Electronic Supplementary Material (ESI) for RSC Advances.

Synthesis of Norbornane Bisether Antibiotics via Silver-mediated Alkylation

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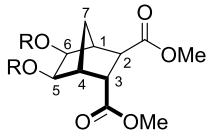
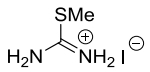
CONTENTS

All norbornane-based compounds are named using the Von-Baeyer system of nomenclature.[1] All other parts of the structure are named following the IUPAC guidelines. Numbering of norbornane protons follows the general structure shown below. Protons on carbon 7 are labelled either *syn* (*s*) or *anti* (*a*).



2-Methylisothiouronium iodide[2] **(18)**

[CAS Reg. No. 14257-47-7]



A mixture of thiourea (10.098 g, 0.133 mol), iodomethane (8.2 mL, 0.133 mol) and MeOH (100 mL) was heated at 65 °C for 90 min. The MeOH was removed *in vacuo* and the resulting yellow solid was transferred to a sintered glass funnel and washed with Et_2O (5 × 50 mL) under vacuum to afford compound **18** (28.261 g, 99%) as an amorphous white powder.

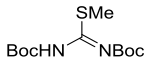
m.p: 115.3–117.6 °C (lit. 117 °C).[3]

^{1}H NMR (270 MHz, DMSO-d_6) δ 2.56 (3H, s, CH_3), 8.89 (4H, br s, NH_2).

^{13}C NMR (67.5 MHz, DMSO-d_6) δ 13.3, 171.1.

***N,N′*-Bis(*tert*-butoxycarbonyl)-*S*-methylisothiourea**[2] **(19)**

[CAS Reg. No. 107819-90-9]



To a stirring solution of 2-methylisothiouronium iodide **18** (9.820 g, 45.03 mmol) in sat. $NaHCO_3$ (50 mL) and CH_2Cl_2 (105 mL) was added Boc_2O (19.668 g, 90.12 mmol) using CH_2Cl_2 (3 × 25 mL). After 48 h the reaction mixture was transferred to a separatory funnel and the organic phase was isolated and the aqueous phase was extracted using CH_2Cl_2 (2 × 50 mL). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude solid was stirred (EtOH/H_2O, 1:9, 100 mL) for 1 h before the mixture was cooled to 0 °C and solid was collected by vacuum filtration, washing with H_2O (EtOH/H_2O, 1:9, 50 mL) gives the title compound (12.257 g, 94%) as a white powder.

m.p: 122.3–123.8 °C (lit. 127 °C).[4]

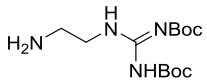
^{1}H NMR (270 MHz, $CDCl_3$) δ 1.51 (9H, br s, *t*-Bu), 1.53 (9H, br s, *t*-Bu), 2.40 (3H, s, CH_3), 11.61 (1H, br s, NH).

^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 28.2, 81.1, 83.4, 150.9, 160.9, 171.6.

HRMS (ESI, *m/z*) for $C_{12}H_{22}N_2O_4S$ $[M + Na]^+$ calc. 313.1193; found 313.1186.

2-[2,3-Bis(*tert*-butoxycarbonyl)guanidino]ethylamine[5] **(14)**

[CAS Reg. No. 203258-44-0]



A solution of *N,N′*-Bis(*tert*-butoxycarbonyl)-*S*-methylisothiourea **19** (20.404 g, 70.27 mmol) in CH_2Cl_2 (110 mL) was added in one portion to a stirred solution of 1,2-ethylenediamine (11.7 mL, 176 mmol) in CH_2Cl_2 (150 mL). The reaction was allowed to stir at 21 °C for 90 min. The reaction mixture was then transferred to a separatory funnel and washed with H_2O (2 × 80 mL), brine (80 mL), then dried ($MgSO_4$) and filtered. The solvent was removed *in vacuo* at ambient temperature to afford **14** (20.696 g, 97%) as a white powder.

m.p: 96.2–100.1 °C.

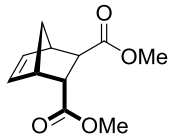
^{1}H NMR (270 MHz, $CDCl_3$) δ 1.50 (9H, br s, *t*-Bu), 1.51 (9H, br s, *t*-Bu), 2.90 (2H, t, J = 6.2 Hz, CH_2), 3.49 (2H, app. q, J_{app} = 5.5 Hz, CH_2), 8.67 (1H, br s, NH), 11.51 (1H, br s, NH).

^{13}C NMR (67.5 MHz, $CDCl_3$) δ 28.2, 28.4, 41.1, 43.5, 79.4, 83.2, 153.3, 156.5, 163.7.

HRMS (ESI, *m/z*) for $C_{13}H_{26}N_4O_4$ $[M + H]^+$ calc. 303.2027; found 303.2032.

Dimethyl bicyclo[2.2.1]hept-5-ene-3-*endo*-2-*exo*-dicarboxylate (17)

[CAS Reg. No. 3014-58-2]



Method A[6]

To the stirring solution of dimethyl fumarate (65.290 g, 0.453 mol) in THF (200 mL), was added freshly cracked cyclopentadiene (40 mL, 0.476 mol), and the reaction was stirred at ambient temperature for 16 h. The solvent was removed under reduced pressure to give the title compound (95.230 g, 99%) as a clear oil.

Method B[7]

A 35 mL microwave vial was charged with dicyclopentadiene (2.0 mL, 15.0 mmol), dimethyl fumarate (2.883 g, 20.0 mmol) and hydroquinone (100 mg, 0.90 mmol), and heated using microwave irradiation to 150 °C for 2 h. The resulting orange oil was purified by flash column chromatography (10% EtOAc in pet. spirits) to give a clear oil (4.137 g, 98%).

R_f = 0.32 (10% EtOAc in pet. spirits).

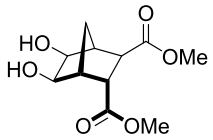
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (1H, dd, *J* = 8.8, 1.7 Hz, H7*s*), 1.61 (1H, d, *J* = 8.8 Hz, H7*a*), 2.68 (1H, dd, *J* = 3.1, 1.2 Hz, H2), 3.12 (1H, br s, H4), 3.25 (1H, br s, H1), 3.37 (1H, app. t, *J* = 5.6 Hz, H3), 3.64 (3H, s, Me), 3.71 (3H, s, Me), 6.06 (1H, dd, *J* = 5.6, 2.8 Hz, H6), 6.27 (1H, dd, *J* = 5.6, 3.1 Hz, H5).

^{13}C NMR (100 MHz, $CDCl_3$) δ 45.5, 46.9, 47.2, 47.5, 47.7, 51.7, 51.9, 135.3, 137.7, 174.0, 175.2.

HRMS (ESI, *m/z*) for $C_{11}H_{14}O_4$ $[M + Na]^+$ calc. 233.0784; found 233.0785.

Dimethyl 5,6-*exo*-dihydroxybicyclo[2.2.1]heptane-3-*endo*-2-*exo*-dicarboxylate (6)

[CAS Reg. No. 1228039-59-5]



Method A[8]

The dimethyl ester **17** (3.054 g, 14.53 mmol) and NMO·H_2O (1.87 g, 16.0 mmol) were dissolved in a solution of H_2O/acetone (1:4, 36 mL) to which OsO_4 (4% in H_2O, 730 µL, 0.40 mol%) was added. The reaction was stirred for 3 d and was then quenched with sat. $NaHSO_3$ (30 mL). The suspension was extracted with EtOAc (4 × 25 mL), and the combined organic phase was washed with brine (25 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give the title compound (3.337 g, 94%) as a white solid.

Method B[9]

To a stirring solution at 0 °C of dimethyl ester **17** (270 mg, 1.28 mmol), *t*-BuOH (4.7 mL) and H_2O (1.2 mL), a solution of $KMnO_4$ (405 mg, 2.56 mmol), K_2CO_3 (212 mg, 1.54 mmol) in H_2O (6.0 mL) was added dropwise. The reaction was stirred for a further 25 min before the reaction mix was quenched with sat. $NaHSO_3$ (25 mL) and extracted with EtOAc (3 × 20 mL). The combined organic phase was washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford the title compound (181 mg, 58%) as a white solid.

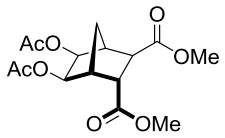
m.p: 89.9–92.3 °C (lit. 81-84 °C).[8]

^{1}H NMR (270 MHz, $CDCl_3$) δ 1.33 (1H, d, *J* = 11.0 Hz, H7*s*), 1.78 (1H, dd, *J* = 11.0, 1.2 Hz, H7*a*), 2.40 (1H, br s, H1), 2.46 (1H, dd, *J* = 4.5, 1.2 Hz, H4), 2.63 (1H, d, *J* = 4.9 Hz, H2), 3.11 (1H, app. t, *J* = 5.1 Hz, H3), 3.62 (3H, s, Me), 3.64 (3H, s, Me), 3.71–3.77 (1H, m, H6), 3.85 (1H, br s, H5).

^{13}C NMR (67.5 MHz, $CDCl_3$) δ 31.8, 44.8, 46.2, 46.4, 48.2, 52.3, 52.5, 70.2, 73.3, 173.2, 174.2.

HRMS (ESI, *m/z*) for $C_{11}H_{16}O_6$ $[M + Na]^+$ calc. 267.0839; found 267.0836.

Shane/SMH04-159B
Single Pulse Experiment



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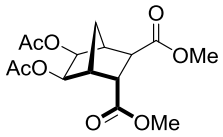

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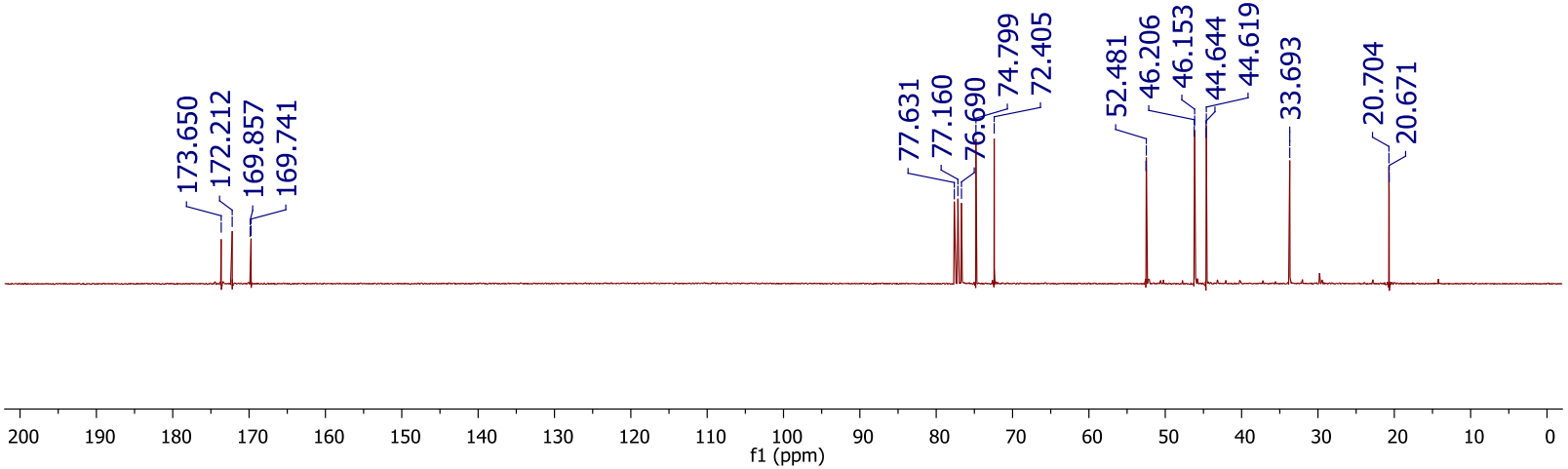

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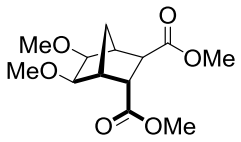

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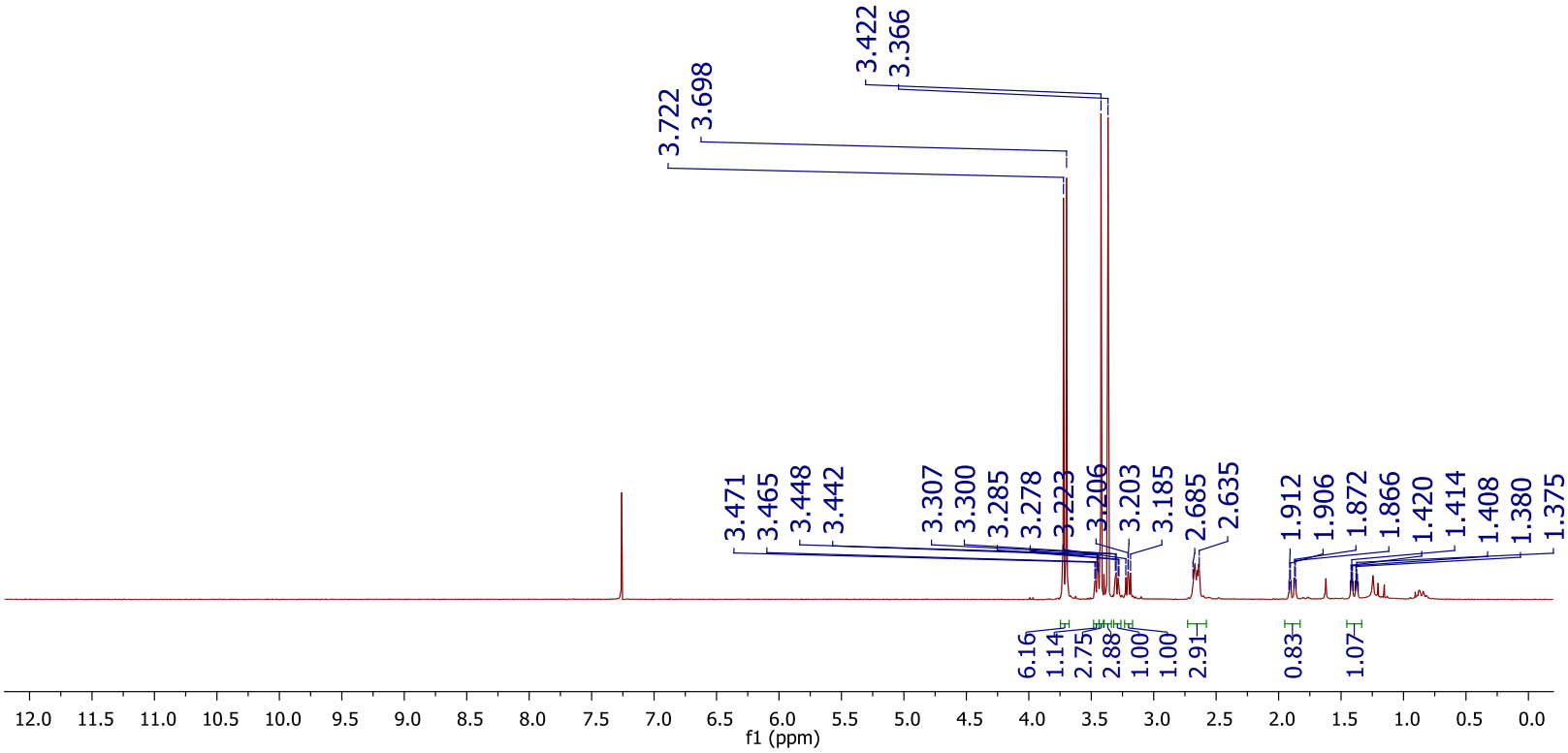

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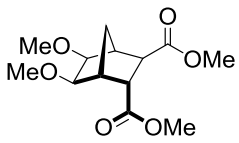

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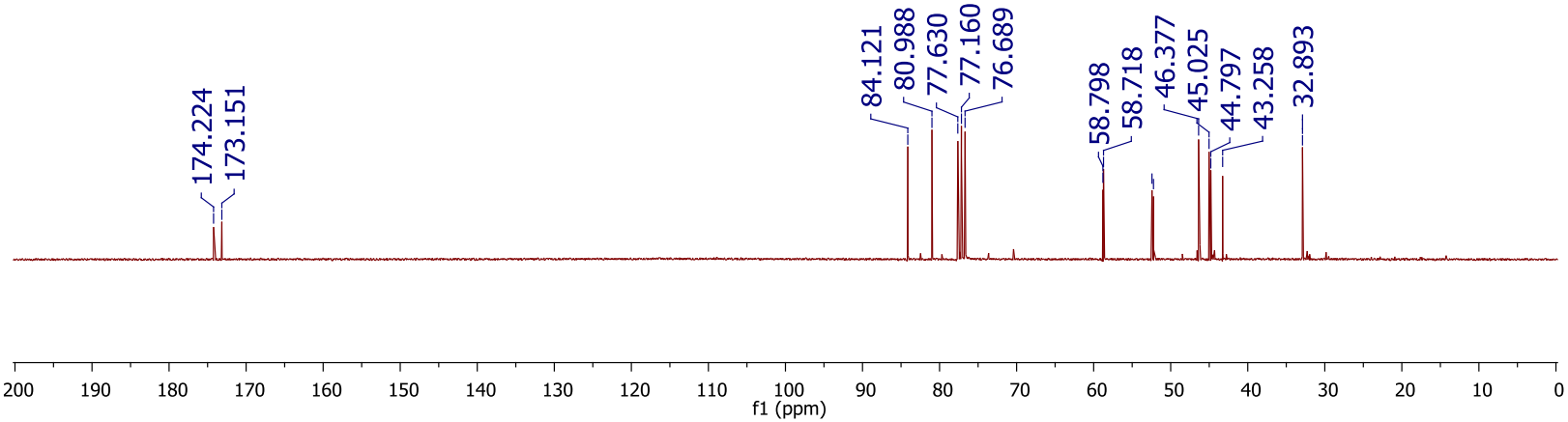
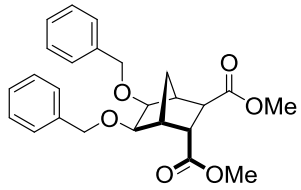


Norbornane diester dibenzyl ether
SMH05-081F-1H



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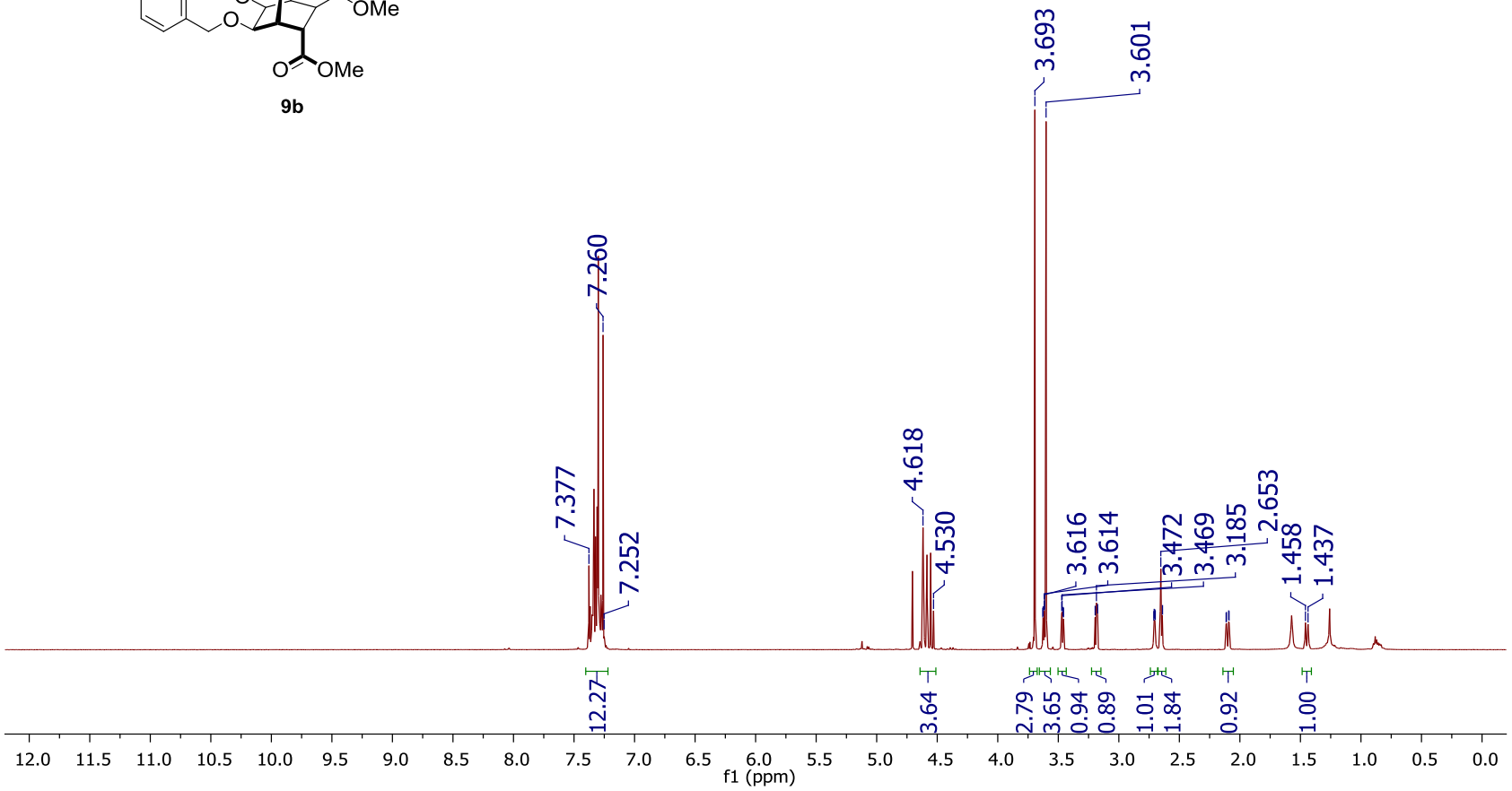

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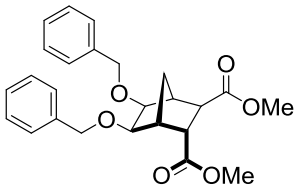

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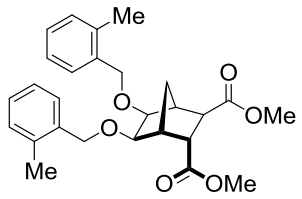

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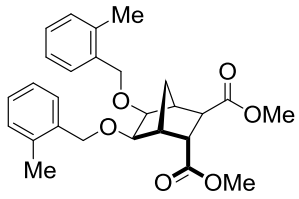

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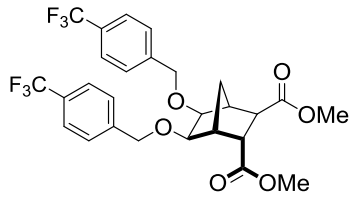

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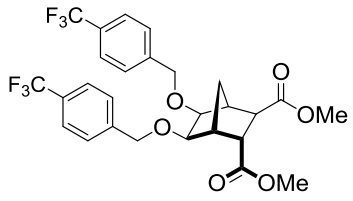

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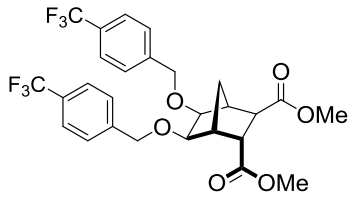

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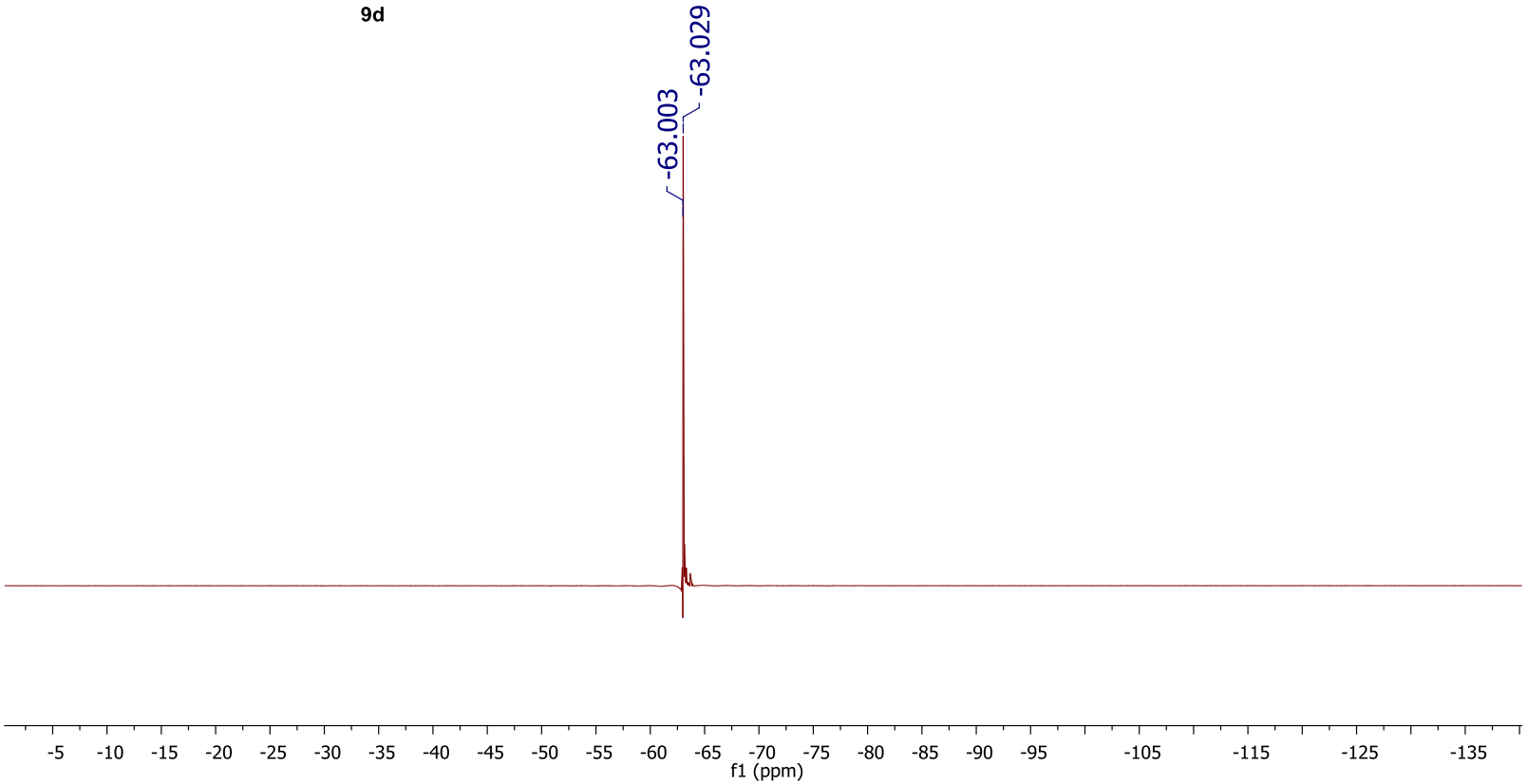

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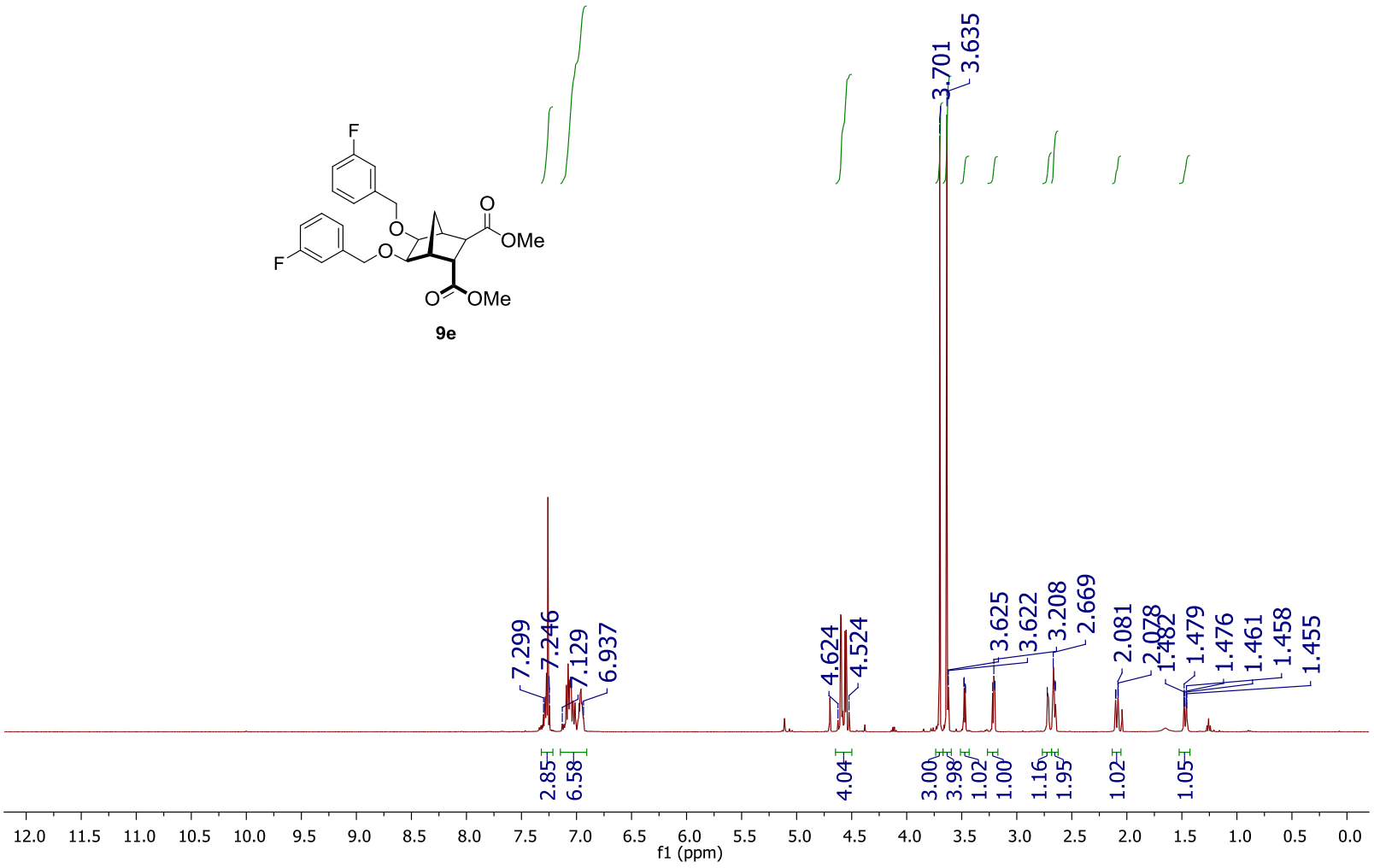

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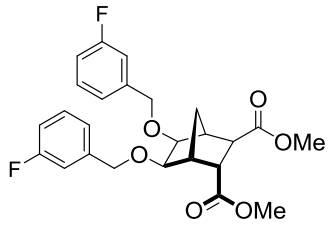

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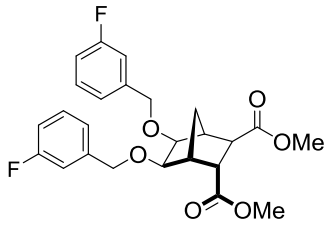

