

# Supplementary Information

## **D-*chiro*-Inositol Ribophostin: a Highly Potent Agonist at D-*myo*-inositol 1,4,5-Trisphosphate Receptors: Synthesis and Biological Activities**

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## S1 Biology

### *Data analysis*

Equilibrium binding and concentration-effect relationships were fitted to Hill equations (GraphPad Prism, version 5) from which  $-\log IC_{50}$  ( $pIC_{50}$ ) and  $-\log EC_{50}$  ( $pEC_{50}$ ) values were obtained. For equilibrium competition binding assays  $pK_d$  values were calculated using the Cheng and Prusoff equation (Cheng *et al.*, 1973). Because  $pEC_{50}$  and  $pK_d$  values are normally distributed, these results are presented as means  $\pm$  SEM from  $n$  independent experiments. For comparisons of ratios between mean values ( $EC_{50}/K_d$ ), statistical analyses compared the differences between their  $-\log$  values ( $pEC_{50}$  and  $pK_d$ ) (Colquhoun, 1971), with the SEM calculated as follows, assuming that the population variances are the same (confirmed using an F test) (Ott *et al.*, 2010):

$$SEM = s_p \sqrt{\frac{1}{n_1} + \frac{1}{n_2}}$$

where,  $s_p$  is the estimate of the population variance:

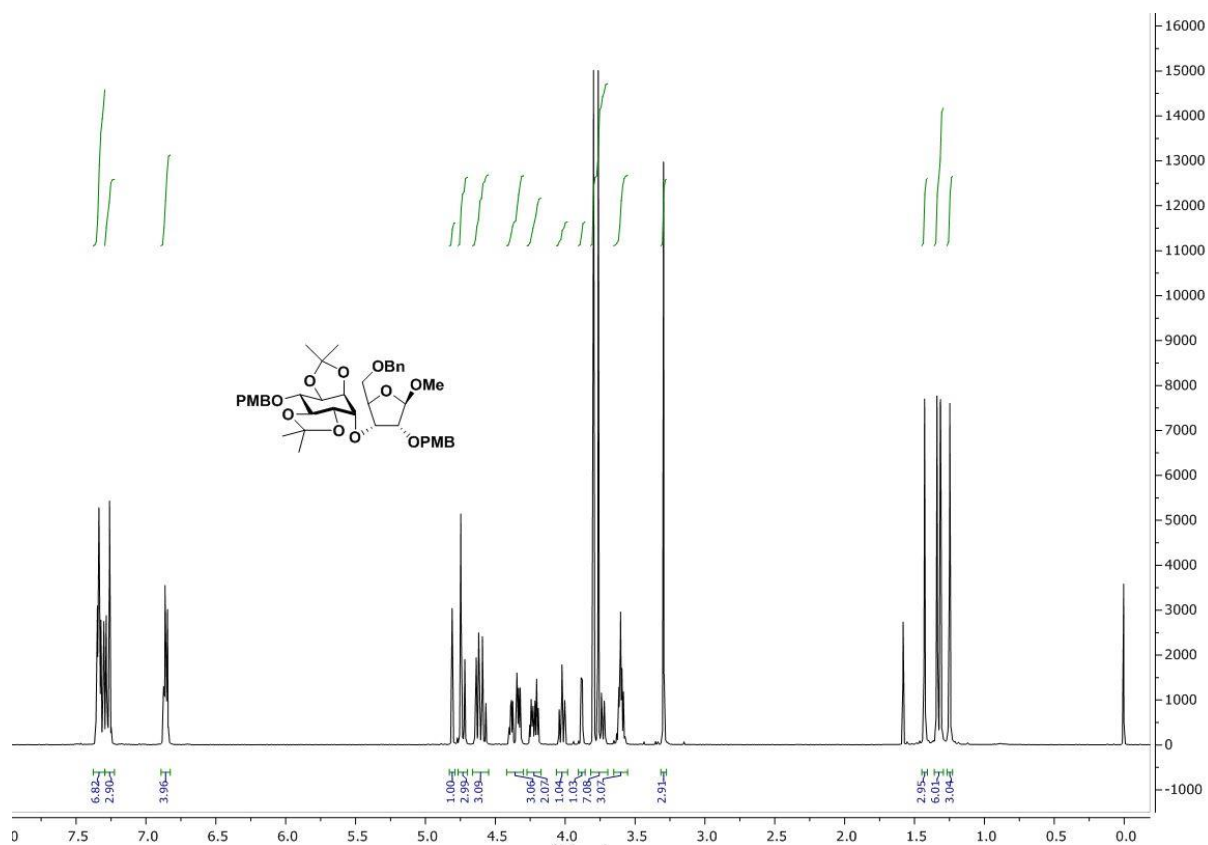
$$s_p = \sqrt{\frac{(n_1 - 1)s_1^2 + (n_2 - 1)s_2^2}{n_1 + n_2 - 2}}$$

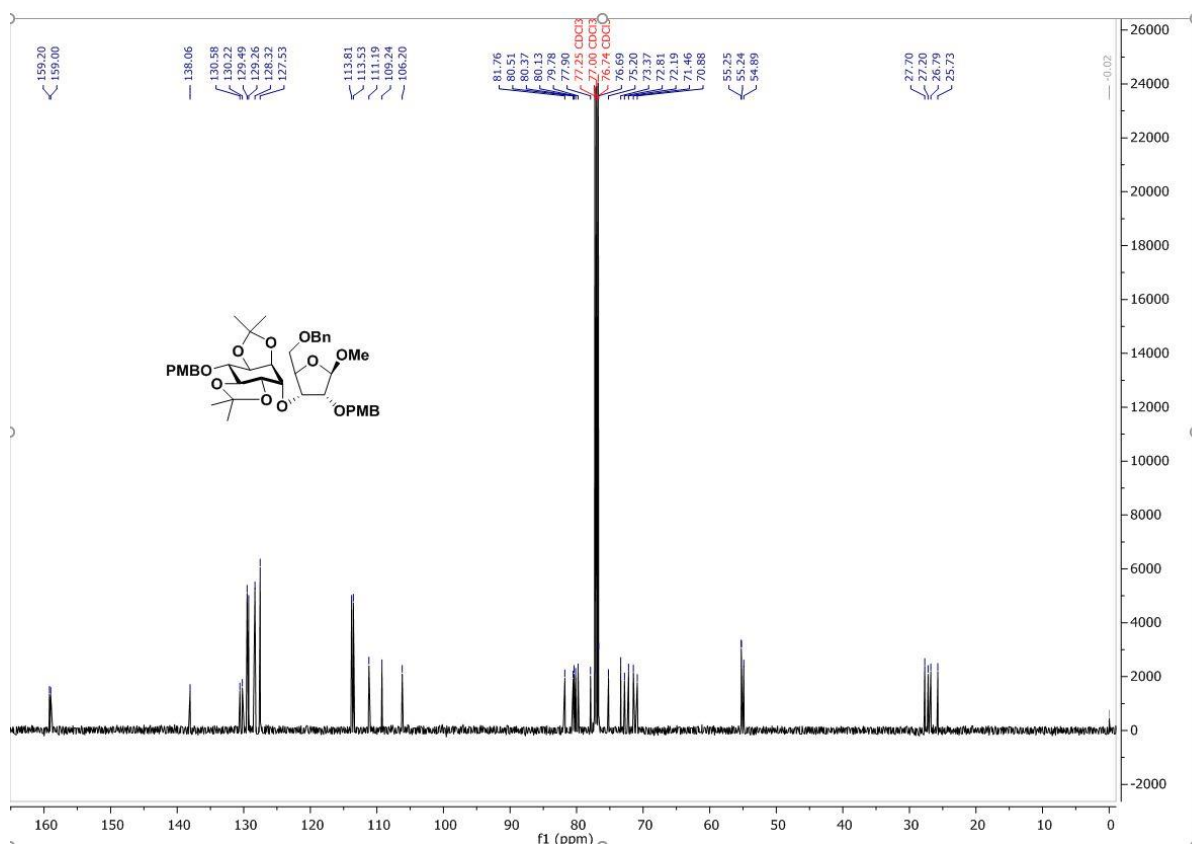
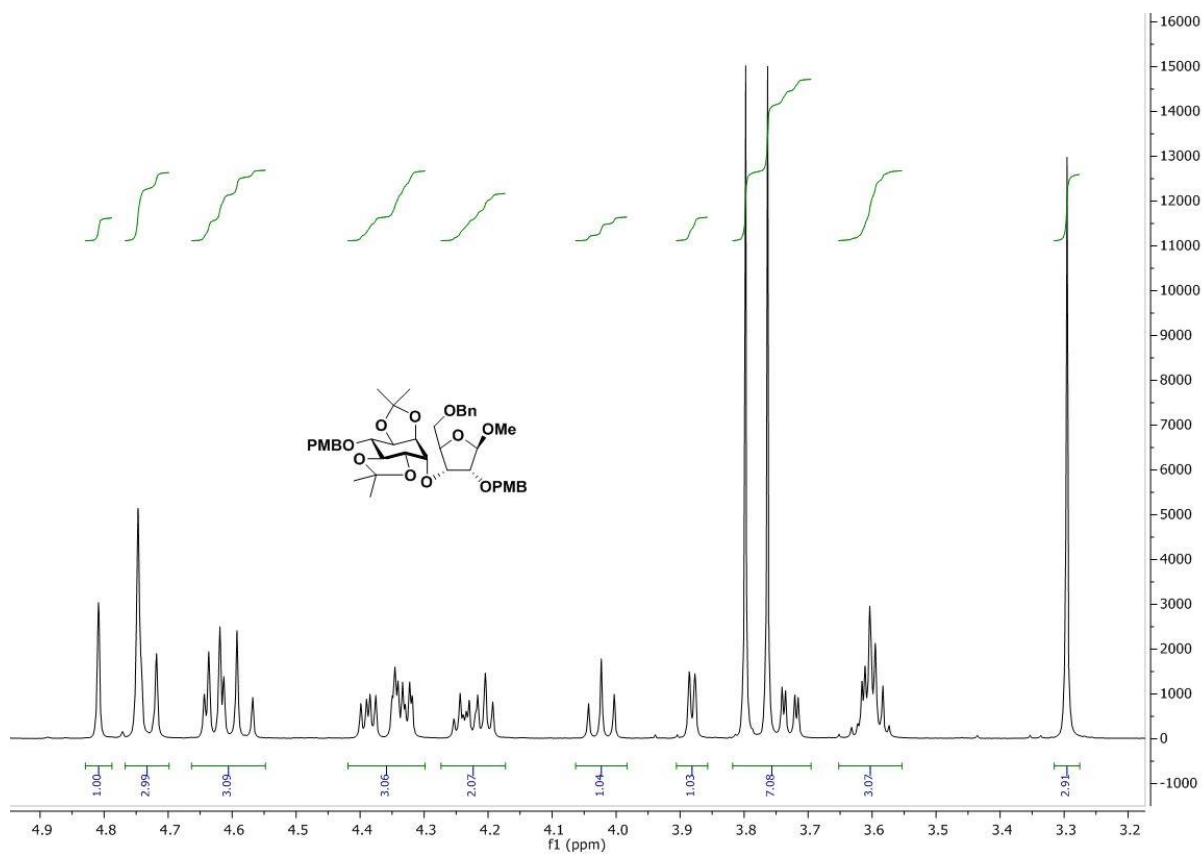
where,  $s_1$  and  $s_2$  are the sample standard deviations, and  $n_1$  and  $n_2$  are the sample sizes. Although all analyses were performed using log values, for greater clarity we present ratios as the antilogs of the means and the 95% confidence interval. Statistical analysis used ANOVA followed by Bonferroni's multiple comparisons test (GraphPad Prism, version 5). \* $P < 0.05$  was considered significant.

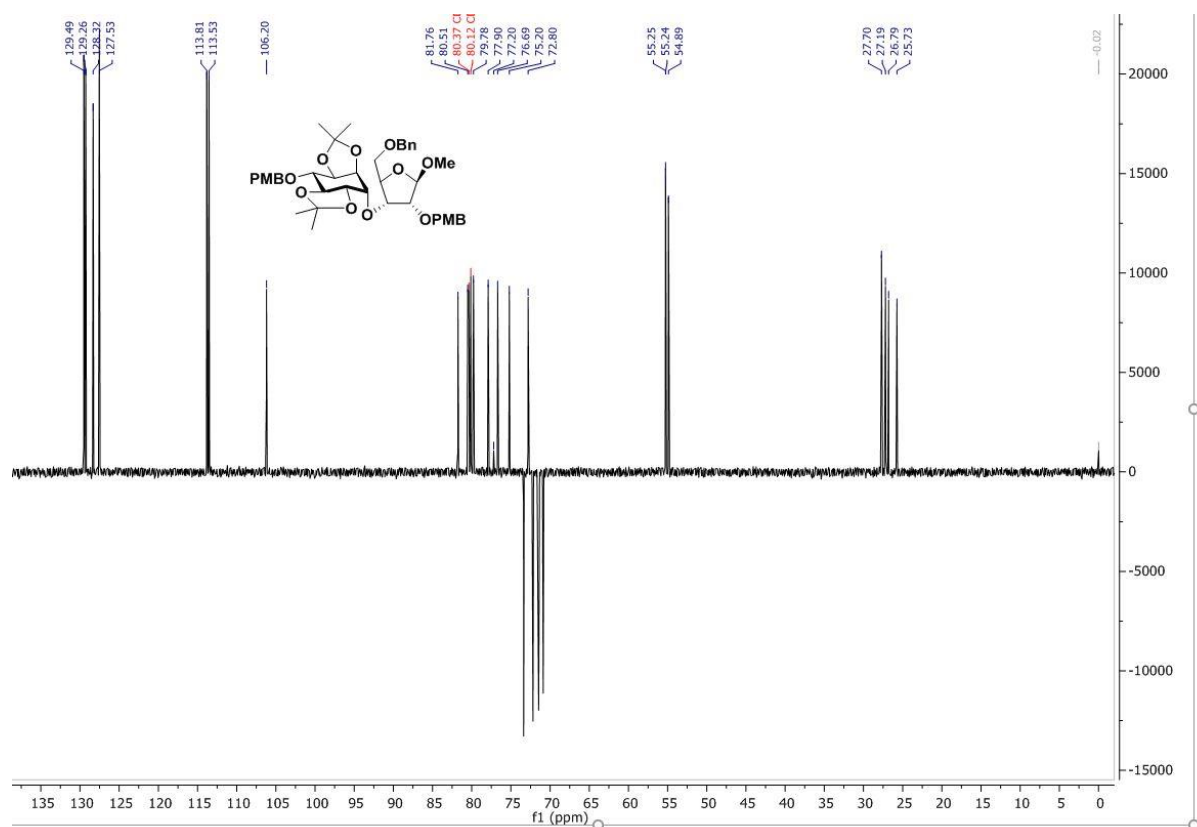
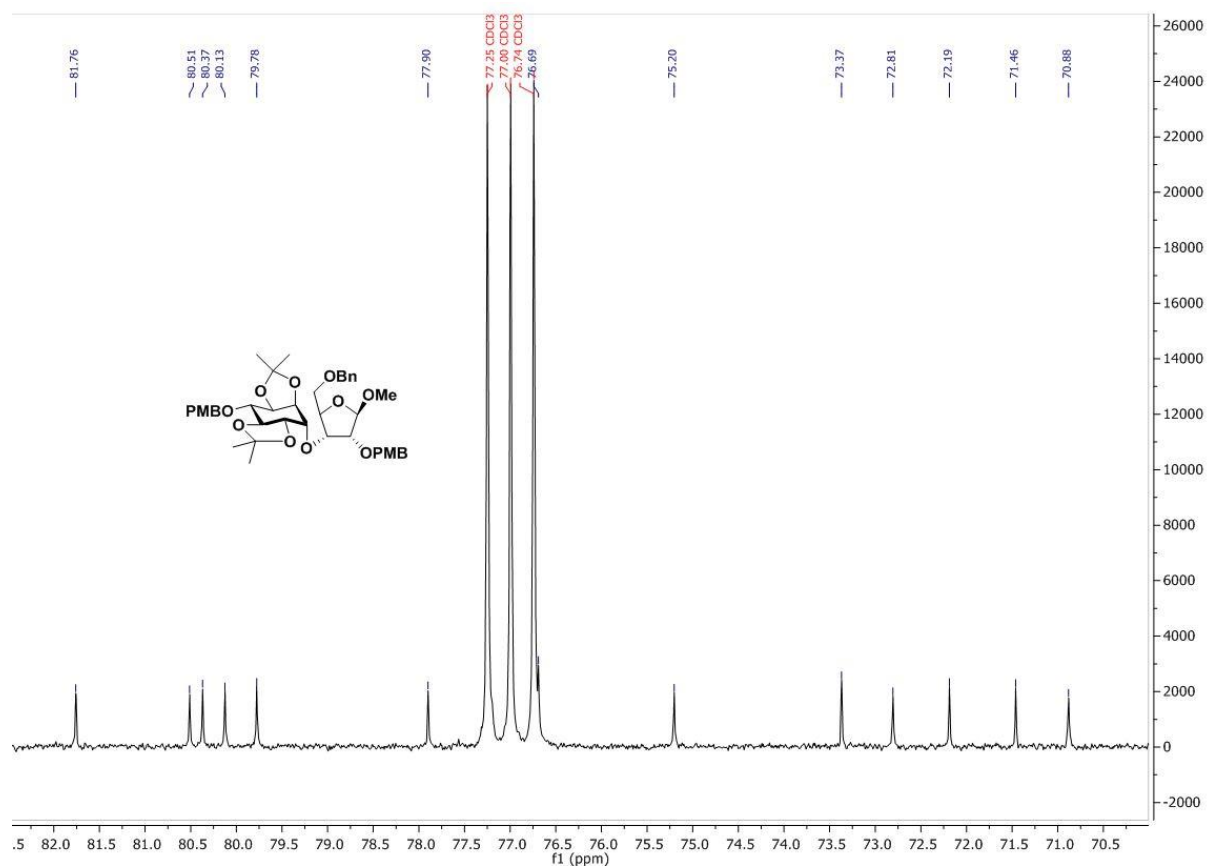
## S2 Chemistry

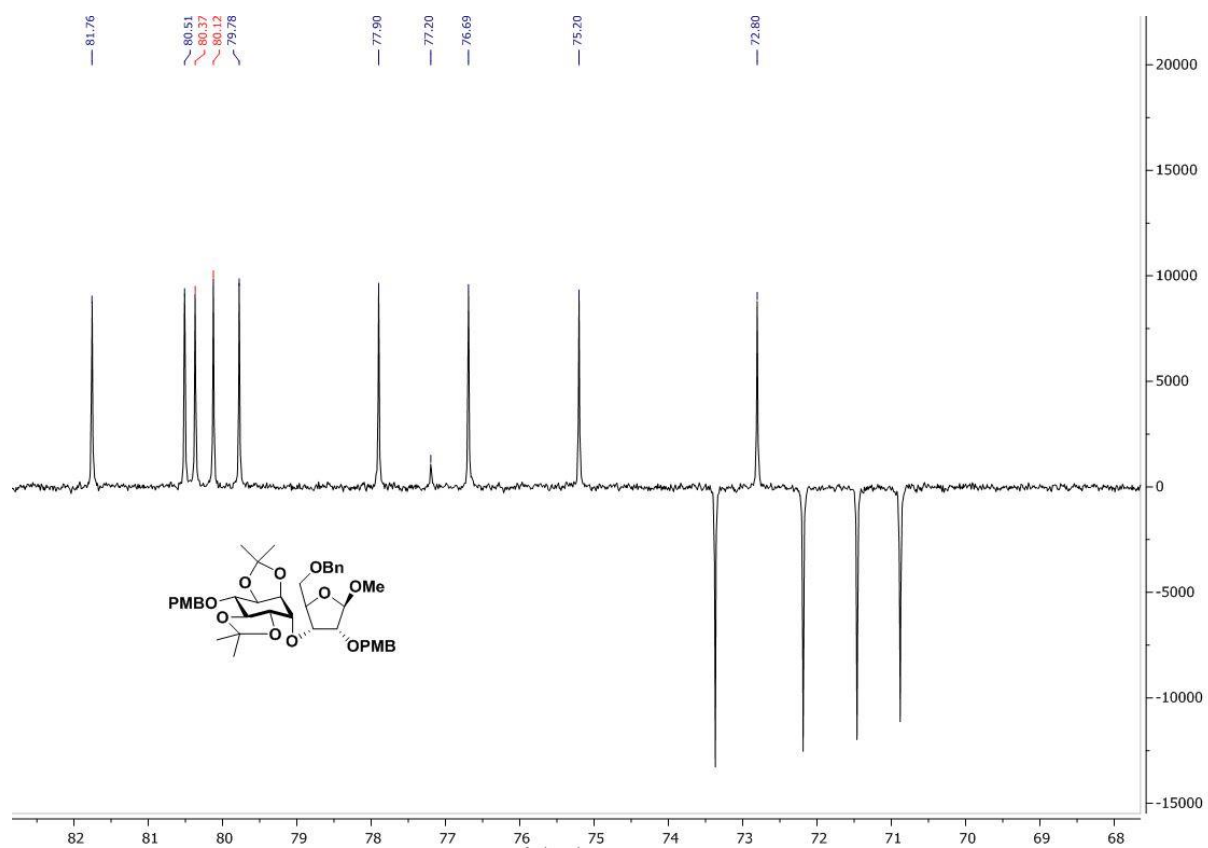
(3a*S*,4*S*,4a*S*,7a*R*,8*R*,8a*S*)-4-(((3*R*,4*R*,5*R*)-2-((benzyloxy)methyl)-5-methoxy-4-((4-methoxybenzyl)oxy)tetrahydrofuran-3-yl)oxy)-8-((4-methoxybenzyl)oxy)-2,2,6,6-tetramethylhexahydrobenzo[1,2-*d*:4,5-*d'*]bis([1,3]dioxole) (13)

