Fe-catalyzed nucleophilic activation of C,Si- versus allylic C-O bonds – catalytic trifluoromethylation of carbonyl groups versus tandem trifluormethylation-allylation of olefins

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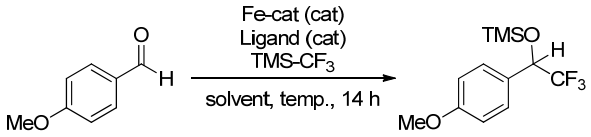
1. General remarks

Reactions with anhydrous solvents were carried out under an atmosphere of N_2 in flame dried Glassware. Anhydrous tetrahydrofuran (THF) and 1,4-dioxane were freshly distilled from sodium-benzophenone prior to use, dichloromethane (DCM) and benzene (PhH) were distilled from CaH_2. Anhydrous *n*-pentane and acetonitrile (MeCN) were obtained by passing them through commercially available columns. Petroleum ether (PE) and ethyl acetate (EtOAc) were distilled prior to use. NMR spectra were recorded at 250 MHz or 300 MHz and calibrated using the residual non-deuterated solvent signal as an internal standard. $CDCl_3$ was passed through a plug of basic aluminium oxide prior to preparation of NMR samples. IR spectra were recorded using a Golden Gate ATR unit. High resolution mass spectra were recorded using electrochemical (EI) or electrospray ionisaton (ESI) using a triple quadrupole detector. For low-resolution mass-spectrometry (GC-MS) a single quadrupole was used.
The starting materials for trifluoromethylated products **22**[1] and **24**[2] were prepared according to previously reported procedures. The activated olefins **25** were prepared from the corresponding aldehydes and malononitrile according to the previously published procedure.[3]

2. General procedures for screening reactions of the trifluoromethylation of aldehydes and ketones



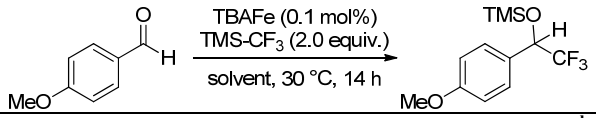
a) Reactions carried out with catalyst loadings > 1mol%:

The appropriate iron-source was added to a flame dried Schlenk-tube together with the appropriate anhydrous solvent (1 mL. *p*-Anisaldehyde (61 µL, 0.50 mmol, 1.0 equiv.) and TMS-CF_3 (148 µL, 1.0 mmol, 2 equiv.) were added and the tube sealed under an atmosphere of N_2. The reaction mixture was heated to the indicated temperature for 14 h. The solvent was removed under reduced pressure and the residue dissolved in $CDCl_3$ (2 mL) and mesitylene (10 µL) added as an internal standard.

b) Reactions carried out with TBAFe loadings < 1 mol%:

A 5 mM stock solution in anhydrous THF (5 mL) of TBAFe (10.3 mg, 0.025 mmol) was prepared in a flame dried Schlenk-tube. When appropriate, a 5 mM stock solution of the ligand in anhydrous THF (5 mL) was prepared in a flame dried Schlenk-tube.
The stock solutions (100 µL for 0.1 mol%) were added to a flame dried Schlenk-tube followed by *p*-anisaldehyde (61 µL, 0.50 mmol, 1.0 equiv.) and TMS-CF_3 (148 µL, 1.0 mmol, 2 equiv.). The appropriate anhydrous solvent was added to obtain a total volume of 1 mL. The reaction mixture was sealed under an atmosphere of N_2 and stirred for 14 h at 30 °C. The solvent was removed under reduced pressure and the residue dissolved in $CDCl_3$ (2 mL) and mesitylene (10 µL) added as an internal standard.

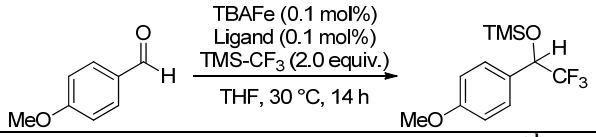
2.1 Solvent-Screening

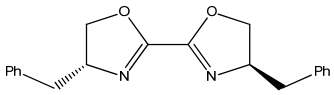
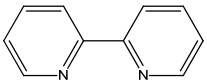
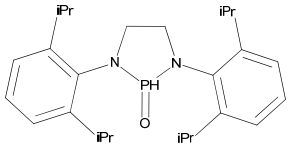


entry	solvent	yield[a,b]
1	THF	35%*
2	1,4-Dioxane	34%*
3	*n*-pentane	35%*
4	PhH	28%*
5	PhMe	33%*
6	CH_2Cl_2	10%*
7	MeCN	< 2%*

[a] Reactions performed on a 0.5 mmol scale in 1 mL solvent. Catalyst was added as a freshly prepared stock-solution in THF (100 µL, 5 mM solution). [b] yields are determined by ^{1}H-NMR in $CDCl_3$ using mesitylene as an internal standard. *averaged over a minimum of 2 runs. n.r.= no reaction.

2.2 Ligand-Screening



Entry	ligand	yield[a,b]	blank[c]
1	PPh_3	27%	n.r.
2	X-Phos	34%	n.r.
3		38%	5%
4		43%	n.r.
5		10%	n.r.
6	DMAP	64%	n.r.[d]
7	pyridine	57%	n.r.
8	*N*,*N*-diethylaninline	40%	n.r.

[a] Reactions performed on a 0.5 mmol scale in 1 mL solvent. Catalyst and ligand were added as a freshly prepared stock-solution in THF (100 µL, 5 mM solution). [b] yields are determined by ^{1}H-NMR in $CDCl_3$ using mesitylene as an internal standard. [c] Reaction carried out in the absence of TBAFe with the ligand present. [d] Even when the reaction was performed with a 10-fold increased amount of DMAP in the absence of TBAFe no reaction was observed. n.r.= no reaction.

3. General procedure for the trifluoromethylation of aldehydes and ketones

Aldehydes and ketones were distilled prior to use where appropriate. A 5 mM stock solution of TBAFe (10.3 mg, 0.025 mmol) and DMAP (3.05 mg, 0.025 mmol) in anhydrous THF (5 mL) was prepared in a flame dried Schlenk-tube. Anhydrous THF (0.5 mL) and the stock solution (1.5 mL, 0.0075 mmol, 0.75 mol% TBAFe and DMAP) were added to a flame dried Schlenk-tube. The appropriate aldehyde (1.00 mmol, 1 equiv.) and TMS-CF_3 (296 µL, 2.00 mmol, 2 equiv.) were added under an atmosphere of N_2 and stirred for 14 h at 30 °C. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel as indicated below to afford the trifluoromethylated silylethers **4 - 24**.

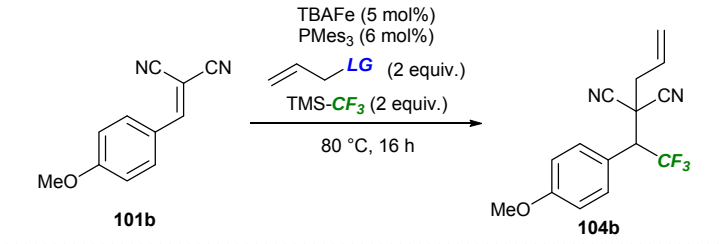
4. General procedure for the tandem trifluormethylation-allylation of olefins

Method A: TBA[Fe] (10.3 mg, 0.025 mmol, 5 mol%) was added to a to a flame dried Schlenk tube and anhydrous DME (1 mL) and allylacetate (108 µL, 1.0 mmol, 2 equiv.) were added. The appropriate olefin (1 equiv.) and TMS-CF_3 (148 µL, 1 mmol, 2 equiv.) were added sequentially. The Schlenk tube was sealed under an atmosphere of dry N_2. The reaction mixture was heated to 80 °C for 16 h. The reaction mixture was cooled to room temperature and the volatile components were removed under reduced pressure. The residue was purified by chromatography on silica gel as indicated below to afford the desired products. In challenging cases additional purification was performed using a semi-preparative HPLC.

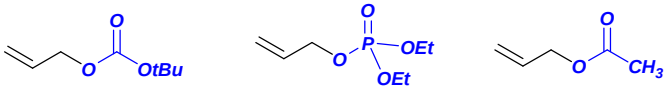
Method B: TBA[Fe] (10.3 mg, 0.025 mmol, 5 mol%) was added to a to a flame dried Schlenk tube and anhydrous DME (1 mL) and allylacetate (54 µL, 0.5 mmol, 1 equiv.) were added. The appropriate olefin (1.5 equiv.) and TMS-CF_3 (148 µL, 1 mmol, 2 equiv.) were added sequentially. The Schlenk tube was sealed under an atmosphere of dry N_2. The reaction mixture was heated to 80 °C for 16 h. The reaction mixture was cooled to room temperature and the volatile components were removed under reduced pressure. The residue was purified by chromatography on silica gel as indicated below to afford the desired products. In challenging cases additional purification was performed using a semi-preparative HPLC.

Screening reactions were performed on an identical scale as indicated above. Yields were determined via ^{19}F-NMR using 1-bromo-4-(trifluoromethyl)benzene as a standard. In certain cases, such as reactions performed in DMF, an aqueous workup was performed.

4.1 Leaving group-screening



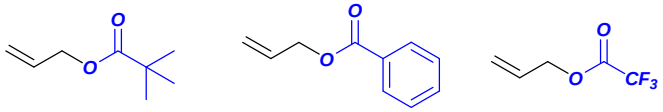
101b **104b**



103a
DMF (33%)
THF (6%)
DME (7%)

103b
DMF (25%)
THF (15%)
DME (23%)

103c
DMF (35%)
THF (54%)
DME (60%)

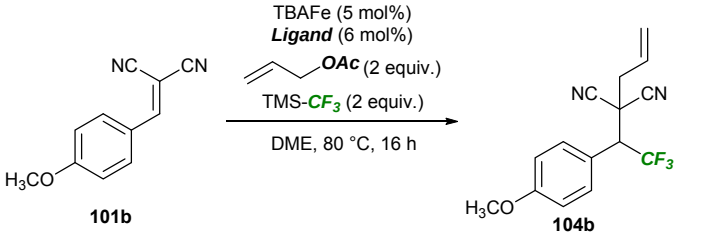


103d
DMF (20%)
THF (20%)
DME (19%)

103e
DMF (19%)
THF (17%)
DME (25%)

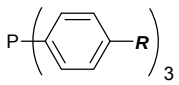
103f
DMF (5%)
THF (traces)
DME (traces)

4.2 Ligand-Screening

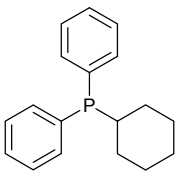


101b **104b**

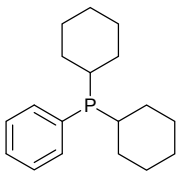
no ligand (64%)



R = H (traces)
R = OCH_3 (traces)
R = F (traces)



(traces)



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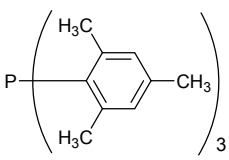
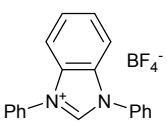
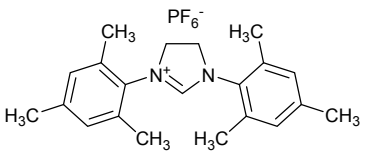


(60%)

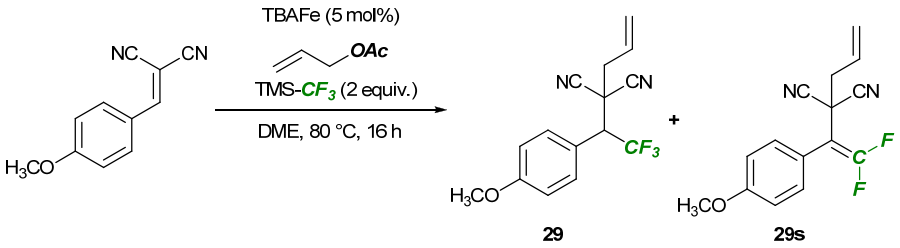


(36%)



(26%)

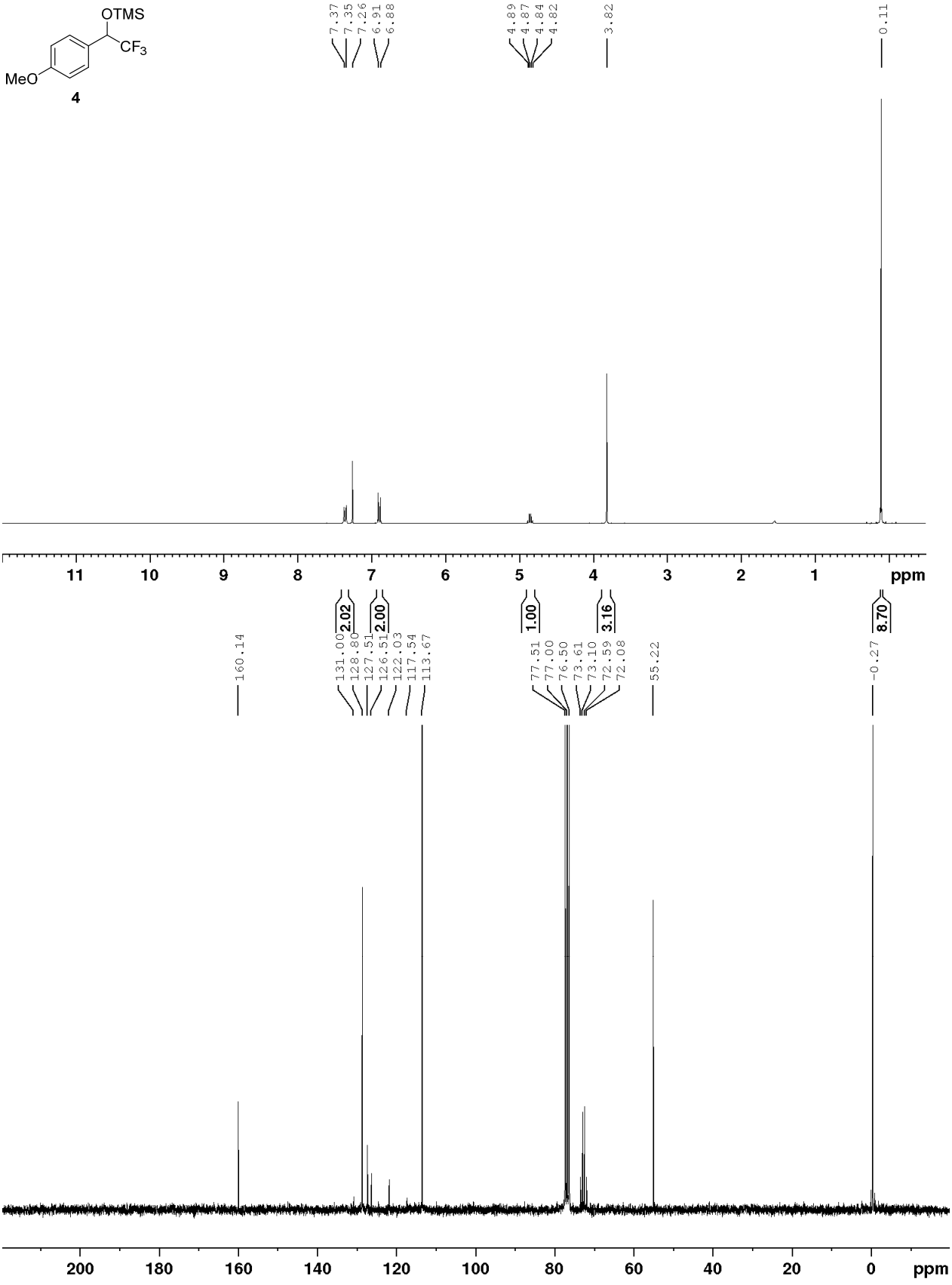
4.3 Adjustment of equivalents

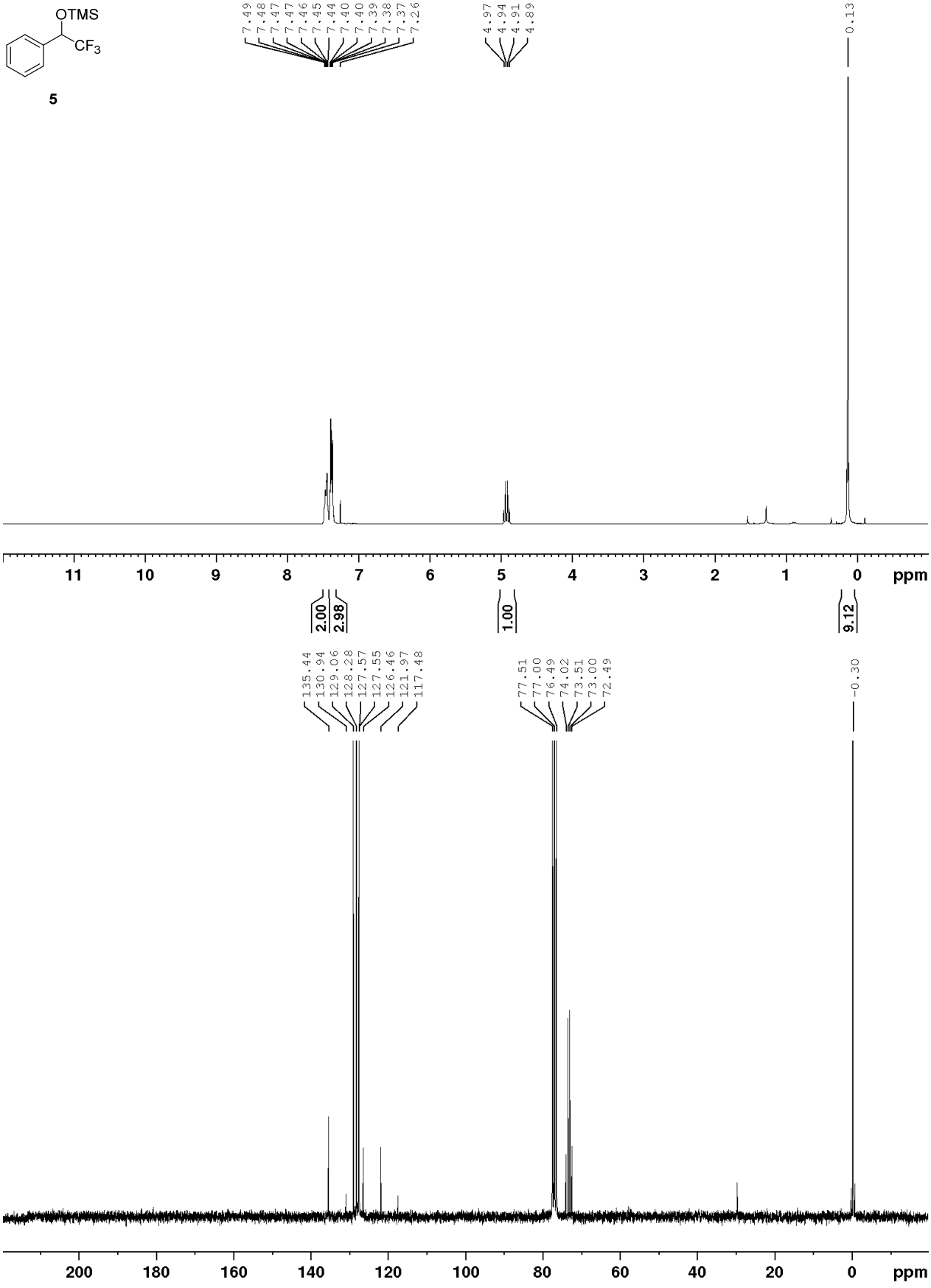


Eintrag[a]	AllylOAc	101b	NMR-Yield 29	NMR-Yield 29s
1	2 equiv.	1 equiv.	64%	16%
2	1 equiv.	1 equiv.	60%	12%
3	1 equiv.	1.5 equiv.	72%	7%
4	1 equiv.	2 equiv.	48%	~ 1%

