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► **To cite this version:**

Laurent Cattiaux, Jean-Maurice Mallet. Self-supported solution synthesis of oligosaccharides using thioglycosides donors. *Tetrahedron*, 2022, 125, pp.133036. 10.1016/j.tet.2022.133036 . hal-04296272

**HAL Id: hal-04296272**

**<https://hal.science/hal-04296272>**

Submitted on 20 Nov 2023

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# Self-supported solution synthesis of oligosaccharides using thioglycoside donors

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## ARTICLE INFO

*Article history:*  
Received  
Revised  
Accepted  
Available online

*Keywords:*  
glycosylation  
thioglycoside  
odorless thiol  
soluble support synthesis  
oligosaccharides

## ABSTRACT

We propose here an alternative to the solution synthesis of oligosaccharides based on a polyol multiglycosylation. This method was illustrated by the successful preparation of a tetraglucoside  $\beta$  (1 $\rightarrow$ 6) equipped with a propargylic linker, ready for conjugation by click chemistry, using overall 5.6 equiv of thioglycosyl donors. Compared to the reported supported solution syntheses of oligosaccharides; the separation here is not based on a specific label (transferring its solubility properties to whole molecules) but on the increase in molecular mass (from 1500 to 15000), allowing a simple separation on a steric exclusion column. Furthermore, the proposed protocol does not require any aqueous workup and use a yellow tracer to visually follow the separation without TLC nor detector.

Dedicated to the memory of Dr. Jacques Esnault (1946-2018)

## Introduction

The chemical synthesis of oligosaccharides proceeds by repeating sequence of glycosylation / deprotection steps and synthesis in solution of oligosaccharides usually required separation and purification at each step which is tedious and time consuming. Solid phase alternatives have been successfully developed and are convenient for the rapid preparation of small amounts of oligosaccharides<sup>1</sup>. In parallel, methods relying of a soluble support have been proposed to overcome certain limitations of the solid phase approach (larger scale, use of poorly reactive donors, etc.). They are based on the properties of the soluble carriers<sup>2</sup>:

- Polyethylene glycol<sup>3</sup> : conjugates not soluble in ethers and purified by selective precipitation.
- perfluorinated groups<sup>4</sup> : conjugates selectively extracted by fluorinated supports (liquid phase F-SPE or beads) or
- imidazolium group<sup>5</sup> : conjugates not soluble in non-polar solvents.

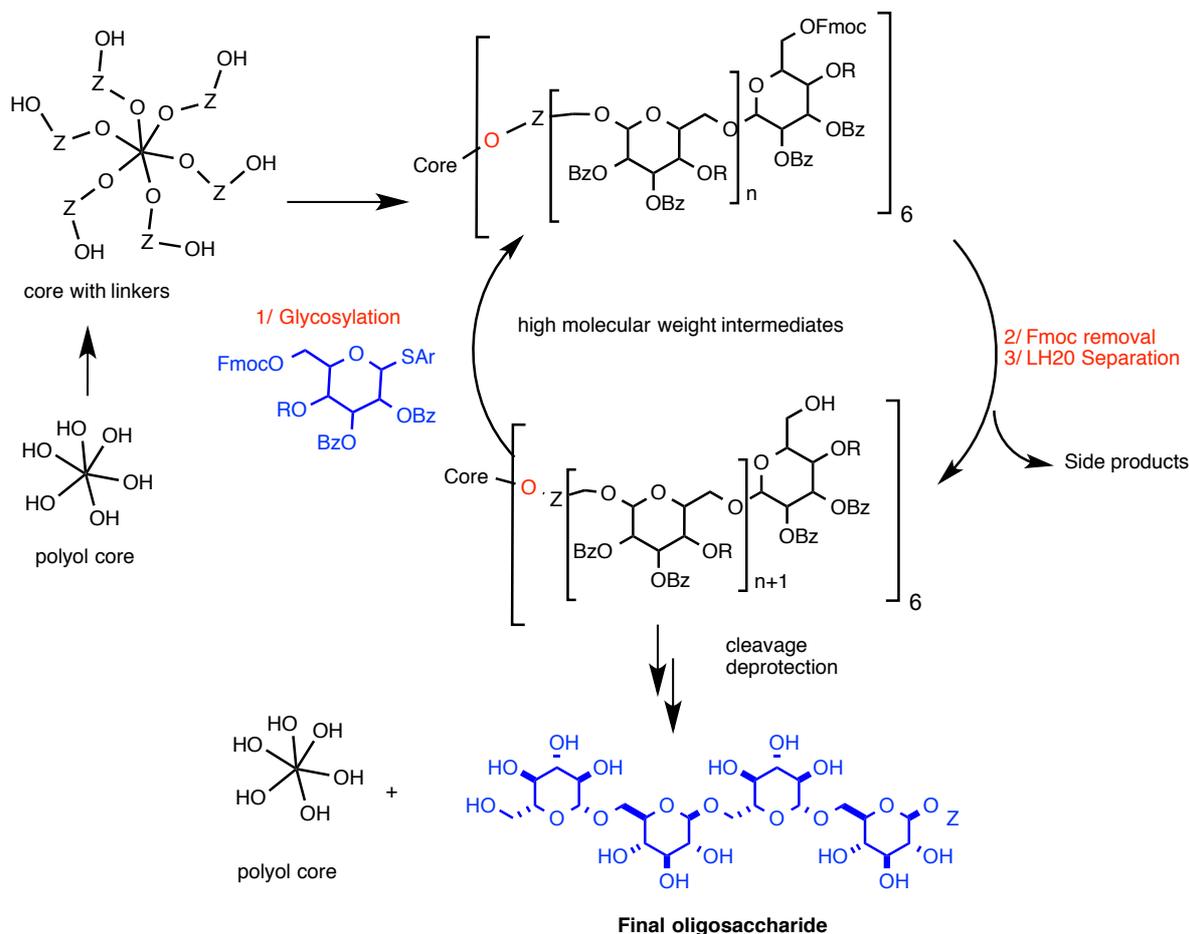
The solubility issues and nucleophilicity of the support may interfere with the glycosylation reactions. In addition, the success of the separation relies mainly on the properties of the support, which must therefore represent most of the conjugates (enough to impose its properties to the whole molecule and thus may represent a large ballast) and therefore limit the scale of synthesis.

## Objectives and principle

To avoid this ballast, we propose here to use a self-supported strategy, creating a macromolecule composed of several copies of the growing oligosaccharide chain: The principle is to use a small polyol core - hexaol for example here (Scheme 1) - which is glycosylated 6 times for the simultaneous construction of six oligosaccharide chains. Each glycosylation step increases the molecular mass by approximately 3000 (+6 monosaccharides at each turn), leading rapidly to macromolecules large enough (MW 4000 to 14000) to be separable from the reactants and side products (MW 600) by size exclusion column. The separation is made simple using a phase with an exclusion limit of about 1500 Daltons) as have the lipophilic Sephadex<sup>(TM)</sup> LH-20<sup>6</sup> (a hydroxypropyl cross linked dextran). In this type of column, all the molecules larger than the size limit will be eluted first in the void volume.

The main expected characteristics of this approach are

- a reduced support / load ratio: the central polyol weights less than 10% and therefore the resulting macromolecule is mainly composed of good “stuff”.
- use of classical solution glycosylation, in particular usual solvents
- simple separation procedure with reliable removal of small molecules independently of their polarities or structures
- well-defined intermediates that allow TLC, NMR analyses for monitoring, if necessary



Scheme 1: Principle of the self supported synthesis for  $\beta$  (1->6) oligoglucose (Z= a linker)

We first want to validate the proposed strategy to prepare a tetrasaccharide of  $\beta$  (1->6) glucose **38** using thioglycoside donors (with the following set of protecting groups Fmoc / Benzoyl / Benzyl) and an ester bond to the hexaol support. (Scheme 1) and to prepare it coupled to propargyl group ready for conjugation via click chemistry. (see Figure 1)

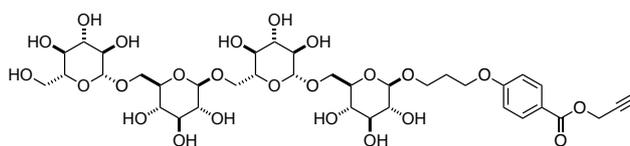


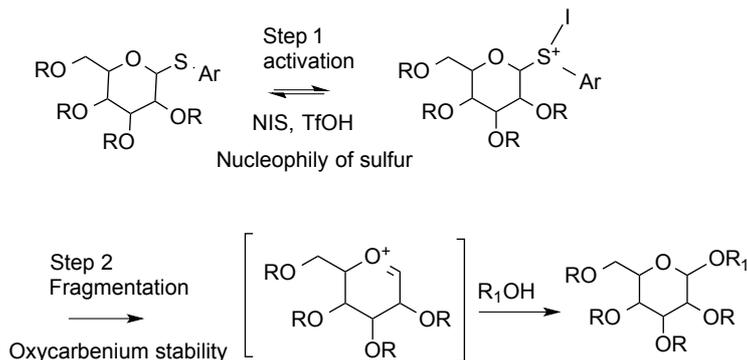
Figure 1: final target **38**

Thioglycosides are stable glycoside donors, easily activated by NIS, TfOH. To guide the structure choice, as a preamble, we propose to compare thioglycosyl donor's reactivities in order to find more reactive ones selecting odorless thiol aglycone.

## Results

### Comparison of thioglycosides reactivities

Scheme 2 describes the mechanism of electrophilic activation of aryl thioglycosides, it shows the two potential key points in the kinetics: the nucleophilicity of sulfur is important for the first step and the stability of the oxycarbenium for the second one.



## Scheme 2: Aryl thioglycoside activation and glycosylation

Several authors had compared reactivities of thioglycosides with various activating promoters and conditions, from weak promoters (such as DMST) to the strongest NIS/TfOH<sup>7,8</sup>. Playing with the nature of the promoters and the temperature, it was thus found possible to activate thioethyl glycoside in the presence of thiophenyl glycoside. In a detailed competition study, Lahman and Oscarson had compared many per-O-benzoylated alkyl thioglycosides activated by DMTST<sup>9</sup>: donors formed from secondary thiols (isopropyl or cyclohexyl) are more reactive than those from primary thiols (ethyl, propyl and butyl). In these conditions, the less reactive was thiophenyl, not activated by DMTST. More recently similar developments came from ring substituted thiophenyl glycosides and selective activation had been described using various activating systems. Reactivities are controlled by the nucleophilicity and electron density at the sulfur atom: pOMe > pBr > pNO<sub>2</sub>; the less reactive p-nitrothiophenyl being only activated by NIS/TfOH.

This p-nitrophenylthio group was exploited further in an “active/latent” thioglycosyl donors approach<sup>10</sup>: in this approach, the deactivated (latent) 4-nitrophenyl thio-glycoside is activated by transformation of the 4-nitro (SnCl<sub>2</sub> then N-acetylation) to a 4-acetamidophenyl (active) donor.

In addition to the nature of thiol, the sugar protecting groups have a strong effect on reactivity and in a paper C.H. Wong and coworkers<sup>11</sup> had described the use of tolyl thioglycosides for their “Programmable One-pot” oligo- saccharide syntheses” modulating their reactivity through the choice of protecting groups: electron withdrawing protecting groups (eg esters) reduce the reactivity (disarmed), electron donating group (eg benzyl) increase the reactivity (armed)

In this work, we want to explore the potential of para octyloxy thiophenyl glycoside and compare it to the first generation thio aryl glycosides that we have used (Mbp). The octyloxy group is chosen in order to keep the thiol completely odorless (commercial methoxy thiophenol stinks even at low concentrations). M. Node group<sup>12,13,14</sup> had already used this thiol for the construction of glycosides.

In order to compare the reactivities of thioglycosides, we provided for the competition of two donors with a limited quantity of promoter: N-iodosuccinimide (NIS) (1 mmol) was added in the presence of TfOH (0.2 equiv vs NIS) to an equimolar mixture of the two thioglycosides to be compared (1 mmol each), glycosyl acceptor (**22**) (1 mmol) in dry dichloromethane at room temperature. At the end of the reaction (15 min), the reaction mixture was neutralized (piperidine) and concentrated. From <sup>13</sup>C and <sup>1</sup>H NMR spectra of the reaction mixture, the amounts of formed glycosides and remaining thioglycosides were evaluated. From these data, their relative reactivity was estimated at room temperature in dichloromethane. <sup>1</sup>H NMR spectra of the mixture were rather complex due to overlapping signals and was used in favorable cases. We found alternatively more convenient and general to focus on anomeric carbons signals, easily extracted from the <sup>13</sup>C spectra: although not usual, we thus had used these C-1 singlet integration, after verification of the linearity of the measurement with preformed mixtures. Results (Table 1), were first expressed in term of remaining unreacted thioglycosides ratio; then assuming that 1 mmol of thioglycoside was consumed, the relative reactivity ratio was estimated.

