**Supporting Information**

# Divergent synthesis of new α-glucosidase inhibitors obtained through a vinyl Grignard-mediated carbocyclisation

Ida M. B. Knudsen, Christinne Hedberg, Lucy Kate Ladefoged, Daisuke Ide, Anne Brinkø, Espen Z. Eikeland, Atsushi Kato and Henrik H. Jensen

## Table of Contents

## Single Crystal X-Ray Diffraction Analysis

Table 1 gives crystallographic information for compound **14** solved using single crystal X-ray diffraction. The structure has been given the CCDC number 1843347. A single crystal, with crystal dimensions 0.4x0.3x0.1 $mm^3$, was mounted on a goniometer and diffraction data was collected using a single crystal X-ray diffractometer. The crystal was found to be stable during the experiment. The diffraction experiment was performed on a SuperNova diffractometer from Agilent Technologies, using $Mo_{K\alpha}$ radiation ($\lambda$ = 0.71073 Å). The diffracted intensities were collected on a CCD detector and data were integrated and corrected for absorption using CrysAlisPro.[1] The structure solution and refinement were carried out with SHELXS/SHELXT, using Olex2.[2,3]

**Table 1.** Crystallographic information for $C_{44}H_{43}N_3O_8$.

| **Sample** | **$C_{44}H_{43}N_3O_8$** |
|---|---|
| **Chemical formula**[a] | $C_{44}H_{43}N_3O_8$ |
| **Space group** | $P2_1$ |
| **Temperature / K** | 100 |
| **a / Å** | 13.67340(19) |
| **b / Å** | 10.41568(13) |
| **c / Å** | 27.6271(4) |
| **β / °** | 103.0654(14) |
| **Volume / Å$^3$** | 3832.73(9) |
| **Z** | 4 |
| **$\rho_{calc}$ / g/cm$^3$** | 1.286 |
| **μ / mm$^{-1}$** | 0.089 |
| **F(000)** | 1568 |
| **$(\sin\theta/\lambda)_{max}$ / Å$^{-1}$** | 0.62 |
| **$N_{Tot,obs}$** | 78664 |
| **$N_{Uniq,obs}$** | 15663 |
| **$N_{Parameters}$** | 993 |
| **Flack parameter** | -0.1(3) |
| **GOF** | 1.060 |
| **$R_{int}$** | 0.0484 |
| **$R_1$, $R_1[F^2>2\sigma(F^2)]$** | 0.0479, 0381 |
| **$wR_2$, $wR_2[F^2>2\sigma(F^2)]$** | 0.889, 0.832 |
| **$\Delta\rho_{max}$, $\Delta\rho_{min}$ / e Å$^{-3}$** | 0.174, -0.176 |

*1*) *C. Pro, Agil. Technol. UK Ltd., UK, Xcalibur/CCD Syst. CrysAlis PRO Softw. Syst. Version* **2010**, *1*. ***2***) Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H. *J. Appl. Crystallogr.* **2009**, *42*, 339–341. ***3***) Sheldrick, G. M. *Acta Cryst. A* **2015**, *71*, 3–8.

## Enzyme assay and Lineweaver-Burk Plots

The enzymes α-glucosidase (from rice and yeast), β-glucosidase (from almond and bovine liver), α-galactosidase (from coffee beans), β-galactosidase (from bovine liver), α-mannosidase (from jack bean), β-mannosidase (from snail), α-L-fucosidase (from bovine kidney), α,α-trehalase (from porcine kidney), amyloglucosidase (from *Aspergillus niger*), α-L-rhamnosidase (from *Penicillium decumbens*), β-glucuronidase (from bovine liver), β-*N*-acetyl-glucosaminidase (from jack bean), α-*N*-acetyl-glucosaminidase (from human, recombinant), *p*-nitrophenyl glycosides, and various disaccharides were purchased from Sigma-Aldrich Co. Brush border membranes were prepared from the rat small intestine according to the method of Kessler et al,[4] and were assayed at pH 6.8 for rat intestinal maltase using maltose. For rat intestinal maltase and sucrase activities, the reaction mixture contained 25 mM maltose and the appropriate amount of enzyme, and the incubations were performed for 10 min at 37 °C. The reaction was stopped by heating at 100 °C for 3 min. After centrifugation (600 g; 10 min), 0.05 mL of the resulting reaction mixture were added to 3 mL of the Glucose CII-test Wako (Wako Pure Chemical Ind., Osaka, Japan). The absorbance at 505 nm was measured to determine the amount of the released D-glucose. Other glycosidase activities were determined using an appropriate *p*-nitrophenyl glycoside as substrate at the optimum pH of each enzyme. The reaction mixture contained 2 mM of the substrate and the appropriate amount of enzyme. The reaction was stopped by adding 2 mL of 400 mM $Na_2CO_3$. The released *p*-nitrophenol was measured spectrometrically at 400 nm.

