Supplementary Information

N-Acyl-, as well as *N*-phosphonoylmethyl- and *N*-phoshinoylmethyl-α-aminophosphonates; A new tandem Kabachnik–Fields protocol

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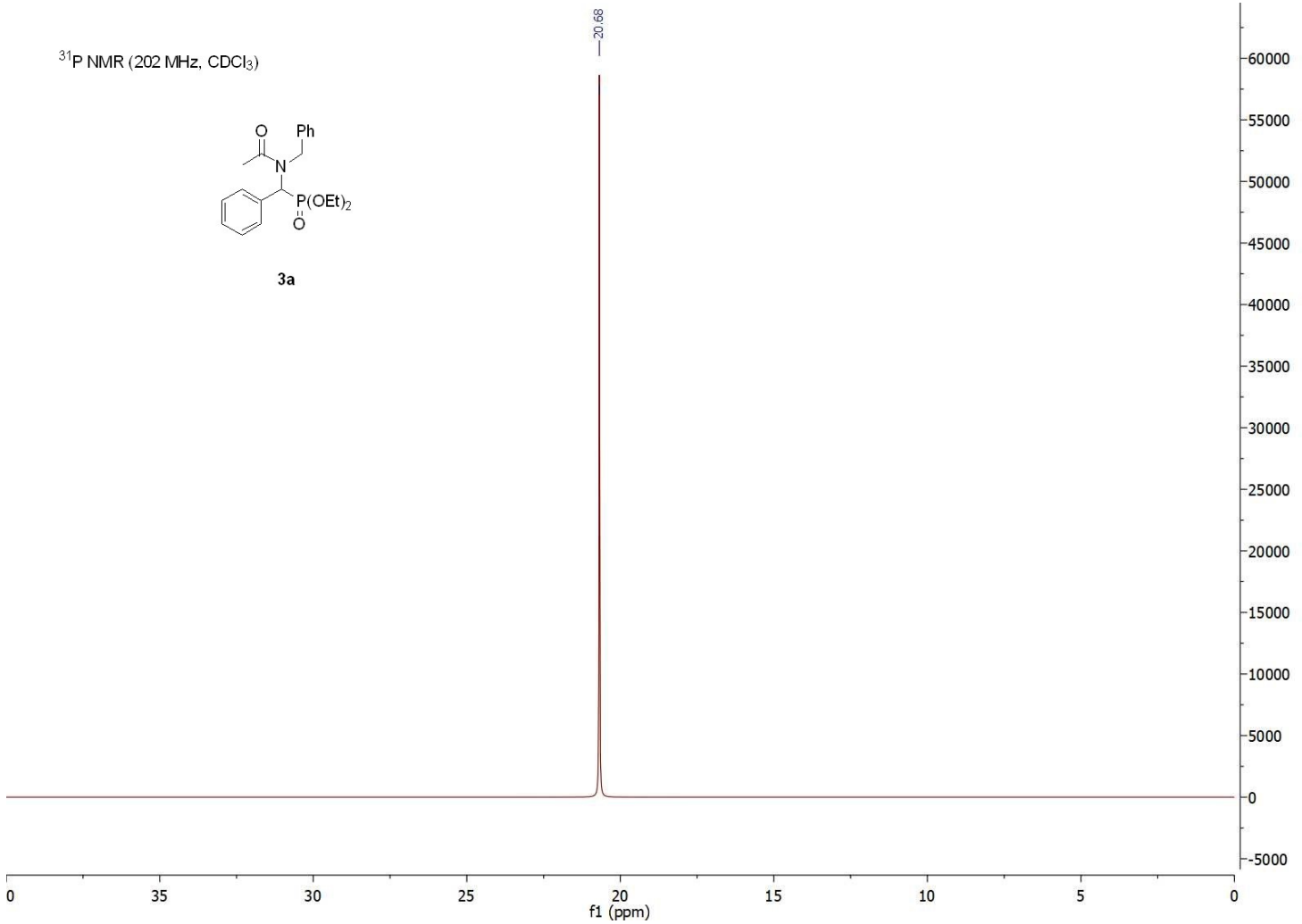
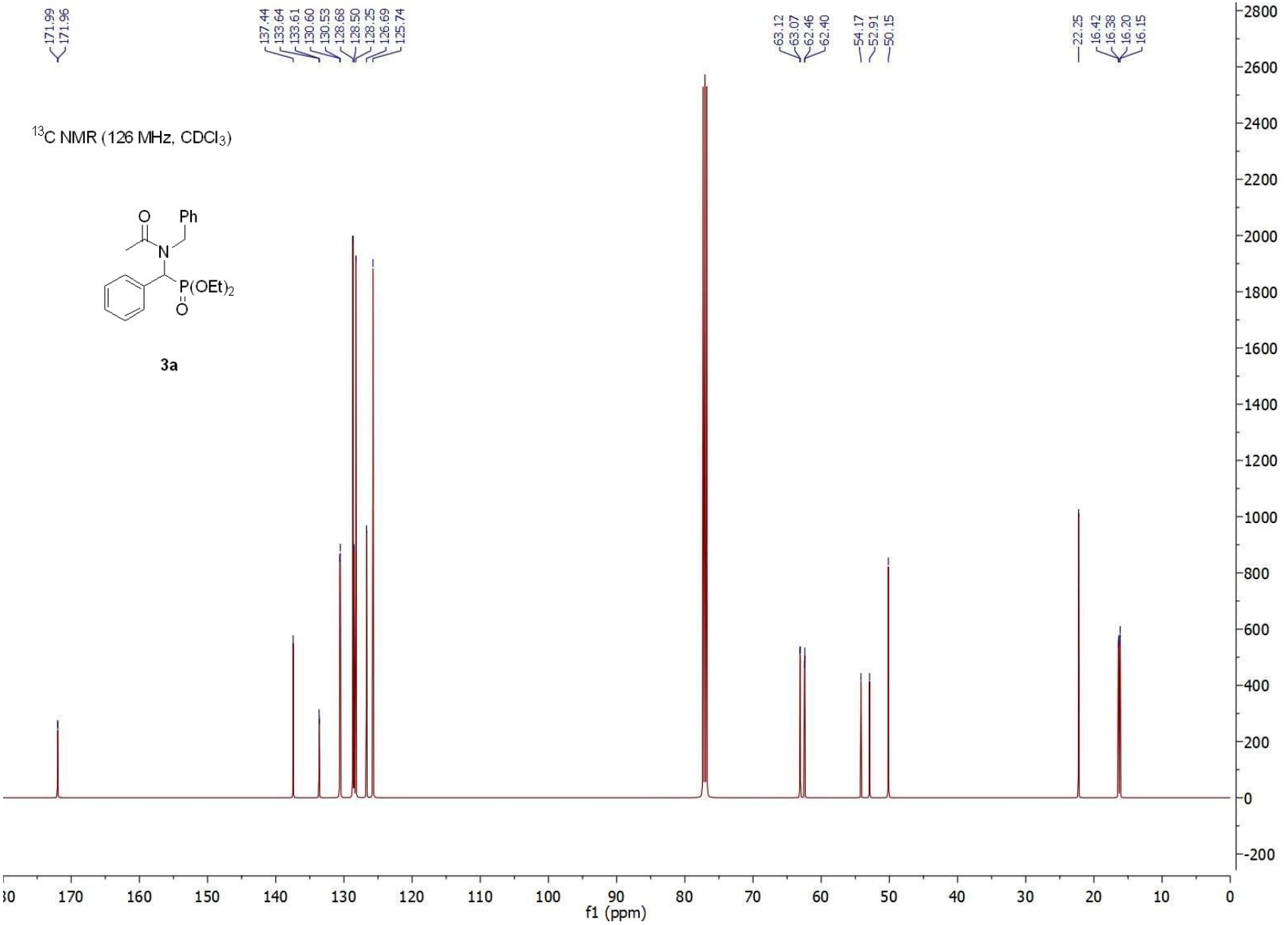
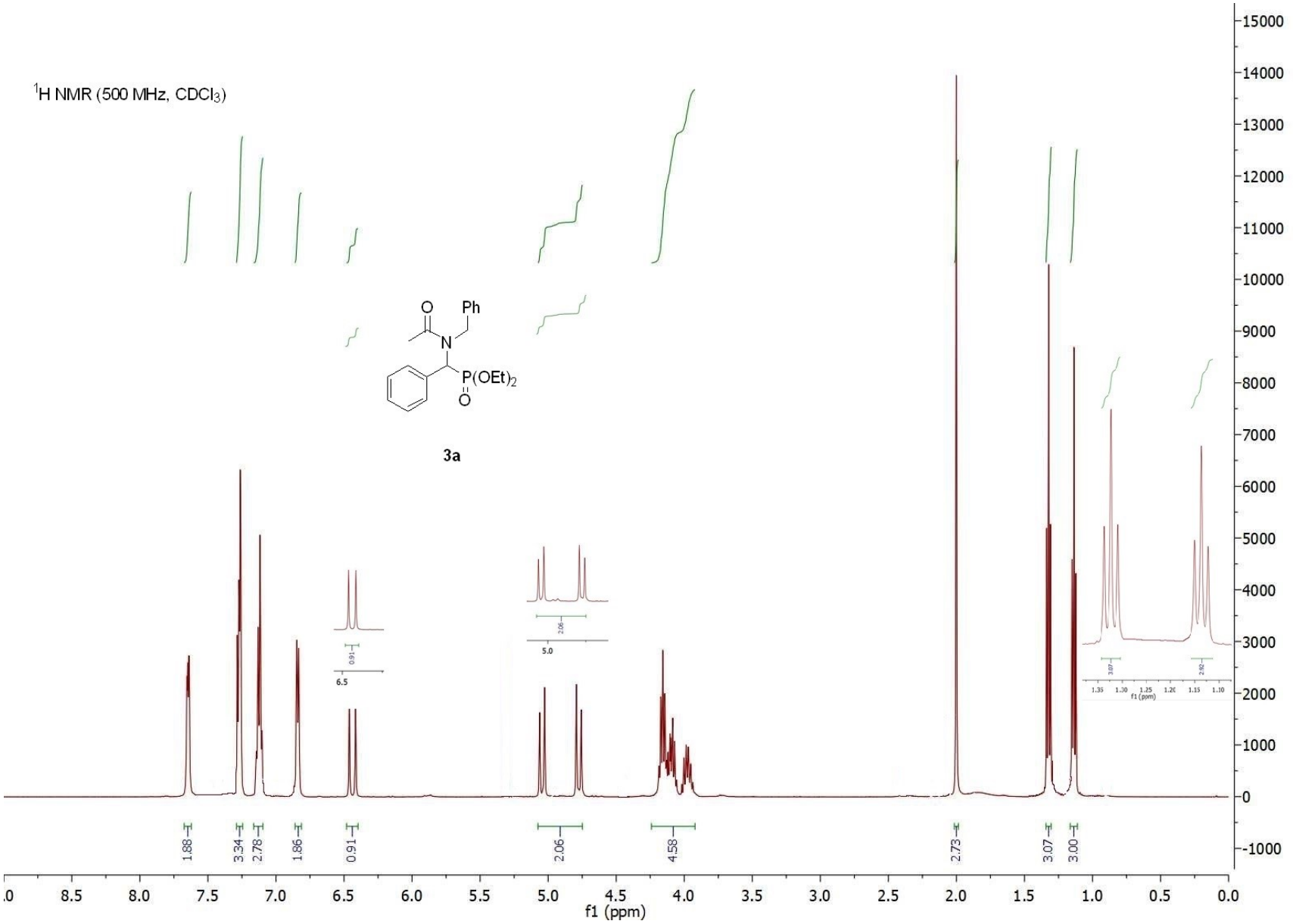
Contents

1.) ^{31}P-, ^{13}C and ^{1}H NMR spectra of the products (3a, 3b, 4a, 4b, 5a-f, 6 and 8)

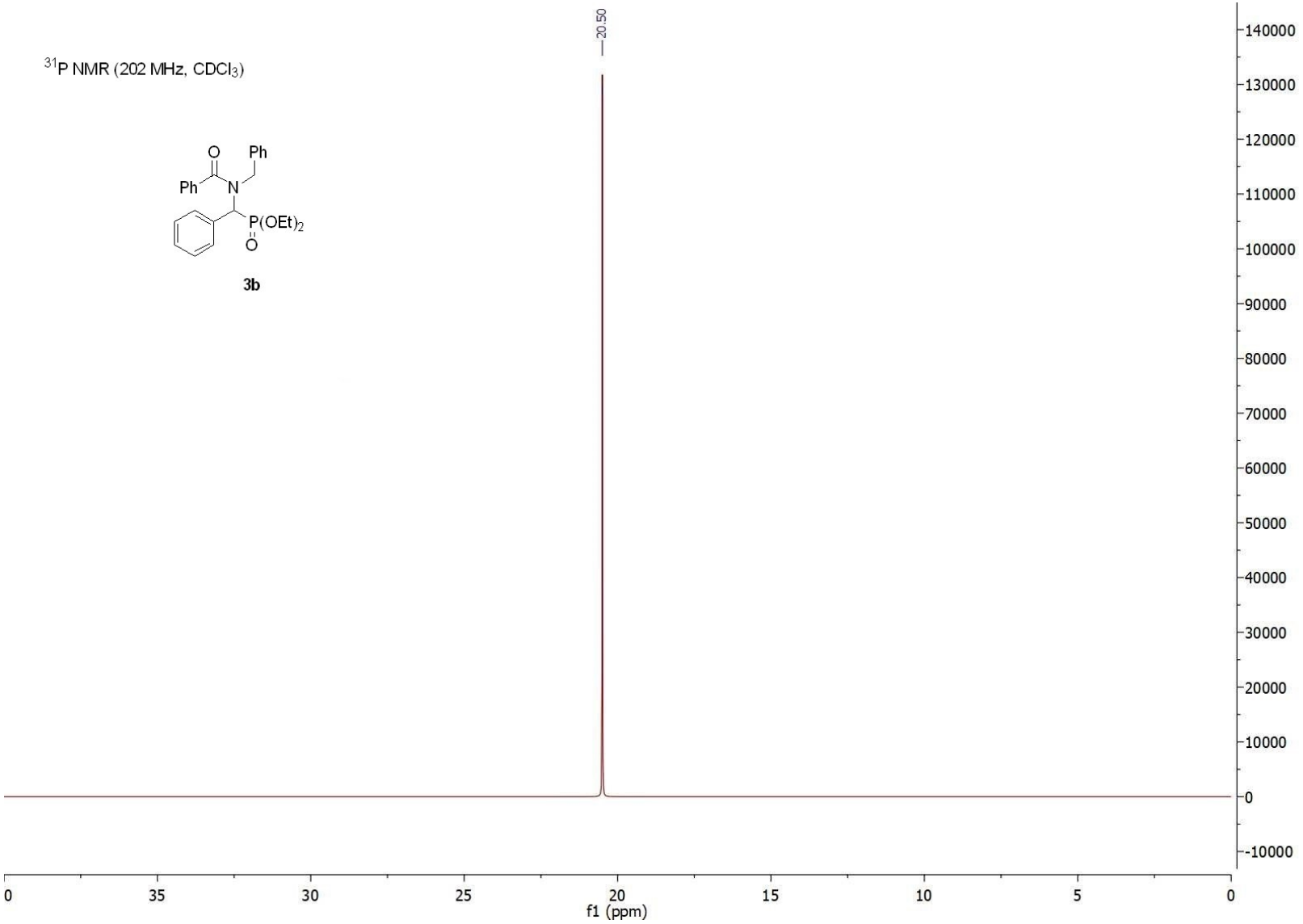
Diethyl (N-benzylacetamido)-benzylphosphonate (3a)



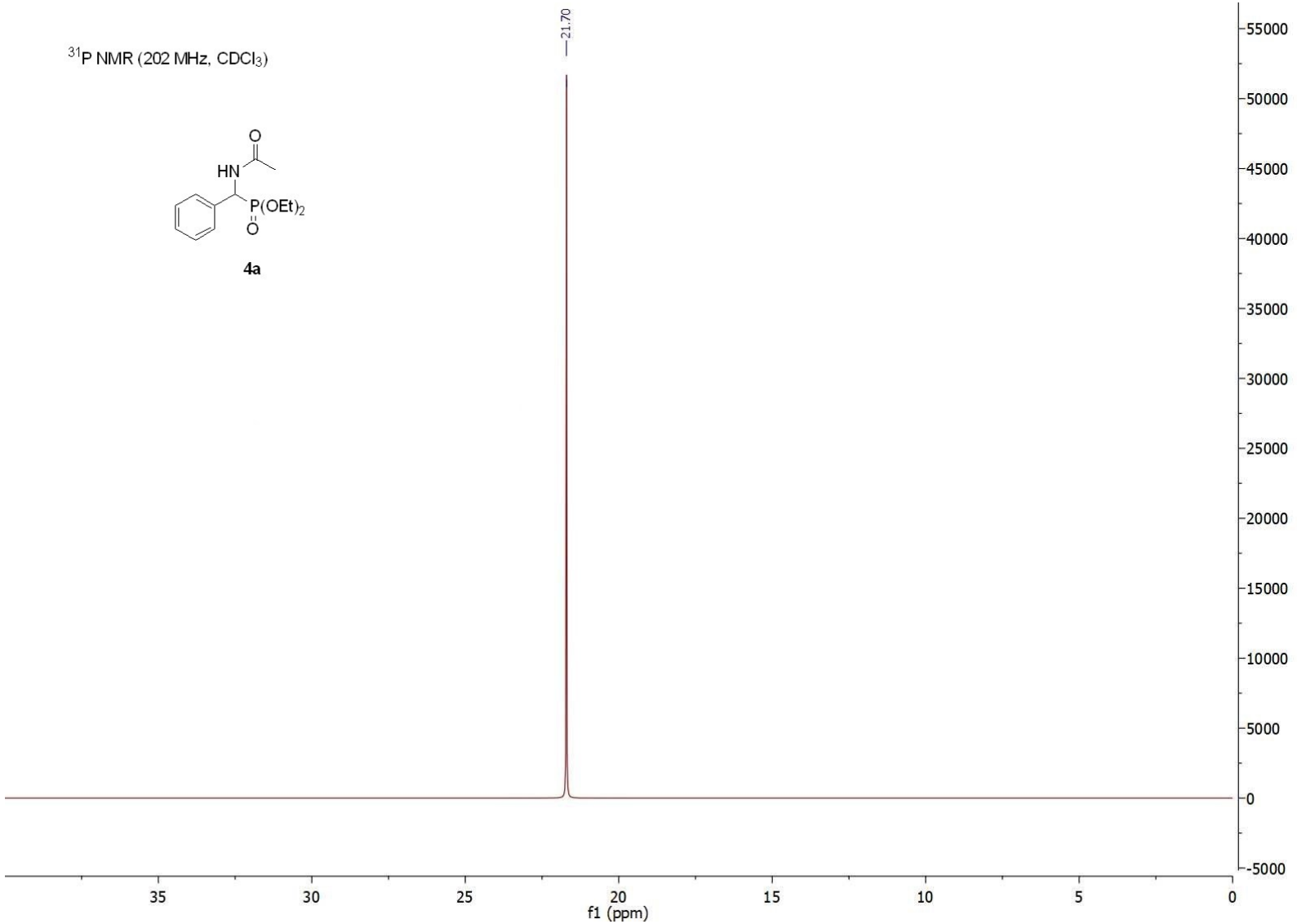

171.99
171.96
137.44
133.64
133.61
130.60
130.53
128.68
128.50
128.25
126.69
125.74
63.12
63.07
62.46
62.40
54.17
52.91
50.15
22.25
16.42
16.38
16.20
16.15
13C NMR (126 MHz, CDCl3)
O
Ph
N
P(OEt)2
O
3a
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

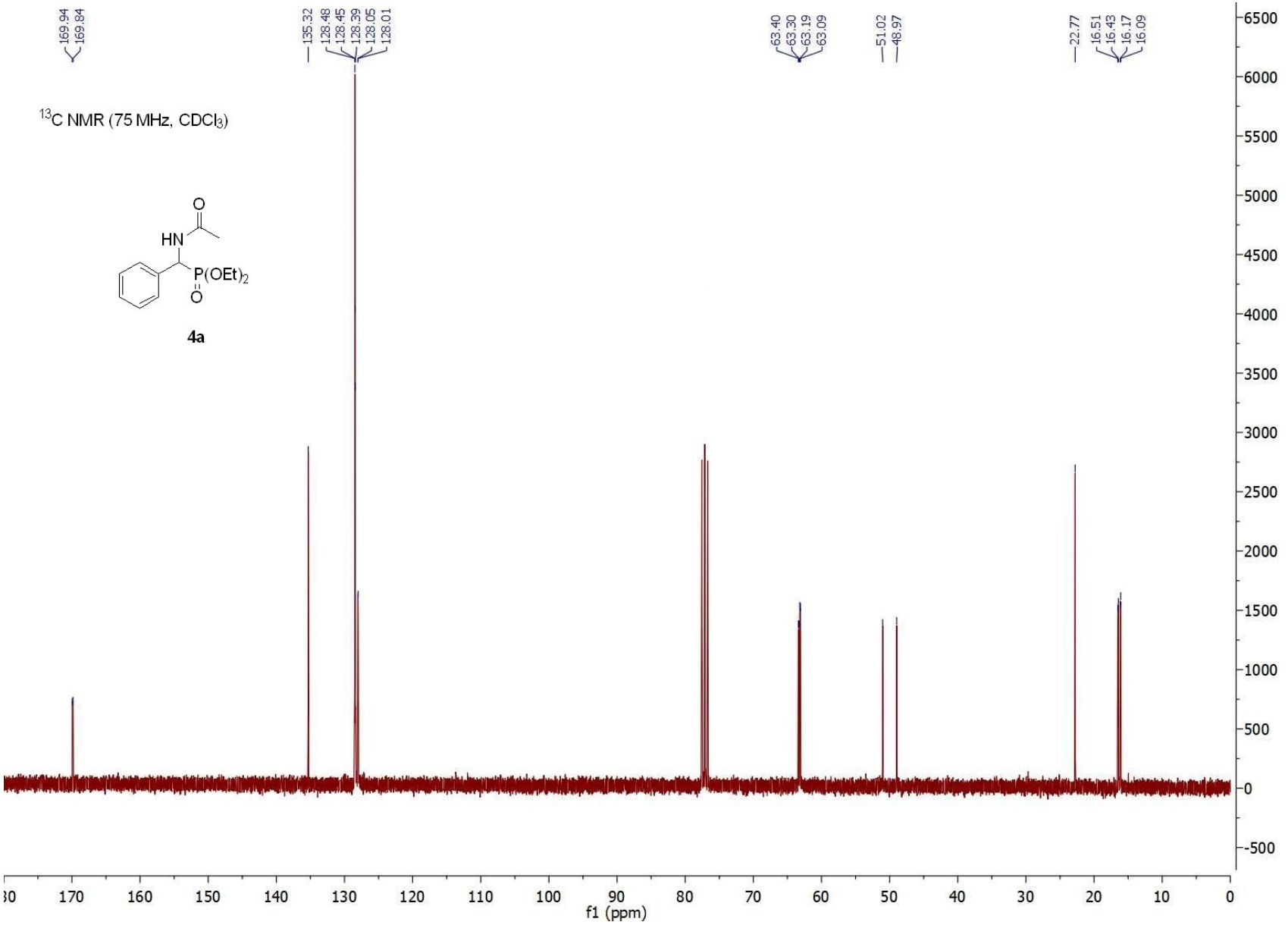

^{1}H NMR (500 MHz, $CDCl_3$)
O
Ph
N
P(OEt)$_2$
O
3a
1.88
3.34
2.78
1.86
0.91
2.06
4.58
2.73
3.07
3.00
f1 (ppm)