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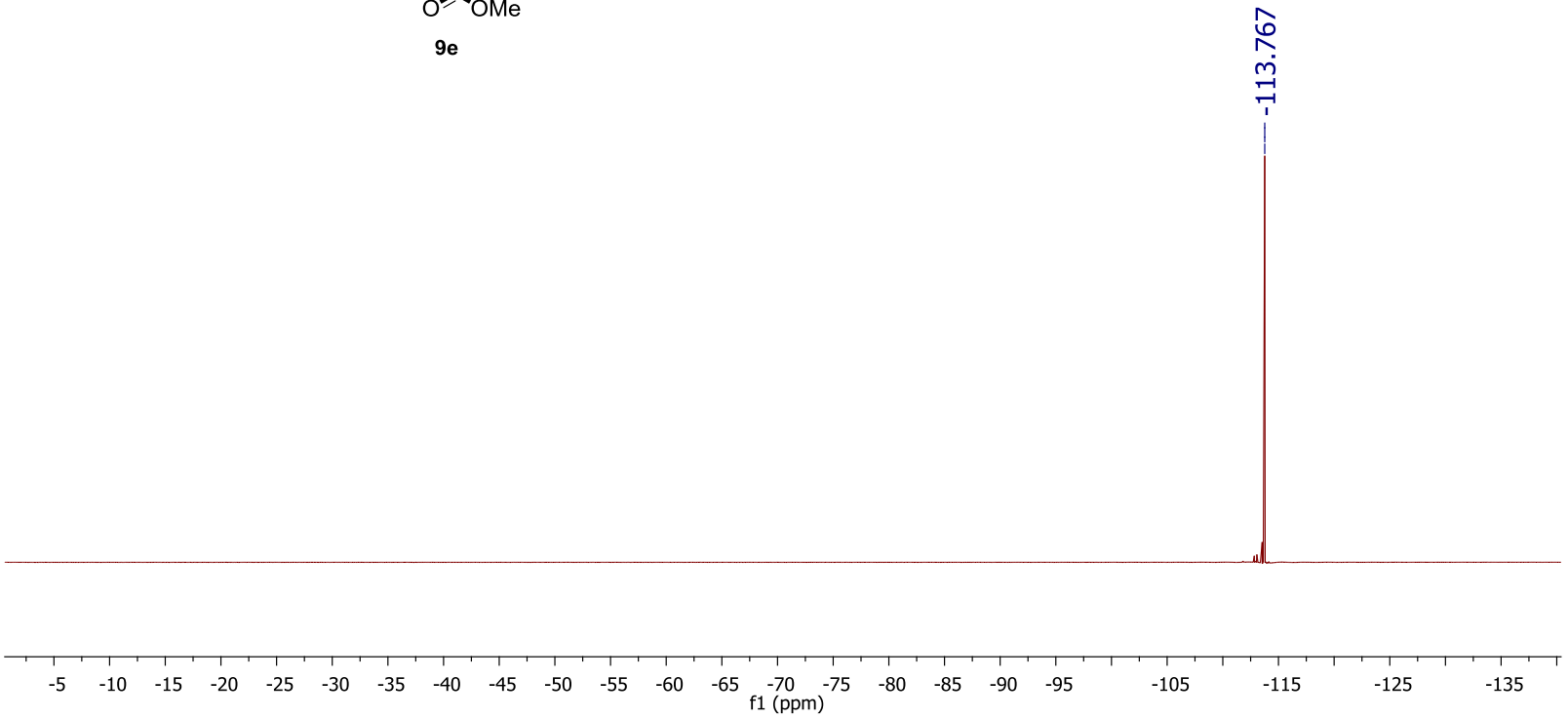

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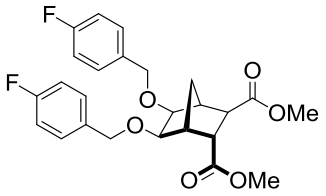

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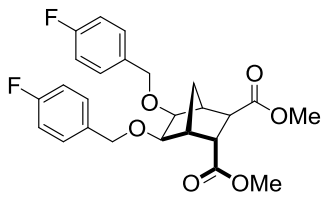

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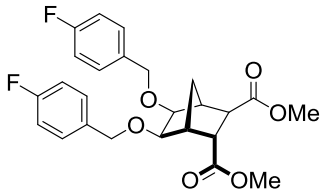

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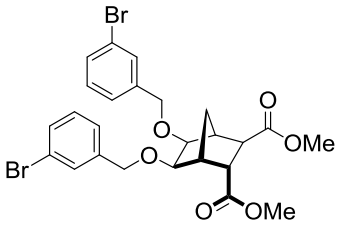

9g

Norbornane diester di benzyl-3-bromo
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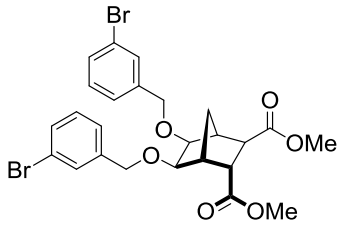

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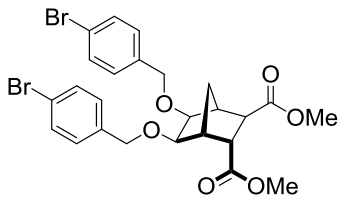

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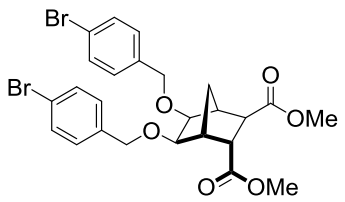

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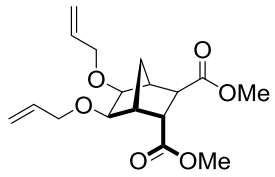
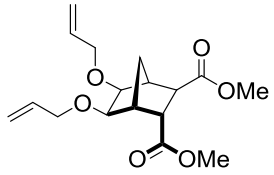
Shane/SMH07-147B
Single Pulse Experiment

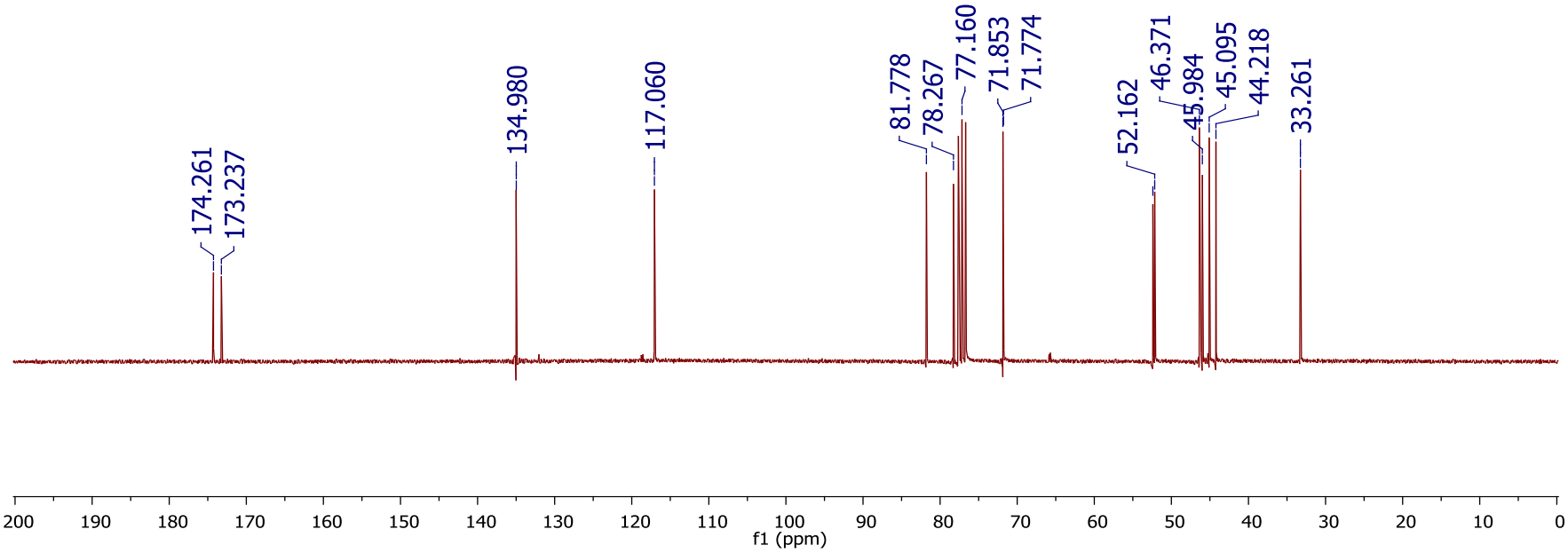


9i

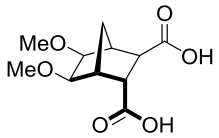
Shane/SMH07-147B-CARBON
Single Pulse with Broadband Decoupling



9i

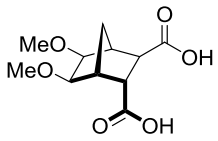


Shane/SMH05-129B2
Single Pulse Experiment



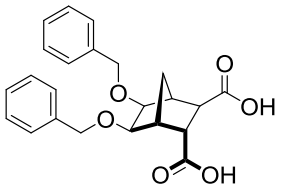
12a

Shane/SMH05-129B-CARBON
Single Pulse with Broadband Decoupling



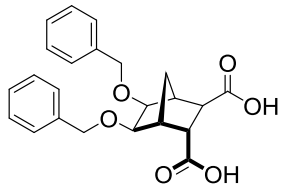
12a

Shane/SMH05-121B
Single Pulse Experiment



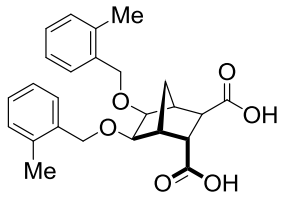
12b

Shane/SMH05-121B-CARBON
Single Pulse with Broadband Decoupling



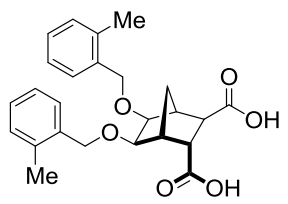
12b

SMH07-123A
SMH07-123A - 1H
PROTON DMSO {C:\Data_500\Shane} nmr 3



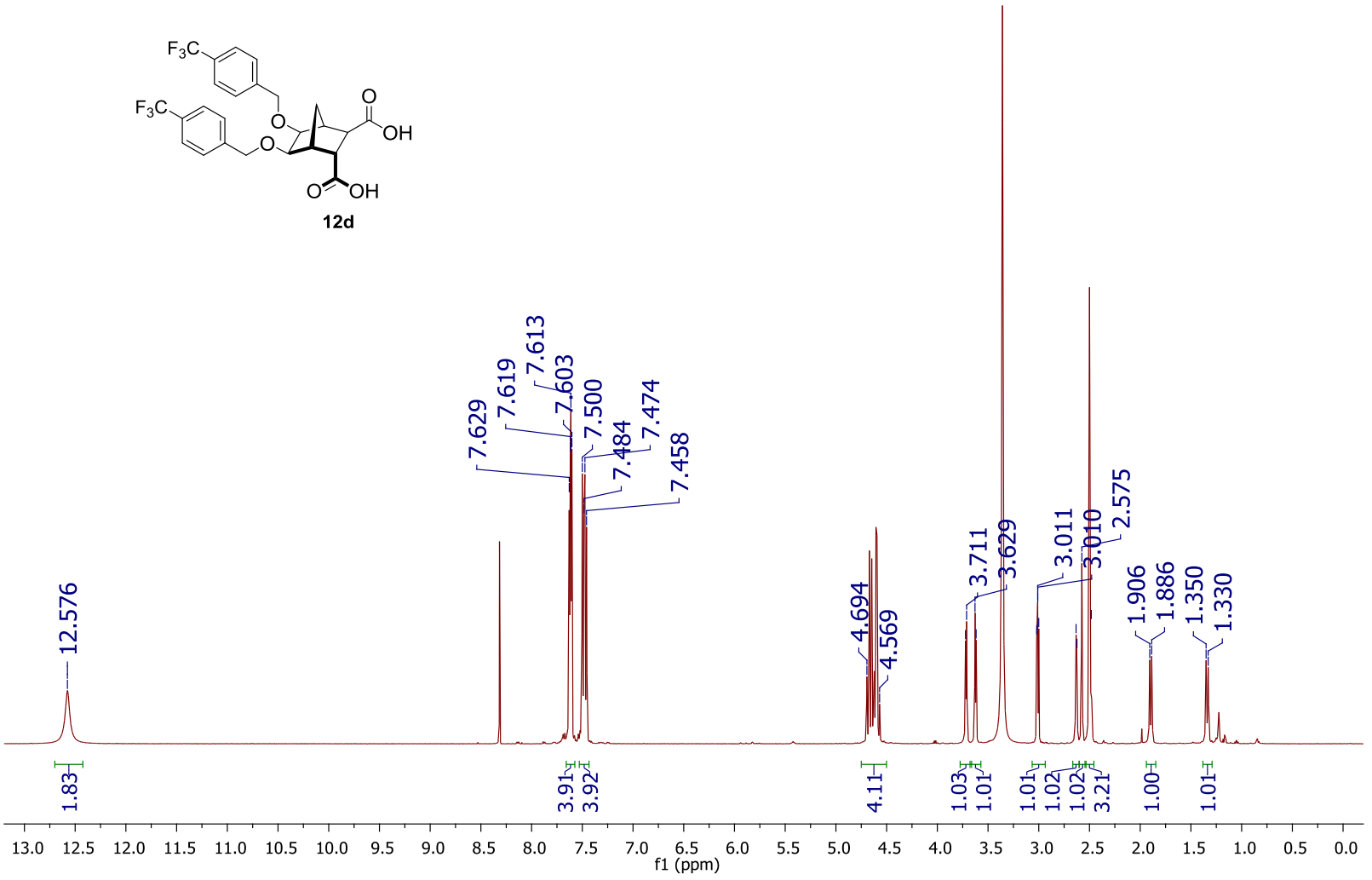
12c

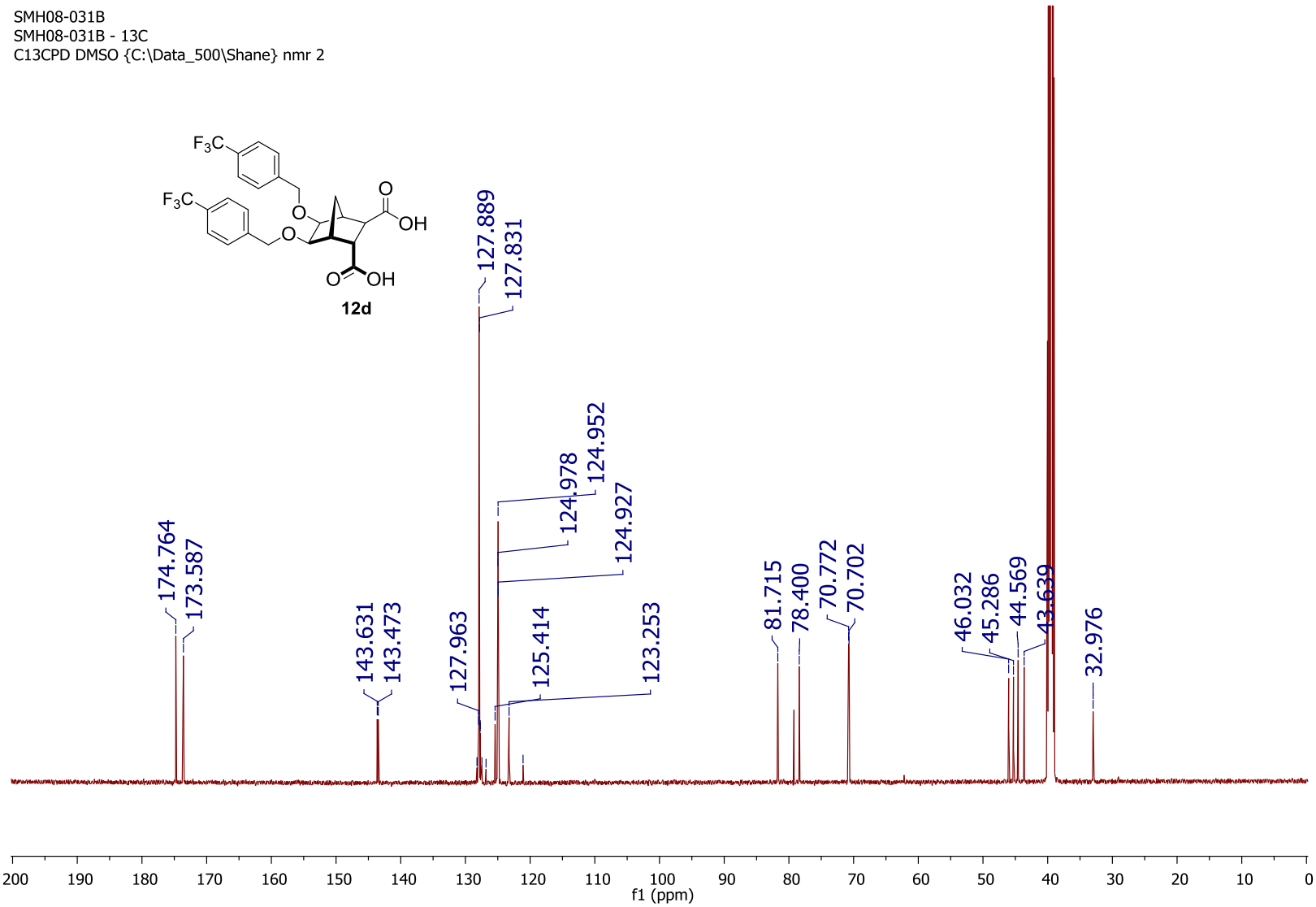
SMH07-123A
SMH07-123A - 13C
C13CPD DMSO {C:\Data_500\Shane} nmr 3



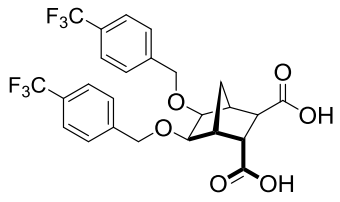
12c

SMH08-031B
SMH08-031B - 1H
PROTON DMSO {C:\Data_500\Shane} nmr 2



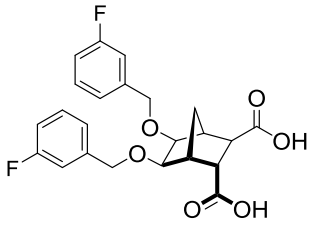

SMH08-031B
SMH08-031B - 13C
C13CPD DMSO {C:\Data_500\Shane} nmr 2
F3C
F3C
O
O
O
OH
O
OH
12d
174.764
173.587
143.631
143.473
127.963
127.889
127.831
125.414
124.978
124.952
124.927
123.253
81.715
78.400
70.772
70.702
46.032
45.286
44.569
43.639
32.976
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

SMH08-031B
SMH08-031B-19F

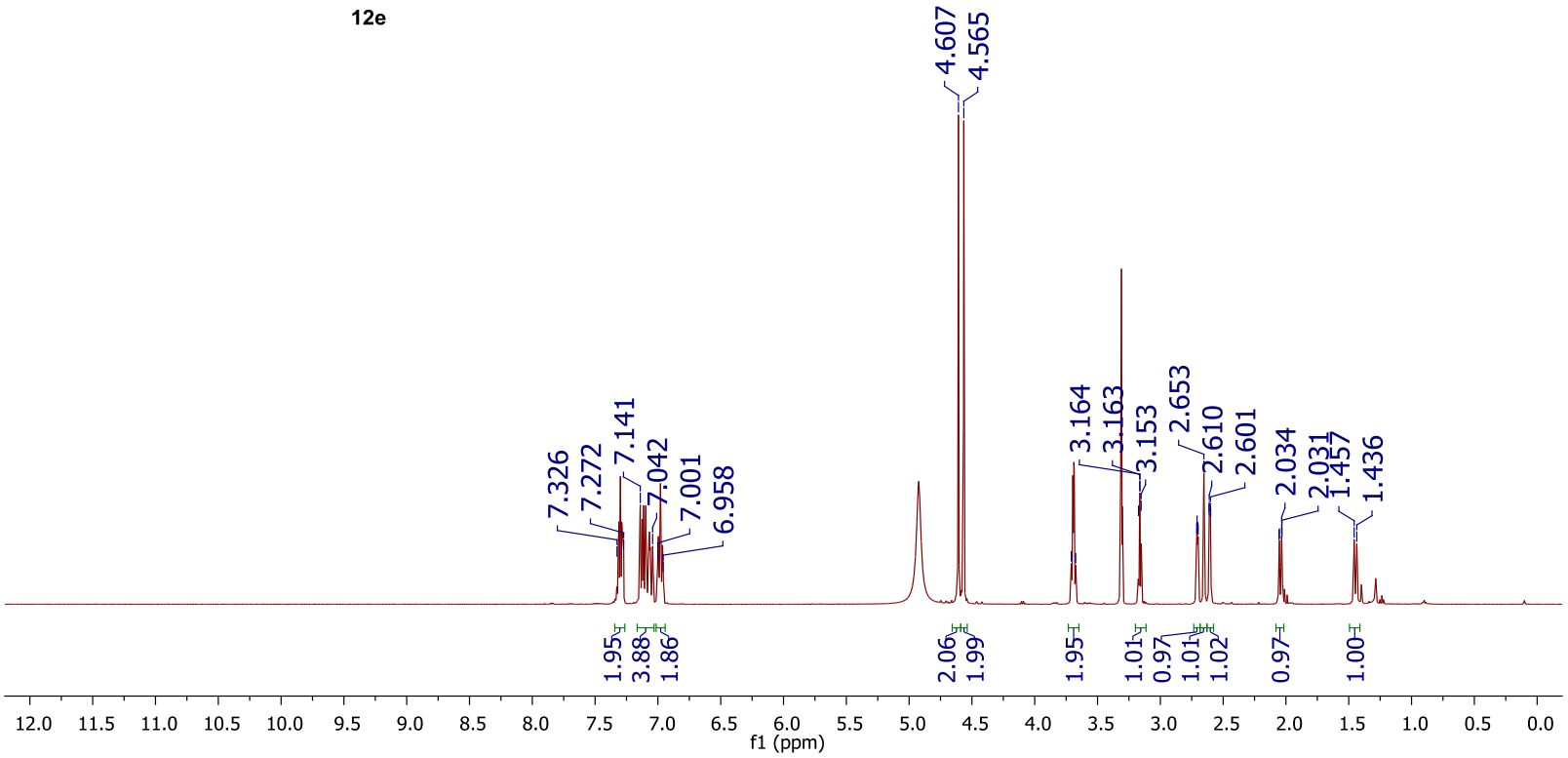


12d

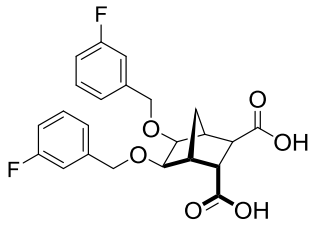
SMH08-053B
SMH08-053B - 1H
PROTON MeOD {C:\Data_500\Shane} nmr 5



12e

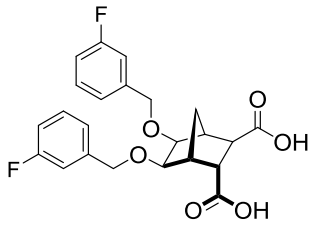


SMH08-053B
SMH08-053B - 13C
C13CPD MeOD {C:\Data_500\Shane} nmr 5

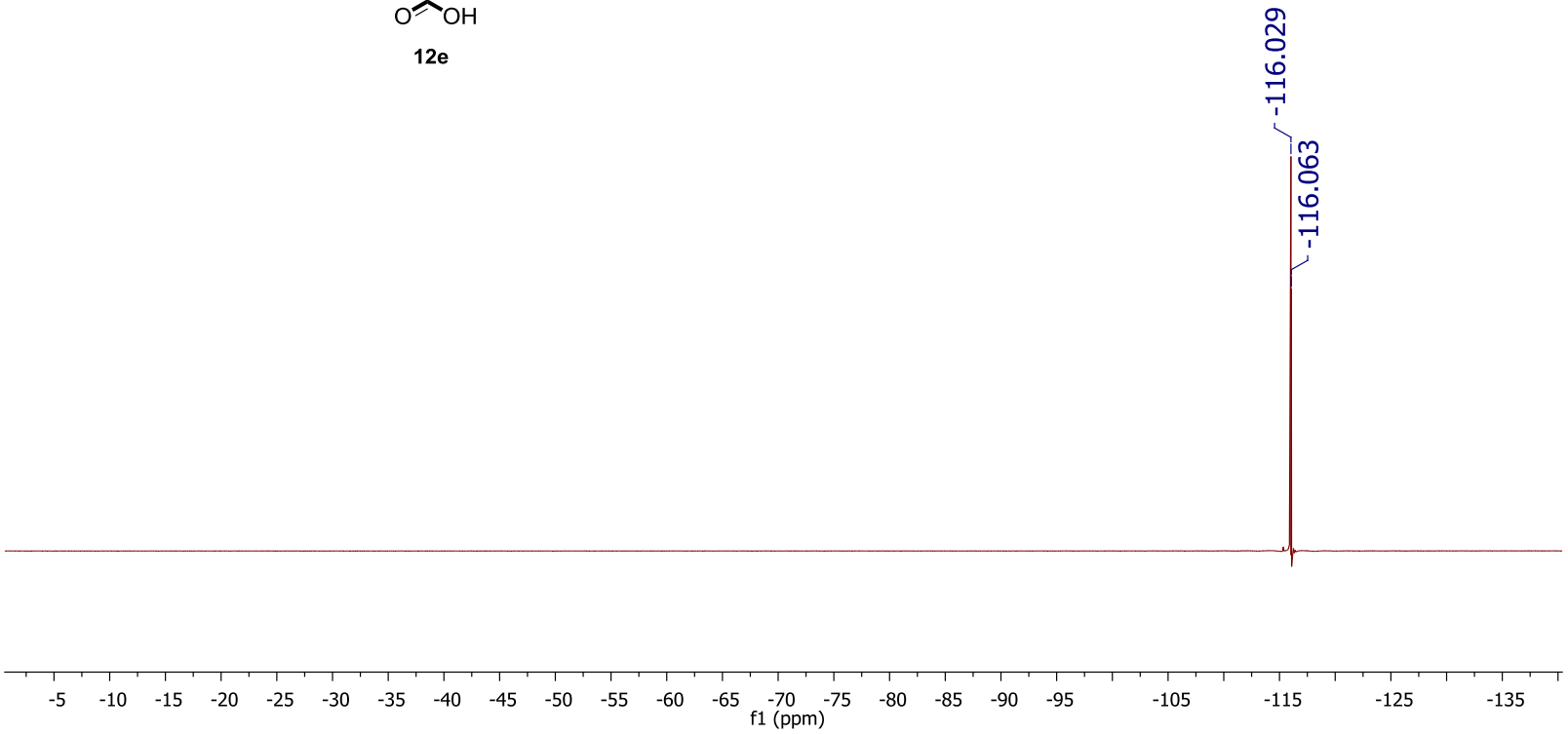


12e

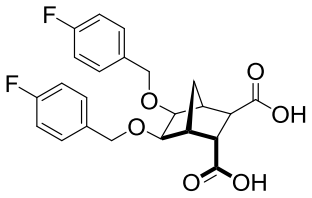
SMH08-053B
SMH08-053B-19F



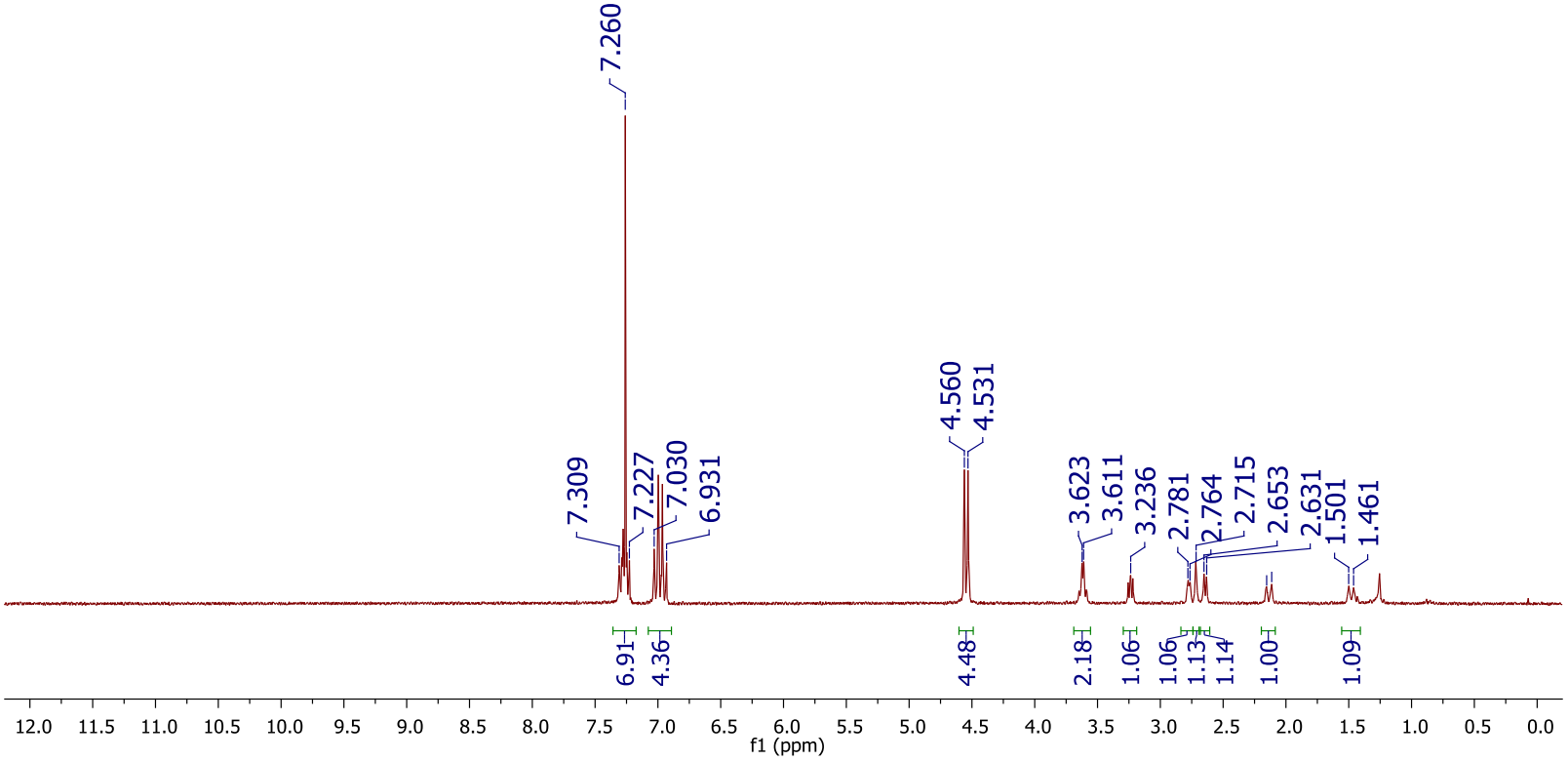
12e



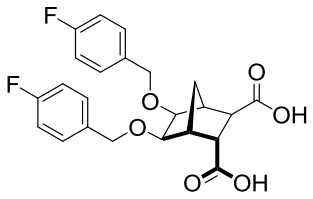
Shane/SMH06-153A
Single Pulse Experiment



