Supplementary Information for

Cap and capture-release techniques applied to solid-phase synthesis of oligosaccharides

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I. Experimental Section

General Methods. NMR spectra were recorded with a 400 MHz NMR spectrometer. Chemical shifts are reported in ppm (δ) and coupling constants (*J*) in hertz (Hz). MS and high-resolution mass spectra (HR MS) were recorded with a mass spectrometer in fast atom bombardment (FAB) mode. Thin layer chromatography (TLC) was performed on silica gel GF_{254} detected by charring with 2% H_2SO_4 in EtOH. Purchased anhydrous solvents and other reagents were used without further purification.

Methyl 3,4-di-O-benzyl-6-O-(t-butyldimethylsilyl)-2-O-levulinoyl-α-D-mannopyranoside (7). To a stirred solution of **6** (160 mg, 0.269 mmol) in CH_2Cl_2 (4 mL) at 0 ^oC was added levulinic acid (0.04 mL, 0.404 mmol) and DMAP (50 mg, 0.404 mmol). After the mixture was stirred for 5 min, DIPC (0.06 mL, 0.404 mmol) was added, and the solution was allowed to slowly warm to room temperature. Four hours later, the reaction mixture was concentrated in vacuo, and the residue was purified by flash silica gel chromatography (toluene:EtOAc = 15:1) to yield **7** (177 mg, 95%) as colorless oil. R_f: 0.52 (toluene:EtOAc = 4:1). $[\alpha]_D^{20}$ +17.1 (c 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.38-7.24 (m, 10 H), 5.33 (dd, *J* = 3.2, 2.0 Hz, 1 H), 4.89 (d, *J* = 10.8 Hz, 1

H), 4.69-4.65 (m, 2 H), 4.62 (d, *J* = 10.8 Hz, 1 H), 4.51 (d, *J* = 10.8 Hz, 1 H), 3.95 (dd, *J* = 9.6, 3.2 Hz, 1 H), 3.89 (dd, *J* = 11.6, 4.8 Hz, 1 H), 3.85-3.78 (m, 2 H), 3.62-3.57 (m, 1 H), 3.34 (s, 3 H), 2.80-2.61 (m, 4 H), 2.18 (s, 3 H), 0.92 (s, 9 H), 0.08 (s, 3 H), 0.06 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) 172.4, 138.9, 138.3, 130.0, 129.2, 128.58, 128.56, 128.3, 128.1, 127.9, 127.8, 98.7, 78.3, 75.4, 74.4, 72.7, 71.8, 69.1, 62.5, 54.9, 38.2, 30.1, 28.3, 26.1, 18.5, 1.3, -4.9, -5.1. FAB HRMS (m/e): cacl. for $C_{31}H_{43}O_7Si$ (M^+ - OCH_3) 555.2779; found 555.2766; cacl. for $C_{32}H_{45}O_8Si$ (M^+ - H) 585.2884, found 585.2870; cacl. for $C_{32}H_{47}O_8Si$ (M + H^+) 587.3040, found 587.2999.

Methyl 3,4-di-O-benzyl-2-O-levulinoyl-α-D-mannopyranoside (8). After **7** (170 mg, 0.246 mmol) was dissolved in THF (1 mL) under nitrogen, TBAF (1M solution in THF, 1.23 mL, 1.23 mmol) and acetic acid (0.077 mL) were added to the solution at 0 ^{o}C. The mixture was warmed to room temperature and stirred overnight. After removal of the solvent in a vacuum, the residue was purified by flash column chromatography (toluene:EtOAc = 1:1) to give **8** (110 mg, 95%) as colorless syrup. R_f: 0.23 (toluene:EtOAc = 1:1). $[\alpha]_D^{20}$ +17.4 (c 0.5 , $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38-7.22 (m, 10 H), 5.33 (dd, *J* = 3.2, 1.6 Hz, 1 H), 4.91 (d, *J* = 11.2 Hz, 1 H), 4.70 (d, *J* = 1.6 Hz, 1 H), 4.68 (d, *J* = 11.2 Hz, 1 H), 4.63 (d, *J* = 11.2 Hz, 1 H), 4.52(d, *J* = 11.2 Hz, 1 H), 3.97 (dd, *J* = 9.2, 3.2 Hz, 1 H), 3.87-3.74 (m, 3 H), 3.68-3.63 (m, 1 H), 3.36 (s, 3 H), 2.82-2.62 (m, 4 H), 2.18 (s, 3 H), 1.95 (dd, *J* = 8.0, 5.2 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) 206.6, 172.3, 138.5, 138.2, 128.7, 128.6, 128.3, 128.2, 128.0, 127.9, 98.9, 78.1, 75.4, 74.3, 71.8, 71.7, 69.1, 62.3, 55.2, 38.3, 30.0, 29.9, 28.4. FAB HRMS (m/e): cacl. for $C_{26}H_{33}O_8$ (M + H^+) 473.2175, found 473.2170; cacl. for $C_{26}H_{31}O_8$ (M^+ - H) 471.2021, found 471.2019; cacl. for $C_{26}H_{32}NaO_8$ (M + Na^+) 495.1995, found 495.1975.

Methyl 3,4-di-O-benzyl-6-O-(3-carboxypropanoyl)-2-O-levulinoyl-α-D-mannopyranoside (2). To a solution of **8** (110 mg, 0.233 mmol) in pyridine (2 mL) were added succinic anhydride (93 mg, 0.932 mmol) and a catalytic amount (100 mg) of DMAP. After stirring overnight, H_2O (1mL) was added and the stirring was continued for another hour. The mixture was diluted with CH_2Cl_2 (50 mL) and washed with 1M HCl solution (2 × 30 mL) and H_2O (2 × 30 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuum to afford **2** (133 mg, 100%): $[\alpha]_D^{20}$ +18.7 (c 3.0 , $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38-7.24 (m, 10 H), 5.34 (dd, *J* = 3.2, 1.6 Hz, 1 H), 4.88 (d, *J* = 10.8 Hz, 1 H), 4.68 (d, *J* = 1.6 Hz, 1 H), 4.67 (d, *J* = 10.8 Hz, 1 H), 4.56 (d, *J* = 10.8 Hz, 1 H), 4.51 (d, *J* = 10.8 Hz, 1 H), 4.37 (s, 1 H), 4.36 (s, 1 H), 3.96 (dd, *J* = 8.8, 3.2 Hz, 1 H),

3.83-3.78 (m, 1 H), 3.71 (t, *J* = 9.6 Hz, 1 H), 3.34 (s, 3 H), 2.82-2.62 (m, 4 H), 2.64 (s, 4 H), 2.17 (s, 3 H). FAB HRMS (m/e): cacl. for $C_{30}H_{36}NaO_{11}$ ($M + Na^+$) 595.2156, found 595.2157.

Ethyl 3,4,6-tri-O-benzyl-2-O-levulinoyl-1-thio-α-D-mannopyranoside (10). Levulinic acid (77 μL, 0.75 mmol) and DMAP (92 mg, 0.75 mmol) was added to a stirred solution of **9** (300 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) at 0 ^oC. Five minutes later, DIPC (0.12 mL, 0.75 mmol) was added, and the solution was allowed to slowly warm to rt. After 4 h of stirring, the reaction mixture was concentrated in vacuo, and the residue was purified by column chromatography (toluene:EtOAc = 10:1) to yield **10** (281 mg, 95%) as colorless syrup. R_f: 0.34 (toluene:EtOAc = 4:1). $[\alpha]_D^{20}$ +20.8 (c 0.3 , $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.41-7.15 (m, 15 H), 5.42 (t, *J* = 2.0 Hz, 1 H), 5.29 (d, *J* = 1.2 Hz, 1 H), 4.85 (d, *J* = 10.4 Hz, 1 H), 4.68 (d, *J* = 3.6 Hz, 2 H), 4.65 (d, *J* = 2.8 Hz, 2 H), 4.51-4.46 (m, 3 H), 4.17-4.11 (m, 1 H), 3.92-3.87 (m, 2 H), 3.82 (dd, *J* = 10.8, 4.0 Hz, 1 H), 3.68 (dd, *J* = 2.8, 1.6 Hz, 1 H), 2.75-2.53 (m, 6 H), 2.13 (s, 3 H), 1.27 (t, *J* = 3.6 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) 206.6, 172.2, 138.6, 138.4, 138.0, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 82.6, 78.7, 75.4, 74.7, 73.6, 72.0, 71.9, 70.9, 69.1, 38.2, 30.0, 28.4, 25.7, 15.1. FAB HRMS (m/e): cacl. for $C_{34}H_{40}NaO_7S$ ($M + Na^+$) 615.2393, found 615.2393.

3,4,6-tri-O-Benzyl-2-O-levulinoyl-α,β-D-mannopyranose (11). To a stirred solution of **10** (250 mg, 0.422 mmol) in CH_3CN (3 mL) and H_2O (0.3 mL) was added NIS (190 mg, 0.844 mmol). The reaction mixture was stirred for 5 min at rt and was then diluted with CH_2Cl_2. The solution was washed with saturated $Na_2S_2O_3$ and brine, and the combined organic layer was dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (toluene:EtOAc = 2:1) to produce **11** (230 mg, 99%) as colorless syrup. R_f: 0.12 (toluene:EtOAc = 4:1). ^1H NMR ($CDCl_3$, 400 MHz, α-anomer as the major product): δ 7.38-7.12 (m, 15 H), 5.35 (dd, *J* = 3.6, 1.6 Hz, 1 H), 5.17 (dd, $J \leq 1$ Hz, 1 H), 4.85 (d, *J* = 11.2 Hz, 1 H), 4.67 (d, *J* = 10.8 Hz, 1 H), 4.58 (d, *J* = 12.0 Hz, 1 H), 4.51-4.45 (m, 3 H), 4.08-4.02 (m, 1 H), 4.01 (dd, *J* = 9.6, 3.6 Hz, 1 H), 3.86 (d, *J* = 3.2 Hz, 1H), 3.76-3.64 (m, 3 H), 2.75-2.64 (m, 4 H), 2.10 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) 206.9, 172.3, 138.5, 138.2, 138.1, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 92.6, 77.9, 75.3, 74.8, 73.6, 71.8, 71.2, 69.5, 69.4, 38.3, 30.0, 28.4. FAB HRMS (m/e): cacl. for $C_{32}H_{36}NaO_8$ ($M + Na^+$) 571.2308, found 571.2303.