<sup>1</sup>H NMR



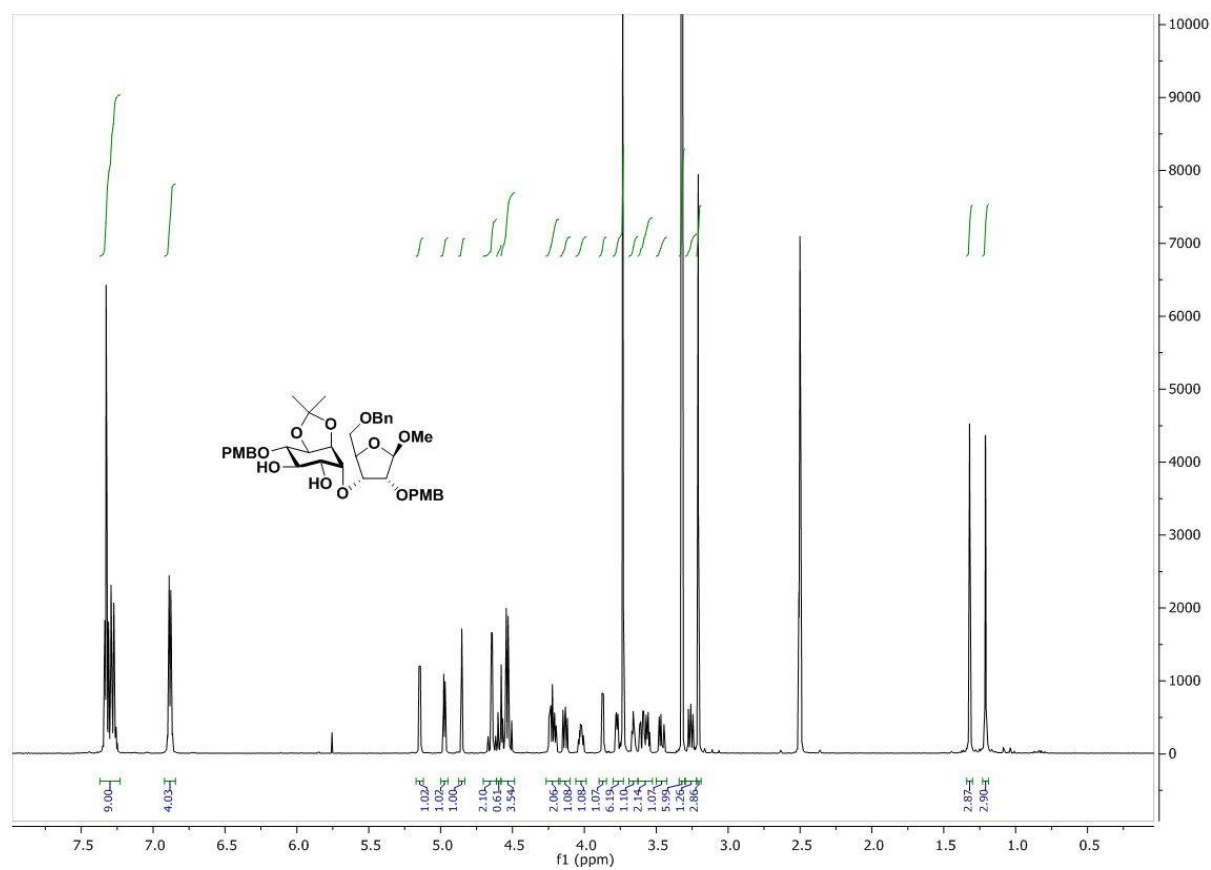


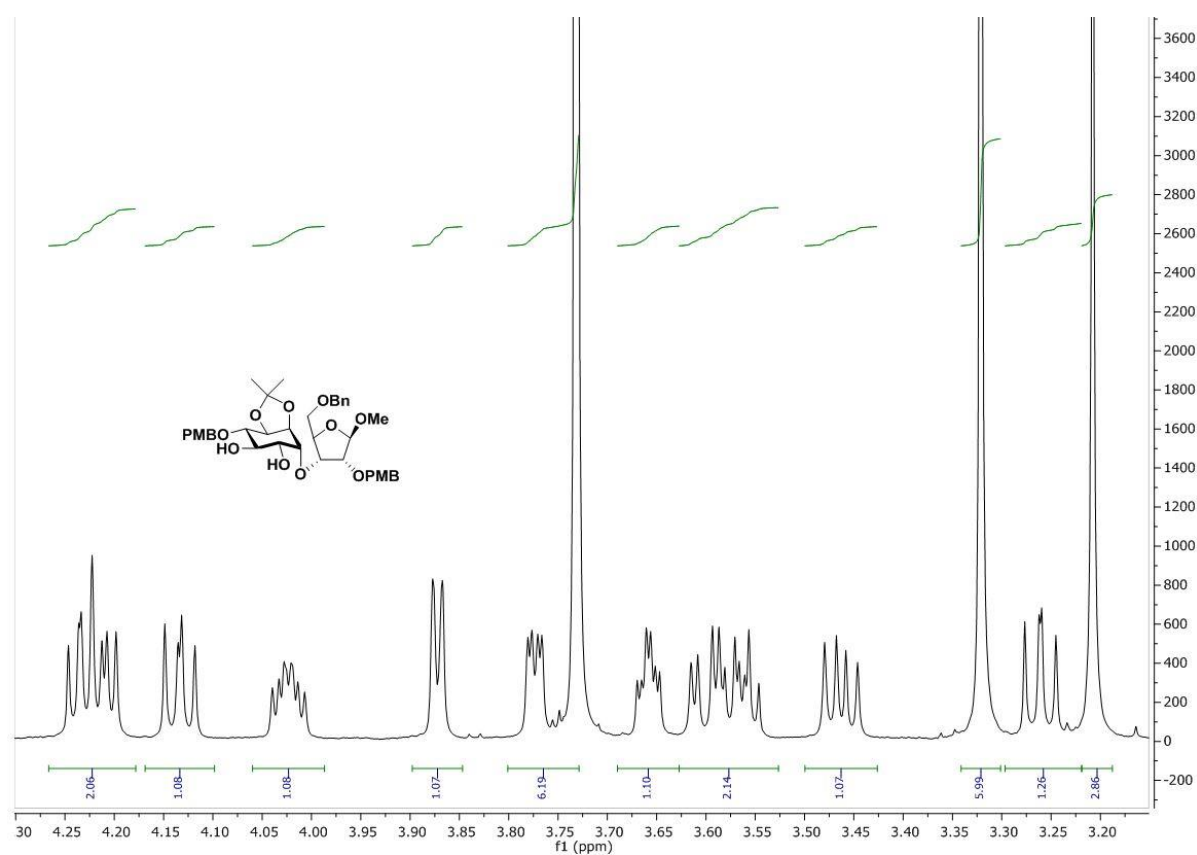
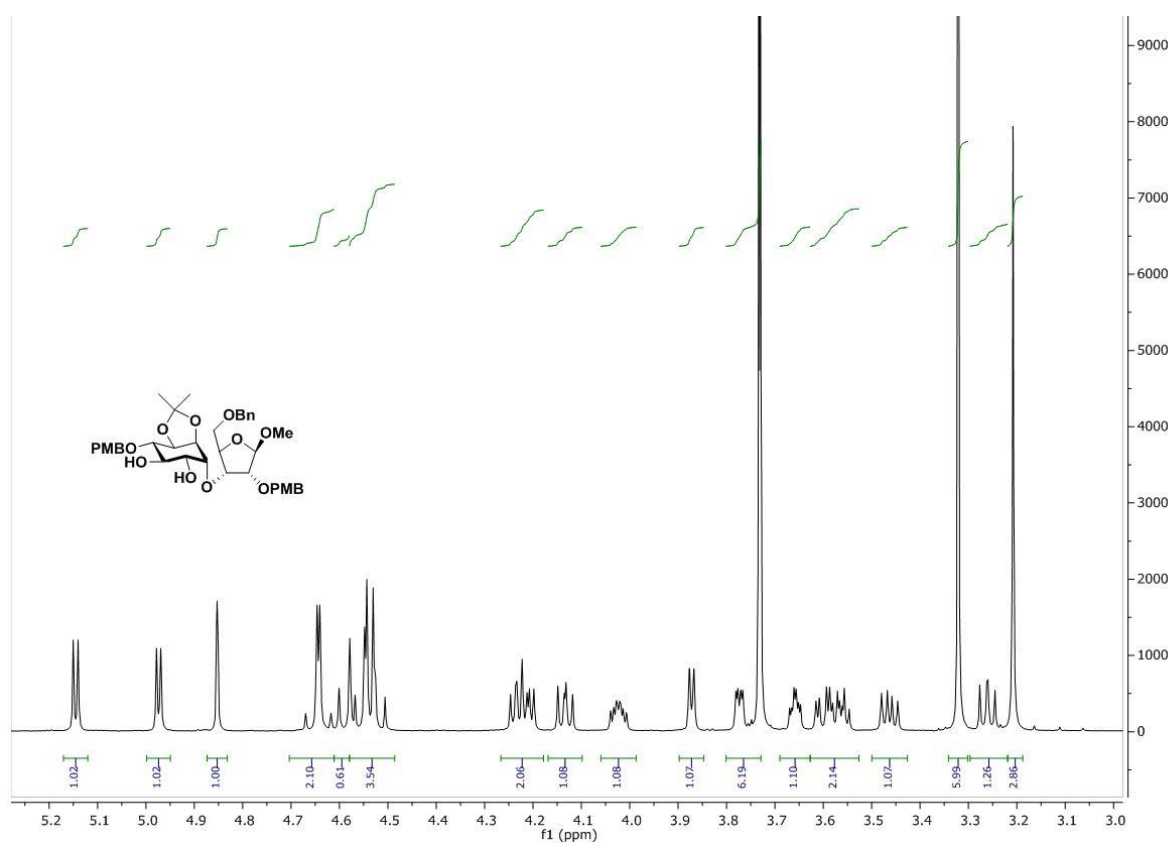




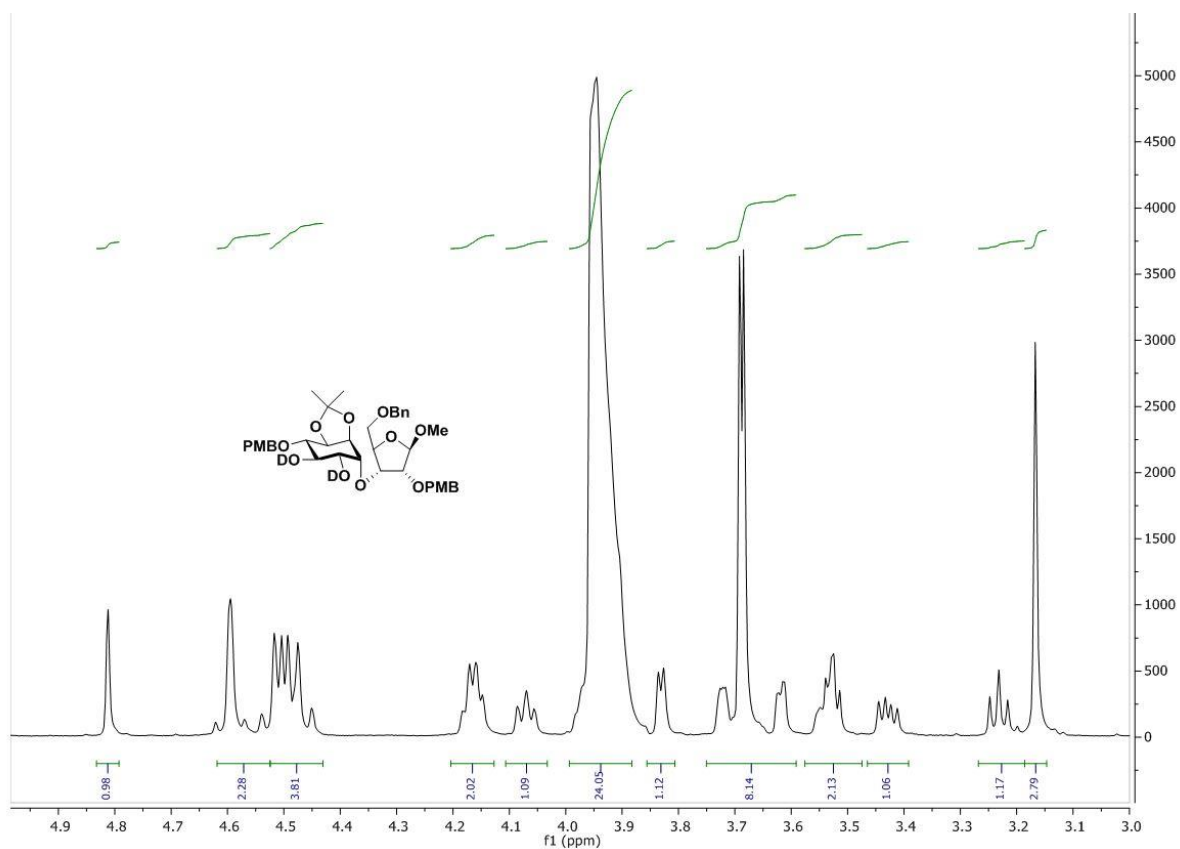
**(3a*S*,4*R*,5*R*,6*R*,7*S*,7a*R*)-4-(((3*R*,4*R*,5*R*)-2-((benzyloxy)methyl)-5-methoxy-4-((4-methoxybenzyl)oxy)tetrahydrofuran-3-yl)oxy)-7-((4-methoxybenzyl)oxy)-2,2-dimethylhexahydrobenzo[*d*][1,3]dioxole-5,6-diol (14)**

<sup>1</sup>H NMR

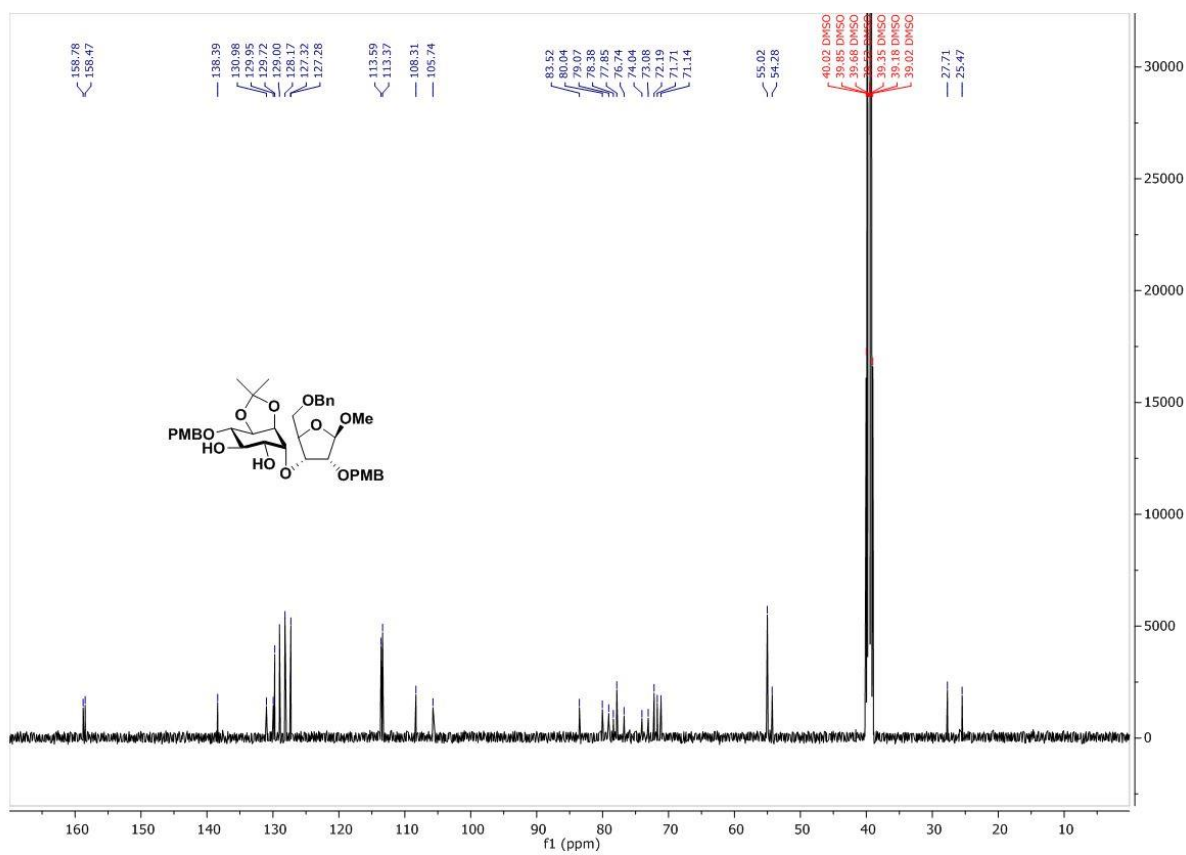


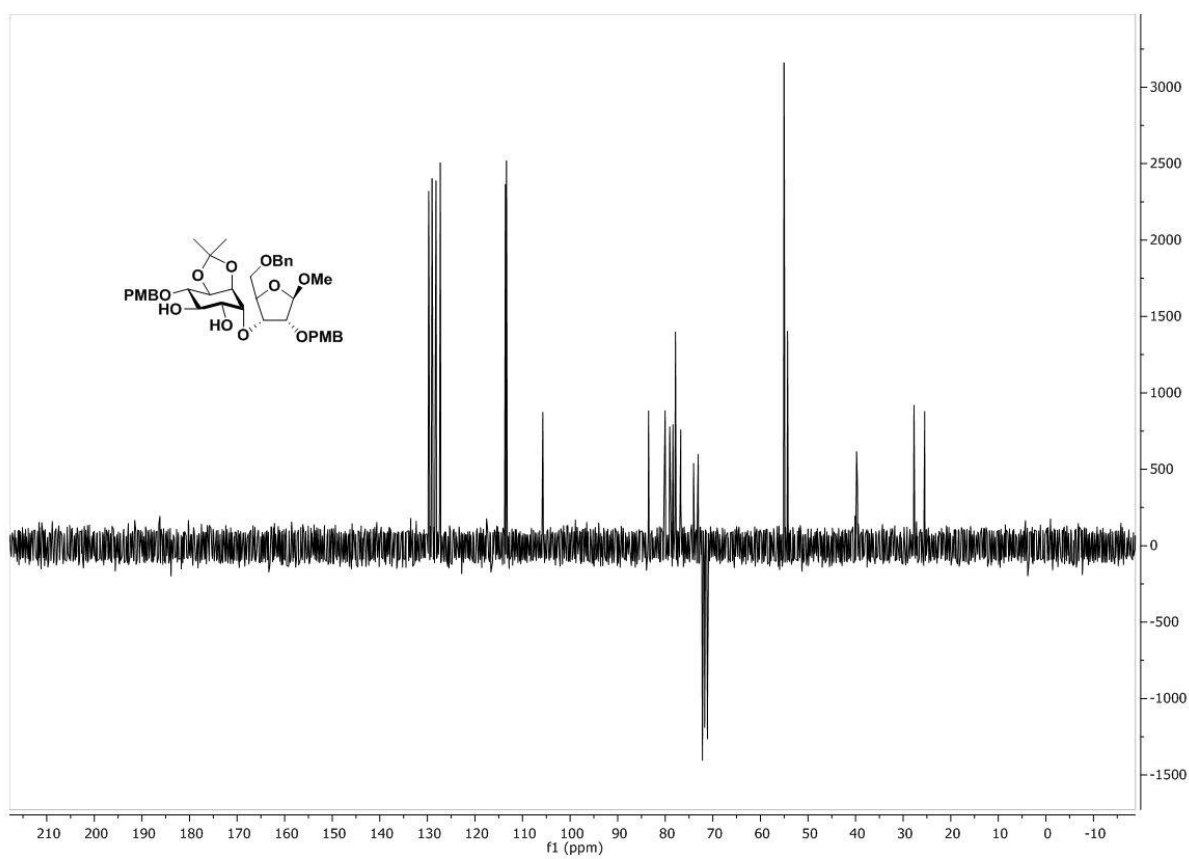
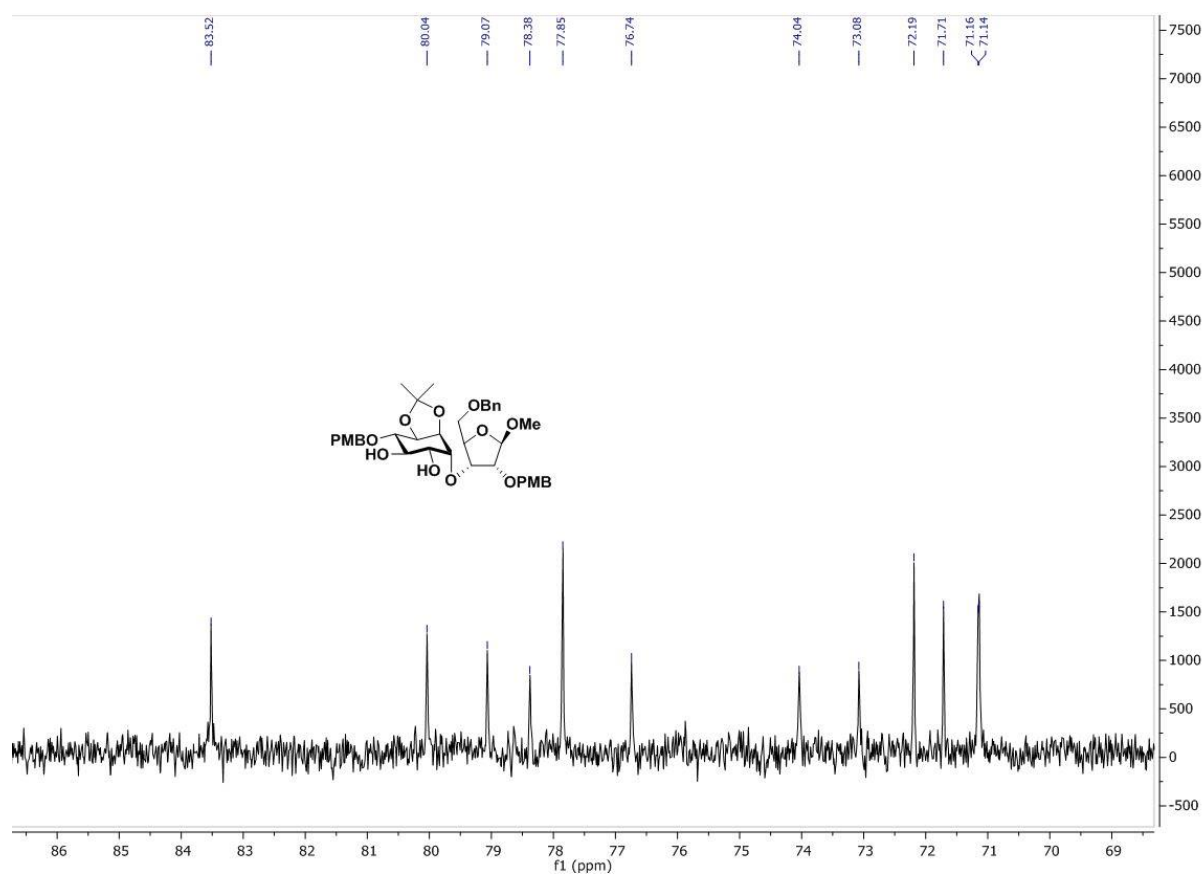


