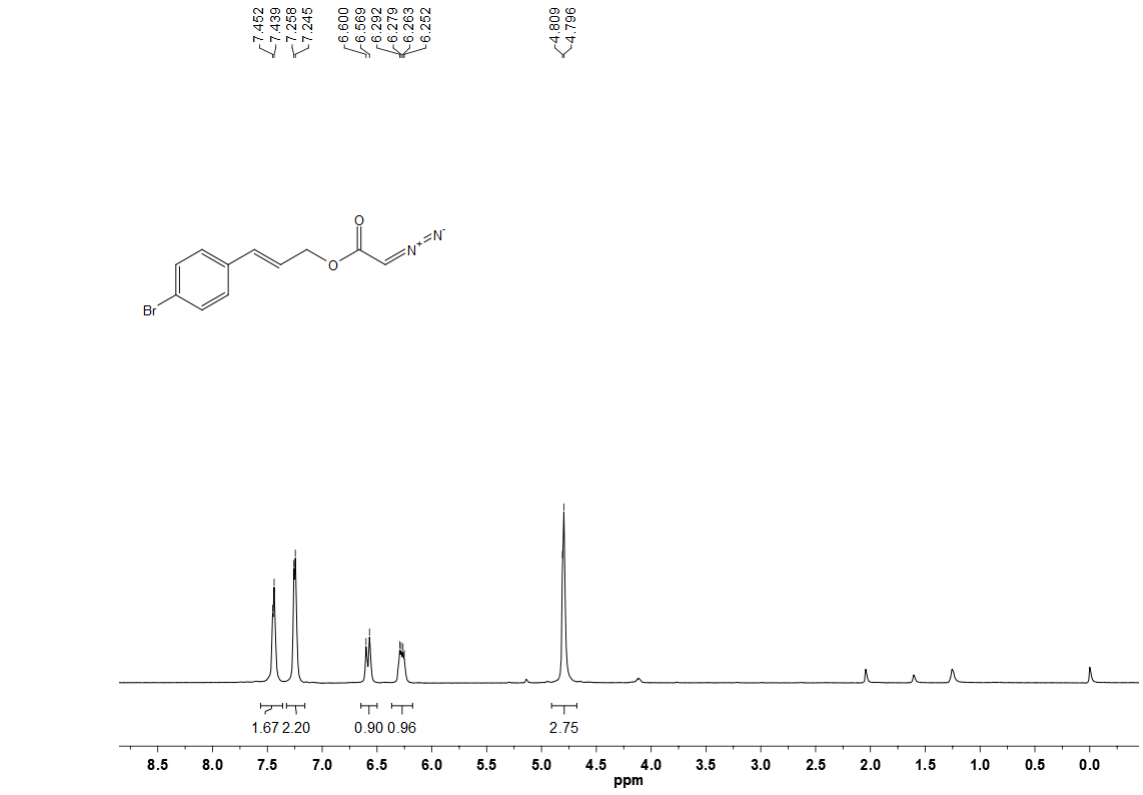

-113.76
1E+05
1E+05
1E+05
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)
O
O
N
N
F

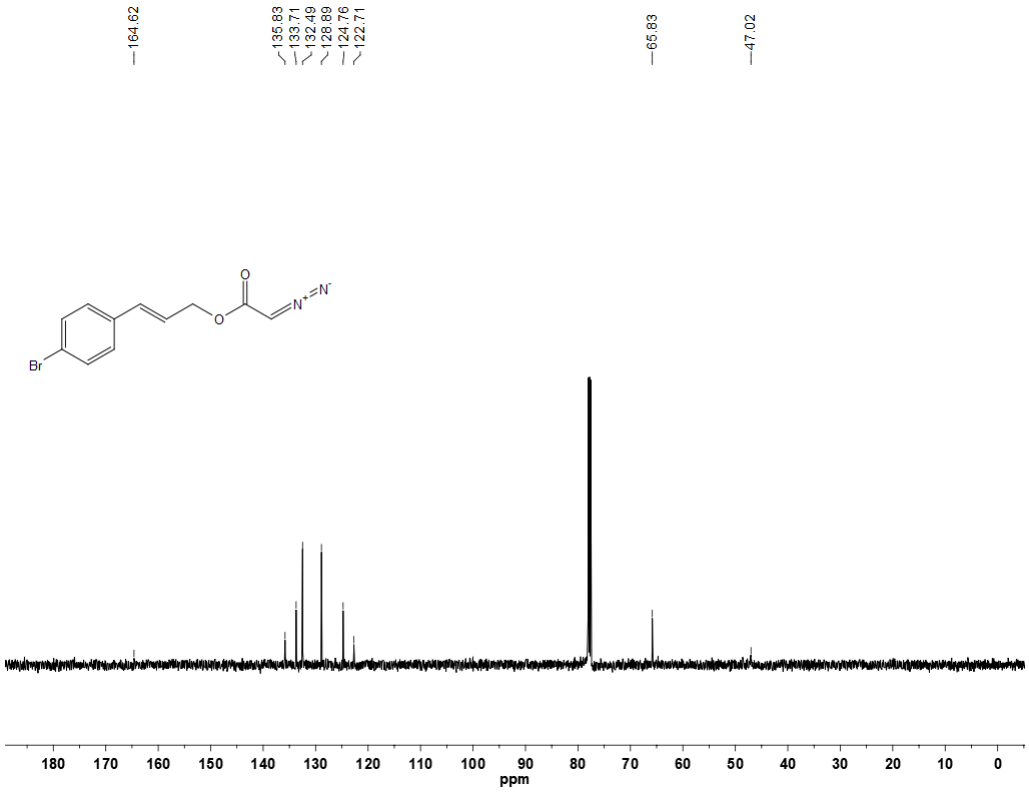
(E)-3-(4-chlorophenyl)allyl 2-diazoacetate (1c): 500 MHz ^{1}H spectrum and 126 MHz ^{13}C spectrum in $CDCl_3$ solvent



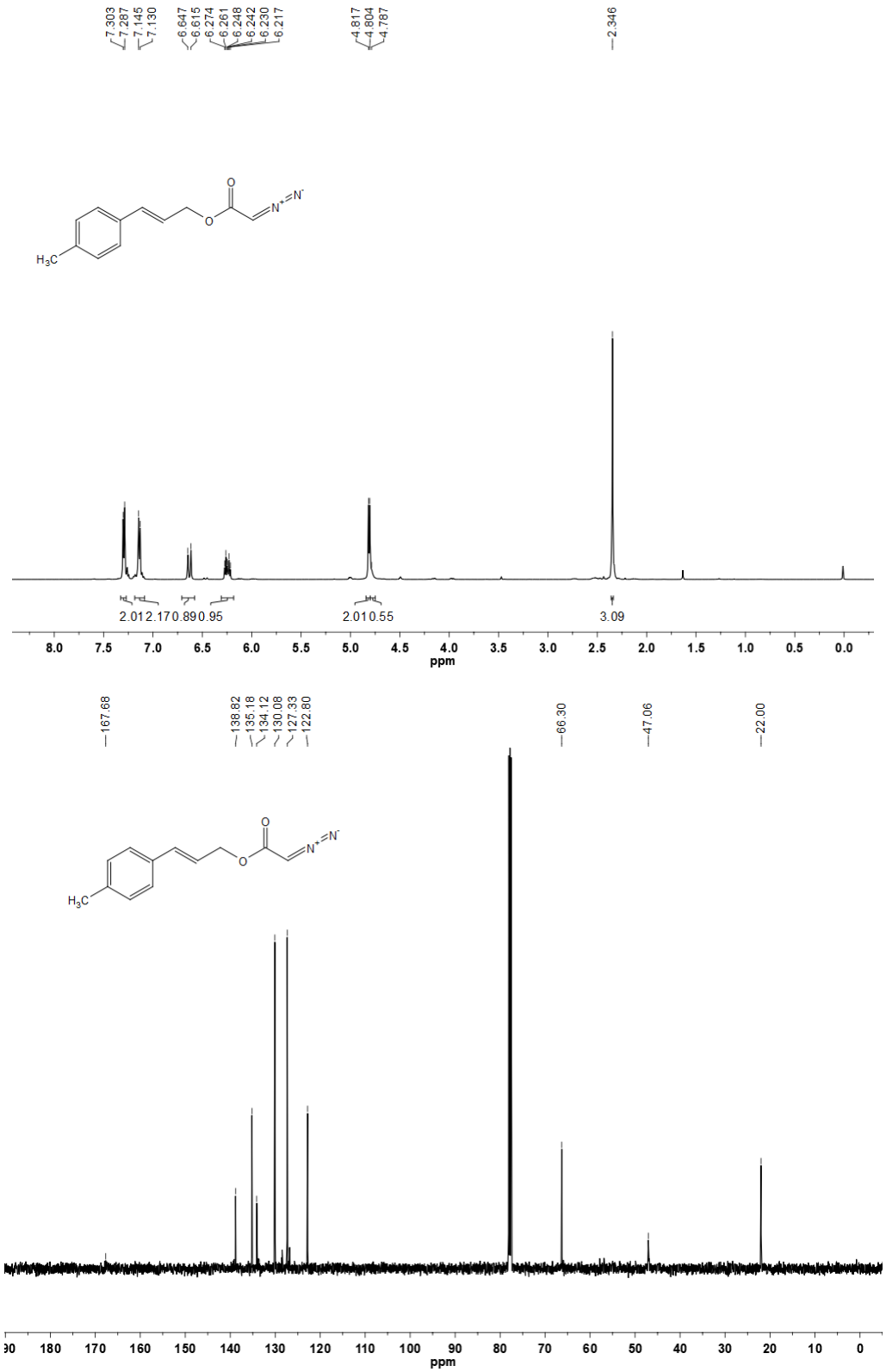


(E)-3-(4-bromophenyl)allyl 2-diazoacetate (1d): 500 MHz ^{1}H spectrum and 126 MHz ^{13}C spectrum in $CDCl_3$ solvent

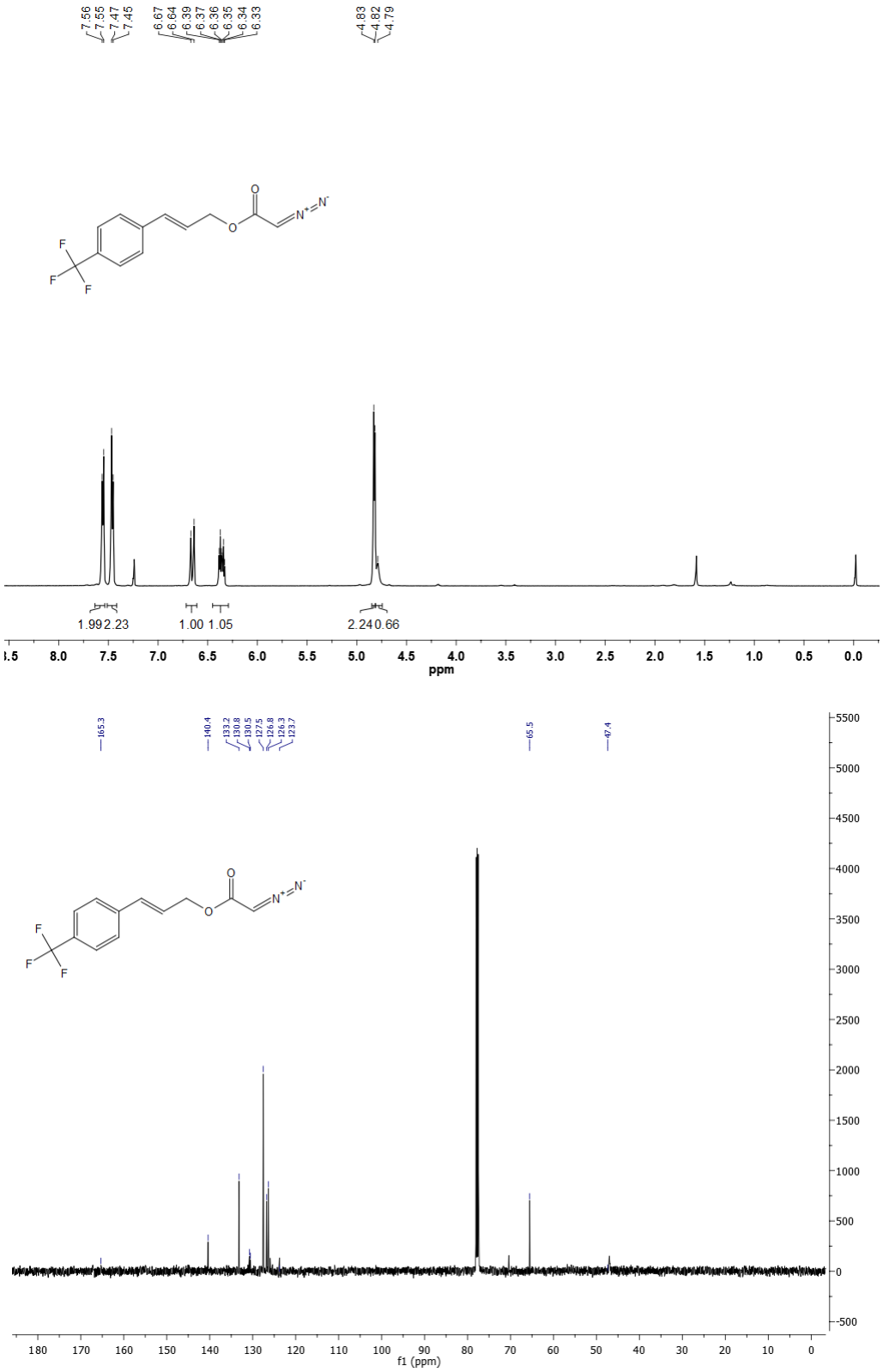


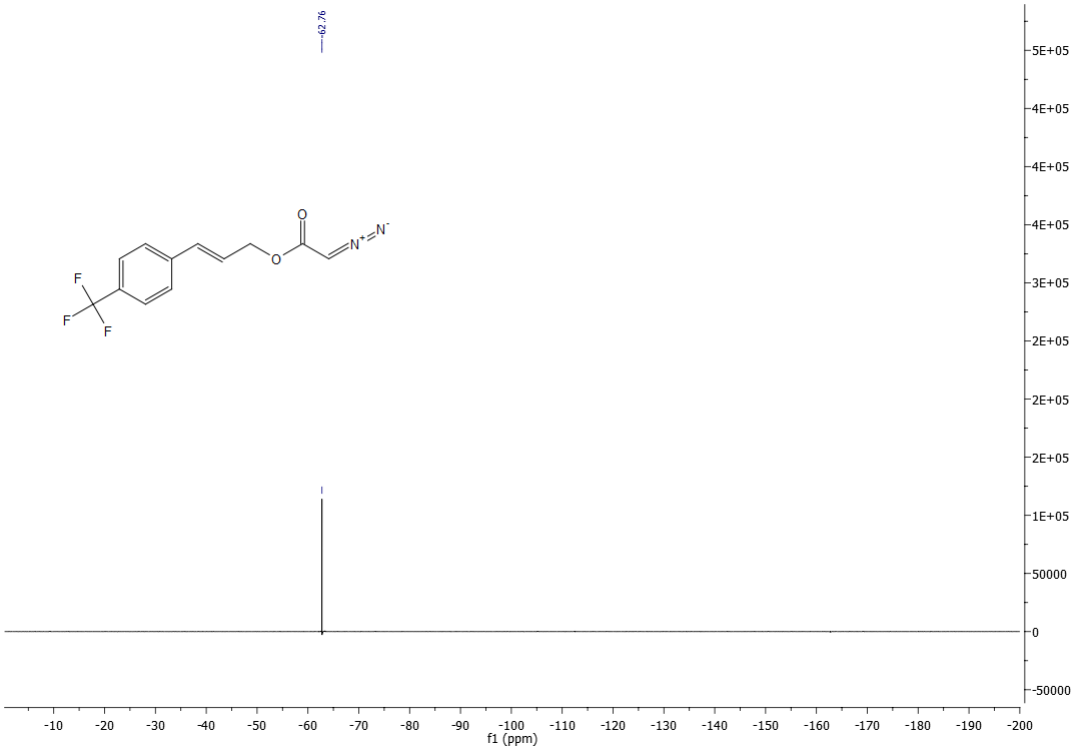


(E)-3-(p-tolyl)allyl 2-diazoacetate (1e): 500 MHz ^{1}H spectrum and 126 MHz ^{13}C spectrum in $CDCl_3$ solvent

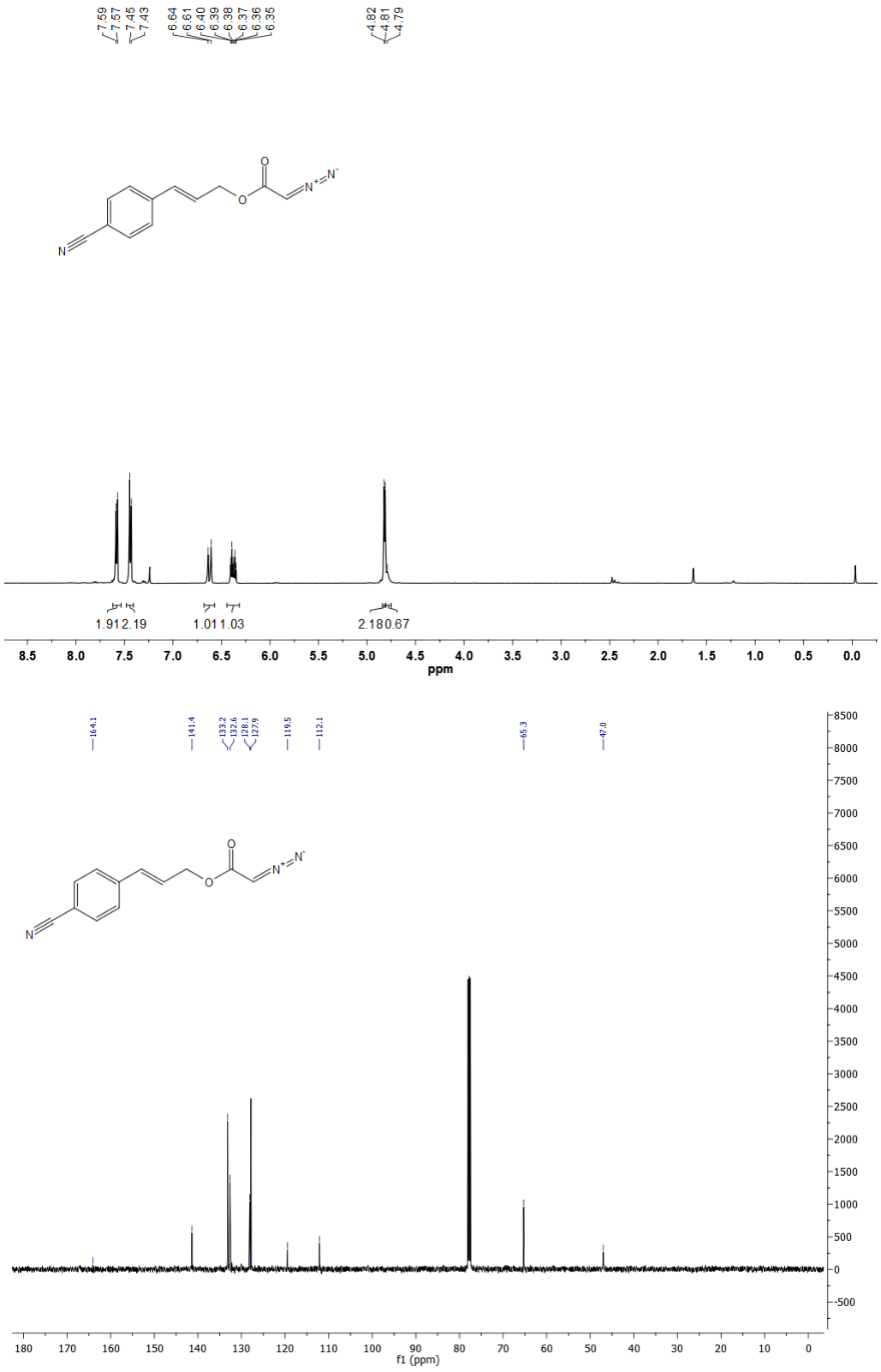


(*E*)-3-(4-(trifluoromethyl)phenyl)allyl 2-diazoacetate (1f): 500 MHz ^{1}H spectrum, 126 MHz ^{13}C spectrum and 375 MHz ^{19}F spectrum in $CDCl_3$ solvent

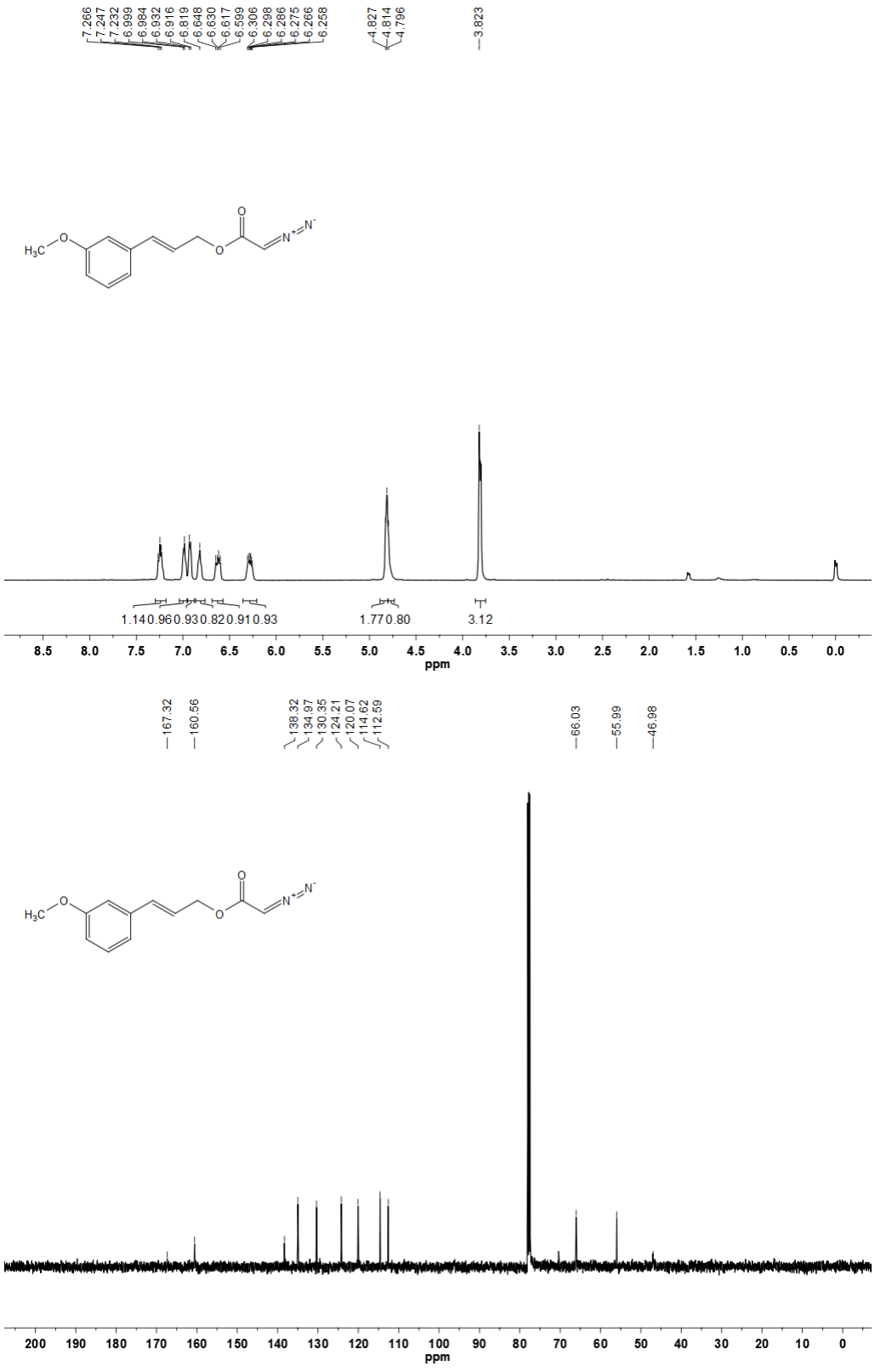



-62.76
F
F
F
O
O
N+
N-
5E+05
4E+05
4E+05
4E+05
3E+05
2E+05
2E+05
2E+05
1E+05
50000
0
-50000
-10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