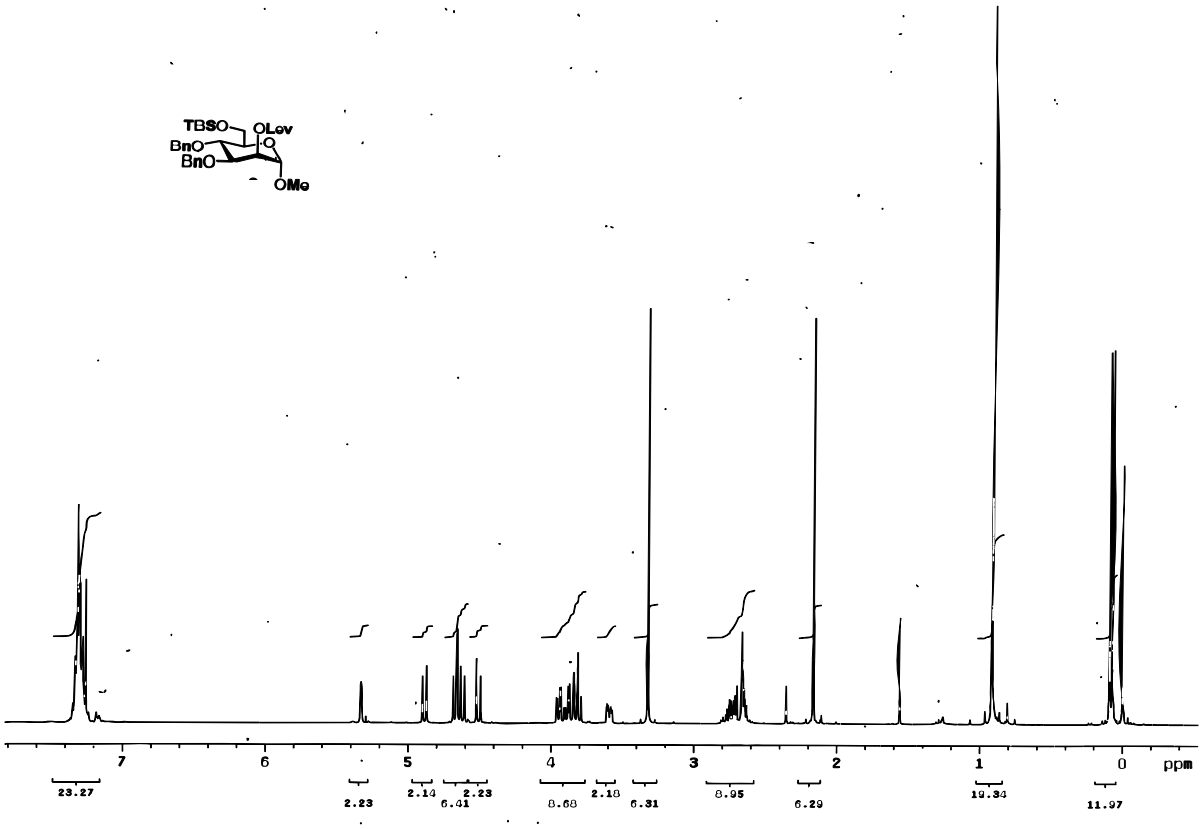
3,4,6-tri-O-Benzyl-2-O-levulinoyl-α-D-mannopyranosyl trichloroimidate (3). After **11** (200 mg, 0.365 mmol) and Cl_3CCN (2 mL) was dissolved in CH_2Cl_2 (1 mL), to the solution was added NaH (1.5 mg, 0.037 mmol) at 0 ^oC. This mixture was stirred for 20 min, before it was concentrated in vacuum. The residue was directly purified by flash column chromatography (hexane:acetone = 4:1) to yield **3** (226 mg, 90%) as colorless syrup. R_f: 0.28 (hexane:acetone = 6:1). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.73 (s, 1 H), 7.38-7.18 (m, 15 H), 6.28 (d, *J* = 2.0 Hz, 1 H), 5.48 (t, *J* = 2.0 Hz, 1 H), 4.87 (d, *J* = 10.8 Hz, 1 H), 4.71 (d, *J* = 11.2 Hz, 1 H), 4.66 (d, *J* = 12.0 Hz, 1 H), 4.56 (d, *J* = 11.2 Hz, 1 H), 4.54 (d, *J* = 10.8 Hz, 1 H), 4.51 (d, *J* = 12.0 Hz, 1 H), 4.03-3.94 (m, 3 H), 3.83 (dd, *J* = 10.8, 3.6 Hz, 1 H), 3.71 (dd, *J* = 11.6, 1.6 Hz, 1 H), 2.80-2.67 (m, 4 H), 2.15 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) 206.5, 172.1, 160.2, 138.4, 138.3, 137.8, 128.7, 128.6, 128.6, 128.5, 128.5, 128.4, 128.3, 128.12, 128.06, 127.9, 95.5, 75.7, 74.5, 73.8, 73.7, 72.1, 68.6, 67.7, 53.7, 38.2, 30.0, 28.3. MS is not available as the sample was unstable.

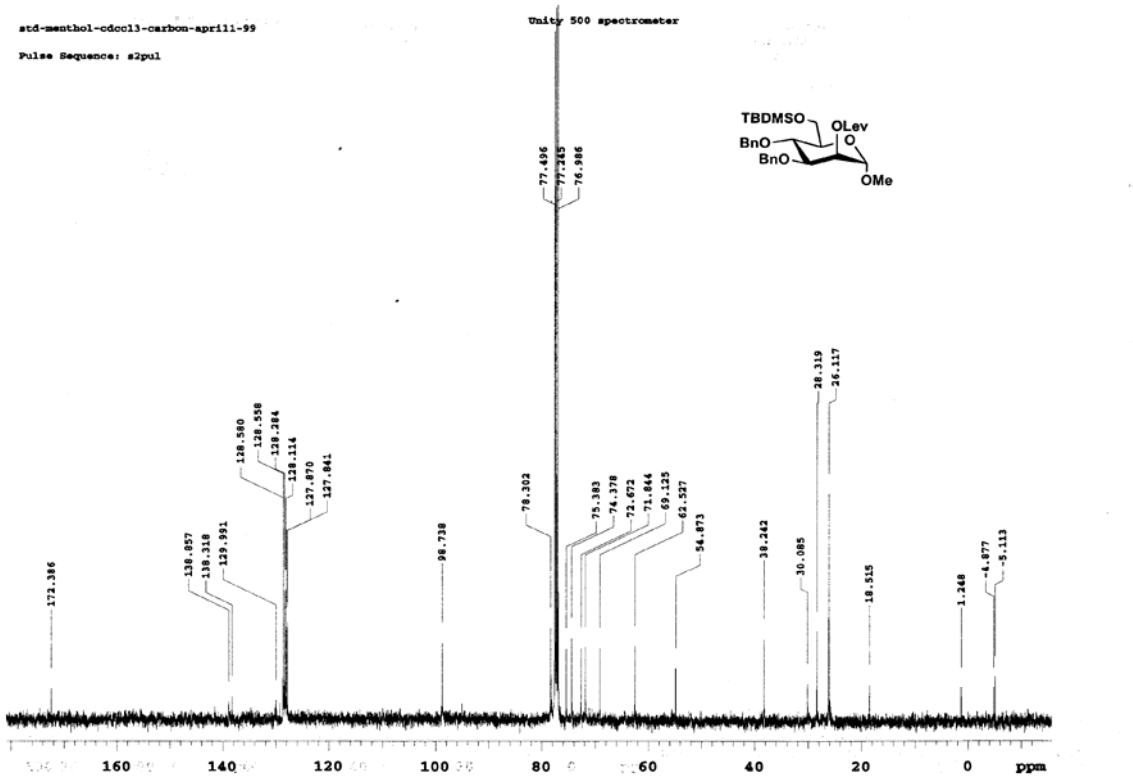
Ethyl 3,4,6-tri-O-benzyl-2-O-(4-(5-(ethoxycarbonyl)pentyloxy)benzyl)-1-thio-α-D-mannopyranoside (12) To a stirred solution of compound **9** (250 mg, 0.417 mmol) in DMF (4 mL) was added NaH (25 mg, 0.626 mmol) at 0^oC. The resultant suspension was stirred for 20 min and then a solution of ethyl 6-(4-bromomethylphenyloxyl)-hexanoate (206 mg, 0.626 mmol) in DMF (1mL) was added dropwise at -5 ^oC. The reaction mixture was stirred at this temperature for 1 h. After MeOH was added to quench the reaction, the reaction mixture was washed with brine, dried over Na_2SO_4 and then concentrated in vacuo. The residue was purified by flash column chromatography (toluene:EtOAc = 20:1) to yield **12** (318 mg, 90%). R_f: 0.34 (toluene:EtOAc = 10:1). $[\alpha]_D^{20}$ +44.9 (c 4.0 , $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.38-7.14 (m, 17 H), 6.80 (d, *J* = 8.8 Hz, 1 H), 5.38 (s, 1 H), 4.88 (d, *J* = 11.2 Hz, 1 H), 4.67-4.64 (m, 2 H), 4.58 (d, *J* = 12.4 Hz, 1 H), 4.54-4.47 (m, 4 H), 4.16-4.09 (m, 3 H), 4.00 (t, *J* = 8.8 Hz, 1 H), 3.92 (t, *J* = 6.4 Hz, 2 H), 3.84-3.78 (m, 3 H), 3.70 (dd, *J* = 10.8, 1.6 Hz, 1 H), 2.68-2.50 (m, 2 H), 2.37-2.30 (m, 3 H), 1.84-1.75 (m, 2 H), 1.75-1.66 (m, 2 H), 1.56-1.46 (m, 2 H), 1.28-1.20 (m, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$) 173.9, 138.8, 138.6, 138.5, 132.2, 130.2, 129.8, 128.6, 128.5, 128.5, 128.1, 127.99, 127.97, 127.8, 127.8, 127.7, 115.0, 114.6, 82.0, 80.5, 75.9, 75.3, 75.3, 73.5, 72.2, 72.1, 71.7, 69.4, 68.3, 67.9, 60.5, 34.5, 34.4, 29.9, 29.2, 29.0, 25.9, 25.8, 25.5, 25.0, 24.9, 15.2, 14.5. FAB HRMS (m/e): cacl. for $C_{44}H_{54}NaO_8S$ ($M + Na^+$) 765.3437, found 765.3438.