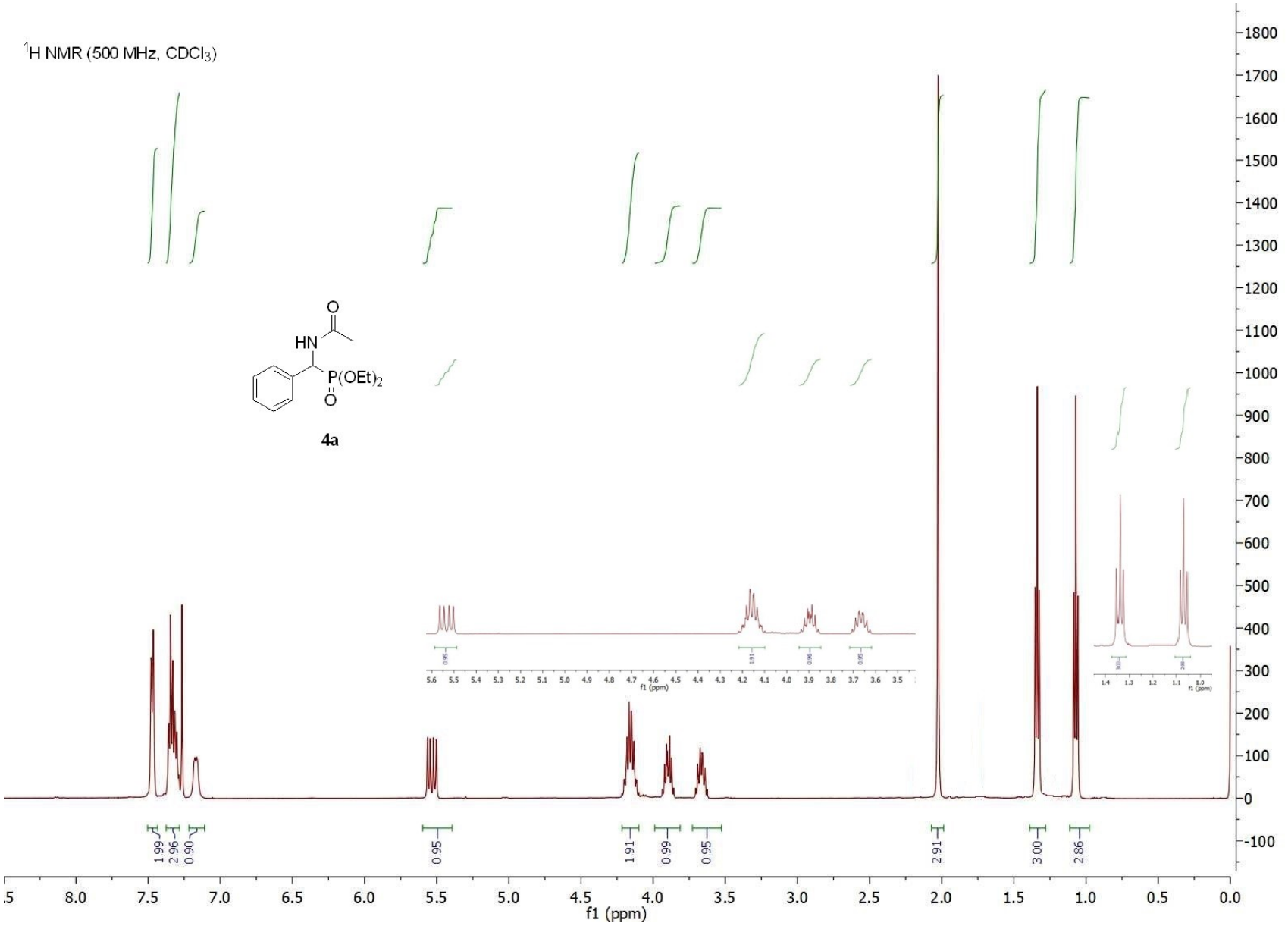
Diethyl (N-benzylbenzamido)-benzylphosphonate (**3b**)



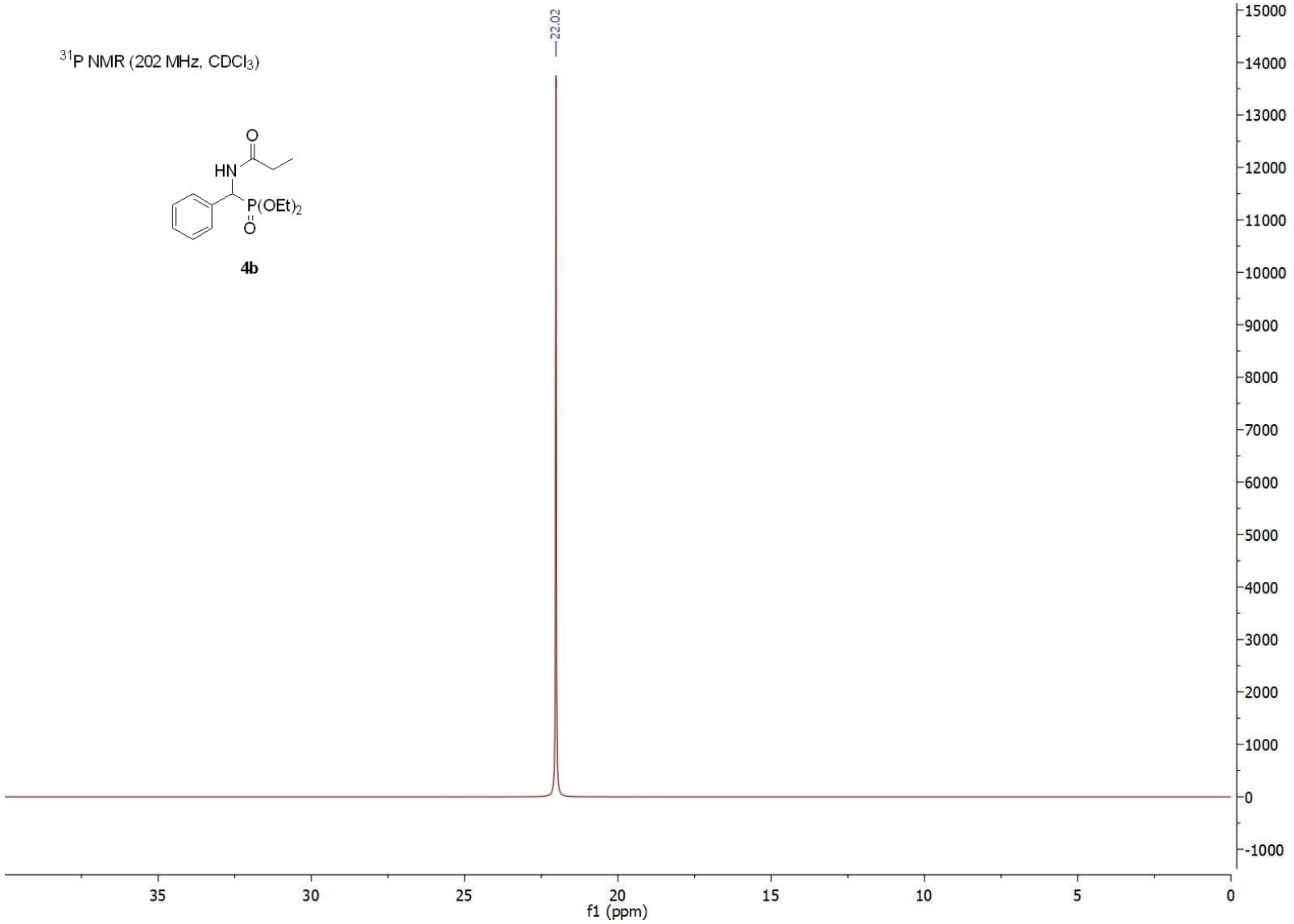
Diethyl acetamido-benzylphosphonate (**4a**)

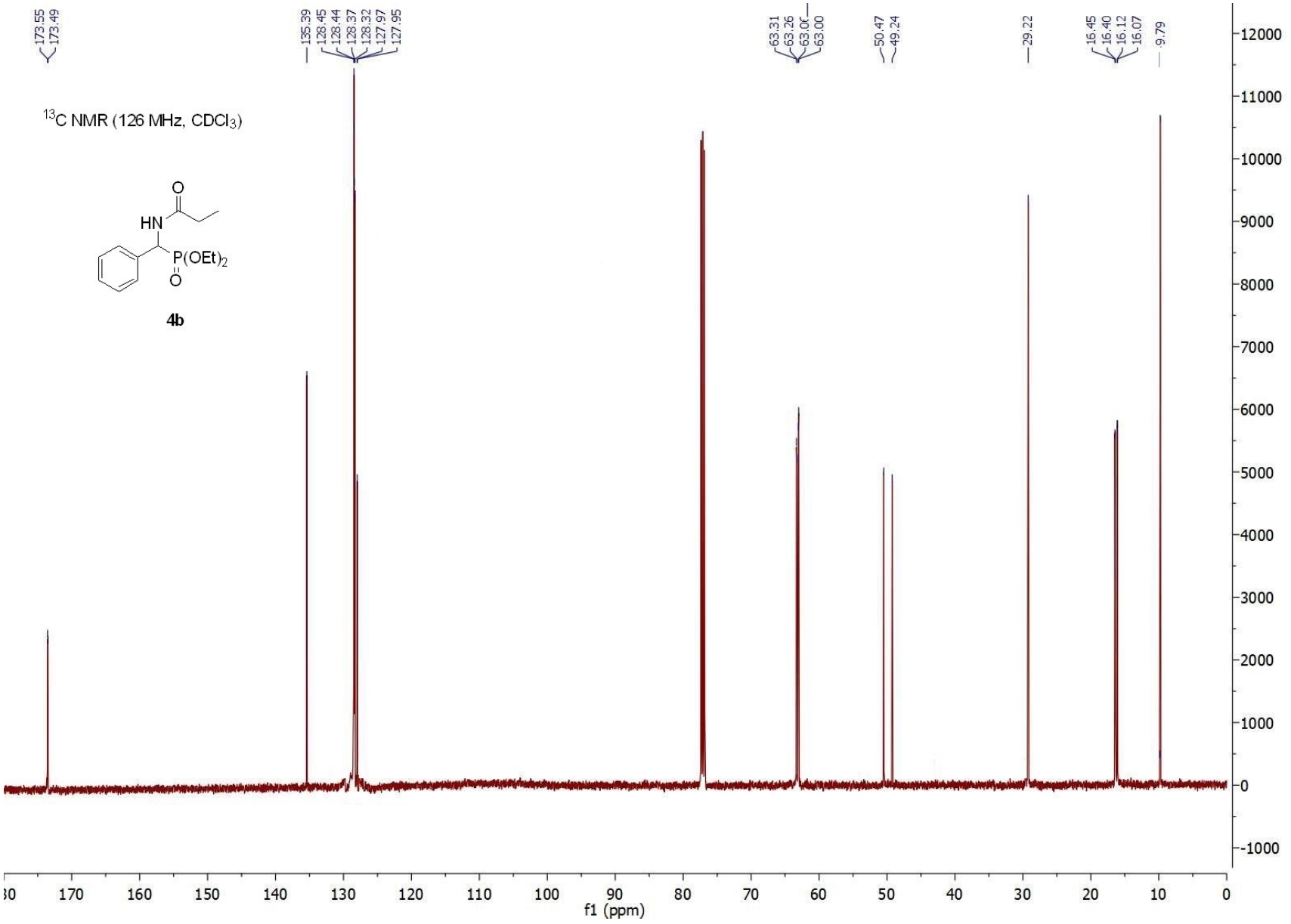


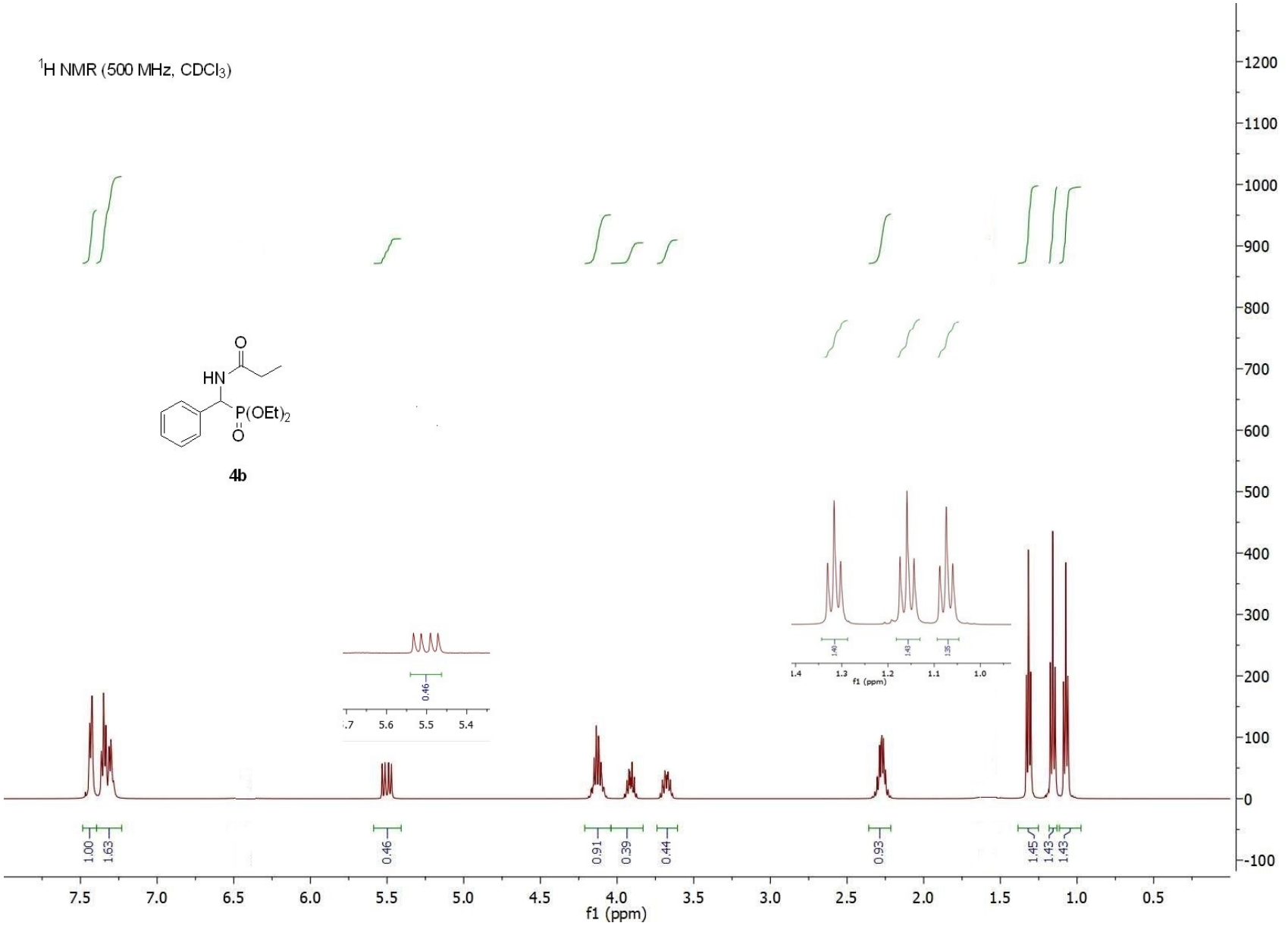

169.94
169.84
135.32
128.48
128.45
128.39
128.05
128.01
63.40
63.30
63.19
63.09
51.02
48.97
22.77
16.51
16.43
16.17
16.09
^{13}C NMR (75 MHz, CDCl$_3$)
HN
O
P(OEt)$_2$
O
4a
f1 (ppm)


1H NMR (500 MHz, CDCl3)
HN
O
P(OEt)2
O
4a
1.99
2.96
0.90
0.95
1.91
0.99
0.95
2.91
3.00
2.86
f1 (ppm)

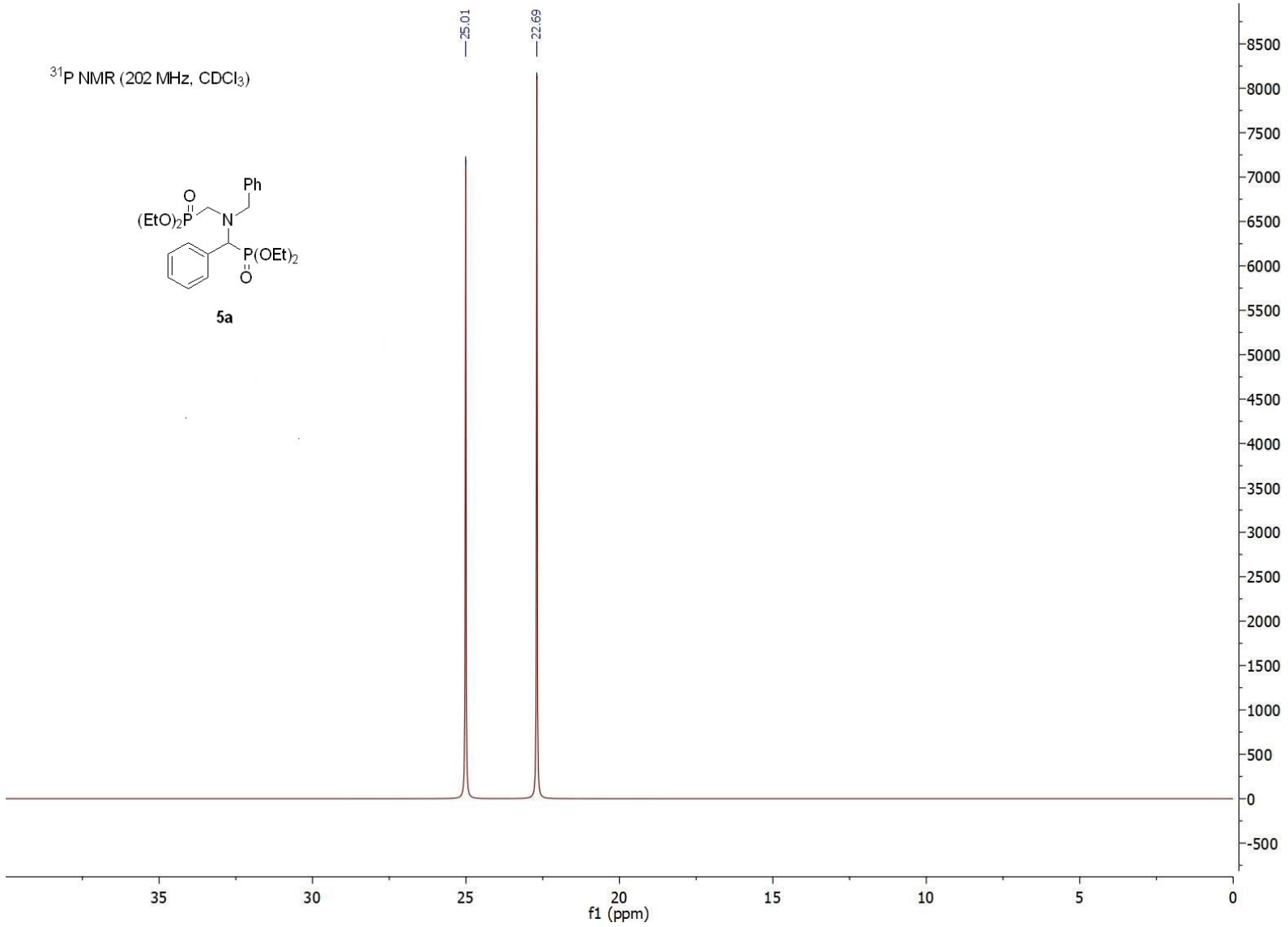
Diethyl propioamido-benzylphosphonate (**4b**)