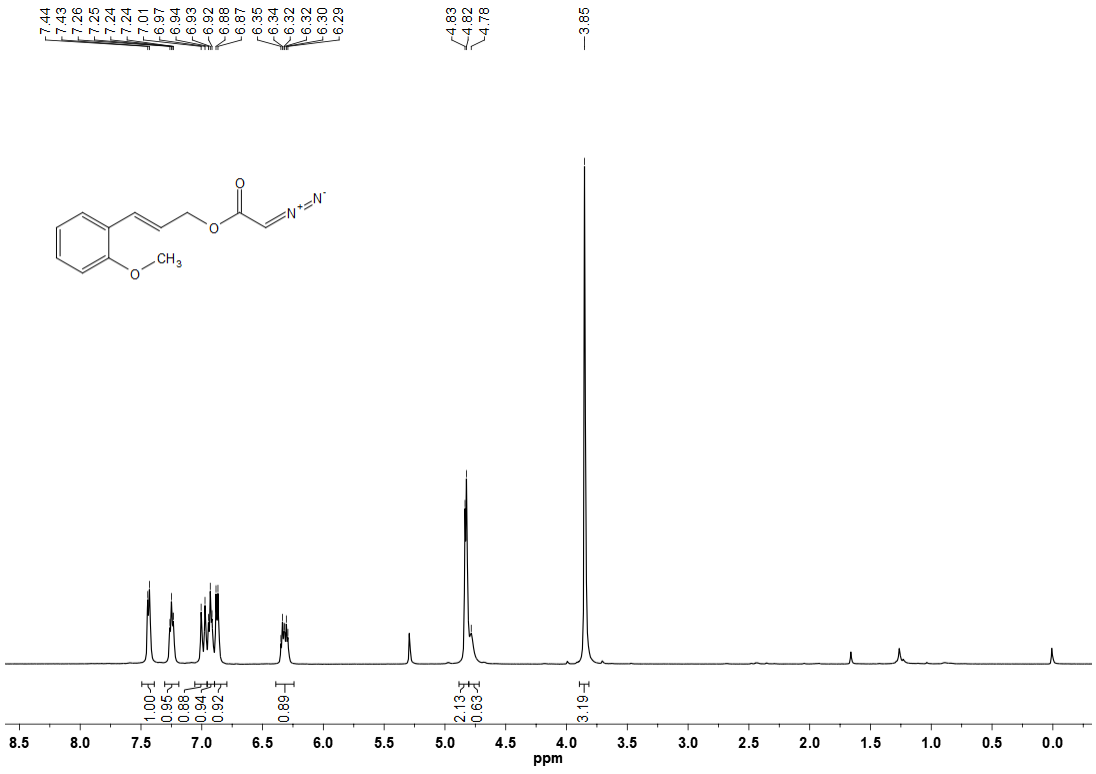
(*E*)-3-(4-cyanophenyl)allyl 2-diazoacetate (1g): 500 MHz ^{1}H spectrum and 126 MHz ^{13}C spectrum in $CDCl_3$ solvent

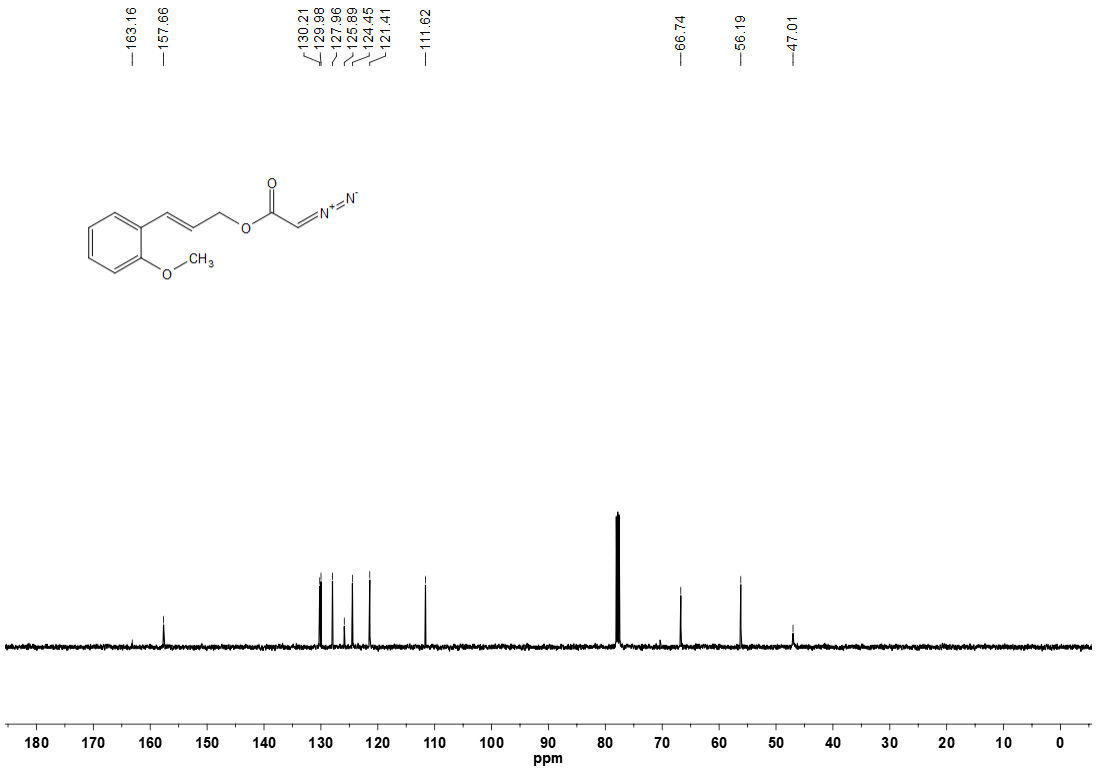


(E)-3-(3-methoxyphenyl)allyl 2-diazoacetate (1h): 500 MHz ^{1}H spectrum and 126 MHz ^{13}C spectrum in $CDCl_3$ solvent

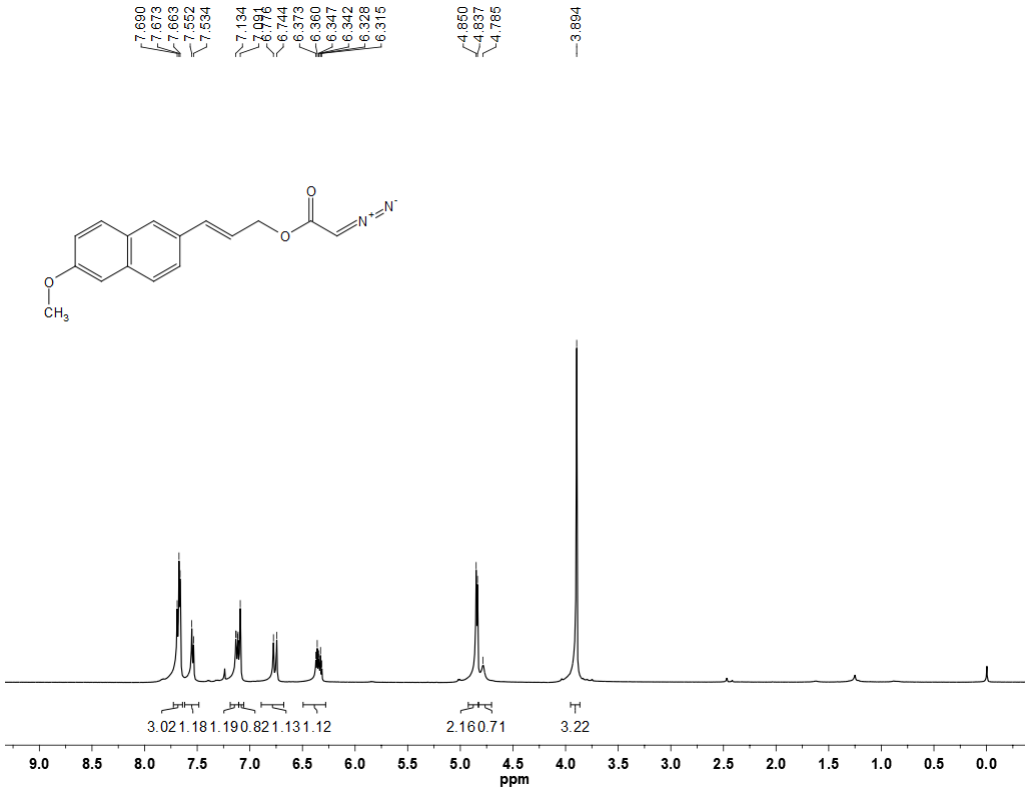


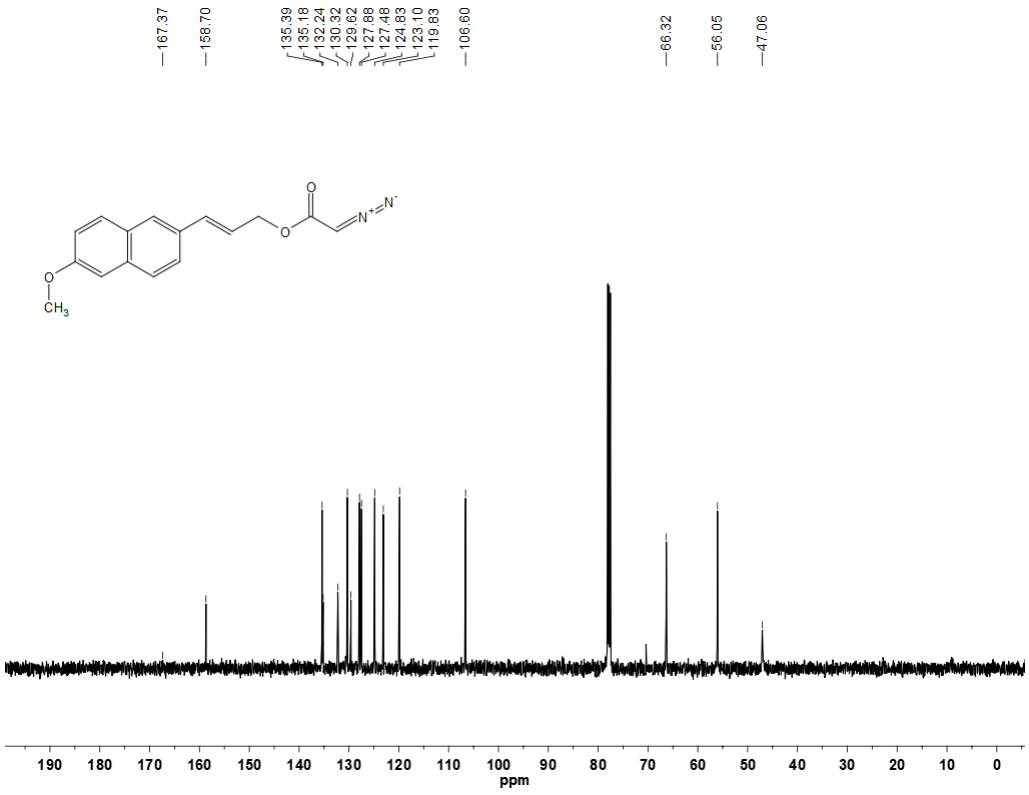
(E)-3-(2-methoxyphenyl)allyl 2-diazoacetate (1i): 500 MHz ^{1}H spectrum and 126 MHz ^{13}C spectrum in $CDCl_3$ solvent



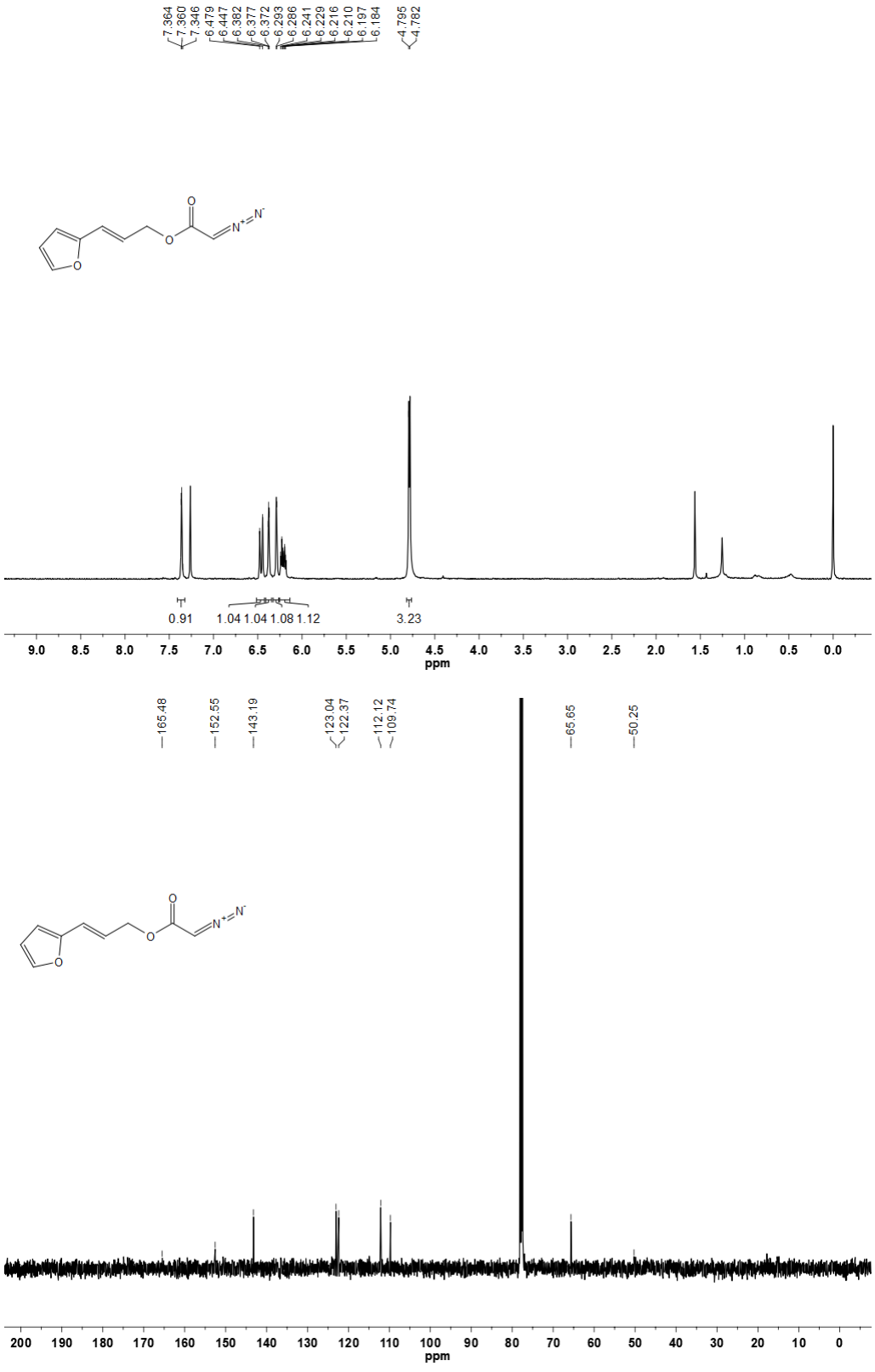


(E)-3-(6-methoxynaphthalen-2-yl)allyl 2-diazoacetate (1j): 500 MHz ^{1}H spectrum and 126 MHz ^{13}C spectrum in $CDCl_3$ solvent

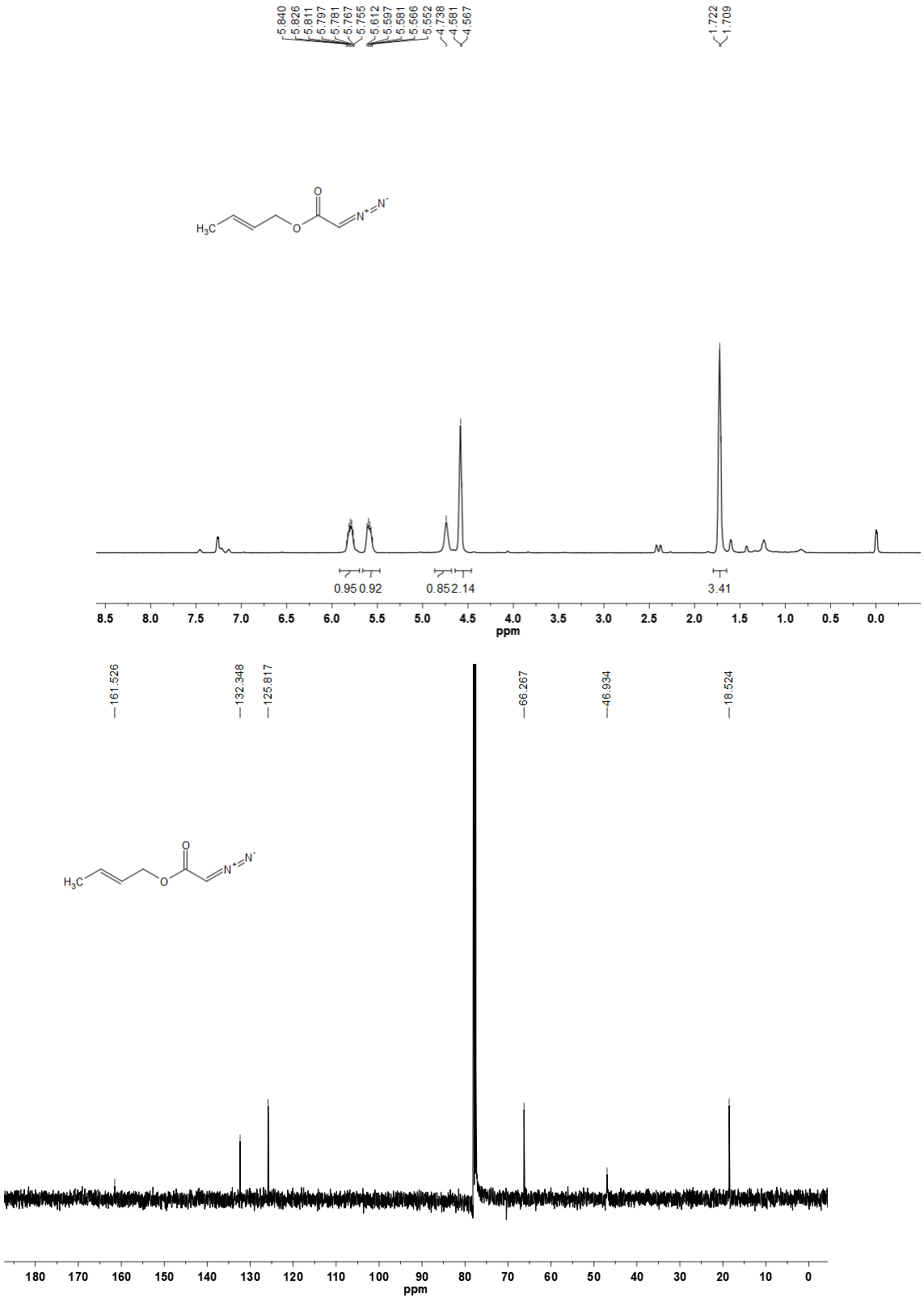




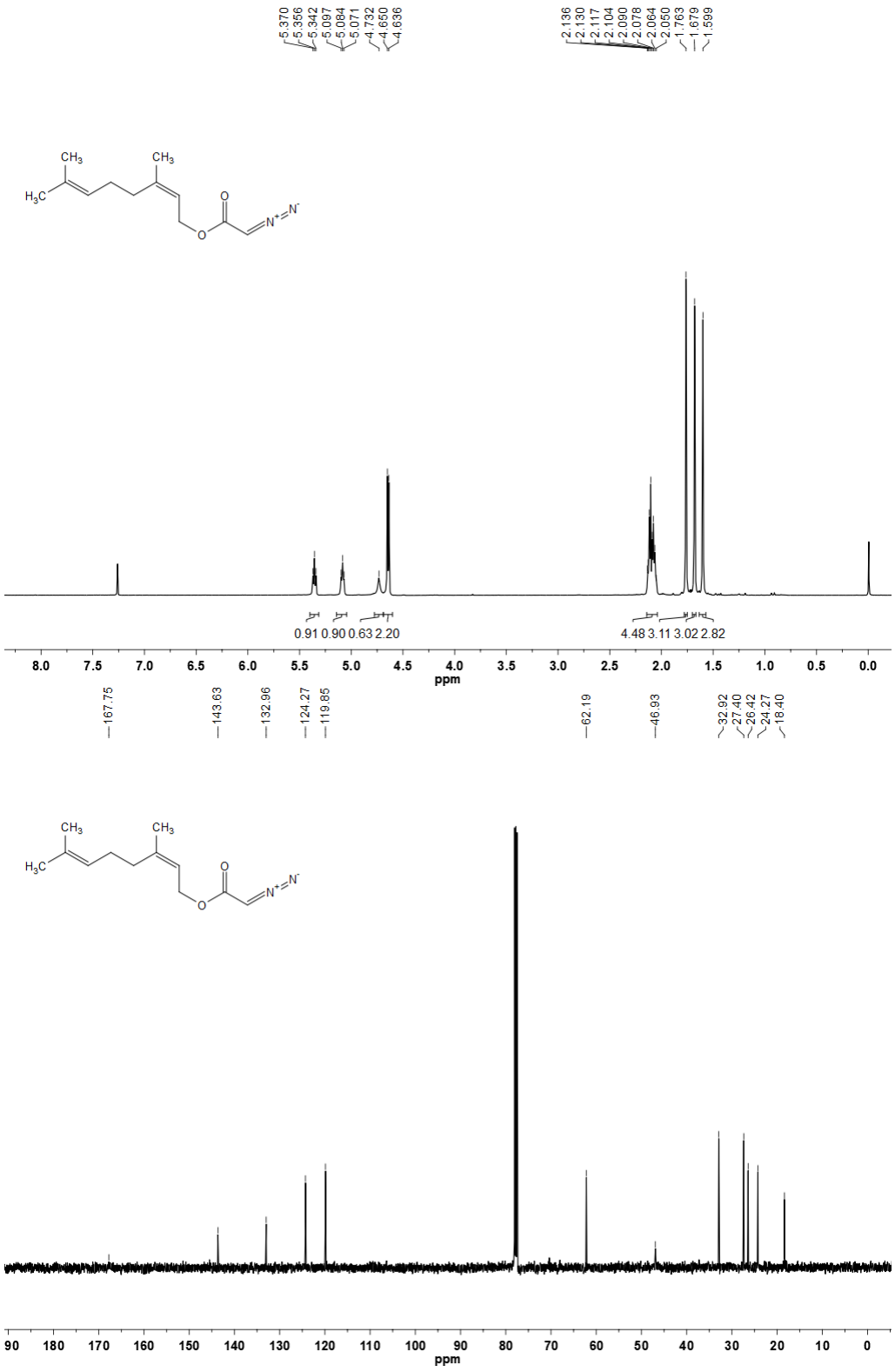
(E)-3-(furan-2-yl)allyl 2-diazoacetate (1k): 500 MHz ^{1}H spectrum and 126 MHz ^{13}C spectrum in $CDCl_3$ solvent



