Supporting Information

Diastereoselective Organocatalytic Addition of α-Angelica Lactone to β-Halo-α-Ketoesters

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Optimization of the addition of α-angelica lactone to β-halo-α-ketoester:

A 1 dram vial was charged sequentially with 1,3,5-trimethoxybenzene (internal standard, 0.1 mmol), β-halo-α-ketoester[1] (0.1 mmol, 1.0 equiv), and solvent (1.0mL). The α-angelica lactone (0.2 mmol, 2.0 equiv) was then added. The reaction was stirred at room temperature for one min and the catalyst was added in one portion. The reaction was stirred at room temperature for the length of the reaction, then concentrated *in vacuo*. The ^{1}H NMR spectra of unpurified reaction mixtures were used to determine NMR yields and dr values. ***(Note 1)***

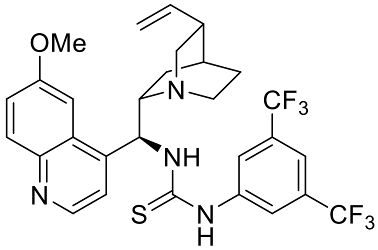
Commentary: Initially, a screen of bases in THF (Table S1, entries 1-5) demonstrated that quinidine was the best base for the reaction. Then, by studying the reaction in different solvents (Table S1, entries 5-10), we found 2-MeTHF to be optimal. We observed that there was no improvement when the reaction time was extended to 24 h, either at -20 ºC (Table S1, entry 11) or room temperature (Table S1, entry 12). Although a low level of enantioselectivity (16% ee) was observed with QN-TU (Table S2, entry 5), no enantioselectivity (0% ee) was observed with quinidine (Table S2, entry 6). In cases where the reactions worked, no minor diastereomers were observed.***(Note 2)*** Optimized conditions are italicized.

Table S1. Base and Solvent Screen.

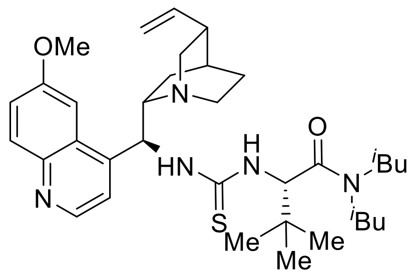
Entry	**Conditions**	**% Yield (^{1}H NMR)**	**dr**
1	10 mol % KO^{t}Bu, THF, 6 h, rt	0	-
2	10 mol % DBU, THF, 6 h, rt	0	-
3	10 mol % TEA, THF, 6 h, rt	Trace product	-
4	10 mol % TMG, THF, 6 h, rt	Trace product	-
5	10 mol % quinidine, THF, 6 h, rt	61	>20:1
6	10 mol % quinidine, EA, 6 h, rt	66	>20:1
7	10 mol % quinidine, DMSO, 6 h, rt	23	n.d.
8	10 mol % quinidine, TBME, 6 h, rt	45	>20:1
9	10 mol % quinidine, Et_2O, 6 h, rt	46	>20:1
10	*10 mol % quinidine, 2-MeTHF, 6 h, rt*	*91*	*>20:1*
11	10 mol % quinidine, 2-MeTHF, 24 h, -20 ºC	43	>20:1
12	10 mol % quinidine, 2-MeTHF, 24 h, rt	53	>20:1

Note 1. We found that the reaction gives a higher NMR yield (70-80%, at least in the parent case) than the isolated yield, and after repeated tries we concluded that the products are not completely stable to silica. This conclusion was supported by the fact that new decomposition products can be observed coming off the column.

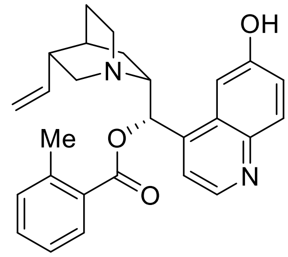
Note 2. In general, we started by looking in the crude NMR spectra to see if anything that could be a diastereomer could be identified. Some cases were clearer than others. The most definitive method that we found to identify diastereomers or γ-addition products was to flash the crude material and then flush the column with x+10% more polar solvent system (where x was the gradient that allowed the product to elute cleanly) in an EA/hexanes gradient for >10 fractions. We then concentrated all fractions on each side of the desired product (more polar and less polar) and if we found anything (^{1}H NMR analysis), we went back to the crude spectra and calculated the dr. It is possible that a minor diastereomer or γ-addition product for some cases might be not isolable due to instability (see Note 1), but this procedure was the best readout feasible with the available data.



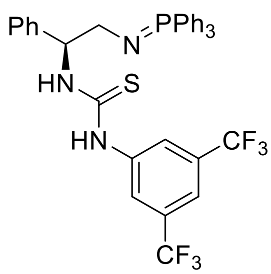
QN-1



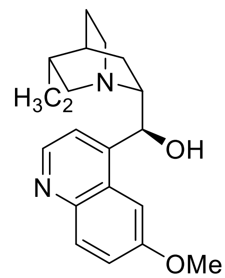
QN-2



QD-1



Ph-Dixon



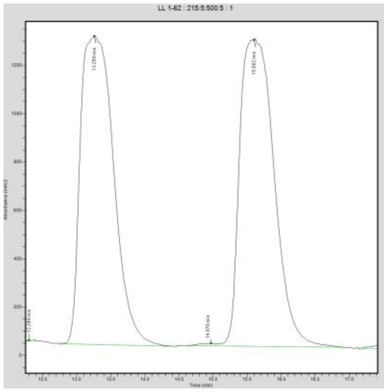
quinidine

Table S2. Enantioselectivity data for chiral catalysts.

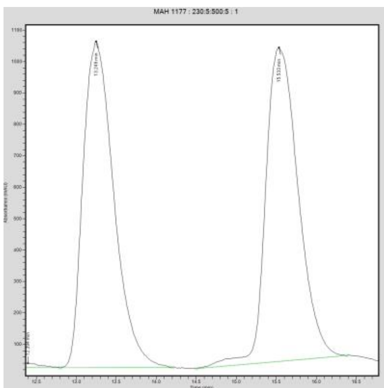
Entry	Conditions	er
1	10 mol % **QN-1**, THF, 21 h, rt	58.0:42.0
2	10 mol % **QN-2**, THF, 6 h, rt	53.5:46.5
3	10 mol % **QD-1**, 2-MeTHF, 6 h, rt	54.0:42.0
4	10 mol % **Ph-Dixon**, THF, 19 h, rt	52.5:47.5
5	10 mol % **Ph-Dixon**, THF, 16 h, -40 ºC	55.5:44.5
6	10 mol % quinidine, THF, 6 h, rt	50.5:49.5

HPLC traces:

With TEA

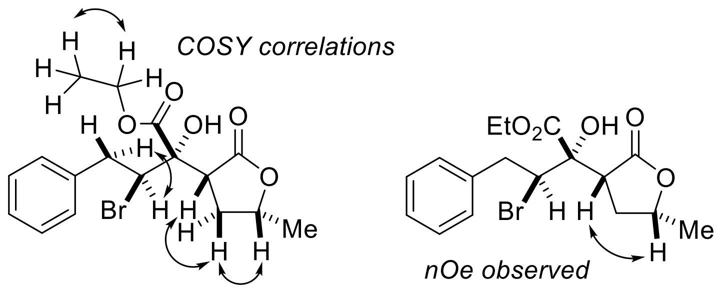


With quinidine:



	Retention time (min)	Peak Area	% Area
With TEA	13.3	43264208.8	49.3
	15.6	44507069.9	50.7
With quinidine	13.2	27679403.6	49.5
	15.5	28248692.7	50.5

Determination of relative configuration of 4a:

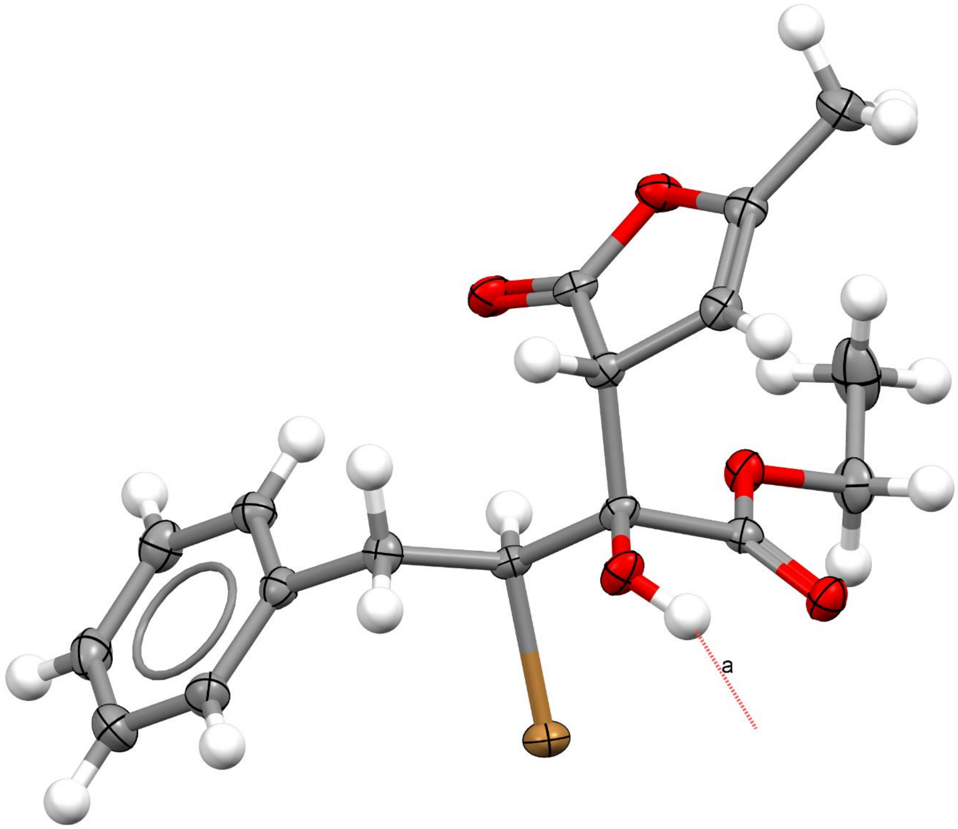


COSY and NOESY experiments were performed on **4a** (see pp. S45-S46) on a 600 MHz NMR spectrometer. COSY analysis allowed the assignment of protons in the 1D ^{1}H NMR spectrum. A characteristic NOE correlation was observed between the indicated protons (which appear at δ 3.77 and δ 4.57), which allowed them to be assigned as *syn* on the lactone.

References:

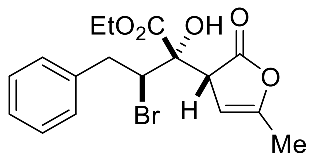
1. a) Steward, K. M., Corbett, M. T., Goodman, C. G., Johnson, J. S. *J. Am. Chem. Soc.* **2012**, *134*, 20197-20206. b) Corbett, M. T., Johnson, J. S. *Angew. Chem. Int. Ed.* **2014**, *53*, 255-259. c) Goodman, C. G., Johnson, J. S. *J. Am. Chem. Soc.* **2014**, *136*, 14698-14701. d) Goodman, C. G., Johnson, J. S. *J. Am. Chem. Soc.* **2015**, *137*, 122-125.

X-ray structure of 3a:

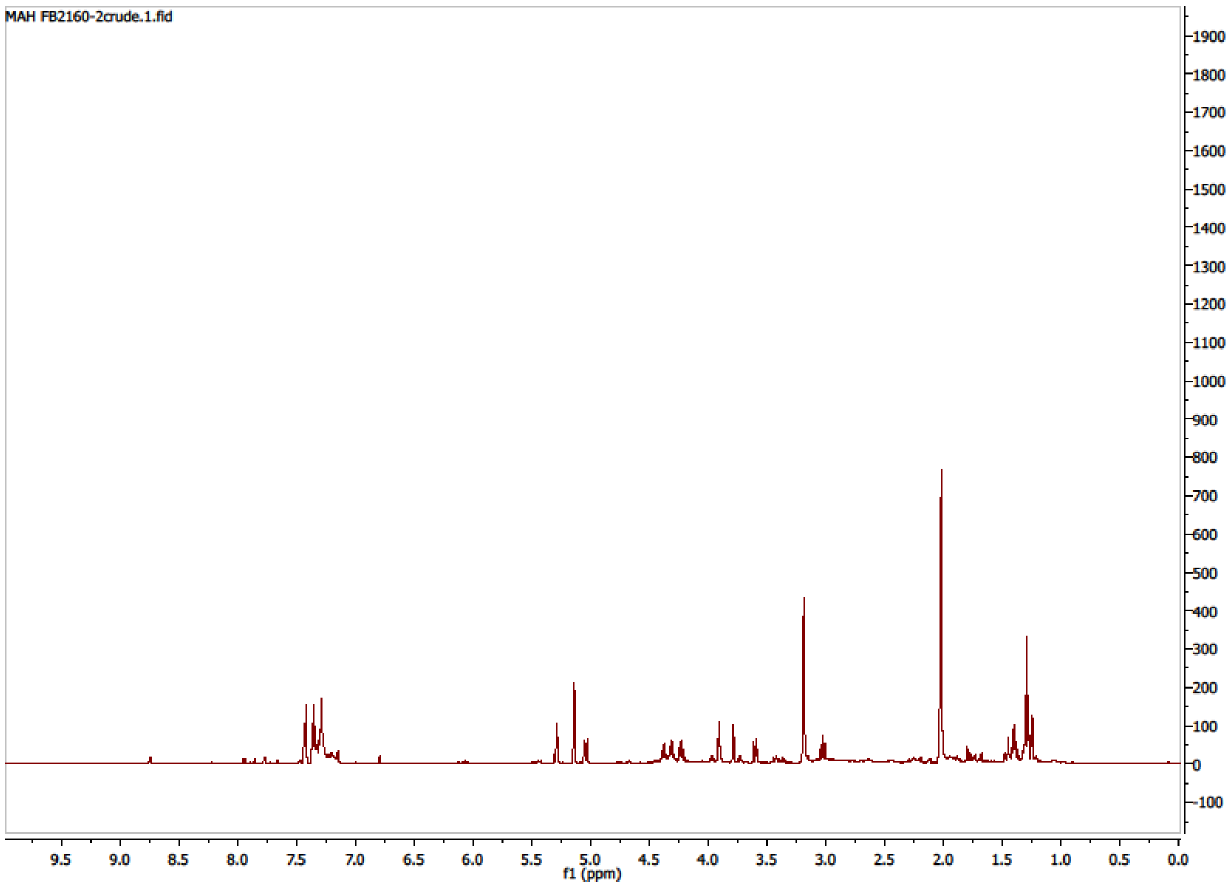


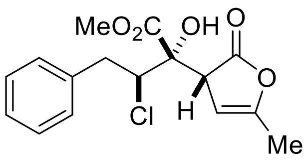
Thermal ellipsoid plot of compound **3a**. Ellipsoids drawn at 50% probability.

