SUPPORTING INFORMATION

Design, Synthesis and Biological Evaluation of Isoxazole-Based ck1 Inhibitors Modified with Chiral Pyrrolidine Scaffolds

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Figure S1. X-ray crystal structure of compound **25d**.

Table S1. Data collection, structure refinement and Ramachrandran plot results of protein crystallization.

Table S2. Selectivity Profile of compound **29d**.

Appendix NMR spectra, HPLC chromatograms and DSC curves.

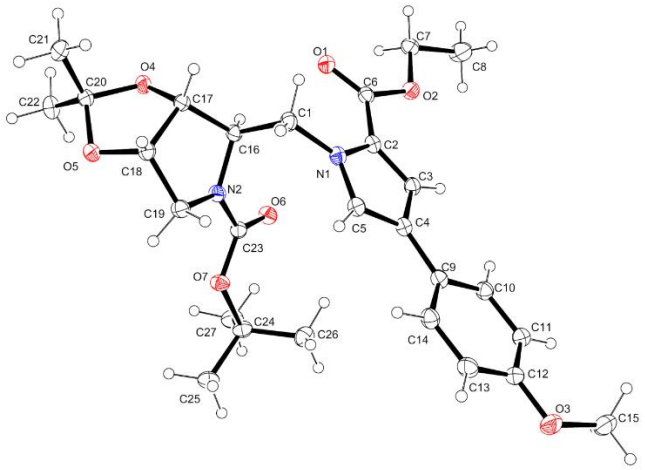

Figure S1. X-ray crystal structure of intermediate compound **25d** (ORTEP drawing with ellipsoids at 30% probability). CCDC 1589043 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

Table S1 Data collection, structure refinement and Ramachrandran plot results of protein crystallization of CK1δ in complex with compound **30a** and **30b**, respectively.

	tCK1δ with 30a	**tCK1δ with 30b**
Data collection		
Space group	P 2_1	P 2_1
Unit cell constants		
a,b,c (Å)	51.5 105.9 71.7	56.1 72.9 90.0
α, β, γ (°)	90 108.9 90	90 90.2 90
Wavelength (Å)	0.989	1.0
Resolution (Å)	67.81 - 1.864 (1.931 - 1.864)	45.01 - 1.83 (1.895 - 1.83)
No. of observations	194079 (10201)	321401 (30355)
No. of unique reflections	58776 (4416)	63861 (6374)
Multiplicity	3.3 (2.3)	5.0 (4.8)
Completeness (%)	97 (72)	99 (99)
R_{merge} (%)	6.8 (73.3)	8.9 (77.1)
R_{meas} (%)	8.2 (92.0)	8.0 (68.6)
$\langle I/\sigma(I)\rangle$	11.42 (1.19)	13.12 (2.41)
$CC_{1/2}$ (%)	99.7 (41.7)	99.8 (78.5)
Refinement		
Reflections used in refinement	58768	63821
Number of Test reflections	1904	1949
R_{work}/R_{free} (%)	18.1/20.7	18.7/20.8
Root-mean-square deviations		
Bond lengths (Å)	0.003	0.005
Bond angles (°)	0.54	0.74
Average B factor (Å^2)		
All macromolecule atoms	34.69	37.21
Solvent molecules	39.31	38.43
Other atoms	48.61	47.22
Ramachandran plot (%)		
Most favored	97.4	97.8
Additionally allowed	2.6	2.2
Disallowed	0	0
PDB entry	6F1W	6F26

Table S2. Selectivity profile of compound **29d**. The inhibitor has been screened at a concentration of 1 μM over a panel of 320 wild-type protein kinases by ProQinase GmbH (Freiburg, Germany) using an activity-based radiometric 33PanQinase® assay. Results are presented as percentage of residual kinase activity relative to

control. The final DMSO concentration was 1 % in each reaction-mix. Classification of protein kinase families refers to Manning *et al.* (Manning, G.; Whyte, D. B.; Martinez, R.; Hunter, T.; Sudarsanam, S. The Protein Kinase Complement of the Human Genome. *Science* **2002**, 298, 1912–1934): AGC = containing PKA, PKG, PKC families; CAMK = containing Cdk, MAPK, GSK3, CLK families; STE = homologs of yeast sterile 7, sterile 11, sterile 20 kinases; TK = tyrosine kinase; TKL = tyrosine kinase-like.

Kinase name	Kinase family	Residual Activity (%)
ABL1	TK	95
ABL2	TK	110
ACK1	TK	96
ACV-R1	TKL	105
ACV-R1B	TKL	103
ACV-R2A	TKL	125
ACV-R2B	TKL	127
ACV-RL1	TKL	115
AKT1 aa106-480	AGC	84
AKT2 aa107-481	AGC	107
AKT3 aa106-479	AGC	95
ALK (GST-HIS-tag)	TK	105
AMPK-alpha1 aa1-550	CAMK	99
ARK5	CAMK	100
ASK1	STE	107
Aurora-A	OTHER	103
Aurora-B	OTHER	96
Aurora-C	OTHER	97
AXL	TK	110
BLK	TK	110
BMPR1A	TKL	96
BMX	TK	96
B-RAF	TKL	95
BRK	TK	131
BRSK1	CAMK	104
BRSK2	CAMK	90
BTK	TK	112
BUB1B	OTHER	90
CAMK1D	CAMK	89
CAMK2A	CAMK	87
CAMK2B	CAMK	102
CAMK2D	CAMK	100
CAMK2G	CAMK	119
CAMK4	CAMK	102
CAMKK1	OTHER	89
CAMKK2	OTHER	97
CDC42BPA	AGC	100
CDC42BPB	AGC	86
CDC7/DBF4	OTHER	94
CDK1/CycA2	CMGC	102
CDK1/CycB1	CMGC	107
CDK1/CycE1	CMGC	100

CDK16/CycY	CMGC	112
CDK19/CycC	CMGC	84
CDK2/CycA2	CMGC	102
CDK2/CycE1	CMGC	93
CDK3/CycC	CMGC	100
CDK3/CycE1	CMGC	103
CDK4/CycD1	CMGC	108
CDK4/CycD3	CMGC	98
CDK5/p25NCK	CMGC	92
CDK5/p35NCK	CMGC	100
CDK6/CycD1	CMGC	104
CDK6/CycD3	CMGC	98
CDK7/CycH/MAT1	CMGC	98
CDK8/CycC	CMGC	106
CDK9/CycK	CMGC	97
CDK9/CycT1	CMGC	103
CHK1	CAMK	97
CHK2	CAMK	97
CK1-alpha1	CK1	16
CK1-delta	CK1	1
CK1-epsilon	CK1	4
CK1-gamma1	CK1	88
CK1-gamma2	CK1	80
CK1-gamma3	CK1	74
CK2-alpha1	OTHER	103
CK2-alpha2	OTHER	111
CLK1	CMGC	97
CLK2	CMGC	116
CLK3	CMGC	92
CLK4	CMGC	104
COT	STE	89
CSF1-R	TK	108
CSK	TK	115
DAPK1	CAMK	101
DAPK2	CAMK	96
DAPK3	CAMK	90
DCAMKL2	CAMK	86
DDR2	TK	95
DMPK	AGC	93
DNA-PK	ATYPICAL	95
DYRK1A	CMGC	120
DYRK1B	CMGC	104
DYRK2	CMGC	96
DYRK3	CMGC	106
DYRK4	CMGC	80
EEF2K	ATYPICAL	99
EGF-R	TK	108
EIF2AK2	OTHER	132
EIF2AK3	OTHER	104

EPHA1	TK	120
EPHA2	TK	103
EPHA3	TK	118
EPHA4	TK	100
EPHA5	TK	103
EPHA6	TK	108
EPHA7	TK	100
EPHA8	TK	113
EPHB1	TK	108
EPHB2	TK	88
EPHB3	TK	138
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ERBB2	TK	121
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ERK1	CMGC	102
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FRK	TK	94
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GRK4	AGC	111
GRK5	AGC	97
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GRK7	AGC	107
GSG2	OTHER	91
GSK3-alpha	CMGC	103
GSK3-beta	CMGC	100
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HIPK3	CMGC	109
HIPK4	CMGC	91
HRI	OTHER	93
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IKK-alpha	OTHER	98
IKK-beta	OTHER	92
IKK-epsilon	OTHER	94
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LCK	TK	96
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LIMK2	TKL	98
LRRK2	TKL	100
LTK	TK	98
LYN	TK	122
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PKC-beta2	AGC	118
PKC-delta	AGC	100
PKC-epsilon	AGC	84
PKC-eta	AGC	113
PKC-gamma	AGC	112
PKC-iota	AGC	88
PKC-mu	AGC	94
PKC-nu	AGC	90

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PLK1	OTHER	98
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PRK1	AGC	94
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PRKG2	AGC	100
PRKX	AGC	92
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ROCK1	AGC	92
ROCK2	AGC	92
RON	TK	115
ROS	TK	88
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RPS6KA3	AGC	107
RPS6KA4	AGC	105
RPS6KA5	AGC	101
RPS6KA6	AGC	89
S6K	AGC	102
S6K-beta	AGC	96
SAK	OTHER	92
SGK1	AGC	102
SGK2	AGC	101
SGK3	AGC	97
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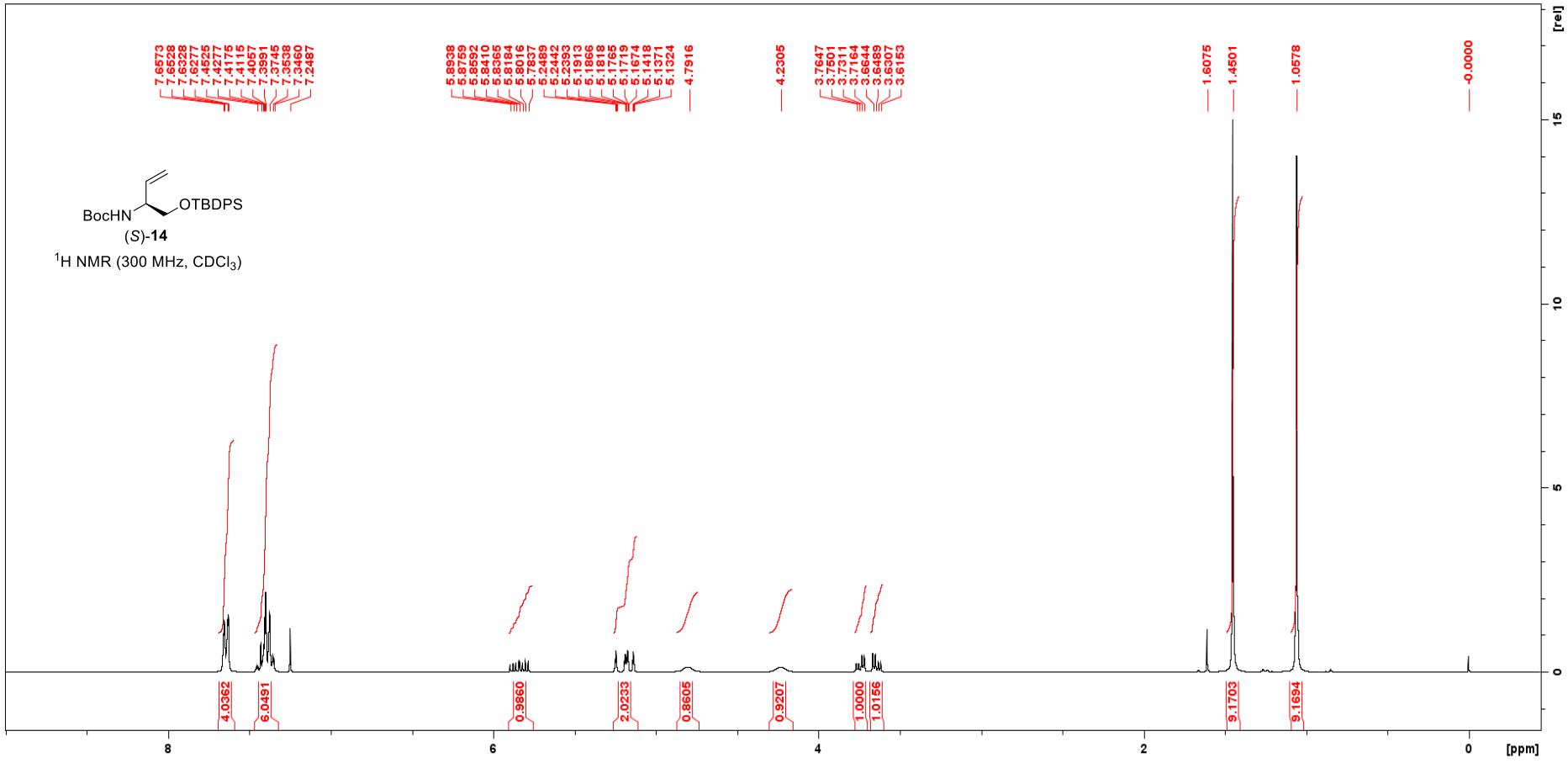
Appendix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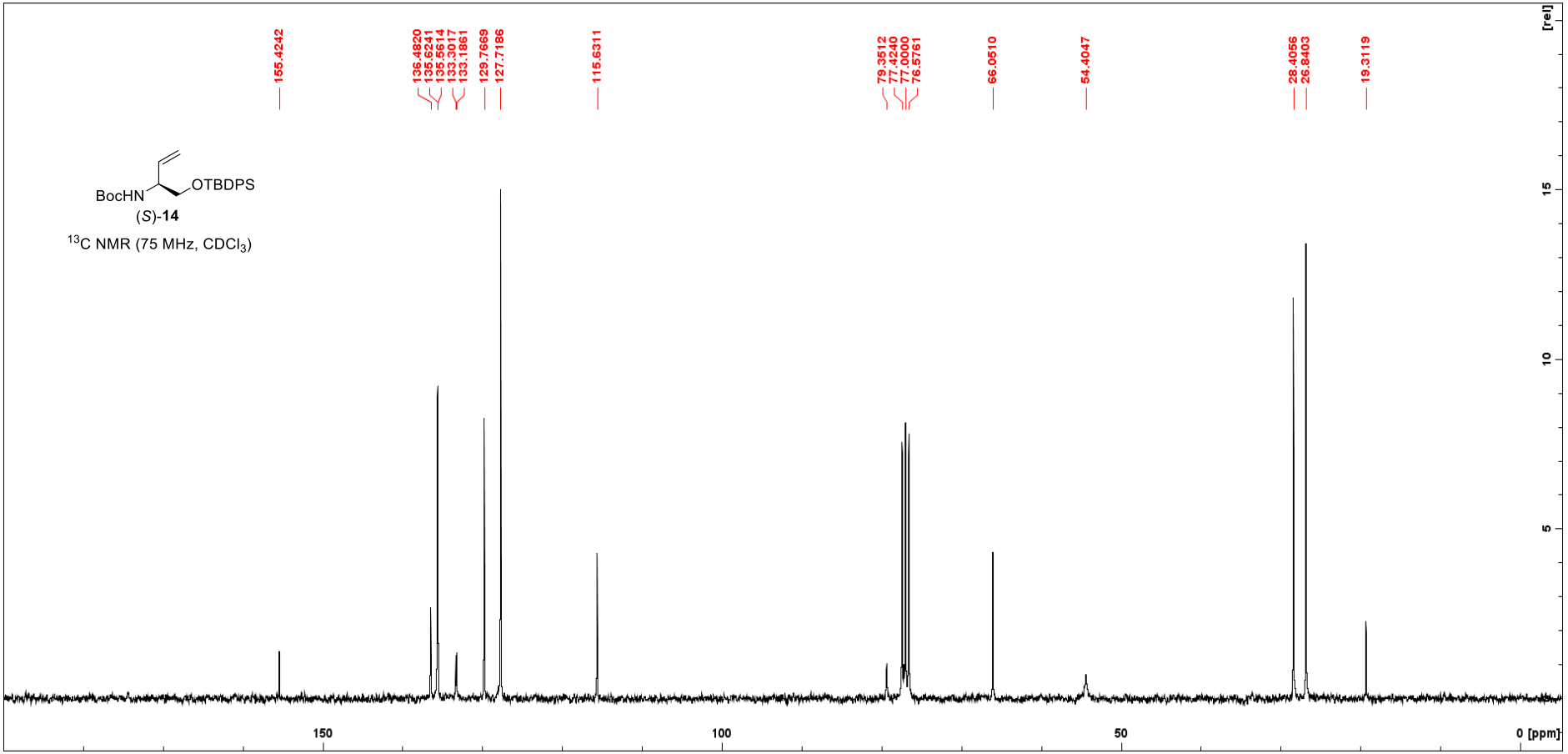
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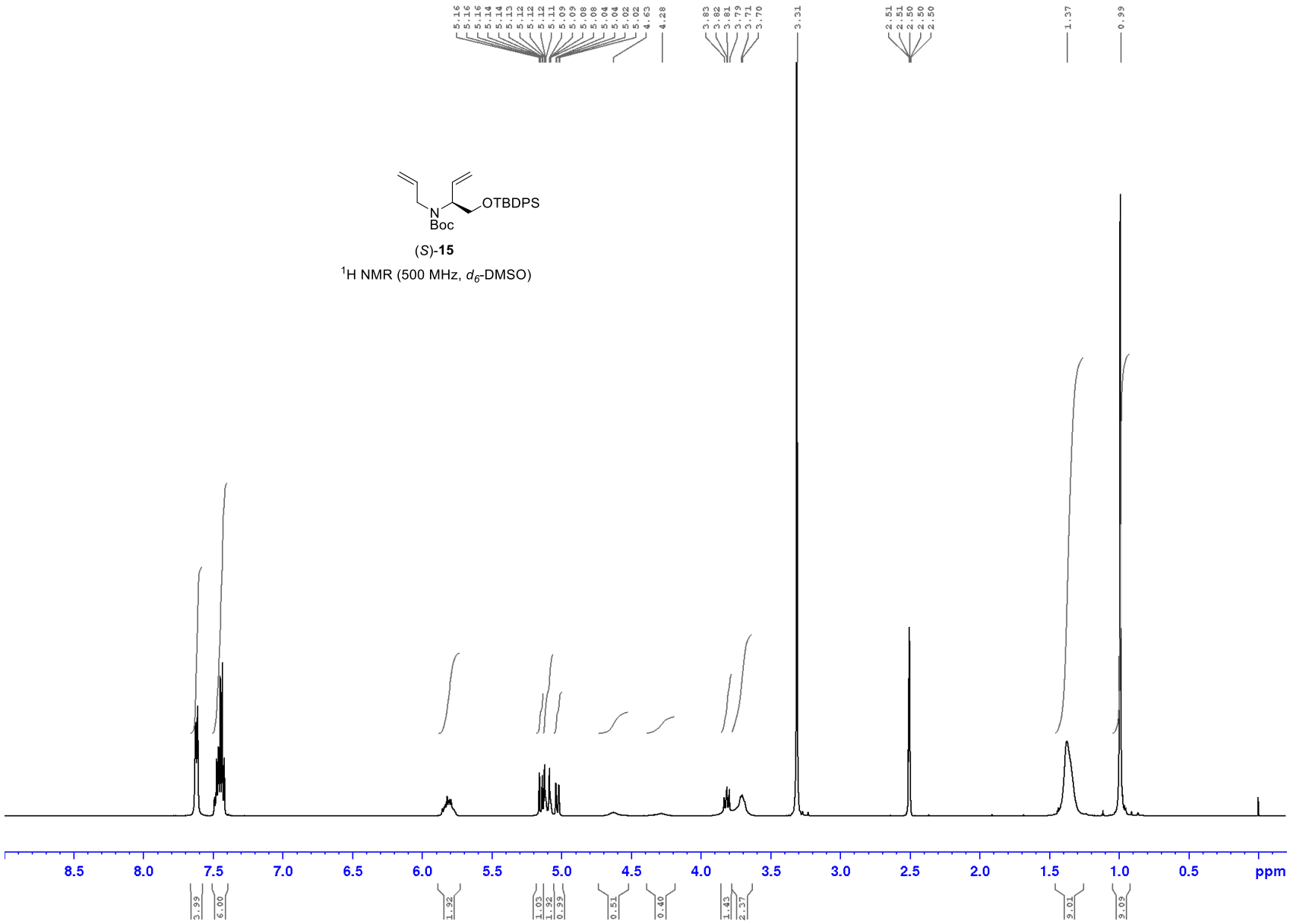

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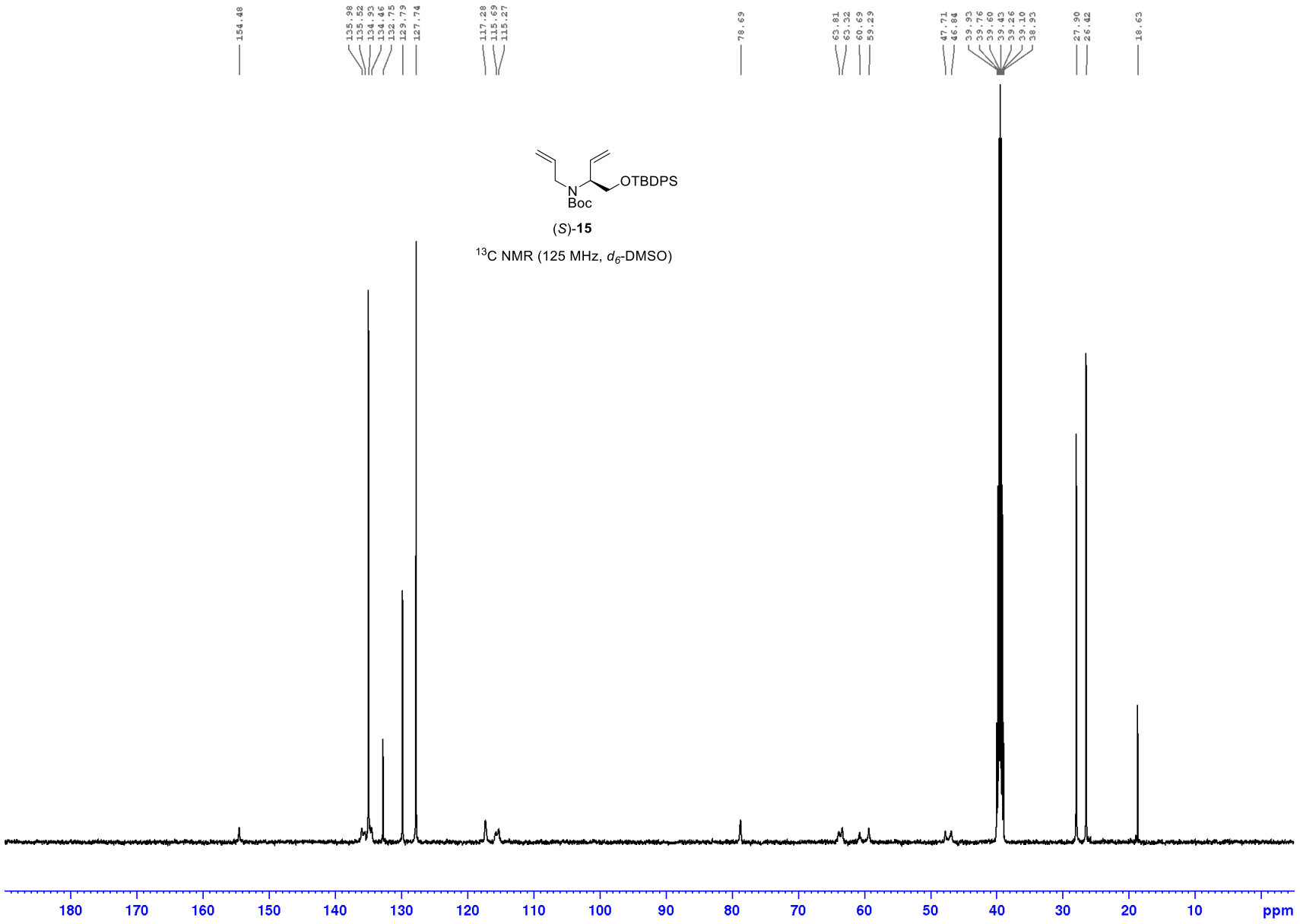

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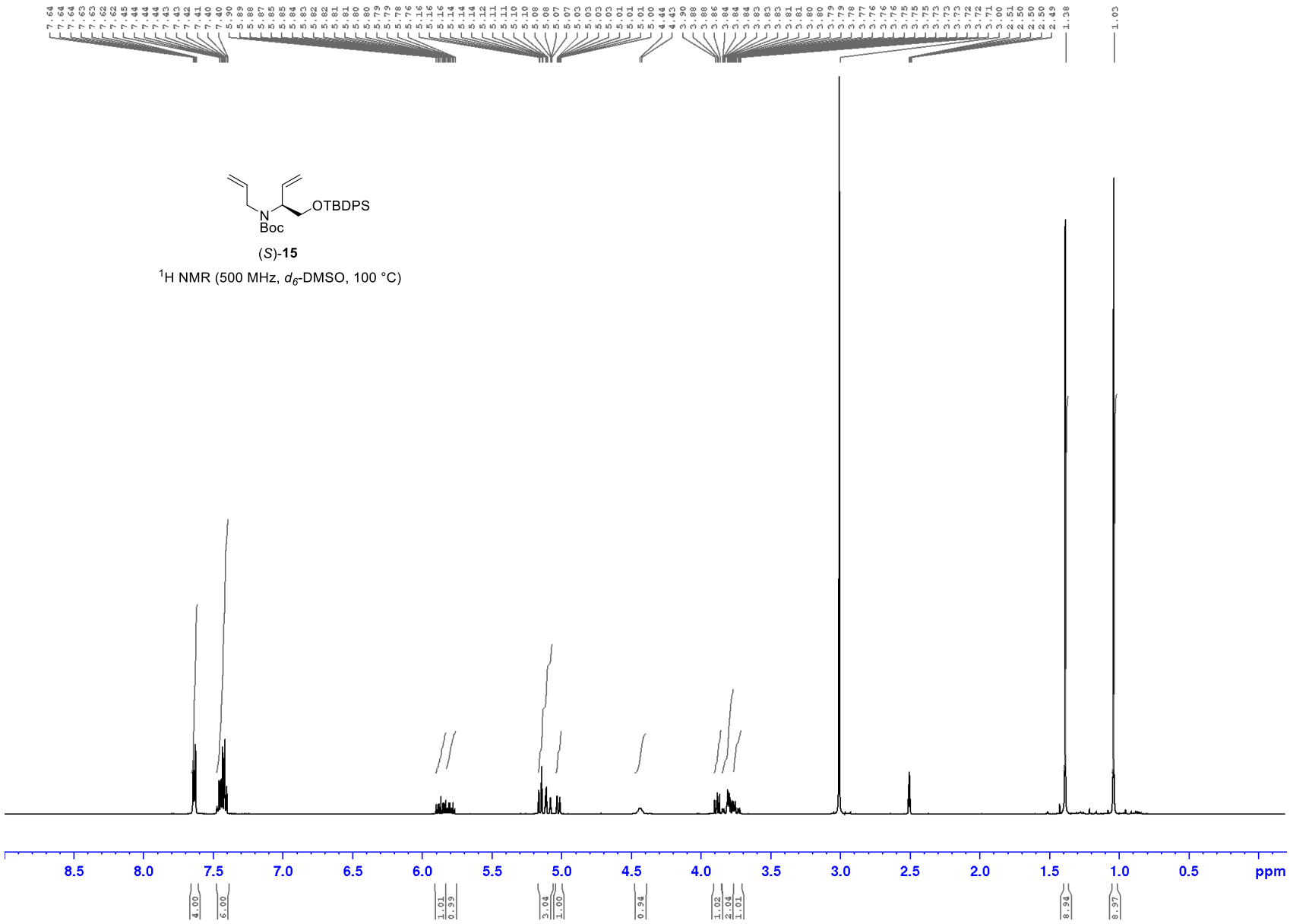
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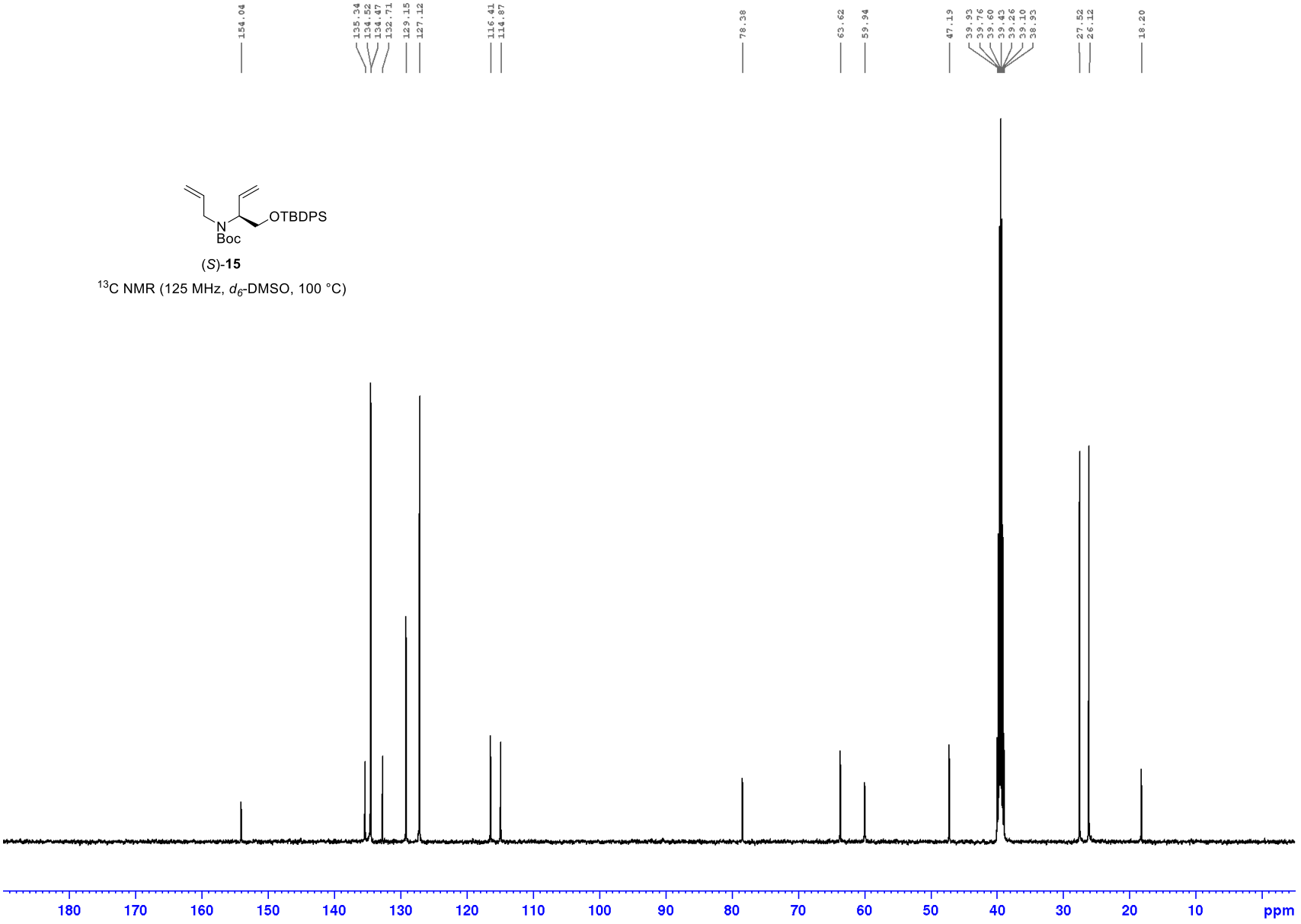

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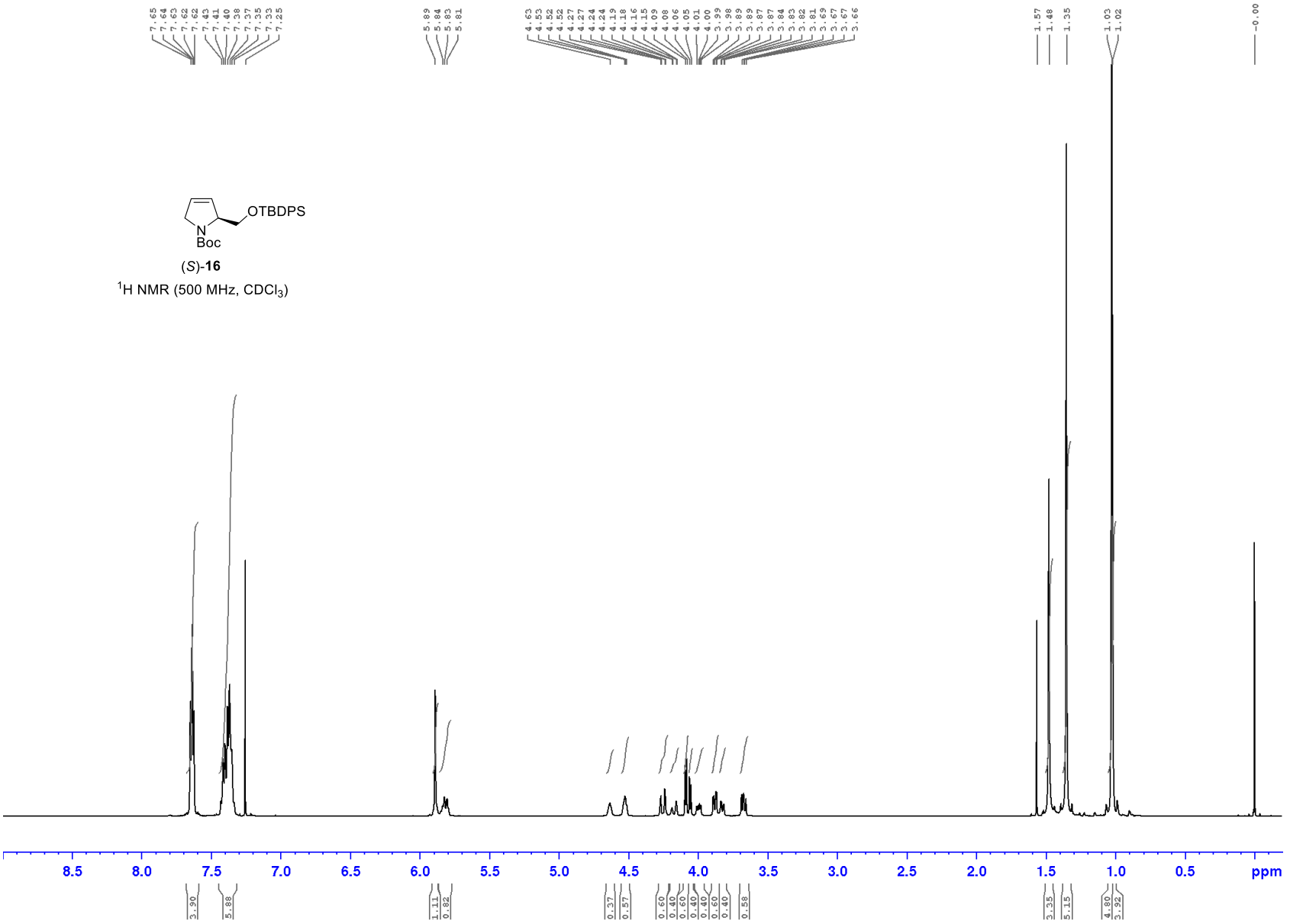

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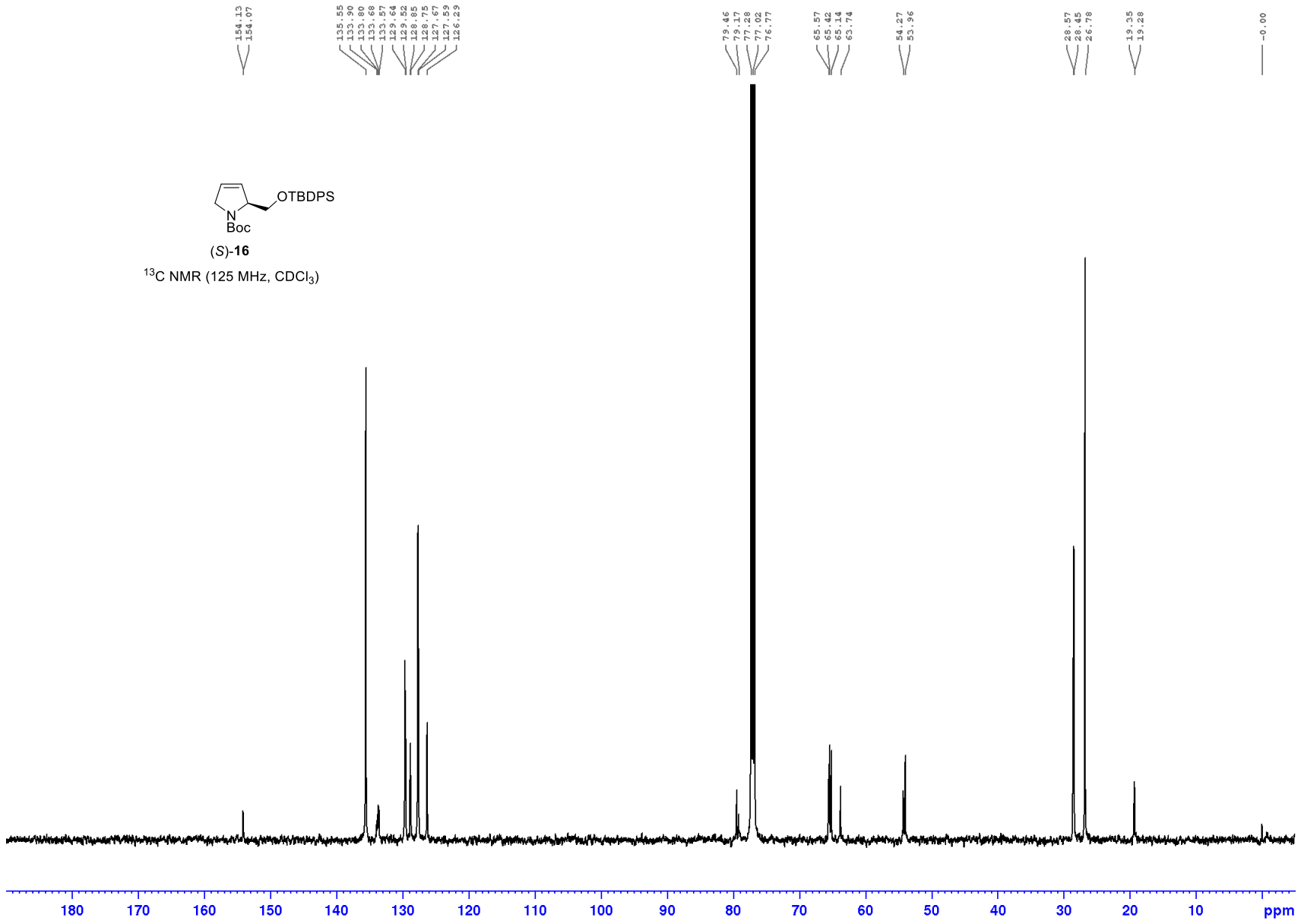

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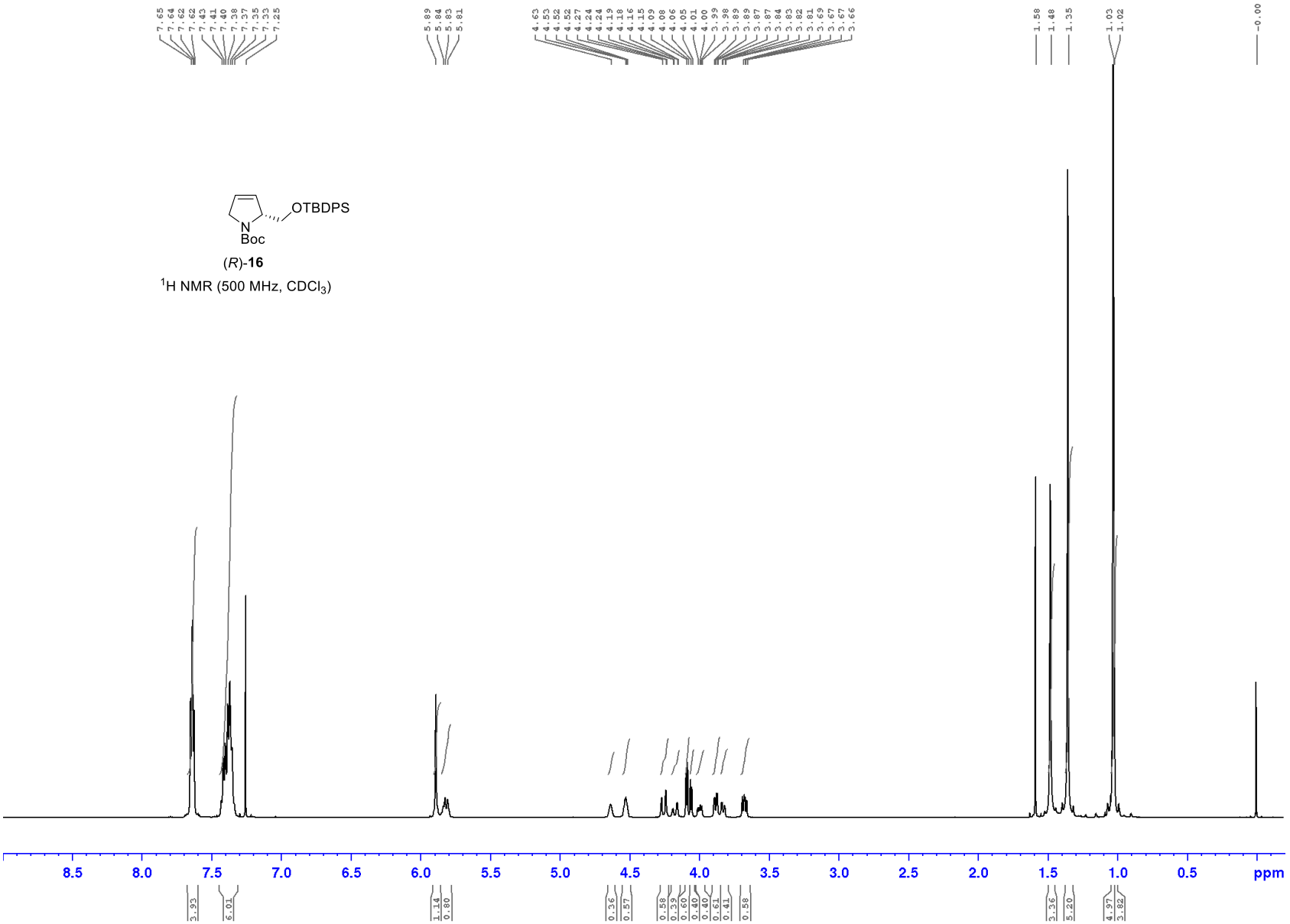
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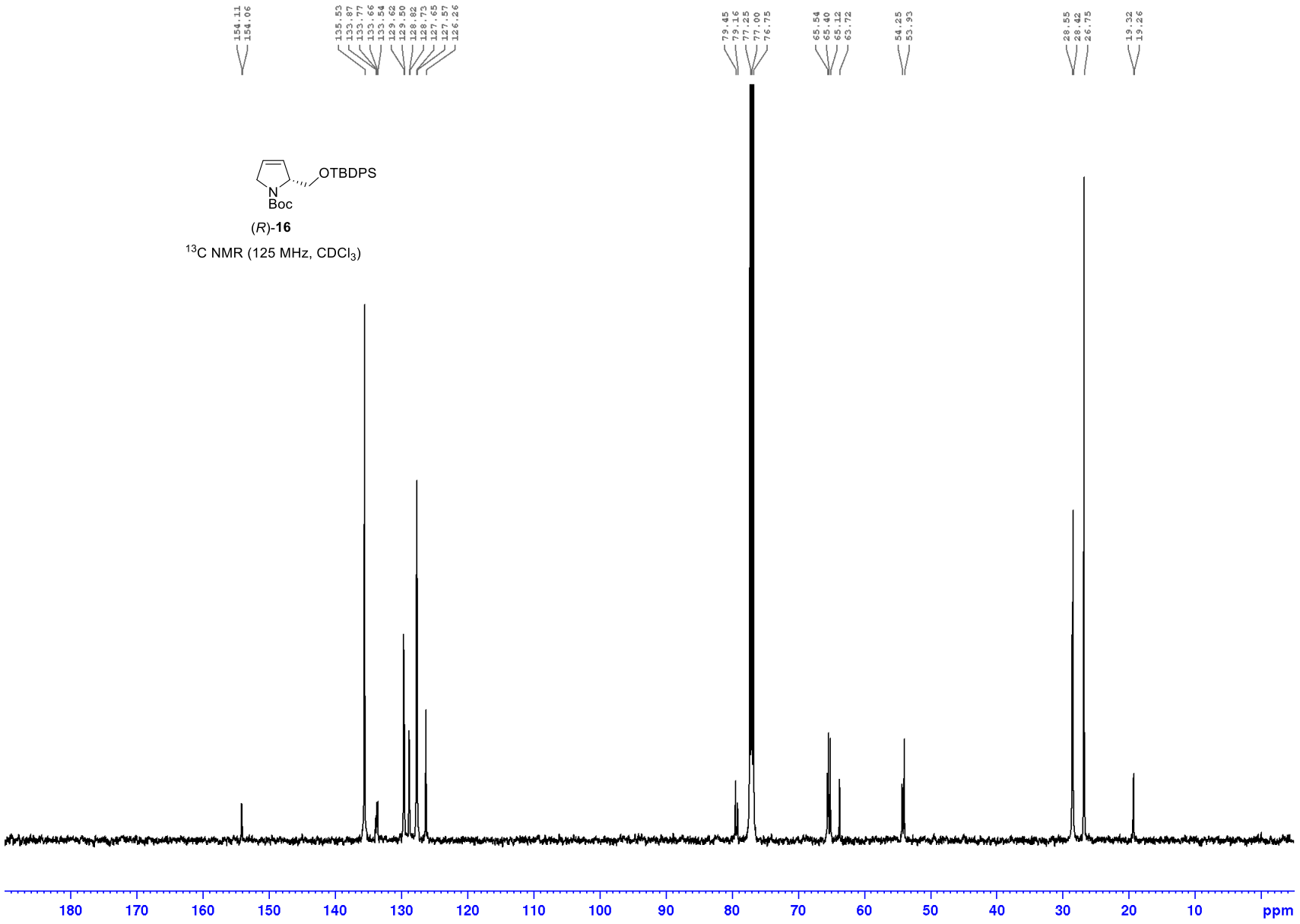
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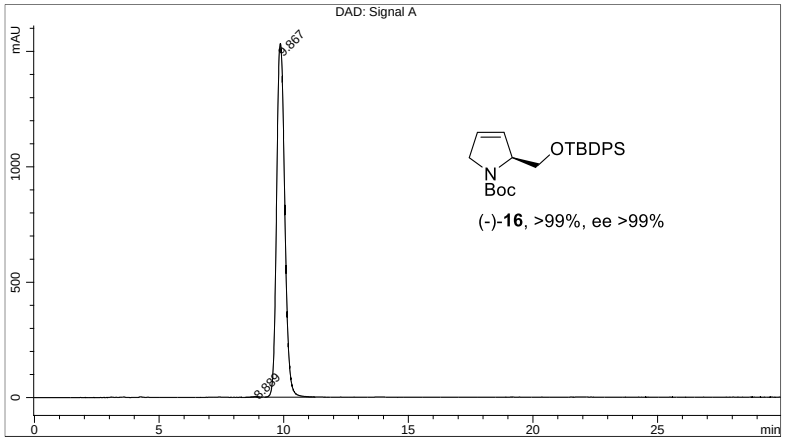
53.93
28.55
28.42
26.75
19.32
19.26
OTBDPS
N
Boc
(R)-16
13C NMR (125 MHz, CDCl3)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

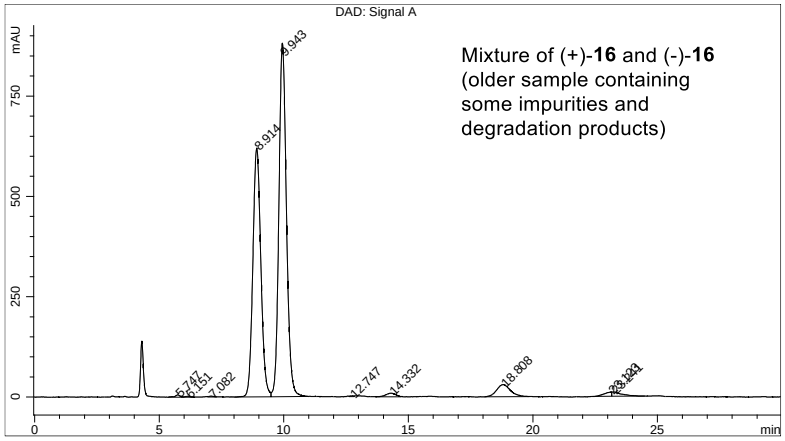
Method conditions:

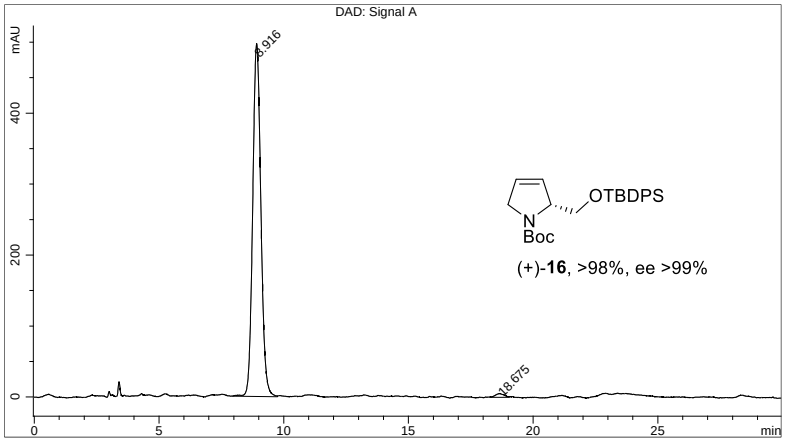
Column: Regis, Pirkle Covalent, (*S*,*S*) Whelk-01, 10/100 Kromasil FEC 250x4.6 mm
Guard: Phenomenex Security Guard CN 4x3 mm
Mobile Phase: 98:2 v/v *n*-Hexane/Ethanol
Flow Rate: 1 mL/min, Detection: UV 210 nm, Column Temp: 20 °C, Injection volume: 10 μL
Sample Solvent: Mobile Phase

I.

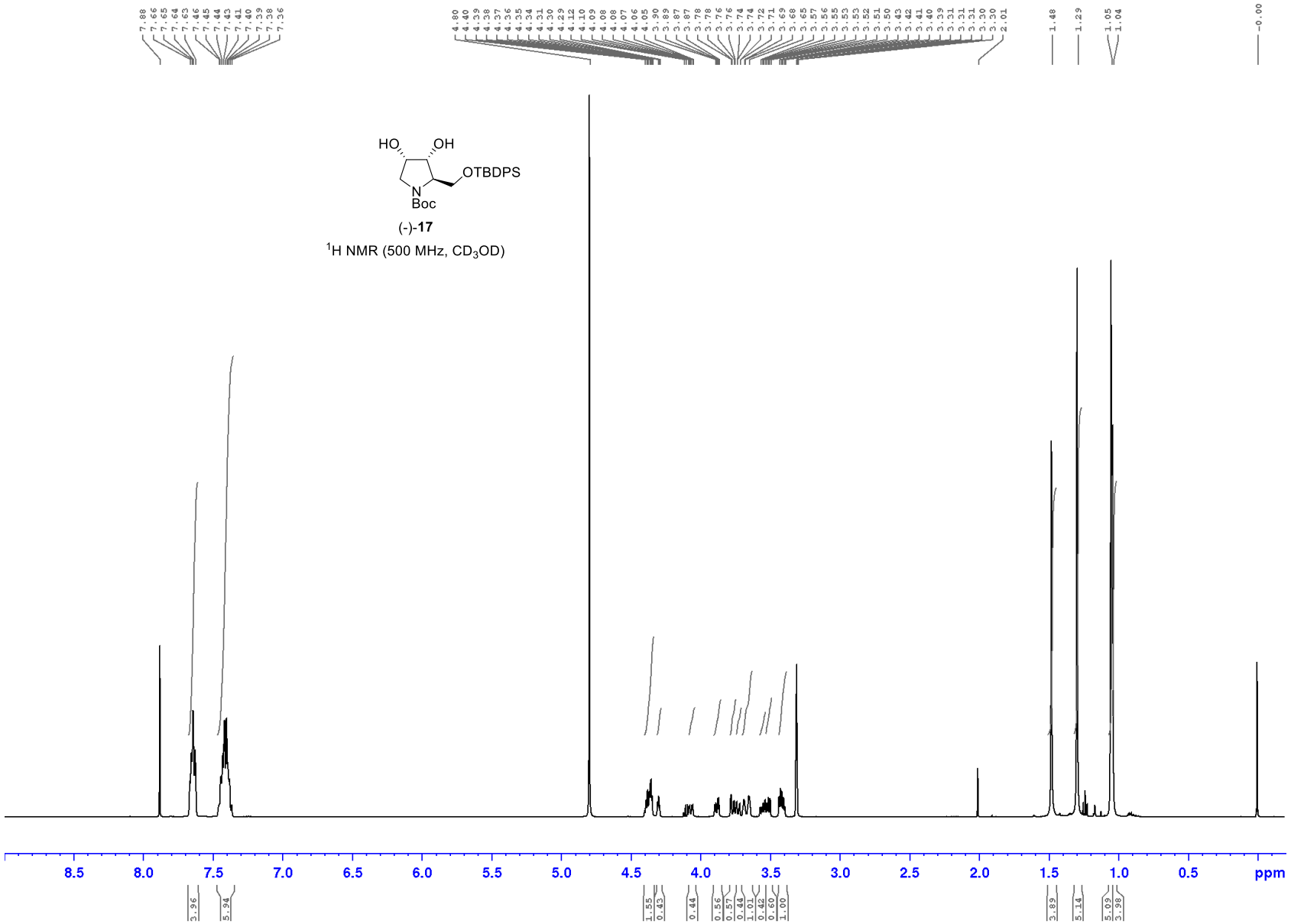


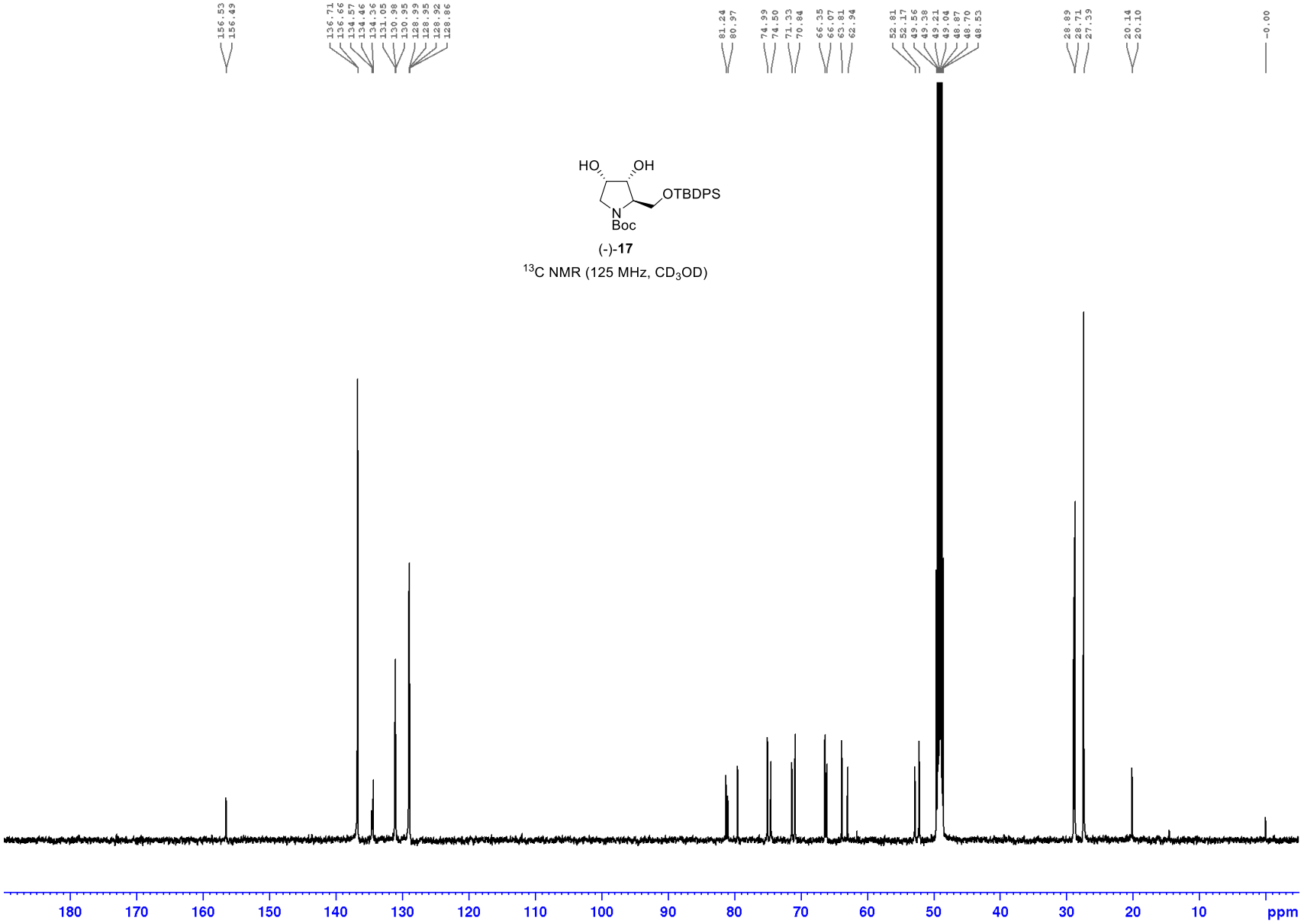
Peak#	RT	Peak Height	Peak Area	Width	Area %
1	8.89 min	2.5712	48.8511	0.2337 min	0.140 %
2	9.87 min	1532.4205	34947.6174	0.3581 min	99.860 %

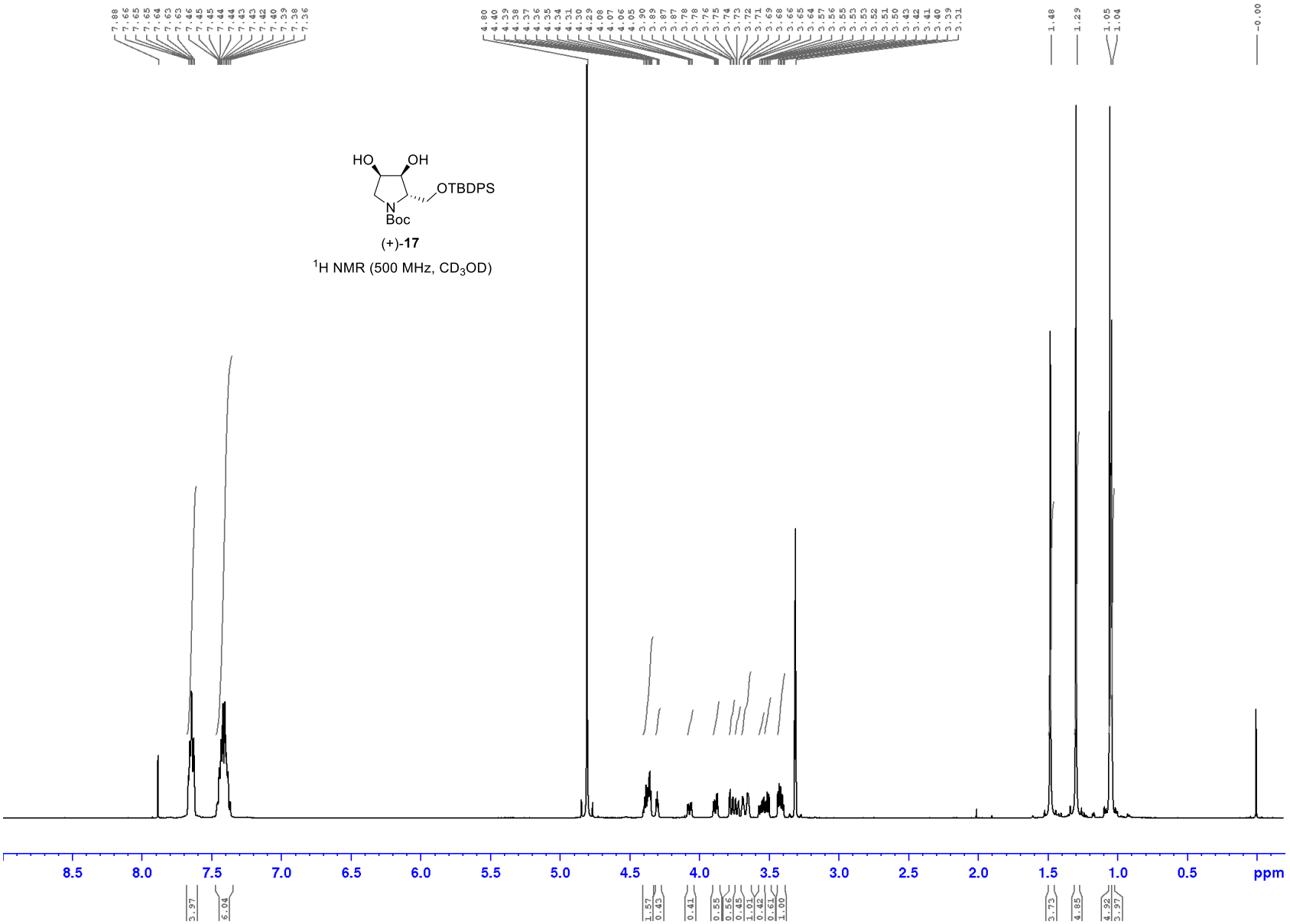


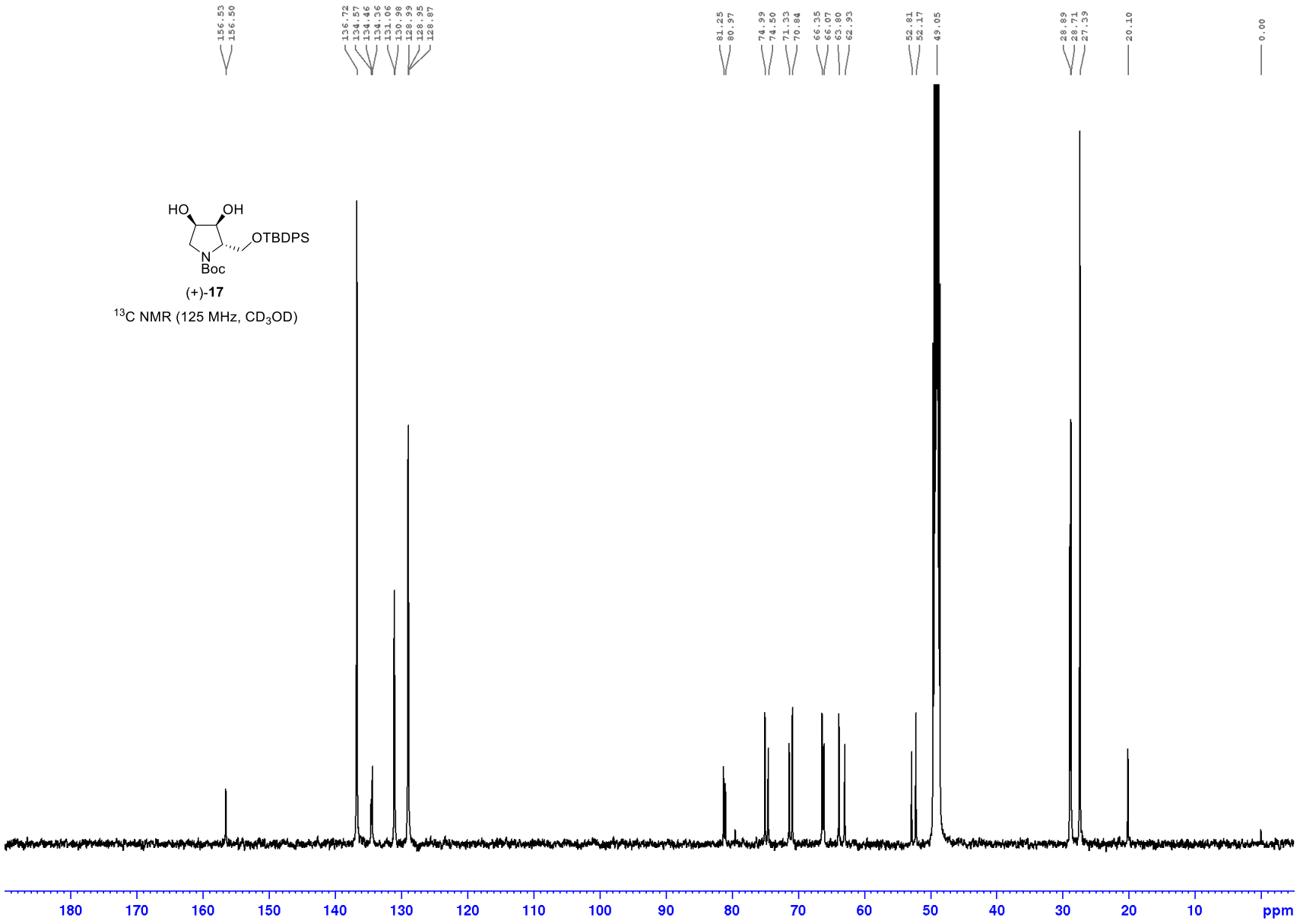


Peak#	RT	Peak Height	Peak Area	Width	Area %
1	8.92 min	497.3479	11352.2258	0.3583 min	98.889 %
2	18.68 min	5.3054	127.5650	0.2925 min	1.111 %


