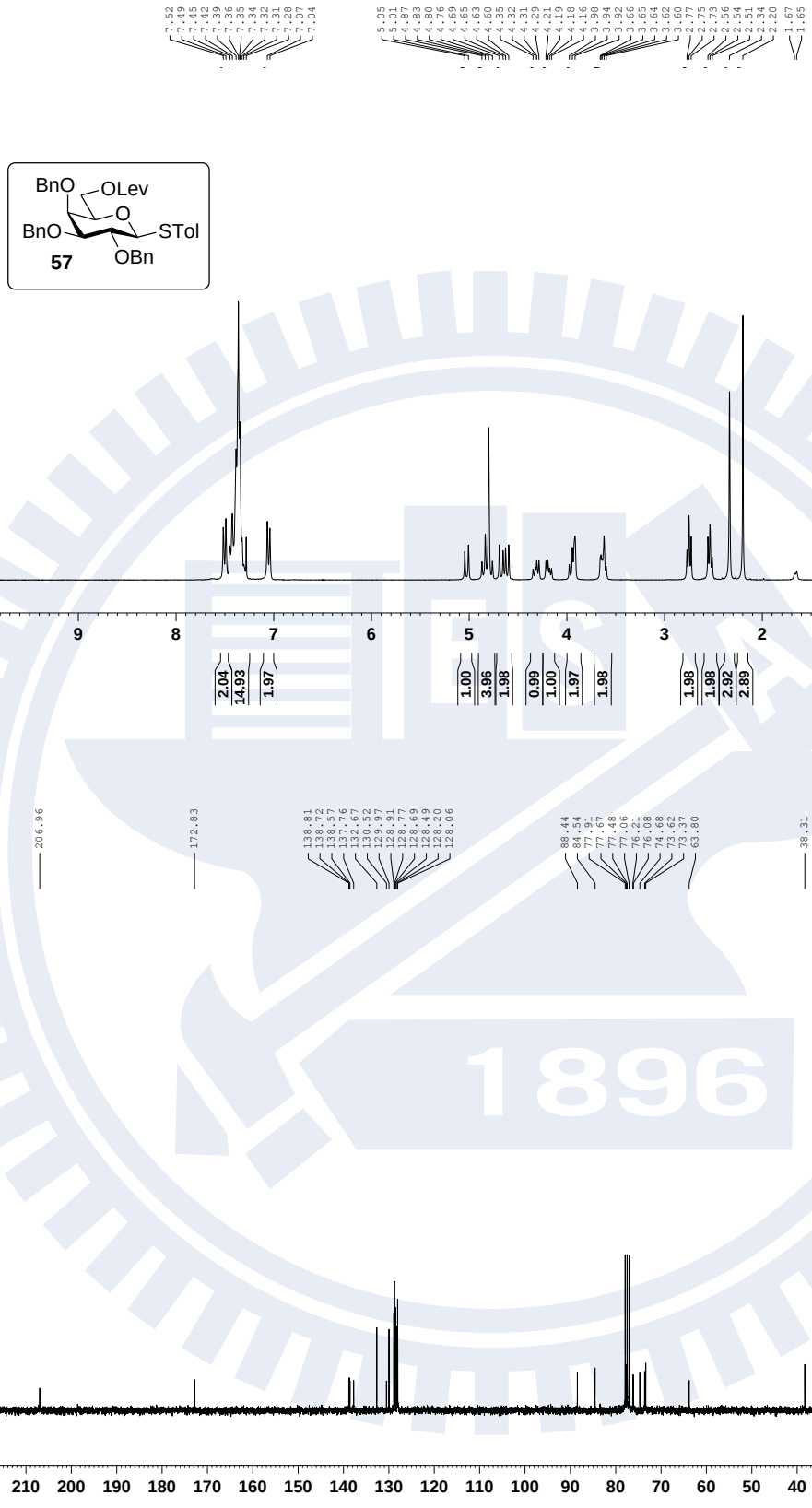
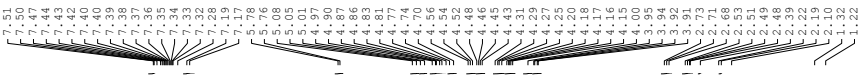
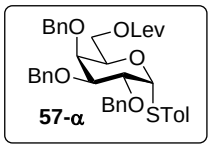
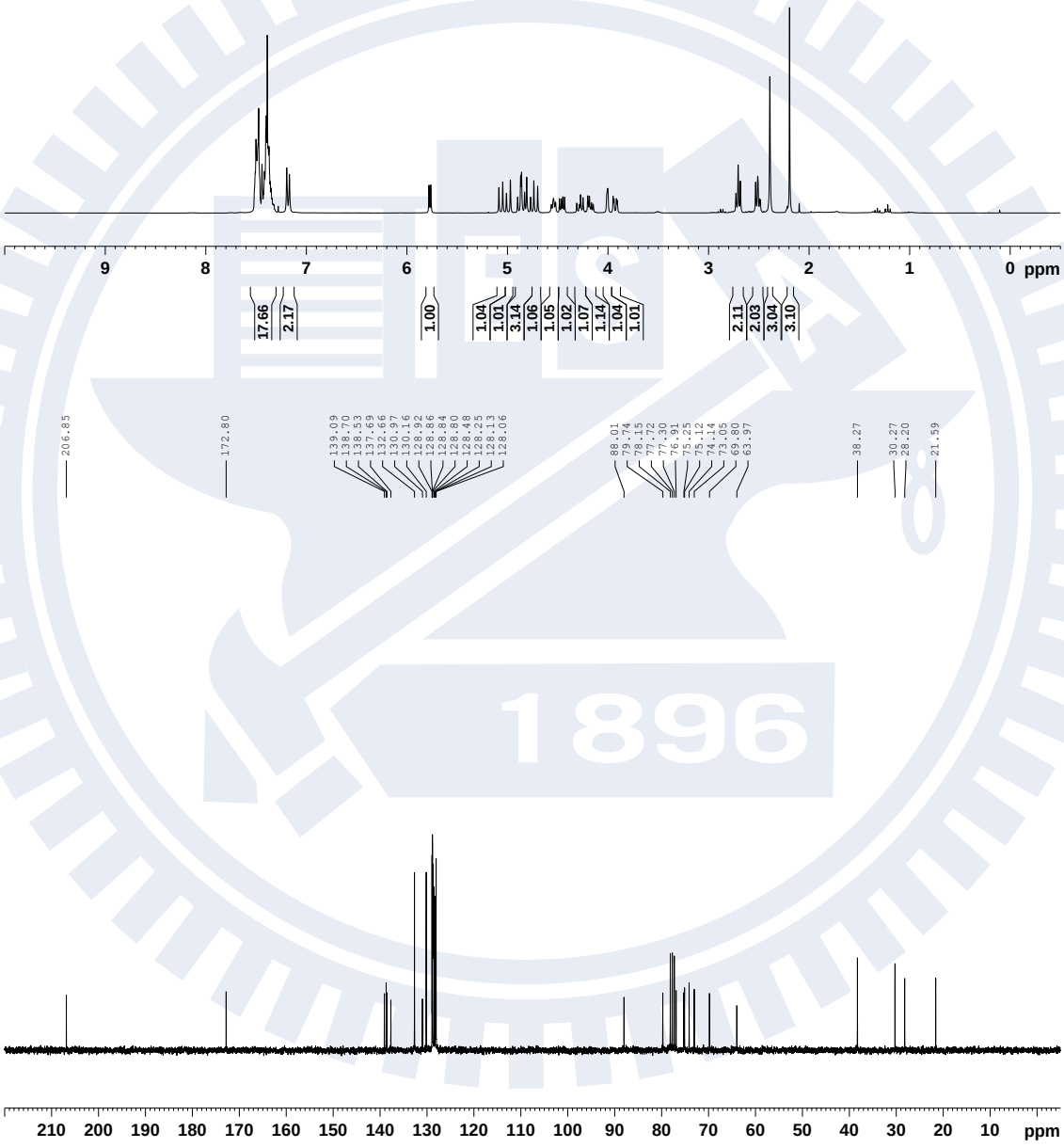
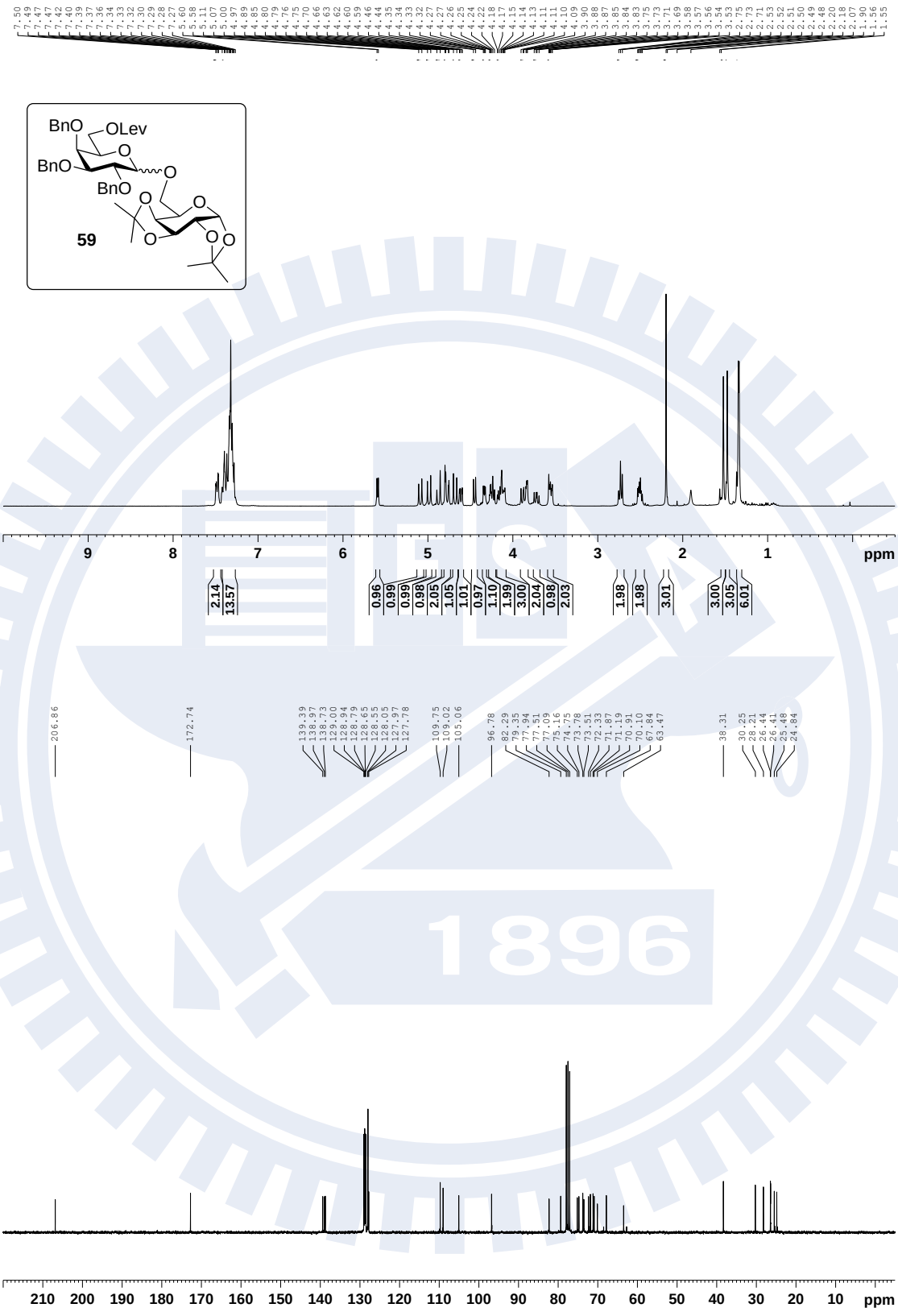
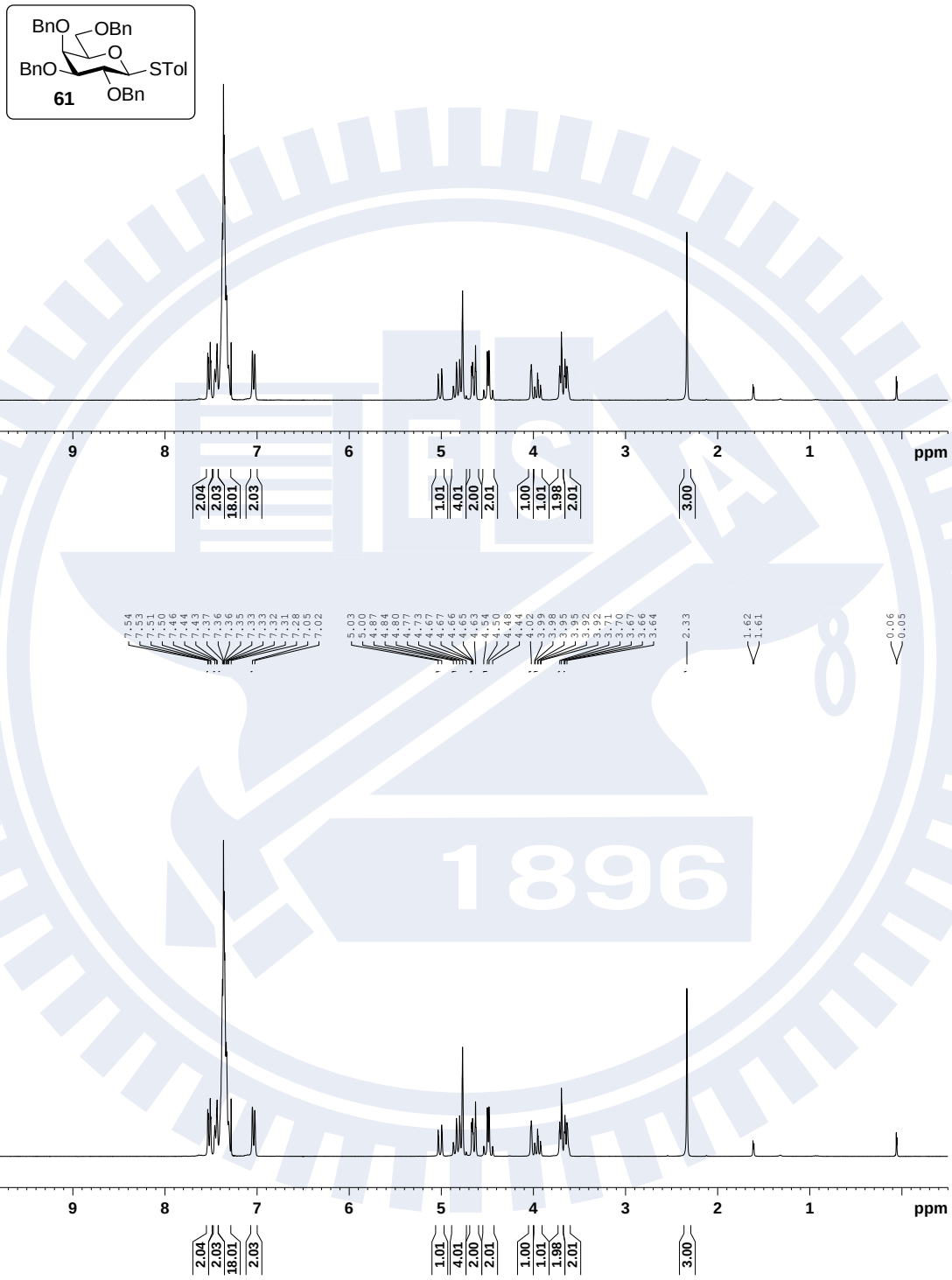

BnO
OLev
O
BnO
STol
OBn
57
ppm
ppm

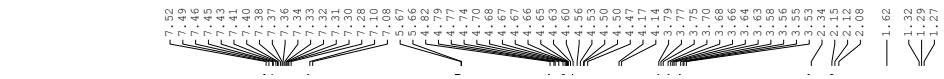


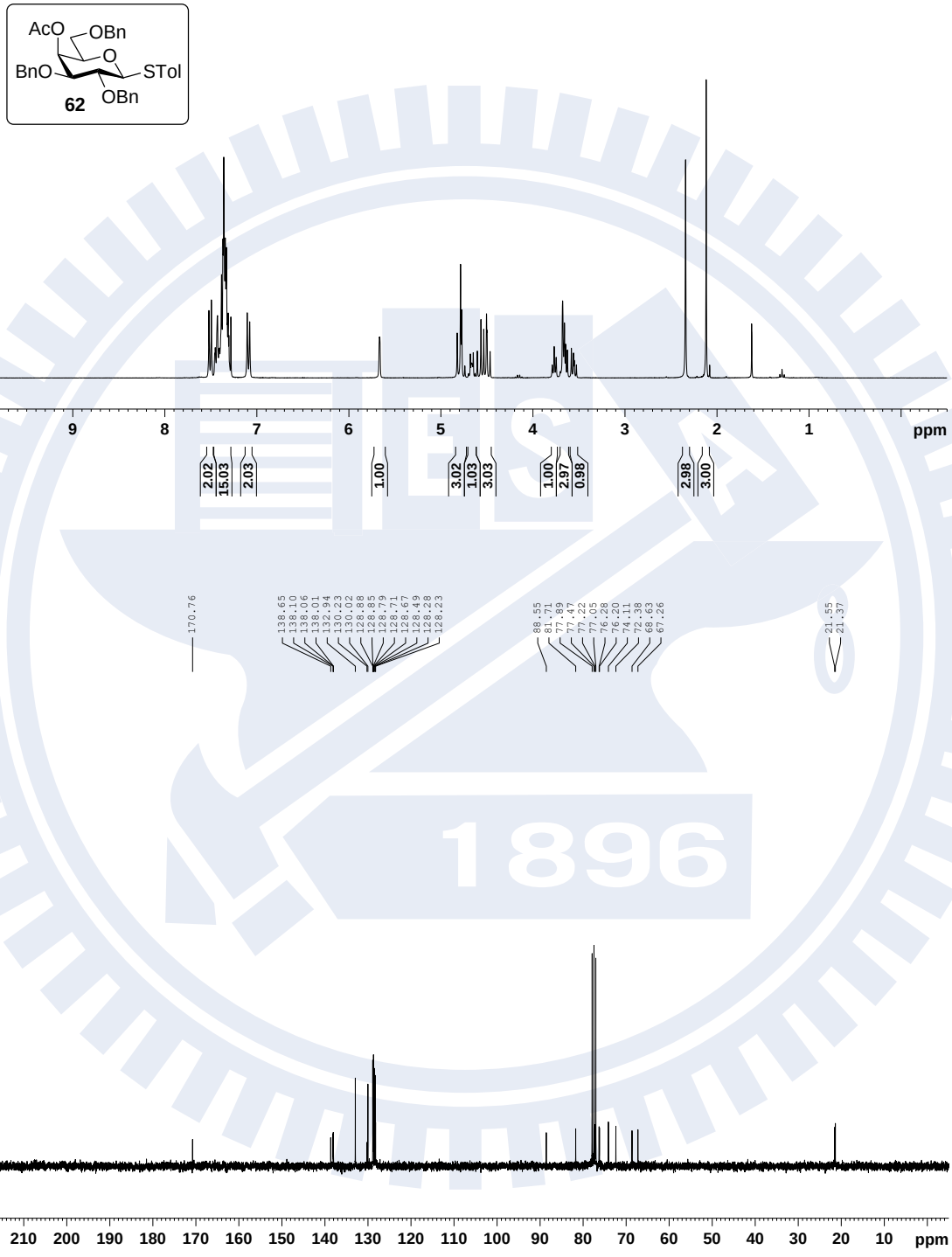

BnO
OLev
O
BnO
BnO
STol
57-α

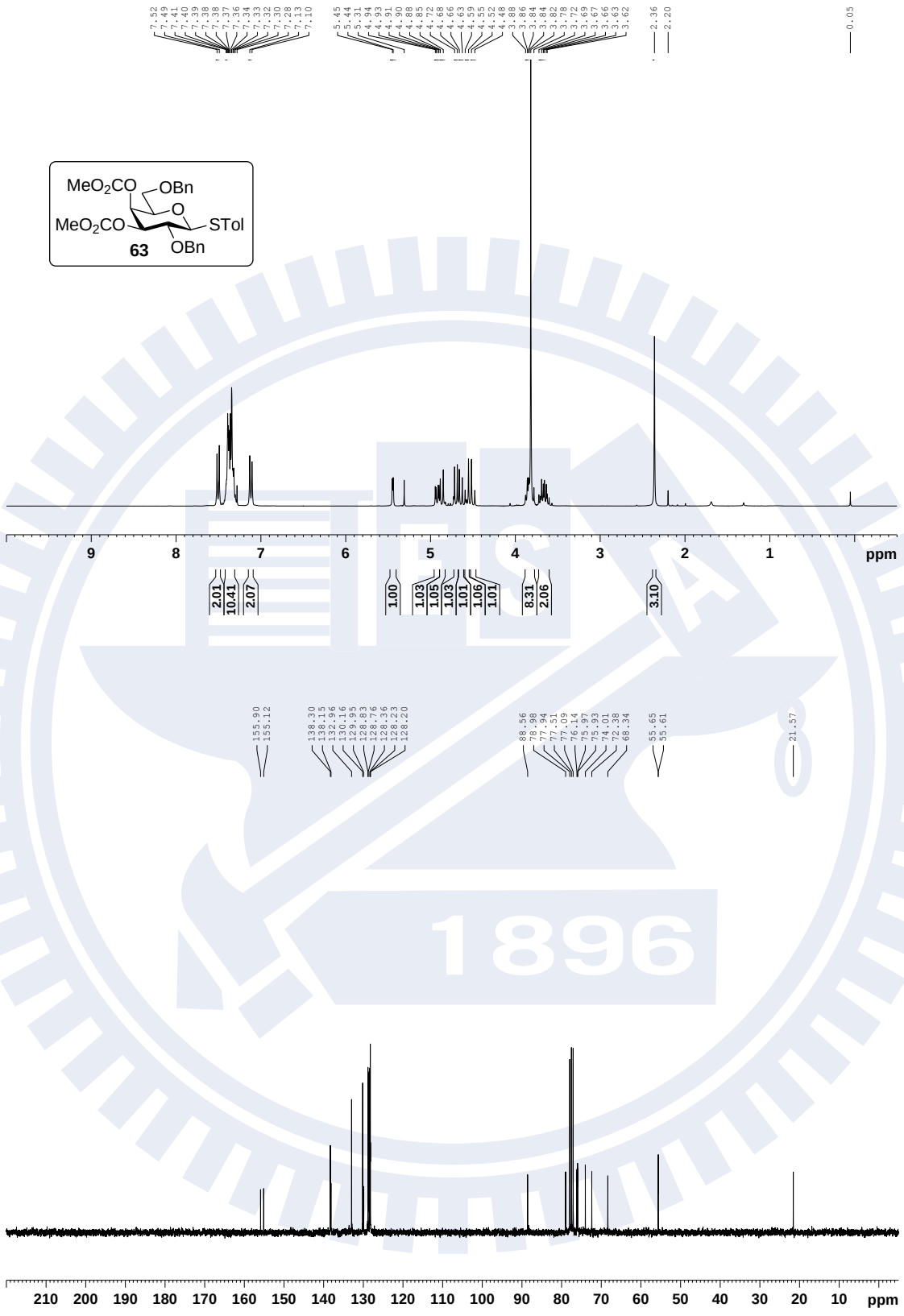

9 8 7 6 5 4 3 2 1 0 ppm
17.66 2.17 1.00 1.04 1.01 3.14 1.06 1.05 1.02 1.07 1.14 1.04 1.01 2.11 2.03 3.04 3.10
206.85 172.80 139.09 138.70 137.53 137.09 132.66 130.97 130.16 128.92 128.86 128.84 128.80 128.48 128.25 128.13 128.06 88.01 79.74 78.15 77.72 77.30 76.91 75.25 75.12 74.14 73.05 69.80 63.97 38.27 30.27 28.20 21.59
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

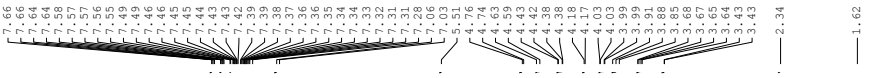

BnO
OLev
O
BnO
O
BnO
O
O
O
O
O
O
59
ppm
ppm

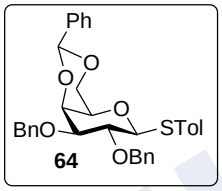

BnO
OBn
O
BnO
STol
OBn
61
9
8
7
6
5
4
3
2
1
ppm
2.04
2.03
18.01
2.03
1.01
4.01
2.00
2.01
1.00
1.01
1.98
2.01
3.00

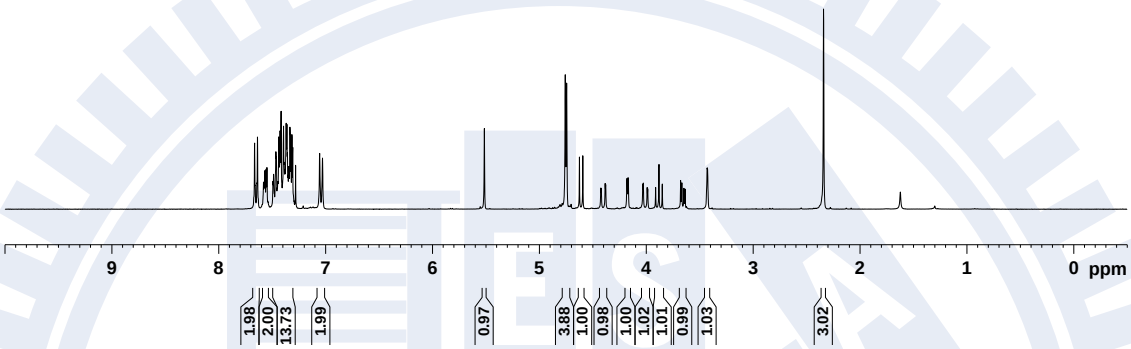


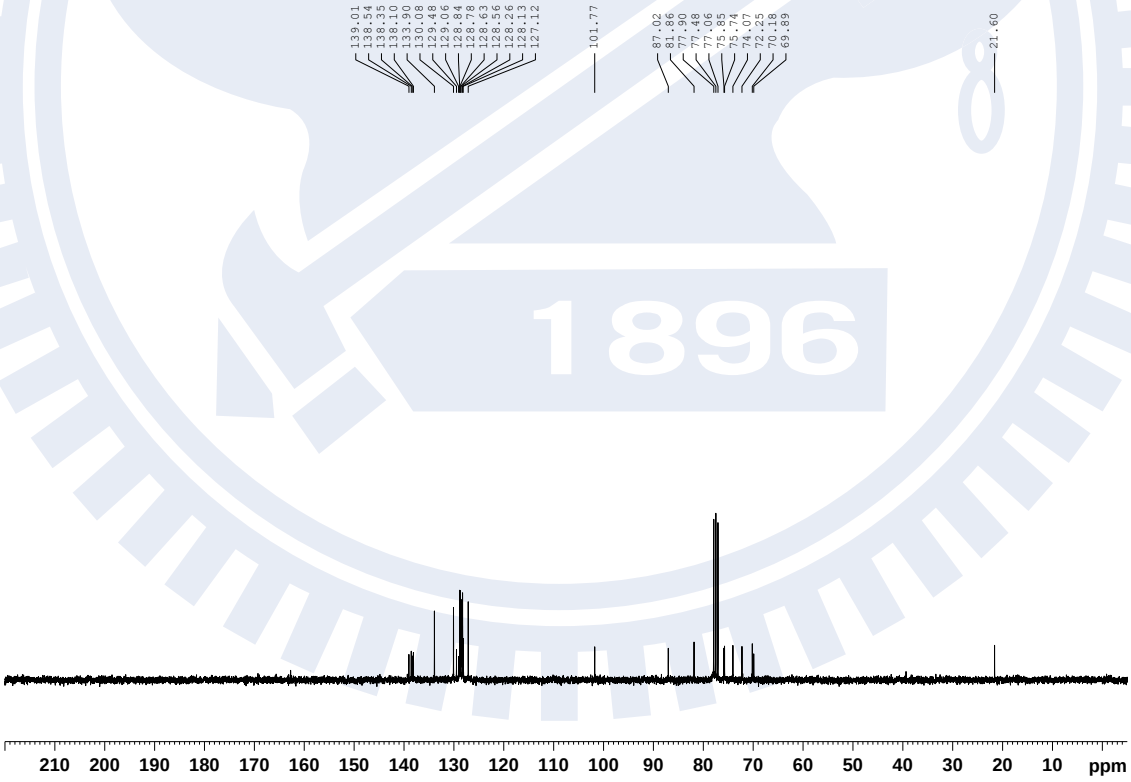

AcO
OBn
O
BnO
STol
OBn
62
9
8
7
6
5
4
3
2
1
ppm
2.02
15.03
2.03
1.00
3.02
1.03
3.03
1.00
2.97
0.98
2.98
3.00
170.76
138.65
138.10
138.06
138.01
132.94
130.23
130.02
128.88
128.85
128.79
128.71
128.67
128.49
128.28
128.23
88.55
81.71
77.89
77.47
77.22
77.05
76.28
76.20
74.11
73.38
68.63
67.26
21.55
21.37
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

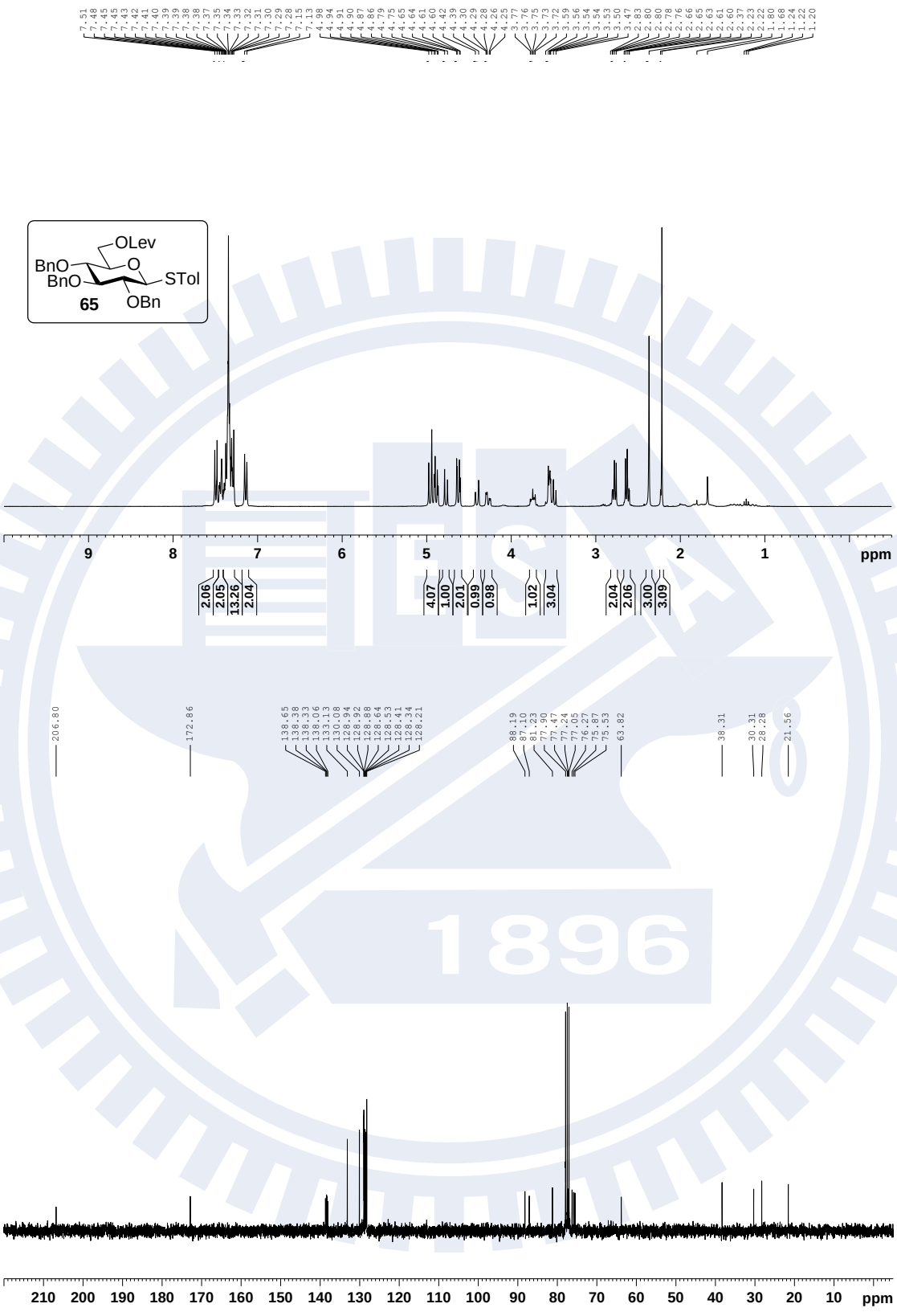

MeO2CO
OBn
O
MeO2CO
STol
63
OBn
ppm
ppm

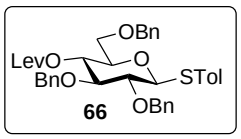


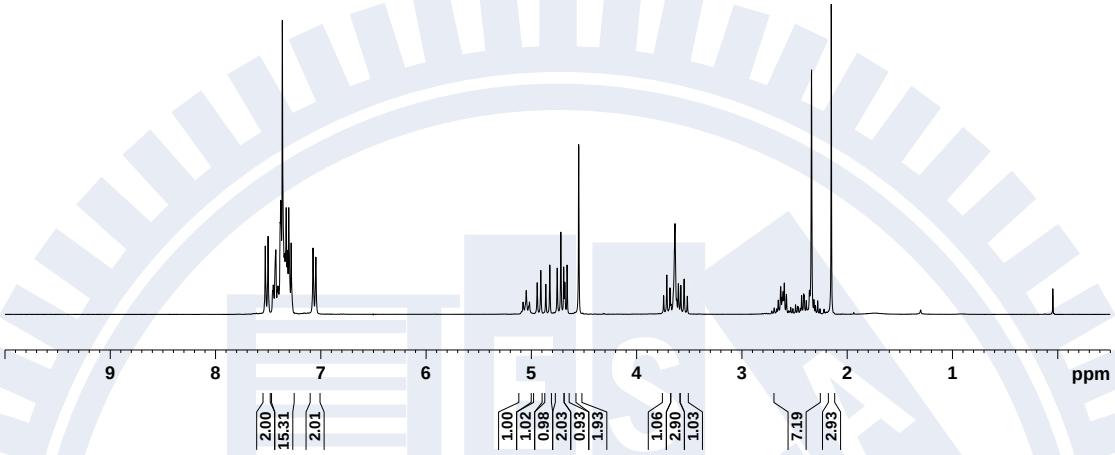

Ph
O
O
O
BnO
STol
OBn
64

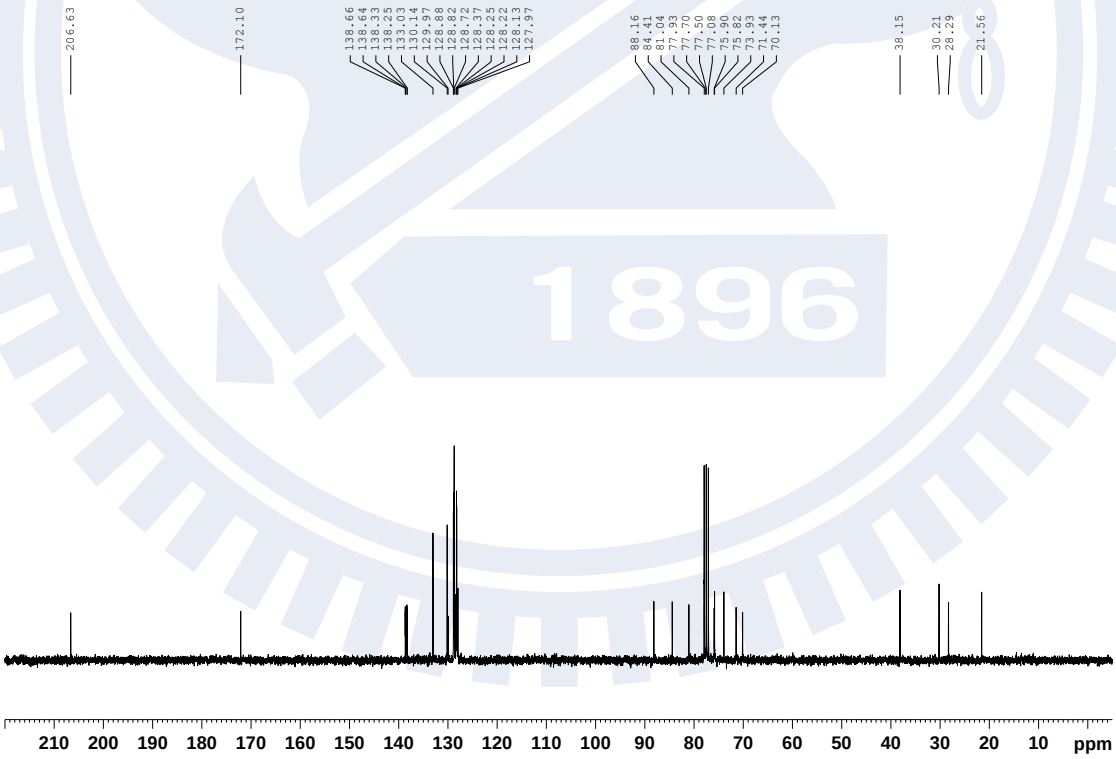

9
8
7
6
5
4
3
2
1
0 ppm
1.98
2.00
13.73
1.99
0.97
3.88
1.00
0.98
1.00
1.02
1.01
0.99
1.03
3.02

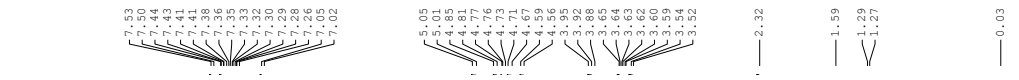

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

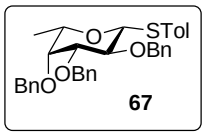

OLev
BnO
O
BnO
STol
65
OBn
9
8
7
6
5
4
3
2
1
ppm
2.06
2.05
13.26
2.04
4.07
1.00
2.01
0.99
0.98
1.02
3.04
2.04
2.06
3.00
3.09
206.80
172.86
138.65
138.38
138.33
138.16
133.13
130.08
128.94
128.92
128.88
128.64
128.53
128.41
128.34
128.21
88.19
87.10
81.23
77.90
77.47
77.24
77.05
76.25
75.87
75.53
63.82
38.31
30.31
28.28
21.56
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

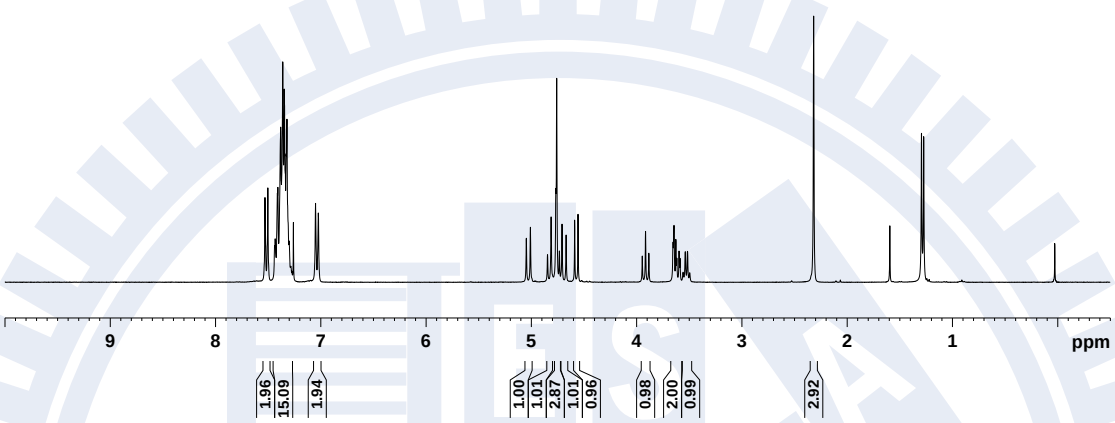

OBn
LevO
O
BnO
STol
66
OBn

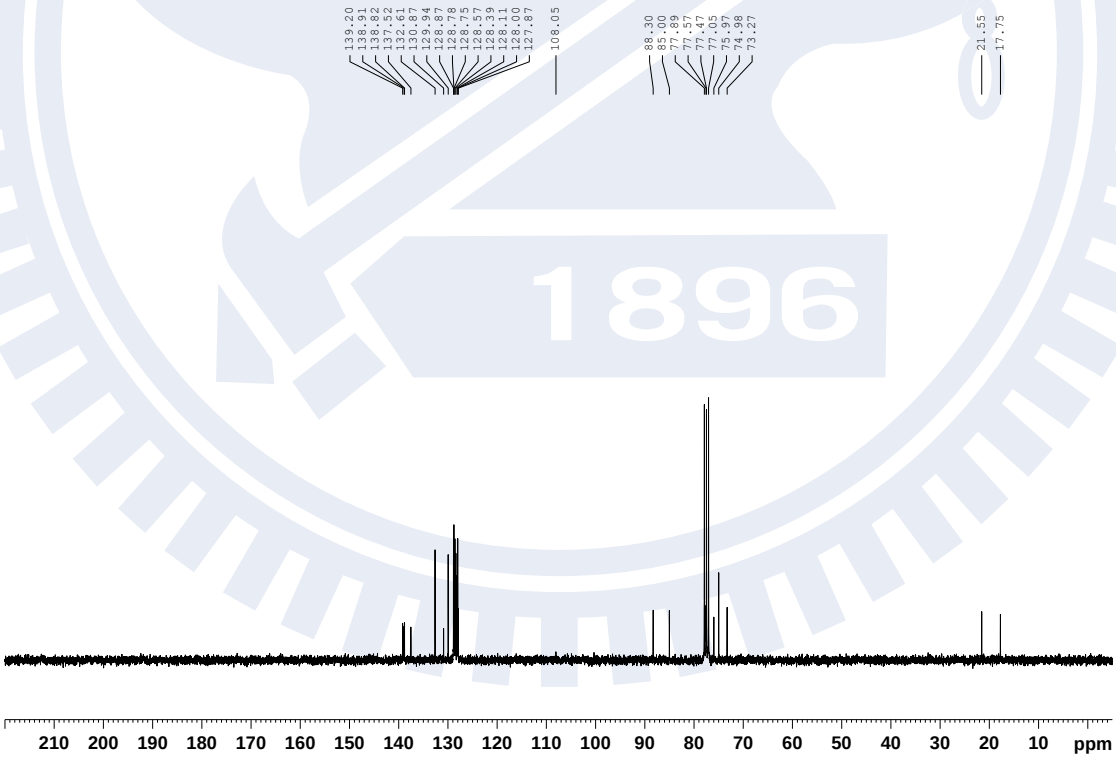

9
8
7
6
5
4
3
2
1
ppm
2.00
15.31
2.01
1.00
1.02
0.98
2.03
0.93
1.93
1.06
2.90
1.03
7.19
2.93

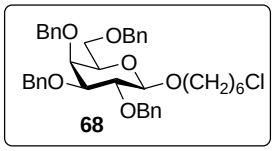

206.63
172.10
138.66
138.64
138.33
138.25
133.03
130.14
129.97
128.88
128.82
128.72
128.37
128.25
128.22
128.13
127.97
88.16
84.41
81.04
77.83
77.70
77.50
77.08
75.90
75.82
73.93
71.44
70.13
38.15
30.21
28.29
21.56
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

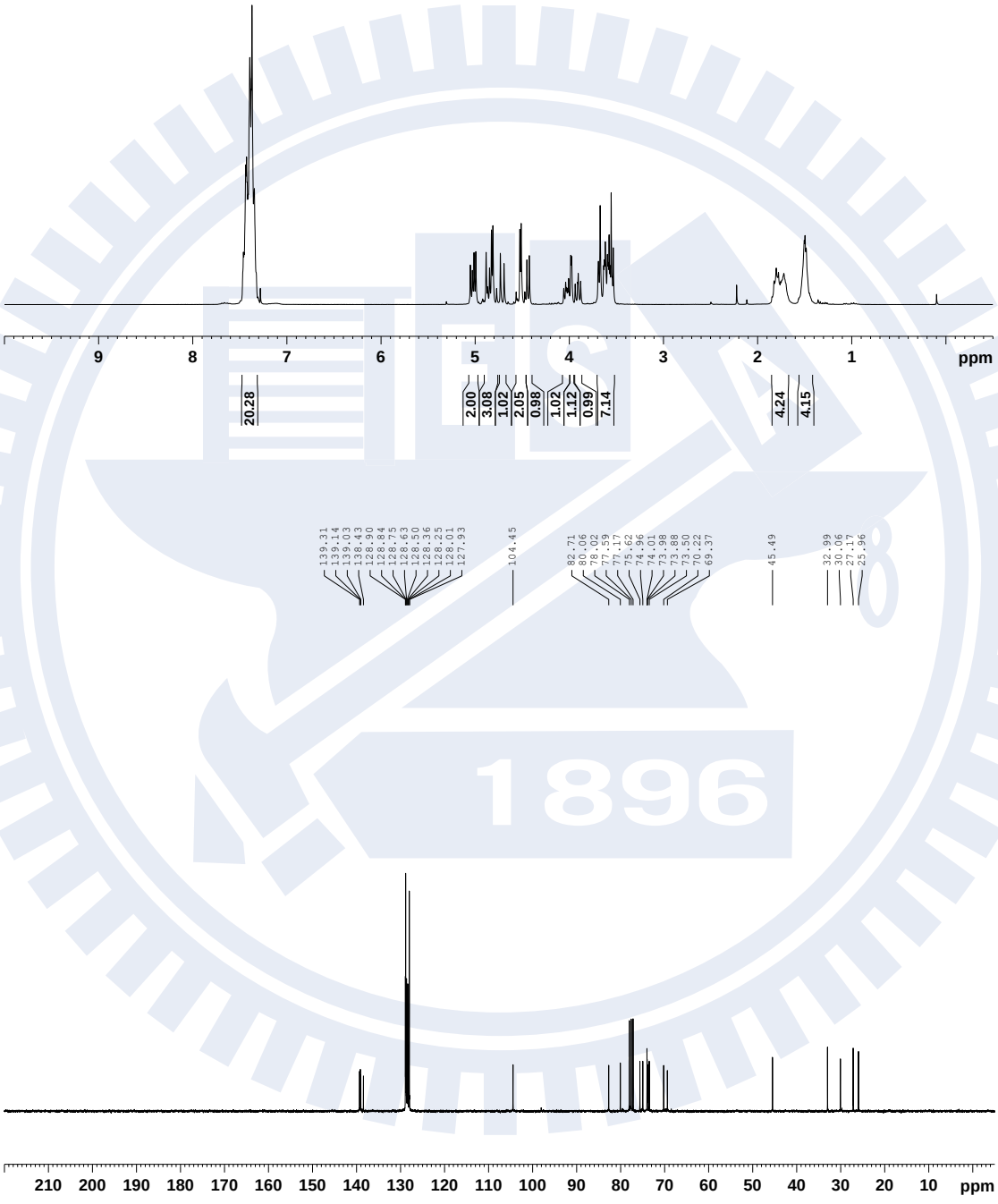


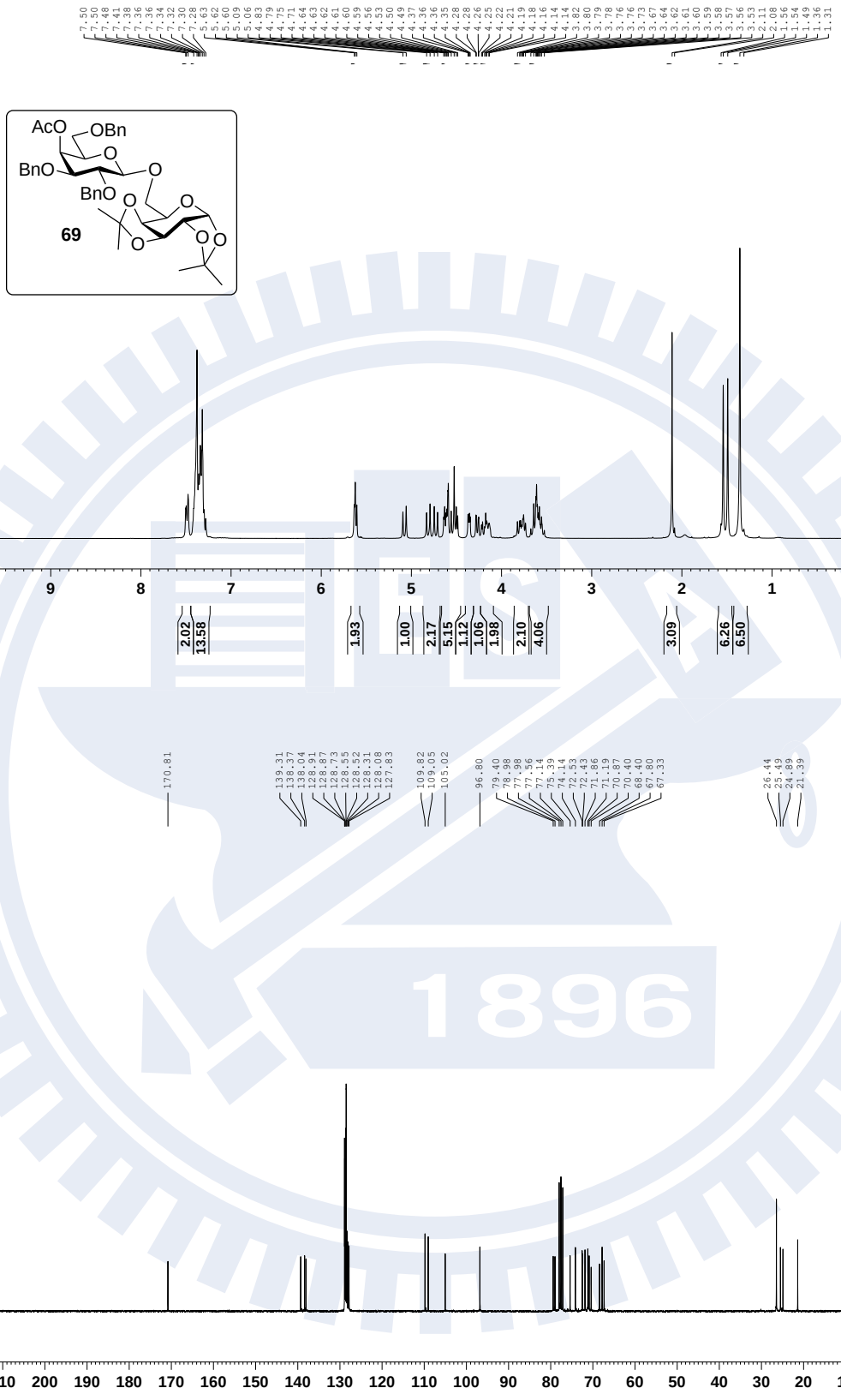

STol
OBn
BnO
OBn
67

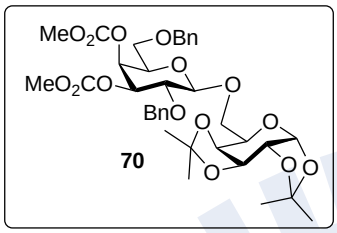

9
8
7
6
5
4
3
2
1
ppm
1.96
15.09
1.94
1.00
1.01
2.87
1.01
0.96
0.98
2.00
0.99
2.92