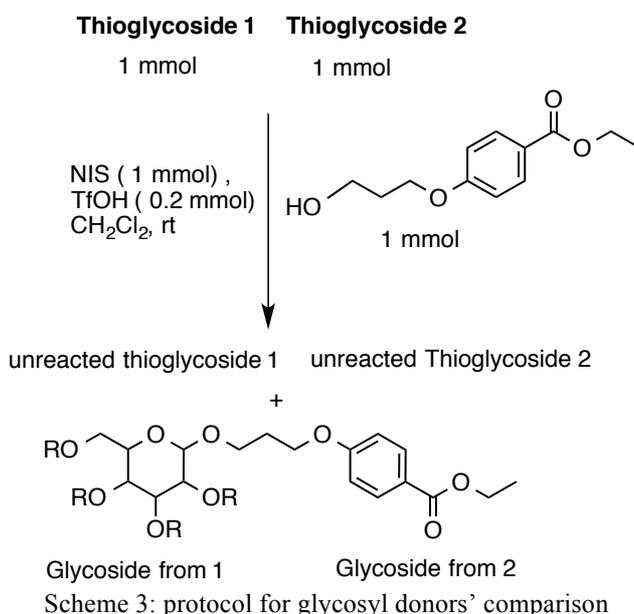


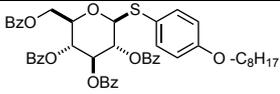
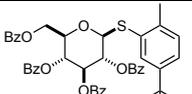
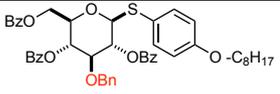
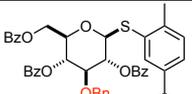
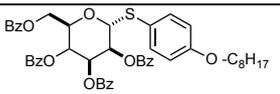
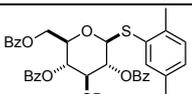
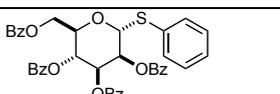
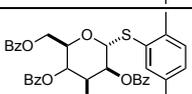
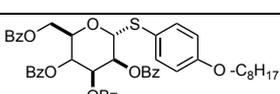
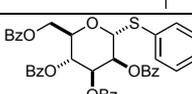
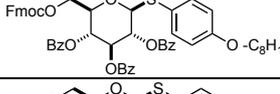
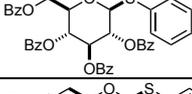
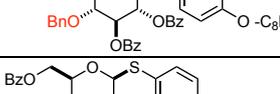
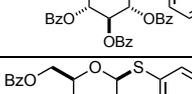
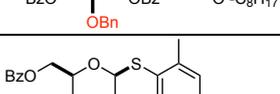
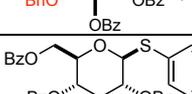
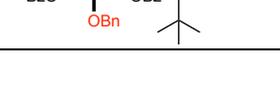
Table I summarized the results – p-Octyloxy thiophenyl derivative (pOPh) are more reactive than methyl tertbutyl thiophenyl (x 1.4 in glucose and x 1.5 in mannose series) from entries 1, 2, 3. In mannose serie, thiophenyl is more reactive than methyl tertbutyl thiophenyl in entry 4.

A more pronounced effect on reactivities came from protecting groups: replacement of a benzoyl by a Fmoc increases reactivity (x 1.4) – (entry 6); replacement of a benzoyl by a benzyl in 3 or 4 position increases reactivity (entries 7, 8, 9)- the effect is important in position 3.

These results are consistent with 1/ a greater nucleophilicity of sulfur in pOPh thioglycoside (that facilitates the formation of the iodosulfonium) and 2/ the fragmentation of this sulfonium is controlled by the stability of the oxycarbenium and favored by electron donating group close to anomeric position.

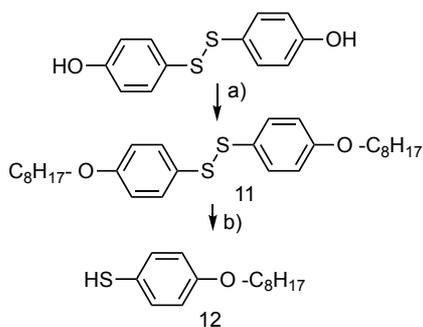
According to these data, pOPh thioglycosides were selected for the supported synthesis.

Table 1 – Thioglycosides reactivity comparison

entry	sugar	variation	donor A (more reactive)	donor B (less reactive)	Ratio of the remaining donors (relative to the less reactive)	Ratio of the consumed donors
1	Glc	Thiol	 <b>1</b> 15	 <b>2</b> 16	0.67/1	1.5
2	Glc	Thiol	 <b>3</b>	 <b>4</b>	0.69/1	1.4
3	Man	Thiol	 <b>5</b>	 <b>6</b> 17	0.67/1	1.5
4	Man	Thiol	 <b>7</b> 18	 <b>6</b>	0.82/1	1.1
5	Man	Thiol	 <b>5</b>	 <b>7</b>	0.76/1	1.3
6	Glc	6 Fmoc vs 6 Bz	 <b>8</b>	 <b>1</b>	0.71/1	1.4
7	Glc	4 Bn vs 4 Bz	 <b>9</b>	 <b>8</b>	0.21/1	4.8
8	Glc	3 Bn vs 4 Bn	 <b>3</b>	 <b>10</b>	0.53/1	1.9
9	Glc	Thiol and 3 Bn vs 3Bz	 <b>4</b>	 <b>1</b>	0.21/1	4.8

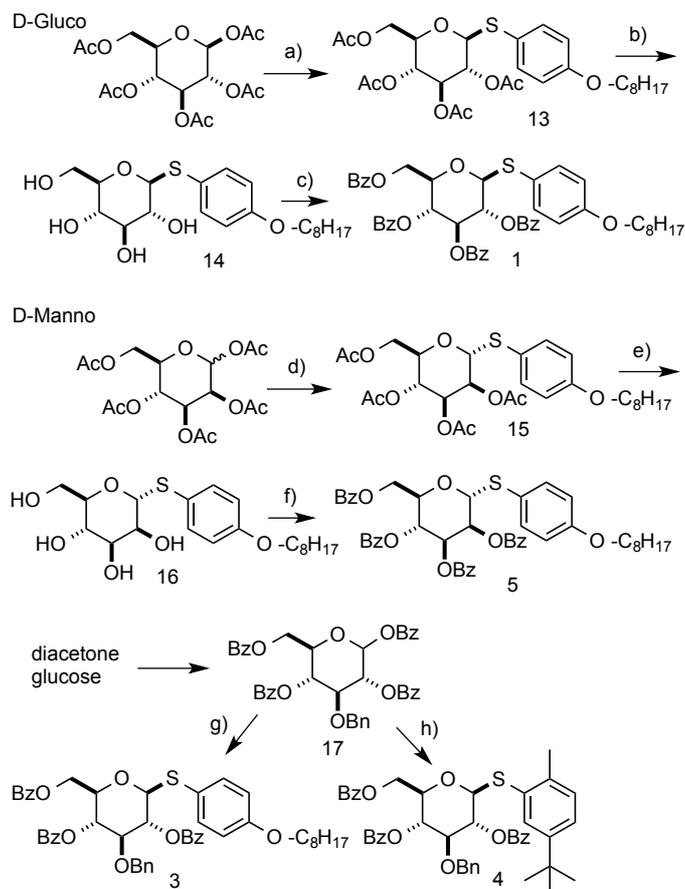
### Synthesis of thioglycosides

Octyloxyphenyl thiophenol **12**<sup>19</sup> was easily prepared (Scheme 4) from the commercial 4,4'-dihydroxyphenylsulfide, alkylation with octyl bromide then reduction of the disulfide **11** using zinc powder in acetic acid (instead of reported less convenient LiAlH<sub>4</sub> of sulfonic acid derivative<sup>19</sup>.)



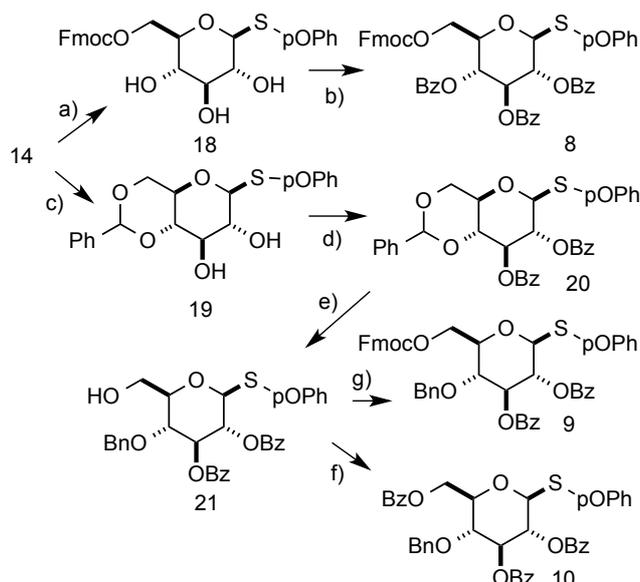
Scheme 4 - Reactions and conditions: a) n-octyl bromide, NaH, DMF, 80°C, 2h; b) Zn, AcOH, CH<sub>2</sub>Cl<sub>2</sub>, 60°C, 1h, 90% two steps

Thioglycosides **1**, **3**, **4**, and **5** were prepared by usual method<sup>20</sup> with the reaction of acylated sugars with the selected thiol in the presence of BF<sub>3</sub>.Et<sub>2</sub>O in dry dichloromethane. The precursors were D-glucose peracetate, D-mannose peracetate and 1,2,4,6-tetra-O-benzoyl-3-O-benzyl D-glucopyranose<sup>21</sup> compound obtained from diacetone glucose (Scheme 5):



Scheme 5 - Reactions and conditions: a) pOPh-SH, BF<sub>3</sub>.Et<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>, 85%; b) MeONa, MeOH, 95%; c) BzCl, Pyr 45% d) pOPh-SH, BF<sub>3</sub>.Et<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>, 92%; e) MeONa, MeOH, 94%; f) BzCl, Pyr 61%; g) pOPh-SH, BF<sub>3</sub>.Et<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>, 50 %; h) Mbp-SH, BF<sub>3</sub>.Et<sub>2</sub>O; CH<sub>2</sub>Cl<sub>2</sub>, 63%

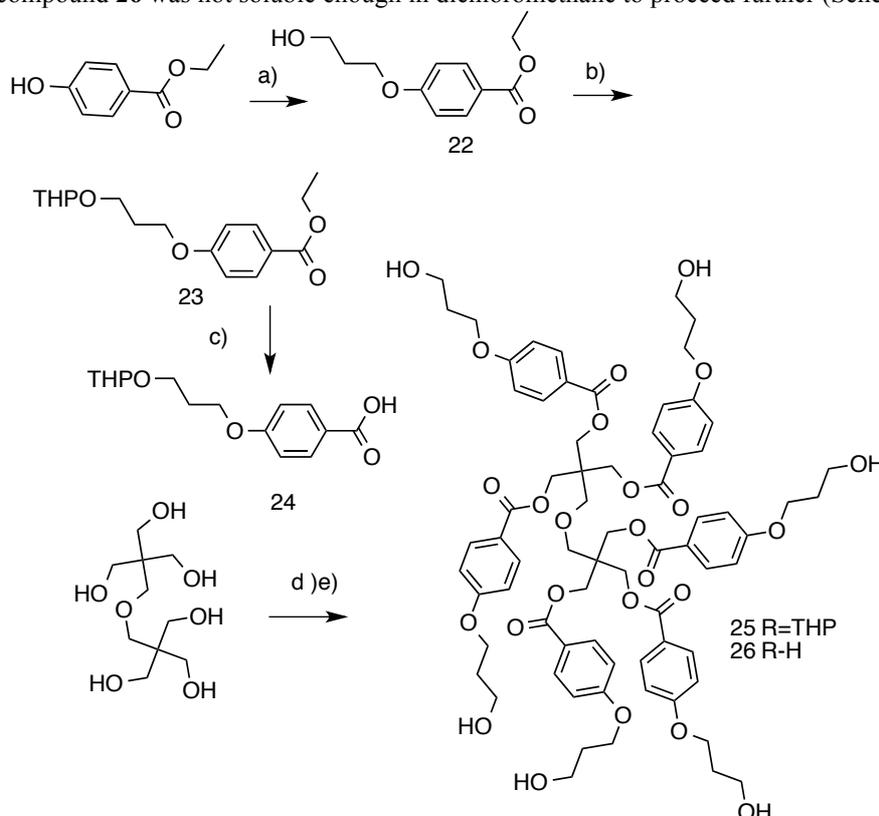
Scheme 6 depicts the Fmoc donors synthesis: **8** was prepared by a selective reaction with FmocCl/ collidine on the primary alcohol, followed by benzylation of the remaining alcohols functions<sup>22</sup>. The introduction of 4-OBn was achieved through ring opening of a benzylidene (**19**-> **20**)<sup>23</sup> then the 6-position was benzoylated (to give **3**) and protected by a Fmoc group to give **9**.



Scheme 6 - Reaction and conditions: a) FmocCl, 2,4,6-collidine, CH<sub>2</sub>Cl<sub>2</sub>, 66%; b) BzCl, Pyr, CH<sub>2</sub>Cl<sub>2</sub>; 71%; c) PhCH(OMe)<sub>2</sub>, CSA, CH<sub>3</sub>CN, 72%; d) Bz<sub>2</sub>O, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 73%; e) BH<sub>3</sub>.THF, TMSOTf, THF, 84%; f) BzCl, Pyr, 71% g) FmocCl, pyr, CH<sub>2</sub>Cl<sub>2</sub>, 72%.

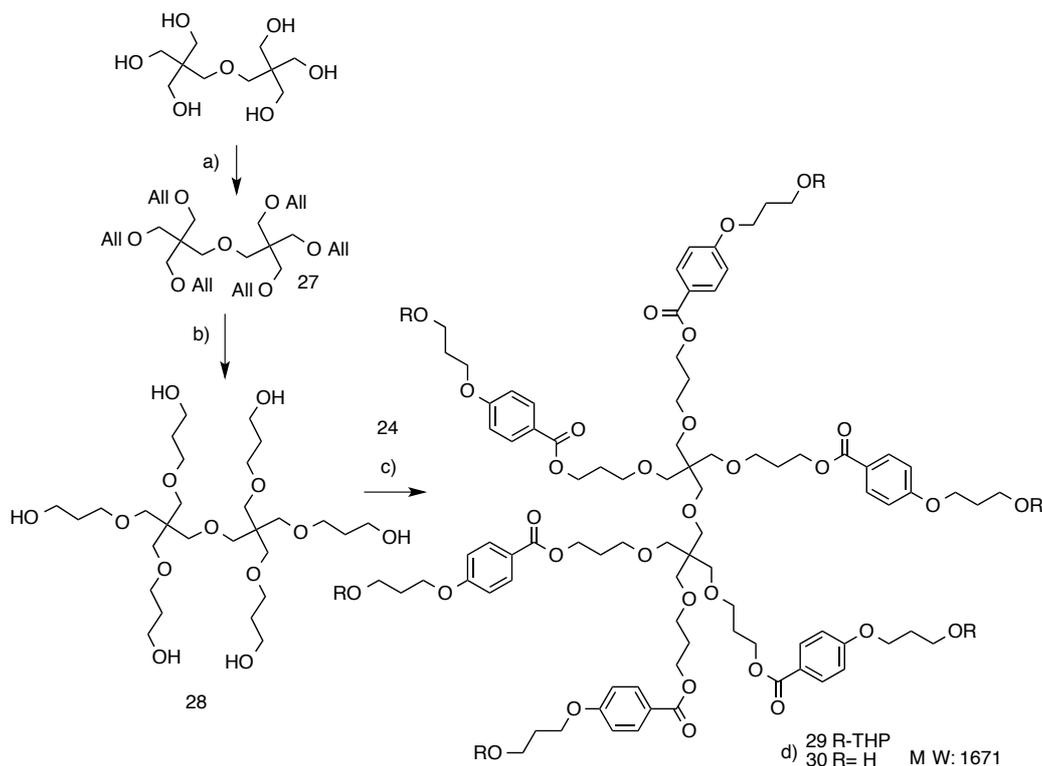
### Linker and polyol core

A known<sup>24</sup> derivative of *para* hydroxyl benzoic acid **24** was selected as spacer in this validation step for its strong UV absorption ( $\epsilon$  20000 @ 257nm) facilitating monitoring and purification of the final product. The preparation is described in Scheme 7<sup>25</sup>. Tetrahydropyranyl ether was selected as a protecting group for the alcohol function of **22**<sup>26</sup>. The desired polyol core needs to be small and symmetrical; we selected a core derived from dipentaerythritol (DPETN) with six hydroxyls. In a first approach, the linker **24** was introduced directly to give **25**. Unfortunately, after THP deprotection, this compound **26** was not soluble enough in dichloromethane to proceed further (Scheme 7).



