Three-step assembly of 4-aminotetrahydropyran-2-ones from isoxazoline-2-oxides

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General Remarks:

Commercial reagents: *m*CPBA, 2,6-lutidine, Boc_2O, DMAP, *t*-BuOK, Pd/C (5 %), Raney Ni, Amberlyst-15® (Aldrich), AcOH (Reakhim); The following reagents were prepared according to literature procedures: *t*-$BuMe_2SiOSO_2CF_3$,[1] *tert*-butyl(1-methoxyvinyloxy)dimethylsilane,[2]

Nitronates 2

3-Methyl-5-phenylisoxazoline 2-oxide **2a**,[3] 5-(4-bromophenyl)-3-methylisoxazoline 2-oxide **2b**,[4] 3-methyl-4-phenylisoxazoline 2-oxide **2c**,[5] 3-methyl-5-methoxycarbonylisoxazoline 2-oxide **2d**,[6] 3,5-dimethyl-5-methoxycarbonyloxazoline 2-oxide **2e**,[6] *cis*-3-benzyl-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*d*]isoxazole 2-oxide **2f**,[3] 3-benzyl-5-phenylisoxazoline 2-oxide **2g**,[6] 3-bromomethyl-5-phenylisoxazoline 2-oxide **2h**[4] were obtained according the indicated literature procedures.

References

[1] Emde H., Domsch D., Feger H., Frick U., Goetz A., Hergott H., Hofmann K., Kober W., Kraegeloh K., Oesterle T., Steppan W., West W., Schimchen G., *Synthesis*, **1982**, 1-26.
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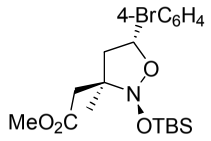
[3] R.A. Kunetsky, A.D. Dilman, M.I. Struchkova, P.A. Belyakov, V.A. Tartakovsky, S.L. Ioffe, *Synthesis*, **2006**, *13*, 2265-2270.
[4] A.A. Mikhaylov, A.D. Dilman, Yu.A. Khomutova, M.I. Struchkova, A.A. Korlyukov, S.L. Ioffe, V.A. Tartakovsky, *Tetrahedron* **2011**, *67*, 4584-4594.
[5] M. Clagett, A. Gooch, P. Graham, N. Holy, B. Mains, J. Strunkl, *J. Org. Chem.* **1976**, *41*, 25, 4033-4035.
[6] R.A. Kunetsky, A.D. Dilman, S.L. Ioffe, M.I. Struchkova, Yu.A. Strelenko, V.A. Tartakovsky, *Org. Lett.* **2003**, *5*, 4907-4909.
[7] V.O. Smirnov, A.S. Sidorenkov, Yu.A. Khomutova, S.L. Ioffe, V.A. Tartakovsky, *Eur. J. Org. Chem.* **2009**, 3066-3074.

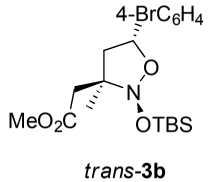
Table SI1. Crystallographic data and refinement parameters for the structures **4b** and **4h**.

	4b	**4h**
Molecular formula	$C_{12}H_{12}BrNO_4$	$C_{12}H_{12}BrNO_4$
Formula weight	314.14	314.14
T, K	100	100
Crystal system	Orthorhombic	Orthorhombic
Space group	$Pna2_1$	$Pna2_1$
Z	4	4
a, Å	6.2850(4)	12.3354(6)
b, Å	19.1650(13)	14.4555(7)
c, Å	10.0101(7)	6.7455(3)
α, °	90.00	90.00
β, °	90.00	90.00
γ, °	90.00	90.00
V, Å^3	1205.74(14)	1202.82(10)
ρ_{calc} (g·cm^{-3})	1.731	1.735
μ, cm^{-1}	34.15	34.24
F(000)	632	632
$2\theta_{max}$, °	60.18	61.04
Reflections collected	21721	15622
Independent reflections (R_{int})	3515 (0.0375)	3668 (0.0321)
Number of reflections with $I > 2\sigma(I)$	3214	3244
Parameters	164	163
R_1 [$I > 2\sigma(I)$]	0.0282	0.0222
wR_2 (all independent reflections)	0.0659	0.0492
Goodness-of-fit (GOF)	1.052	1.006
ρ_{min}/ρ_{max} (e·Å^{-3})	1.405/-0.382	0.377/-0.529



trans-**3b**

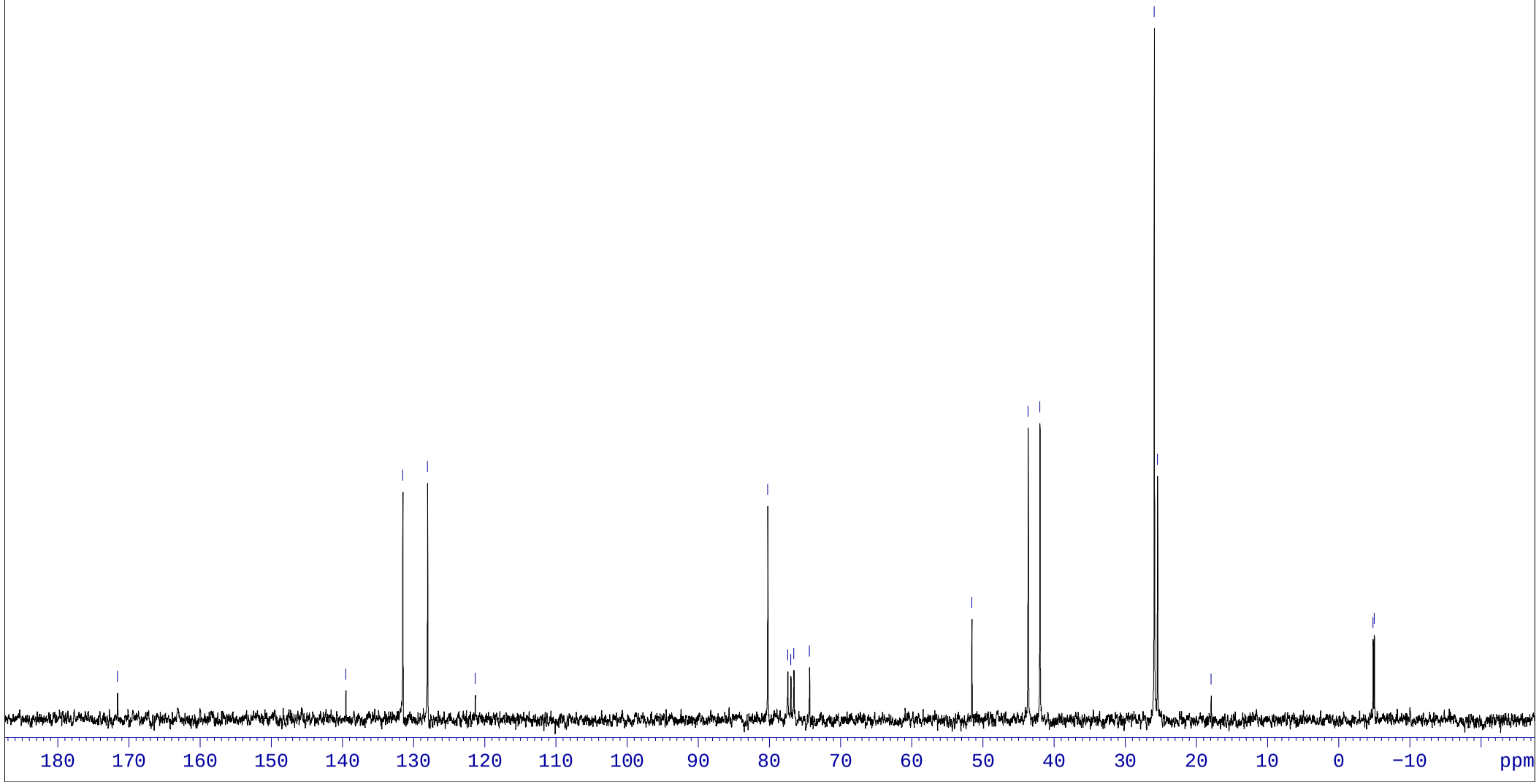
^{1}H NMR, 300 MHz

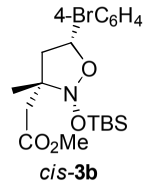


trans-**3b**

^{13}C NMR, 300 MHz

171.62
139.53
131.53
128.06
121.35
80.26
77.43
77.01
76.59
74.39
51.57
43.67
42.01
25.94
25.49
17.95
-4.81
-4.98

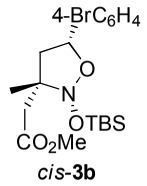




cis-**3b**

^{1}H NMR, 300 MHz

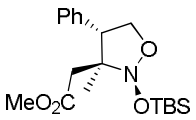
323K



cis-**3b**

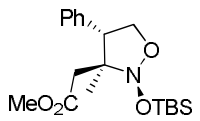
^{13}C NMR, 300 MHz

323K



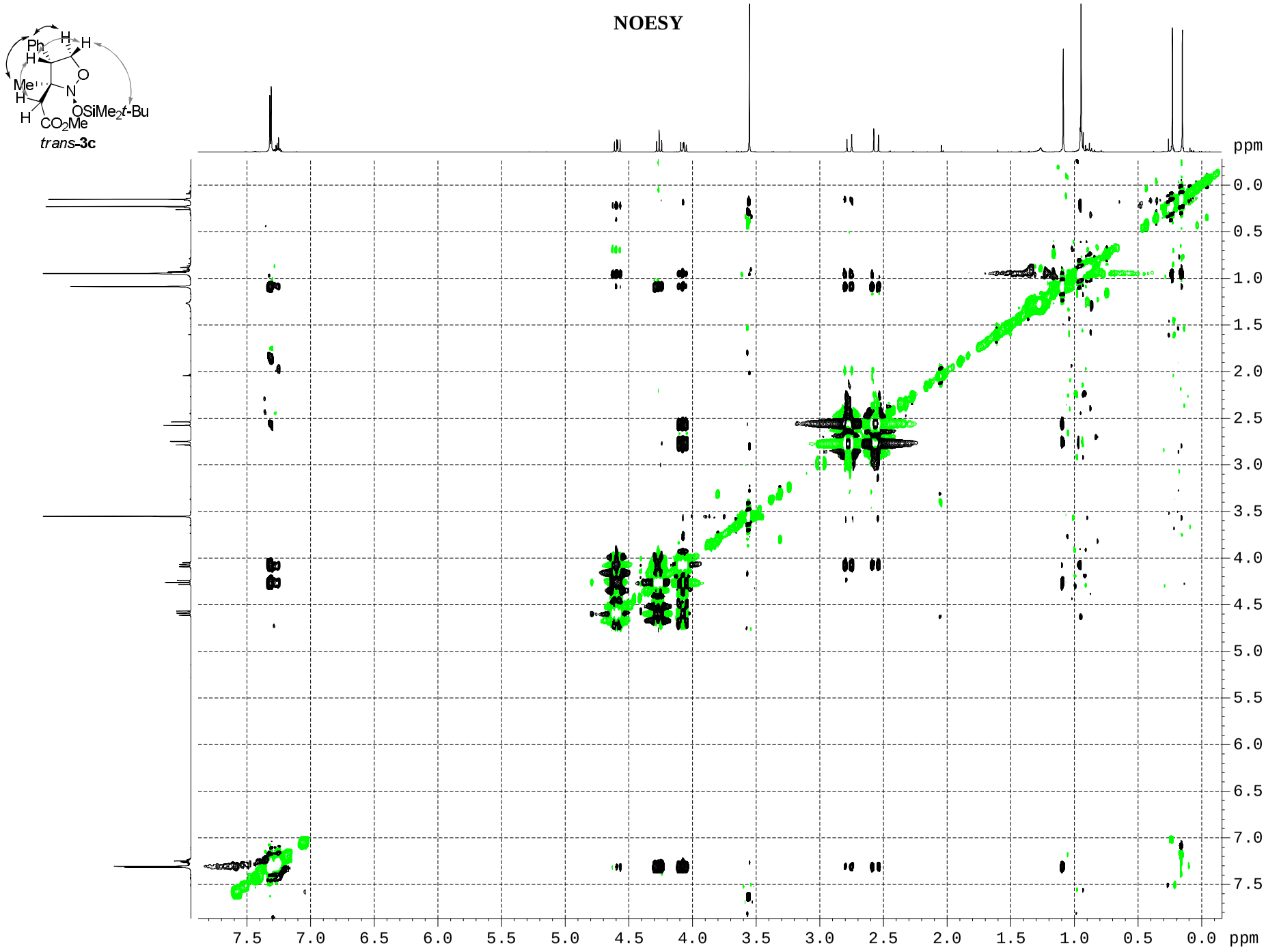
trans-**3c**

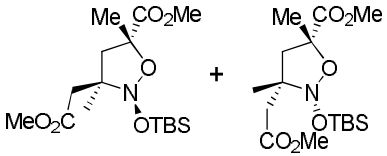
^{1}H NMR, 400 MHz



trans-**3c**

^{13}C NMR, 400 MHz


NOESY
Ph
H
H
H
O
Me
H
N
OSiMe2t-Bu
H
CO2Me
trans-3c
ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm



trans-**3e** *cis*-**3e**

trans/*cis* 5.2:1

^{1}H NMR, 400 MHz

^{13}C NMR, 400 MHz

trans-**3e**

trans/*cis* 5.2:1

cis-**3e**

174.02
171.41
88.60
77.41
77.09
76.78
74.43
52.63
52.25
51.70
51.66
46.47
44.13
42.29
42.09
29.76
28.52
26.07
26.04
25.78
25.17
24.31
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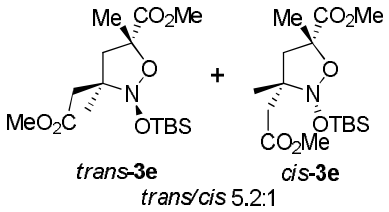
17.80
-2.88
-4.42
-4.88
-4.98