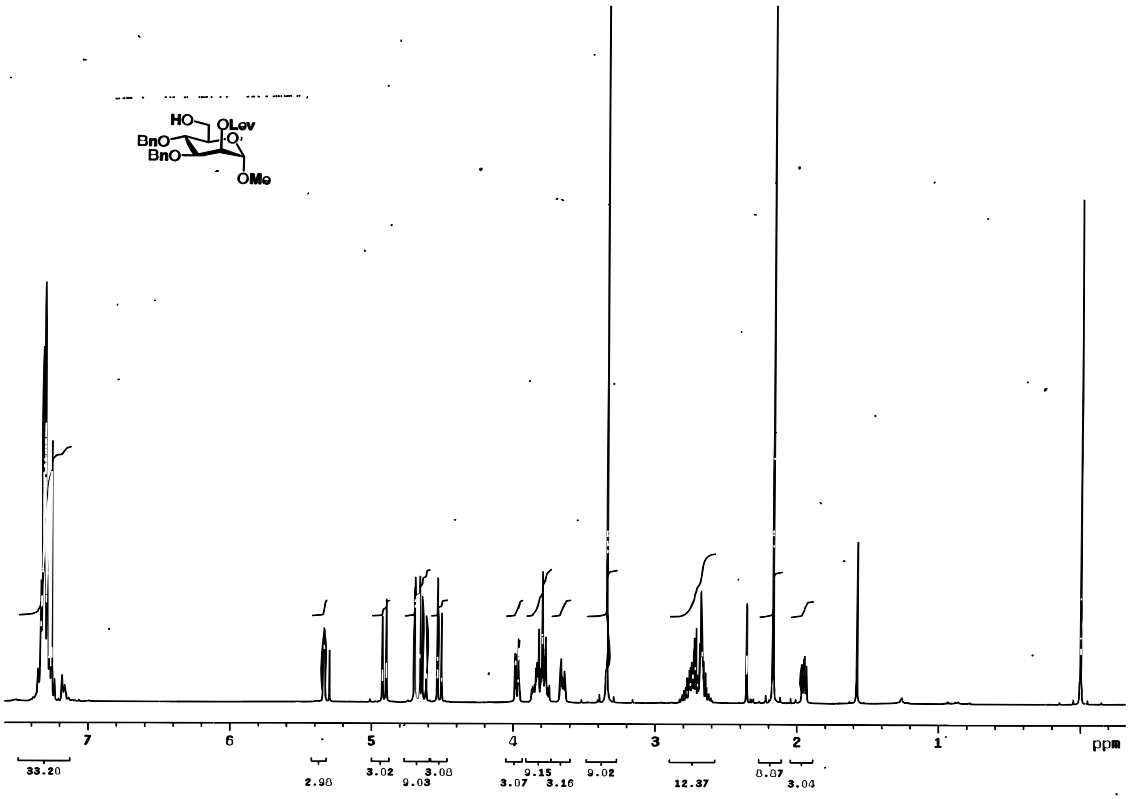
3,4,6-tri-O-Benzyl-2-O-(4-(5-(ethoxycarbonyl)pentyloxy)benzyl)-α-D-mannopyranose (13). To a stirred solution of **12** (250 mg, 0.337 mmol) in CH_3CN (3 mL) and H_2O (0.3 mL) was added NIS (152 mg, 0.674 mmol). The reaction mixture was stirred at rt for 5 min. Then, the mixture was diluted with CH_2Cl_2 and washed with saturated $Na_2S_2O_3$ and brine. The organic layer was combined, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (toluene:EtOAc = 5:1) to yield **13** (233mg, 99%) as colorless syrup. R_f : 0.20 (toluene:EtOAc = 5:1). ^{1}H NMR ($CDCl_3$, 400 MHz, α-anomer as the major product): δ 7.38-7.12 (m, 17 H), 6.77 (d, *J* = 8.8 Hz, 1 H), 5.19 (t, *J* = 2.4 Hz, 1 H), 4.85 (d, *J* = 10.8 Hz, 1 H), 4.70-4.44 (m, 7 H), 4.10 (q, *J* = 7.2 Hz, 2 H), 4.02-3.96 (m, 1 H), 3.94-3.86 (m, 3 H), 3.82 (t, *J* = 9.6 Hz, 1 H), 3.76 (t, *J* = 2.4 Hz, 1 H), 3.71-3.61 (m, 2 H), 2.91 (d, *J* = 3.2 Hz, 1 H), 2.31 (t, *J* = 7.6 Hz, 2 H), 1.82-1.73 (m, 2 H), 1.72-1.63 (m, 2 H), 1.52-1.44 (m, 2 H), 1.23 (t, *J* = 7.2 Hz, 3 H).

3,4,6-tri-O-Benzyl-2-O-(4-(5-(ethoxycarbonyl)pentyloxy)benzyl)-α-D-mannopyranosyl trichloroimidate (4). After **13** (200 mg, 0.287 mmol) and Cl_3CCN (2 mL) was dissolved in CH_2Cl_2 (1m L), to the solution was added NaH (1.2 mg, 0.029 mmol) with stirring at 0 ^{o}C. Twenty minutes later, the reaction mixture was concentrated in vacuo and the residue was purified by flash column chromatography (toluene:EtOAc = 30:1) to yield **4** (216 mg, 90%) as colorless syrup. The ^{13}C NMR spectrum was not measured for **4**, because this glycosyl immidate was relatively unstable. R_f: 0.42 (toluene:EtOAc = 8:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.53 (s, 1 H), 7.36-7.14 (m, 17 H), 6.81 (d, *J* = 8.8 Hz, 2 H), 6.35 (d, *J* = 1.6 Hz, 1 H), 4.74-4.50 (m, 7 H), 4.16-4.09 (m, 3 H), 3.99-3.88 (m, 4 H), 3.86 (t, *J* = 2.4 Hz, 1 H), 3.81 (dd, *J* = 11.2, 4.4 Hz, 1 H), 3.72 (dd, *J* = 11.2, 1.6 Hz, 1 H), 2.33(t, *J* = 8.0 Hz, 2 H), 1.84-1.75 (m, 2 H), 1.75-1.65 (m, 2 H), 1.55-1.44 (m, 2 H), 1.25 (t, *J* = 7.2 Hz, 3 H). MS is not available as the sample was unstable.

