Supporting Information

Synthesis of fluorinated carbocyclic pyrimidine nucleoside analogues

Caecilie M. M. Benckendorff,[a,b] Valentyna D. Slyusarchuk,[b] Ningwu Huang,[c] Marcelo A. Lima,[a] Mark Smith[c] and Gavin J. Miller [a,b,*]

[a]Centre for Glycosciences, Keele University, Keele, Staffordshire, ST5 5BG, UK
[b]Lennard-Jones Laboratory, School of Chemical and Physical Sciences, Keele University, Keele, Staffordshire, ST5 5BG, UK
[c]Riboscience LLC, 428 Oakmead Pkwy, Sunnyvale, CA 94085, USA
[*]g.j.miller@keele.ac.uk

Table of contents:

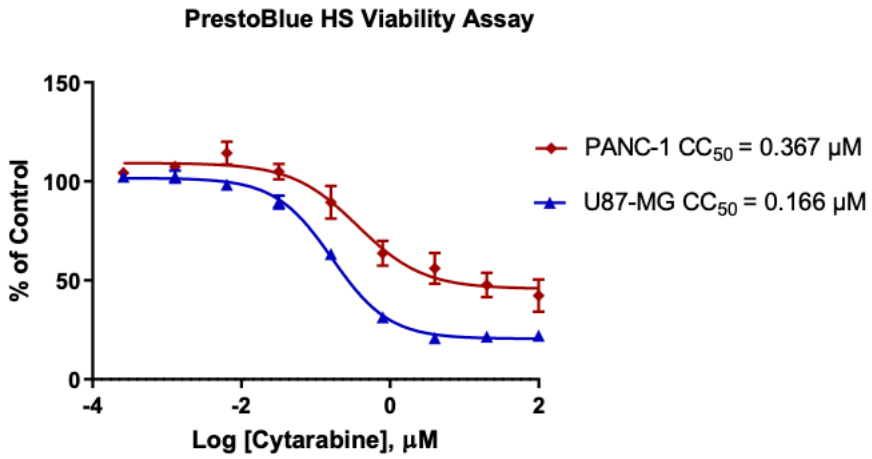
S1. Cytotoxicity assays

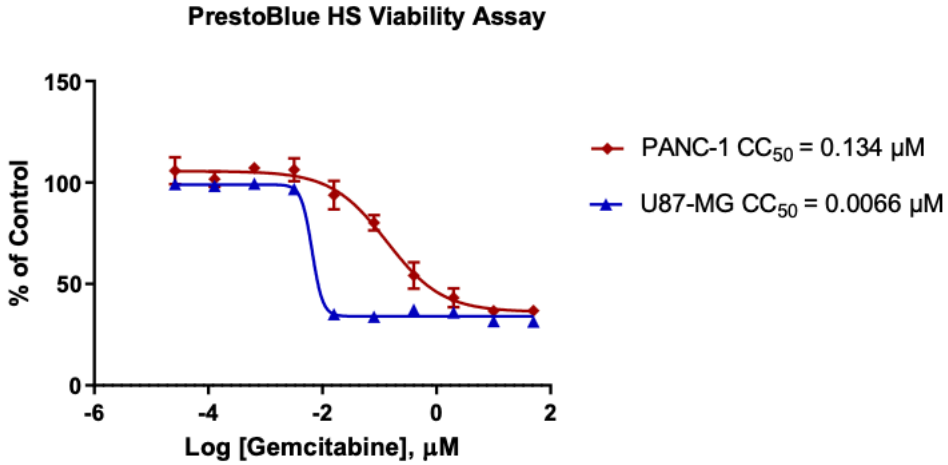
S1.1. PrestoBlue™ HS & CyQUANT™ XTT assays

Testing compound stock solution, 20 mM in DMSO: 20 mM DMSO stock solutions were diluted for 20-fold in EMEM medium, followed by 1:10x dilution in EMEM with 5% DMSO, add 11.1 µL of the 10-fold diluted compounds into the cells with 100 µL medium, final DMSO concentration in each well is 0.5%. The cells treated with medium with 0.5% DMSO served as DMSO control. The final compound concentrations were 100 µM and 10 µM, respective, in duplicate. Reference compound Gemcitabine stock was 1 mM in H_2O. Gemcitabine top concentration for both PANC-1 and U87-MG was 10 µM, followed by 8 points of 5-fold serial dilutions in EMEM medium. The tenth point contained no compounds, only medium served as DMSO control. In addition, a single point of 50 µM Gemcitabine, in quadruplet, for both PANC-1 and U87-MG, was tested in the plate treated with compounds. Reference compound Cytarabine stock was 2 mM in DMSO. The top concentration for both PANC-1 and U87-MG was 100 µM, followed by 8 points of 3-fold serial dilutions in EMEM medium with 0.5% DMSO. The tenth point contained no compounds, only medium with 0.5% DMSO served as DMSO control.

The cells were seeded in a density of 3000 cells/well/100 µL for both PANC-1 cells and U87-MG cells on 96-well black plates with clear bottom and clear plates, respectively, and incubated at 37 °C with 5% CO_2 for 24 h. On day two, 10 µL of the serial diluted compounds were added onto the plate with cells in duplicate. The top concentration of the testing compound was 100 µM, and 10 µM, respectively, in duplicate. The final DMSO concentration in the assay for all wells was 0.5%. The top concentrations of references were indicated above #8. Incubate the cells with the compounds for three days at 37 °C with 5% CO_2. After the cells were treated with compounds for 72h, cell viabilities were determined using PrestoBlue™ HS Cell Viability Reagent (Invitrogen, catalog# P50200). Briefly, 10 µL of PrestoBlue™ HS Cell Viability Reagent was added to cells in the 96-well black plates with clear bottom and was incubated at 37 °C for 10 minutes. The fluorescence signal, which was positively correlated with viable cell counts, was measured with Fluorescence excitation/emission maxima: 560/590 nm on an EnSpire plate reader. The fluorescence signals from 4 wells containing only medium were used as background which was subtracted from all other testing wells. The wells treated with only 0.5% DMSO or medium only (for Gemcitabine) were DMSO or medium control, were set as 100% of cell viability. All the wells with treated cells will be as % of the Control.

S1.2 Control viability assays





S1.3 Biological data

% of Control, Viability Assay												
ID	PrestoBlue HS		CyQUANT XTT		CellTiter-Glo		PrestoBlue HS		CyQUANT XTT		CellTiter-Glo	
	U87-MG						PANC-1					
	100 µM	10 µM	100 µM	10 µM	100 µM	11.1 µM	100 µM	10 µM	100 µM	10 µM	100 µM	11.1 µM
22	102.3	103.6	110.8	108.7	97.7	115.8	107.1	108.6	109.4	106.2	99.5	74.1
23	105.7	104.3	113.9	113.5	127.7	96.1	110.5	110.9	106.7	107.9	96.7	117.6
26	42.4	62.8	67.0	82.9	67.2	76.9	69.5	101.8	75.0	106.5	89.9	93.7
27	93.3	96.3	104.1	105.2	87.1	87.1	110.9	103.6	103.1	100.2	97.8	91.4
32	101.7	102.3	110.3	112.7	95.8	104.9	116.3	109.5	109.1	108.3	106.9	113.7
33	102.3	102.1	103.2	104.5	121.6	110.9	103.8	109.3	104.5	104.4	117.6	96.2
34	98.6	101.5	112.4	103.4	102.9	101.1	89.3	102.5	102.2	101.8	127.9	127.4
35	101.2	101.5	102.9	105.0	96.8	96.3	101.6	101.1	103.5	105.2	122.8	124.0
39	108.4	100.5	117.0	109.9	82.2	91.0	110.2	108.4	108.6	109.4	112.9	82.3
40	100.3	98.7	114.6	109.2	83.7	85.7	111.5	103.4	108.0	106.7	111.1	87.9

S2. X-Ray Crystallography Data

Crystal and refinement parameters are given in Table 1. All data were collected on a Bruker D8 Quest ECO diffractometer using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) and a Photon II-C14 CPAD detector. Crystals were mounted on Mitegen micromounts in NVH immersion oil, and all collections were carried out at 150 K using an Oxford cryostream. Data collections were carried out using φ and ω scans, with collections and data reductions carried out in the Bruker APEX-3 suite of programs.[1] Multi-scan absorption corrections were applied for all datasets using SADABS.[2] The data were solved with the intrinsic phasing routine in SHELXT,[3] and all data were refined on F^2 with full-matrix least squares procedures in SHELXL,[4] operating within the OLEX-2 GUI.[5] All non-hydrogen atoms were refined with anisotropic displacement parameters. Carbon-bound hydrogen atoms were placed in riding positions and refined with isotropic displacement parameters equal to 1.2 or 1.5 times the isotropic equivalent of their carrier atom. Absolute configurations in each case were assigned based on the known configurations of carbons C2 and C3. CCDC 2193041 – 2193043.

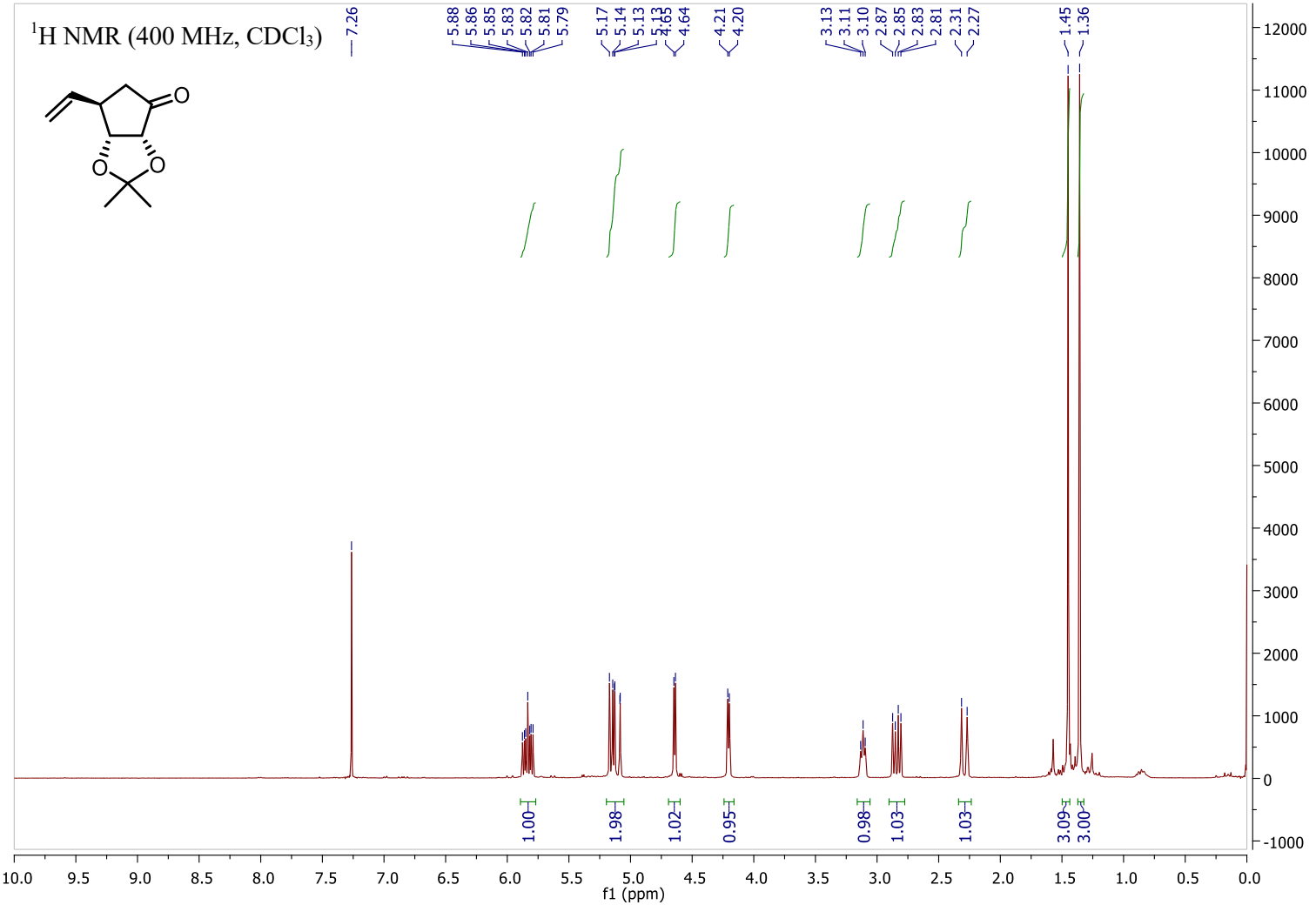
Table 1: Crystal data and structure refinement for Compounds 8, 11 and 16 (left to right)

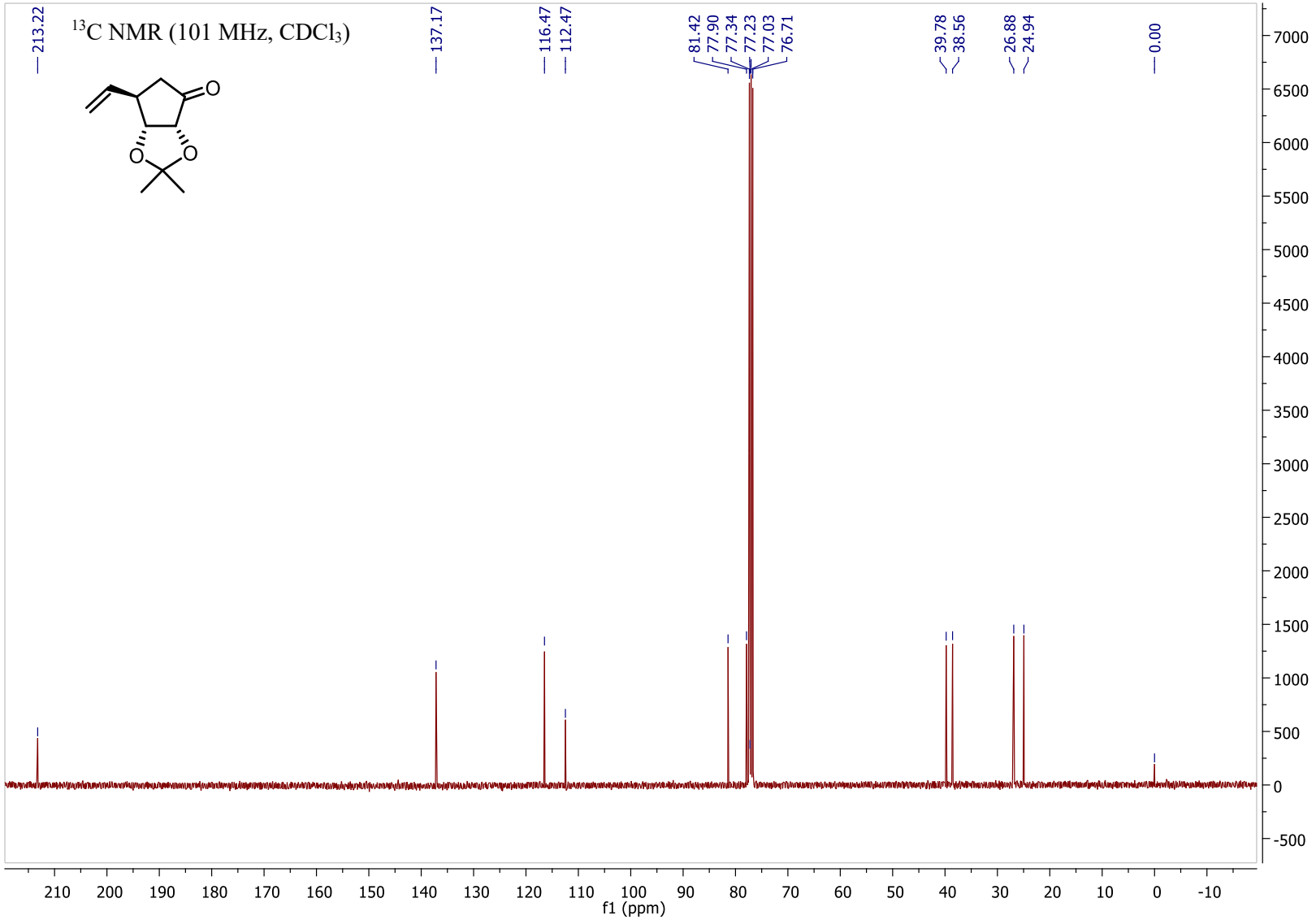
Identification code	Compound **8**	Compound **11**	Compound **16**
Empirical formula	$C_{10}H_{15}FO_3$	$C_{10}H_{15}FO_3$	$C_9H_{14}F_2O_4$
Formula weight	202.22	202.22	224.2
Temperature/K	150	150	150
Crystal system	trigonal	monoclinic	trigonal
Space group	$P3_2$	$P2_1$	$P3_2$
a/Å	11.884(3)	7.6334(3)	12.3659(5)
b/Å	11.884(3)	5.7702(2)	12.3659(5)
c/Å	6.298(2)	11.1406(5)	5.8839(4)
α/°	90	90	90
β/°	90	100.4260(10)	90
γ/°	120	90	120
Volume/Å^3	770.2(4)	482.60(3)	779.20(8)
Z	3	2	3
ρ_{calc}g/cm^3	1.308	1.392	1.433
μ/mm^{-1}	0.106	0.113	0.133
F(000)	324	216	354
Crystal size/mm^3	0.15 × 0.14 × 0.09	0.17 × 0.08 × 0.07	0.32 × 0.2 × 0.09
Radiation	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)
2Θ range for data collection/°	6.858 to 61.044	5.998 to 61.1	6.59 to 54.952
Index ranges	$-16 \le h \le 15$, $-16 \le k \le 16$, $-9 \le l \le 9$	$-10 \le h \le 10$, $-8 \le k \le 8$, $-15 \le l \le 15$	$-16 \le h \le 16$, $-16 \le k \le 15$, $-7 \le l \le 7$
Reflections collected	15475	15047	9224
Independent reflections	3119 [R_{int} = 0.0724, R_{sigma} = 0.0742]	2937 [R_{int} = 0.0424, R_{sigma} = 0.0376]	2375 [R_{int} = 0.0334, R_{sigma} = 0.0301]
Data/restraints/parameters	3119/2/132	2937/2/132	2375/3/144

Goodness-of-fit on F^2	1.053	1.054	1.042
Final R indexes [I>=2σ (I)]	R_1 = 0.0542, wR_2 = 0.0805	R_1 = 0.0394, wR_2 = 0.0832	R_1 = 0.0319, wR_2 = 0.0680
Final R indexes [all data]	R_1 = 0.0914, wR_2 = 0.0896	R_1 = 0.0487, wR_2 = 0.0871	R_1 = 0.0391, wR_2 = 0.0714
Largest diff. peak/hole / e $Å^{-3}$	0.18/-0.23	0.28/-0.20	0.14/-0.16
Flack parameter	0.0(5)	-0.1(3)	-0.2(3)
CCDC number	2193041	2193042	2193043

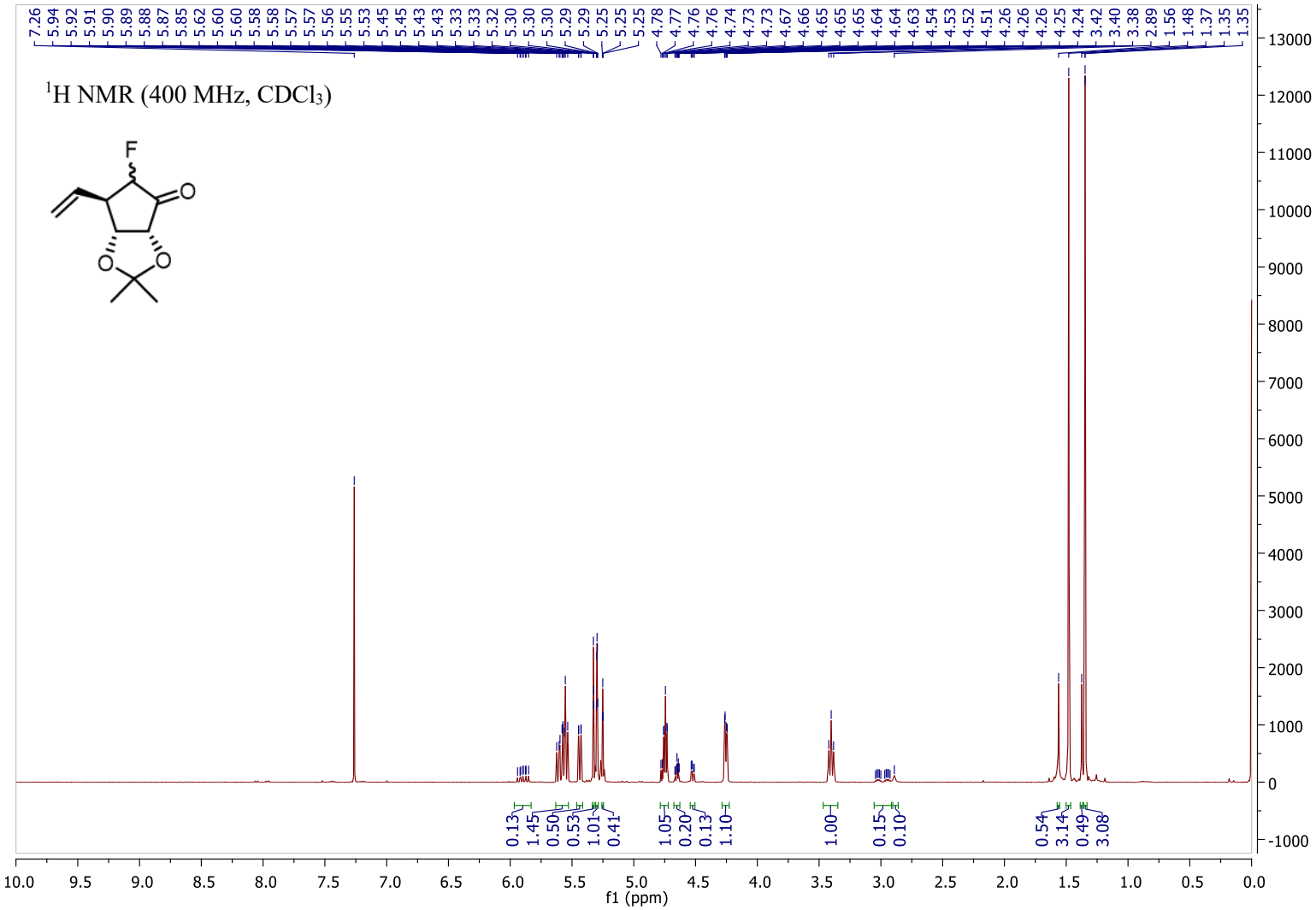
S3. NMR Spectra Compounds 2-40

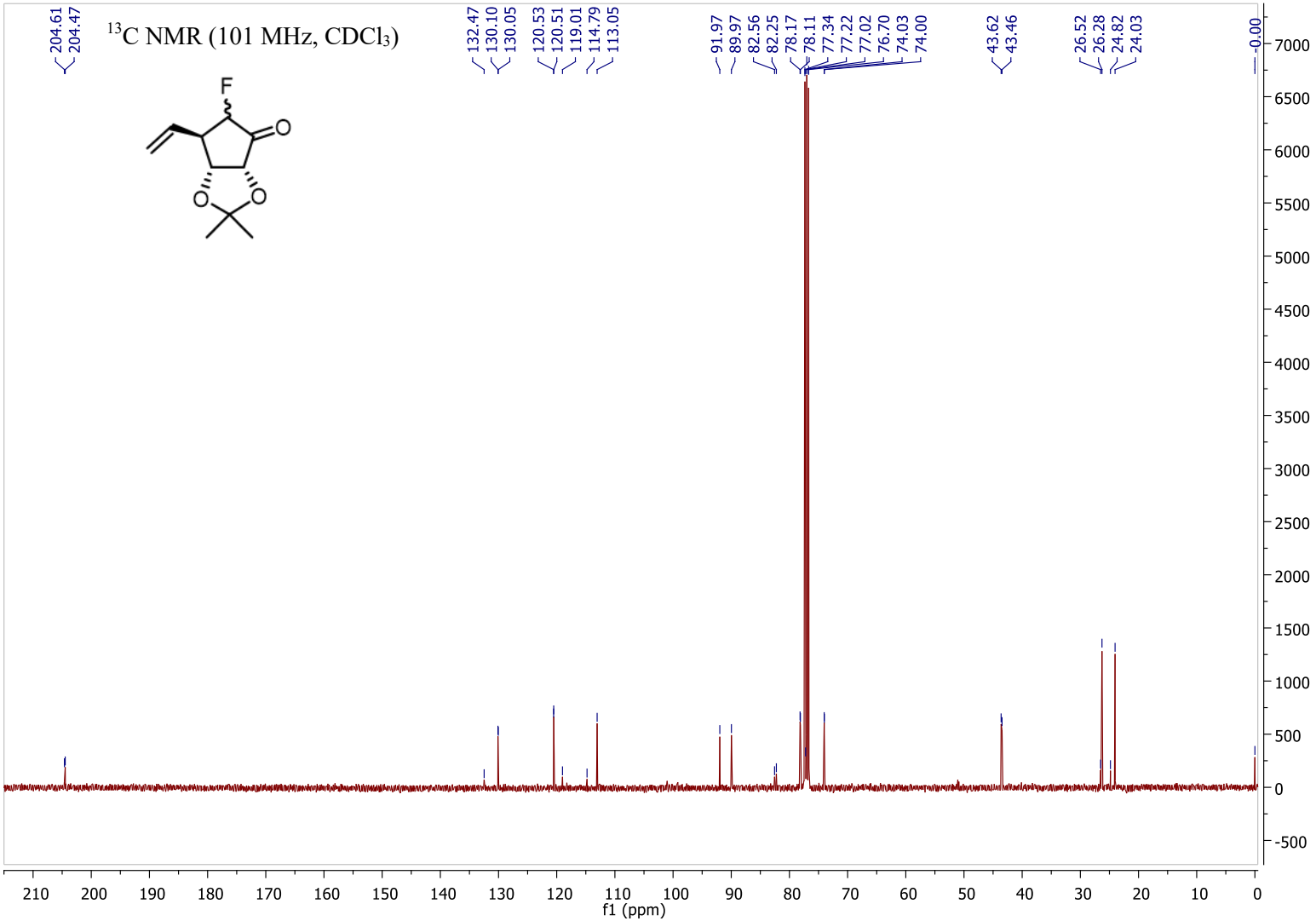
(2R,3R,4R)-2,3-*O*-isopropylidene-4-vinylcyclopentan-1-one, 2



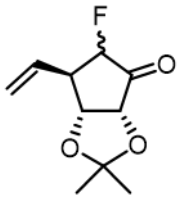

^{13}C NMR (101 MHz, $CDCl_3$)
213.22
137.17
116.47
112.47
81.42
77.90
77.34
77.23
77.03
76.71
39.78
38.56
26.88
24.94
0.00
f1 (ppm)

(2R,3R,4R)-2,3-*O*-isopropylidene-4-vinyl-7-α/β-fluorocyclopentan-1-one, 4-®/4-(*S*)

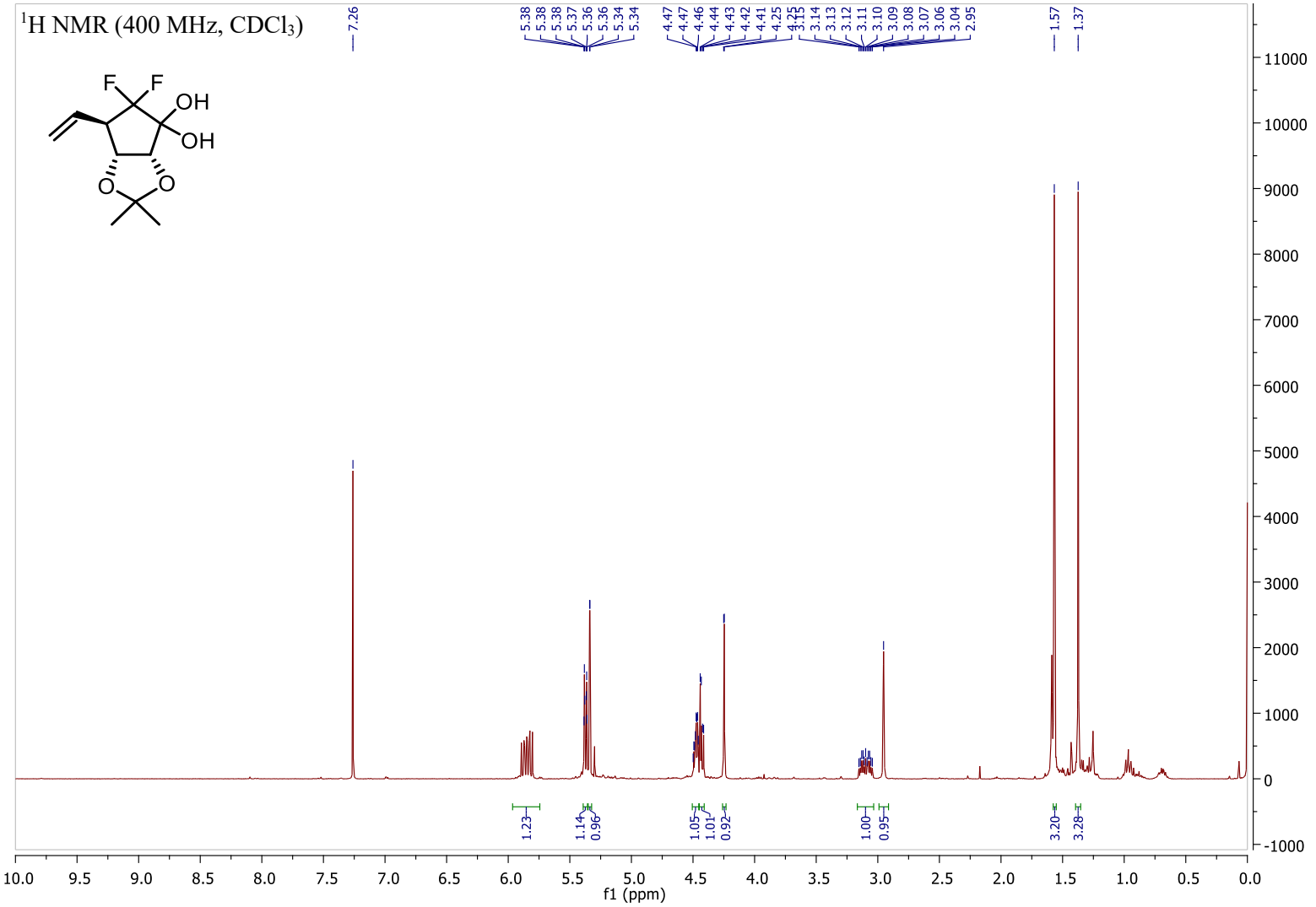


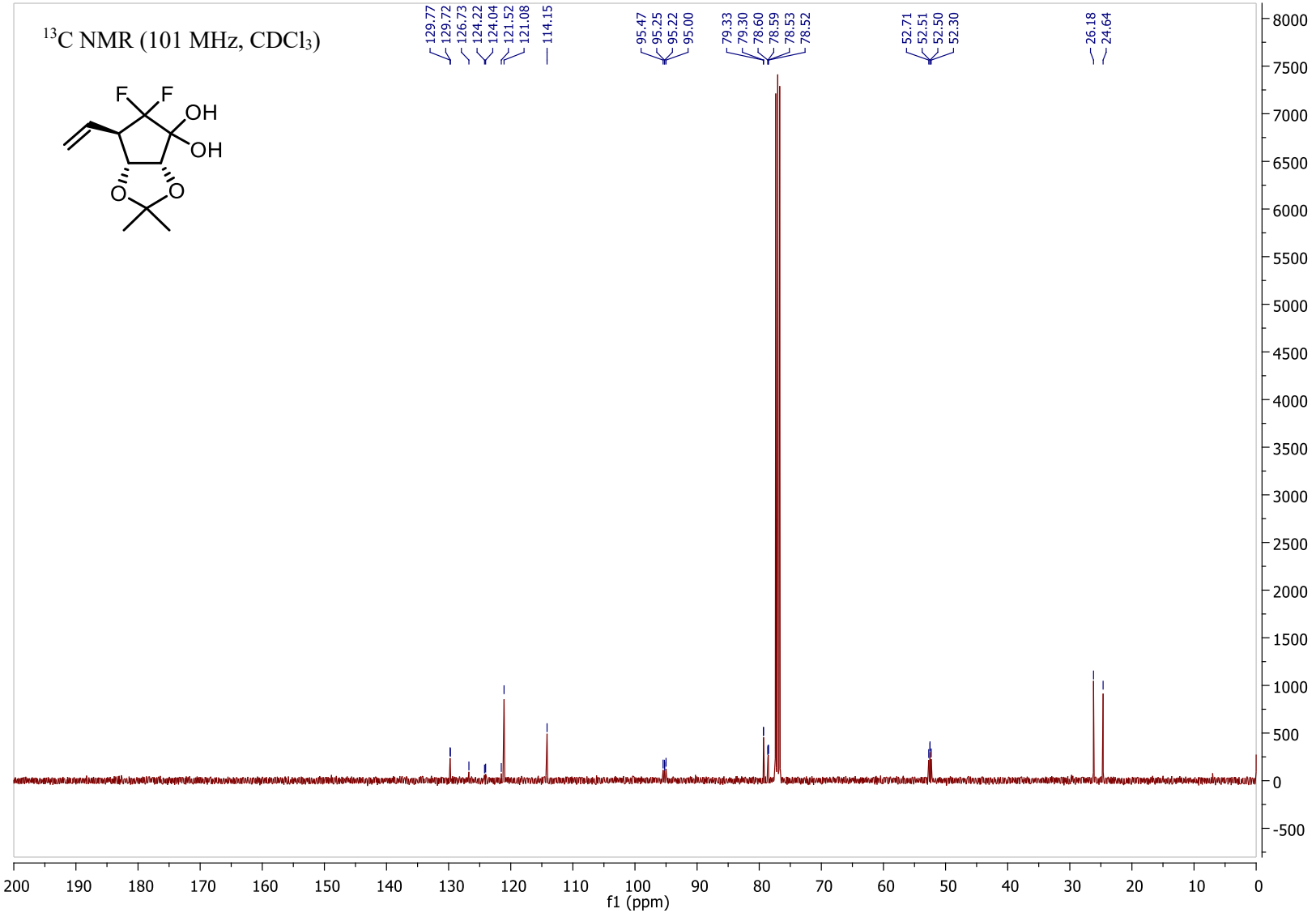

^{13}C NMR (101 MHz, $CDCl_3$)
F
O
O
O
204.61
204.47
132.47
130.10
130.05
120.53
120.51
119.01
114.79
113.05
91.97
89.97
82.56
82.25
78.17
78.11
77.34
77.22
77.02
76.70
74.03
74.00
43.62
43.46
26.52
26.28
24.82
24.03
-0.00
f1 (ppm)

^{19}F NMR (377 MHz, $CDCl_3$)

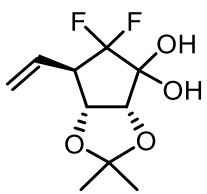


(2R,3R,4R)-2,3-*O*-isopropylidene-4-vinyl-7-*gem*-difluorocyclopentan-1-one, 7

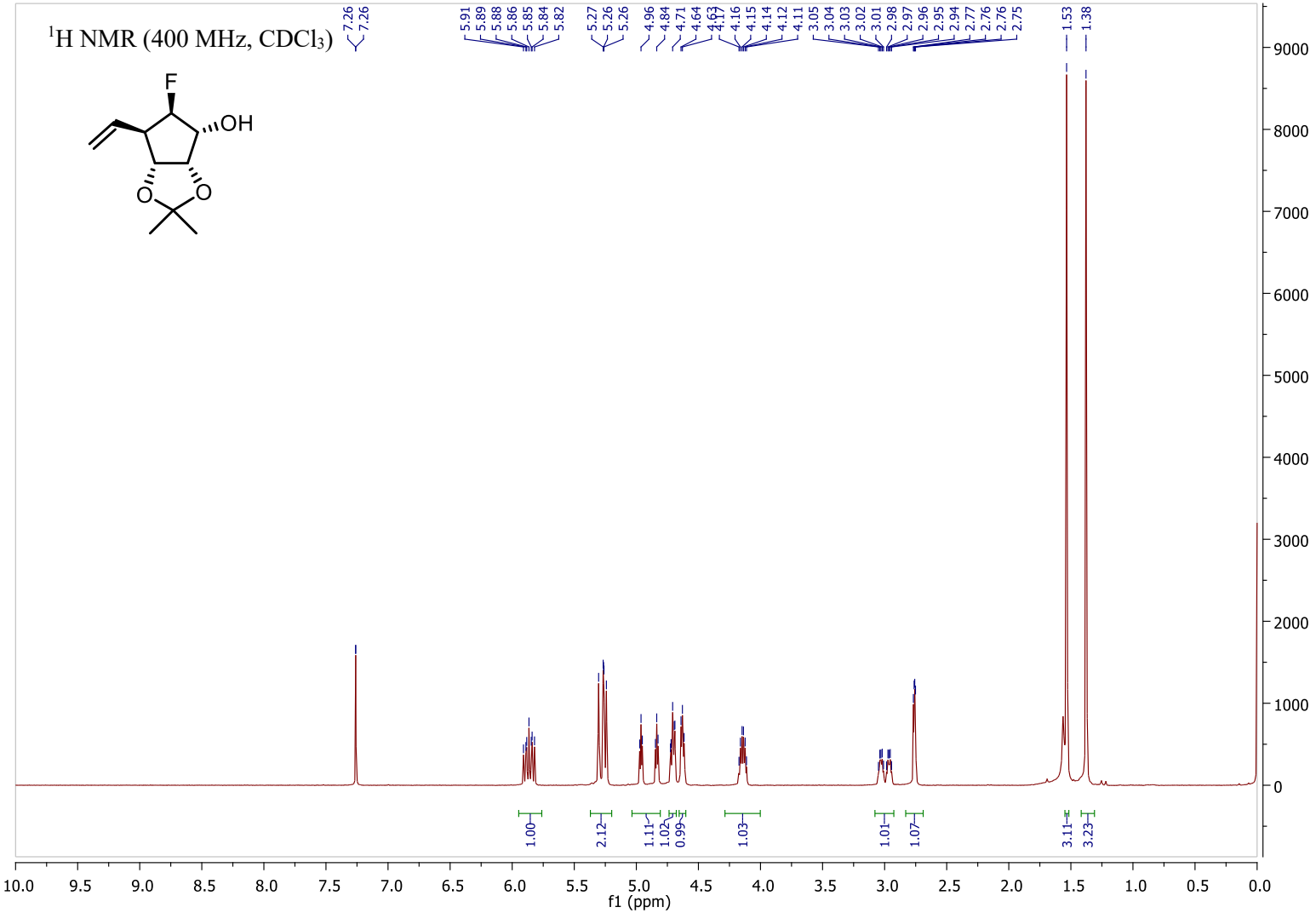


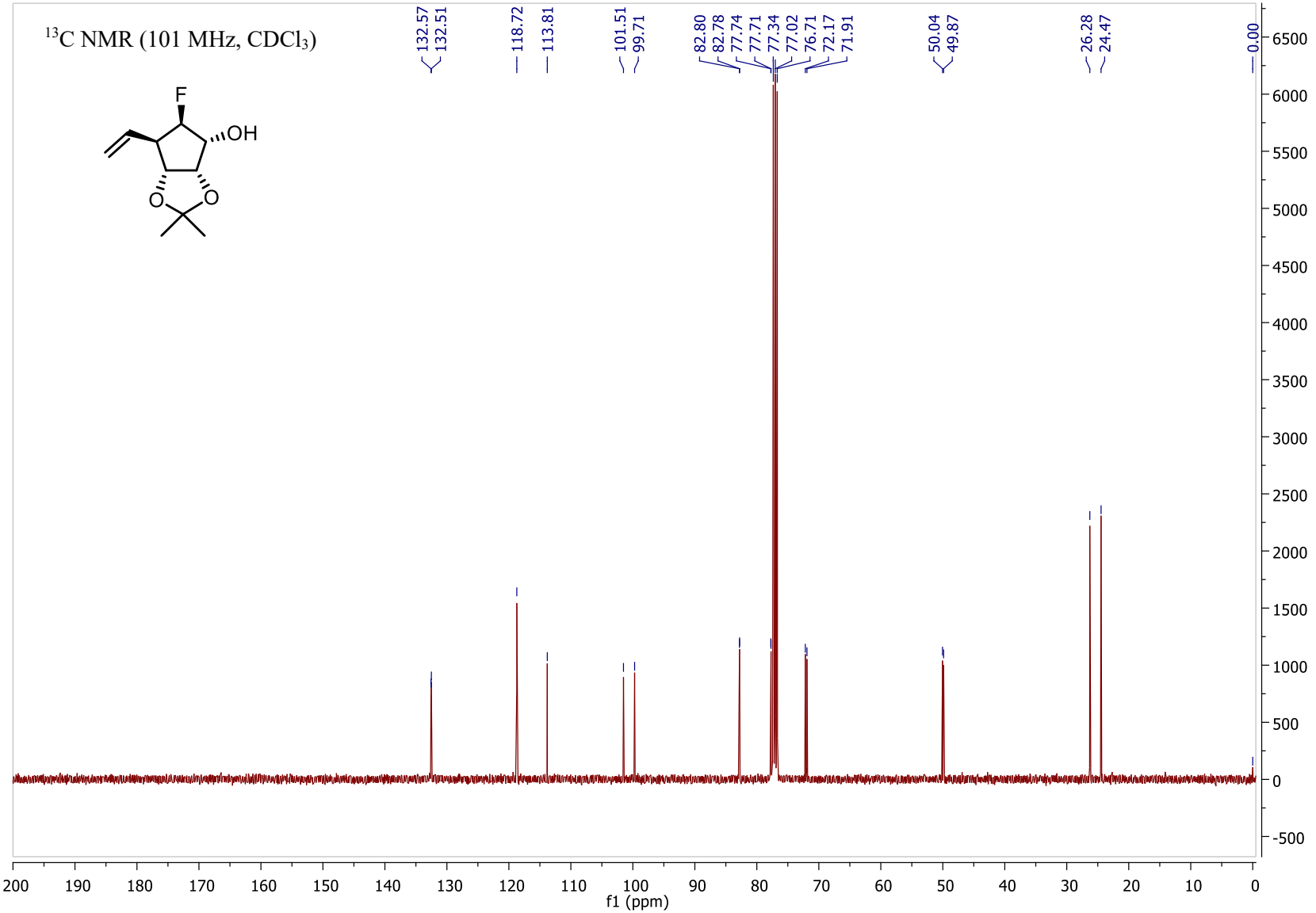

^{13}C NMR (101 MHz, $CDCl_3$)
F
F
OH
OH
O
O
129.77
129.72
126.73
124.22
124.04
121.52
121.08
114.15
95.47
95.25
95.22
95.00
79.33
79.30
78.60
78.59
78.53
78.52
52.71
52.51
52.50
52.30
26.18
24.64
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

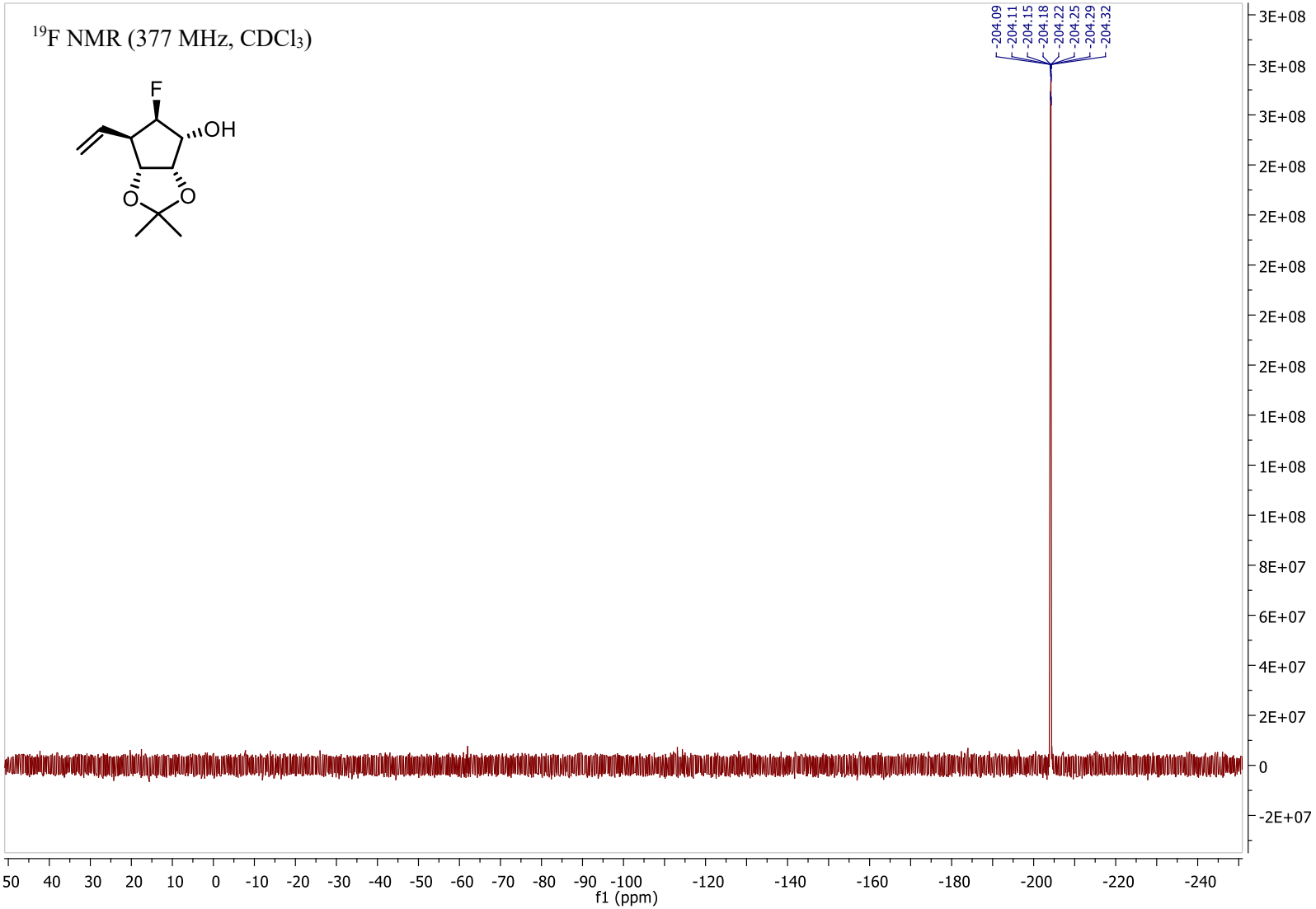
^{19}F NMR (377 MHz, $CDCl_3$)



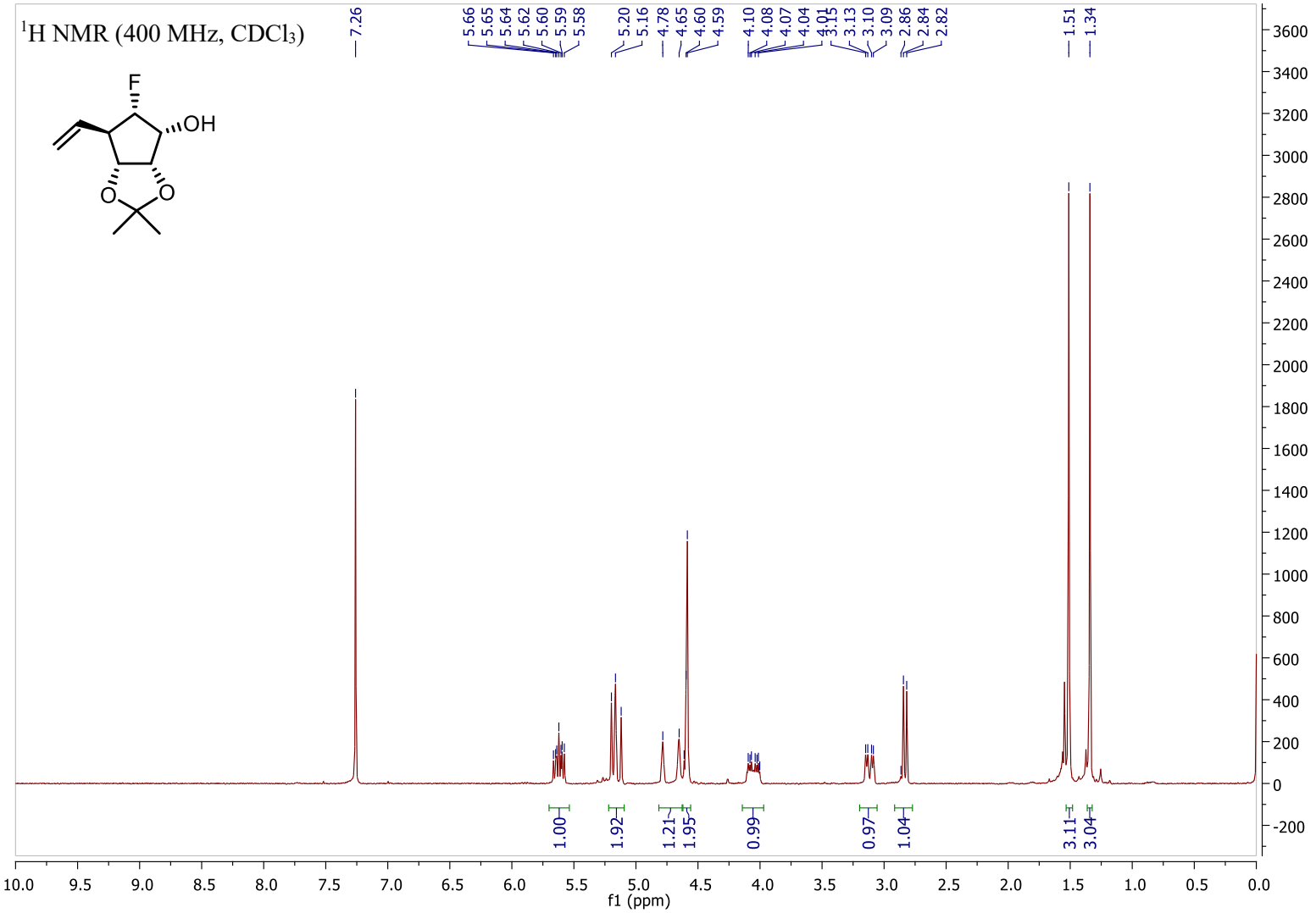
(1R,2S,3R,4R,6R)-2,3-O-isopropylidine-4-vinyl-7-fluorocyclopentan-1-ol, 10

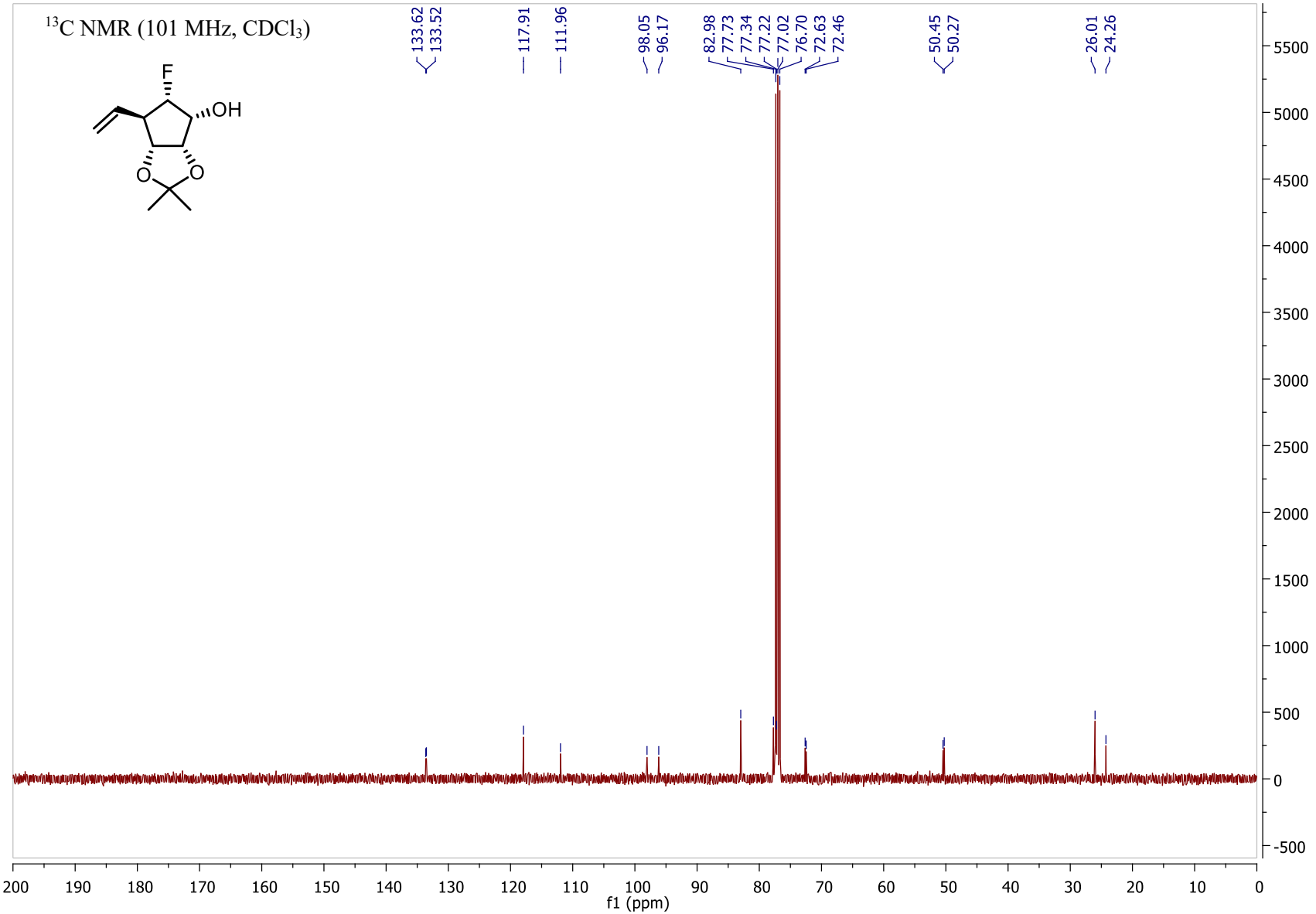



^{13}C NMR (101 MHz, $CDCl_3$)
F
OH
O
O
132.57
132.51
118.72
113.81
101.51
99.71
82.80
82.78
77.74
77.71
77.34
77.02
76.71
72.17
71.91
50.04
49.87
26.28
24.47
0.00
f1 (ppm)

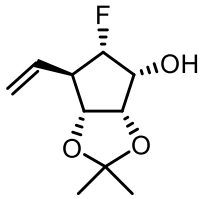

^{19}F NMR (377 MHz, $CDCl_3$)
F
OH
O
O
-204.09
-204.11
-204.15
-204.18
-204.22
-204.25
-204.29
-204.32
3E+08
3E+08
3E+08
2E+08
2E+08
2E+08
2E+08
2E+08
1E+08
1E+08
1E+08
8E+07
6E+07
4E+07
2E+07
0
-2E+07
50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -120 -140 -160 -180 -200 -220 -240
f1 (ppm)