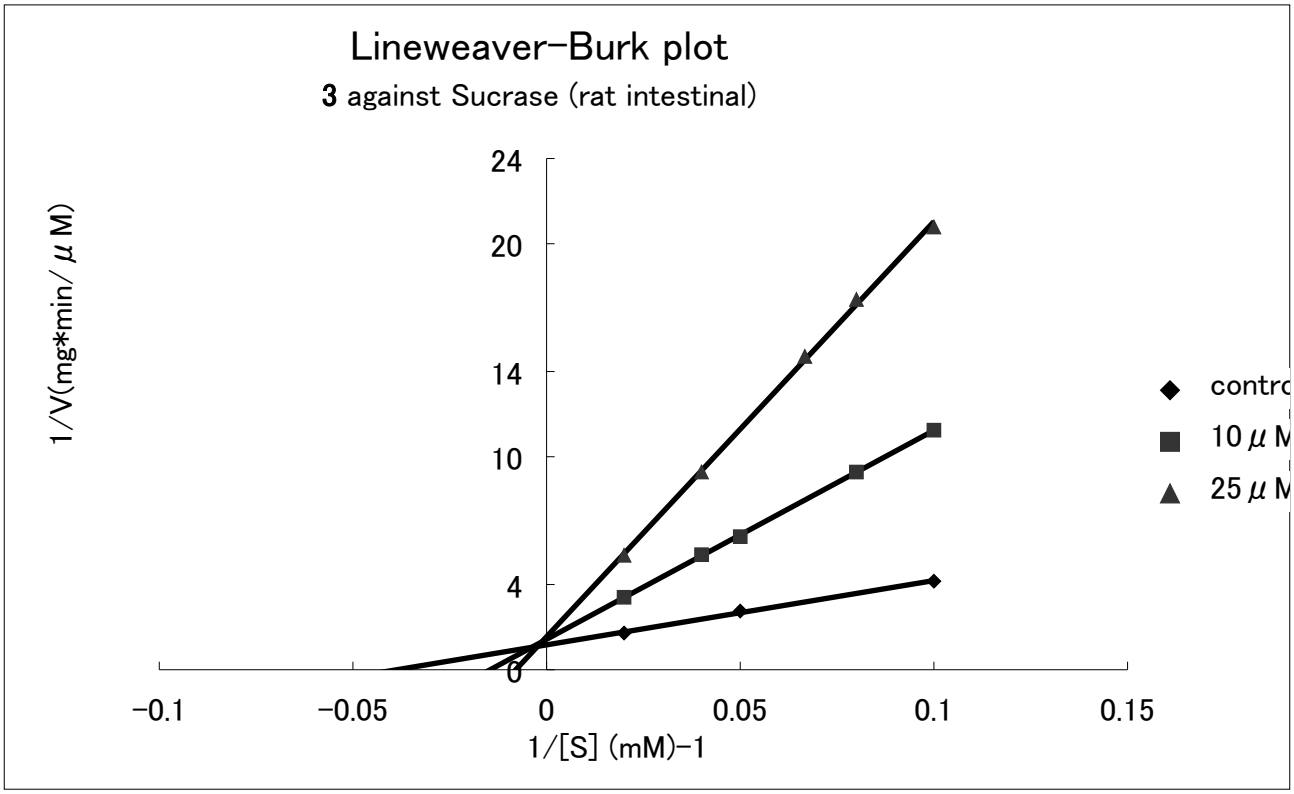



**Figure 1** Lineweaver-Burk plot, compound **3**

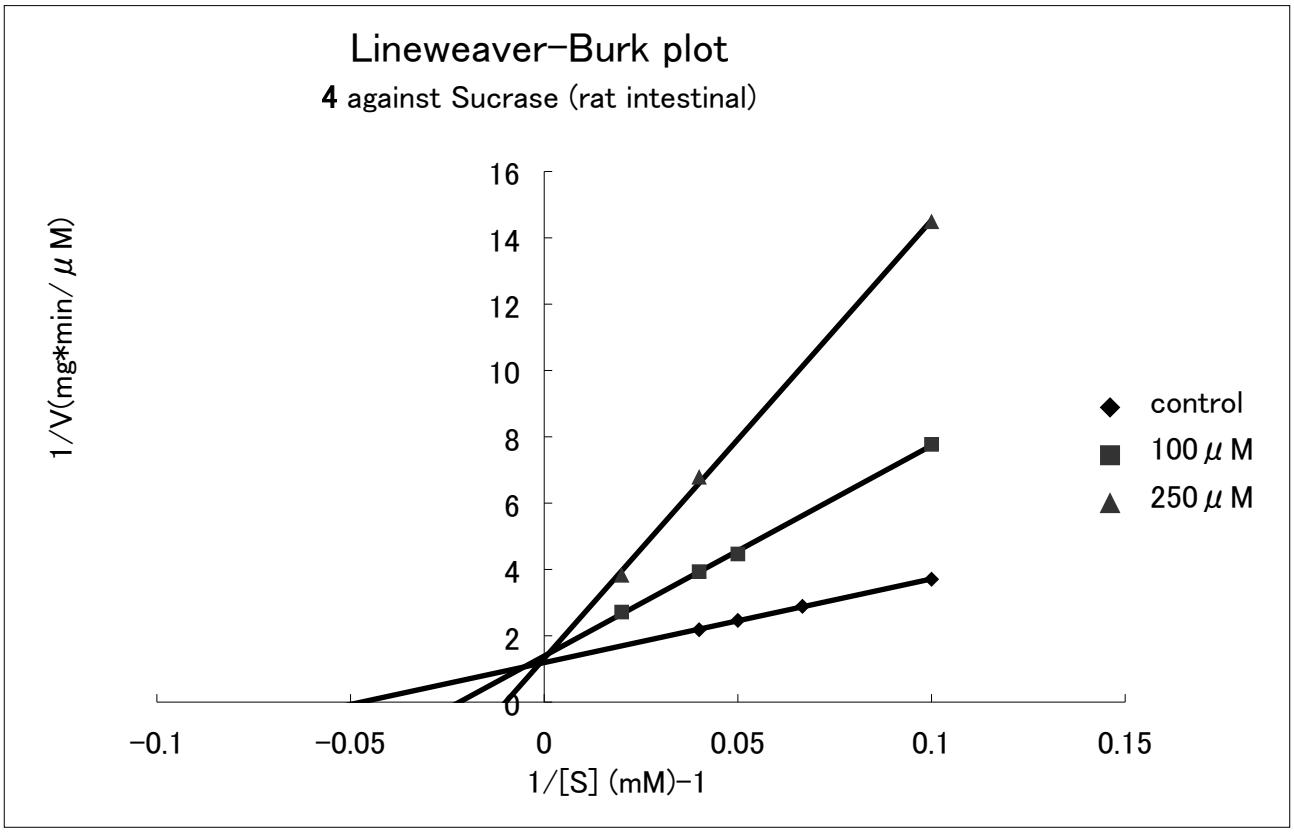



**Figure 2** Lineweaver-Burk plot, compound **4**

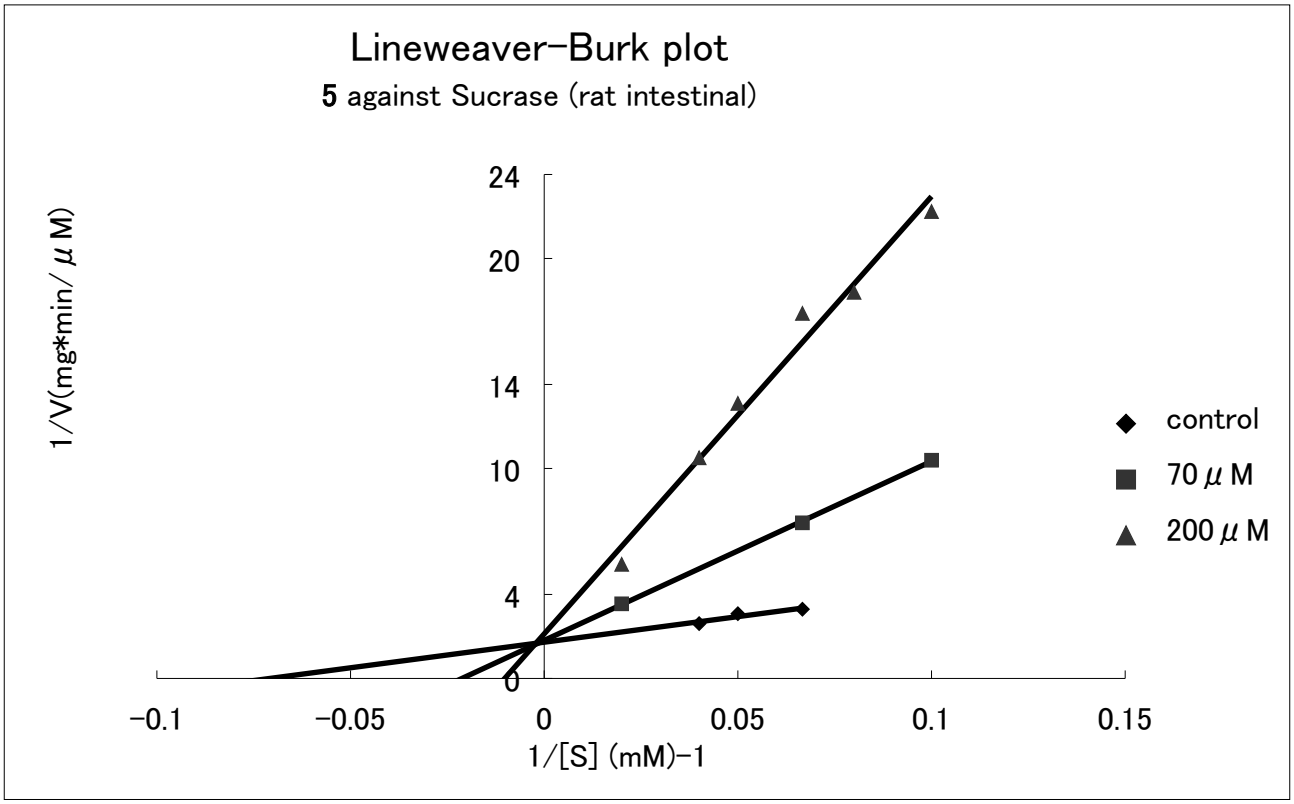



**Figure 3** Lineweaver-Burk plot, compound **5**

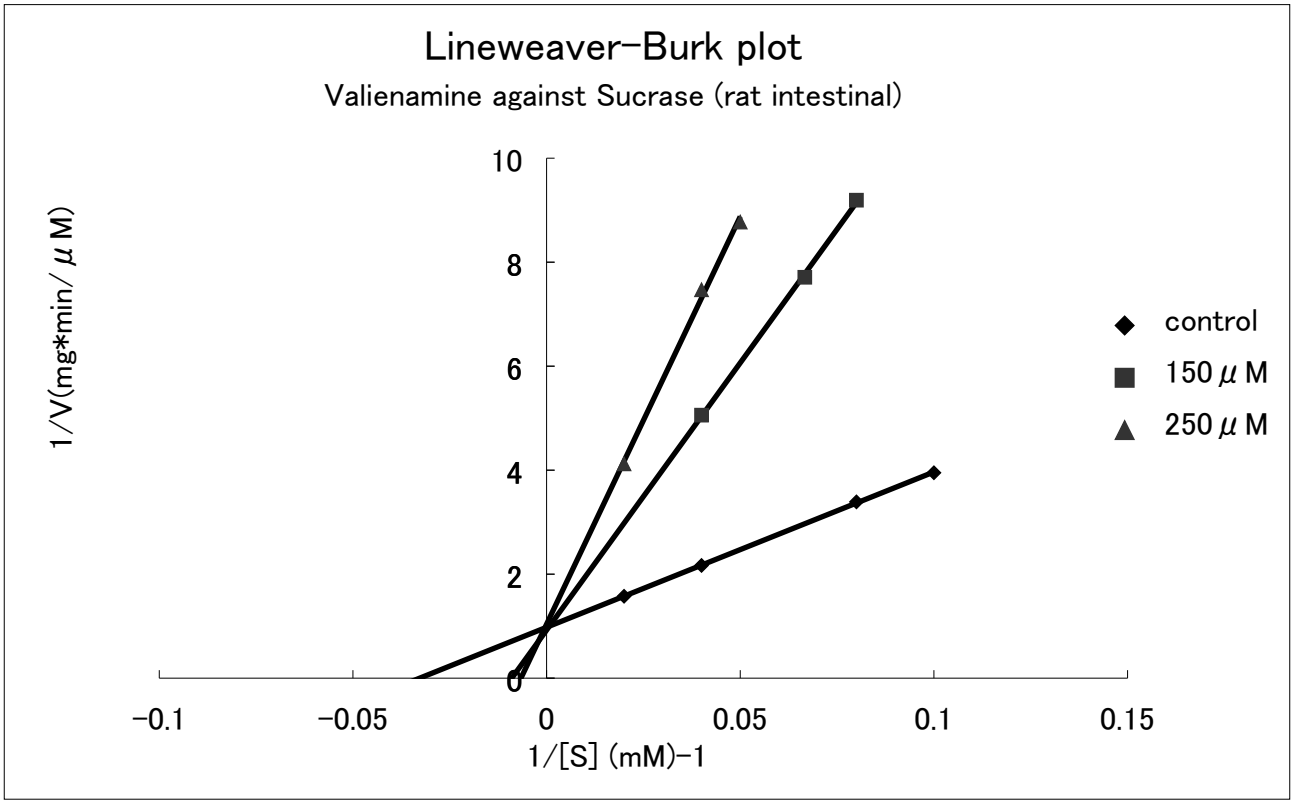



**Figure 4** Lineweaver-Burk plot, valienamine

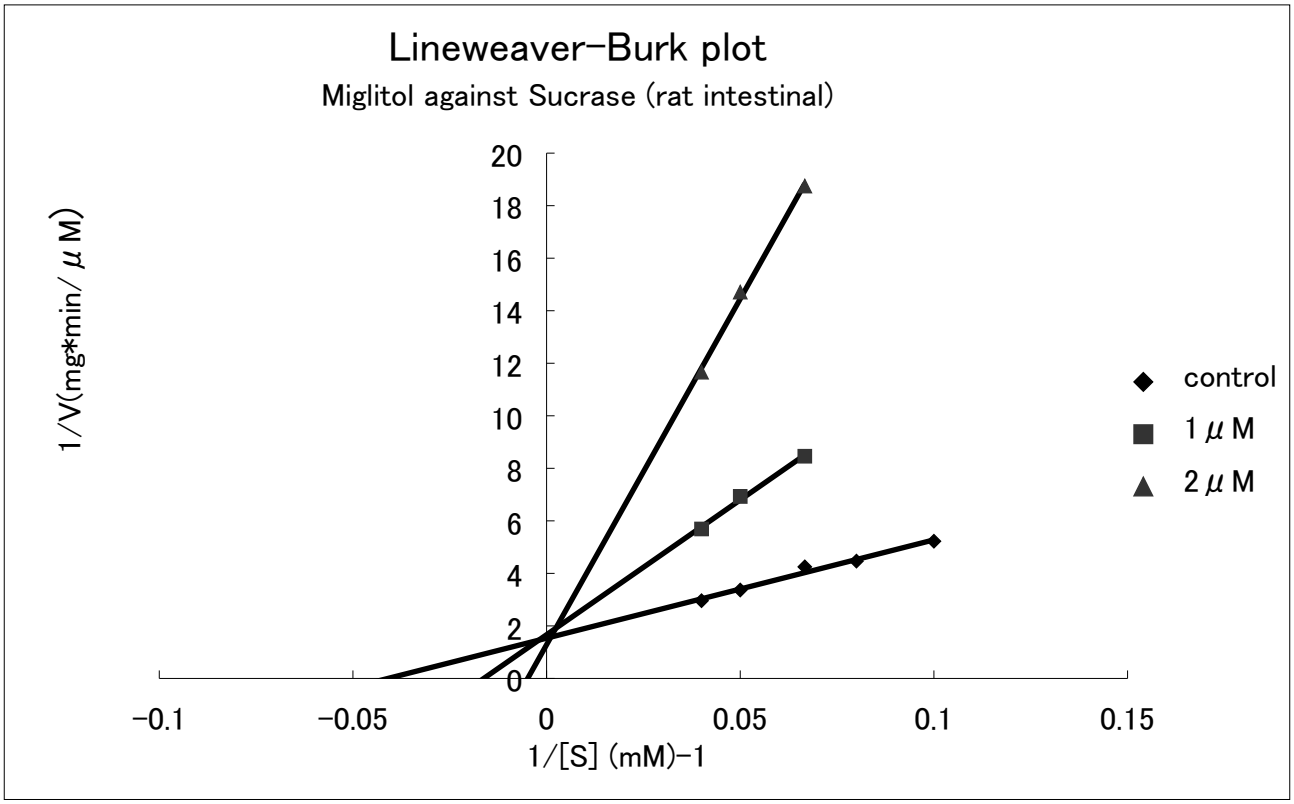



**Figure 5** Lineweaver-Burk plot, miglitol

## Docking Methods

Five homology models of the rat sucrase domain (uniprot ID P23739) were constructed using MODELLER[5] 9.19 based on the human isomaltase domain (PDB ID 3LPP[6], chain B) and the best model was selected based on DOPE score. The model was prepared using the Preparation Wizard within the Schrödinger Suite 2015 using default settings. Protonation states of relevant residues were determined using PROPKA 3[7] except for the nucleophile and proton donor, which were modelled as deprotonated and protonated, respectively. Asp1273, Asp1512, and Glu1451 were thus modelled as protonated, while histidines 1124, 1134, 1468, 1508, 1612, 1617, 1686, and 1698 were modelled in the ε–tautomeric state. All other residues were modelled in their default states. The model was validated by predicting the binding of sucrose using the induced fit docking protocol (IFD)[8] in a manner consistent with available data (data not shown).

The ligands were drawn from scratch in maestro and their protonation state was checked with Epik[9] before being subjected to minimisation and a conformational search using a conjugate gradient algorithm within Schrödinger Suite 2015. The lowest-energy conformation was selected as starting structure for the docking calculations.

The docking calculations were performed using the IFD standard protocol.[8] The binding site was defined as the centroid of Asp1399 and Asp1512 and molecules were described using the OPLS2.1 force field.[10] The second docking step was performed in extra precision. All other settings were default.

## References


(1) C. Pro, *Agil. Technol. UK Ltd., UK, Xcalibur/CCD Syst. CrysAlis PRO Softw. Syst. Version* **2010**, *1*.

(2) O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard, H. Puschmann, *J. Appl. Crystallogr.* **2009**, *42*, 339–341.

(3) G. M. Sheldrick, *Acta Cryst. A* **2015**, *71*, 3–8.

(4) M. Kessler, O. Acuto, C. Storelli, H. Murer, M. Müller, G. Semenza, *Biochim. Biophys. Acta - Biomembr.* **1978**, *506*, 136–154.

(5) A. Šali, *Mol. Med. Today* **1995**, *1*, 270–277.

(6) L. Sim, C. Willemsma, S. Mohan, H. Y. Naim, B. M. Pinto, D. R. Rose, *J. Biol. Chem.* **2010**, *285*, 17763–17770.

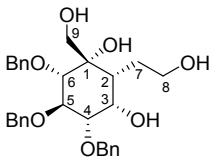
(7) M. H. M. Olsson, C. R. Søndergaard, M. Rostkowski, J. H. Jensen, *J. Chem. Theory Comput.* **2011**, *7*, 525–537.

(8) W. Sherman, T. Day, M. P. Jacobson, R. A. Friesner, R. Farid, *J. Med. Chem.* **2006**, *49*, 534–553.

(9) J. C. Shelley, A. Cholleti, L. L. Frye, J. R. Greenwood, M. R. Timlin, M. Uchimaya, *J. Comput. Aided. Mol. Des.* **2007**, *21*, 681–691.

(10) D. Shivakumar, J. Williams, Y. Wu, W. Damm, J. Shelley, W. Sherman, *J. Chem. Theory Comput.* **2010**, *6*, 1509–1519.

# $^{1}$H- and $^{13}$C-NMR spectra

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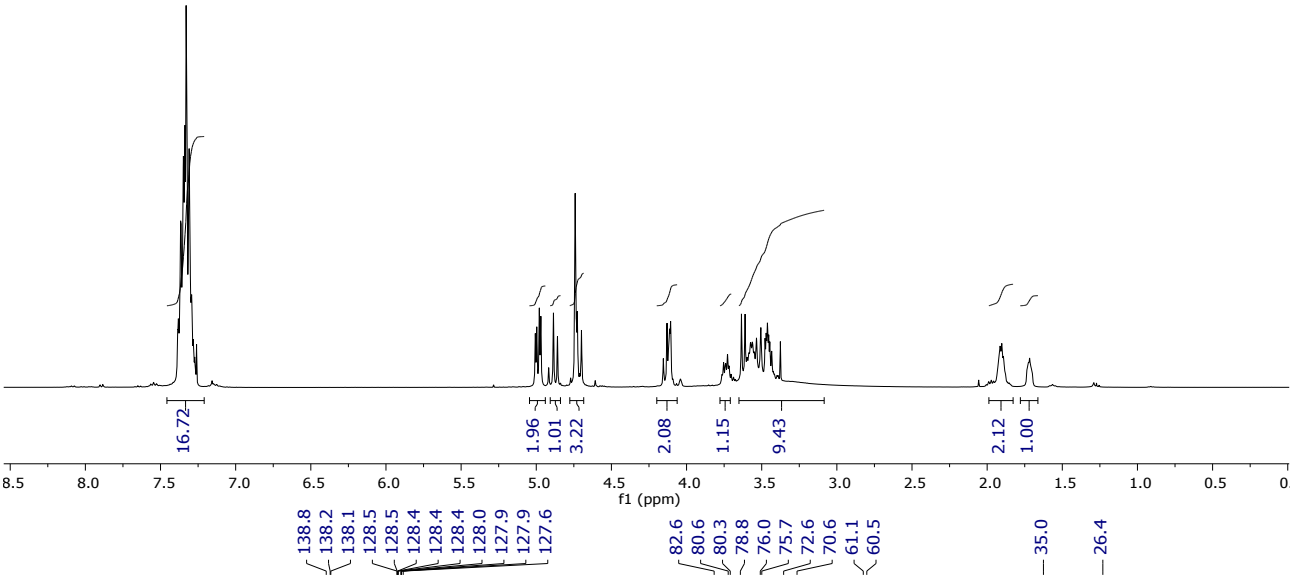