[a] Reactions were performed on a 0.5 mmol scale in 1 mL DME. Yields were determined via ^{19}F-NMR using 4-Bromobenzotrifluoride as a standard.

5. ^{1}H- and ^{13}C-NMR-Spectra of trifluoromethylated products 4 – 24 and 29 – 35, 37, 38, 40 and 41

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7.37
7.26
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4.94
4.91
4.89
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11
10
9
8
7
6
5
4
3
2
1
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2.98
1.00
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130.94
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127.55
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121.97
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76.49
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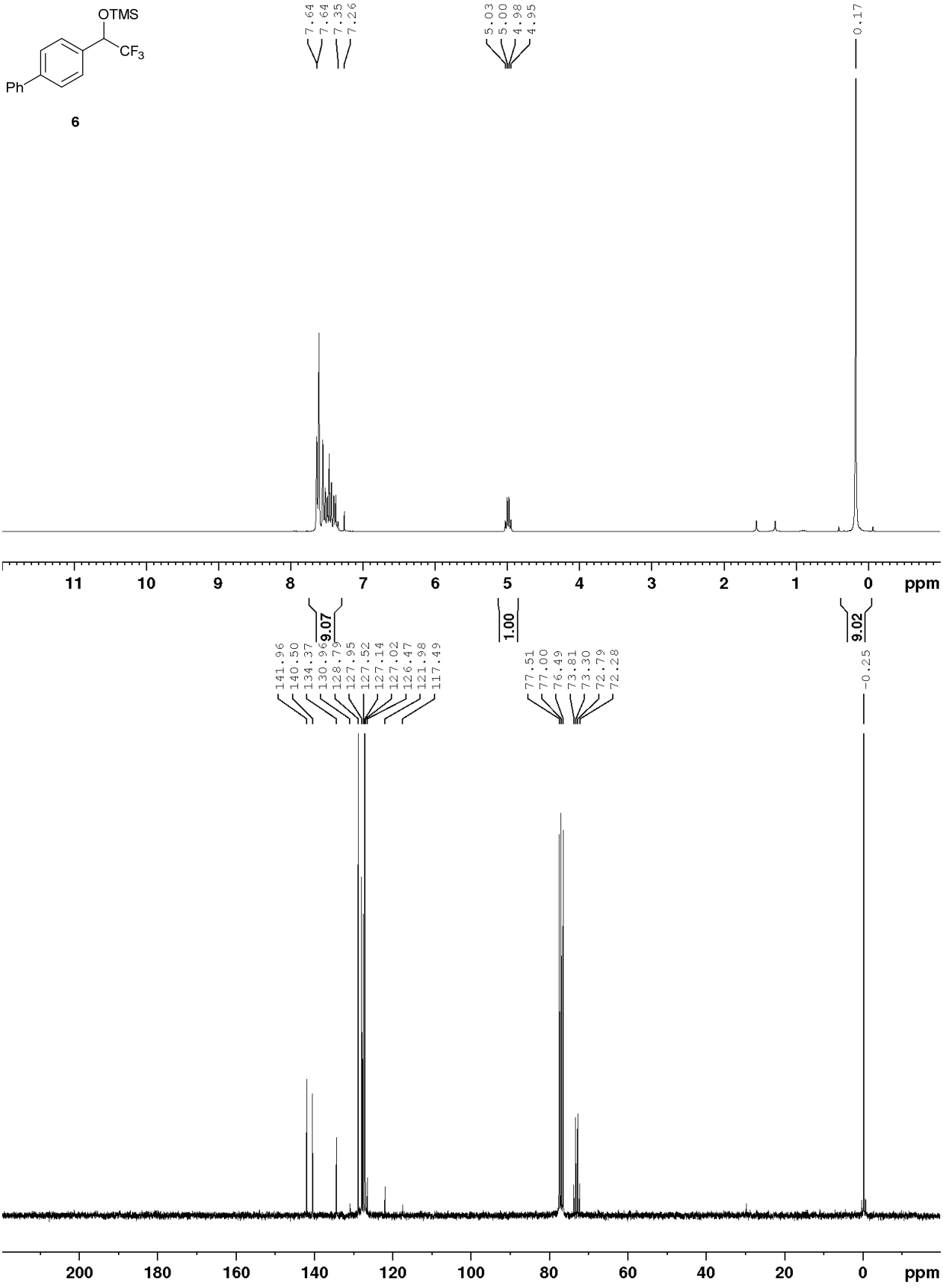
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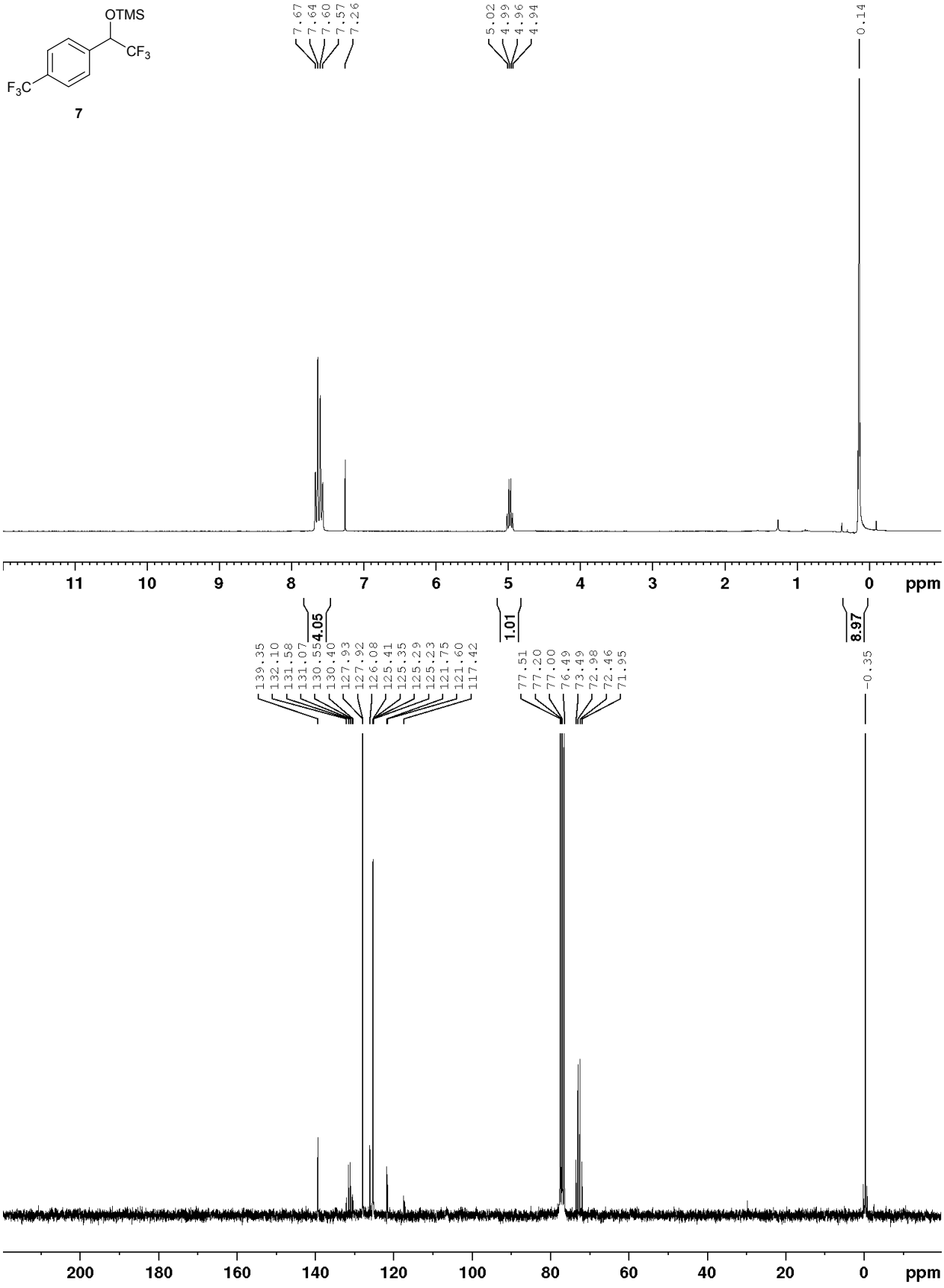
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10
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127.93
127.92
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125.29
125.23
121.75
121.60
117.42
77.51
77.20
77.00
76.49
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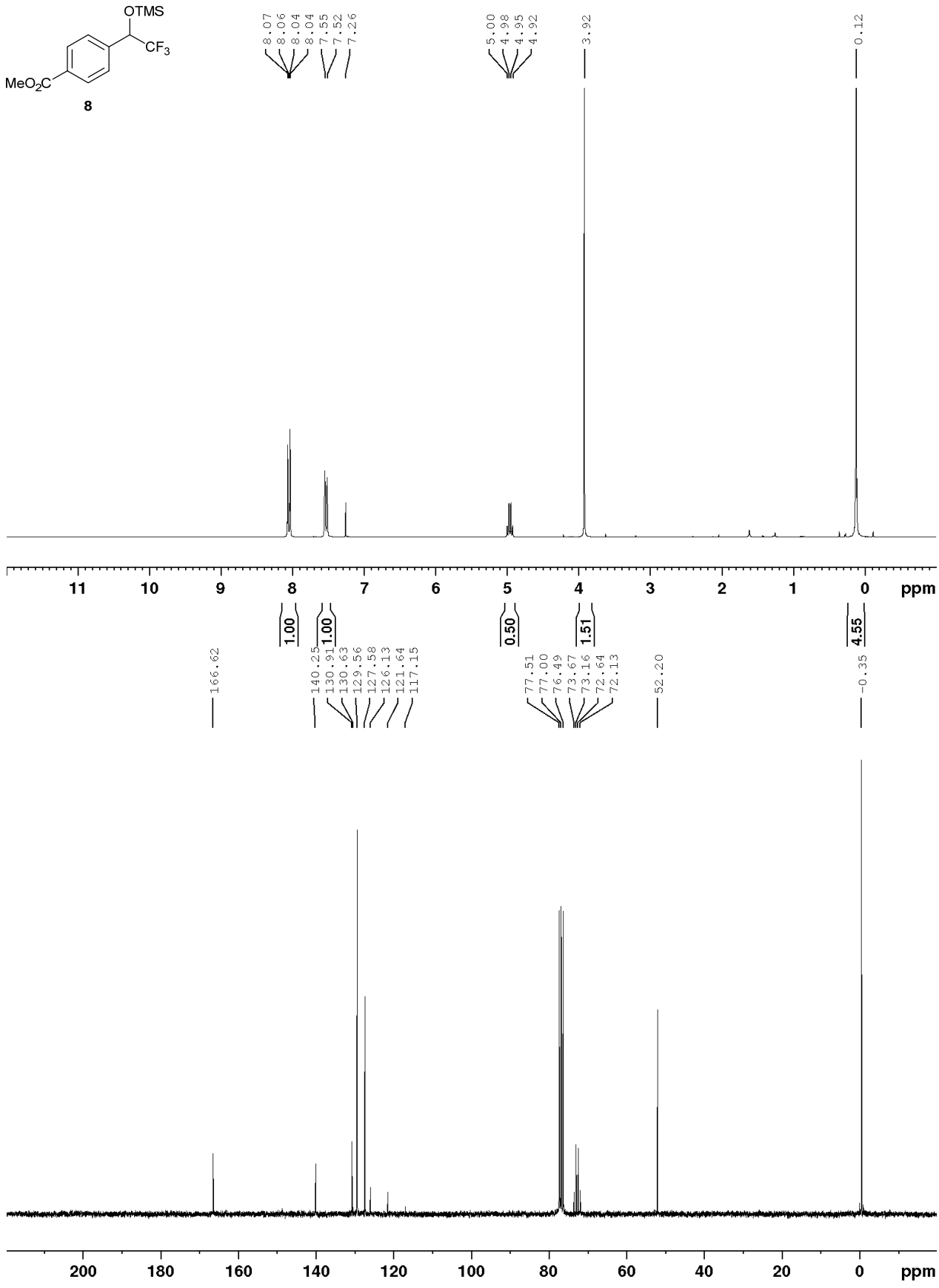
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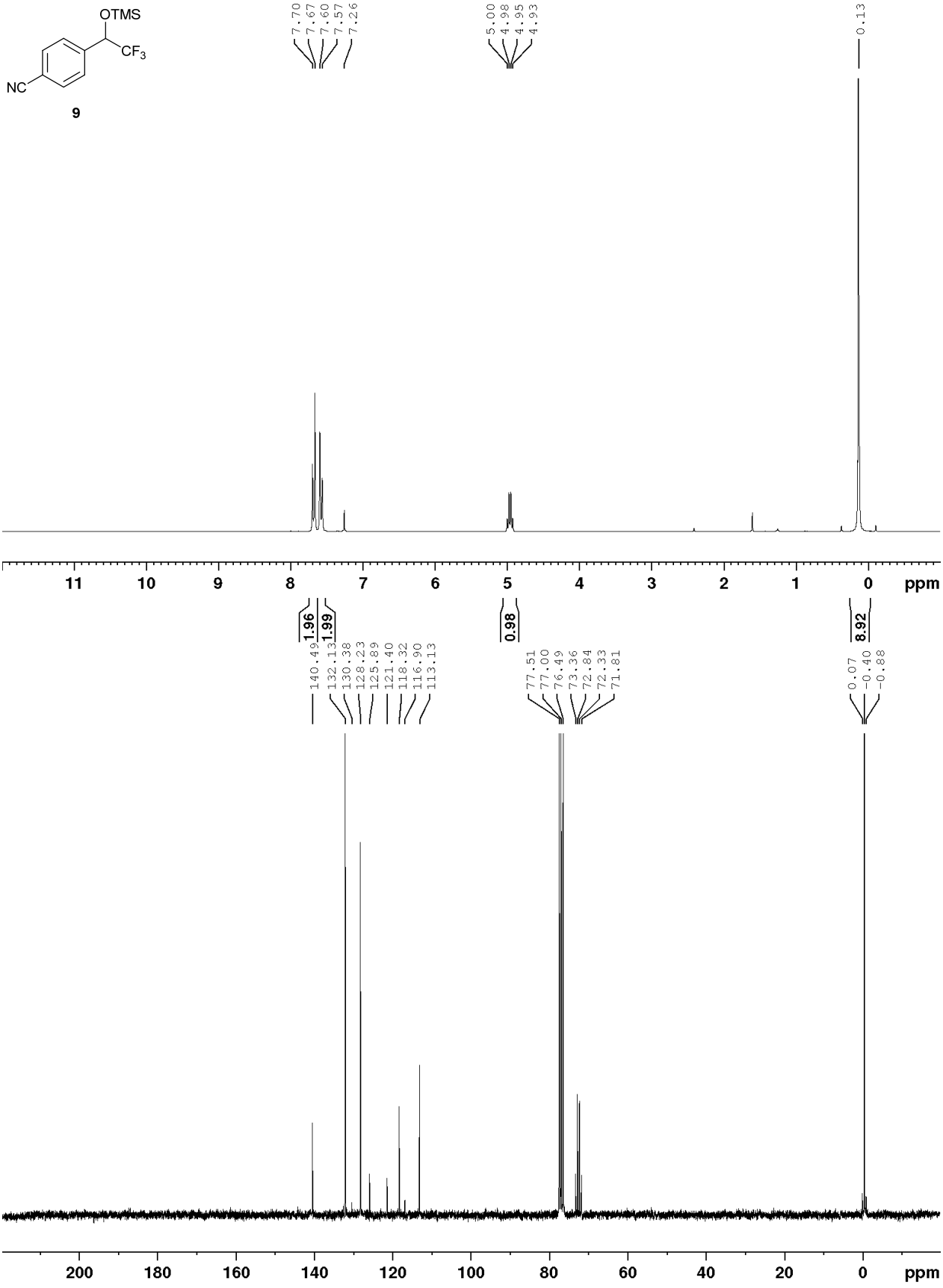
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11
10
9
8
7
6
5
4
3
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ppm
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1.99
0.98
8.92
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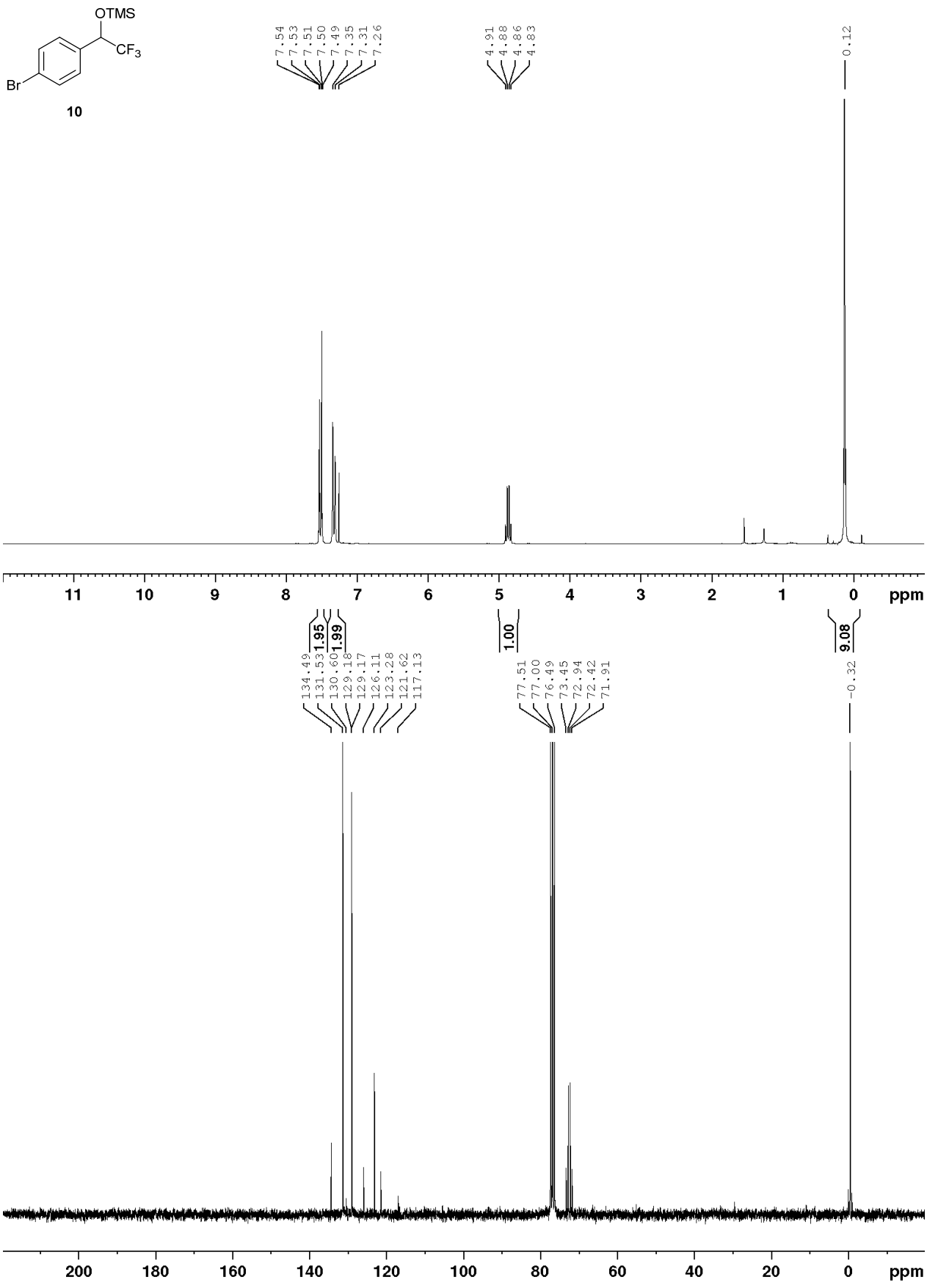
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8
7
6
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1.00
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131.53
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129.18
129.17
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123.28
121.62
117.13
77.51
77.00
76.49