Scheme 7- reaction and conditions: a) 3-chloropropanol, K<sub>2</sub>CO<sub>3</sub>, methylethylketone, reflux, 48h, 53%; b) 3,4-dihydro-2H-pyran, CSA, CH<sub>2</sub>Cl<sub>2</sub>, 84%; c) NaOH, EtOH, H<sub>2</sub>O, 76%, d) EDC, CH<sub>2</sub>Cl<sub>2</sub>, 50 °C 95%; e) PTSA, H<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub>, RT, 32%

It was decided to add a short C3 spacer to prepare **28**, soluble in dichloromethane (DPETN is not soluble in  $\text{CH}_2\text{Cl}_2$ ). This elongated core was made in 2 steps: per allylation gives **27** <sup>27</sup> followed by hydroboration using 9-BBN <sup>28,29</sup> (Scheme 8)



Scheme 8 - Reactions and conditions: a) Allyl bromide, NaH (60% in oil), DMF, 75%, b) 9-BBN, THF 100 °C, 2h then 3M aq NaOH;  $\text{H}_2\text{O}_2$ ; 63%; c) EDC,  $\text{CH}_2\text{Cl}_2$ , 60 °C, 18h, 95%, d) PTSA,  $\text{H}_2\text{O}/\text{MeOH}/\text{CH}_2\text{Cl}_2$ , 70 °C, 3h, 82%

From this compound **28**, the final core **30** was prepared by acylation and THP removal (Scheme 8). Hopefully, it was found soluble in dichloromethane.

## Glycosylations

For the preparation of  $\beta$  (1->6) oligoglucosides, we tried first the glycosylation of the model alcohol **22** with 6-O-Fmoc-2,3,4-O-tri benzoyl glycoside donors **8**, but surprisingly, we have noticed that despite the various 6-O-fmoc removal reactions we have used (piperidine / DBU/ fluoride anion), it always lead in some extend, to benzoyl migration from the 4 to 6 position.

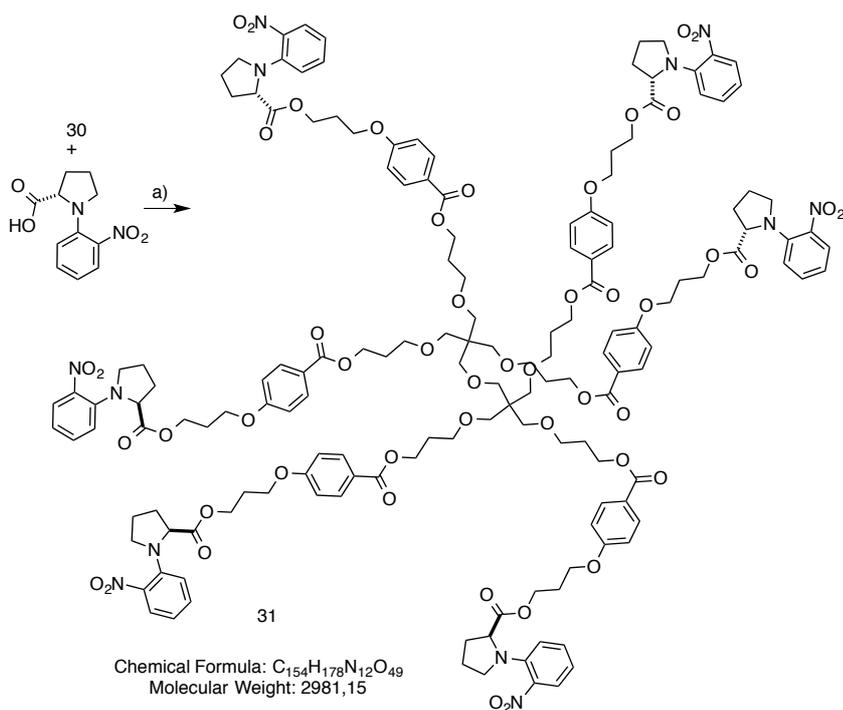
As in supported synthesis, the two regioisomers are not separable and will lead to a very complex oligosaccharide mixture; we had preferred then to change the 4-O-benzoyl to a 4-O-benzyl group (block **9**) to prevent the formation of isomers. In that case, no migration was observed, even in prolonged contact with piperidine.

We have already observed this migration in mannoside derivatives <sup>17</sup> (from position 3 to position 2) and this fact clearly further limits the interest of adjacent benzoyl protective groups in supported synthesis (4,6 or cis diol)

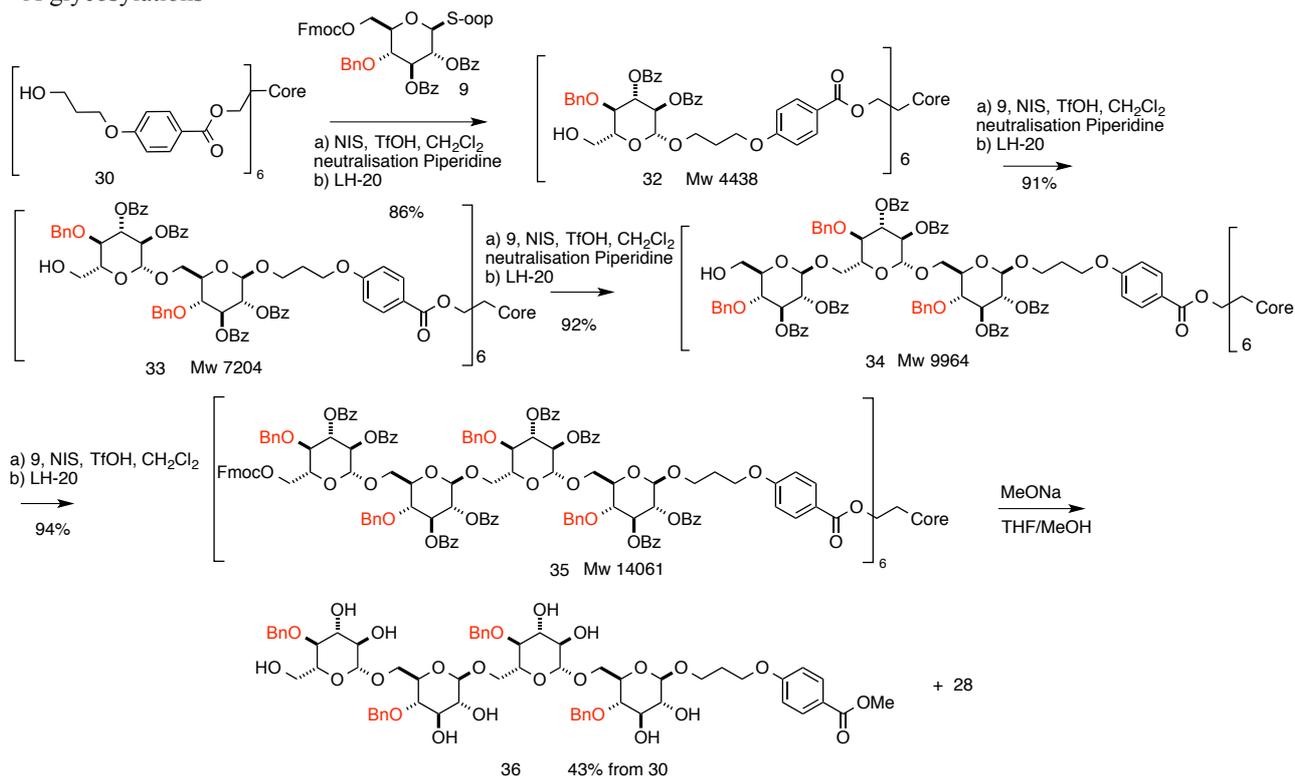
Scheme 10 represented the synthesis of tetrasaccharide **36**. NIS and TfOH were added to a solution of glycosyl donor (1.2 equiv / OH) and glycosyl acceptor. After 15 minutes the reaction mixture was neutralized with piperidine (which also removed the Fmoc) and concentrated to dryness. A solution of the residue in dichloromethane / methanol 1/1 was then eluted from a Sephadex <sup>TM</sup> LH-20 column: the high molecular weight compound was first eluted and collected.

To facilitate this step, we have prepared and added into the reaction mixture a small amount (about 2 mg) of an inert yellow orange compound with a molecular weight of 2900 - this yellow tracer ( $\epsilon$  8000  $\text{mol}^{-1} \text{cm}^{-1}$  at 411 nm in  $\text{CH}_2\text{Cl}_2/\text{MeOH}$ ) elutes with the desired product and indicates visually the end of the elution (see Figure 2). This compound was easily prepared from the hexaol core and 2-nitrophenyl L-proline <sup>30</sup> (See preparation Scheme 9)

This sequence was repeated four times to give **35**. Small excess (1.2 equivalent/ OH) of thioglycoside was used for each glycosylation. The tetrasaccharide preparation was found more difficult and 1.2 equivalents of thioglycoside had led to incomplete glycosylation (noticed in <sup>13</sup>C NMR) and 2 equivalents were used instead. This unexpected lower reactivity was attributed to the too high molecular weight of the glycosyl acceptors **34** (10kDa). As example, anomeric carbon signals of the supported glycosides in <sup>13</sup>C NMR were shown in (Table 2). TLC controls can be used to check the disappearance of thioglycosides – the polymer is not moving in TLC.

Scheme 9 – Reaction and conditions: a) EDC, HCl, DMAP,  $CH_2Cl_2$ , DMF, 50 °C, 18h, 37%

## A glycosylations



Scheme 10 – Supported synthesis process (A) and final steps (B)

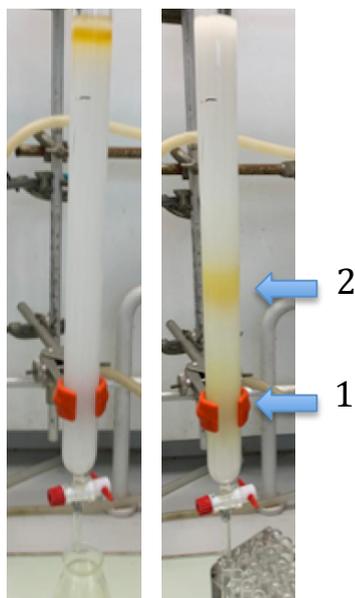
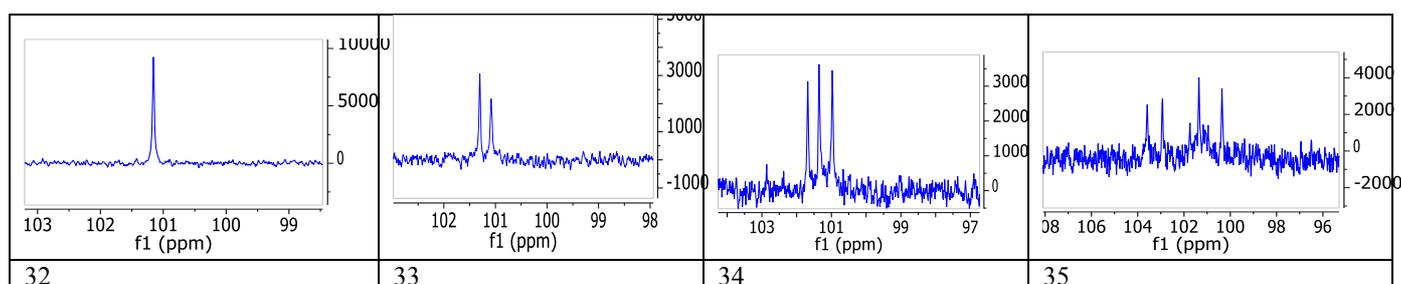


Figure 2 – Sephadex LH20 column purification using yellow tracer: first eluted yellow ring (1) = yellow tracer and large molecules. Second eluted yellow ring (2): colored iodinated side products

Table 2 –  $^{13}\text{C}$  NMR of supported intermediates – anomeric region



#### 4/ Cleavage and final steps

The supported tetrasaccharide **35** was treated with sodium methylate in methanol/THF to remove the support and the benzoyl groups and give the partially deprotected tetrasaccharide **36** as a methyl ester after LH20 column purification. The support core and trace of tri and di saccharides were also recovered. The yellow indicator is cleaved also by sodium methylate to give colorless compounds, polyol core, L-proline methyl ester, and 2-nitroanisole (transesterification and SN Ar), they were removed by LH20 purification steps

Removal of benzyl groups ( $\text{H}_2$ , Pd/C) and trans-esterification with an excess of propargyl alcohol, used as solvent in the presence of catalytic sodium gave the final tetrasaccharidic target **38** with a 58 % isolated yield (after HPLC purification). This transesterification approach directly yielded a ‘clickable’ intermediate for conjugates preparation and example <sup>31</sup> of the use of propargyl esters are reported.