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

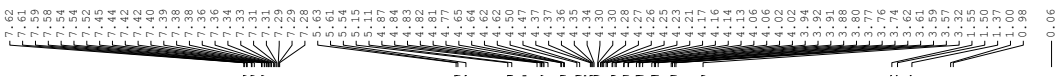

BnO
OBn
O
BnO
O(CH2)6Cl
OBn
68

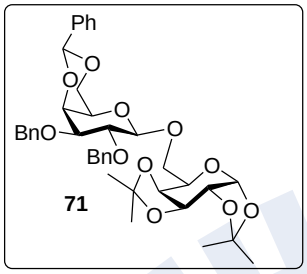

ppm
20.28
2.00
3.08
1.02
2.05
0.98
1.02
1.12
0.99
7.14
4.24
4.15
ppm

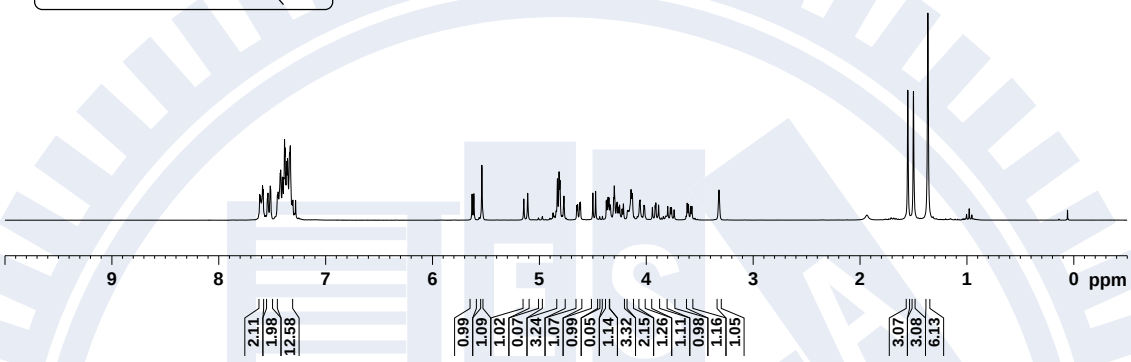

AcO
OBn
BnO
BnO
69
9
8
7
6
5
4
3
2
1
ppm
2.02
13.58
1.93
1.00
2.17
5.15
1.12
1.06
1.98
2.10
4.06
3.09
6.26
6.50
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

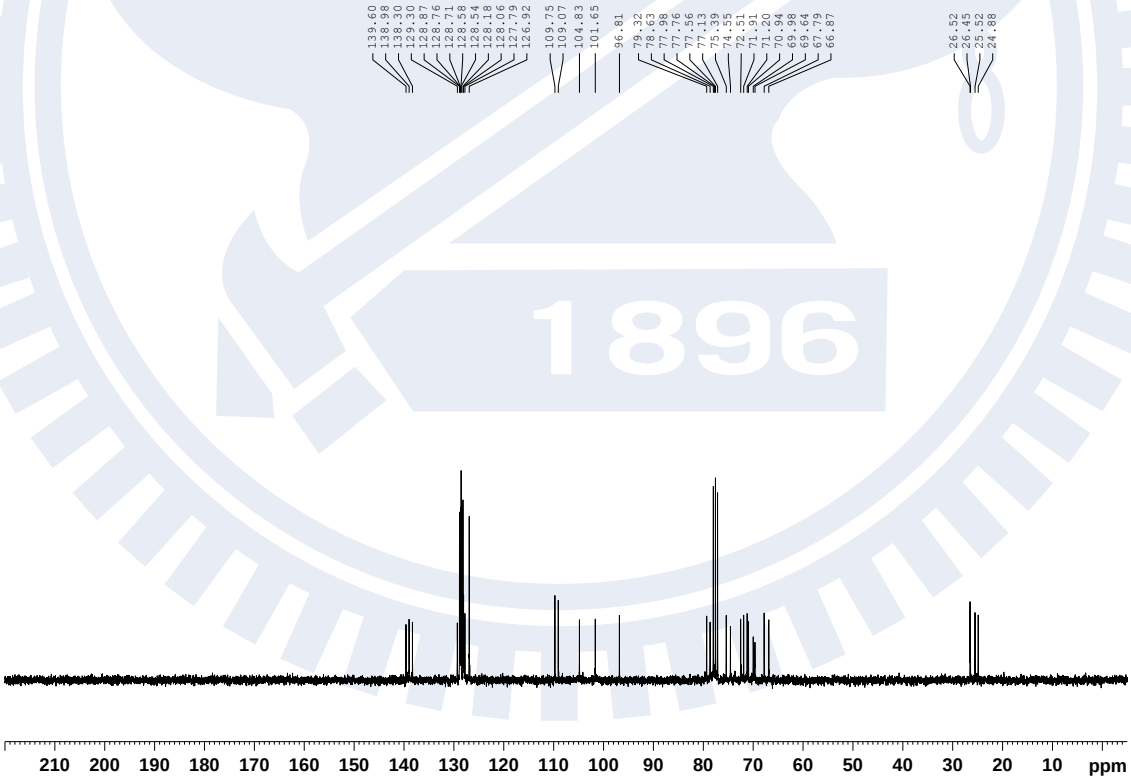

MeO2CO
OBn
O
MeO2CO
O
BnO
O
O
O
O
O
O
70

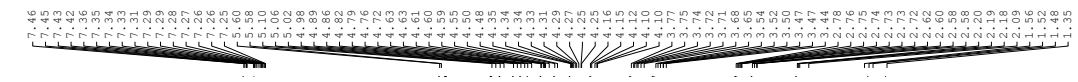
ppm
10.33
1.00
0.98
1.04
1.05
5.20
1.12
1.04
2.18
3.37
7.87
3.05
3.13
6.13
ppm

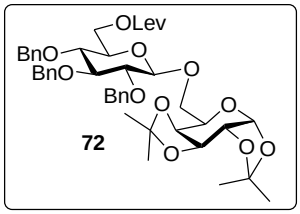


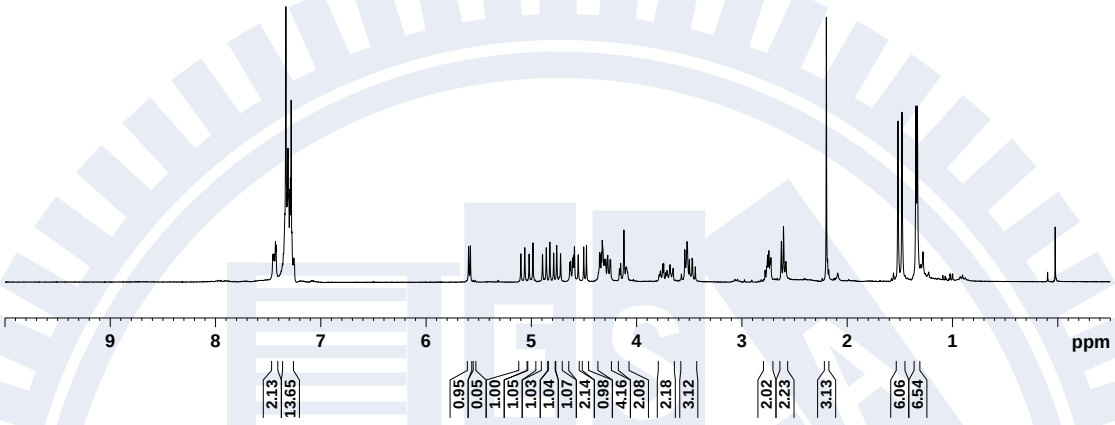

Ph
O
O
O
O
BnO
O
BnO
O
O
O
O
O
71

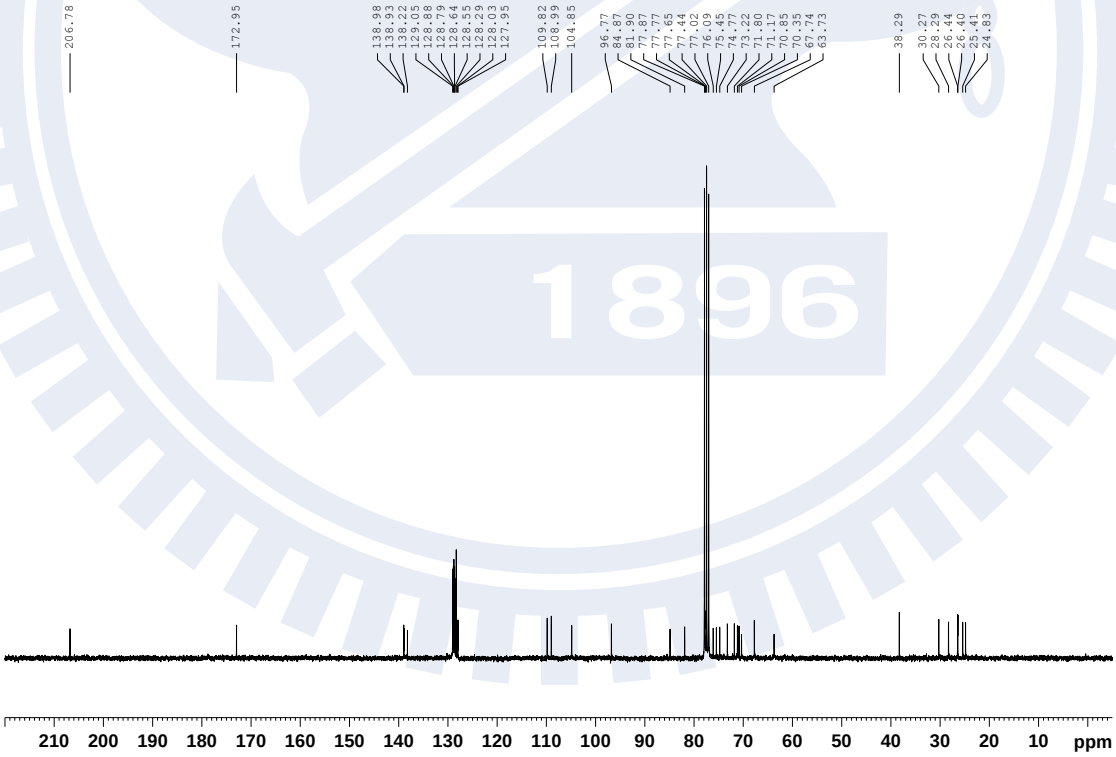

9
8
7
6
5
4
3
2
1
0
ppm
2.11
1.98
12.58
0.99
1.09
1.02
0.07
3.24
1.07
0.99
0.05
1.14
3.32
2.15
1.26
1.11
0.98
1.16
1.05
3.07
3.08
6.13

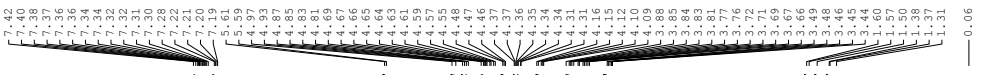

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

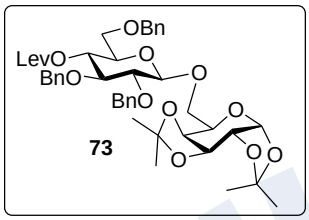


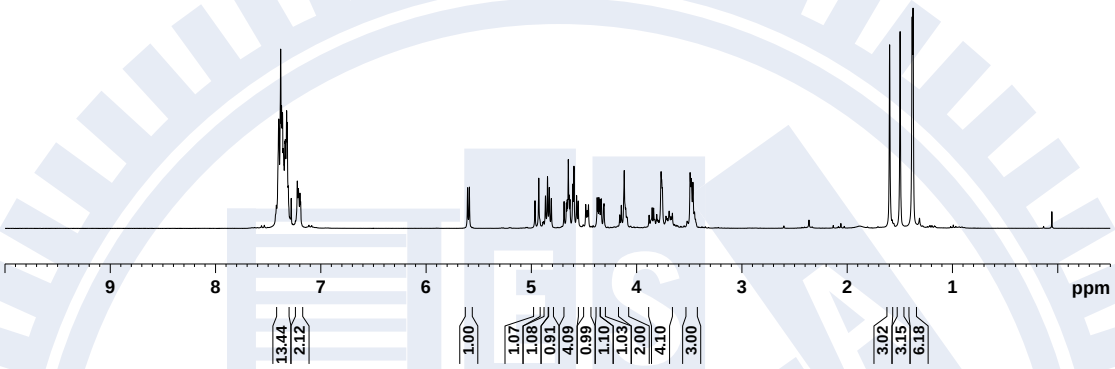

OLev
BnO
BnO
BnO
O
O
O
O
O
O
O
O
72

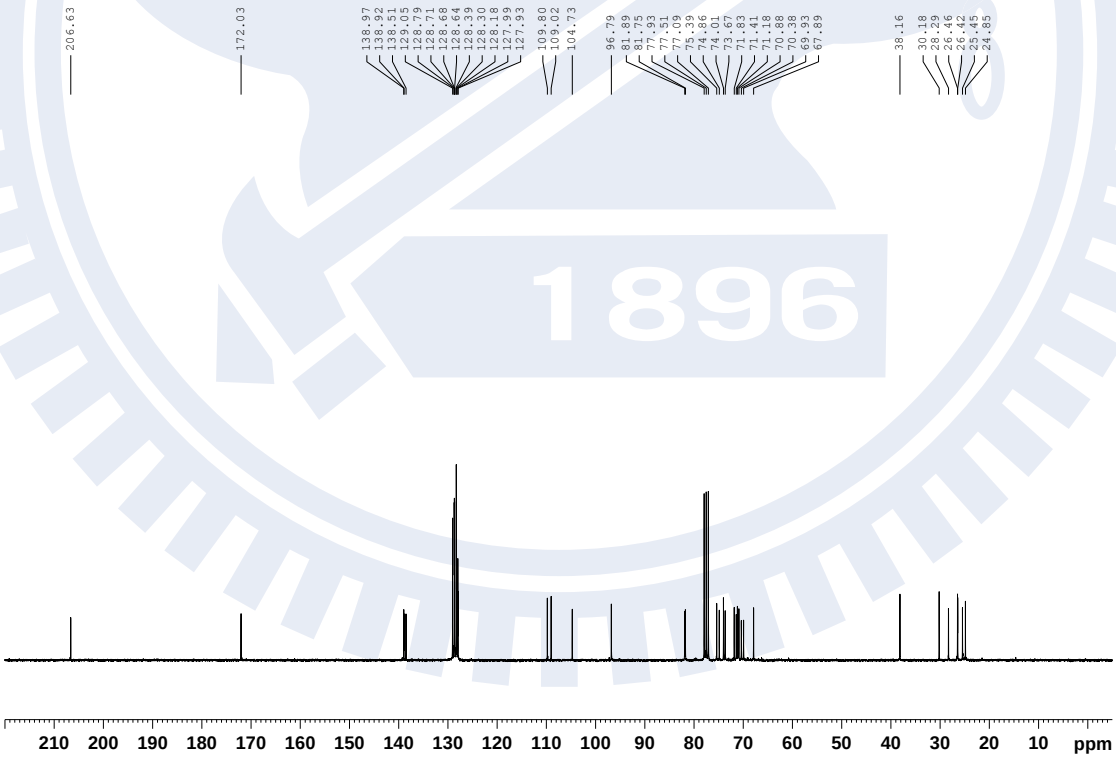

9
8
7
6
5
4
3
2
1
ppm
2.13
13.65
0.95
0.05
1.00
1.05
1.03
1.04
1.07
2.14
0.98
4.16
2.08
2.18
3.12
2.02
2.23
3.13
6.06
6.54


206.78
172.95
138.98
138.93
138.22
129.05
128.88
128.79
128.64
128.55
128.29
128.03
127.95
109.82
108.99
104.85
96.77
84.87
81.90
77.87
77.77
77.65
77.44
77.02
76.09
75.45
74.77
73.22
71.80
71.17
70.85
70.35
67.74
63.73
38.29
30.27
28.29
26.44
26.40
25.41
24.83
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm




OBn
LevO
BnO
BnO
O
O
O
O
O
O
O
73


9
8
7
6
5
4
3
2
1
ppm
13.44
2.12
1.00
1.07
1.08
0.91
4.09
0.99
1.10
1.03
2.00
4.10
3.00
3.02
3.15
6.18


206.63
172.03
138.97
138.92
138.51
129.05
128.79
128.71
128.68
128.64
128.39
128.30
128.18
127.99
127.93
109.80
109.02
104.73
96.79
81.89
81.75
77.93
77.51
77.09
75.39
74.86
74.01
73.67
71.83
71.41
71.18
70.88
70.38
69.93
67.89
38.16
30.18
28.29
26.46
26.42
25.45
24.85
210
200
190
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170
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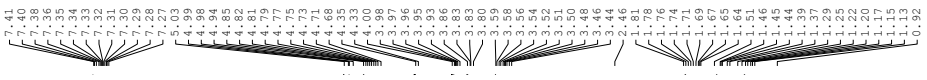
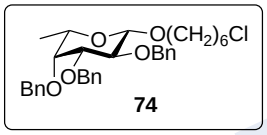
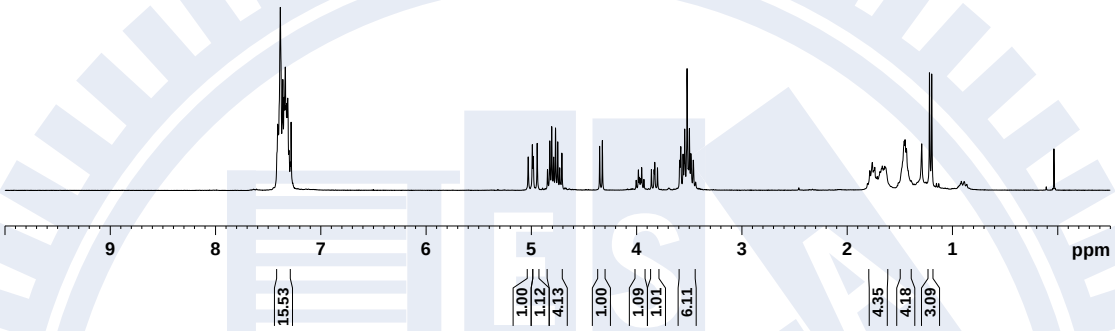
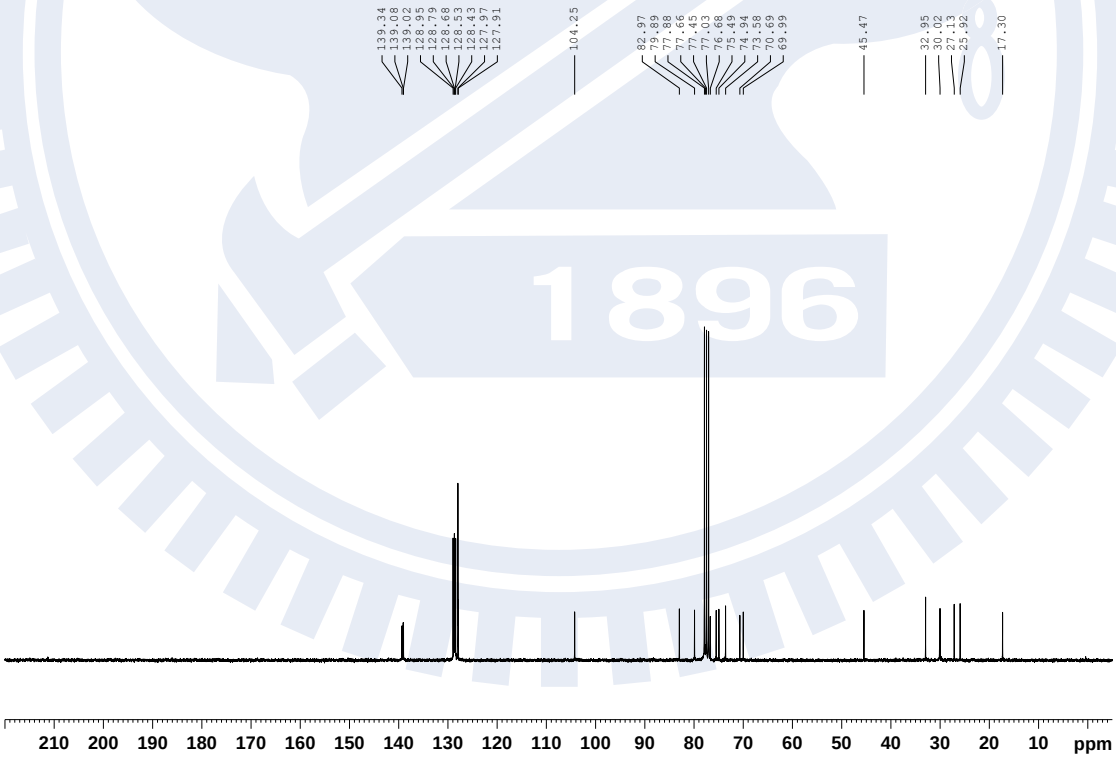
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

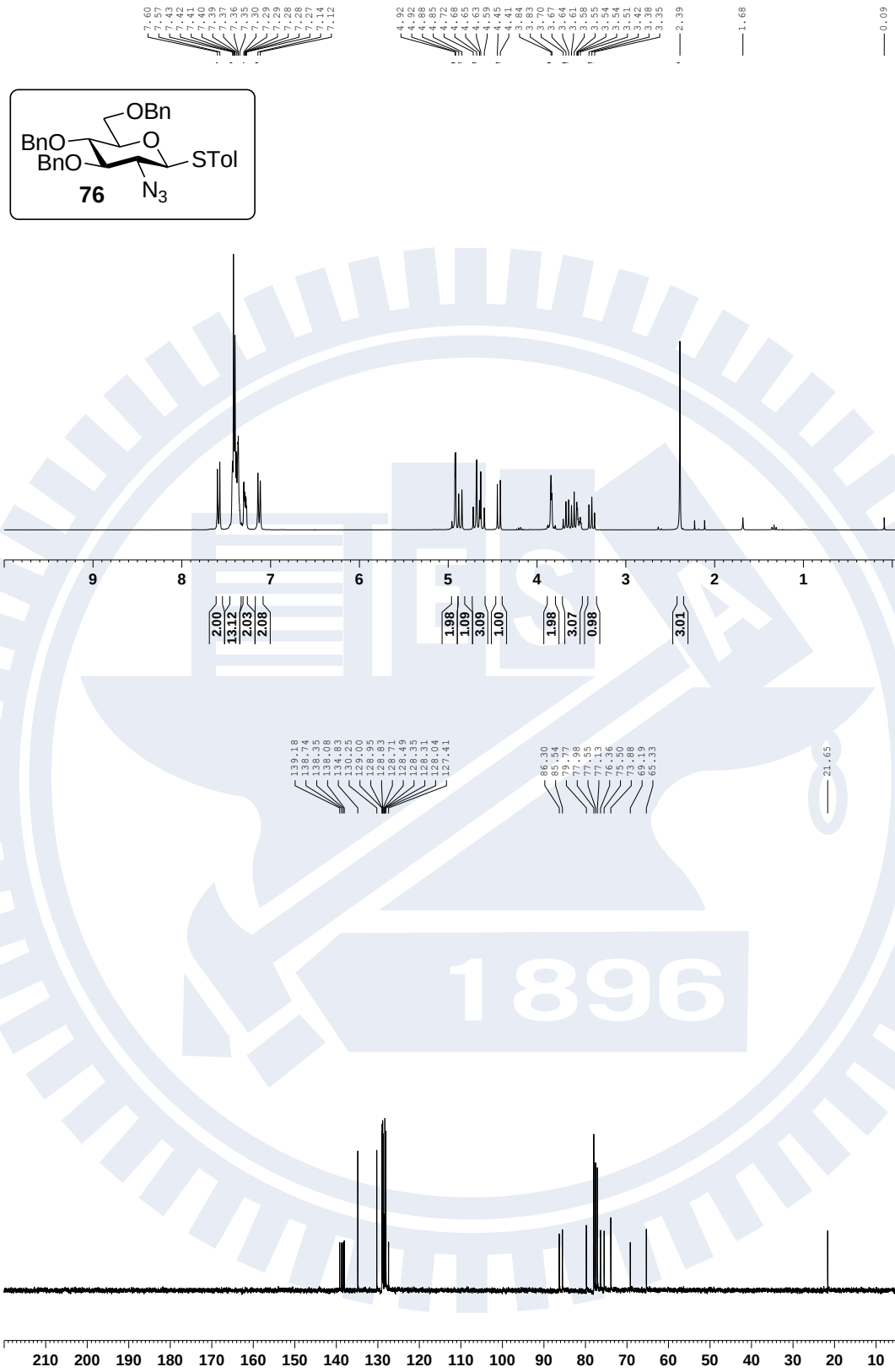


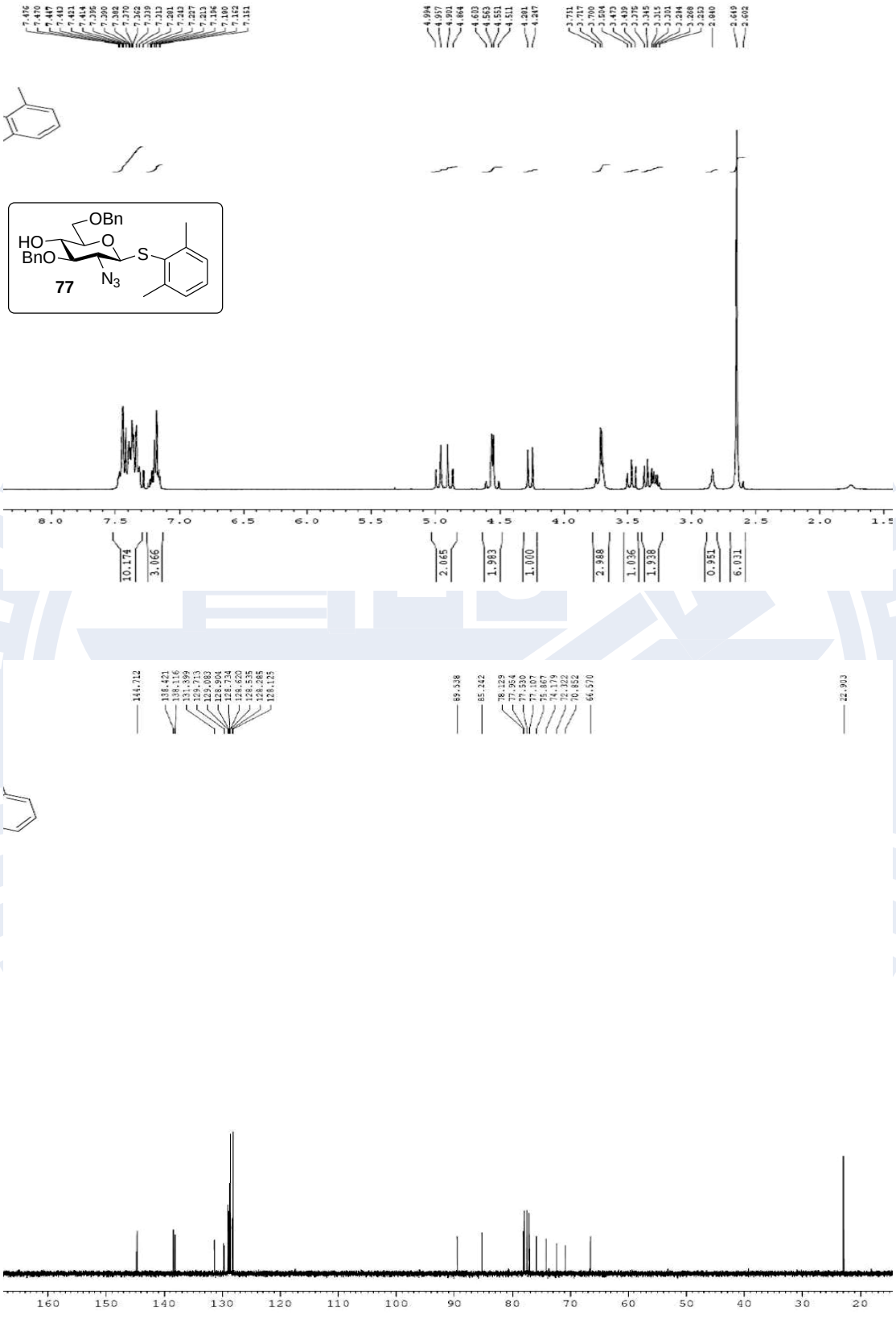

O(CH2)6Cl
OBn
BnO
OBn

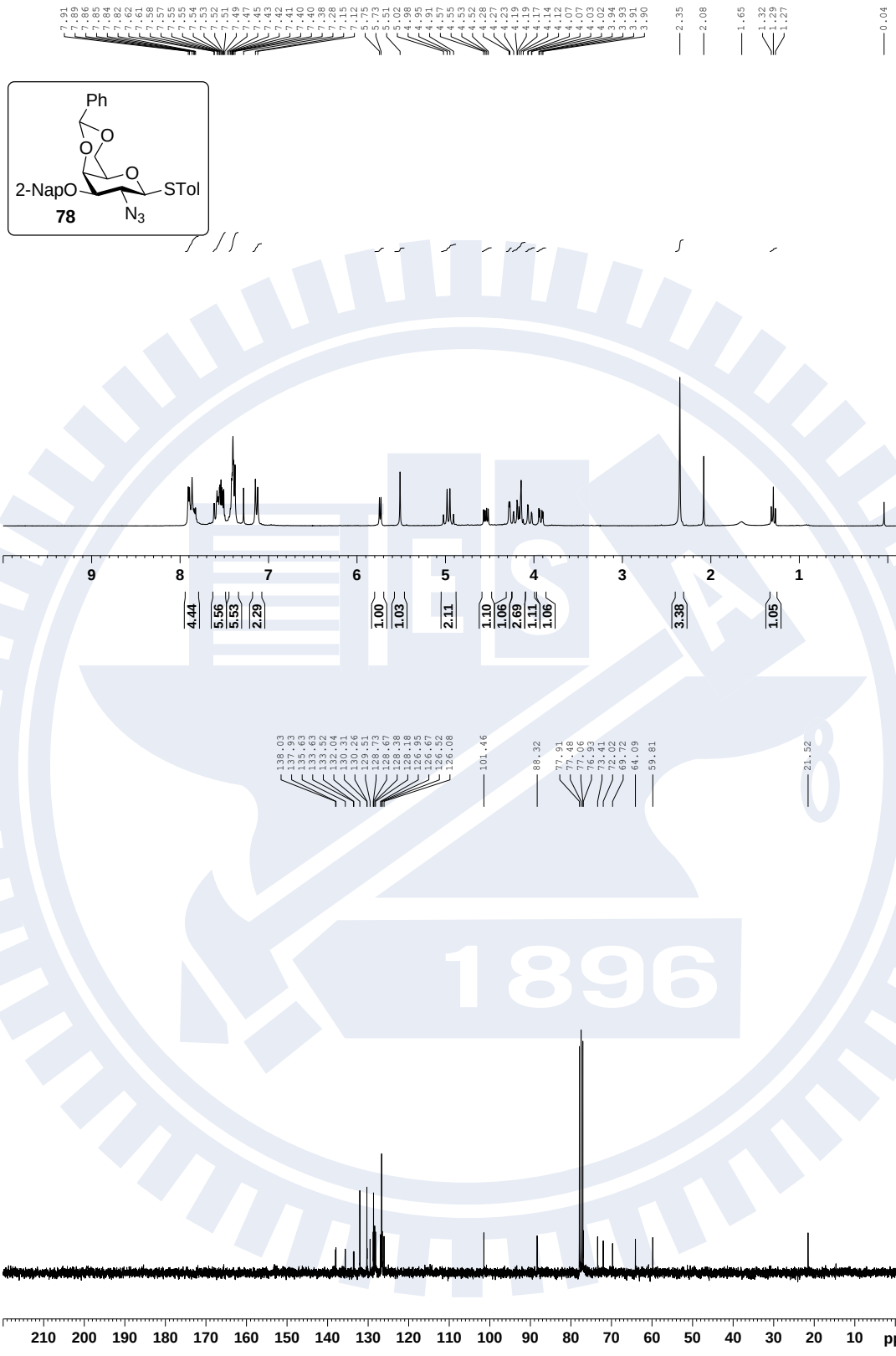
74

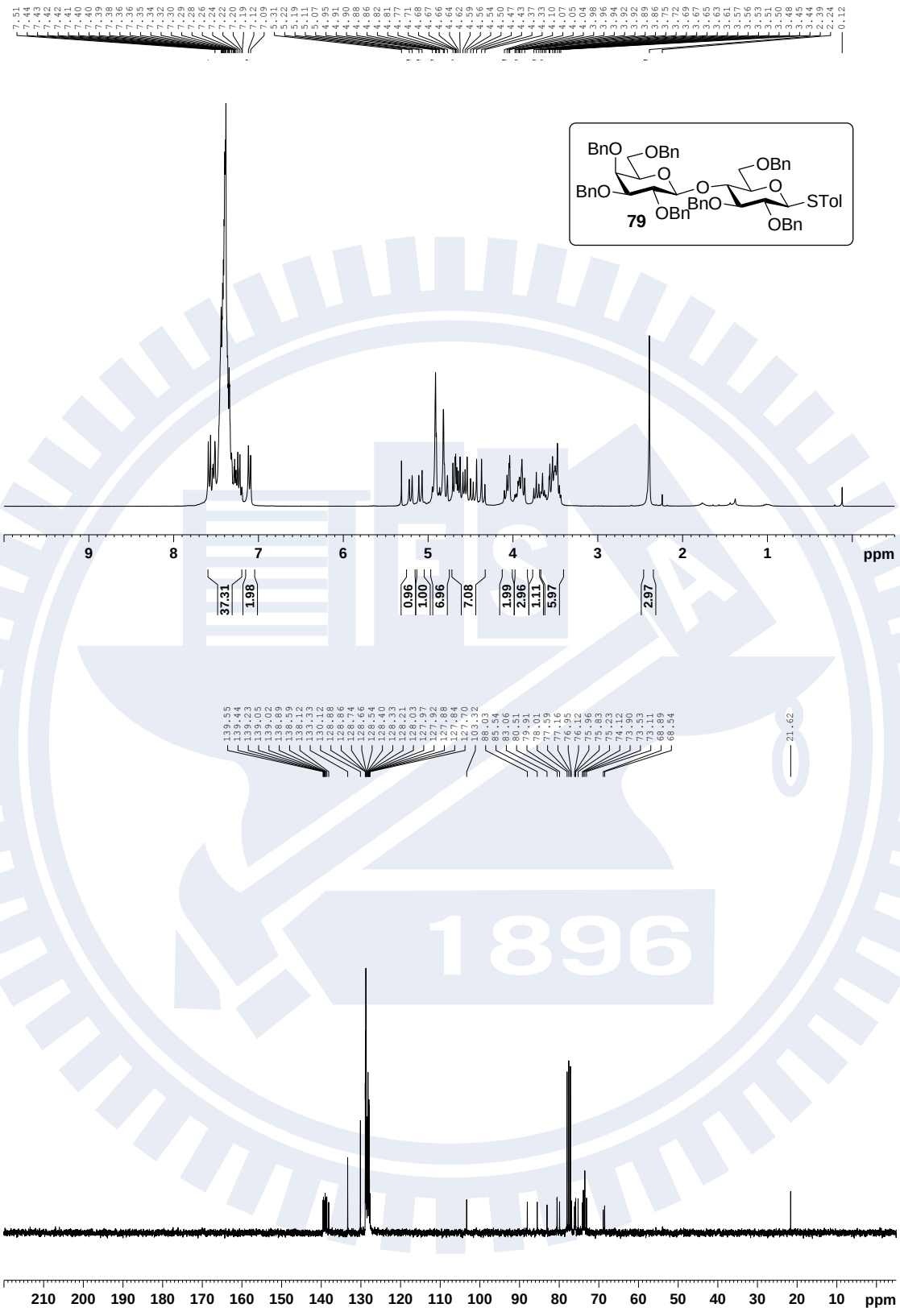

9
8
7
6
5
4
3
2
1
ppm
15.53
1.00
1.12
4.13
1.00
1.09
1.01
6.11
4.35
4.18
3.09

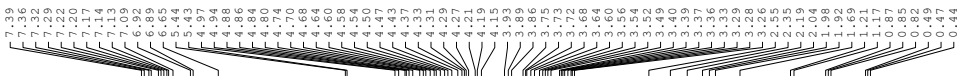

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

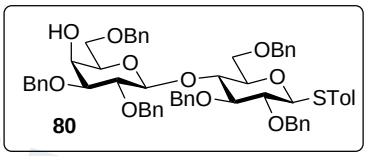

OBn
BnO
O
BnO
STol
N3
76
ppm
ppm

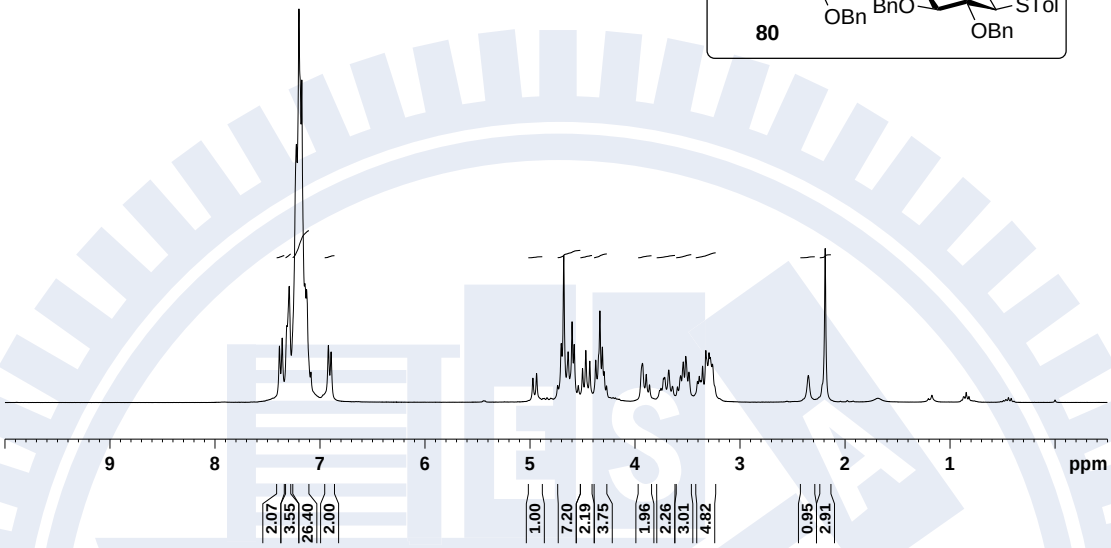

OBn
HO
O
S
BnO
N3
77

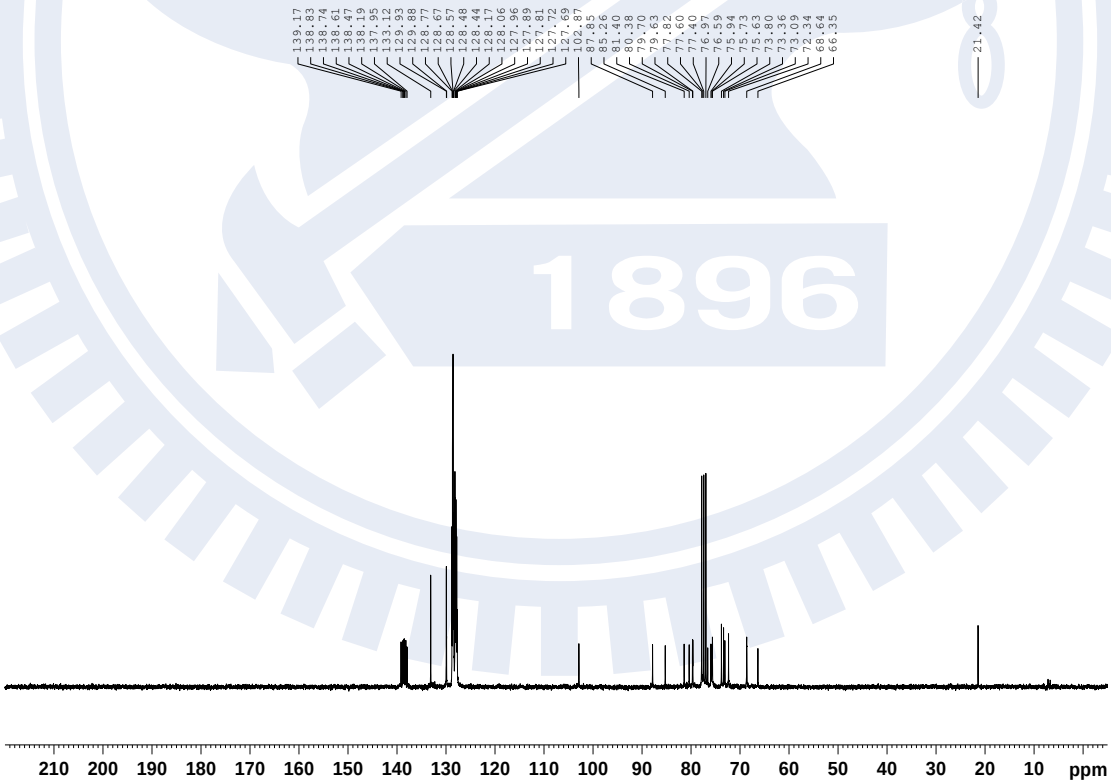

Ph
O
O
O
2-NapO
STol
78
N_3
9
8
7
6
5
4
3
2
1
ppm
4.44
5.56
5.53
2.29
1.00
1.03
2.11
1.10
1.06
2.69
1.11
1.06
3.38
1.05
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

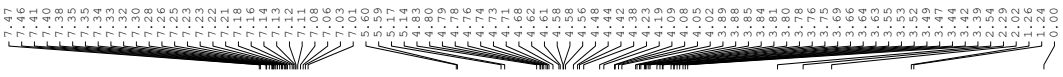

BnO
OBn
O
BnO
OBn
O
BnO
OBn
STol
OBn
79
ppm
37.31
1.98
0.96
1.00
6.96
7.08
1.99
2.96
1.11
5.97
2.97
21.62
ppm

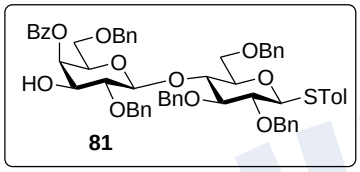



HO
OBn
O
BnO
OBn
O
OBn
O
BnO
STol
OBn
80

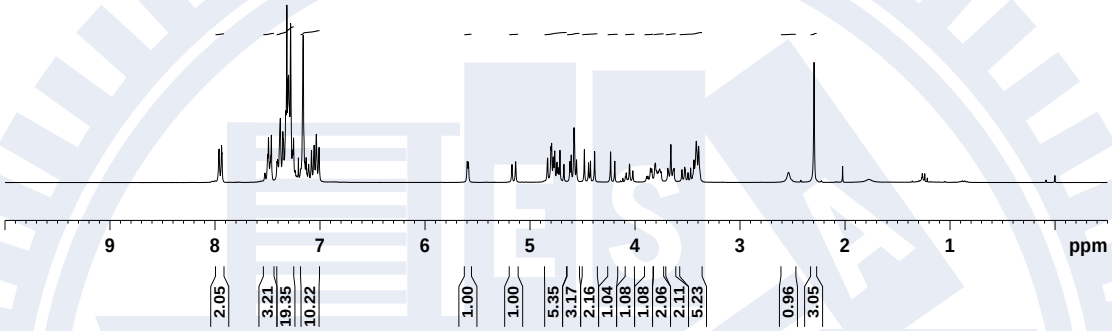

9
8
7
6
5
4
3
2
1
ppm
2.07
3.55
26.40
2.00
1.00
7.20
2.19
3.75
1.96
2.26
3.01
4.82
0.95
2.91

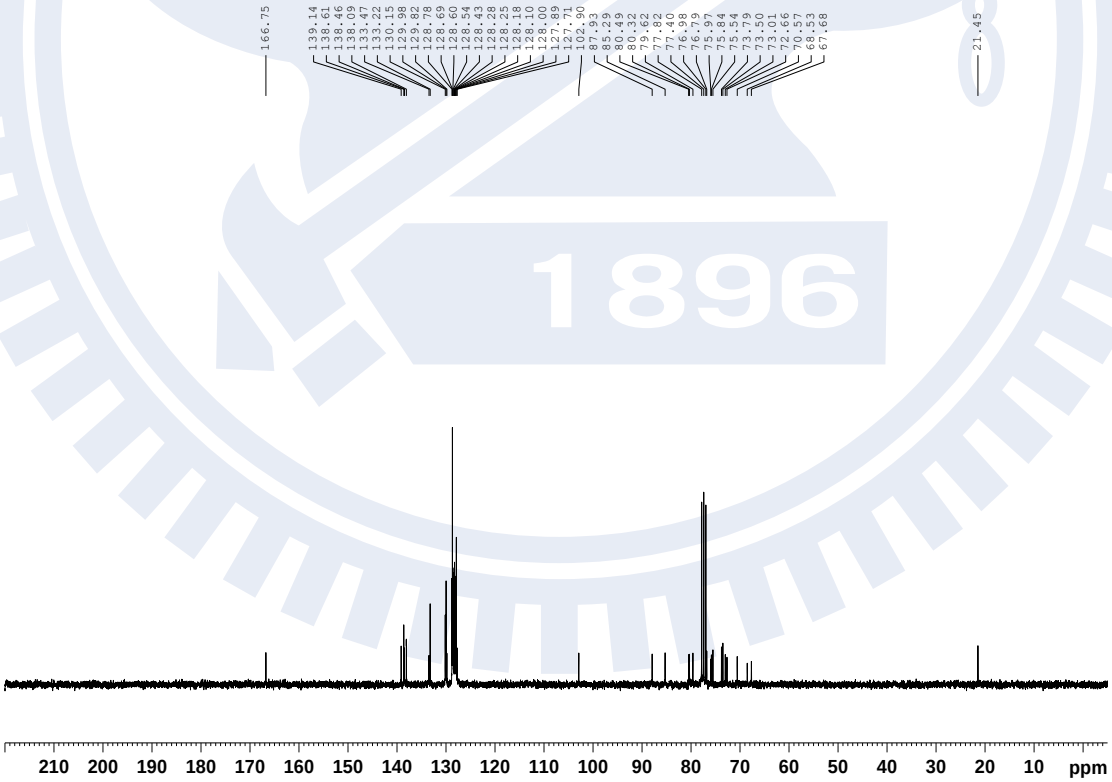

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

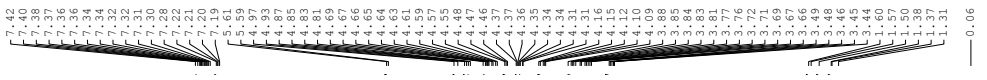


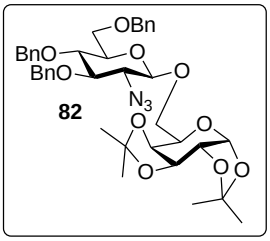

BzO
OBn
O
HO
O
OBn
BnO
OBn
O
STol
OBn

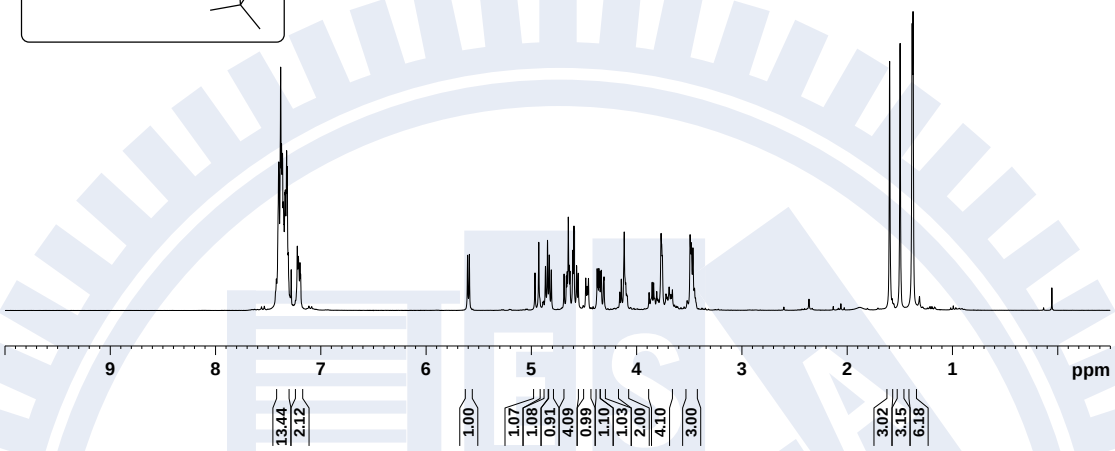
81

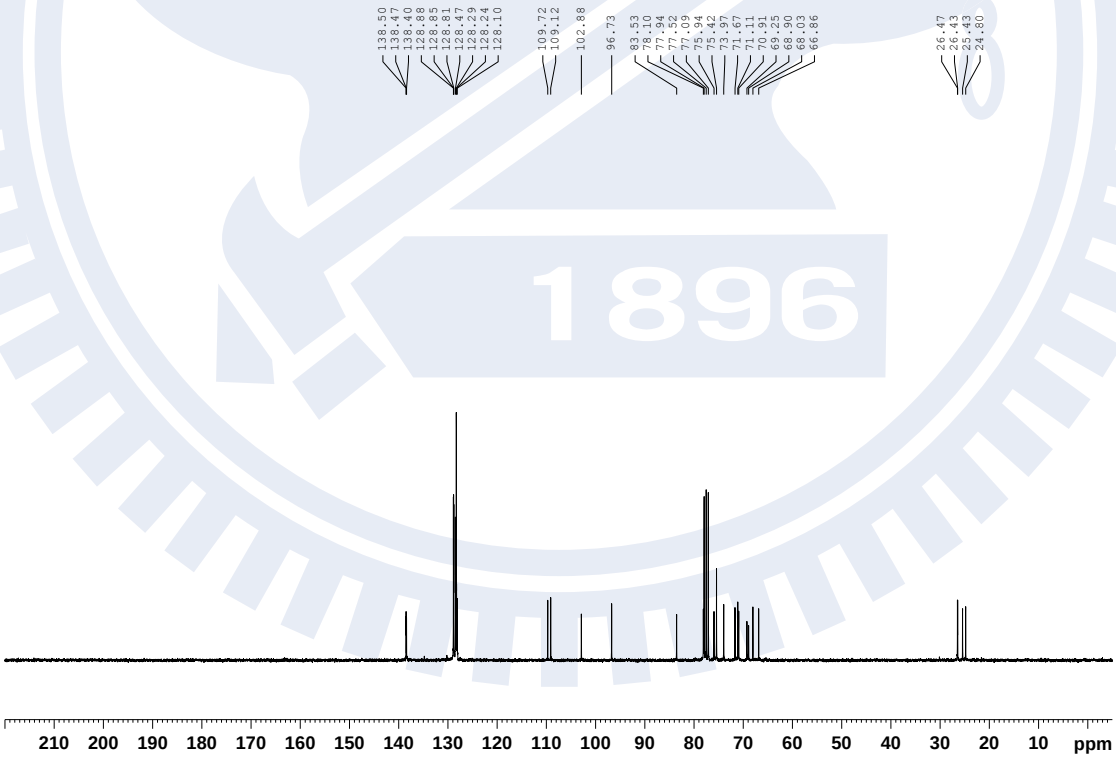

9
8
7
6
5
4
3
2
1
ppm
2.05
3.21
19.35
10.22
1.00
1.00
5.35
3.17
2.16
1.04
1.08
1.08
2.06
2.11
5.23
0.96
3.05