(1R,2S,3R,4R,6S)-2,3-O-isopropylidine-4-vinyl-7-fluorocyclopentan-1-ol, 8



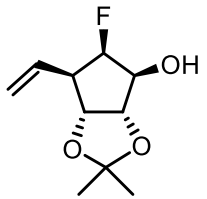

^{13}C NMR (101 MHz, $CDCl_3$)
F
OH
O
O
133.62
133.52
117.91
111.96
98.05
96.17
82.98
77.73
77.34
77.22
77.02
76.70
72.63
72.46
50.45
50.27
26.01
24.26
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

^{19}F NMR (377 MHz, $CDCl_3$)

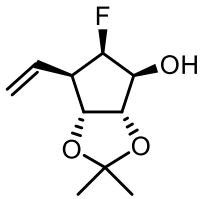


(1S,2S,3R,4R, 6R)-2,3-*O*-isopropylidine-4-vinyl-7-fluorocyclopentan-1-ol, 11

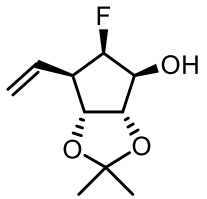
^{1}H NMR (400 MHz, $CDCl_3$)



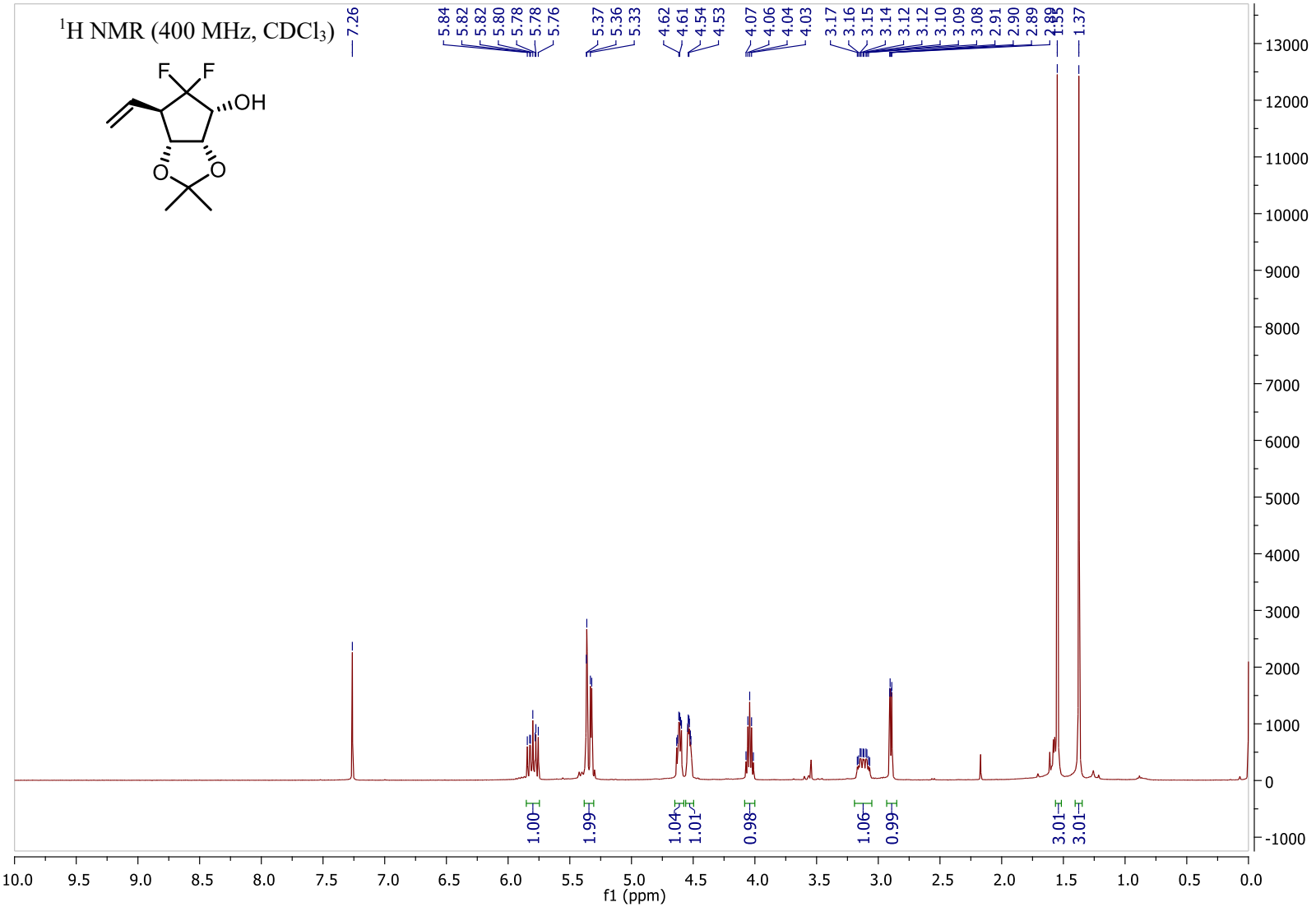
^{13}C NMR (101 MHz, $CDCl_3$)

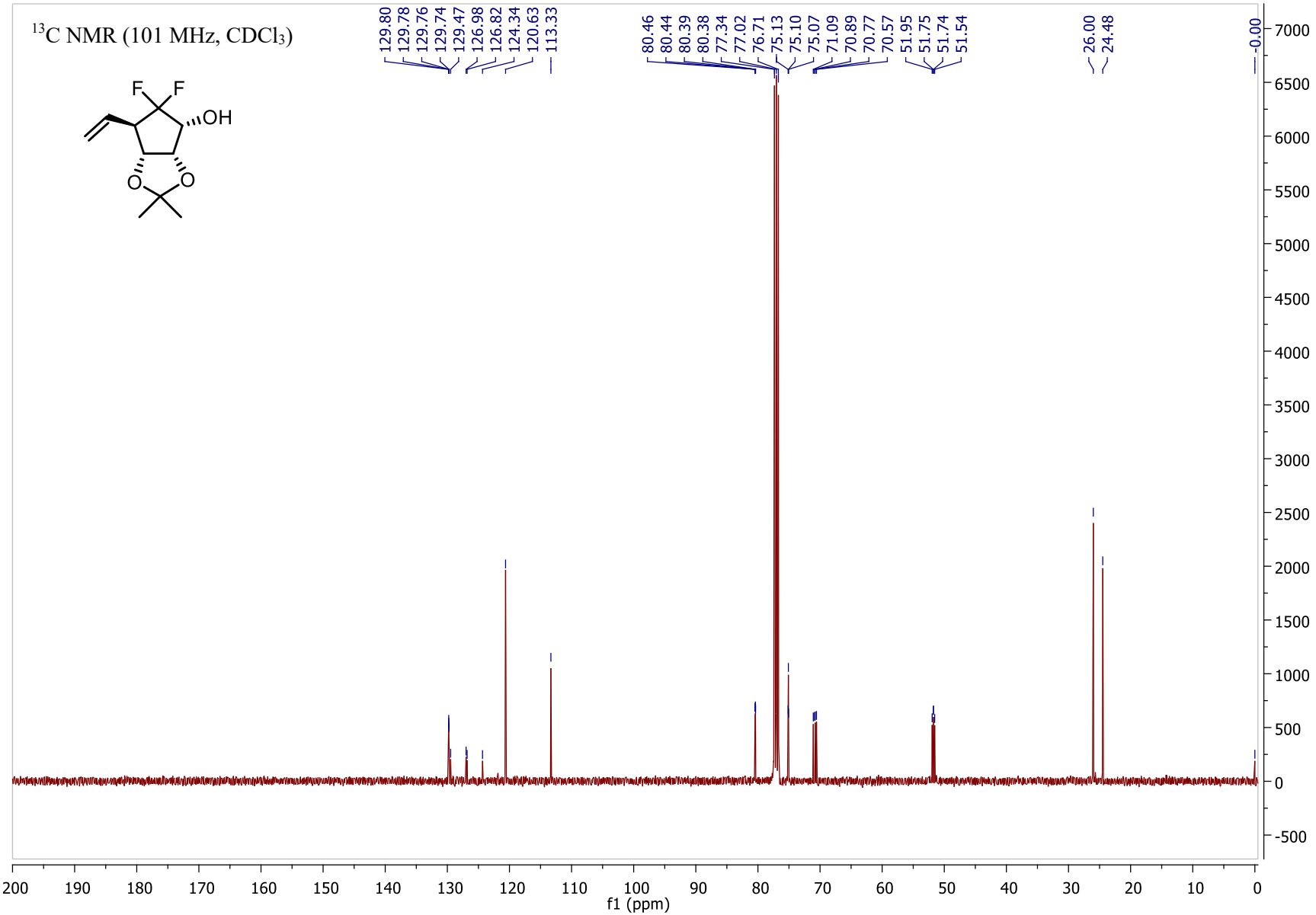


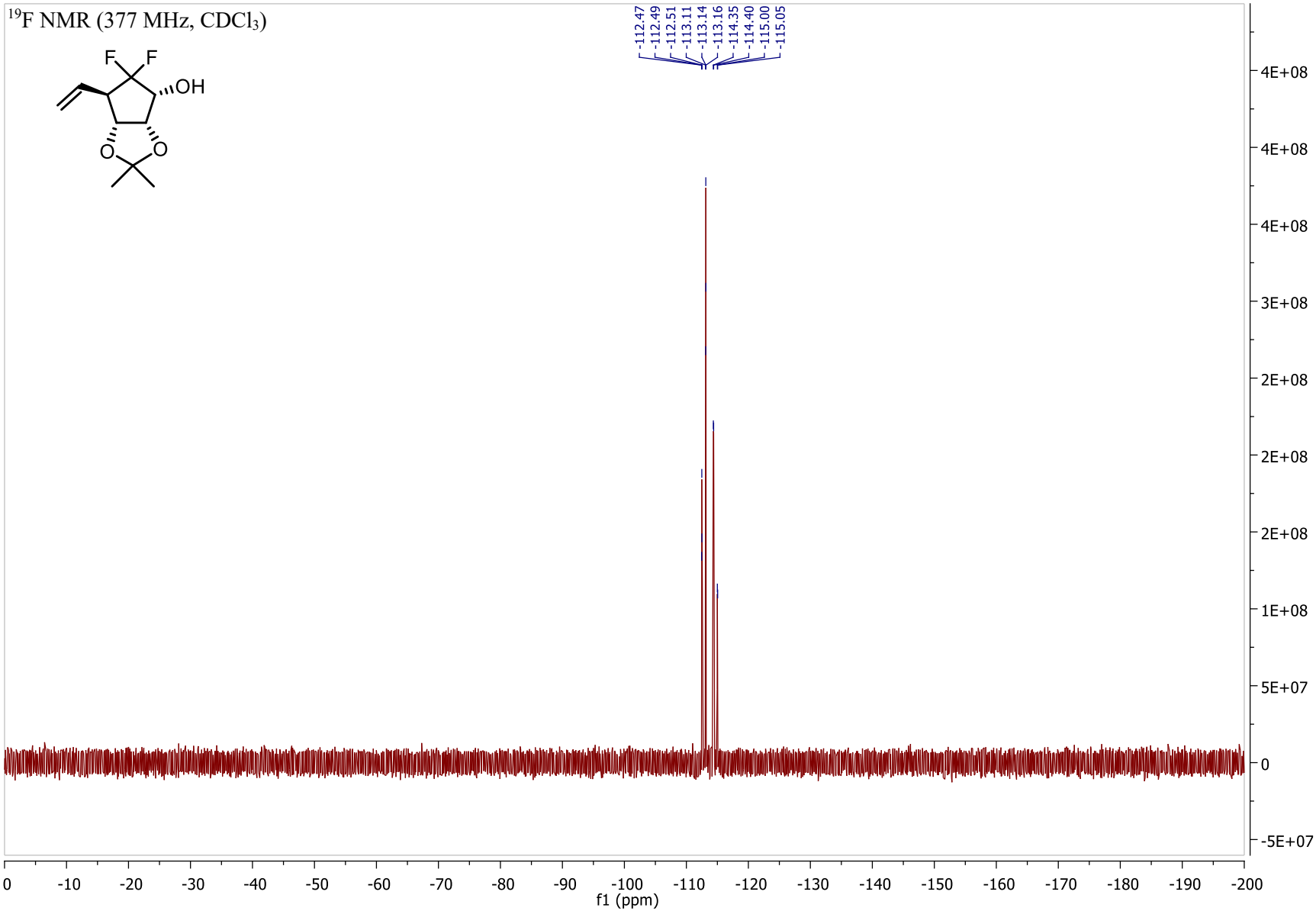
^{19}F NMR (377 MHz, $CDCl_3$)



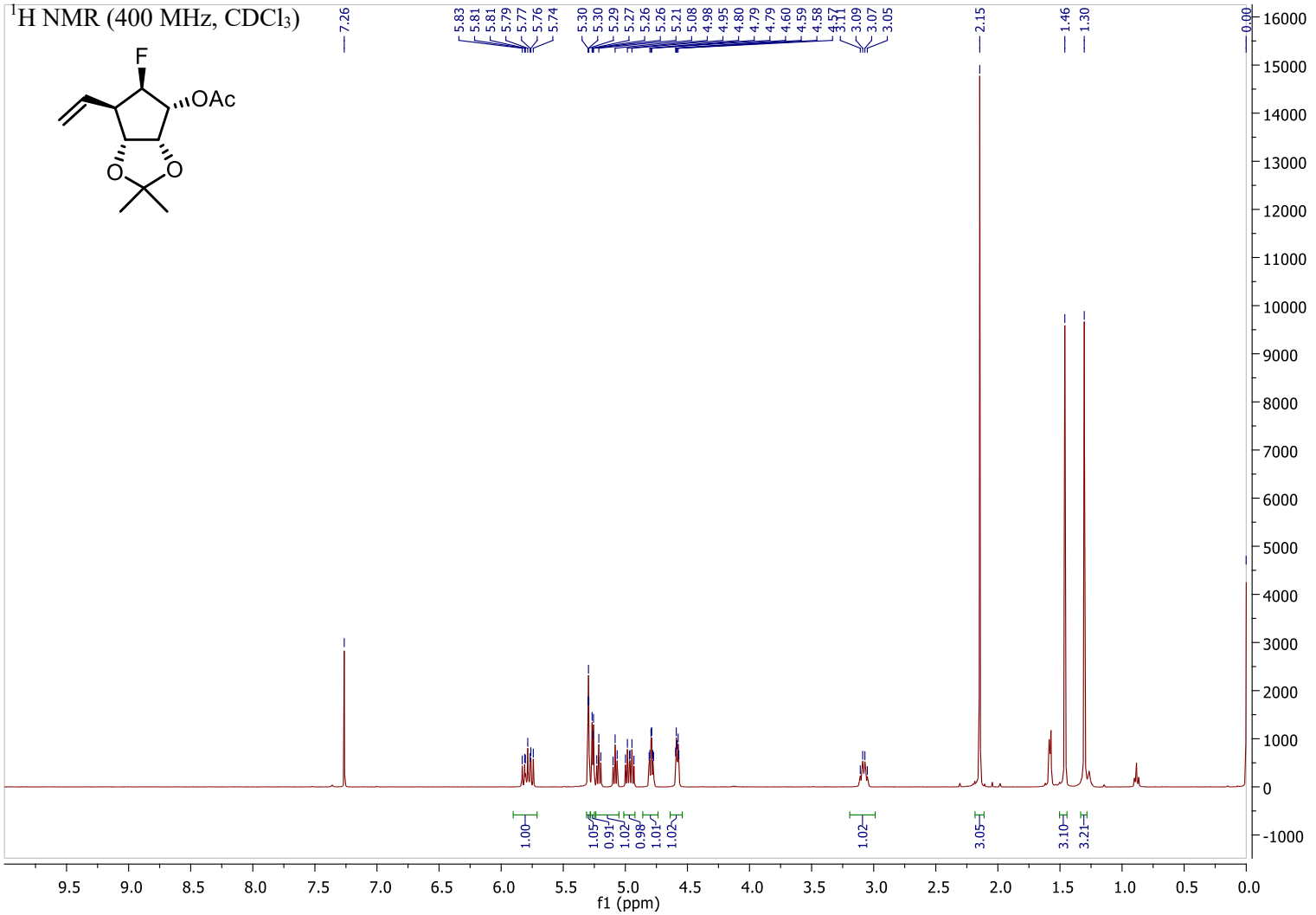
(1R,2S,3R,4R)-2,3-O-isopropylidine-4-vinyl-7-gem-difluorocyclopentan-1-ol, 12

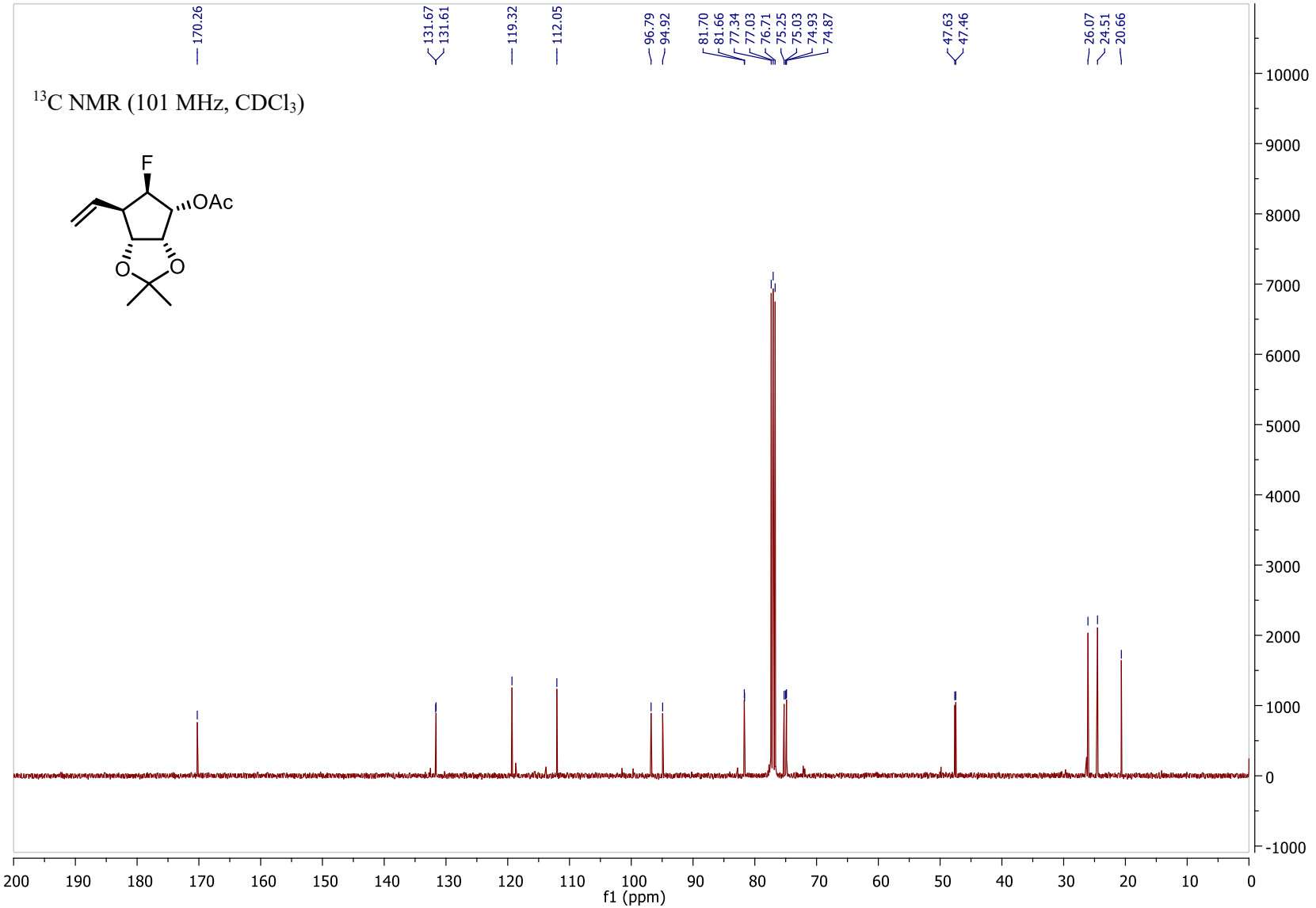



^{13}C NMR (101 MHz, $CDCl_3$)
F
F
OH
O
O
129.80
129.78
129.76
129.74
129.47
126.98
126.82
124.34
120.63
113.33
80.46
80.44
80.39
80.38
77.34
77.02
76.71
75.13
75.10
75.07
71.09
70.89
70.77
70.57
51.95
51.75
51.74
51.54
26.00
24.48
-0.00
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

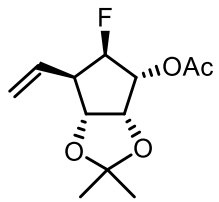

19F NMR (377 MHz, CDCl3)
F
F
OH
O
O
-112.47
-112.49
-112.51
-113.11
-113.14
-113.16
-114.35
-114.40
-115.00
-115.05
4E+08
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
-5E+07
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

(1R,2R,3R,4R,7R)-1-*O*-acetate-2,3-*O*-isopropylidine-4-vinyl-7-fluorocyclopentane, 13

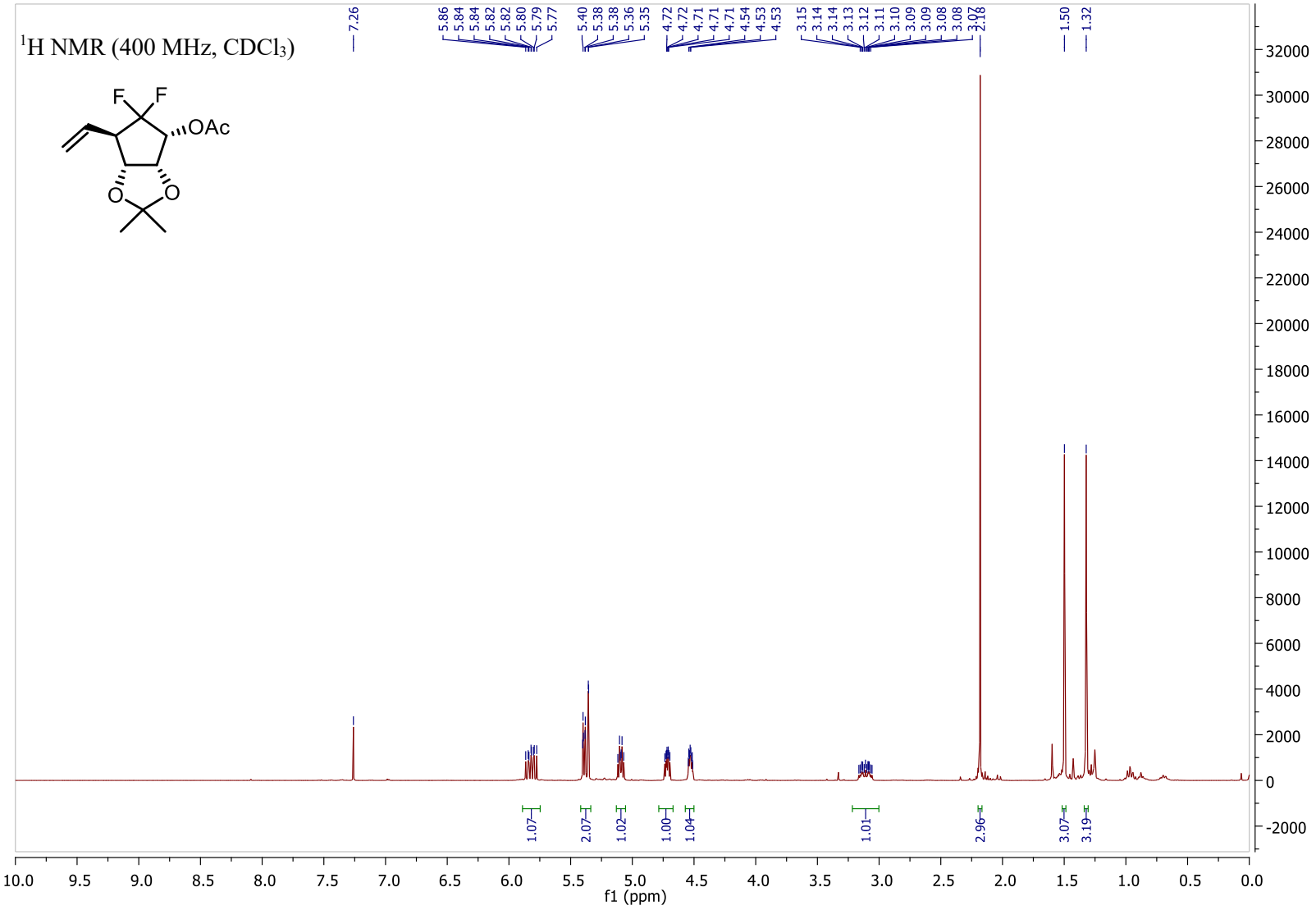


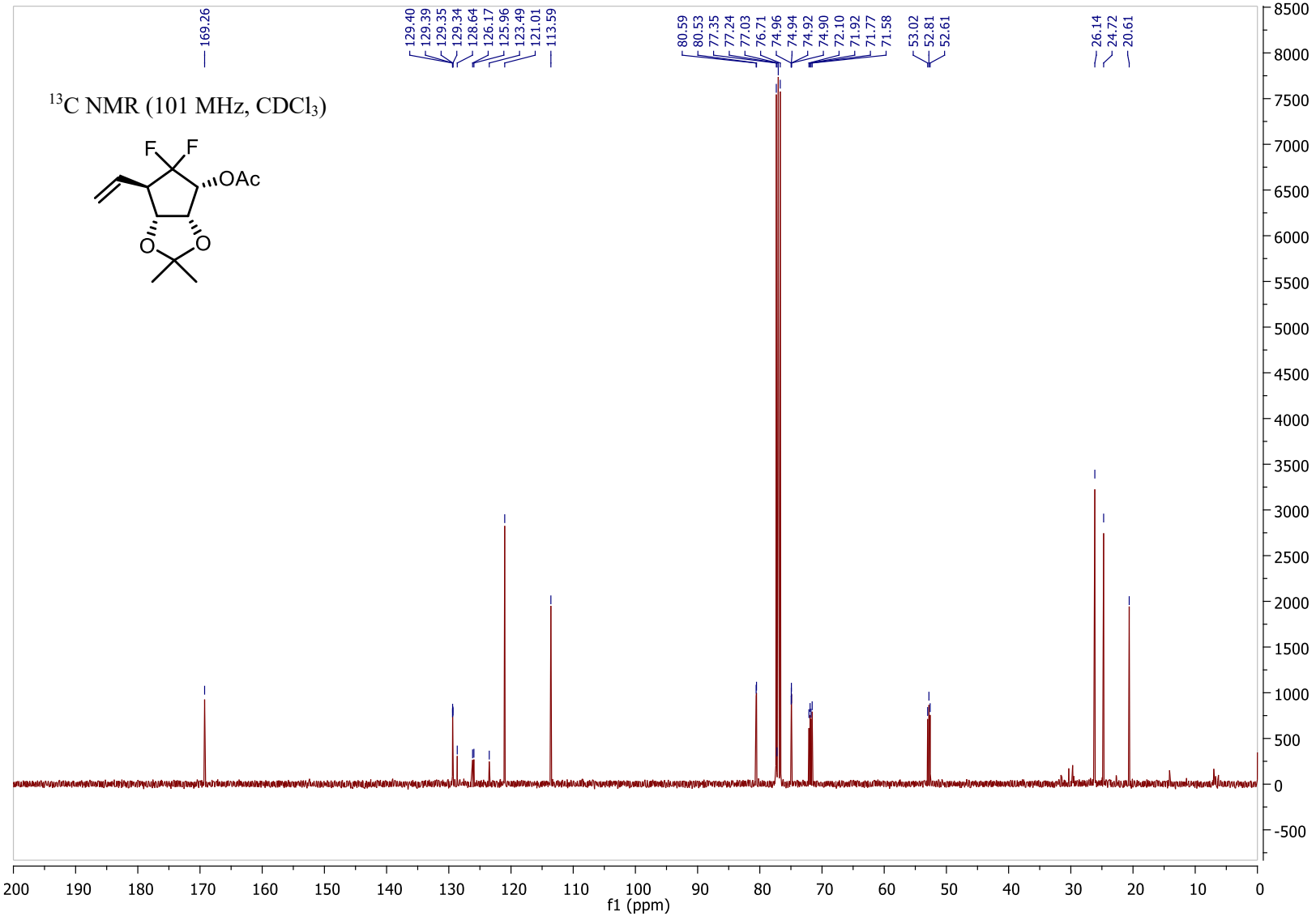

170.26
131.67
131.61
119.32
112.05
96.79
94.92
81.70
81.66
77.34
77.03
76.71
75.25
75.03
74.93
74.87
47.63
47.46
26.07
24.51
20.66
13C NMR (101 MHz, CDCl3)
F
OAc
O
O
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

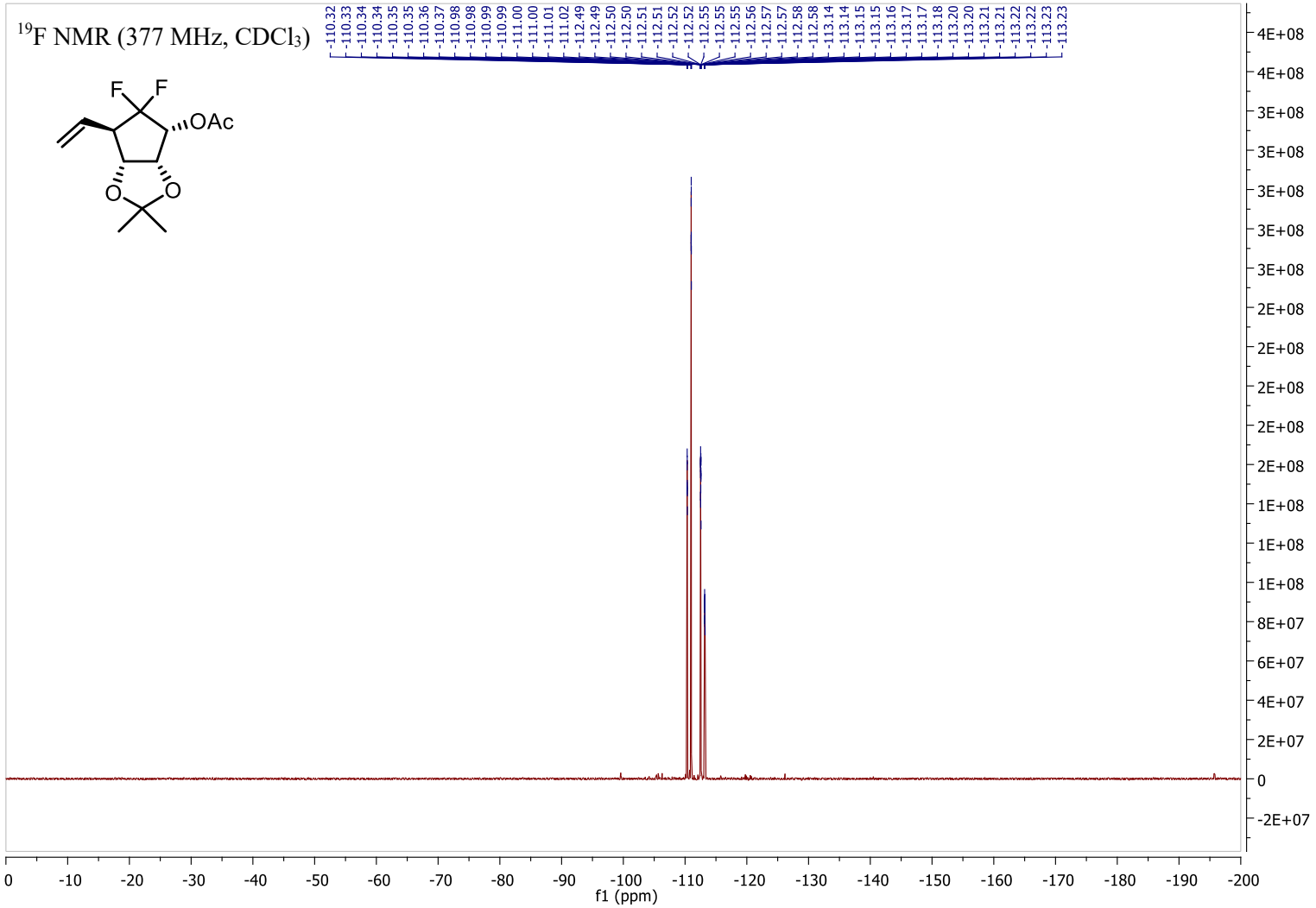
^{19}F NMR (377 MHz, $CDCl_3$)



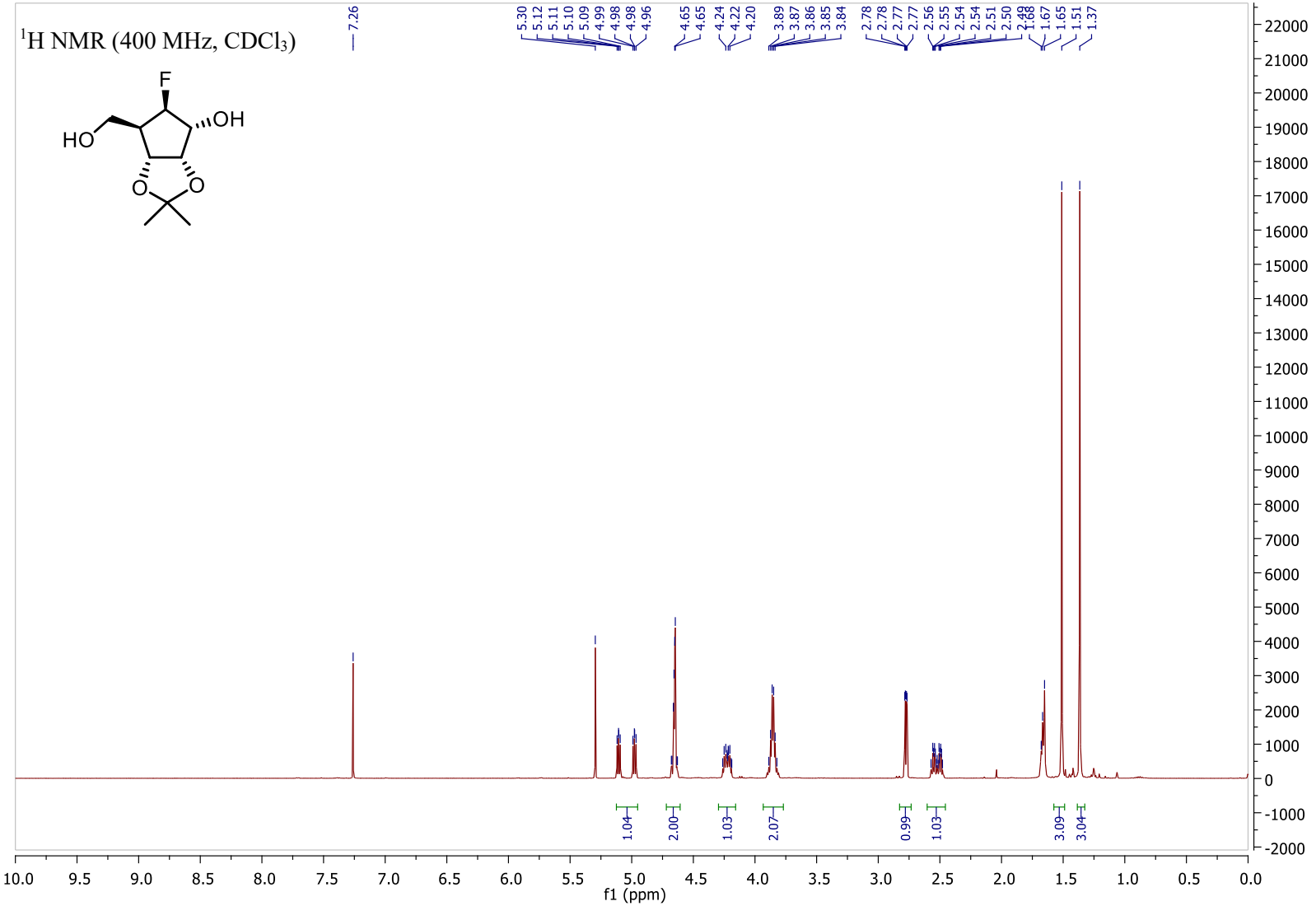
(1R,2R,3R,4R)-1-*O*-acetate-2,3-*O*-isopropylidine-4-vinyl-7-*gem*-difluorocyclopentane, 14

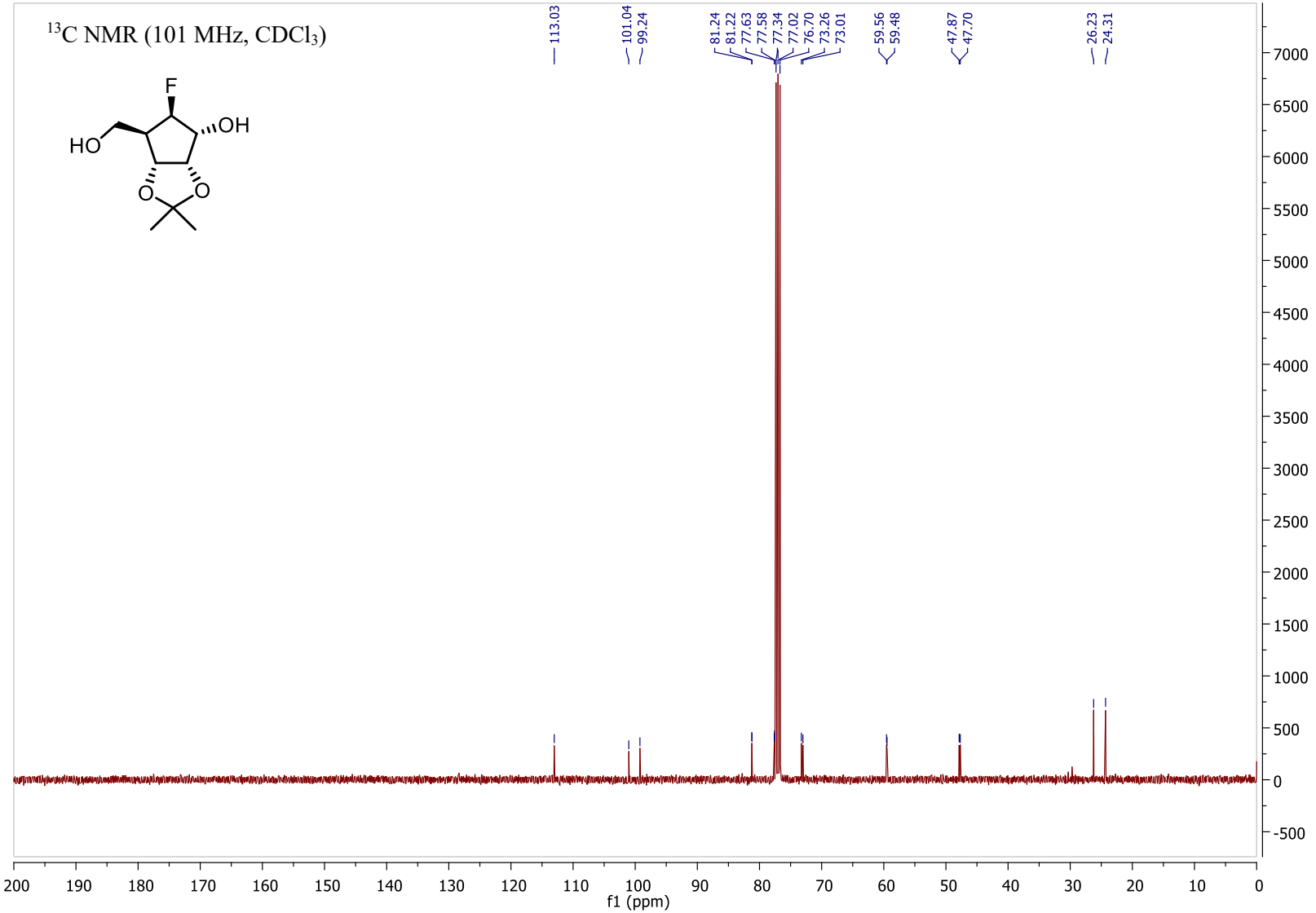



169.26
129.40
129.39
129.35
129.34
128.64
126.17
125.96
123.49
121.01
113.59
80.59
80.53
77.35
77.24
77.03
76.71
74.96
74.94
74.92
74.90
72.10
71.92
71.77
71.58
53.02
52.81
52.61
26.14
24.72
20.61
13C NMR (101 MHz, CDCl3)
F
F
OAc
O
O
8500
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

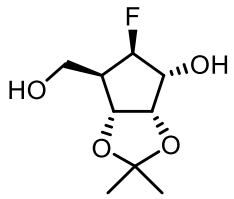

19F NMR (377 MHz, CDCl3)
F
F
OAc
O
O
-110.32
-110.33
-110.34
-110.34
-110.35
-110.35
-110.36
-110.37
-110.98
-110.98
-110.99
-110.99
-111.00
-111.00
-111.01
-111.02
-112.49
-112.49
-112.50
-112.50
-112.51
-112.51
-112.52
-112.52
-112.55
-112.55
-112.55
-112.56
-112.57
-112.57
-112.58
-112.58
-113.14
-113.14
-113.15
-113.15
-113.16
-113.17
-113.17
-113.18
-113.20
-113.20
-113.21
-113.21
-113.22
-113.22
-113.23
-113.23
4E+08
4E+08
3E+08
3E+08
3E+08
3E+08
3E+08
2E+08
2E+08
2E+08
2E+08
2E+08
2E+08
1E+08
1E+08
1E+08
8E+07
6E+07
4E+07
2E+07
0
-2E+07
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

(1R,2S,3R,4R,6R)-2,3-*O*-isopropylidine-4-hydroxymethyl-6-fluorocyclopentan-1-ol, 15

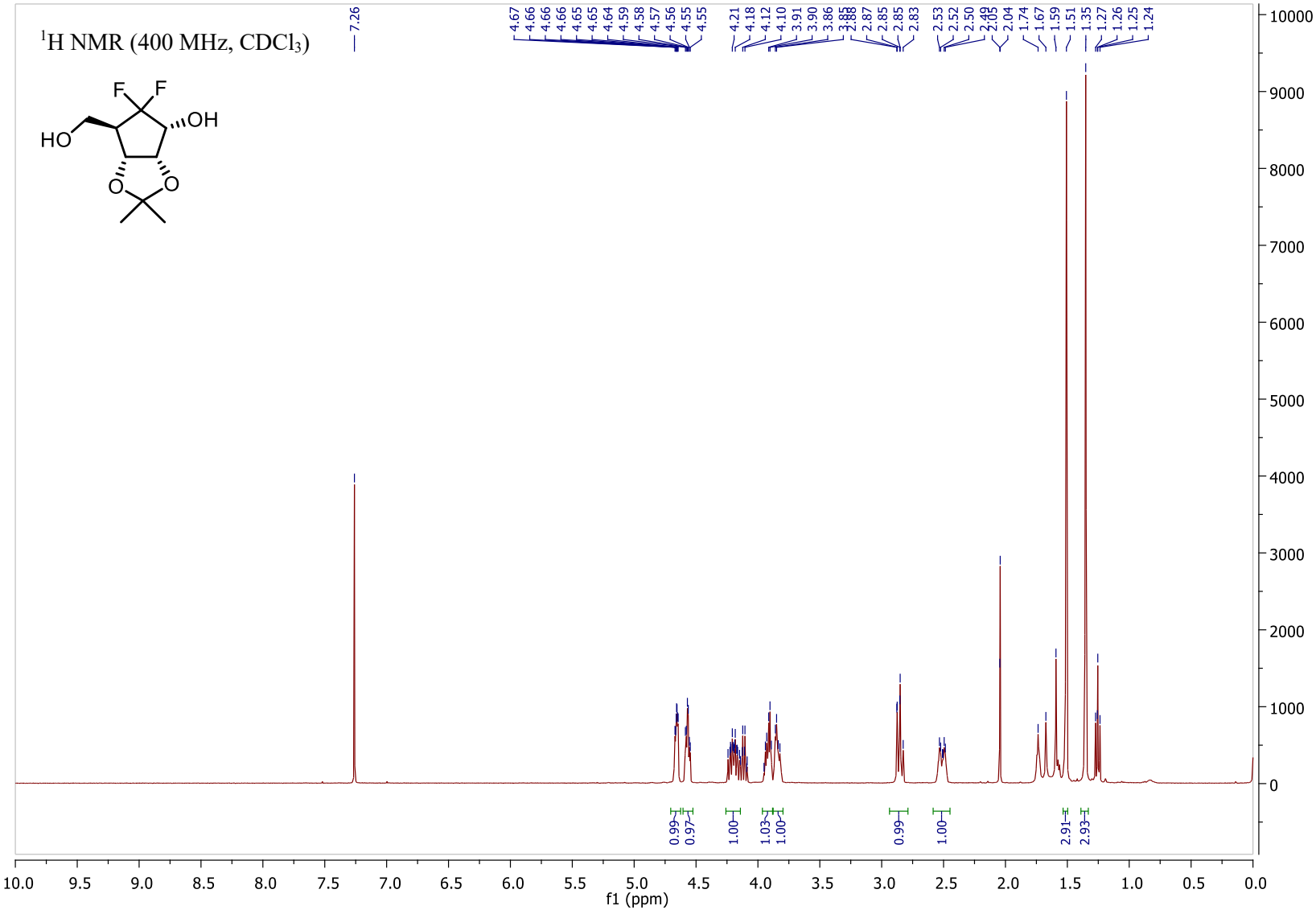


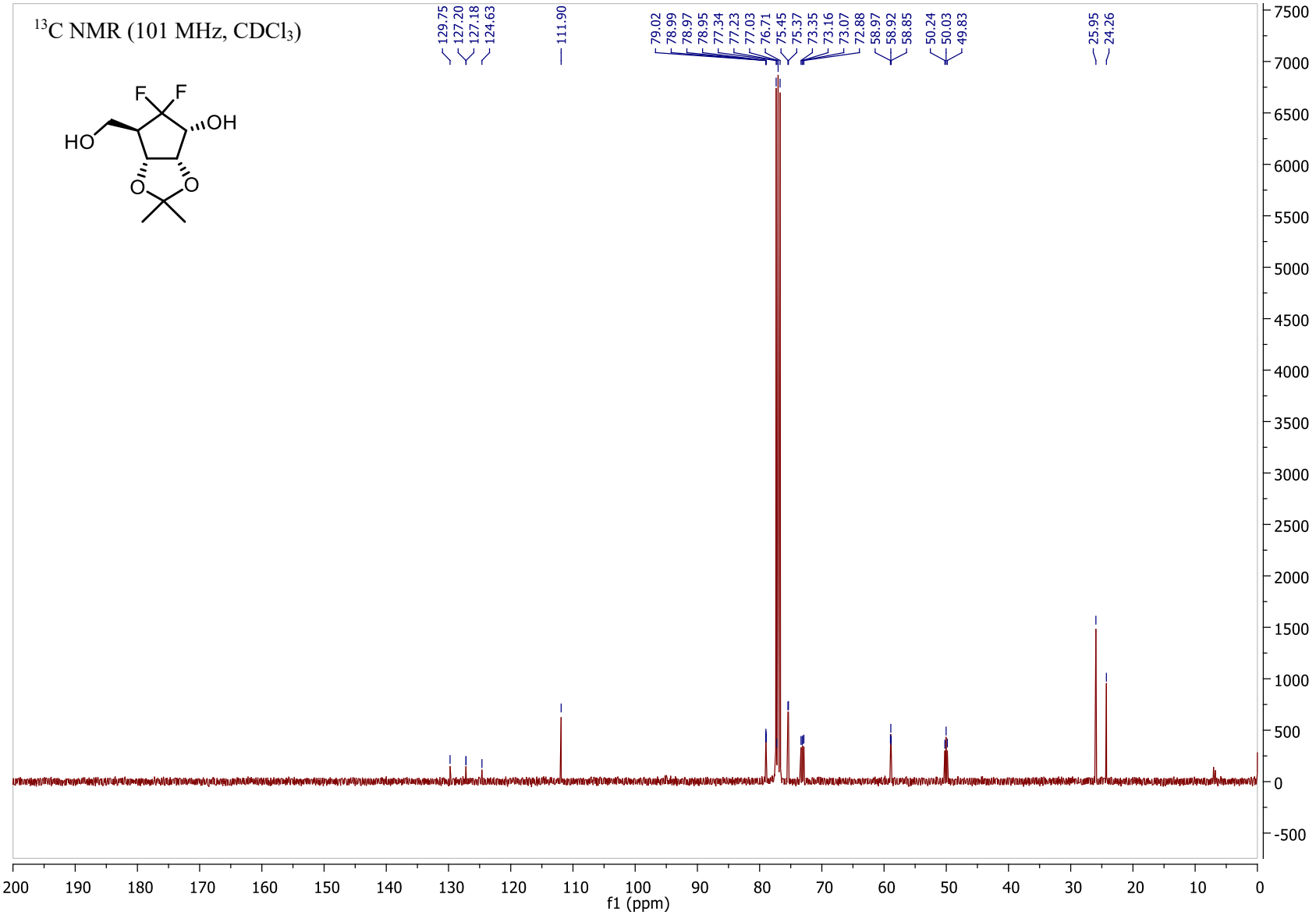

^{13}C NMR (101 MHz, $CDCl_3$)
F
HO
OH
O
O
113.03
101.04
99.24
81.24
81.22
77.63
77.58
77.34
77.02
76.70
73.26
73.01
59.56
59.48
47.87
47.70
26.23
24.31
f1 (ppm)

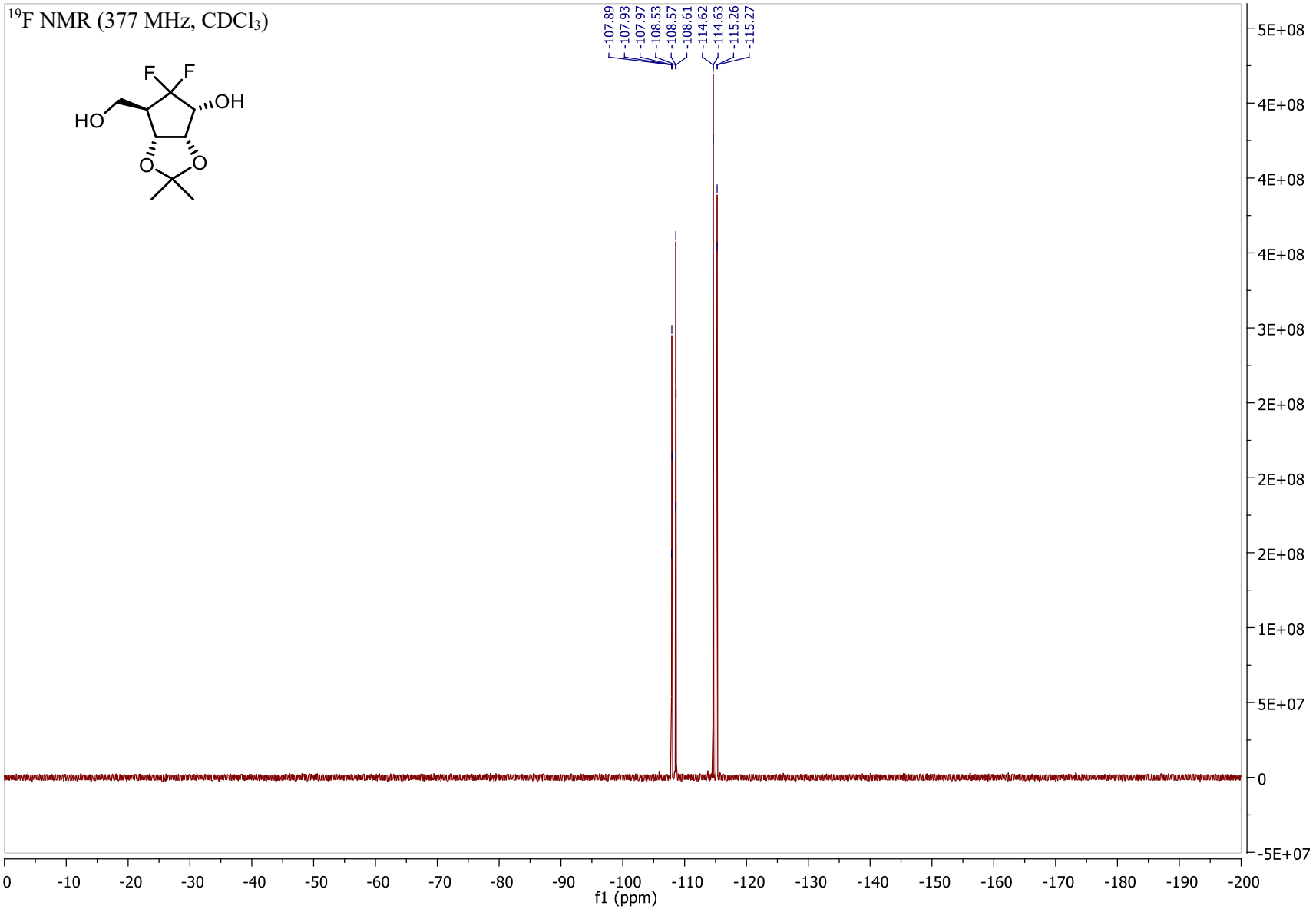
^{19}F NMR (377 MHz, $CDCl_3$)



(1R,2S,3R,4R)-2,3-*O*-isopropylidine-4-hydroxymethyl-6-*gem*-difluorocyclopentan-1-ol, 16

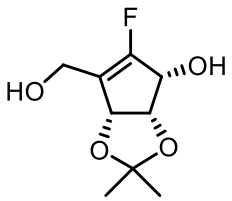



^{13}C NMR (101 MHz, $CDCl_3$)
F
F
HO
OH
O
O
129.75
127.20
127.18
124.63
111.90
79.02
78.99
78.97
78.95
77.34
77.23
77.03
76.71
75.45
75.37
73.35
73.16
73.07
72.88
58.97
58.92
58.85
50.24
50.03
49.83
25.95
24.26
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

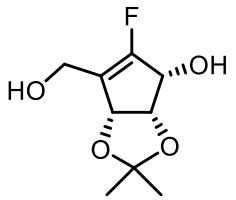

19F NMR (377 MHz, CDCl3)
F
F
HO
OH
O
O
-107.89
-107.93
-107.97
-108.53
-108.57
-108.61
-114.62
-114.63
-115.26
-115.27
5E+08
4E+08
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
-5E+07
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

(1R, 2S, 3R)-2,3-*O*-isopropylidine-4-hydroxymethyl-6-fluoro-4,6-cyclopenten-1-ol, 17