#### Conclusion

We have proposed here a potentially general strategy for the synthesis of oligosaccharides based on high molecular weight intermediates and their separation in a size exclusion column. Here we have explored 6 arms core leading to a rapid increase in molecular weight (up to 14 kDa for the supported tetrasaccharide containing 24 glucose units). Three or four branched cores can be advantageously used for the preparation of longer oligosaccharides.

Associated with the use of a yellow tracer, this procedure allows a fast synthesis: no aqueous treatment, no TLC control, neither NMR are needed. The scale is only limited by the size of the separation column.

Finally, the trans esterification of the methyl ester with propargyl alcohol (or azido propanol) afforded a reactive tetrasaccharide ready to be clicked.

#### Experimental part

**General methods** - All solvents and chemicals were purchased from Sigma Aldrich and TCI and used without further purification. Air or water sensitive reactions were performed under a dry atmosphere of argon. Column chromatography was

performed using Armen Spot 2 Flash System with 40–63  $\mu\text{m}$  silica gel. TLC was performed on Silica Gel 60 F254 (E. Merck) and was revealed under UV lamp at 254 nm and/or with sulfuric acid.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker instruments, operating at a  $^1\text{H}$  frequency of 300 MHz. Chemical shifts are given in parts per million (ppm) using solvent residual signals as the reference and coupling constants (J) are given in Hertz (Hz). High Resolution Mass Spectra (HRMS) were recorded at the Institut Parisien de Chimie Moléculaire (FR 2769) of Sorbonne Université (electrospray source). MALDI-TOF spectra were recorded at the Institut de Biologie Paris-Seine (Paris, France) using the Applied Biosystems 4700 Proteomics Analyzer instrument. (CyHex=cyclohexane)

***p*-Octyloxyphenyl 2,3,4,6-tetra-O-benzoyl-1-thio- $\beta$ -D-glucopyranoside (1)** – [CAS Registry Number 1242659-84-2] To a suspension of **13** (1.12 g, 1.86 mmol, 1 equiv.) in dry MeOH (10 mL) at 0 °C was added sodium (9 mg, 0.394 mmol, 0.2 equiv.). The reaction was stirred at room temperature overnight then neutralized by Amberlite IR 120  $\text{H}^+$  resin and concentrated to afford **14**. The white solid was dissolved in dry pyridine (10 mL) under argon and benzoyl chloride (1.38 mL, 11.83 mmol, 6 equiv.) was slowly added at 0 °C. The mixture was stirred 4 hours at room temperature under argon then concentrated. A solution of the residue in  $\text{CH}_2\text{Cl}_2$  (20 mL), was washed with aq 1M HCl (10 mL) and sat aq  $\text{NaHCO}_3$ . The organic layer was dried  $\text{MgSO}_4$  and concentrated. The residue was purified by column chromatography on silica gel (CyHex 100% then CyHex/AcOEt 90:10) to give pure **1** (732 mg, 45%) as white foam.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.07 – 8.02 (m, 2H, H ar), 8.02 – 7.96 (m, 2H, H ar), 7.93 – 7.86 (m, 2H, H ar), 7.83 – 7.77 (m, 2H, H ar), 7.62 – 7.22 (m, 14H), 6.71 – 6.62 (m, 2H, H ar), 5.89 (t,  $J$  = 9.5 Hz, 1H,  $\text{H}_3$ ), 5.58 (t,  $J$  = 9.8 Hz, 1H,  $\text{H}_4$ ), 5.42 (t,  $J$  = 9.7 Hz, 1H,  $\text{H}_2$ ), 4.91 (d,  $J$  = 10.0 Hz, 1H,  $\text{H}_1$ ), 4.69 (dd,  $J$  = 12.2, 2.8 Hz, 1H,  $\text{H}_{6a}$ ), 4.47 (dd,  $J$  = 12.2, 5.5 Hz, 1H,  $\text{H}_{6b}$ ), 4.21 – 4.11 (m, 1H,  $\text{H}_5$ ), 3.84 (t,  $J$  = 6.6 Hz, 2H,  $\text{OCH}_2\text{CH}_2$ ), 1.83 – 1.68 (m, 2H,  $\text{OCH}_2\text{CH}_2$ ), 1.51 – 1.26 (m, 10H, 5  $\times$   $\text{CH}_2$ ), 0.97 – 0.83 (m, 3H,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  166.2 (CO Bz), 166.0 (CO Bz), 165.3 (CO Bz), 165.2 (CO Bz), 160.1 ( $\text{C}_q$  ar), 136.6 (C ar), 133.6 (C ar), 133.4 (C ar), 133.3 (C ar), 133.2 (C ar), 130.0 (C ar), 130.0 (C ar), 129.9 (C ar), 129.8 ( $\text{C}_q$  ar), 129.5 ( $\text{C}_q$  ar), 129.0 ( $\text{C}_q$  ar), 128.9 ( $\text{C}_q$  ar), 128.6 (C ar), 128.4 (C ar), 120.8 ( $\text{C}_q$  ar), 115.0 (C ar), 86.4 ( $\text{C}_1$ ), 76.4 ( $\text{C}_5$ ), 74.4 ( $\text{C}_3$ ), 70.6 ( $\text{C}_2$ ), 69.5 ( $\text{C}_4$ ), 68.2 ( $\text{OCH}_2\text{CH}_2$ ), 63.2 ( $\text{C}_6$ ), 32.0 ( $\text{CH}_2$ ), 29.5 ( $\text{CH}_2$ ), 29.4 ( $\text{CH}_2$ ), 29.3 ( $\text{OCH}_2\text{CH}_2$ ), 26.2 ( $\text{CH}_2$ ), 22.8 ( $\text{CH}_2$ ), 14.2 ( $\text{CH}_3$ ).

***p*-Octyloxyphenyl 2,4,6-tri-O-benzoyl-3-O-benzyl-1-thio- $\beta$ -D-glucopyranoside (3)** - To a solution of **17** (294 mg, 0.4277 mmol, 1 equiv) and *p*-Octyloxybenzenethiol (153 mg, 0.6415 mmol, 1.5 equiv.) in dry  $\text{CH}_2\text{Cl}_2$  (5 mL) was added under argon at 0 °C  $\text{BF}_3$  etherate (107  $\mu\text{L}$ , 0.8554 mmol, 2 equiv.). The reaction was stirred from 0 °C to room temperature under argon for 3 h and water (3 mL) was added to the solution. The mixture was stirred vigorously and the aqueous layer was discarded. The resulting organic layer was washed with sat aq  $\text{NaHCO}_3$  (3 mL), dried over  $\text{MgSO}_4$  and concentrated. The residue was purified by column chromatography on silica gel (CyHex 100% then CyHex/AcOEt/ $\text{Et}_2\text{O}$  80:10:10) to give pure **3** (170 mg, 50%) as white foam. ESI-HRMS  $m/z$   $[\text{M}+\text{Na}]^+$  calculated for  $\text{C}_{48}\text{H}_{50}\text{NaO}_9\text{S}$ : 825.3068, found: 825.3052  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.14 – 7.94 (m, 6H, H ar), 7.66 – 7.35 (m, 12H, H ar), 7.06 – 6.89 (m, 4H, H ar), 6.60 (d,  $J$  = 8.5 Hz, 2H, H ar), 5.47 (t,  $J$  = 9.5 Hz, 1H,  $\text{H}_4$ ), 5.31 (t,  $J$  = 9.4 Hz, 1H,  $\text{H}_2$ ), 4.77 (d,  $J$  = 9.9 Hz, 1H,  $\text{H}_1$ ), 4.65 (dd,  $J$  = 12.1, 2.1 Hz, 1H,  $\text{H}_{6a}$ ), 4.53 (s, 2H,  $\text{CH}_2$  Bn), 4.38 (dd,  $J$  = 12.1, 5.7 Hz, 1H,  $\text{H}_{6b}$ ), 4.07 (t,  $J$  = 9.1 Hz, 1H,  $\text{H}_3$ ), 4.05 – 3.94 (m, 1H,  $\text{H}_5$ ), 3.80 (t,  $J$  = 6.5 Hz, 2H,  $\text{OCH}_2\text{CH}_2$ ), 1.82 – 1.67 (m, 2H,  $\text{OCH}_2\text{CH}_2$ ), 1.49 – 1.22 (m, 10H, 5  $\times$   $\text{CH}_2$ ), 0.89 (app. t,  $J$  = 6.8 Hz, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  166.2 (CO Bz), 165.1 (CO Bz), 165.1 (CO Bz), 159.9 ( $\text{C}_q$  ar), 137.2 ( $\text{C}_q$  ar), 136.3 (C ar), 133.6 (C ar), 133.4 (C ar), 133.2 (C ar), 130.0 (C ar), 130.0 (C ar), 130.0 (C ar), 129.9 ( $\text{C}_q$  ar), 129.4 ( $\text{C}_q$  ar), 128.6 (C ar), 128.5 (C ar), 128.3 (C ar), 128.2 (C ar), 127.8 (C ar), 121.4 ( $\text{C}_q$  ar), 115.0 (C ar), 86.5 ( $\text{C}_1$ ), 81.2 ( $\text{C}_3$ ), 76.3 ( $\text{C}_5$ ), 74.5 ( $\text{CH}_2$  Bn), 72.4 ( $\text{C}_2$ ), 70.9 ( $\text{C}_4$ ), 68.1 ( $\text{OCH}_2\text{CH}_2$ ), 63.4 ( $\text{C}_6$ ), 32.0 ( $\text{CH}_2$ ), 29.5 ( $\text{CH}_2$ ), 29.4 ( $\text{CH}_2$ ), 29.3 ( $\text{OCH}_2\text{CH}_2$ ), 26.2 ( $\text{CH}_2$ ), 22.8 ( $\text{CH}_2$ ), 14.2 ( $\text{CH}_3$ ).

**2-Methyl-5-tert-butylphenyl 2,4,6-tri-O-benzoyl-3-O-benzyl-1-thio- $\alpha,\beta$ -D-glucopyranose (4)** - To a solution of **17** (30 g, 43.7 mmol, 1 equiv) in dry  $\text{CH}_2\text{Cl}_2$  (300 mL) were added under argon at 0 °C 2-methyl-5-tert-butylthiophenol (12 mL, 65.6 mmol, 1.5 equiv) and  $\text{BF}_3$  etherate (11 mL, 87.4 mmol, 2 equiv). The reaction was stirred from 0 °C to room temperature under argon for 4 h and water (100 mL) was added to the solution. The mixture was stirred vigorously and the aqueous layer was discarded. The resulting organic layer was washed with sat aq  $\text{NaHCO}_3$  (100 mL), dried over  $\text{MgSO}_4$ , concentrated and the residue was purified by column chromatography on silica gel (CyHex 100% then CyHex/AcOEt 90:10) containing first fractions with the 2 anomers (2.9 g) following by pure fractions containing only the  $\beta$  anomer **4** as a white powder (20.5 g, 63%). ESI-HRMS  $m/z$   $[\text{M}+\text{NH}_4]^+$  calculated for  $\text{C}_{45}\text{H}_{48}\text{NO}_8\text{S}$ : 762.3095, found: 762.3097.  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta$  8.17 – 7.96 (m, 6H, H ar), 7.71 – 6.94 (m, 17H, H ar), 5.63 (t,  $J$  = 9.6 Hz, 1H,  $\text{H}_4$ ), 5.52 (t,  $J$  = 9.9 Hz, 1H,  $\text{H}_2$ ), 4.89 (d,  $J$  = 10.1 Hz, 1H,  $\text{H}_1$ ), 4.69 – 4.54 (m, 3H,  $\text{CH}_2$ ,  $\text{H}_{6a}$ ), 4.46 (dd,  $J$  = 12.2, 5.2 Hz, 1H,  $\text{H}_{6b}$ ), 4.13 (t,  $J$  = 9.1 Hz, 1H,  $\text{H}_3$ ), 4.08 – 3.97 (m, 1H,  $\text{H}_5$ ), 2.29 (s, 3H,  $\text{CH}_3$  thio), 1.25 (s, 9H, *t*Bu).  $^{13}\text{C}$  NMR (63 MHz,  $\text{CDCl}_3$ )  $\delta$  166.3 (CO Bz), 165.0 (2), 149.6 ( $\text{C}_q$  ar), 138.0 ( $\text{C}_q$  ar), 137.1 ( $\text{C}_q$  ar), 133.4 (C ar), 133.3 (C ar), 133.0 (C ar), 131.8 ( $\text{C}_q$  ar), 131.0 (C ar), 130.0 (C ar), 129.9 (C ar), 129.8 (C ar), 129.8 (C ar), 129.3 ( $\text{C}_q$  ar), 128.5 (C ar), 128.3 (C ar), 128.1 (C ar), 128.1 (C ar), 127.7 (C ar), 125.7 (C ar), 87.9 ( $\text{C}_1$ ), 80.9 ( $\text{C}_3$ ), 76.1 ( $\text{C}_5$ ), 74.2 ( $\text{CH}_2$ ), 72.5 ( $\text{C}_2$ ), 70.9 ( $\text{C}_4$ ), 63.6 ( $\text{C}_6$ ), 34.4 ( $\text{C}_q$  *t*Bu), 31.2 (*t*Bu), 20.5 ( $\text{CH}_3$  thio).