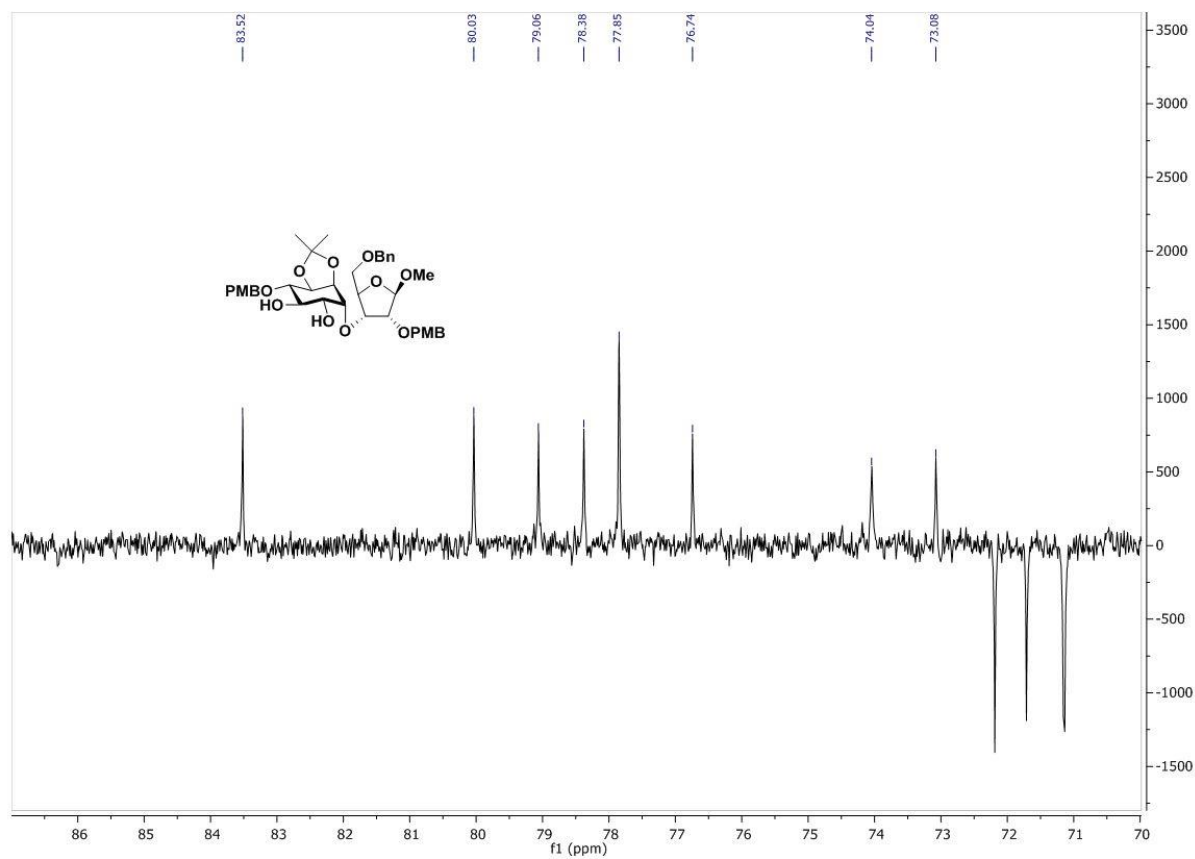




$^{13}\text{C}$  NMR

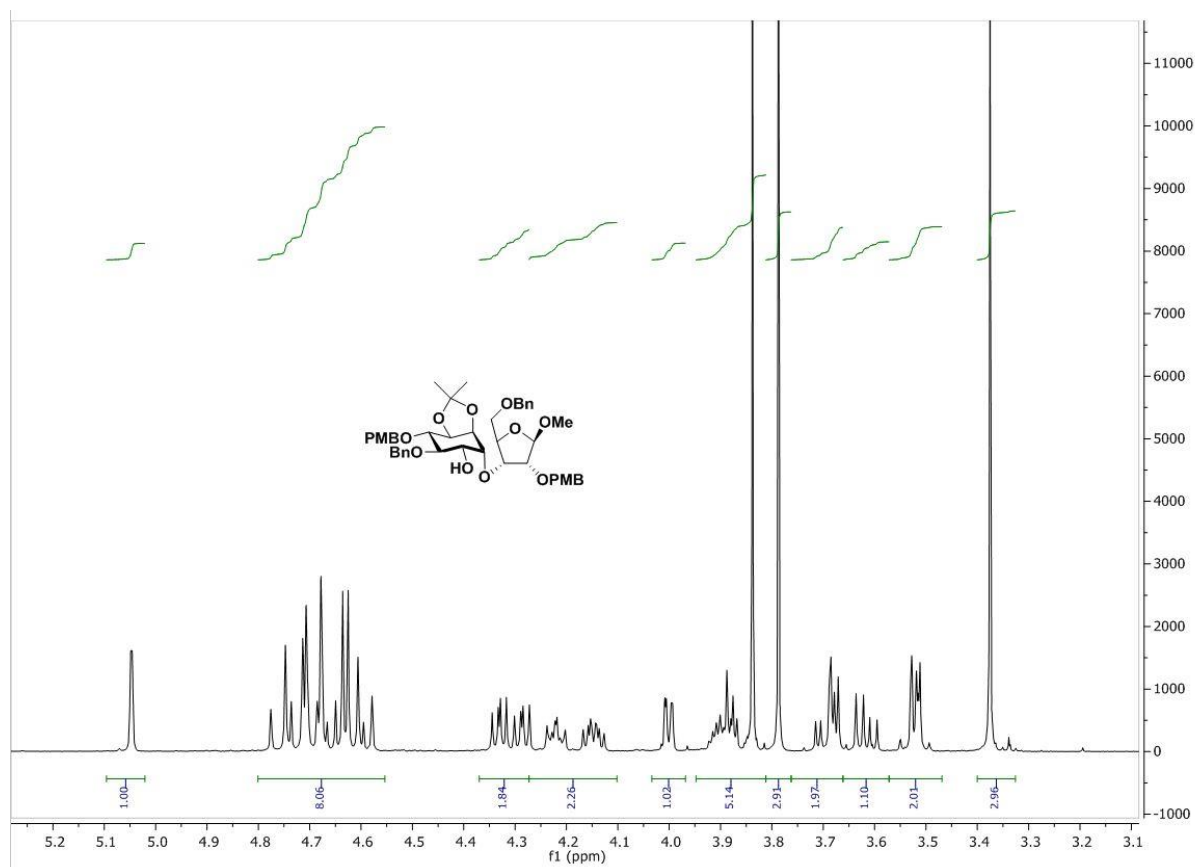
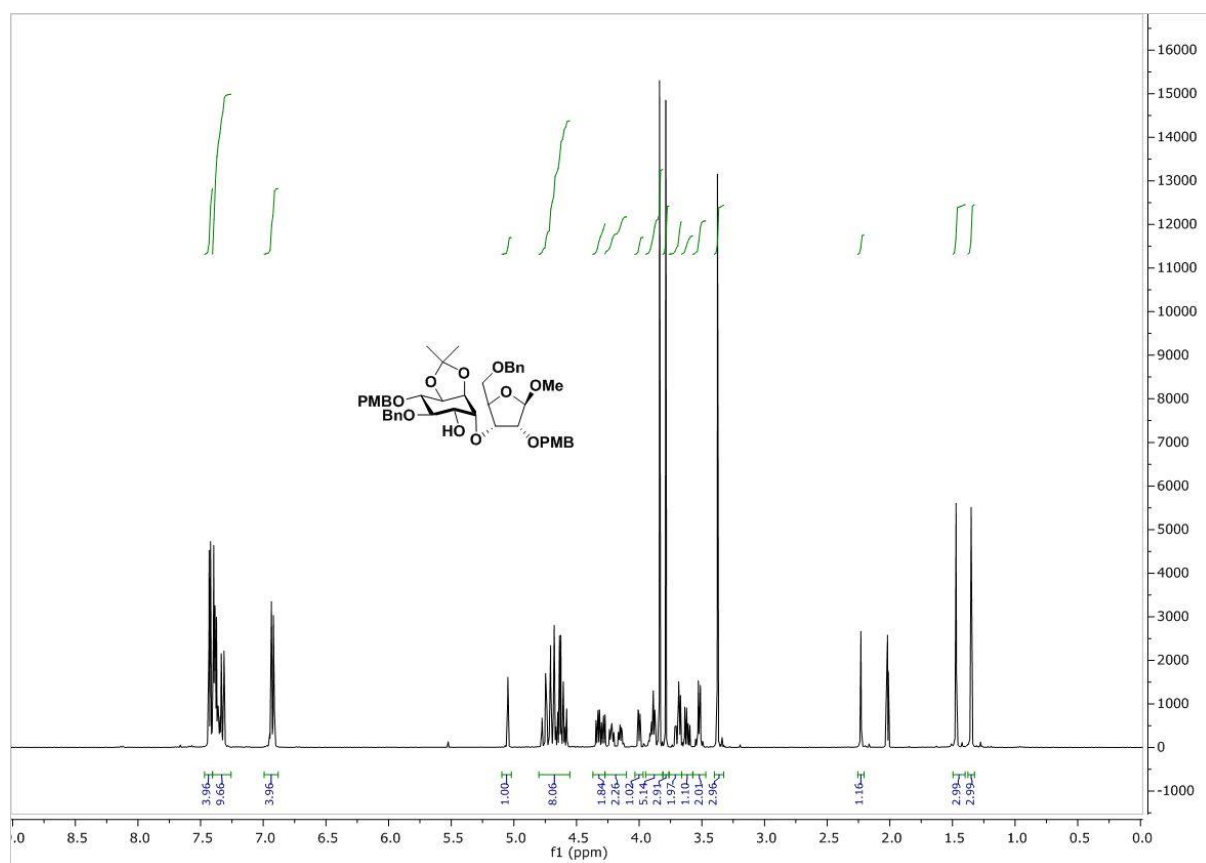




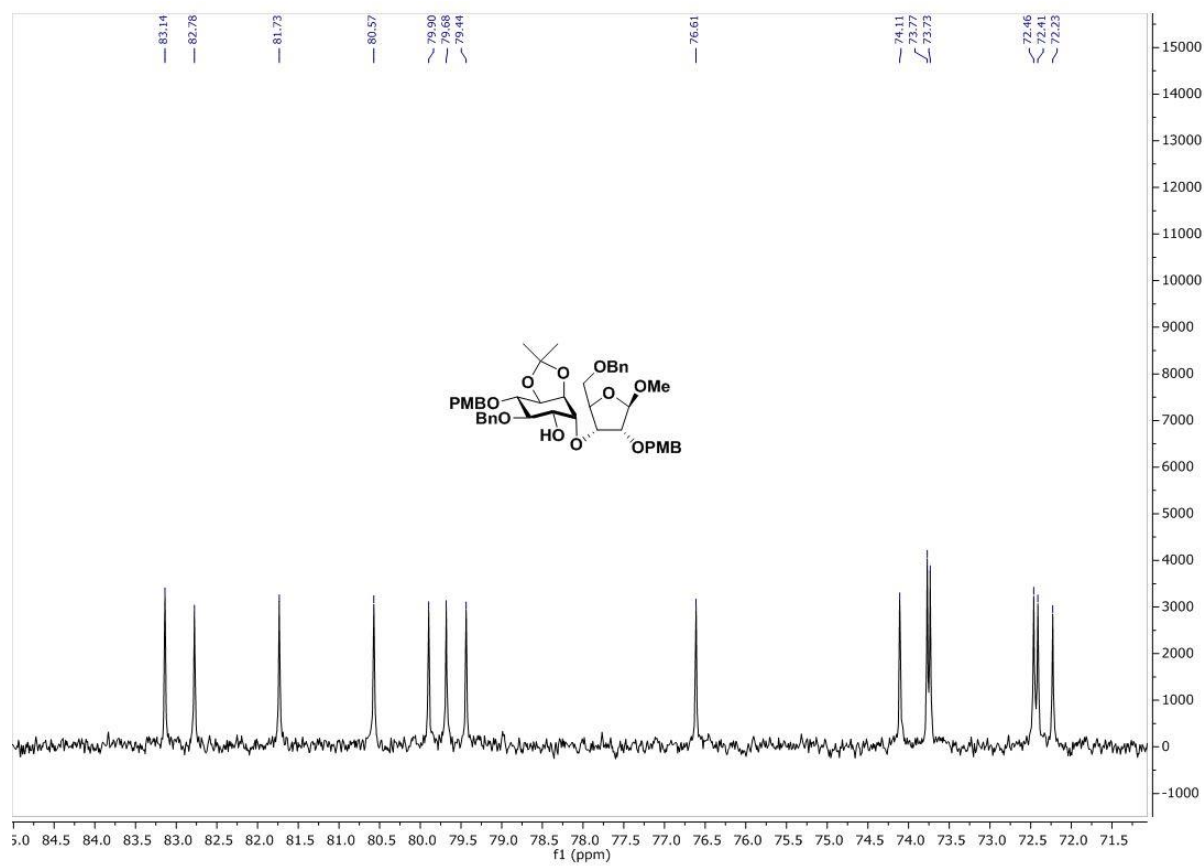
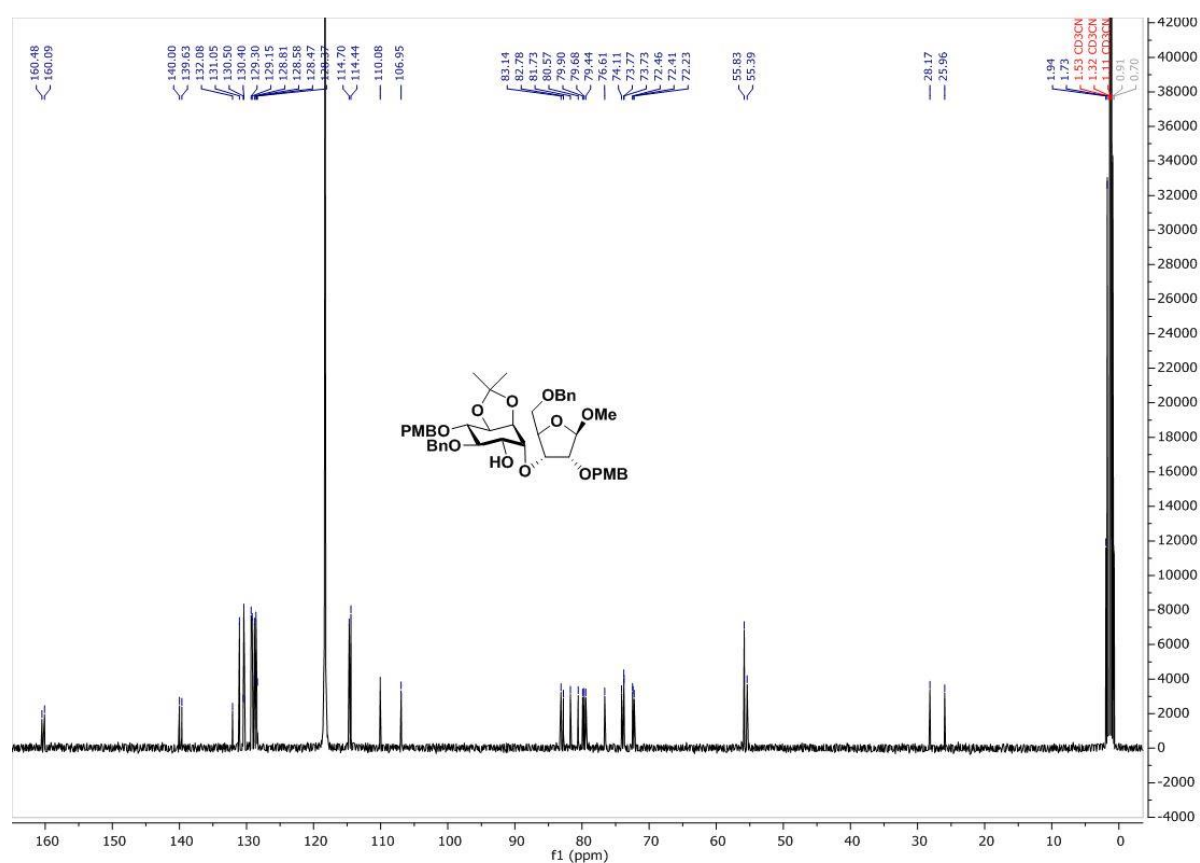


**(3a*S*,4*R*,5*R*,6*R*,7*S*,7a*R*)-6-(benzyloxy)-4-(((3*R*,4*R*,5*R*)-2-((benzyloxy)methyl)-5-methoxy-4-((4-methoxybenzyl)oxy)tetrahydrofuran-3-yl)oxy)-7-((4-methoxybenzyl)oxy)-2,2-dimethylhexahydrobenzo[*d*][1,3]dioxol-5-ol (15)**

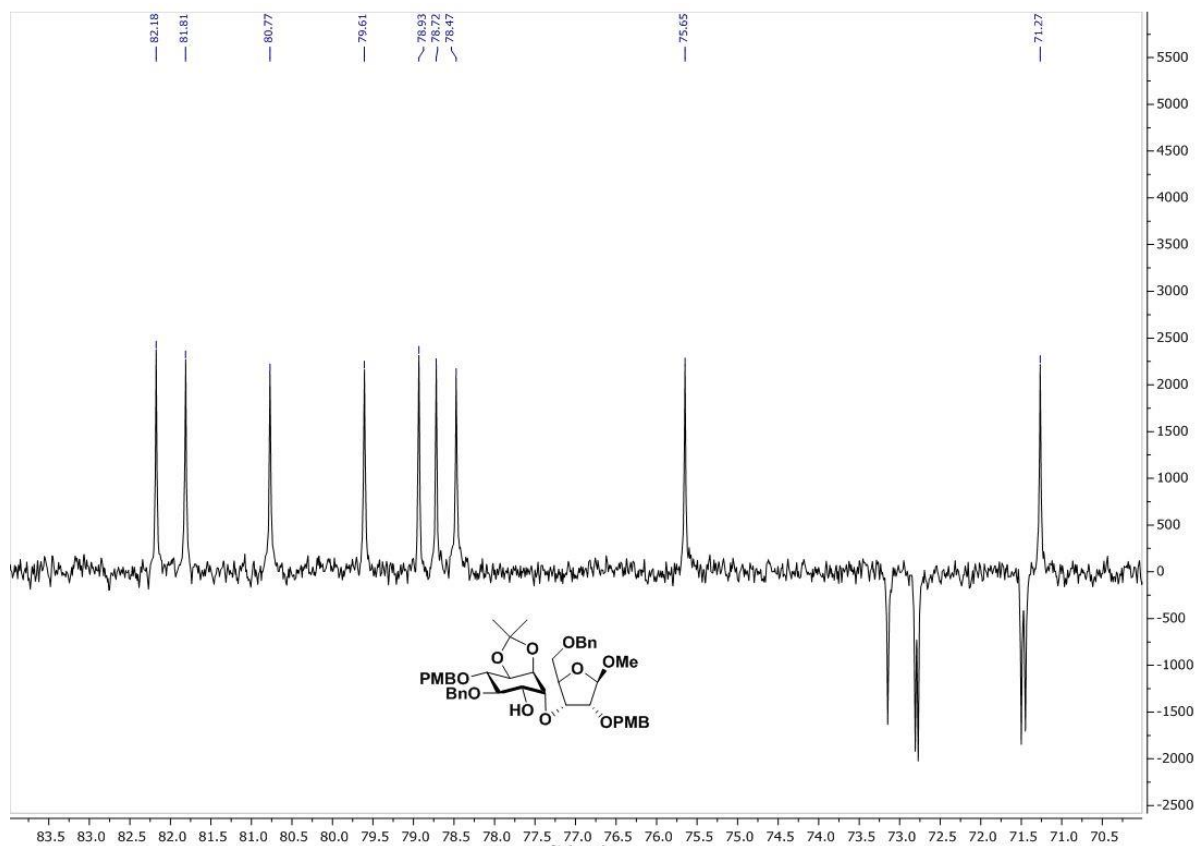
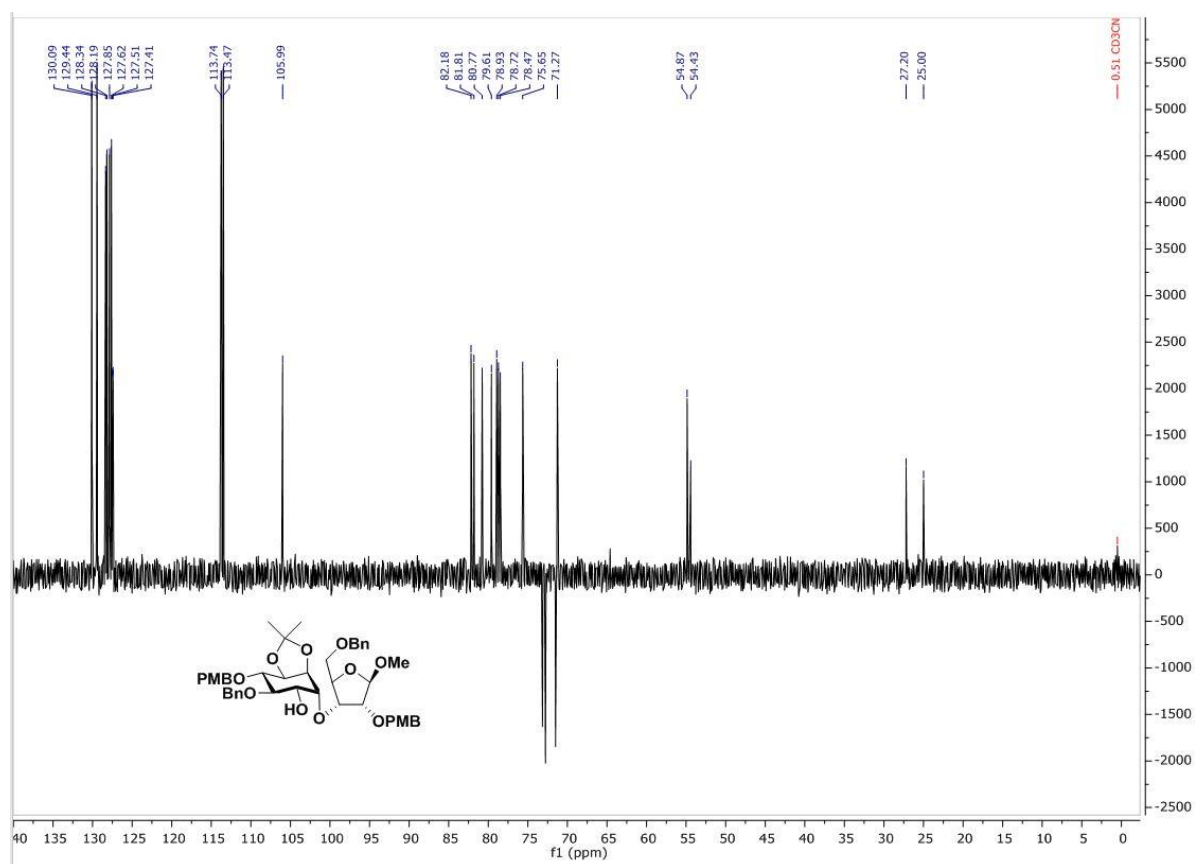
<sup>1</sup>H NMR