II. Selected NMR spectra:



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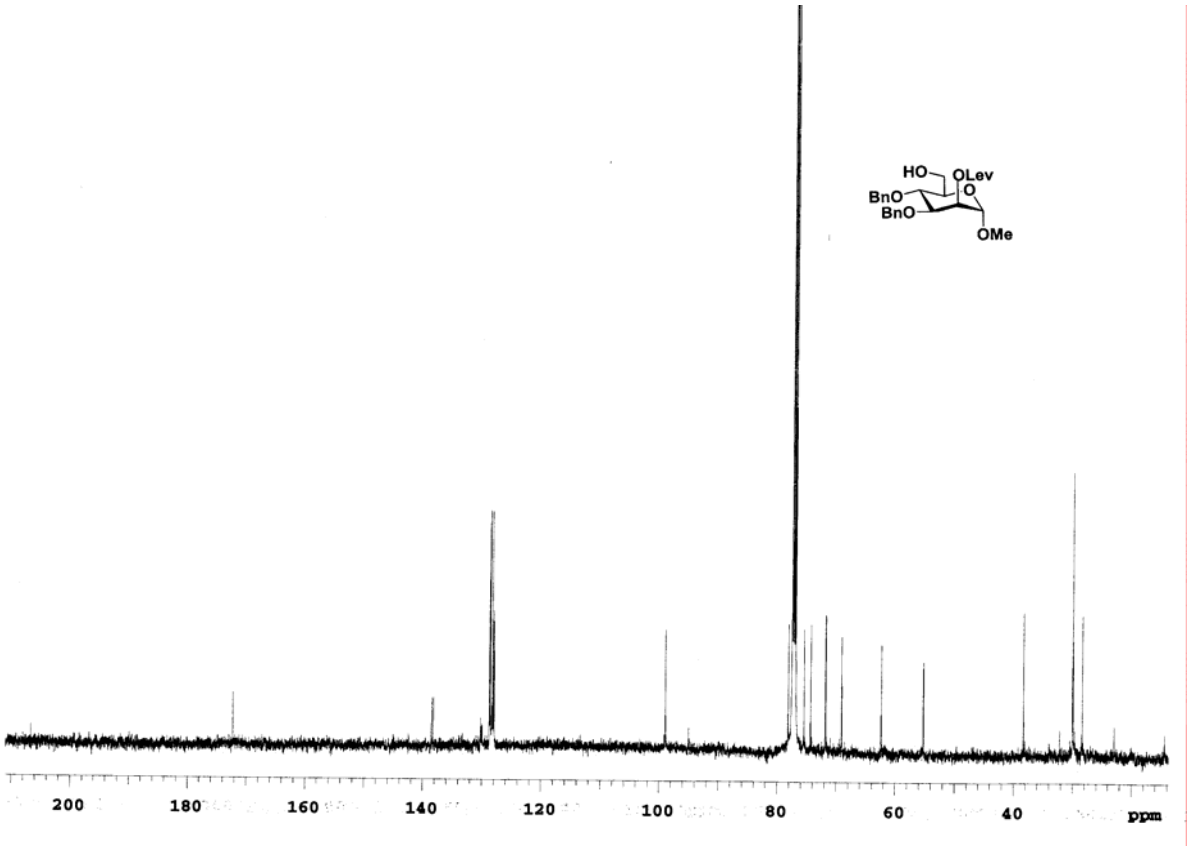
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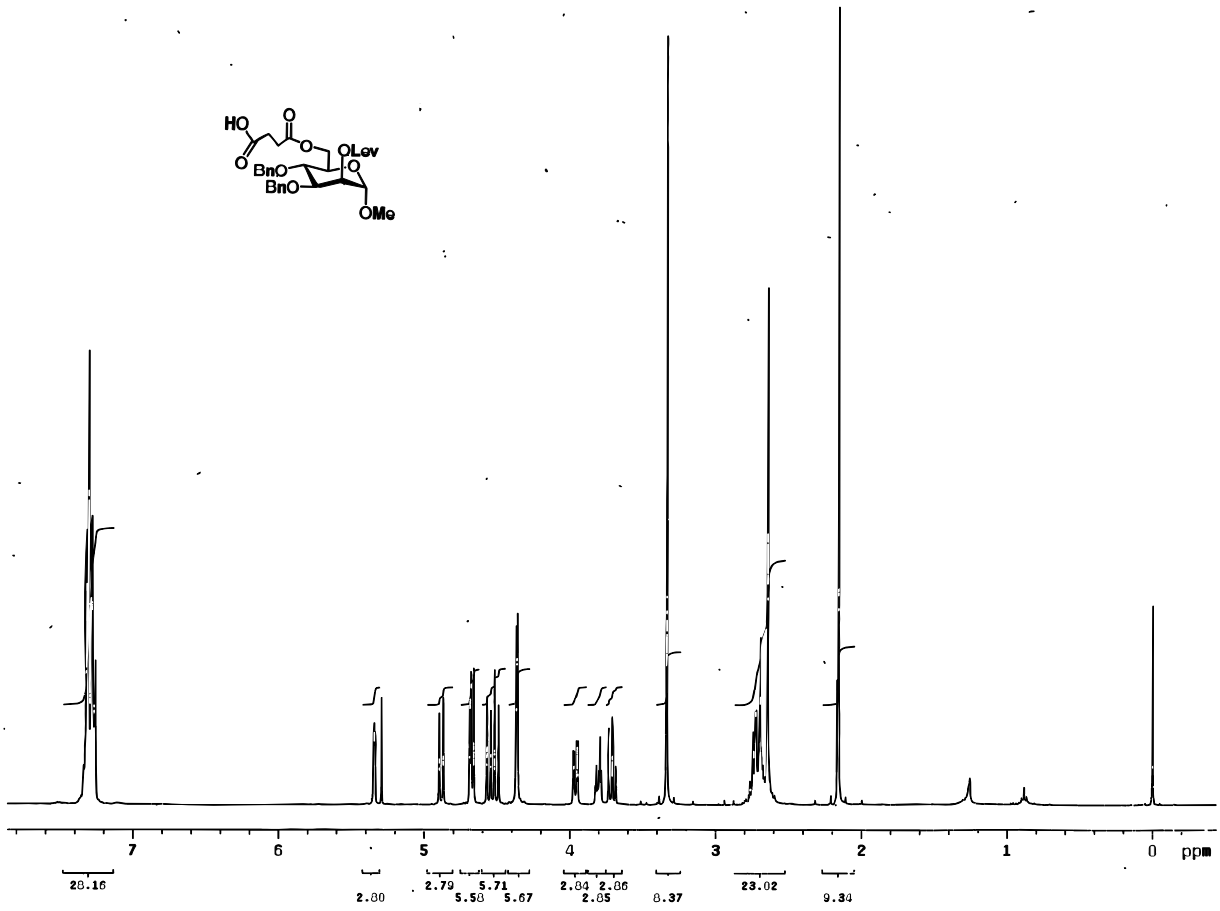
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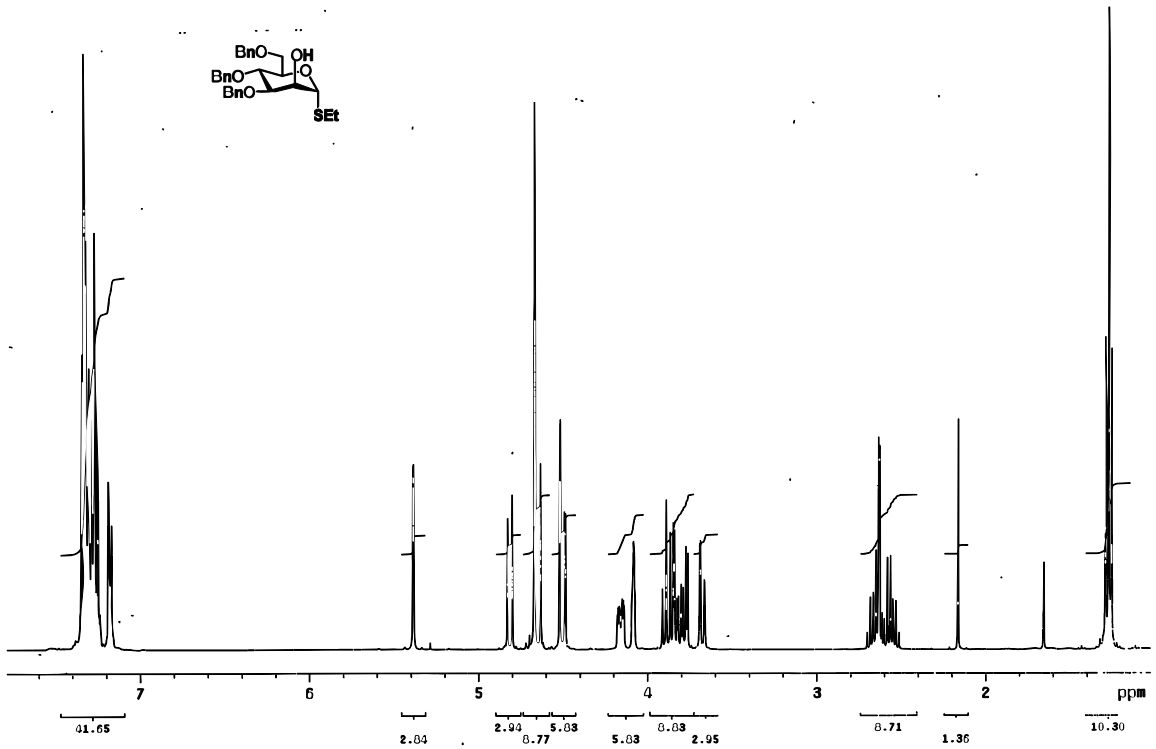