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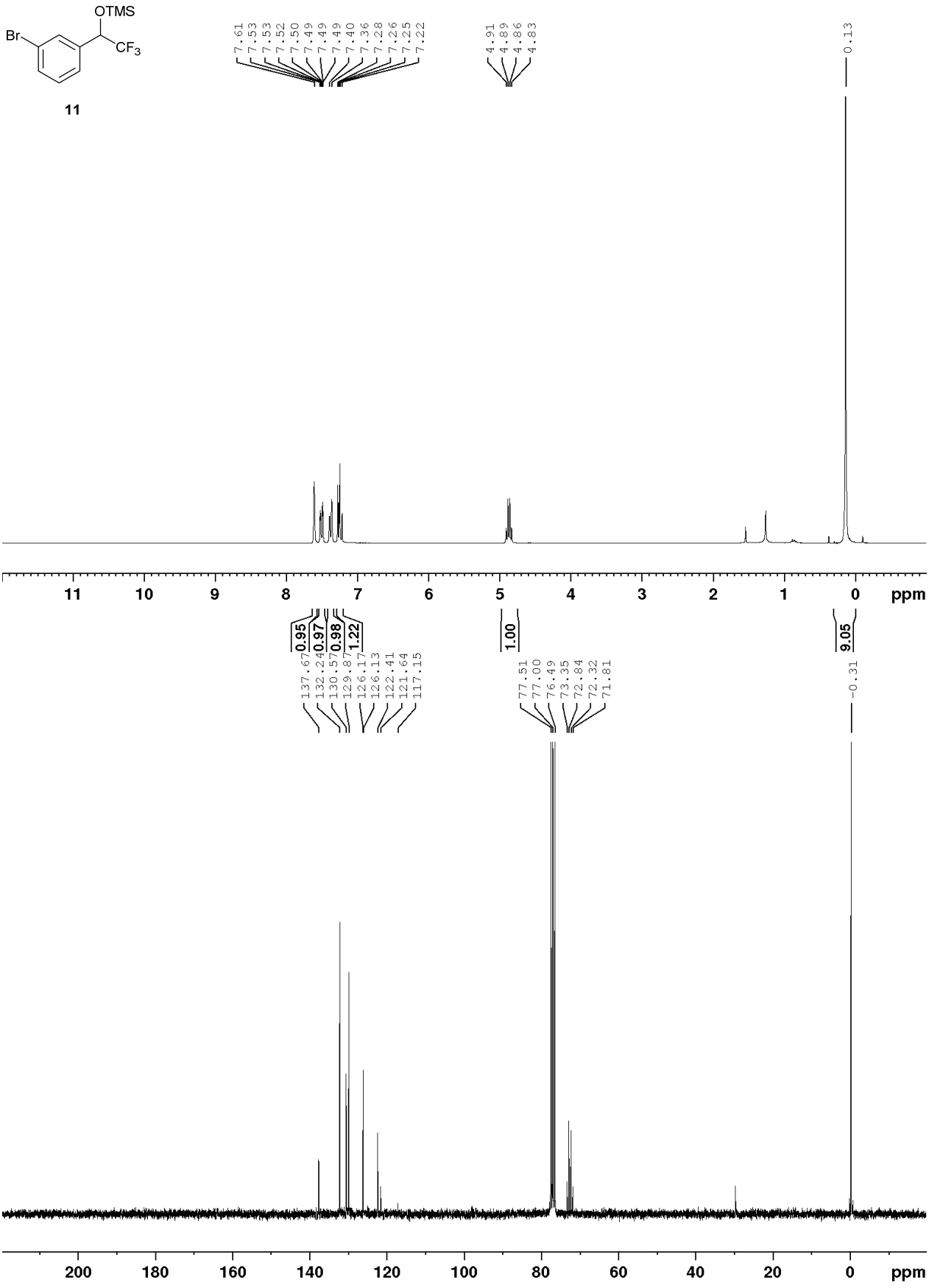
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10
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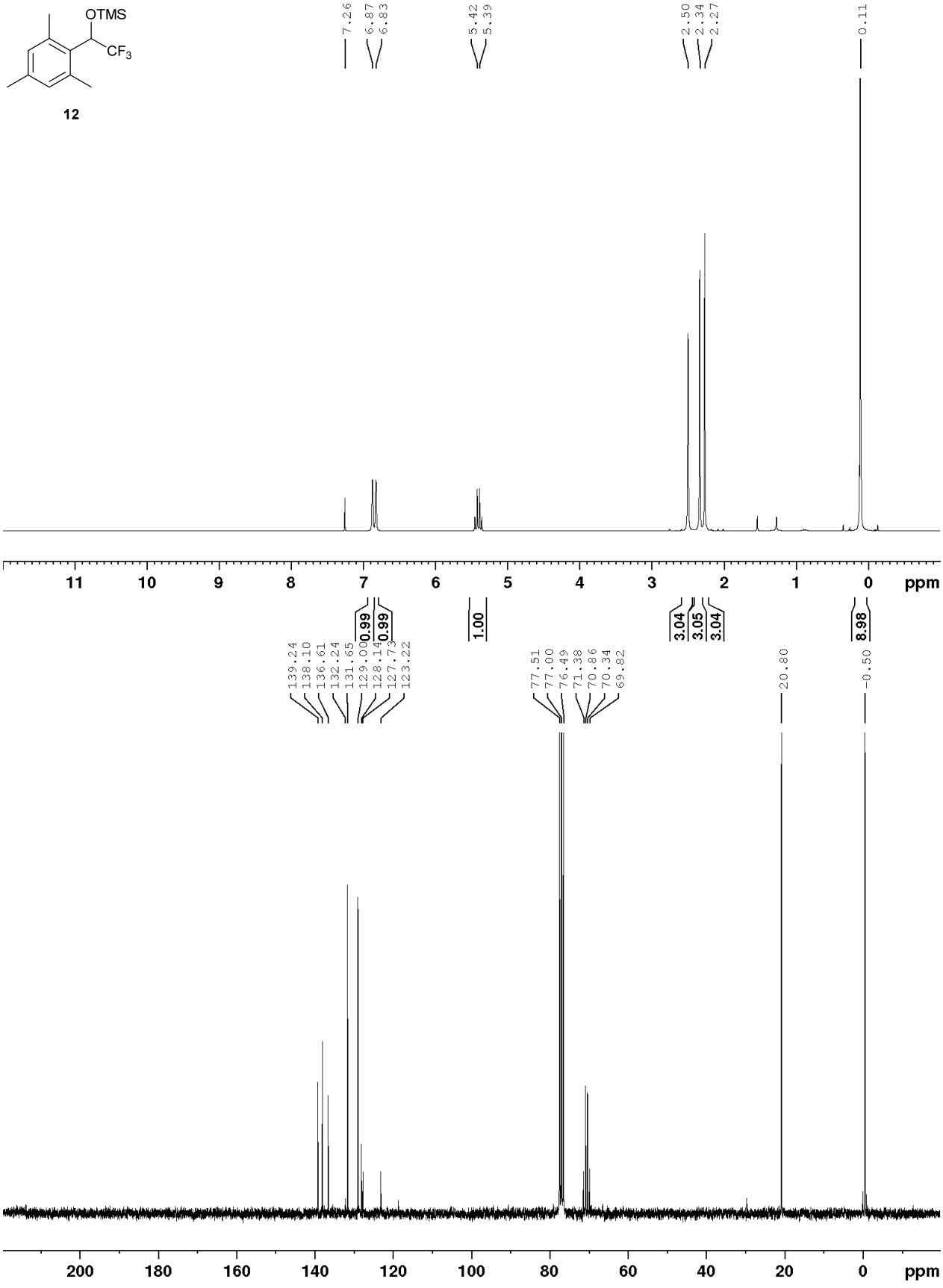
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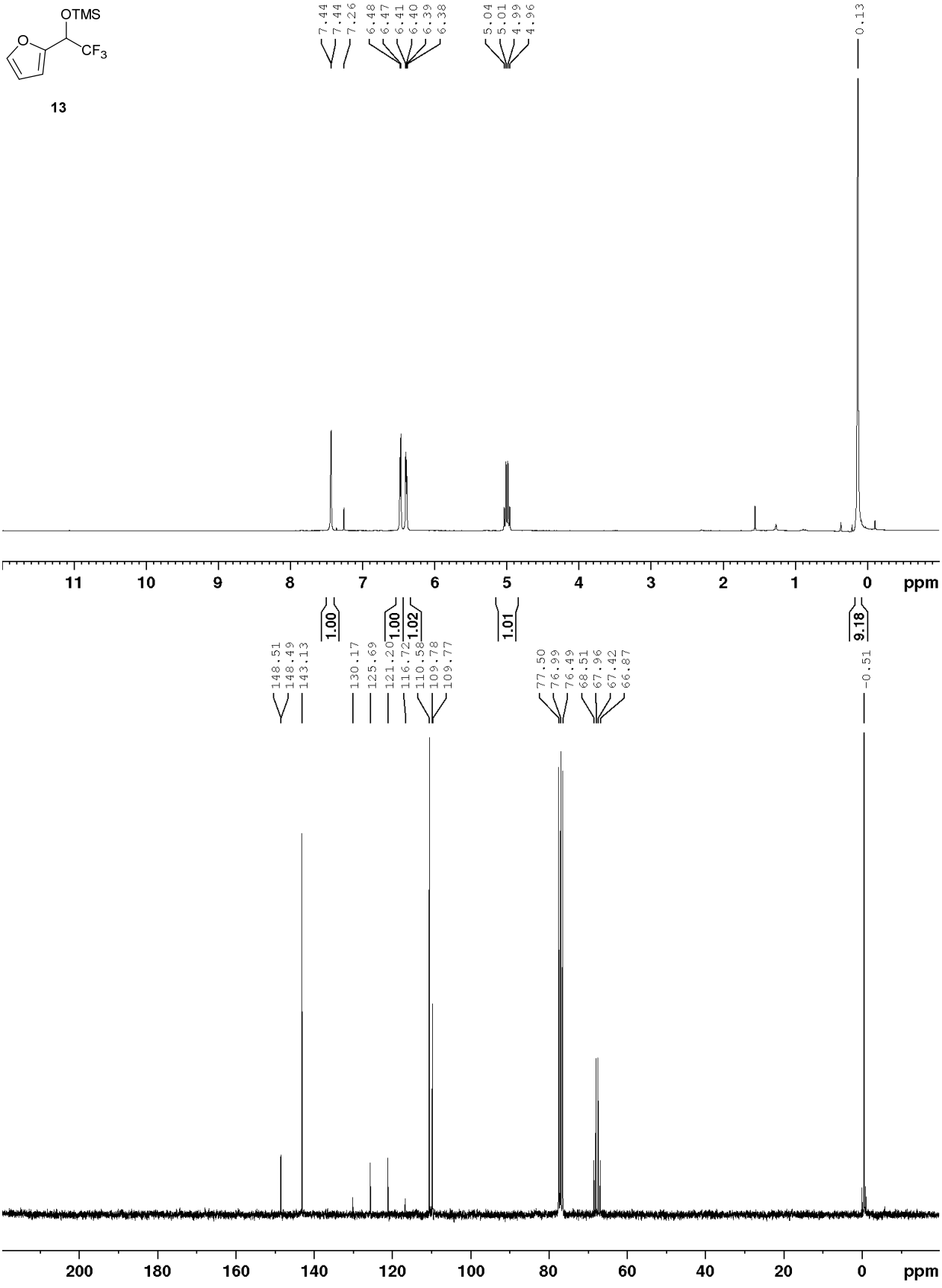
ppm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O
CF3
13
7.44
7.44
7.26
6.48
6.47
6.41
6.40
6.39
6.38
5.04
5.01
4.99
4.96
0.13
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.00
1.02
1.01
9.18
148.51
148.49
143.13
130.17
125.69
121.20
116.72
110.58
109.78
109.77
77.50
76.99
76.49
68.51
67.96
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120
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40
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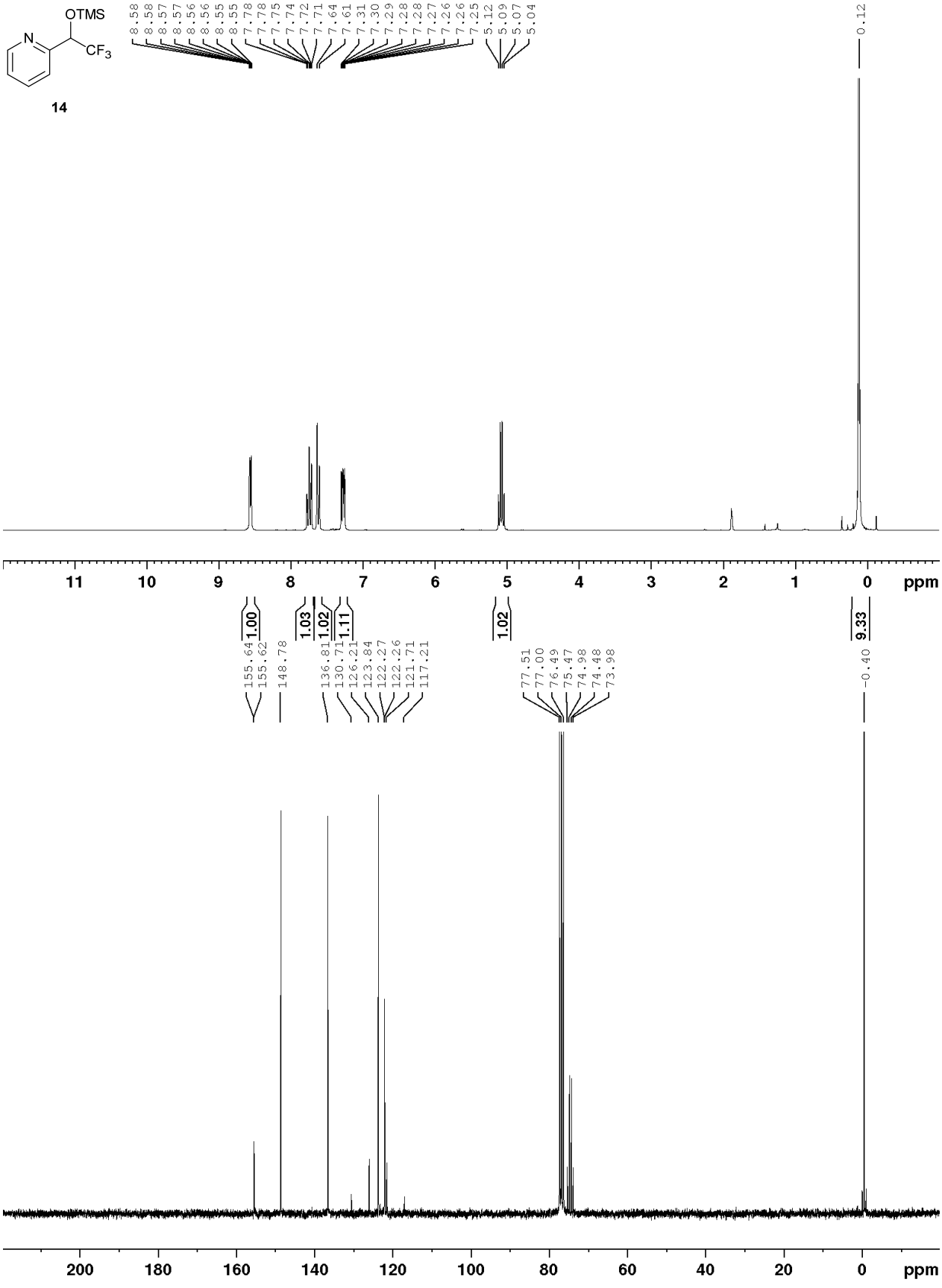
OTMS
N
CF3
14
8.58
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8.57
8.57
8.56
8.56
8.55
8.55
7.78
7.75
7.74
7.72
7.71
7.64
7.61
7.31
7.30
7.29
7.28
7.28
7.27
7.26
7.26
7.25
5.12
5.09
5.07
5.04
0.12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.03
1.02
1.11
1.02
9.33
155.64
155.62
148.78
136.81
130.71
126.21
123.84
122.27
122.26
121.71
117.21
77.51
77.00
76.49
75.47
74.98
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73.98
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120
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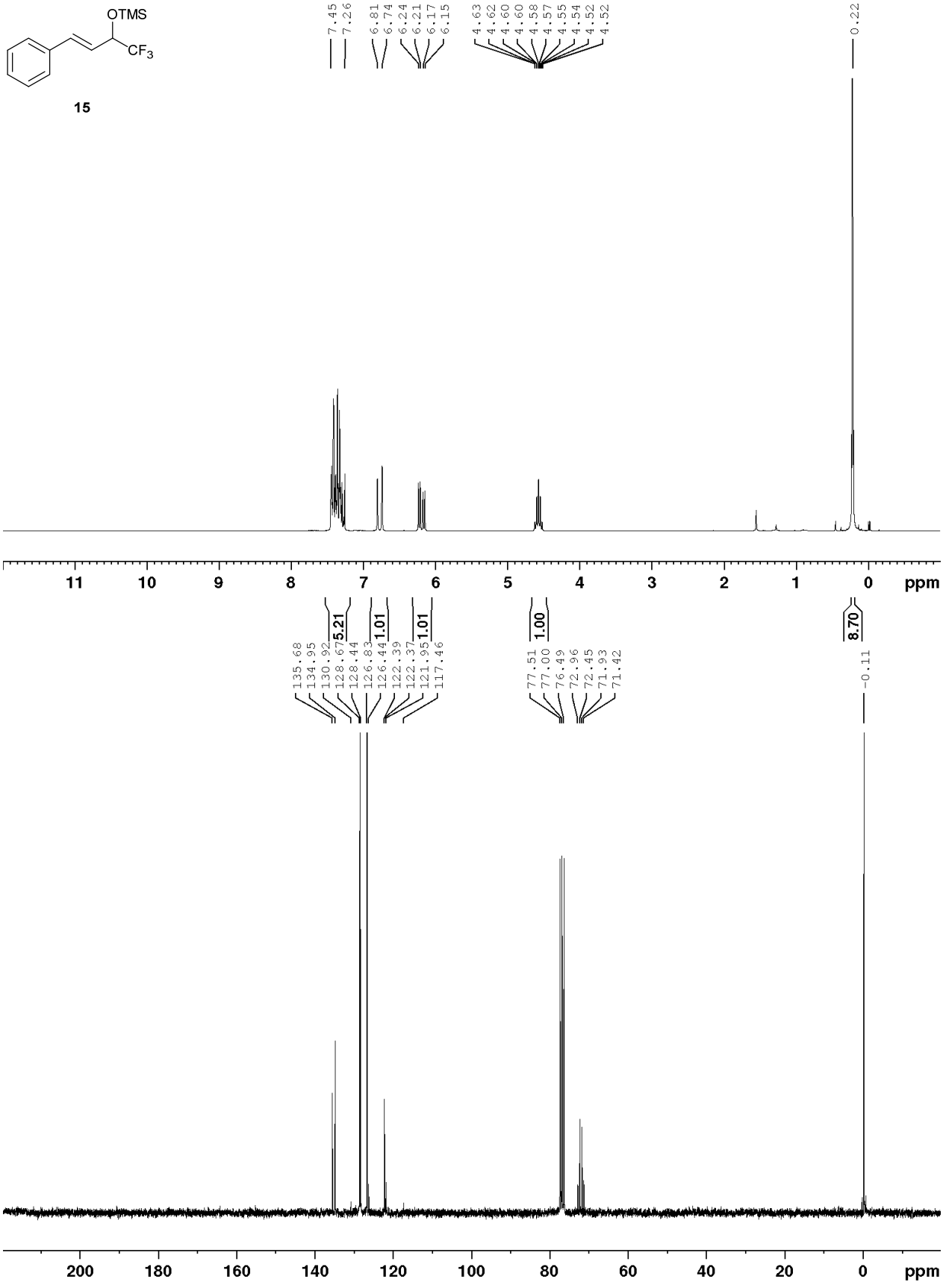
0
ppm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CF3
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7.45
7.26
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6.74
6.24
6.21
6.17
6.15
4.63
4.62
4.60
4.60
4.58
4.57
4.55
4.54
4.52
4.52
0.22
11
10
9
8
7
6
5
4
3
2
1
0
ppm
135.68
134.95
130.92
128.67
128.44
126.83
126.44
122.39
122.37
121.95
117.46
5.21
1.01
1.01
77.51
77.00
76.49
72.96
72.45
71.93
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8.70
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120
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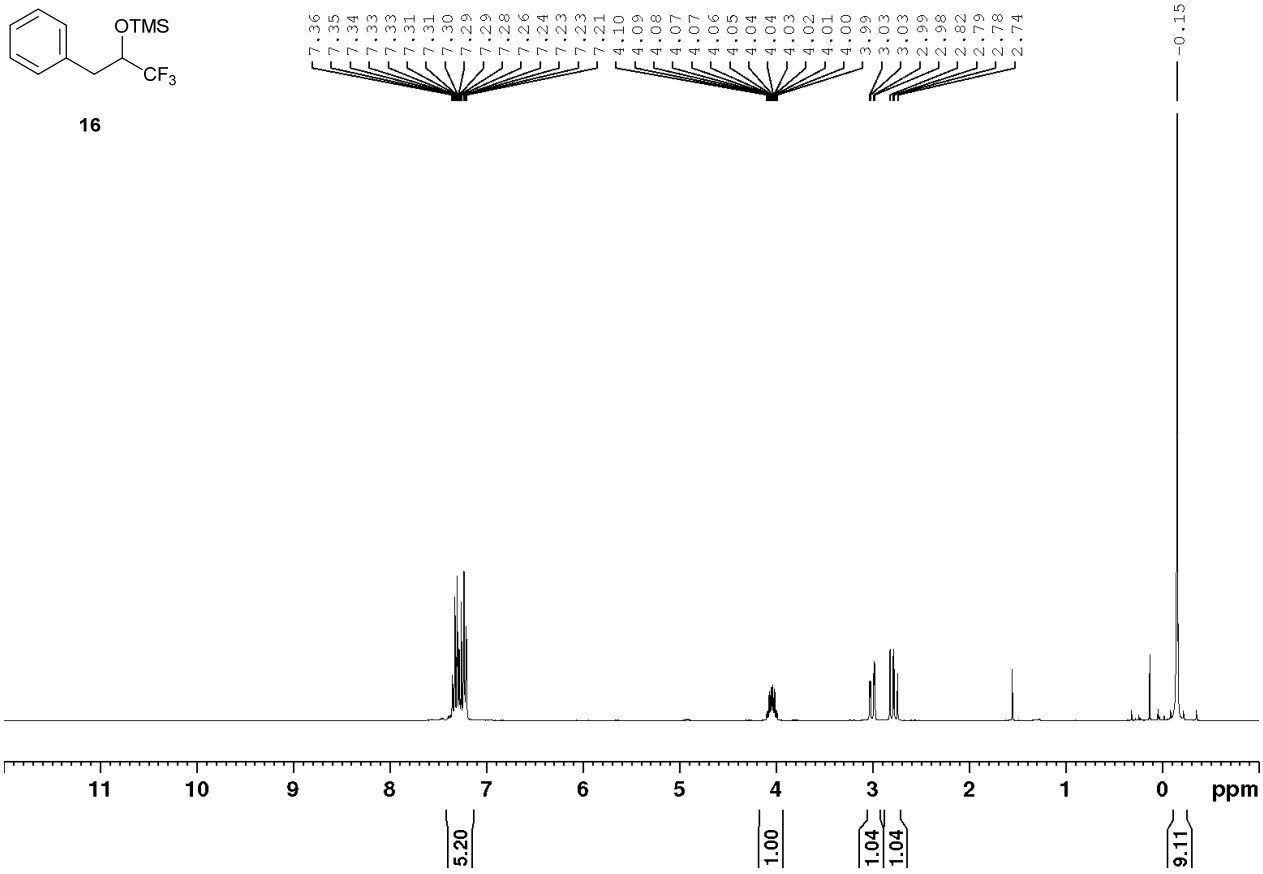
ppm