# $^{13}\text{C}$ NMR

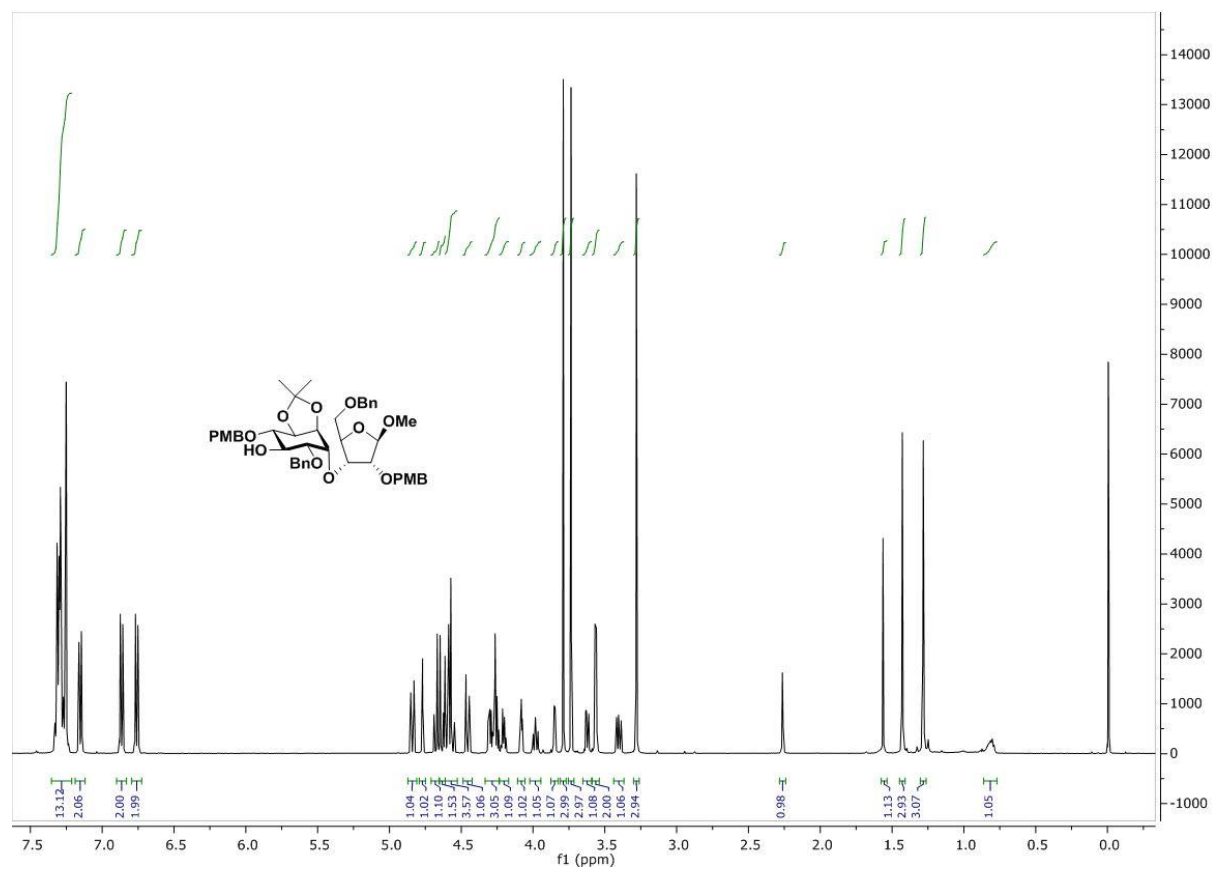


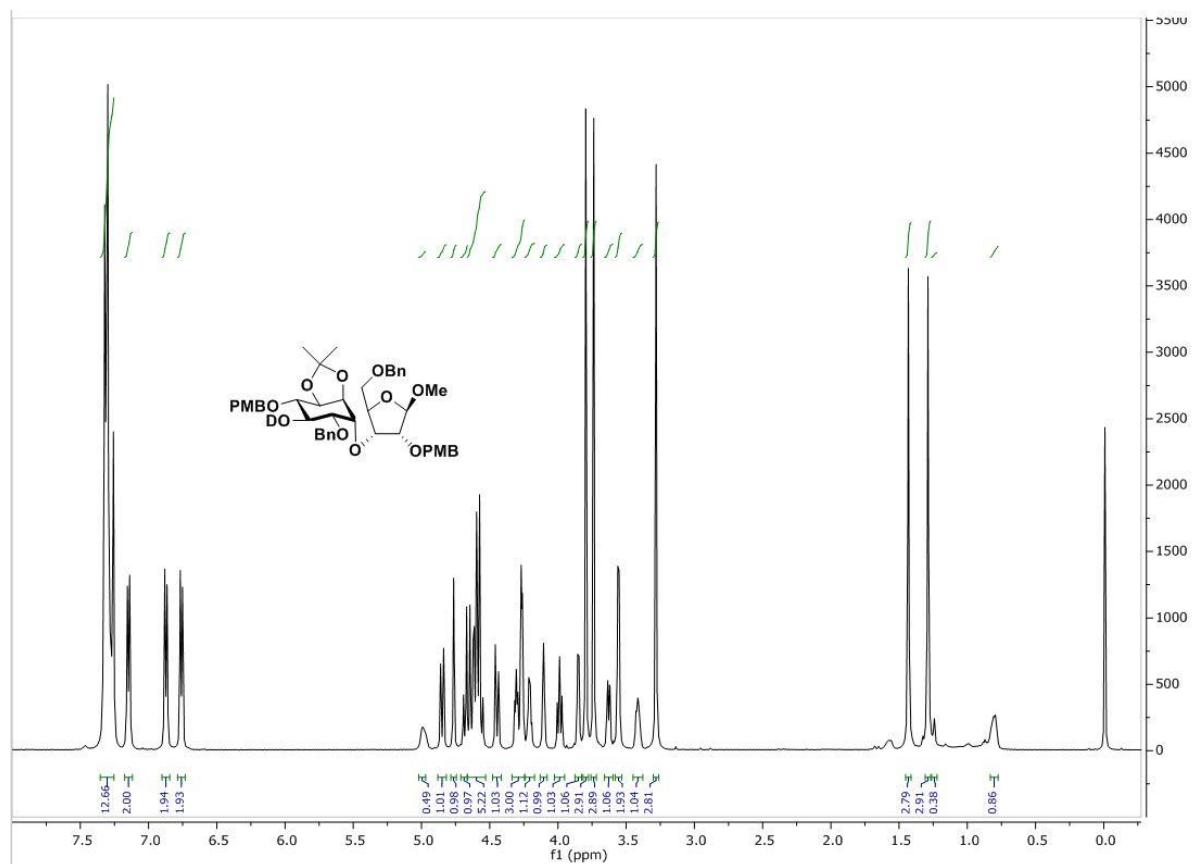
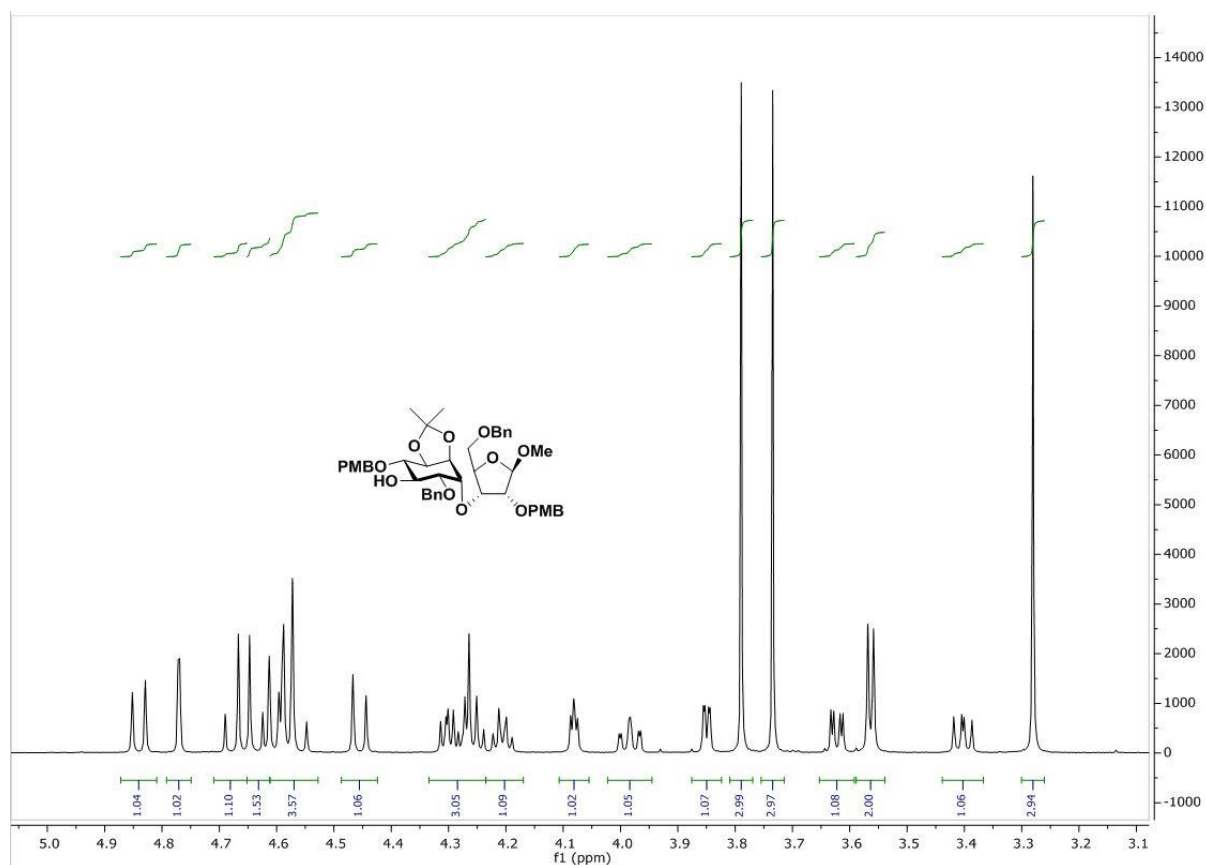
# $^{13}\text{C}$ DEPT NMR



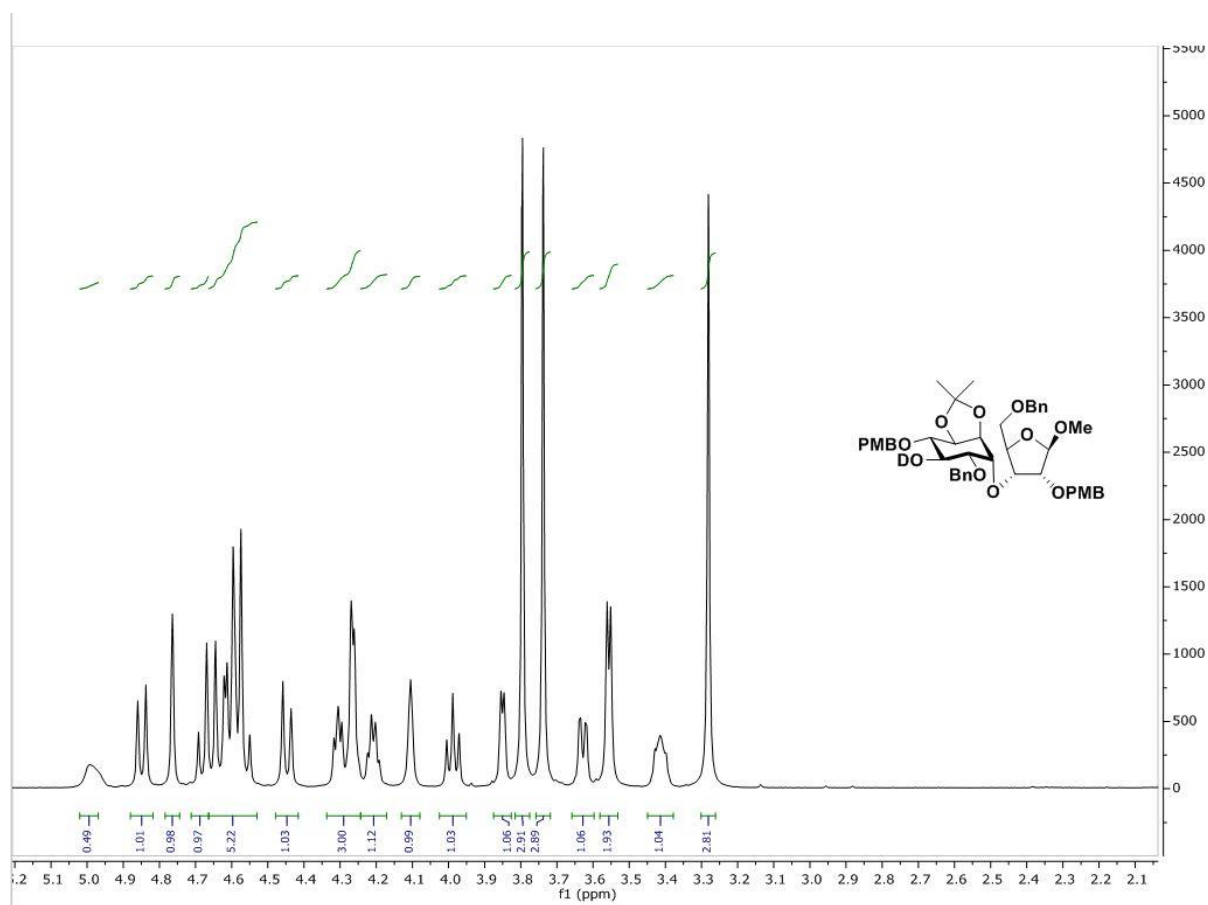
**(3*aR*,4*S*,5*R*,6*R*,7*R*,7*aS*)-6-(benzyloxy)-7-(((3*R*,4*R*,5*R*)-2-((benzyloxy)methyl)-5-methoxy-4-((4-methoxybenzyl)oxy)tetrahydrofuran-3-yl)oxy)-4-((4-methoxybenzyl)oxy)-2,2-dimethylhexahydrobenzo[*d*][1,3]dioxol-5-ol (16)**

<sup>1</sup>H NMR

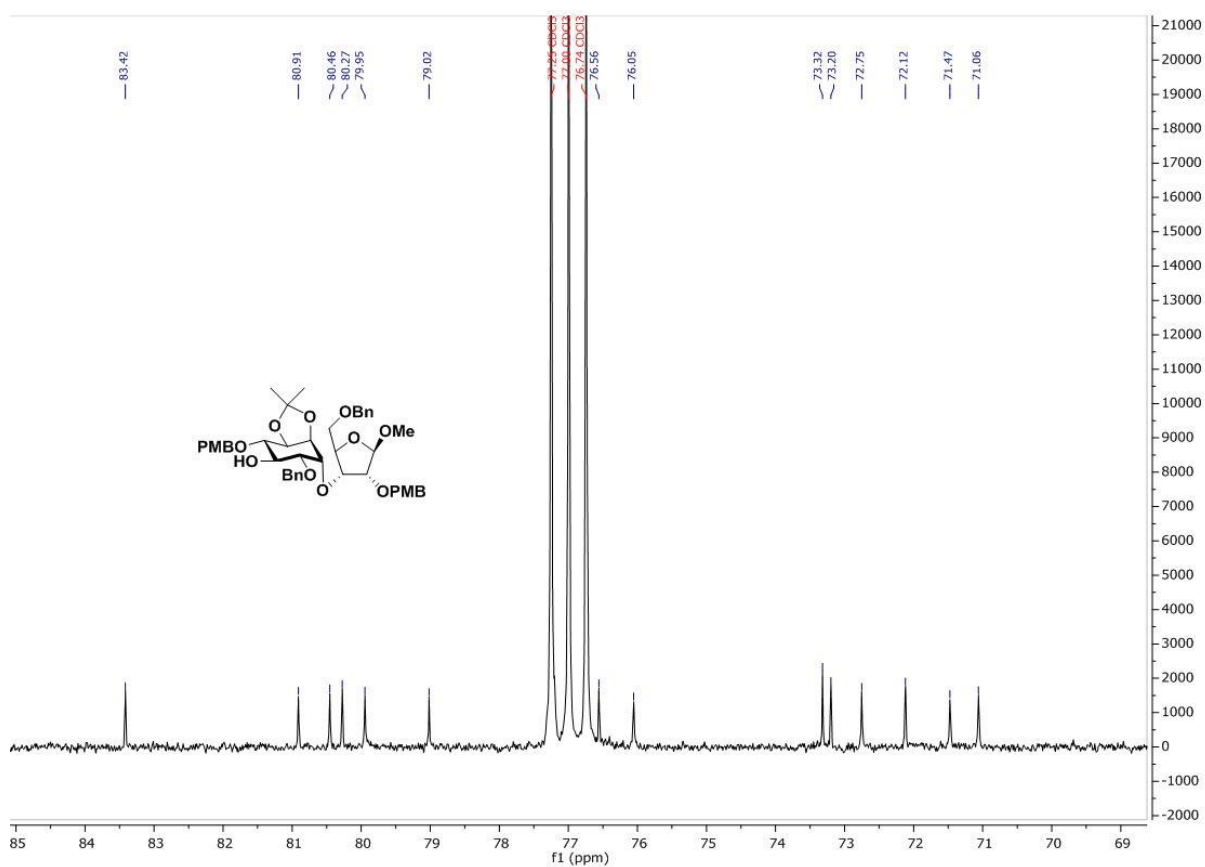
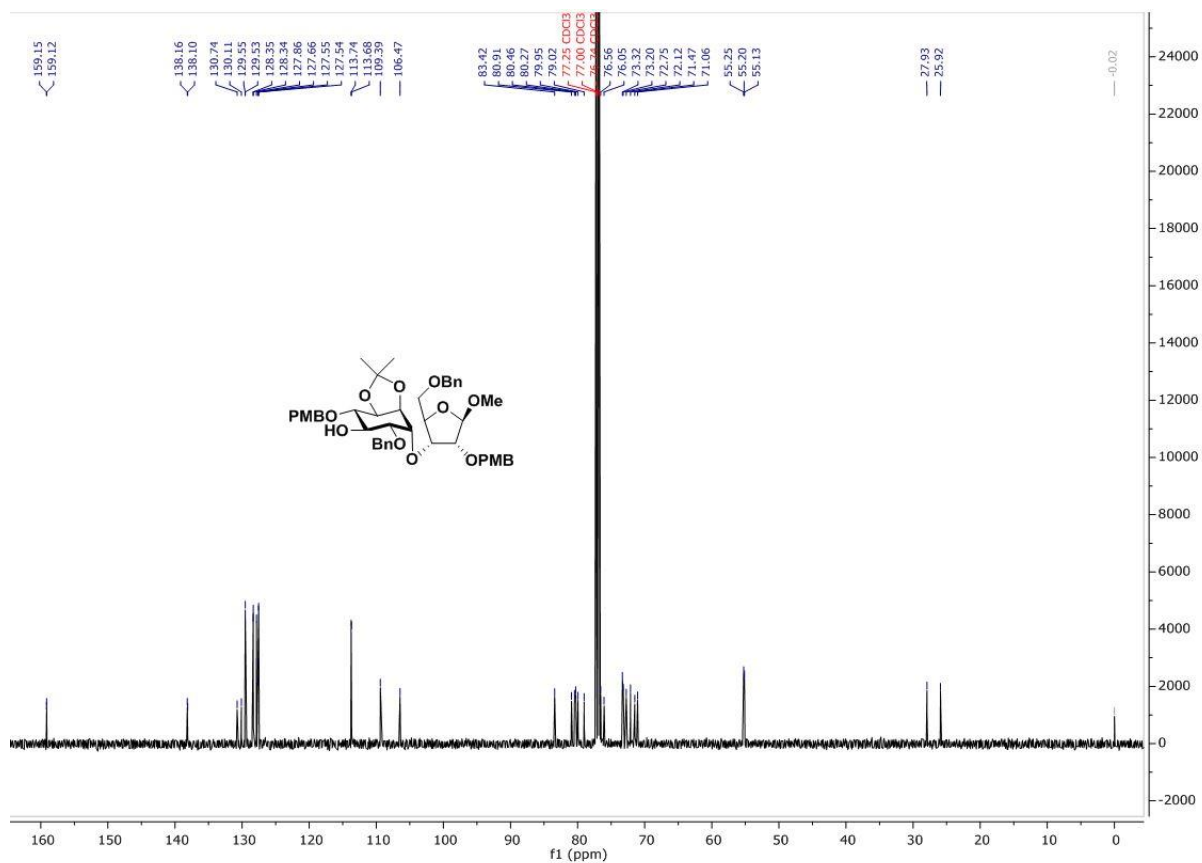