Crude ^{1}H NMR spectra:



3a

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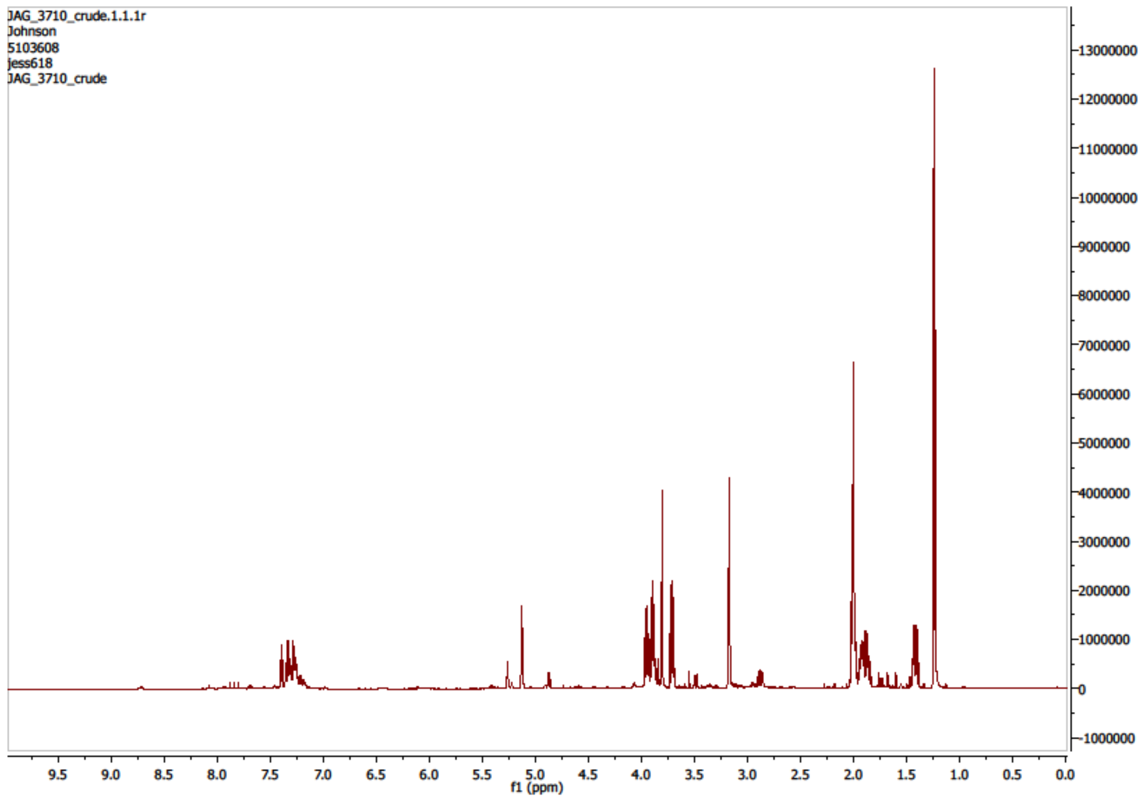
O
Cl
H
Me

3b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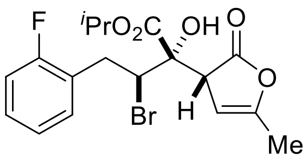
Johnson
5103608
jess618
JAG_3710_crude
f1 (ppm)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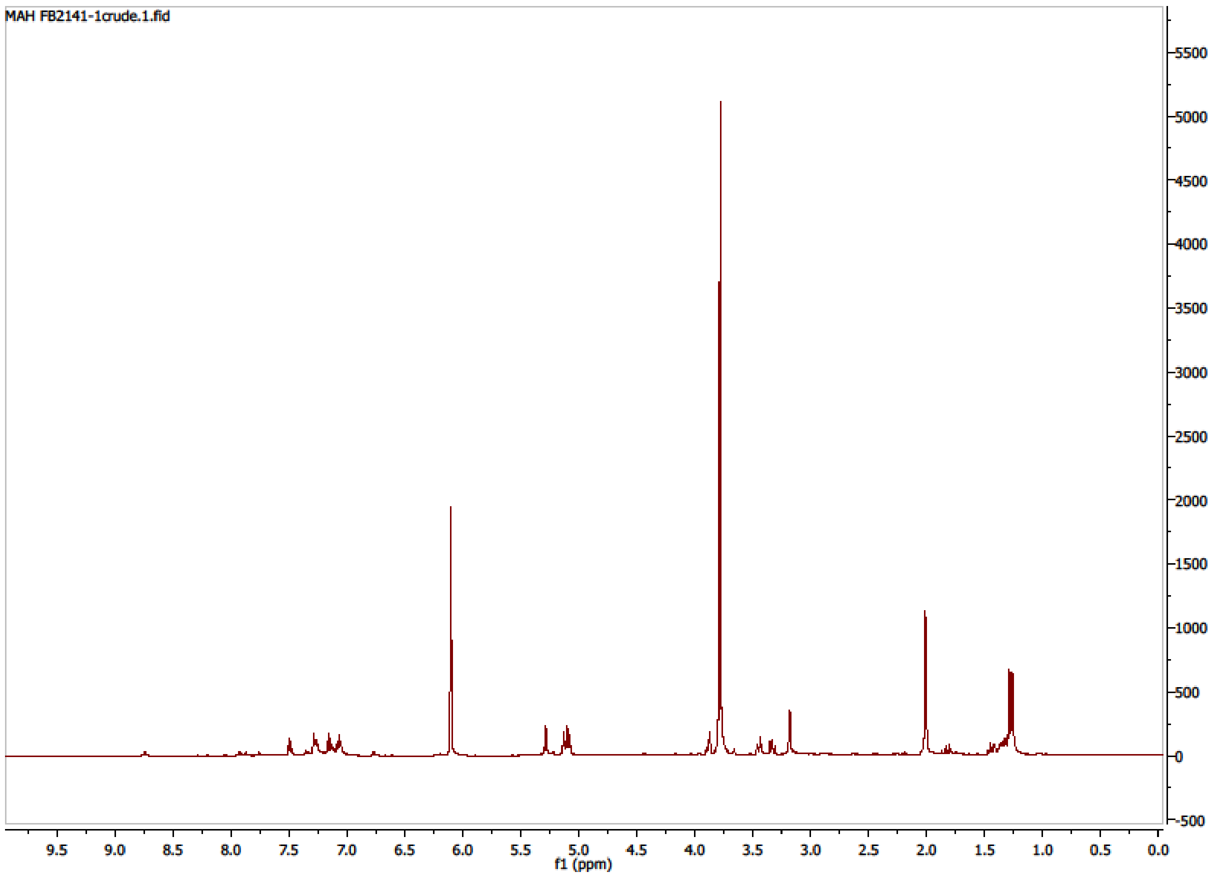
O
O
Br
H
Me

3c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4500
4000
3500
3000
2500
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1000
500
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9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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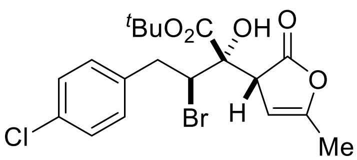
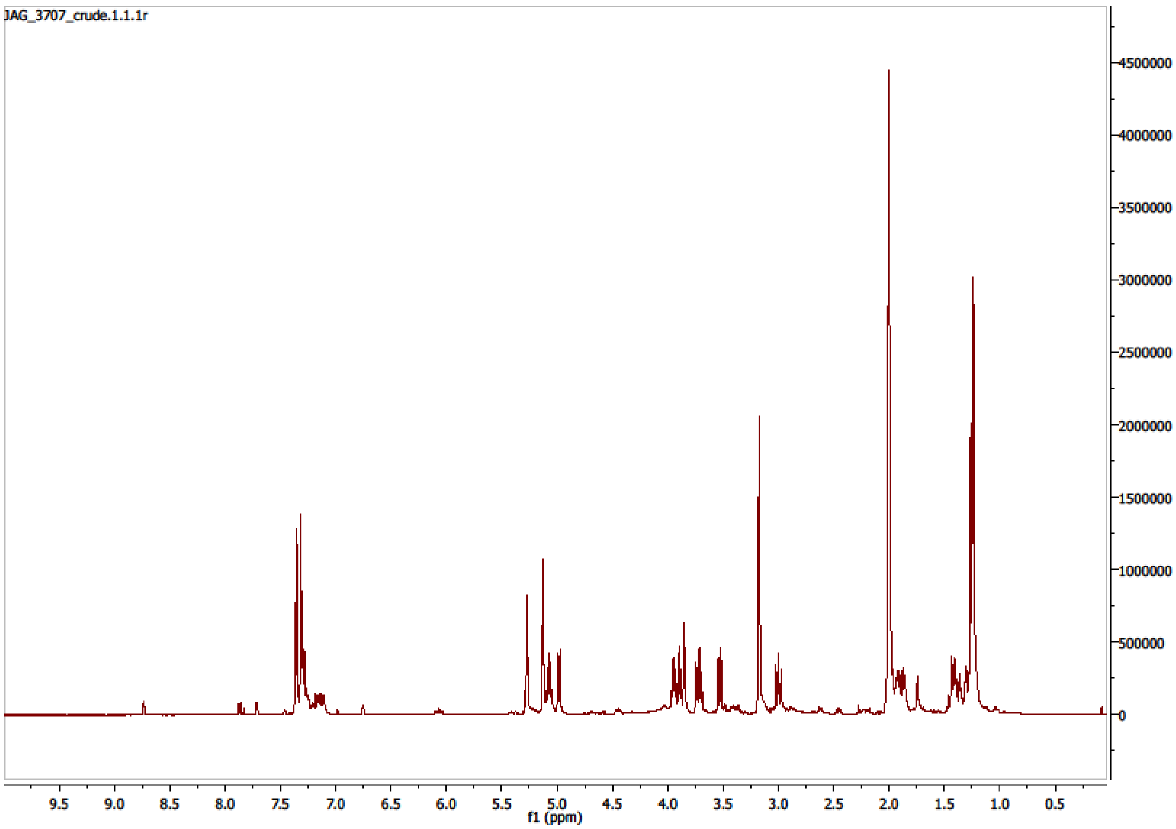
0.0
f1 (ppm)



3d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2000000
1500000
1000000
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0
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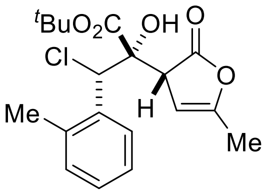
f1 (ppm)



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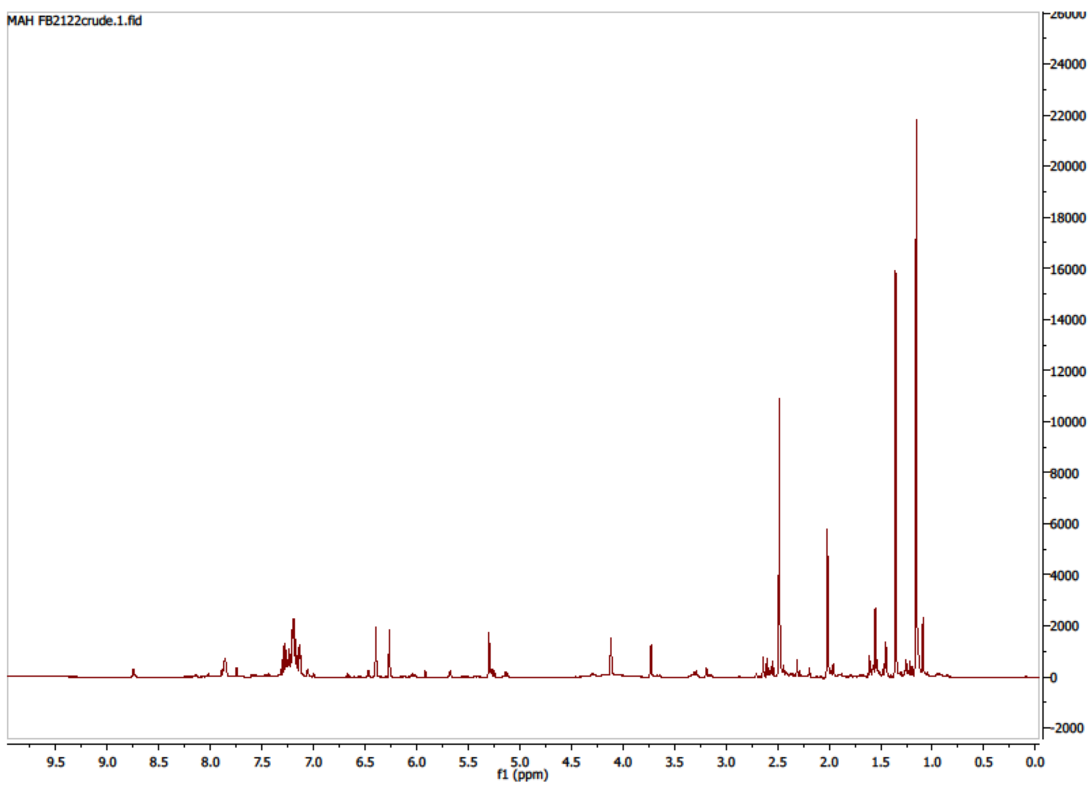

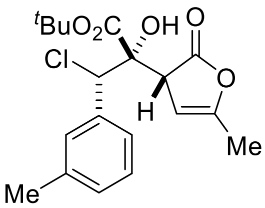

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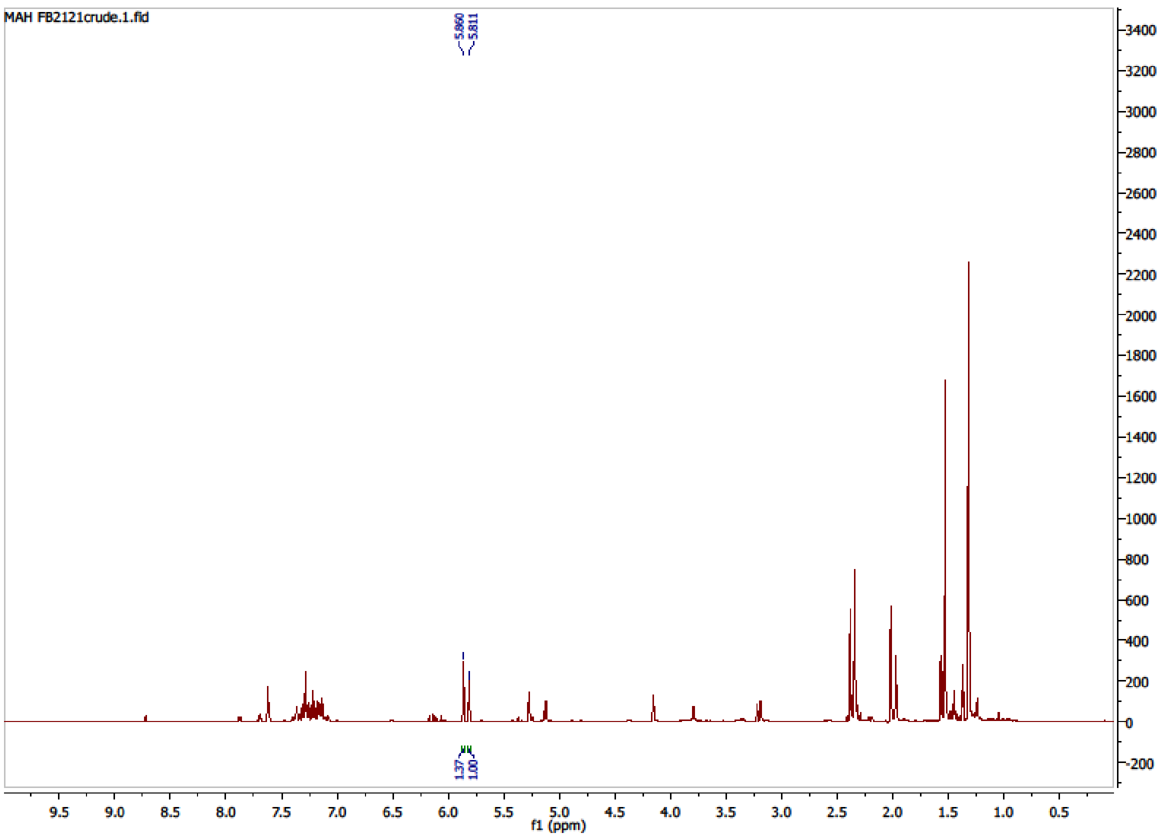
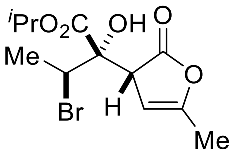
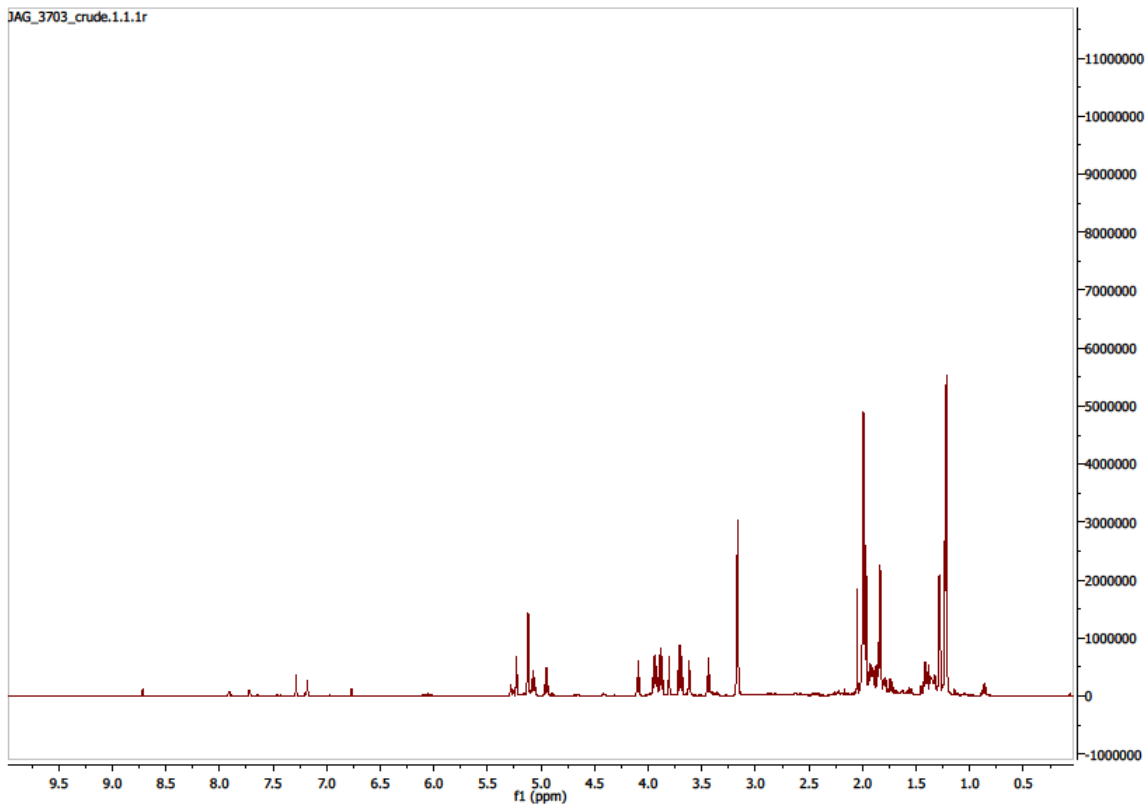
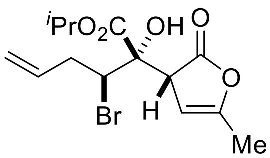