HO
OH
OTBDPS
N
Boc
(-)-17
1H NMR (500 MHz, CD3OD)
7.88 7.66 7.65 7.64 7.63 7.46 7.45 7.44 7.43 7.41 7.40 7.39 7.38 7.36
4.80 4.40 4.39 4.38 4.37 4.36 4.35 4.34 4.31 4.30 4.29 4.12 4.10 4.09 4.08 4.08 4.07 4.06 4.05 3.90 3.89 3.87 3.87 3.78 3.78 3.76 3.76 3.74 3.74 3.72 3.71 3.69 3.68 3.65 3.57 3.56 3.55 3.53 3.53 3.52 3.51 3.50 3.43 3.42 3.41 3.40 3.39 3.31 3.31 3.31 3.30 3.30 2.01
1.48 1.29 1.05 1.04
-0.00
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
3.96 5.94 1.55 0.43 0.44 0.56 0.57 0.44 1.01 0.42 0.60 1.00 3.89 5.14 5.09 3.98

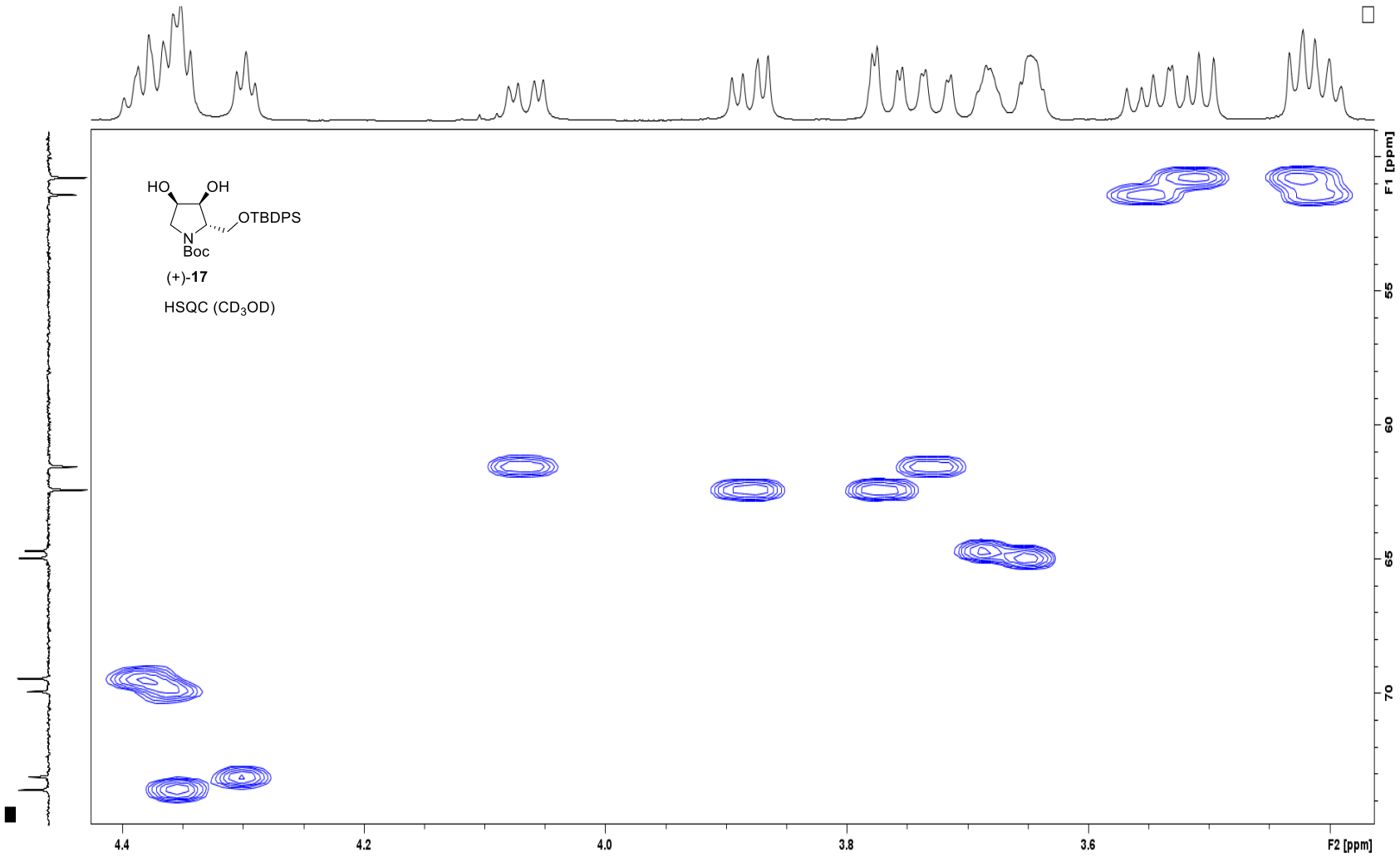

156.53
156.49
136.71
136.66
134.57
134.46
134.36
131.05
130.98
130.95
128.99
128.95
128.92
128.86
81.24
80.97
74.99
74.50
71.33
70.84
66.35
66.07
63.81
62.94
52.81
52.17
49.56
49.38
49.21
49.04
48.87
48.70
48.53
28.89
28.71
27.39
20.14
20.10
-0.00
HO
OH
OTBDPS
N
Boc
(-)-17
13C NMR (125 MHz, CD3OD)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

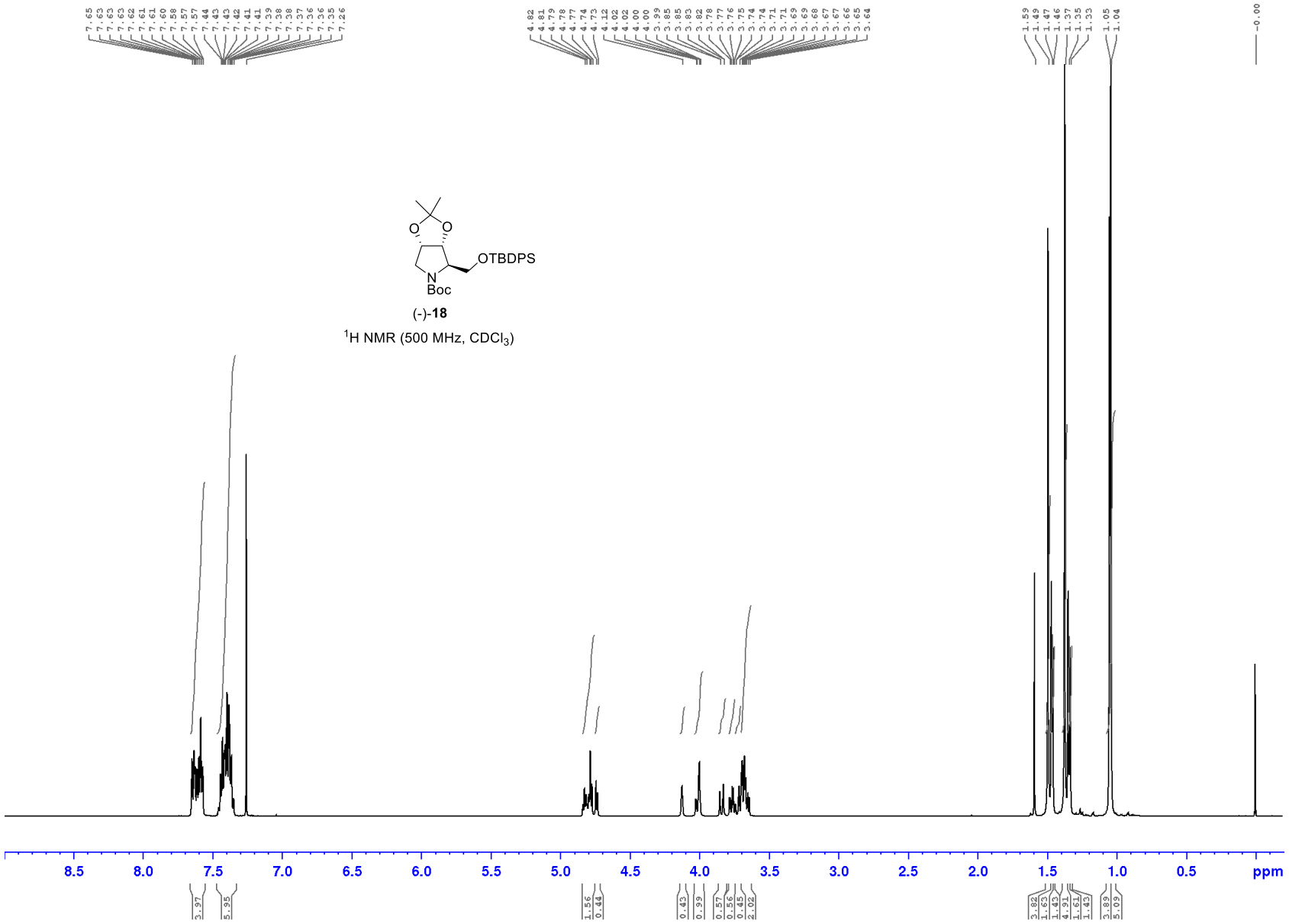

HO
OH
OTBDPS
N
Boc
(+)-17
1H NMR (500 MHz, CD3OD)
7.88 7.66 7.65 7.65 7.64 7.63 7.63 7.46 7.45 7.45 7.44 7.44 7.43 7.43 7.42 7.40 7.39 7.38 7.36
4.80 4.40 4.39 4.38 4.37 4.36 4.35 4.34 4.31 4.30 4.29 4.08 4.07 4.06 4.05 3.90 3.89 3.87 3.87 3.78 3.78 3.76 3.75 3.74 3.73 3.72 3.71 3.69 3.68 3.66 3.65 3.64 3.57 3.56 3.55 3.53 3.53 3.52 3.51 3.50 3.43 3.42 3.41 3.40 3.39 3.31
1.48 1.29 1.05 1.04
-0.00
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
3.97 6.04 1.57 0.43 0.41 0.55 0.56 0.45 1.01 0.42 0.61 1.00 3.73 4.85 4.92 3.97



(+)-**17**

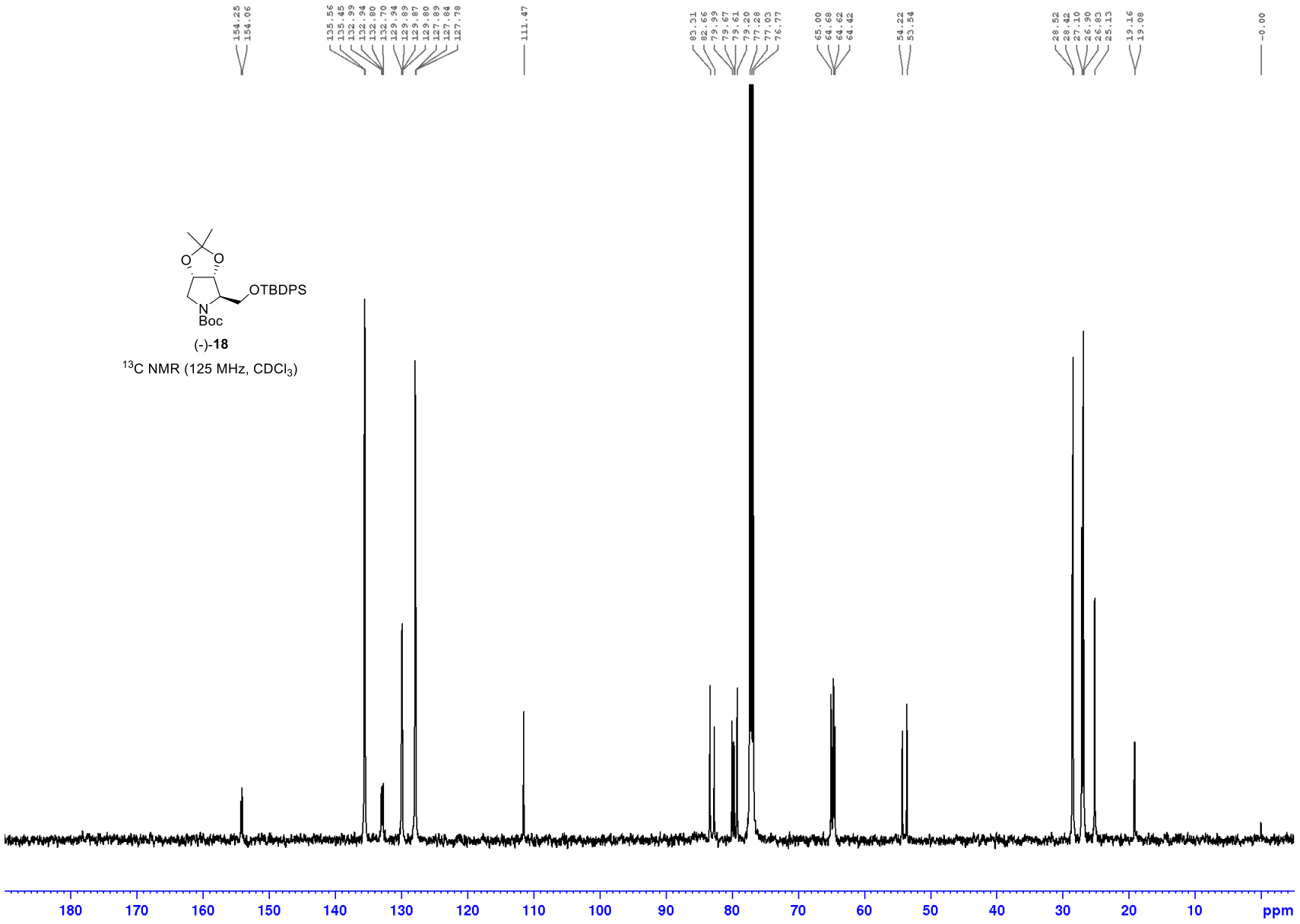
^{13}C NMR (125 MHz, CD_3OD)

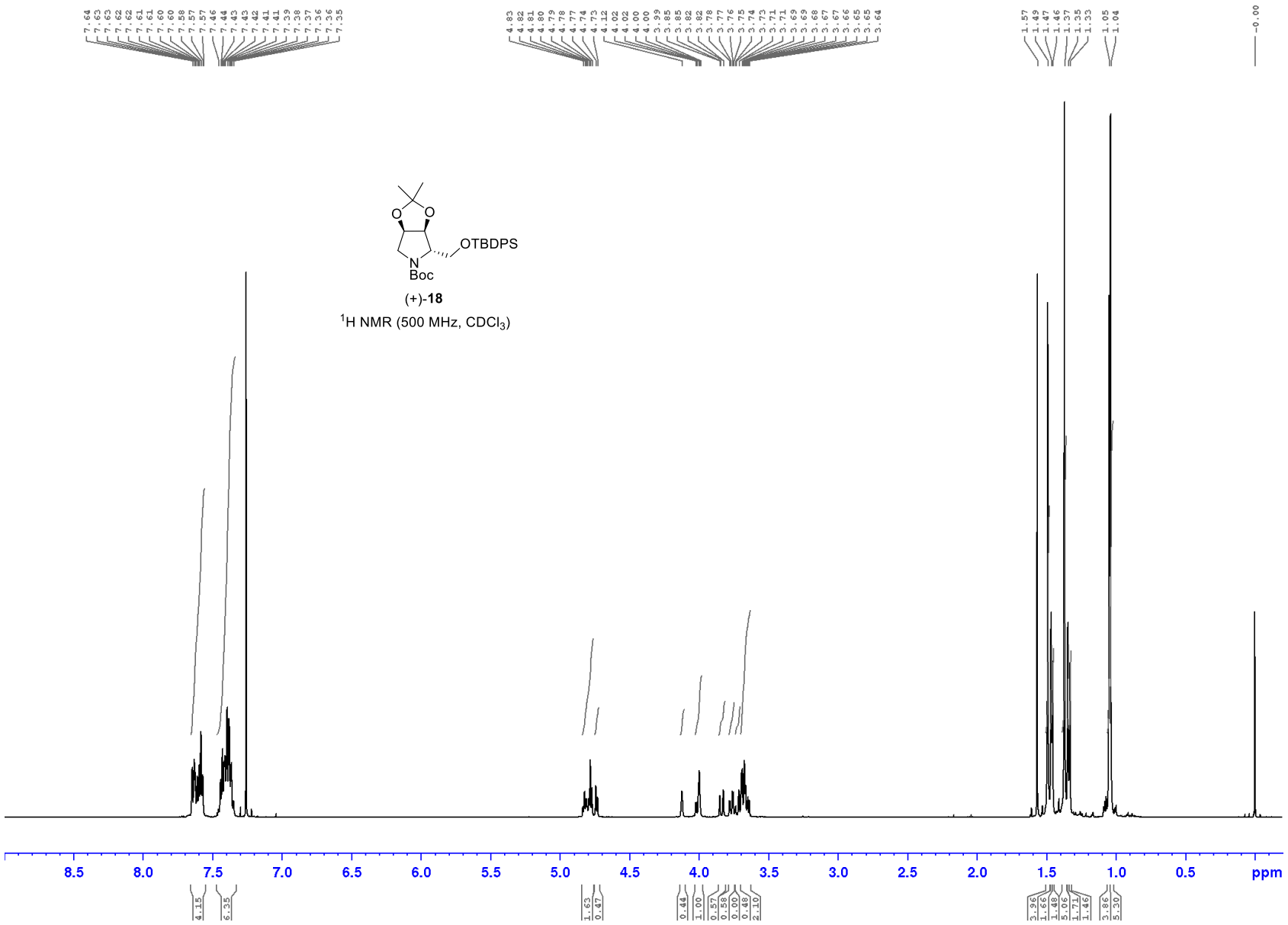

HO
OH
OTBDPS
N
Boc
(+)-17
HSQC (CD3OD)
F1 [ppm]
55
60
65
70
4.4
4.2
4.0
3.8
3.6
F2 [ppm]

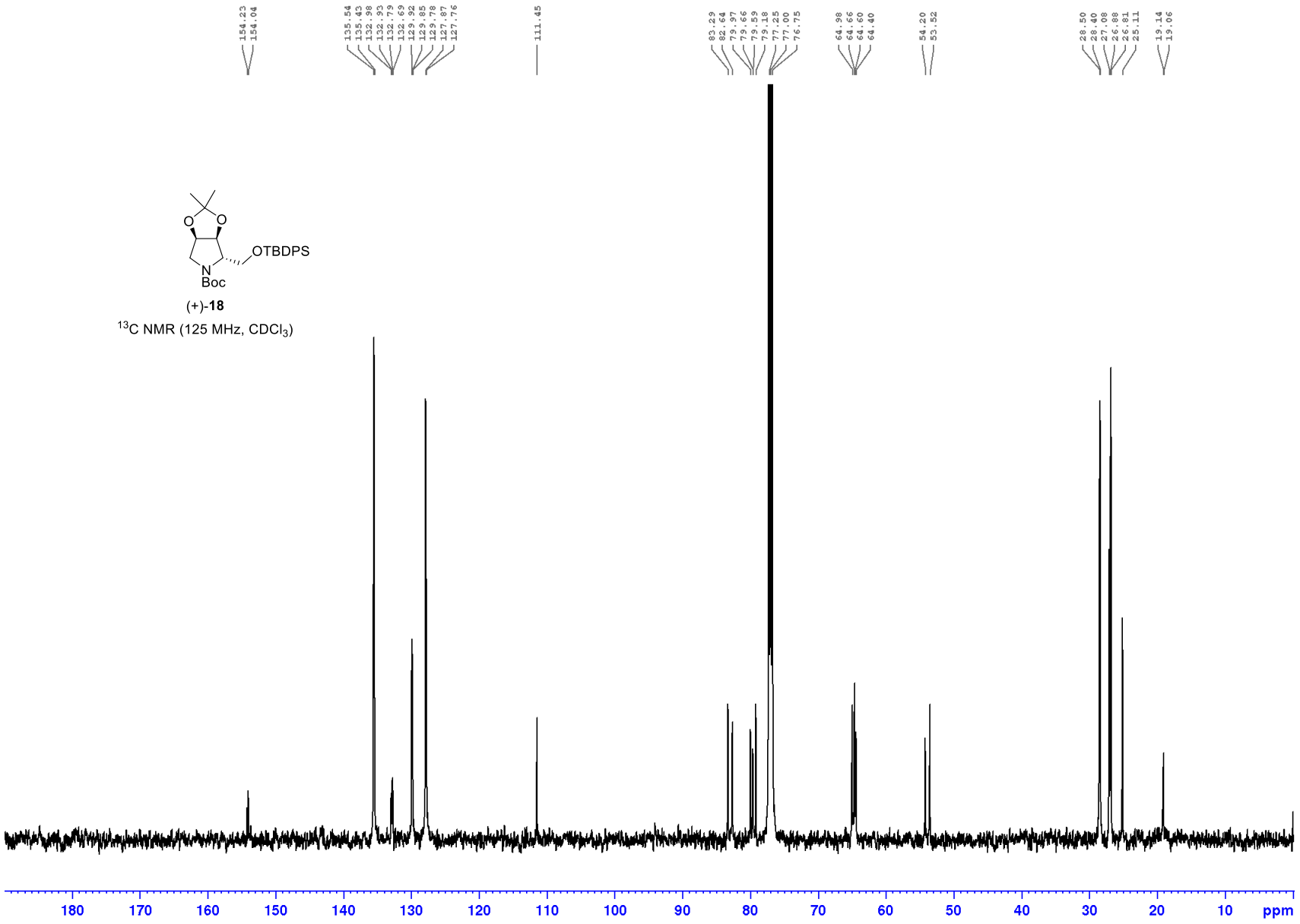


(-)-**18**

^{1}H NMR (500 MHz, $CDCl_3$)

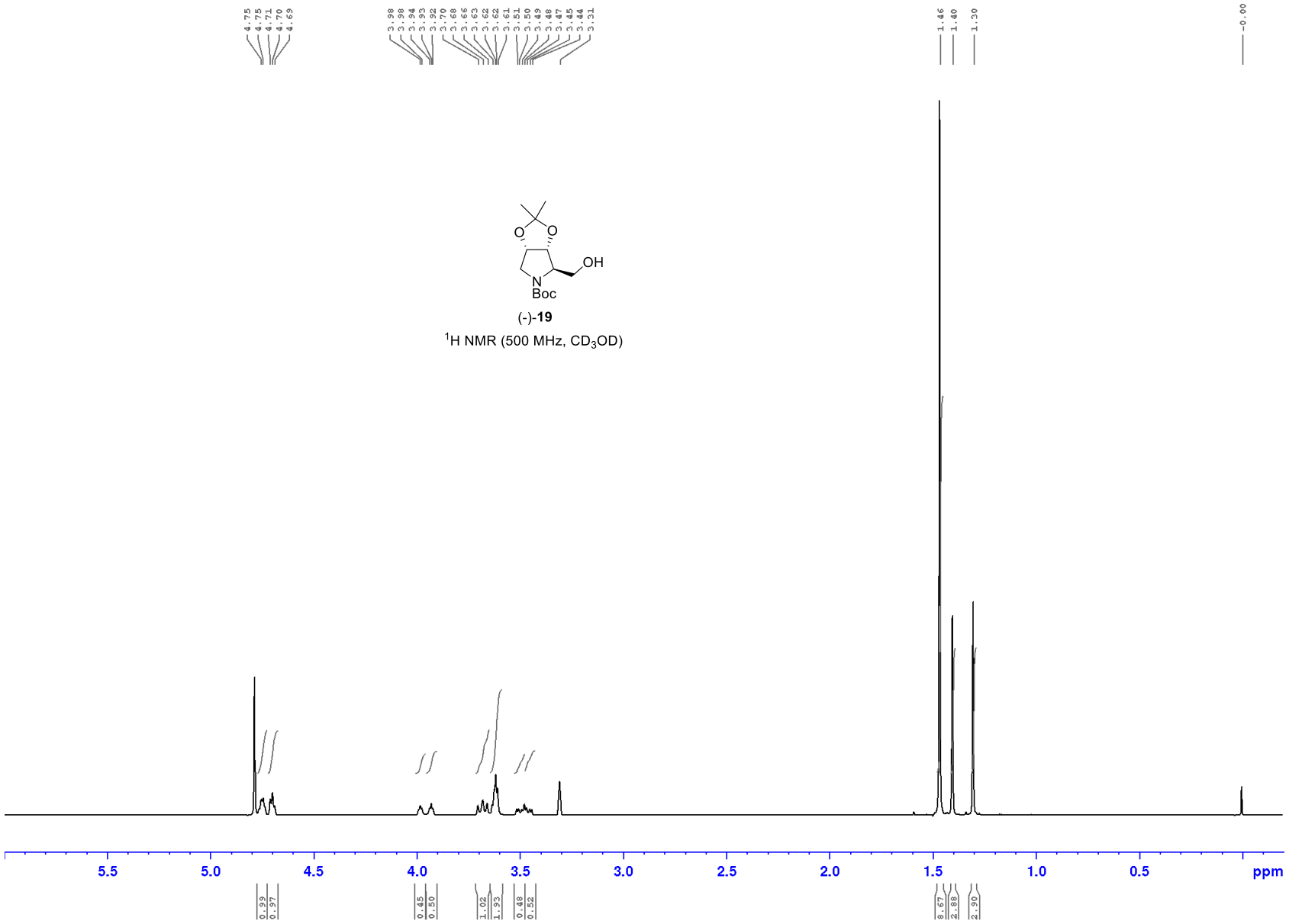

154.25
154.06
135.56
135.45
132.99
132.94
132.80
132.70
129.94
129.89
129.87
129.80
127.89
127.84
127.78
111.47
83.31
82.66
79.99
79.67
79.61
79.20
77.28
77.03
76.77
65.00
64.68
64.62
64.42
54.22
53.54
28.52
28.42
27.10
26.90
26.83
25.13
19.16
19.08
-0.00
O
O
OTBDPS
N
Boc
(-)-18
13C NMR (125 MHz, CDCl3)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


7.64 7.63 7.63 7.62 7.62 7.61 7.61 7.60 7.60 7.58 7.57 7.57 7.46 7.44 7.43 7.43 7.42 7.41 7.41 7.39 7.38 7.37 7.36 7.36 7.35
4.83 4.82 4.81 4.80 4.79 4.78 4.77 4.74 4.73 4.12 4.02 4.02 4.00 4.00 3.99 3.85 3.85 3.82 3.78 3.77 3.76 3.75 3.74 3.73 3.71 3.71 3.69 3.69 3.68 3.67 3.67 3.66 3.65 3.65 3.64
1.57 1.49 1.47 1.46 1.37 1.35 1.33 1.05 1.04
0.00
OTBDPS
N
Boc
(+)-18
1H NMR (500 MHz, CDCl3)
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
4.15 6.35 1.63 0.47 0.44 1.00 0.57 0.58 0.00 0.48 2.10 3.96 1.66 1.48 5.06 1.71 1.46 3.86 5.30



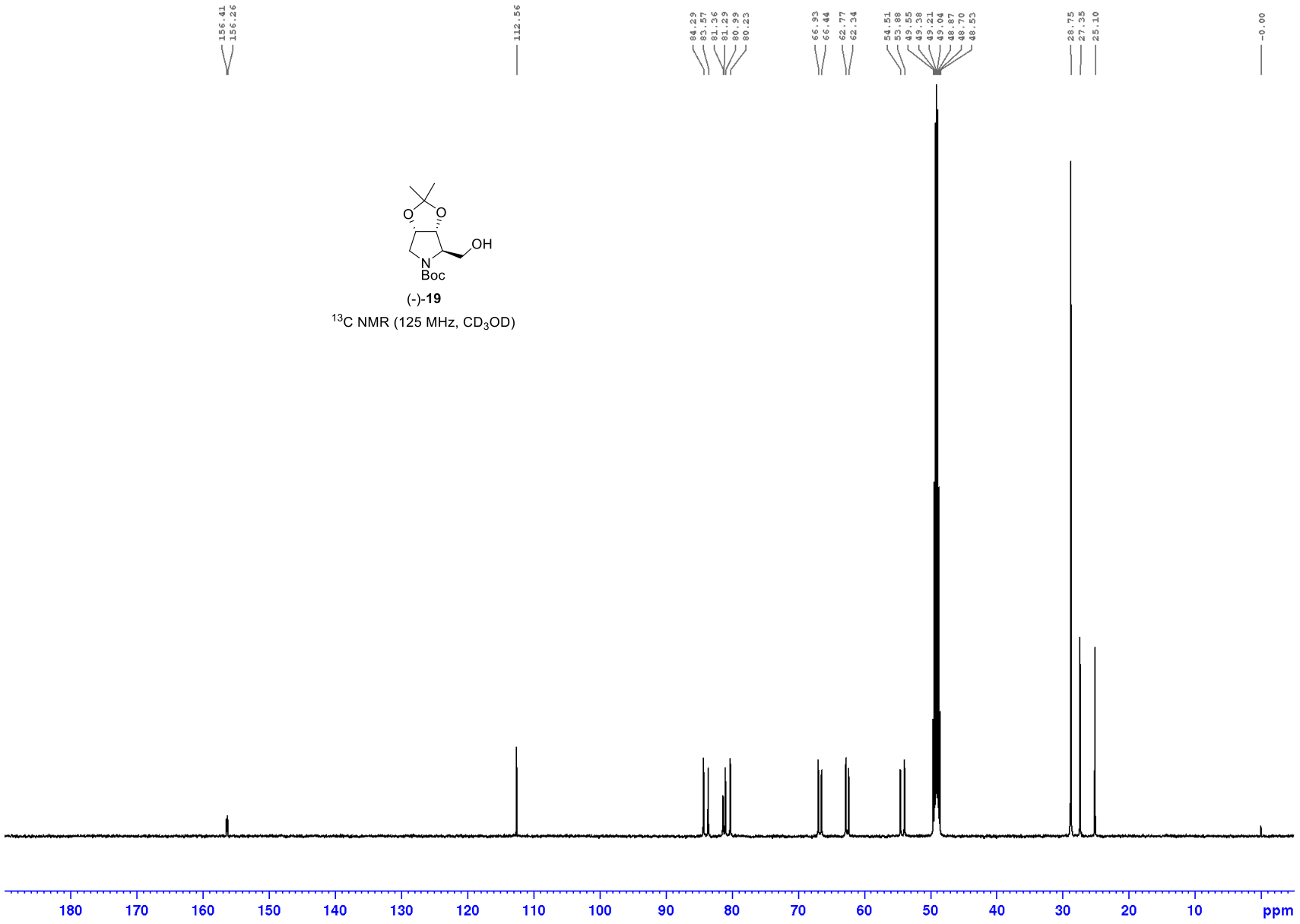
(+)-**18**

^{13}C NMR (125 MHz, $CDCl_3$)



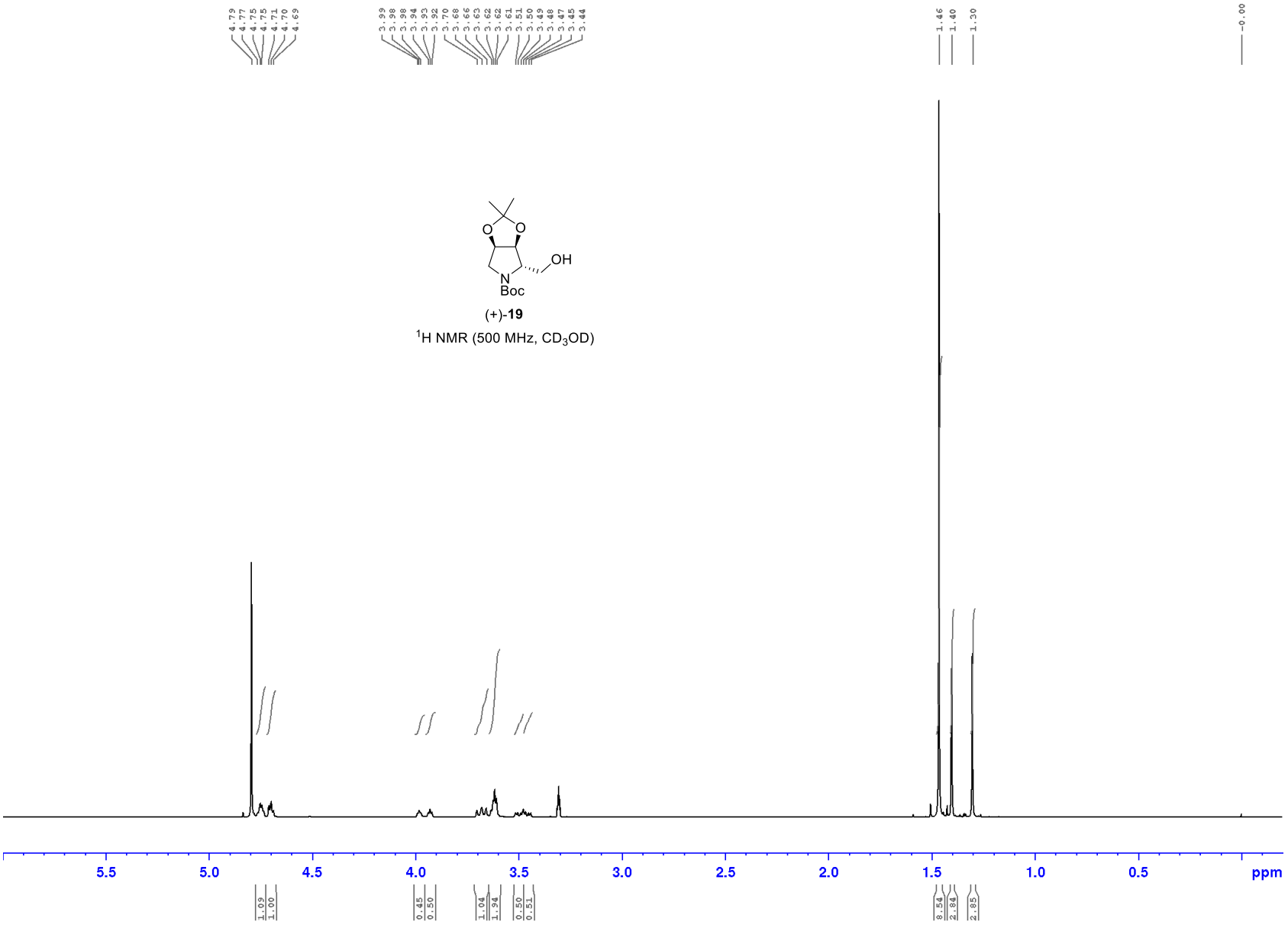
(-)-**19**

^{1}H NMR (500 MHz, CD_3OD)



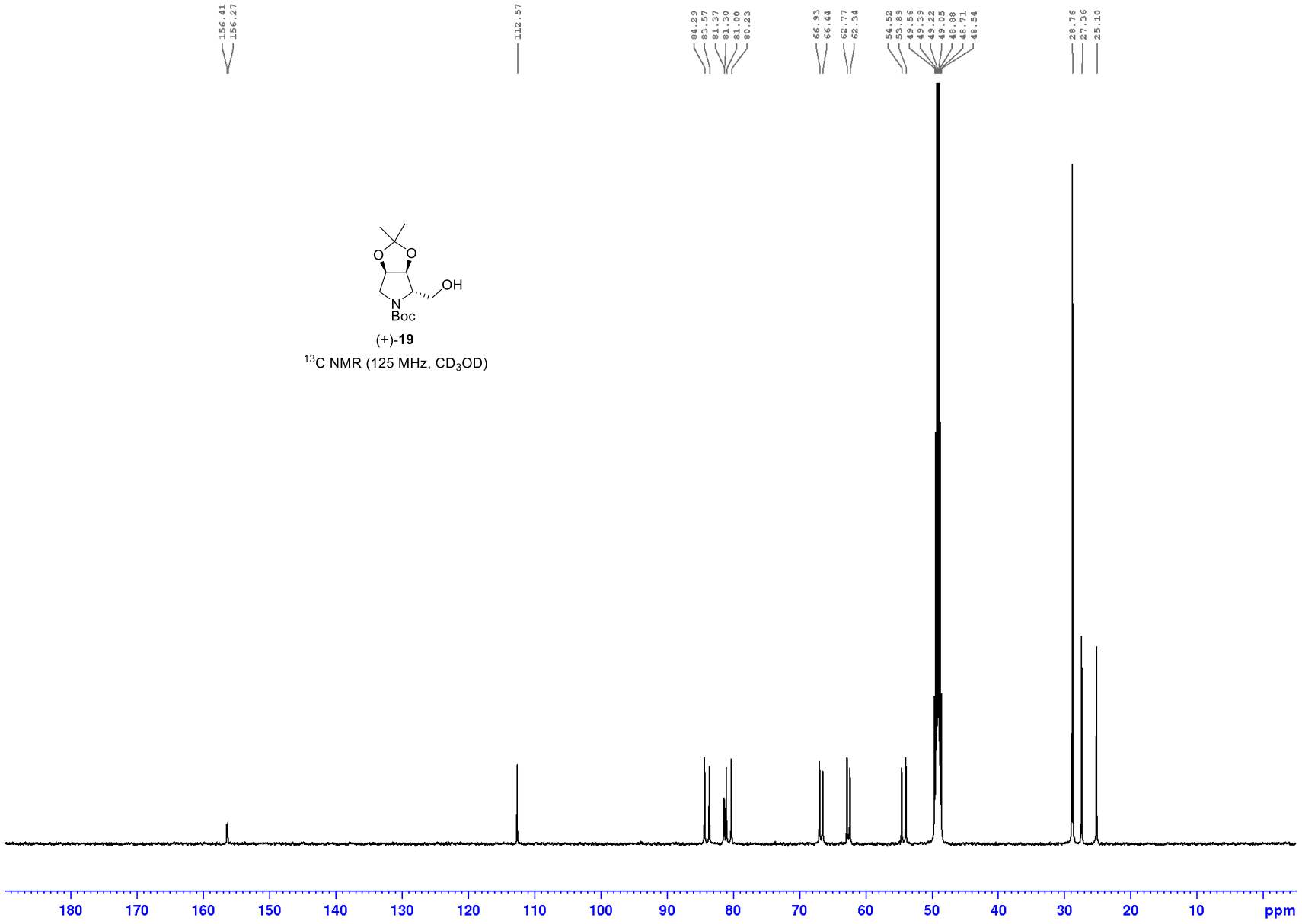
(-)-**19**

^{13}C NMR (125 MHz, CD_3OD)



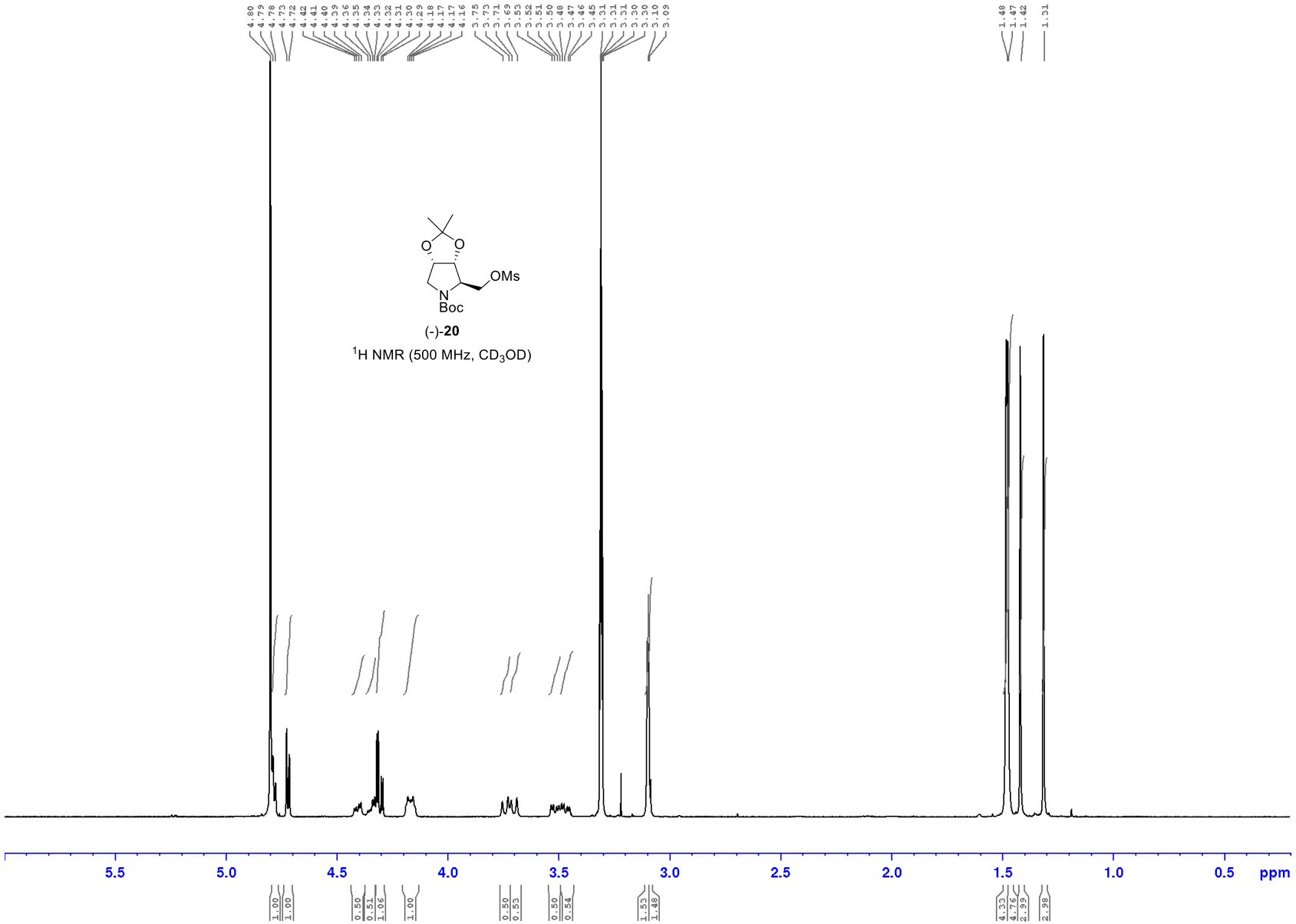
(+)-**19**

^{1}H NMR (500 MHz, CD_3OD)



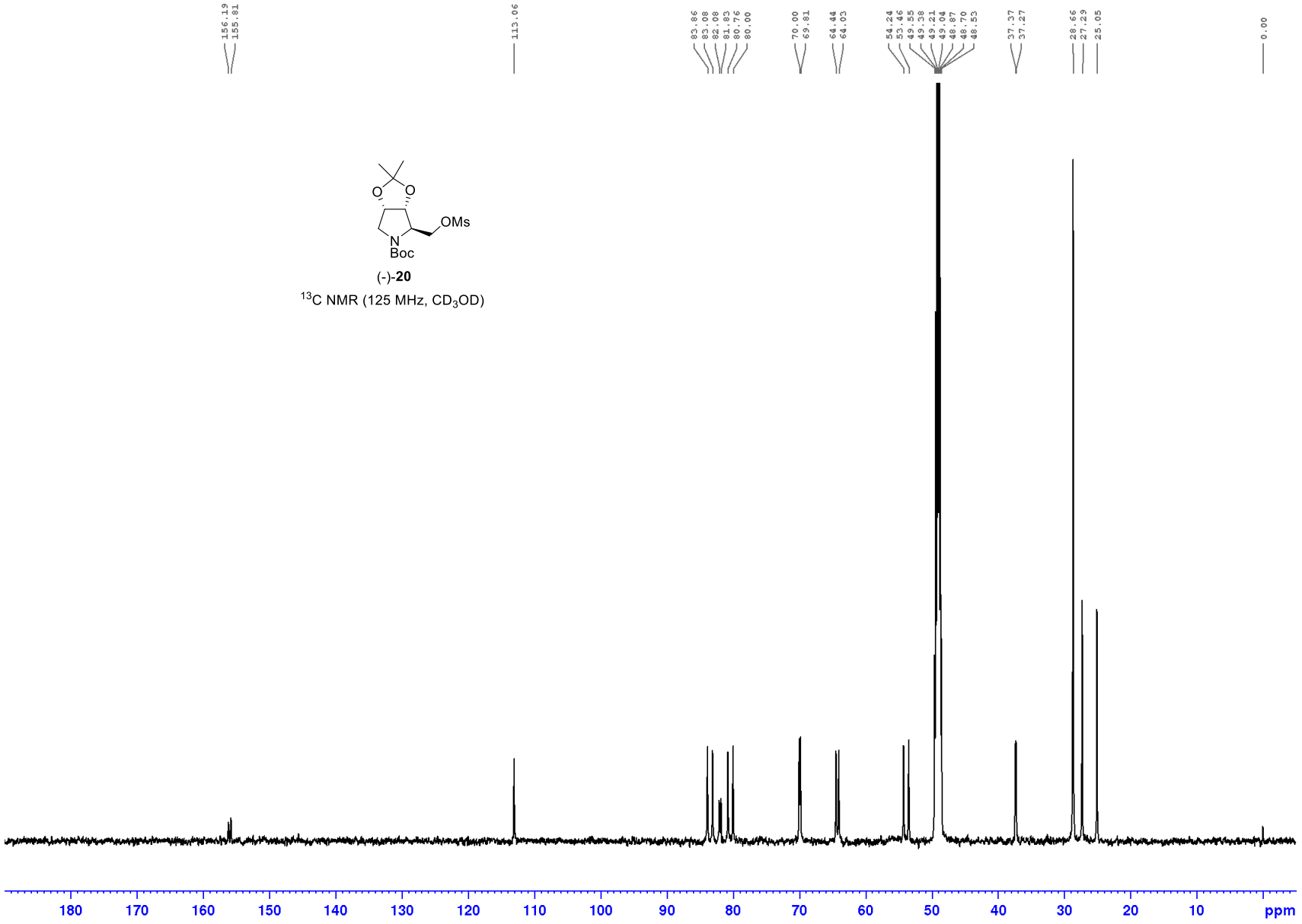
(+)-**19**

^{13}C NMR (125 MHz, CD_3OD)



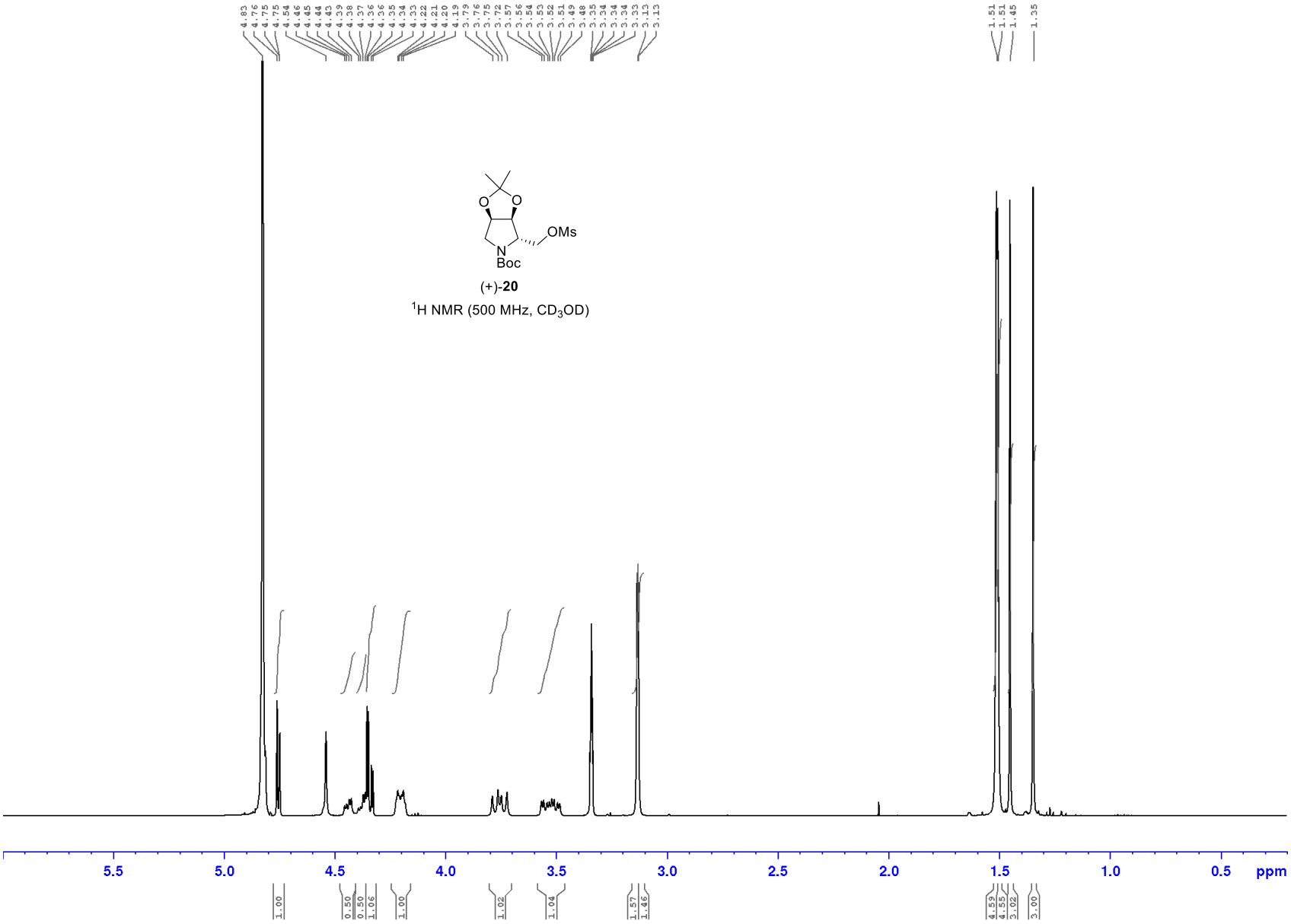
(-)-**20**

^{1}H NMR (500 MHz, CD_3OD)



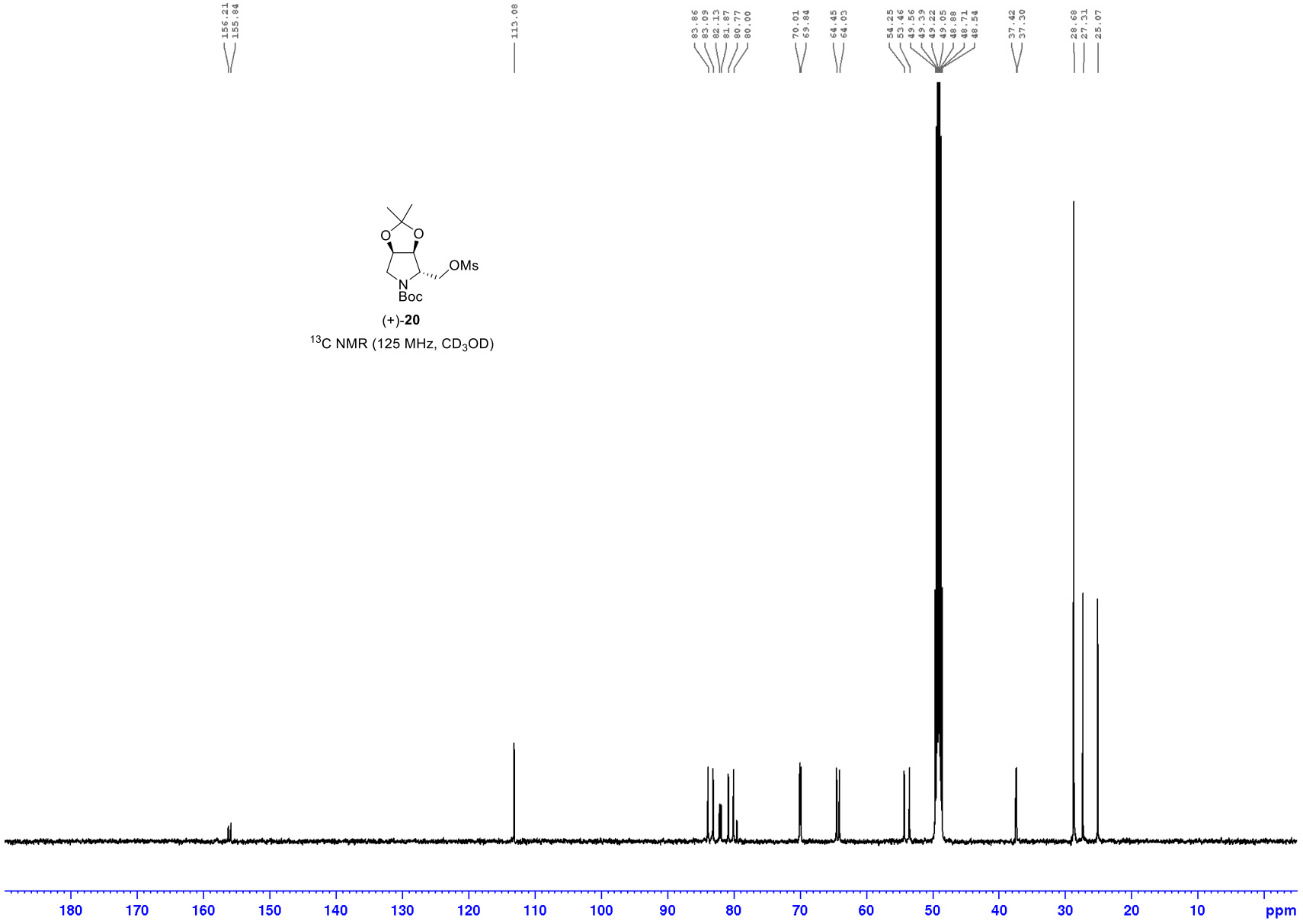
(-)-**20**

^{13}C NMR (125 MHz, CD_3OD)



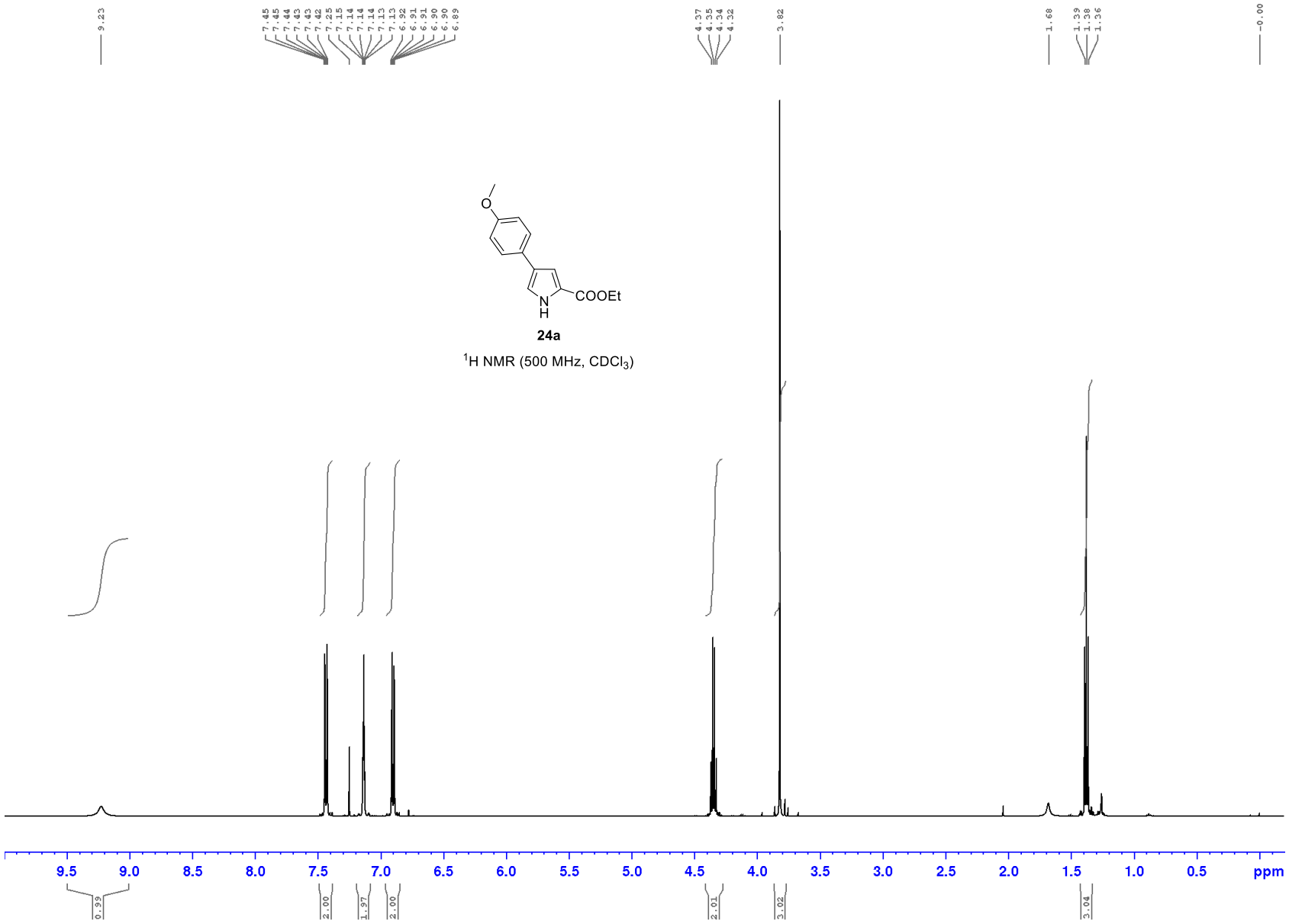
(+)-**20**

^{1}H NMR (500 MHz, CD_3OD)



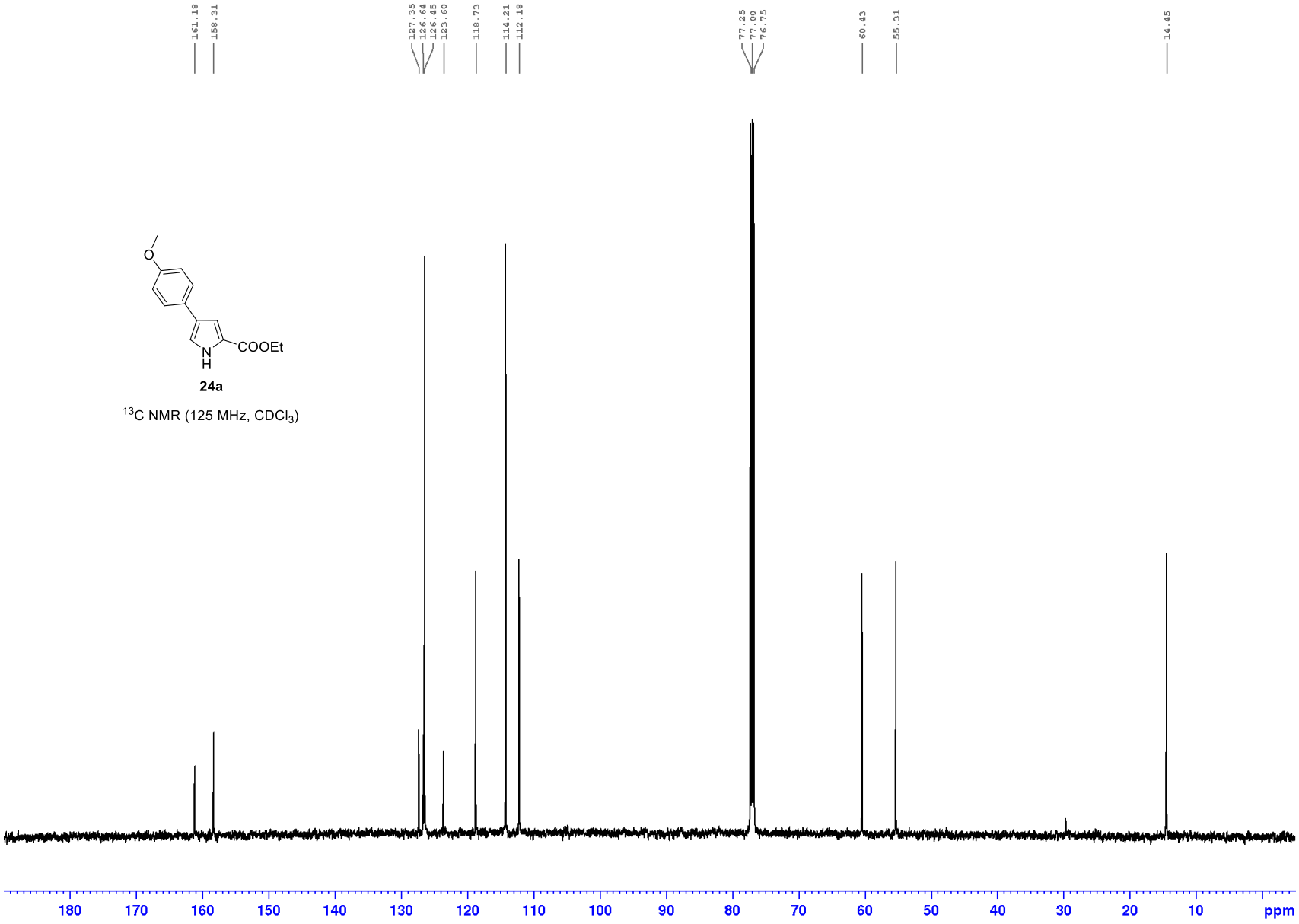
(+)-**20**

^{13}C NMR (125 MHz, CD_3OD)



24a

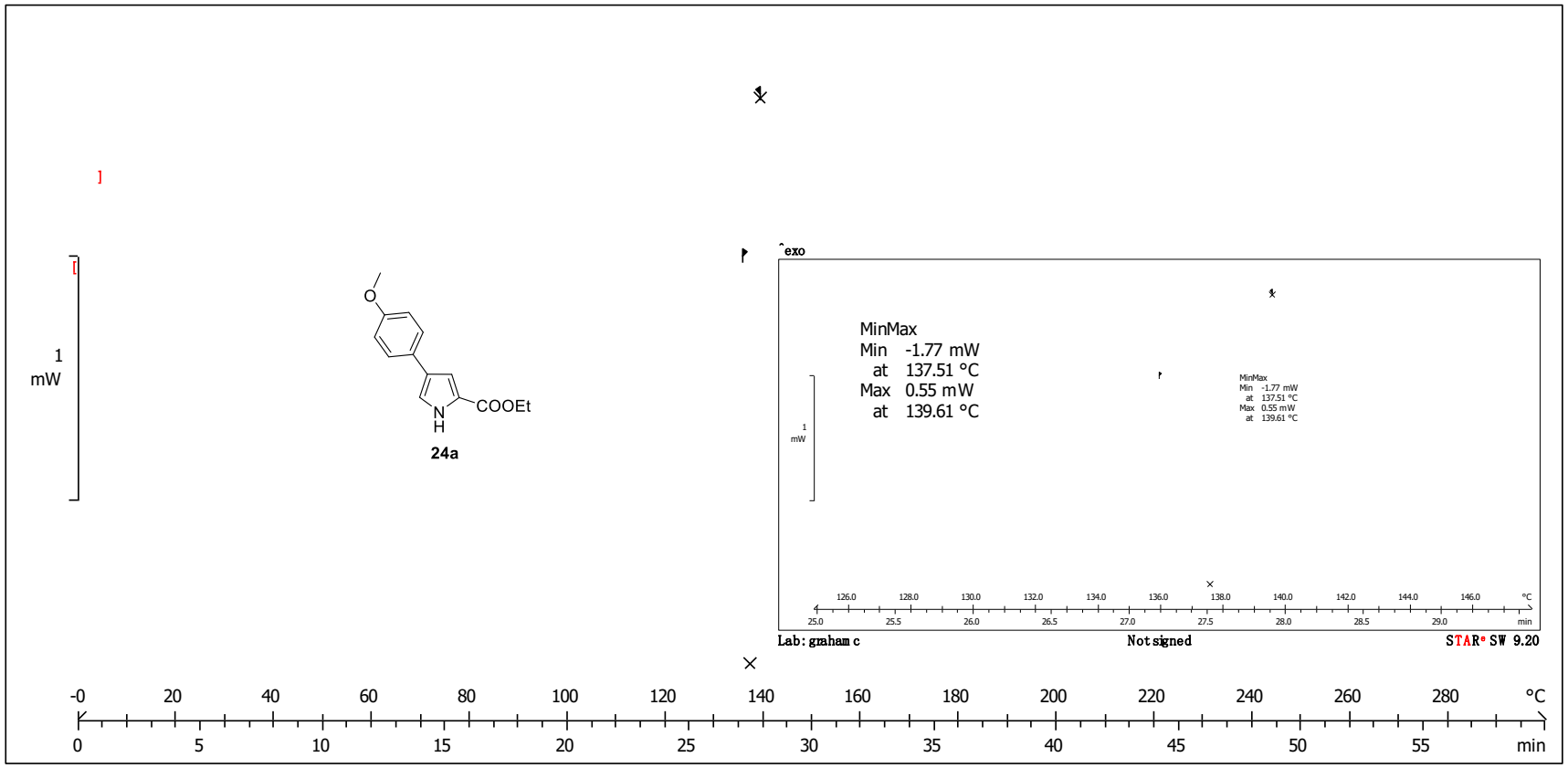
^{1}H NMR (500 MHz, $CDCl_3$)