***p*-Octyloxyphenyl 2,3,4,6-tetra-O-benzoyl-1-thio- $\alpha$ -D-mannopyranoside (5)** To a solution of **16** (242 mg, 0.605 mmol, 1 equiv.) in dry pyridine (4 mL) was added under argon benzoyl chloride (420  $\mu\text{L}$ , 3.63 mmol, 6 equiv.). The reaction was stirred overnight at room temperature then concentrated. The residue was taken up in  $\text{CH}_2\text{Cl}_2$  (5 mL) and washed with aq 1M HCl (2 mL) and sat aq  $\text{NaHCO}_3$  (2 mL). The organic layer was dried over magnesium sulfate and concentrated. The residue was then purified by column chromatography on silica gel (CyHex/ $\text{Et}_2\text{O}$  95:5 then CyHex/AcOEt 9:1) to give pure **5** as a beige solid (301 mg, 61%). APCI-HRMS  $m/z$   $[\text{M}+\text{H}]^+$  calculated for  $\text{C}_{48}\text{H}_{49}\text{O}_{10}\text{S}$ : 817.3041, found: 817.3046.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.10 – 8.03 (m, 3H, H ar), 8.03 – 7.98 (m, 2H), 7.89 – 7.84 (m, 2H, H ar), 7.65 – 7.35 (m, 12H, H ar), 7.30 (d,  $J$  = 7.9 Hz, 1H, H ar), 6.77 – 6.70 (m, 2H, H ar), 6.12 (t,  $J$  = 10.0 Hz, 1H,  $\text{H}_4$ ), 5.97 (dd,  $J$  = 3.2, 1.7 Hz, 1H,  $\text{H}_2$ ), 5.88 (dd,

$J = 10.1, 3.2$  Hz, 1H, H<sub>3</sub>), 5.62 (d,  $J = 1.5$  Hz, 1H, H<sub>1</sub>), 5.12 – 5.00 (m, 1H, H<sub>5</sub>), 4.67 (dd,  $J = 12.2, 2.5$  Hz, 1H, H<sub>6a</sub>), 4.58 (dd,  $J = 12.2, 5.3$  Hz, 1H, H<sub>6b</sub>), 3.87 (t,  $J = 6.6$  Hz, 2H, OCH<sub>2</sub>), 1.84 – 1.69 (m, 2H, OCH<sub>2</sub>CH<sub>2</sub>), 1.50 – 1.23 (m, 10H, 5 × CH<sub>2</sub>), 0.88 (app. t, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 166.17 (CO Bz), 165.54 (CO Bz), 165.46 (CO Bz), 165.35 (CO Bz), 159.77 (C<sub>q</sub> ar), 135.16 (C ar), 133.53 (C ar), 133.29 (C ar), 133.06 (C ar), 129.90 – 129.79 (C ar), 129.31 (C<sub>q</sub> ar), 128.96 (C<sub>q</sub> ar), 128.92 (C<sub>q</sub> ar), 128.62 – 128.36 (C ar), 122.37 (C<sub>q</sub> ar), 115.43 (C ar), 86.89 (C<sub>1</sub>), 71.86 (C<sub>2</sub>), 70.42 (C<sub>3</sub>), 69.75 (C<sub>5</sub>), 68.12 (OCH<sub>2</sub>), 67.27 (C<sub>4</sub>), 63.20 (C<sub>6</sub>), 31.82 (CH<sub>2</sub>), 29.34 (CH<sub>2</sub>), 29.25 (CH<sub>2</sub>), 29.15 (OCH<sub>2</sub>CH<sub>2</sub>), 26.02 (CH<sub>2</sub>), 22.67 (CH<sub>2</sub>), 14.11 (CH<sub>3</sub>).

***p*-Octyloxyphenyl 2,3,4-tri-*O*-benzoyl-6-*O*-fluorenylmethoxycarbonyl 1-thio-β-*D*-glucopyranoside (8)** - To a solution of **18** (5.03 g, 8.073 mmol, 1 equiv.) in a mixture of CH<sub>2</sub>Cl<sub>2</sub> /pyridine 75: 25 v: v (106 mL) at 0 °C was added benzoyl chloride (9.4 mL, 80.73 mmol, 10 equiv.). The solution was stirred from 0 °C to room temperature for 1h30 then excess MeOH was carefully added and concentrated. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (100mL). The solution was washed with aq 1M HCl (1 x 50 mL) and sat aq sodium bicarbonate (2 x 50 mL). The organic layer was dried over magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (CyHex 100% then CyHex/AcOEt 90:10). The residue was taken in cyclohexane and the mixture was let overnight at room temperature. The formed precipitate was filtered off and dried under P<sub>2</sub>O<sub>5</sub> to get **8** (5.46 g, 71%) as a white solid. ESI-HRMS  $m/z$  [M+NH<sub>4</sub>]<sup>+</sup> calculated for C<sub>56</sub>H<sub>58</sub>NO<sub>11</sub>S: 952.3725, found: 952.3717. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.08 – 7.24 (m, 25H, H ar), 6.87 (d,  $J = 8.6$  Hz, 2H, H ar thioaryl), 5.91 (t,  $J = 9.5$  Hz, 1H, H<sub>3</sub>), 5.60 – 5.40 (m, 2H, H<sub>2</sub>, H<sub>4</sub>), 4.93 (d,  $J = 10.0$  Hz, 1H, H<sub>1</sub>), 4.55 – 4.34 (m, 4H, CH<sub>2</sub> Fmoc, H<sub>6</sub>), 4.28 (t,  $J = 7.5$  Hz, 1H, CH Fmoc), 4.12 (dt,  $J = 9.3, 4.3$  Hz, 1H, H<sub>5</sub>), 3.92 (t,  $J = 6.5$  Hz, 2H, OCH<sub>2</sub>), 1.85 – 1.69 (m, 2H, OCH<sub>2</sub>CH<sub>2</sub>), 1.50 – 1.22 (m, 10H, 5 × CH<sub>2</sub>), 0.91 (t,  $J = 6.5$  Hz, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 165.9 (CO Bz), 165.4 (CO Bz), 165.1 (CO Bz), 160.2 (CO Fmoc), 155.0 (C<sub>q</sub> ar), 143.5 (C<sub>q</sub> ar), 143.4 (C<sub>q</sub> ar), 141.4 (C<sub>q</sub> ar), 141.4 (C<sub>q</sub> ar), 136.6 (C ar), 133.7 (C ar), 133.4 (C ar), 133.4 (C ar), 130.0 (C ar), 130.0 (C ar), 129.9 (C ar), 129.4 (C<sub>q</sub> ar), 128.9 (C<sub>q</sub> ar), 128.8 (C<sub>q</sub> ar), 128.6 (C ar), 128.6 (C ar), 128.4 (C ar), 128.0 (C ar), 127.4 (C ar), 125.4 (C ar), 125.4 (C ar), 120.9 (C<sub>q</sub> ar), 120.2 (C ar), 115.1 (C ar), 86.5 (C<sub>1</sub>), 76.2 (C<sub>5</sub>), 74.3 (C<sub>3</sub>), 70.5 (C<sub>2</sub>), 70.4 (CH<sub>2</sub> Fmoc), 69.5 (C<sub>4</sub>), 68.2 (OCH<sub>2</sub>), 66.6 (C<sub>6</sub>), 46.8 (CH Fmoc), 31.9 (CH<sub>2</sub>), 29.5 (CH<sub>2</sub>), 29.4 (CH<sub>2</sub>), 29.3 (OCH<sub>2</sub>CH<sub>2</sub>), 26.1 (CH<sub>2</sub>), 22.8 (CH<sub>2</sub>), 14.3 (CH<sub>3</sub>).

***p*-Octyloxyphenyl 2,3-di-*O*-benzoyl-4-*O*-benzyl-6-*O*-fluorenylmethoxycarbonyl-1-thio-β-*D*-glucopyranoside (9)** - To a solution of **21** (3.23 g, 4.64 mmol, 1 equiv.) in dry CH<sub>2</sub>Cl<sub>2</sub> (30mL) and dry pyridine (3 mL) at 0°C under argon was added Fmoc chloride (1.44 g, 5.55 mmol, 1.2 equiv.). Then the reaction mixture stirred for 3 hours at room temperature and diluted with CH<sub>2</sub>Cl<sub>2</sub> (20 mL) then washed with aq HCl 1M (2 × 20 mL) and sat aq NaHCO<sub>3</sub> (2 × 20 mL); dried over magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (CyHex / AcOEt 95:5) to give pure **9** (3.07 g, 72%) as a white foam. APCI-HRMS  $m/z$  [M+H]<sup>+</sup> calculated for C<sub>56</sub>H<sub>57</sub>O<sub>10</sub>S: 921.3667, found: 921.3679. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.04 – 7.92 (m, 4H, H ar), 7.81 (d,  $J = 7.4$  Hz, 2H, H ar), 7.70 (d,  $J = 7.5$  Hz, 2H, H ar), 7.59 – 7.34 (m, 10H, H ar), 7.23 – 7.11 (m, 5H, H ar), 6.84 (d,  $J = 8.8$  Hz, 2H, H ar), 5.77 (t,  $J = 9.2$  Hz, 1H, H<sub>3</sub>), 5.36 (t,  $J = 9.7$  Hz, 1H, H<sub>2</sub>), 4.82 (d,  $J = 10.0$  Hz, 1H, H<sub>1</sub>), 4.66 – 4.30 (m, 7H, CH<sub>2</sub> Bn, CH Fmoc, CH<sub>2</sub> Fmoc, H<sub>6</sub>), 3.96 – 3.76 (m, 4H, OCH<sub>2</sub>, H<sub>4</sub>, H<sub>5</sub>), 1.74 (p,  $J = 6.6$  Hz, 2H, OCH<sub>2</sub>CH<sub>2</sub>), 1.48 – 1.21 (m, 10H, 5 × CH<sub>2</sub>), 0.97 – 0.86 (m, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 165.7 (CO Bz), 165.3 (CO Bz), 159.9 (C<sub>q</sub> ar), 155.0 (CO Fmoc), 143.4 (C<sub>q</sub> ar), 143.3 (C<sub>q</sub> ar), 141.3 (C<sub>q</sub> ar), 136.9 (C<sub>q</sub> ar), 136.3 (C ar), 133.3 (C ar), 133.3 (C ar), 129.9 (C ar), 129.8 (C ar), 129.4 (C<sub>q</sub> ar), 129.4 (C<sub>q</sub> ar), 128.5 (C ar), 128.4 (C ar), 128.4 (C ar), 128.3 (C ar), 128.1 (C ar), 128.0 (C ar), 127.3 (C ar), 125.3 (C ar), 125.2 (C ar), 121.3 (C<sub>q</sub> ar), 120.1 (C ar), 114.9 (C ar), 86.5 (C<sub>1</sub>), 77.1 (C<sub>5</sub>), 76.5 (C<sub>3</sub>), 75.6 (C<sub>4</sub>), 74.9 (CH<sub>2</sub> Bn), 70.7 (C<sub>2</sub>), 70.2 (CH<sub>2</sub> Fmoc), 68.1 (OCH<sub>2</sub>), 66.3 (C<sub>6</sub>), 46.8 (CH Fmoc), 31.8 (CH<sub>2</sub>), 29.4 (OCH<sub>2</sub>CH<sub>2</sub>), 29.3 (CH<sub>2</sub>), 29.2 (CH<sub>2</sub>), 26.0 (CH<sub>2</sub>), 22.7 (CH<sub>2</sub>), 14.2 (CH<sub>3</sub>).

***p*-Octyloxybenzenethiol (12)** – [CAS Registry Number 102231-96-9] -To a solution of bis(4-hydroxyphenyl) disulfide (5.0, g, 19.97 mmol, 1 equiv.) and octyl bromide (10.3 mL, 59.91 mmol, 3 equiv.) in dry DMF was added portionwise sodium hydride 60% (1.76g, 43.93 mmol, 2.2 equiv.). The mixture was heated at 80 °C for 2 hours under argon then sodium hydride was quenched with MeOH (50 mL). The solvents were evaporated and the crude was diluted with AcOEt (100 mL). The solution was washed with H<sub>2</sub>O (2 x 50 mL) and brine (1 x 50 mL). The organic layer was dried over magnesium sulfate and concentrated. The residue **11** was dried overnight under P<sub>2</sub>O<sub>5</sub> and used without any purification. **11** [CAS Registry Number: 2637522-64-4] was dissolved under argon in a mixture of CH<sub>2</sub>Cl<sub>2</sub> (60 mL) and AcOH (120 mL) then zinc powder (32 g, 500 mmol, 25 equiv. previously activated by washing with HCl 10%, H<sub>2</sub>O, EtOH and Et<sub>2</sub>O) was added. The mixture was heated at 60 °C for 1 hour and filtrated through Celite. The filtrate was evaporated and the residue was purified by column chromatography on silica gel (CyHex 100%) to get **12** (9.1g, 96%) as a pale yellow oil. APCI-HRMS  $m/z$  [M]<sup>+</sup> calculated for C<sub>14</sub>H<sub>22</sub>OS: 238.1391, found: 238.1386. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.28 (dd,  $J = 6.9, 1.6$  Hz, 2H, H ar), 6.92 – 6.75 (m, 2H, H ar), 3.94 (t,  $J = 6.6$  Hz, 2H, OCH<sub>2</sub>), 3.37 (s, 1H, SH), 1.79 (m, 2H, OCH<sub>2</sub>CH<sub>2</sub>), 1.56 – 1.22 (m, 10H, 5 × CH<sub>2</sub>), 1.03 – 0.82 (m, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 158.1 (C<sub>q</sub> ar), 132.5 (C ar), 119.5 (C<sub>q</sub> ar), 115.3 (C ar), 68.1 (OCH<sub>2</sub>), 31.9 (CH<sub>2</sub>), 29.4 (CH<sub>2</sub>), 29.3 (CH<sub>2</sub>), 29.3 (CH<sub>2</sub>), 26.1 (CH<sub>2</sub>), 22.7 (CH<sub>2</sub>), 14.2 (CH<sub>3</sub>).

