Electronic Supplementary Information

Synthesis of 12β-methyl-18-*nor*-avicholic acid analogues as potential TGR5 agonists

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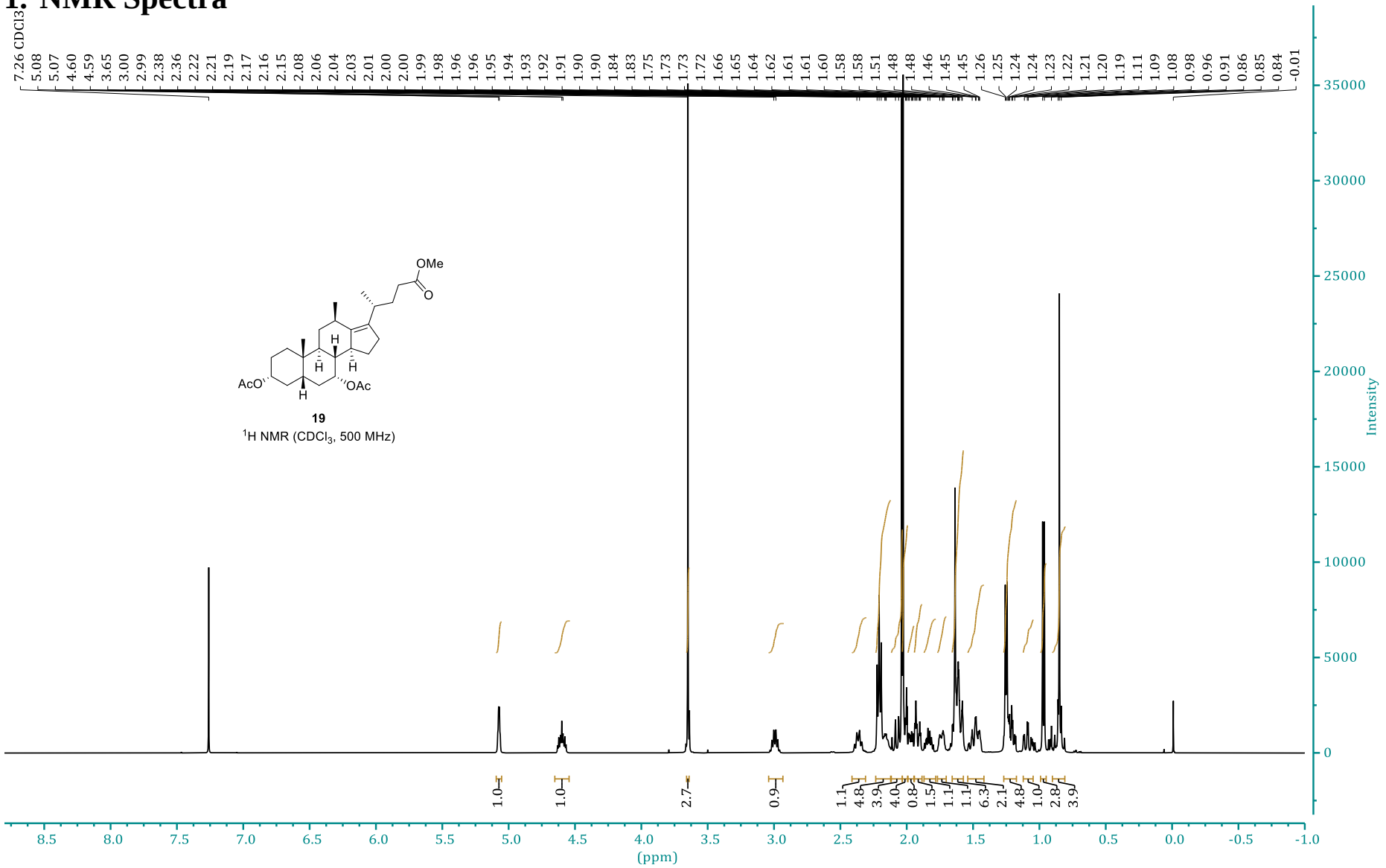
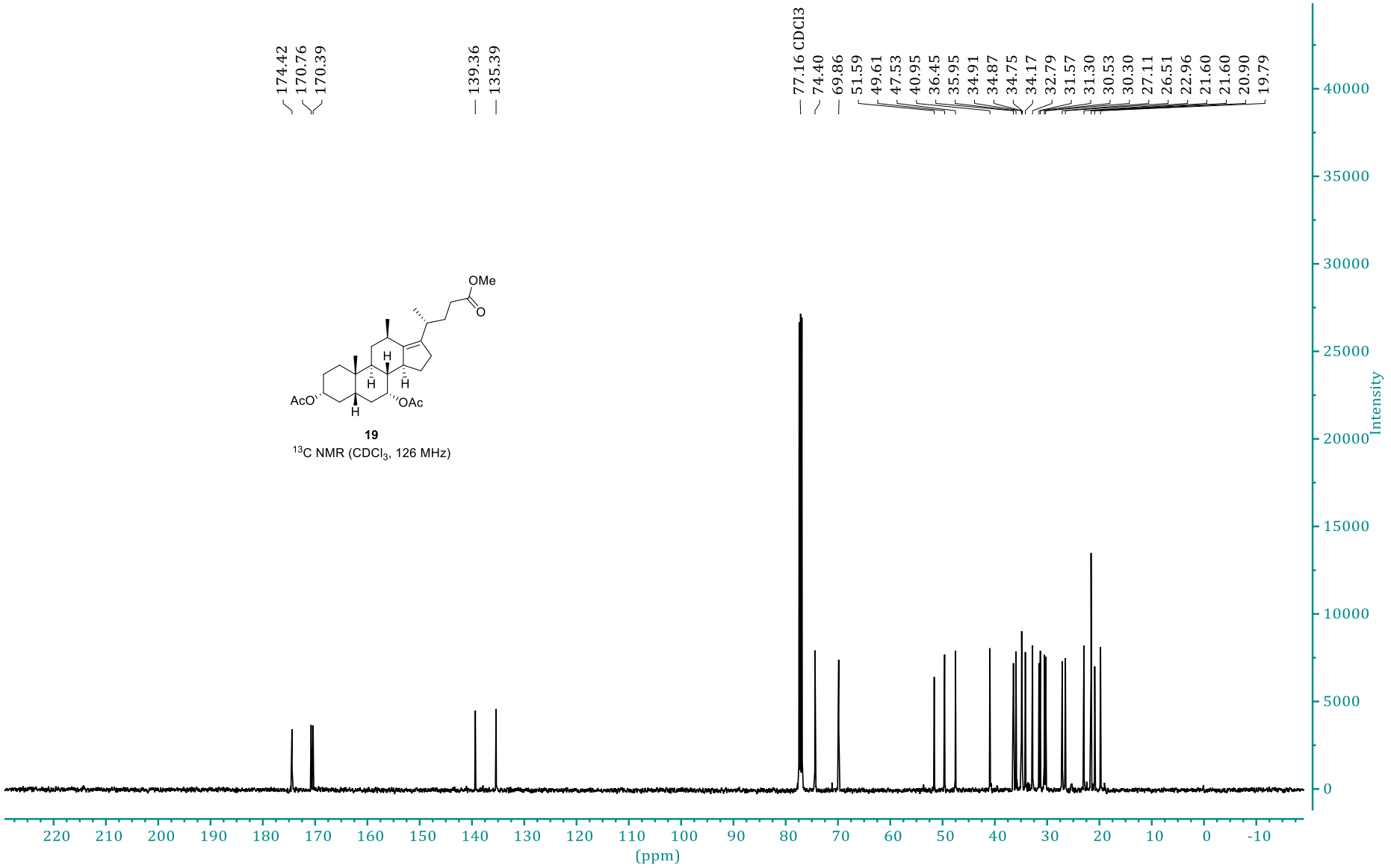
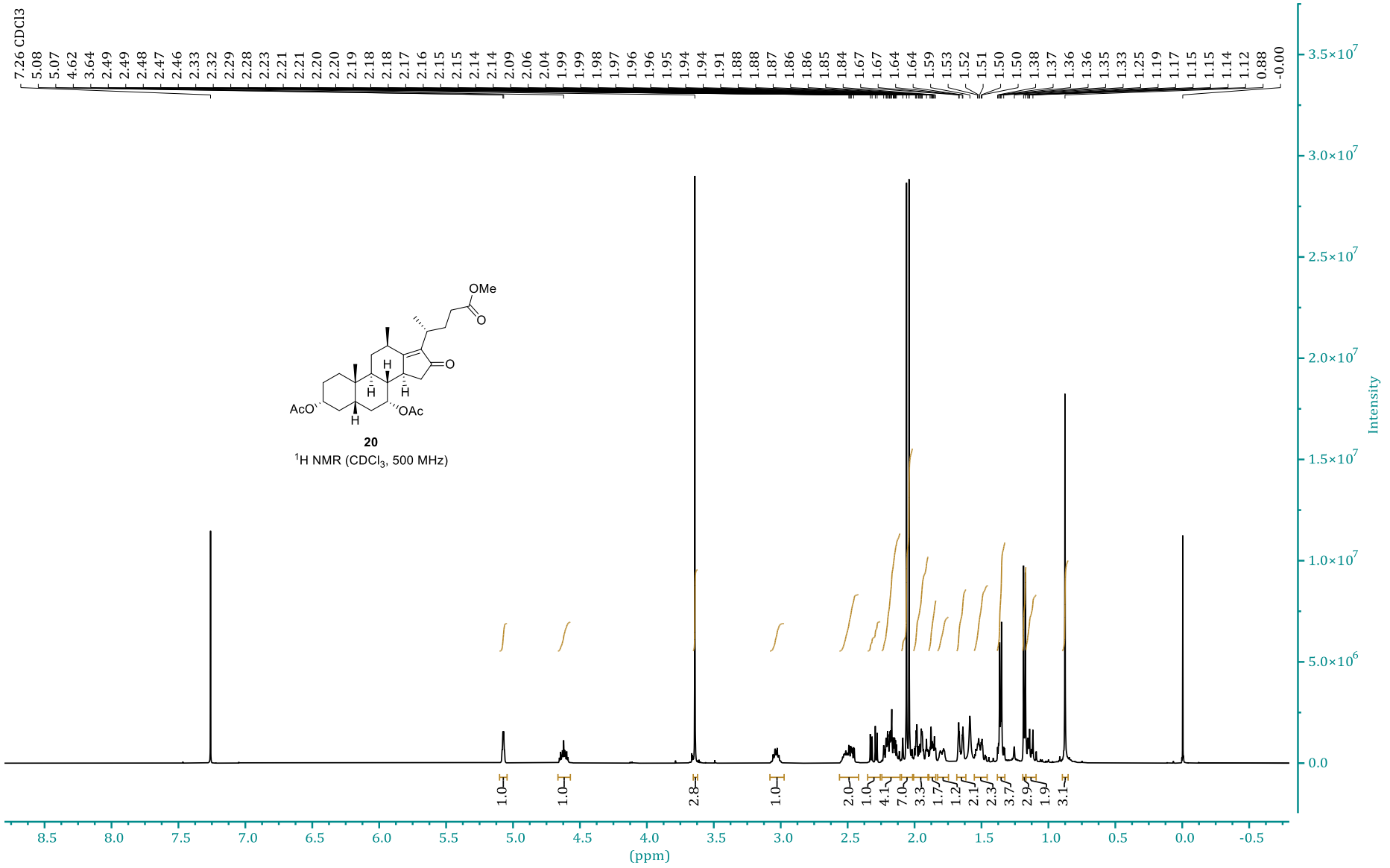
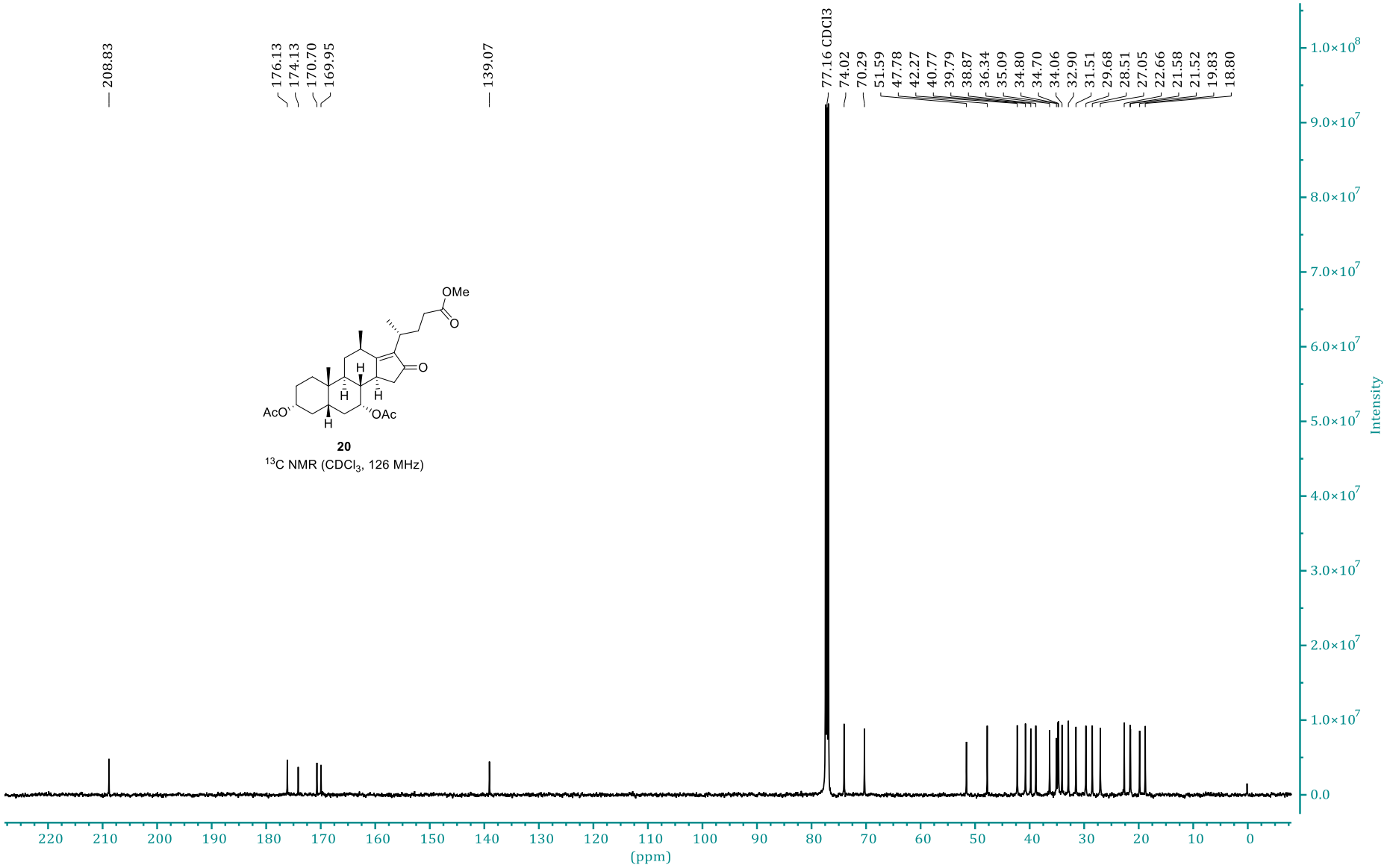
1. NMR Spectra



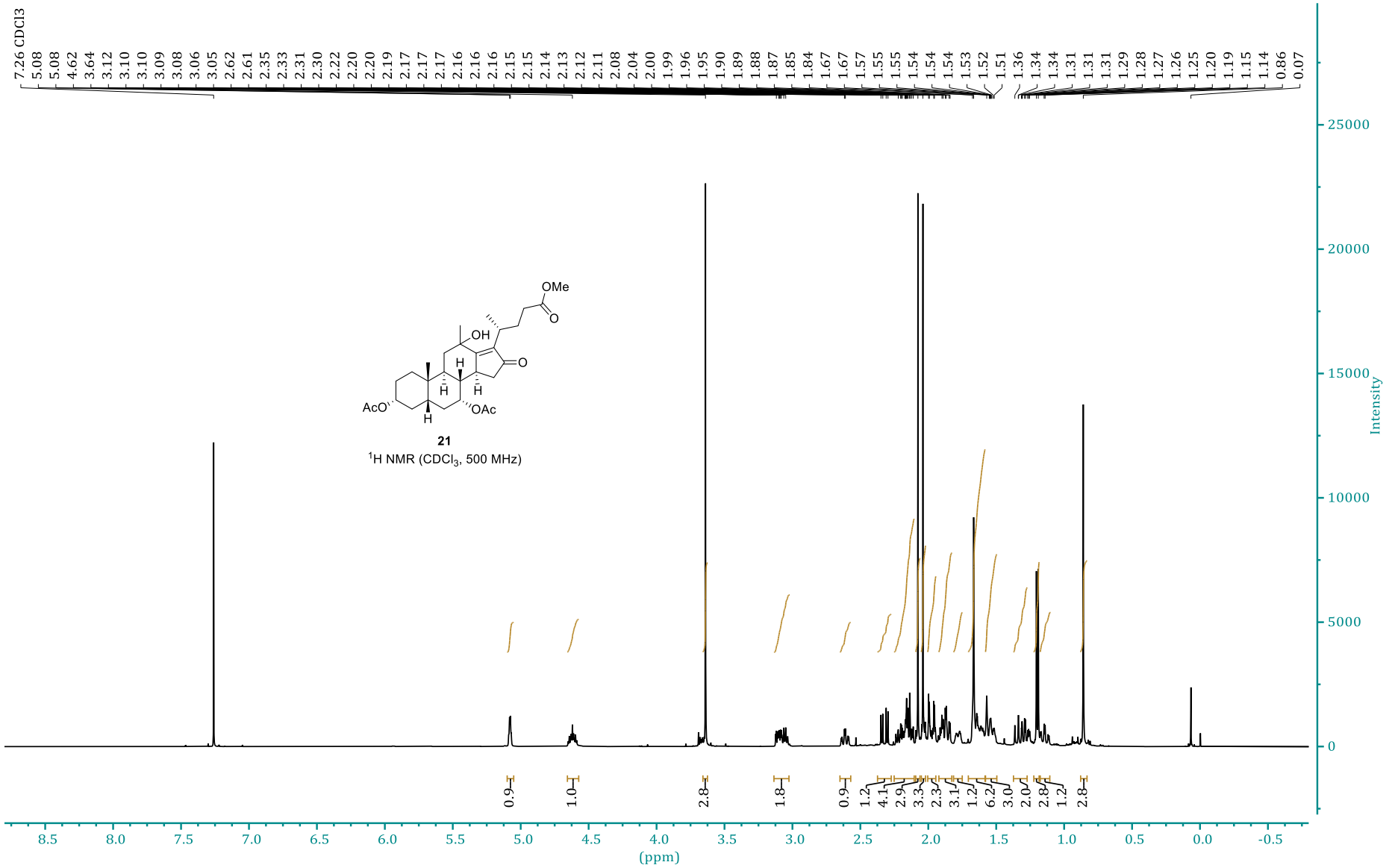

174.42
170.76
170.39
139.36
135.39
77.16 CDCl3
74.40
69.86
51.59
49.61
47.53
40.95
36.45
35.95
34.91
34.87
34.75
34.17
32.79
31.57
31.30
30.53
30.30
27.11
26.51
22.96
21.60
21.60
20.90
19.79
OMe
O
AcO
OAc
H
H
H
H
19
13C NMR (CDCl3, 126 MHz)
Intensity
40000
35000
30000
25000
20000
15000
10000
5000
0
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
(ppm)

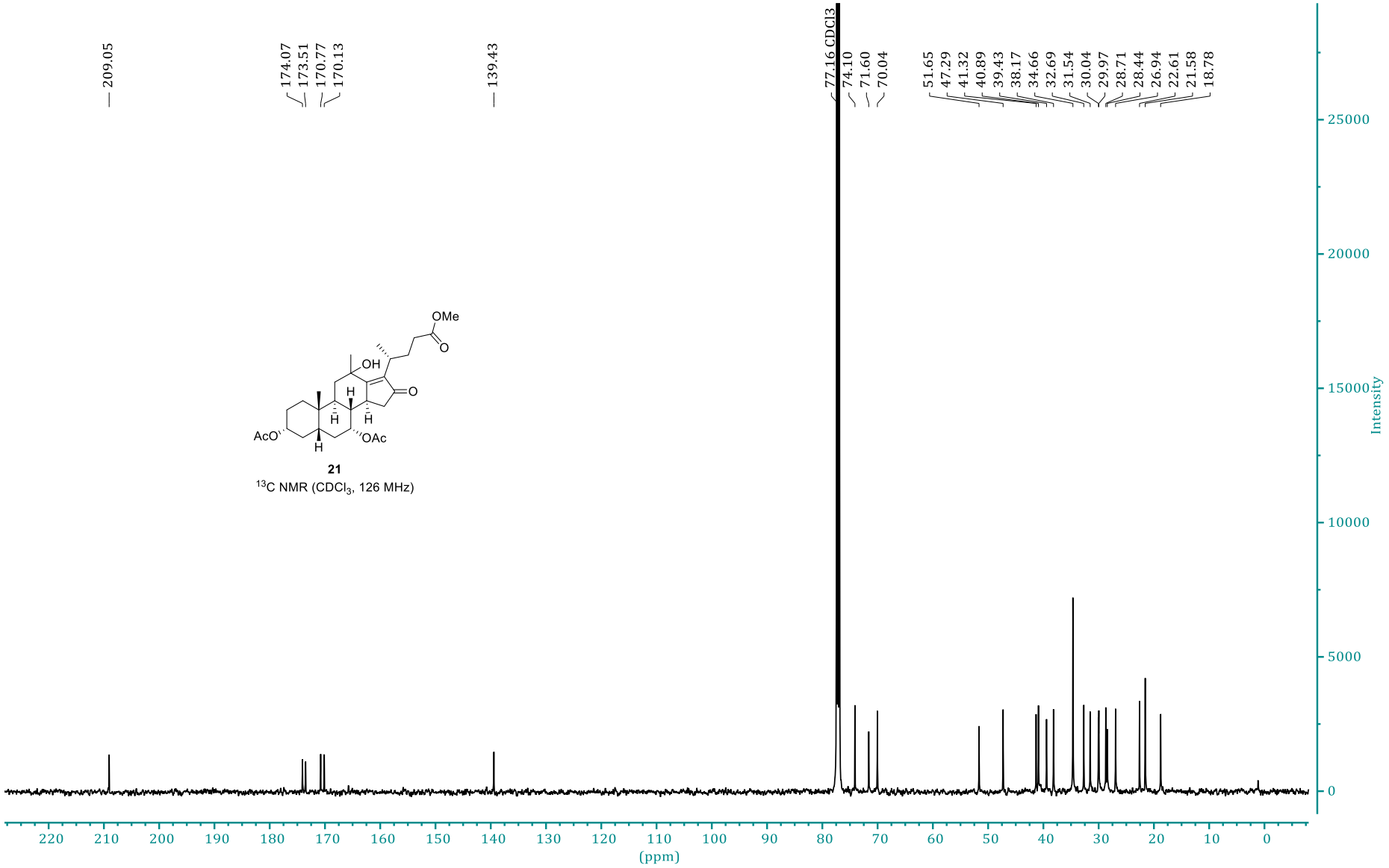

7.26 CDCl3
5.08 5.07 4.62 3.64 2.49 2.49 2.48 2.47 2.46 2.33 2.32 2.29 2.28 2.23 2.21 2.21 2.20 2.20 2.19 2.18 2.18 2.17 2.16 2.15 2.15 2.14 2.14 2.09 2.06 2.04 1.99 1.99 1.98 1.97 1.96 1.96 1.95 1.94 1.94 1.91 1.88 1.88 1.87 1.86 1.86 1.85 1.84 1.67 1.67 1.64 1.64 1.59 1.53 1.52 1.51 1.50 1.50 1.38 1.37 1.36 1.36 1.35 1.33 1.25 1.19 1.17 1.15 1.15 1.14 1.12 0.88 -0.00
OMe
O
O
H
H
H
H
AcO
OAc
20
1H NMR (CDCl3, 500 MHz)
Intensity
3.5×10^7
3.0×10^7
2.5×10^7
2.0×10^7
1.5×10^7
1.0×10^7
5.0×10^6
0.0
1.0 1.0 2.8 1.0 2.0 1.0 4.1 7.0 3.3 1.7 1.2 2.1 2.3 3.7 2.9 1.9 3.1
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)



20

^{13}C NMR ($CDCl_3$, 126 MHz)


7.26 CDCl3
5.08 5.08 4.62 3.64 3.12 3.10 3.10 3.09 3.08 3.06 3.05 2.62 2.61 2.35 2.33 2.31 2.30 2.22 2.20 2.20 2.19 2.17 2.17 2.17 2.16 2.16 2.16 2.15 2.15 2.14 2.13 2.12 2.11 2.08 2.04 2.00 1.99 1.96 1.95 1.90 1.89 1.88 1.87 1.85 1.84 1.67 1.67 1.57 1.55 1.55 1.54 1.54 1.54 1.53 1.52 1.51 1.36 1.34 1.34 1.31 1.31 1.31 1.29 1.28 1.27 1.26 1.25 1.20 1.19 1.15 1.14 0.86 0.07
OMe
O
OH
O
H
H
H
AcO
OAc
H
21
1H NMR (CDCl3, 500 MHz)
Intensity
25000
20000
15000
10000
5000
0
0.9 1.0 2.8 1.8 0.9 1.2 4.1 2.9 3.3 2.3 3.1 1.2 6.2 3.0 2.0 2.8 1.2 2.8
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)



21

^{13}C NMR ($CDCl_3$, 126 MHz)

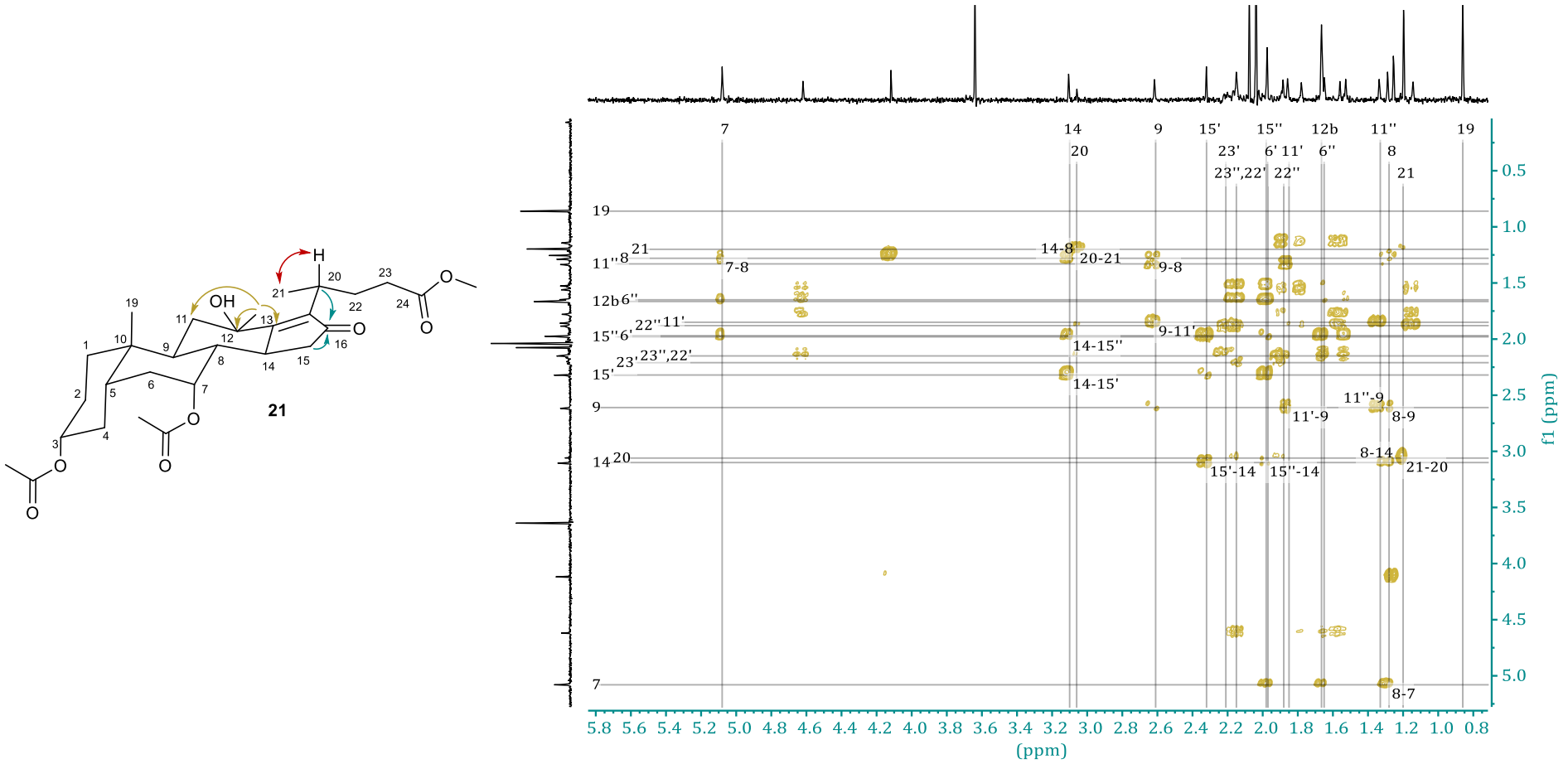


Figure S1: H-H COSY spectrum of compound **21**; **Grey gridlines** - coupling between C and D ring protons; key cross peaks labelled; PSYCHE spectrum superimposed on the F1 and F2 axis. **Red** - COSY interaction between H-21 methyl protons and H-20; **Yellow** - HMBC interactions to C-12β; **Blue** - HMBC interactions to C-16. Stereochemistry at C-12 is not defined.

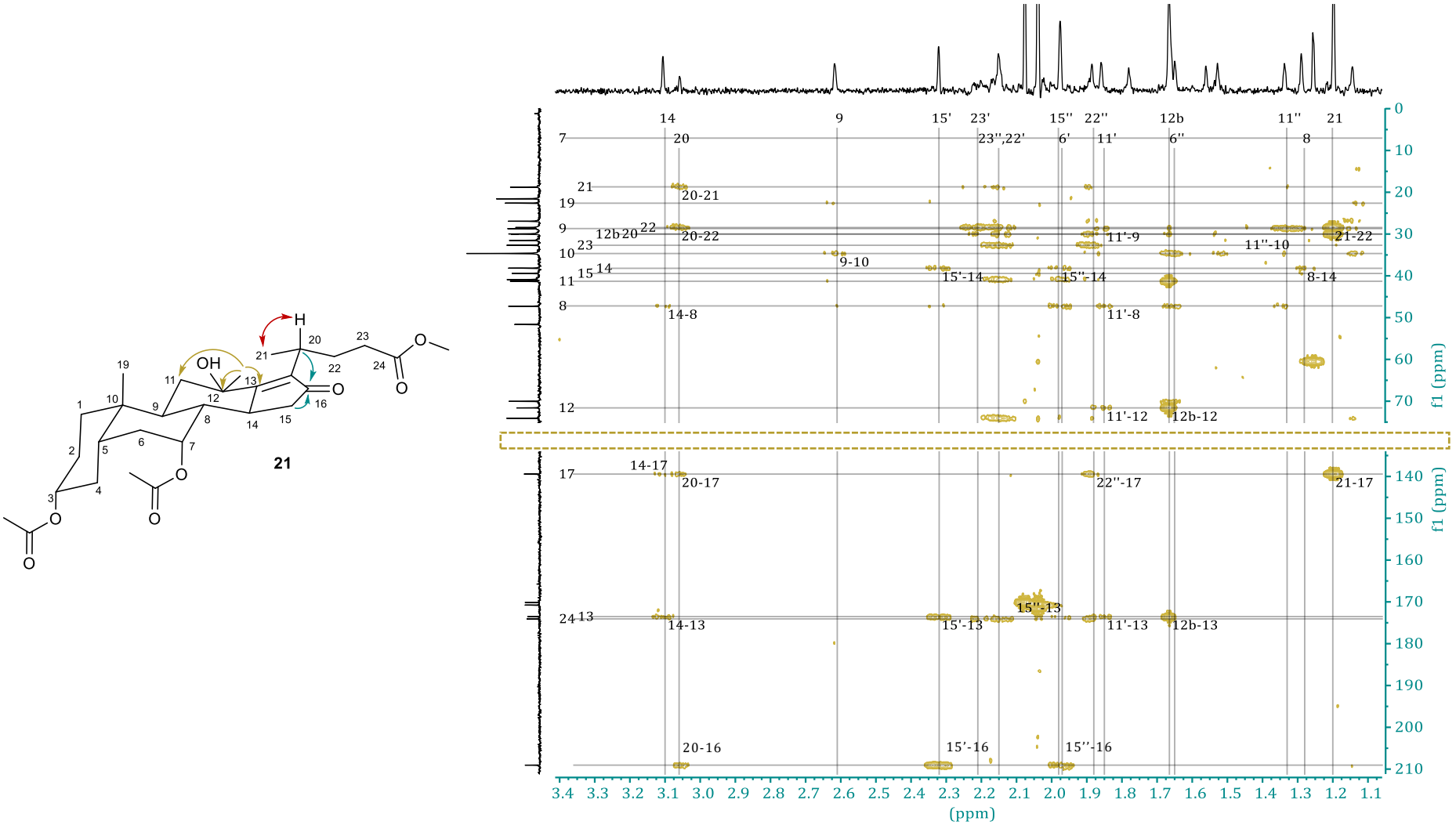
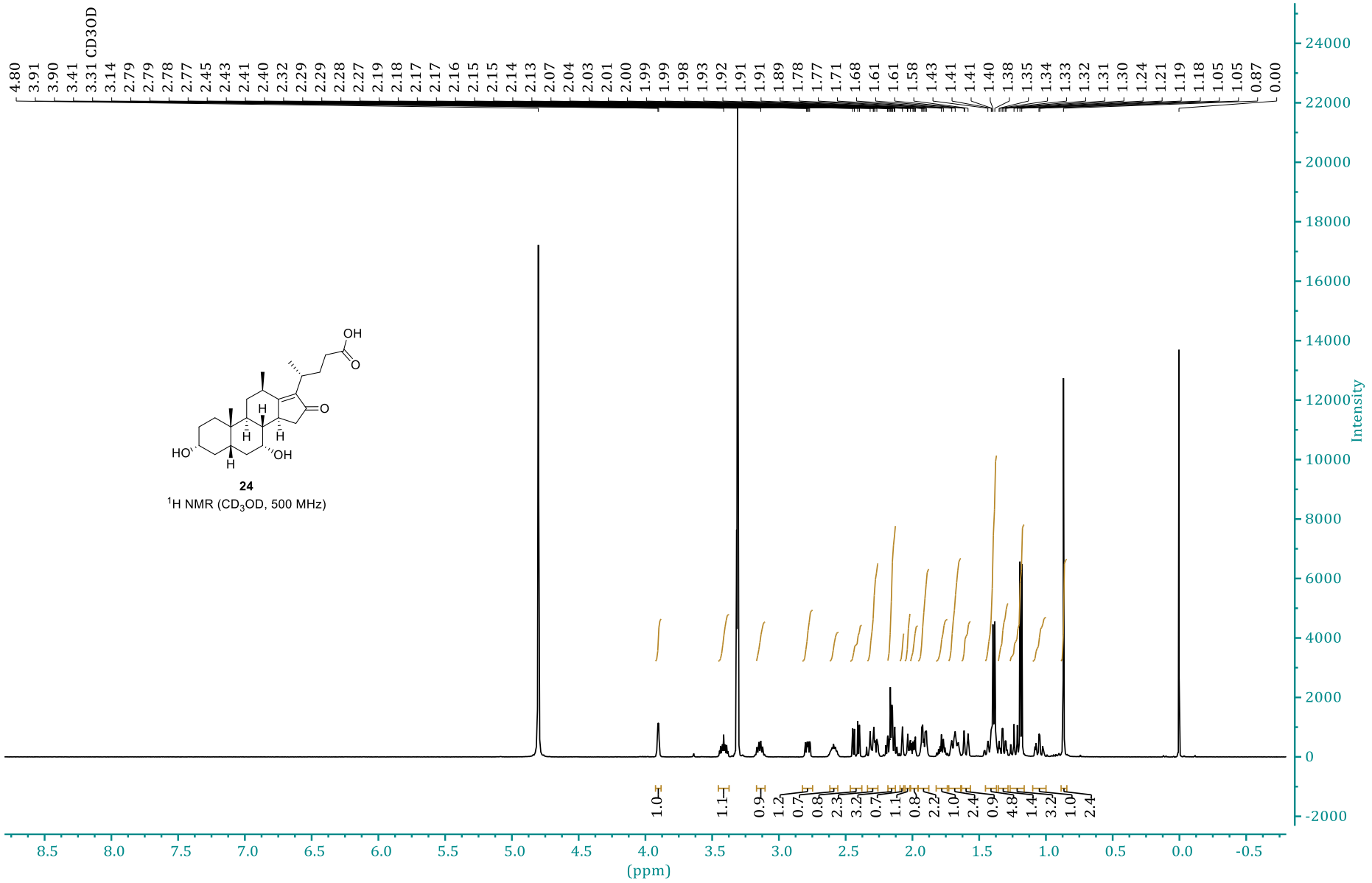
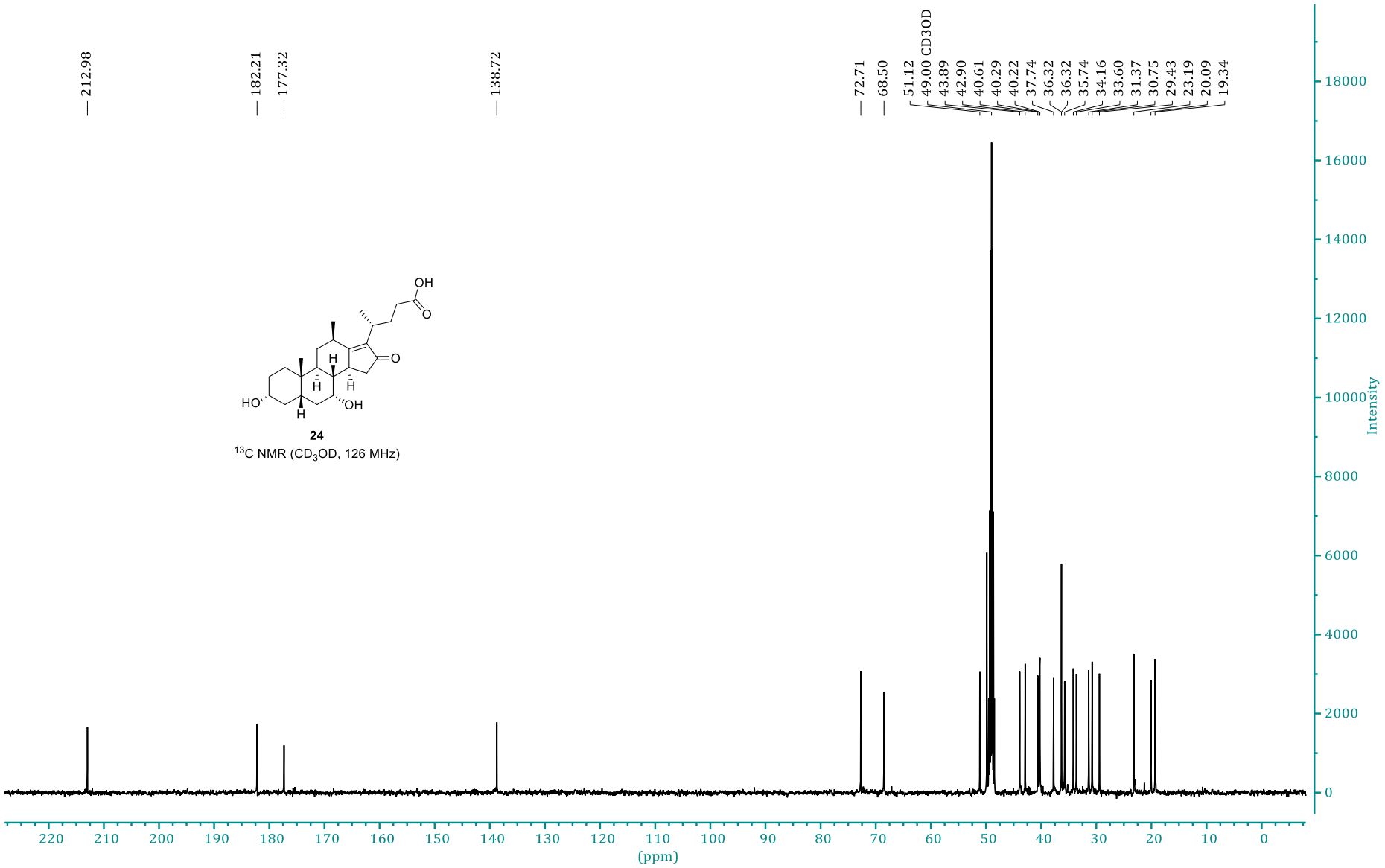
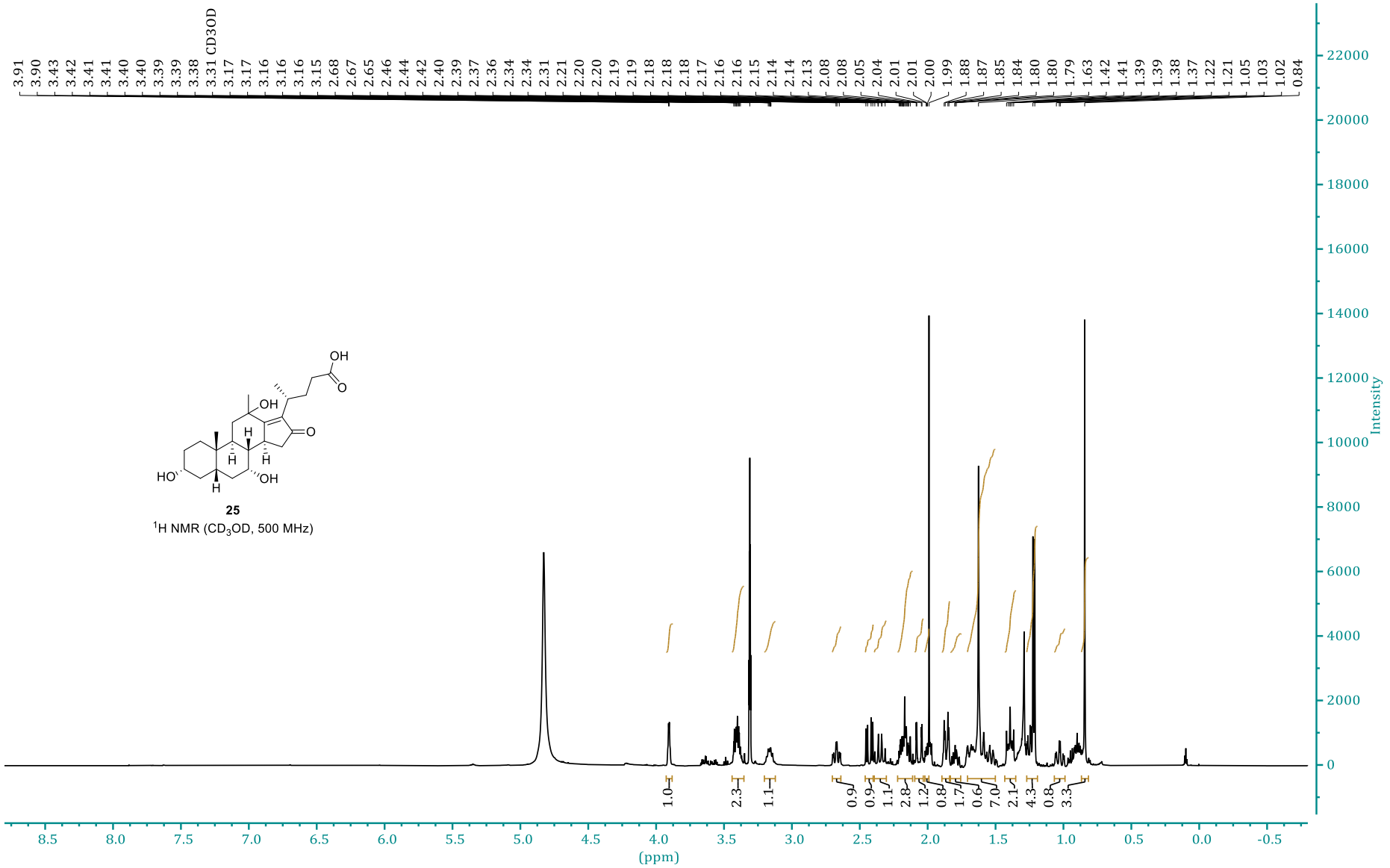


Figure S2: HMBC spectrum of compound **21**; **Grey gridlines** - coupling between C and D ring centres; key cross peaks labelled; PSYCHE spectrum superimposed on the F2 axis. **Red** - COSY interaction between H-21 methyl protons and H-20; **Yellow** - HMBC interactions to C-12β; **Blue** - HMBC interactions to C-16. Stereochemistry at C-12 is not defined.