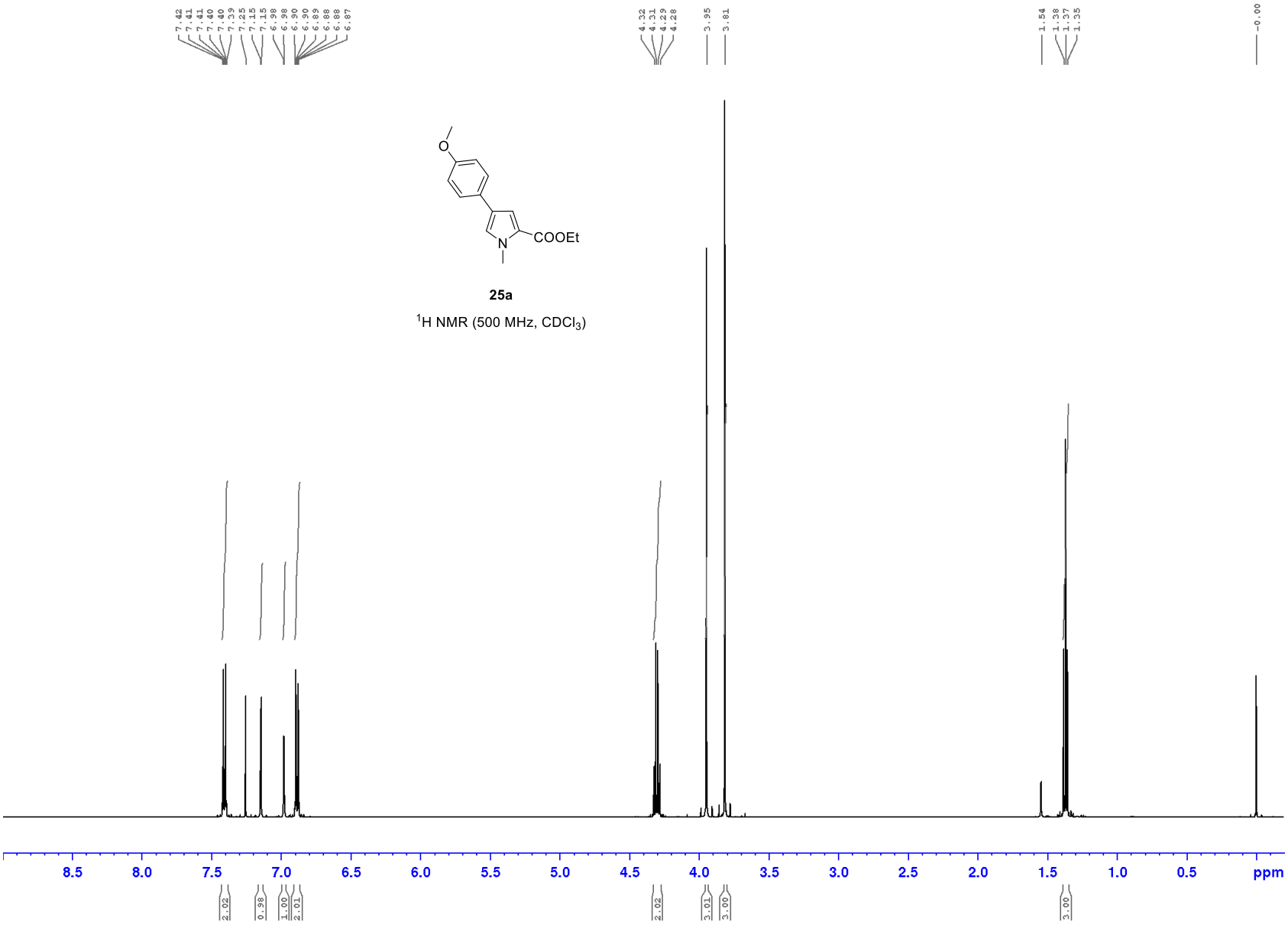
24a

^{13}C NMR (125 MHz, $CDCl_3$)

^exo

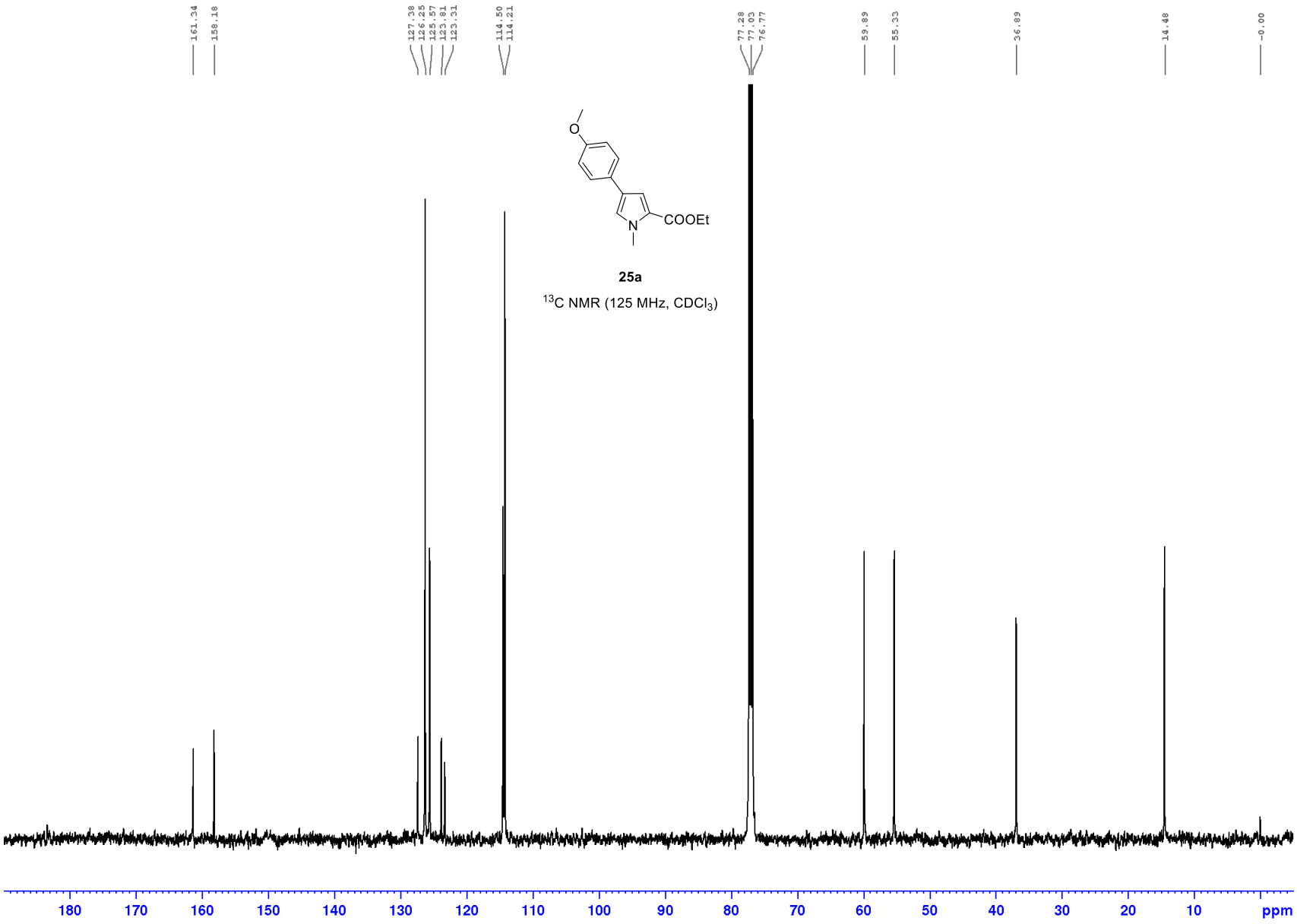


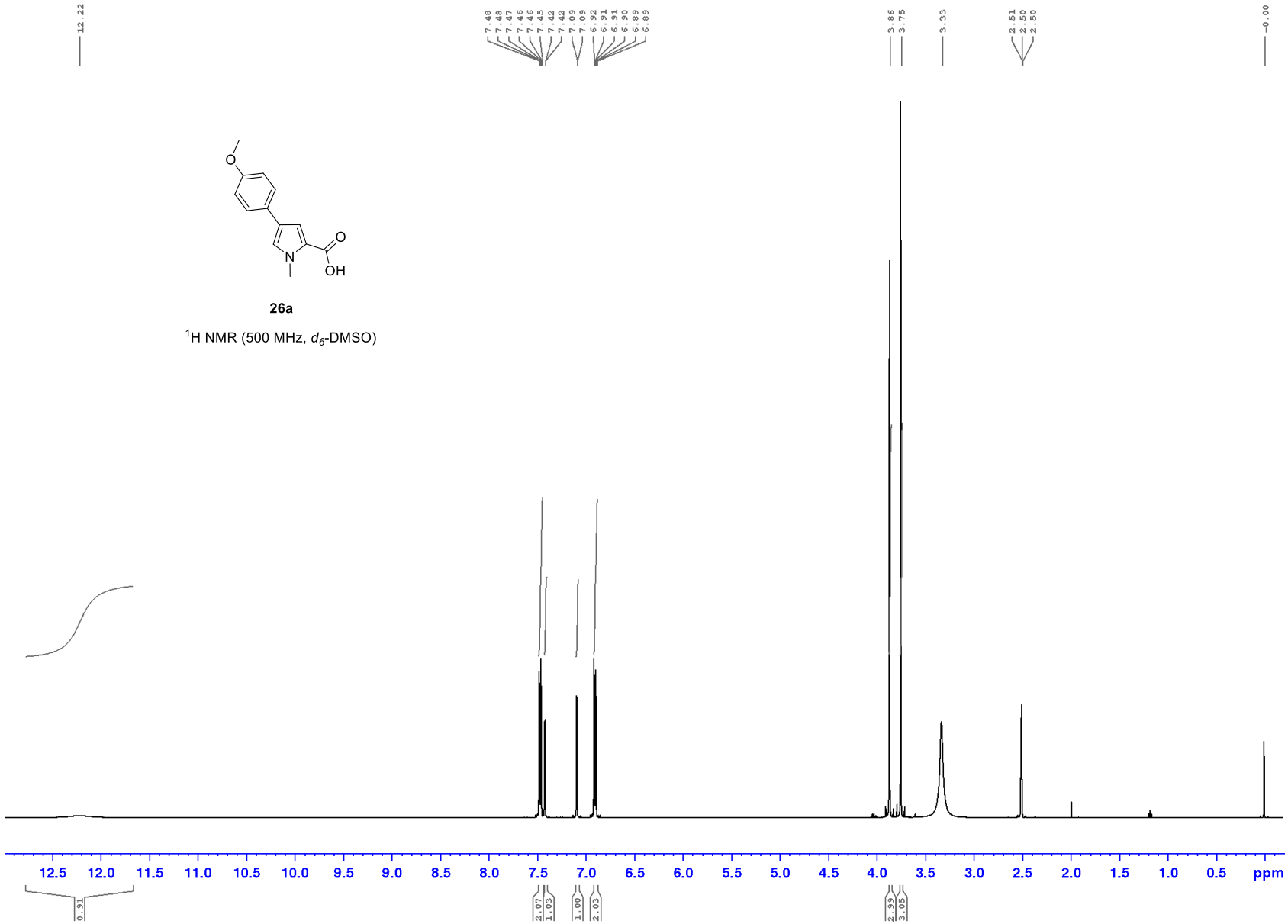
Lab: graham c Not signed STARe SW 9.20



25a

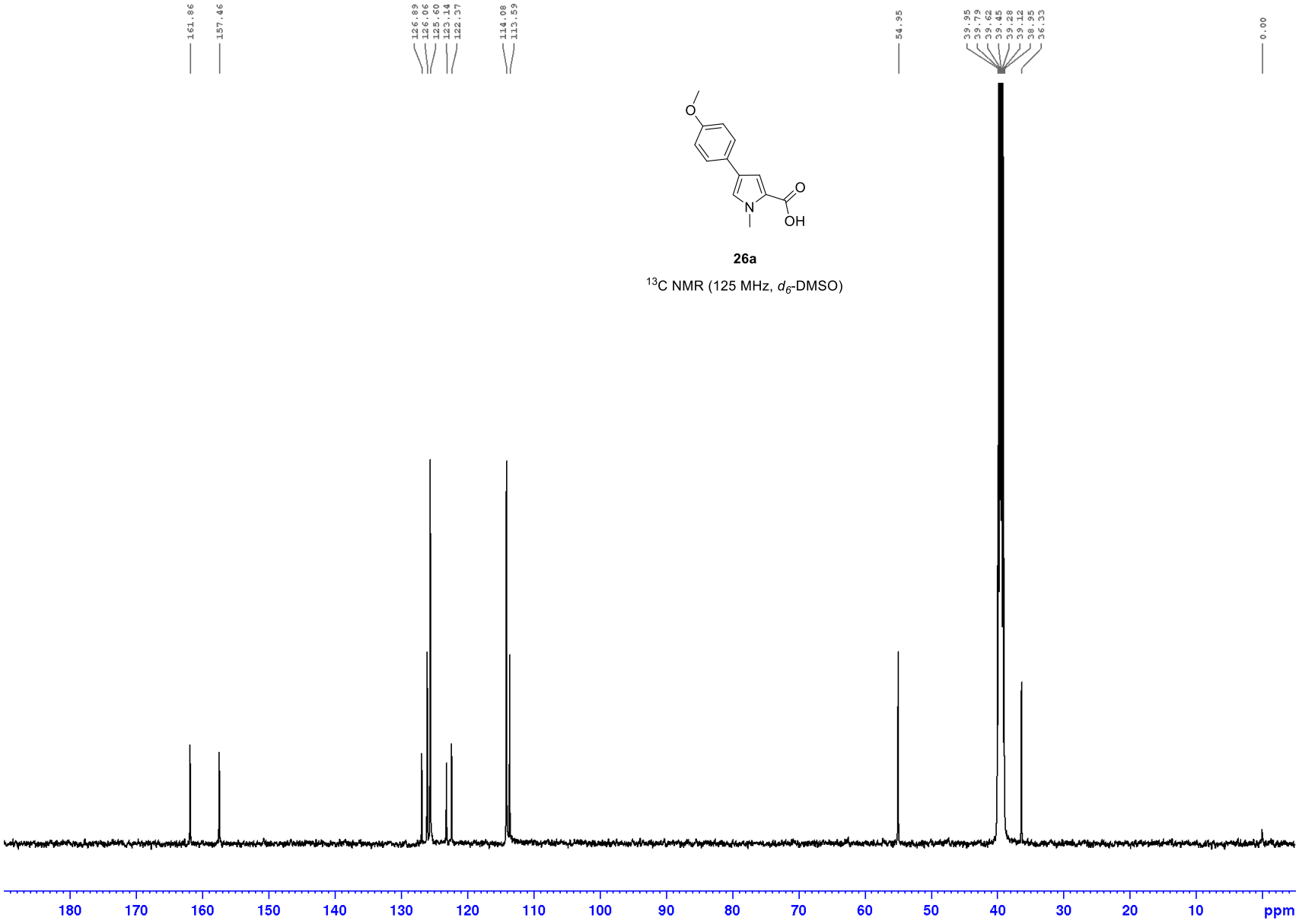
^{1}H NMR (500 MHz, $CDCl_3$)


161.34
158.18
127.38
126.25
125.57
123.81
123.31
114.50
114.21
77.28
77.03
76.77
59.89
55.33
36.89
14.48
0.00
O
N
COOEt
25a
13C NMR (125 MHz, CDCl3)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm



26a

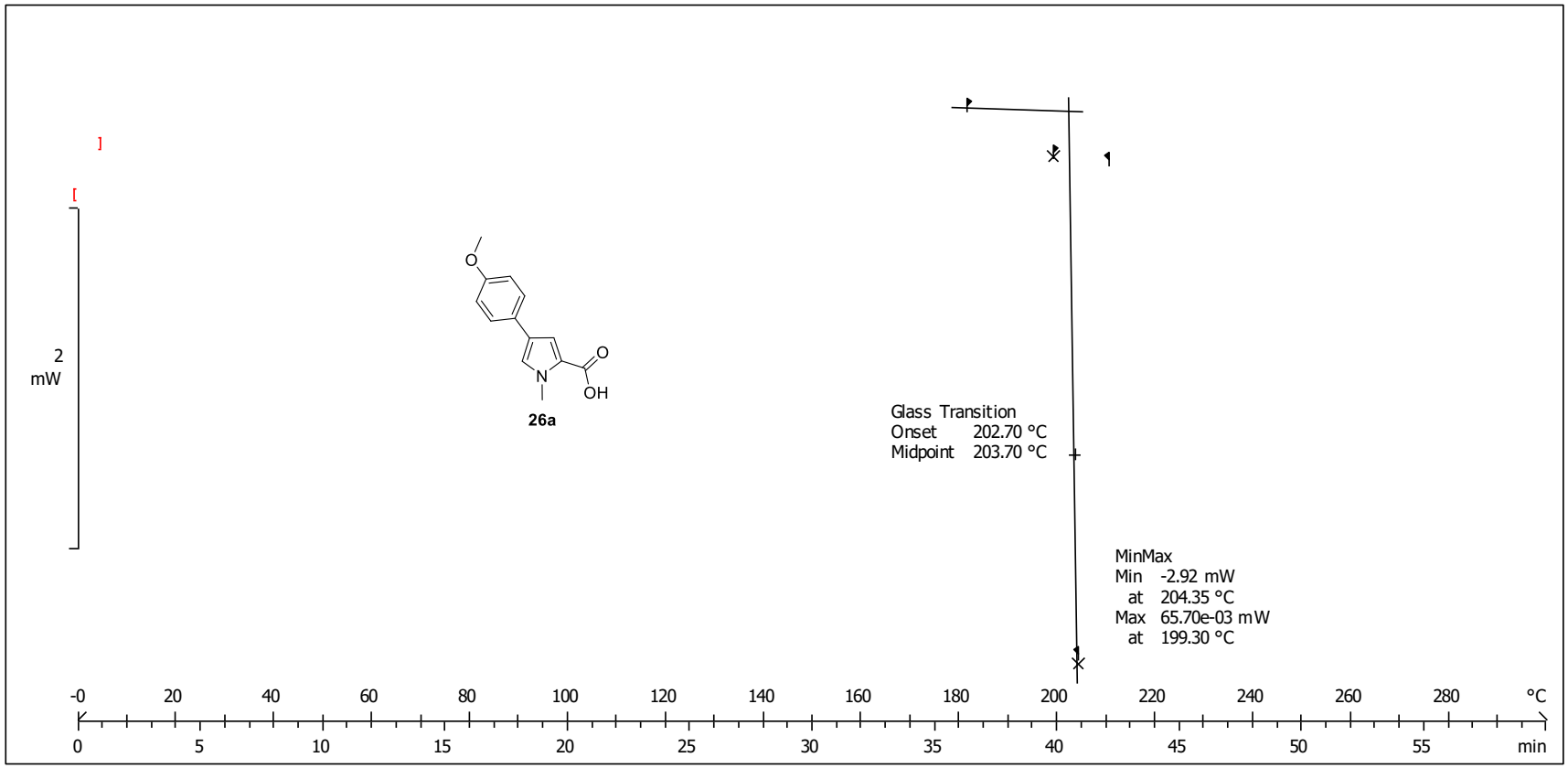
^{1}H NMR (500 MHz, d_6-DMSO)



26a

^{13}C NMR (125 MHz, d_6-DMSO)

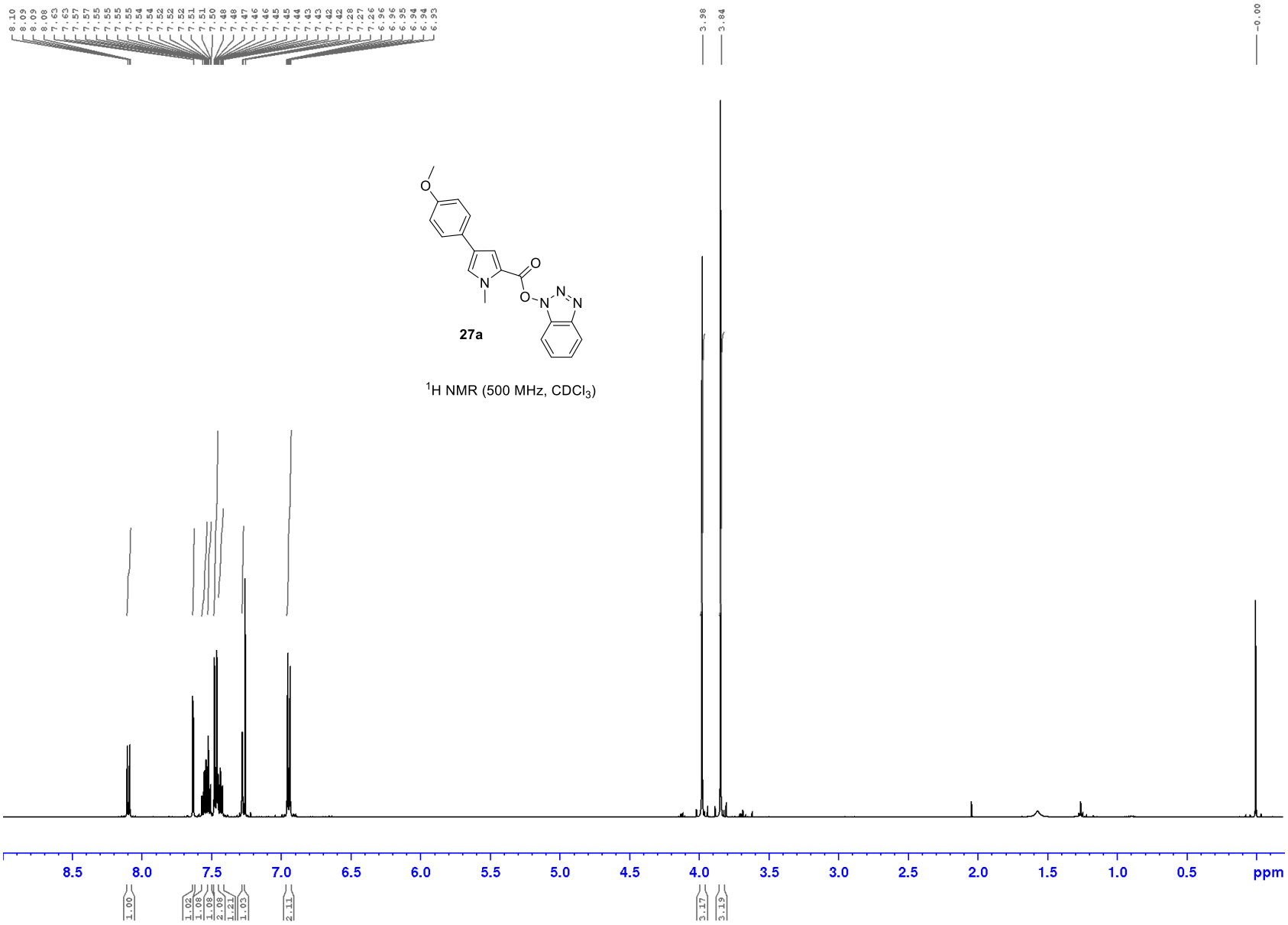
^exo

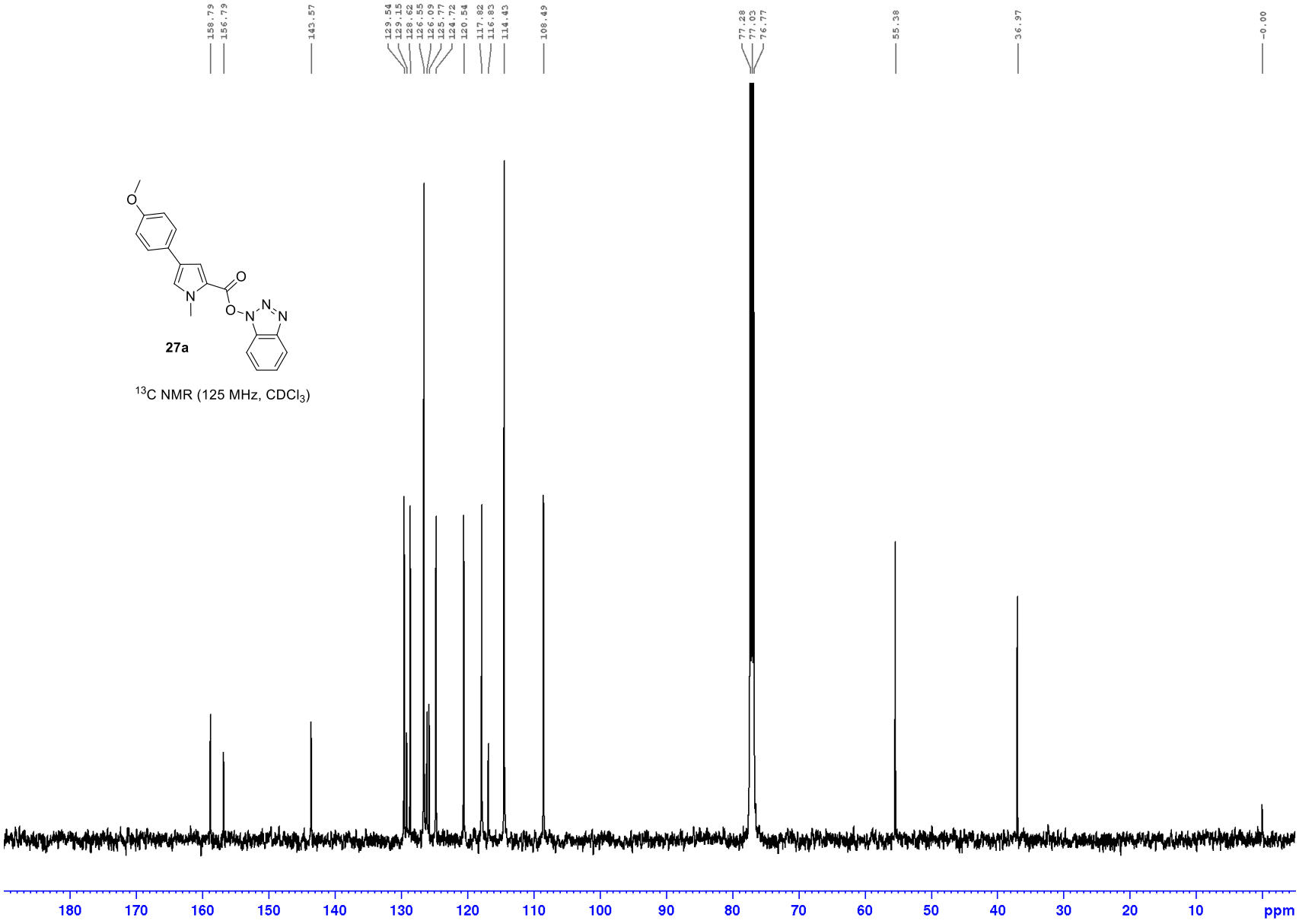


Lab: graham c

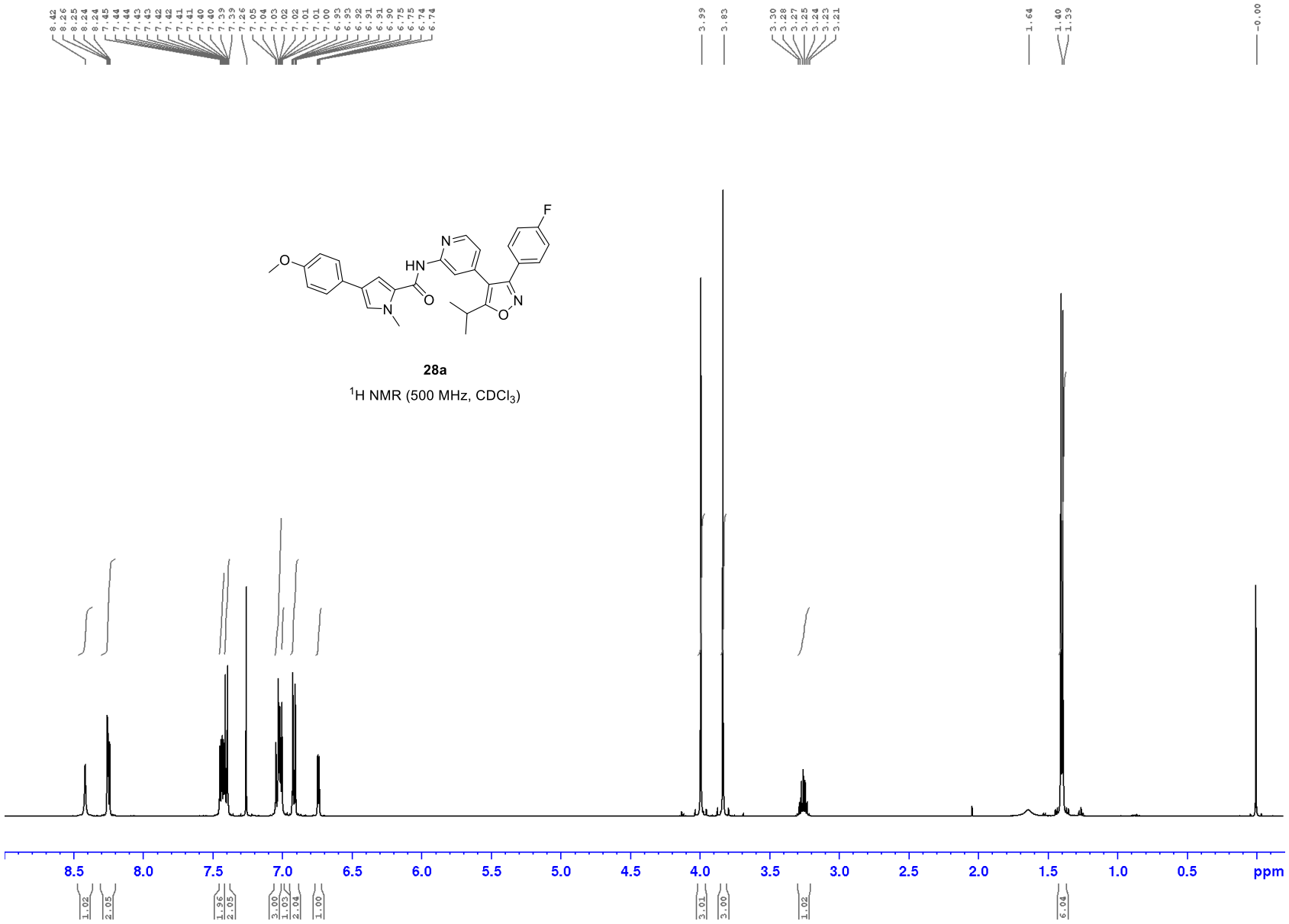
Not signed

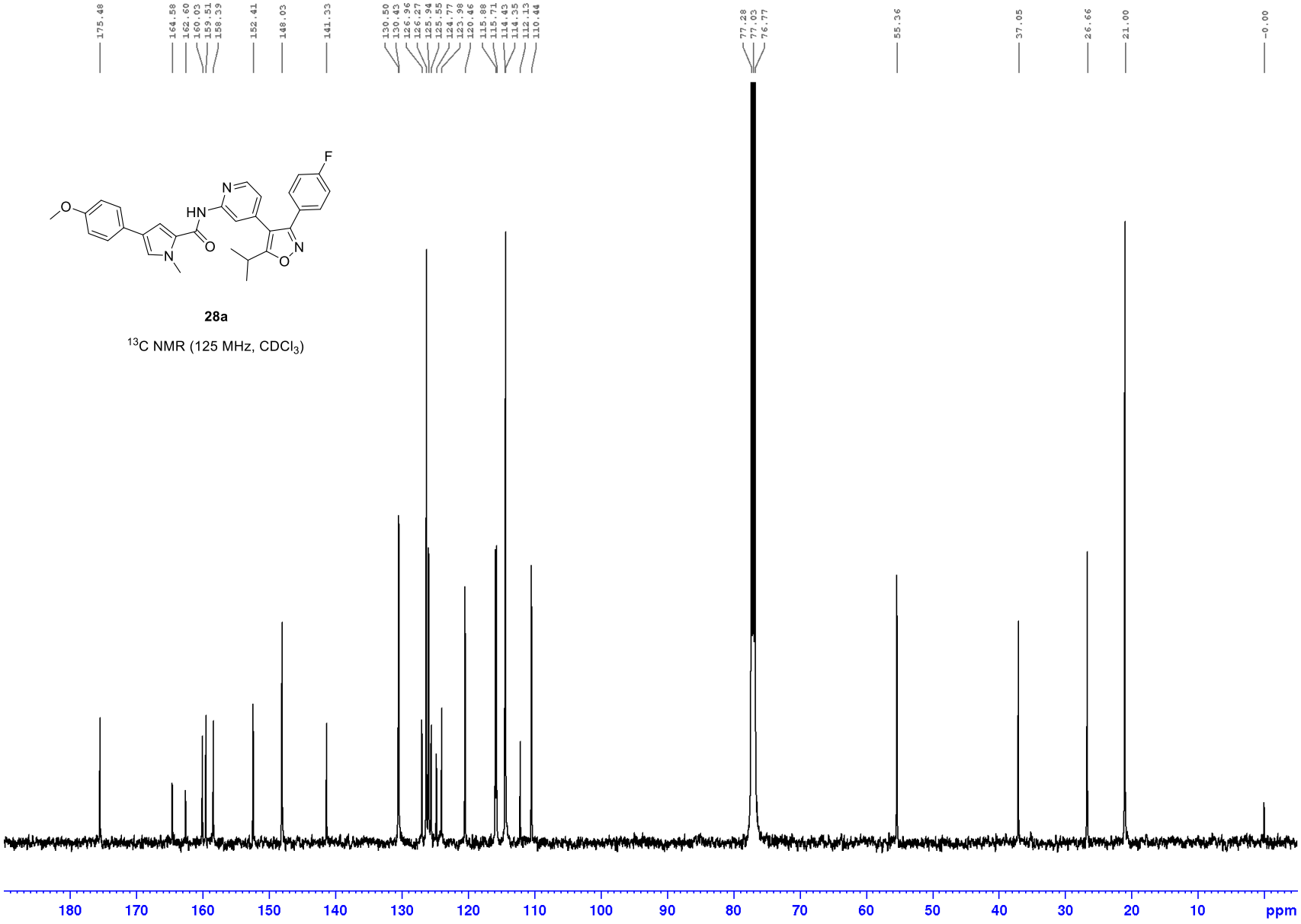
STARe SW 9.20


8.10
8.09
8.09
8.08
7.63
7.57
7.57
7.55
7.55
7.55
7.55
7.54
7.54
7.52
7.52
7.52
7.51
7.51
7.50
7.48
7.48
7.47
7.46
7.46
7.45
7.45
7.44
7.43
7.43
7.42
7.42
7.28
7.27
7.26
6.96
6.96
6.95
6.94
6.94
6.93
3.98
3.84
0.00
O
O
N
O
N
N
N
27a
1H NMR (500 MHz, CDCl3)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
1.02
1.08
1.08
2.08
1.21
1.03
2.11
3.17
3.19



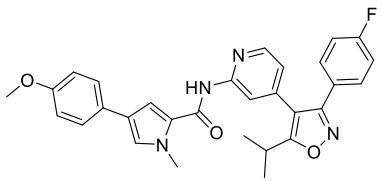
^{13}C NMR (125 MHz, $CDCl_3$)


8.42
8.26
8.25
8.24
8.24
7.45
7.44
7.44
7.43
7.43
7.42
7.42
7.41
7.41
7.40
7.40
7.39
7.39
7.26
7.05
7.04
7.03
7.02
7.02
7.01
7.01
7.00
6.93
6.93
6.92
6.91
6.91
6.90
6.75
6.74
6.74
3.99
3.83
3.30
3.28
3.27
3.25
3.24
3.23
3.21
1.64
1.40
1.39
-0.00
F
N
HN
O
O
N
N
O
28a
1H NMR (500 MHz, CDCl3)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.02
2.05
1.96
2.05
3.00
1.03
2.04
1.00
3.01
3.00
1.02
6.04



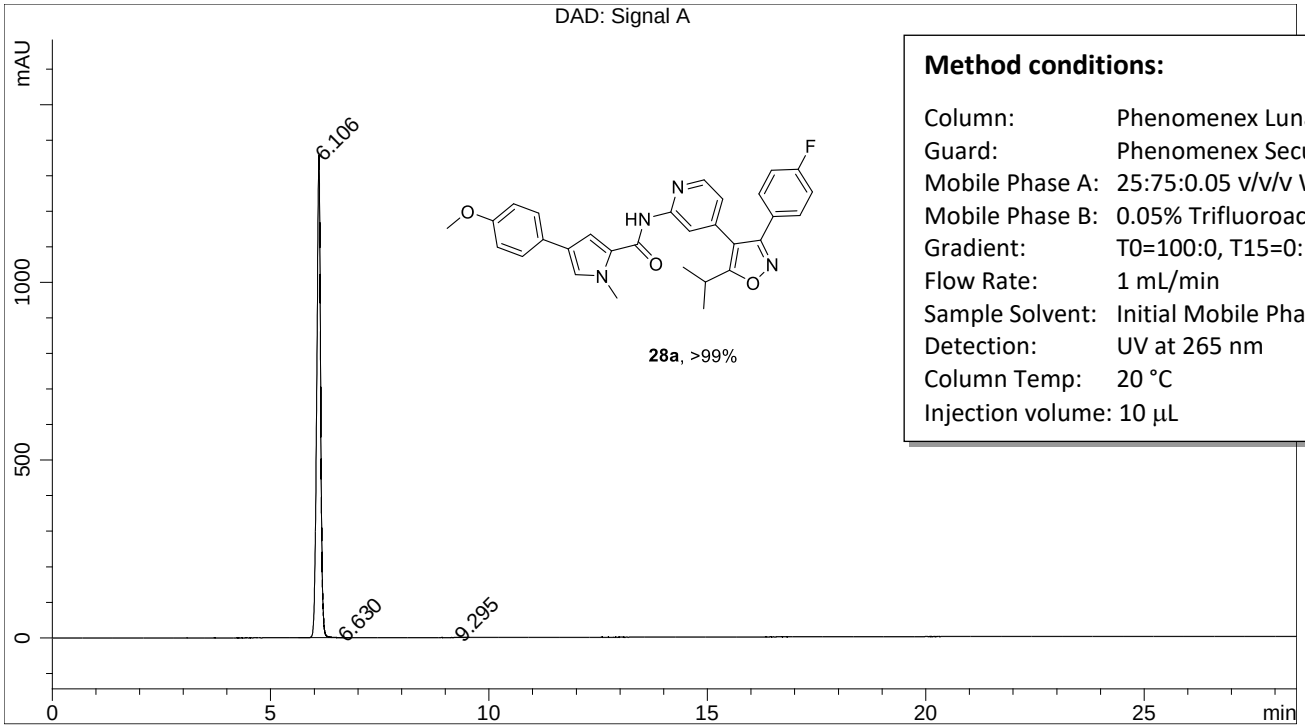
28a

^{13}C NMR (125 MHz, $CDCl_3$)



28a

^{19}F NMR (470 MHz, $CDCl_3$)



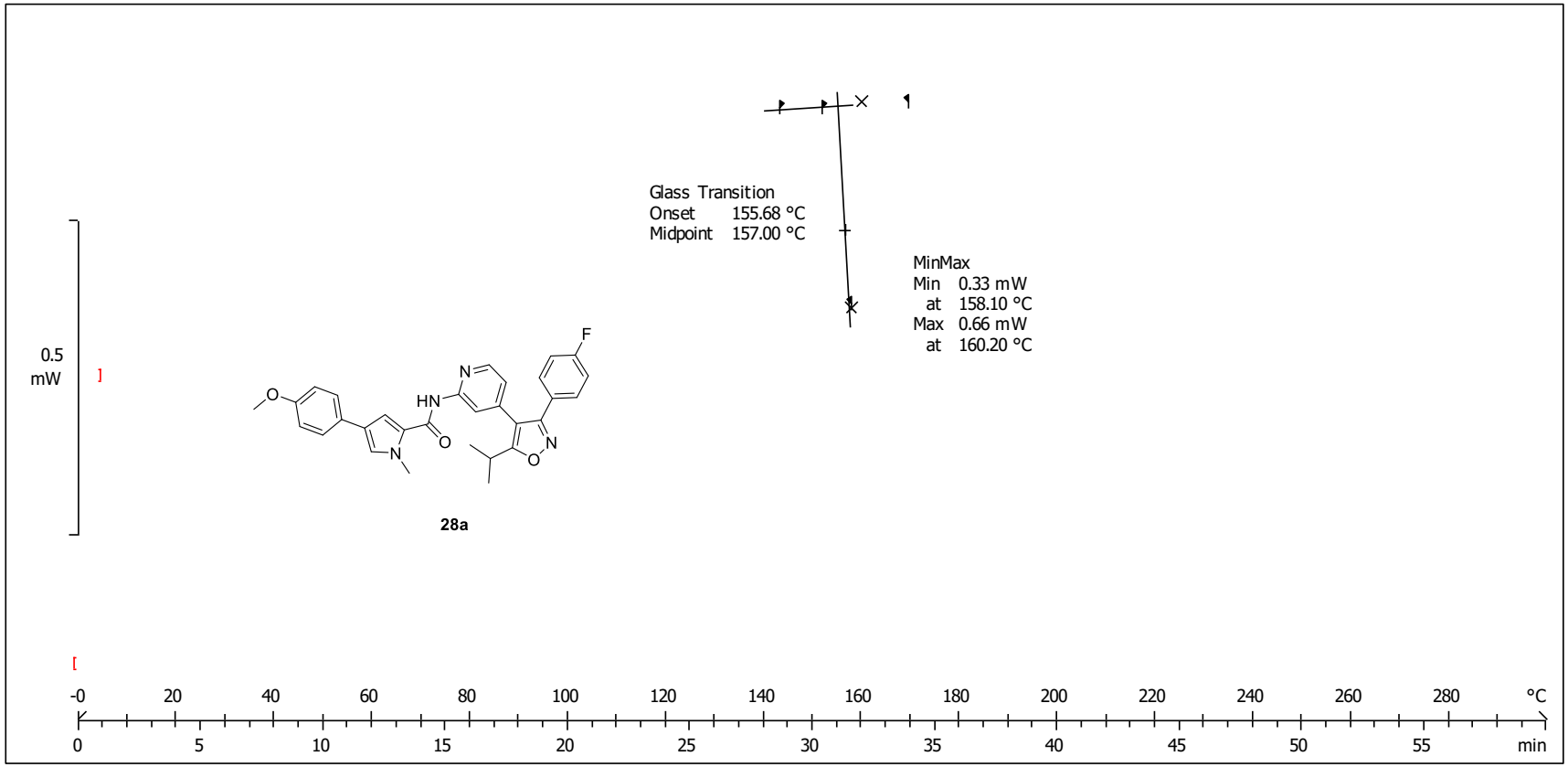
28a, >99%

Method conditions:

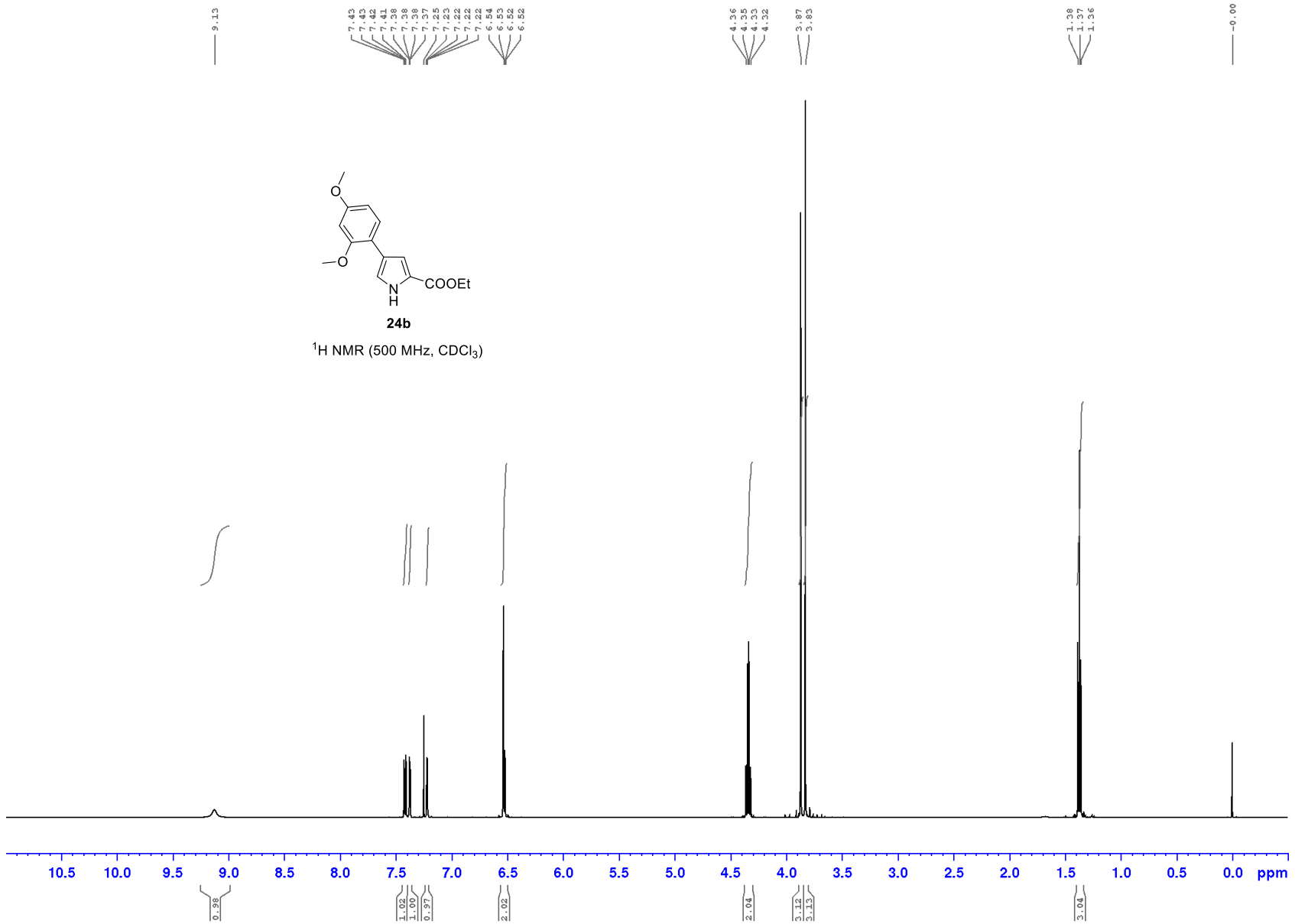
Column:	Phenomenex Luna C18(2) 5 µm 250x4.6 mm
Guard:	Phenomenex Security Guard C18 RP 4x3 mm
Mobile Phase A:	25:75:0.05 v/v/v Water/Acetonitrile/Trifluoroacetic acid
Mobile Phase B:	0.05% Trifluoroacetic acid in Acetonitrile
Gradient:	T0=100:0, T15=0:100, T25=0:100, T27=100:0, T30=100:0
Flow Rate:	1 mL/min
Sample Solvent:	Initial Mobile Phase
Detection:	UV at 265 nm
Column Temp:	20 °C
Injection volume:	10 µL

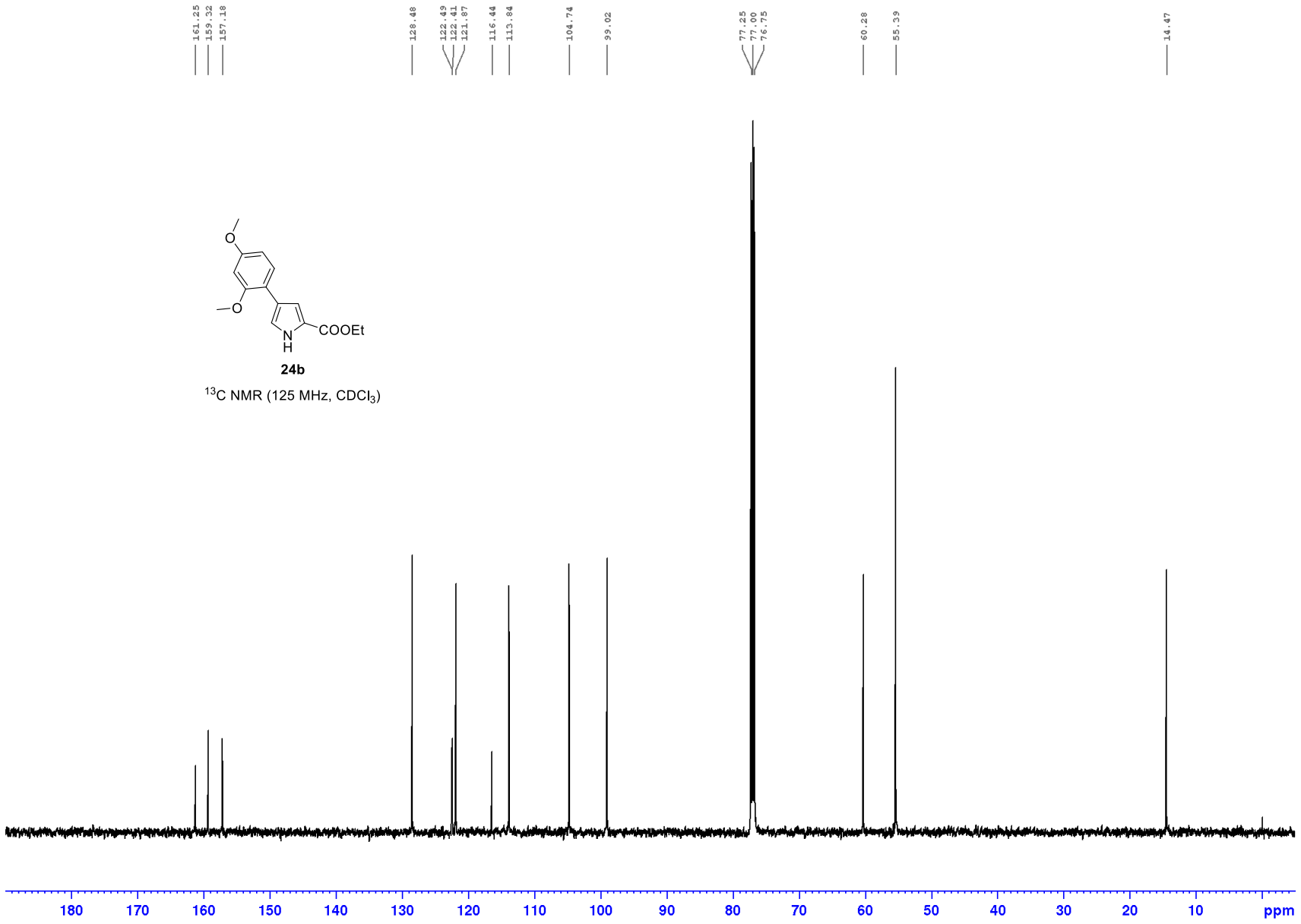
Peak#	RT	Peak Height	Peak Area	Width	Area %
1	6.11 min	1352.9101	8365.3259	0.0961 min	99.935 %
2	6.63 min	0.2620	2.1450	0.1075 min	0.026 %
3	9.29 min	0.3148	3.3145	0.1348 min	0.040 %

^exo



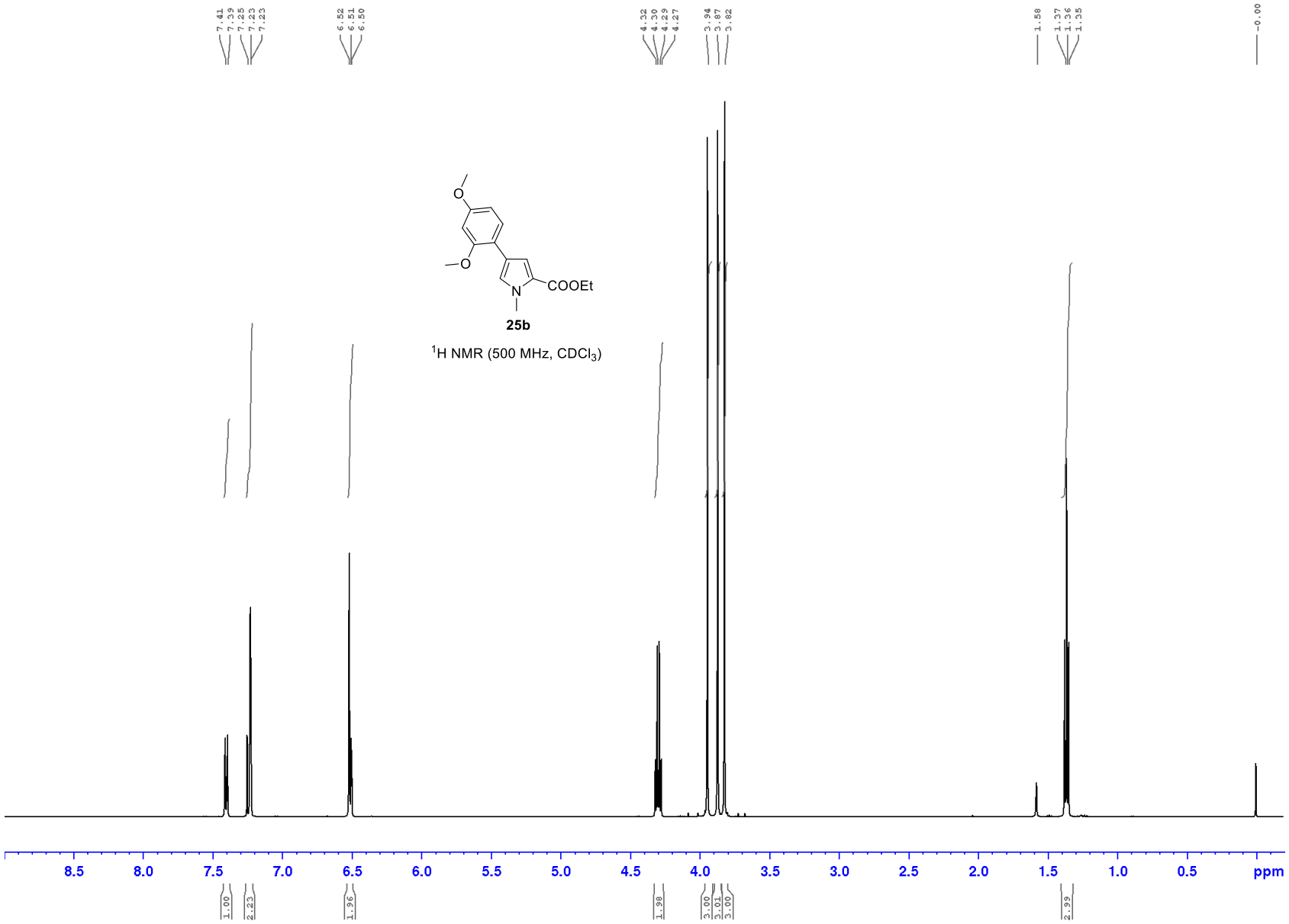
Lab: graham c Not signed STARe SW 9.20

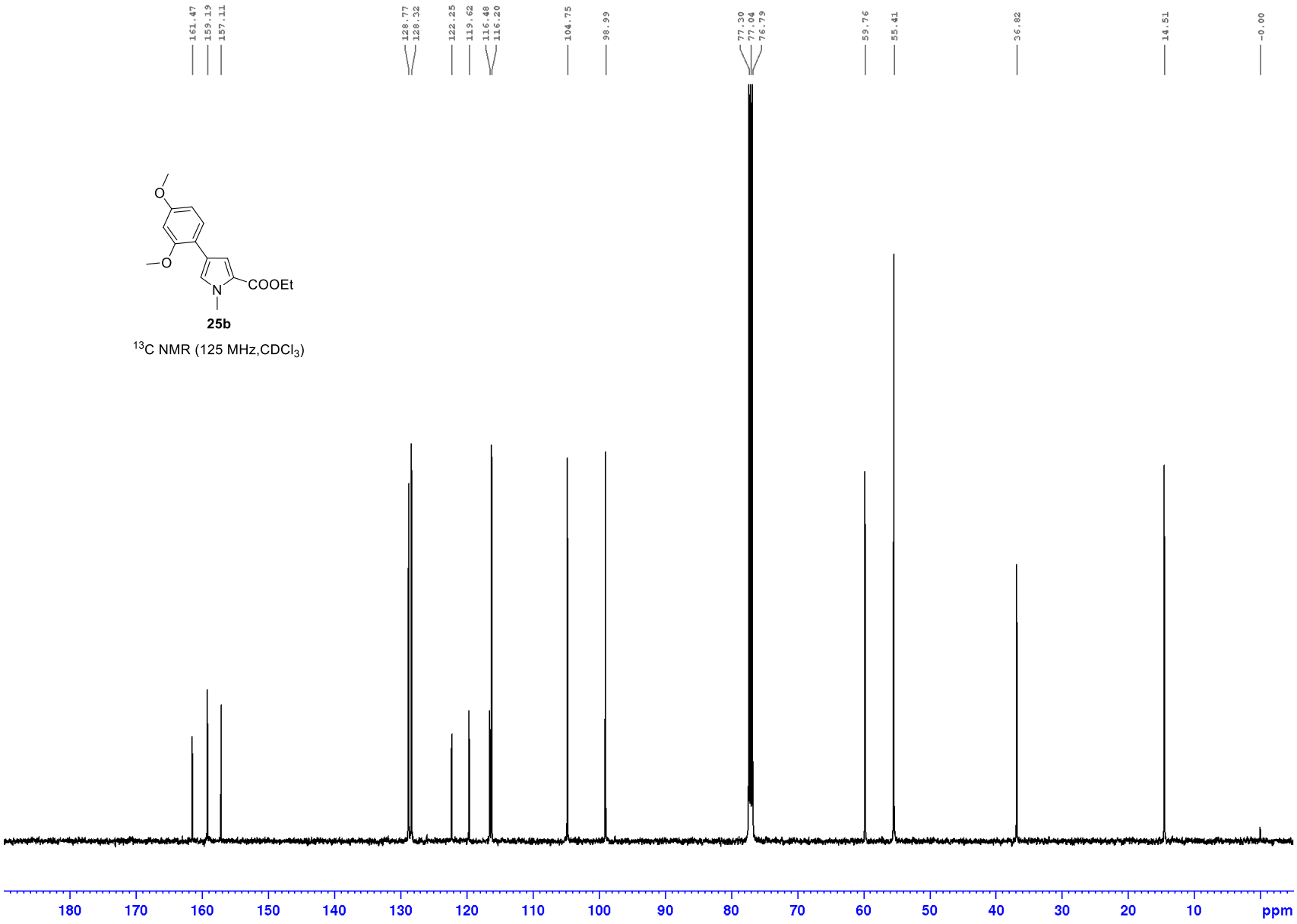

9.13
7.43
7.43
7.42
7.41
7.38
7.38
7.38
7.37
7.25
7.23
7.22
7.22
7.22
6.54
6.53
6.52
6.52
4.36
4.35
4.33
4.32
3.87
3.83
1.38
1.37
1.36
0.00
O
O
N
H
COOEt
24b
1H NMR (500 MHz, CDCl3)
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
0.98
1.02
1.00
0.97
2.02
2.04
3.12
3.13
3.04

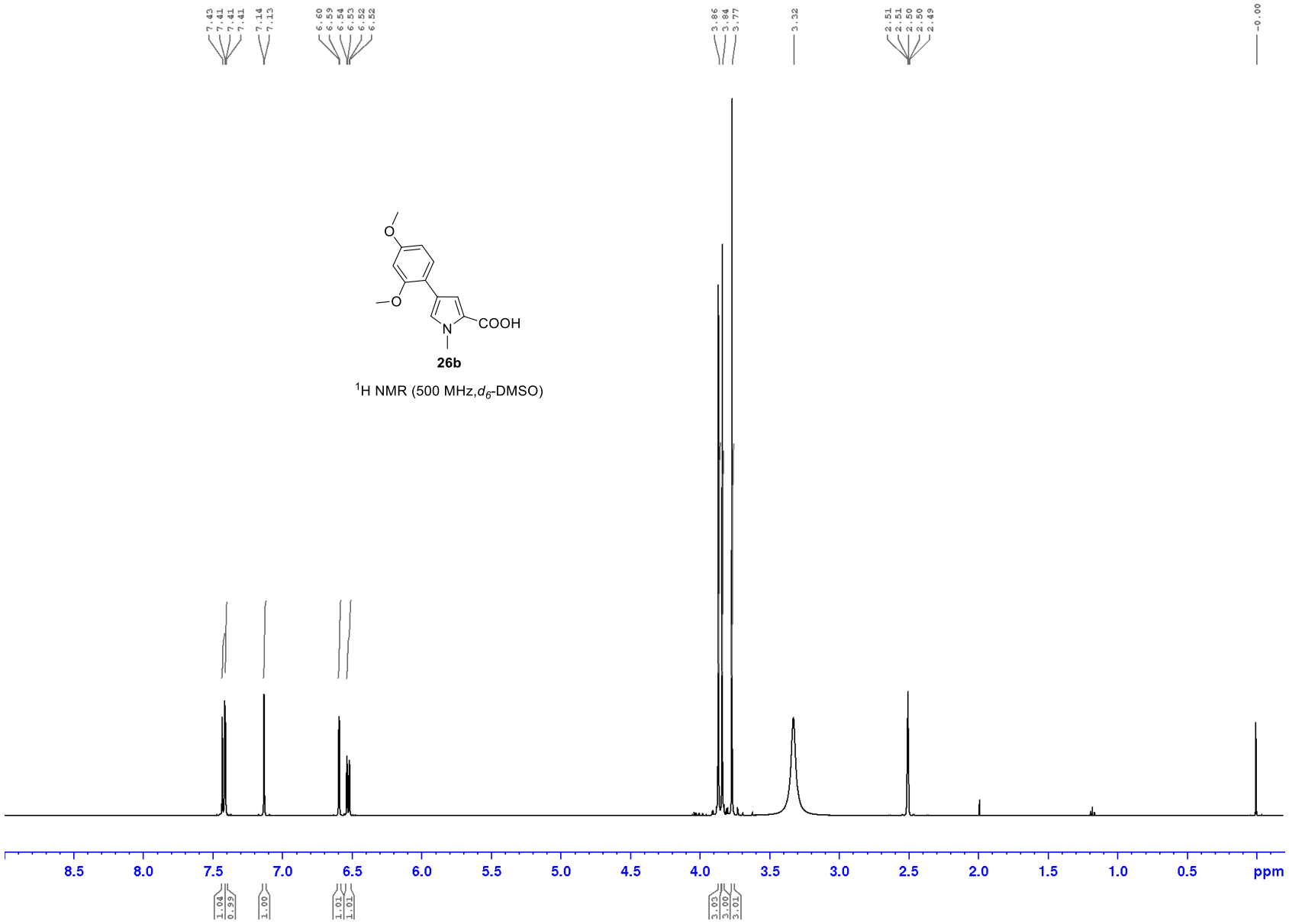


24b

^{13}C NMR (125 MHz, $CDCl_3$)

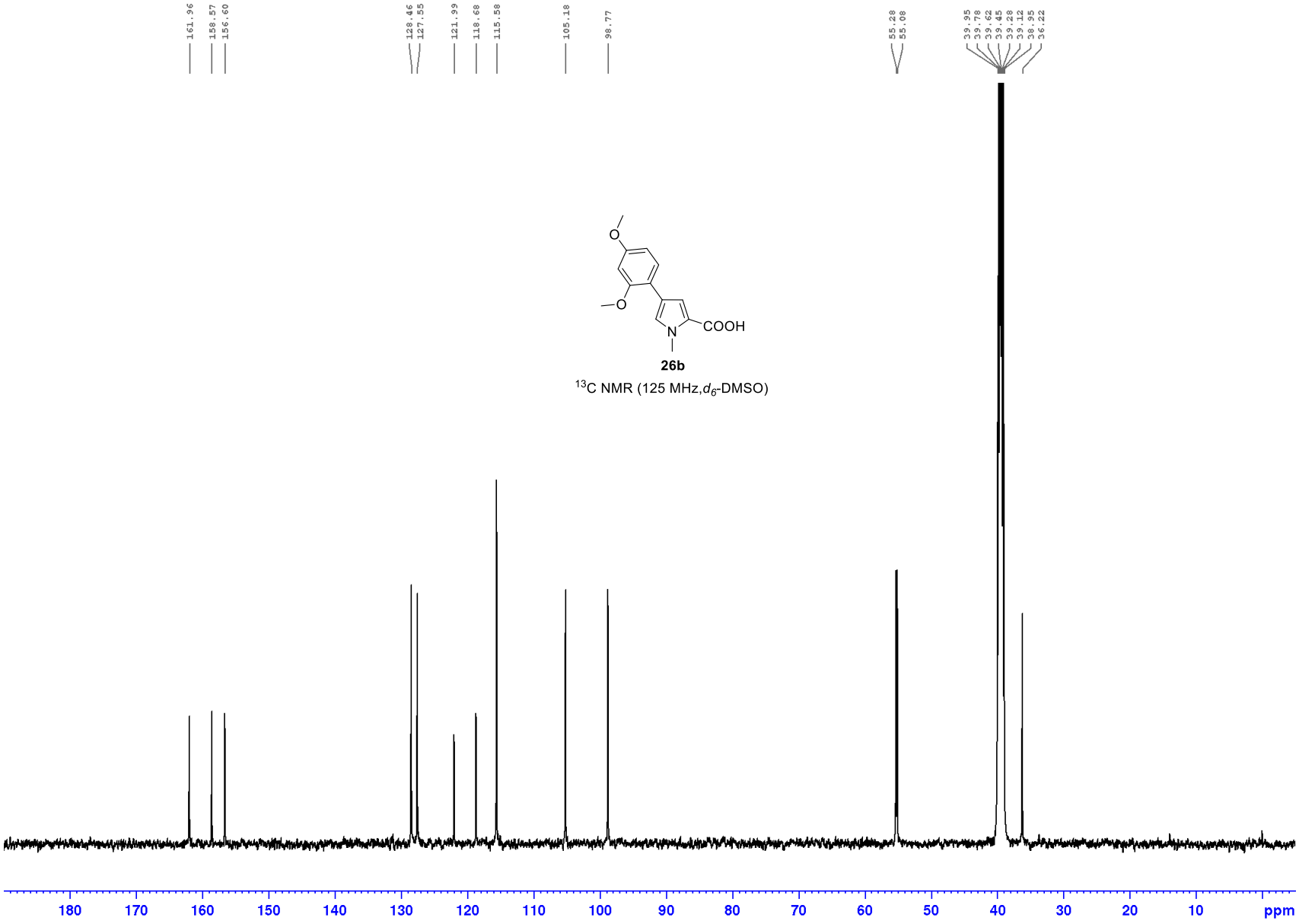

7.41
7.39
7.25
7.23
7.23
6.52
6.51
6.50
4.32
4.30
4.29
4.27
3.94
3.87
3.82
1.58
1.37
1.36
1.35
0.00
O
O
N
COOEt
25b
1H NMR (500 MHz, CDCl3)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
2.23
1.96
1.98
3.00
3.01
3.00
2.99