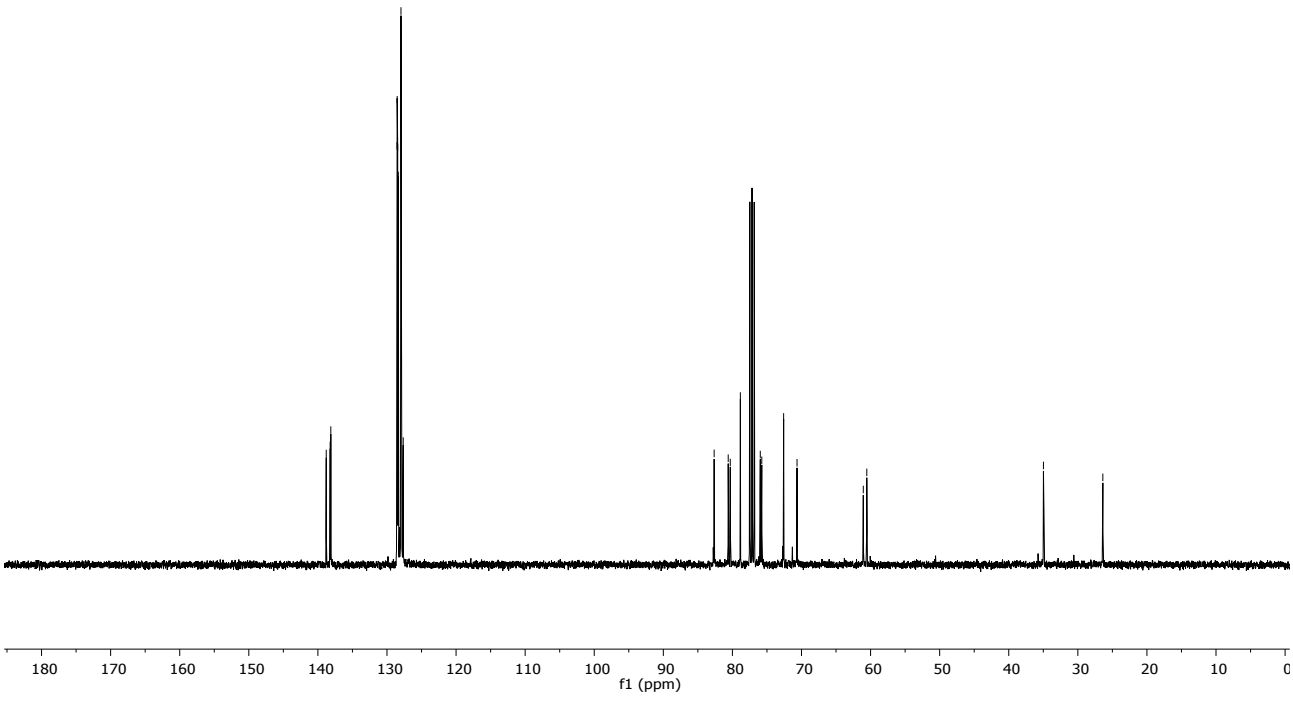

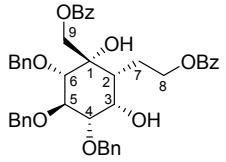
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1
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6
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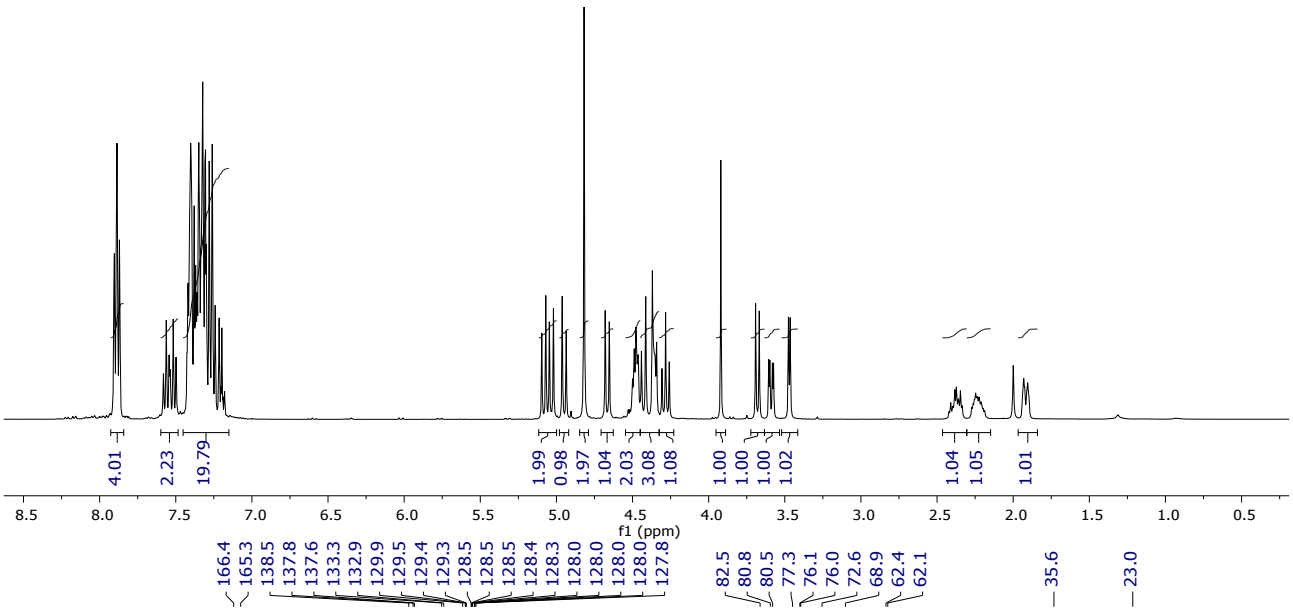
7
8
5
3
BnO
4
OH
OBn

