

Iodide-Mediated Synthesis of Spirooxindolo dihydrofurans from Iodonium Ylides and 3-Alkylidene-2-oxindoles

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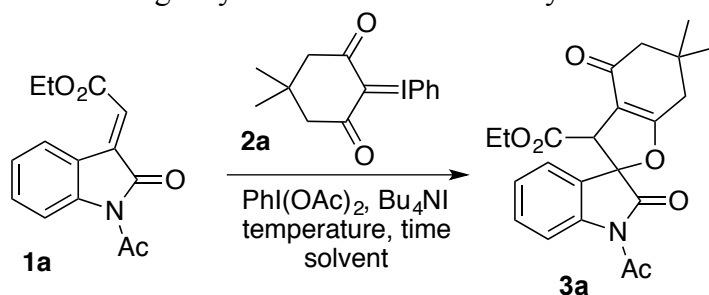
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Table SI-1: Optimization of the Dihydrofuran Synthesis:

The reaction was optimized using alkylidene **1a** and iodonium ylide **2a**.^a



entry	solvent (0.1 M)	temperature (°C)	2a (equiv)	$\text{PhI}(\text{OAc})_2$ (equiv)	TBAI	Time (hr)	conv. ^b (%)	Yield ^c
1	MeCN	rt	1.0	1.0	0.3	5	100	64
2	MeCN	0	1.0	0.3	0.3	5	98	71
3	MeCN	60	1.0	0.3	0.3	5	96	77
4	MeCN	rt	1.1	0.3	0.3	5	93	76
5	MeCN	rt	1.2	0.3	0.3	5	93	84

6	MeCN	rt	1.5	0.3	0.3	5	91	79
7	MeCN	rt	2.0	0.3	0.3	5	94	78
8	MeCN	rt	1.0	0.3	0.3	5	97	83
9	DCM	rt	1.0	0.3	0.3	5	42	38
10	DCM	rt	1.0	0.3	0.3	25	60	54
11	DCE	rt	1.0	0.3	0.3	5	63	46
12	Toluene	rt	1.0	0.3	0.3	5	97	78
13	DCM	reflux	1.0	0.3	0.3	5	100	75
14	MeCN	rt	1.0	0.1	0.1	68	-	0
15	MeCN	rt	1.0	0.2	0.2	18	87	72
16	MeCN	rt	1.0	0.5	0.5	5	100	72
17	MeCN	rt	1.0	1.0	1.0	3	100	56
18	MeCN	rt	1.0	-	-	5	8	<5%
19	MeCN	rt	1.0	-	0.3	5	83	81
20	MeCN	rt	1.0	0.3	0	5	19	10
21	MeCN	rt	1.0	-	0.1	20	54	48
22	MeCN	rt	1.0	-	0.3	20	97	94
23	MeCN	rt	1.0	-	0.5	20	98	97
24	MeCN	60	1.0	-	0.3	5	99	96
25	MeCN	82	1.0	-	0.3	3	97	93
26	MeCN ^d	rt	1.0	-	0.3	3.5	82	73
27	MeCN	rt	1.1	-	0.3	20	100	97
28	MeCN	60	1.1	-	0.3	1	100	97
29	MeCN	82	1.1	-	0.3	0.5	100	95
30	MeCN ^b	60	1.0	0	0.3	3	90	89
31	MeCN ^b	82	1.0	0	0.3	3	83	79
32	MeCN ^b	60	1.1	0	0.3	4	100	97

^aReaction Conditions: **1a** (0.1 mmol) is combined with ylide **2a**, PhI(OAc)₂ and Bu₄NI in solvent (0.1 M) and the reaction is stirred at the indicated temperature for the indicated length of time.

^bConversions listed as >95% indicate that less than 5 mol% of **1a** remained according to quantitative ¹H NMR analysis. ^cYield determined by ¹H NMR, using hexamethyldisiloxane as internal standard. ^dReaction concentration was 0.2 M. ^eAlkylidene **1e** was used in these experiments.

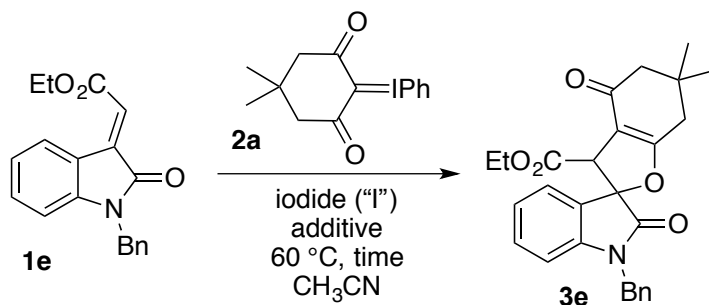
Notes:

- Using the conditions previously reported, at various temperatures, the reaction worked well but the yields were moderate to good. (entries 1-3)
- Increasing the amount of ylide **2a** had little effect on the reaction. We elected to optimize using equimolar ratio of **1a** and **2a**. (entries 1, 4-7)

- Varying solvents showed MeCN to be best, however the reaction could be accelerated with heating. (entries 8-13)
- Varying the loading of the PhI(OAc)₂ / Bu₄NI mixture resulted in similar conversions. (entries 14-17)
- Control experiments: the reaction worked very well with only Bu₄NI. (entries 18-20)
- Varying the loading of Bu₄NI, and the temperature and concentration of MeCN gave high yields and conversions. (entries 21-26)
- Increasing the loading of **2a** gave complete conversion and high yields. Reactions at either 60 °C or reflux were similar yielding, and occurred in similar times. (entries 27-29)
- Testing the reactions with alkene **1e** show the reactions at 60 °C to be better (entries 30-31), and reacting **1e** with 1.1 equiv of **2a** gave **3e** in 97% yield.

Table SI-2: Control Experiments:

The reaction was optimized using alkylidene **1e** and oxonium ylide **2a**.^a



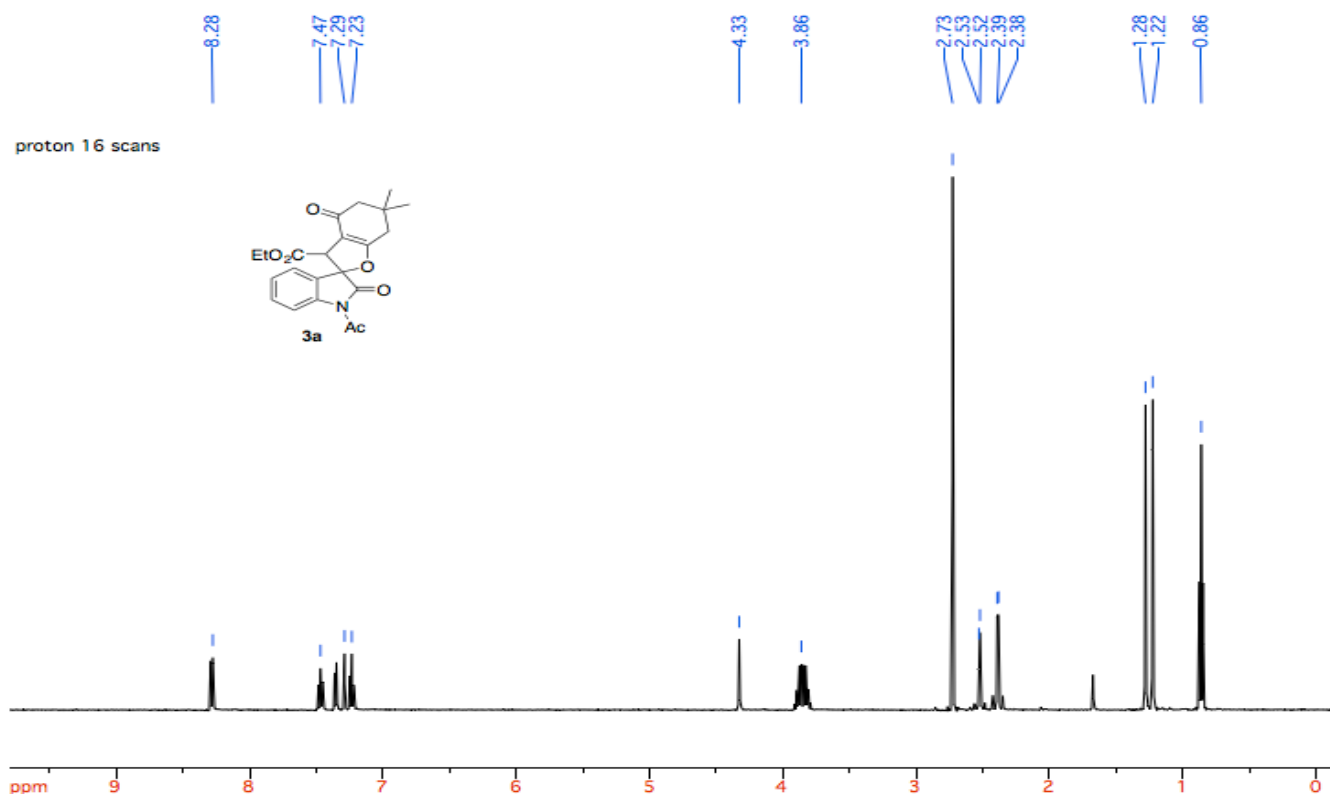
entry	"I" (equiv)	additive (equiv)	Time (hr)	conv. ^b (%)	Yield ^c
1	Bu ₄ NI (0.3)	-	4	100	97
2	-	-	4	8	-
3 ^d	0.3	-	2	25	-
4 ^d	-	-	2	<5%	-
5	I ₂	-	4	10	0
6	NaI	-	4	70	55
7	-	Bu ₄ NBr (0.3)	4	32	31
8	-	Bu ₄ NCl (0.3)	4	19	17
9	Bu ₄ NI (0.3)	BHT (0.3)	4	100	95
10	Bu ₄ NI (0.3)	DDQ (0.3)	4	17	13
11 ^d	Bu ₄ NI (0.3)	DDQ (0.3)	2	100	-
12 ^d	-	DDQ (0.3)	2	77	-

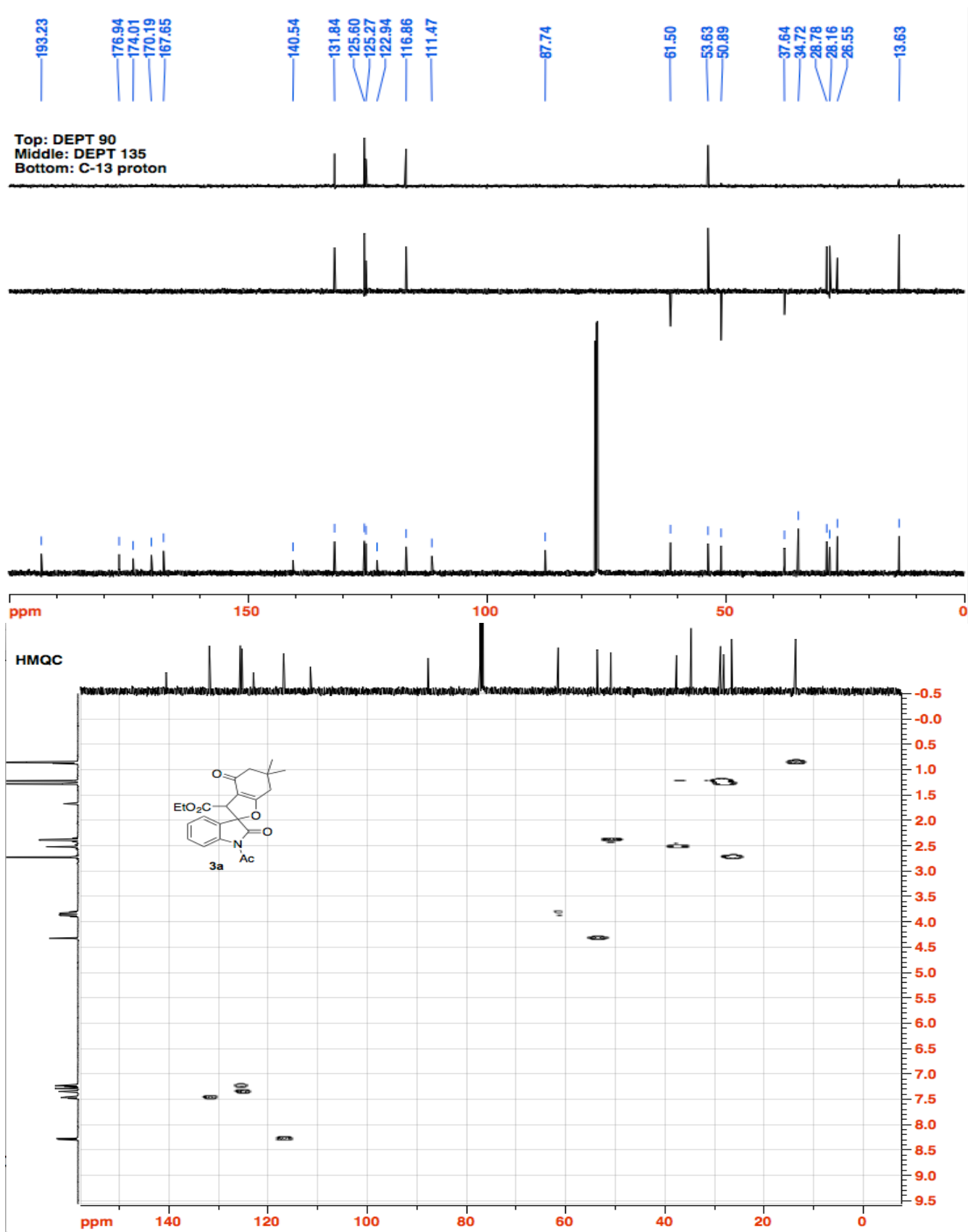
^aReaction Conditions: **1e** (0.1 mmol) is combined with **2a** (1.1 equiv, 0.11 mmol), the iodine source ("I") and the additive in CH₃CN (0.1 M) and the reaction is stirred at the indicated temperature for the indicated length of time. ^bConversion and yield determined by ¹H NMR, using hexamethyldisiloxane as internal standard. ^dSubstrate **1e** was omitted. Conversion refers to ylide (**2a**) consumption.

Notes:

- The standard reaction (entry 1) fails without Bu₄NI (entry 2), which is consistent with the control experiments performed with substrate **1a** (see Table SI-1, entries 18-19).
- The ylide is slightly decomposed (25% consumption) by Bu₄NI over 2 hours at 60 °C, however the ylide alone is only slightly decomposed under these conditions (entries 3,4).
- NaI could be used instead of Bu₄NI, but not I₂, and though Bu₄NCl and Bu₄NBr could be used, the yields were greatly decreased (entries 5-8).
- Adding the radical inhibitor BHT failed to suppress the reaction, giving **3e** in 95% yield (entry 9).
- Adding the radical inhibitor DDQ caused the reaction to fail, with only 13% of **3e** produced (entry 10).
- Reacting **2a** with Bu₄NI and DDQ resulted in complete decomposition of the ylide (entry 11), and heating **2a** with DDQ alone also resulted in 77% consumption of the ylide. It appears that **2a** is being chemically degraded by DDQ under the reaction conditions, and that the result of entry 10 is a by-product thereof.

NMR Spectra Used for Structural Elucidation of **3a**:





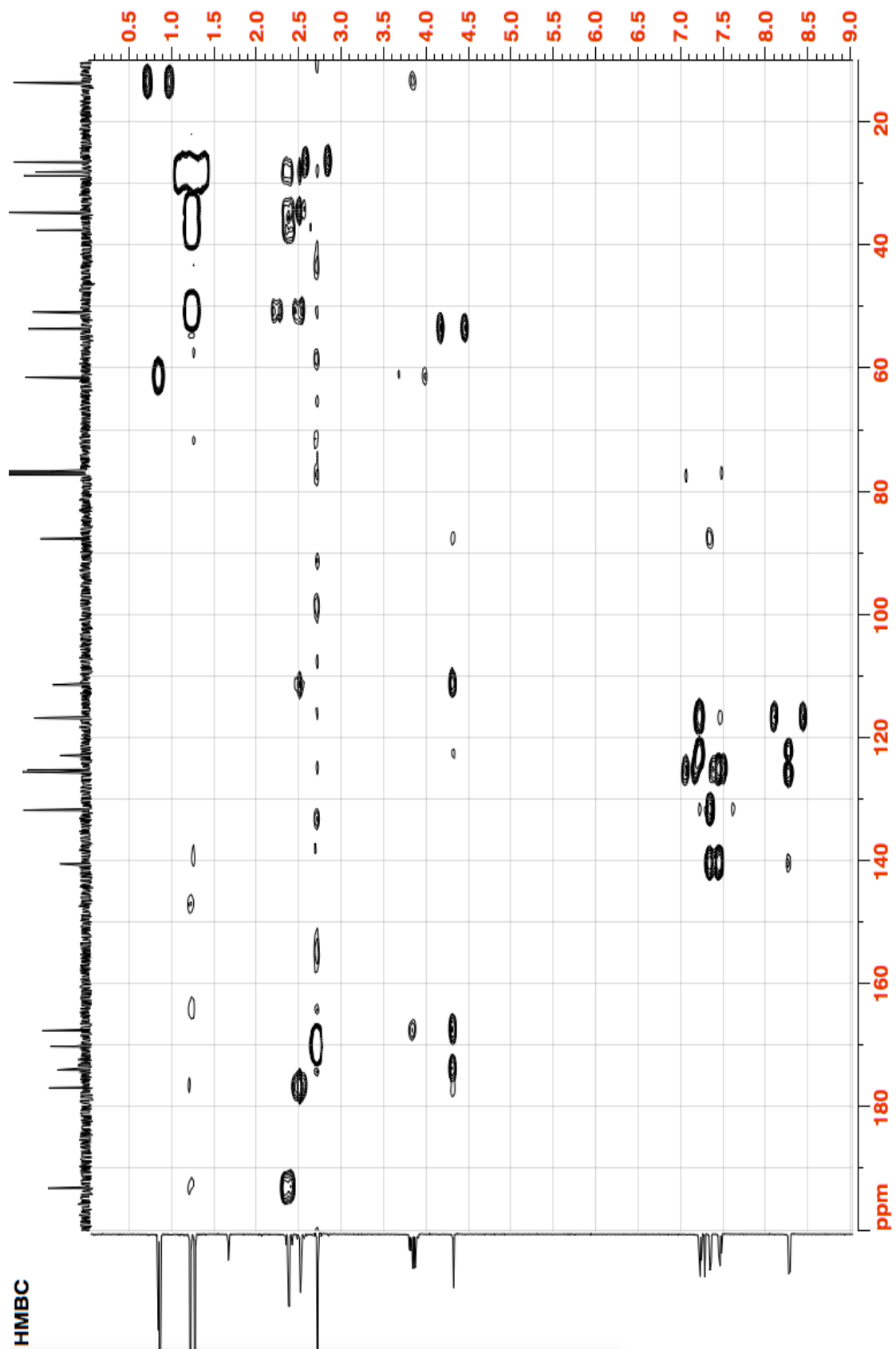
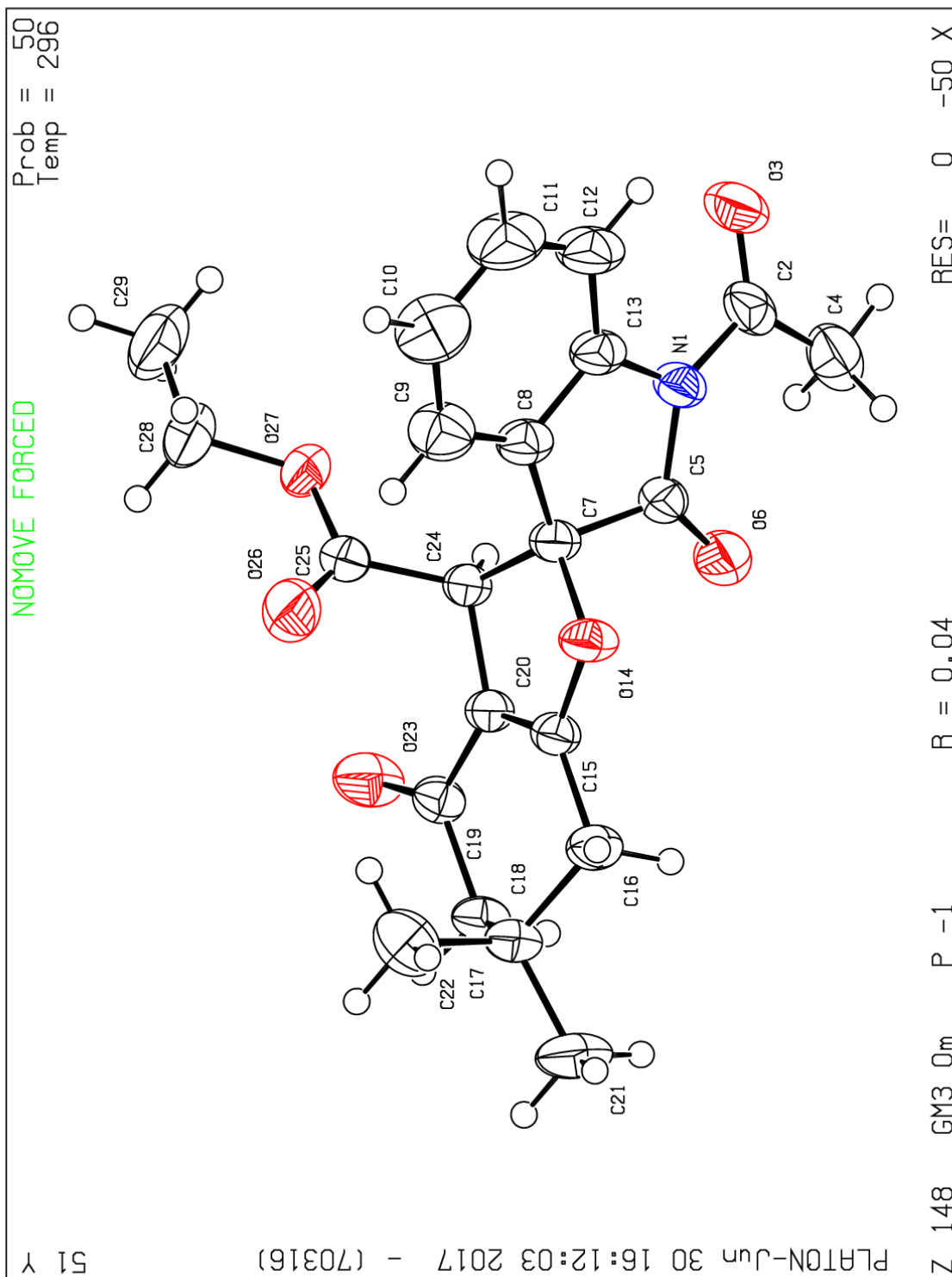
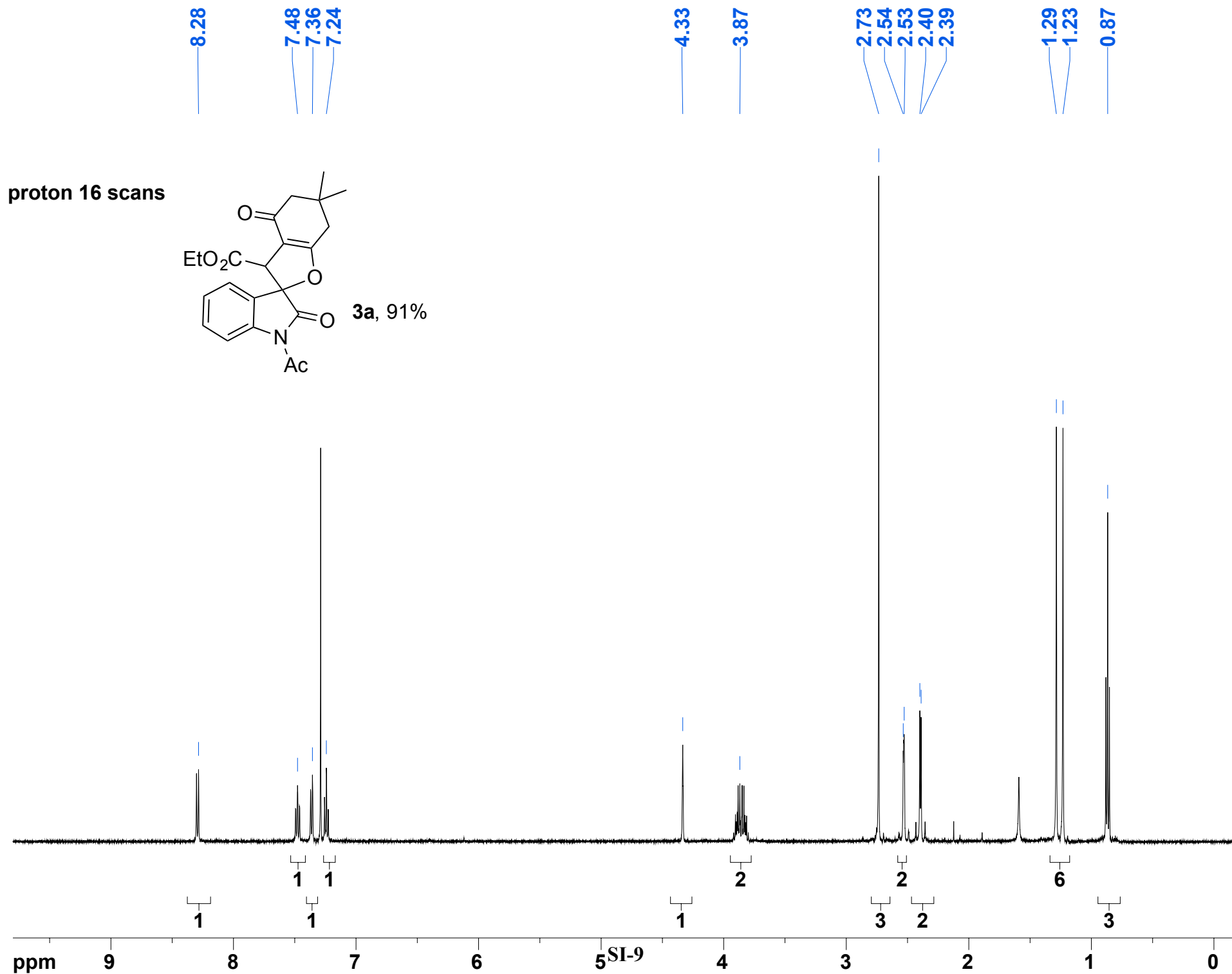
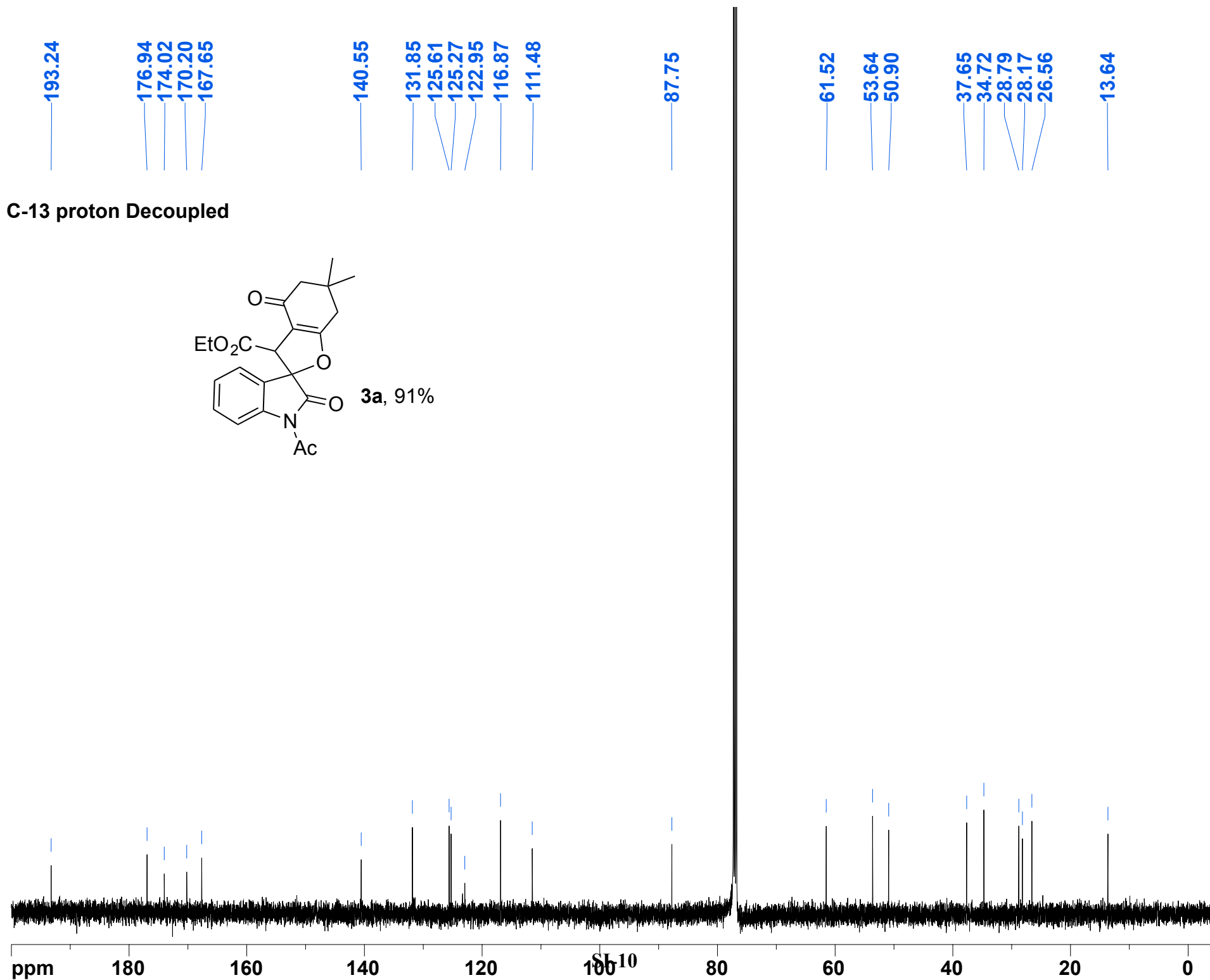


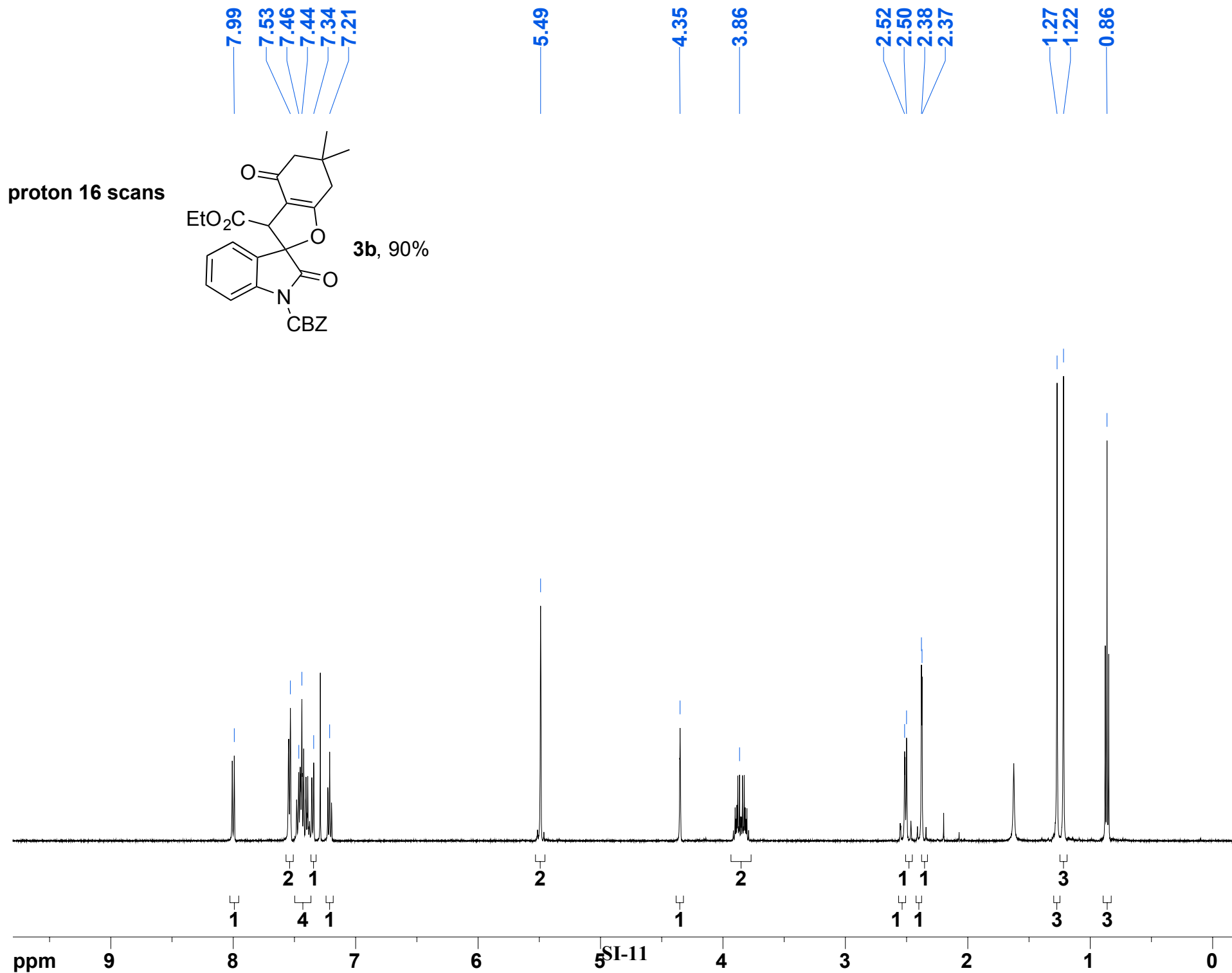
Figure SI-1: ORTEP representation (50% probability) of the crystal structure of 3a.