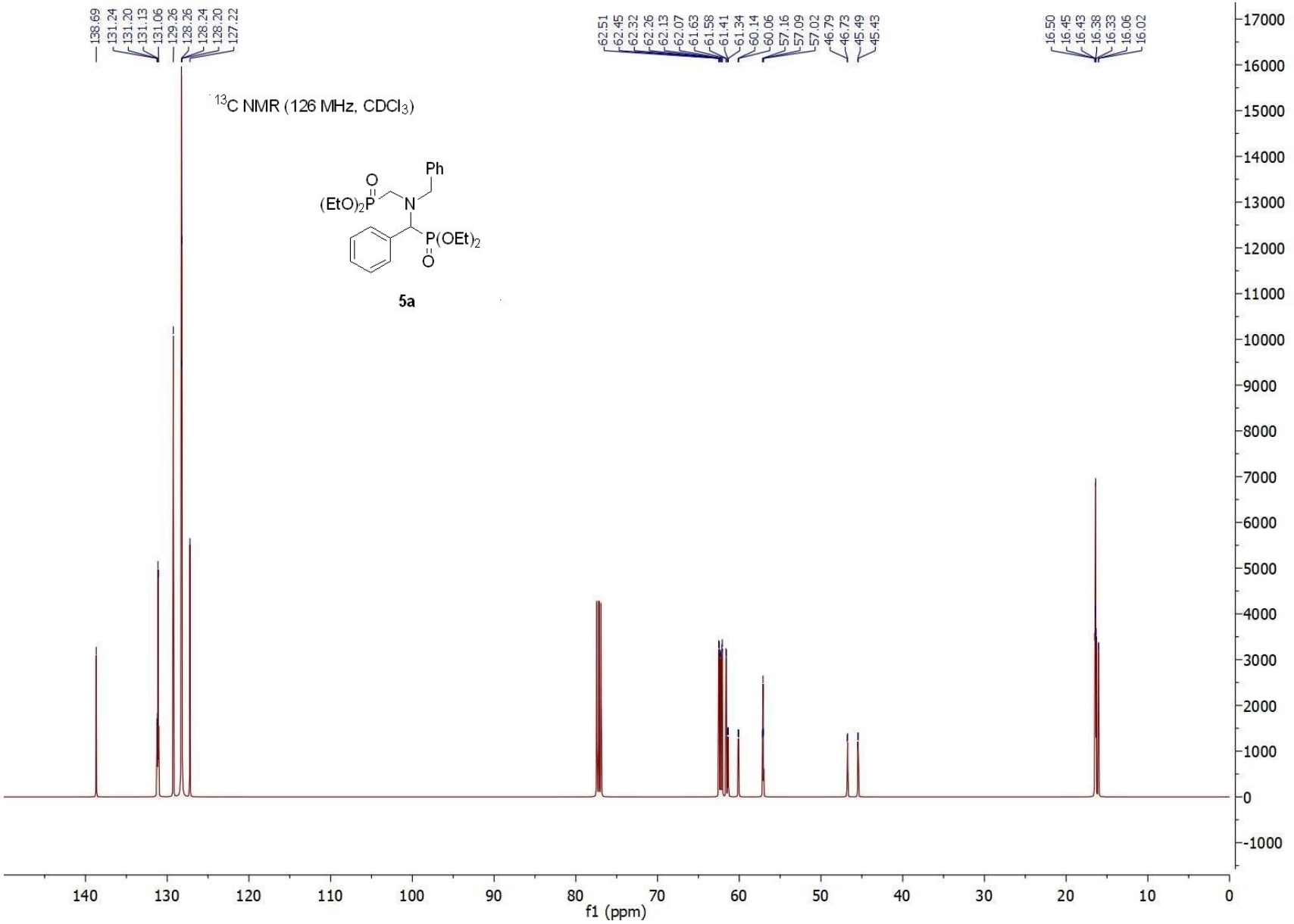


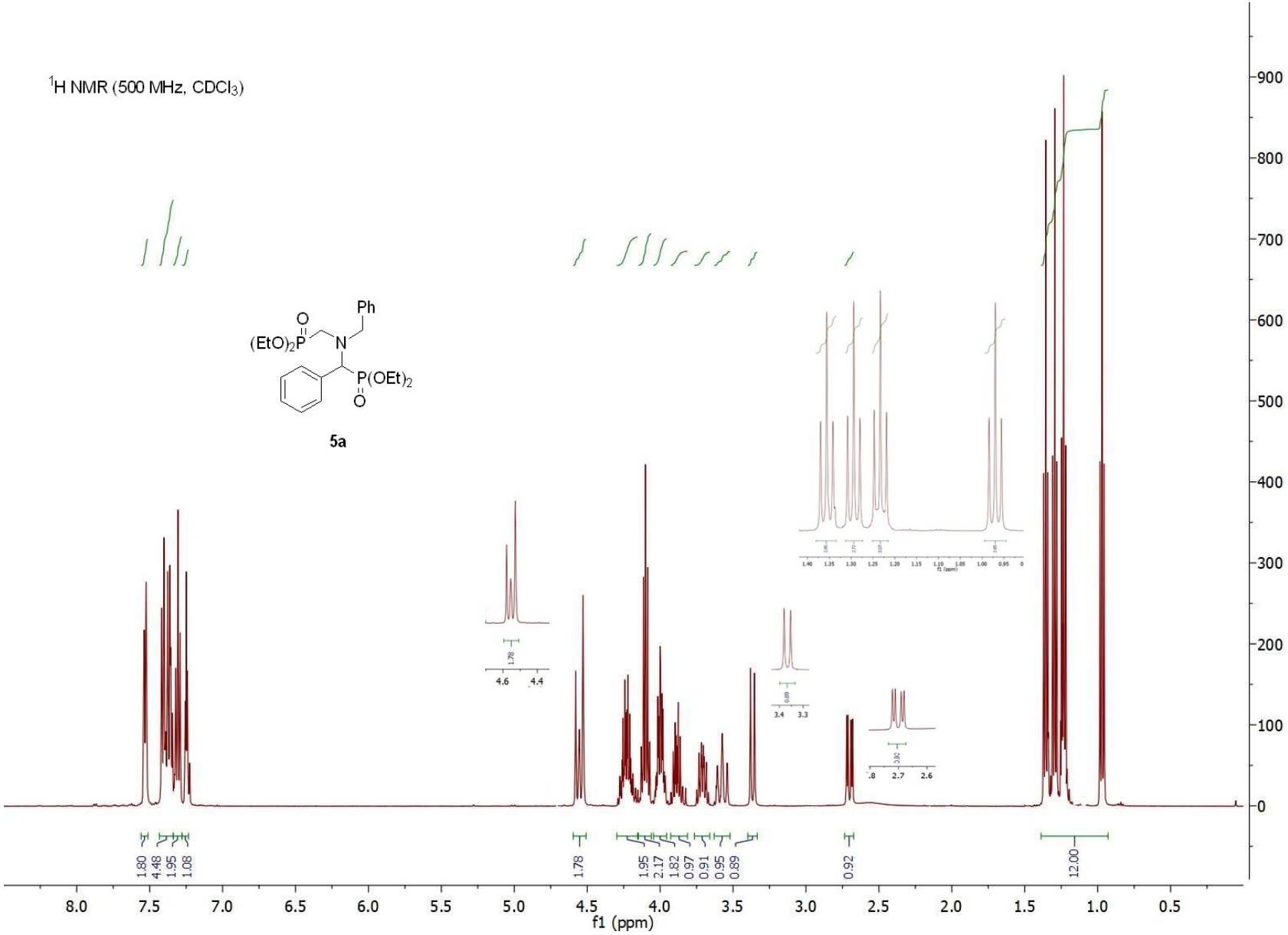

173.55
173.49
135.39
128.45
128.44
128.37
128.32
127.97
127.95
63.31
63.26
63.06
63.00
50.47
49.24
29.22
16.45
16.40
16.12
16.07
9.79
^{13}C NMR (126 MHz, CDCl$_3$)
HN
P(OEt)$_2$
4b
f1 (ppm)


1H NMR (500 MHz, CDCl3)
HN
O
P(OEt)2
O
4b
1.00
1.63
0.46
0.91
0.39
0.44
0.93
1.45
1.43
1.43
f1 (ppm)

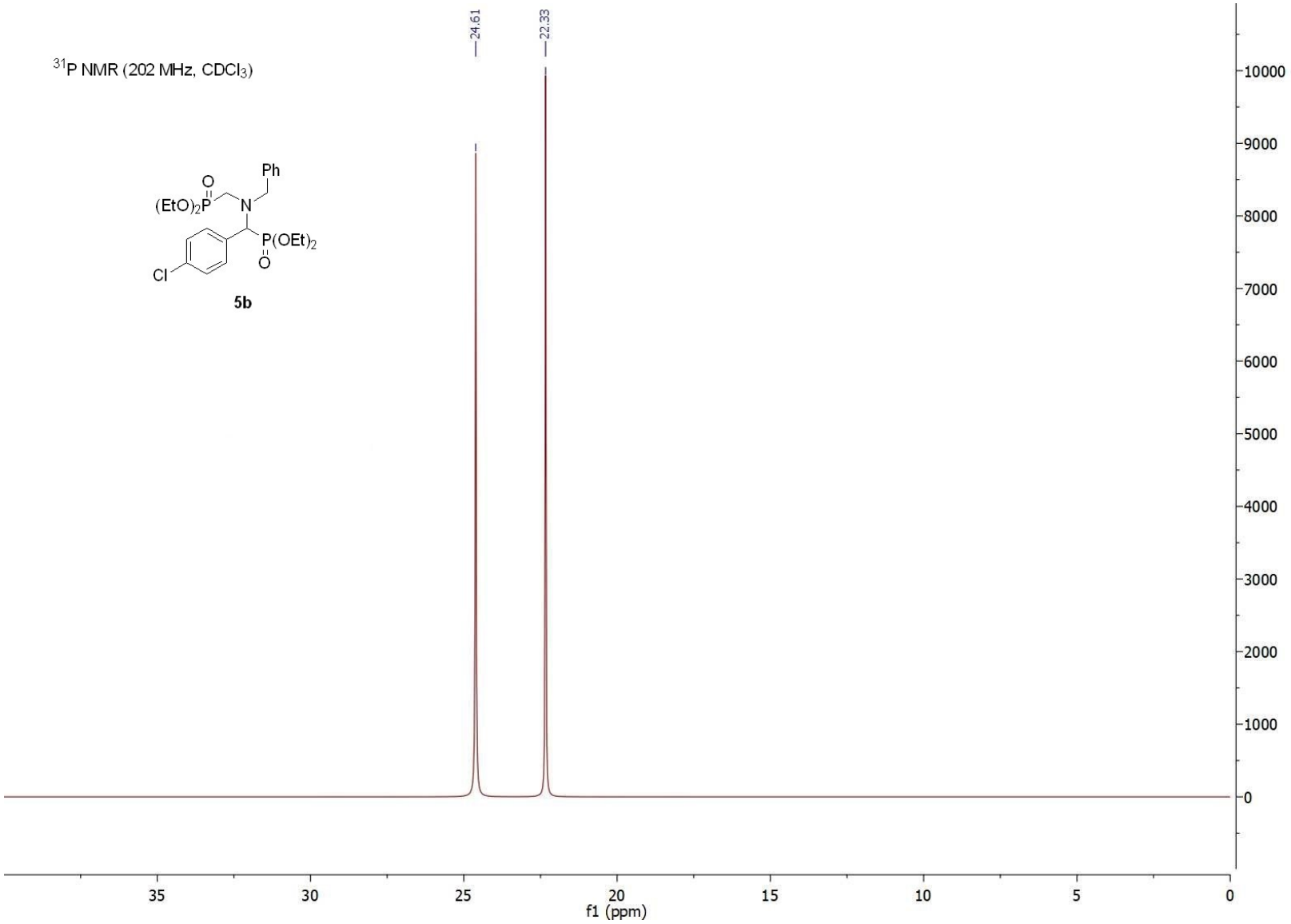
Diethyl diethylphosphonoylmethyl-.benzyl-amino-benzylphosphonate (**5a**)

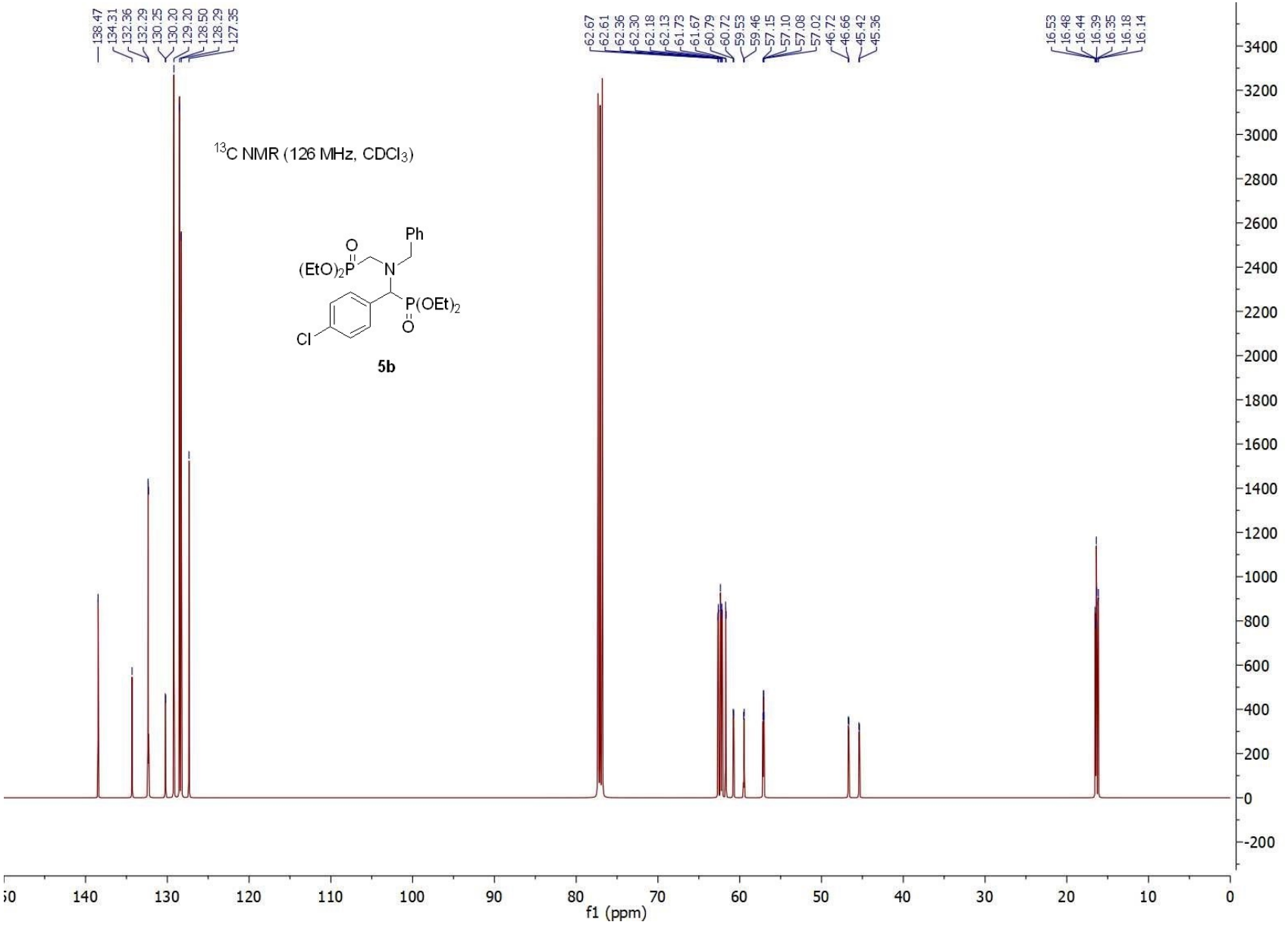


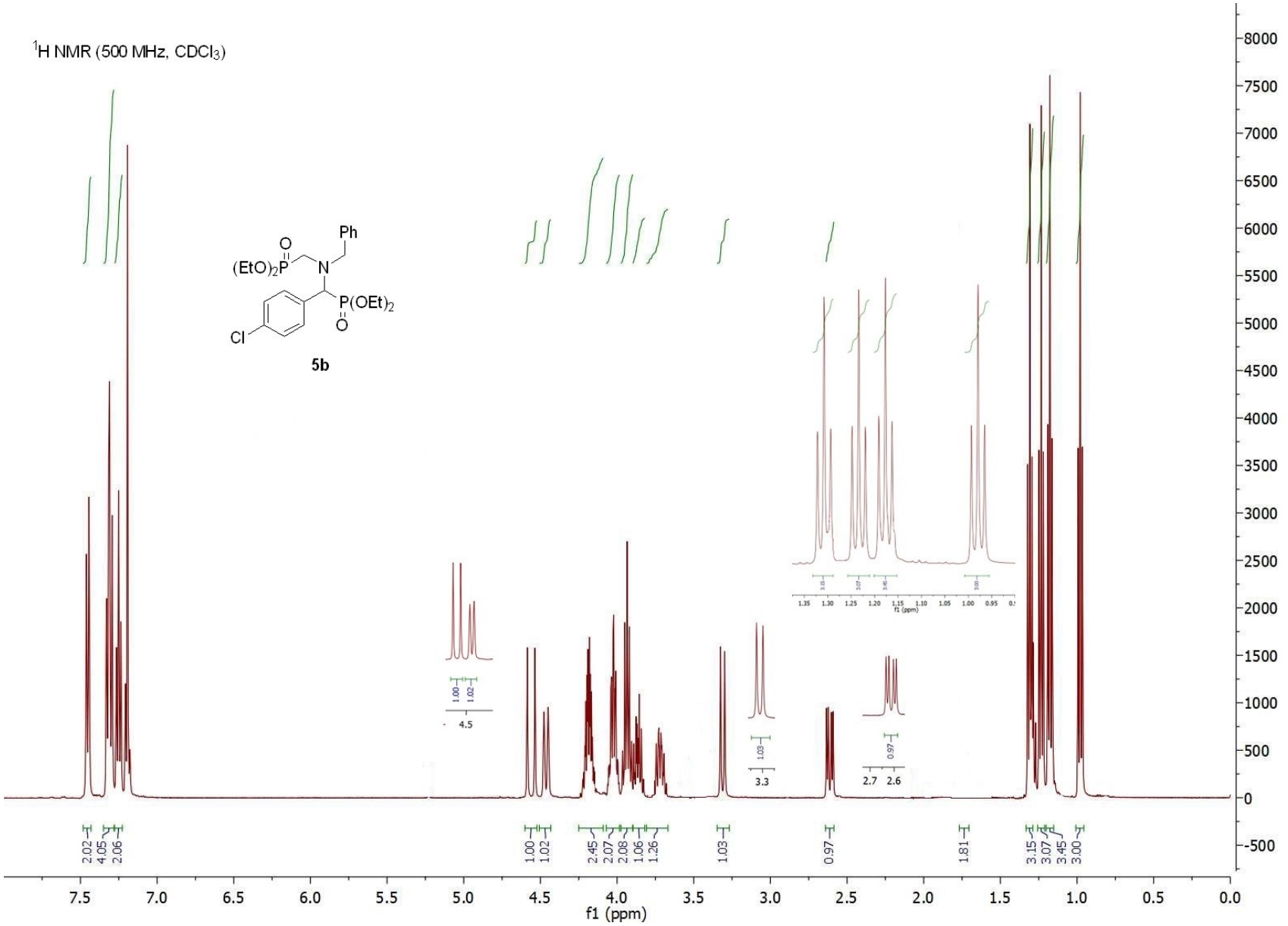

138.69
131.24
131.20
131.13
131.06
129.26
128.26
128.24
128.20
127.22
62.51
62.45
62.32
62.26
62.13
62.07
61.63
61.58
61.41
61.34
60.14
60.06
57.16
57.09
57.02
46.79
46.73
45.49
45.43
16.50
16.45
16.43
16.38
16.33
16.06
16.02
13C NMR (126 MHz, CDCl3)
Ph
O
(EtO)2P
N
P(OEt)2
O
5a
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


1H NMR (500 MHz, CDCl3)
Ph
O
(EtO)2P
N
P(OEt)2
O
5a
1.80
4.48
1.95
1.08
1.78
1.95
2.17
1.82
0.97
0.91
0.95
0.89
0.92
12.00
f1 (ppm)

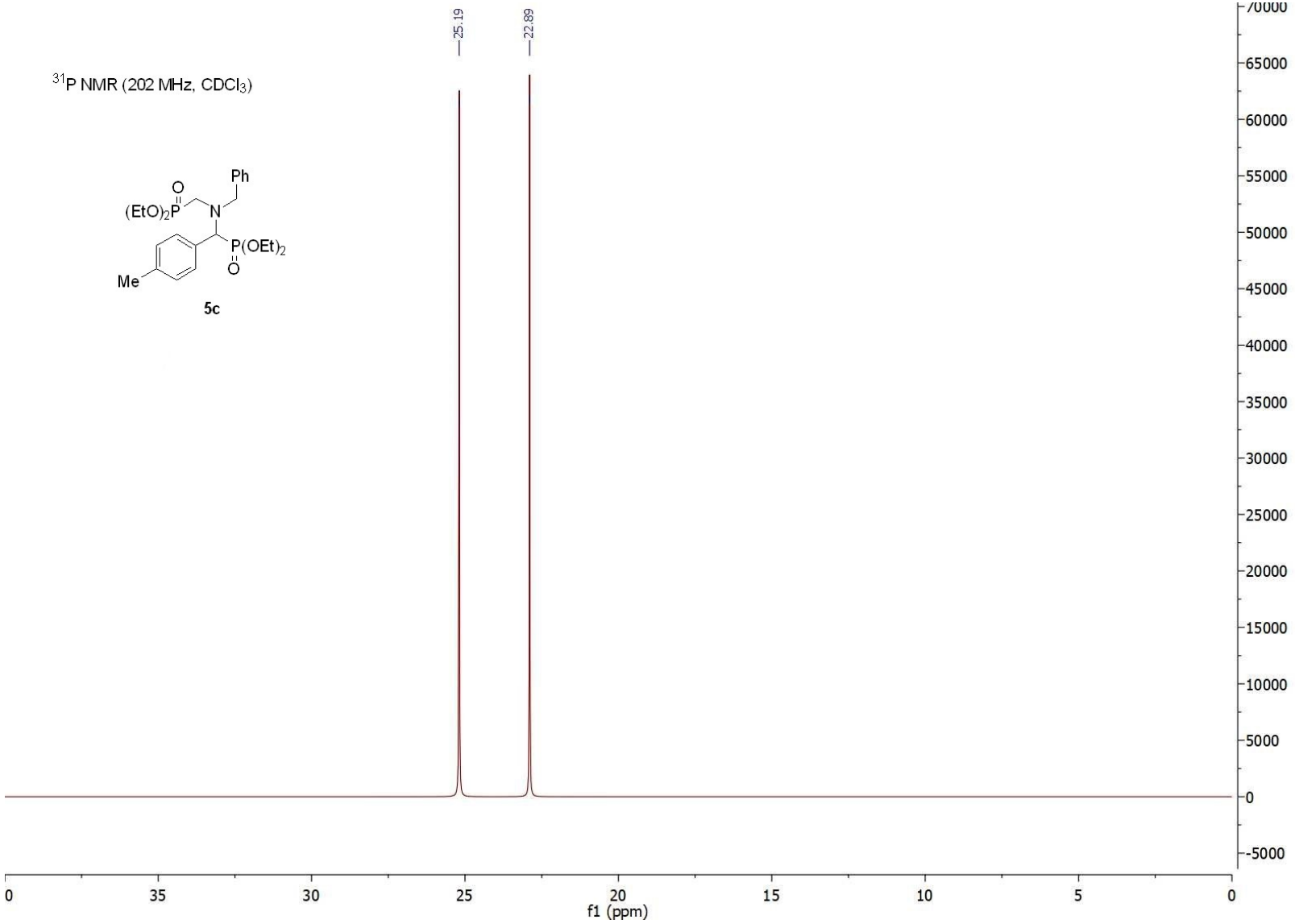
Diethyl diethylphosphonoylmethyl-benzyl-amino-4-chlorobenzylphosphonate (**5b**)