OTMS
CF3
16
7.36
7.35
7.34
7.33
7.33
7.31
7.31
7.30
7.29
7.29
7.28
7.26
7.24
7.23
7.23
7.21
4.10
4.09
4.08
4.07
4.07
4.06
4.05
4.04
4.04
4.03
4.02
4.01
4.00
3.99
3.03
3.03
2.99
2.98
2.82
2.79
2.78
2.74
-0.15
11
10
9
8
7
6
5
4
3
2
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ppm
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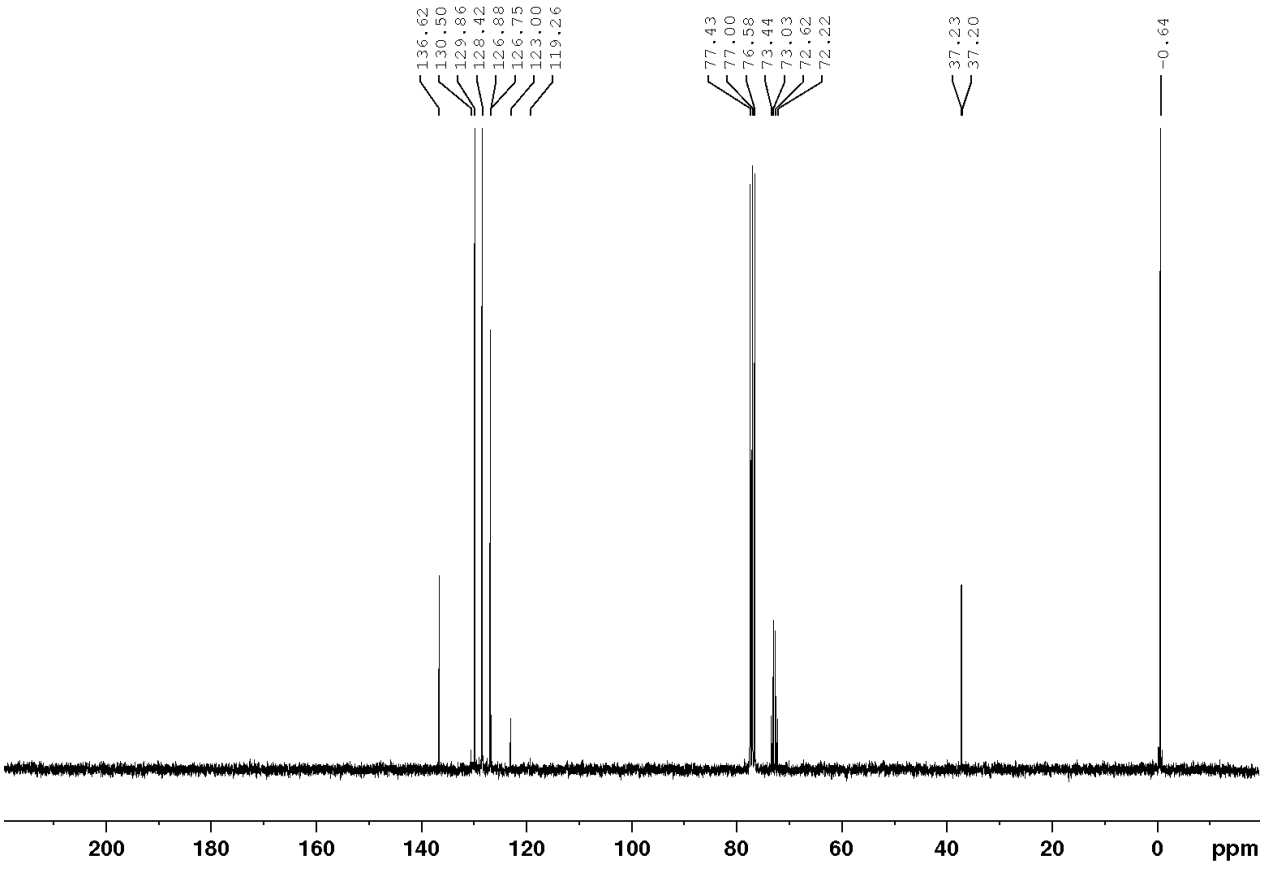
1.00
1.04
1.04
9.11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128.42
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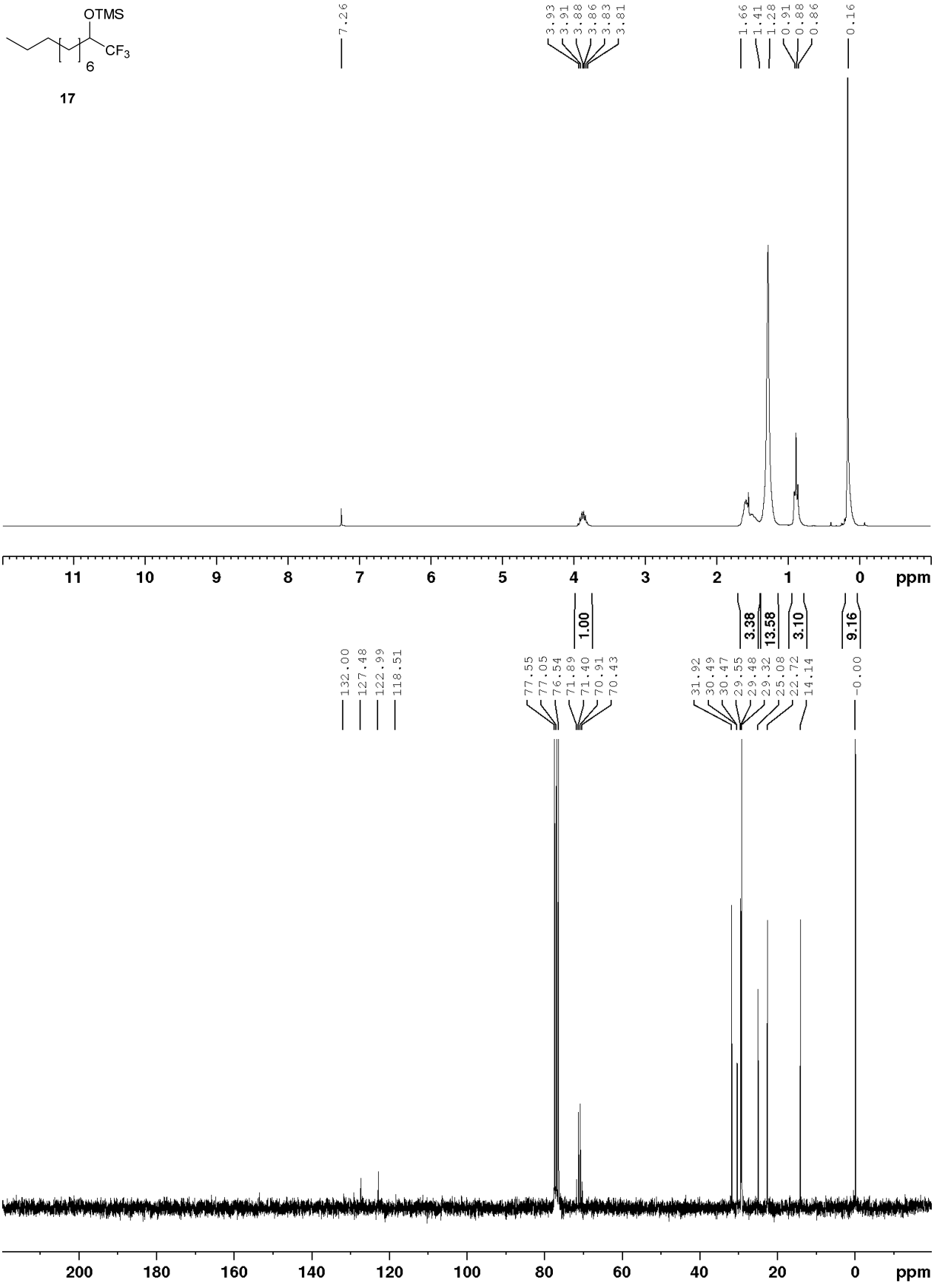
126.75
123.00
119.26
77.43
77.00
76.58
73.44
73.03
72.62
72.22
37.23
37.20
-0.64
200
180
160
140
120
100
80
60
40
20
0
ppm