4.80
3.91
3.90
3.41
3.31 CD3OD
3.14
2.79
2.79
2.78
2.77
2.45
2.43
2.41
2.40
2.32
2.29
2.28
2.27
2.19
2.18
2.17
2.17
2.16
2.15
2.15
2.14
2.13
2.07
2.04
2.03
2.01
2.00
1.99
1.99
1.98
1.93
1.92
1.91
1.91
1.89
1.78
1.77
1.71
1.68
1.61
1.61
1.58
1.43
1.41
1.41
1.40
1.38
1.35
1.34
1.33
1.32
1.31
1.30
1.24
1.21
1.19
1.18
1.05
1.05
0.87
0.00
OH
O
O
H
H
H
HO
OH
H
24
1H NMR (CD3OD, 500 MHz)
1.0
1.1
0.9
1.2
0.7
0.8
2.3
3.2
0.7
1.1
0.8
2.2
1.0
2.4
0.9
4.8
1.4
3.2
1.0
2.4
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
Intensity
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
(ppm)


212.98
182.21
177.32
138.72
72.71
68.50
51.12
49.00 CD3OD
43.89
42.90
40.61
40.29
40.22
37.74
36.32
36.32
35.74
34.16
33.60
31.37
30.75
29.43
23.19
20.09
19.34
OH
O
O
H
H
H
HO
OH
H
24
13C NMR (CD3OD, 126 MHz)
Intensity
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)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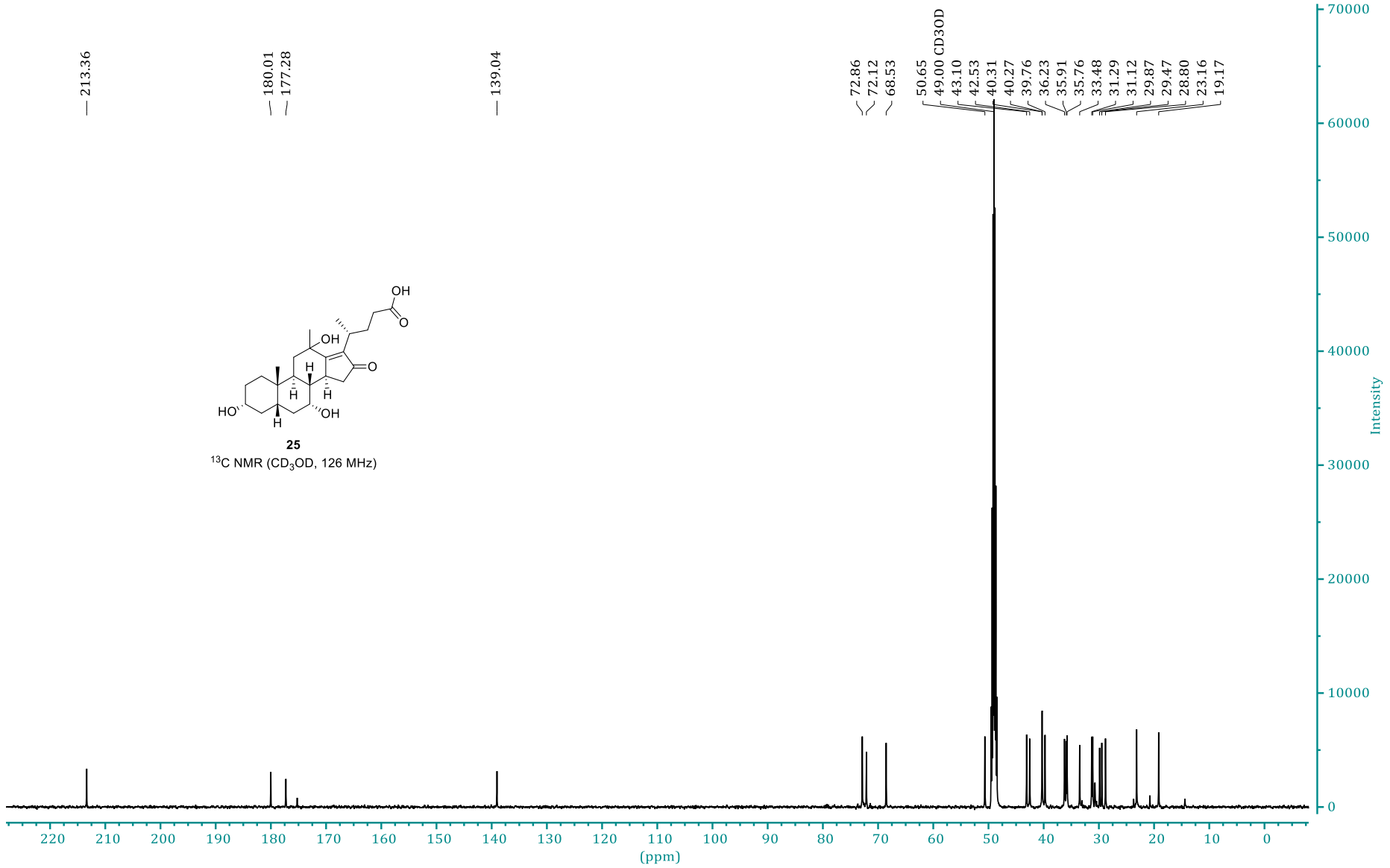
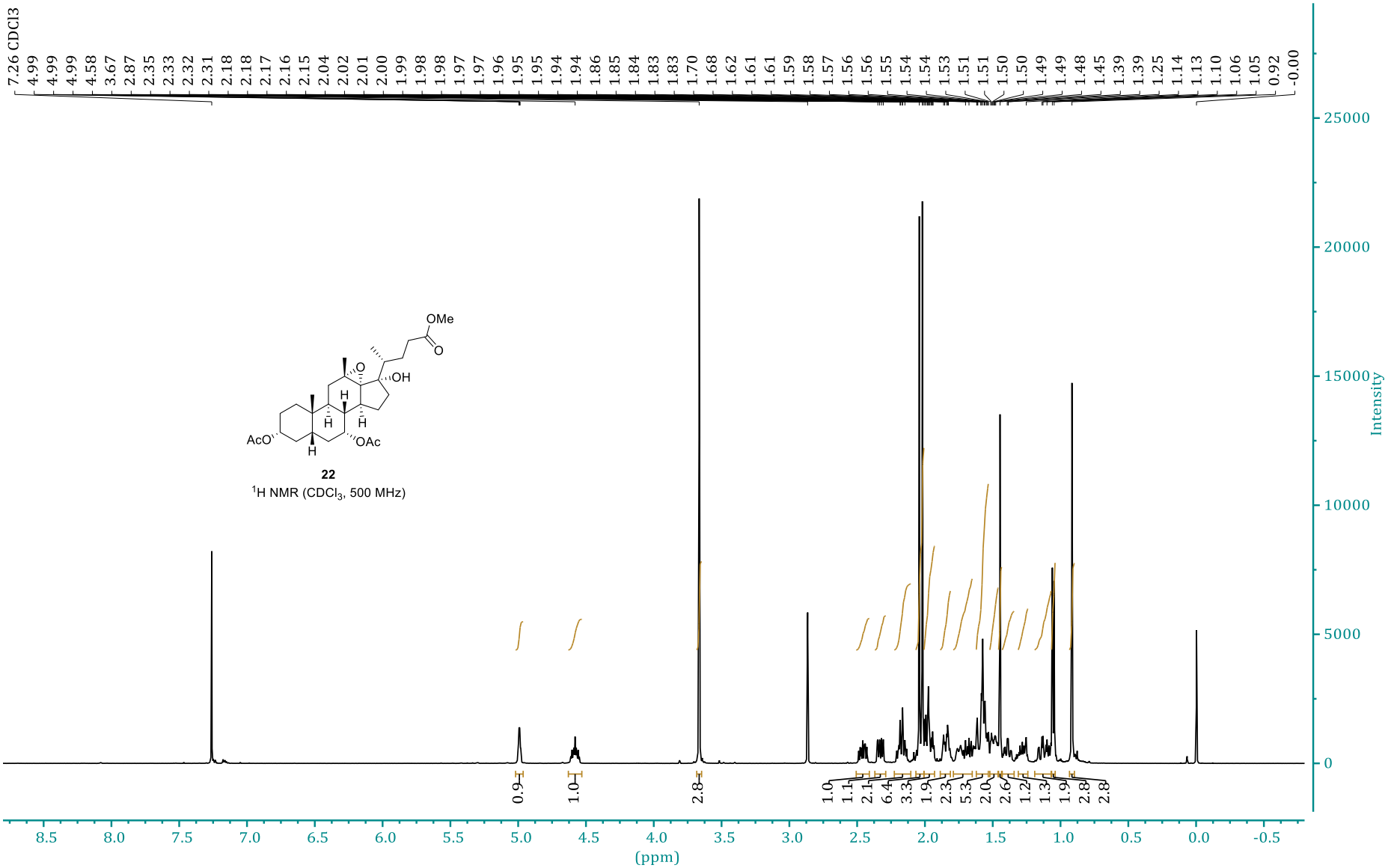
OH
O
OH
O
H
H
H
HO
OH
H
25
1H NMR (CD3OD, 500 MHz)
1.0 2.3 1.1 0.9 0.9 1.1 2.8 1.2 0.8 1.7 0.6 7.0 2.1 4.3 0.8 3.3
Intensity
22000 20000 18000 16000 14000 12000 10000 8000 6000 4000 2000 0
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)


213.36
180.01
177.28
139.04
72.86
72.12
68.53
50.65
49.00 CD3OD
43.10
42.53
40.31
40.27
39.76
36.23
35.91
35.76
33.48
31.29
31.12
29.87
29.47
28.80
23.16
19.17
OH
O
OH
H
O
H
H
HO
H
OH
25
13C NMR (CD3OD, 126 MHz)
70000
60000
50000
40000
30000
20000
10000
0
Intensity
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)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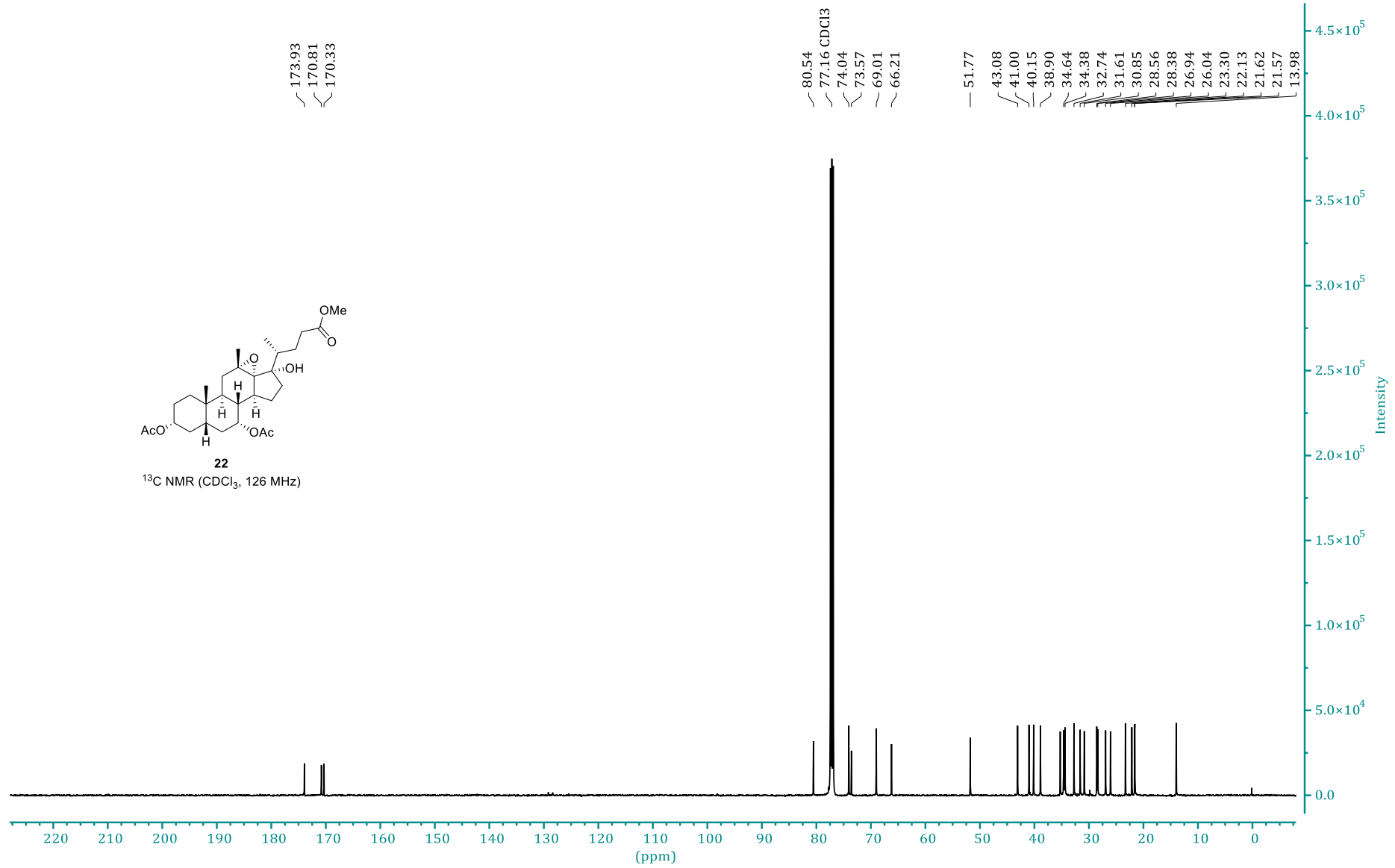
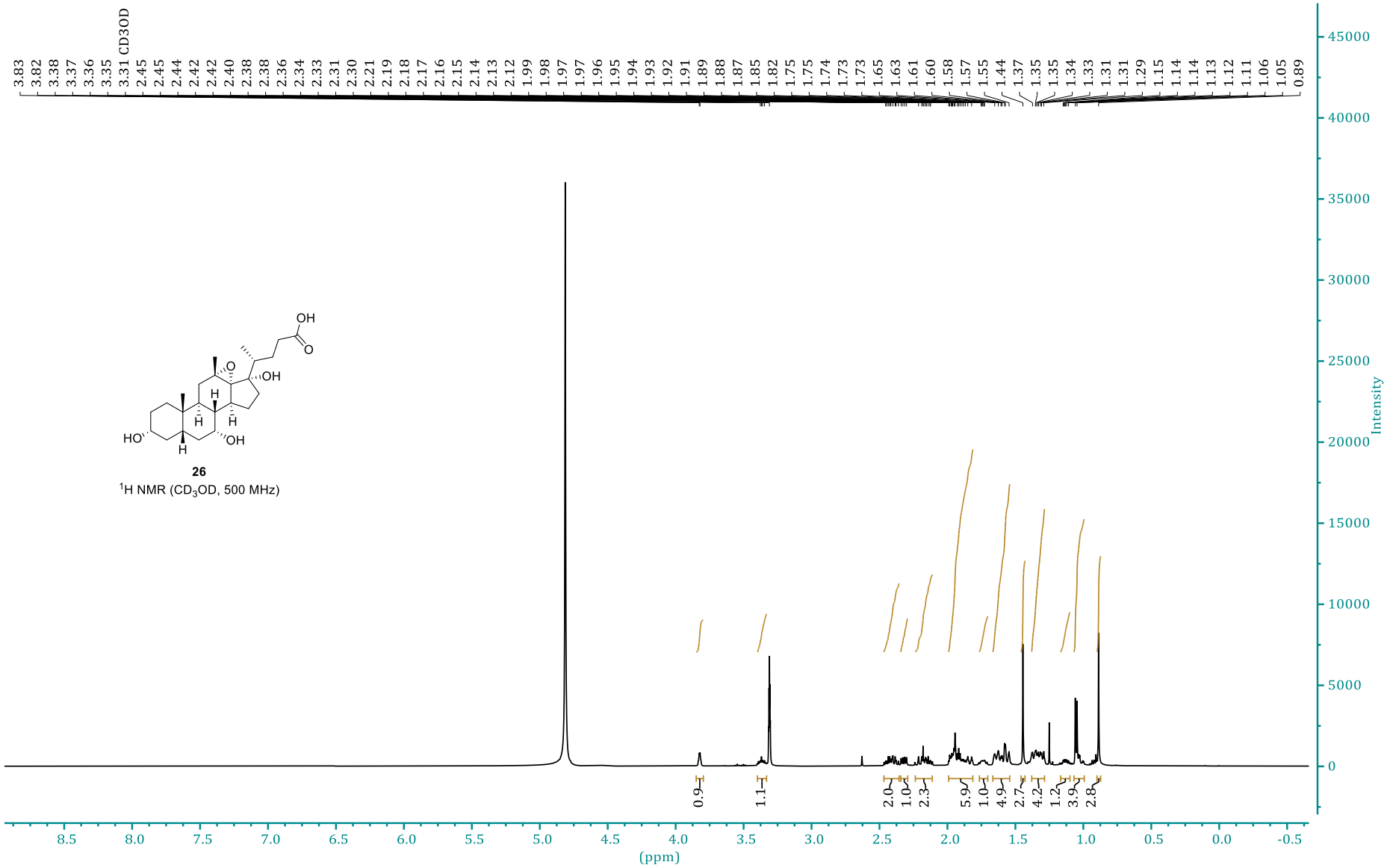
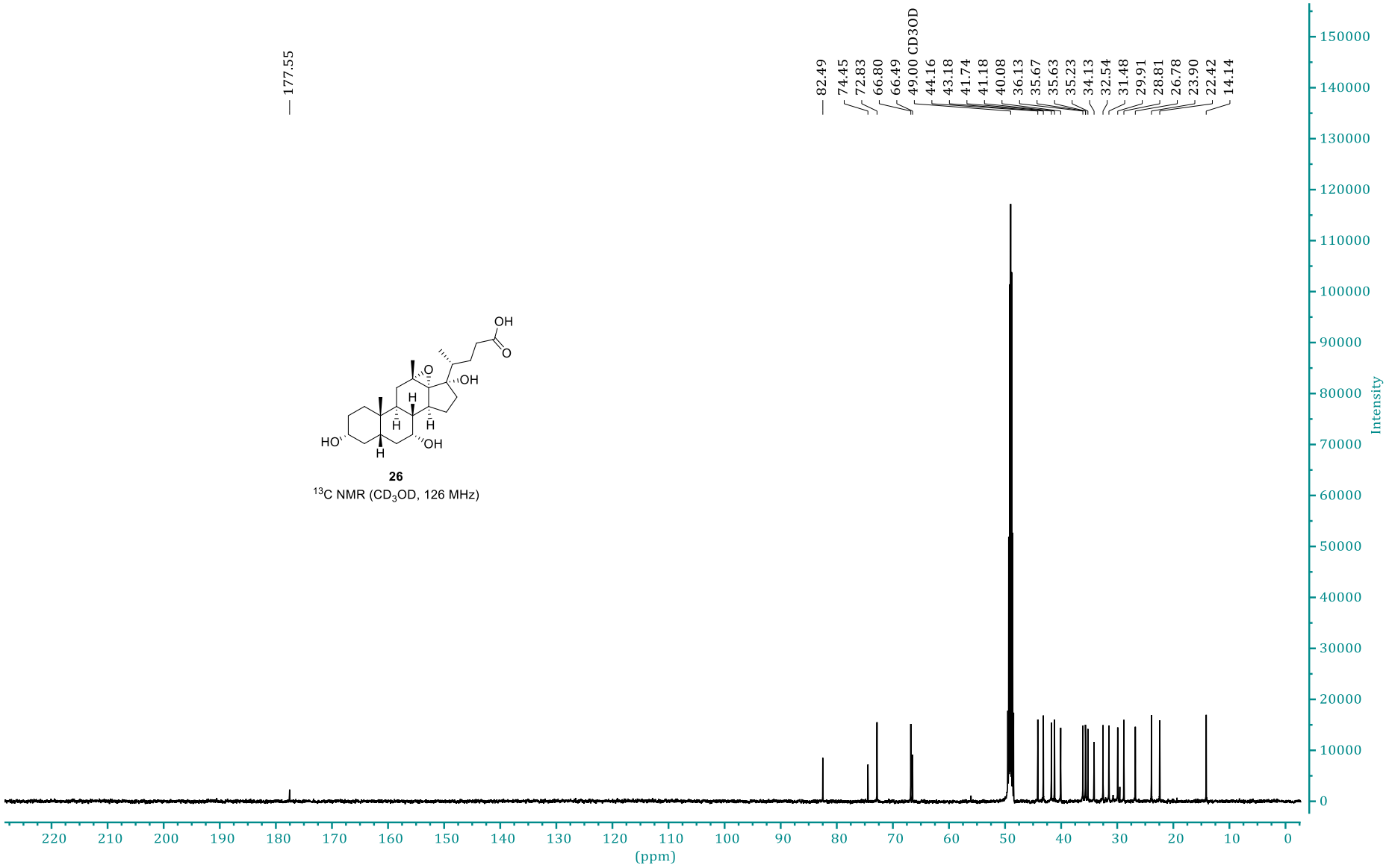
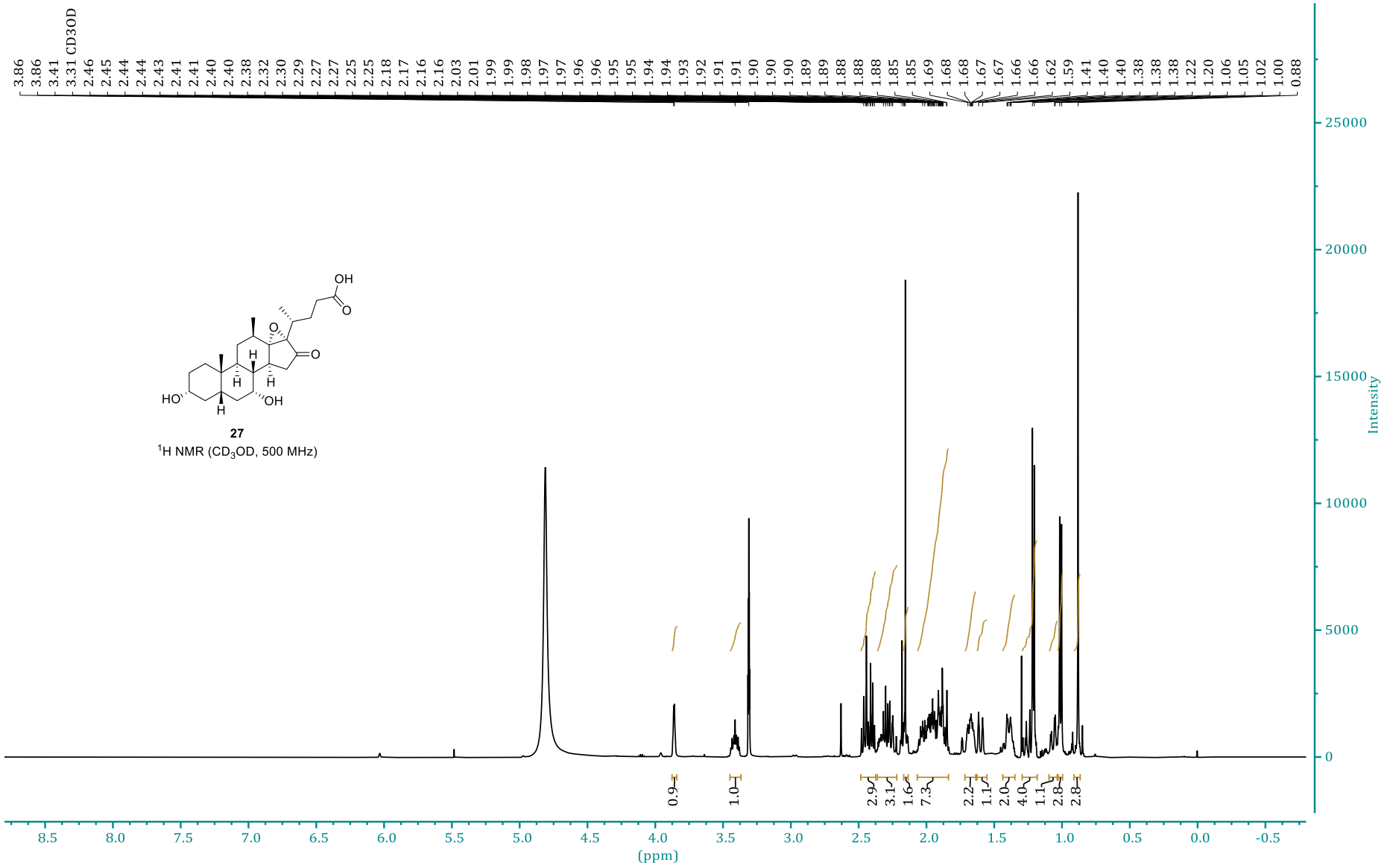
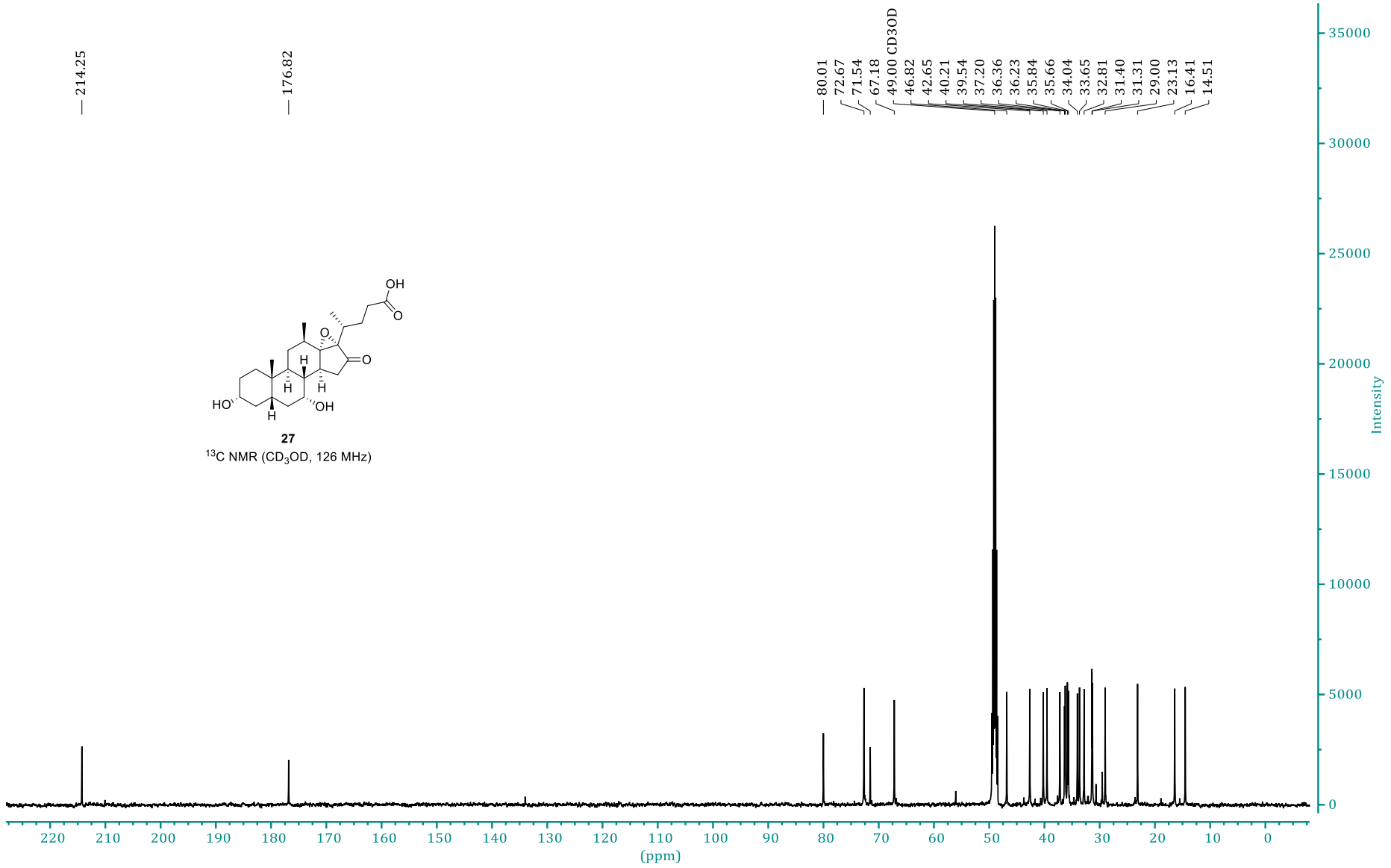
4.99 4.99 4.99 4.58 3.67 2.87 2.35 2.33 2.32 2.31 2.18 2.18 2.17 2.16 2.15 2.04 2.02 2.01 2.00 1.99 1.98 1.98 1.97 1.97 1.96 1.95 1.95 1.94 1.94 1.86 1.85 1.84 1.83 1.83 1.70 1.68 1.62 1.61 1.61 1.59 1.58 1.57 1.56 1.56 1.55 1.54 1.54 1.53 1.51 1.51 1.50 1.50 1.49 1.49 1.48 1.45 1.39 1.39 1.25 1.14 1.13 1.10 1.06 1.05 0.92 -0.00
OMe
O
OH
O
H
H
H
AcO
OAc
H
22
1H NMR (CDCl3, 500 MHz)
Intensity
25000
20000
15000
10000
5000
0
0.9 1.0 2.8 1.0 1.1 2.1 6.4 3.3 1.9 2.3 5.3 2.0 2.6 1.2 1.3 1.9 2.8 2.8
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)

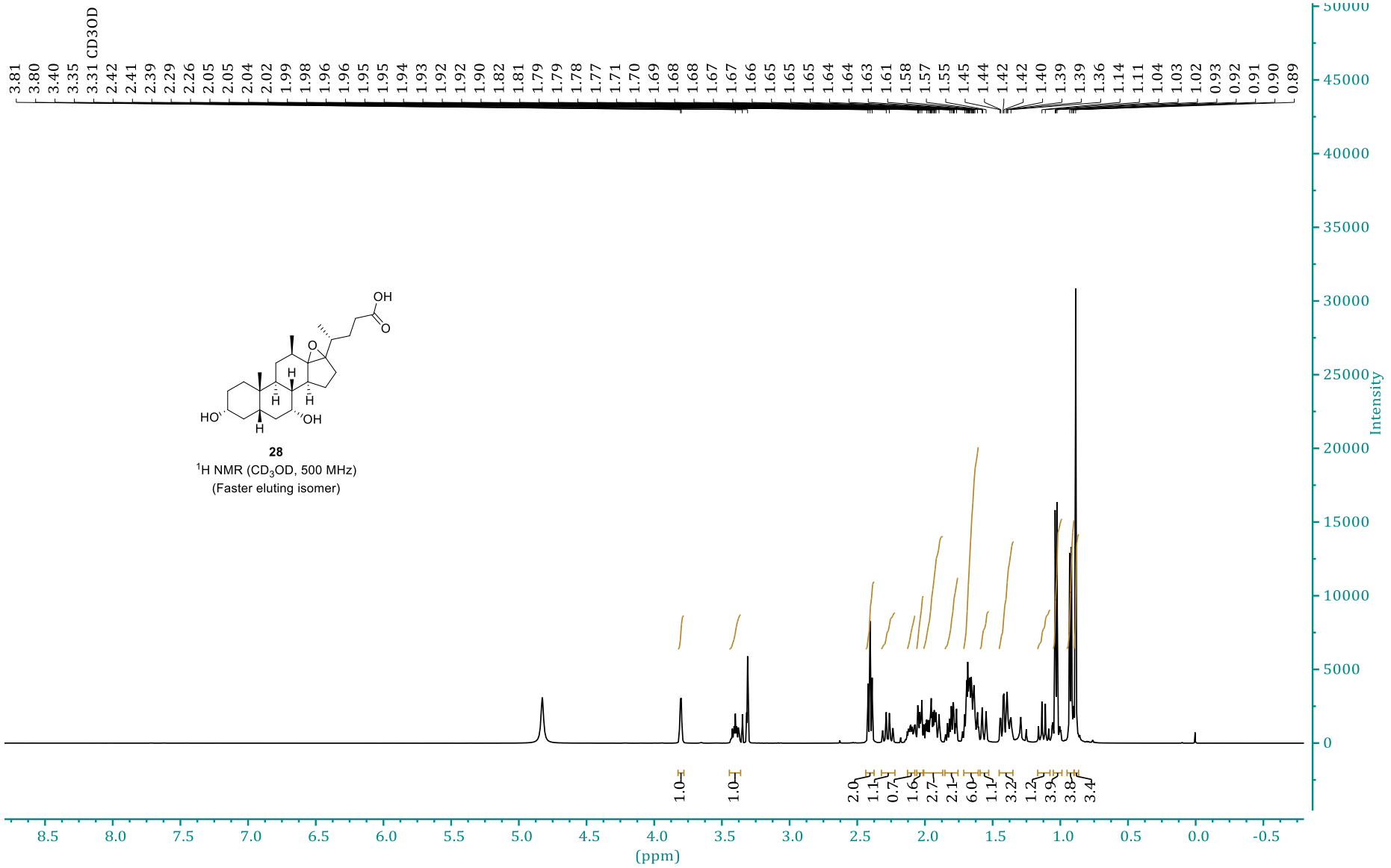

173.93
170.81
170.33
80.54
77.16 CDCl3
74.04
73.57
69.01
66.21
51.77
43.08
41.00
40.15
38.90
34.64
34.38
32.74
31.61
30.85
28.56
28.38
26.94
26.04
23.30
22.13
21.62
21.57
13.98
OMe
O
OH
O
H
H
H
AcO
OAc
H
22
13C NMR (CDCl3, 126 MHz)
4.5×10^5
4.0×10^5
3.5×10^5
3.0×10^5
2.5×10^5
2.0×10^5
1.5×10^5
1.0×10^5
5.0×10^4
0.0
Intensity
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)


3.83 3.82 3.38 3.37 3.36 3.35 3.31 CD3OD 2.45 2.44 2.42 2.42 2.40 2.38 2.38 2.36 2.34 2.33 2.31 2.30 2.21 2.19 2.18 2.17 2.16 2.15 2.14 2.13 2.12 1.99 1.98 1.97 1.97 1.96 1.95 1.94 1.93 1.92 1.91 1.89 1.88 1.87 1.85 1.82 1.75 1.75 1.74 1.73 1.73 1.65 1.63 1.61 1.60 1.58 1.57 1.55 1.44 1.37 1.35 1.35 1.34 1.33 1.31 1.31 1.29 1.15 1.14 1.14 1.13 1.12 1.11 1.06 1.05 0.89
OH
O
O
OH
H
H
H
HO
OH
H
26
1H NMR (CD3OD, 500 MHz)
0.9 1.1 2.0 1.0 2.3 5.9 1.0 4.9 2.7 4.2 1.2 3.9 2.8
Intensity
(ppm)


177.55
82.49
74.45
72.83
66.80
66.49
49.00 CD3OD
44.16
43.18
41.74
41.18
40.08
36.13
35.67
35.63
35.23
34.13
32.54
31.48
29.91
28.81
26.78
23.90
22.42
14.14
OH
O
O
OH
H
H
H
HO
OH
H
26
13C NMR (CD3OD, 126 MHz)
Intensity
150000
140000
130000
120000
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)


3.86 3.86 3.41 3.31 CD3OD 2.46 2.45 2.44 2.44 2.43 2.41 2.41 2.40 2.40 2.38 2.32 2.30 2.29 2.27 2.27 2.25 2.25 2.18 2.17 2.16 2.16 2.03 2.01 1.99 1.99 1.98 1.97 1.97 1.96 1.96 1.95 1.95 1.94 1.94 1.93 1.92 1.91 1.91 1.90 1.90 1.90 1.89 1.89 1.88 1.88 1.88 1.85 1.85 1.69 1.68 1.68 1.67 1.67 1.66 1.66 1.62 1.59 1.41 1.40 1.40 1.38 1.38 1.38 1.22 1.20 1.06 1.05 1.02 1.00 0.88
OH
O
O
H
O
HO
H
H
H
OH
27
1H NMR (CD3OD, 500 MHz)
25000
20000
15000
10000
5000
0
Intensity
0.9 1.0 2.9 3.1 1.6 7.3 2.2 1.1 2.0 4.0 1.1 2.8 2.8
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)


214.25
176.82
80.01
72.67
71.54
67.18
49.00 CD3OD
46.82
42.65
40.21
39.54
37.20
36.36
36.23
35.84
35.66
34.04
33.65
32.81
31.40
31.31
29.00
23.13
16.41
14.51
OH
O
O
H
H
H
O
HO
OH
H
27
13C NMR (CD3OD, 126 MHz)
Intensity
35000
30000
25000
20000
15000
10000
5000
0
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)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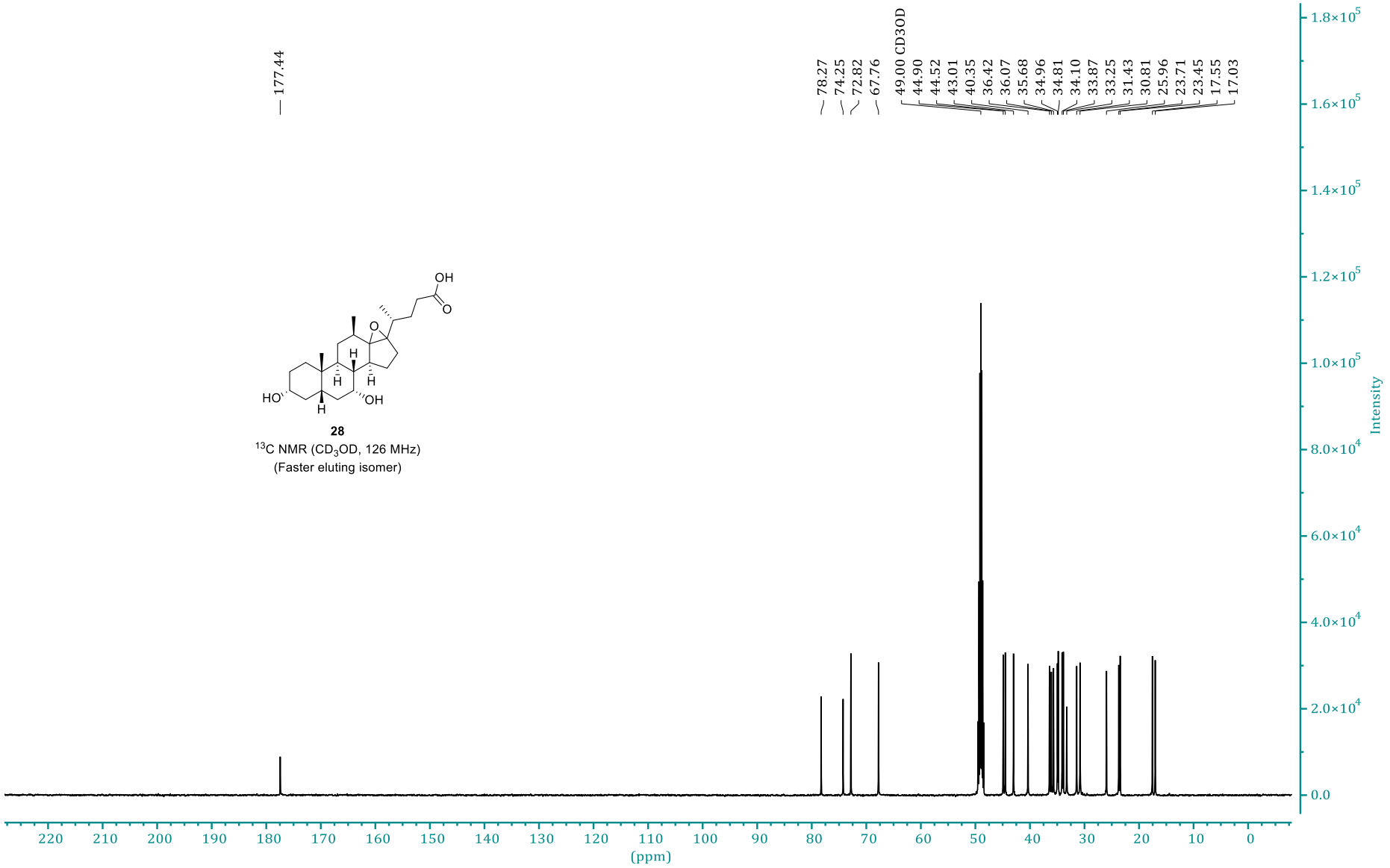
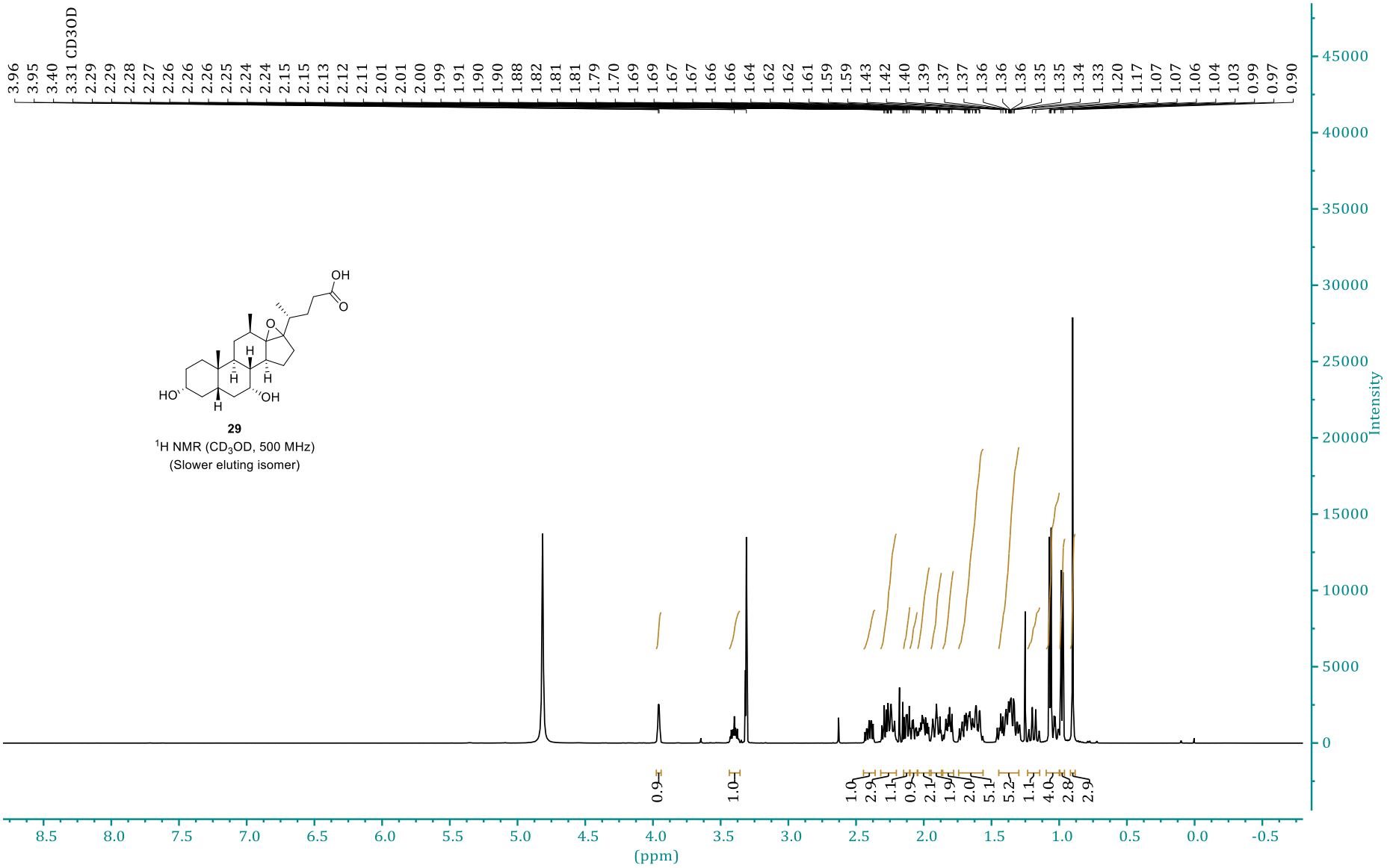
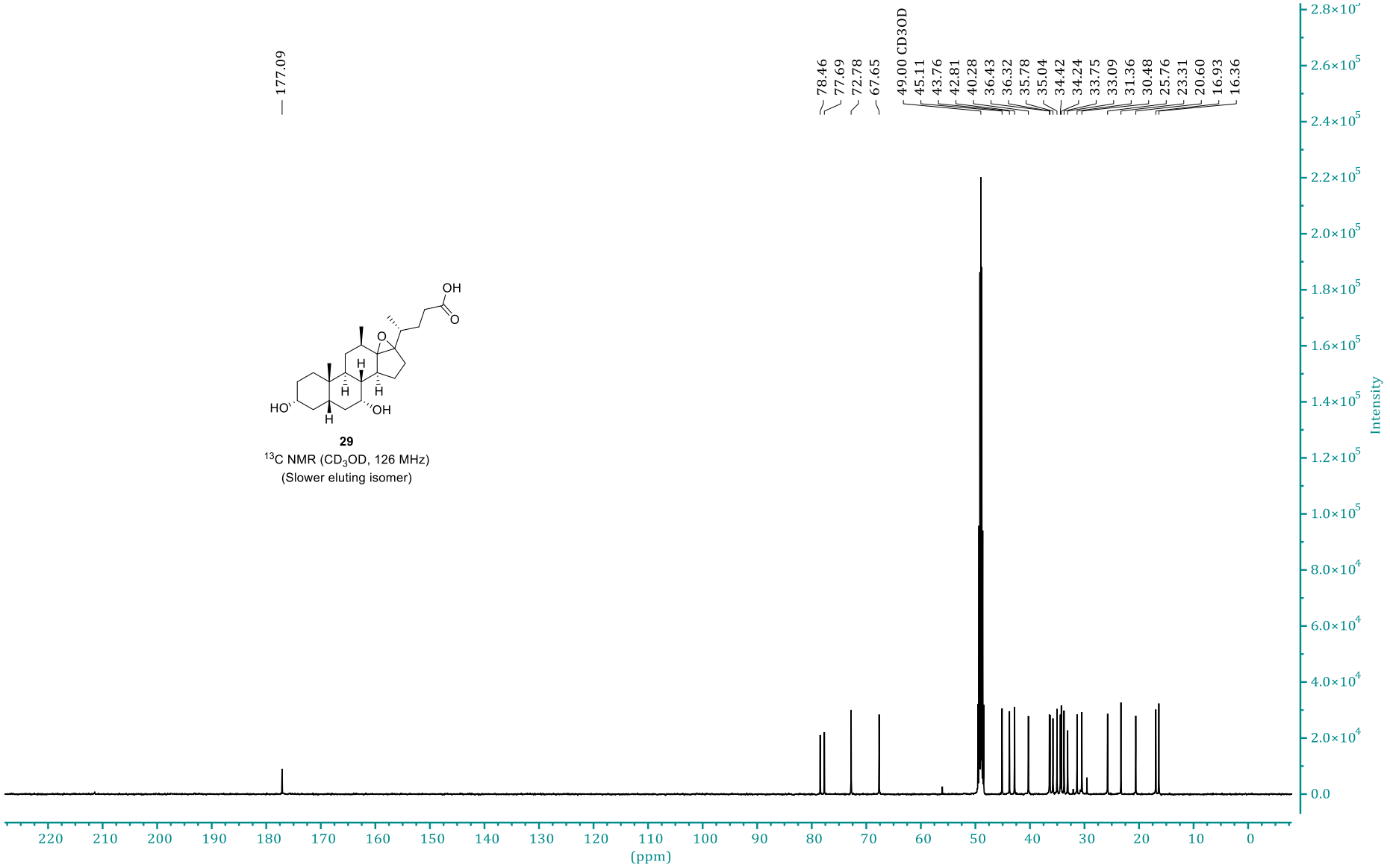
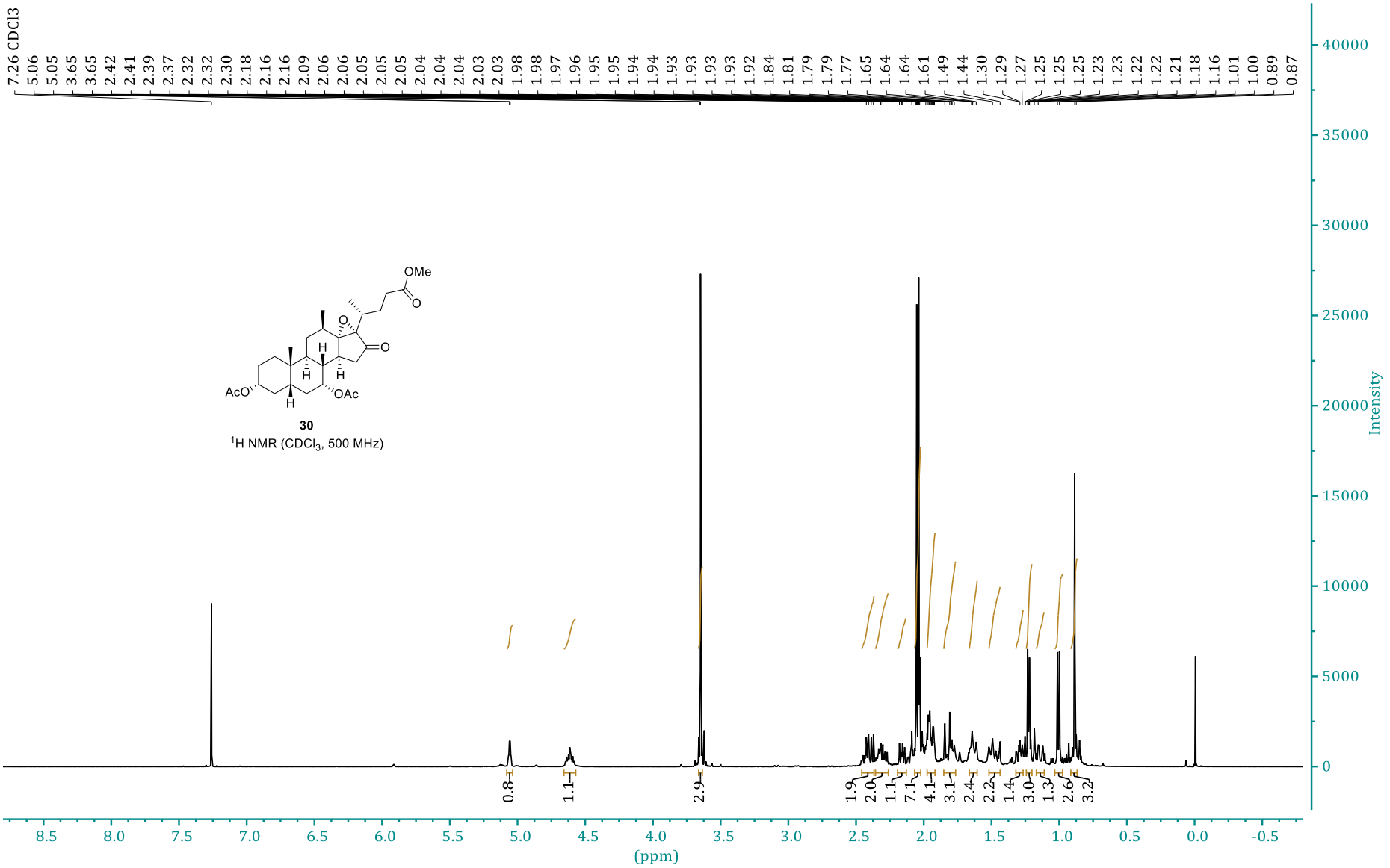
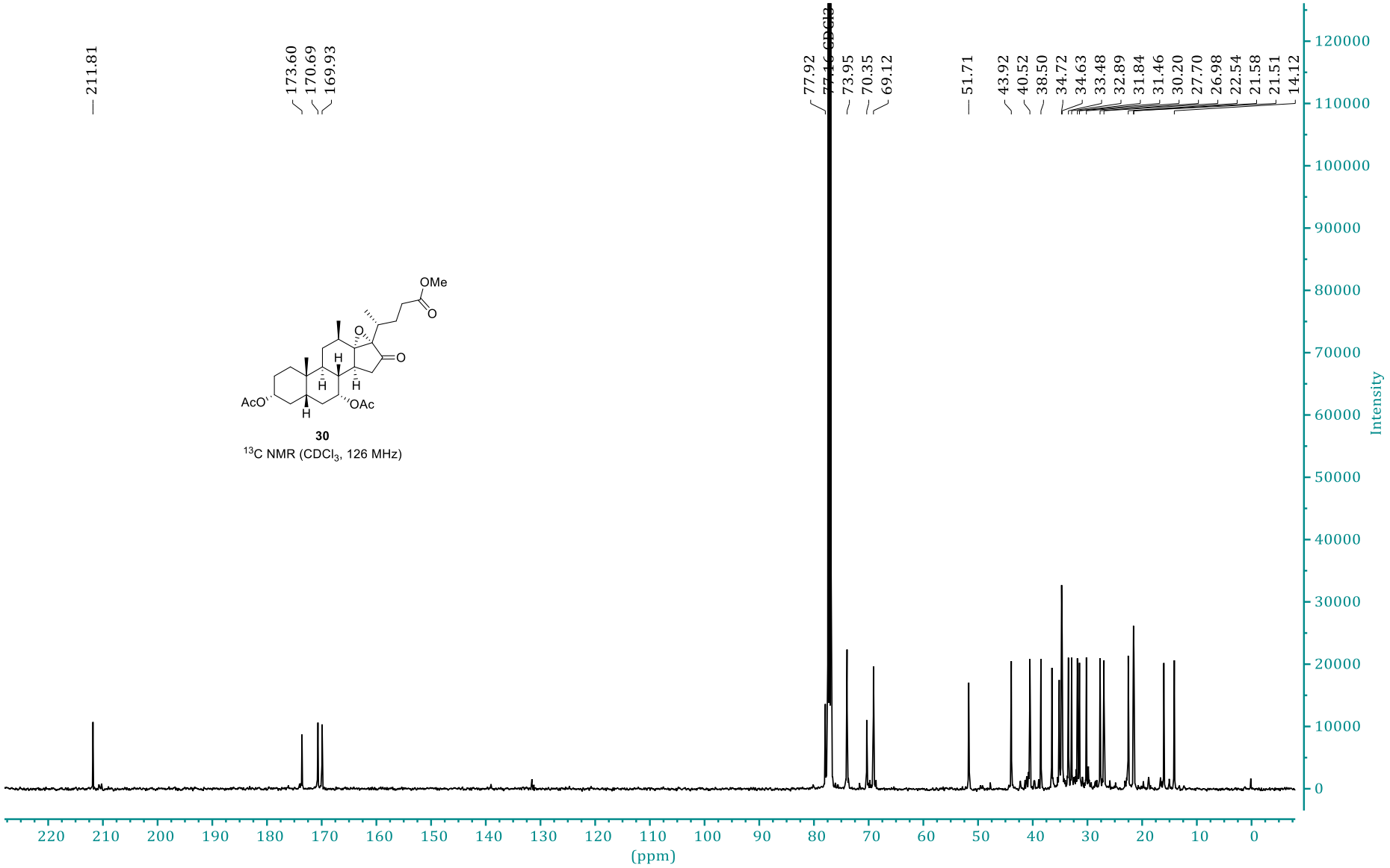
OH
O
O
H
H
H
HO
H
OH
28
1H NMR (CD3OD, 500 MHz)
(Faster eluting isomer)
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
Intensity
1.0 1.0 2.0 1.1 0.7 1.6 2.7 2.1 6.0 1.1 3.2 1.2 3.9 3.8 3.4
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)