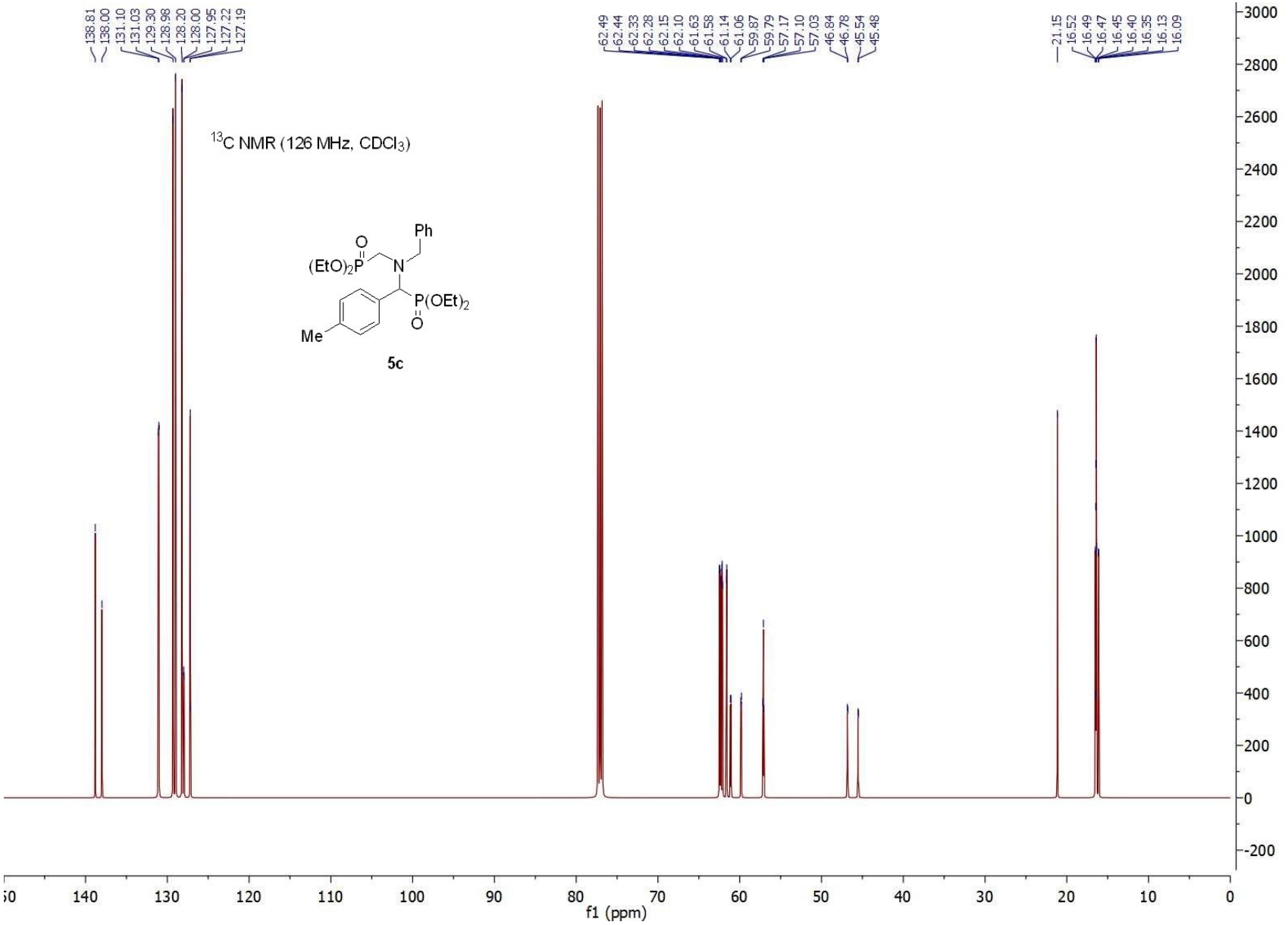


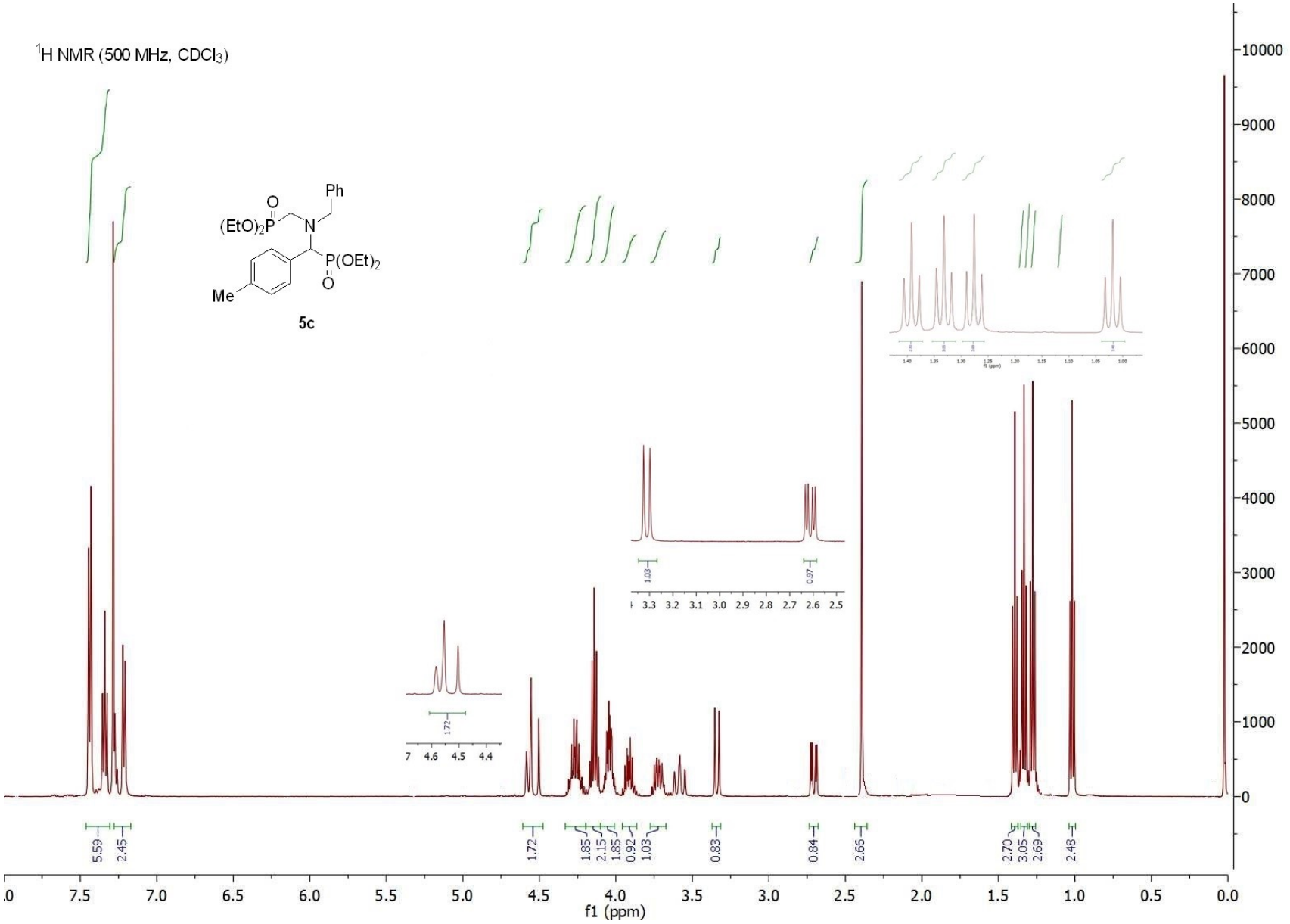

138.47
134.31
132.36
132.29
130.25
130.20
129.20
128.50
128.29
127.35
62.67
62.61
62.36
62.30
62.18
62.13
61.73
61.67
60.79
60.72
59.53
59.46
57.15
57.10
57.08
57.02
46.72
46.66
45.42
45.36
16.53
16.48
16.44
16.39
16.35
16.18
16.14
^{13}C NMR (126 MHz, $CDCl_3$)
Ph
O
$(EtO)_2P$
N
$P(OEt)_2$
O
Cl
5b
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


^{1}H NMR (500 MHz, $CDCl_3$)
Ph
O
$(EtO)_2P$
N
$P(OEt)_2$
O
Cl
5b
f1 (ppm)

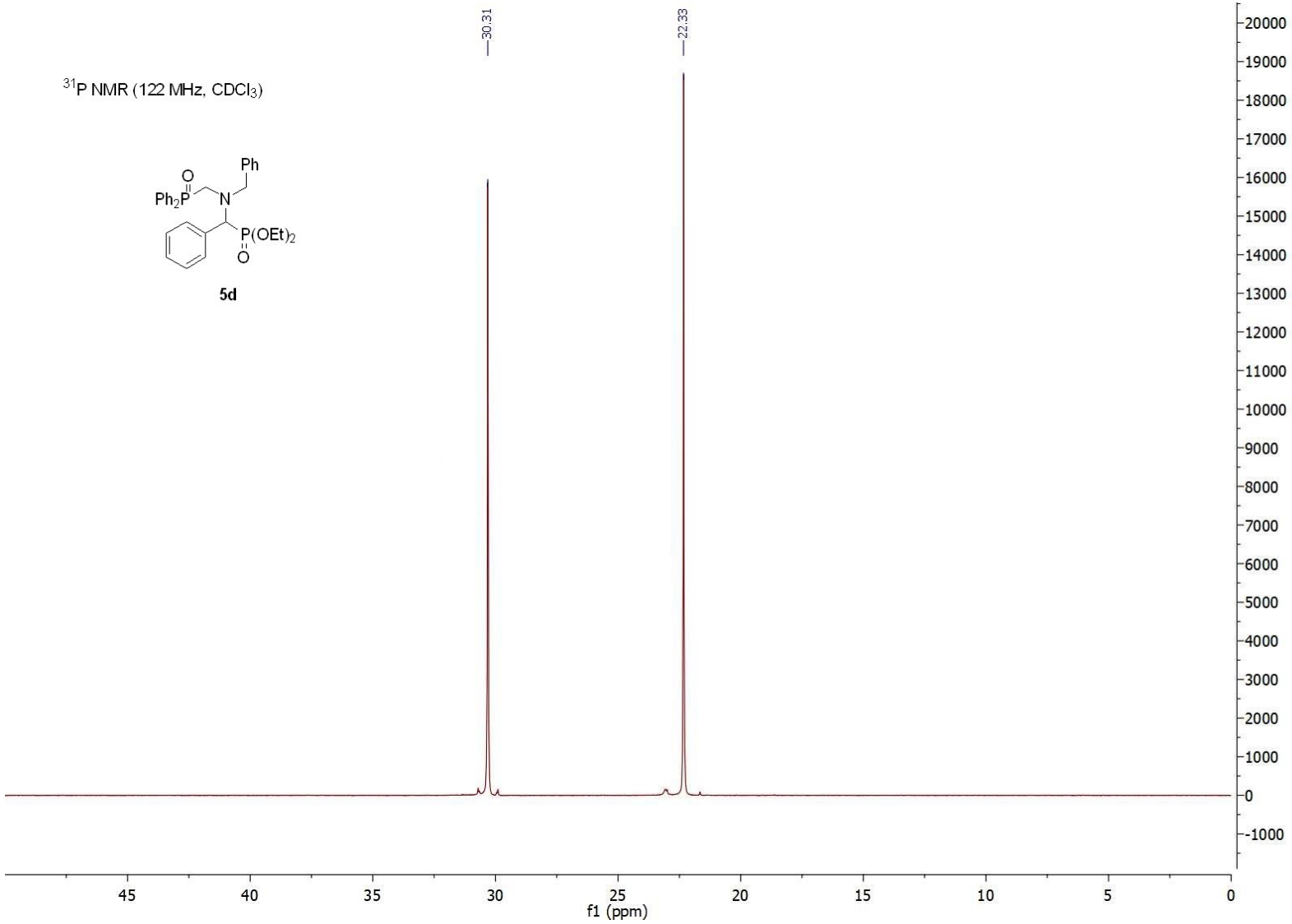
Diethyl diethylphosphonoylmethyl-benzyl-amino-4-methylbenzylphosphonate (**5c**)

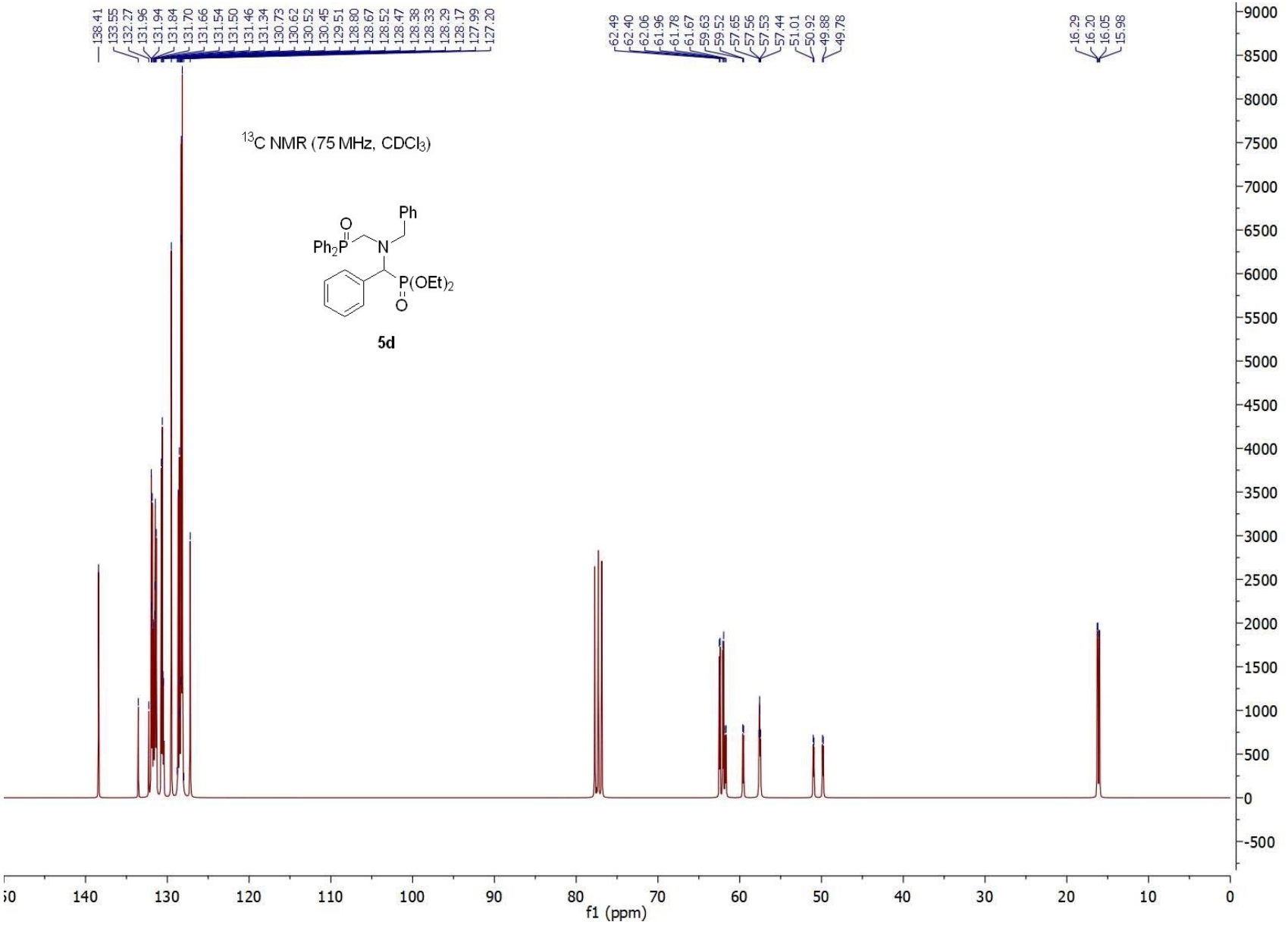


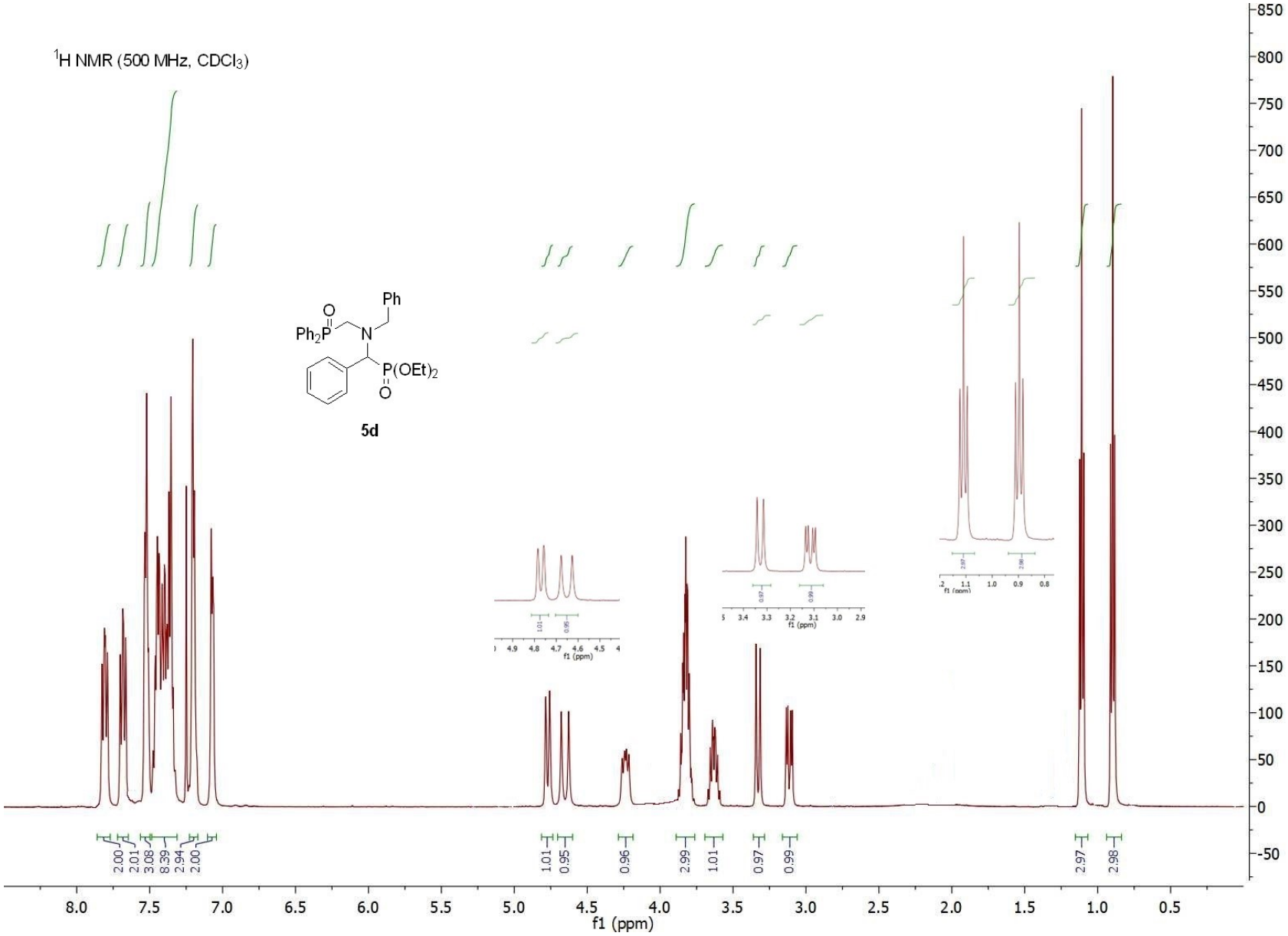

138.81
138.00
131.10
131.03
129.30
128.98
128.20
128.00
127.95
127.22
127.19
62.49
62.44
62.33
62.28
62.15
62.10
61.63
61.58
61.14
61.06
59.87
59.79
57.17
57.10
57.03
46.84
46.78
45.54
45.48
21.15
16.52
16.49
16.47
16.45
16.40
16.35
16.13
16.09
^{13}C NMR (126 MHz, $CDCl_3$)
Ph
O
$(EtO)_2P$
N
$P(OEt)_2$
O
Me
5c
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


1H NMR (500 MHz, CDCl3)
Ph
O
(EtO)2P
N
P(OEt)2
O
Me
5c
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
5.59
2.45
1.72
1.85
2.15
1.85
0.92
1.03
0.83
0.84
2.66
2.70
3.05
2.69
2.48
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

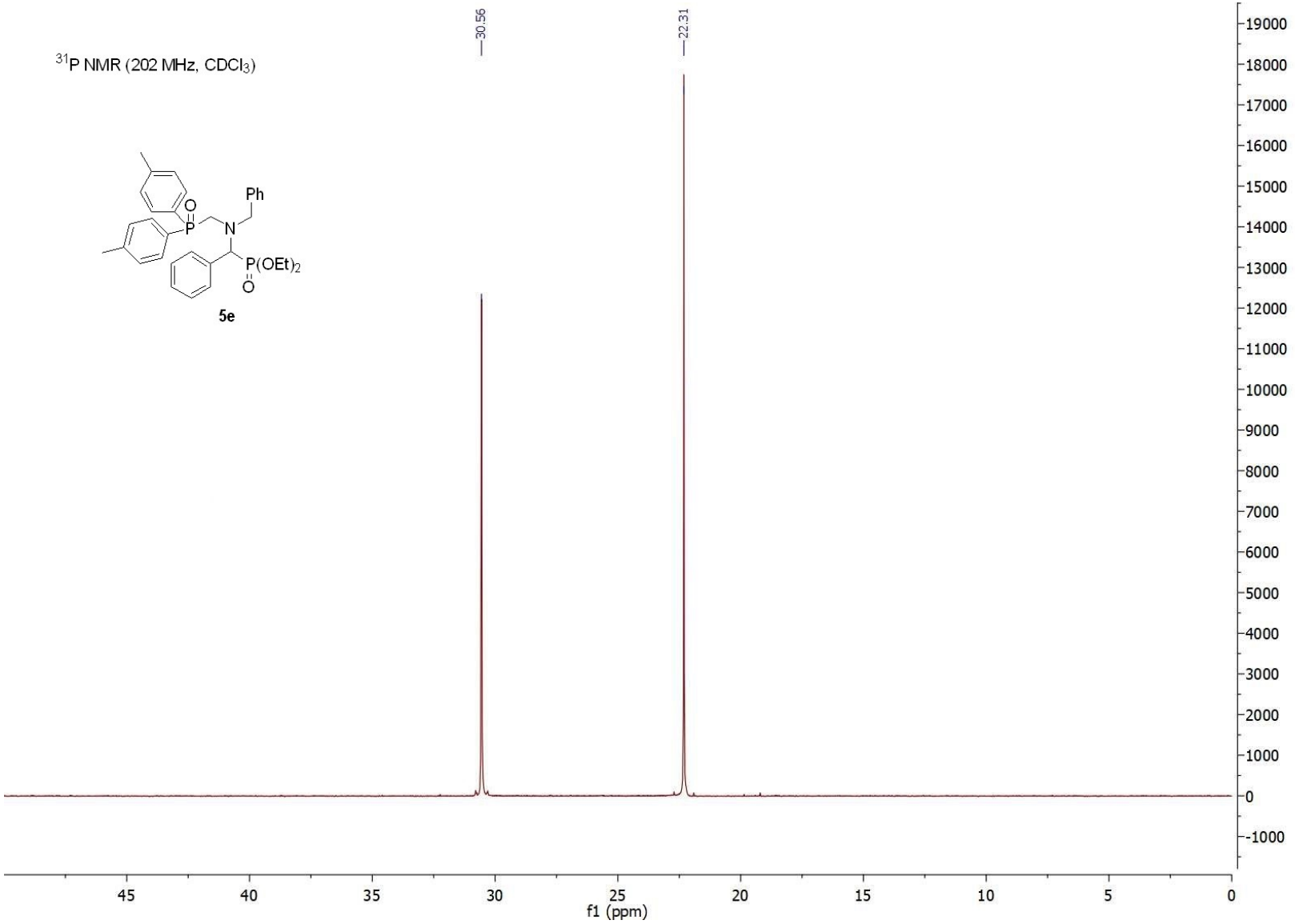
Diethyl diphenylphosphinoylmethyl-benzyl-amino-benzylphosphonate (**5d**)