161.47
159.19
157.11
128.77
128.32
122.25
119.62
116.48
116.20
104.75
98.99
77.30
77.04
76.79
59.76
55.41
36.82
14.51
0.00
O
O
N
COOEt
25b
13C NMR (125 MHz,CDCl3)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm



26b

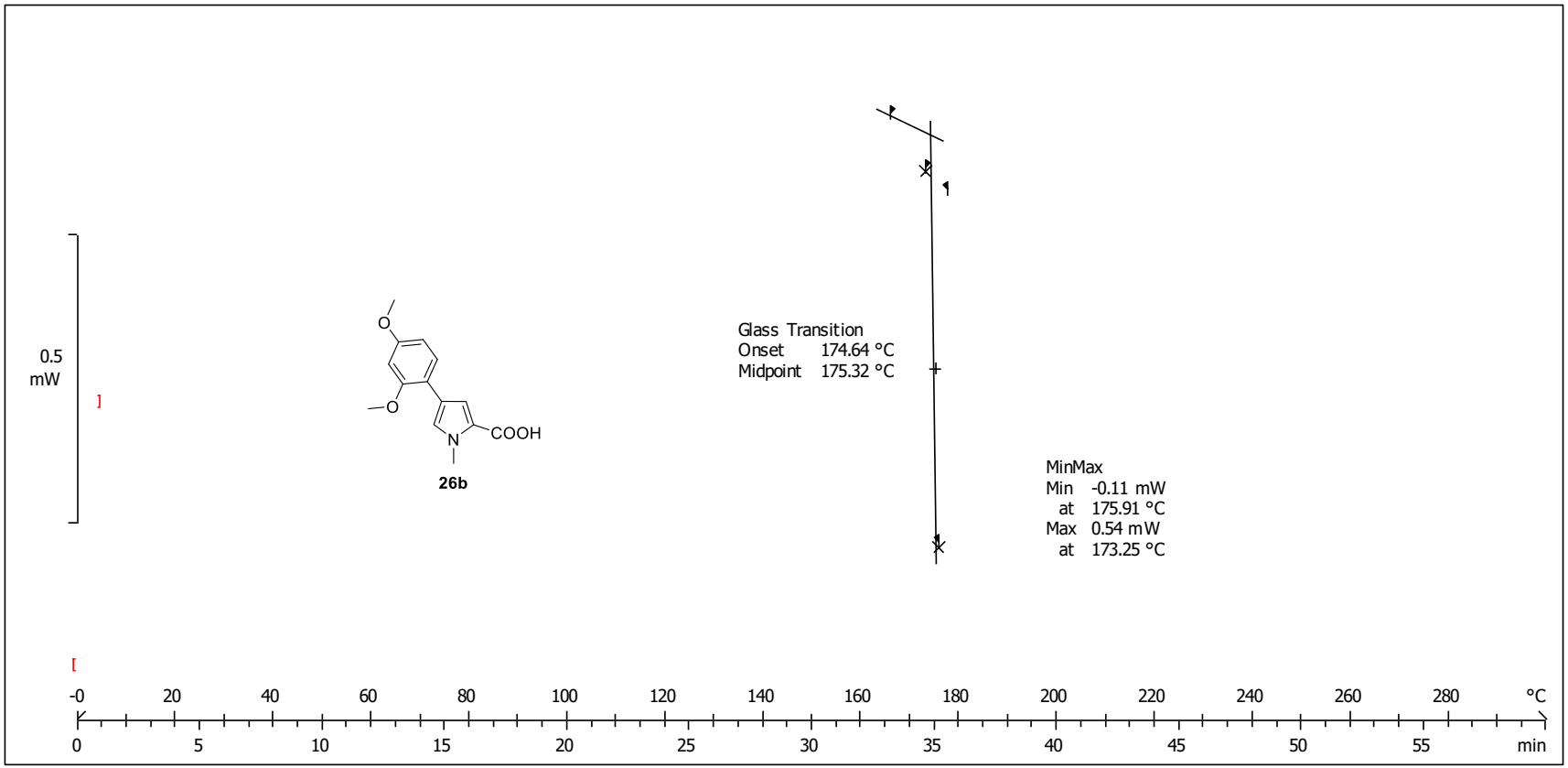
^{1}H NMR (500 MHz,d_6-DMSO)



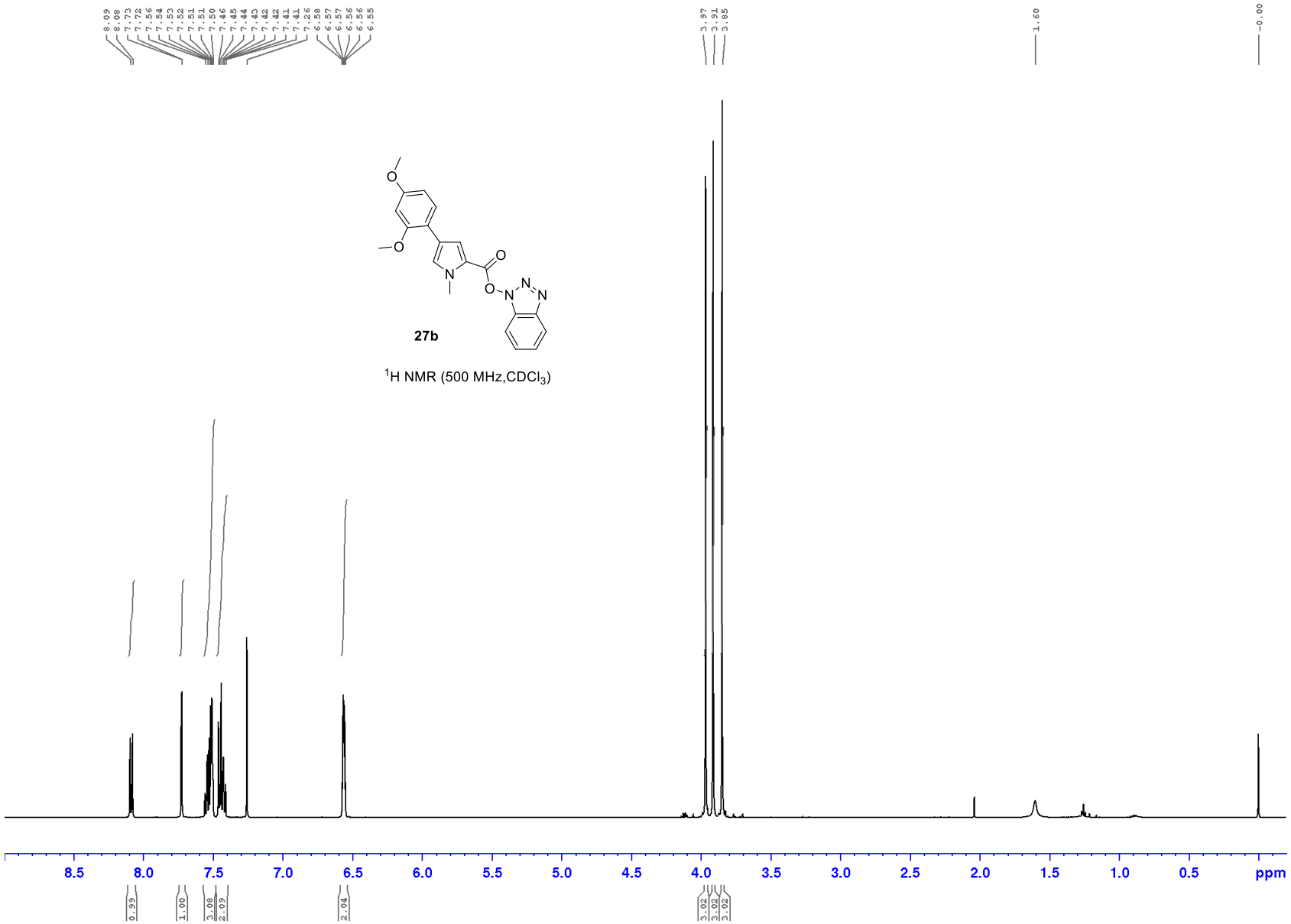
26b

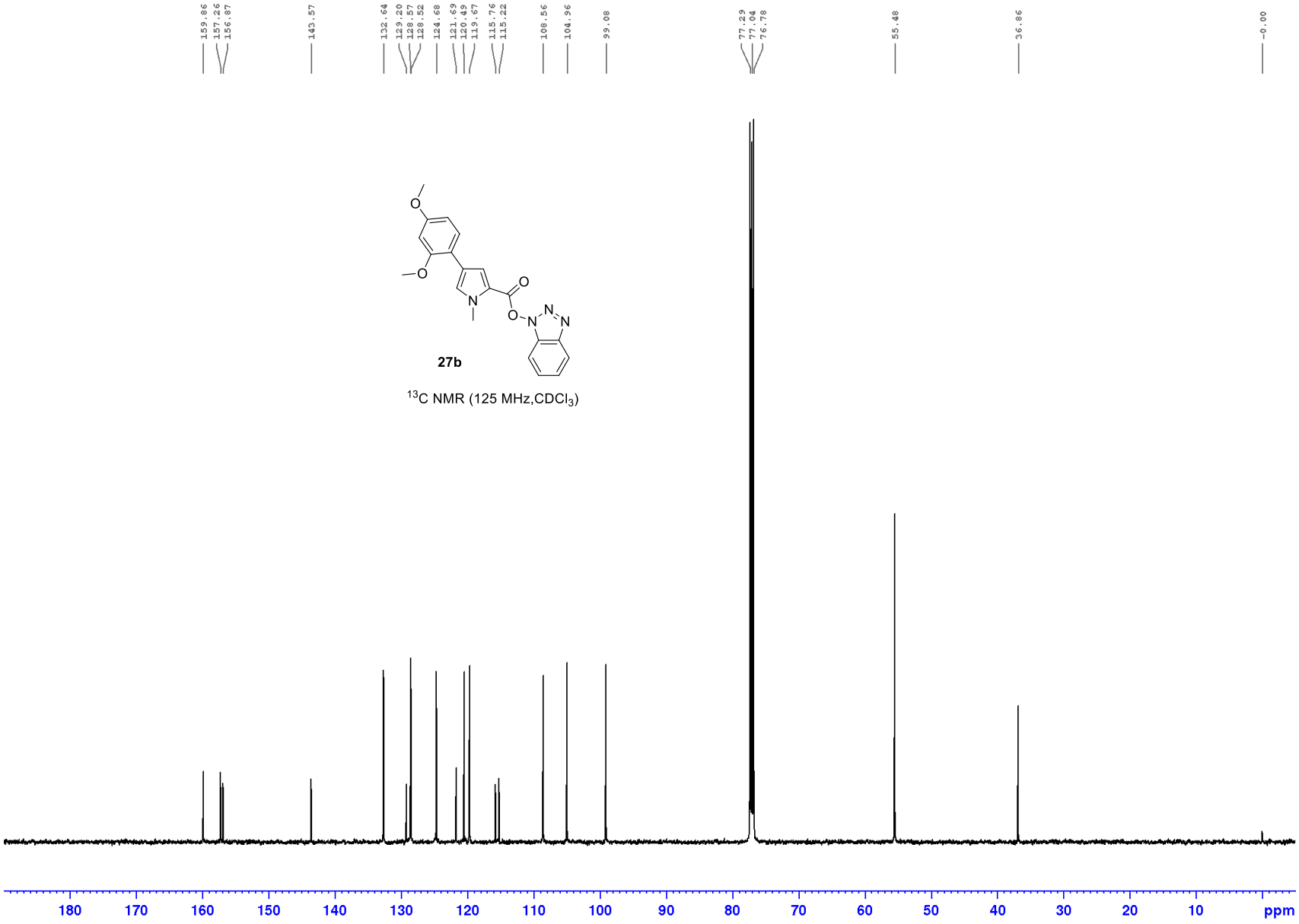
^{13}C NMR (125 MHz,d_6-DMSO)

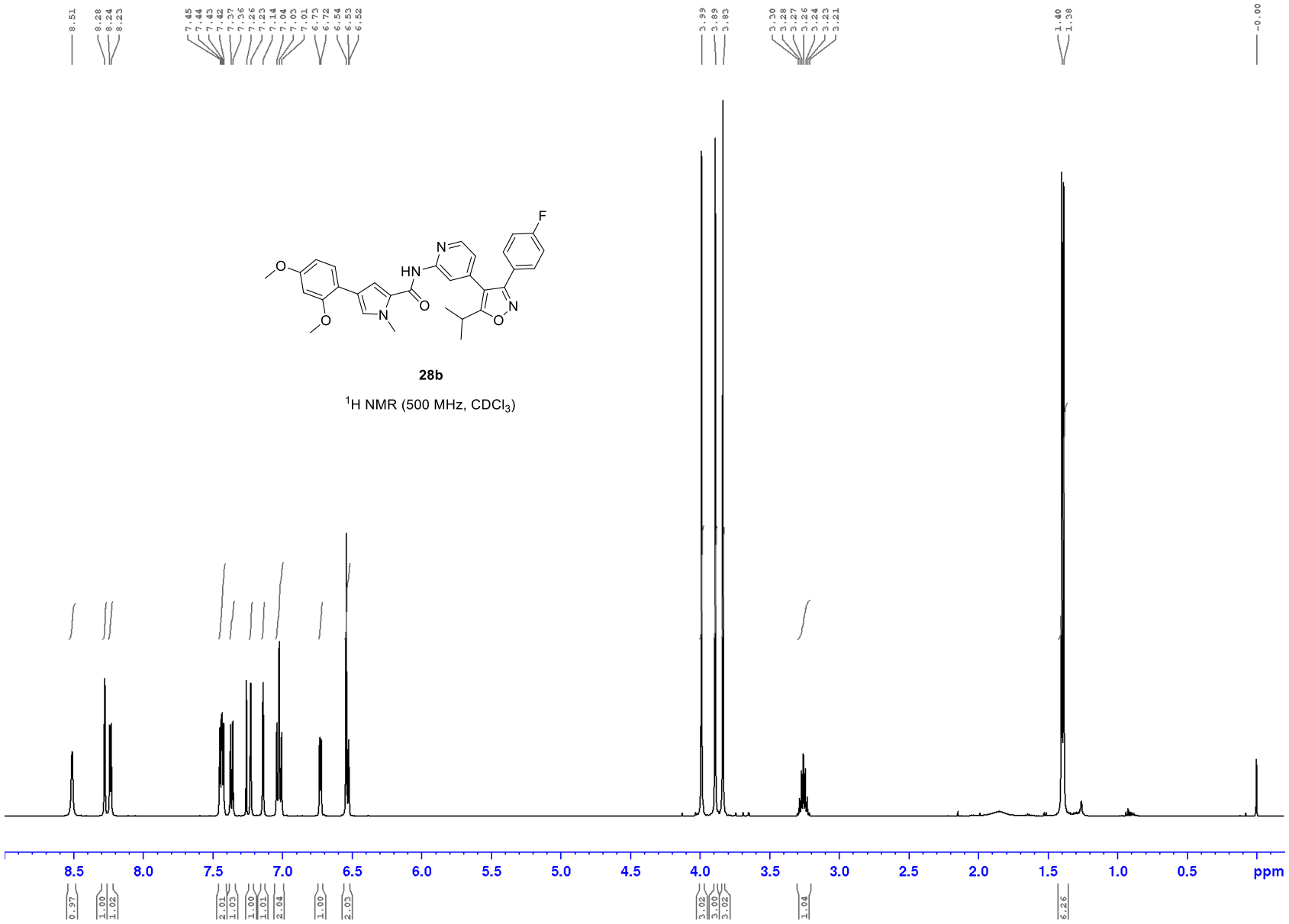
^exo

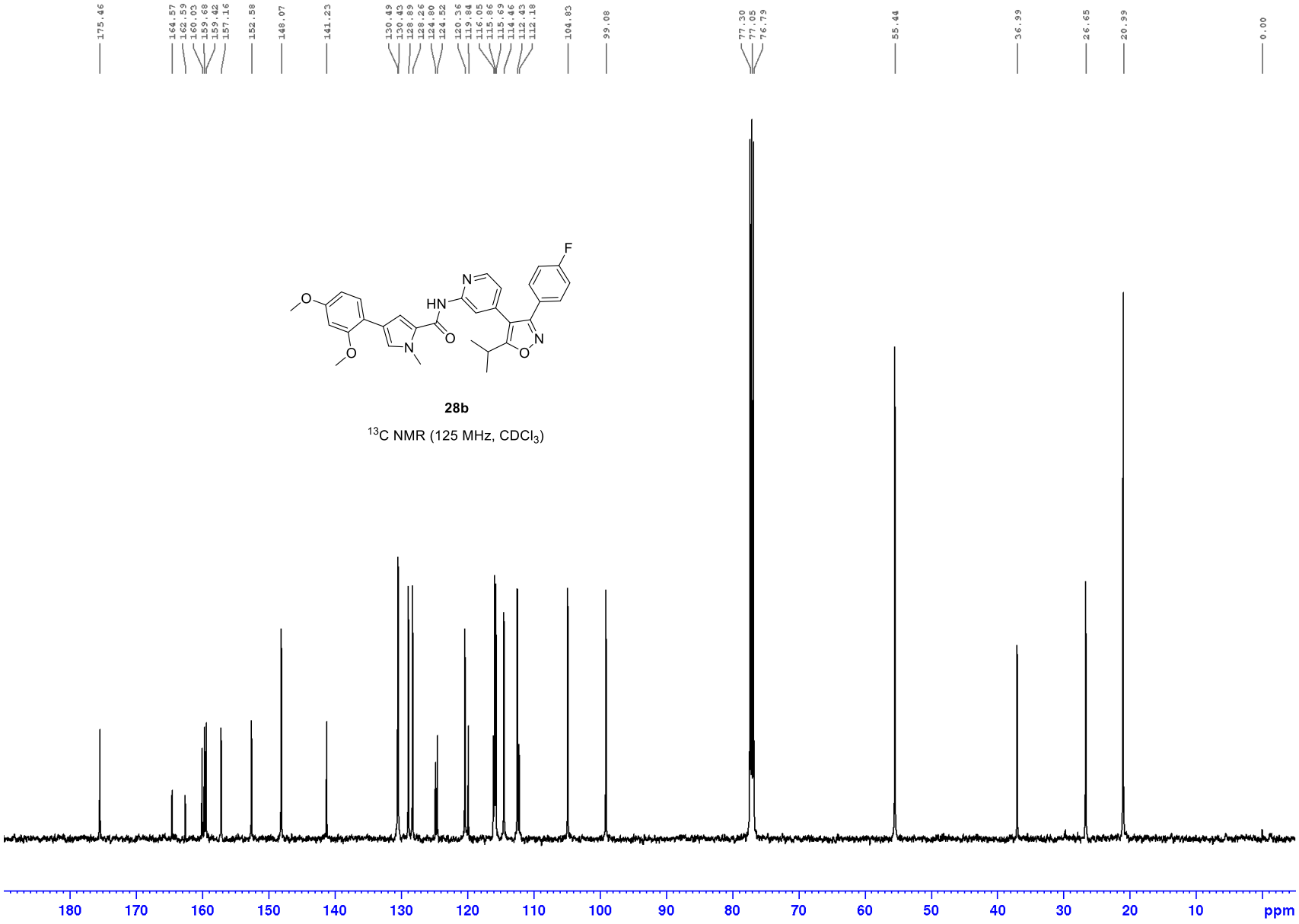


Lab: graham c Not signed STARe SW 9.20


8.09
8.08
7.73
7.72
7.56
7.54
7.53
7.52
7.51
7.51
7.50
7.46
7.45
7.44
7.43
7.42
7.42
7.41
7.41
7.26
6.58
6.57
6.57
6.56
6.56
6.55
3.97
3.91
3.85
1.60
0.00
27b
^{1}H NMR (500 MHz,$CDCl_3$)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
0.99
1.00
3.08
2.09
2.04
3.02
3.02
3.02

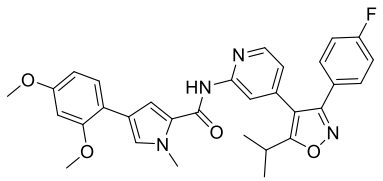

159.86
157.26
156.87
143.57
132.64
129.20
128.57
128.52
124.68
121.69
120.49
119.67
115.76
115.22
108.56
104.96
99.08
77.29
77.04
76.78
55.48
36.86
0.00
O
O
N
O
O
N
N
N
27b
^{13}C NMR (125 MHz,$CDCl_3$)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


8.51
8.28
8.24
8.23
7.45
7.44
7.43
7.42
7.37
7.36
7.26
7.23
7.14
7.04
7.03
7.01
6.73
6.72
6.54
6.53
6.52
3.99
3.89
3.83
3.30
3.28
3.27
3.26
3.24
3.23
3.21
1.40
1.38
0.00
F
N
HN
O
O
O
N
N
O
28b
1H NMR (500 MHz, CDCl3)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
0.97
1.00
1.02
2.01
1.03
1.00
1.01
2.04
1.00
2.03
3.02
3.00
3.02
1.04
6.26



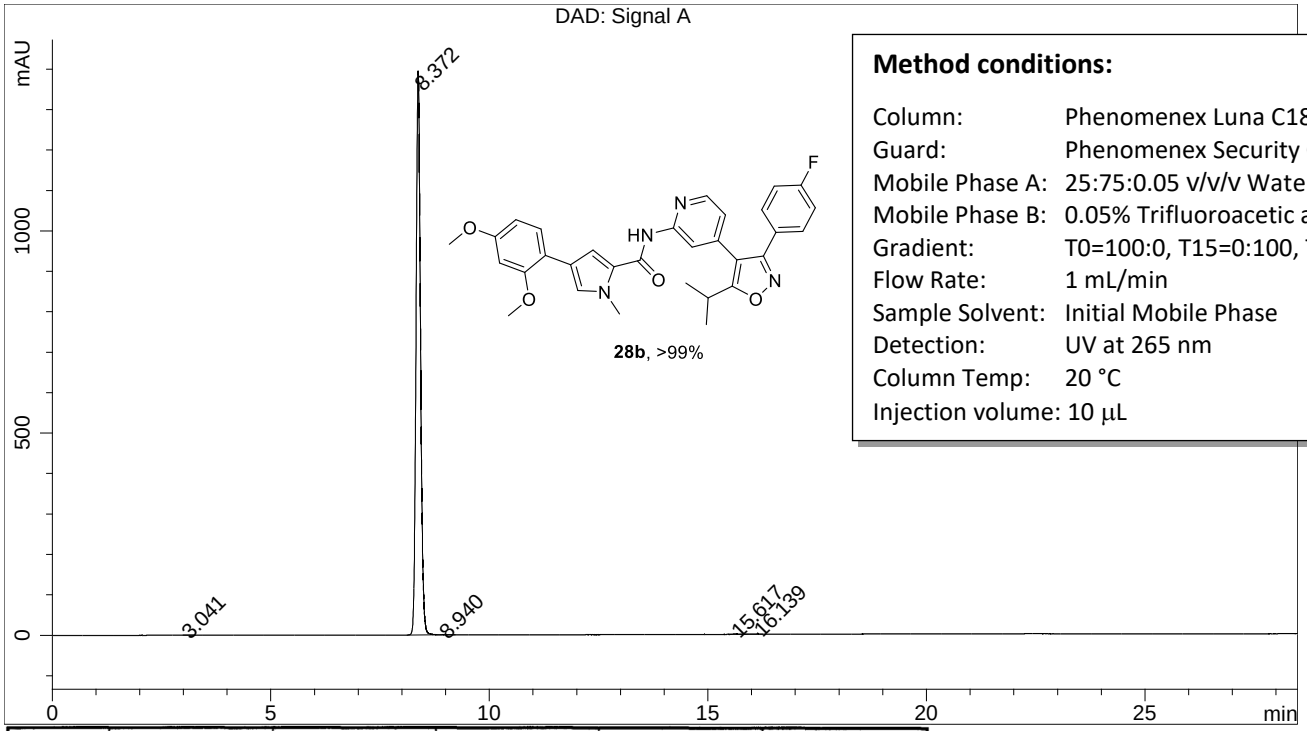
28b

^{13}C NMR (125 MHz, $CDCl_3$)



28b

^{19}F NMR (470 MHz, $CDCl_3$)

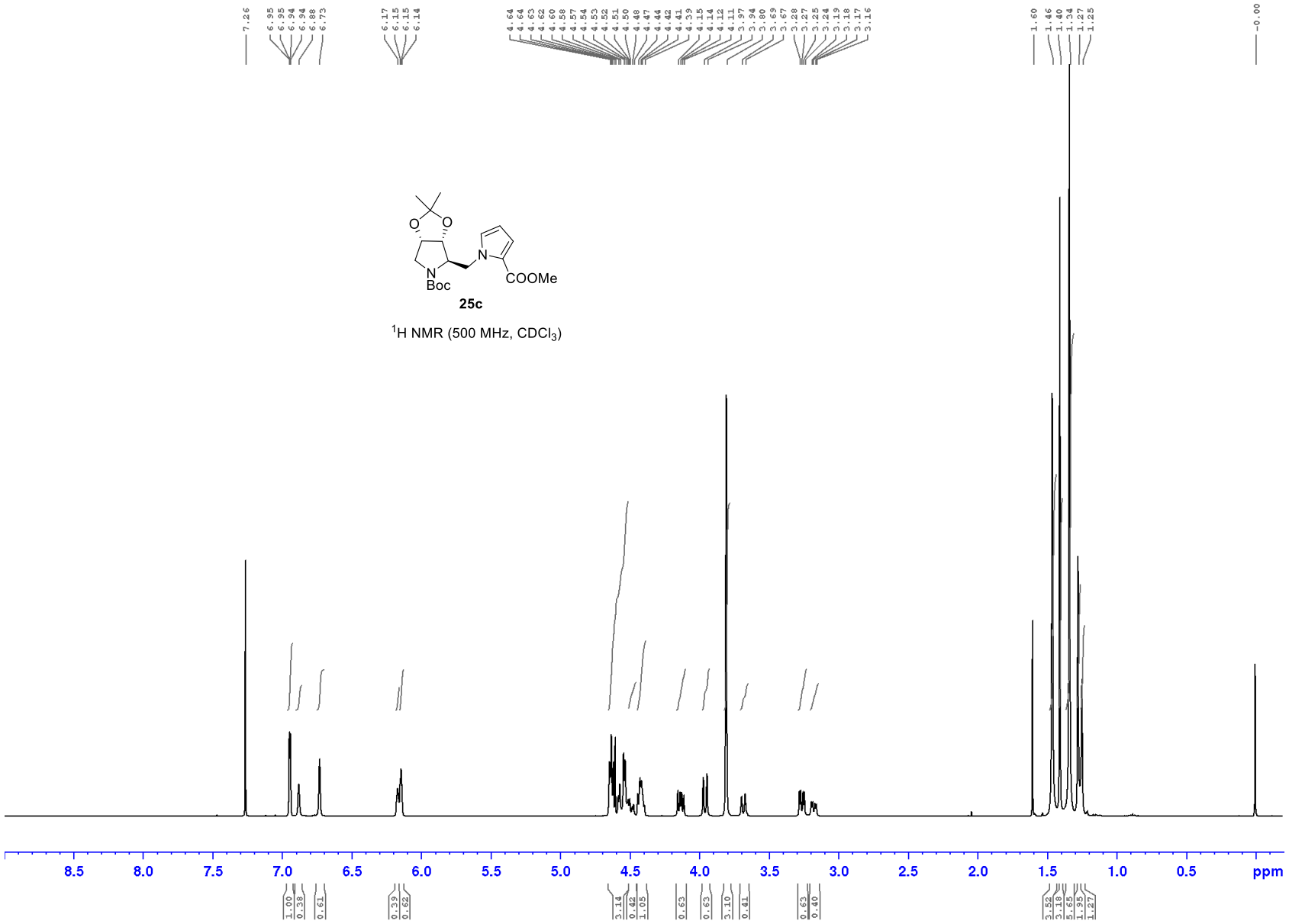


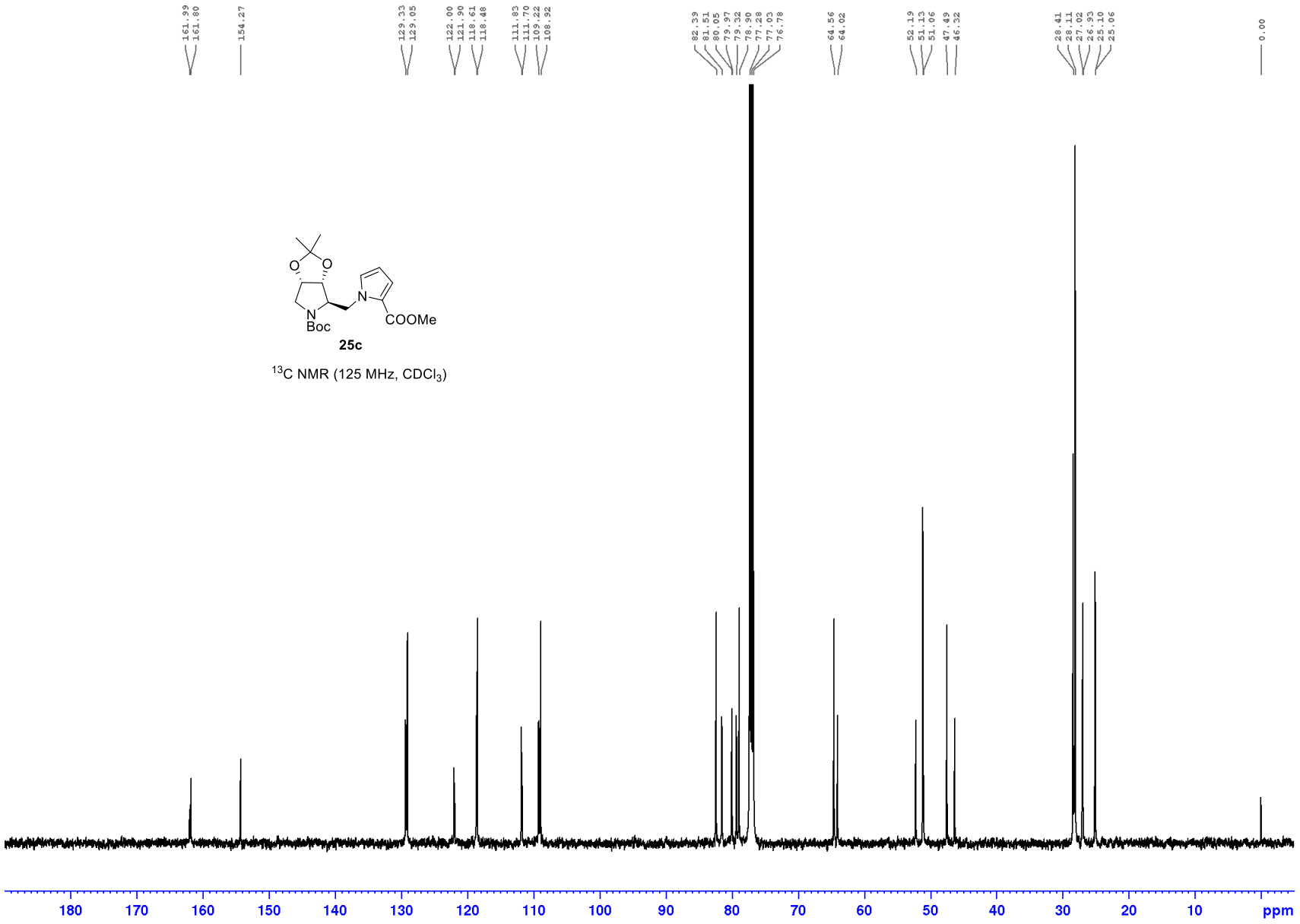
28b, >99%

Method conditions:

Column:	Phenomenex Luna C18(2) 5 μm 250x4.6 mm
Guard:	Phenomenex Security Guard C18 RP 4x3 mm
Mobile Phase A:	25:75:0.05 v/v/v Water/Acetonitrile/Trifluoroacetic acid
Mobile Phase B:	0.05% Trifluoroacetic acid in Acetonitrile
Gradient:	T0=100:0, T15=0:100, T25=0:100, T27=100:0, T30=100:0
Flow Rate:	1 mL/min
Sample Solvent:	Initial Mobile Phase
Detection:	UV at 265 nm
Column Temp:	20 °C
Injection volume:	10 μL

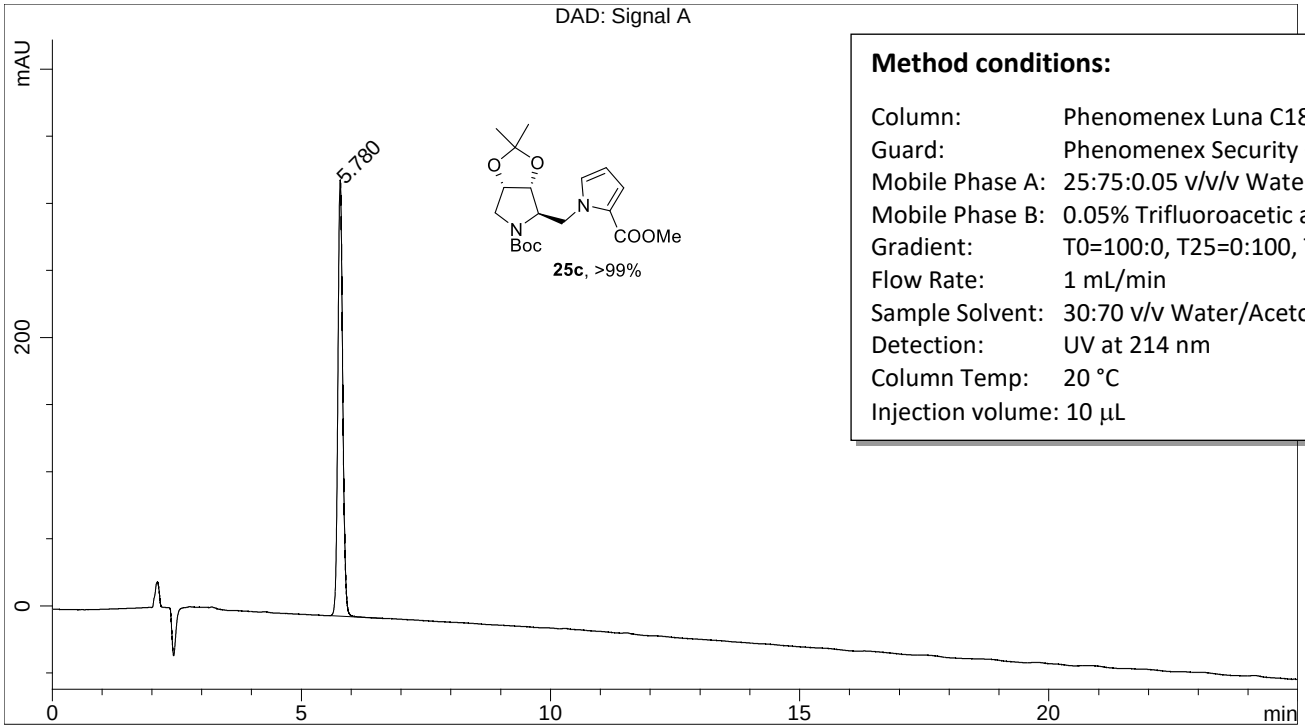
Peak#	RT	Peak Height	Peak Area	Width	Area %
1	3.04 min	0.4687	3.8309	0.1193 min	0.038 %
2	8.37 min	1389.5451	9946.2299	0.1115 min	99.712 %
3	8.94 min	0.7167	7.3591	0.1398 min	0.074 %
4	15.62 min	1.4388	11.2009	0.1148 min	0.112 %
5	16.14 min	2.6214	6.3085	0.0401 min	0.063 %


7.26
6.95
6.95
6.94
6.94
6.88
6.73
6.17
6.15
6.15
6.14
4.64
4.64
4.63
4.62
4.60
4.58
4.57
4.54
4.53
4.52
4.51
4.50
4.48
4.47
4.44
4.42
4.41
4.39
4.15
4.14
4.12
4.11
3.97
3.94
3.80
3.69
3.67
3.28
3.27
3.25
3.24
3.19
3.18
3.17
3.16
1.60
1.46
1.40
1.34
1.27
1.25
0.00
O
O
N
N
Boc
COOMe
25c
^{1}H NMR (500 MHz, $CDCl_3$)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
0.38
0.61
0.39
0.62
3.14
0.42
1.05
0.63
0.63
3.10
0.41
0.63
0.40
3.52
3.18
5.65
1.95
1.27



25c

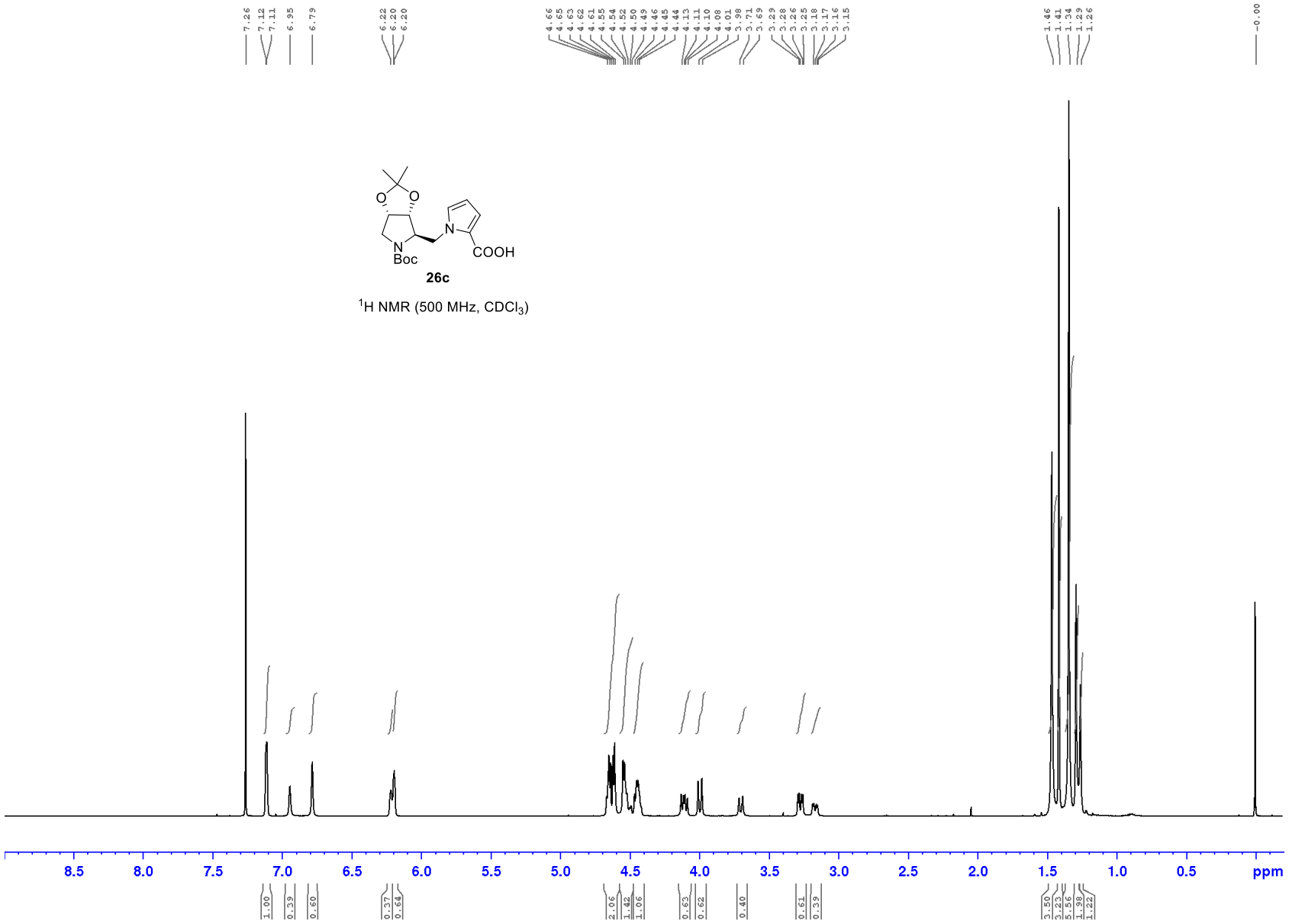
^{13}C NMR (125 MHz, $CDCl_3$)



Method conditions:

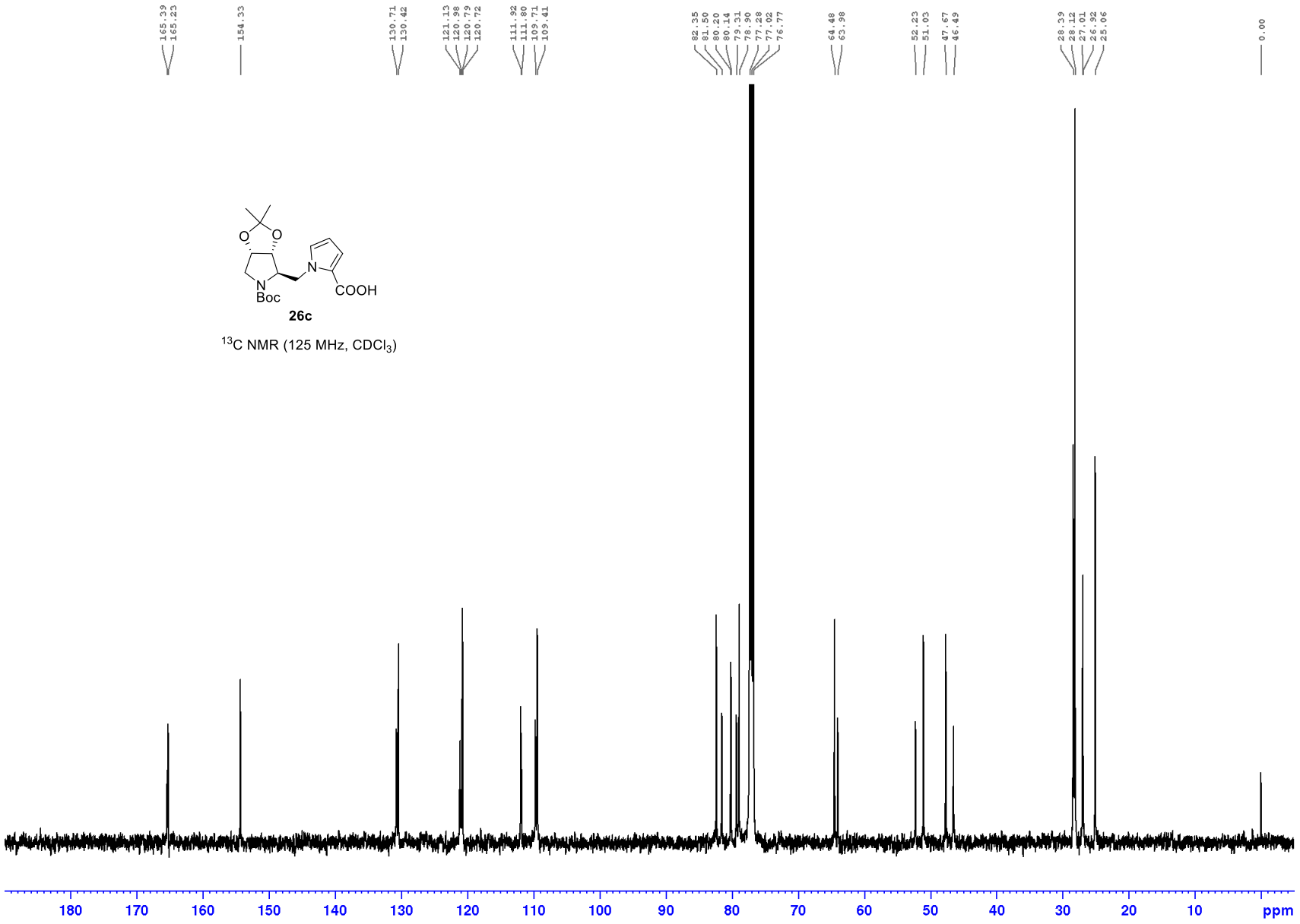
Column:	Phenomenex Luna C18(2) 5 µm 250x4.6 mm
Guard:	Phenomenex Security Guard C18 RP 4x3 mm
Mobile Phase A:	25:75:0.05 v/v/v Water/Acetonitrile/Trifluoroacetic acid
Mobile Phase B:	0.05% Trifluoroacetic acid in Acetonitrile
Gradient:	T0=100:0, T25=0:100, T27=100:0, T30=100:0
Flow Rate:	1 mL/min
Sample Solvent:	30:70 v/v Water/Acetonitrile
Detection:	UV at 214 nm
Column Temp:	20 °C
Injection volume:	10 µL

Peak#	RT	Peak Height	Peak Area	Width	Area %
1	5.78 min	325.2087	2212.8561	0.1054 min	100.000 %



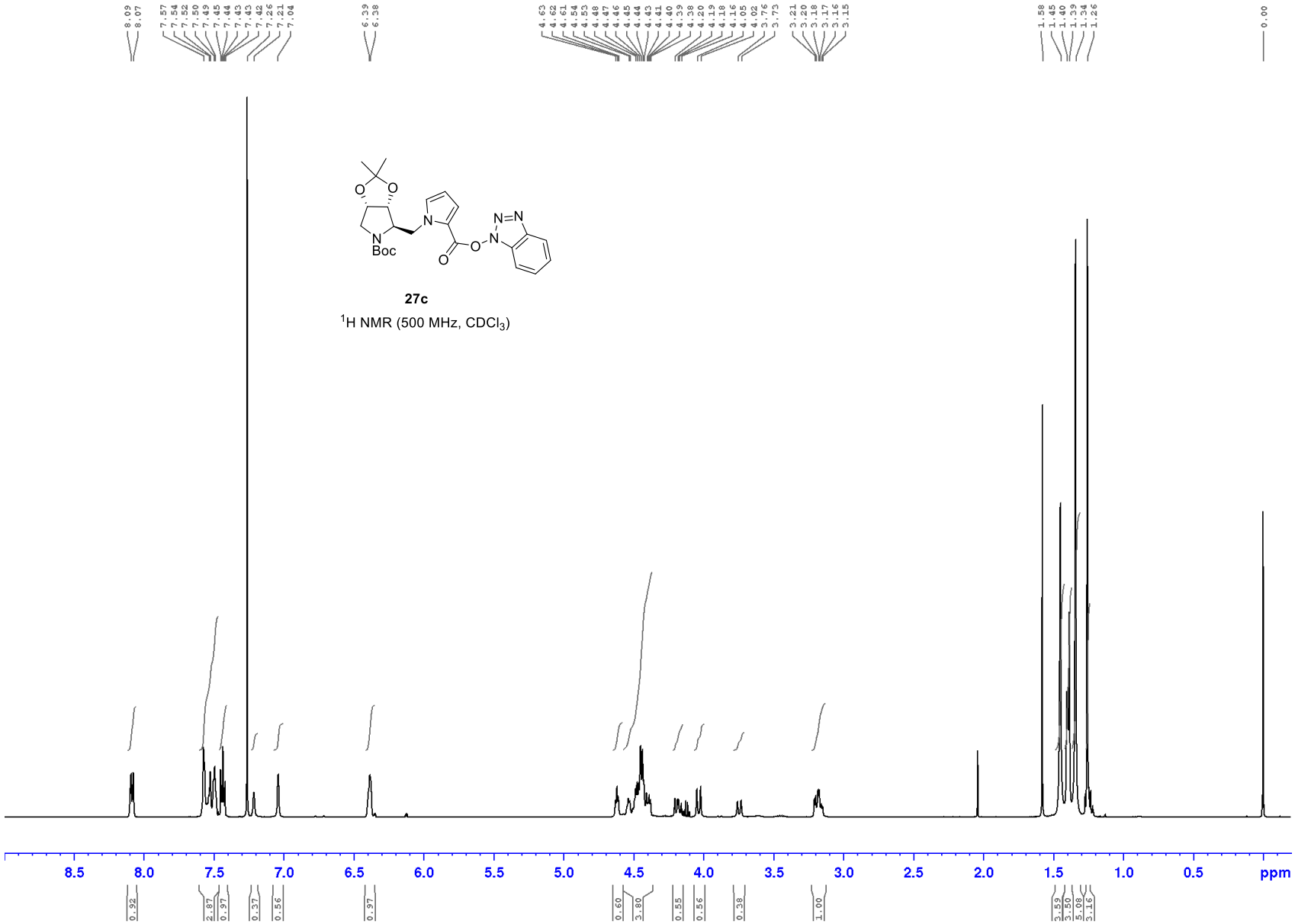
26c

^{1}H NMR (500 MHz, $CDCl_3$)



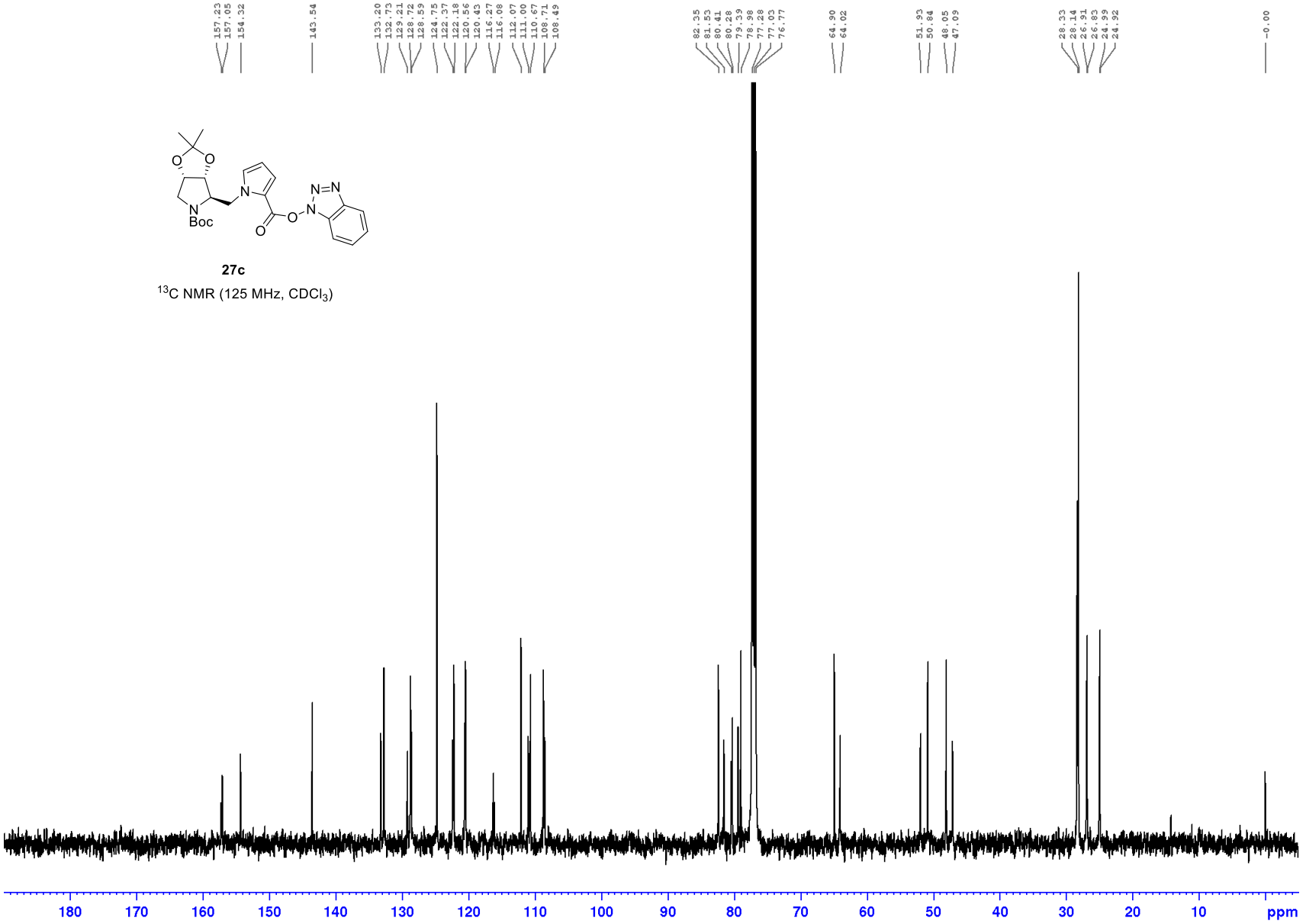
26c

^{13}C NMR (125 MHz, $CDCl_3$)



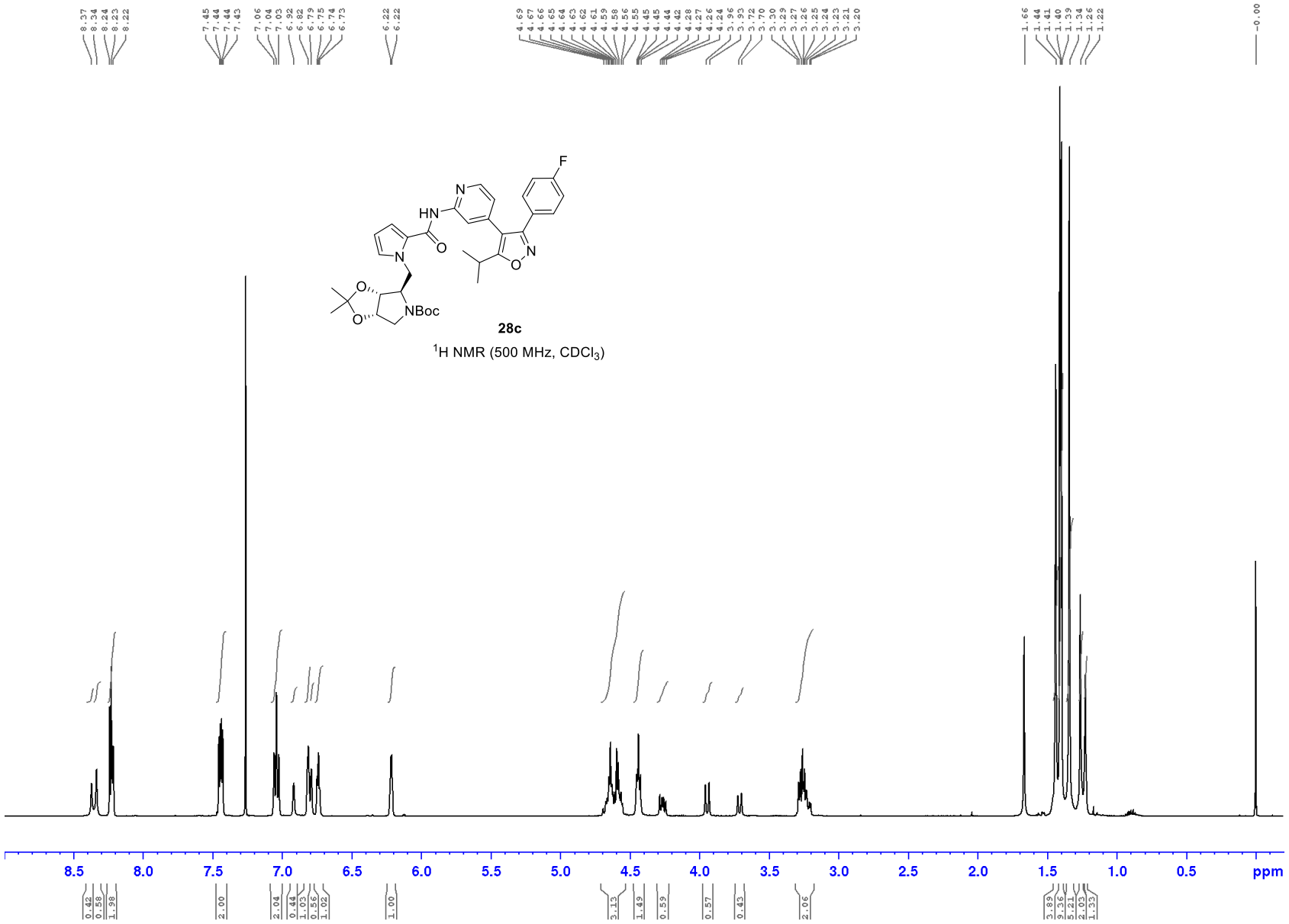
27c

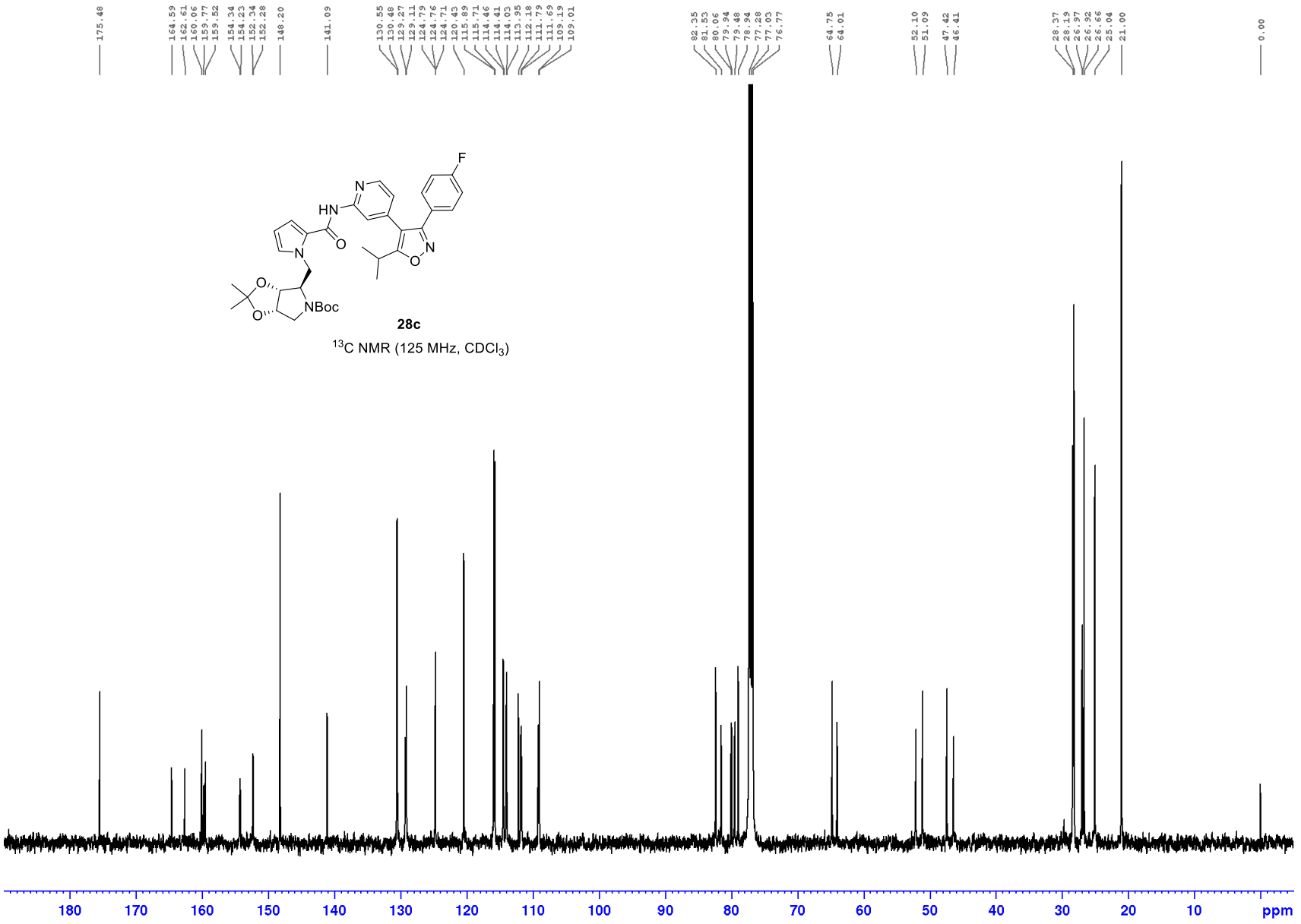
^{1}H NMR (500 MHz, $CDCl_3$)

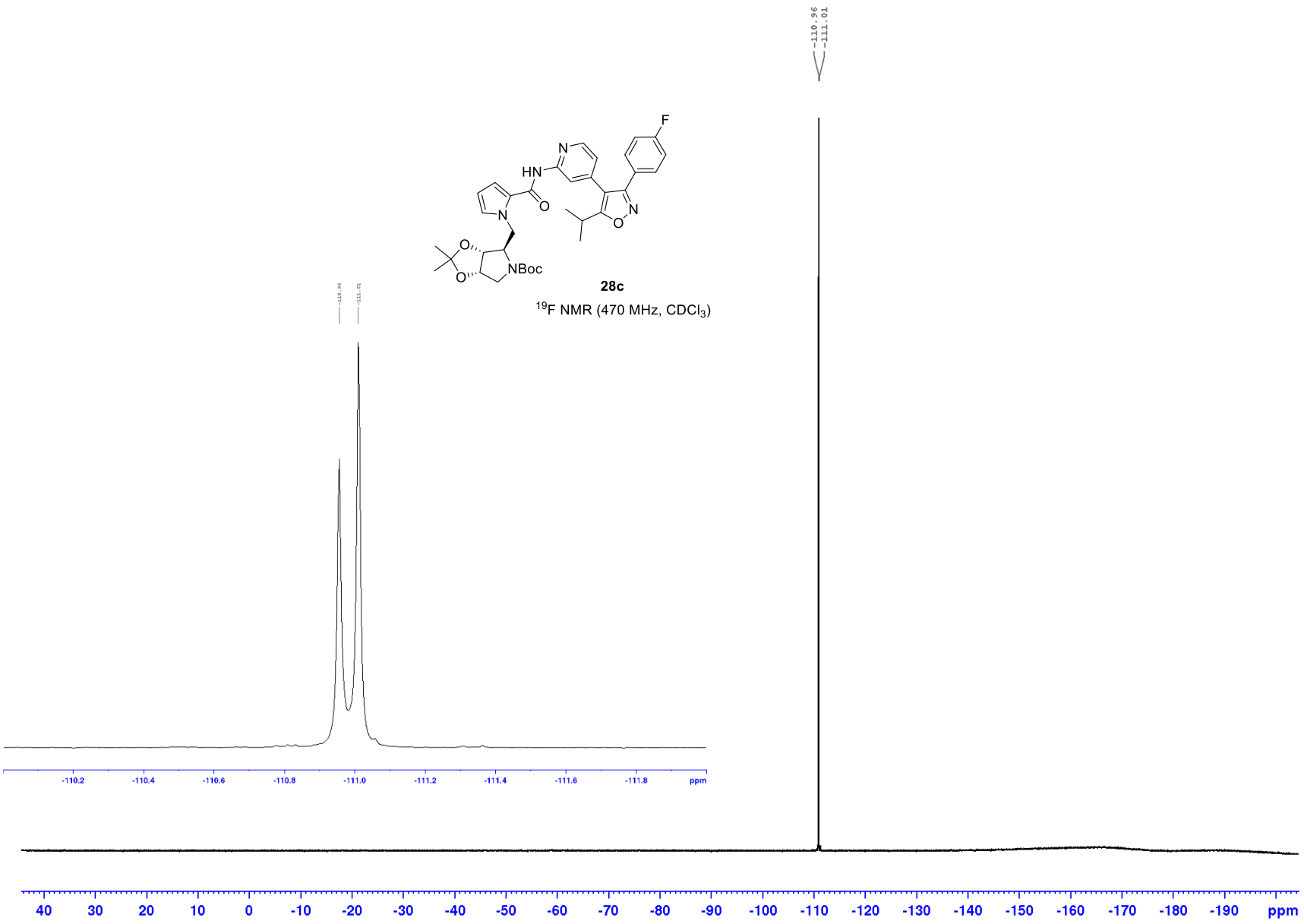


27c

^{13}C NMR (125 MHz, $CDCl_3$)

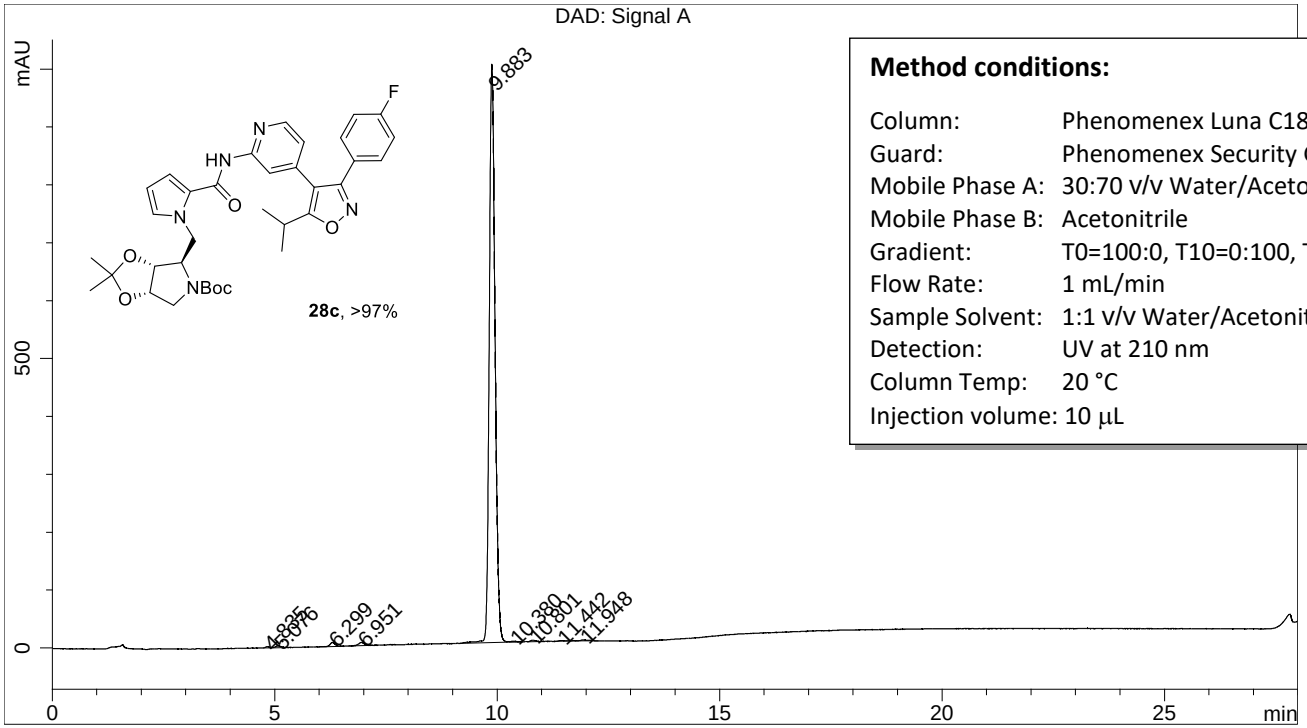

8.37
8.34
8.24
8.23
8.22
7.45
7.44
7.44
7.43
7.06
7.04
7.03
6.92
6.82
6.79
6.75
6.74
6.73
6.22
6.22
4.69
4.67
4.66
4.65
4.64
4.63
4.62
4.61
4.59
4.58
4.56
4.55
4.45
4.44
4.42
4.28
4.27
4.26
4.24
3.96
3.93
3.72
3.70
3.30
3.29
3.27
3.26
3.25
3.24
3.23
3.21
3.20
1.66
1.44
1.41
1.40
1.39
1.34
1.26
1.22
0.00
F
N
HN
O
N
O
N
O
O
NBoc
28c
^{1}H NMR (500 MHz, $CDCl_3$)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
0.42
0.58
1.98
2.00
2.04
0.44
1.03
0.56
1.02
1.00
3.13
1.49
0.59
0.57
0.43
2.06
3.89
9.36
5.21
2.03
1.33