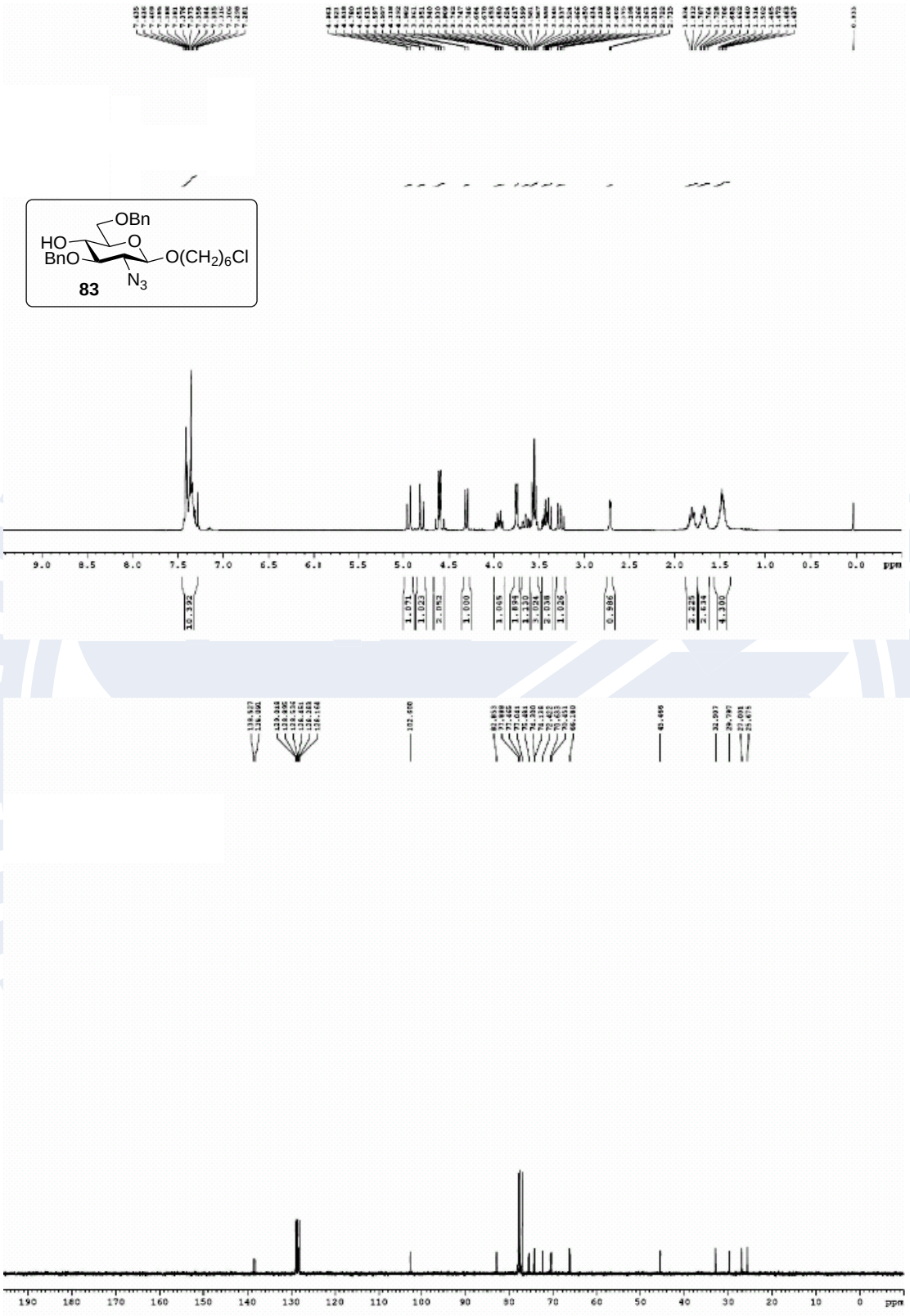

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

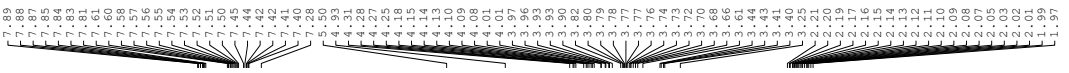


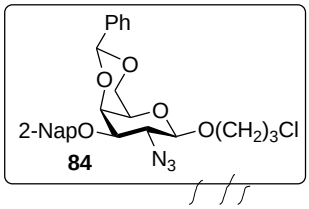

OBn
BnO
BnO
O
O
N3
82
O
O
O
O
O

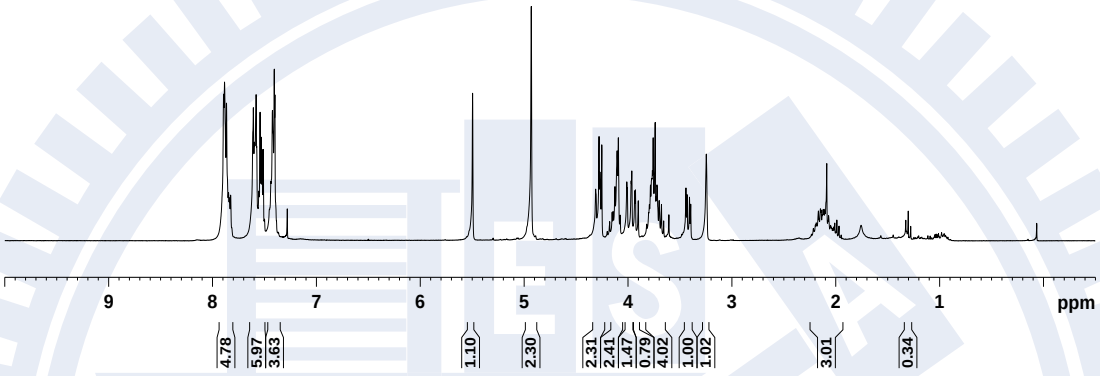

9
8
7
6
5
4
3
2
1
ppm
13.44
2.12
1.00
1.07
1.08
0.91
4.09
0.99
1.10
1.03
2.00
4.10
3.00
3.02
3.15
6.18

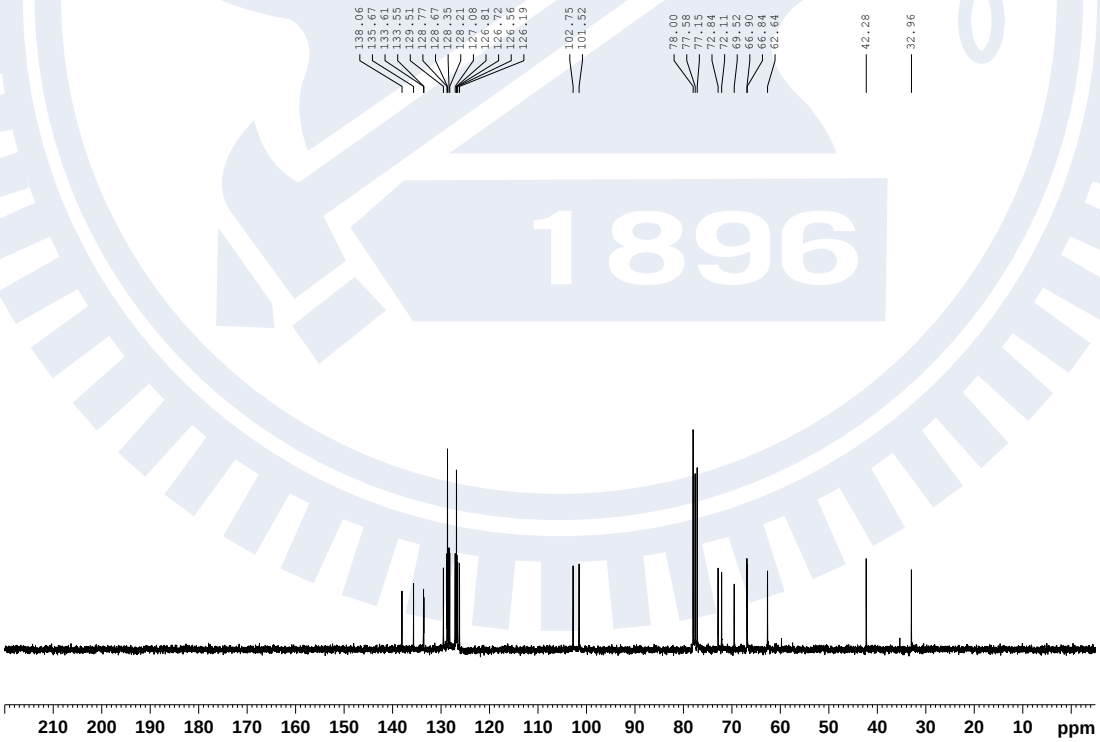

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

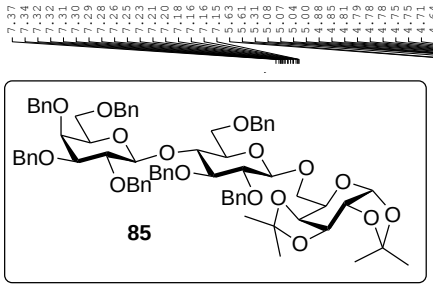

OBn
HO
O
BnO
O(CH2)6Cl
N3
83

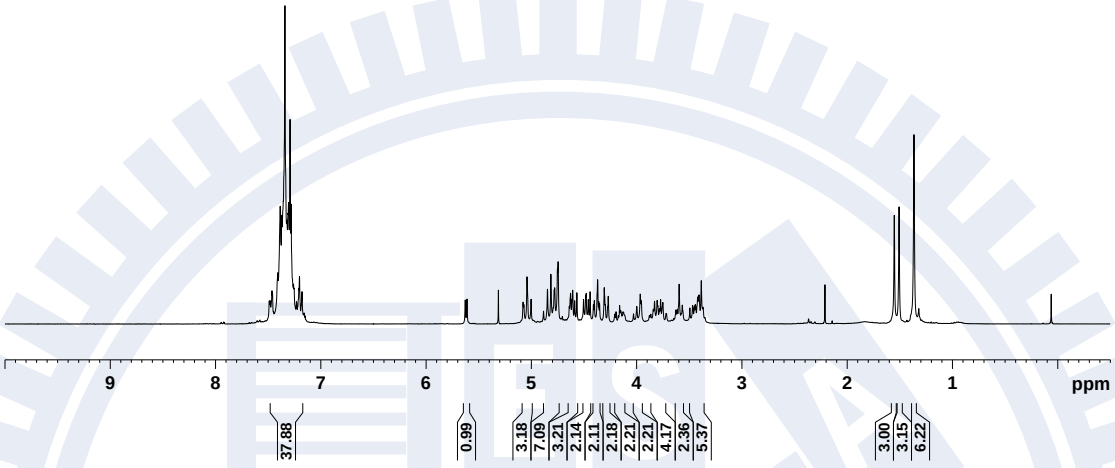


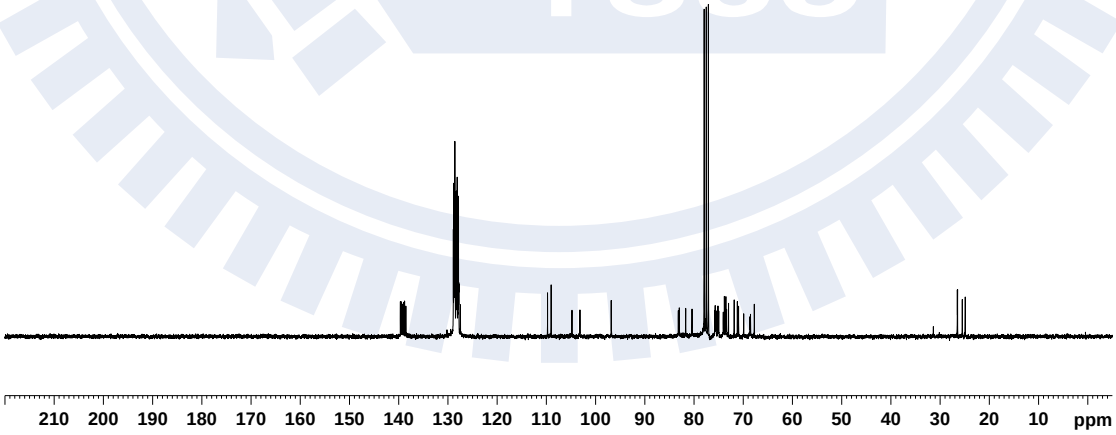

Ph
O
O
O
2-NapO
O(CH2)3Cl
N3
84

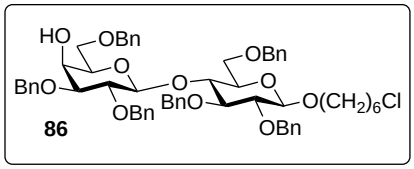

9
8
7
6
5
4
3
2
1
ppm
4.78
5.97
3.63
1.10
2.30
2.31
2.41
1.47
0.79
4.02
1.00
1.02
3.01
0.34

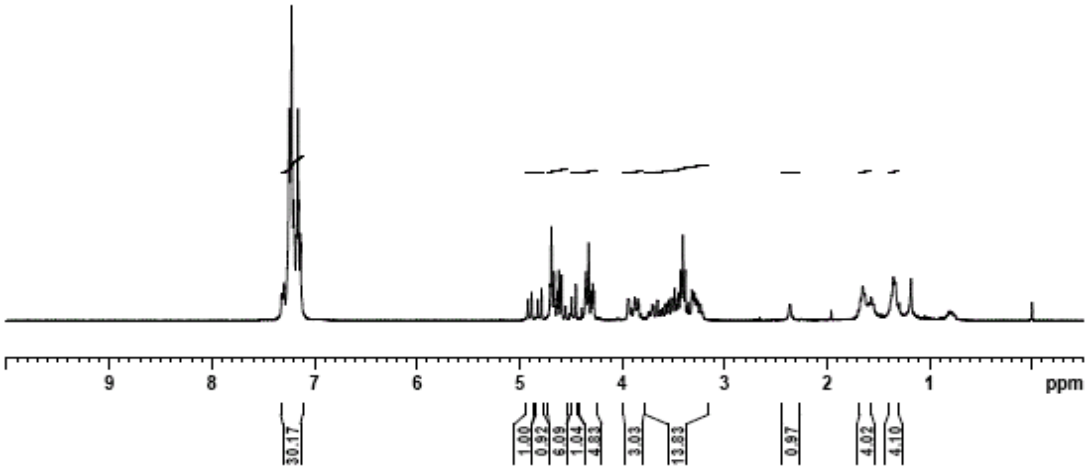

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

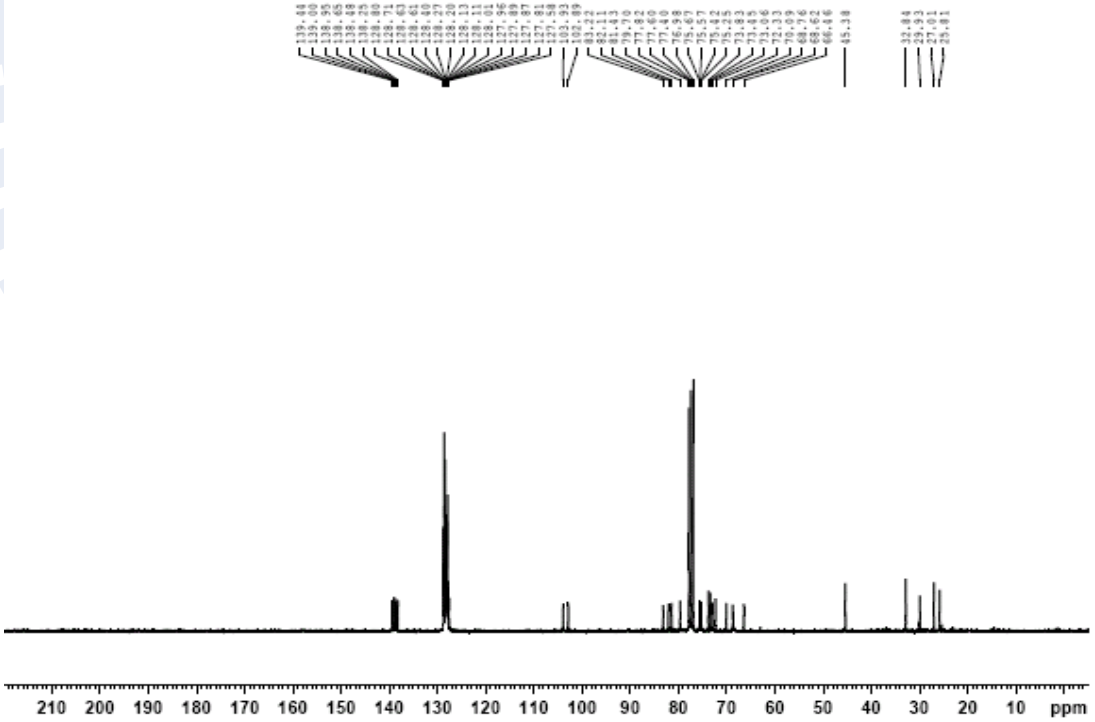

BnO
OBn
O
BnO
OBn
O
BnO
OBn
O
BnO
O
O
O
O
O
85

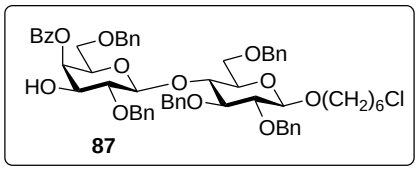

9
8
7
6
5
4
3
2
1
ppm
37.88
0.99
3.18
7.09
3.21
2.14
2.11
2.18
2.21
2.21
4.17
2.36
5.37
3.00
3.15
6.22


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

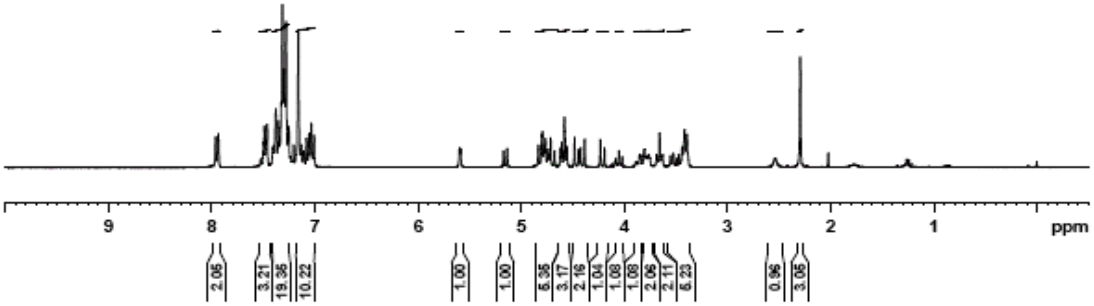

HO
OBn
O
BnO
OBn
O
BnO
OBn
O
OBn
O(CH2)6Cl
86

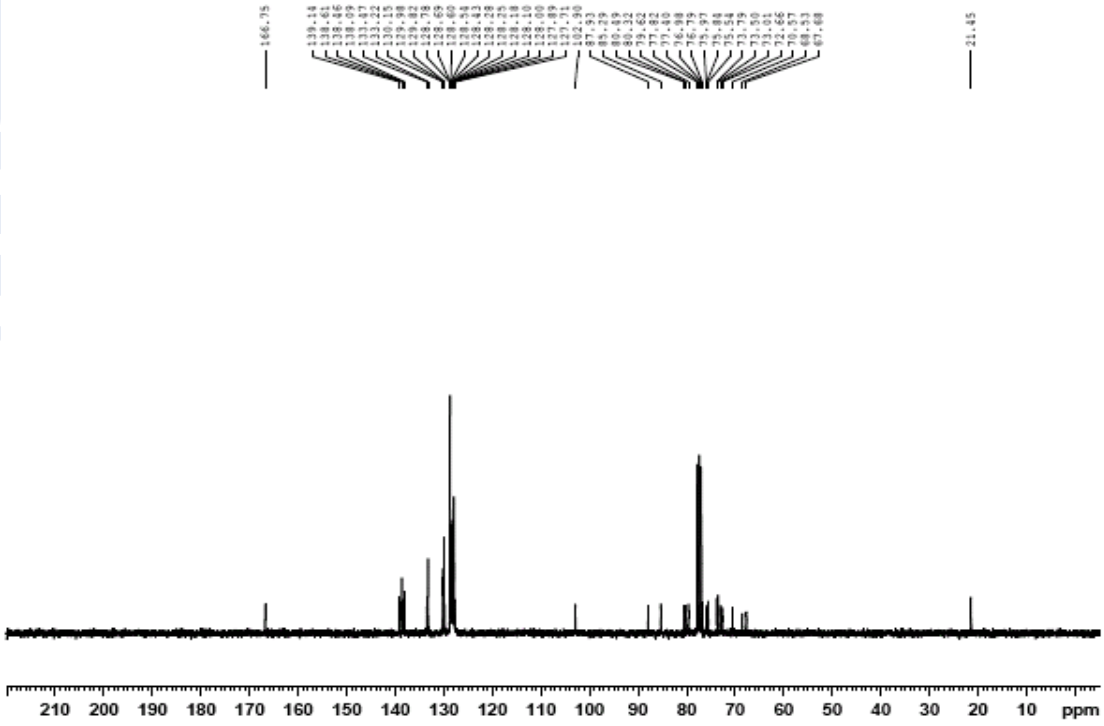

9
8
7
6
5
4
3
2
1
ppm
30.17
1.00
0.92
6.09
1.04
4.83
3.03
13.83
0.97
4.02
4.10

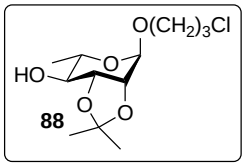

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

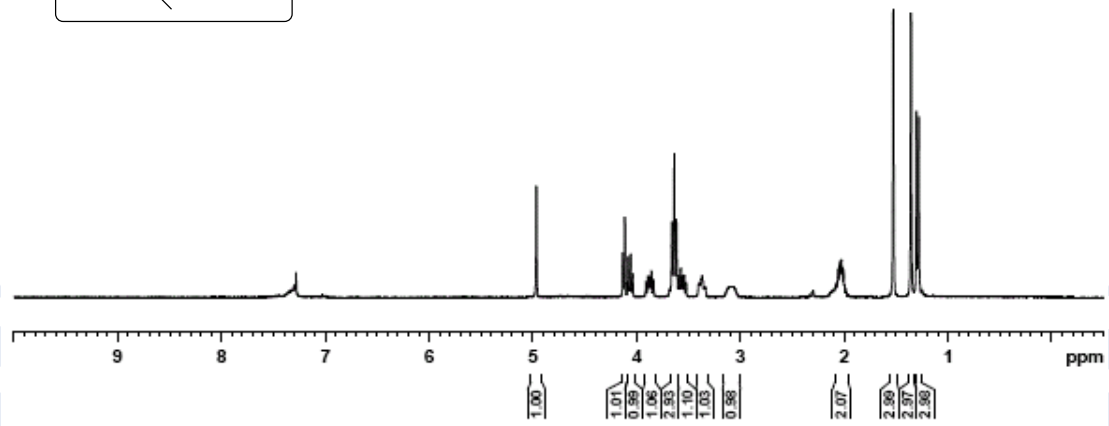

BzO
OBn
O
HO
OBn
O
BnO
OBn
O
OBn
O(CH2)6Cl

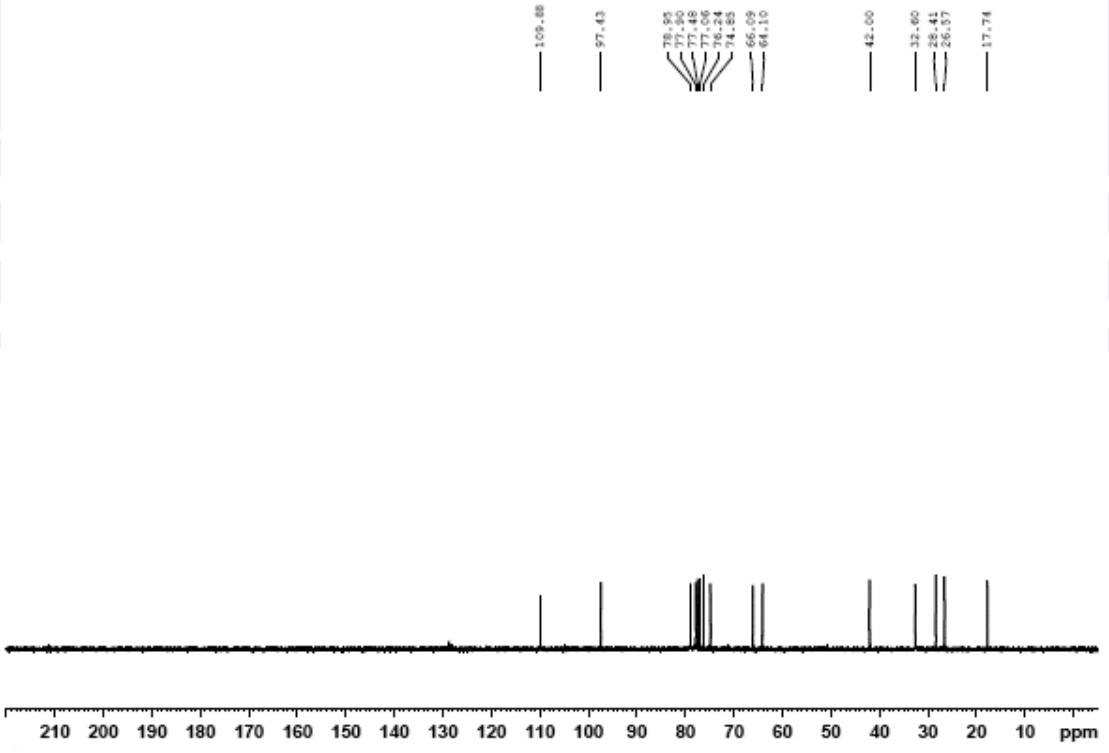
87

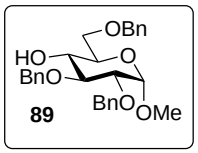

9
8
7
6
5
4
3
2
1
ppm
2.05
3.21
19.36
10.22
1.00
1.00
6.35
3.17
2.16
1.04
1.08
1.08
2.06
2.11
6.23
0.96
3.06

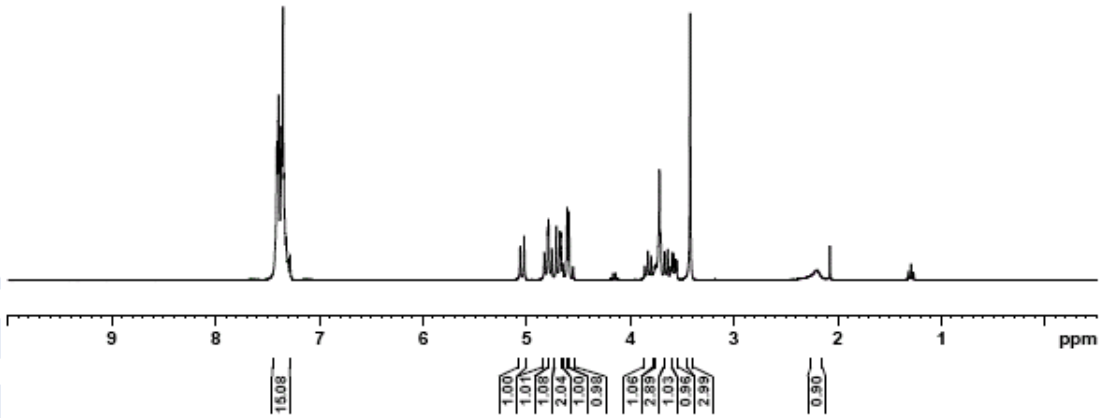

166.75
139.14
138.61
138.46
138.09
137.52
130.15
129.98
129.82
129.78
129.69
129.60
128.54
128.43
128.28
128.26
128.18
128.10
128.00
127.89
127.71
102.90
97.93
85.39
80.39
80.32
79.62
77.40
76.99
76.79
75.97
75.84
75.54
73.79
73.30
72.66
70.57
68.53
67.68
21.45
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

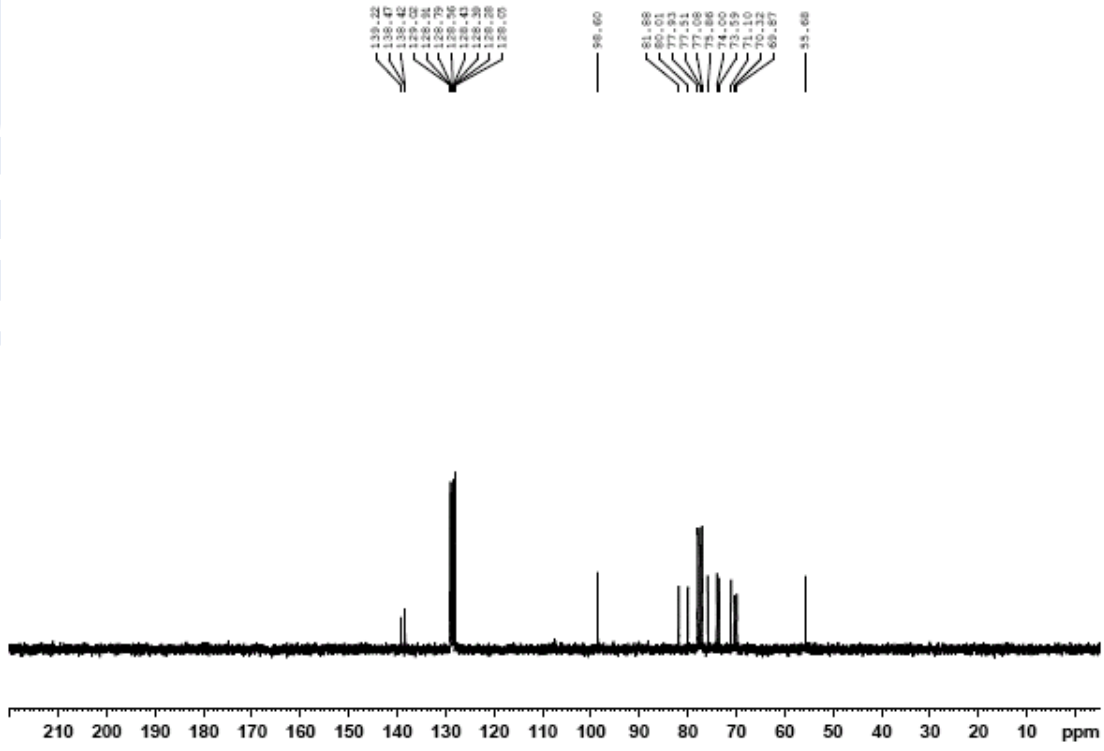

O(CH2)3Cl
HO
O
O
O
88

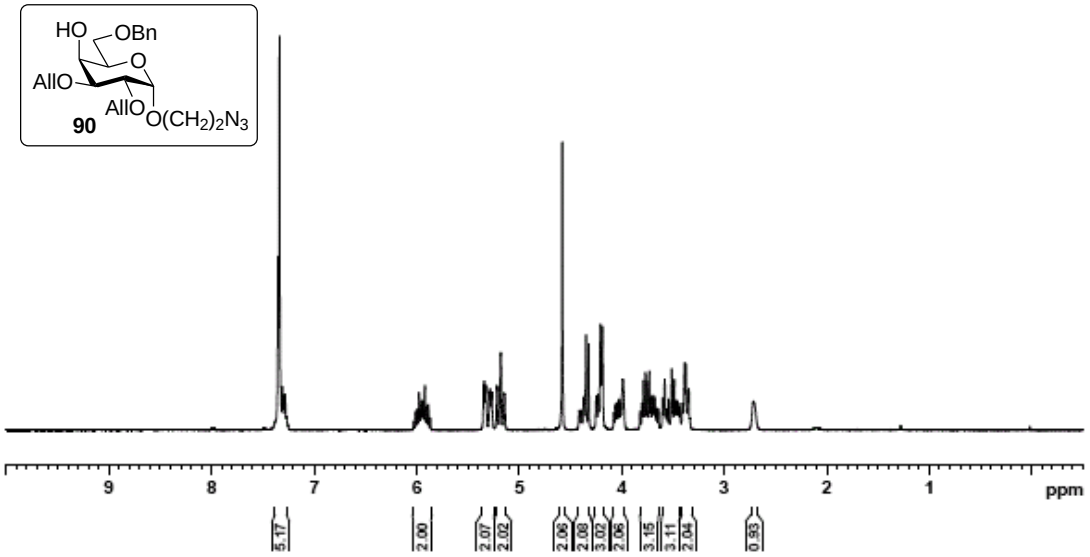

9
8
7
6
5
4
3
2
1
ppm


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


OBn
HO
O
BnO
BnO
OMe
89


9
8
7
6
5
4
3
2
1
ppm
15.08
1.00
1.01
1.08
2.04
1.00
0.98
1.06
2.89
1.03
0.96
2.99
0.90


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


HO
OBn
O
AllO
AllO
O(CH2)2N3
90
9
8
7
6
5
4
3
2
1
ppm
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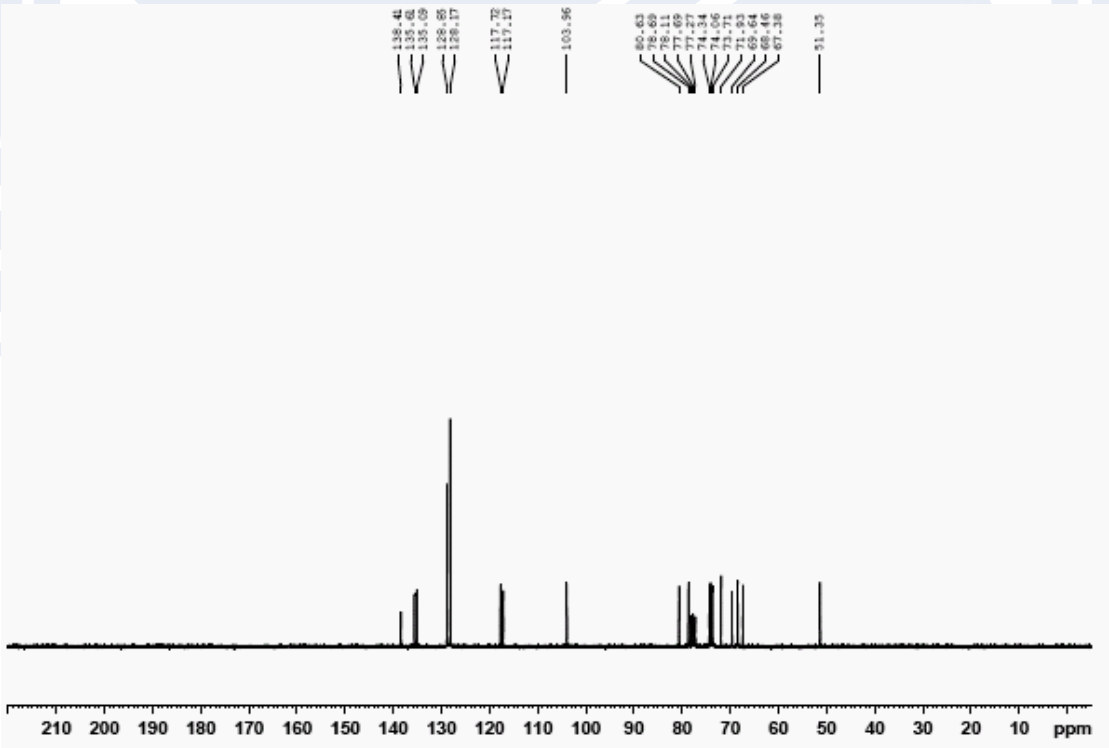
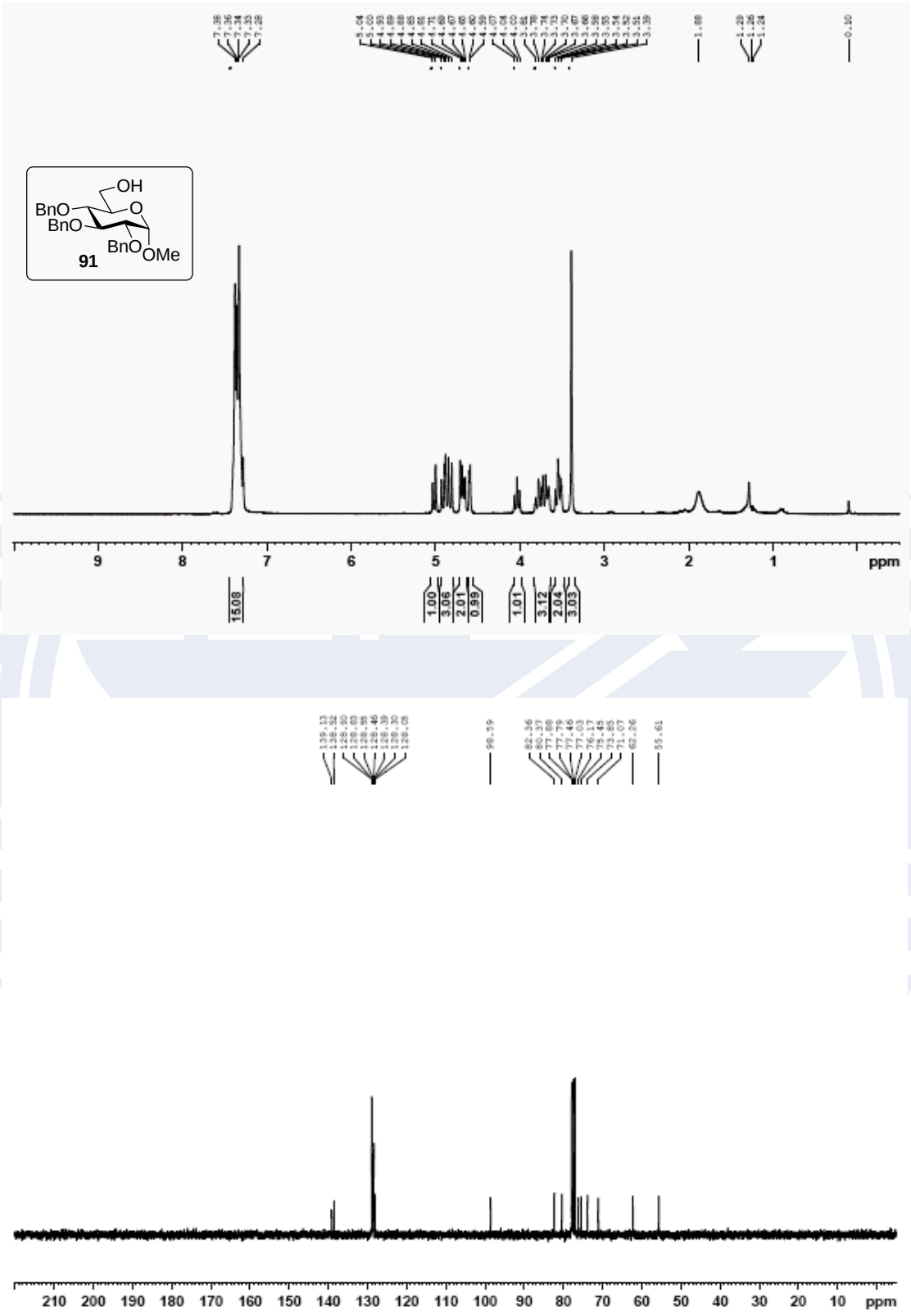
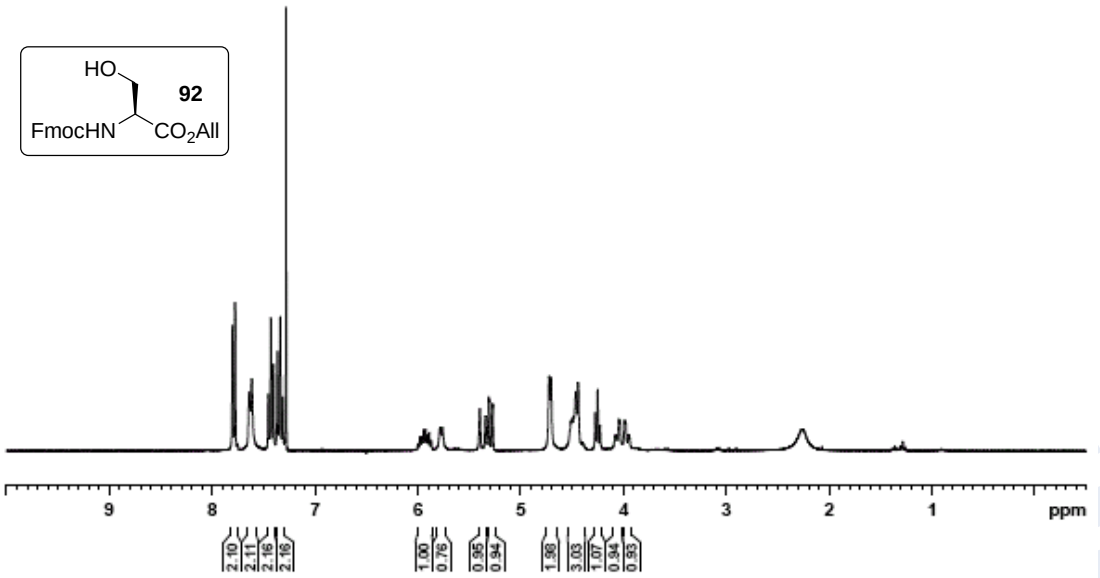
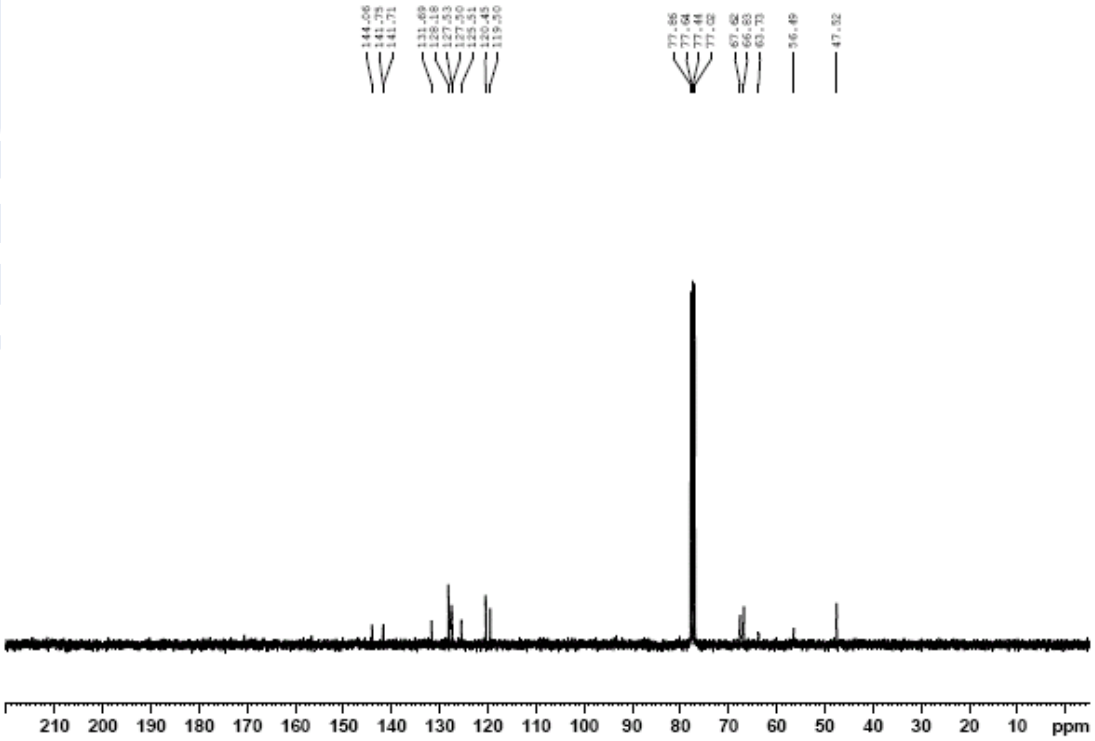
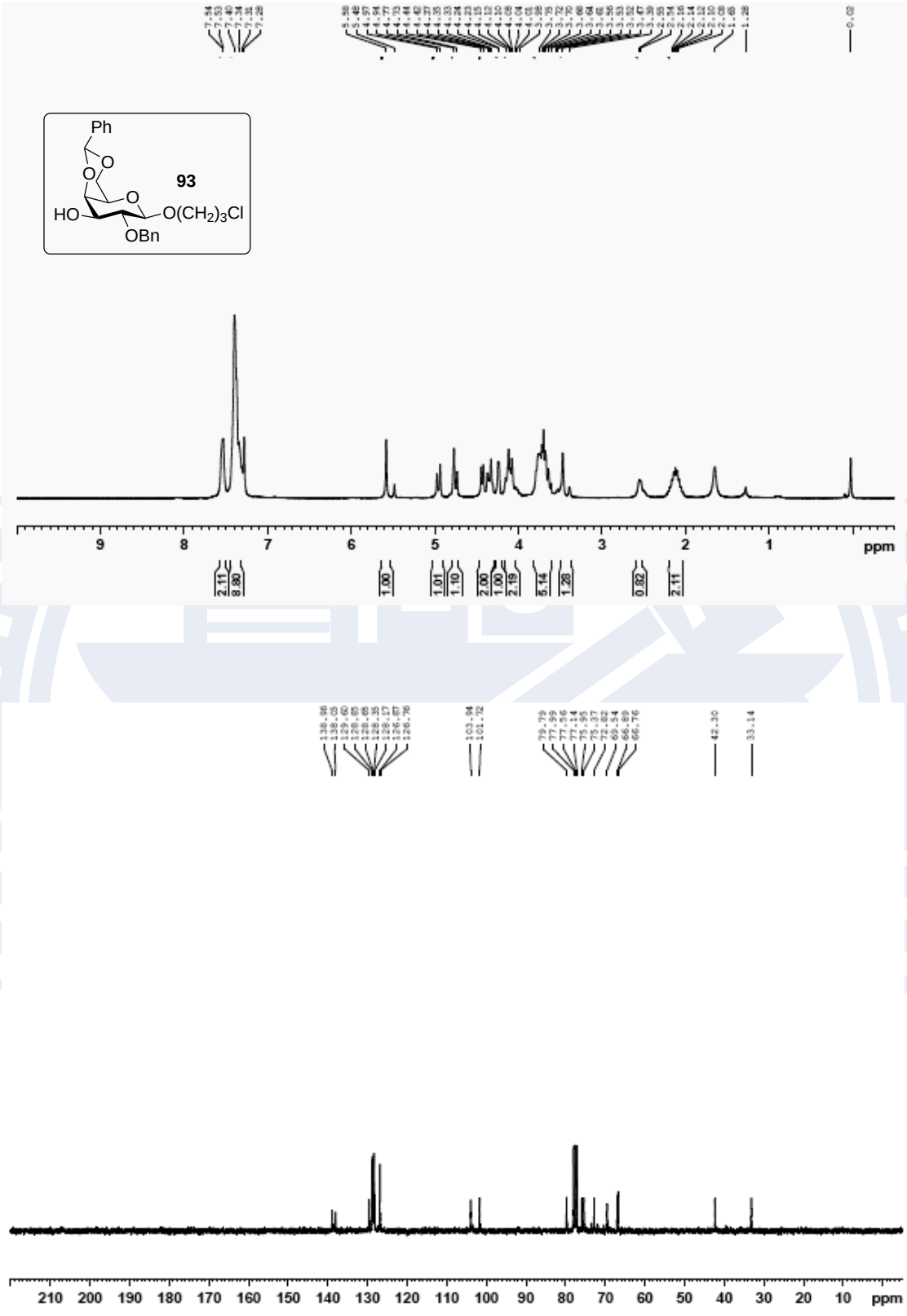
2.00
2.07
2.02
2.08
2.08
3.02
2.06
3.15
3.11
2.04
0.83

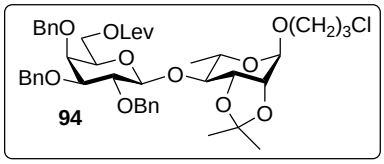

138.44
135.68
135.09
128.85
128.17
117.72
117.17
103.96
80.63
78.69
78.11
77.69
77.27
74.34
74.06
73.71
73.03
69.64
68.46
67.38
51.35
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


OH
BnO
O
BnO
BnO
OMe
91
9
8
7
6
5
4
3
2
1
ppm
15.08
1.00
3.06
2.01
0.99
1.01
3.12
2.04
3.03
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