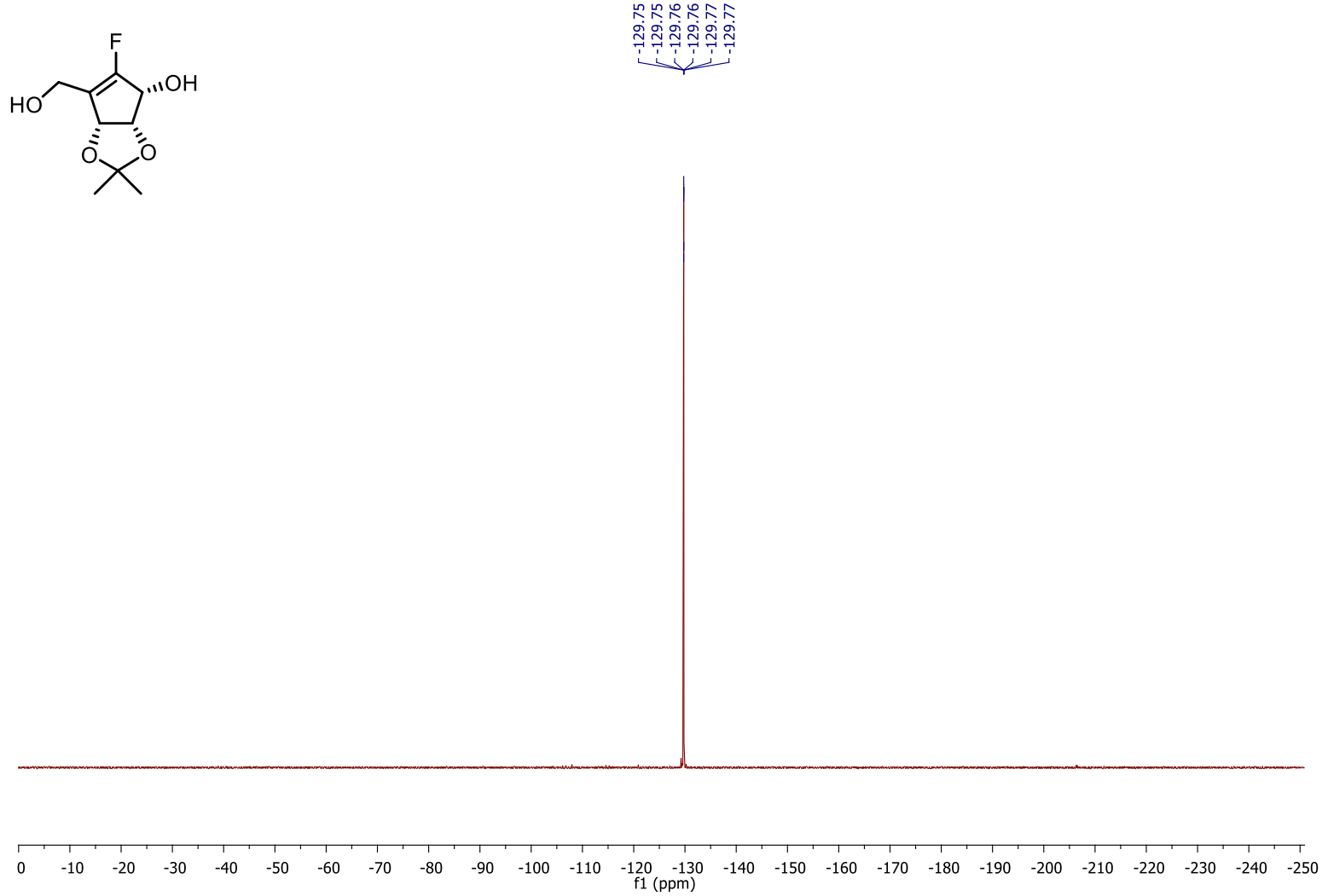
^{1}H NMR (400 MHz, $CDCl_3$)



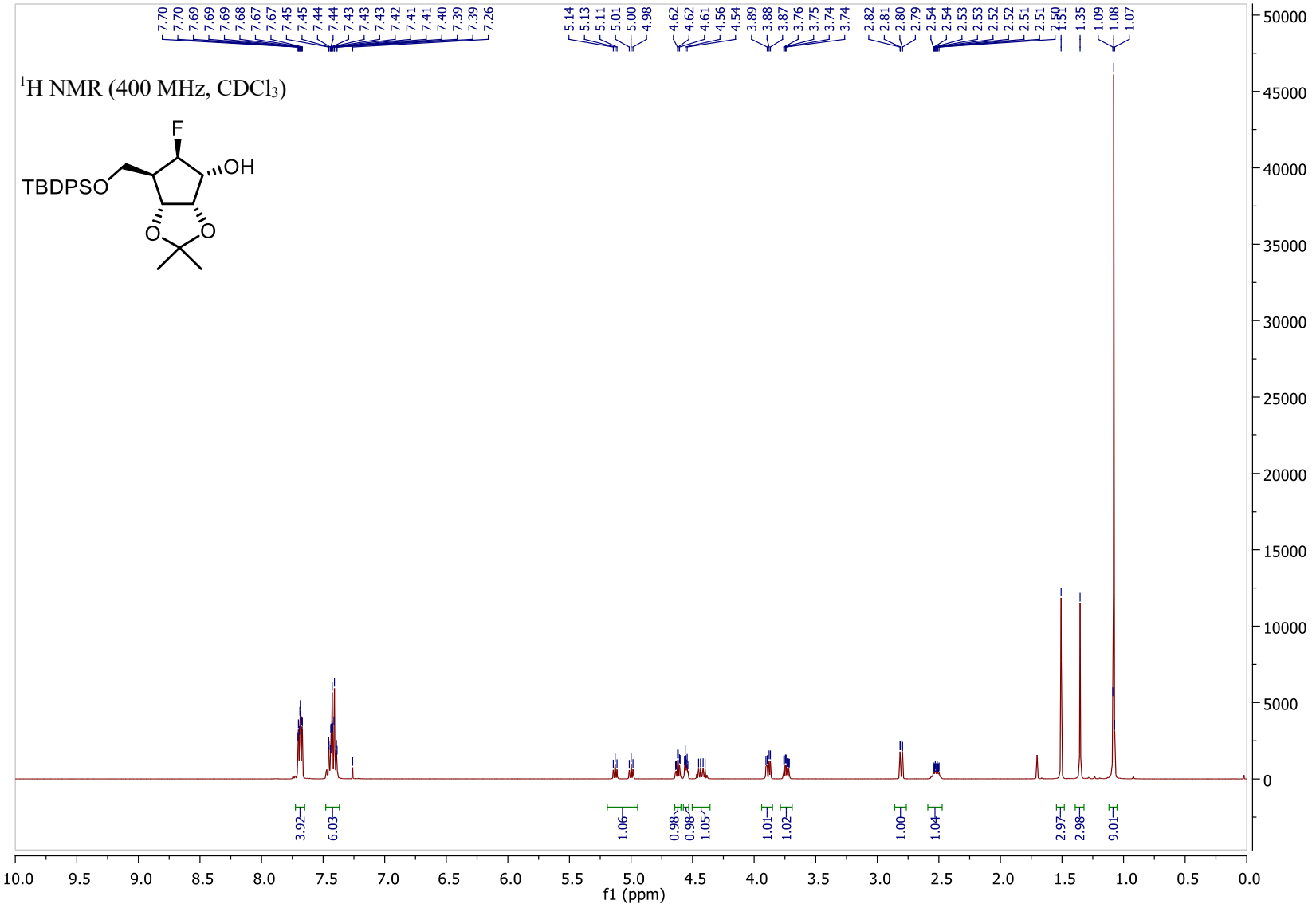
^{13}C NMR (101 MHz, $CDCl_3$)

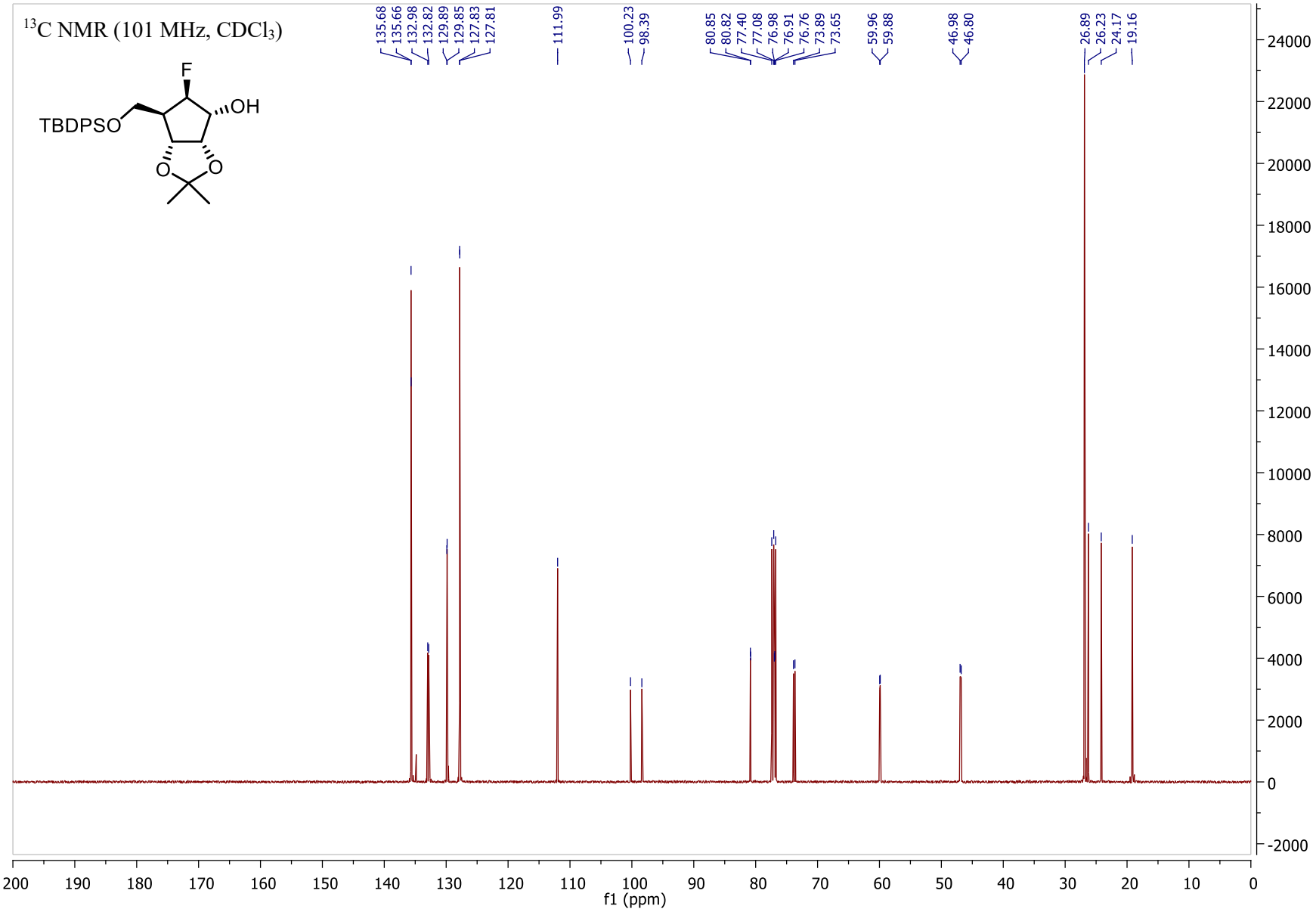


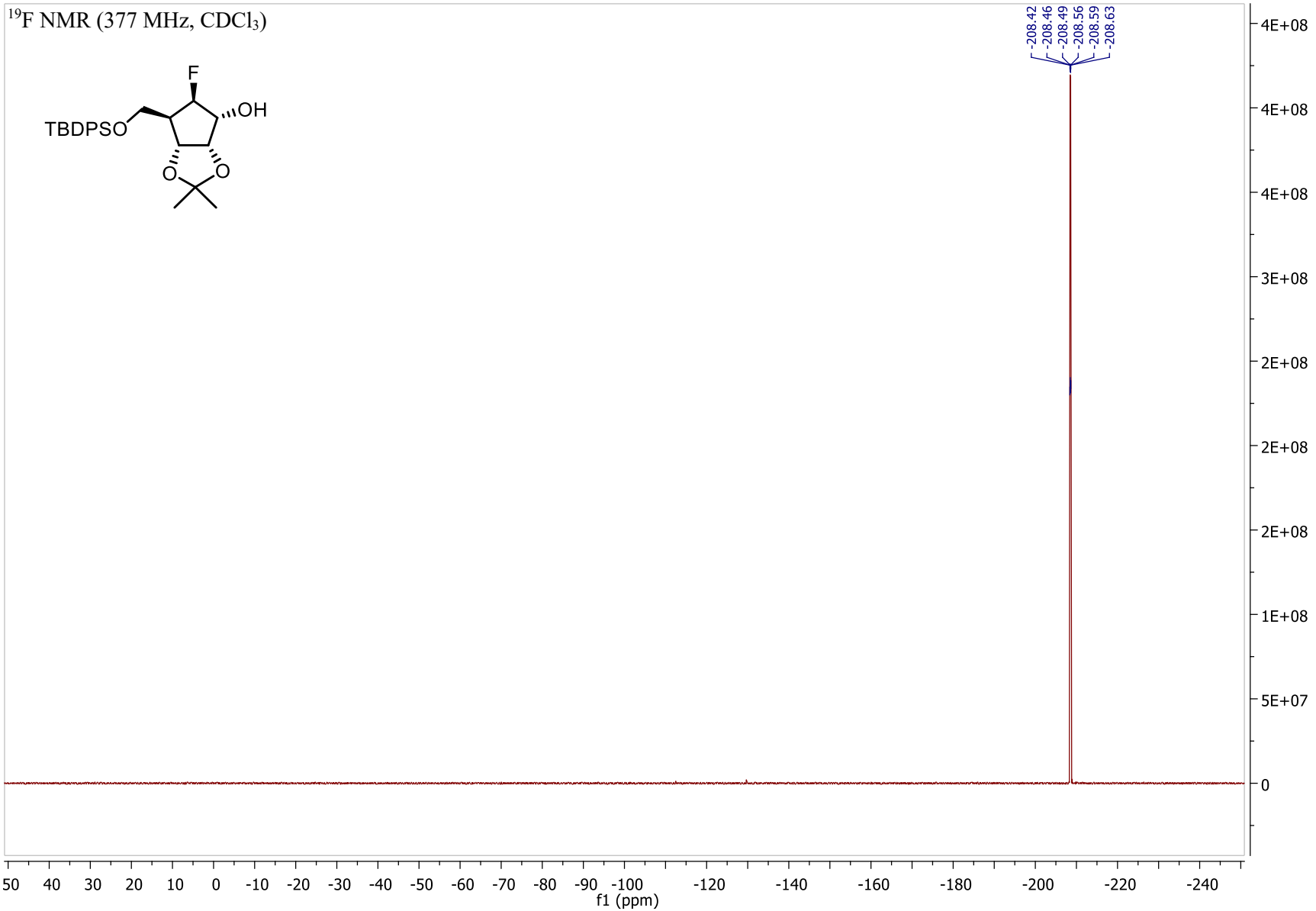
^{19}F NMR (377 MHz, $CDCl_3$)



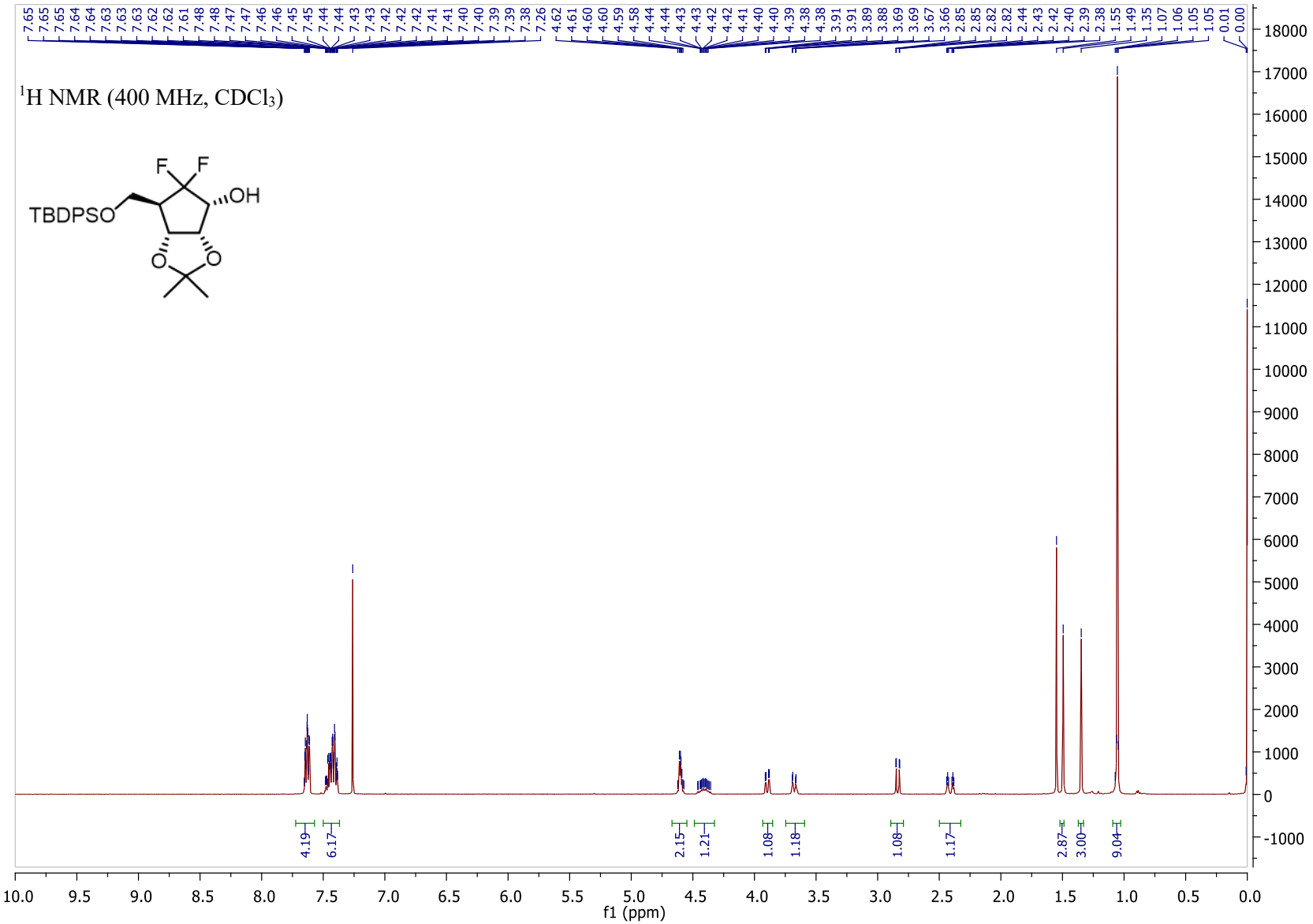
(1R,2S,3R,4S,6R)-2,3-*O*-isopropylidine-4-*O*-(*tert*-butyldiphenylsilyl)methyl-6-fluorocyclopentan-1-ol

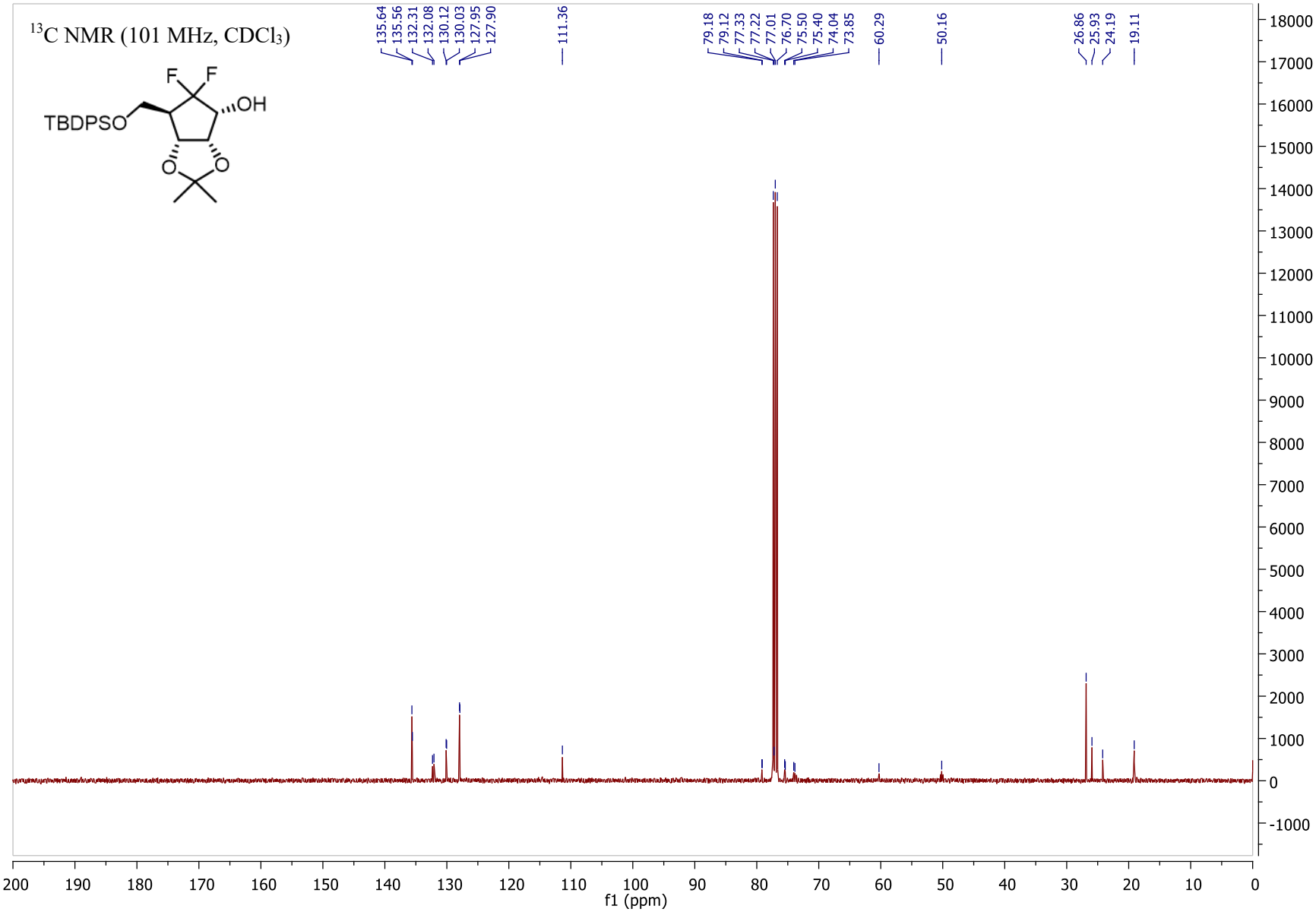


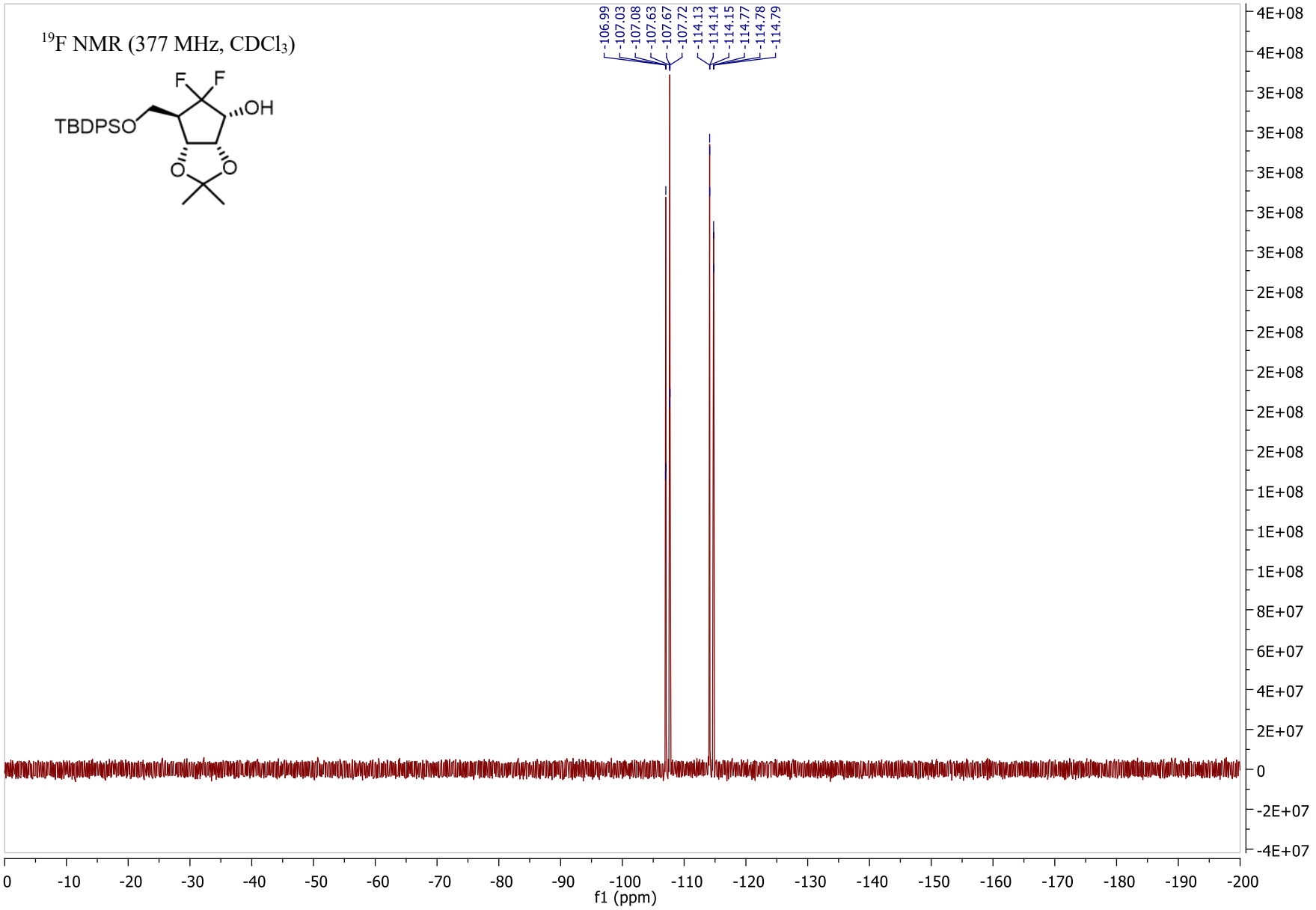

^{13}C NMR (101 MHz, $CDCl_3$)
F
OH
TBDPSO
O
O
135.68
135.66
132.98
132.82
129.89
129.85
127.83
127.81
111.99
100.23
98.39
80.85
80.82
77.40
77.08
76.98
76.91
76.76
73.89
73.65
59.96
59.88
46.98
46.80
26.89
26.23
24.17
19.16
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


19F NMR (377 MHz, CDCl3)
F
OH
TBDPSO
O
O
-208.42
-208.46
-208.49
-208.56
-208.59
-208.63
4E+08
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -120 -140 -160 -180 -200 -220 -240
f1 (ppm)

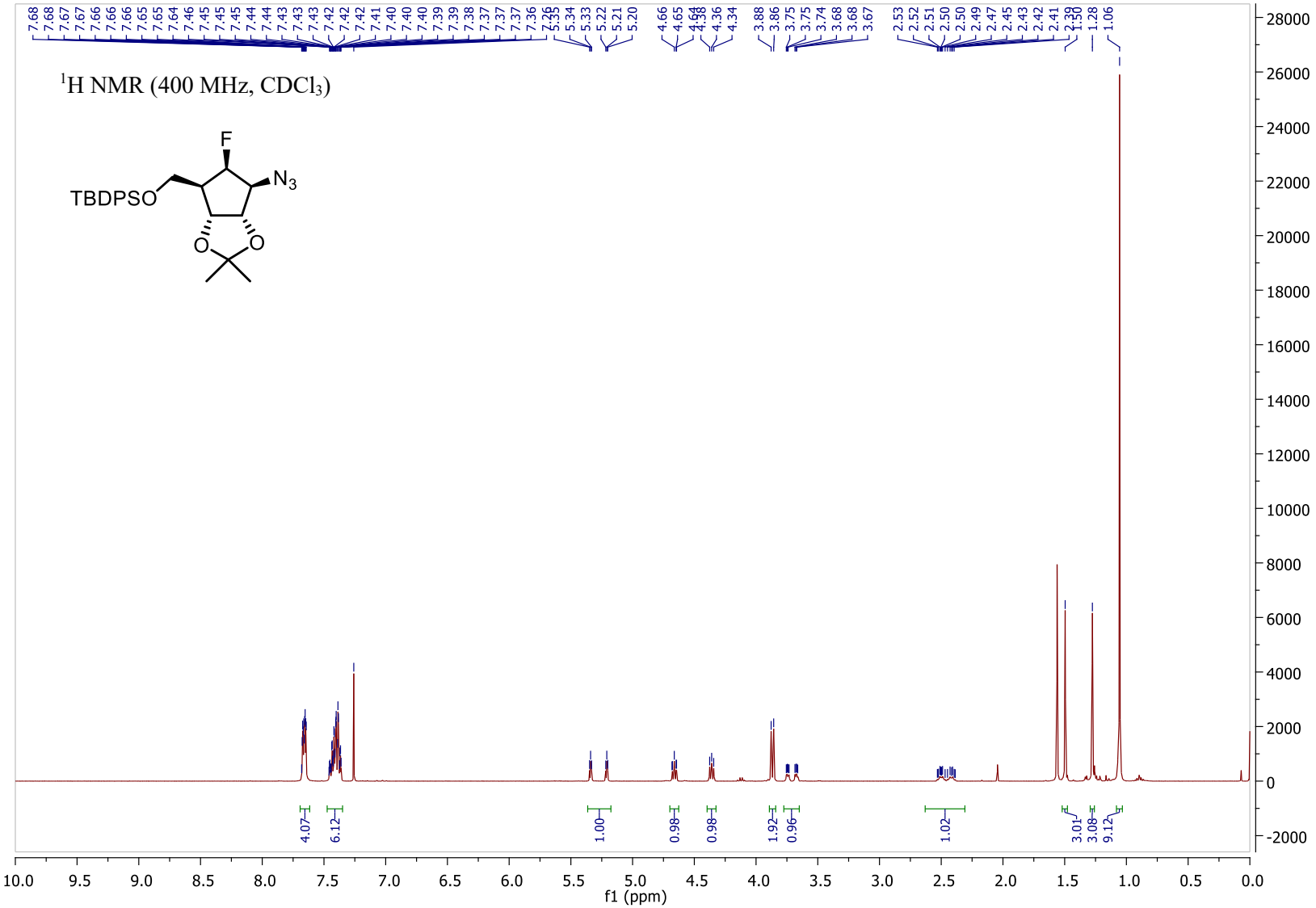
(1R,2S,3R,4S)-2,3-*O*-isopropylidine-4-*O*-(*tert*-butyldiphenylsilyl)methyl-6-*gem*-difluorocyclopentan-1-ol

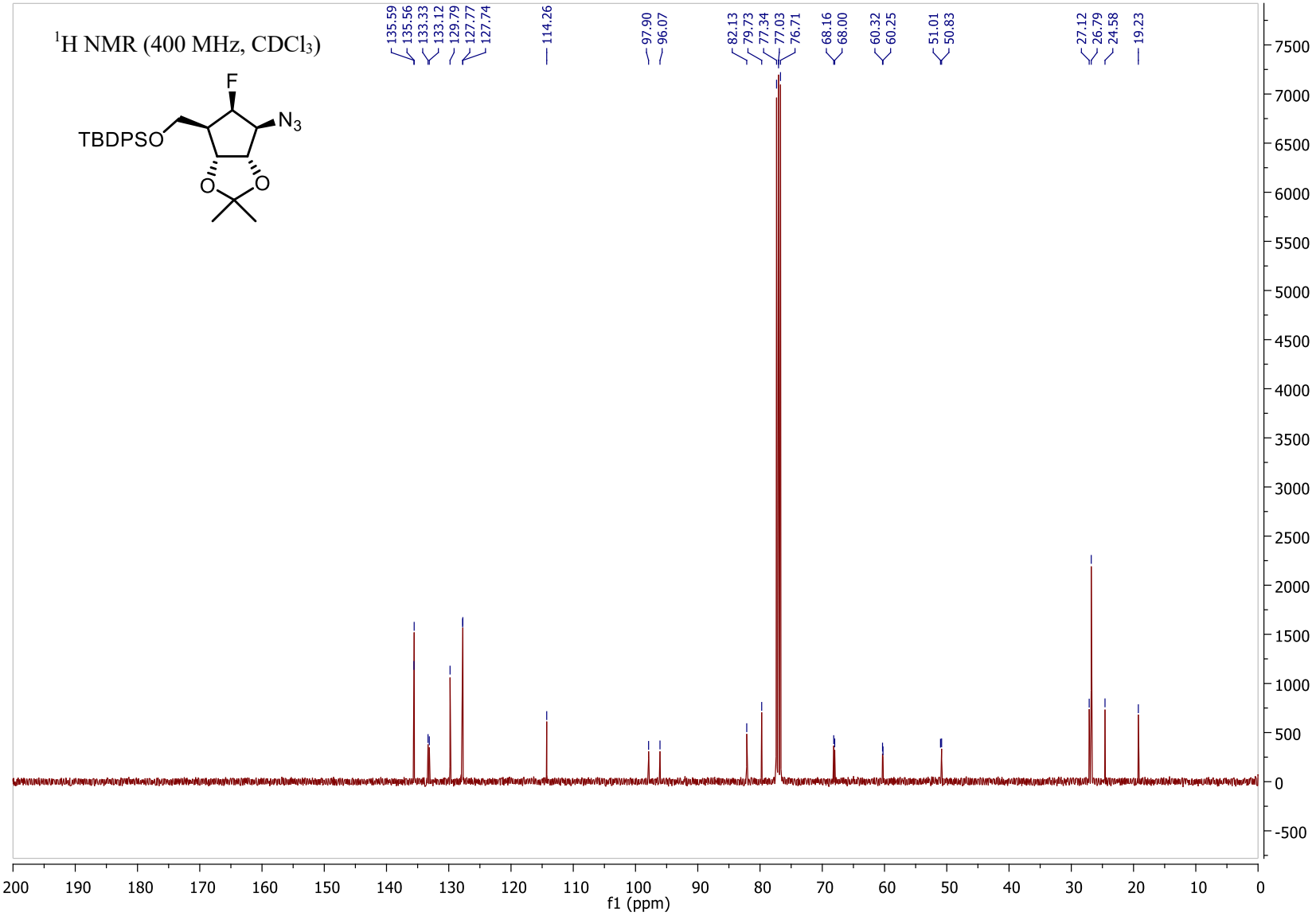


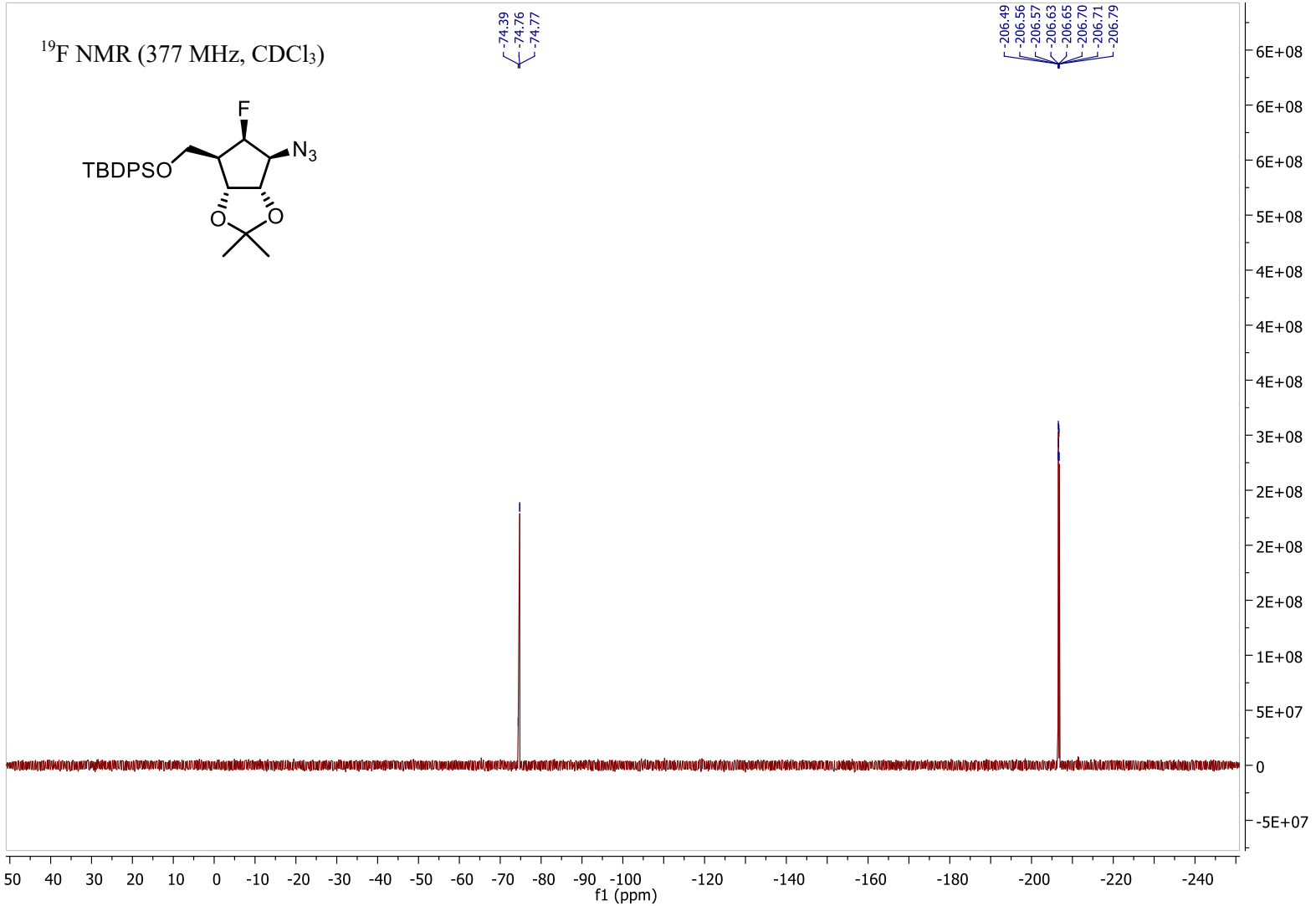

^{13}C NMR (101 MHz, $CDCl_3$)
F
F
OH
TBDPSO
O
O
135.64
135.56
132.31
132.08
130.12
130.03
127.95
127.90
111.36
79.18
79.12
77.33
77.22
77.01
76.70
75.50
75.40
74.04
73.85
60.29
50.16
26.86
25.93
24.19
19.11
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


^{19}F NMR (377 MHz, $CDCl_3$)
F
F
TBDPSO
OH
O
O
-106.99
-107.03
-107.08
-107.63
-107.67
-107.72
-114.13
-114.14
-114.15
-114.77
-114.78
-114.79
4E+08
4E+08
3E+08
3E+08
3E+08
3E+08
3E+08
2E+08
2E+08
2E+08
2E+08
2E+08
1E+08
1E+08
1E+08
8E+07
6E+07
4E+07
2E+07
0
-2E+07
-4E+07
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

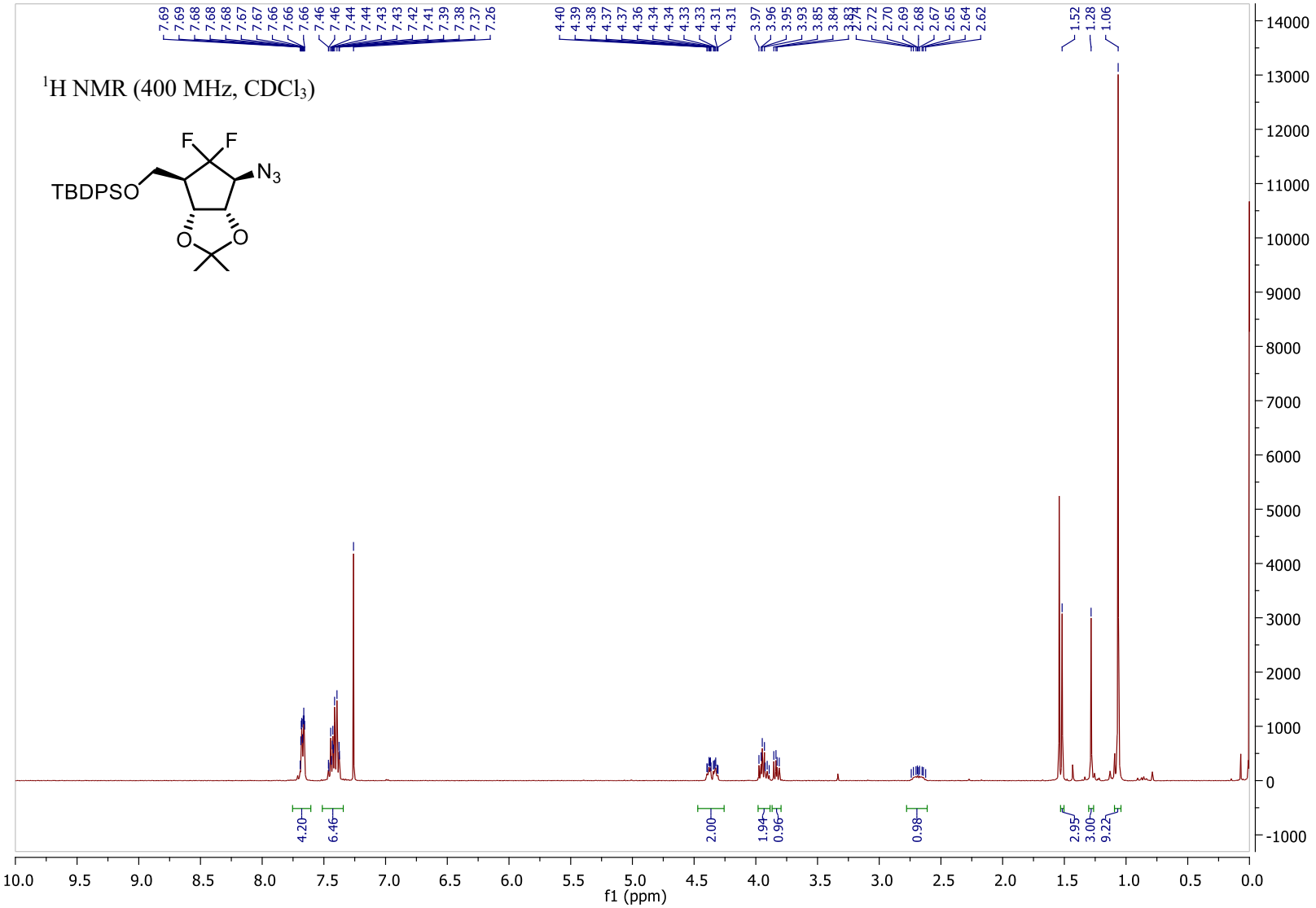
(1S,2S,3R,4S,6R)-1-azido-2,3-*O*-isopropylidine-4-*O*-(*tert*-butyldiphenylsilyl)methyl-6-fluorocyclopentan-1-ol, 18

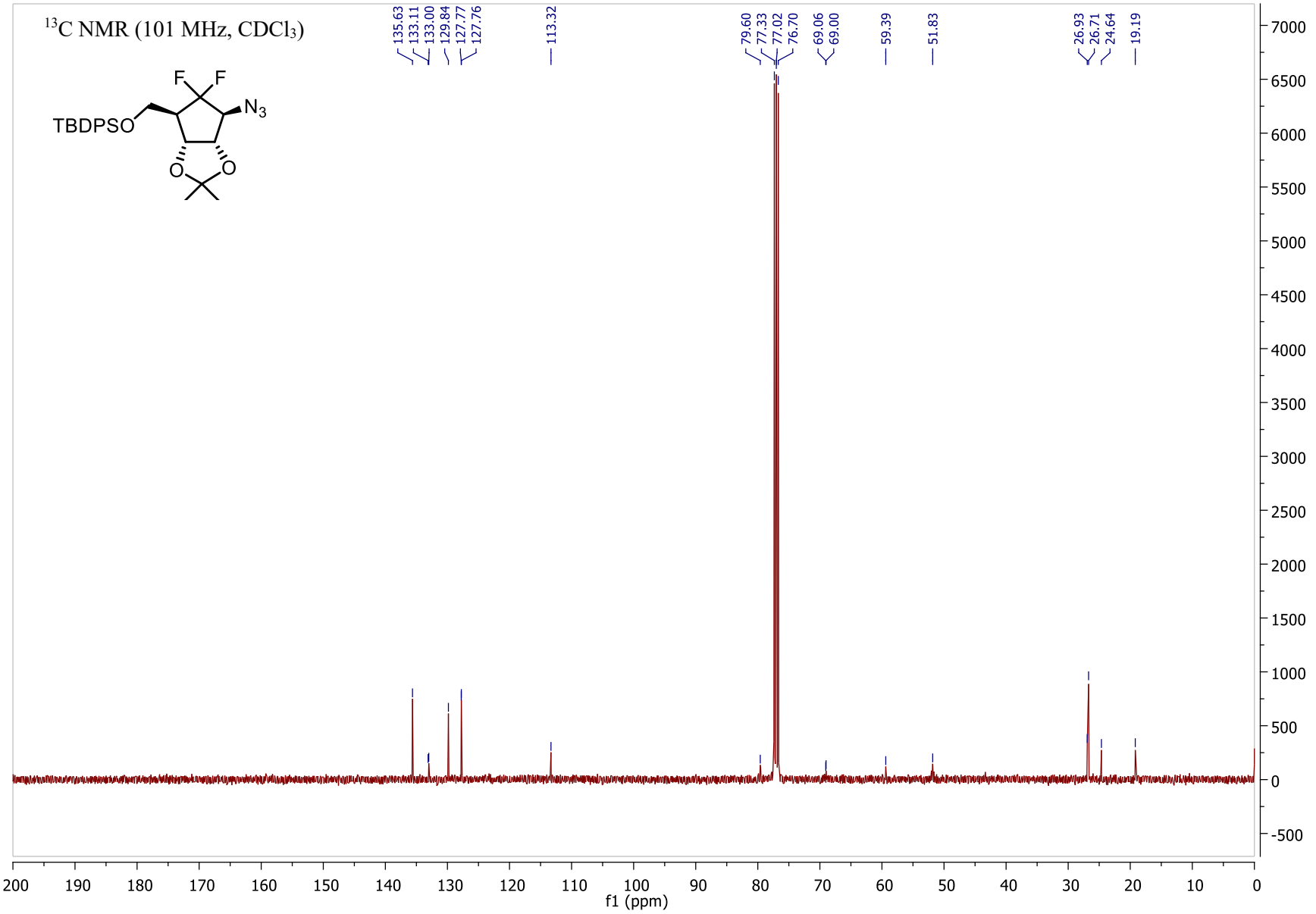


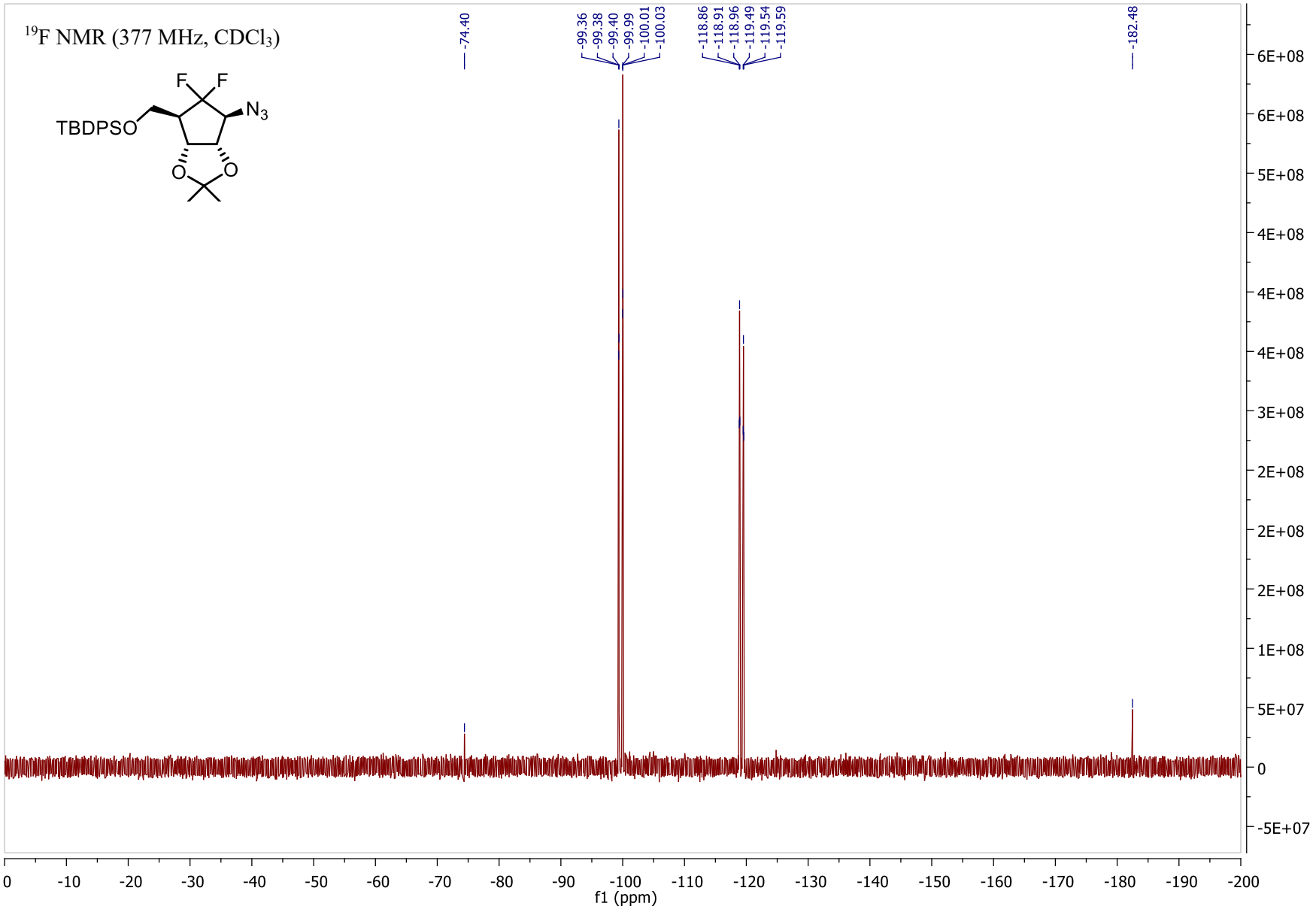

^{1}H NMR (400 MHz, $CDCl_3$)
F
TBDPSO
N_3
O
O
135.59
135.56
133.33
133.12
129.79
127.77
127.74
114.26
97.90
96.07
82.13
79.73
77.34
77.03
76.71
68.16
68.00
60.32
60.25
51.01
50.83
27.12
26.79
24.58
19.23
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


^{19}F NMR (377 MHz, $CDCl_3$)
F
N_3
TBDPSO
O
O
-74.39
-74.76
-74.77
-206.49
-206.56
-206.57
-206.63
-206.65
-206.70
-206.71
-206.79
6E+08
6E+08
6E+08
5E+08
4E+08
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
-5E+07
50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -120 -140 -160 -180 -200 -220 -240
f1 (ppm)

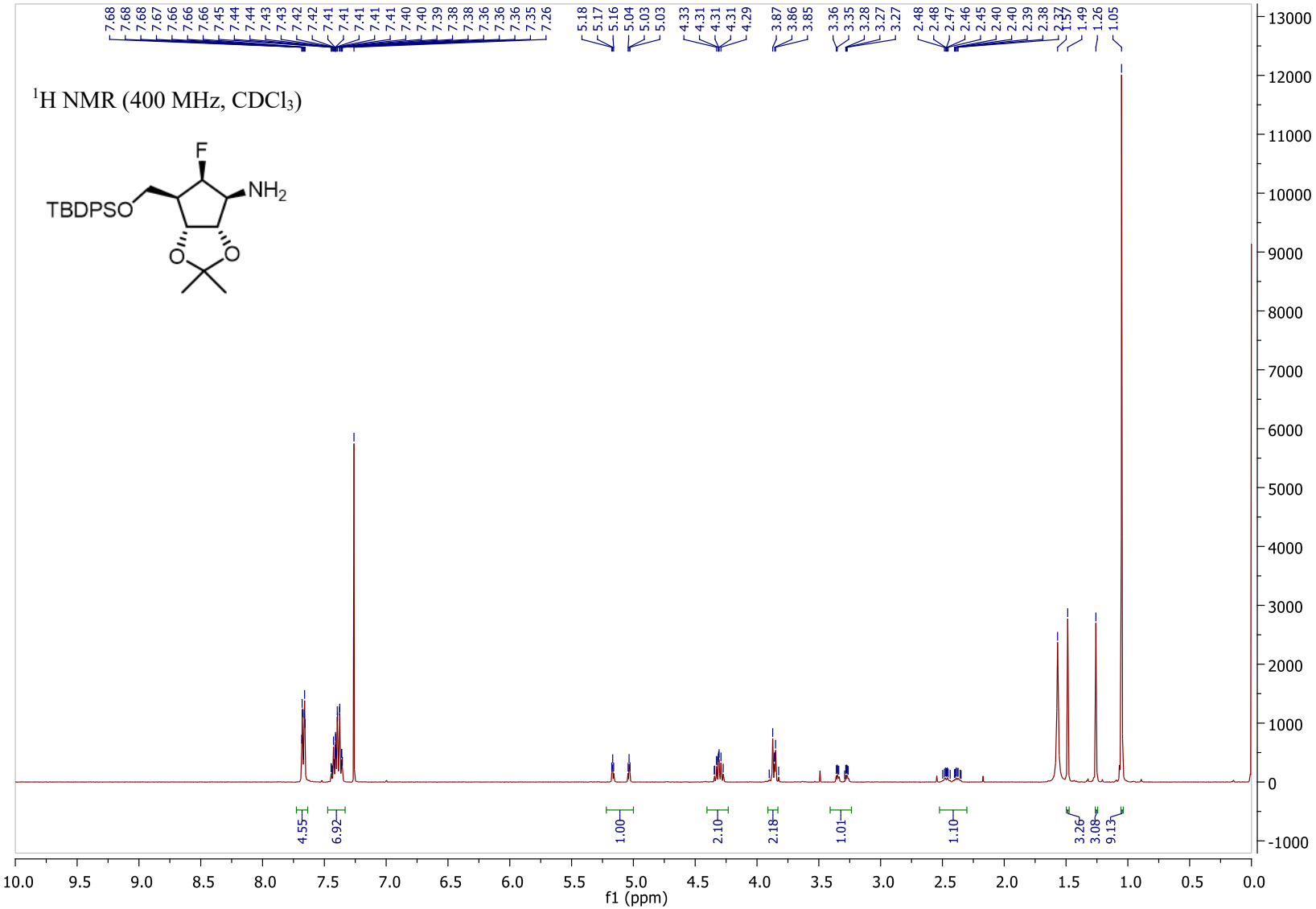
(1S,2S,3R,4S)-1-azido-2,3-*O*-isopropylidine-4-*O*-(*tert*-butyldiphenylsilyl)methyl-6-*gem*-difluorocyclopentane, 19