175.48
164.59
162.61
160.06
159.77
159.52
154.34
154.23
152.34
152.28
148.20
141.09
130.55
130.48
129.27
129.11
124.79
124.76
124.71
120.43
115.89
115.71
114.46
114.41
114.03
113.95
112.18
111.79
111.69
109.19
109.01
82.35
81.53
80.06
79.94
79.48
78.94
77.28
77.03
76.77
64.75
64.01
52.10
51.09
47.42
46.41
28.37
28.19
26.97
26.92
26.66
25.04
21.00
0.00
F
N
HN
O
N
N
O
O
O
NBoc
28c
13C NMR (125 MHz, CDCl3)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm



28c

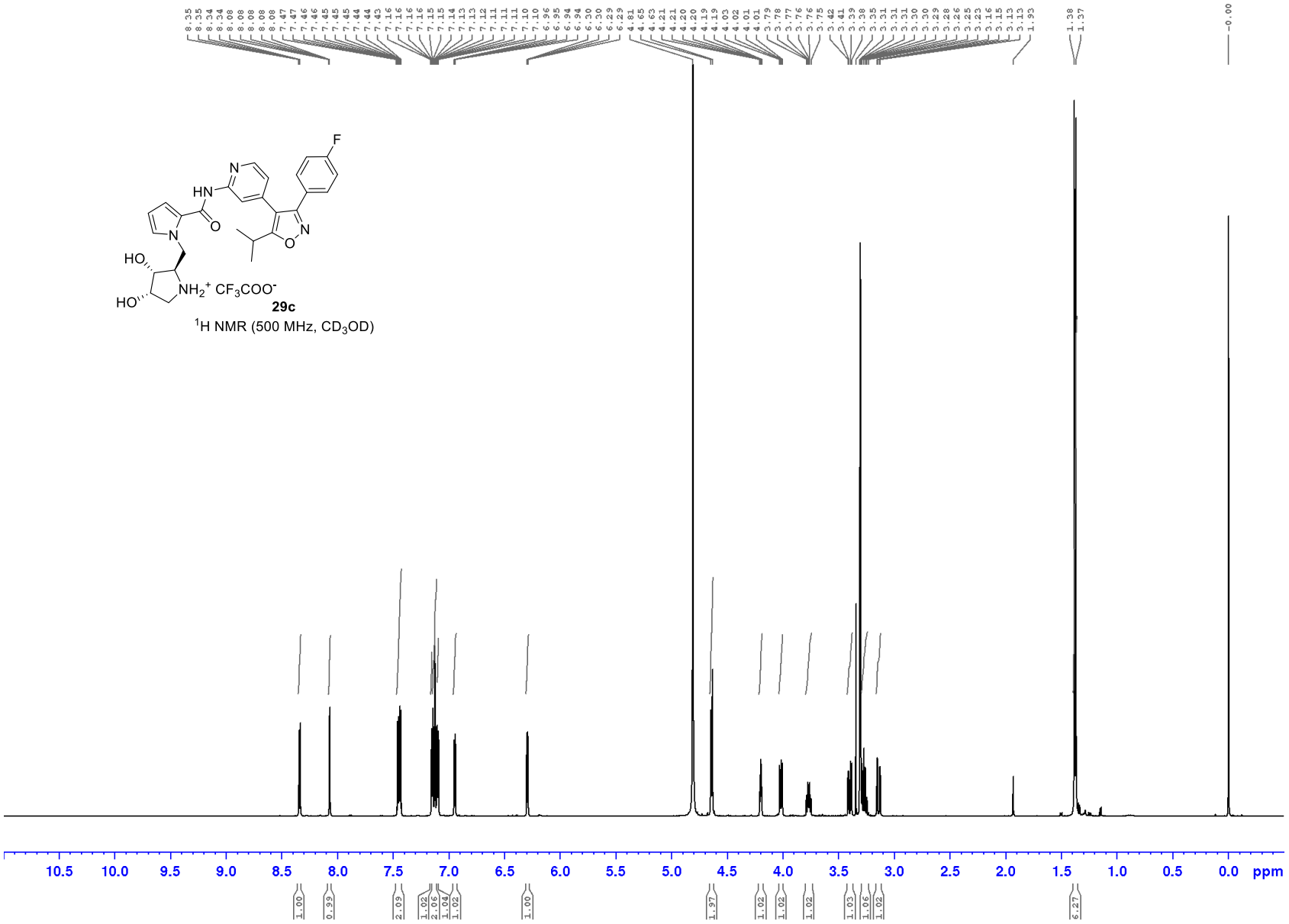
^{19}F NMR (470 MHz, $CDCl_3$)

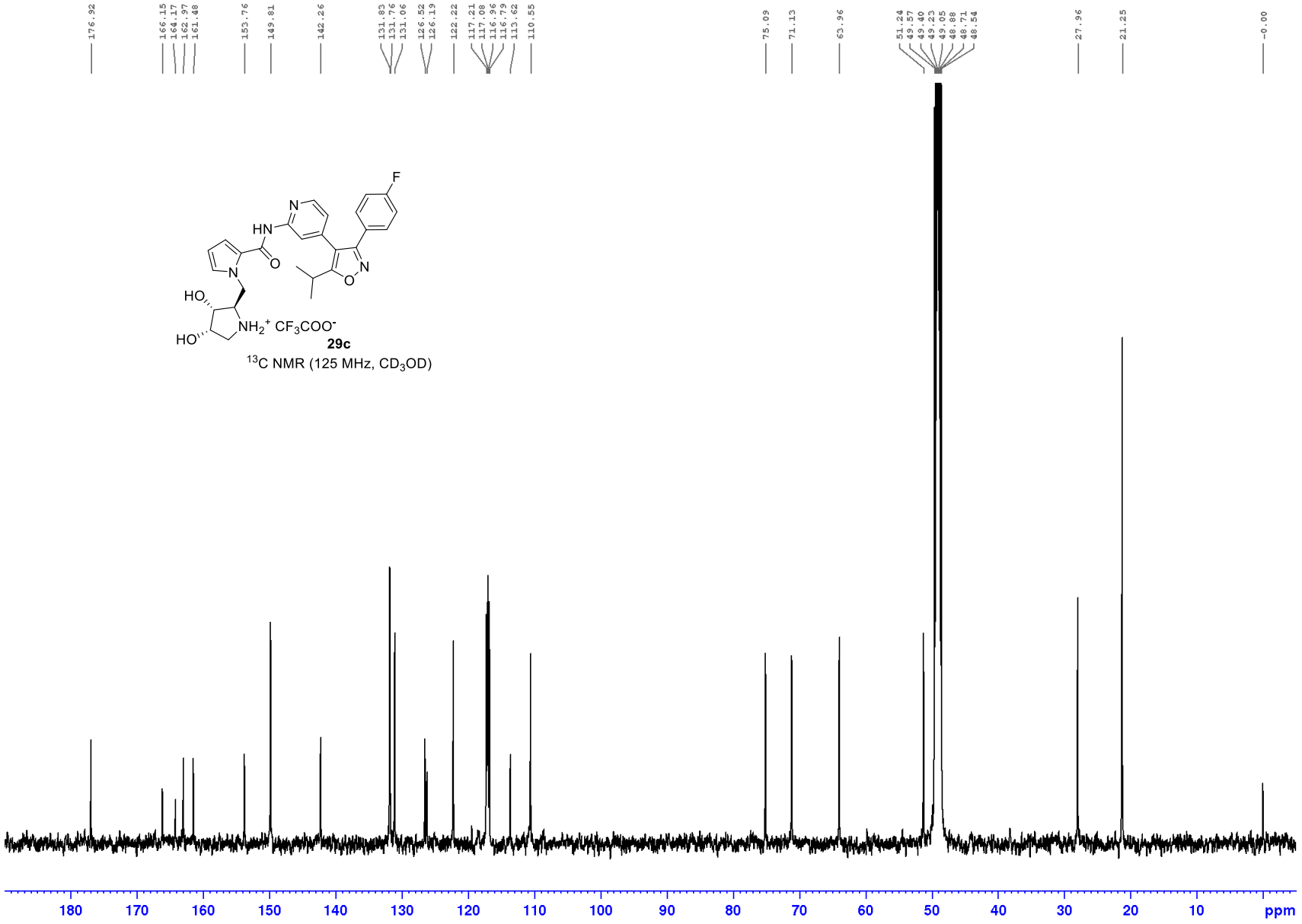


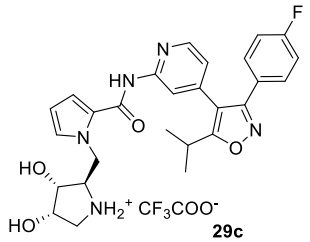
Method conditions:

Column:	Phenomenex Luna C18(2) 5 μm 250x4.6 mm
Guard:	Phenomenex Security Guard C18 RP 4x3 mm
Mobile Phase A:	30:70 v/v Water/Acetonitrile
Mobile Phase B:	Acetonitrile
Gradient:	T0=100:0, T10=0:100, T25=0:100, T26=100:0, T30=100:0
Flow Rate:	1 mL/min
Sample Solvent:	1:1 v/v Water/Acetonitrile
Detection:	UV at 210 nm
Column Temp:	20 °C
Injection volume:	10 μL

Peak#	RT	Peak Height	Peak Area	Width	Area %
1	4.83 min	2.3223	14.7241	0.0980 min	0.158 %
2	5.08 min	3.4751	31.9179	0.1292 min	0.343 %
3	6.30 min	6.9134	61.4995	0.1318 min	0.661 %
4	6.95 min	5.7545	58.5387	0.1447 min	0.629 %
5	9.88 min	998.8265	9064.9607	0.1399 min	97.416 %
6	10.38 min	1.4228	11.7902	0.1147 min	0.127 %
7	10.80 min	2.4543	22.0884	0.1290 min	0.237 %
8	11.44 min	1.2435	10.5461	0.1089 min	0.113 %
9	11.95 min	1.9822	29.3470	0.1847 min	0.315 %

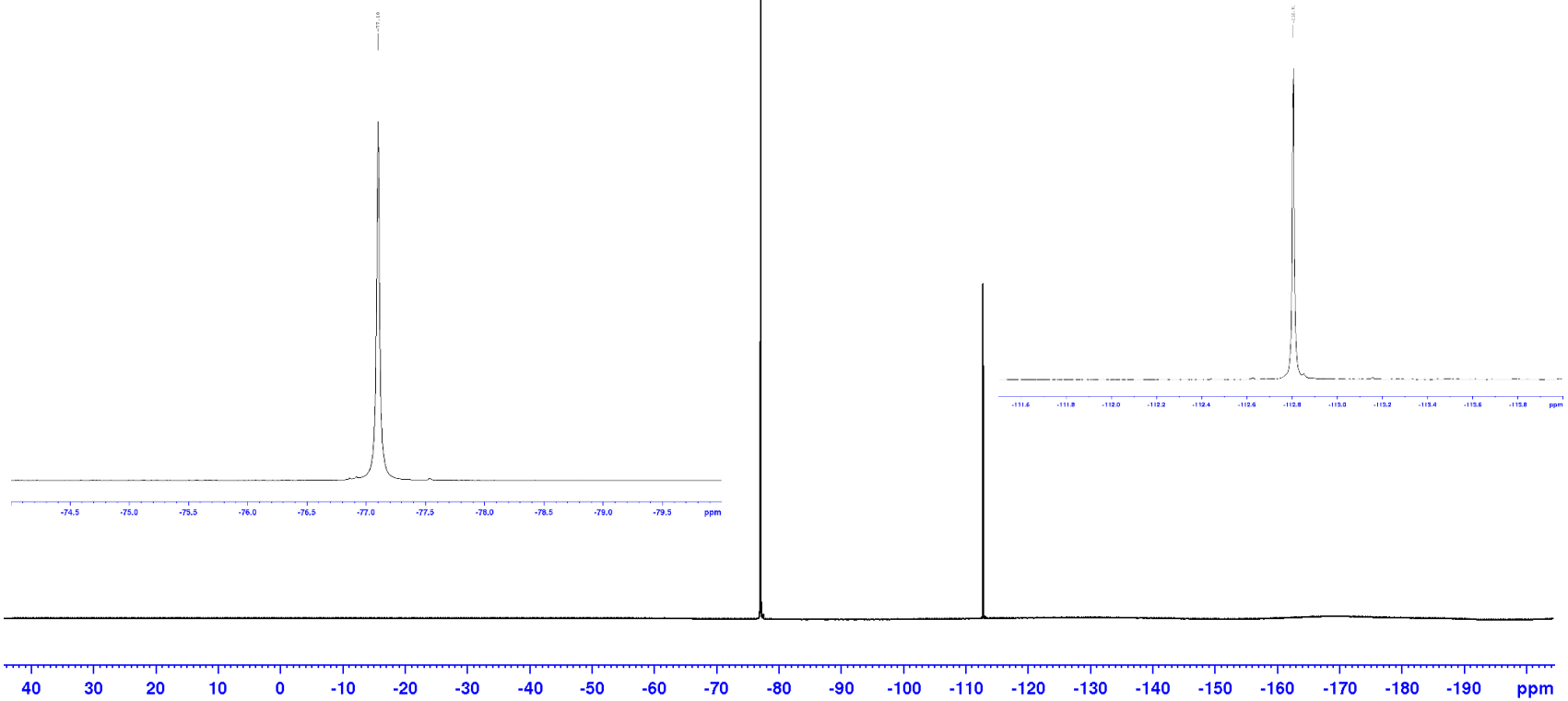

F
N
HN
O
N
O
N
HO
HO
NH2+ CF3COO-
29c
1H NMR (500 MHz, CD3OD)
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.00 0.99 2.09 1.02 2.06 1.04 1.02 1.00 1.97 1.02 1.02 1.02 1.03 1.06 1.02 6.27

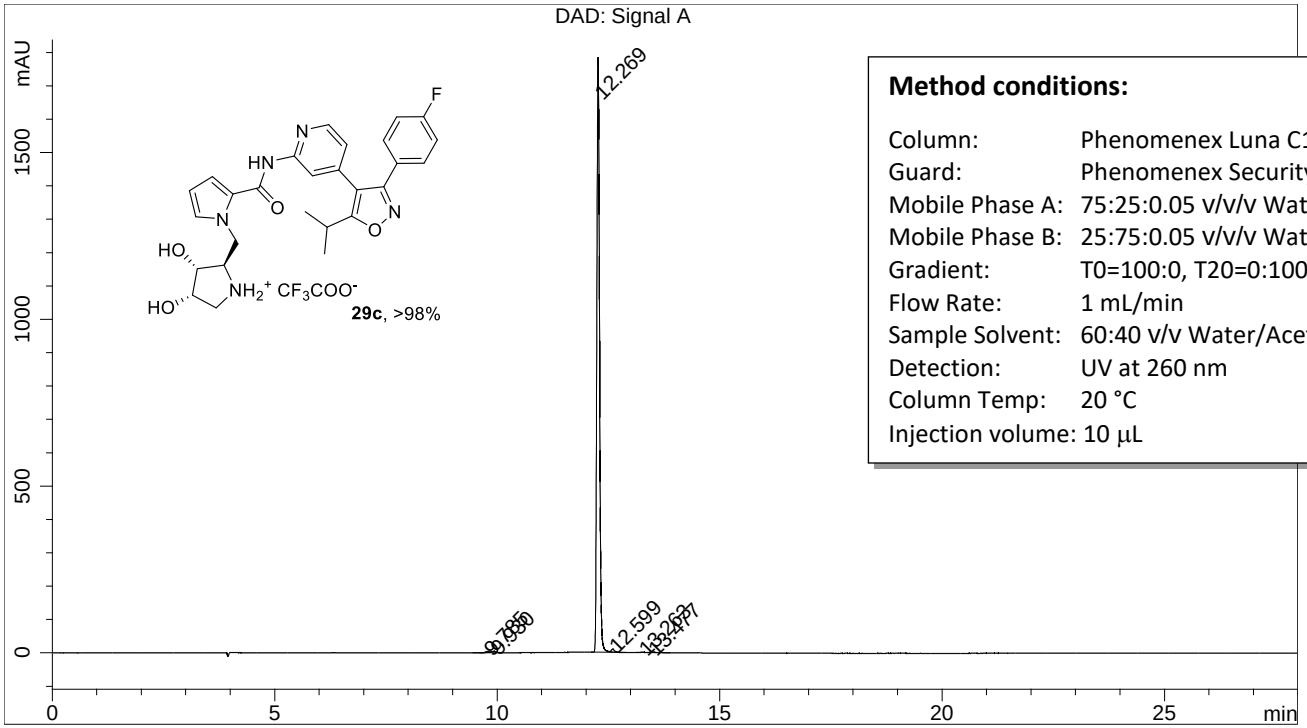

176.92
166.15
164.17
162.97
161.48
153.76
149.81
142.26
131.83
131.76
131.06
126.52
126.19
122.22
117.21
117.08
116.96
116.79
113.62
110.55
75.09
71.13
63.96
51.24
49.57
49.40
49.23
49.05
48.88
48.71
48.54
27.96
21.25
-0.00
F
N
HN
O
N
N
O
HO
HO
NH2+ CF3COO-
29c
13C NMR (125 MHz, CD3OD)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm



29c

^{19}F NMR (470 MHz, CD_3OD)

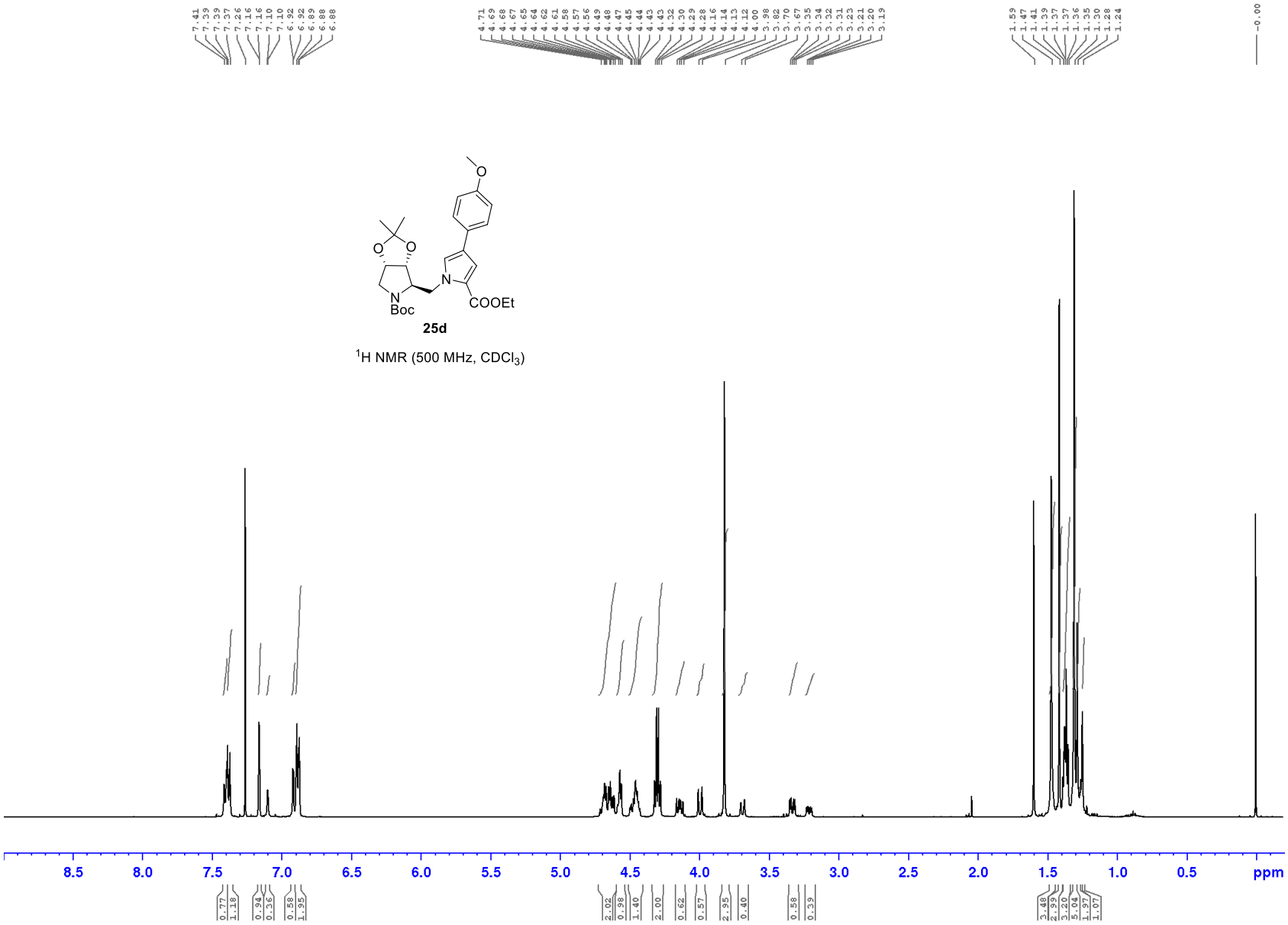


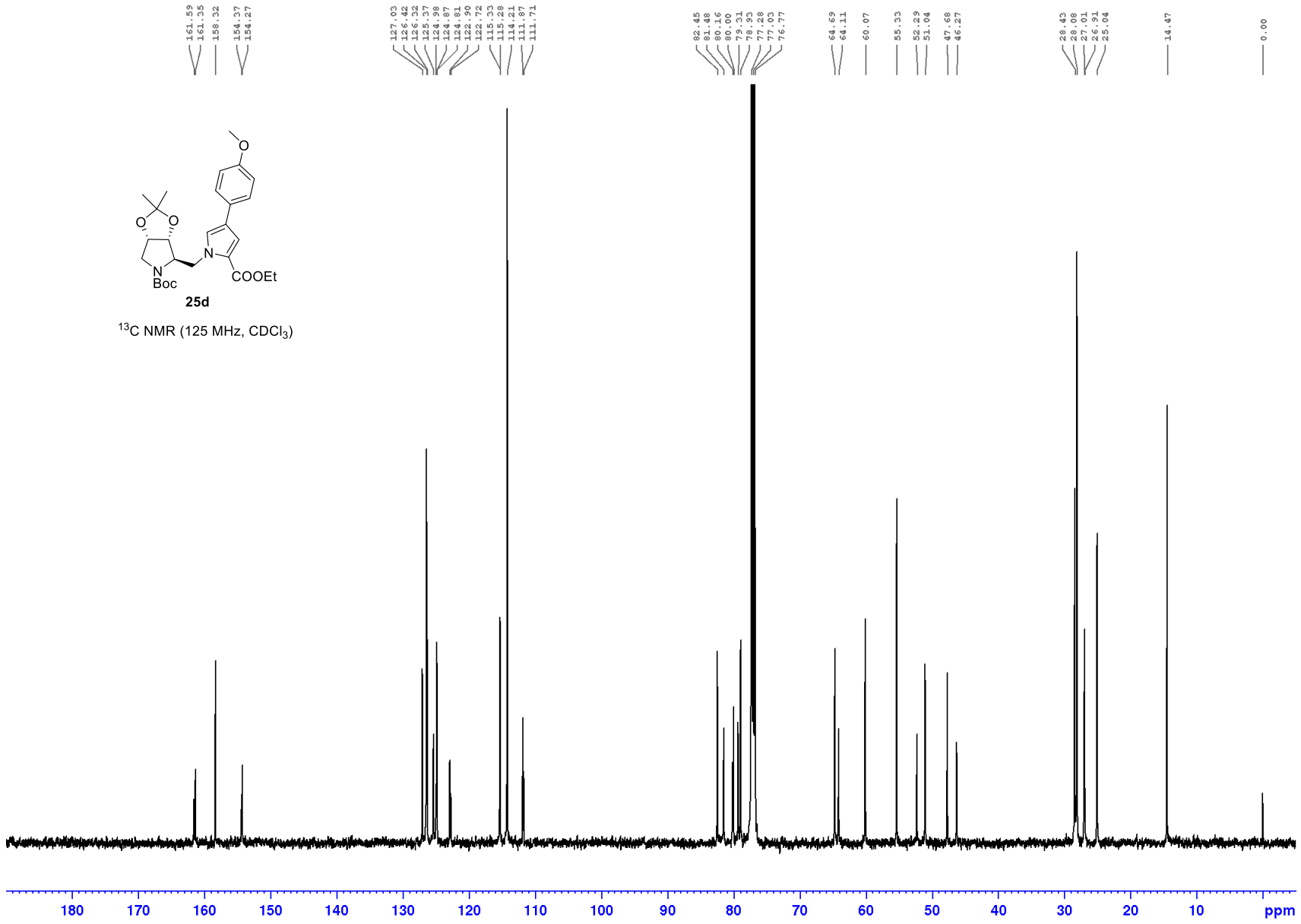


Method conditions:

Column:	Phenomenex Luna C18(2) 5 μm 250x4.6 mm
Guard:	Phenomenex Security Guard C18 RP 4x3 mm
Mobile Phase A:	75:25:0.05 v/v/v Water/Acetonitrile/Trifluoroacetic acid
Mobile Phase B:	25:75:0.05 v/v/v Water/Acetonitrile/Trifluoroacetic acid
Gradient:	T0=100:0, T20=0:100, T26=0:100, T27=100:0, T30=100:0
Flow Rate:	1 mL/min
Sample Solvent:	60:40 v/v Water/Acetonitrile
Detection:	UV at 260 nm
Column Temp:	20 °C
Injection volume:	10 μL

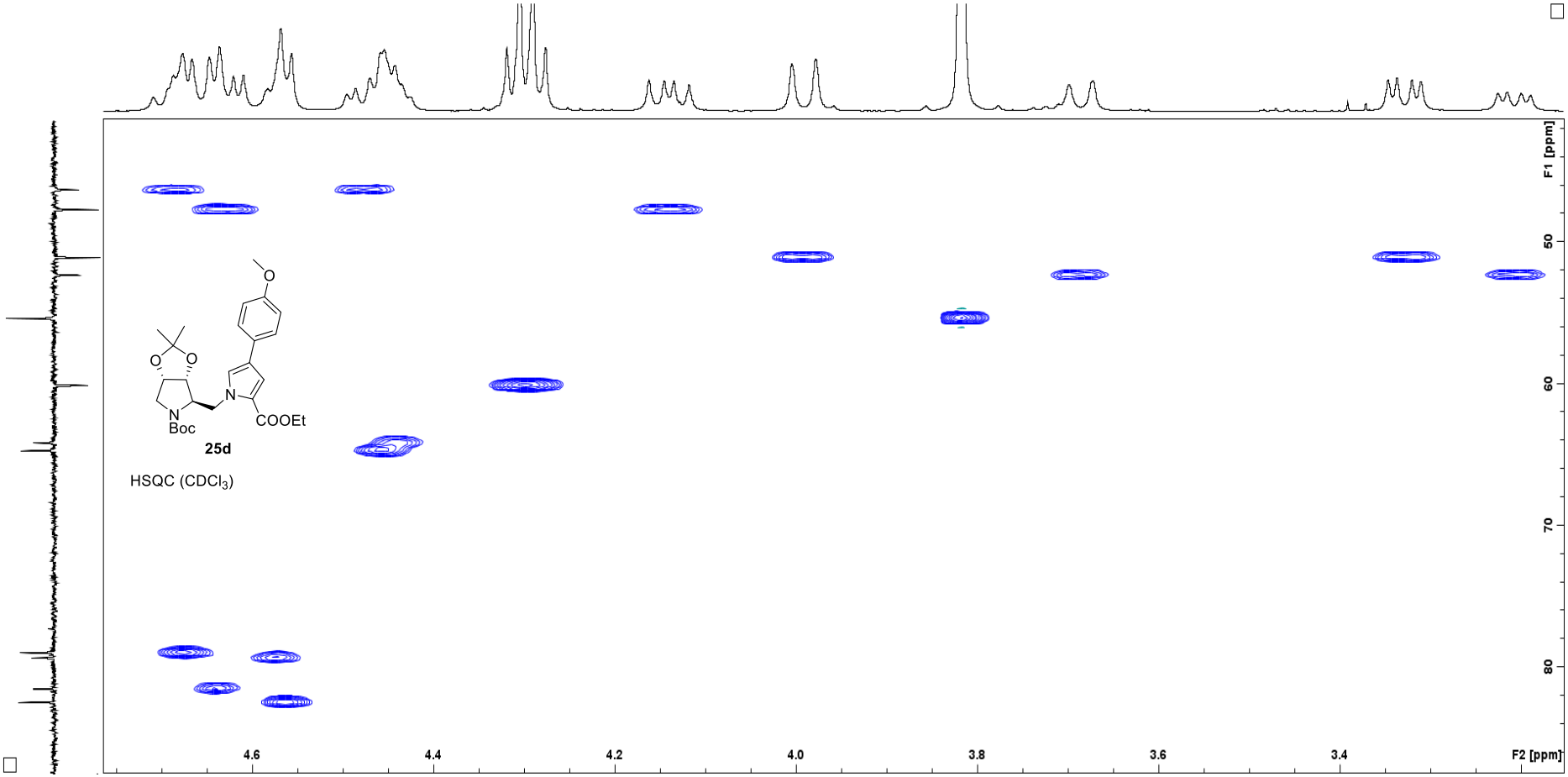
Peak#	RT	Peak Height	Peak Area	Width	Area %
1	9.78 min	3.3588	21.7818	0.0997 min	0.285 %
2	9.93 min	4.2122	32.2209	0.1092 min	0.422 %
3	12.27 min	1769.7216	7532.3801	0.0697 min	98.550 %
4	12.60 min	9.1386	46.6471	0.0796 min	0.610 %
5	13.26 min	1.4128	10.1541	0.1079 min	0.133 %

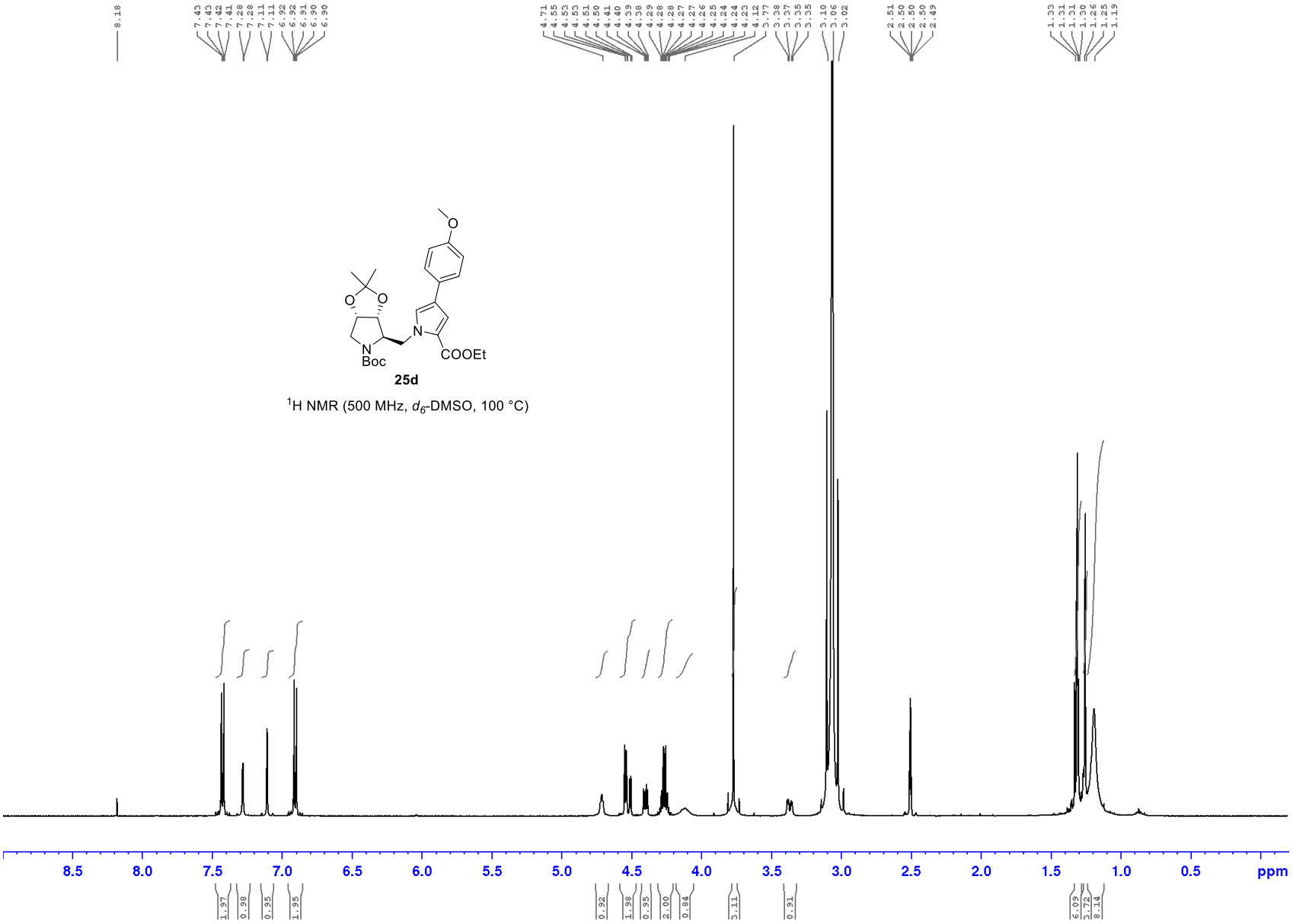

7.41
7.39
7.39
7.37
7.26
7.16
7.16
7.10
7.10
6.92
6.92
6.89
6.88
6.88
4.71
4.69
4.68
4.67
4.65
4.64
4.62
4.61
4.58
4.57
4.56
4.49
4.48
4.47
4.45
4.44
4.43
4.32
4.30
4.29
4.28
4.16
4.14
4.13
4.12
4.00
3.98
3.82
3.70
3.67
3.35
3.34
3.32
3.31
3.23
3.21
3.20
3.19
1.59
1.47
1.41
1.39
1.37
1.37
1.36
1.35
1.30
1.28
1.24
-0.00
O
O
O
N
N
Boc
COOEt
25d
^{1}H NMR (500 MHz, $CDCl_3$)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
0.77
1.18
0.94
0.36
0.58
1.95
2.02
0.98
1.40
2.00
0.62
0.57
2.95
0.40
0.58
0.39
3.48
2.99
3.20
5.04
1.97
1.07



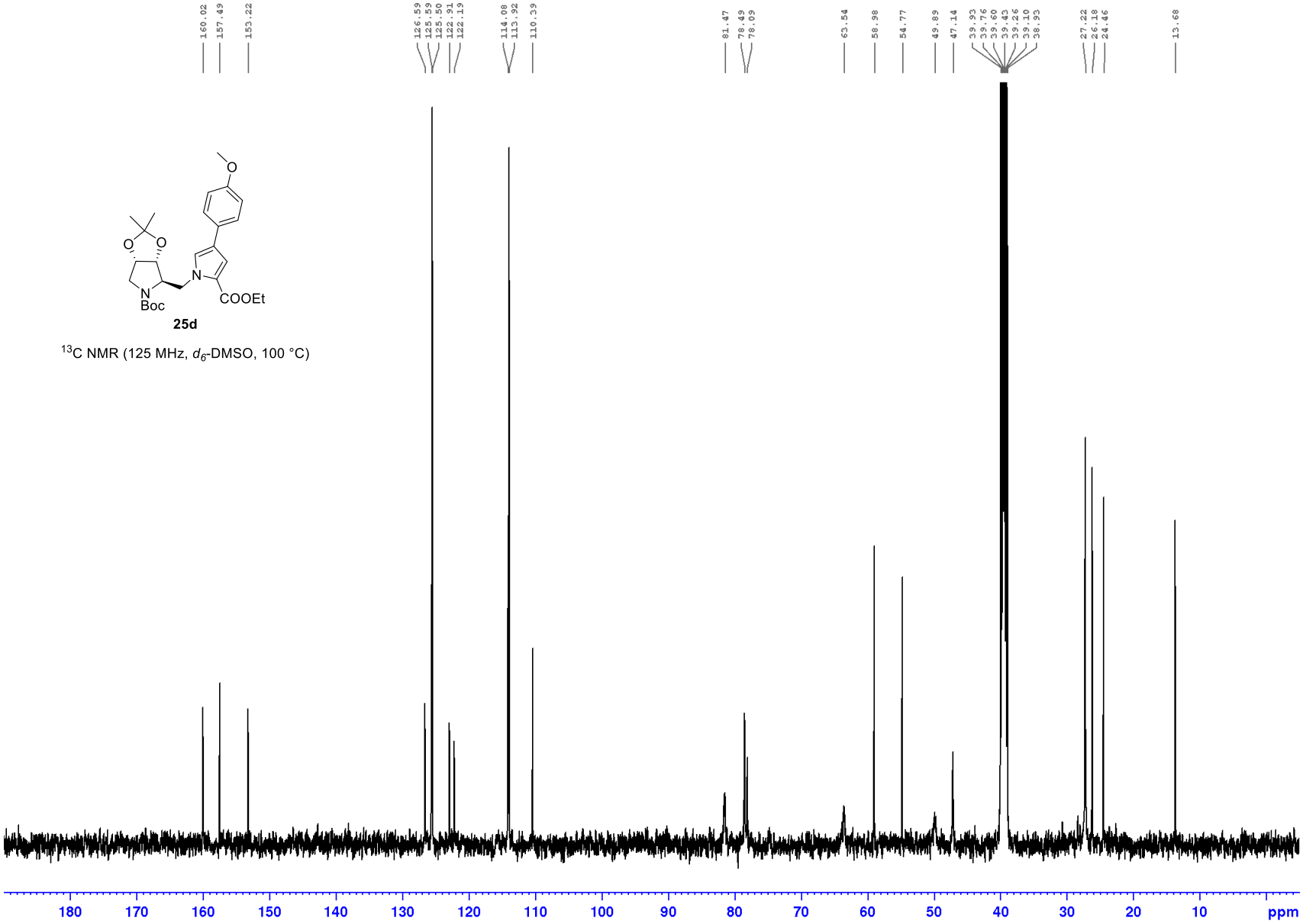
25d

^{13}C NMR (125 MHz, $CDCl_3$)


O
O
O
N
N
Boc
COOEt
25d
HSQC ($CDCl_3$)
F1 [ppm]
50
60
70
80
4.6
4.4
4.2
4.0
3.8
3.6
3.4
F2 [ppm]



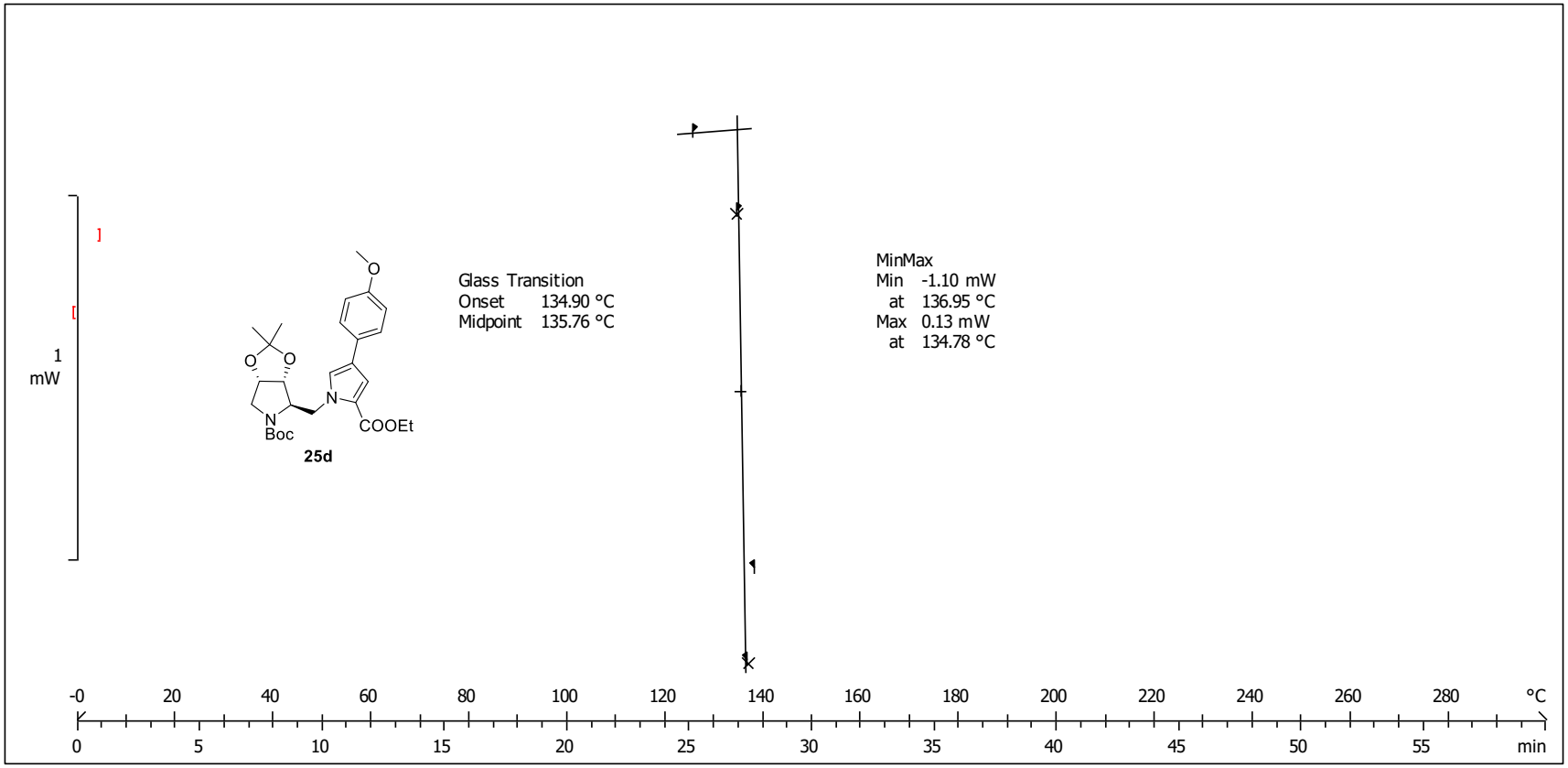
^{1}H NMR (500 MHz, d_6-DMSO, 100 °C)



25d

^{13}C NMR (125 MHz, d_6-DMSO, 100 °C)

^exo



Lab: graham c Not signed STARe SW 9.20

Method conditions:

Column: Regis, Pirkle Covalent, (*S*,*S*) Whelk-01, 10/100 Kromasil FEC 250x4.6 mm

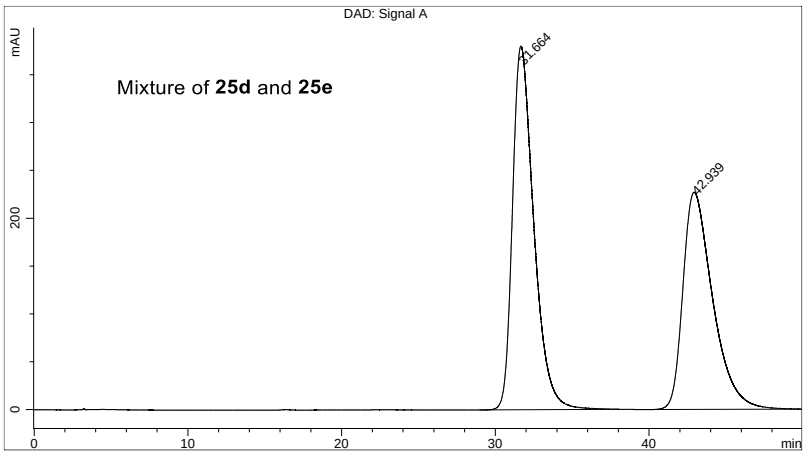
Guard: Phenomenex Security Guard CN 4x3 mm

Mobile Phase: 90:10 v/v *n*-Hexane/2-Propanol

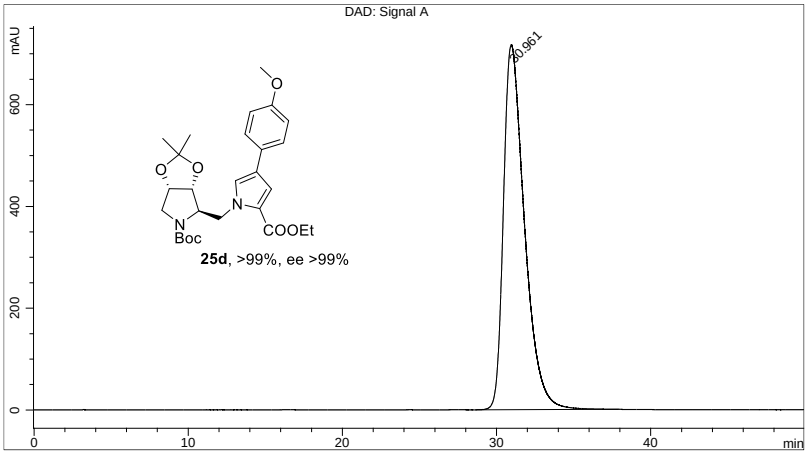
Flow Rate: 1 mL/min, Detection: UV 252 nm, Column Temp: 20 °C, Injection volume: 10 μL

Sample Solvent: 80:20 v/v *n*-Hexane/2-Propanol

I.

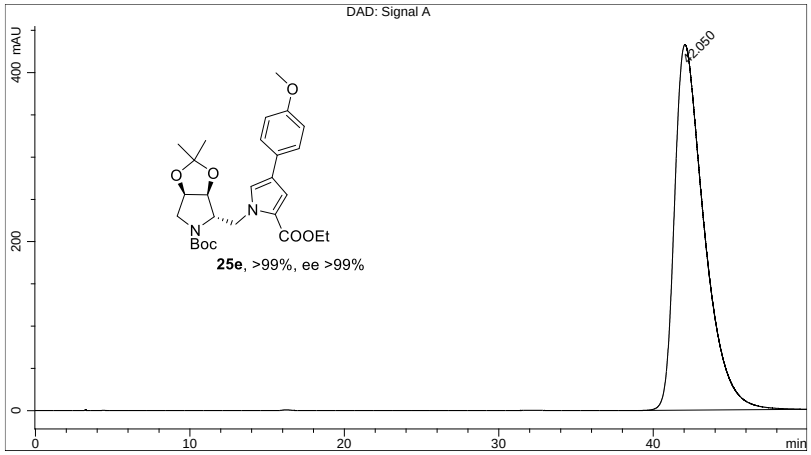


II.

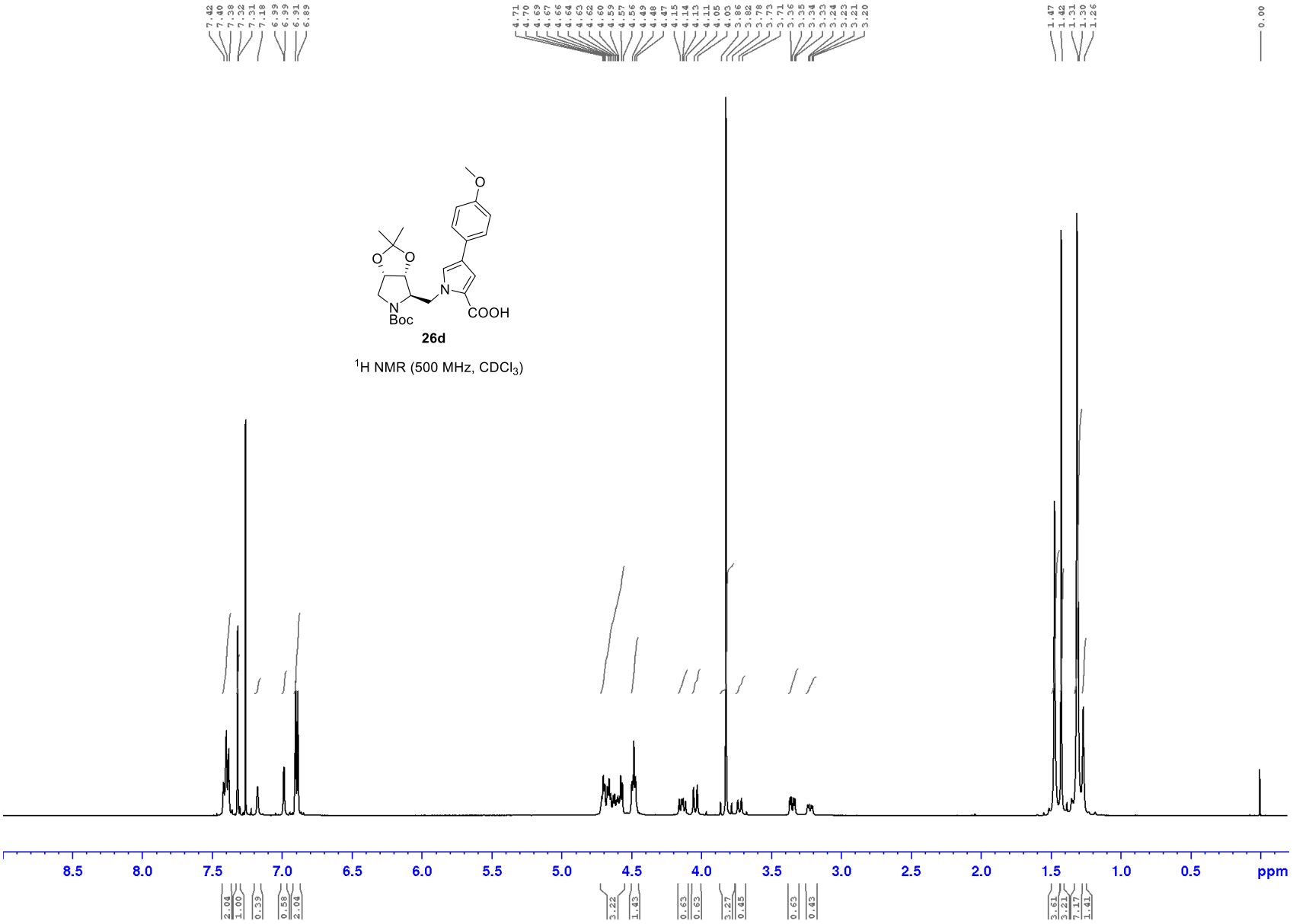


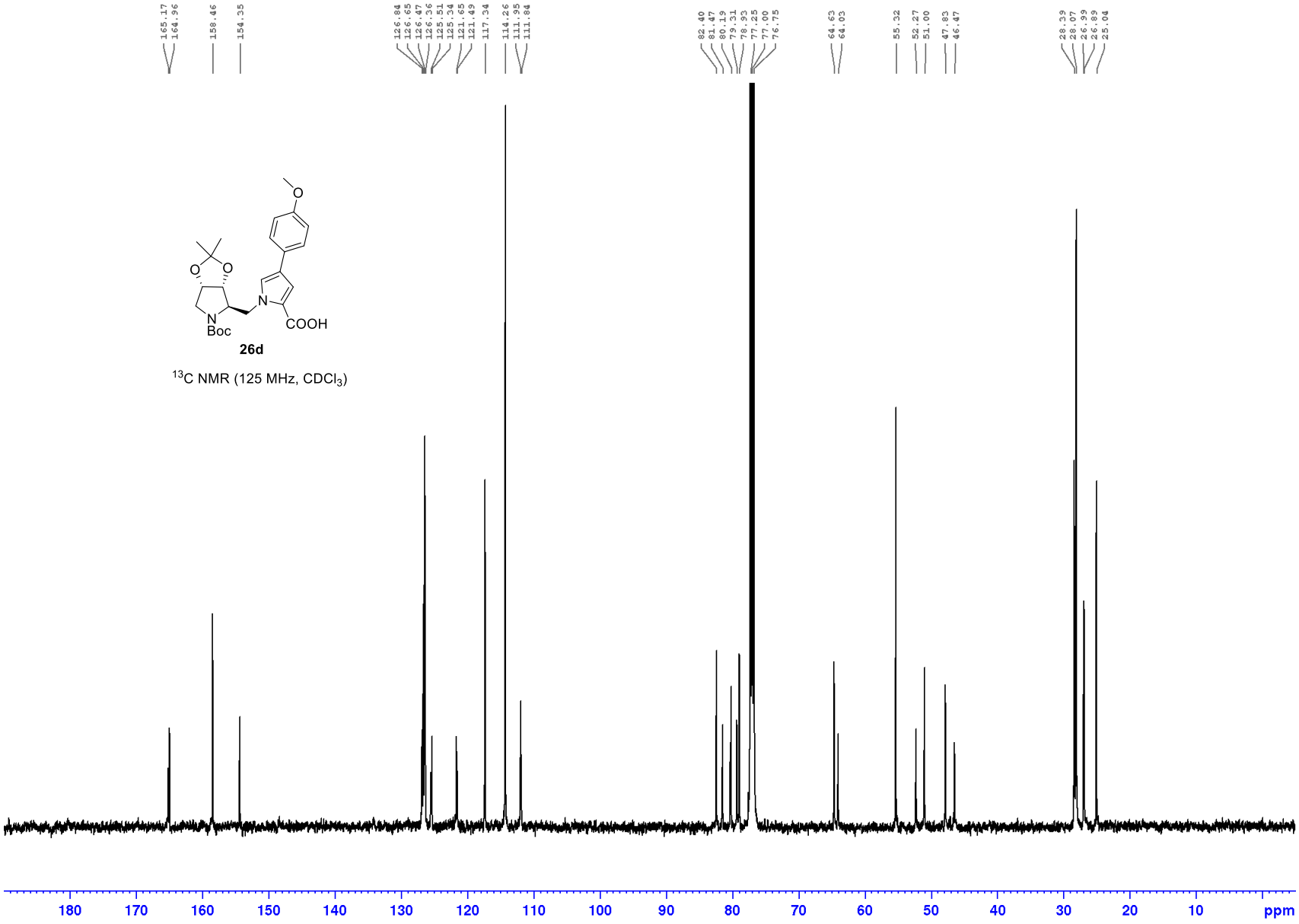
Peak#	RT	Peak Height	Peak Area	Width	Area %
1	30.96 min	717.4117	67894.0505	1.4181 min	100.000 %

III.



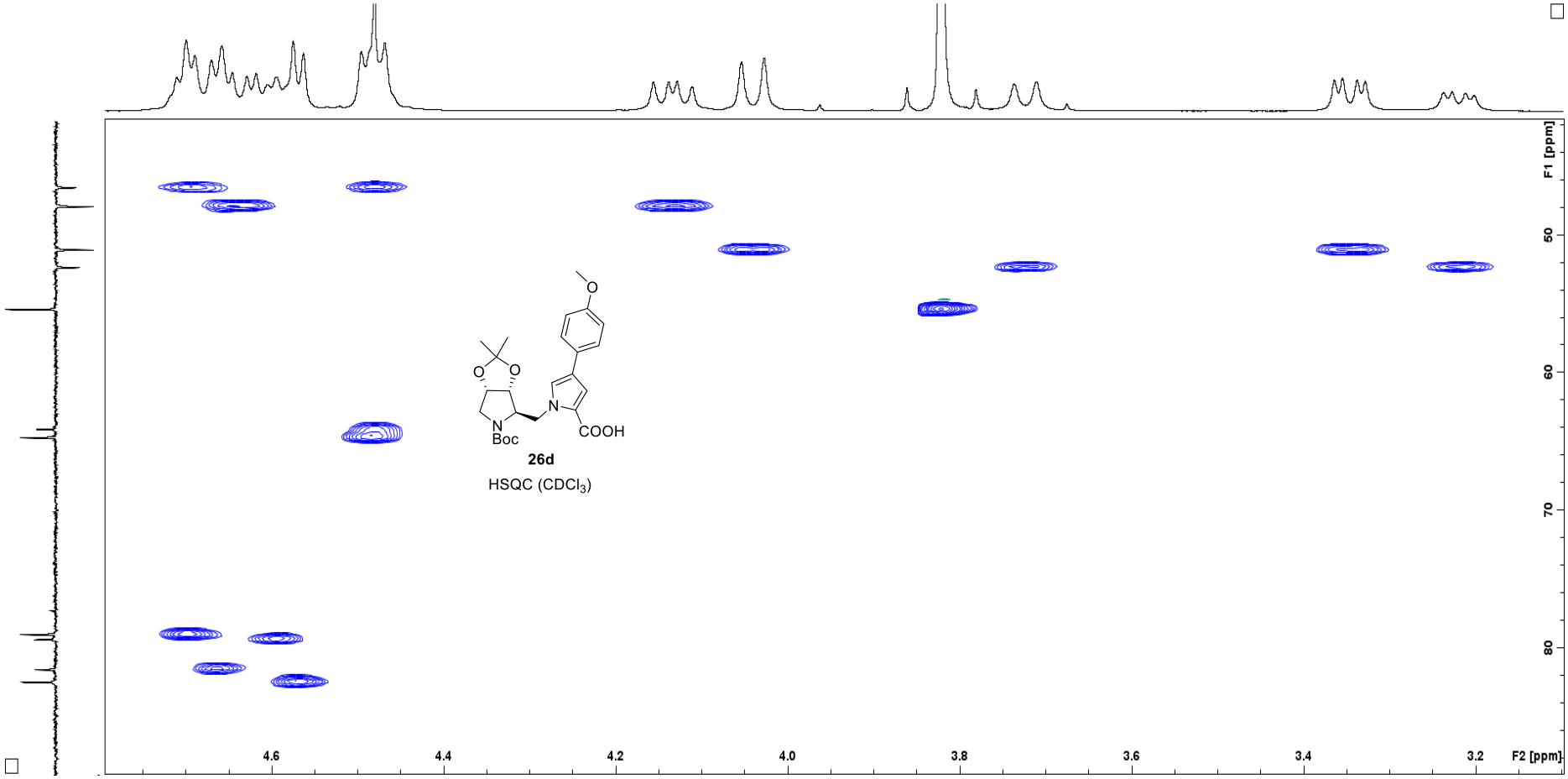
Peak#	RT	Peak Height	Peak Area	Width	Area %
1	42.05 min	432.5118	57452.0998	1.9637 min	100.000 %


7.42
7.40
7.38
7.32
7.31
7.18
6.99
6.99
6.91
6.89
4.71
4.70
4.69
4.67
4.66
4.64
4.63
4.62
4.60
4.59
4.57
4.56
4.49
4.48
4.47
4.15
4.14
4.13
4.11
4.05
4.03
3.86
3.82
3.78
3.73
3.71
3.36
3.35
3.34
3.33
3.24
3.23
3.21
3.20
1.47
1.42
1.31
1.30
1.26
0.00
O
O
O
N
N
Boc
COOH
26d
^{1}H NMR (500 MHz, $CDCl_3$)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.04
1.00
0.39
0.58
2.04
3.22
1.43
0.63
0.63
3.27
0.45
0.63
0.43
3.61
3.21
7.17
1.41



26d

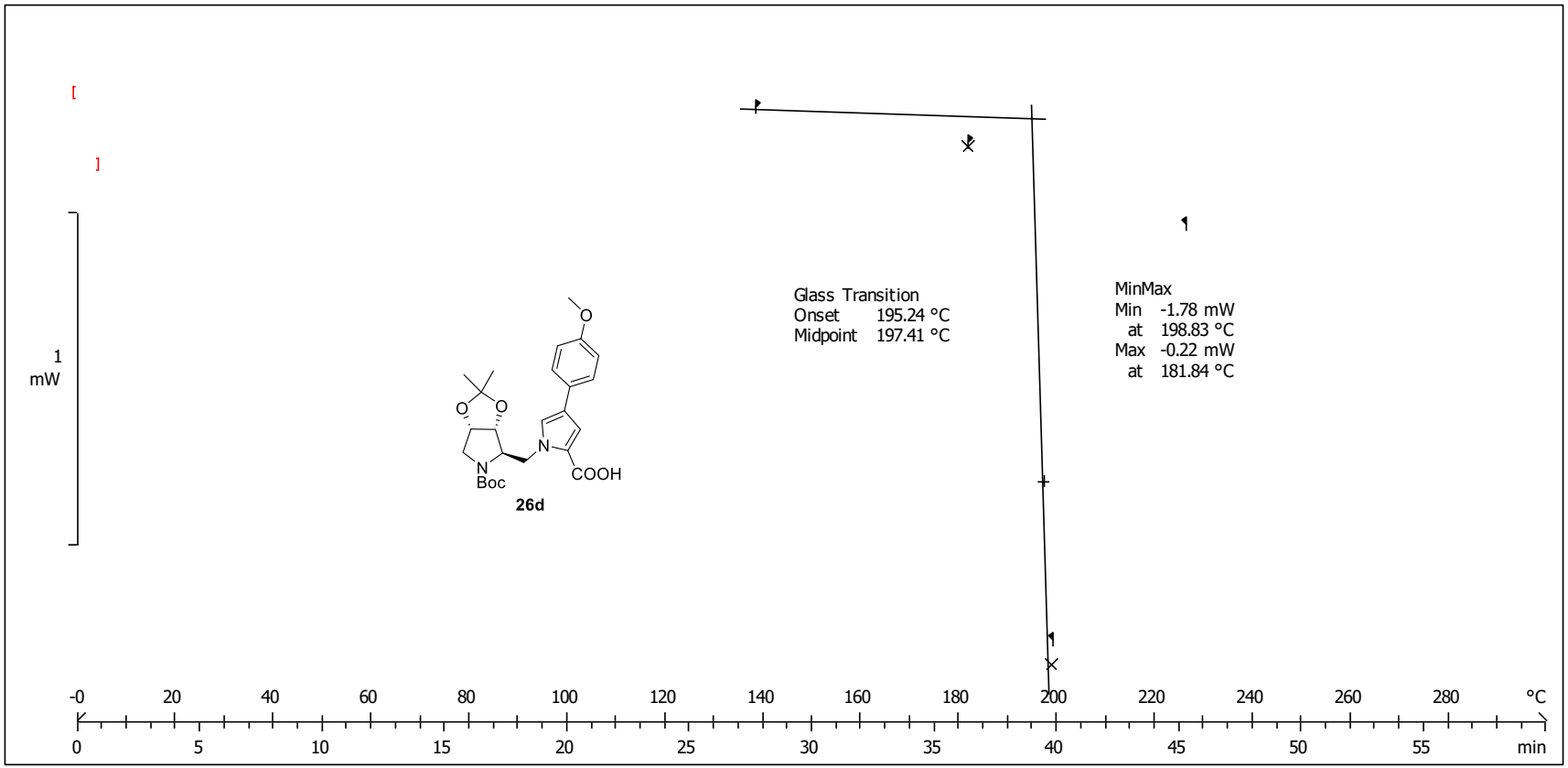
^{13}C NMR (125 MHz, $CDCl_3$)



