Promotional effect of ionic liquids in electrophilic fluorination of methylated uracils

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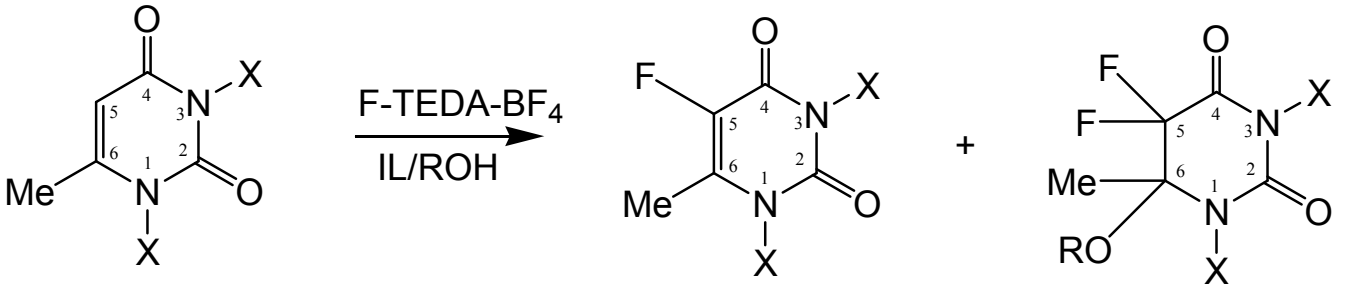
Electronic Supplementary Information



X = H, **1**,
X = Me, **2**

X = H, **3**,
X = Me, **4**

X = H, R = Me **5**,
X = Me, R = Me, **6**,
X = H, R = Et, **7**,
X = Me, R = Et, **8**

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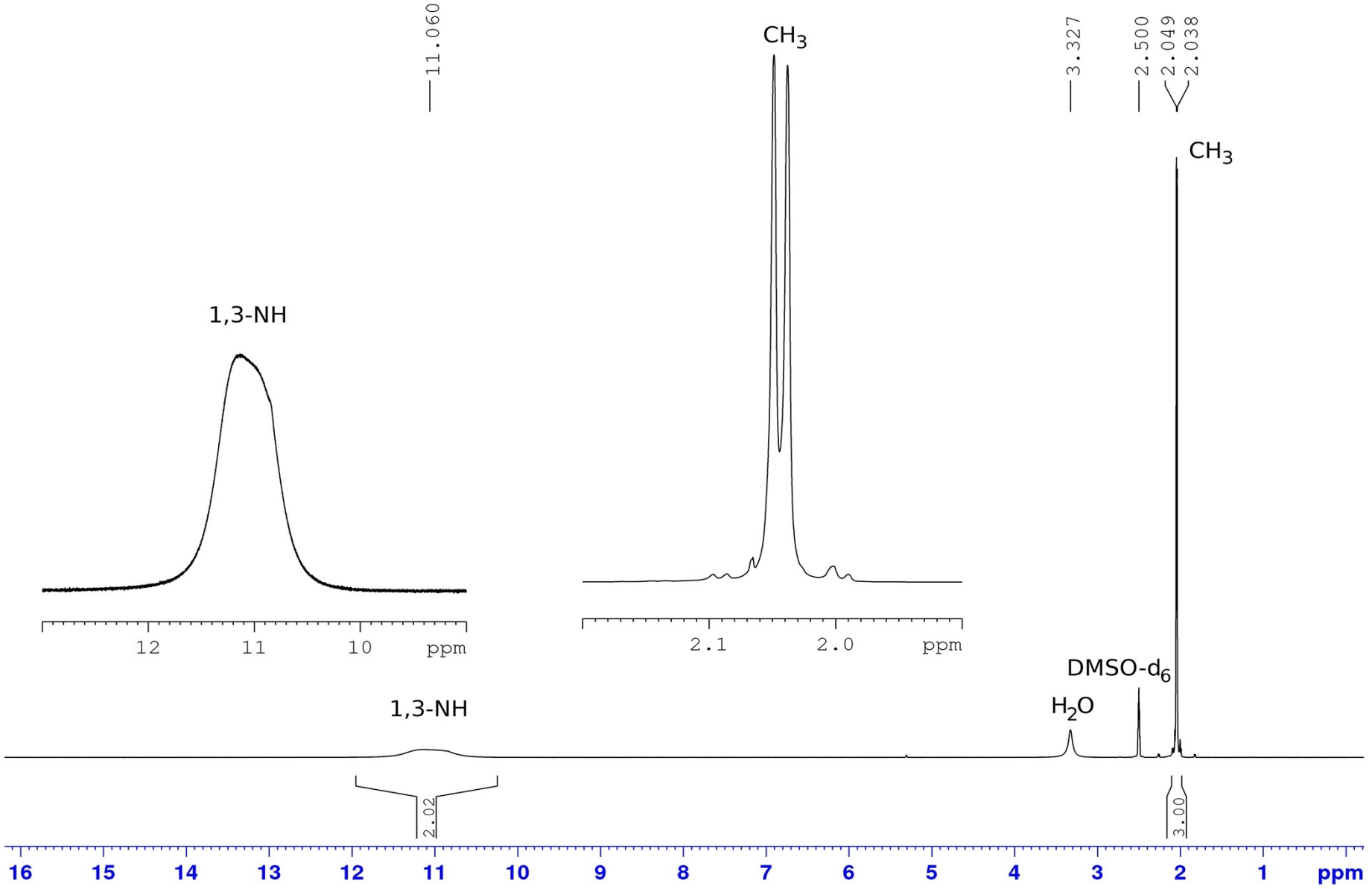
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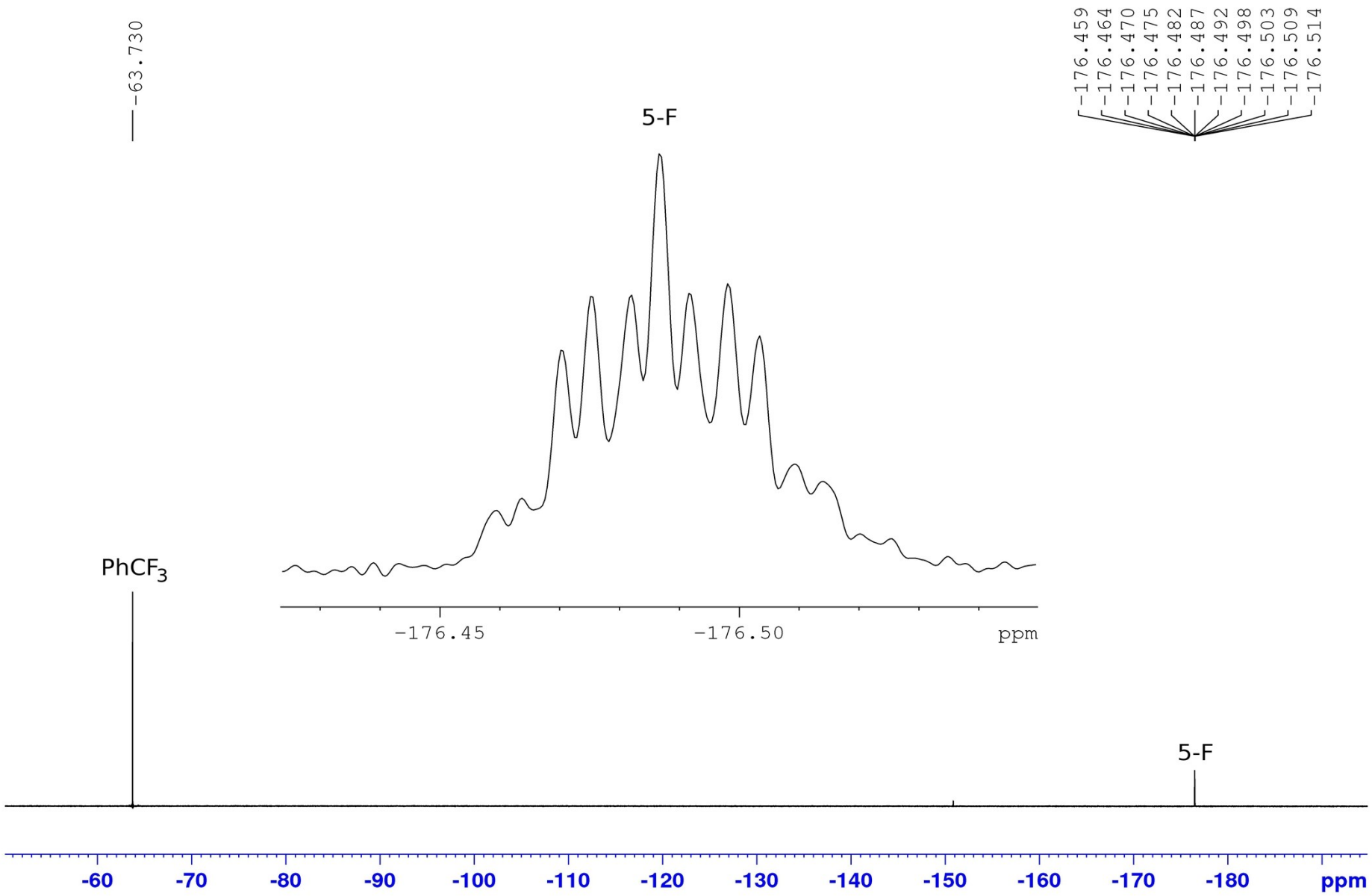
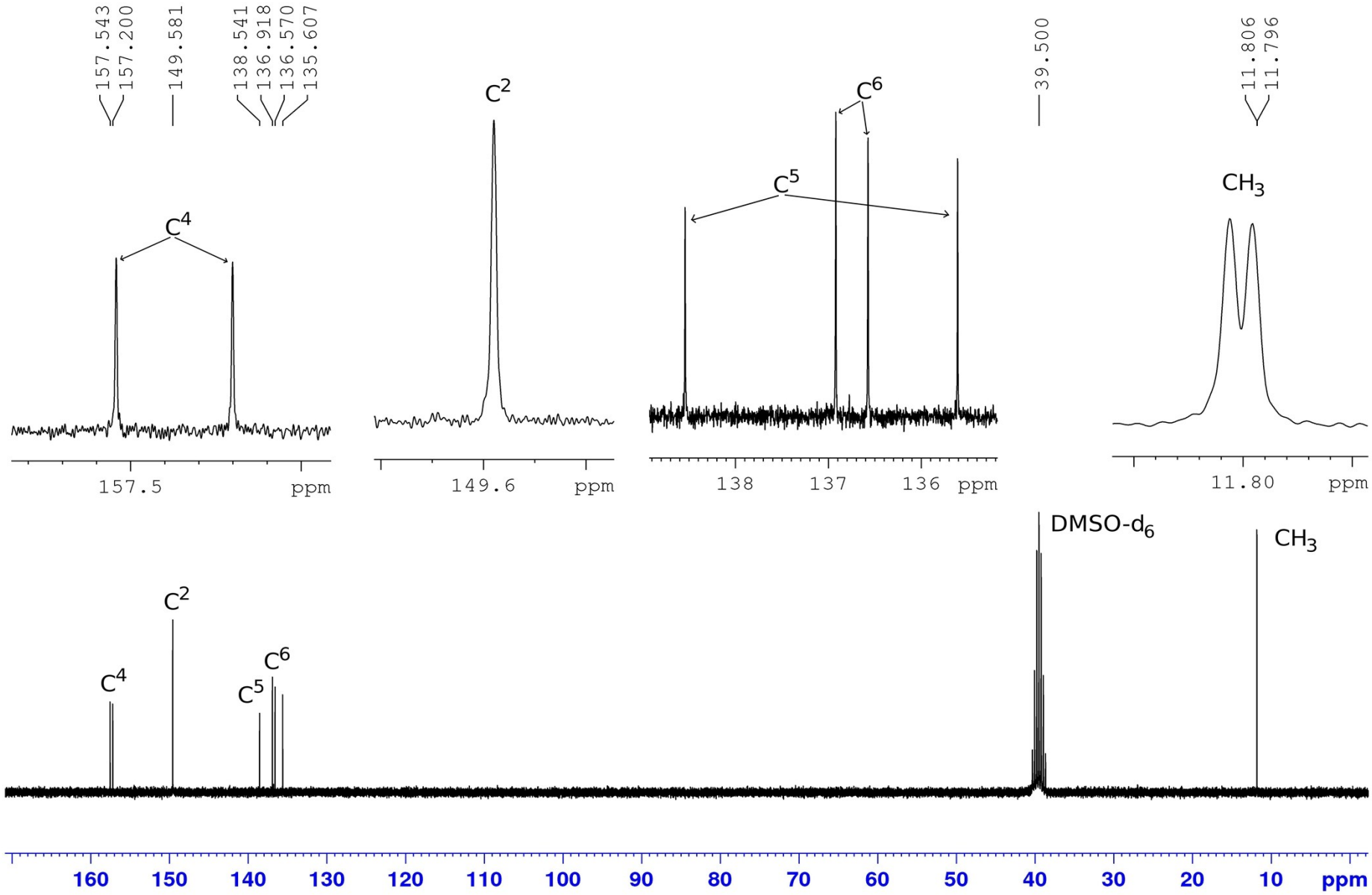
CH3
3.327
2.500
2.049
2.038
CH3
1,3-NH
12
11
10
ppm
2.1
2.0
ppm
DMSO-d6
H2O
1,3-NH
2.02
3.00
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm

^{19}F NMR spectrum of 5-fluoro-6-methyluracil (**3**) in DMSO-d_6 at 25 ^{o}C

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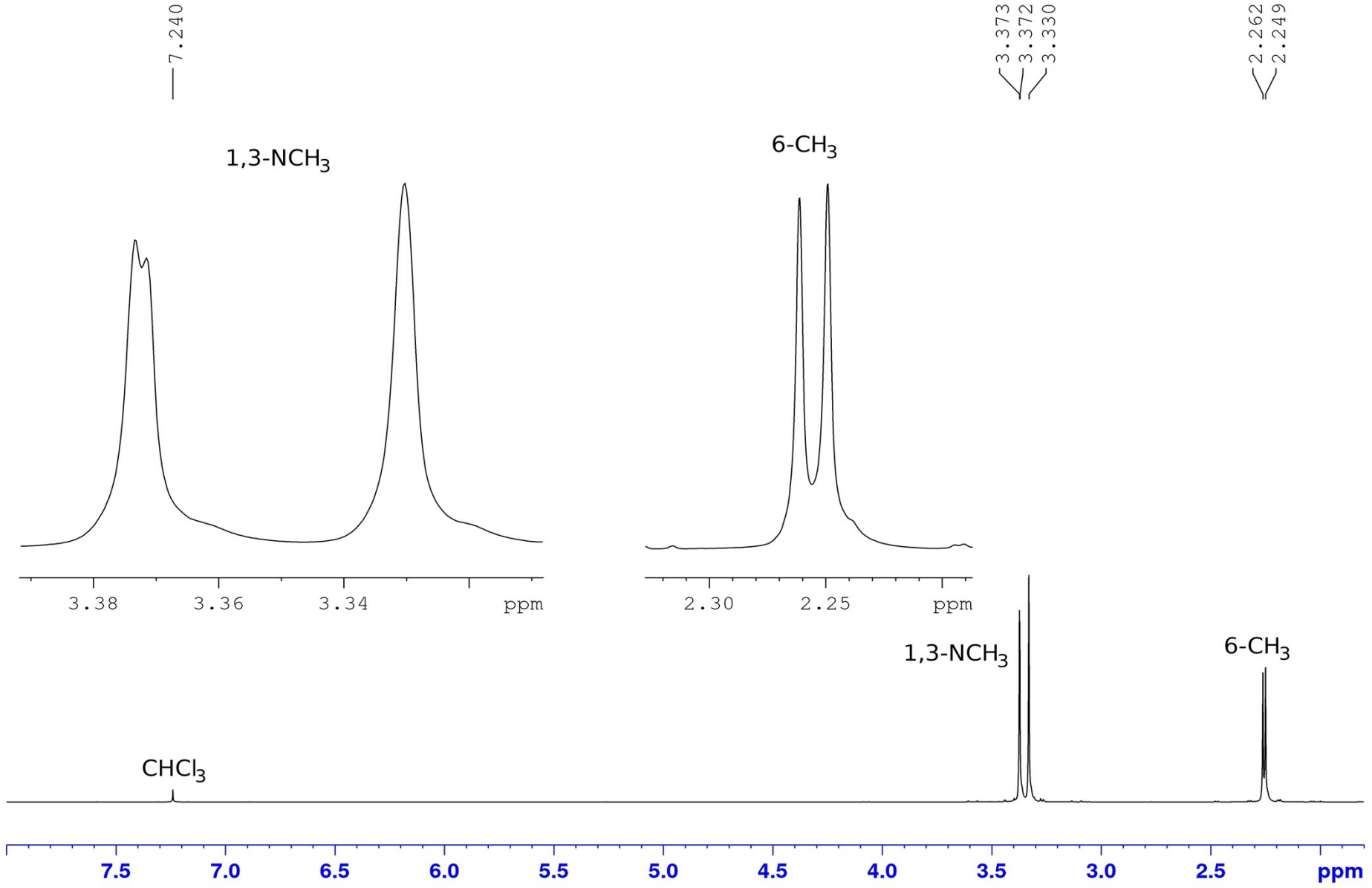
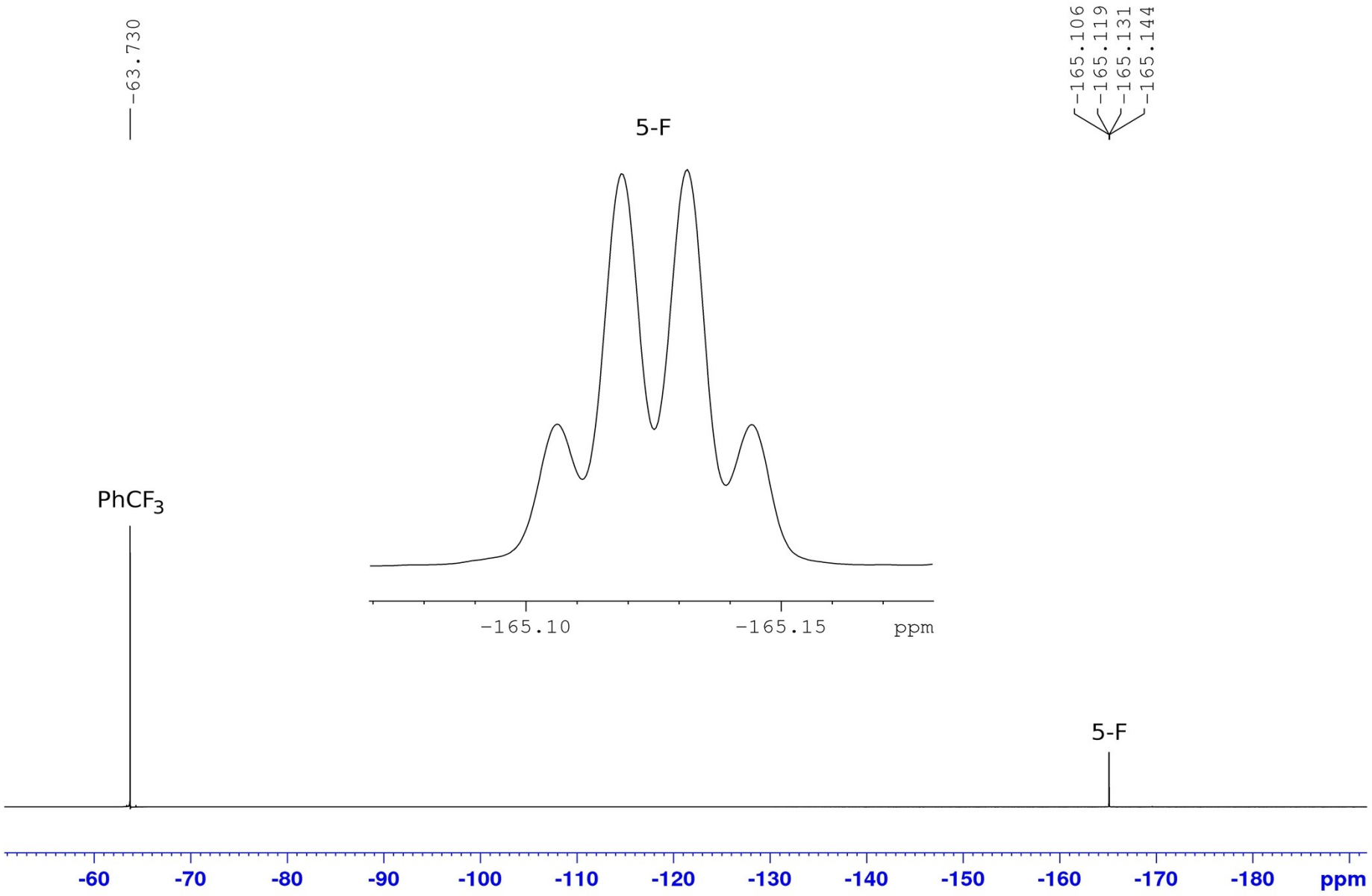
149.581
138.541
136.918
136.570
135.607
39.500
11.806
11.796
C4
C2
C5
C6
CH3
157.5 ppm
149.6 ppm
138 137 136 ppm
11.80 ppm
DMSO-d6
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