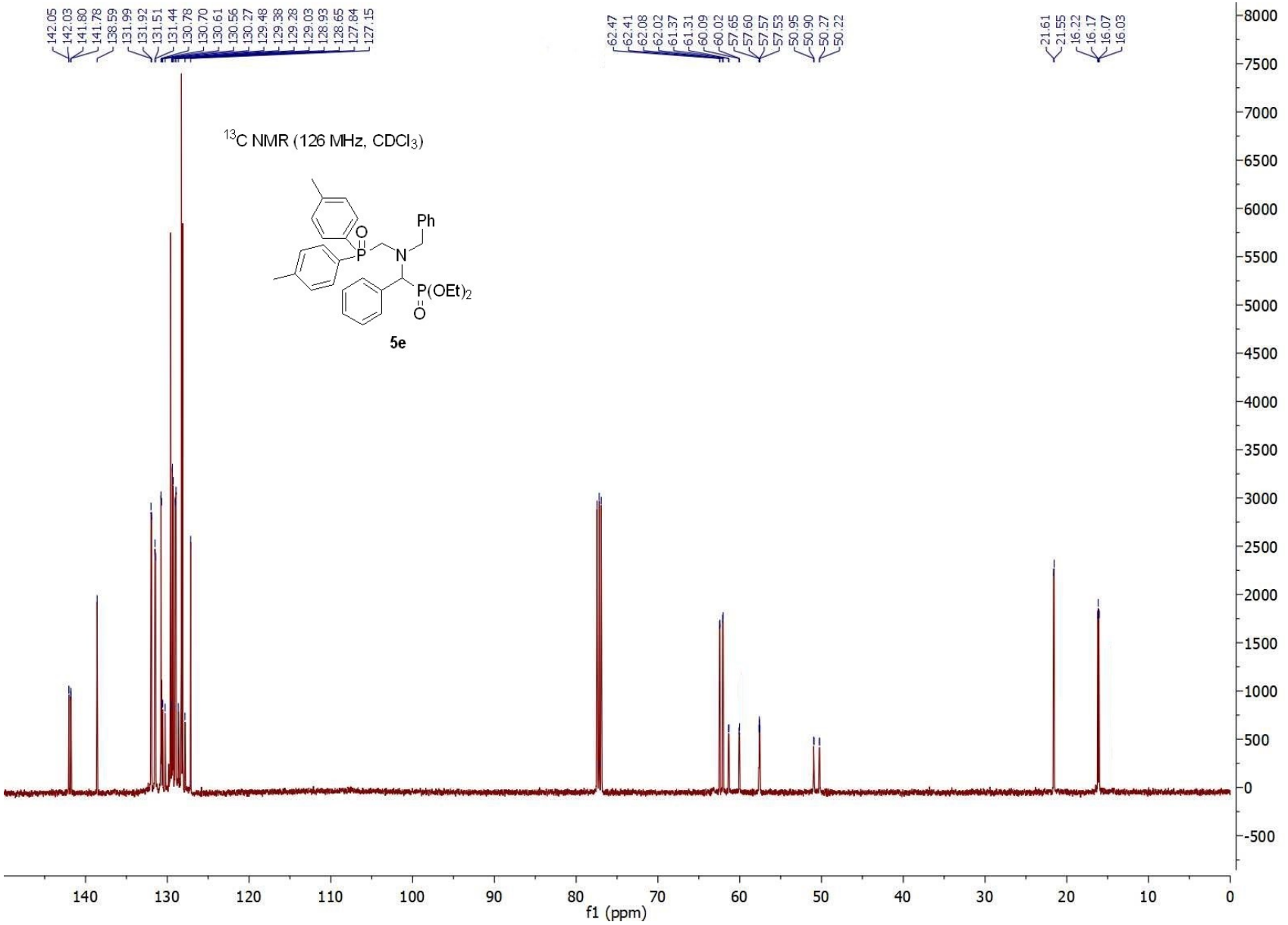


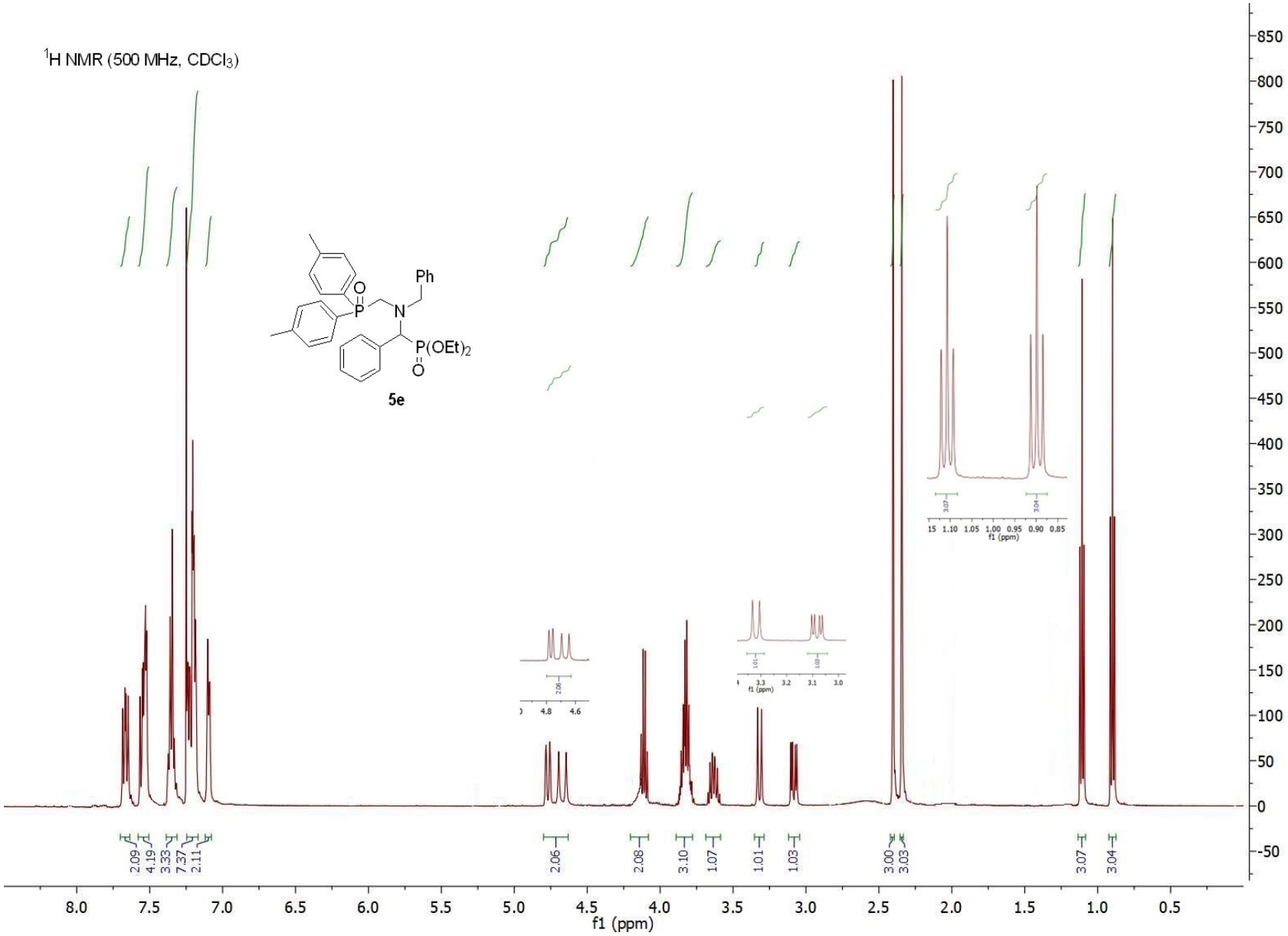

138.41
133.55
132.27
131.96
131.94
131.84
131.70
131.66
131.54
131.50
131.46
131.34
130.73
130.62
130.52
130.45
129.51
128.80
128.67
128.52
128.47
128.38
128.33
128.29
128.17
127.99
127.20
62.49
62.40
62.06
61.96
61.78
61.67
59.63
59.52
57.65
57.56
57.53
57.44
51.01
50.92
49.88
49.78
16.29
16.20
16.05
15.98
13C NMR (75 MHz, CDCl3)
Ph
O
Ph2P
N
P(OEt)2
O
5d
9000
8500
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


1H NMR (500 MHz, CDCl3)
Ph
O
Ph2P
N
P(OEt)2
O
5d
2.00
2.01
3.08
8.39
2.94
2.00
1.01
0.95
0.96
2.99
1.01
0.97
0.99
2.97
2.98
f1 (ppm)

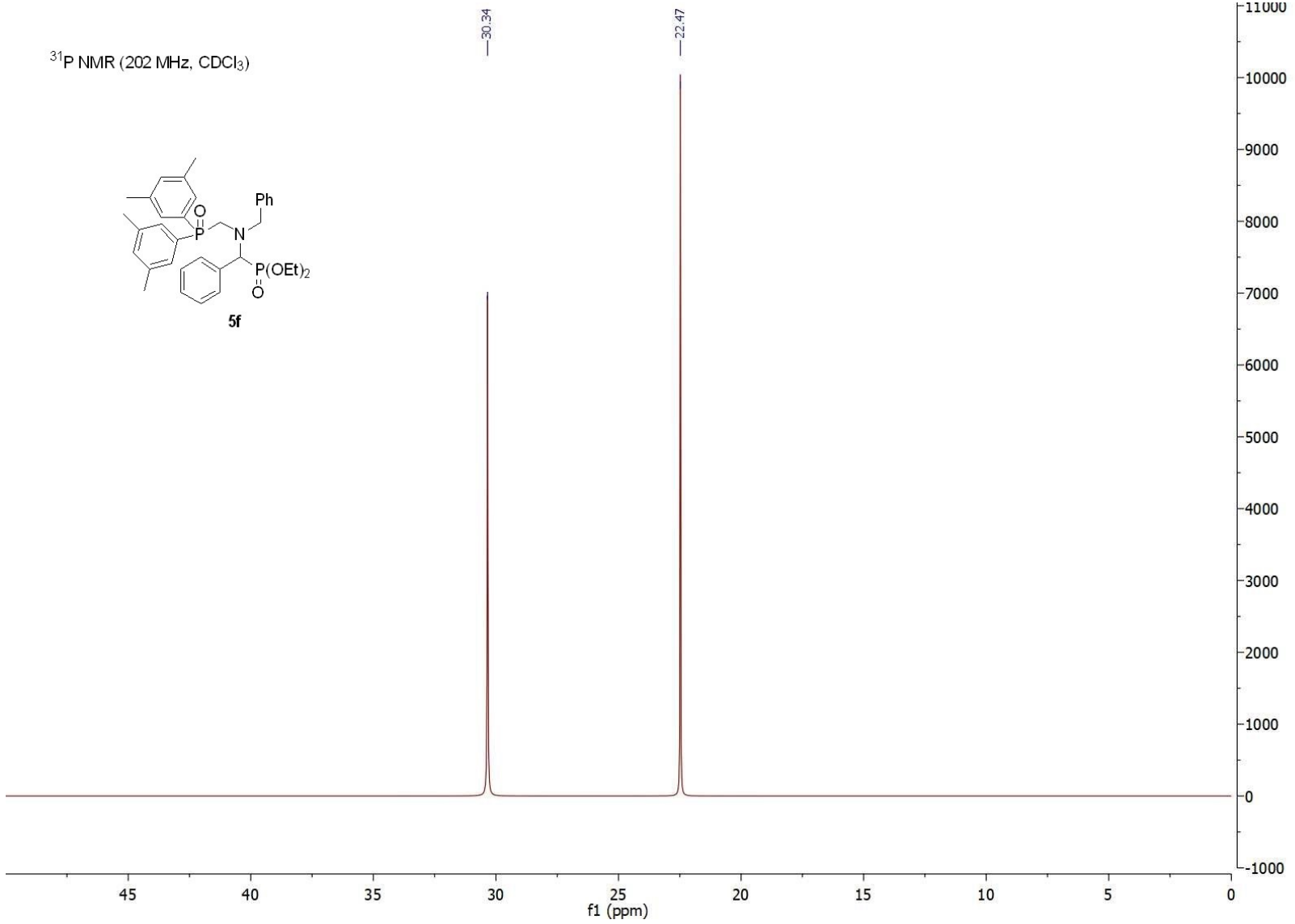
Diethyl bis(4-methylphenyl)phosphinoylmethyl-benzyl-amino-benzylphosphonate (**5e**)

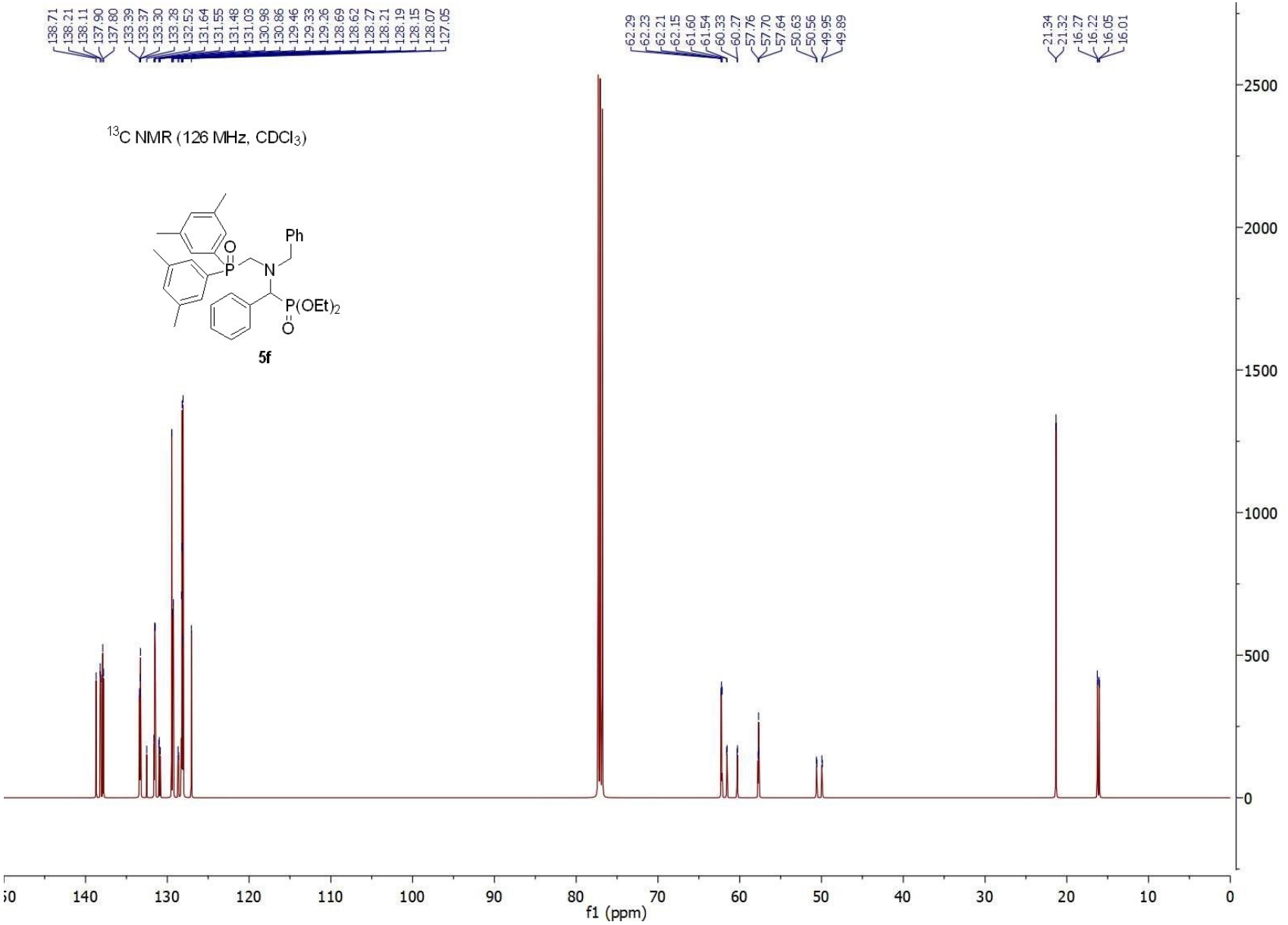


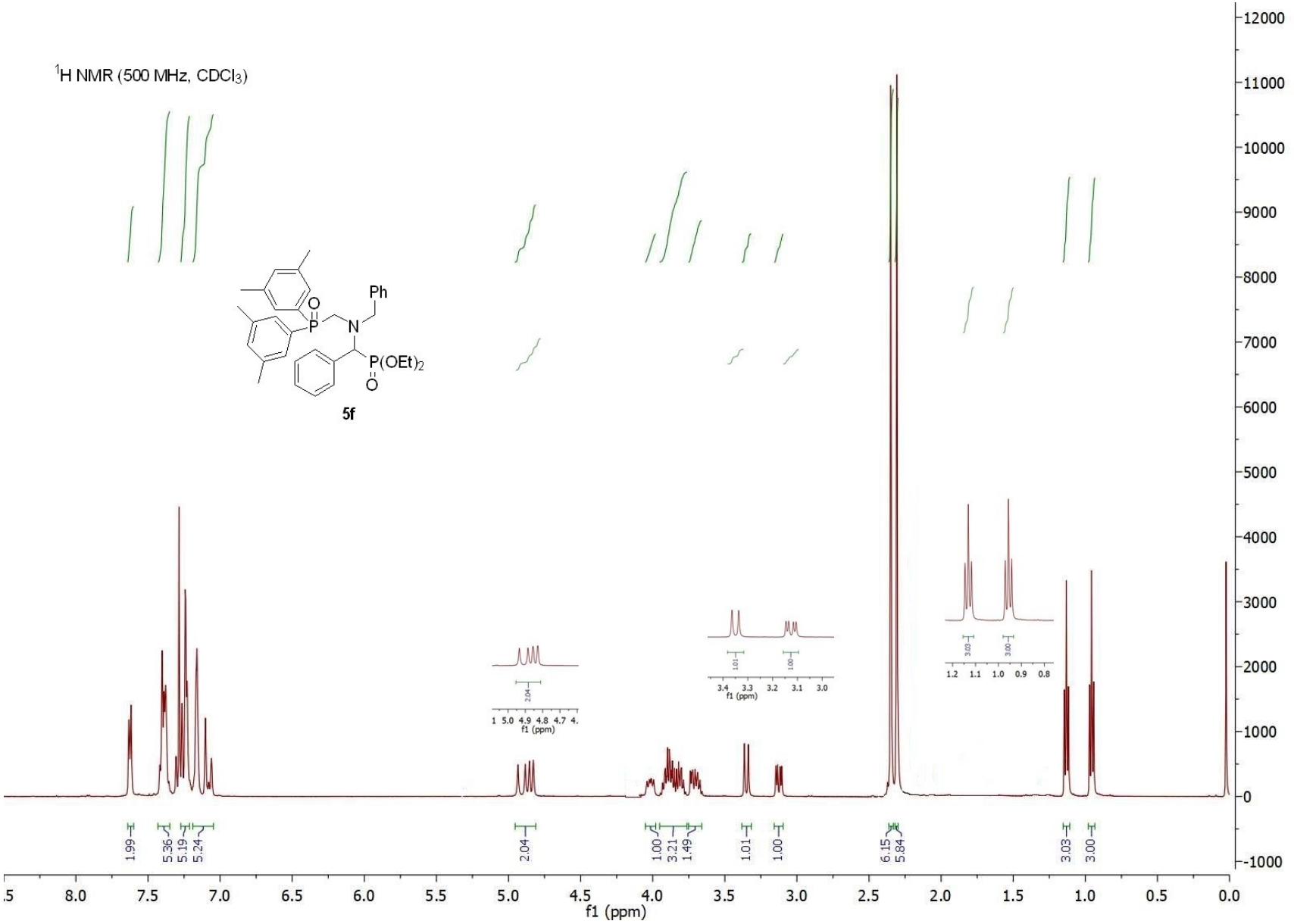

142.05
142.03
141.80
141.78
138.59
131.99
131.92
131.51
131.44
130.78
130.70
130.61
130.56
130.27
129.48
129.38
129.28
129.03
128.93
128.65
127.84
127.15
62.47
62.41
62.08
62.02
61.37
61.31
60.09
60.02
57.65
57.60
57.57
57.53
50.95
50.90
50.27
50.22
21.61
21.55
16.22
16.17
16.07
16.03
13C NMR (126 MHz, CDCl3)
Ph
O
P
N
P(OEt)2
O
5e
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


1H NMR (500 MHz, CDCl3)
Ph
O
P
N
P(OEt)2
O
5e
2.09
4.19
3.33
7.37
2.11
2.06
2.08
3.10
1.07
1.01
1.03
3.00
3.03
3.07
3.04
f1 (ppm)

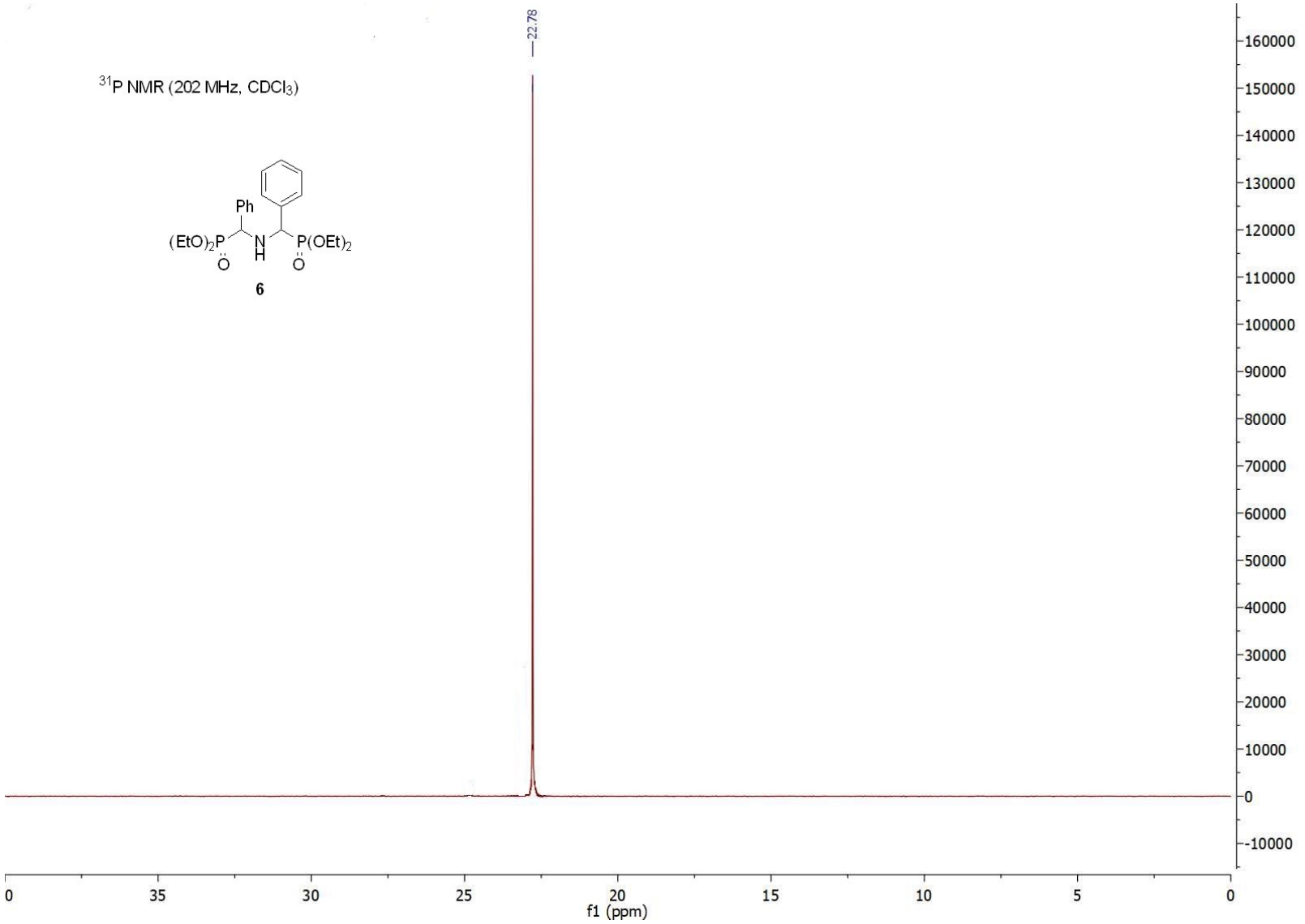
Diethyl bis(3,5-dimethylphenyl)phosphinoylmethyl-benzyl-amino-benzylphosphonate (**5f**)