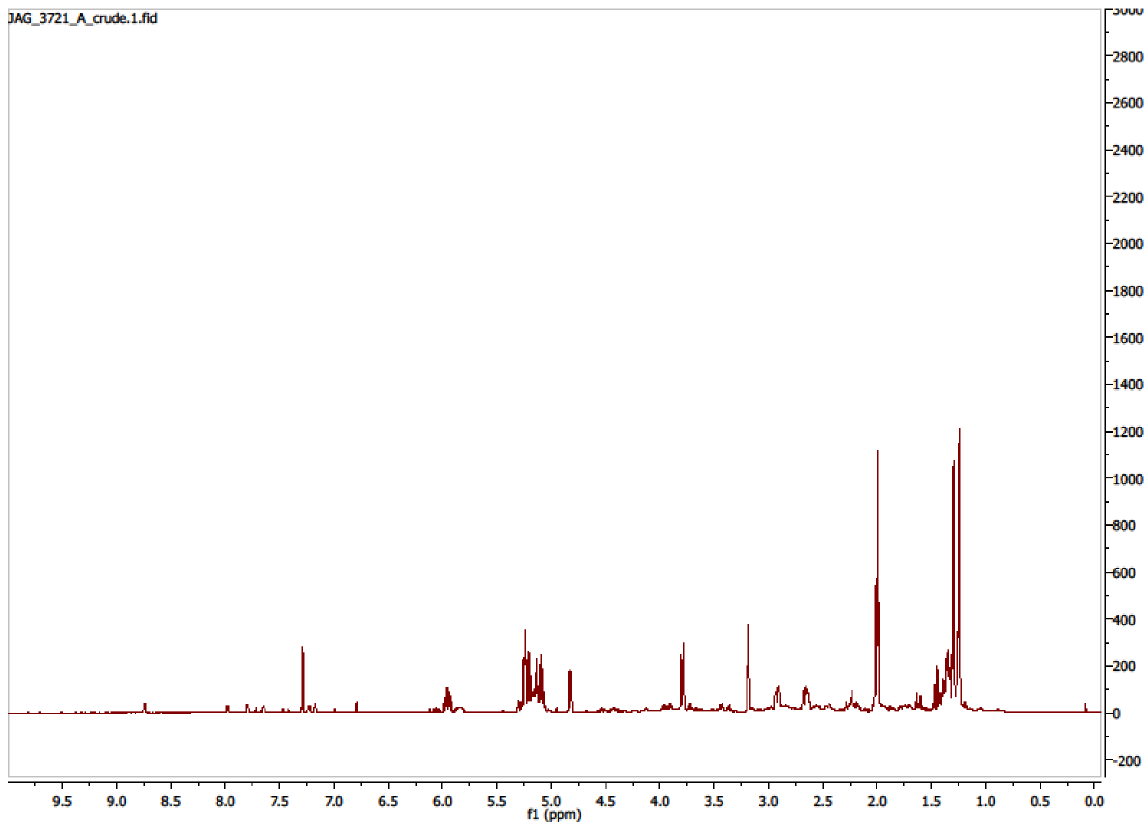


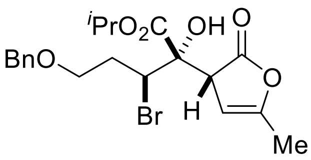
3g



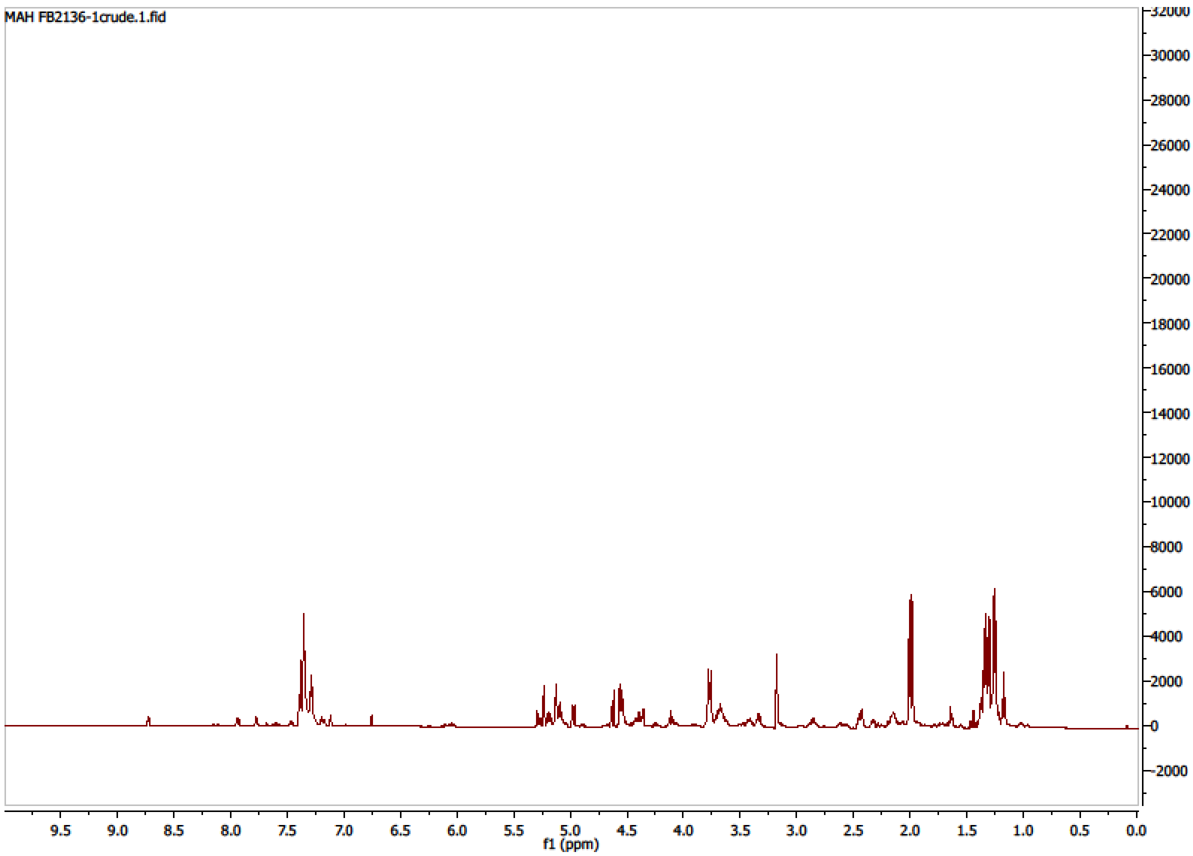


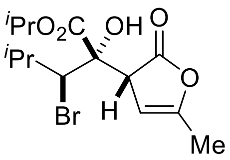
3h





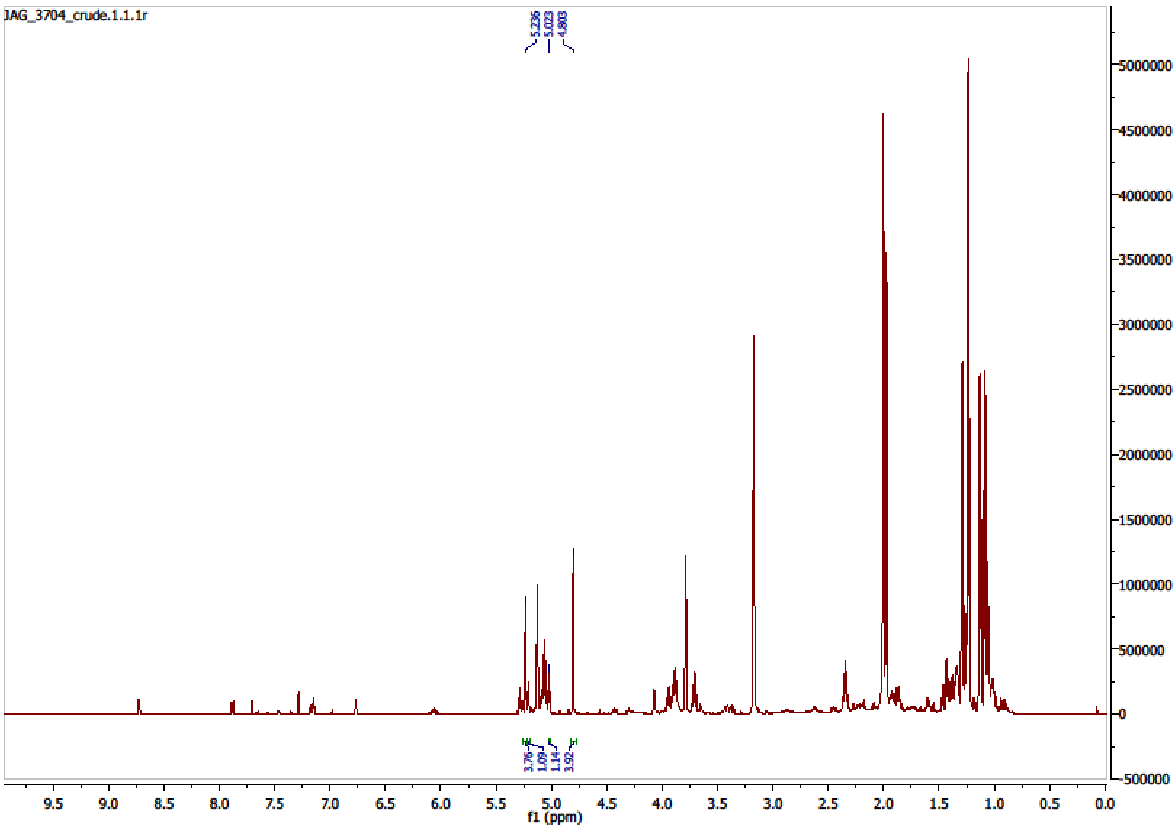
3i





ⁱPrO2C
OH
O
ⁱPr
O
Br
H
Me

3j



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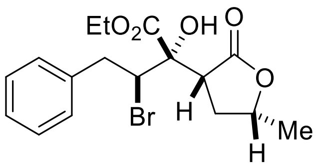
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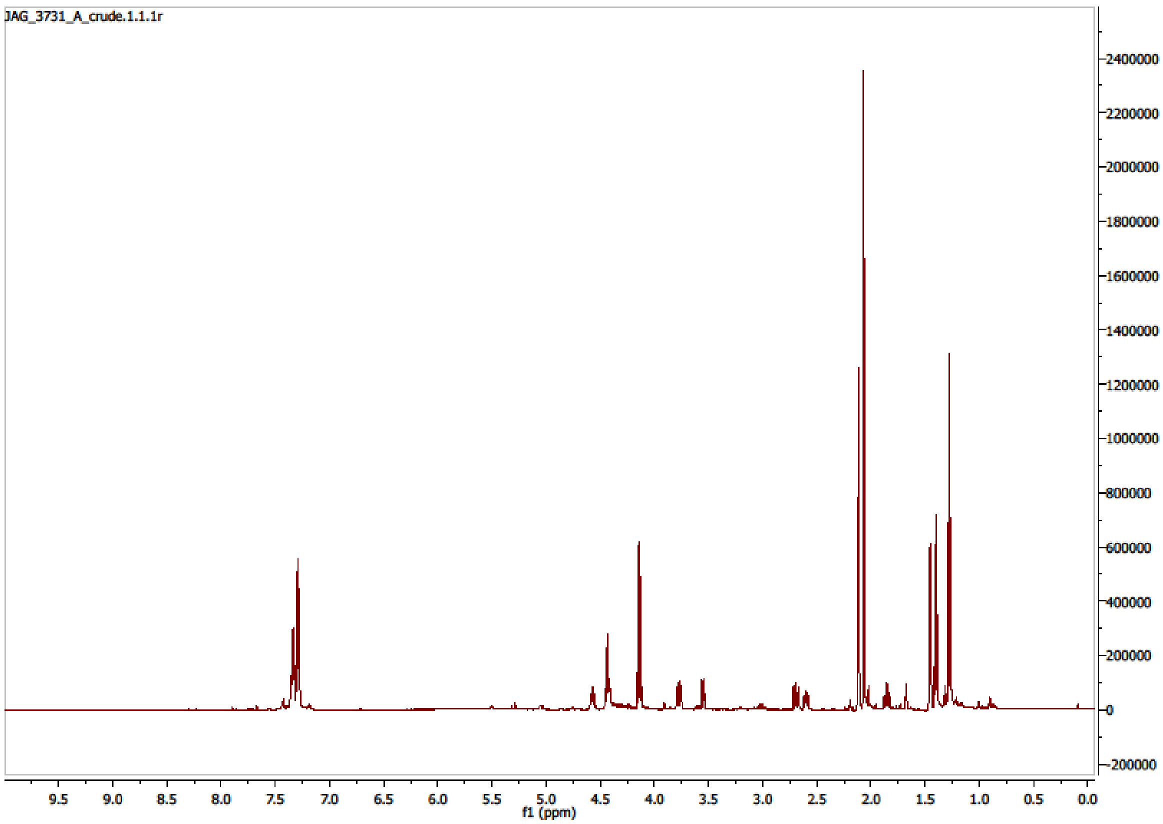
O
Br
H
Me
H