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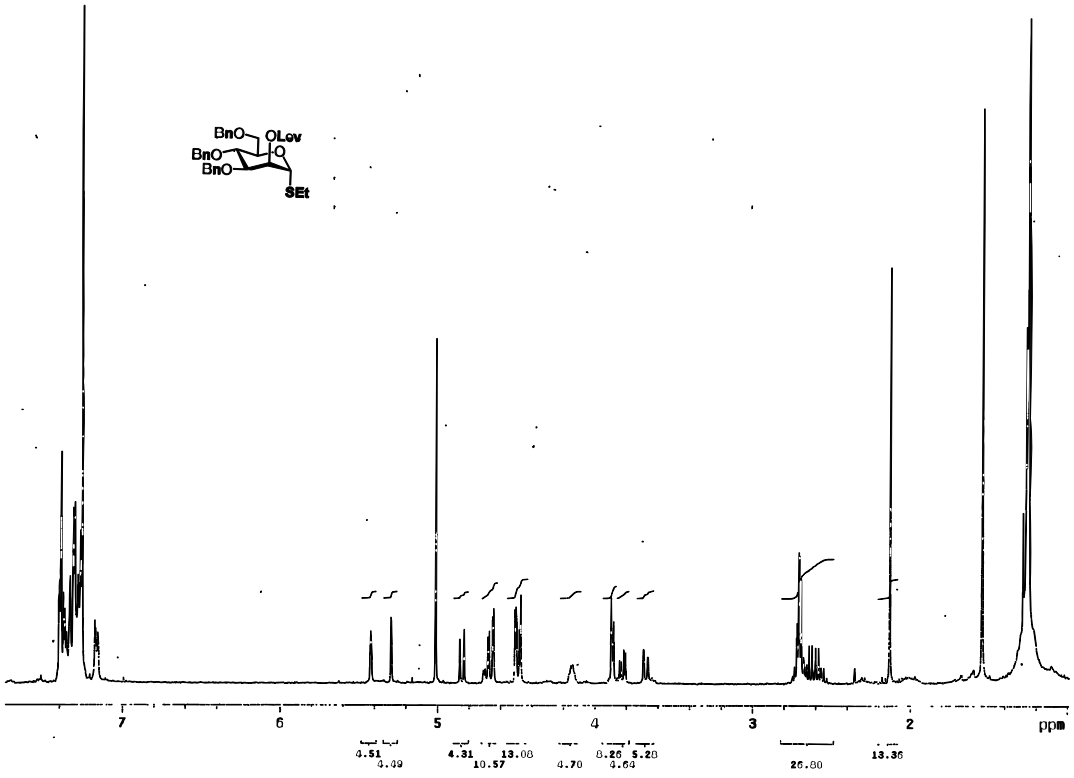
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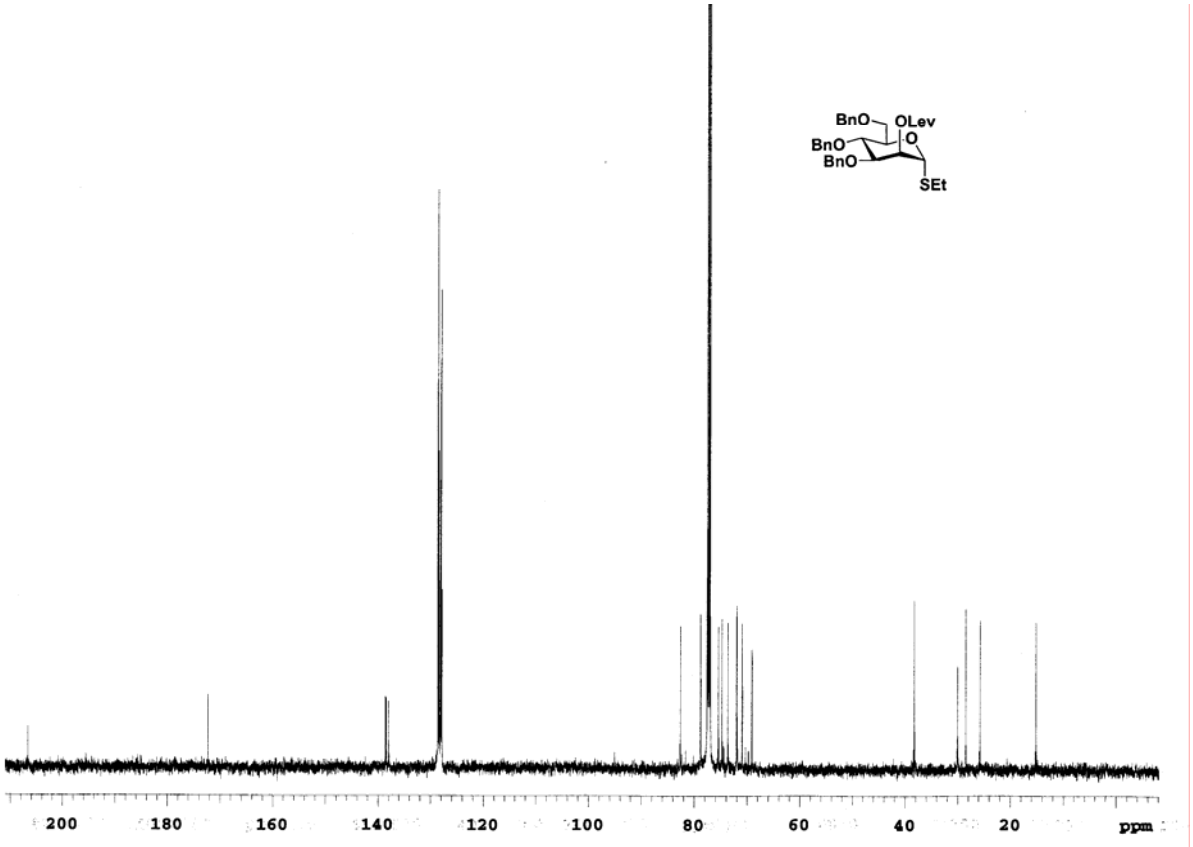
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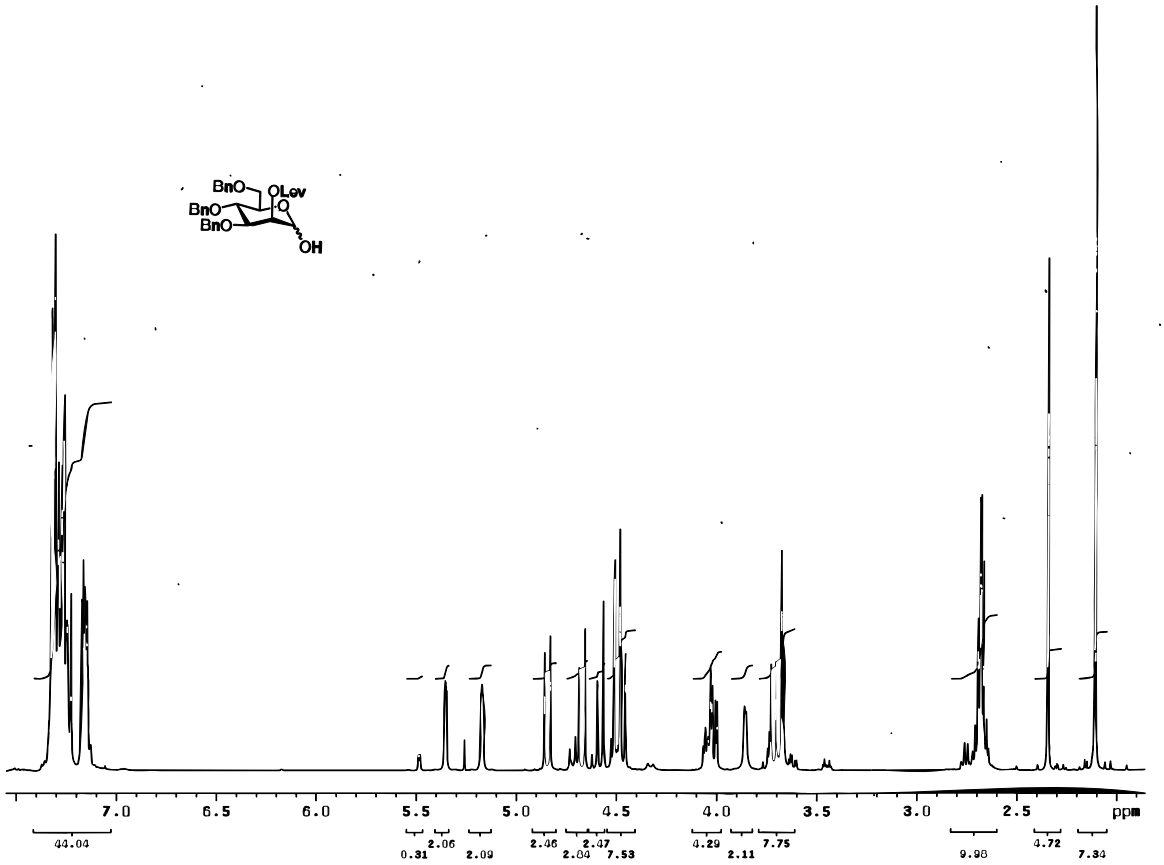
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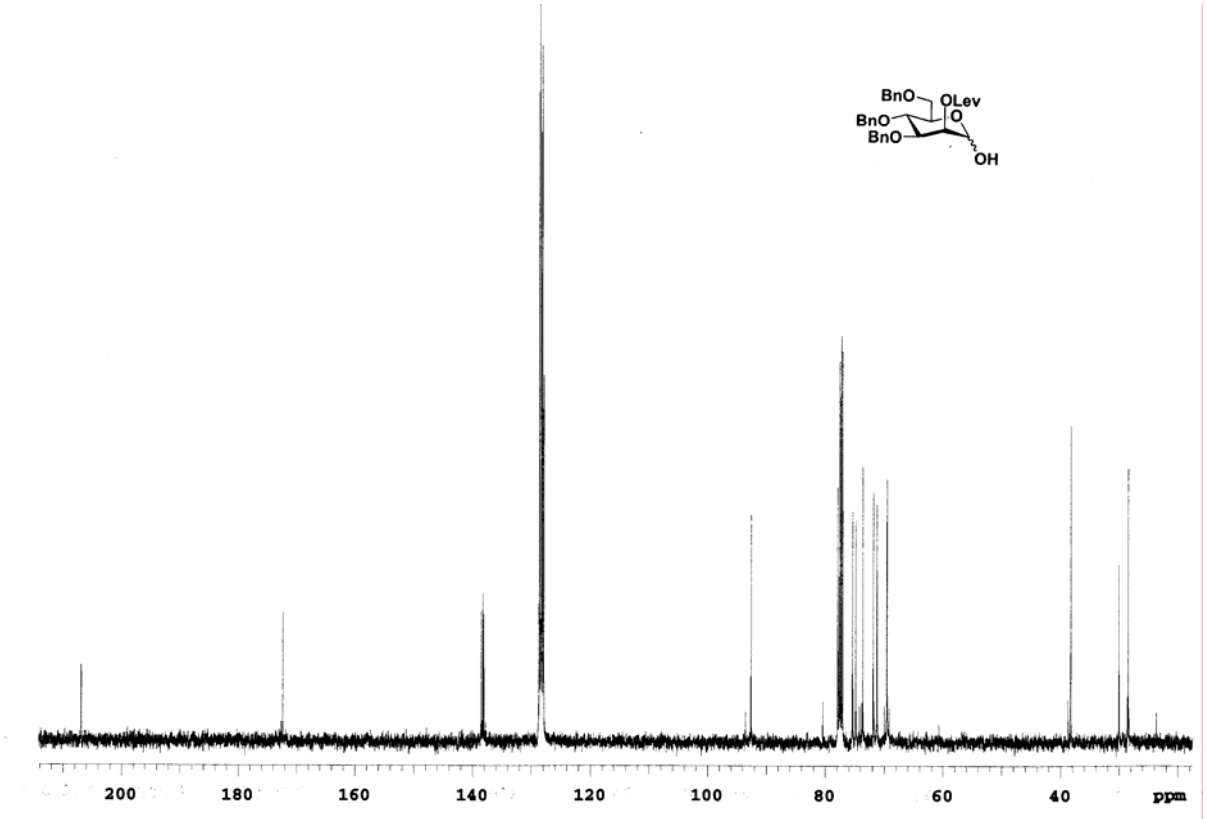