177.44
78.27
74.25
72.82
67.76
49.00 CD3OD
44.90
44.52
43.01
40.35
36.42
36.07
35.68
34.96
34.81
34.10
33.87
33.25
31.43
30.81
25.96
23.71
23.45
17.55
17.03
OH
O
O
H
H
H
HO
OH
28
13C NMR (CD3OD, 126 MHz)
(Faster eluting isomer)
Intensity
1.8×10^5
1.6×10^5
1.4×10^5
1.2×10^5
1.0×10^5
8.0×10^4
6.0×10^4
4.0×10^4
2.0×10^4
0.0
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)


3.96 3.95 3.40 3.31 CD3OD 2.29 2.29 2.28 2.27 2.26 2.26 2.26 2.25 2.24 2.24 2.15 2.15 2.13 2.12 2.11 2.01 2.01 2.00 1.99 1.91 1.90 1.90 1.88 1.82 1.81 1.81 1.79 1.70 1.69 1.69 1.67 1.67 1.66 1.66 1.64 1.62 1.62 1.61 1.59 1.59 1.43 1.42 1.40 1.39 1.37 1.37 1.36 1.36 1.36 1.35 1.35 1.34 1.33 1.20 1.17 1.07 1.07 1.06 1.04 1.03 0.99 0.97 0.90
OH
O
O
H
H
H
HO
OH
H
29
1H NMR (CD3OD, 500 MHz)
(Slower eluting isomer)
Intensity
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
0.9 1.0 1.0 2.9 1.1 0.9 2.1 1.9 2.0 5.1 5.2 1.1 4.0 2.8 2.9
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)

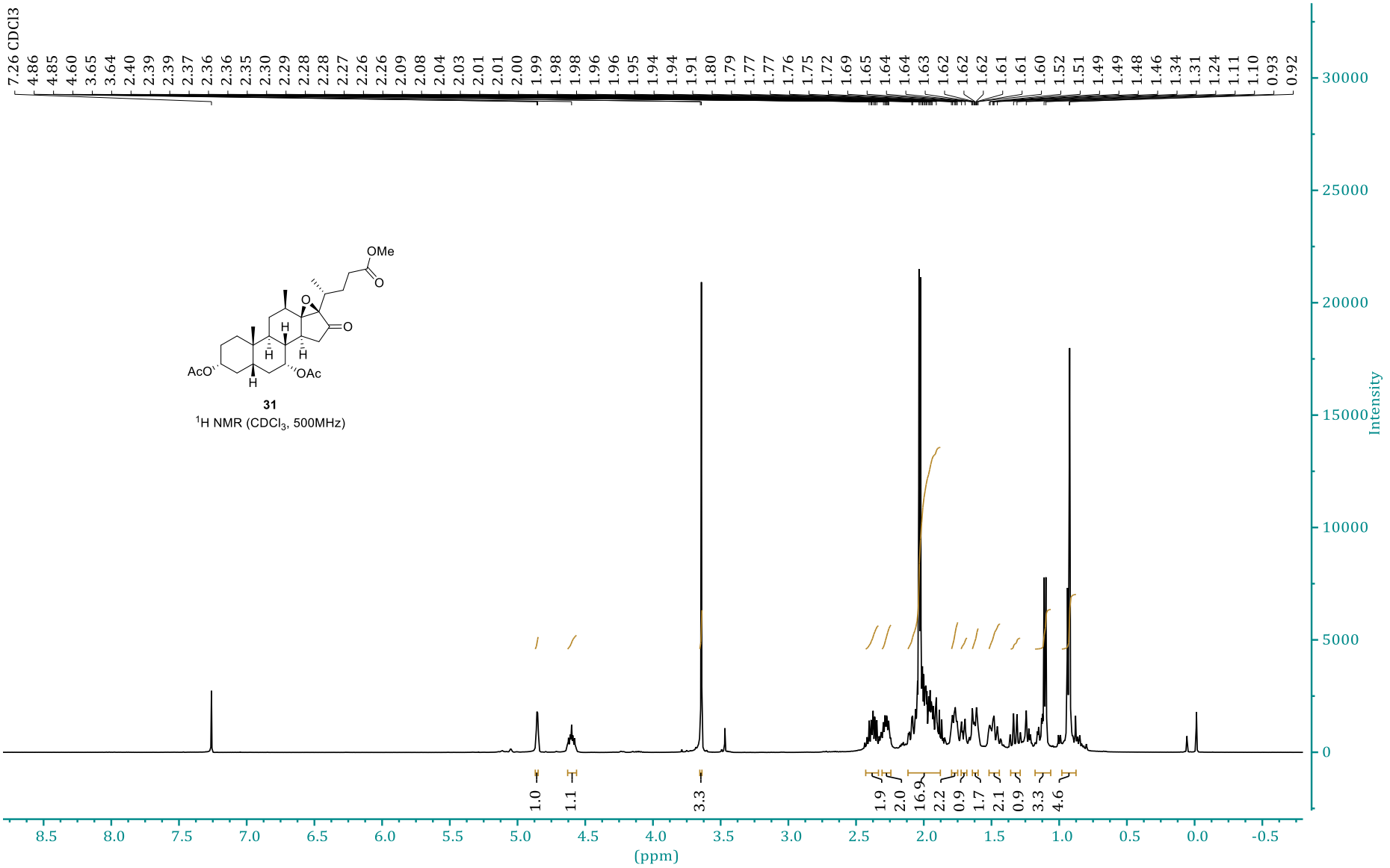

177.09
78.46
77.69
72.78
67.65
49.00 CD3OD
45.11
43.76
42.81
40.28
36.43
36.32
35.78
35.04
34.42
34.24
33.75
33.09
31.36
30.48
25.76
23.31
20.60
16.93
16.36
OH
O
O
H
H
H
HO
OH
H
29
13C NMR (CD3OD, 126 MHz)
(Slower eluting isomer)
Intensity
(ppm)

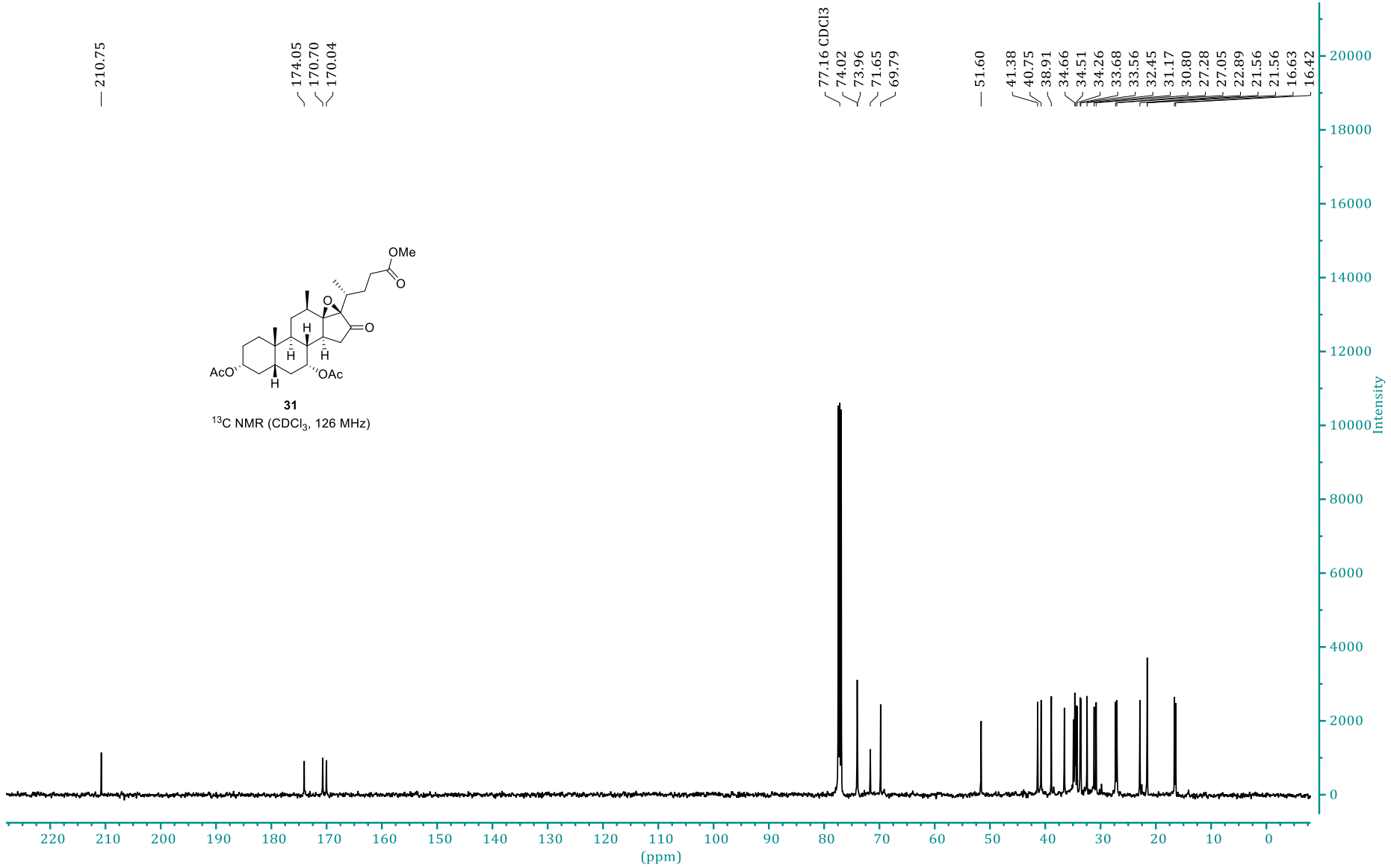

7.26 CDCl3
5.06 5.05 3.65 3.65 2.42 2.41 2.39 2.37 2.32 2.32 2.30 2.18 2.16 2.16 2.09 2.06 2.06 2.05 2.05 2.05 2.04 2.04 2.04 2.03 2.03 1.98 1.98 1.97 1.96 1.95 1.95 1.94 1.94 1.93 1.93 1.93 1.93 1.92 1.84 1.81 1.79 1.79 1.77 1.65 1.64 1.64 1.61 1.49 1.44 1.30 1.29 1.27 1.25 1.25 1.25 1.23 1.23 1.22 1.22 1.21 1.18 1.16 1.01 1.00 0.89 0.87
OMe
O
O
O
H
H
H
H
AcO
OAc
30
1H NMR (CDCl3, 500 MHz)
0.8 1.1 2.9 1.9 2.0 1.1 7.1 4.1 3.1 2.4 2.2 1.4 3.0 1.3 2.6 3.2
40000 35000 30000 25000 20000 15000 10000 5000 0
Intensity
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)



30

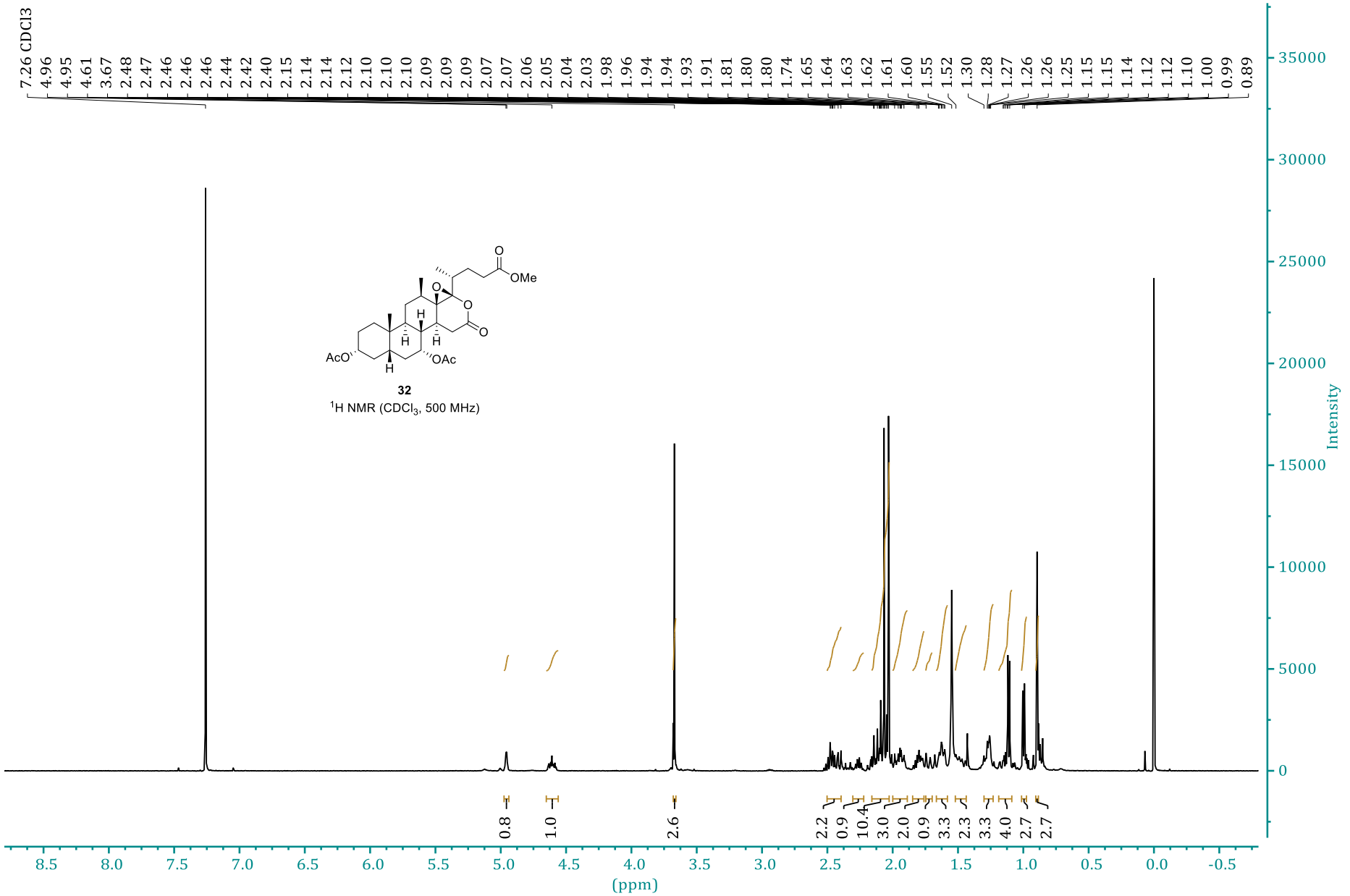
^{13}C NMR ($CDCl_3$, 126 MHz)

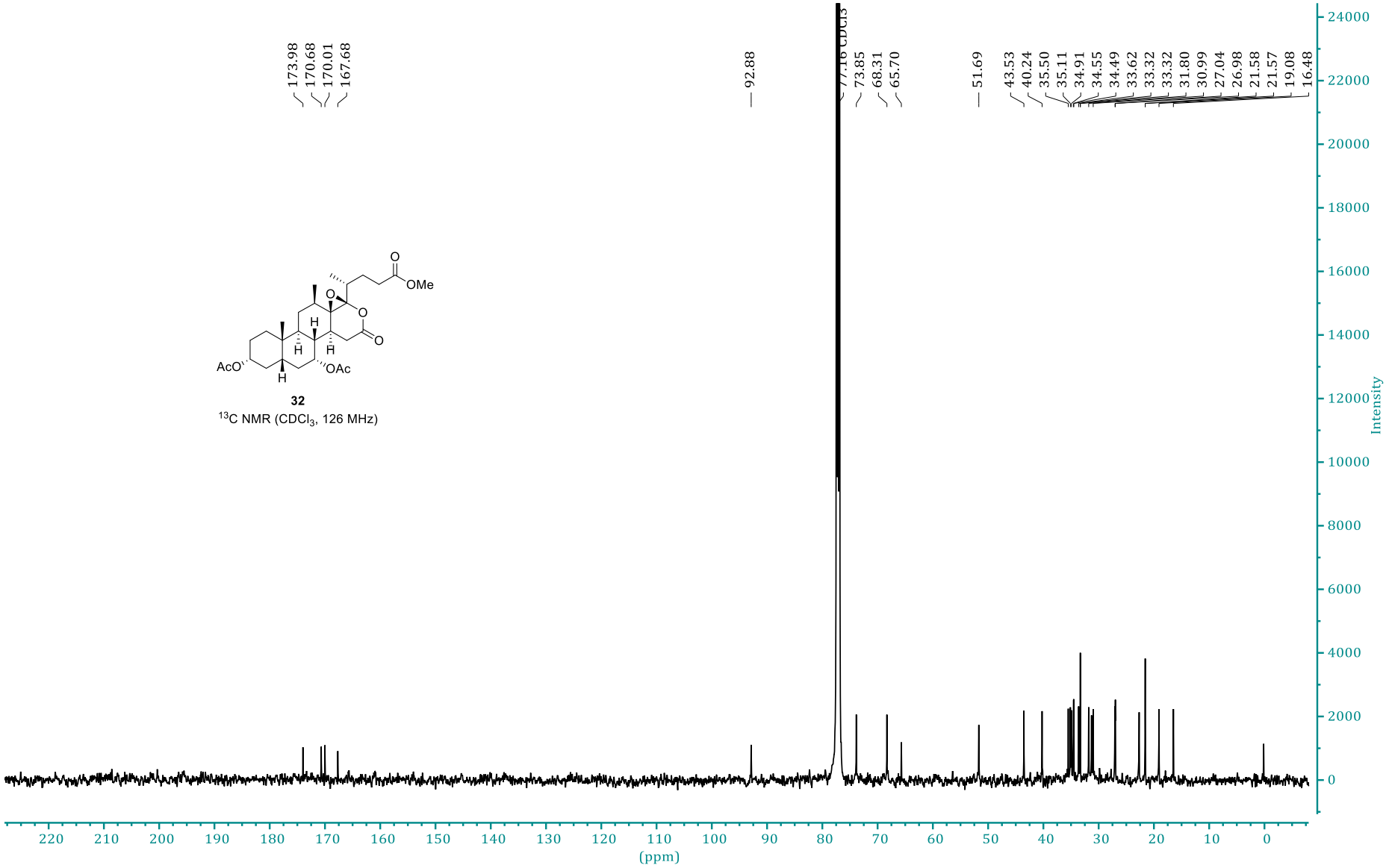

7.26 CDCl3
4.86 4.85 4.60 3.65 3.64 2.40 2.39 2.39 2.37 2.36 2.36 2.35 2.30 2.29 2.28 2.28 2.27 2.26 2.26 2.09 2.08 2.04 2.03 2.01 2.01 2.00 1.99 1.98 1.98 1.96 1.96 1.95 1.94 1.94 1.91 1.80 1.79 1.77 1.77 1.76 1.75 1.72 1.69 1.65 1.64 1.64 1.63 1.62 1.62 1.62 1.61 1.61 1.60 1.52 1.51 1.49 1.49 1.48 1.46 1.34 1.31 1.24 1.11 1.10 0.93 0.92
OMe
O
O
O
H
H
H
H
AcO
OAc
31
1H NMR (CDCl3, 500MHz)
Intensity
30000
25000
20000
15000
10000
5000
0
1.0 1.1 3.3 1.9 2.0 16.9 2.2 0.9 1.7 2.1 0.9 3.3 4.6
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)



31

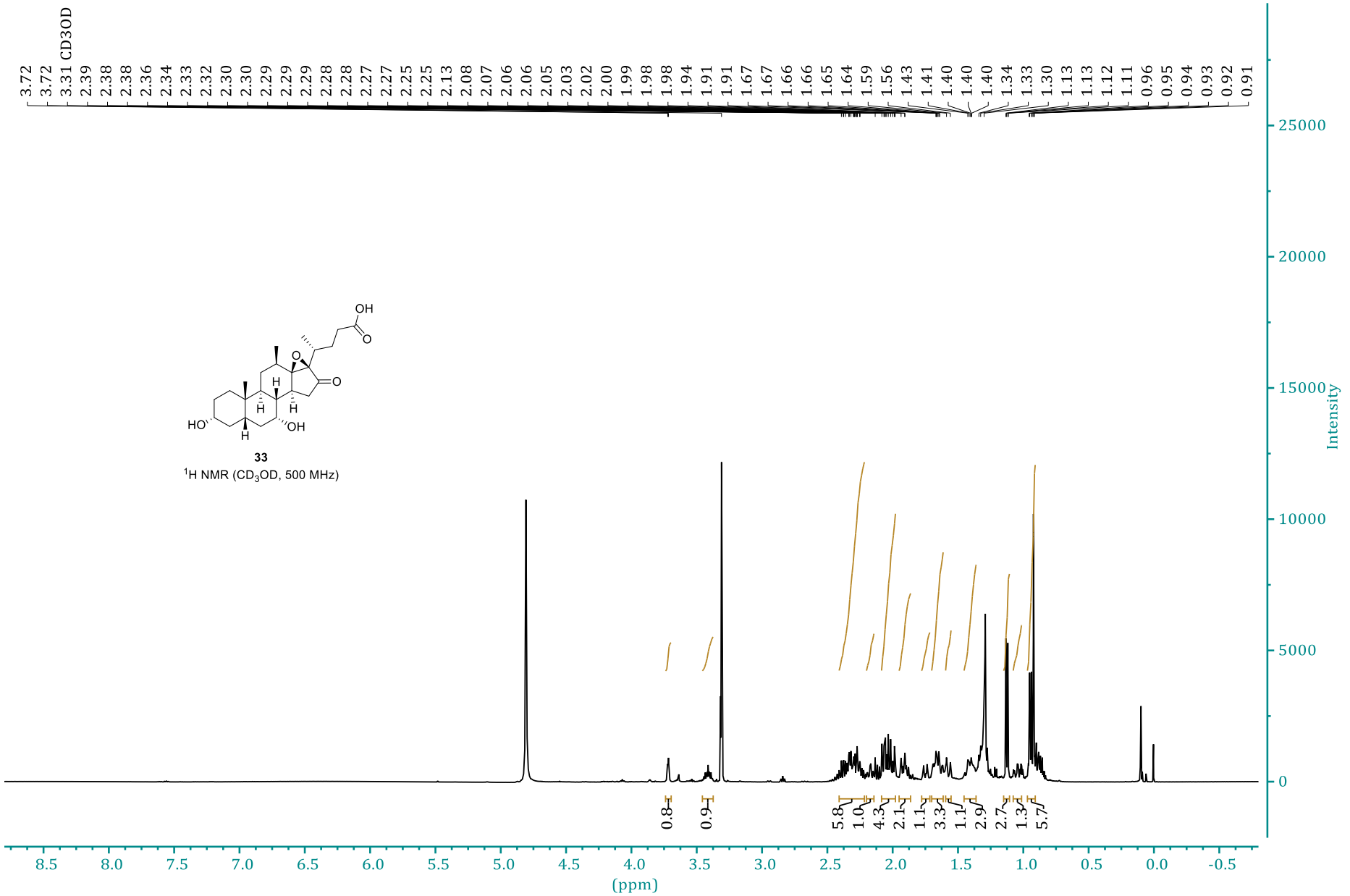
^{13}C NMR ($CDCl_3$, 126 MHz)

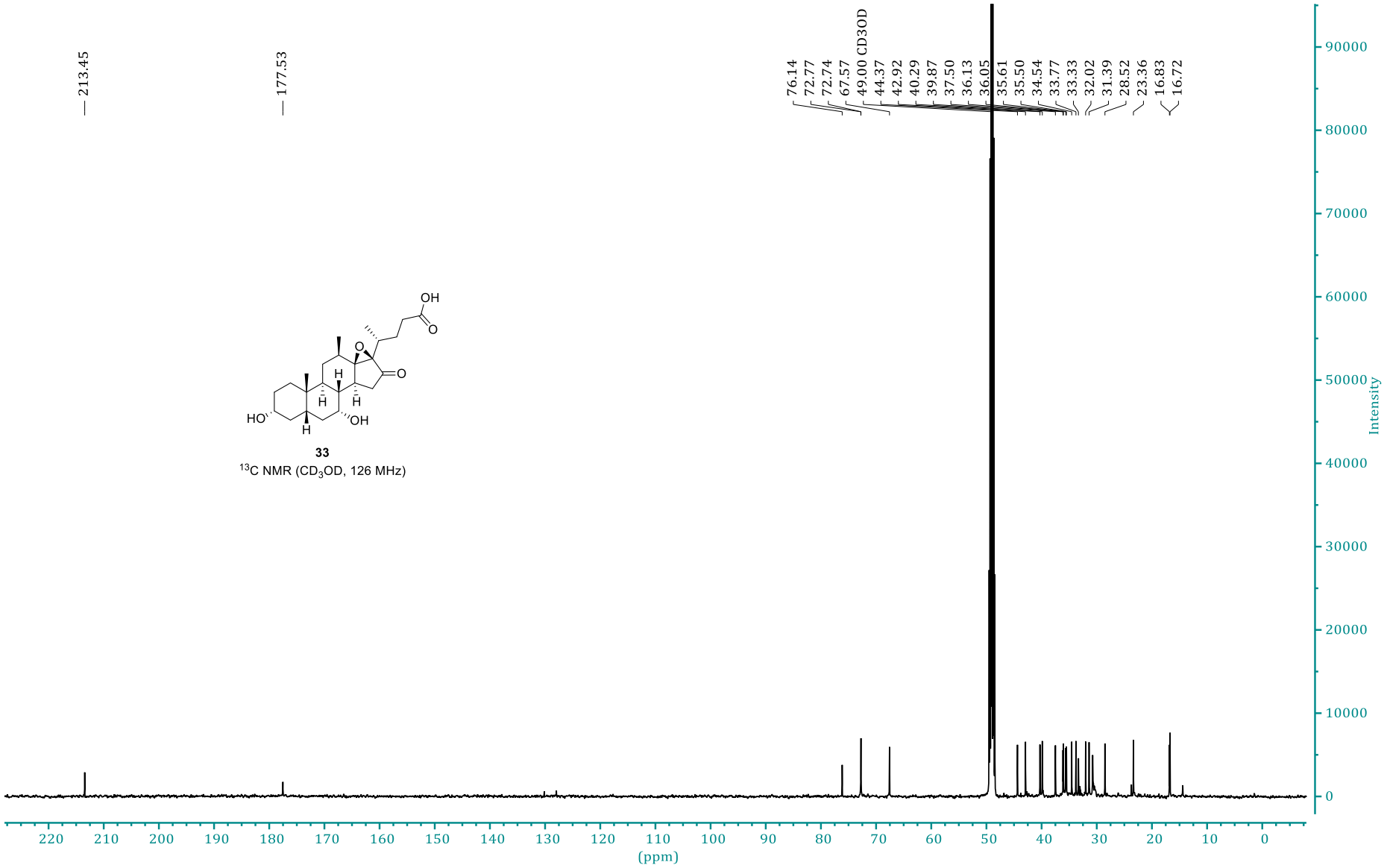

7.26 CDCl3
4.96 4.95 4.61 3.67 2.48 2.47 2.46 2.46 2.46 2.44 2.42 2.40 2.15 2.14 2.14 2.12 2.10 2.10 2.10 2.09 2.09 2.09 2.07 2.07 2.06 2.05 2.04 2.03 1.98 1.96 1.94 1.94 1.93 1.91 1.81 1.80 1.80 1.74 1.65 1.64 1.63 1.62 1.61 1.60 1.55 1.52 1.30 1.28 1.27 1.26 1.26 1.25 1.15 1.15 1.14 1.12 1.12 1.10 1.00 0.99 0.89
OMe
O
AcO
OAc
H
32
1H NMR (CDCl3, 500 MHz)
Intensity
35000
30000
25000
20000
15000
10000
5000
0
0.8 1.0 2.6 2.2 0.9 10.4 3.0 2.0 0.9 3.3 2.3 3.3 4.0 2.7 2.7
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)



32

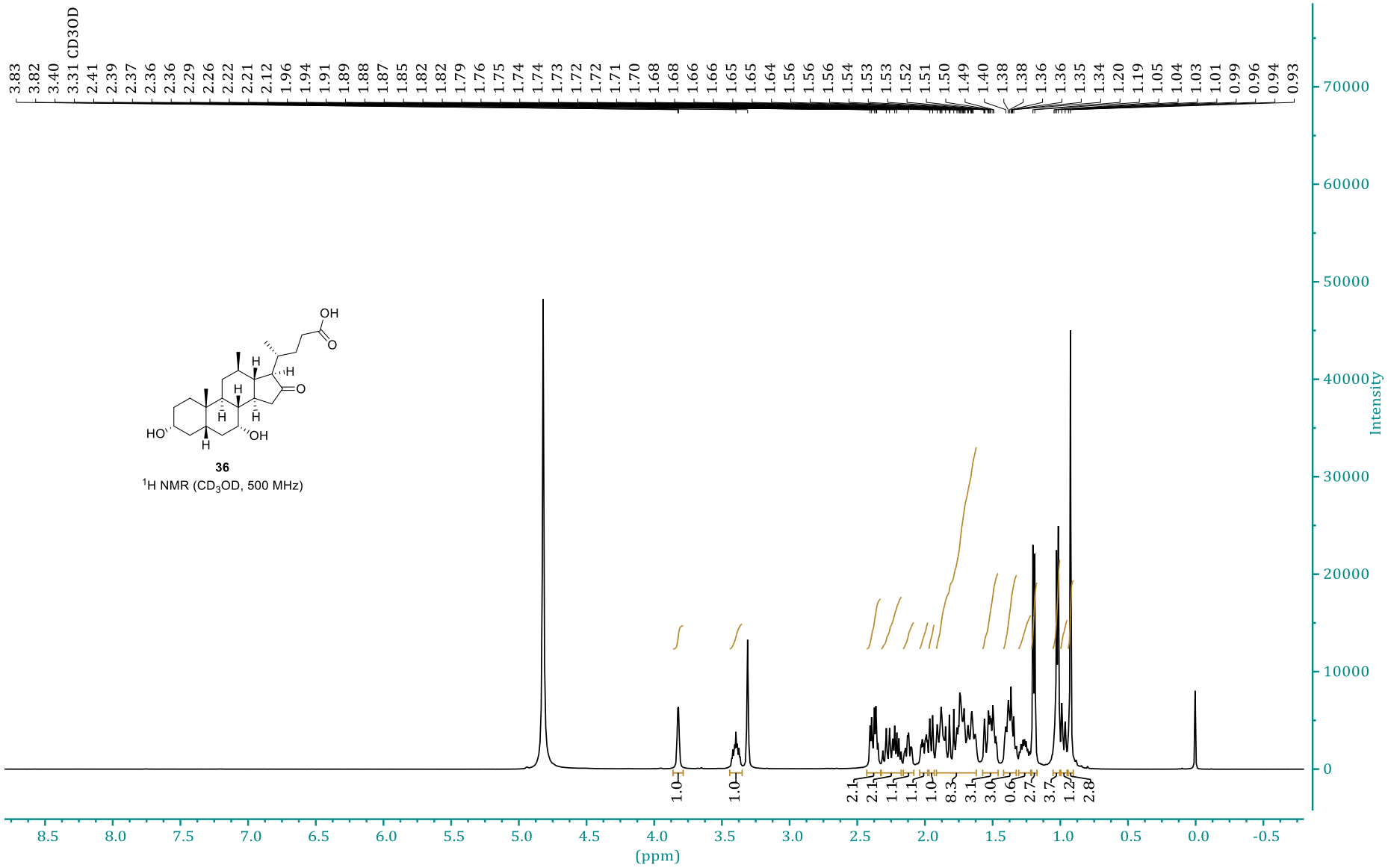
^{13}C NMR ($CDCl_3$, 126 MHz)

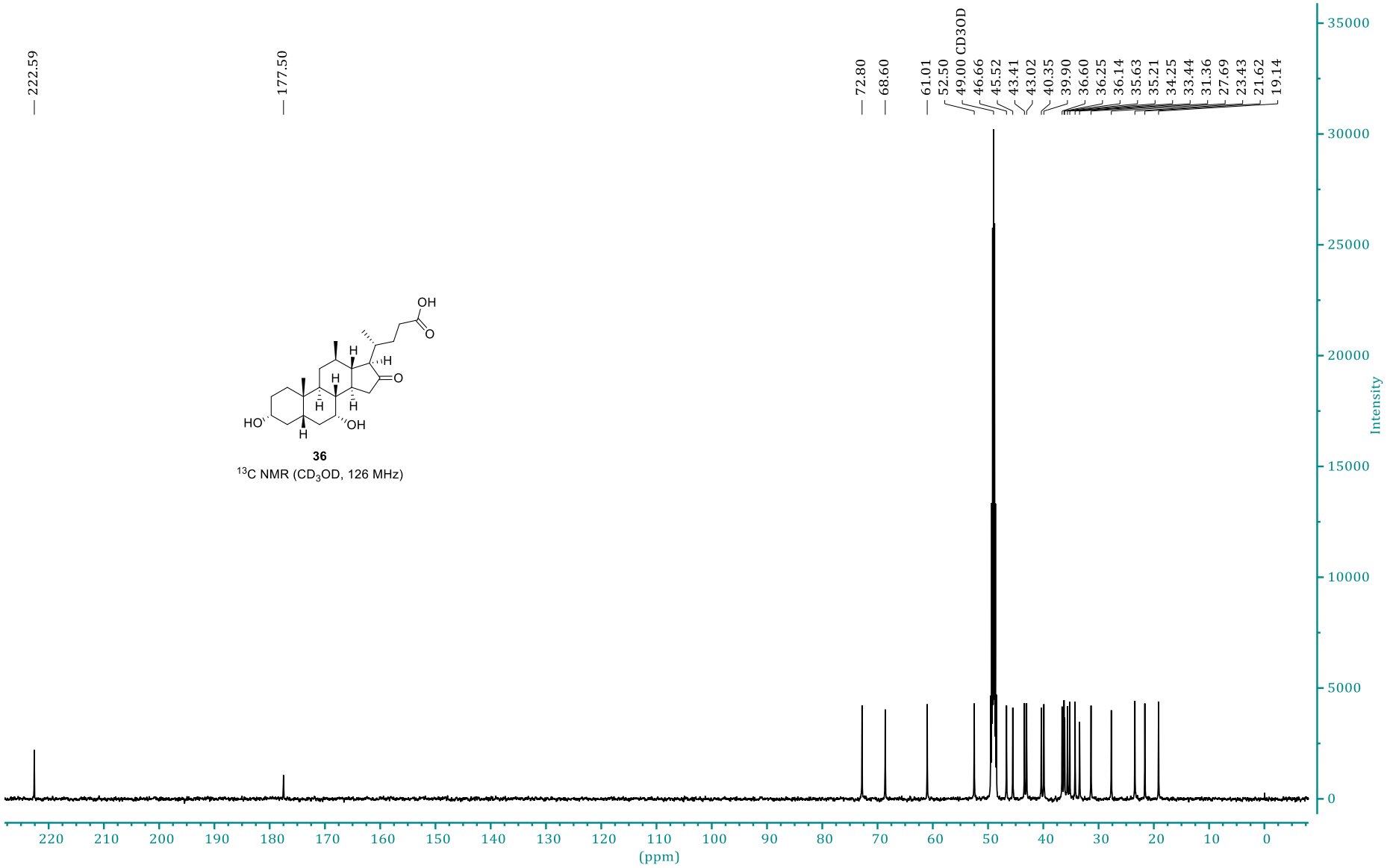

3.72
3.72
3.31 CD3OD
2.39
2.38
2.38
2.36
2.34
2.33
2.32
2.30
2.30
2.29
2.29
2.29
2.28
2.28
2.27
2.27
2.25
2.25
2.13
2.08
2.07
2.06
2.06
2.05
2.03
2.02
2.00
1.99
1.98
1.98
1.94
1.91
1.91
1.67
1.67
1.66
1.66
1.65
1.64
1.59
1.56
1.43
1.41
1.40
1.40
1.40
1.34
1.33
1.30
1.13
1.13
1.12
1.11
0.96
0.95
0.94
0.93
0.92
0.91
OH
O
O
H
H
H
HO
OH
H
33
1H NMR (CD3OD, 500 MHz)
25000
20000
15000
10000
5000
0
Intensity
0.8
0.9
5.8
1.0
4.3
2.1
1.1
3.3
1.1
2.9
2.7
1.3
5.7
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
(ppm)

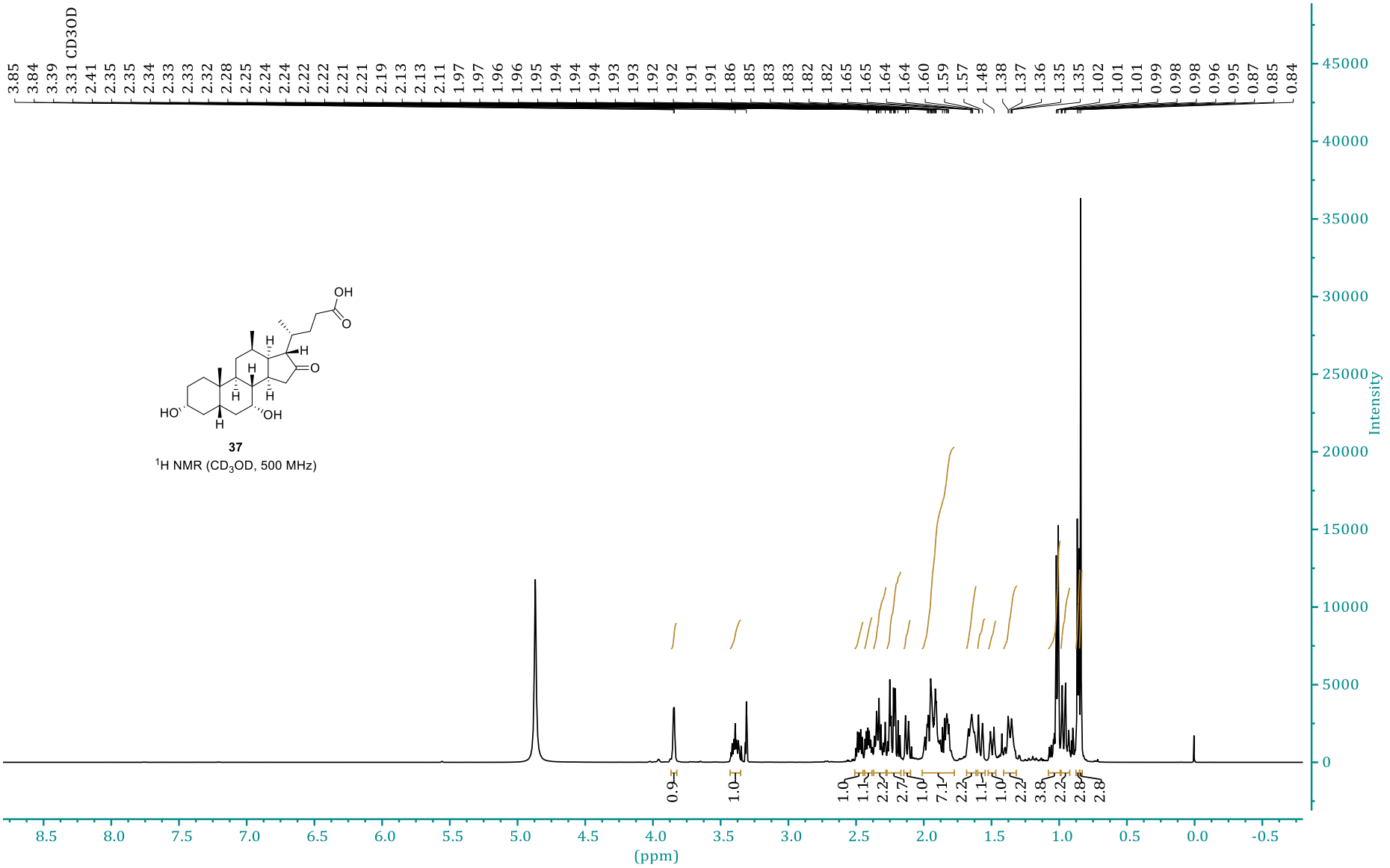


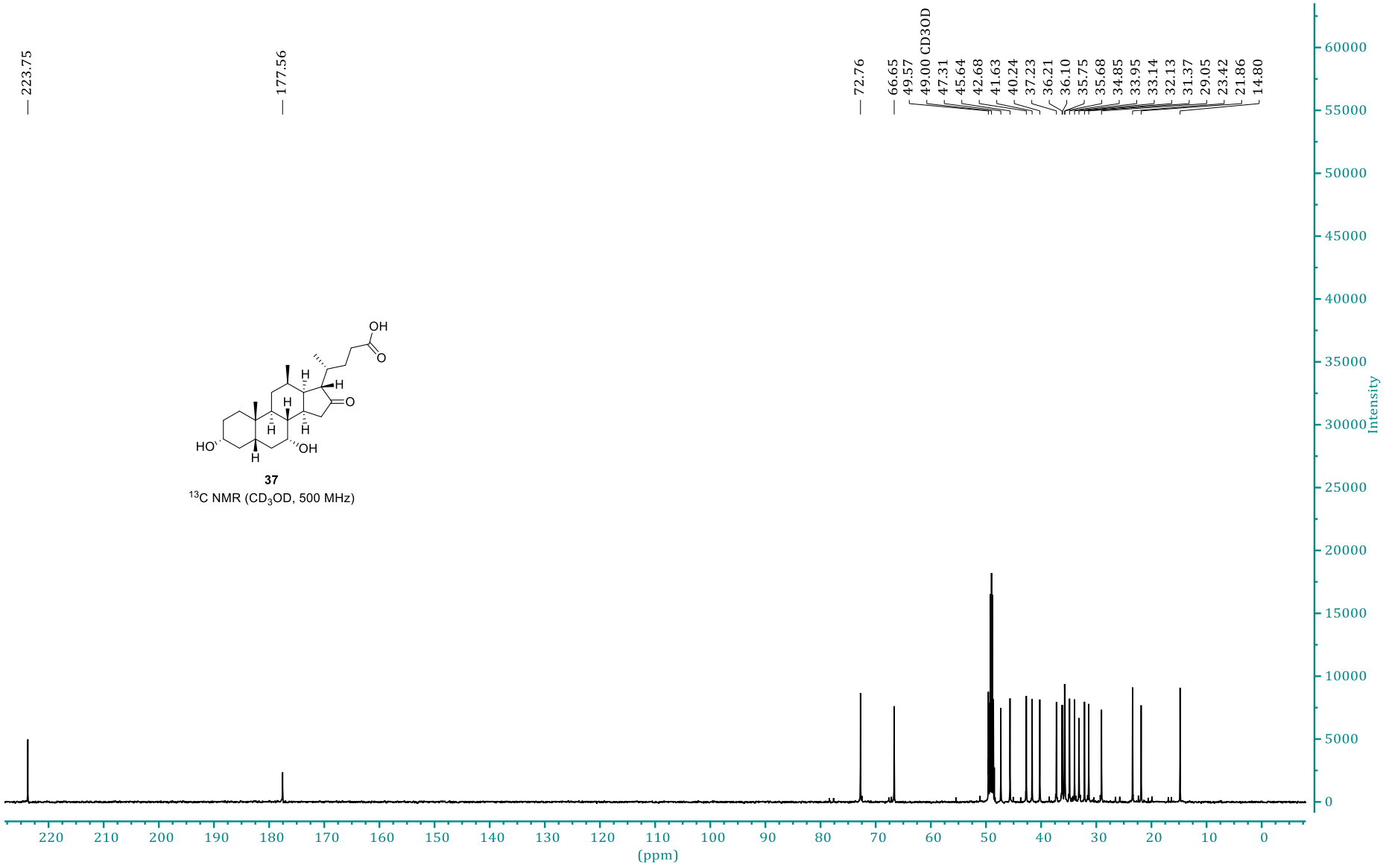
33

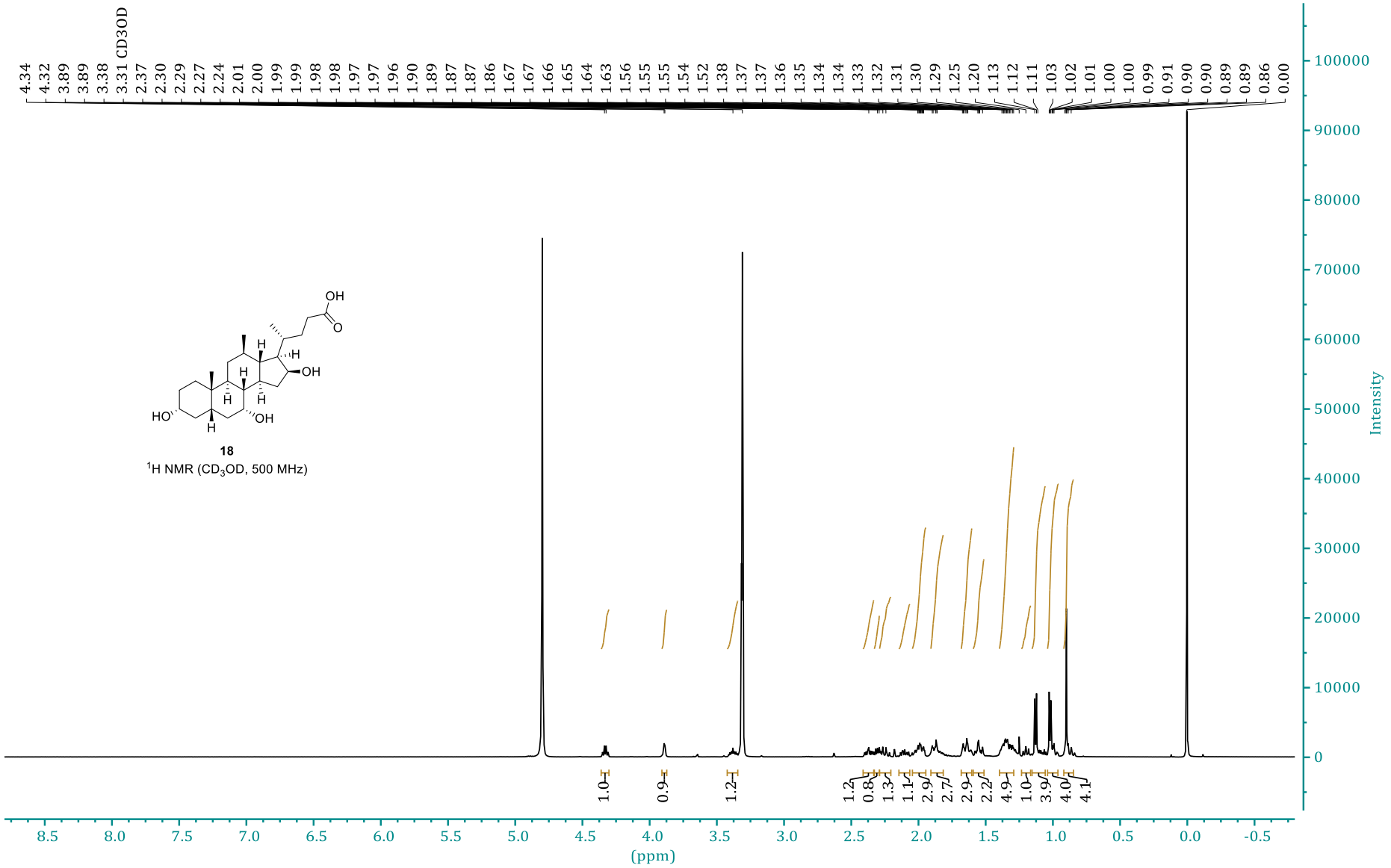
^{13}C NMR (CD_3OD, 126 MHz)