OTMS
CF3
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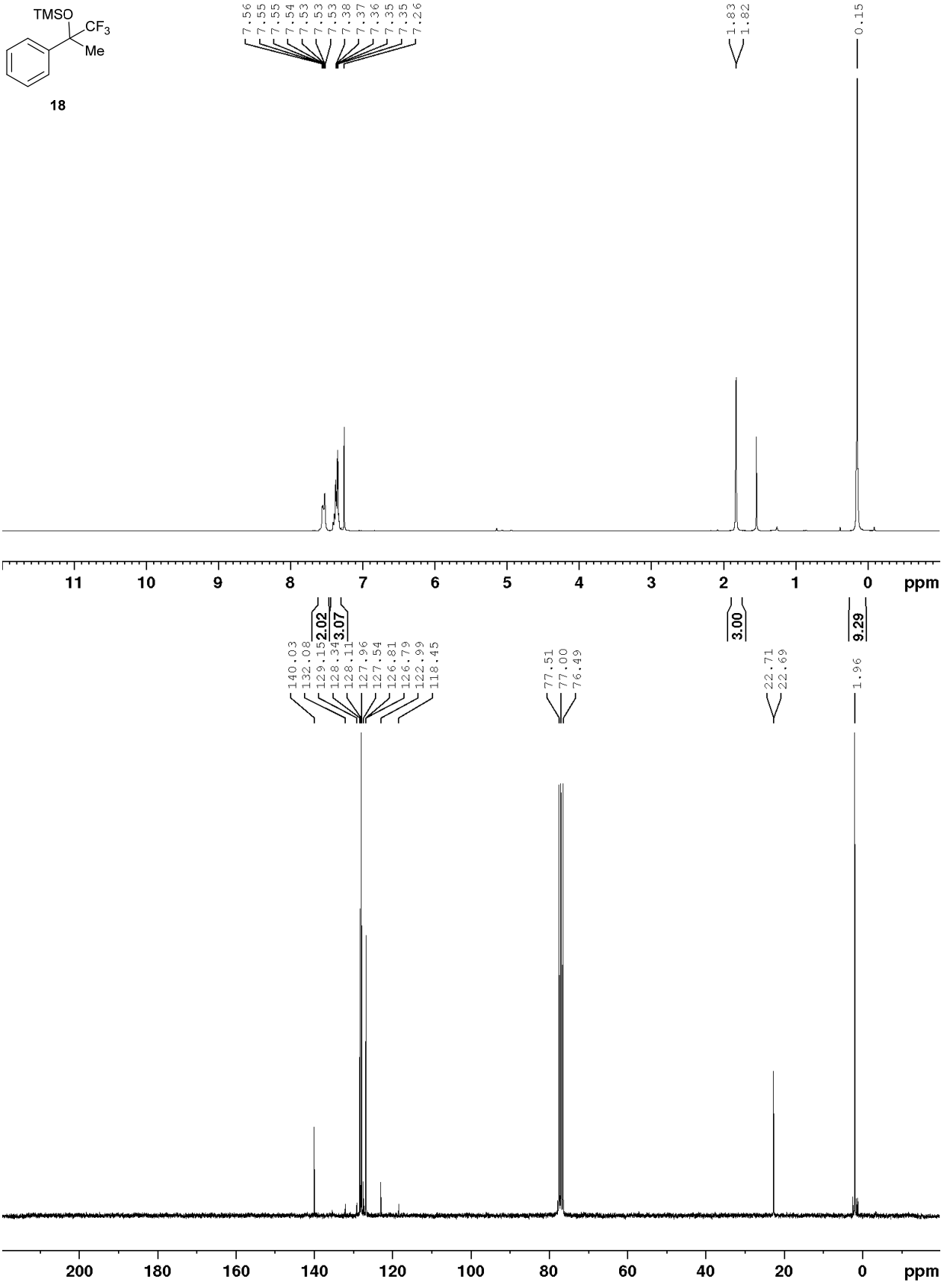
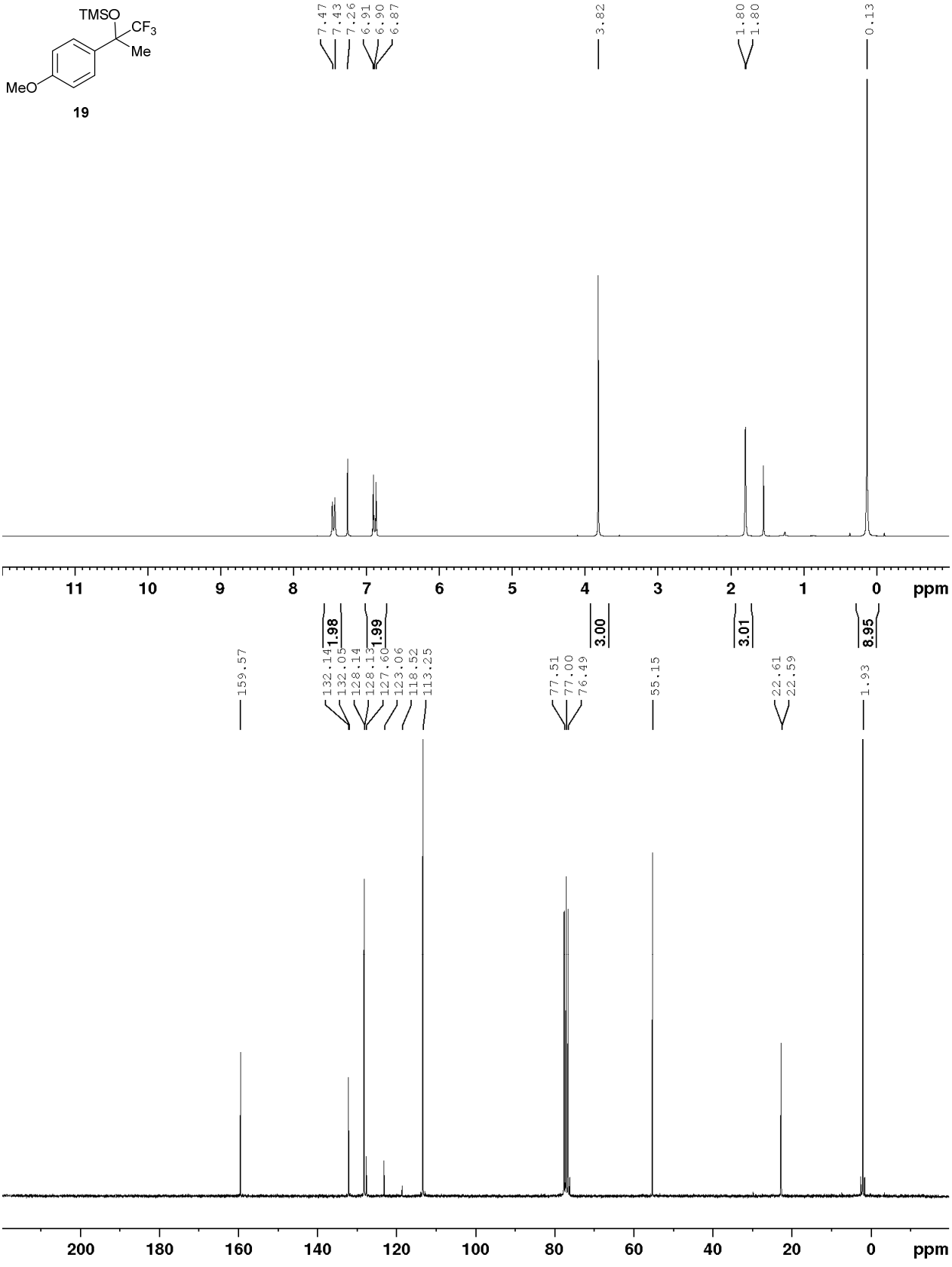
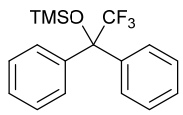
17
7.26
3.93
3.91
3.88
3.86
3.83
3.81
1.66
1.41
1.28
0.91
0.88
0.86
0.16
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
3.38
13.58
3.10
9.16
132.00
127.48
122.99
118.51
77.55
77.05
76.54
71.89
71.40
70.91
70.43
31.92
30.49
30.47
29.55
29.48
29.32
25.08
22.72
14.14
-0.00
200
180
160
140
120
100
80
60
40
20
0
ppm

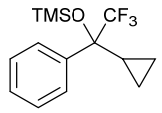

TMSO
CF3
Me
18
7.56
7.55
7.55
7.54
7.53
7.53
7.53
7.38
7.37
7.36
7.35
7.35
7.26
1.83
1.82
0.15
11
10
9
8
7
6
5
4
3
2
1
0
ppm
2.02
3.07
3.00
9.29
140.03
132.08
129.15
128.34
128.11
127.96
127.54
126.81
126.79
122.99
118.45
77.51
77.00
76.49
22.71
22.69
1.96
200
180
160
140
120
100
80
60
40
20
0
ppm


TMSO
CF3
Me
MeO
19
7.47
7.43
7.26
6.91
6.90
6.87
3.82
1.80
1.80
0.13
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.98
1.99
3.00
3.01
8.95
159.57
132.14
132.05
128.14
128.13
127.60
123.06
118.52
113.25
77.51
77.00
76.49
55.15
22.61
22.59
1.93
200
180
160
140
120
100
80
60
40
20
0
ppm


TMSO
CF3

20

7.44
7.39
7.35
7.30
7.26
-0.05
11
10
9
8
7
6
5
4
3
2
1
0
ppm
4.05
5.95
9.00
140.92
132.05
128.27
128.19
128.17
127.83
127.48
122.91
118.34
82.67
82.21
81.76
81.31
77.53
77.02
76.51
1.27
200
180
160
140
120
100
80
60
40
20
0
ppm


TMSO
CF3

21

7.62
7.55
7.41
7.31
7.30
7.26
1.43
1.40
1.37
1.34
1.32
0.61
0.49
0.11
11
10
9
8
7
6
5
4
3
2
1
0
ppm
2.00
3.02
1.17
4.10
9.08
138.88
132.92
128.34
128.18
127.87
126.86
123.76
119.18
80.08
79.65
79.21
78.77
77.51
77.00
76.49
17.36
1.88
1.67
1.50
240
220
200
180
160
140
120
100
80
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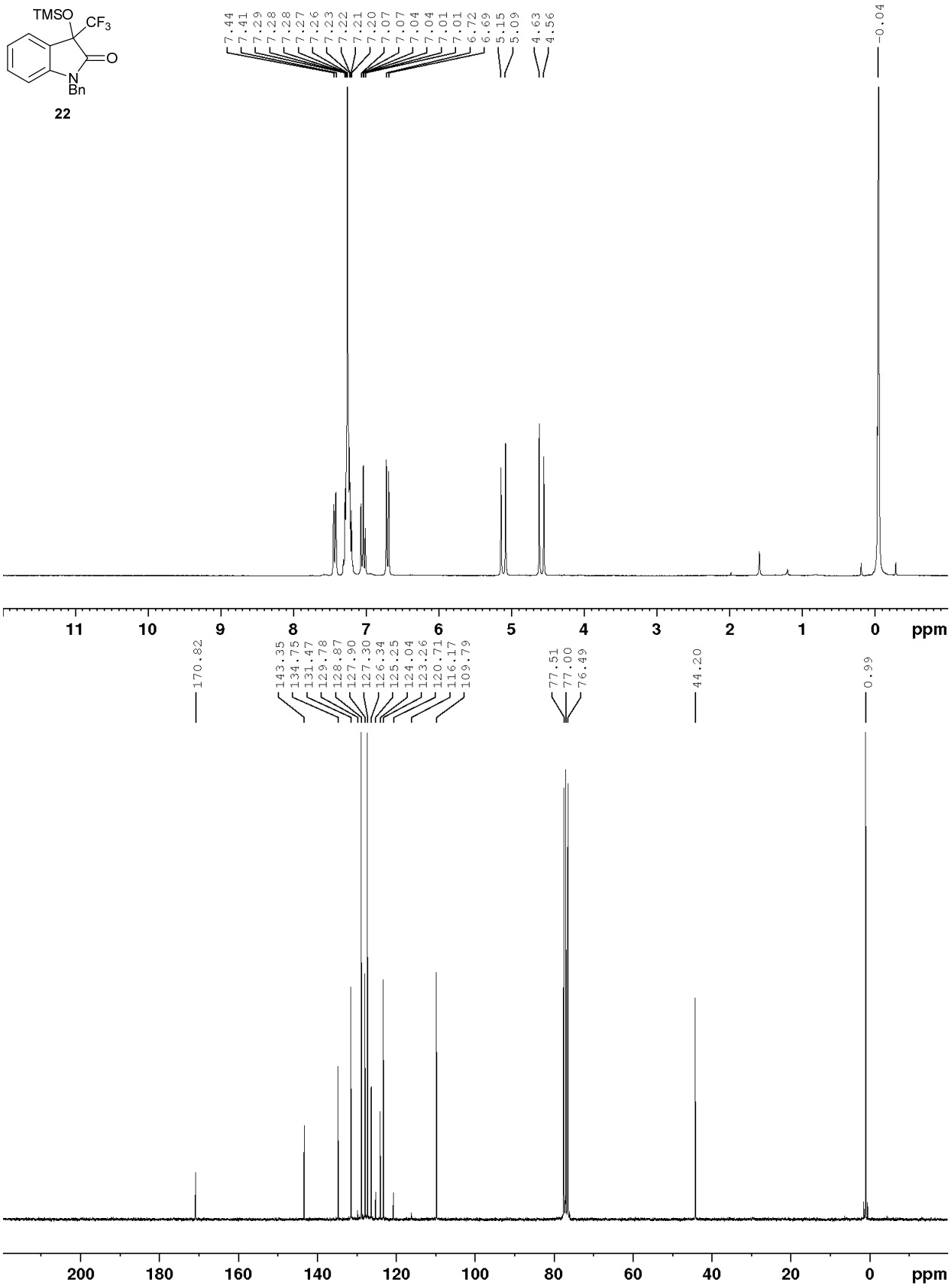
40
20
0
-20
ppm