12f

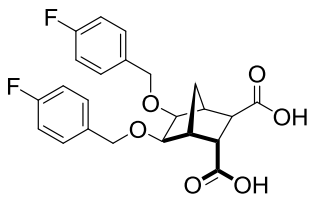


Shane/SMH06-153A-Carbon
Single Pulse with Broadband Decoupling

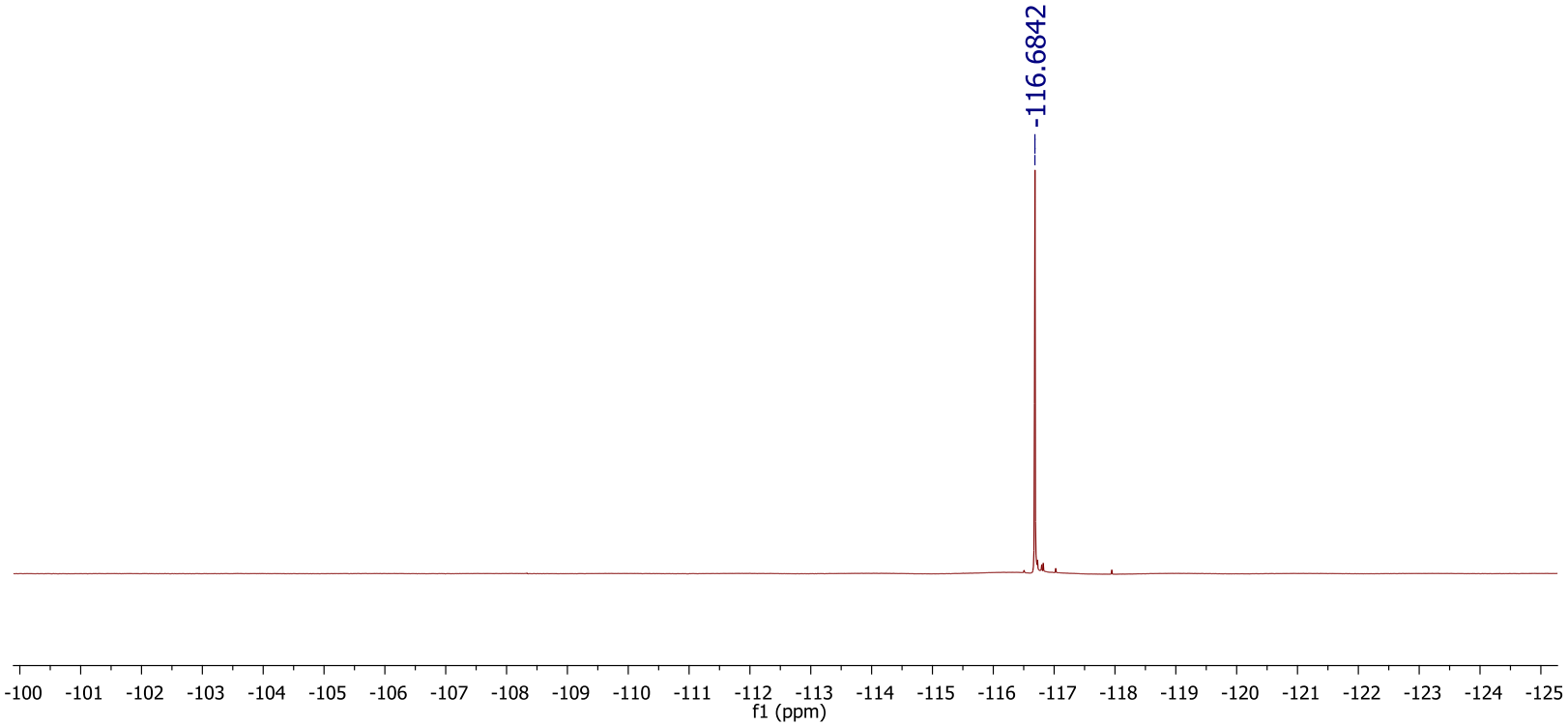


12f

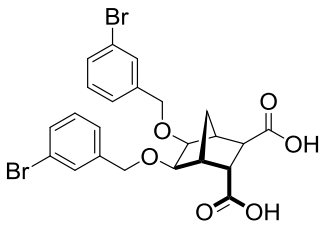
SMH08-145A
SMH08-145A-19F



12f

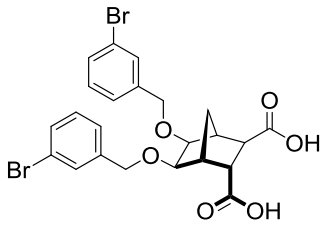


Shane/SMH06-139B
Single Pulse Experiment



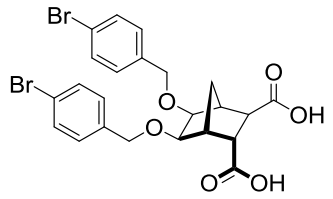
12g

Shane/SMH06-139B-13C
Single Pulse with Broadband Decoupling

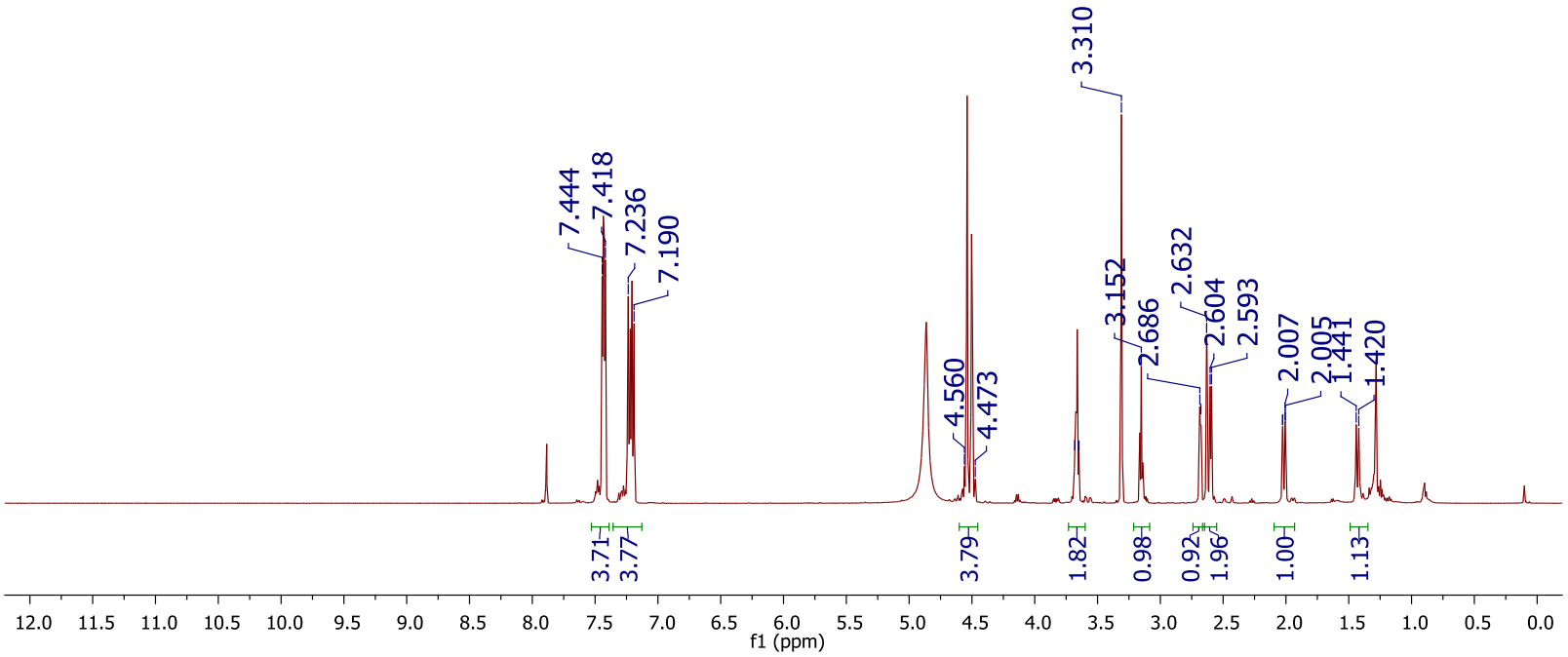


12g

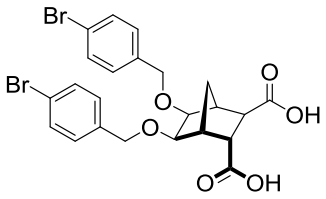
SMH06-129D
SMH06-129D - 1H
PROTON MeOD {C:\Data_500\Shane} nmr 15



12h

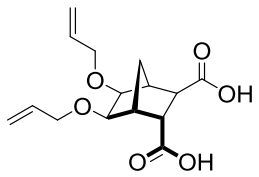


SMH06-129D
SMH06-129D - 13C
C13CPD MeOD {C:\Data_500\Shane} nmr 15

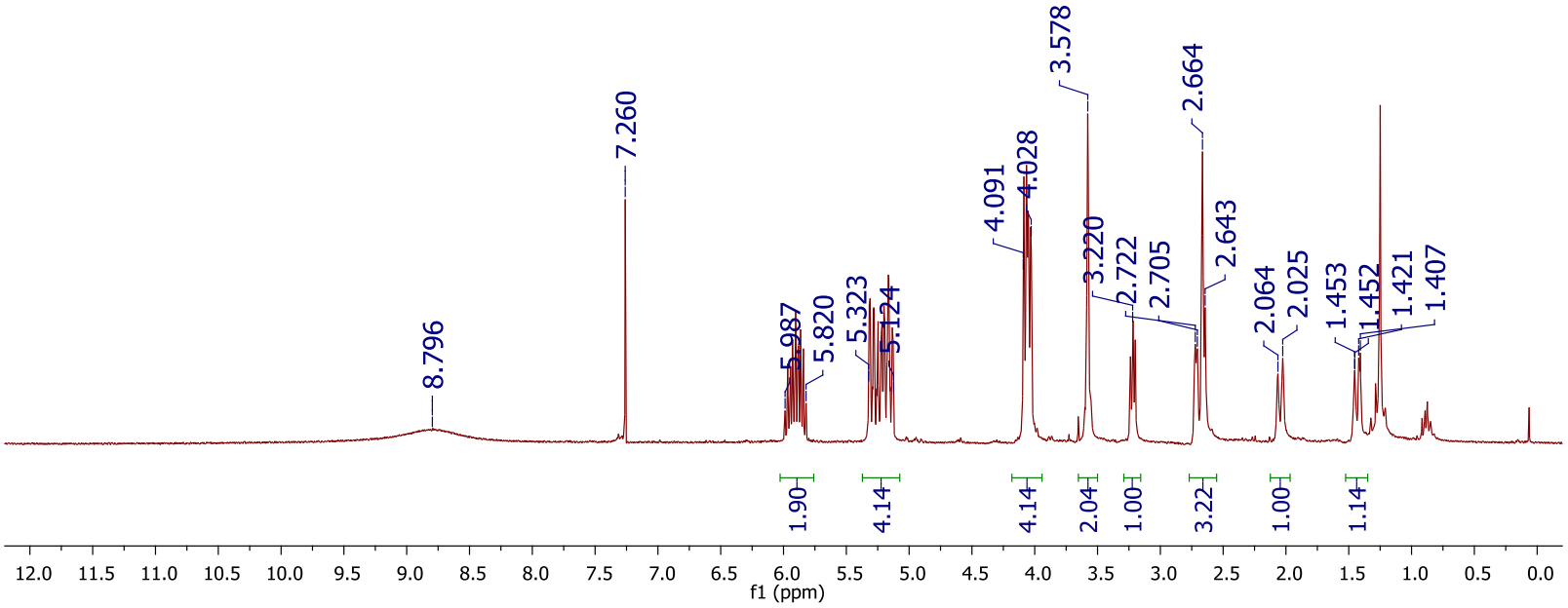


12h

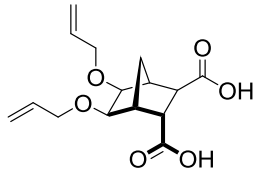
Shane/SMH06-045B
Single Pulse Experiment



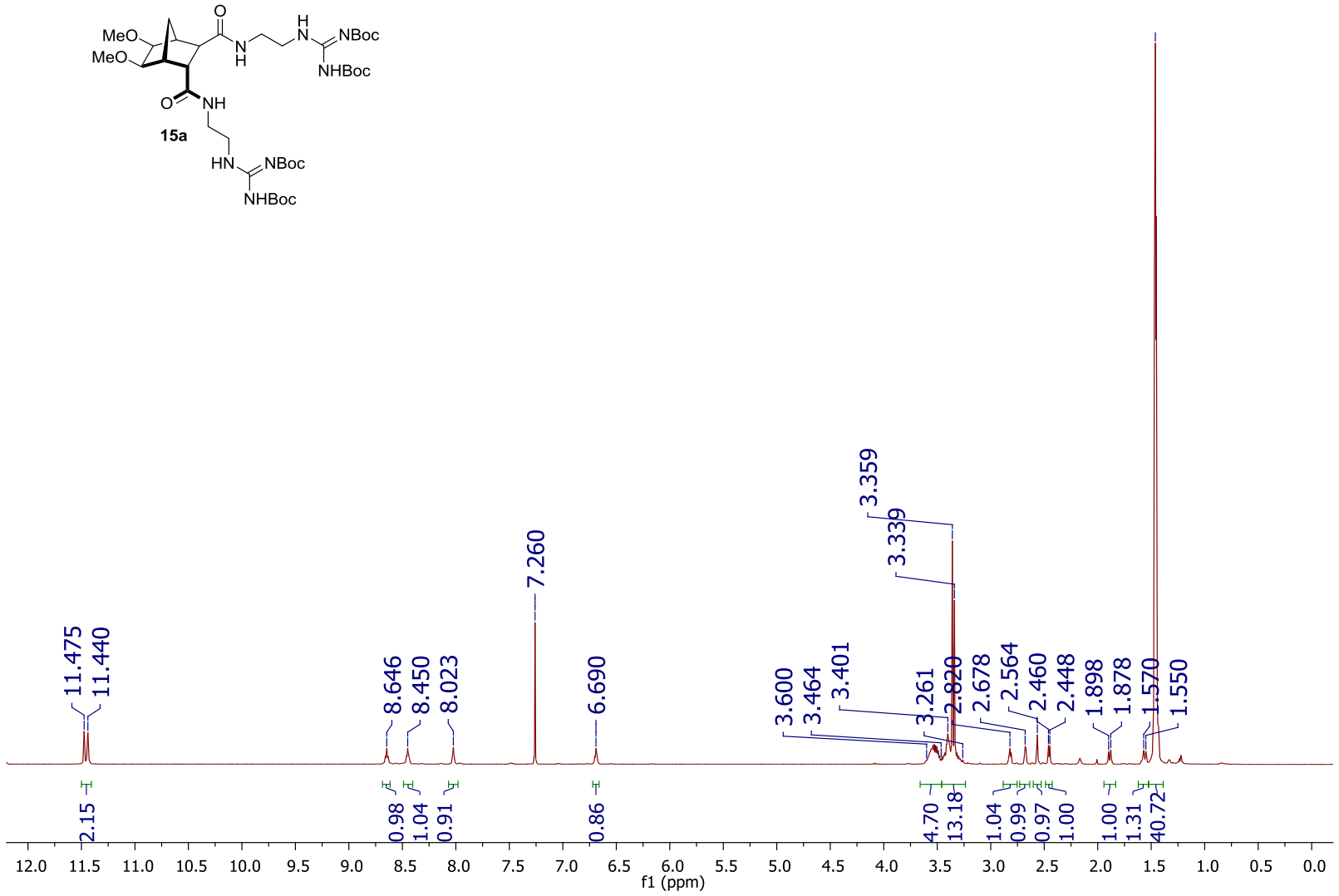
12i

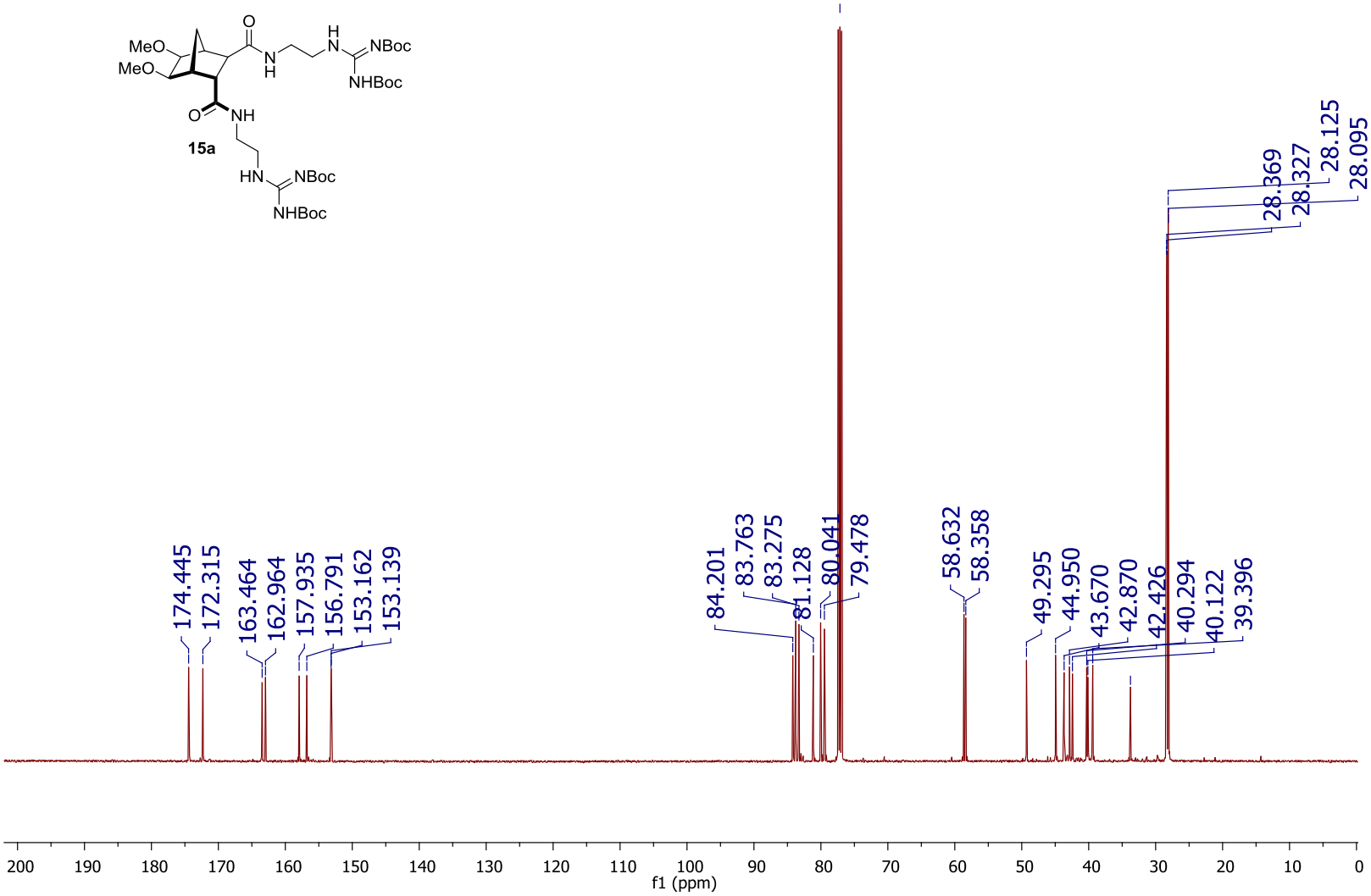


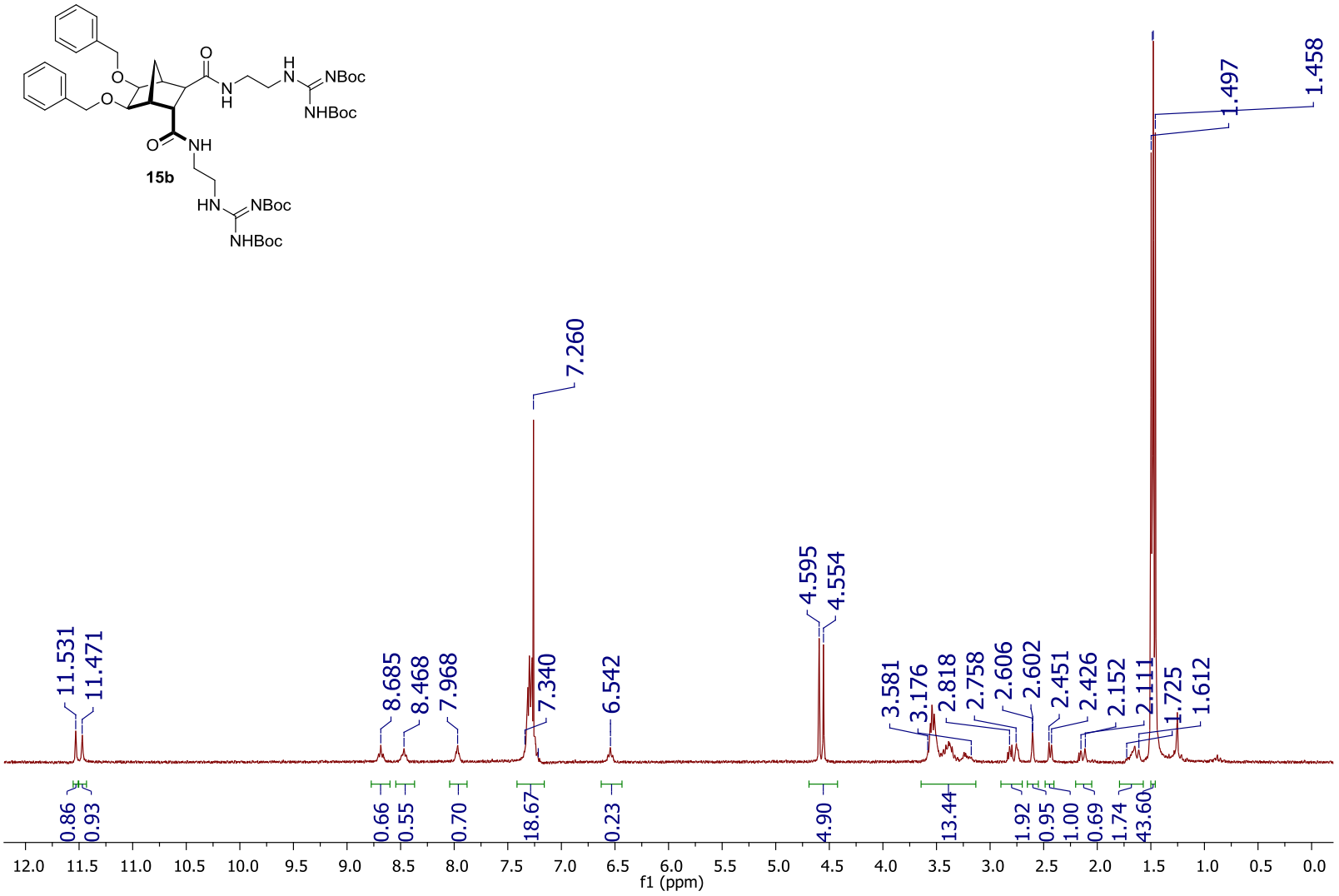
SMH06-045B
SMH06-045B 13C
C13CPD CDCl3 {C:\Data_500\Shane} nmr 14

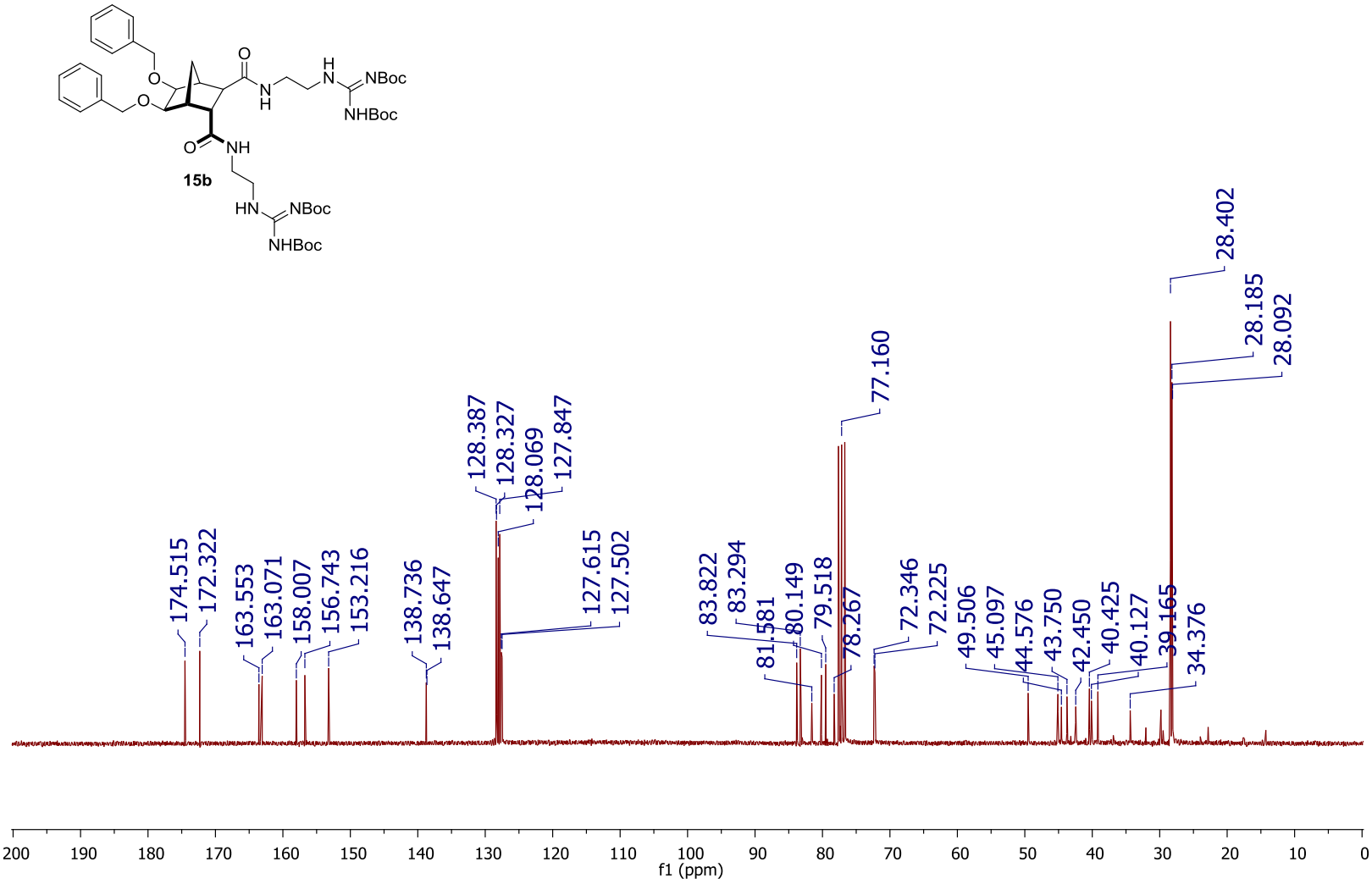


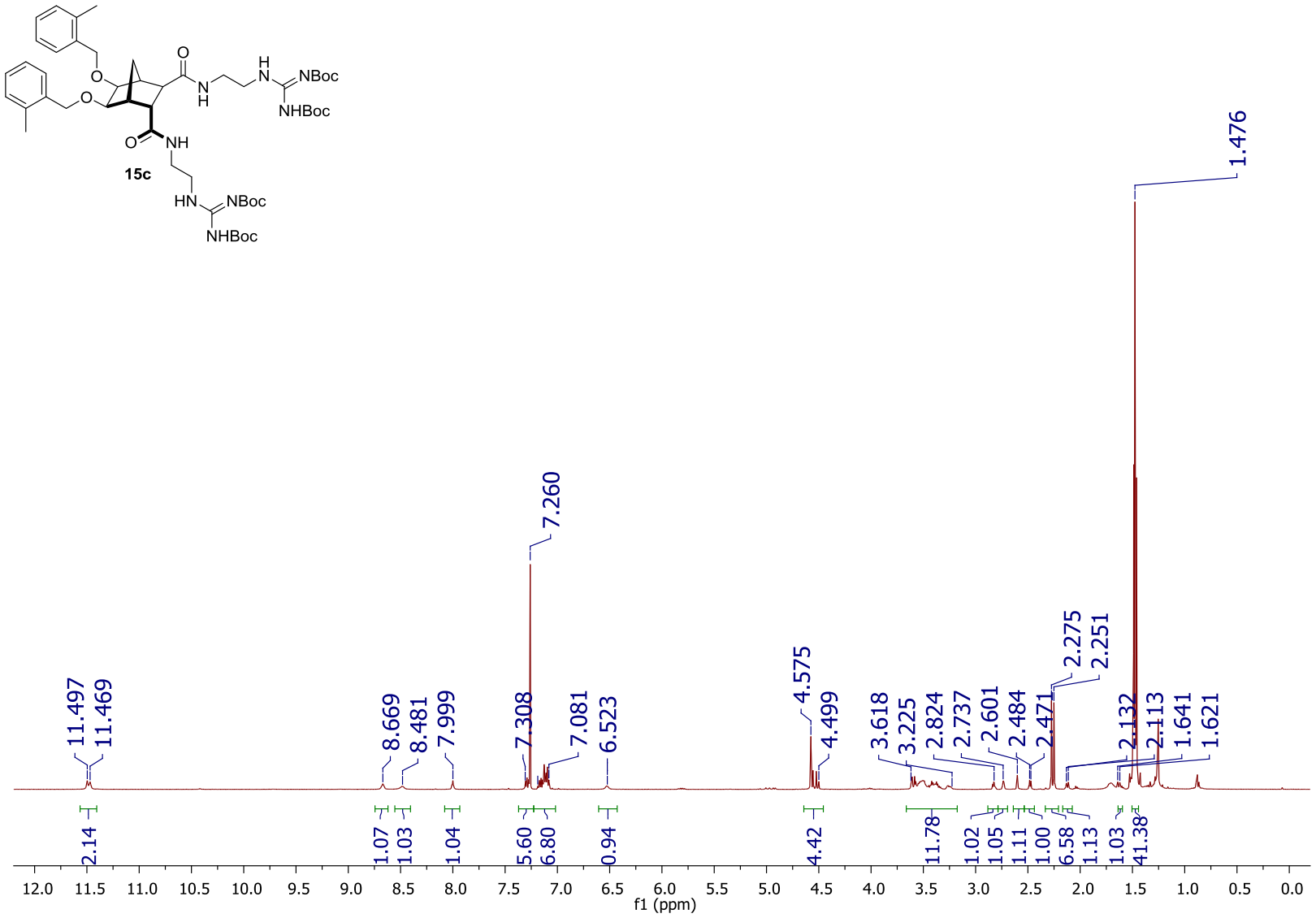
12i

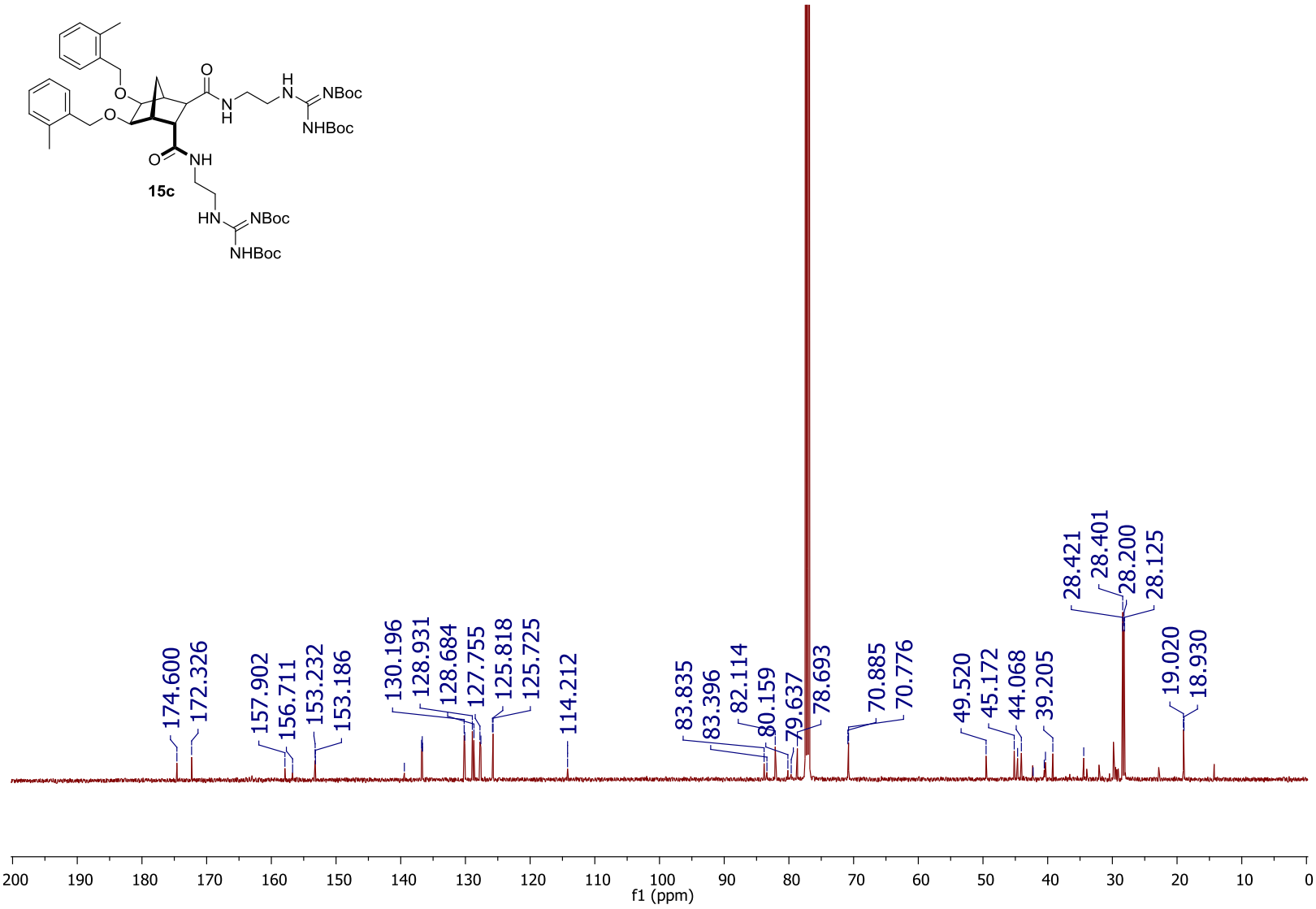

MeO
MeO
O
N
H
H
N
NBoc
NHBoc
O
NH
15a
HN
NBoc
NHBoc
11.475
11.440
8.646
8.450
8.023
7.260
6.690
3.600
3.464
3.401
3.359
3.339
3.261
2.820
2.678
2.564
2.460
2.448
1.898
1.878
1.570
1.550
2.15
0.98
1.04
0.91
0.86
4.70
13.18
1.04
0.99
0.97
1.00
1.00
1.31
40.72
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
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
f1 (ppm)