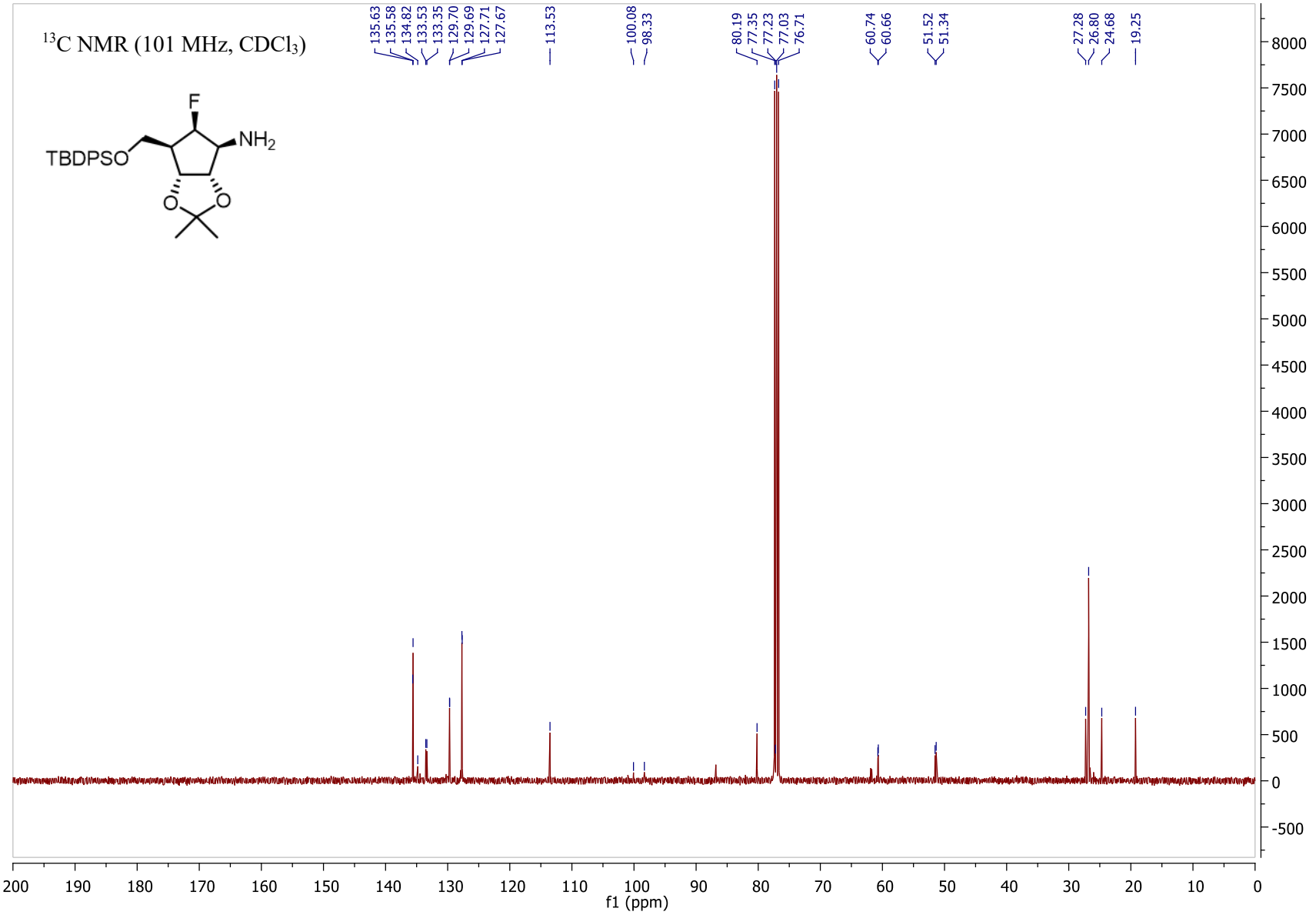



^{13}C NMR (101 MHz, $CDCl_3$)
F
F
N_3
TBDPSO
O
O
135.63
133.11
133.00
129.84
127.77
127.76
113.32
79.60
77.33
77.02
76.70
69.06
69.00
59.39
51.83
26.93
26.71
24.64
19.19
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

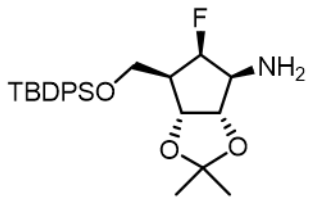

^{19}F NMR (377 MHz, $CDCl_3$)
F
F
N3
TBDPSO
O
O
-74.40
-99.36
-99.38
-99.40
-99.99
-100.01
-100.03
-118.86
-118.91
-118.96
-119.49
-119.54
-119.59
-182.48
6E+08
6E+08
5E+08
4E+08
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
-5E+07
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

(1S,2S,3R,4S,6R)-1-amino-2,3-*O*-isopropylidine-4-*O*-(*tert*-butyldiphenylsilyl)methyl-6-fluorocyclopentane

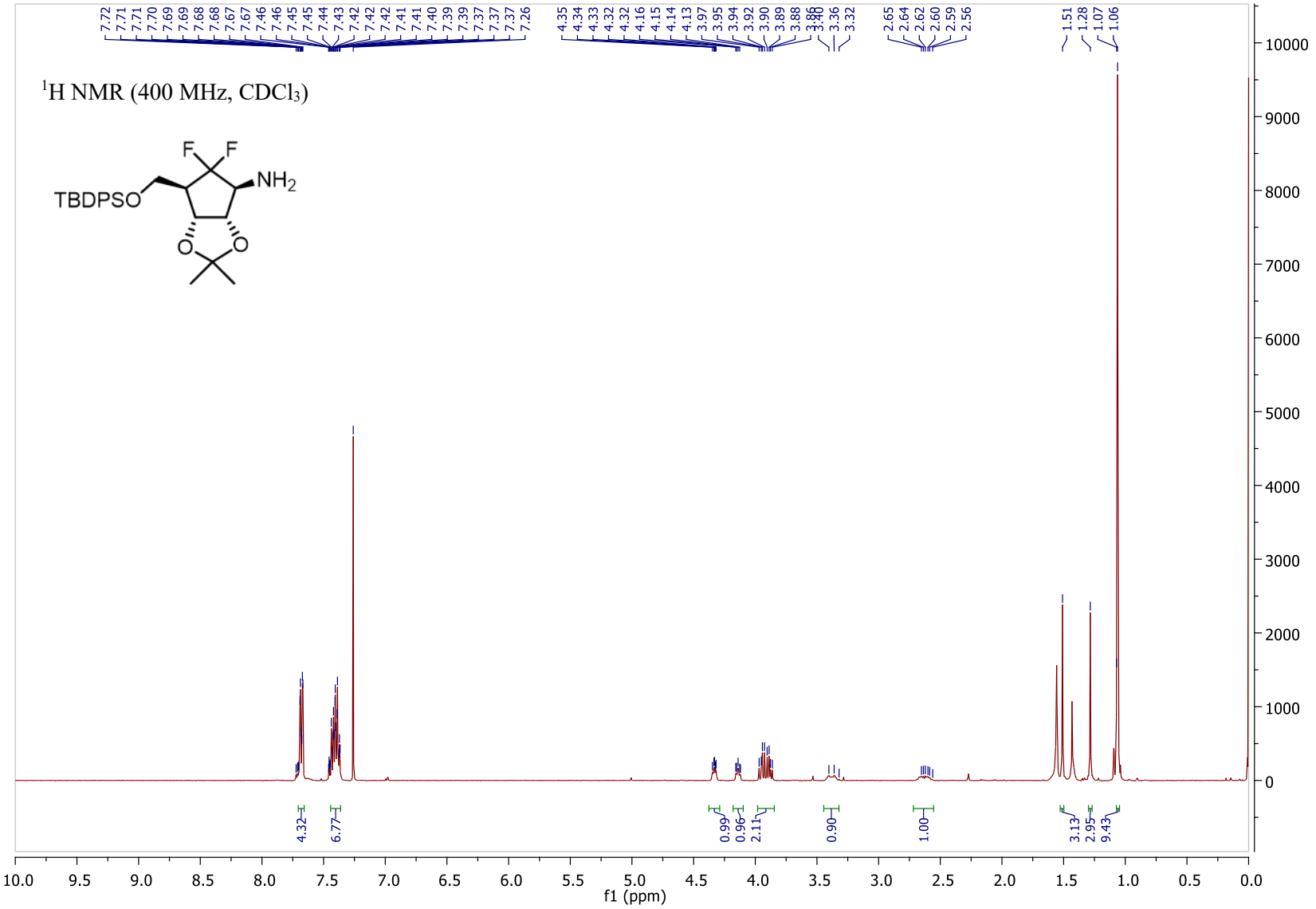


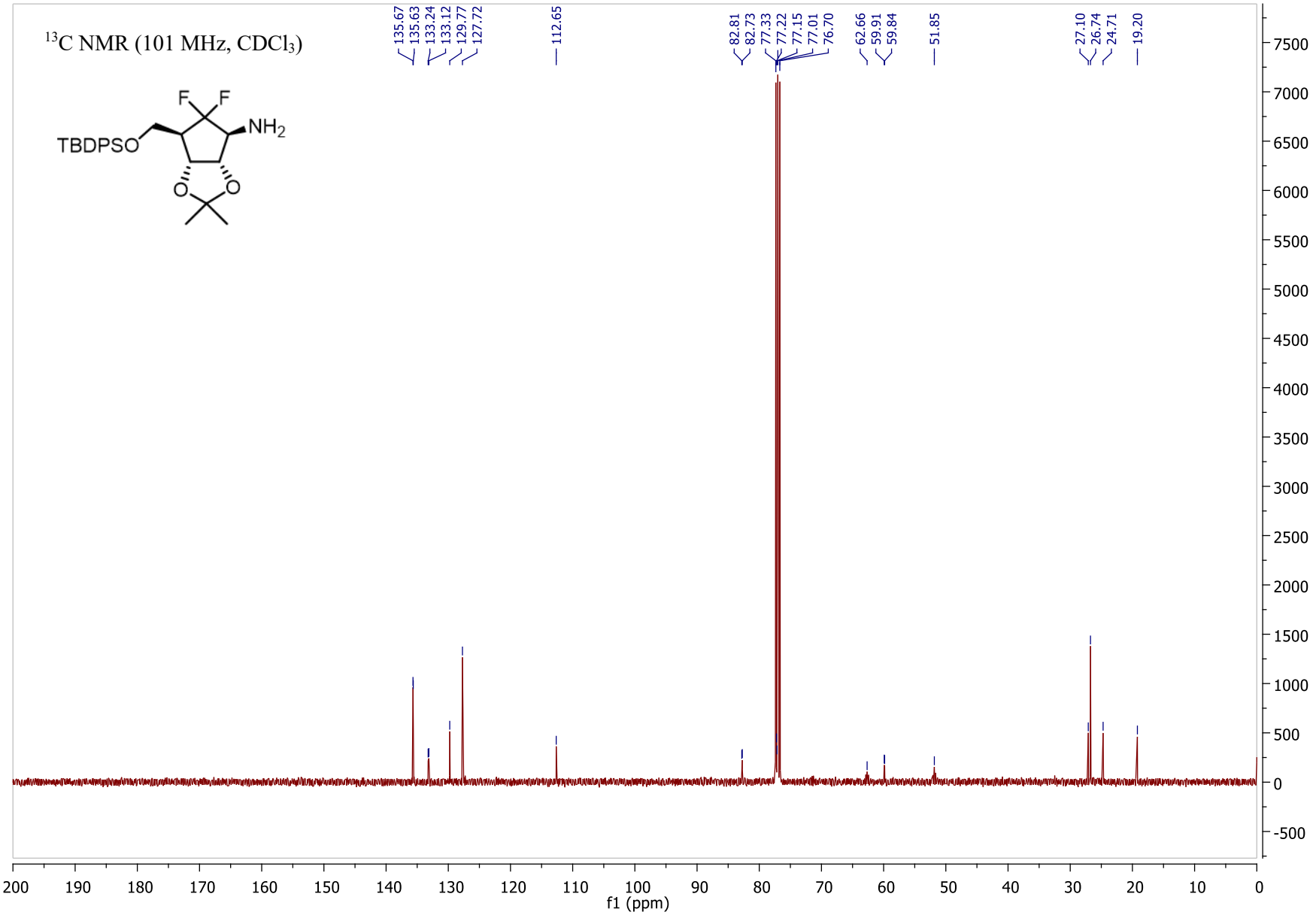

^{13}C NMR (101 MHz, $CDCl_3$)
F
TBDPSO
NH_2
O
O
135.63
135.58
134.82
133.53
133.35
129.70
129.69
127.71
127.67
113.53
100.08
98.33
80.19
77.35
77.23
77.03
76.71
60.74
60.66
51.52
51.34
27.28
26.80
24.68
19.25
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

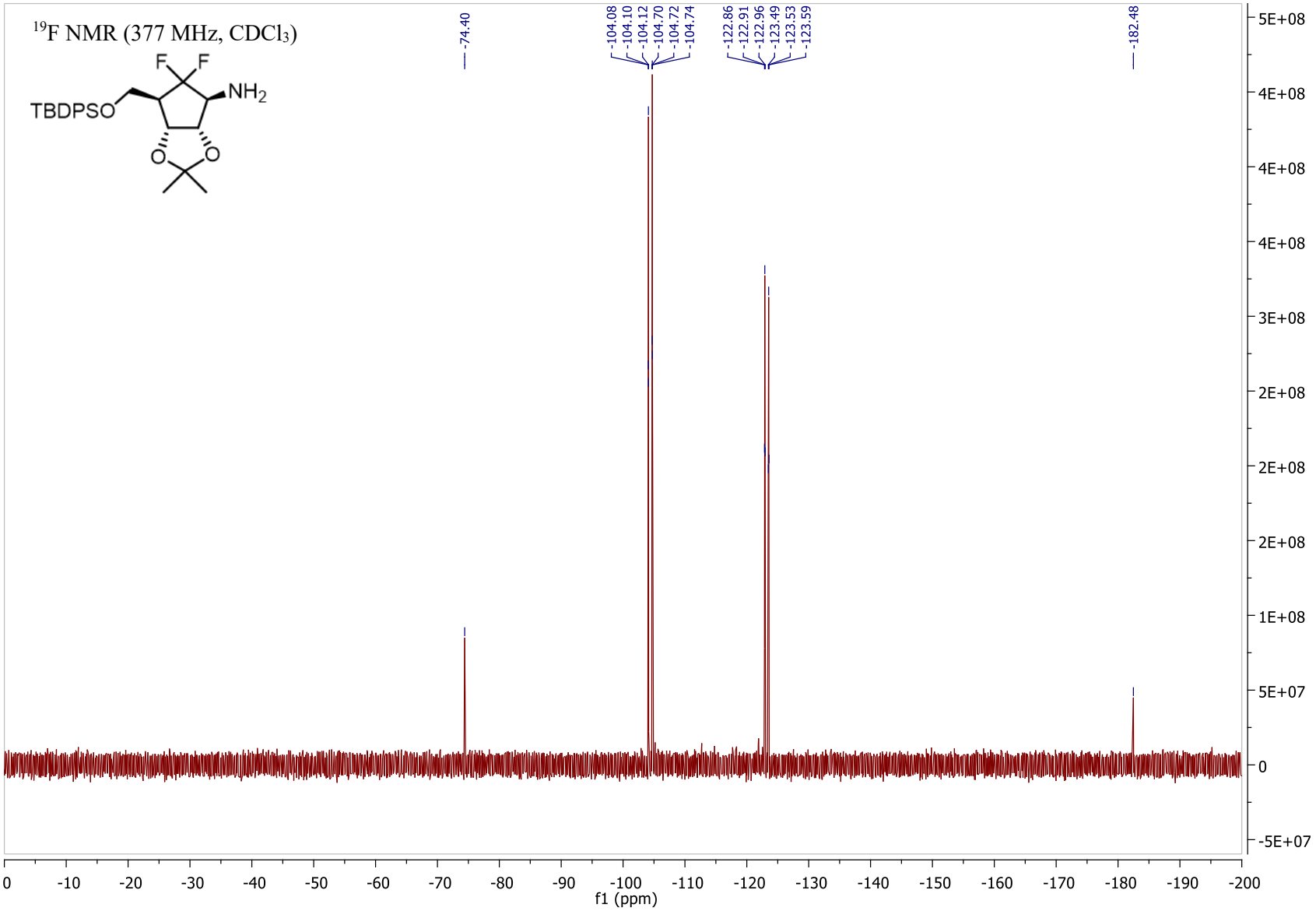
^{19}F NMR (377 MHz, $CDCl_3$)



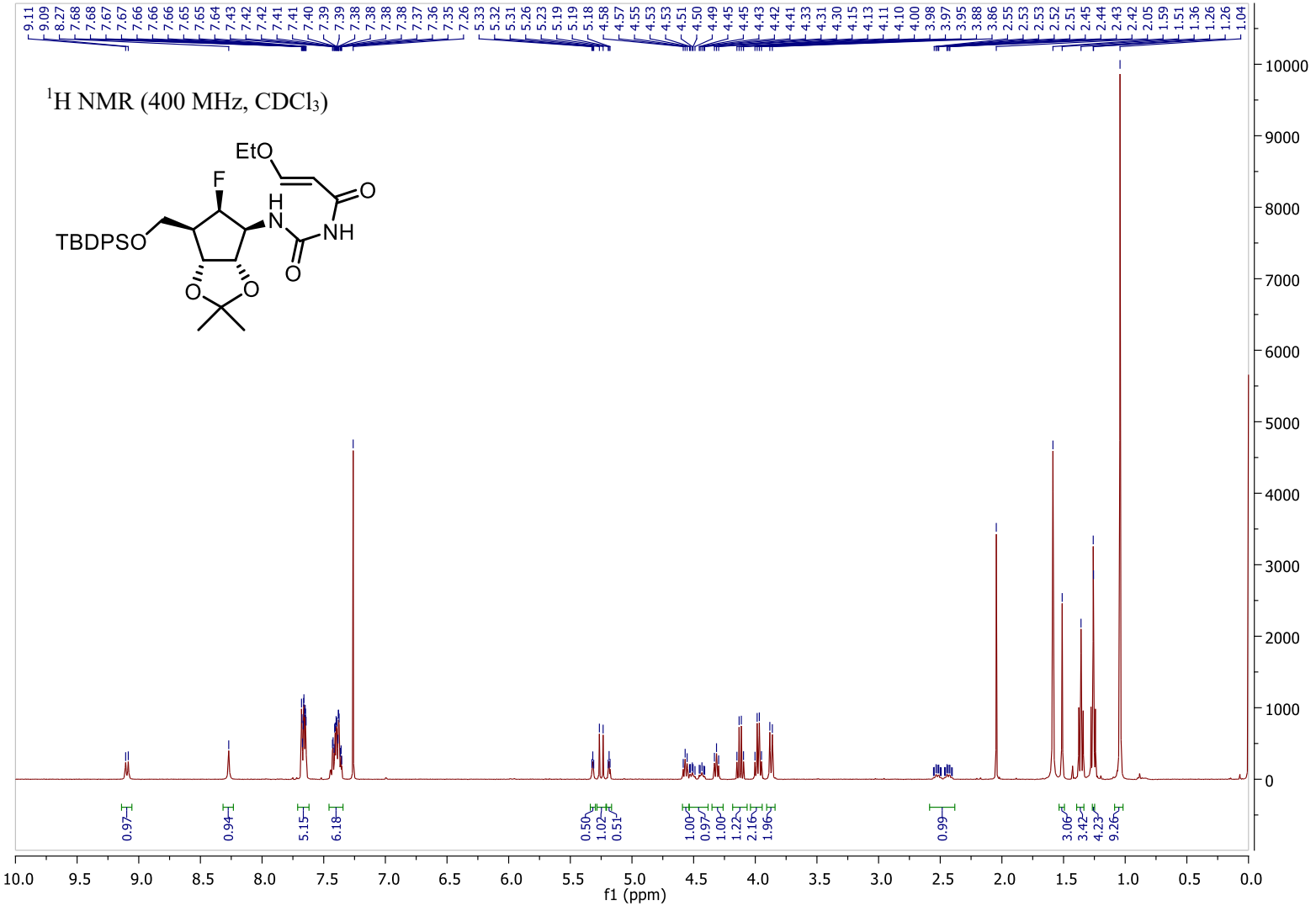
(1S,2S,3R,4S)-1-amino-2,3-*O*-isopropylidine-4-*O*-(*tert*-butyldiphenylsilyl)methyl-6-*gem*-difluorocyclopentane

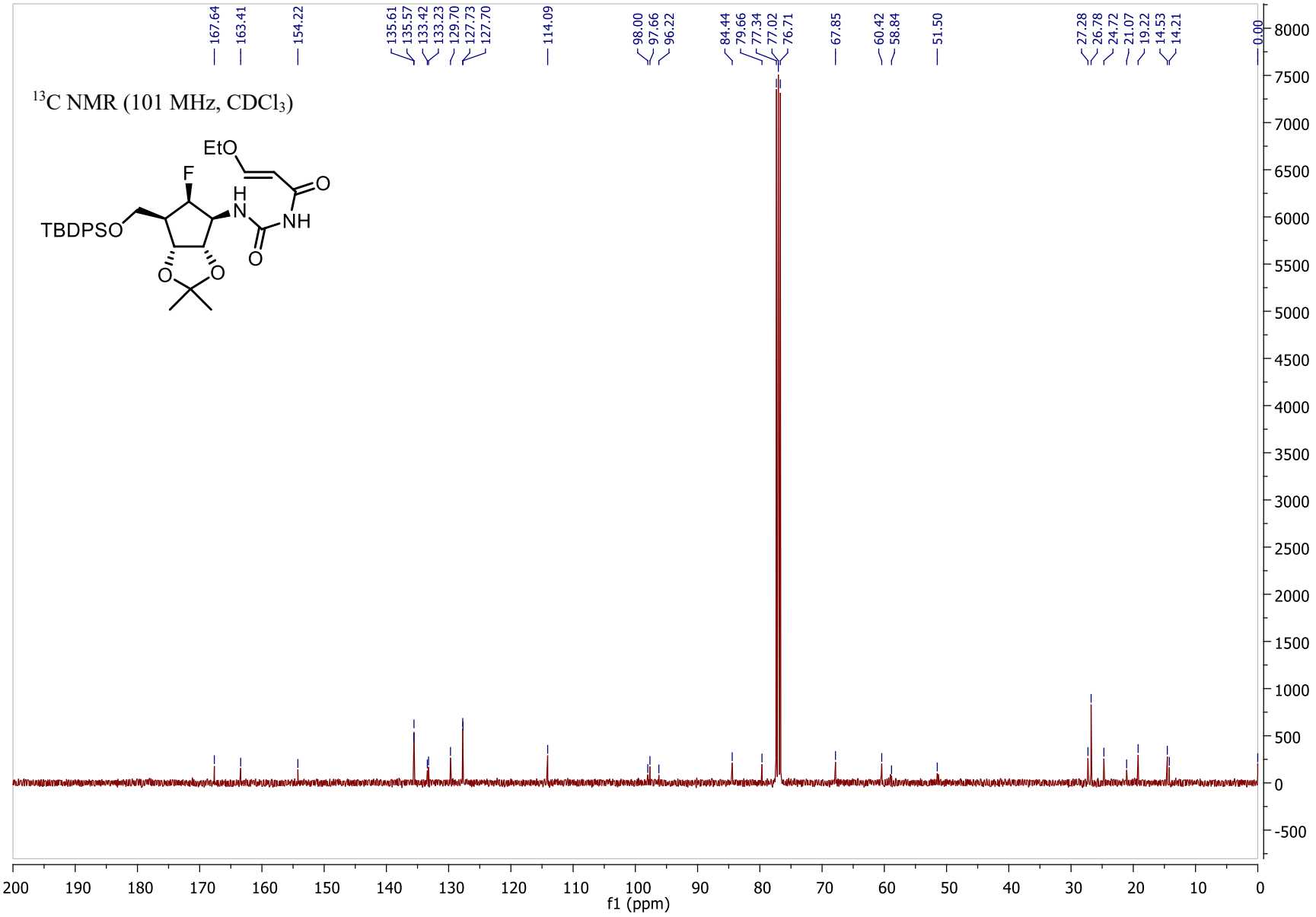


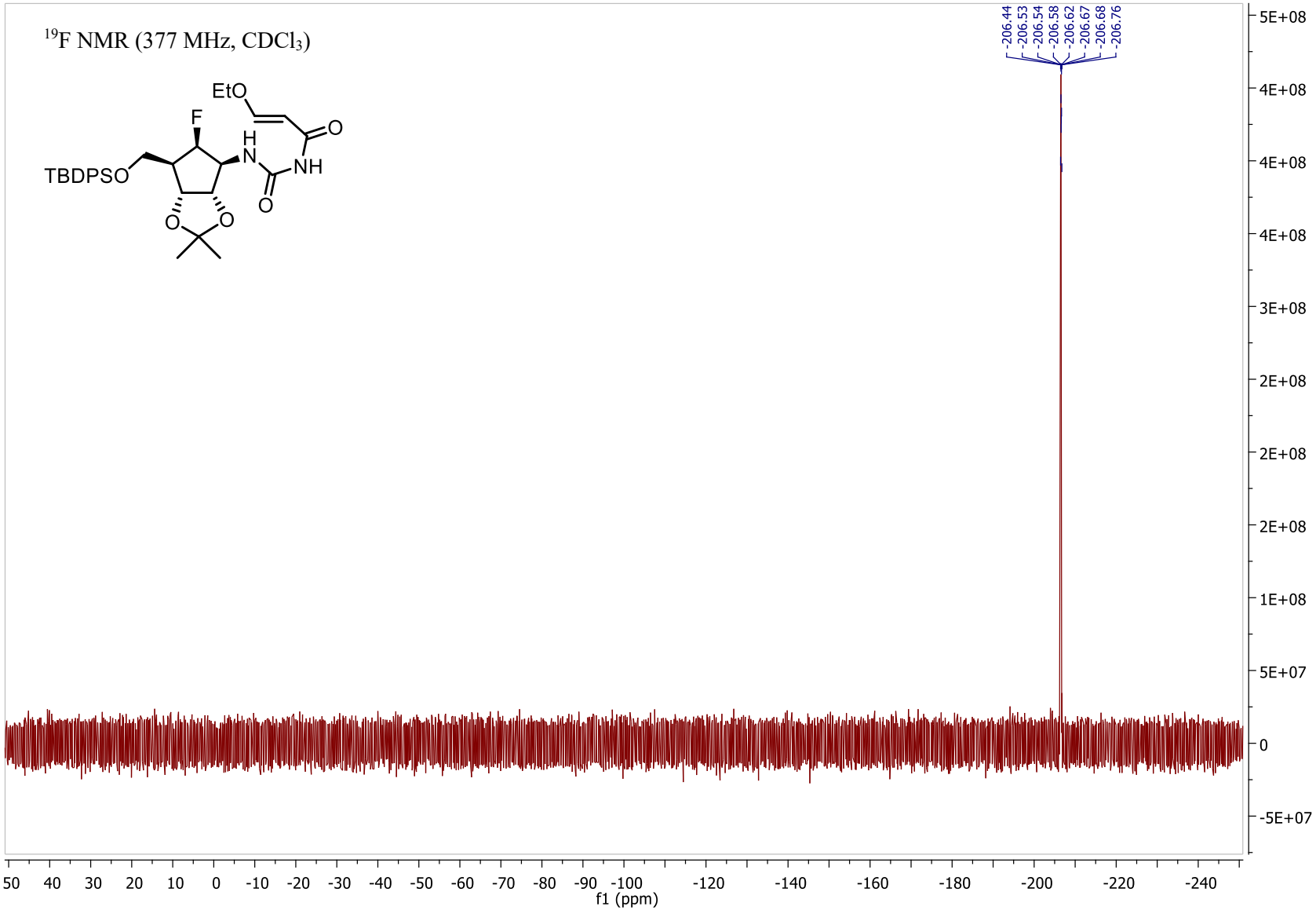

^{13}C NMR (101 MHz, $CDCl_3$)
F
F
NH2
TBDPSO
O
O
135.67
135.63
133.24
133.12
129.77
127.72
112.65
82.81
82.73
77.33
77.22
77.15
77.01
76.70
62.66
59.91
59.84
51.85
27.10
26.74
24.71
19.20
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


^{19}F NMR (377 MHz, CDCl$_3$)
F
F
NH$_2$
TBDPSO
O
O
-74.40
-104.08
-104.10
-104.12
-104.70
-104.72
-104.74
-122.86
-122.91
-122.96
-123.49
-123.53
-123.59
-182.48
5E+08
4E+08
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
-5E+07
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

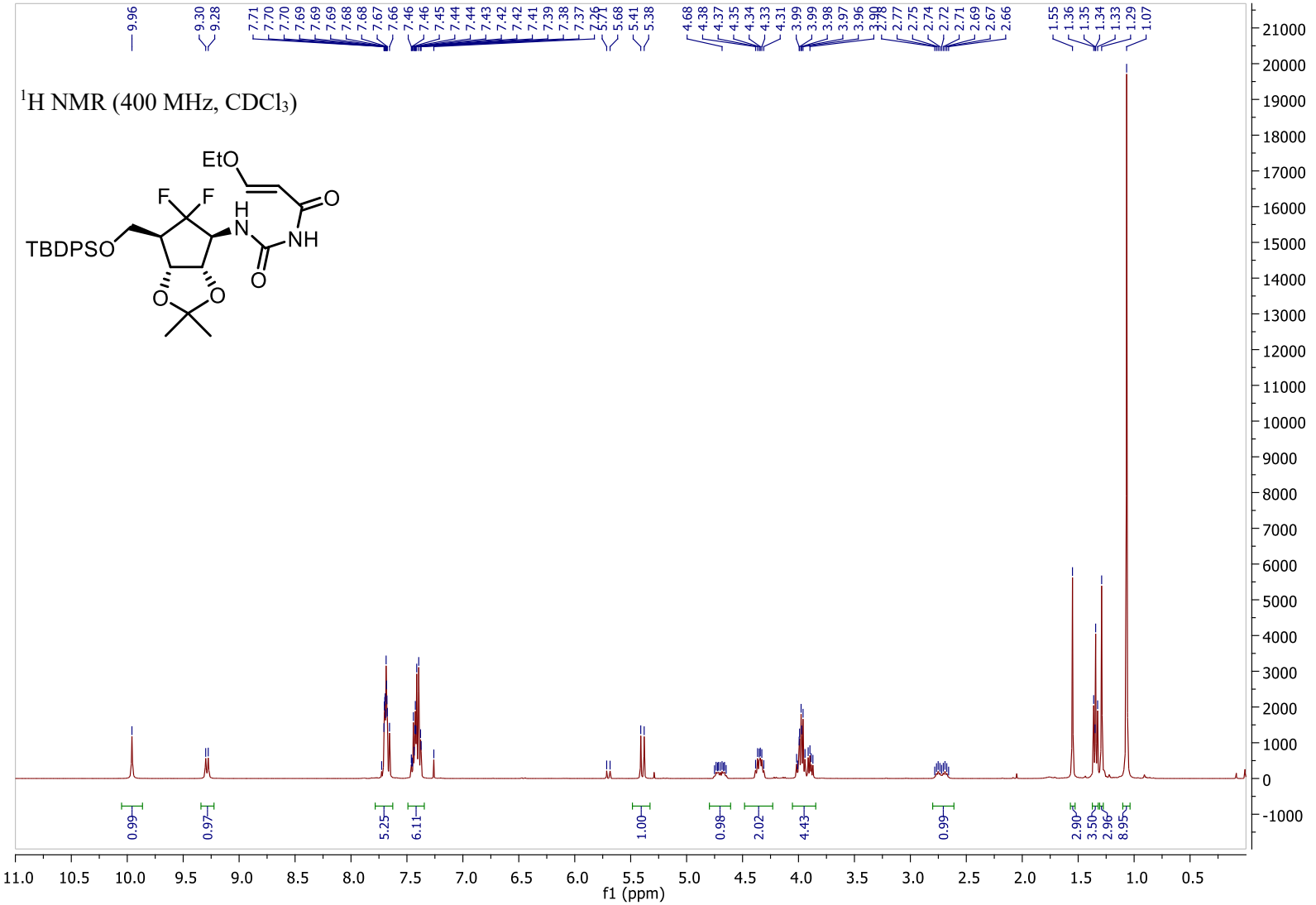
(1'S,2'S,3'R,4'S,6'R)-1'-(6-ethoxyacryloylurea)-2',3'-*O*-isopropylidine-4'-*O*-(*tert*-butyldiphenylsilyl)methyl-6'-fluorocyclopentane, 20

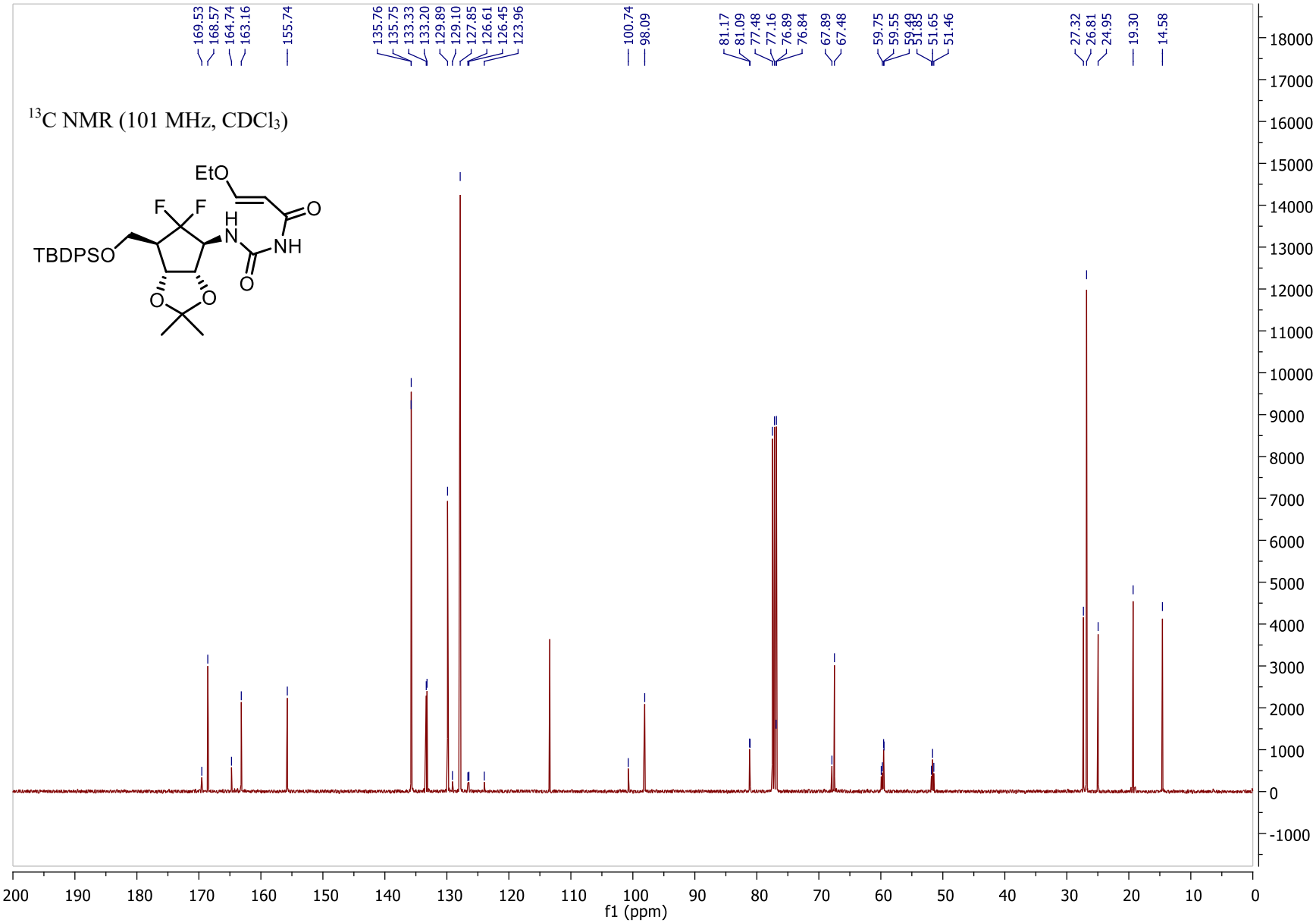


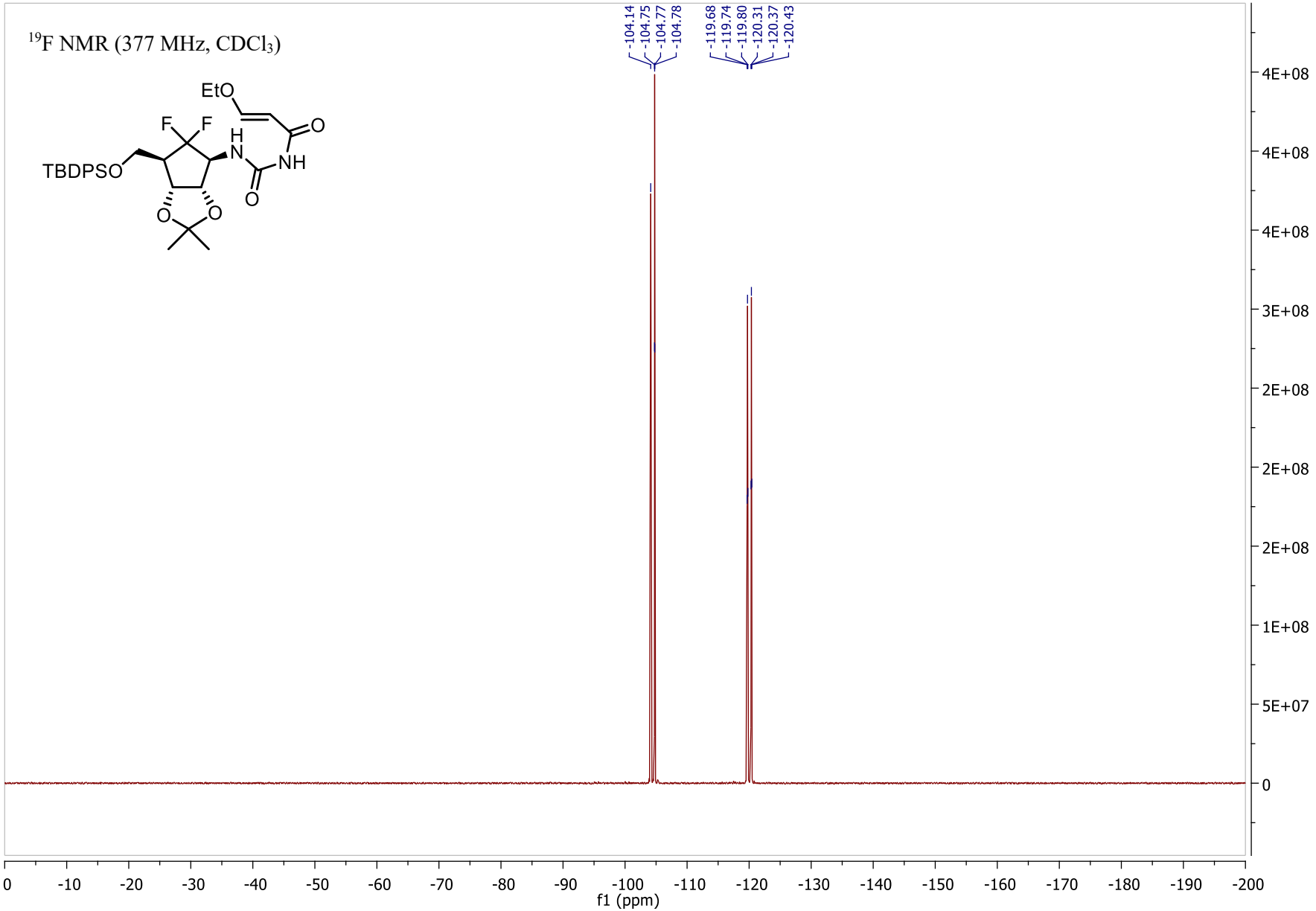

167.64
163.41
154.22
135.61
135.57
133.42
133.23
129.70
127.73
127.70
114.09
98.00
97.66
96.22
84.44
79.66
77.34
77.02
76.71
67.85
60.42
58.84
51.50
27.28
26.78
24.72
21.07
19.22
14.53
14.21
0.00
13C NMR (101 MHz, CDCl3)
EtO
F
H
N
NH
O
O
TBDPSO
O
O
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


^{19}F NMR (377 MHz, $CDCl_3$)
EtO
F
H
N
O
NH
O
TBDPSO
O
O
-206.44
-206.53
-206.54
-206.58
-206.62
-206.67
-206.68
-206.76
5E+08
4E+08
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
-5E+07
50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -120 -140 -160 -180 -200 -220 -240
f1 (ppm)

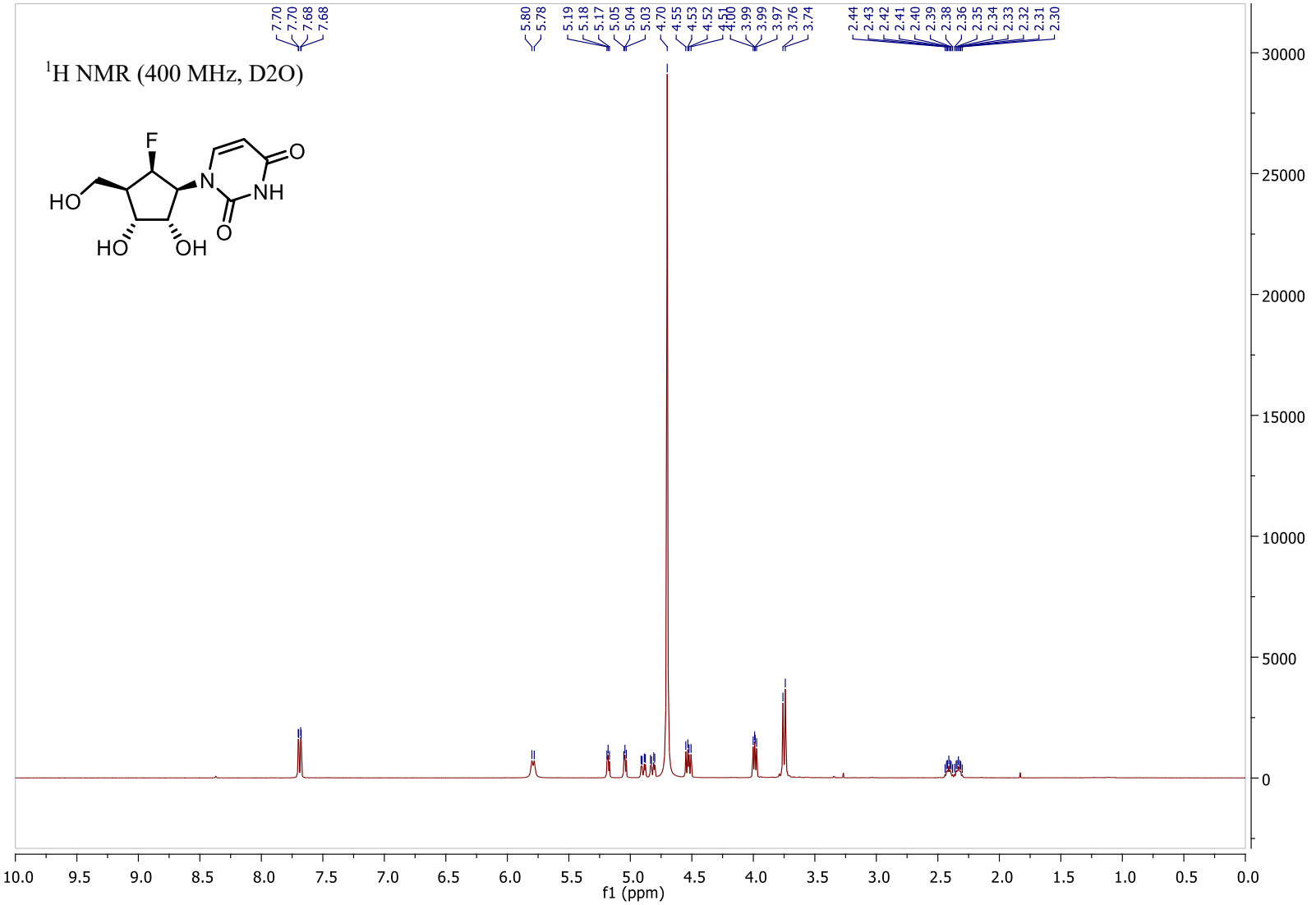
(1'S,2'S,3'R,4'S)-1'-(6-ethoxyacryloylurea)-2',3'-*O*-isopropylidine-4'-*O*-(*tert*-butyldiphenylsilyl)methyl-6'-*gem*-difluorocyclopentane, 21

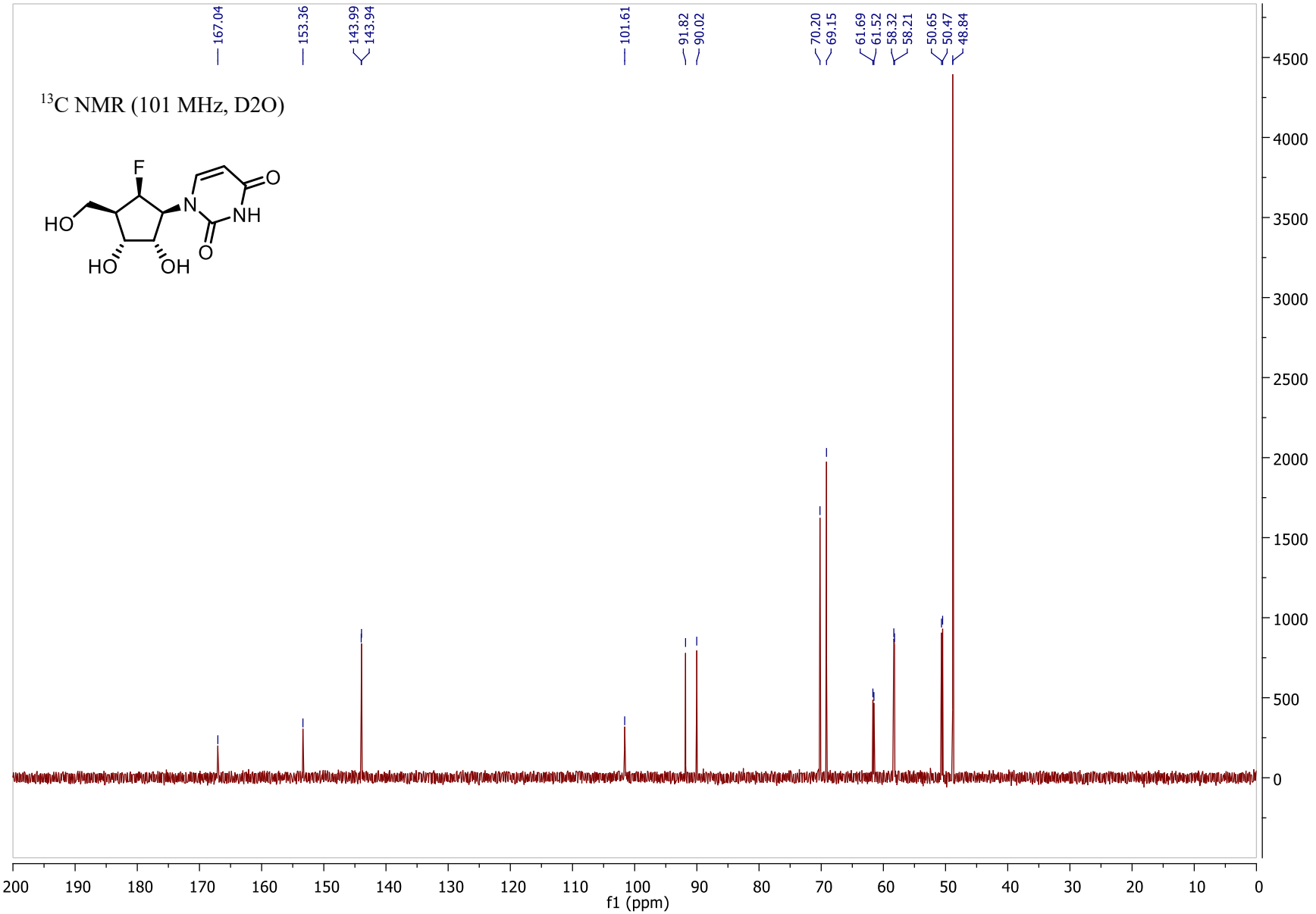


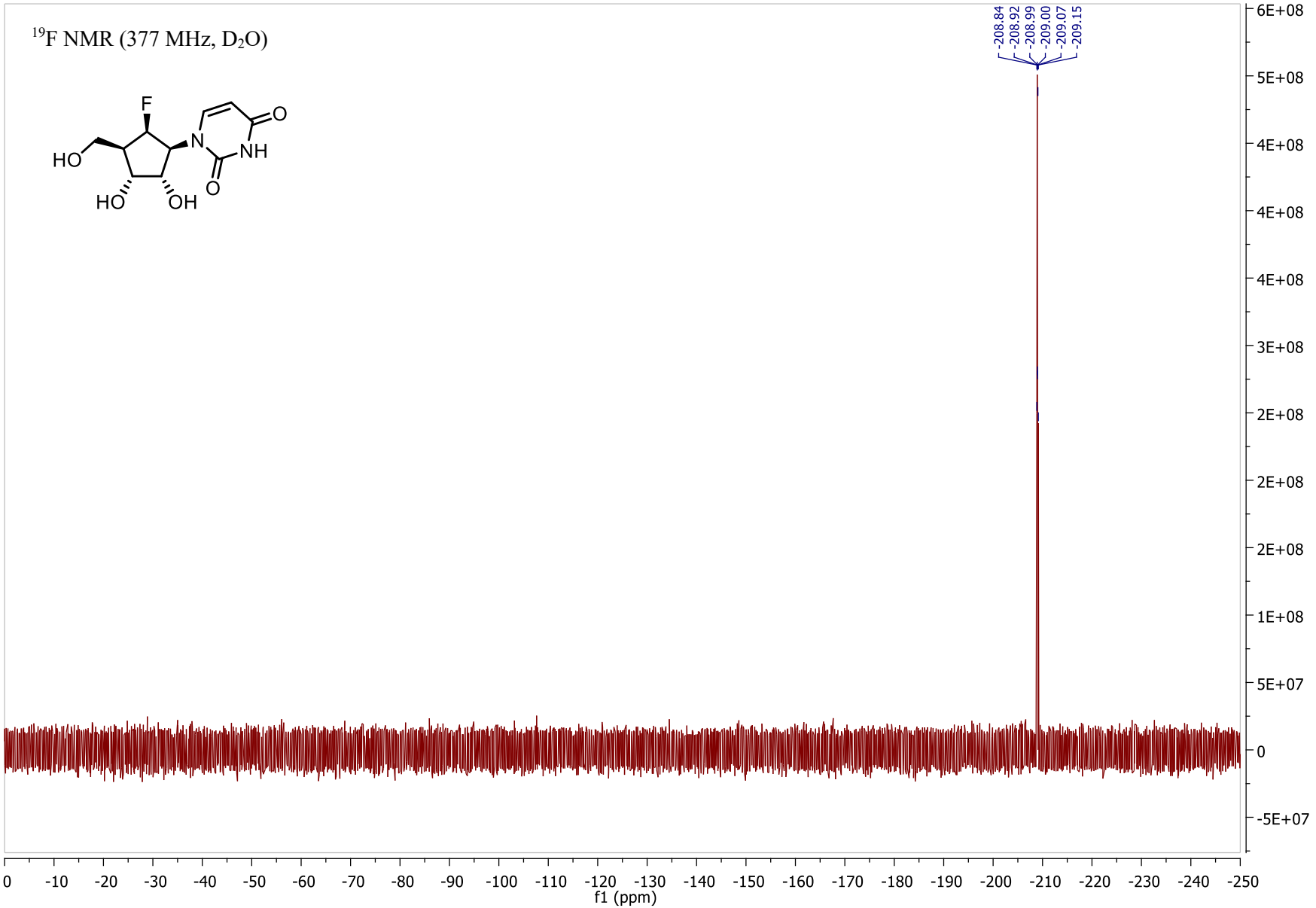

169.53
168.57
164.74
163.16
155.74
135.76
135.75
133.33
133.20
129.89
129.10
127.85
126.61
126.45
123.96
100.74
98.09
81.17
81.09
77.48
77.16
76.89
76.84
67.89
67.48
59.75
59.55
59.49
51.85
51.65
51.46
27.32
26.81
24.95
19.30
14.58
^{13}C NMR (101 MHz, CDCl$_3$)
EtO
F
F
H
N
O
NH
O
TBDPSO
O
O
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


^{19}F NMR (377 MHz, $CDCl_3$)
EtO
F
F
H
N
O
NH
O
TBDPSO
O
O
-104.14
-104.75
-104.77
-104.78
-119.68
-119.74
-119.80
-120.31
-120.37
-120.43
4E+08
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