TMSO
CF3
O
N
Bn
22
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7.41
7.29
7.28
7.27
7.26
7.23
7.22
7.21
7.20
7.07
7.07
7.04
7.04
7.01
7.01
6.72
6.69
5.15
5.09
4.63
4.56
-0.04
11
10
9
8
7
6
5
4
3
2
1
0
ppm
170.82
143.35
134.75
131.47
129.78
128.87
127.90
127.30
126.34
125.25
124.04
123.26
120.71
116.17
109.79
77.51
77.00
76.49
44.20
0.99
200
180
160
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120
100
80
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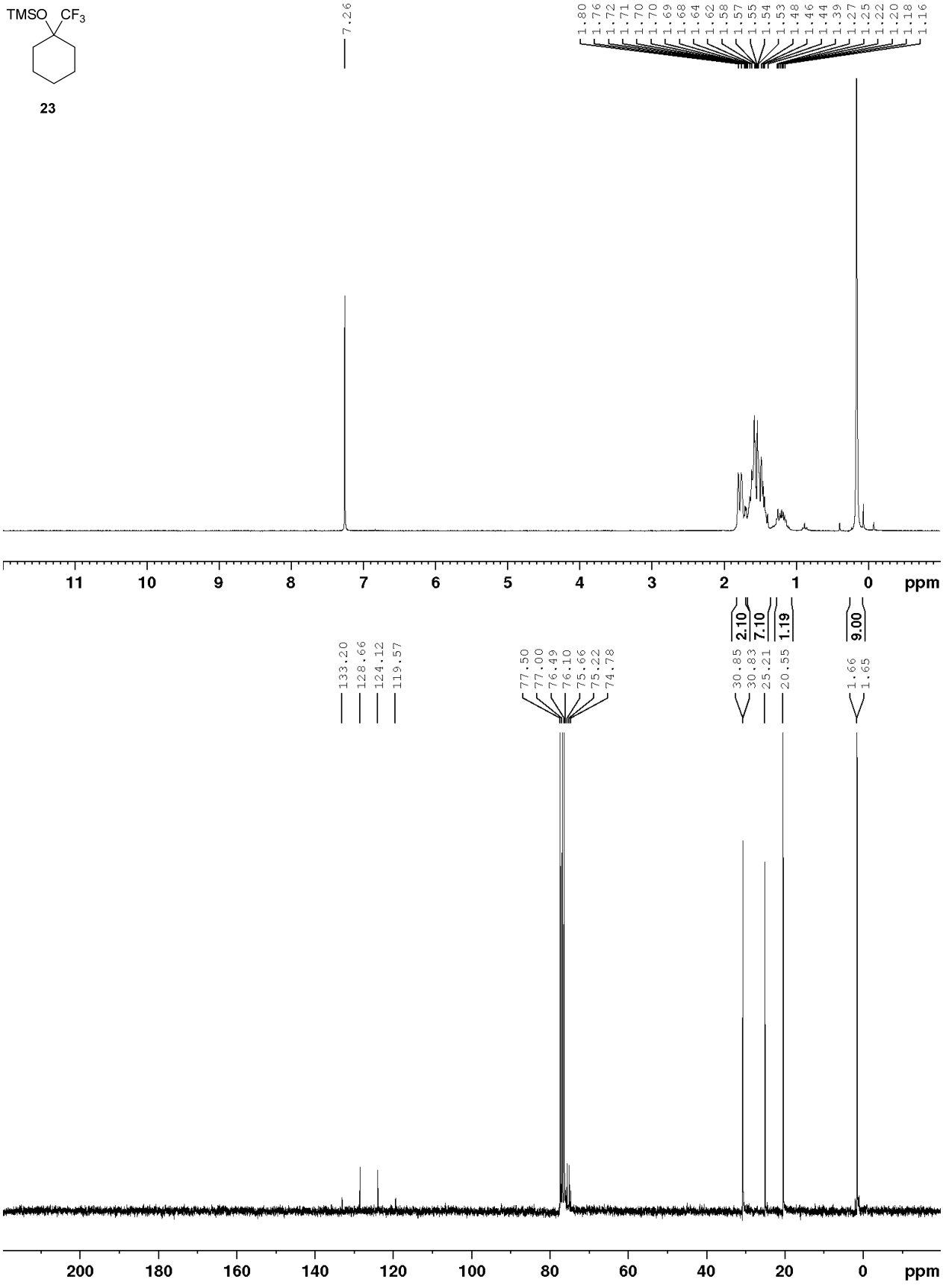
40
20
0
ppm


TMSO
CF3
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7.26
1.80
1.76
1.72
1.71
1.70
1.70
1.69
1.68
1.64
1.62
1.58
1.57
1.55
1.54
1.53
1.48
1.46
1.44
1.39
1.27
1.25
1.22
1.20
1.18
1.16
11
10
9
8
7
6
5
4
3
2
1
0
ppm
133.20
128.66
124.12
119.57
77.50
77.00
76.49
76.10
75.66
75.22
74.78
30.85
30.83
25.21
20.55
1.66
1.65
2.10
7.10
1.19
9.00
200
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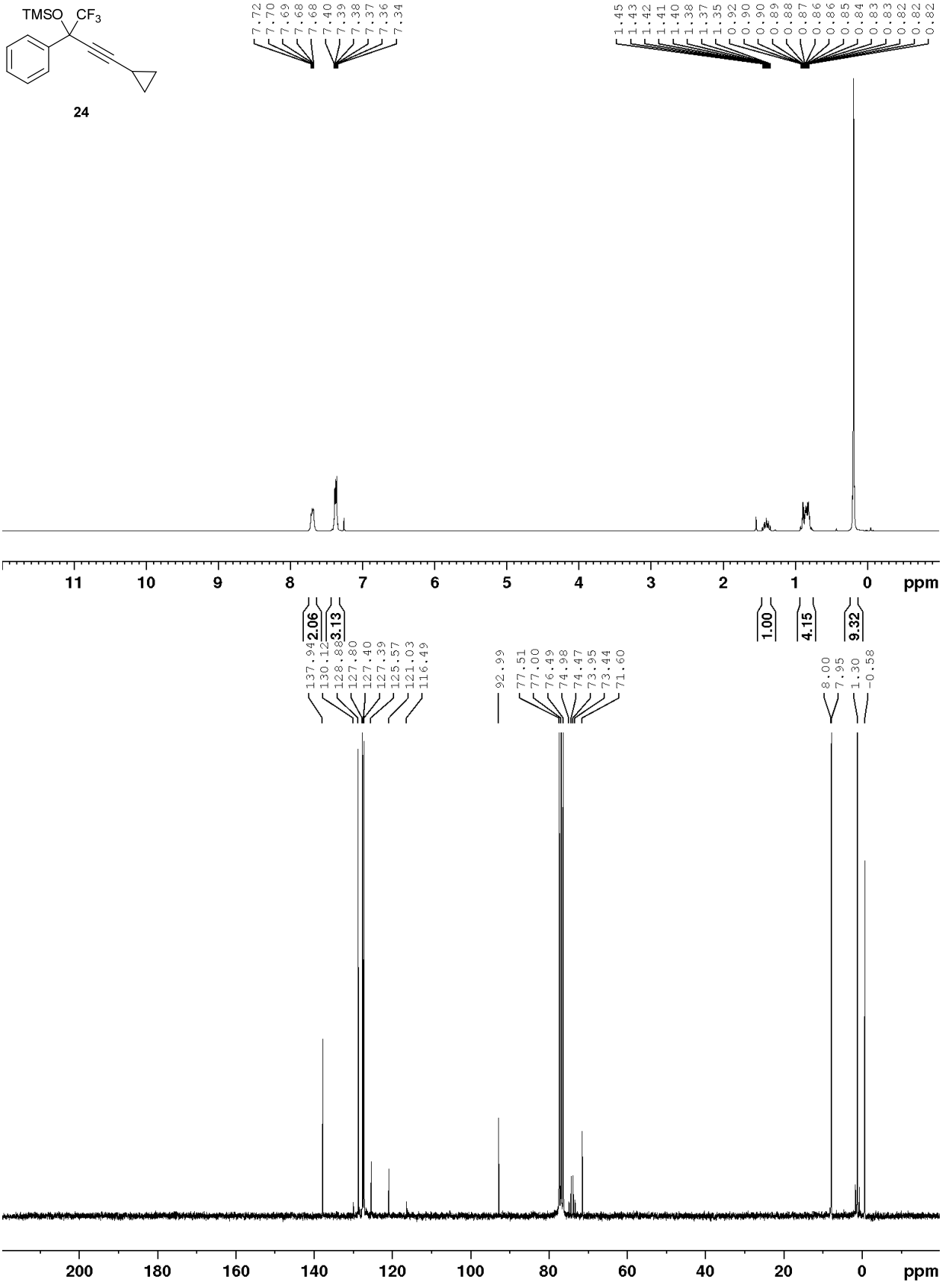
140
120
100
80
60
40
20
0
ppm


TMSO
CF3
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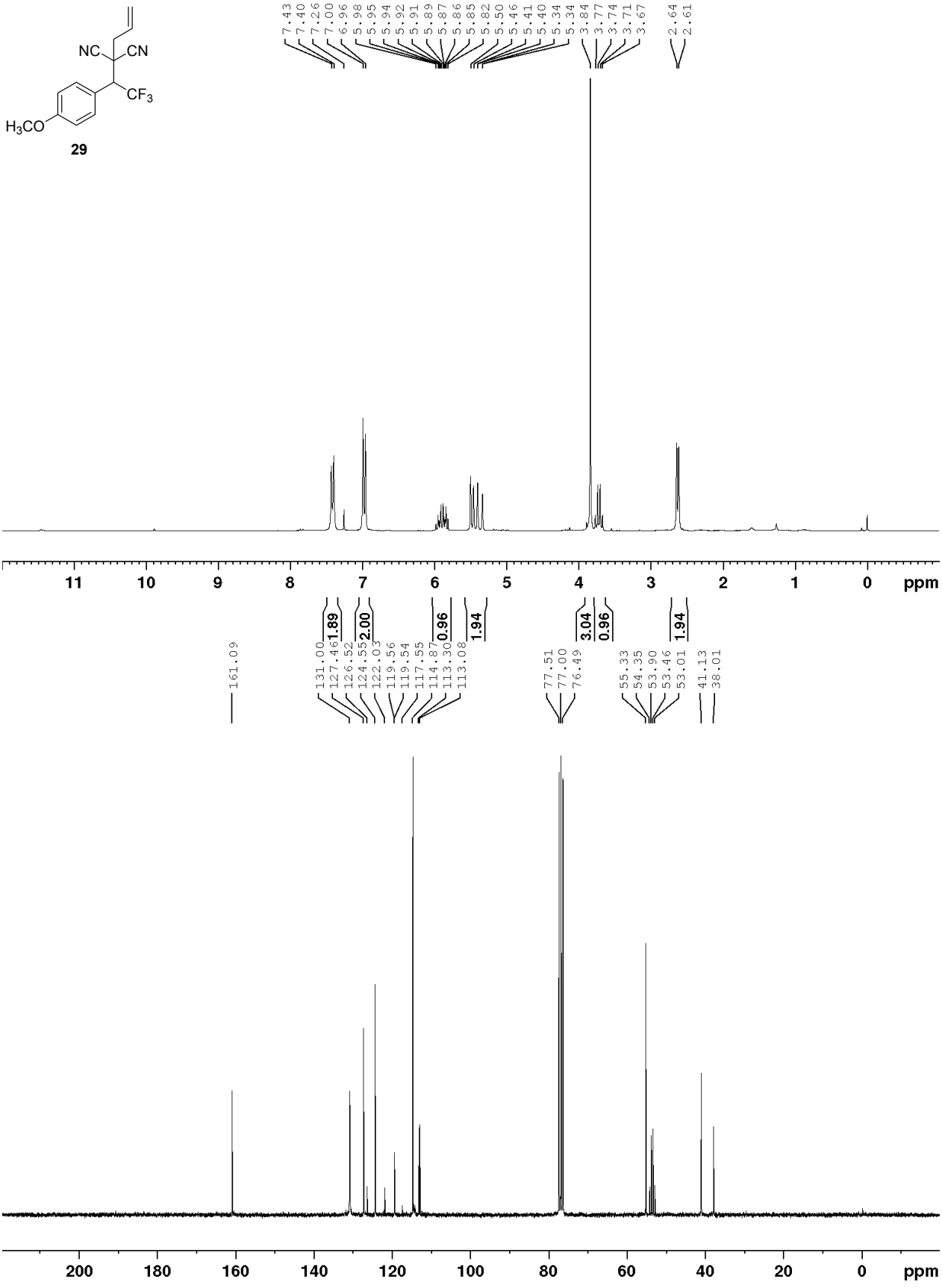
7.68
7.68
7.40
7.39
7.38
7.37
7.36
7.34
1.45
1.43
1.42
1.41
1.40
1.38
1.37
1.35
0.92
0.90
0.90
0.89
0.88
0.87
0.86
0.86
0.85
0.84
0.83
0.82
0.82
0.82
11
10
9
8
7
6
5
4
3
2
1
0
ppm
2.06
3.13
1.00
4.15
9.32
137.94
130.12
128.88
127.80
127.40
127.39
125.57
121.03
116.49
92.99
77.51
77.00
76.49
74.98
74.47
73.95
73.44
71.60
8.00
7.95
1.30
-0.58
200
180
160
140
120
100
80
60
40
20
0
ppm


NC
CN
CF3
H3CO
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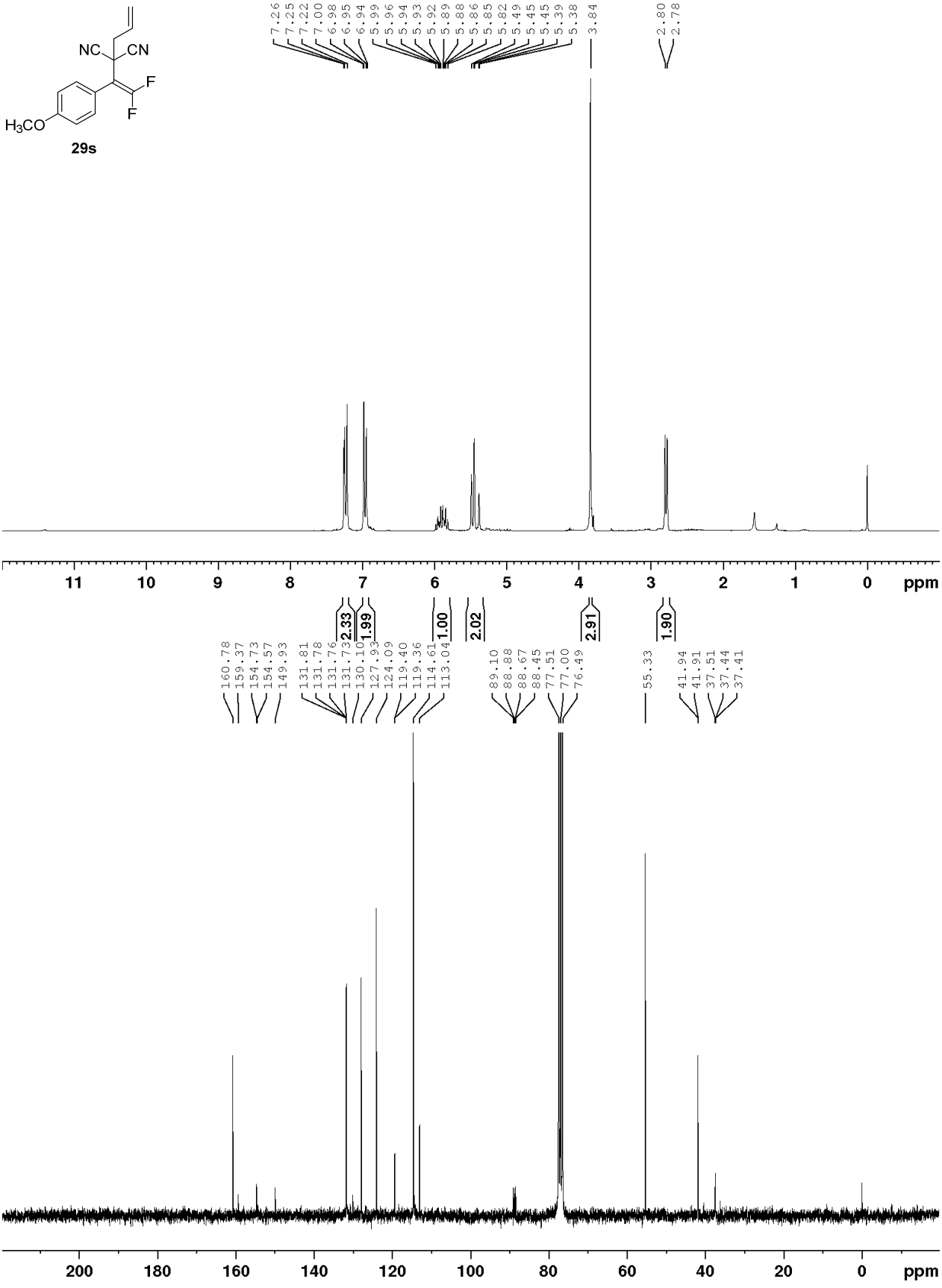
7.40
7.26
7.00
6.96
5.98
5.95
5.94
5.92
5.91
5.89
5.87
5.86
5.85
5.82
5.50
5.46
5.41
5.40
5.34
5.34
3.84
3.77
3.74
3.71
3.67
2.64
2.61
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.89
2.00
0.96
1.94
3.04
0.96
1.94
161.09
131.00
127.46
126.52
124.55
122.03
119.56
119.54
117.55
114.87
113.30
113.08
77.51
77.00
76.49
55.33
54.35
53.90
53.46
53.01
41.13
38.01
200
180
160
140
120
100
80
60
40
20
0
ppm


NC
CN
F
F
H3CO
29s
7.26
7.25
7.22
7.00
6.98
6.95
6.94
5.99
5.96
5.94
5.93
5.92
5.89
5.88
5.86
5.85
5.82
5.49
5.45
5.45
5.39
5.38
3.84
2.80
2.78
11
10
9
8
7
6
5
4
3
2
1
0
ppm
2.33
1.99
1.00
2.02
2.91
1.90
160.78
159.37
154.73
154.57
149.93
131.81
131.78
131.76
131.73
130.10
127.93
124.09
119.40
119.36
114.61
113.04
89.10
88.88
88.67
88.45
77.51
77.00
76.49
55.33
41.94
41.91
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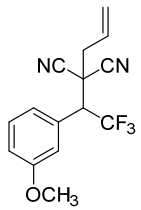
37.44
37.41
200
180
160
140
120
100
80
60
40
20
0
ppm