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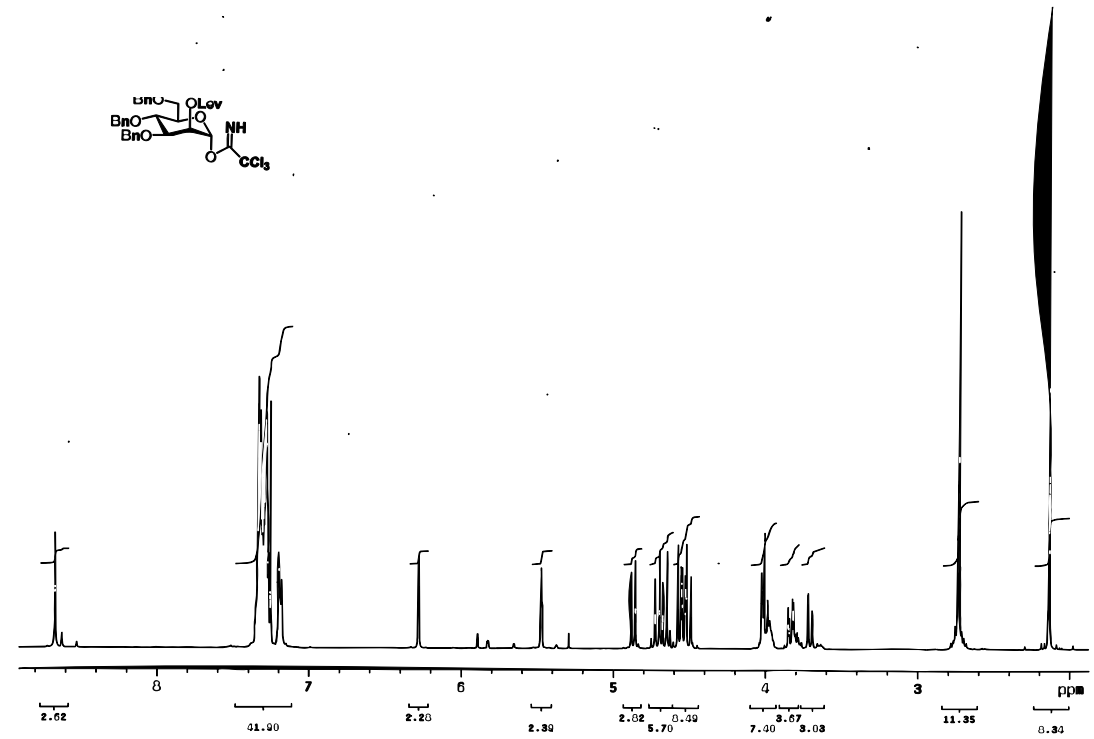
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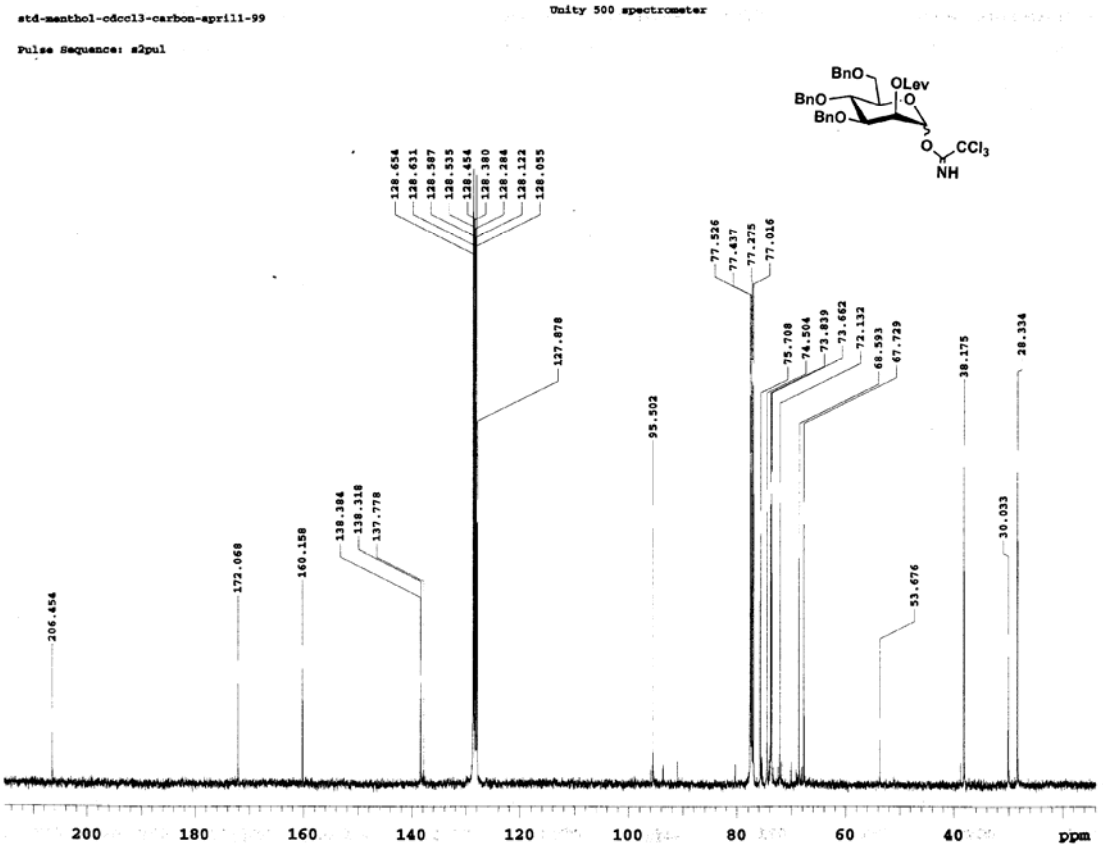
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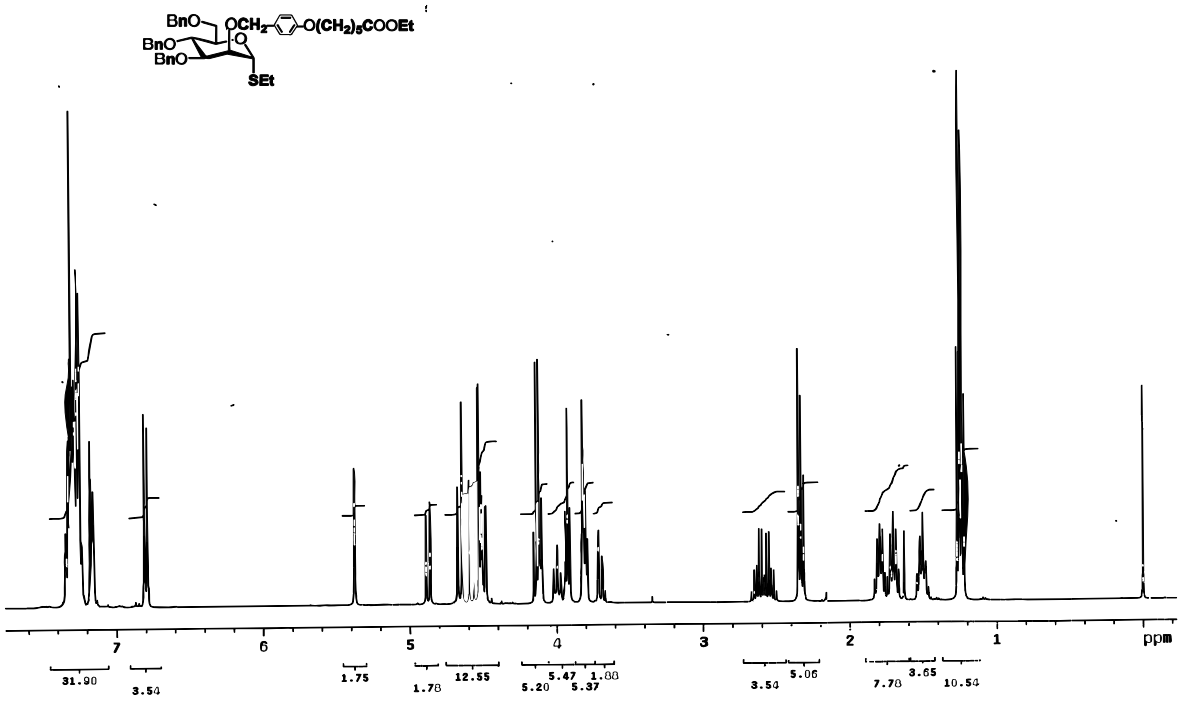
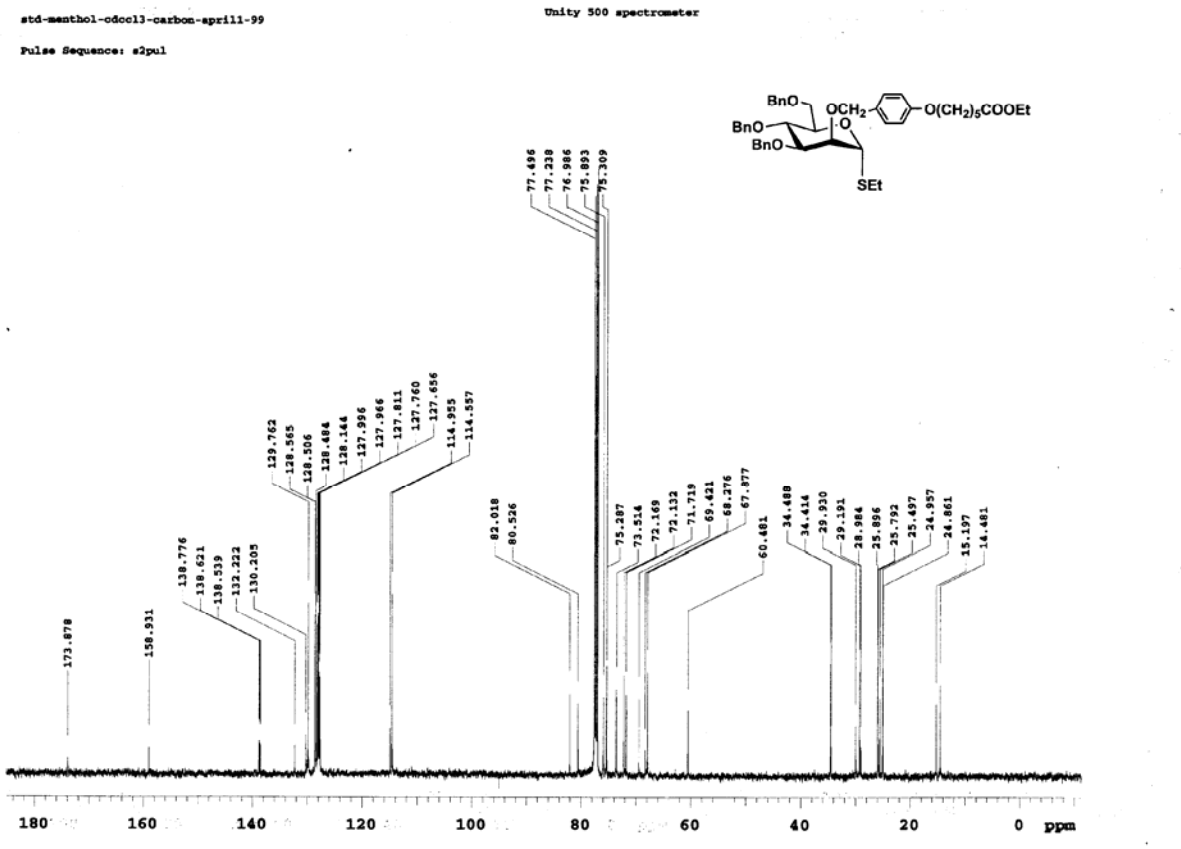
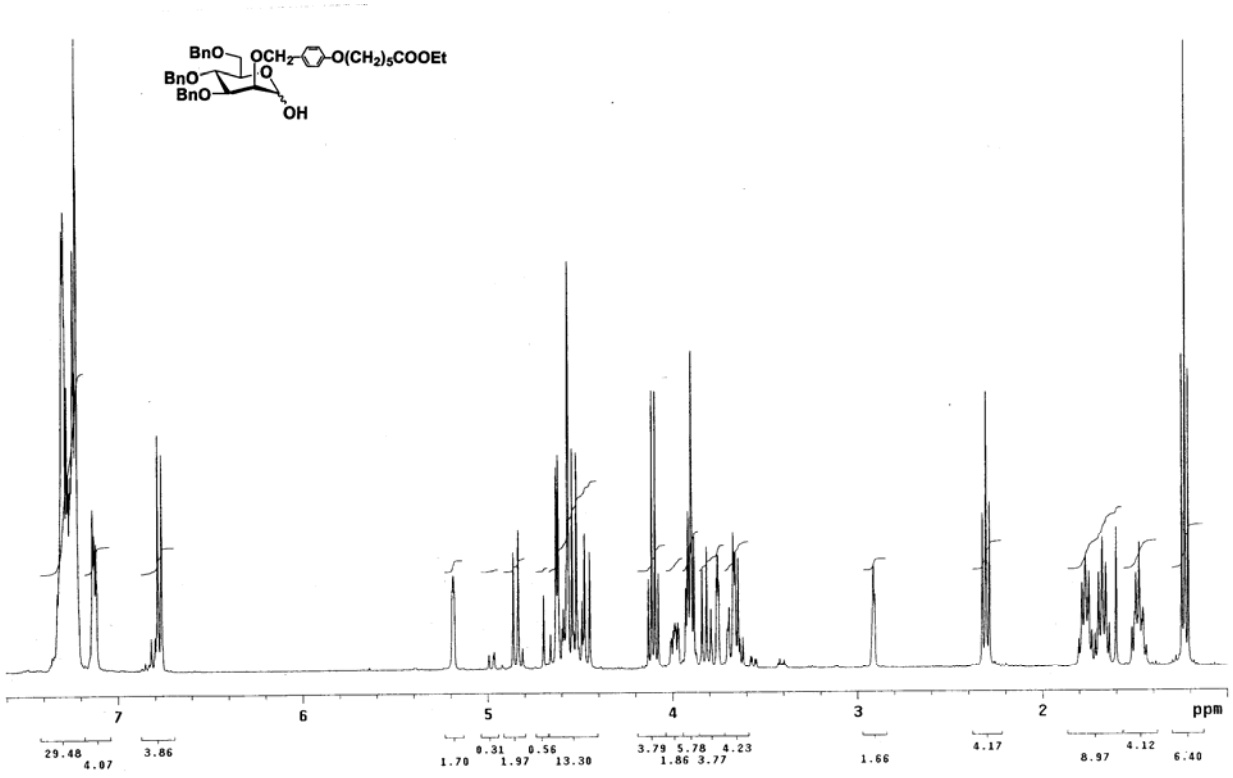