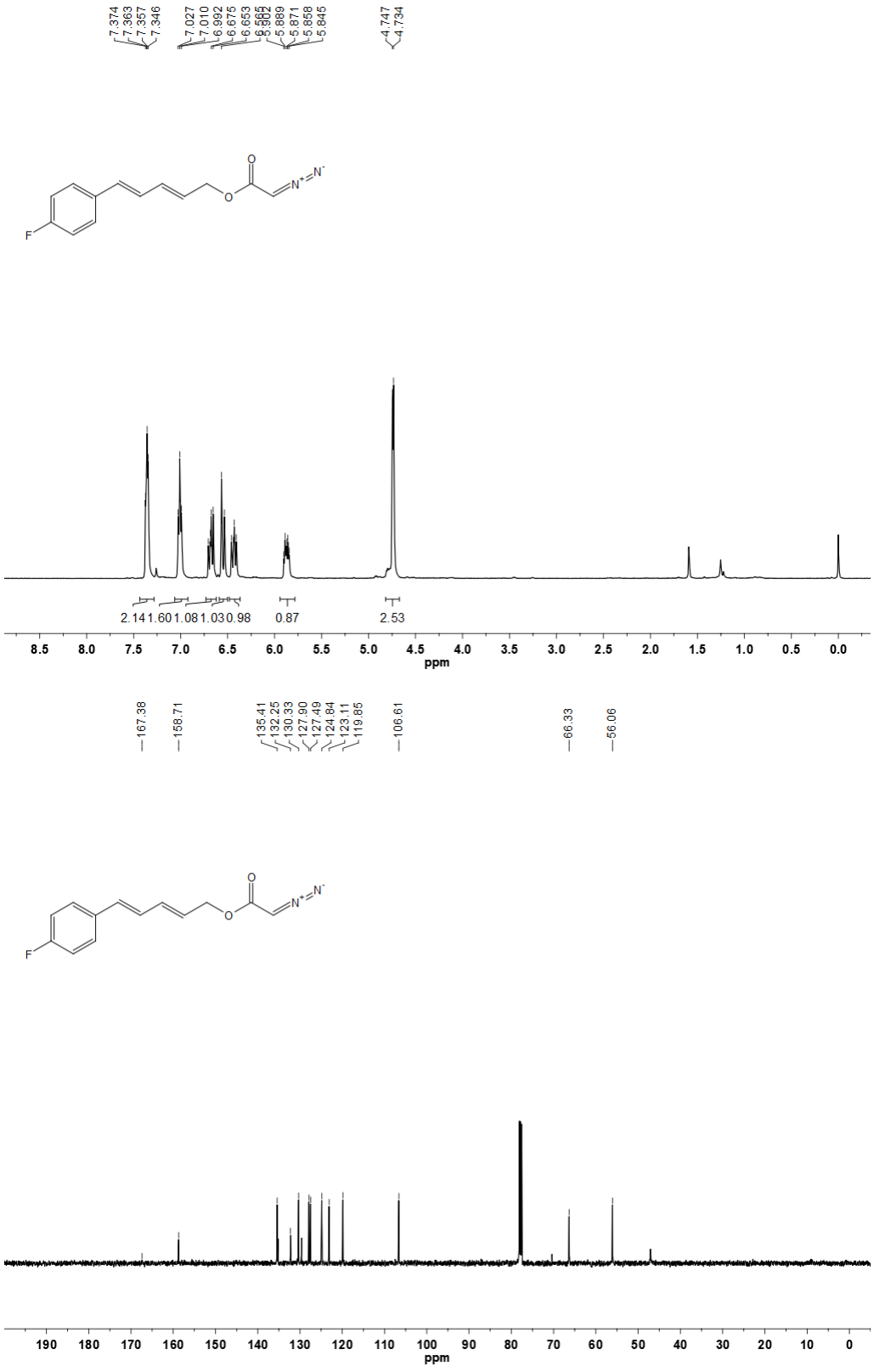
(E)-but-2-en-1-yl 2-diazoacetate (1l): 500 MHz ^{1}H spectrum and 126 MHz ^{13}C spectrum in $CDCl_3$ solvent



(E)-3,7-dimethylocta-2,6-dien-1-yl 2-diazoacetate (1m): 500 MHz ^{1}H spectrum and 126 MHz ^{13}C spectrum in $CDCl_3$ solvent

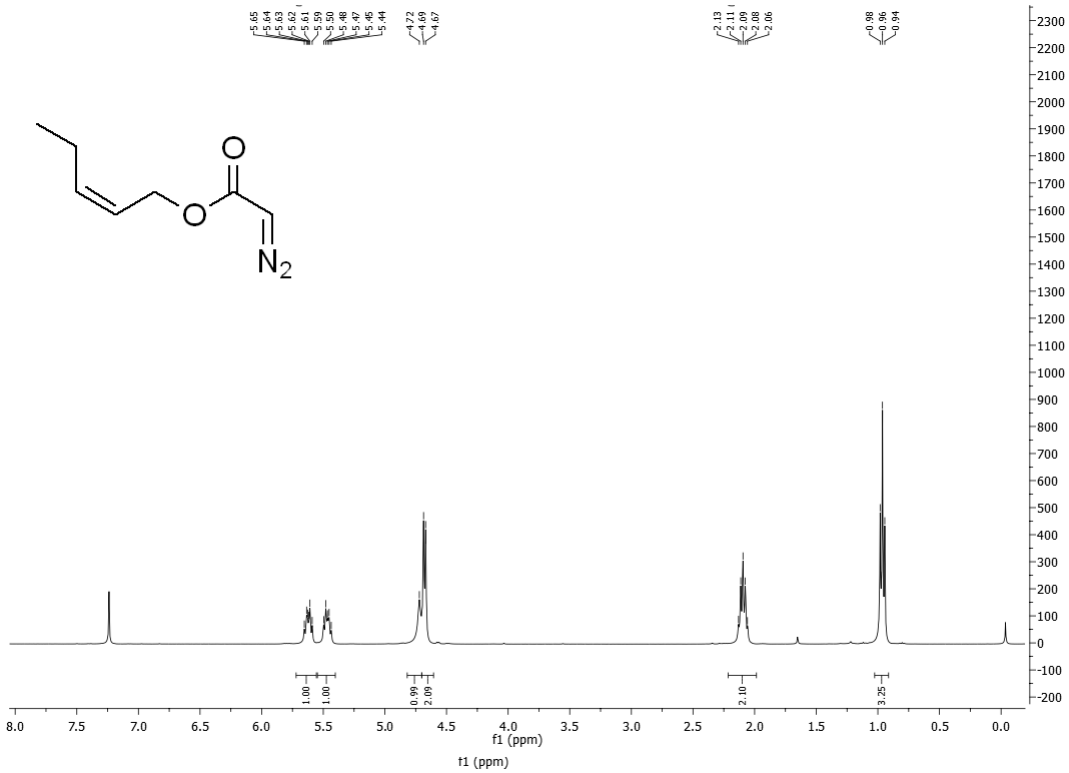


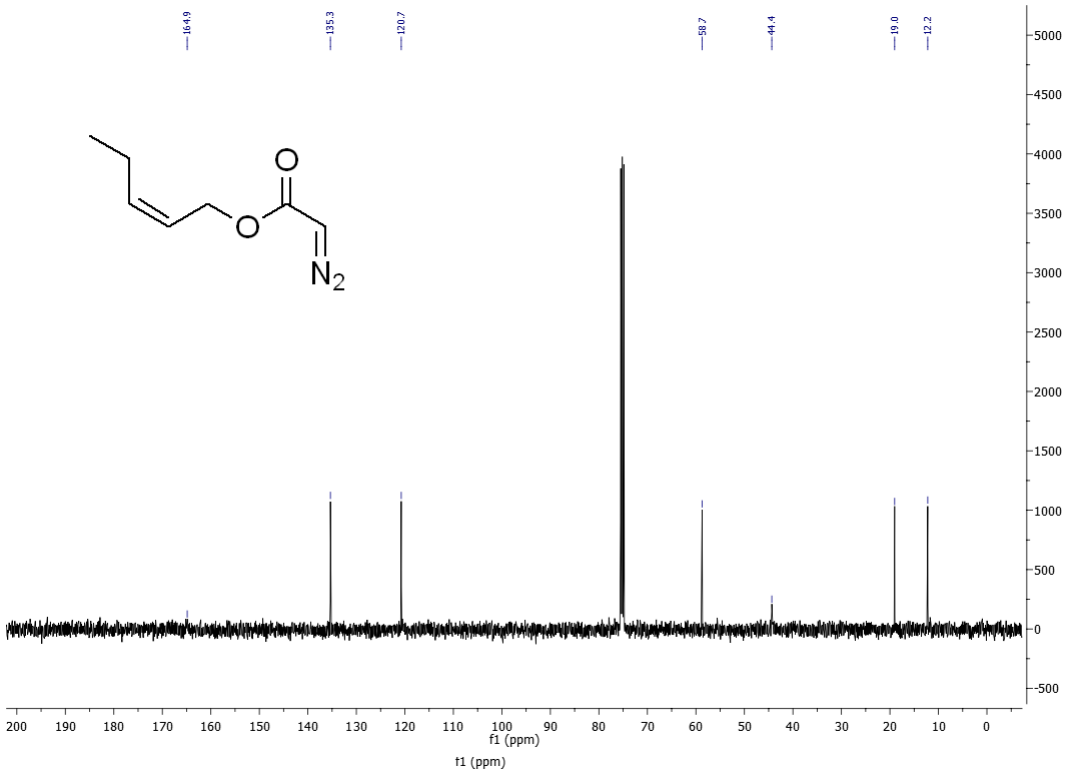
(2E,4E)-5-(4-fluorophenyl)penta-2,4-dien-1-yl 2-diazoacetate (1n): 500 MHz ^{1}H spectrum, 126 MHz ^{13}C spectrum and 375 MHz ^{19}F spectrum in $CDCl_3$ solvent



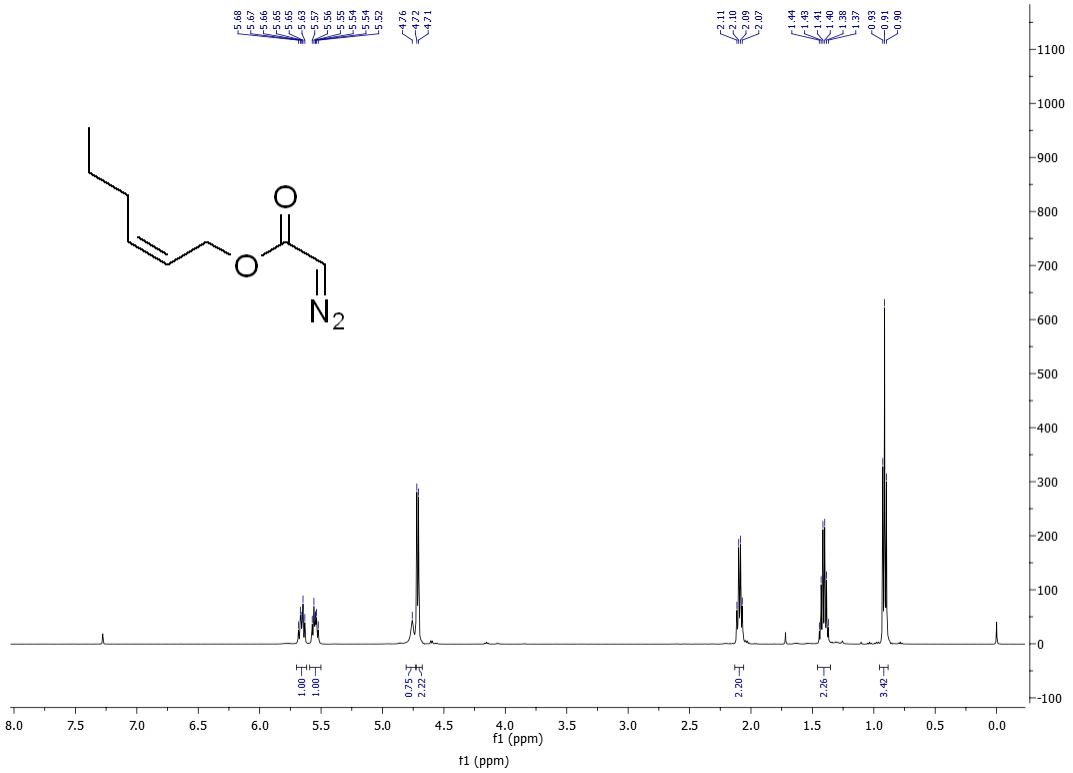

-113.93
O
O
N+
N-
F
80000
75000
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
-10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

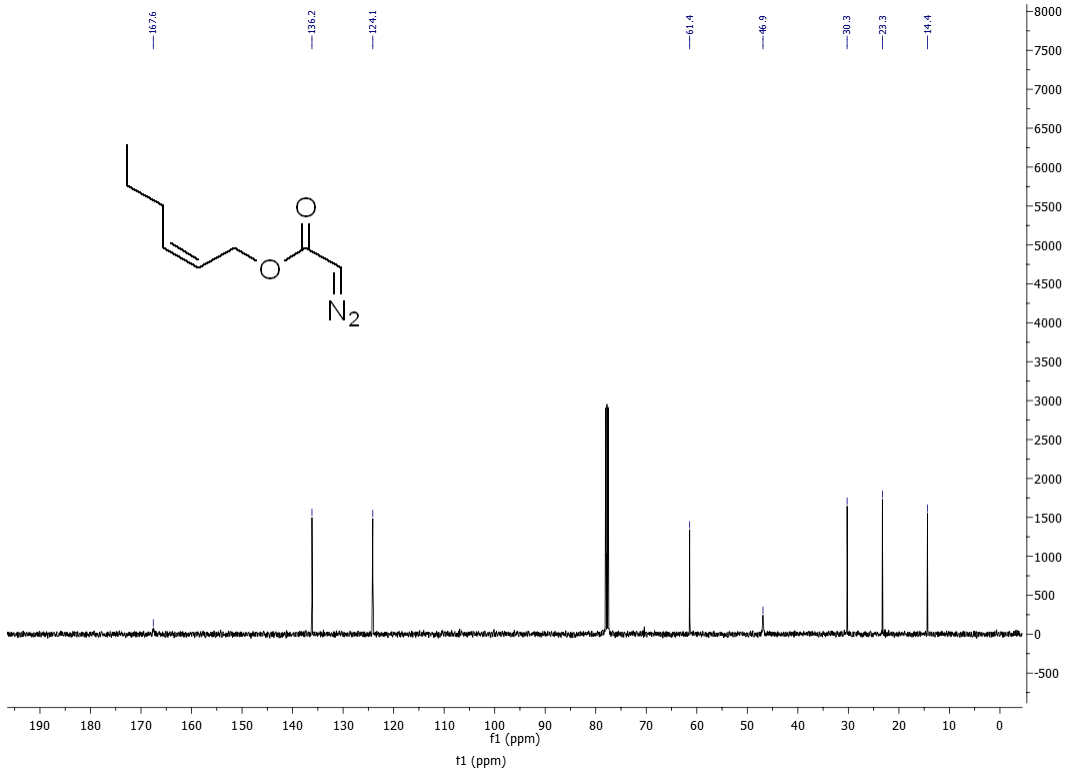
(*Z*)-pent-2-en-1-yl 2-diazoacetate (1o): 500 MHz ^{1}H spectrum and 126 MHz ^{13}C spectrum in $CDCl_3$ solvent



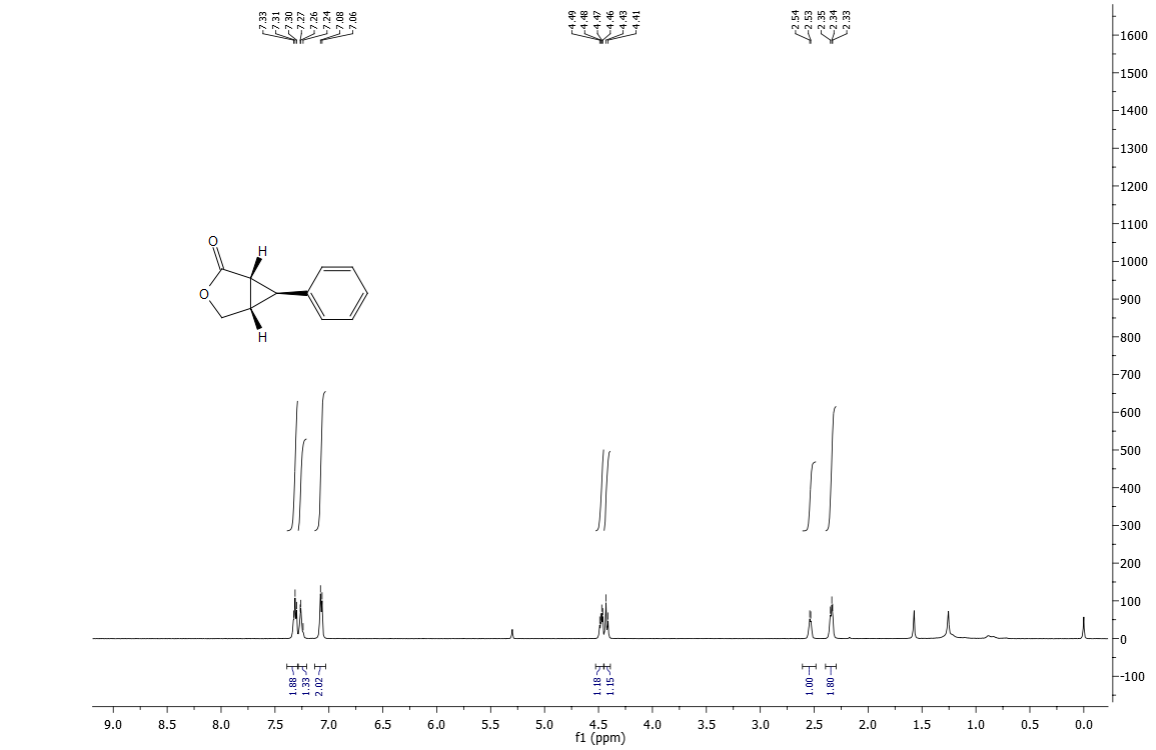


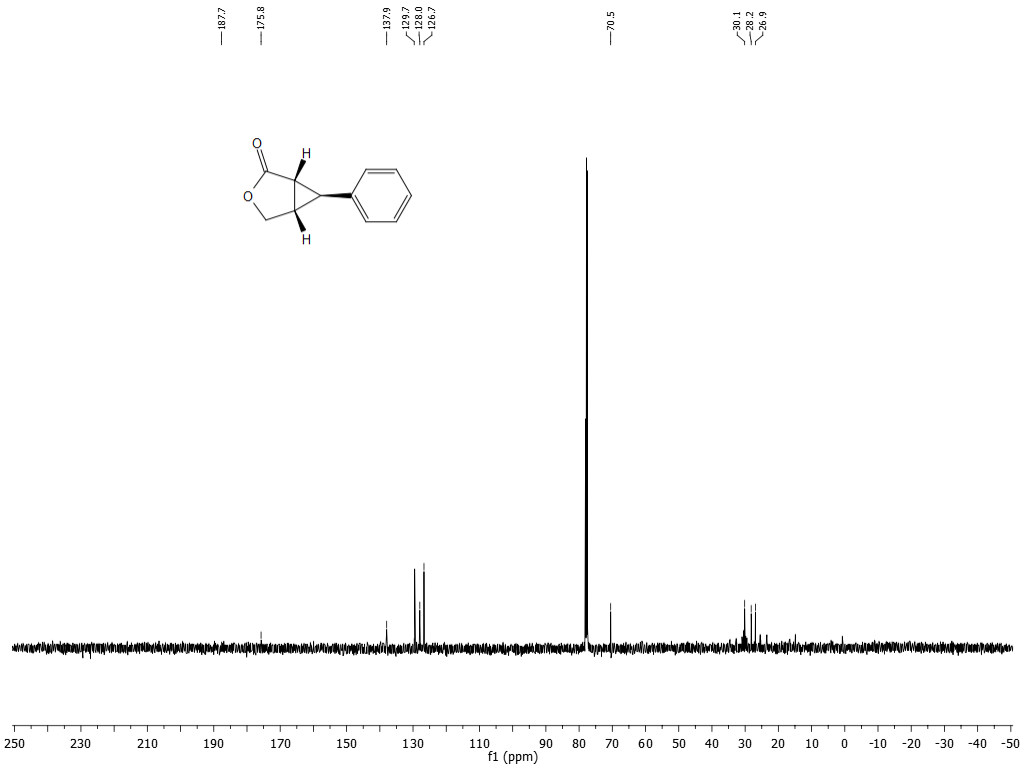
(*Z*)-hex-2-en-1-yl 2-diazoacetate (1p): 500 MHz ^{1}H spectrum and 126 MHz ^{13}C spectrum in $CDCl_3$ solvent