4a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-200000
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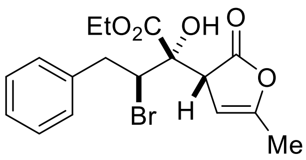
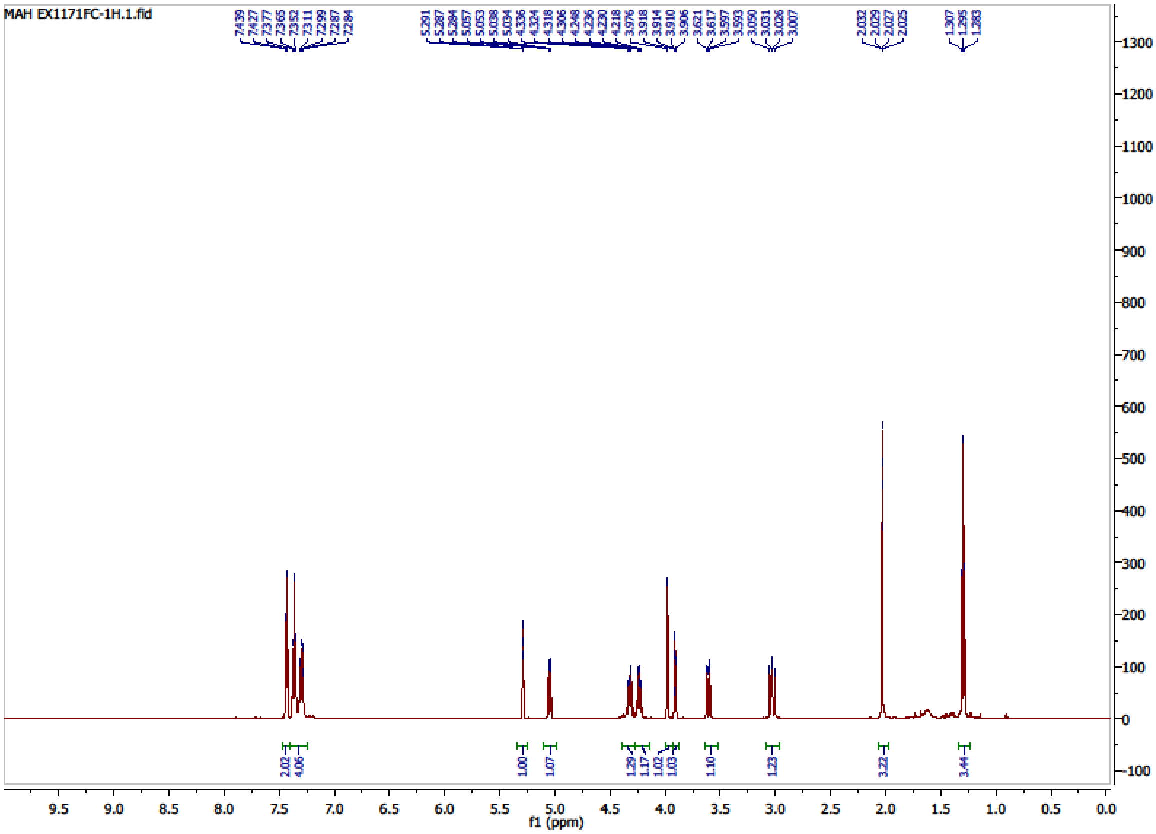
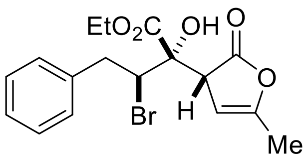
f1 (ppm)

[1]H and [13]C NMR spectra of new compounds:

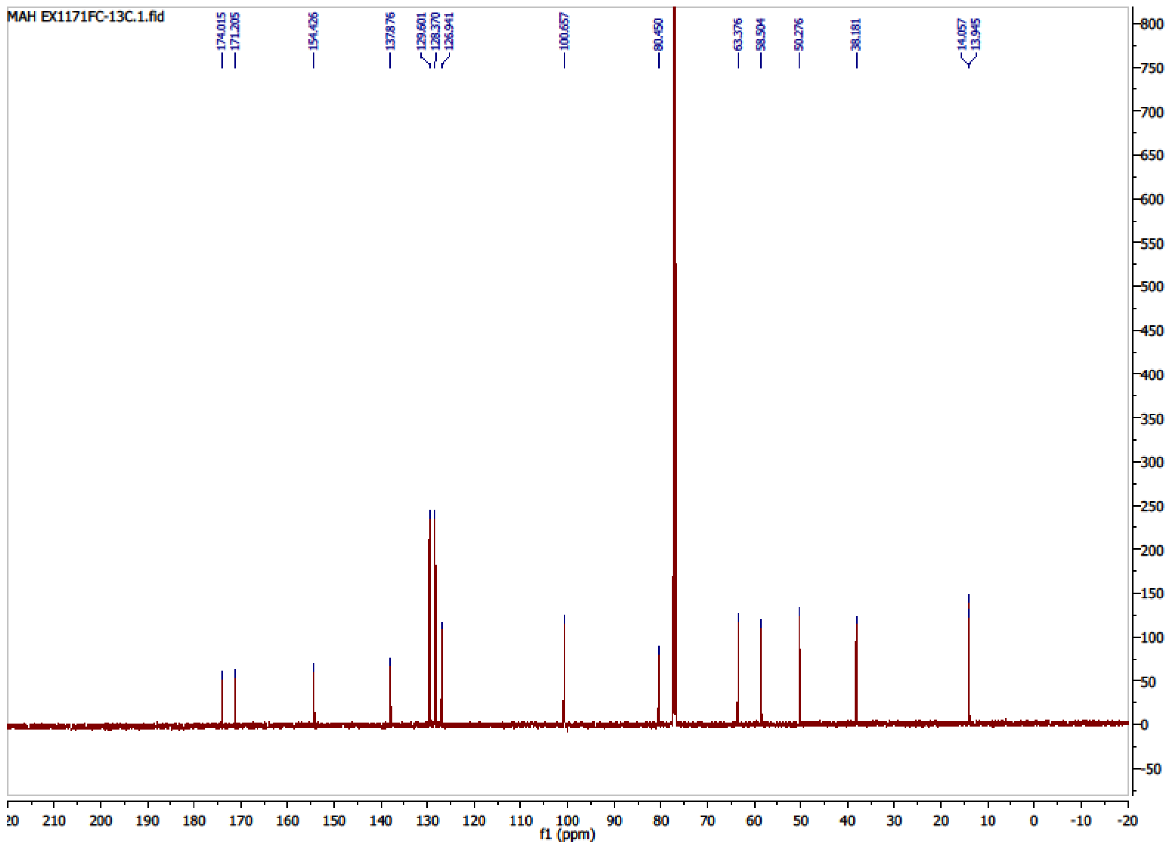


3a





3a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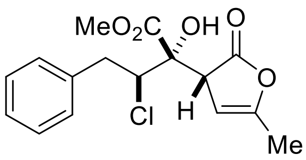
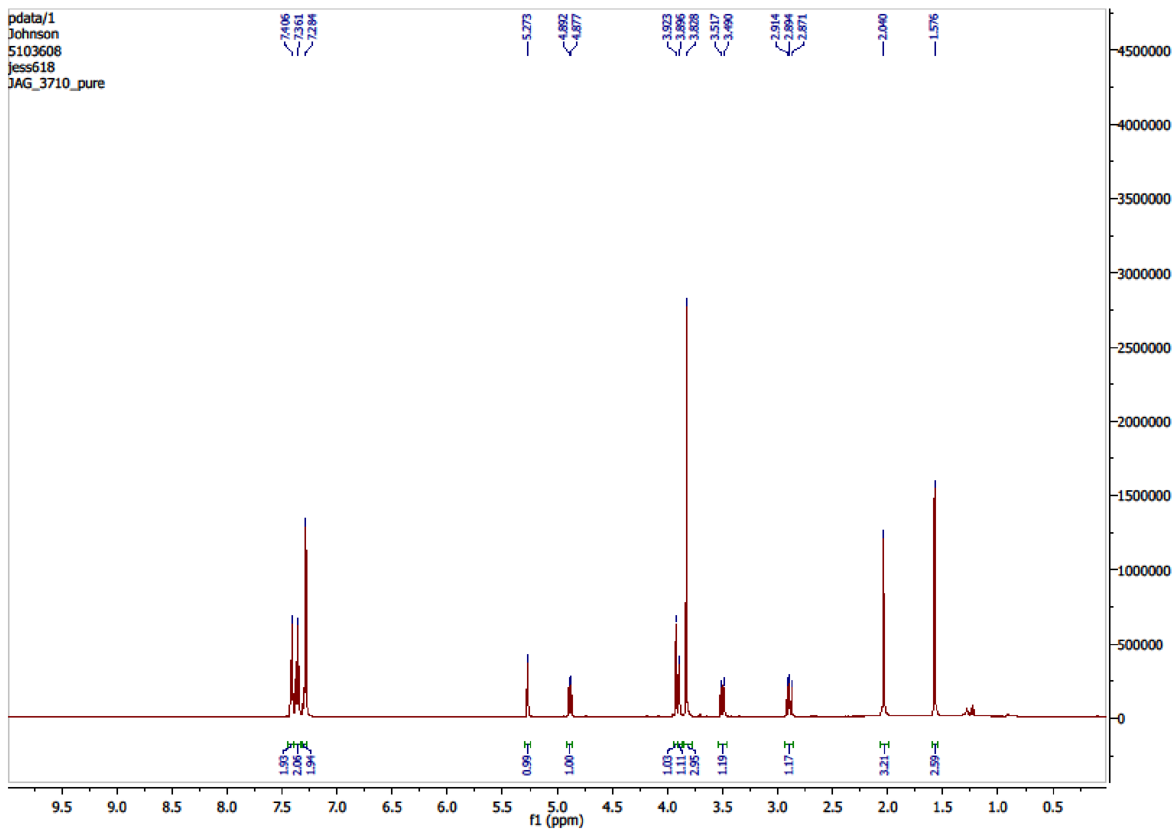
f1 (ppm)


MeO2C
OH
O
O
Cl
H
Me

3b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jess618
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3.828
3.517
3.490
2.914
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4500000
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3000000
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1000000
500000
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1.03
1.11
2.95
1.19
1.17
3.21
2.59
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8.5
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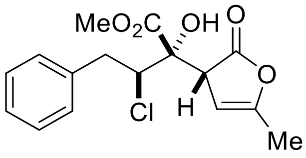
0.5
f1 (ppm)



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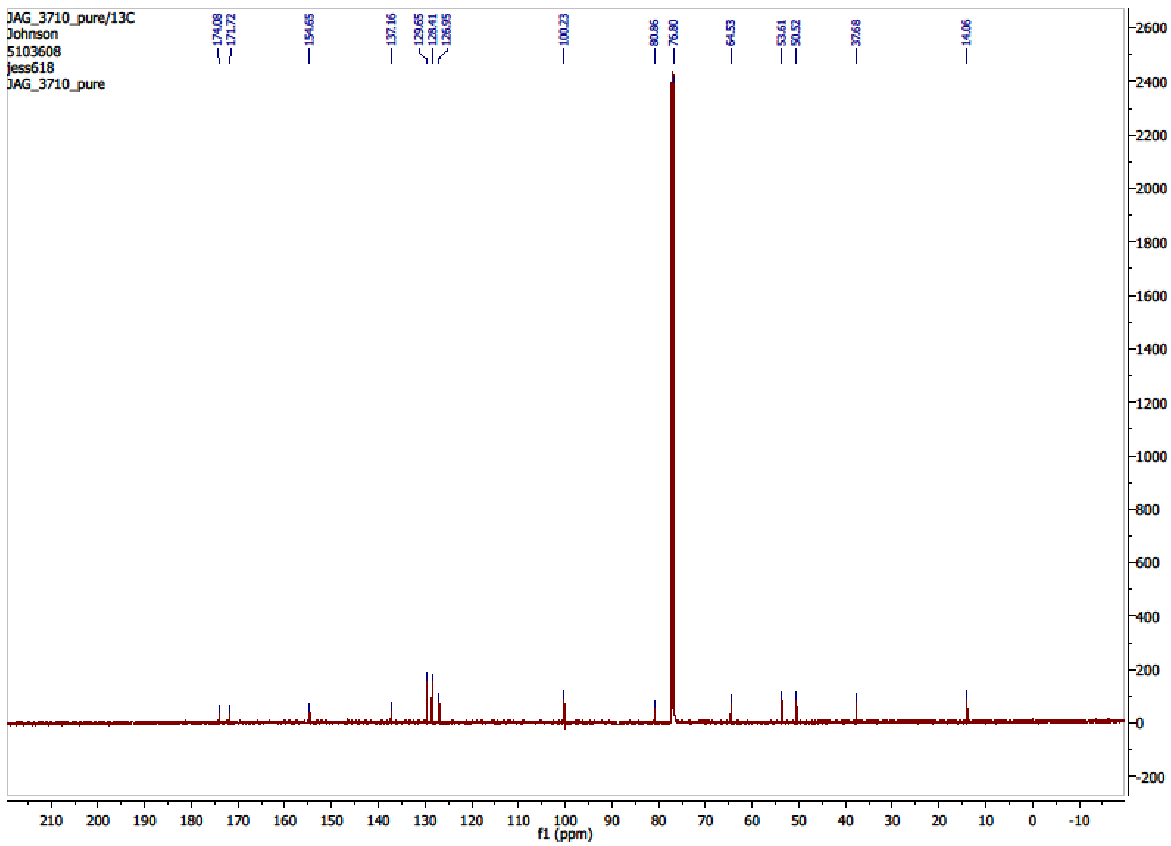

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Johnson
5103608
jess618
JAG_3710_pure
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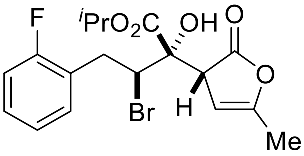
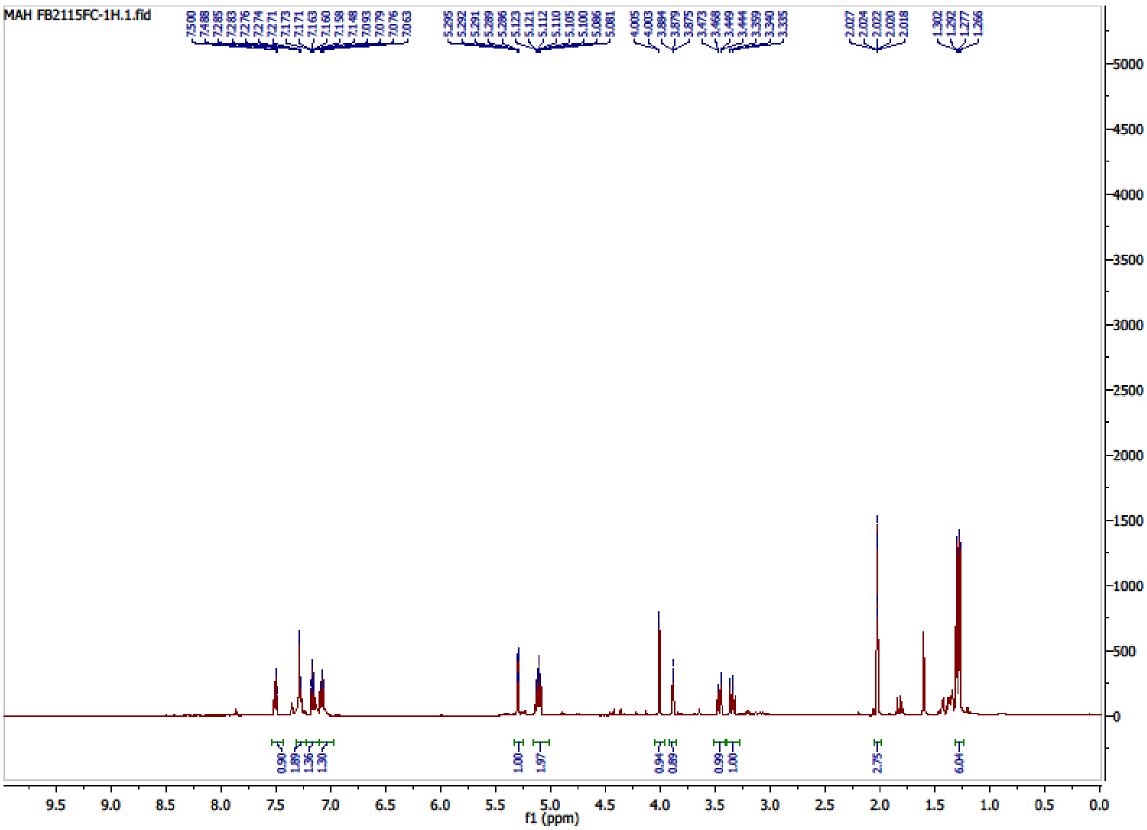
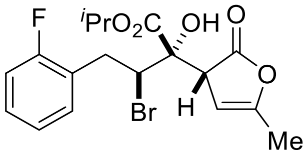
f1 (ppm)