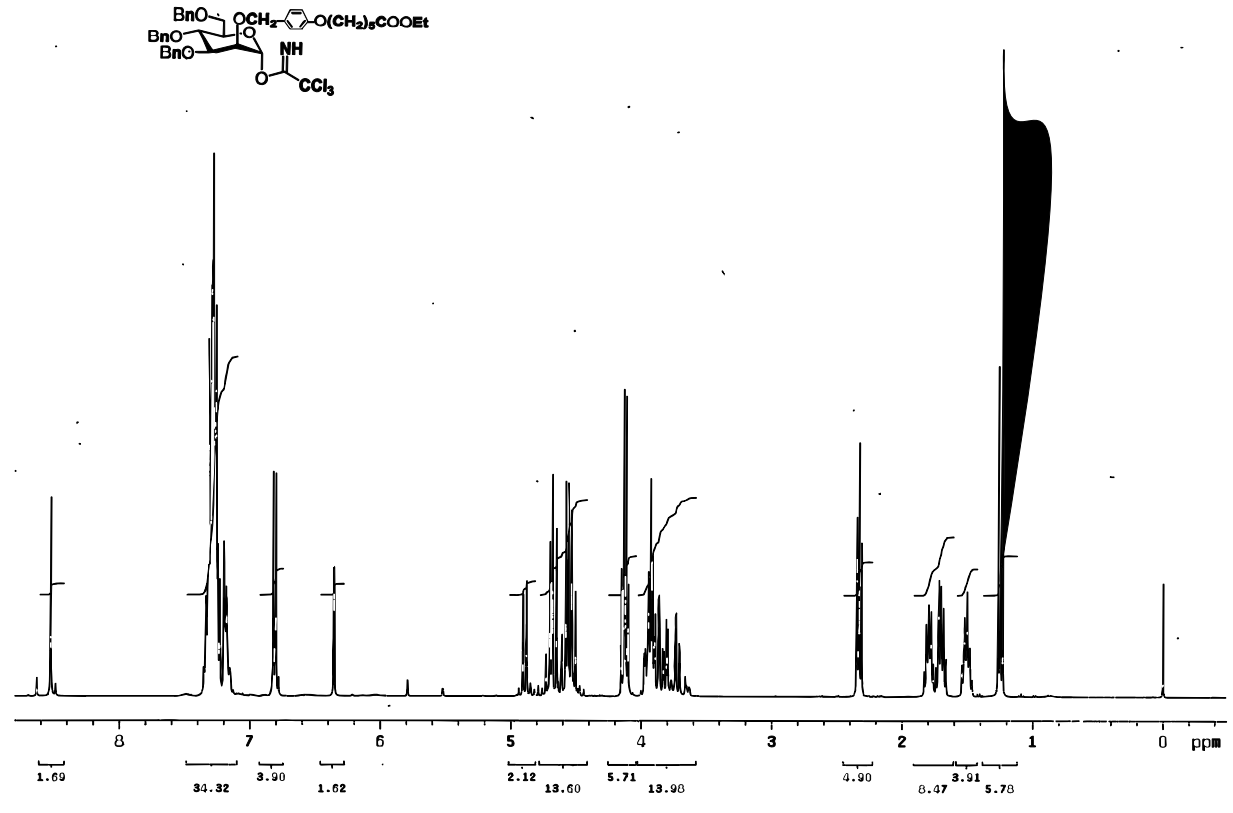
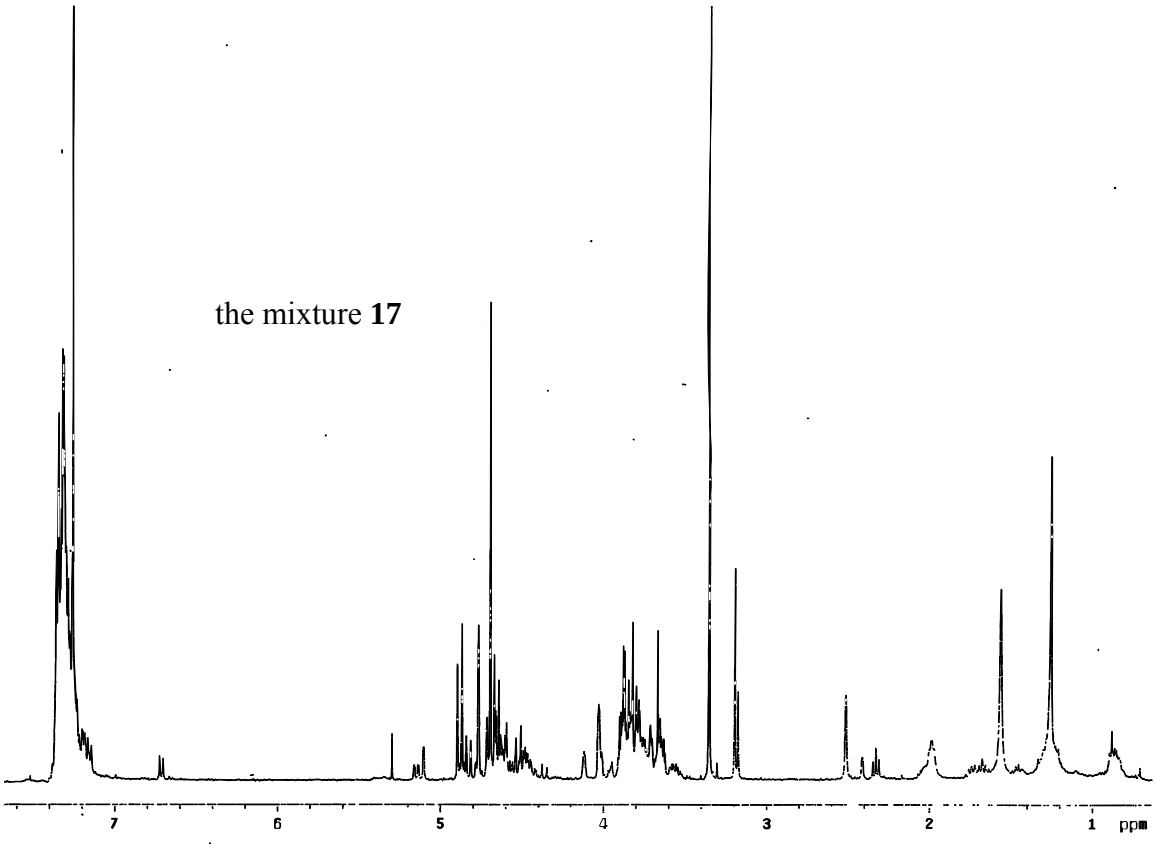
128.587
128.535
128.454
128.380
128.284
128.122
128.055
127.878
95.502
77.526
77.437
77.275
77.016
75.708
74.504
73.839
73.662
72.132
68.593
67.729
38.175
28.334
30.033
53.676
206.454
172.068
160.158
138.384
138.318
137.778
200
180
160
140
120
100
80
60
40
ppm