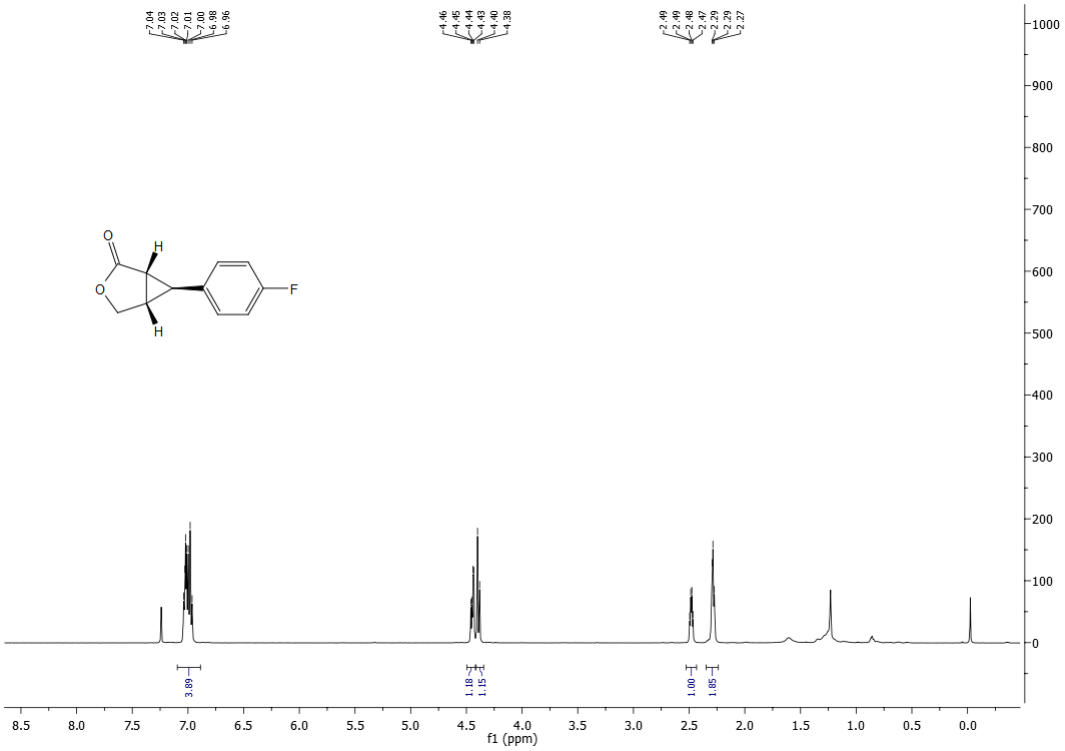


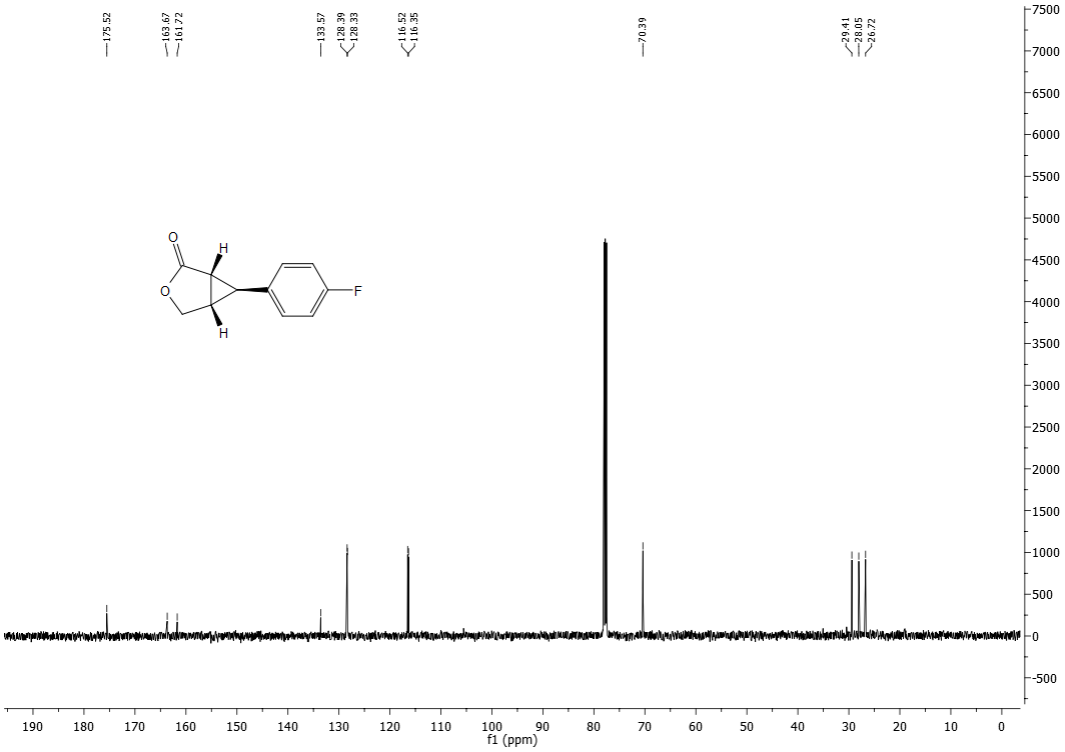
(1R,5S,6S)-6-phenyl-3-oxabicyclo[3.1.0]hexan-2-one (2a): 500 MHz ^{1}H spectrum and 126 MHz ^{13}C spectrum in $CDCl_3$ solvent

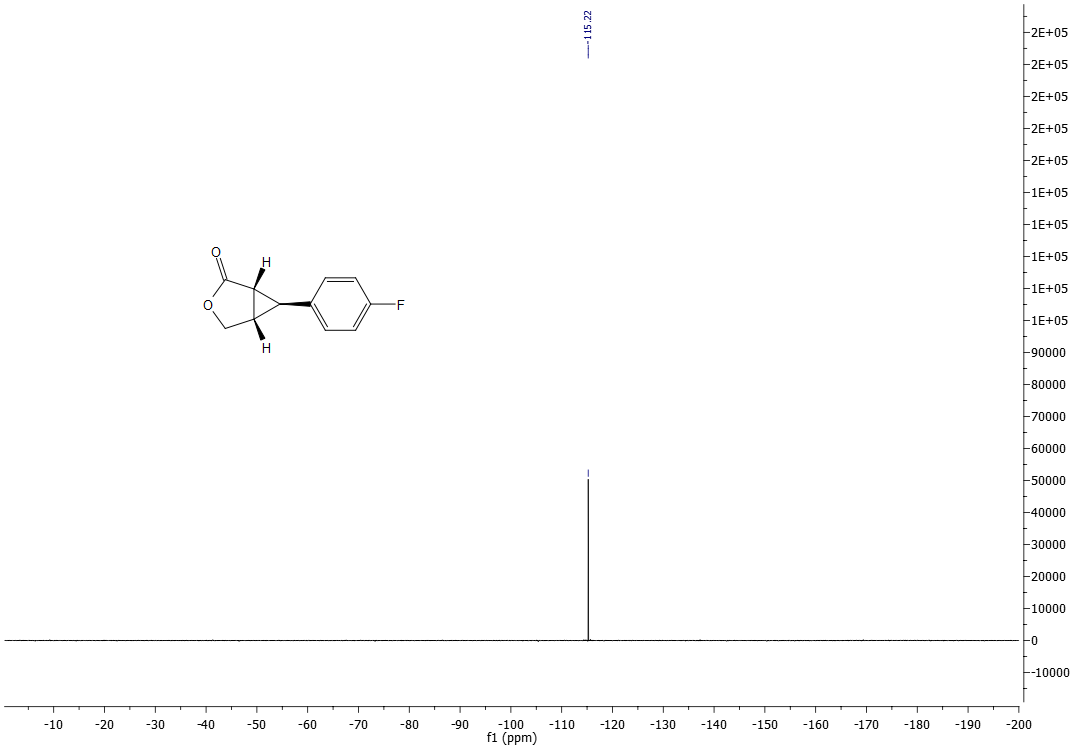




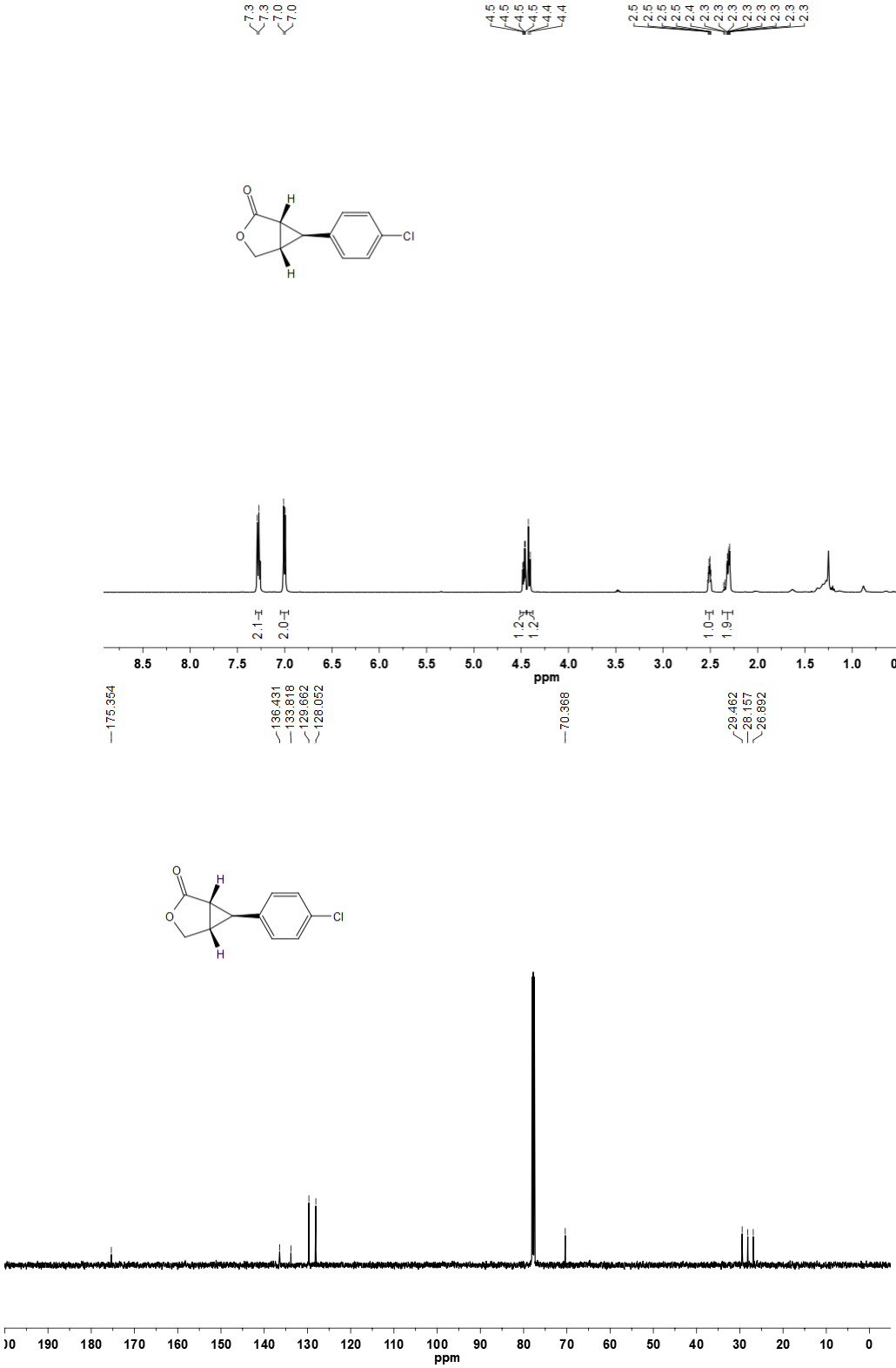
(1R,5S,6S)-6-(4-fluorophenyl)-3-oxabicyclo[3.1.0]hexan-2-one (2b): 500 MHz ^{1}H spectrum, 126 MHz ^{13}C spectrum and 375 MHz ^{19}F spectrum in $CDCl_3$ solvent



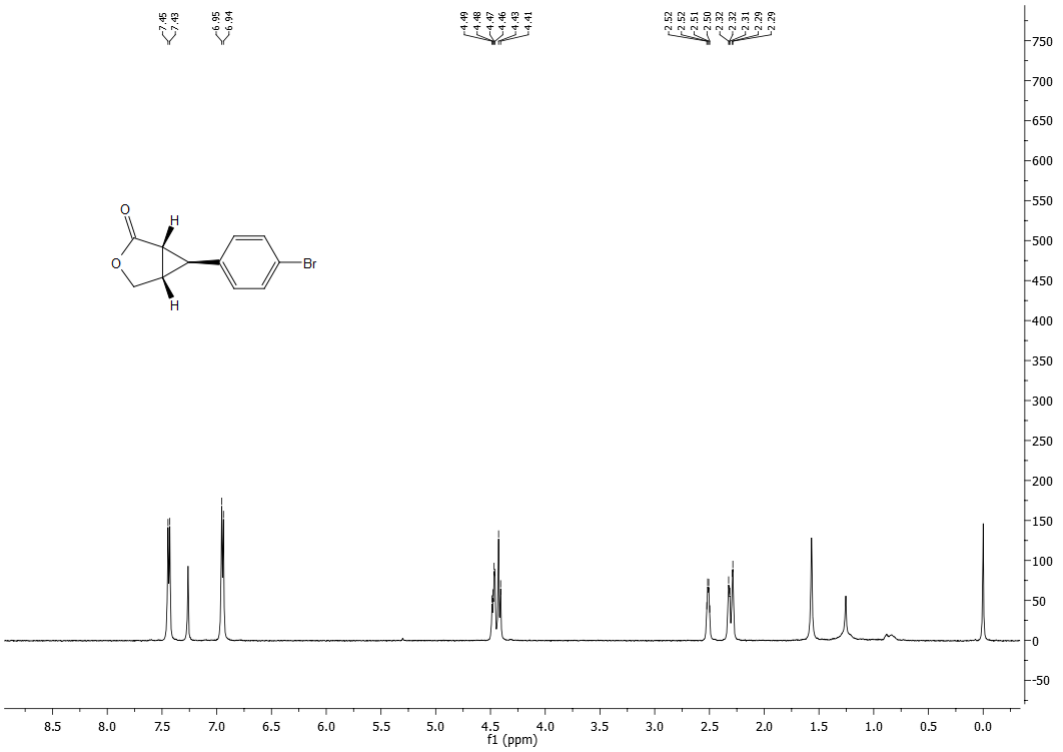


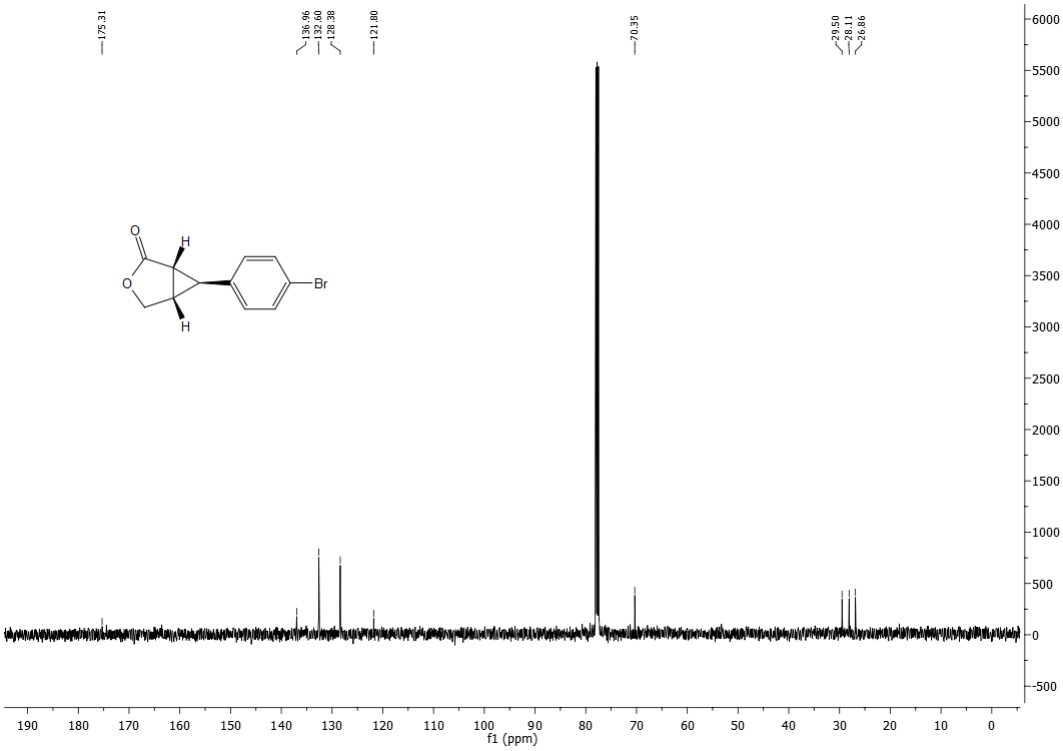

-115.22
O
H
O
F
H
2E+05
2E+05
2E+05
2E+05
2E+05
1E+05
1E+05
1E+05
1E+05
1E+05
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

(1R,5S,6S)-6-(4-chlorophenyl)-3-oxabicyclo[3.1.0]hexan-2-one (2c): 500 MHz ^{1}H spectrum and 126 MHz ^{13}C spectrum in $CDCl_3$ solvent

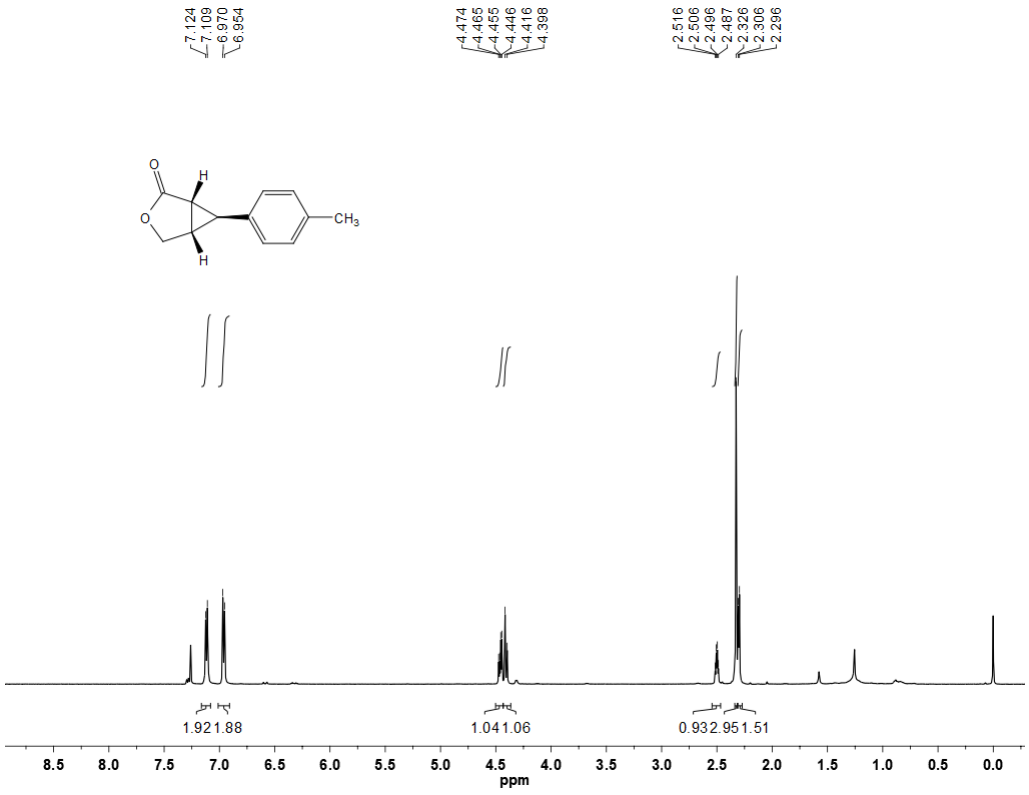


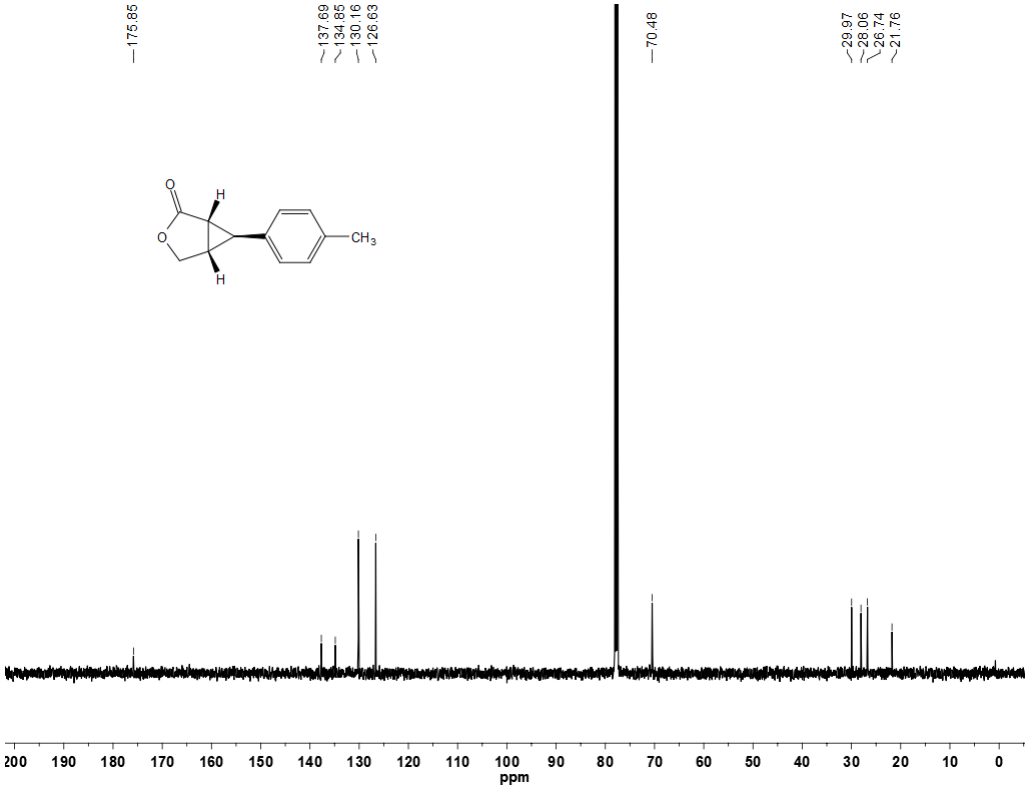
(1R,5S,6S)-6-(4-bromophenyl)-3-oxabicyclo[3.1.0]hexan-2-one (2d): 500 MHz ^{1}H spectrum and 126 MHz ^{13}C spectrum in $CDCl_3$ solvent