[1]H NMR spectrum of 5-fluoro-1,3,6-trimethyluracil (**4**) in $CDCl_3$ at 25 °C

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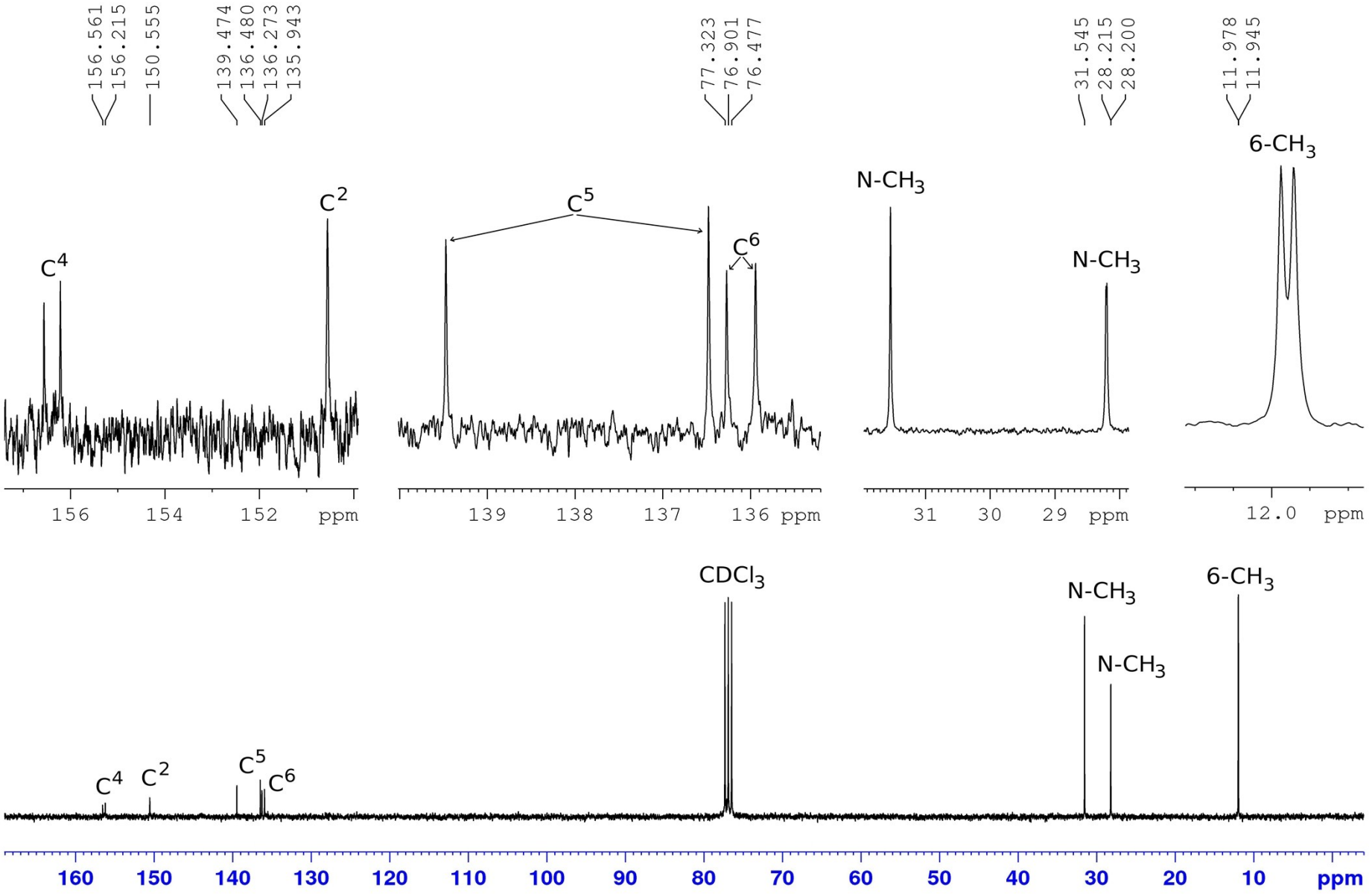
-165.106
-165.119
-165.131
-165.144
5-F
PhCF3
-165.10
-165.15
ppm
5-F
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
ppm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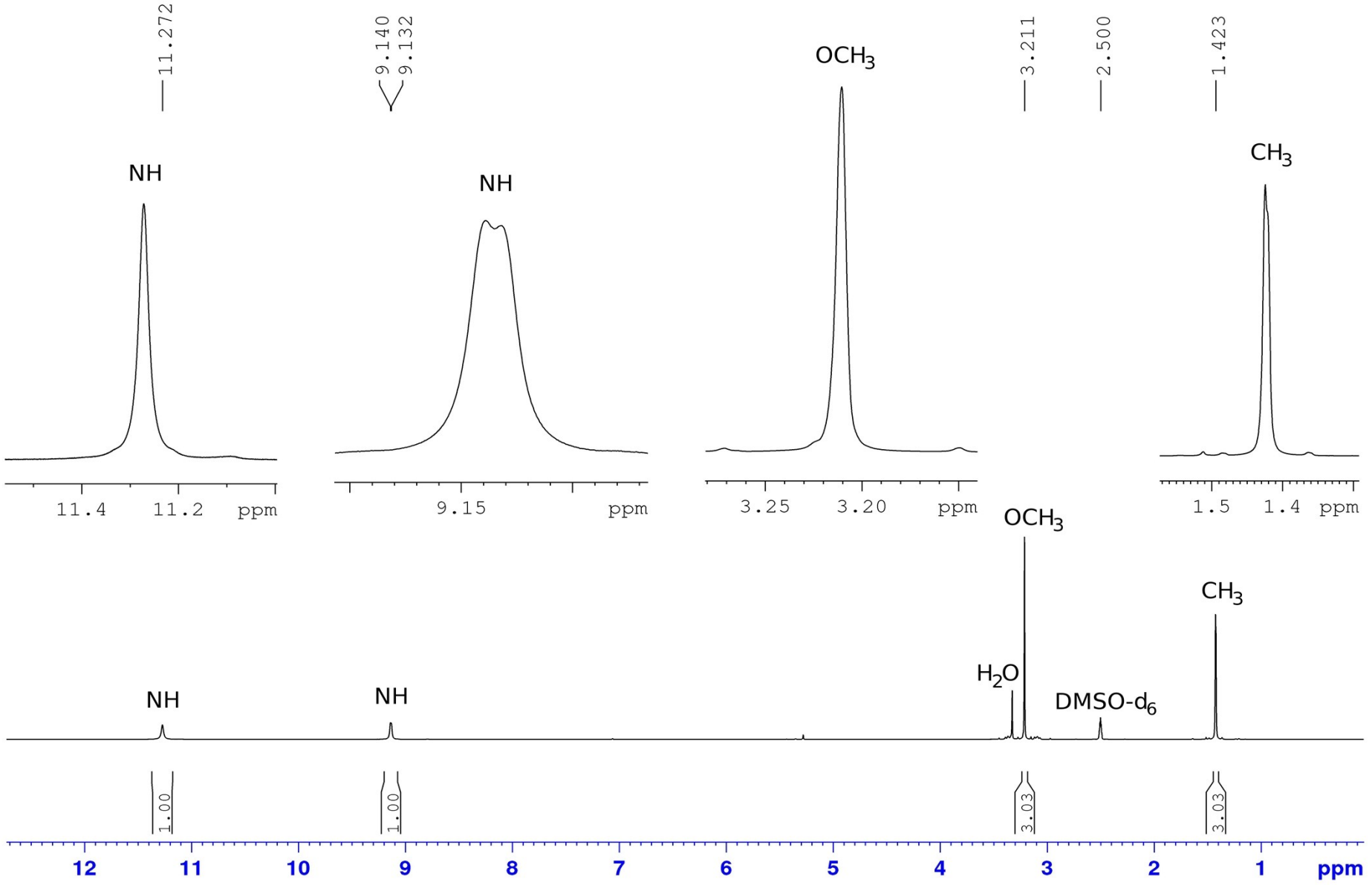
156.215
150.555
139.474
136.480
136.273
135.943
77.323
76.901
76.477
31.545
28.215
28.200
11.978
11.945
C4
C2
C5
C6