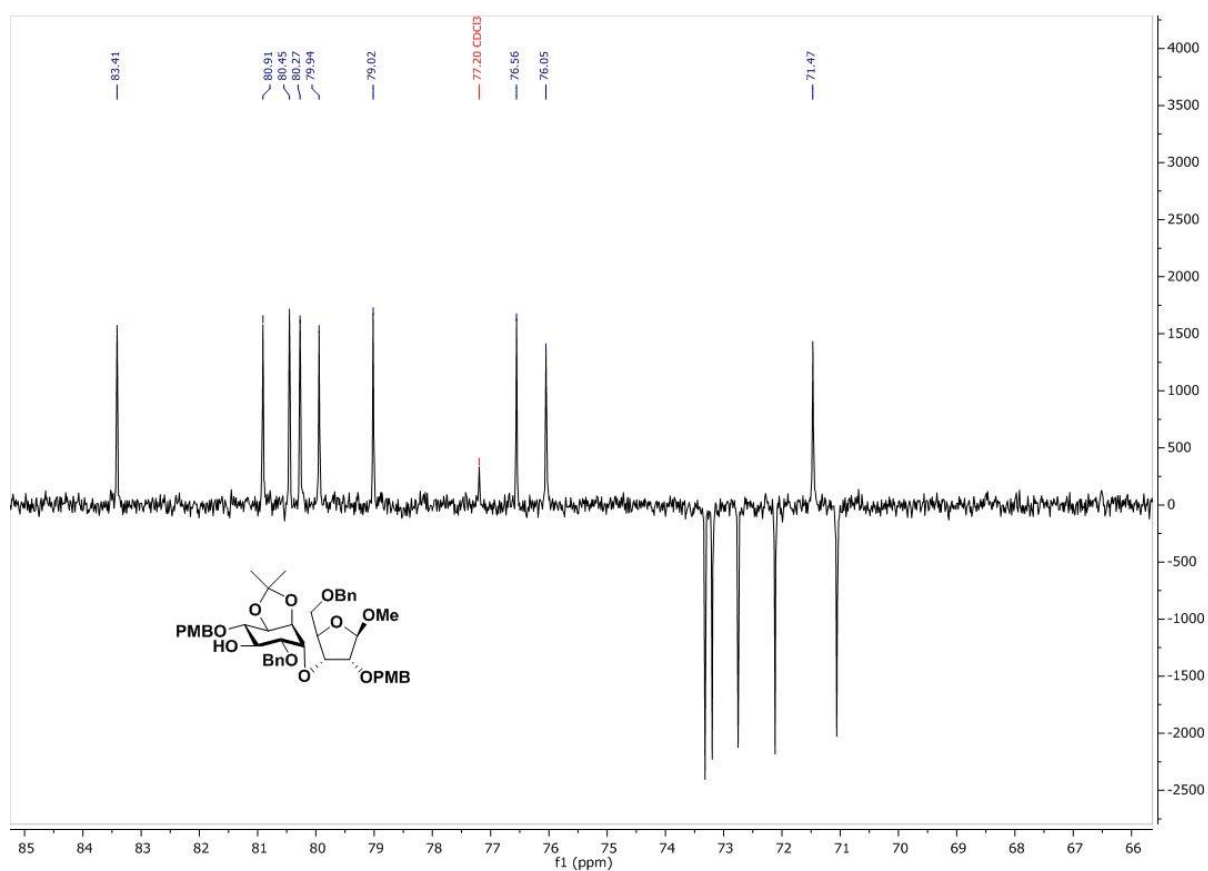
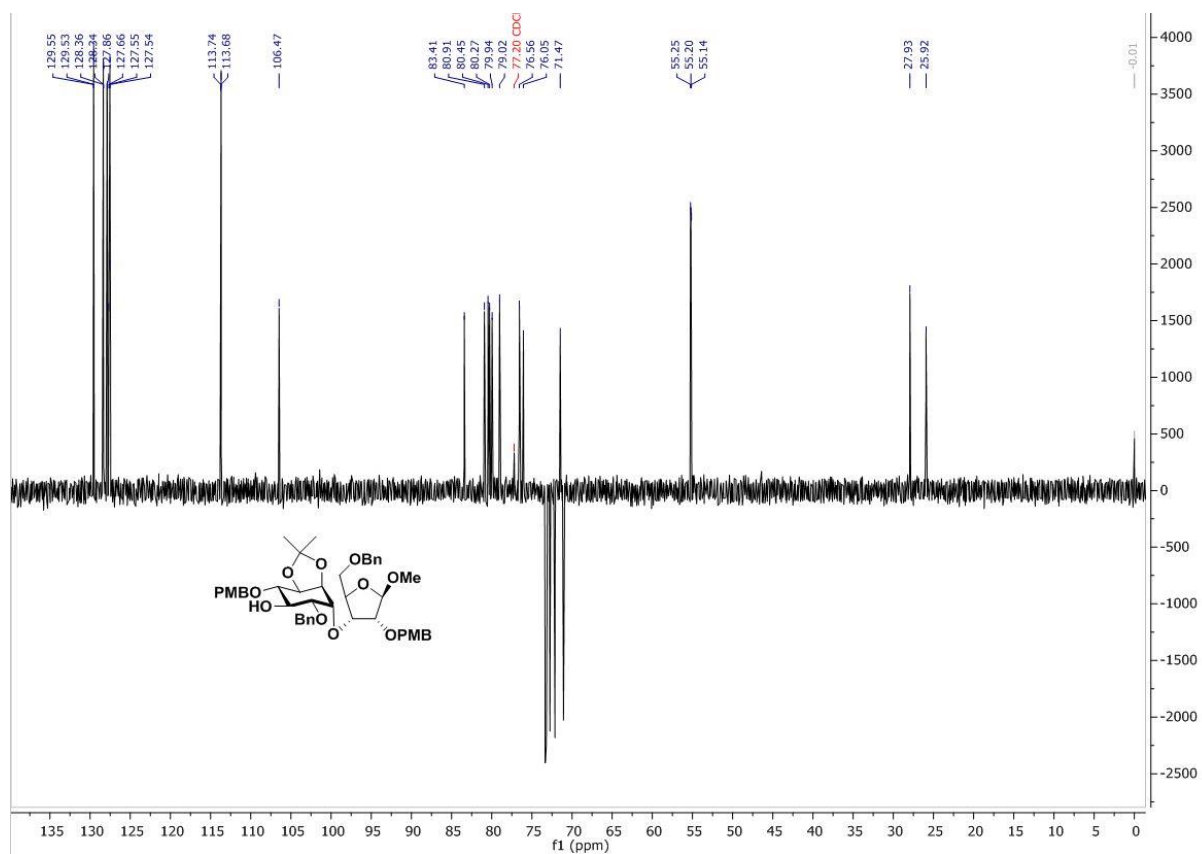


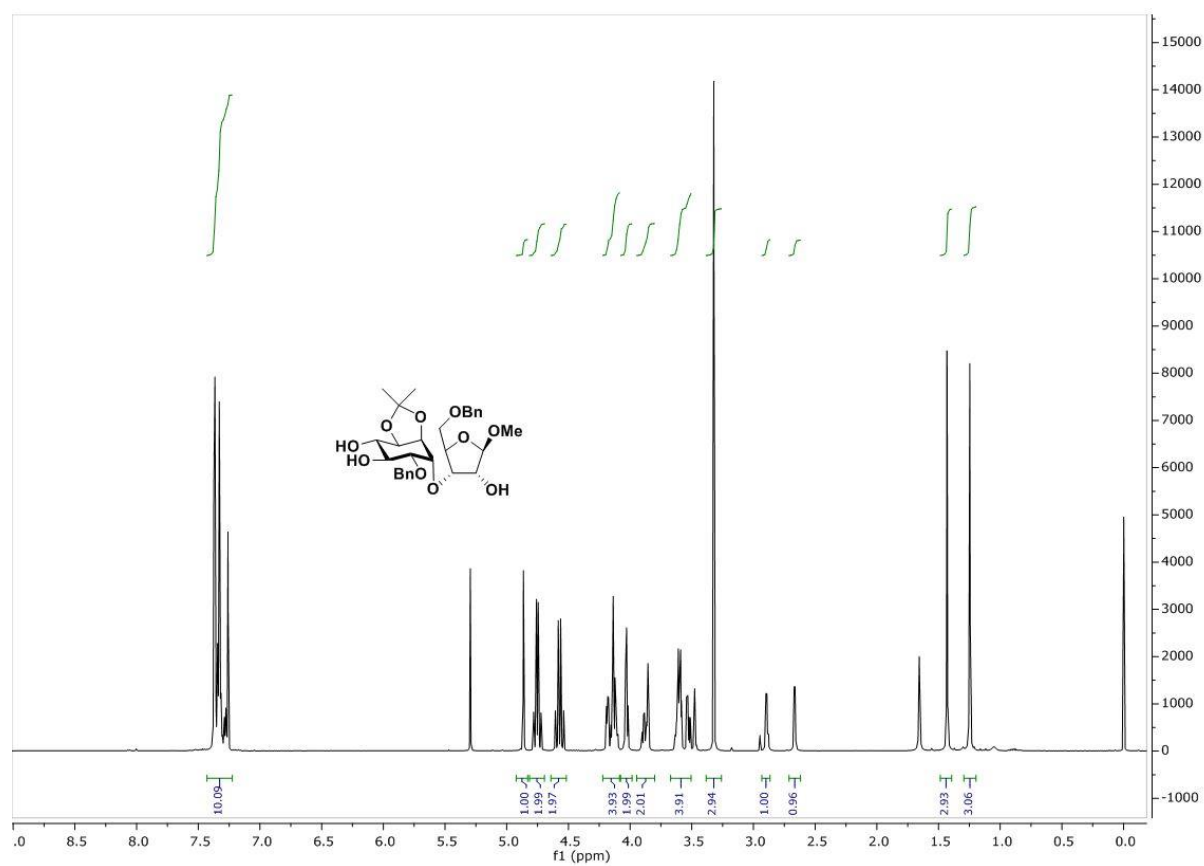


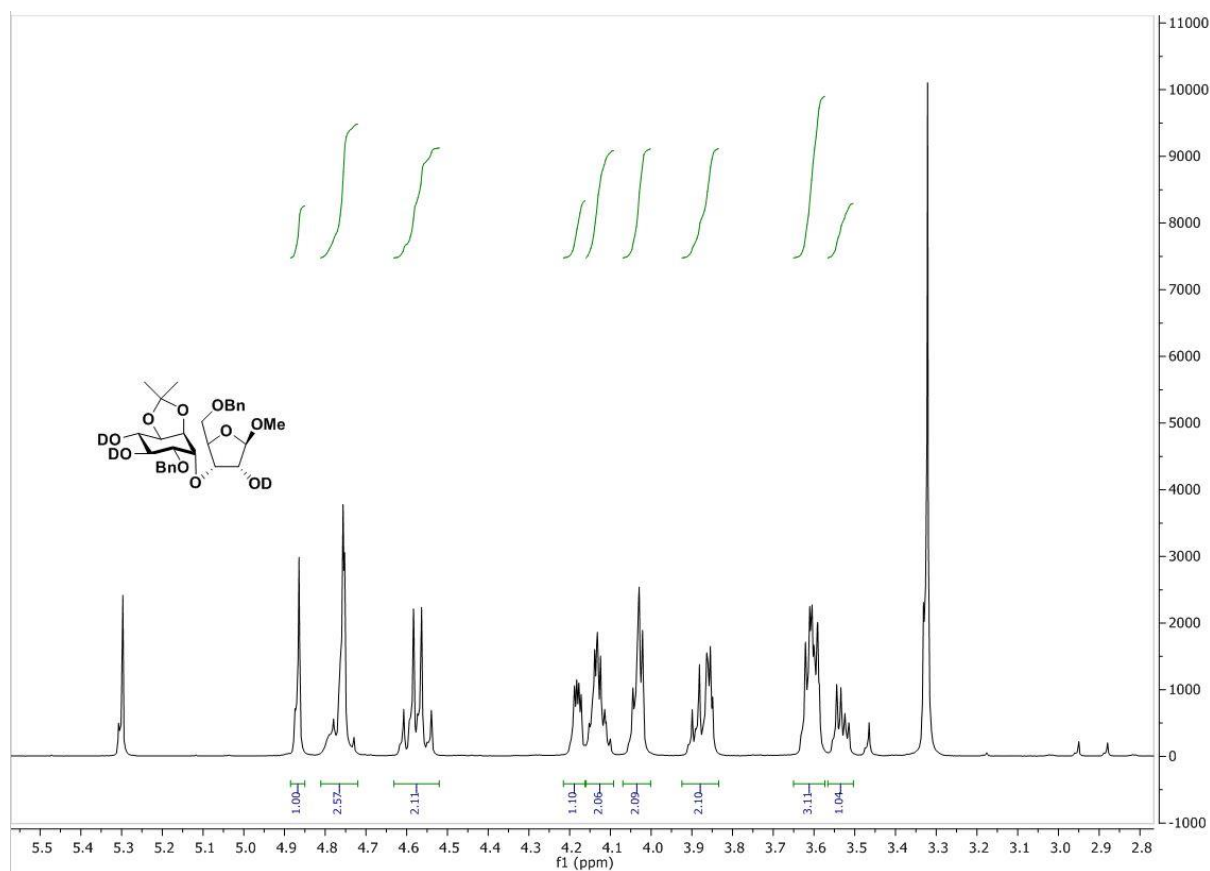
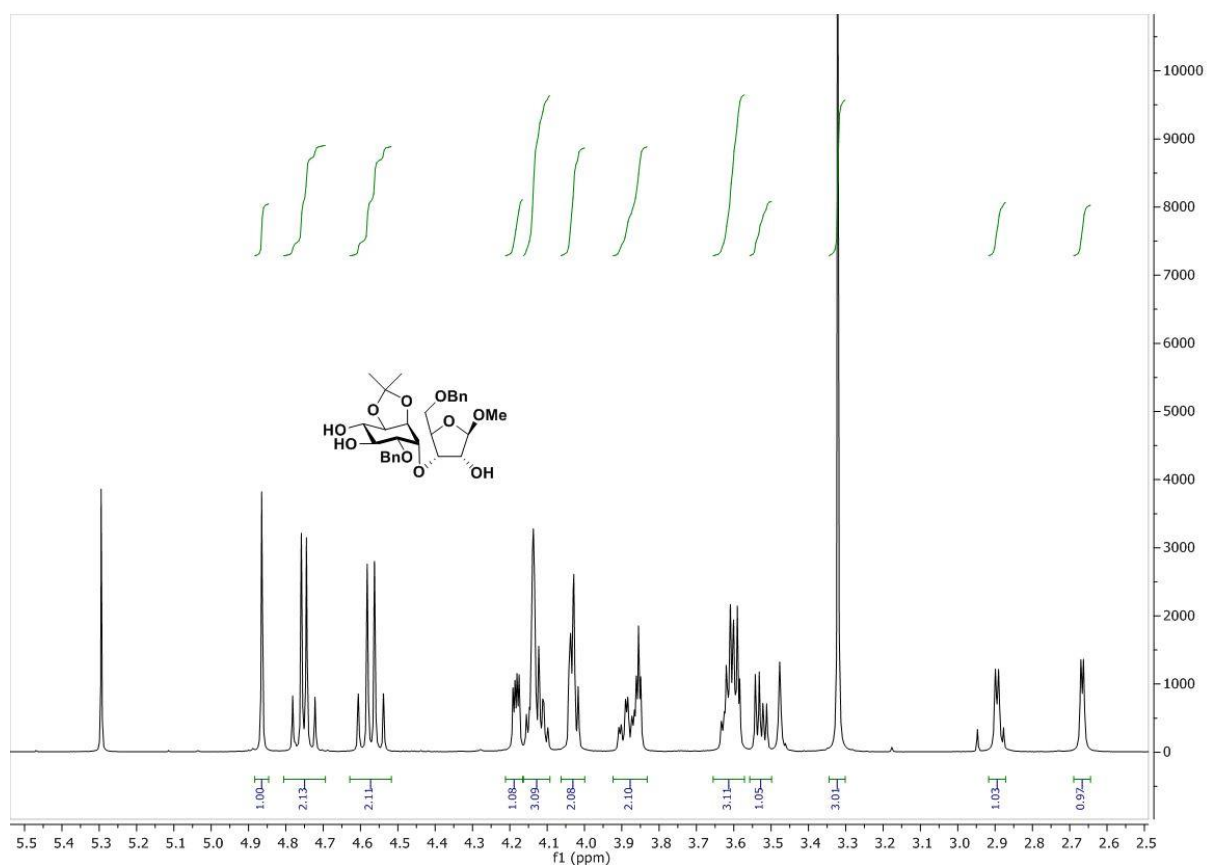


$^{13}\text{C}$  NMR





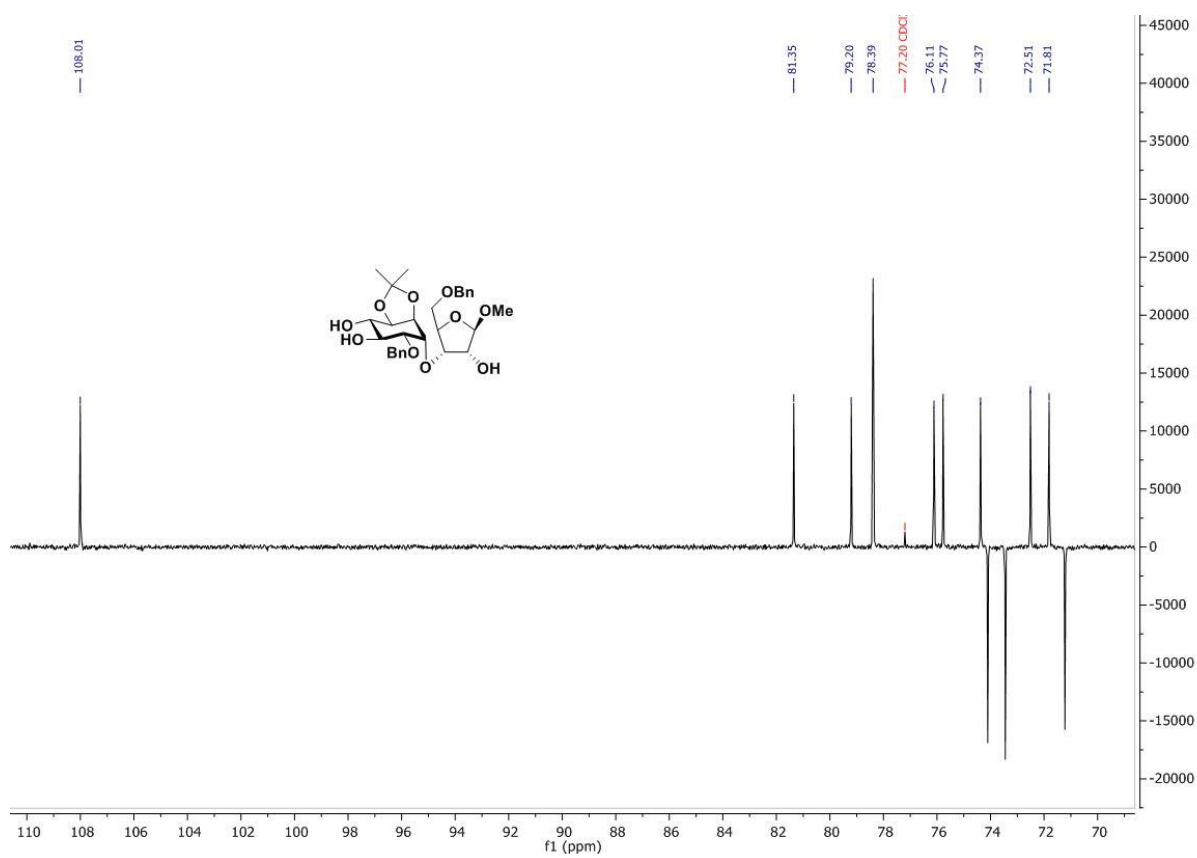
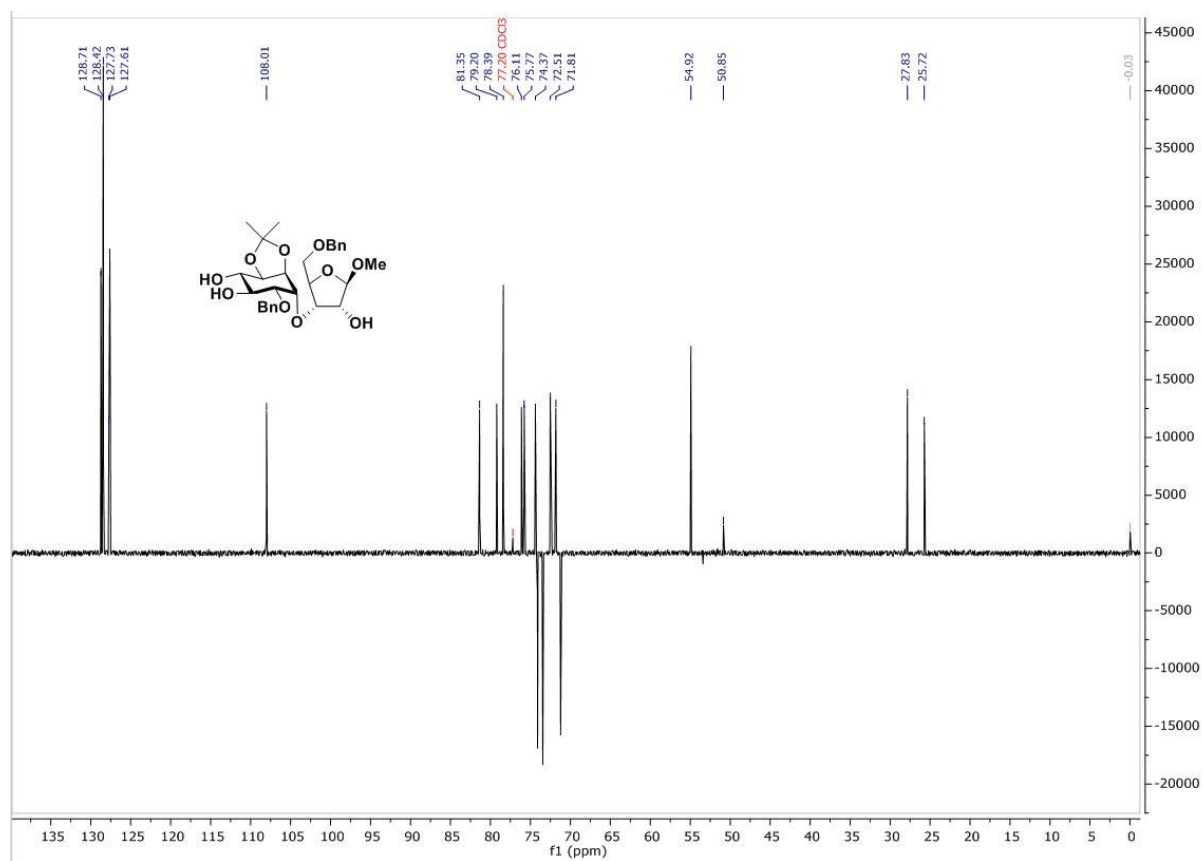
<sup>1</sup>H NMR