NC
CN
CF3
OCH3

30

7.40
7.39
7.37
7.26
7.06
7.04
7.03
7.02
5.95
5.93
5.92
5.91
5.90
5.89
5.88
5.86
5.50
5.48
5.40
5.40
5.37
5.37
5.30
3.84
3.74
3.72
3.70
3.69
2.64
2.63
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
2.89
0.99
1.00
1.02
3.06
1.03
2.04
160.16
130.60
129.07
127.42
125.26
124.71
123.01
121.95
115.95
115.30
113.22
113.01
77.25
77.00
76.75
55.36
54.64
54.42
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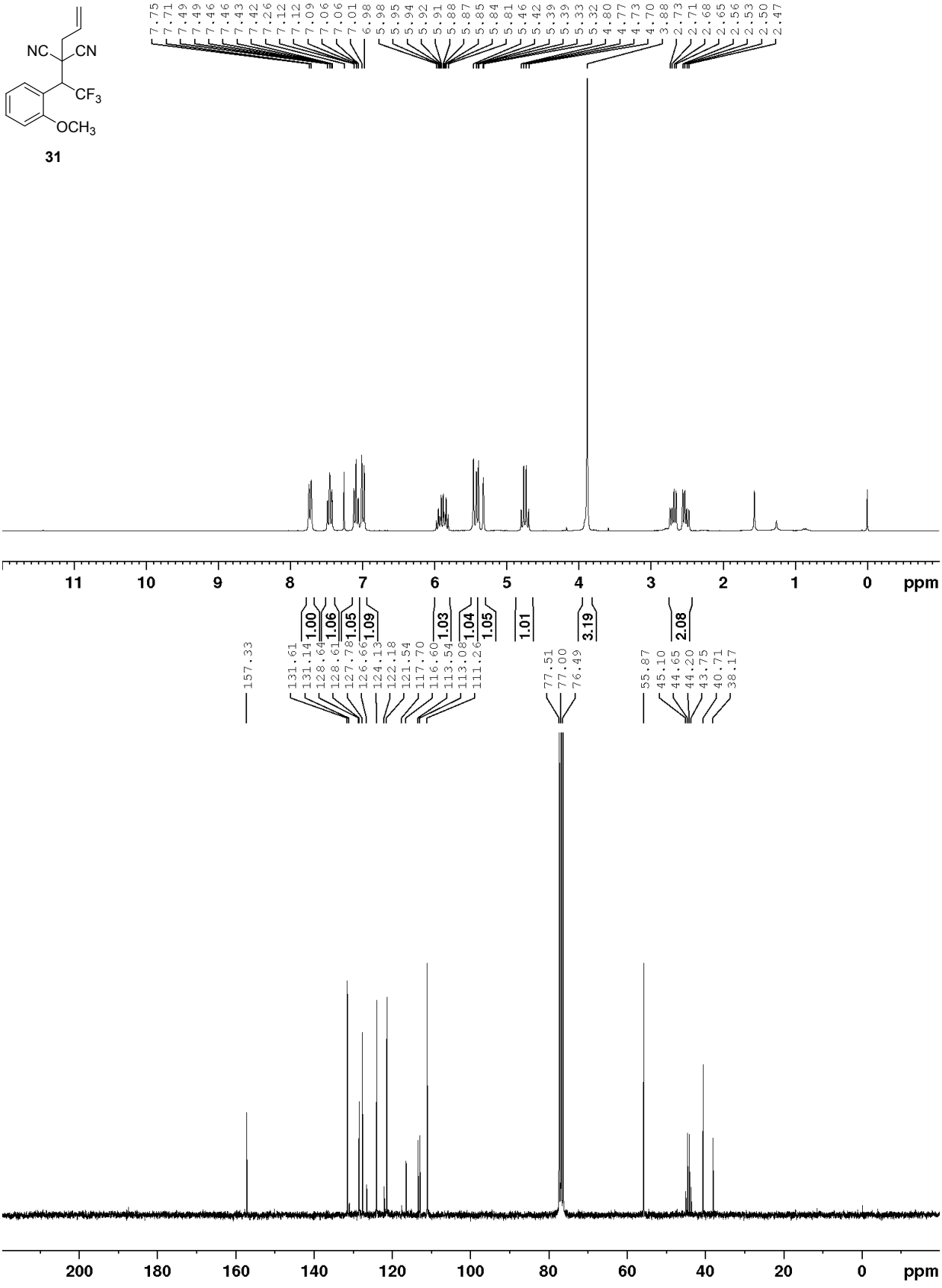
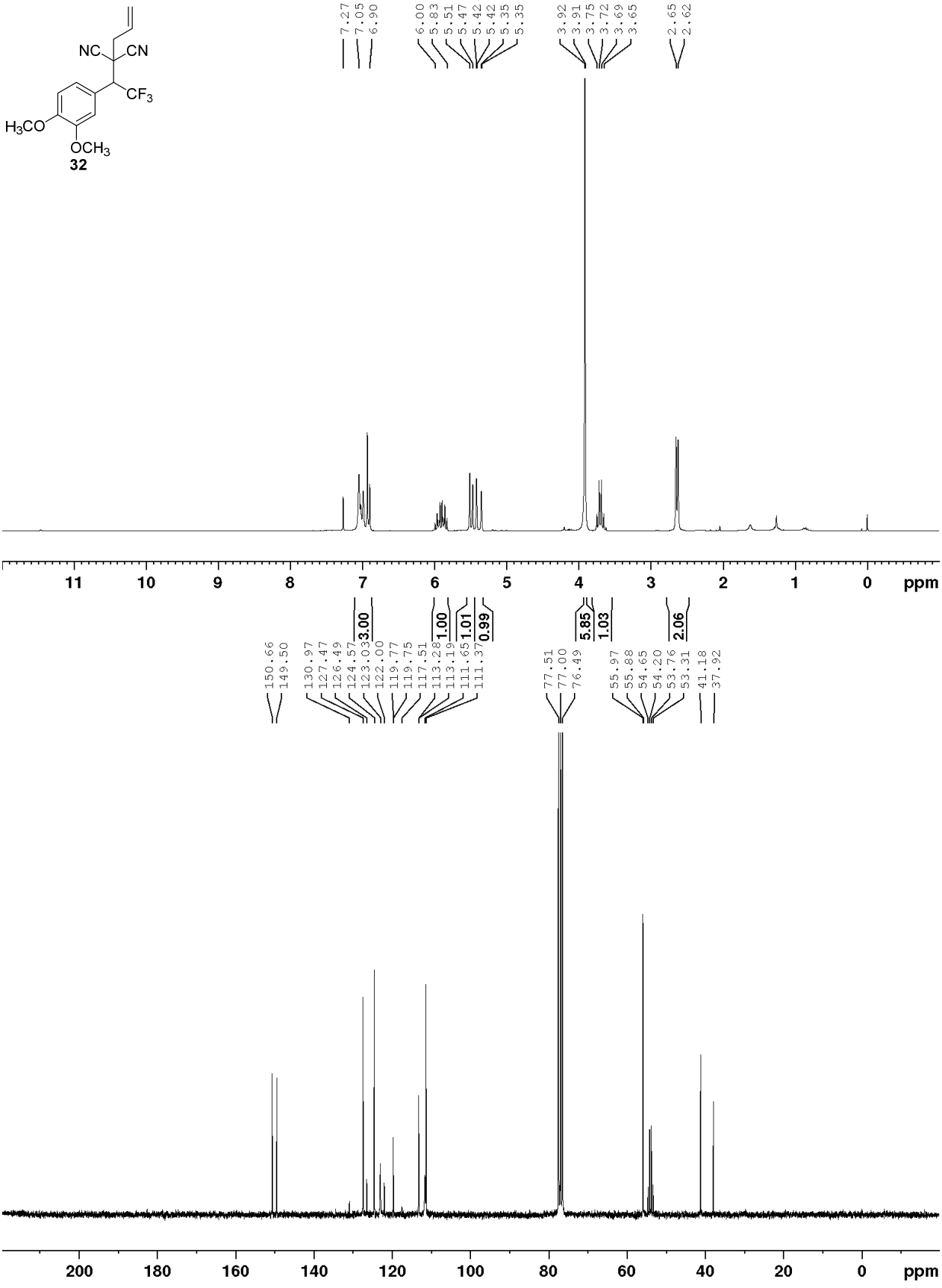
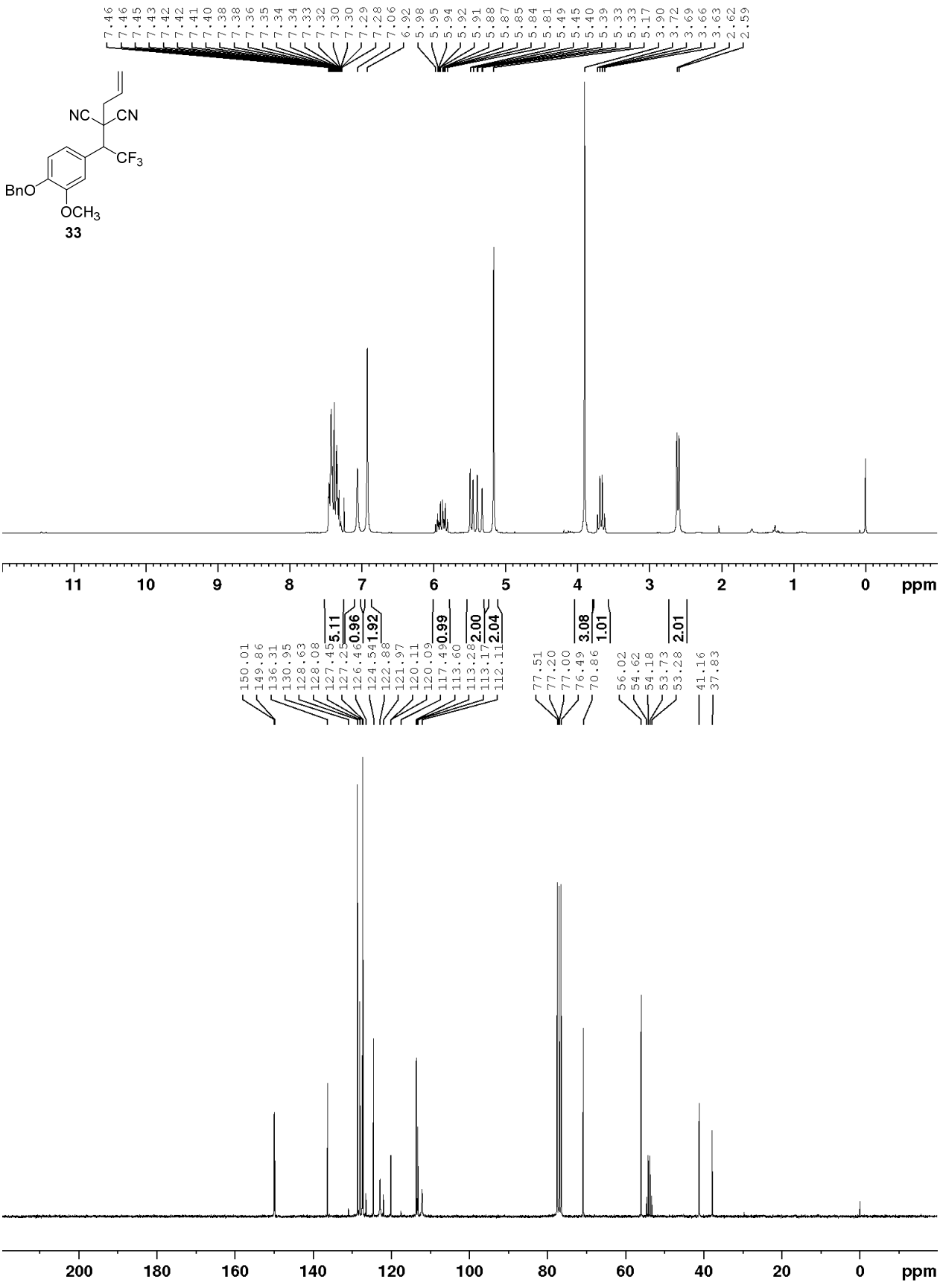
53.97
41.24
37.74
220
200
180
160
140
120
100
80
60
40
20
0
ppm


NC
CN
CF3
OCH3
31
7.75 7.71 7.49 7.49 7.46 7.46 7.43 7.42 7.26 7.12 7.12 7.09 7.06 7.06 7.01 6.98 5.98 5.95 5.94 5.92 5.91 5.88 5.87 5.85 5.84 5.81 5.46 5.42 5.39 5.39 5.33 5.32 4.80 4.77 4.73 4.70 3.88 2.73 2.71 2.68 2.65 2.56 2.53 2.50 2.47
11 10 9 8 7 6 5 4 3 2 1 0 ppm
1.00 1.06 1.05 1.09 1.03 1.04 1.05 1.01 3.19 2.08
157.33 131.61 131.14 128.64 128.61 127.78 126.66 124.13 122.18 121.54 117.70 116.60 113.54 113.08 111.26 77.51 77.00 76.49 55.87 45.10 44.65 44.20 43.75 40.71 38.17
200 180 160 140 120 100 80 60 40 20 0 ppm


NC
CN
CF3
H3CO
OCH3
32
7.27
7.05
6.90
6.00
5.83
5.51
5.47
5.42
5.35
5.35
3.92
3.91
3.75
3.72
3.69
3.65
2.65
2.62
11
10
9
8
7
6
5
4
3
2
1
0
ppm
3.00
1.00
1.01
0.99
5.85
1.03
2.06
150.66
149.50
130.97
127.47
126.49
124.57
123.03
122.00
119.77
119.75
117.51
113.28
113.19
111.65
111.37
77.51
77.00
76.49
55.97
55.88
54.65
54.20
53.76
53.31
41.18
37.92
200
180
160
140
120
100
80
60
40
20
0
ppm