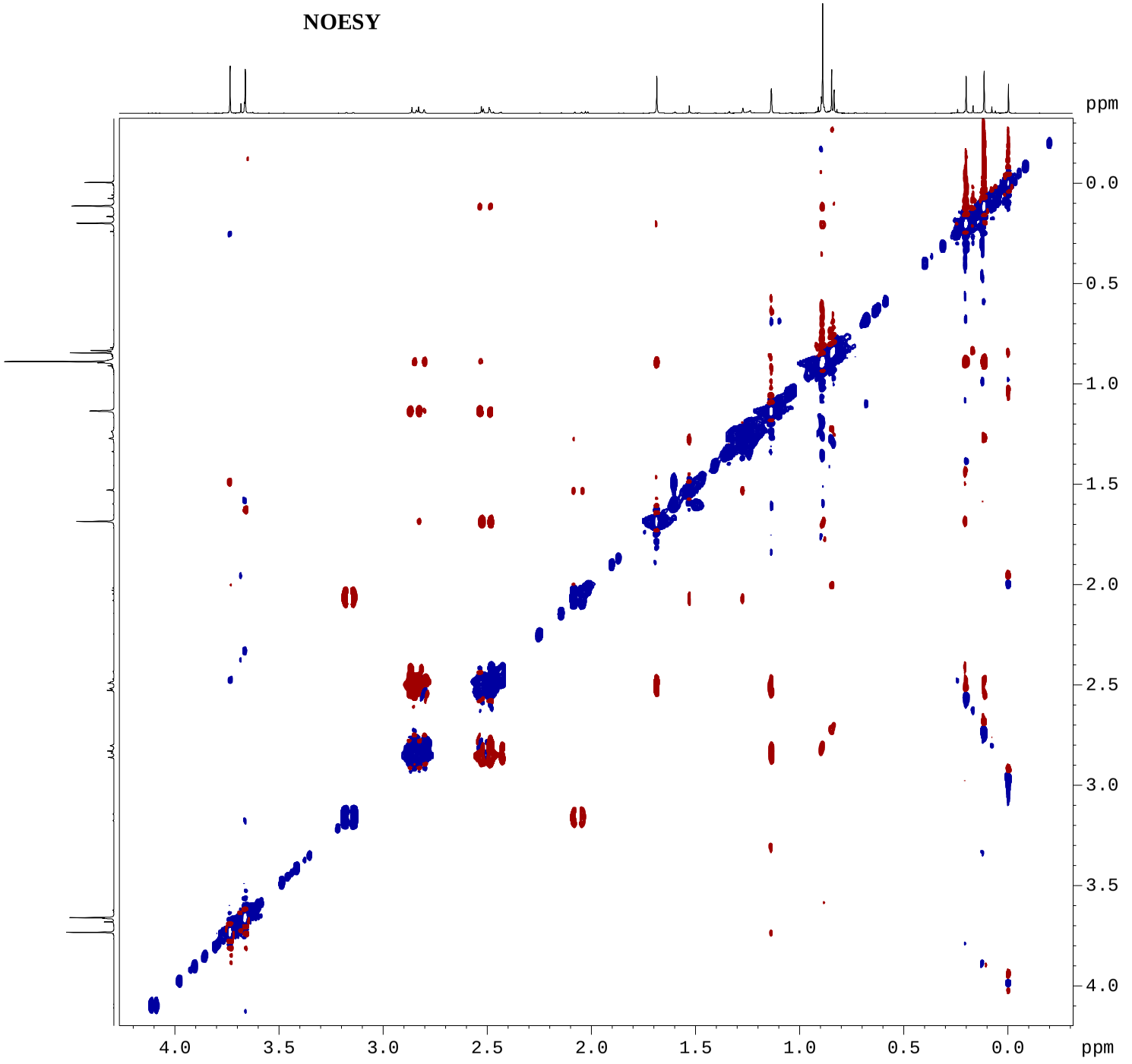


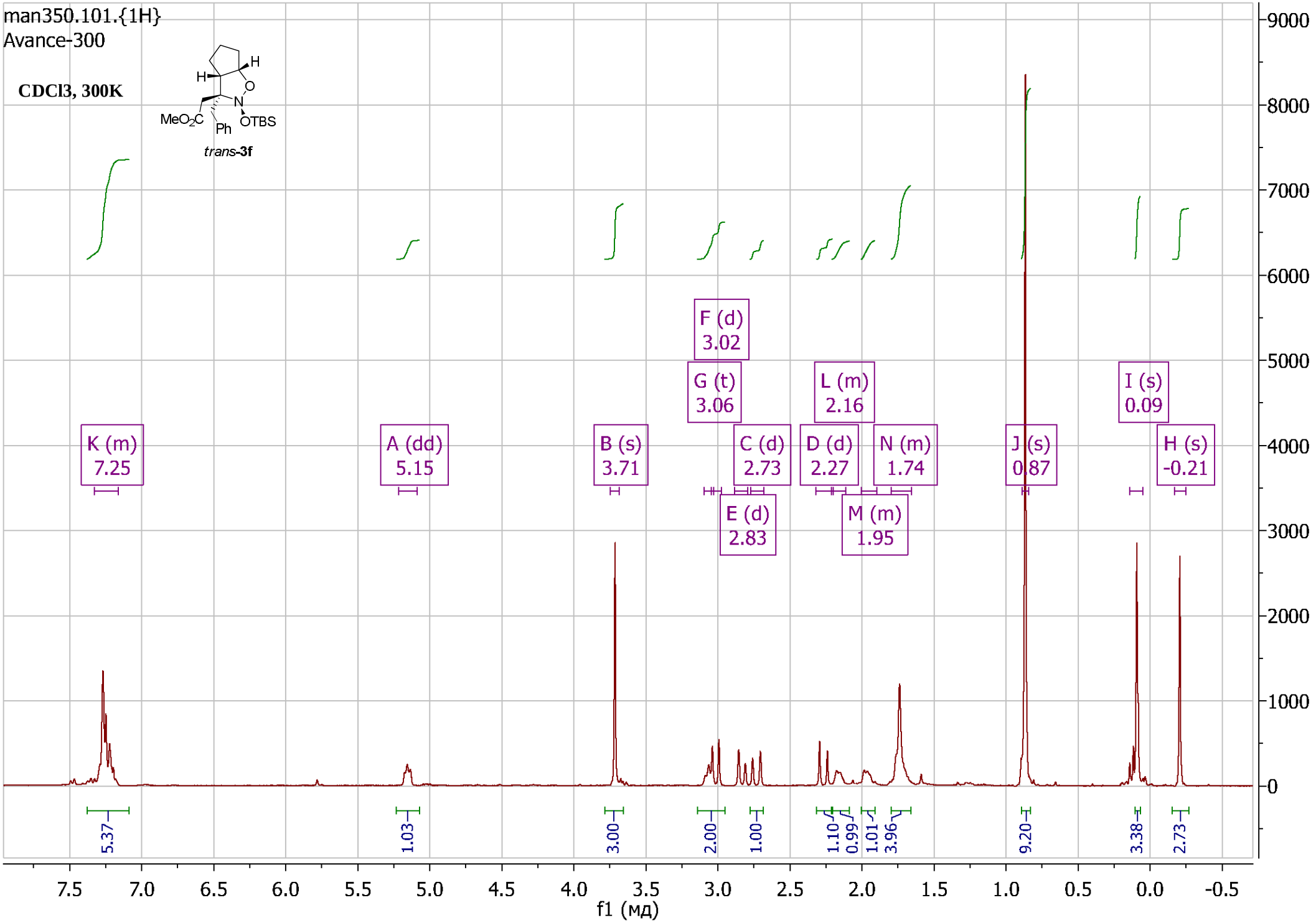
trans-**3e**

cis-**3e**

trans/*cis* 5.2:1

NOESY

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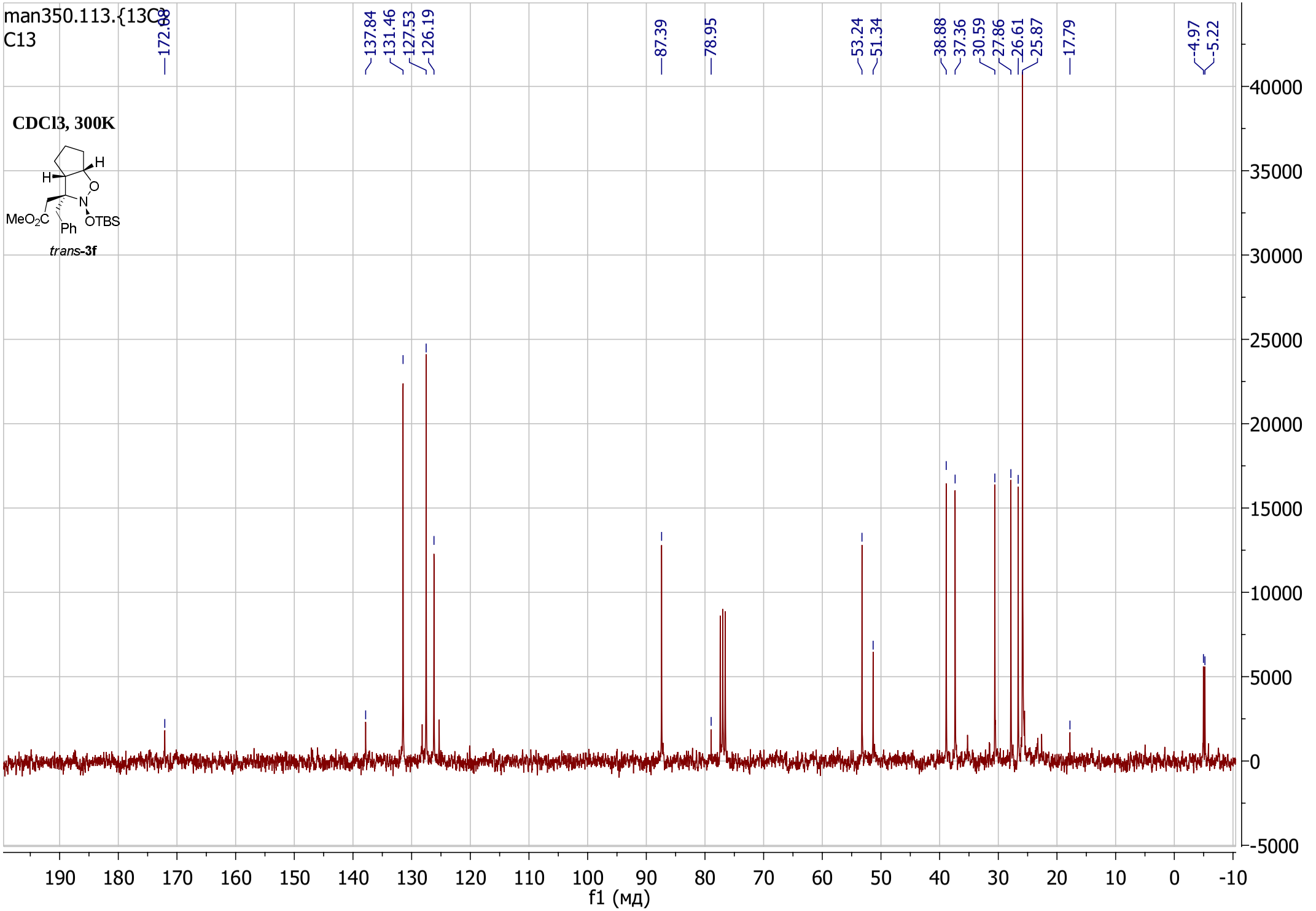
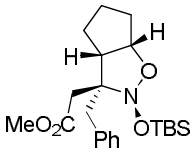
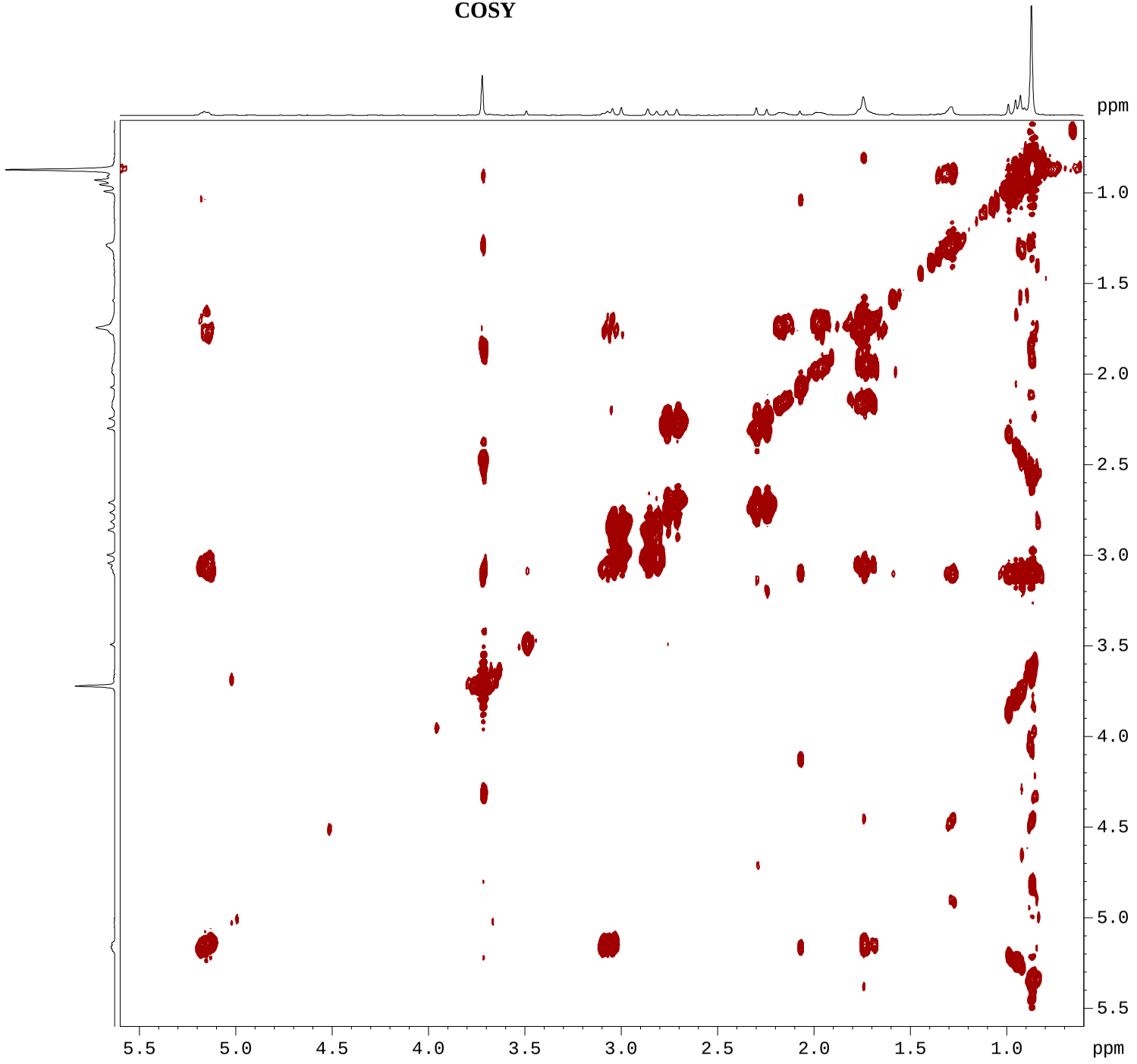
Avance-300
CDCl3, 300K
trans-3f
K (m) 7.25
A (dd) 5.15
B (s) 3.71
F (d) 3.02
G (t) 3.06
C (d) 2.73
E (d) 2.83
L (m) 2.16
D (d) 2.27
M (m) 1.95
N (m) 1.74
J (s) 0.87
I (s) 0.09
H (s) -0.21
5.37