**11**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1.99
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2.03
3.08
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1.00
1.02
1.04
1.05
1.01
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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0.5
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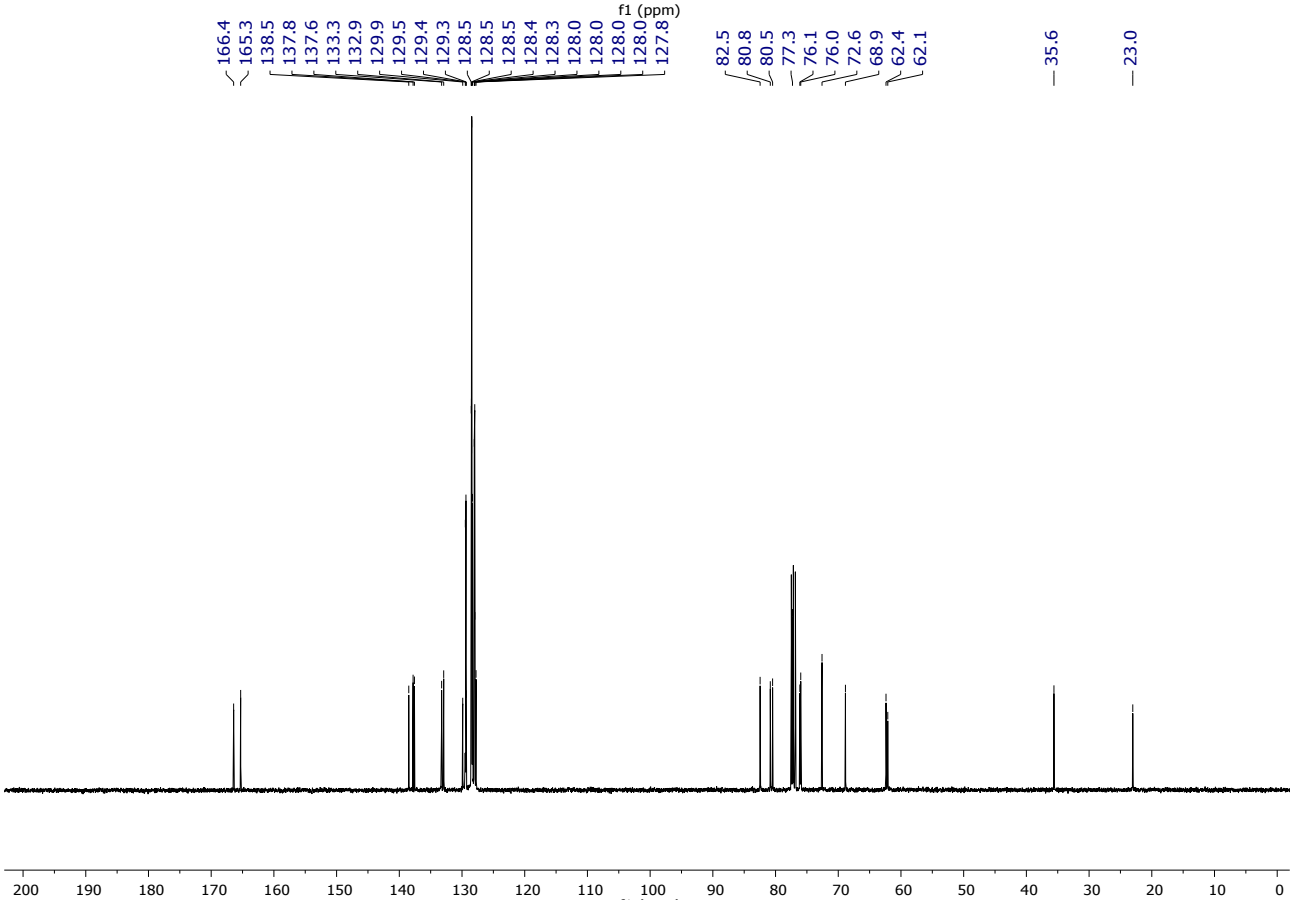
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165.3
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128.5
128.5
128.4
128.3
128.0
128.0
128.0
128.0
127.8
82.5
80.8
80.5
77.3
76.1
76.0
72.6
68.9
62.4
62.1
35.6
23.0
200
190
180
170
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150
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110
100
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60
50
40
30
20
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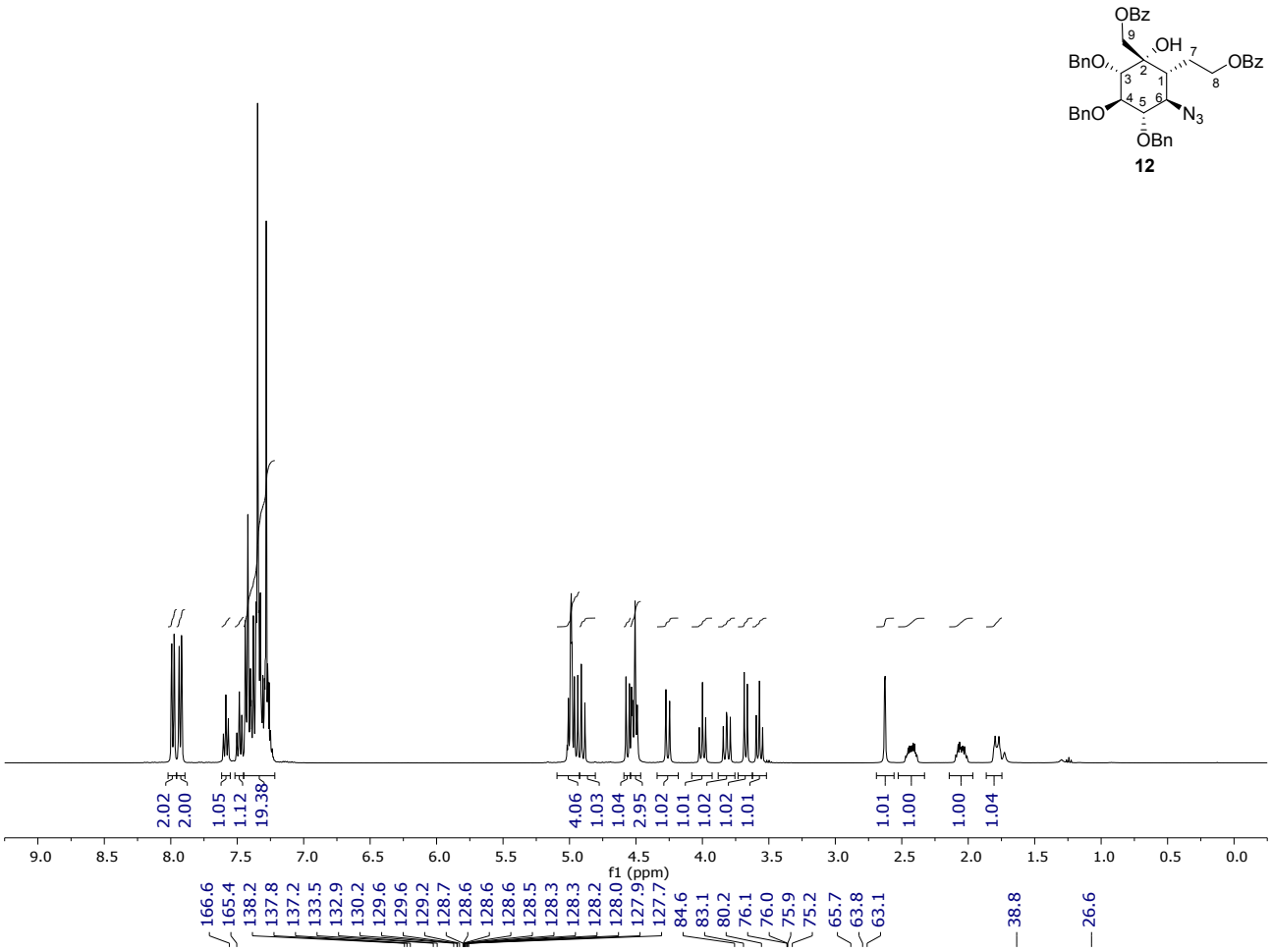
0
f1 (ppm)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OBz
BnO
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OBn
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1.05
1.12
19.38
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1.04
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1.02
1.02
1.01
1.01
1.00
1.00
1.04
f1 (ppm)
166.6
165.4
138.2
137.8
137.2
133.5
132.9
130.2
129.6
129.6
129.2
128.7
128.6
128.6
128.6
128.5
128.3
128.3
128.2
128.0
127.9
127.7
84.6
83.1
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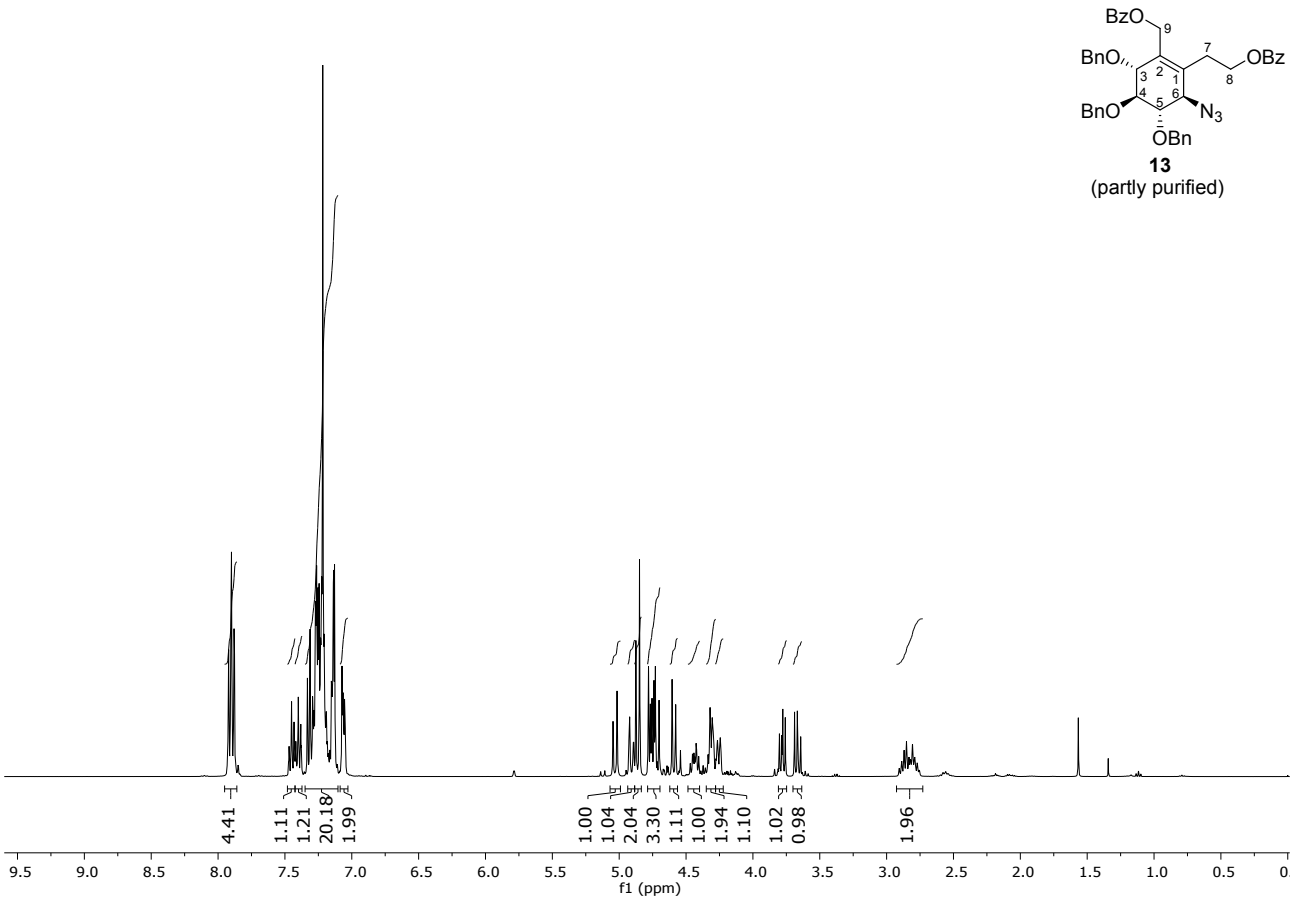
63.8
63.1
38.8
26.6
f1 (ppm)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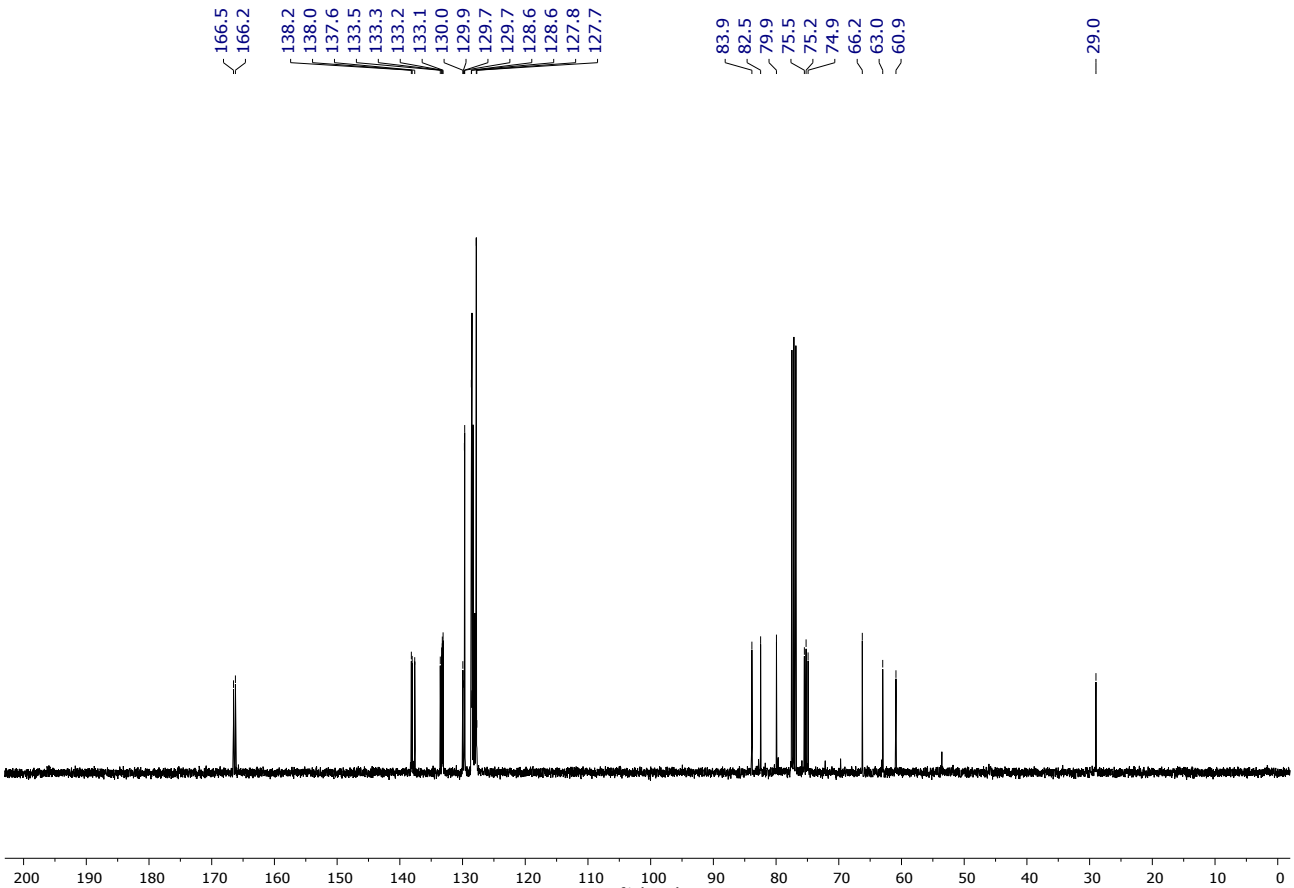