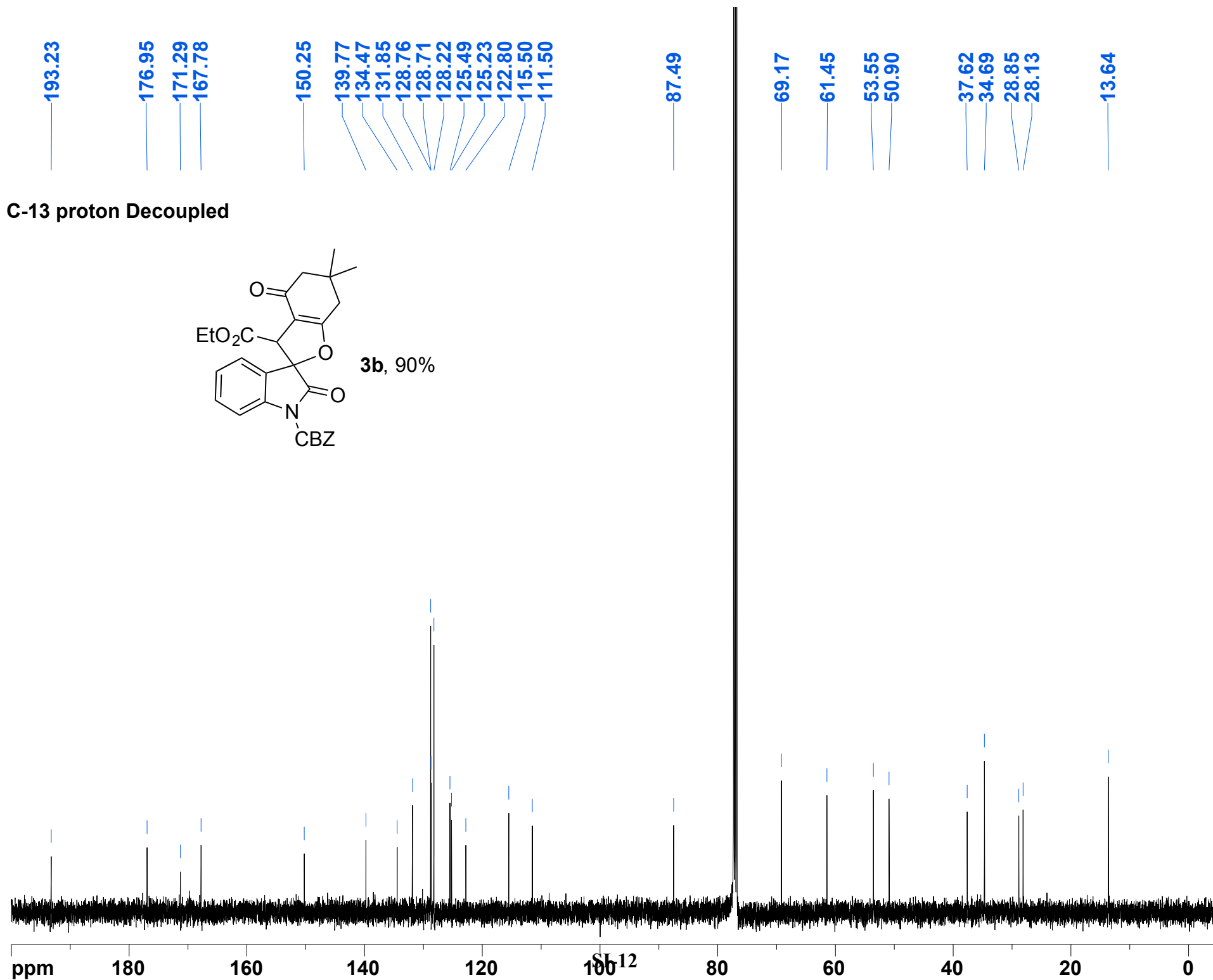


^1H , ^{13}C and ^{19}F Spectra of New Compounds

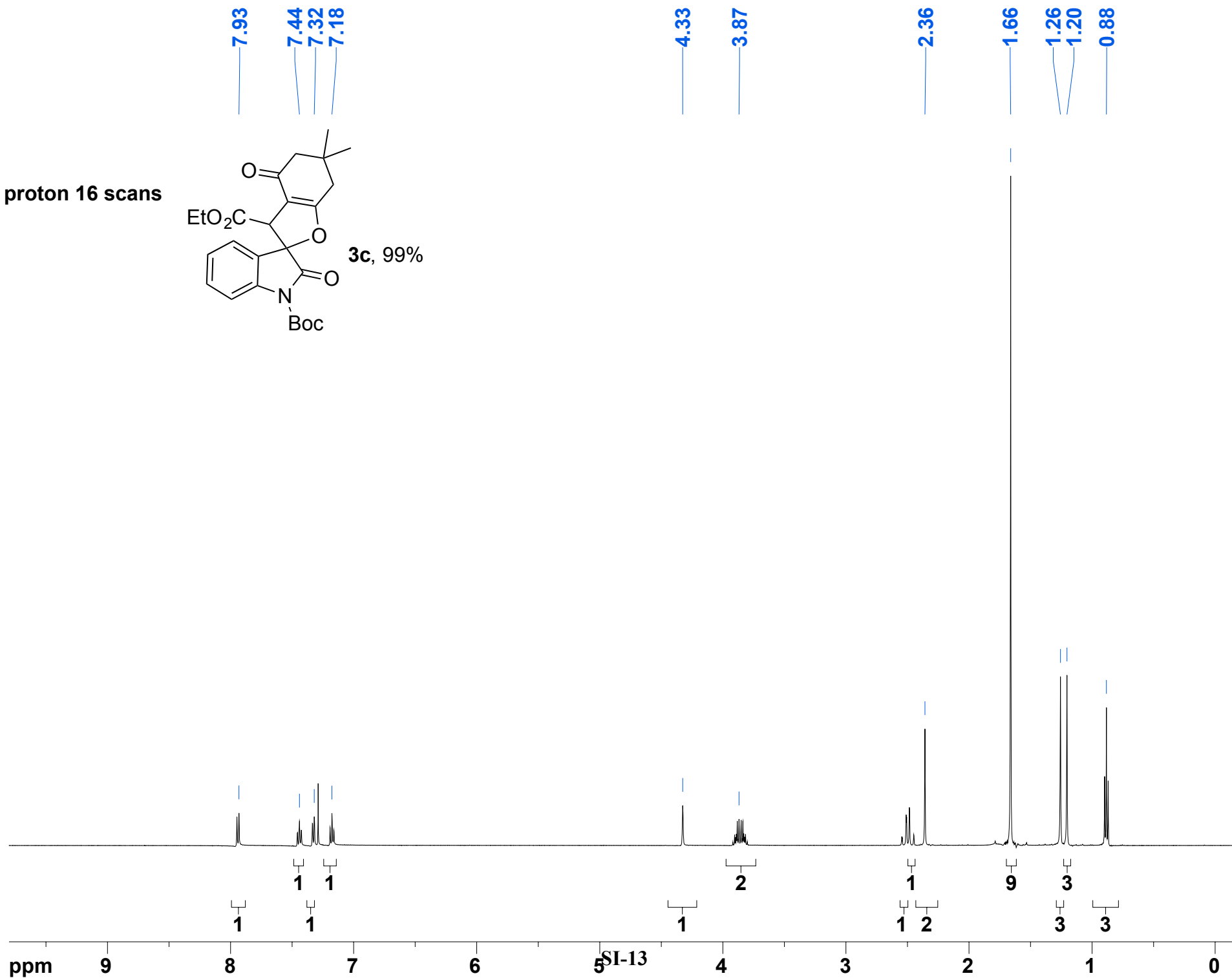
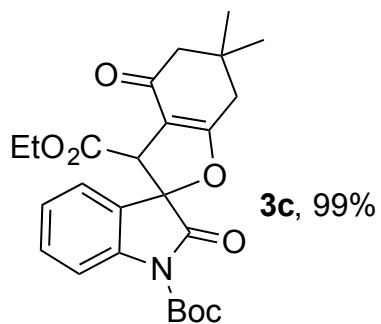


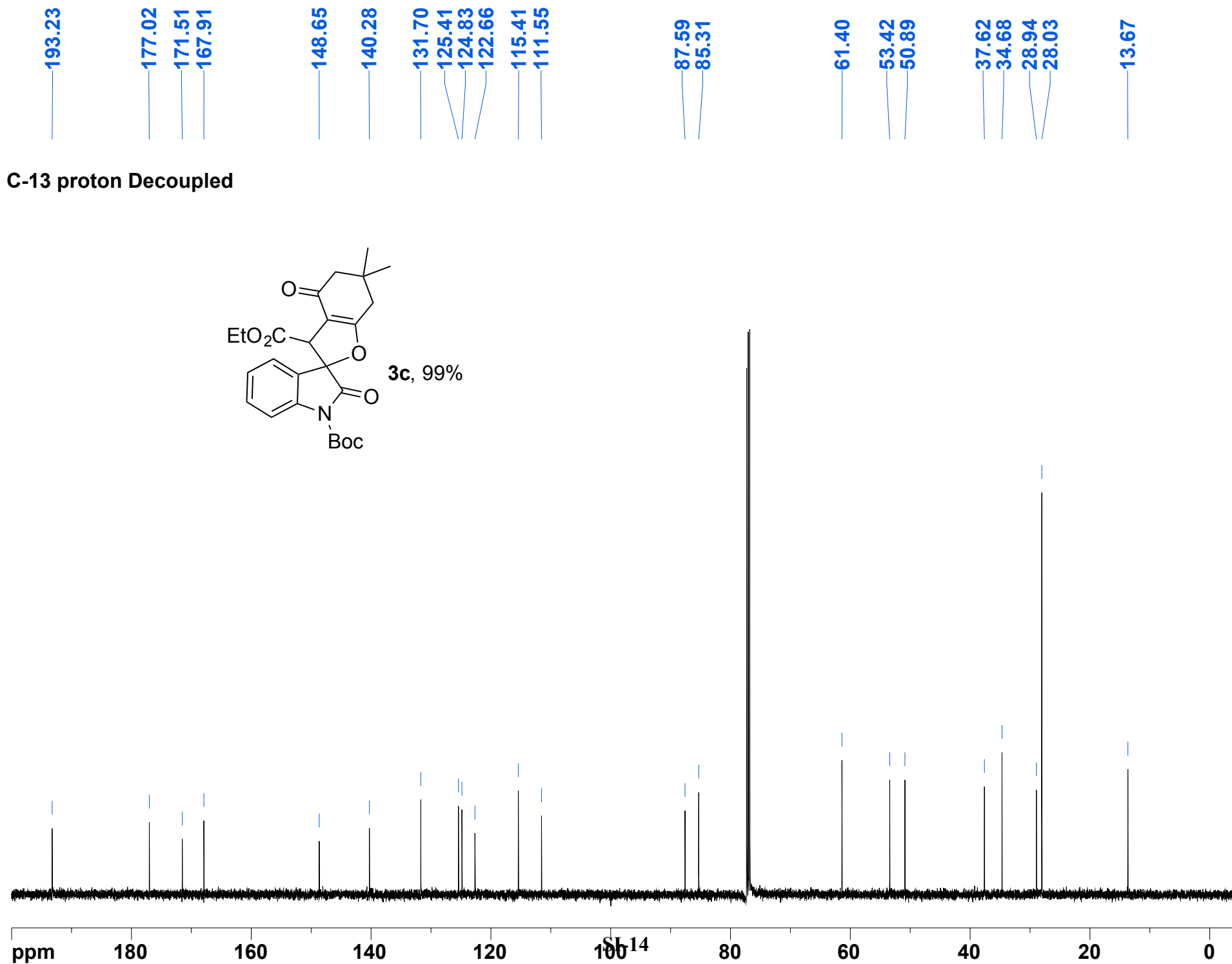






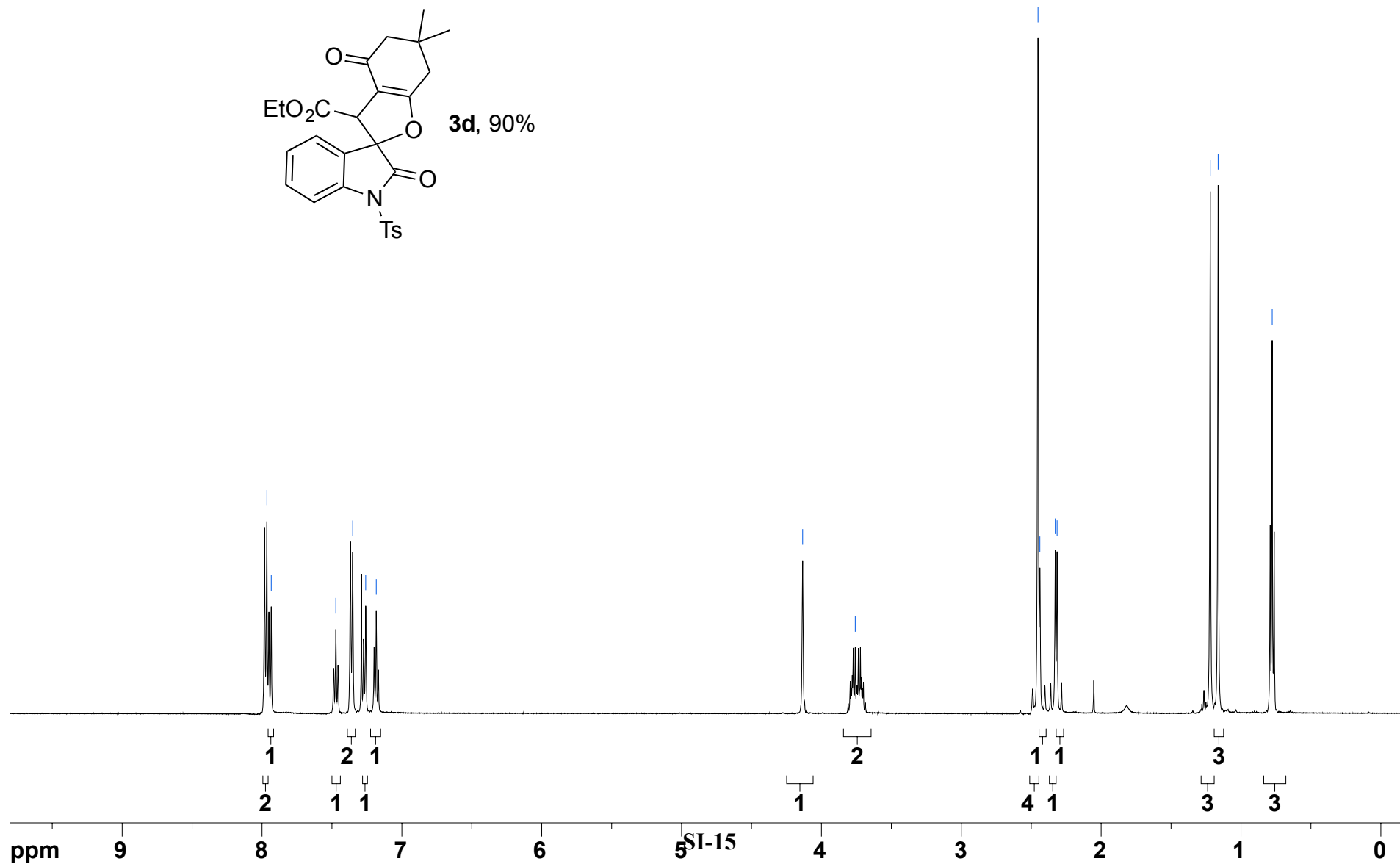
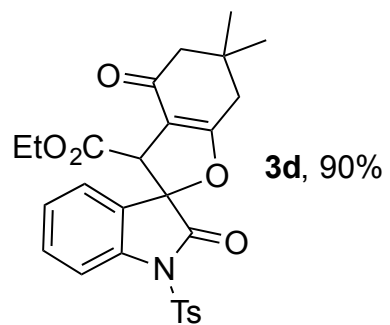
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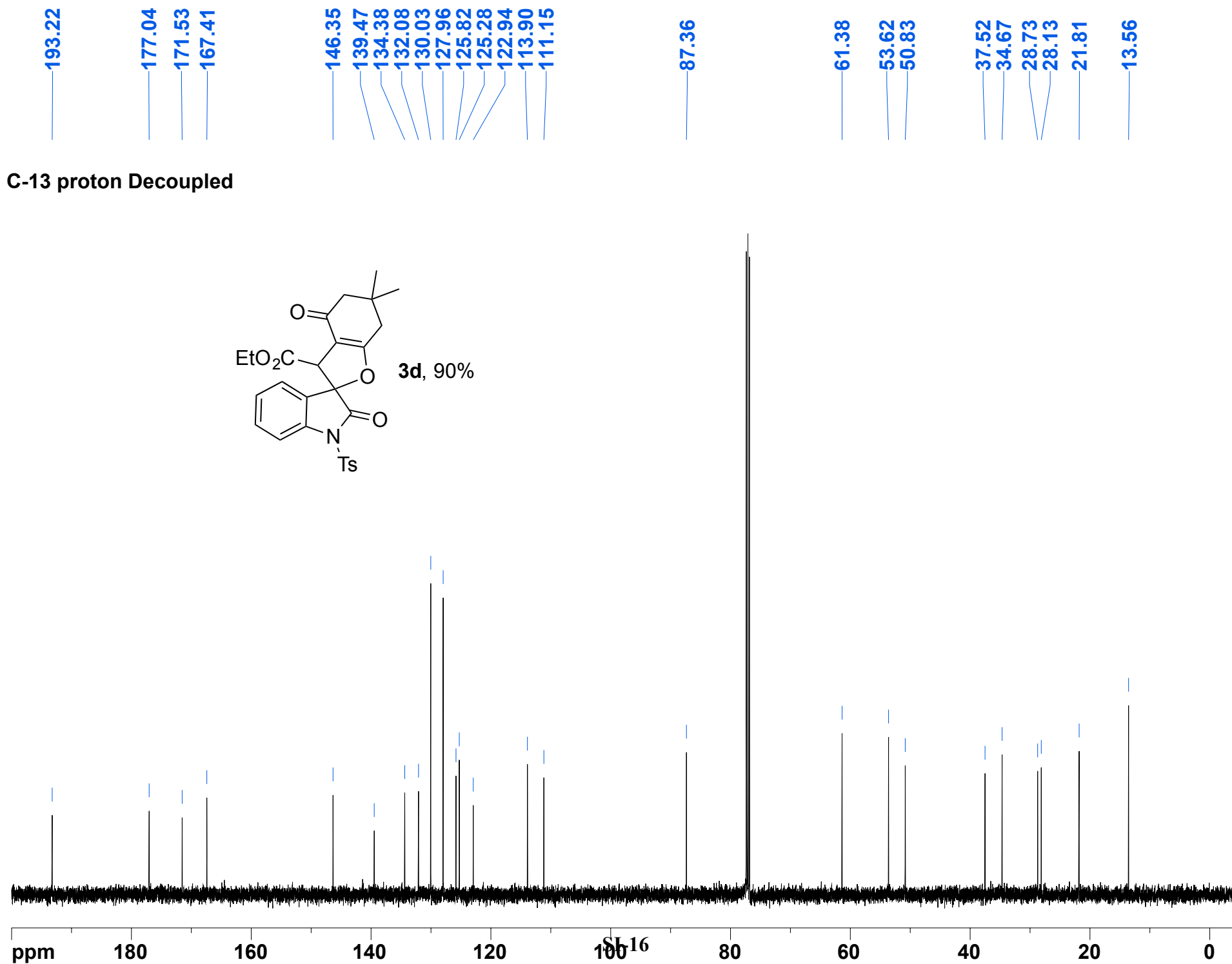




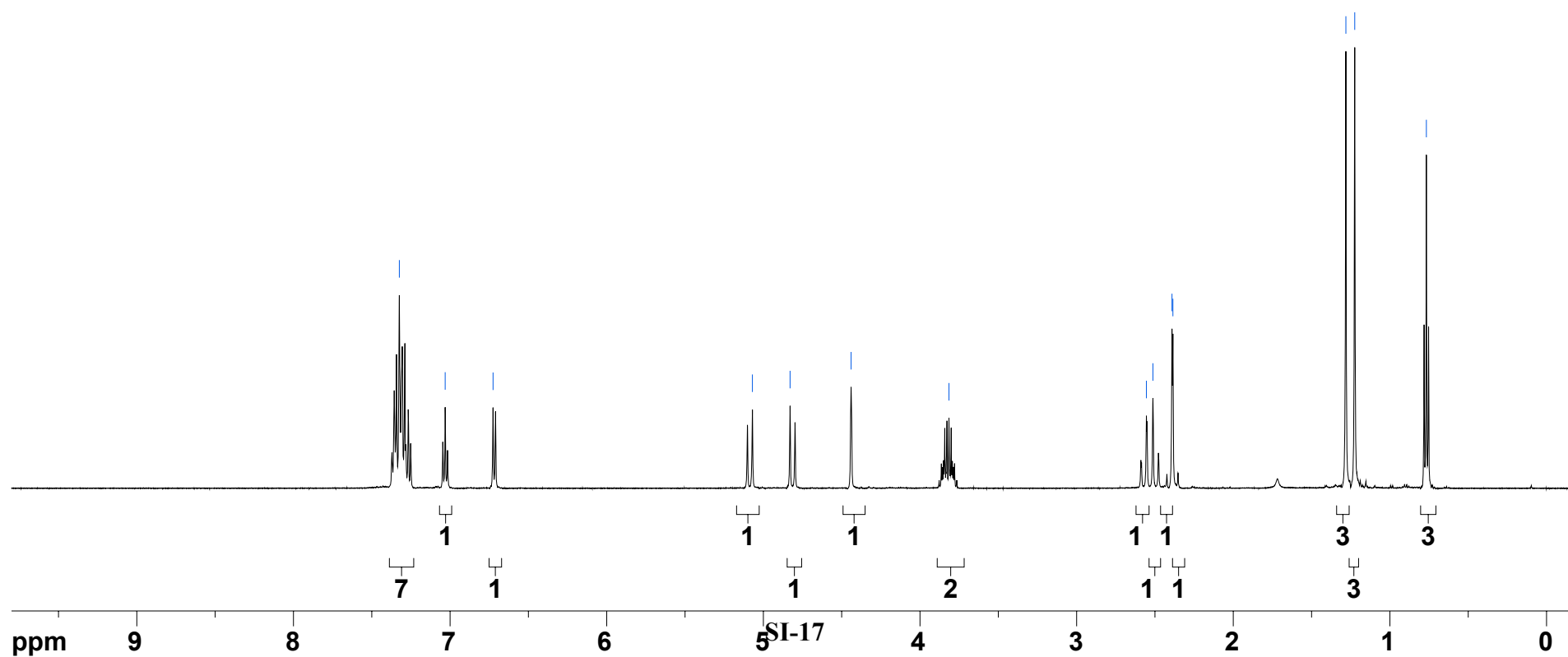
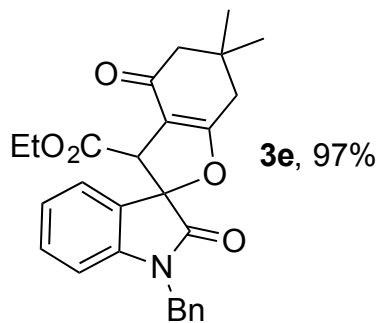