1.03
3.00
2.00
1.00
1.10
0.99
1.01
3.96
9.20
3.38
2.73
f1 (мд)


man350.113.{13C}
C13
172.88
137.84
131.46
127.53
126.19
87.39
78.95
53.24
51.34
38.88
37.36
30.59
27.86
26.61
25.87
17.79
-4.97
-5.22
CDCl3, 300K
H
H
O
N
MeO2C
Ph
OTBS
trans-3f
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (мд)

COSY



trans-**3f**



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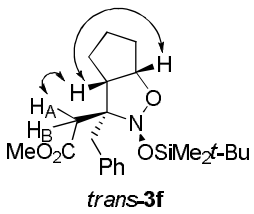
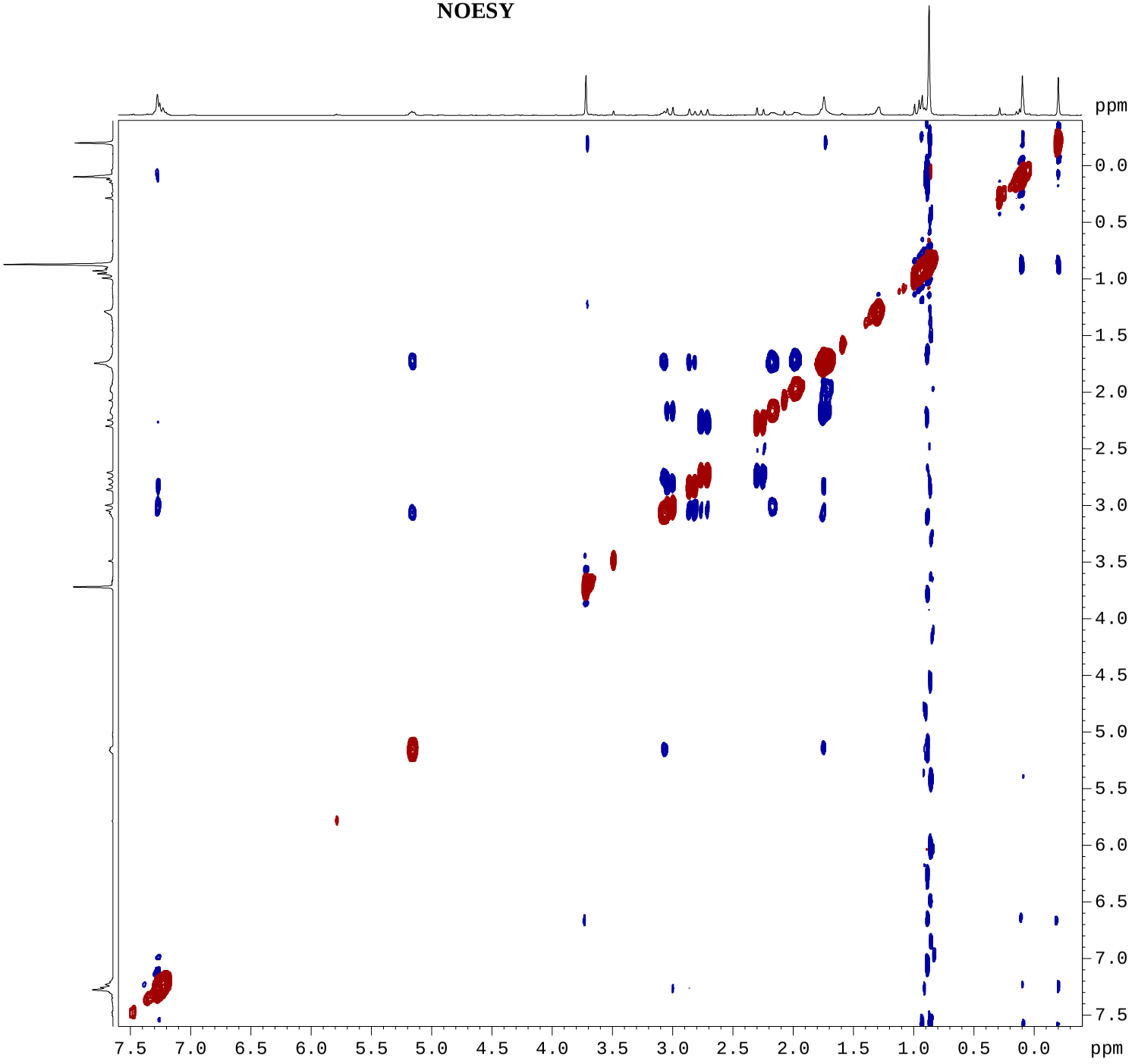
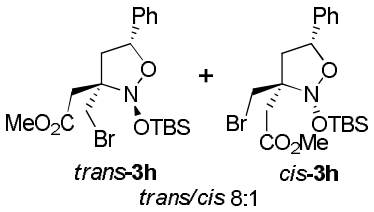