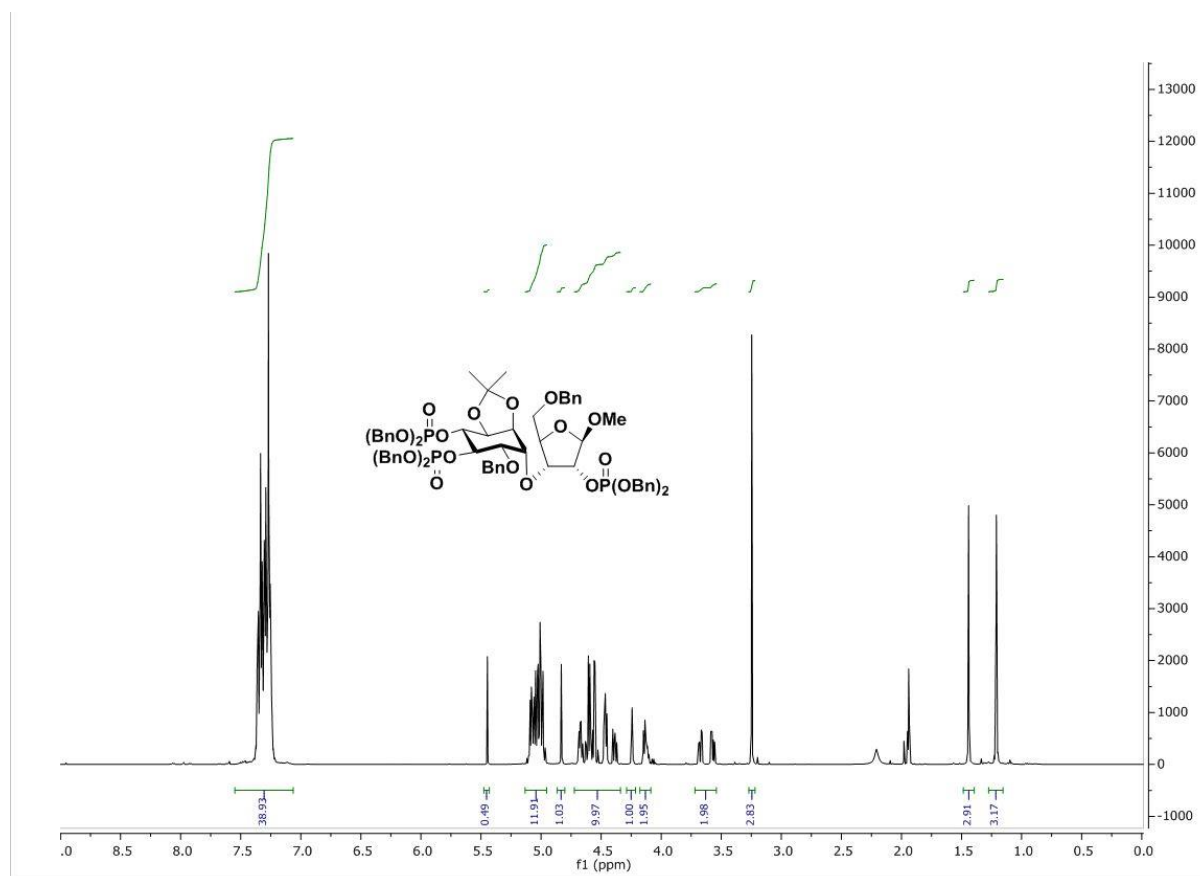


Chemical structure of compound 10 is shown in the center of the spectrum. The structure is a bicyclic molecule with a furanose ring fused to a pyranose ring. It has a BnO group, a Me group, and a HO group.

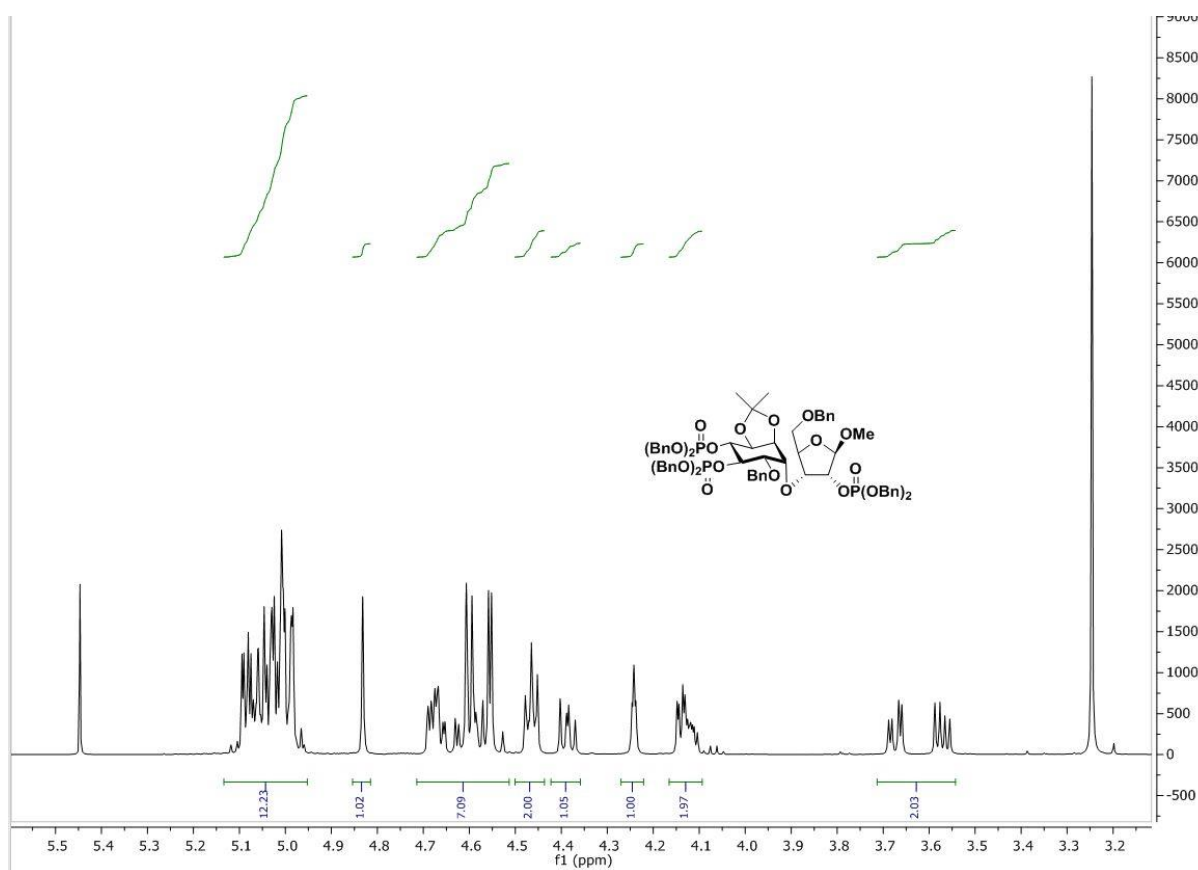
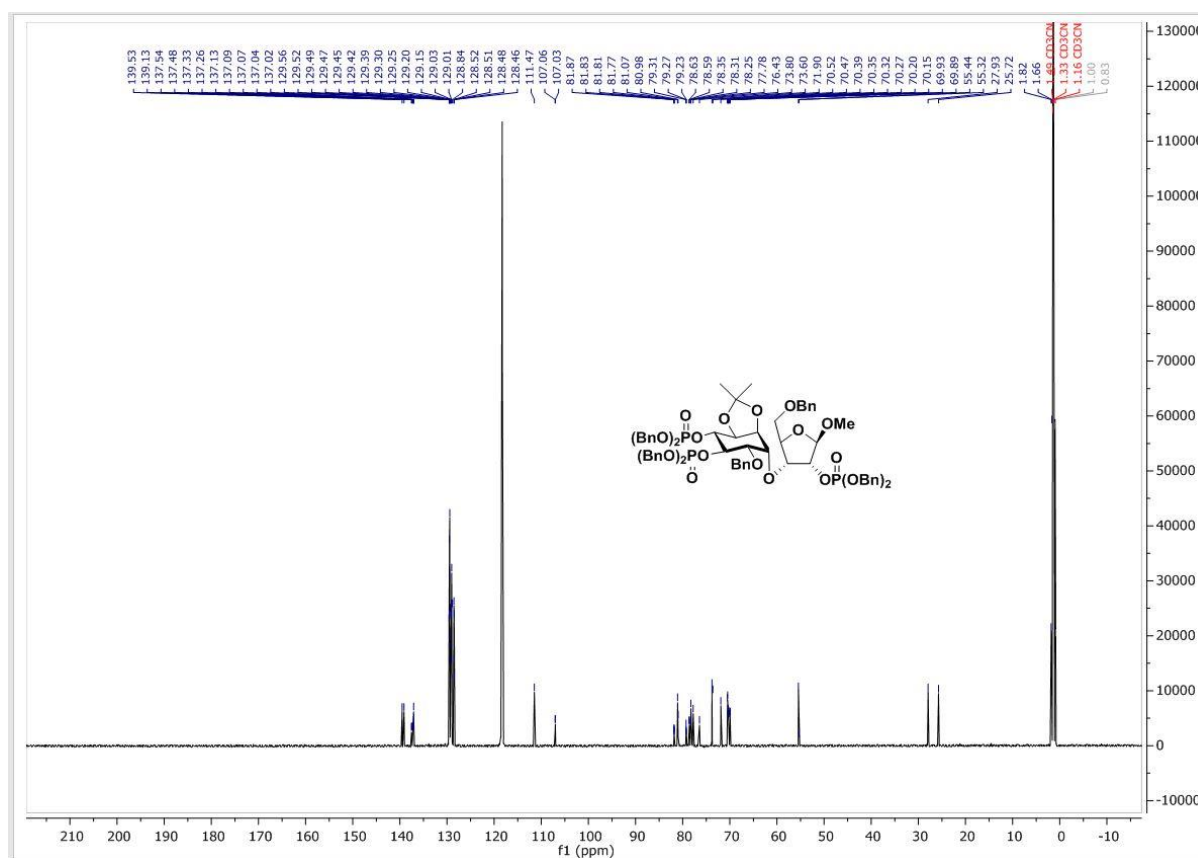
Peak list (ppm): 137.60, 136.83, 128.71, 128.42, 127.72, 127.61, 109.89, 108.01, 81.35, 79.21, 78.39, 77.25, 76.99, 76.81, 76.12, 75.78, 74.38, 74.10, 73.45, 72.51, 71.82, 71.22, 54.92, 53.40, 50.84, 27.83, 25.72, -0.03.