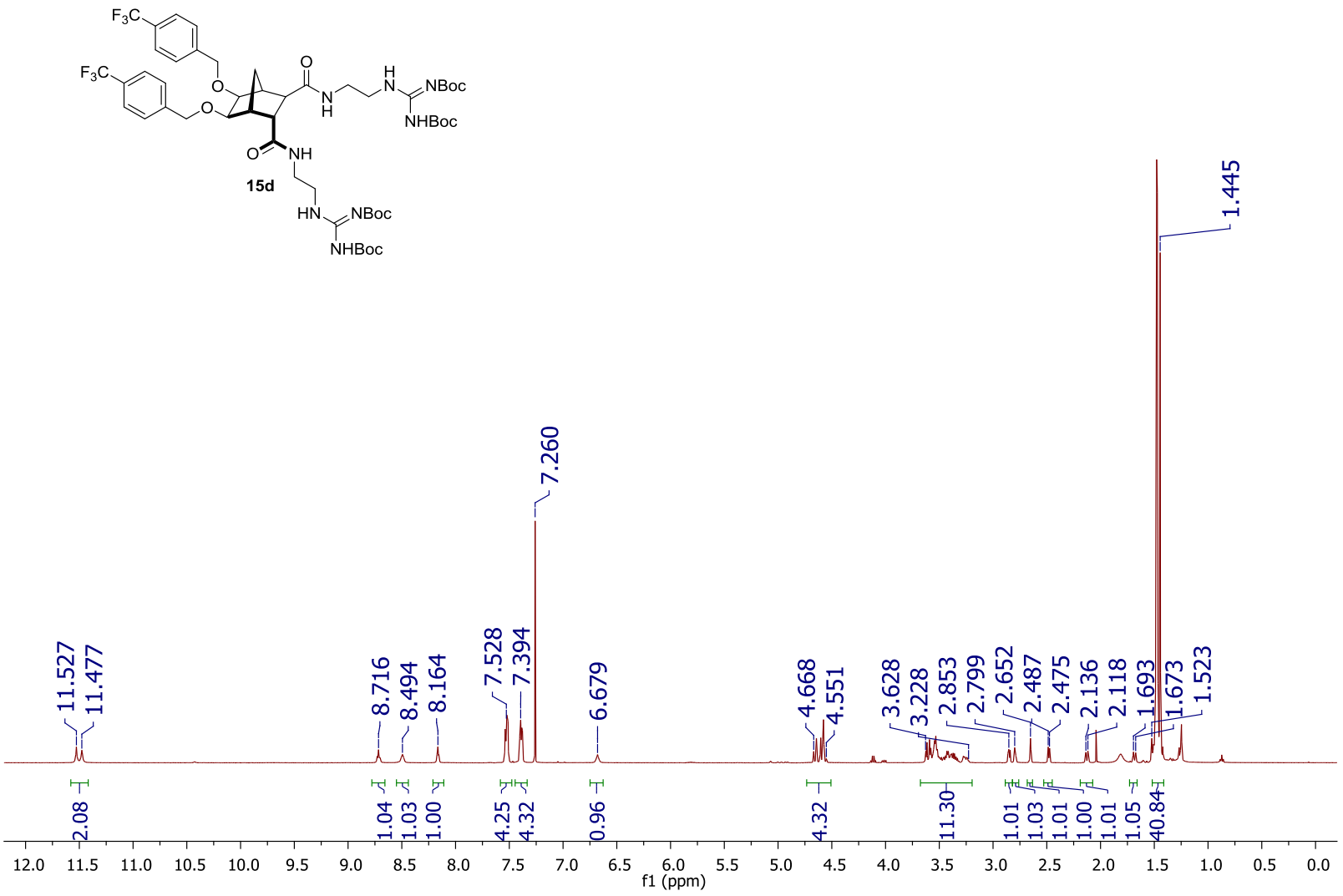

MeO
MeO
O
N
H
H
N
NBoc
NHBoc
O
NH
15a
HN
NBoc
NHBoc
174.445
172.315
163.464
162.964
157.935
156.791
153.162
153.139
84.201
83.763
83.275
81.128
80.041
79.478
58.632
58.358
49.295
44.950
43.670
42.870
42.426
40.294
40.122
39.396
28.369
28.327
28.125
28.095
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

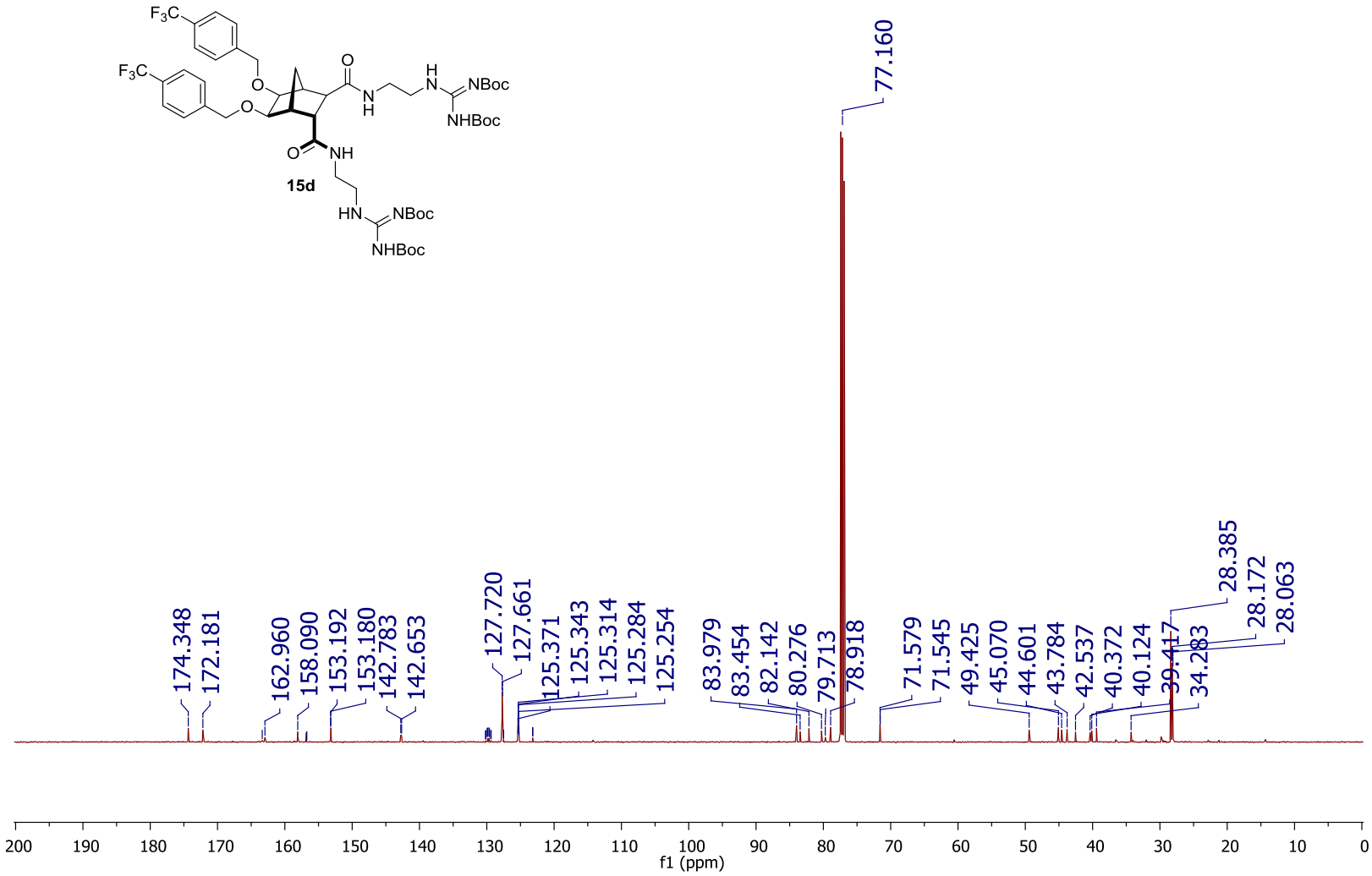

15b
11.531
11.471
8.685
8.468
7.968
7.340
7.260
6.542
4.595
4.554
3.581
3.176
2.818
2.758
2.606
2.602
2.451
2.426
2.152
2.111
1.725
1.612
1.497
1.458
0.86
0.93
0.66
0.55
0.70
18.67
0.23
4.90
13.44
1.92
0.95
1.00
0.69
1.74
43.60
f1 (ppm)

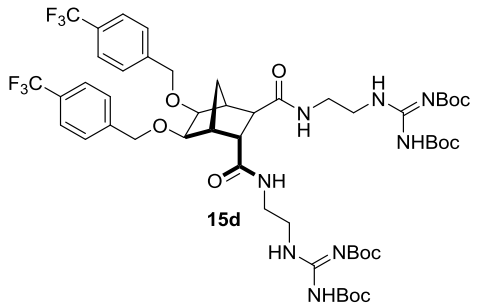

15b
174.515
172.322
163.553
163.071
158.007
156.743
153.216
138.736
138.647
128.387
128.327
128.069
127.847
127.615
127.502
83.822
83.294
81.581
80.149
79.518
78.267
77.160
72.346
72.225
49.506
45.097
44.576
43.750
42.450
40.425
40.127
39.165
34.376
28.402
28.185
28.092
f1 (ppm)


15c
11.497
11.469
8.669
8.481
7.999
7.308
7.260
7.081
6.523
4.575
4.499
3.618
3.225
2.824
2.737
2.601
2.484
2.471
2.275
2.251
2.132
2.113
1.641
1.621
1.476
2.14
1.07
1.03
1.04
5.60
6.80
0.94
4.42
11.78
1.02
1.05
1.11
1.00
6.58
1.13
1.03
41.38
f1 (ppm)

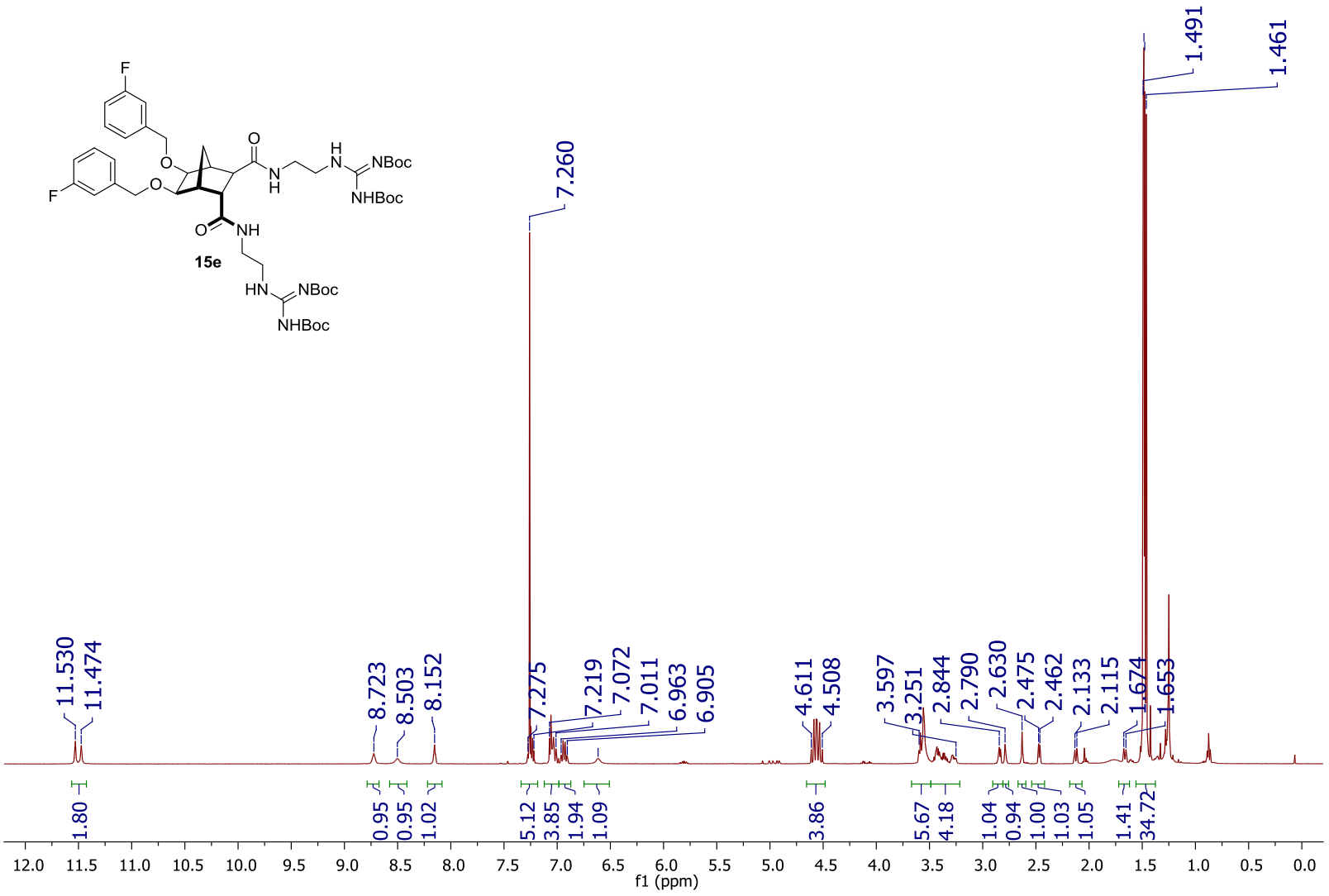

15c
174.600
172.326
157.902
156.711
153.232
153.186
130.196
128.931
128.684
127.755
125.818
125.725
114.212
83.835
83.396
82.114
80.159
79.637
78.693
70.885
70.776
49.520
45.172
44.068
39.205
28.421
28.401
28.200
28.125
19.020
18.930
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

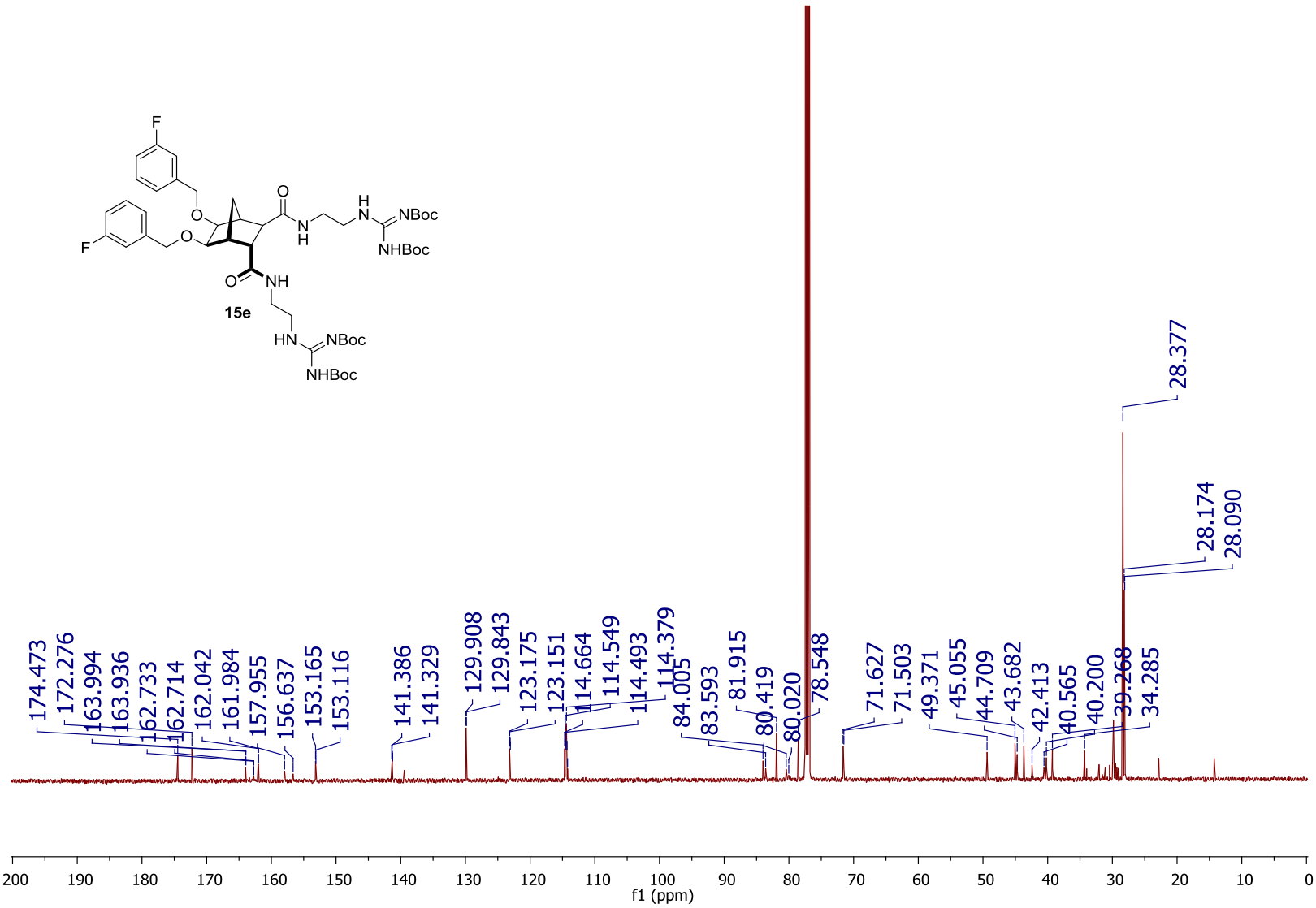

F3C
F3C
O
O
O
O
H
N
N
NBoc
NHBoc
NH
15d
HN
NBoc
NHBoc
11.527
11.477
8.716
8.494
8.164
7.528
7.394
7.260
6.679
4.668
4.551
3.628
3.228
2.853
2.799
2.652
2.487
2.475
2.136
2.118
1.693
1.673
1.523
1.445
2.08
1.04
1.03
1.00
4.25
4.32
0.96
4.32
11.30
1.01
1.03
1.01
1.00
1.01
1.05
40.84
12.0
11.5
11.0
10.5
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
f1 (ppm)

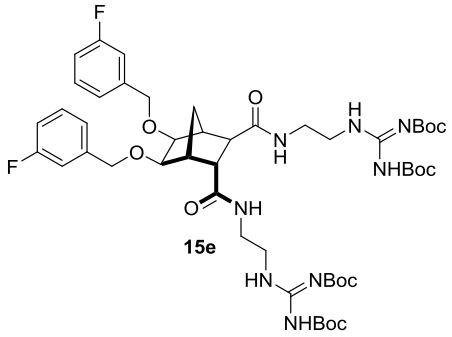

F3C
F3C
O
O
O
N
H
H
N
NBoc
NHBoc
O
NH
15d
HN
NBoc
NHBoc
77.160
174.348
172.181
162.960
158.090
153.192
153.180
142.783
142.653
127.720
127.661
125.371
125.343
125.314
125.284
125.254
83.979
83.454
82.142
80.276
79.713
78.918
71.579
71.545
49.425
45.070
44.601
43.784
42.537
40.372
40.124
39.417
34.283
28.385
28.172
28.063
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


F3C
F3C
O
O
O
N
H
H
N
NBoc
NHBoc
O
NH
15d
HN
NBoc
NHBoc

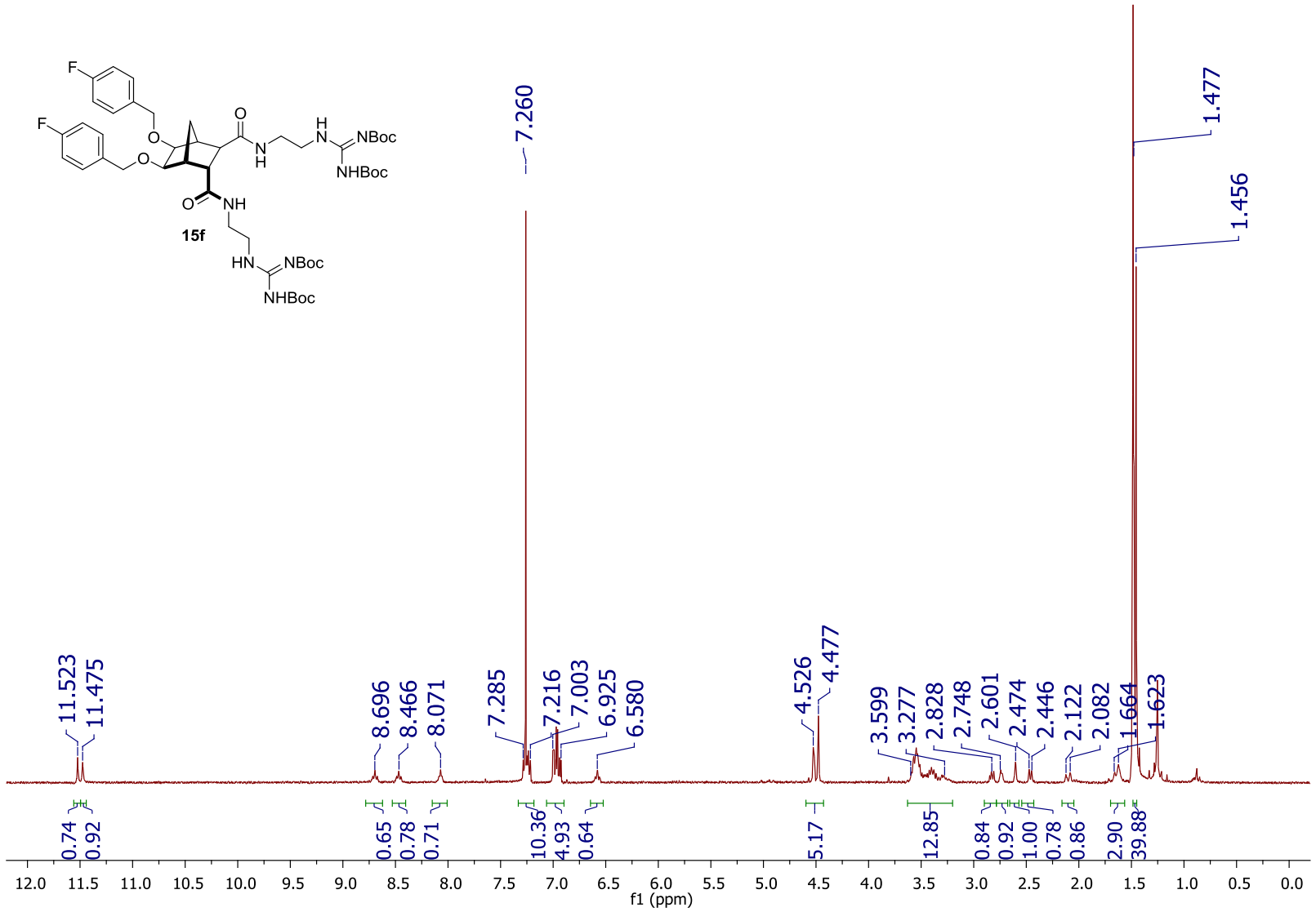
-62.970
-5
-10
-15
-20
-25
-30
-35
-40
-45
-50
-55
-60
-65
-70
-75
-80
-85
-90
-95
-105
-115
-125
-135
f1 (ppm)

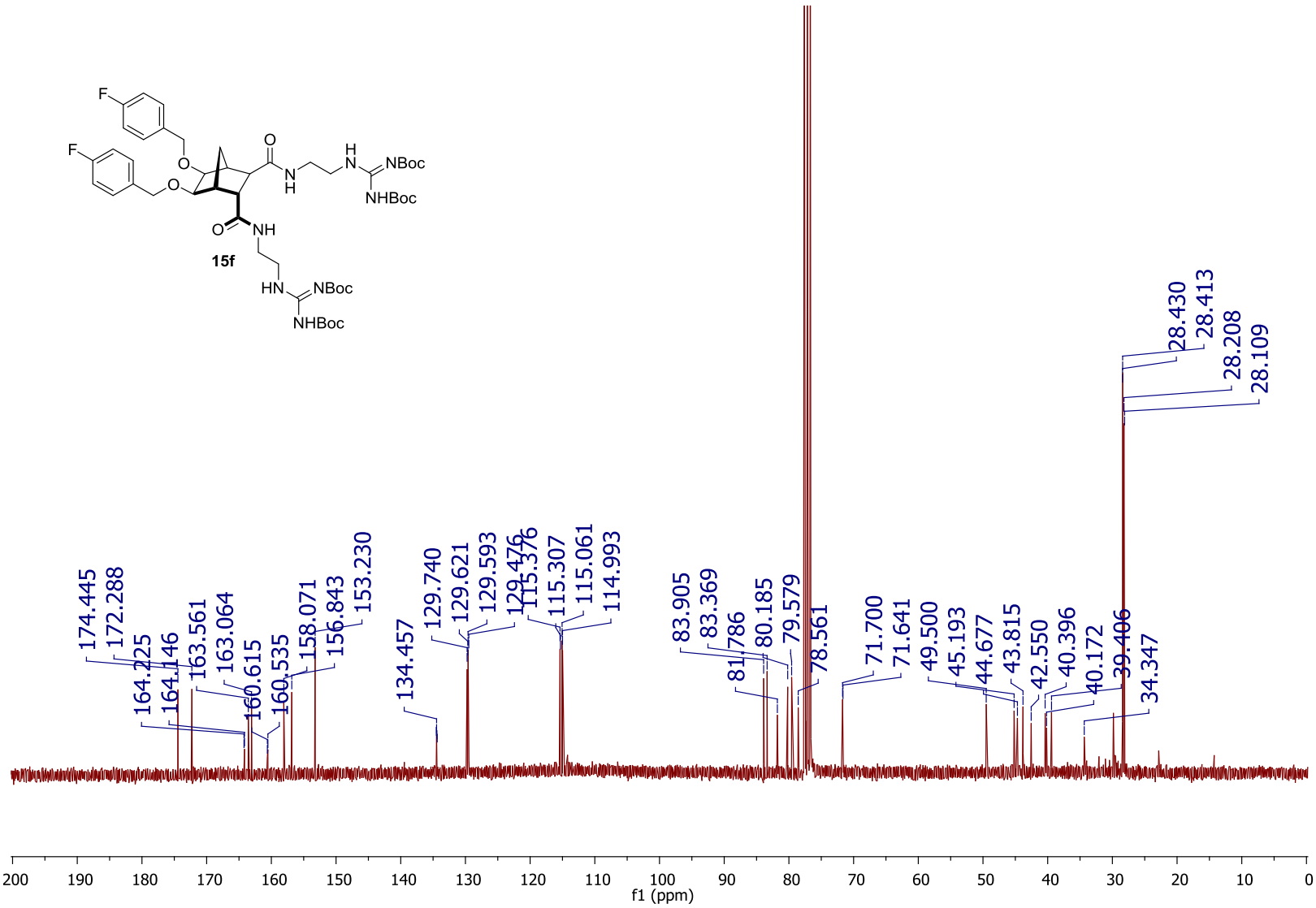

F
F
O
O
O
O
NH
NBoc
NHBoc
15e
HN
NBoc
NHBoc
11.530
11.474
8.723
8.503
8.152
7.260
7.275
7.219
7.072
7.011
6.963
6.905
4.611
4.508
3.597
3.251
2.844
2.790
2.630
2.475
2.462
2.133
2.115
1.674
1.653
1.491
1.461
1.80
0.95
0.95
1.02
5.12
3.85
1.94
1.09
3.86
5.67
4.18
1.04
0.94
1.00
1.03
1.05
1.41
34.72
12.0
11.5
11.0
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
f1 (ppm)

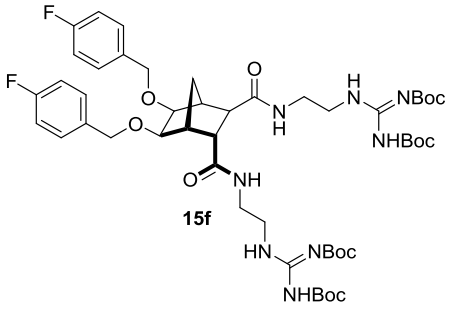

F
F
O
O
O
N
H
N
H
NBoc
NHBoc
O
NH
HN
NBoc
NHBoc
15e
174.473
172.276
163.994
163.936
162.733
162.714
162.042
161.984
157.955
156.637
153.165
153.116
141.386
141.329
129.908
129.843
123.175
123.151
114.664
114.549
114.493
114.379
84.005
83.593
81.915
80.419
80.020
78.548
71.627
71.503
49.371
45.055
44.709
43.682
42.413
40.565
40.200
39.268
34.285
28.377
28.174
28.090
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


F
F
O
O
O
NH
NBoc
NHBoc
15e
HN
NBoc
NHBoc

-113.913
-113.862
-5
-10
-15
-20
-25
-30
-35
-40
-45
-50
-55
-60
-65
-70
-75
-80
-85
-90
-95
-105
-115
-125
-135
f1 (ppm)

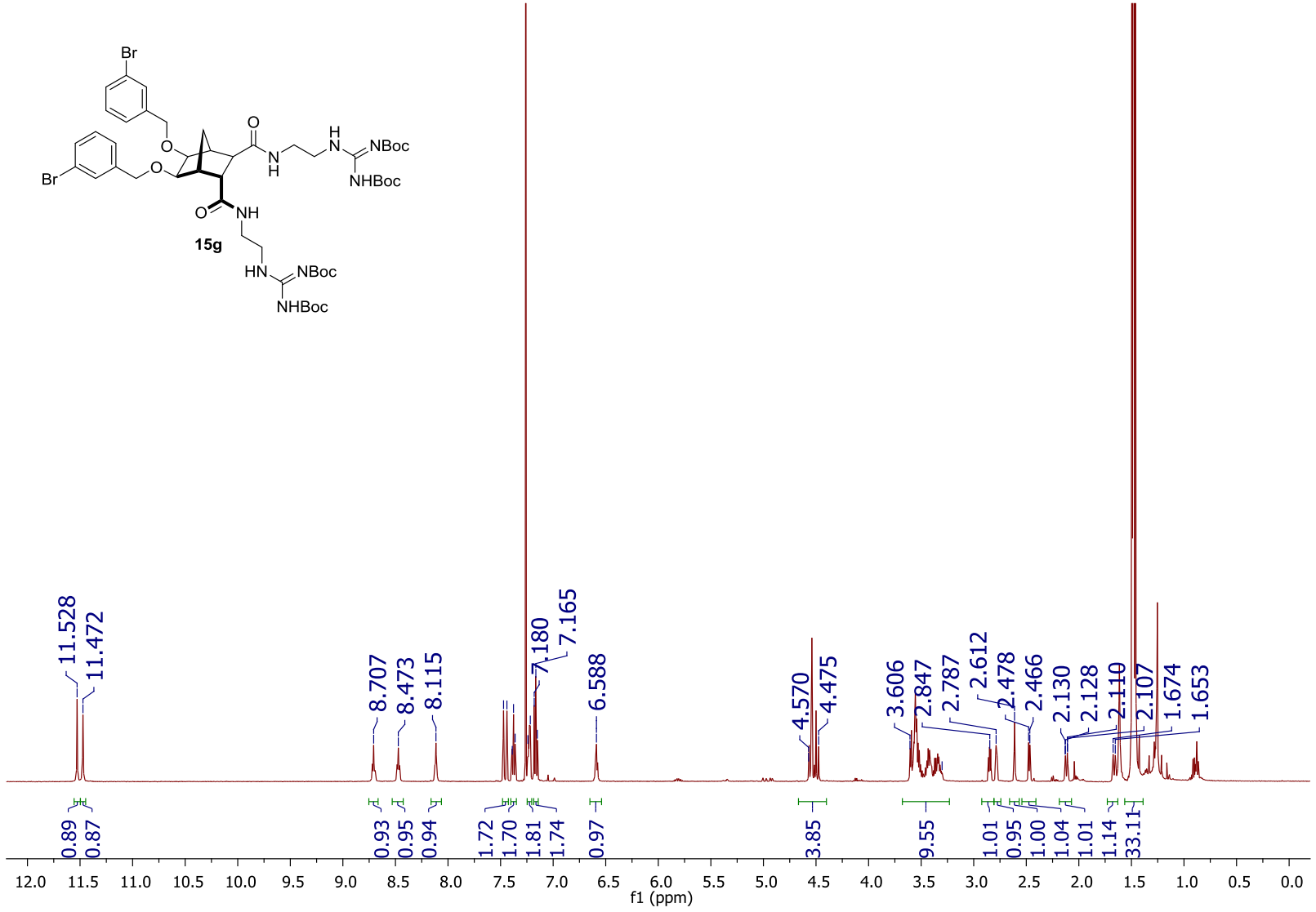

15f
F
F
O
O
O
O
NH
NBoc
NHBoc
HN
NBoc
NHBoc
11.523
11.475
8.696
8.466
8.071
7.285
7.260
7.216
7.003
6.925
6.580
4.526
4.477
3.599
3.277
2.828
2.748
2.601
2.474
2.446
2.122
2.082
1.664
1.623
1.477
1.456
0.74
0.92
0.65
0.78
0.71
10.36
4.93
0.64
5.17
12.85
0.84
0.92
1.00
0.78
0.86
2.90
39.88
f1 (ppm)