trans-**3f**





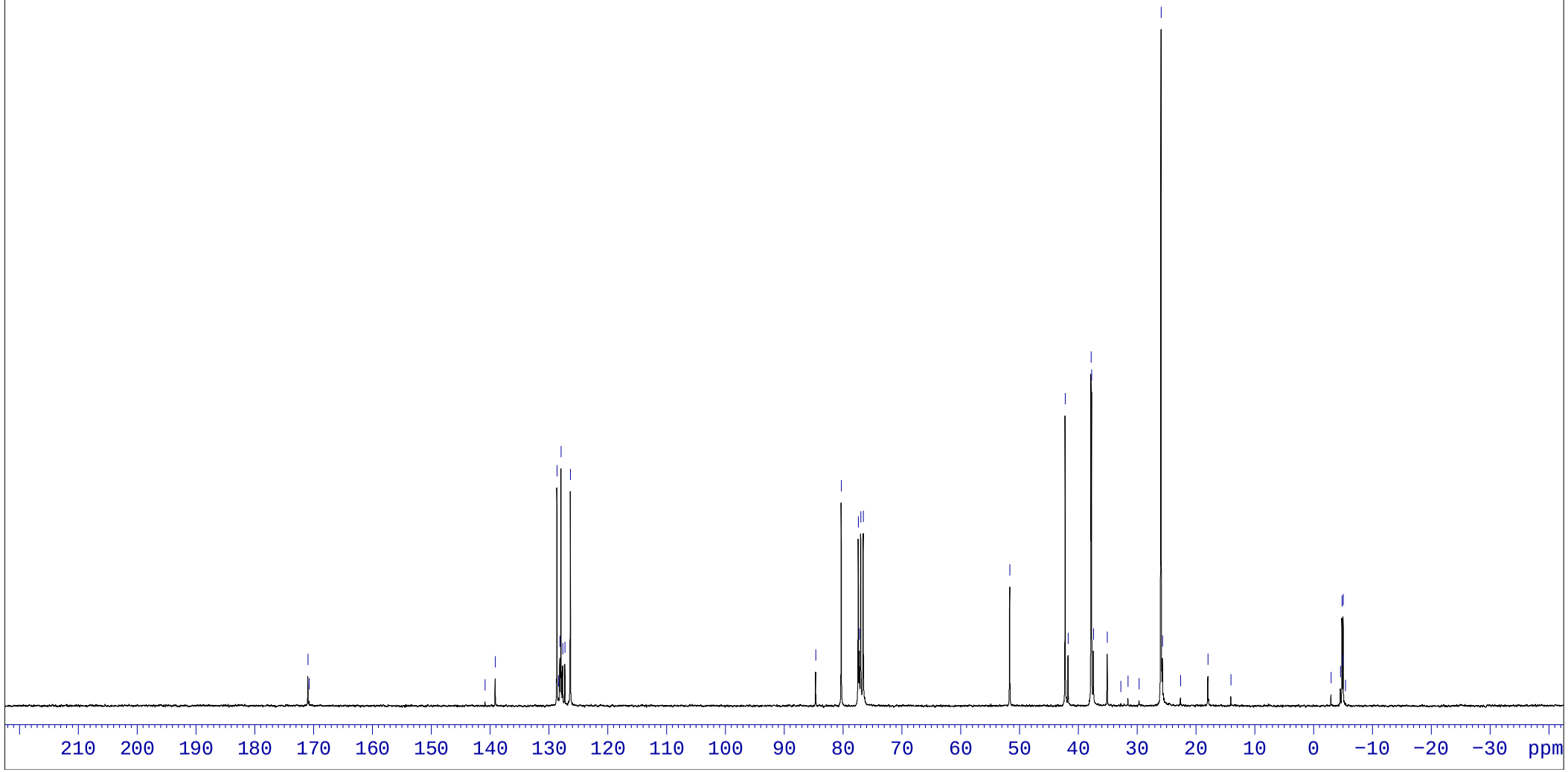
trans-**3h** + *cis*-**3h**

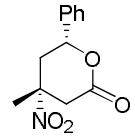
trans/*cis* 8:1

^{1}H NMR, 300 MHz

trans-**3h**
cis-**3h**
trans/*cis* 8:1

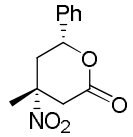
^{13}C NMR, 300 MHz





4a

^{1}H NMR, 300 MHz



4a

^{13}C NMR, 300 MHz

137.25
129.29
129.06
126.07
84.32
77.61
77.34
77.18
76.76
41.93
40.17
25.91

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

11 Mar 2011

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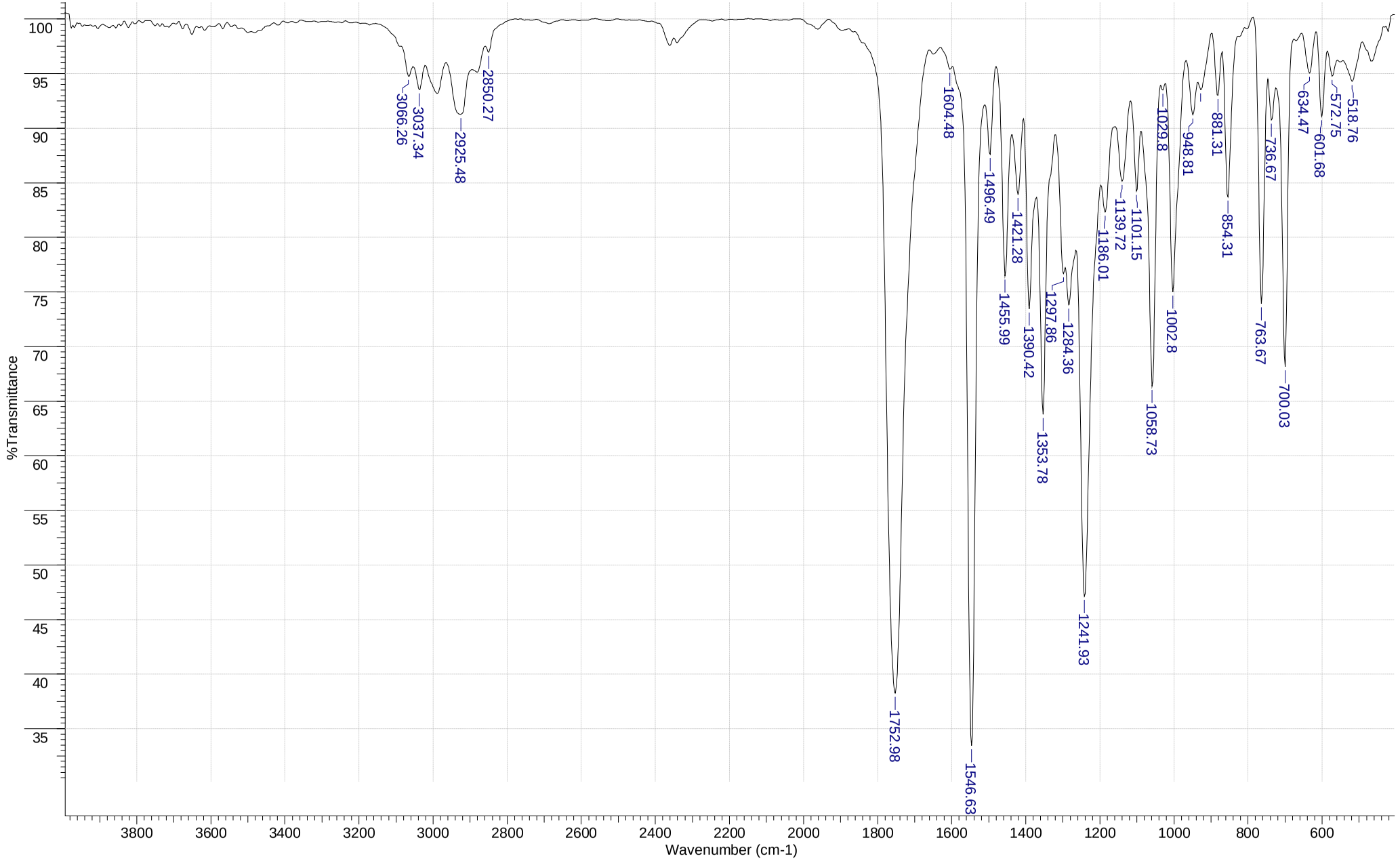
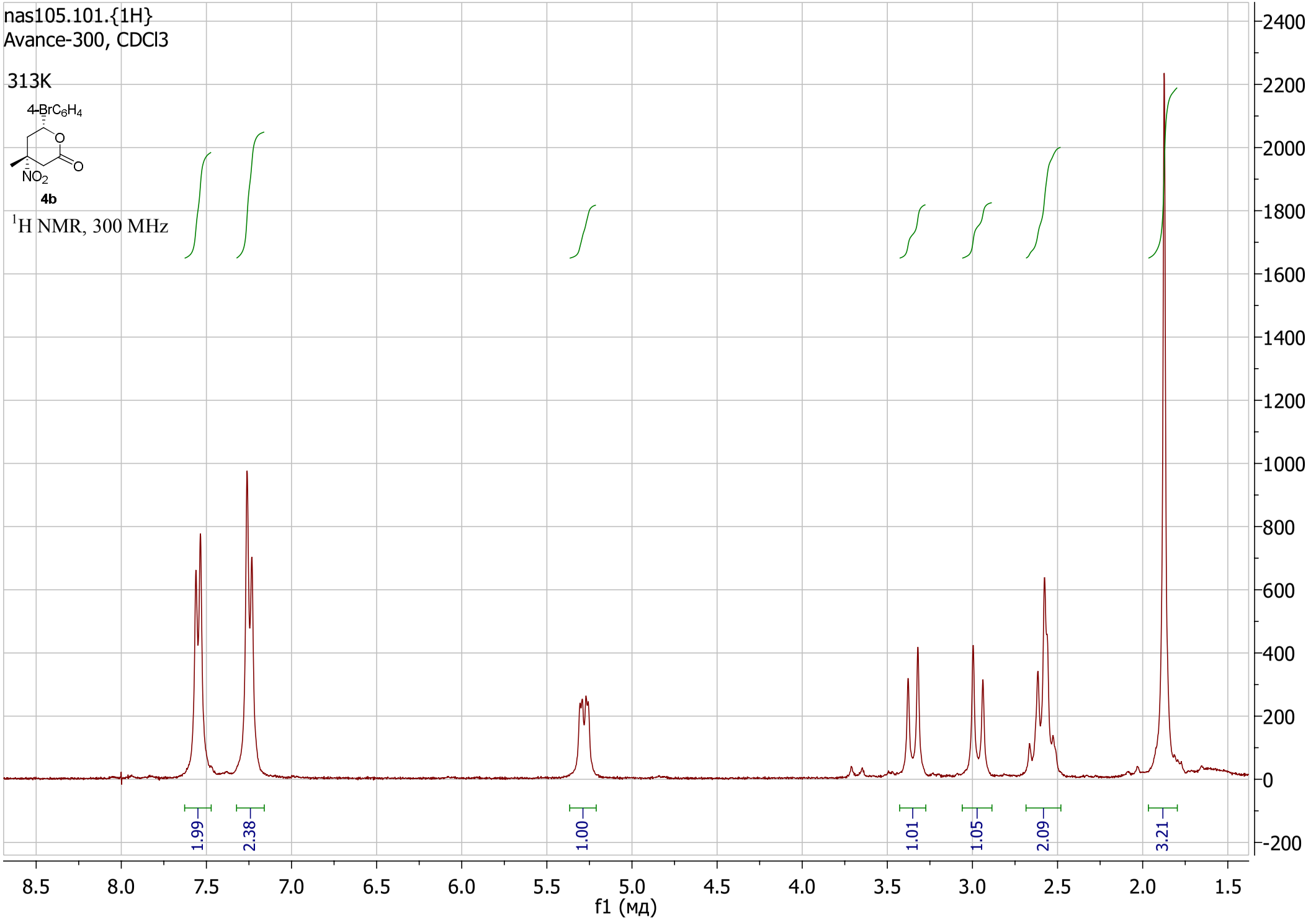
Y Axis	%Transmittance	***Spectrum Range*** 399.1927 - 3999.6403			***Points Count***	1868	***Data Spacing*** 1.9285