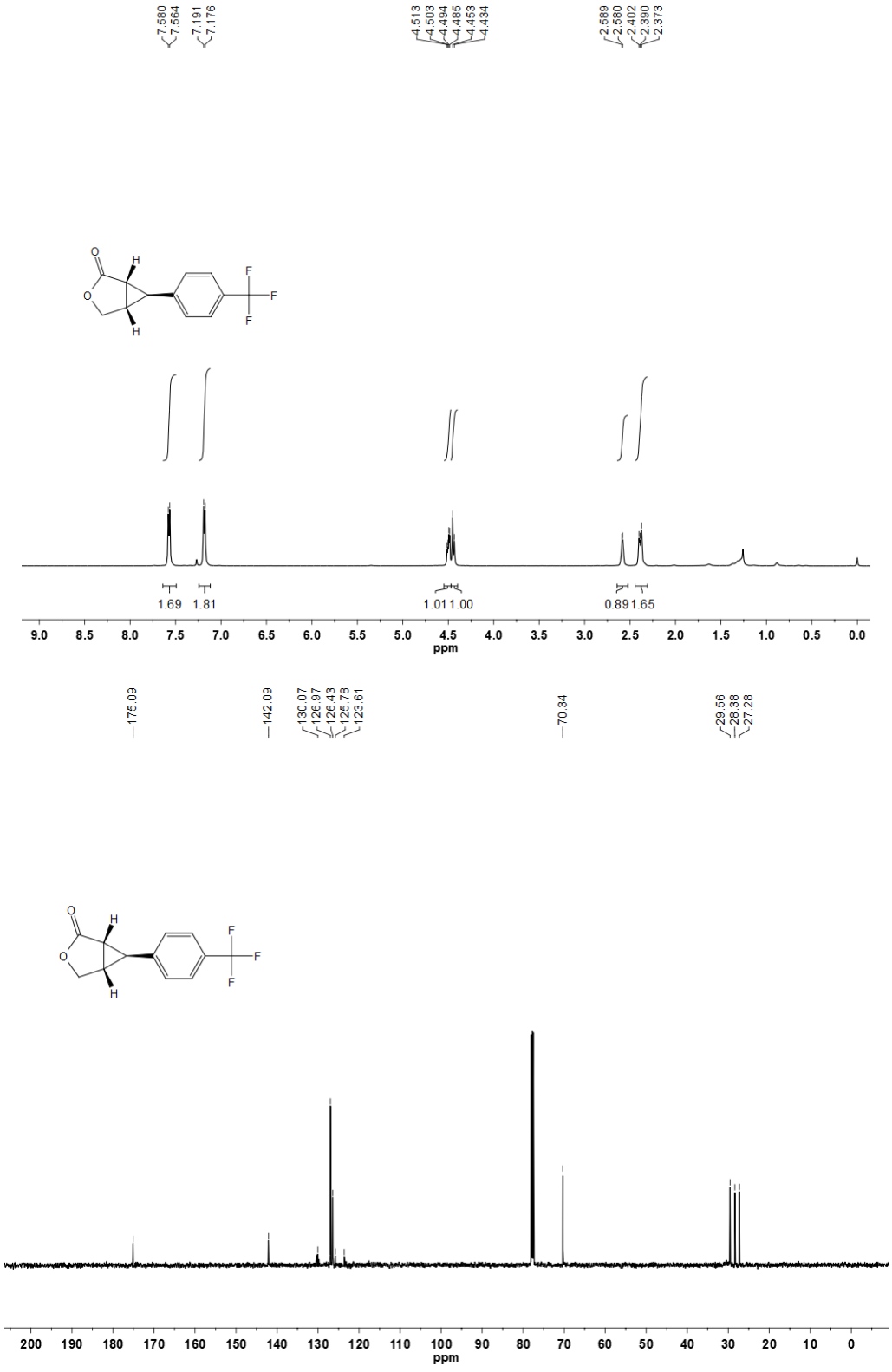


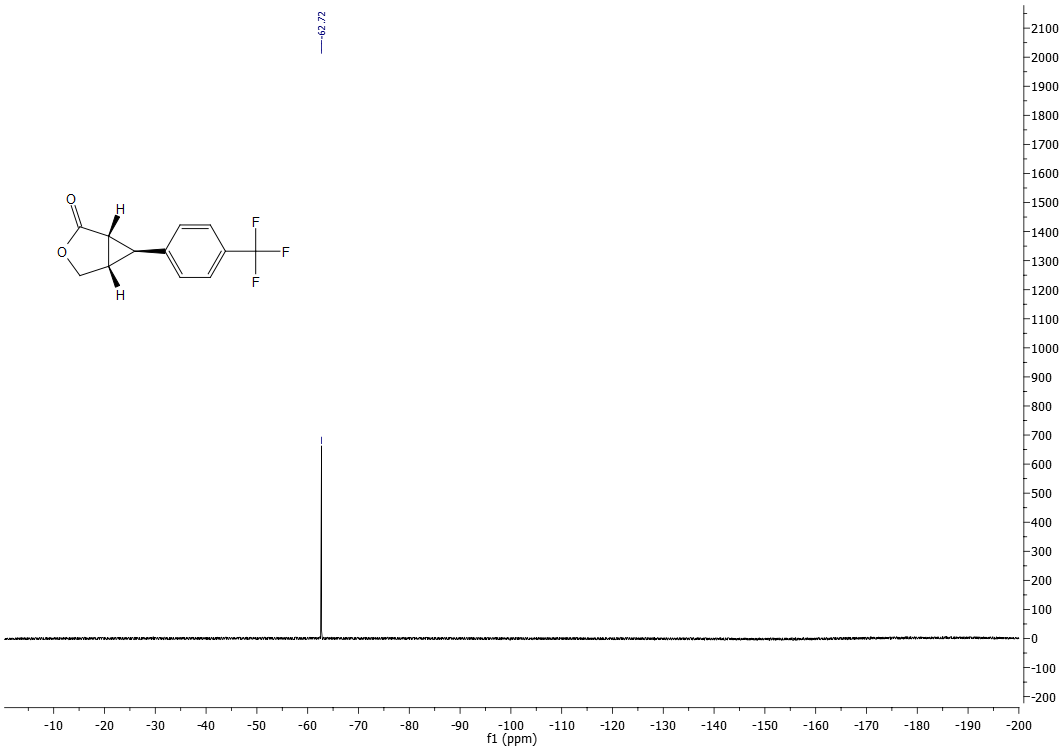
(1R,5S,6S)-6-(p-tolyl)-3-oxabicyclo[3.1.0]hexan-2-one (2e): 500 MHz ^{1}H spectrum and 126 MHz ^{13}C spectrum in $CDCl_3$ solvent



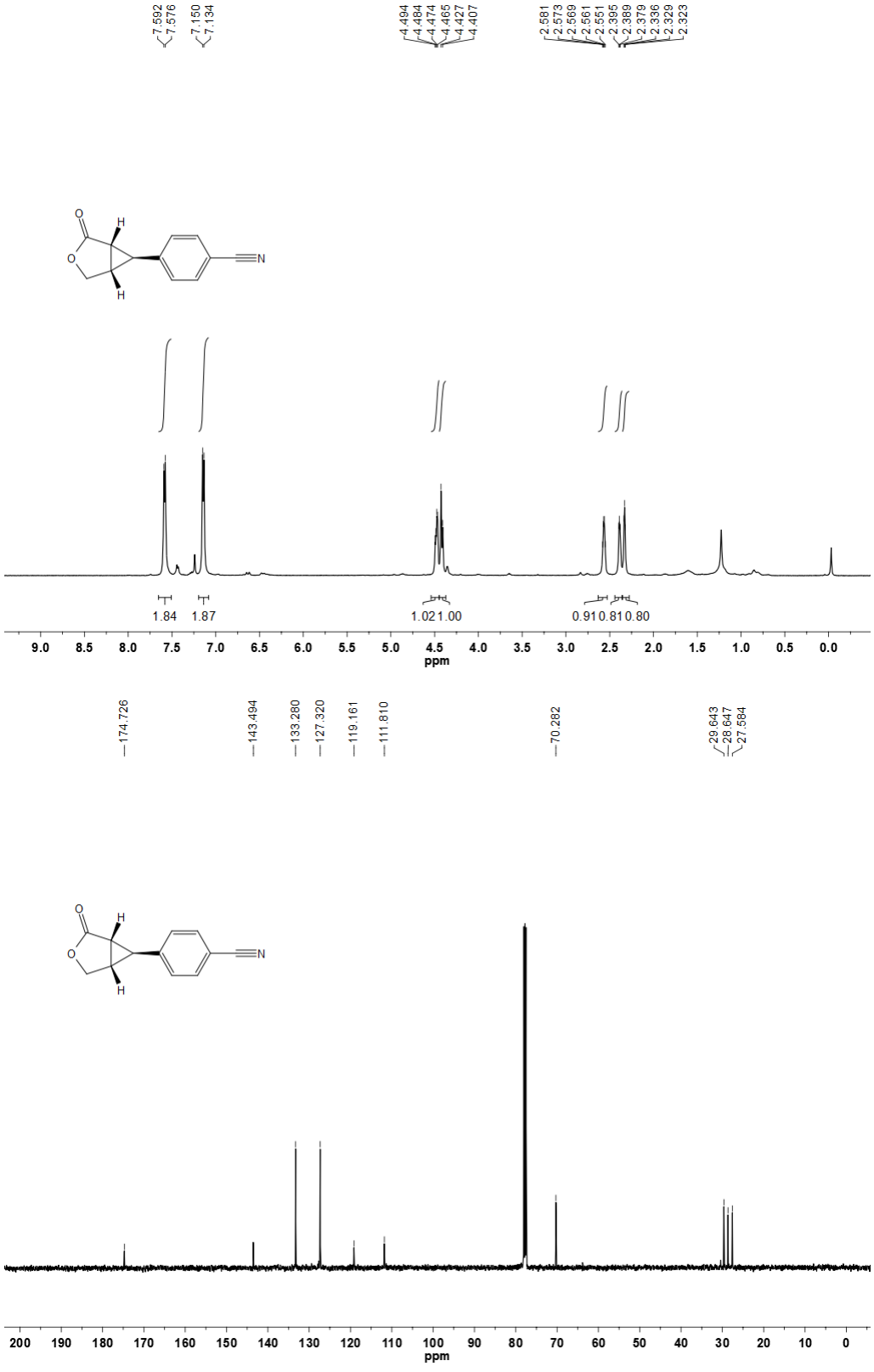


(1R,5S,6S)-6-(4-(trifluoromethyl)phenyl)-3-oxabicyclo[3.1.0]hexan-2-one (2f): 500 MHz ^{1}H spectrum, 126 MHz ^{13}C spectrum and 375 MHz ^{19}F spectrum in $CDCl_3$ solvent

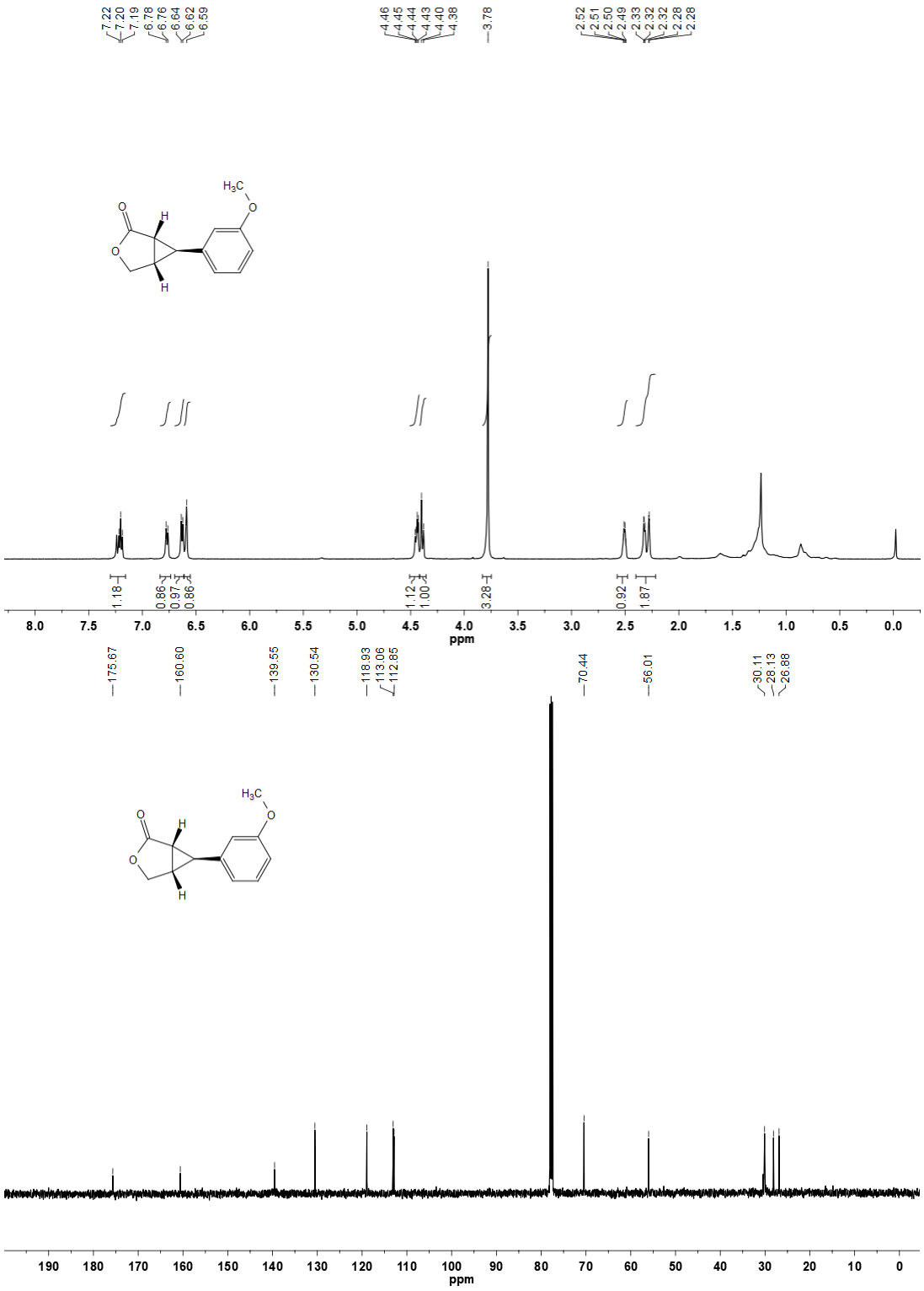



-62.72
O
H
O
F
F
F
H
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-200
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

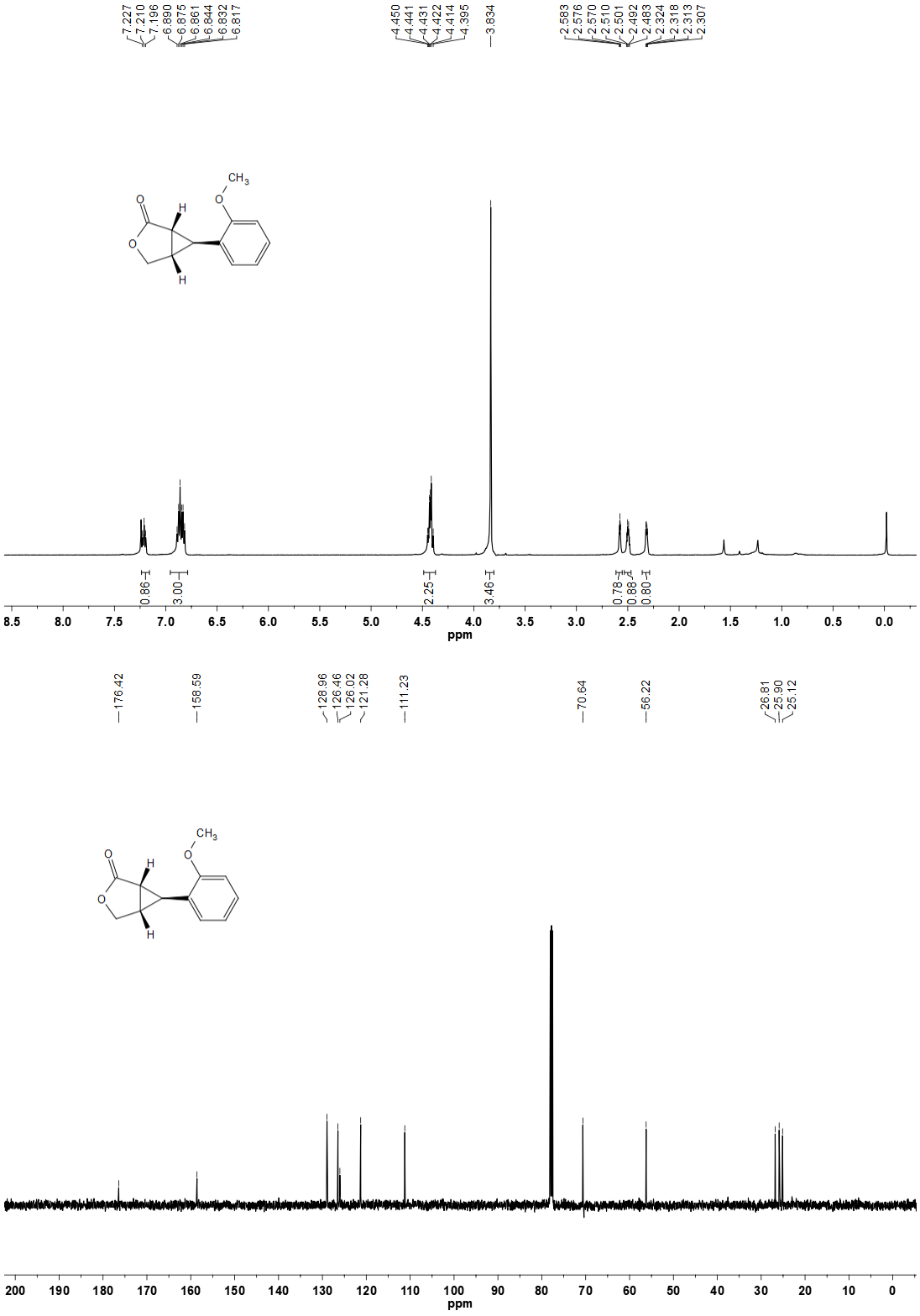
4-((1R,5S,6S)-2-oxo-3-oxabicyclo[3.1.0]hexan-6-yl)benzonitrile (2g): 500 MHz ^{1}H spectrum and 126 MHz ^{13}C spectrum in $CDCl_3$ solvent



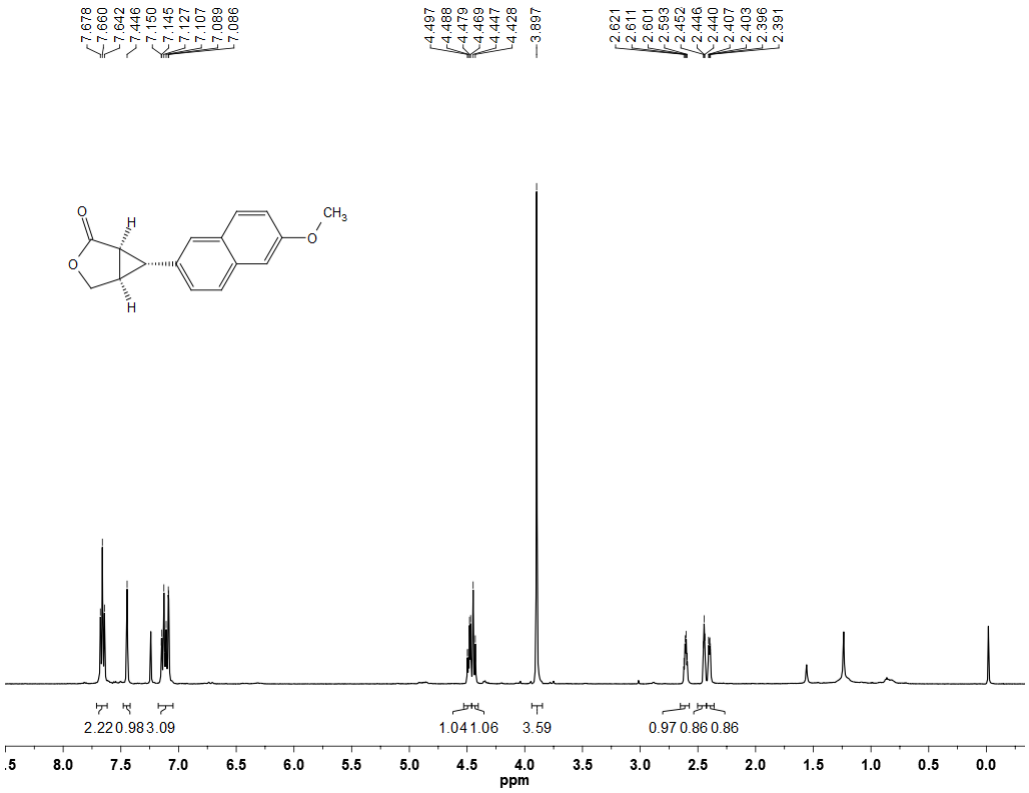
(1R,5S,6S)-6-(3-methoxyphenyl)-3-oxabicyclo[3.1.0]hexan-2-one (2h): 500 MHz ^{1}H spectrum and 126 MHz ^{13}C spectrum in $CDCl_3$ solvent