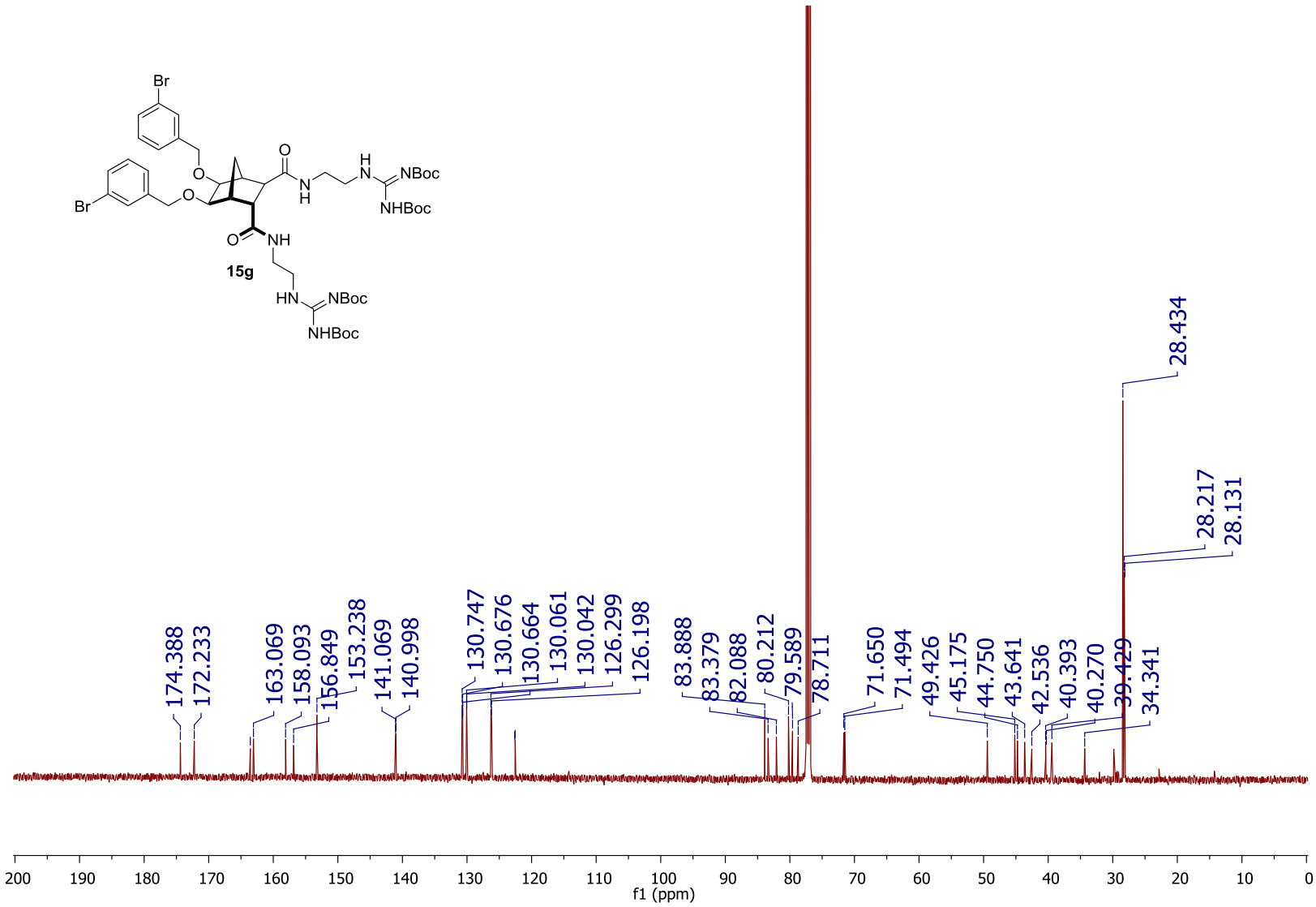

15f
174.445
172.288
164.225
164.146
163.561
163.064
160.615
160.535
158.071
156.843
153.230
134.457
129.740
129.621
129.593
129.476
129.376
115.307
115.061
114.993
83.905
83.369
81.786
80.185
79.579
78.561
71.700
71.641
49.500
45.193
44.677
43.815
42.550
40.396
40.172
39.406
34.347
28.430
28.413
28.208
28.109
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

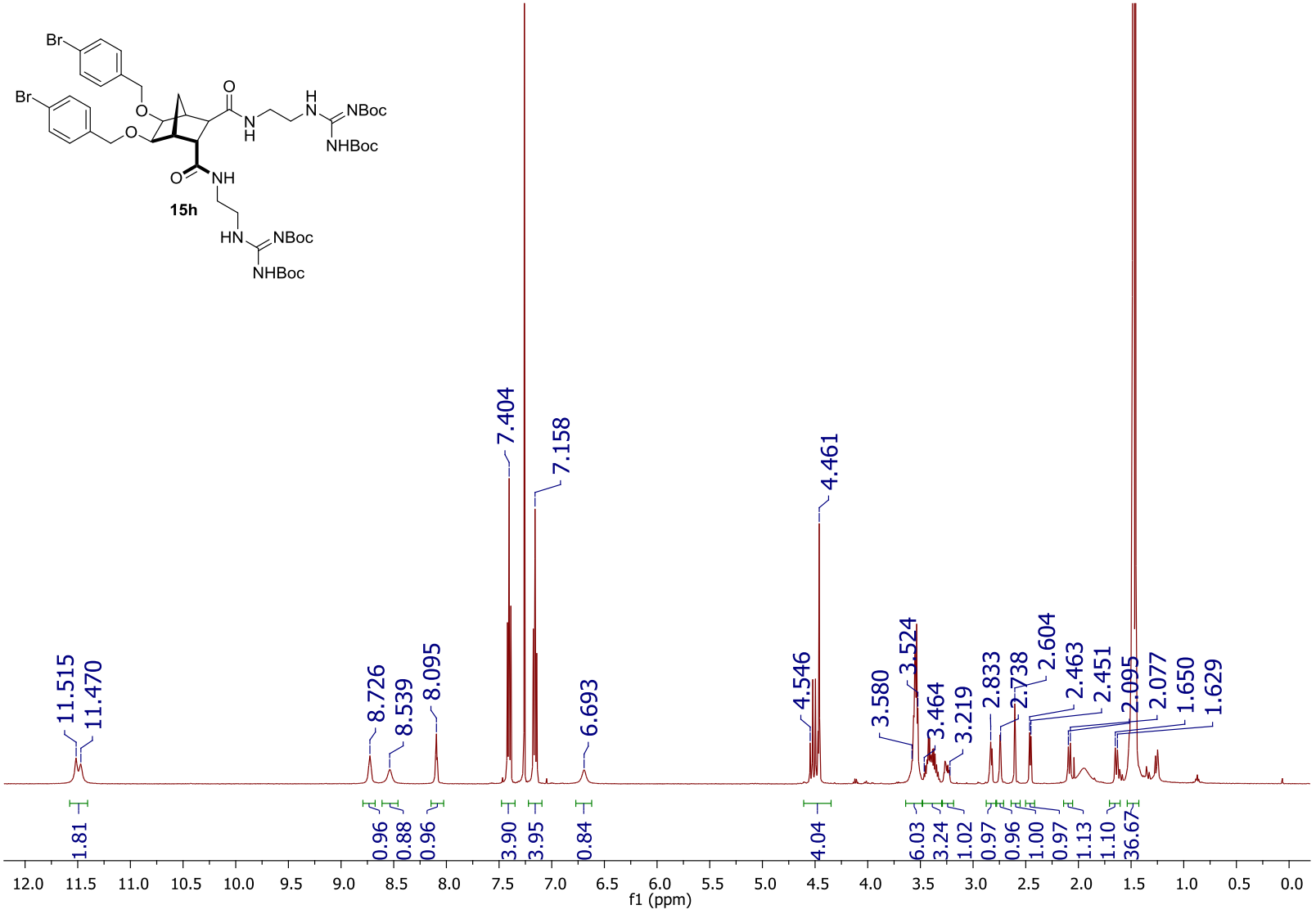

F
F
O
O
O
O
N
H
H
N
NBoc
NHBoc
O
NH
HN
NBoc
NHBoc

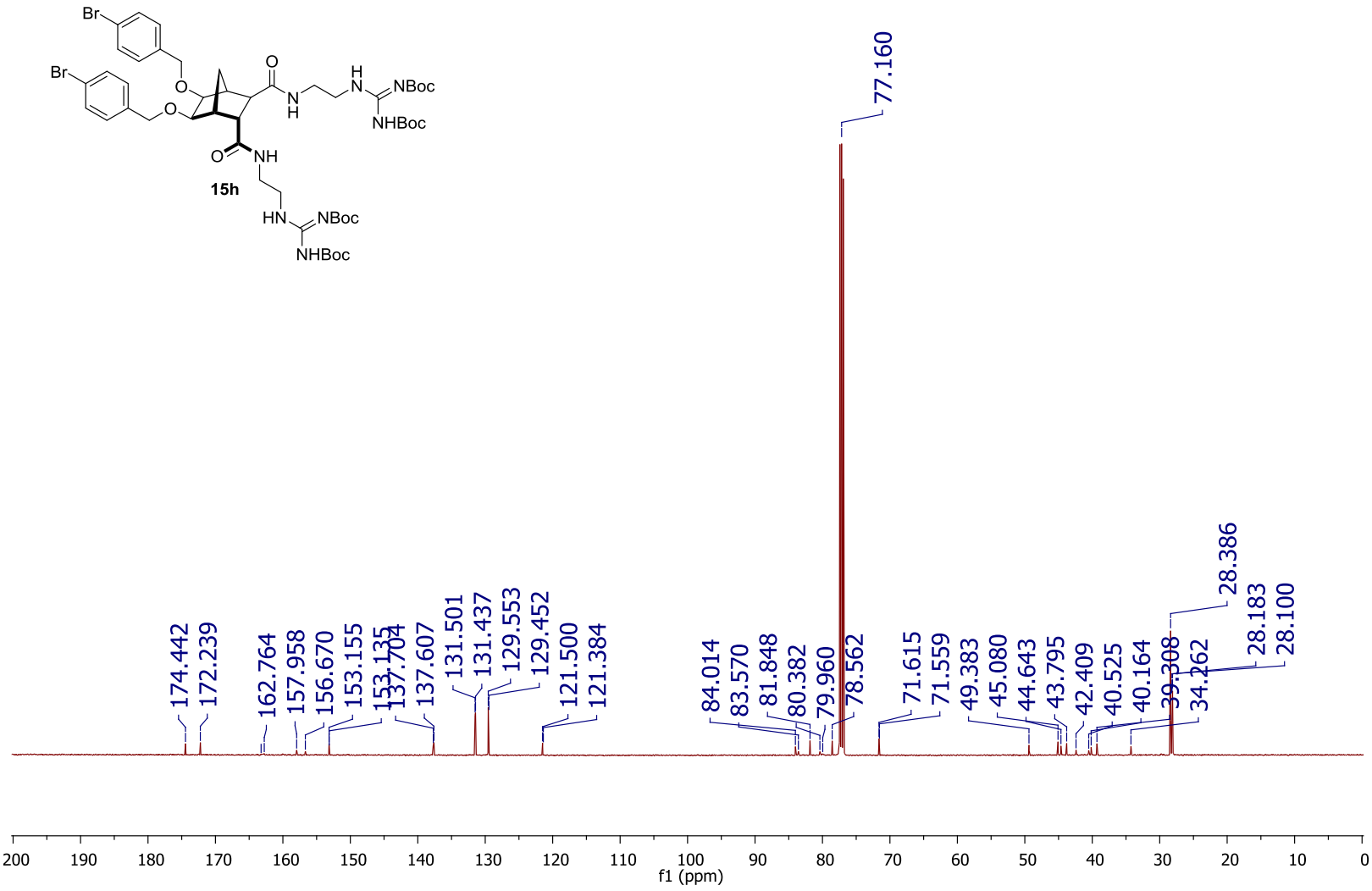
15f

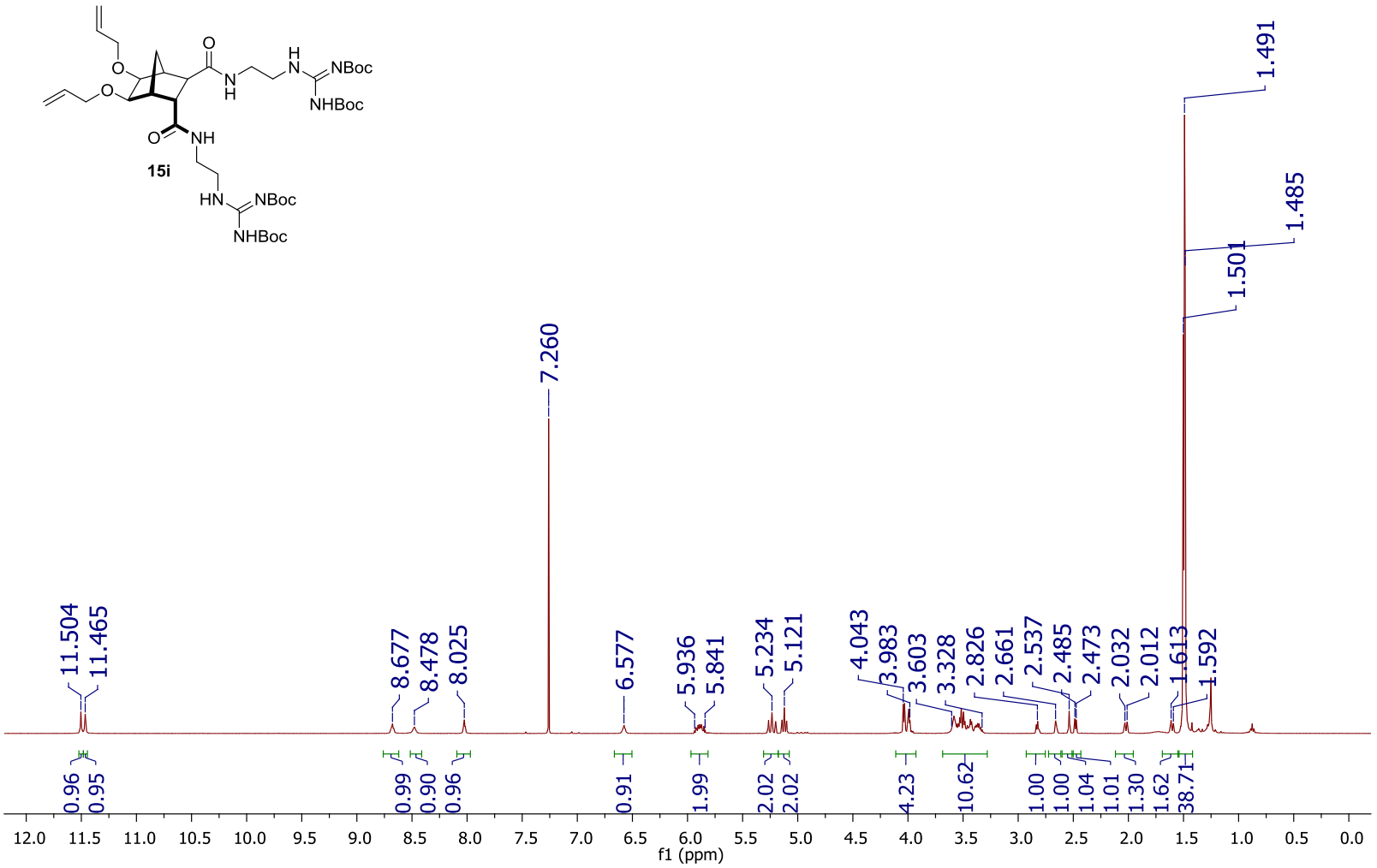
-115.097
-115.165
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
f1 (ppm)

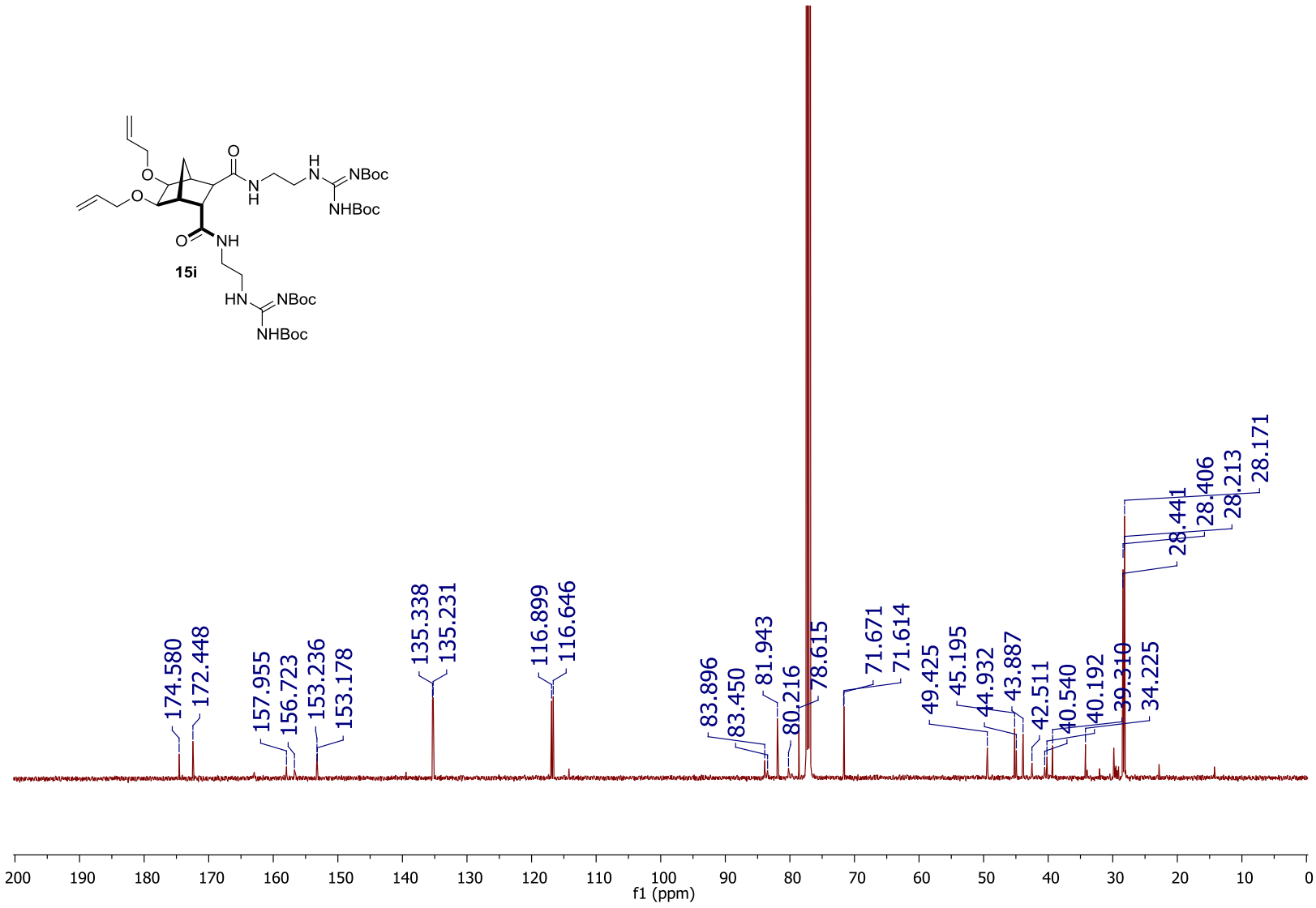

Br
Br
O
O
O
NH
NBoc
NHBoc
15g
HN
NBoc
NHBoc
11.528
11.472
8.707
8.473
8.115
7.180
7.165
6.588
4.570
4.475
3.606
2.847
2.787
2.612
2.478
2.466
2.130
2.128
2.110
2.107
1.674
1.653
0.89
0.87
0.93
0.95
0.94
1.72
1.70
1.81
1.74
0.97
3.85
9.55
1.01
0.95
1.00
1.04
1.01
1.14
33.11
f1 (ppm)

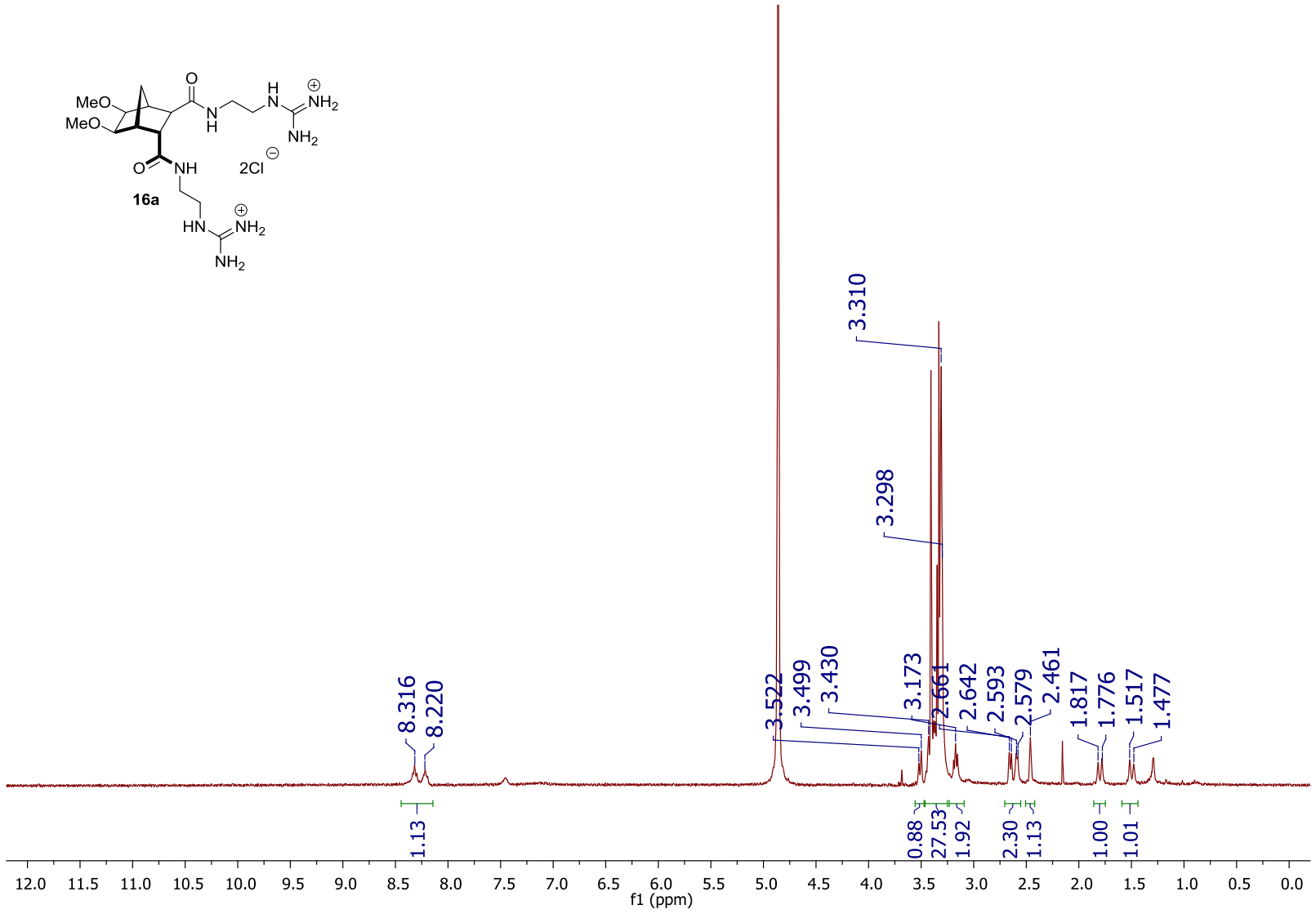

Br
Br
O
O
O
N
H
H
N
NBoc
NHBoc
O
NH
15g
HN
NBoc
NHBoc
174.388
172.233
163.069
158.093
156.849
153.238
141.069
140.998
130.747
130.676
130.664
130.061
130.042
126.299
126.198
83.888
83.379
82.088
80.212
79.589
78.711
71.650
71.494
49.426
45.175
44.750
43.641
42.536
40.393
40.270
39.429
34.341
28.434
28.217
28.131
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

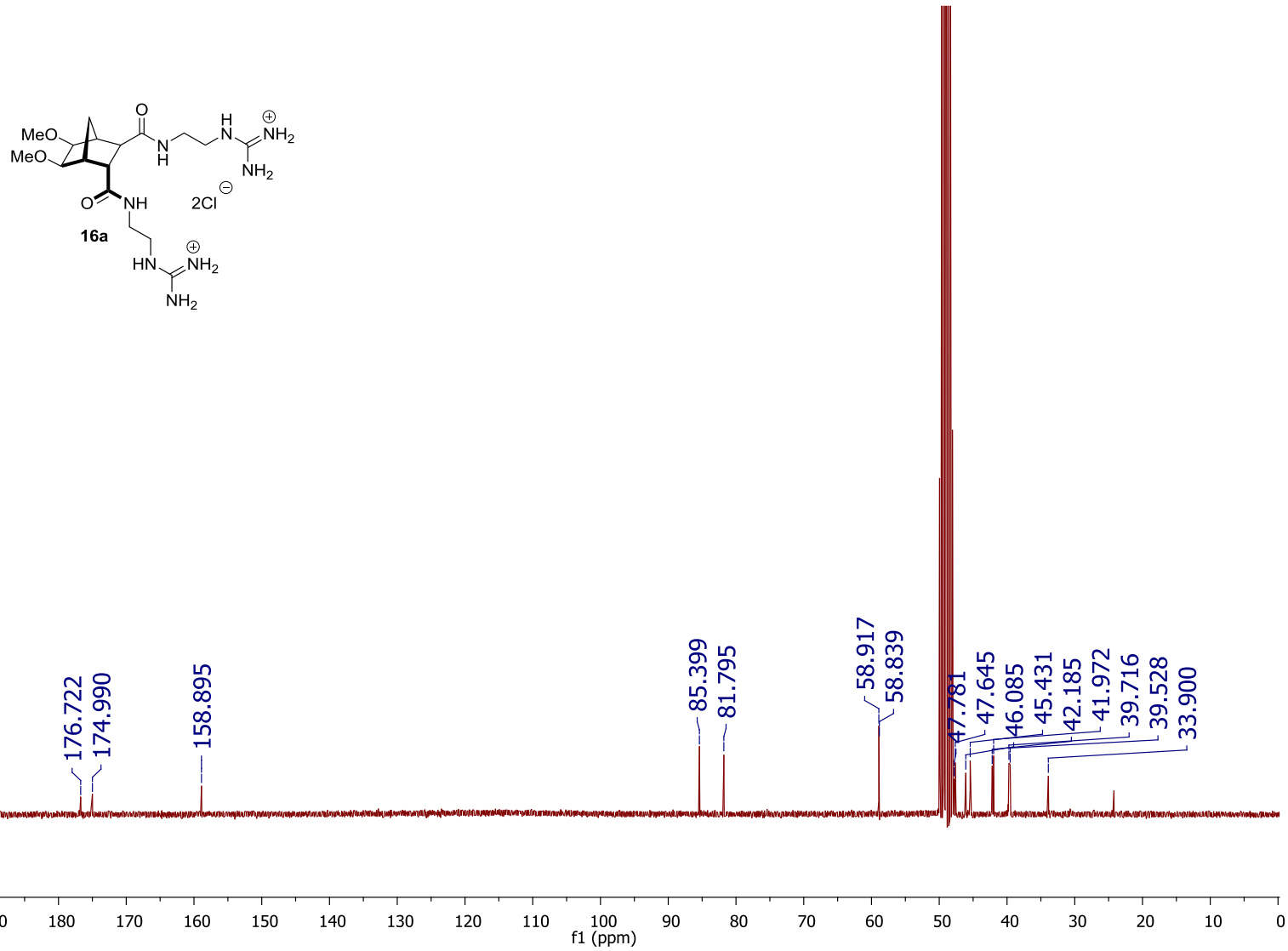

Br
Br
O
O
O
O
H
N
N
NBoc
NHBoc
NH
HN
NBoc
NHBoc
15h
11.515
11.470
8.726
8.539
8.095
7.404
7.158
6.693
4.546
4.461
3.580
3.524
3.464
3.219
2.833
2.738
2.604
2.463
2.451
2.095
2.077
1.650
1.629
1.81
0.96
0.88
0.96
3.90
3.95
0.84
4.04
6.03
3.24
1.02
0.97
0.96
1.00
0.97
1.13
1.10
36.67
12.0
11.5
11.0
10.5
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
f1 (ppm)

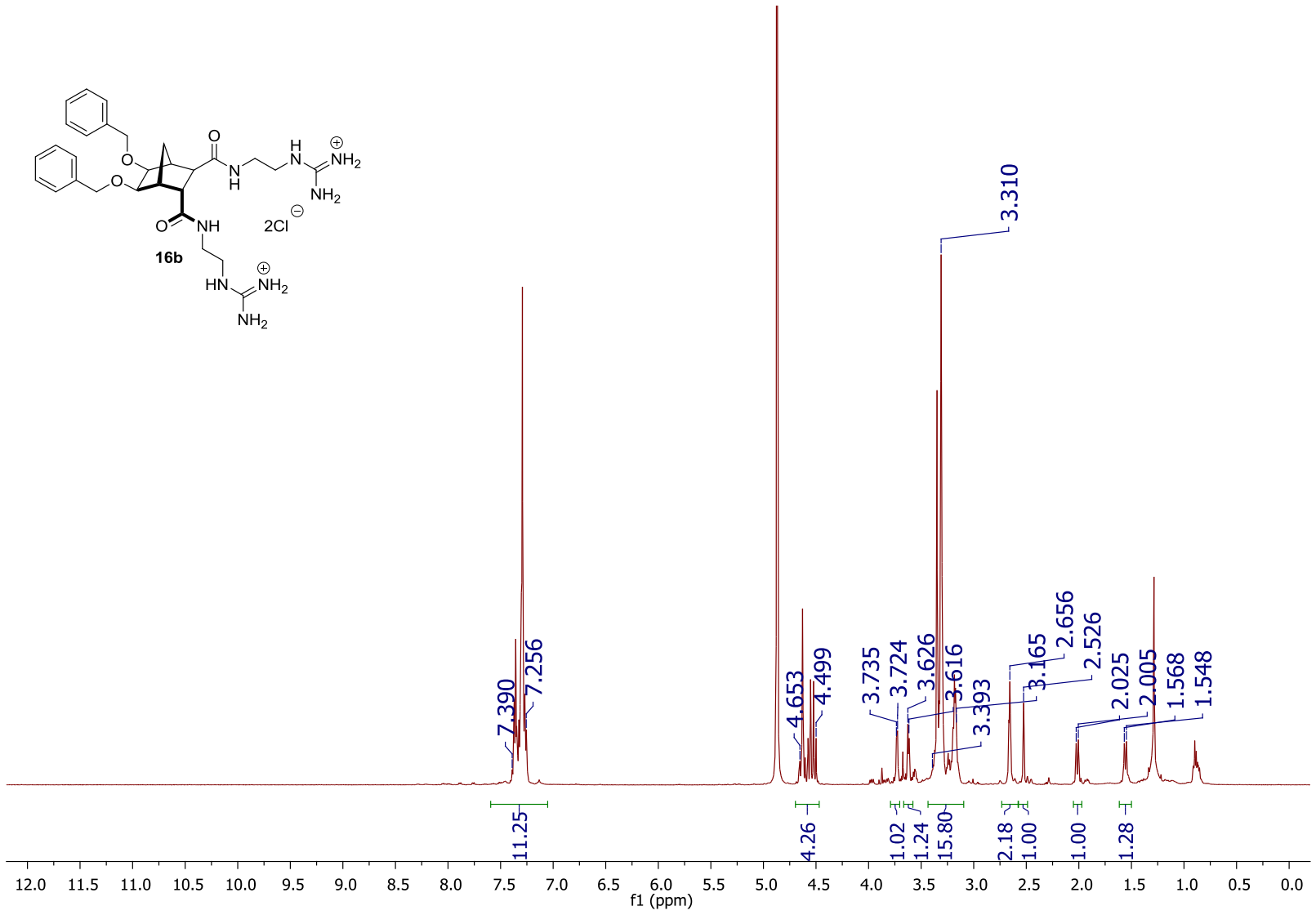

Br
Br
O
O
O
O
N
H
H
N
NBoc
NHBoc
NH
15h
HN
NBoc
NHBoc
77.160
174.442
172.239
162.764
157.958
156.670
153.155
153.135
137.704
137.607
131.501
131.437
129.553
129.452
121.500
121.384
84.014
83.570
81.848
80.382
79.960
78.562
71.615
71.559
49.383
45.080
44.643
43.795
42.409
40.525
40.164
39.308
34.262
28.386
28.183
28.100
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