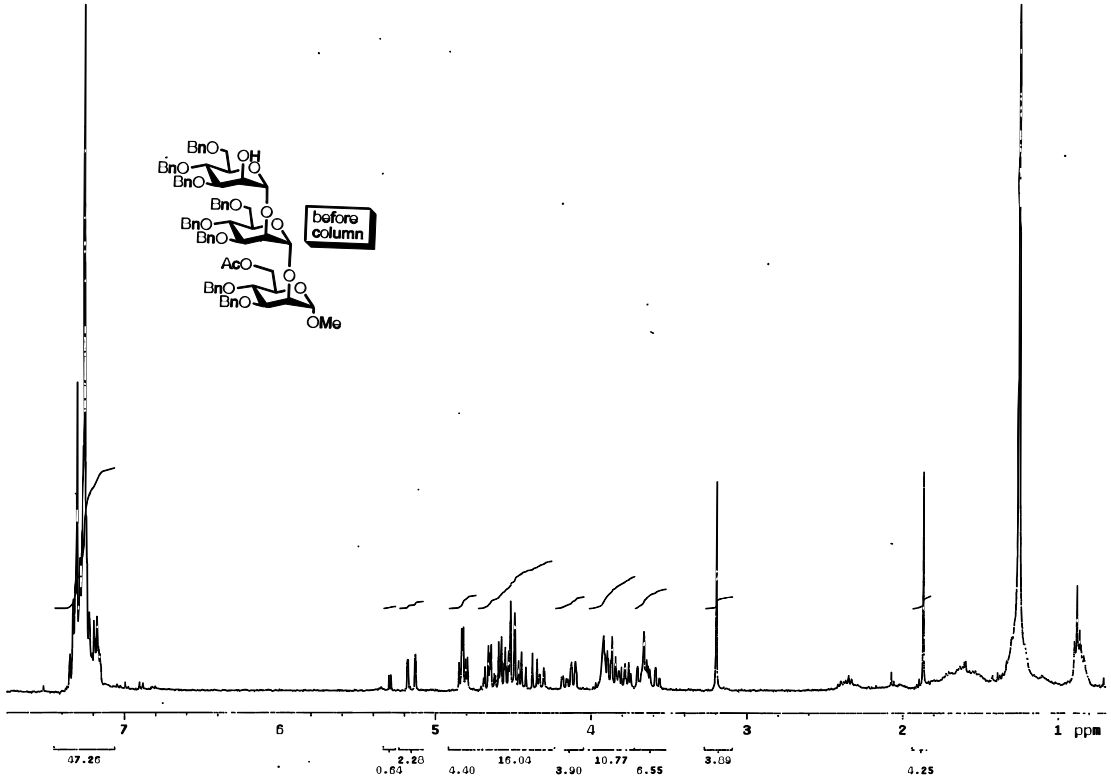

BnO
BnO
BnO
OCH2
O(CH2)5COOEt
SEt
7
6
5
4
3
2
1
ppm
31.90
3.54
1.75
1.78
12.55
5.20
5.47
5.37
1.00
3.54
5.06
7.70
3.65
10.54

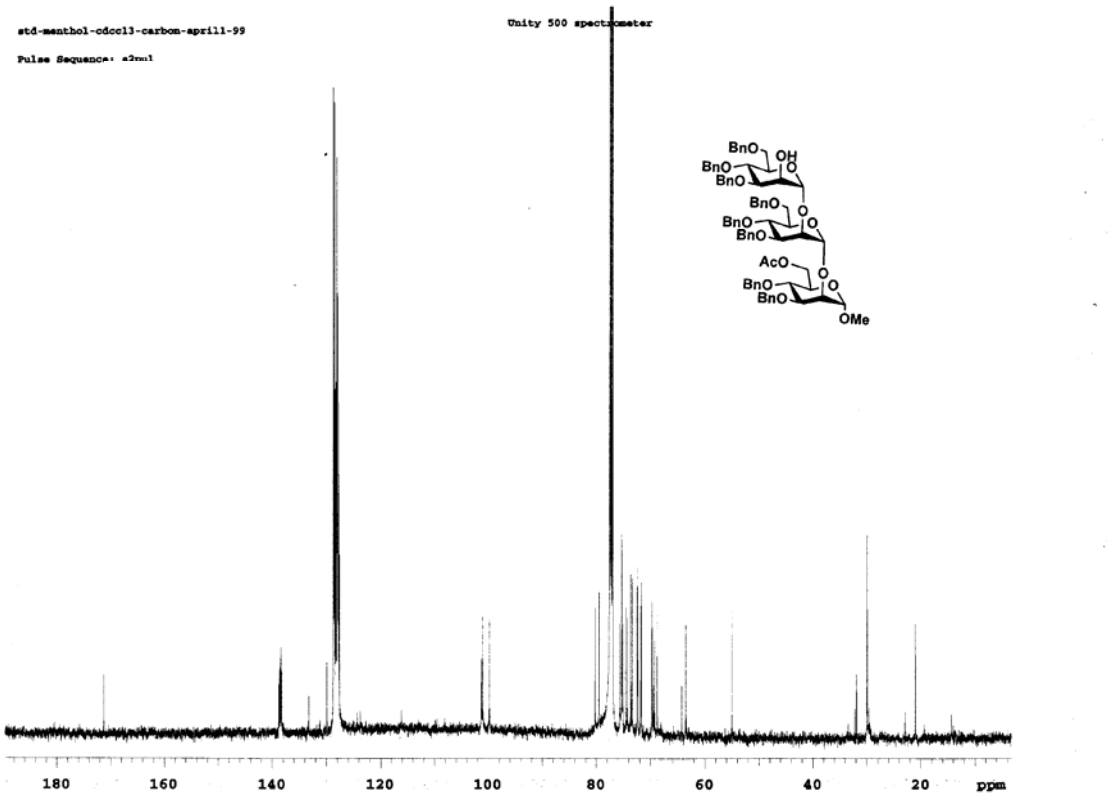

std-menthol-cdcl3-carbon-april1-99
Pulse Sequence: s2pul
Unity 500 spectrometer
BnO
BnO
BnO
OCH2
O(CH2)5COOEt
SEt
77.496
77.238
76.986
75.893
75.309
173.878
158.931
138.776
138.621
138.539
132.222
130.205
129.762
128.565
128.506
128.484
128.144
127.996
127.966
127.811
127.760
127.656
114.955
114.557
82.018
80.526
75.287
73.514
72.169
72.132
71.719
69.421
68.276
67.977
60.481
34.488
34.414
29.930
29.191
28.984
25.896
25.792
25.497
24.957
24.861
15.197
14.481
180
160
140
120
100
80
60
40
20
0
ppm

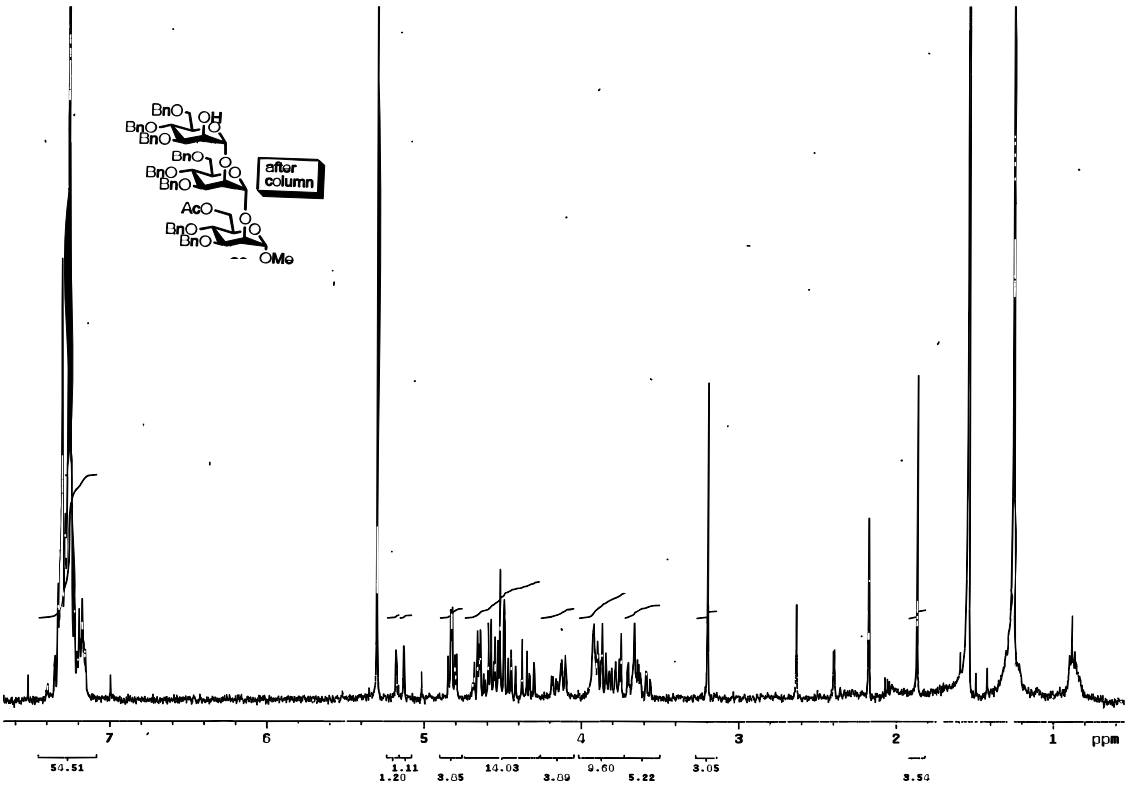

BnO
BnO
BnO
OCH2
O(CH2)5COOEt
OH
7
6
5
4
3
2
ppm
29.48
4.07
3.86
1.70
0.31
1.97
0.56
13.30
3.79
5.78
4.23
1.86
3.77
1.66
4.17
8.97
4.12
6.40


BnO
BnO
BnO
OCH2
O(CH2)5COOEt
NH
CCl3
8
7
6
5
4
3
2
1
0
ppm
1.69
34.32
3.90
1.62
2.12
13.60
5.71
13.98
4.90
8.47
3.91
5.78


the mixture **17**
7
6
5
4
3
2
1 ppm


BnO
OH
BnO
BnO
BnO
BnO
BnO
AcO
BnO
BnO
OMe
before column
7
6
5
4
3
2
1 ppm
47.26
2.28
0.63
4.40
16.03
3.90
10.77
6.55
3.09
4.25


std-menthol-cdcl3-carbon-april1-99
Unity 500 spectrometer
BnO
OH
AcO
OMe
180
160
140
120
100
80
60
40
20
ppm


after column
7
6
5
4
3
2
1
ppm
50.51
1.11
1.20
3.85
14.03
3.89
9.60
5.22
3.05
3.54