BnO
7
OBz
2
3
1
8
4
6
5
BnO
N3
OBn
13
(partly purified)
4.41
1.11
1.21
20.18
1.99
1.00
1.04
2.04
3.30
1.11
1.00
1.94
1.10
1.02
0.98
1.96
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
f1 (ppm)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128.6
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127.8
127.7
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82.5
79.9
75.5
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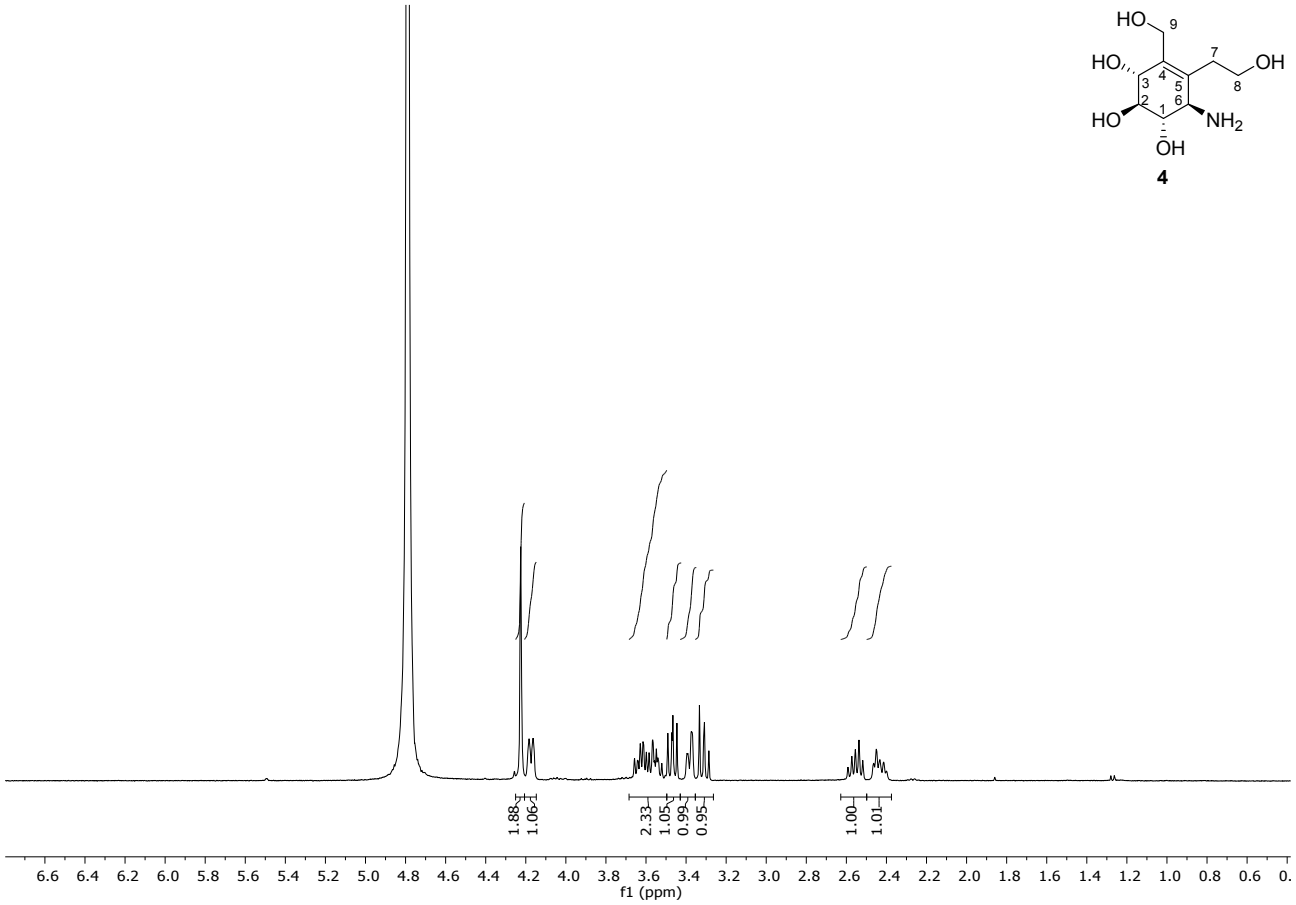
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OH
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2
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HO
NH2
OH
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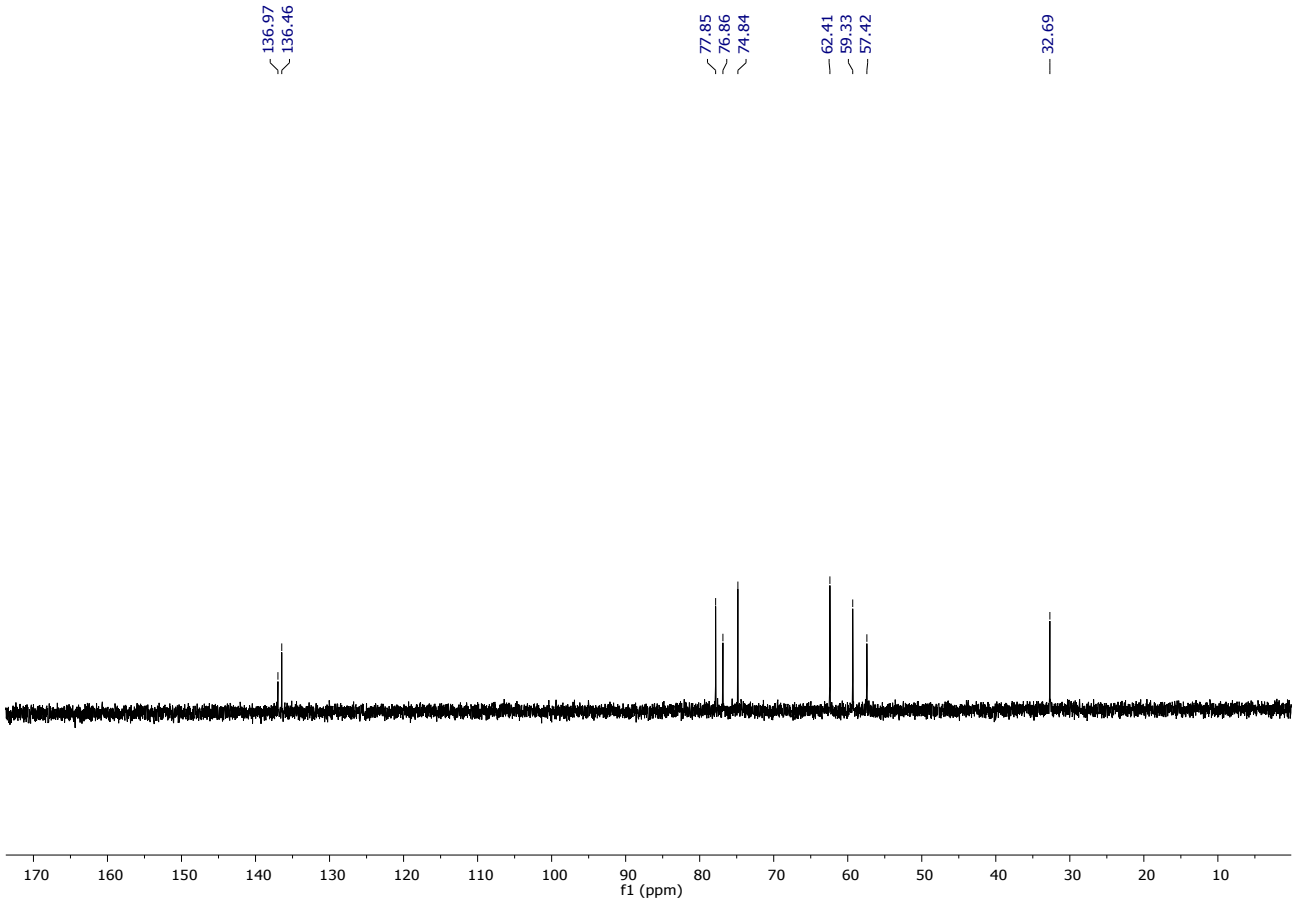
2.33
1.05
0.99
0.95
1.00
1.01
6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6 0.
f1 (ppm)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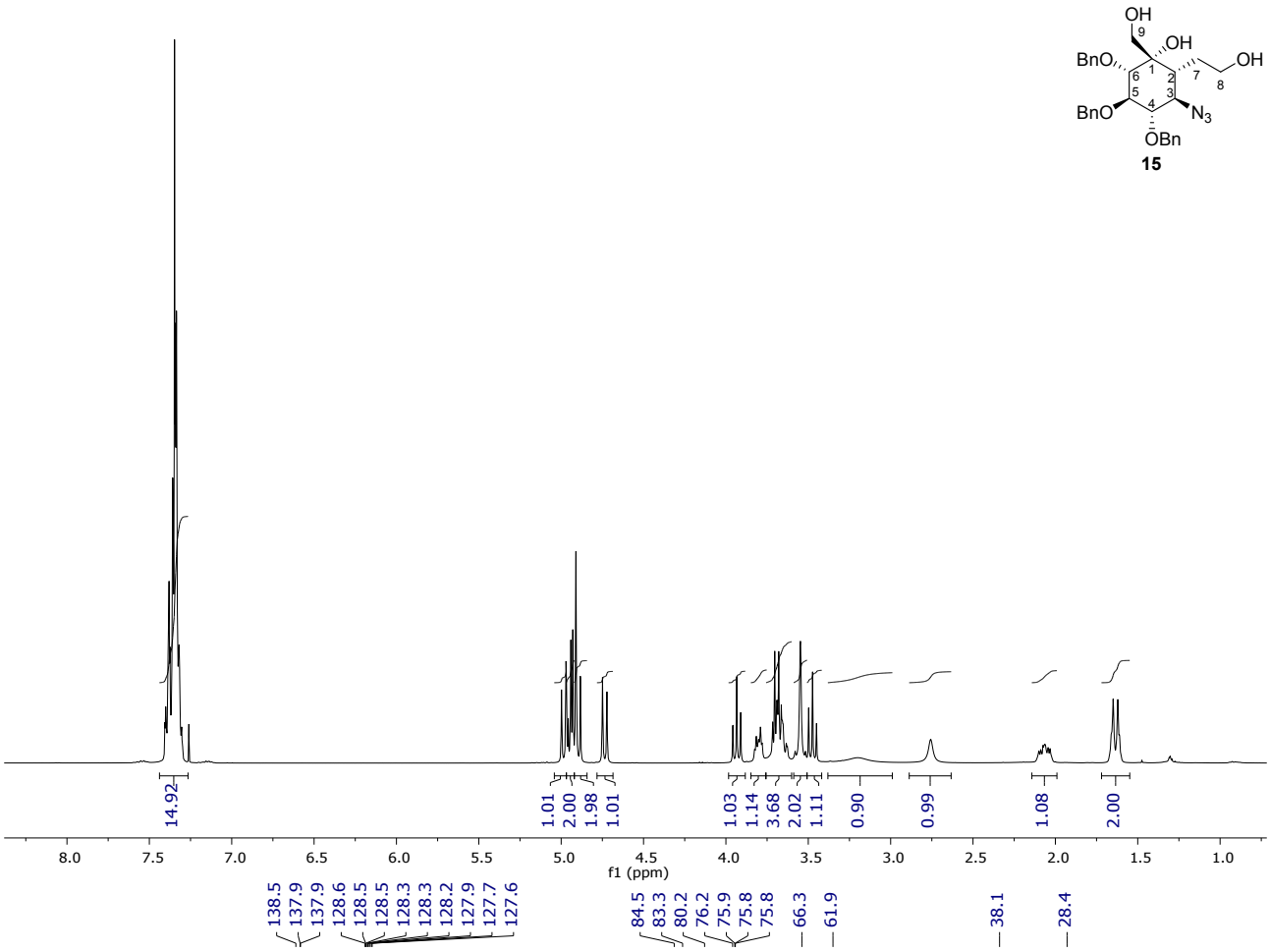
f1 (ppm)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2.00
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1.03
1.14
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0.90
0.99
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2.00
f1 (ppm)
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137.9
137.9
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128.3
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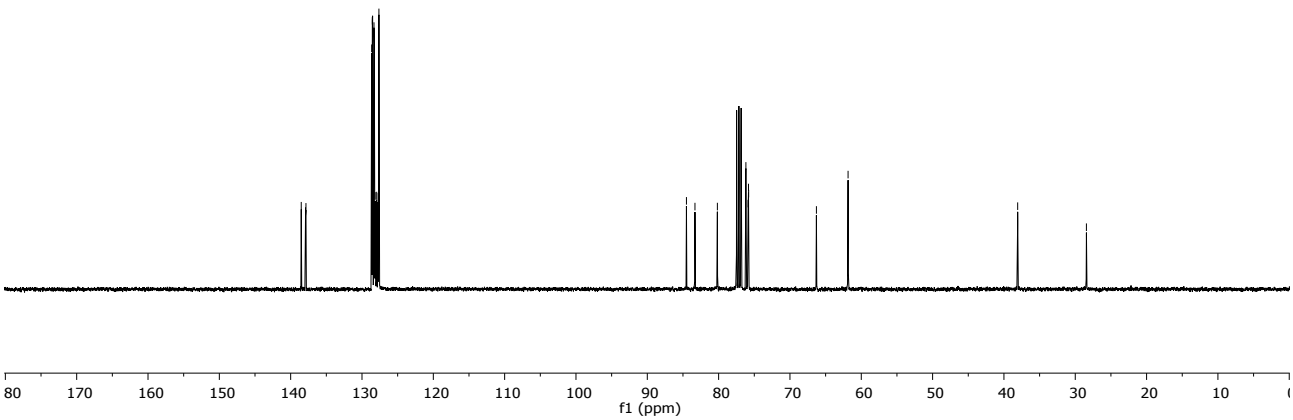
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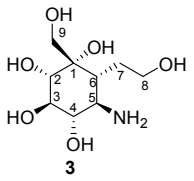
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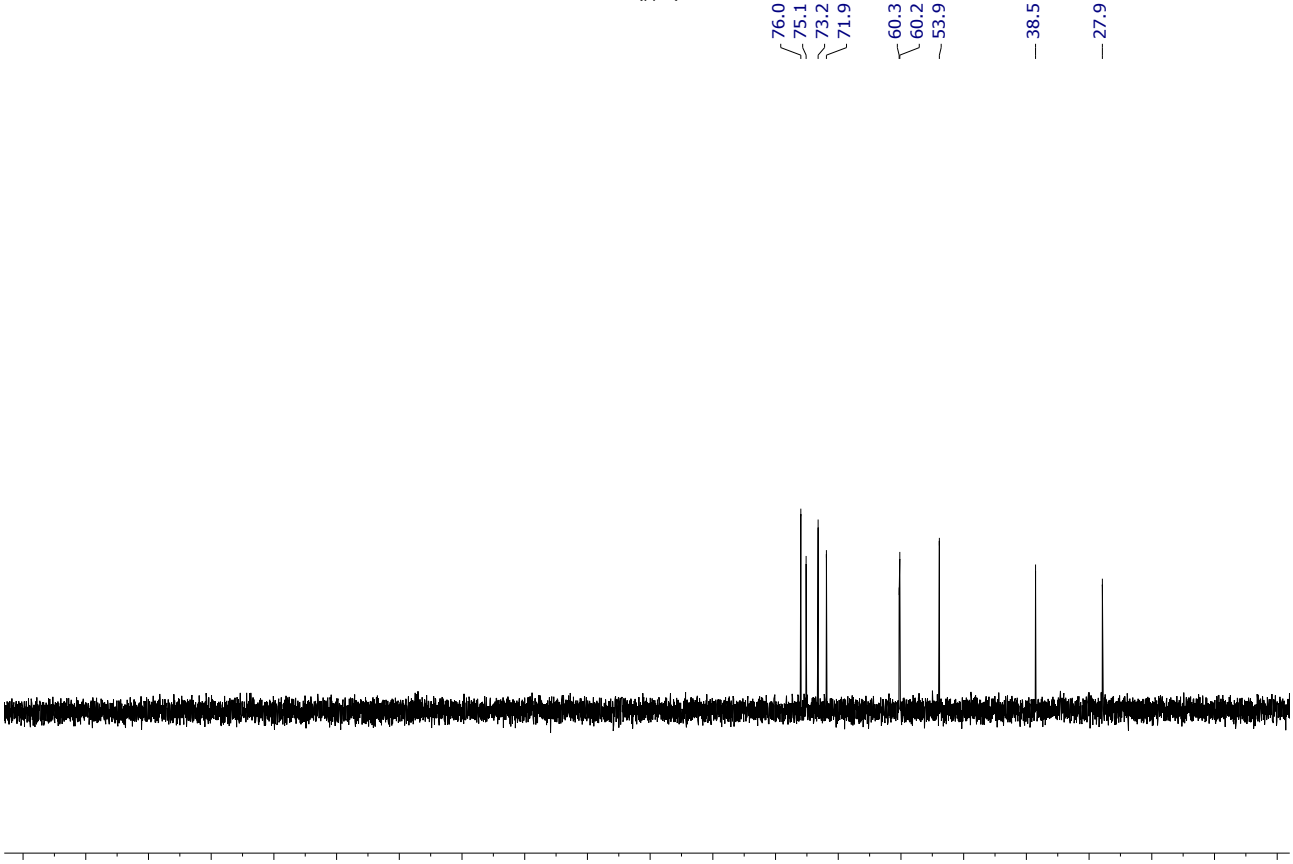
OH
HO
1
2
7
OH
8
6
3
5
HO
NH2
4
OH