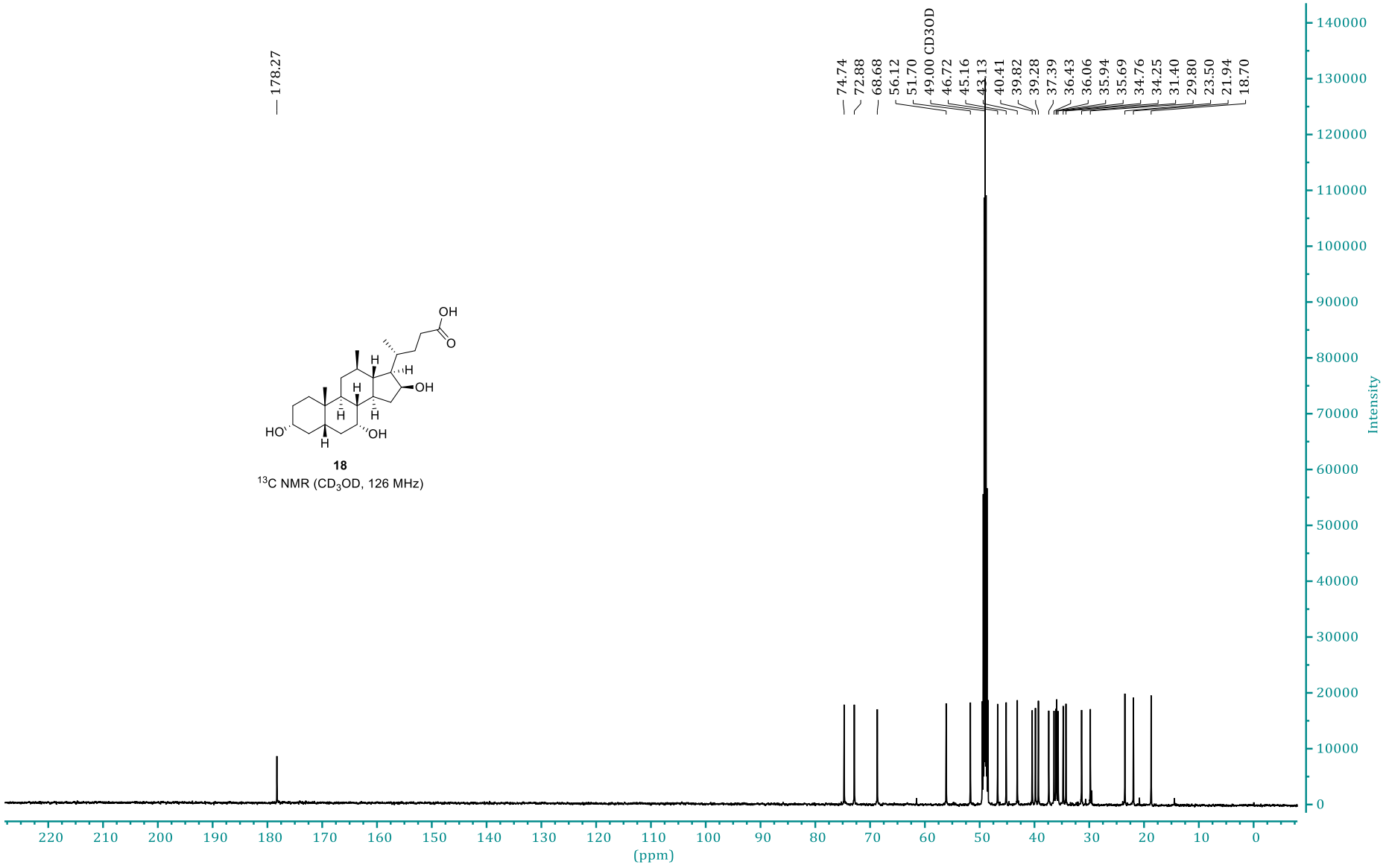

3.83
3.82
3.40
3.31 CD3OD
2.41
2.39
2.37
2.36
2.36
2.29
2.26
2.22
2.21
2.12
1.96
1.94
1.91
1.89
1.88
1.87
1.85
1.82
1.82
1.79
1.76
1.75
1.74
1.74
1.73
1.72
1.72
1.71
1.70
1.68
1.68
1.66
1.66
1.65
1.65
1.64
1.56
1.56
1.54
1.53
1.53
1.52
1.51
1.50
1.49
1.40
1.38
1.38
1.36
1.36
1.35
1.34
1.20
1.19
1.05
1.04
1.03
1.01
0.99
0.96
0.94
0.93
OH
O
H
H
H
O
H
H
H
HO
OH
H
36
1H NMR (CD3OD, 500 MHz)
1.0
1.0
2.1
2.1
1.1
1.1
1.0
8.3
3.1
3.0
0.6
2.7
3.7
1.2
2.8
70000
60000
50000
40000
30000
20000
10000
0
Intensity
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
(ppm)


222.59
177.50
72.80
68.60
61.01
52.50
49.00 CD3OD
46.66
45.52
43.41
43.02
40.35
39.90
36.60
36.25
36.14
35.63
35.21
34.25
33.44
31.36
27.69
23.43
21.62
19.14
OH
O
H
H
H
O
H
H
H
HO
OH
H
36
13C NMR (CD3OD, 126 MHz)
35000
30000
25000
20000
15000
10000
5000
0
Intensity
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)


3.85 3.84 3.39 3.31 CD3OD 2.41 2.35 2.35 2.34 2.33 2.33 2.32 2.28 2.25 2.24 2.24 2.22 2.22 2.21 2.21 2.19 2.13 2.13 2.11 1.97 1.97 1.96 1.96 1.95 1.94 1.94 1.94 1.93 1.93 1.92 1.92 1.91 1.91 1.86 1.85 1.83 1.83 1.82 1.82 1.65 1.65 1.64 1.64 1.60 1.59 1.57 1.48 1.38 1.37 1.36 1.35 1.35 1.02 1.01 1.01 0.99 0.98 0.98 0.96 0.95 0.87 0.85 0.84
OH
O
H
H
H
O
H
H
H
HO
OH
H
37
1H NMR (CD3OD, 500 MHz)
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
Intensity
0.9 1.0 1.0 1.1 2.2 2.7 1.0 7.1 2.2 1.1 1.0 2.2 3.8 2.2 2.8 2.8
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)


223.75
177.56
72.76
66.65
49.57
49.00 CD3OD
47.31
45.64
42.68
41.63
40.24
37.23
36.21
36.10
35.75
35.68
34.85
33.95
33.14
32.13
31.37
29.05
23.42
21.86
14.80
OH
O
H
H
H
O
H
H
HO
OH
H
37
13C NMR (CD3OD, 500 MHz)
Intensity
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)


4.34 4.32 3.89 3.89 3.38 3.31 CD3OD 2.37 2.30 2.29 2.27 2.24 2.01 2.00 1.99 1.99 1.98 1.98 1.97 1.97 1.96 1.90 1.89 1.87 1.87 1.86 1.67 1.67 1.66 1.65 1.64 1.63 1.56 1.55 1.55 1.54 1.52 1.38 1.37 1.37 1.36 1.35 1.34 1.34 1.33 1.32 1.31 1.30 1.29 1.25 1.20 1.13 1.12 1.11 1.03 1.02 1.01 1.00 1.00 0.99 0.91 0.90 0.90 0.89 0.89 0.86 0.00
OH
O
H
H
OH
H
H
H
HO
OH
H
18
1H NMR (CD3OD, 500 MHz)
1.0 0.9 1.2 1.2 0.8 1.3 1.1 2.9 2.7 2.9 2.2 4.9 1.0 3.9 4.0 4.1
Intensity
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)


178.27
74.74
72.88
68.68
56.12
51.70
49.00 CD3OD
46.72
45.16
43.13
40.41
39.82
39.28
37.39
36.43
36.06
35.94
35.69
34.76
34.25
31.40
29.80
23.50
21.94
18.70
OH
O
H
H
H
OH
H
H
HO
OH
H
18
13C NMR (CD3OD, 126 MHz)
Intensity
(ppm)

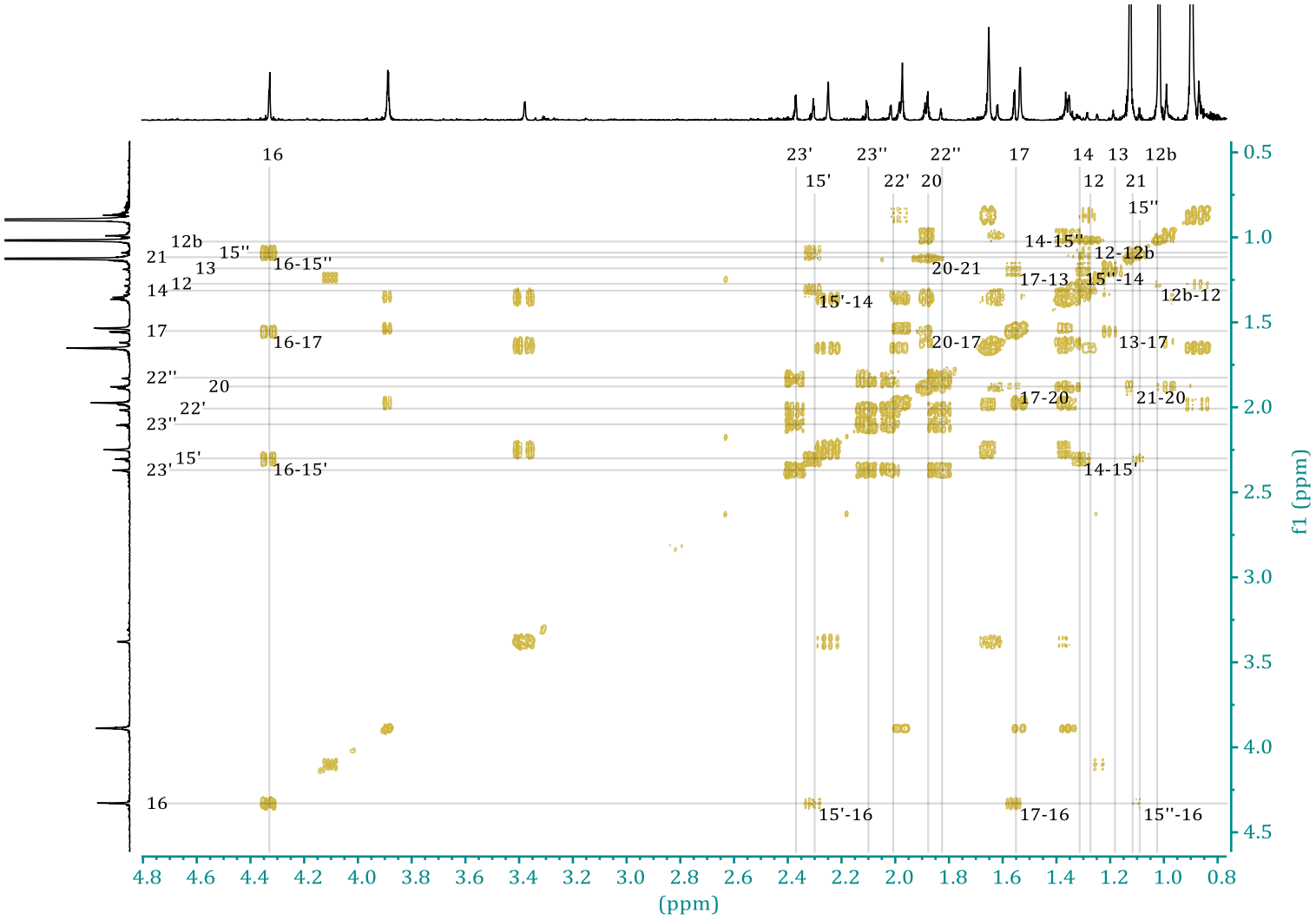


Figure S3. H-H COSY spectrum of alcohol **18**; **Grey gridlines** - coupling between C and D ring protons; key cross peaks labelled; PSYCHE spectrum superimposed on the F1 and F2 axis.

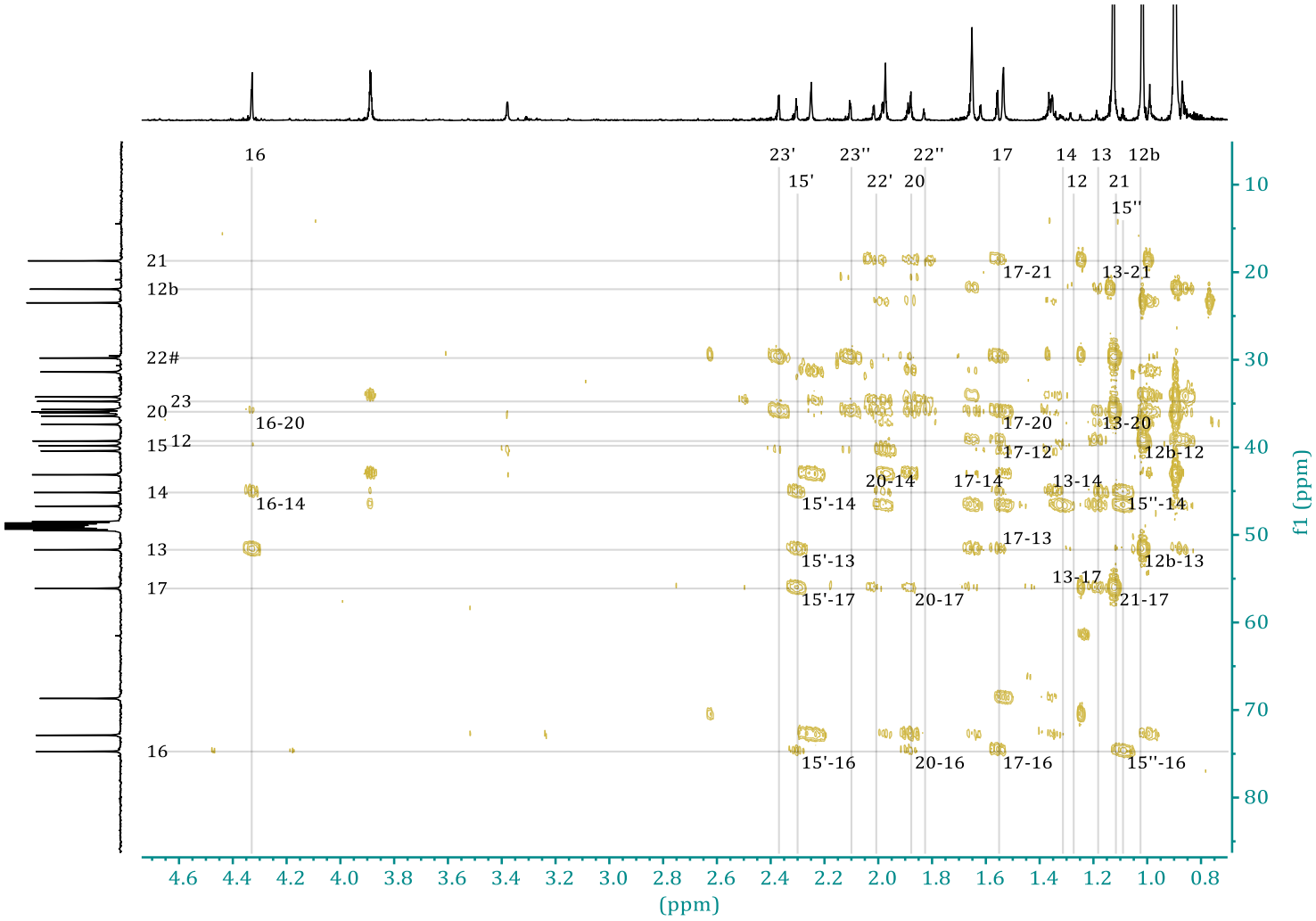


Figure S4. HMBC spectrum of alcohol **18**; **Grey gridlines** - coupling between C and D ring centres; key cross peaks labelled; PSYCHE spectrum superimposed on the F2 axis.

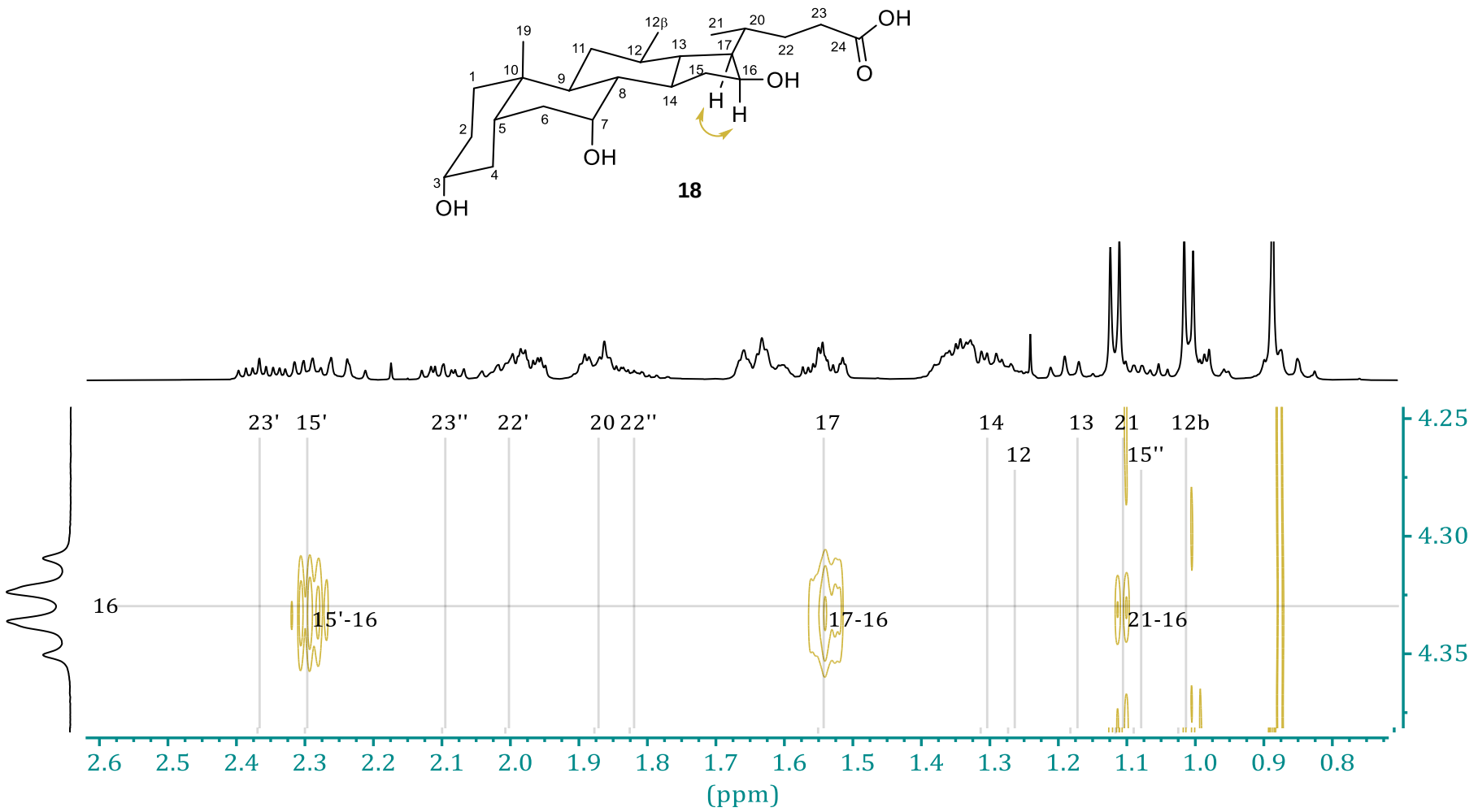
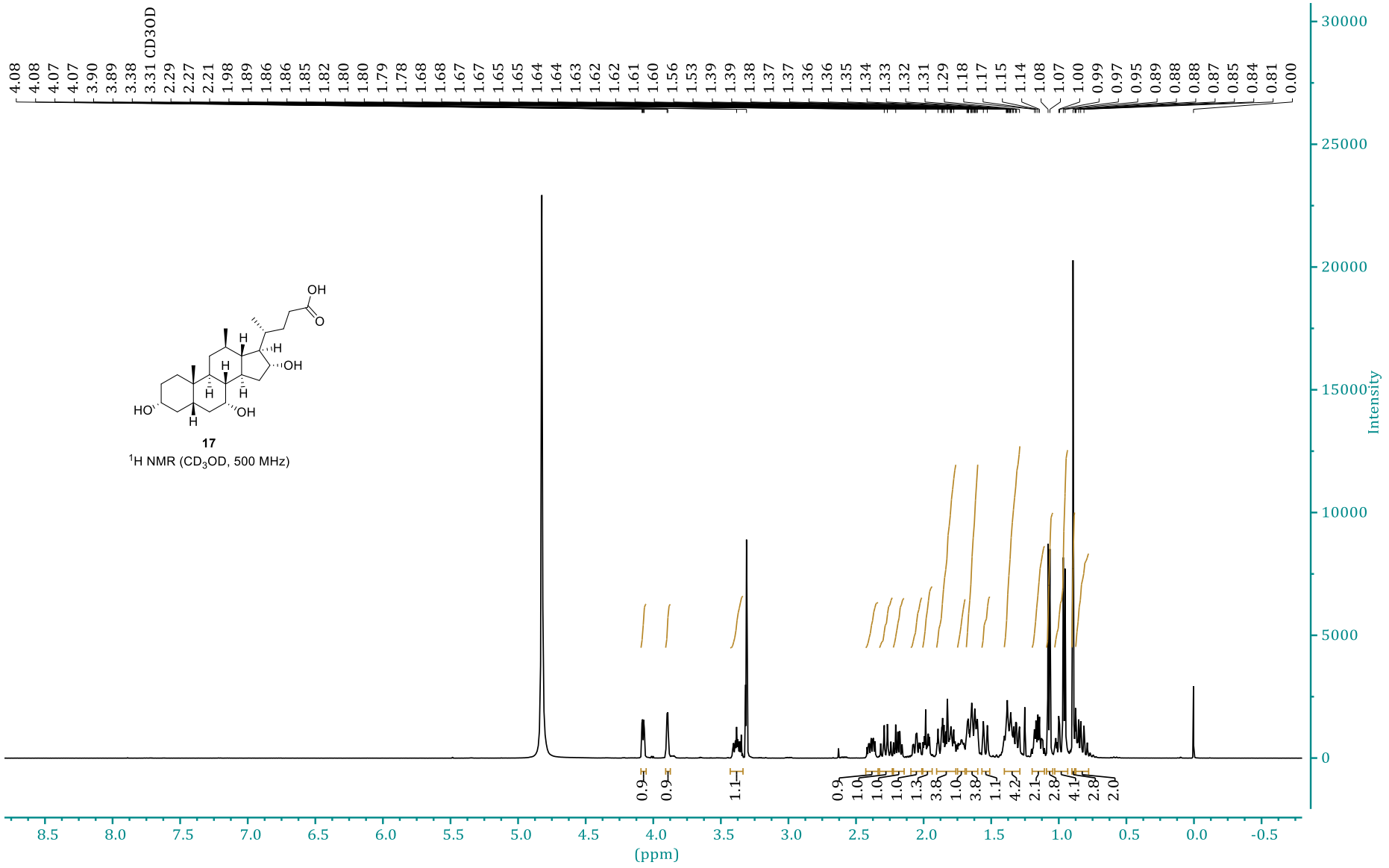
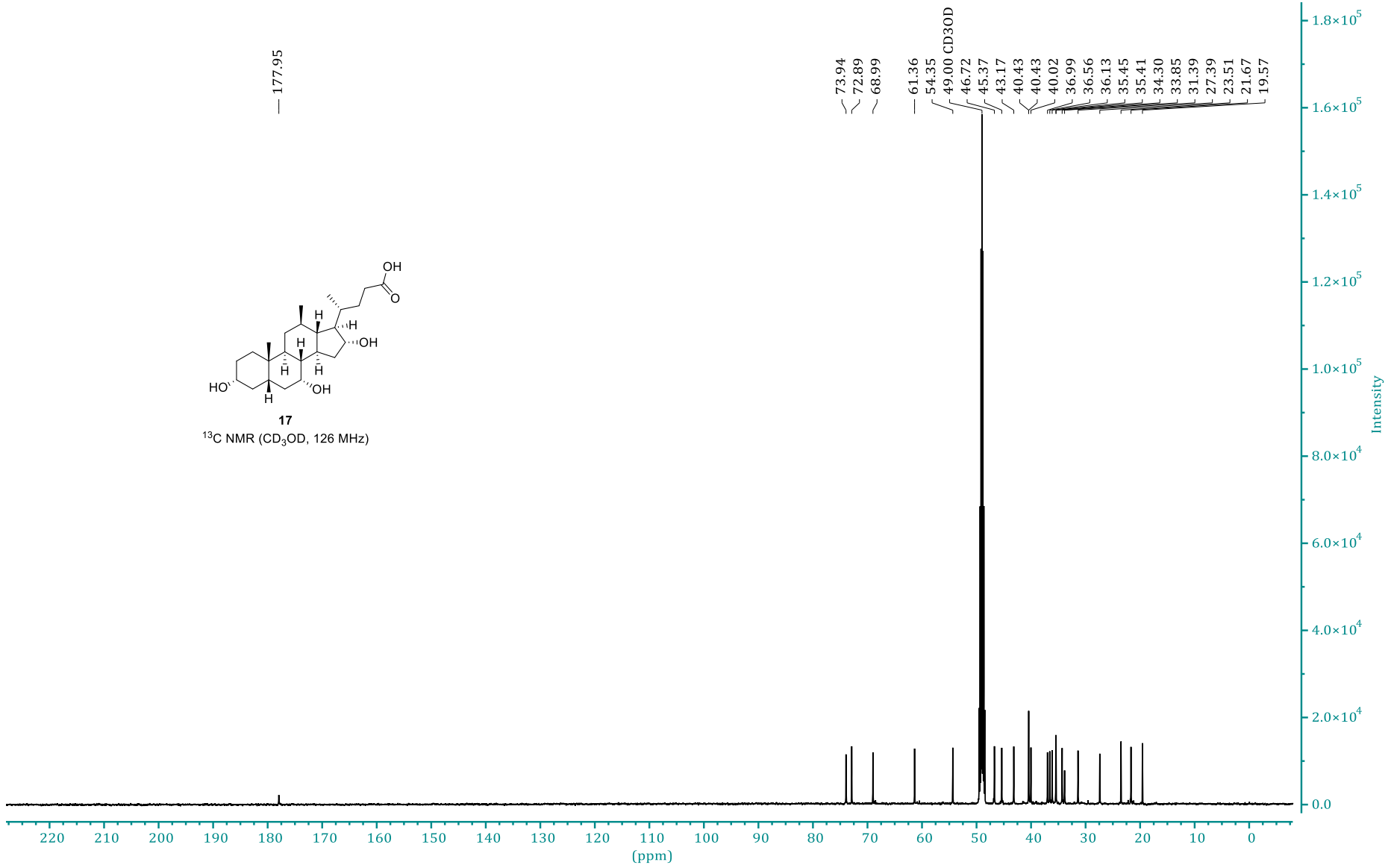


Figure S5. NOESY interaction from H-16 to the H-17 proton signal of alcohol **18**.


4.08 4.08 4.07 4.07 3.90 3.89 3.38 3.31 CD3OD 2.29 2.27 2.21 1.98 1.89 1.86 1.86 1.85 1.82 1.80 1.80 1.79 1.78 1.68 1.68 1.67 1.67 1.65 1.65 1.64 1.64 1.63 1.62 1.62 1.61 1.60 1.56 1.53 1.39 1.39 1.38 1.37 1.37 1.36 1.36 1.35 1.34 1.33 1.32 1.31 1.29 1.18 1.17 1.15 1.14 1.08 1.07 1.00 0.99 0.97 0.95 0.89 0.88 0.88 0.87 0.85 0.84 0.81 0.00
OH
O
H
H
OH
H
H
H
HO
OH
H
17
1H NMR (CD3OD, 500 MHz)
30000
25000
20000
15000
10000
5000
0
Intensity
0.9 0.9 1.1 0.9 1.0 1.0 1.0 1.3 3.8 1.0 3.8 1.1 4.2 2.1 2.8 4.1 2.8 2.0
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)


177.95
73.94
72.89
68.99
61.36
54.35
49.00 CD3OD
46.72
45.37
43.17
40.43
40.43
40.02
36.99
36.56
36.13
35.45
35.41
34.30
33.85
31.39
27.39
23.51
21.67
19.57
OH
O
H
H
H
OH
HO
OH
17
13C NMR (CD3OD, 126 MHz)
Intensity
(ppm)

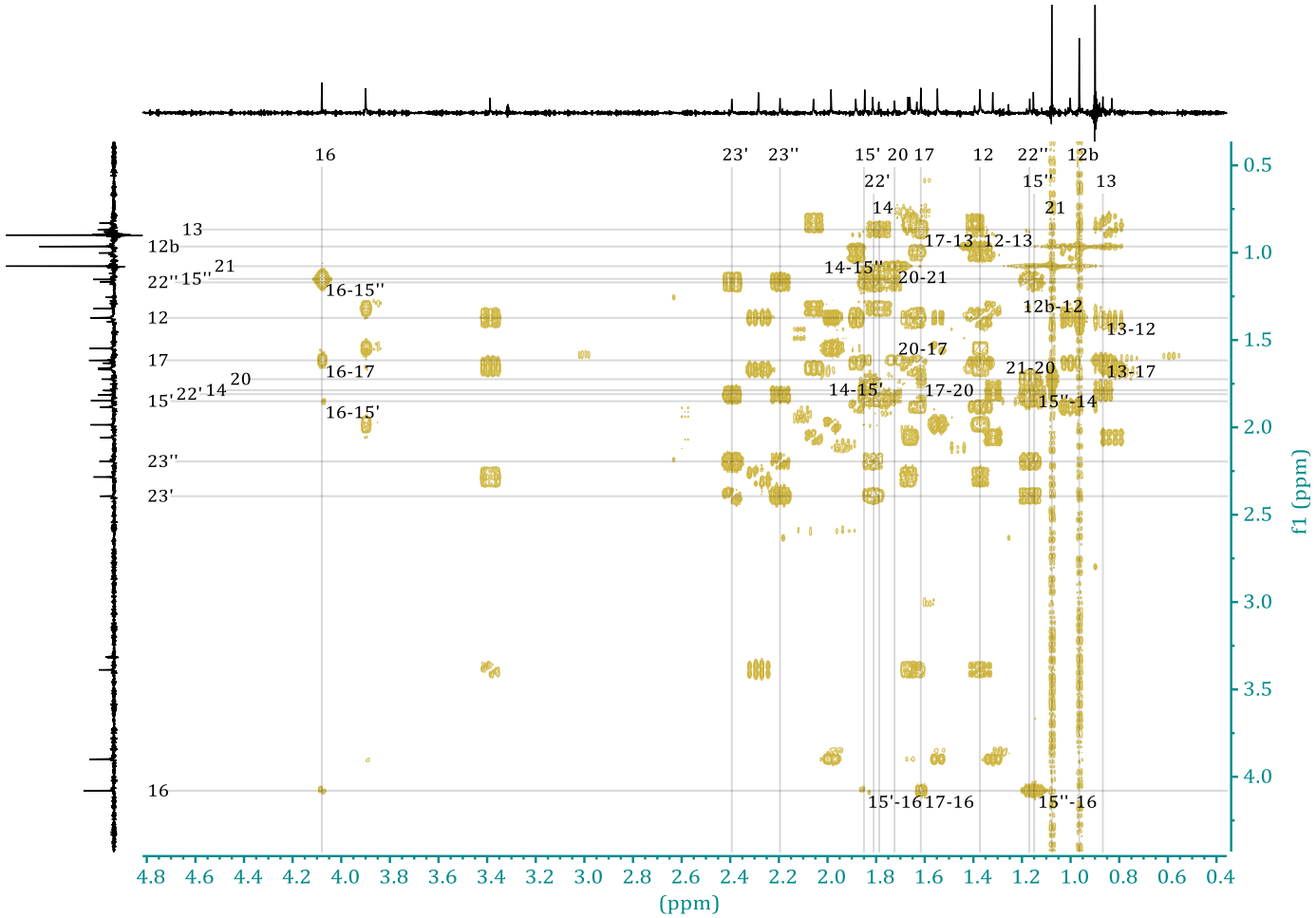


Figure S6. H-H COSY spectrum of alcohol **17**; **Grey gridlines** - coupling between C and D ring protons; key cross peaks labelled; PSYCHE spectrum superimposed on the F1 and F2 axis.

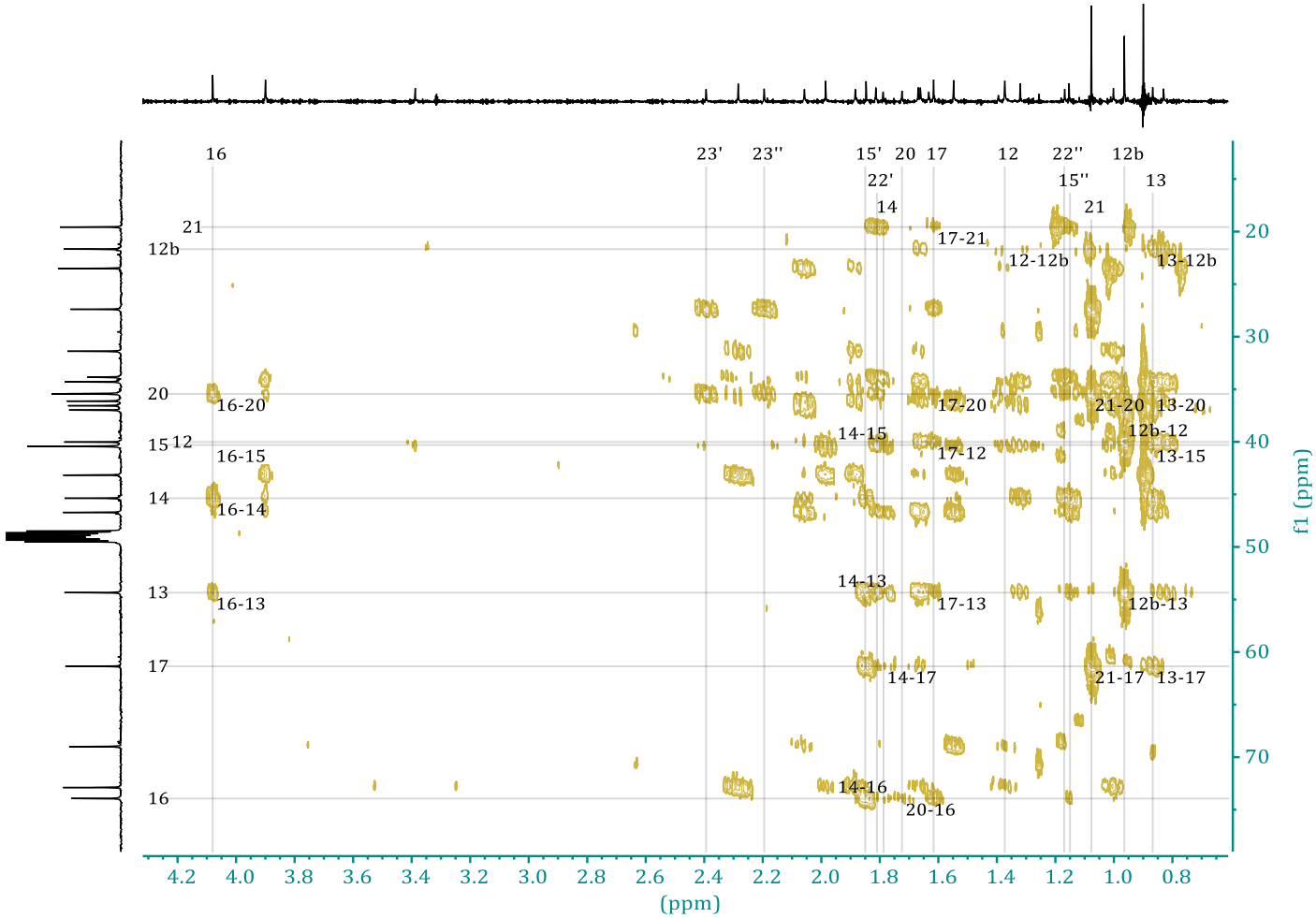


Figure S7. HMBC spectrum of alcohol **17**; **Grey gridlines** - coupling between C and D ring centres; key cross peaks labelled; PSYCHE spectrum superimposed on the F2 axis.

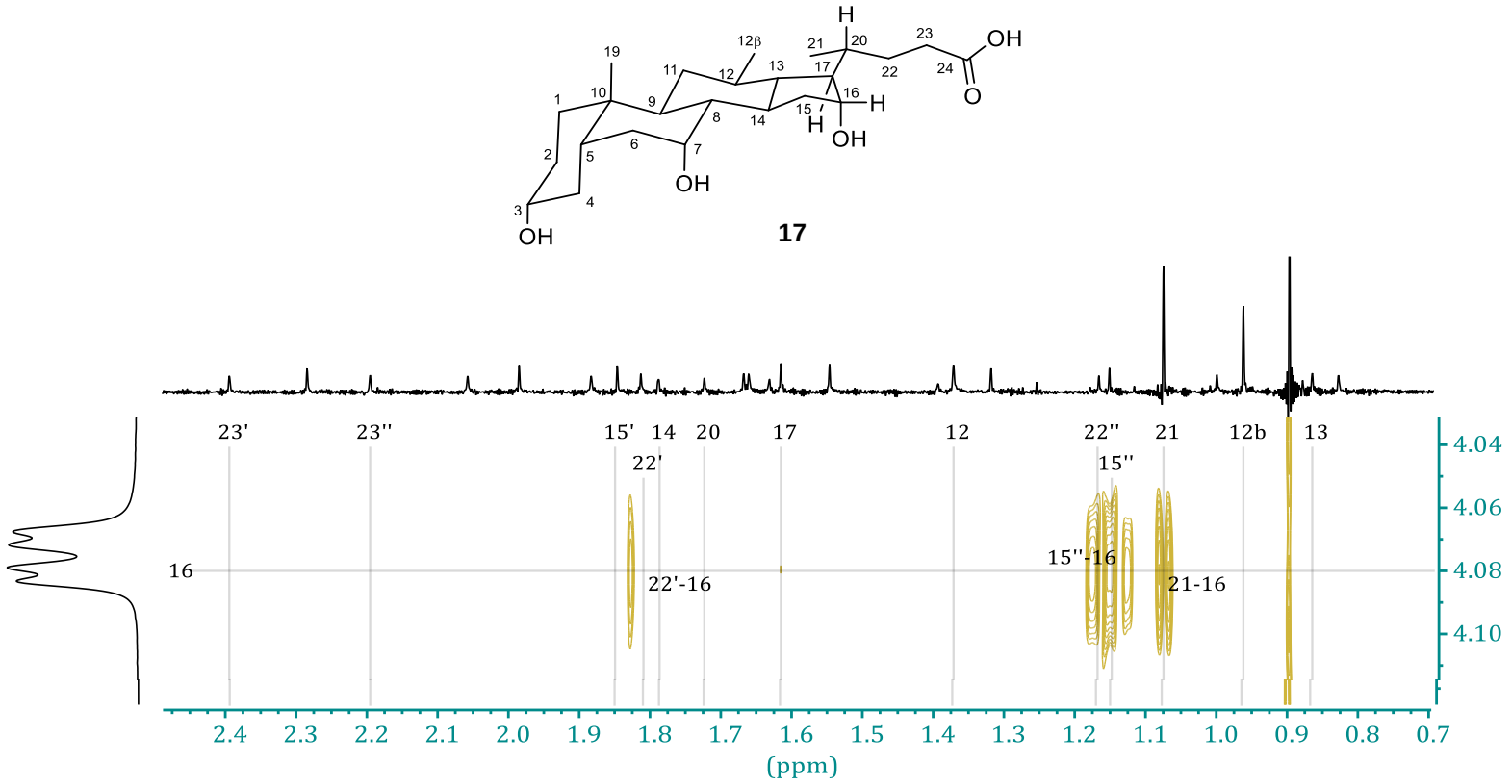
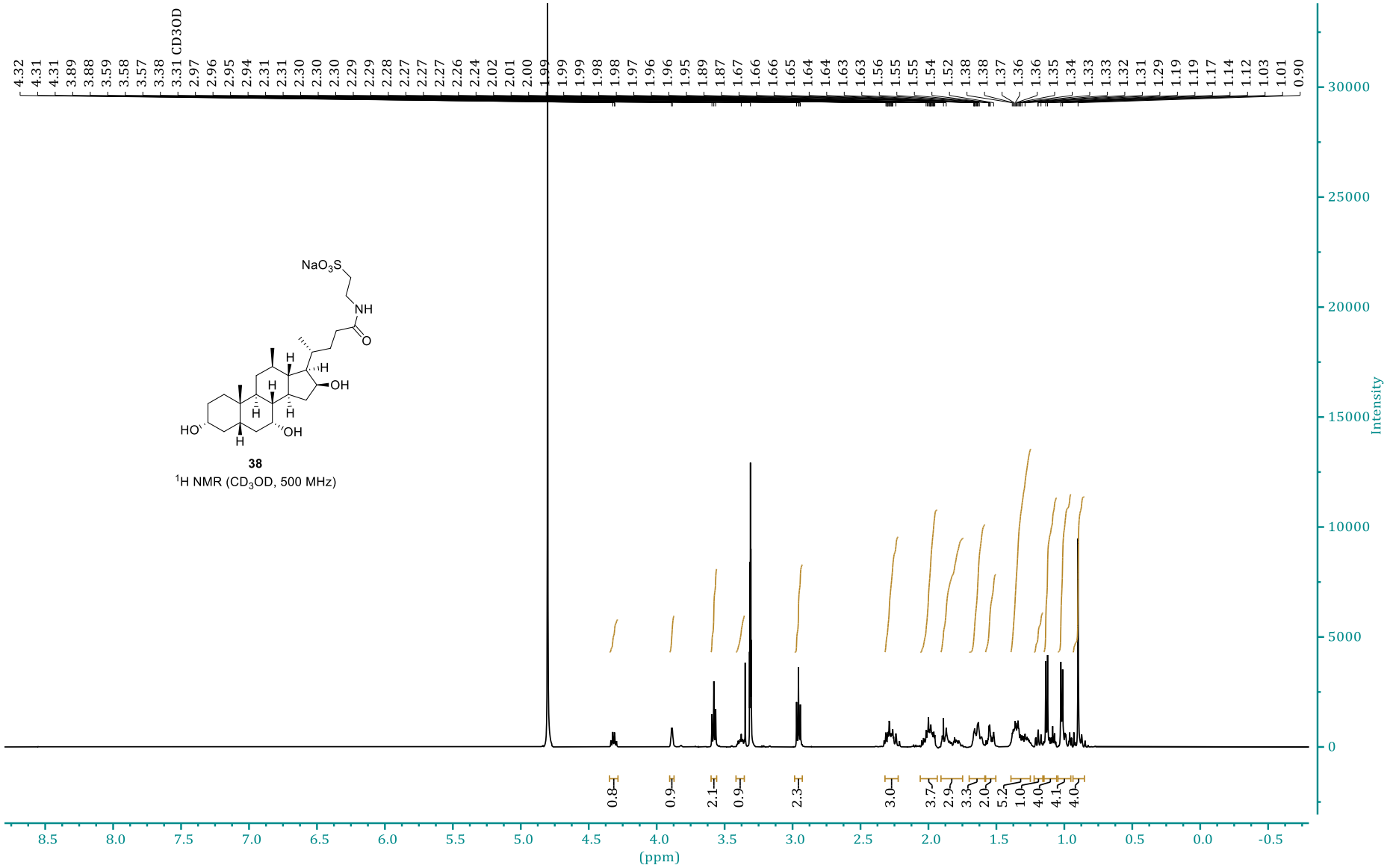
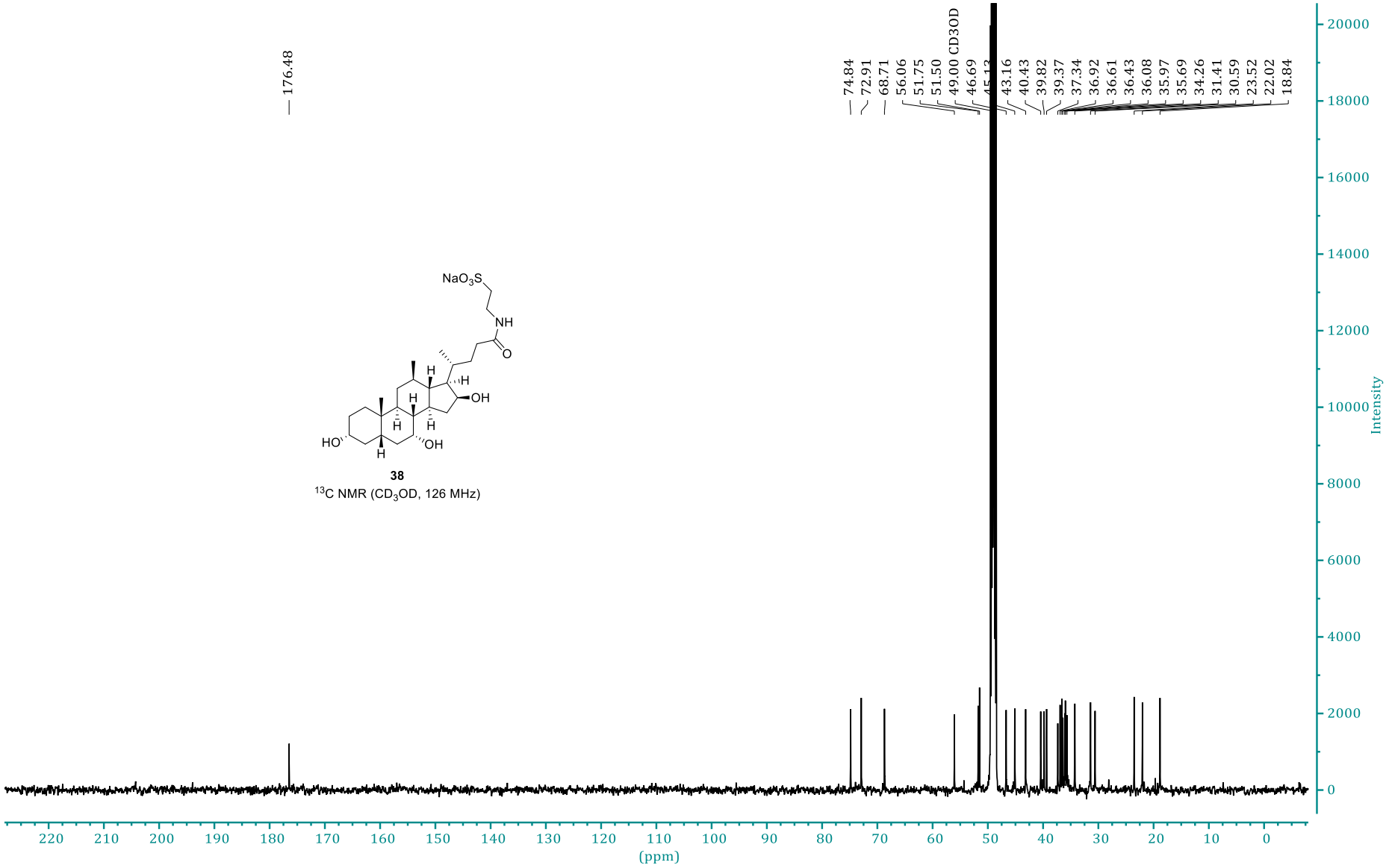
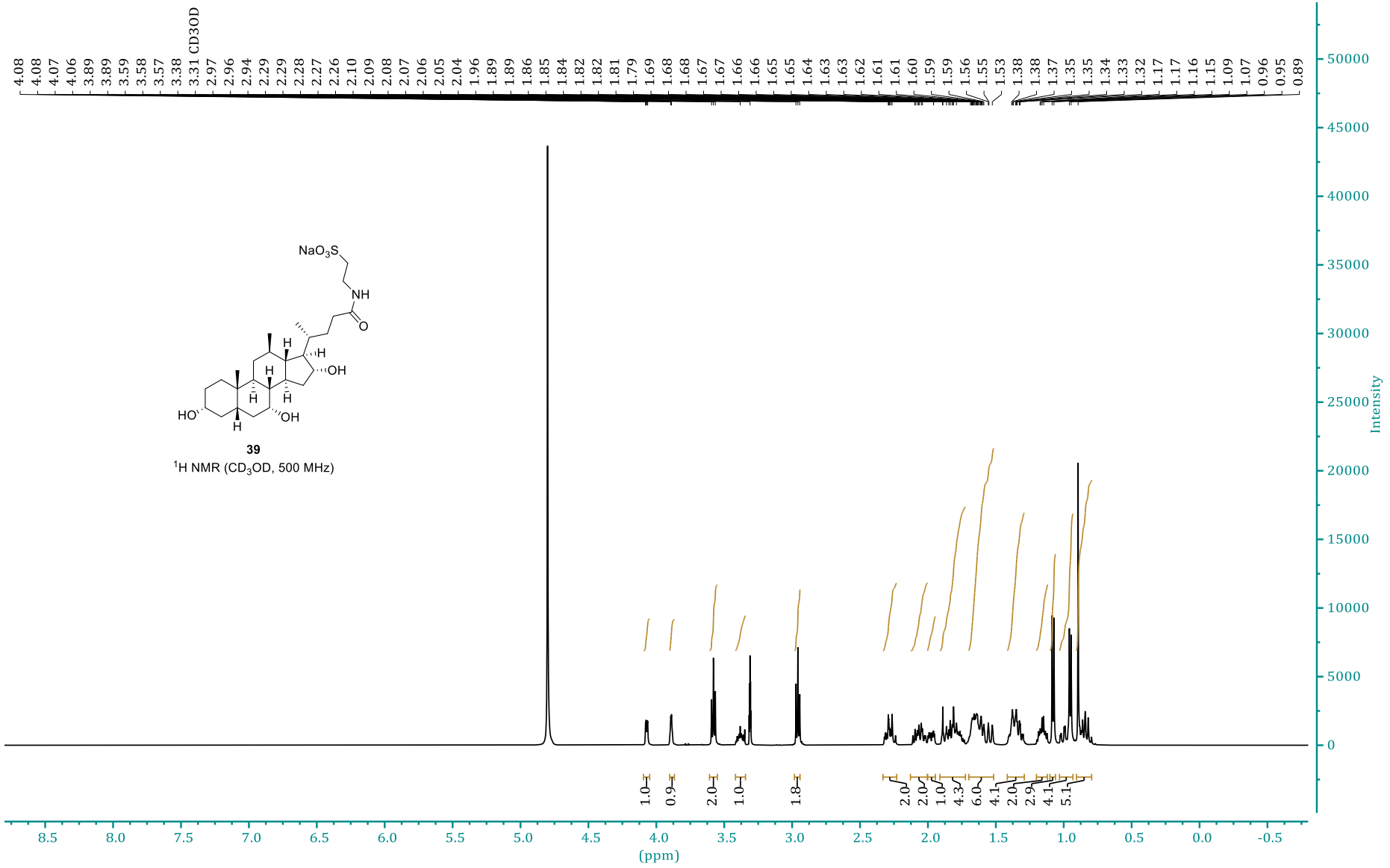
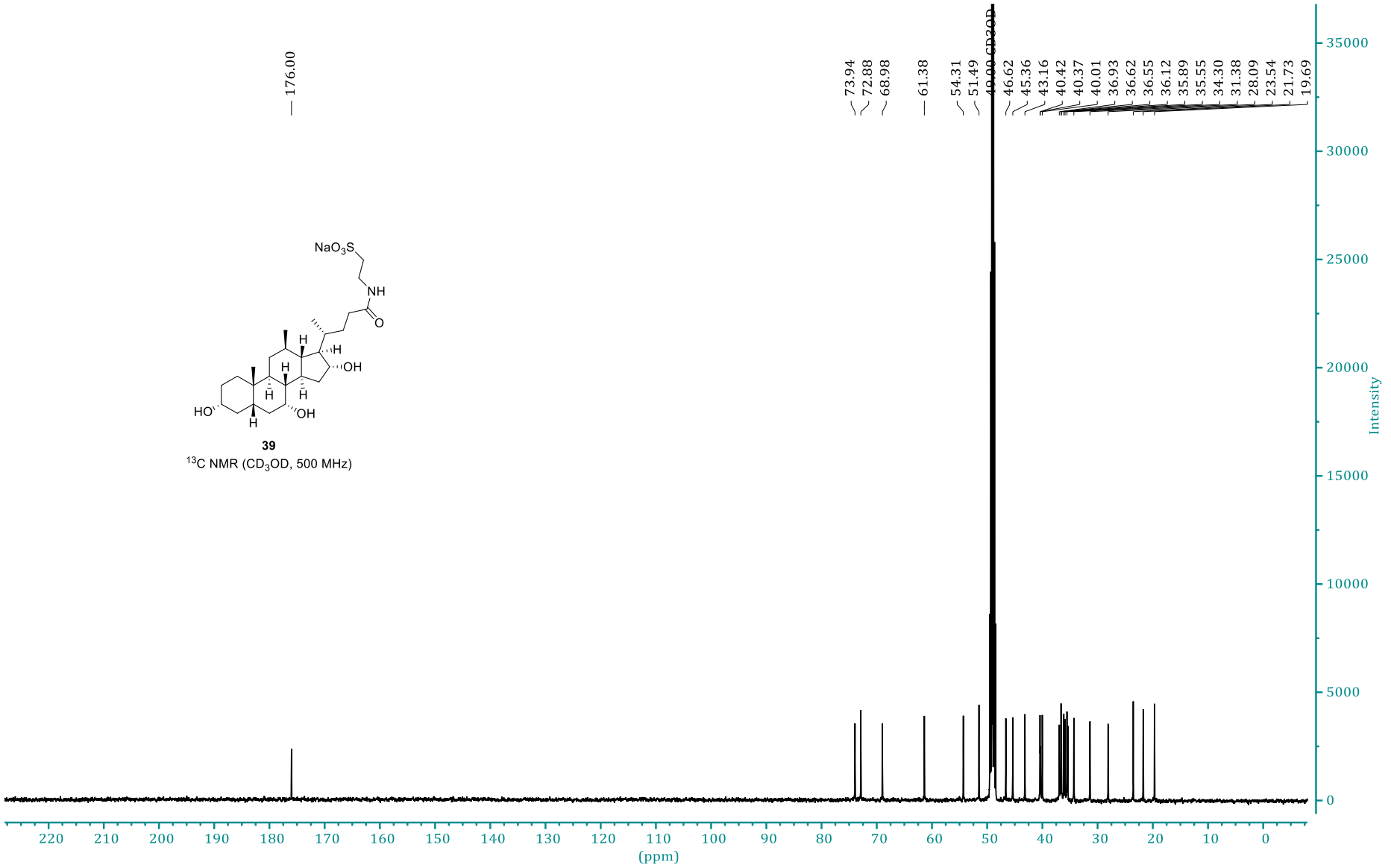