3c




F
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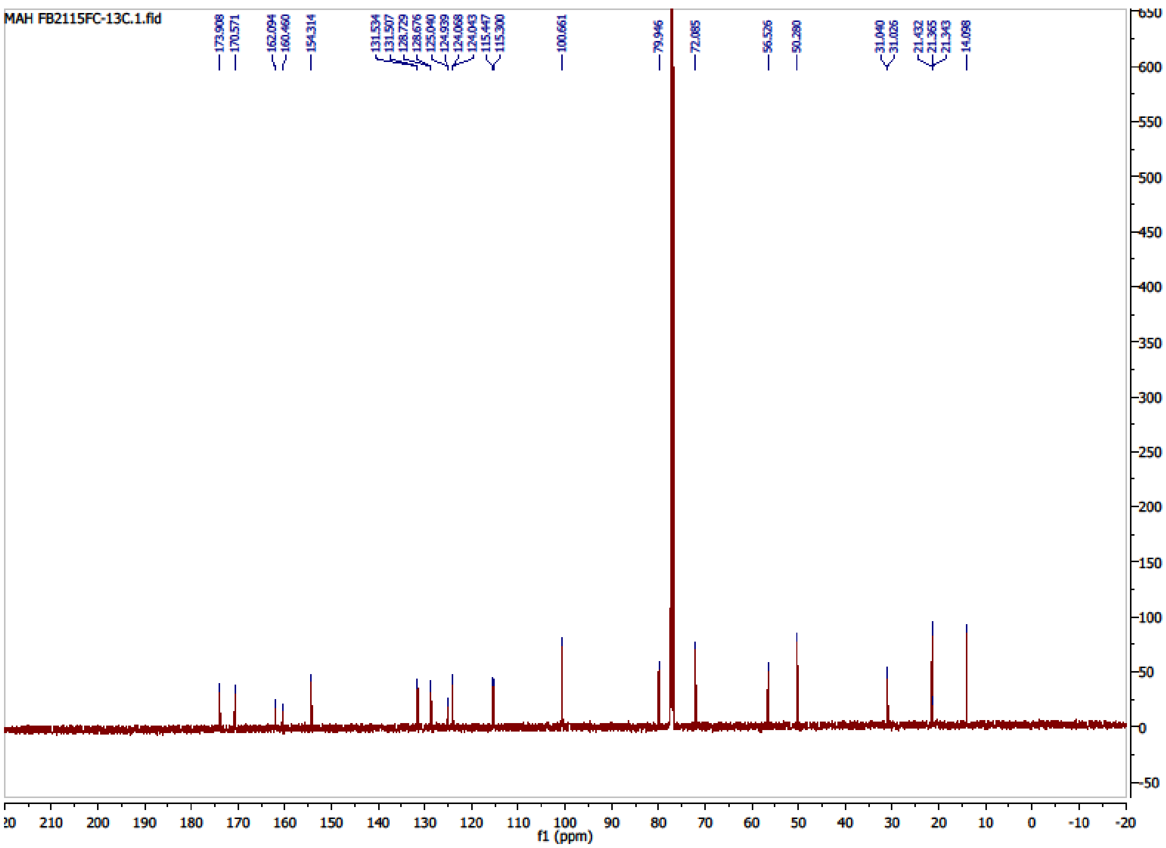
O
Br
H
Me

3c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115.300
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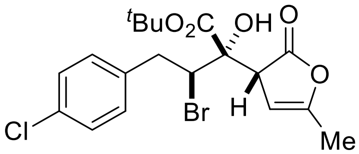
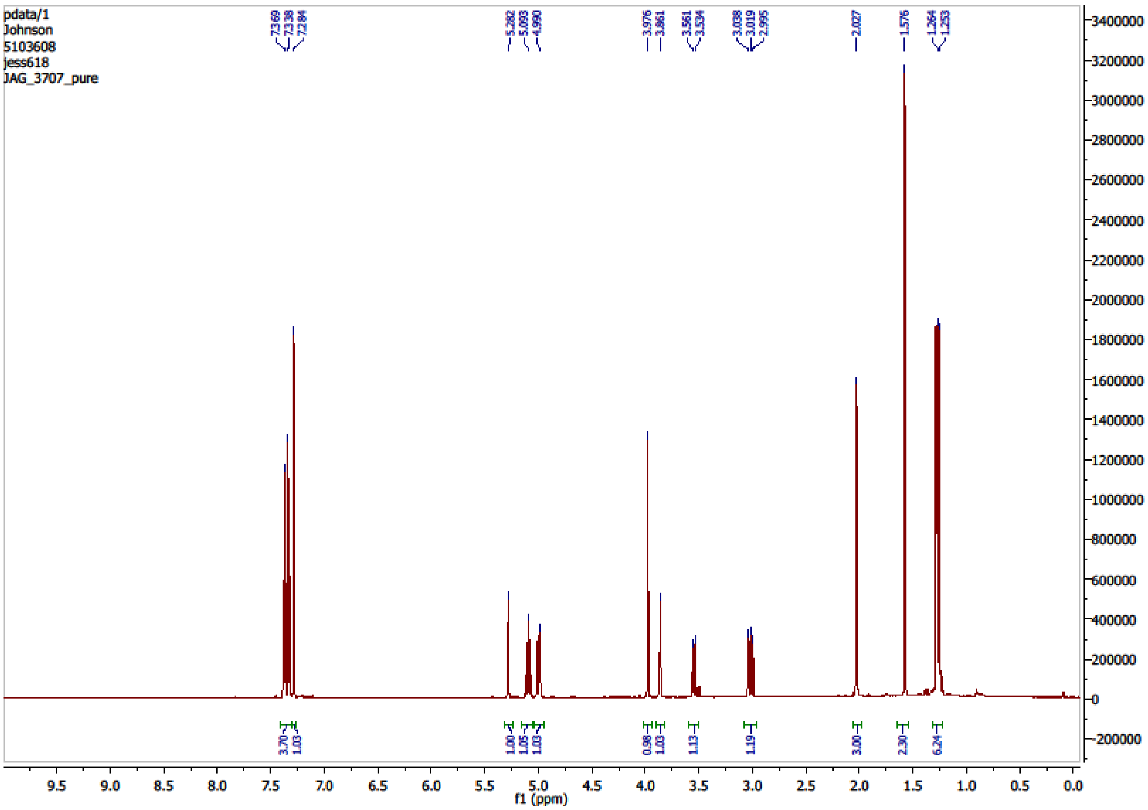
f1 (ppm)



^{t}BuO$_2$C
OH
O
O
Cl
Br
H
Me

3d



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Johnson
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jess618
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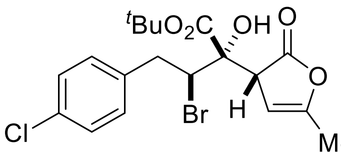
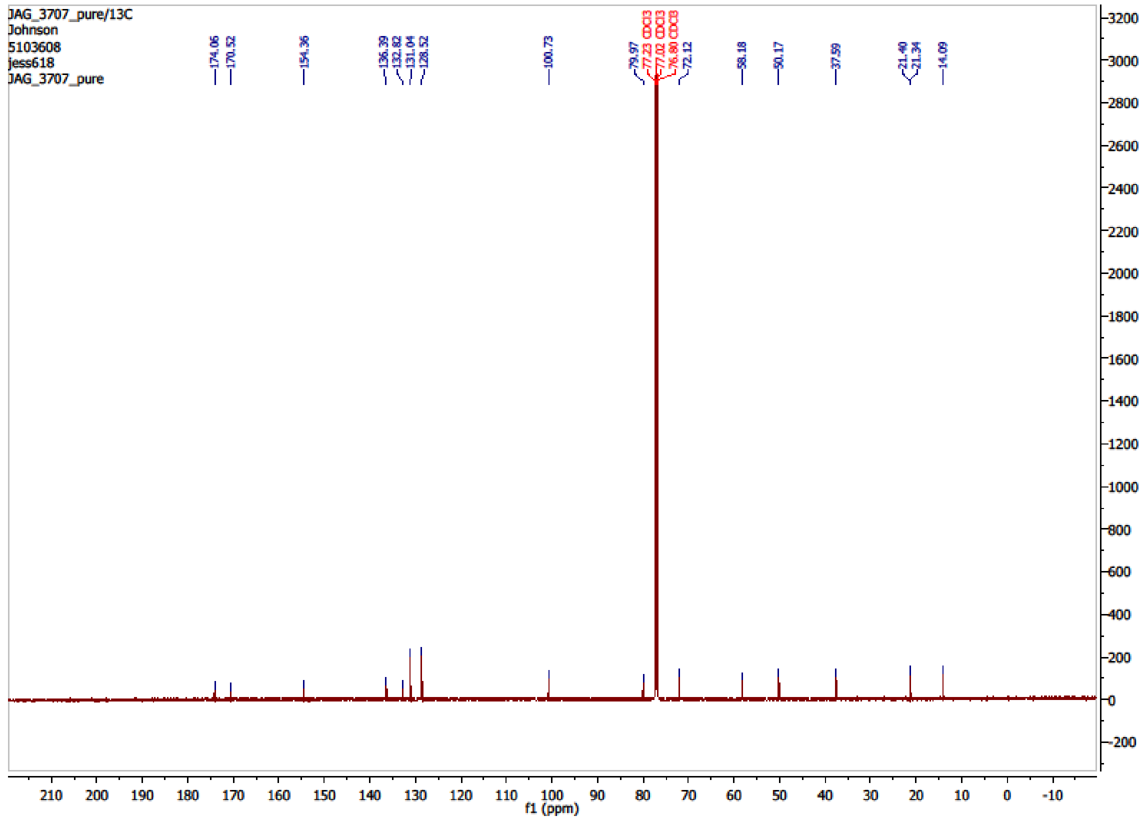
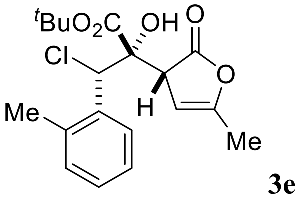
f1 (ppm)



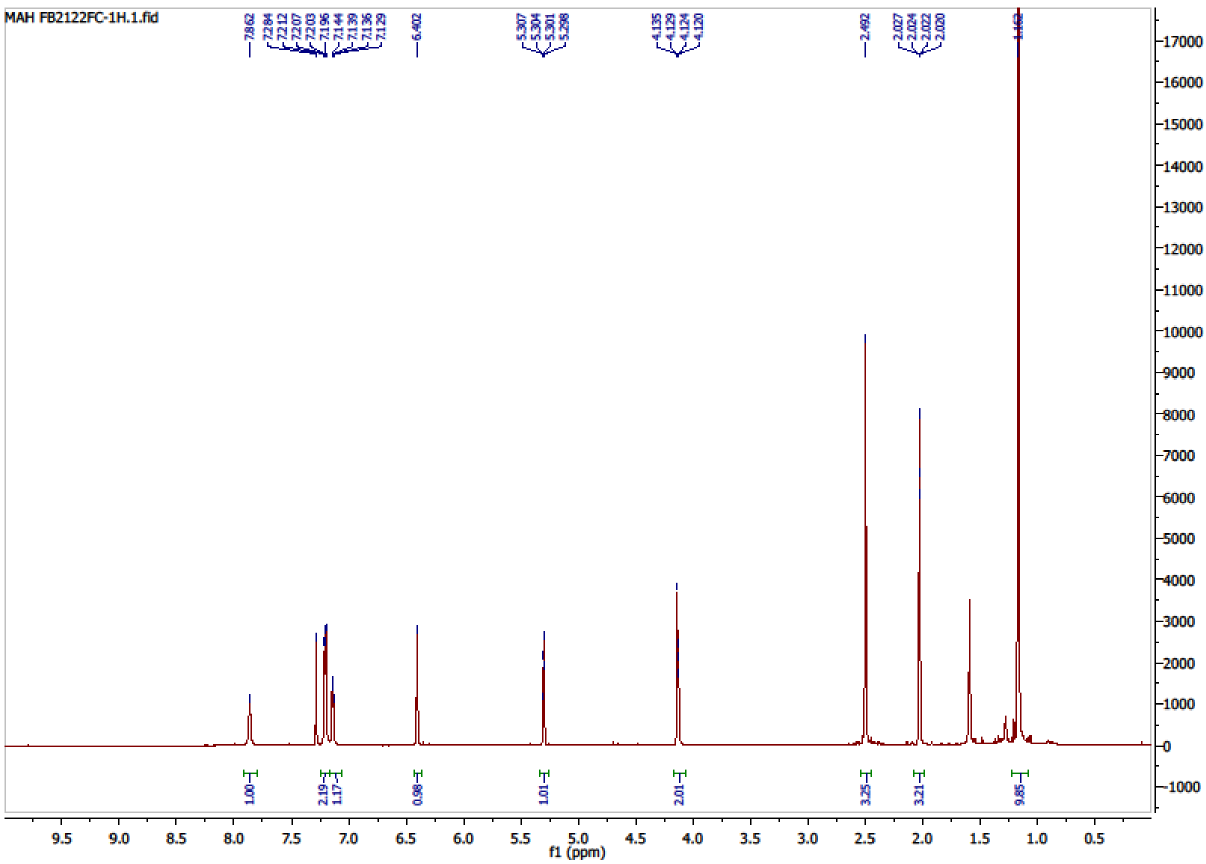
3d

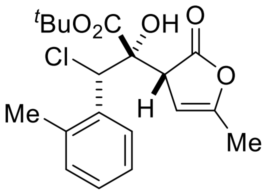


JAG_3707_pure/13C
Johnson
5103608
jess618
JAG_3707_pure
174.06
170.52
154.36
136.39
132.82
131.04
128.52
100.73
79.97
77.23 CDCl3
77.02 CDCl3
76.80 CDCl3
72.12
58.18
50.17
37.59
21.40
21.34
14.09
f1 (ppm)