**3**


1.07
1.95
1.07
2.07
1.04
0.97
0.97
2.00
7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6 0.4 0.2
f1 (ppm)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75.1
73.2
71.9
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60.2
53.9
38.5
27.9
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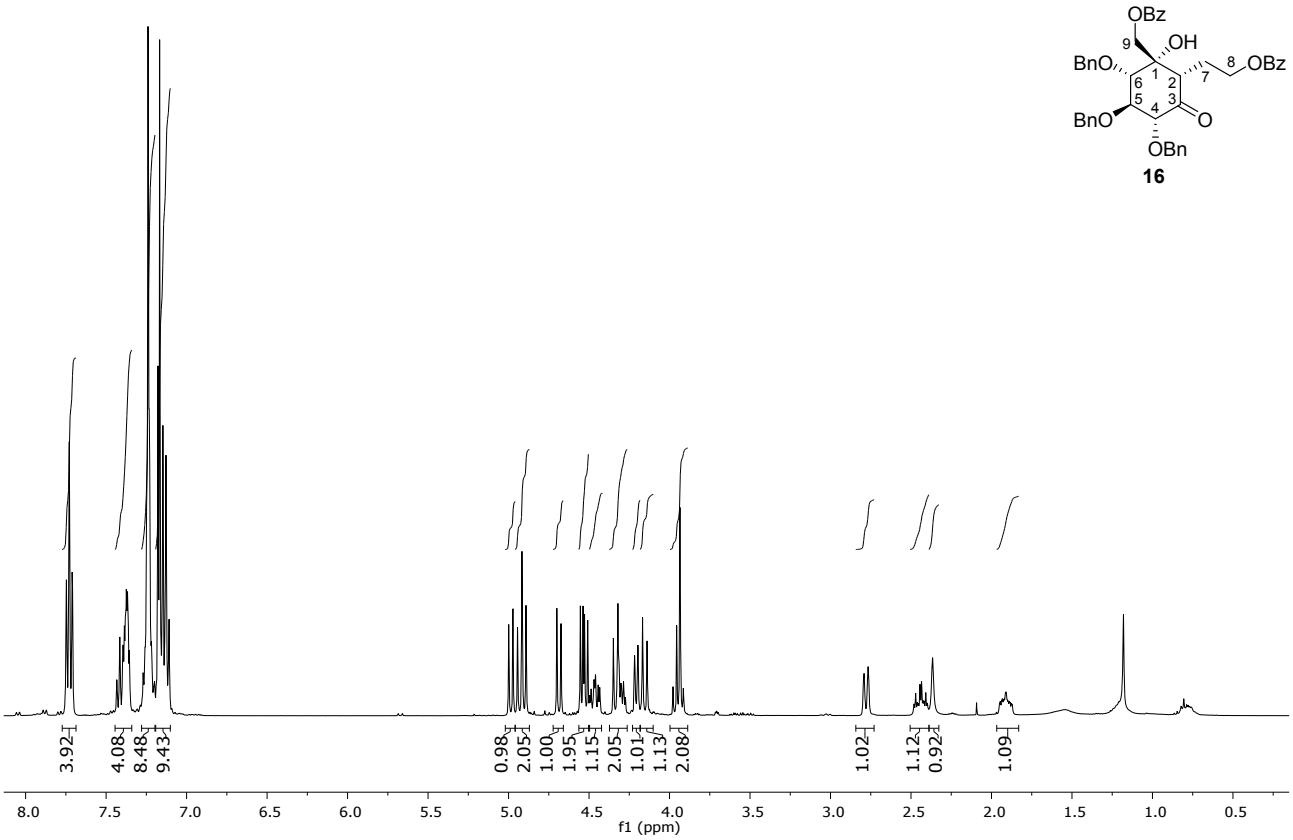
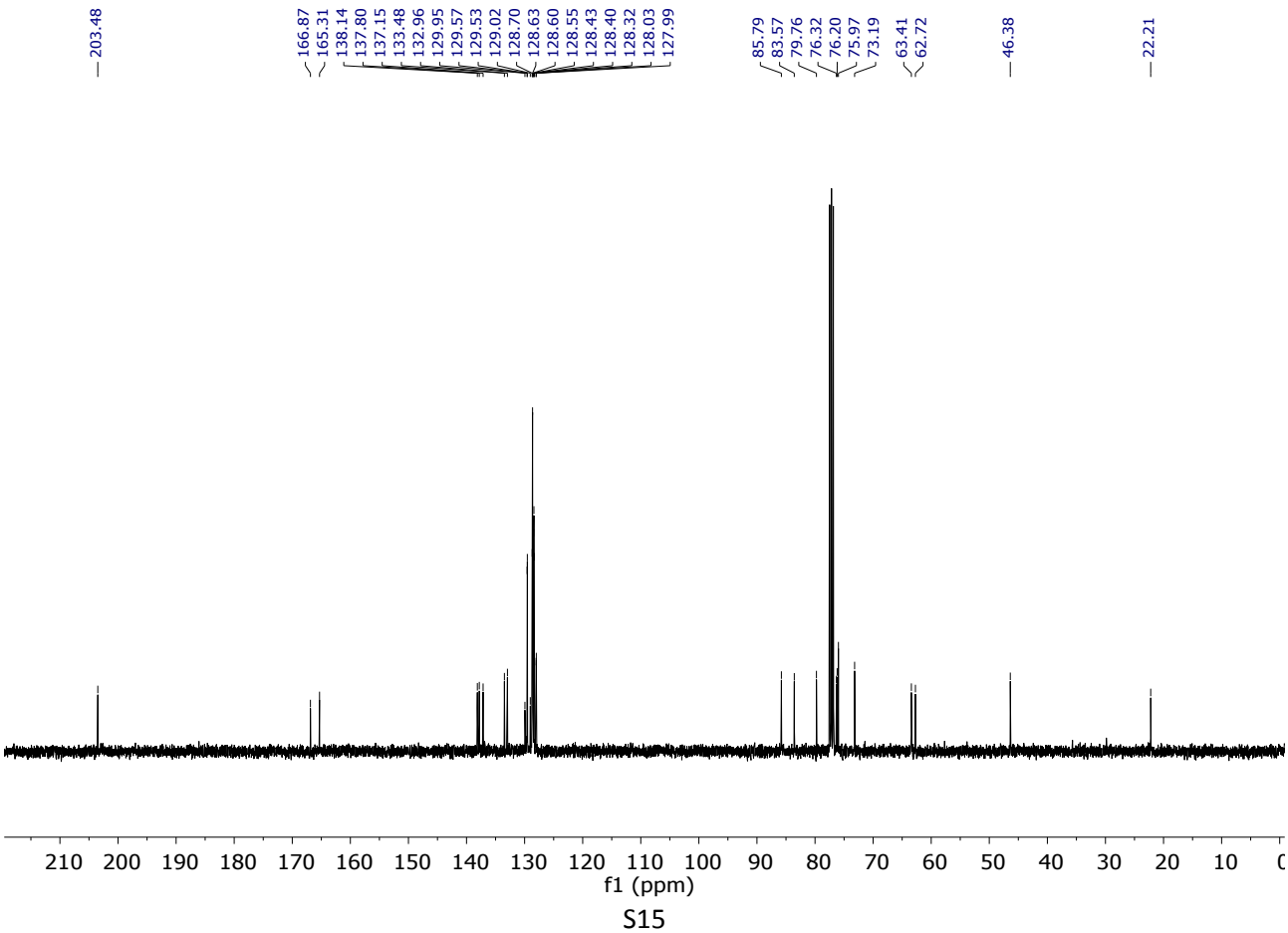
f1 (ppm)


OBz
OH
BnO
OBz
BnO
O
OBn
16
3.92
4.08
8.48
9.43
0.98
2.05
1.00
1.95
1.15
2.05
1.01
1.13
2.08
1.02
1.12
0.92
1.09
f1 (ppm)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128.63
128.60
128.55
128.43
128.40
128.32
128.03
127.99
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62.72
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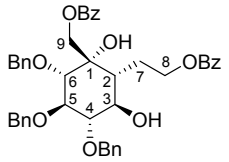
22.21
f1 (ppm)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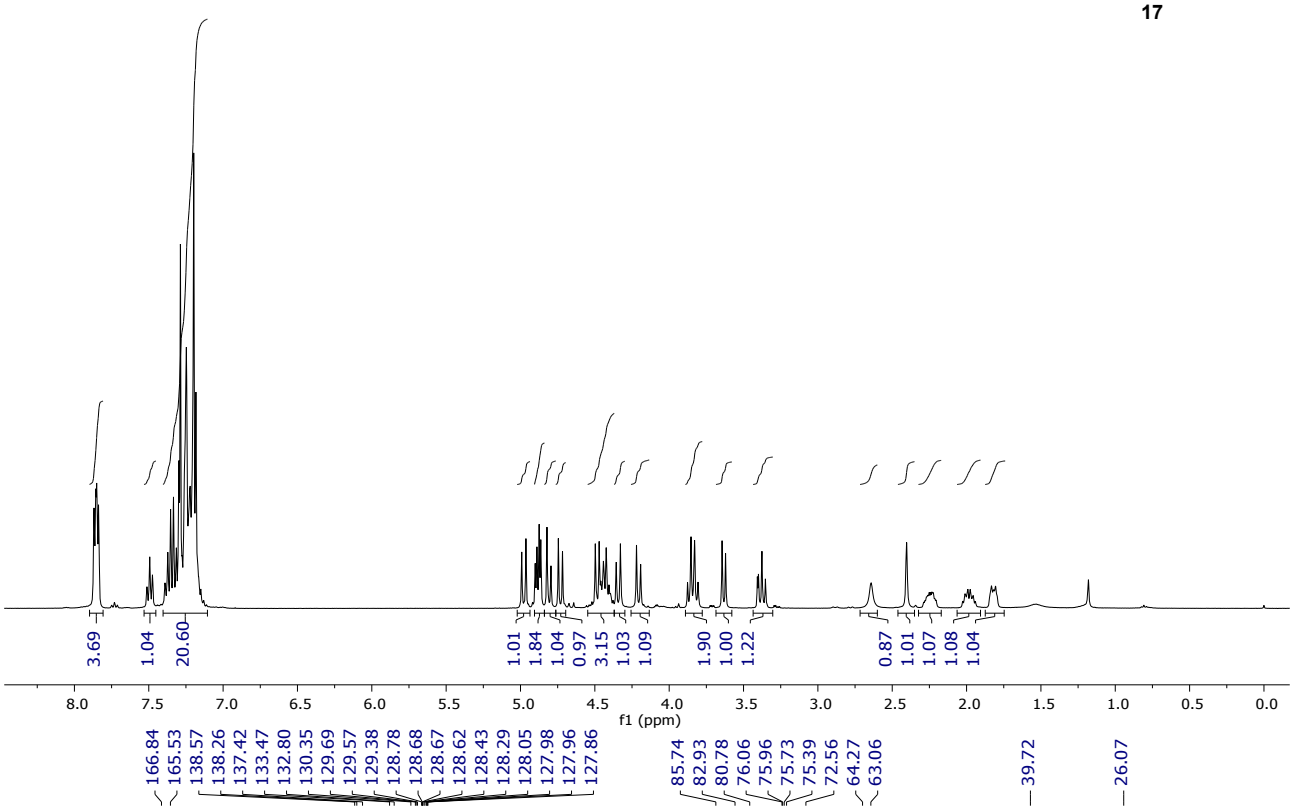
OBz
BnO
OH
OBn
1
2
3
4
5
6
7
8
9

**17**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1.84
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0.97
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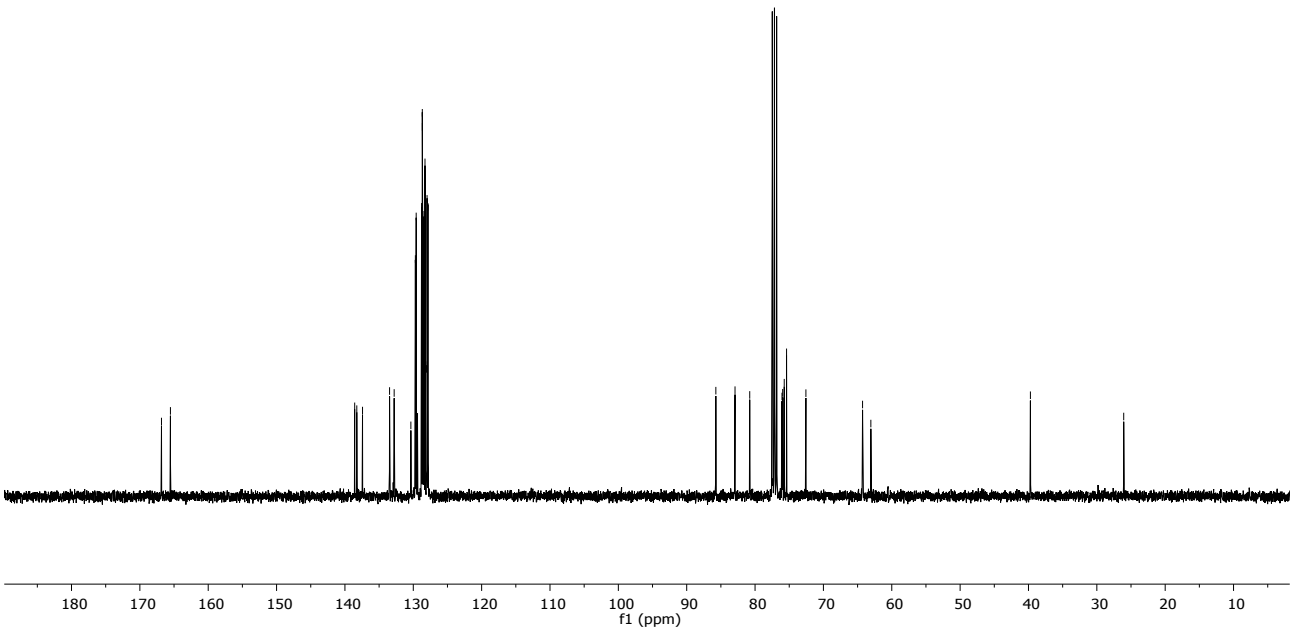
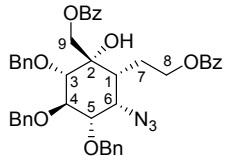
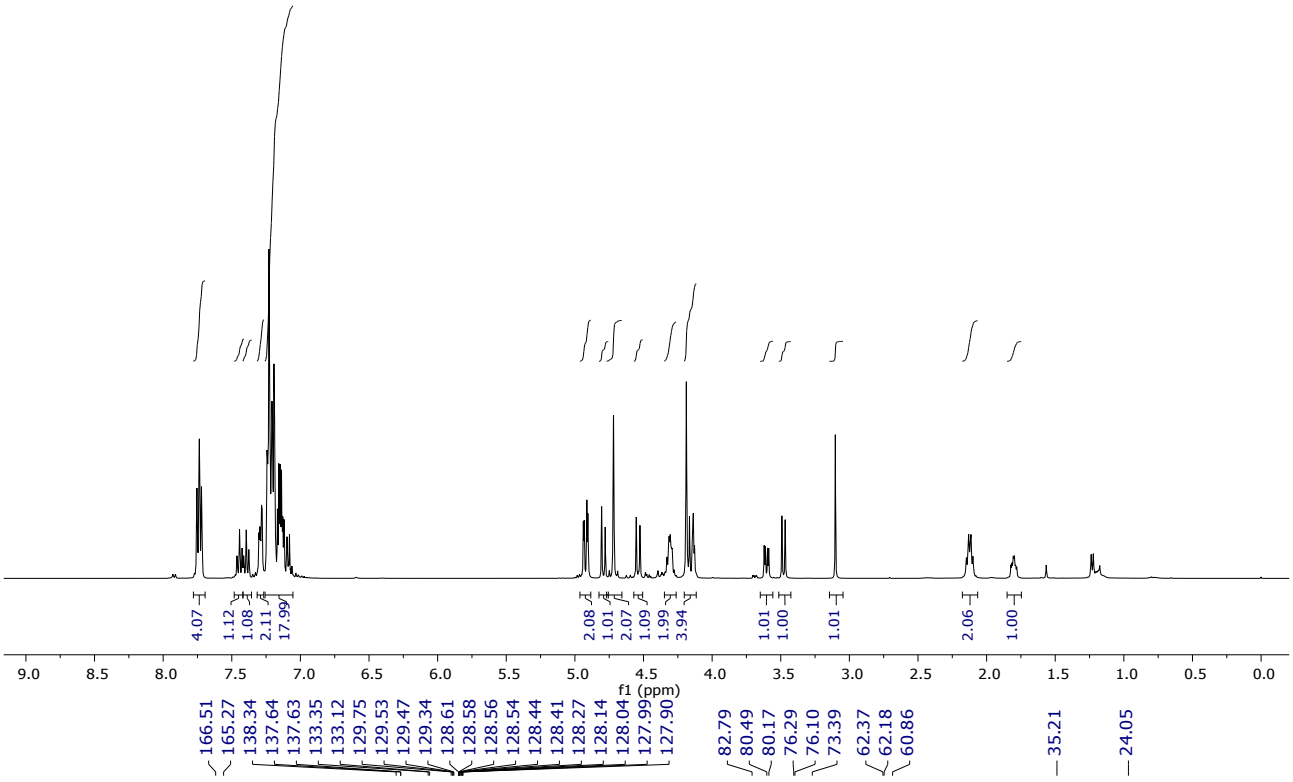
1.03
1.09
1.90
1.00
1.22
0.87
1.01
1.07
1.08
1.04
f1 (ppm)