***p*-Octyloxyphenyl 2,3,4,6-tetra-*O*-acetyl 1-thio-β-*D*-glucopyranoside (13)**- [CAS Registry Number 1242659-80-8] To a solution of 1,2,3,4,6-penta-*O*-acetyl- β-*D*-glucopyranoside (9.61 g, 24.64 mmol, 1 equiv.) and *p*-Octyloxybenzenethiol **4** (8.50 g, 36.96 mmol, 1.5 equiv.) in dry CH<sub>2</sub>Cl<sub>2</sub> (25 mL) at 0 °C was added boron trifluoride etherate (15.5 mL, 123 mmol, 5 equiv.). The mixture was stirred for 1h30 at room temperature, diluted with CH<sub>2</sub>Cl<sub>2</sub> (75mL), washed with water (1× 50 mL) and a sat aq NaHCO<sub>3</sub> (2 × 50 mL). The organic layer was dried over magnesium sulfate, and concentrated. The residue was purified by column chromatography on silica gel (CyHex 100% then CyHex/AcOEt 80:20) to give **13** (11.90 g, 85%) as a white solid (ESI-HRMS  $m/z$  [M+NH<sub>4</sub>]<sup>+</sup> calculated for C<sub>28</sub>H<sub>44</sub>NO<sub>10</sub>S: 586.2680, found: 586.2683. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.52 – 7.36 (m, 2H, H ar thioaryl), 6.91 – 6.72 (m, 2H, H ar thioaryl), 5.19 (t,  $J = 9.4$  Hz, 1H, H<sub>3</sub>), 4.98 (t,  $J = 9.8$  Hz, 1H, H<sub>4</sub>), 4.88 (dd,  $J = 9.9, 9.3$  Hz, 1H, H<sub>2</sub>), 4.54 (d,  $J = 10.0$  Hz, 1H, H<sub>1</sub>), 4.22 – 4.14 (m, 2H, H<sub>6</sub>), 3.94 (t,  $J = 6.6$  Hz,

2H, OCH<sub>2</sub>), 3.66 (ddd,  $J = 10.0, 4.2, 3.2$  Hz, 1H, H<sub>5</sub>), 2.09 (s, 3H, CH<sub>3</sub> Ac), 2.07 (s, 3H, CH<sub>3</sub> Ac), 2.00 (s, 3H, CH<sub>3</sub> Ac), 1.97 (s, 3H, CH<sub>3</sub> Ac), 1.77 (dt,  $J = 14.5, 6.6$  Hz, 2H, OCH<sub>2</sub>CH<sub>2</sub>), 1.51 – 1.21 (m, 10H, 5 × CH<sub>2</sub>), 0.93 – 0.83 (m, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 170.7 (CO Ac), 170.3 (CO Ac), 169.5 (CO Ac), 169.3 (CO Ac), 160.2 (C<sub>q</sub> ar), 136.6 (C ar), 120.7 (C<sub>q</sub> ar), 115.0 (C ar), 85.9 (C<sub>1</sub>), 75.9 (C<sub>3</sub>), 74.2 (C<sub>3</sub>), 70.0 (C<sub>2</sub>), 68.3 (C<sub>4</sub>), 68.3 (OCH<sub>2</sub>), 62.2 (C<sub>6</sub>), 31.9 (CH<sub>2</sub>), 29.5 (CH<sub>2</sub>), 29.3 (CH<sub>2</sub>), 29.3 (CH<sub>2</sub>), 26.2 (CH<sub>2</sub>), 22.8 (CH<sub>2</sub>), 20.9 (CH<sub>3</sub> Ac), 20.9 (CH<sub>3</sub> Ac), 20.7 (CH<sub>3</sub> Ac), 20.7 (CH<sub>3</sub> Ac), 14.2 (CH<sub>3</sub>).

***p*-Octyloxyphenyl 1-thio-β-D-glucopyranoside (14)**, [CAS Registry Number 1242659-87-5] To a solution of **13** (11.85 g, 20.86 mmol, 1 equiv.) in dry MeOH (230 mL) at 0 °C was added carefully sodium (108 mg, 4.68 mmol, 0.2 equiv.). The reaction was stirred at room temperature overnight then neutralized by Amberlite IR 120 H<sup>+</sup> resin and concentrated to give *p*-octyloxyphenyl 1-thio-α-D-glucopyranoside **14** as a white solid (7.91 g, 95%). ESI-HRMS  $m/z$  [M+NH<sub>4</sub>]<sup>+</sup> calculated for C<sub>20</sub>H<sub>36</sub>NO<sub>6</sub>S: 418.2258, found: 418.2258. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.41 (d,  $J = 9.3$  Hz, 2H, H ar thioaryl), 6.75 (d,  $J = 9.3$  Hz, 2H, thioaryl), 4.51 (d,  $J = 9.5$  Hz, 1H, H<sub>1</sub>), 3.83 (br s, 4H, OCH<sub>2</sub>, H<sub>6</sub>), 3.59 (br s, 2H, H<sub>3</sub>, H<sub>4</sub>), 3.47 – 3.36 (m, 1H, H<sub>2</sub>), 3.32 (br s, 1H, H<sub>5</sub>), 1.81 – 1.66 (m, 2H, OCH<sub>2</sub>CH<sub>2</sub>), 1.49 – 1.22 (m, 10H, 5 × CH<sub>2</sub>), 0.95 – 0.81 (m, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 159.7 (C<sub>q</sub> ar), 135.5 (C ar), 122.3 (C<sub>q</sub> ar), 115.3 (C ar), 89.1 (C<sub>1</sub>), 79.5 (C<sub>5</sub>), 78.0 (C<sub>3</sub> or C<sub>4</sub>), 72.4 (C<sub>2</sub>), 69.6 (C<sub>3</sub> or C<sub>4</sub>), 68.3 (OCH<sub>2</sub>), 61.9 (C<sub>6</sub>), 32.0 (CH<sub>2</sub>), 29.6 (OCH<sub>2</sub>CH<sub>2</sub>), 29.4 (2 × CH<sub>2</sub>), 26.2 (CH<sub>2</sub>), 22.8 (CH<sub>2</sub>), 14.2 (CH<sub>3</sub>).

***p*-Octyloxyphenyl 2,3,4,6-tetra-O-acetyl-1-thio-α-D-mannopyranoside (15)** [CAS Registry Number 916497-79-5] To a solution of 1,2,3,4,6-penta-O-acetyl-α,β-D-mannopyranoside (6.40 g, 16.4 mmol, 1 equiv.) and *p*-Octyloxybenzenethiol (5.16 g, 21.7 mmol, 1.3 equiv.) in freshly distilled CH<sub>2</sub>Cl<sub>2</sub> (160 mL) cooled in an ice bath was slowly added under argon BF<sub>3</sub>·Et<sub>2</sub>O (10.3 mL, 82 mmol, 5 equiv.). The solution was then warmed up at room temperature and stirred overnight under argon. The reaction was diluted with CH<sub>2</sub>Cl<sub>2</sub>, washed with water then with a saturated aqueous solution of NaHCO<sub>3</sub>. The organic layer was dried over magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (CyHex 100% then CyHex/AcOEt 90:10) giving a mixture of *p*-Octyloxyphenyl-2-3-4-6-tetra-O-acetyl-1-thio-D-mannopyranoside anomers (6.02 g) and pure *p*-Octyloxyphenyl-2-3-4-6-tetra-O-acetyl-1-thio-α-D-mannopyranoside (2.53 g), both as a white solid (92%). ESI-HRMS  $m/z$  [M+NH<sub>4</sub>]<sup>+</sup> calculated for C<sub>28</sub>H<sub>44</sub>NO<sub>10</sub>S: 586.2680, found: 586.2683. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) (anomer α) δ 7.39 (d,  $J = 8.8$  Hz, 1H, H ar), 6.82 (d,  $J = 8.9$  Hz, 1H, H ar), 5.53 – 5.44 (m, 1H, H Man), 5.36 – 5.27 (m, 3H, H<sub>1</sub>, 2 × H Man), 4.56 (m, 1H, H<sub>5</sub>), 4.29 (dd,  $J = 12.2, 5.9$  Hz, 1H, H<sub>6a</sub>), 4.10 (dd,  $J = 12.2, 2.4$  Hz, 1H, H<sub>6b</sub>), 3.91 (t,  $J = 6.5$  Hz, 2H, OCH<sub>2</sub>CH<sub>2</sub>), 2.12 (s, 3H, CH<sub>3</sub> Ac), 2.06 (s, 6H, 2 × CH<sub>3</sub> Ac), 2.00 (s, 3H, CH<sub>3</sub> Ac), 1.84 – 1.68 (m, 2H, OCH<sub>2</sub>CH<sub>2</sub>), 1.37 – 1.19 (m, 10H, 5 × CH<sub>2</sub>), 0.97 – 0.78 (m, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 170.6 (CO Ac), 170.0 (CO Ac), 169.9 (CO Ac), 169.8 (CO Ac), 159.9 (C<sub>q</sub> ar), 135.2 (C ar), 122.4 (C<sub>q</sub> ar), 115.4 (C ar), 86.7 (C<sub>1</sub>), 70.9 (C Man), 69.5 (C Man), 68.2 (OCH<sub>2</sub>), 66.6 (C Man), 62.7 (C<sub>6</sub>), 31.9 (CH<sub>2</sub>), 29.4 (CH<sub>2</sub>), 29.3 (CH<sub>2</sub>), 29.2 (CH<sub>2</sub>), 26.1 (CH<sub>2</sub>), 22.7 (CH<sub>2</sub>), 21.0 (CH<sub>3</sub> Ac), 20.8 (CH<sub>3</sub> Ac), 20.7 (CH<sub>3</sub> Ac), 14.2 (CH<sub>3</sub>).

***p*-Octyloxyphenyl 1-thio-α-D-mannopyranoside (16)** – [CAS Registry Number 916497-86-4] To a suspension of **15** (2.53 g, 4.45 mmol, 1 equiv.) in dry MeOH (45 mL) at 0 °C was added sodium (2 × 10 mg, 0.89 mmol, 0.2 equiv.), the mixture was stirred at room temperature for 2h under argon. The reaction was neutralized with Amberlite IR 120 (H<sup>+</sup>) resin. The filtrate was concentrated and dried over P<sub>2</sub>O<sub>5</sub> giving **16** (952 mg, 94%) as a white solid. APCI-HRMS  $m/z$  [M]<sup>+</sup> calculated for C<sub>20</sub>H<sub>32</sub>O<sub>6</sub>S: 400.1920, found: 400.1913. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.27 (d,  $J = 8.6$  Hz, 2H, H ar), 6.71 (d,  $J = 8.8$  Hz, 2H, H ar), 5.34 (s, 1H, H<sub>1</sub>), 4.18 (s, 1H, H Man), 4.09 – 3.91 (m, 3H, 2 × H Man, H<sub>6a</sub>), 3.89 – 3.66 (m, 4H, H Man, H<sub>6b</sub>, OCH<sub>2</sub>), 1.70 (p,  $J = 6.5$  Hz, 2H, OCH<sub>2</sub>CH<sub>2</sub>), 1.46 – 1.21 (m, 10H, 5 × CH<sub>2</sub>), 0.87 (app. t, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 159.44 (C<sub>q</sub> ar), 134.79 (2 × C ar), 123.58 (C<sub>q</sub> ar), 115.33 (2 × C ar), 89.47 (C<sub>1</sub>), 73.39 (C Man), 72.65 (C Man), 72.15 (C Man), 68.19 (OCH<sub>2</sub>), 66.46 (C Man), 61.11 (C<sub>6</sub>), 31.99 (CH<sub>2</sub>), 29.57 (OCH<sub>2</sub>CH<sub>2</sub>), 29.41 (2 × CH<sub>2</sub>), 26.19 (CH<sub>2</sub>), 22.81 (CH<sub>2</sub>), 14.25 (CH<sub>2</sub>).

**1,2,4,6-Tetra-O-benzoyl-3-O-benzyl-β-D-glucopyranose (17)** – [CAS Registry Number 30572-04-4, 182698-05-1] To a solution of 1,2:5,6-di-O-isopropylidene-α-D-glucopyranose (40 g, 0.1538 mol, 1 equiv) in dry DMF (500 mL) was added under argon benzyl bromide (28 mL, 0.230 mol, 1.5 equiv). Sodium hydride 60% in mineral oil (12.3 g, 0.3076 mol, 2 equiv) was added portionwise over a period of 45 minutes and the mixture was stirring for 2h at room temperature. Sodium hydride was then carefully neutralized with MeOH (100 mL) and the solvents were removed under reduced pressure. The residue obtained was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (400 mL), washed with water (200 mL) and the organic layer was dried over magnesium sulfate and concentrated. The residue was dissolved in H<sub>2</sub>O (400 mL) and Amberlite IR-120 H<sup>+</sup> resin (80 g) was added. The mixture was stirring under reflux overnight and the resin was filtered off under Celite. The filtrate containing the 3-O-benzyl-α,β-D-glucopyranose was concentrated and the residue was drying overnight under P<sub>2</sub>O<sub>5</sub>. The orange solid obtained was dissolved in pyridine (300 mL) and benzoyl chloride (107 mL, 0.923 mol, 6 equiv) was slowly added under argon at 0°C in the presence of cat amount of DMAP. The reaction mixture was stirred 3 h at room temperature and concentrated. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (400 mL), washed with aq 1M HCl (2 200 mL) and sat aq NaHCO<sub>3</sub>. The final organic layer was dried over magnesium sulfate and concentrated. Ethanol was added to the residue obtained to precipitate the compound which after filtration and drying gives **17** as a white powder (37.5 g, 36% (3 steps)). <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ 8.09 – 7.95 (m, 8H, H ar), 7.68 – 7.33 (m, 12H, H ar), 7.03 (app. s, 5H, H ar), 6.20 (d,  $J = 7.8$  Hz, 1H, H<sub>1</sub>), 5.84 – 5.66 (m, 2H, H<sub>2</sub>, H<sub>4</sub>), 4.66 (s, 2H, CH<sub>2</sub>), 4.62 (d,  $J = 2.8$  Hz, 1H, H<sub>6a</sub>), 4.45 (dd,  $J = 12.2, 4.9$  Hz, 1H, H<sub>6b</sub>), 4.34 – 4.23 (m, 1H, H<sub>5</sub>), 4.23 (t,  $J = 8.6$  Hz, 1H, H<sub>3</sub>). <sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>) δ 166.3 (CO Bz), 165.1 (CO Bz), 164.9 (CO Bz), 137.1 – 127.9 (C ar), 92.7 (C<sub>1</sub>), 79.3 (C<sub>3</sub>), 74.4 (CH<sub>2</sub>), 73.2 (C<sub>5</sub>), 72.2 (C<sub>2</sub>), 70.4 (C<sub>4</sub>), 63.0 (C<sub>6</sub>).