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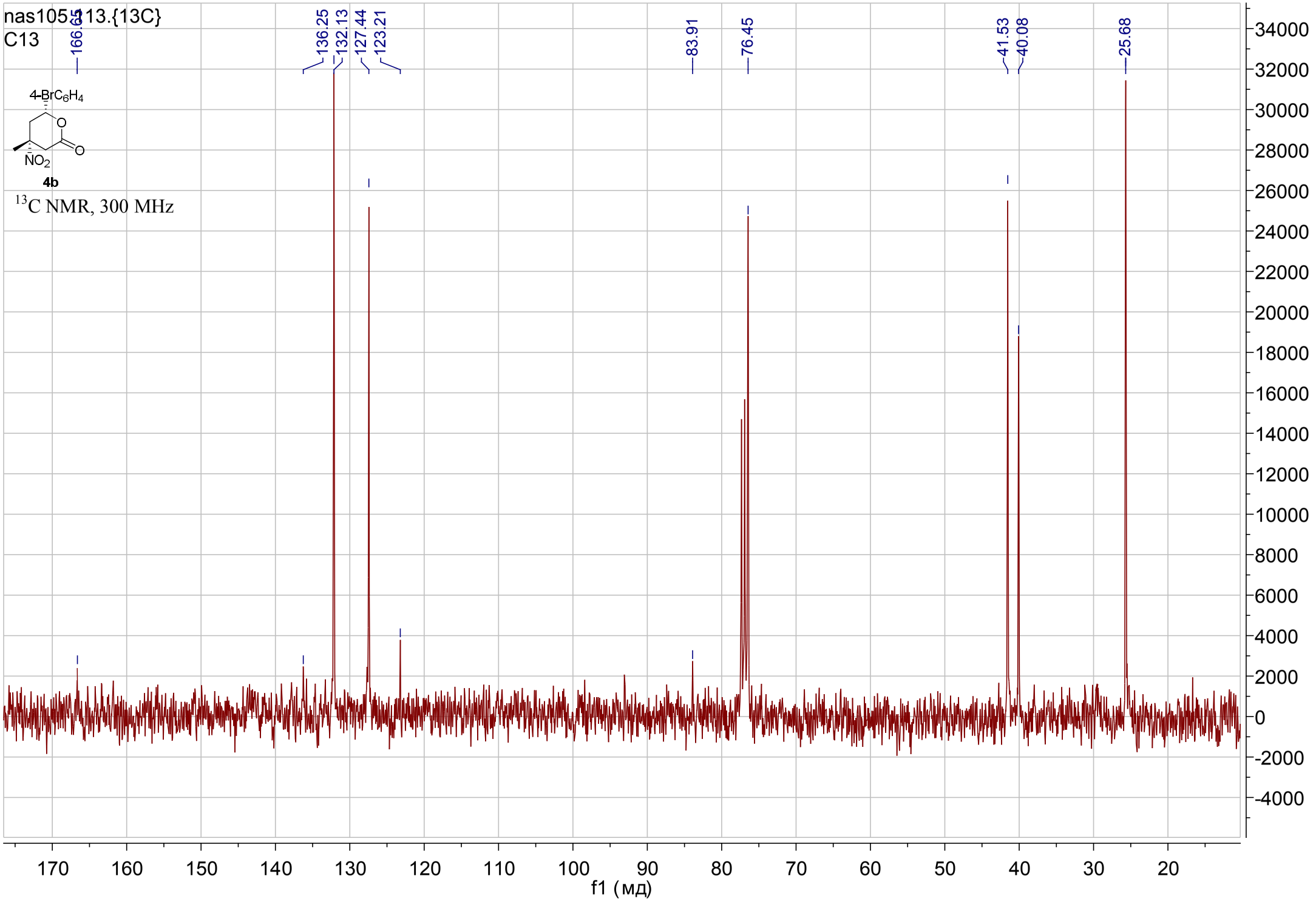
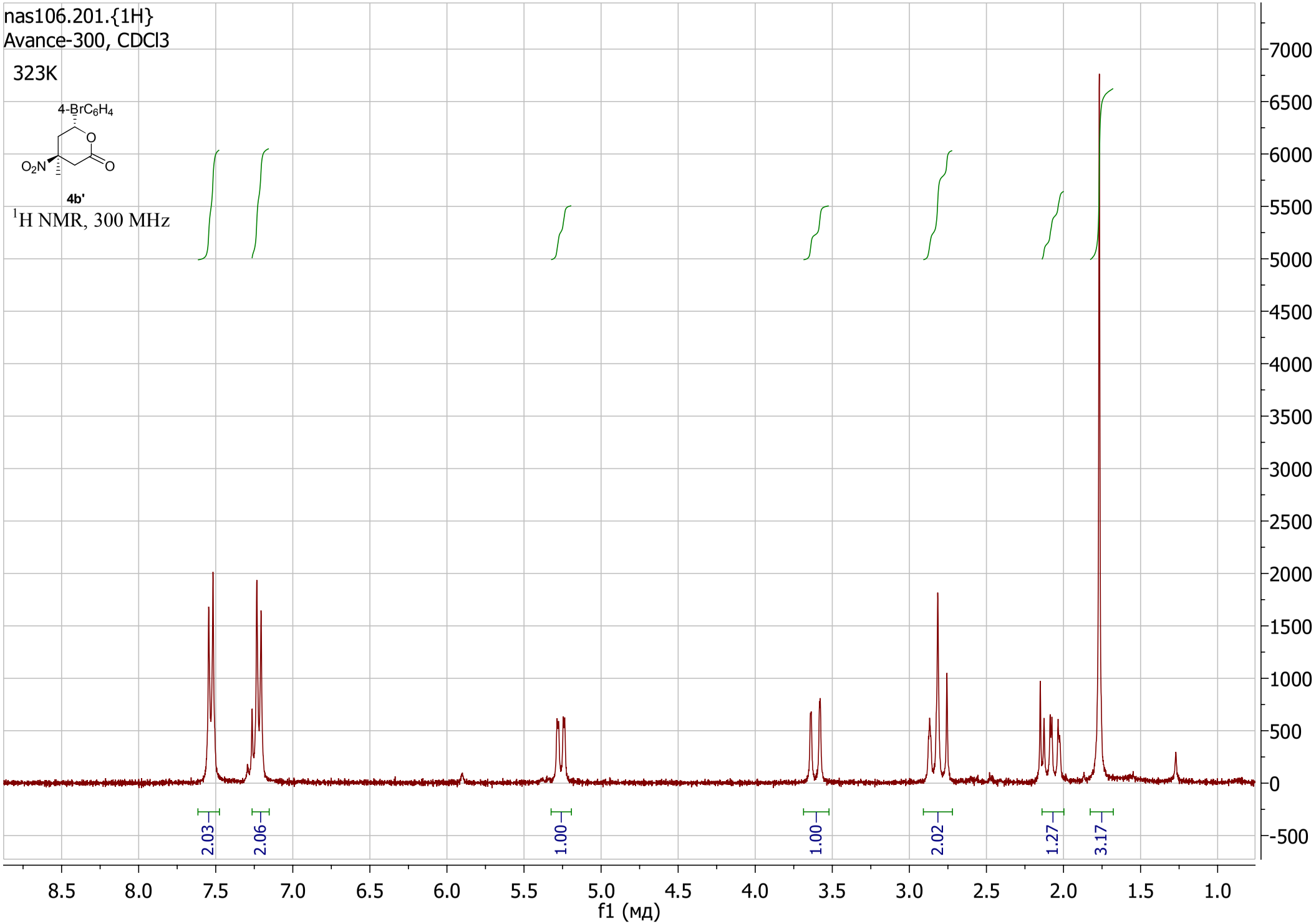
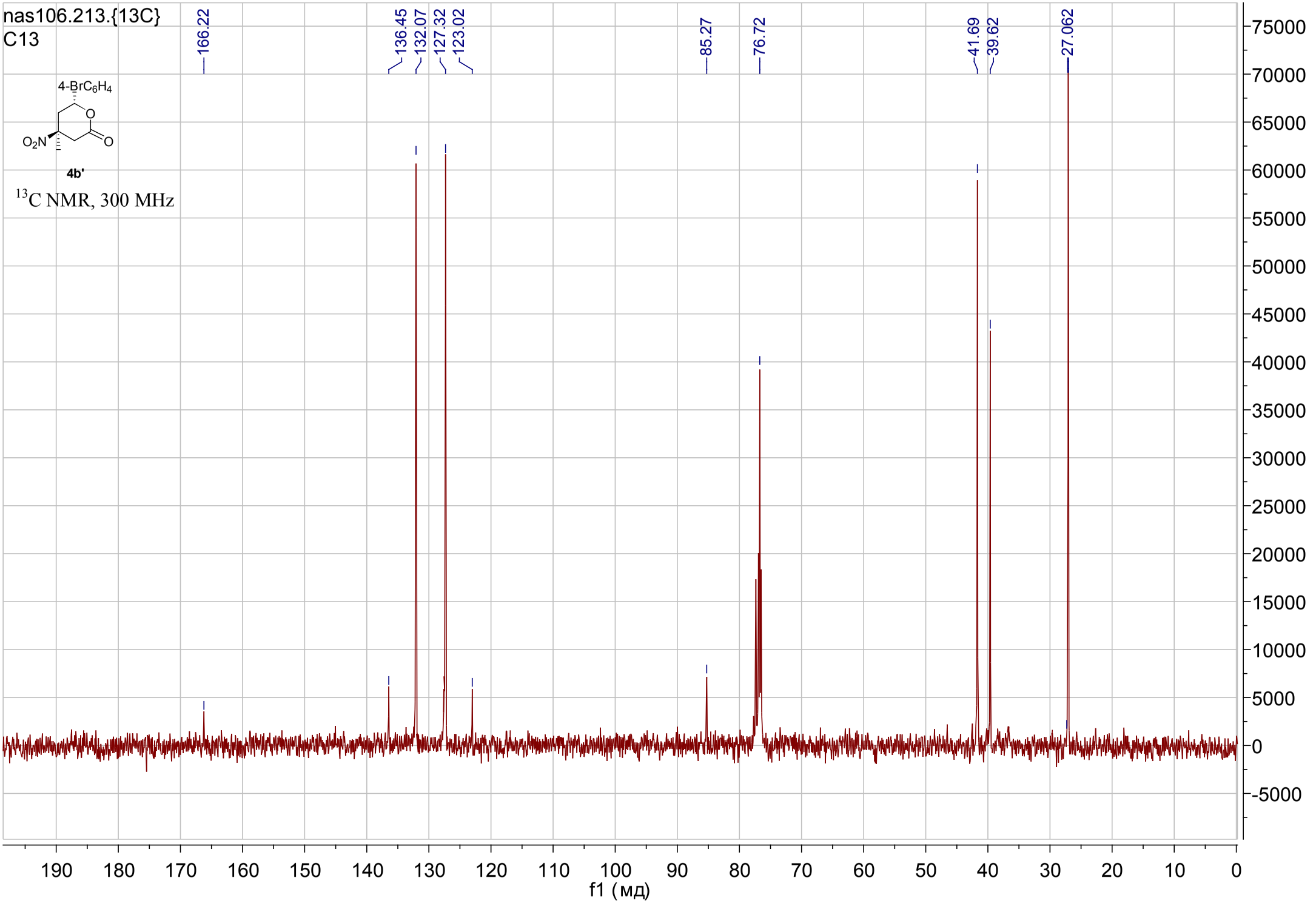
Avance-300, CDCl3
313K
4-BrC6H4
O
O
NO2
4b
1H NMR, 300 MHz
1.99
2.38
1.00
1.01
1.05
2.09
3.21
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (мд)


nas105-113.{13C}
C13
166.65
136.25
132.13
127.44
123.21
83.91
76.45
41.53
40.08
25.68
4-BrC6H4
NO2
4b
13C NMR, 300 MHz
34000
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
-4000
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (мд)


nas106.201.{1H}
Avance-300, CDCl3
323K
4-BrC6H4
O2N
O
O
4b'
1H NMR, 300 MHz
2.03
2.06
1.00
1.00
2.02
1.27
3.17
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
f1 (мд)
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500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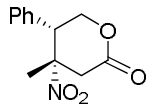
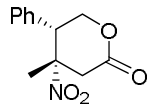
C13
166.22
136.45
132.07
127.32
123.02
85.27
76.72
41.69
39.62
27.062
4-BrC6H4
O2N
O
O
4b'
13C NMR, 300 MHz
75000
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (мд)



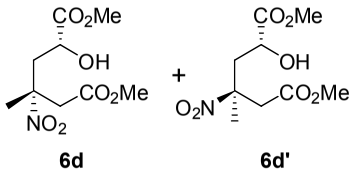
4c

^{1}H NMR, 400 MHz



4c

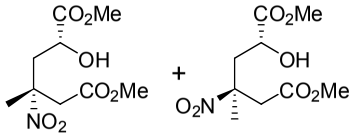
^{13}C NMR, 400 MHz



6d **6d'**

15:1

^{1}H NMR, 300 MHz

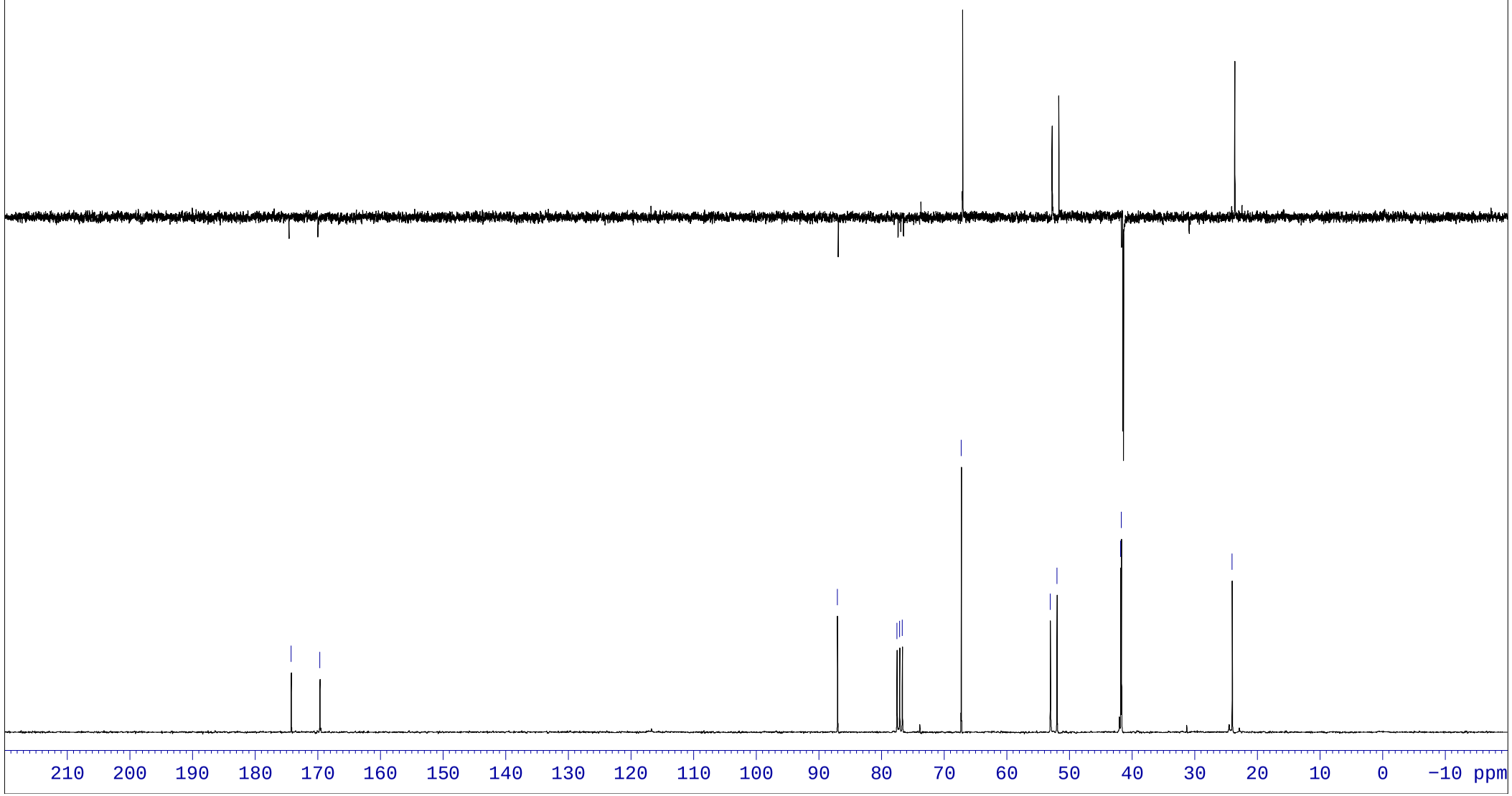


6d **6d'**

15:1

^{13}C NMR, 300 MHz

174.27 169.69 87.06 77.55 77.12 76.70 67.29 53.08 52.00 41.85 41.73 24.05



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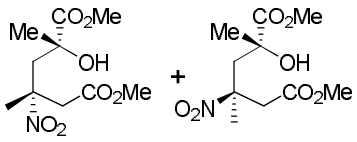


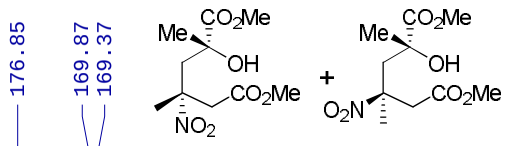
6e **6e'**

6.3:1

^{1}H NMR, 300 MHz

The Best Applied NMR!