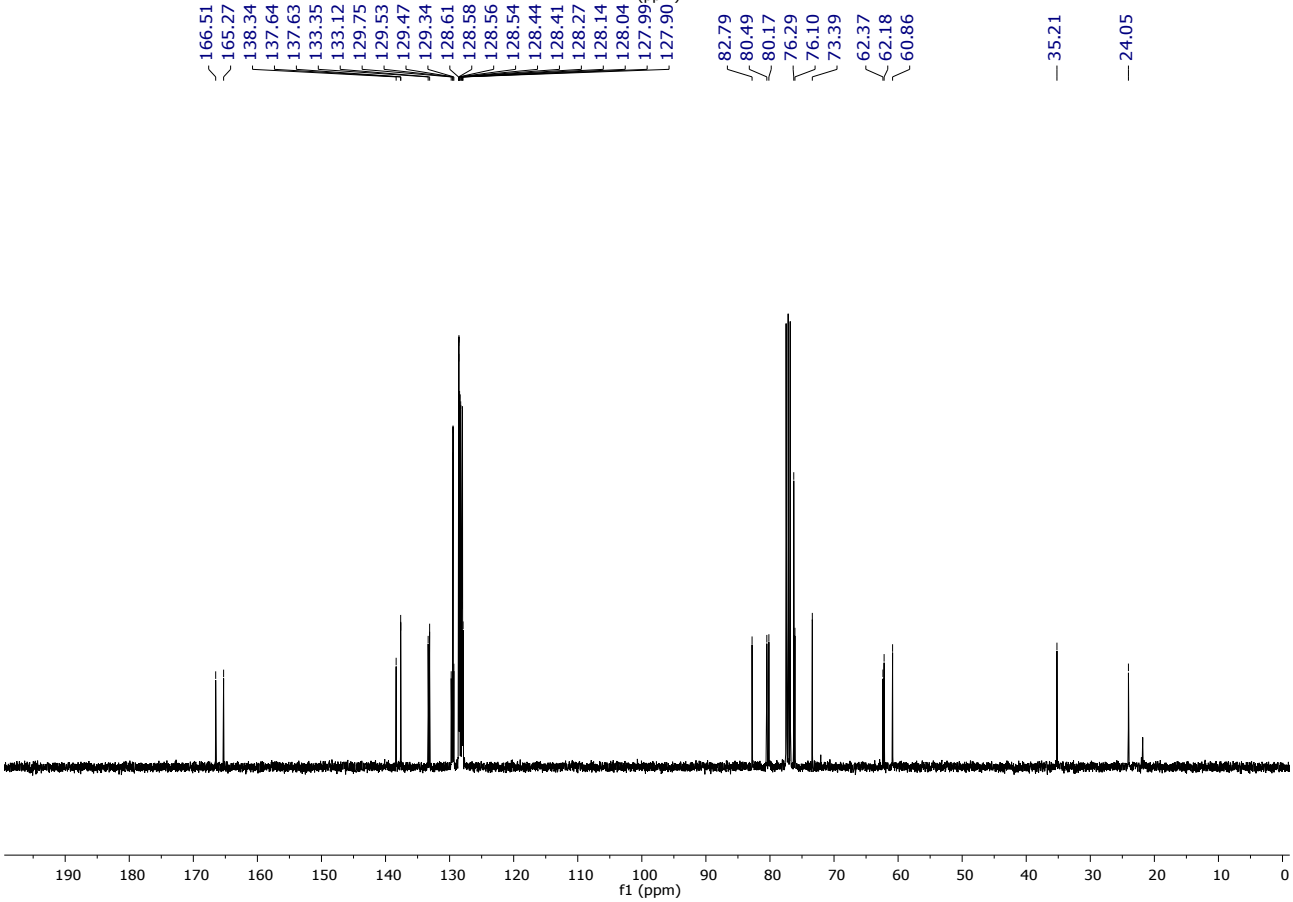

166.84
165.53
138.57
138.26
137.42
133.47
132.80
130.35
129.69
129.57
129.38
128.78
128.68
128.67
128.62
128.43
128.29
128.05
127.98
127.96
127.86
85.74
82.93
80.78
76.06
75.96
75.73
75.39
72.56
64.27
63.06
39.72
26.07

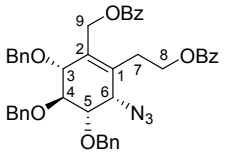

f1 (ppm)


OBz
9
OH
BnO
2
8
OBz
3
1
7
4
6
5
BnO
N3
OBn

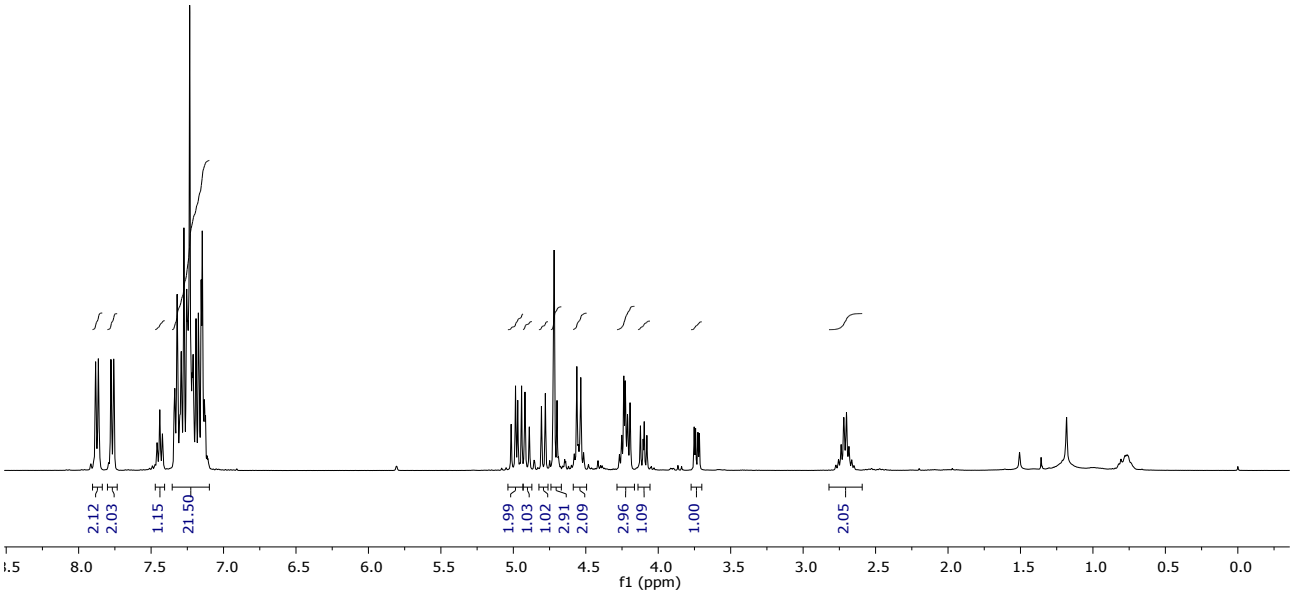
**18**

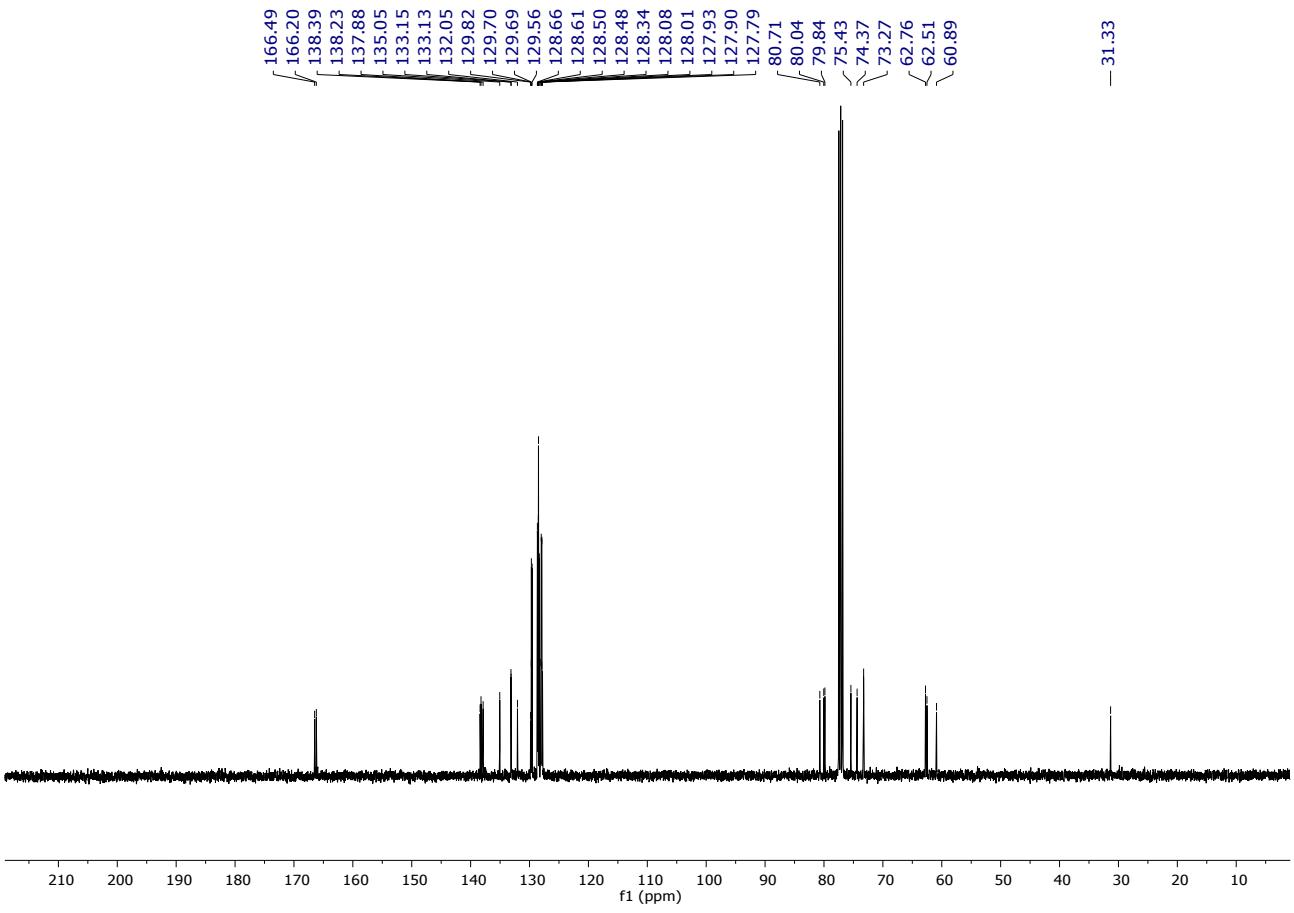

4.07
1.12
1.08
2.11
17.99
2.08
1.01
2.07
1.09
1.99
3.94
1.01
1.00
1.01
2.06
1.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

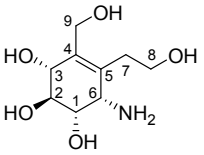

166.51
165.27
138.34
137.64
137.63
133.35
133.12
129.75
129.53
129.47
129.34
128.61
128.58
128.56
128.54
128.44
128.41
128.27
128.14
128.04
127.99
127.90
82.79
80.49
80.17
76.29
76.10
73.39
62.37
62.18
60.86
35.21
24.05
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)