***p*-Octyloxyphenyl 6-O-fluorenylmethoxycarbonyl-1-thio-β-D-glucopyranoside (18)** - To a solution of **14** (4.82 g, 12.04 mmol, 1 equiv.) in dry CH<sub>2</sub>Cl<sub>2</sub> (40 mL) was added 2,4,6-collidine (7.9 mL, 60.2 mmol, 5 equiv.). The mixture was warmed

(40°C) to facilitate solubilization then Fmoc-Cl (4.65 g, 18.06 mmol, 1.5 equiv.) was added. The reaction was stirred for 2 hours at room temperature then diluted with CH<sub>2</sub>Cl<sub>2</sub>, washed with aq 1M HCl, and aq sat NaHCO<sub>3</sub> and brine. The organic layer was dried over magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (CyHex 100% then CyHex/AcOEt 20:80) to give **18** (5.03 g, 66%) as a white foam. *R*<sub>f</sub>: 0.35 (AcOEt 100%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.62 (d, *J* = 7.4 Hz, 2H, H ar Fmoc), 7.49 (d, *J* = 7.3 Hz, 2H, H ar Fmoc), 7.38 (d, *J* = 8.4 Hz, 2H, H ar thioaryl), 7.26 (t, *J* = 7.3 Hz, 2H, H ar Fmoc), 7.17 (t, *J* = 7.3 Hz, 2H, H ar Fmoc), 6.66 (d, *J* = 8.3 Hz, 2H, H ar thioaryl), 4.57 – 4.18 (m, 5H, H<sub>1</sub>, H<sub>6</sub>, CH<sub>2</sub> Fmoc), 4.12 (t, *J* = 7.3 Hz, 1H, CH Fmoc), 3.65 (t, *J* = 6.3 Hz, 2H, OCH<sub>2</sub>), 3.60 – 3.24 (m, 3H, H<sub>2</sub>, H<sub>3</sub>, H<sub>4</sub>), 1.71 – 1.47 (m, 2H, OCH<sub>2</sub>CH<sub>2</sub>), 1.14 (br s, 10H, 5 × CH<sub>2</sub>), 0.78 (t, *J* = 6.5 Hz, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 159.8 (CO Fmoc), 155.6 (C<sub>q</sub> ar), 143.4 (C<sub>q</sub> ar), 143.4 (C<sub>q</sub> ar), 141.3 (C<sub>q</sub> ar), 135.5 (C ar), 132.8 (C ar), 127.9 (C ar), 127.3 (C ar), 125.3 (C ar), 121.6 (C<sub>q</sub> ar), 120.1 (C ar), 115.4 (C ar), 115.3 (C ar), 115.2 (C ar), 88.4 (C<sub>1</sub>), 77.8 (C<sub>sugar</sub>), 77.5 (C<sub>sugar</sub>), 72.0 (C<sub>sugar</sub>), 70.3 (CH<sub>2</sub> Fmoc), 70.0 (C<sub>sugar</sub>), 68.1 (OCH<sub>2</sub>), 67.3 (C<sub>6</sub>), 46.8 (CH Fmoc), 31.9 (CH<sub>2</sub>), 29.5 (CH<sub>2</sub>), 29.3 (CH<sub>2</sub>), 29.3 (CH<sub>2</sub>), 26.1 (CH<sub>2</sub>), 22.7 (CH<sub>2</sub>), 14.2 (CH<sub>3</sub>).

***p*-Octyloxyphenyl 4,6-O-benzylidene-1-thio-β-D-glucopyranoside (19) - 13** (12.50g, 20.01 mmol, 1 equiv.) was deacetylated and the residue was dissolved in acetonitrile (110 mL) in the presence of camphorsulfonic acid (1.68 g, 8.804 mmol, 0.4 equiv.) and benzaldehyde dimethyl acetal (10 mL, 66.04 mmol, 3 equiv.). The mixture was refluxed for 3 hours then triethylamine (1.5 mL, 11.00 mmol, 0.5 mmol) was added. The reaction mixture was concentrated and the residue was purified by column chromatography on silica gel (CyHex / AcOEt 70:30) to give pure **19** as a white solid (7.70 g, 72%, 2 steps). APCI-HRMS *m/z* [M+H]<sup>+</sup> calculated for C<sub>27</sub>H<sub>37</sub>O<sub>6</sub>S: 489.2305, found: 489.2305. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.56 – 7.40 (m, 4H, H ar), 7.40 – 7.31 (m, 3H, H ar), 6.93 – 6.81 (m, 2H, H ar), 5.49 (s, 1H, H benzylidene), 4.45 (d, *J* = 9.6 Hz, 1H, H<sub>1</sub>), 4.35 (dd, *J* = 10.5, 4.3 Hz, 1H, H<sub>6a</sub>), 3.95 (t, *J* = 6.6 Hz, 2H, OCH<sub>2</sub>), 3.84 – 3.67 (m, 2H, H<sub>4</sub>, H<sub>6b</sub>), 3.50 – 3.41 (m, 2H, H<sub>5</sub>, H<sub>3</sub>), 3.36 (dd, *J* = 9.6, 8.5 Hz, 1H, H<sub>2</sub>), 2.96 (br s, 2H, OH), 1.79 (p, *J* = 6.6 Hz, 2H, OCH<sub>2</sub>CH<sub>2</sub>), 1.55 – 1.22 (m, 10H, 5 × CH<sub>2</sub>), 0.98 – 0.82 (m, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 160.1 (C<sub>q</sub> ar), 137.0 (C<sub>q</sub> ar), 136.3 (C ar), 129.4 (C ar), 128.5 (C ar), 126.4 (C ar), 120.5 (C<sub>q</sub> ar), 115.3 (C ar), 102.0 (C benzylidene), 88.8 (C<sub>1</sub>), 80.4 (C<sub>3</sub> or C<sub>5</sub>), 74.6 (C<sub>4</sub>), 72.4 (C<sub>2</sub>), 70.6 (C<sub>3</sub> or C<sub>5</sub>), 68.7 (C<sub>6</sub>), 68.3 (OCH<sub>2</sub>), 31.9 (CH<sub>2</sub>), 29.5 (OCH<sub>2</sub>CH<sub>2</sub>), 29.4 (CH<sub>2</sub>), 29.3 (CH<sub>2</sub>), 26.2 (CH<sub>2</sub>), 22.8 (CH<sub>2</sub>), 14.2 (CH<sub>3</sub>).

***p*-Octyloxyphenyl 2,3-di-O-benzoyl-4,6-O-benzylidene-1-thio-β-D-glucopyranoside (20)** - To a solution of pure **19** (7.70 g, 15.77 mmol, 1 equiv.) in dry CH<sub>2</sub>Cl<sub>2</sub> (80 mL) under argon were added benzoic anhydride (15.85 g, 47.31 mmol, 3 equiv.), triethylamine (8.8 mL, 63.08 mmol, 4 equiv.) and DMAP (385 mg, 3.154 mmol, 0.2 equiv.). The reaction was stirred at room temperature overnight, diluted with CH<sub>2</sub>Cl<sub>2</sub>, washed with aq 1M HCl and aq sat NaHCO<sub>3</sub>. The organic layer was dried over magnesium sulfate and concentrated. The residue was mixed with MeOH 300 mL (sonication) then was kept at 7 °C for 1 hour and the solid was filtered and dried under vacuum giving pure **20** as a white solid (7.96 g, 73%). APCI-HRMS *m/z* [M+H]<sup>+</sup> calculated for C<sub>41</sub>H<sub>45</sub>O<sub>8</sub>S: 697.2830, found: 697.2833. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.99 (d, *J* = 7.5 Hz, 2H, H ar), 7.93 (d, *J* = 7.5 Hz, 2H, H ar), 7.60 – 7.28 (m, 13H, H ar), 6.84 (d, *J* = 8.6 Hz, 2H, H ar), 5.77 (t, *J* = 9.4 Hz, 1H, H<sub>3</sub>), 5.52 (s, 1H, H benzylidene), 5.41 (t, *J* = 9.5 Hz, 1H, H<sub>2</sub>), 4.88 (d, *J* = 10.0 Hz, 1H, H<sub>1</sub>), 4.45 (dd, *J* = 10.4, 4.6 Hz, 1H, H<sub>6a</sub>), 3.95 (t, *J* = 6.5 Hz, 2H, OCH<sub>2</sub>), 3.91 – 3.79 (m, 2H, H<sub>4</sub>, H<sub>6b</sub>), 3.79 – 3.64 (m, 1H, H<sub>5</sub>), 1.88 – 1.73 (m, 2H, OCH<sub>2</sub>CH<sub>2</sub>), 1.54 – 1.19 (m, 10H, 5 × CH<sub>2</sub>), 0.99 – 0.84 (m, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 165.7 (CO Bz), 165.3 (CO Bz), 160.2 (C<sub>q</sub> ar), 136.9 (C<sub>q</sub> ar), 136.6 (C ar), 133.4 (C ar), 133.2 (C ar), 130.7 (C ar), 130.0 (C ar), 129.9 (C ar), 129.6 (C<sub>q</sub> ar), 129.5 (C<sub>q</sub> ar), 129.2 (C ar), 128.5 (C ar), 128.4 (C ar), 128.3 (C ar), 126.3 (C ar), 121.1 (C<sub>q</sub> ar), 115.1 (C ar), 101.6 (C benzylidene), 87.4 (C<sub>1</sub>), 78.7 (C<sub>4</sub>), 73.5 (C<sub>3</sub>), 71.2 (C<sub>2</sub> or C<sub>5</sub>), 71.0 (C<sub>2</sub> or C<sub>5</sub>), 68.7 (C<sub>6</sub>), 68.3 (OCH<sub>2</sub>), 32.0 (CH<sub>2</sub>), 29.5 (OCH<sub>2</sub>CH<sub>2</sub>), 29.4 (CH<sub>2</sub>), 29.3 (CH<sub>2</sub>), 26.2 (CH<sub>2</sub>), 22.8 (CH<sub>2</sub>), 14.2 (CH<sub>3</sub>).

***p*-Octyloxyphenyl 2,3-di-O-benzoyl-4-O-benzyl-1-thio-β-D-glucopyranoside (21)** – compound **20** (4.00 g, 5.747 mmol, 1 equiv.) was dissolved under argon in a borane tetrahydrofuran complex solution 1.0 M in THF (29 mL, 28.74 mmol, 5 equiv.) followed by the addition of TMSOTf (156 μL, 0.862 mmol, 0.15 equiv.). The reaction was stirred for 5 hours at room temperature under argon then neutralized by the addition of triethylamine (240 μL, 1.724 mmol, 0.3 equiv.) followed by the slow and careful addition of methanol. The mixture was concentrated and the residue was coevaporated with MeOH (5 × 50 mL). The final residue was purified by column chromatography on silica gel (CyHex / AcOEt 85:15) to give pure **21** (3.23 g, 84%) as a clear white oil. ESI-HRMS *m/z* [M+Na]<sup>+</sup> calculated for C<sub>41</sub>H<sub>46</sub>NaO<sub>8</sub>S: 721.2806, found: 721.2806. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.00 – 7.94 (m, 2H, H ar), 7.94 – 7.87 (m, 2H, H ar), 7.57 – 7.45 (m, 2H, H ar), 7.44 – 7.32 (m, 6H, H ar), 7.19 – 7.09 (m, 5H, H ar), 6.87 – 6.80 (m, 2H, H ar), 5.72 (t, *J* = 9.4 Hz, 1H, H<sub>3</sub>), 5.36 – 5.22 (m, 1H, H<sub>2</sub>), 4.81 (d, *J* = 9.9 Hz, 1H, H<sub>1</sub>), 4.57 (s, 2H, CH<sub>2</sub> Bn), 4.02 – 3.91 (m, 3H, OCH<sub>2</sub>, H<sub>6a</sub>), 3.87 (t, *J* = 9.5 Hz, 1H, H<sub>4</sub>), 3.83 – 3.73 (m, 1H, H<sub>6b</sub>), 3.67 – 3.56 (m, 1H, H<sub>5</sub>), 1.97 (br s, 1H, OH), 1.78 (p, *J* = 6.6 Hz, 2H, OCH<sub>2</sub>CH<sub>2</sub>), 1.54 – 1.21 (m, 10H, 5 × CH<sub>2</sub>), 0.97 – 0.84 (m, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 165.8 (CO Bz), 165.4 (CO Bz), 160.1 (C<sub>q</sub> ar), 137.2 (C<sub>q</sub> ar), 136.3 (C ar), 133.3 (C ar), 133.3 (C ar), 130.0 (C ar), 129.8 (C ar), 129.5 (C<sub>q</sub> ar), 129.5 (C<sub>q</sub> ar), 128.5 (C ar), 128.3 (C ar), 128.1 (C ar), 121.3 (C<sub>q</sub> ar), 115.2 (C ar), 86.5 (C<sub>1</sub>), 79.6 (C<sub>5</sub>), 76.4 (C<sub>3</sub>), 75.5 (C<sub>4</sub>), 75.0 (CH<sub>2</sub> Bn), 71.0 (C<sub>2</sub>), 68.2 (OCH<sub>2</sub>), 61.9 (C<sub>6</sub>), 31.9 (CH<sub>2</sub>), 29.5 (OCH<sub>2</sub>CH<sub>2</sub>), 29.3 (CH<sub>2</sub>), 26.2 (CH<sub>2</sub>), 22.8 (CH<sub>2</sub>), 14.2 (CH<sub>3</sub>).