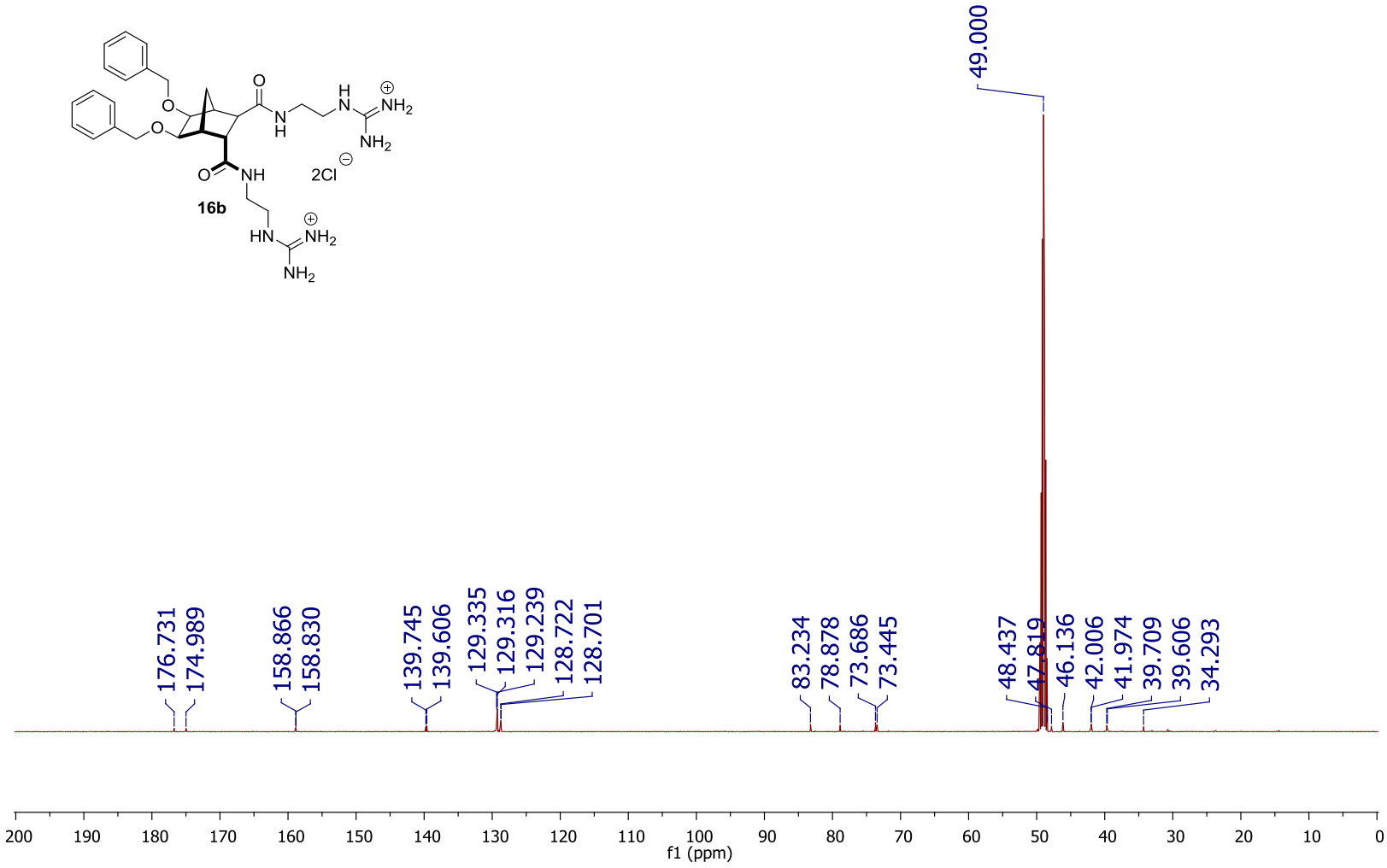

15i
11.504
11.465
8.677
8.478
8.025
7.260
6.577
5.936
5.841
5.234
5.121
4.043
3.983
3.603
3.328
2.826
2.661
2.537
2.485
2.473
2.032
2.012
1.613
1.592
1.491
1.485
1.501
0.96
0.95
0.99
0.90
0.96
0.91
1.99
2.02
2.02
4.23
10.62
1.00
1.00
1.04
1.01
1.30
1.62
38.71
f1 (ppm)

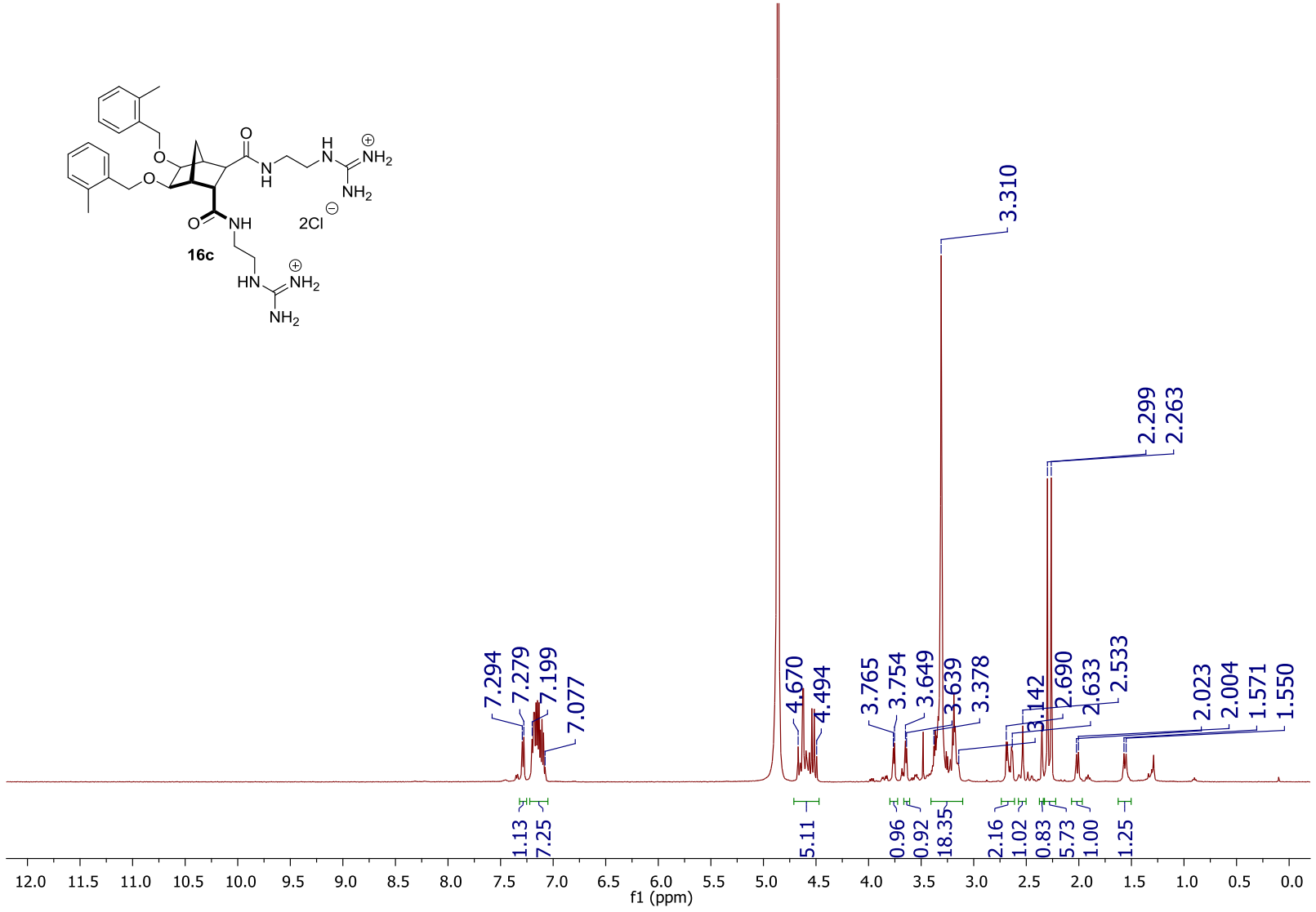

15i
174.580
172.448
157.955
156.723
153.236
153.178
135.338
135.231
116.899
116.646
83.896
83.450
81.943
80.216
78.615
71.671
71.614
49.425
45.195
44.932
43.887
42.511
40.540
40.192
39.310
34.225
28.441
28.406
28.213
28.171
f1 (ppm)

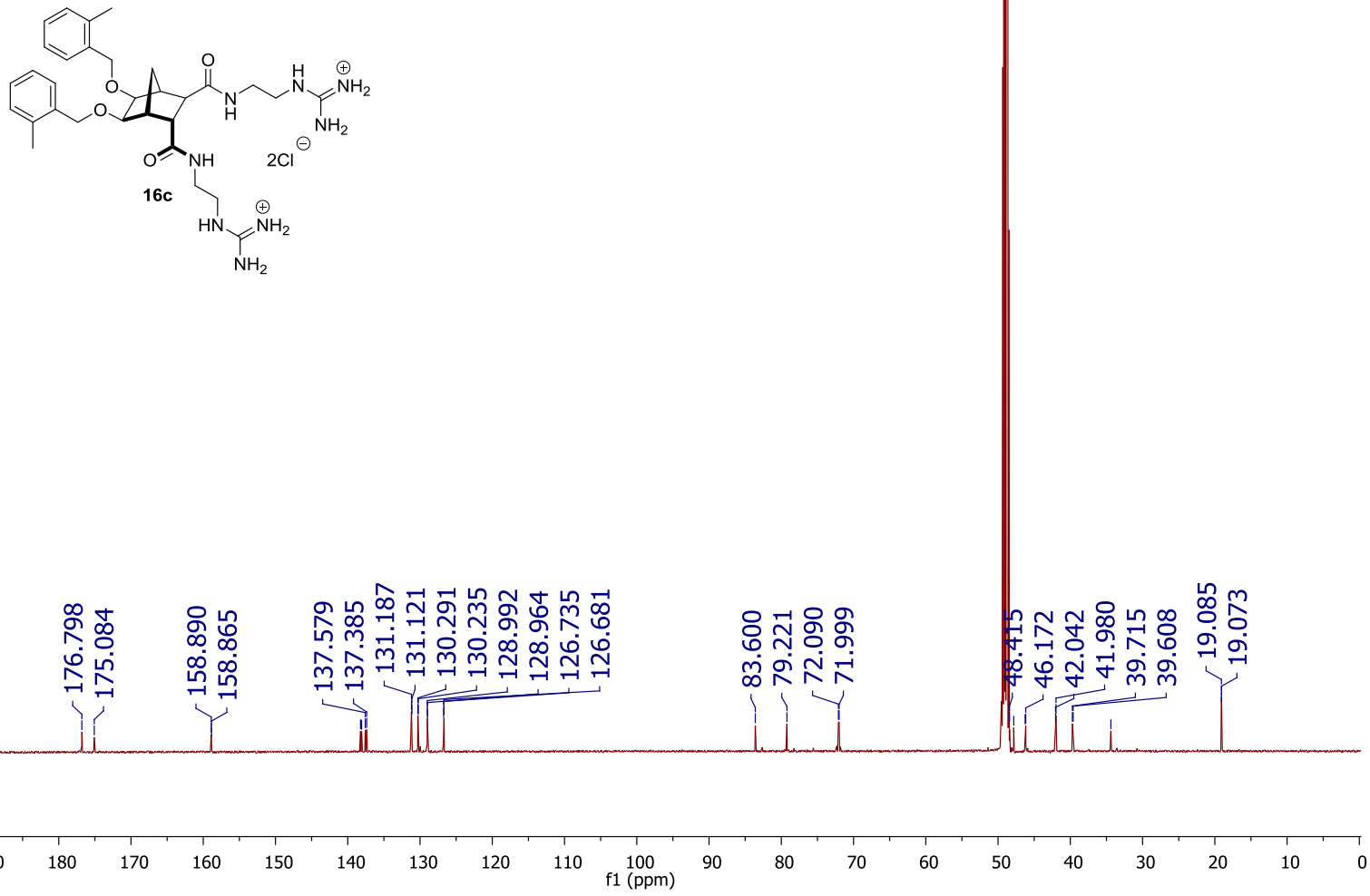

MeO
MeO
O
N
H
H
N
NH2
NH2
O
NH
2Cl
16a
HN
NH2
NH2
8.316
8.220
3.522
3.499
3.430
3.310
3.298
3.173
2.661
2.642
2.593
2.579
2.461
1.817
1.776
1.517
1.477
1.13
0.88
27.53
1.92
2.30
1.13
1.00
1.01
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

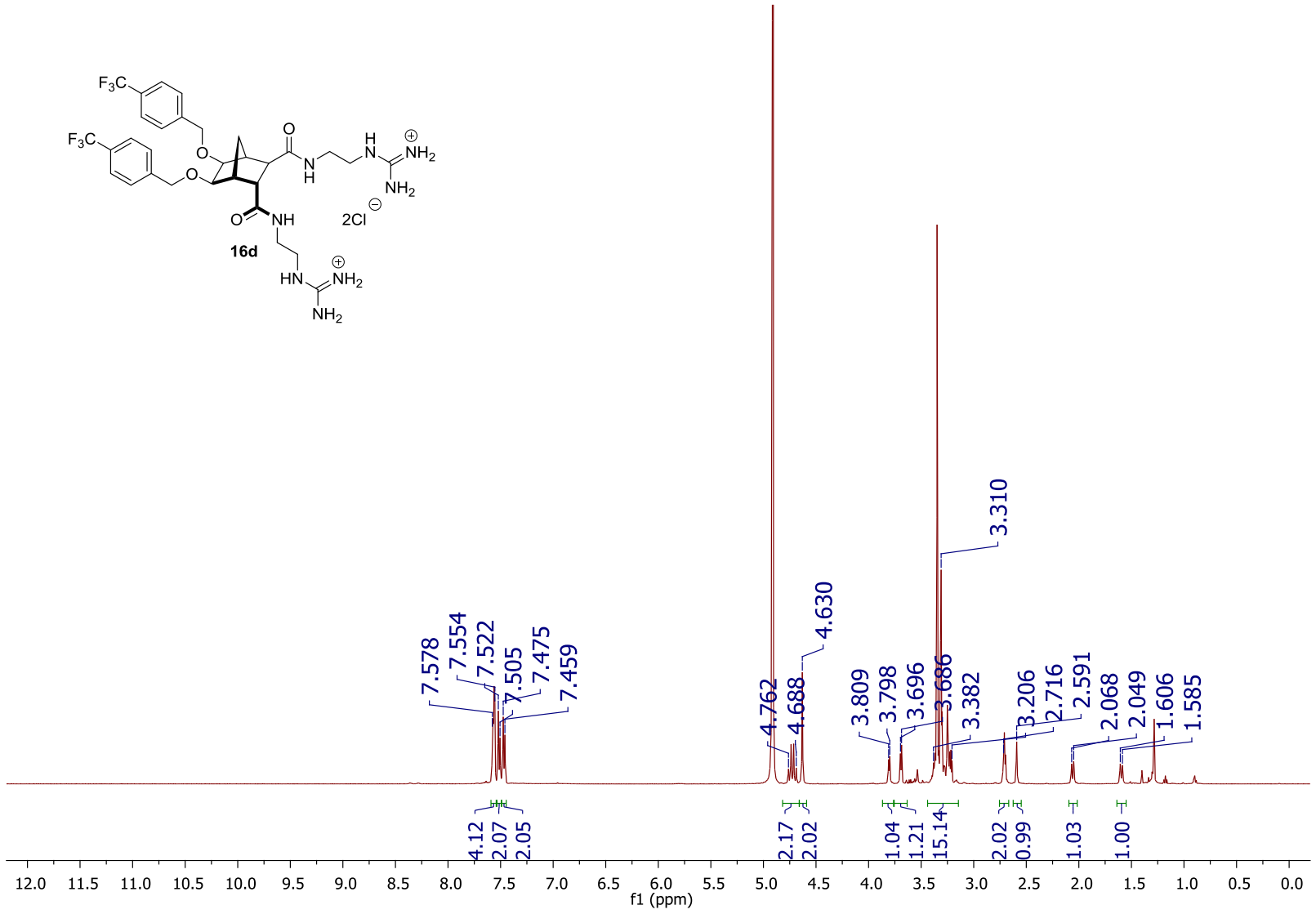

MeO
MeO
O
N
H
H
N
NH2
NH2
O
NH
2Cl
16a
HN
NH2
NH2
176.722
174.990
158.895
85.399
81.795
58.917
58.839
47.781
47.645
46.085
45.431
42.185
41.972
39.716
39.528
33.900
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

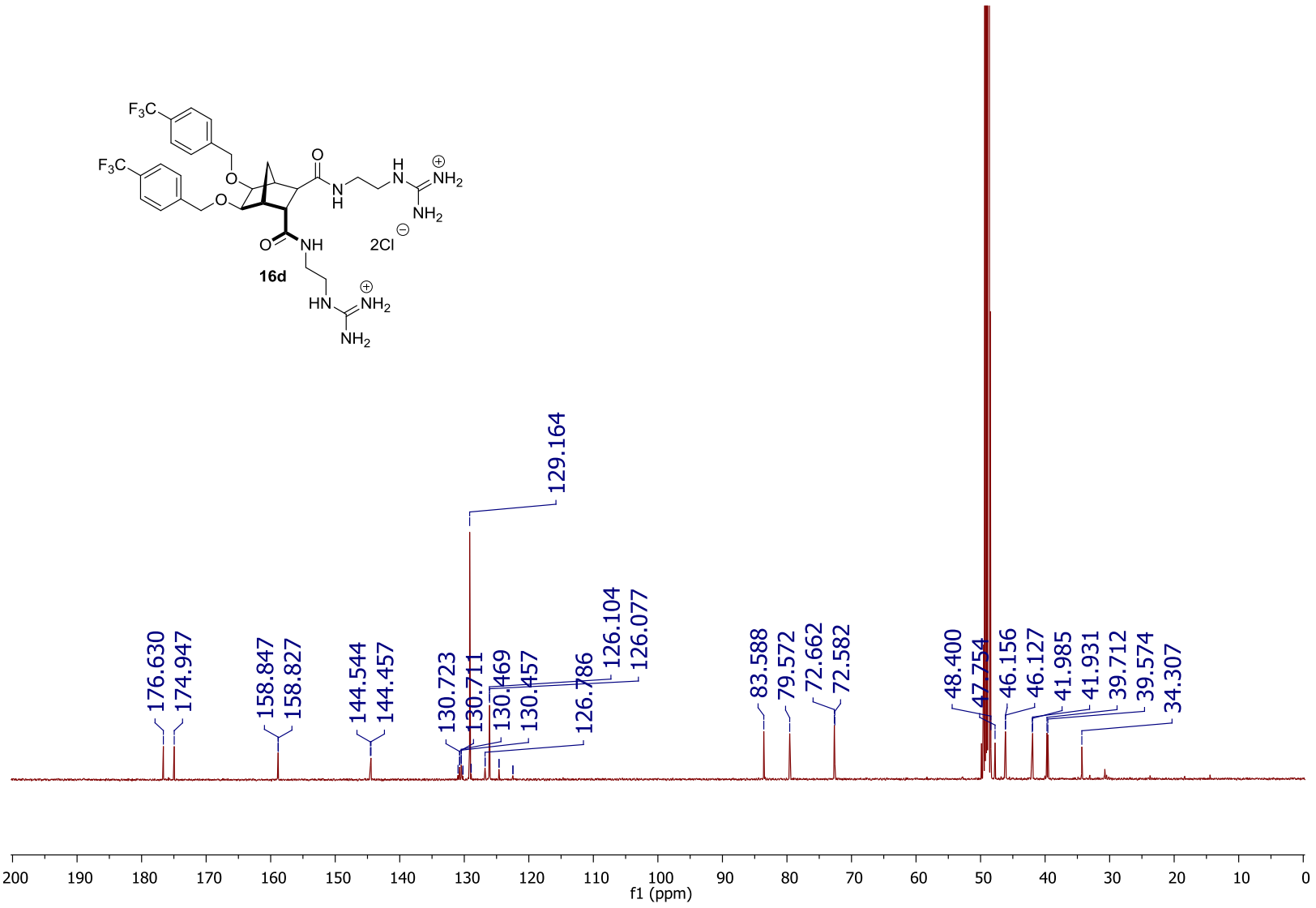

16b
2Cl
3.310
7.390
7.256
4.653
4.499
3.735
3.724
3.626
3.616
3.393
3.165
2.656
2.526
2.025
2.005
1.568
1.548
11.25
4.26
1.02
1.24
15.80
2.18
1.00
1.00
1.28
f1 (ppm)

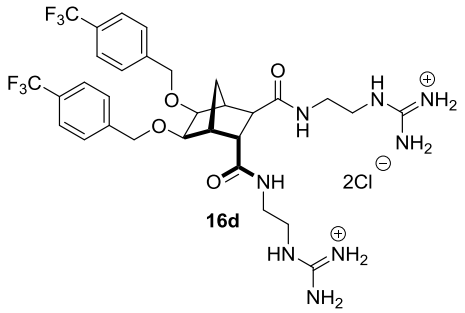

16b
2Cl
49.000
176.731
174.989
158.866
158.830
139.745
139.606
129.335
129.316
129.239
128.722
128.701
83.234
78.878
73.686
73.445
48.437
47.819
46.136
42.006
41.974
39.709
39.606
34.293
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

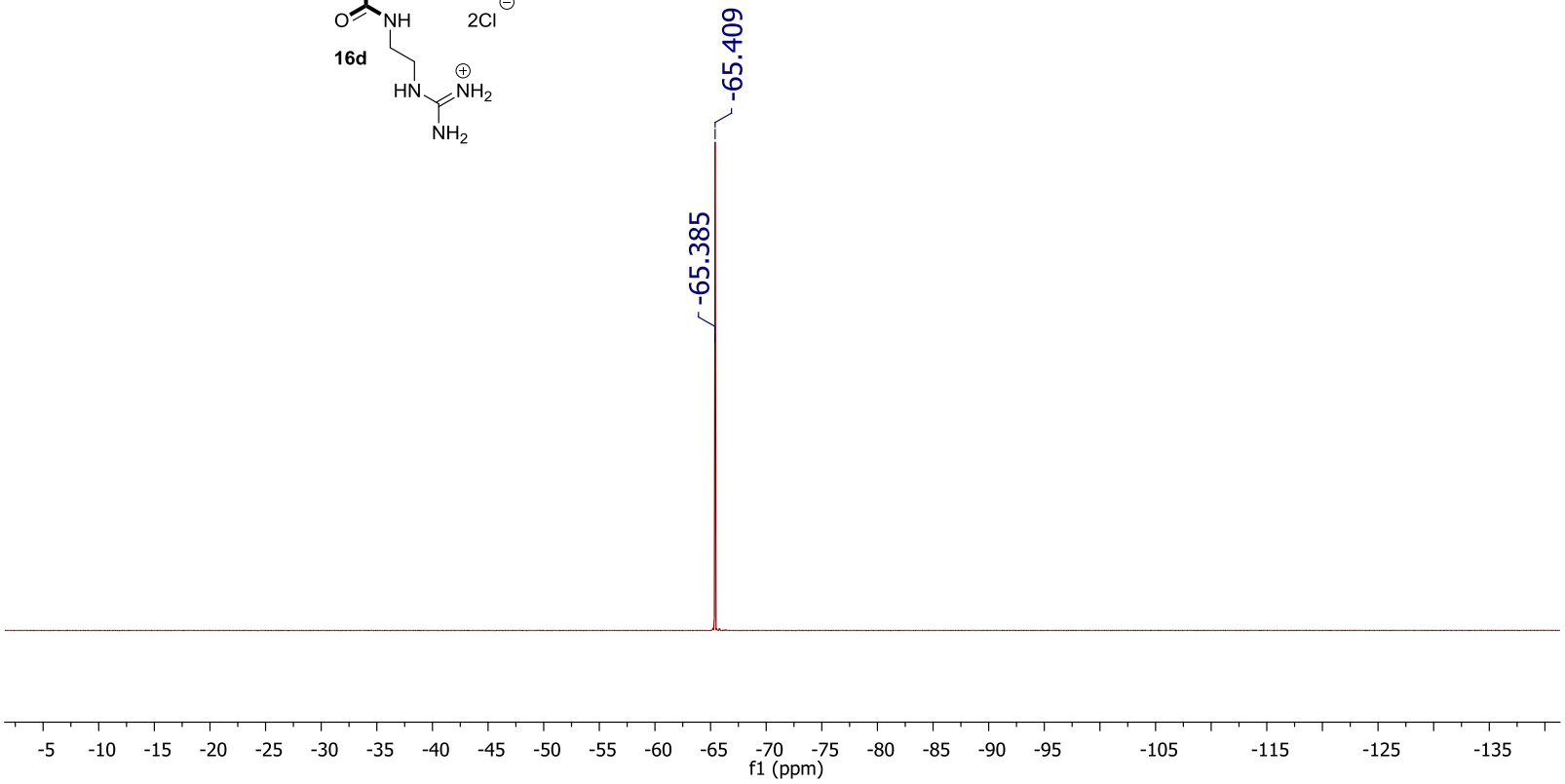

16c
2Cl
7.294
7.279
7.199
7.077
4.670
4.494
3.765
3.754
3.649
3.639
3.378
3.310
3.142
2.690
2.633
2.533
2.299
2.263
2.023
2.004
1.571
1.550
1.13
7.25
5.11
0.96
0.92
18.35
2.16
1.02
0.83
5.73
1.00
1.25
f1 (ppm)

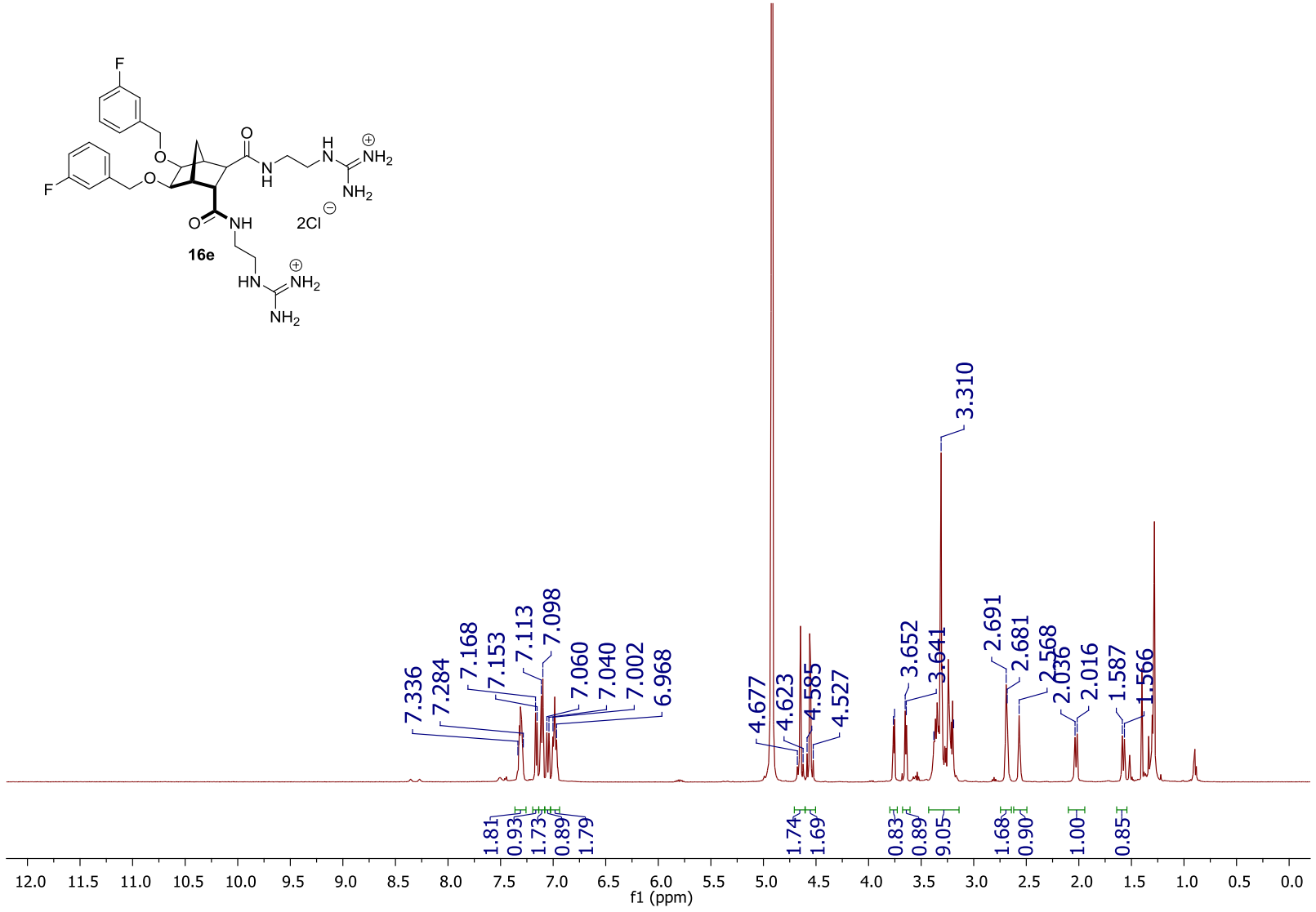

16c
2Cl
176.798
175.084
158.890
158.865
137.579
137.385
131.187
131.121
130.291
130.235
128.992
128.964
126.735
126.681
83.600
79.221
72.090
71.999
48.415
46.172
42.042
41.980
39.715
39.608
19.085
19.073
f1 (ppm)


F3C
F3C
O
O
O
O
N
H
H
N
NH2
NH2
2Cl
O
NH
16d
HN
NH2
NH2
7.578
7.554
7.522
7.505
7.475
7.459
4.762
4.688
4.630
3.809
3.798
3.696
3.686
3.382
3.310
3.206
2.716
2.591
2.068
2.049
1.606
1.585
4.12
2.07
2.05
2.17
2.02
1.04
1.21
15.14
2.02
0.99
1.03
1.00
12.0
11.5
11.0
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
f1 (ppm)


16d
2Cl
176.630
174.947
158.847
158.827
144.544
144.457
130.723
130.711
130.469
130.457
126.786
126.104
126.077
129.164
83.588
79.572
72.662
72.582
48.400
47.754
46.156
46.127
41.985
41.931
39.712
39.574
34.307
f1 (ppm)