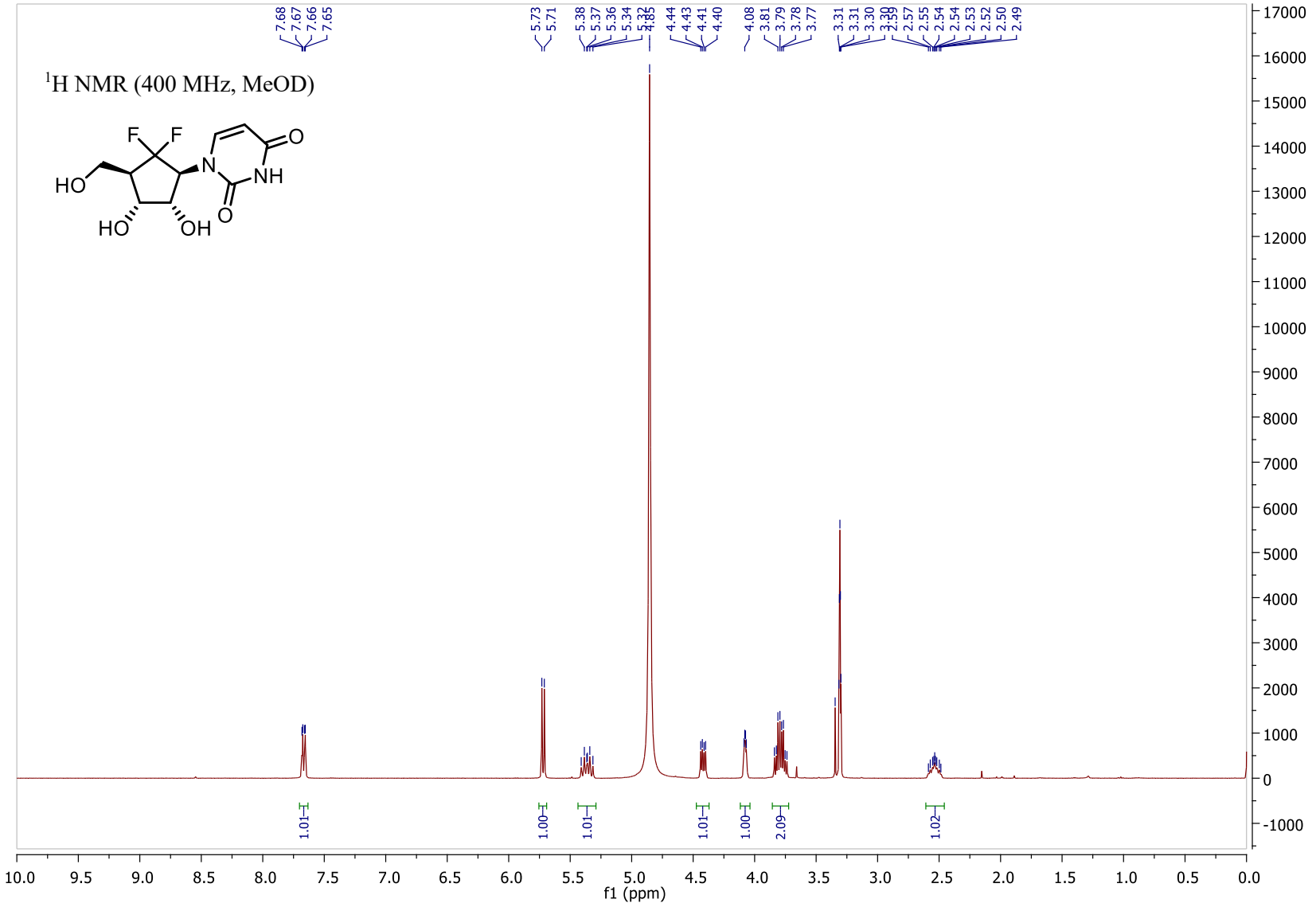
(6'R)-6'-fluorocarbauridine, 22

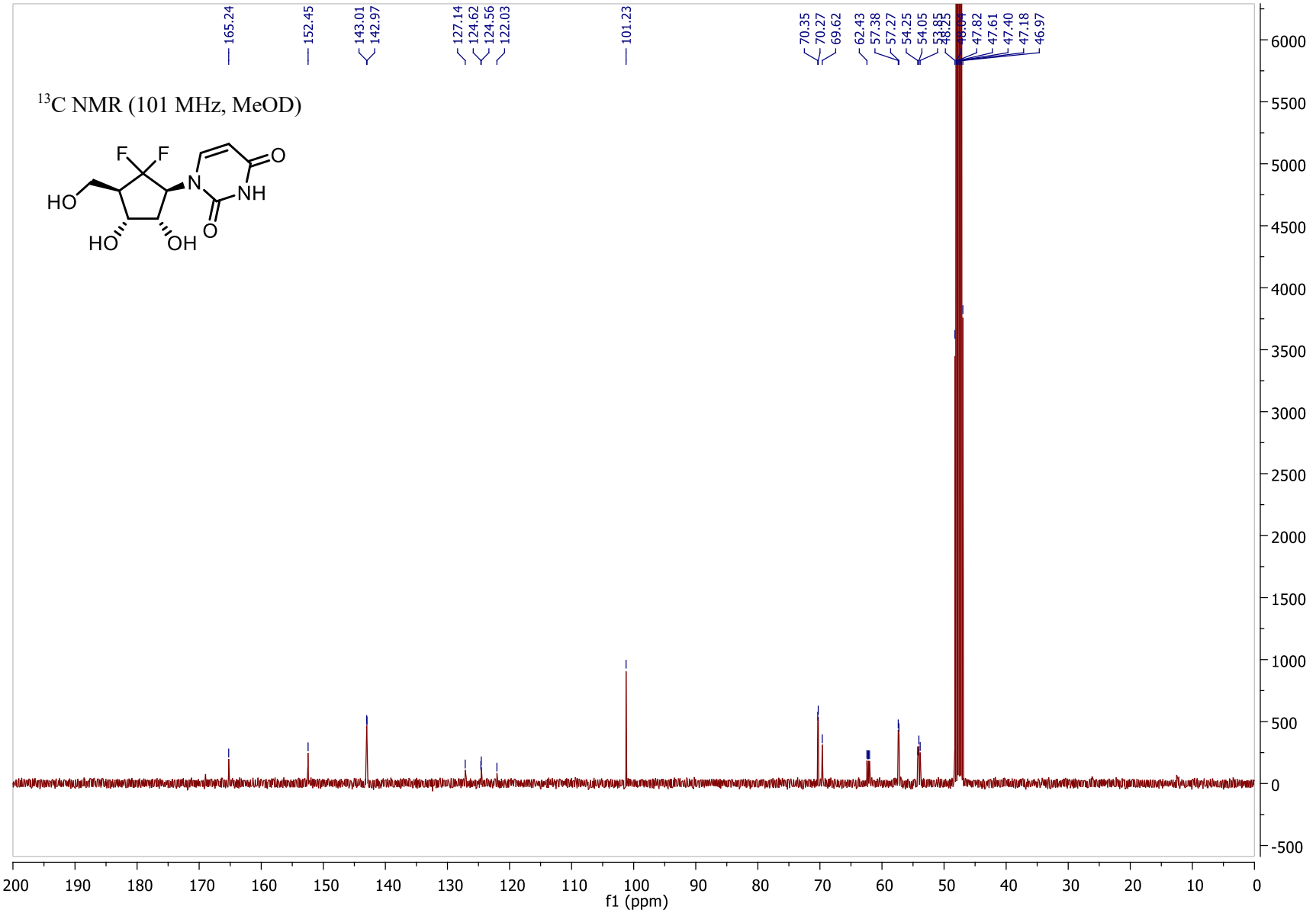


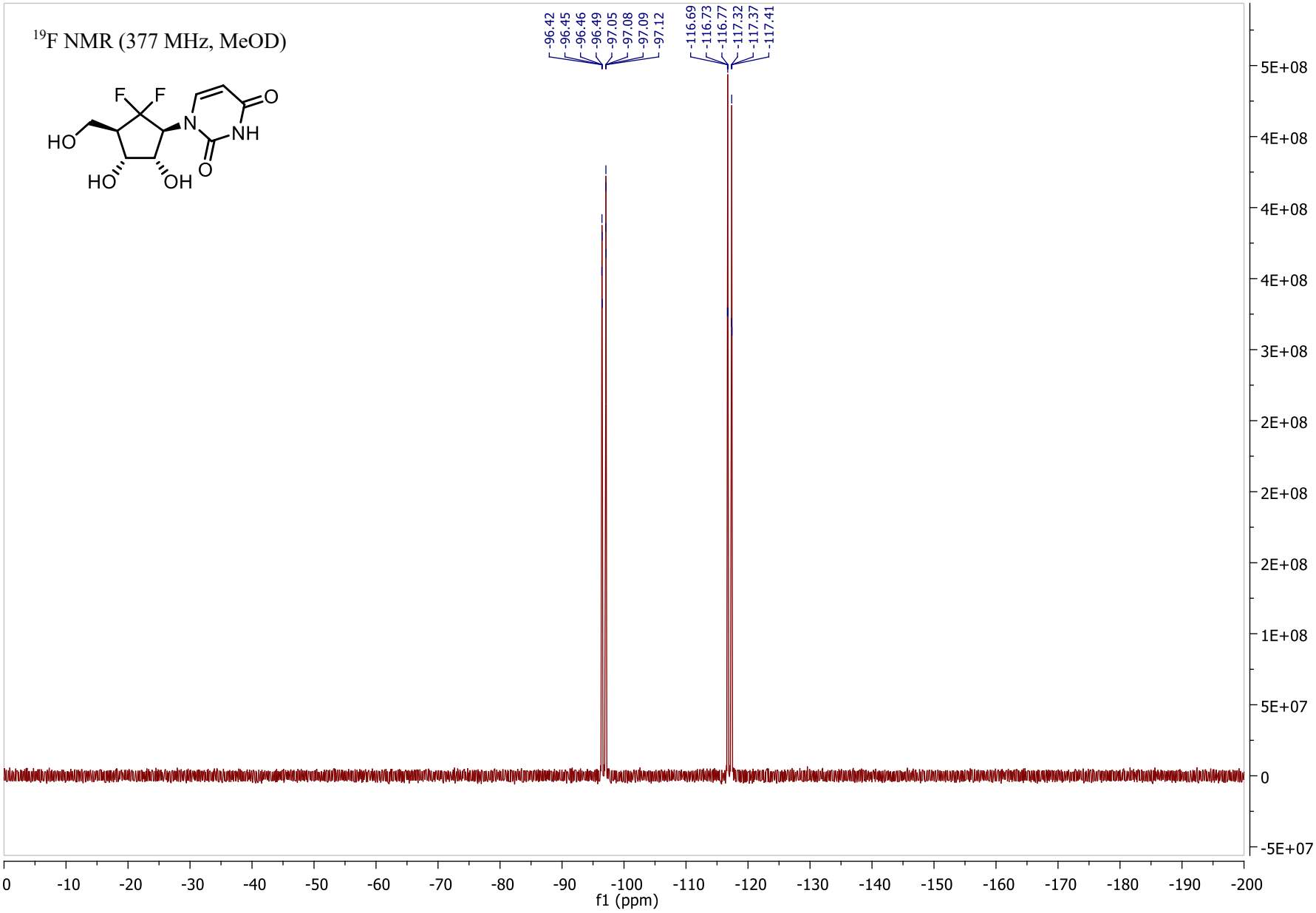

167.04
153.36
143.99
143.94
101.61
91.82
90.02
70.20
69.15
61.69
61.52
58.32
58.21
50.65
50.47
48.84
13C NMR (101 MHz, D2O)
F
HO
HO
OH
N
NH
O
O
4500
4000
3500
3000
2500
2000
1500
1000
500
0
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


19F NMR (377 MHz, D2O)
F
HO
N
NH
O
O
HO
OH
-208.84
-208.92
-208.99
-209.00
-209.07
-209.15
6E+08
5E+08
4E+08
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
-5E+07
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250
f1 (ppm)

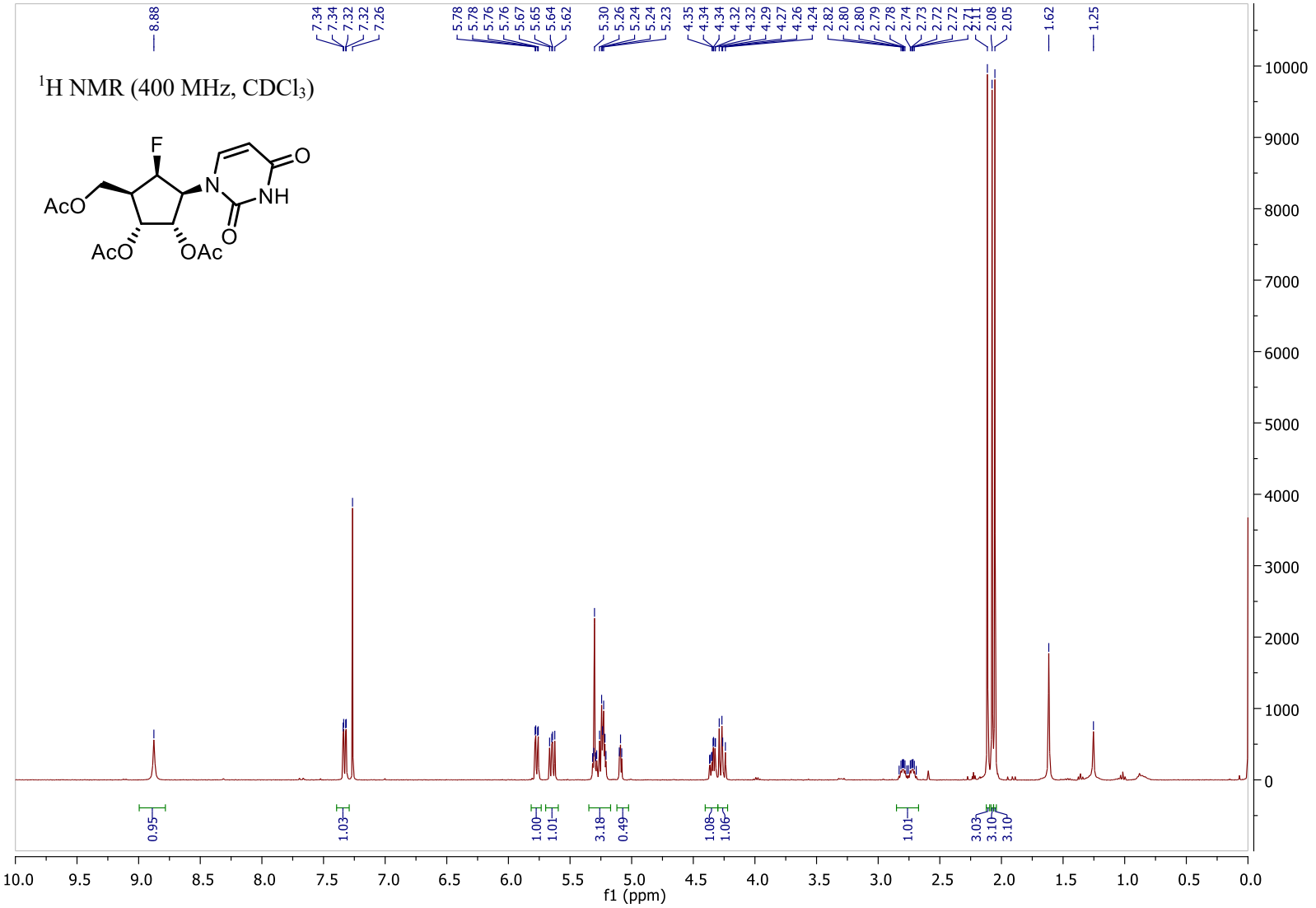
6'-*gem*-difluorocarbauridine, 23

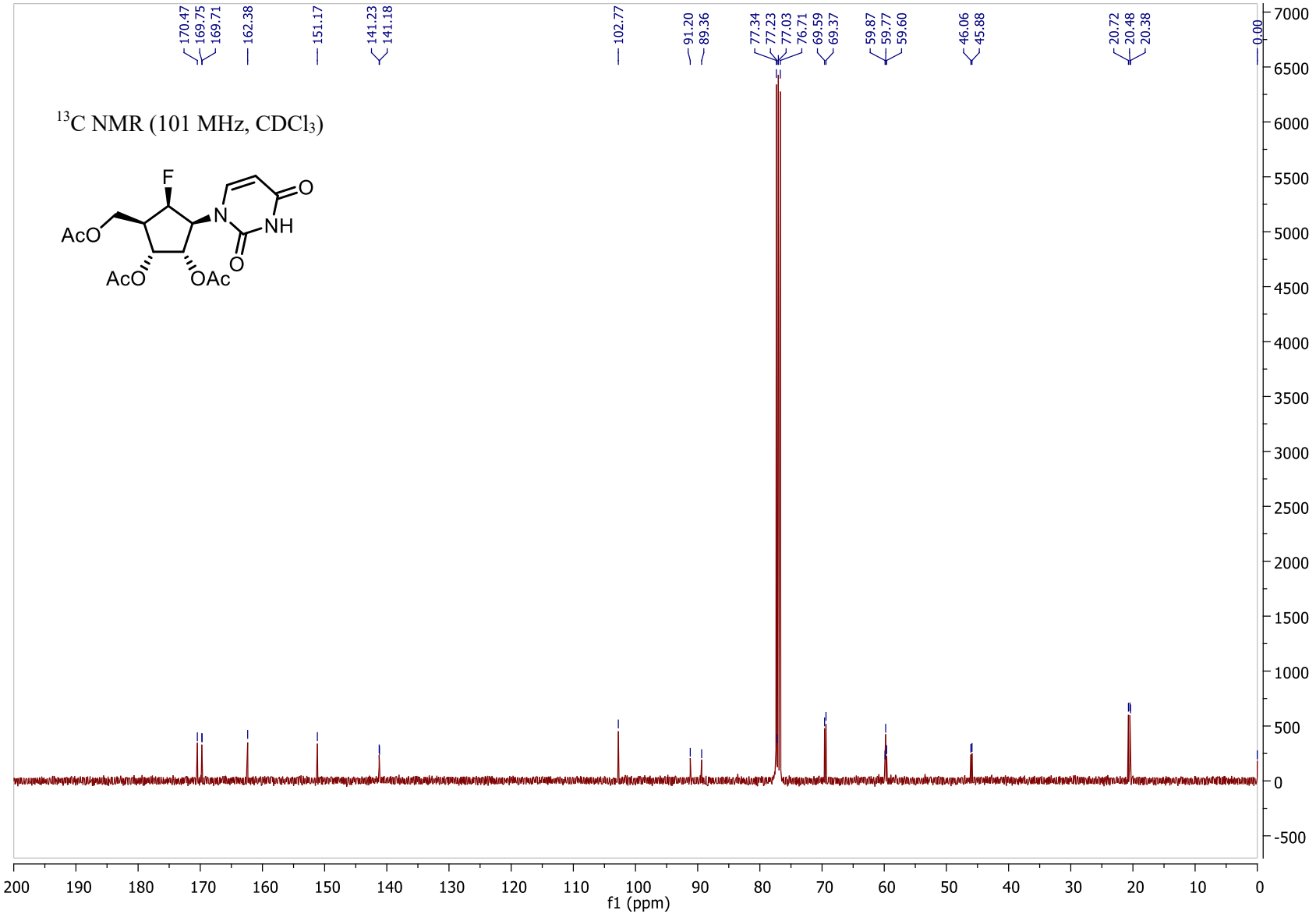


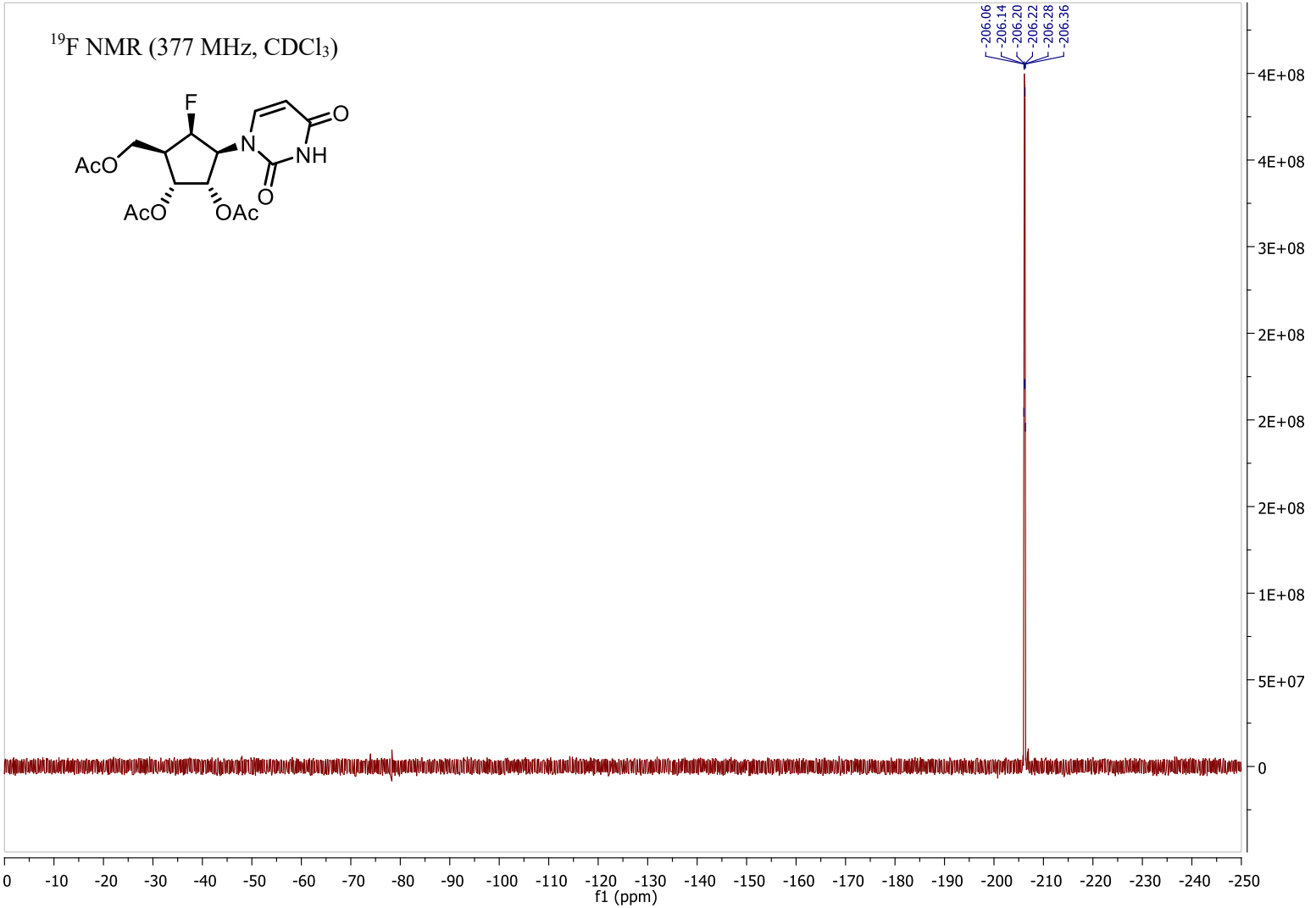

165.24
152.45
143.01
142.97
127.14
124.62
124.56
122.03
101.23
70.35
70.27
69.62
62.43
57.38
57.27
54.25
54.05
47.82
47.61
47.40
47.18
46.97
^{13}C NMR (101 MHz, MeOD)
F
F
O
N
NH
HO
HO
OH
O
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


^{19}F NMR (377 MHz, MeOD)
F
F
HO
HO
OH
N
NH
O
O
-96.42
-96.45
-96.46
-96.49
-97.05
-97.08
-97.09
-97.12
-116.69
-116.73
-116.77
-117.32
-117.37
-117.41
5E+08
4E+08
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
-5E+07
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

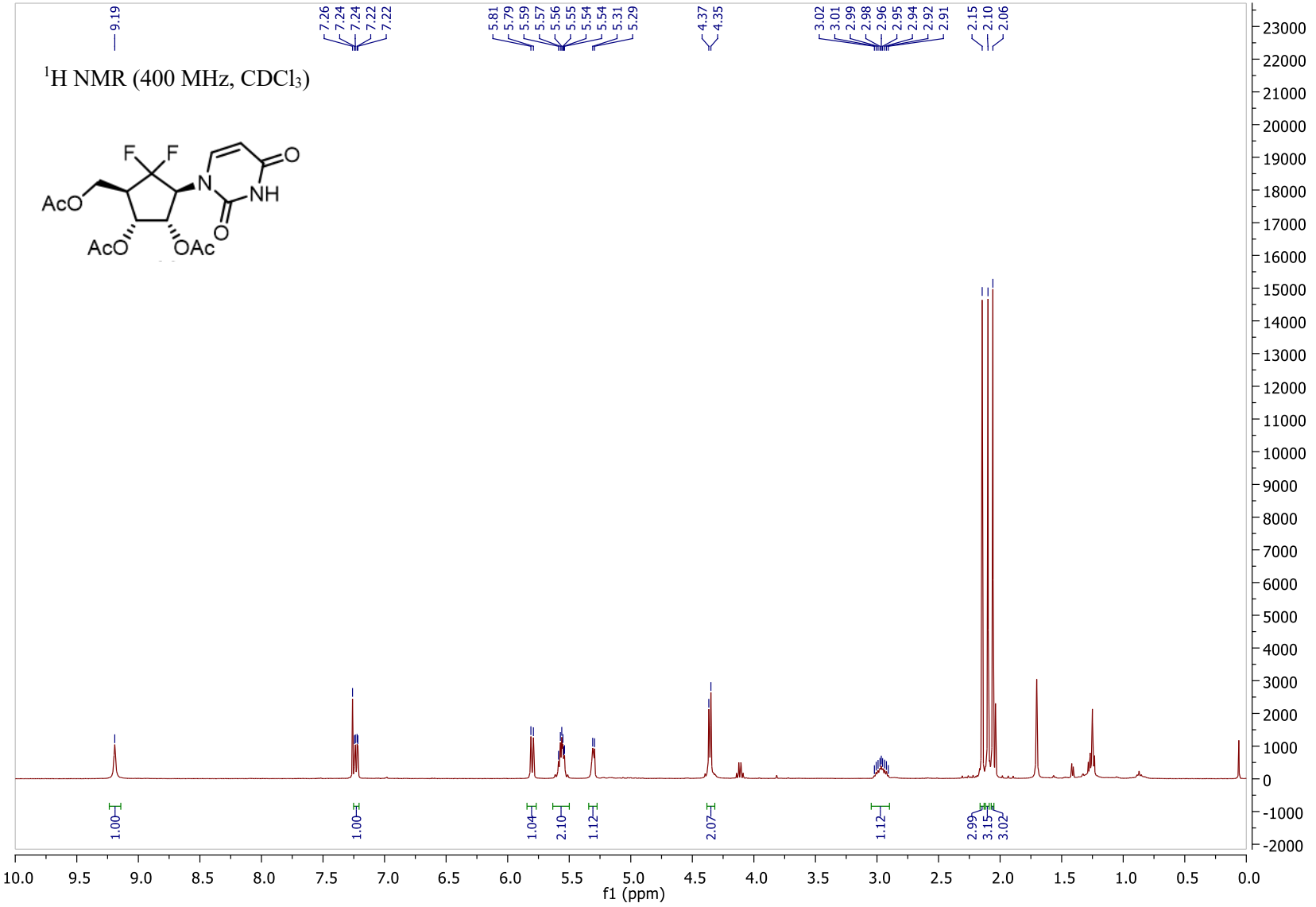
(6'R)-2',3',5'-tri-*O*-acetatyl-6'-fluorocarbauridine, 24

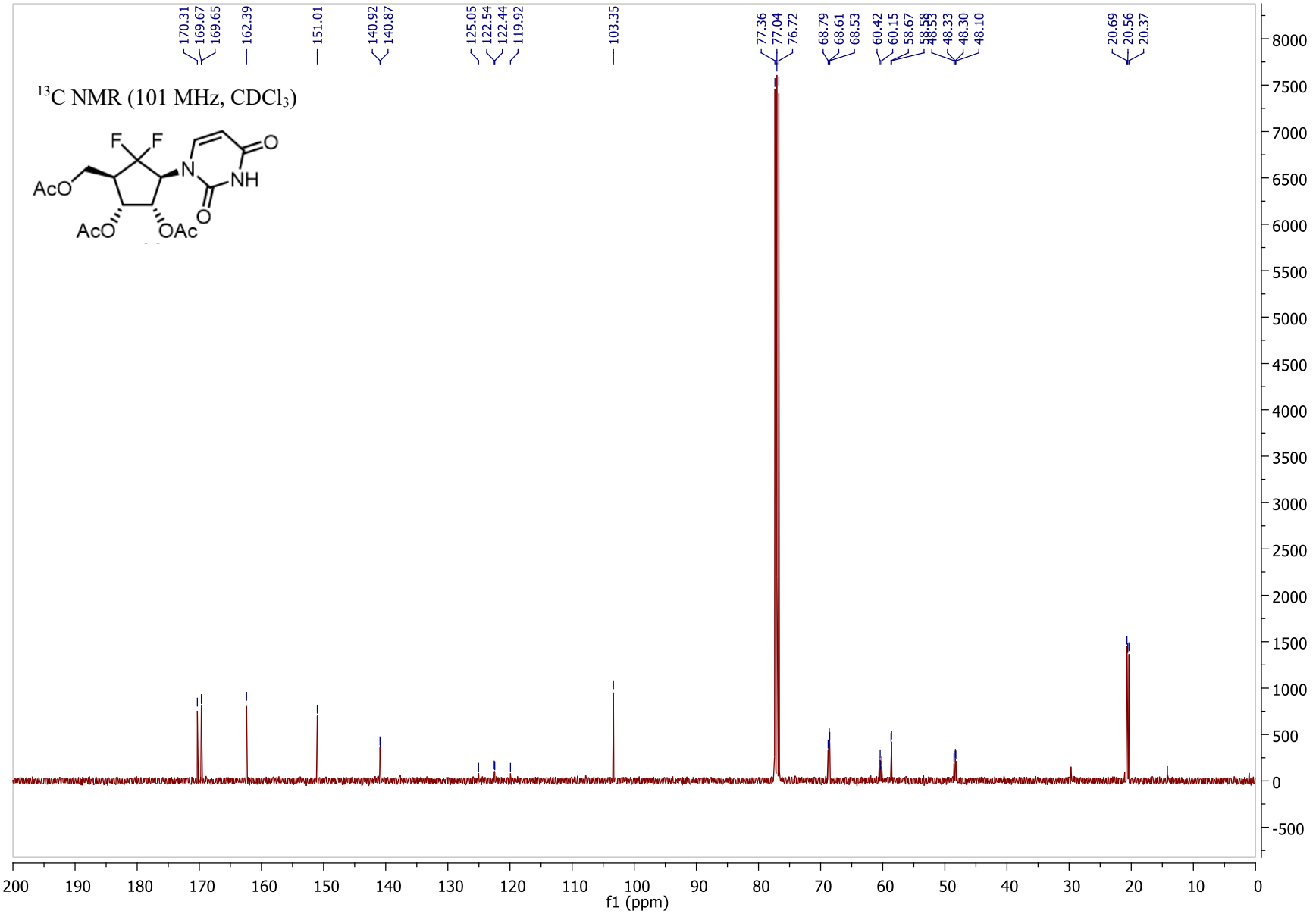


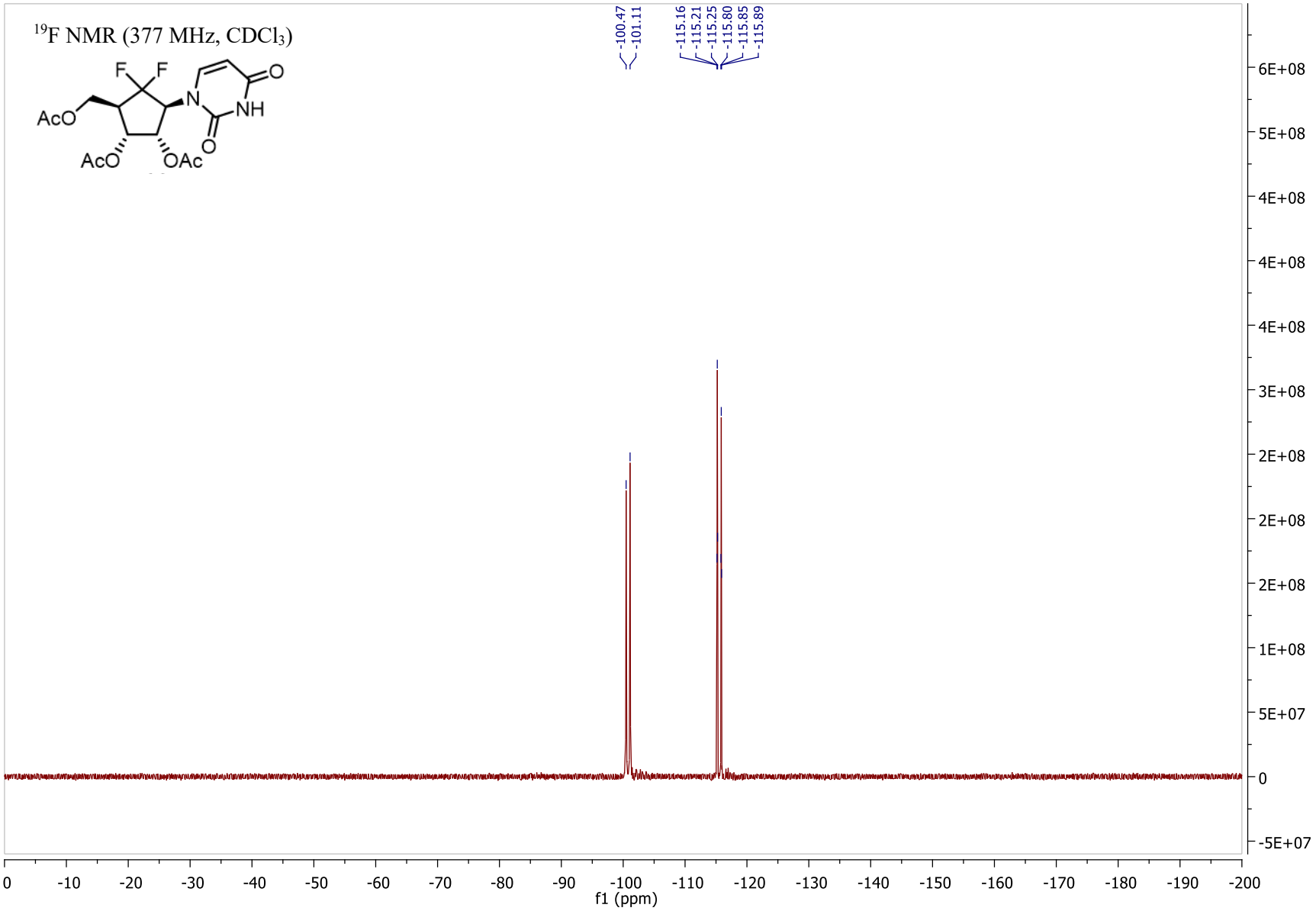

170.47
169.75
169.71
162.38
151.17
141.23
141.18
102.77
91.20
89.36
77.34
77.23
77.03
76.71
69.59
69.37
59.87
59.77
59.60
46.06
45.88
20.72
20.48
20.38
0.00
^{13}C NMR (101 MHz, CDCl$_3$)
F
AcO
AcO
OAc
N
NH
O
O
f1 (ppm)


^{19}F NMR (377 MHz, $CDCl_3$)
F
AcO
AcO
OAc
N
NH
O
O
-206.06
-206.14
-206.20
-206.22
-206.28
-206.36
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250
f1 (ppm)

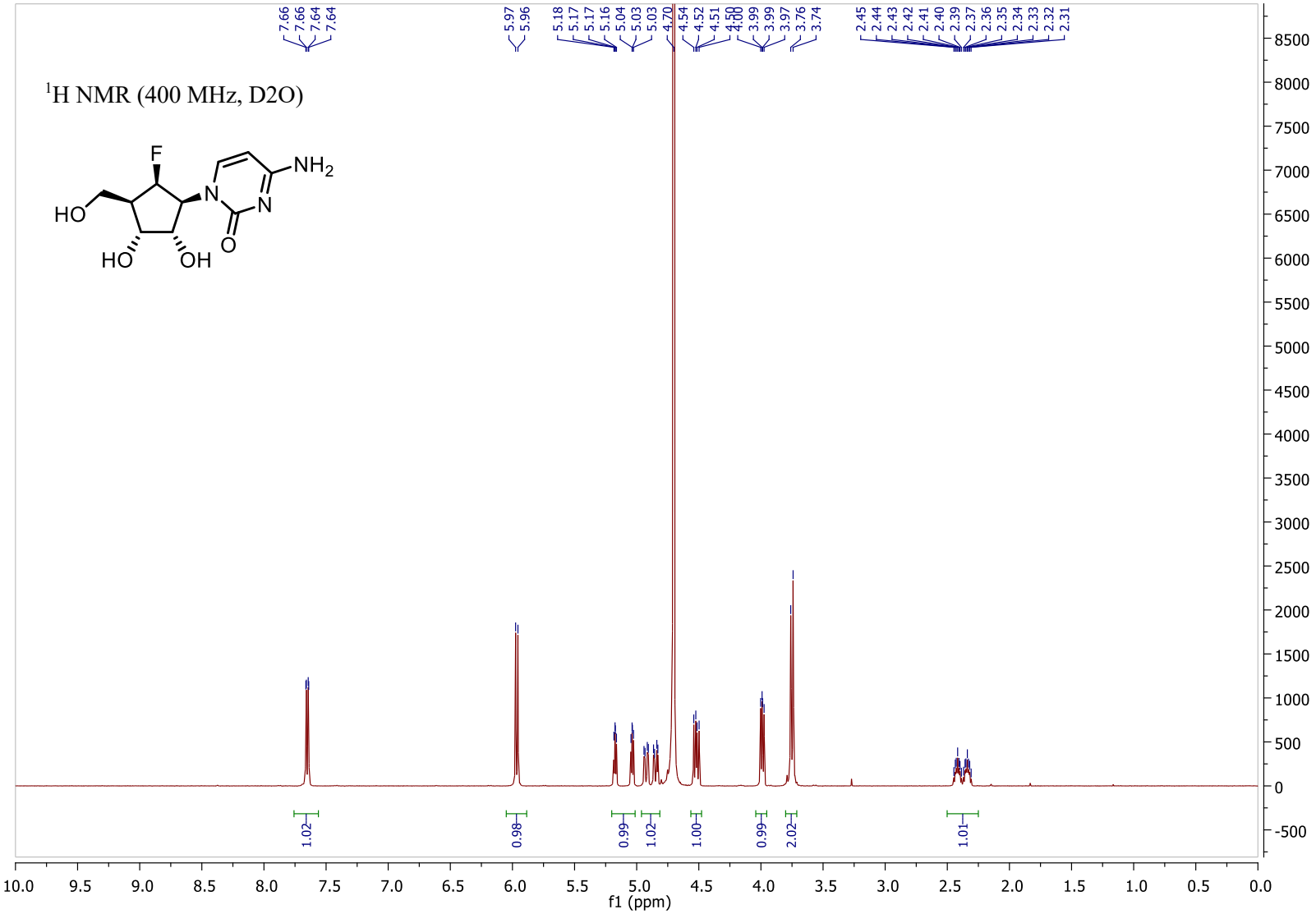
2',3',5'-tri-*O*-acetyl-6'-*gem*-difluorocarbauridine, 25

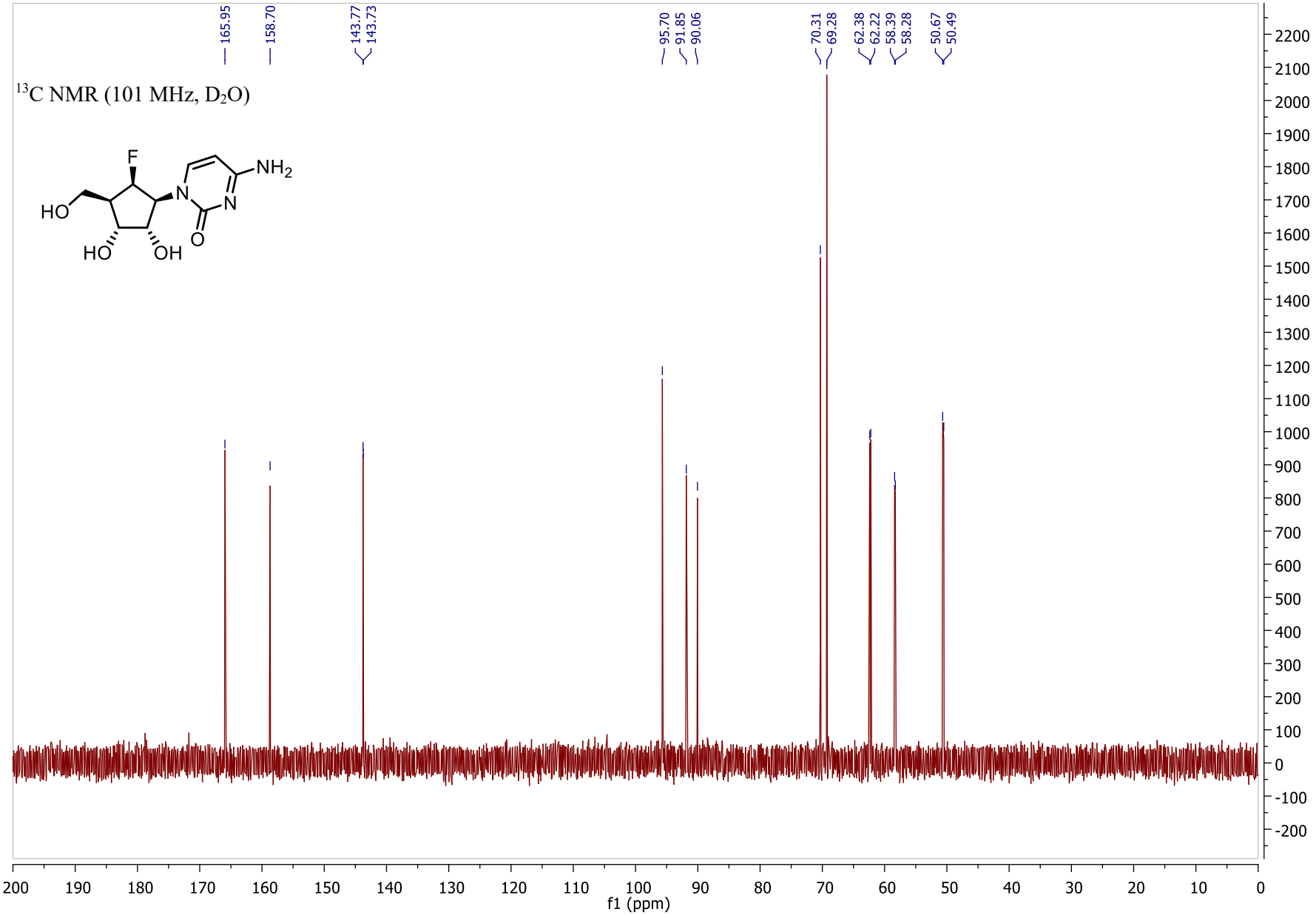


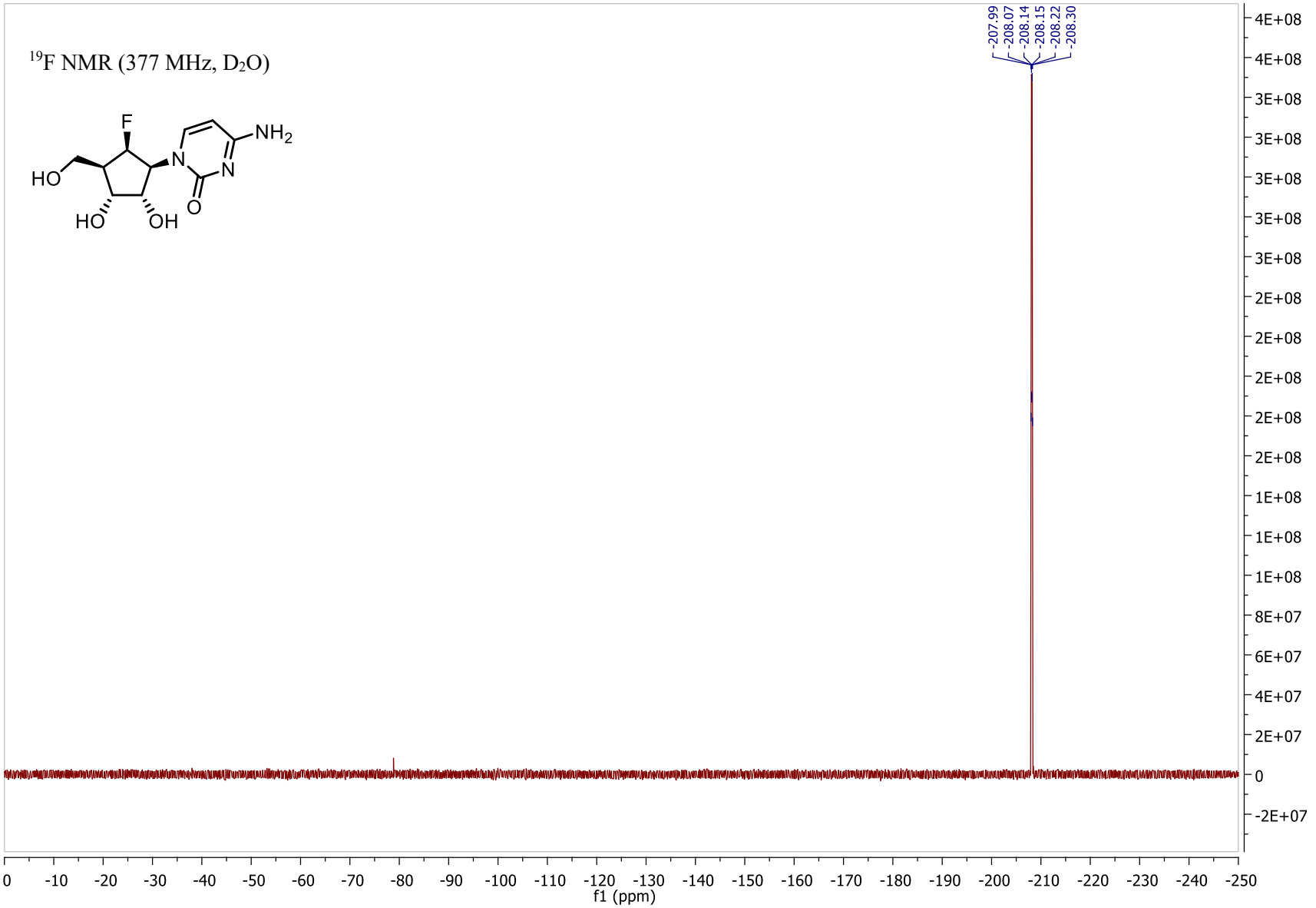

170.31
169.67
169.65
162.39
151.01
140.92
140.87
125.05
122.54
122.44
119.92
103.35
77.36
77.04
76.72
68.79
68.61
68.53
60.42
60.15
58.67
48.33
48.30
48.10
20.69
20.56
20.37
^{13}C NMR (101 MHz, CDCl$_3$)
F
F
O
N
NH
O
AcO
AcO
OAc
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


^{19}F NMR (377 MHz, $CDCl_3$)
F
F
AcO
N
NH
O
O
AcO
OAc
-100.47
-101.11
-115.16
-115.21
-115.25
-115.80
-115.85
-115.89
6E+08
5E+08
4E+08
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
-5E+07
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

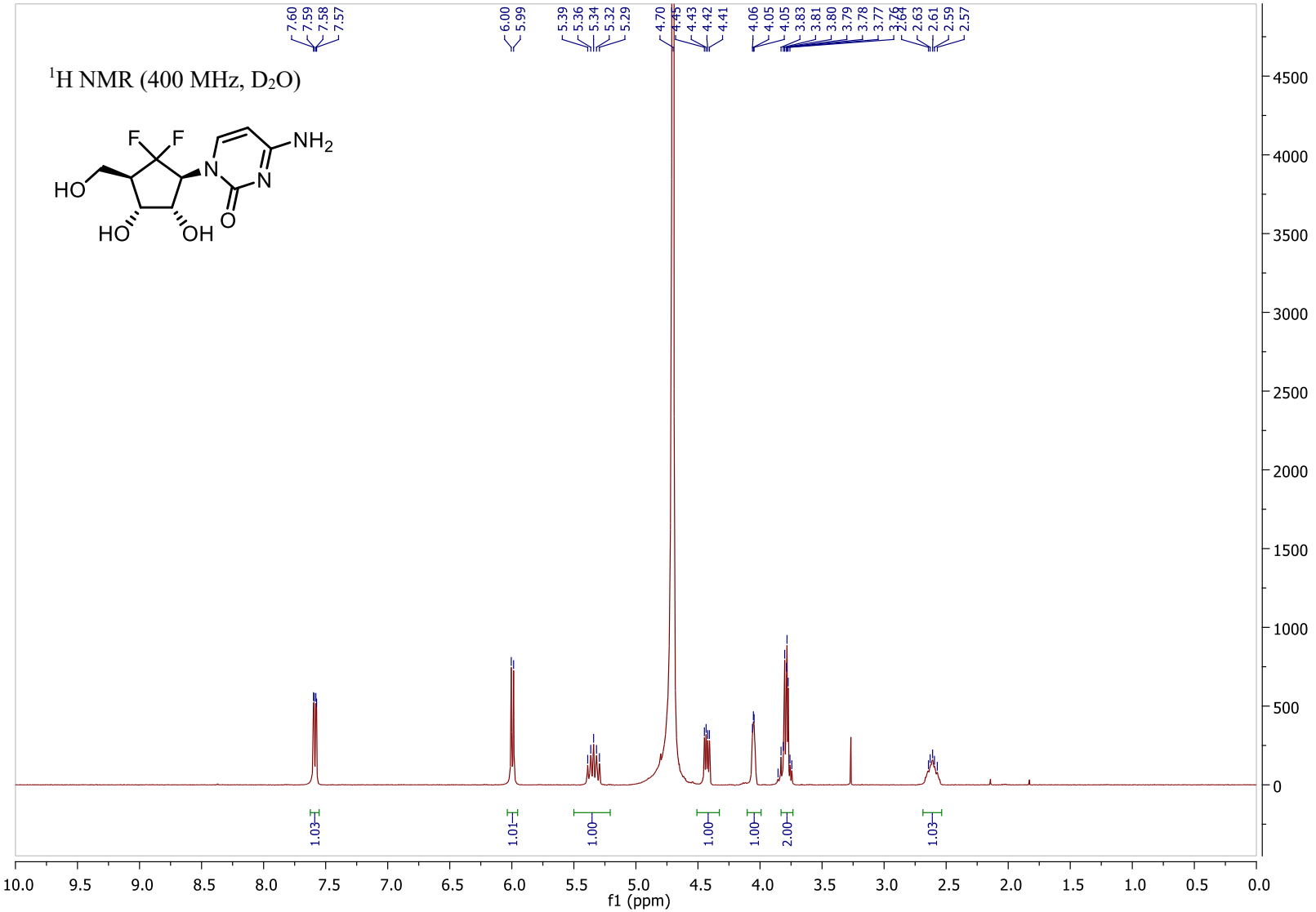
(6'R)-6'-fluorocarbacytidine, 26

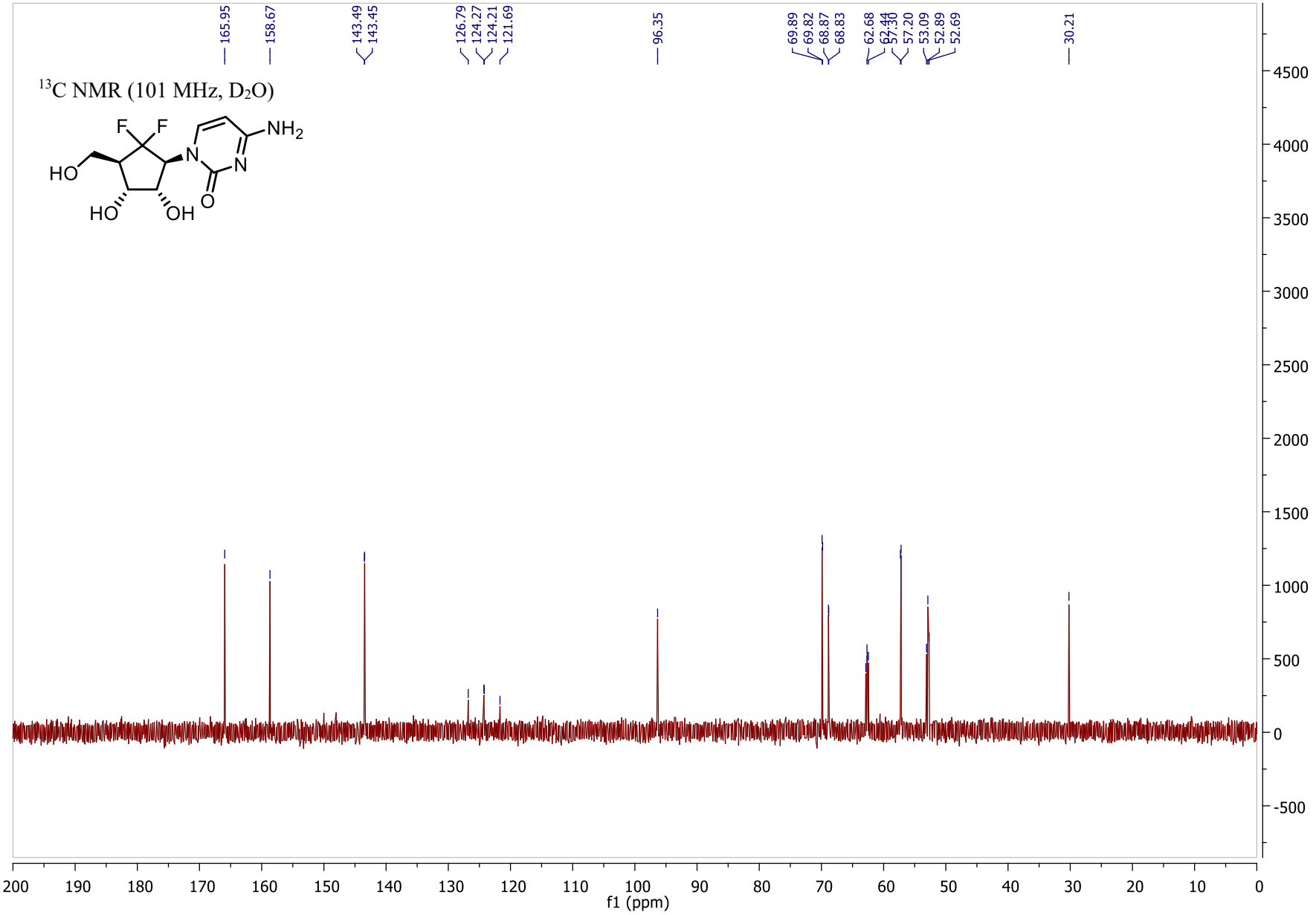


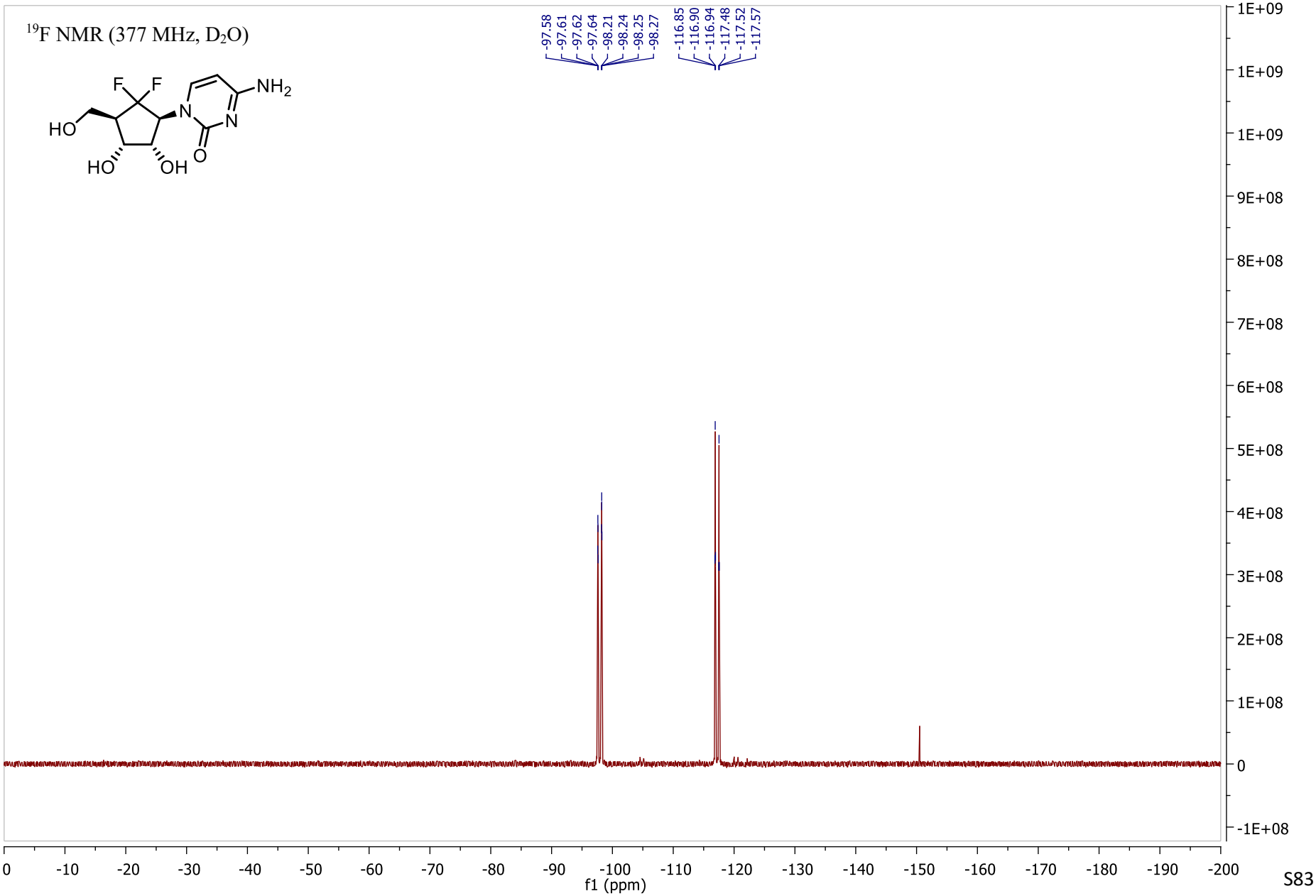

165.95
158.70
143.77
143.73
95.70
91.85
90.06
70.31
69.28
62.38
62.22
58.39
58.28
50.67
50.49
^{13}C NMR (101 MHz, D_2O)
F
NH$_2$
HO
N
N
O
HO
OH
f1 (ppm)