N-CH3
N-CH3
6-CH3
156
154
152
ppm
139
138
137
136
ppm
31
30
29
ppm
12.0
ppm
CDCl3
N-CH3
N-CH3
6-CH3
C4
C2
C5
C6
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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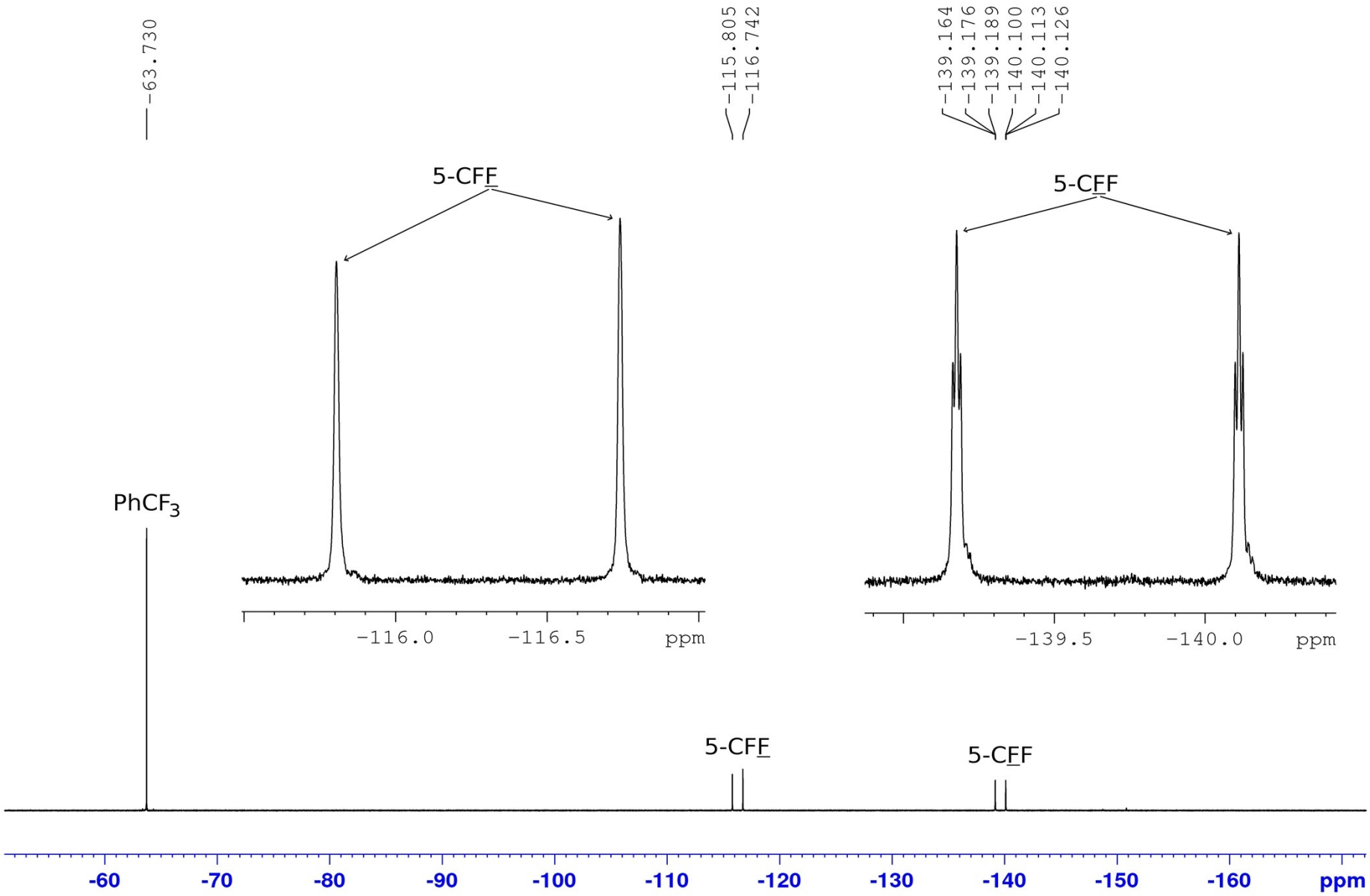
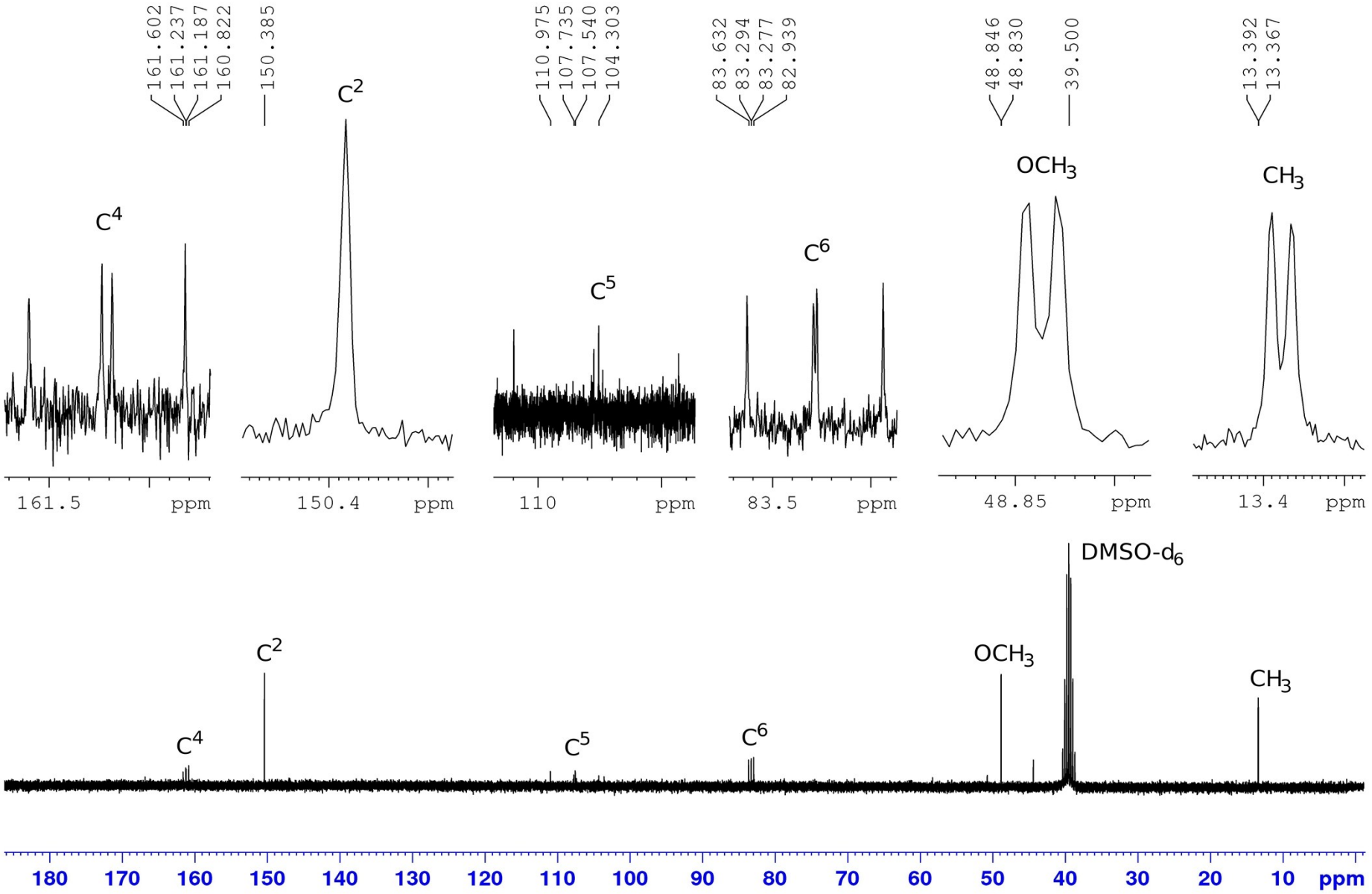
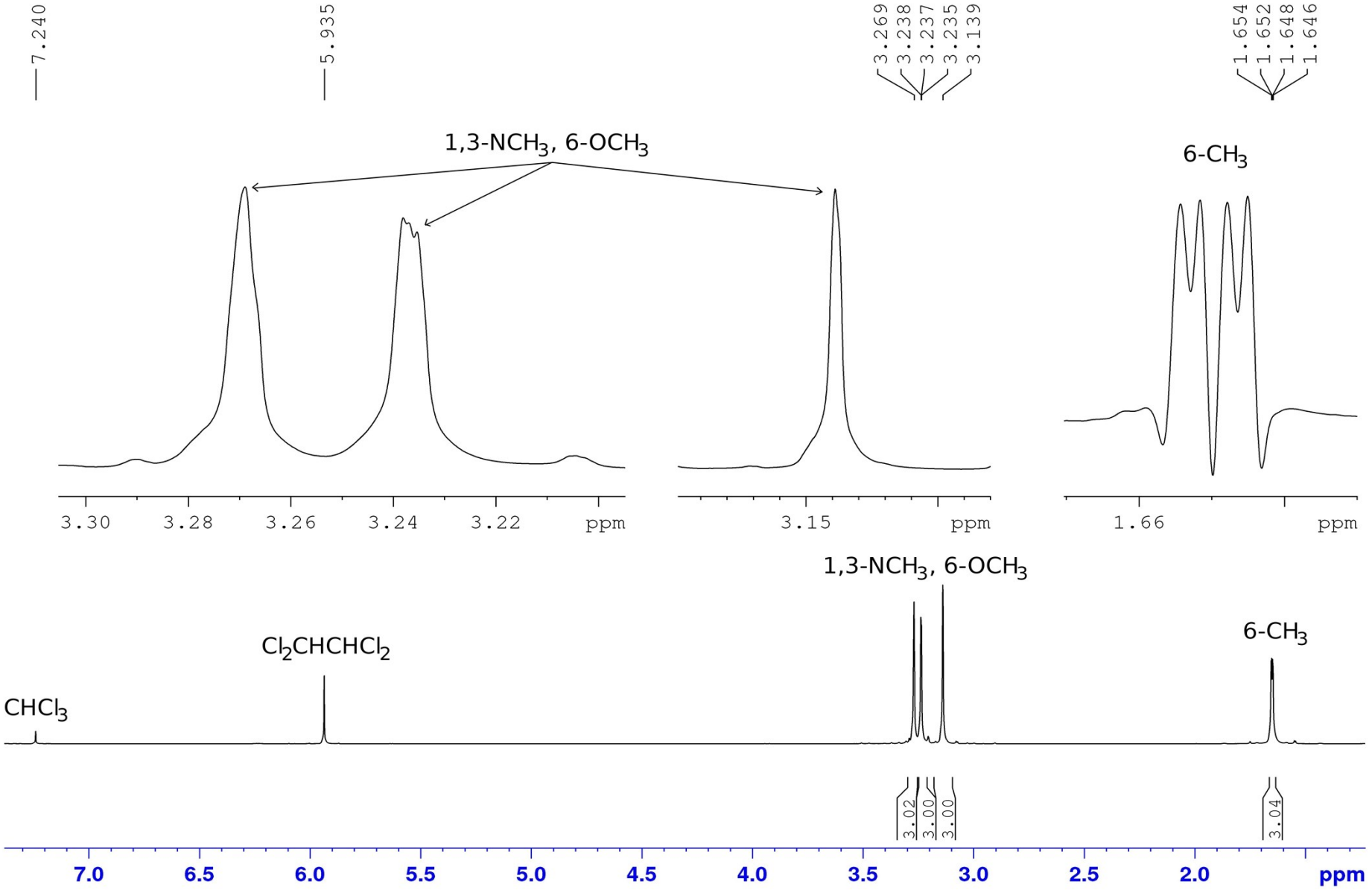
9.140
9.132
OCH3
3.211
2.500
1.423
NH
NH
CH3
11.4
11.2
ppm
9.15
ppm
3.25
3.20
ppm
1.5
1.4
ppm
OCH3
CH3
H2O
DMSO-d6
NH
NH
1.00
1.00
3.03
3.03
12
11
10
9
8
7
6
5
4
3
2
1
ppm