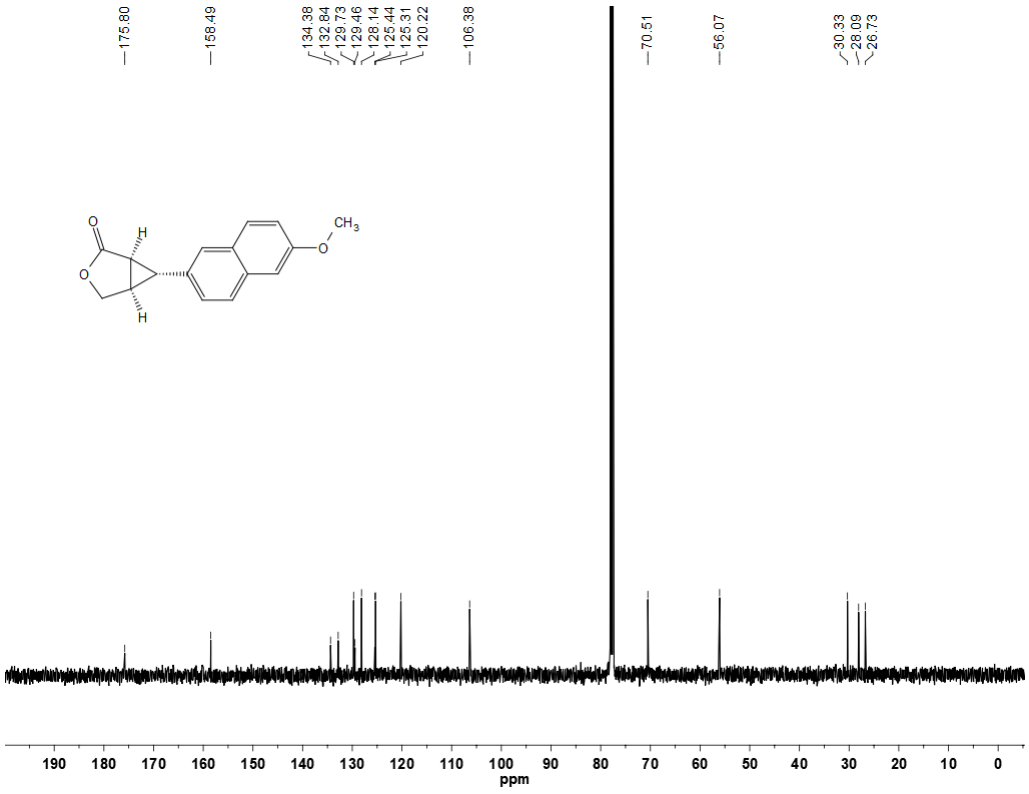


(1R,5S,6S)-6-(2-methoxyphenyl)-3-oxabicyclo[3.1.0]hexan-2-one (2i): 500 MHz ^{1}H spectrum and 126 MHz ^{13}C spectrum in $CDCl_3$ solvent

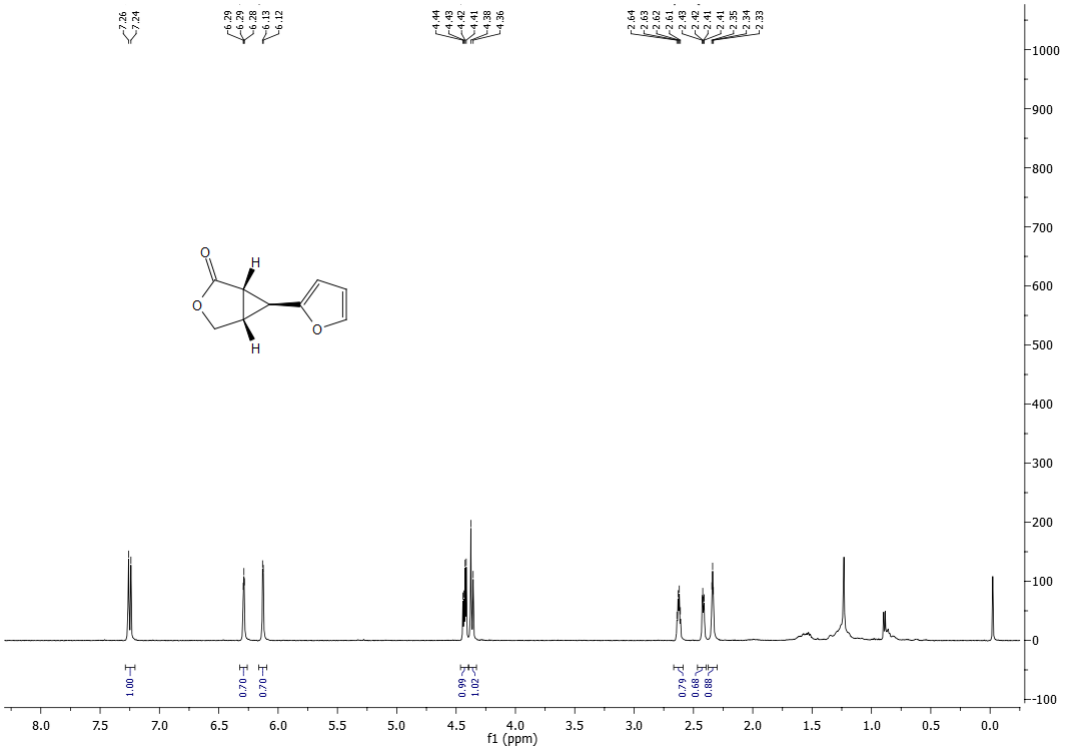


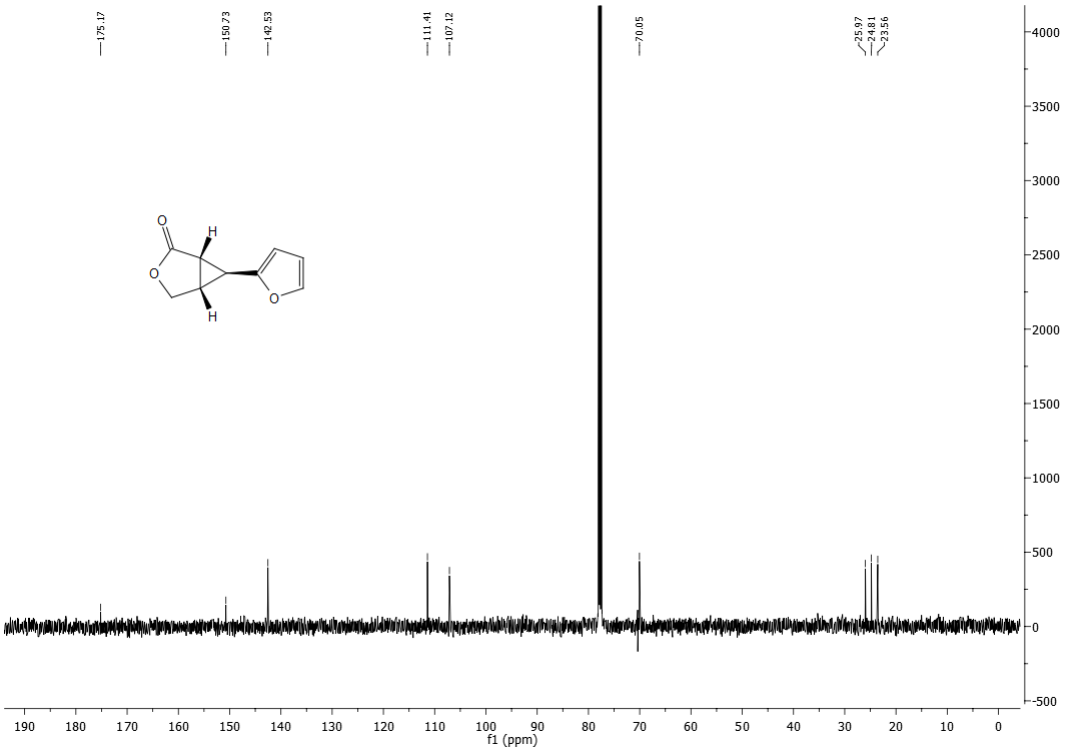
(1S,5R,6R)-6-(6-methoxynaphthalen-2-yl)-3-oxabicyclo[3.1.0]hexan-2-one (3j): 500 MHz ^{1}H spectrum and 126 MHz ^{13}C spectrum in $CDCl_3$ solvent



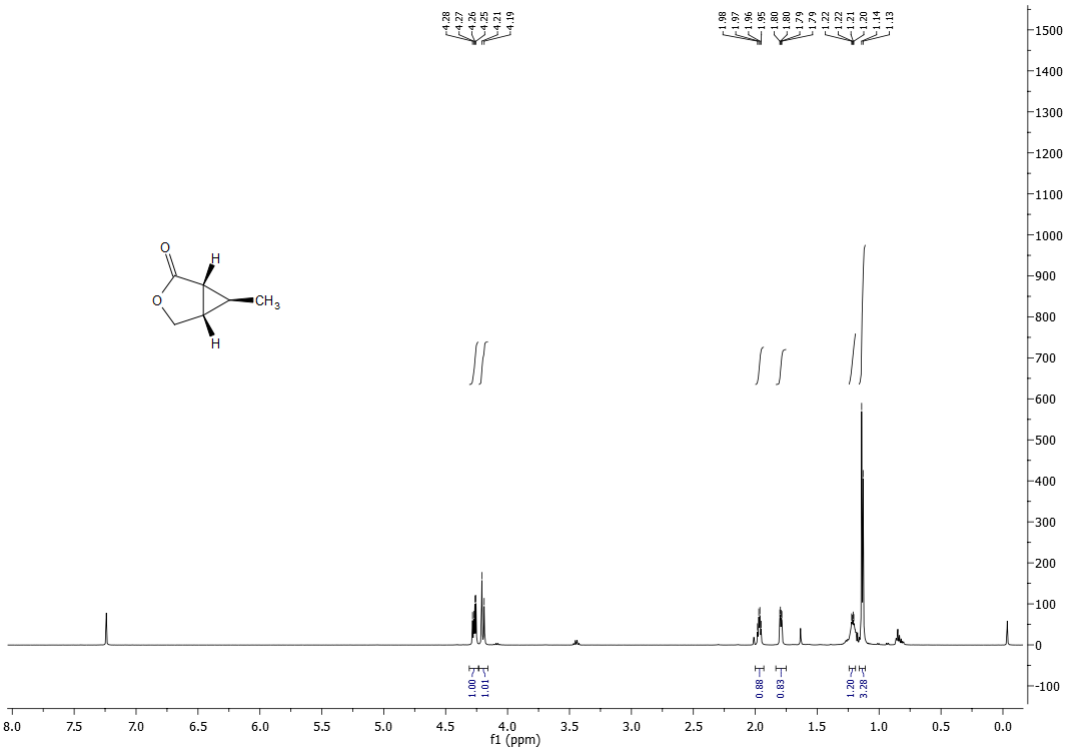


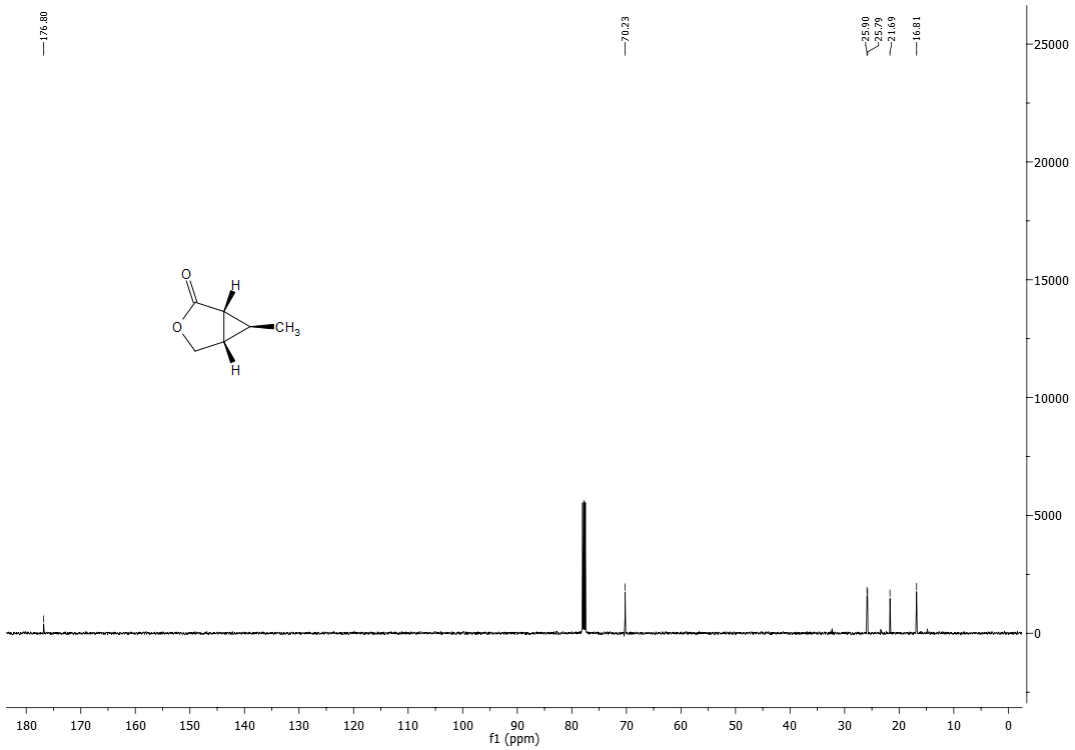
(1S,5S,6S)-6-(furan-2-yl)-3-oxabicyclo[3.1.0]hexan-2-one (2k): 500 MHz ^{1}H spectrum and 126 MHz ^{13}C spectrum in $CDCl_3$ solvent



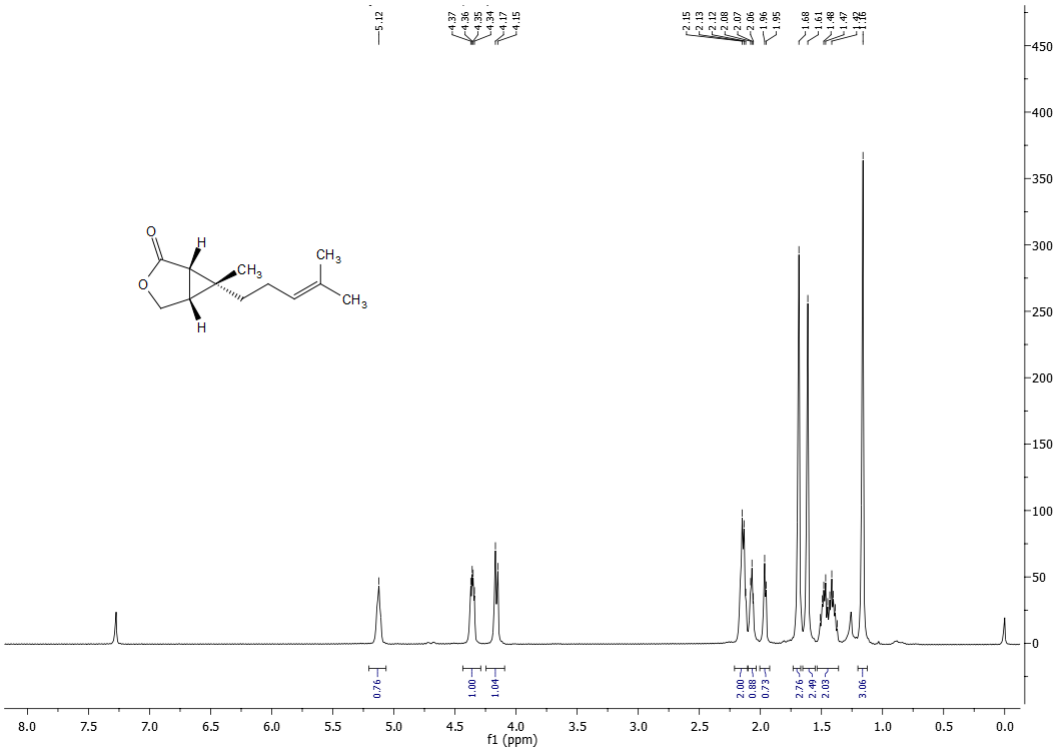


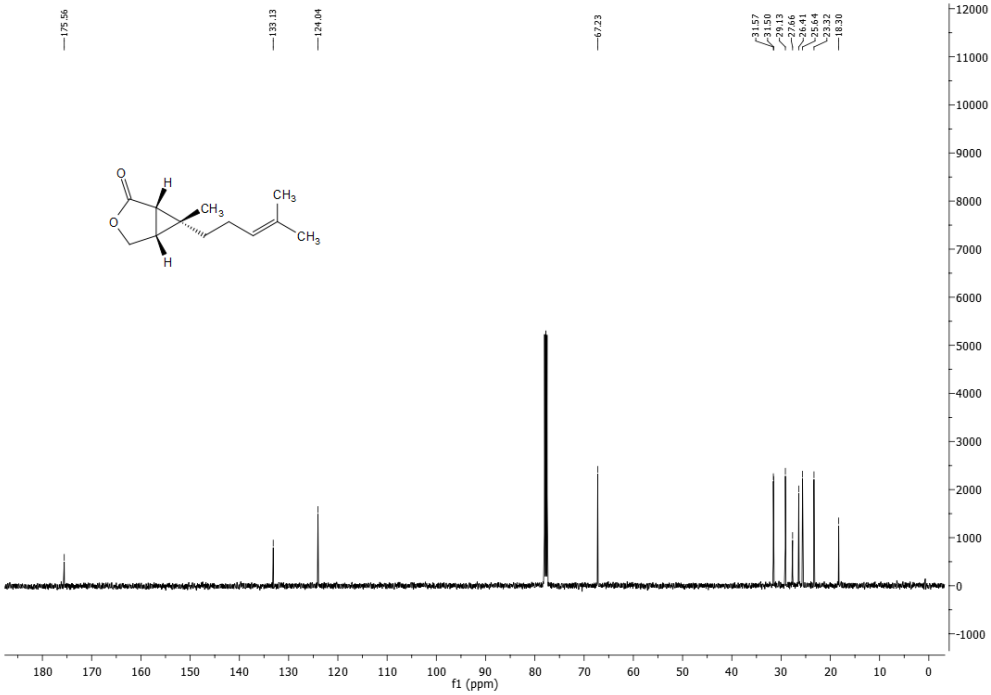
(1R,5S,6S)-6-methyl-3-oxabicyclo[3.1.0]hexan-2-one (2l): 500 MHz ^{1}H spectrum and 126 MHz ^{13}C spectrum in $CDCl_3$ solvent



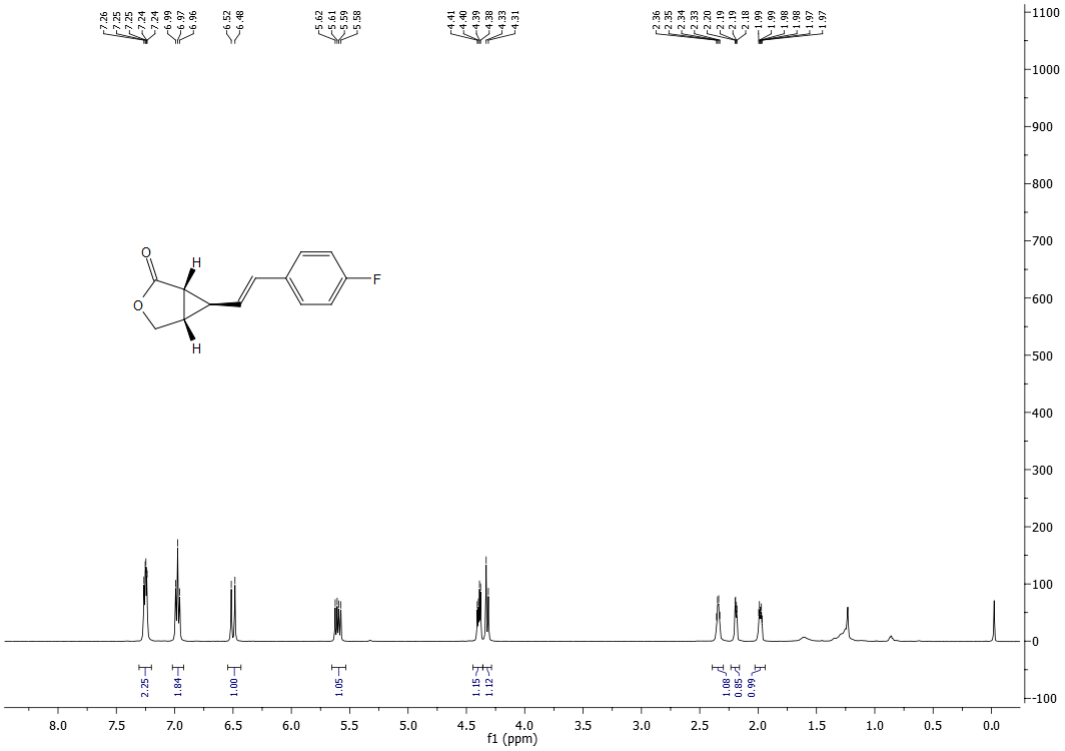


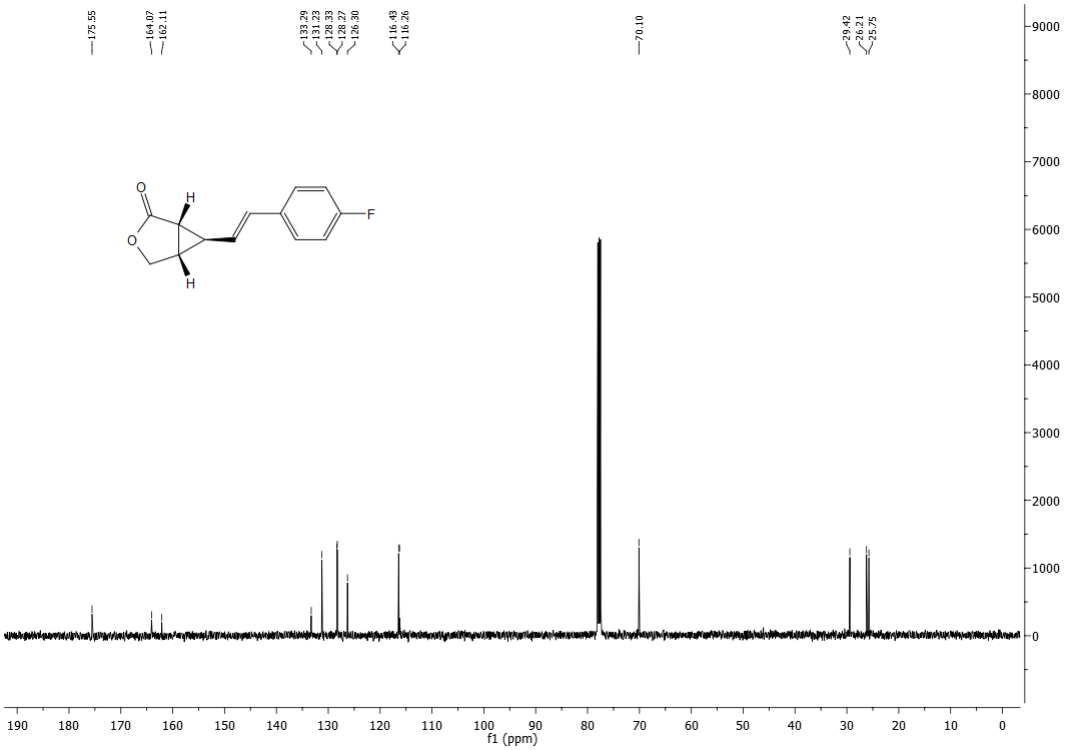
(1S,5R,6S)-6-methyl-6-(4-methylpent-3-en-1-yl)-3-oxabicyclo[3.1.0]hexan-2-one (2m): 500 MHz ^{1}H spectrum and 126 MHz ^{13}C spectrum in $CDCl_3$ solvent