^{19}F NMR (377 MHz, D_2O)
F
NH2
N
N
HO
O
HO
OH
-207.99
-208.07
-208.14
-208.15
-208.22
-208.30
4E+08
4E+08
3E+08
3E+08
3E+08
3E+08
3E+08
2E+08
2E+08
2E+08
2E+08
2E+08
1E+08
1E+08
1E+08
8E+07
6E+07
4E+07
2E+07
0
-2E+07
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250
f1 (ppm)

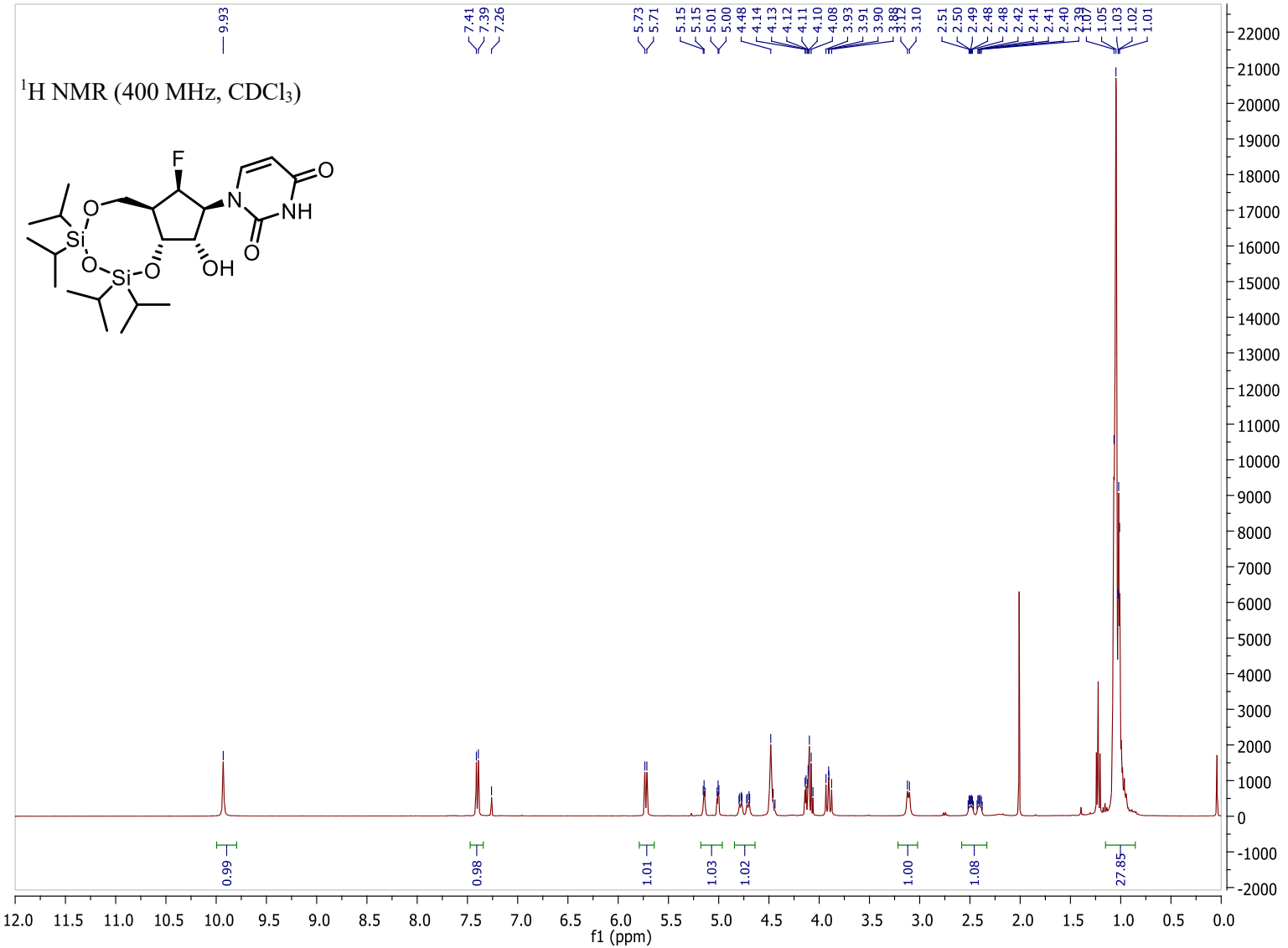
6'-*gem*-difluorocarbacytidine, 27

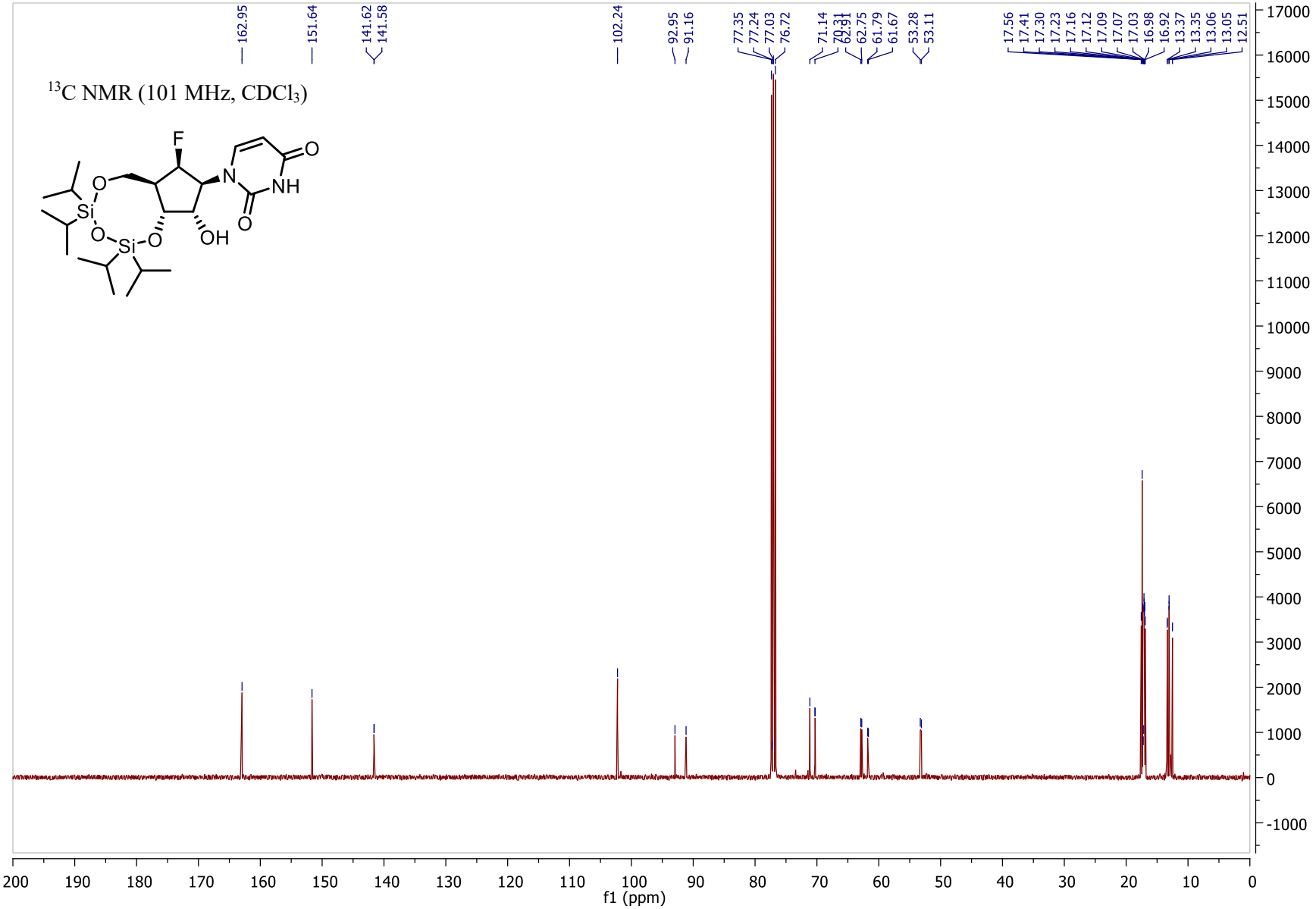



165.95
158.67
143.49
143.45
126.79
124.27
124.21
121.69
96.35
69.89
69.82
68.87
68.83
62.68
62.44
57.30
57.20
53.09
52.89
52.69
30.21
13C NMR (101 MHz, D2O)
F
F
NH2
HO
N
N
O
HO
OH
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

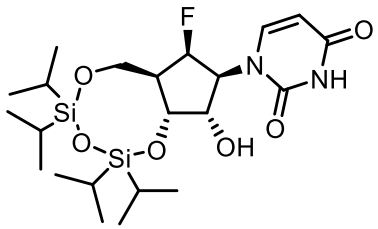

^{19}F NMR (377 MHz, D_2O)
F
F
HO
HO
OH
N
N
O
NH_2
-97.58
-97.61
-97.62
-97.64
-98.21
-98.24
-98.25
-98.27
-116.85
-116.90
-116.94
-117.48
-117.52
-117.57
1E+09
1E+09
1E+09
9E+08
8E+08
7E+08
6E+08
5E+08
4E+08
3E+08
2E+08
1E+08
0
-1E+08
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

(6'R)-3',5'-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-6'-fluorocarbauridine, 28

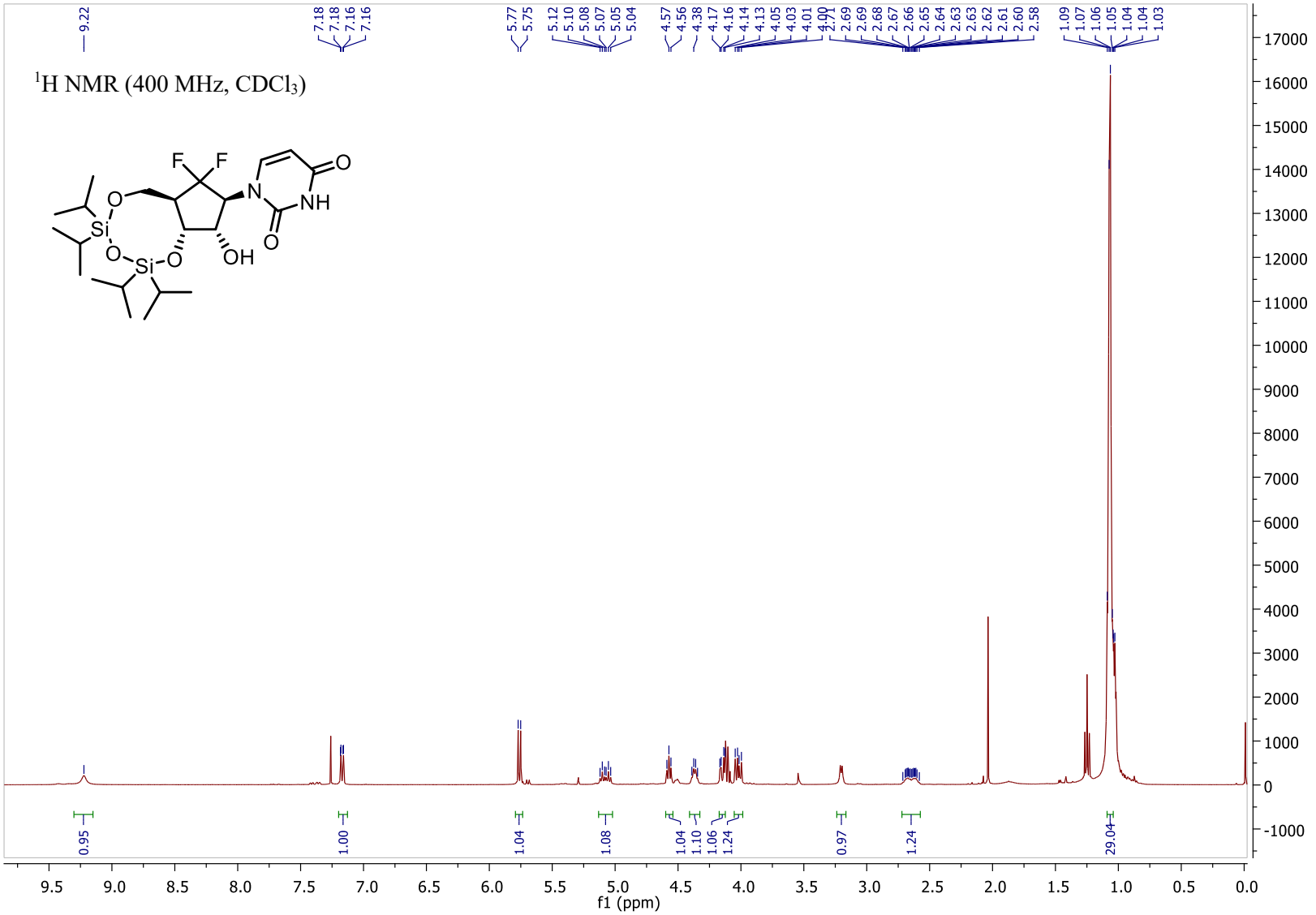


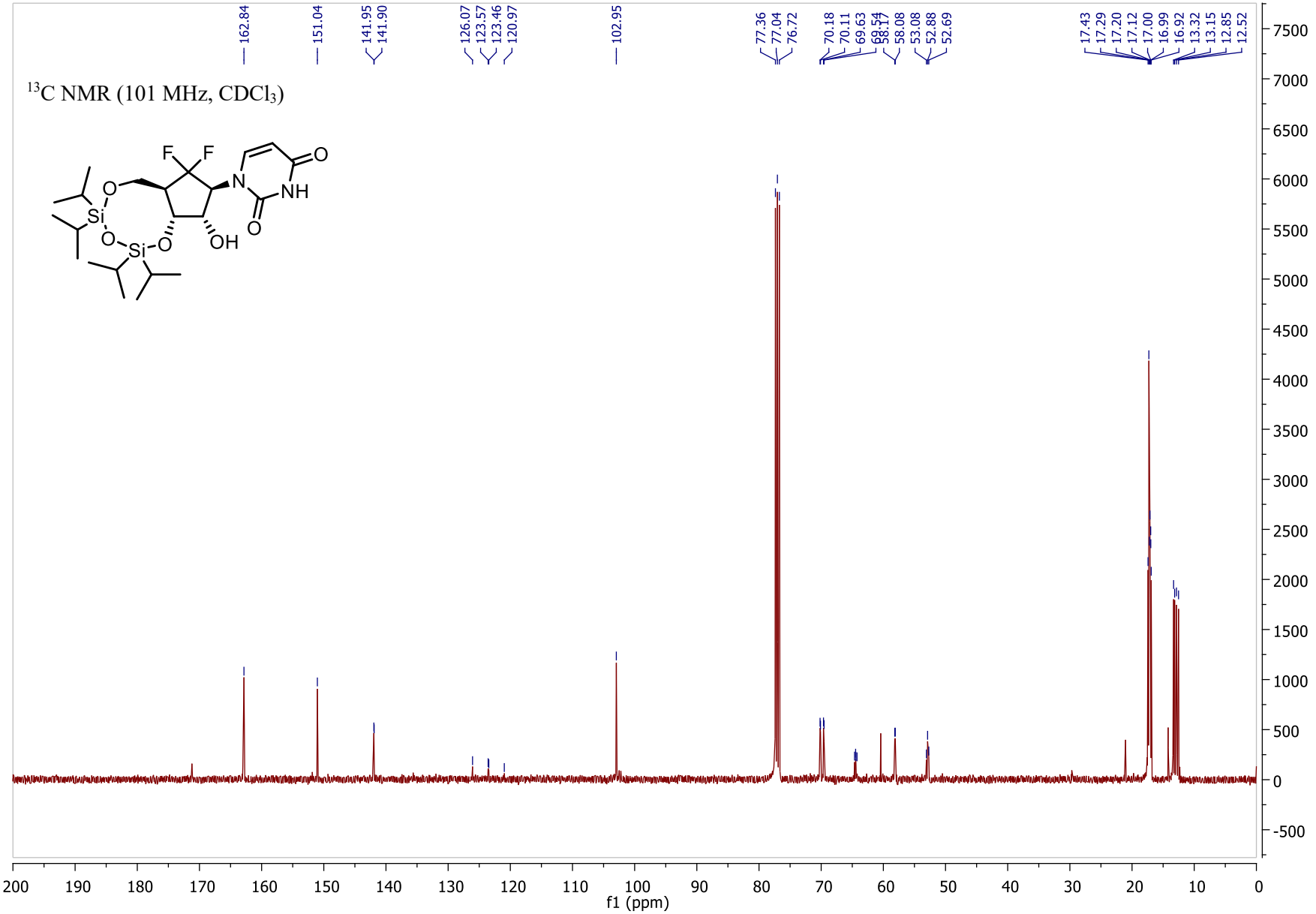

^{13}C NMR (101 MHz, $CDCl_3$)
F
O
N
NH
O
O
Si
O
Si
O
OH
162.95
151.64
141.62
141.58
102.24
92.95
91.16
77.35
77.24
77.03
76.72
71.14
70.31
62.91
62.75
61.79
61.67
53.28
53.11
17.56
17.41
17.30
17.23
17.16
17.12
17.09
17.07
17.03
16.98
16.92
13.37
13.35
13.06
13.05
12.51
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

^{19}F NMR (377 MHz, $CDCl_3$)

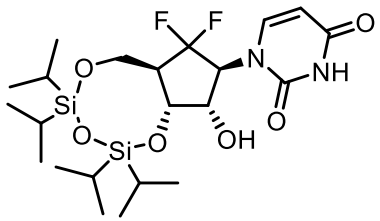


3',5'-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-6'-*gem*-difluorocarbauridine, 29

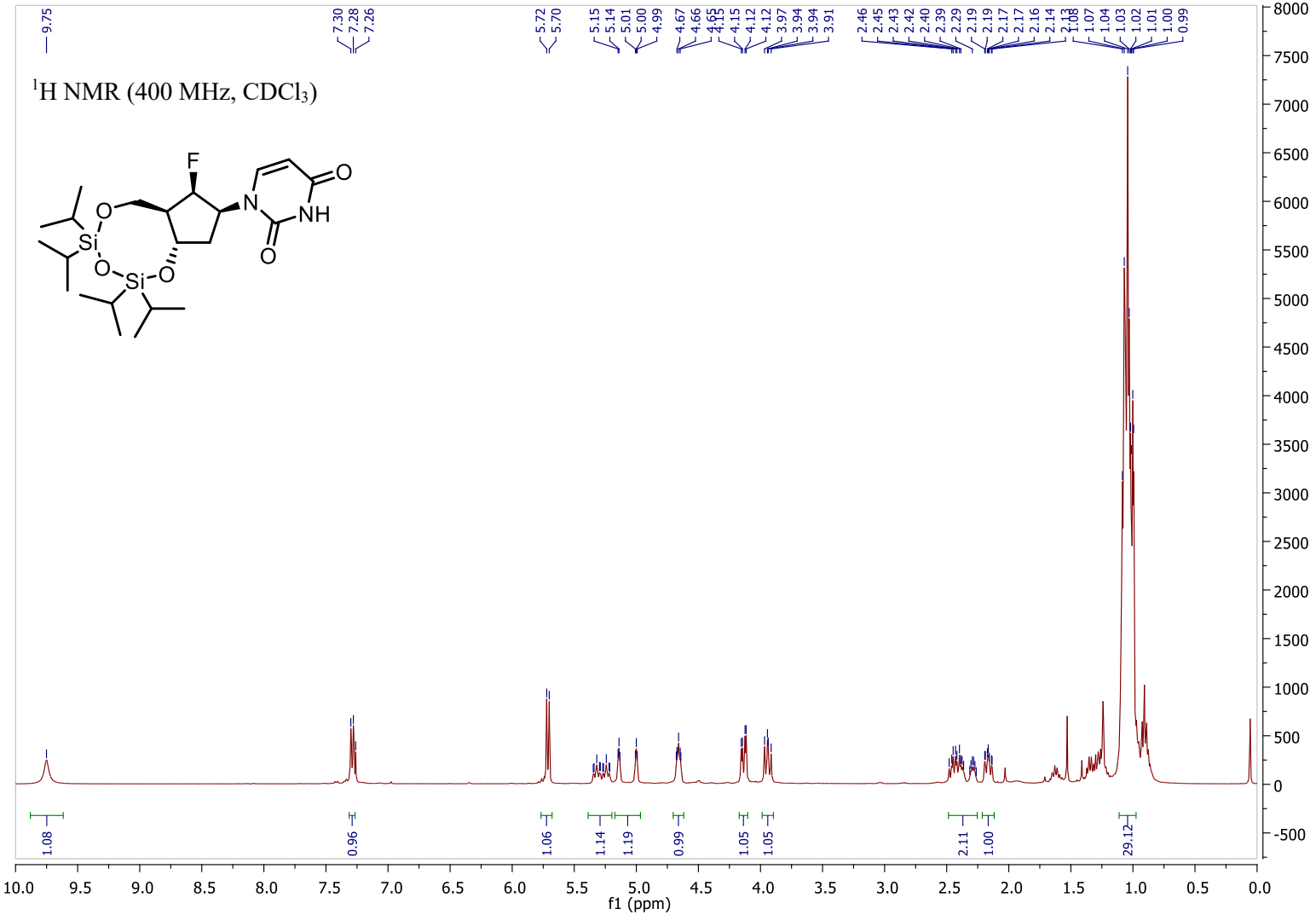


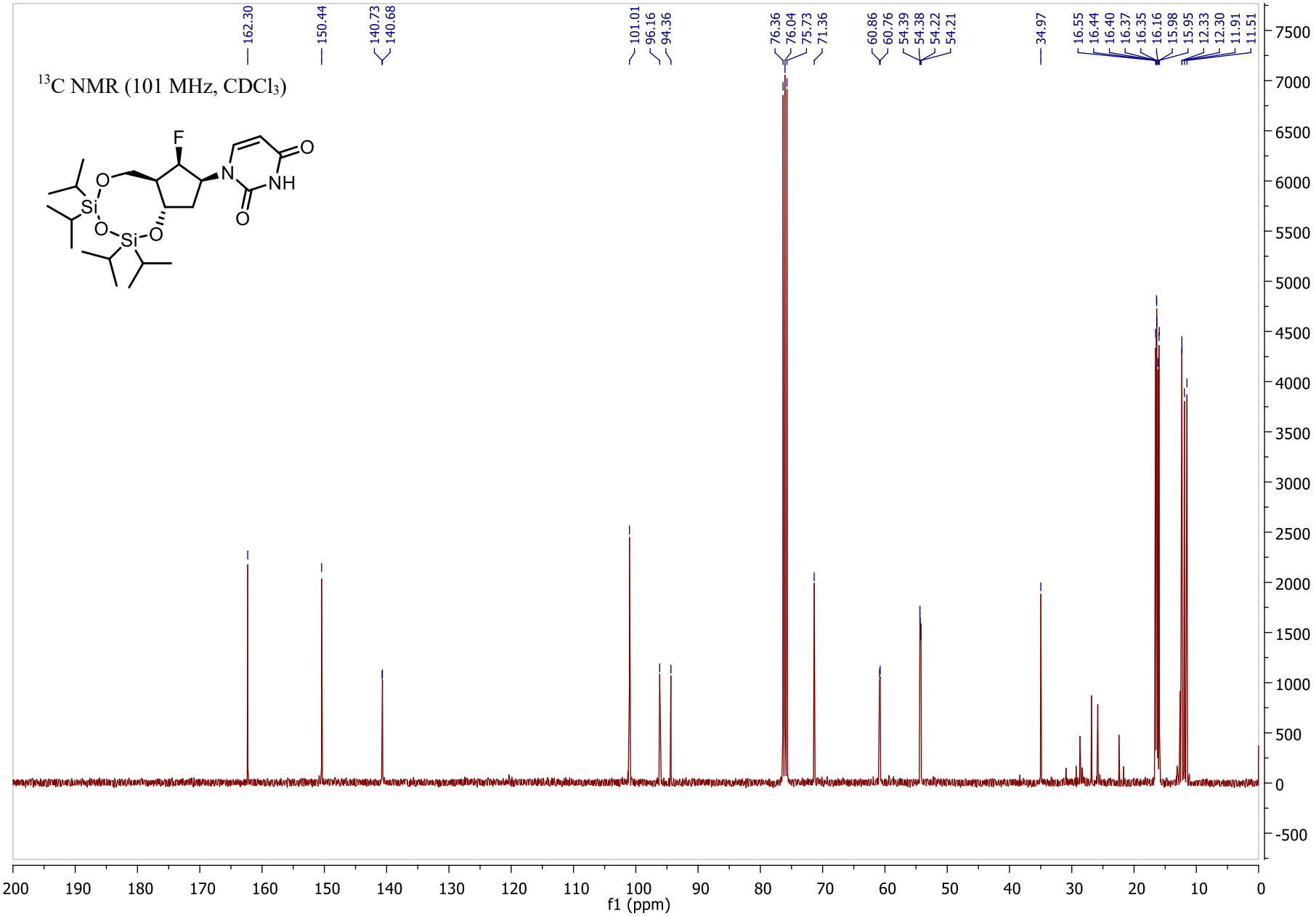

162.84
151.04
141.95
141.90
126.07
123.57
123.46
120.97
102.95
77.36
77.04
76.72
70.18
70.11
69.63
68.54
68.17
58.08
53.08
52.88
52.69
17.43
17.29
17.20
17.12
17.00
16.99
16.92
13.32
13.15
12.85
12.52
13C NMR (101 MHz, CDCl3)
F
F
O
N
NH
O
O
Si
O
Si
O
OH
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

^{19}F NMR (377 MHz, $CDCl_3$)

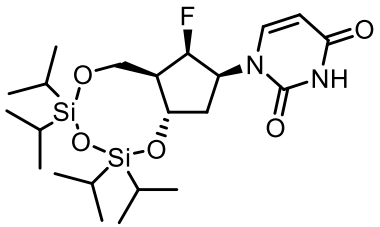


(6'R)-2'-deoxy-3',5'-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-6'-fluorocarbauridine, 30

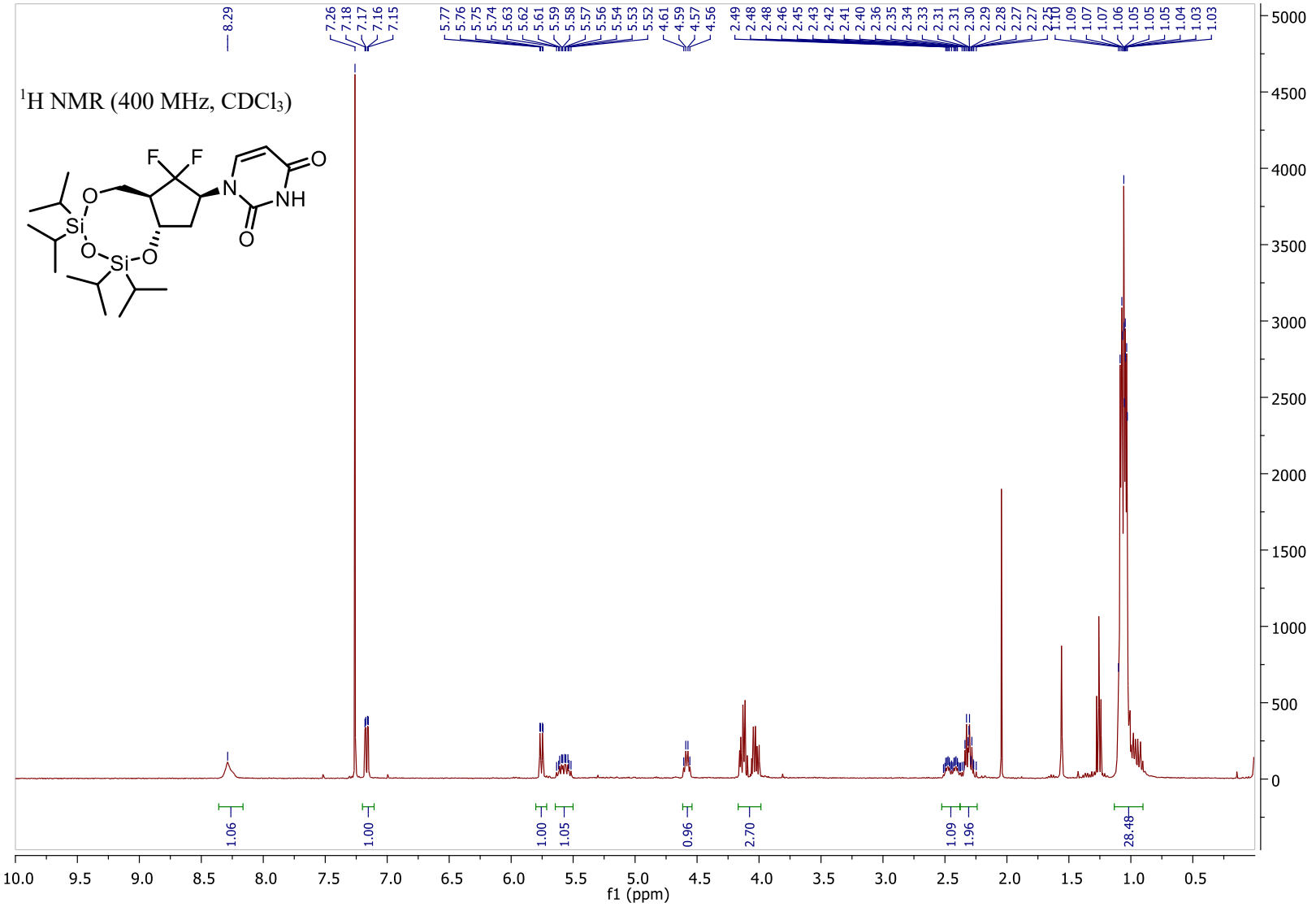


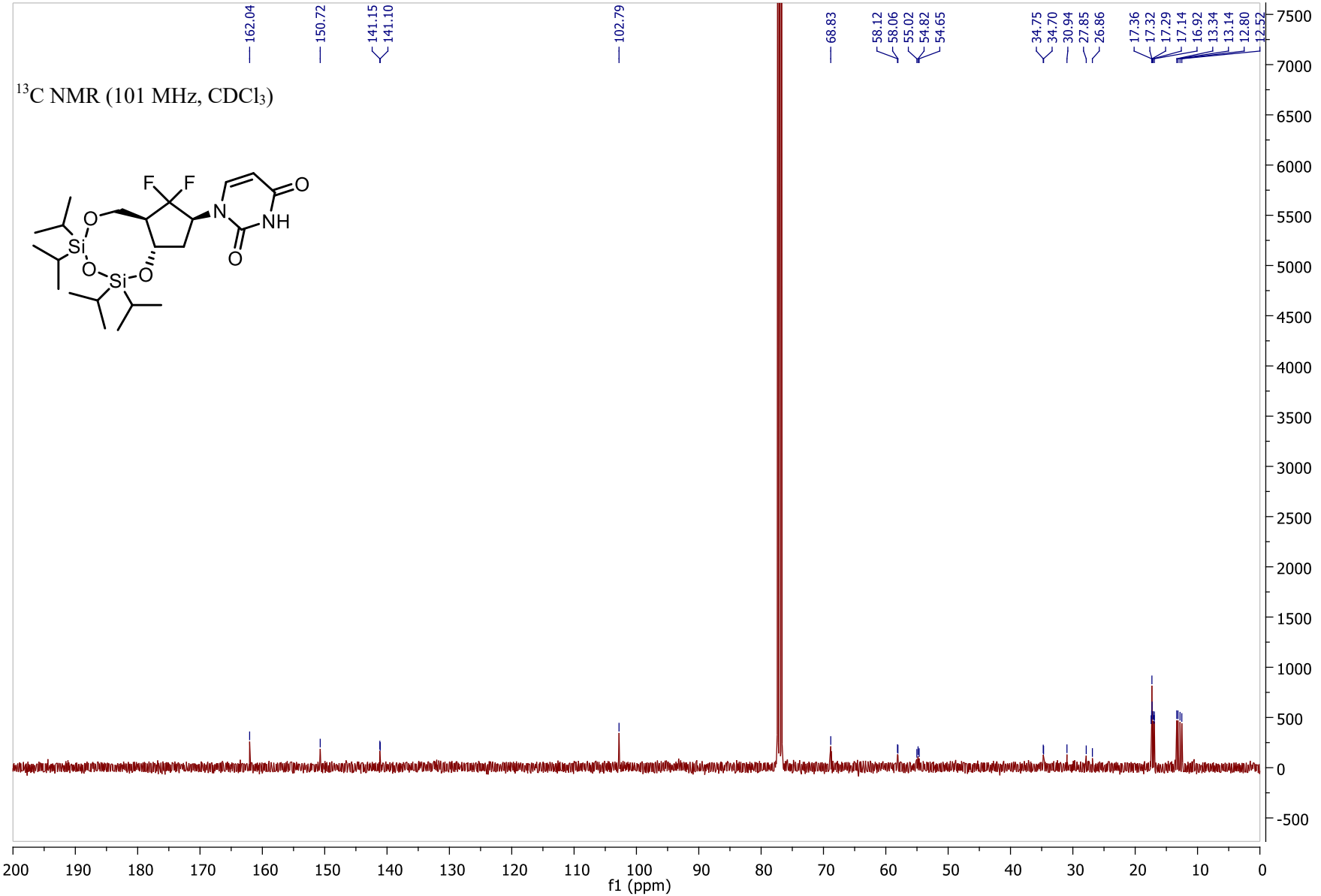

^{13}C NMR (101 MHz, $CDCl_3$)
162.30
150.44
140.73
140.68
101.01
96.16
94.36
76.36
76.04
75.73
71.36
60.86
60.76
54.39
54.38
54.22
54.21
34.97
16.55
16.44
16.40
16.37
16.35
16.16
15.98
15.95
12.33
12.30
11.91
11.51
F
O
N
NH
O
O
Si
O
Si
O
f1 (ppm)

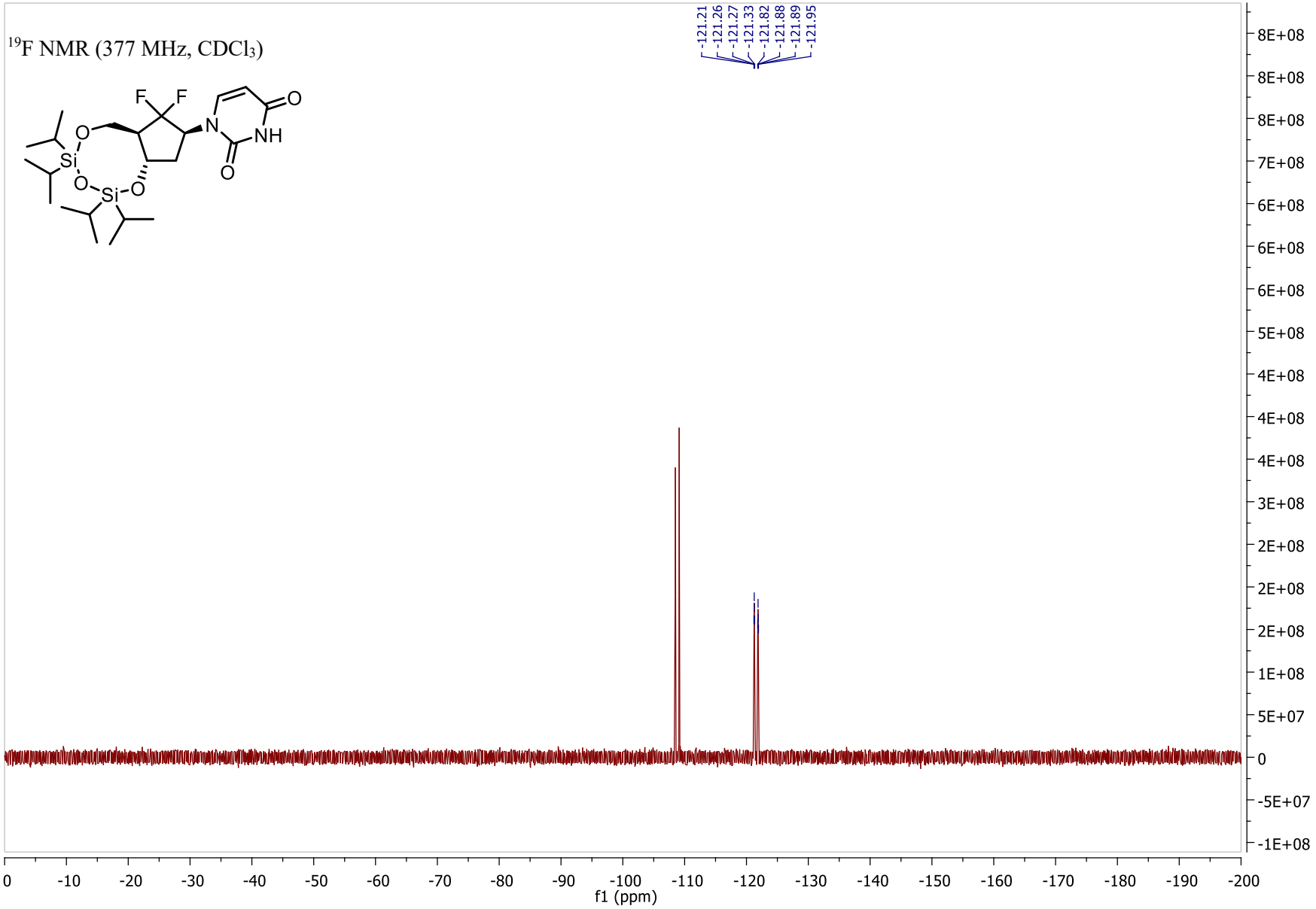
^{19}F NMR (377 MHz, $CDCl_3$)



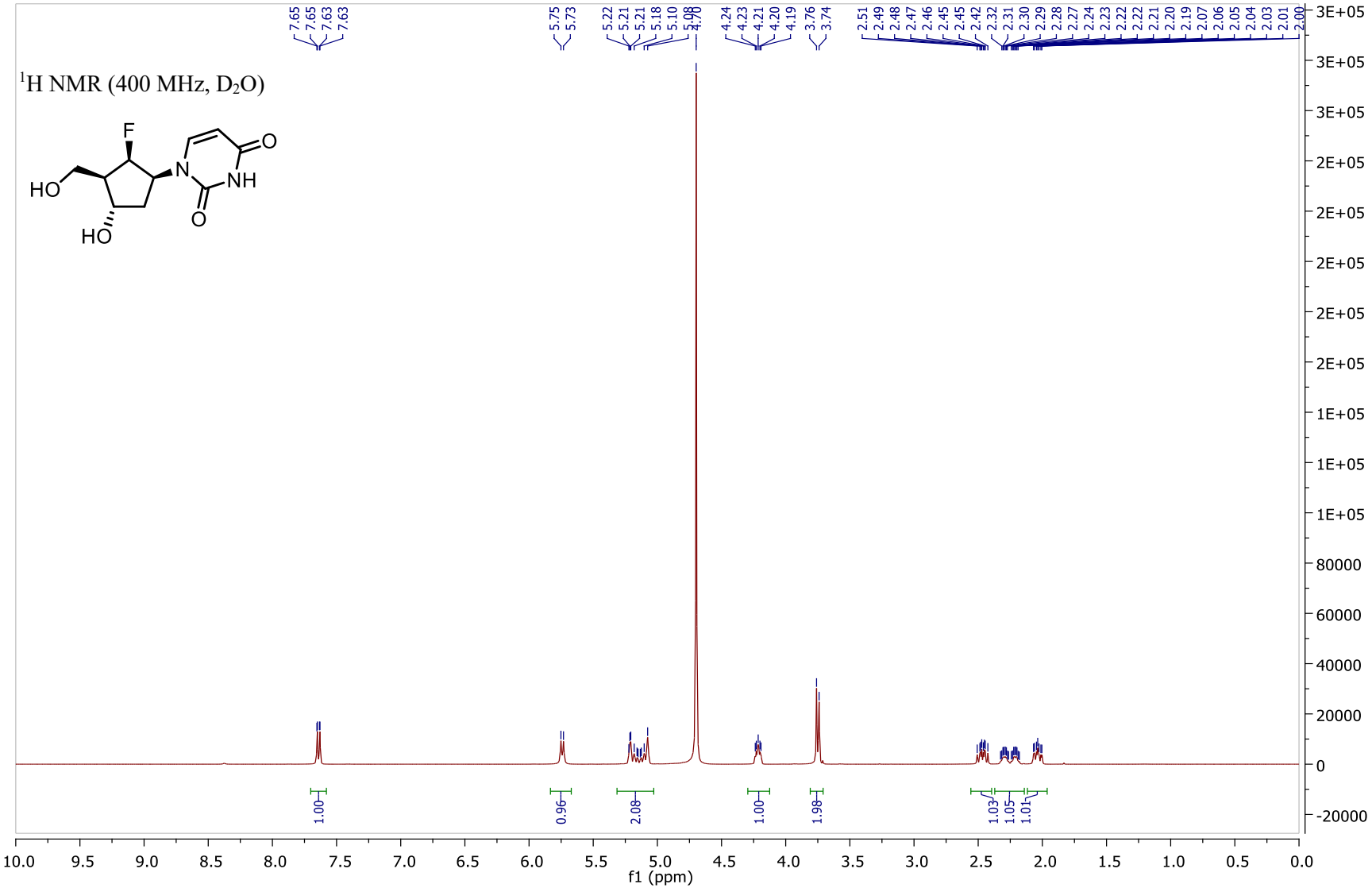
2’-deoxy-3’,5’-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-6’-*gem*-difluorocarbauridine, 31

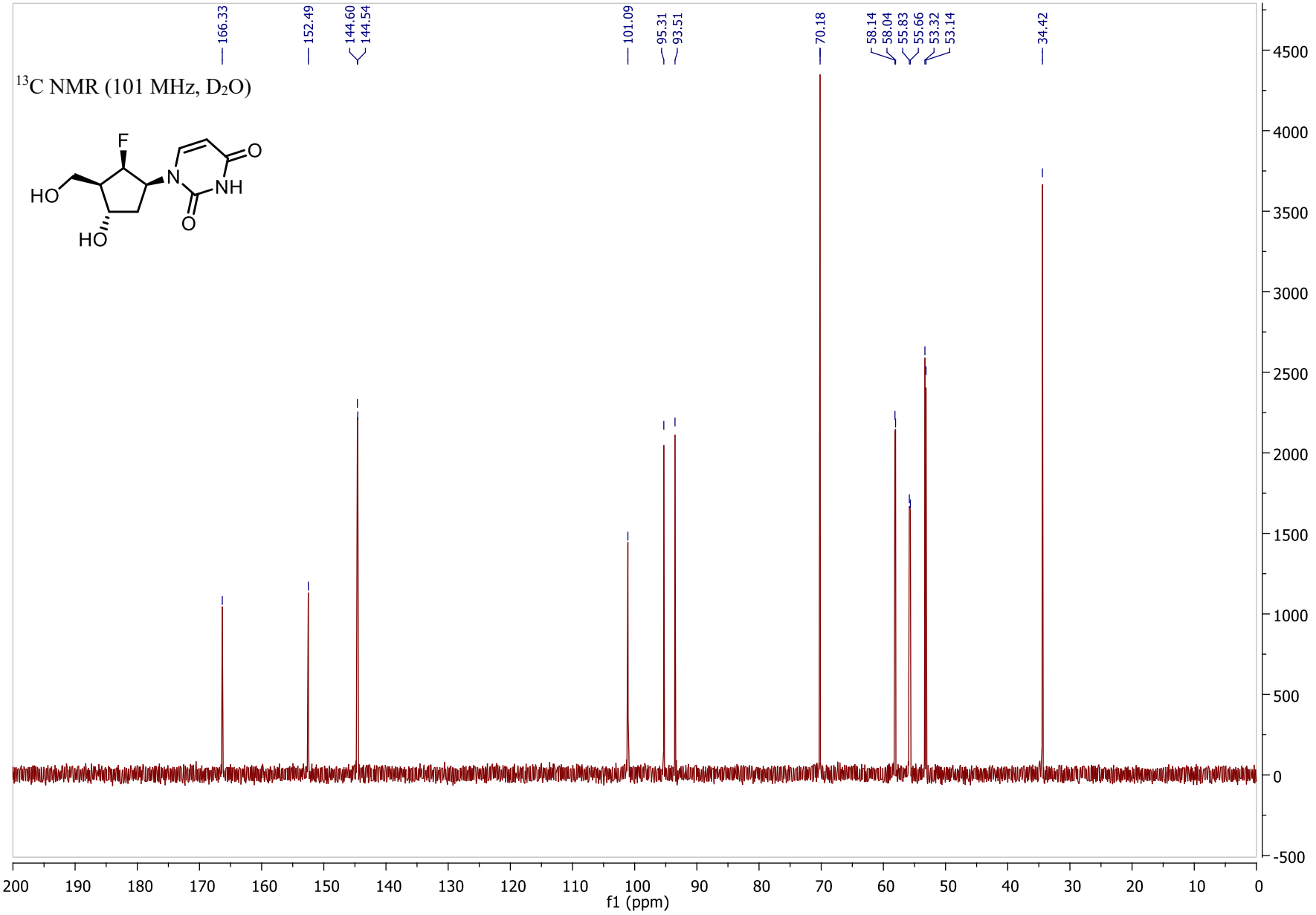



^{13}C NMR (101 MHz, $CDCl_3$)
162.04
150.72
141.15
141.10
102.79
68.83
58.12
58.06
55.02
54.82
54.65
34.75
34.70
30.94
27.85
26.86
17.36
17.32
17.29
17.14
16.92
13.34
13.14
12.80
12.52
F
F
O
N
NH
O
O
Si
O
Si
O
f1 (ppm)

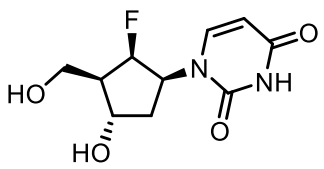

^{19}F NMR (377 MHz, $CDCl_3$)
-121.21
-121.26
-121.27
-121.33
-121.82
-121.88
-121.89
-121.95
F
F
O
N
NH
O
O
Si
O
Si
O
8E+08
8E+08
8E+08
7E+08
6E+08
6E+08
6E+08
5E+08
4E+08
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
-5E+07
-1E+08
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

(6'R)-2'-deoxy-6'-fluorocarbauridine, 32

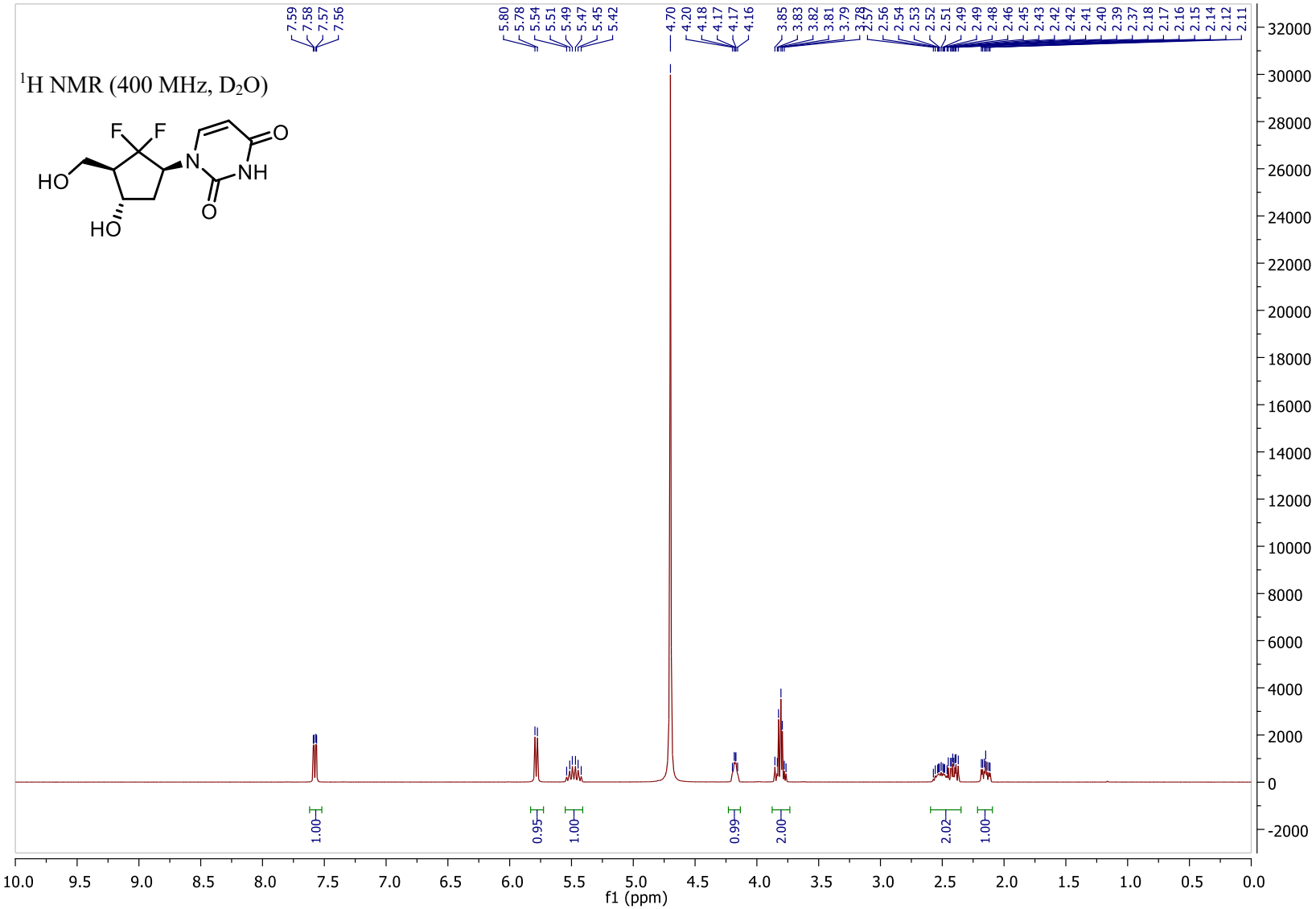


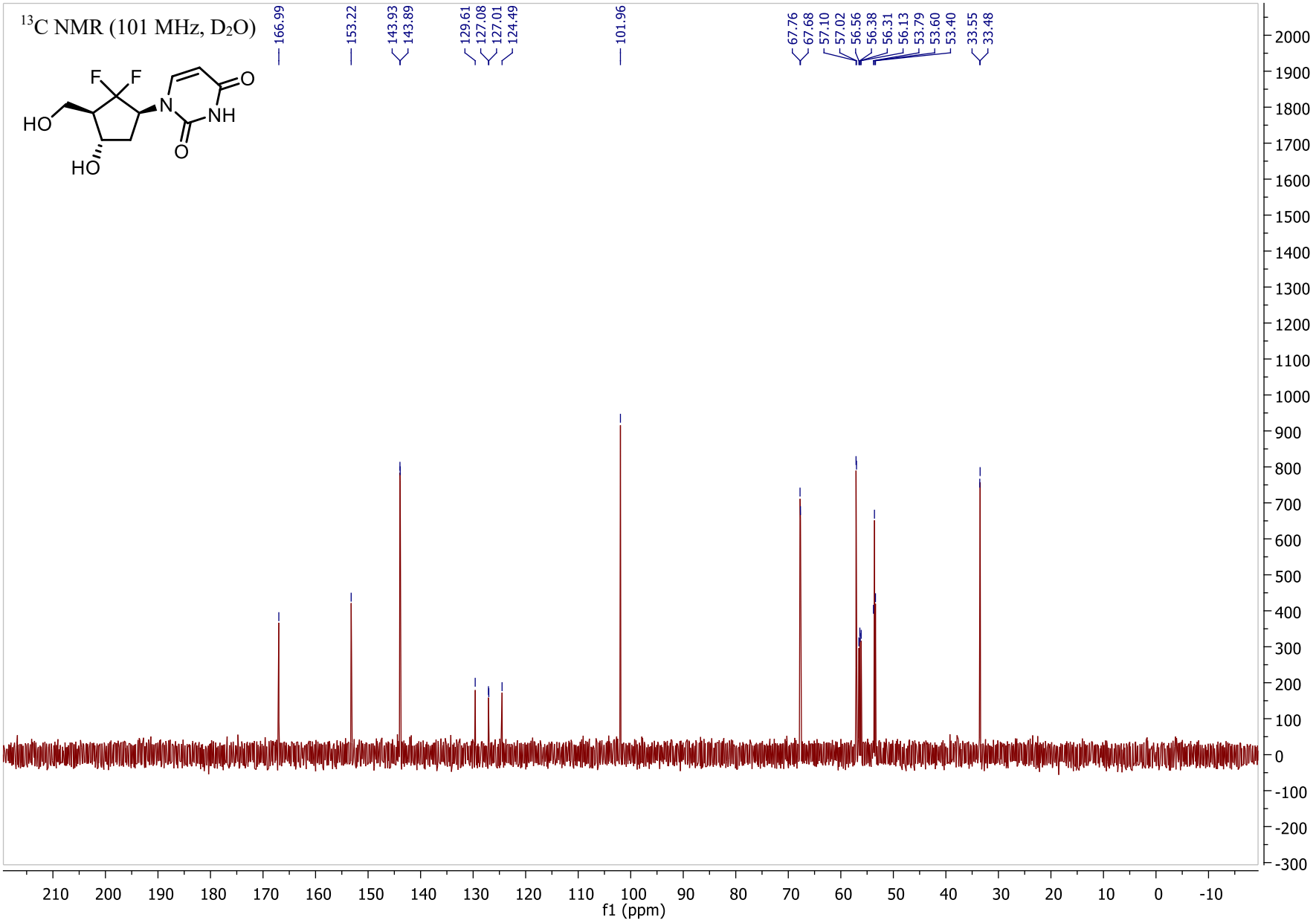

166.33
152.49
144.60
144.54
101.09
95.31
93.51
70.18
58.14
58.04
55.83
55.66
53.32
53.14
34.42
^{13}C NMR (101 MHz, D_2O)
F
HO
HO
N
NH
O
O
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