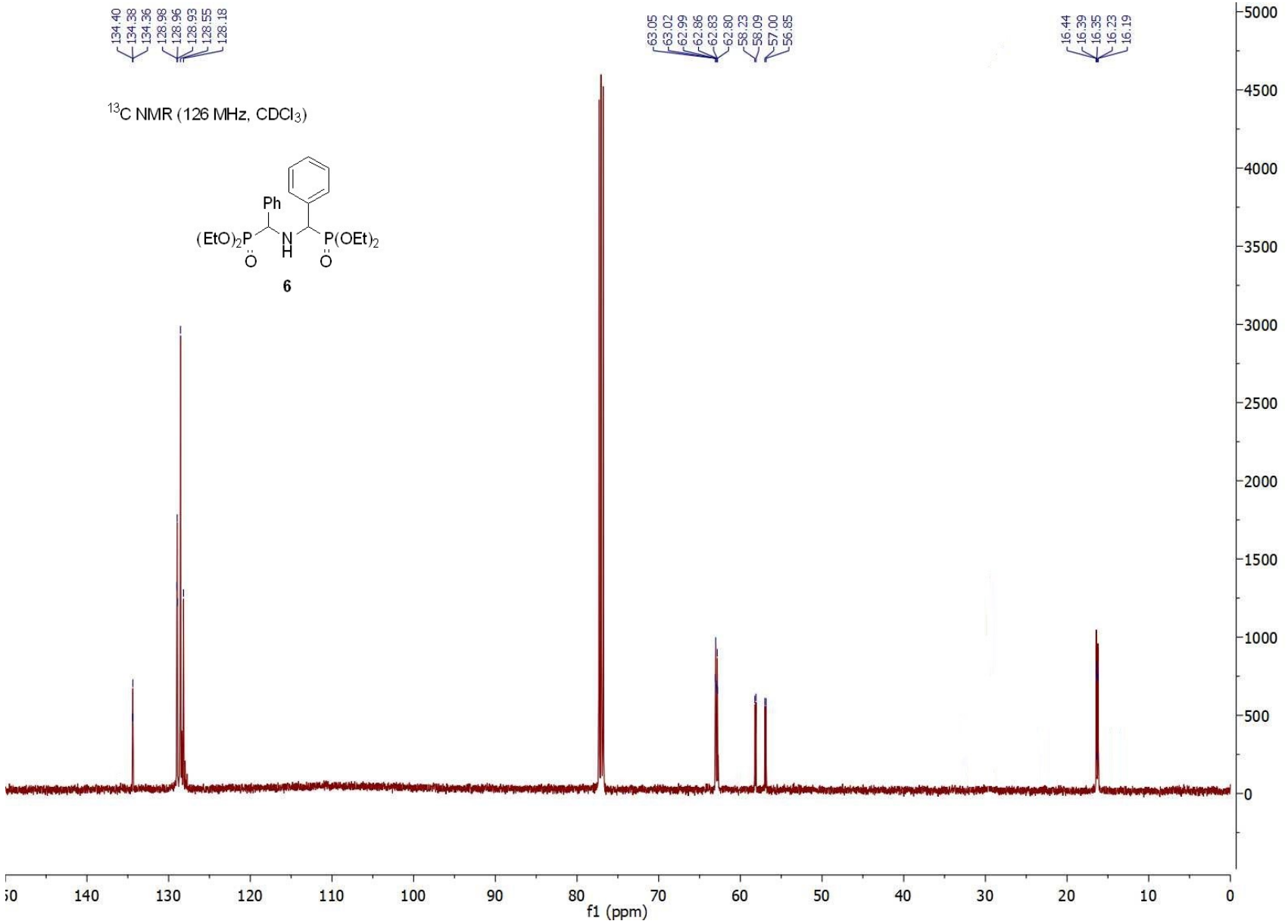


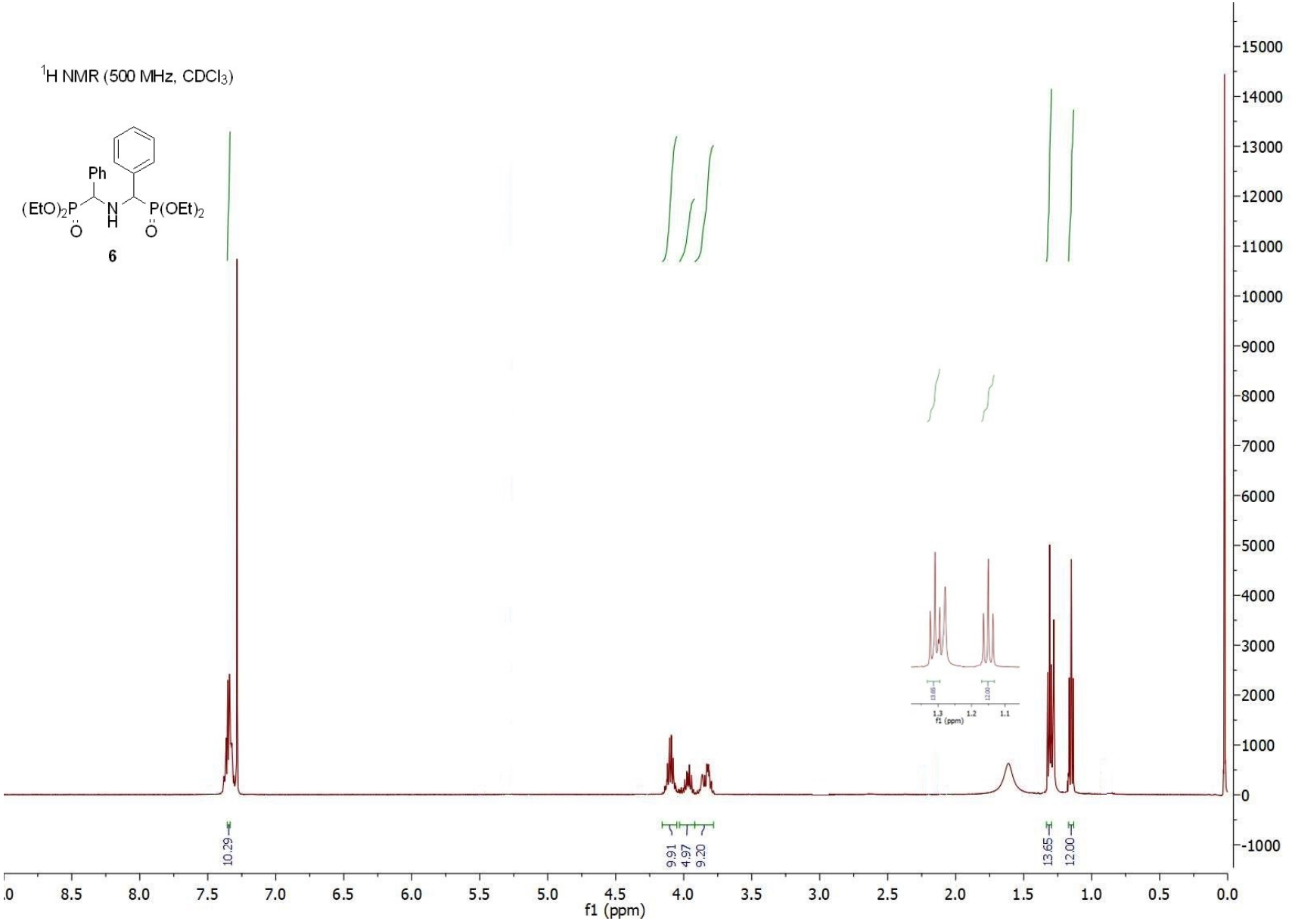

138.71
138.21
138.11
137.90
137.80
133.39
133.37
133.30
133.28
132.52
131.64
131.55
131.48
131.03
130.98
130.86
129.46
129.33
129.26
128.69
128.62
128.27
128.21
128.19
128.15
128.07
127.05
62.29
62.23
62.21
62.15
61.60
61.54
60.33
60.27
57.76
57.70
57.64
50.63
50.56
49.95
49.89
21.34
21.32
16.27
16.22
16.05
16.01
13C NMR (126 MHz, CDCl3)
Ph
O
P
N
P(OEt)2
O
5f
2500
2000
1500
1000
500
0
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


^{1}H NMR (500 MHz, $CDCl_3$)
Ph
O
P
N
P(OEt)$_2$
O
5f
1.99
5.36
5.19
5.24
2.04
1.00
3.21
1.49
1.01
1.00
6.15
5.84
3.03
3.00
f1 (ppm)

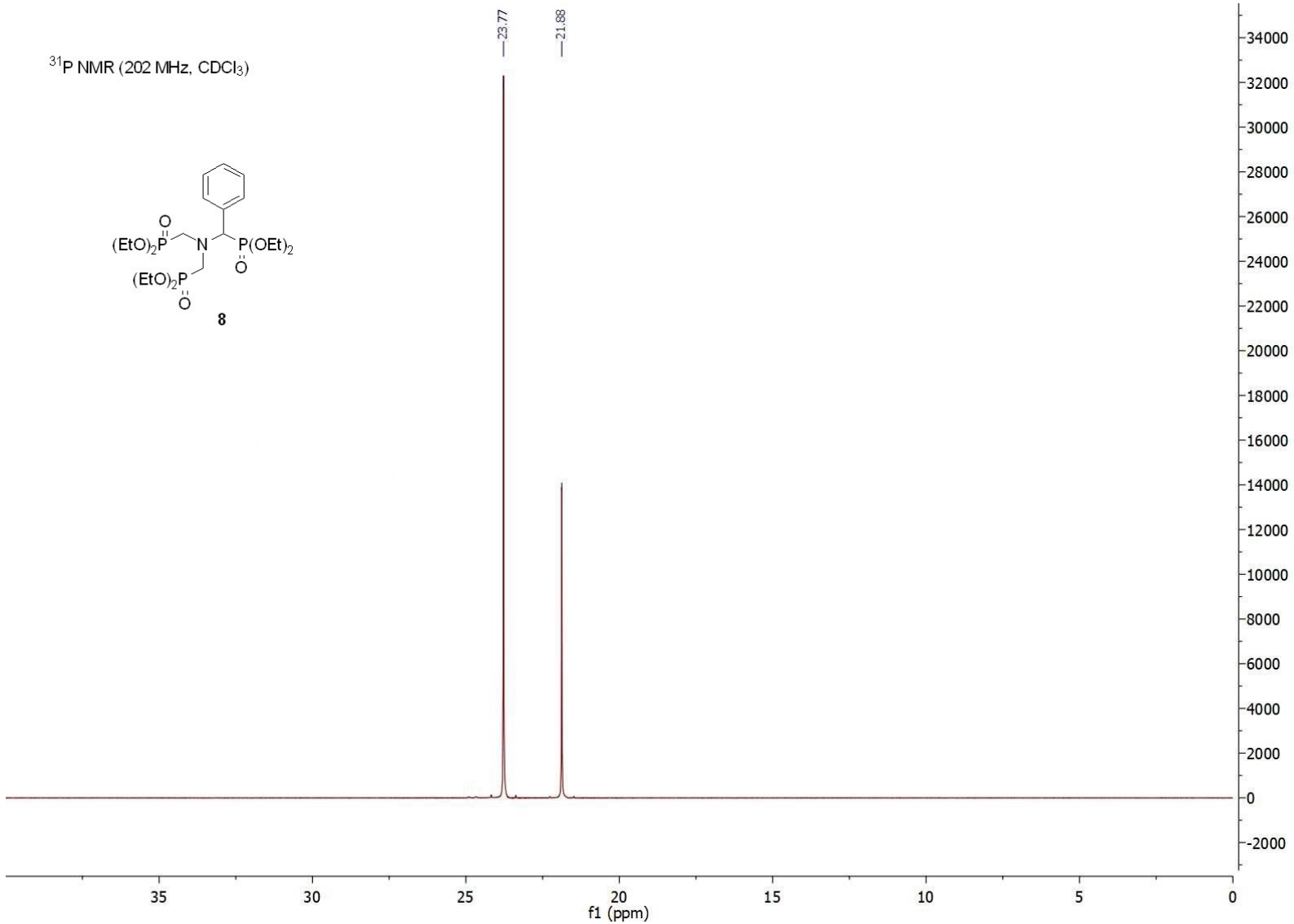
Bis(diethylphosphonoyl-phenylmethyl)amine (**6**)

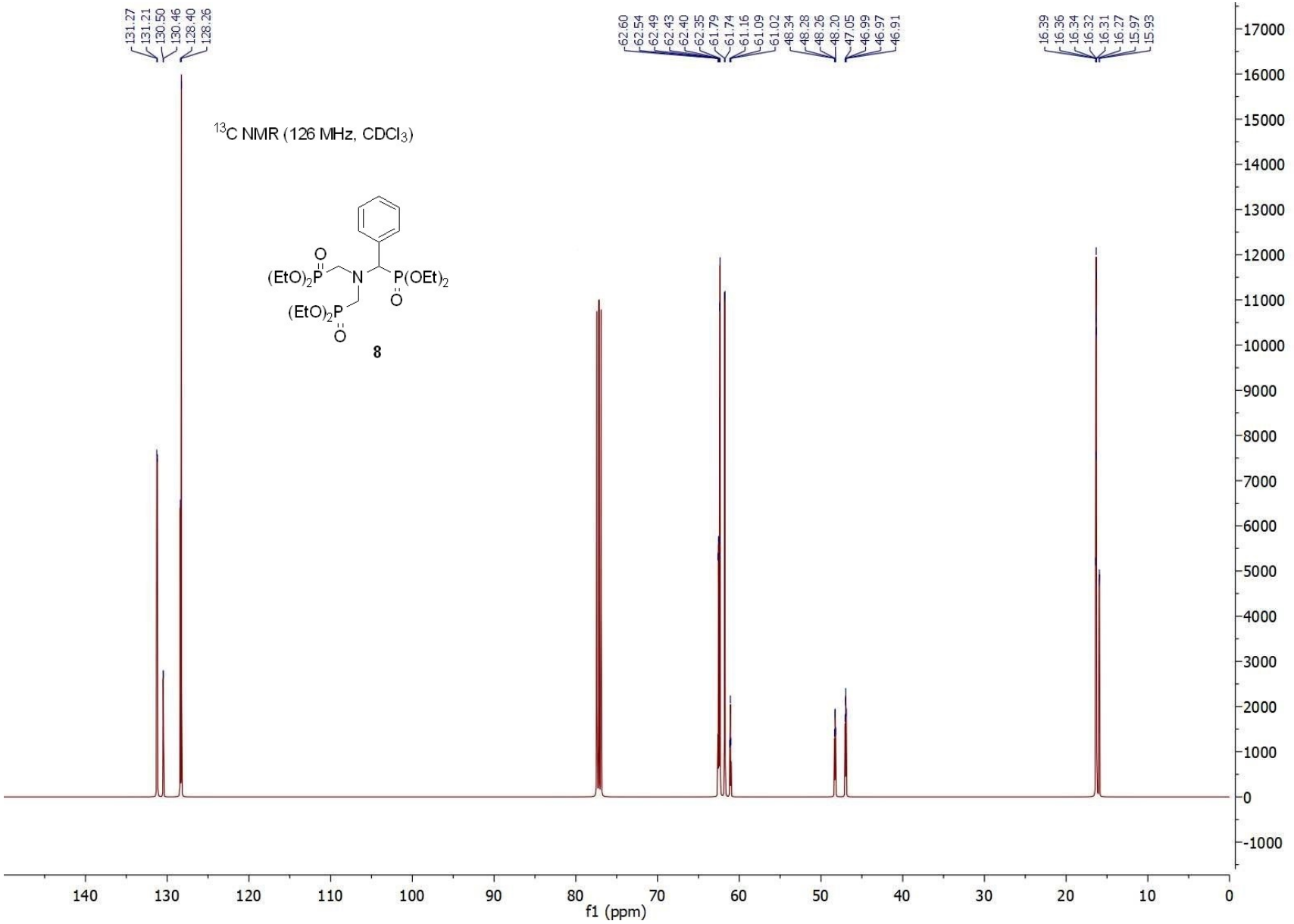


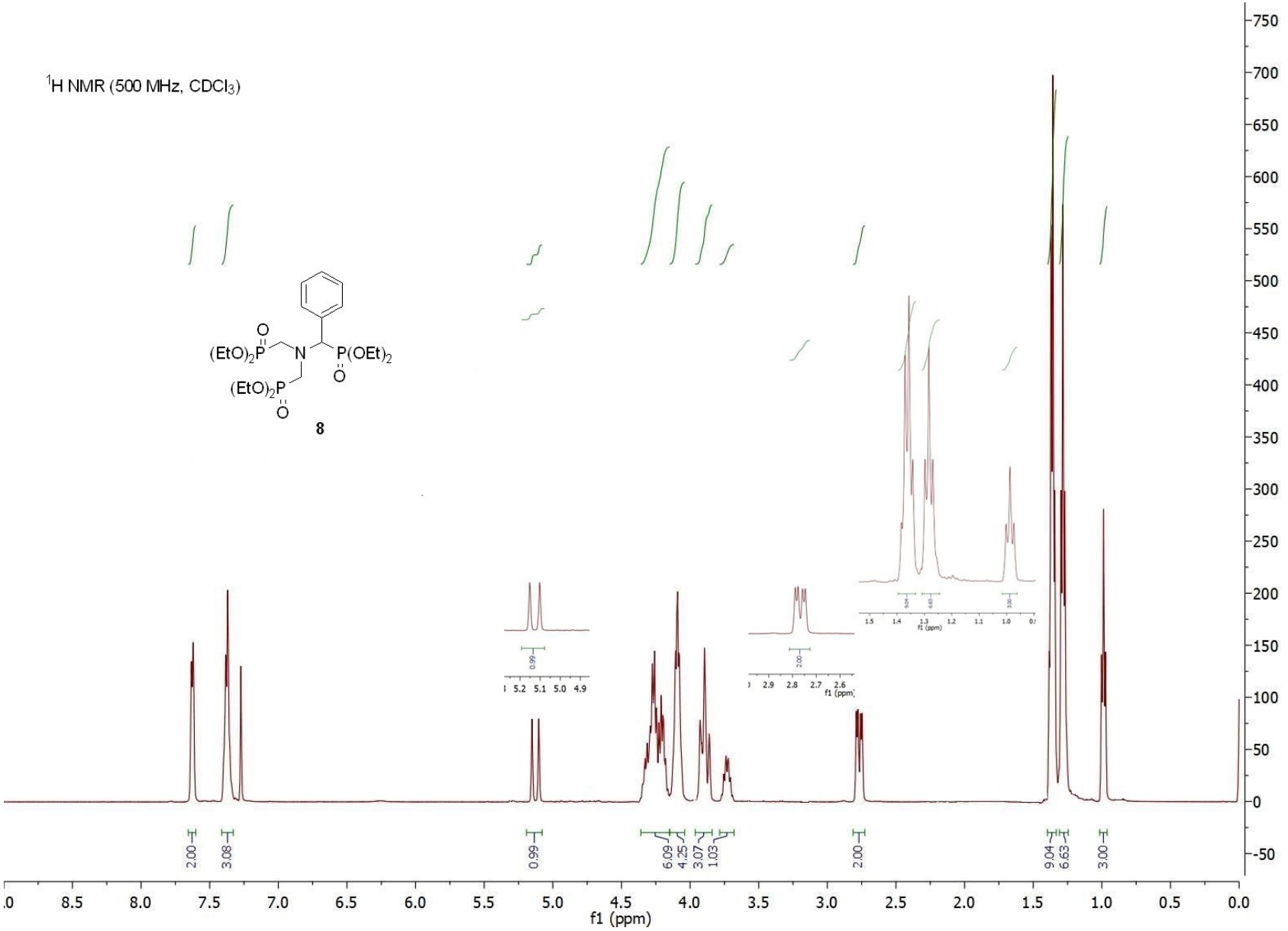

134.40
134.38
134.36
128.98
128.96
128.93
128.55
128.18
63.05
63.02
62.99
62.86
62.83
62.80
58.23
58.09
57.00
56.85
16.44
16.39
16.35
16.23
16.19
^{13}C NMR (126 MHz, $CDCl_3$)
Ph
$(EtO)_2P$
N
H
$P(OEt)_2$
O
O
6
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


^{1}H NMR (500 MHz, $CDCl_3$)
Ph
$(EtO)_2P$
N
H
$P(OEt)_2$
O
O
6
10.29
9.91
4.97
9.20
13.65
12.00
f1 (ppm)

Bis(diethylphosphonoylmethyl)-(diethylphosphonoylbenzyl)amine (**8**)




131.27
131.21
130.50
130.46
128.40
128.26
62.60
62.54
62.49
62.43
62.40
62.35
61.79
61.74
61.16
61.09
61.02
48.34
48.28
48.26
48.20
47.05
46.99
46.97
46.91
16.39
16.36
16.34
16.32
16.31
16.27
15.97
15.93
^{13}C NMR (126 MHz, $CDCl_3$)
$(EtO)_2P$
N
$P(OEt)_2$
$(EtO)_2P$
8
f1 (ppm)


^{1}H NMR (500 MHz, $CDCl_3$)
8
f1 (ppm)

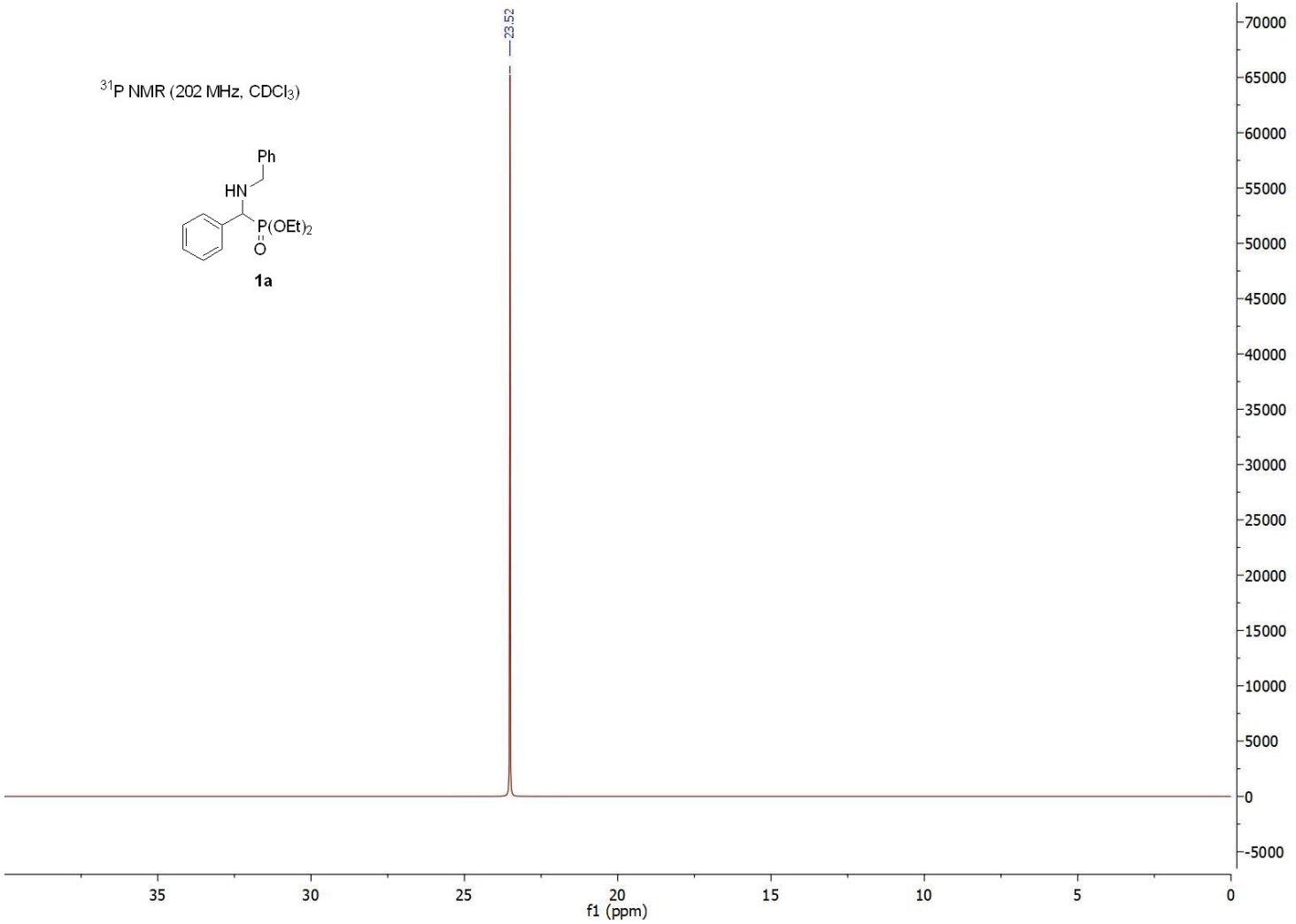
2.1) Experimental parameters and identification of the starting materials (1a-c)