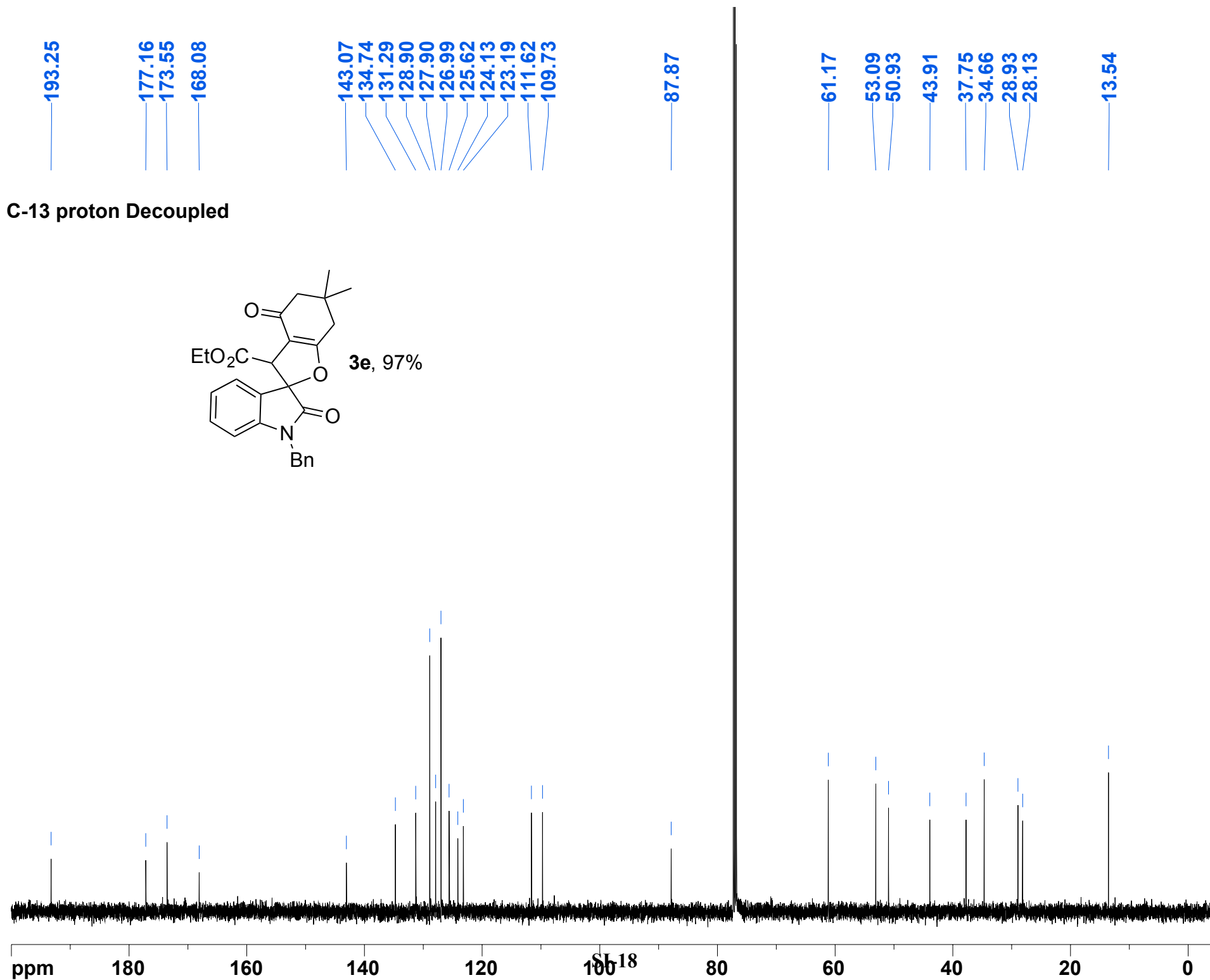
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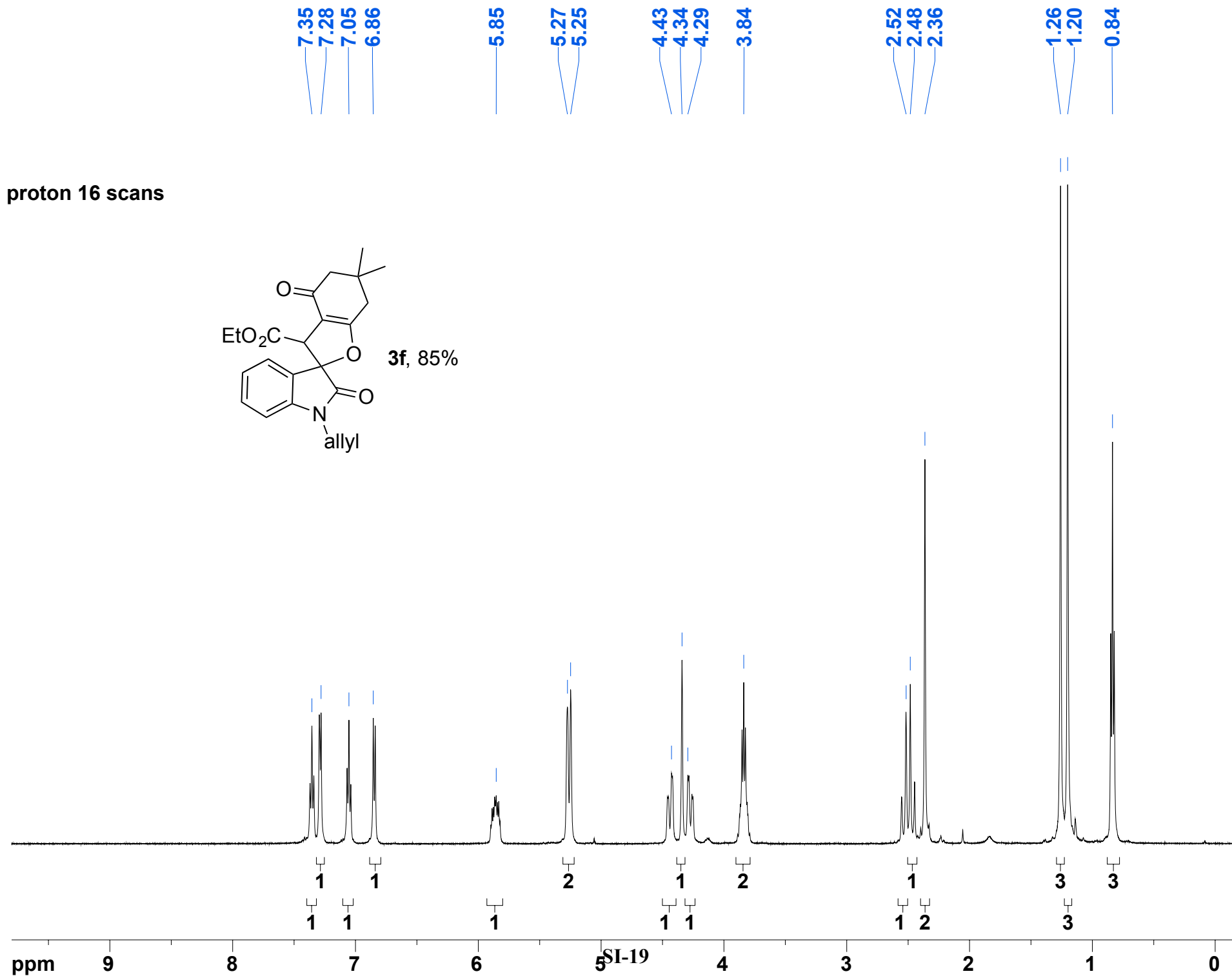


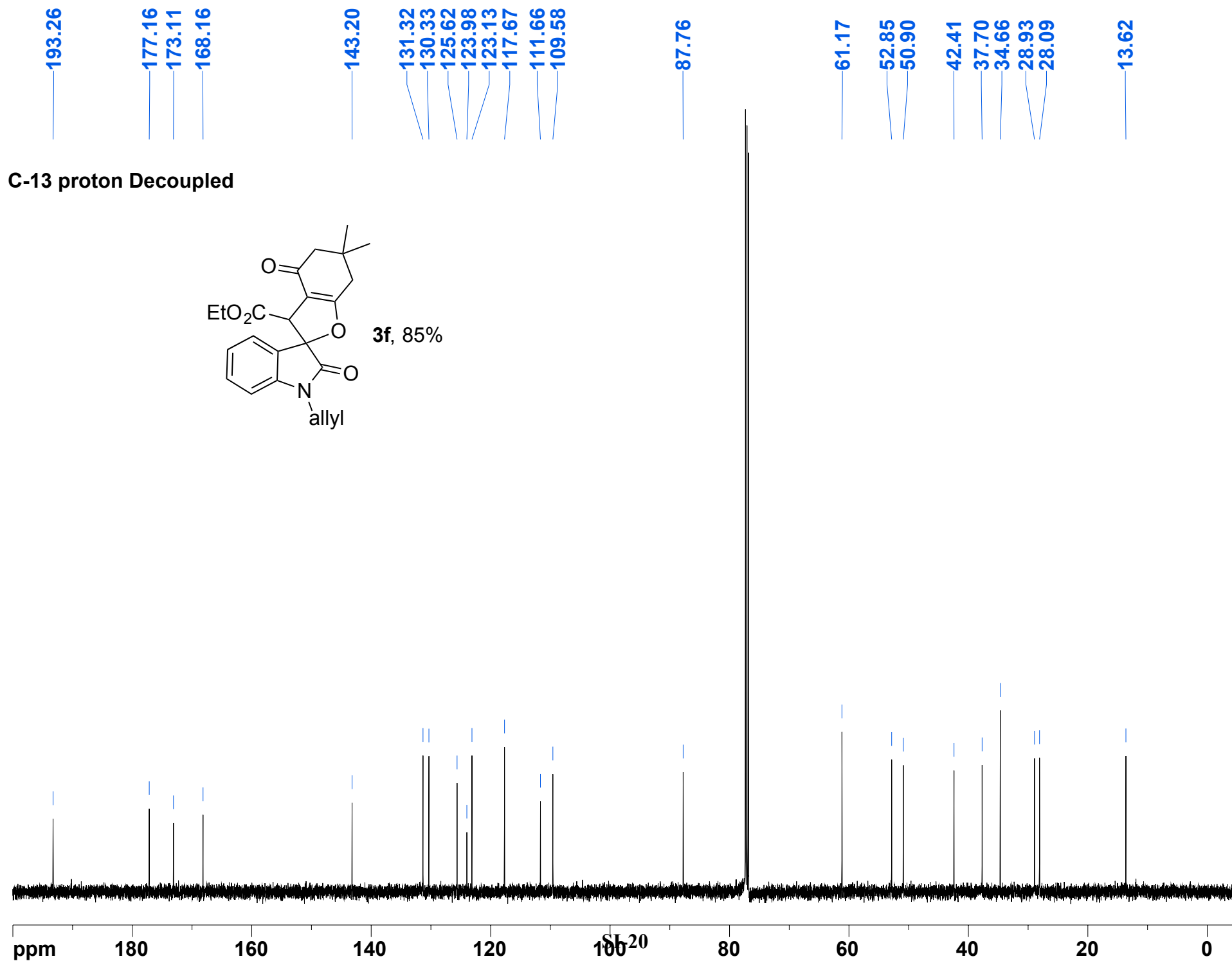


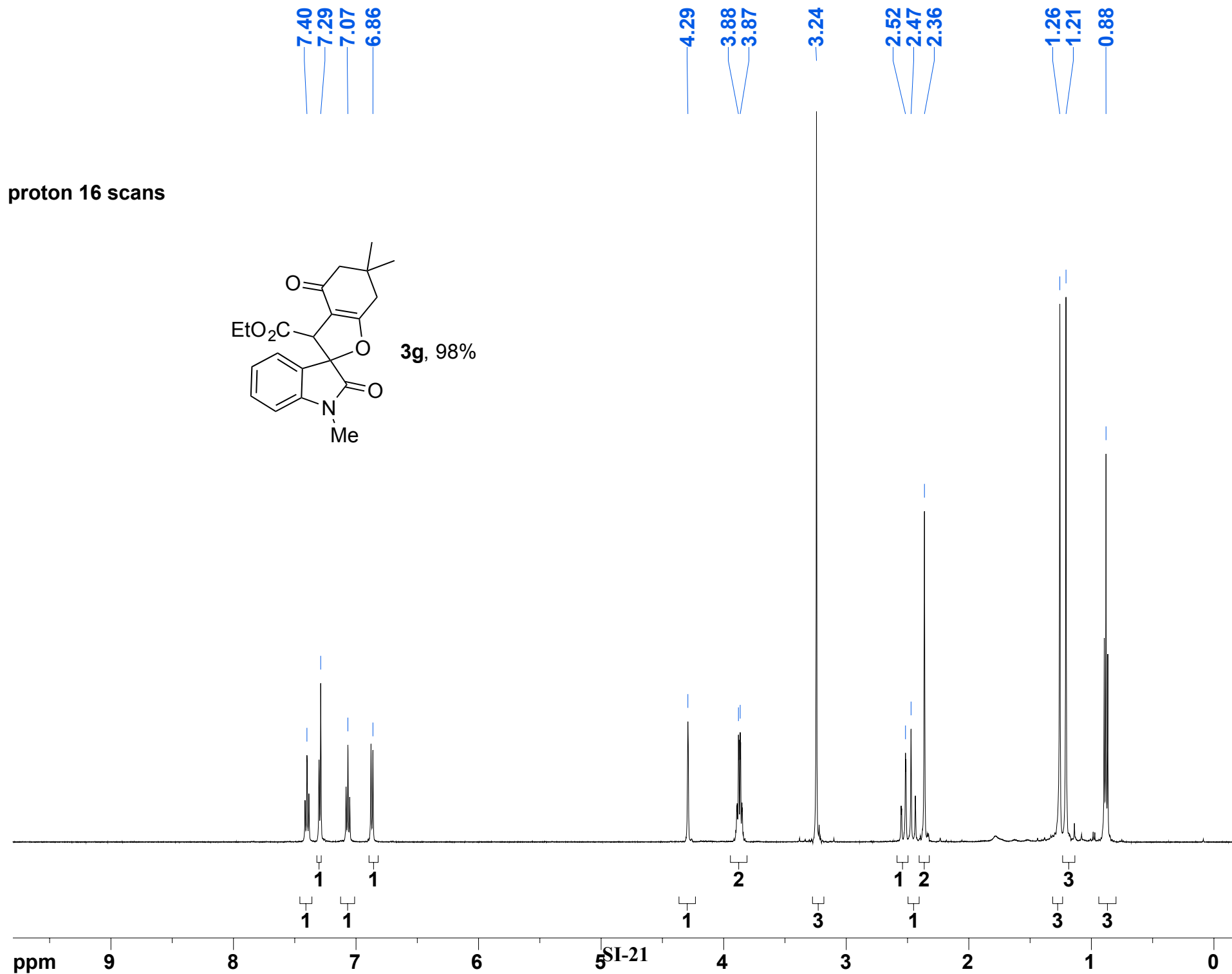
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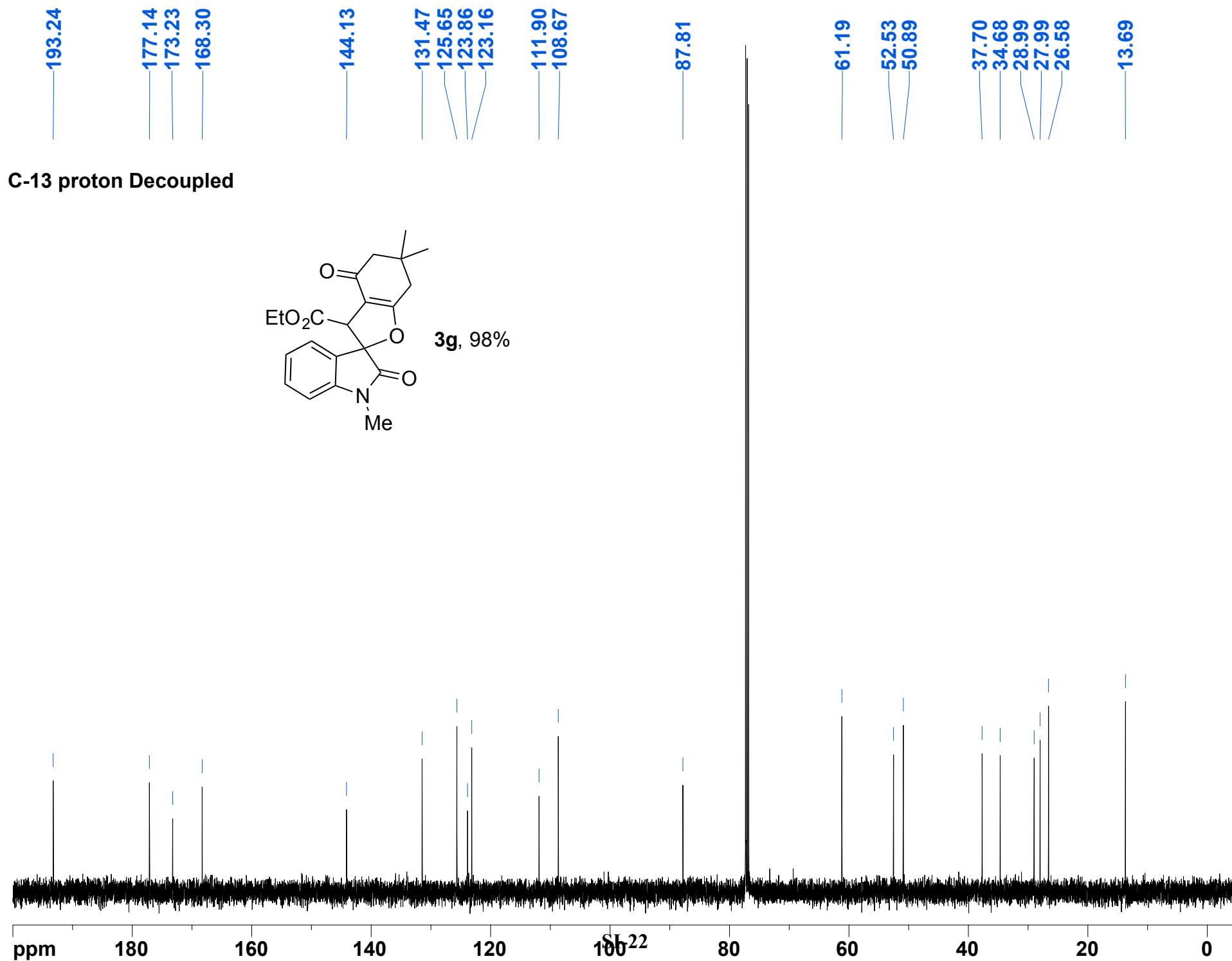