^{19}F NMR spectrum of 5,5-difluoro-6-methoxy-6-methyl-5,6-dihydrouracil (**5**) in DMSO-d_6 at 25 ^{o}C



^{13}C NMR spectrum of 5,5-difluoro-6-methoxy-6-methyl-5,6-dihydrouracil (**5**) in DMSO-d_6 at 25 ^{o}C

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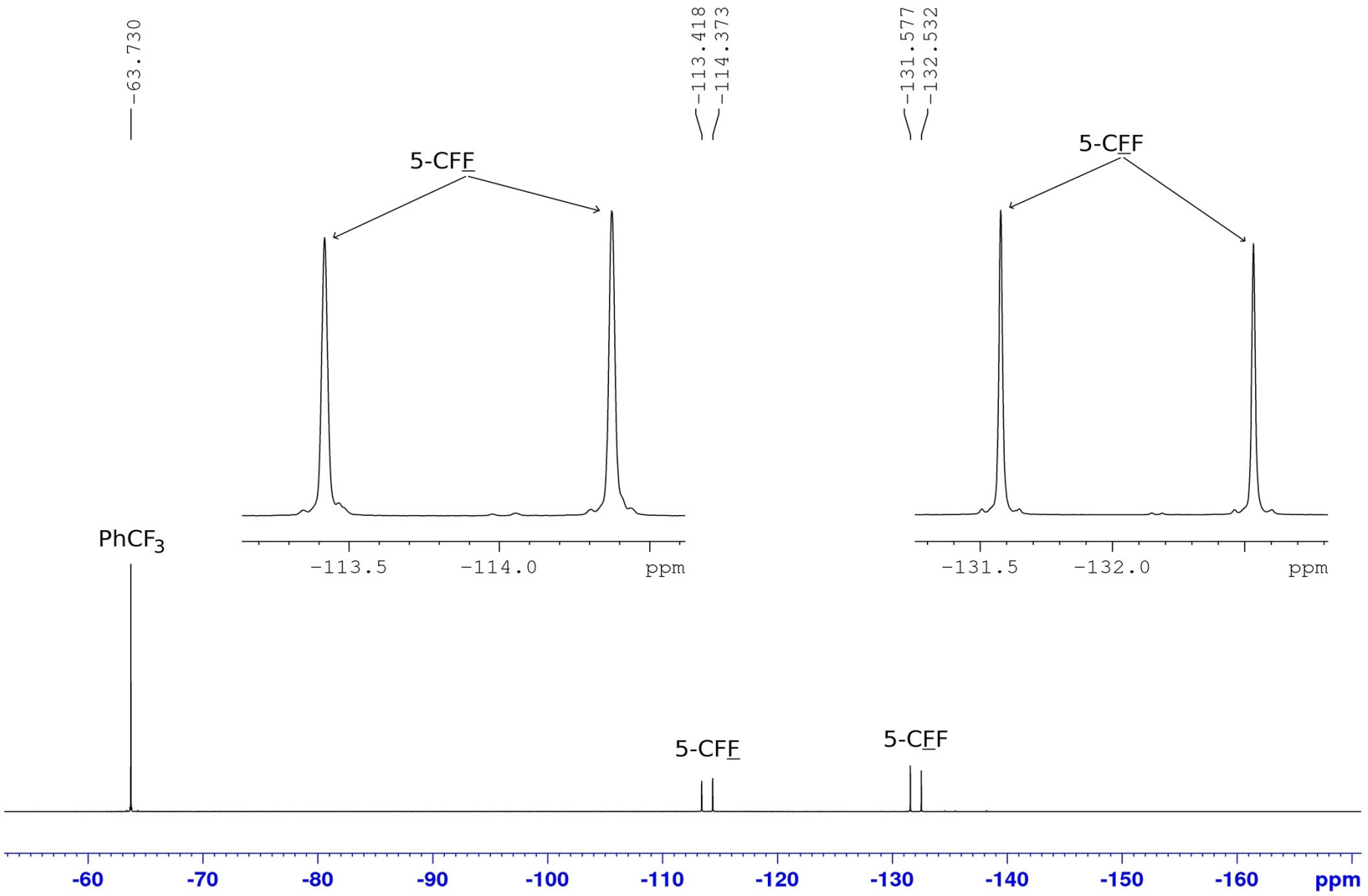
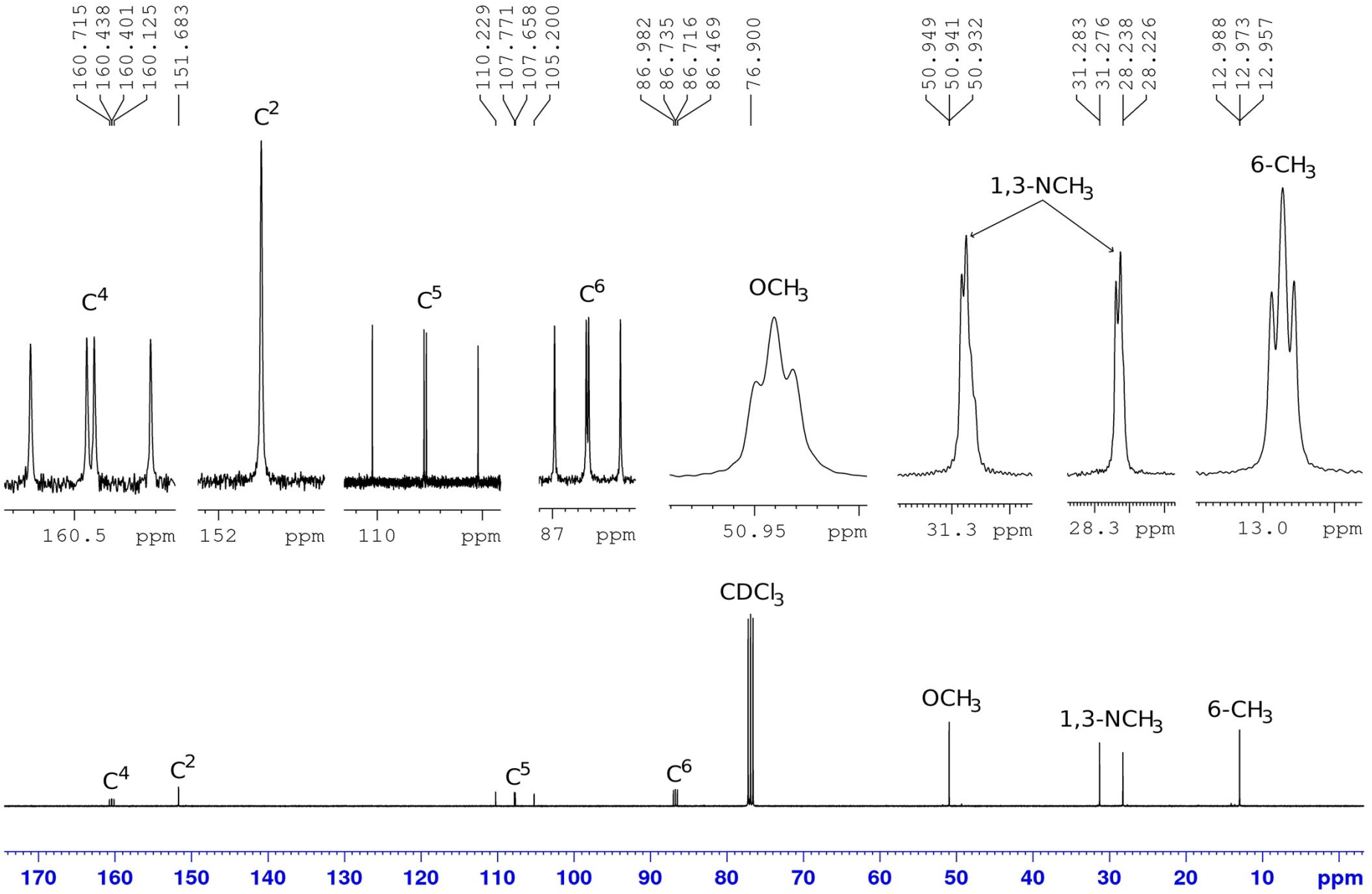
5.935
3.269
3.238
3.237
3.235
3.139
1.654
1.652
1.648
1.646
1,3-NCH3, 6-OCH3
6-CH3
3.30
3.28
3.26
3.24
3.22
ppm
3.15
ppm
1.66
ppm
1,3-NCH3, 6-OCH3
Cl2CHCHCl2
CHCl3
6-CH3
3.02
3.00
3.00
3.04
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm

^{19}F NMR spectrum of 5,5-difluoro-6-methoxy-1,3,6-trimethyl-5,6-dihydrouracil (**6**) in $CDCl_3$ at 25°C