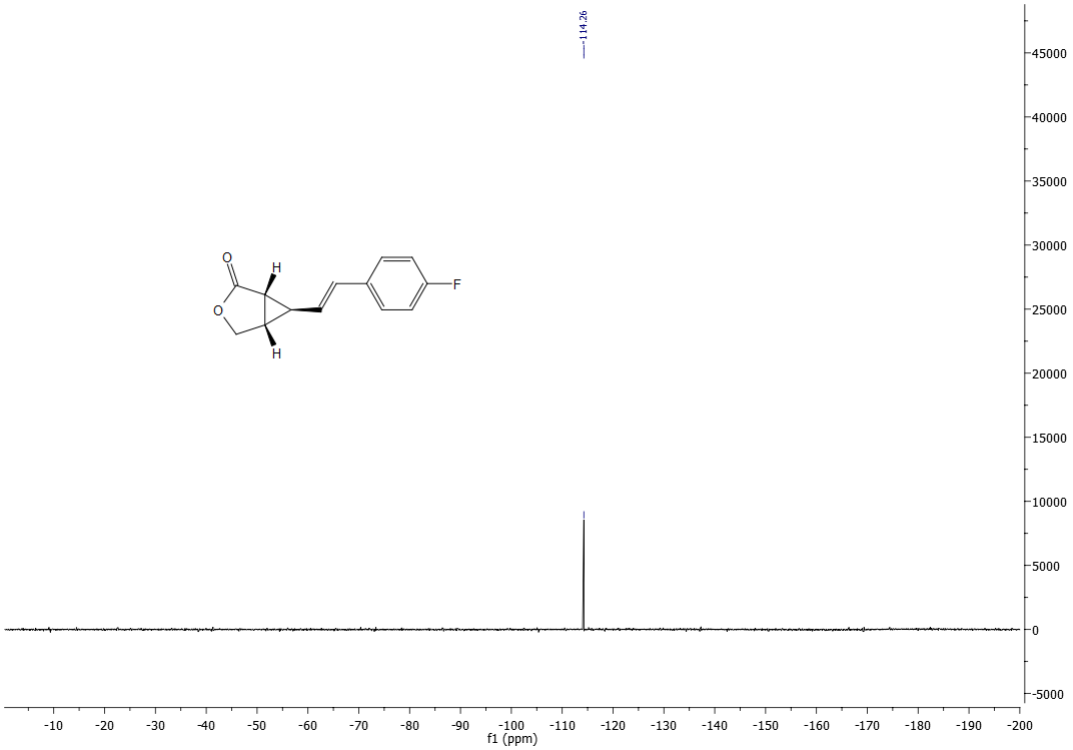




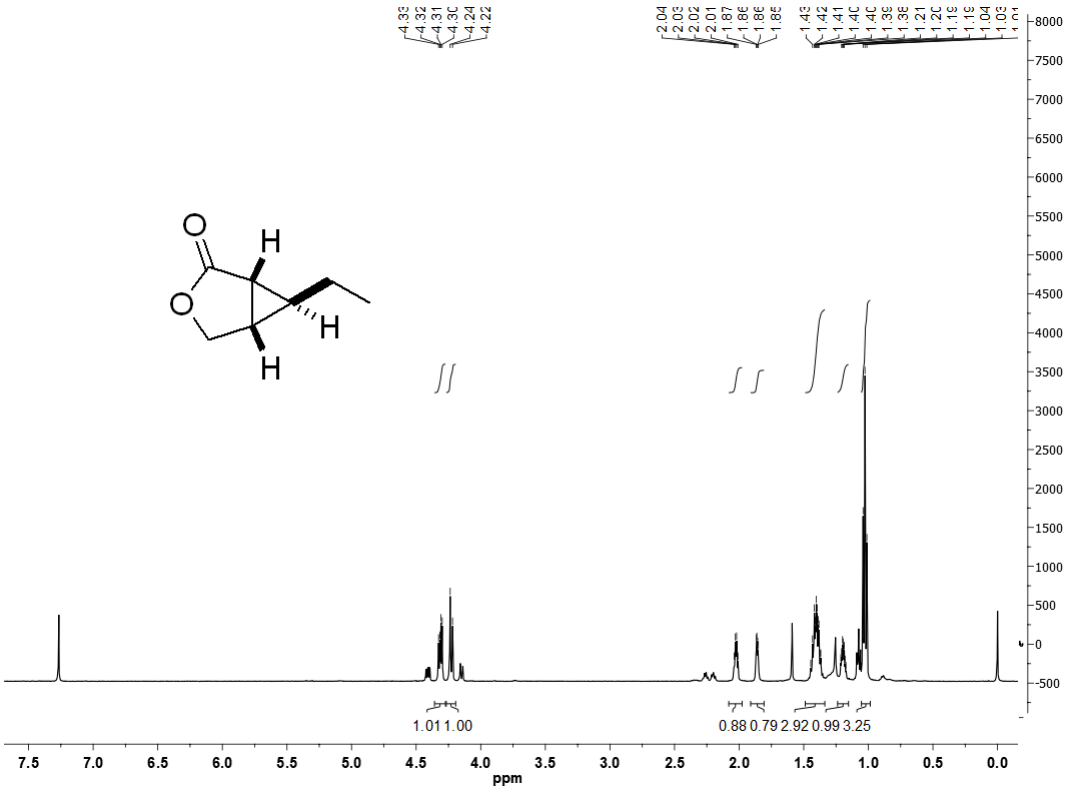
(1R,5S,6S)-6-((E)-4-fluorostyryl)-3-oxabicyclo[3.1.0]hexan-2-one (2n): 500 MHz ^{1}H spectrum, 126 MHz ^{13}C spectrum and 375 MHz ^{19}F spectrum in $CDCl_3$ solvent

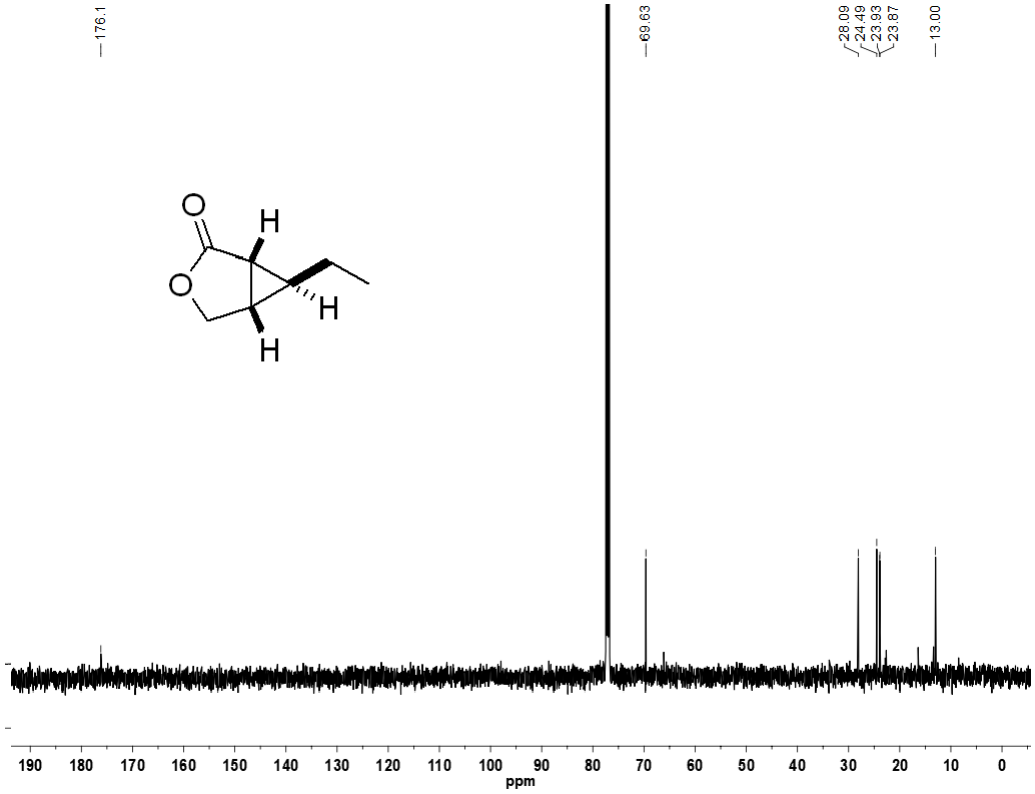




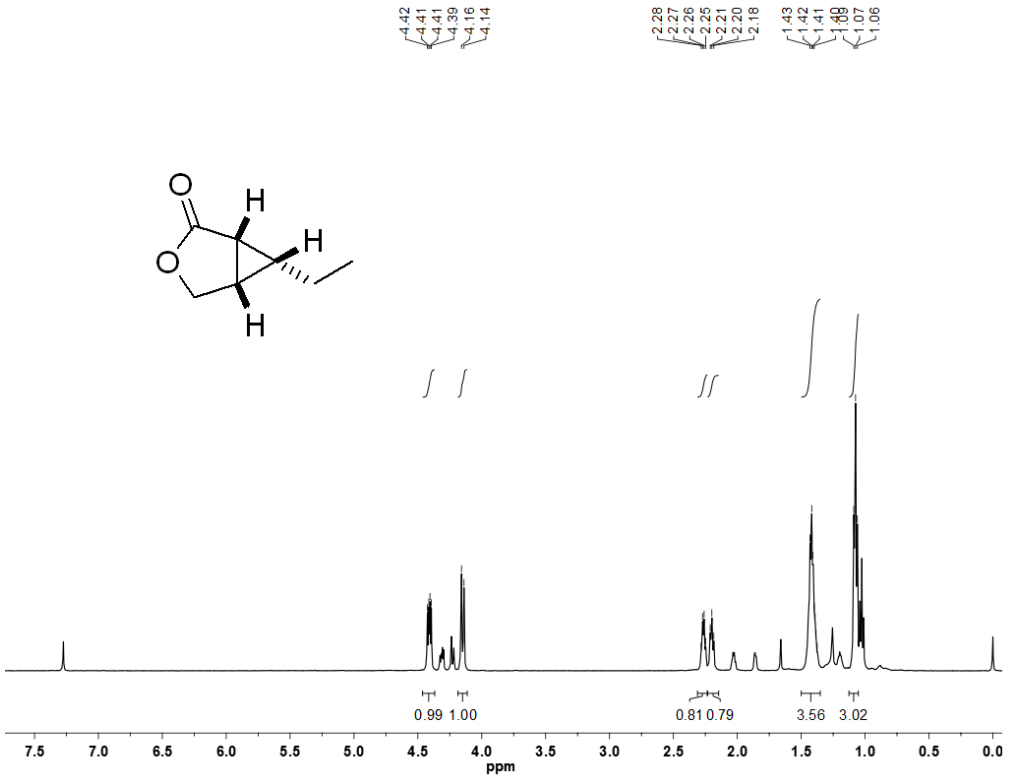

-114.26
O
H
O
H
F
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
-10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

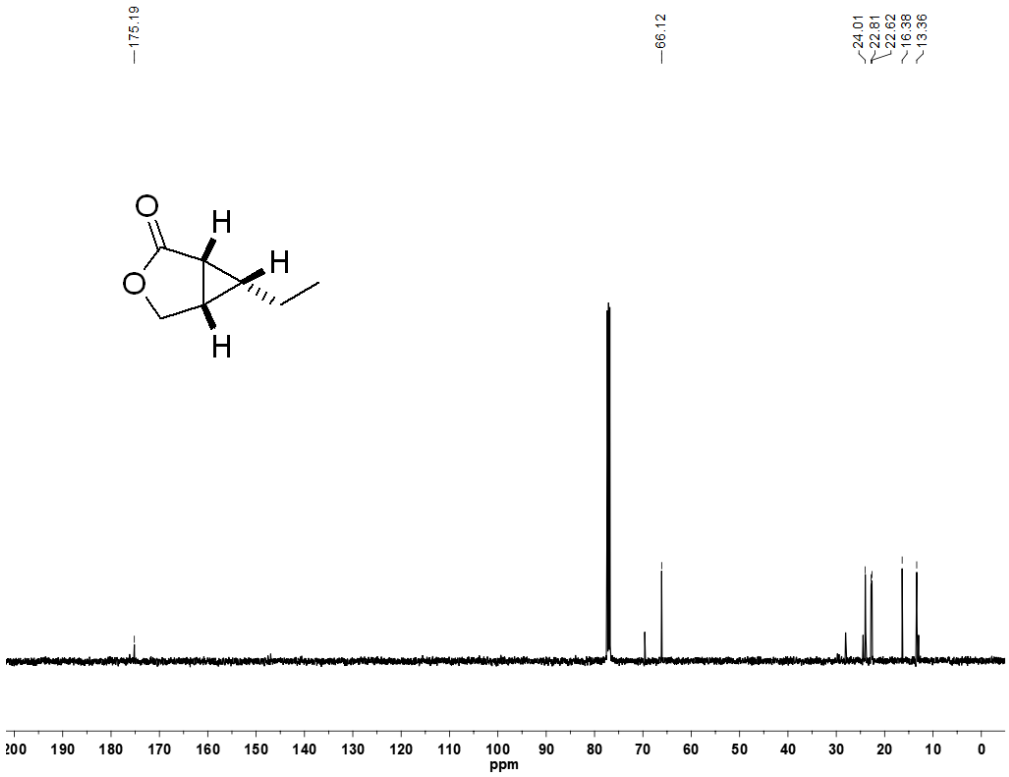
(1R,5S,6S)-6-ethyl-3-oxabicyclo[3.1.0]hexan-2-one (2o) – Diastereomer 1 (9:1 mixture with Diastereomer 2): 500 MHz ^{1}H spectrum and 126 MHz ^{13}C spectrum in $CDCl_3$ solvent



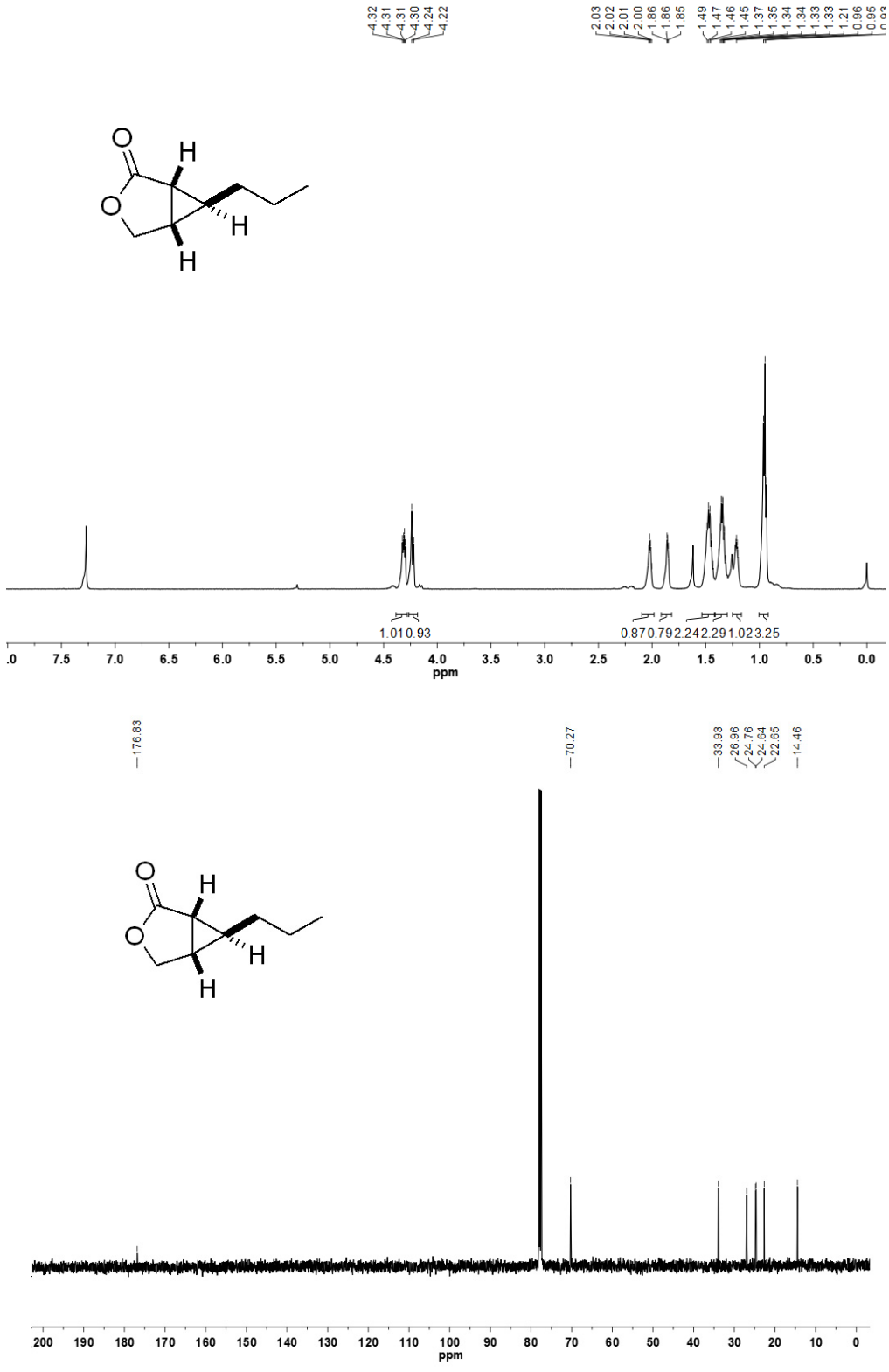


(1R,5S,6R)-6-ethyl-3-oxabicyclo[3.1.0]hexan-2-one (2o) – Diastereomer 2 (8:2 mixture with Diastereomer 1): 500 MHz ^{1}H spectrum and 126 MHz ^{13}C spectrum in $CDCl_3$ solvent

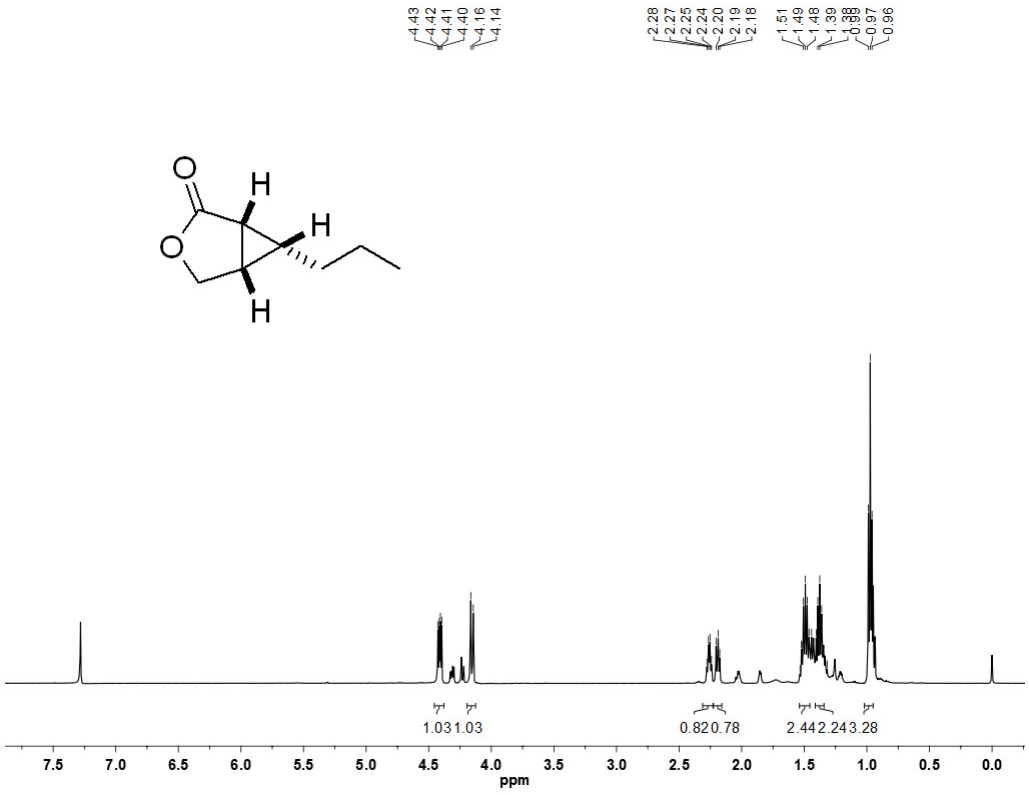


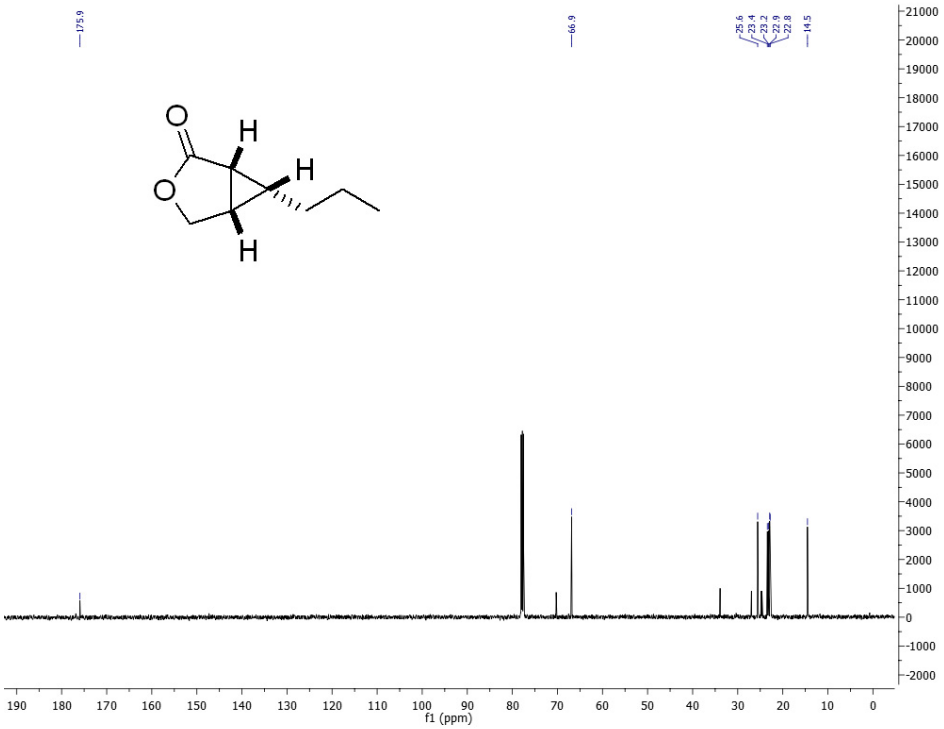


(1R,5S,6S)-6-propyl-3-oxabicyclo[3.1.0]hexan-2-one (2p) - Diastereomer 1 (95:5 mixture with Diastereomer 2): 500 MHz ^{1}H spectrum and 126 MHz ^{13}C spectrum in $CDCl_3$ solvent