Product	T (°C)	t (min)	Yield (%)	δ_P ($CDCl_3$) (ppm)	δ_P^{lit} (ppm)	[M+H]
1a	100	45	85	23.5	23.7 [A]	334
1b	100	40	95	22.9	22.9 [A]	368
1c	100	90	87	23.7	23.7 [B]	348

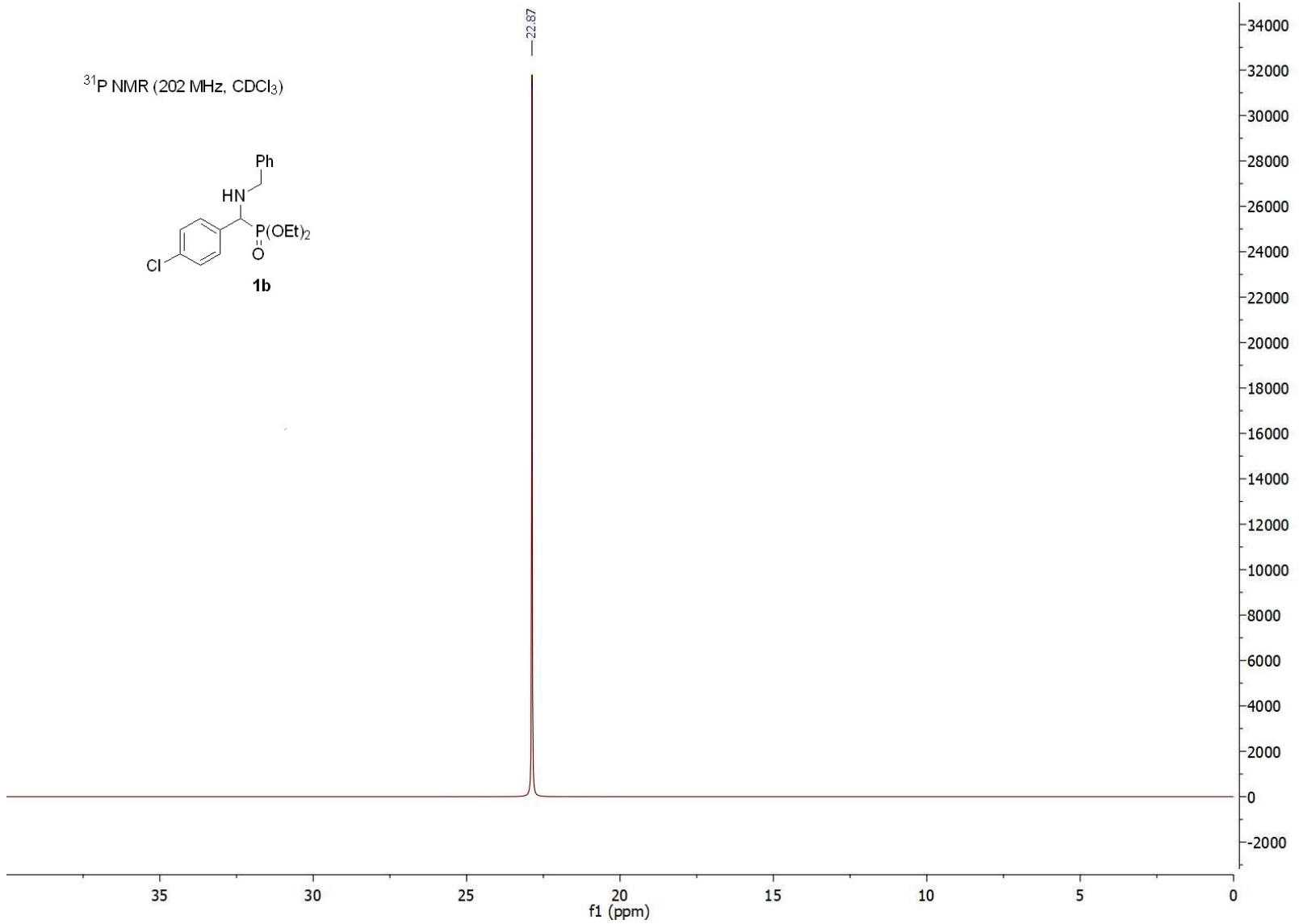
A P. R. Varga, E. Dinnyési, S. Tóth, G. Szakács and G. Keglevich, Drug Des. Discov., 2022, in press.
B N. Z. Kiss, A. Kaszás, L. Drahos, Z. Mucsi and G. Keglevich, *Tetrahedron Lett.*, 2012, **53**, 207.

2.2) ^{31}P NMR of starting materials (1a, 1b and 1c)

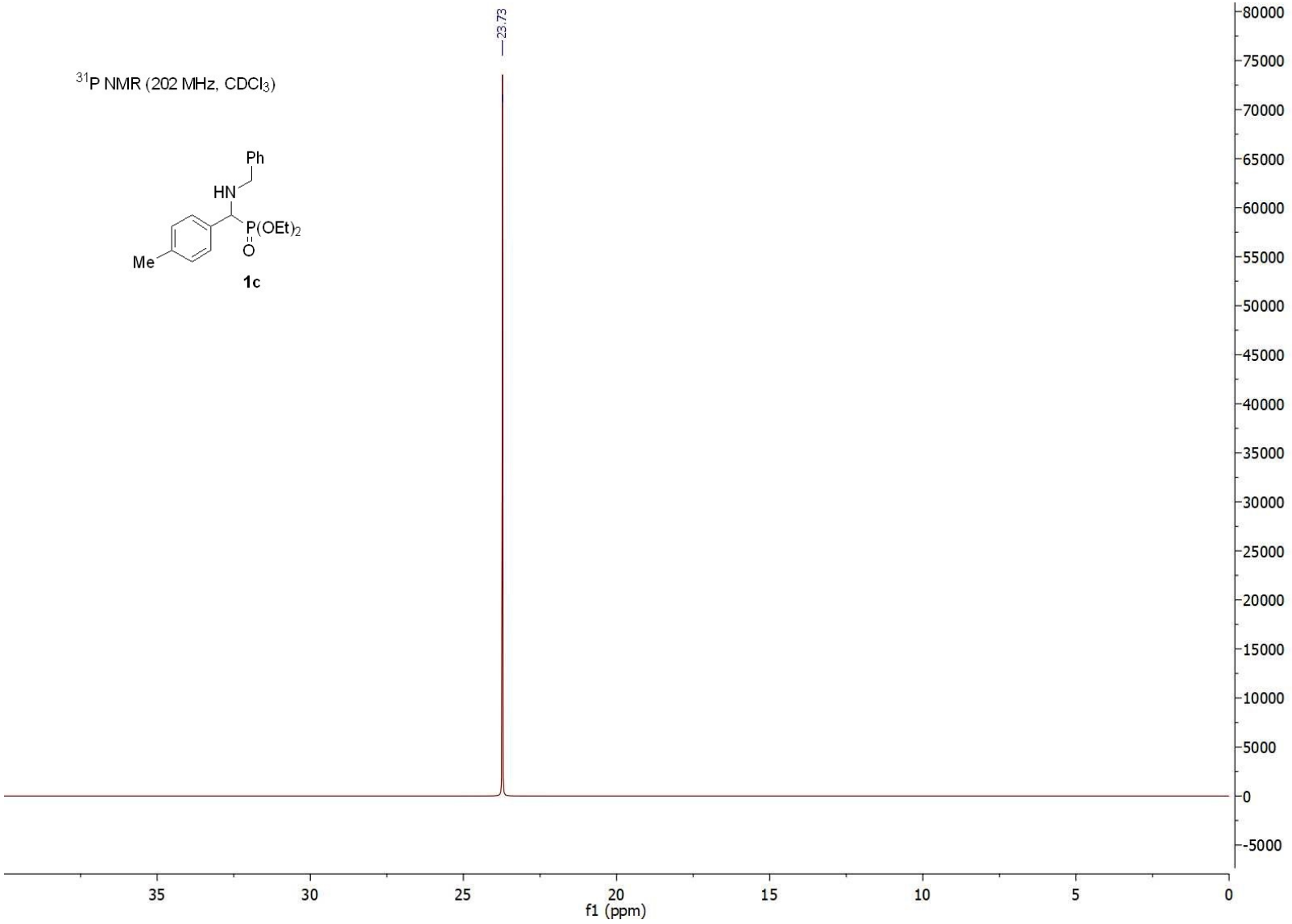
Diethyl α-benzylamino-benzylphosphonate (**1a**)



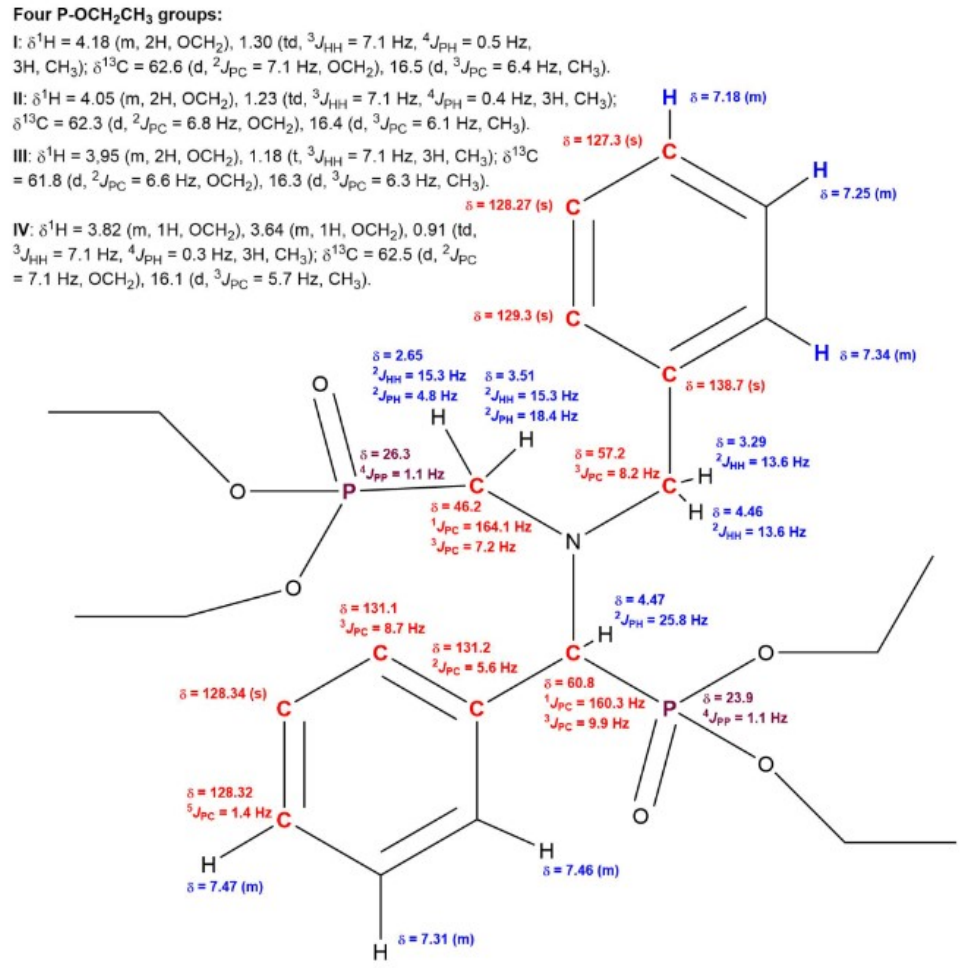
Diethyl α-benzylamino-4-chlorobenzylphosphonate (**1b**)



Diethyl α-benzylamino-4-methylbenzylphosphonate (**1c**)



3.) ^{13}C and ^{1}H NMR data of compounds **5a**, **5b**, **5c** and **5d** obtained by a 2D NMR study



5b

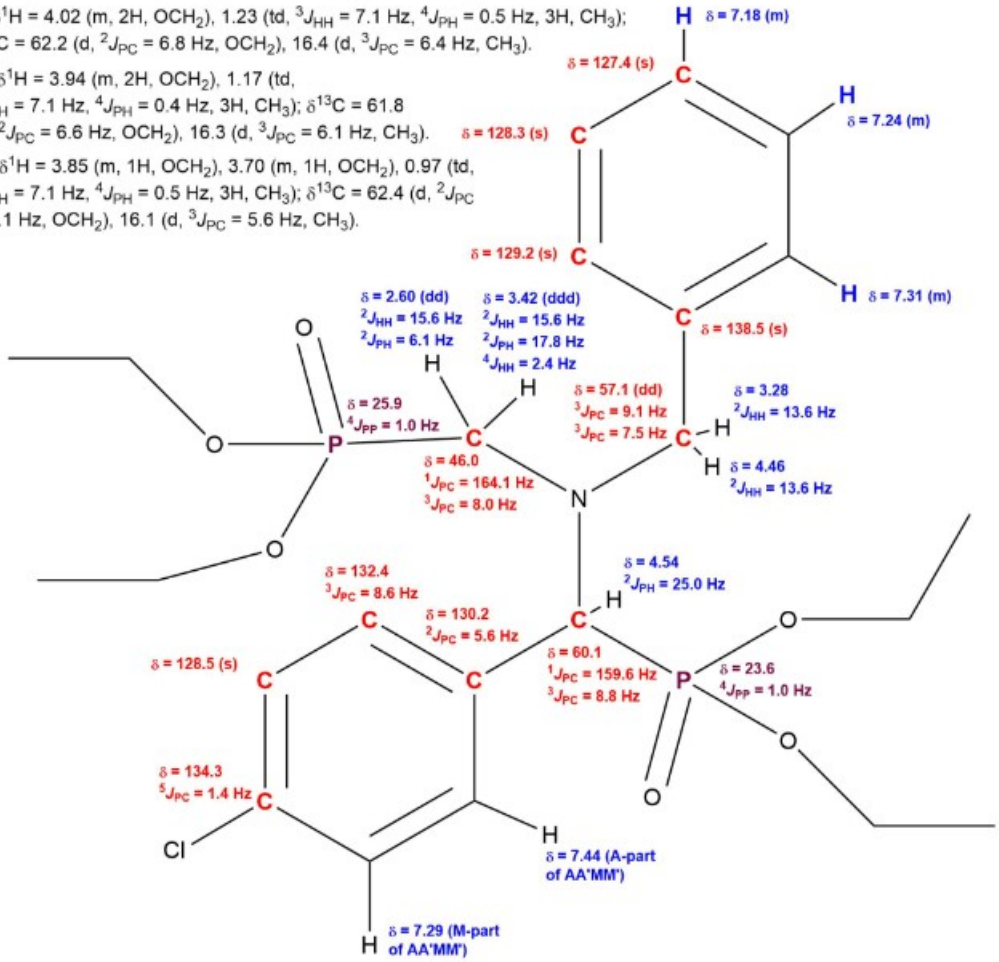
Four P-OCH_2CH_3 groups:

I: δ^1H = 4.18 (m, 2H, OCH_2), 1.31 (td, $^3J_{HH}$ = 7.1 Hz, $^4J_{PH}$ = 0.6 Hz, 3H, CH_3); δ^{13}C = 62.7 (d, $^2J_{PC}$ = 7.1 Hz, OCH_2), 16.5 (d, $^3J_{PC}$ = 6.4 Hz, CH_3).

II: δ^1H = 4.02 (m, 2H, OCH_2), 1.23 (td, $^3J_{HH}$ = 7.1 Hz, $^4J_{PH}$ = 0.5 Hz, 3H, CH_3); δ^{13}C = 62.2 (d, $^2J_{PC}$ = 6.8 Hz, OCH_2), 16.4 (d, $^3J_{PC}$ = 6.4 Hz, CH_3).

III: δ^1H = 3.94 (m, 2H, OCH_2), 1.17 (td, $^3J_{HH}$ = 7.1 Hz, $^4J_{PH}$ = 0.4 Hz, 3H, CH_3); δ^{13}C = 61.8 (d, $^2J_{PC}$ = 6.6 Hz, OCH_2), 16.3 (d, $^3J_{PC}$ = 6.1 Hz, CH_3).

IV: δ^1H = 3.85 (m, 1H, OCH_2), 3.70 (m, 1H, OCH_2), 0.97 (td, $^3J_{HH}$ = 7.1 Hz, $^4J_{PH}$ = 0.5 Hz, 3H, CH_3); δ^{13}C = 62.4 (d, $^2J_{PC}$ = 7.1 Hz, OCH_2), 16.1 (d, $^3J_{PC}$ = 5.6 Hz, CH_3).



5c

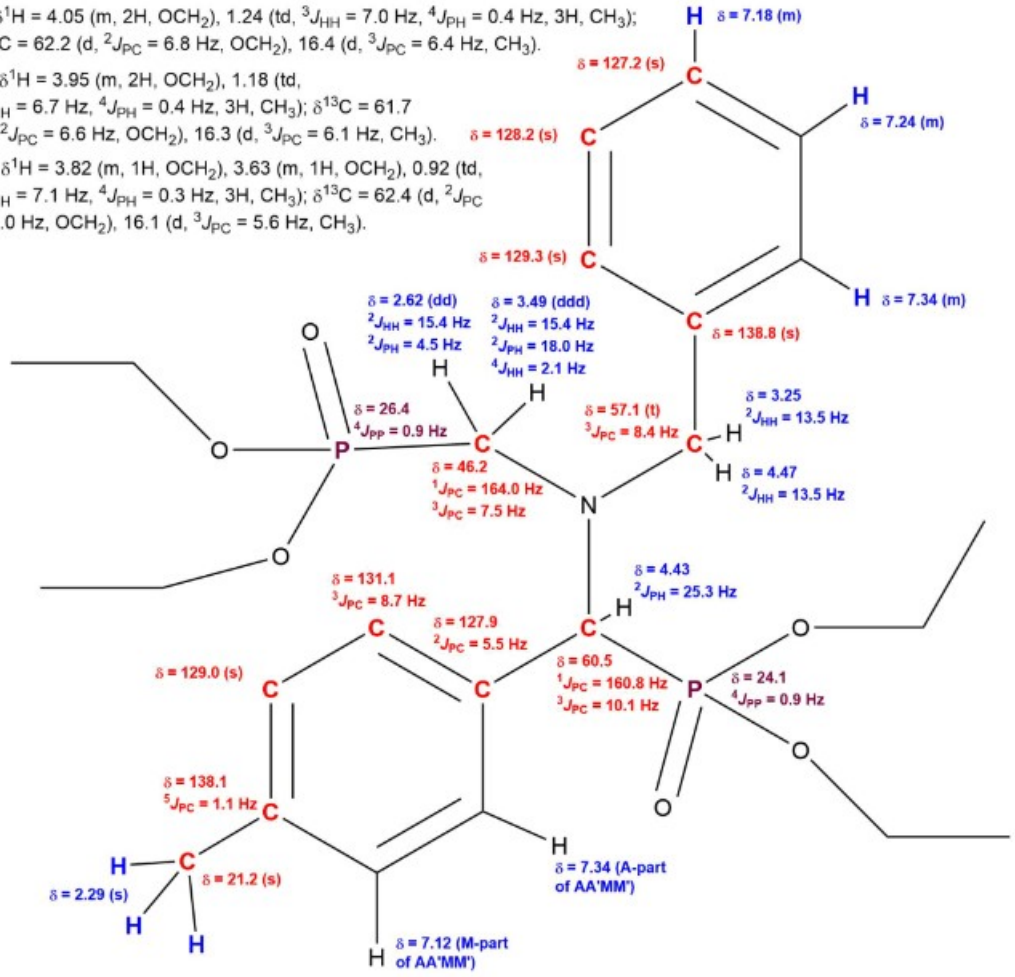
Four P-OCH_2CH_3 groups:

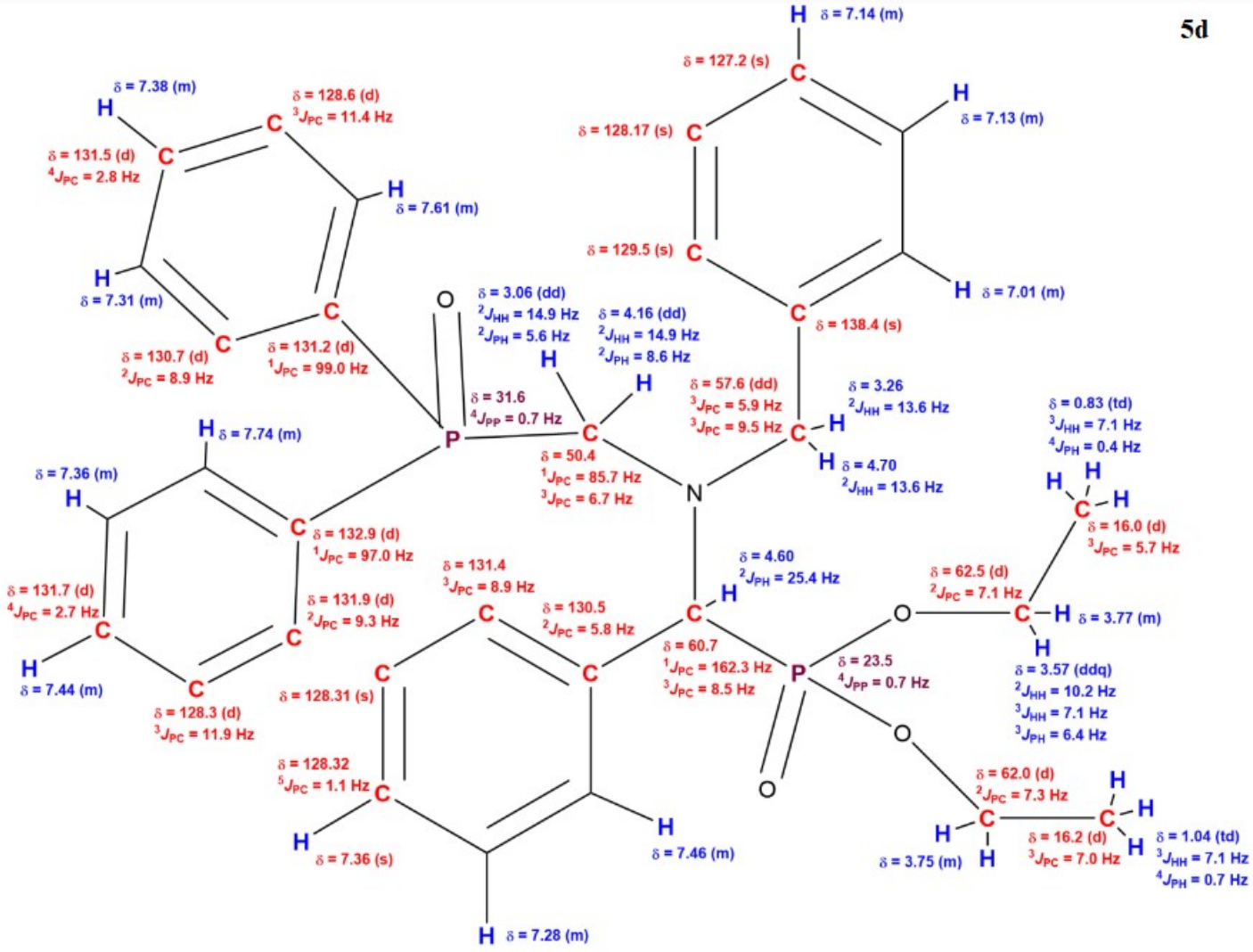
I: δ^1H = 4.17 (m, 2H, OCH_2), 1.30 (td, $^3J_{HH}$ = 7.6 Hz, $^4J_{PH}$ = 0.5 Hz, 3H, CH_3); δ^{13}C = 62.5 (d, $^2J_{PC}$ = 7.1 Hz, OCH_2), 16.5 (d, $^3J_{PC}$ = 6.4 Hz, CH_3).