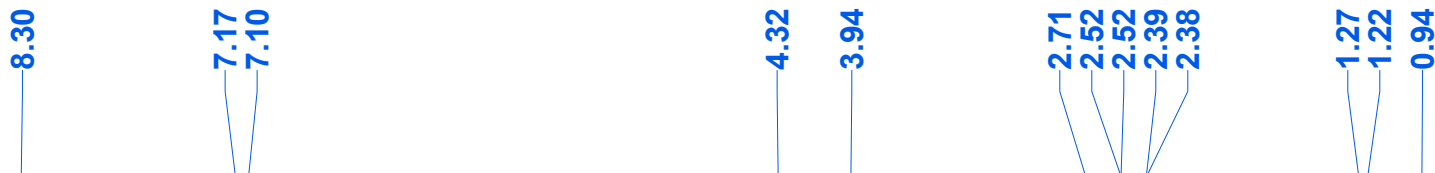




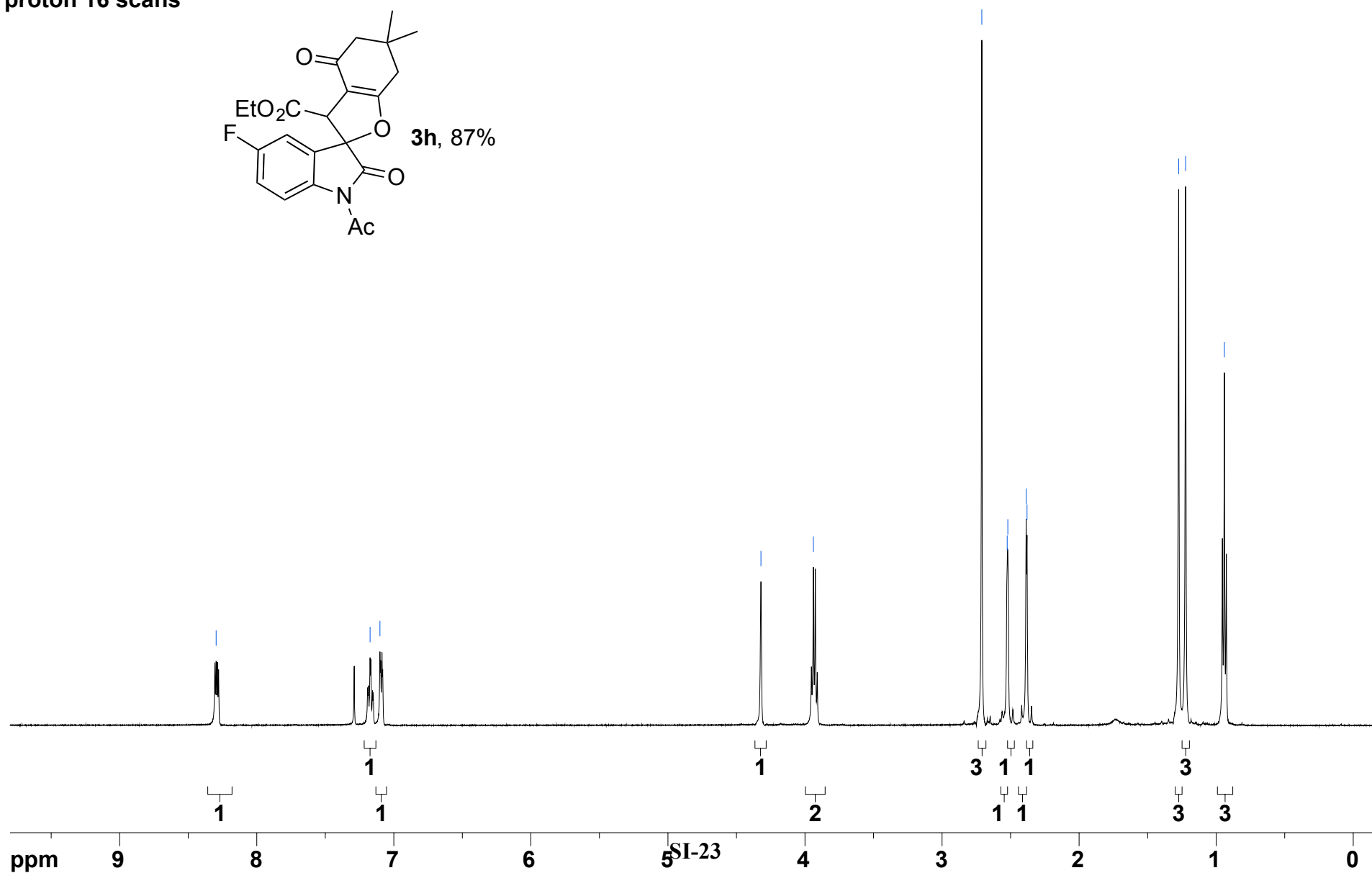
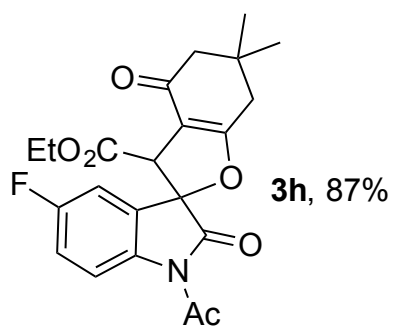


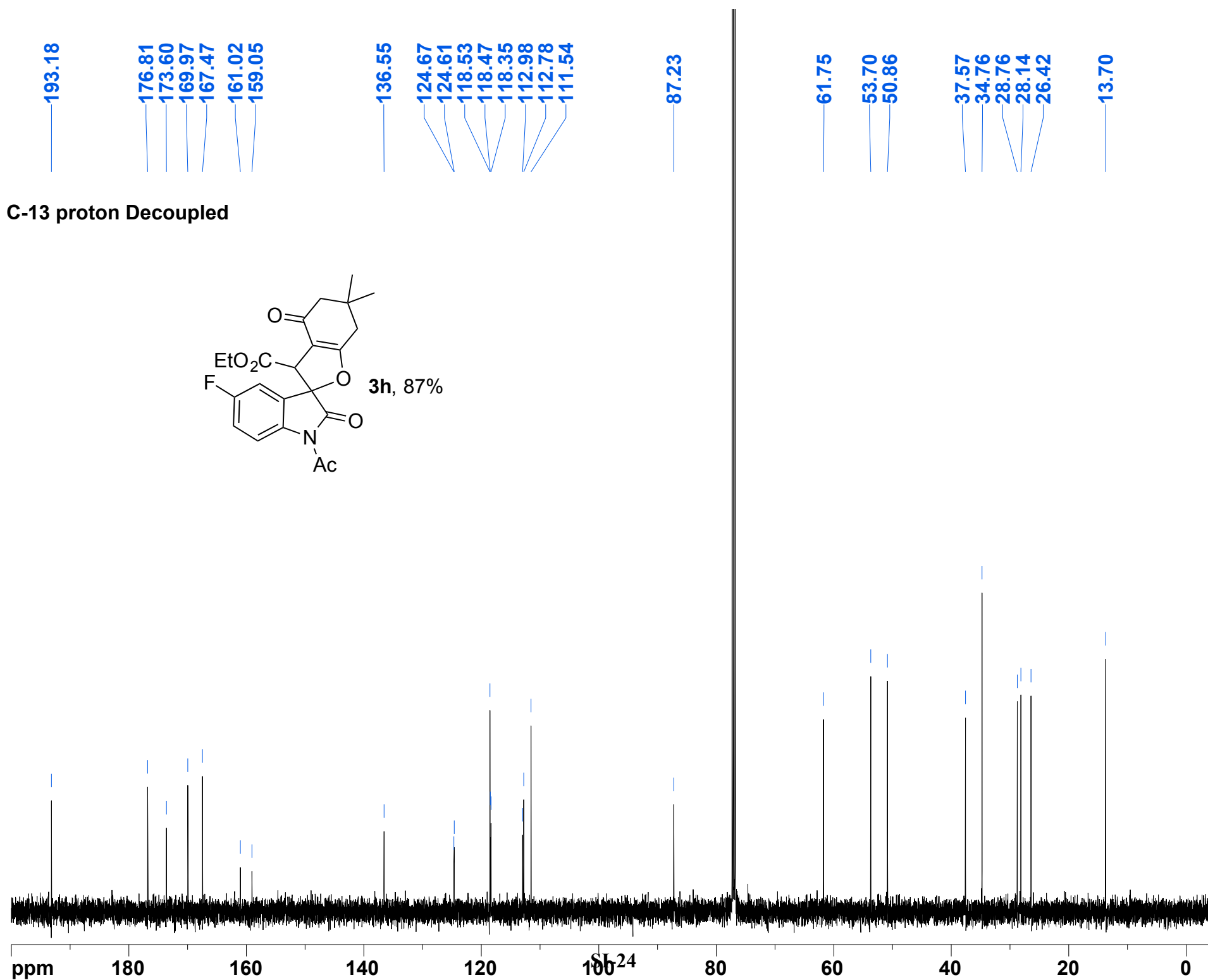






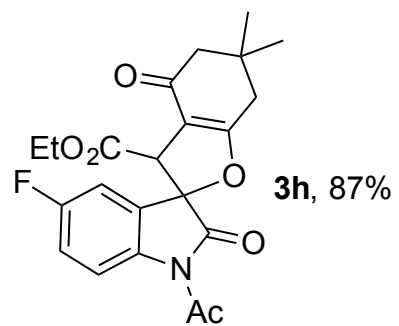
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-114.73

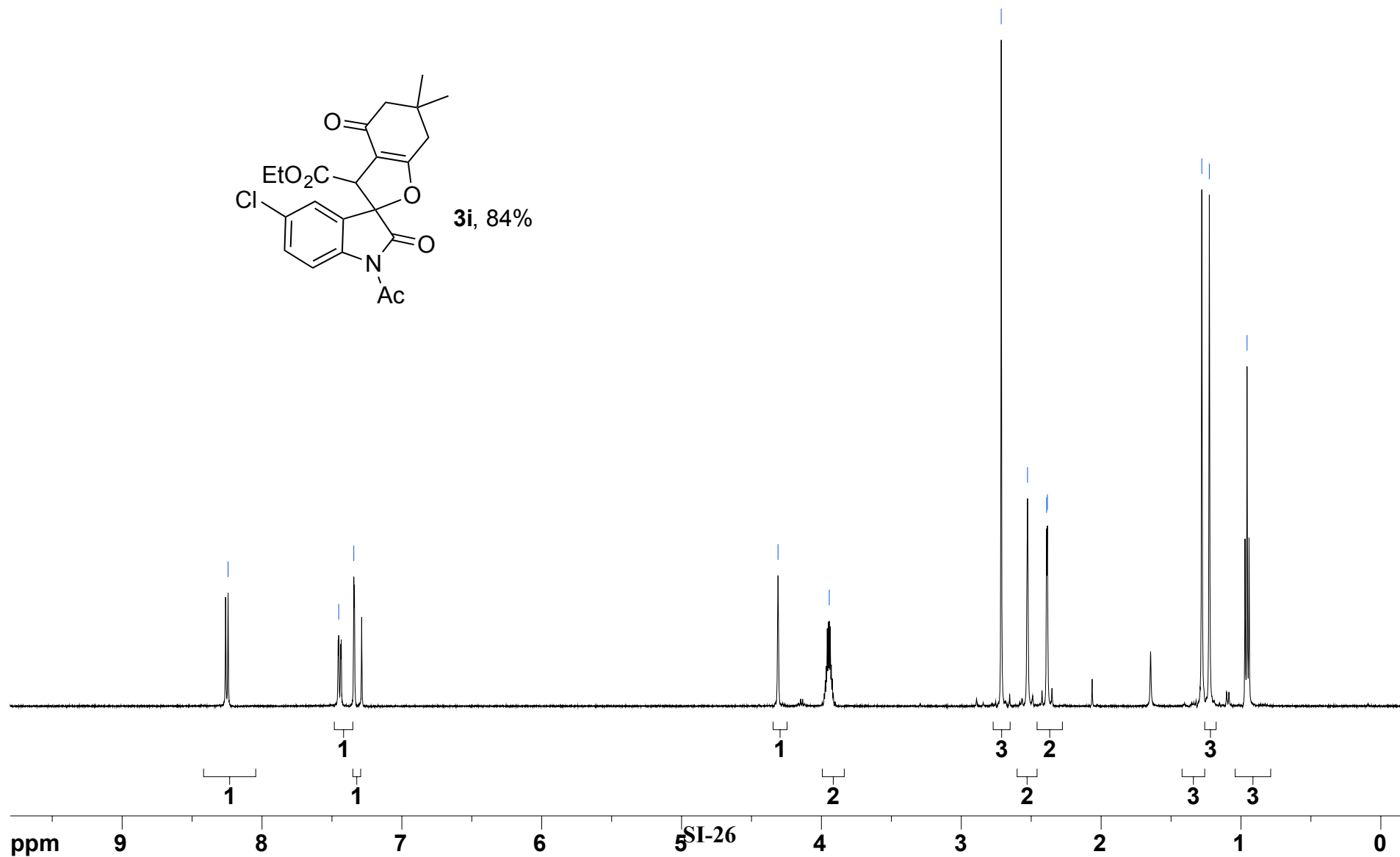
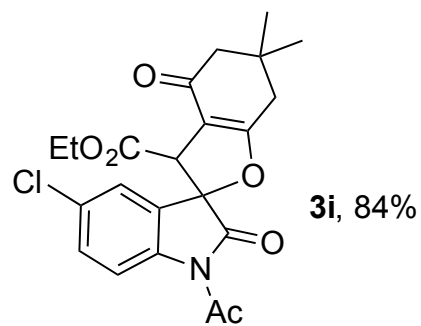
F-19 Observed No H1 Decoupling referenced to TFA at -76.5 ppm