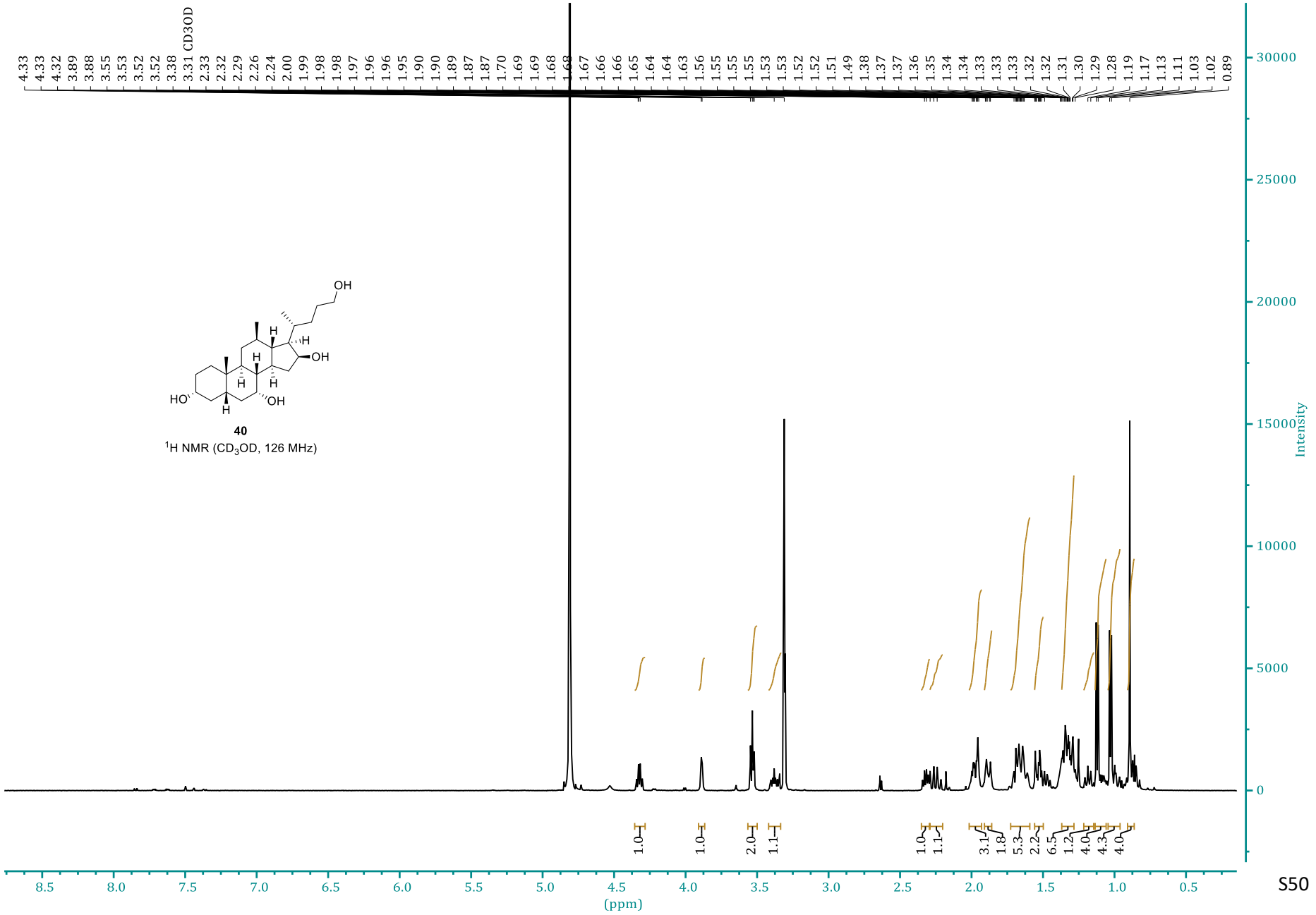
Figure S8. NOESY spectrum of alcohol **17** demonstrating a lack of signals between H-16 and H-17.

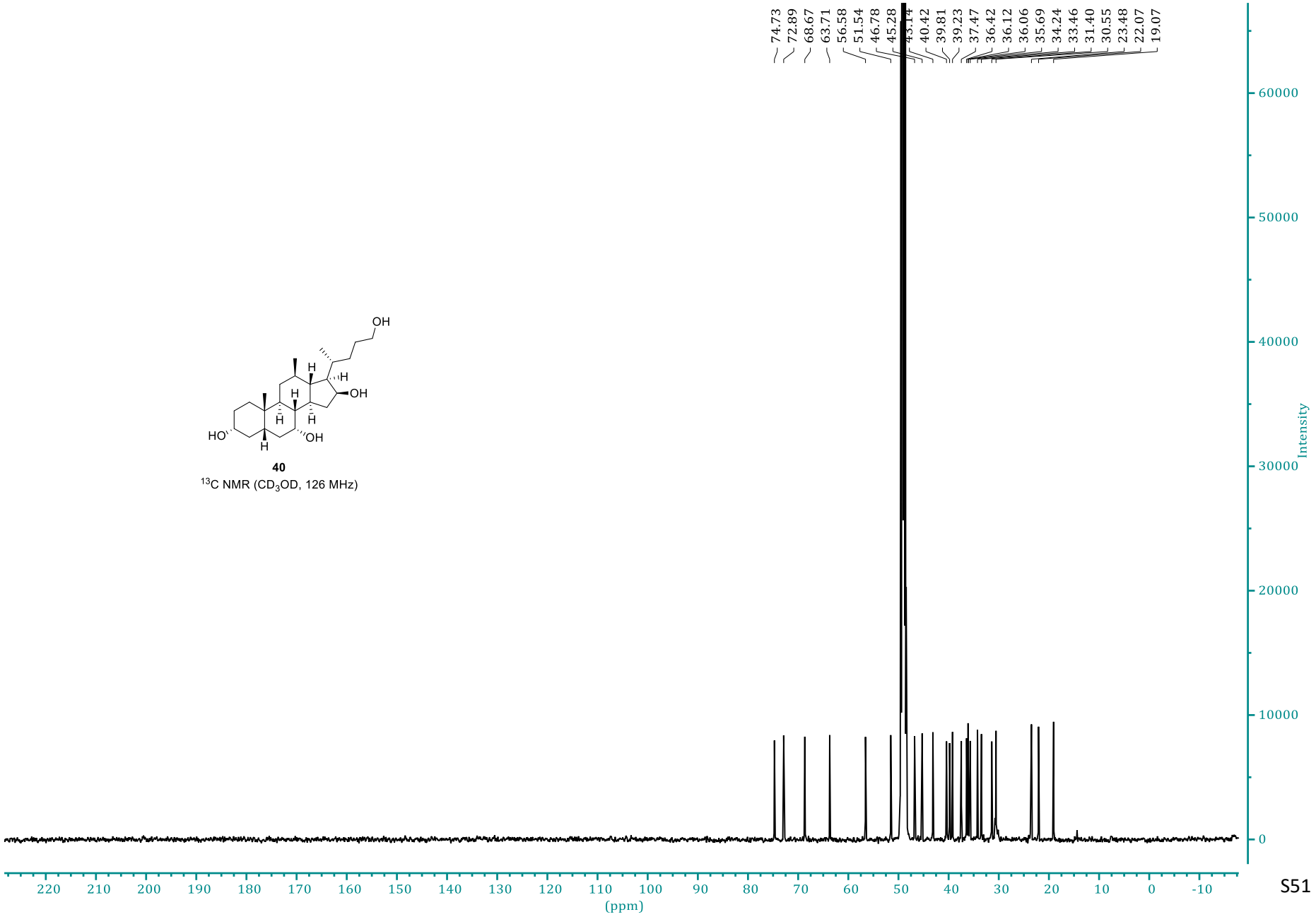

4.32 4.31 4.31 3.89 3.88 3.59 3.58 3.57 3.38 3.31 CD3OD 2.97 2.96 2.95 2.94 2.31 2.31 2.30 2.30 2.30 2.29 2.29 2.28 2.27 2.27 2.27 2.26 2.24 2.02 2.01 2.00 1.99 1.99 1.99 1.98 1.98 1.97 1.96 1.96 1.95 1.89 1.87 1.67 1.66 1.66 1.65 1.64 1.64 1.63 1.63 1.56 1.55 1.55 1.54 1.52 1.38 1.38 1.37 1.36 1.36 1.35 1.34 1.33 1.33 1.32 1.31 1.29 1.19 1.19 1.17 1.14 1.12 1.03 1.01 0.90
NaO3S
NH
O
H
H
H
H
H
OH
HO
OH
H
38
1H NMR (CD3OD, 500 MHz)
Intensity
30000
25000
20000
15000
10000
5000
0
0.8 0.9 2.1 0.9 2.3 3.0 3.7 2.9 3.3 2.0 5.2 1.0 4.0 4.1 4.0
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)


176.48
74.84
72.91
68.71
56.06
51.75
51.50
49.00 CD3OD
46.69
45.13
43.16
40.43
39.82
39.37
37.34
36.92
36.61
36.43
36.08
35.97
35.69
34.26
31.41
30.59
23.52
22.02
18.84
NaO3S
NH
O
H
H
OH
HO
OH
H
H
H
38
13C NMR (CD3OD, 126 MHz)
Intensity
(ppm)


4.08 4.08 4.07 4.06 3.89 3.89 3.59 3.58 3.57 3.38 3.31 CD3OD 2.97 2.96 2.94 2.29 2.29 2.28 2.27 2.26 2.10 2.09 2.08 2.07 2.06 2.05 2.04 1.96 1.89 1.89 1.86 1.85 1.84 1.82 1.82 1.81 1.79 1.69 1.68 1.68 1.67 1.67 1.66 1.66 1.65 1.65 1.64 1.63 1.63 1.62 1.61 1.61 1.60 1.59 1.59 1.56 1.55 1.53 1.38 1.38 1.37 1.35 1.35 1.34 1.33 1.32 1.17 1.17 1.16 1.15 1.09 1.07 0.96 0.95 0.89
NaO3S
NH
O
HO
OH
OH
H
39
1H NMR (CD3OD, 500 MHz)
Intensity
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
1.0 0.9 2.0 1.0 1.8 2.0 2.0 1.0 4.3 6.0 4.1 2.0 2.9 4.1 5.1
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)

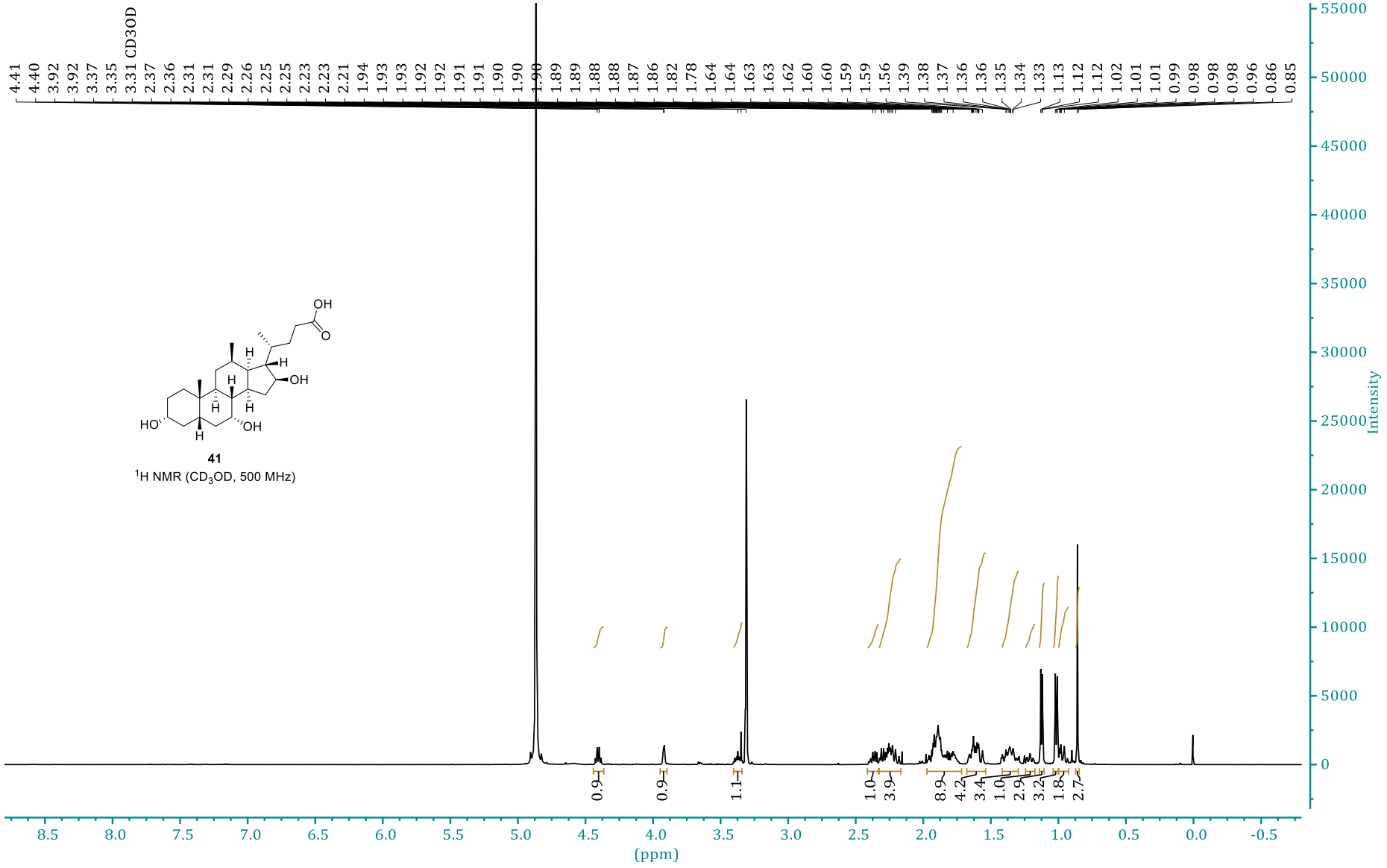

176.00
73.94
72.88
68.98
61.38
54.31
51.49
49.00 CD3OD
46.62
45.36
43.16
40.42
40.37
40.01
36.93
36.62
36.55
36.12
35.89
35.55
34.30
31.38
28.09
23.54
21.73
19.69
NaO3S
NH
O
H
H
OH
H
H
H
H
HO
OH
H
39
13C NMR (CD3OD, 500 MHz)
Intensity
35000
30000
25000
20000
15000
10000
5000
0
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)

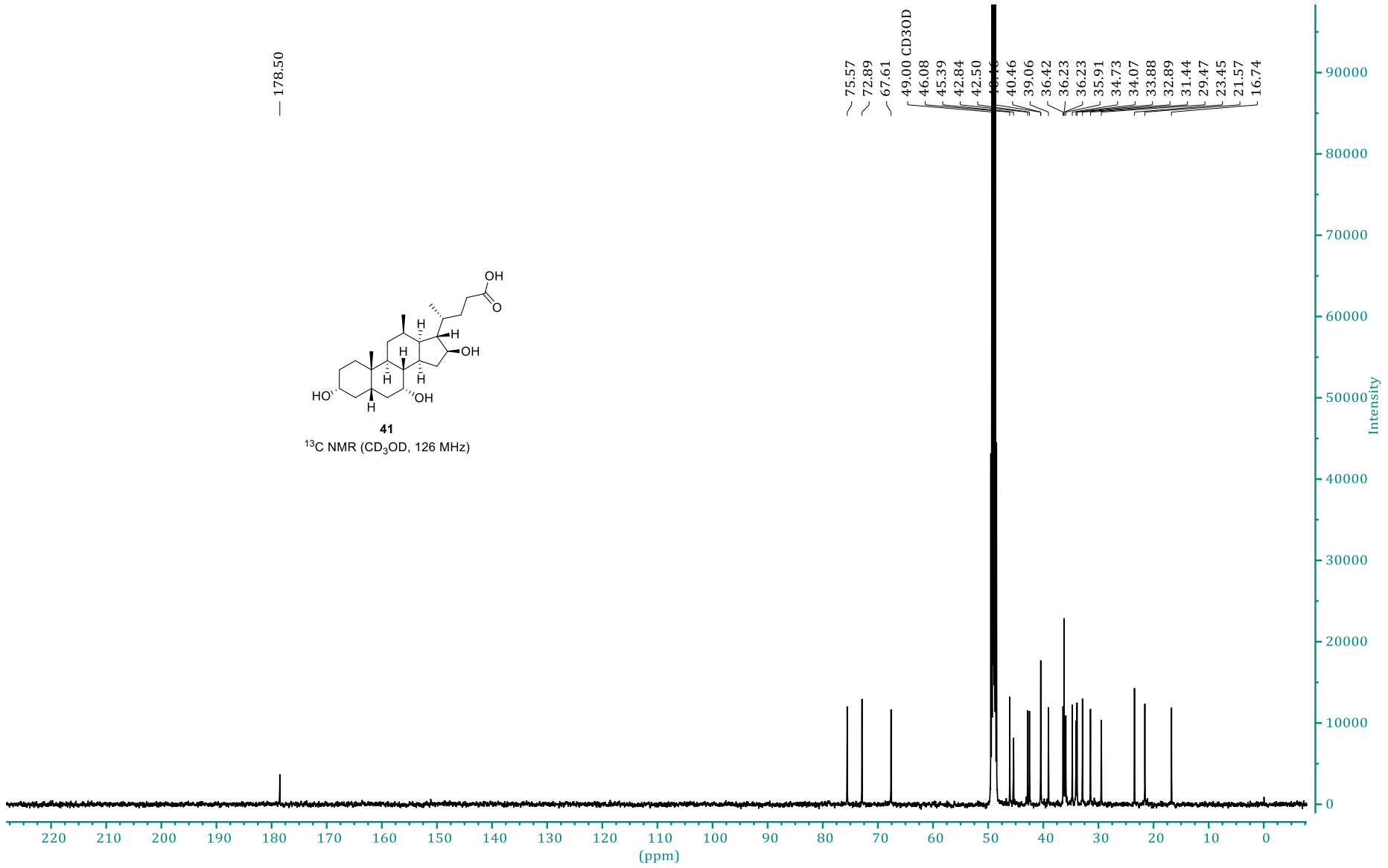

4.33 4.33 4.32 3.89 3.88 3.55 3.53 3.52 3.52 3.38 3.31 CD3OD 2.33 2.32 2.29 2.26 2.24 2.00 1.99 1.98 1.98 1.97 1.96 1.96 1.95 1.90 1.90 1.89 1.87 1.87 1.70 1.69 1.69 1.68 1.68 1.67 1.66 1.66 1.65 1.64 1.64 1.63 1.56 1.55 1.55 1.55 1.53 1.53 1.52 1.52 1.51 1.49 1.38 1.37 1.37 1.36 1.35 1.34 1.34 1.33 1.33 1.33 1.32 1.32 1.31 1.30 1.29 1.28 1.19 1.17 1.13 1.11 1.03 1.02 0.89
OH
H
H
OH
H
H
HO
OH
H
40
1H NMR (CD3OD, 126 MHz)
30000
25000
20000
15000
10000
5000
0
Intensity
1.0 1.0 2.0 1.1 1.0 1.1 3.1 1.8 5.3 2.2 6.5 1.2 4.0 4.3 4.0
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)



40

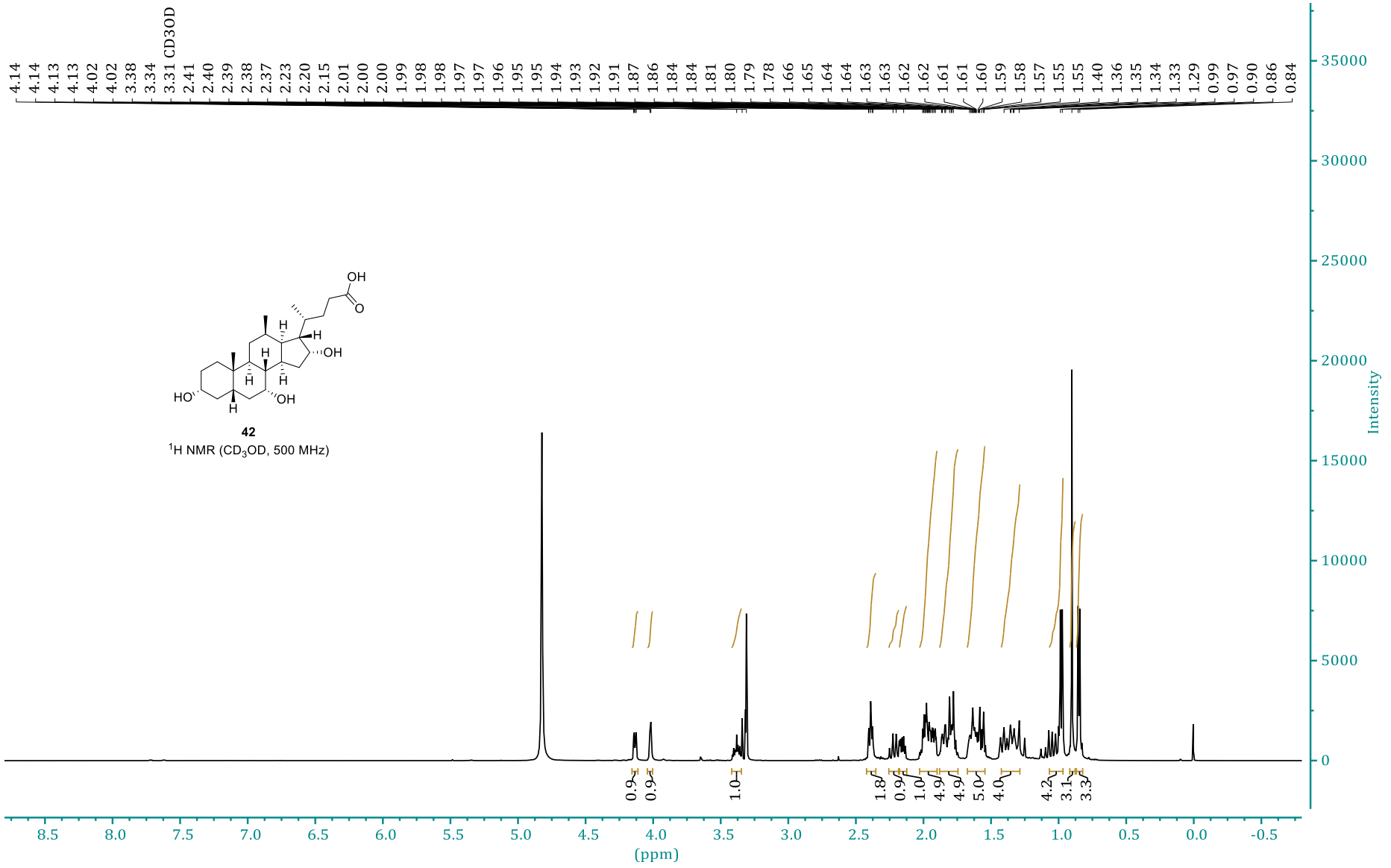
^{13}C NMR (CD_3OD, 126 MHz)

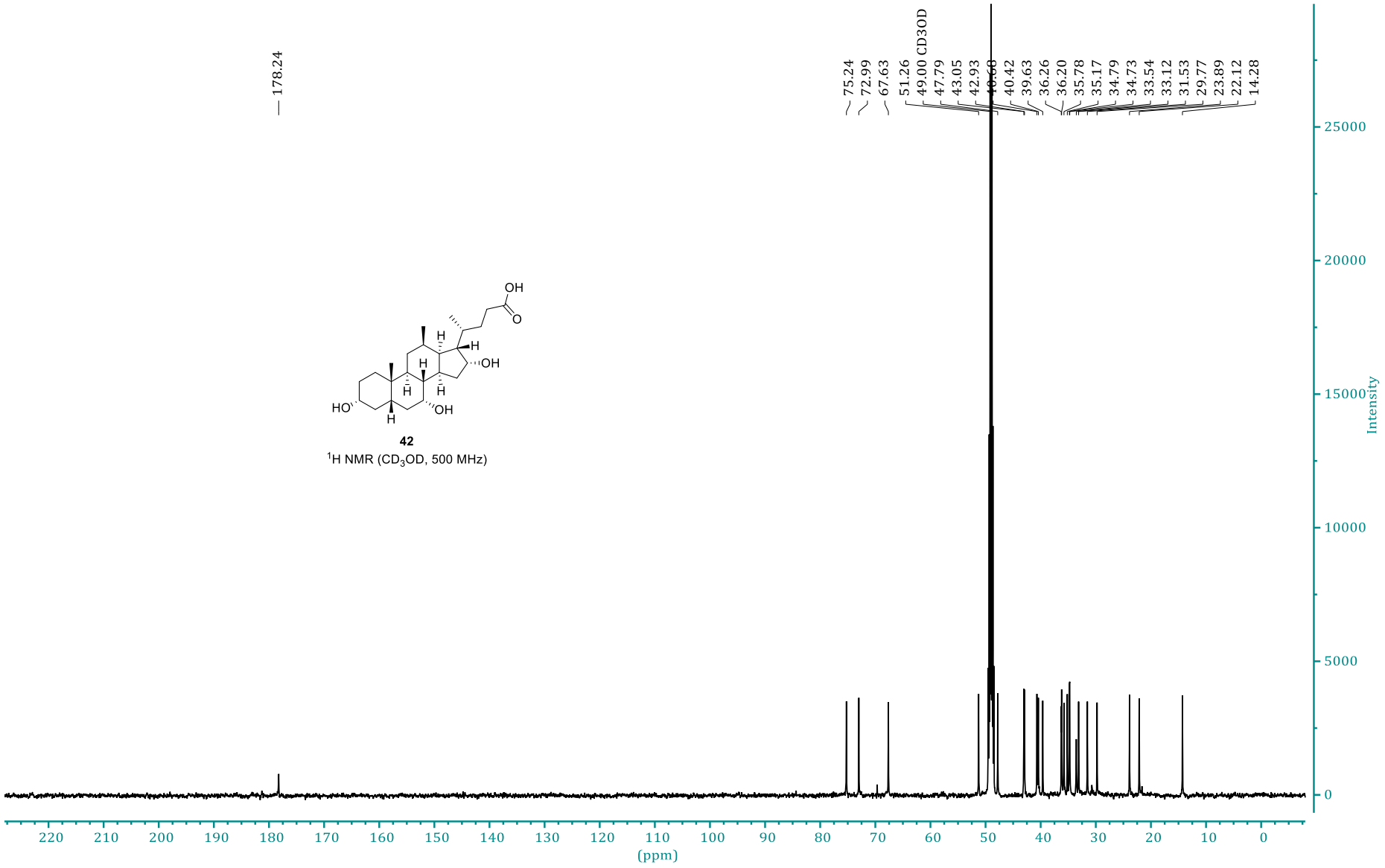

4.41 4.40 3.92 3.92 3.37 3.35 3.31 CD3OD 2.37 2.36 2.31 2.31 2.29 2.26 2.25 2.25 2.23 2.23 2.21 1.94 1.93 1.93 1.92 1.92 1.91 1.91 1.90 1.90 1.90 1.89 1.89 1.88 1.88 1.87 1.86 1.82 1.78 1.64 1.64 1.63 1.63 1.62 1.60 1.60 1.59 1.59 1.56 1.39 1.38 1.37 1.36 1.36 1.35 1.34 1.33 1.13 1.12 1.12 1.02 1.01 1.01 0.99 0.98 0.98 0.98 0.96 0.86 0.85
OH
O
H
H
OH
H
HO
OH
H
H
H
41
1H NMR (CD3OD, 500 MHz)
0.9 0.9 1.1 1.0 3.9 8.9 4.2 3.4 1.0 2.9 3.2 1.8 2.7
55000 50000 45000 40000 35000 30000 25000 20000 15000 10000 5000 0
Intensity
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)

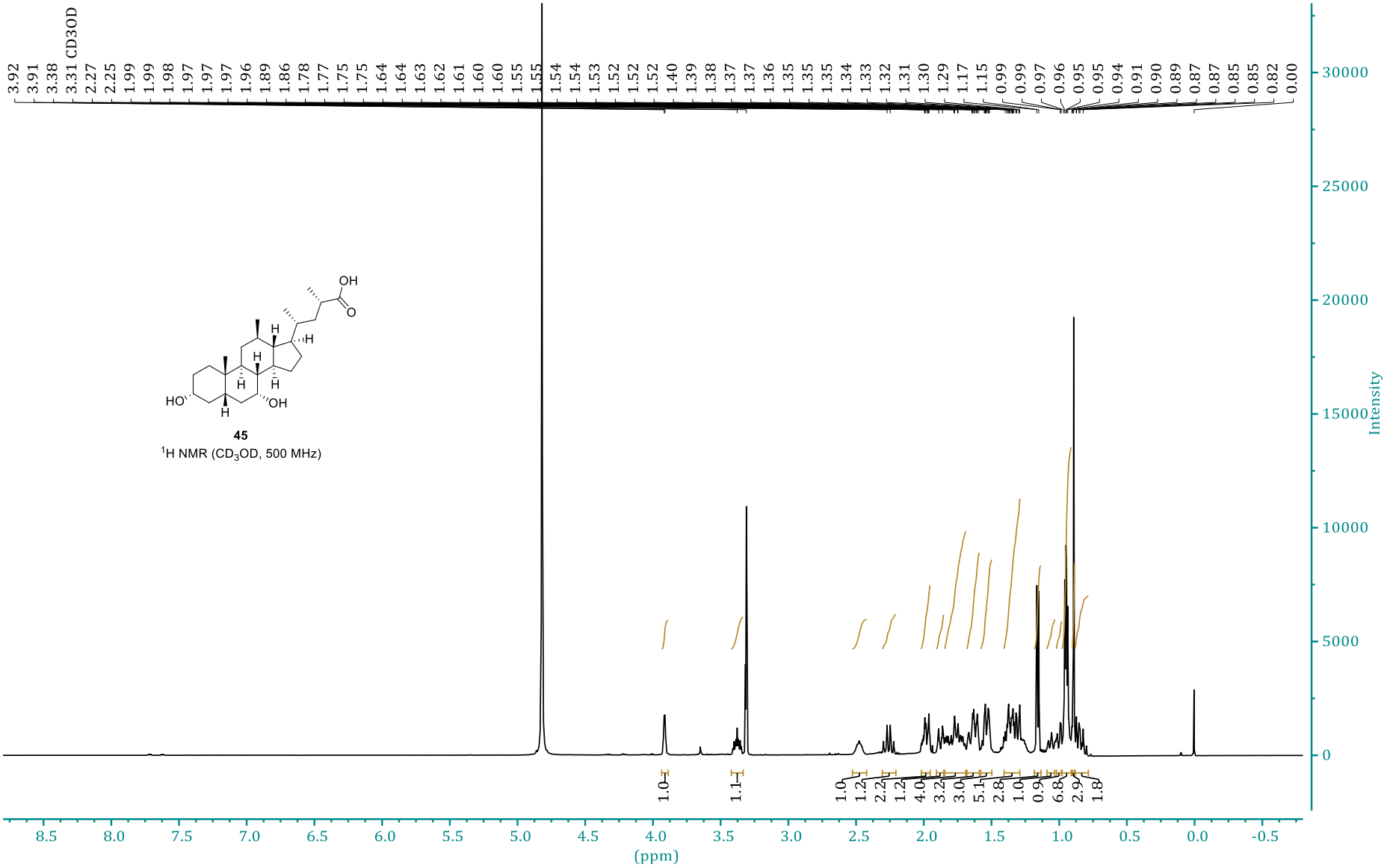


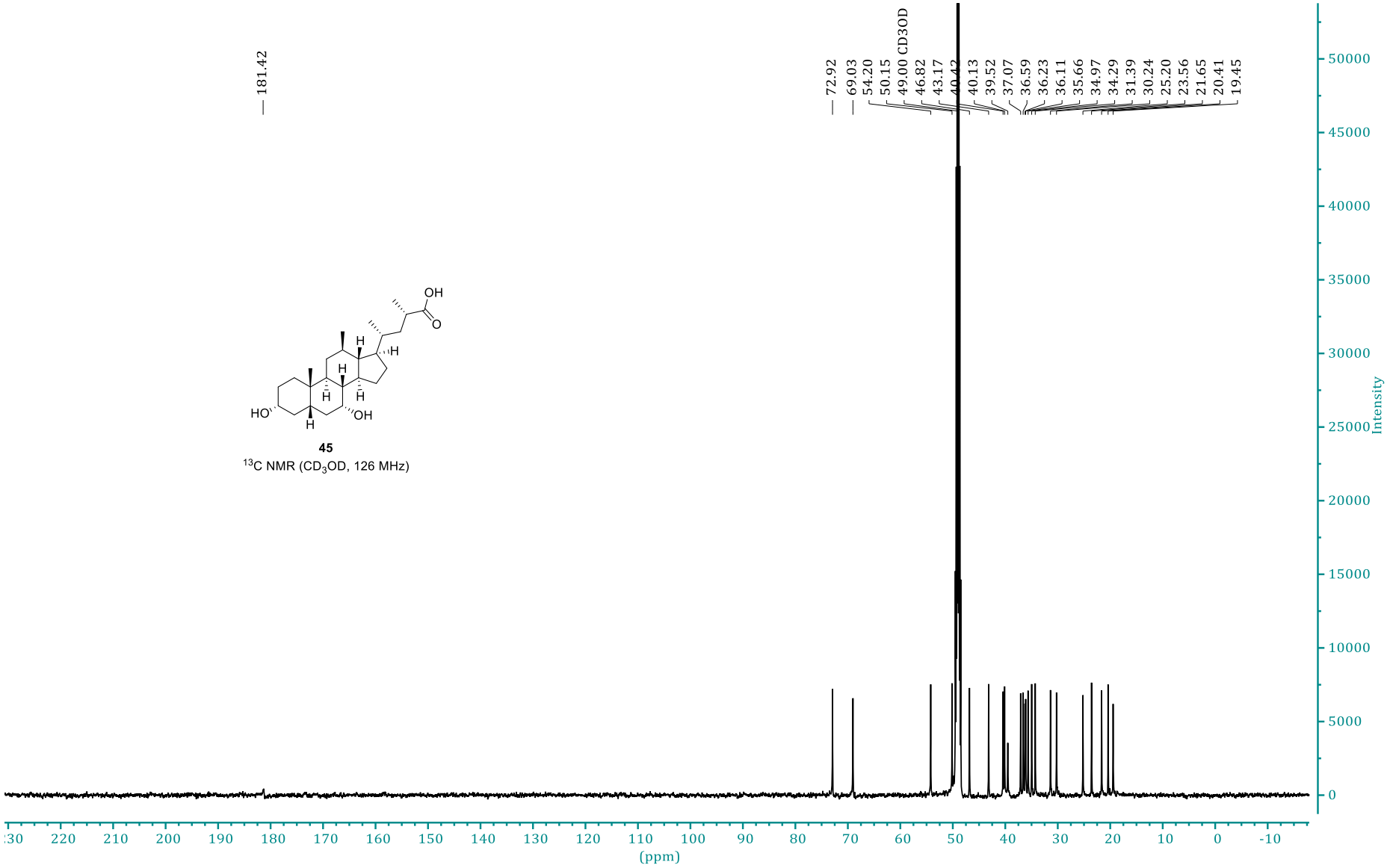
41

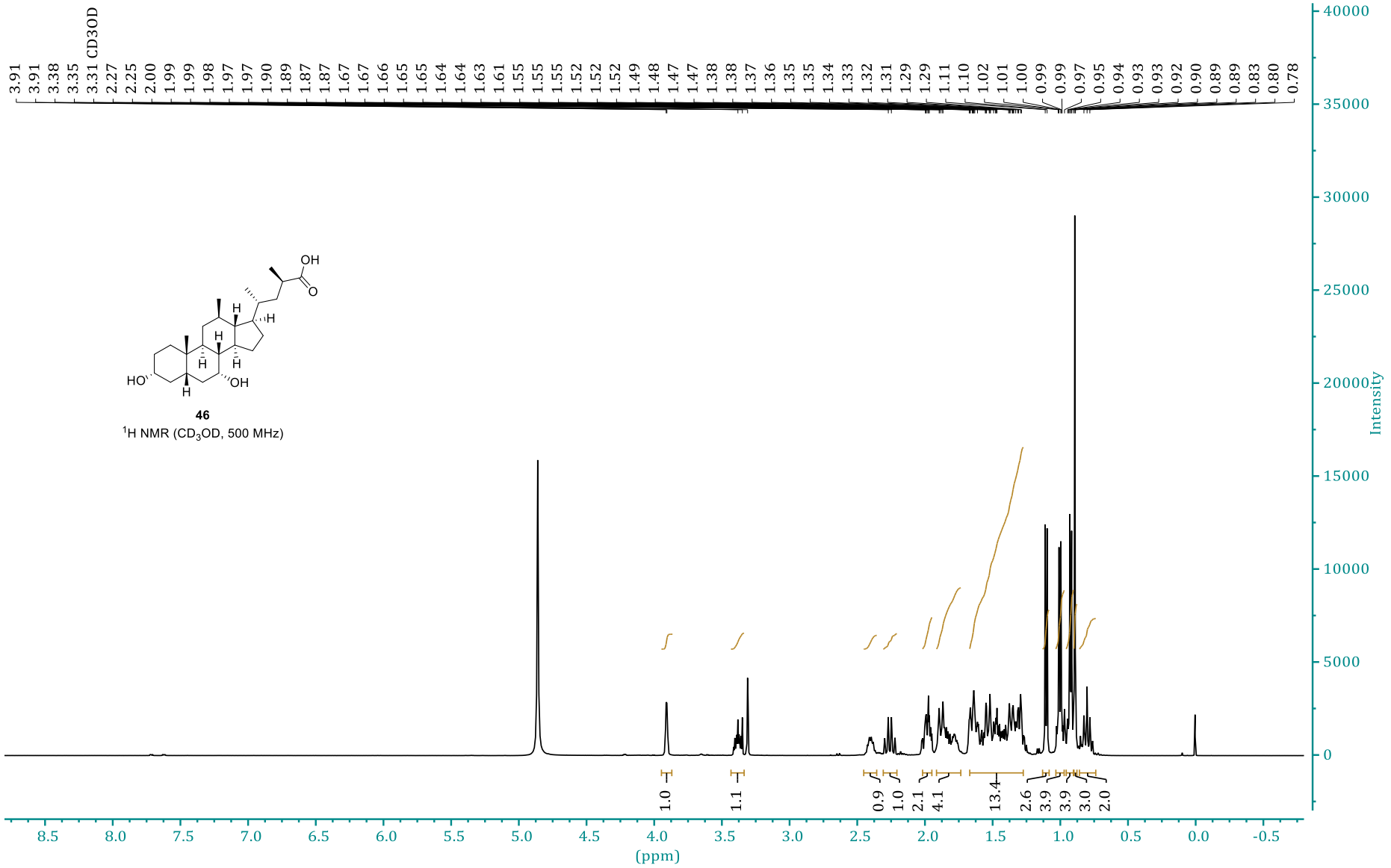
^{13}C NMR (CD_3OD, 126 MHz)

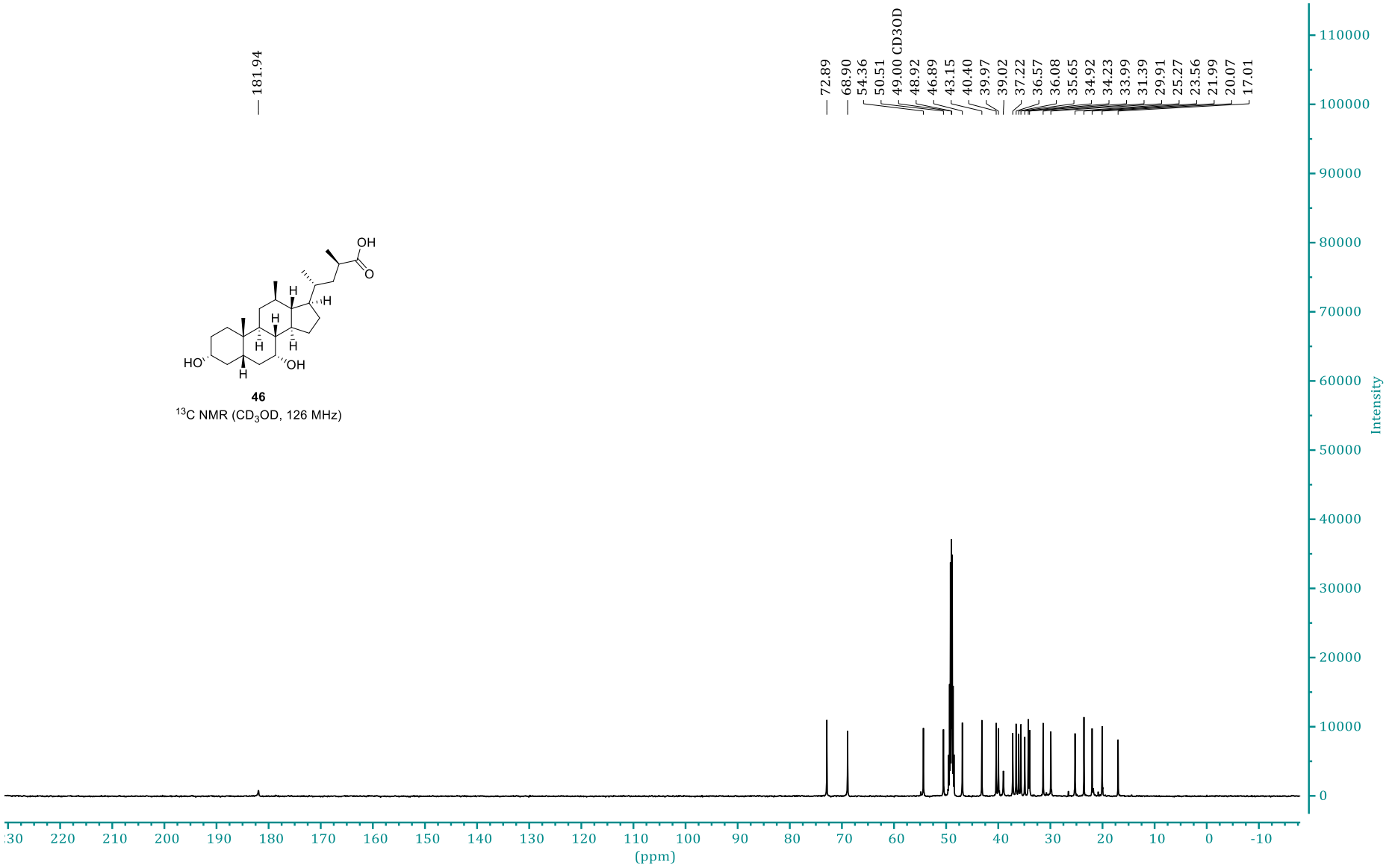

4.14 4.14 4.13 4.13 4.02 4.02 3.38 3.34 3.31 CD3OD 2.41 2.40 2.39 2.38 2.37 2.23 2.20 2.15 2.01 2.00 2.00 1.99 1.98 1.98 1.97 1.97 1.96 1.95 1.95 1.94 1.93 1.92 1.91 1.87 1.86 1.84 1.84 1.81 1.80 1.79 1.78 1.66 1.65 1.64 1.64 1.63 1.63 1.62 1.62 1.61 1.61 1.60 1.59 1.58 1.57 1.55 1.55 1.40 1.36 1.35 1.34 1.33 1.29 0.99 0.97 0.90 0.86 0.84
OH
O
H
H
H
OH
HO
H
H
H
OH
42
1H NMR (CD3OD, 500 MHz)
35000
30000
25000
20000
15000
10000
5000
0
Intensity
0.9 0.9 1.0 1.8 0.9 1.0 4.9 4.9 5.0 4.0 4.2 3.1 3.3
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)


178.24
75.24
72.99
67.63
51.26
49.00 CD3OD
47.79
43.05
42.93
40.68
40.42
39.63
36.26
36.20
35.78
35.17
34.79
34.73
33.54
33.12
31.53
29.77
23.89
22.12
14.28
OH
O
H
H
H
H
H
OH
HO
OH
H
42
1H NMR (CD3OD, 500 MHz)
25000
20000
15000
10000
5000
0
Intensity
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)


3.92
3.91
3.38
3.31 CD3OD
2.27
2.25
1.99
1.99
1.98
1.97
1.97
1.97
1.96
1.89
1.86
1.78
1.77
1.75
1.75
1.64
1.64
1.63
1.62
1.61
1.60
1.60
1.55
1.55
1.54
1.54
1.53
1.52
1.52
1.52
1.40
1.39
1.38
1.37
1.37
1.36
1.35
1.35
1.34
1.33
1.32
1.31
1.30
1.29
1.17
1.15
0.99
0.99
0.97
0.96
0.95
0.95
0.94
0.91
0.90
0.89
0.87
0.87
0.85
0.85
0.82
0.00
OH
O
H
H
H
H
H
H
HO
OH
45
1H NMR (CD3OD, 500 MHz)
Intensity
30000
25000
20000
15000
10000
5000
0
1.0
1.1
1.0
1.2
2.2
1.2
4.0
3.2
3.0
5.1
2.8
1.0
0.9
6.8
2.9
1.8
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
(ppm)