7.46
7.46
7.45
7.43
7.42
7.42
7.41
7.40
7.38
7.38
7.36
7.35
7.34
7.34
7.33
7.32
7.30
7.30
7.29
7.28
7.06
6.92
5.98
5.95
5.94
5.92
5.91
5.88
5.87
5.85
5.84
5.81
5.49
5.45
5.40
5.39
5.33
5.33
5.17
3.90
3.72
3.69
3.66
3.63
2.62
2.59
NC
CN
CF3
BnO
OCH3
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2.04
3.08
1.01
2.01
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130.95
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128.08
127.45
127.25
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124.54
122.88
121.97
120.11
120.09
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113.28
113.17
112.11
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77.20
77.00
76.49
70.86
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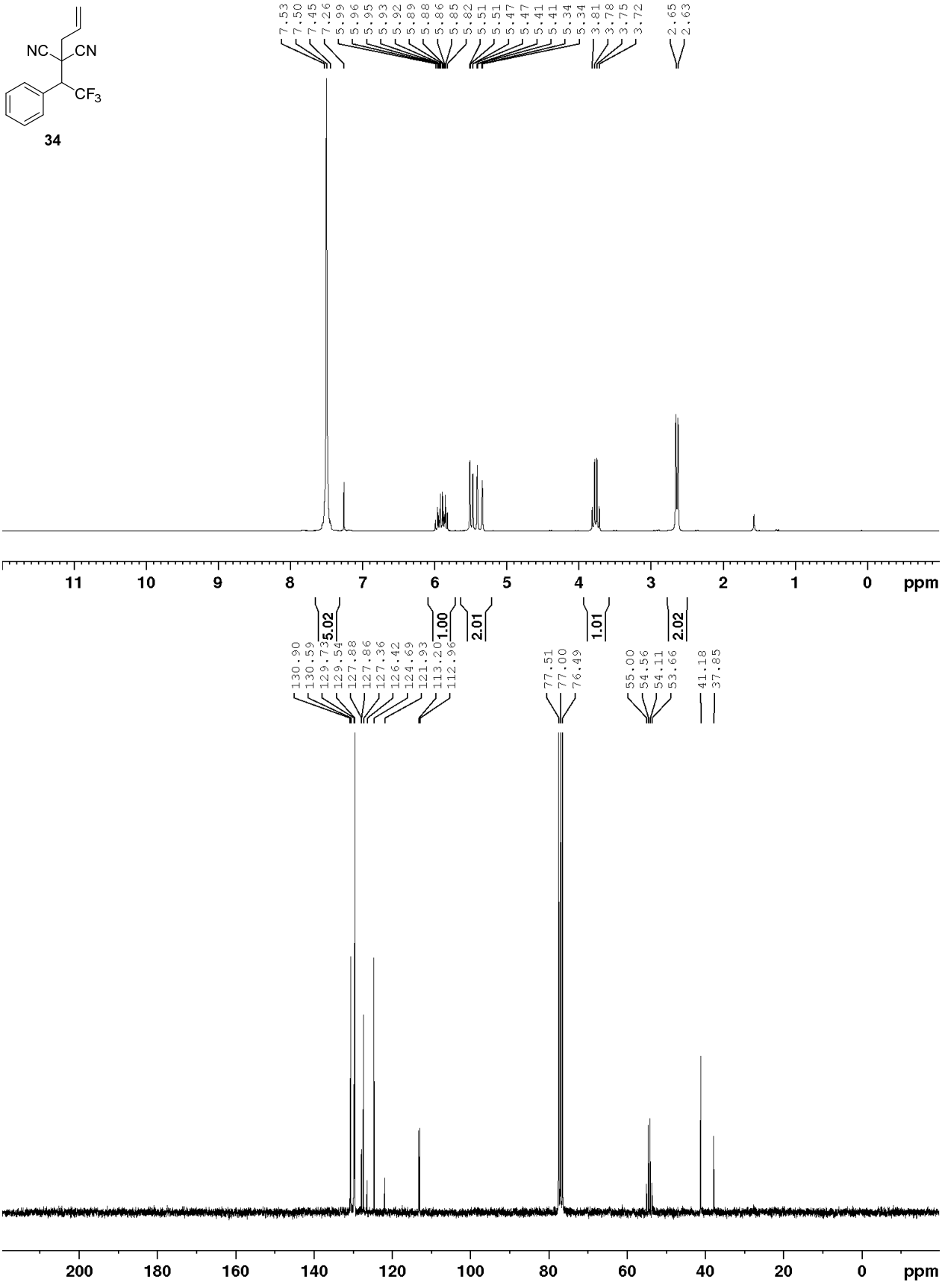
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5.88
5.86
5.85
5.82
5.51
5.51
5.47
5.47
5.41
5.41
5.34
5.34
3.81
3.78
3.75
3.72
2.65
2.63
11
10
9
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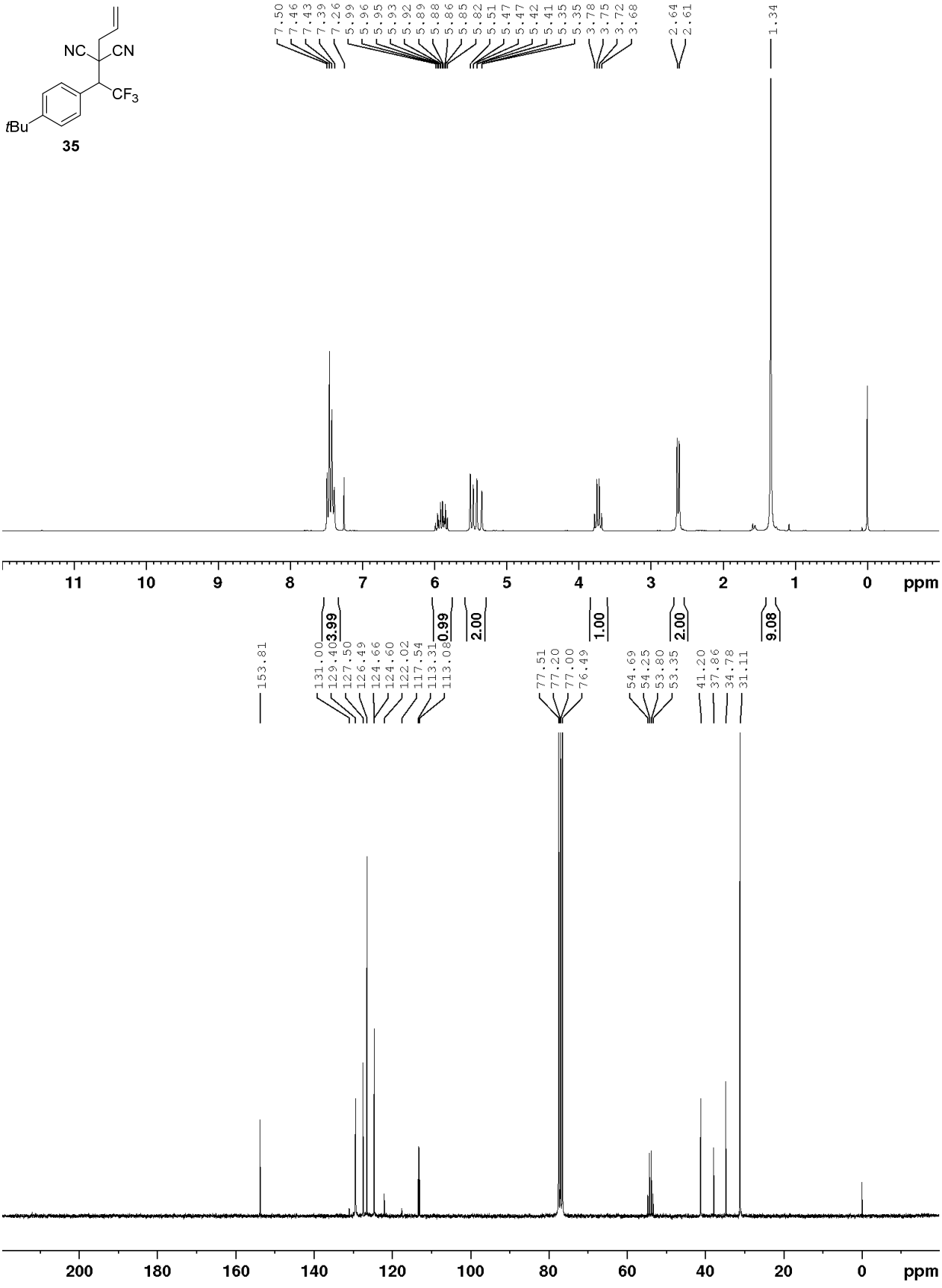
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5.86
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5.82
5.51
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3.75
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1.34
11
10
9
8
7
6
5
4
3
2
1
0
ppm
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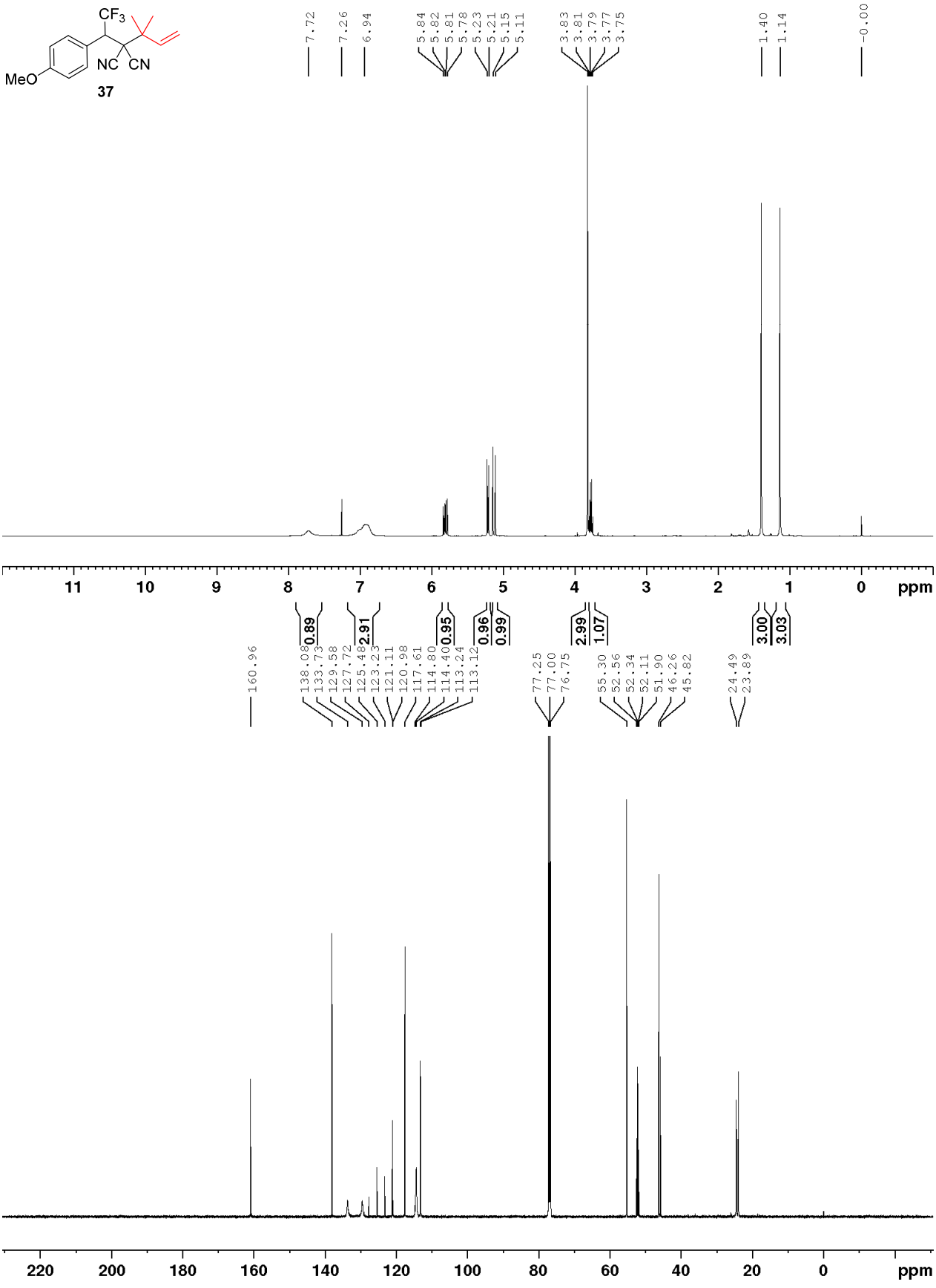
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0.96
0.99
2.99
1.07
3.00
3.03
160.96
138.08
133.73
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125.48
123.23
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120.98
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114.80
114.40
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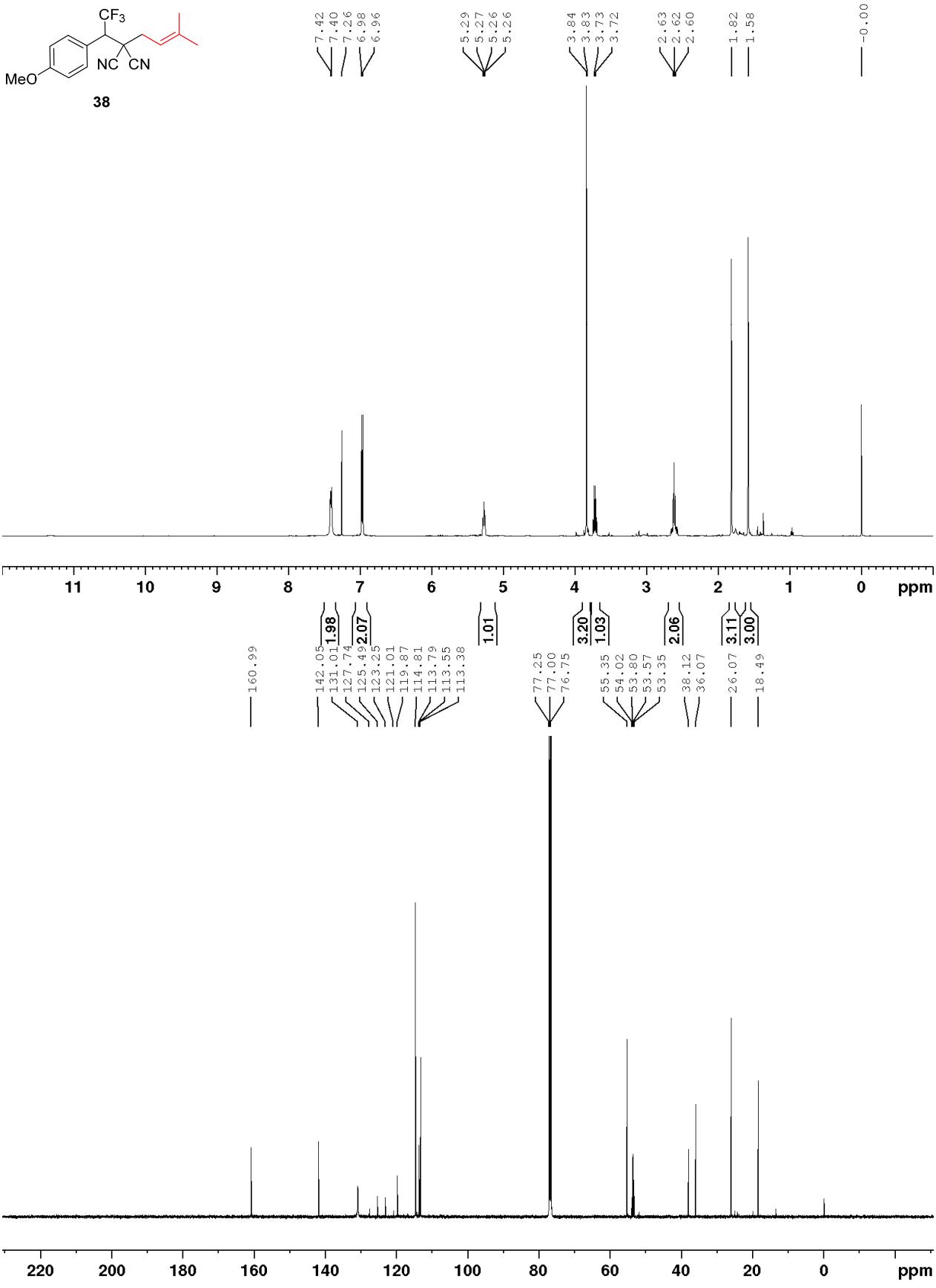
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MeO
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3.83
3.73
3.72
2.63
2.62
2.60
1.82
1.58
-0.00
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.98
2.07
1.01
3.20
1.03
2.06
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3.00
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131.01
127.74
125.49
123.25
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77.25
77.00
76.75
55.35
54.02
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53.35
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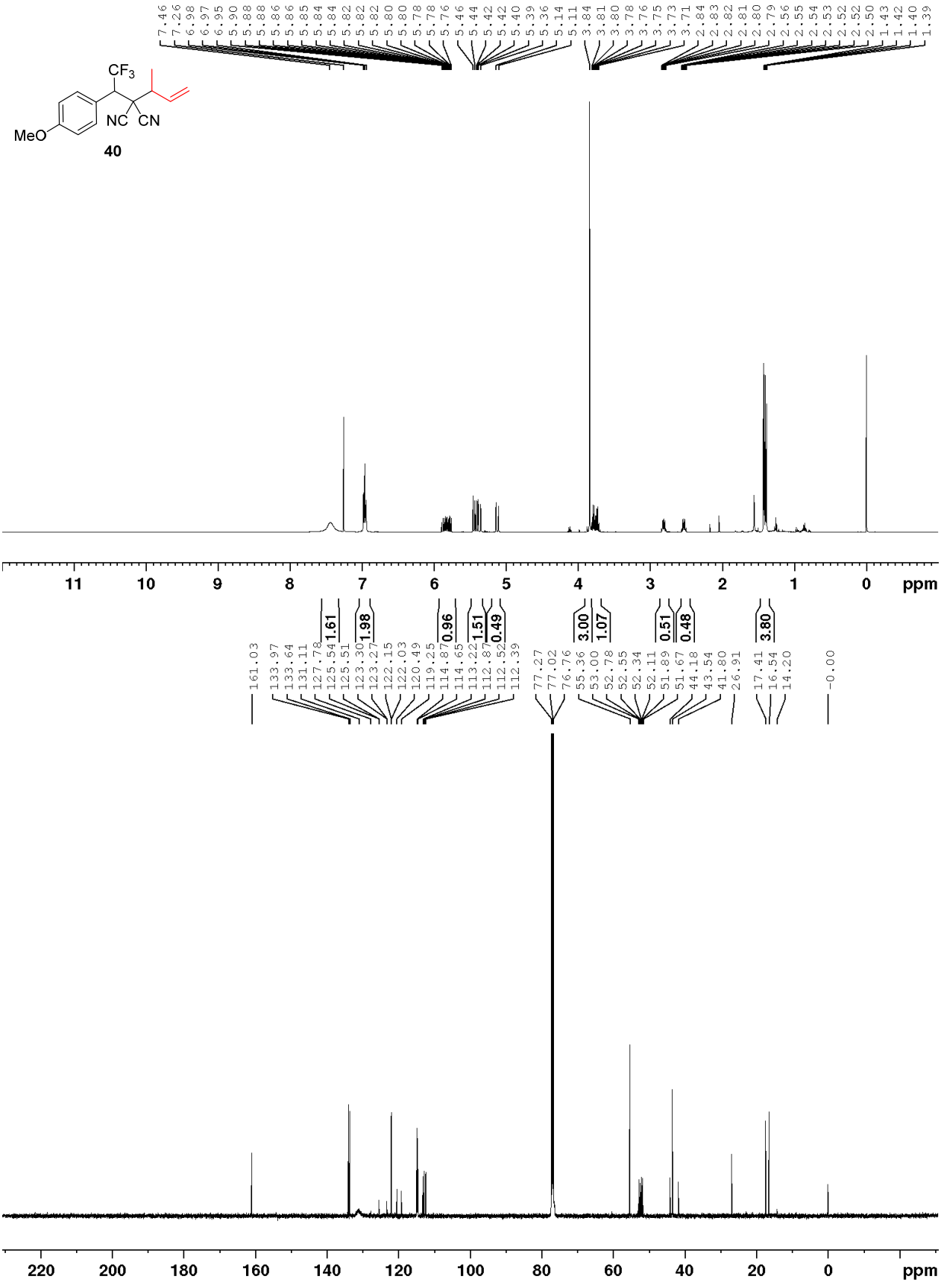
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5.82
5.82
5.82
5.80
5.80
5.78
5.78
5.76
5.46
5.44
5.42
5.42
5.40
5.39
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5.14
5.11
3.84
3.81
3.80
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3.76
3.75
3.73
3.71
2.84
2.83
2.82
2.81
2.80
2.79
2.56
2.55
2.54
2.53
2.52
2.52
2.50
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CF3
NC CN
MeO
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5
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2
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0
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140
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ppm

6. References

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