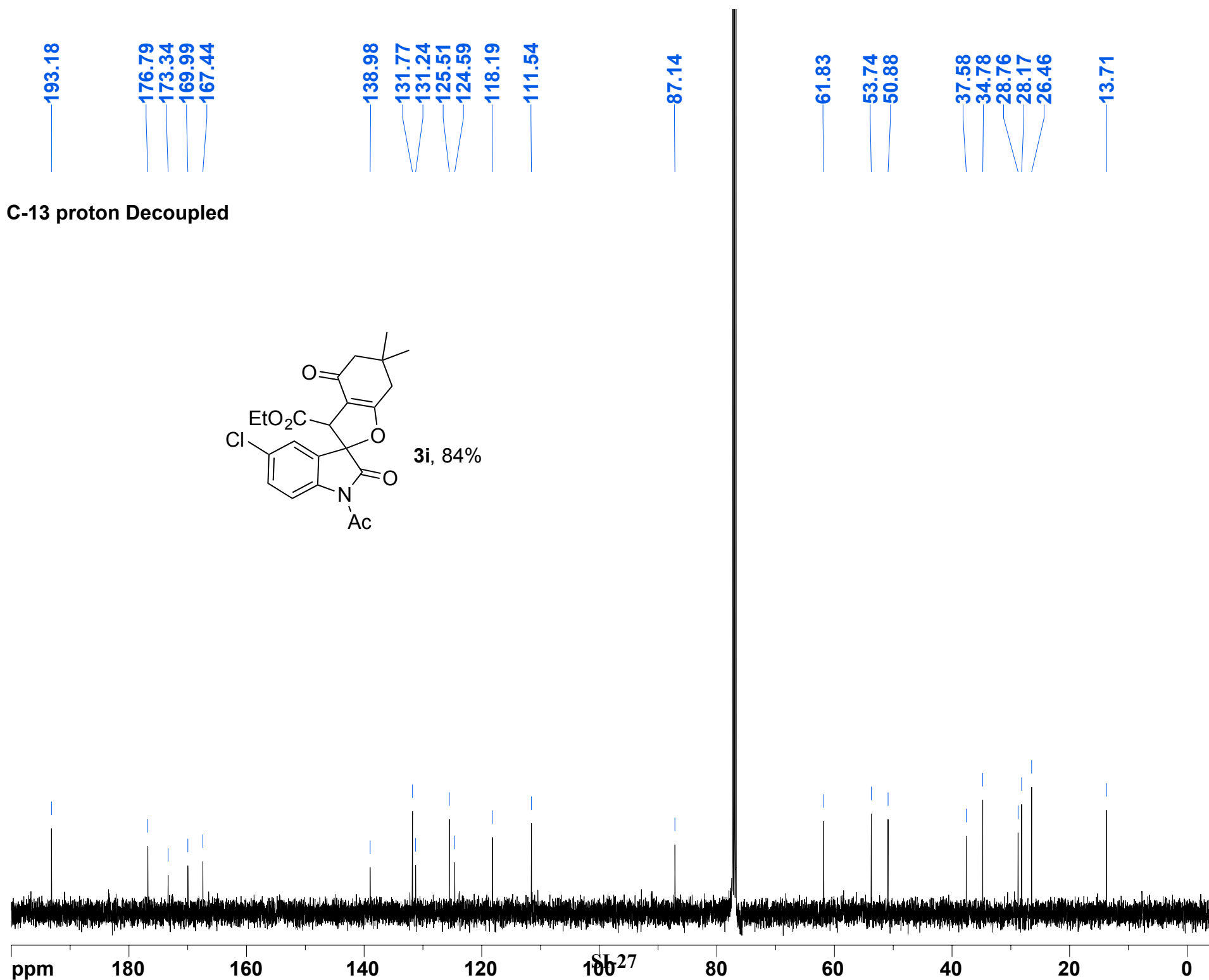


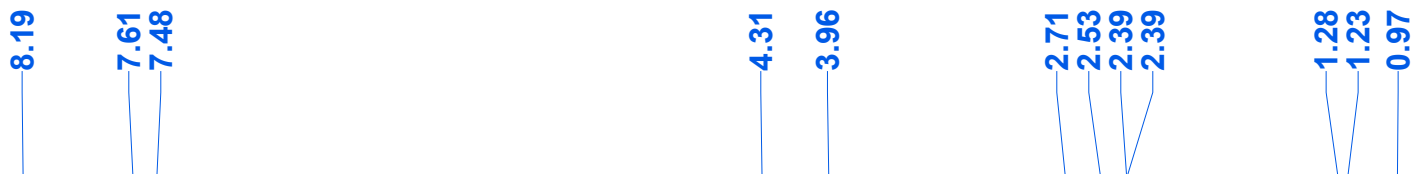
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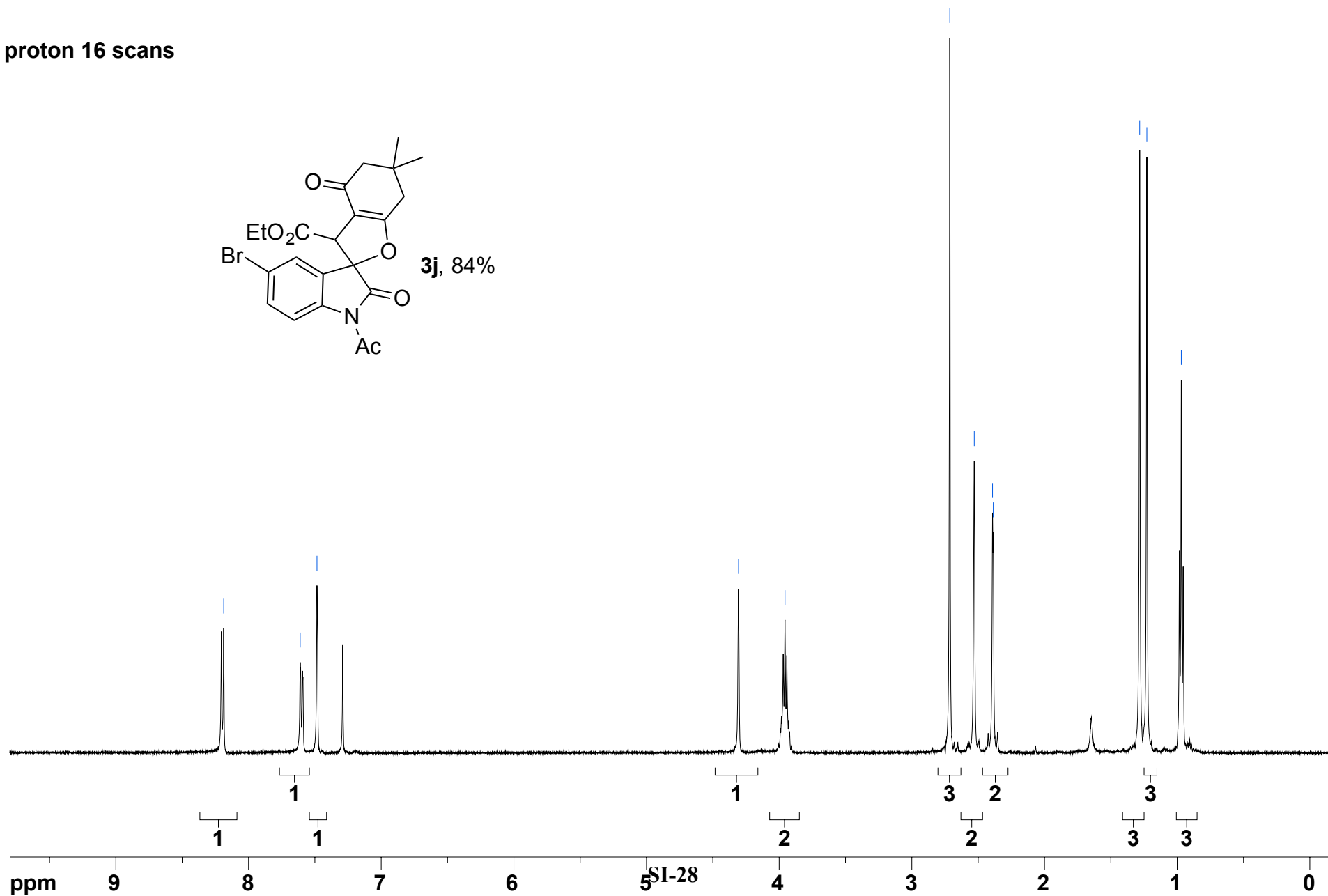
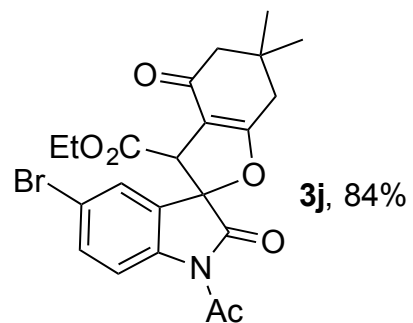
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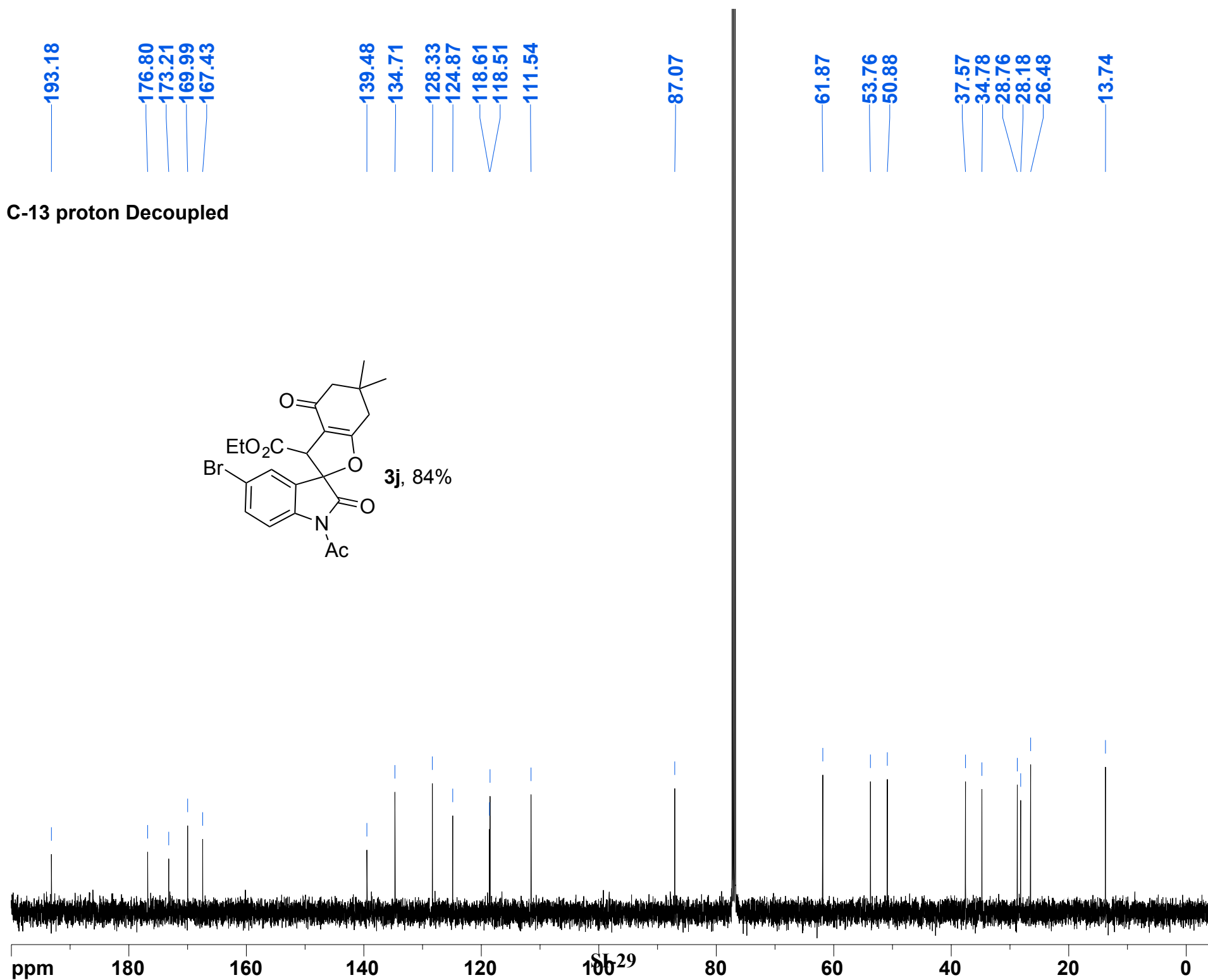


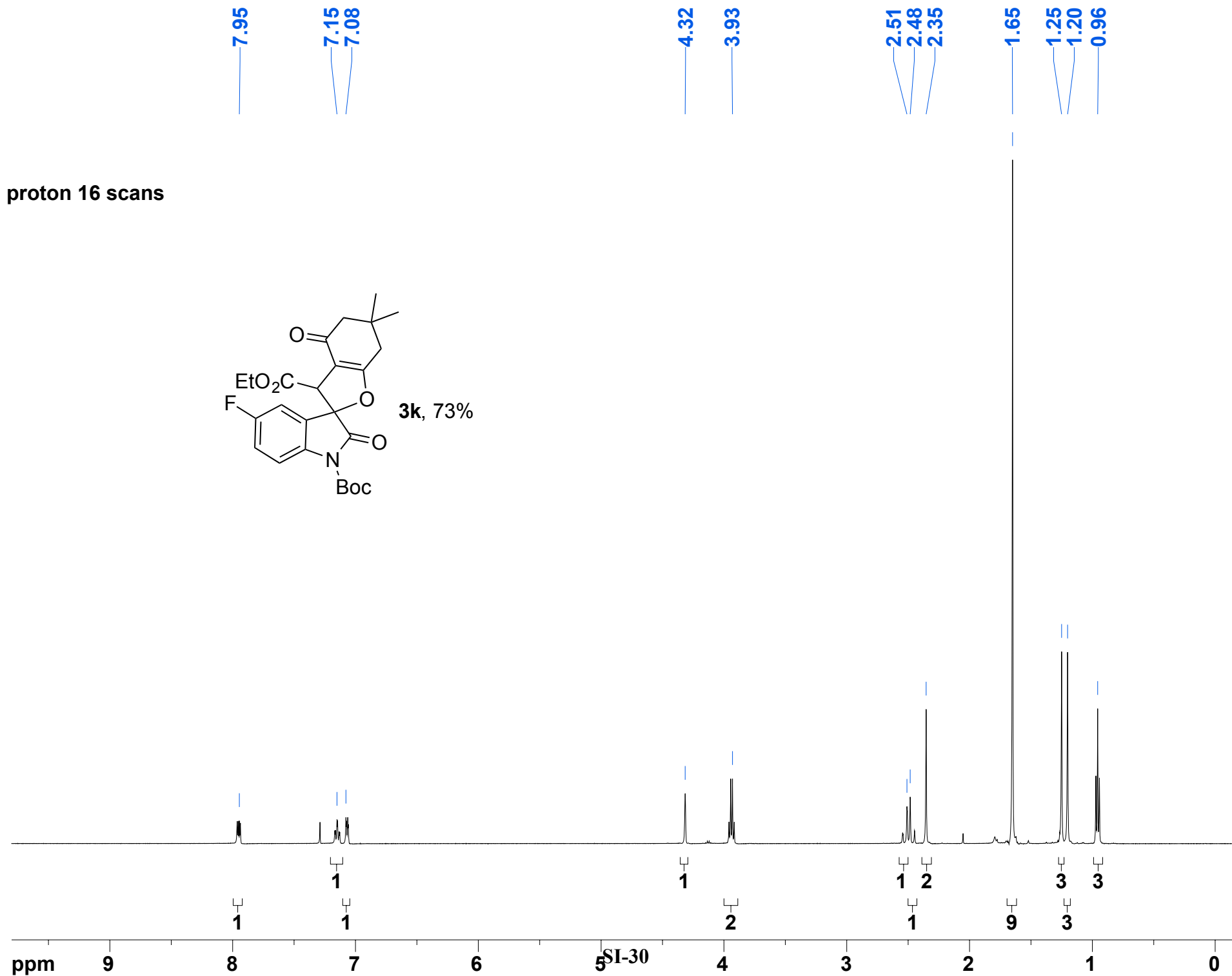




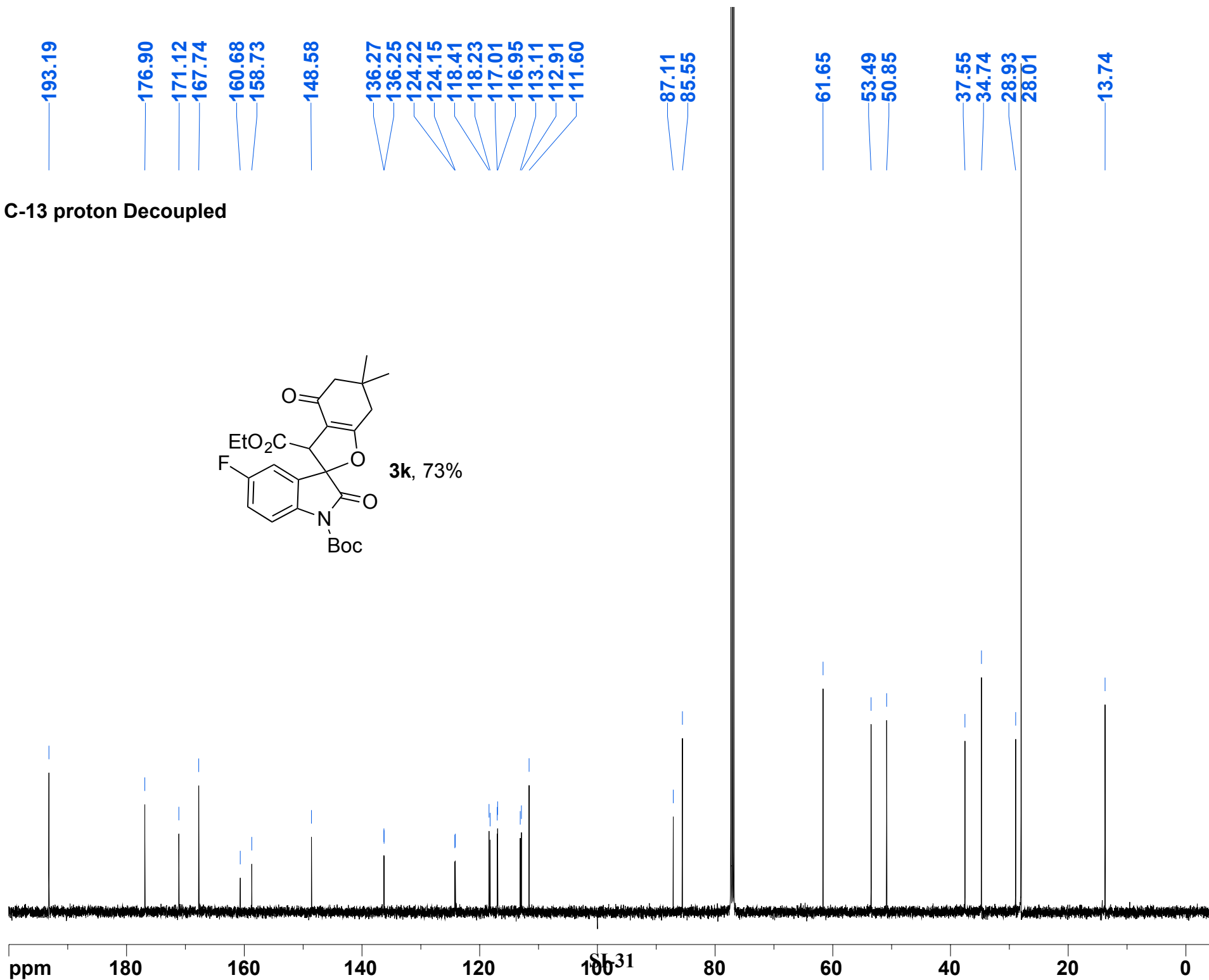
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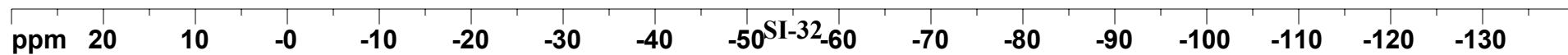
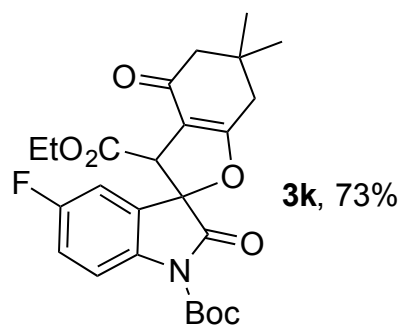


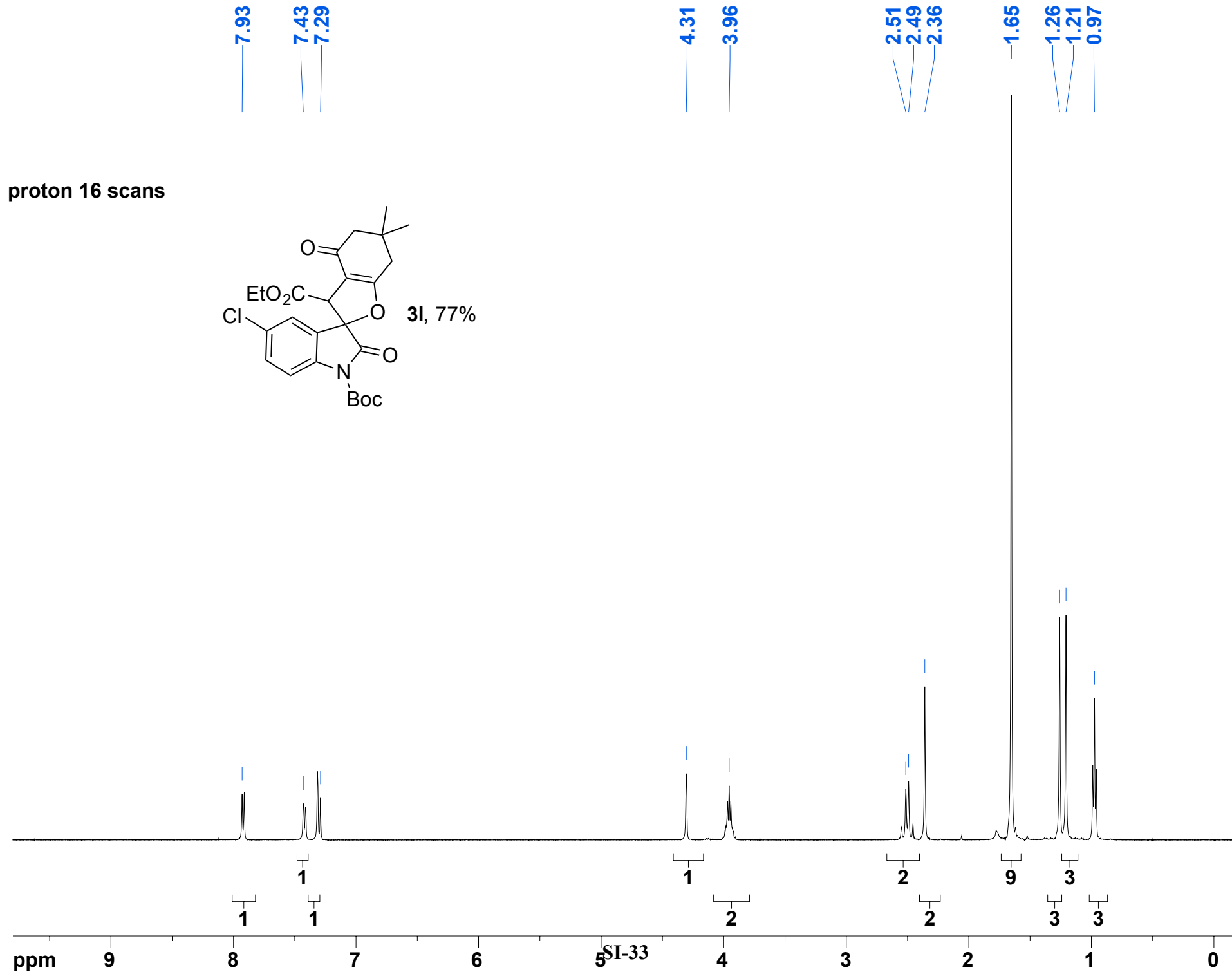
C-13 proton Decoupled

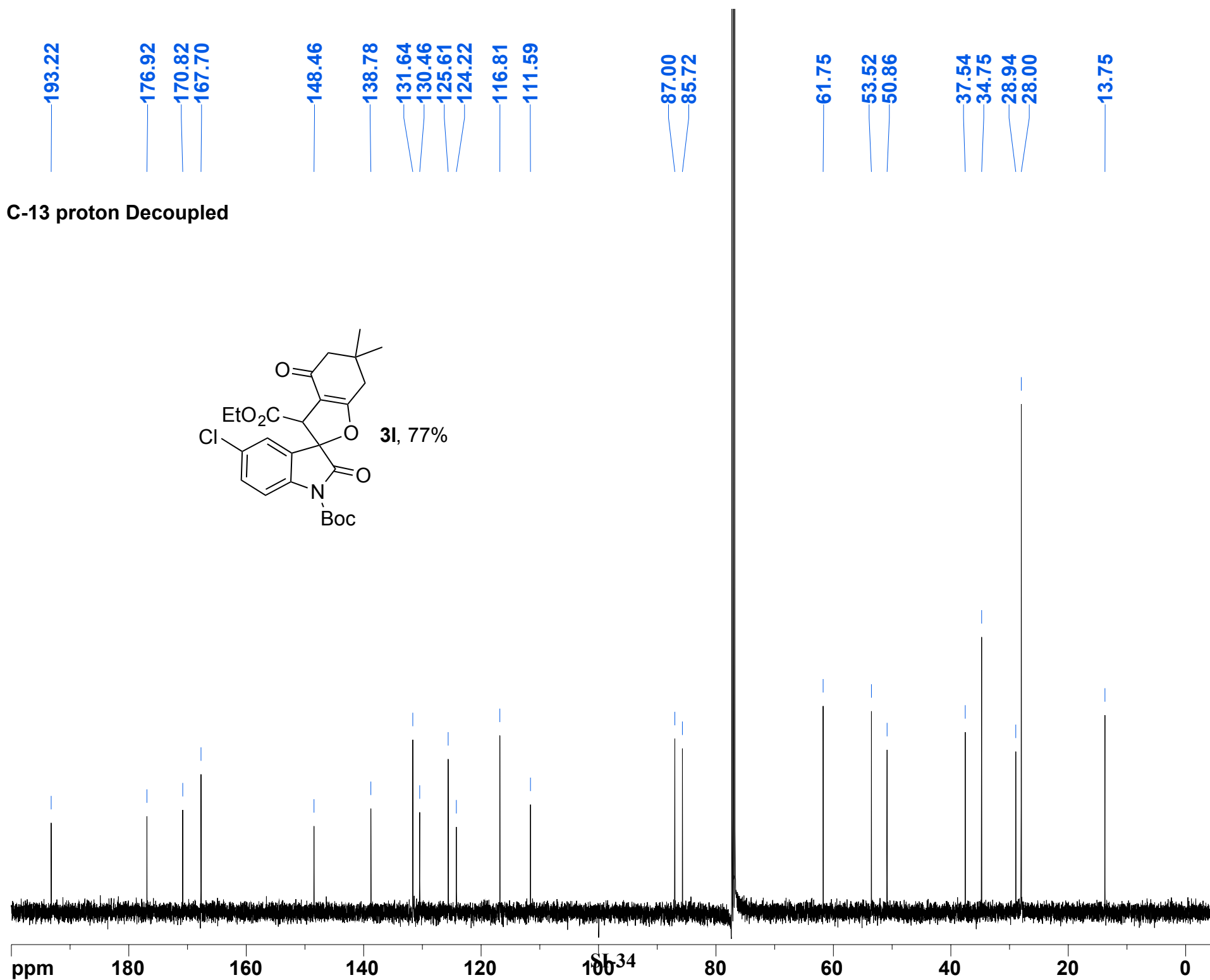


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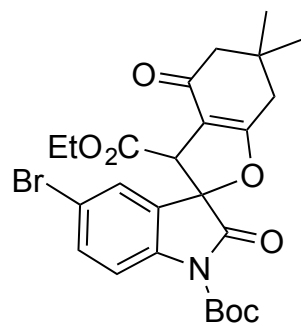
F-19 Observed No H1 Decoupling referenced to TFA at -76.5 ppm