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160.125
151.683
110.229
107.771
107.658
105.200
86.982
86.735
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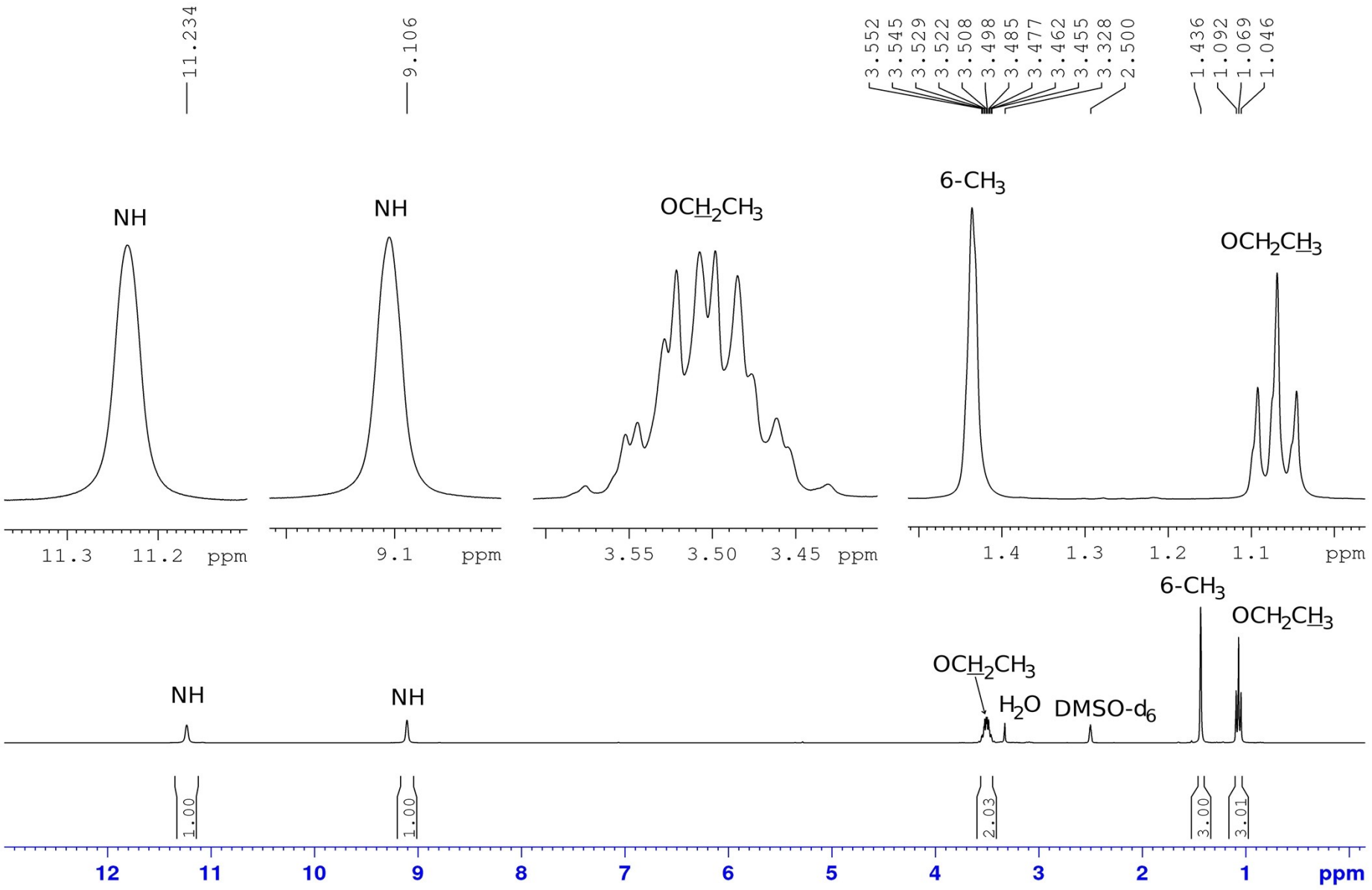
76.900
50.949
50.941
50.932
31.283
31.276
28.238
28.226
12.988
12.973
12.957
C4
C2
C5
C6
OCH3
1,3-NCH3
6-CH3
160.5 ppm
152 ppm
110 ppm
87 ppm
50.95 ppm
31.3 ppm
28.3 ppm
13.0 ppm
CDCl3
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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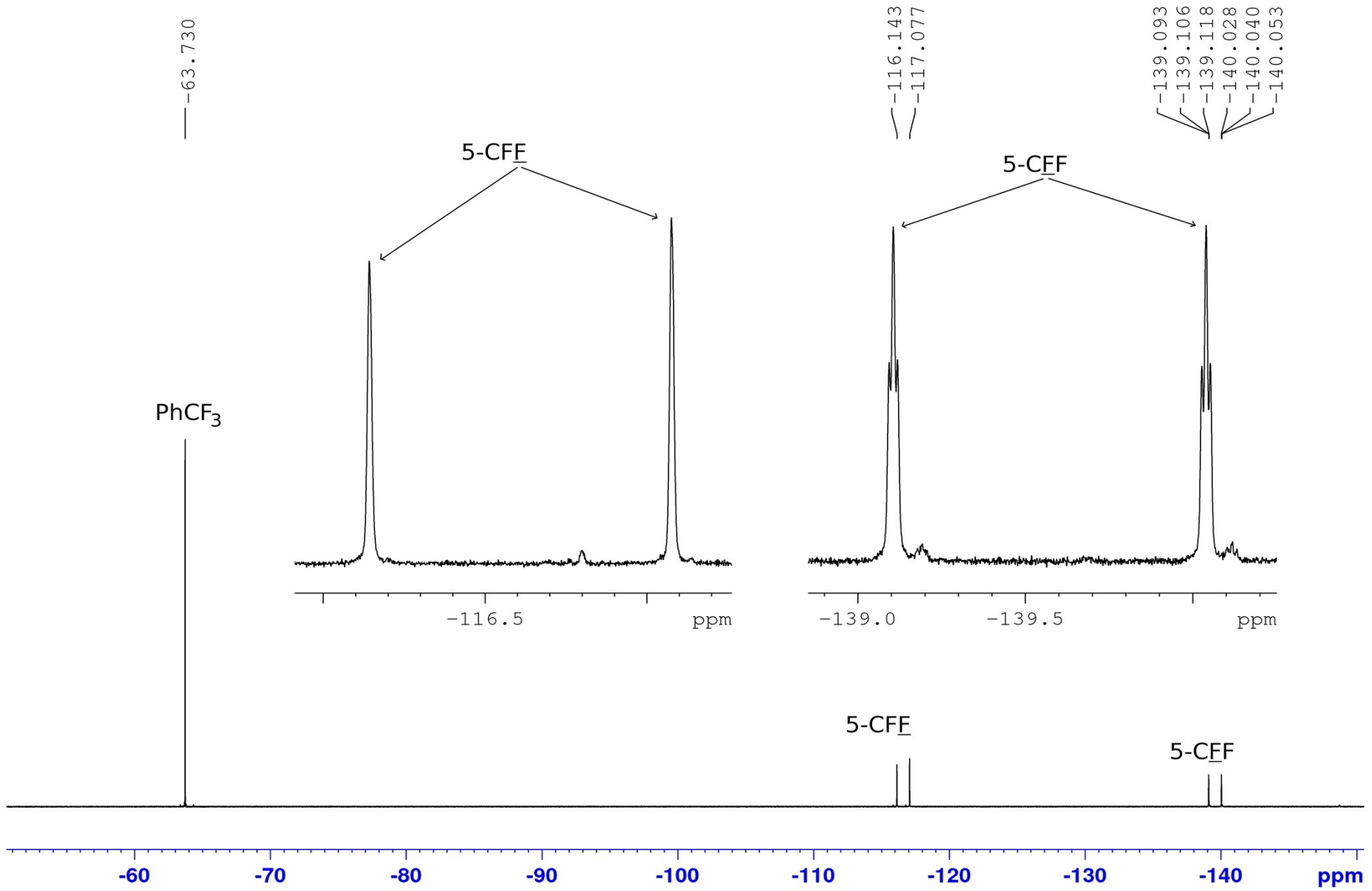
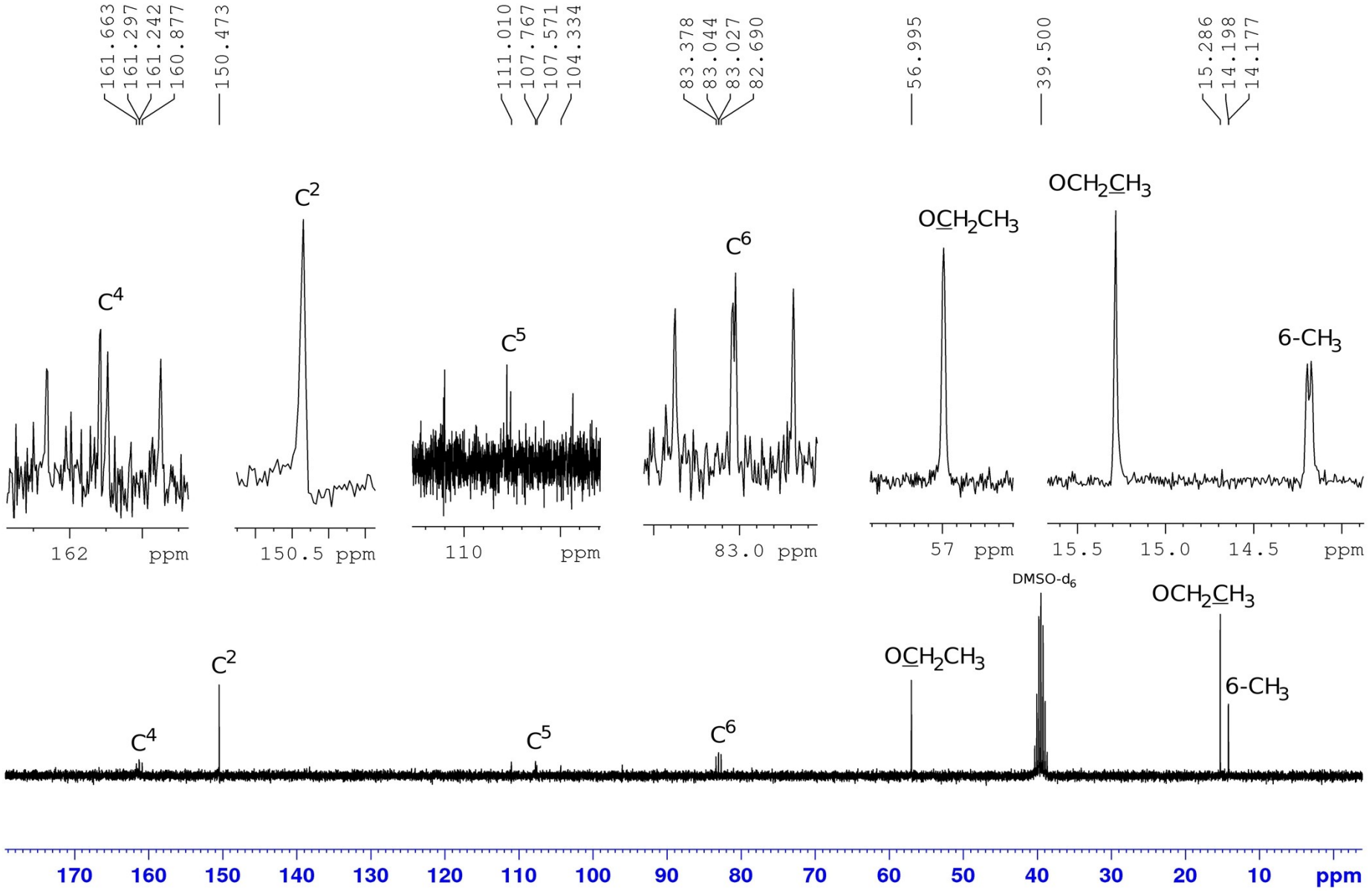
3.522
3.508
3.498
3.485
3.477
3.462
3.455
3.328
2.500
1.436
1.092
1.069
1.046
NH
NH
OCH2CH3
6-CH3
OCH2CH3
11.3
11.2
ppm
9.1
ppm
3.55
3.50
3.45
ppm
1.4
1.3
1.2
1.1
ppm
6-CH3
OCH2CH3
OCH2CH3
NH
NH
H2O
DMSO-d6
1.00
1.00
2.03
3.00
3.01
12
11
10
9
8
7
6
5
4
3
2
1
ppm