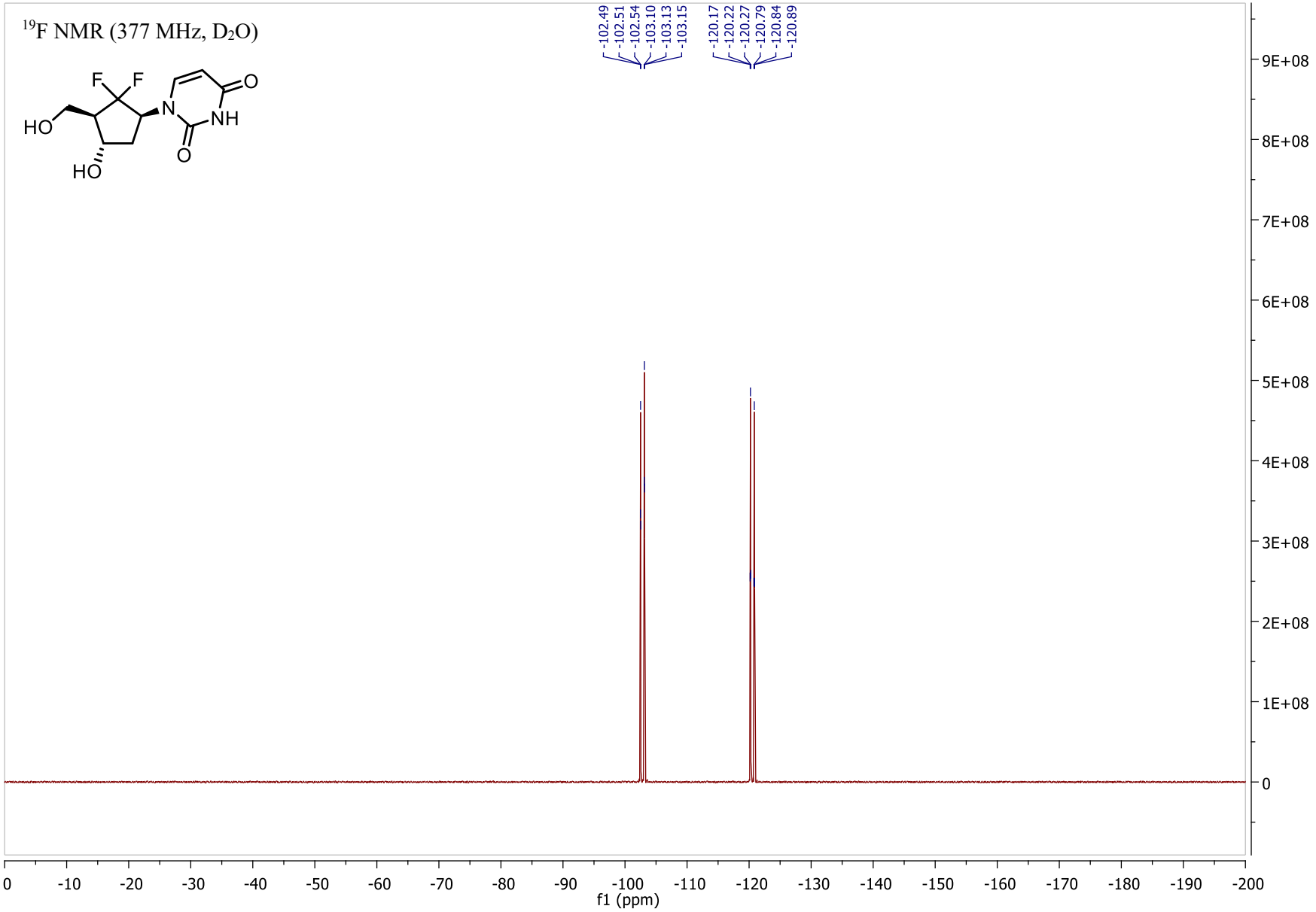
^{19}F NMR (377 MHz, D_2O)



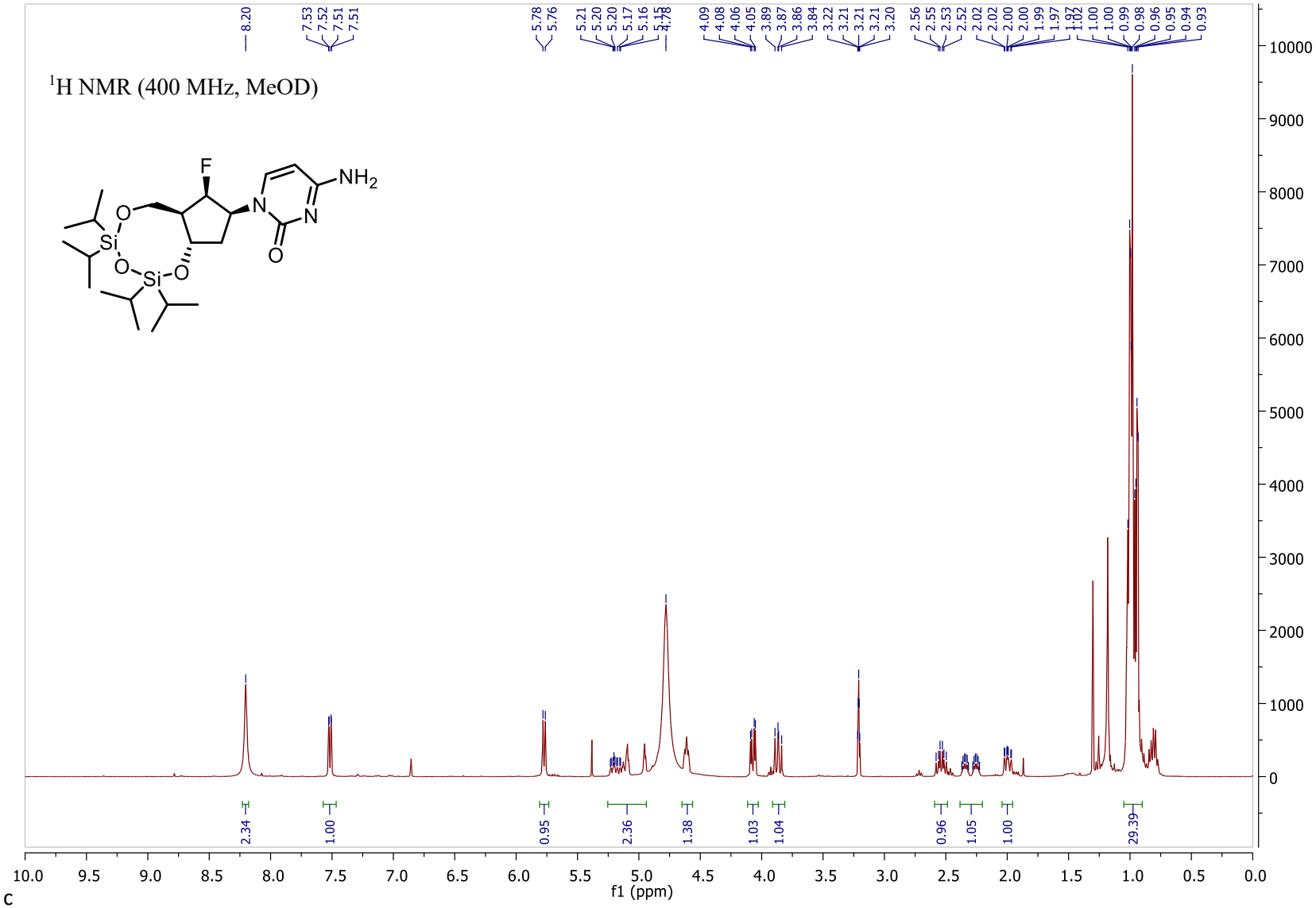
2’-deoxy-6’-*gem*-diflurocarbauridine, 33



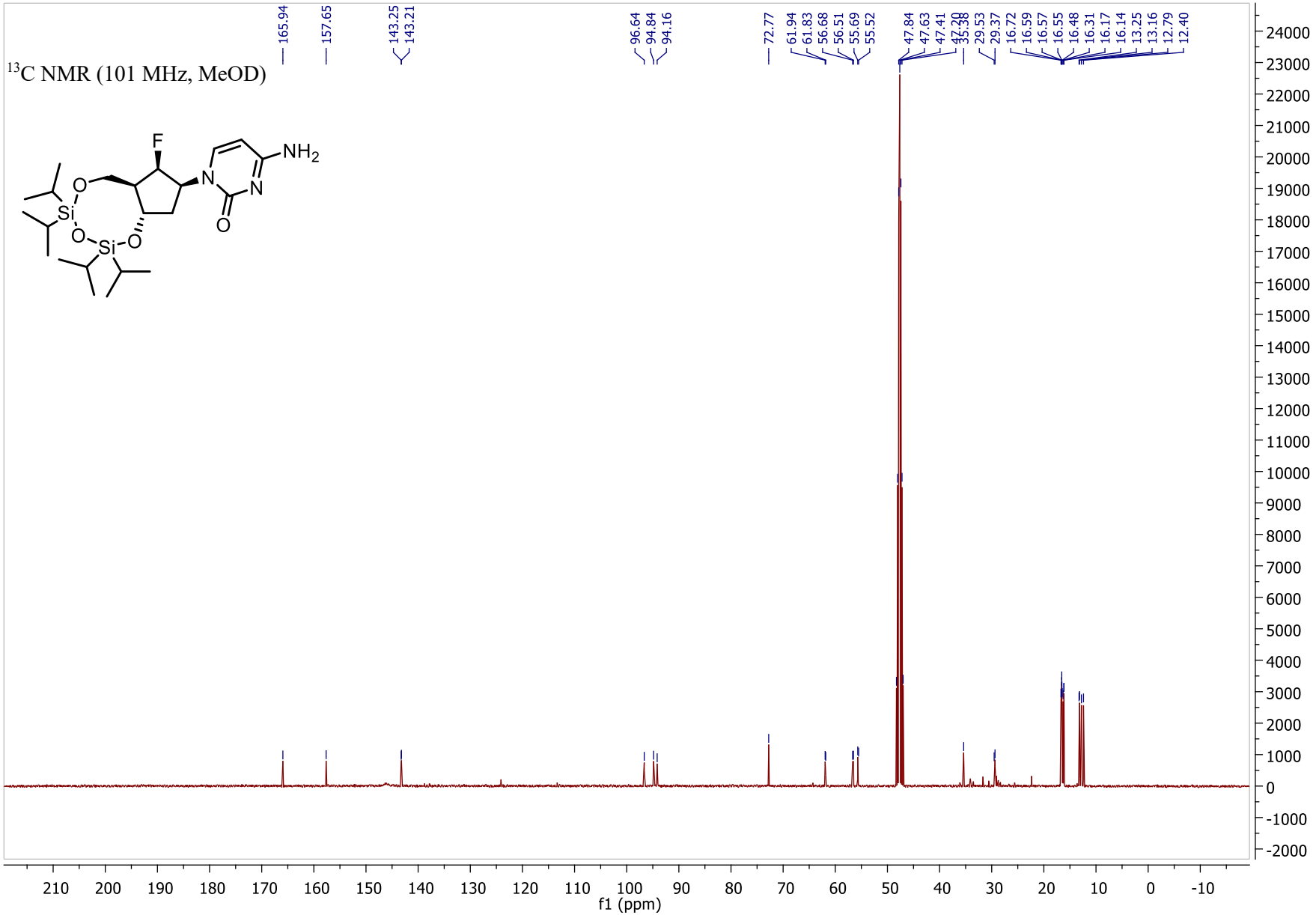

^{13}C NMR (101 MHz, D_2O)
166.99
153.22
143.93
143.89
129.61
127.08
127.01
124.49
101.96
67.76
67.68
57.10
57.02
56.56
56.38
56.31
56.13
53.79
53.60
53.40
33.55
33.48
F
F
HO
HO
N
NH
O
O
f1 (ppm)


19F NMR (377 MHz, D2O)
F
F
HO
HO
N
NH
O
O
-102.49
-102.51
-102.54
-103.10
-103.13
-103.15
-120.17
-120.22
-120.27
-120.79
-120.84
-120.89
9E+08
8E+08
7E+08
6E+08
5E+08
4E+08
3E+08
2E+08
1E+08
0
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

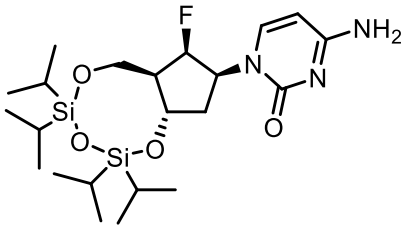
(6'R)-2'-deoxy-3',5'-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-6'-fluorocarbacytidine



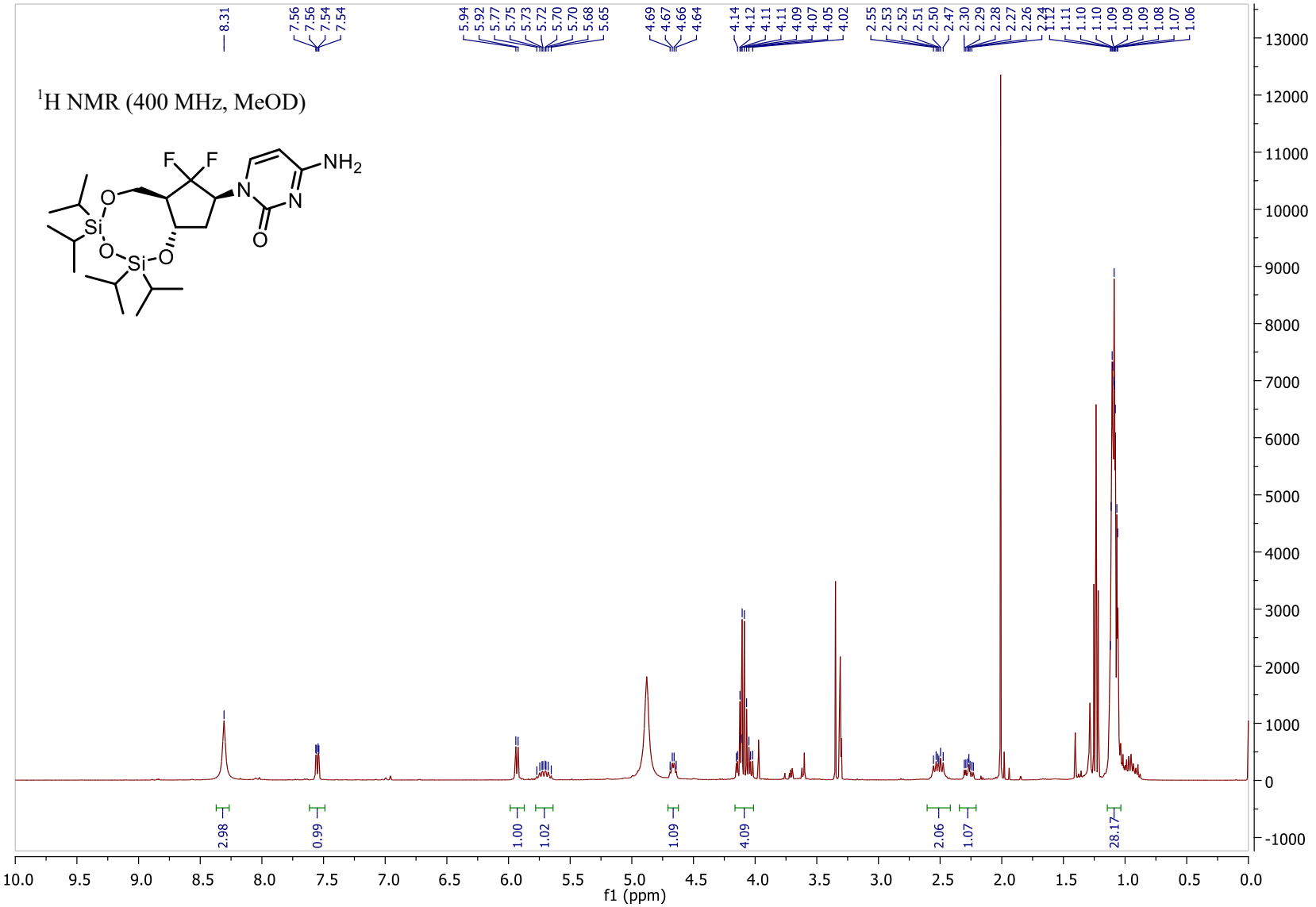
c

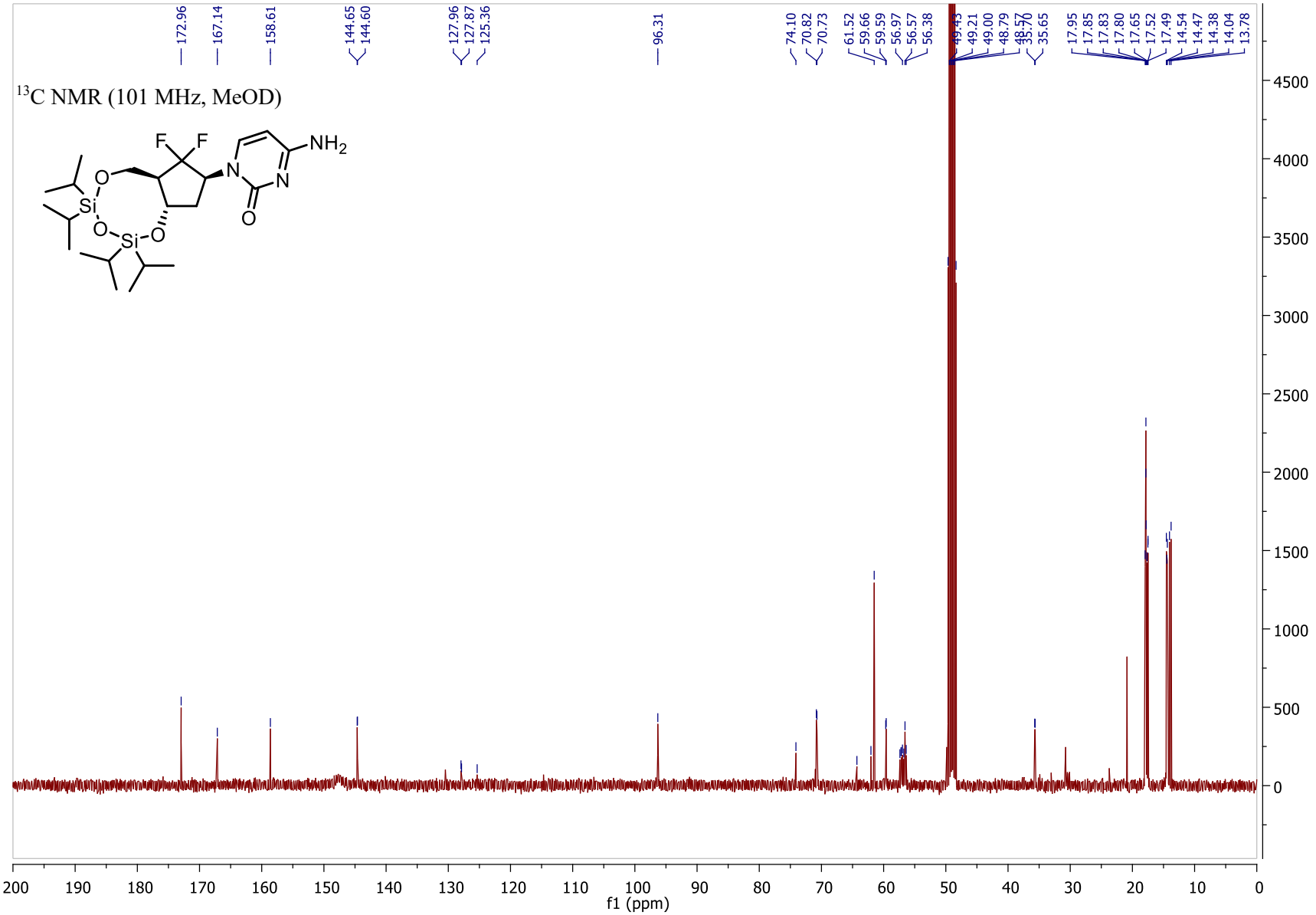

^{13}C NMR (101 MHz, MeOD)
165.94
157.65
143.25
143.21
96.64
94.84
94.16
72.77
61.94
61.83
56.68
56.51
55.69
55.52
47.84
47.63
47.41
47.20
35.38
29.53
29.37
16.72
16.59
16.57
16.55
16.48
16.31
16.17
16.14
13.25
13.16
12.79
12.40
F
NH2
N
N
O
O
Si
O
Si
O
f1 (ppm)

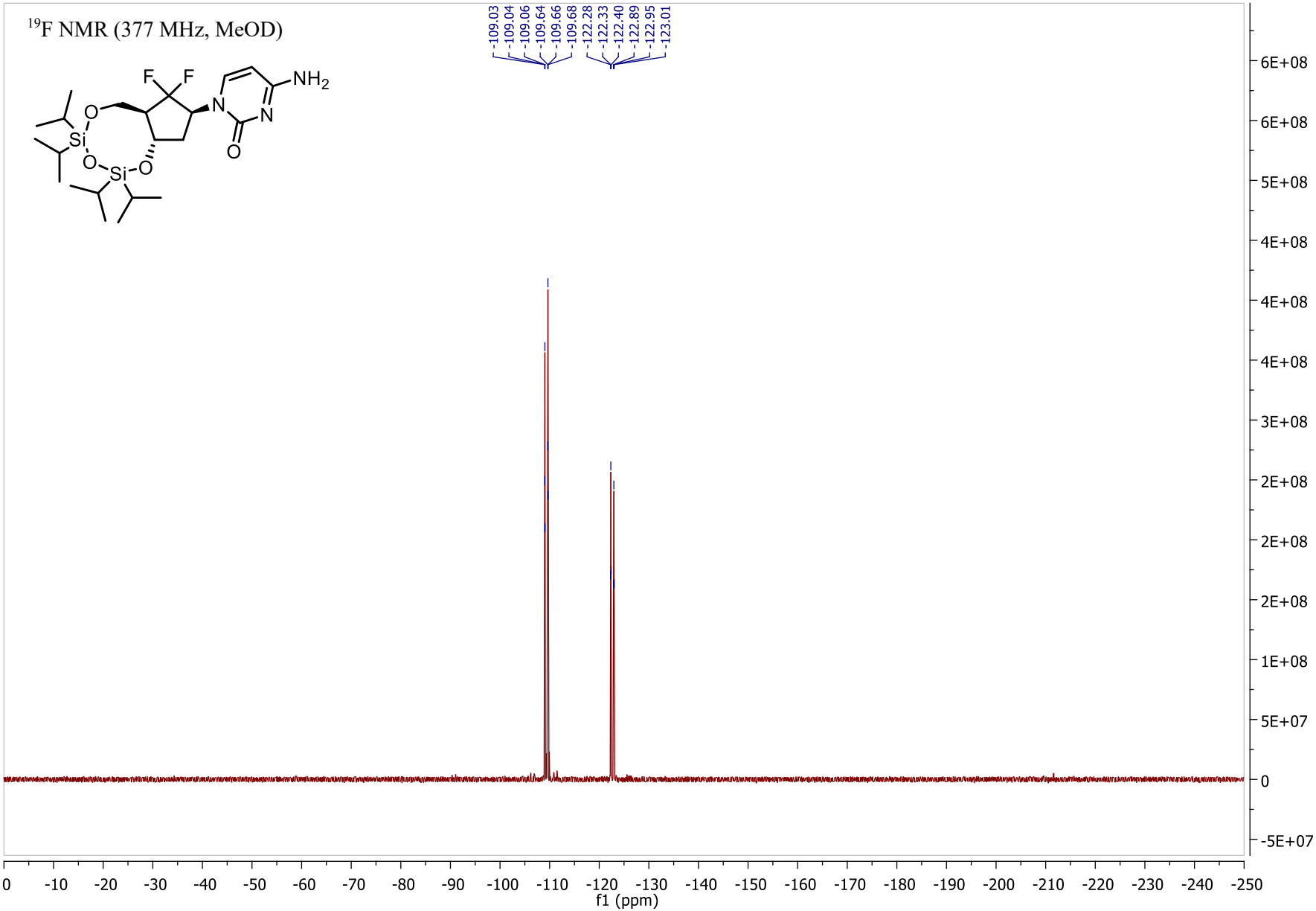
^{19}F NMR (377 MHz, MeOD)



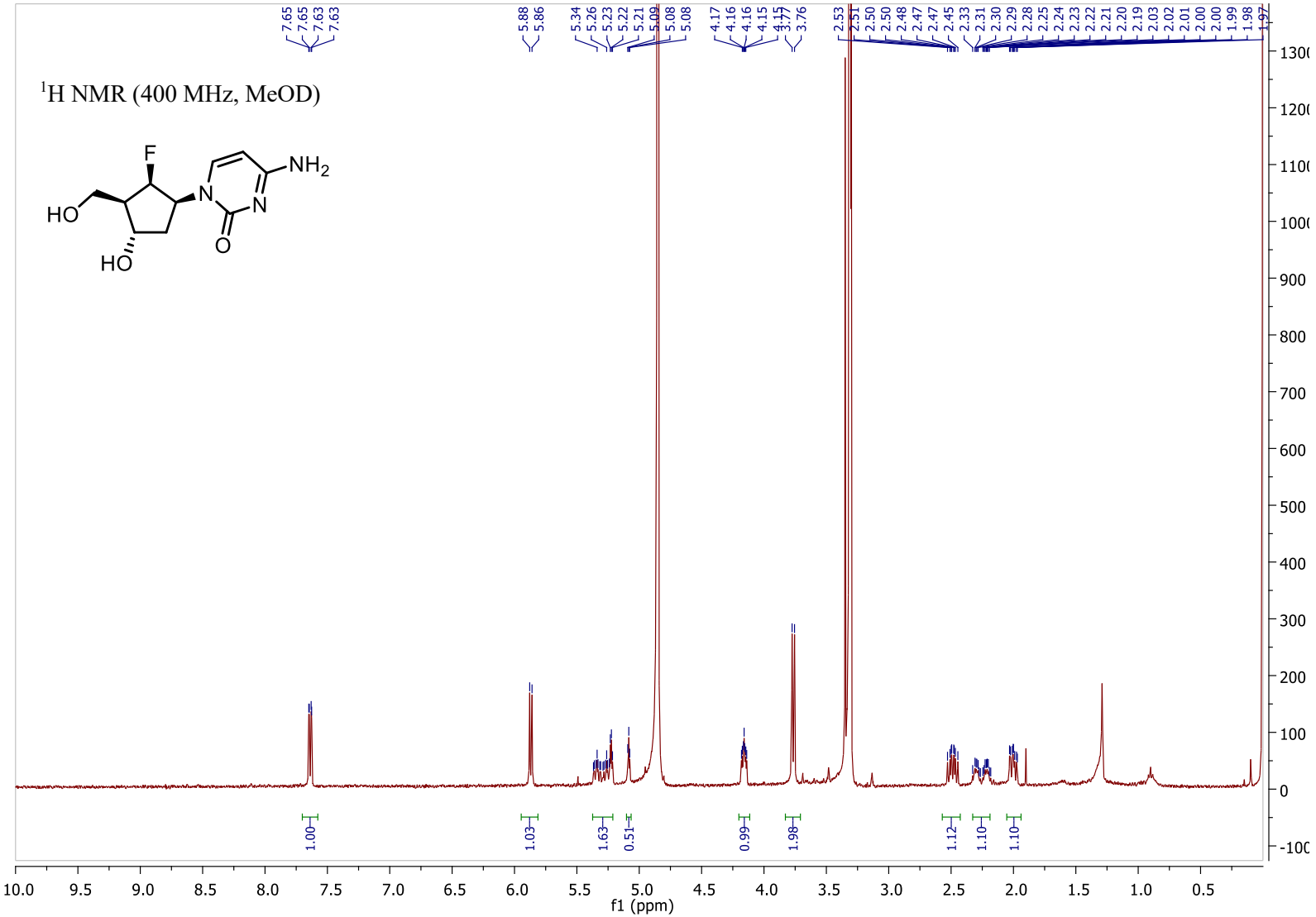
2’-deoxy-3’,5’-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-6’-*gem*-difluorocarbacytidine

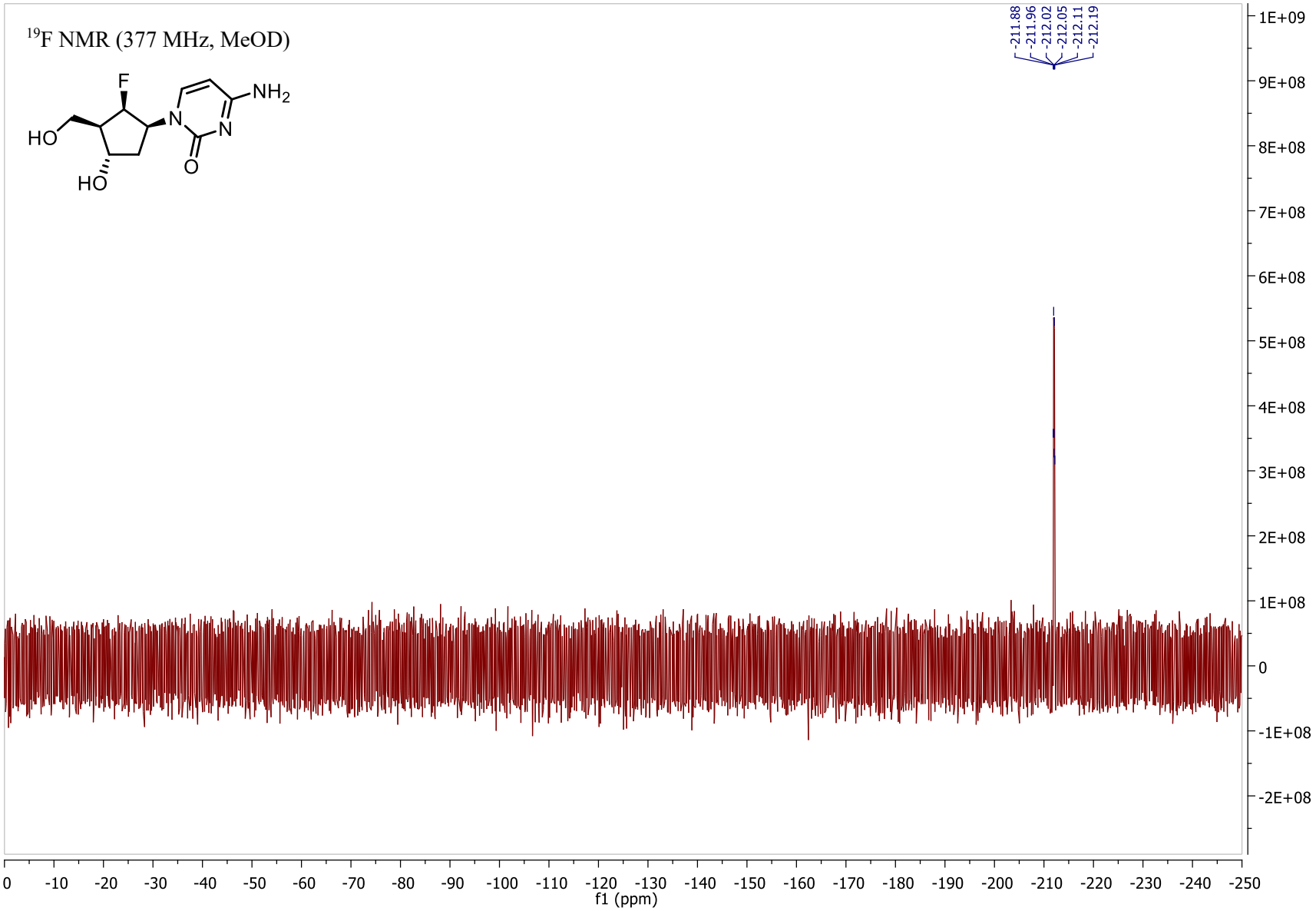



172.96
167.14
158.61
144.65
144.60
127.96
127.87
125.36
96.31
74.10
70.82
70.73
61.52
59.66
59.59
56.97
56.57
56.38
49.43
49.21
49.00
48.79
48.57
48.36
35.65
17.95
17.85
17.83
17.80
17.65
17.52
17.49
14.54
14.47
14.38
14.04
13.78
13C NMR (101 MHz, MeOD)
F
F
NH2
N
N
O
O
Si
O
Si
O
4500
4000
3500
3000
2500
2000
1500
1000
500
0
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

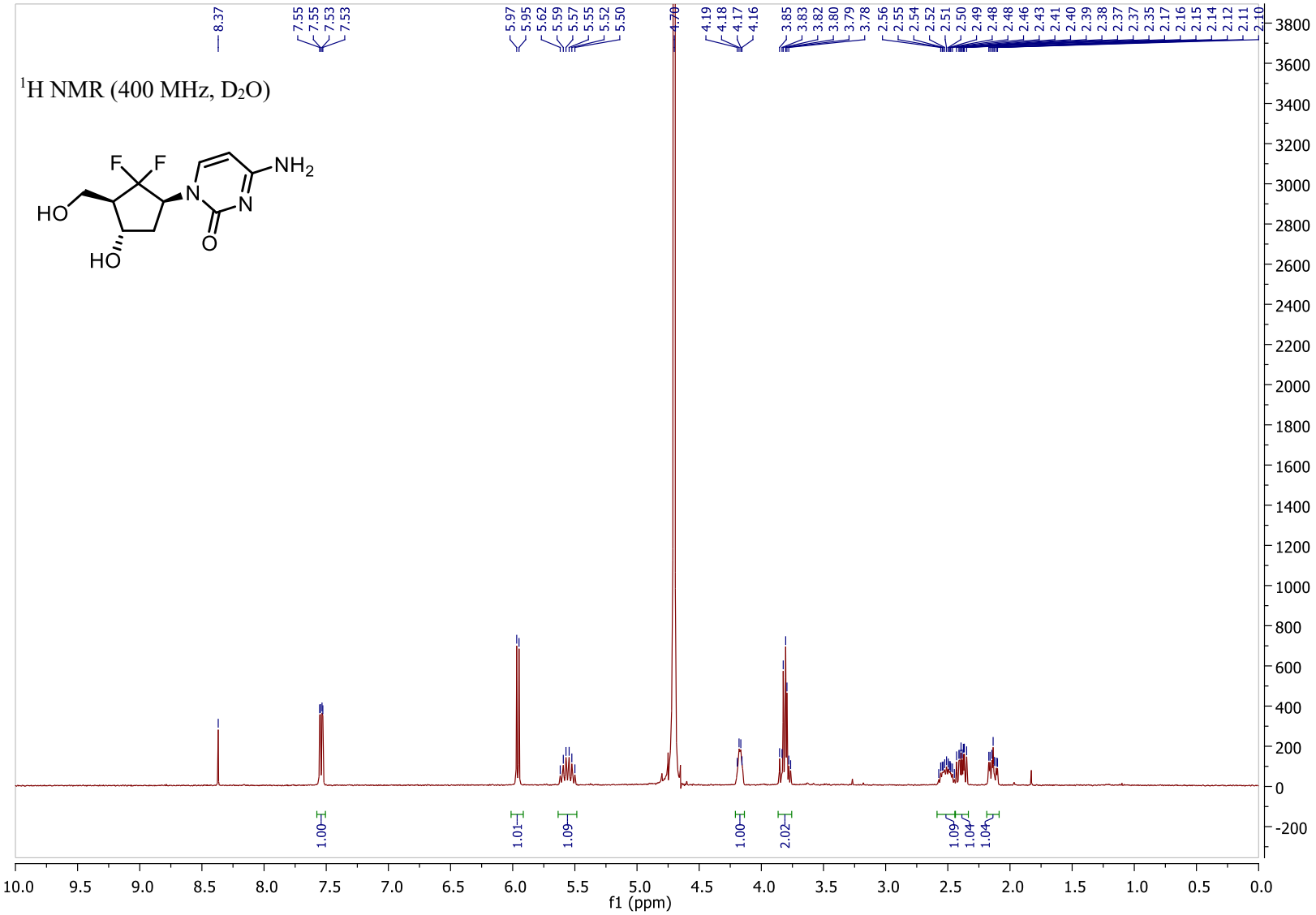

^{19}F NMR (377 MHz, MeOD)
-109.03
-109.04
-109.06
-109.64
-109.66
-109.68
-122.28
-122.33
-122.40
-122.89
-122.95
-123.01
F
F
NH2
N
N
O
O
Si
O
Si
O
6E+08
6E+08
5E+08
4E+08
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
-5E+07
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250
f1 (ppm)

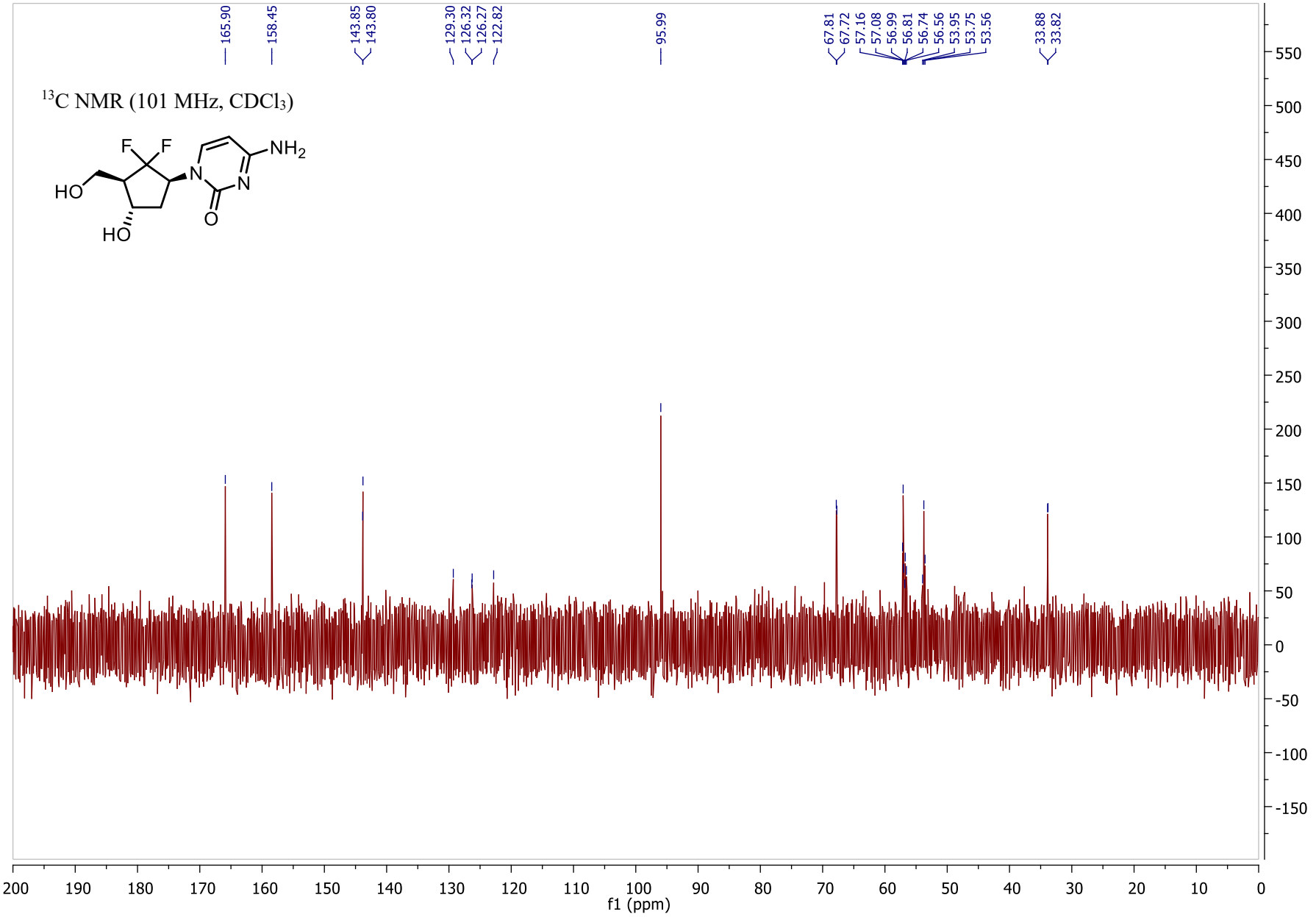
(6'R)-2'-deoxy-6'-fluorocarbacytidine, 34

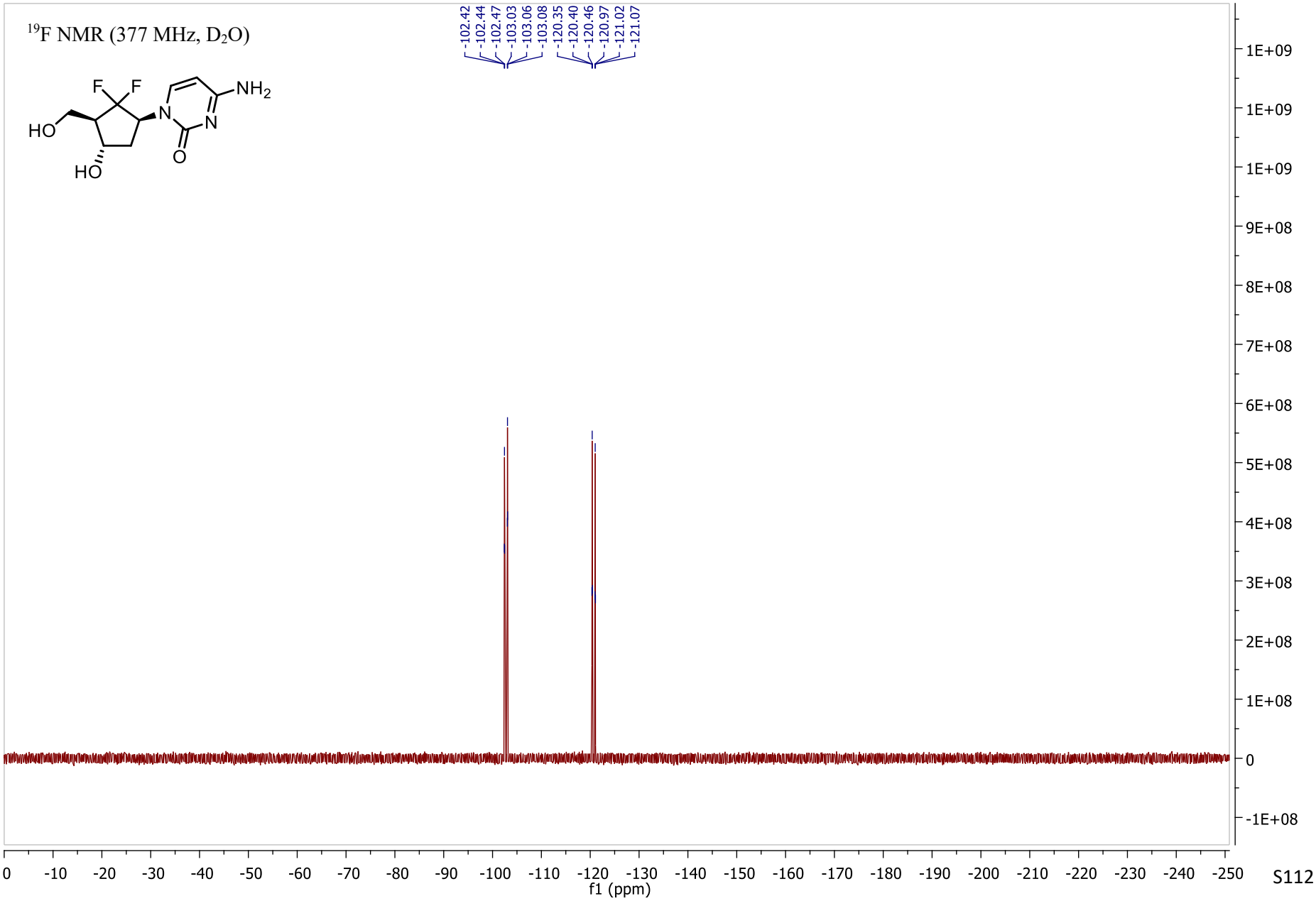



19F NMR (377 MHz, MeOD)
F
NH2
HO
N
N
HO
O
-211.88
-211.96
-212.02
-212.05
-212.11
-212.19
1E+09
9E+08
8E+08
7E+08
6E+08
5E+08
4E+08
3E+08
2E+08
1E+08
0
-1E+08
-2E+08
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250
f1 (ppm)

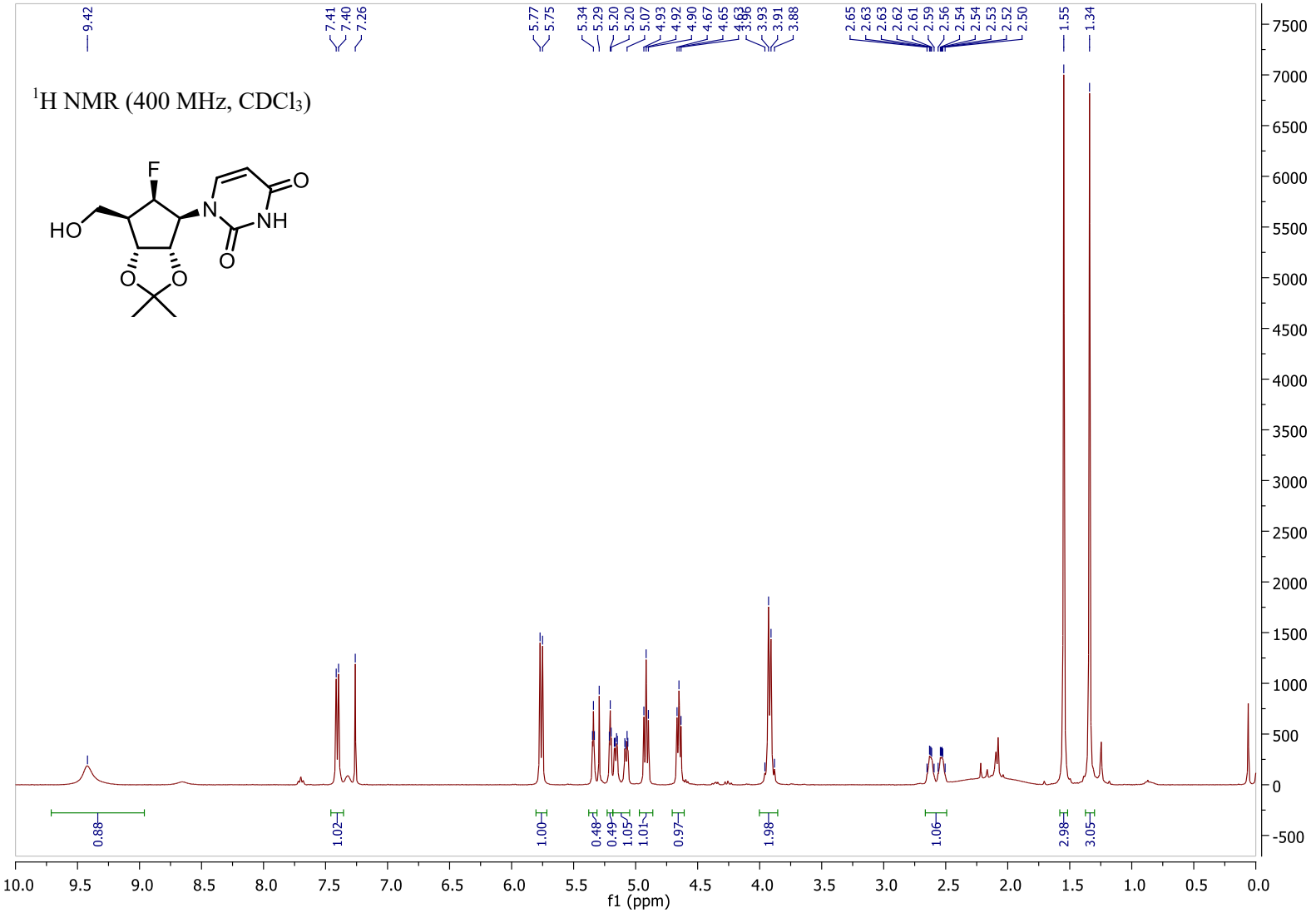
2’-deoxy-6’-*gem*-difluorocarbacytidine, 35

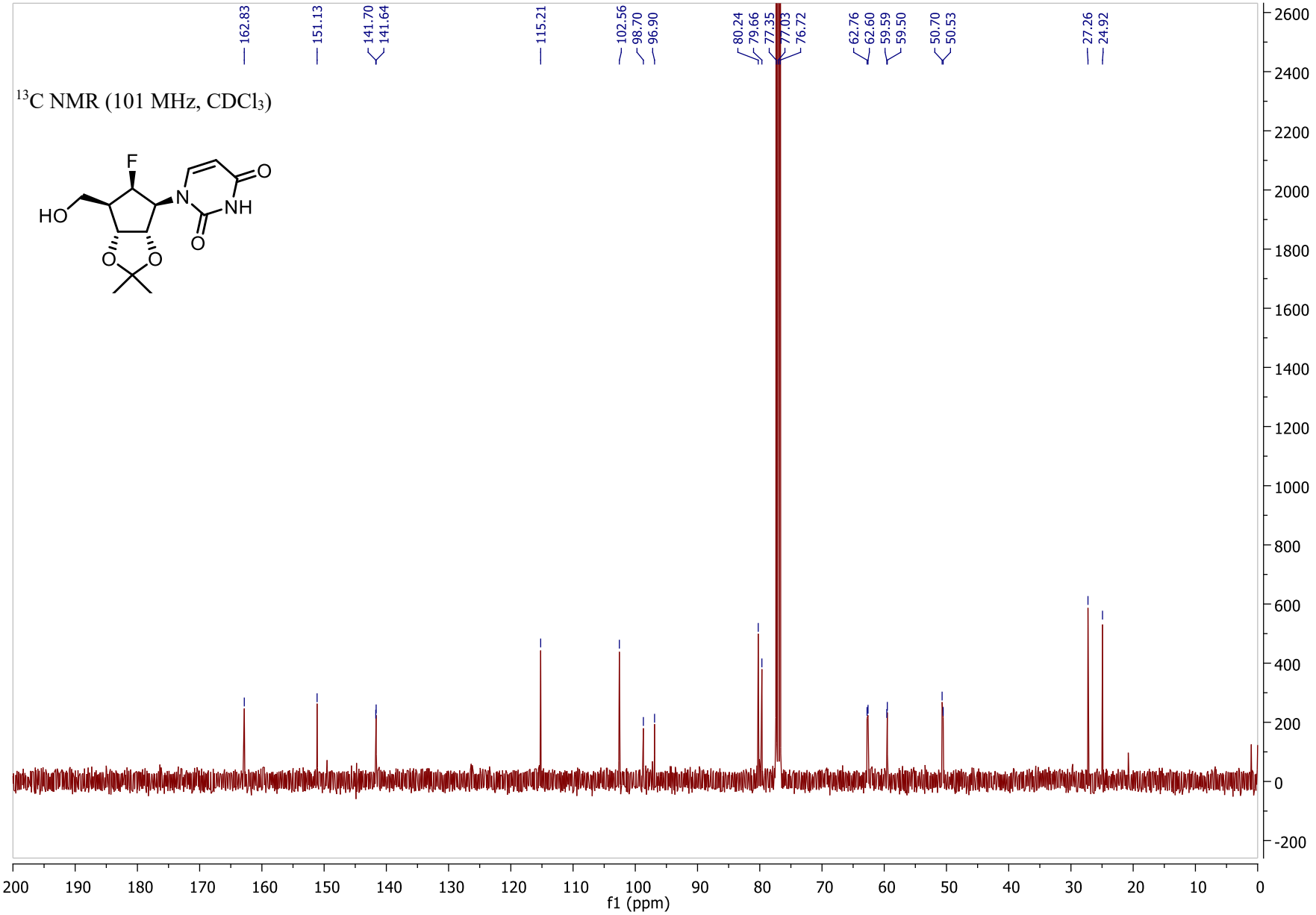



165.90
158.45
143.85
143.80
129.30
126.32
126.27
122.82
95.99
67.81
67.72
57.16
57.08
56.99
56.81
56.74
56.56
53.95
53.75
53.56
33.88
33.82
^{13}C NMR (101 MHz, CDCl$_3$)
F
F
NH$_2$
HO
N
N
O
HO
f1 (ppm)

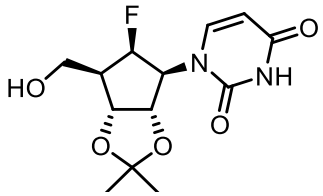

^{19}F NMR (377 MHz, D_2O)
-102.42
-102.44
-102.47
-103.03
-103.06
-103.08
-120.35
-120.40
-120.46
-120.97
-121.02
-121.07
F
F
NH2
HO
HO
N
N
O
1E+09
1E+09
1E+09
9E+08
8E+08
7E+08
6E+08
5E+08
4E+08
3E+08
2E+08
1E+08
0
-1E+08
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250
f1 (ppm)

(6'R)-2',3'-*O*-isopropylidine-6'-fluorocarbauridine, 36

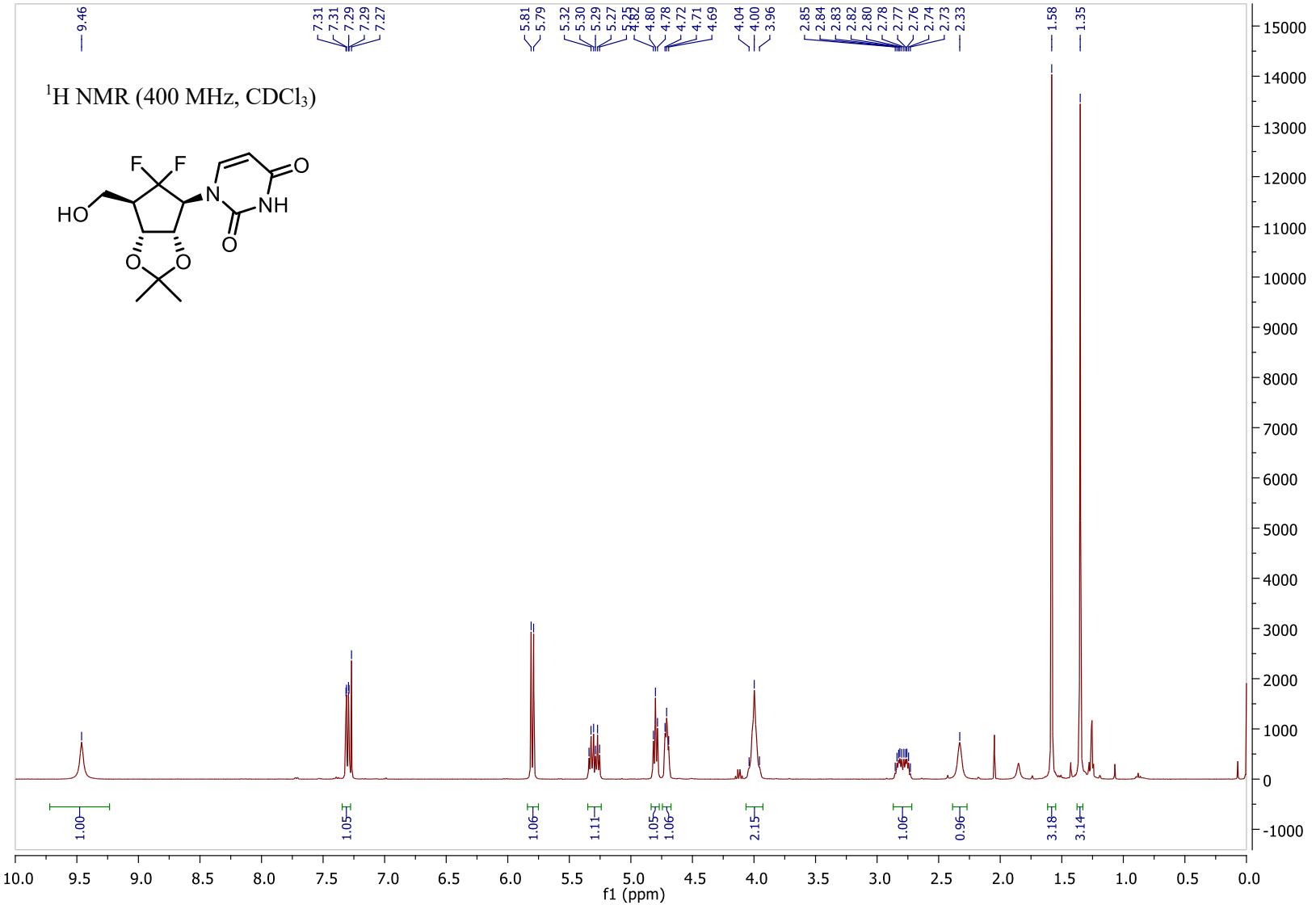


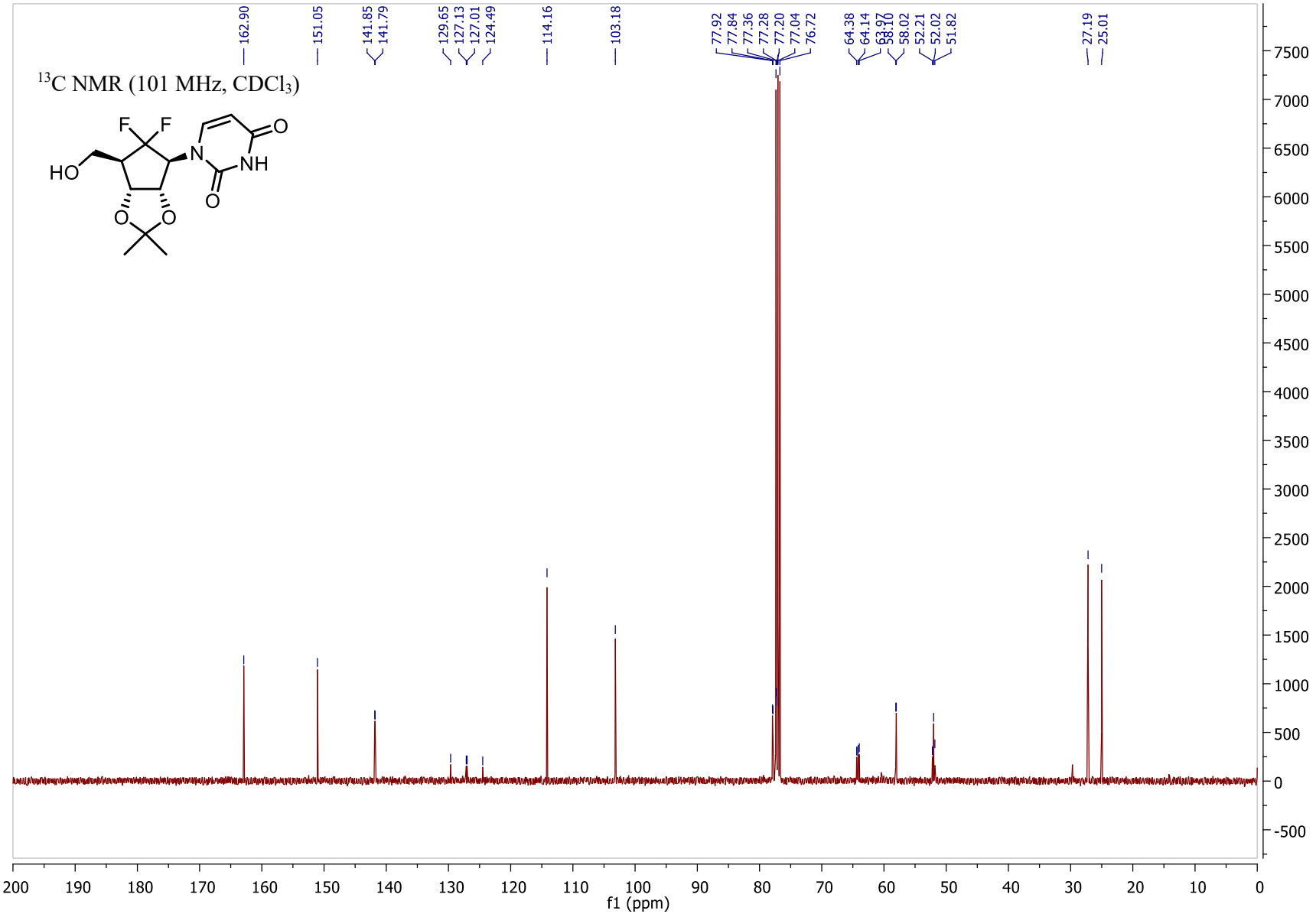

^{13}C NMR (101 MHz, CDCl$_3$)
162.83
151.13
141.70
141.64
115.21
102.56
98.70
96.90
80.24
79.66
77.35
77.03
76.72
62.76
62.60
59.59
59.50
50.70
50.53
27.26
24.92
F
HO
N
NH
O
O
O
O
f1 (ppm)