**19**
(partly purified)

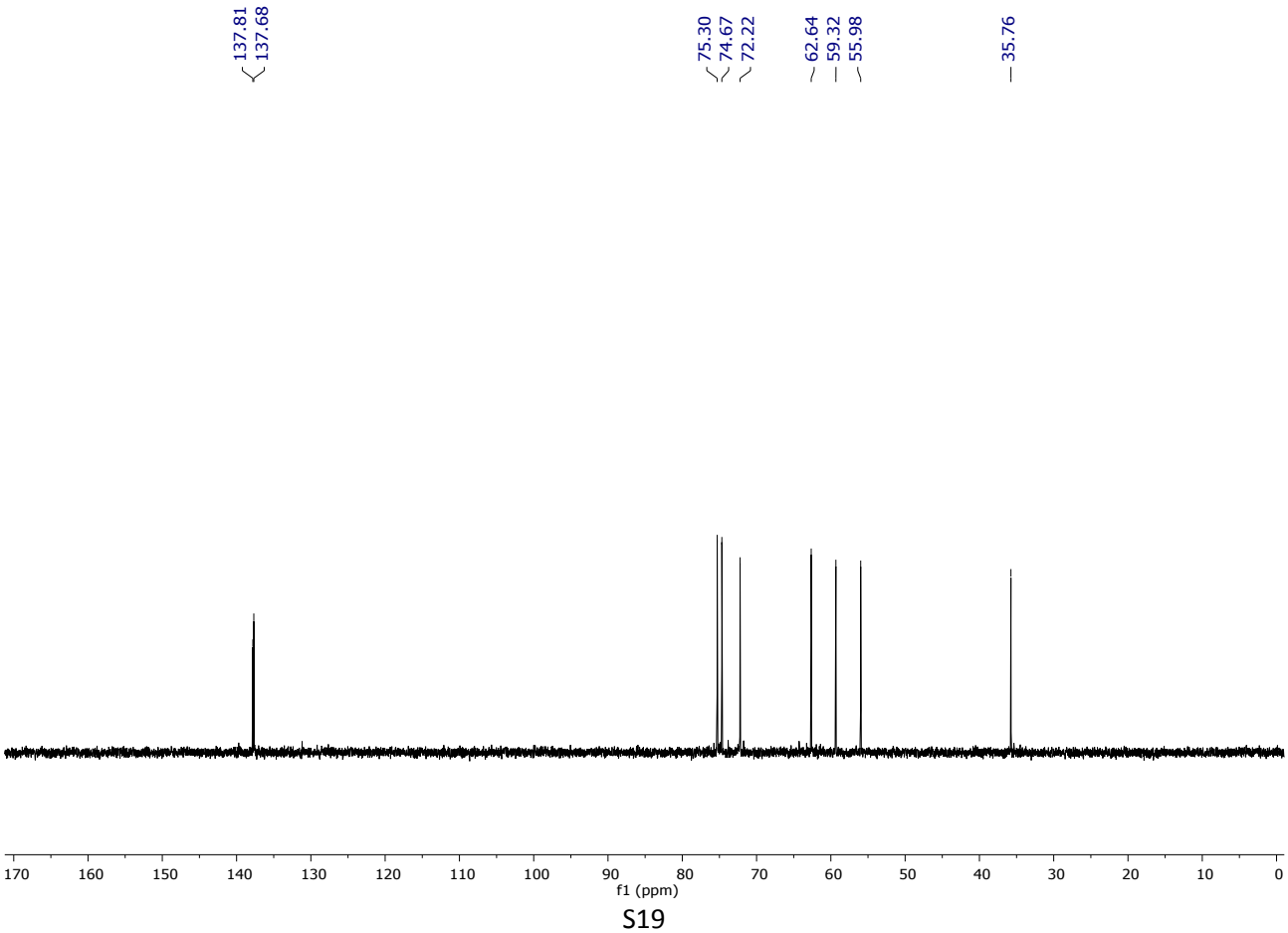


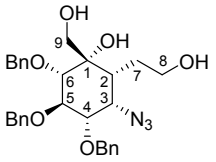




9
OH
4
HO
8
OH
3
5
7
2
6
1
HO
NH2
OH

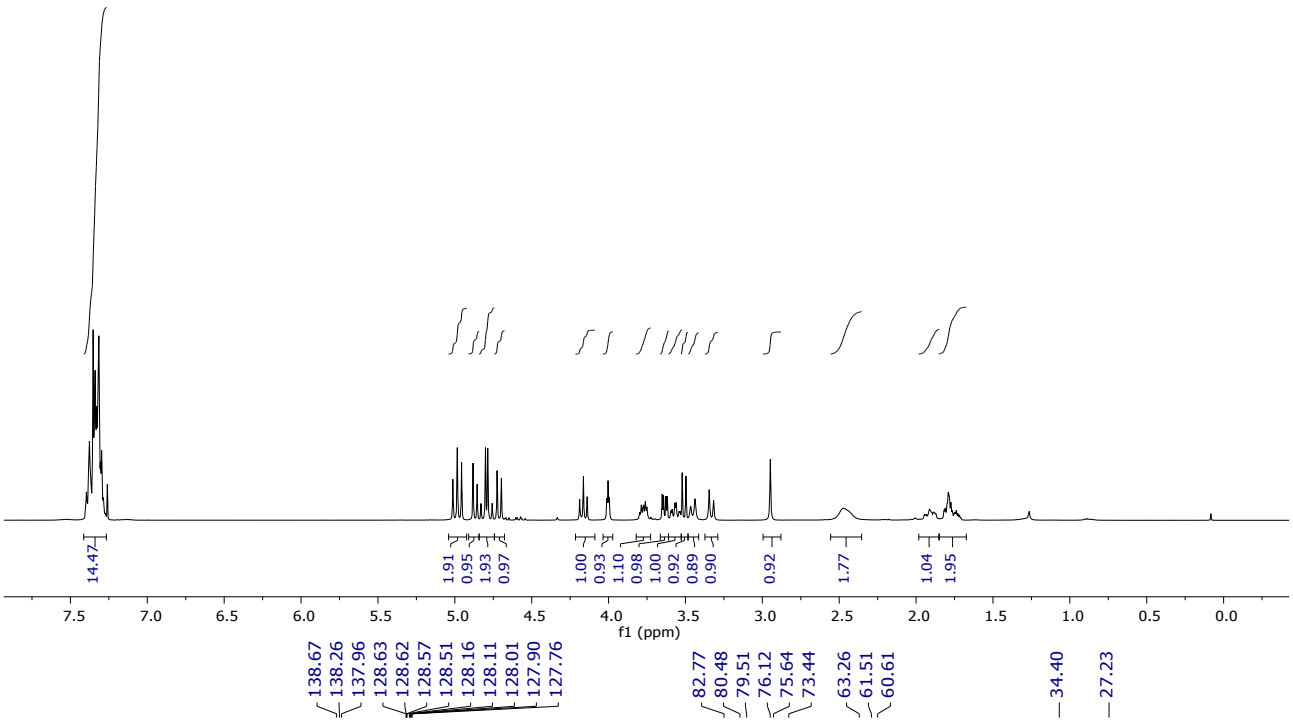
**6**


1.10
0.99
1.00
4.36
0.93
1.91
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.
f1 (ppm)

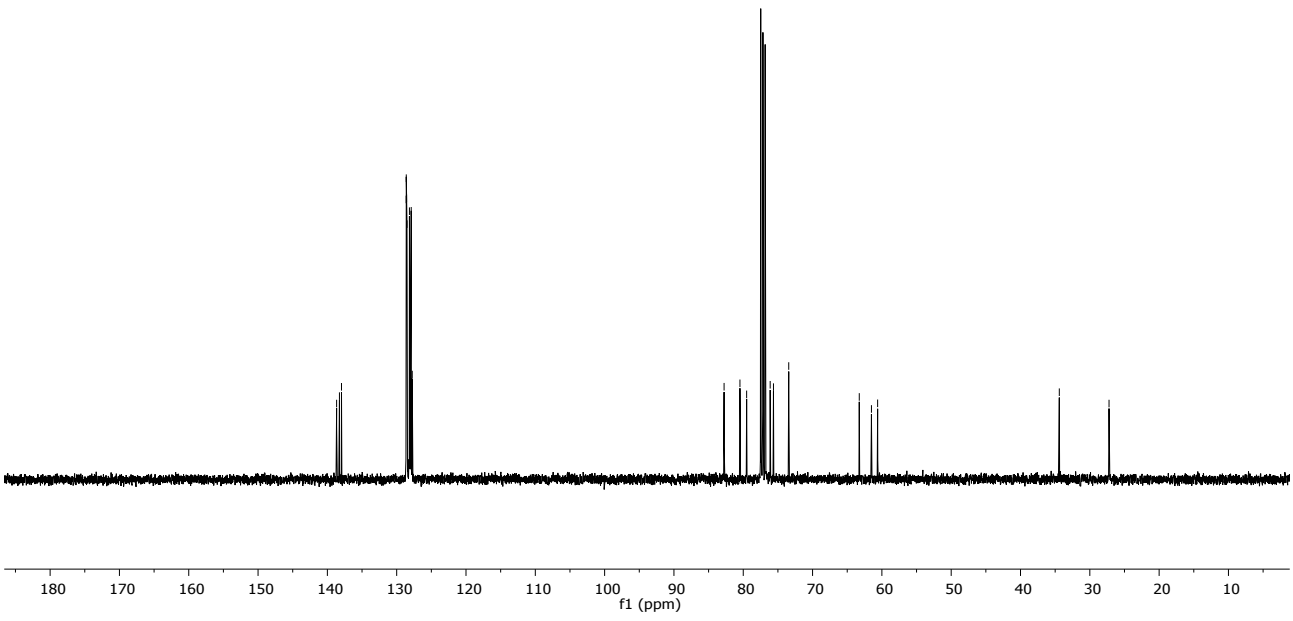

137.81
137.68
75.30
74.67
72.22
62.64
59.32
55.98
35.76
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

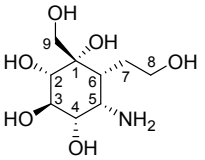

OH
9
OH
BnO
1
8
OH
6
2
7
5
3
4
BnO
N3
OBn

**21**


14.47
1.91
0.95
1.93
0.97
1.00
0.93
1.10
0.98
1.00
0.92
0.89
0.90
0.92
1.77
1.04
1.95
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

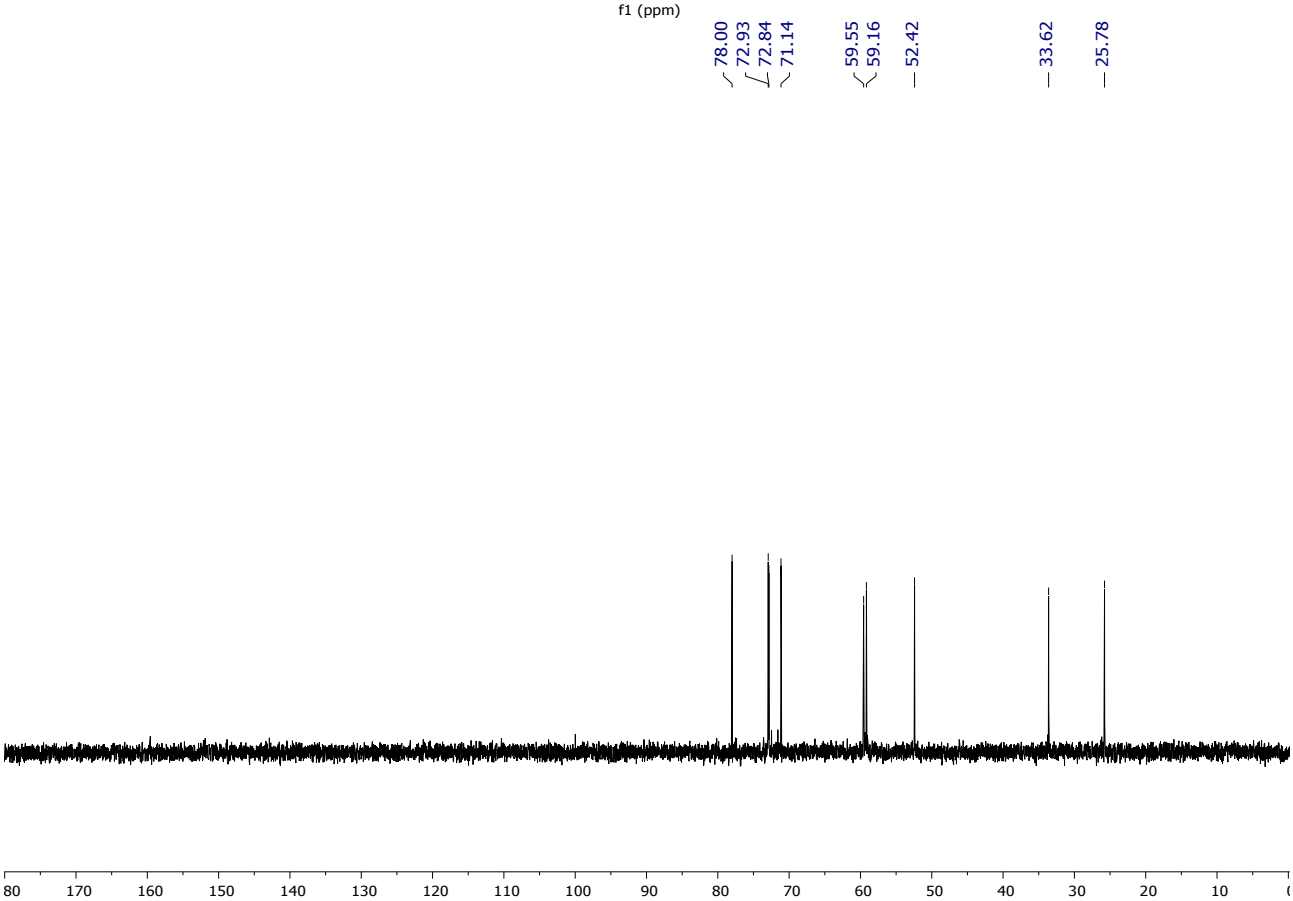

138.67
138.26
137.96
128.63
128.62
128.57
128.51
128.16
128.11
128.01
127.90
127.76
82.77
80.48
79.51
76.12
75.64
73.44
63.26
61.51
60.61
34.40
27.23


180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


OH
9
OH
HO
1
8
OH
2
6
7
3
5
4
HO
NH2
OH

**5**


1.03
2.07
2.04
3.00
2.97
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
f1 (ppm)


78.00
72.93
72.84
71.14
59.55
59.16
52.42
33.62
25.78
80
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)