F3C
F3C
O
O
O
NH
2Cl
16d
HN
NH2
NH2
NH
NH2
NH2


-65.409
-65.385
-5
-10
-15
-20
-25
-30
-35
-40
-45
-50
-55
-60
-65
-70
-75
-80
-85
-90
-95
-105
-115
-125
-135
f1 (ppm)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7.153
7.113
7.098
7.060
7.040
7.002
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4.623
4.585
4.527
3.652
3.641
3.310
2.691
2.681
2.568
2.536
2.016
1.587
1.566
1.81
0.93
1.73
0.89
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1.69
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0.89
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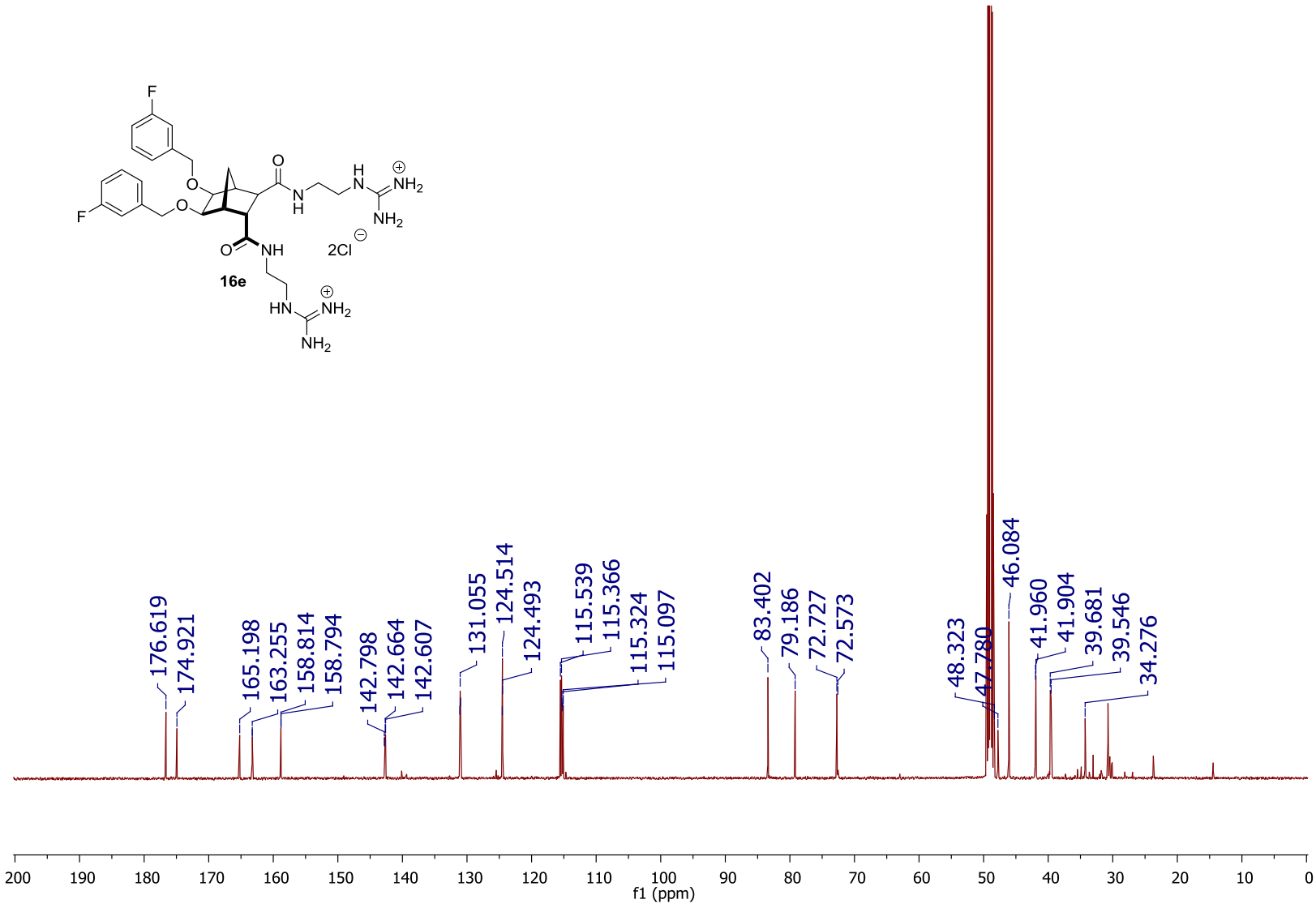
0.90
1.00
0.85
f1 (ppm)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O
O
NH
2Cl
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HN
NH2
NH2
NH2
NH2
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158.814
158.794
142.798
142.664
142.607
131.055
124.514
124.493
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115.366
115.324
115.097
83.402
79.186
72.727
72.573
48.323
47.780
46.084
41.960
41.904
39.681
39.546
34.276
200
190
180
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90
80
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50
40
30
20
10
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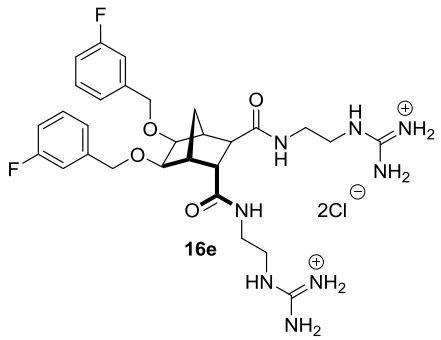
f1 (ppm)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F
O
O
O
N
H
H
N
NH2
NH2
2Cl
O
NH
HN
NH2
NH2

16e

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-116.031
-5
-10
-15
-20
-25
-30
-35
-40
-45
-50
-55
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-80
-85
-90
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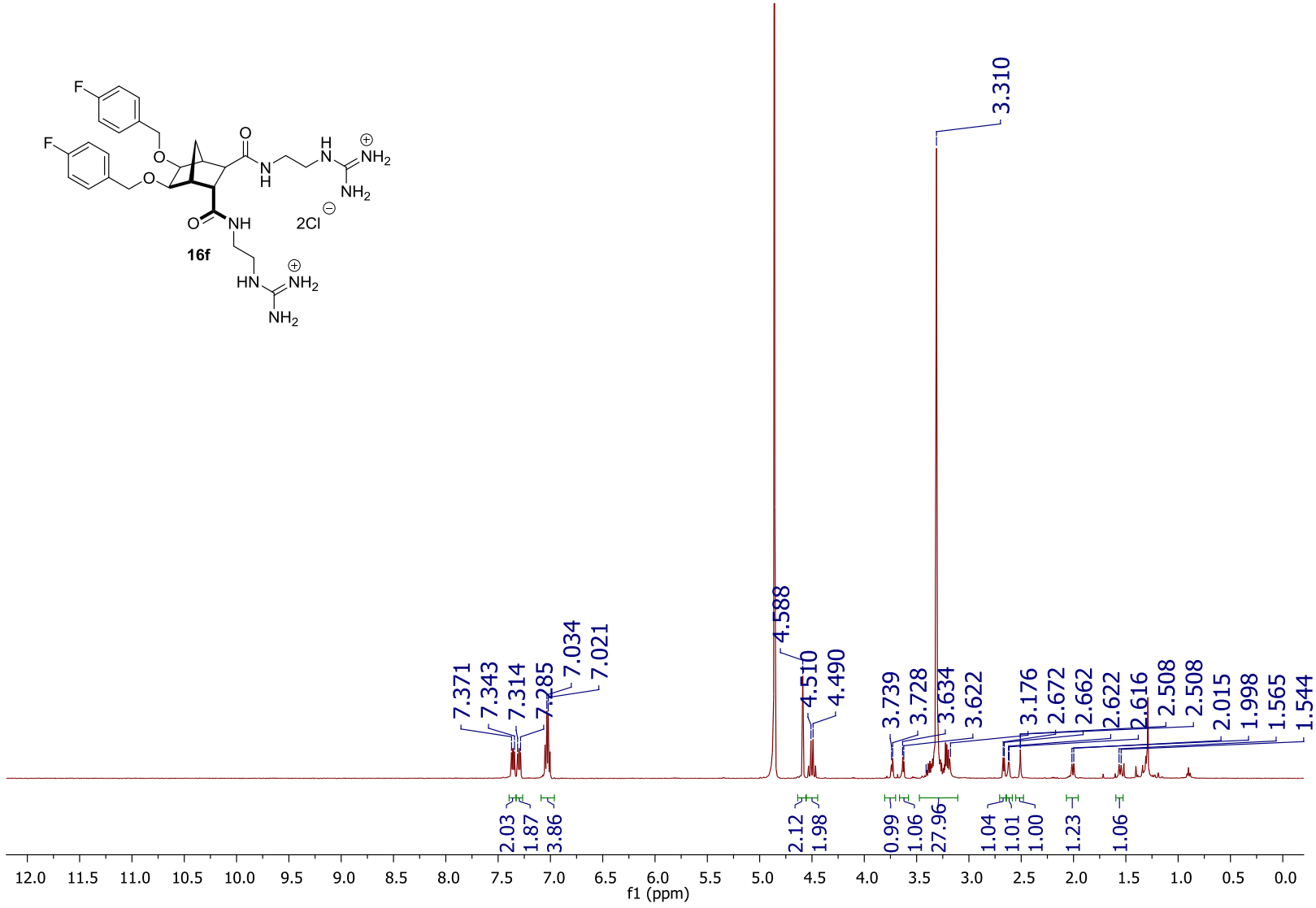
-105
-115
-125
-135
f1 (ppm)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4.490
3.739
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3.634
3.622
3.310
3.176
2.672
2.662
2.622
2.616
2.508
2.508
2.015
1.998
1.565
1.544
2.03
1.87
3.86
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1.00
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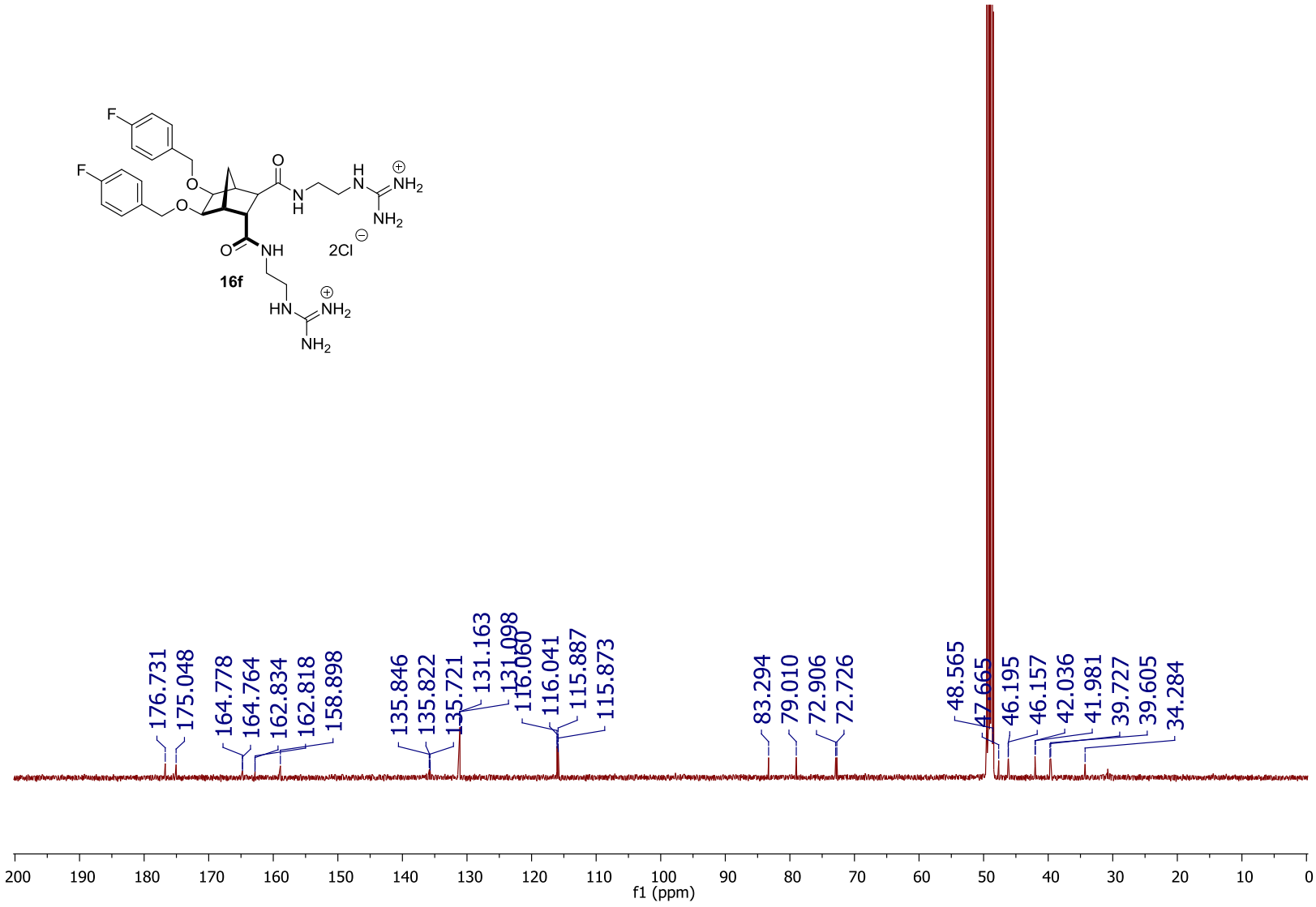
1.06
f1 (ppm)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F
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O
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H
H
N
NH2
NH2
2Cl
O
NH
16f
HN
NH2
NH2
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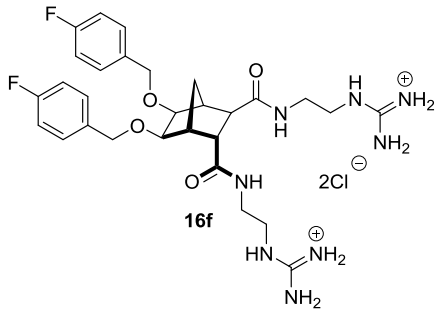
175.048
164.778
164.764
162.834
162.818
158.898
135.846
135.822
135.721
131.163
131.098
116.060
116.041
115.887
115.873
83.294
79.010
72.906
72.726
48.565
47.665
46.195
46.157
42.036
41.981
39.727
39.605
34.284
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


F
F
O
O
O
NH
2Cl
HN
NH2
NH2
NH2
NH2
16f

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-118.041
-5
-10
-15
-20
-25
-30
-35
-40
-45
-50
-55
-60
-65
-70
-75
-80
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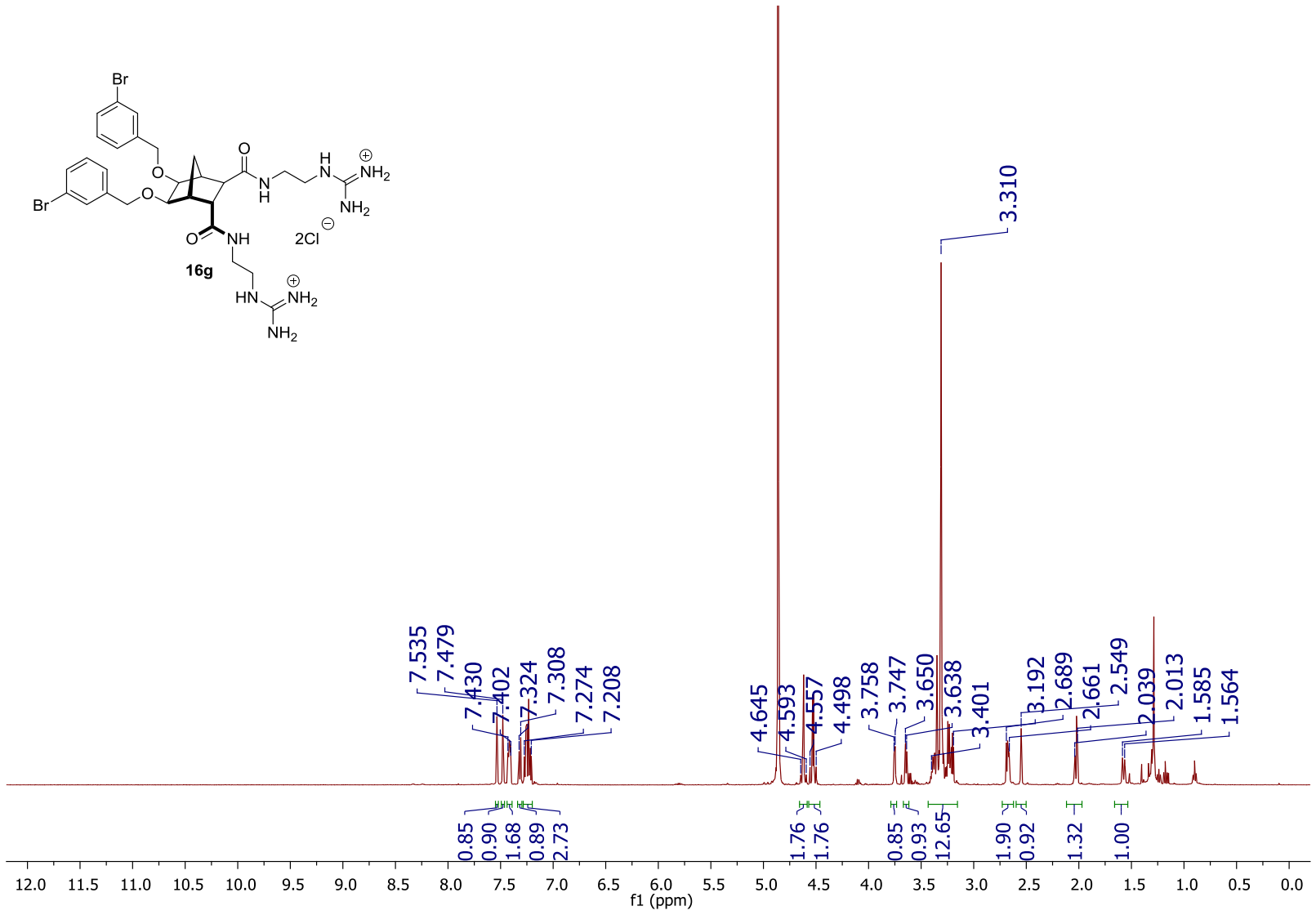
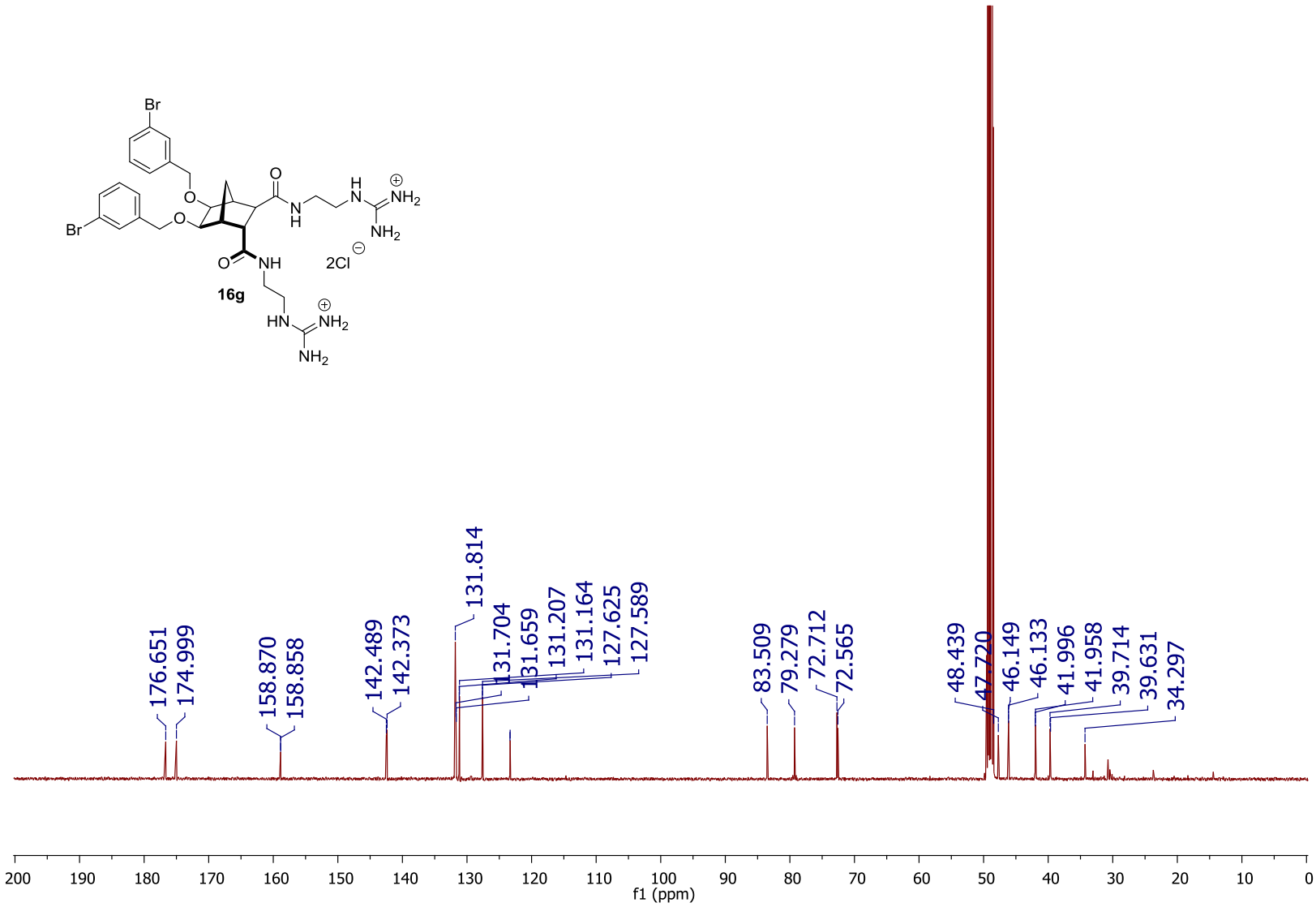
-90
-95
-105
-115
-125
-135
f1 (ppm)


Br
Br
O
O
O
N
H
H
N
NH2
NH2
2Cl
O
NH
16g
HN
NH2
NH2
3.310
7.535
7.479
7.430
7.402
7.324
7.308
7.274
7.208
4.645
4.593
4.557
4.498
3.758
3.747
3.650
3.638
3.401
3.192
2.689
2.661
2.549
2.039
2.013
1.585
1.564
0.85
0.90
1.68
0.89
2.73
1.76
1.76
0.85
0.93
12.65
1.90
0.92
1.32
1.00
12.0
11.5
11.0
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
f1 (ppm)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Br
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O
O
N
H
H
N
NH2
NH2
2Cl
O
NH
16g
HN
NH2
NH2
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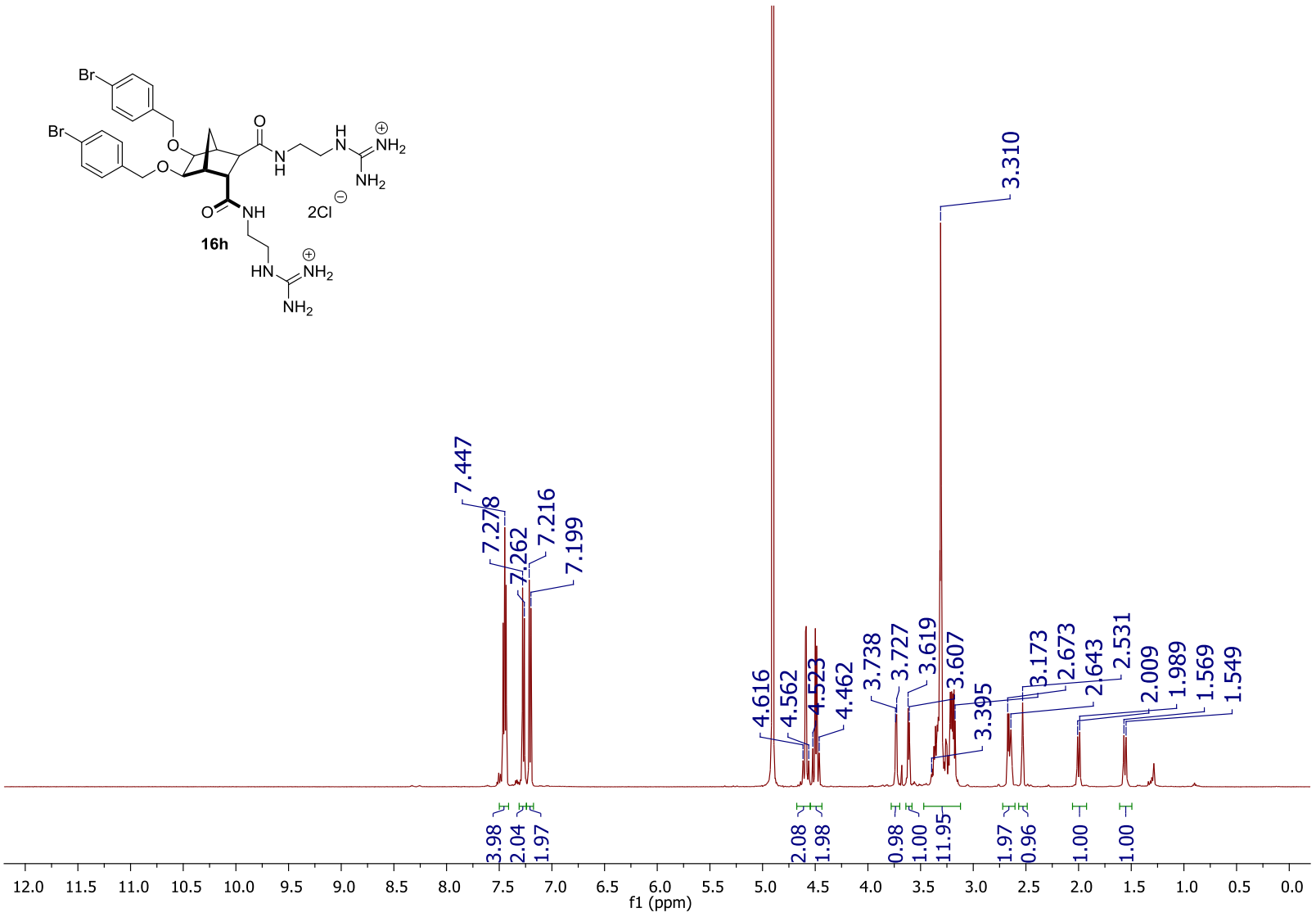
174.999
158.870
158.858
142.489
142.373
131.814
131.704
131.659
131.207
131.164
127.625
127.589
83.509
79.279
72.712
72.565
48.439
47.720
46.149
46.133
41.996
41.958
39.714
39.631
34.297
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Br
Br
O
O
O
N
H
H
N
NH2
NH2
2Cl
O
NH
16h
HN
NH2
NH2
7.447
7.278
7.262
7.216
7.199
4.616
4.562
4.523
4.462
3.738
3.727
3.619
3.607
3.395
3.310
3.173
2.673
2.643
2.531
2.009
1.989
1.569
1.549
3.98
2.04
1.97
2.08
1.98
0.98
1.00
11.95
1.97
0.96
1.00
1.00
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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4.5
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3.5
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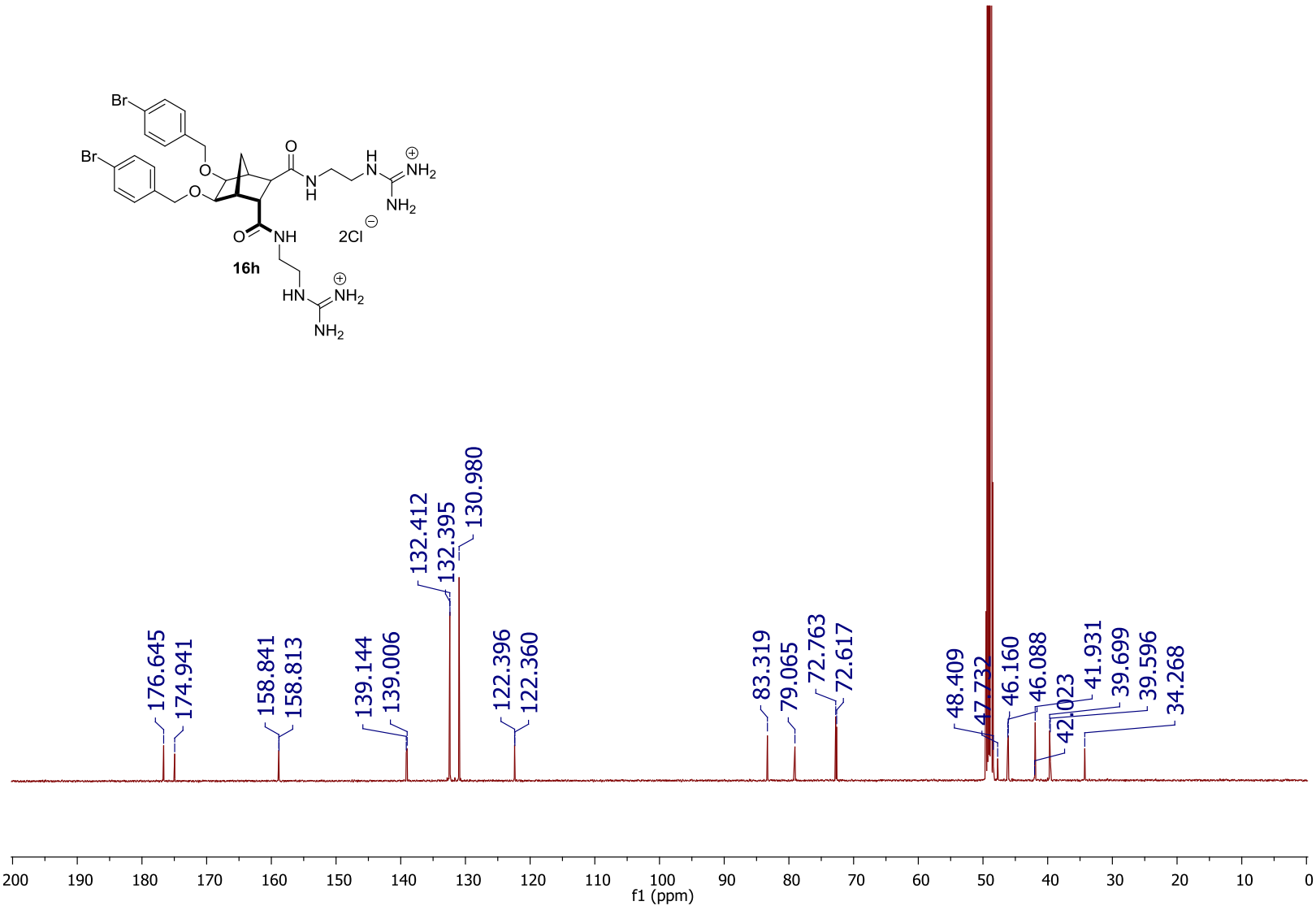
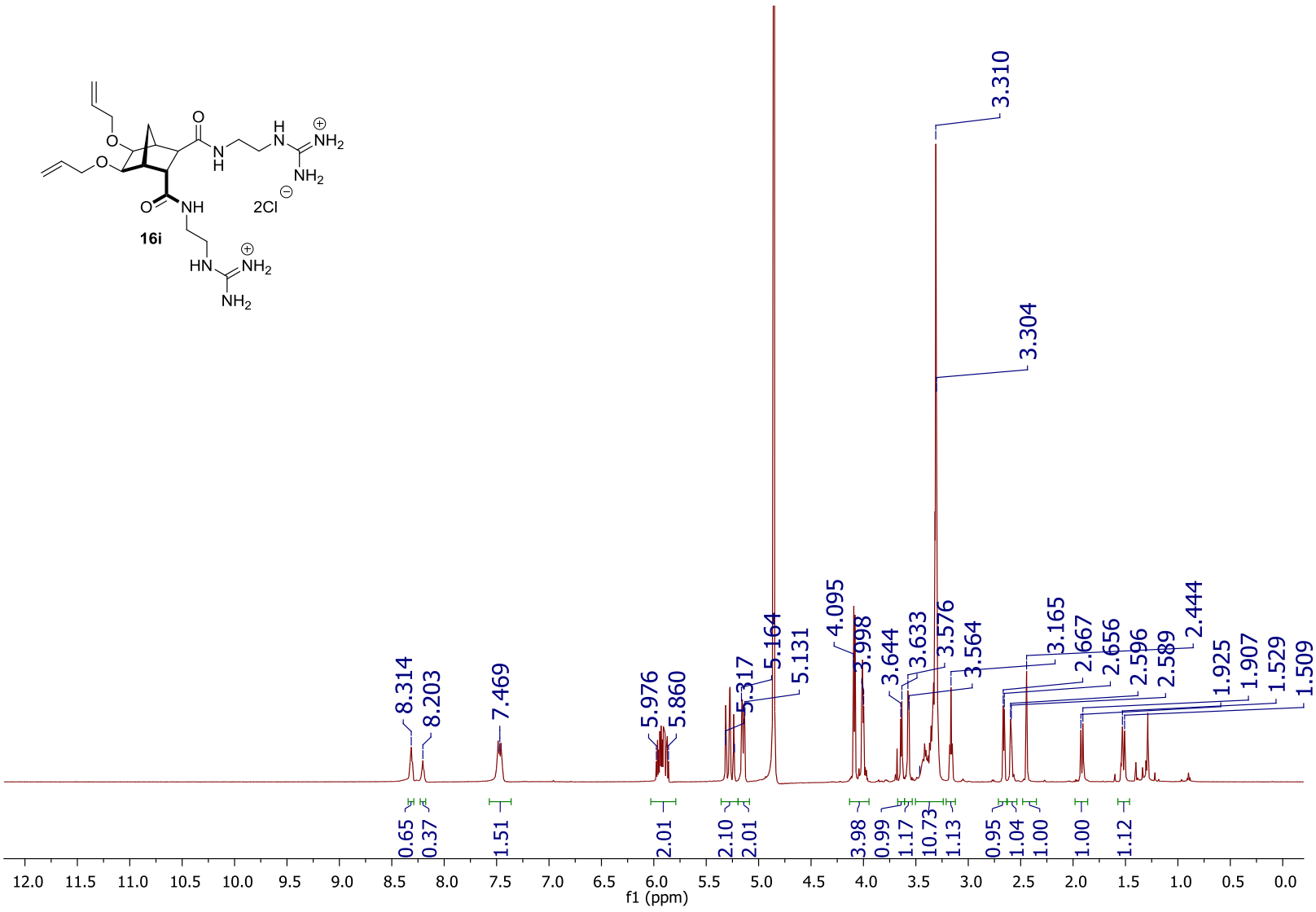
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