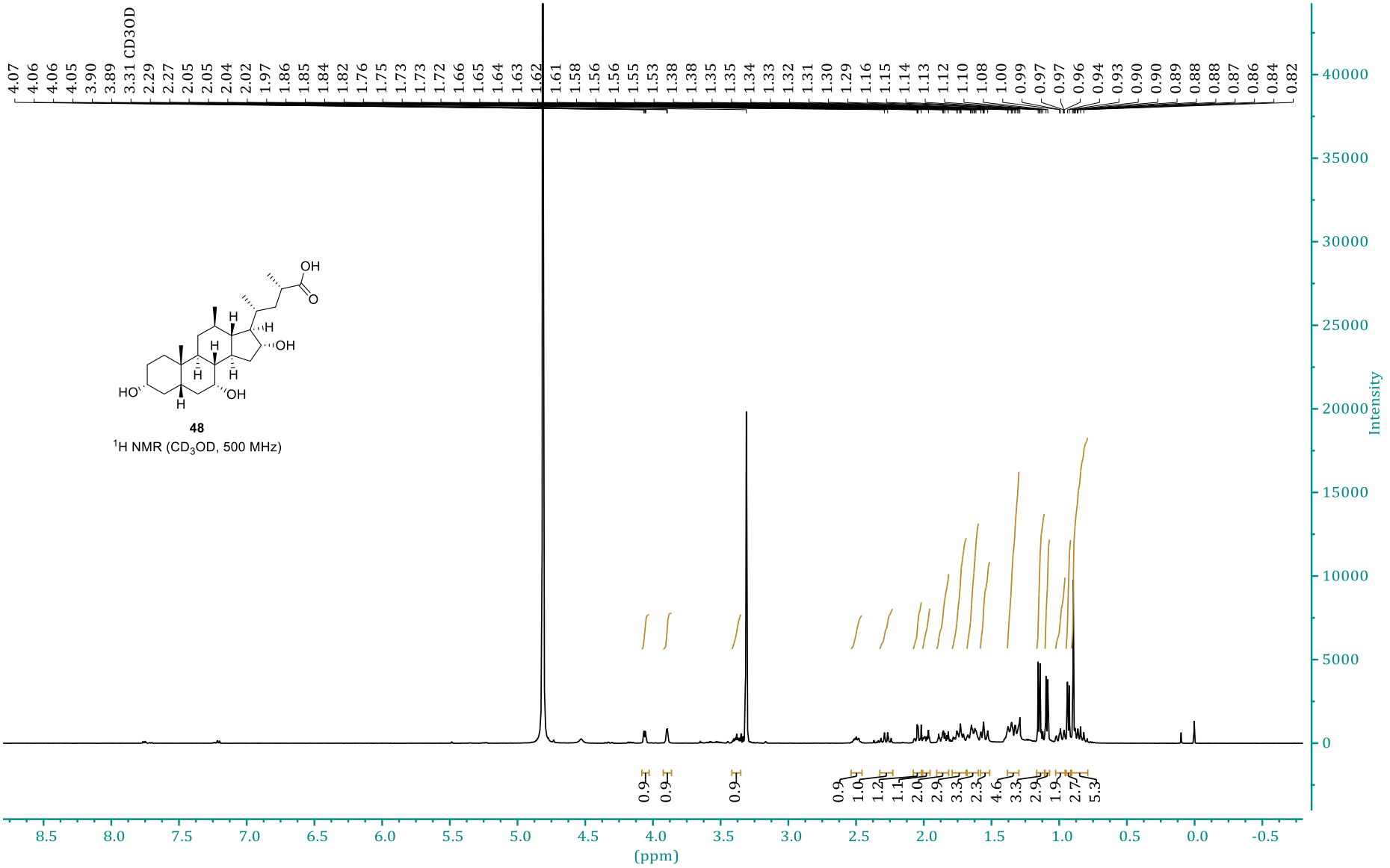

181.42
72.92
69.03
54.20
50.15
49.00 CD3OD
46.82
43.17
40.42
40.13
39.52
37.07
36.59
36.23
36.11
35.66
34.97
34.29
31.39
30.24
25.20
23.56
21.65
20.41
19.45
OH
O
H
H
H
H
H
HO
OH
H
45
13C NMR (CD3OD, 126 MHz)
Intensity
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
(ppm)

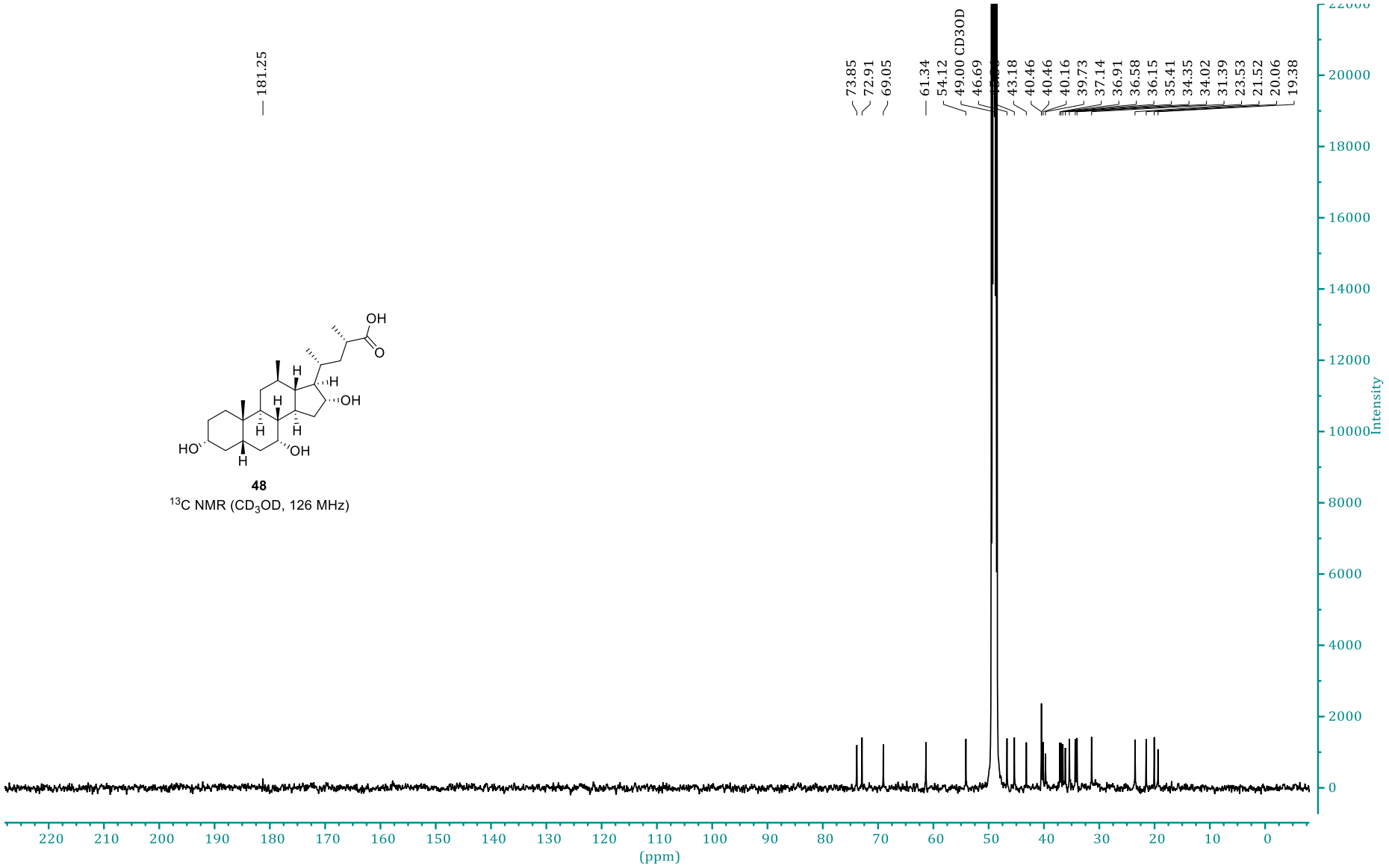

3.91 3.91 3.38 3.35 3.31 CD3OD 2.27 2.25 2.00 1.99 1.99 1.98 1.97 1.97 1.90 1.89 1.87 1.87 1.67 1.67 1.66 1.65 1.65 1.64 1.64 1.63 1.61 1.55 1.55 1.55 1.52 1.52 1.52 1.49 1.48 1.47 1.47 1.38 1.38 1.37 1.36 1.35 1.35 1.34 1.33 1.32 1.31 1.29 1.29 1.11 1.10 1.02 1.01 1.00 0.99 0.99 0.97 0.95 0.94 0.93 0.93 0.92 0.90 0.89 0.89 0.83 0.80 0.78
OH
O
H
H
H
H
H
HO
OH
H
46
1H NMR (CD3OD, 500 MHz)
40000
35000
30000
25000
20000
15000
10000
5000
0
Intensity
1.0 1.1 0.9 1.0 2.1 4.1 13.4 2.6 3.9 3.9 3.0 2.0
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)



46

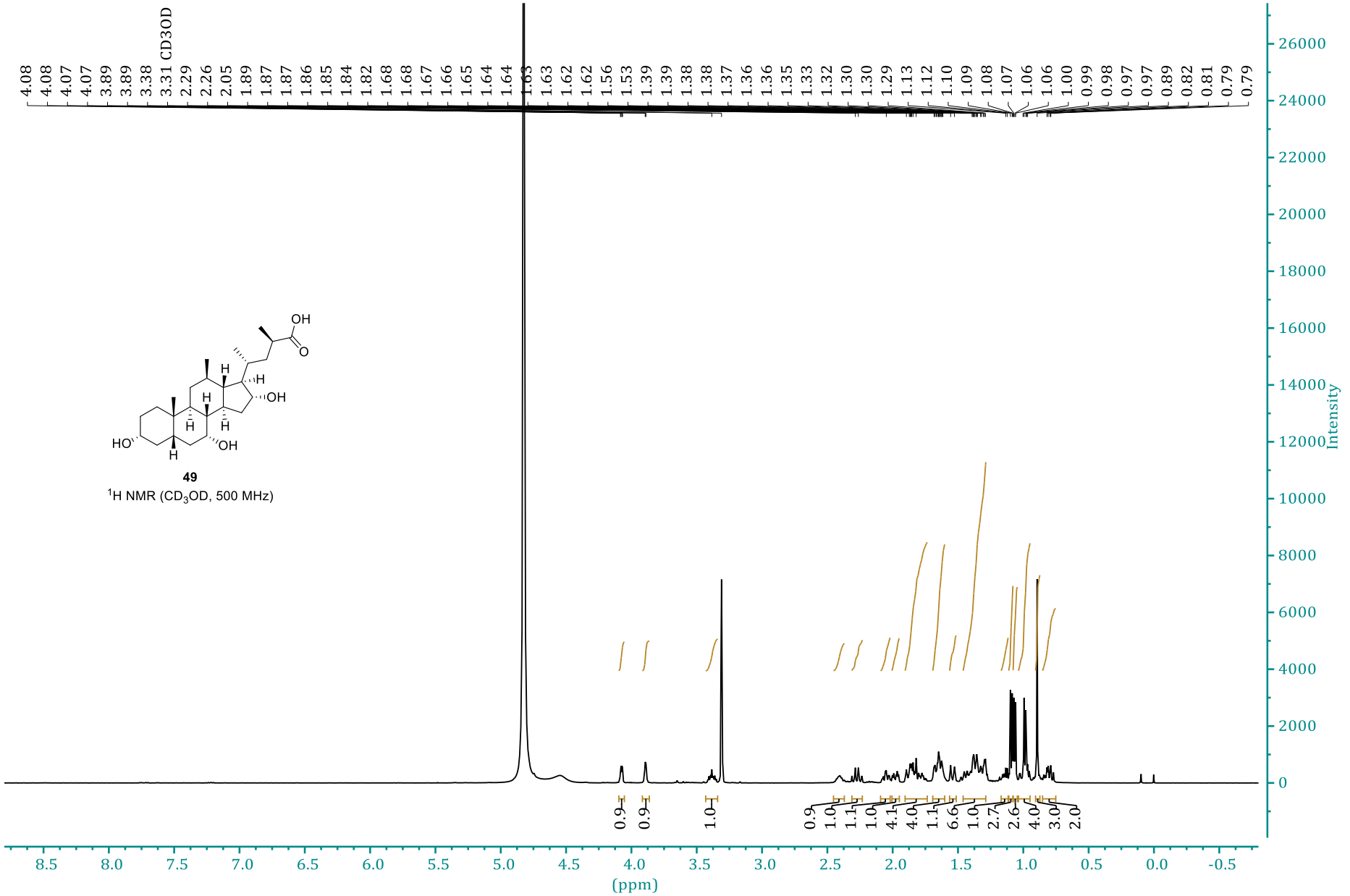
^{13}C NMR (CD_3OD, 126 MHz)

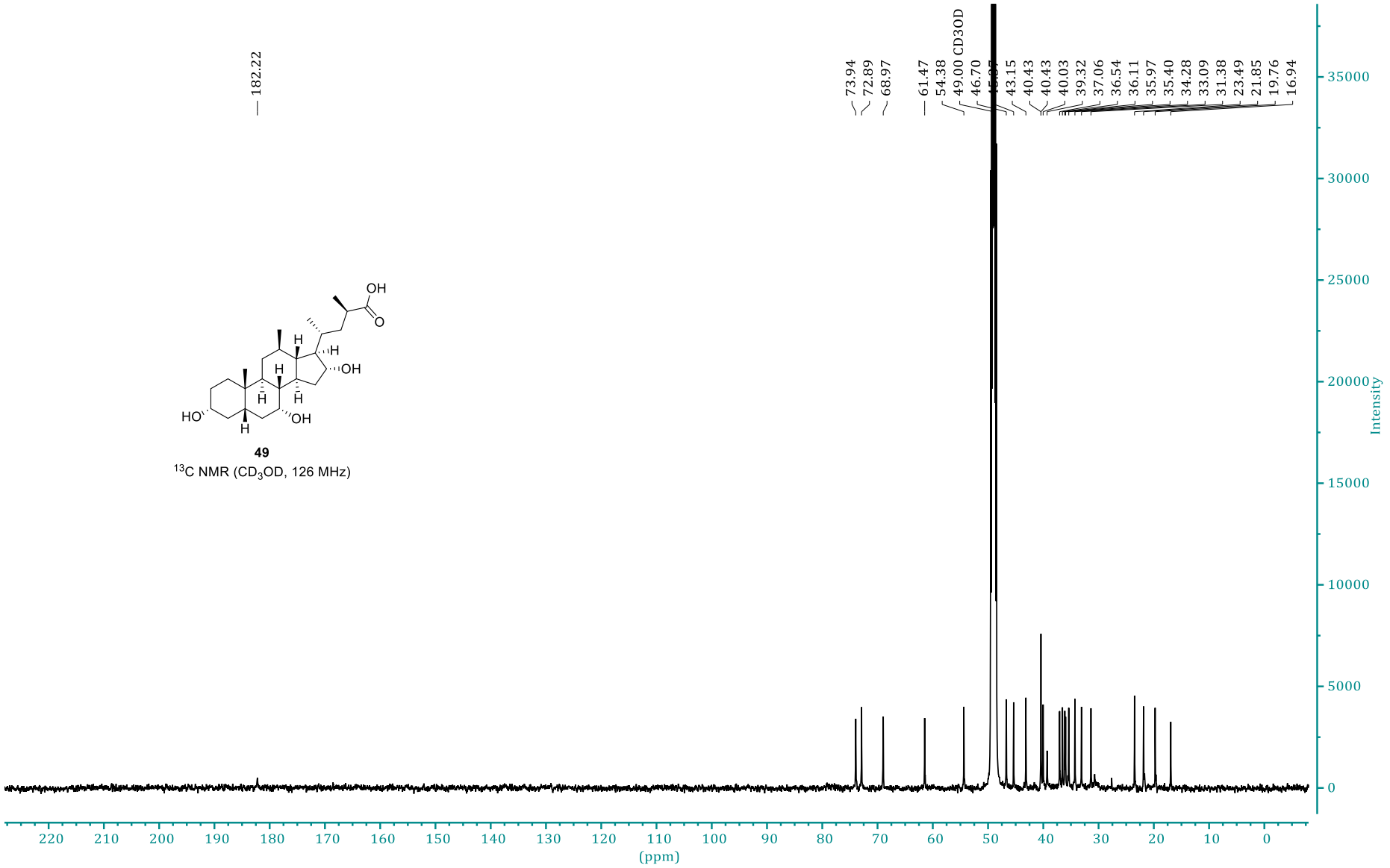

4.07 4.06 4.06 4.05 3.90 3.89 3.31 CD3OD 2.29 2.27 2.05 2.05 2.04 2.02 1.97 1.86 1.85 1.84 1.82 1.76 1.75 1.73 1.73 1.72 1.66 1.65 1.64 1.63 1.62 1.61 1.58 1.56 1.56 1.55 1.53 1.38 1.38 1.35 1.35 1.34 1.33 1.32 1.31 1.30 1.29 1.16 1.15 1.14 1.13 1.12 1.10 1.08 1.00 0.99 0.97 0.97 0.96 0.94 0.93 0.90 0.90 0.89 0.88 0.88 0.87 0.86 0.84 0.82
OH
O
H
H
OH
H
H
H
HO
OH
H
48
1H NMR (CD3OD, 500 MHz)
Intensity
40000
35000
30000
25000
20000
15000
10000
5000
0
0.9 0.9 0.9 0.9 1.0 1.2 1.1 2.0 2.9 3.3 2.3 4.6 3.3 2.9 1.9 2.7 5.3
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)



48

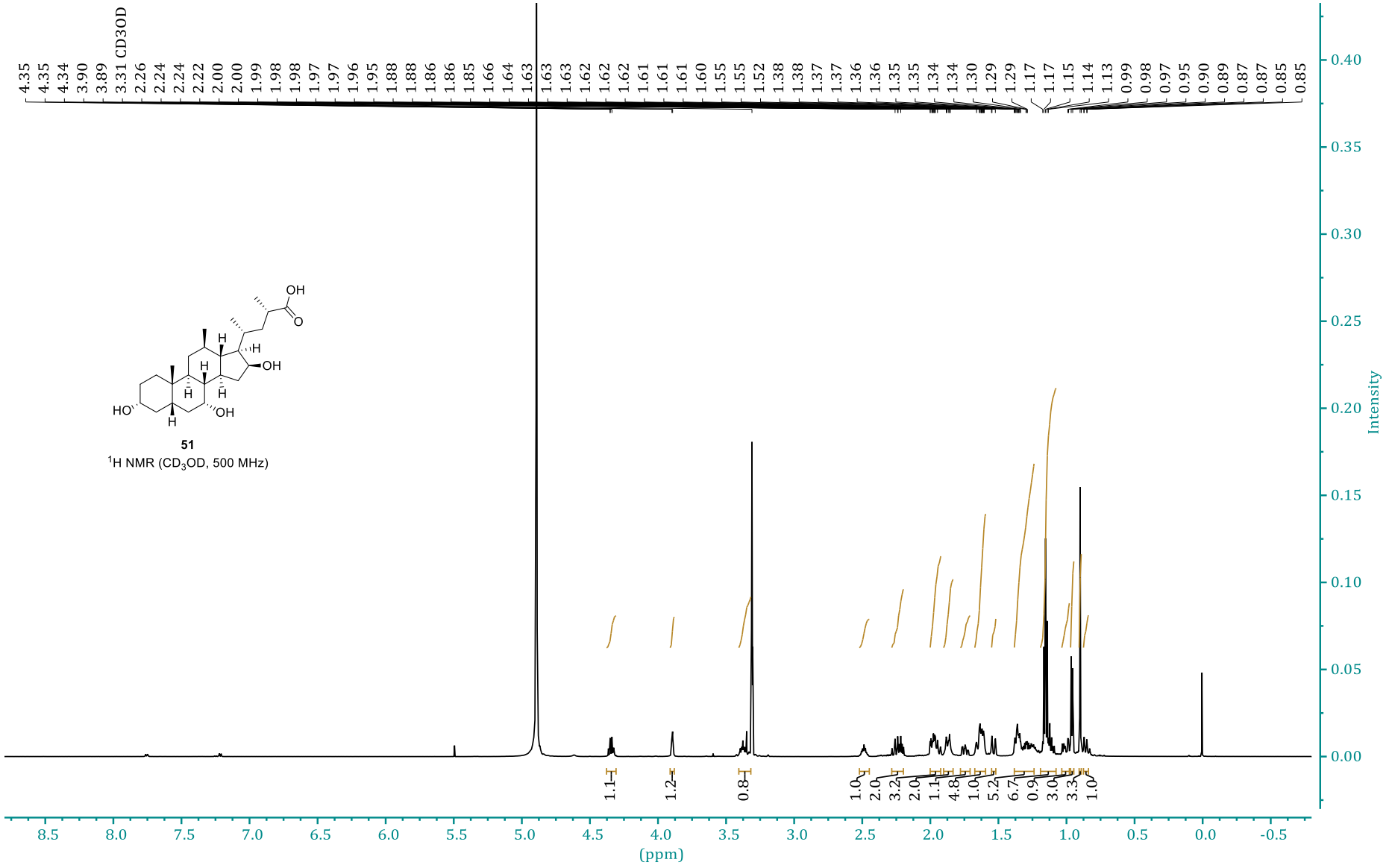
^{13}C NMR (CD_3OD, 126 MHz)

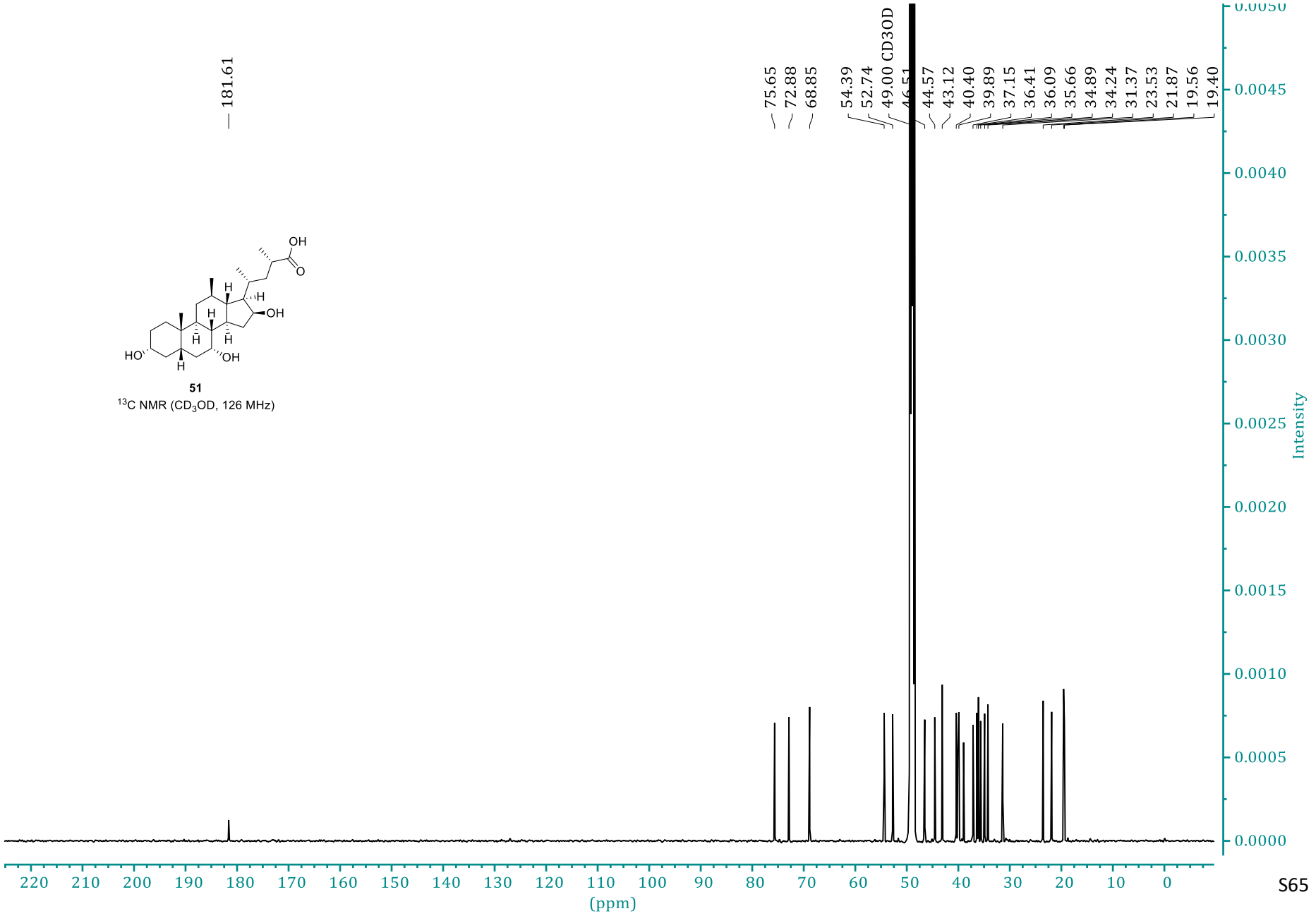

4.08 4.08 4.07 4.07 3.89 3.89 3.38 3.31 CD3OD 2.29 2.26 2.05 1.89 1.87 1.87 1.86 1.85 1.84 1.82 1.68 1.68 1.67 1.66 1.65 1.64 1.64 1.63 1.63 1.62 1.62 1.56 1.53 1.39 1.39 1.38 1.38 1.37 1.36 1.36 1.35 1.33 1.32 1.30 1.30 1.29 1.13 1.12 1.10 1.09 1.08 1.07 1.06 1.06 1.00 0.99 0.98 0.97 0.97 0.89 0.82 0.81 0.79 0.79
OH
O
H
H
H
OH
H
H
H
HO
OH
H
49
1H NMR (CD3OD, 500 MHz)
0.9 0.9 1.0 0.9 1.0 1.1 1.0 4.1 4.0 1.1 6.6 1.0 2.7 2.6 4.0 3.0 2.0
Intensity
(ppm)



49

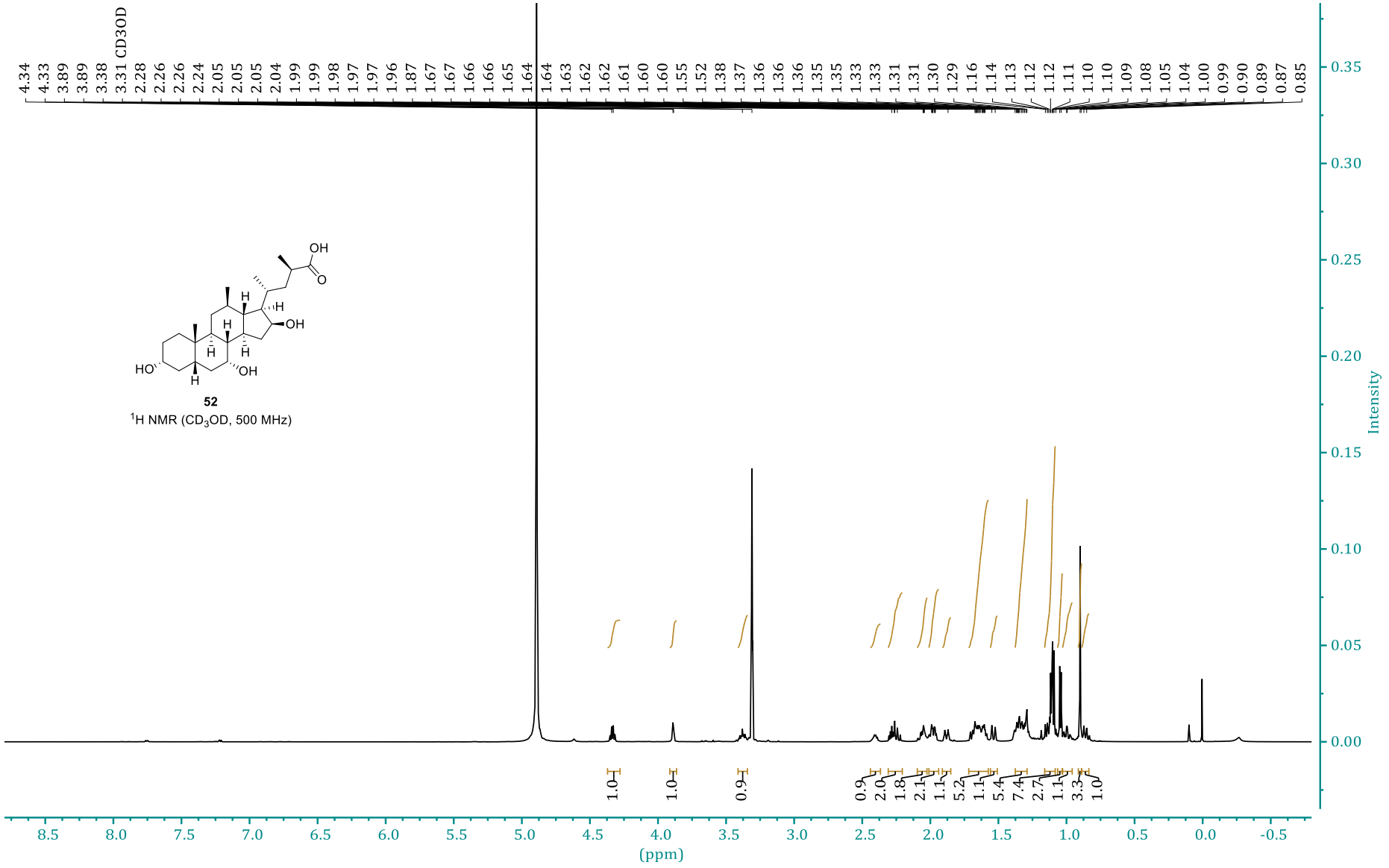
^{13}C NMR (CD_3OD, 126 MHz)

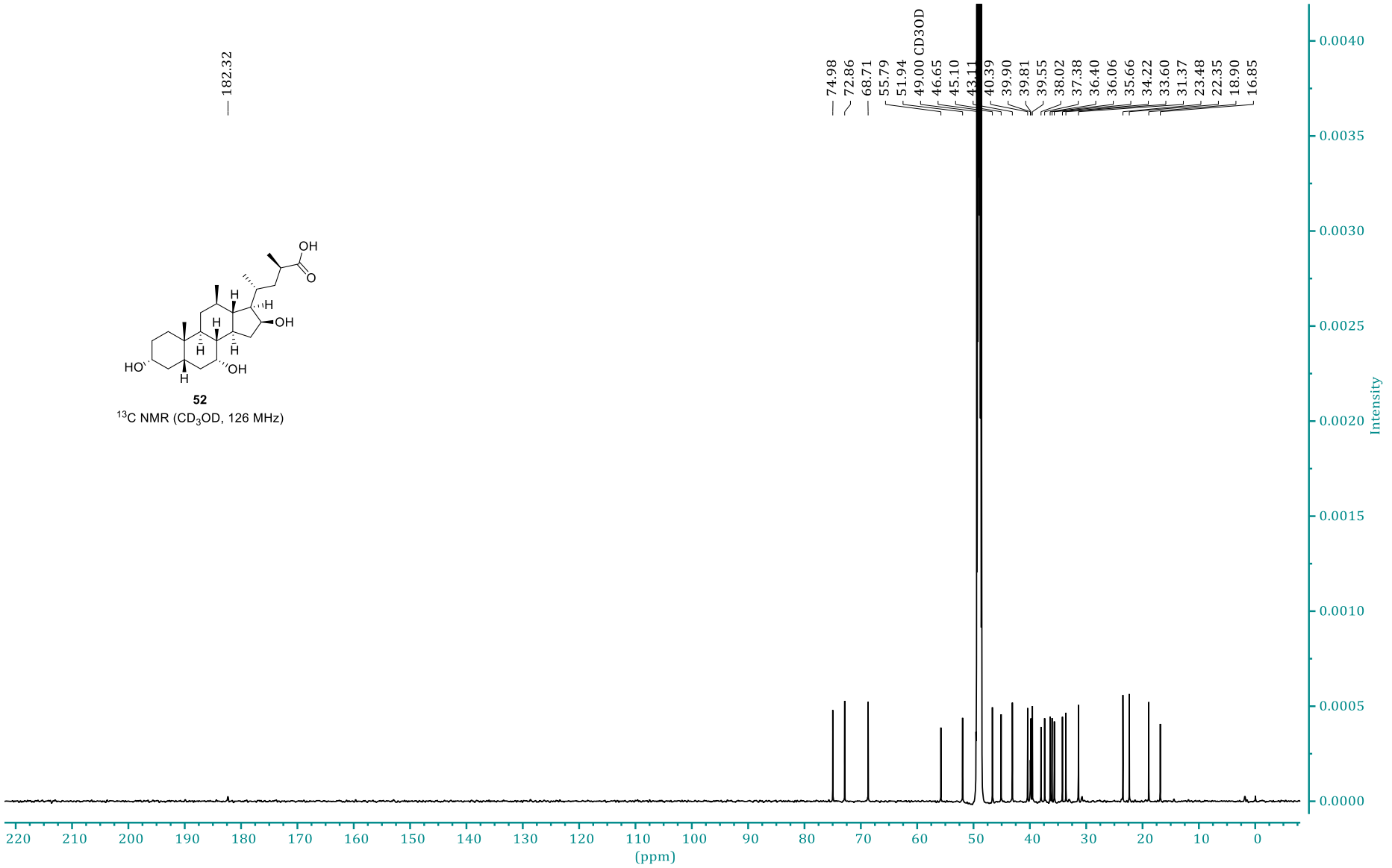

4.35 4.35 4.34 3.90 3.89 3.31 CD3OD 2.26 2.24 2.24 2.22 2.00 2.00 1.99 1.98 1.98 1.97 1.97 1.96 1.95 1.88 1.88 1.86 1.86 1.85 1.66 1.64 1.63 1.63 1.63 1.63 1.62 1.62 1.62 1.61 1.61 1.61 1.60 1.55 1.55 1.52 1.38 1.38 1.37 1.37 1.36 1.36 1.35 1.35 1.34 1.34 1.30 1.29 1.29 1.17 1.17 1.15 1.14 1.13 0.99 0.98 0.97 0.95 0.90 0.89 0.87 0.87 0.85 0.85
OH
O
H
H
H
OH
H
H
HO
OH
H
51
1H NMR (CD3OD, 500 MHz)
1.1 1.2 0.8 1.0 2.0 3.2 2.0 1.1 4.8 1.0 5.2 6.7 0.9 3.0 3.3 1.0
Intensity
0.40 0.35 0.30 0.25 0.20 0.15 0.10 0.05 0.00
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)



51

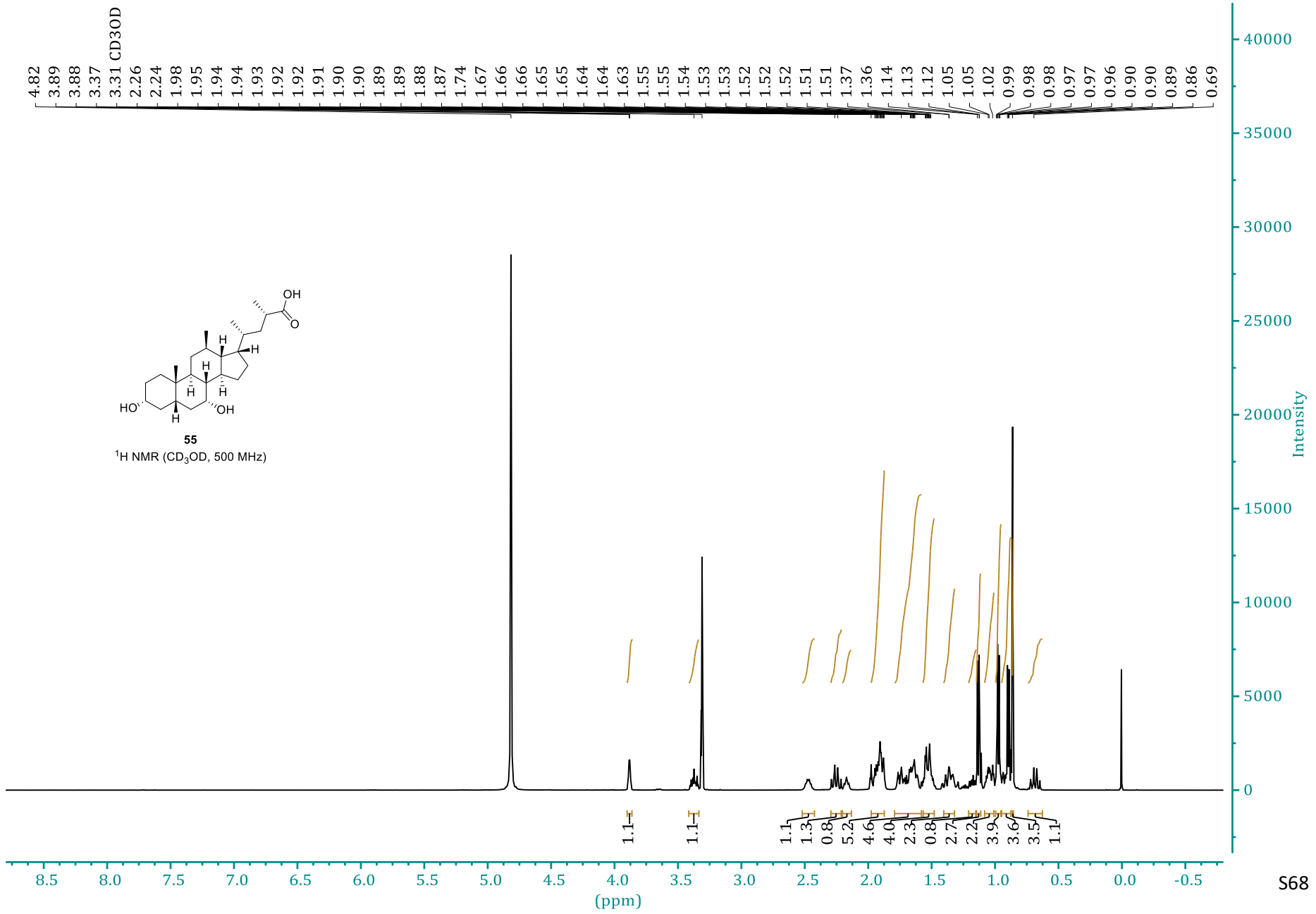
^{13}C NMR (CD_3OD, 126 MHz)

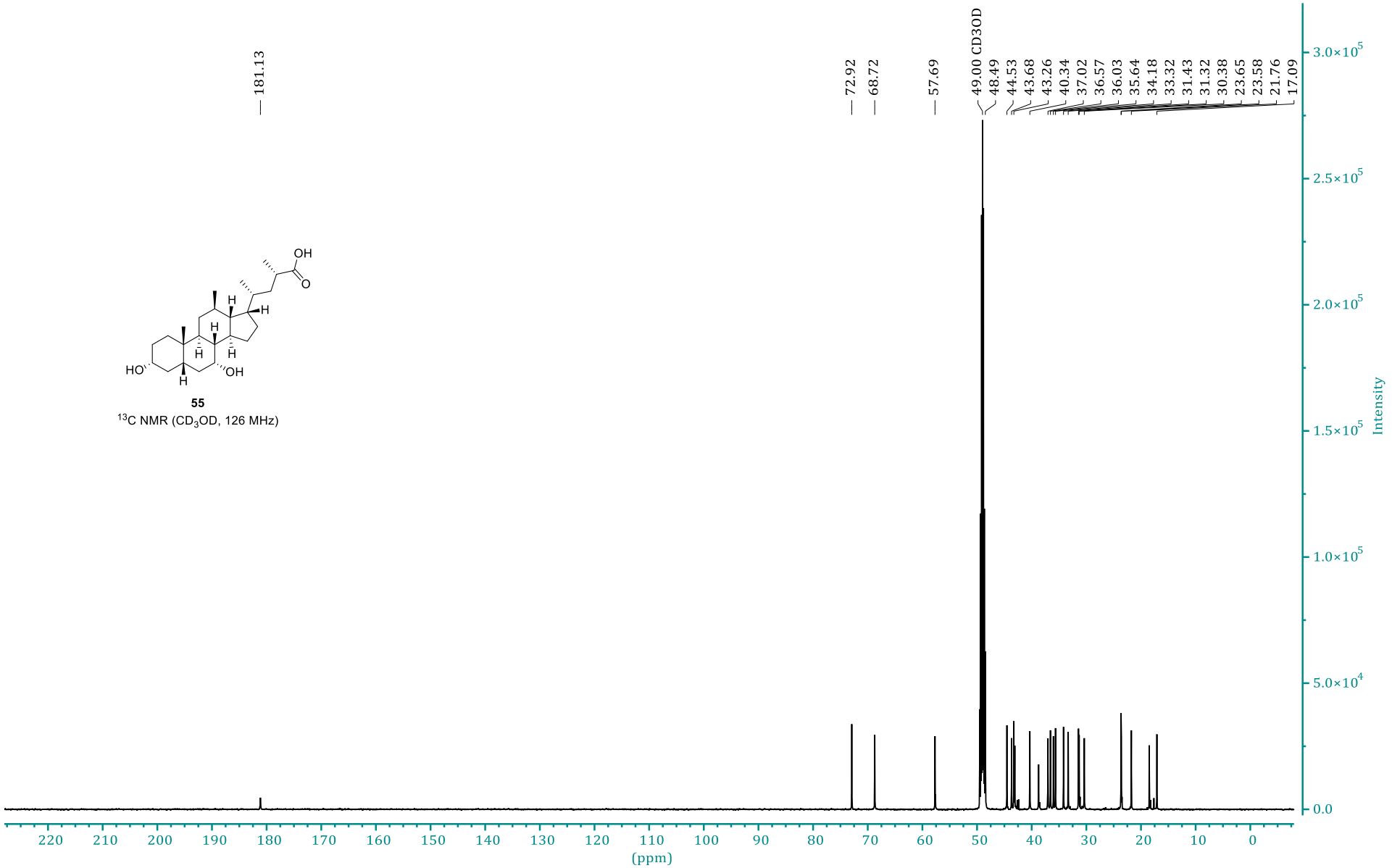

4.34 4.33 3.89 3.89 3.38 3.31 CD3OD 2.28 2.26 2.26 2.24 2.05 2.05 2.05 2.04 1.99 1.99 1.98 1.97 1.97 1.96 1.87 1.67 1.67 1.66 1.66 1.65 1.64 1.64 1.63 1.62 1.62 1.61 1.60 1.60 1.55 1.52 1.38 1.37 1.36 1.36 1.36 1.35 1.35 1.33 1.33 1.31 1.31 1.30 1.29 1.16 1.14 1.13 1.12 1.12 1.11 1.10 1.10 1.09 1.08 1.05 1.04 1.00 0.99 0.90 0.89 0.87 0.85
OH
O
H
H
H
OH
H
H
HO
OH
H
52
1H NMR (CD3OD, 500 MHz)
Intensity
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
1.0 1.0 0.9 0.9 2.0 1.8 2.1 1.1 5.2 1.1 5.4 7.4 2.7 1.1 3.3 1.0
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)



52

^{13}C NMR (CD_3OD, 126 MHz)


4.82 3.89 3.88 3.37 3.31 CD3OD 2.26 2.24 1.98 1.95 1.94 1.94 1.93 1.92 1.92 1.91 1.90 1.90 1.89 1.89 1.88 1.87 1.74 1.67 1.66 1.66 1.65 1.65 1.64 1.64 1.63 1.55 1.55 1.54 1.53 1.53 1.52 1.52 1.52 1.51 1.51 1.37 1.36 1.14 1.13 1.12 1.05 1.05 1.02 0.99 0.98 0.98 0.97 0.97 0.96 0.90 0.90 0.89 0.86 0.69
OH
O
H
H
H
H
H
HO
OH
H
55
1H NMR (CD3OD, 500 MHz)
40000
35000
30000
25000
20000
15000
10000
5000
0
Intensity
1.1 1.1 1.1 1.3 0.8 5.2 4.6 4.0 2.3 0.8 2.7 2.2 3.9 3.6 3.5 1.1
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)



55

^{13}C NMR (CD_3OD, 126 MHz)

2. HPLC Analysis

2.1 General HPLC Conditions

Mass spectrometer ran with electrospray ionisation (ESI) in negative mode for all methods described.

HPLC Method A

Column: Phenomenex Kinetex 2.6 µM C-18, pore size = 100 Å C-18 100×30 mm
Column Temperature: 40 °C
Detection: CAD
Flow Rate: 0.5 mL/min
Sample Solvent: Methanol (2 µL injection)
Mobile Phase A: Water + 0.1% Formic Acid
Mobile Phase B: Methanol

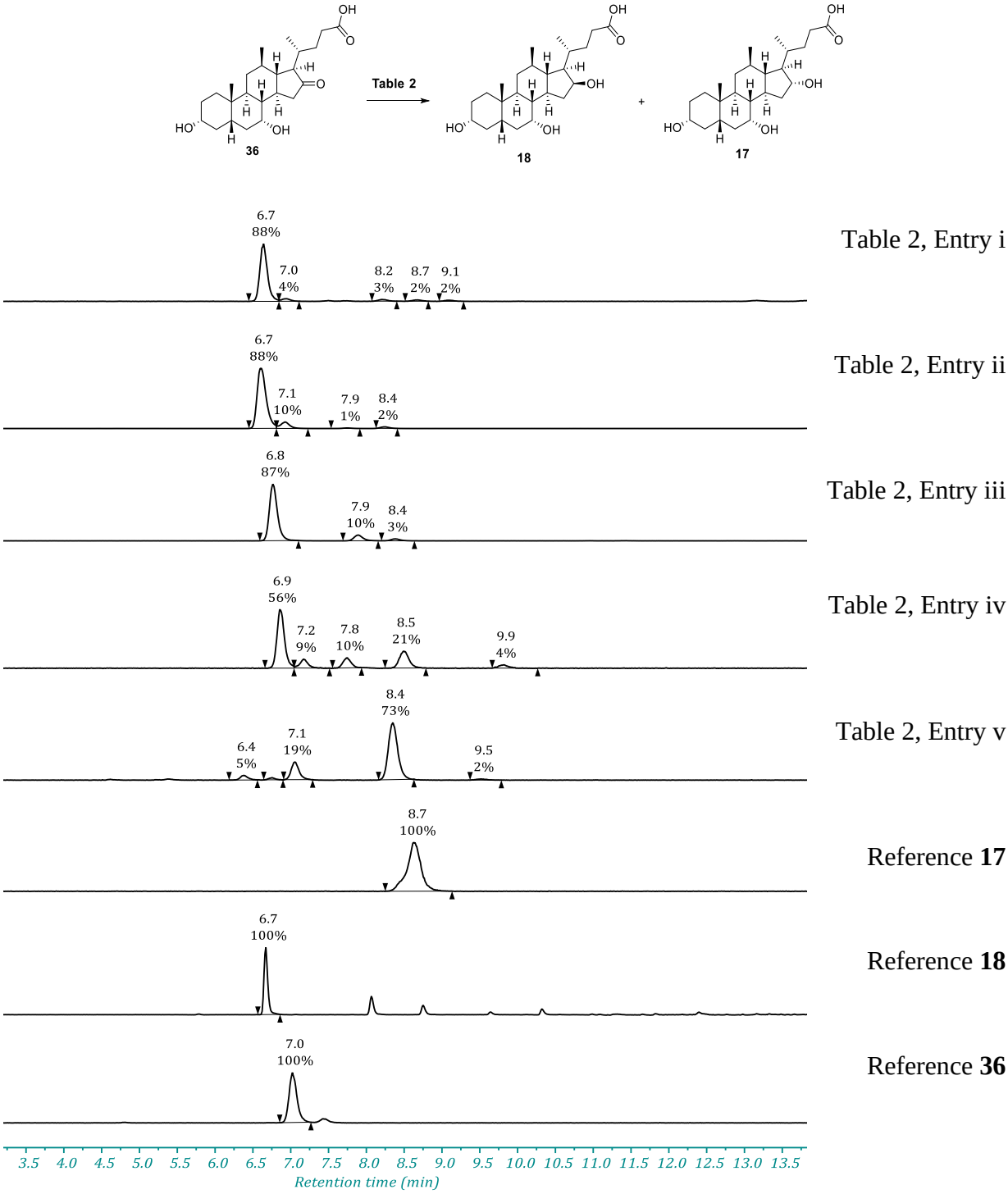
HPLC Method B

Column: Phenomenex Kinetex 2.6 µM C-18, pore size = 100 Å C-18 50×30 mm
Column Temperature: 40 °C
Detection: ELSD (40 °C)
Flow Rate: 1 mL/min
Sample Solvent: Methanol (1 µL injection)
Mobile Phase A: Water + 0.1% Formic Acid
Mobile Phase B: Methanol

HPLC Method C

Column: Poroshell 2.6 µM C-18, pore size = 100 Å C-18 100×30 mm
Column Temperature: 40 °C
Detection: ELSD (60 °C)
Flow Rate: 1 mL/min
Sample Solvent: Methanol (1 µL injection)
Mobile Phase A: 5 mM Ammonium Formate and 0.012% Formic acid in Water
Mobile Phase B: 5 mM Ammonium Formate and 0.012% Formic acid in Methanol

2.2. HPLC analysis of reaction mixtures isolated from the reduction of 36

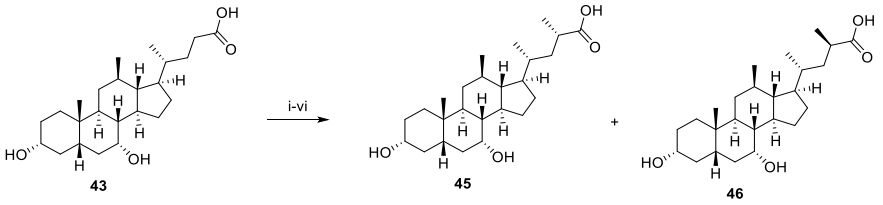


HPLC Method: **A**

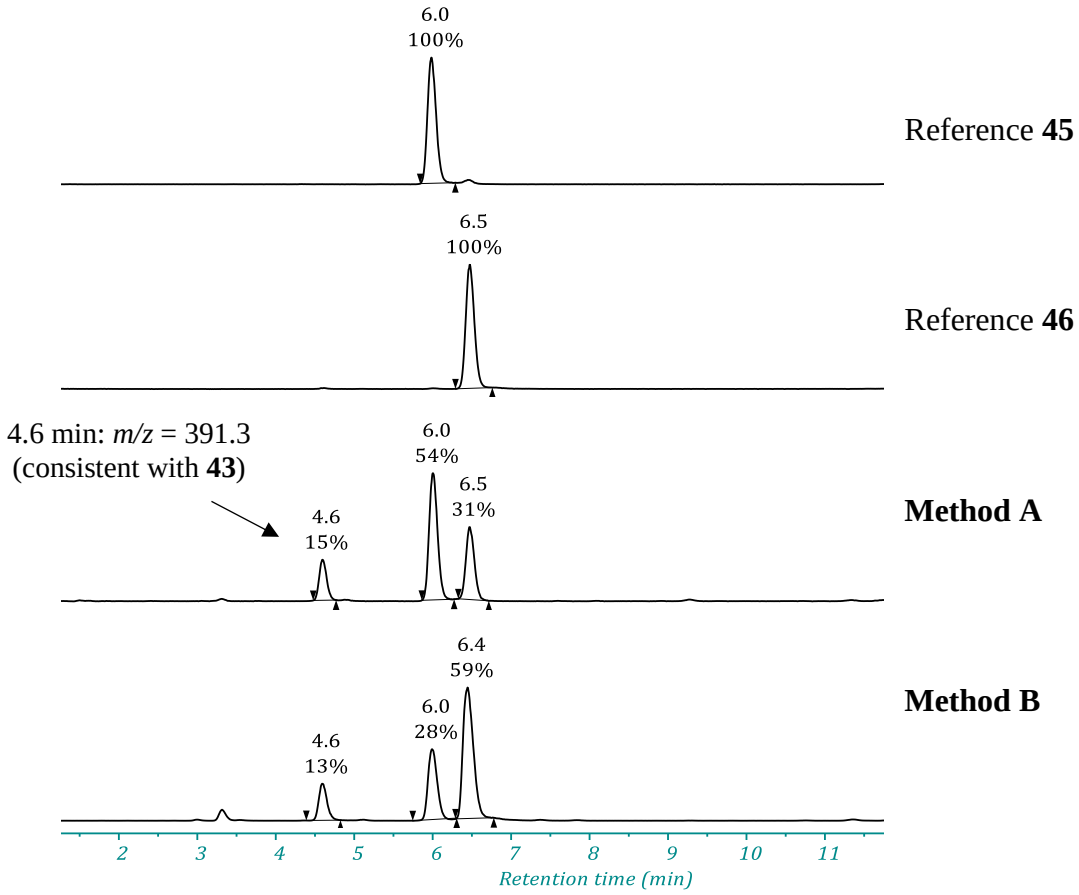
Solvent Gradient (%B): T0=30, T1=50, T13=55, T14=100, T15.5=100, T16=30, T17=30

2.3. HPLC analysis of reaction mixtures isolated from the C23-methylation of 43

Scheme S1. C23-methylation of **43**.[a]



[a]Reaction conditions: i) *p*TSA, MeOH; ii) DHP, *p*TSA, dioxane; iii) **Method A**: LDA, MeI, THF or **Method B**: KHMDS, HMPA, MeI, THF; iv) 2 M $HCl_{(aq)}$, MeOH; v) 2 M $NaOH_{(aq)}$, MeOH; vi) 2 M $HCl_{(aq)}$.