^{19}F NMR spectrum of 5,5-difluoro-6-ethoxy-6-methyl-5,6-dihydrouracil (**7**) in DMSO-d_6 at 25 ^{o}C

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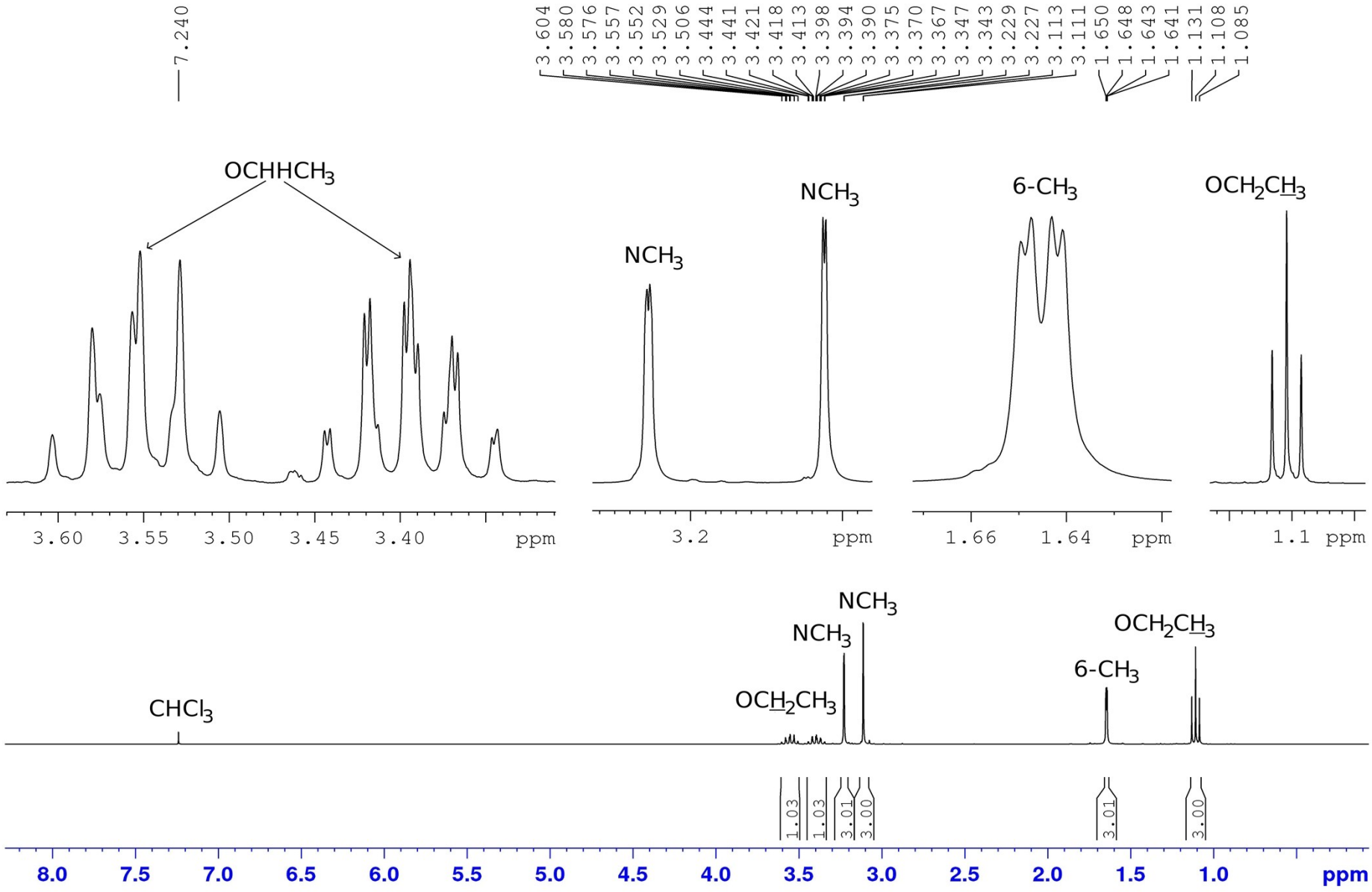
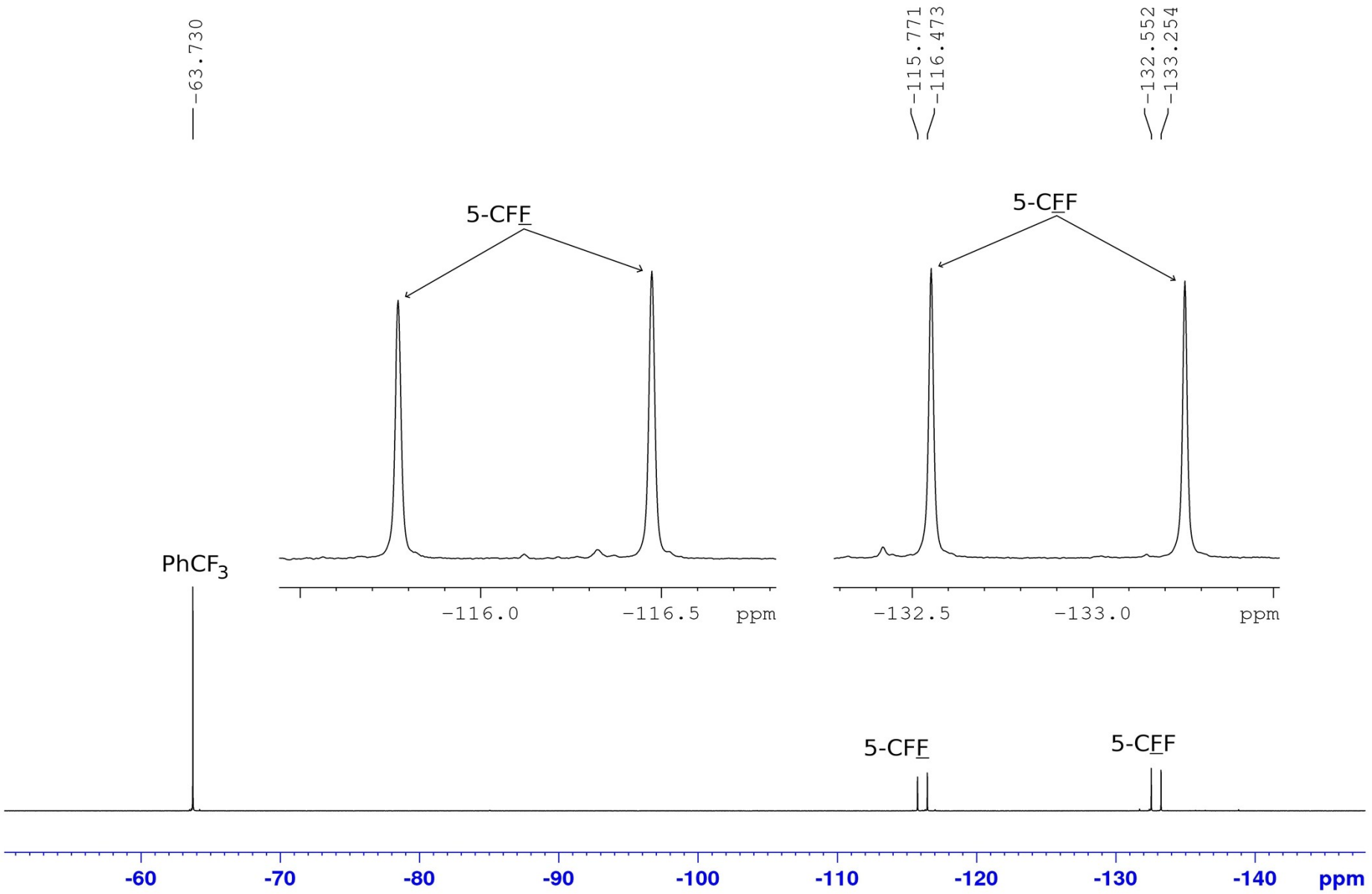
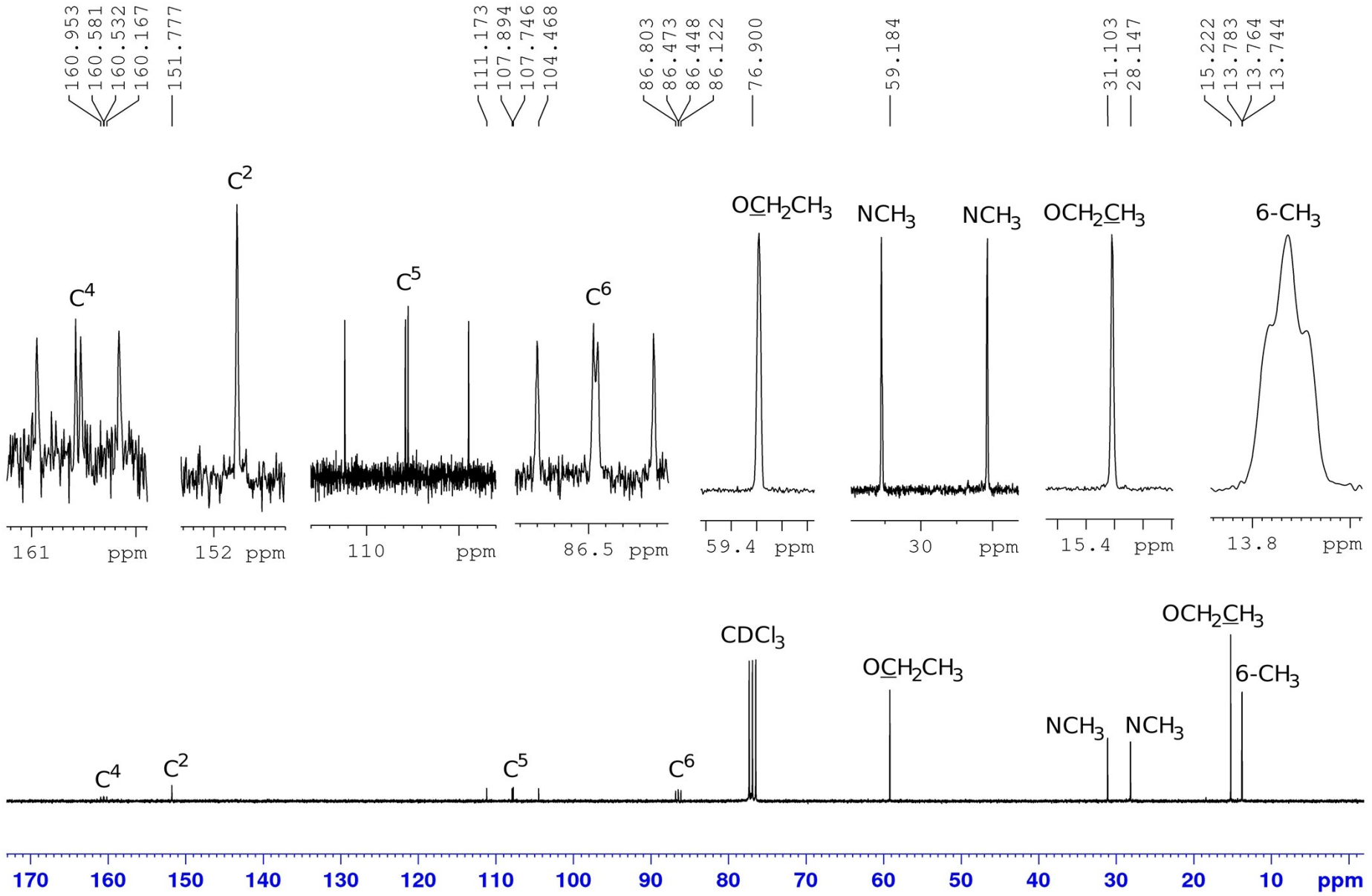
161.242
160.877
150.473
111.010
107.767
107.571
104.334
83.378
83.044
83.027
82.690
56.995
39.500
15.286
14.198
14.177
C4
C2
C5
C6
OCH2CH3
OCH2CH3
6-CH3
162 ppm
150.5 ppm
110 ppm
83.0 ppm
57 ppm
15.5
15.0
14.5
ppm
DMSO-d6
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