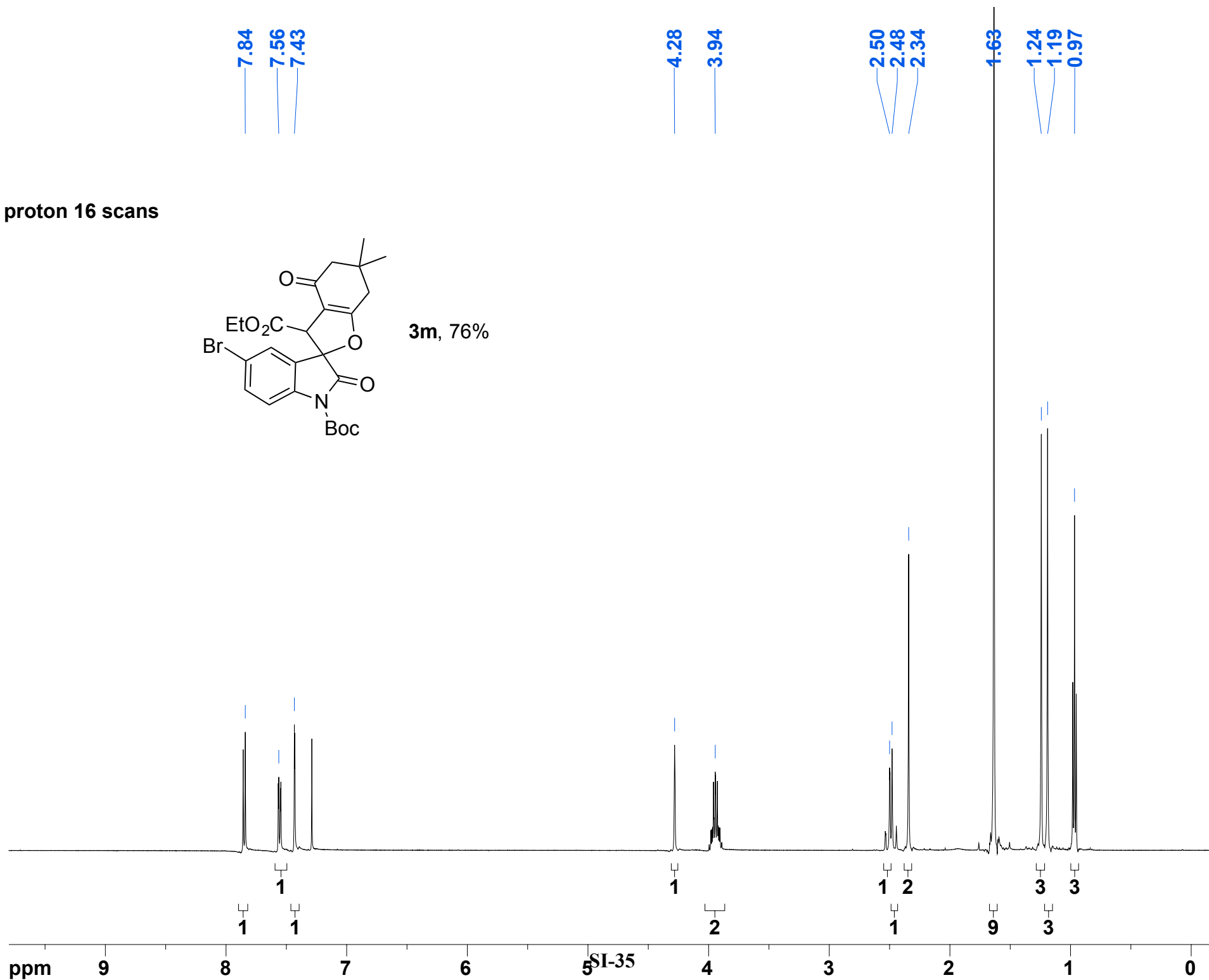


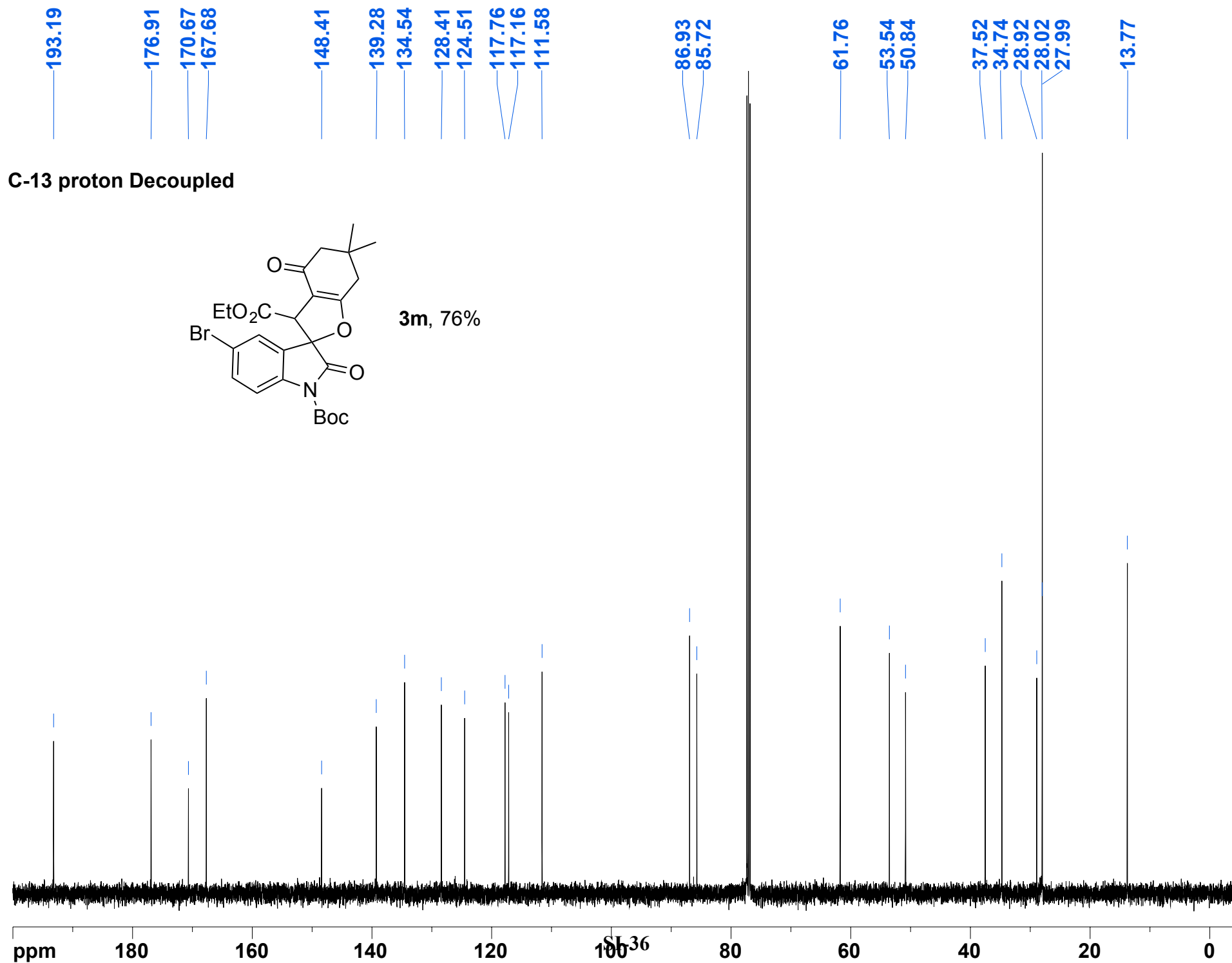


proton 16 scans



3m, 76%



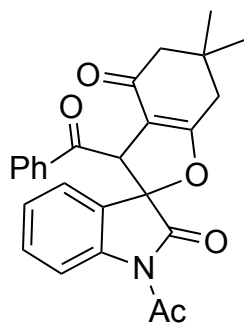


3n, 99%

ppm

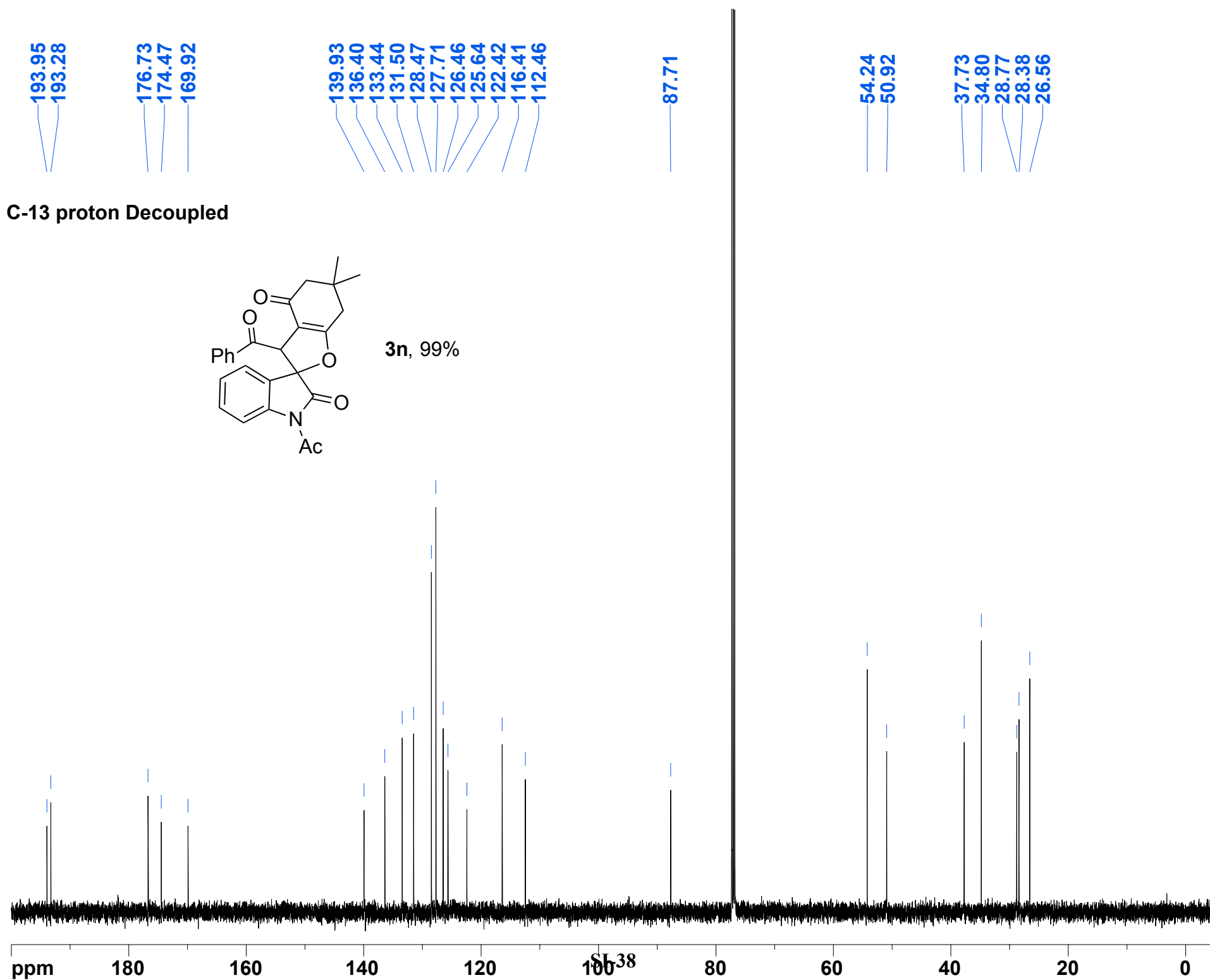
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SI-37



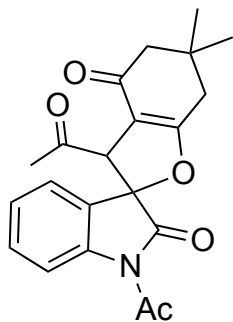
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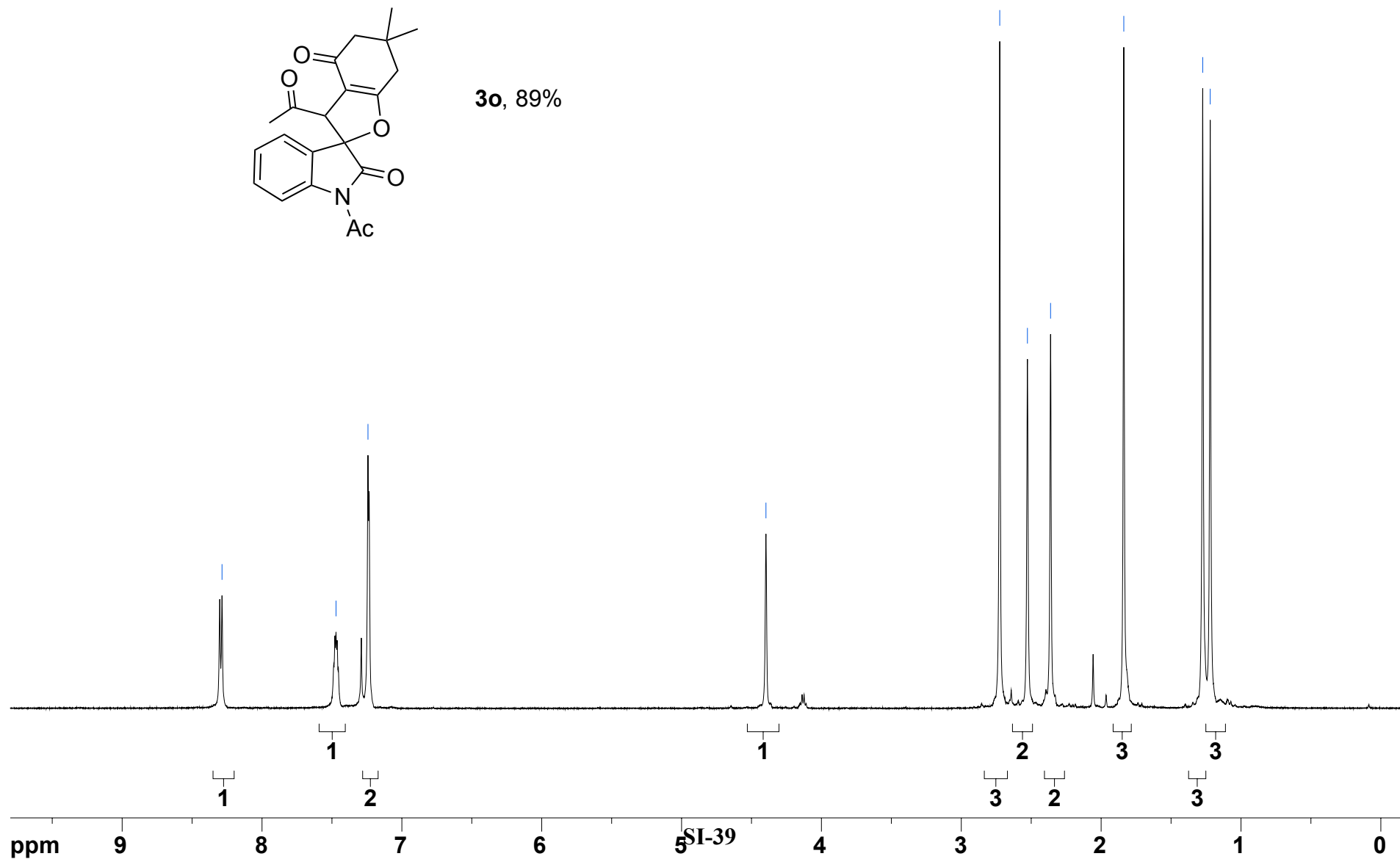