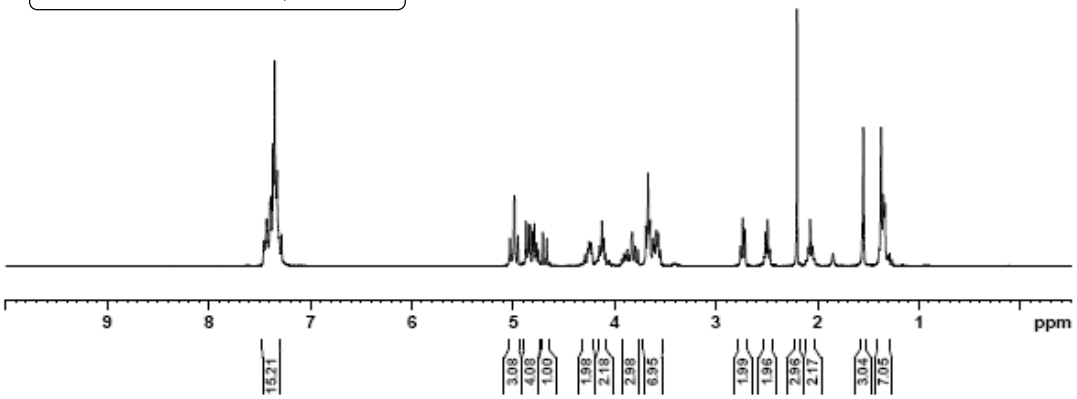

HO
92
FmocHN
CO2All
9
8
7
6
5
4
3
2
1
ppm


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

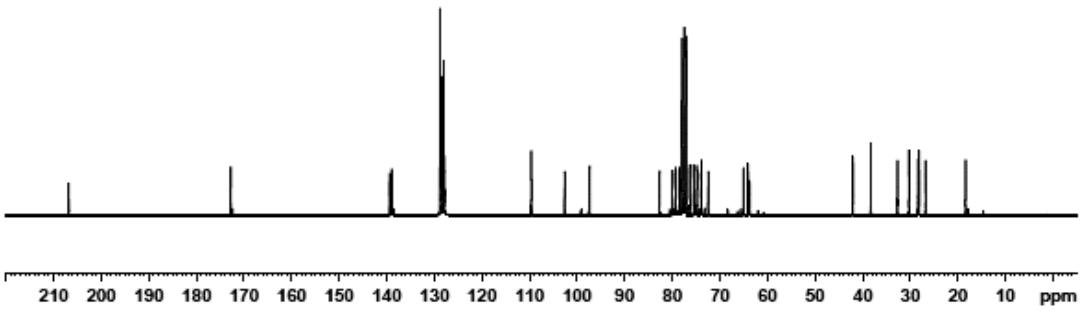

Ph
O
O
O
93
HO
O(CH2)3Cl
OBn
9
8
7
6
5
4
3
2
1
ppm
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

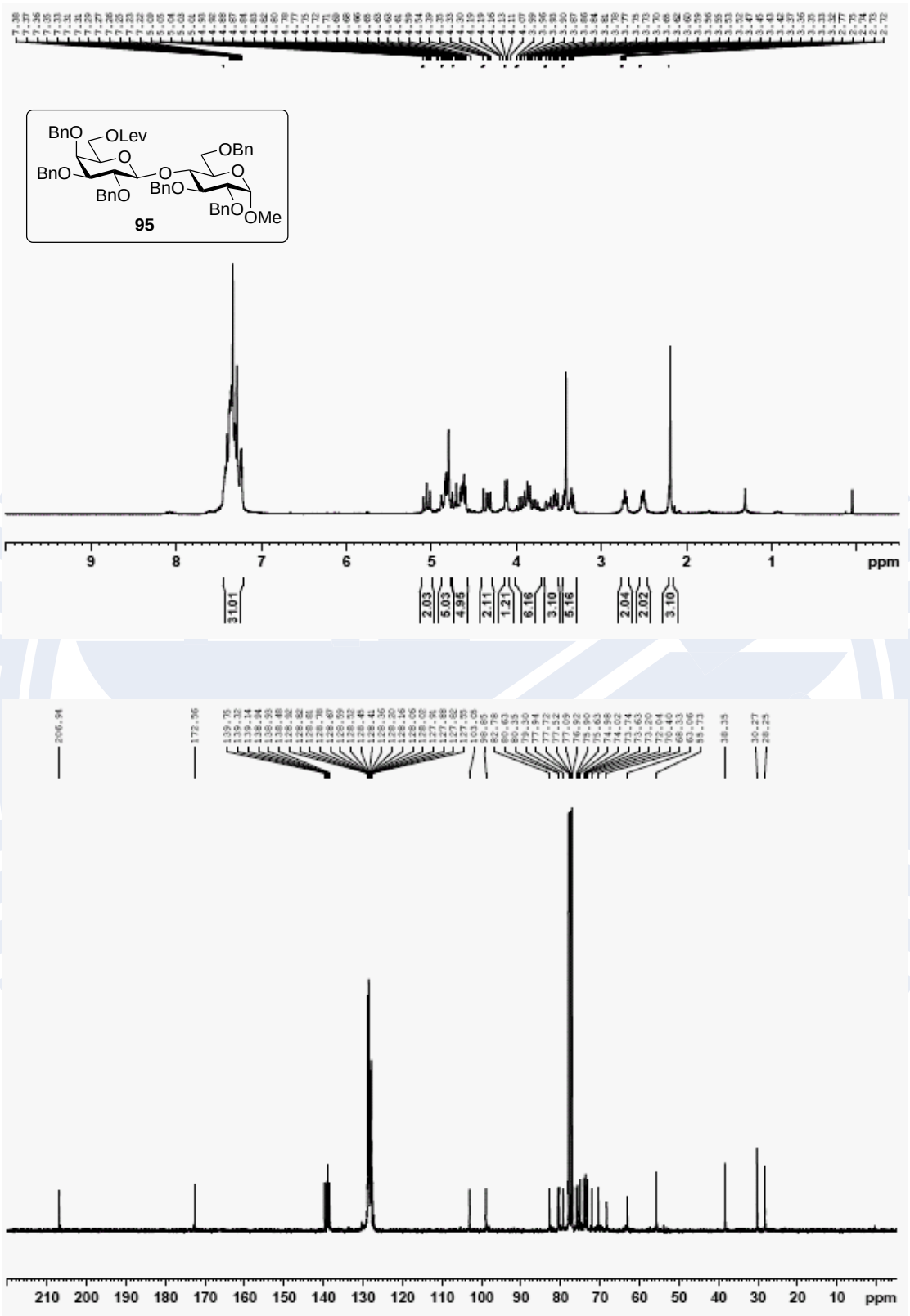

BnO
OLev
O
BnO
O
OBn
O(CH2)3Cl
O
O
O
O

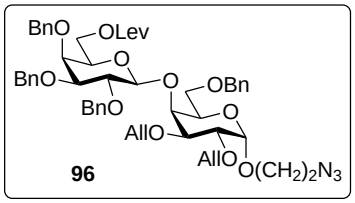
94

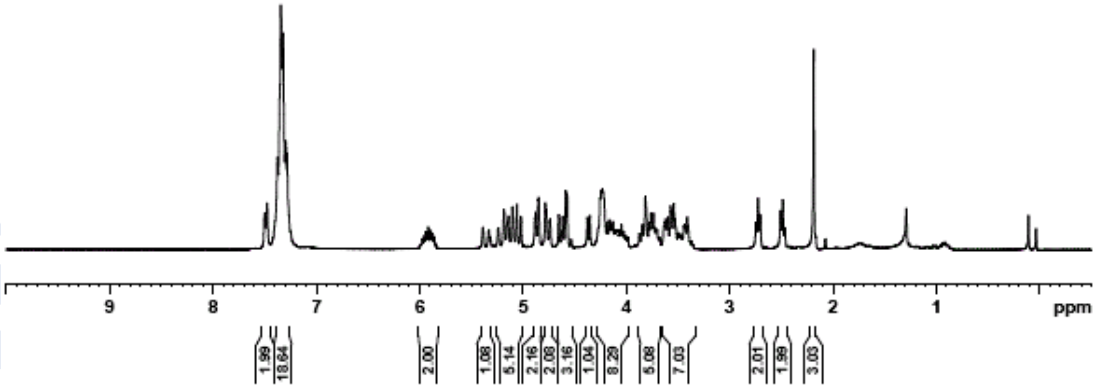

9
8
7
6
5
4
3
2
1
ppm
15.21
3.08
4.03
1.00
1.98
2.18
2.98
6.95
1.99
1.96
2.96
2.17
3.04
7.05

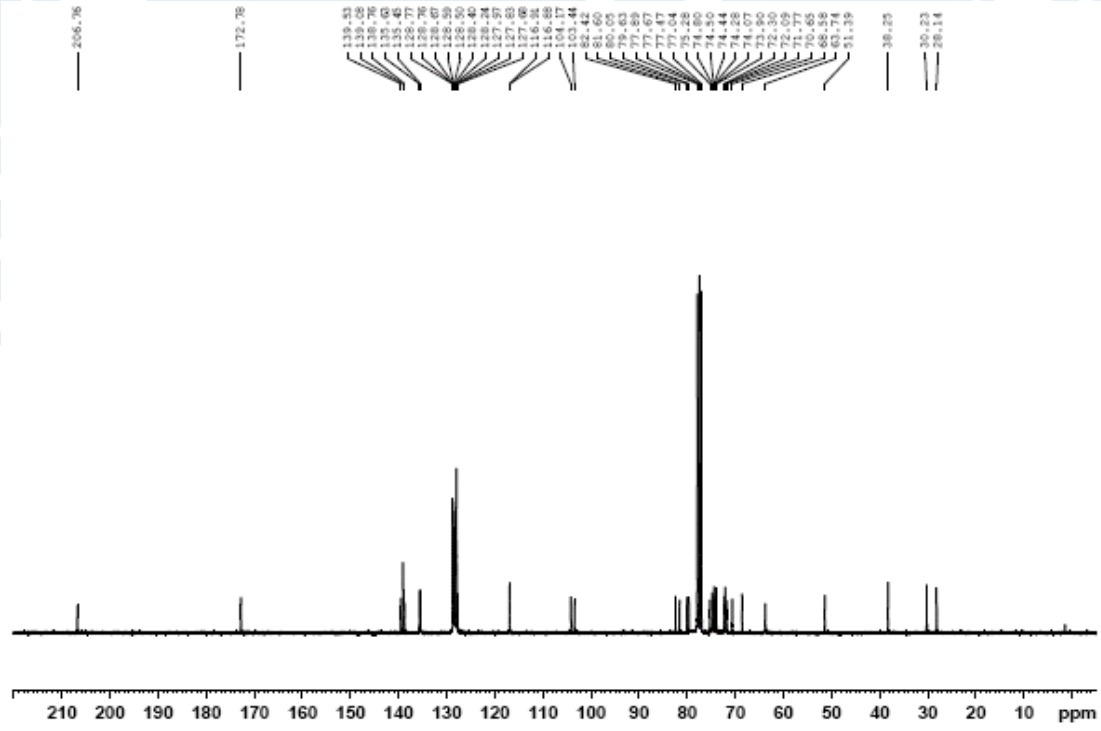

206.86
172.81
139.37
138.88
138.52
128.84
128.72
128.67
128.51
128.11
128.04
127.88
127.80
109.63
102.62
97.41
82.71
79.92
79.32
78.55
77.95
77.53
77.10
76.33
75.49
74.84
73.71
73.88
72.44
65.02
64.13
63.76
42.07
38.28
32.68
30.27
28.34
28.14
26.78
18.35

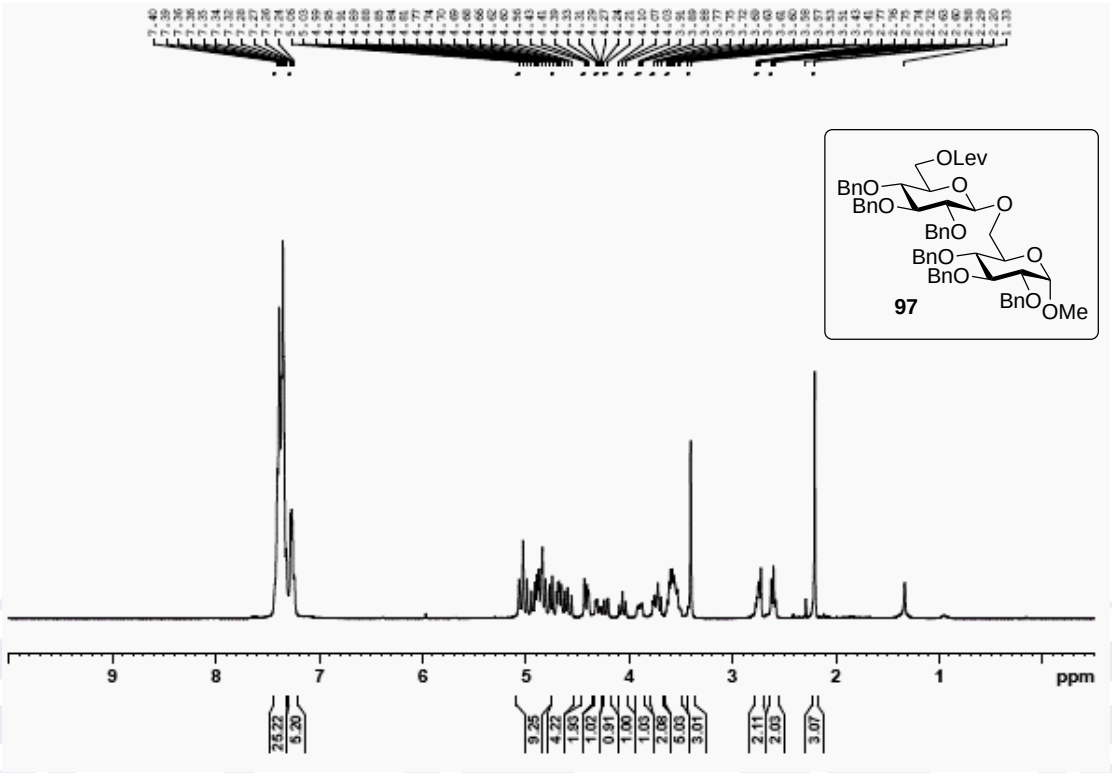

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

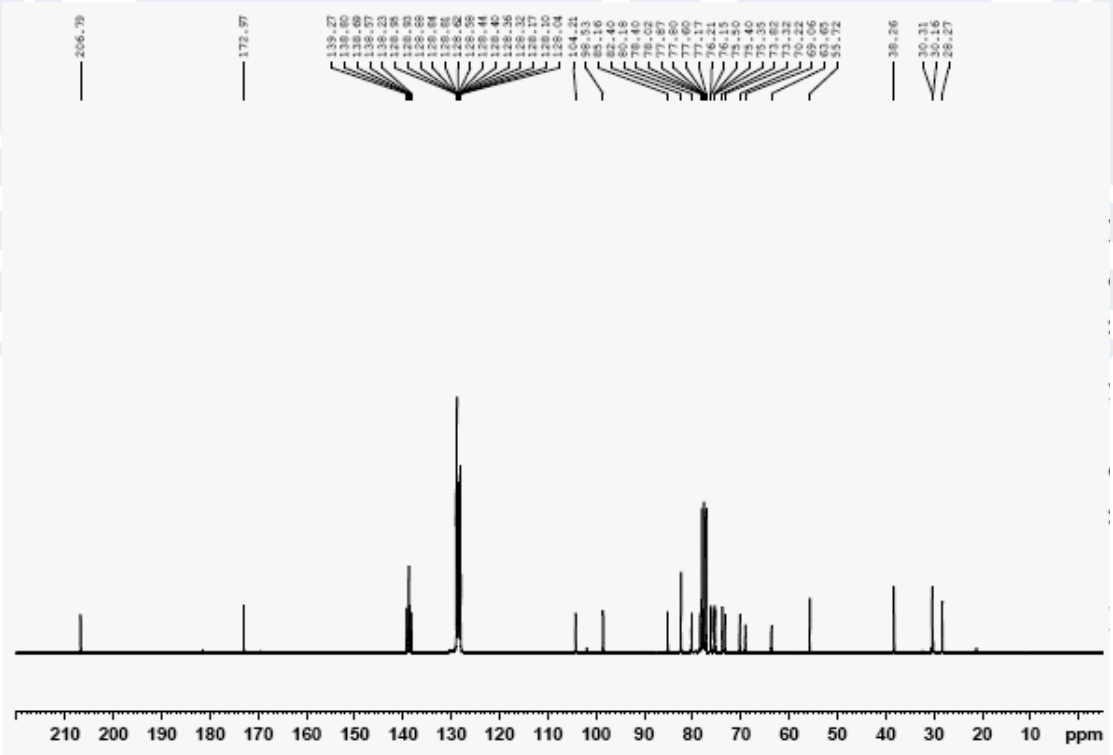

BnO
OLev
O
BnO
BnO
O
OBn
O
BnO
BnO
OMe
95
ppm
3.01
2.03
5.03
4.95
2.11
1.21
6.16
3.10
5.16
2.04
2.02
3.10
206.94
172.56
139.75
139.32
139.14
138.94
138.93
138.48
128.62
128.56
128.47
128.39
128.32
128.45
128.41
128.36
128.20
128.16
128.08
128.00
127.98
127.88
127.82
127.55
103.05
96.85
82.78
80.03
80.00
79.84
77.72
77.32
77.09
76.82
75.90
75.63
74.98
74.74
73.63
73.20
72.04
70.40
68.33
63.06
53.73
38.35
30.27
28.23
ppm

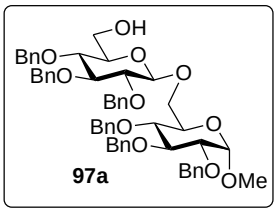

BnO
OLev
O
BnO
O
OBn
BnO
O
AllO
AllO
O(CH2)2N3
96


9
8
7
6
5
4
3
2
1
ppm
1.99
18.64
2.00
1.08
5.14
2.16
2.06
3.16
1.04
8.29
5.08
7.03
2.01
1.98
3.03


206.76
172.78
139.53
139.08
138.76
138.60
135.45
128.77
128.76
128.67
128.59
128.49
128.24
127.97
127.83
127.68
116.88
104.17
103.44
82.42
81.60
80.05
79.63
77.89
77.67
77.47
77.04
76.28
75.80
74.90
74.44
74.28
74.07
73.90
72.90
72.09
71.77
71.46
68.58
63.74
51.39
38.25
30.23
28.14
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

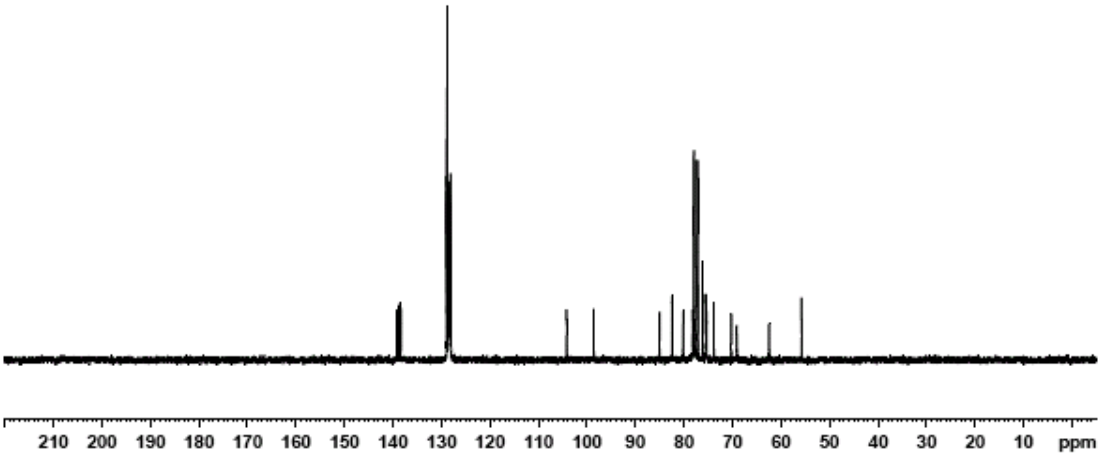

OLev
BnO
BnO
O
O
BnO
BnO
O
BnO
BnO
OMe
97
9
8
7
6
5
4
3
2
1
ppm
25.72
5.20
9.25
4.22
1.93
1.02
0.91
1.00
1.03
2.08
5.03
3.01
2.11
2.03
3.07

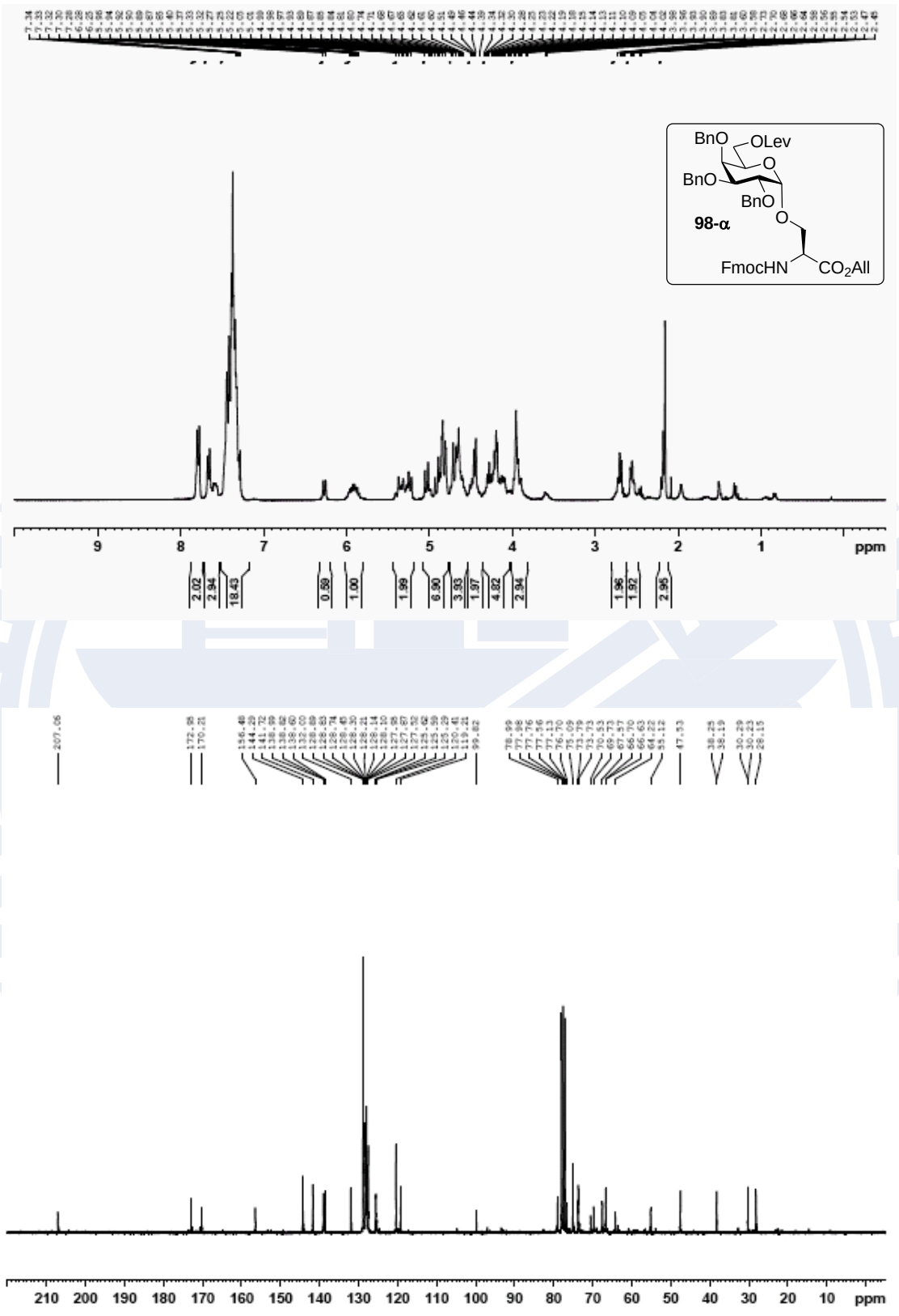

206.79
172.97
139.27
138.80
138.57
138.23
128.98
128.88
128.84
128.66
128.58
128.44
128.40
128.36
128.32
128.17
128.10
128.04
104.21
98.53
85.16
82.40
80.18
78.40
78.02
77.87
77.60
77.17
76.21
76.15
75.50
75.40
75.35
73.82
73.32
70.22
69.56
69.06
55.72
38.26
30.31
30.16
28.27
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

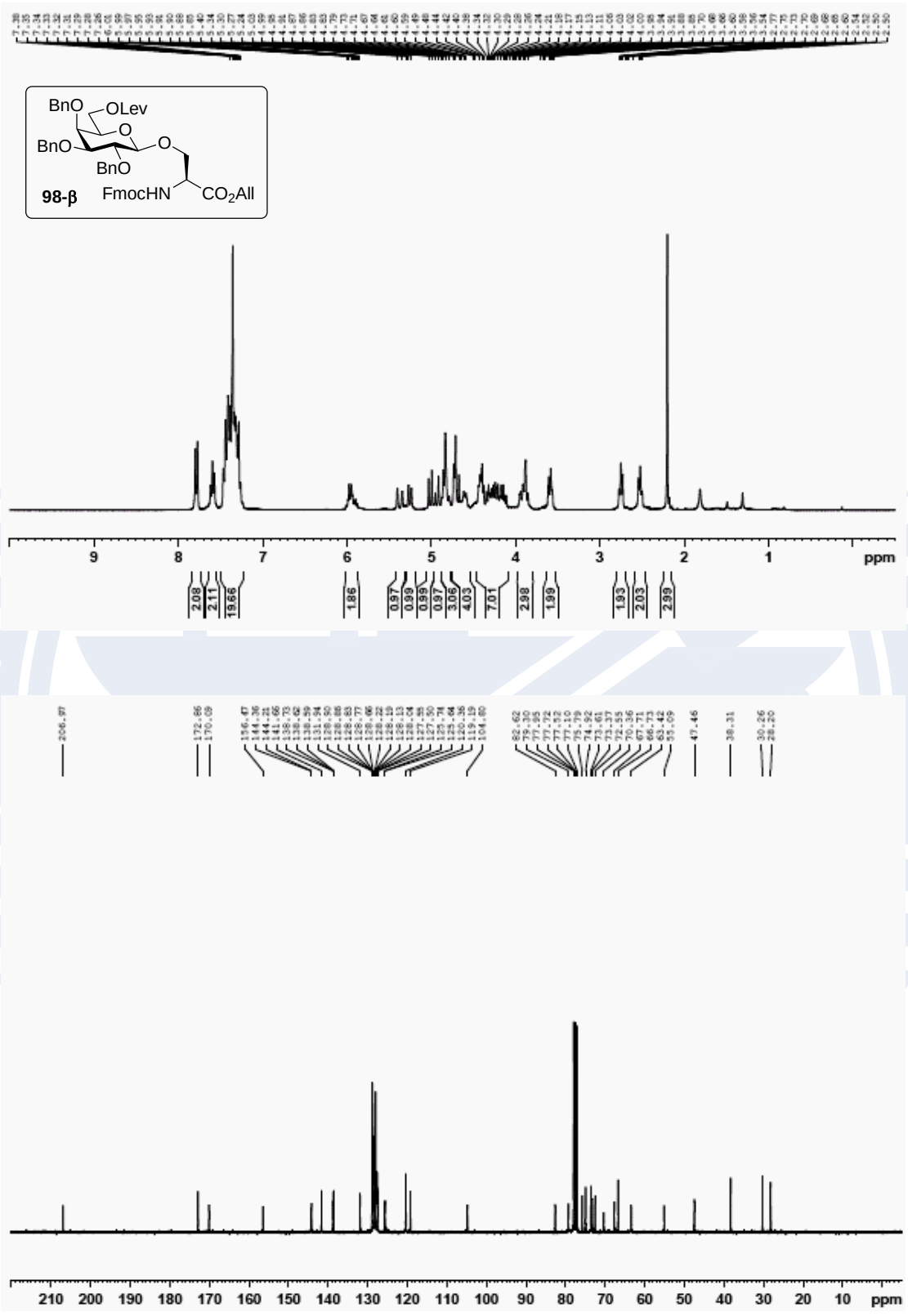

OH
BnO
BnO
O
O
BnO
BnO
BnO
O
BnO
OMe

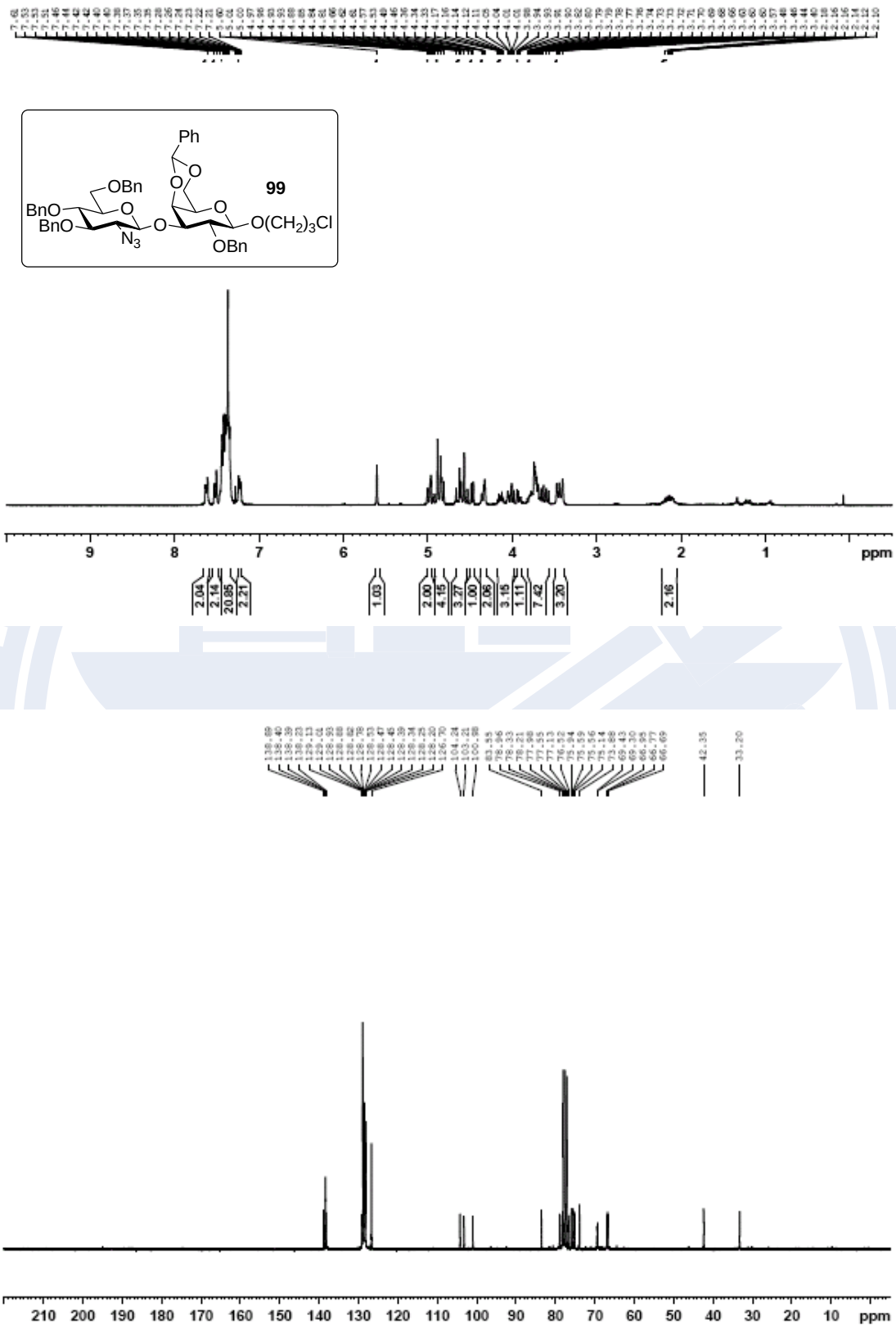
97a

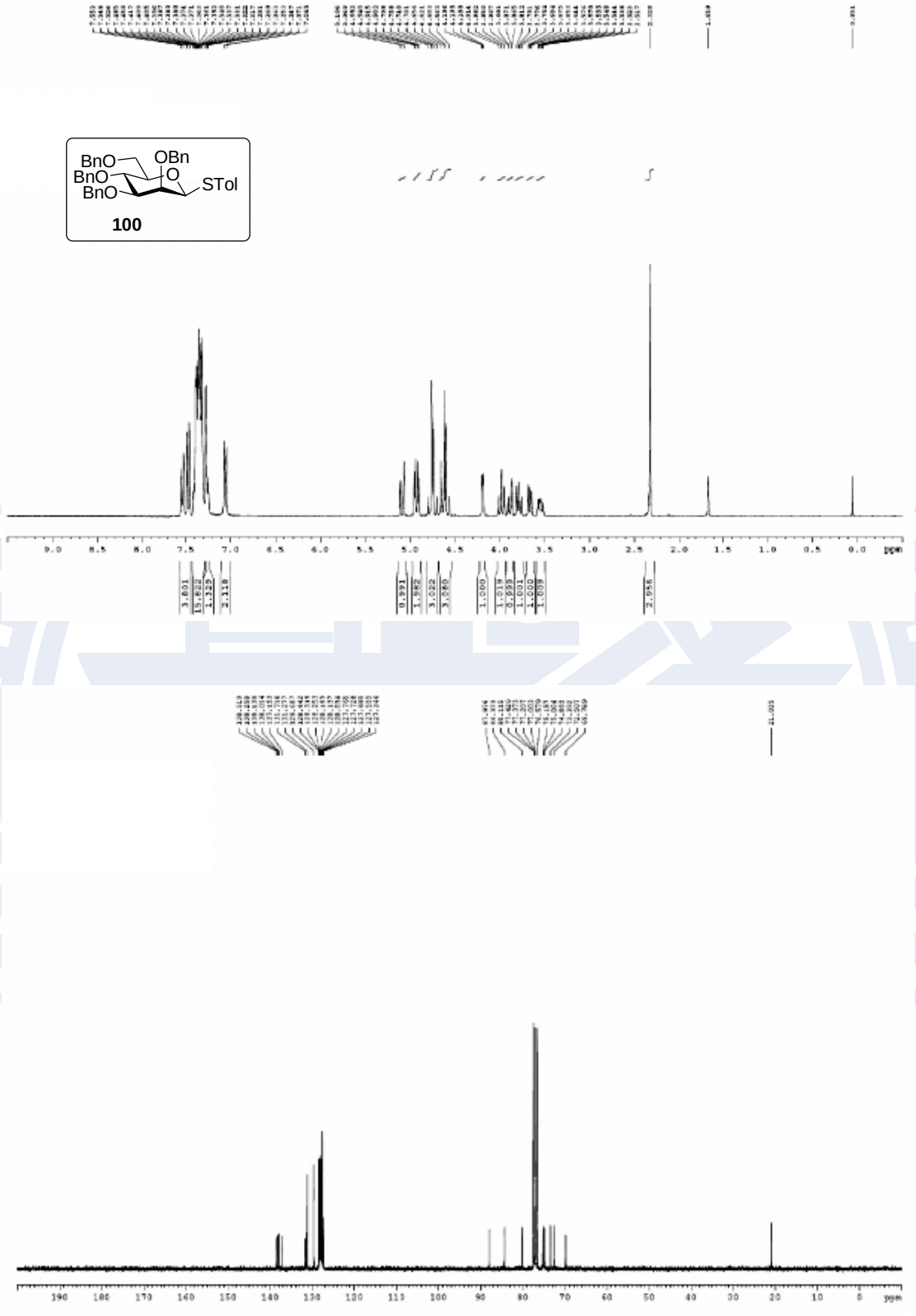
9
8
7
6
5
4
3
2
1
ppm
25.87
5.09
3.95
5.12
3.98
1.01
1.00
1.00
1.11
2.18
7.96
4.14
0.56

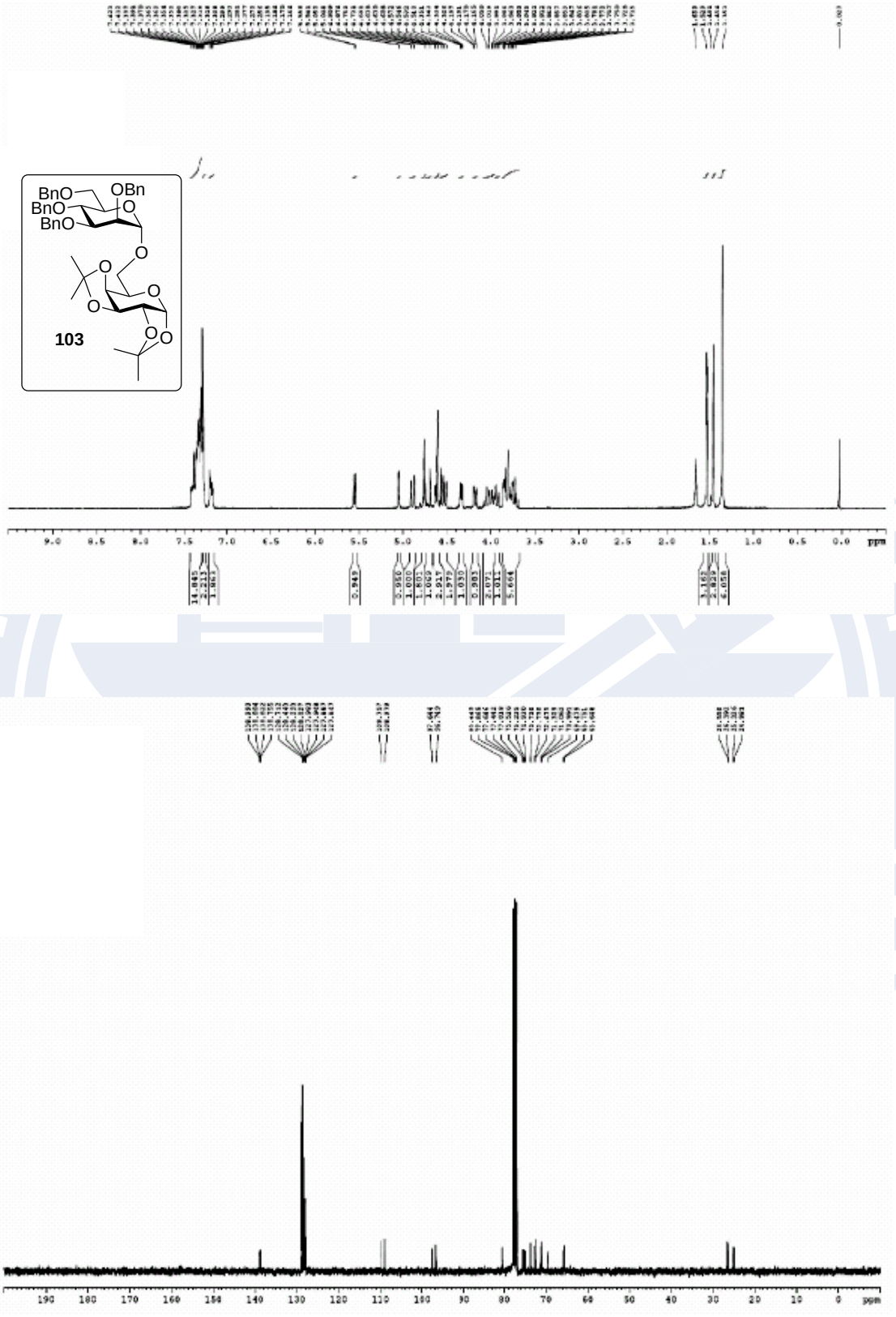

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

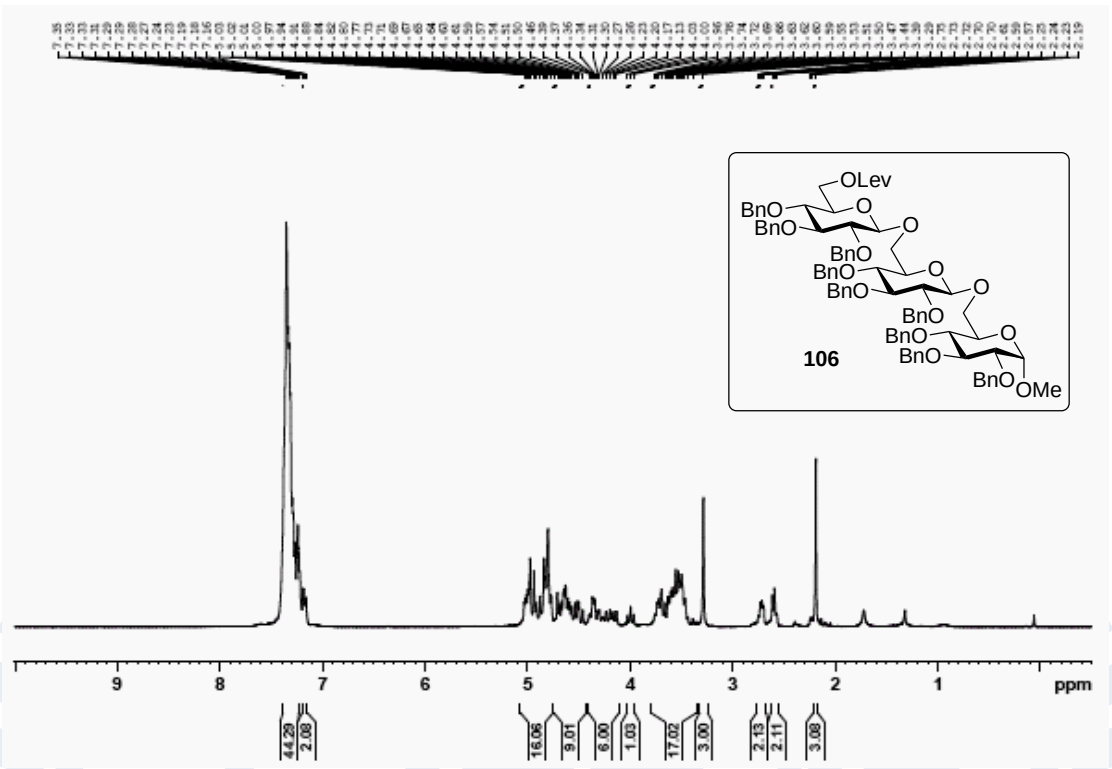

BnO
OLev
O
BnO
BnO
O
98-α
FmocHN
CO2All
ppm
2.02
2.94
18.43
0.59
1.00
1.99
6.90
3.93
1.97
4.82
2.94
1.96
1.92
2.95
207.06
172.89
170.21
99.62
47.53
38.25
38.19
30.29
30.23
28.15
ppm

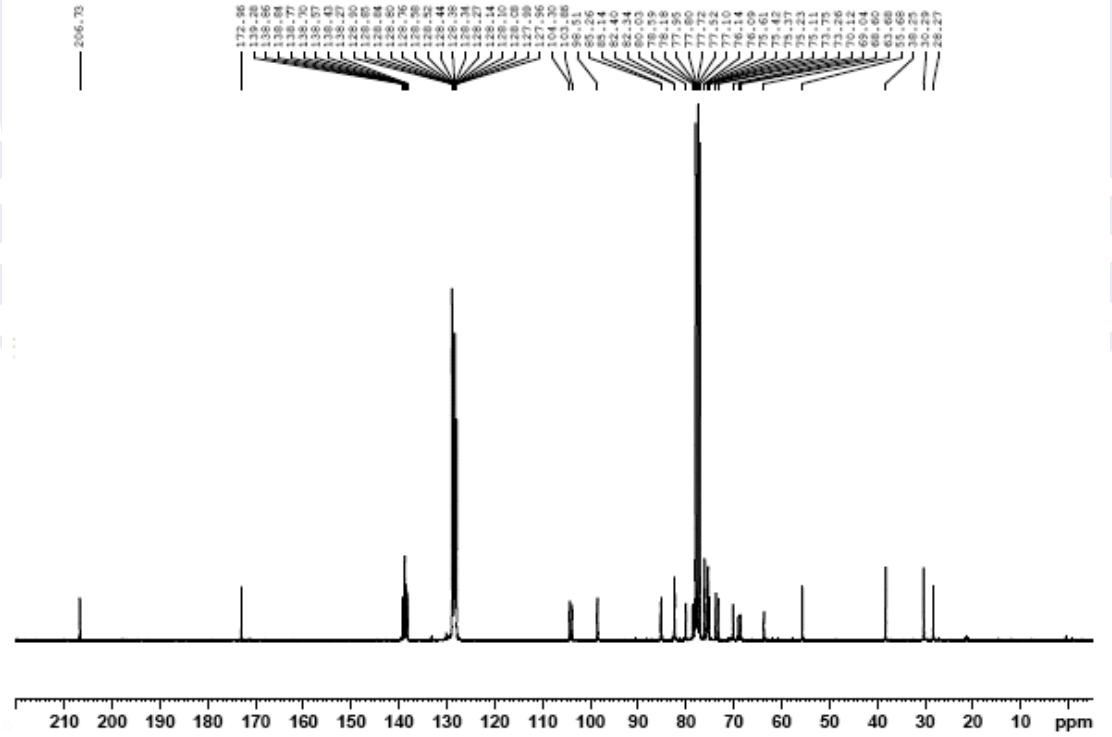

BnO
OLev
O
BnO
O
BnO
98-β
FmocHN
CO2All
ppm
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

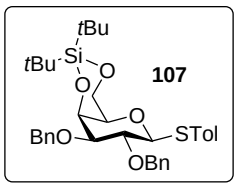

Ph
OBn
BnO
BnO
N3
99
O(CH2)3Cl
OBn
ppm
2.04
2.14
20.85
2.21
1.03
2.00
4.15
3.27
1.00
2.06
3.15
1.11
7.42
3.20
2.16
42.35
33.20
ppm


BnO
BnO
BnO
OBn
O
STol
100

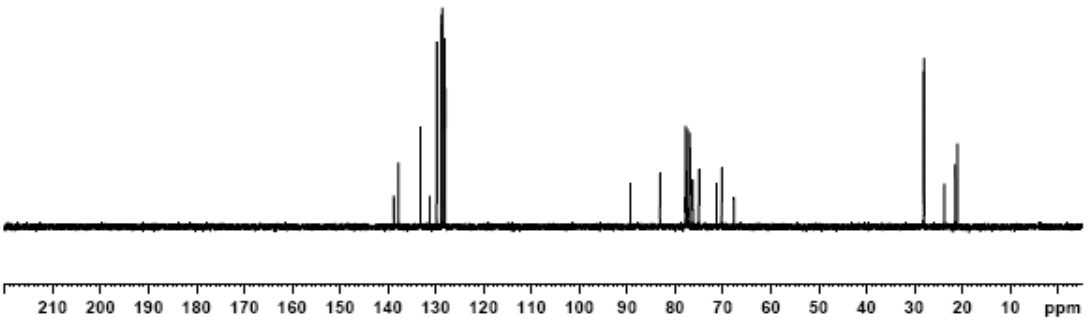

BnO
BnO
BnO
OBn
O
O
O
O
O
O
O
O
103
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

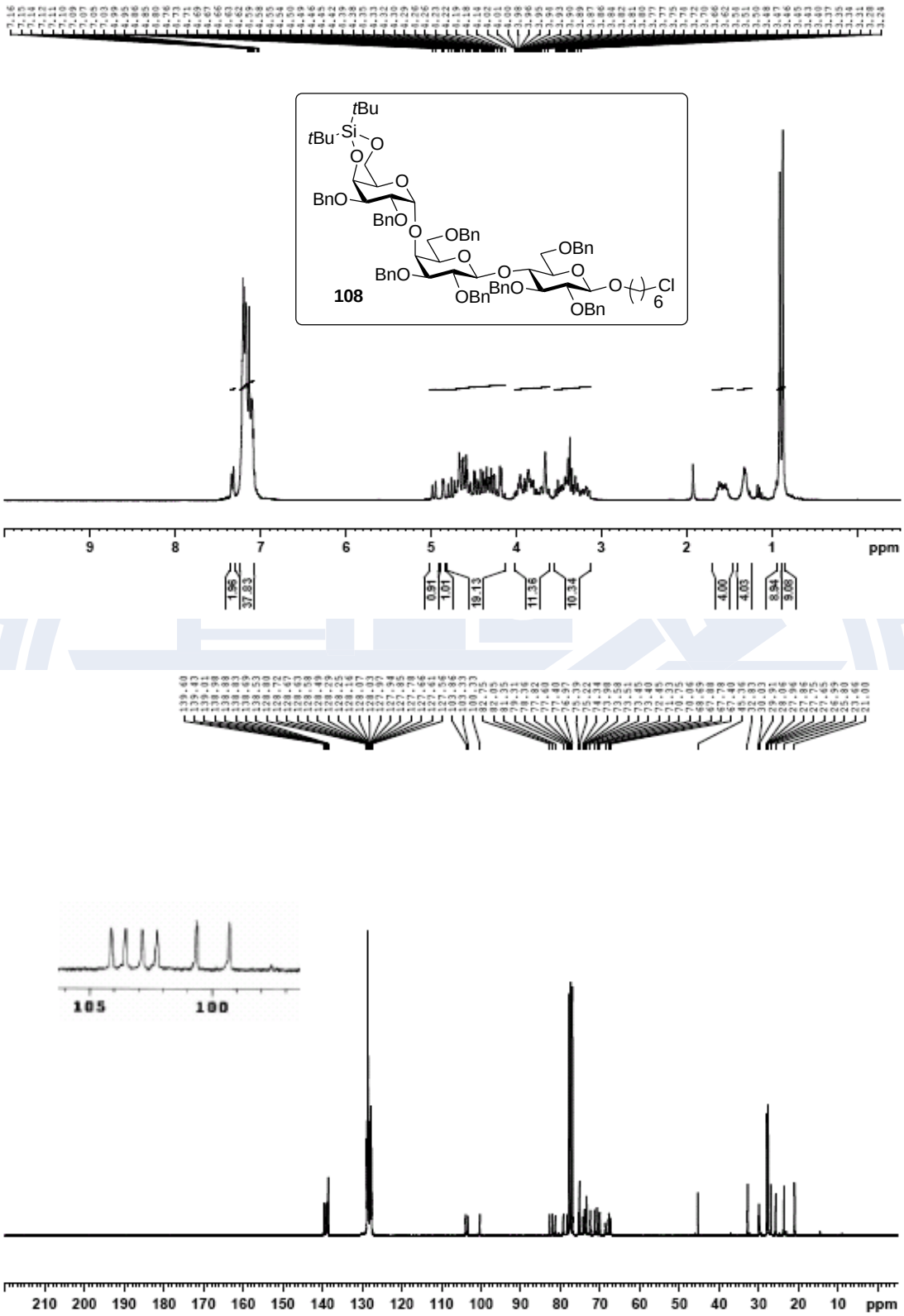

OLev
BnO
BnO
O
BnO
BnO
BnO
O
O
BnO
BnO
O
BnO
BnO
106
OMe
9
8
7
6
5
4
3
2
1
ppm
44.29
2.08
16.06
9.01
6.00
1.03
17.02
3.00
2.13
2.11
3.08