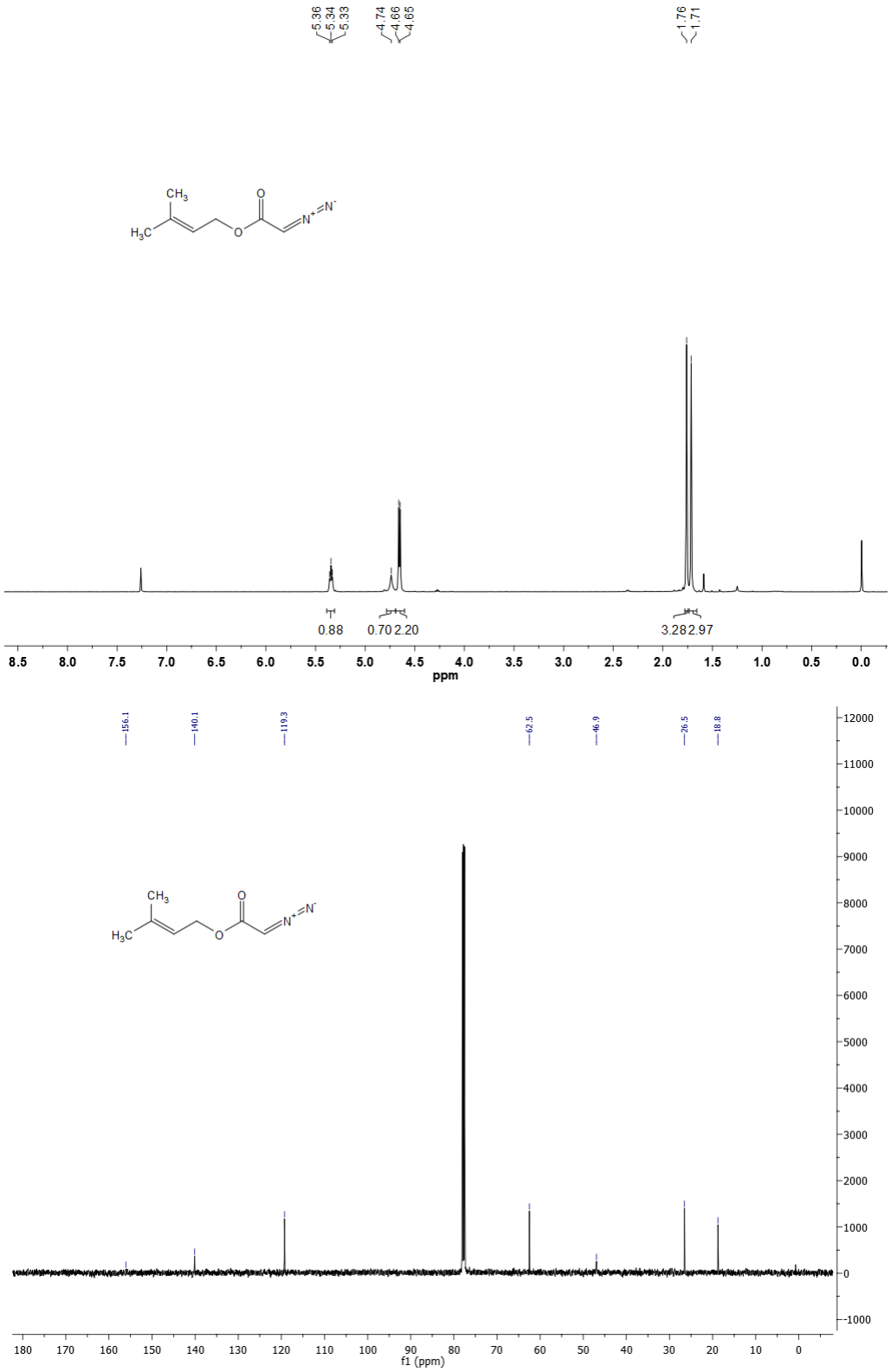


(1R,5S,6R)-6-propyl-3-oxabicyclo[3.1.0]hexan-2-one (2p) - Diastereomer 2 (8:2 mixture with 20% Diastereomer 1): 500 MHz ^{1}H spectrum and 126 MHz ^{13}C spectrum in $CDCl_3$ solvent

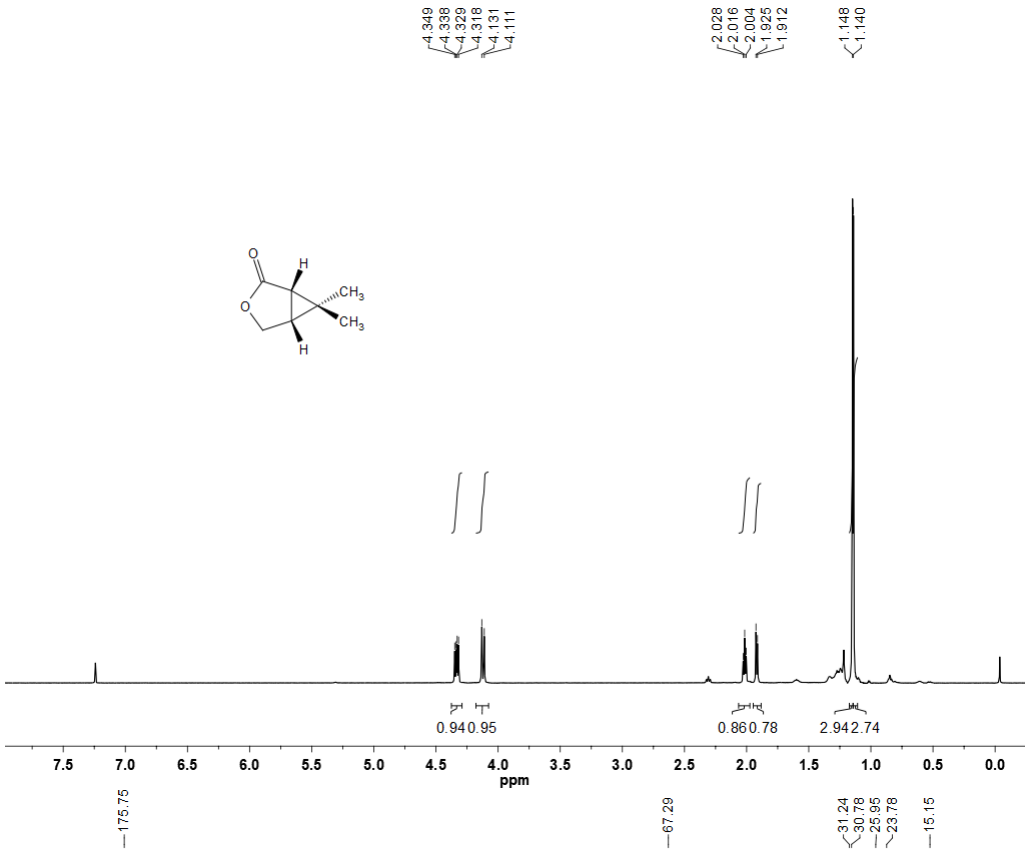


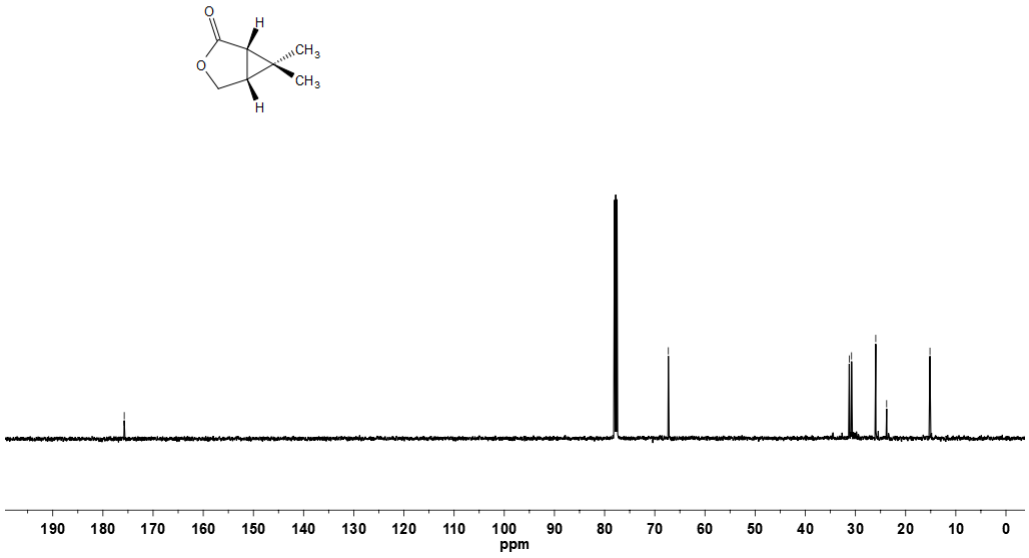

175.9
66.9
25.6
23.4
23.2
22.9
22.8
14.5
O
O
H
H
H
f1 (ppm)

3-methylbut-2-en-1-yl 2-diazoacetate (4): 500 MHz ^{1}H spectrum and 126 MHz ^{13}C spectrum in $CDCl_3$ solvent

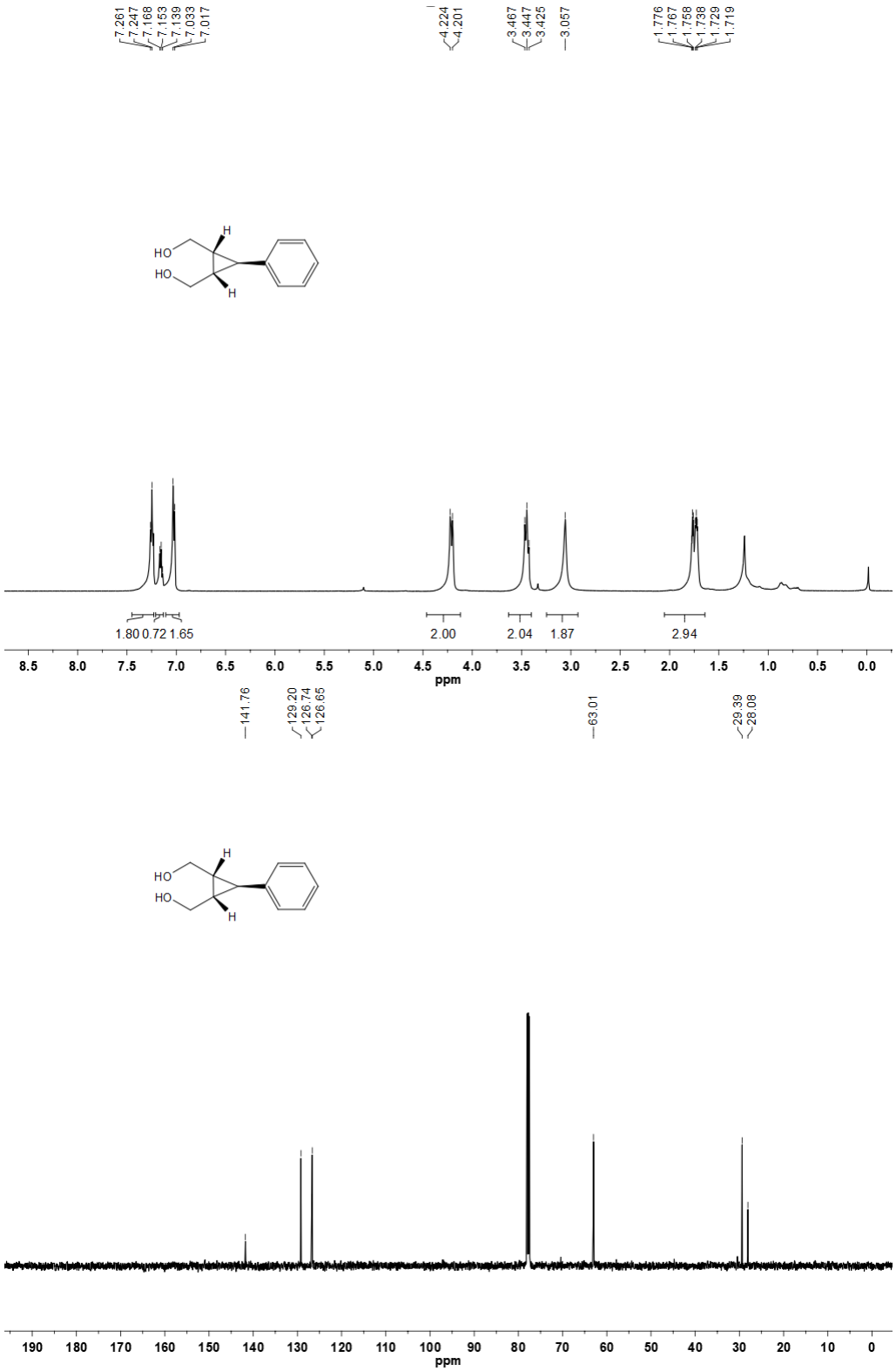


(1S,5R)-6,6-dimethyl-3-oxabicyclo[3.1.0]hexan-2-one (5): 500 MHz ^{1}H spectrum and 126 MHz ^{13}C spectrum in $CDCl_3$ solvent

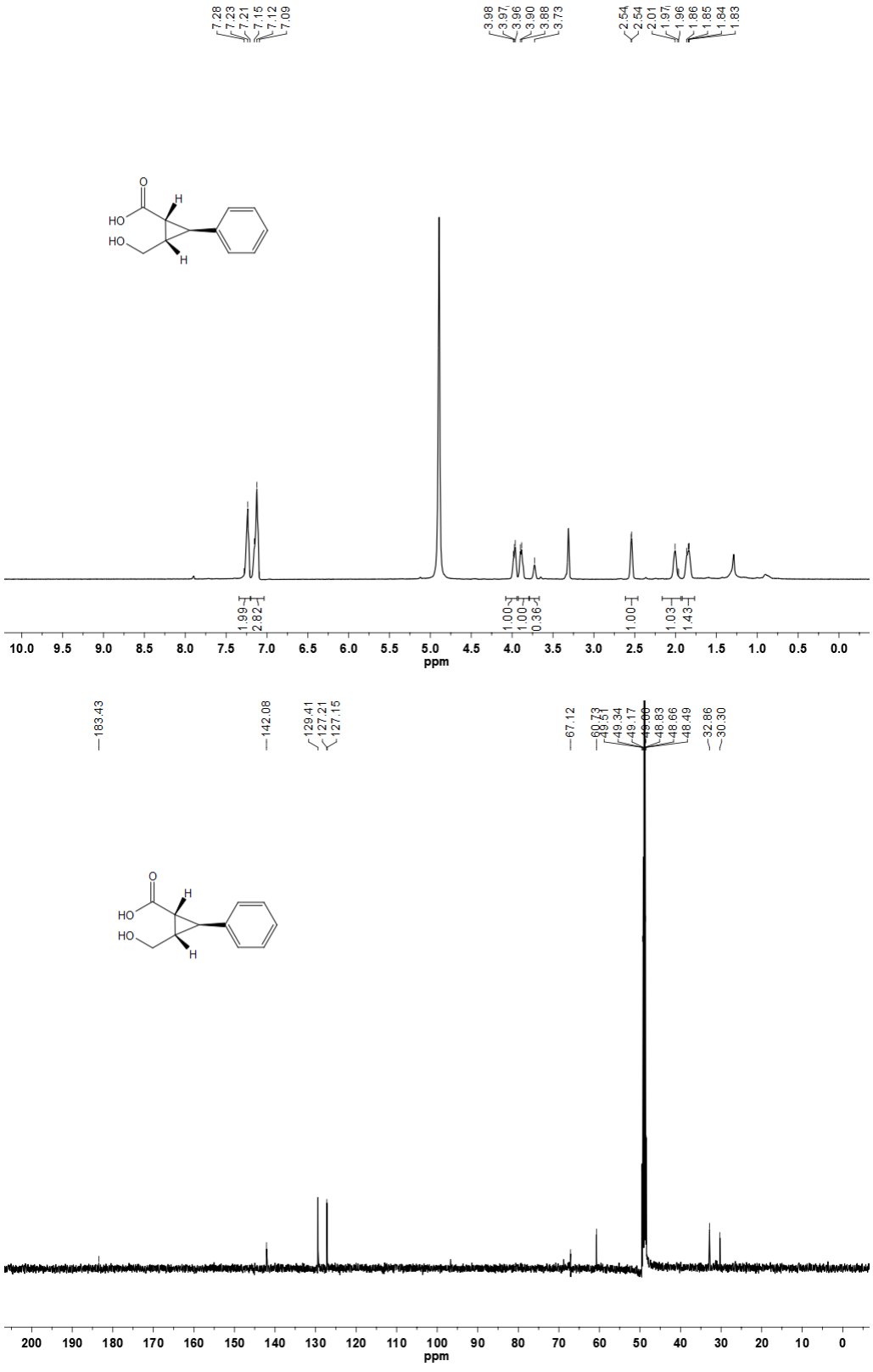




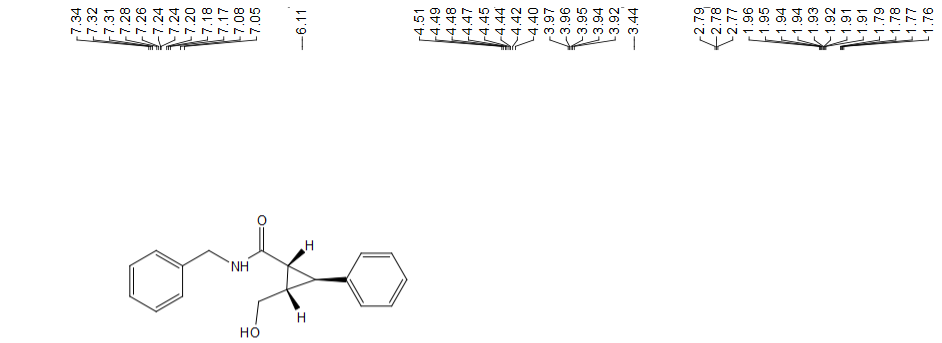
((1R,2S,3s)-3-phenylcyclopropane-1,2-diyl)dimethanol (6): 500 MHz ^{1}H spectrum and 126 MHz ^{13}C spectrum in $CDCl_3$ solvent

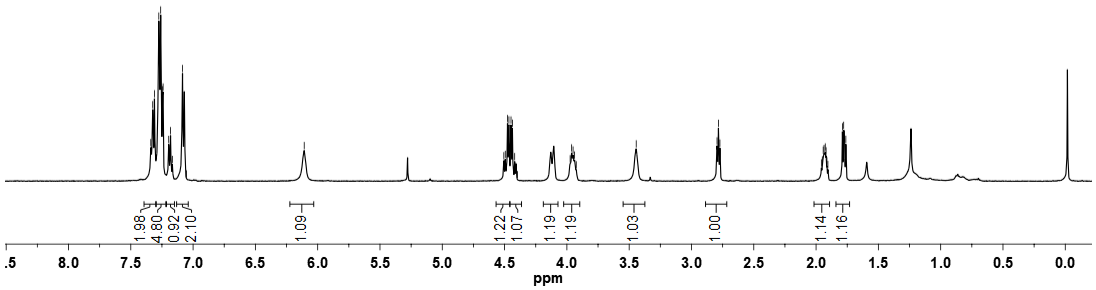


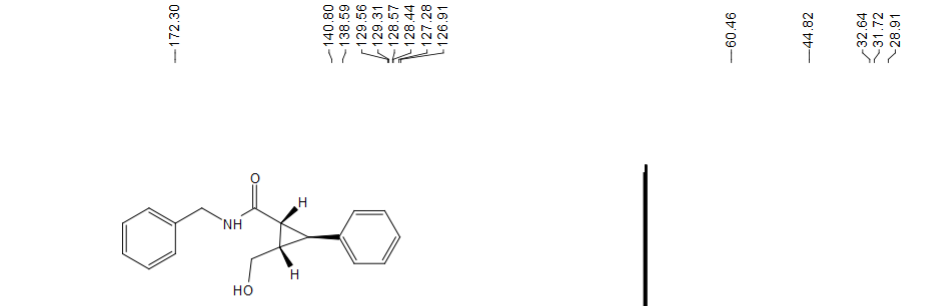
(1R,2S,3S)-2-(hydroxymethyl)-3-phenylcyclopropane-1-carboxylic acid (7): 500 MHz ^{1}H spectrum and 126 MHz ^{13}C spectrum in CD_3OD solvent

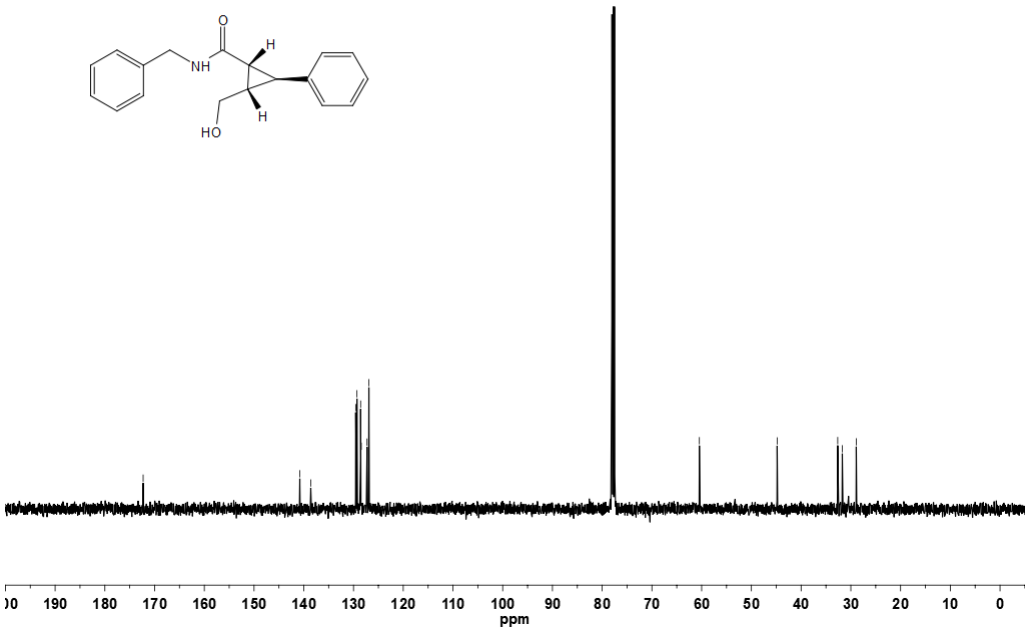


(1R,2S,3S)-*N*-benzyl-2-(hydroxymethyl)-3-phenylcyclopropane-1-carboxamide (8): 500 MHz ^{1}H spectrum and 126 MHz ^{13}C spectrum in $CDCl_3$ solvent









(1S,6R,7S)-7-phenyl-4-oxa-2-azabicyclo[4.1.0]heptan-3-one (9): 500 MHz ^{1}H spectrum and 126 MHz ^{13}C spectrum in $CDCl_3$ solvent