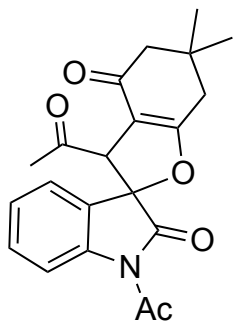
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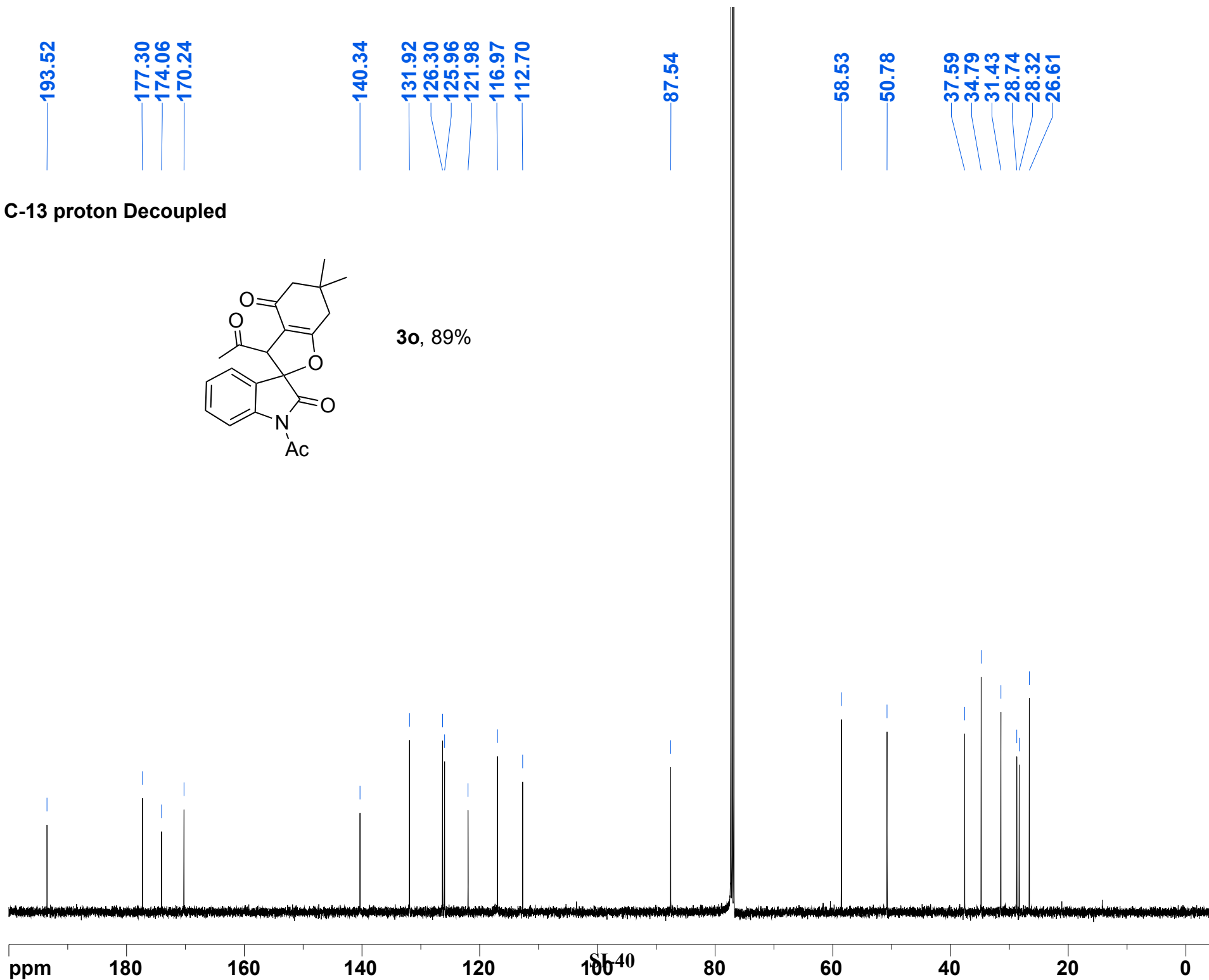
3o, 89%

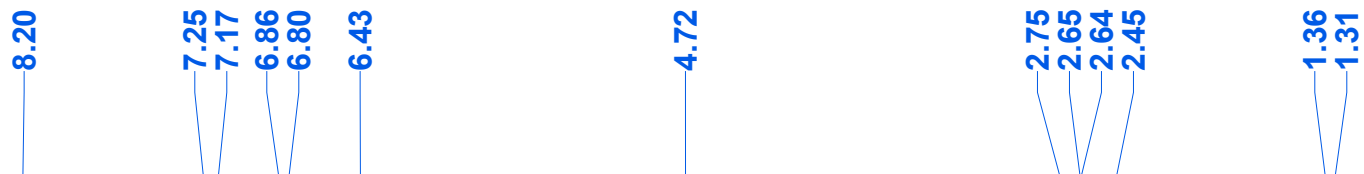


C-13 proton Decoupled

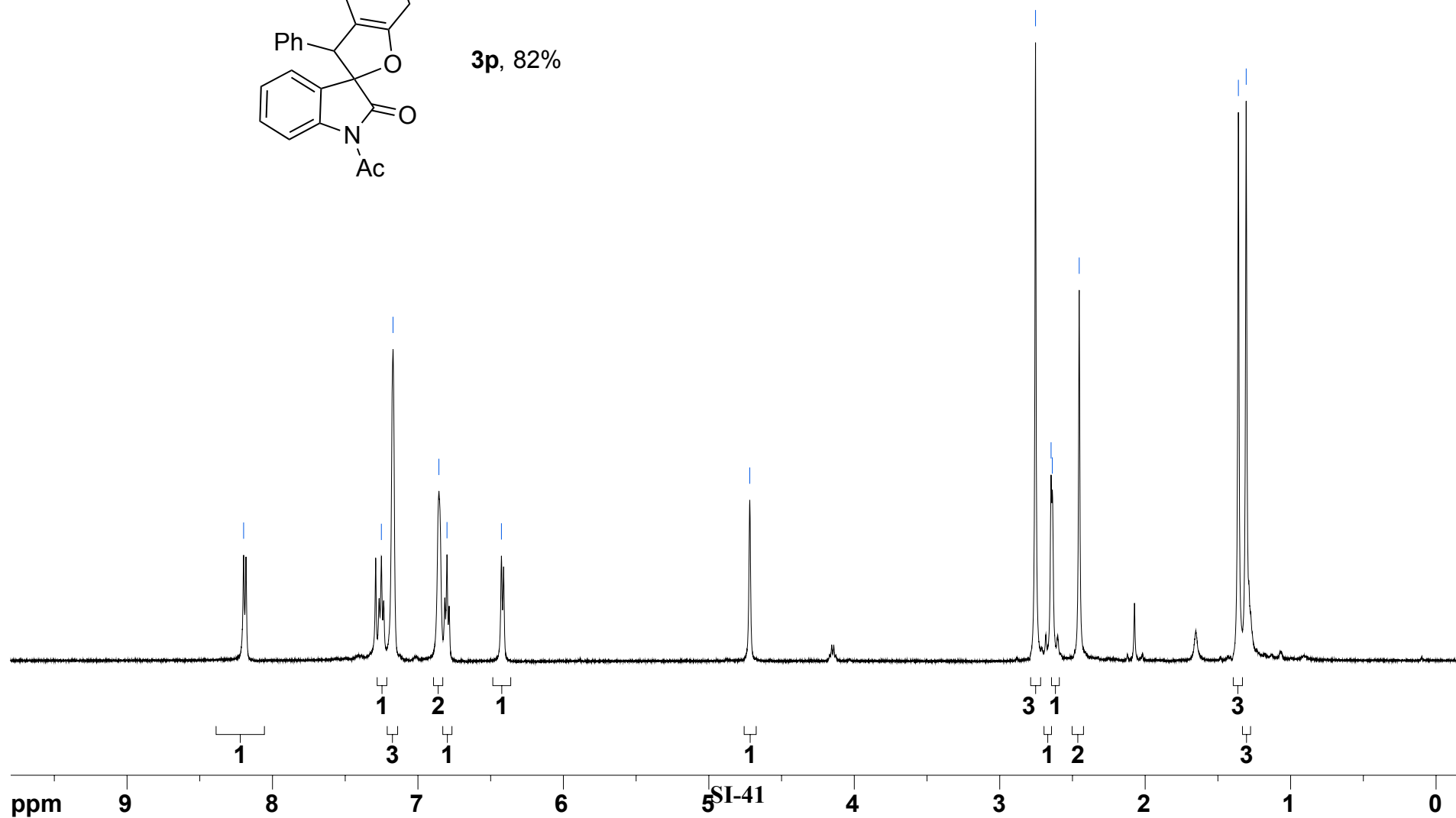
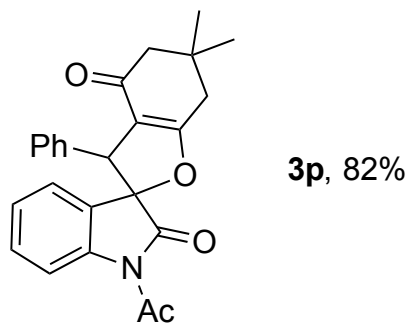


3o, 89%

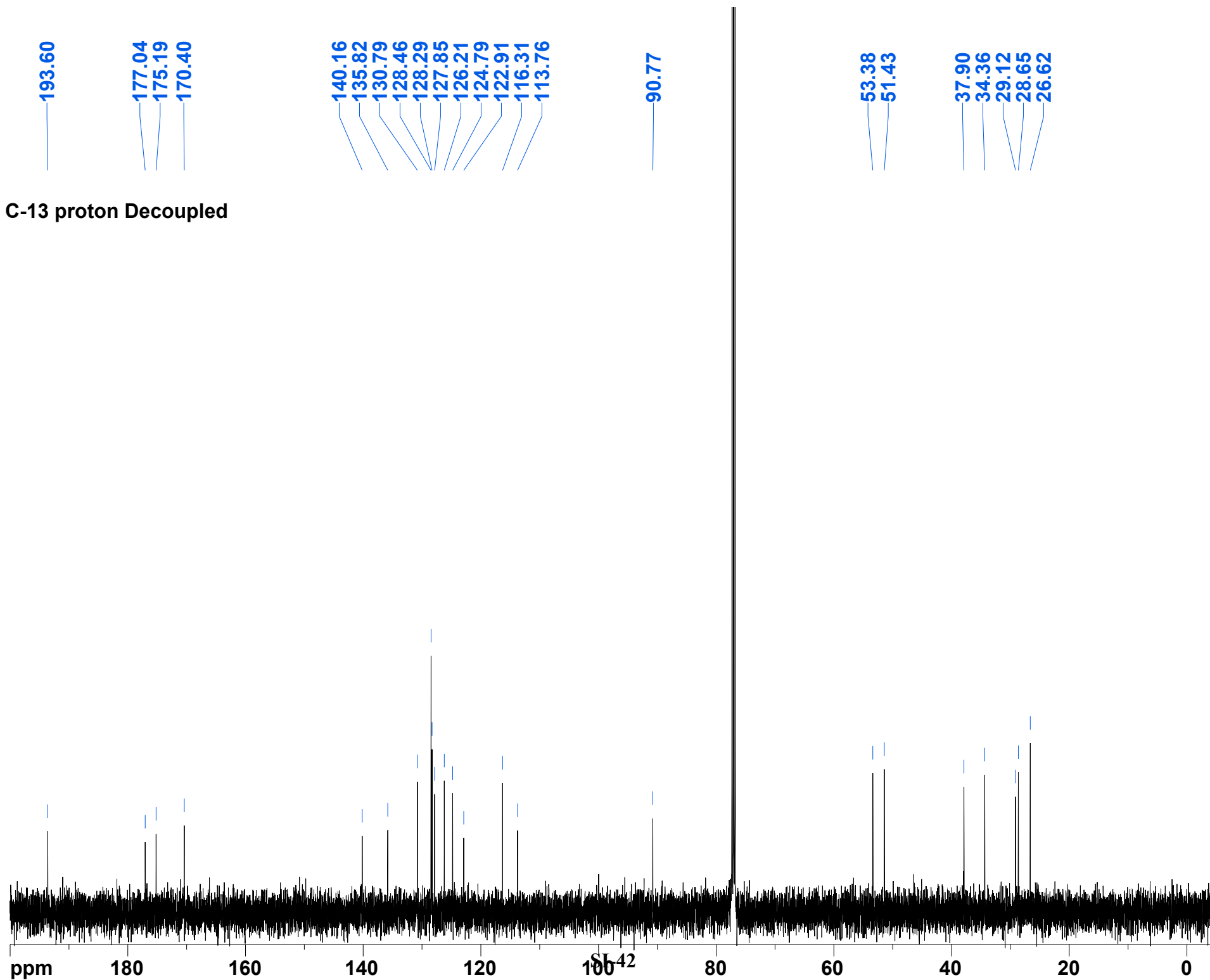


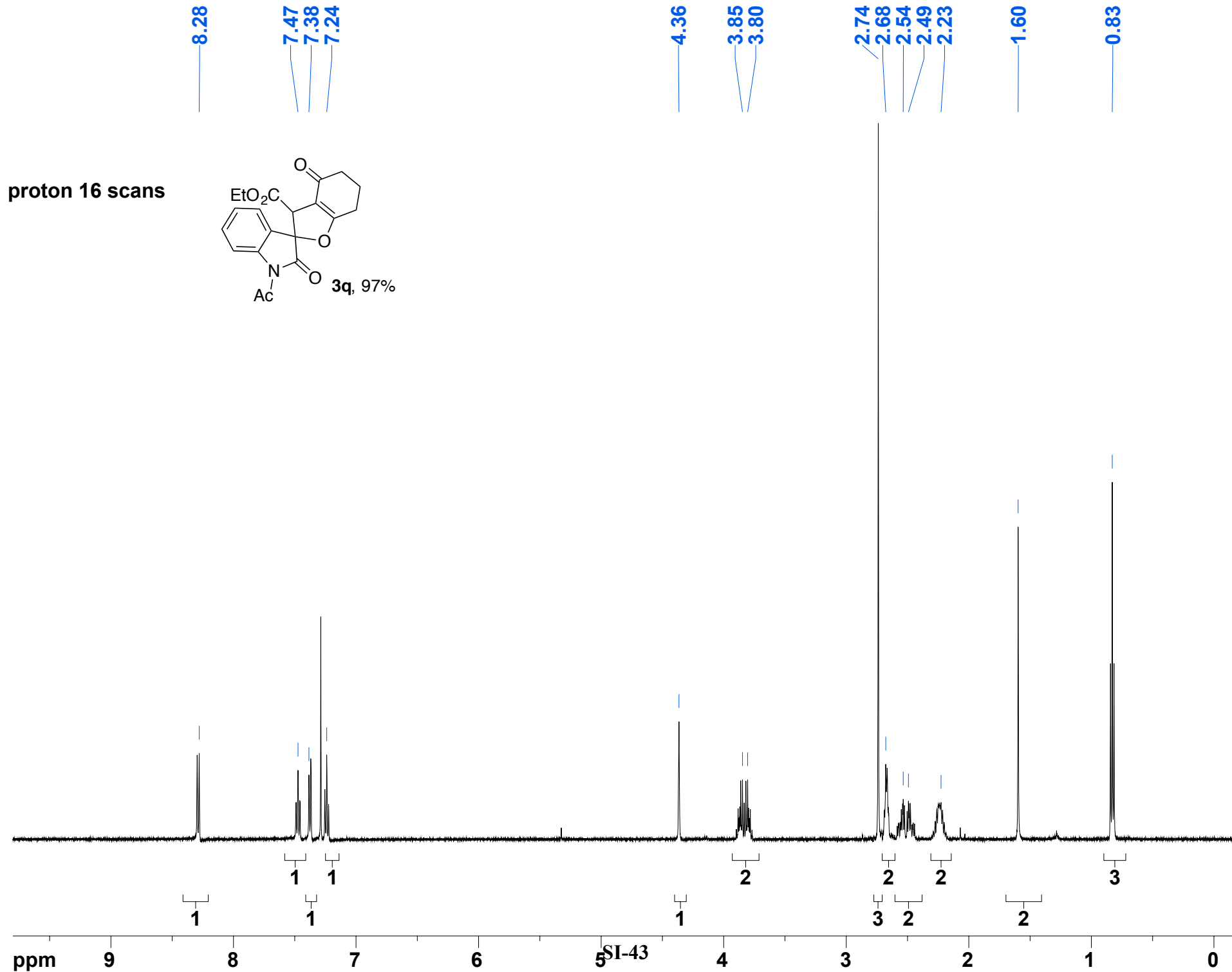


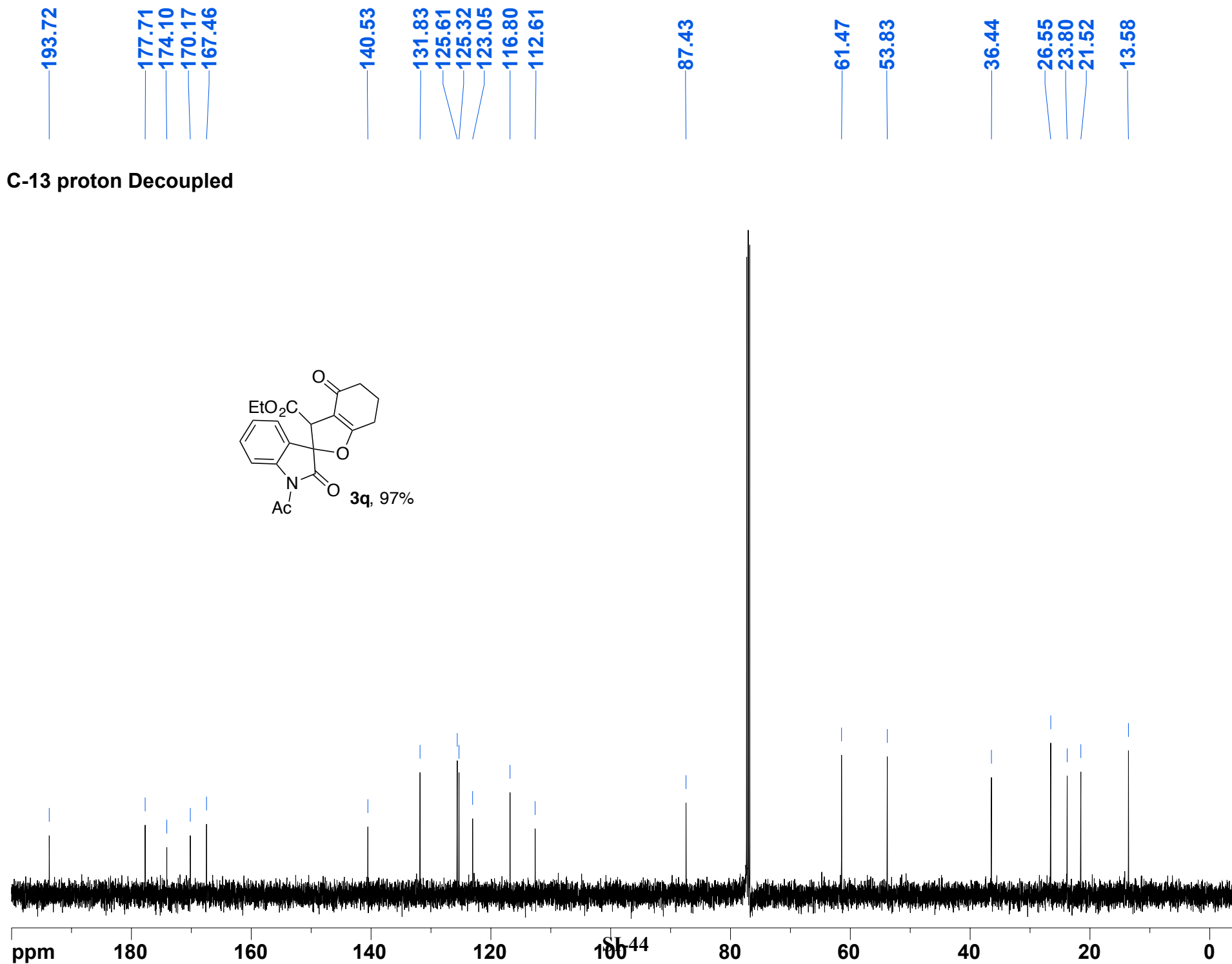
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C-13 proton Decoupled







0.88

3s, 54%