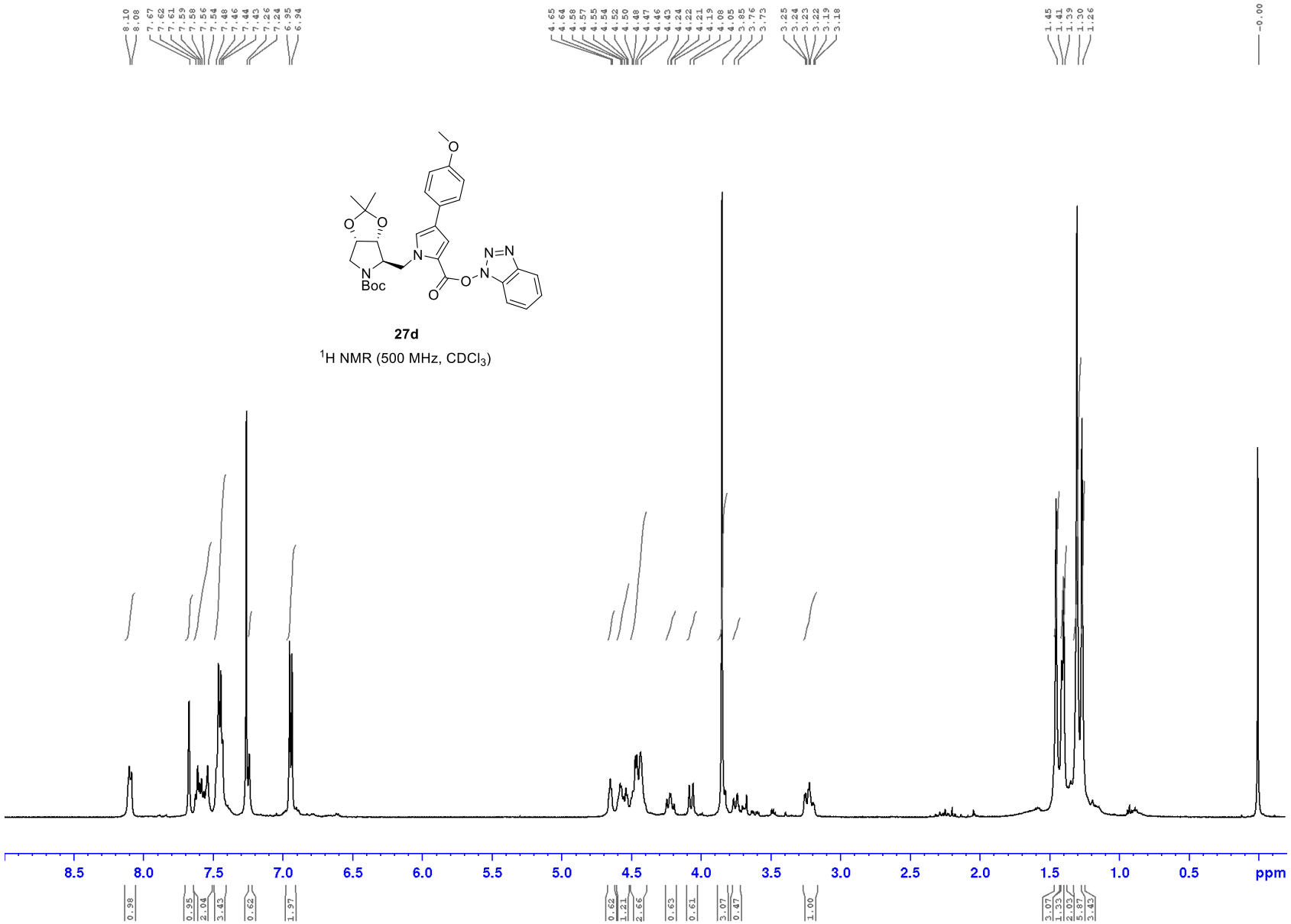
26d

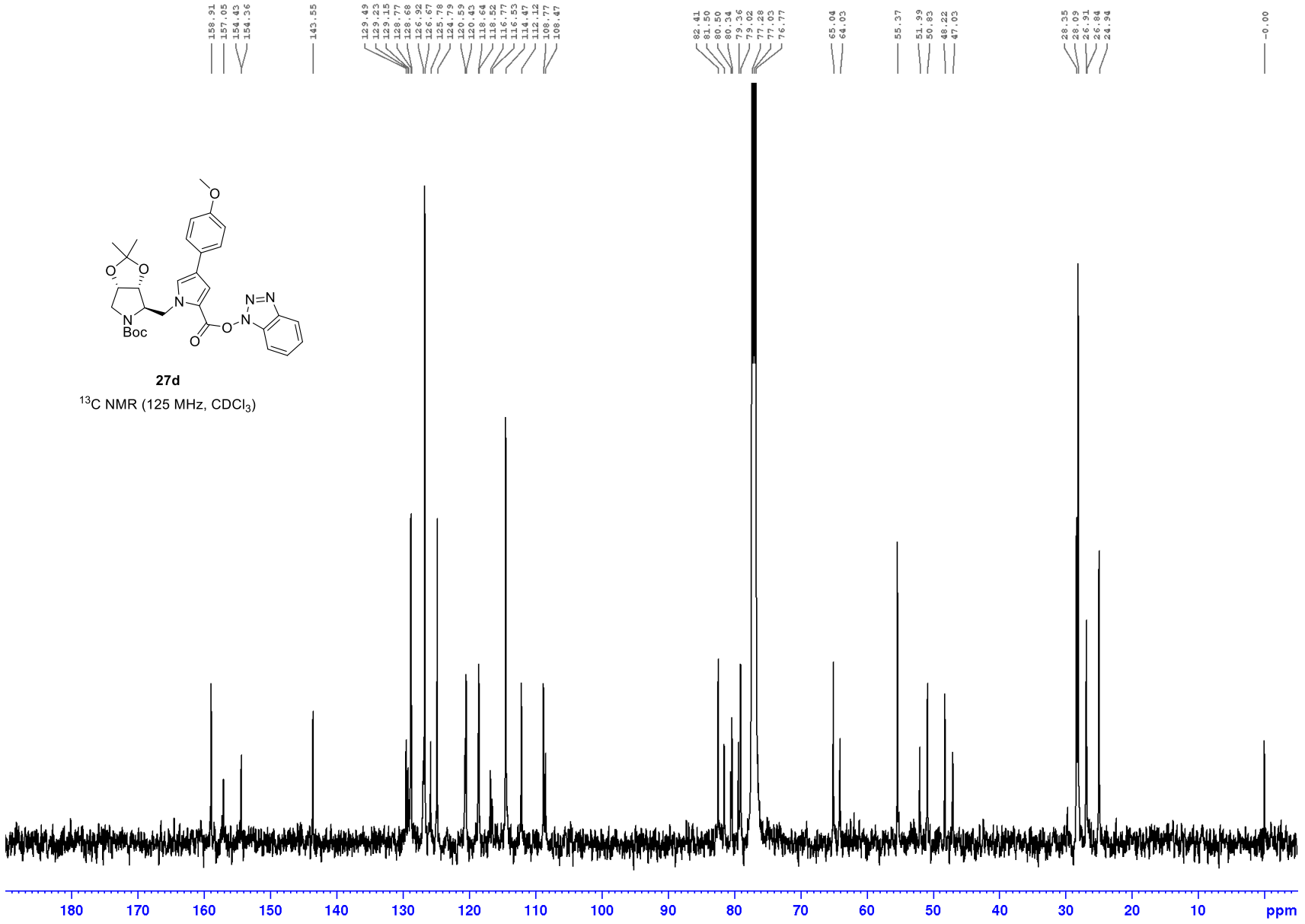
HSQC ($CDCl_3$)

^exo



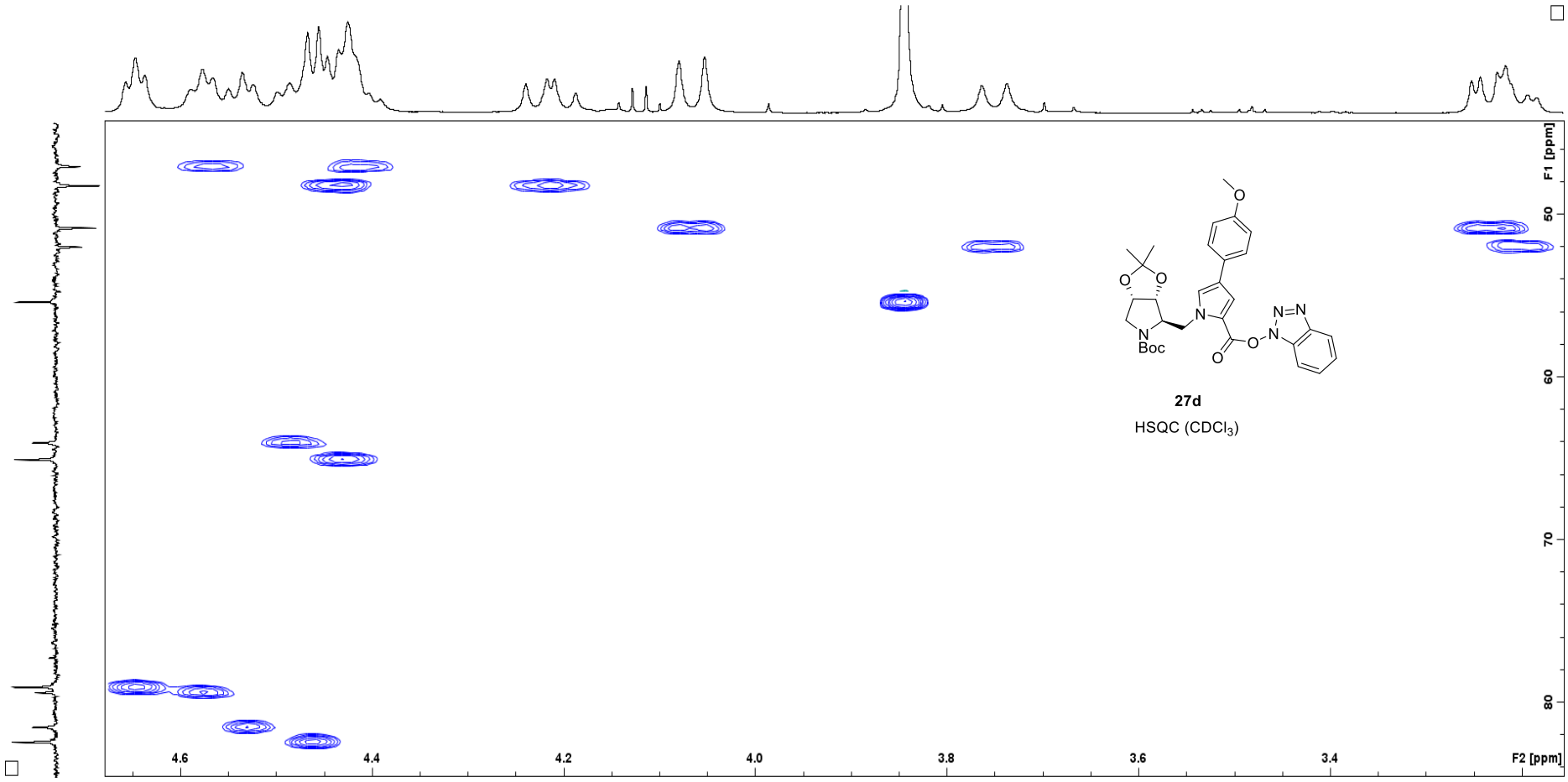
Lab: graham c Not signed STARe SW 9.20


8.10
8.08
7.67
7.62
7.61
7.59
7.58
7.56
7.54
7.48
7.46
7.44
7.43
7.26
7.24
6.95
6.94
4.65
4.64
4.58
4.57
4.55
4.54
4.52
4.50
4.48
4.47
4.46
4.43
4.24
4.22
4.21
4.19
4.08
4.05
3.85
3.76
3.73
3.25
3.24
3.23
3.22
3.19
3.18
1.45
1.41
1.39
1.30
1.26
0.00
O
O
O
N
N
Boc
N=N
O
O
N
27d
1H NMR (500 MHz, CDCl3)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
0.98
0.95
2.04
3.43
0.62
1.97
0.62
1.21
2.66
0.63
0.61
3.07
0.47
1.00
3.07
1.33
2.03
5.87
3.43



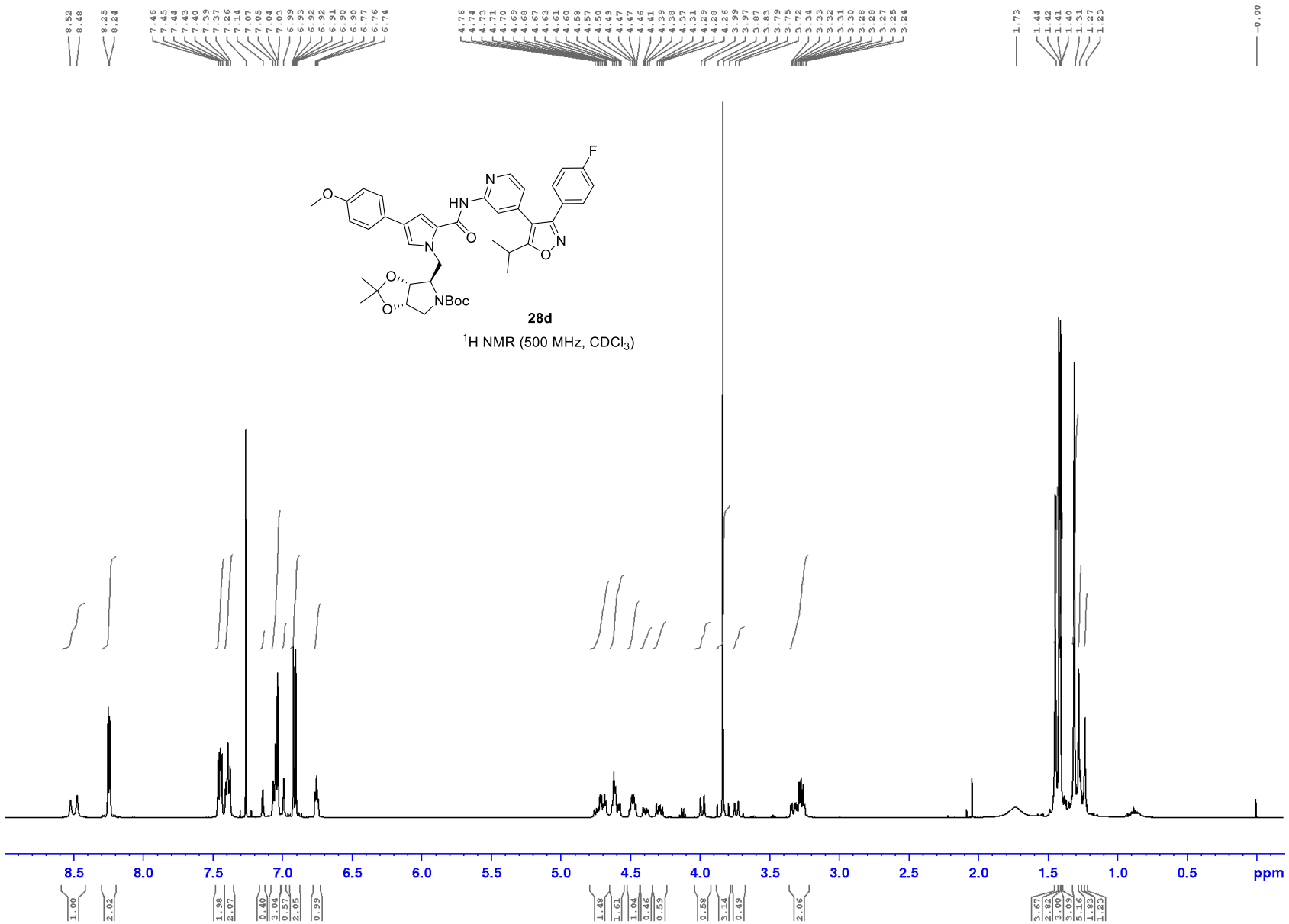
27d

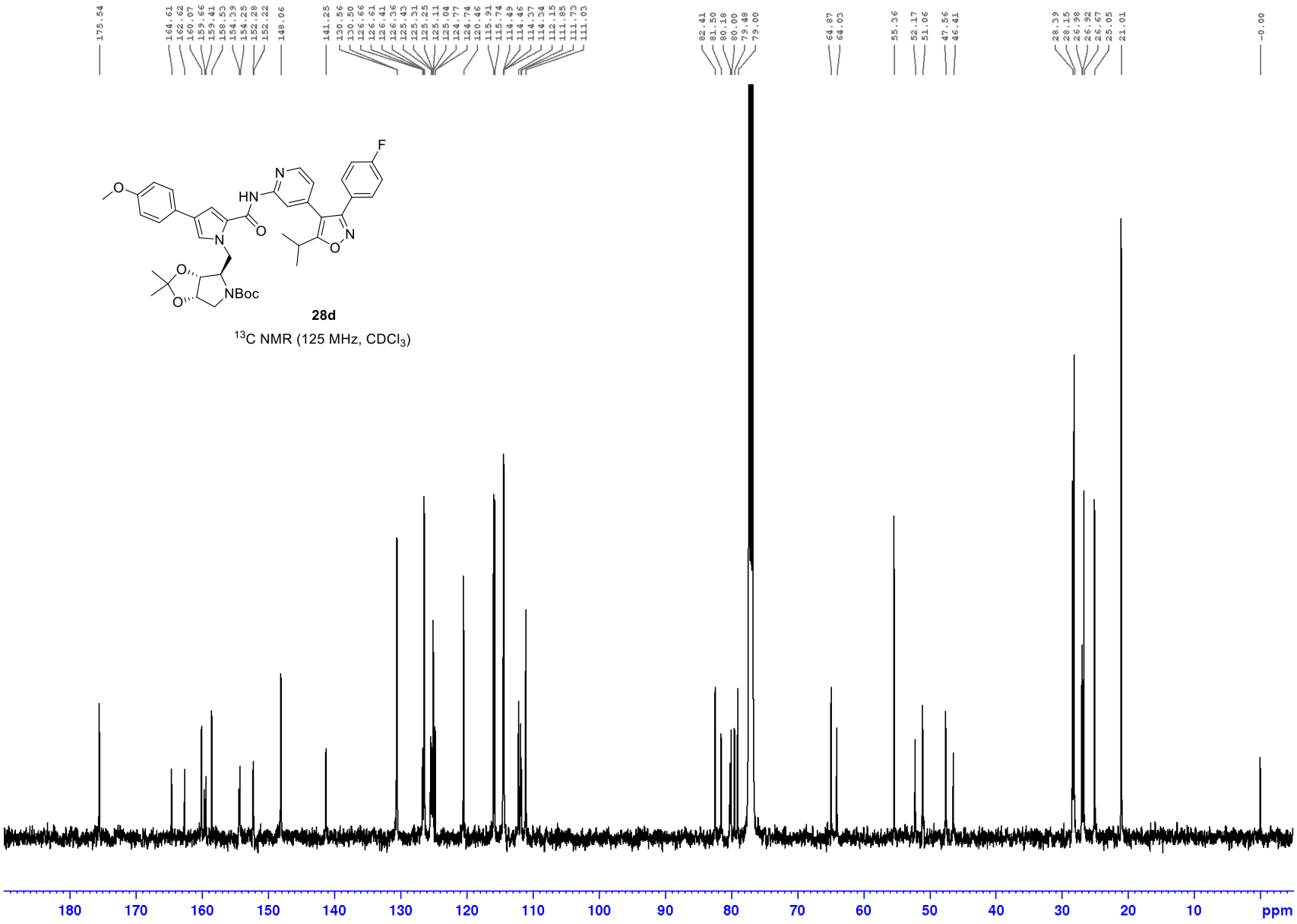
^{13}C NMR (125 MHz, $CDCl_3$)

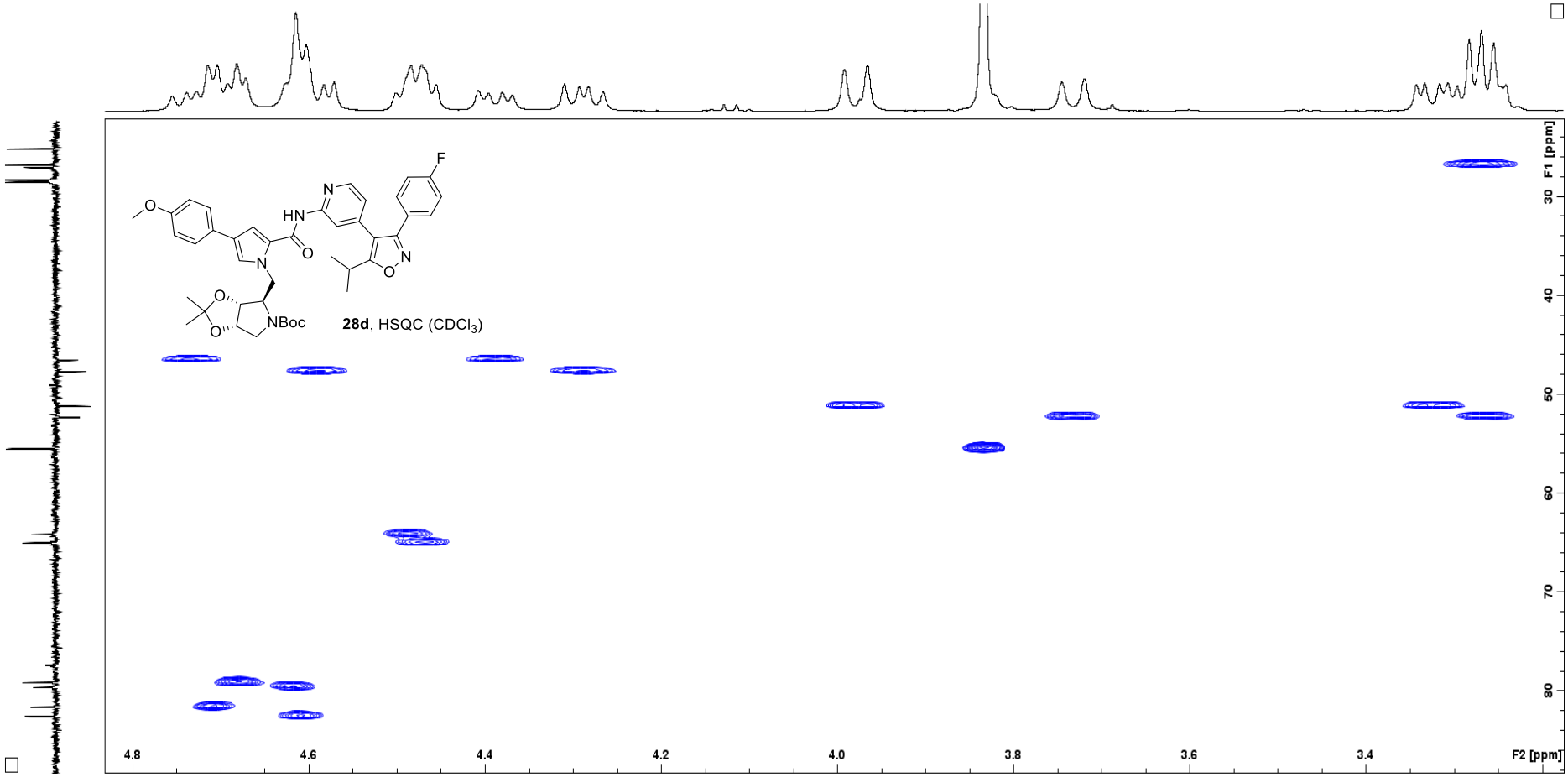


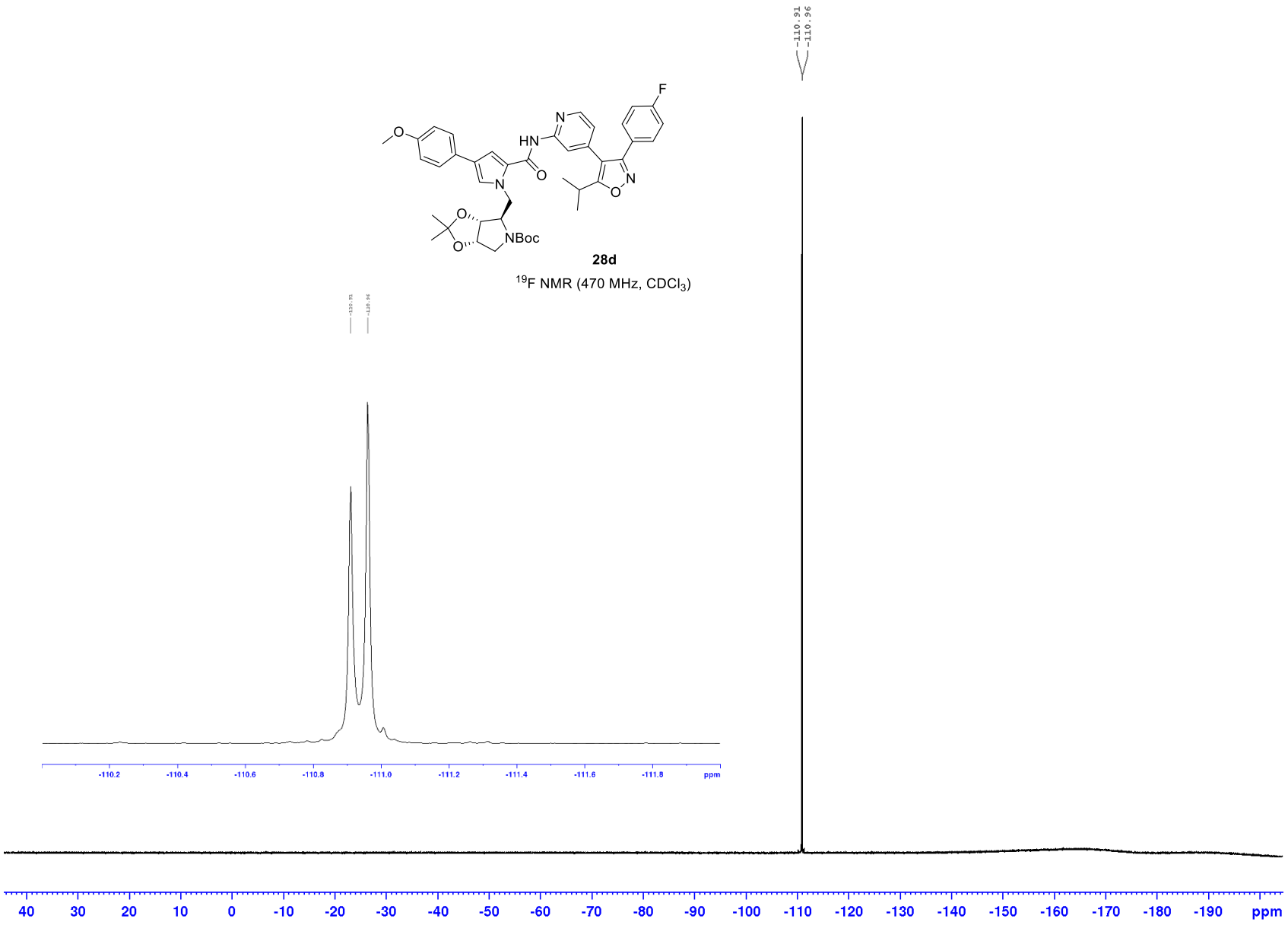
27d

HSQC ($CDCl_3$)


8.52
8.48
8.25
8.24
7.46
7.45
7.44
7.43
7.40
7.39
7.37
7.26
7.14
7.07
7.05
7.04
7.03
6.99
6.93
6.92
6.92
6.91
6.90
6.77
6.76
6.74
4.76
4.74
4.73
4.71
4.70
4.69
4.68
4.67
4.63
4.61
4.60
4.58
4.57
4.50
4.49
4.47
4.47
4.46
4.41
4.39
4.38
4.37
4.31
4.29
4.28
4.26
3.99
3.97
3.87
3.83
3.79
3.75
3.72
3.34
3.33
3.32
3.31
3.30
3.28
3.28
3.27
3.25
3.24
1.73
1.44
1.42
1.41
1.40
1.31
1.27
1.23
-0.00
F
N
HN
O
O
N
N
O
O
O
NBoc
28d
1H NMR (500 MHz, CDCl3)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
2.02
1.98
2.07
0.40
3.04
0.57
2.05
0.99
1.48
1.61
1.04
0.46
0.59
0.58
3.14
0.49
2.06
3.67
2.82
3.00
3.09
5.16
1.85
1.23

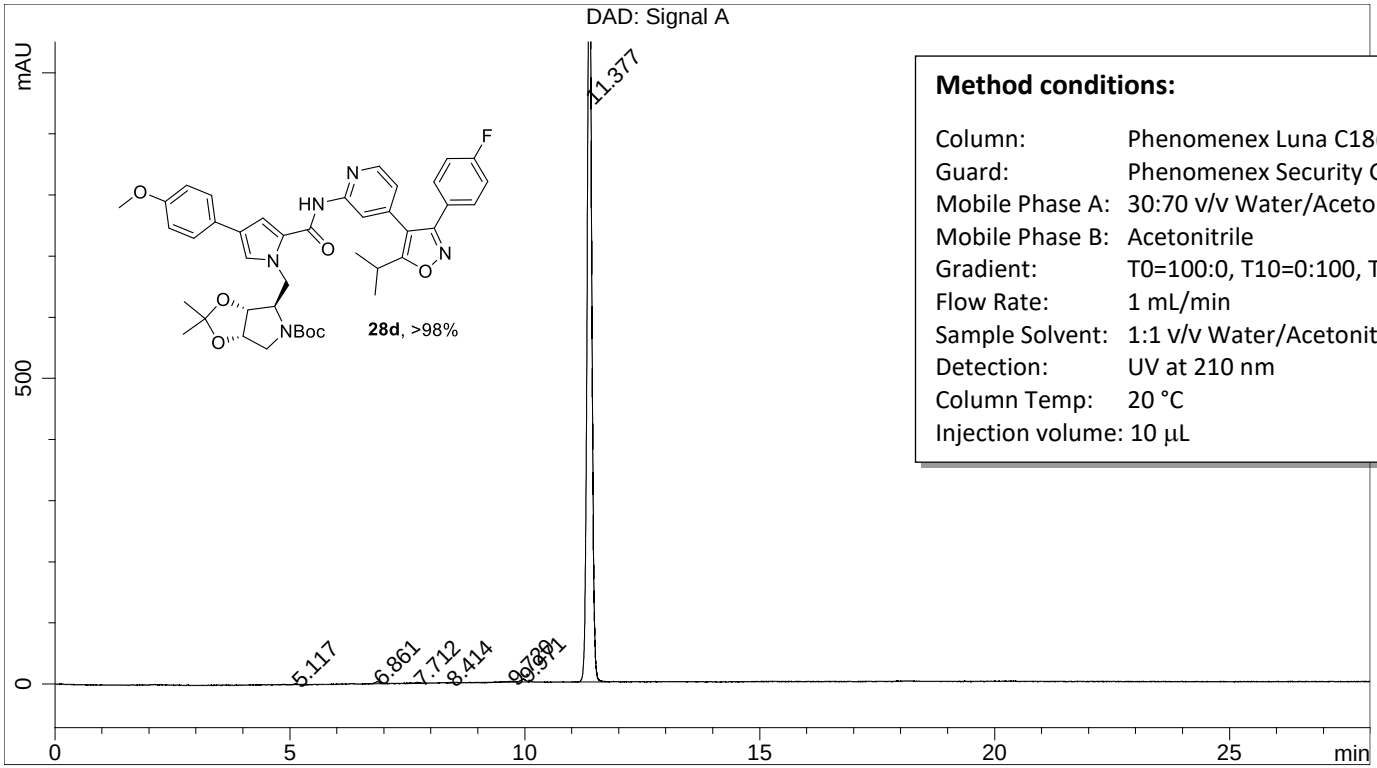

175.54
164.61
162.62
160.07
159.66
159.41
158.53
154.39
154.25
152.28
152.22
148.06
141.25
130.56
130.50
126.66
126.61
126.41
126.36
125.43
125.31
125.25
125.11
125.04
124.77
124.74
120.46
115.91
115.74
114.49
114.46
114.37
114.34
112.15
111.85
111.73
111.03
82.41
81.50
80.18
80.00
79.48
79.00
64.87
64.03
55.36
52.17
51.06
47.56
46.41
28.39
28.15
26.98
26.92
26.67
25.05
21.01
-0.00
F
N
HN
O
O
N
O
N
O
O
O
NBoc
28d
13C NMR (125 MHz, CDCl3)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


F
N
HN
O
O
N
N
O
O
O
NBoc
28d, HSQC (CDCl3)
F1 [ppm]
30
40
50
60
70
80
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
F2 [ppm]



28d

^{19}F NMR (470 MHz, $CDCl_3$)



Method conditions:

Column:	Phenomenex Luna C18(2) 5 µm 250x4.6 mm
Guard:	Phenomenex Security Guard C18 RP 4x3 mm
Mobile Phase A:	30:70 v/v Water/Acetonitrile
Mobile Phase B:	Acetonitrile
Gradient:	T0=100:0, T10=0:100, T25=0:100, T26=100:0, T30=100:0
Flow Rate:	1 mL/min
Sample Solvent:	1:1 v/v Water/Acetonitrile
Detection:	UV at 210 nm
Column Temp:	20 °C
Injection volume:	10 µL

Peak#	RT	Peak Height	Peak Area	Width	Area %
1	5.12 min	1.5319	14.7393	0.1223 min	0.172 %
2	6.86 min	3.6116	31.2759	0.1250 min	0.365 %
3	7.71 min	1.4833	16.2153	0.1475 min	0.189 %
4	8.41 min	1.0054	3.6716	0.0606 min	0.043 %
5	9.72 min	1.6941	33.2017	0.2406 min	0.387 %
6	9.97 min	4.8560	37.5696	0.1163 min	0.438 %
7	11.38 min	1234.8694	8438.0219	0.1057 min	98.406 %

Method conditions:

Column: Regis, Pirkle Covalent, (*S*,*S*) Whelk-01, 10/100 Kromasil FEC 250x4.6 mm

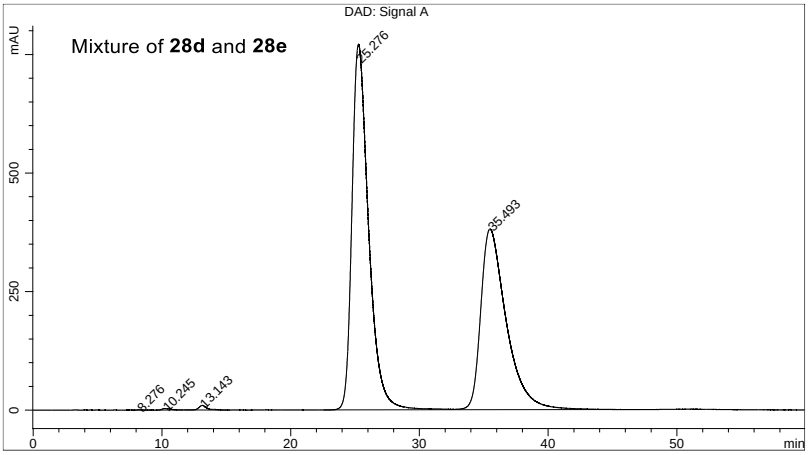
Guard: Phenomenex Security Guard CN 4x3 mm

Mobile Phase: 60:40 v/v *n*-Hexane/2-Propanol

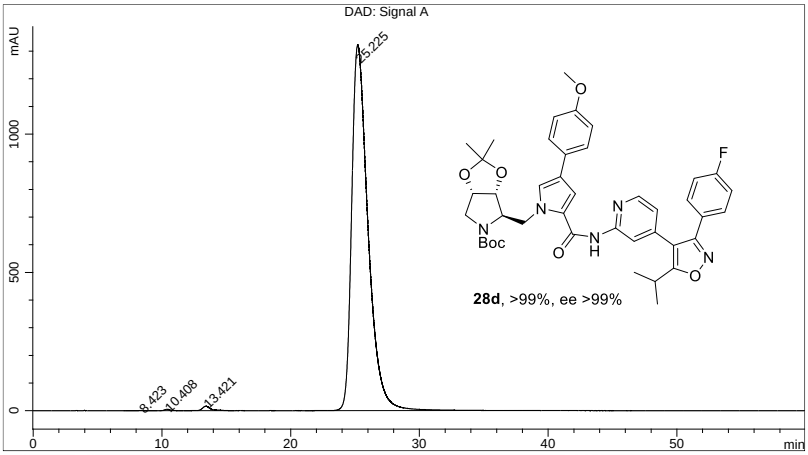
Flow Rate: 1 mL/min, Detection: UV 262 nm; Column Temp: 30 °C; Injection volume: 20 μL

Sample Solvent: 50:50 v/v *n*-Hexane/2-Propanol

I.

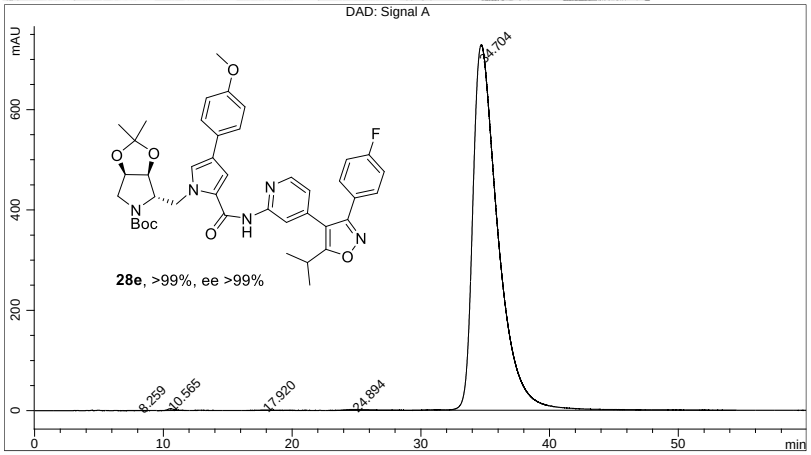


II.

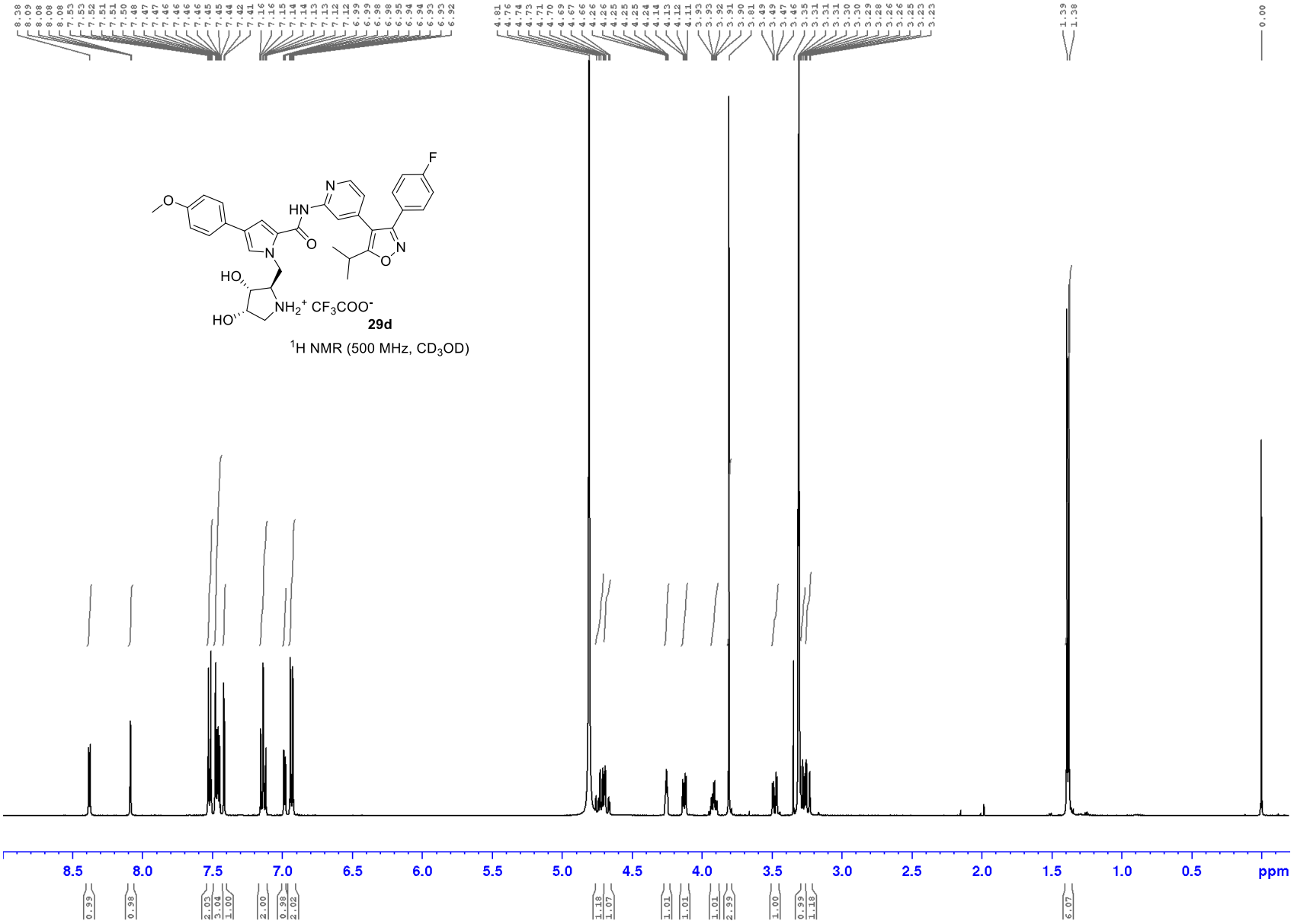


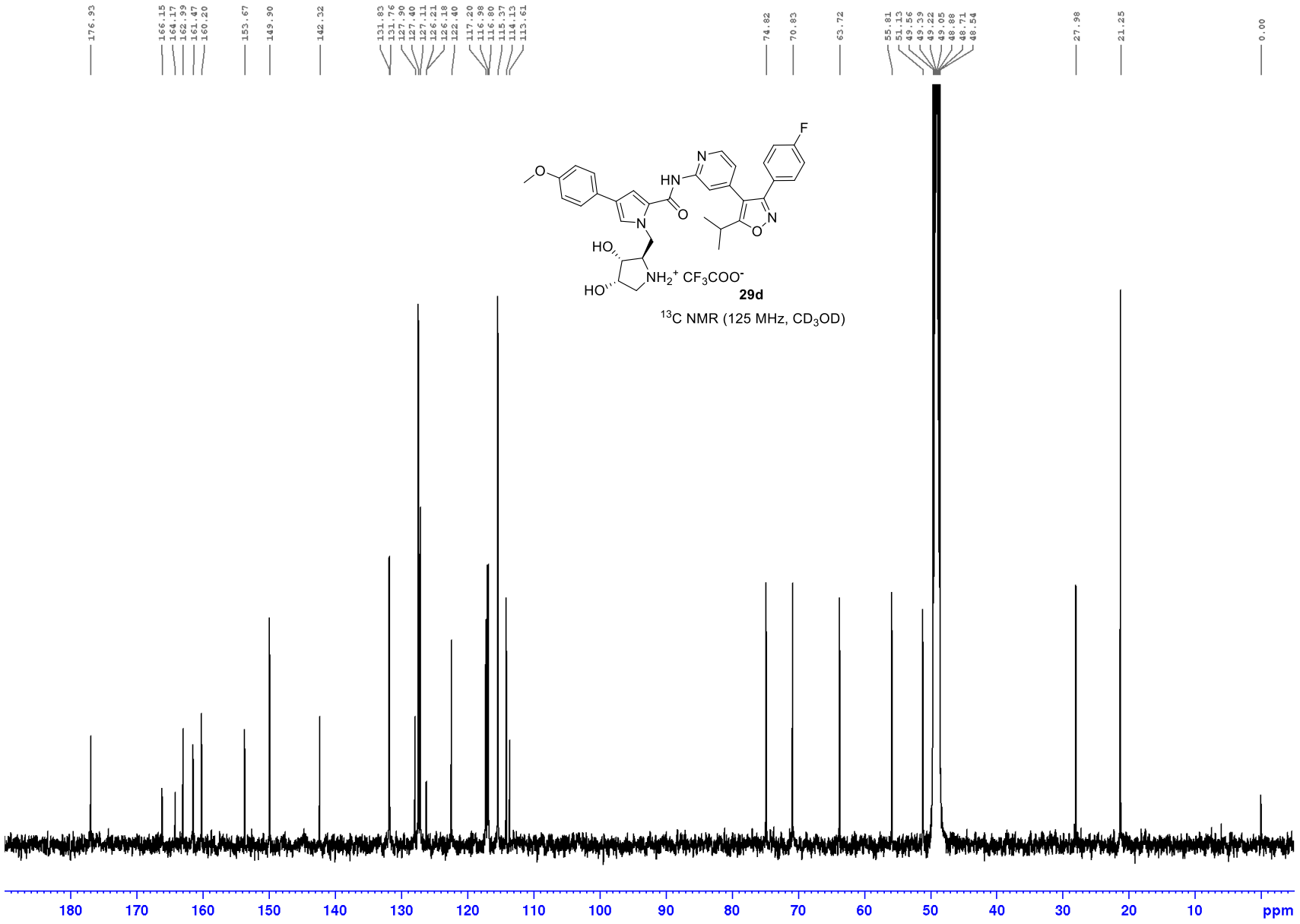
III.

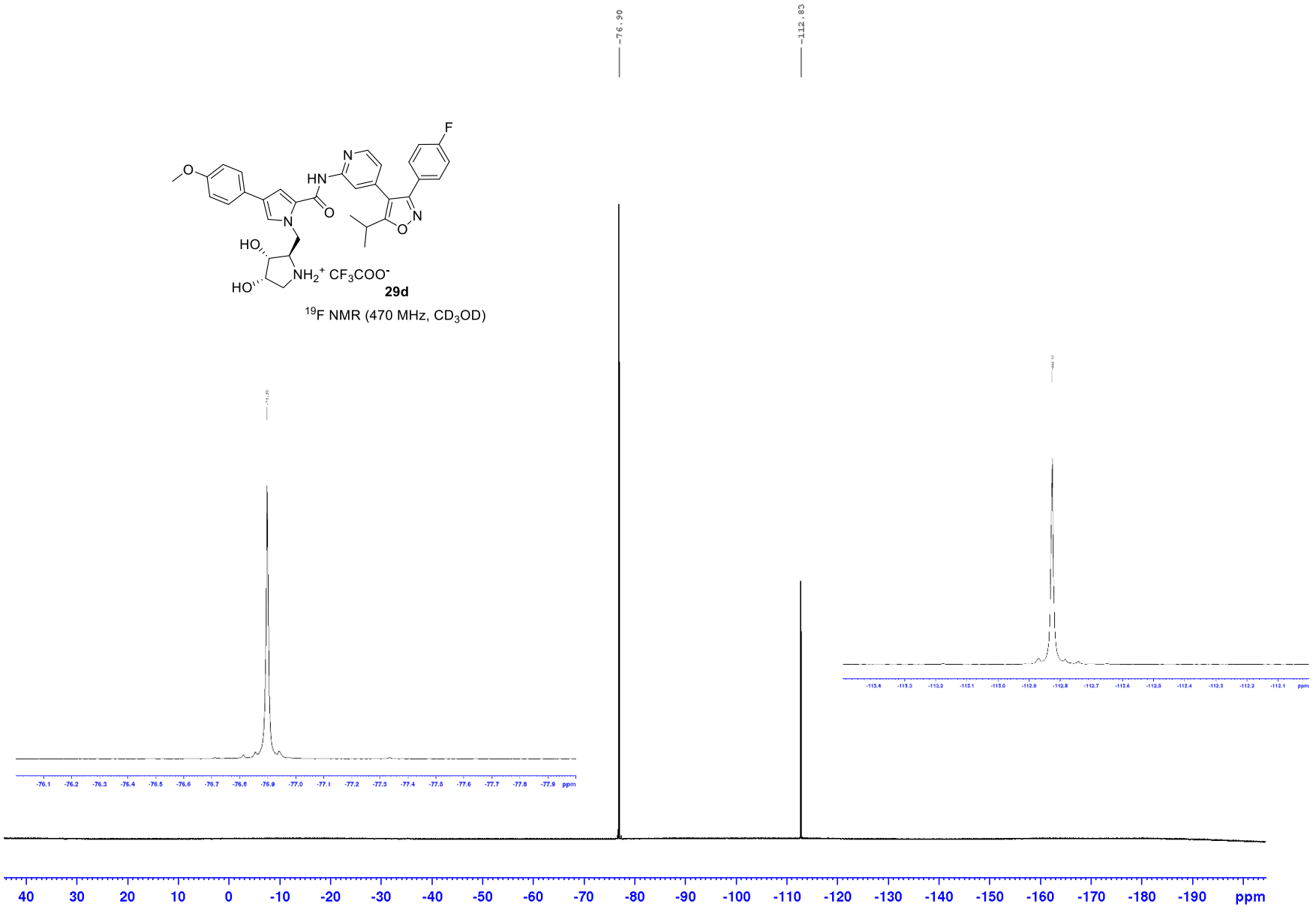
Peak#	RT	Peak Height	Peak Area	Width	Area %
1	8.42 min	1.1081	45.3935	0.5899 min	0.038 %
2	10.41 min	5.1416	165.9663	0.5046 min	0.141 %
3	13.42 min	16.2204	743.3455	0.6947 min	0.629 %
4	25.22 min	1322.4860	117138.2230	1.3374 min	99.192 %

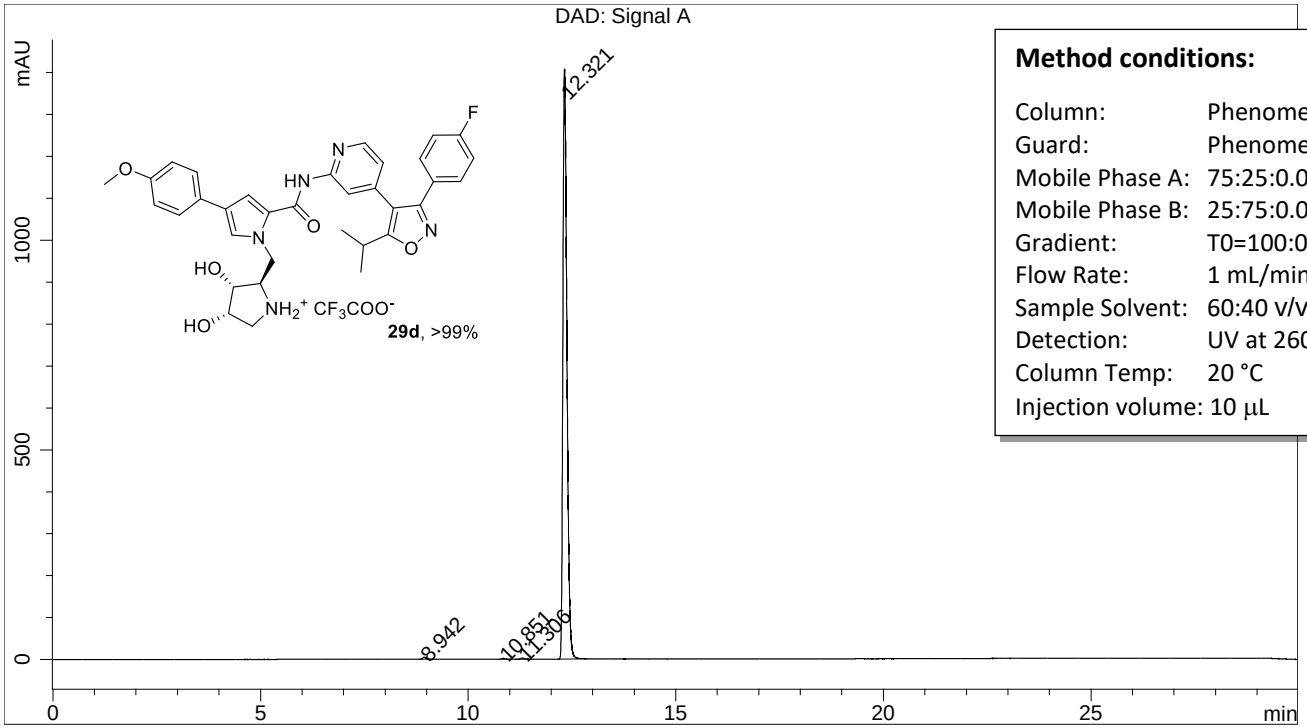


Peak#	RT	Peak Height	Peak Area	Width	Area %
1	8.26 min	0.5522	30.3446	0.7531 min	0.030 %
2	10.56 min	3.5442	144.4777	0.6036 min	0.145 %
3	17.92 min	0.8498	93.8782	1.3848 min	0.094 %
4	24.89 min	1.9045	325.1486	2.0718 min	0.326 %
5	34.70 min	728.4776	99166.4506	2.0202 min	99.405 %


F
O
HN
N
O
N
HO
HO
NH2+ CF3COO-
29d
1H NMR (500 MHz, CD3OD)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


176.93
166.15
164.17
162.99
161.47
160.20
153.67
149.90
142.32
131.83
131.76
127.90
127.40
127.11
126.21
126.18
122.40
117.20
116.98
116.80
115.37
114.13
113.61
74.82
70.83
63.72
55.81
51.13
49.56
49.39
49.22
49.05
48.88
48.71
48.54
27.98
21.25
0.00
F
N
HN
O
O
N
N
O
HO
HO
NH2+ CF3COO-
29d
13C NMR (125 MHz, CD3OD)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


-76.90
-112.83
F
N
HN
O
O
N
N
O
HO
NH2+ CF3COO-
HO
29d
19F NMR (470 MHz, CD3OD)
-76.1 -76.2 -76.3 -76.4 -76.5 -76.6 -76.7 -76.8 -76.9 -77.0 -77.1 -77.2 -77.3 -77.4 -77.5 -77.6 -77.7 -77.8 -77.9 ppm
-113.4 -113.3 -113.2 -113.1 -113.0 -112.9 -112.8 -112.7 -112.6 -112.5 -112.4 -112.3 -112.2 -112.1 ppm
40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 ppm

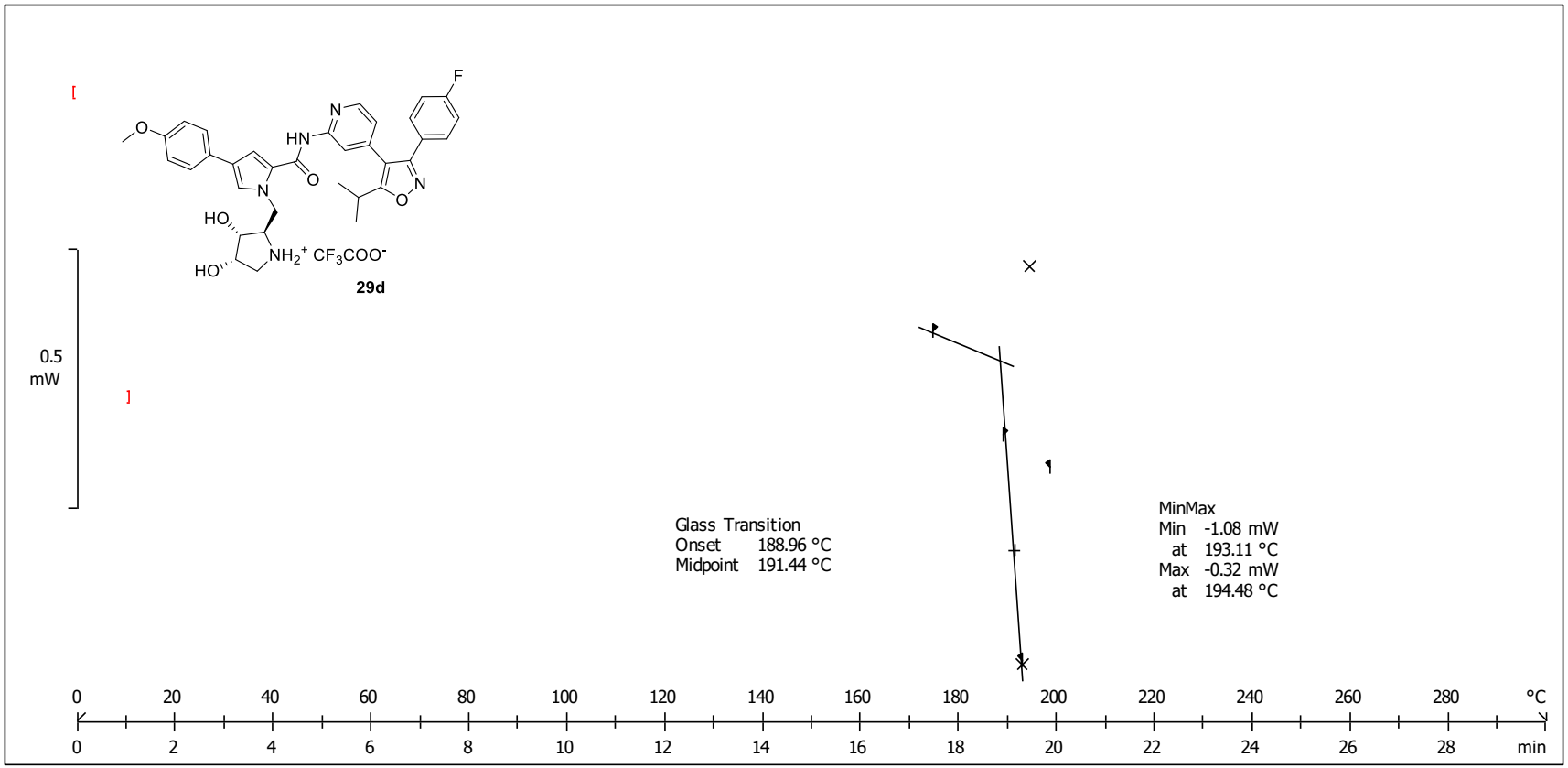


Method conditions:

Column:	Phenomenex Luna C18(2) 5 µm 250x4.6 mm
Guard:	Phenomenex Security Guard C18 RP 4x3 mm
Mobile Phase A:	75:25:0.05 v/v/v Water/Acetonitrile/Trifluoroacetic acid
Mobile Phase B:	25:75:0.05 v/v/v Water/Acetonitrile/Trifluoroacetic acid
Gradient:	T0=100:0, T20=0:100, T26=0:100, T27=100:0, T30=100:0
Flow Rate:	1 mL/min
Sample Solvent:	60:40 v/v Water/Acetonitrile
Detection:	UV at 260 nm
Column Temp:	20 °C
Injection volume:	10 µL

Peak#	RT	Peak Height	Peak Area	Width	Area %
1	8.94 min	5.1111	31.7862	0.0976 min	0.331 %
2	10.85 min	1.8254	8.6396	0.0692 min	0.090 %
3	11.31 min	2.6939	14.1085	0.0781 min	0.147 %
4	12.32 min	1407.4973	9553.6108	0.1052 min	99.432 %

^exo



Lab: graham c Not signed STARe SW 9.20

Method conditions:

Column: Phenomenex Lux Cellulose-2 5 μm 250x4.6 mm

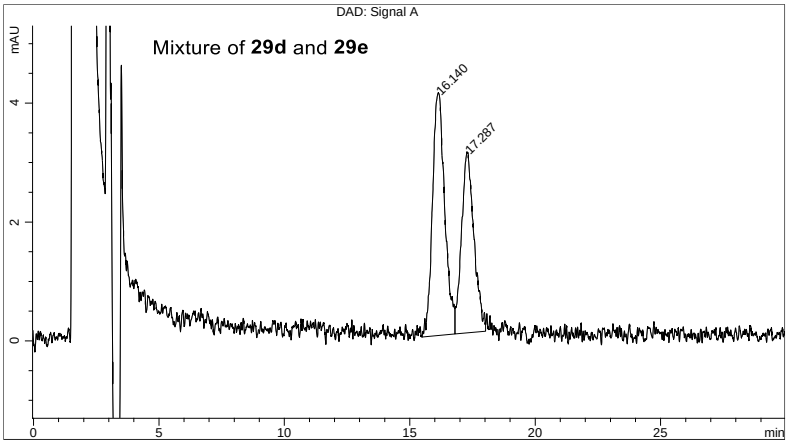
Guard: Phenomenex Security Guard Celluose-1 4x3 mm

Mobile Phase: 100:0.05 v/v Acetonitrile/Trifluoroacetic Acid

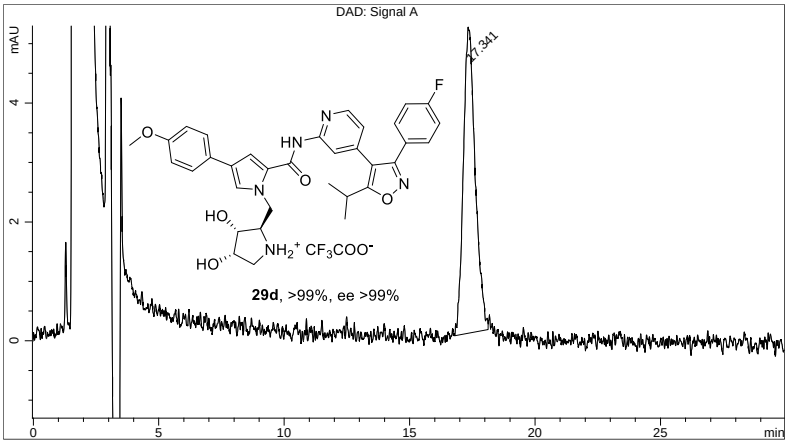
Flow Rate: 1 mL/min, Detection: UV 262 nm; Column Temp: 40 °C; Injection volume: 20 μL

Sample Solvent: 80:10:10 v/v/v *n*-Hexane/methanol/2-Propanol

I.

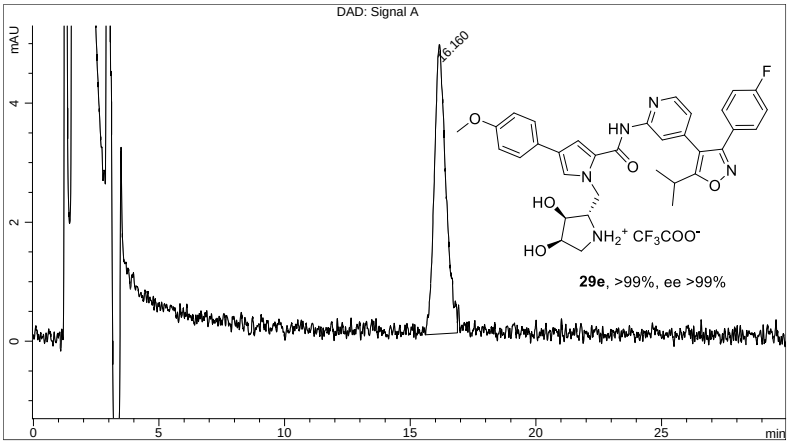


II.

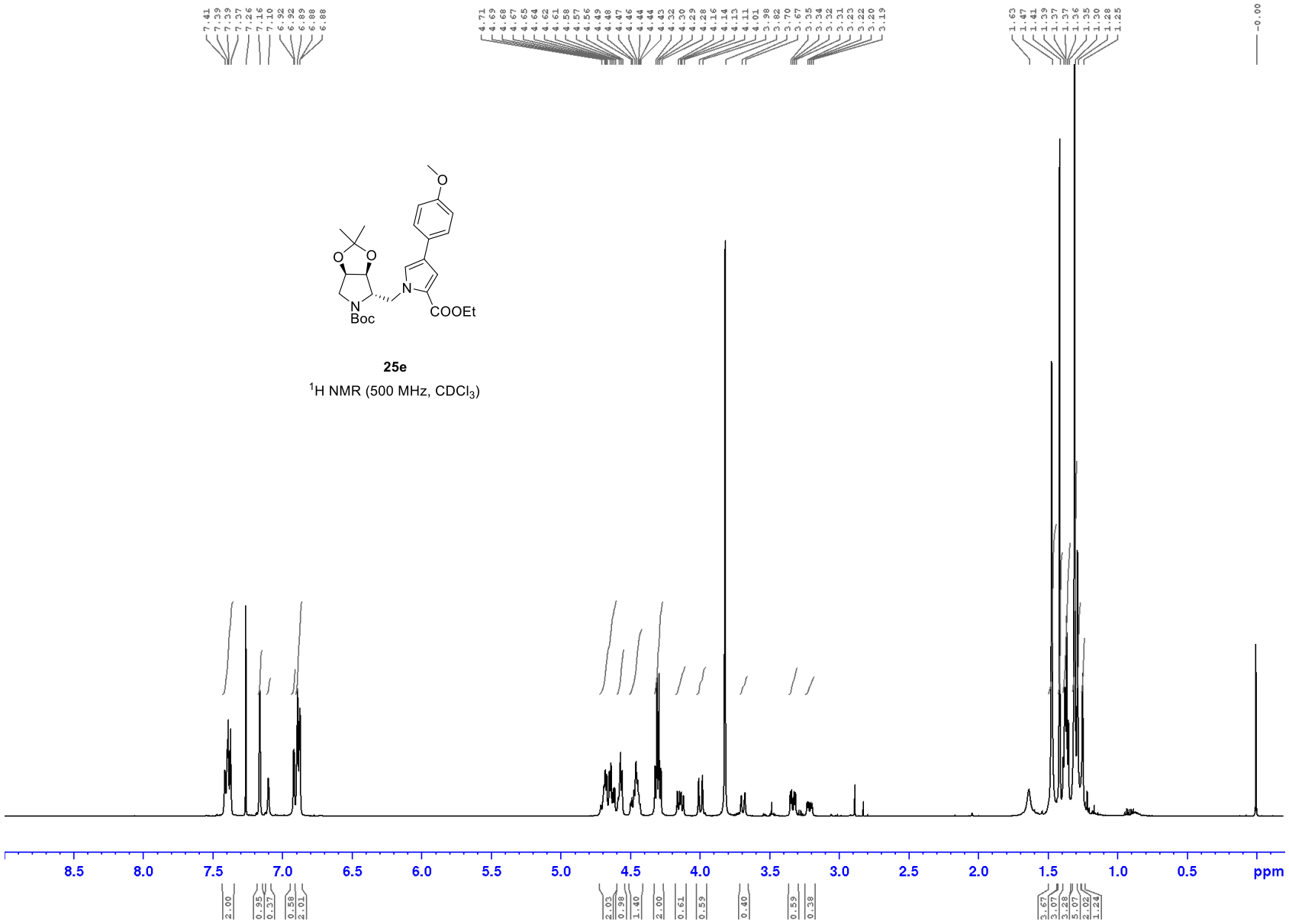


Peak#	RT	Peak Height	Peak Area	Width	Area %
1	17.34 min	5.1435	167.1707	0.3912 min	100.000 %

III.