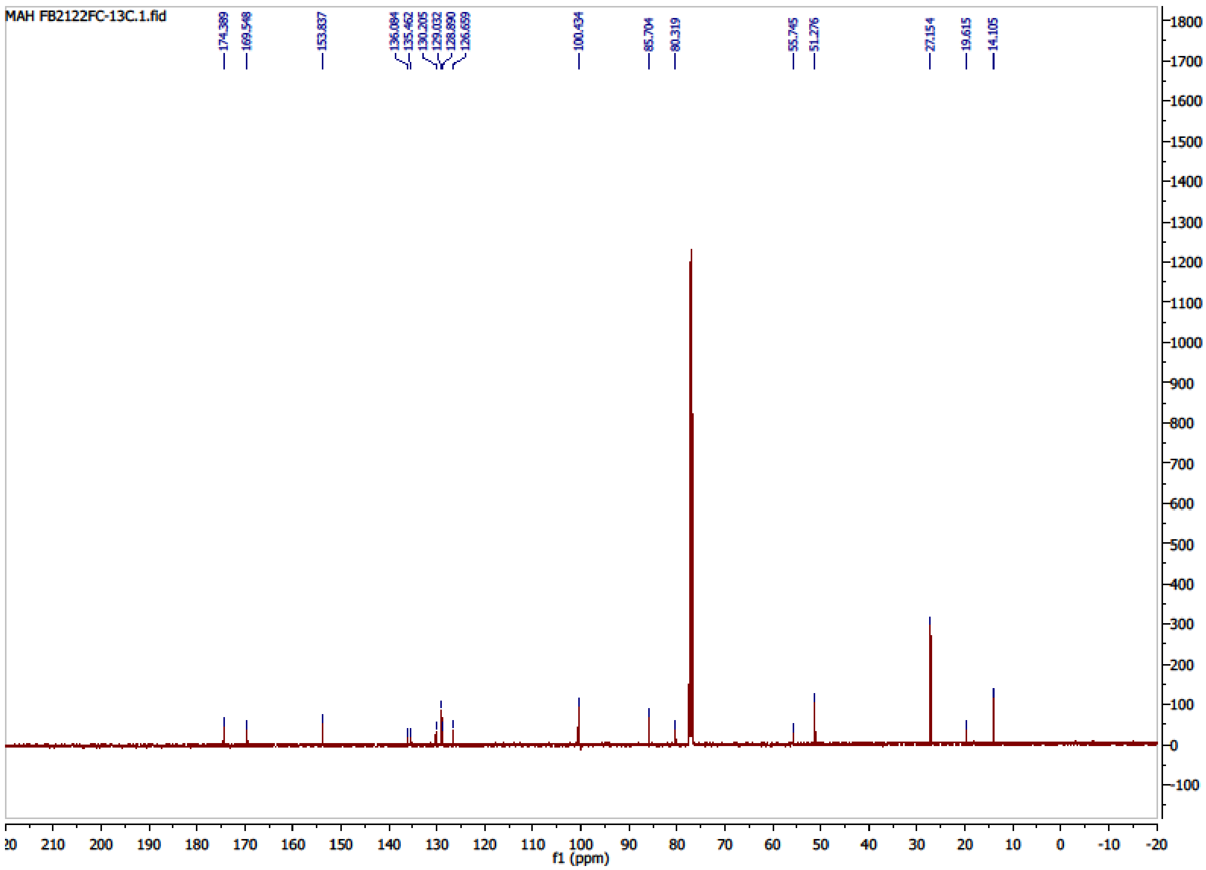
3e



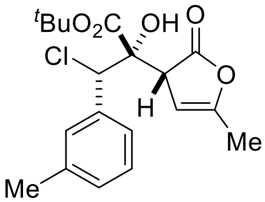


ᵗBuO2C
OH
O
Cl
O
Me
H
Me

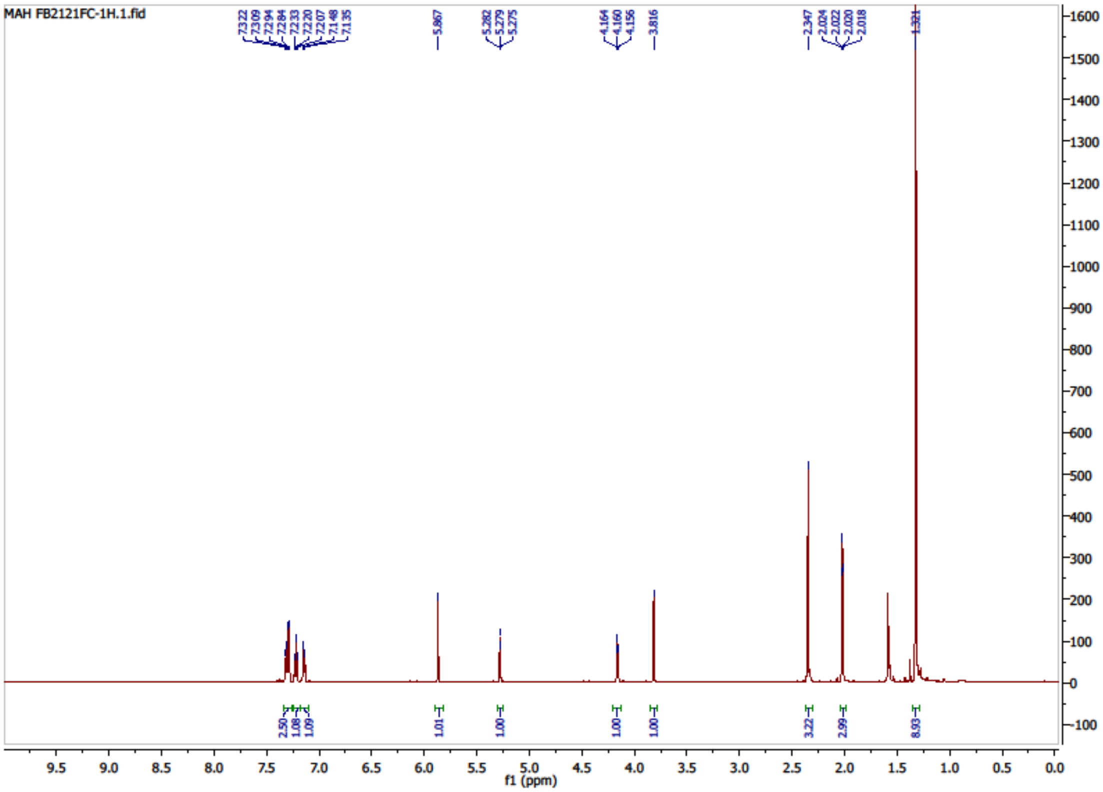
3e

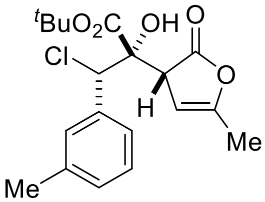


MAH FB2122FC-13C.1.fid
174.389
169.548
153.837
136.084
135.462
130.205
129.032
128.890
126.659
100.434
85.704
80.319
55.745
51.276
27.154
19.615
14.105
f1 (ppm)

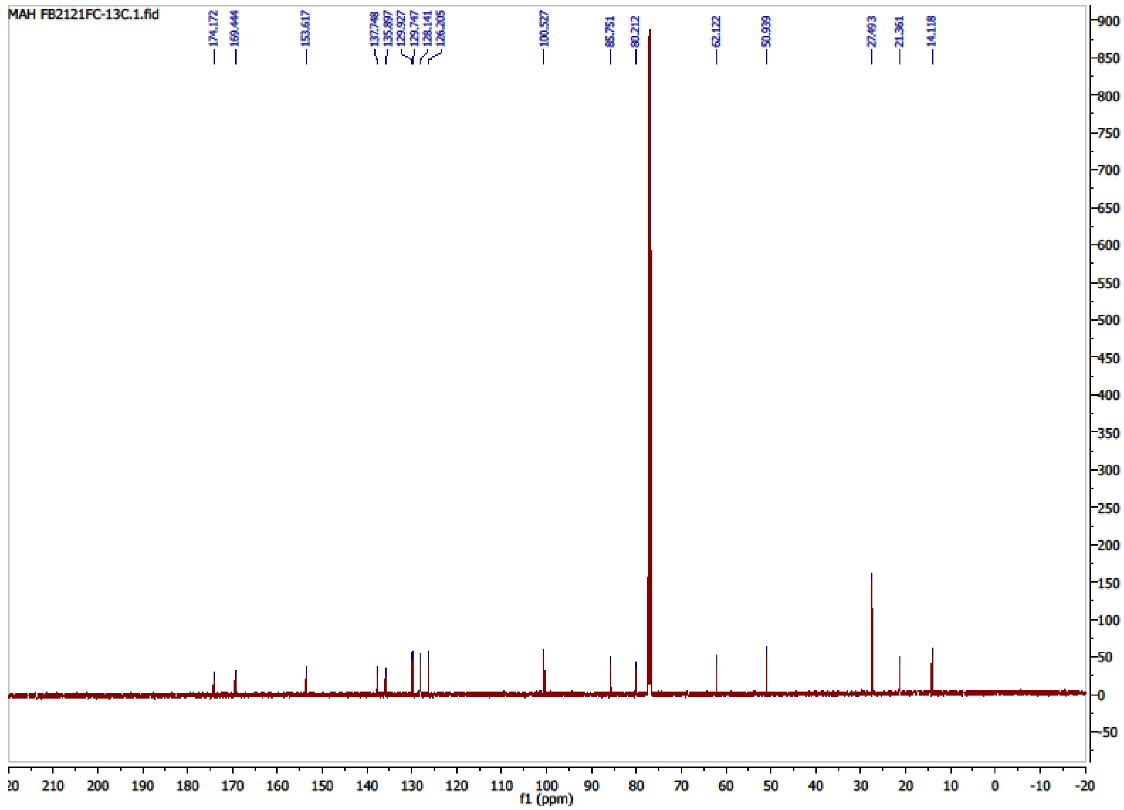


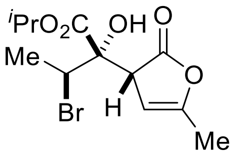
3f




tBuO2C
OH
O
Cl
O
H
Me
Me

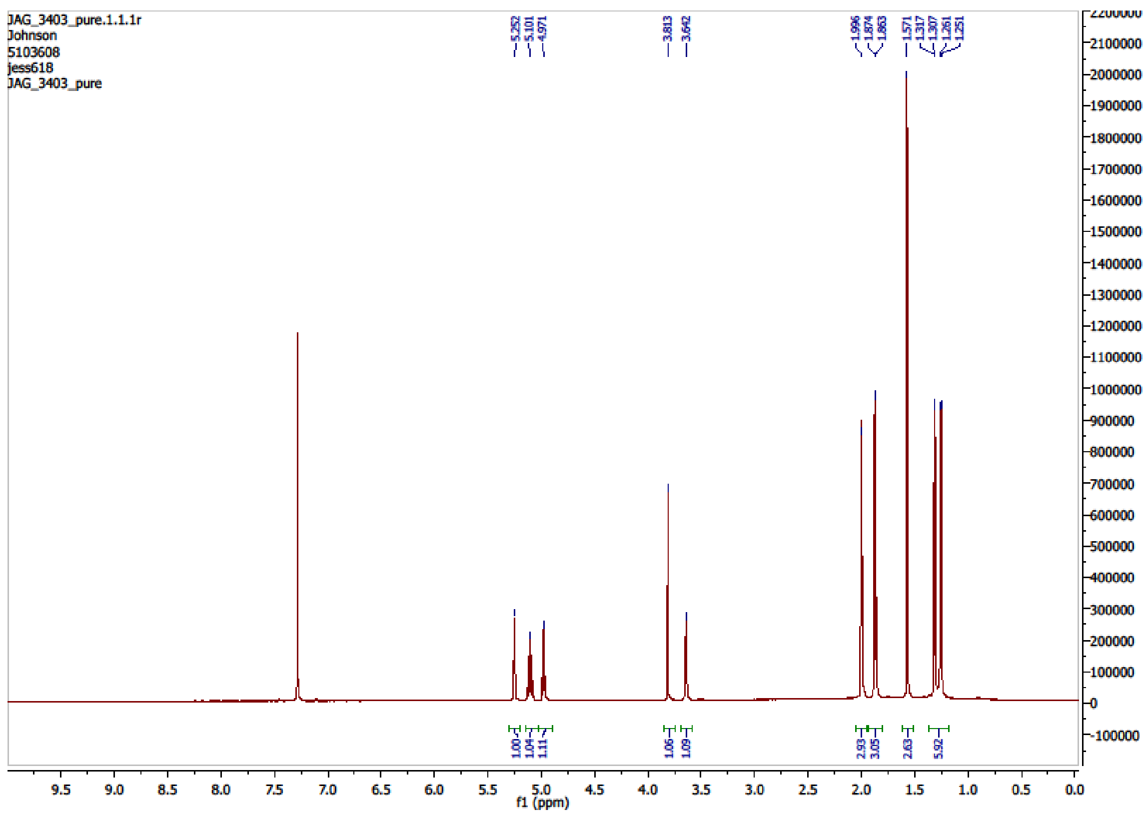
3f


MAH FB2121FC-13C.1.fid
174.172
169.444
153.617
137.748
135.897
129.927
129.747
128.141
126.205
100.527
85.751
80.212
62.122
50.939
27.493
21.361
14.118
f1 (ppm)

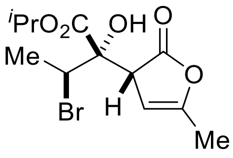


iPrO2C
OH
O
Me
O
Br
H
Me

3g

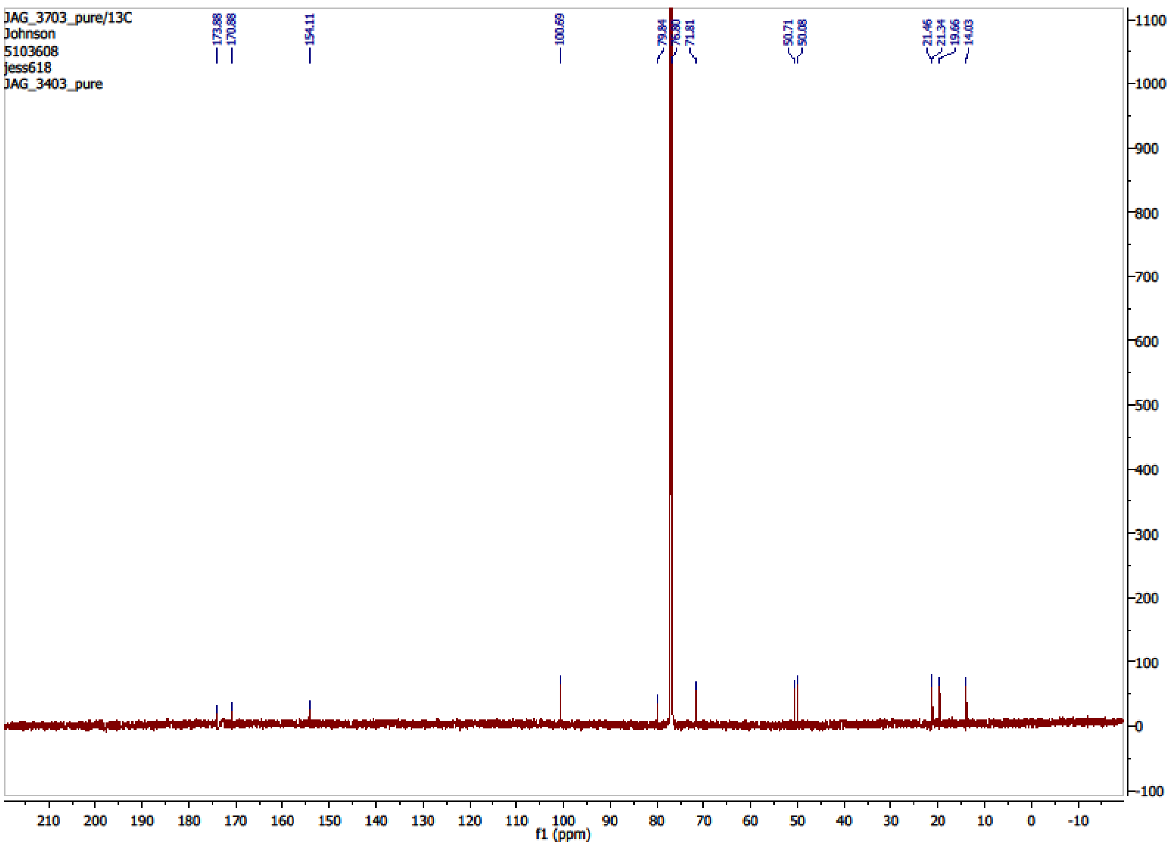


JAG_3403_pure.1.1.1r
Johnson
5103608
jess618
JAG_3403_pure
5.252
5.101
4.971
3.813
3.642
1.996
1.874
1.863
1.571
1.317
1.307
1.261
1.251
1.00
1.04
1.11
1.06
1.09
2.93
3.05
2.63
5.92
f1 (ppm)

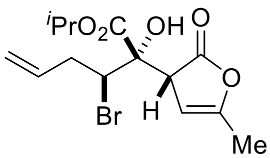


^{i}PrO$_2$C
OH
O
Me
O
Br
H
Me

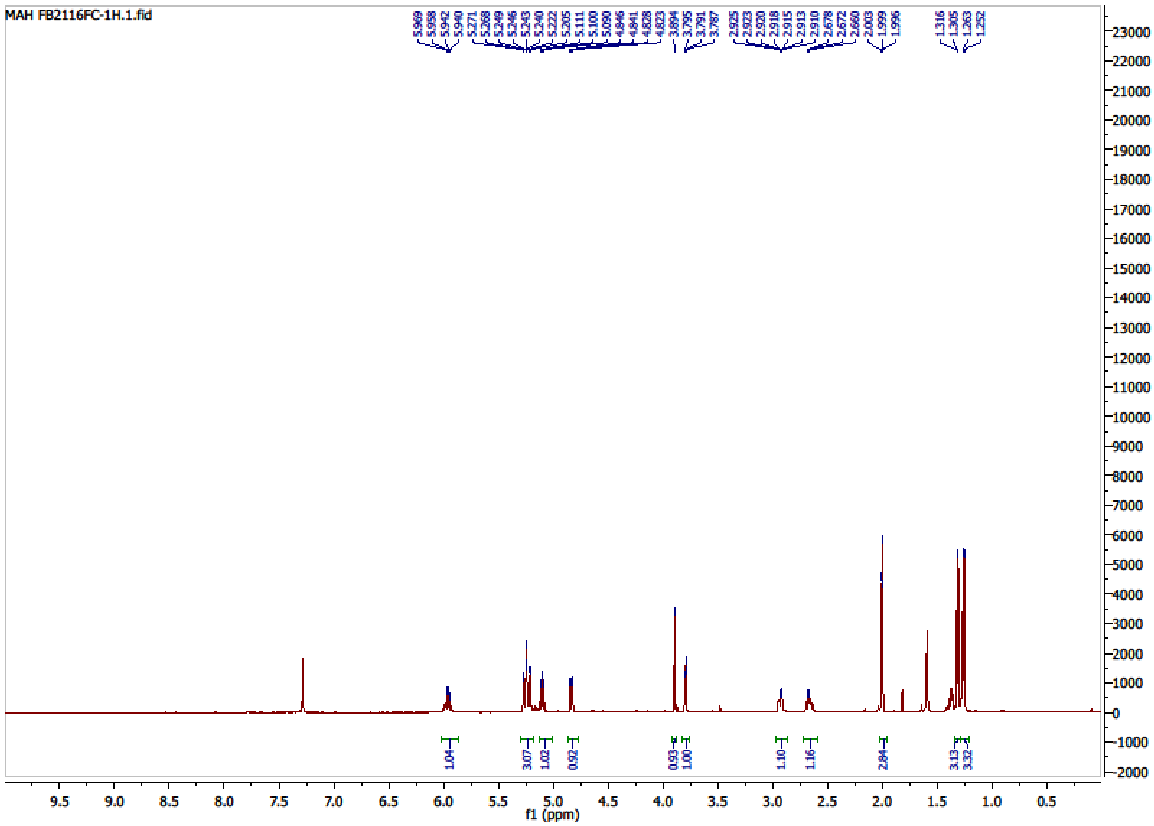
3g

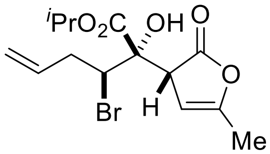


JAG_3703_pure/13C
Johnson
5103608
jess618
JAG_3403_pure
173.88
170.88
154.11
100.69
79.84
76.80
71.81
50.71
50.08
21.46
21.34
19.66
14.03
f1 (ppm)