/ILDT nas176201−C13dc

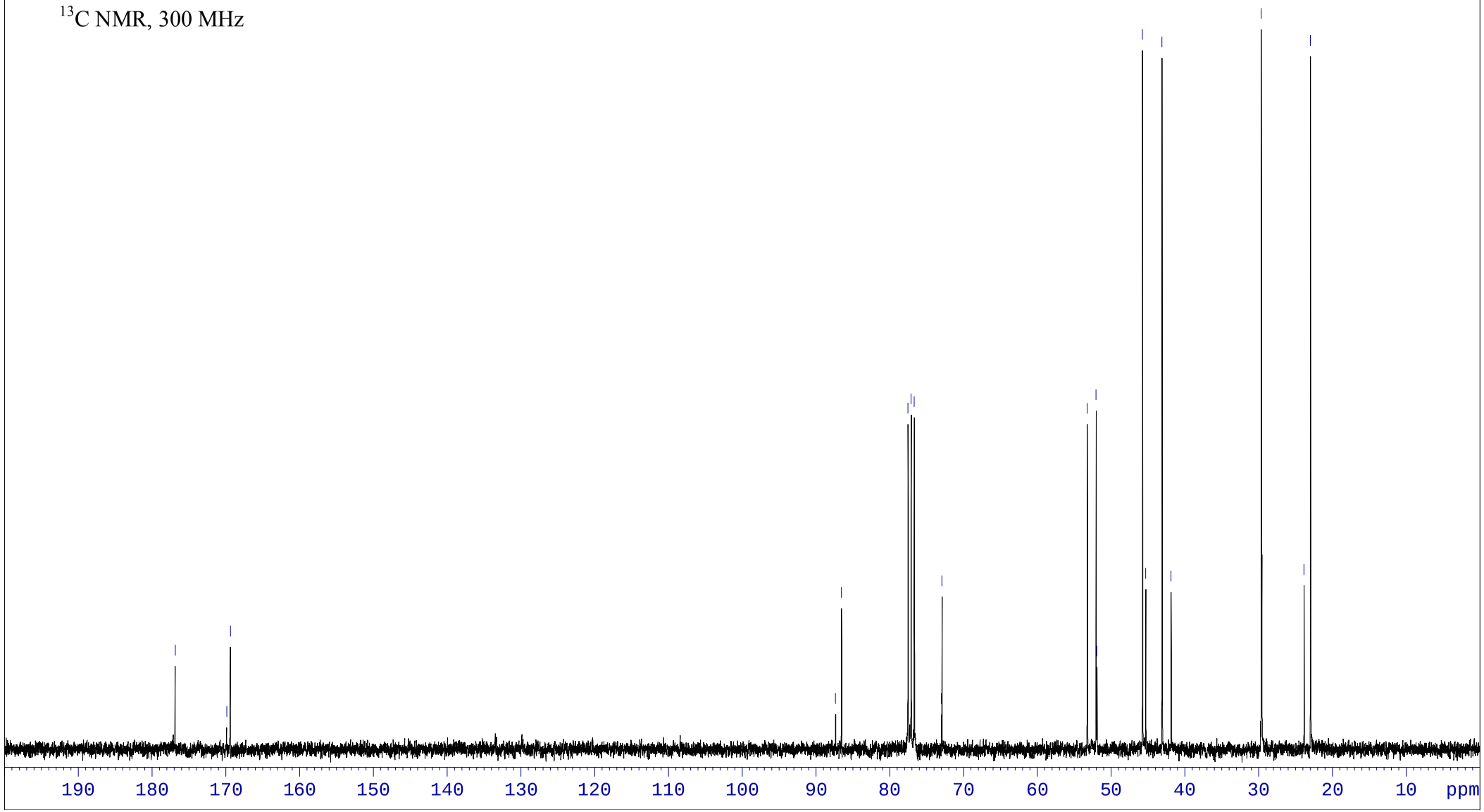


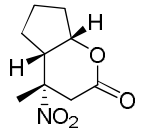
6e + **6e'**

6.3:1

^{13}C NMR, 300 MHz

176.85 169.87 169.37 87.37 86.56 77.54 77.12 76.69 73.01 72.93 53.24 52.05 51.93 45.76 45.31 43.11 41.88 29.65 29.59 23.86 22.99