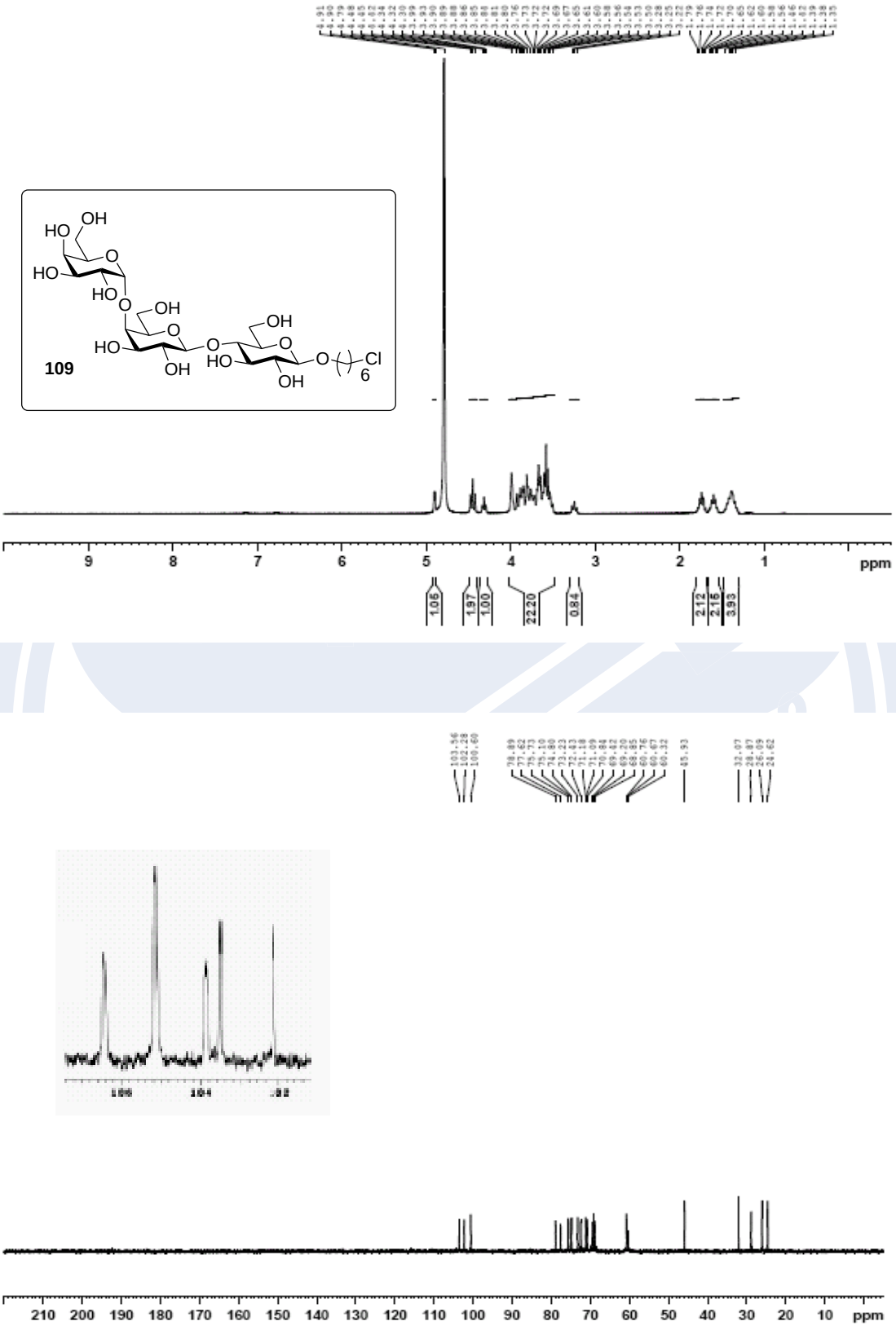

206.73
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

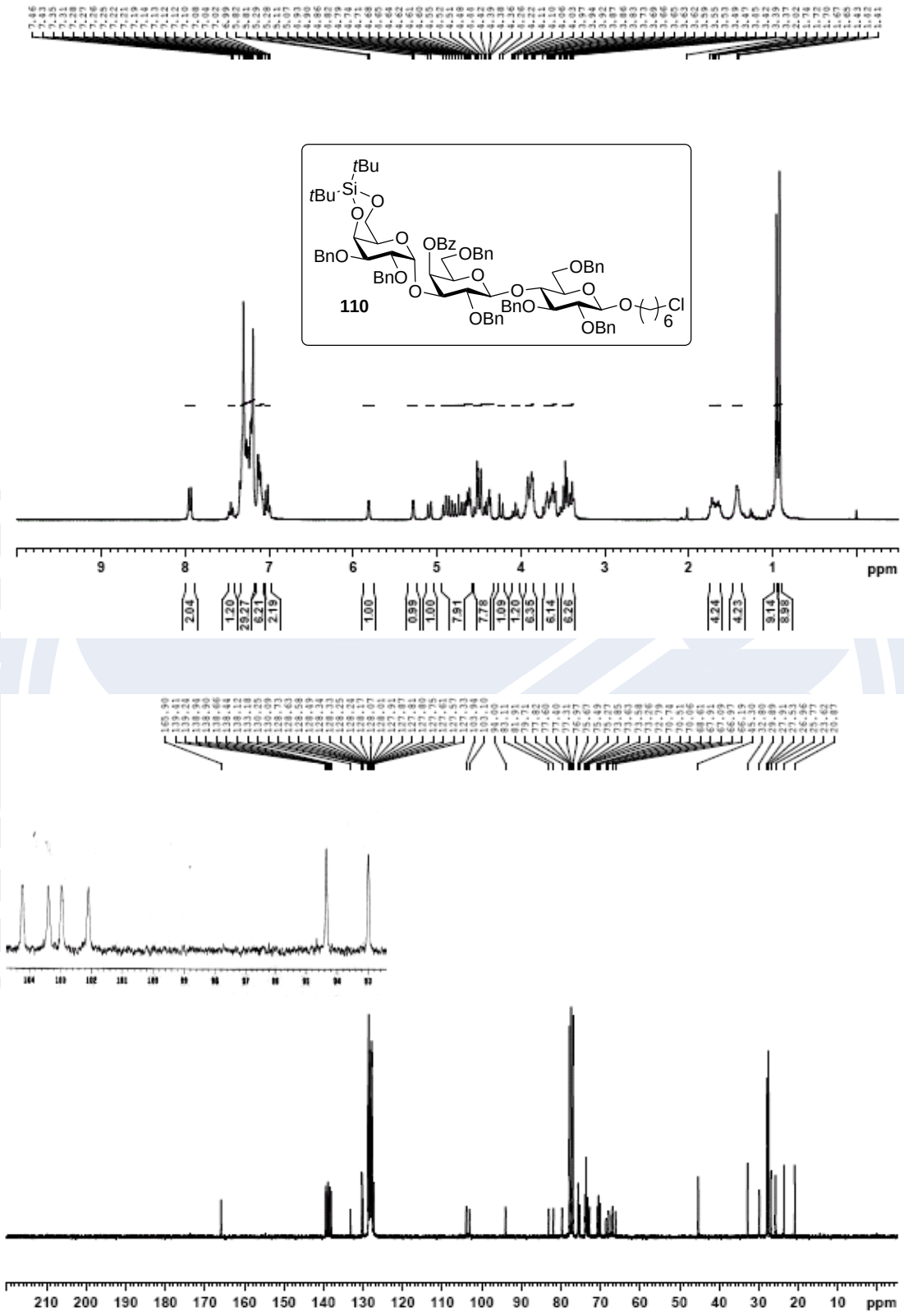

tBu
tBu
Si
O
O
107
O
BnO
STol
OBn

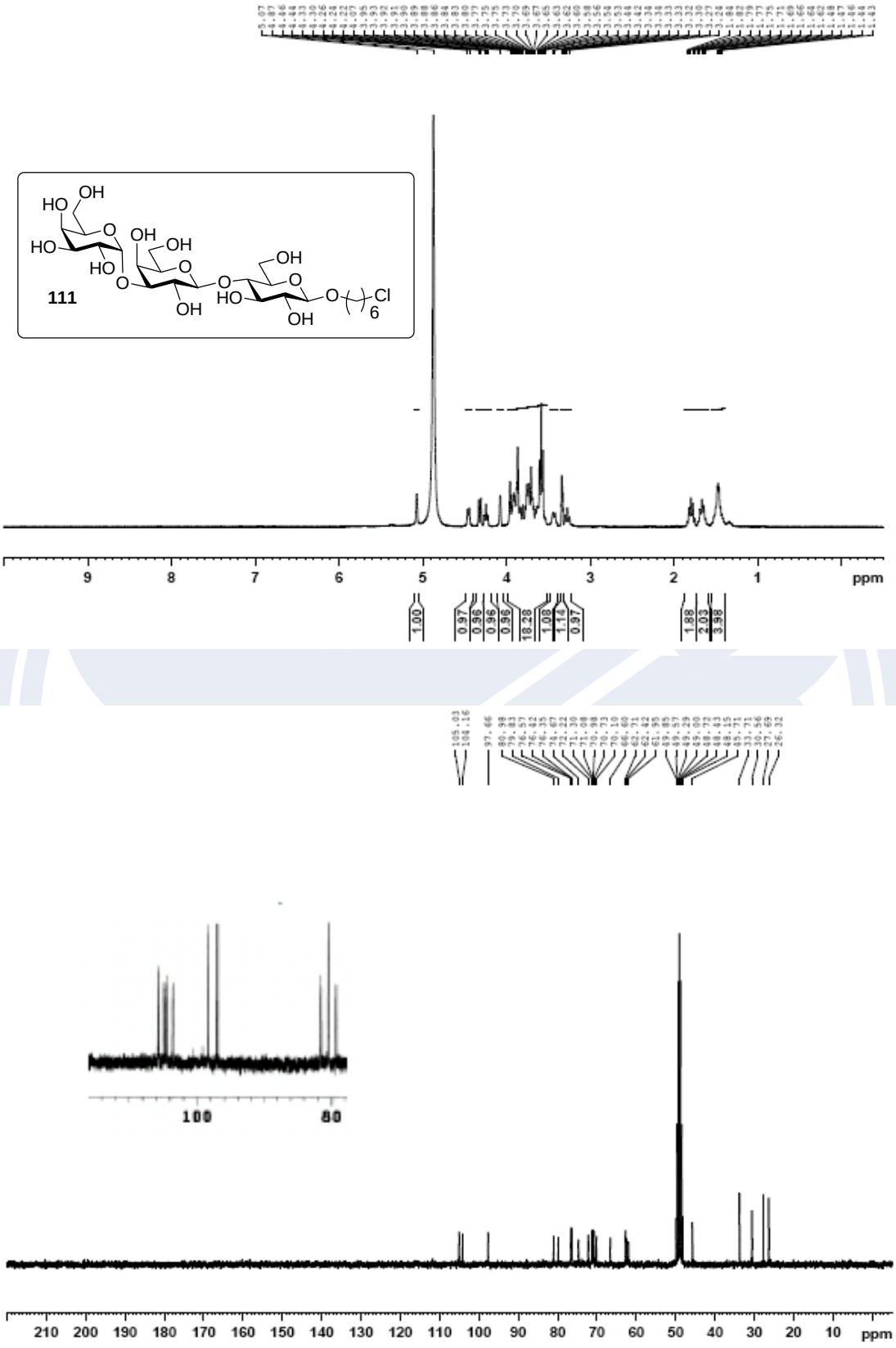
9
8
7
6
5
4
3
2
1
ppm
11.89
1.99
1.97
2.03
1.00
1.00
2.00
0.99
0.99
0.97
2.98
8.50
8.91

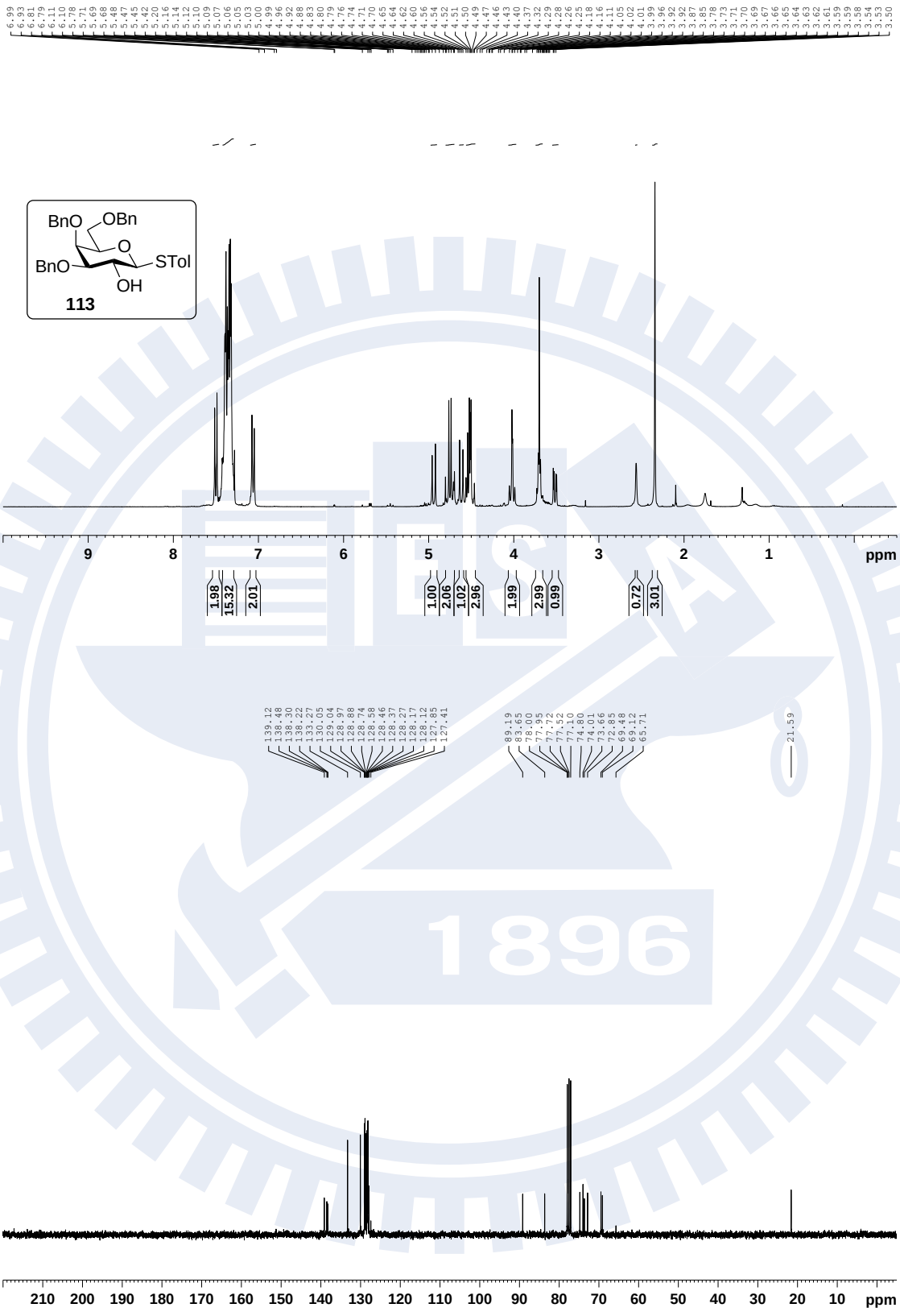

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


tBu
tBu
Si
O
O
O
BnO
BnO
O
OBn
O
BnO
OBn
O
O
OBn
BnO
O
O
Cl
6
OBn
108
9
8
7
6
5
4
3
2
1
ppm
1.96
37.83
0.91
1.01
19.15
11.36
10.34
4.00
4.05
8.94
9.06
105
100
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


109
ppm
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


tBu
tBu
Si
O
O
O
BnO
BnO
O
OBz
OBn
O
O
OBn
BnO
O
O
OBn
OBn
O
Cl
6
110
9
8
7
6
5
4
3
2
1
ppm
2.04
1.20
2.827
6.21
2.19
1.00
0.98
1.00
7.91
7.78
1.09
1.20
6.35
6.14
6.26
4.24
4.23
9.14
8.98
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


111
ppm
ppm


BnO
OBn
O
BnO
STol
OH
113
9
8
7
6
5
4
3
2
1
ppm
1.98
15.32
2.01
1.00
2.06
1.02
2.96
1.99
2.99
0.99
0.72
3.01
21.59
210
200
190
180
170
160
150
140
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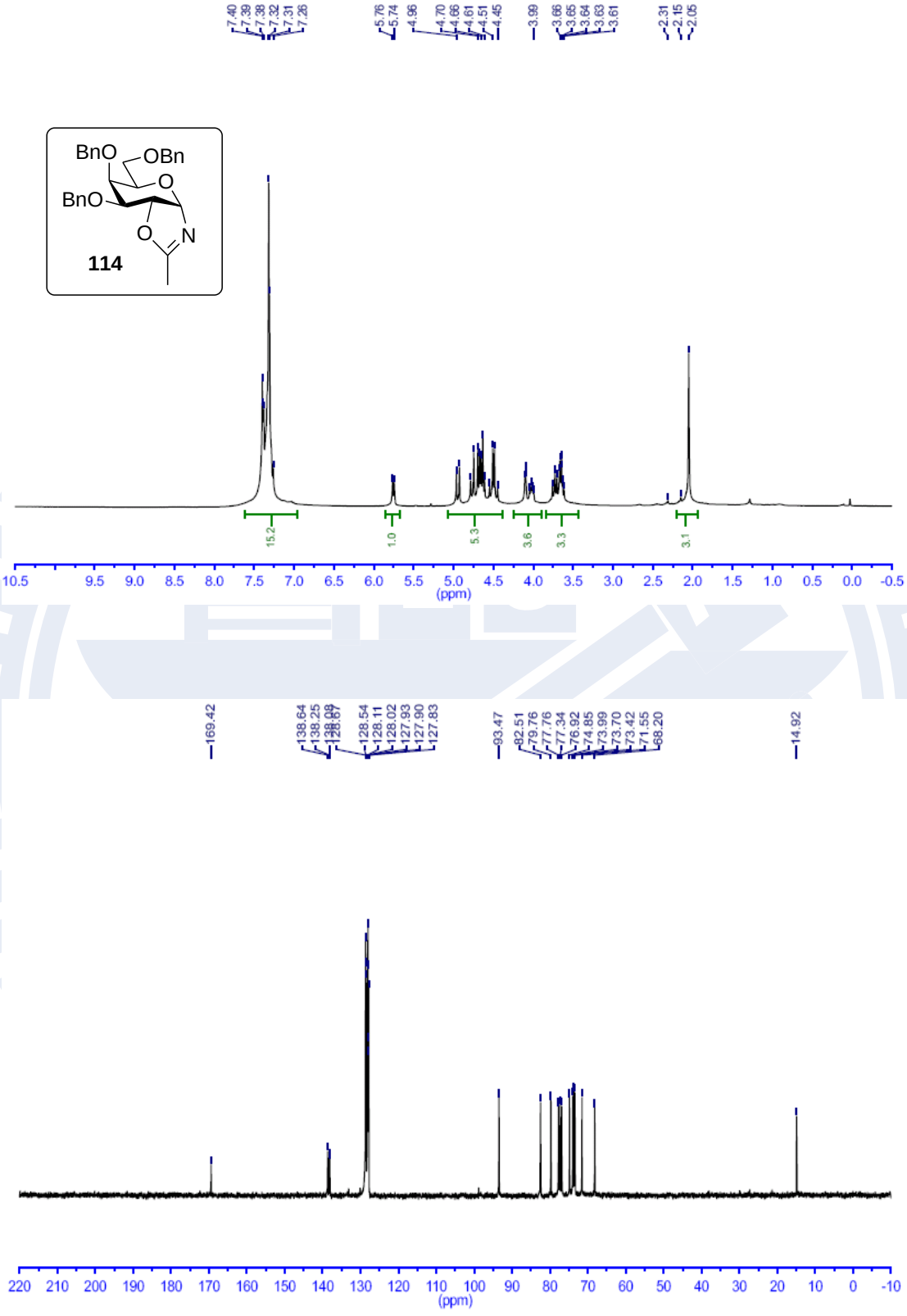
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220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
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第三章

正交醣基化反應與反應活性基礎-化學選擇性醣基化策略於低濃度醣基化反應條件之測試

3.1 寡糖合成策略之介紹

在獲得低濃度 1,2-反式 β 醣基化反應的初步成功後，下一步的研究方向便是嘗試將此方法作進一步的衍伸與應用。

回顧文獻，科學家們將各個醣基建構單元 (glycosyl building block) 組合成寡糖分子時，可從兩個合成方向著手，一是由還原端 (reducing end) 開始合成；另一則是由非還原端 (non-reduceing end) 開始合成。

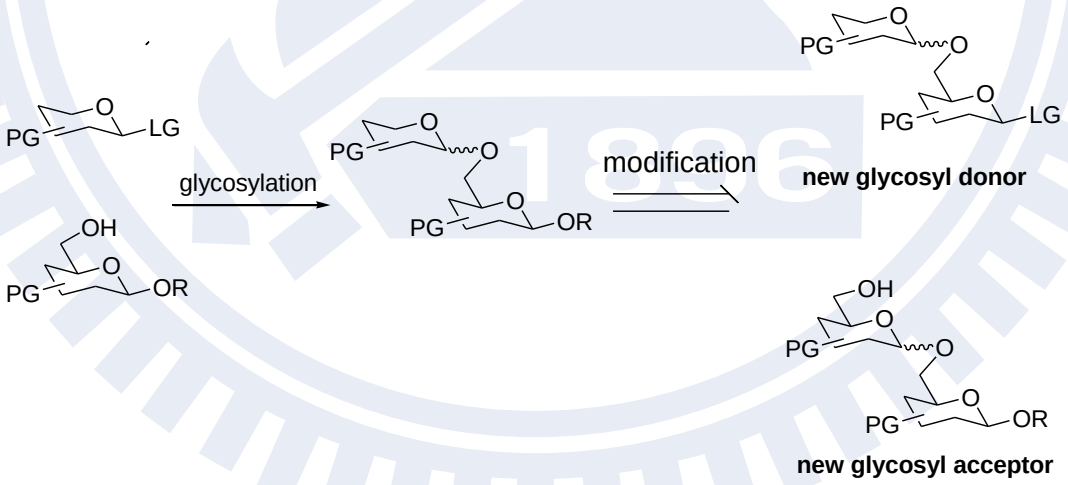


圖 3.1. 由還原端開始的寡糖合成策略

由非還原端進行寡醣組合的濫觴，該屬 Nicolaou 教授與其學生 1984 年嘗試發展「兩階段活化」 (two stage activation) 合成方法：將

醣基氟化物 (glycosyl flouride) 與一具有羥基的硫糖混合在一起，醣基氟化物可以在二氯化錫與過氯化銀下被活化，再與硫糖組合成雙糖。將反應純化後發現此雙糖上的硫酚基團並未被活化，而此雙糖可以再用於其它反應 (圖 3.2)。[1]

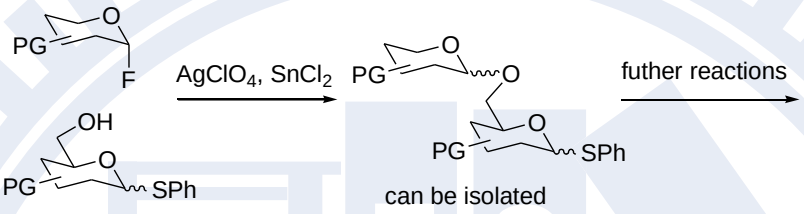
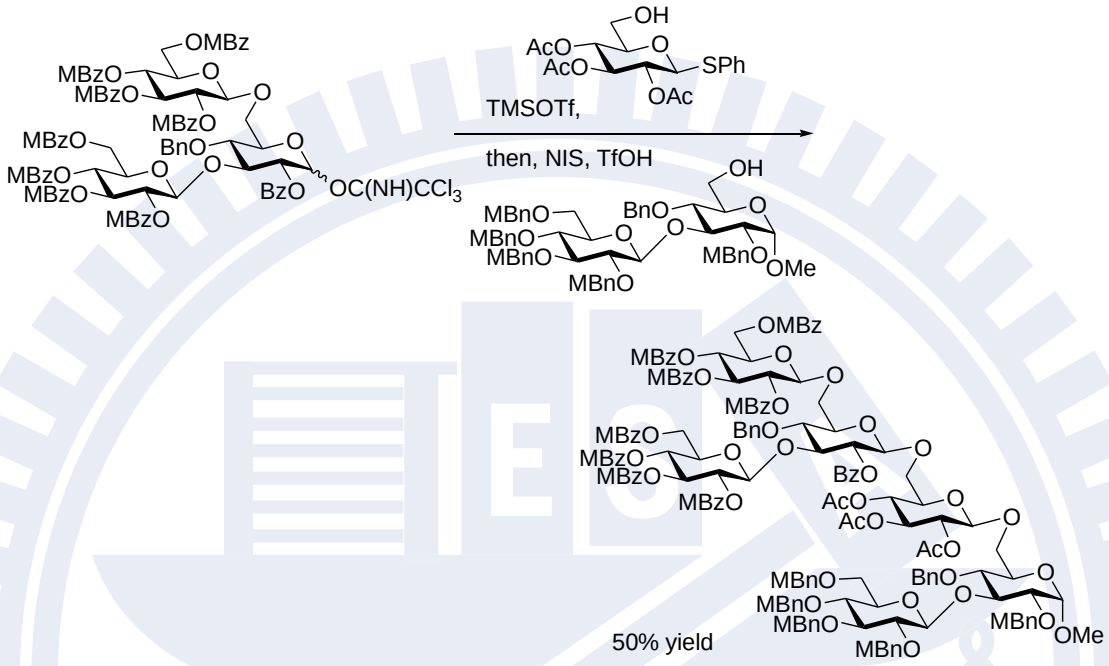


圖 3.2. Two stage：醣基氟化物的獨立活化

之後，Ogawa 實驗室在 1994 年提出「正交醣基化反應」的概念，發現以 Cp_2HfCl_2 與三氟甲磺酸銀 (triflouromethylsulfonic silver, AgOTf) 混合做為活化系統，可以在不影響硫糖上的硫醇基團下，單獨活化醣基氟化物；而 *N*-碘化丁二醯胺 (*N*-iodosuccinimide, NIS) 與催化量三氟甲磺酸銀的活化系統卻可以單獨活化硫糖而不會影響到醣基氟化物；因此可以利用醣基氟化物與硫糖進行交互活化，進而簡單的製備寡糖。[2]

同樣在 1994 年，Takahashi 團隊發表了利用醣基三氯乙亞胺酸酯 (glycosyl trichloroacetimidate) 與硫糖搭配，先以三甲矽烷基三氟甲磺酸 (trimethylsilyl triflate, TMSOTf) 活化醣基三氯乙亞胺酸酯、使之與硫糖橋接後，再於同一鍋反應中加入另一醣基受體、*N*-碘化丁二醯

胺、三氟甲磺酸進行第二次醣基化反應，可以在一鍋反應中進行兩步驟合成，得到 50% 的預計六醣產物 (流程 3.1)。[3]



流程 3.1. Takahashi's 正交醣基化反應合成策略

藉由這些研究，科學家們察覺到：1. 一個羥基不完全保護、同時在端點具有離去基團的醣基建構單元，既可做為醣予體，又可以做為醣受體。這類雙向功能的分子可以配合另一個醣予體 (非還原端起點) 進行醣基化反應；2. 若可以設計兩個不同的離去基團，具有相對應的活化系統各自活化而不會干擾，使反應後的醣產物能保有原本的離去基團，就不需要對產物再做修飾，可以直接進行下一次醣基化反應；甚至在一鍋反應中做到連續多次醣基化反應，減少耗時費力的純化步驟次數、提昇合成效率；這些概念也引發了「一鍋化醣基化反應 (one-pot glycosylation, OPG)」的研究熱潮。

由非還原端進行寡醣合成的醣基化反應策略，約略可分為三個大類：(1) 正交醣基化反應策略：組合數個具有不同離去基團的醣基建構單元，配合相對應其離去基團的活化試劑系統分別活化、進行醣基化反應；(2) 化學選擇醣基化反應策略 (chemoselective glycosylation)：利用修飾醣基建構單元的活性，使得離去基團可以在相同或相近的活化系統中依次活化；此一項目又可以細分成 (i) 將羥基或胺基的保護基團進行修飾、(ii) 利用構型改變醣基予體活性、(iii) 針對離去基團進行修飾、(iv) 利用醣基受體親核性差異進行寡糖合成；(3) 預先活化 (pre-activation)，先讓醣基予體和活化試劑作用，除去離去基團並產生一活化中間物後，再將醣基受體加入反應中進行醣基化反應；此策略又稱作反覆式醣基化反應策略 (iterative glycosylation strategy)。以下逐一簡單介紹。[4]

3.1.1 正交醣基化反應策略：不同離去基團活化系統的搭配

如前所提，科學家們開發了眾多種類的離去基-活化系統，測試了數種搭配組合，以期達到正交醣基化反應的目標。舉例來說：醣基溴化物 (glycosyl bromide) 予體與硫醣、[3,5] 醣基氟化物予體與硫醣、[2] 醣基碘化物 (glycosyl iodide) 予體與硫醣、[6] 醣基三氯乙亞胺酸酯予體與硫醣、[3] 醣基亞碸 (glycosyl sulfoxide) 予體與硫醣、[7] 醣基亞磷酸

酯 (glycosyl phsphite) 予體搭配硫醣、[8] 醣基亞磷酸酯 (glycosyl phsphite) 予體搭配硒醣、[6] 醣基磷酸酯 (glycosyl phosphate) 予體與硫醣、[9] 醣基三氟乙亞胺酸酯予體搭配 4-戊烯基醣 (4-pantenyl glycoside)、[10]SBox 醣 (benzoxalyl thioglycoside) 與硫醣、[11]STaz 醣 (thiazolyl thioglycoside) 與硫醣、[12] 醣基氟化物予體與 glycal 醣受體、[13] 醣基氟化物予體與 BCB 醣受體等等 (glycal 醣受體與 BCB 醣受體較接近於非還原端醣單元) (圖 3.3)。[14]

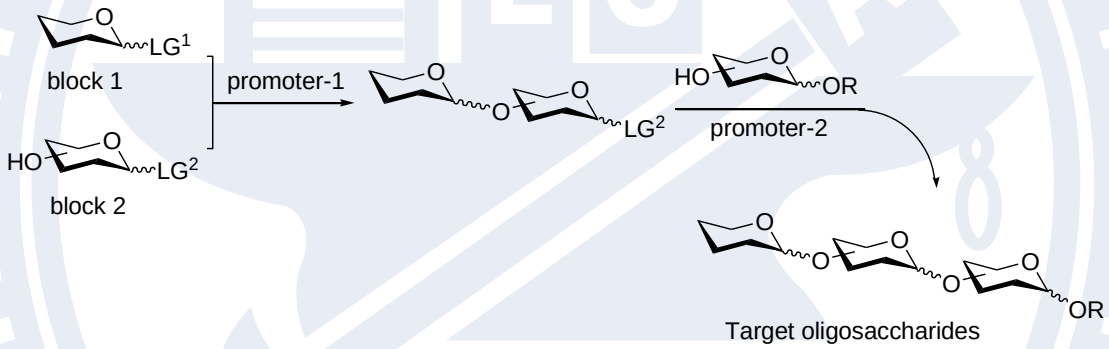
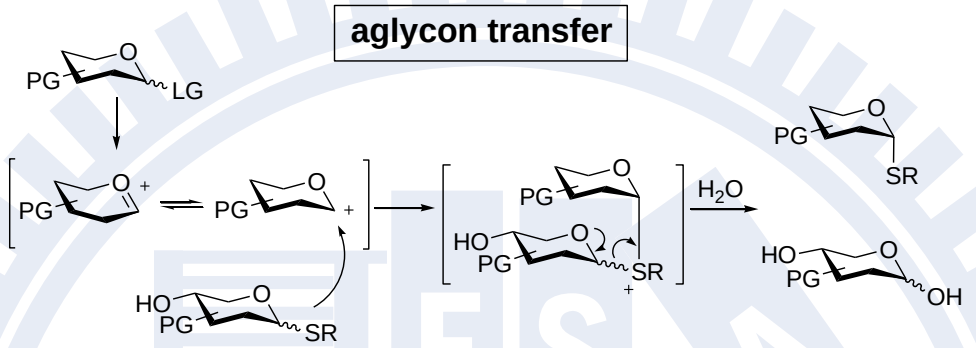


圖 3.3. 正交醣基化反應：不同離去基系統的寡醣合成策略

經由這些研究，我們可以發現：1. 受限於離去基團的特質與活性，並不是任何的離去基團與活化系統都可以交互搭配，往往需要設計較為活潑的醣基予體與較為溫和的活化試劑搭配較為不活潑的醣基受體才有較好的接合效果；2. 要設計新的離去基-活化試劑系統並非易事，隨之而來的修飾工作與不同系統的使用也增加了操作上的複雜性。3. 離去基活化後的醣基陽離子本身也是一個親電子體

(electrophile)，可能與醣受體產生非醣基轉移 (aglycon transfer) 或其它的旁反應 (流程 3.2)。[15] 有鑑於此，科學家們思考：若簡化使用單一或相近的活化系統中，是否可以選擇性進行活化醣予體呢?



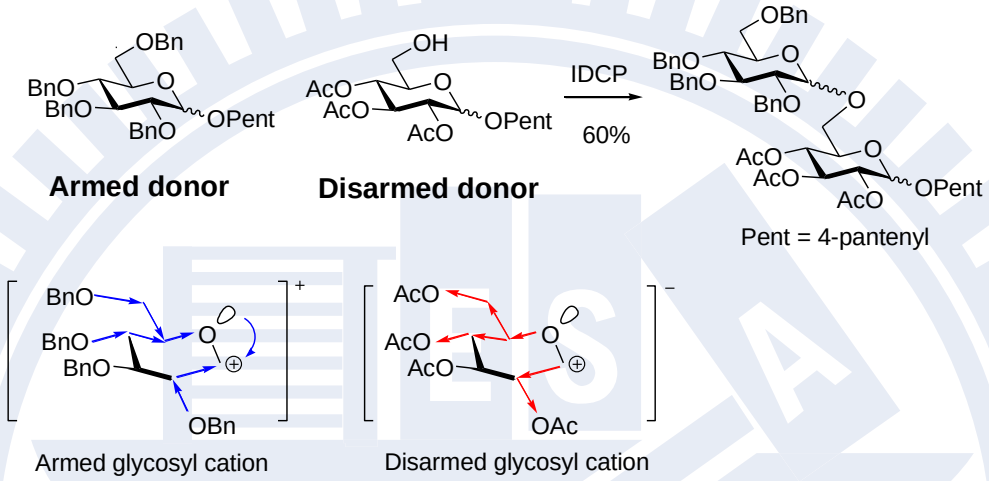
流程 3.2. 非醣基轉移反應推測機構

3.1.2 化學選擇醣基化反應策略：改變建構單元活性

3.1.2.1 修飾醣基單元的保護基團

在 1988 年，Mootoo 教授與 Fraser-Reid 教授提出了「armed-disarmed」的概念。[16]他們發現醣基單元的保護基團會影響其作為予體的活性，醚類保護基會增加醣基單元的活性，而酯類保護基則會降低醣基單元的活性。推測造成活性梯度差異的原因在於電子效應，醚類保護基的拉電子能力較小，亦較能穩定離去基團活化後的醣基陽離子；而酯類保護基或碳酸酯類保護基等具有羰基的官能基團則恰相反。[17]依此原則，可以在不改變離去基團與活化系統下，選擇性先活化活性較大的醣基單元，進行醣基化反應 (流程 3.3)。

因此,「改變醣基建構單元的活性,在單一或相近的活化試劑下,依活性大小選擇性活化醣予體進行寡醣合成」的概念,開始被廣泛應用於寡醣合成,此又被稱為「化學選擇醣基化反應策略」。



流程 3.3. Armed-disarmed 策略與電子效應解釋

之後,翁啟惠教授與其學生嘗試將此概念延伸,針對6類醣分子(各自活性也有區分:岩藻糖、半乳糖、葡萄糖、甘露糖、乳糖、葡萄糖胺),以硫苷基作為離去基,用11種不同的保護基修飾成50個醣予體做系統化的測試,單純用 NIS 與 TfOH 的活化系統量化各醣基單元的相對活性數值 (related reactivity value, RRV),並將此數值輸入電腦,以期利用電腦程式遵照活性梯度預測、設計,在一鍋反應中將數個醣基單元依次活化橋接,建立「可程式化的一鍋化寡醣合成」(programmable one pot glycosylation synthesis),或稱為「活性基礎一鍋化醣基化反應策略」(reactivity based one pot glycosylation

strategy)，並以此成功建構出數種寡醣分子 (圖 3.4)。[18,19]

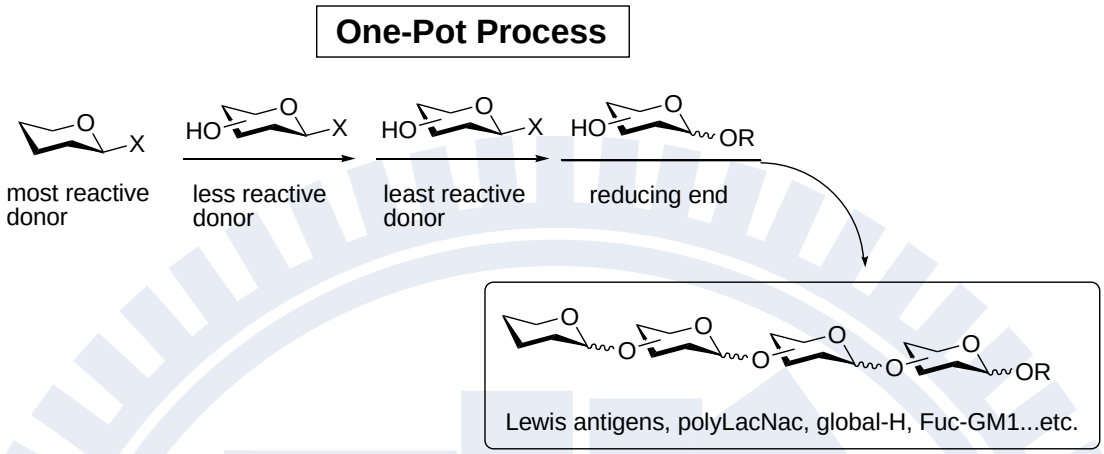
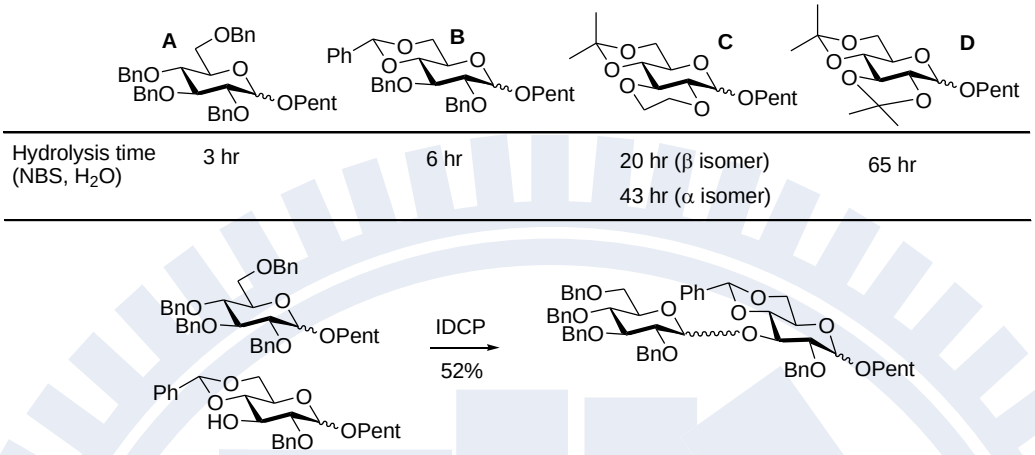


圖3.4. 活性基礎一鍋化醣基化反應策略

3.1.2.2　利用保護基團影響醣分子構型改變醣予體活性

除了電子效應以外，有些保護基團則會改變醣的構型，使得醣基單元的反應性改變。Fraser-Reid 教授發現 4,6-縮醛基保護的醣基單元 **B** 不易被 *N*-溴化丁二醯亞胺水解，亦指醣予體活性降低。[20]推測因為此融合雙環結構的扭轉張力 (torsional strain) 使醣予體活化後的醣基陽離子較不穩定，因此離去基相對不易被活化。若是 2,3-, 4,6-羥基均用縮醛基保護形成融合三環結構 (化合物 **C**, **D**)，則會更加降低醣予體的活性。而Steven V. Ley 教授用縮醛基保護醣予體的3,4-羥基；[21] Boons 教授用環碳酸酯基 (cyclic carbonates) 保護醣予體的2,3-羥基，同樣發現到醣予體活性的下降；[22a]而本實驗室對於葡萄糖胺基 2,3-oxazolindone 衍生物的相關研究中，也觀察到相類似的現象

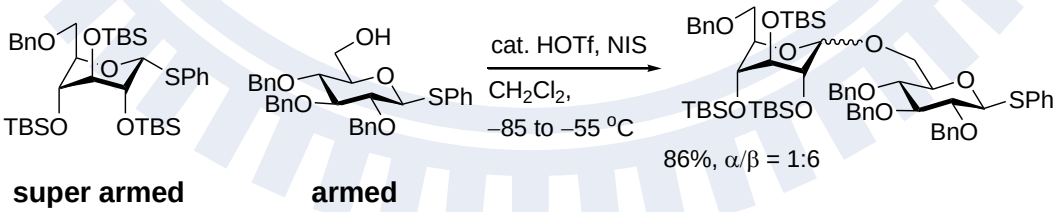
(流程 3.4)。[22b]



	A	B	C	D
Hydrolysis time (NBS, H_2O)	3 hr	6 hr	20 hr (β isomer) 43 hr (α isomer)	65 hr

流程 3.4. 扭轉張力效應降低醣予體活性與其合成應用

構型的改變不僅可以降低醣予體活性，Bols 教授實驗團隊發現若用 TBS 保護醣基單元，會將一般處於 $^4C_1$ 構型的 D-式醣轉為 $^1C_4$ 構型，利用軸向斥力使離去基相對容易離去、配合矽烷基的推電子效應穩定醣基陽離子，形成比全苄基醣予體更加活潑的醣基單元；或可稱此種矽烷基醣予體為「super-armed donor」(流程 3.5)。[23]

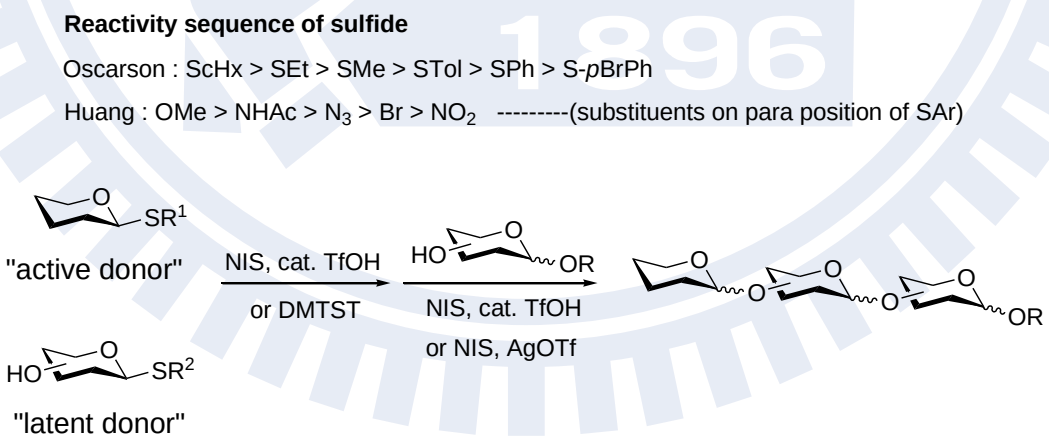


流程 3.5. super-armed donor與armed donor的寡糖合成應用

3.1.2.3. 針對離去基團進行修飾

除了改變保護基團影響醣單元活性外，離去基團本身也具有活性

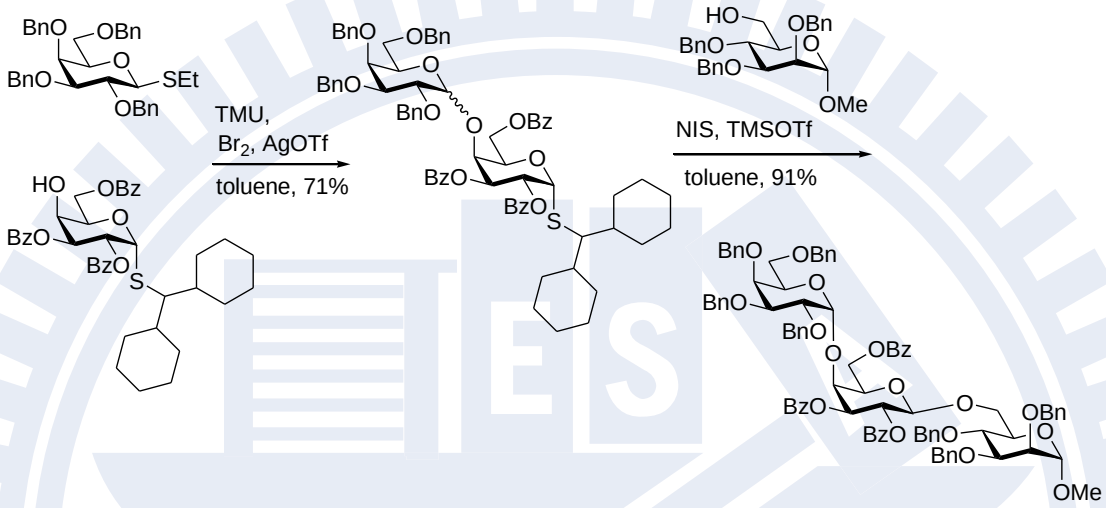
差異。Roy 教授與其學生提出「active-latent」概念：硫酚在苯環上對位取代基，例如：甲基、甲氧基、乙醯胺基可提升硫醣予體的活性，稱為「active」；相對的，硝基則會降低硫醣予體活性，稱為「latent」。[24] 之後，Oscarson 實驗室以 HPLC 分析不同的硫醇與硫酚離去基團的活化速率來判斷硫醣予體的活性大小，發現一般硫醇的活性比硫酚為大，硫環己烷的相對活性最大，而苯環上有鹵素取代的硫酚則相對活性較小。[25] 而 2009 年，黃雪飛教授則使用了不同的幾個醣單元在不同的溶劑系統將其活性表現做一量化比較；並指出醣予體端點氫原子的 ^{1}H-NMR 訊號，其化學位移與活性上有相對關係：化學位移越大者其予體活性越小，反之越大；經由他們的努力，確立了電子效應對離去基的影響，並將此概念應用於寡糖合成中 (流程 3.6)。[26]



流程 3.6. 「Active-latent」寡糖合成策略

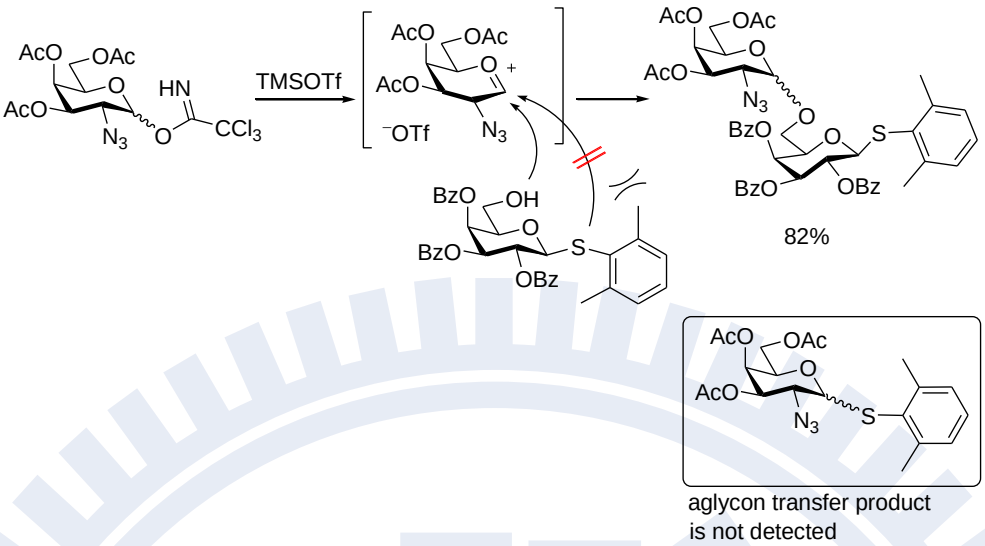
在取代基的電子效應之外，Boons 教授則發現：採用立體障礙較

大的烷基硫醇作為離去基的硫糖予體，其活性較乙基硫醇為低，在溴與三氟甲磺酸銀的系統下，可以選擇性先活化乙基硫醇得到預計雙糖產物 (流程 3.7)。[27]



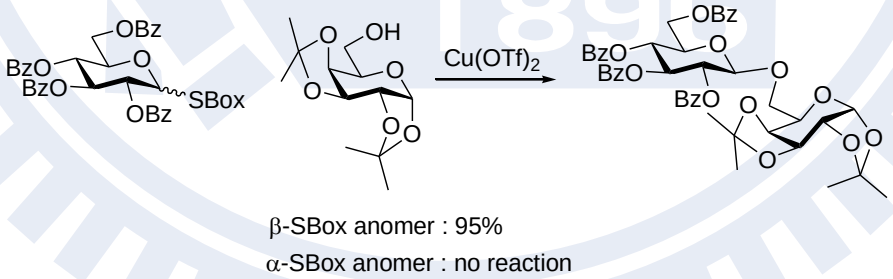
流程 3.7. 離去基的立體障礙對活性影響與其合成應用

之後，Gildersleeve 教授的研究也驗證了硫酚的苯環上取代基會影響醣予體的活性，拉電子基與立障較大的取代基都會降低醣予體活性；Gildersleeve 教授 [28] 並更進一步利用立障較大的 2,6-二甲苯硫酚作為離去基，減少了正交醣基化反應的旁反應 (非糖基轉移, aglycon transfer) (流程 3.8)。[28]



流程 3.8. 利用離去基的立障減少非糖基轉移

此外，Crich 實驗室發現離去基的位向也會影響到活性，在 4,6-縮醛保護的葡萄糖基亞碸 (glucosyl sulfoxide)，β-位向的離去基有較好的活性而 α-位向的離去基的活性較低，在以 SBox 為離去基時也發現有相同的現象 (流程 3.9)。[29]