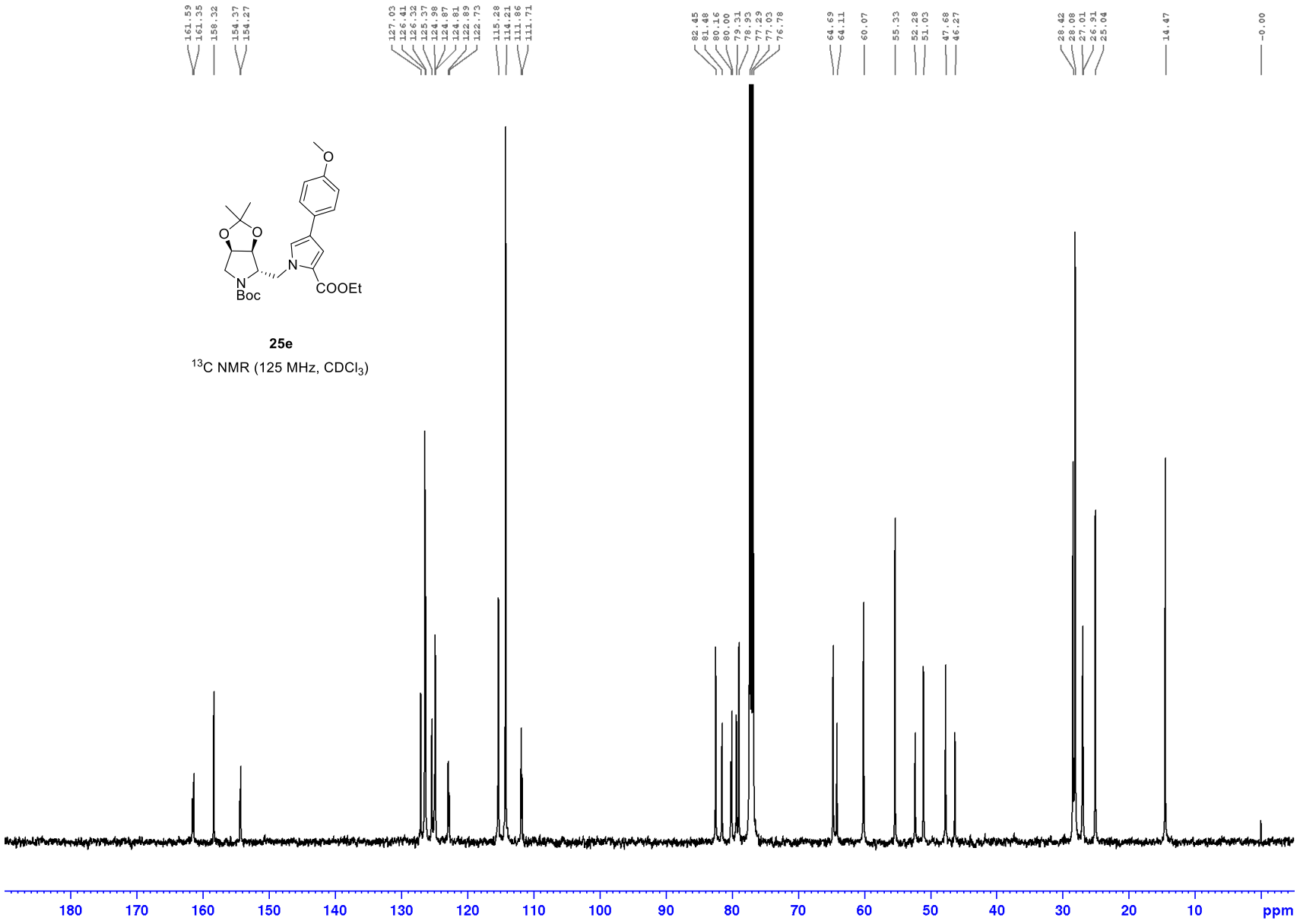


Peak#	RT	Peak Height	Peak Area	Width	Area %
1	16.16 min	4.8606	153.8371	0.4172 min	100.000 %



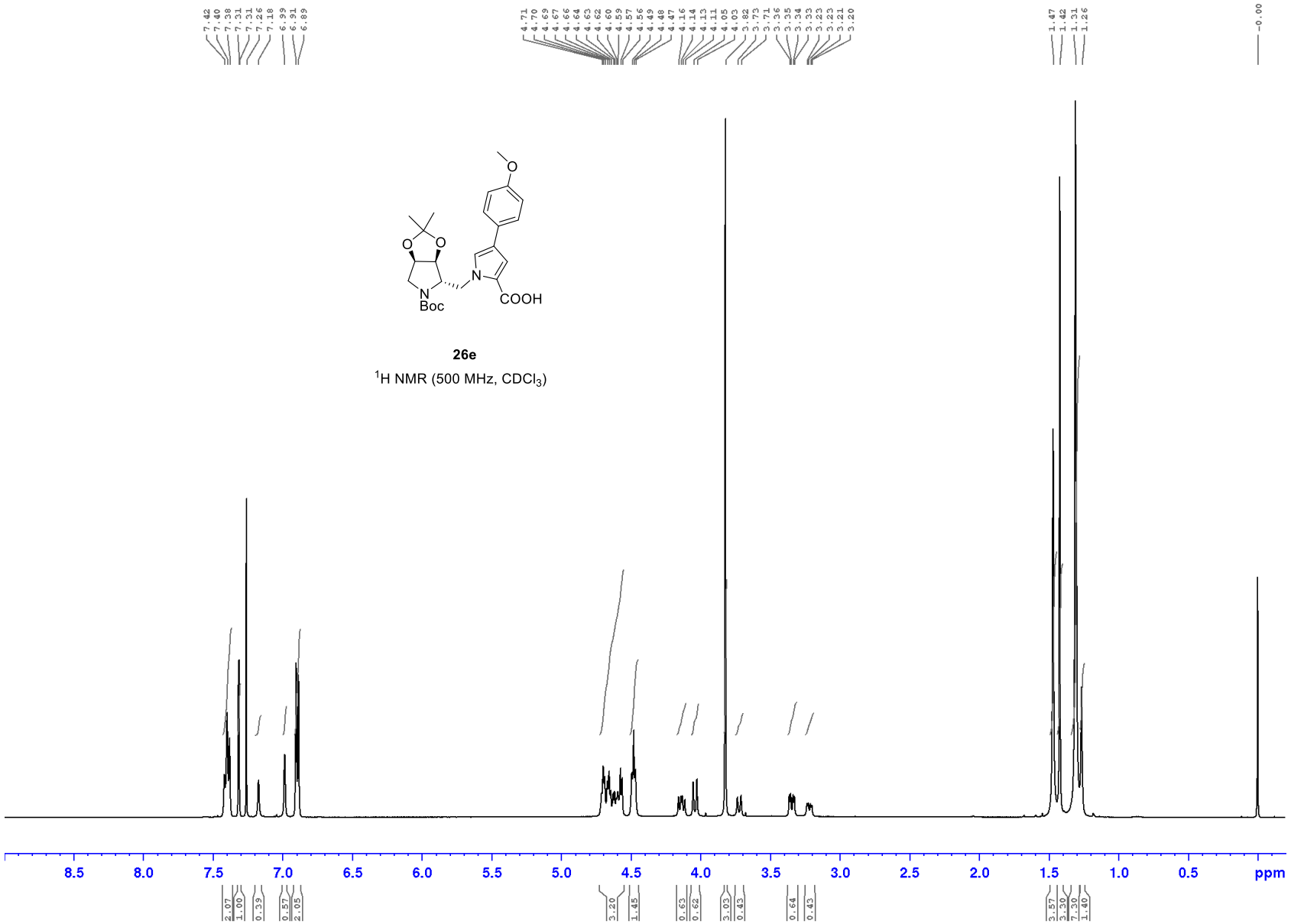
25e

^{1}H NMR (500 MHz, $CDCl_3$)



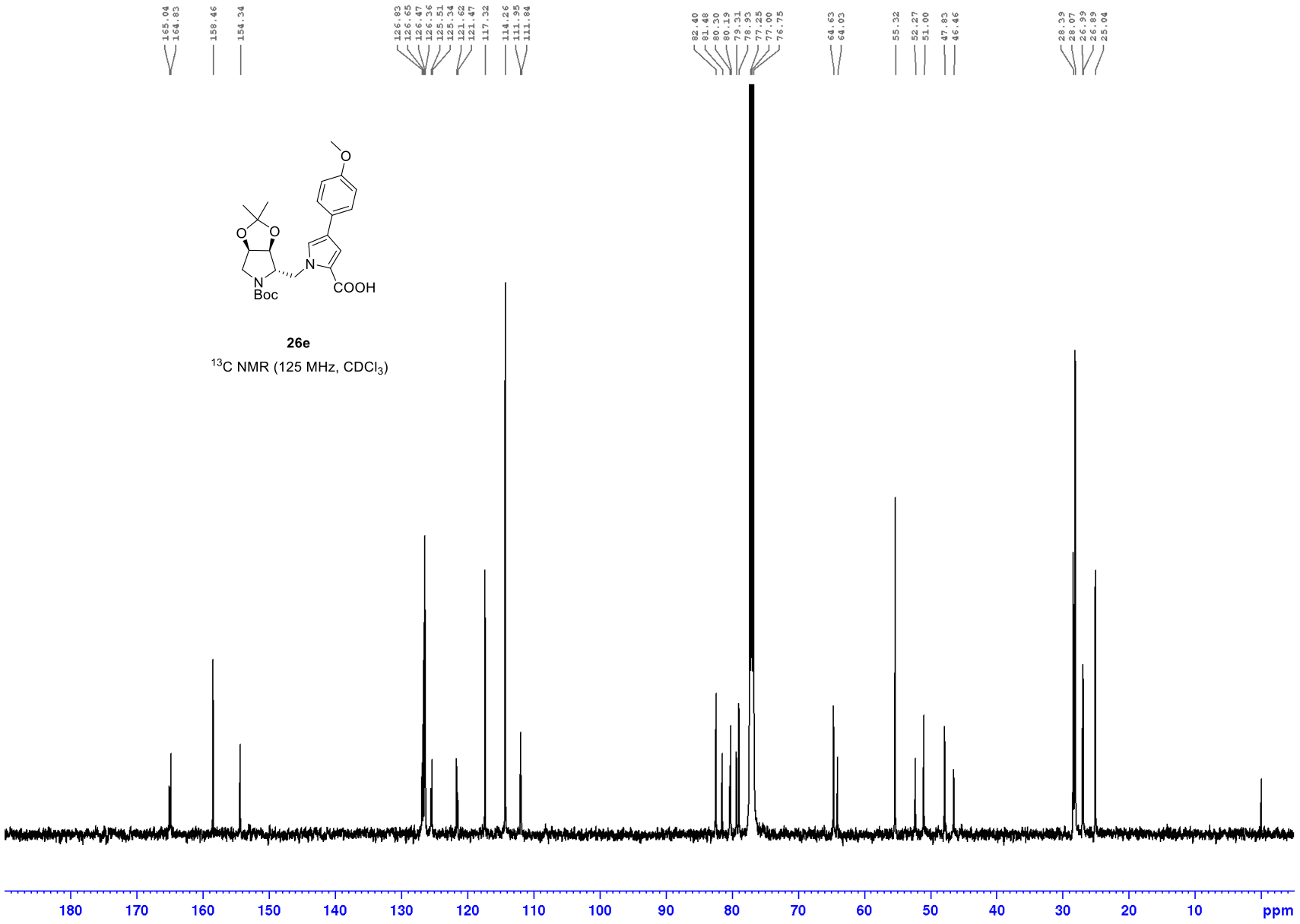
25e

^{13}C NMR (125 MHz, $CDCl_3$)



26e

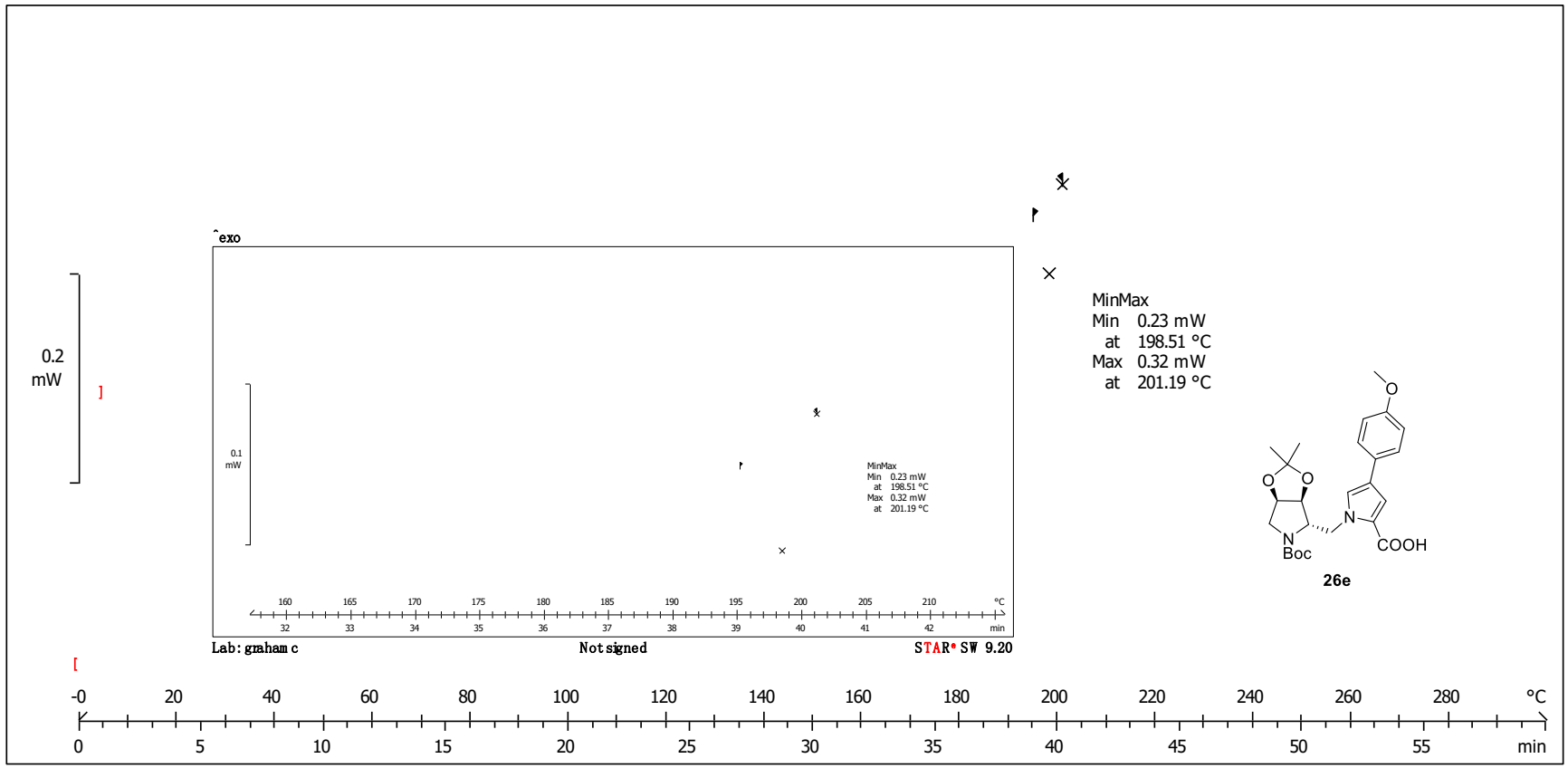
^{1}H NMR (500 MHz, $CDCl_3$)



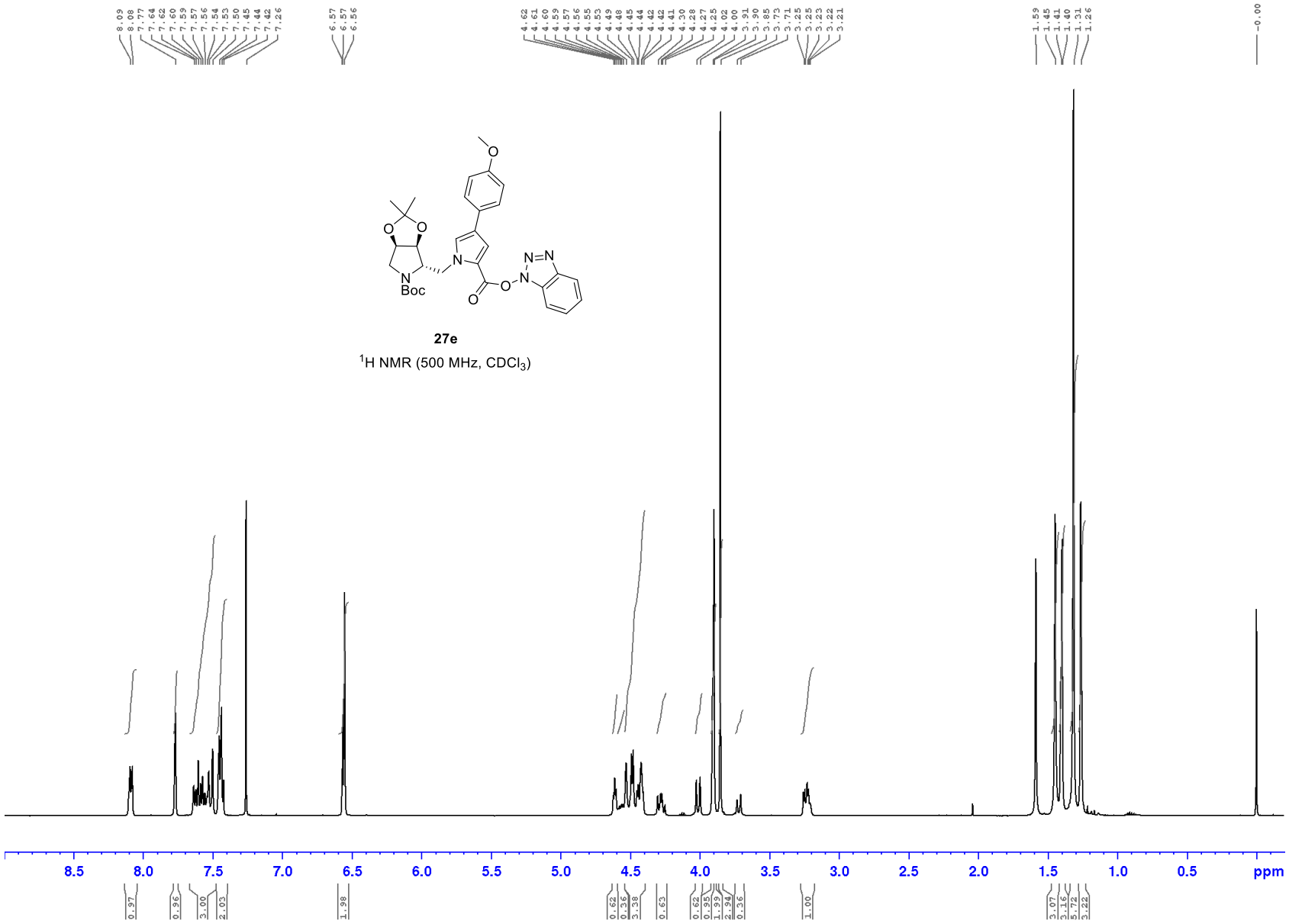
26e

^{13}C NMR (125 MHz, $CDCl_3$)

^exo

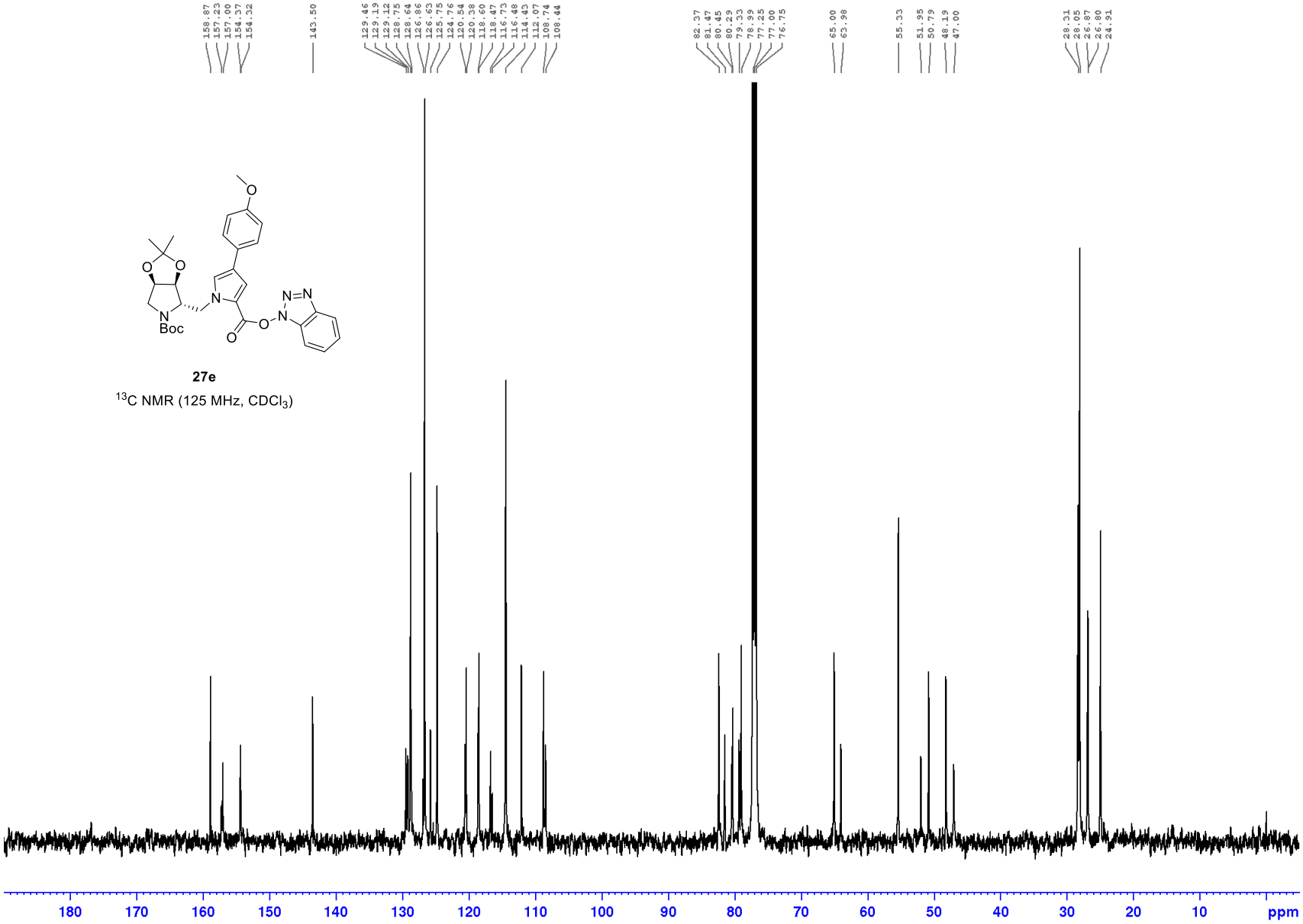


Lab: graham c Not signed STARe SW 9.20



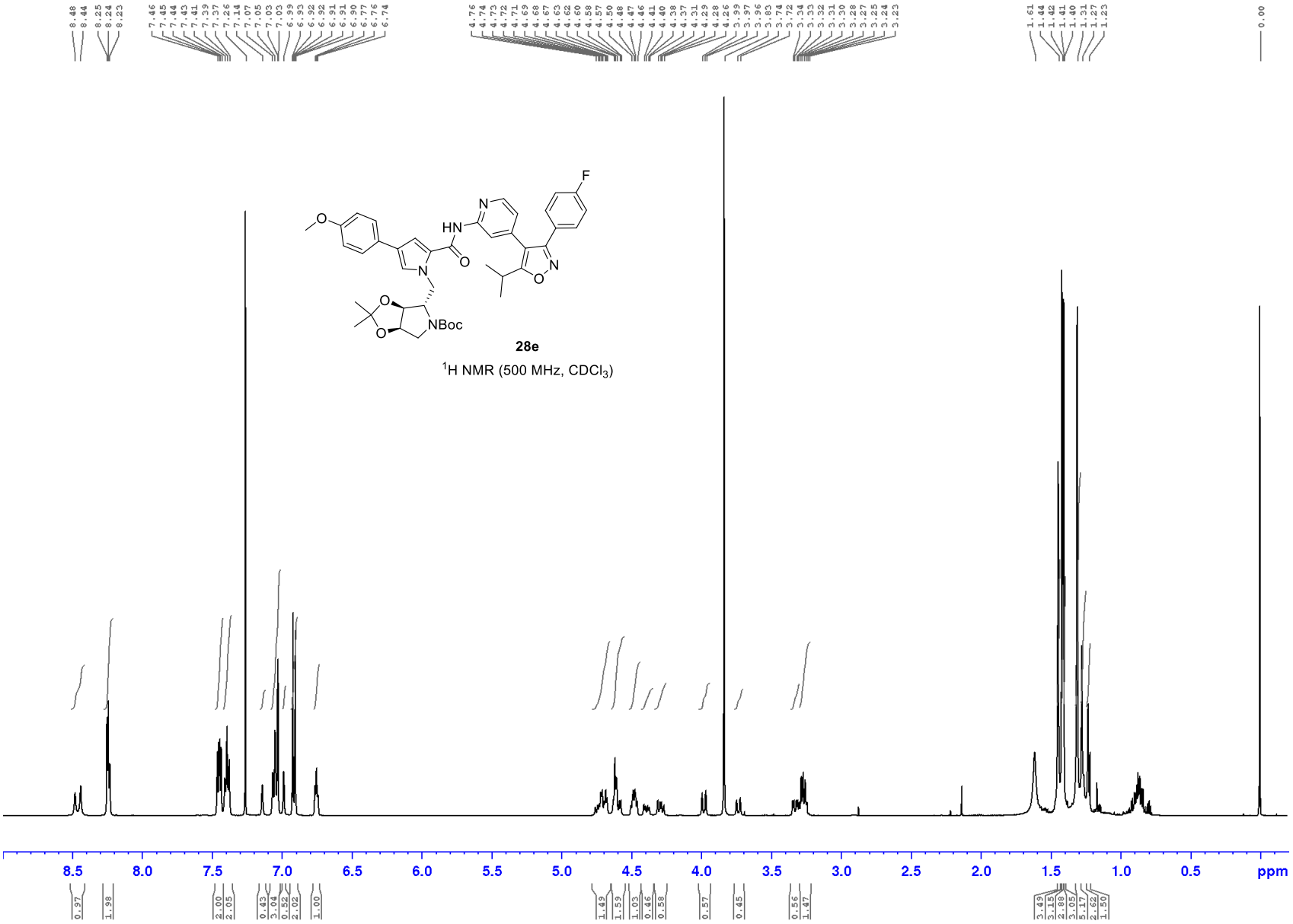
27e

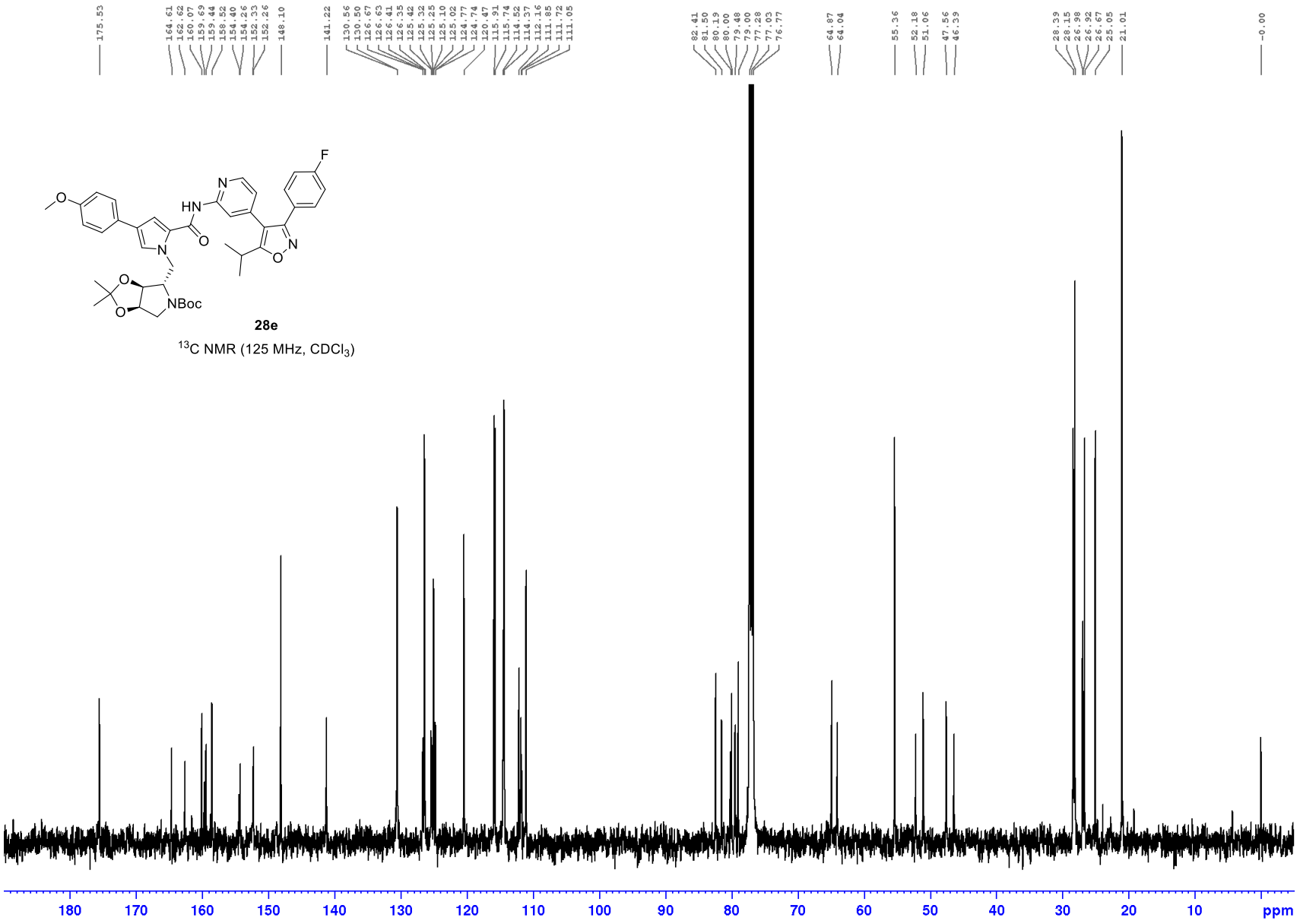
^{1}H NMR (500 MHz, $CDCl_3$)

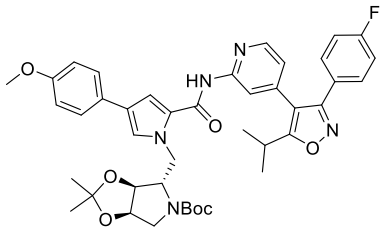


27e

^{13}C NMR (125 MHz, $CDCl_3$)

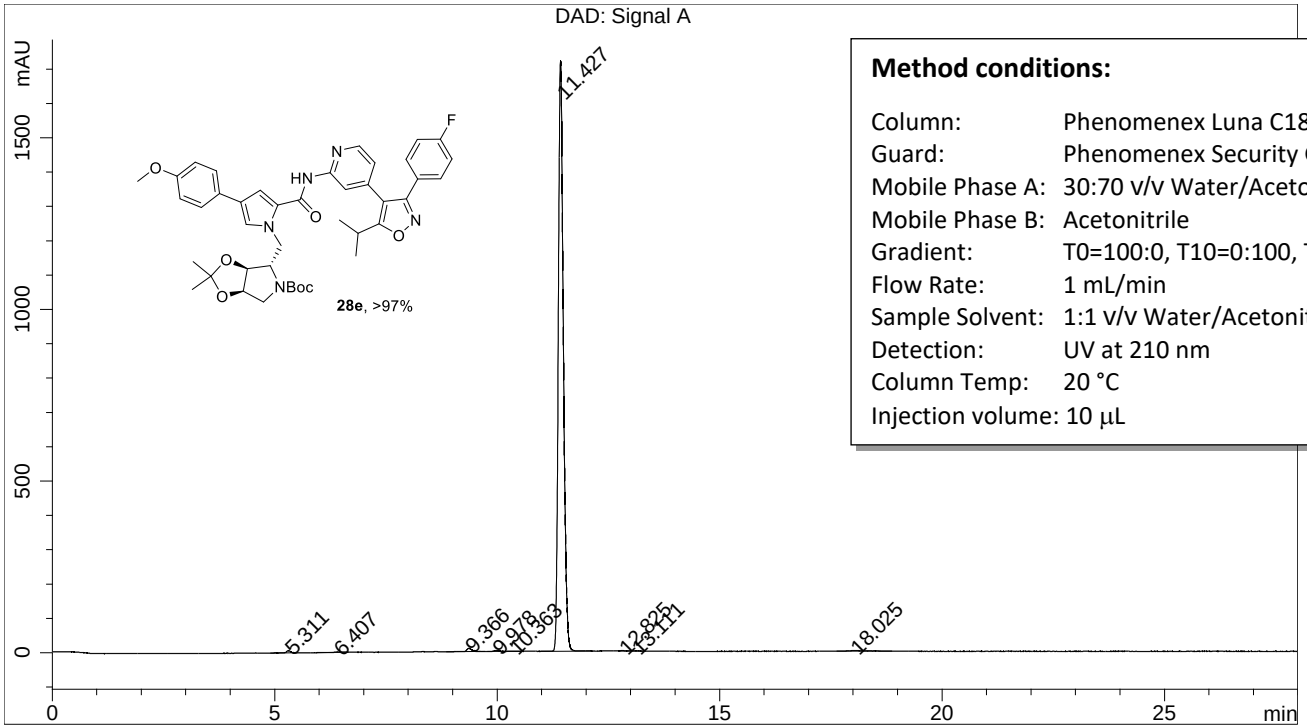

8.48
8.44
8.25
8.24
8.23
7.46
7.45
7.44
7.43
7.41
7.39
7.37
7.26
7.14
7.07
7.05
7.03
7.03
6.99
6.93
6.92
6.92
6.91
6.91
6.90
6.77
6.76
6.74
4.76
4.74
4.73
4.72
4.71
4.69
4.68
4.67
4.63
4.62
4.60
4.58
4.57
4.50
4.48
4.47
4.46
4.41
4.40
4.38
4.37
4.31
4.29
4.28
4.26
3.99
3.97
3.96
3.83
3.74
3.72
3.34
3.33
3.32
3.31
3.30
3.28
3.27
3.25
3.24
3.23
1.61
1.44
1.42
1.41
1.40
1.31
1.27
1.23
0.00
F
N
HN
O
O
N
O
N
O
O
O
NBoc
28e
1H NMR (500 MHz, CDCl3)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
0.97
1.98
2.00
2.05
0.43
3.04
0.52
2.02
1.00
1.49
1.59
1.03
0.46
0.58
0.57
0.45
0.56
1.47
3.49
3.15
2.88
3.05
5.17
2.62
1.50


175.53
164.61
162.62
160.07
159.69
159.44
158.52
154.40
154.26
152.33
152.26
148.10
141.22
130.56
130.50
126.67
126.63
126.41
126.35
125.42
125.32
125.25
125.10
125.02
124.77
124.74
120.47
115.91
115.74
114.52
114.37
112.16
111.85
111.72
111.05
82.41
81.50
80.19
80.00
79.48
79.00
77.28
77.03
76.77
64.87
64.04
55.36
52.18
51.06
47.56
46.39
28.39
28.15
26.98
26.92
26.67
25.05
21.01
0.00
F
N
HN
O
O
N
O
N
O
O
NBoc
28e
13C NMR (125 MHz, CDCl3)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm



28e

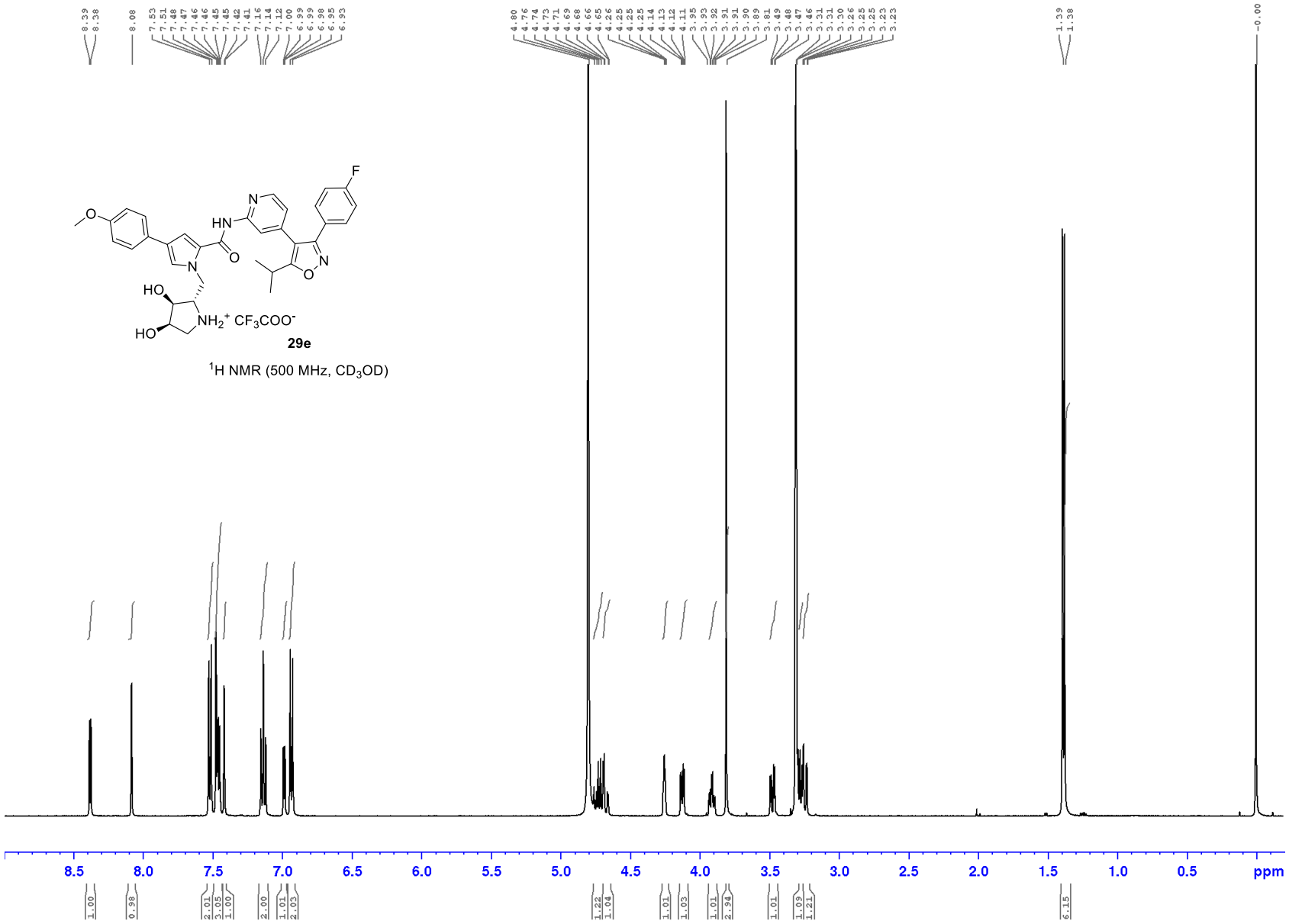
^{19}F NMR (470 MHz, $CDCl_3$)

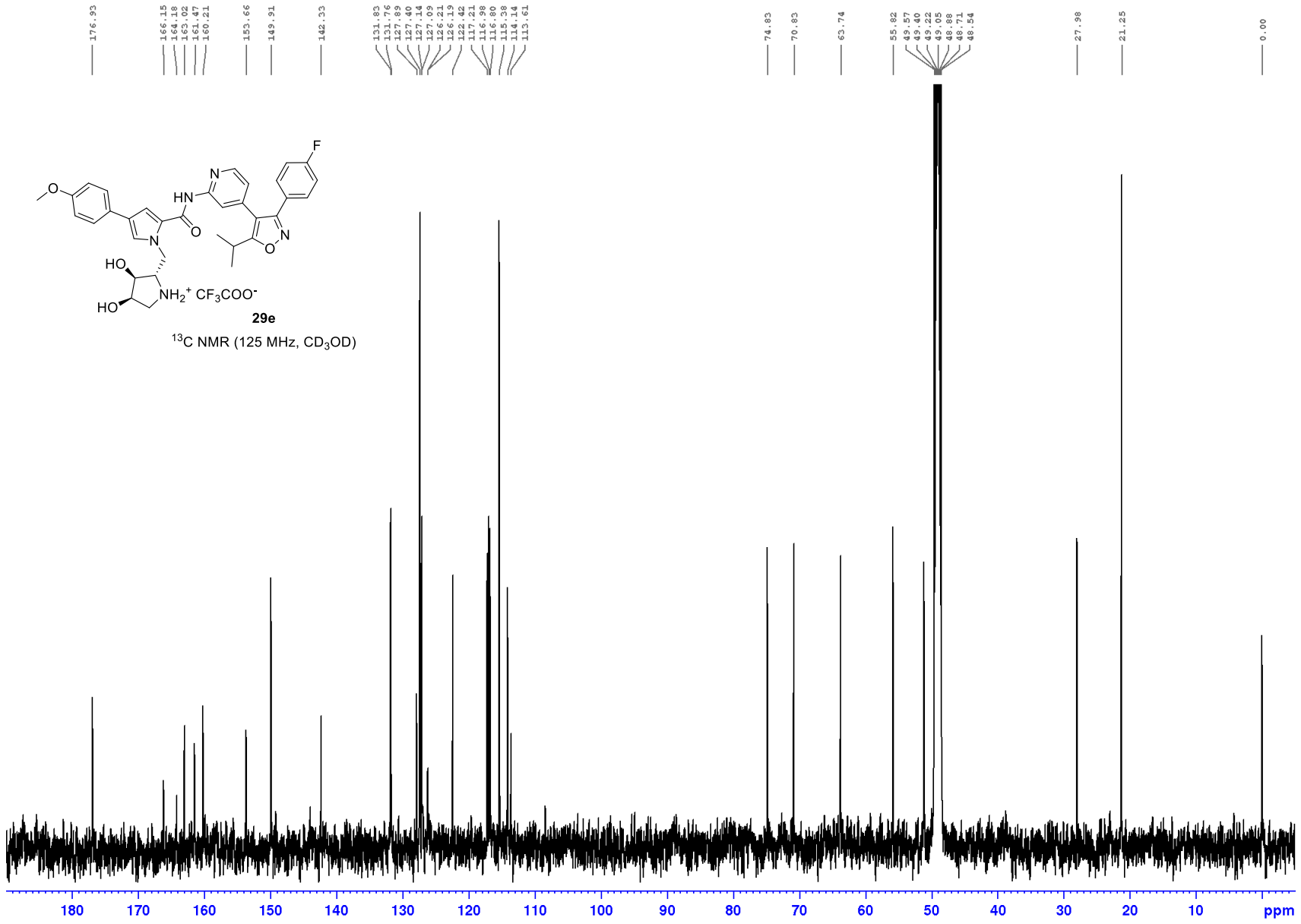


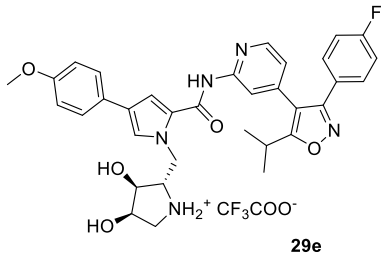
Method conditions:

Column:	Phenomenex Luna C18(2) 5 µm 250x4.6 mm
Guard:	Phenomenex Security Guard C18 RP 4x3 mm
Mobile Phase A:	30:70 v/v Water/Acetonitrile
Mobile Phase B:	Acetonitrile
Gradient:	T0=100:0, T10=0:100, T25=0:100, T26=100:0, T30=100:0
Flow Rate:	1 mL/min
Sample Solvent:	1:1 v/v Water/Acetonitrile
Detection:	UV at 210 nm
Column Temp:	20 °C
Injection volume:	10 µL

Peak#	RT	Peak Height	Peak Area	Width	Area %
1	5.31 min	6.6002	48.4855	0.1117 min	0.349 %
2	6.41 min	1.3068	18.4396	0.1906 min	0.133 %
3	9.37 min	9.4901	88.9598	0.1414 min	0.641 %
4	9.98 min	3.1652	27.9908	0.1332 min	0.202 %
5	10.36 min	1.1050	11.4327	0.1327 min	0.082 %
6	11.43 min	1719.9163	13595.5158	0.1222 min	97.890 %
7	12.83 min	1.3024	9.0087	0.1067 min	0.065 %
8	13.11 min	1.2935	18.4022	0.1840 min	0.132 %
9	18.02 min	2.2031	70.2830	0.3862 min	0.506 %

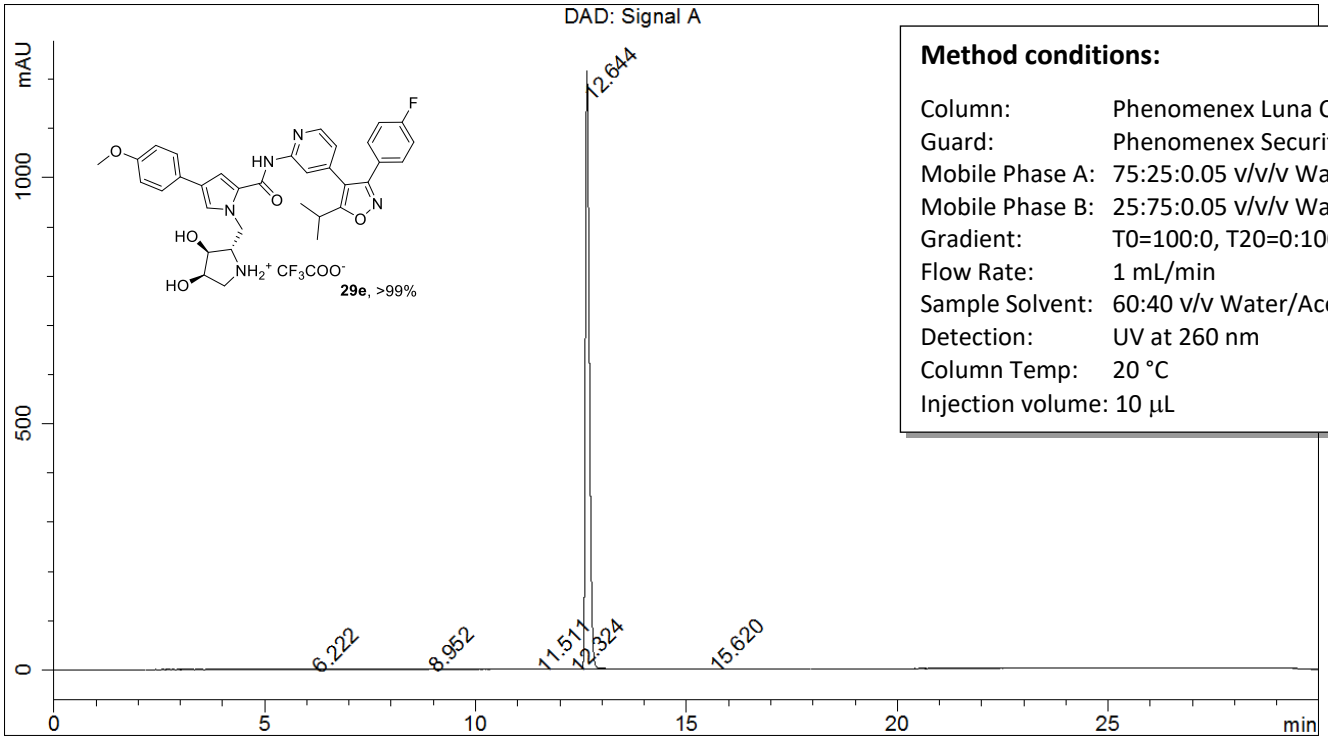

8.39
8.38
8.08
7.53
7.51
7.48
7.47
7.46
7.46
7.45
7.45
7.42
7.41
7.16
7.14
7.12
7.00
6.99
6.98
6.95
6.93
4.80
4.76
4.74
4.73
4.71
4.69
4.68
4.66
4.65
4.26
4.25
4.25
4.25
4.14
4.13
4.12
4.11
3.95
3.93
3.92
3.91
3.91
3.90
3.89
3.81
3.49
3.48
3.47
3.46
3.31
3.31
3.30
3.26
3.25
3.25
3.23
3.23
1.39
1.38
0.00
F
N
HN
O
O
N
N
O
N
HO
HO
NH2+ CF3COO-
29e
1H NMR (500 MHz, CD3OD)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
0.98
2.01
3.05
1.00
2.00
1.01
2.03
1.22
1.04
1.01
1.03
1.01
2.94
1.01
1.09
1.21
6.15


176.93
166.15
164.18
163.02
161.47
160.21
153.66
149.91
142.33
131.83
131.76
127.89
127.40
127.14
127.09
126.21
126.19
122.42
117.21
116.98
116.80
115.38
114.14
113.61
74.83
70.83
63.74
55.82
49.57
49.40
49.22
49.05
48.88
48.71
48.54
27.98
21.25
0.00
HO
HO
NH2+ CF3COO-
29e
13C NMR (125 MHz, CD3OD)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm



29e

^{19}F NMR (470 MHz, CD_3OD)

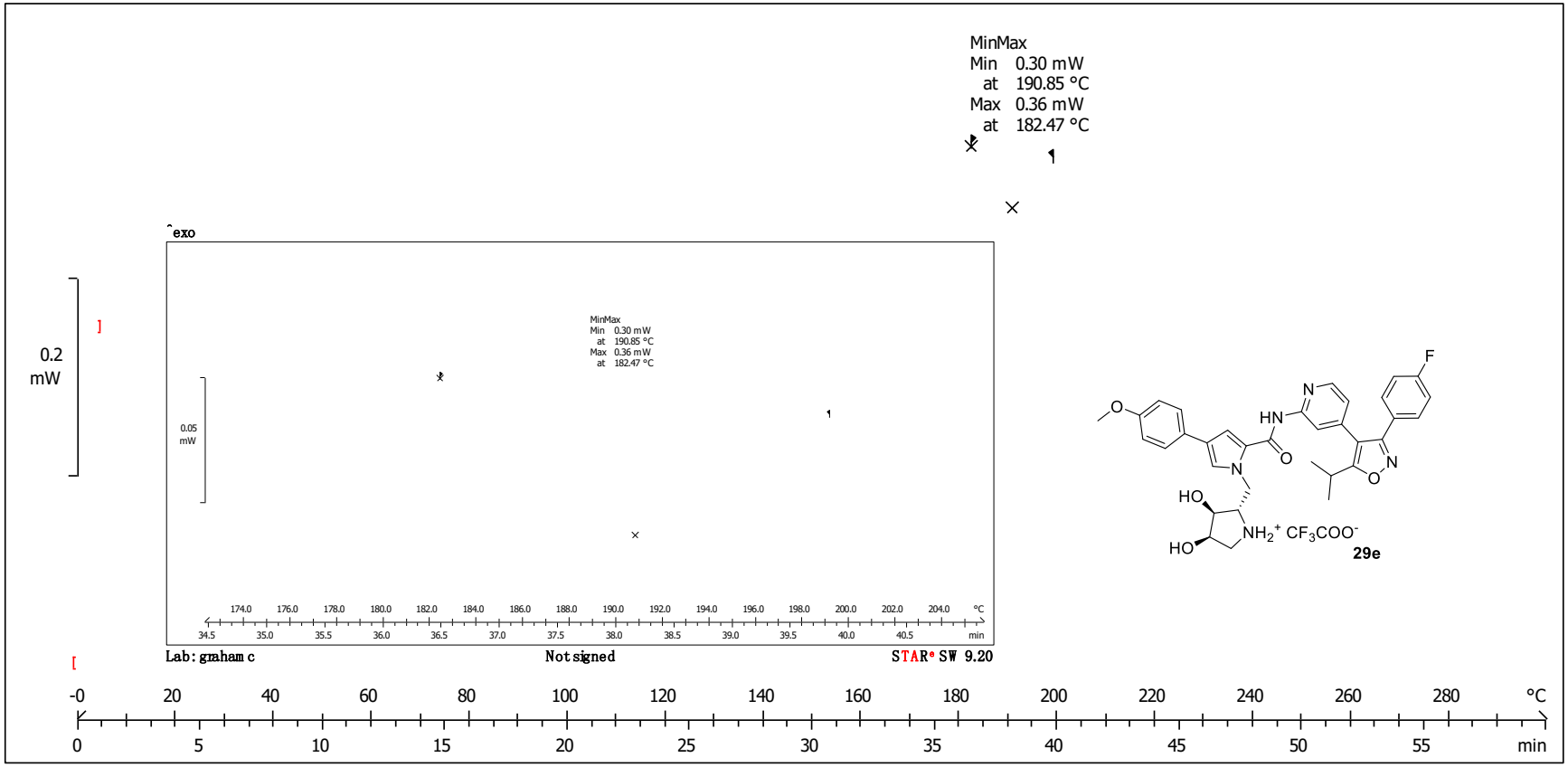


Method conditions:

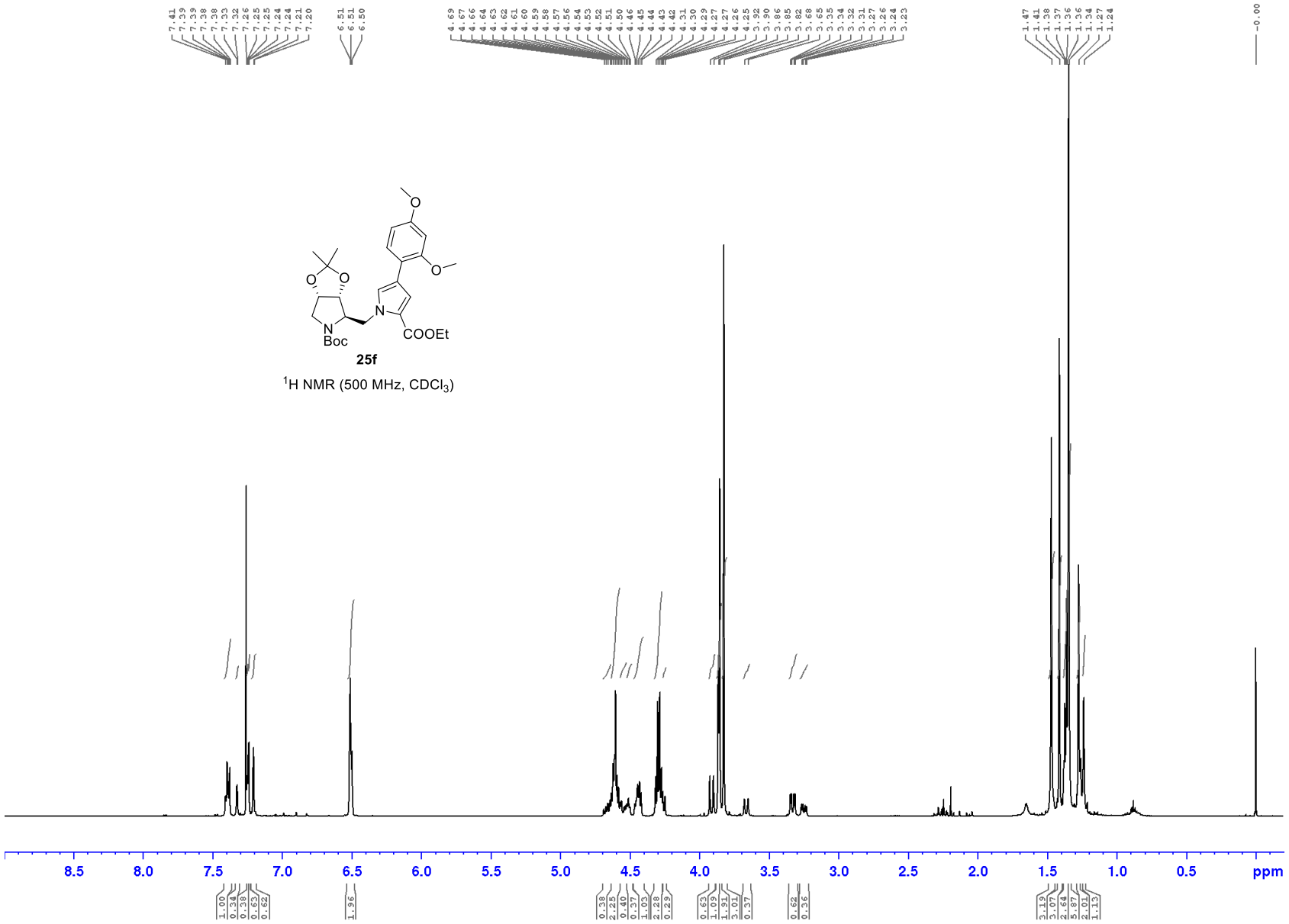
Column:	Phenomenex Luna C18(2) 5 µm 250x4.6 mm
Guard:	Phenomenex Security Guard C18 RP 4x3 mm
Mobile Phase A:	75:25:0.05 v/v/v Water/Acetonitrile/Trifluoroacetic acid
Mobile Phase B:	25:75:0.05 v/v/v Water/Acetonitrile/Trifluoroacetic acid
Gradient:	T0=100:0, T20=0:100, T26=0:100, T27=100:0, T30=100:0
Flow Rate:	1 mL/min
Sample Solvent:	60:40 v/v Water/Acetonitrile
Detection:	UV at 260 nm
Column Temp:	20 °C
Injection volume:	10 µL

Peak#	RT	Peak Height	Peak Area	Width	Area %
1	6.22 min	0.3135	2.4773	0.1062 min	0.032 %
2	8.95 min	0.9501	7.0386	0.1104 min	0.090 %
3	11.51 min	0.3280	2.4689	0.1098 min	0.032 %
4	12.32 min	0.2550	2.5112	0.1369 min	0.032 %
5	12.64 min	1212.4782	7789.9356	0.1010 min	99.782 %
6	15.62 min	0.3299	2.5140	0.1049 min	0.032 %

^exo



Lab: graham c Not signed STARe SW 9.20


7.41
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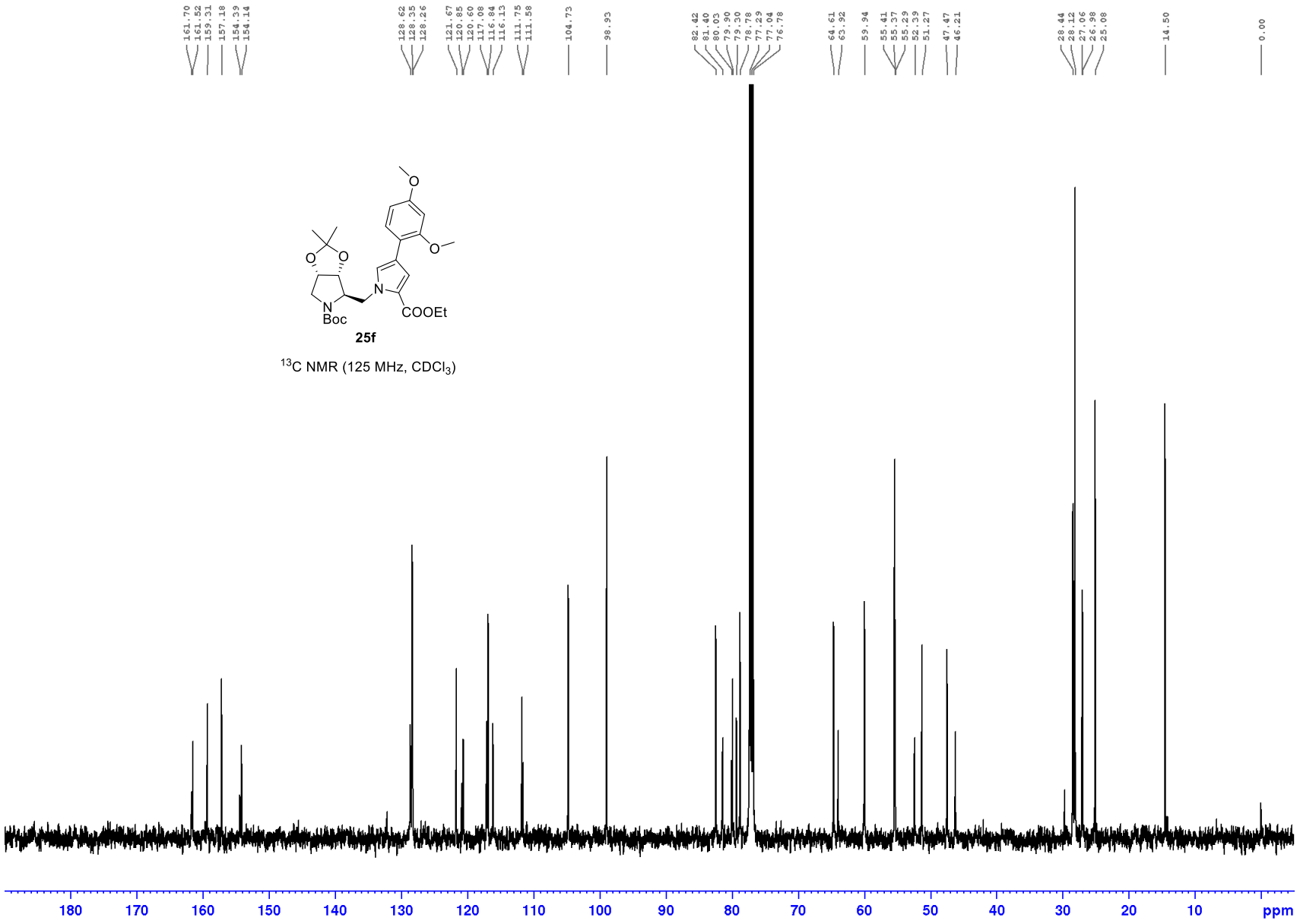
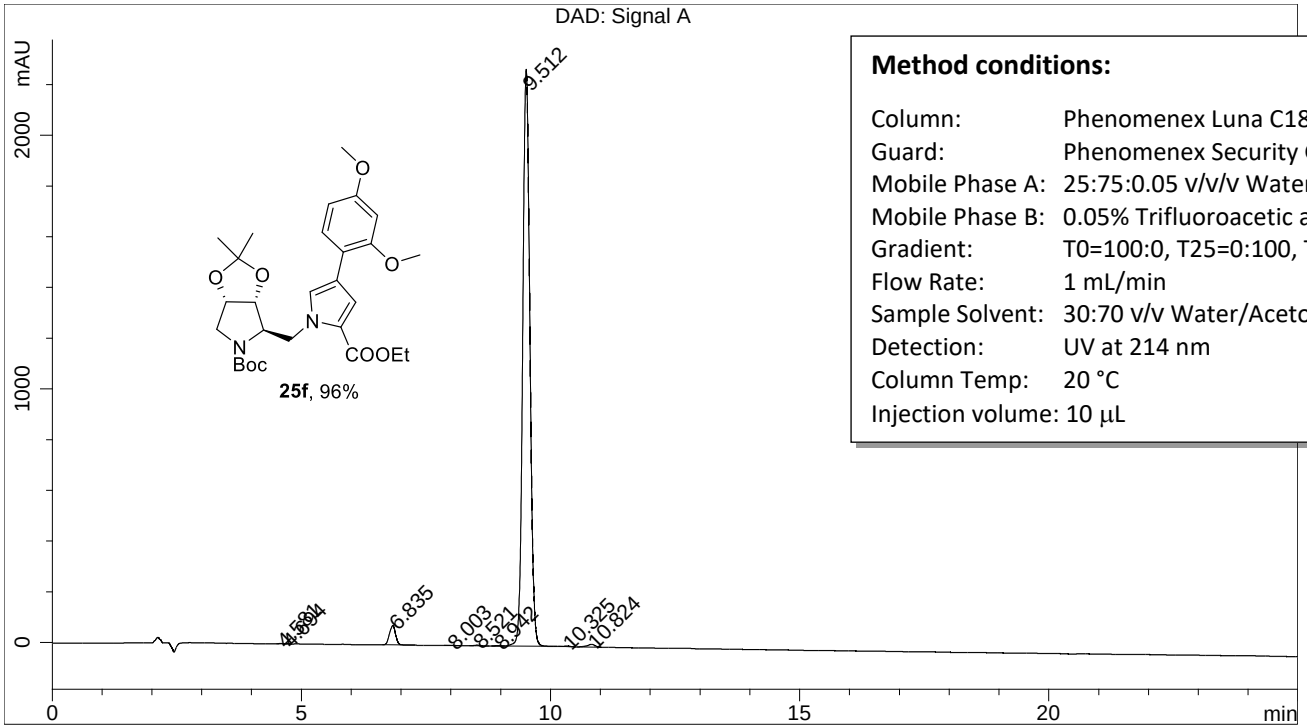
7.39
7.38
7.38
7.33
7.32
7.26
7.25
7.25
7.24
7.24
7.21
7.20
6.51
6.51
6.50
4.69
4.67
4.66
4.64
4.63
4.62
4.61
4.60
4.59
4.58
4.57
4.56
4.54
4.53
4.52
4.51
4.50
4.46
4.45
4.44
4.43
4.42
4.31
4.30
4.29
4.27
4.27
4.26
4.25
3.92
3.90
3.86
3.85
3.82
3.68
3.65
3.35
3.34
3.32
3.31
3.27
3.26
3.24
3.23
1.47
1.41
1.38
1.37
1.36
1.36
1.34
1.27
1.24
0.00
O
O
O
O
N
N
Boc
COOEt
25f
1H NMR (500 MHz, CDCl3)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
0.34
0.38
0.63
0.62
1.96
0.38
2.25
0.40
0.37
1.03
2.28
0.29
0.63
1.09
1.91
3.01
0.37
0.62
0.36
3.19
3.07
2.64
5.87
2.01
1.15