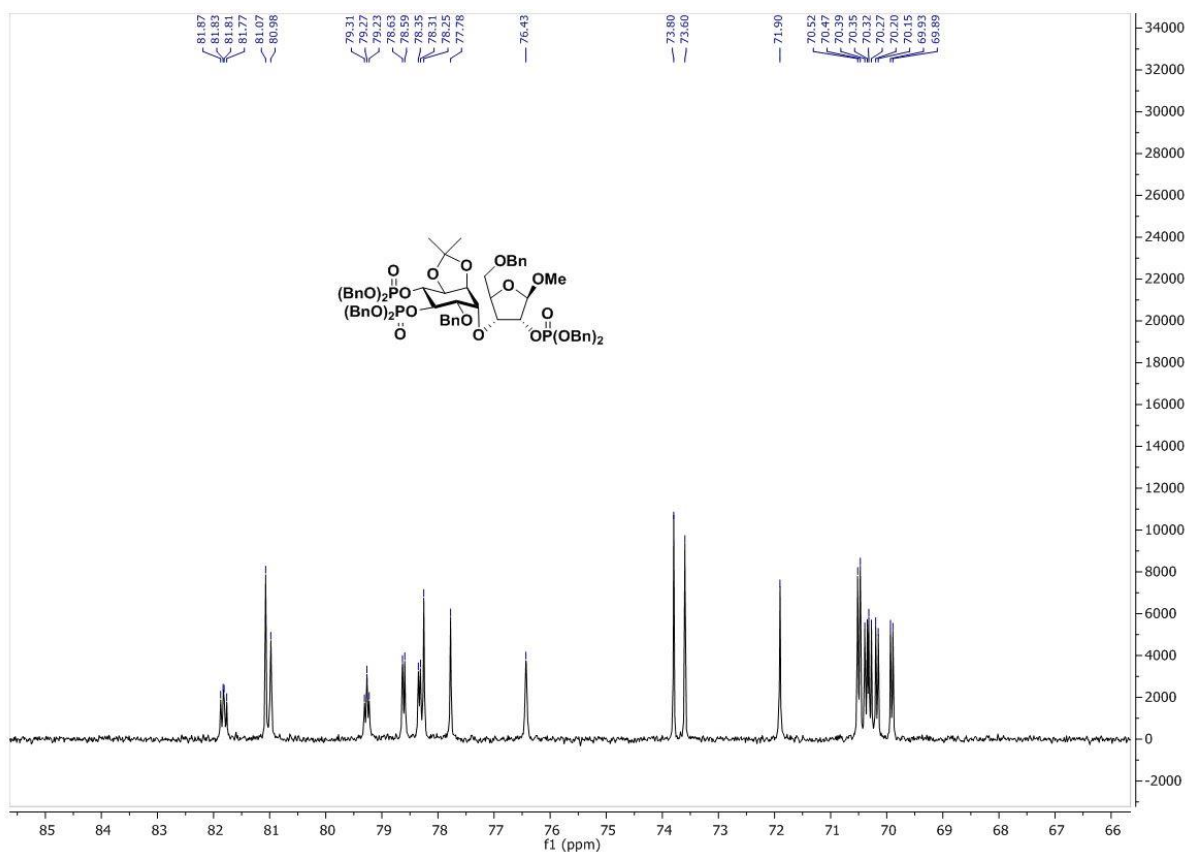




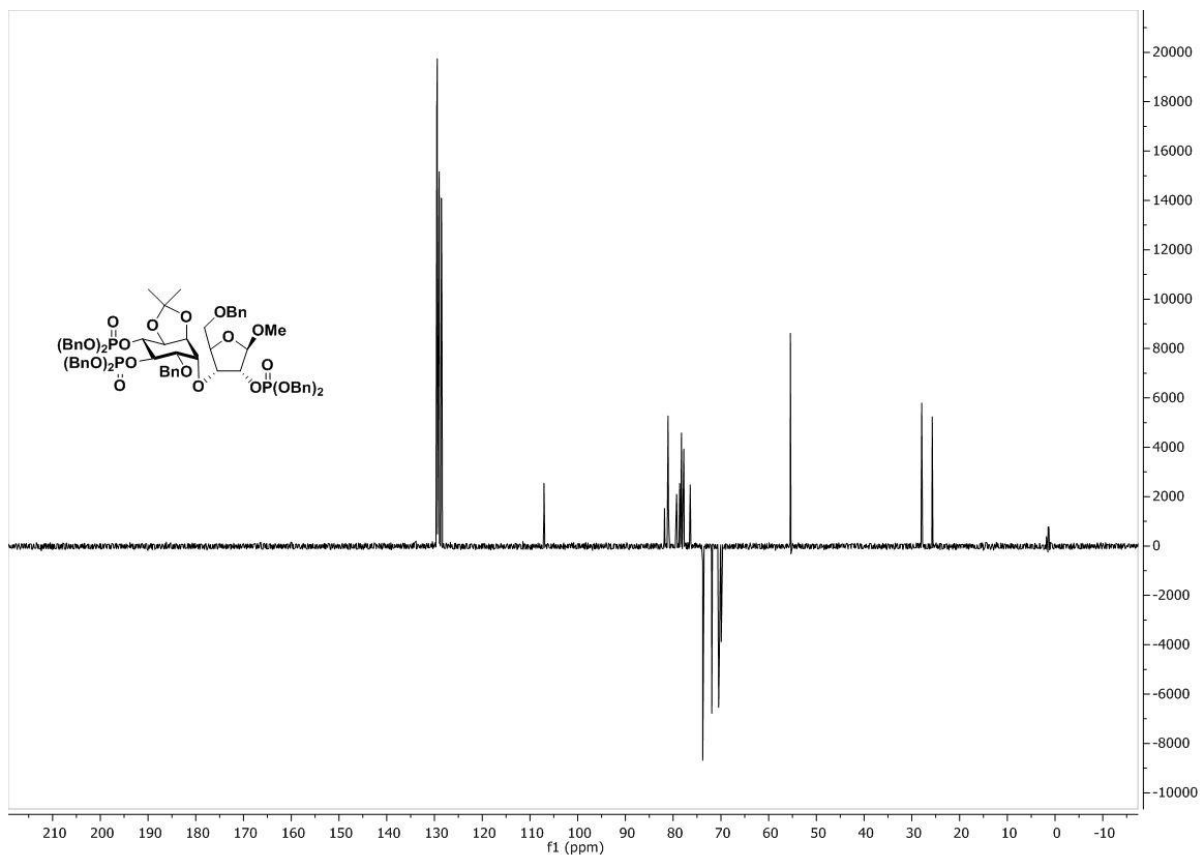
<sup>1</sup>H NMR

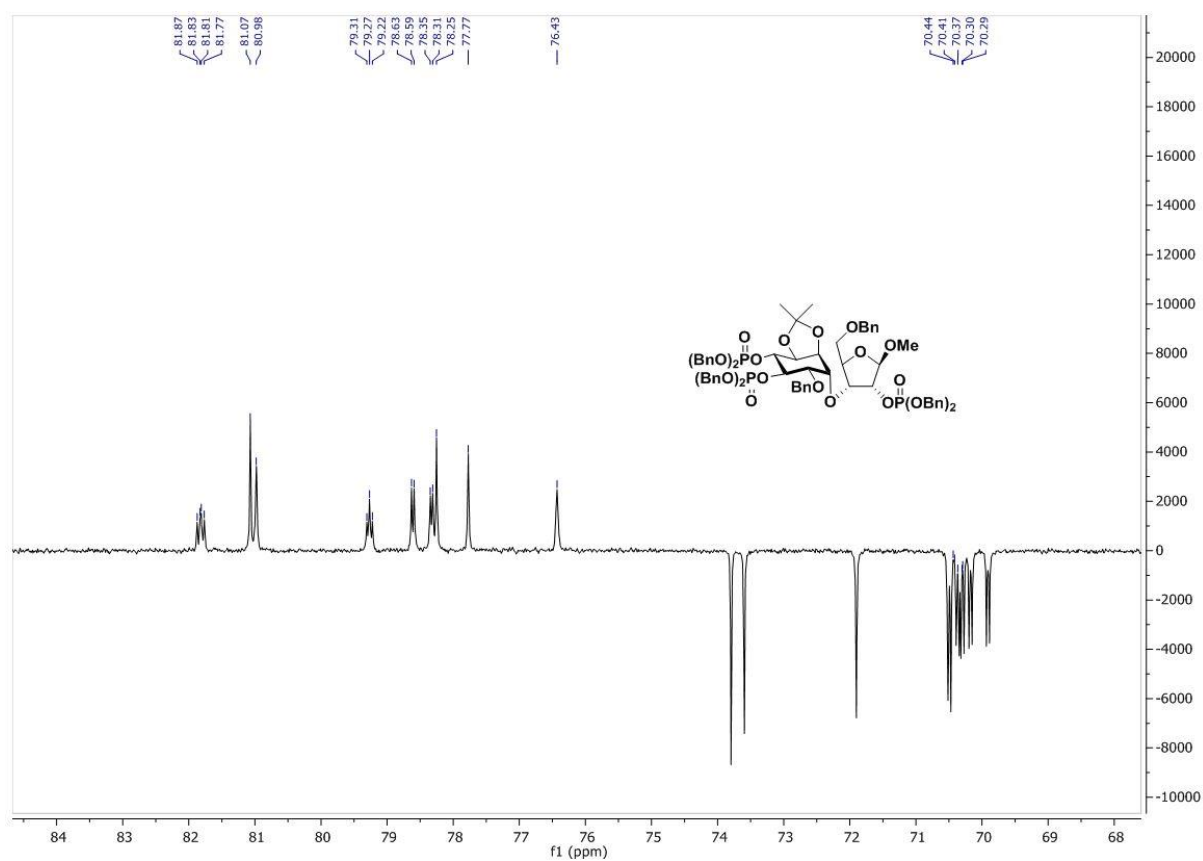


<sup>13</sup>C NMR

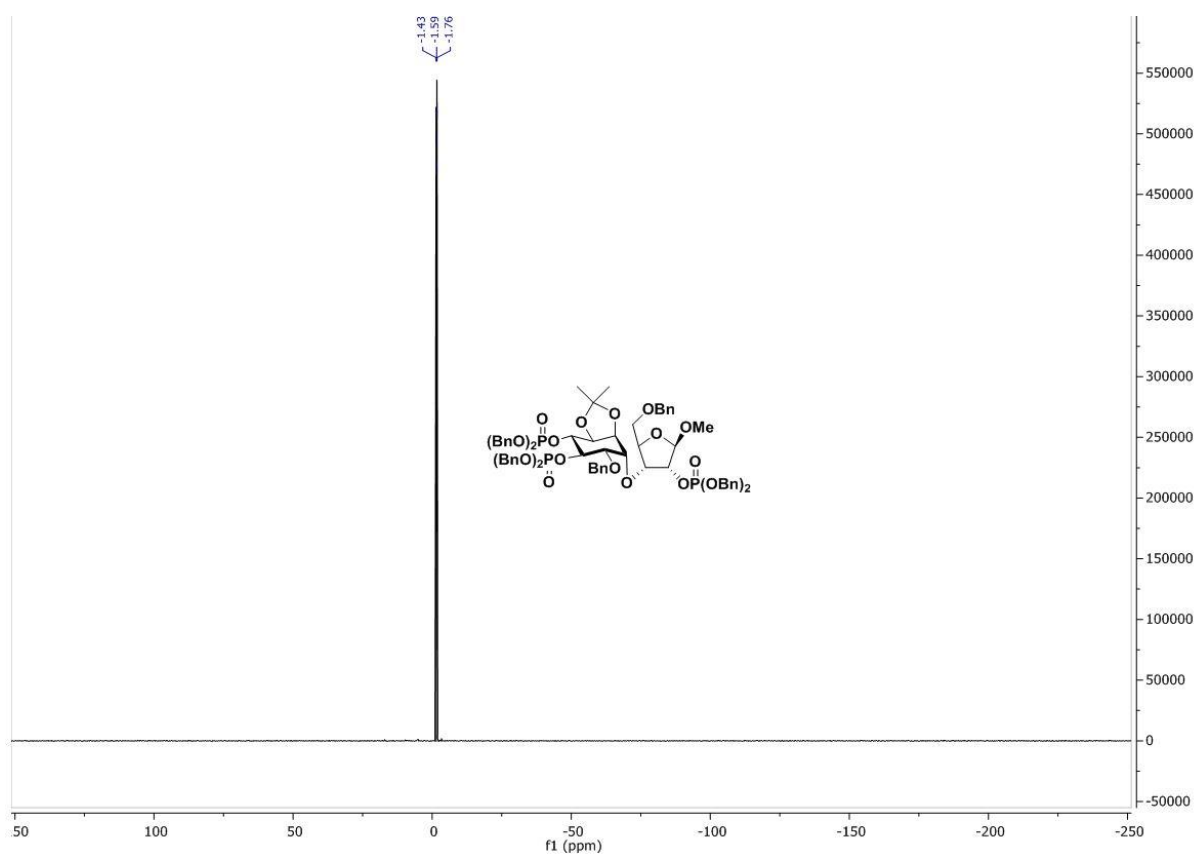


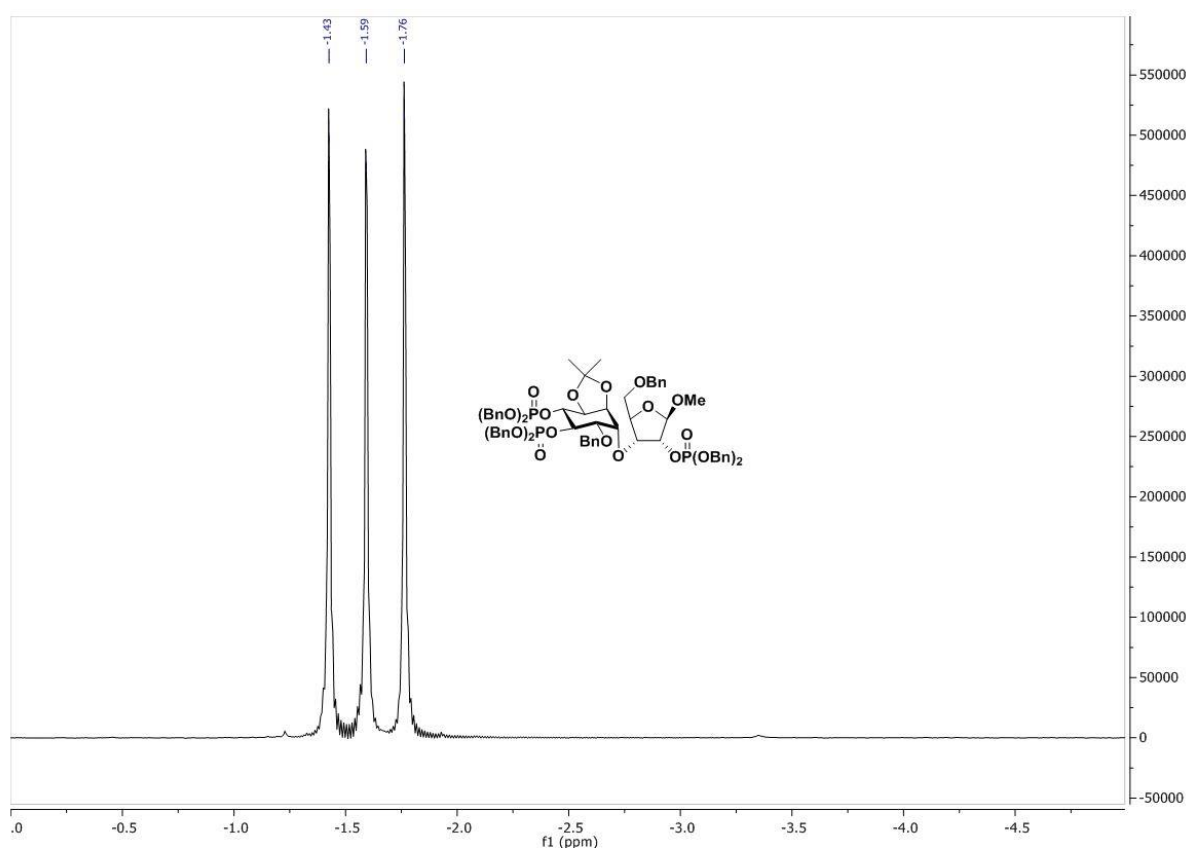
<sup>13</sup>C NMR 135 DEPT





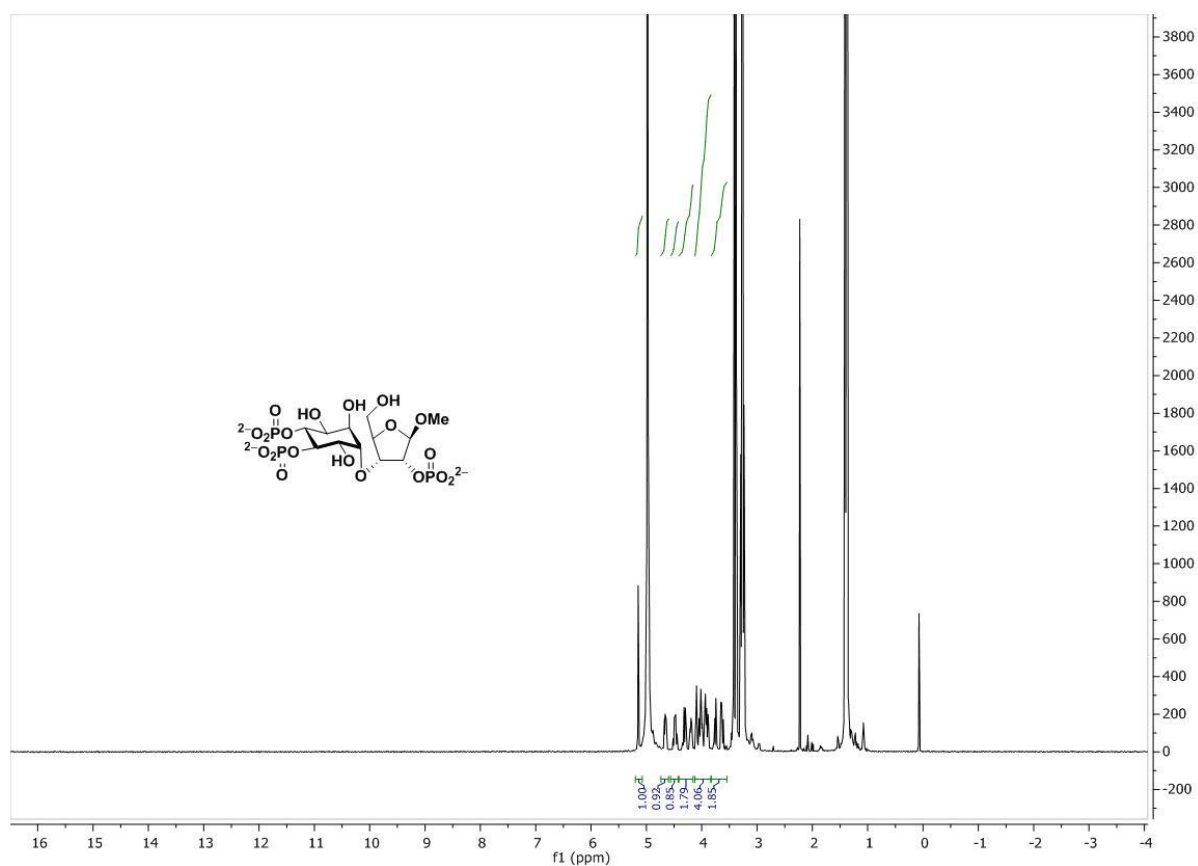
<sup>31</sup>P NMR

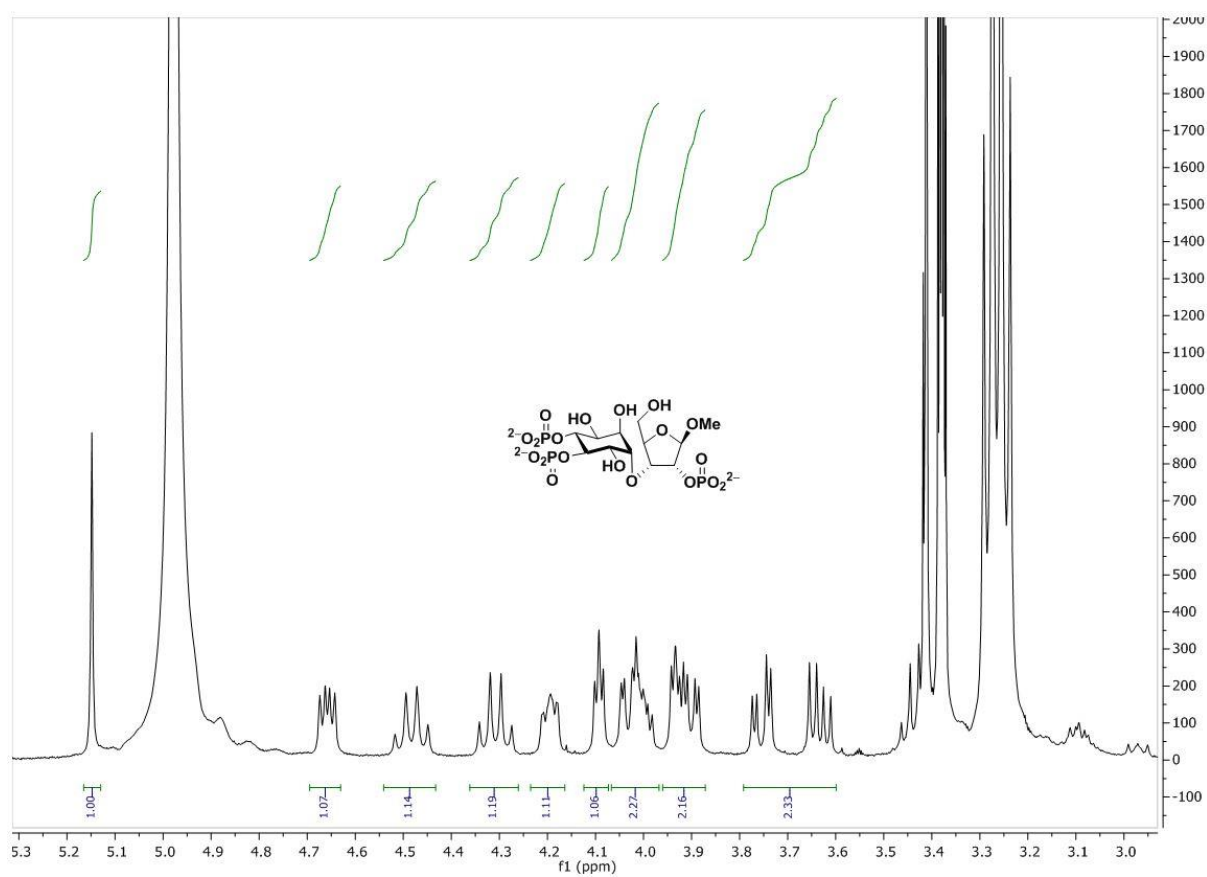




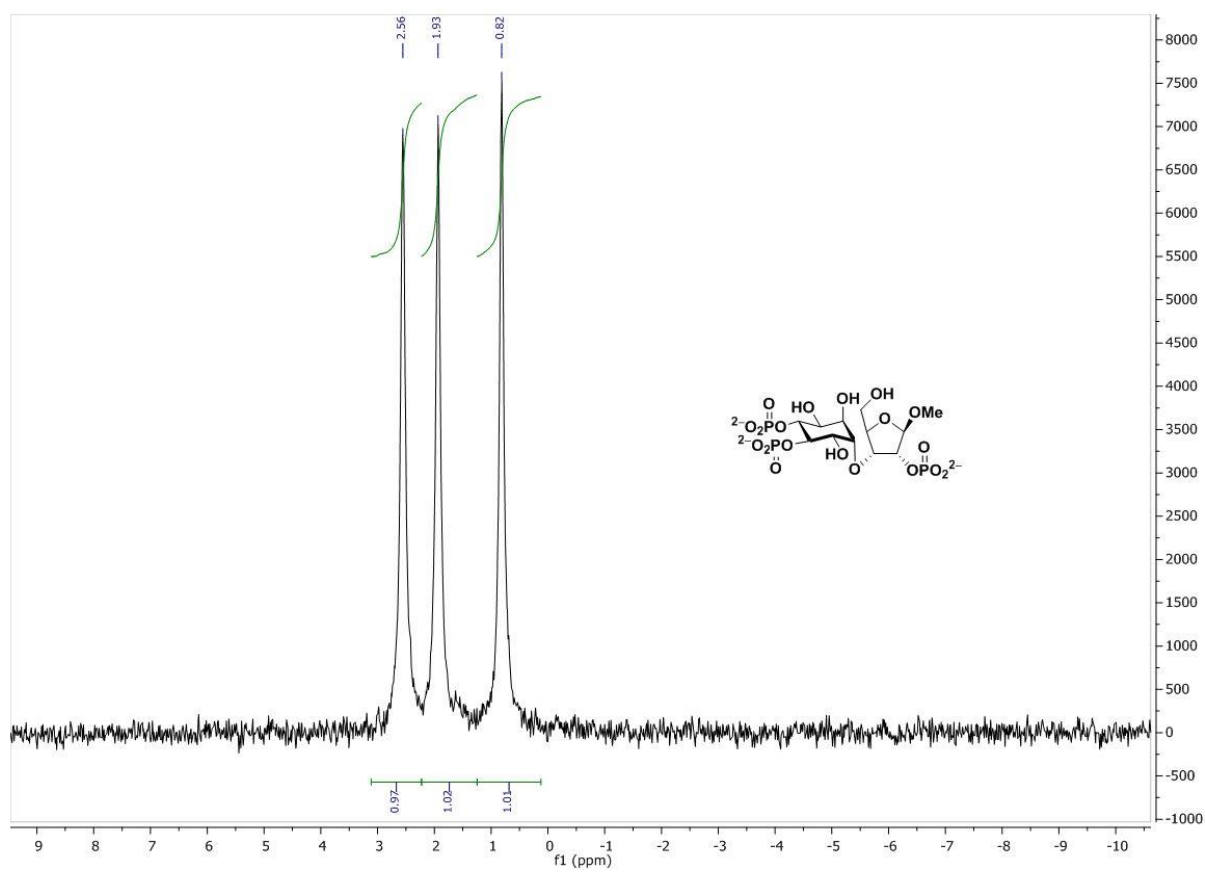
**(2*R*,3*S*,4*R*,5*S*,6*S*)-3,4,6-trihydroxy-5-(((3*R*,4*R*,5*R*)-2-(hydroxymethyl)-5-methoxy-4-(phosphonatooxy)tetrahydrofuran-3-yl)oxy)cyclohexane-1,2-diyl bis(phosphate) (10)**