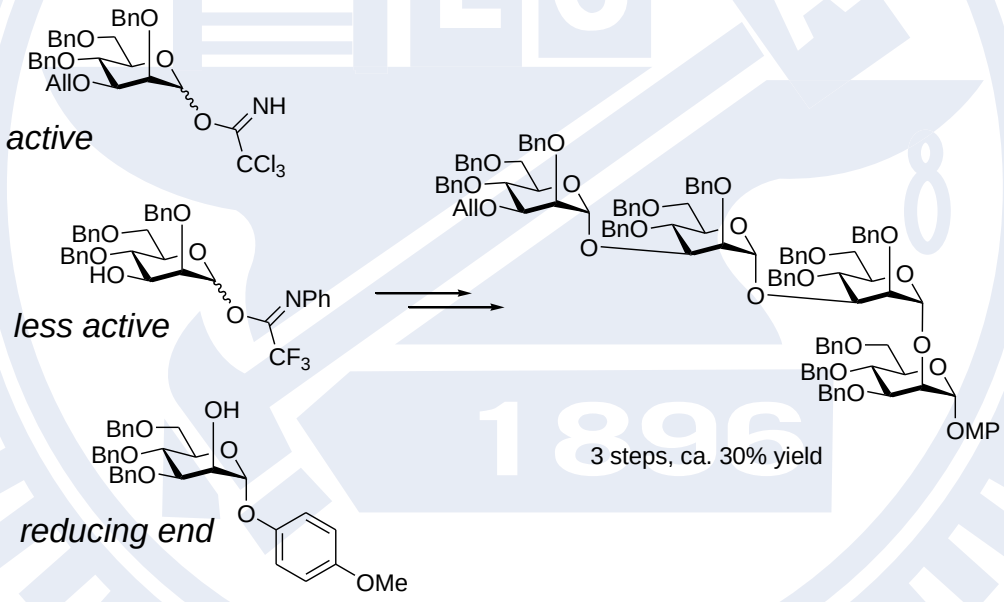


流程 3.9. 離去基位向影響糖予體活性

不只是改變離去基結構會影響醣予體活性，Ley 教授與其學生利用硒醣 (selenoglycoside) 予體相對於硫醣予體有較高活性，可以搭配縮醛基改變醣構型降低活性，搭配組合製備出高甘露醣型式 (high

mannose type) 的九醣體。[30]

除了硫醣家族，Iadonisi 實驗室嘗試將「active-latent」應用於醣基乙亞胺酸酯類予體上：使用較溫和的三氟磺酸鐿 ($Yb(OTf)_3$) 或三氟磺酸鉍 ($Bi(OTf)_3$) 作為活化催化劑，先活化相對活潑的醣基三氯乙亞胺酸酯予體，接合相較穩定的醣基三氟乙亞胺酸酯單元 (glycosyl triflouroacetamide) 後，再加入還原端醣受體與另一催化量活化試劑於反應中進行第二次醣基化反應 (流程 3.10)。[31]

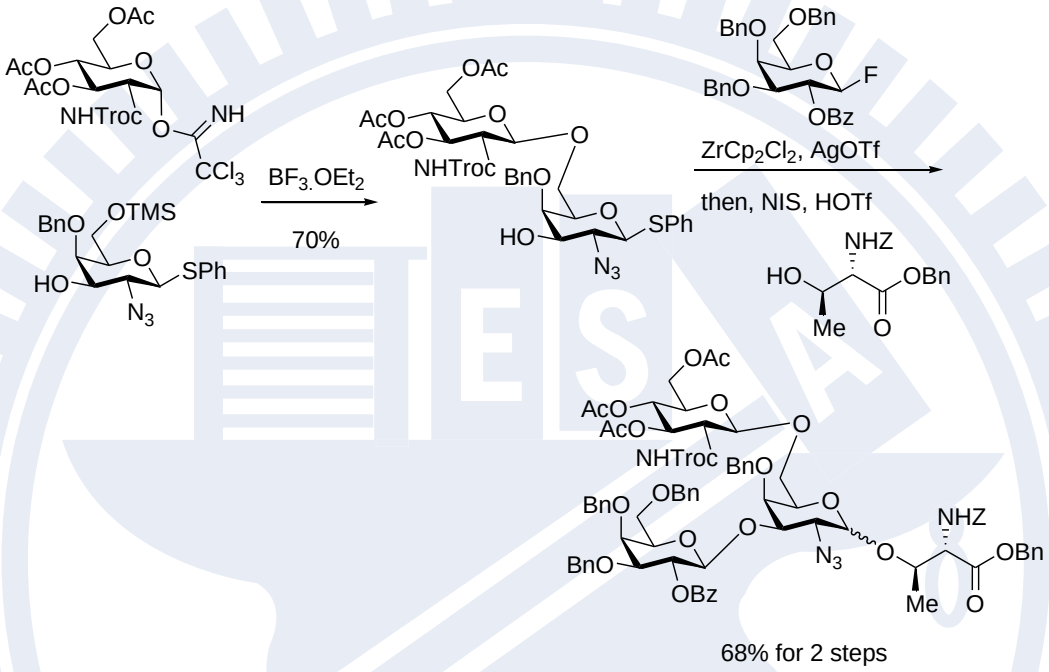


流程 3.10. 醣基乙亞胺酸酯類予體的正交醣基化反應

3.1.2.4 利用醣基受體親核性差異進行寡糖合成

除了探討醣予體的修飾、活化系統的改變，利用醣受體本身親核基的活性差異進行選擇性醣基化反應，也可說是化學選擇醣基化反應策略。例如：Takahashi 教授利用一級羥基與二級羥基的親核性不同

混合正交醣基化反應策略，合成 core-2 黏蛋白抗原。[32] 而 Magnusson 實驗室利用羥基鄰近保護基 (例如：*N*-tetrachlorophthaloyl) 的立體障礙形成遮蔽降低羥基的親核性製備 Lewis-a 抗原等等 (流程 3.11)。[33]



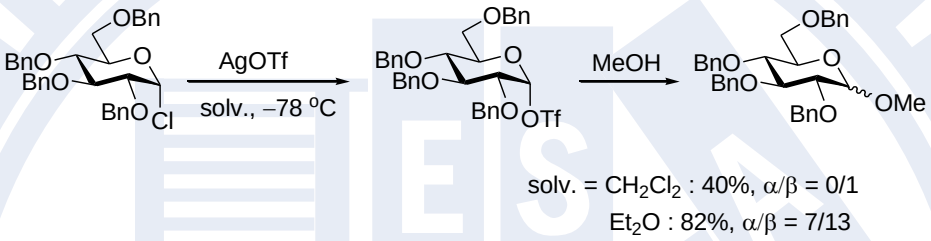
流程 3.11. 化學選擇性合成 core-2 黏蛋白抗原

3.1.3 預先活化 (preactiviation)與連續式醣基化反應策略 (iterative glycosylation strategy)

在寡醣的合成中，羥基的修飾是難以避免的必經步驟。而為了做到選擇性活化的目標，對醣基單元的修飾與設計可說更加繁瑣而且需要依賴相當的經驗。於是，科學家們想到，若可以讓醣予體在沒有醣受體的狀況下，單獨先活化形成一種活性物種狀態，再將醣受體加入反應中進行醣基化反應，那就可以將醣基單元保護基與離去基的修飾

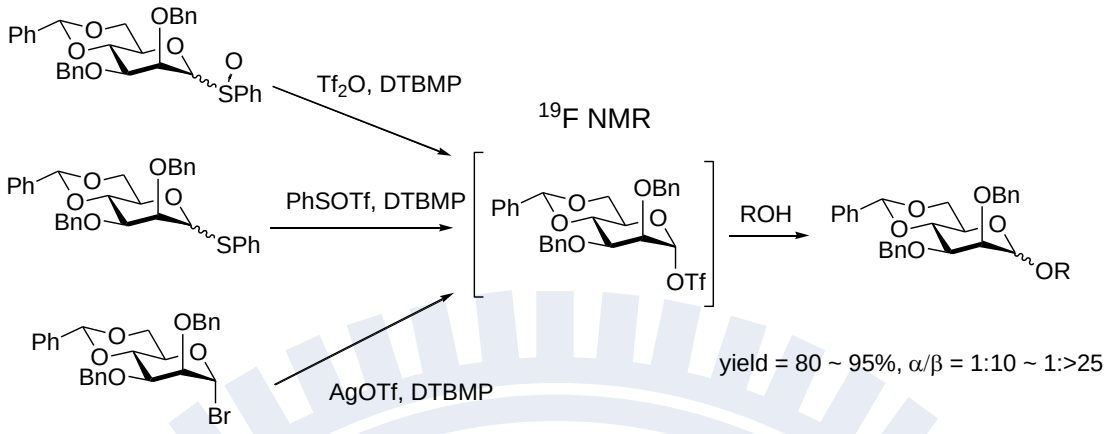
步驟降到最低，增進寡醣的合成效率。

Kronzer 與 Schuerch 在 1973 年，首先使用三氟甲磺酸銀與葡萄糖基氯化物在 –78 °C 下先混合，形成一葡萄糖基三氟甲磺酸 (glucosyl triflate) 中間產物後，再加入甲醇進行醣基化反應，可說是最早的預先活化醣基化反應 (流程 3.12)。[34]



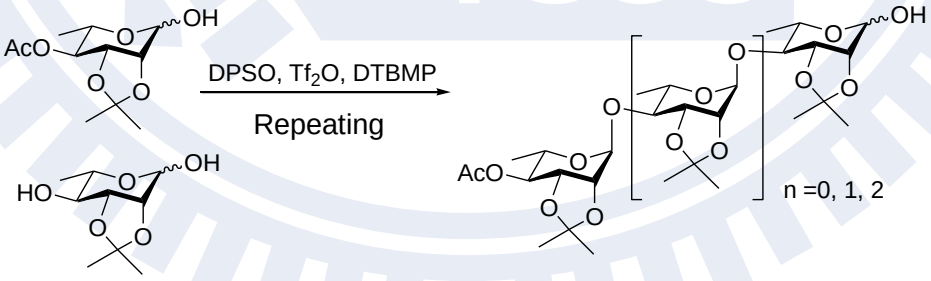
流程 3.12. 葡萄糖基氯化物的預先活化醣基化反應

而後 Khane 實驗室使用三氟甲磺酸酐與醣基亞碸混合後、再將醣受體加入反應中可以得到醣基化產物，並以此進行一鍋化醣基化反應得到 Ciclamycin 三糖；[35] 而 Crich 教授則針對 4,6- 縮醛保護的甘露糖基亞碸與硫糖進行研究，並在 1997 年、1998 年分別用不同的醣予體得到 ^{19}F-NMR 的圖譜，建議在醣基化反應有活性物種 α-醣基三氟甲磺酸 (α-glycosyl triflate) 的存在，此活性物種會影響醣苷鍵的立體選擇性而生成 1,2-順式鍵結 (流程 3.13)。[36]



流程 3.13. Crich 實驗室建議存在 α-glycosyl triflate

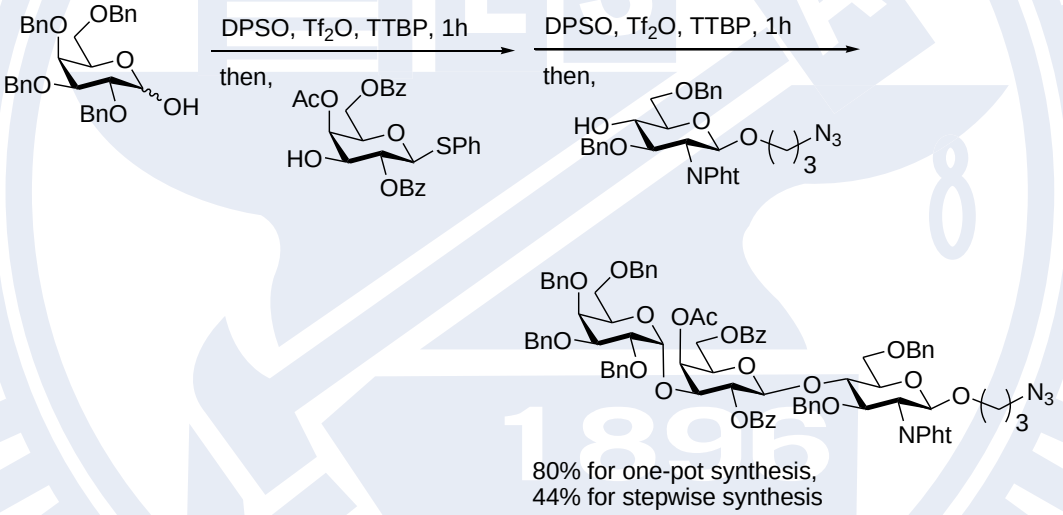
2001 年，David Gin 教授與其學生發表將二苯基亞碸 (DPSO, diphenylsulfoxide)、三氟甲磺酸酐與醣基半縮醛 (glycosyl hemiacetal) 先於低溫下混合，再將半縮醛醣受體加入此混合物進行脫水醣基化反應 (dehydrative glycosylation)，形成端點具有半縮醛基寡醣分子；此分子可以直接再繼續進行預先活化醣基化反應，這個策略被稱為「連續式醣基化反應策略」(流程 3.14)。[37]



流程 3.14. Gin 教授的連續式脫水醣基化反應策略

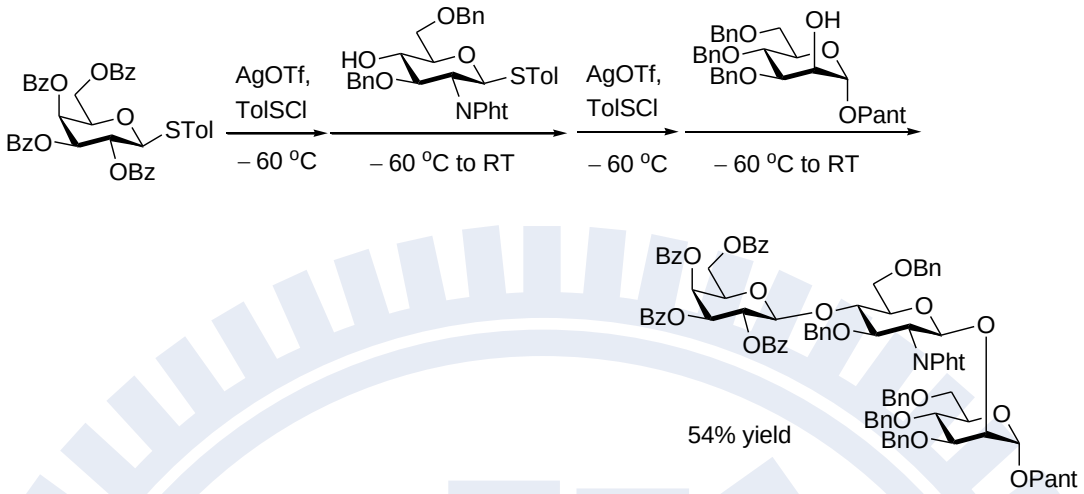
同年，日本京都大學的 Yamago 教授利用溴對硒糖進行硒酚基轉換為 β-溴基後，再以 C-2 鄰基效應穩定 β-溴基離去的醣基陽離子

進行寡糖合成；[38]之後在 2004 年，Yamago 教授又利用數種活性相近的硫醣分子與 BSP-Tf_2O-DTBMP 活化系統以預先活化的方法進行醣基化反應，並分別測試了 BSP-Tf_2O-DTBMP 與各種 phenyl sulfonic triflate 的活化效果，驗證連續式醣基化反應策略在硫醣的可行性。[39]而荷蘭的 van der Marel 實驗室綜合了醣基半縮醛與硫糖，進行兩種不同離去基的「一鍋化連續式醣基化反應」，並與分段式寡醣合成 (stpeswise oligosaccharides synthesis) 的效率作一比較 (流程 3.15)。[40]



流程 3.15. 兩種離去基的一鍋化連續式醣基化反應

而在北京的葉新山教授與在美國的黃雪飛教授合作發表了單用一種離去基的「一鍋化連續式寡醣合成 (one-pot iterative glycosylation)」，利用苄基硫三氟甲磺酸 (tolyl sulfenic triflate, TolSOTf) 的活化系統，不需要考慮醣分子活性大小，以預先活化的策略、一鍋化合成數種不同位向橋接的寡糖分子 (流程 3.16)。[41]



流程 3.16. 一鍋化連續式醣基化反應

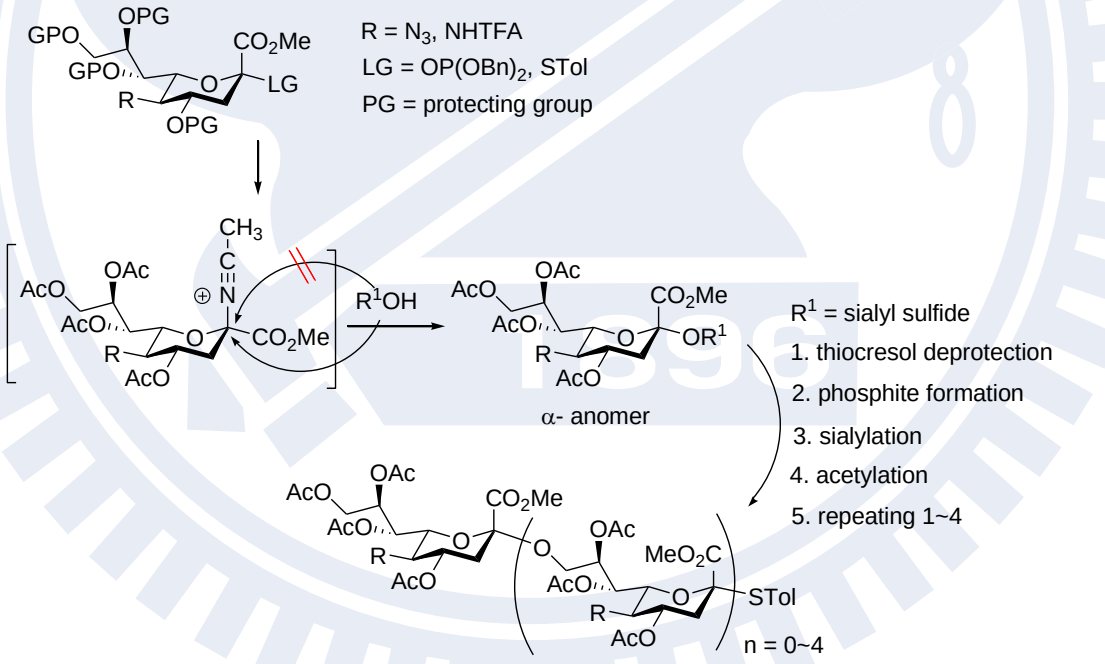
綜合來說，現今建構寡醣已然有許多策略可供使用，科學家們也往往在設計上採用不只一種策略合成寡醣分子 (hybrid strategy)，其中的巧思可謂千變萬化。

3.1.4 研究動機與實驗設計

回顧在低濃度醣基化反應的研究中，本實驗室初步測試採用相較穩定、容易修飾的硫醣予體與還原端醣受體進行醣基化反應。這樣的策略在寡糖合成上相對受到較多的限制。參照現有合成策略，於是問自己:「是否可將不同於硫醣的醣予體，應用在低濃度腈類溶劑系統，發展正交醣基化反應或化學選擇醣基化反應？」、「降低醣予體的活性似乎對低濃度醣基化反應影響不大，那降低醣受體的活性是否也可以得到相似的產率與選擇性？」

再翻看文獻，已經有不少文獻記載著數種醣予體在腈類溶劑系統中進行醣基化反應；比如說：醣基溴化物、[42]醣基三氯乙亞胺酸酯、[43]醣基三氟乙亞胺酸酯、[44]醣基磺元酸酯 (glycosyl xanthate)、[45]4-戊烯基醣、[46]碳酸酯基醣、[47]醣基亞磷酸酯、[48,49]醣基磷二醯胺 (glycossyl phosphorodiamidate)、[50]醣基磷酸酯等等；[51]發現以上各研究多在較高的反應物濃度 (受質濃度在 100 mM ~ 36 mM 之間) 中進行探討。

再介紹在腈類溶劑系統中的正交醣基化反應，多半是唾液酸的醣基化反應預期得到 α-位向的醣苷鍵結的相關研究。

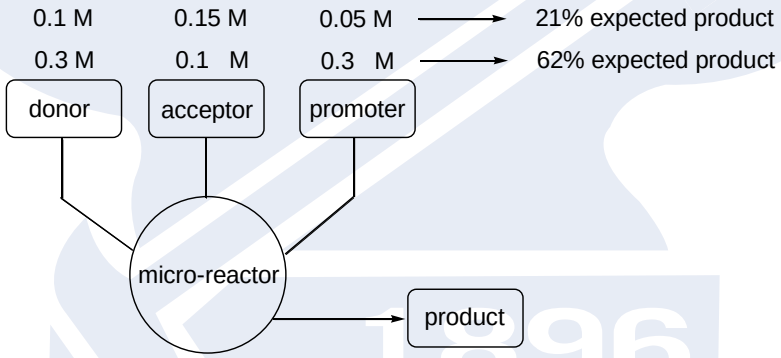


流程3.17. 林俊成教授的唾液酸寡糖合成

林俊成教授與翁啟惠教授利用唾液酸基亞磷酸酯 (sialiyl phosphite) 醣予體與唾液酸基對-硫甲苯 (sialyl *p*-thiocresol) 醣受

體，進行醣基化反應，並將雙糖產物的硫苄基修飾為亞磷酸酯基、再進行一次醣基化反應，可得到極佳選擇性的唾液酸四糖體 (流程3.17)。[49]

Fukase 實驗室則使用唾液酸基三氟乙亞胺酸酯與苯基硫乳糖在微型反應器 (micro-reaactor) 中進行醣基化反應，Fukase 教授將醣予體、醣受體與活化試劑分成三個管線注入微型反應器中，並發現：控制醣予體、醣受體與活化試劑注入反應器的濃度，可以得到較好的產率 (流程3.18)。[44]

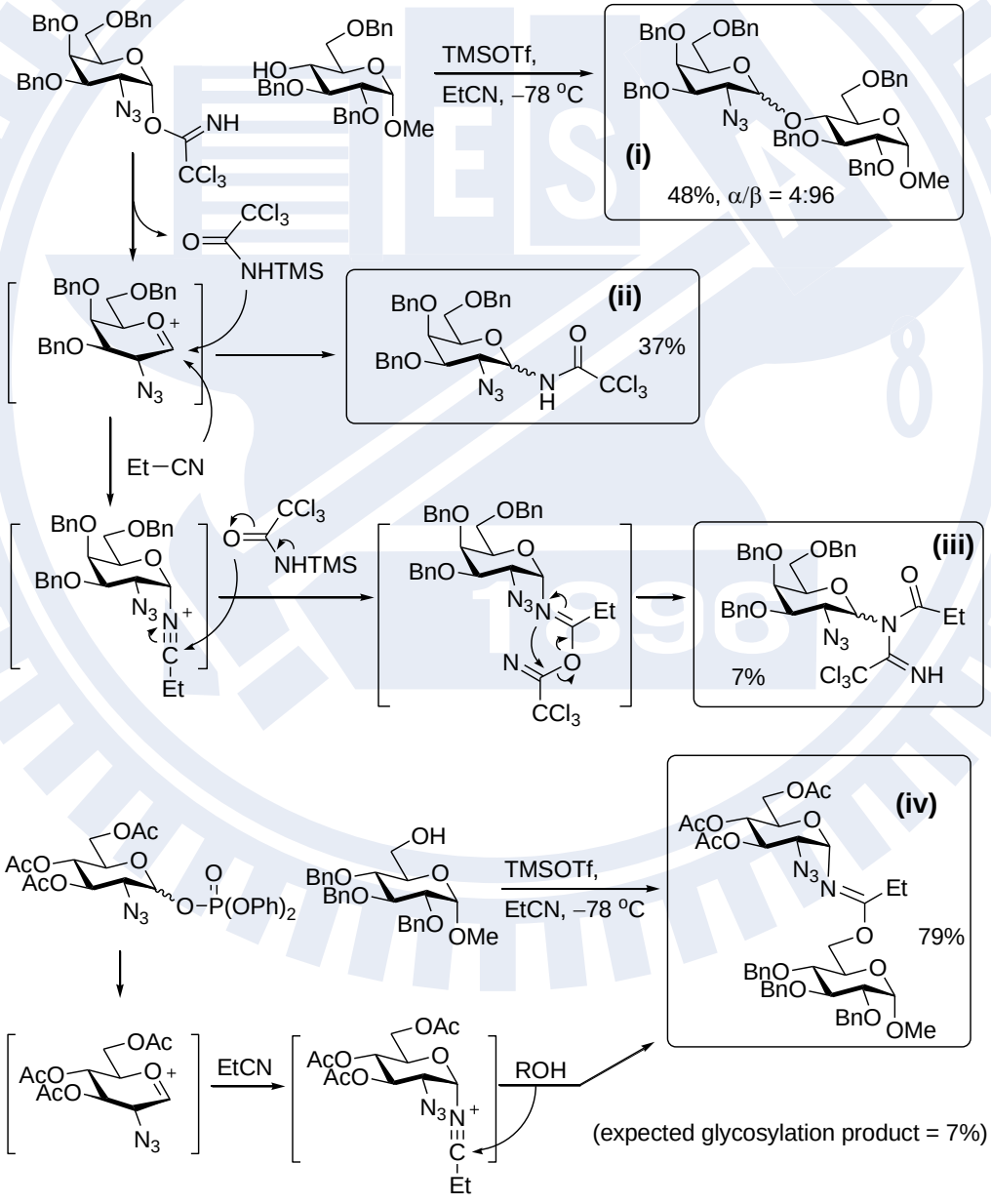


流程3.18. Fukase 實驗室的微型反應器合成唾液酸寡醣

Nakahara 教授與其學生則嘗試利用硫苯基半乳糖予體與葡萄糖胺受體或半乳糖受體建構具有 β-1→4 或 β-1→3 醣苷鍵的雙糖分子，發現修飾半乳糖的3,4-羥基為對-甲氧苄基保護的醣予體可得到較好的 β-1→3 選擇性。[52]

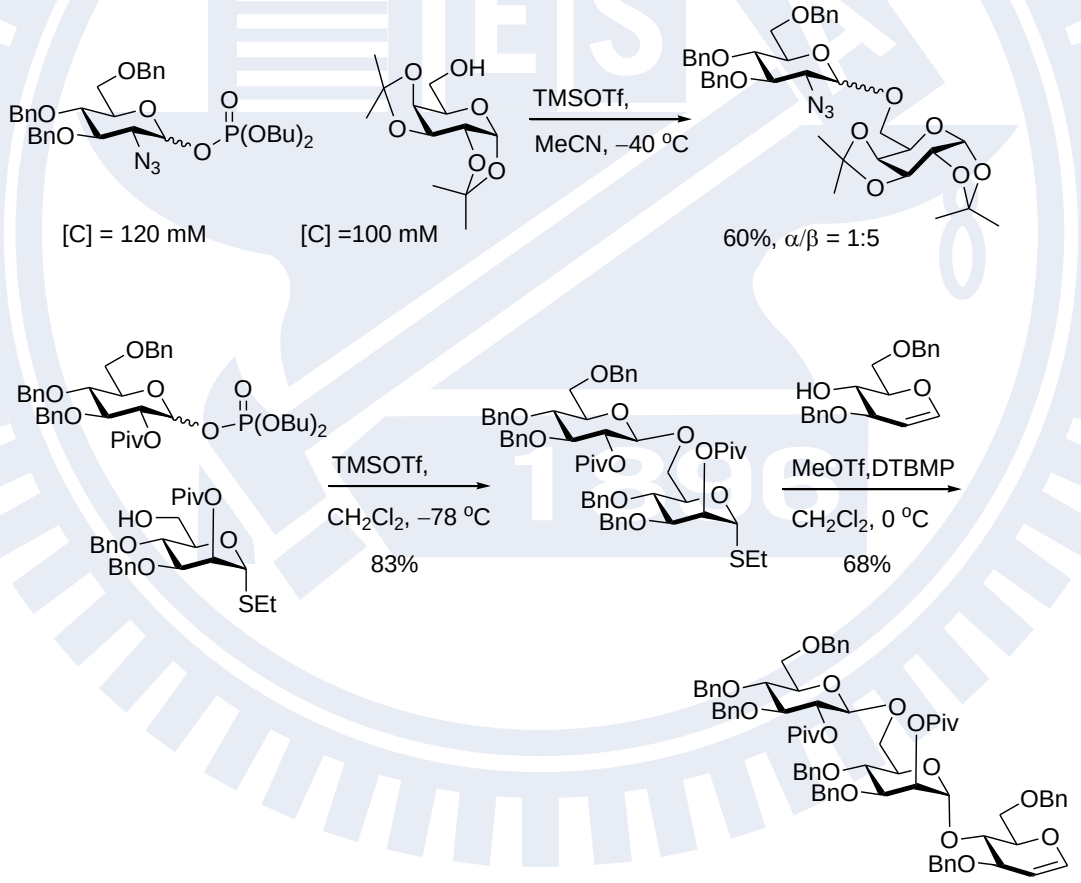
Ikegami 教授與Hashimoto 教授使用唾液酸基磷二醯胺 (sialyl

phosphorodiamidate) 作為醣基單元，並修飾糖分子的保護基改變予體活性，進行 armed-disarmed 化學選擇性醣基化反應； Hashimoto 教授[50d]更利用唾液酸基亞磷酸酯作為醣予體，與半乳糖基磷二醯胺作為醣受體 (galactosyl tetramethylphosphorodiamidate)，進行 active-latent 的醣基化反應。[50]



流程3.19. Hashimoto 教授觀察到的副產物與推測的反應機構

之後，Hashimoto 教授將數種醣分子修飾為含磷離去基的醣基單元進行了詳細的研究，並將其活化系統配合腈類溶劑應用在選擇性唾液酸寡糖合成上。[48,50,51] Hashimoto 教授在其研究中發現到：當較低活性的醣予體、或親核性較低的醣受體 (例如：葡萄糖的 4-羥基) 在低溫下、腈類溶劑系統中進行醣基化反應，容易進行 Ritter 反應或其他的旁反應 (流程3.19)。[51c]



流程3.20. 醣基磷酸酯利用 C2-鄰基效應的正交醣基化反應

此外， Seeberger 教授也嘗試以醣基磷酸酯作為醣予體，在二氯

甲烷溶劑系統中進行正交醣基化反應的探討；[53]但是當 Seeberger 教授將葡萄糖胺基磷酸酯與甘露糖基磷酸酯應用於腈類溶劑中進行醣基化反應時，未能得到令人滿意的醣苷鍵選擇性 (流程 3.20)。[53a]

歸納來說，利用腈類溶劑、沒有C-2鄰基效應的系統中進行正交醣基化反應或化學選擇醣基化反應，並未被詳細研究或廣泛應用於唾液酸以外的糖分子上。因此，在低濃度腈類溶劑中進行由非還原端開始的寡糖合成，甚或在一鍋化反應中建構寡醣是值得探討的方向。

3.2 結果與討論

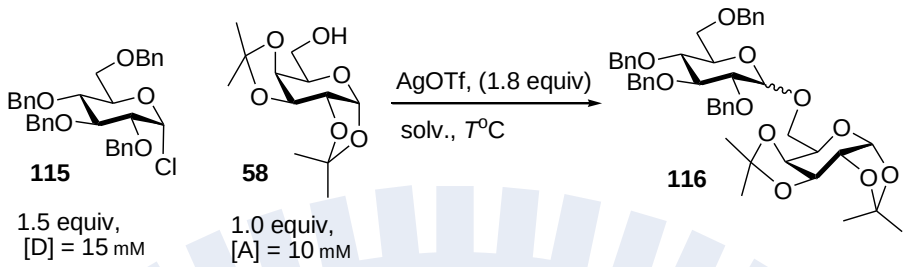
3.2.1 正交醣基化反應的測試

3.2.1.1 醣基氯化物的測試

本實驗室由張智為博士發展了利用 2,4,6-三聚氯胺 (trichlorotriazine, TCT) 與二甲基甲醯胺 (*N*,*N*-dimethyl formamide, DMF) 形成 Vilsmeier-Haack 試劑，對不同保護基修飾的醣基半縮醛進行氯化反應，可製備不同醣基氯 (glycosyl chloride）分子。[54]

以半乳糖基氯化物 **115** 作為醣予體，與市售半乳糖受體 **58** 在低濃度腈類溶劑系統、三氟甲磺酸銀為活化劑的條件下進行醣基化反應 (表 3.1)。

表 3.1. 醣基氯化物的測試



entry	CH_2Cl_2 : MeCN : EtCN	T (°C)	time (h)	yield (%), α : β
1	25%: 50%: 25%	-70 to -50	18	0
2	25%: 50%: 25%	-20 to 25	48	0
3	90%: 10%: 0%	-20 to 0	5	30, 1 : 2
4	80%: 20%: 0%	-20 to 25	12	<10

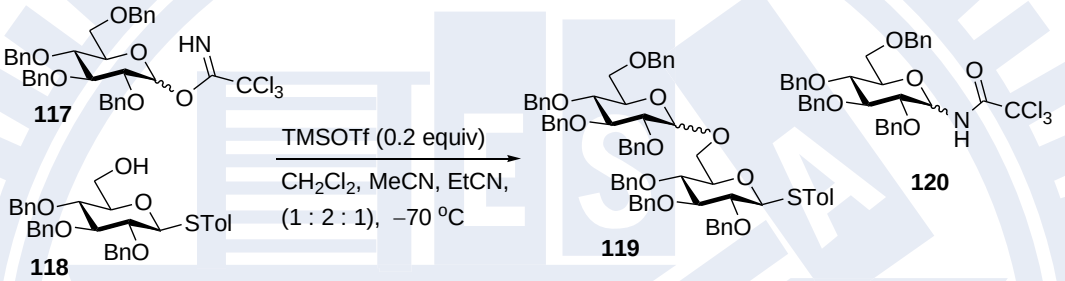
在 −70 °C 到 −50 °C 的條件下，並未觀察到醣基氯被活化的現象 (表 3.1，實驗 1)。查閱文獻，Koenigs-Knorr 反應若在腈類溶劑系統中進行，往往需要在室溫下進行反應 (以醣基溴化物或醣基氟化物為例)。[42,55] 因此再測試溫度效應，將反應設計在室溫下進行，但仍未觀察到醣基氯被活化的現象 (表 3.1，實驗 2)。之後嘗試降低腈類溶劑比例，終於得到 30% 預計的雙糖產物 **116** (表 3.1，實驗 3、4)。

歸納結果：當腈類溶劑超過反應體積 20%，醣基化反應速率將會相對降低；也不排除因為醣基氯化物的活性相較溴化物或碘化物為低，故在腈類溶劑進行 Koenigs-Knorr 反應的速率相應較低。

3.2.1.2 醣基三氯乙醯胺酯的測試

接下來改用較高活性的醣基三氯乙醯胺酯做測試。以全苄基保護的葡萄糖基三氯乙醯胺酯 **117** 為醣予體、6-羥基硫葡萄糖 **118** 作為受體，0.2 當量三甲矽烷基三氟磺酸、–70 °C 下進行反應 (表 3.2)。

表 3.2. 醣基三氯乙醯胺酯的測試



1.0 equiv, [A] = 10 mM

entry	Donor (equiv)	Time (h)	**119** (%), α : β	**120** (%)
1	1.2	1.5	65, 1 : >19	15%
2	1.6	0.5	85, 1 : >19	20%
3	1.6	0.5	87, 1 : >19	17% [a]

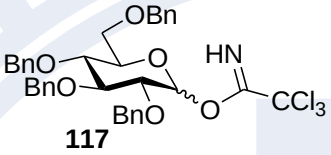
[a] 逆向加藥順序 (inverse addition)。

以 1.2 當量的醣予體 **117** 進行反應，可以得到 65% 的產率與超過 95% 的選擇性 (表 3.2，實驗 1)；當醣予體增加為 1.6 當量時，預計雙糖 **119** 的產率提升到 85%。但以上兩個反應也產生了約 20% 的副產物 **120** (表 3.2，實驗 1、2)。

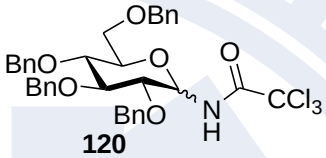
此副產物 ^{1}H NMR 圖譜具有 5.6 ppm 的三重峰訊號，^{13}C NMR

則失去了醣予體在 98 ppm 的 C-1 訊號，但仍有 161 ppm 的醯胺訊號。經由 NMR 圖譜與文獻比對後，判斷為 1-三氯乙醯胺產物，推測為離去基重排或回攻醣基陽離子後的結果 (表 3.3)。[56]

表 3.3. 旁產物判定



117



120

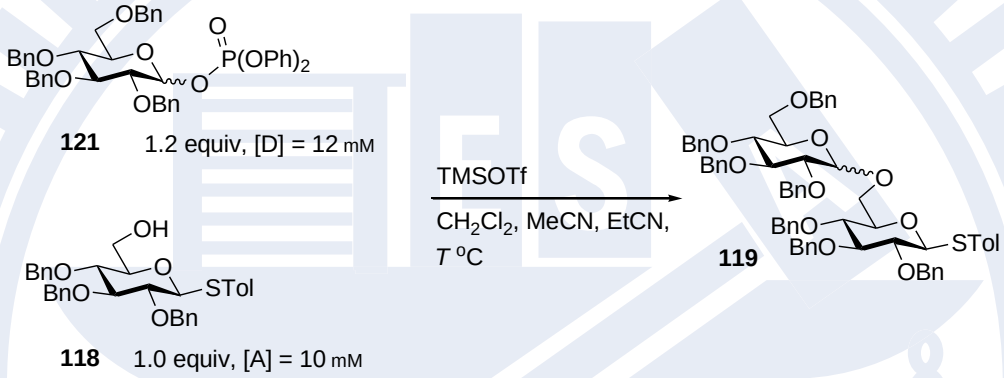
Compound	^{1}H NMR H-1 (ppm)	^{13}C NMR C-1 (ppm)	[Ref]
117	5.4	96, 101	--
120	5.2, 5.6	81, 78	56

此副產物需要分離除去，若不純化而直接進行一鍋化醣基化反應，則可能會造成更多的旁反應。此外，在文獻中記載：當使用活性較高的醣予體進行醣基化反應時，德國 Schmidt 教授曾經使用逆向加藥 (inverse addition) 的方法得到較好的產率，也就是說先將醣受體與活化試劑先在低溫時混合，然後再慢慢加入醣予體於反應中。但此方法在測試中並沒有對低濃度醣基化反應有明顯改善 (表 3.2，實驗 3)。[57]

3.2.1.3 醣基磷酸酯予體的測試

之後嘗試以醣基磷酸酯與硫糖進行正交醣基化反應測試，用全苄基保護的葡萄糖基二苯磷酸酯 **121** 為醣予體、6-羥基硫葡萄糖 **122** 為醣受體，三甲矽烷基三氟甲磺酸為活化試劑。(表 3.4)

表 3.4. 醣基磷酸酯對應一級羥基受體的測試



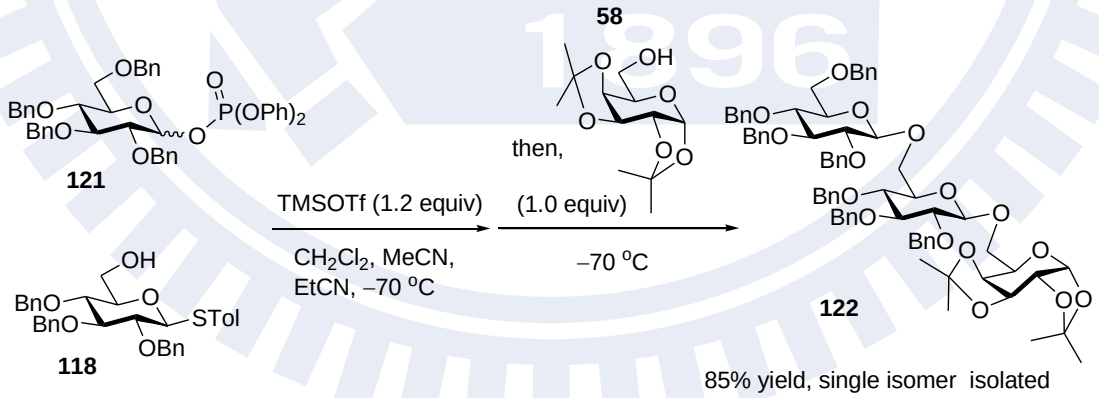
entry	TMSOTf (equiv)	T (°C)	time (h)	**119** (%), α : β
1	0.2	-70 to -40	6	30, 1 : >19
2	1.2	-70	1	82, 1 : >19
3	0.2 to 0.7	-70 to -40	5	56, 1 : 12 [a]
4	1.2	-10 to 0	0.5	70, 1.2 : 1 [b]

[a][A] = 30 mM，[b] 僅用 CH_2Cl_2 為反應溶劑，[A] = 30 mM。

起初嘗試在對應於醣予體 0.2 當量的活化劑下測試，但醣受體即使在升溫到 –40 °C 下也未能耗盡，若此時中止反應，分離純化後可以得到約 30%的預計產物；由 NMR 圖譜判斷有大於 95%的 β-鍵結產物 (表 3.4，實驗 1)。將此結果與文獻上的記載相較，推測磷酸酯

活化離去後形成的副產物，可能會與醣受體競爭、回攻醣基陽離子，若增加活化劑當量則可能避免這個效應；果不其然，當使用等同醣予體當量的活化劑進行醣基化反應，在−70 °C、一小時內即完成橋接，選擇性上也沒有明顯的劣化 (表 3.4，實驗 2)。

若將反應濃度提升為 30 mM，並減少活化試劑為 0.2 當量，反應在 TLC 的觀察上與實驗 1 無異，此時將活化試劑追加到 0.7 當量，則反應有明顯變化，此時中止反應可得到 56%的預計產物，而選擇性也有下降 (表 3.4，實驗 3)。若僅使用二氯甲烷作為反應溶劑、等同醣予體 **121** 當量的活化試劑、−10 °C 左右進行對照實驗，反應在一小時內結束，可得到 70% 的雙糖產物 **119**，端點鍵結選擇性如預期地降低 (表 3.4，實驗 4)。



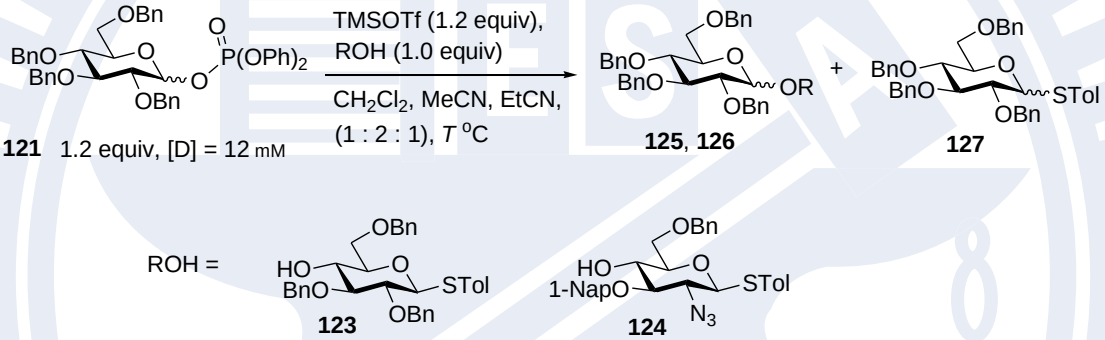
流程 3.21. 一鍋二步合成 β 1→6 鍵結三糖分子 **122**

在得到一級羥基醣受體的初步結果後，便開始嘗試一鍋二步的寡糖合成，首先在 −70 °C 下混合化合物 **121** 與醣受體 **118**，再加入以

等同醣予體 **121** 當量的活化試劑，待醣受體耗盡後再加入半乳糖受體 **58** 與 *N*-碘化丁二醯胺進行第二次醣基化反應。當反應完成後，中止反應並分離純化可得到 85% 的預計三糖產物 **122** (流程 3.21)，在核磁共振圖譜上判斷選擇性大於 95%。

此結果鼓勵我們進行二級羥基醣受體的試 (表 3.5)。

表 3.5. 對二級羥基糖受體的測試



entry	Acceptor (equiv)	T (°C)	time (h)	Product (%), α : β
1	**123**, 1.0	–70 to –40	8	**125**, 53, 1 : >10 [a]
2	**123**, 1.0	–70 to –50	6	**125**, 55, 1 : >10 [b]
3	**124**, 1.0	–70 to –50	6	**126**, 44, 1 : >10 [c]
4	**124**, 1.0	–70 to –60	8	**126**, 47, 1 : >10 [d]

[a] 得到 10% 非糖基轉移產物與 30% 糖受體 **123**，[b] 逆向加藥順序、回收 30%糖受體 **123**，[c] 回收 45%糖受體 **124**，[d] 逆向加藥順序、回收 30%糖受體 **124**。

以葡萄糖基二苯磷酸酯 **121** 為醣予體、4-羥基硫葡萄糖 **123** 為醣受體、以等同醣予體當量的三甲矽烷基三氟甲磺酸進行反應，即使溫

度上升到–40 °C，經過 8 小時後，醣受體並沒有耗盡。此時將反應中止分離純化，可回收到約 30% 的醣受體，53% 的預計雙糖 **125**，計算轉換產率 (conversion yield) 約有 80%，其中 β-鍵結產物占了 90%。但此反應也相對得到約 10% 非糖基轉移副產物 **127** (表 3.5，實驗 1)。接著嘗試逆向加藥，先在 –70 °C 下混合醣受體 **123** 與活化試劑預先約 15 分鐘後，再將醣予體 **121** 溶於二氯甲烷中注入反應 (50 mM，5 分鐘)，再緩緩升溫到 –50 °C。但如此操作並未得到更好的改善結果 (表 3.5，實驗 2)。

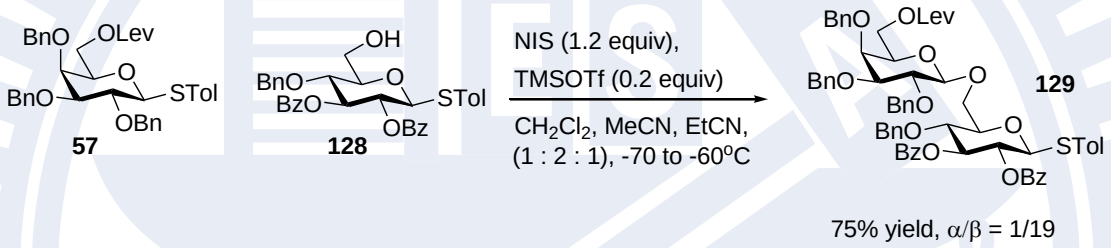
除了葡萄糖分子外，同時也嘗試以 4-羥基硫葡萄糖胺基 **124** 作為醣受體進行測試，但與葡萄糖 **123** 相似，在等同醣予體當量的活化試劑下，升高溫度並不能促使反應完成；若此時中止反應，在分離純化後可回收到 45% 的醣受體 **124** 與 44% 的雙糖產物 **126** (表 3.5，實驗 3)，由與對照實驗比較 NMR 圖譜得知此雙糖產物中約有 >90% 的 β-產物 (表 3.5，實驗 4)。

根據文獻記載，醣基磷酸酯醣予體多半與過量的二級羥基醣受體、1.5 倍於醣受體當量的活化試劑進行醣基化反應；此部分的實驗將朝著這個方向繼續進行研究，以期可以達到理想的效果。

3.2.2　化學選擇醣基化反應的測試

從過去實驗中發現：當以 disarmed 的保護基修飾羥基、降低醣予體的活性時，在低濃度醣基化反應中並沒有明顯的不良影響。因此引發利用醣基單元活性的不同進行化學選擇醣基化反應的興趣。

首先用硫半乳糖 **57** 作為醣予體，2,3-羥基以苯甲醯基保護的 6-羥基葡萄糖基對甲苯硫酚 **128** 為醣受體進行測試 (流程 3.22)。



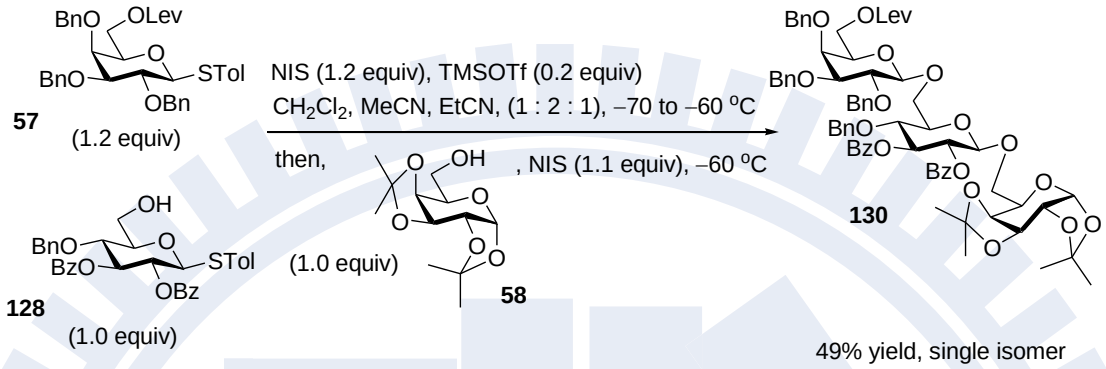
流程 3.22. 化學選擇性醣基化反應測試

在–70 °C 下中止反應時，反應並未完全完成 (回收到約 10% 醣予體)，得到 60% 的預計產物 **129**；當把反應溫度由–70 °C 升高到– 60 °C，可以得到較好的產率 (75%)，而 α/β-選擇性 = 1 : 19。

在得到初步的結果後，我們嘗試進行一鍋二步的反應活性基礎寡糖合成 (流程 3.23)。

首先將 1.2 當量的醣予體 **57** 與 1.0 當量的醣受體 **128** 溶於乙腈混合溶劑系統中，在–70 °C 下加入 1.2 當量的 *N*-碘化丁二醯胺與 0.2 當量的三甲矽基三氟甲磺酸之後緩緩升高溫度到– 60 °C，由 TLC 觀察

到醣受體耗盡後，再將 1 當量的半乳糖受體 **58** 與 1 當量 *N*-碘化丁二醯胺加入反應，在 $-60\ ^{o}C$ 進行第二次醣基化反應。



流程 3.23. 一鍋二步三聚糖合成測試

待反應完成後，以三乙胺終止並分離純化，可得到約 49%的預計三糖產物 **130**，就核磁共振圖譜中判斷應有大於 95% 的單一立體異構物 (流程 3.23)。

3.3 結論

由以上的實驗測試我們推測在腈類溶劑中進行正交醣基化反應或活性基礎化學選擇性醣基化反應是可行的，藉由初步的實驗結果，我們猜想將兩者搭配以合成多糖分子的策略應可能做到，但有關磷酸酯基的活化問題與是否更換其它離去基團，應需要更多的測試。

而反應活性基礎的醣基化反應上，尚有許多可以進行的實驗，相信低濃度醣基化反應能給予寡醣合成策略的設計多一些選擇。

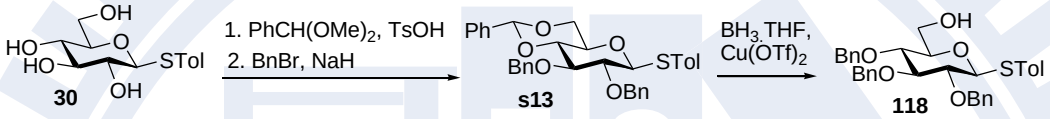
3.4 實驗部份

3.4.1 一般實驗方法敘述

請參考 1.4.1 的描述

3.4.2 化合物的合成方法與物理數據

For ***p*-Tolyl 2,3,4-tri-*O*-benzyl-1-β-D-thioglucopyranoside (118)**:



White solid (60% from **30**); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52–7.46 (m, 4H, ArH), 7.43–7.31 (m, 13H, ArH), 7.17 (d, *J* = 10.9 Hz, 2H ArH), 5.01–4.90 (m, 4H), 4.82 (d, *J* = 10.2 Hz, 1H), 4.72 (d, *J* = 10.2 Hz, 2H), 3.95 (dd, *J* = 2.1, 12 Hz, 1H), 3.82-3.744 (m, 2H), 3.65 (t, *J* = 9.3 Hz, 1H), 3.533 (t, *J* = 9.3 Hz, 1H), 3.47–3.42 (m, 1H), 2.36 (s, 3H, CH_3).