25f

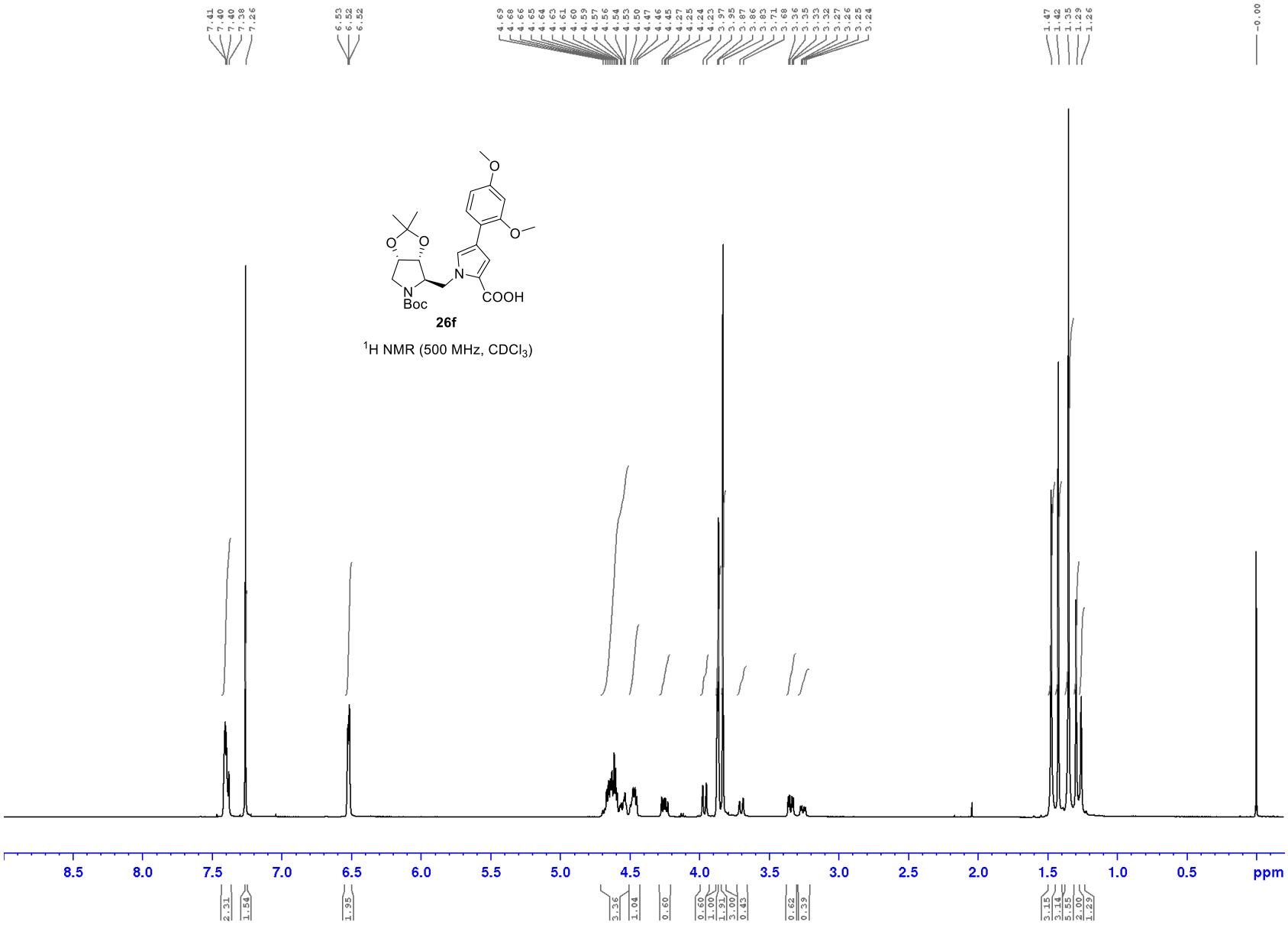
^{13}C NMR (125 MHz, $CDCl_3$)

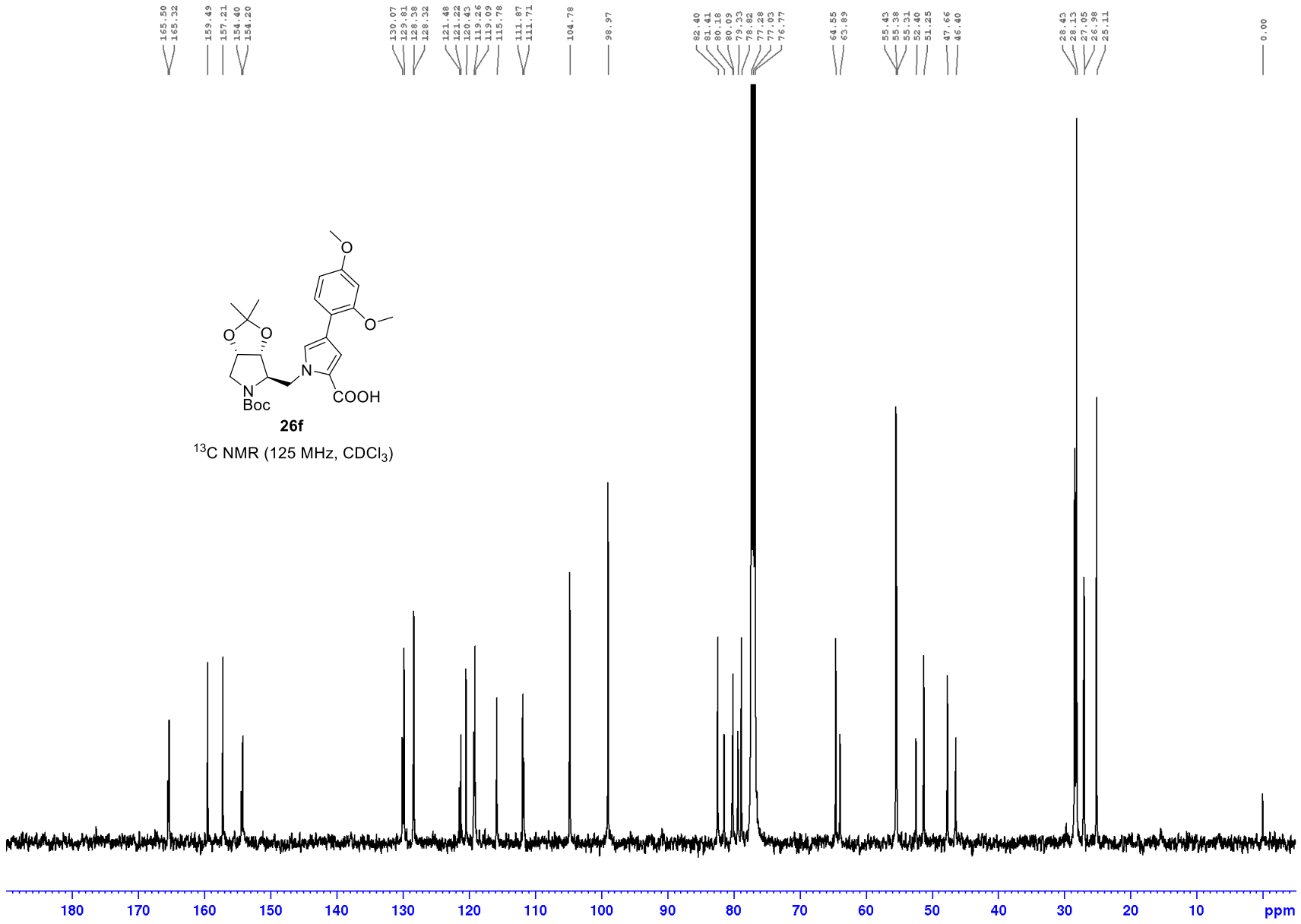


Method conditions:

Column:	Phenomenex Luna C18(2) 5 μm 250x4.6 mm
Guard:	Phenomenex Security Guard C18 RP 4x3 mm
Mobile Phase A:	25:75:0.05 v/v/v Water/Acetonitrile/Trifluoroacetic acid
Mobile Phase B:	0.05% Trifluoroacetic acid in Acetonitrile
Gradient:	T0=100:0, T25=0:100, T27=100:0, T30=100:0
Flow Rate:	1 mL/min
Sample Solvent:	30:70 v/v Water/Acetonitrile
Detection:	UV at 214 nm
Column Temp:	20 °C
Injection volume:	10 μL

Peak#	RT	Peak Height	Peak Area	Width	Area %
1	4.58 min	1.5802	7.3159	0.0700 min	0.031 %
2	4.69 min	1.1586	5.6539	0.0739 min	0.024 %
3	6.83 min	76.3939	659.8776	0.1388 min	2.795 %
4	8.00 min	1.1227	10.1224	0.1182 min	0.043 %
5	8.52 min	2.6948	21.8419	0.1166 min	0.093 %
6	8.94 min	2.0132	14.1223	0.1058 min	0.060 %
7	9.51 min	2275.5883	22691.4871	0.1543 min	96.128 %
8	10.33 min	2.4873	22.3606	0.1309 min	0.095 %
9	10.82 min	11.1983	121.0166	0.1591 min	0.513 %
10	26.50 min	2.9797	51.6757	0.2053 min	0.219 %

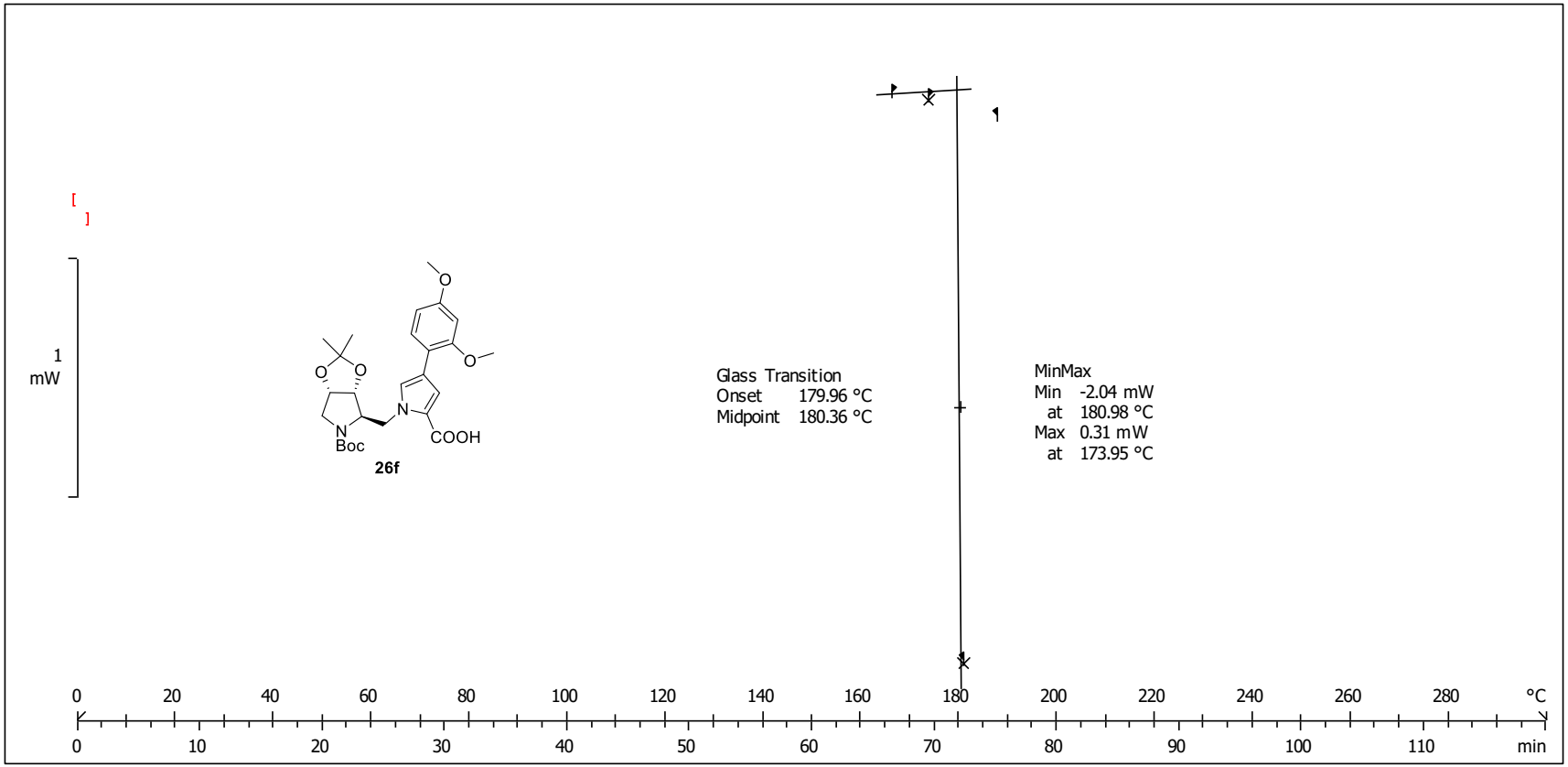

7.41
7.40
7.40
7.38
7.26
6.53
6.52
6.52
4.69
4.68
4.66
4.65
4.64
4.63
4.61
4.60
4.59
4.57
4.56
4.54
4.53
4.50
4.47
4.46
4.45
4.27
4.25
4.24
4.23
3.97
3.95
3.87
3.86
3.83
3.71
3.68
3.36
3.35
3.33
3.32
3.27
3.26
3.25
3.24
1.47
1.42
1.35
1.29
1.26
-0.00
O
O
O
O
N
N
Boc
COOH
26f
1H NMR (500 MHz, CDCl3)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.31
1.54
1.95
3.36
1.04
0.60
0.60
1.00
1.91
3.00
0.43
0.62
0.39
3.15
3.14
5.55
2.00
1.29



26f

^{13}C NMR (125 MHz, $CDCl_3$)

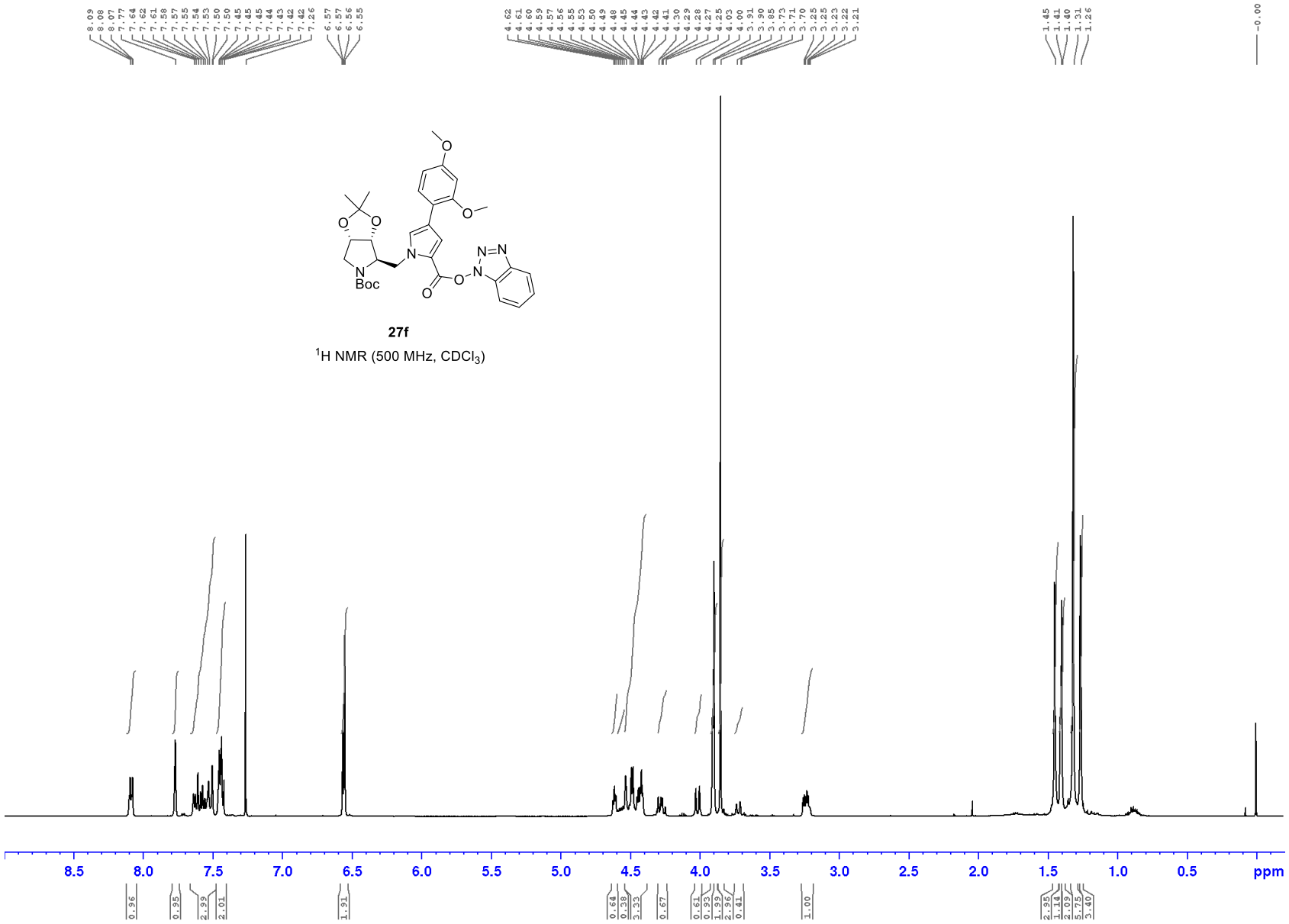
^exo



Lab: graham c

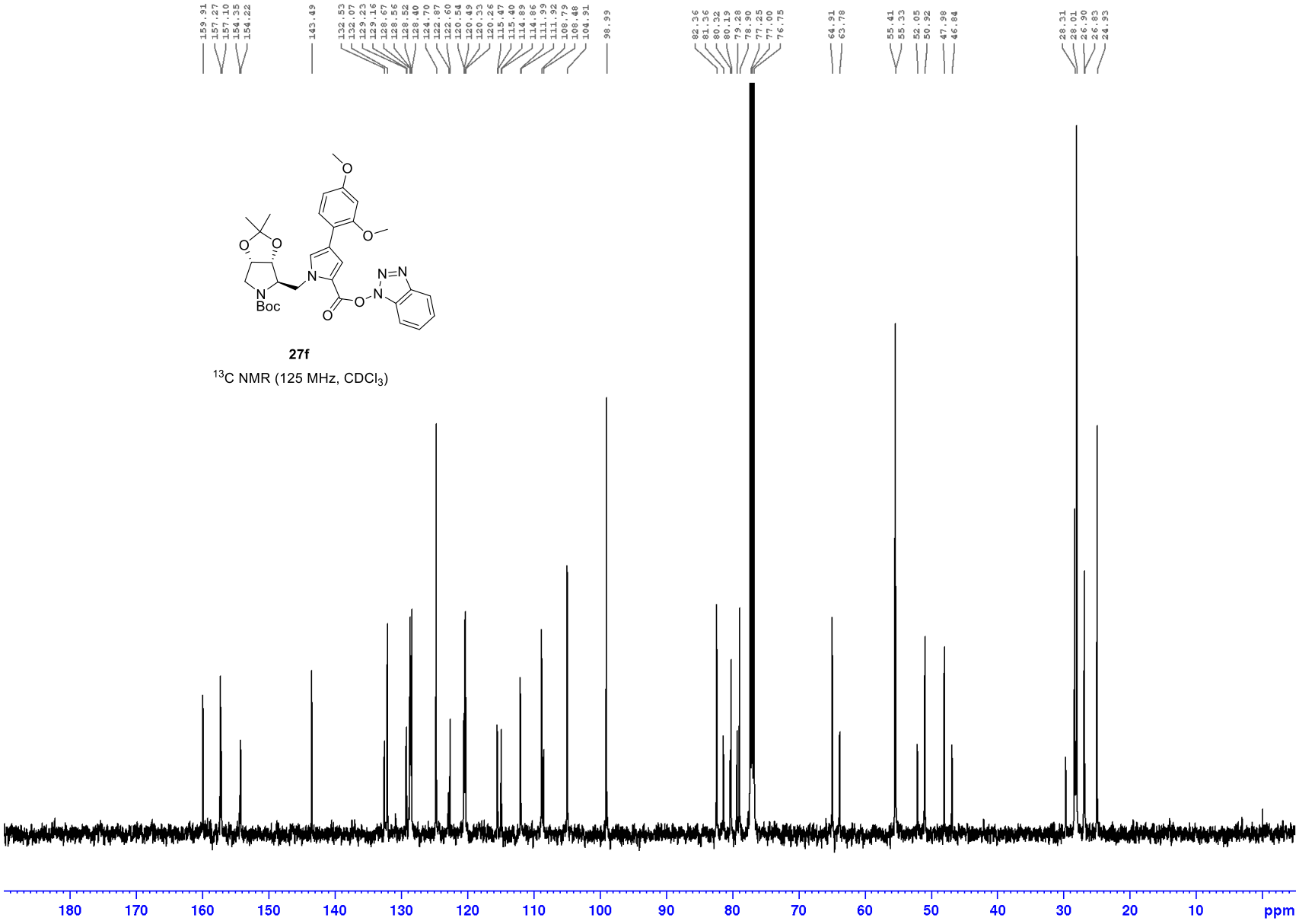
Not signed

STARe SW 9.20



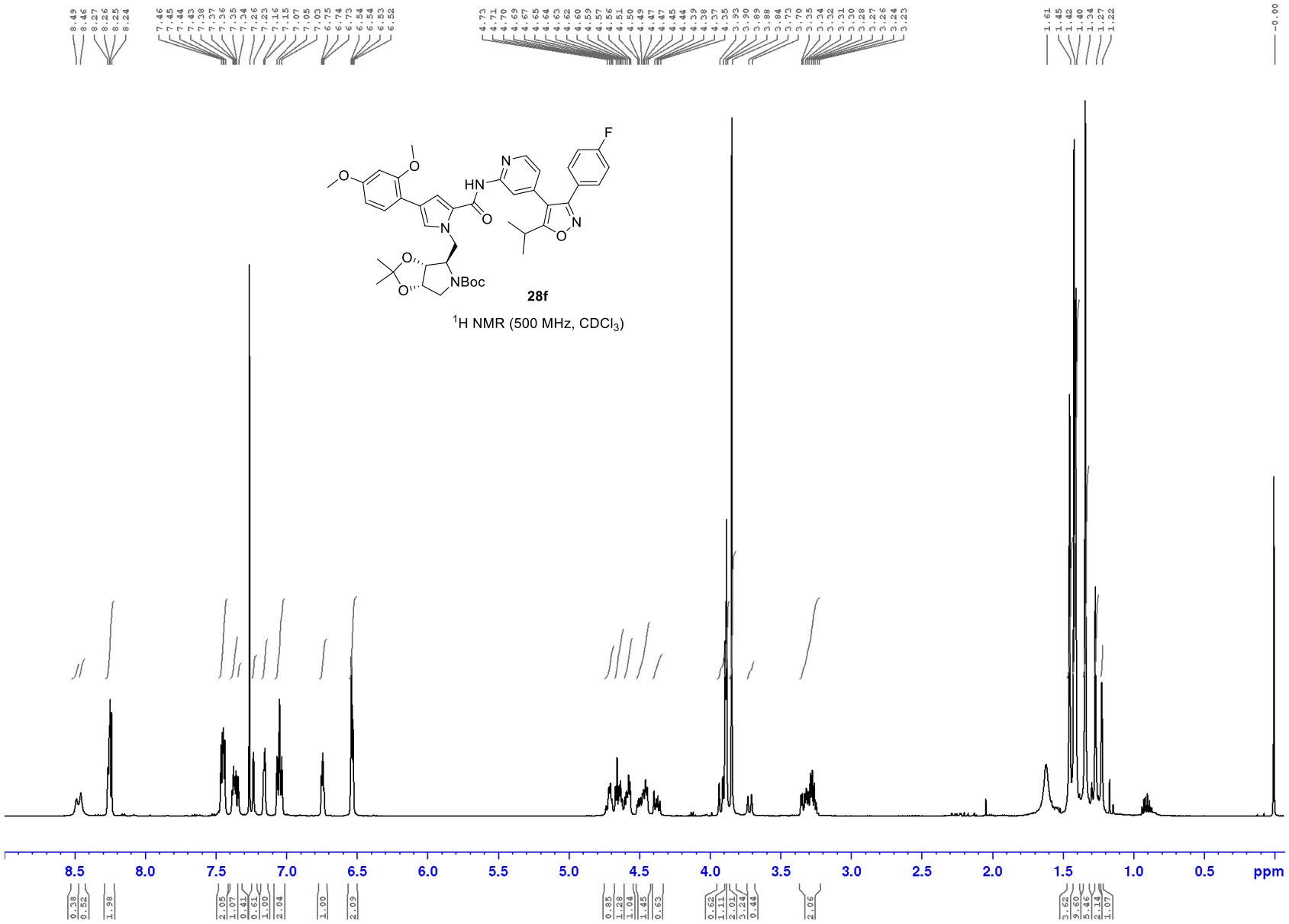
27f

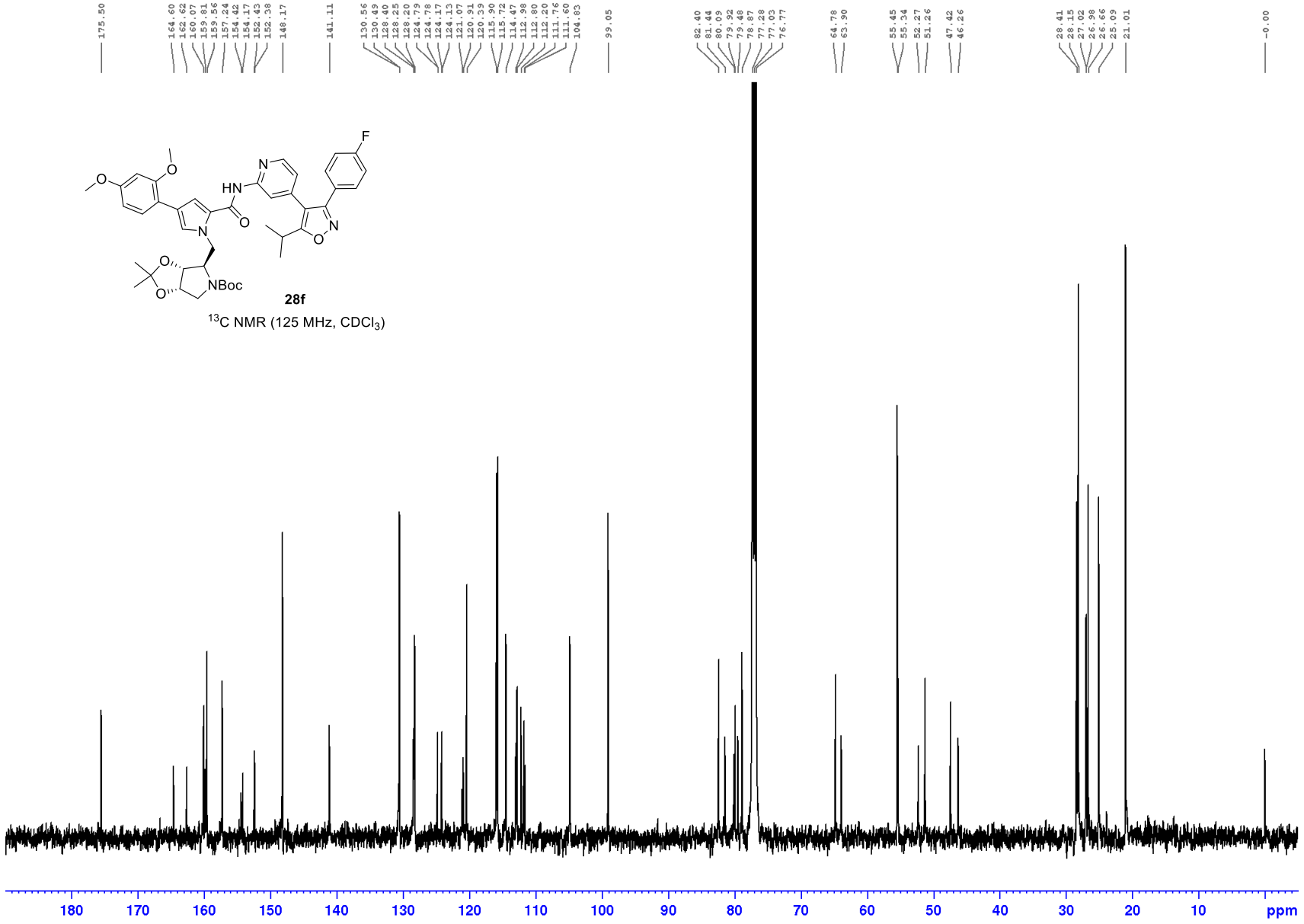
^{1}H NMR (500 MHz, $CDCl_3$)

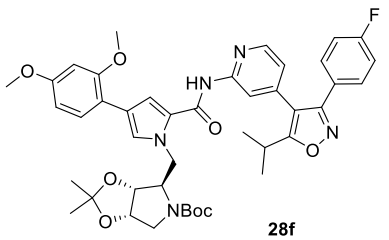


27f

^{13}C NMR (125 MHz, $CDCl_3$)

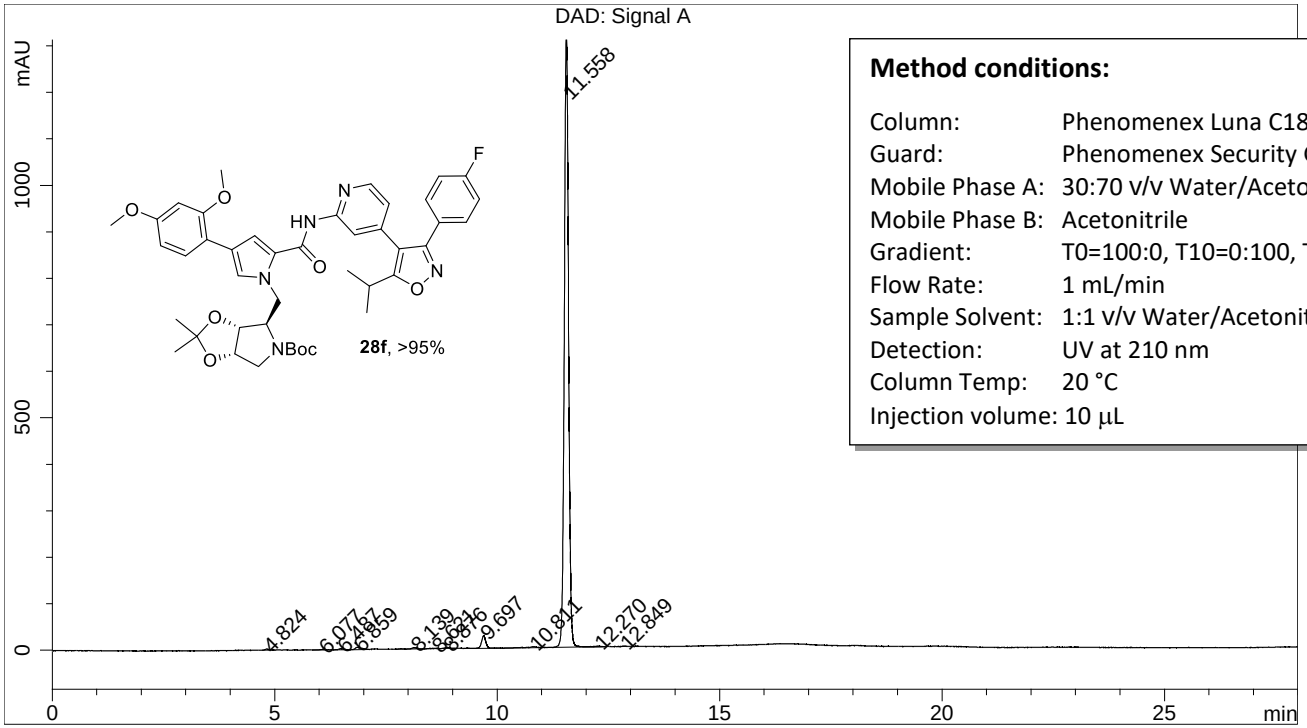

8.49
8.46
8.27
8.26
8.25
8.24
7.46
7.45
7.44
7.43
7.38
7.37
7.36
7.35
7.34
7.26
7.23
7.16
7.15
7.07
7.05
7.03
6.75
6.74
6.73
6.54
6.54
6.53
6.52
4.73
4.71
4.70
4.69
4.67
4.65
4.64
4.63
4.60
4.59
4.57
4.56
4.51
4.50
4.49
4.47
4.47
4.45
4.44
4.39
4.38
4.37
4.35
3.93
3.90
3.89
3.88
3.84
3.73
3.70
3.35
3.34
3.32
3.31
3.30
3.28
3.27
3.26
3.24
3.23
1.61
1.45
1.42
1.40
1.34
1.27
1.22
-0.00
F
N
HN
O
O
O
N
N
O
O
O
NBoc
28f
^{1}H NMR (500 MHz, $CDCl_3$)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
0.38
0.52
1.98
2.05
1.07
0.41
0.61
1.00
2.04
1.00
2.09
0.85
1.28
1.04
1.45
0.63
0.62
1.11
2.01
3.24
0.44
2.06
3.62
9.60
5.46
2.14
1.07


175.50
164.60
162.62
160.07
159.81
159.56
157.24
154.42
154.17
152.43
152.38
148.17
141.11
130.56
130.49
128.40
128.25
128.20
124.79
124.78
124.17
124.13
121.07
120.91
120.39
115.90
115.72
114.47
112.98
112.80
112.20
111.76
111.60
104.83
99.05
82.40
81.44
80.09
79.92
79.48
78.87
77.28
77.03
76.77
64.78
63.90
55.45
55.34
52.27
51.26
47.42
46.26
28.41
28.15
27.02
26.98
26.66
25.09
21.01
-0.00
F
N
HN
O
O
O
N
O
N
O
O
NBoc
28f
^{13}C NMR (125 MHz, $CDCl_3$)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm



28f

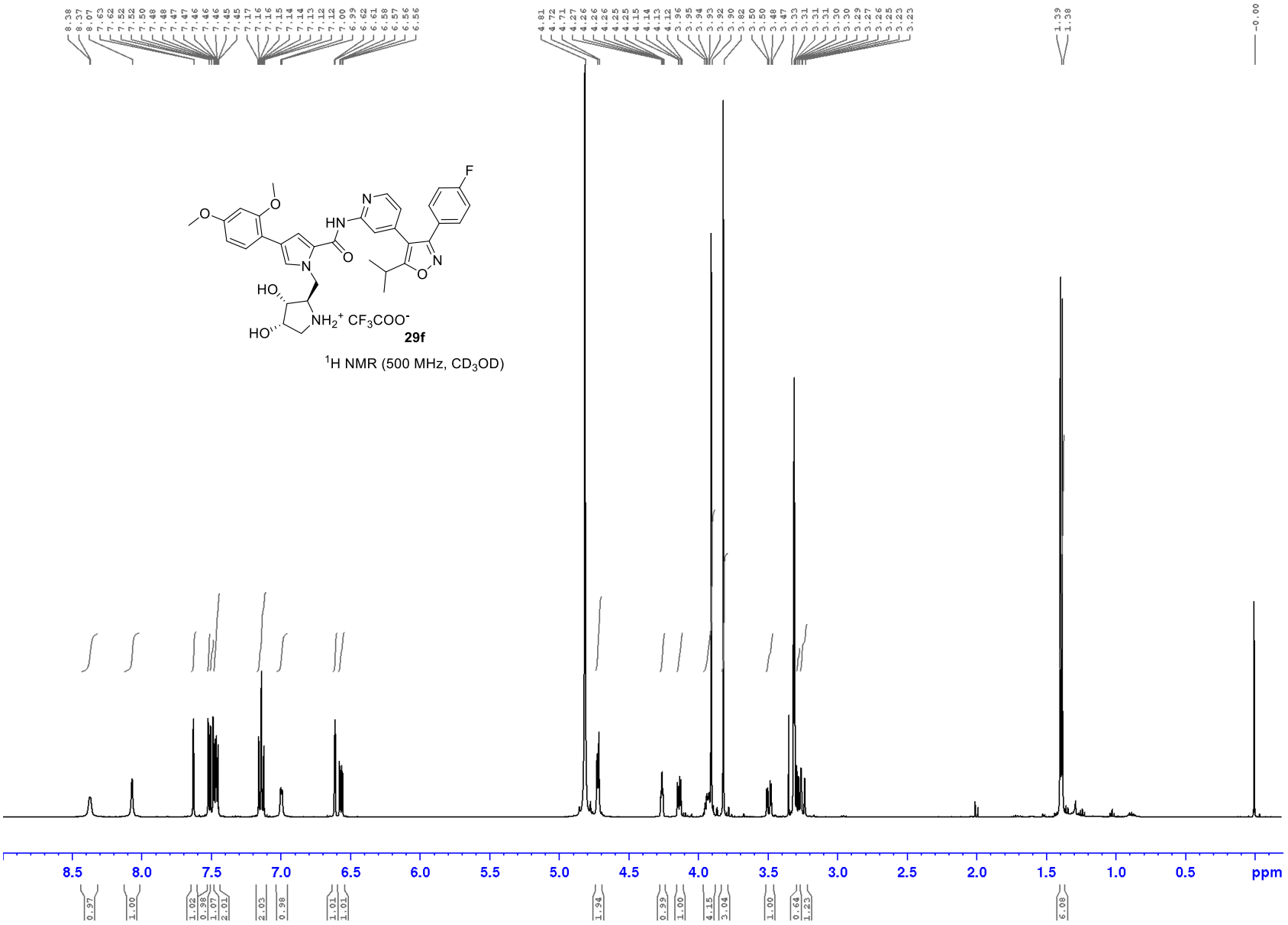
^{19}F NMR (470 MHz, $CDCl_3$)

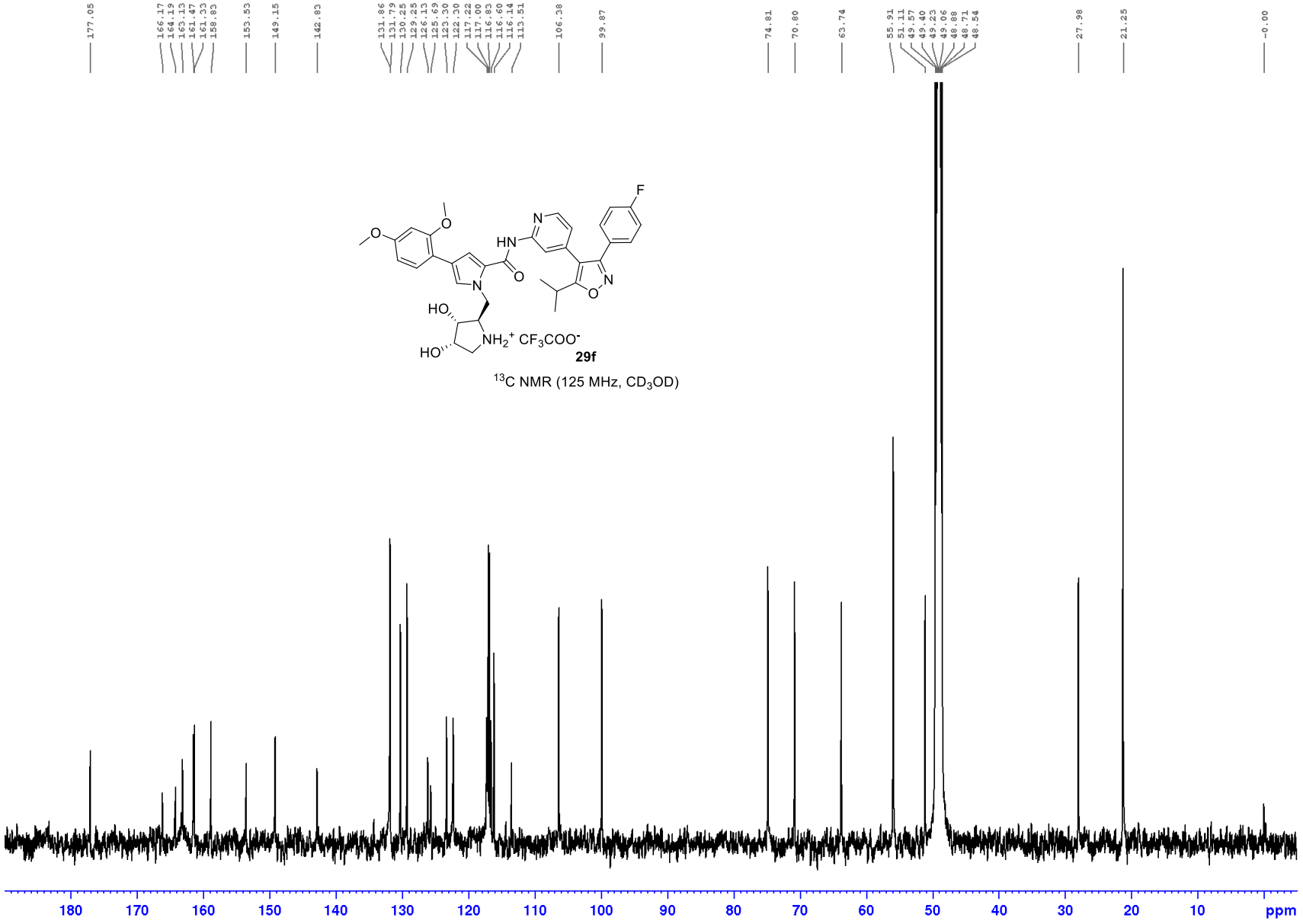


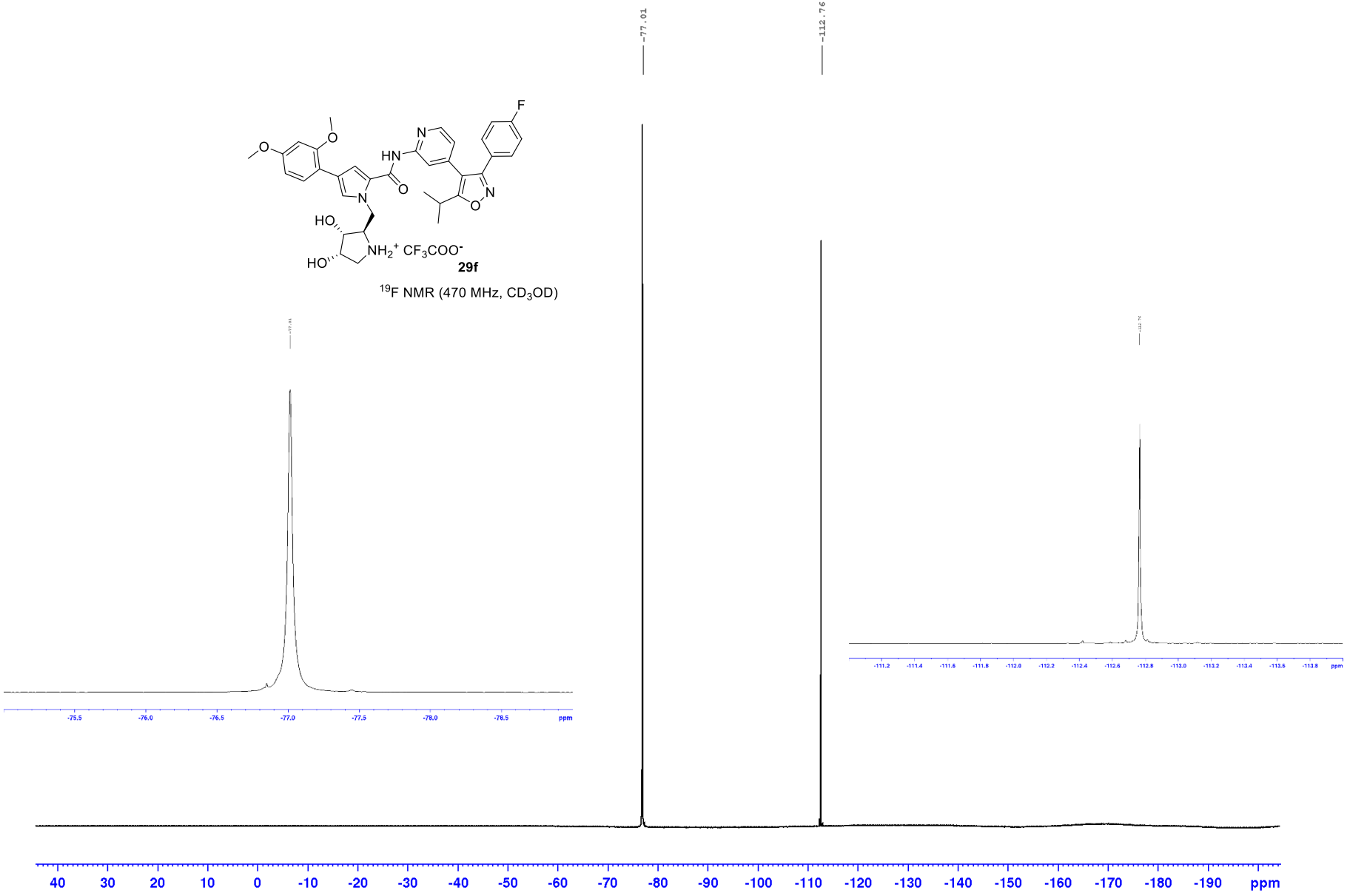
Method conditions:

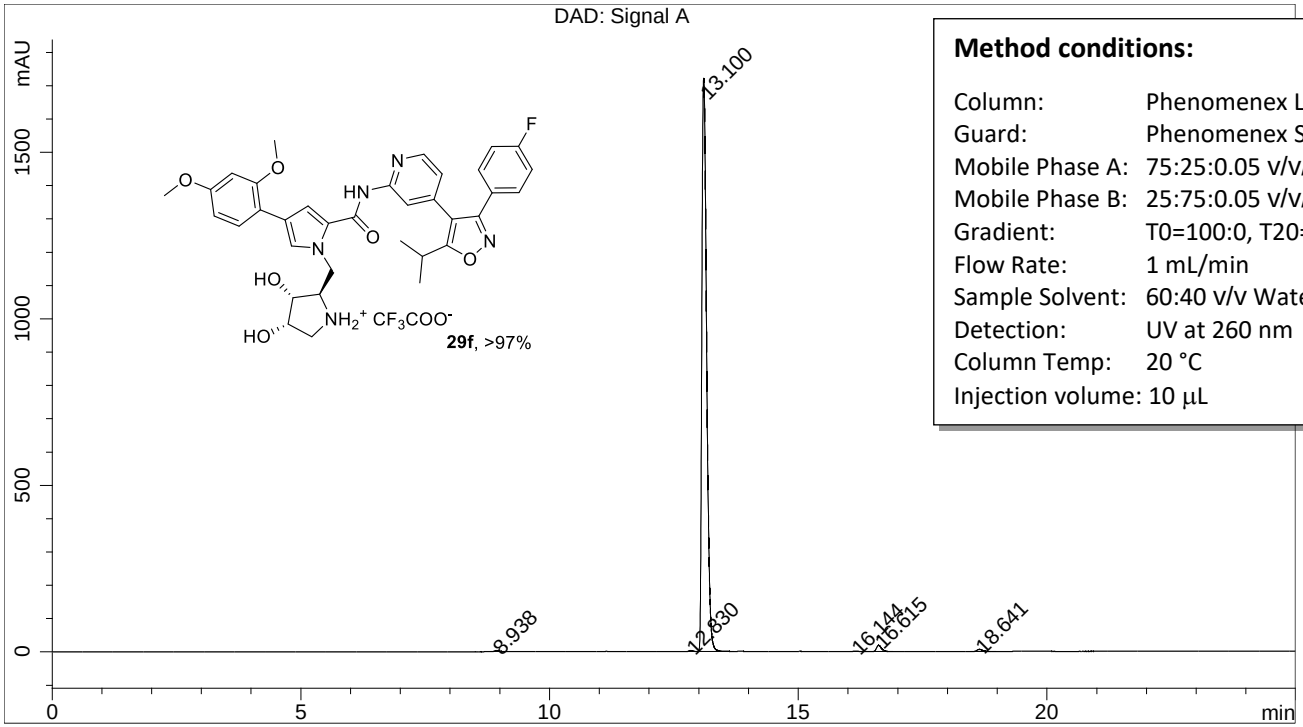
Column:	Phenomenex Luna C18(2) 5 μm 250x4.6 mm
Guard:	Phenomenex Security Guard C18 RP 4x3 mm
Mobile Phase A:	30:70 v/v Water/Acetonitrile
Mobile Phase B:	Acetonitrile
Gradient:	T0=100:0, T10=0:100, T25=0:100, T26=100:0, T30=100:0
Flow Rate:	1 mL/min
Sample Solvent:	1:1 v/v Water/Acetonitrile
Detection:	UV at 210 nm
Column Temp:	20 °C
Injection volume:	10 μL

Peak#	RT	Peak Height	Peak Area	Width	Area %
1	4.82 min	2.7041	17.6194	0.0960 min	0.191 %
2	6.08 min	1.2853	9.6737	0.1018 min	0.105 %
3	6.49 min	2.7224	21.8489	0.1076 min	0.236 %
4	6.86 min	5.2495	52.2254	0.1381 min	0.565 %
5	8.14 min	2.7890	28.8267	0.1546 min	0.312 %
6	8.62 min	1.1863	11.9298	0.1333 min	0.129 %
7	8.88 min	2.4926	18.0094	0.1003 min	0.195 %
8	9.70 min	27.1837	199.0857	0.1114 min	2.155 %
9	10.81 min	2.6208	43.3878	0.2111 min	0.470 %
10	11.56 min	1328.6727	8803.4072	0.1033 min	95.278 %
11	12.27 min	2.0066	27.2528	0.1785 min	0.295 %
12	12.85 min	1.0242	6.4870	0.1079 min	0.070 %


8.38
8.37
8.07
7.63
7.62
7.52
7.52
7.50
7.48
7.48
7.47
7.47
7.46
7.46
7.46
7.45
7.45
7.17
7.16
7.16
7.15
7.14
7.14
7.13
7.12
7.12
7.00
6.99
6.62
6.61
6.58
6.57
6.56
6.56
4.81
4.72
4.71
4.27
4.26
4.26
4.26
4.25
4.25
4.15
4.14
4.13
4.12
3.96
3.95
3.94
3.93
3.92
3.90
3.82
3.50
3.50
3.48
3.47
3.33
3.31
3.31
3.31
3.30
3.30
3.29
3.27
3.26
3.25
3.23
3.23
1.39
1.38
0.00
F
N
HN
O
O
O
N
N
O
N
HO
HO
NH2+ CF3COO-
29f
1H NMR (500 MHz, CD3OD)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
0.97
1.00
1.02
0.98
1.07
2.01
2.03
0.98
1.01
1.01
1.94
0.99
1.00
4.15
3.04
1.00
0.64
1.23
6.08


177.05
166.17
164.19
163.13
161.47
161.33
158.83
153.53
149.15
142.83
131.86
131.79
130.25
129.25
126.13
125.69
123.30
122.30
117.22
117.00
116.83
116.60
116.14
113.51
106.38
99.87
74.81
70.80
63.74
55.91
51.11
49.57
49.40
49.23
49.06
48.88
48.71
48.54
27.98
21.25
-0.00
F
N
HN
O
O
N
O
N
HO
HO
NH2+ CF3COO-
29f
13C NMR (125 MHz, CD3OD)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

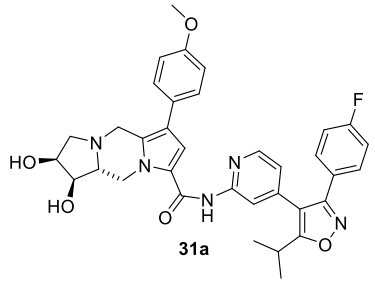

-77.01
-112.76
F
N
HN
O
O
O
N
N
O
HO
HO
NH2+ CF3COO-
29f
19F NMR (470 MHz, CD3OD)
-75.5
-76.0
-76.5
-77.0
-77.5
-78.0
-78.5
ppm
-111.2
-111.4
-111.6
-111.8
-112.0
-112.2
-112.4
-112.6
-112.8
-113.0
-113.2
-113.4
-113.6
-113.8
ppm
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
ppm



Method conditions:

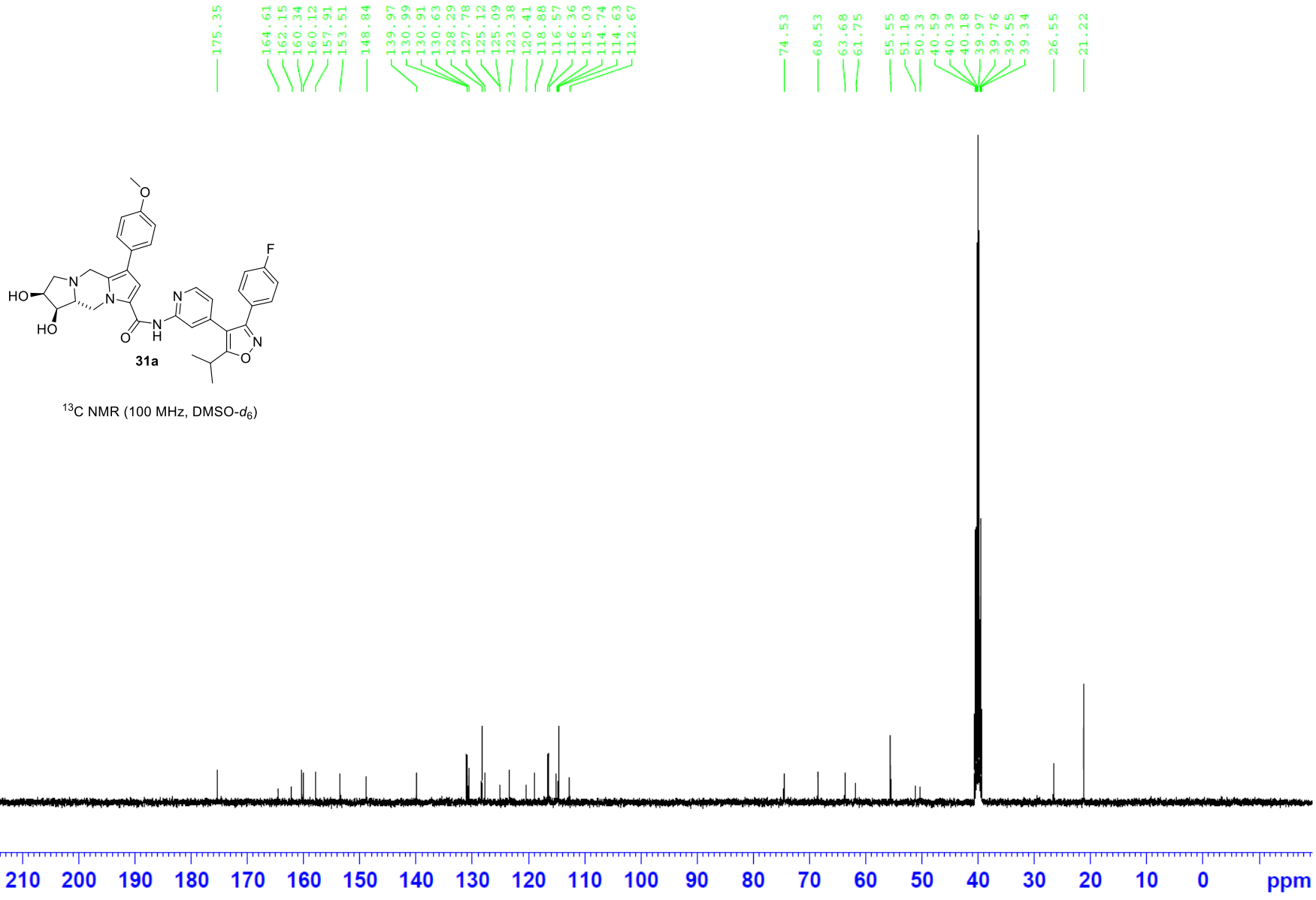
Column:	Phenomenex Luna C18(2) 5 μm 250x4.6 mm
Guard:	Phenomenex Security Guard C18 RP 4x3 mm
Mobile Phase A:	75:25:0.05 v/v/v Water/Acetonitrile/Trifluoroacetic acid
Mobile Phase B:	25:75:0.05 v/v/v Water/Acetonitrile/Trifluoroacetic acid
Gradient:	T0=100:0, T20=0:100, T26=0:100, T27=100:0, T30=100:0
Flow Rate:	1 mL/min
Sample Solvent:	60:40 v/v Water/Acetonitrile
Detection:	UV at 260 nm
Column Temp:	20 °C
Injection volume:	10 μL

Peak#	RT	Peak Height	Peak Area	Width	Area %
1	8.94 min	3.6413	24.8796	0.1027 min	0.212 %
2	12.83 min	3.3515	17.0175	0.0772 min	0.145 %
3	13.10 min	1721.5908	11488.2133	0.1049 min	97.975 %
4	16.14 min	1.3090	11.8367	0.1195 min	0.101 %
5	16.61 min	18.8908	132.0386	0.1045 min	1.126 %
6	18.64 min	6.3362	51.7068	0.1212 min	0.441 %

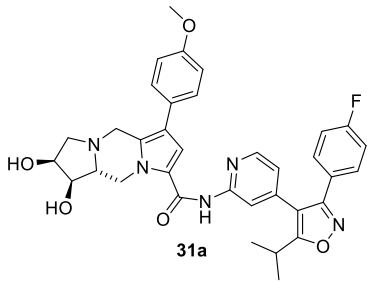


31a

^{1}H NMR (400 MHz, DMSO-d_6)

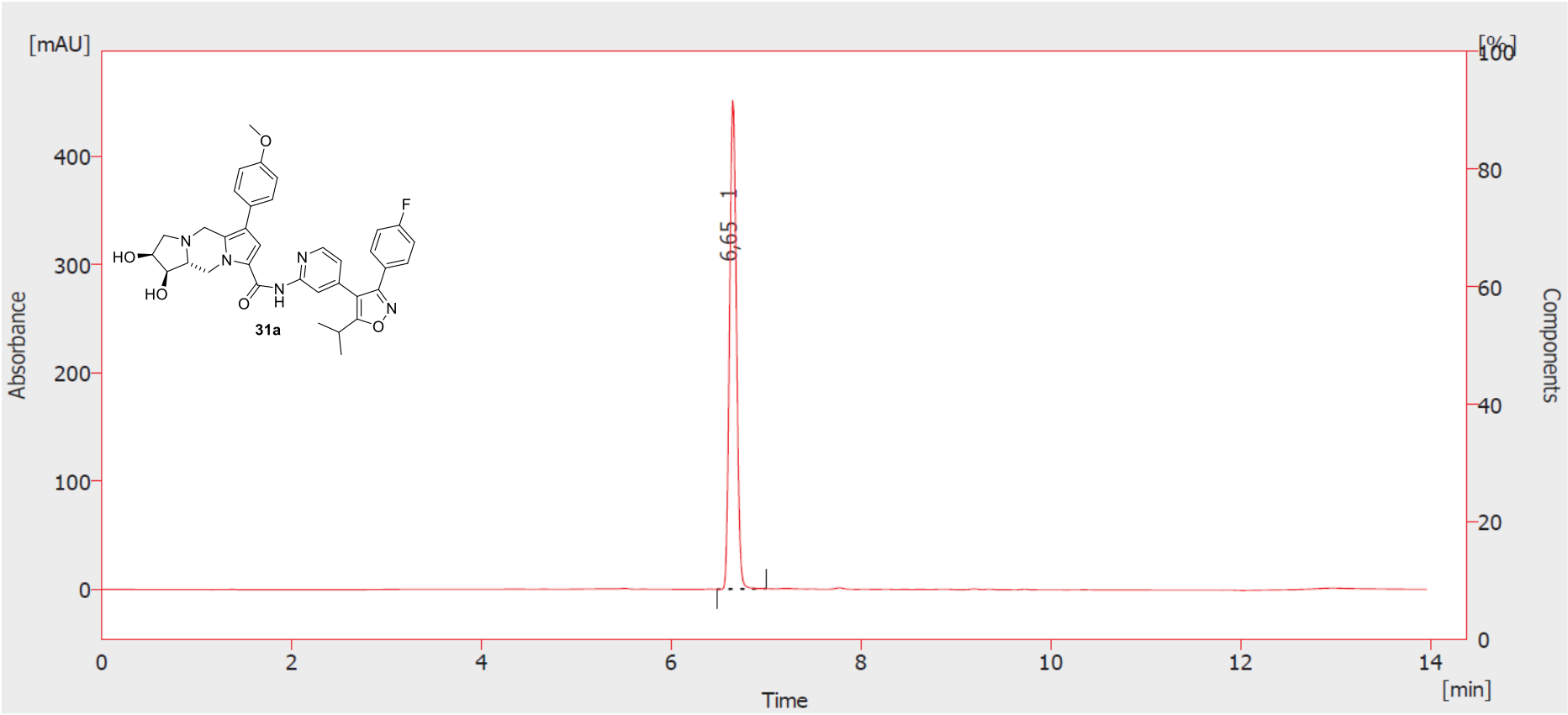


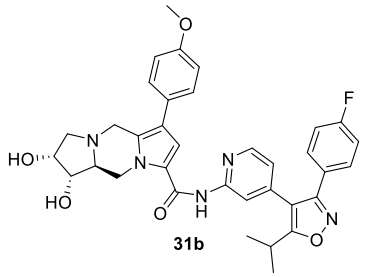
^{13}C NMR (100 MHz, DMSO-d_6)



31a

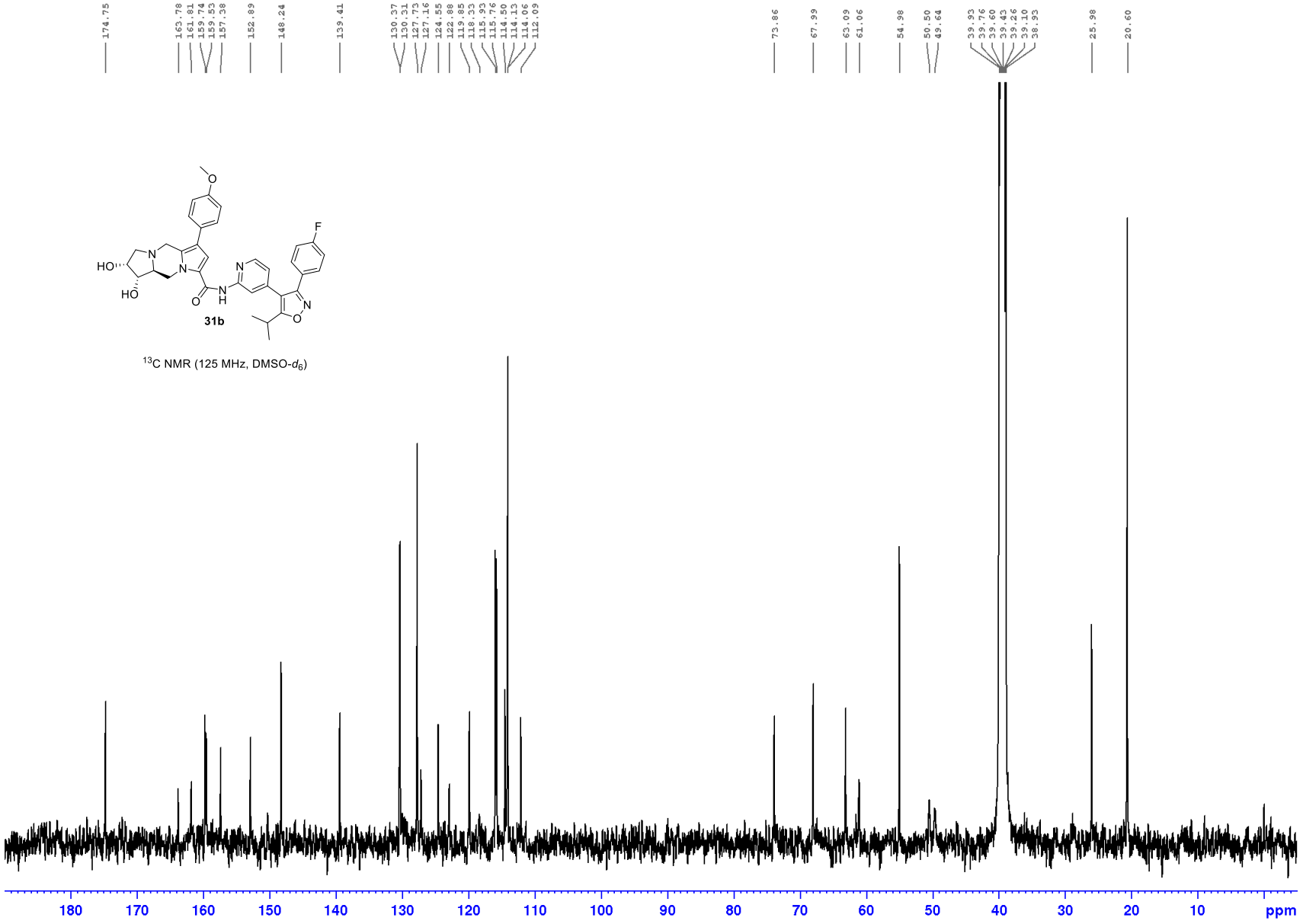
^{19}F NMR (376.7 MHz, DMSO-d_6)


[mAU]
[%]
Absorbance
Components
Time
[min]
6,65 1
31a
HO
HO
O
N
H
F
0
100
200
300
400
20
40
60
80
2
4
6
8
10
12
14

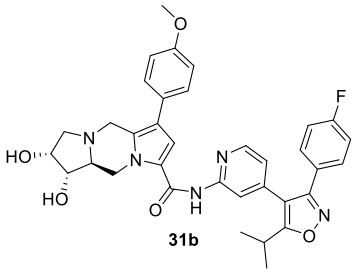


31b

^{1}H NMR (500 MHz, DMSO-d_6)



^{13}C NMR (125 MHz, DMSO-d_6)



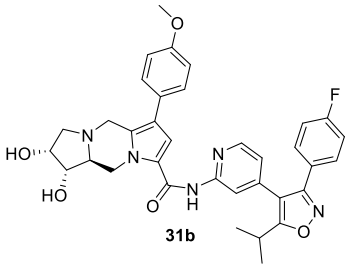
31b

^{19}F NMR (470 MHz, DMSO-d_6)

ALE379F2-3_LCMS

Column: UPLC BEH C18 1.7u 50x2.1mm
Program: 25-75%B over 10min
B: 0.1%FA in ACN
Flow: 0.5mL/min
Temp.: 40 C

1: TOF MS ES+
BPI
1.89e7



31b