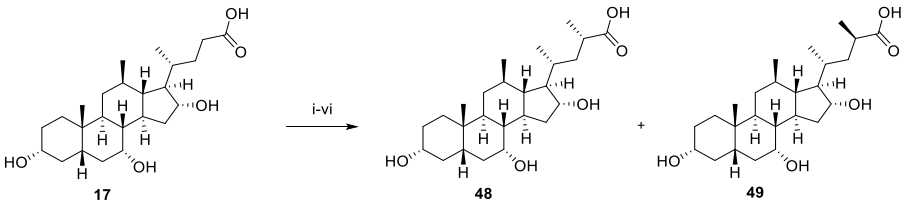


HPLC Method: **A**

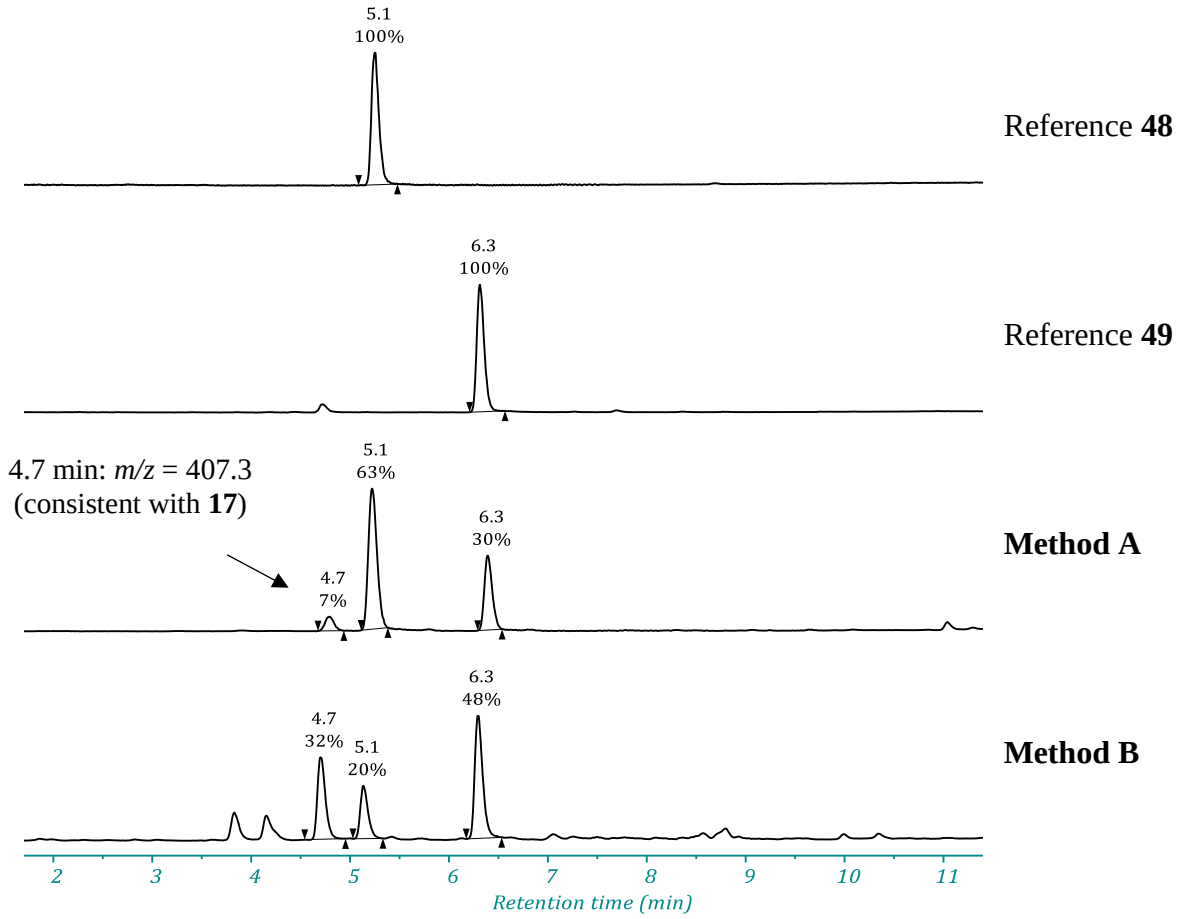
Solvent Gradient (%B): T0=60, T10=70, T11=100, T12=100, T14=60, T16=60

2.4. HPLC analysis of reaction mixture from the C23-methylation of 17

Scheme S2. C23-methylation of **17**.[a]



[a]Reaction and conditions: i) *p*TSA, MeOH; ii) DHP, *p*TSA, dioxane; iii) **Method A**: LDA, MeI, THF or **Method B**: KHMDS, HMPA, MeI, THF; iv) 2 M HCl(aq), MeOH; v) 2 M NaOH(aq), MeOH; vi) 2 M HCl(aq).

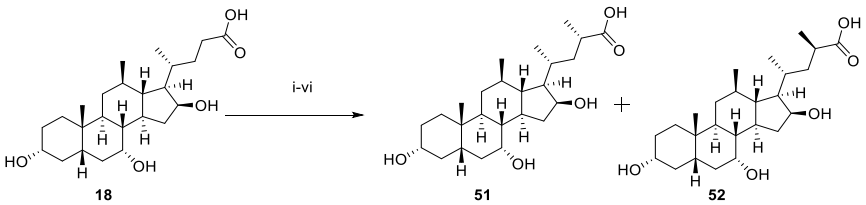


HPLC Method: **A**

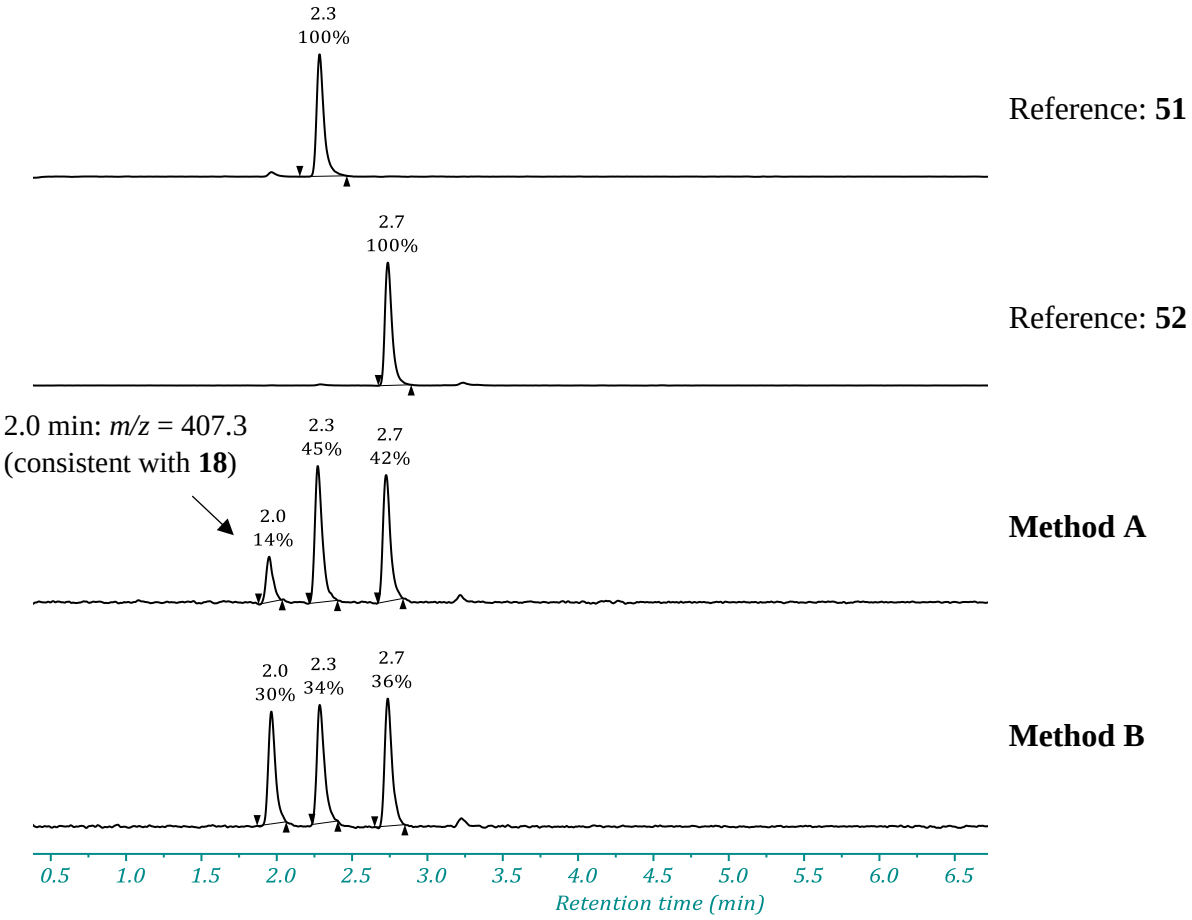
Solvent Gradient (%B): T0=50, T10=80, T11=100, T13=100, T14=50, T16=50

2.5. HPLC analysis of reaction mixture from the C23-methylation of 18

Scheme S3. C23-methylation of **18**.[a]



[a]Reaction and conditions: i) *p*TSA, MeOH; ii) DHP, *p*TSA, dioxane; iii) **Method A**: LDA, MeI, THF or **Method B**: KHMDS, HMPA, MeI, THF; iv) 2 M HCl(aq), MeOH; v) 2 M NaOH(aq), MeOH; vi) 2 M HCl(aq).

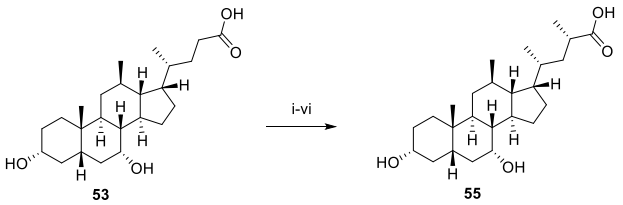


HPLC Method: **B**

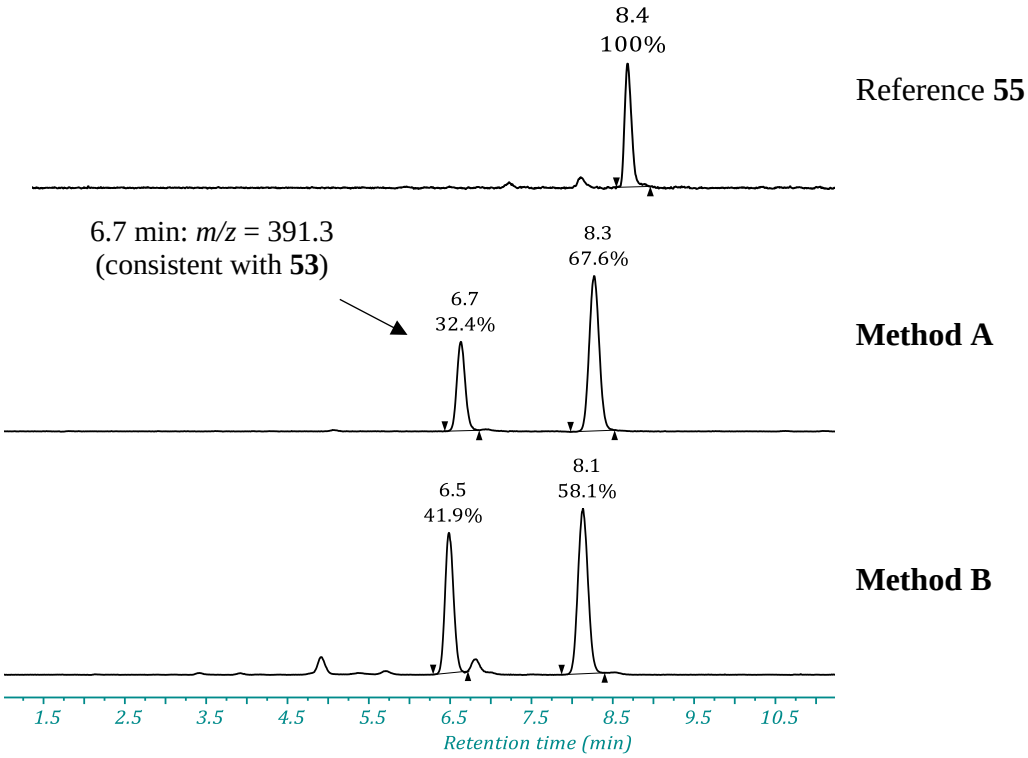
Solvent Gradient (%B): T0=50, T6=100, T8=100, T9=50, T10=50

2.6. HPLC analysis of reaction mixture from the C23-methylation of 53

Scheme S4. C23-methylation of **53**.[a]



[a]Reaction and conditions: i) *p*TSA, MeOH; ii) DHP, *p*TSA, dioxane; iii) **Method A**: LDA, MeI, THF or **Method B**: KHMDS, HMPA, MeI, THF; iv) 2 M HCl(aq), MeOH; v) 2 M NaOH(aq), MeOH; vi) 2 M HCl(aq).

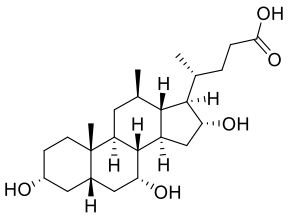


HPLC Method: **A**

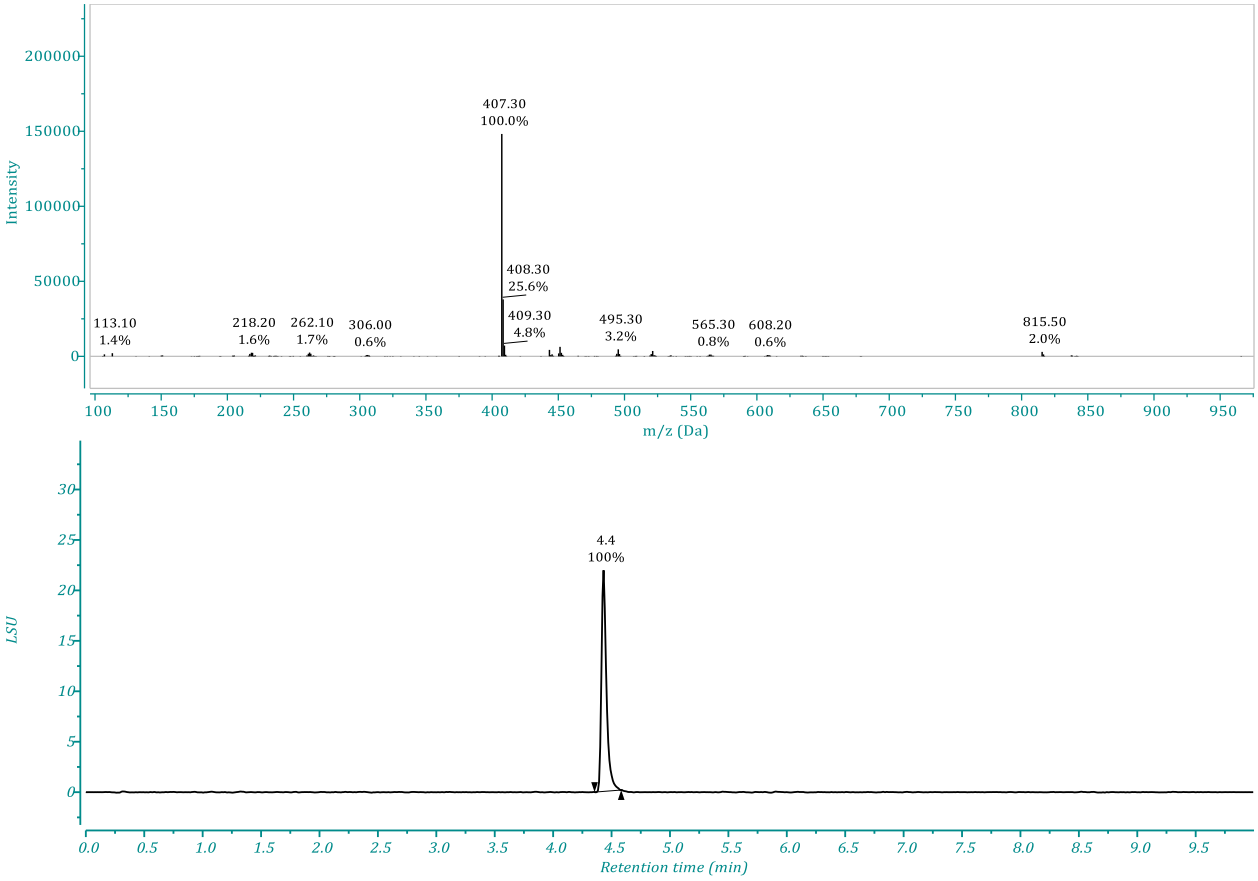
Solvent Gradient (%B): T0=60, T10=70, T11=100, T12=100, T14=60, T16=60