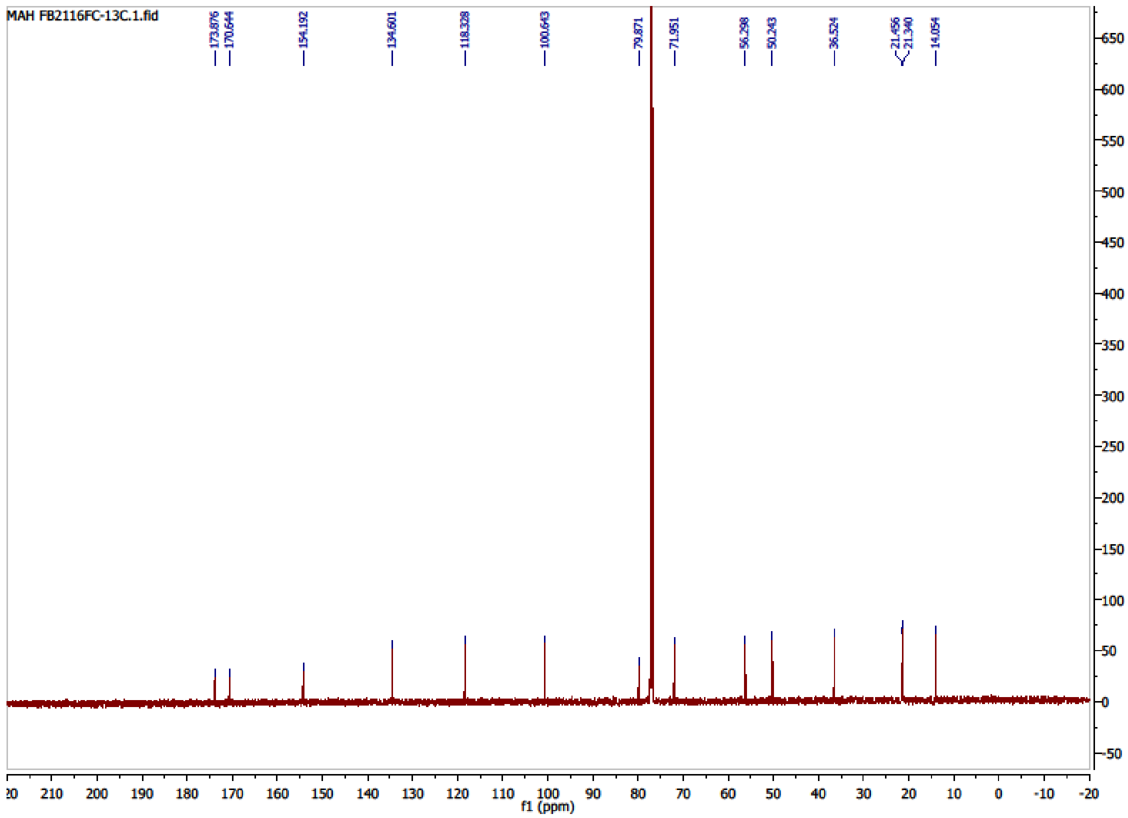


3h

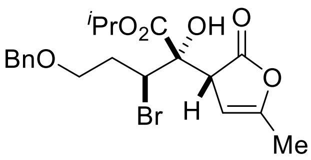




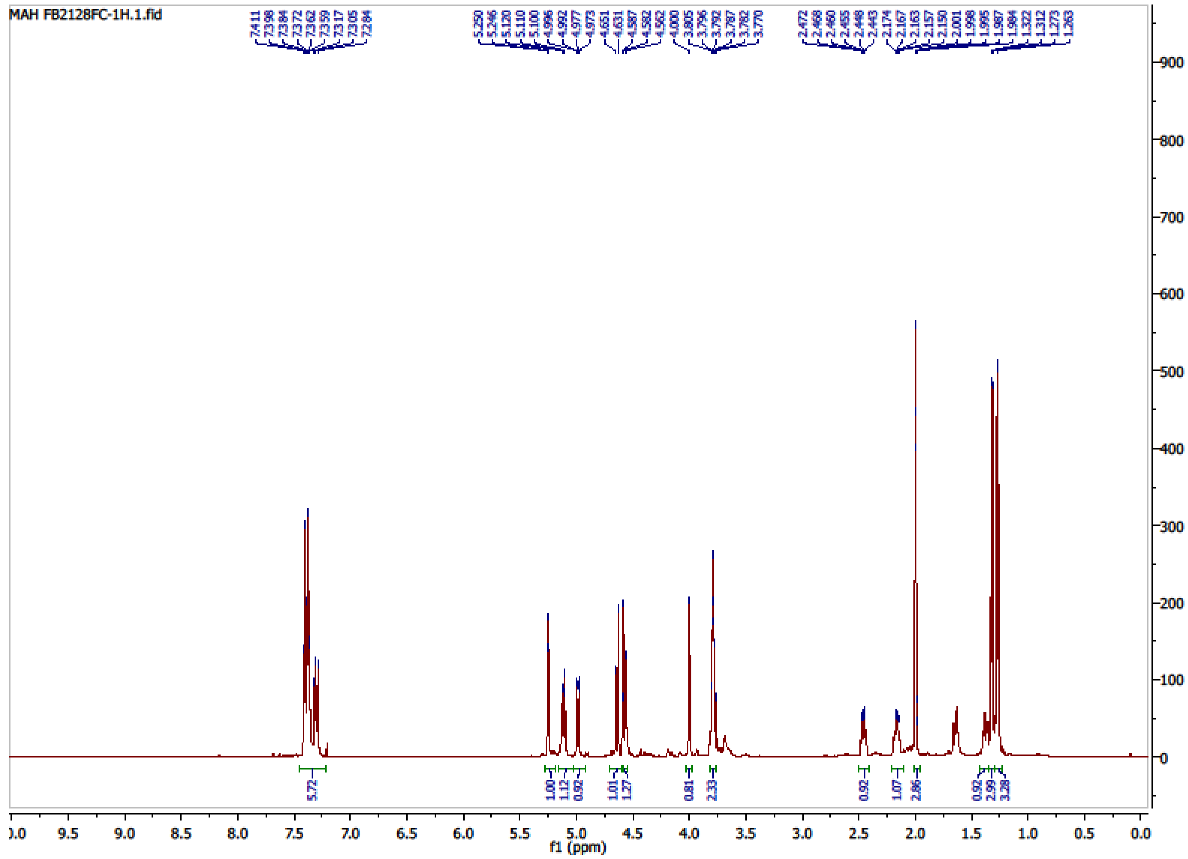
3h

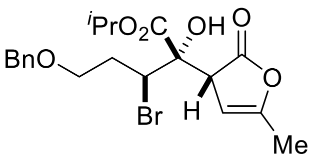


MAH FB2116FC-13C.1.fid
173.876
170.644
154.192
134.601
118.328
100.643
79.871
71.951
56.298
50.243
36.524
21.456
21.340
14.054
f1 (ppm)



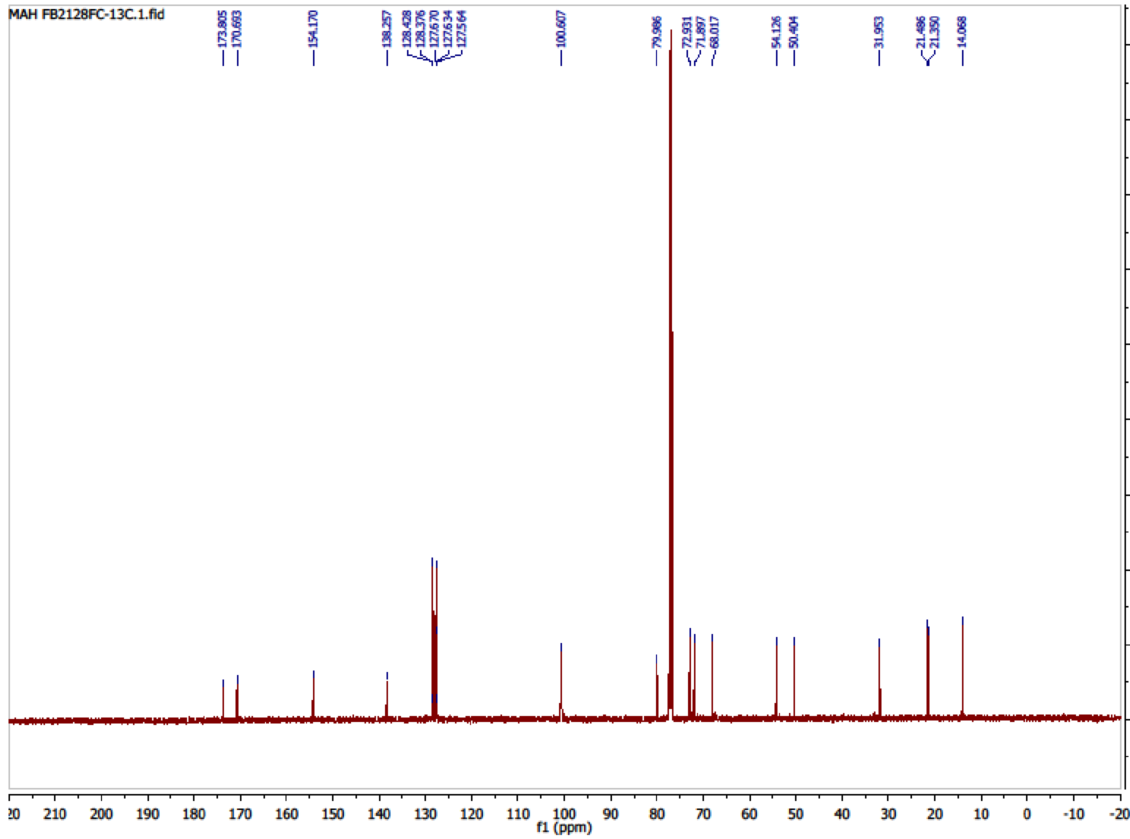
3i



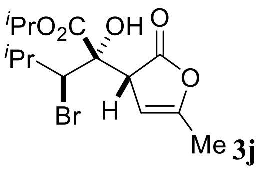


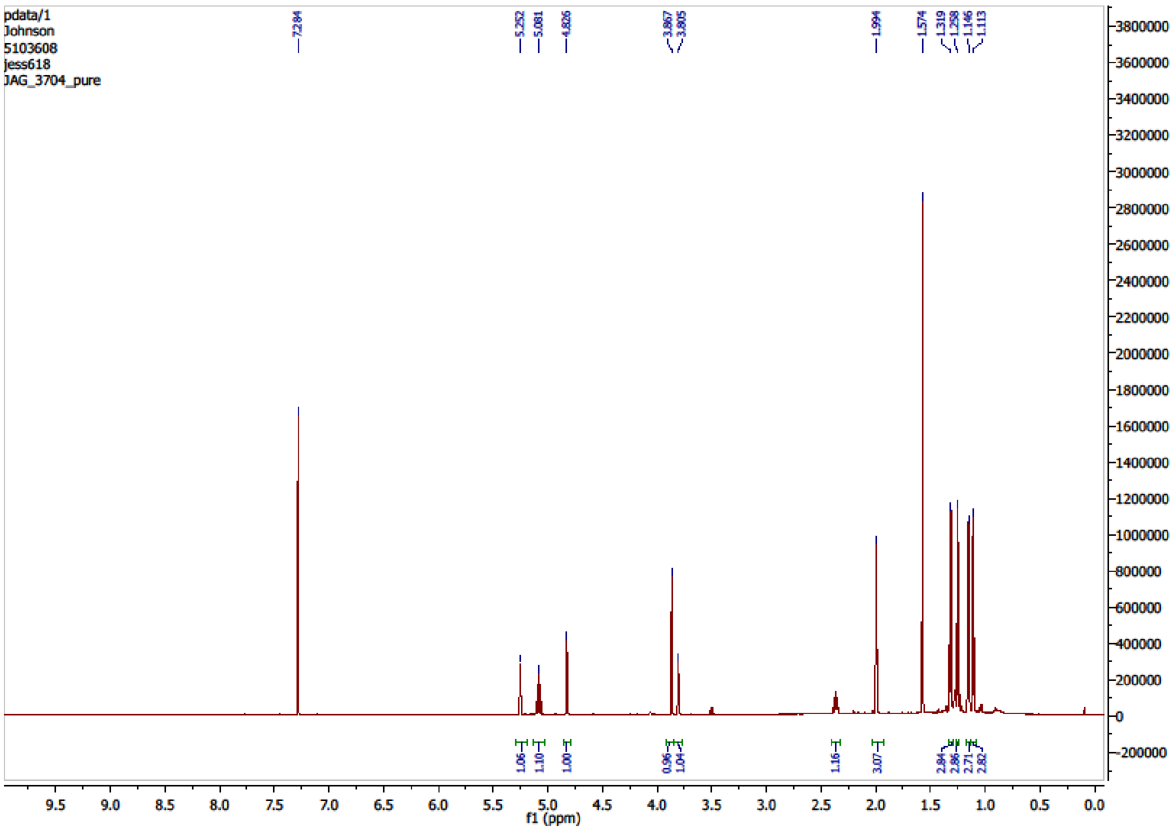
^{i}PrO$_2$C
OH
O
BnO
O
Br
H
Me

3i

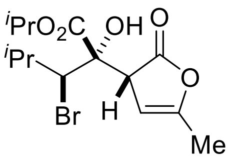


MAH FB2128FC-13C.1.fid
173.805
170.693
154.170
138.257
128.428
128.376
127.670
127.634
127.564
100.607
79.986
72.931
71.897
68.017
54.126
50.404
31.953
21.486
21.350
14.068
f1 (ppm)

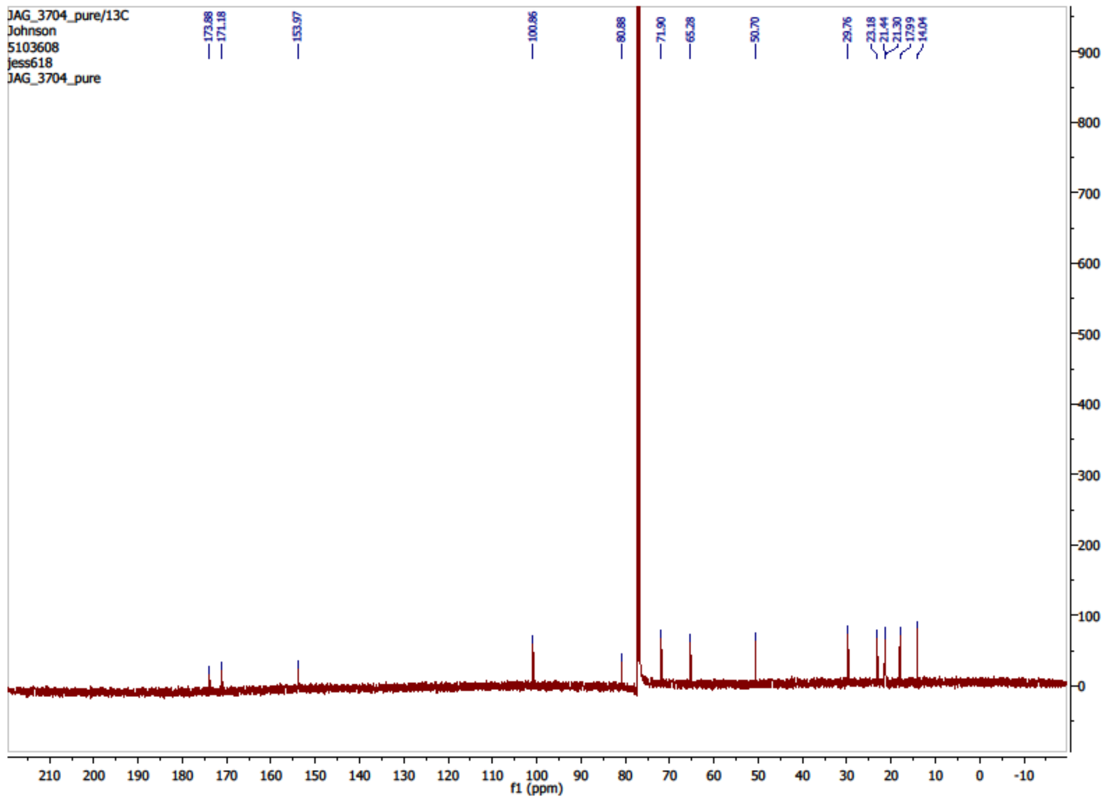


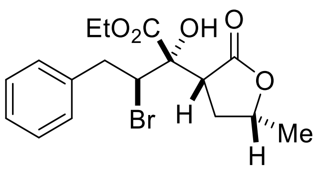


pdata/1
Johnson
5103608
jess618
JAG_3704_pure
f1 (ppm)