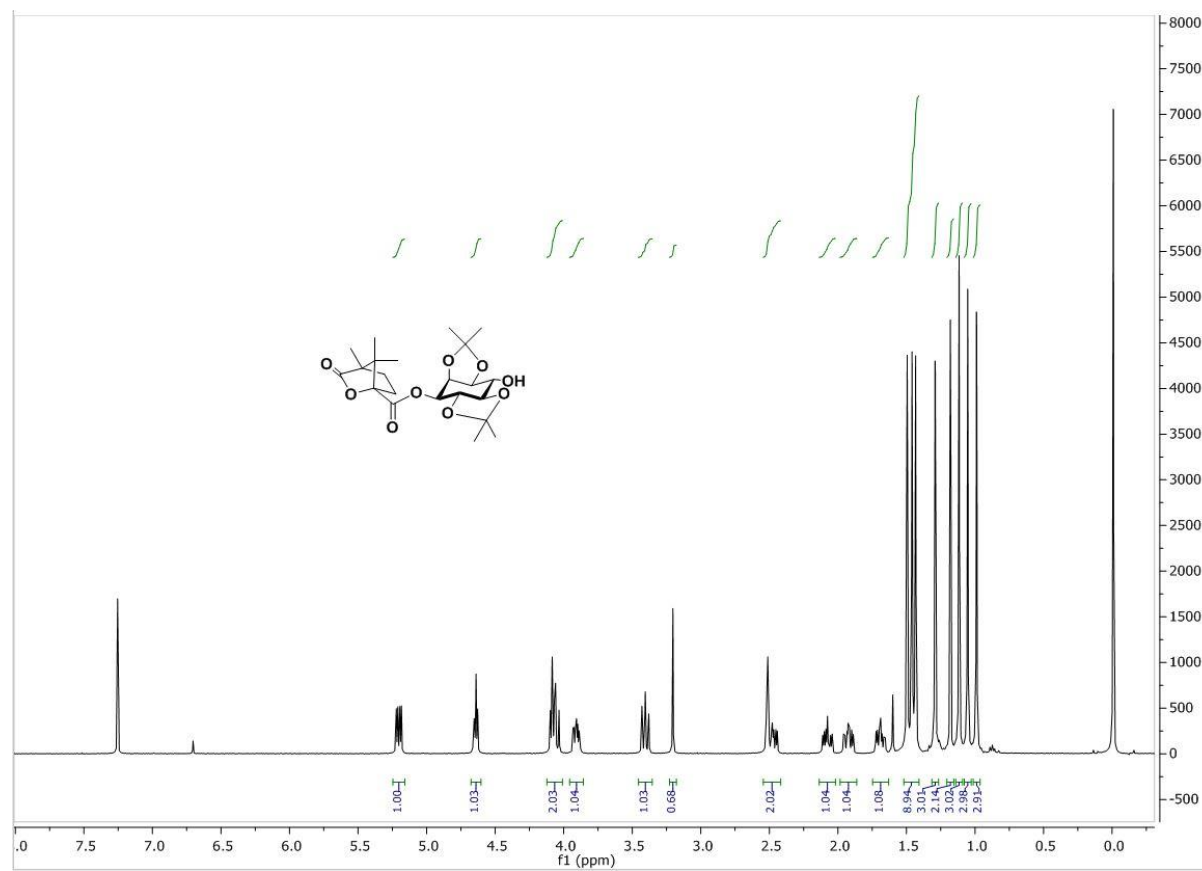
<sup>1</sup>H NMR



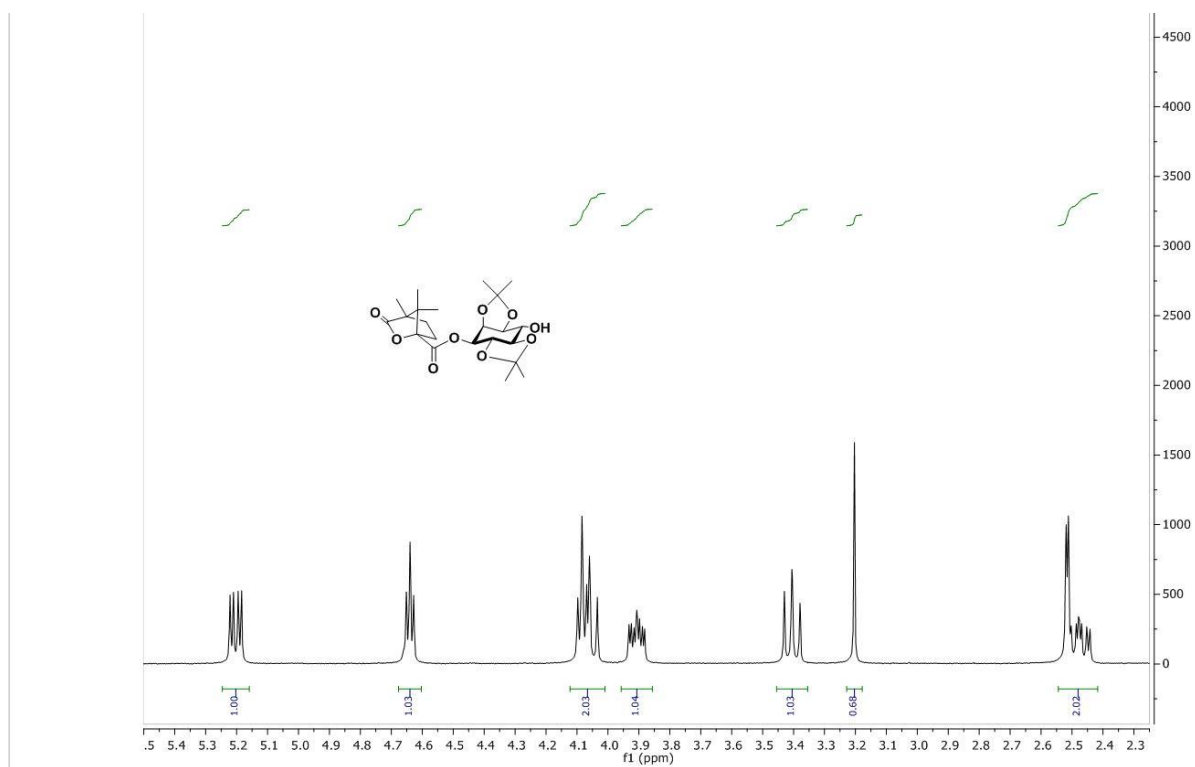


$^{31}\text{P}$  NMR

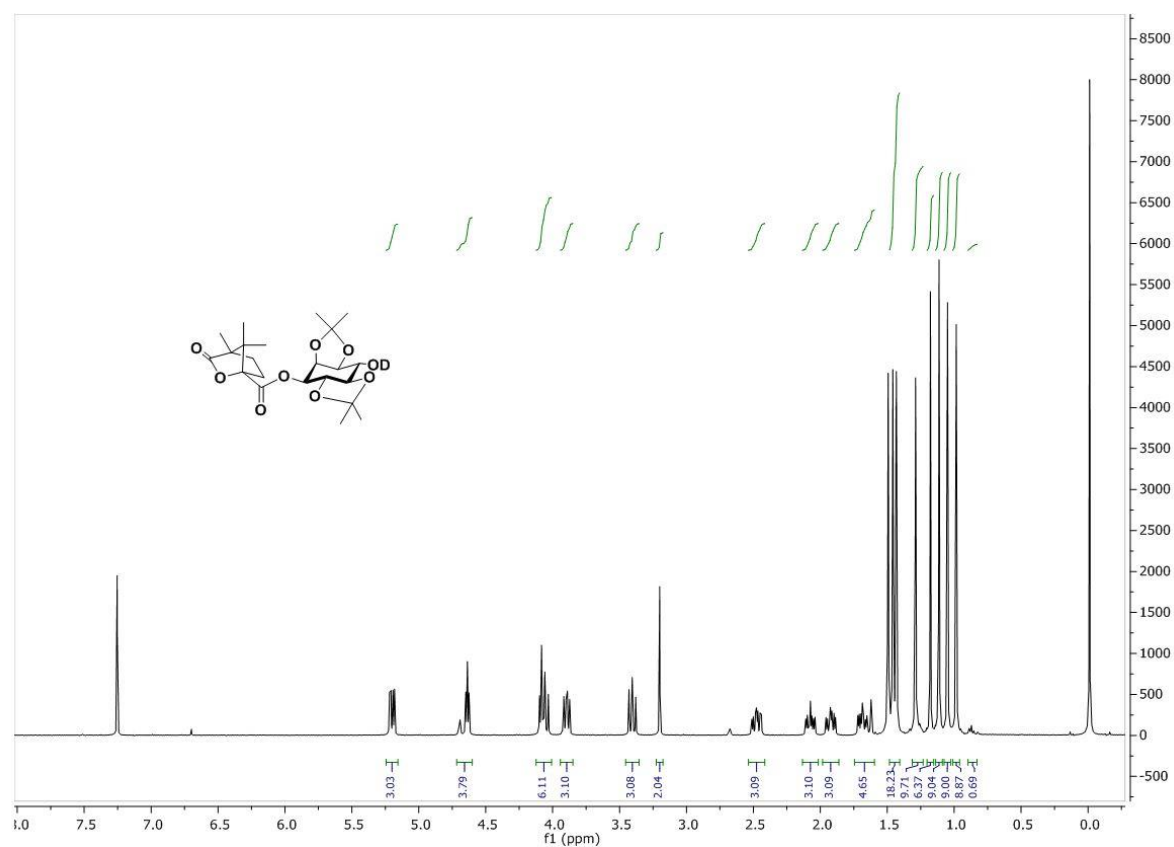


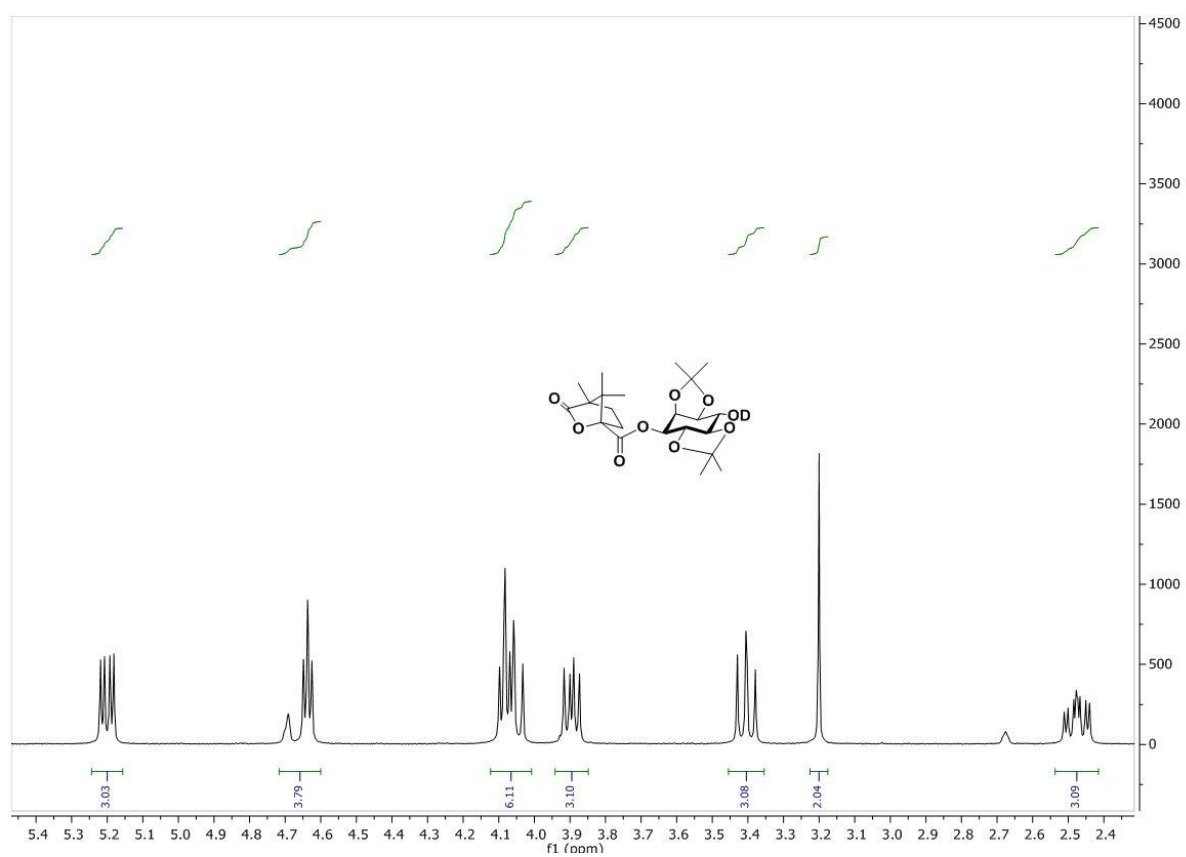
<sup>1</sup>H NMR



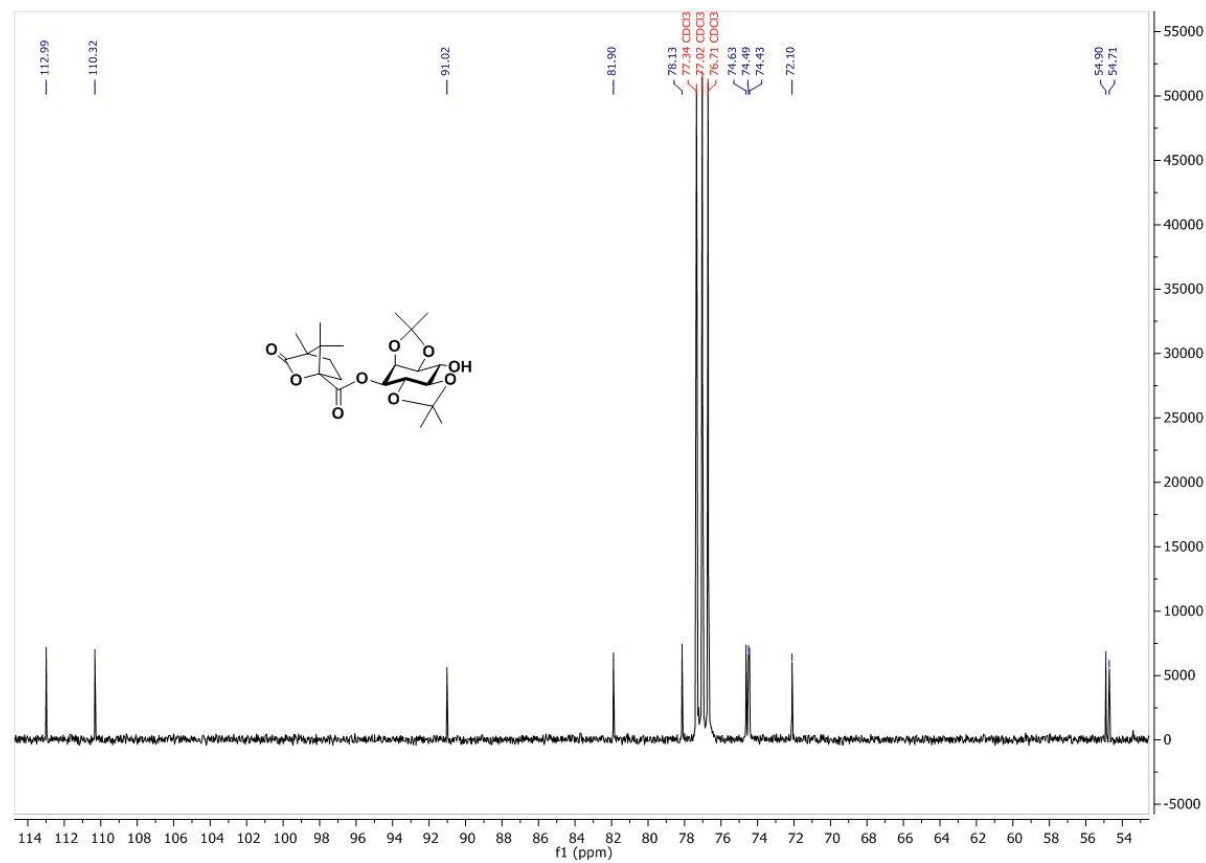
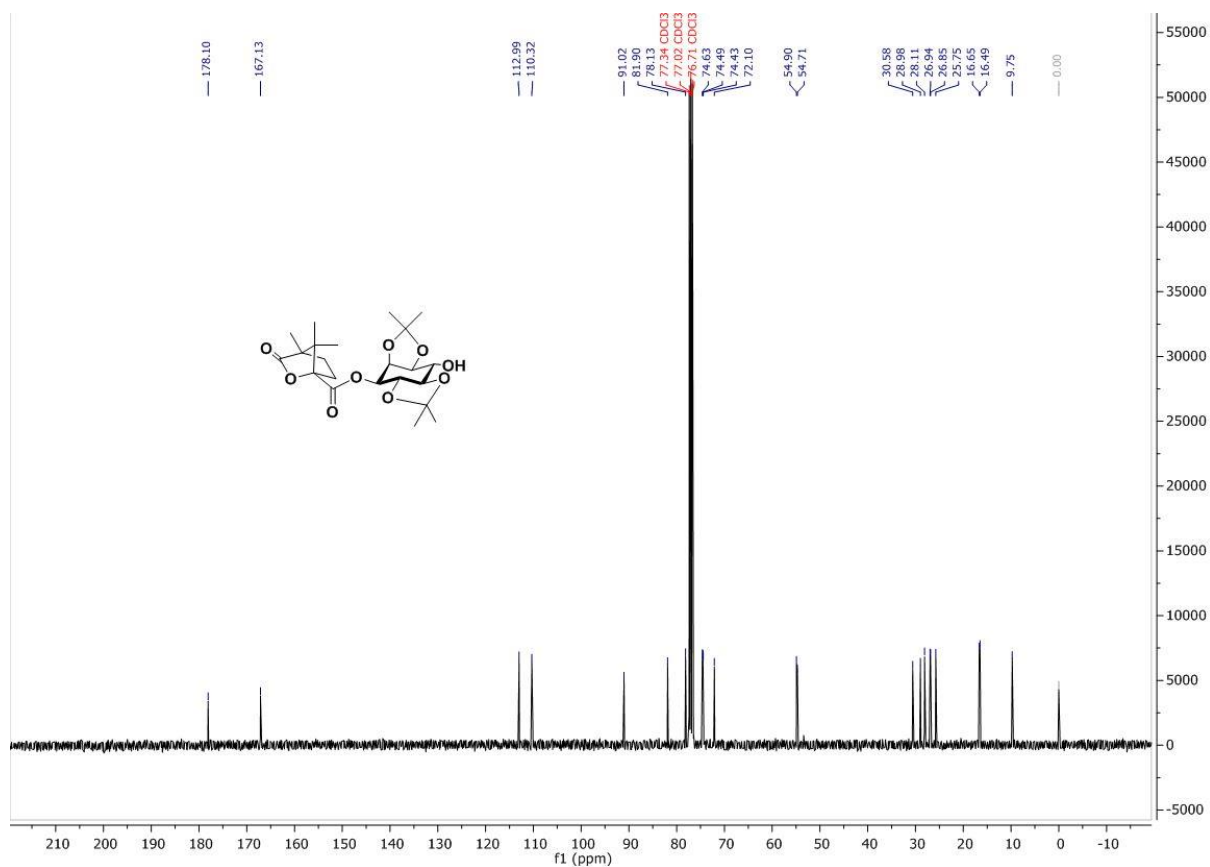


<sup>1</sup>H NMR D<sub>2</sub>O exch.





$^{13}\text{C}$  NMR

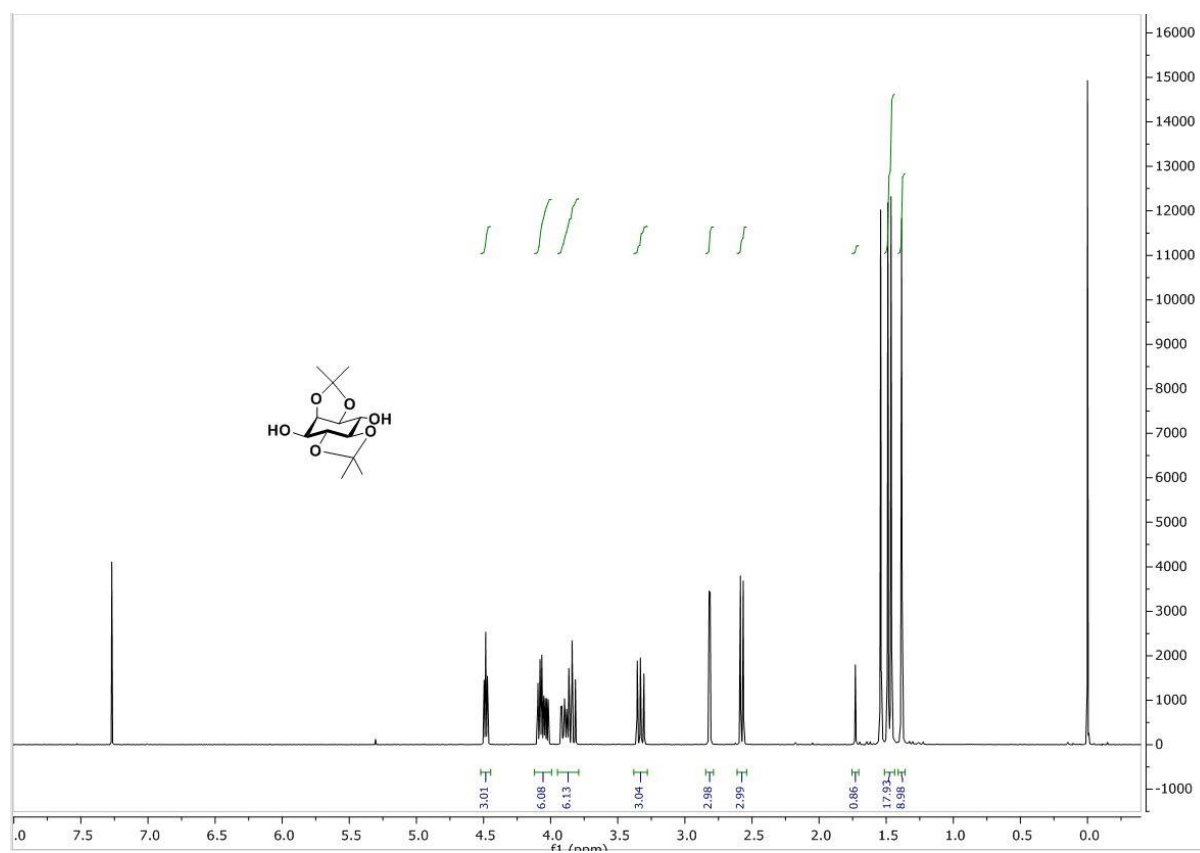


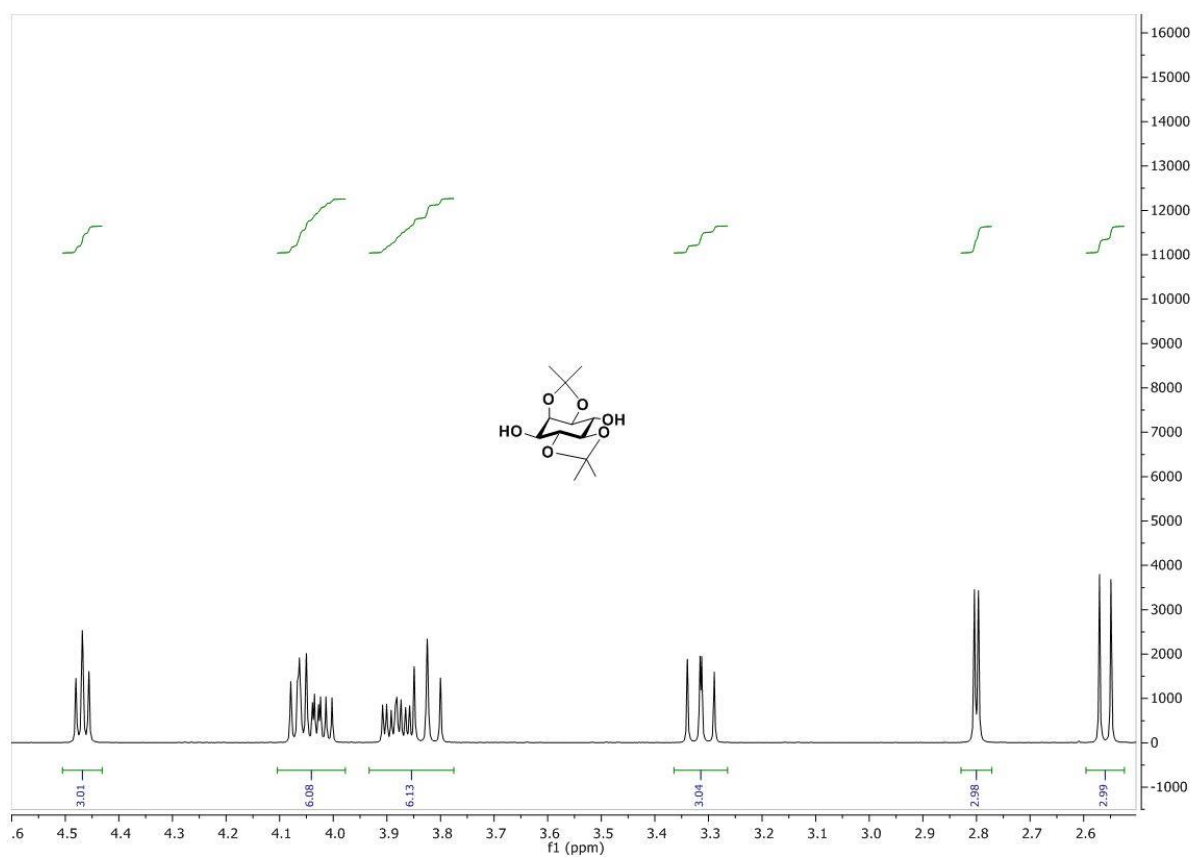
<sup>13</sup>C NMR 135 DEPT



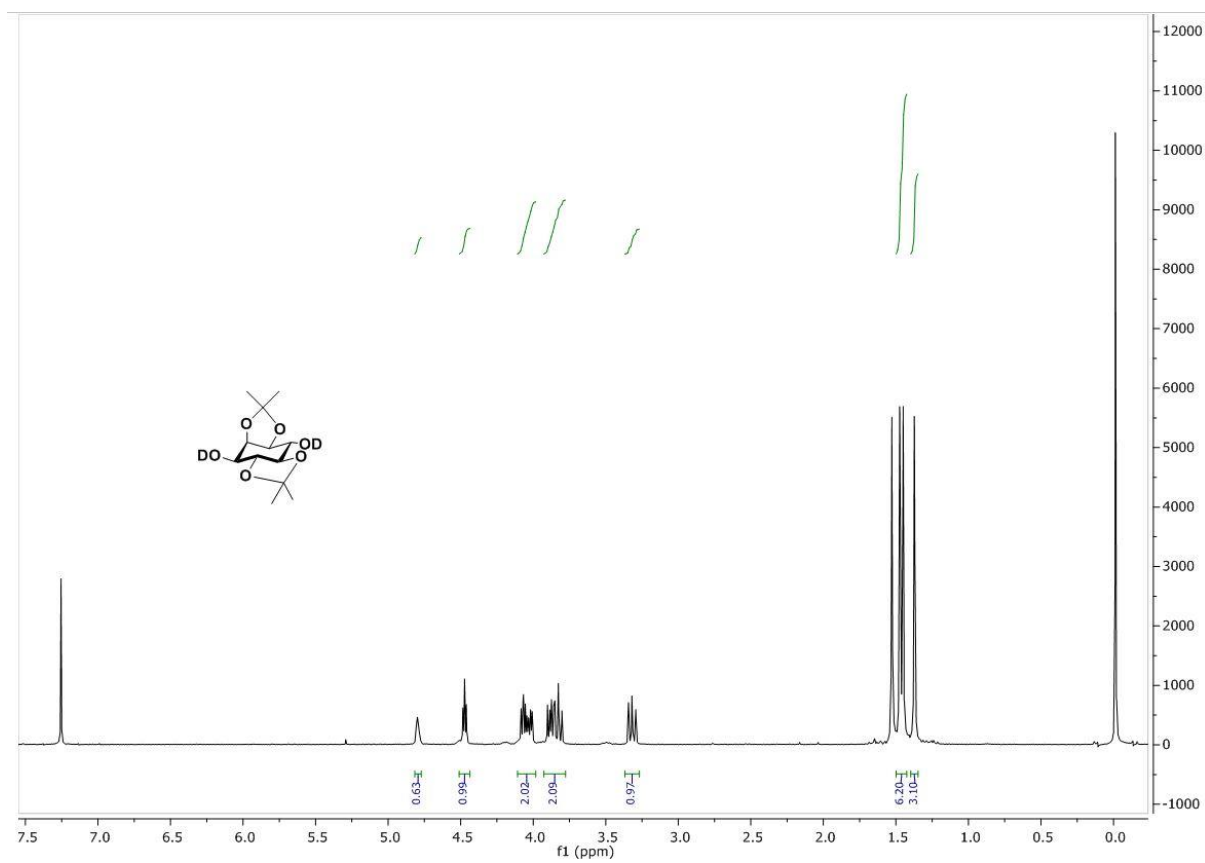
**D-1,2:4,5-Di-*O*-isopropylidene-*myo*-inositol (22)**

<sup>1</sup>H NMR





<sup>1</sup>H NMR D<sub>2</sub>O exch



# $^{13}\text{C}$ NMR