For ***p*-Tolyl 2,3,4-tri-*O*-benzyl-6-*O*-(2′,3′,4′,6′-tetra-*O*-benzyl-1-β-D-glucopyranosyl)-1-β-D-thioglucopyranoside (119):** Add TMSOTf (42 μL, 0.234 mmol) into a cooled mixture of glycosyl donor **121** (176 mg, 0.234 mmol) and glycosyl acceptor **118** (100 mg, 0.18 mmol) in a mixed solvent of CH_2Cl_2, CH_3CN, and EtCN (1:2:1 v/v, overall volume = 18 mL) at –70 ^{o}C under N_2. After completed, add Et_3N (0.05 mL, 0.4 mmol) into reaction. The quenched reaction crude is then extracted with CH_2Cl_2 (30 mL) and saturated aqueous $NaHCO_3$ (20 mL). The separated organic layer is dried over $MgSO_4$, filtered, concentrated and then purified through column chromatography (SiO_2 gel, hexane/AcOEt /CH_2Cl_2= 4:1:1 to 2:1:1) to afford the expected

glycosylated disaccharide **119** as white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51–7.49 (d, *J* = 10.9 Hz, 2H ArH), 7.47–7.16 (m, 35H, ArH), 7.08–7.05 (d, *J* = 11 Hz, 2H ArH), 5.02–4.83 (m, 8H), 4.79–4.56 (m, 8H), 4.47 (d, *J* = 7.8 Hz, 1H), 4.23 (d, *J* = 10.9 Hz, 1H), 3.81–3.62 (m, 8H), 3.57–3.46 (m, 4H), 2.35 (s, 3H, $ArCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.1, 138.9, 138.87, 138.63, 138.61, 138.56, 138.49, 137.85, 128.96, 128.84, 128.83, 128.80, 128.73, 128.63, 128.5, 128.39, 128.33, 128.28, 128.2, 128.1, 128.05, 127.99, 127.91, 88.1, 87.2, 85.2, 82.7, 81.2, 79.3, 78.4, 78.3, 76.2, 75.8, 75.4, 75.3, 75.26, 73.9, 69.4, 69.1, 21.1.

3,4,6,-Tri-*O*-benzyl-D-glucopyranosyl phosphate (121): Diphenyl chlorophosphate (0.42 mL, 2.0 mmol) was added to a stirred solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (0.9 g, 1.67 mmol) and DMAP (0.6 g, 5.0 mmol) in CH_2Cl_2 (10 mL) at 0 ^{o}C. After completed, the reaction was quenched with icy $NaHCO_3$ (10 mL), followed by stirring for 10 min. The mixture was poured into a two-layer mixture of CH_2Cl_2 (10 mL) and extracted with CH_2Cl_2 (30 mL×2). The organic extract was successively washed with saturated aqueous $NaHCO_3$ (30 mL) and brine (30 mL), and dried over anhydrous $MgSO_4$. Filtration and evaporation in vacuo furnished the crude product, which was purified by column chromatography (hexane/AcOEt = 3:1 with 3% Et_3N) to give diphenyl phosphate **121** (880 mg, 70%) as a white solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42–7.19 (m, 30H, ArH), 6.06 (dd, *J* = 3.2, 6.5 (*J*H-P) Hz, 1H, H-1), 4.99 (d, *J* = 10.9 Hz, 1H), 4.94–4.84 (m, 3H), 4.75 (d, *J* = 10.9 Hz, 1H), 4.67–4.50 (m, 3H), 4.01 (t, *J* = 8.7 Hz, 1H), 3.91–3.81 (m, 2H), 3.78–3.71 (m, 2H), 3.35 (dd, *J* = 1.6, 11.0 Hz, 1H); ^{13}C NMR (75 MHz,

$CDCl_3$): δ150.9, 138.9, 138.5, 138.3, 130.2, 130.9, 128.9, 128.7, 128.6, 128.5, 128.4, 128.38, 128.3, 128.27, 128.2, 230.9, 120.93, 120.7, 120.65, 97.55, 97.47, 81.5, 79.6, 79.5, 77.0, 76.2, 75.7, 73.9, 73.5, 73.2, 68.0.

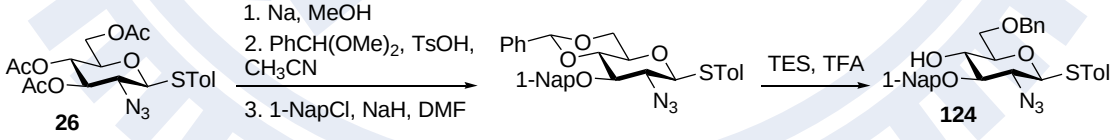
1,2;3,4-di-*O*-isopropylidinyl-6-*O*-[2',3',4'-tri-*O*-benzyl-1-β-D-glucopyranosyl-6'-*O*-(2",3",4",6"-tetra-*O*-benzyl-1-β-D-glucopyranosyl)-1-β-D-galactopyranoside (122): Add TMSOTf (46μL, 0.257 mmol) into a cooled mixture of glycosyl donor **121** (194 mg, 0.257 mmol) and glycosyl acceptor **118** (110 mg, 0.198 mmol) in a mixed solvent of CH_2Cl_2, CH_3CN, and EtCN (1:2:1 v/v, overall volume = 20 mL) at −70 ^oC under N_2. After completed, add glycosyl accepter **58** (51 mg, 0.198 mmol, dissolved in 1 mL CH_2Cl_2) and NIS (47 mg, 0.208 mmol) into reaction at −70 ^oC. After completion juged from TLC, add Et_3N (0.05 mL, 0.4 mmol) into reaction. The quenched reaction crude is then broughted to rt. Saturated aqueous $NaHCO_3$ (20 mL) and a small lumps of $Na_2S_2O_3$ are added into the crude. The vigorously stirring crude is then dried over $MgSO_4$, filtered, concentrated, and purified by column chromatography (SiO_2 gel, hexane/AcOEt /CH_2Cl_2= 6:1:1 to 2:1:1) to afford the expected glycosylated disaccharide **122** as white solid; ^1H NMR (300 MHz, $CDCl_3$): δ7.56–7.29 (m, 35H, ArH), 5.65 (d, J = 5.1 Hz, 1H), 5.2–5.02 (m, 5H), 4.94–4.82 (m, 6H), 4.74–4.58 (m, 6H), 4.57–4.52 (m, 2H), 4.39 (dd, J = 2.4, 4.8 Hz, 1H), 4.33 (d, J = 10.2 Hz, 1H), 4.21 (dd, J = 3, 10.5 Hz, 1H), 4.15–4.09 (m, 2H), 3.83–3.54 (m, 12H), 1.64 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 1.53 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ139.2, 139.1, 138.9, 138.7, 138.67, 129.2, 128.9, 128.8, 128.7, 128.69, 12836, 128.46, 128.4, 128.3, 128.2, 128.1,

1280, 127.9, 109.8, 109.0, 104.9, 104.4, 96.8, 85.3, 84.9, 82.3, 82.0, 78.5, 78.3, 76.2, 76.1, 75.5, 75.4, 75.3, 75.2, 75.1, 74.7, 74.0, 71.8, 71.2, 70.9, 70.5, 69.4, 69.2, 67.9, 26.6, 26.5, 25.5, 24.8.

_p_-Tolyl 2,3,4-tri-_O_-benzyl-6-_O_-(2′,3′,4′,6′-tetra-_O_-benzyl-1-β-D-glucopyranosyl)-1-β-D-thioglucopyranoside (123):

white solid (58% from **30**) ; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58–7.28 (m, 17H, ArH), 7.15–7.12 (d, J = 9.8 Hz, 2H, ArH), 5.03-4.98 (m, 2H), 4.87 (d, J = 11.4 Hz, 1H), 4.83 (d, J = 10.2 Hz, 1H), 4.72 (d, J = 9.3 Hz, 1H, H-1), 4.68 (d, J = 12 Hz, 1H), 4.62 (d, J = 11.7 Hz, 1H), 3.90–3.80 (m, 2H), 3.73 (dt, J = 1.8, 10.2 Hz, 1H), 3.63 (d, J = 8.7 Hz, 1H), 3.59-3.50 (m, 2H), 2.77 (brs, 1H, OH), 2.39 (s, 3H, CH_3).

_p_-Tolyl 6-_O_-benzyl-2-azido-2-deoxy-3-_O_-(1-naphthylmethyl)-1-β-D-thioglucopyranoside (124):



Colourless oil (55% from **26**); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20 (d, J = 8.4 Hz, 1H, ArH), 7.84 (t, J = 7.8 Hz, 2H, ArH), 7.58–7.41 (m, 4H, ArH), 7.35–7.30 (m, 5H), 7.06 (d, J = 7 Hz, 2H, ArH), 5.33 (d, J = 11.4 Hz, 1H), 5.27 (d, J = 12 Hz, 1H), 4.59 (d, J = 12 Hz, 1H), 4353 (d, J = 12 Hz, 1H), 4.39 (d, J = 9.6 Hz, 1H), 3.79–3.68 (m, 2H), 3.59 (t, J = 9.3 Hz, 1H), 3.46–3.39 (m, 2H), 3.29 (t, J = 9.9 Hz, 1H, H-2), 2.60 (brs, H, OH), 2.34

(s, 3H, CH_3).

***p*-Tolyl 2,3,6-tri-*O*-benzyl-4-*O*-(2′,3′,4′,6′-tetra-*O*-benzyl-1-β-D-glucopyranosyl)-1-β-D-thioglucopyranoside (125):**

Add TMSOTf (47 μL, 0.26 mmol) into a cooled mixture of glycosyl donor **121** (195 mg, 0.26 mmol) and glycosyl acceptor **123** (120 mg, 0.22 mmol) in a mixed solvent of CH_2Cl_2, CH_3CN, and EtCN (1:2:1 v/v, overall volume = 22 mL) at −70 ^oC under N_2. After completed, add Et_3N (0.1 mL, 0.8 mmol) into reaction. The quenched reaction crude is then extracted with CH_2Cl_2 (30 mL) and saturated aqueous $NaHCO_3$ (20 mL). The separated organic layer is dried over $MgSO_4$, filtered, concentrated and then purified through column chromatography (SiO_2 gel, hexane/AcOEt /CH_2Cl_2 = 6:1:1 to 2:1:1) to afford the expected glycosylated disaccharide **125** as white solid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.52–7.49 (d, *J* = 10.9 Hz, 2H ArH), 7.41–7.30 (m, 29H, ArH), 7.25–7.19 (m, 6H, ArH), 7.05 (d, *J* = 11 Hz, 2H ArH), 5.17 (d, *J* = 11.1 Hz, 1H), 4.93 (d, *J* = 10.8 Hz, 1H), 4.86–4.72 (m, 7H), 4.62–4.49 (m, 5H), 4.43 (s, 1H), 4.07 (t, *J* = 9.3 Hz, 1H), 3.89 (dd, *J* = 3.9, 11.1 Hz, 1H), 3.78 (d, *J* = 11.4 Hz, 1H), 3.72–3.57 (m, 7H), 3.49–3.36 (m, 4H), 2.34 (s, 3H, $ArCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.6, 138.99, 138.85, 138.8, 138.75, 138.7, 138.6, 138.1, 128.8, 128.77, 128.7, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.05, 127.9, 127.8, 127.7, 102.96, 88.0, 85.5, 85.4, 83.2, 80.5, 79.7, 78.4, 77.7, 76.8, 76.1, 75.8, 75.4, 75.3, 73.7, 73.6, 69.3, 68.6, 21.6.

***p*-Tolyl 6-*O*-benzyl-2-azido-2-deoxy-3-*O*-(1-naphthylmethyl)-4-*O*-(2′,3′,4′,6′-tetra-*O*-benzyl-1-β-D-glucopyranosyl)-1-β-D-thioglucopyranoside (126):**

Add TMSOTf (44 μL, 0.24 mmol) into a cooled mixture of glycosyl

donor **121** (184 mg, 0.24 mmol) and glycosyl acceptor **124** (110 mg, 0.20 mmol) in a mixed solvent of CH_2Cl_2, CH_3CN, and EtCN (1:2:1 v/v, overall volume = 20 mL) at −70 °C under N_2. After completed, add Et_3N (0.1 mL, 0.8 mmol) into reaction. The quenched reaction crude is then extracted with CH_2Cl_2 (30 mL) and saturated aqueous $NaHCO_3$ (20 mL). The separated organic layer is dried over $MgSO_4$, filtered, concentrated and then purified through column chromatography (SiO_2 gel, hexane/AcOEt /CH_2Cl_2 = 6:1:1 to 2:1:1) to afford the expected glycosylated disaccharide **126** as white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.22 (d, *J* = 8.1 Hz, 1H, ArH), 7.88 (d, *J* = 7.5 Hz, 1H, ArH), 7.81 (d, *J* = 8.1 Hz, 1H, ArH), 7.64–7.51 (m, 5H, ArH), 7.42–7.30 (m, 26H, ArH), 7.24–7.14 (m, 8H, ArH), 7.09 (d, *J* = 7.8 Hz, 2H, ArH), 5.62 (d, *J* = 11.4 Hz, 1H), 5.26 (d, *J* = 11.7 Hz, 1H), 4.98 (d, *J* = 10.8 Hz, 1H), 4.91–4.52 (m, 5H), 5.67–4.45 (m, 6H), 4.37 (d, *J* = 10.2 Hz, 1H), 4.30 (d, *J* = 12 Hz, 1H), 4.24 (d, *J* = 12 Hz, 1H), 4.08 (t, *J* = 9.3 Hz, 1H), 3.96 (dd, *J* = 3.6, 11.4 Hz, 1H), 3.79 (d, *J* = 11.1 Hz, 1H), 3.73–3.38 (m, 10H), 3.30 (t, *J* = 9.9 Hz, 1H), 2.35 (s, 3H, $ArCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.1, 139.0, 138.8 ,138.7, 138.66, 138.58, 134.7, 134.5, 134.1, 132.2, 130.2, 128.8, 128.7, 128.6, 128.4, 128.35, 128.3, 128.2, 128.1, 128.05, 128.0, 127.8, 127.77, 127.4, 127.2, 126.6, 126.0, 125.6, 103.0, 86.7, 85.4, 83.2, 83.1, 79.9, 78.4, 76.6, 76.1, 75.6, 75.5, 75.3, 73.7, 73.6, 73.5, 69.3, 68.3, 21.6.

***p*-Tolyl 2,3-di-*O*-benzoyl-4-*O*-benzyl-6-*O*-(2′,3′,4′-tri-*O*-benzyl-6′-*O*-levulinoyl-1-β-D-galactopyranosyl)-1-β-D-thioglucopyranoside (129):** Add NIS (47 mg, 0.21 mmol) and TMSOTf (7 μL, 0.04 mmol) into a cooled mixture of glycosyl donor **57** (137 mg, 0.21 mmol) and glycosyl acceptor **128** (100 mg, 0.17 mmol) in a mixed solvent of CH_2Cl_2, CH_3CN, and EtCN (1:2:1 v/v, overall volume = 17 mL) at −70 °C under N_2. The reaction temperature is brought to −60 °C for 30 min. Upon completed,

add Et_3N (0.08, 0.6 mmol) into reaction. The crude is then added saturated $NaHCO_{3(aq)}$ (0.2 mL) and a small lump of $Na_2S_2O_{3(s)}$. After the dark color of crude ceased, the reaction mixture is then droed over $MgSO_4$, filtered, concentrated, and purified by column chromotagraphy (SiO_2 gel, hexane/AcOEt /CH_2Cl_2 = 6:1:1 to 2:1:1) to afford the expected glycosylated disaccharide **129** as colourless foam. ^{1}H NMR (300 MHz, $CDCl_3$): δ8.05 (d, *J* = 8.1 Hz, 1H, ArH), 7.93 (d, *J* = 7.8 Hz, 1H, ArH), 7.57–7.50 (m, 2H, ArH), 7.47–7.30 (m, 22H, ArH), 7.19–7.16 (m, 3H), 7.09 (d, *J* = 7.8 Hz, 2H, ArH), 5.74 (t, *J* = 9 Hz, 1H), 5.35 (t, *J* = 9 Hz, 1H), 5.04 (t, *J* = 11.7 Hz, 1H), 4.96–4.82 (m, 5H), 4.75 (d, *J* = 11.7 Hz, 1H), 3.67 (d, *J* = 7.8 Hz, 1H), 3.93 (d, *J* = 7.8 Hz, 1H), 3.89–3.75 (m, 5H), 3.59–3.50 (m, 2H), 2.76–2.72 (m, 2H, Lev-CH_2), 2.53–2.49 (m, 2H, Lev-CH_2), 2.46 (s, 3H, Lev-CH_3), 2.34 (s, 3H, ArCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ206.5, 172.8, 166.1, 165.7, 139.1, 138.8, 138.7, 138.5, 137.8, 133.6, 133.57, 130.3, 130.2, 130.1, 129.9, 129.8, 128.9, 128.8, 128.7, 128.5, 128.3, 128.2, 128.1, 127.9, 104.7, 86.2, 82.6, 79.7, 79.4, 76.7, 75.7, 75.1, 74.8, 73.7, 73.5, 72.5, 71.2, 68.9, 63.6, 38.3, 30.3, 28.2, 21.5.

1,2;3,4-di-*O*-isopropylidinyl-6-*O*-[4´-*O*-benzyl-2´,3´-di-*O*-benzoyl--1-β-D-glucopyranosyl-6'-*O*-(2´´,3´´,4´´-tri-*O*-benzyl,6´´-*O*- levulinoyl -1-β-D-galactopyranosyl)-1-β-D-galactopyranoside (130): Add NIS (57 mg, 0.25 mmol) and TMSOTf (9 μL, 0.05 mmol) into a cooled mixture of glycosyl donor **57** (161 mg, 0.25 mmol) and glycosyl acceptor **128** (120 mg, 0.21 mmol) in a mixed solvent of CH_2Cl_2, CH_3CN, and EtCN (1:2:1 v/v, overall volume = 21 mL) at –70 ^{o}C under N_2. The reaction temperature is brought to –60 ^{o}C for 30 min. Upon completed, add another NIS (57 mg, 0.25 mmol) and glycosyl aceeptor **58** (53 mg, 0.21 mmol) into reaction. After completed, add Et_3N (0.08, 0.6 mmol) into

reaction. The crude is then added saturated $NaHCO_{3(aq)}$ (0.2 mL) and a small lump of $Na_2S_2O_{3(s)}$. After the dark color of crude ceased, the reaction mixture is then droed over $MgSO_4$, filtered, concentrated, and purified by column chromotagraphy (SiO_2 gel, hexane/AcOEt /CH_2Cl_2 = 6:1:1 to 2:1:1) to afford the expected glycosylated trisaccharide **130** as colourless foam; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01–7.88 (m, 4H, ArH), 7.53–7.29 (d, *J* = 5.1 Hz, 1H), 7.19–7.14 (m, 3H, ArH), 7.09–7.06 (m, 2H, ArH), 5.68 (t, *J* = 8.1 Hz, 1H), 5.38 (m, 2H), 5.04 (d, *J* = 10.2 Hz, 1H), 5.02 (d, *J* = 10.2 Hz, 1H), 4.91–4.77 (m, 4H), 4.68 (d, *J* = 11.4 Hz, 1H), 4.53–4.39 (m, 4H), 4.30-4.25 (m, 2H), 4.20-4.16 (m, 2H), 4.06 (dd, *J* = 1.5, 8.1 Hz, 1H), 3.99–3.91 (m, 2H), 3.87-3.74 (m, 6H), 3.57–3.53 (m, 2H), 2.74–2.72 (m, 2H, Lev-CH_2), 2.70–2.52 (m, 2H, Lev-CH_2), 2.42 (s, 3H, Lev-CH_3), 1.37 (s, 3H, CH_3), 1.22 (s, 3H, CH_3), 1.20 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.4, 172.4, 165.6, 165.3, 138.7, 138.3, 138.25, 137.4, 133.0, 132.8, 129.9, 129.7, 129.5, 129.4, 128.4, 128.3, 128.27, 128.2, 128.18, 128.1, 127.8, 127.64, 127.60, 127.5, 127.4, 109.4, 108.3, 104.0, 101.2, 96.4, 82.2, 78.9, 77.2, 75.2, 75.1, 74.7, 74.5, 74.3, 73.2, 73.0, 72.0, 70.7, 70.4, 68.3, 68.0, 67.1, 63.1, 37.8, 29.8, 27.7, 25.8, 25.7, 24.8, 24.1.

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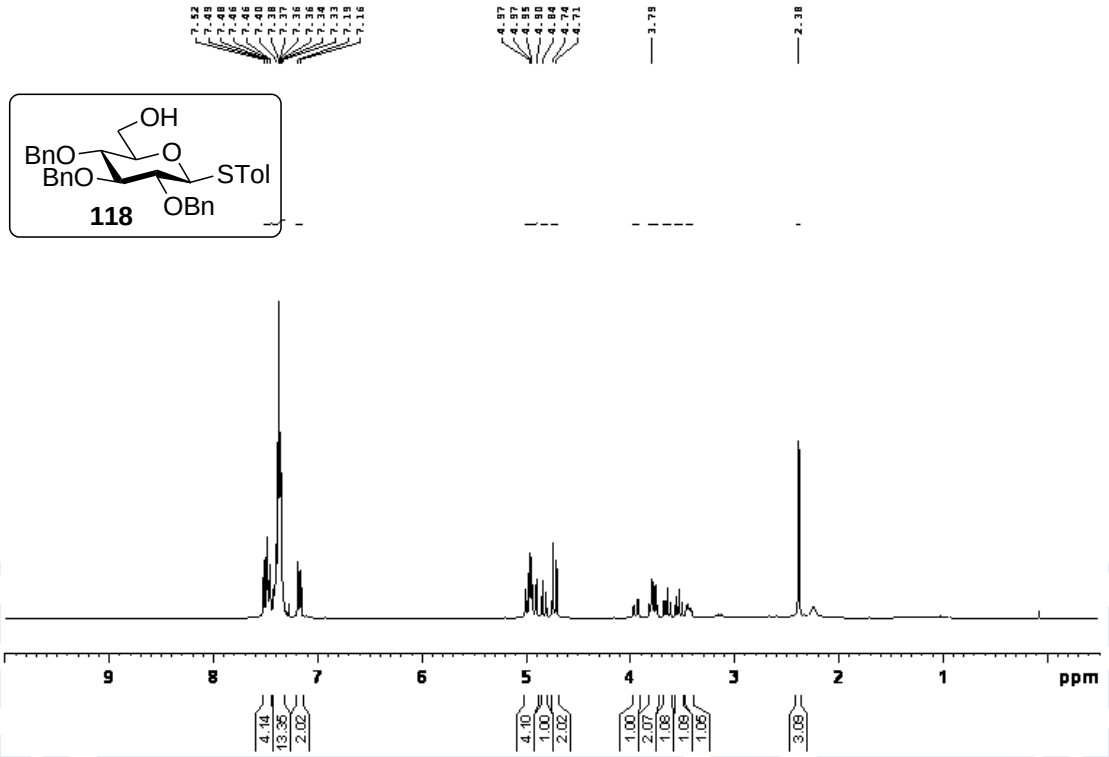

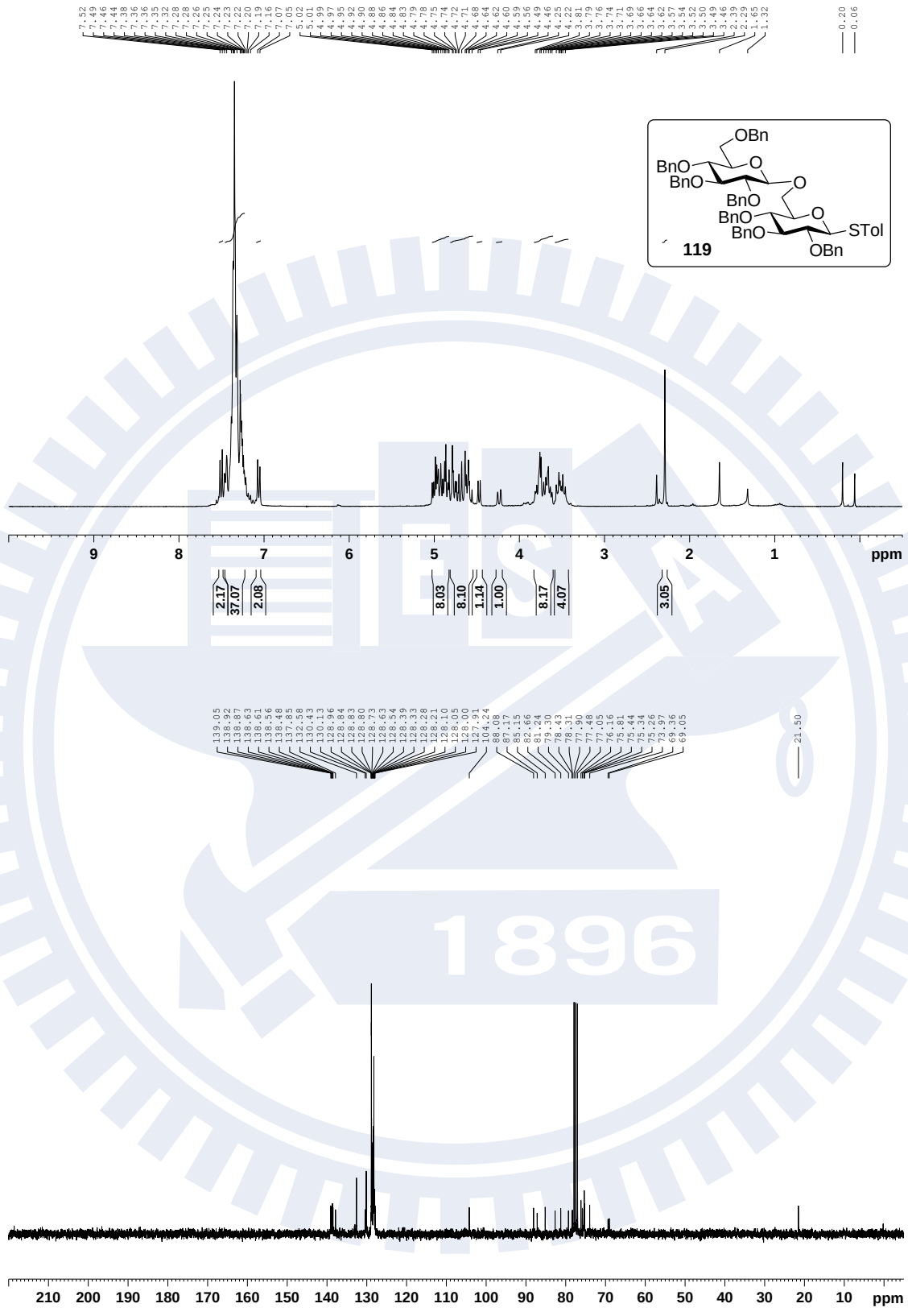
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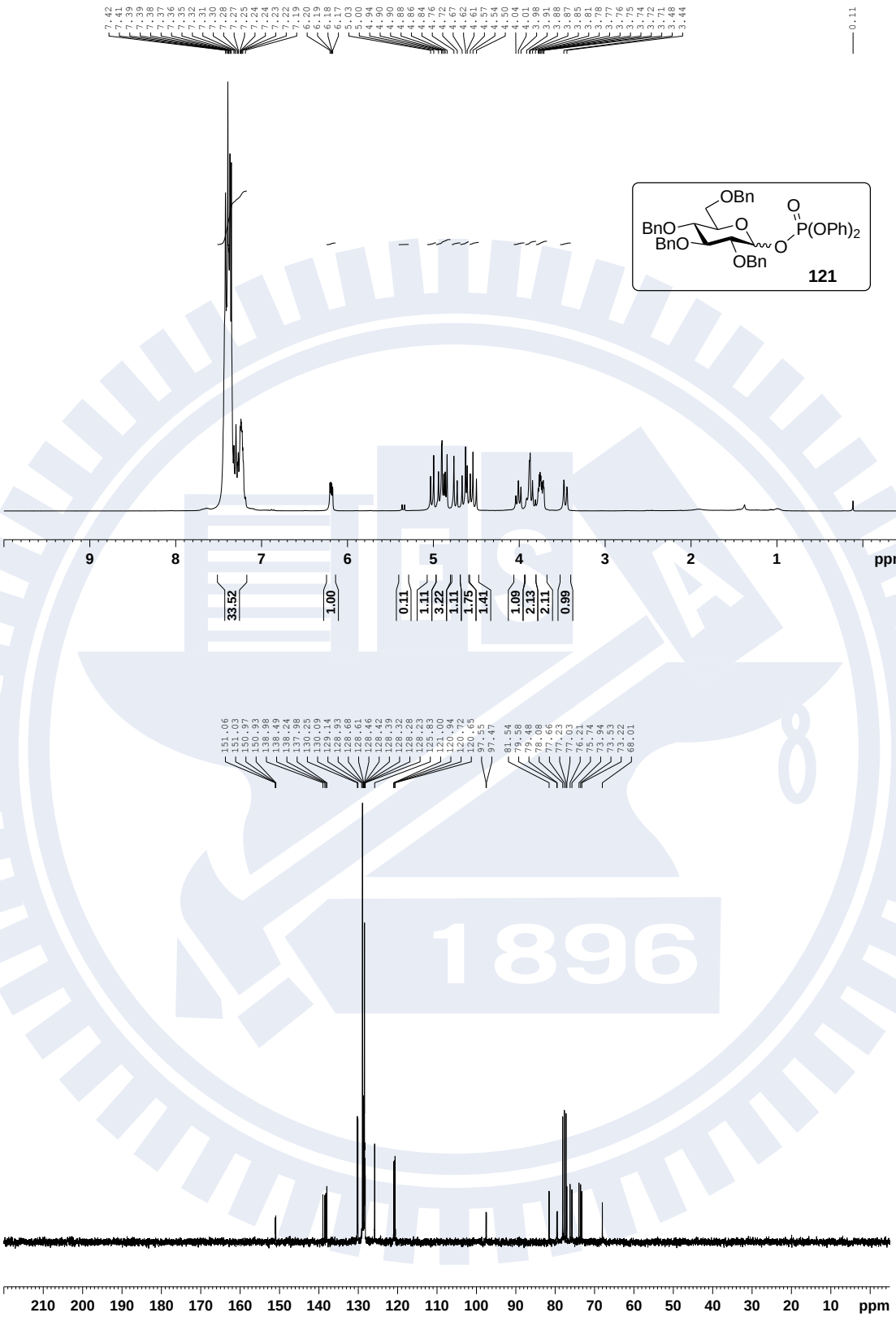
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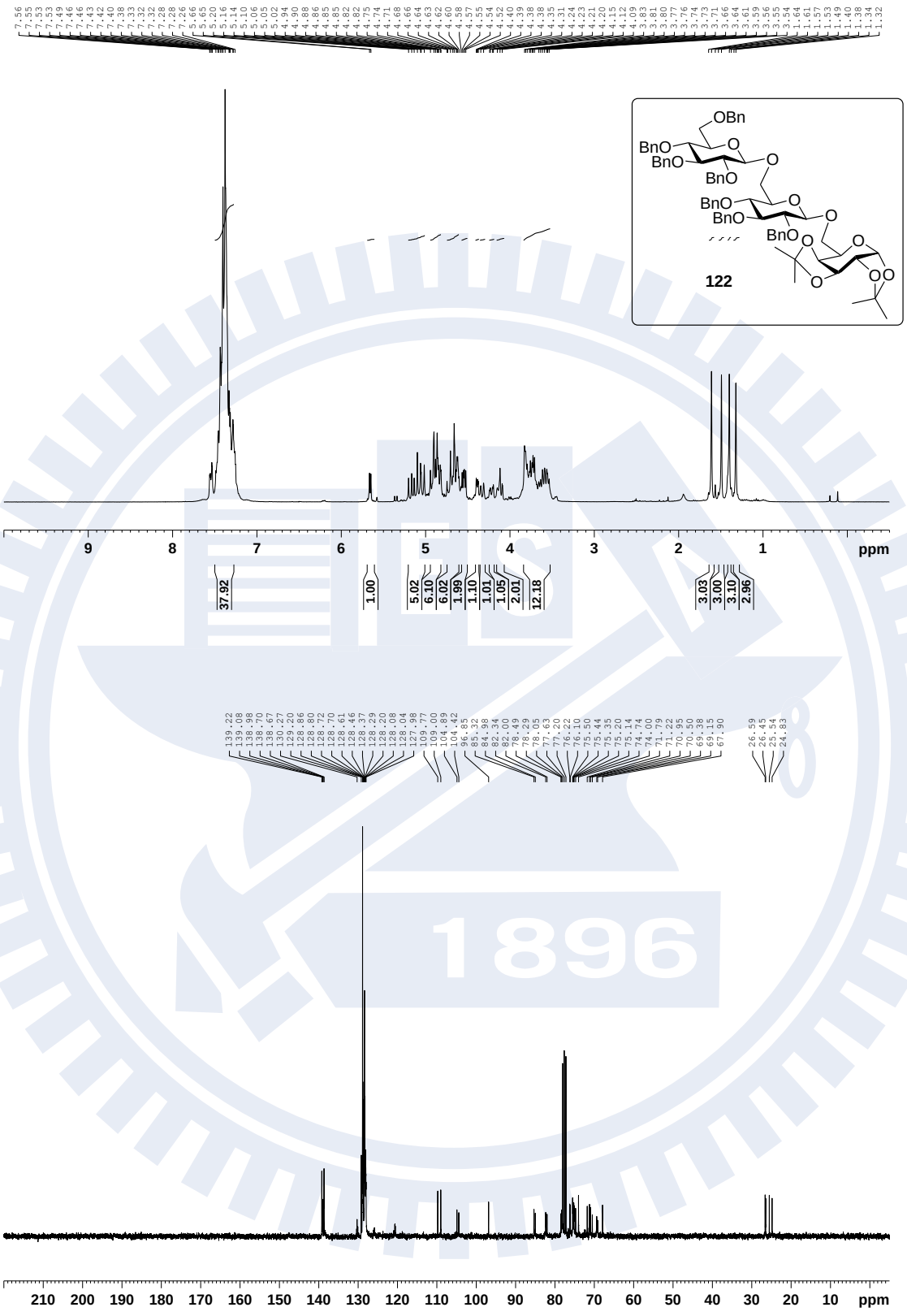
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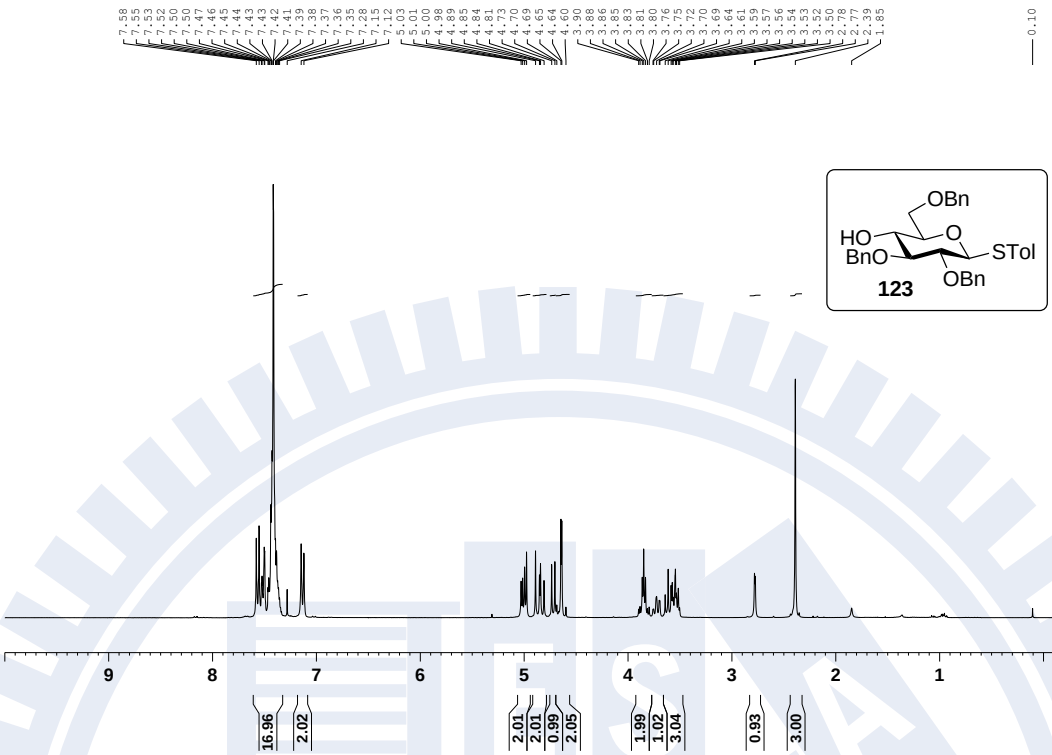
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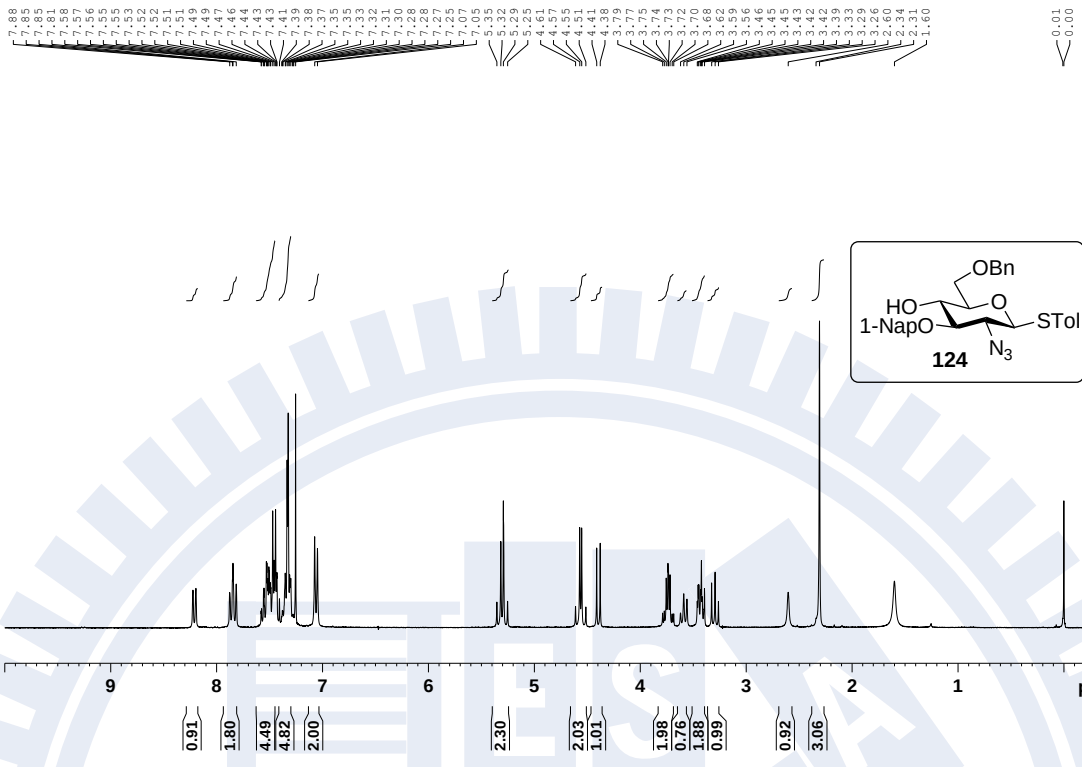
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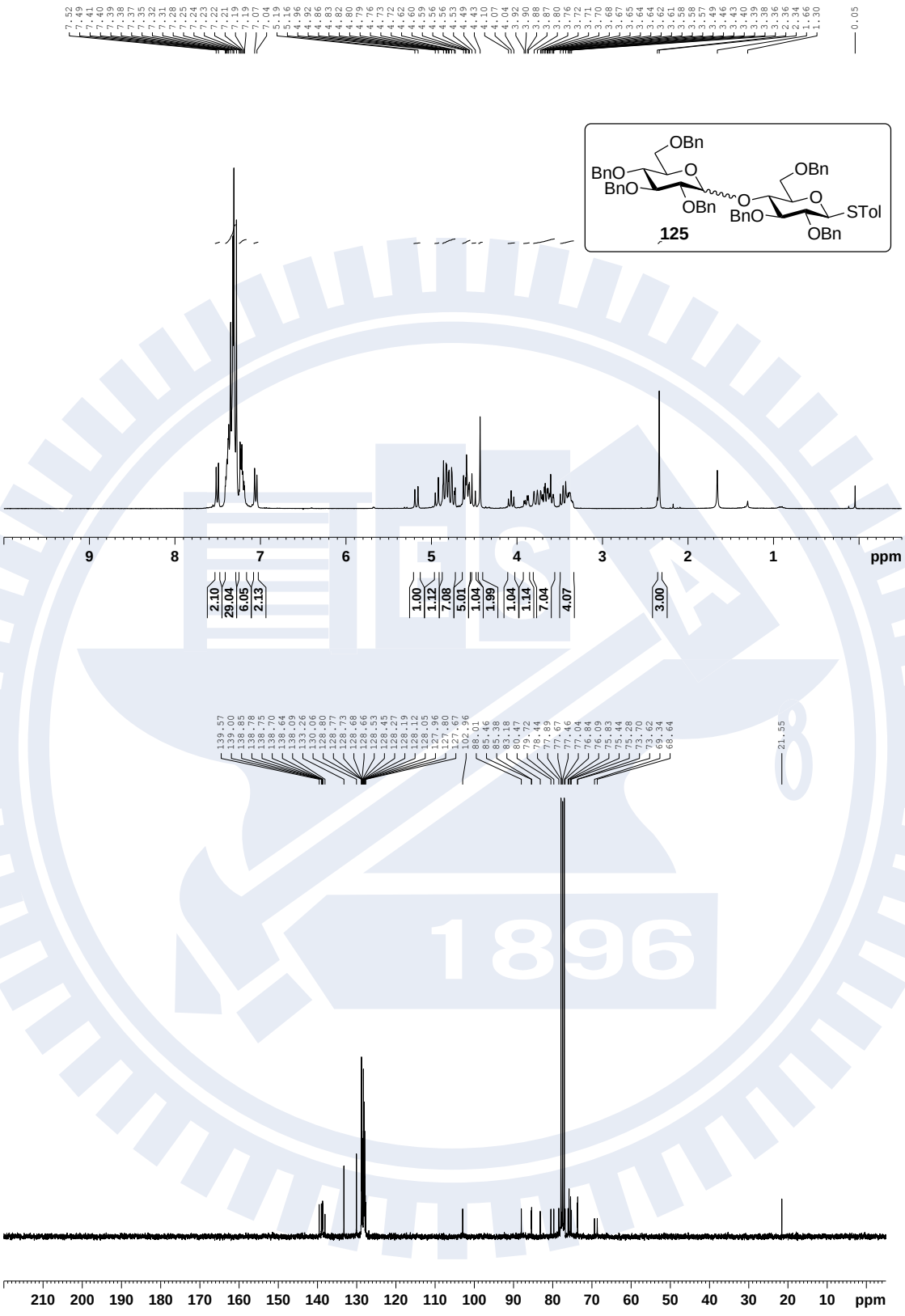
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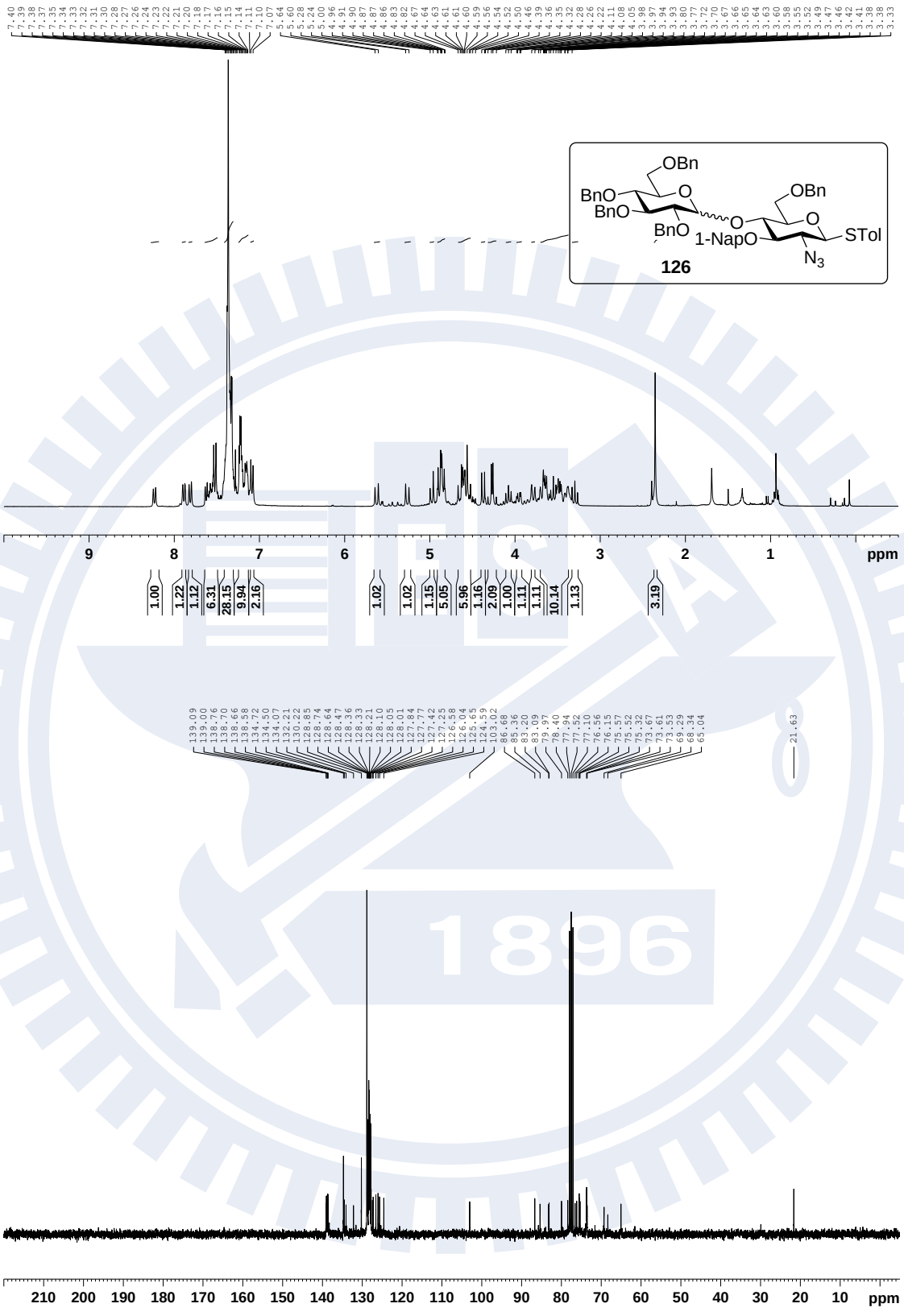
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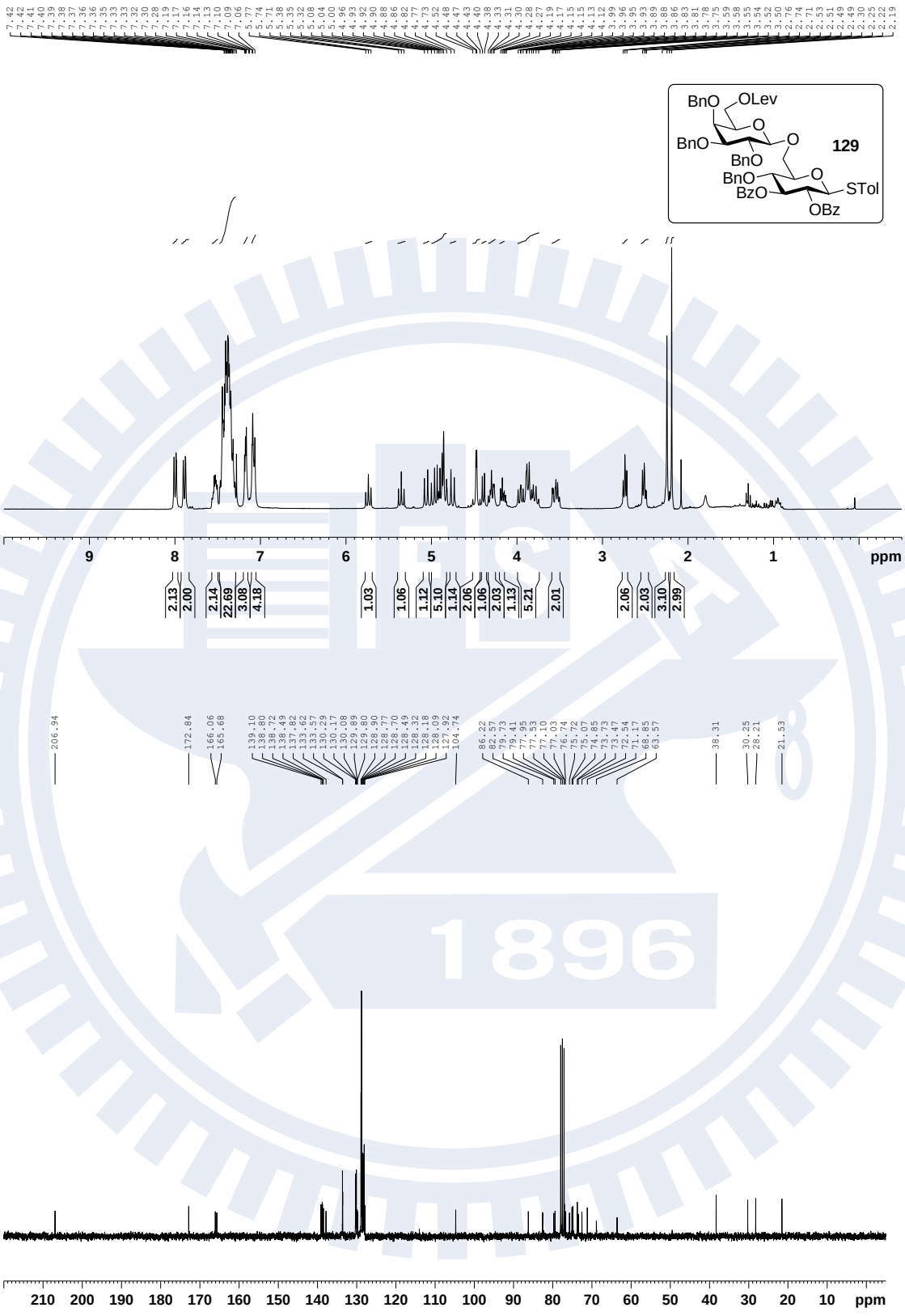
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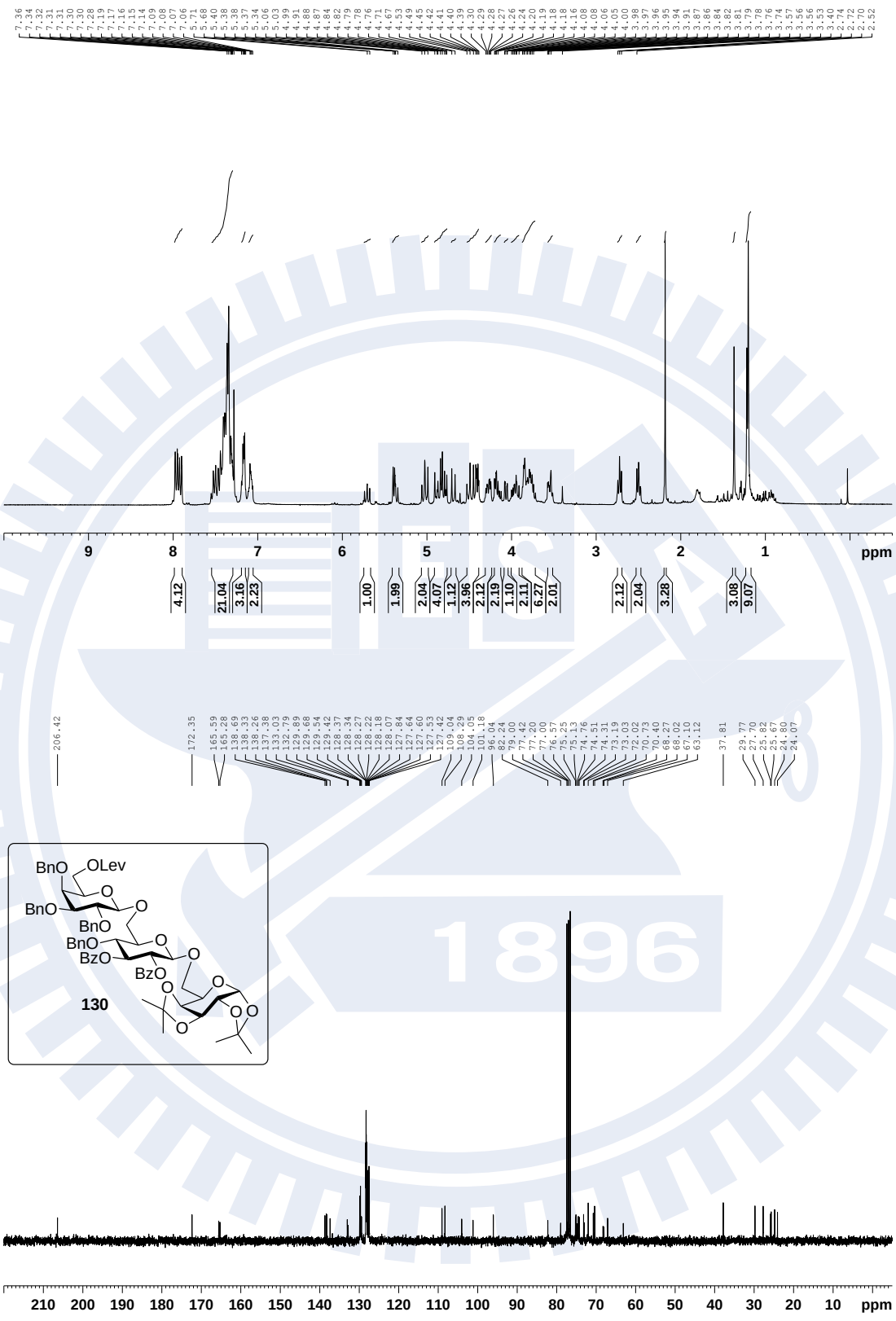
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Tetrahedron Letters 50 (2009) 333–336

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Diastereoselective electrophilic α-amination of camphor N^1-acyl N^2-phenylpyrazolidinones: the metal enolate-dependent synthesis of two possible hydrazide diastereomers

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ARTICLE INFO

Article history:
Received 10 September 2008
Revised 30 October 2008
Accepted 4 November 2008
Available online 7 November 2008

Keywords:
Amination
Reversal of stereoselectivity
Chiral auxiliary

ABSTRACT

Complementary approaches under enolate amination reactions for the synthesis of both α-hydrazidoacyl diastereomers have been achieved. Both isomers are obtained with high to excellent chemical yields and high stereoselectivities (up to >95:5 dr) when aryl-substituted camphor N^1-acylN^2-phenylpyrazolidinone was treated with potassium hexamethyldisilylamide (KHMDS) and lithium hexamethyldisilylamide (LHMDS), respectively, followed by the addition of di-*tert*-butyl azodicarboxylate. The nondestructive removal of the chiral auxiliary, which can be carried out under mild condition, afforded the hydrazido alcohol with high enantiomeric ratio. The facial stereoselectivity and stereochemical course of the reactions are discussed.