4f

^{1}H NMR, 300 MHz

^{13}C NMR, 300 MHz

4f

167.28

132.23
129.71
129.04
128.32

89.94

82.28

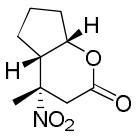
45.58
44.92

34.26
32.77

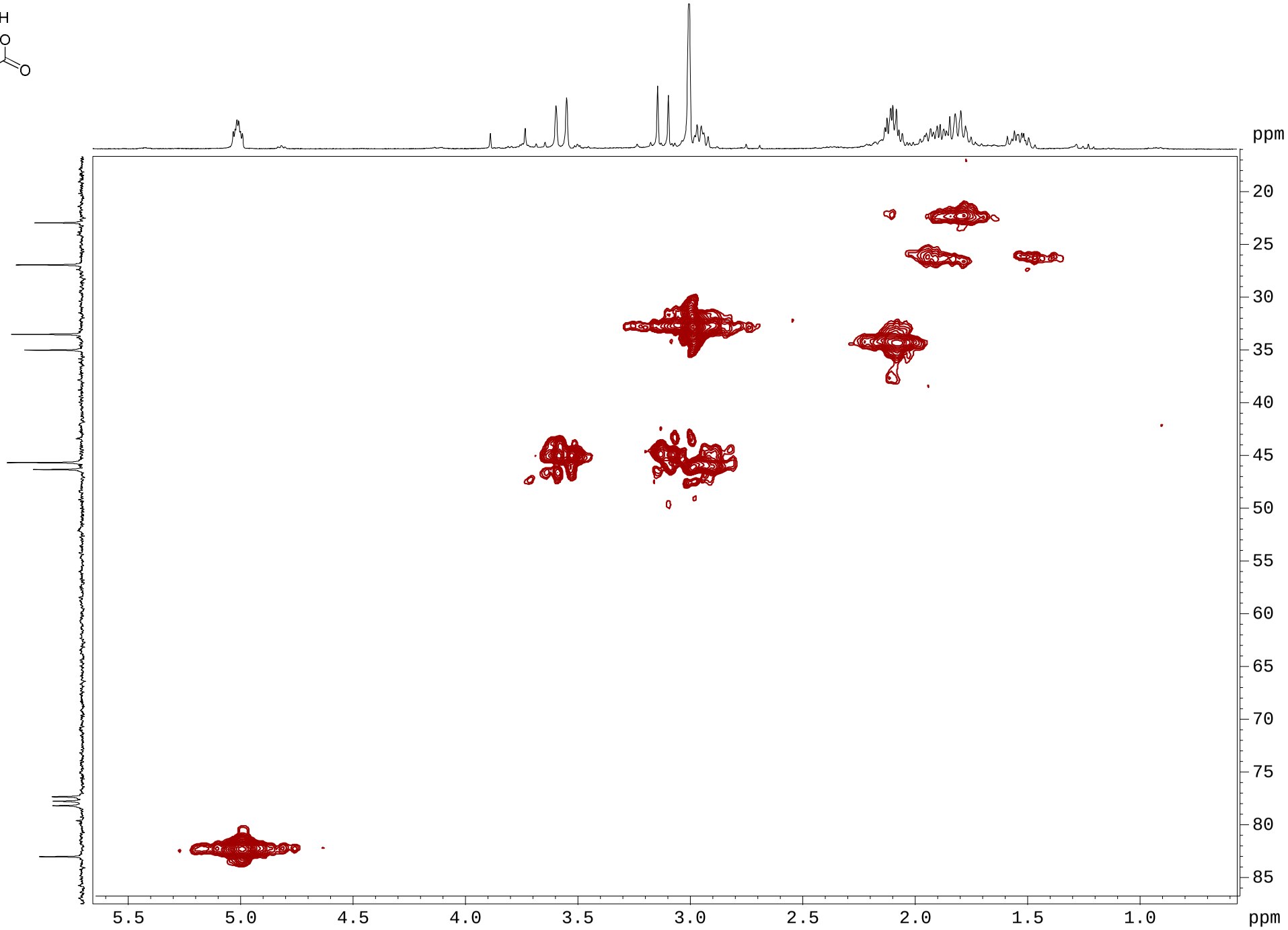
26.18

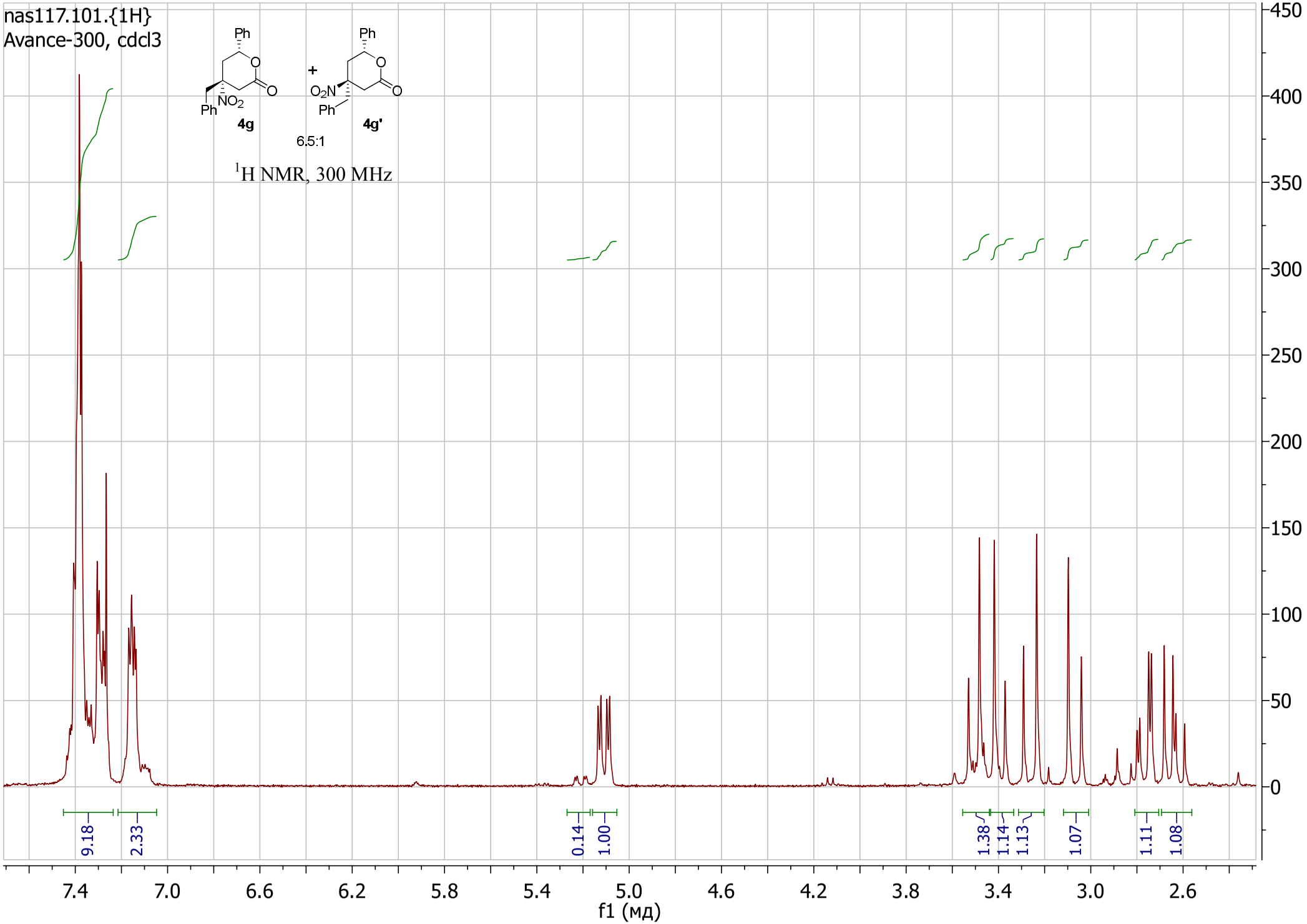
22.20

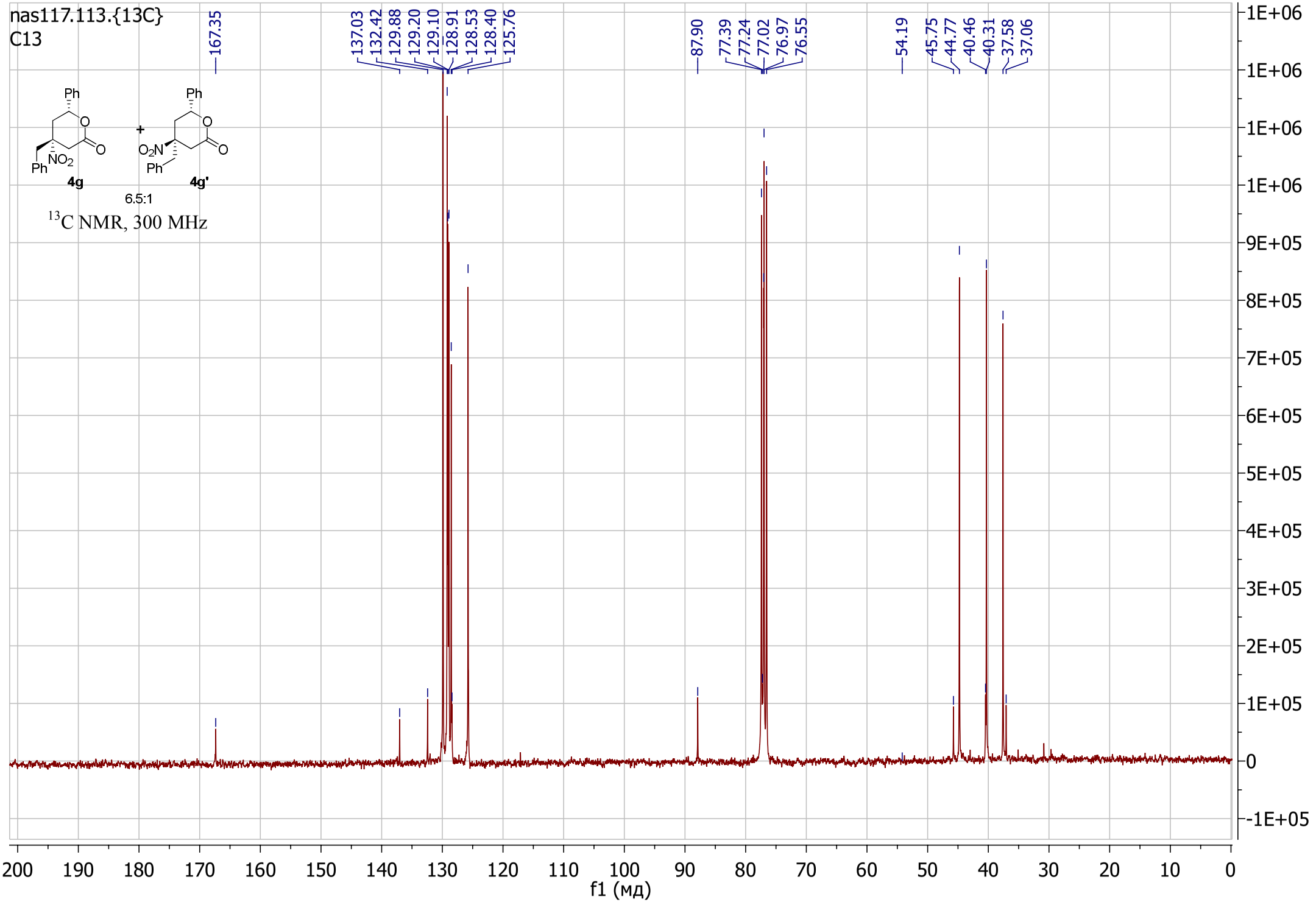
HSQC


H
H
O
O
NO2

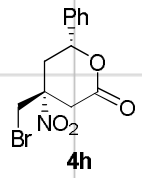
4f


ppm
20
25
30
35
40
45
50
55
60
65
70
75
80
85
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


nas117.101.{1H}
Avance-300, cdcl3
Ph
O
O
NO2
Ph
4g
+
O2N
Ph
4g'
6.5:1
1H NMR, 300 MHz
9.18
2.33
0.14
1.00
1.38
1.14
1.13
1.07
1.11
1.08
7.4
7.0
6.6
6.2
5.8
5.4
5.0
4.6
4.2
3.8
3.4
3.0
2.6
f1 (мд)
450
400
350
300
250
200
150
100
50
0

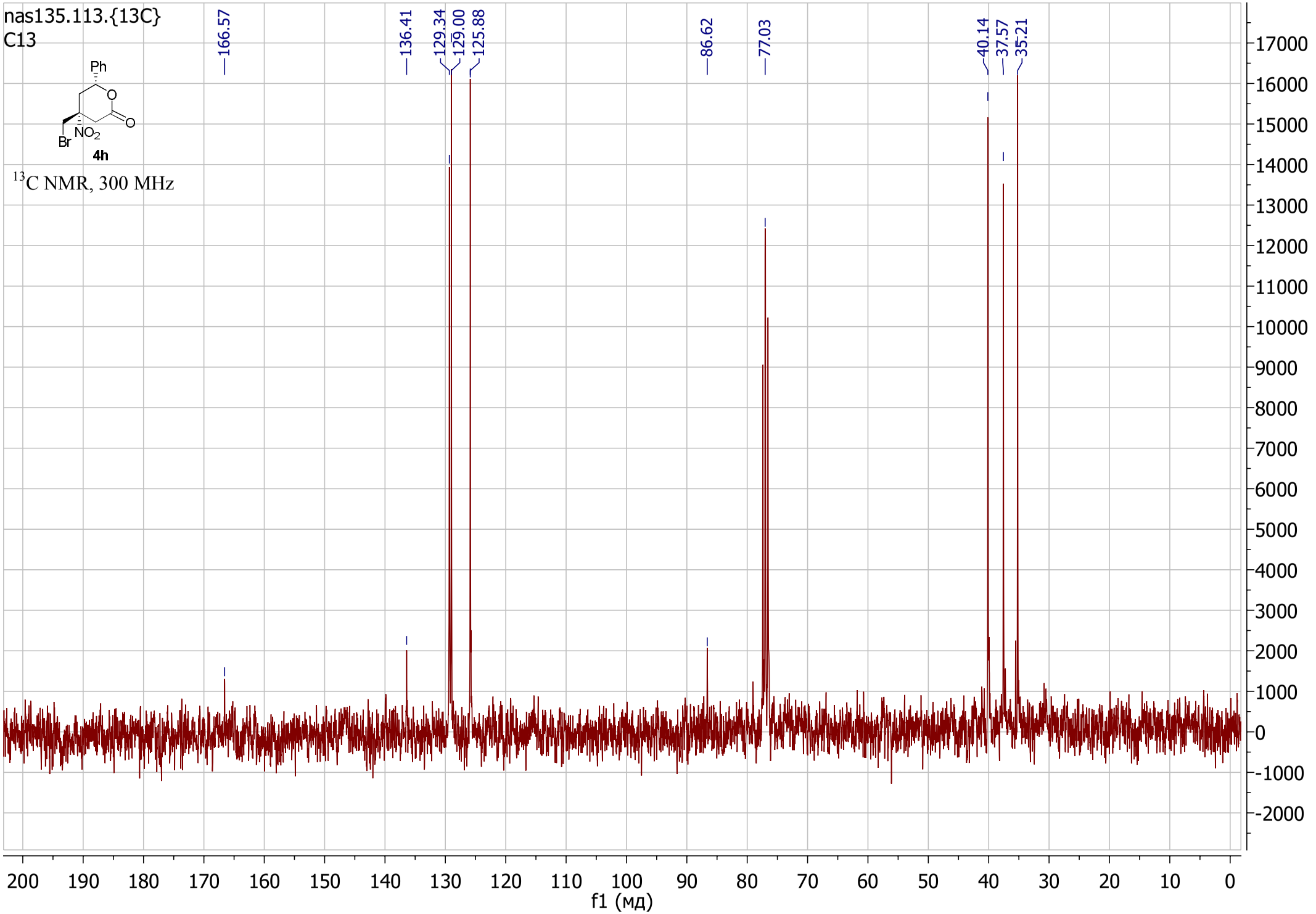

nas117.113.{13C}
C13
167.35
137.03
132.42
129.88
129.20
129.10
128.91
128.53
128.40
125.76
87.90
77.39
77.24
77.02
76.97
76.55
54.19
45.75
44.77
40.46
40.31
37.58
37.06
Ph
O
O
Ph
NO2
4g
+
O2N
Ph
4g'
6.5:1
13C NMR, 300 MHz
1E+06
9E+05
8E+05
7E+05
6E+05
5E+05
4E+05
3E+05
2E+05
1E+05
0
-1E+05
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (мд)

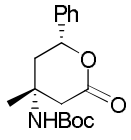
nas135.101.{1H}
Avance-300



4h

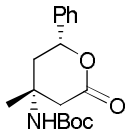
^{1}H NMR, 300 MHz


nas135.113.{13C}
C13
166.57
136.41
129.34
129.00
125.88
86.62
77.03
40.14
37.57
35.21
Ph
O
O
NO2
Br
4h
13C NMR, 300 MHz
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-2000
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (мд)