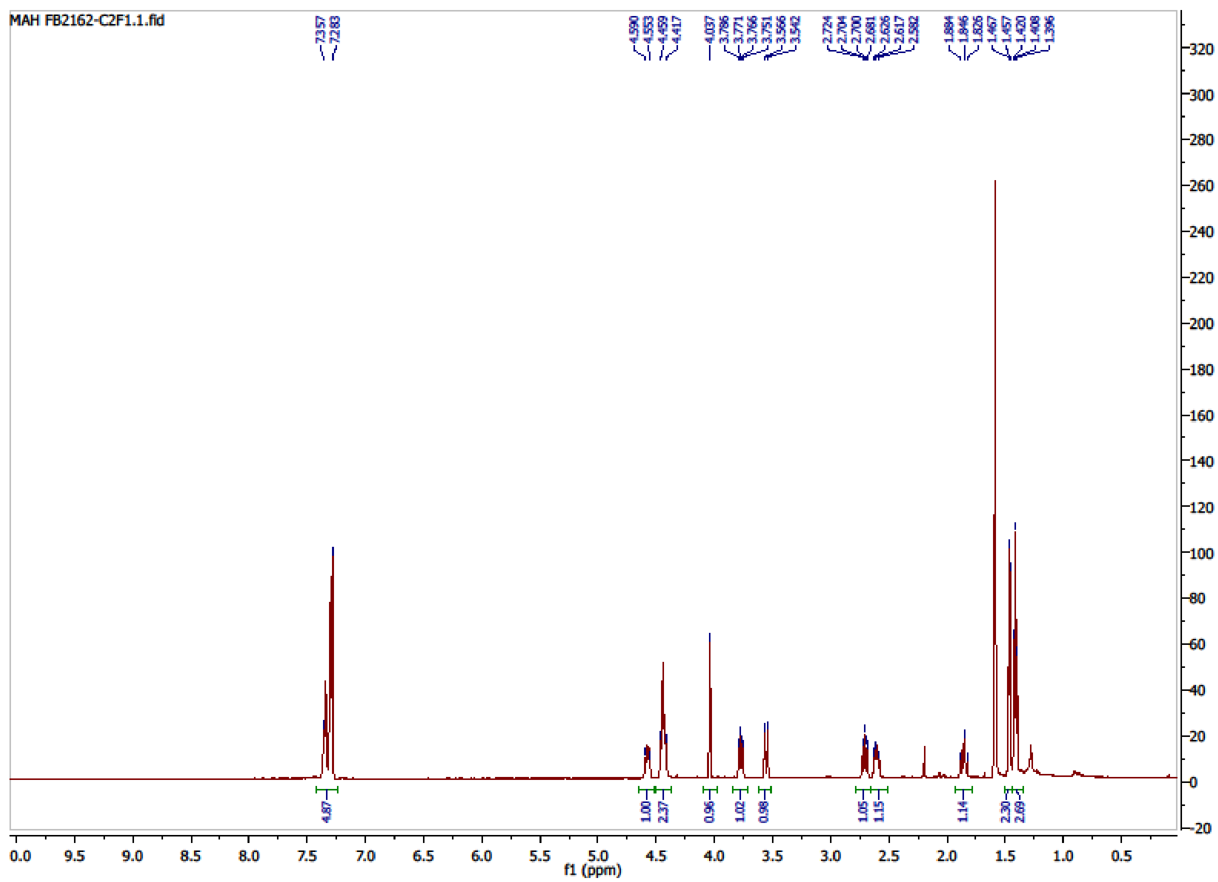


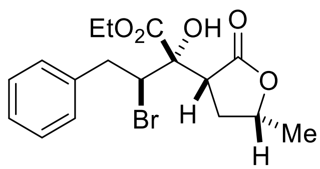
3j

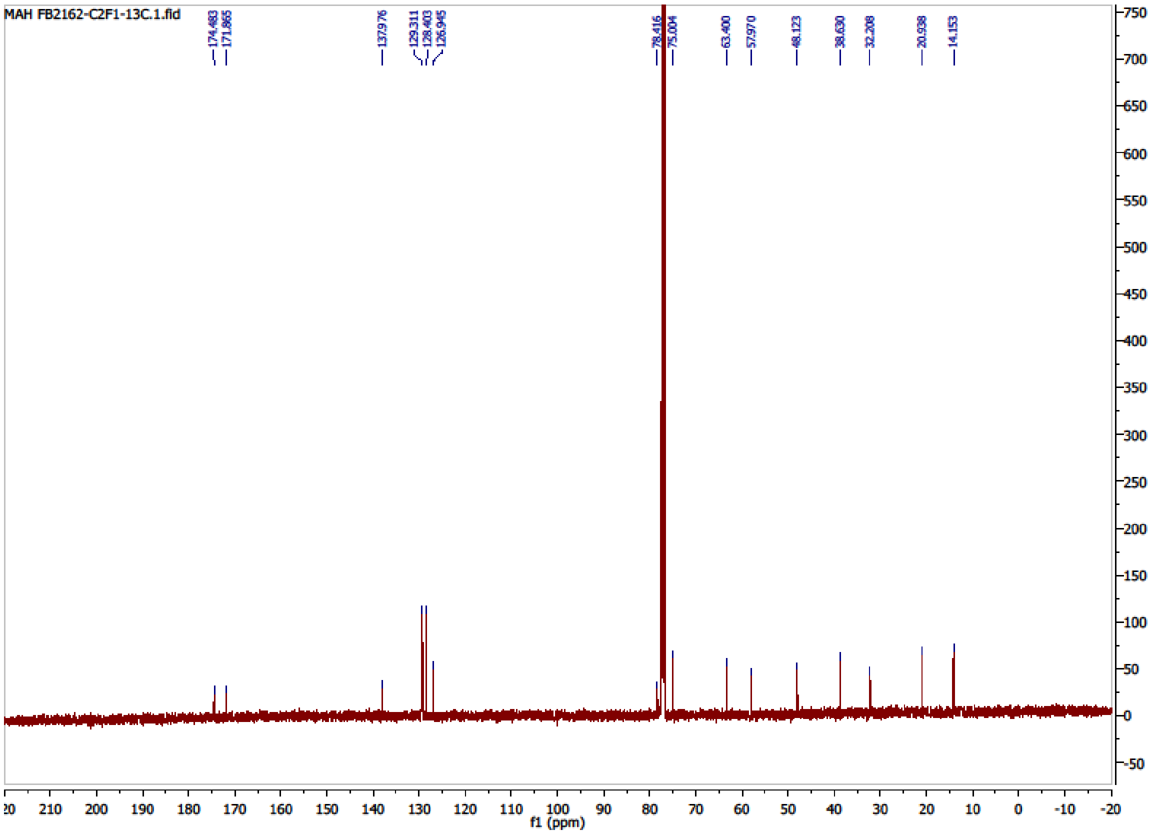

JAG_3704_pure/13C
Johnson
5103608
jess618
JAG_3704_pure
173.88
171.18
153.97
100.86
80.88
71.90
65.28
50.70
29.76
23.18
21.44
21.30
17.99
14.04
f1 (ppm)



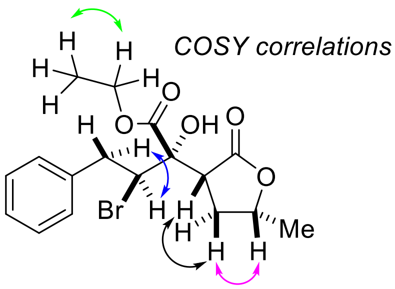
4a



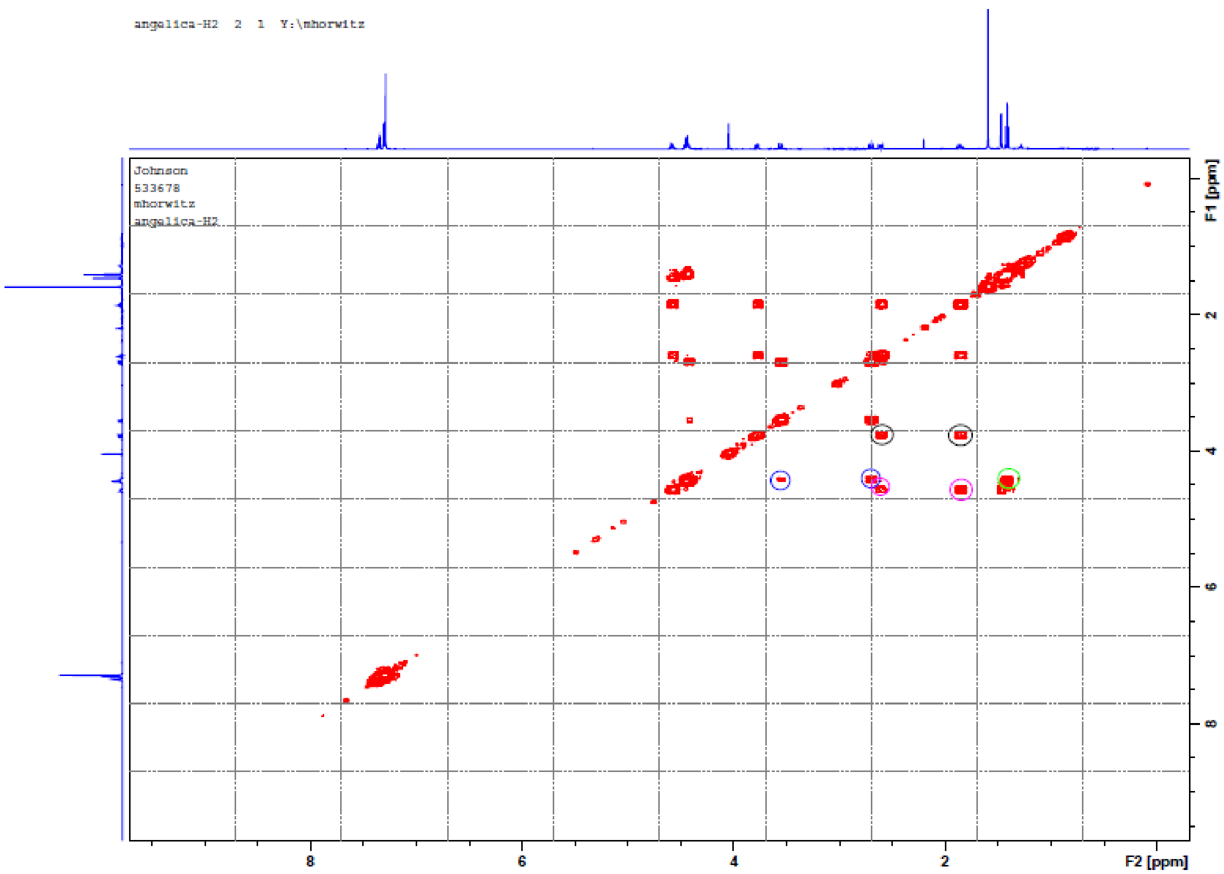

EtO2C
OH
O
O
Br
H
H
Me
4a

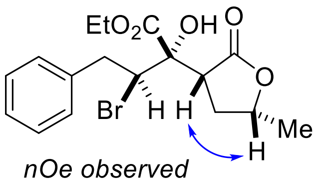

MAH FB2162-C2F1-13C.1.fid
174.483
171.865
137.976
129.311
128.403
126.945
78.416
75.004
63.400
57.970
48.123
38.630
32.208
20.938
14.153
f1 (ppm)

2D NMR experiments on 4a:

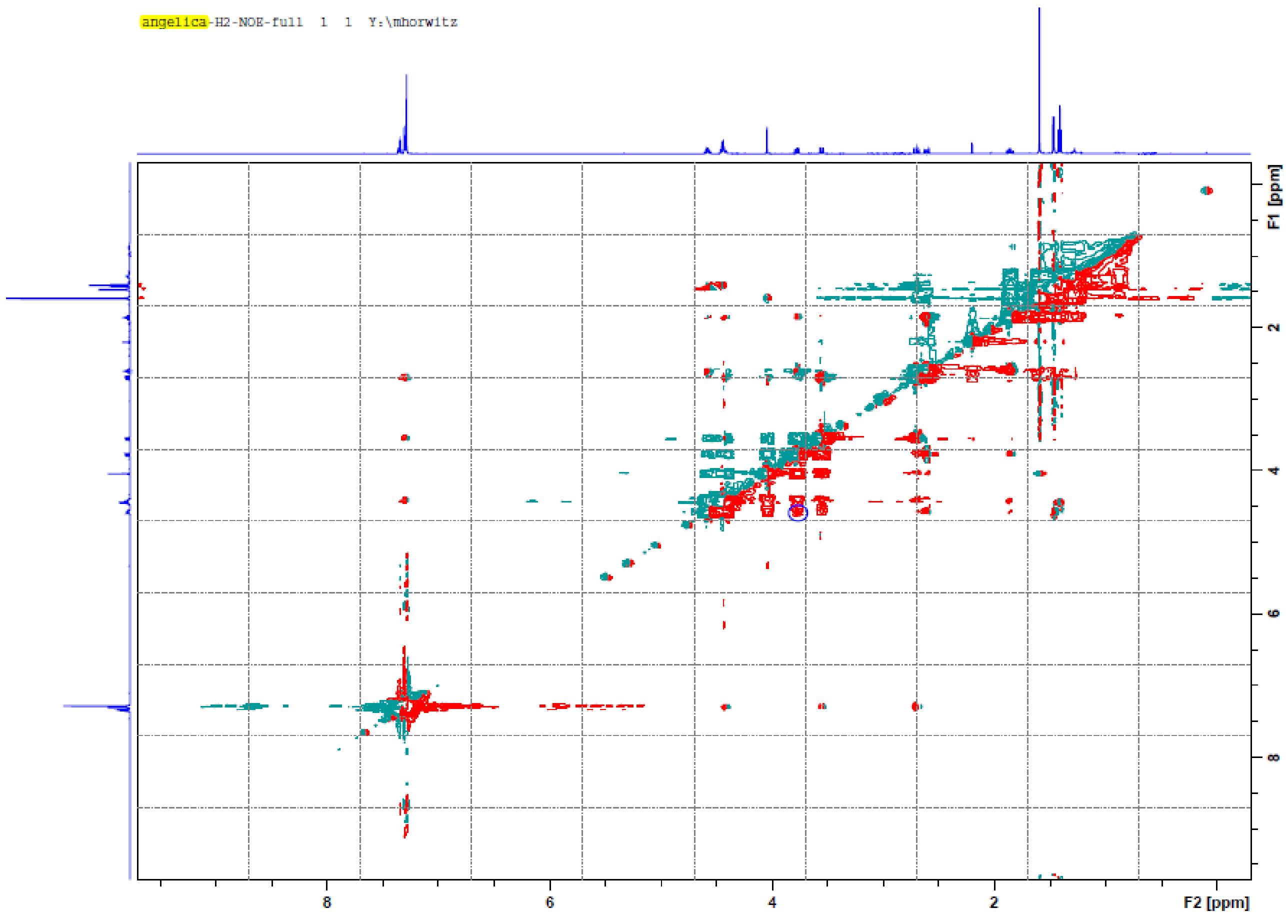


[1]H COSY:




EtO2C
OH
O
O
Me
Br
H
H
H
nOe observed

[1]H nOe:


angelica-H2-NOE-full 1 1 Y:\mhorwitz
F1 [ppm]
F2 [ppm]
2
4
6
8