The electrophilic α-amination of carbonyl compounds constitutes one of the fundamental challenges in modern organic synthesis.[1] Several asymmetric variants have been developed in recent years for the construction of the nitrogenous molecules by using azodicarboxylates as the nitrogen source. The resulting hydrazine derivatives serve as versatile precursors for the preparation of α-amino acids, α-hydrazino acids, and other important synthetic intermediates.[2] The metal-based catalytic enantioselective α-amination of *N*-acyloxazolidinones,[3] α-keto esters,[4] and β-keto esters[5] provides an easy entry to optically active α-amino acids and α-amino-β-hydroxy esters with high to excellent enantioselectivities. More recently, the organocatalytic electrophilic α-amination of unmodified aldehydes, α-cyanoacetate, and β-keto esters has also been reported.[6] On the other hand, only limited examples of diastereoselective electrophilic amination of metal enolates have been documented.[7] The metal enolate-based methodology for the carbon–nitrogen bond formation remained unexplored. Further, from a practical synthetic point of view, the preparation of both stereoisomers from the same chiral source has many synthetic advantages and has received considerable attention in recent years.[8] The stereochemical outcomes can be influenced by several factors such as solvent, the structure of metal-substrate complex, and reagent components employed. We have recently developed a novel camphor-derived auxiliary, camphor *N*-phenyl pyrazolidinone, that has proved to be effective in asymmetric synthesis.[8i] We wish to report herein that electrophilic amination of chiral

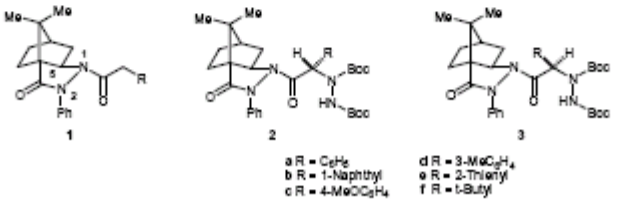

Figure 1.

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doi:10.1016/j.tetlet.2008.11.008

N^1-acyl N^2-phenylpyrazolidinones to give α-aminated derivatives with excellent chemical yield and high diastereoselectivity in the presence of di-*tert*-butyl azodicarboxylate. In addition, the stereochemical course of the α-amination is metal enolate dependent. The facial stereoselectivity and the stereochemical course of the reactions are discussed.

The starting camphor N^1-acyl N^2-phenylpyrazolidinones 1a–f can be readily prepared from camphor *N*-phenylpyrazolidinone following standard acylation conditions (Fig. 1). The phenylacetyl-substituted pyrazolidinone 1a was chosen as a probe substrate, and di-*tert*-butyl azodicarboxylate was used as the electrophilic nitrogen source. The desired hydrazides were obtained with low to moderate chemical yields by treatment of 1a, when LDA, *n*-BuLi, and KO^{t}Bu were used followed by the addition of di-*tert*-butyl azodicarboxylate at −78 °C (data not shown). A reasonable chemical yield (53%) was achieved, when 1a was treated with KHMDS in CH_2Cl_2 at −78 °C followed by the addition of an electrophile (Table 1, entry 1). No reaction occurred when the reaction was carried out in Et_2O (entry 2). The chemical yield was improved to 91%, when the same reaction was carried out in THF (entry 3). We were not able to interpret the ^{1}H NMR spectrum of the crude products for the determination of stereoselectivity. This is due to the presence of isomer and the tautomeric forms caused by the restricted rotation about the Boc groups in the hydrazide, which has been documented in the literature.[9] The spectrum of a purified hydrazide 2a is interpretable, although with the presence of tautomers. A careful analysis of ^{1}H NMR spectrum of hydrazide 2a indicated the characteristic C-5 methine proton (this nomenclature system) that appears at 3.49 ppm, while the carbonyl α-methine proton located at 6.01 ppm. However, two NH proton signals appear at 6.76 and 6.49 ppm, respectively, in a ratio of 1.9:1.0. High performance liquid chromatography (HPLC) studies indicated only one diastereomer in the purified product. A 2D NMR experiment (HMQC) was carried out, and the results indicate that both signals appearing at 6.76 and 6.49 ppm come from the same NH proton. In addition, variable-temperature studies of ^{1}H NMR spectra demonstrated the existence of structural conformers in hydrazide 2a. An equilibrium mixture of at least two structural conformers of 2a in $CDCl_3$ was proposed.[10] The newly generated stereogenic carbon center in the major diastereomer 2a was assigned as an *S* configuration by single crystallographic X-ray analysis.

In addition to the steric hindrance, the tautomeric equilibration of 2a in solution may also associate with the hydrogen bonds and the preferential disposition of the carbonyl dipoles. A close look of the X-ray crystallographic ORTEP structure of 2a shows that the NH forms hydrogen bonds with the nearby carbonyl groups (Fig. 2).

To our surprise, the newly generated stereogenic center of the aminated adduct was reversed, when LHMDS was used. Treatment of 1a with LHMDS at −78 °C gave 3a as the major diastereomer with 90% de (entry 4). The distinct characteristics of ^{1}H NMR spectrum in 3a are worth noting. In addition to the two signals of the hydrazide NH proton at 6.68 and 6.49 ppm, the C-5 methine proton also appeared as a set of two signals at 4.41 and 4.31 ppm, respectively, in the same ratio of 1.8:1.0, similar to that of NH signals. The significant chemical shift difference of C-5 proton signal in ^{1}H NMR spectrum between hydrazides 2a (3.49 ppm) and 3a (4.41 and 4.31 ppm) can be attributed to the diamagnetic anisotropy effect of the phenyl substituent. *This represents, to the best of our knowledge, the first example of a complementary electrophilic α-amination reaction for the synthesis of both diastereomeric hydrazides by simply changing the base.*[11] Having developed reaction conditions that afford complementary diastereomers in the amination reactions, we sought to test the scope and feasibility of the auxiliary architecture.

Table 1
Diastereoselective amination of camphor N^1-acyl N^2-phenylpyrazolidinones 1a–e[a]

Entry	R =	Solvent	Base	Yield (%)[b]	Dr (2:3)[c]
1	(1a) C_6H_5	CH_2Cl_2	KHMDS	53	87:13
2	(1a) C_6H_5	Et_2O	KHMDS	0	—
3	(1a) C_6H_5	THF	KHMDS	91	93[d]:07
4	(1a) C_6H_5	THF	LHMDS	94	05:95
5	(1a) C_6H_5	THF	Mixed bases[e]	92	77:23
6	(1a) C_6H_5	THF	Mixed bases[f]	90	44:56
7	(1b) 1-Naphthyl	THF	KHMDS	90	93:07
8	(1b) 1-Naphthyl	THF	LHMDS	91	05:95
9	(1c) 4-$MeOC_6H_4$	THF	KHMDS	90	95:05
10	(1c) 4-$MeOC_6H_4$	THF	LHMDS	88	08:92
11	(1d) 3-MeC_6H_4	THF	KHMDS	75	95:05
12	(1d) 3-MeC_6H_4	THF	LHMDS	81	05:95
13	(1e) 2-Thienyl	THF	KHMDS	90	90:10
14	(1e) 2-Thienyl	THF	LHMDS	63	08:92

[a] Unless otherwise specified, all reactions were carried out in the solvent indicated at −78 °C using 1 (0.81 mmol), base (0.93 mmol), and di-*tert*-butyl azodicarboxylate (0.85 mmol).
[b] Total isolated yield (2+3).
[c] Ratios of diastereomers were determined by ^{1}H NMR analysis of relevant peaks and by HPLC analyses of crude products (Agilent Technologies, ZORBAX SIL, 4.6 × 250 mm, hexanes/IPA = 96.7/3.3, flow rate = 0.5 mL/min).
[d] The absolute stereochemistry of the newly generated stereogenic center in 2a was established by single crystallographic X-ray analysis. The absolute stereochemistry of 2b–e and 3b–e is assigned by ^{1}H NMR spectra analyses (see text).
[e] KHMDS (0.6 equiv) was added followed by the addition of LHMDS (0.6 equiv).
[f] LHMDS (0.6 equiv) was added followed by the addition of KHMDS (0.6 equiv).

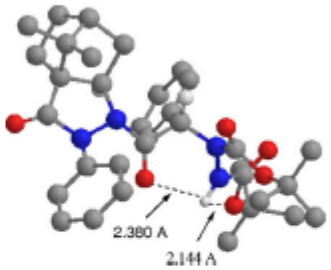
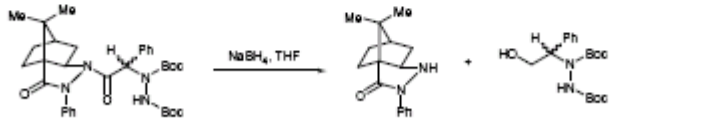


Figure 2. A Chem3D structural drawing of 2a regenerated from the X-ray crystal coordinates. All hydrogens (except for C2 proton) are omitted for the sake of clarity.



Scheme 1. Recovery of chiral auxiliary from hydrazides 2a and 3a.

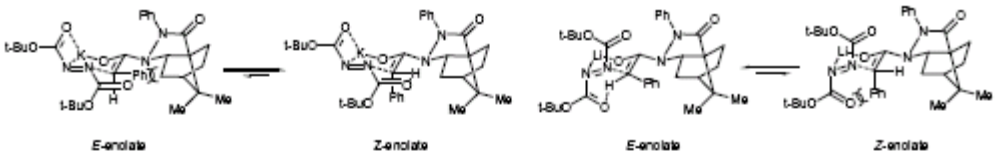
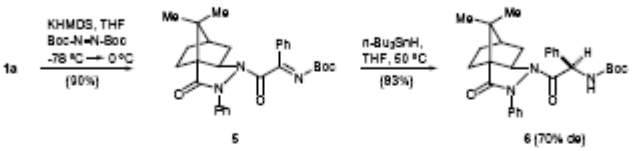


Figure 3. Proposed transition state of the electrophilic amination of 1a using KHMDS and LHMDS as a base.



Scheme 2. Preparation of (*R*)-α-amino carbonyl 6.

This complementary amination process is applicable to various aryl-substituted substrates **1b–e**. Toward this end, good to high levels of stereoselectivities of the aminating adducts with *S* configuration (except for **2e** due to the priority numbering) were obtained, when **1b–e** were treated with KHMDS followed by the addition of di-*tert*-butyl azodicarboxylate (entries 7, 9, 11, and 13). The ^{1}H NMR signal of the corresponding C-5 methine proton in **2b–e** consistently appeared in a range of 3.50–3.62 ppm. On the other hand, reversal of stereoselectivity of the aminated adducts **3b–e** (*R* configuration, except for **3e**) was observed when LHMDS was used under the same conditions (entries 8, 10, 12, and 14). The ^{1}H NMR signal of the C-5 methine protons in **3b–e** appears in a range of 4.41–4.53 ppm as expected. The characteristic features of the ^{1}H NMR spectra of the hydrazides **2** and **3** permitted the assignment of the newly generated stereogenic centers. No reaction occurred when a bulky substituent **1f** (R = *t*-butyl) was used. To complete one cycle of the chiral auxiliary, the aminated adducts (*S*)-**2a** and (*R*)-**3a** were then subjected to reduction conditions. Exposure of **2a** to $NaBH_4$ in THF at ambient temperature provided the desired hydrazido alcohol (*S*)-**4** (65%) ($[\alpha]_D$ +34.5 (*c* 1.0, $CHCl_3$)), and camphor N^2-phenylpyrazolidinone was recovered in 84% yield (Scheme 1). Similar conditions were applied to give (*R*)-**4** ($[\alpha]_D$ −39.0 (*c* 1.0, $CHCl_3$)) with 82% yield, when **3a** was used.

The mechanistic explanation for the asymmetric amination has not yet been elucidated at this moment and can be rationalized by the structurally well-defined metal enolate geometries in the transition states as depicted in Figure 3.[9a] The hydrogen bond formed between the α-hydrogen and the carbonyl group of di-*tert*-butyl azodicarboxylate may play a role in stabilizing the favored enolate complexes. The eight-membered potassium *Z*-enolate is preferentially formed, when **1a** is treated with KHMDS to give the corresponding adduct **2a**. On the other hand, the six-membered lithium *E*-enolate is energetically favored, when LHMDS is used, resulting in the formation of **3a** as the major isomer. The size of the metal counterion may also be important in forming the eight-membered and six-membered enolates.

An interesting imino intermediate **5** was isolated, when the amination reaction was carried out at −78 °C followed by warm up to 0 °C gradually (Scheme 2). When phenylacetyl-substituted pyrazolidinone **1a** was treated with KHMDS and di-*tert*-butyl azodicarboxylate at −78 °C and warmed up to 0 °C over a period of 5 h, the imino product **5** was isolated with high chemical yield. On the other hand, when the reaction temperature was raised to −30 °C, hydrazide **2a** was isolated as the major product (70%), and the imino intermediate **5** was obtained with 20% chemical yield. Tributyltin hydride reduction of **5** in THF afforded the Boc-protected (*R*)-α-amino product **6** (70% de) as the major diastereomer in a total of 83% chemical yield. The hydride attacks from the bottom *si* face of the imino functionality in **5**.[12]

In conclusion, complementary metal enolate amination of the auxiliary-derived *N*-acyls was developed for the synthesis of two possible hydrazide diastereomers. Either isomer can be obtained with excellent chemical yield and high diastereoselectivity (up to 90% de), when aryl-substituted camphor N^1-acyl N^2-phenylpyrazolidinones are treated with KHMDS and LHMDS, respectively, followed by the addition of di-*tert*-butyl azodicarboxylate. This extends the synthetic applications to the versatile and general utility of camphor N^2-phenylpyrazolidinone as a good stereocontrolling element in diastereoselective reaction.

Acknowledgments

This work was supported by the National Science Council of the Republic of China (NSC 96-2113-M-003-005-MY3) and the National Taiwan Normal University (96TOP001). Our gratitude goes to the Academic Paper Editing Clinic, NTNU, and we are also grateful to the National Center for High-Performance Computing for computer time and facilities.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.11.003.

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10. Variable-temperature ^{1}H NMR studies of 2a showed that the conformeric ratio increases with increasing temperature. For example, the conformeric ratio of hydrazide 2a is 1.5 when the spectrum was recorded at −15 °C. The ratio was increased to 1.7 (at 5 °C), to 1.9 (at 25 °C) and further to 2.3 (at 55 °C). Interestingly, a third conformer appears when the temperature was decreased to −55 °C.
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12. The absolute stereochemistry of the minor (*S*)-α-amino diastereomer 6 was confirmed by single crystallographic X-ray analysis.

Tetrahedron Letters 50 (2009) 4536–4540

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A mild and general method for preparation of α-glycosyl chlorides

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ARTICLE INFO

Article history:
Received 7 April 2009
Revised 19 May 2009
Accepted 22 May 2009
Available online 27 May 2009

ABSTRACT

A mild and efficient chlorination method for production of glycosyl chlorides is first described which employs inexpensive trichlorotriazine (TCT) and DMF as a chlorination reagent and is compatible with typical acid-labile hydroxyl protecting functions. The scope and limitations, reaction mechanism and its application in the sequential glycosylations are discussed.

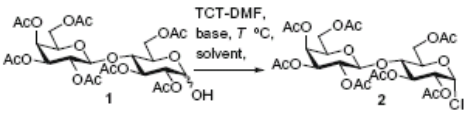
Developing inexpensive and operationally simple procedures for organic reactions is always attractive to chemists, which is illustrated by the application of trichlorotriazine (TCT) in functional group conversions.[1–7] As for example, TCT and DMF (TCT–DMF adduct) have been used for chlorination of aliphatic alcohols,[8] but there have not been any elaborative studies about using such TCT–DMF adduct for chlorination of glycosyl substrates.

Glycosyl chlorides constitute an important class of carbohydrate building blocks in oligosaccharide synthesis;[9] moreover, they are precursors for preparing O-glycosides,[10] C-glycosides,[11a] N-glycosides,[11b] and glycals.[12] Therefore, a facile production of glycosyl chlorides is highly desired. Typical preparation of glycosyl chlorides involves the treatment of peracyl glycosyl substrates with highly acidic reagents that renders them incompatible with acid-labile protecting functions.[13,14] Though milder reagents for chlorination of glycosyl hemiacetals have been developed including PPh_3–CCl_4,[15a] Viehe's salt,[15b] chloroenamine,[15c] chlorodiphenyl phosphate,[15d] and triphosgene,[15e] either such reagents are not commercially available or their efficiency is inadequate for disarmed glycosyl substrates.[15b,c] To pursue a milder and efficient method for glycosyl chloride production, we herein describe for the first time the use of inexpensive TCT and DMF for preparation of glycosyl chlorides, and its applications in sequential functional group transformations and glycosylations.

In the model study, peracetyl lactosyl hemiacetal **1** dissolving in CH_2Cl_2 was treated with pre-mixed TCT (1.1 equiv) and DMF (ca. 2.2 equiv) at room temperature based on literature procedure (Table 1, entry 1).[8d] Disappointingly, the expected lactosyl chloride **2** was furnished in moderate 58% yield after 48 h. Such a sluggish reaction is attributed to the highly disarmed nature of peracetyl-protected substrate and sub-optimal reaction conditions.[16] After some experimentations, several reaction parameters are found essential for TCT–DMF chlorination which include: (1) addition of proton scavenger to reaction mixture such as diazabicyclo-[5.4.0]-undec-7-ene (DBU), triethylamine or K_2CO_3; (2) application of higher reaction temperature (45–60 °C); and (3) optimization of TCT–DMF stoichiometric ratio to ca. 1:4. With all these parameters in hands, reaction times of chlorination were dramatically reduced to 1.5–4 h and yields were improved to 75–87% (Table 1, entries 2–6).

Based on the aforementioned parameters, we explored the scope and limitations of TCT–DMF chlorination (Table 2, entries a–r). Thus various glycosyl substrates **3a–20a** were prepared by standard methods and treated with either chlorination protocol A or chlorination protocol B.[17,18] Protocol A employs DBU (1 equiv) as the base and is performed in dichloroethane (DCE) at 60 °C. This protocol is presumably suitable for less reactive glycosyl substrates such as **3a–10a**, **14a**, and **20a** (Table 2, entries a–h, l, and r). While protocol B employs excess K_2CO_3 (5 equiv) and is conducted in CH_2Cl_2 at 45 °C (Table 2, entries i–k and m–q), both K_2CO_3- and TCT-derived byproduct of protocol B are readily precipitated in

Table 1
Elucidation of essential reaction conditions of TCT–DMF chlorination



Entry	Base	Solvent	*T* (°C)	Time (h)	Yield[a] (%)
1	None	CH_2Cl_2	25	48	58
2	None	DCE	60	4	85
3	DBU	DCE	60	1.5	87
4	DBU	DCE	50	2.5	83
5	Et_3N	DCE	50	4	81
6	K_2CO_3	CH_2Cl_2	45	4	75[b]

[a] Isolated yield via brief chromatography purification.
[b] 5.0 equiv of K_2CO_3 was used.

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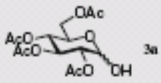
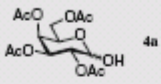
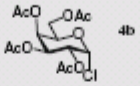
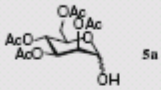
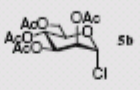
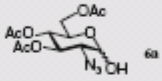
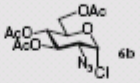
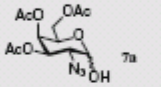
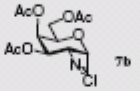
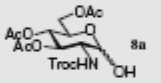
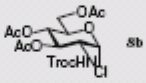
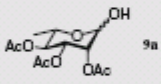
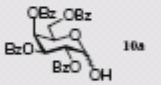
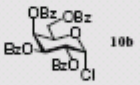
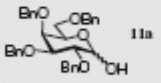
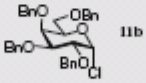
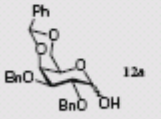
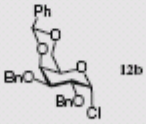
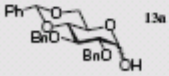
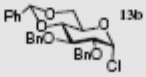
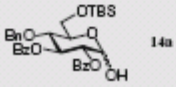
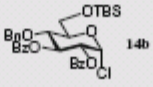
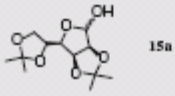
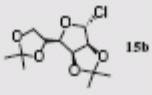
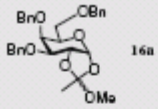
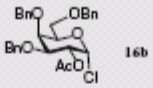
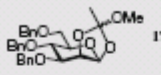
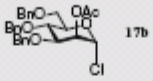
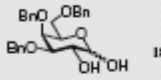
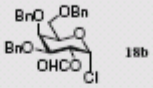
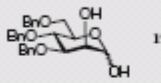
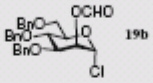
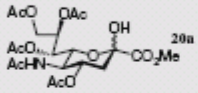
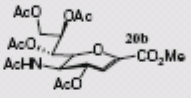
0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.05.077

Table 2
Examination of TCT–DMF chlorination of glycosyl hemiacetals 3a–20a

Entry	Glycosyl substrate	Product	Protocol,[a] time	Yield[b] (%)
a	 3a	 3b	A, 4 h	89
b	 4a	 4b	A, 2 h	90
c	 5a	 5b	A, 2 h	92
d	 6a	 6b	A, 1.5 h	76
e	 7a	 7b	A, 2 h	88
f	 8a	 8b	A, 3 h	75
g	 9a	 9b	A, 1 h	79
h	 10a	 10b	A, 1 h	80
i	 11a	 11b	B, 4 h	82
j	 12a	 12b	B, 4 h	85
k	 13a	 13b	B, 3 h	82
l	 14a	 14b	A, 2 h	67
m	 15a	 15b	B, 2 h	89

(continued on next page)

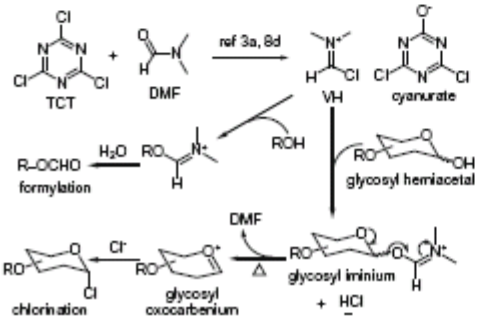
Table 1 (continued)

Entry	Glycosyl substrate	Product	Protocol,[a] time	Yield[b] (%)
n	 16a	 16b	B,[c] 2 h	85
o	 17a	 17b	B,[c] 2 h	92
p	 18a	 18b	B, 3 h	70
q	 19a	 19b	B, 2 h	95
r	 20a	 20b	A,[d] 3 h	85

[a] Protocol A = TCT (1.1 equiv), DMF (4 equiv), DBU (1.0 equiv) in DCE at 60 °C. Protocol B = TCT (1.1 equiv), DMF (4 equiv), K_2CO_3 (5 equiv) in CH_2Cl_2 at 45 C.
[b] Isolated yield after brief chromatography purification.
[c] Base was omitted.
[d] 65 C was applied.

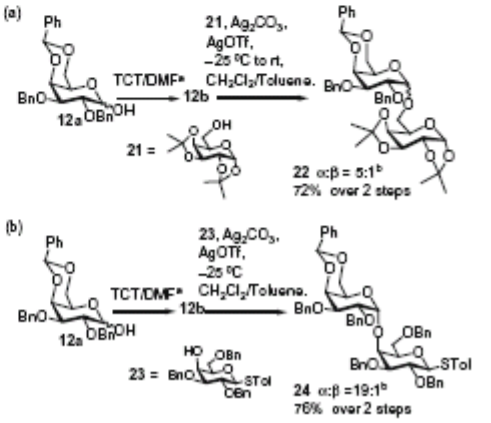
Et_2O and thus they can be removed by simple filtration. Such physical features render protocol B particularly suitable for incorporation to sequential functional group transformations.

With the exception of Neu5Ac hemiacetal **20a** (Table 2, entry r), TCT–DMF chlorination of **3a–19a** produced the corresponding α-glycosyl chlorides **3b–19b** as the single anomers in 67–95% yields at 1–4 h time frames; the observed α-selectivities can be partially attributed to anomeric effect and thermodynamic reaction conditions.[19] Though β-glycosyl chloride formation was reported in previous study, however no such β-glycosyl chlorides were isolated in present chlorination experiments.[20] This may be ascribed to the decomposition of the unstable β-glycosyl anomers during chromatography purification.



Scheme 1. Plausible mechanism of TCT–DMF chlorination of glycosyl hemiacetals.

The TCT–DMF chlorination is compatible with different acid-labile hydroxyl protecting functions such as alkylidene acetals and silyl ether functions (Table 2, entries j–m). Consequently with the current method, glycosyl chlorides in different protecting group settings are easily prepared. In addition, we envisaged that omitting the base in TCT–DMF chlorination can effect a one-pot conversion of glycosyl orthoester to glycosyl chloride. It should



Scheme 2. Sequential chlorination–glycosylation. [a] Protocol B: TCT (1 equiv), DMF (4 equiv), K_2CO_3 (5 equiv) in CH_2Cl_2 at 45 °C. [b] α-/β-Anomer ratio was determined by ^1H NMR analysis.

be mentioned that similar conversion explained in previous study requires four reaction steps.[21] Thus treatment of glycosyl orthoesters **16a**, **17a** with the modified procedure of protocol B resulted in the formation of glycosyl chlorides **16b**, **17b** in high yields (Table 2, entries n and o).[22]

Particularly intriguing is the chlorination of glycosyl hemiacetals **18a** and **19a**; each of these substrates contains non-anomeric and anomeric hydroxyl functions. Applying TCT–DMF chlorination protocol B resulted in chemoselective anomeric hydroxyl chlorination and C-2 hydroxyl formylation. No traces of crossly functionalized products were detected. (Table 2, entries p and q).

Although TCT–DMF chlorination is useful for a wide range of glycosyl substrates, its application to Neu5Ac hemiacetal **20a** gave rise to elimination product, Neu5Ac glycal **20b** (Table 2, entry r). This result may be explained by the high propensity of Neu5Ac glycosyl chloride for elimination. Nevertheless, Neu5Ac glycal **20b** is the valuable precursor for preparing sialidase inhibitors;[23] thus by serendipity, our method provides an easy entry to Neu5Ac glycal derivative.

It is worth mentioning that armed glycosyl chlorides (**11b**–**13b** and **16b**–**19b**) are prone to decomposition; nevertheless, brief chromatography purification over short pad of silica gel is tolerable. However, a prolonged contact would lead to substantial decomposition of both armed and disarmed glycosyl chlorides; while the extent of decomposition is much greater for the armed chlorides than for the disarmed chlorides.[24] Noted that TCT–DMF chlorination method is amenable to larger scale preparation (5–10 g of glycosyl hemiacetal), for which a slightly longer reaction time is required.

Based on the literature review and experimental observations, a plausible mechanism of TCT–DMF chlorination is outlined in Scheme 1.[8a,d] At first, TCT was reacted with DMF giving Vilsmeier–Haack (VH) adduct and cyanurate; VH-adduct was then coupled to glycosyl hemiacetal furnishing glycosyl iminium. The presence of glycosyl iminium was supported by isolation of its hydrolyzed product, glycosyl formate (data not shown). Subsequent cleavage of the 'exo' anomeric C–O bond in glycosyl iminium was promoted by the 'push and pull' stereoelectronic feature of substrate, which generated glycosyl oxocarbenium. Note that the absence of such a stereoelectronic feature as is the case in aliphatic alcohol results in hydroxyl formylation. Final coupling of oxocarbenium intermediate with chloride ion furnished α-glycosyl chloride.

As glycosyl chlorides are versatile donors for Koenigs–Knorr glycosylation,[25] it is reasonable to streamline TCT–DMF chlorination and Koenigs–Knorr glycosylation to a sequential process such that apparently glycosyl hemiacetals act as donors for glycosylations. Kobayashi reported for direct activation of glycosyl hemiacetals with the Appel-Lee (PPh_3–CBr_4) reagent and DMF, though the glycosylations were slow (required 1–3 days).[26] In present context, α-galactopyranosyl hemiacetal **12a** was first treated with TCT–DMF protocol B giving galactopyranosyl chloride **12b** (Scheme 2a). Crude galactopyranosyl chloride **12b** obtained after simple filtration and solvent removal was used directly as a donor for glycosylation of acceptor **21** without tedious chromatography isolation of glycosyl chloride. Desired disaccharide **22** was obtained in 72% overall yield as a 5:1 α:β-anomeric mixture. Such sequential chlorination–glycosylation also works well for thioglycoside acceptor rendering an orthogonal glycosylation possible (Scheme 2b). Thus **12a** was chlorinated and thereof glycosylated with thiogalactopyranoside **23** furnishing thioglycoside **24** in 76% overall yield and excellent α-selectivity.

In summary, we report for the first time a mild and efficient TCT–DMF chlorination method for different carbohydrate substrates including glycosyl hemiacetals and glycosyl orthoesters. Based on this new chlorination method, glycosyl chlorides in different protecting group settings become easily available, which in turn enables the development of sequential chlorination–glycosylation. Such a mild chlorination method should find useful for oligosaccharide synthesis.

Acknowledgments

We thank the National Science Council, Taiwan (96-2113-M-009-016) and the Institute Francais de Taipei for financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.05.077.

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18. TCT–DMF chlorination protocol A: DMF (1.55 mL, 20.0 mmol) was added to 2,4,6-trichloro-[1,3,5]-triazine (TCT) (1.0 g, 5.5 mmol) and the resulting suspension was stirred at rt for 15 min under N_2. Glycosyl hemiacetal (5.0 mmol) (**1**, **3a**, **4a**, **5a**, **6a**, **7a**, **8a**, **9a**, **10a**, or **14a**) in dichloroethane solution (DCE) was added to the TCT–DMF suspension followed by addition of DBU (0.8 mL, 5.5 mmol). The reaction mixture was stirred at 60 °C and progress of reaction was monitored by TLC (ca. 1–4 h). Upon completion of chlorination, the temperature was brought to rt and Et_2O was added to the mixture for the precipitation of cyanuric salt. After removal of cyanuric salt by filtration, the combined filtrate was concentrated to yield the crude glycosyl chloride. Further purification was performed by brief chromatography elution over a short pad of silica gel to furnish the respective α-glycosyl chloride **2**, **3b**, **4b**, **5b**, **6b**, **7b**, **8b**, **9b**, **10b**, or **14b**. TCT–DMF chlorination protocol B (**11a**, **12a**, **13a**, **15a**, **16a**, **17a**, **18a**, **19a**): Similar to protocol A except that CH_2Cl_2 and 5 mol equiv of K_2CO_3, were used as solvent and proton scavenger, respectively, to replace DCE and DBU in protocol A. The reaction was conducted at 45 °C and for glycosyl orthoesters **16a** and **17a**, K_2CO_3 was omitted. Subsequent workup followed the same procedure as described in protocol A above and the respective α-glycosyl chloride **11b**, **12b**, **13b**, **15b**, **16b**, **17b**, **18b**, or **19b** was obtained.
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Tetrahedron Letters xxx (2010) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Joined use of oxazolidinone and desymmetric amino protection: a new strategy for protection of glucosamine

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ARTICLE INFO

Article history:
Received 25 December 2009
Revised 3 February 2010
Accepted 5 February 2010
Available online xxxx

ABSTRACT

Joined use of *N*-benzyl oxazolidinone and *N*-benzyl-*N*-benzyloxycarbonyl (*N*-BnCbz) desymmetric amino-protecting function is reported. The new synthetic approach enables the facile preparation of type 1 and type 2 LacNAc disaccharides in satisfactory yields. One-pot deprotection of *N*-BnCbz and *O*-benzyl ether is achieved by hydrogenolysis under mild conditions.

A number of naturally occurring glycoconjugates contain *N*-acetyl glucosamines that glycosylate at C-3 and C-4 positions.[1] Typical examples are the Lewis blood group antigens, which contain either Gal-β(1→3)-GlcNAc (type 1 LacNAc) or Gal-β(1→4)-GlcNAc (type 2 LacNAc) backbone.[2] Some of these blood group antigens such as Lewis Y antigen have been proven to be specific tumor markers for cancer diseases; thus, they are attractive targets for various biomedical investigations.[3] To sustain these research activities, the supply of pure oligosaccharide samples and their conjugates is crucial. One of the important factors in oligosaccharide synthesis is the effective formation of glycosidic bonds. However, due to steric hindrance and hydrogen-bonding interaction, the C-3 and C-4 hydroxyl functions in *N*-acetyl glucosamine are weakly nucleophilic, and therefore glycosylations of these hydroxyl functions are often problematic.[4,5] To solve these problems, different amino-protecting groups have been designed, which include *N*-phthaloyl (*N*-Phth),[6] *N*-tetrachlorophthaloyl (*N*-TCPhth),[7] *N*-dithiasuccinoyl (*N*-Dts),[8] *N*-trichloroethoxycarbonyl (*N*-Troc),[9] *N*-trichloroacetyl (*N*-TCA),[10] *N*-trifluoroacetyl (*N*-TFA),[11] *N*,*N*-diacetyl (*N*-Ac_2),[12] *N*-*p*-nitrobenzyloxy-carbonyl (*N*-PNZ),[13] *N*-dimethylphosphoryl (*N*-DMP),[14] and others.[15] In routine practice, the amino function of glucosamine is often masked with a protecting function in the early stage of synthesis. After a series of protecting group manipulations and glycosylations, this amino-protecting group has to be removed in the final stage. This standard strategy demands the use of a robust protecting function to survive different conditions, but such a function has to be taken off in the end. Therefore, it is not easy to design a single protecting function embracing both features. A point in case is the use of *N*-Phth protection, which is stable to different reaction conditions,[5] but its removal is non-trivial.[15,16]

In 2001, Kerns and co-workers reported using N-unprotected oxazolidinone for the protection of C-3 hydroxyl and C-2 amino functions in glucosamine.[17] This function was later elaborated to *N*-acetyl[18–22] and *N*-benzyl oxazolidinone derivatives.[23–25] The primary goal of using oxazolidinone function is to search for a good α-directing glucosamine donor.[17] Subsequent studies reveal some degree of inconsistency in the stereochemical preference of glycosylations.[22,25,26] We speculated that other than stereochemical preference, the unique feature of *N*-benzyl oxazolidinone may impart additional utilities (Fig. 1).

Our rationale is grounded on the following facts. Firstly, the 'tied-up' C-3 hydroxyl and C-2 amino functions reduce the steric hindrance at C-4 position and therefore should facilitate its glycosylation.[21] Secondly, the oxazolidinone protection has been shown to decrease the reactivity of the anomeric-leaving function,[22,27] which paves the way for the reactivity-based glycosylation.[28] Thirdly, the hydrolytic opening of oxazolidinone and reprotection of amine function lead to the formation of desymmetric amino-protected glucosamine, which to the best of our knowledge has rarely been studied in the literature.[9b] In the light of the discussion above, this study reports a useful strategy for the protection of glucosamine capitalizing the *N*-benzyl oxazolidinone and its derived desymmetric *N*-benzyl-*N*-benzyloxycarbonyl (*N*-BnCbz) functions.

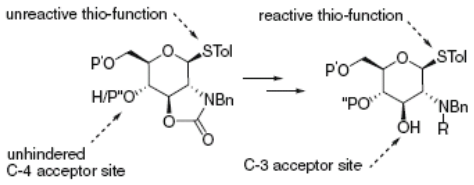

Figure 1. *N*-Benzyl oxazolidinone-protected glucosamine and its derived disubstituted-desymmetric amino-protected glucosamine.

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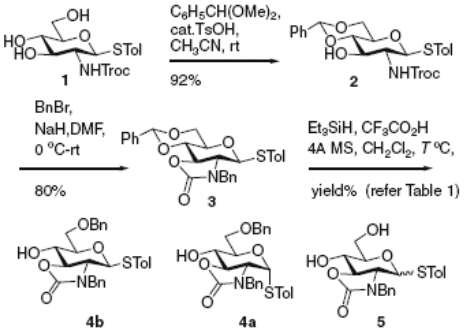
0040-4039/$ - see front matter © 2010 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2010.02.021

In the beginning, 2-Troc-2-deoxy thioglucopyranoside **1** prepared from glucosamine[28] was converted to 4,6-*O*-benzylidene-2*N*-benzyl-2,3-*N*,*O*-carbonyl-2-deoxy thioglucopyranoside **3** via benzylidene acetal intermediate **2** (Scheme 1).[25] However, the reductive ring opening of benzylidene acetal **3** required considerable experimentation (Table 1). Previous efforts using either sodium cyanoborohydride–hydrogen chloride ($NaBH_3CN/HCl$)[29] or triethylsilane–boron trifluoride etherate ($Et_3SiH/BF_3{\cdot}Et_2O$)[30] led to β→α anomerization. This undesirable reaction is attributable to the coordination of BF_3 to ring oxygen atom that promotes the endocyclic cleavage of C1–O5 linkage.[24,31] After some investigations, using triethylsilane–trifluoroacetic acid (Et_3SiH/TFA) at low reaction temperature was found to be effective for the reduction of β→α anomerization.[32] To our delight, *N*-benzyl-2,3-*N*,*O*-carbonyl-protected β-thioglucopyranoside **4b** was formed exclusively in high 80% yield at −20 °C (Table 1, entry 3). However, anomerization of **4b** to α-anomer **4a** and trace amount of complete deacetalation product **5** were observed at higher reaction temperatures (Table 1, entries 1 and 2). Noted that the use of the literature procedure resulted in a 1:6 α/β-anomeric mixture (Table 1, entry 4).[24] The β-anomeric configuration of **4b** was supported by the ^{13}C chemical shift at 86.7 ppm and $^1J_{CH}$ coupling constant of 161 Hz.[33]

After the preparation of glucosamine acceptor **4b**, this study proceeded to synthesize a desymmetric amino-protected glucosamine acceptor (Scheme 2). In this regard, *N*-benzyl oxazolidinone-protected glucosamine thioglycoside **6**[25] was treated with *t*-BuOK to produce benzylamine derivative **7**,[25] which was chemoselectively converted to desymmetric *N*-benzyl-*N*-benzyloxycarbonyl (*N*-BnCbz)-protected glucosamine thioglycoside **8**.[34] Subsequent glycosylation of aglycon acceptor **9** with thioglycoside **8** using *N*-iodosuccinimide (NIS) and trimethylsilyl trifluoromethanesulfonate (TMSOTf) as promoters furnished glucosamine glycoside **10**.[35] Noted that the assignment of ^1H NMR spectra of **8** and **10** was difficult due to the peak broadening of the resonance signals.[36] Nonetheless, their preliminary identifications were evidenced by HRMS.

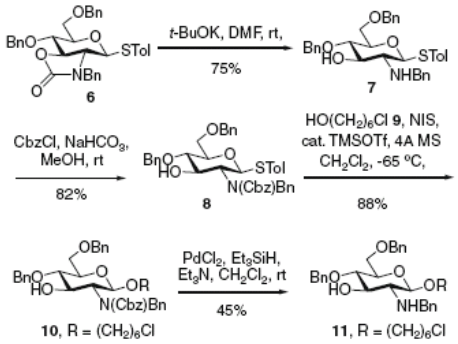


Scheme 1. Synthesis of glucosamine acceptor 4b.

Table 1
Reaction conditions and results of reductive benzylidene ring opening of thioglycoside **3**

Entry	Acid (equiv)	Et_3SiH (equiv)	*T* (°C)	Yield (%) of 4[a]	α:β
1	TFA (6)	5	25	35	1:1
2	TFA (6)	5	0	57	1:10
3	TFA (6)	5	−20	80	β only
4	BF_3 (2)	12	−20	65	1:6[b]

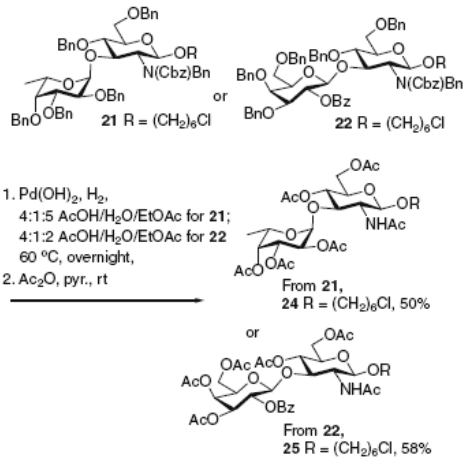
[a] Total yield of **4a** and **4b** after chromatography purification.
[b] The method was referred to Ref. 23.



Scheme 2. Synthesis of desymmetric (*N*-BnCbz)-protected glucosamine acceptor **10**.

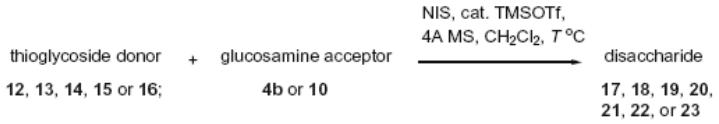
Further support of their structures could be obtained by high temperature NMR spectroscopy, as demonstrated for glycoside **10** (ca VT-NMR from rt to 100 °C in deuterated DMSO solvent).[37] The broadening of resonance signal is due to the presence of the Cbz carbamate function because such a broadening phenomenon had gone for glucosamine glycoside **11**, in which the Cbz function was removed.

With glucosamine acceptors **4b** and **10** in hand, the stage was ready to study their glycosylations with known thioglycosides **12**–**16** (Table 2).[38] Glycosylations of **4b** with thiogalactopyranoside **12** and thiofucopyranoside **13** produced Gal-α(1→4)-GlcNAc disaccharide **17** and Fuc-α(1→4)-GlcNAc disaccharide **18** as the single anomers (Table 2, entries 1 and 2). Intriguingly, the thiotolyl function in thioglycoside **18** underwent β→α anomerization forming an inseparable 1:3.5 α/β-anomeric mixture. Though this anomerization can be explained by C1–O5 endocyclic bond cleavage as described before,[31] it is unclear why the same anomerization did not occur in the glycosylation of **12**. Due to the deactivation of oxazolidinone function, self-condensation of **4b** did not occur under the present reaction conditions.[22,27] Glycosylations of **4b** with thioglycosides **14** and **15** furnished type 2 LacNAc disaccharides **19** and **20** in high yields (Table 2, entries 3 and 4). For glycosylations of

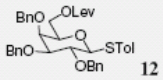
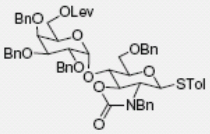
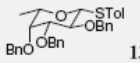
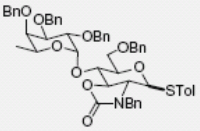
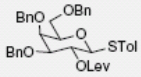
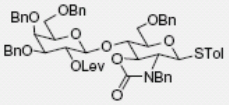
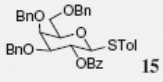
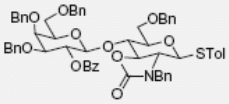
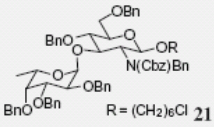
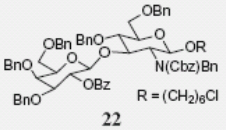
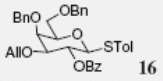
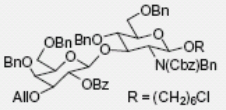


Scheme 3. Deprotection of disaccharides **21** and **22**.

Table 2
Glycosylation studies of glucosamine acceptors **4b** and **10**



12, **13**, **14**, **15** or **16**; **4b** or **10**; **17**, **18**, **19**, **20**, **21**, **22**, or **23**

Entry	Thioglycoside donor	Glucosamine acceptor	*T* (°C)	Disaccharide product	Yield (%)
1	 **12**	**4b**	−70	 **17**	70
2	 **13**	**4b**	−60	 **18** (α:β = 1:3.5)	85
3	 **14**	**4b**	−65	 **19**	65
4	 **15**	**4b**	−70	 **20**	80
5	**13**	**10**	−70	 R = $(CH_2)_6Cl$ **21**	93
6	**15**	**10**	−65	 R = $(CH_2)_6Cl$ **22**	80
7	 **16**	**10**	−65	 R = $(CH_2)_6Cl$ **23**	73

glucosamine acceptor **10**, thioglycoside donors **13**, **15**, and **16** were employed. All the glycosylations furnished the expected disaccharide products **21**–**23** in high (73–93%) yields (Table 2, entries 5–7). For NMR spectroscopy of disaccharides **21**–**23**, the phenomenon of resonance peak broadening was also observed.

After studying the glycosylation properties of glucosamine acceptors **4b** and **10**, we next explored appropriate deprotection methods for selected disaccharide products. As the deprotection methods for oxazolidinone have already been developed,[23] this study focused on the deprotection of desymmetric amino protection of Fuc-α(1→3)-GlcNAc glycoside **21** and type 1 LacNAc glycoside **22** (Scheme 3). An advantage of using *N*-Cbz protection in glucosamine is that it can be removed along with the benzyl ether and benzylamine functions during Pd-catalyzed hydrogenolysis.[39]

In our hands, the optimization of reaction conditions was required. Ultimately, $Pd(OH)_2$ was found to be the most effective catalyst for the deprotection of *N*-BnCbz and *O*-Bn in **21** and **22** (Scheme 3).[23,40,41] Both hydrogenolysis reactions were performed in $AcOH/H_2O/EtOAc$ solvent mixtures under 1 atm H_2 at 60 °C. For NMR characterization, the resulting debenzylated products were further acetylated to produce the peracetyl Fuc-α(1→3)-GlcNAc glycoside **24** and type 1 LacNAc glycoside **25**.

In summary, this study reports a versatile amino protection strategy for glucosamine by the joined use of *N*-benzyl oxazolidinone and desymmetric *N*-BnCbz function. The scope of investigation includes the installation, deprotection, and application of these protecting functions. As glucosamine constitutes the key component in different oligosaccharide structures, the results of this study should be found useful for their preparation.

Acknowledgments

We express our thanks to the National Science Council for financial support of this work (Grant No. NSC 97-2113-M-009 -007) and Mr. Tsung-Yi Chen for MS analysis.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.021.

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