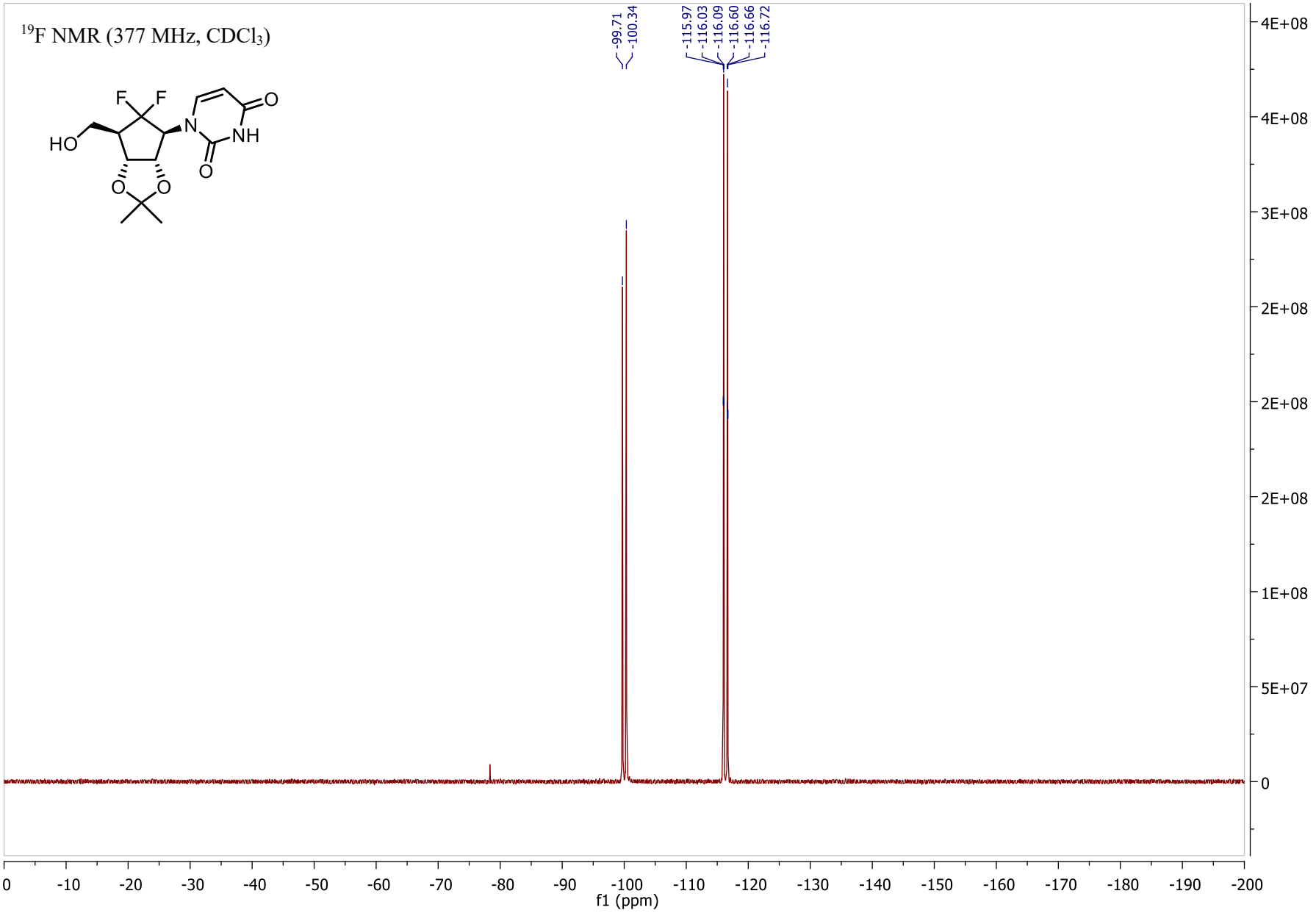
^{19}F NMR (377 MHz, $CDCl_3$)



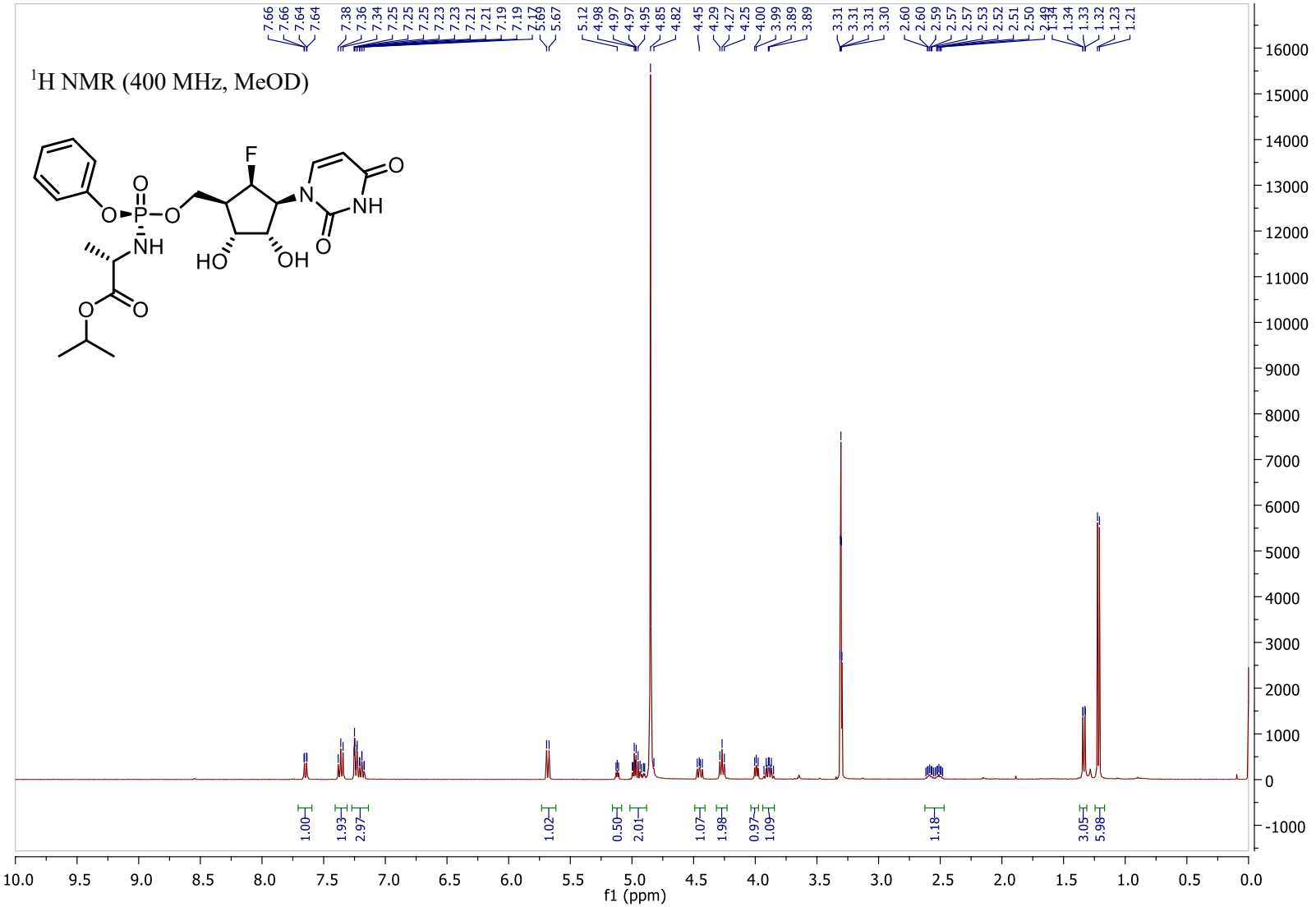
2',3'-*O*-isopropylidine-6'-*gem*-difluorocarbauridine, 37

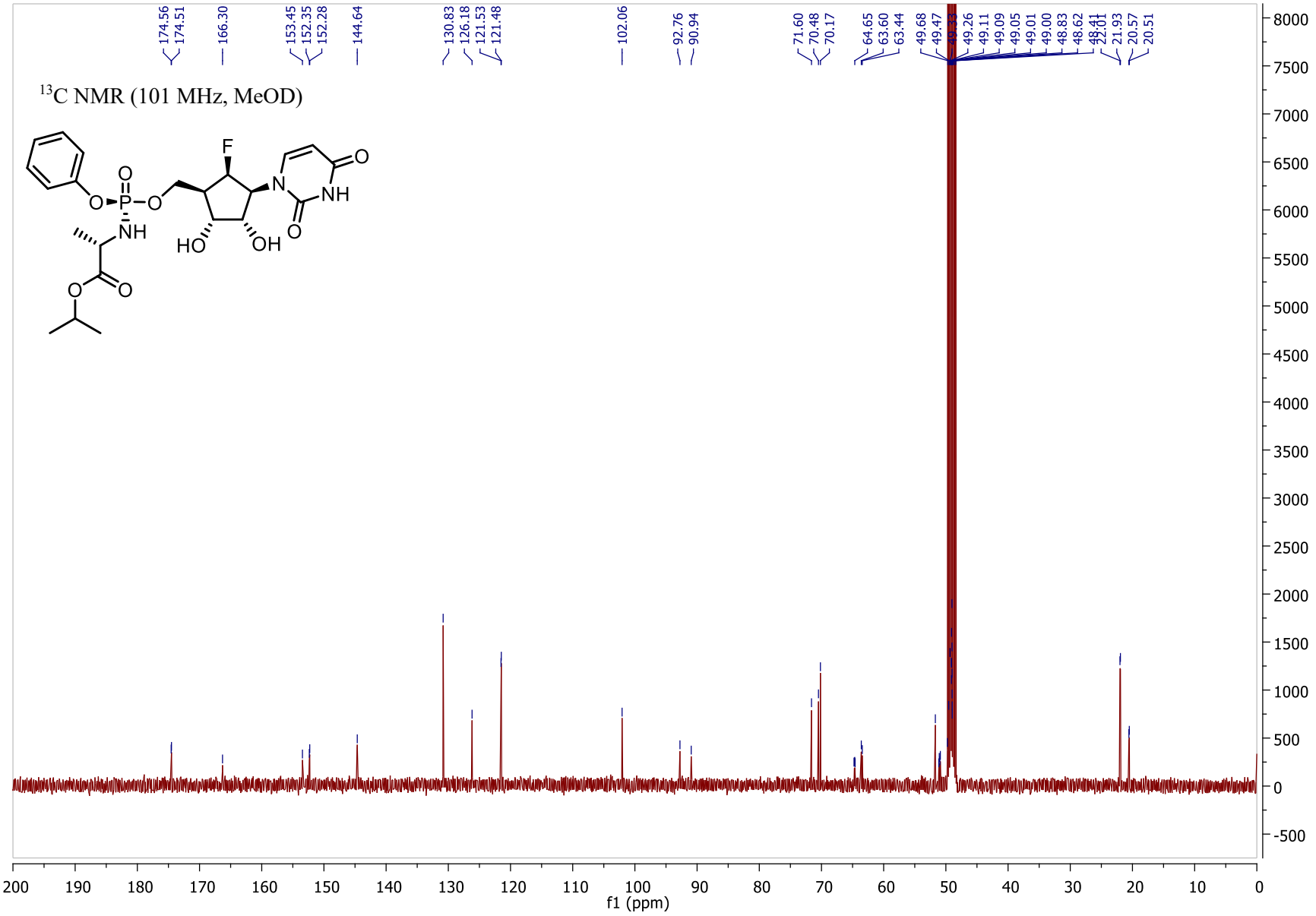



^{13}C NMR (101 MHz, $CDCl_3$)
F
F
HO
N
NH
O
O
O
O
162.90
151.05
141.85
141.79
129.65
127.13
127.01
124.49
114.16
103.18
77.92
77.84
77.36
77.28
77.20
77.04
76.72
64.38
64.14
63.97
58.10
58.02
52.21
52.02
51.82
27.19
25.01
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

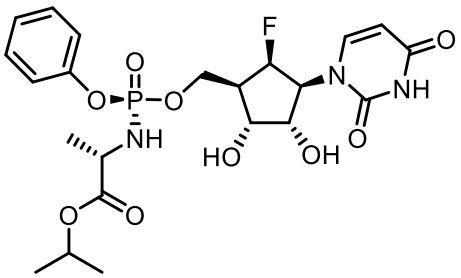

^{19}F NMR (377 MHz, $CDCl_3$)
-99.71
-100.34
-115.97
-116.03
-116.09
-116.60
-116.66
-116.72
F
F
HO
N
NH
O
O
O
O
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

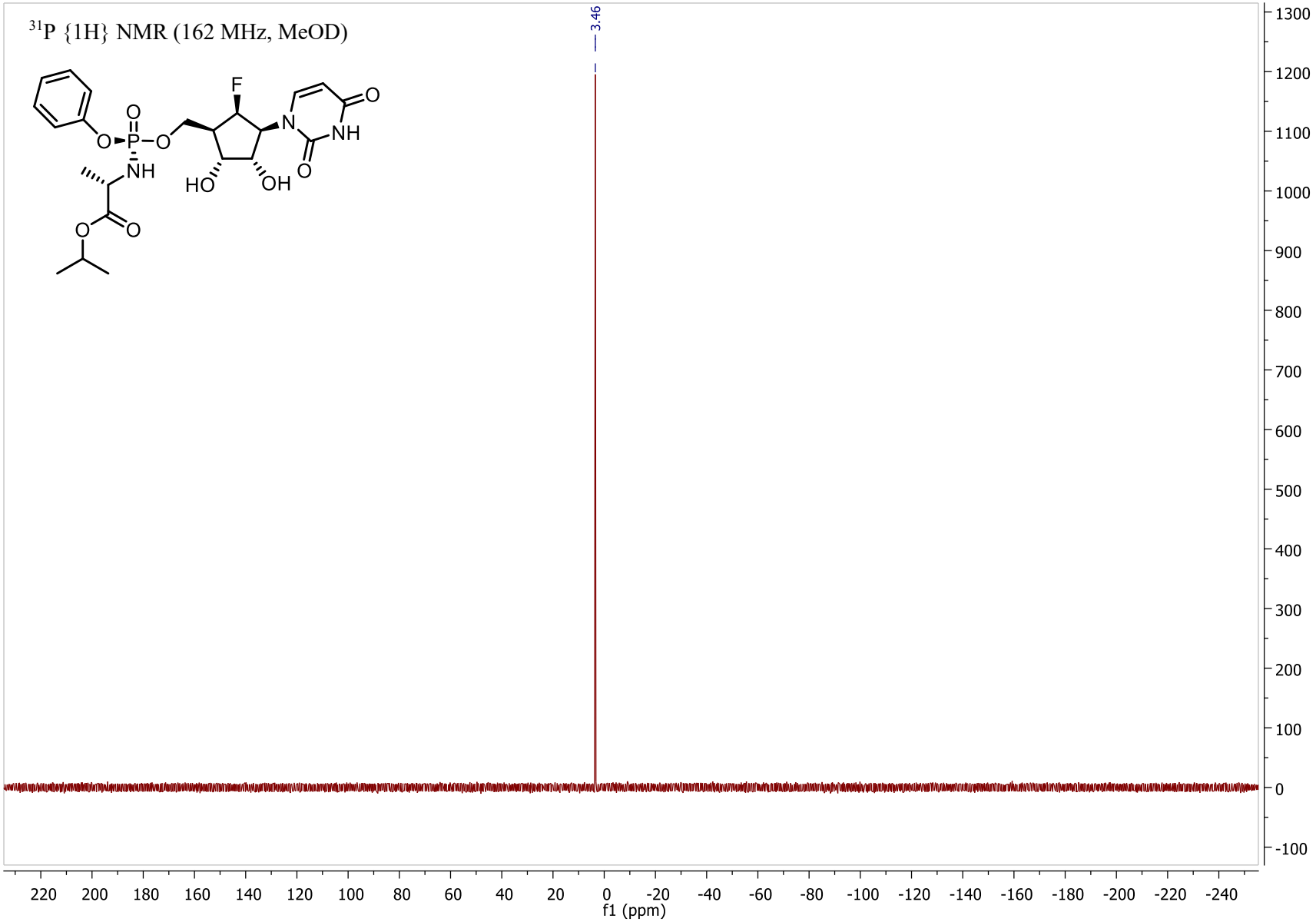
[P(S),6'R]-5'-[phenoxy(isopropyl-L-alaninate)]phosphate-6'-fluorocarbauridine, 39



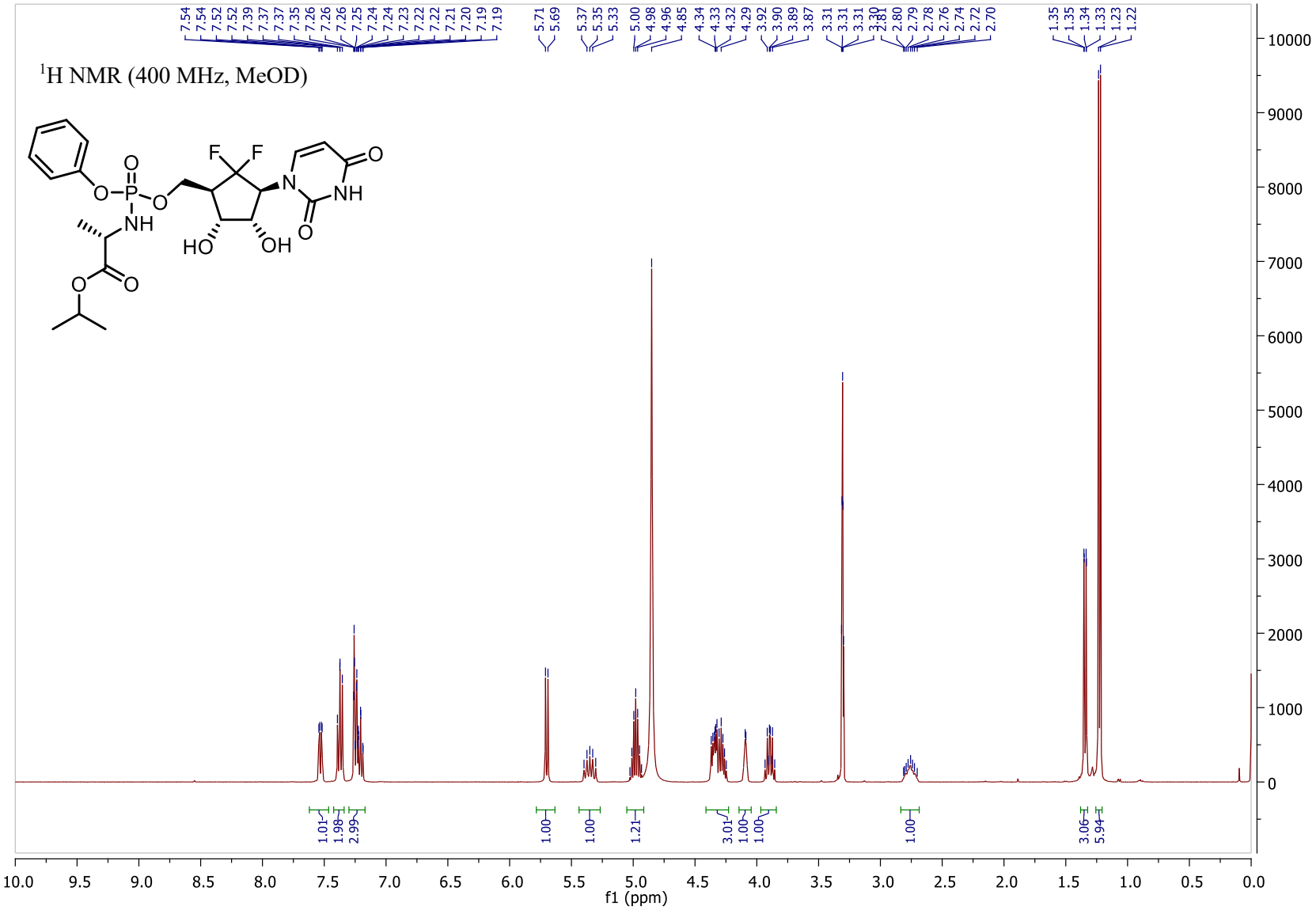

174.56
174.51
166.30
153.45
152.35
152.28
144.64
130.83
126.18
121.53
121.48
102.06
92.76
90.94
71.60
70.48
70.17
64.65
63.60
63.44
49.68
49.47
49.33
49.26
49.11
49.09
49.05
49.01
49.00
48.83
48.62
48.41
48.21
21.93
20.57
20.51
^{13}C NMR (101 MHz, MeOD)
F
O
O
P
O
O
NH
HO
OH
N
NH
O
O
O
O
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

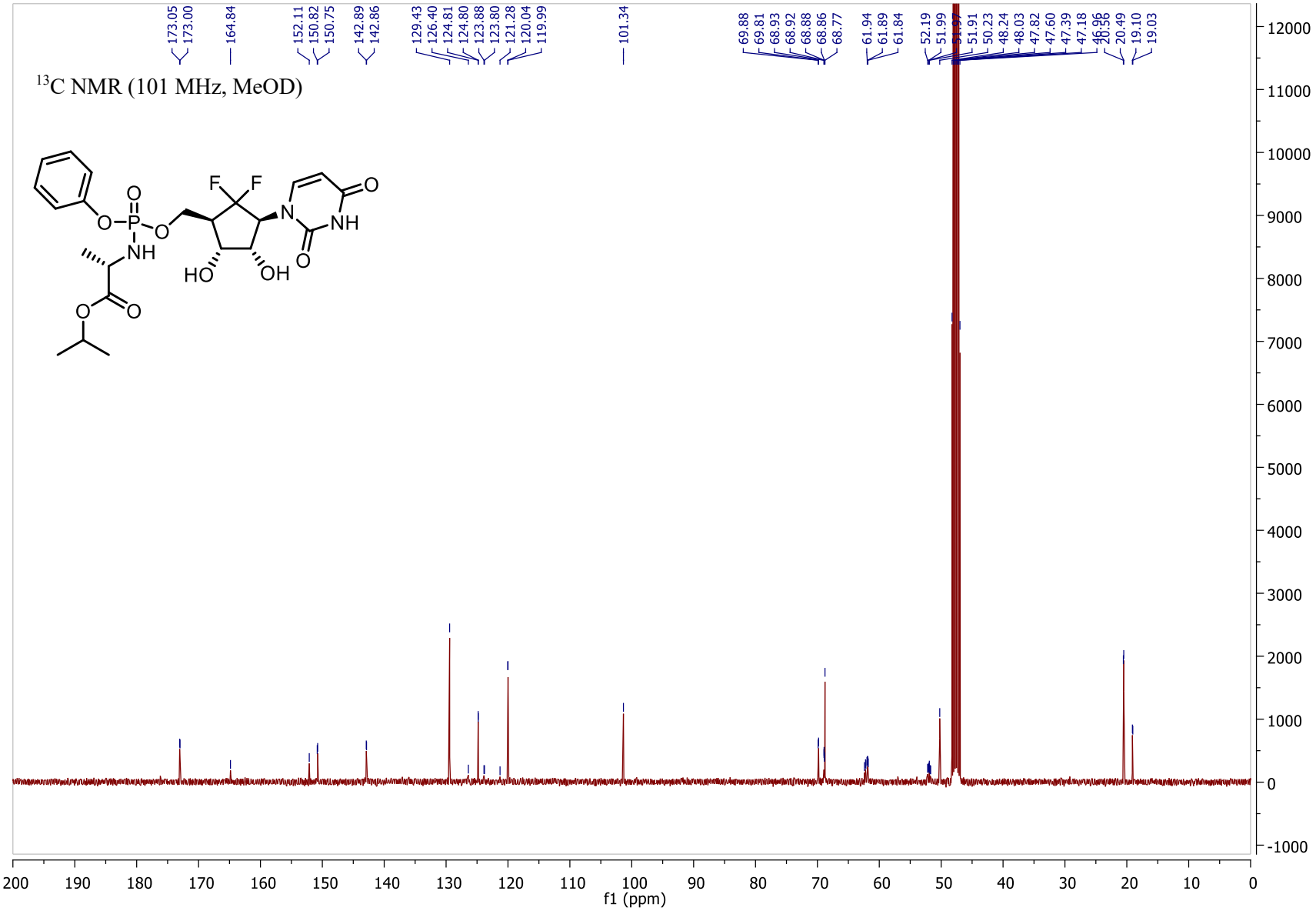
^{19}F NMR (377 MHz, MeOD)

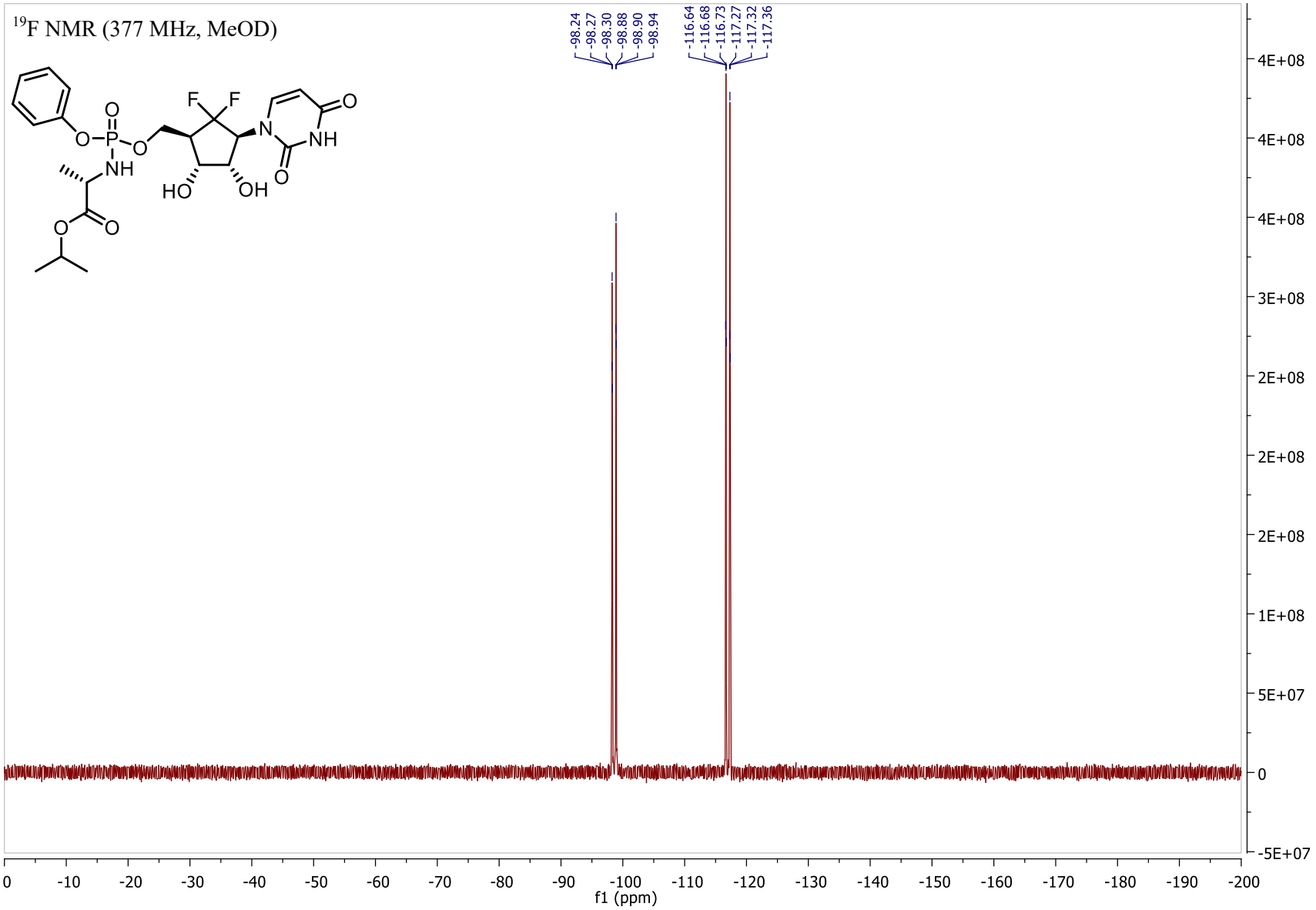


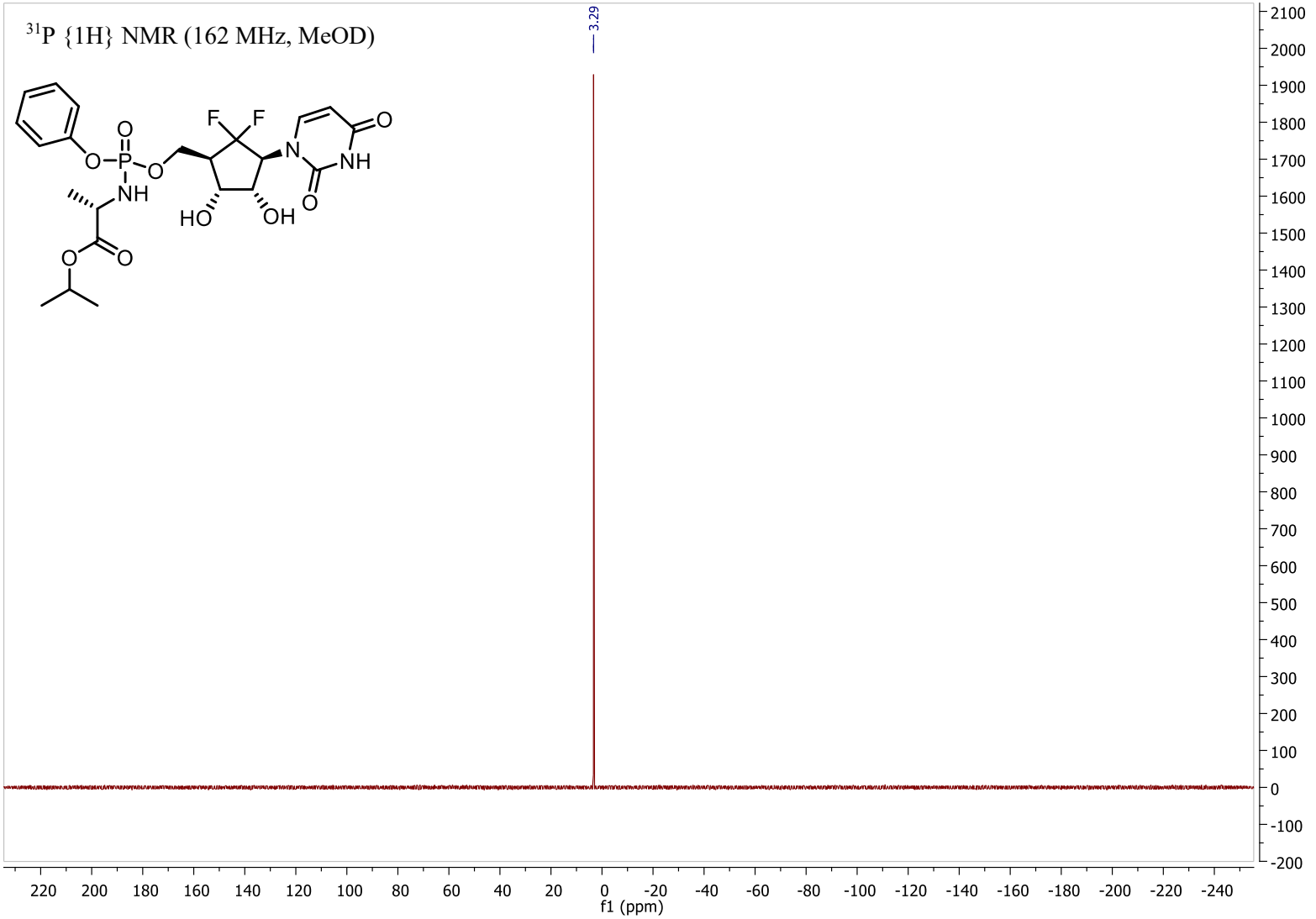

31P {1H} NMR (162 MHz, MeOD)
3.46
F
O
O
P
O
O
NH
HO
OH
N
NH
O
O
O
O
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
f1 (ppm)

[P(S)]-5'-[phenoxy(isopropyl-L-alaninate)]phosphate-6'-*gem*-difluorocarbauridine, 40




173.05
173.00
164.84
152.11
150.82
150.75
142.89
142.86
129.43
126.40
124.81
124.80
123.88
123.80
121.28
120.04
119.99
101.34
69.88
69.81
68.93
68.92
68.88
68.86
68.77
61.94
61.89
61.84
52.19
51.99
51.97
51.91
50.23
48.24
48.03
47.82
47.60
47.39
47.18
46.96
46.56
20.49
19.10
19.03
13C NMR (101 MHz, MeOD)
F
F
O
O
P
O
NH
HO
OH
N
NH
O
O
O
O
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

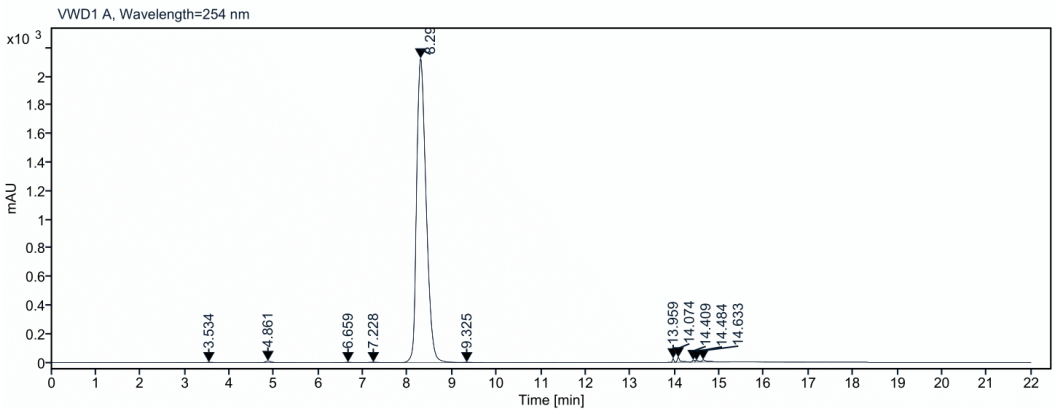

19F NMR (377 MHz, MeOD)
-98.24
-98.27
-98.30
-98.88
-98.90
-98.94
-116.64
-116.68
-116.73
-117.27
-117.32
-117.36
4E+08
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
-5E+07
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)


31P {1H} NMR (162 MHz, MeOD)
3.29
F
F
O
O
P
O
O
NH
N
NH
O
HO
OH
O
O
O
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-200
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
f1 (ppm)

S4. Analytical HPLC traces

(6'R)-6'-fluorocarbauridine, 22

Injection volume: 100.000

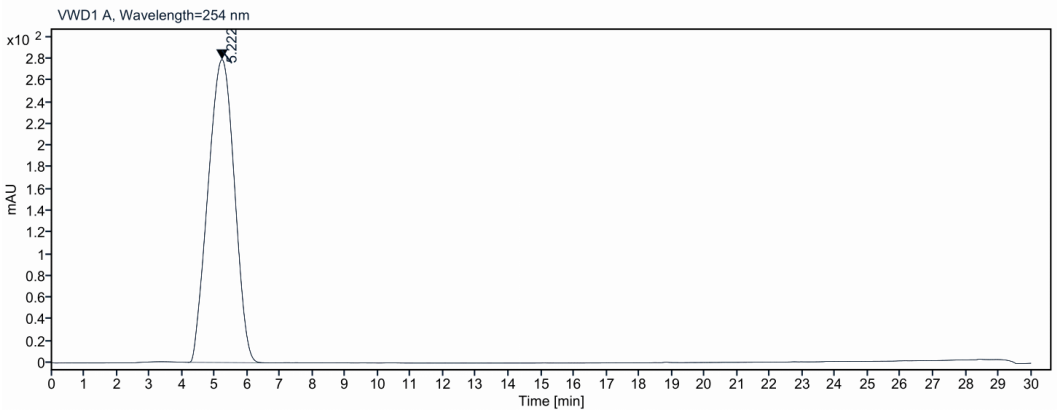


Signal: VWD1 A, Wavelength=254 nm

RT [min]	Type	Width [min]	Area	Height	Area%	Name
3.534	VB	0.1213	15.6467	1.9669	0.0487	
4.861	BV R	0.1476	105.9897	11.0772	0.3297	
6.659	BB	0.1757	29.6856	2.5812	0.0923	
7.228	BB	0.2646	42.5403	2.5371	0.1323	
8.290	BV R	0.2319	31448.5234	2127.6111	97.8177	
9.325	VB E	0.2426	29.6049	1.8028	0.0921	
13.959	BV	0.0356	61.5502	26.9799	0.1914	
14.074	VV R	0.0707	169.0330	33.8756	0.5258	
14.409	BV	0.0536	52.1228	14.2621	0.1621	
14.484	VV	0.0770	64.8160	11.2930	0.2016	
14.633	VB	0.1082	130.6185	16.0069	0.4063	
		Sum	32150.1311			

6’-*gem*-difluorocarbauridine, 23

Injection volume: 10.000

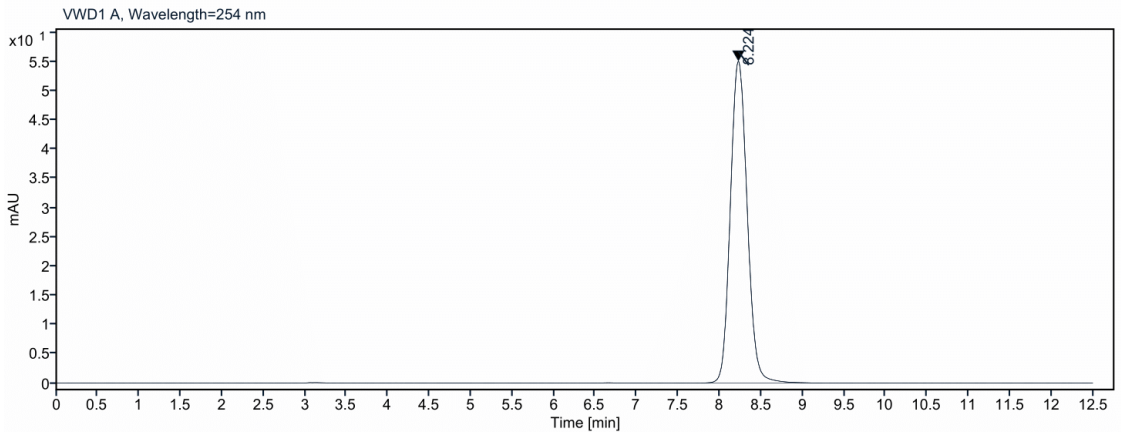


Signal: VWD1 A, Wavelength=254 nm

RT [min]	Type	Width [min]	Area	Height	Area%	Name
5.222	BB	0.8771	15628.0771	278.9569	100.0000	
		Sum	15628.0771			

(6’R)-6’-fluorocarbacytidine, 26

Injection volume: 10.000

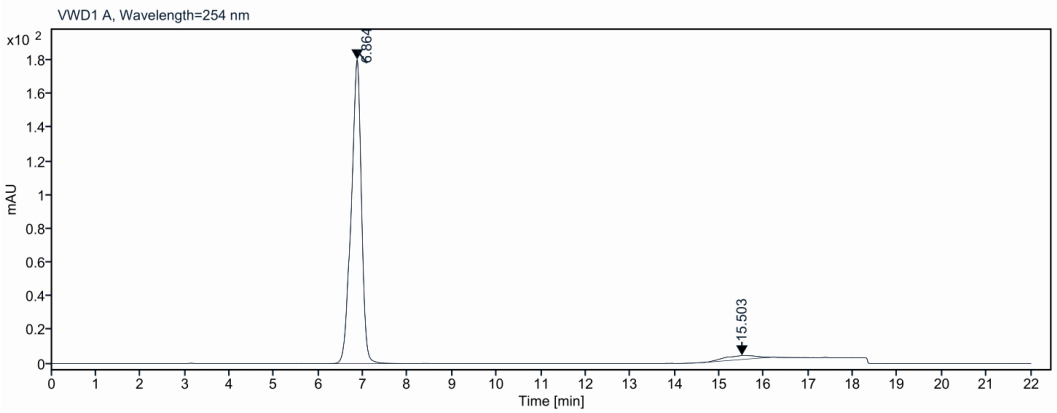


Signal: VWD1 A, Wavelength=254 nm

RT [min]	Type	Width [min]	Area	Height	Area%	Name
8.224	BB	0.2225	778.8843	55.0890	100.0000	
		Sum	778.8843			

6’-*gem*-difluorocarbacytidine, 27

Injection volume: 50.000

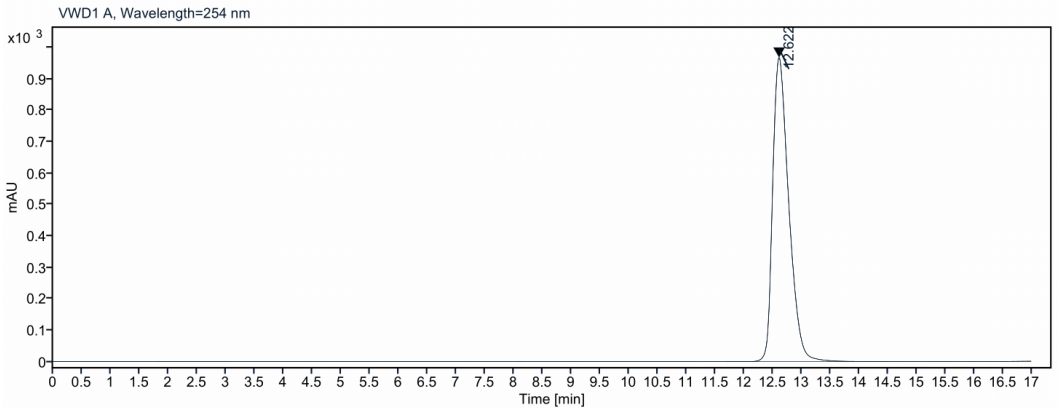


Signal: VWD1 A, Wavelength=254 nm

RT [min]	Type	Width [min]	Area	Height	Area%	Name
6.864	BB	0.2352	2864.7566	180.4935	96.1473	
15.503	BB	0.5787	114.7917	2.3550	3.8527	
		Sum	2979.5483			

(6’R)-2’-deoxy-6’-fluorocarbauridine, 32

Injection volume: 100.000

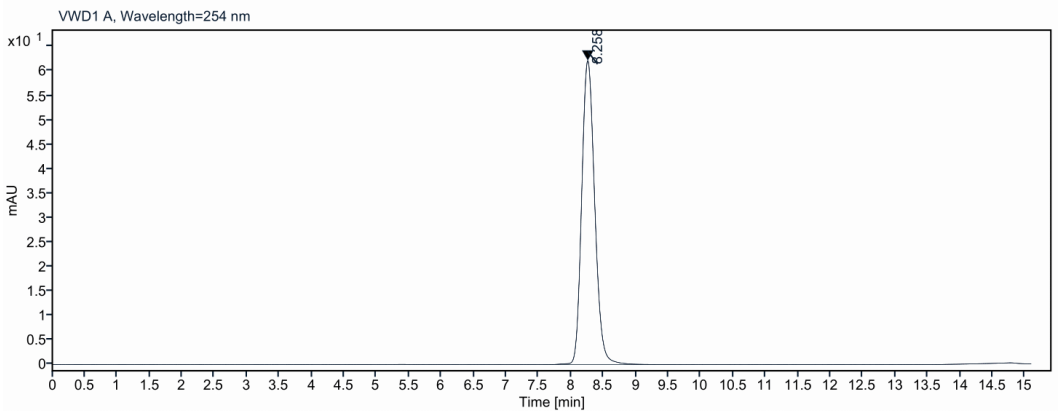


Signal: VWD1 A, Wavelength=254 nm

RT [min]	Type	Width [min]	Area	Height	Area%	Name
12.622	BB	0.3008	18820.7617	968.1412	100.0000	
		Sum	18820.7617			

2’-deoxy-6’-*gem*-diflurocarbauridine, 33

Injection volume: 10.000

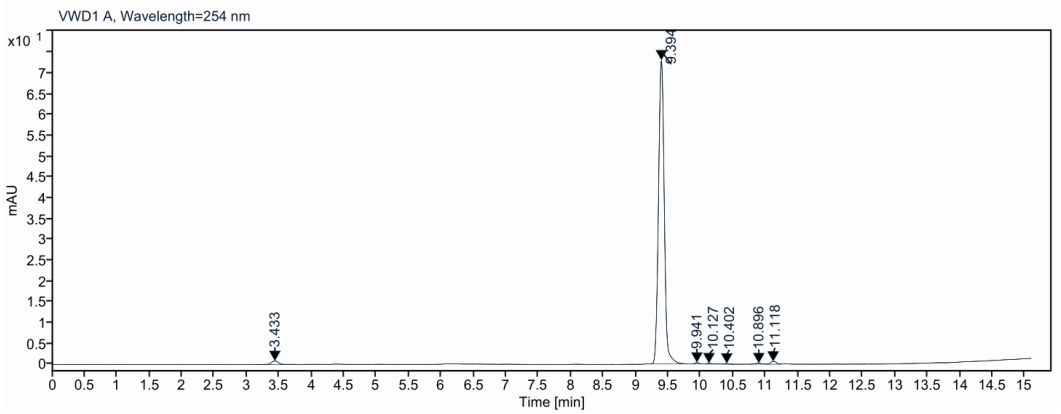


Signal: VWD1 A, Wavelength=254 nm

RT [min]	Type	Width [min]	Area	Height	Area%	Name
8.258	BB	0.2171	865.9586	62.1328	100.0000	
		Sum	865.9586			

(6’R)-2’-deoxy-6’-fluorocarbacytidine, 34

Injection volume: 50.000

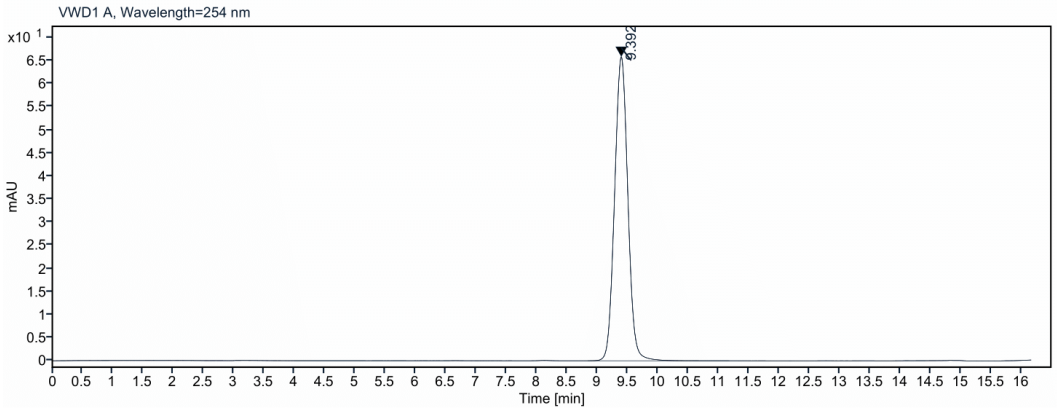


Signal: VWD1 A, Wavelength=254 nm

RT [min]	Type	Width [min]	Area	Height	Area%	Name
3.433	BB	0.1253	6.8946	0.8624	1.4755	
9.394	MM	0.1031	451.0885	72.9289	96.5342	
9.941	MM	0.0665	1.3480	0.3380	0.2885	
10.127	MM	0.0932	1.1137	0.1992	0.2383	
10.402	MM	0.1199	1.1447	0.1591	0.2450	
10.896	MM	0.0982	1.3438	0.2281	0.2876	
11.118	MM	0.1093	4.3505	0.6634	0.9310	
		Sum	467.2838			

2’-deoxy-6’-*gem*-difluorocarbacytidine, 35

Injection volume: 100.000

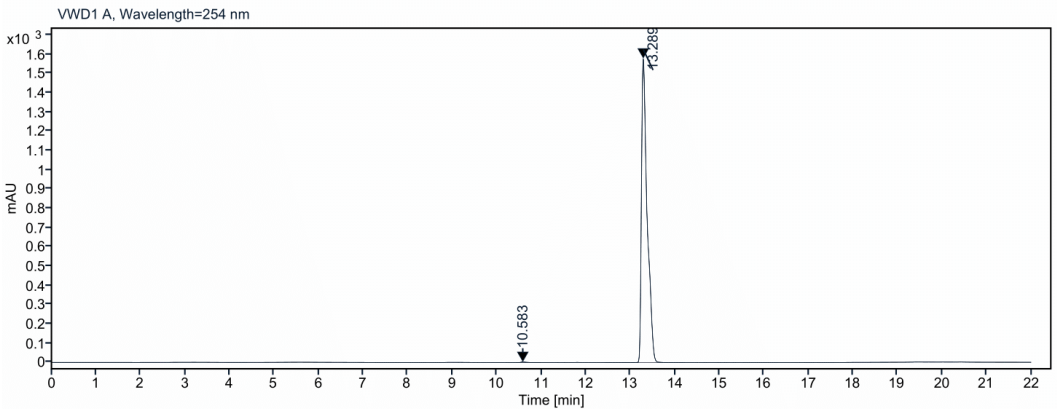


Signal: VWD1 A, Wavelength=254 nm

RT [min]	Type	Width [min]	Area	Height	Area%	Name
9.392	BB	0.2374	1000.1068	65.7621	100.0000	
		Sum	1000.1068			

[P(S),6’R]-5’-[phenoxy(isopropyl-L-alaninate)]phosphate-6’-fluorocarbauridine, 39

Injection volume: 20.000

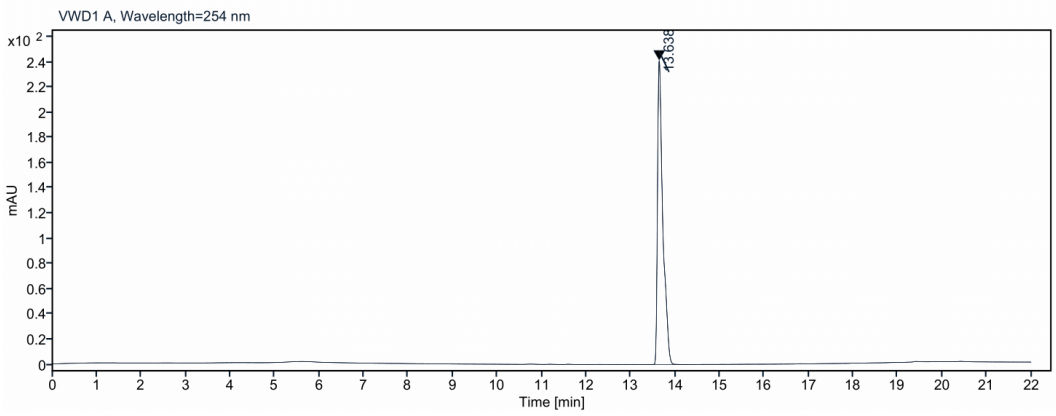


Signal: VWD1 A, Wavelength=254 nm

RT [min]	Type	Width [min]	Area	Height	Area%	Name
10.583	BB	0.1303	33.7797	3.7620	0.2394	
13.289	VB R	0.1296	14075.0127	1577.6689	99.7606	
		Sum	14108.7924			

[P(S)]-5'-[phenoxy(isopropyl-L-alaninate)]phosphate-6'-*gem*-difluorocarbauridine, 40

Injection volume: 5.000



Signal: VWD1 A, Wavelength=254 nm

RT [min]	Type	Width [min]	Area	Height	Area%	Name
13.638	BB	0.1227	2008.7583	241.1332	100.0000	
		Sum	2008.7583			

S5. References

1. *Bruker APEX-3*, Bruker-AXS Inc., Madison, WI, 2016.

2. *SADABS*, Bruker-AXS Inc., Madison, WI, 2016.

3. G. M. Sheldrick, *Acta Crystallogr., Sect. A: Found. Adv*., 2015, **71**, 3–8.

4. G. M. Sheldrick, *Acta Crystallogr., Sect. C: Struct. Chem.*, 2015, **71**, 3–8.

5. O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, *J. Appl. Crystallogr.*, 2009, **42**, 339–341.