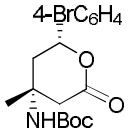
Boc-**1a**

^{1}H NMR, 300 MHz



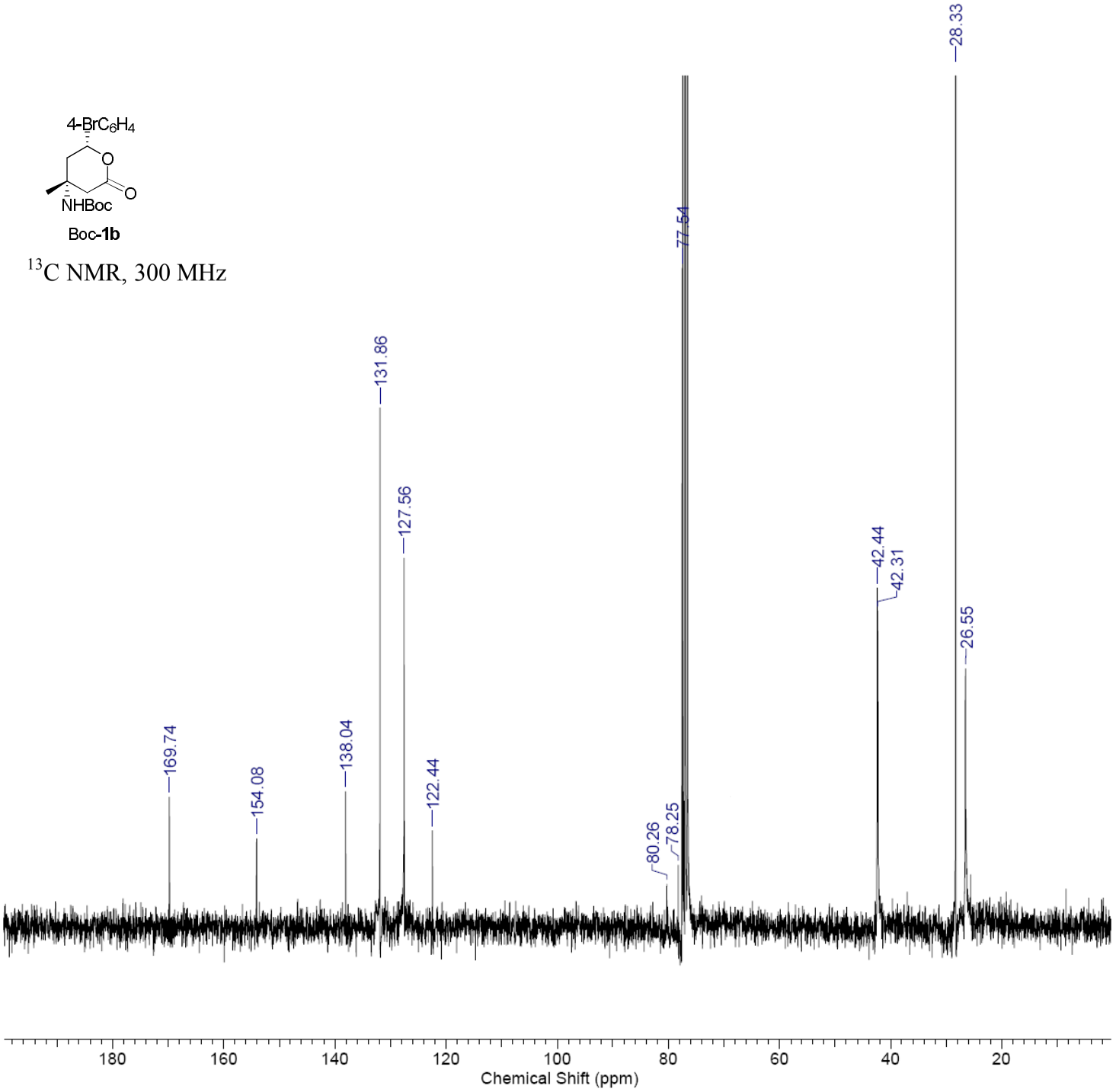
Boc-**1a**

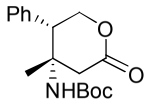
^{13}C NMR, 300 MHz



Boc-**1b**

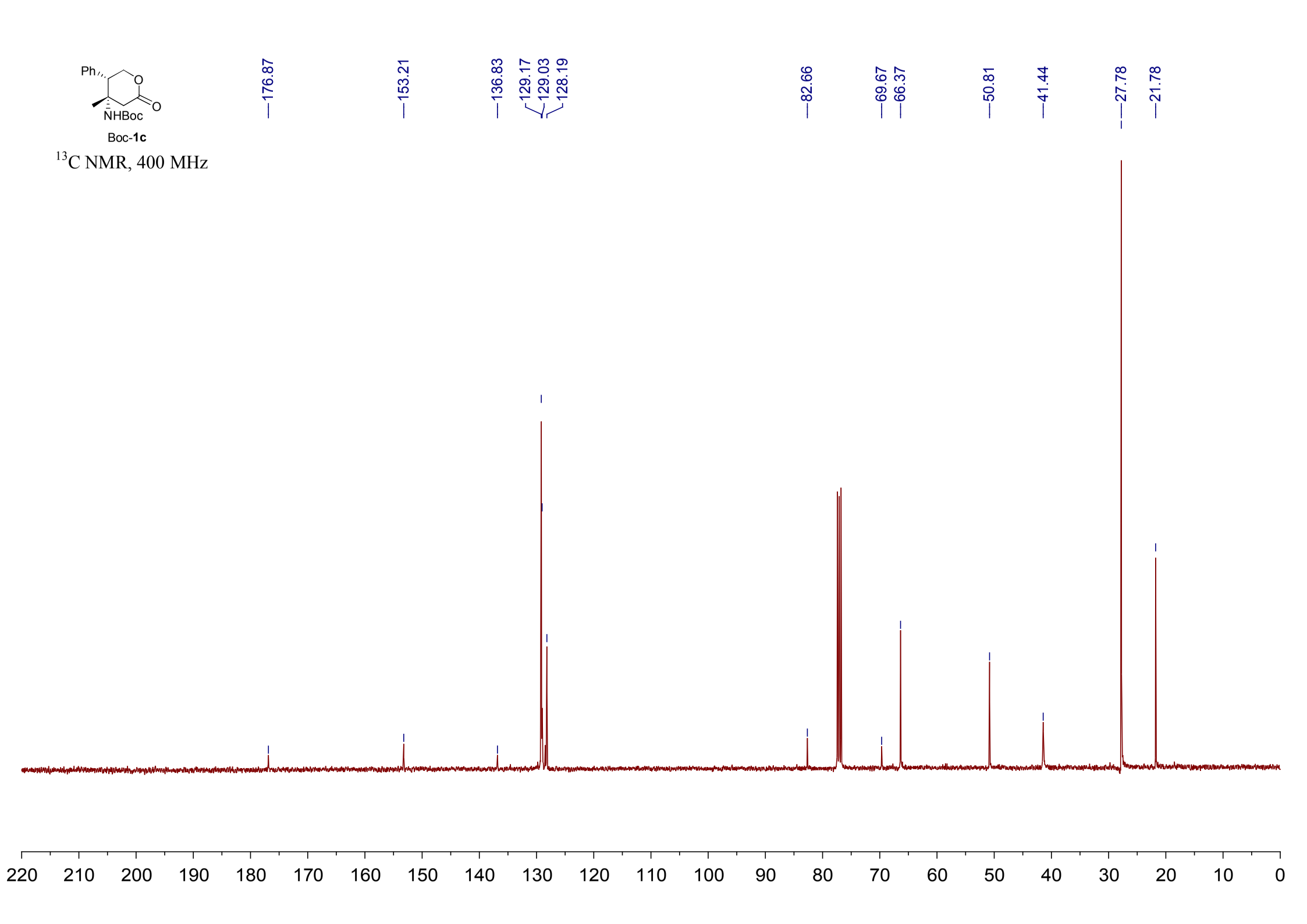
^{1}H NMR, 300 MHz


4-BrC6H4
O
O
NHBoc
Boc-1b
13C NMR, 300 MHz
169.74
154.08
138.04
131.86
127.56
122.44
80.26
78.25
77.54
42.44
42.31
28.33
26.55
180
160
140
120
100
80
60
40
20
Chemical Shift (ppm)



Boc-**1c**

^{1}H NMR, 400 MHz


Ph
O
O
NHBoc
Boc-1c
13C NMR, 400 MHz
176.87
153.21
136.83
129.17
129.03
128.19
82.66
69.67
66.37
50.81
41.44
27.78
21.78
220
210
200
190
180
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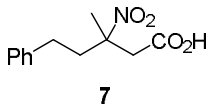
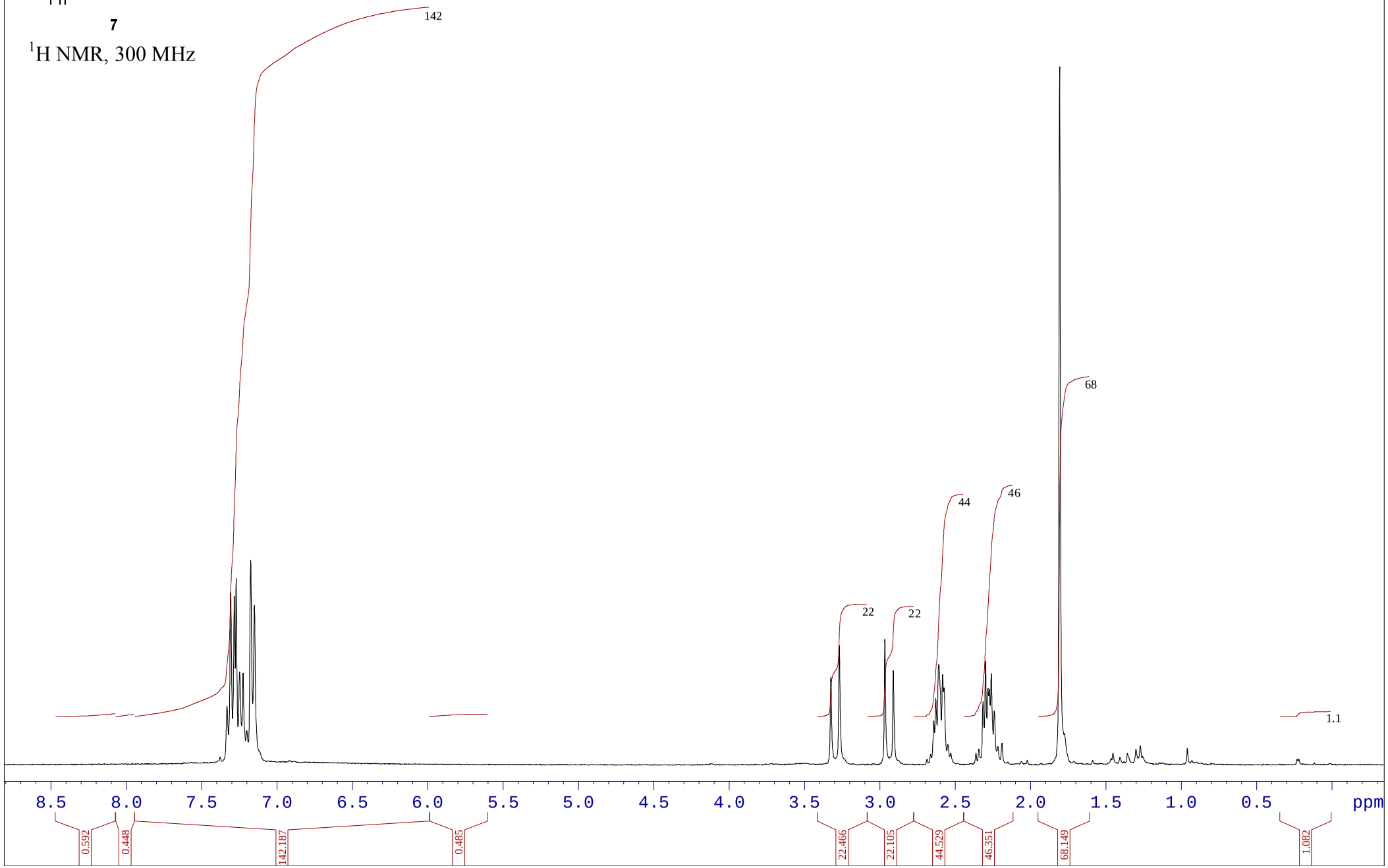
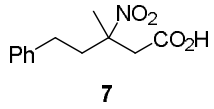
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0



7

^{1}H NMR, 300 MHz

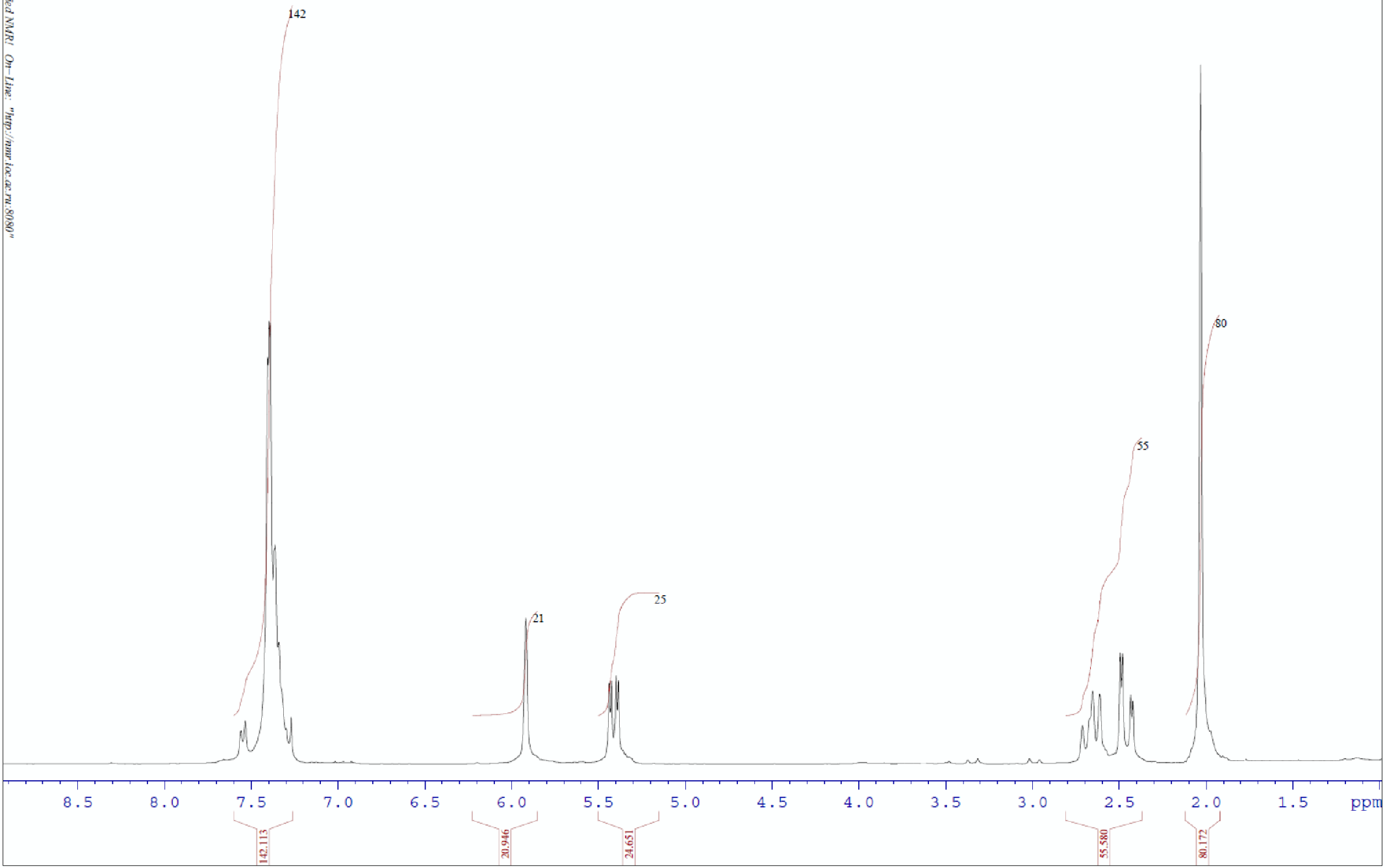




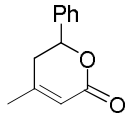
7

^{13}C NMR, 300 MHz

/ILDT nas064.001

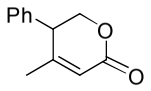


{13C}
Avance-300, CDCl3



5a

^{13}C NMR, 300 MHz



5c

^{1}H NMR, 400 MHz

^{13}C NMR, 400 MHz

5c

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

164.22
159.20
137.12
129.09
128.12
128.00
117.71
71.70
45.16
21.72