7.240
3.604
3.580
3.576
3.557
3.552
3.529
3.506
3.444
3.441
3.421
3.418
3.413
3.398
3.394
3.390
3.375
3.370
3.367
3.347
3.343
3.229
3.227
3.113
3.111
1.650
1.648
1.643
1.641
1.131
1.108
1.085
OCHHCH3
NCH3
NCH3
6-CH3
OCH2CH3
3.60 3.55 3.50 3.45 3.40 ppm
3.2 ppm
1.66 1.64 ppm
1.1 ppm
CHCl3
NCH3
NCH3
OCH2CH3
6-CH3
OCH2CH3
1.03
1.03
3.01
3.00
3.01
3.00
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 ppm

^{19}F NMR spectrum of 5,5-difluoro-6-ethoxy-1,3,6-trimethyl-5,6-dihydrouracil (**8**) in $CDCl_3$ at 25 °C

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160.581
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111.173
107.894
107.746
104.468
86.803
86.473
86.448
86.122
76.900
59.184
31.103
28.147
15.222
13.783
13.764
13.744
C4
C2
C5
C6
OCH2CH3
NCH3
NCH3
OCH2CH3
6-CH3
161 ppm
152 ppm
110 ppm
86.5 ppm
59.4 ppm
30 ppm
15.4 ppm
13.8 ppm
CDCl3
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

Study of F-TEDA-BF_4 transfer into CH_3OD-IL from F-TEDA-BF_4/IL/CH_3OD. A mixture of finely powdered F-TEDA-BF_4 (10 mg, 0.028 mmol) and the ionic liquid (65 eq.) was kept in an ultrasound bath (frequency 42 kHz; Branson 1510R-MTH) for 2 h. After adding CH_3OD (1 mL), the mixture was stirred for 1 h. The liquid phase was separated from a precipitate on a centrifuge and analysed by ^{19}F NMR spectroscopy with $C_6H_5CF_3$ as an internal standard.

Table 1. F-TEDA-BF_4 transfer into CH_3OD-IL from F-TEDA-BF_4/IL/CH_3OD

Run	IL	^{19}F NMR data for F-TEDA-Y in CH_3OD-IL at 25°C[a]	F-TEDA-Y in CH_3OD-IL (mg)[b]
1	[Emim][NTf_2]	48.5	10.0
2	[Bmim][HSO_4]	48.3	10.0
3	[Pyr][OTf]	48.0	9.3
4	[Bmim][OTf]	48.2	8.1
5	[Emim][OTf]	48.1	6.6
6	[Bmim][BF_4]	48.0	4.2
7	[Bmim][PF_6]	48.3	1.0

[a]Chemical shifts of NF are given in parts per million (ppm) from $CFCl_3$.
[b]Amounts of dissolved F-TEDA-Y were determined by ^{19}F NMR.

Preparation of crystals of *cis*-5-fluoro-6-methoxy-1,3,6-trimethyl-5,6-dihydrouracil (10a) for X-ray analysis. A solution of 1,3,6-trimethyluracil (**2**) (0.05 g, 0.32 mmol) and F-TEDA-BF_4 (0.115 g, 0.032 mmol) in MeOH (2.5 mL) and MeCN (7.5 mL) was stirred for 5 h at room temperature under an argon atmosphere, the solvents were evaporated with air flow, the resulting solid was dried in *vacuo*. The purification by colum chromatography on SiO_2 (EtOAc as eluent) afforded a fraction containing mainly the two isomers of 5-fluoro-6-methoxy-1,3,6-trimethyl-5,6-dihydrouracil (**10a,b**) in ~96:4 ratio. The colourless crystals of *cis*-isomer (**10a**) suitable for X-ray analysis were obtained after recrystallization from *n*-hexane-$CHCl_3$. M.p. 107-109 °C. δ_H(300 MHz; $CDCl_3$): 4.83 (1 H, d, *J* 47.2, 5-H), 3.25 (3 H, s, Me), 3.21 (3 H, s, Me), 3.13 (3 H, d, *J* 0.7, Me), 1.69 (3 H, d, *J* 1, 6-Me); δ_F(300 MHz; $CDCl_3$): -206.2 (d, *J* 47.2, 5-F)]. HRMS-EI calcd for $C_8H_{13}FN_2O_3$: 204.0905, found: 204.0907.

Table 1S. Crystal data and structure refinement for compound 10a.

Empirical formula	$C_8H_{13}FN_2O_3$
Formula weight	204.20
Temperature	200(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, $P2_1/n$
Unit cell dimensions	a = 7.8529(2) Å, α = 90 deg.
	b = 8.0661(3) Å, β = 102.589(1) deg.
	c = 15.1957(6) Å, γ = 90 deg.
Volume	939.39(6) $Å^3$
Z, Calculated density	4, 1.444 Mg/m^3
Absorption coefficient	0.123 mm^{-1}
F(000)	432
Crystal size	0.20 x 0.20 x 0.29 mm
Theta range for data collection	2.71 to 27.50 deg.
Limiting indices	-10<=h<=10, -10<=k<=10, -19<=l<=19
Reflections collected / unique	16435 / 2157 [R(int) = 0.0341]
Completeness to theta = 27.50	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9288 and 0.9703
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2257 / 0 / 131
Goodness-of-fit on F^2	0.979
Final R indices [I>2σ(I)]	R_1 = 0.0366, wR_2 = 0.1004
R indices (all data)	R_1 = 0.0450, wR_2 = 0.1067
Largest diff. peak and hole	0.334 and -0.191 e.$Å^{-3}$
CCDC number	1475851

Table 2S. Bond lengths [Å] and angles [deg] for compound 10a.

F1-C5	1.3855(14)	O1-C2-N3	119.18(12)
O1-C2	1.2137(15)	N1-C2-N3	116.98(11)
N1-C2	1.3628(16)	C10-O3-C6	116.87(10)
N1-C6	1.4652(15)	C4-N3-C2	123.52(11)
N1-C7	1.4673(16)	C4-N3-C8	119.42(11)
O2-C4	1.2146(16)	C2-N3-C8	116.94(11)
C2-N3	1.4173(16)	O2-C4-N3	123.53(13)
O3-C10	1.4259(16)	O2-C4-C5	122.51(12)
O3-C6	1.4255(14)	N3-C4-C5	113.93(10)
N3-C4	1.3682(17)	F1-C5-C4	108.69(10)
N3-C8	1.4704(17)	F1-C5-C6	110.89(10)
C4-C5	1.5152(18)	C4-C5-C6	110.37(10)
C5-C6	1.5200(17)	O3-C6-N1	111.11(10)
C6-C9	1.5199(17)	O3-C6-C9	112.70(10)
C2-N1-C6	121.48(10)	N1-C6-C9	112.42(10)
C2-N1-C7	116.67(11)	O3-C6-C5	104.08(9)
C6-N1-C7	121.80(10)	N1-C6-C5	105.53(9)
O1-C2-N1	123.84(12)	C9-C6-C5	110.43(10)

CCDC 1475851 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.