Br
Br
O
O
O
N
H
H
N
NH2
NH2
2Cl
O
NH
16h
HN
NH2
NH2
176.645
174.941
158.841
158.813
139.144
139.006
132.412
132.395
130.980
122.396
122.360
83.319
79.065
72.763
72.617
48.409
47.732
46.160
46.088
42.023
41.931
39.699
39.596
34.268
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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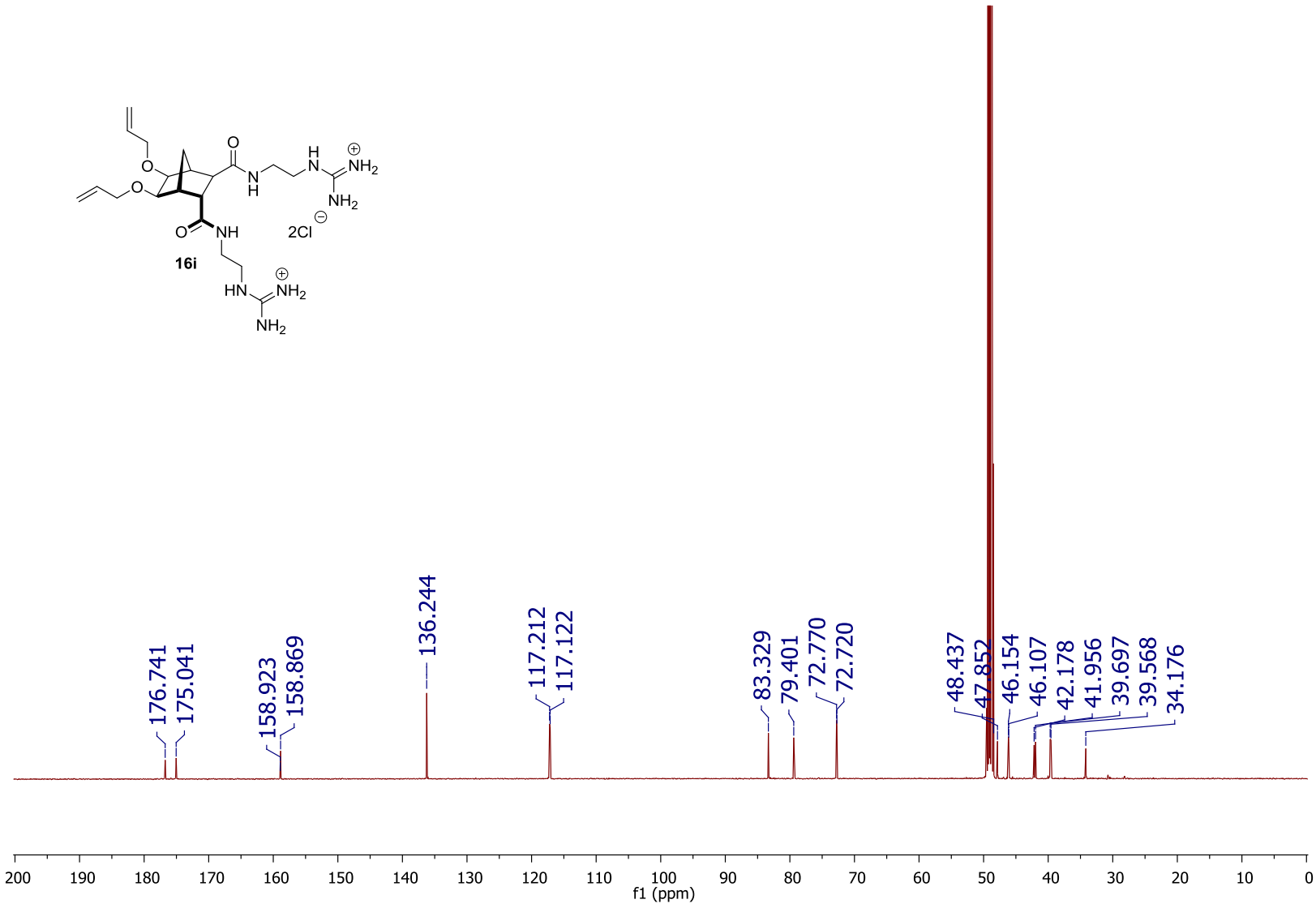
5.976
5.860
5.317
5.164
5.131
4.095
3.998
3.644
3.633
3.576
3.564
3.310
3.304
3.165
2.667
2.656
2.596
2.589
2.444
1.925
1.907
1.529
1.509
0.65
0.37
1.51
2.01
2.10
2.01
3.98
0.99
1.17
10.73
1.13
0.95
1.04
1.00
1.00
1.12
f1 (ppm)


16i
2Cl
176.741
175.041
158.923
158.869
136.244
117.212
117.122
83.329
79.401
72.770
72.720
48.437
47.852
46.154
46.107
42.178
41.956
39.697
39.568
34.176
f1 (ppm)

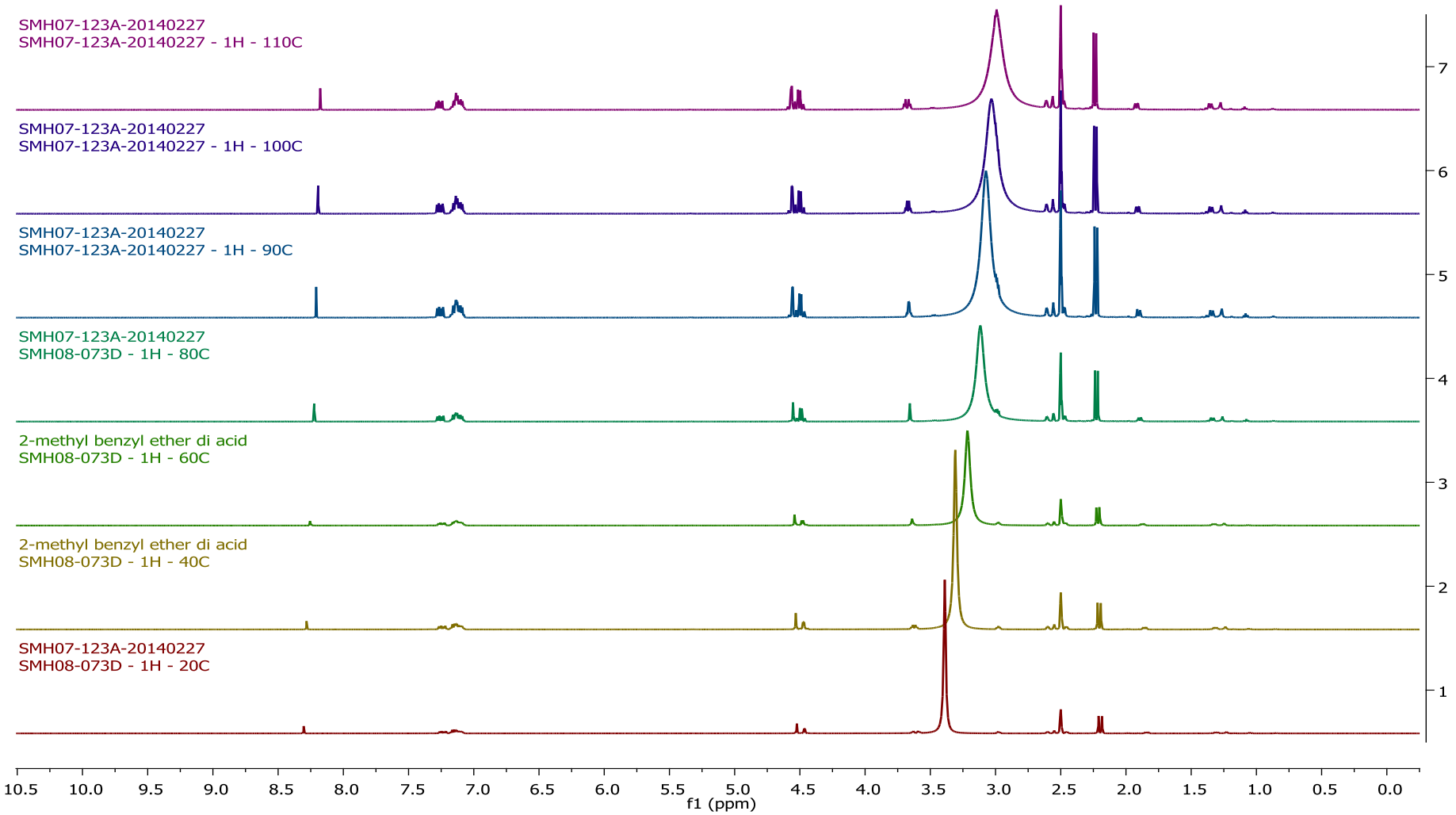


Figure S1: VT ^{1}H NMR (500 MHz) of **12c** in DMSO-d_6 (20–110 °C)

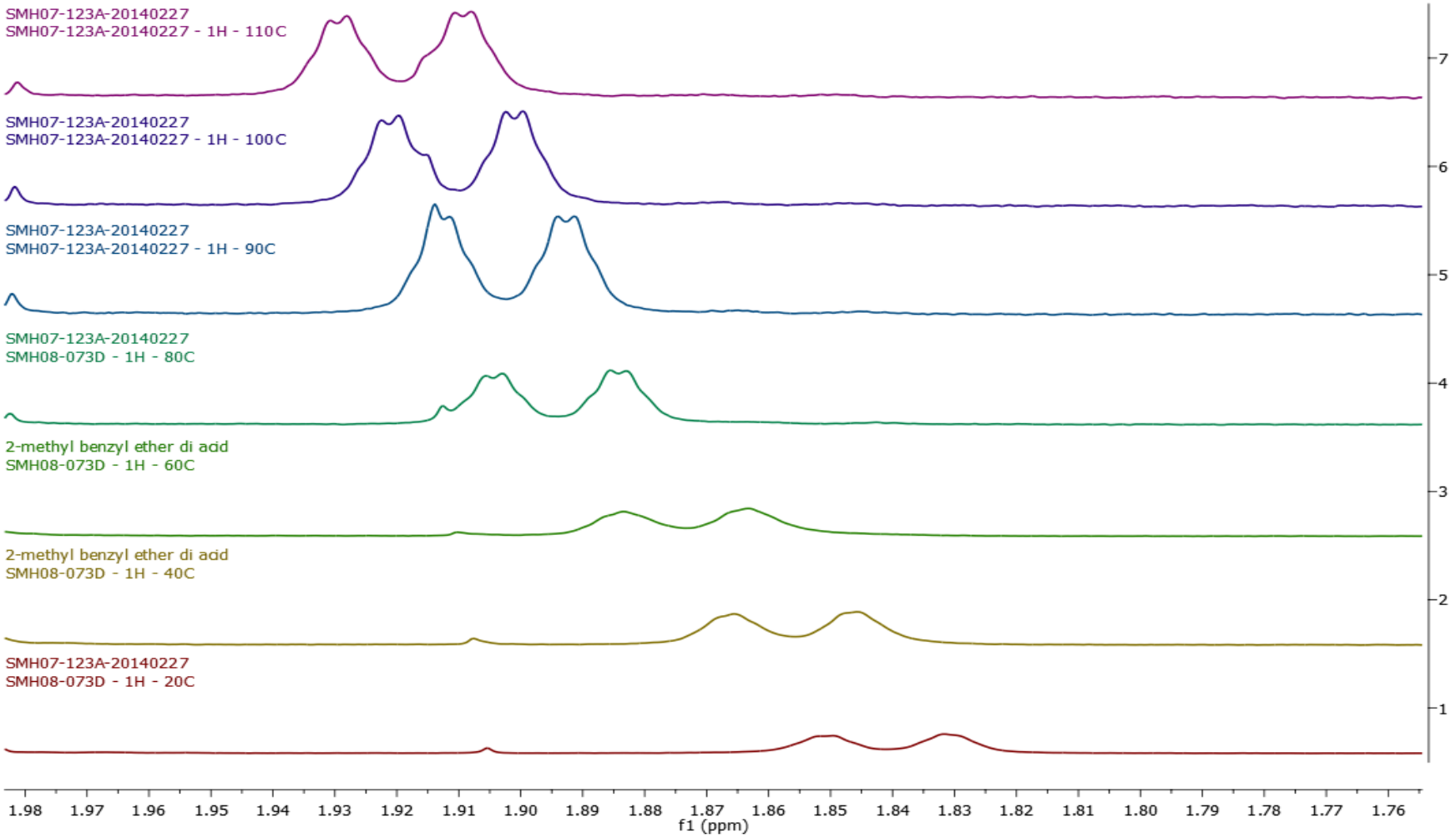


Figure S2: Expansion (1.76–1.98 ppm) of VT ^{1}H NMR (500 MHz) of **12c** in DMSO-d_6 (20–110 °C)

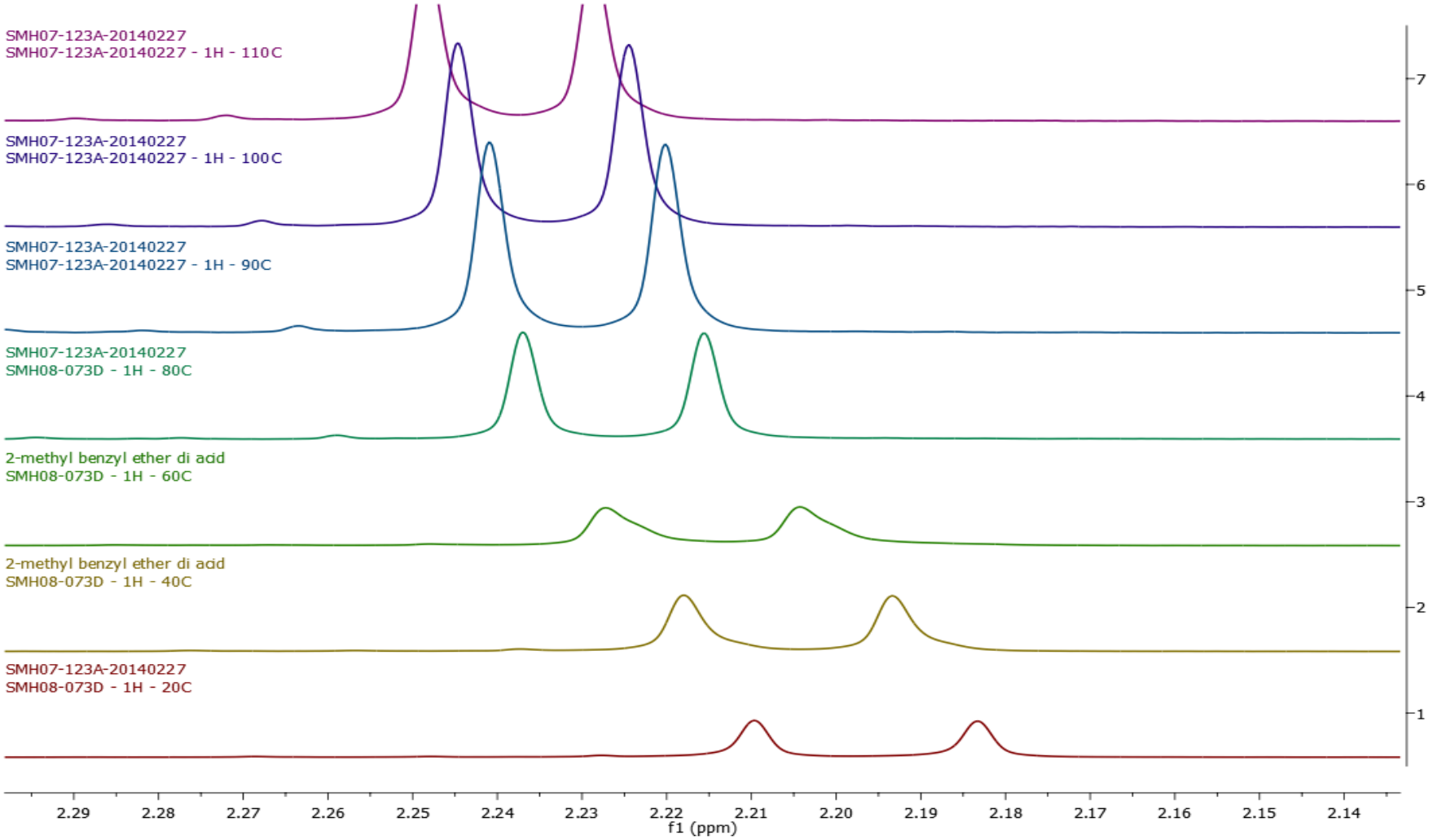


Figure S3: Expansion (2.14–2.29 ppm) of VT ^{1}H NMR (500 MHz) of **12c** in DMSO-d_6 (20–110 °C)

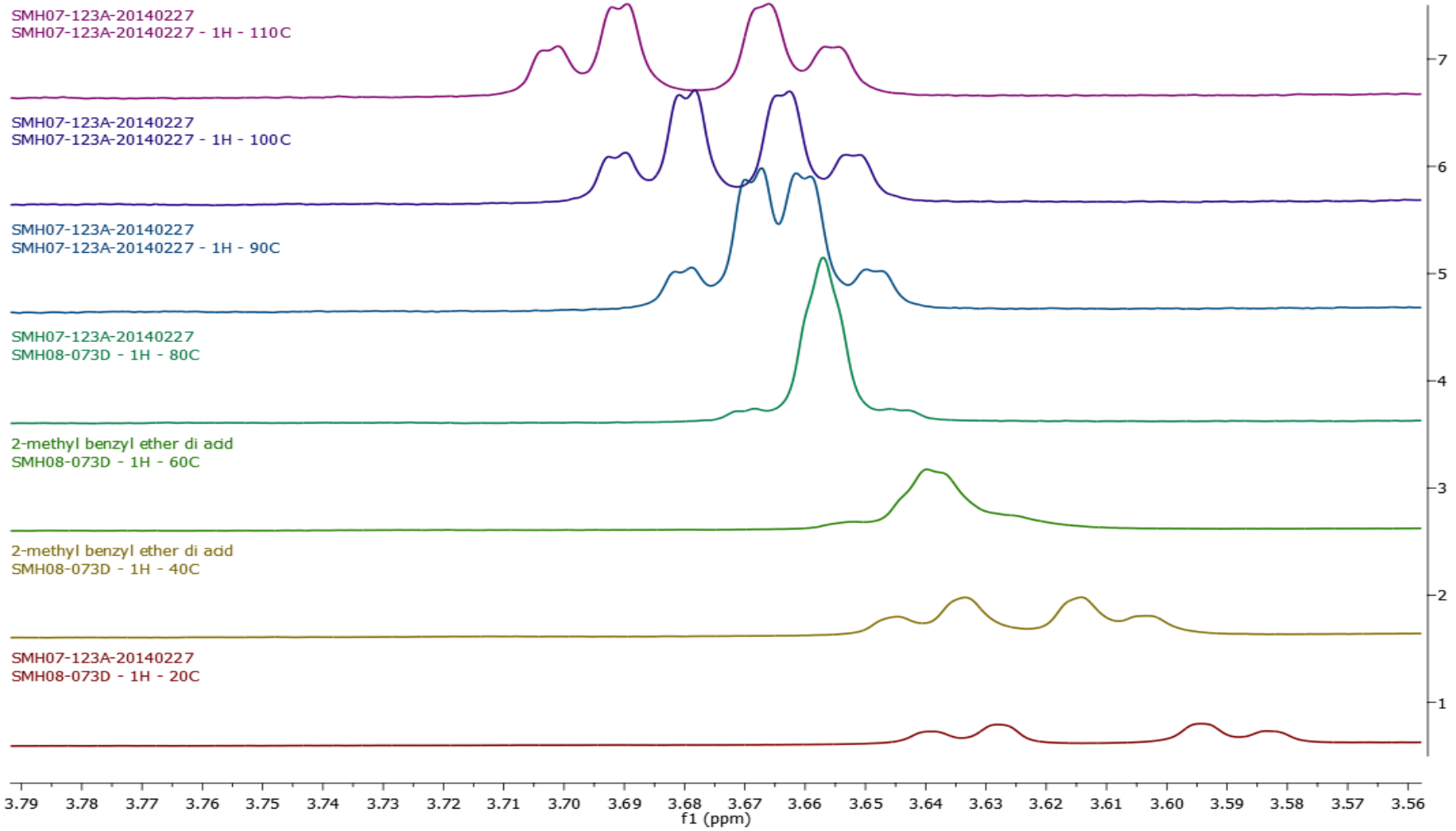


Figure S4: Expansion (3.56–3.79 ppm) of VT ^{1}H NMR (500 MHz) of **12c** in DMSO-d_6 (20–110 °C)

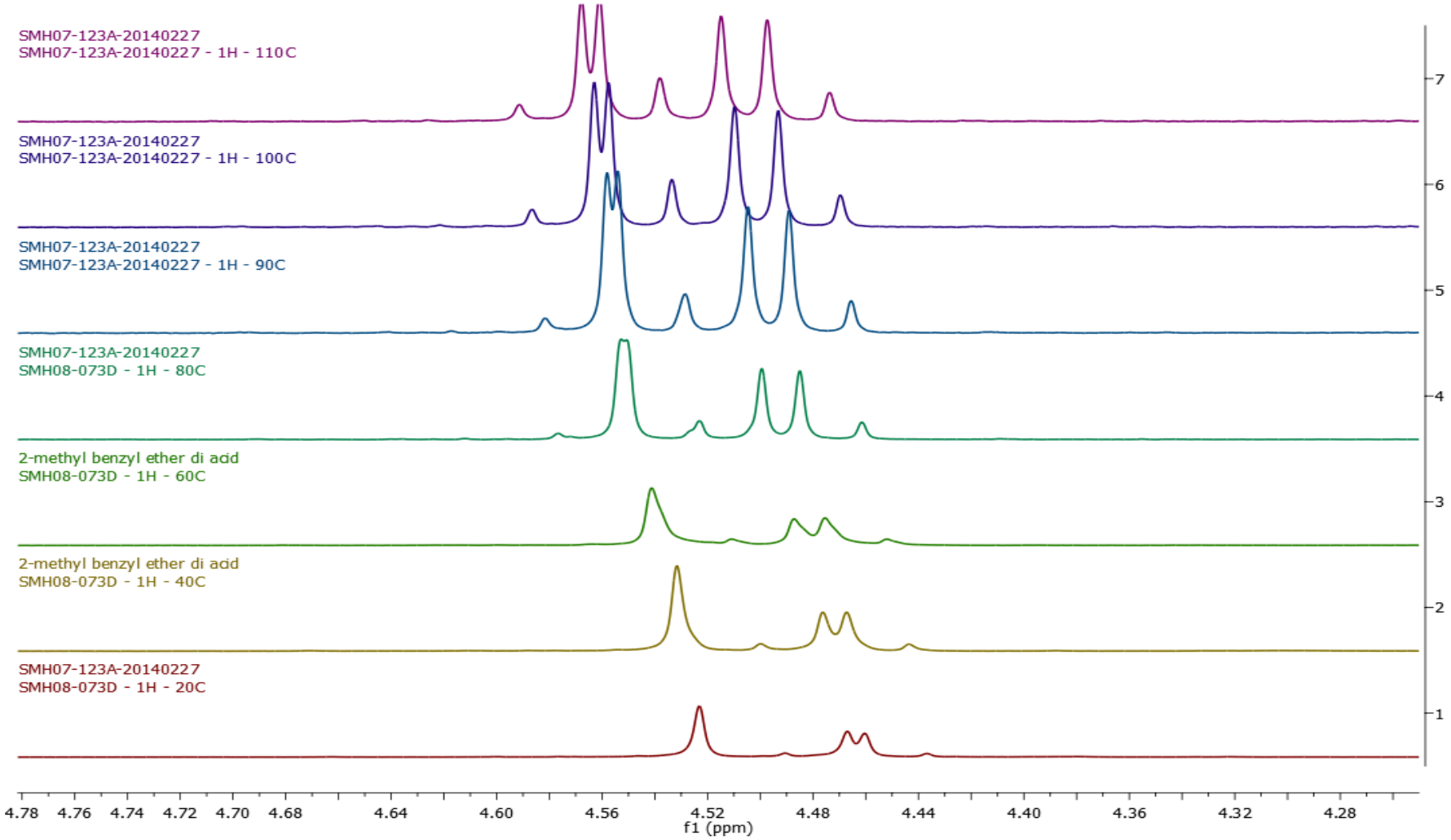
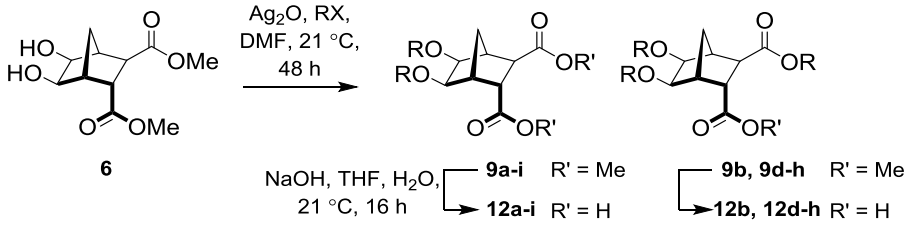
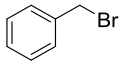
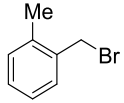
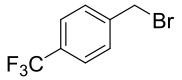
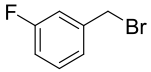
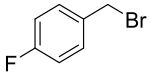
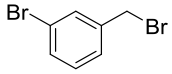
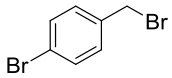
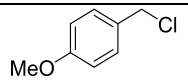
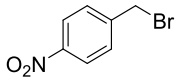
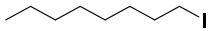


Figure S5: Expansion (4.26–4.78 ppm) of VT ^{1}H NMR (500 MHz) of **12c** in DMSO-d_6 (20–110 °C)

Table S1: Ester by-products of bis-alkylation step



Entry	Alkylating Agent (RX)	Product	Yield (%)[a]
1	MeI	**12a**	48
2		**12b**	37 (7)
3		**12c**	17
4		**12d**	51 (6)
5		**12e**	55 (12)
6		**12f**	25 (9)
7		**12g**	24 (8)
8		**12h**	28 (12)

9			NR
10			NR
12			NR
13		**12i**	25

[a] Yield calculated over two steps.

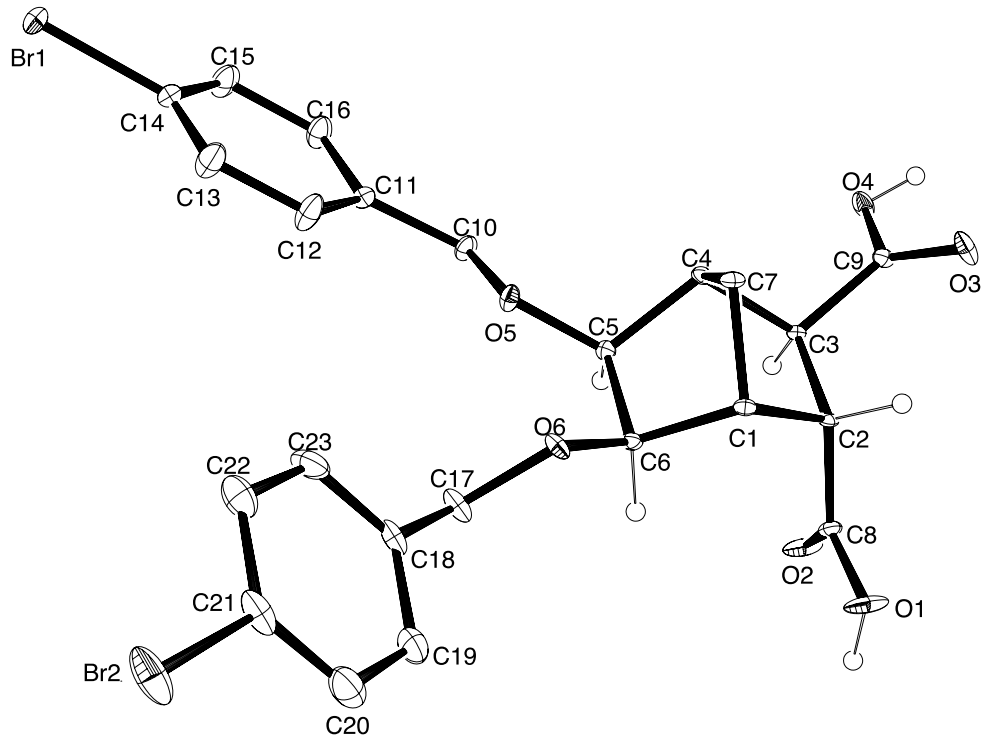


Figure S6. Thermal ellipsoid plot of one of the two independent molecules of **12h**. Ellipsoids are at the 20% probability level.

Crystal data for **12h**. 2($C_{23}H_{22}Br_2O_6$). (CH_3CH_2OH), M = 1138.52, T = 130.0 K, λ= 1.54180, 554.22, space group P c, a = 13.3929(1) b = 5.4658(1), c =33.5433(4) *Å*, β= 97.438(1)° V 2434.81(6) $Å^3$, Z = 4, Z' = 2, D_c = 1.512 Mg M^{-3} μ(Cu-Kα) 4.519 mm^{-1}, F(000) =1112, crystal size 0.54 x 0.49 x 0.38 mm^3, 16695 reflections measured, 8602 independent reflections [R(int) = 0.0230], the final R was 0.0431 [I > 2σ(I)8569 data] and *w*R(F^2) was 0.1162 (all data), Absolute structure parameter 0.15(2) .

Table S2: Bacterial strains used for Minimum Inhibitory Concentration (MIC) and disk diffusion (DD) assay

Organism	Strain	Strain description	Assay
Escherichia coli	ATCC 25922	FDA strain Seattle 1946	MIC
Klebsiella pneumoniae	ATCC 13883	Control strain	DD
Klebsiella pneumoniae	ATCC 700603	Multi-drug resistant	MIC
Acinetobacter baumannii	ATCC 19606	Type strain	MIC/DD
Pseudomonas aeruginosa	ATCC 27853	Type strain	MIC/DD
Staphylococcus aureus	ATCC 43300	MRSA (methicillin resistant *S. aureus*)	MIC/DD
Enterococcus faecium	ATCC 700221	VRE (vancomycin resistant Enterococcus)	DD
Staphylococcus aureus	Clinical isolate	mMRSA (multi-resistant methicillin resistant *S. aureus)*	MIC
Staphylococcus aureus	NARSA-NRS 17	GISA (glycopeptide-intermediate *S. aureus*)	MIC
Staphylococcus aureus	NARSA-NRS 1	VISA (vancomycin-intermediate *S. aureus*)	MIC
Staphylococcus aureus	Clinical isolate	MRSA	MIC
Staphylococcus aureus	NARSA-VRS 10	Glycopeptide resistant Staphylococci	MIC
Streptococcus pneumoniae	ATCC 700677	Multi-drug resistant	MIC
Enterococcus faecalis	Clinical isolate	VanA (vancomycin resistant)	MIC

References

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