2.7. Purity of compounds tested for biological activity as determined by HPLC analysis

2.7.1 LCMS analysis of compound **17**



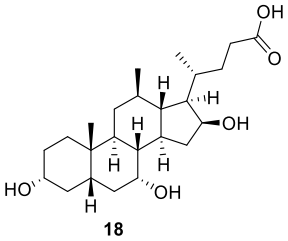
17



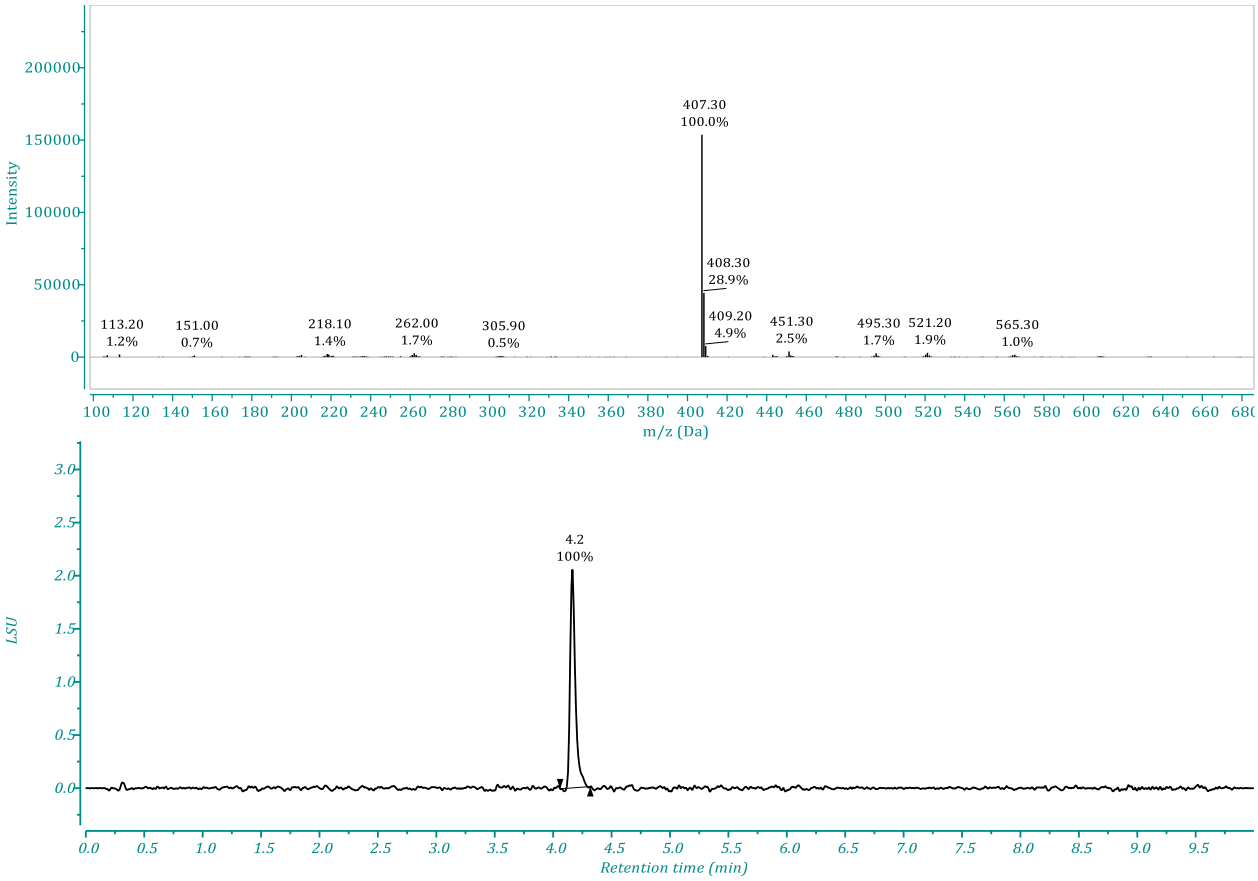
HPLC Method: **B**

Solvent Gradient (%B): T0=30, T7=100, T9=100, T9.5=30, T10=30

2.7.2. LCMS analysis of compound **18**



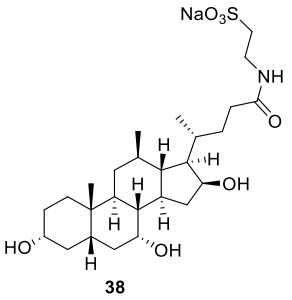
18



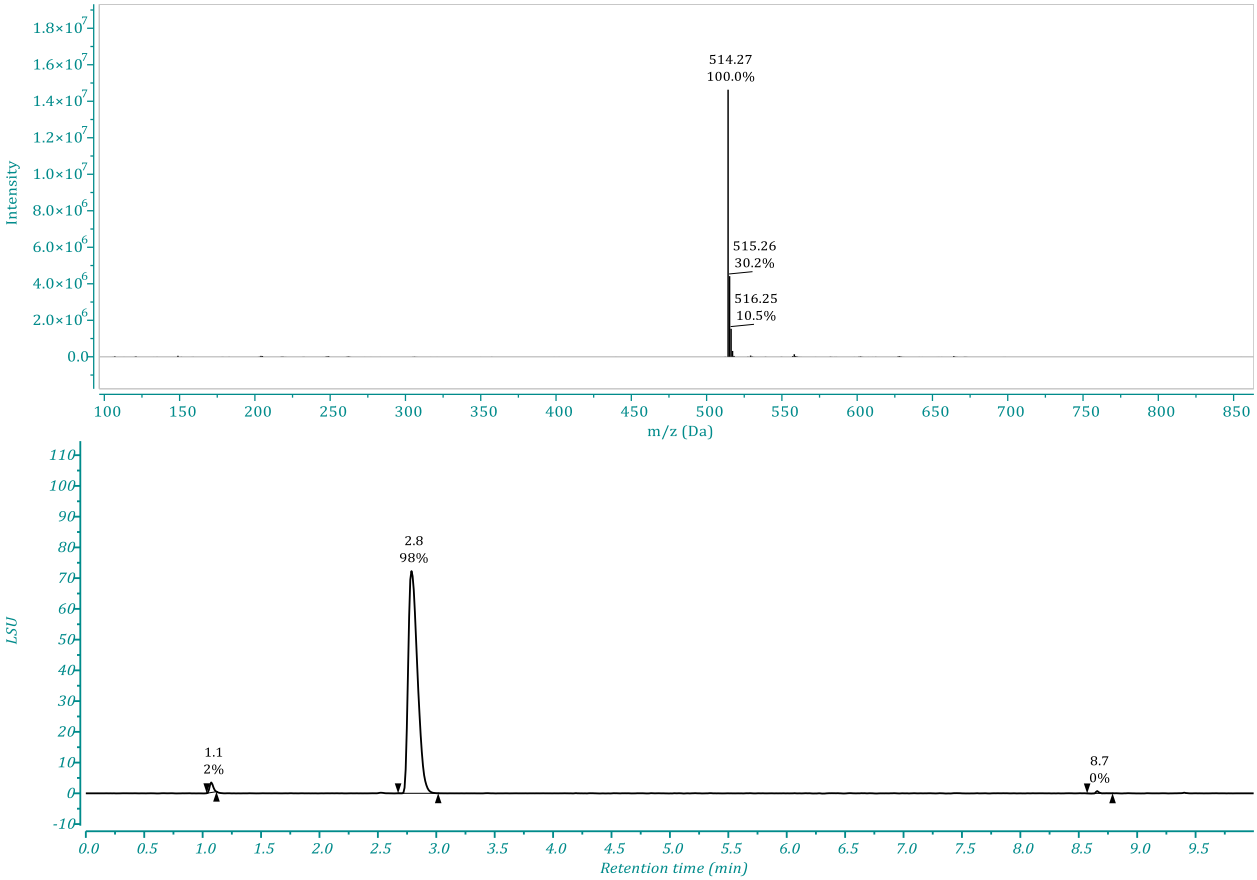
HPLC Method: **B**

Solvent Gradient (%B): T0=30, T7=100, T9=100, T9.5=30, T10=30

2.7.3. LCMS analysis of compound **38**



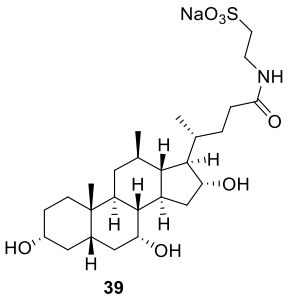
38



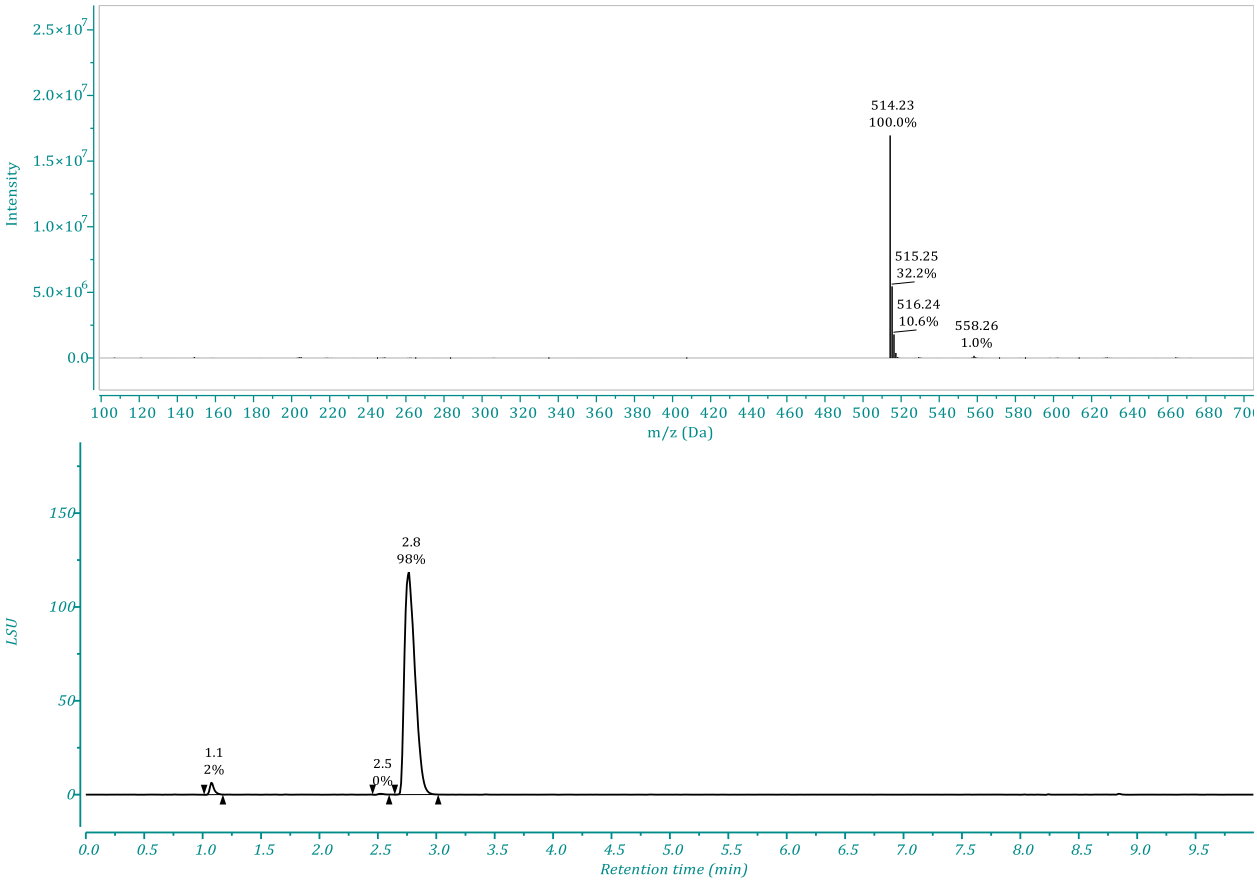
HPLC Method: **C**

Solvent Gradient (%B): T0=50, T7=100, T9=100, T9.5=50, T10=50

2.7.4 LCMS analysis of compound **39**



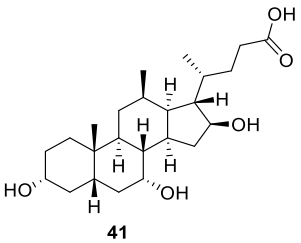
39



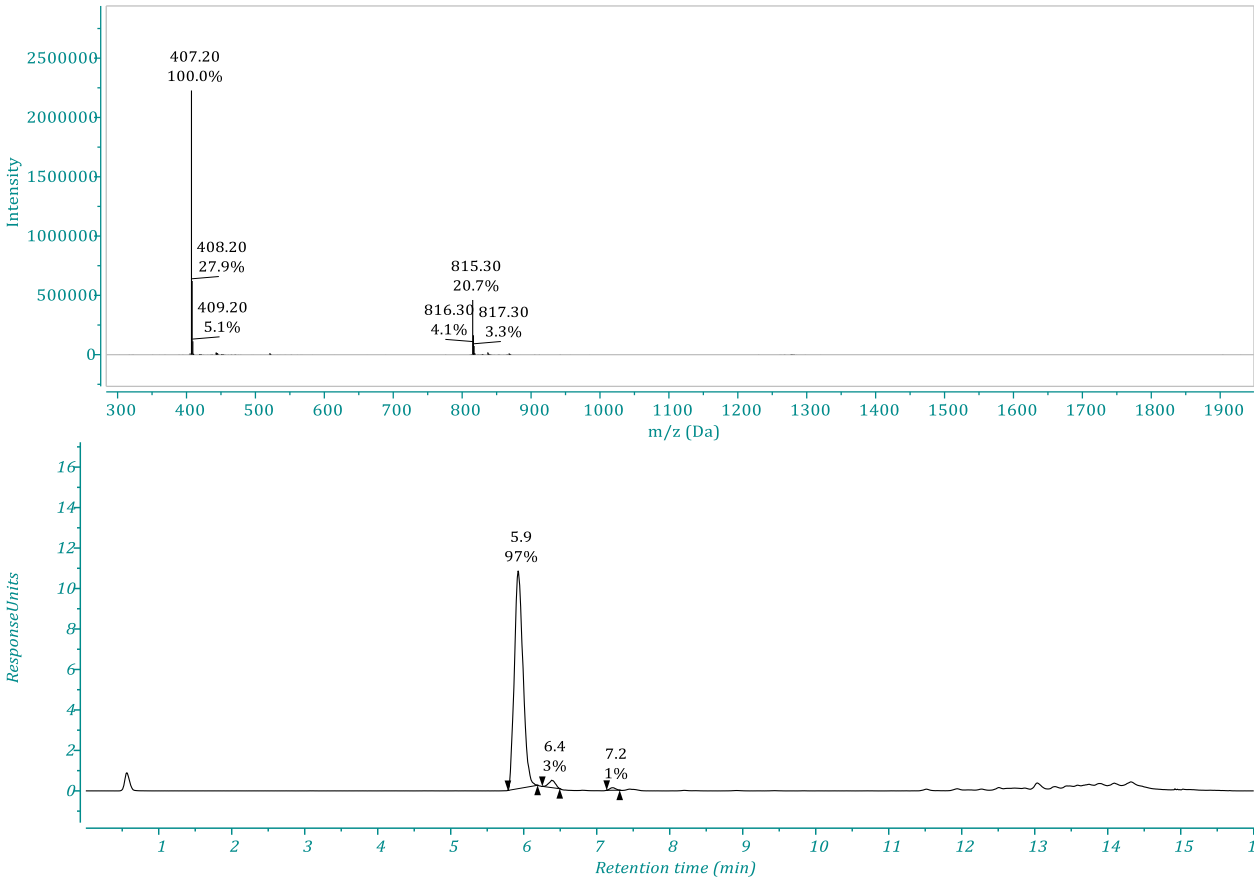
HPLC Method: **C**

Solvent Gradient (%B): T0=50, T7=100, T9=100, T9.5=50, T10=50

2.7.5. LCMS analysis of compound **41**



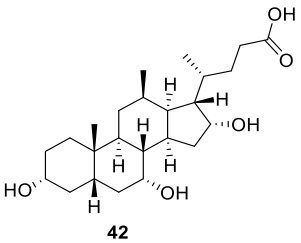
41



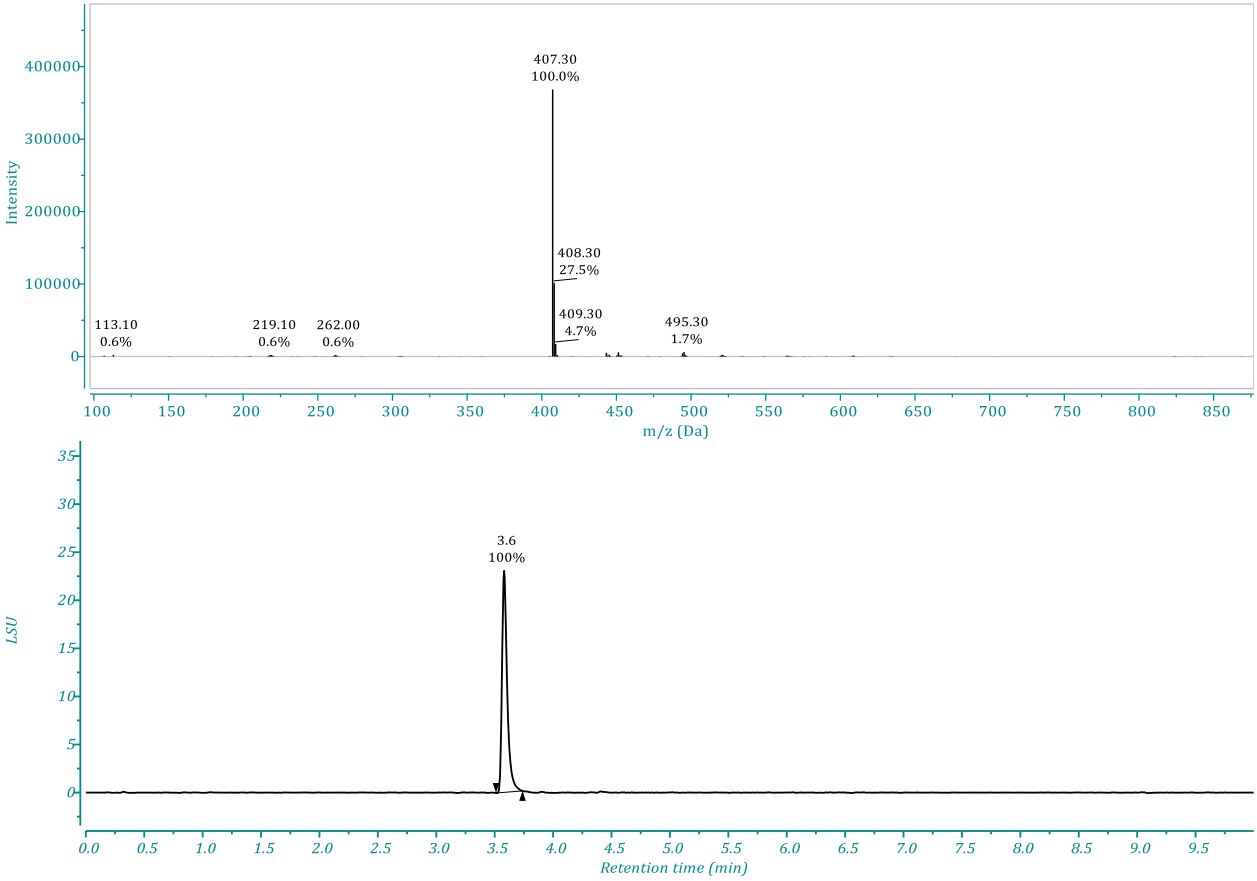
HPLC Method: **A**

Solvent Gradient (%B): T0=30, T12=100, T13=100, T14=30, T16=30

2.7.6. LCMS analysis of compound **42**



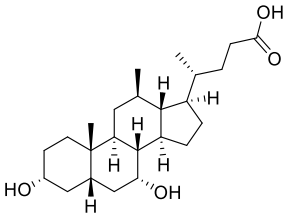
42



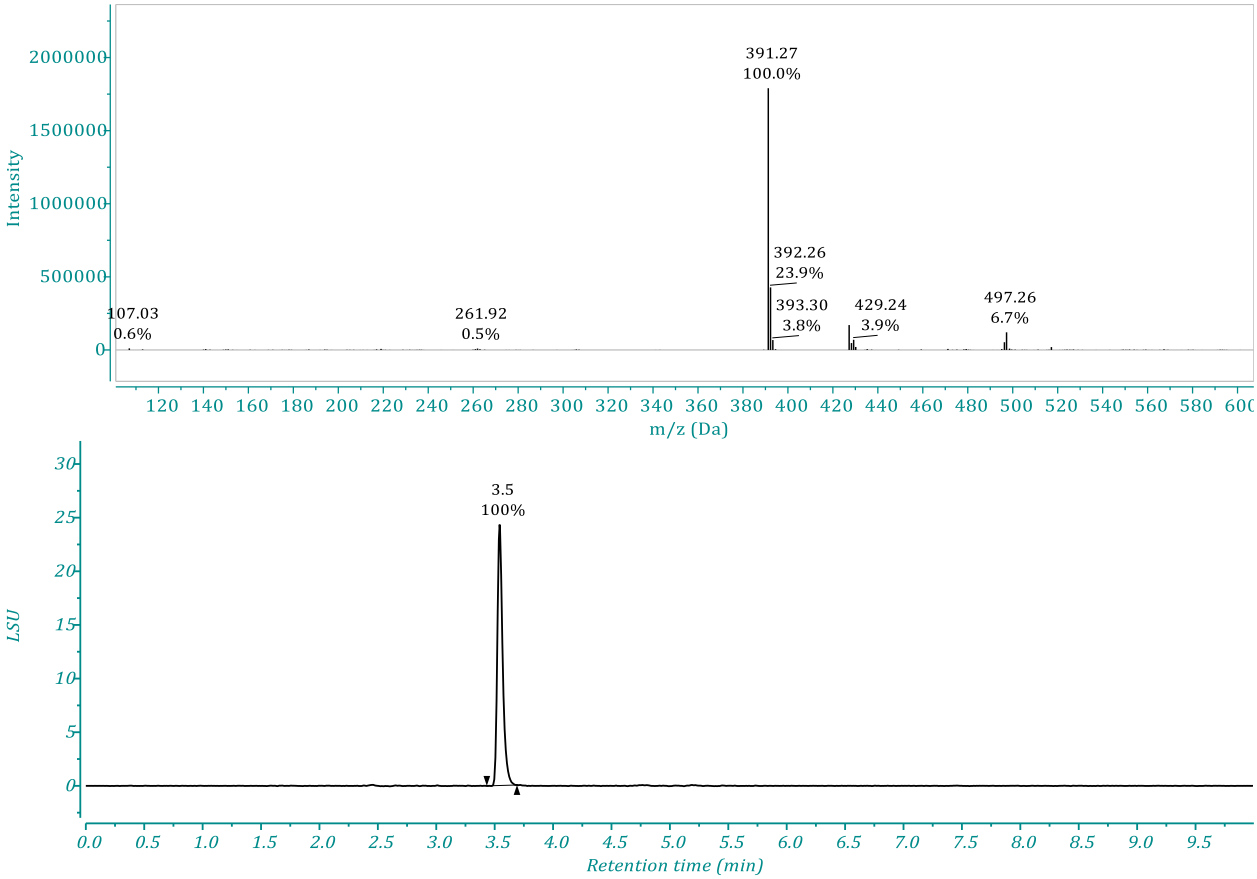
HPLC Method: **B**

Solvent Gradient (%B): T0=30, T7=100, T9=100, T9.5=30, T10=30

2.7.7. LCMS analysis of compound **43**



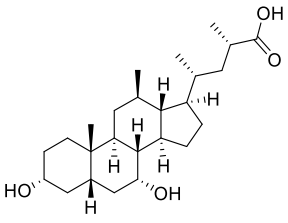
43



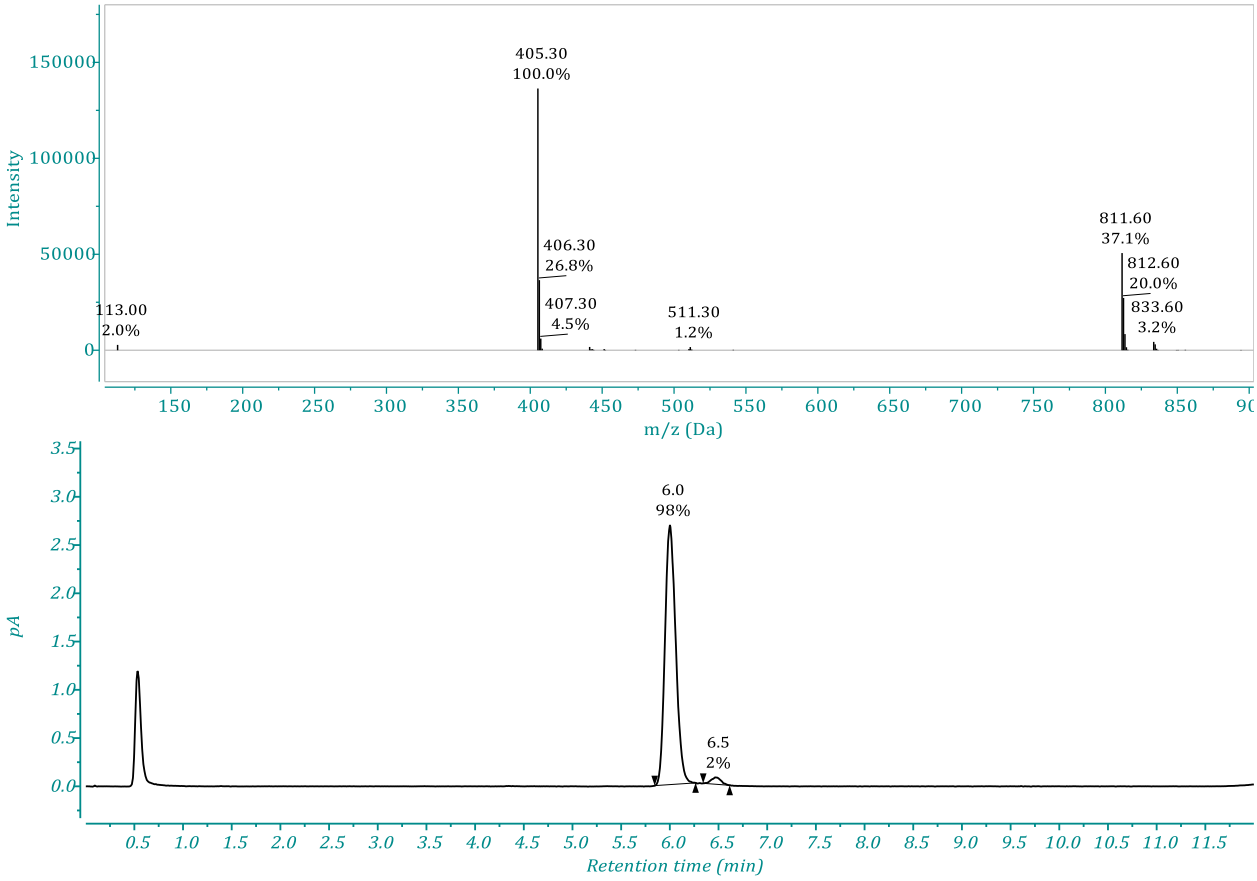
HPLC Method: **B**

Solvent Gradient (%B): T0=70, T7=100, T9=100, T9.5=70, T10=70

2.7.8. LCMS analysis of compound **45**



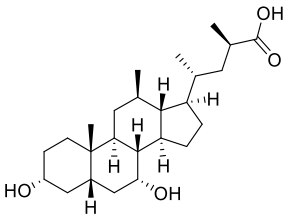
45



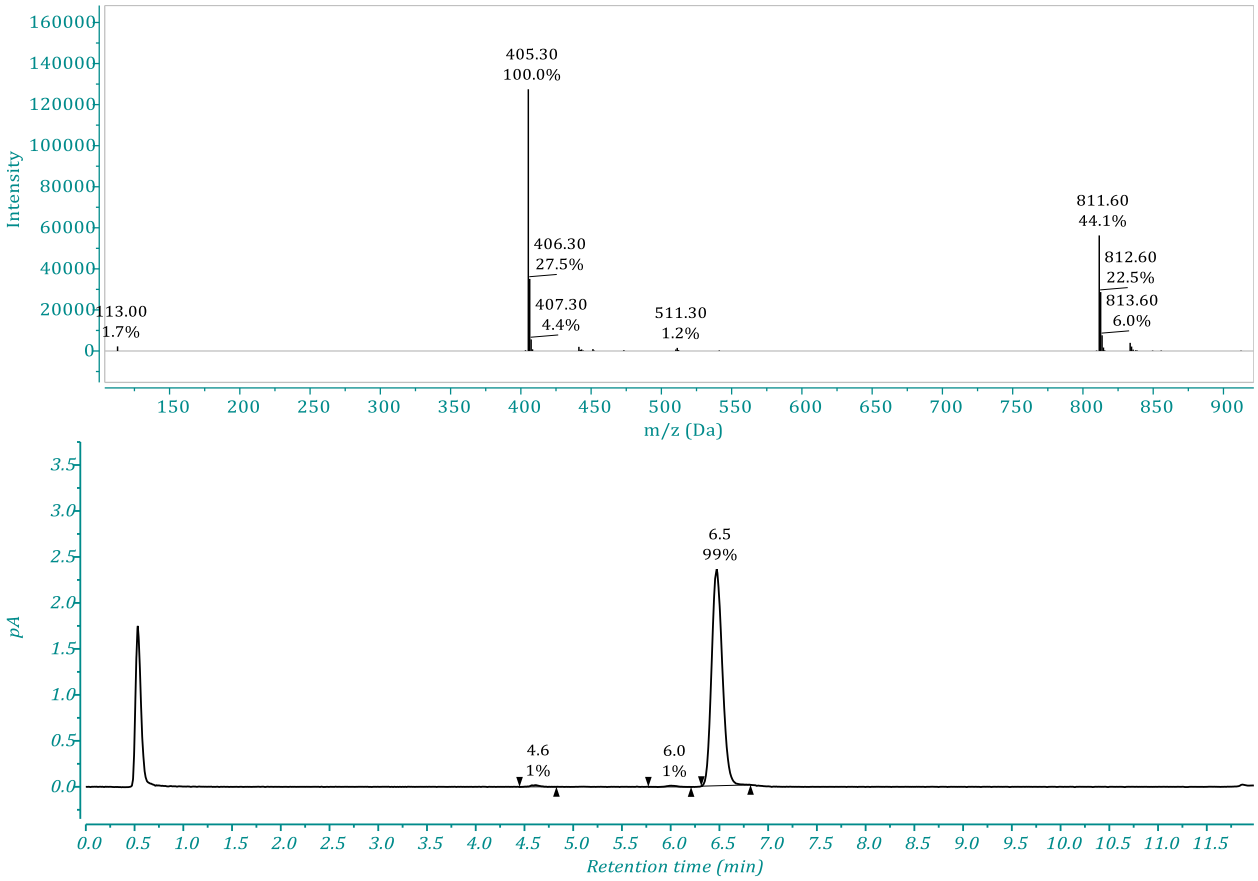
HPLC Method: **A**

Solvent Gradient (%B): T0=60, T10=70, T11=100, T12=100, T14=60, T16=60

2.7.9. LCMS analysis of compound **46**



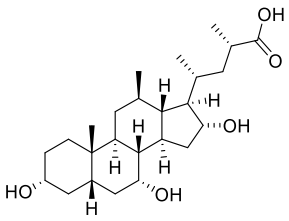
46



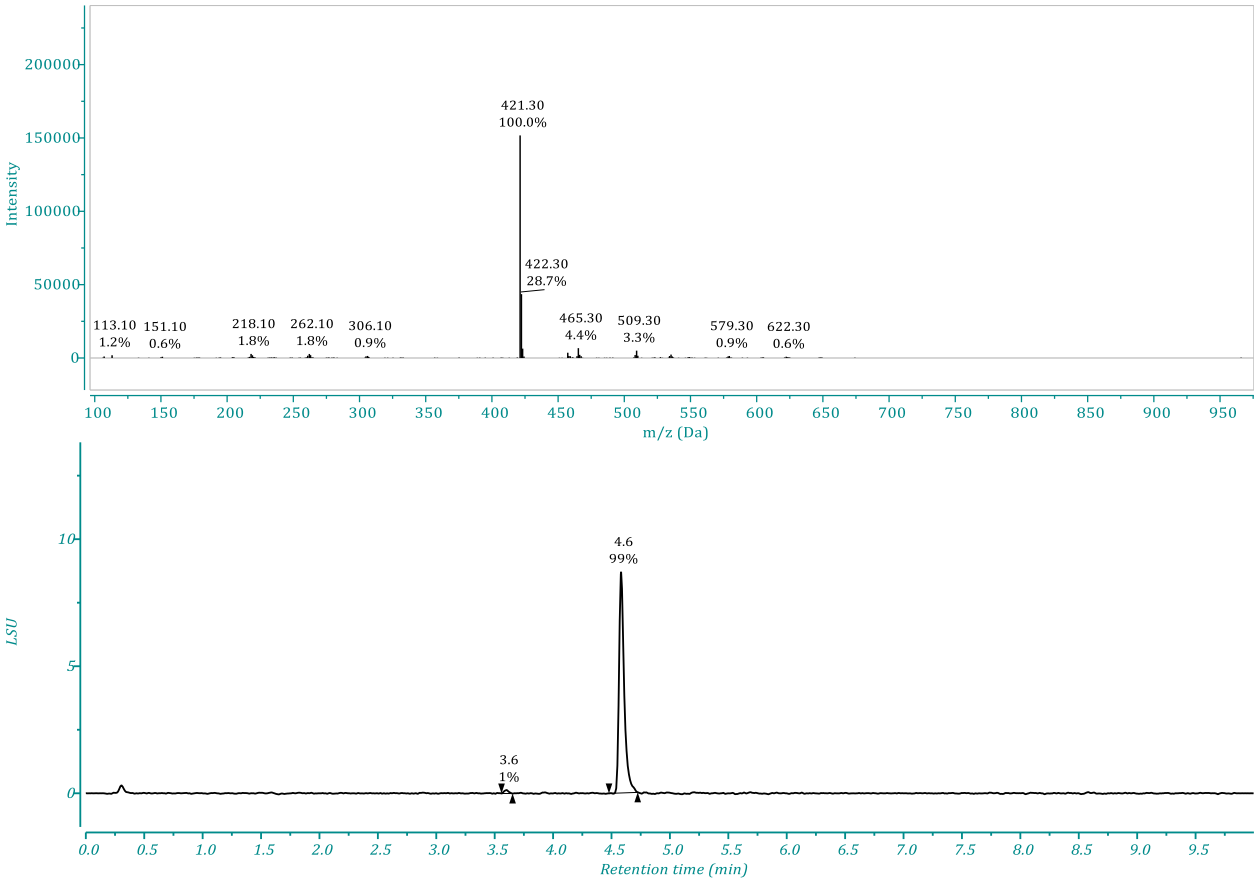
HPLC Method: **A**

Solvent Gradient (%B): T0=60, T10=70, T11=100, T12=100, T14=60, T16=60

2.7.10. LCMS analysis of compound **48**



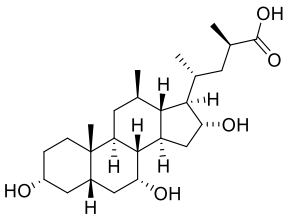
48



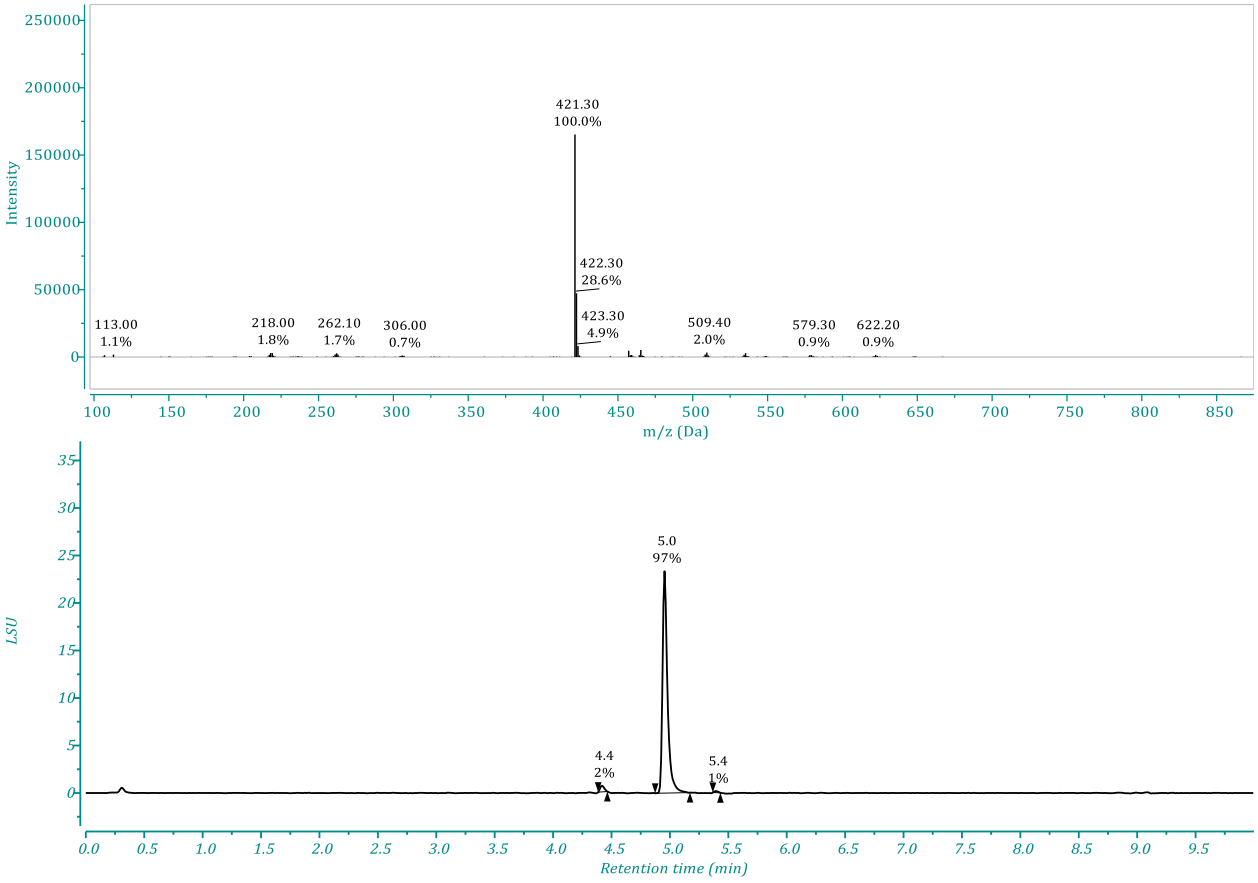
HPLC Method: **B**

Solvent Gradient (%B): T0=30, T7=100, T9=100, T9.5=30, T10=30

2.7.11. LCMS analysis of compound **49**



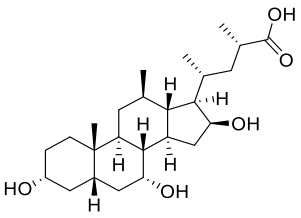
49



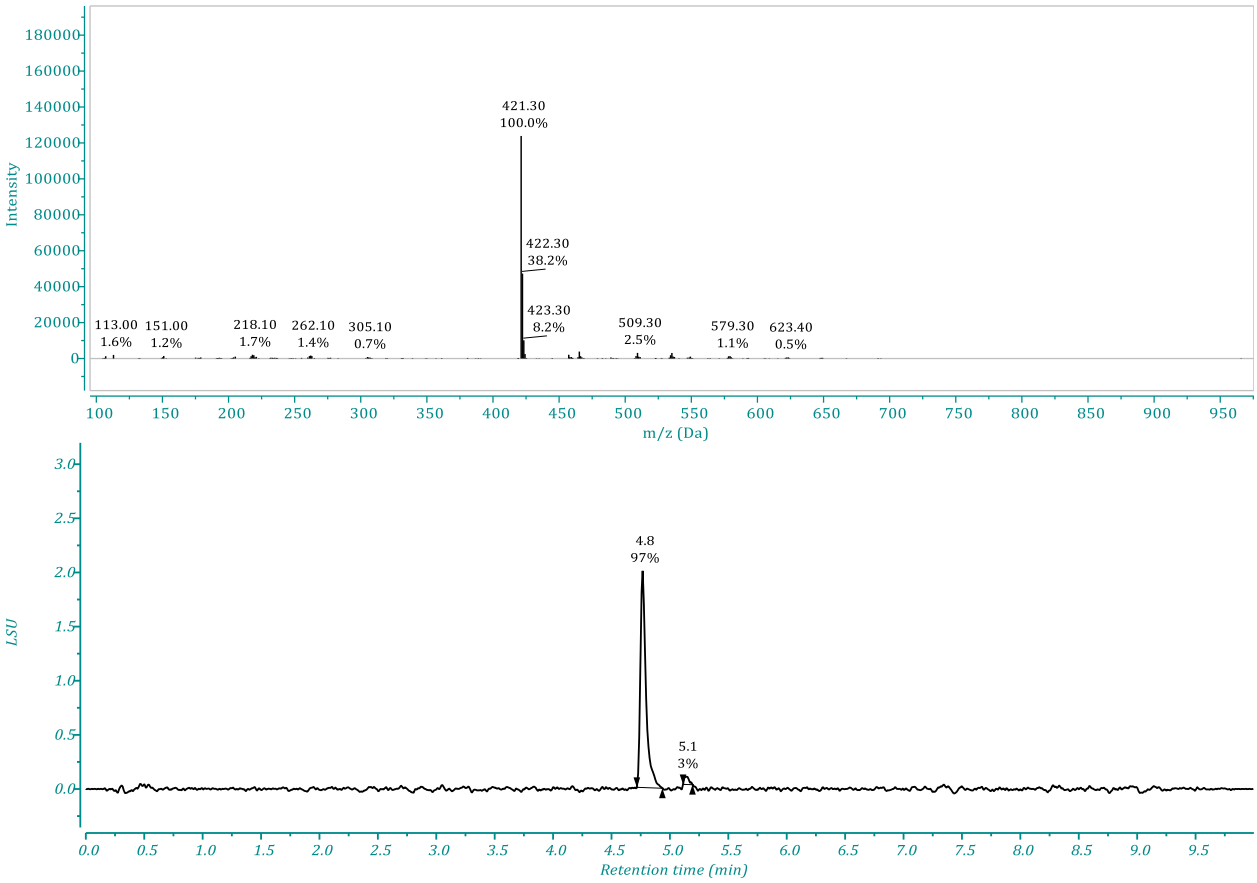
HPLC Method: **B**

Solvent Gradient (%B): T0=30, T7=100, T9=100, T9.5=30, T10=30

2.7.12. LCMS analysis of compound **51**



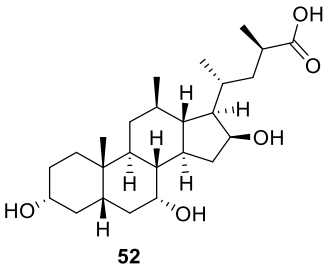
51



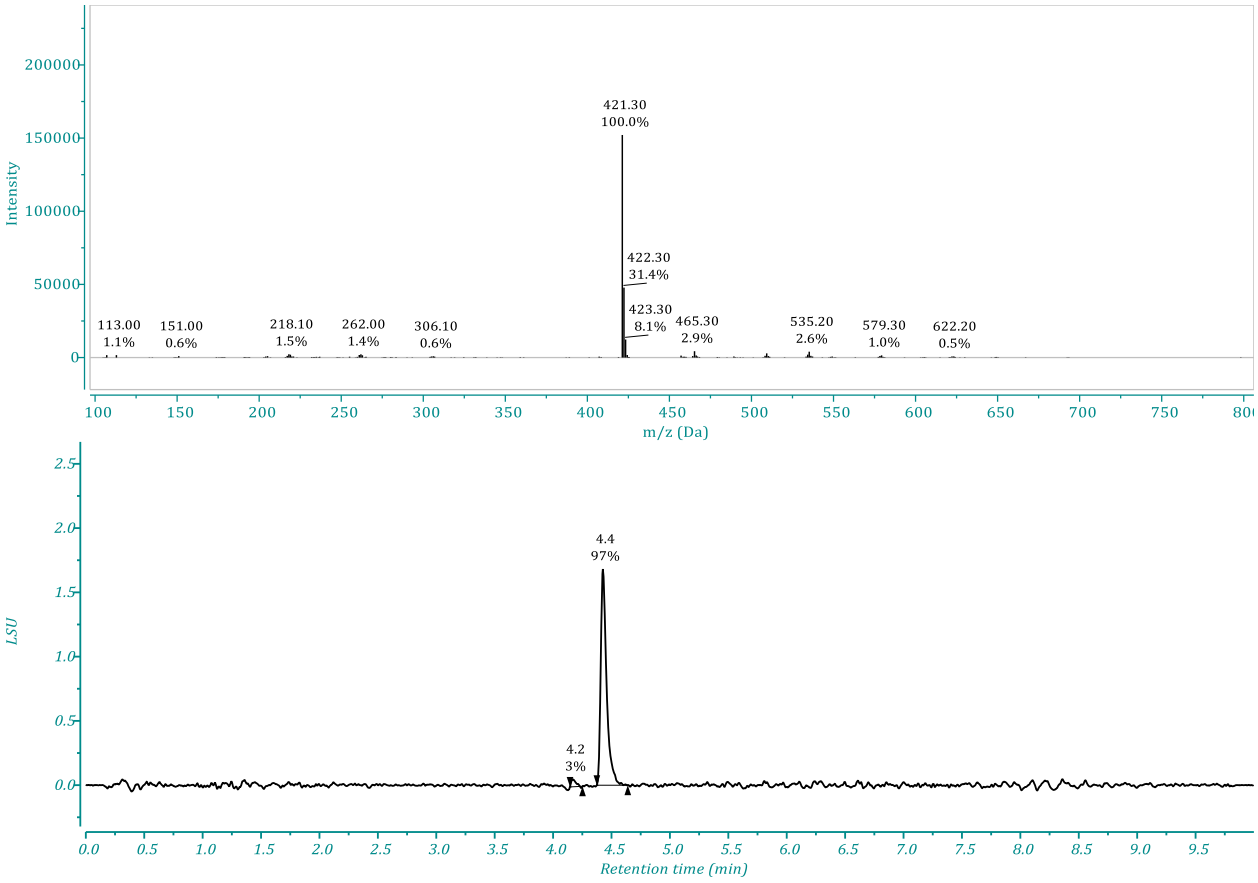
HPLC Method: **B**

Solvent Gradient (%B): T0=30, T7=100, T9=100, T9.5=30, T10=30

2.7.13. LCMS analysis of compound **52**



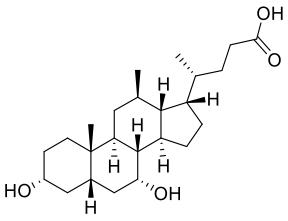
52



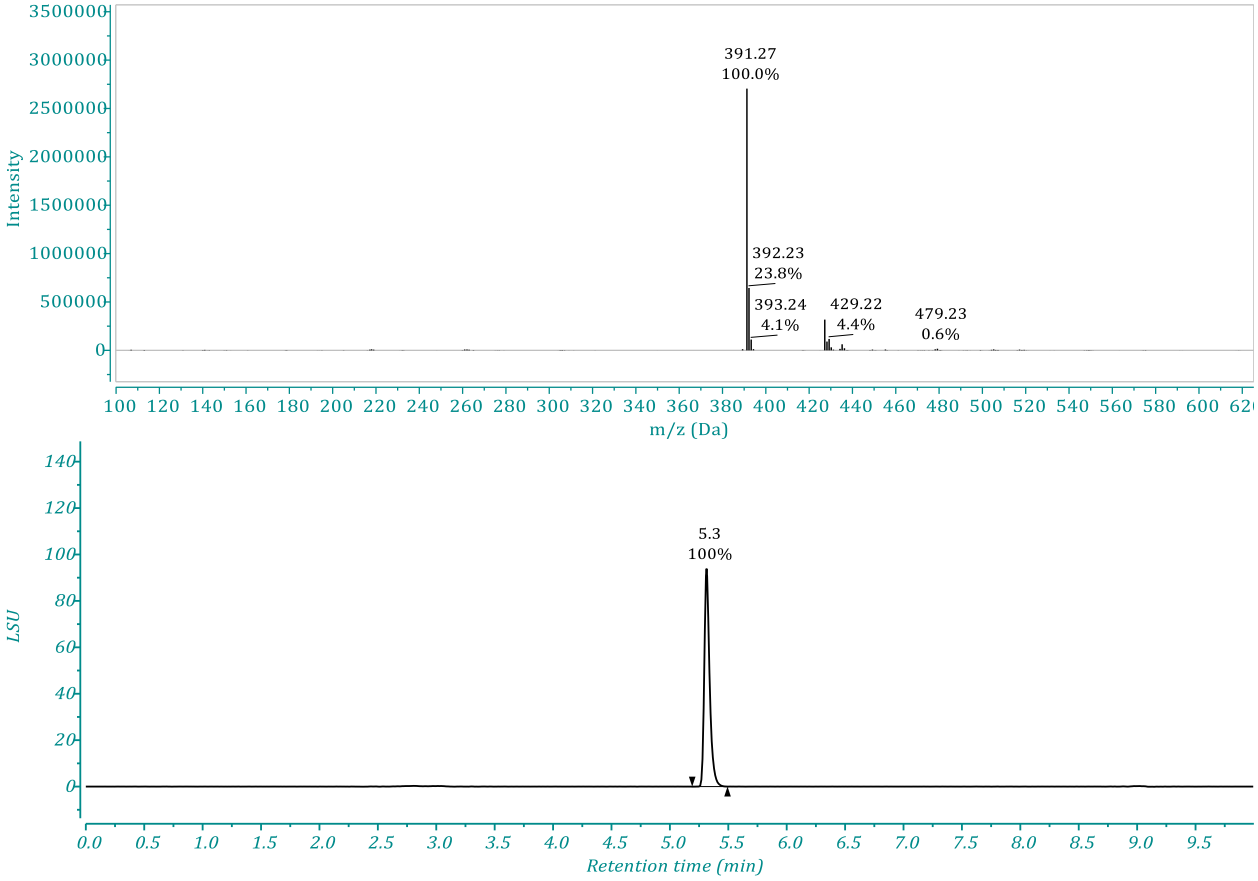
HPLC Method: **B**

Solvent Gradient (%B): T0=30, T7=100, T9=100, T9.5=30, T10=30

2.7.14. LCMS analysis of compound **53**



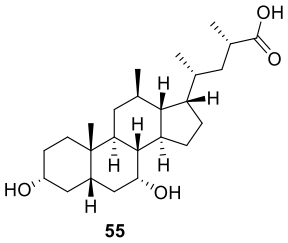
53



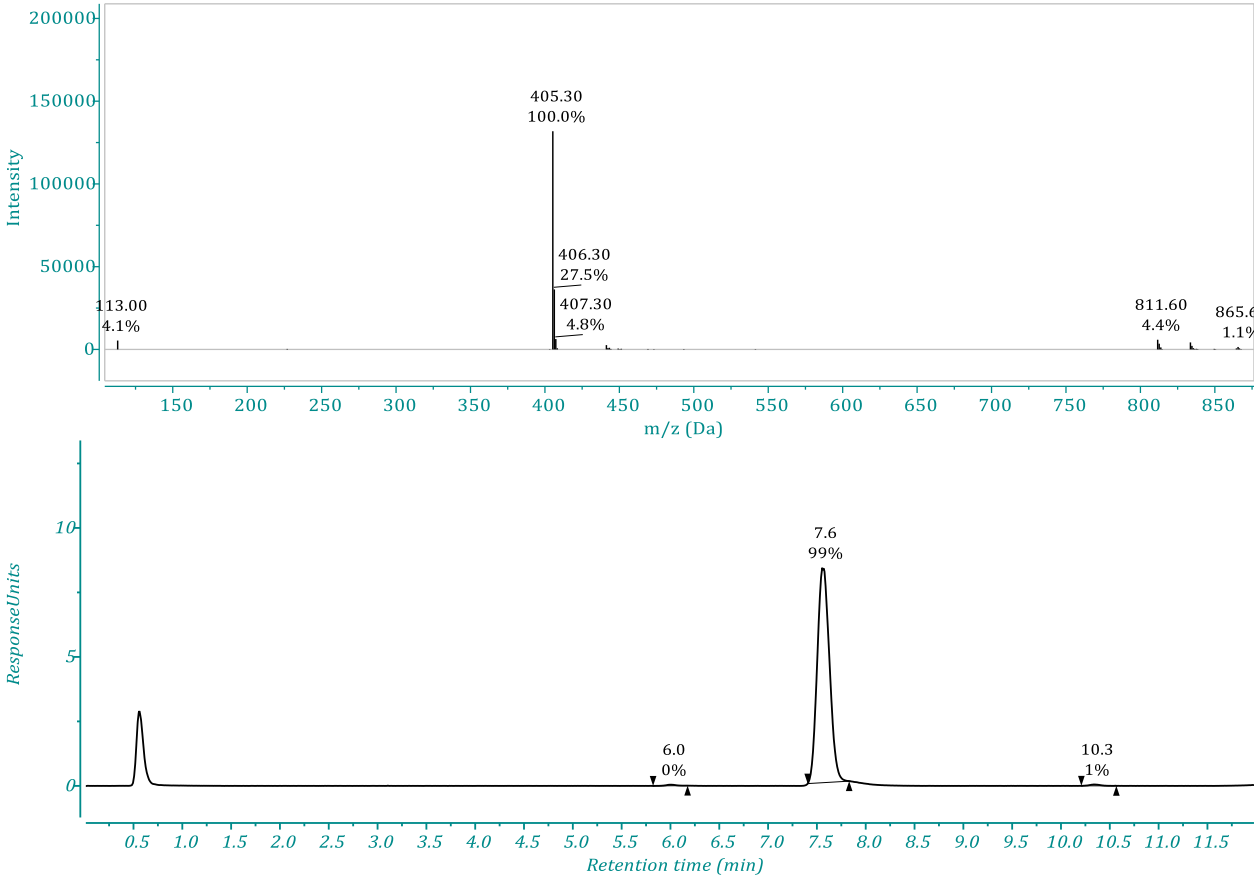
HPLC Method: **B**

Solvent Gradient (%B): T0=70, T7=100, T9=100, T9.5=70, T10=70

2.7.15. LCMS analysis of compound **55**



55



HPLC Method: **A**

Solvent Gradient (%B): T0=60, T10=70, T11=100, T12=100, T14=60, T16=60

3. X-Ray Diffraction Data

All datasets were collected on an Agilent SuperNova diffractometer fitted with an EOS S2 detector at 120 K and using CuKα radiation (λ = 1.54184 Å). All ORTEP plots are with 30% probability ellipsoids. Minor disordered components and/or solvent molecules have been omitted for clarity.

3.1. Crystal structure data and structure refinement

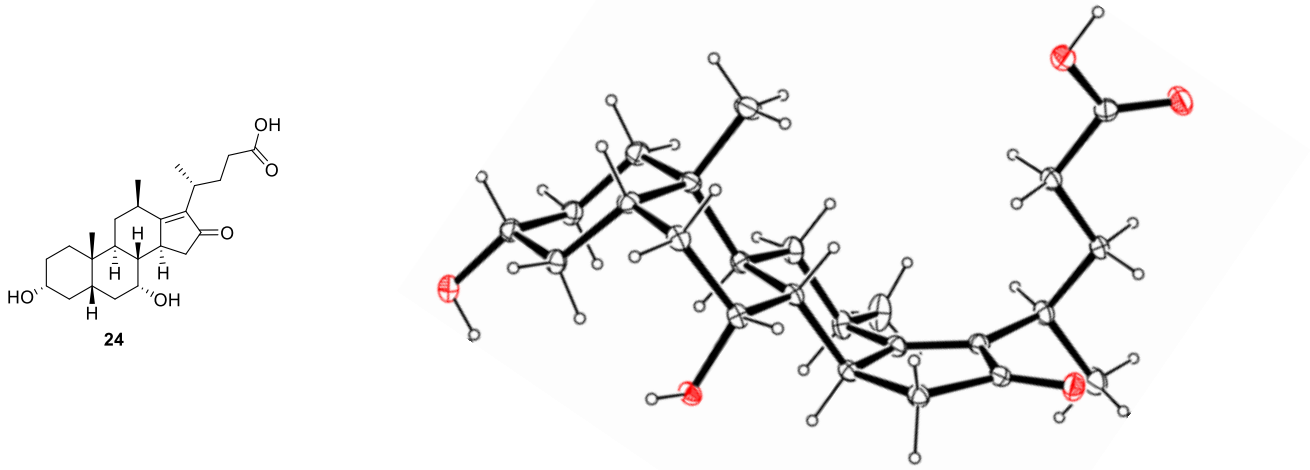


Figure S9. ORTEP diagram of **24** with 30% probability ellipsoids.

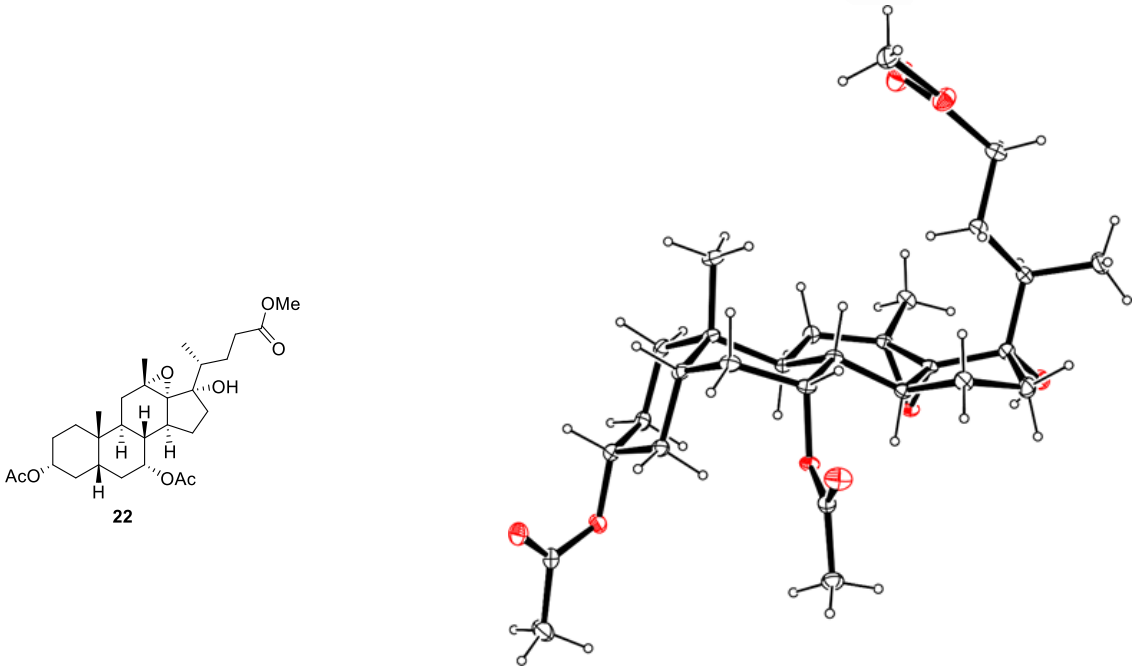


Figure S10. ORTEP diagram of **22** with 30% probability ellipsoids.

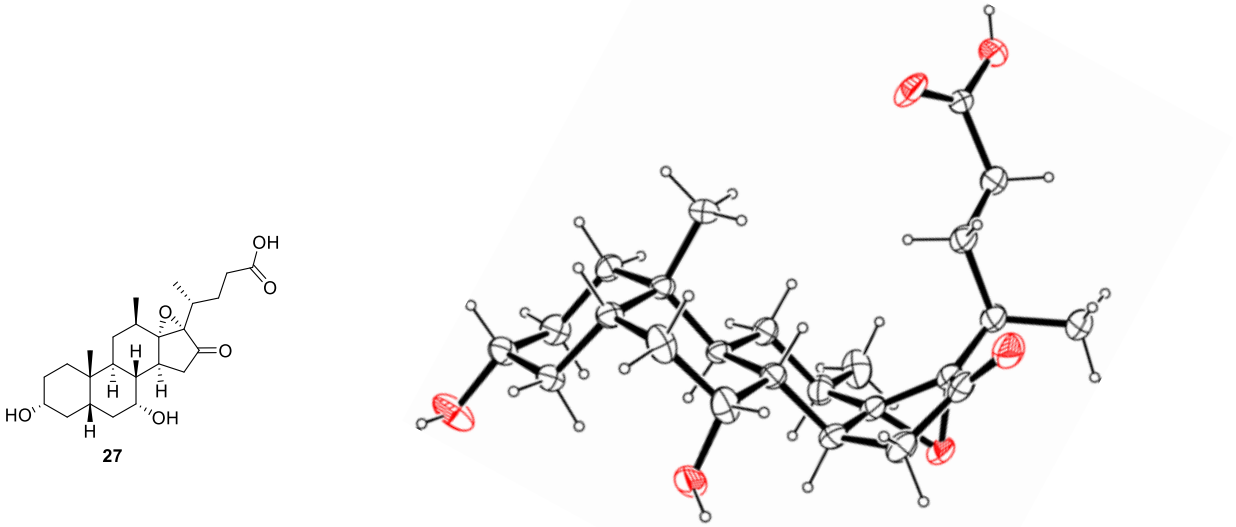
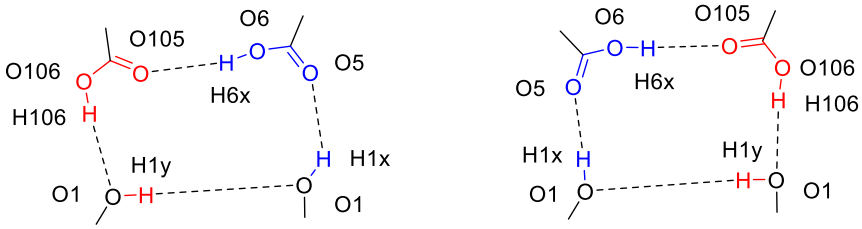


Figure S11. ORTEP diagram of **27** with 30% probability ellipsoids. Disorder omitted for clarity.



Note all oxygen and hydrogen atoms are 50% occupancy, except for O1. This strategy was employed instead of reducing the symmetry to handle the two hydrogen bonding scenarios, which are related by a 2-fold rotation. The carboxylic acid is rotationally disordered, labelled as C24, O5, O6 and C124, O105, O106. The symmetry generated alternate disorder partners are hydrogen bonded to each other. E.g. O6-H6x hydrogen bonds to O105; O106-H106 to O1; O1-H1y to O1; and O1-H1x to O5.

Figure S12. Interpretation of the frustrated hydrogen bonding network in **27**.

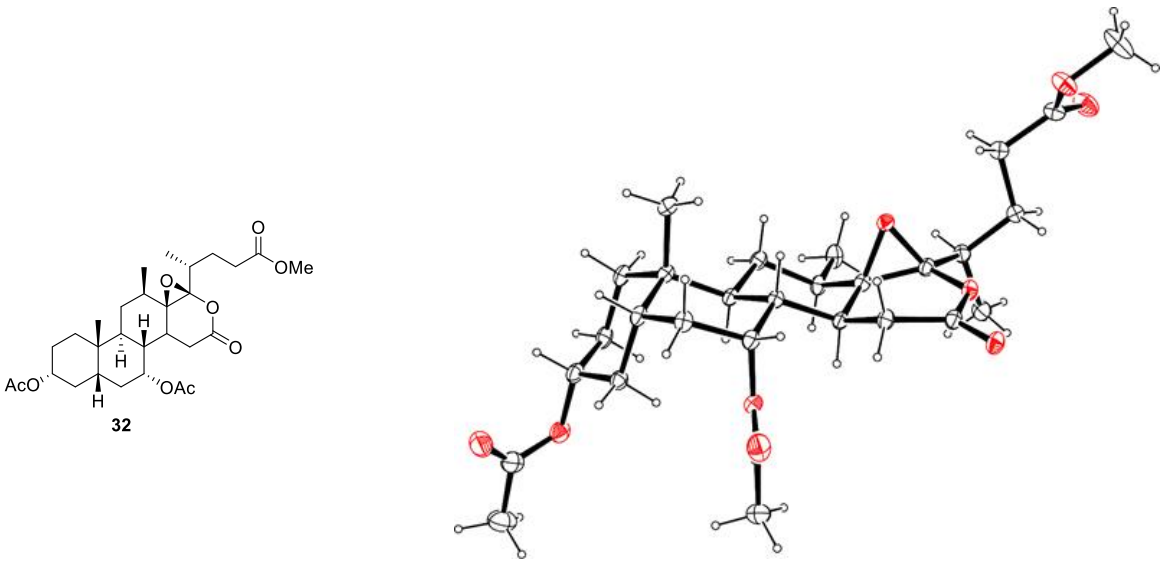


Figure S13. ORTEP diagram of **32** with 30% probability ellipsoids.

Table S1. Crystal data and structure refinement for **22**, **24**, **27** and **32**.

Identification code	**22**	**24**	**27**	**32**
CCDC identifier	2115802	2115801	2115803	2115798
Empirical formula	$C_{29}H_{44}O_8$	$C_{24}H_{36}O_5$	$C_{24}H_{36}O_6$ [+solvent]	$C_{29}H_{42}O_9$ [+solvent]
Formula weight (g/mol)	520.64	404.53	420.53	534.62
Crystal system	Orthorhombic	Orthorhombic	Orthorhombic	Monoclinic
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12$	$P2_1$
Unit cell dimensions				
a (Å)	9.97027(8)	8.9657(2)	20.4236(3)	14.8186(4)
b (Å)	13.27902(10)	13.2198(2)	11.2645(2)	6.1275(2)
c (Å)	20.9040(2)	18.8147(3)	10.8753(2)	17.0159(4)
α (°)	90	90	90	90
β (°)	90	90	90	103.869(3)
γ (°)	90	90	90	90
Volume ($Å^3$)	2767.60(4)	2230.01(7)	2501.99(7)	1500.02(8)
Z	4	4	4	2
Calculated density (Mg/m^3)	1.250	1.205	1.116	1.184
Absorption coefficient (mm^{-1})	0.732	0.664	0.640	0.716
F (000)	1128	880	912	576
Crystal size (mm^3)	0.275 × 0.223 × 0.112	0.082 × 0.074 × 0.056	0.222 × 0.207 × 0.161	0.325 × 0.062 × 0.051
Theta range for data collection	3.944 to 73.649°	4.701 to 71.774°	4.065 to 73.599°	3.558 to 73.518°
Index ranges	$-12 \le h \le 10$ $-16 \le k \le 15$ $-25 \le l \le 23$	$-11 \le h \le 10$ $-12 \le k \le 16$ $-22 \le l \le 23$	$-23 \le h \le 25$ $-14 \le k \le 13$ $-13 \le l \le 13$	$-16 \le h \le 18$ $-7 \le k \le 7$ $-20 \le l \le 21$
Reflections collected	28399	12295	24718	23846
Independent reflections	5569 [R(int) = 0.0286]	4355 [R(int) = 0.0253]	4933 [R(int) = 0.0263]	6013 [R(int) = 0.0508]
Completeness to theta	100% to 67.684°	99.9% to 67.684°	98.7% to 67.684°	99.9% to 67.684°
Data / restraints / parameters	5569 / 0 / 340	4355 / 0 / 274	4933 / 4 / 306	6013 / 1 / 349
Goodness-of-fit on F^2	1.044	1.296	1.044	1.037
Final R indices [I>2sigma(I)]	R1 = 0.0271 wR2 = 0.0690	R1 = 0.0299 wR2 = 0.0978	R1 = 0.0396 wR2 = 0.1052	R1 = 0.0410 wR2 = 0.1022
R indices (all data)	R1 = 0.0279 wR2 = 0.0697	R1 = 0.0331 wR2 = 0.0989	R1 = 0.0407 wR2 = 0.1065	R1 = 0.0443 wR2 = 0.1045
Absolute structure parameter	0.02(5)	0.04(8)	-0.03(6)	0.27(12)
Largest diff. peak and hole ($e.Å^{-3}$)	0.161 and -0.147	0.220 and -0.212	0.174 and -0.207	0.160 and -0.254

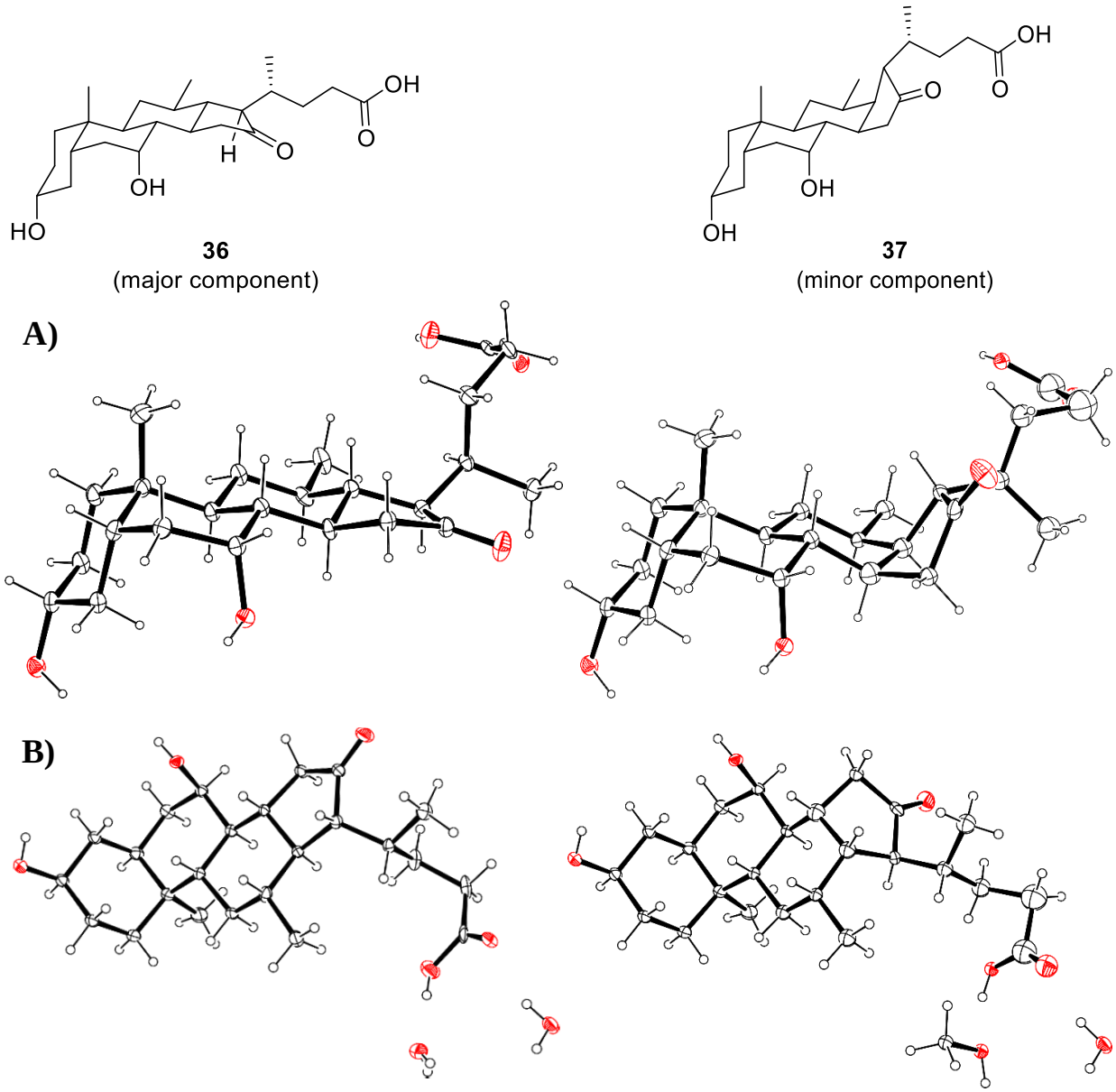


Figure S14. ORTEP diagram of **36** and **37** with 30% probability ellipsoids. Left: major component (*ca.* 80%); Right: Minor component (*ca.* 20%); A) Side view with solvent omitted for clarity; B) Alternative view with solvent shown (one full occupancy water and a 20% occupancy methanol in minor component and 80% occupancy water molecule in major component).

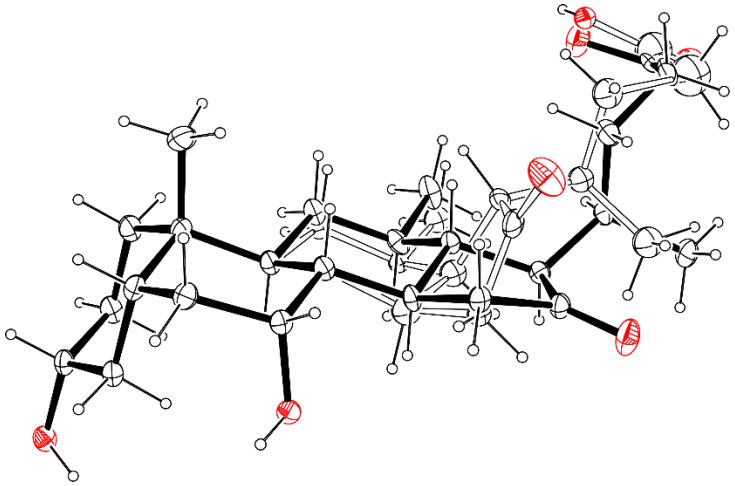
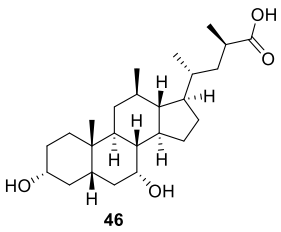


Figure S15. ORTEP diagram showing overlapping crystal structures of **36** and **37** with 30% probability ellipsoids. Minor component shown with open bonds. Solvent molecules omitted for clarity.



46

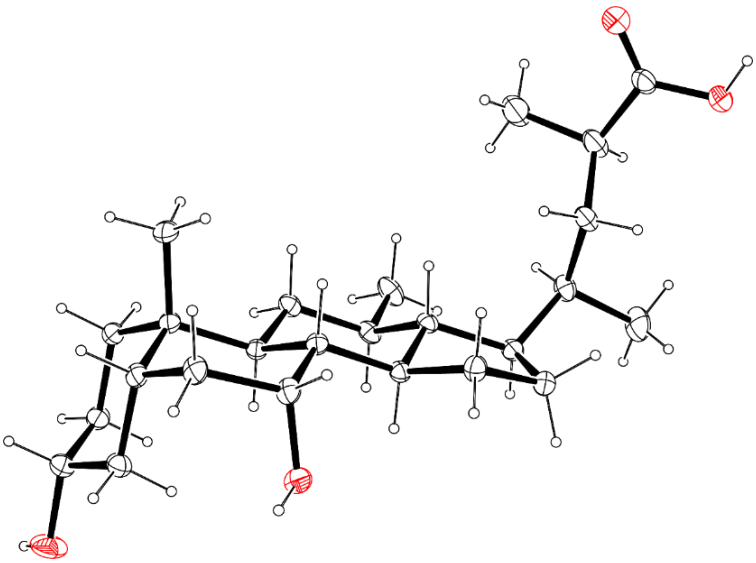


Figure S16. ORTEP diagram of **46** with 30% probability ellipsoids. Two water molecules omitted for clarity.

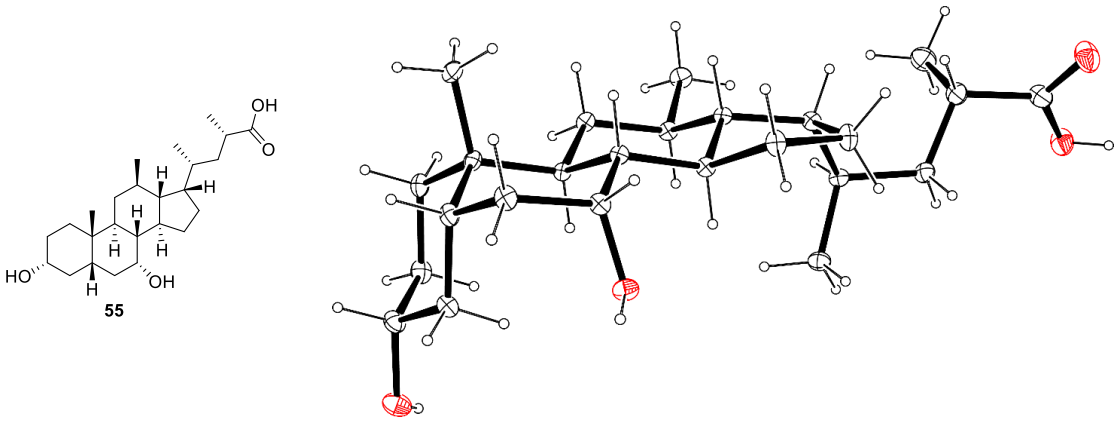


Figure S17. ORTEP diagram **55** with 30% probability ellipsoids. Two water molecules omitted for clarity.

Table S2. Crystal data and structure refinement for **36**, **37**, **46** and **55**

Identification code	**36/37**	**46**	**55**
CCDC identifier	2115799	2115804	2115800
Empirical formula	$C_{24}H_{38}O_5 \cdot 1.8H_2O \cdot 0.2MeOH$	$C_{25}H_{42}O_4$ [+solvent]	$C_{25}H_{42}O_4 \cdot 2H_2O$
Formula weight (g/mol)	445.27	406.58	442.62
Crystal system	Orthorhombic	Hexagonal	Orthorhombic
Space group	$P2_12_12_1$	$P6_5$	$P2_12_12_1$
Unit cell dimensions			
a (Å)	8.31799(11)	32.2679(2)	7.4781(4)
b (Å)	10.12992(17)	32.2679(2)	12.8100(8)
c (Å)	28.0673(4)	6.19392(4)	25.4104(14)
α (°)	90	90	90
β (°)	90	90	90
γ (°)	90	120	90
Volume ($Å^3$)	2364.97(6)	5585.20(5)	2434.2(2)
Z	4	6	4
Calculated density (Mg/m^3)	1.251	0.725* (squeeze)	1.208
Absorption coefficient (mm^{-1})	0.732	0.375	0.674
F (000)	974	1344	976
Crystal size (mm^3)	0.50 × 0.20 × 0.10	0.616 × 0.205 × 0.124	0.397 × 0.081 × 0.035
Theta range for data collection	4.641 to 73.642°	4.186 to 73.295°	3.479 to 73.774°
Index ranges	$-10 \le h \le 6$ $-12 \le k \le 12$ $-34 \le l \le 34$	$-39 \le h \le 39$ $-39 \le k \le 39$ $-7 \le l \le 6$	$-5 \le h \le 9$ $-15 \le k \le 15$ $-28 \le l \le 31$
Reflections collected	34923	70968	24184
Independent reflections	4791 [R(int) = 0.0368]	6921 [R(int) = 0.0259]	4919 [R(int) = 0.0459]
Completeness to theta	100% to 67.684°	99.9% to 67.684°	100% to 67.684°
Data / restraints / parameters	4791 / 45 / 376	6921 / 1 / 269	4919 / 4 / 296
Goodness-of-fit on F^2	1.043	1.047	1.095
Final R indices [I>2sigma(I)]	R1 = 0.0369 wR2 = 0.0966	R1 = 0.0243 wR2 = 0.0631	R1 = 0.0427 wR2 = 0.1128
R indices (all data)	R1 = 0.0378 wR2 = 0.0975	R1 = 0.0247 wR2 = 0.0634	R1 = 0.0453 wR2 = 0.1149
Absolute structure parameter	-0.03(5)	-0.04(4)	-0.11(12)
Largest diff. peak and hole ($e.Å^{-3}$)	0.165 and -0.223	0.140 and -0.095	0.366 d -0.248