II: δ^1H = 4.05 (m, 2H, OCH_2), 1.24 (td, $^3J_{HH}$ = 7.0 Hz, $^4J_{PH}$ = 0.4 Hz, 3H, CH_3); δ^{13}C = 62.2 (d, $^2J_{PC}$ = 6.8 Hz, OCH_2), 16.4 (d, $^3J_{PC}$ = 6.4 Hz, CH_3).

III: δ^1H = 3.95 (m, 2H, OCH_2), 1.18 (td, $^3J_{HH}$ = 6.7 Hz, $^4J_{PH}$ = 0.4 Hz, 3H, CH_3); δ^{13}C = 61.7 (d, $^2J_{PC}$ = 6.6 Hz, OCH_2), 16.3 (d, $^3J_{PC}$ = 6.1 Hz, CH_3).

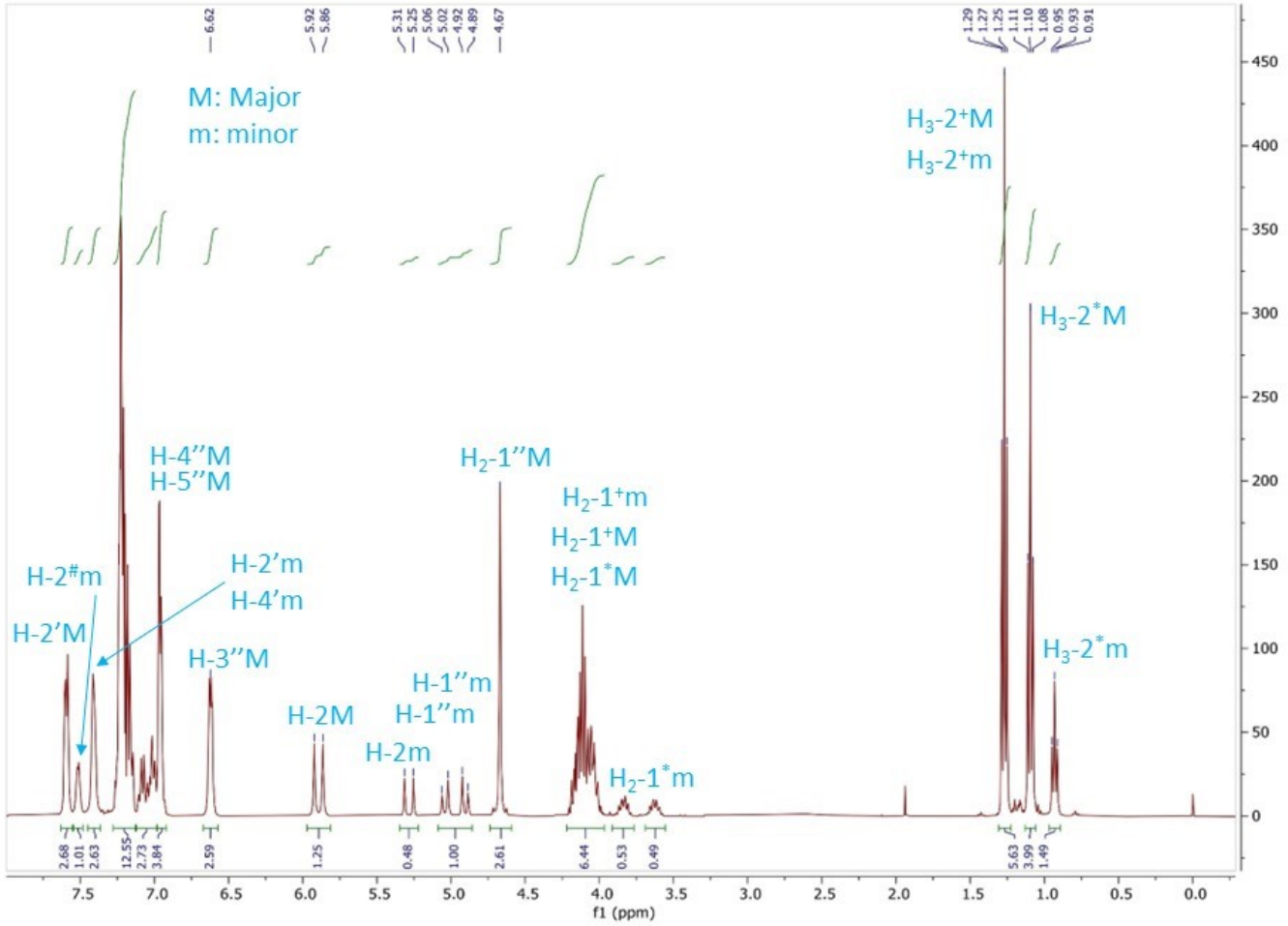
IV: δ^1H = 3.82 (m, 1H, OCH_2), 3.63 (m, 1H, OCH_2), 0.92 (td, $^3J_{HH}$ = 7.1 Hz, $^4J_{PH}$ = 0.3 Hz, 3H, CH_3); δ^{13}C = 62.4 (d, $^2J_{PC}$ = 7.0 Hz, OCH_2), 16.1 (d, $^3J_{PC}$ = 5.6 Hz, CH_3).



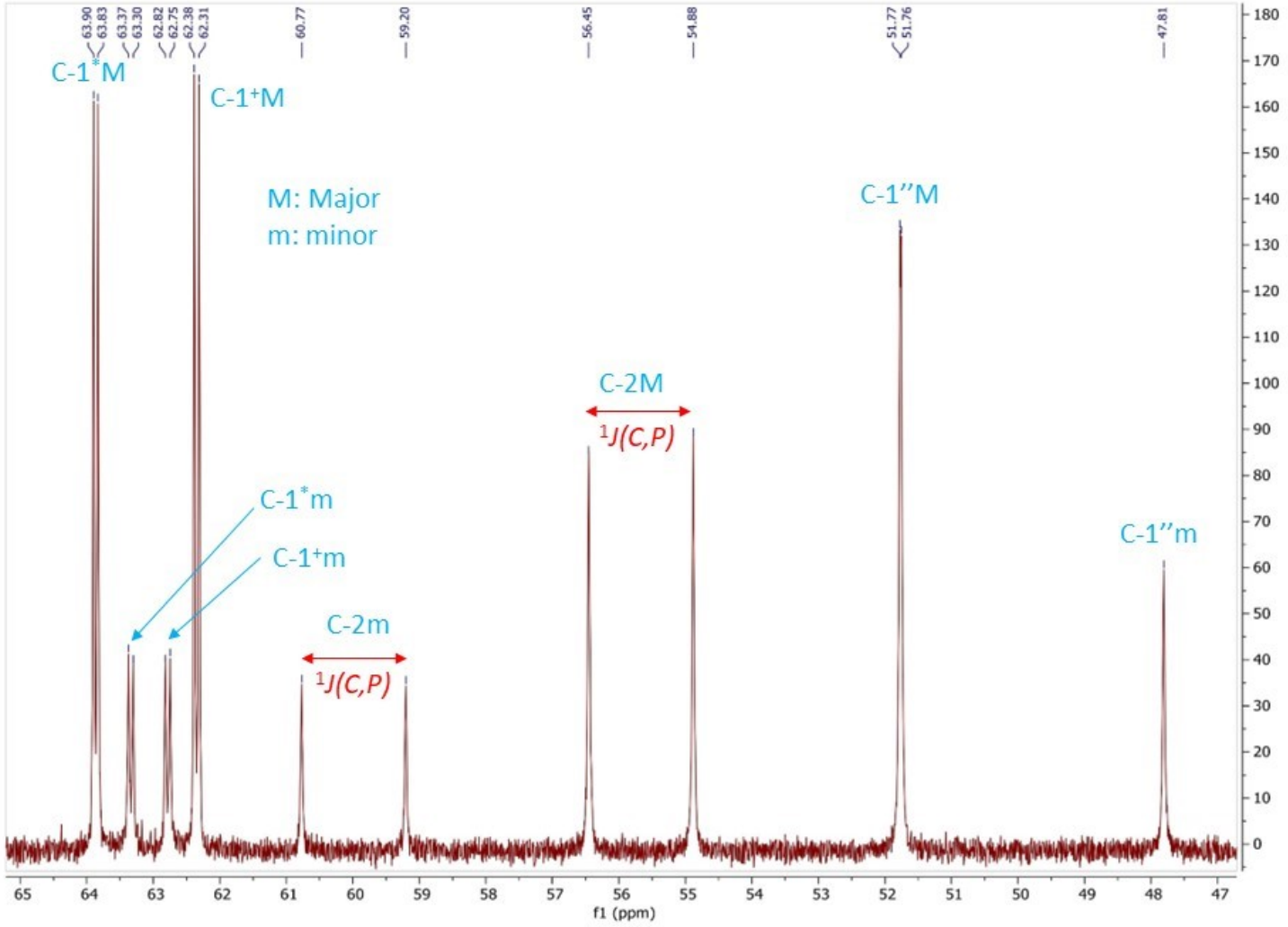

5d
δ = 7.14 (m)
δ = 127.2 (s)
δ = 7.13 (m)
δ = 128.17 (s)
δ = 129.5 (s)
δ = 7.01 (m)
δ = 138.4 (s)
δ = 7.38 (m)
δ = 128.6 (d)
3JPC = 11.4 Hz
δ = 131.5 (d)
4JPC = 2.8 Hz
δ = 7.61 (m)
δ = 7.31 (m)
δ = 130.7 (d)
2JPC = 8.9 Hz
δ = 131.2 (d)
1JPC = 99.0 Hz
δ = 3.06 (dd)
2JHH = 14.9 Hz
2JPH = 5.6 Hz
δ = 4.16 (dd)
2JHH = 14.9 Hz
2JPH = 8.6 Hz
δ = 31.6
4JPP = 0.7 Hz
δ = 57.6 (dd)
3JPC = 5.9 Hz
3JPC = 9.5 Hz
δ = 3.26
2JHH = 13.6 Hz
δ = 4.70
2JHH = 13.6 Hz
δ = 50.4
1JPC = 85.7 Hz
3JPC = 6.7 Hz
δ = 0.83 (td)
3JHH = 7.1 Hz
4JPH = 0.4 Hz
δ = 16.0 (d)
3JPC = 5.7 Hz
δ = 7.74 (m)
δ = 7.36 (m)
δ = 132.9 (d)
1JPC = 97.0 Hz
δ = 131.7 (d)
4JPC = 2.7 Hz
δ = 131.9 (d)
2JPC = 9.3 Hz
δ = 7.44 (m)
δ = 128.3 (d)
3JPC = 11.9 Hz
δ = 131.4
3JPC = 8.9 Hz
δ = 130.5
2JPC = 5.8 Hz
δ = 4.60
2JPH = 25.4 Hz
δ = 62.5 (d)
2JPC = 7.1 Hz
δ = 3.77 (m)
δ = 60.7
1JPC = 162.3 Hz
3JPC = 8.5 Hz
δ = 23.5
4JPP = 0.7 Hz
δ = 3.57 (ddq)
2JHH = 10.2 Hz
3JHH = 7.1 Hz
3JPH = 6.4 Hz
δ = 128.31 (s)
δ = 128.32
5JPC = 1.1 Hz
δ = 7.36 (s)
δ = 7.46 (m)
δ = 62.0 (d)
2JPC = 7.3 Hz
δ = 3.75 (m)
δ = 16.2 (d)
3JPC = 7.0 Hz
δ = 1.04 (td)
3JHH = 7.1 Hz
4JPH = 0.7 Hz
δ = 7.28 (m)

4.) ^{1}H and ^{13}C NMR spectra on the equilibrium of the rotamers of **3b**

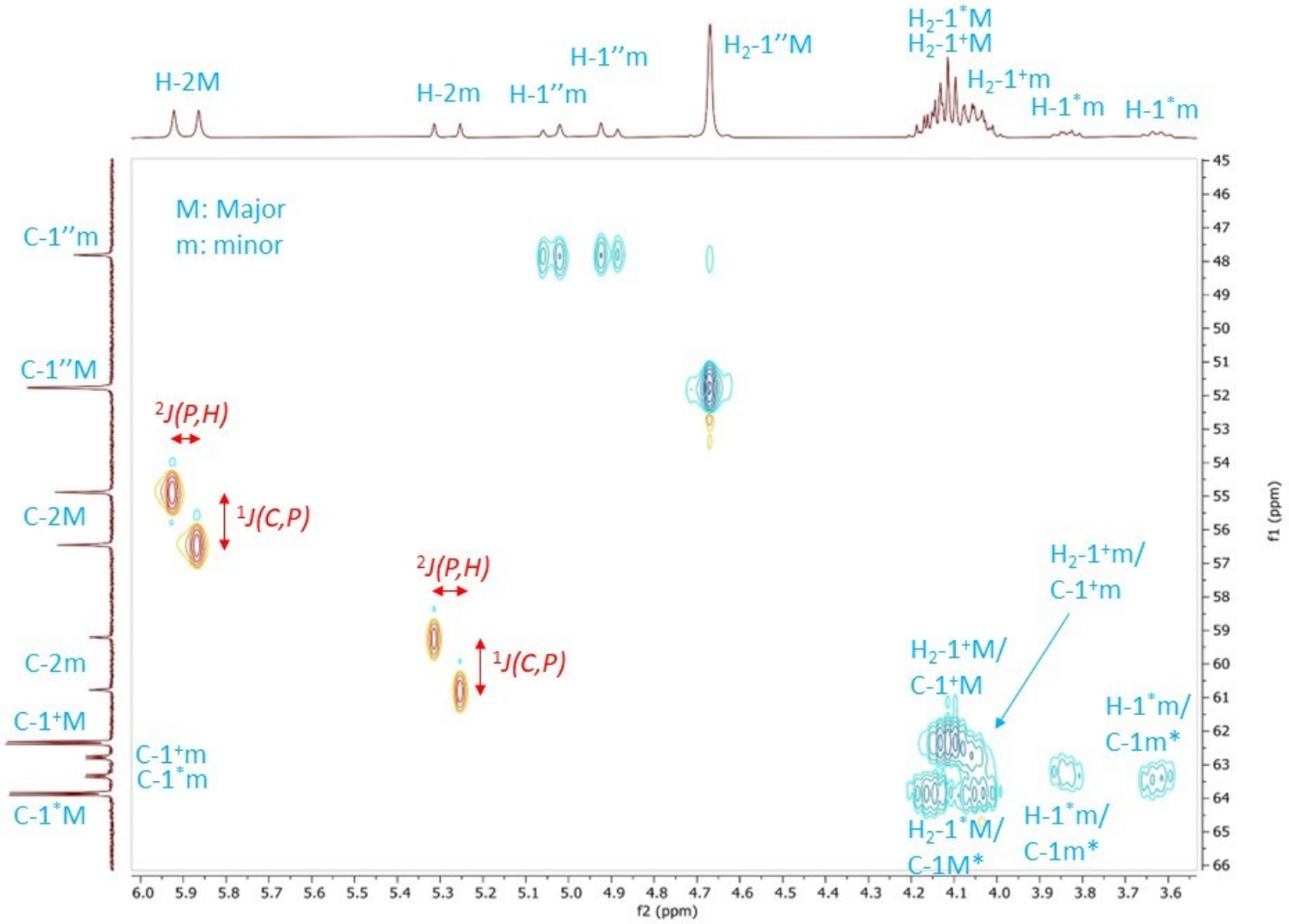
Segment of the ^{1}H NMR spectrum on the equilibrium of the rotamers of **3b**



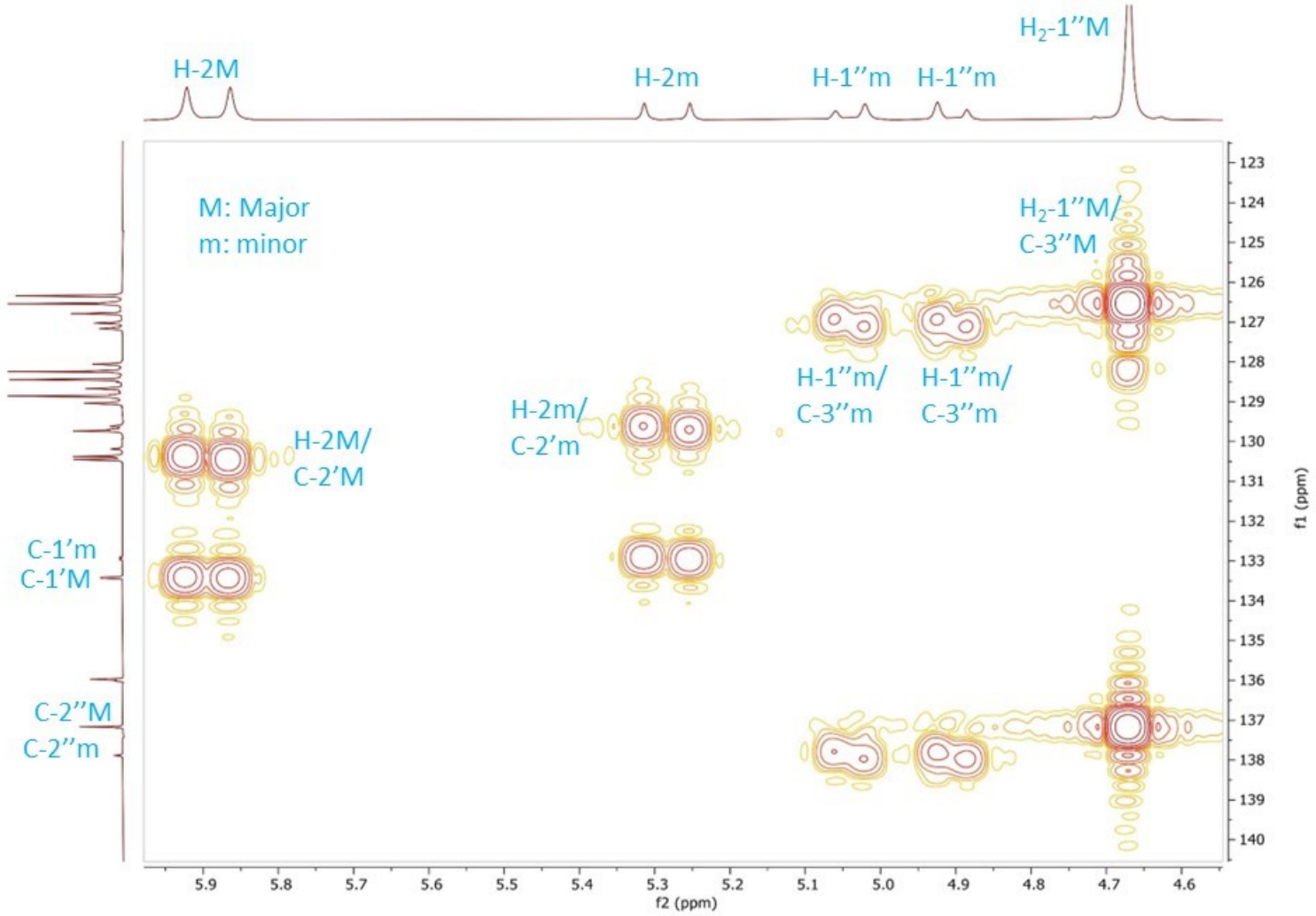
Segment of the ^{13}C NMR spectrum on the equilibrium of the rotamers of **3b**



Segment of the HSQC NMR spectrum on the equilibrium of the rotamers of **3b**

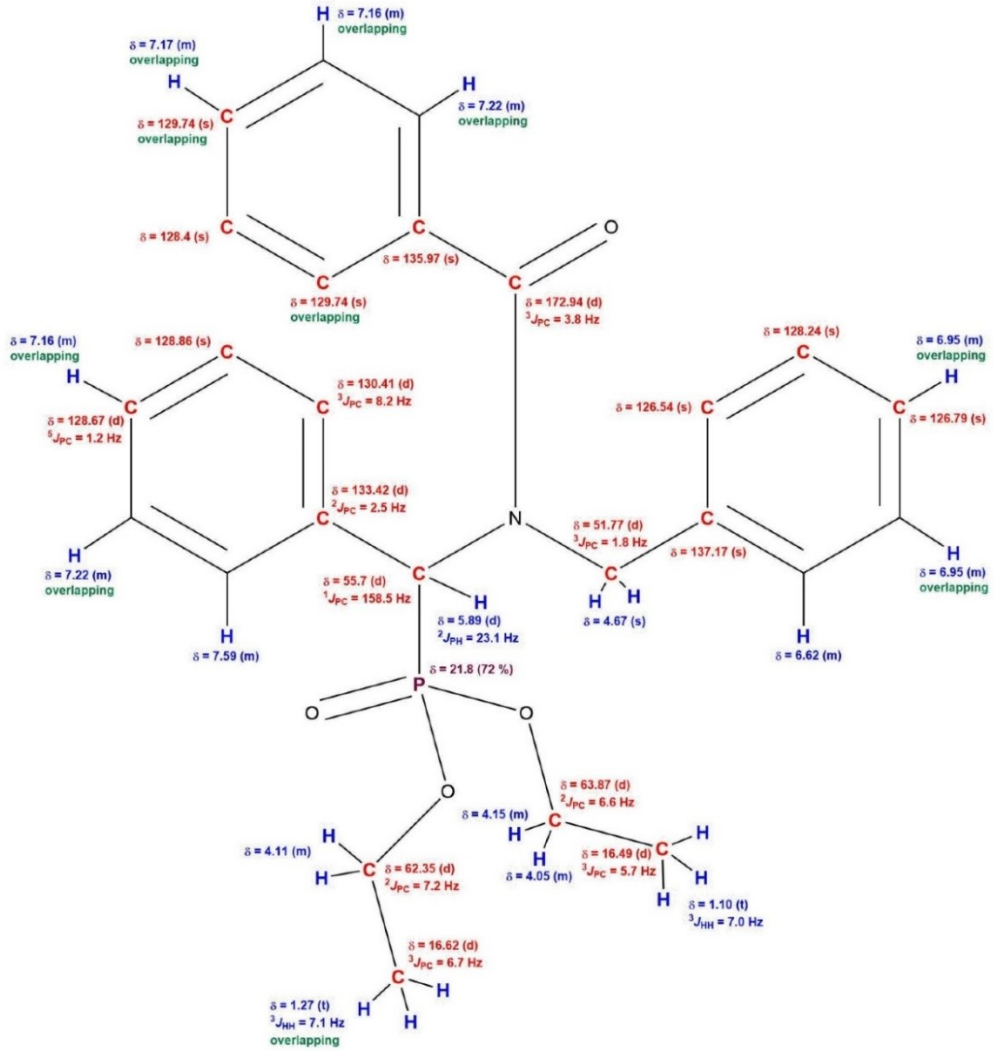


Segment of the HMBC NMR spectrum on the equilibrium of the rotamers of **3b**



^{13}C and ^{1}H NMR data for the two rotamers:

3b-A (72%)



^{13}C and ^{1}H NMR data for the two rotamers:

3b-B (28%)