**Ethyl 4-(3-Hydroxypropyloxy)benzoate (22)** – [CAS Registry Number 46731-01-5] - A solution of ethyl 4-hydroxybenzoate (10.0 g, 60.24 mmol, 1 equiv.), 3-chloro-1-propanol (5.04 mL, 60.24 mmol, 1 equiv.) and anhydrous potassium carbonate (12.5 g, 90.36 mmol, 1.5 equiv.) in methyl ethyl ketone (75 mL) was refluxed for 2 days. The mixture was cooled down at room temperature then water was added (75 mL). The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 50mL). The combined organic layers were dried over magnesium sulfate, and concentrated. The residue was purified by column chromatography on silica gel (Cyhex 100% then CyHex/AcOEt 70:30) to give **22** (7.2 g, 53%) as a white solid. ESI-HRMS *m/z* [M+H]<sup>+</sup> calculated for C<sub>12</sub>H<sub>17</sub>O<sub>4</sub>: 225.1121, found: 225.1122. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.08 – 7.88 (m, 2H, H ar), 7.00 – 6.80

(m, 2H, H ar), 4.33 (q,  $J = 7.2$  Hz, 2H, CH<sub>2</sub> ethyl), 4.16 (t,  $J = 6.1$  Hz, 2H, CH<sub>2</sub> CH<sub>2</sub>-O-), 3.86 (t,  $J = 5.9$  Hz, 2H, CH<sub>2</sub>-OH), 2.19 – 1.95 (m, 2H, CH<sub>2</sub> propyl), 1.37 (t,  $J = 7.1$  Hz, 3H, CH<sub>3</sub> Ethyl). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 166.5 (CO ester), 162.6 (C<sub>q</sub> ar), 131.7 (C ar), 123.1 (C<sub>q</sub> ar), 114.3 (C ar), 65.6 (CH<sub>2</sub>-O-), 60.8 (CH<sub>2</sub> ethyl), 60.1 (CH<sub>2</sub>-OH), 32.0 (CH<sub>2</sub> propyl), 14.5 (CH<sub>3</sub> ethyl).

**Ethyl 4-(3-((tetrahydro-2H-pyran-2-yl)oxy) propoxy) benzoate (23)** - To a solution of **22** (3.15 g, 14.04 mmol, 1 equiv.) and 3,4-sihydro-2H-pyran (3.9 mL, 42.13 mmol, 3 equiv) in freshly distilled CH<sub>2</sub>Cl<sub>2</sub> (35mL) was added camphorsulfonic acid (326mg, 1.40 mmol, 0.1 equiv.) under argon. The reaction was stirred for 3 hours at room temperature under argon then neutralized with N(Et)<sub>3</sub> (390 μl, 2.80 mmol, 0.2 equiv.). The solution was diluted with CH<sub>2</sub>Cl<sub>2</sub> then washed with water and a saturated solution of sodium bicarbonate. The organic layer was dried over magnesium sulfate, and concentrated. The residue obtained was purified by column chromatography on silica gel (Cyhex 100% then CyHex/AcOEt 95: 5) to give **23** (3.63 g, 84%) as a clear white oil. *R*<sub>f</sub>: 0.18 (CyHex/AcOEt 95: 5). APCI- HRMS *m/z* [M+H]<sup>+</sup> calculated for C<sub>17</sub>H<sub>25</sub>O<sub>5</sub>: 309.1697, found: 309.1696. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.07 – 7.91 (m, 2H, H ar), 6.99 – 6.85 (m, 2H, H ar), 4.59 (t,  $J = 3.4$  Hz, 1H, CH THP), 4.34 (q,  $J = 7.1$  Hz, 2H, CH<sub>2</sub> ethyl), 4.13 (t,  $J = 6.3$  Hz, 2H, CH<sub>2</sub>-O-), 3.93 (dt,  $J = 9.8, 6.1$  Hz, 1H, CH<sub>a</sub>H<sub>b</sub>-OTHP), 3.88 – 3.78 (m, 1H, CH<sub>a</sub>H<sub>b</sub> THP), 3.57 (dt,  $J = 9.8, 6.1$  Hz, 1H, CH<sub>a</sub>H<sub>b</sub>-OTHP), 3.53 – 3.43 (m, 1H, CH<sub>a</sub>H<sub>b</sub> THP), 2.09 (p,  $J = 6.2$  Hz, 2H, CH<sub>2</sub> propyl), 1.91 – 1.44 (m, 6H, 3 x CH<sub>2</sub> THP), 1.37 (t,  $J = 7.2$  Hz, 3H, CH<sub>3</sub> ethyl). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 166.5 (CO ester), 162.9 (C<sub>q</sub> ar), 131.6 (Car), 122.9 (C<sub>q</sub> ar), 114.2 (Car), 99.1 (CH THP), 65.3 (CH<sub>2</sub>-O-), 64.0 (CH<sub>2</sub> THP or CH<sub>2</sub>-OTHP), 62.5 (CH<sub>2</sub> THP or CH<sub>2</sub>-OTHP), 60.7 (CH<sub>2</sub> ethyl), 30.8 (CH<sub>2</sub> propyl), 29.7 (CH<sub>2</sub> THP), 25.6 (CH<sub>2</sub> THP), 19.7 (CH<sub>2</sub> THP), 14.5 (CH<sub>3</sub> ethyl).

**4-(3-((tetrahydro-2H-pyran-2-yl)oxy)propoxy) benzoic acid (24)** – [CAS Registry Number 1535219-49-8] To a solution of **23** (1.34 g, 4.344 mmol, 1 equiv.) in a mixture of H<sub>2</sub>O / EtOH 1: 1 (20 mL) was added sodium hydroxide (868 mg, 21.42 mmol, 5 equiv.). The reaction mixture was heated at 60 °C for 5 hours then the pH was adjusted around 6-7 with aq 1M HCl and concentrated. The residue was extracted with CH<sub>2</sub>Cl<sub>2</sub> (5 x 20 mL). The organic layer was dried over magnesium sulfate and concentrated to afford **24** (924 mg, 76%) as a white solid. ESI-HRMS *m/z* [M-H]<sup>-</sup> calculated for C<sub>15</sub>H<sub>19</sub>O<sub>5</sub>: 279.1238, found: 279.1240. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.05 (d,  $J = 8.9$  Hz, 2H, Har), 6.94 (d,  $J = 8.9$  Hz, 2H, H ar), 4.61 (t,  $J = 3.4$  Hz, 1H, CH THP), 4.16 (t,  $J = 6.3$  Hz, 2H, CH<sub>2</sub>-O-), 3.94 (dt,  $J = 9.9, 6.1$  Hz, 1H, CH<sub>a</sub>H<sub>b</sub>-OTHP), 3.90 – 3.79 (m, 1H, CH<sub>a</sub>H<sub>b</sub> THP), 3.59 (dt,  $J = 9.9, 6.1$  Hz, 1H, CH<sub>a</sub>H<sub>b</sub>-OTHP), 3.55 – 3.46 (m, 1H, CH<sub>a</sub>H<sub>b</sub> THP), 2.22 – 2.04 (m, 2H, CH<sub>2</sub> propyl), 1.93 – 1.67 (m, 2H, CH<sub>2</sub> THP), 1.67 – 1.46 (m, 4H, 2 x CH<sub>2</sub> THP). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 171.7 (COOH), 163.7 (C<sub>q</sub> ar), 132.5 (Car), 121.7 (C<sub>q</sub> ar), 114.4 (C ar), 99.1 (CH THP), 65.4 (CH<sub>2</sub>-O-), 63.9 (CH<sub>2</sub> THP or CH<sub>2</sub>-OTHP), 62.6 (CH<sub>2</sub> THP or CH<sub>2</sub>-OTHP), 30.8 (CH<sub>2</sub> propyl), 29.7 (CH<sub>2</sub> THP), 25.6 (CH<sub>2</sub> THP), 19.7 (CH<sub>2</sub> THP).

**Compound 25** - A solution of **24** (1.525 g, 5.446 mmol, 12 equiv), EDC. HCl (870 mg, 4.539 mmol, 10 equiv.) and DMAP (554 mg, 4.539 mmol, 10 equiv.) in dry DMF (10 mL) was firstly prepared. This solution was stirred and heated (40 °C) until solubilization of compounds. A second solution containing dipentaerythritol (115 mg, 0.4539 mmol, 1 equiv.) in dry DMF (10 mL) was prepared in parallel and heated until solubilization. Once solubilized the second solution was cool down at room temperature and added to the solution of activated acid. The final solution was stirred overnight at 50 °C under argon then concentrated. H<sub>2</sub>O (20 mL) was added to the residue and the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (5 x 10 mL). The organic layer was dried over magnesium sulfate, and concentrated. The residue was purified by column chromatography on silica gel (CyHex / AcOEt 60:40) to give pure compound **25** as a beige solid (574 mg, 70%). *R*<sub>f</sub>: 0.15 (CyHex / AcOEt 60:40) (ESI-HRMS *m/z* [M+NH<sub>4</sub>]<sup>+</sup> calculated for C<sub>100</sub>H<sub>134</sub>NO<sub>31</sub>: 1844.8934, found: 1844.8927. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.93 – 7.81 (m, 12H, H<sub>f</sub>), 6.92 – 6.71 (m, 12H, H<sub>g</sub>), 4.64 – 4.56 (m, 6H, CH THP), 4.52 (s, 12H, H<sub>c</sub>), 4.09 (t,  $J = 6.4$  Hz, 12H, H<sub>i</sub>), 3.92 (dt,  $J = 9.8, 6.1$  Hz, 6H, H<sub>k</sub>), 3.82 (ddd,  $J = 11.1, 7.8, 3.4$  Hz, 6H, 6 x CH<sub>1</sub>H<sub>2</sub> THP), 3.71 (s, 4H, H<sub>a</sub>), 3.56 (dt,  $J = 10.1, 6.2$  Hz, 6H, H<sub>k</sub>), 3.52 – 3.44 (m, 6H, 6 x CH<sub>1</sub>H<sub>2</sub> THP), 2.13 – 2.02 (m, 12H, H<sub>j</sub>), 1.87 – 1.64 (m, 12H, 6 x CH<sub>2</sub> THP), 1.64 – 1.44 (m, 24H, 12 x CH<sub>2</sub> THP). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 165.8 (C<sub>d</sub>), 163.0 (C<sub>e</sub>), 131.7 (C<sub>f</sub>), 122.0 (C<sub>h</sub>), 114.3 (C<sub>g</sub>), 99.1 (CH THP), 70.6 (C<sub>a</sub>), 65.3 (C<sub>i</sub>), 63.9 (C<sub>k</sub> or CH<sub>1</sub>H<sub>2</sub> THP), 63.3 (C<sub>e</sub>), 62.4 (C<sub>k</sub> or CH<sub>1</sub>H<sub>2</sub> THP), 44.0 (C<sub>b</sub>), 30.8 (6 x CH<sub>2</sub> THP), 29.6 (C<sub>j</sub>), 25.6 (6 x CH<sub>2</sub> THP), 19.7 (6 x CH<sub>2</sub> THP).

**Compound 26-** To a solution of compound **25** (574 mg, 0.3143 mmol, 1 equiv.) in a mixture of CH<sub>2</sub>Cl<sub>2</sub> / MeOH 1: 1 (10 mL) was added PTSA (30 mg, 0.1572 mmol, 0.5 equiv.). The reaction mixture was stirred at room temperature for 3 hours and concentrated. The residue was purified by column chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90:10) to give pure compound **26** as a white oil (334mg, 80%). *R*<sub>f</sub>: 0.35 (CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90:10) . <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.84 (d,  $J = 8.7$  Hz, 12H, H<sub>f</sub>), 6.78 (d,  $J = 8.7$  Hz, 12H, H<sub>g</sub>), 4.51 (s, 12H, H<sub>c</sub>), 4.10 (t,  $J = 6.0$  Hz, 12H, H<sub>i</sub>), 3.85 (t,  $J = 5.8$  Hz, 12H, H<sub>k</sub>), 3.71 (s, 4H, H<sub>a</sub>), 2.13 (br s, 6H, OH), 2.09 – 1.98 (m, 12H, H<sub>j</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 165.8 (C<sub>d</sub>), 162.8 (C<sub>e</sub>), 131.8 (C<sub>f</sub>), 122.2 (C<sub>h</sub>), 114.2 (C<sub>g</sub>), 70.5 (C<sub>a</sub>), 65.6 (C<sub>i</sub>), 63.6 (C<sub>e</sub>), 59.9 (C<sub>k</sub>), 44.0 (C<sub>b</sub>), 32.0 (C<sub>j</sub>).

**Compound 27** [CAS Registry Number 64340-67-6] -To a solution of dipentaerythritol (2.00 g, 7.87 mmol, 1 equiv.) in dry DMF (30 mL) was slowly added at 0 °C, sodium hydride (60% dispersion in mineral oil, 3.15 g, 78.7 mmol, 10 equiv.). After the end of the addition of sodium hydride the solution was stirred at 0 °C for 20 minutes. It was followed by the slow addition of allyl bromide (8.2 mL, 94.4 mmol, 12 equiv.) at 0°C. The reaction mixture was stirred for 5 hours at room temperature and quenched with methanol and concentrated. The residue was dissolved in AcOEt (50 mL) and washed with water (2 x 25 mL). The organic layer was dried over magnesium sulfate, filtered off and concentrated under reduced pressure to give **27** as a colorless oil (2.91 g, 75%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 5.87 (ddt,  $J = 17.2, 10.5, 5.3$  Hz, 6H), 5.31 – 5.02 (m, 12H), 3.93 (dt,  $J = 5.3, 1.5$  Hz, 12H), 3.43 (s, 12H), 3.39 (s, 4H).

**Compound 28** - **27** (2.89 g, 5.843 mmol, 1 equiv.) was dissolved in a solution of 9-BBN (0.5M) in THF (140 mL, 70.1 mmol, 2 equiv / Allyl). The solution was refluxed for 2 hours under argon. Then, the solution was cooled at 0 °C and the

excess of 9-BBN was quenched with cold water (45 mL). Then, sodium hydroxide 3M (150 mL) and hydrogen peroxide 35% wt (150 mL) were added carefully at 0 °C. The mixture was stirred from 0 °C to room temperature overnight and solid K<sub>2</sub>CO<sub>3</sub> was added until saturation. The top layer was discarded and the K<sub>2</sub>CO<sub>3</sub> containing layer was extracted with THF (3x100 mL). The resulting organic layer was dried over MgSO<sub>4</sub> and evaporated. The crude was purified by column chromatography on silica gel (DCM / MeOH 90:10) to get compound **28** (2.22 g, 63%) as a colorless oil. R<sub>f</sub>: 0.15 (CyHex/AcOEt 60:40). ESI-HRMS m/z [M+Na]<sup>+</sup> calculated for C<sub>28</sub>H<sub>58</sub>NaO<sub>13</sub>: 625.3770, found: 625.3768. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 3.70 (t, J = 5.5 Hz, 12H, H<sub>f</sub>), 3.54 (t, J = 5.6 Hz, 12H, H<sub>d</sub>), 3.36 (s, 12H, H<sub>c</sub>), 3.32 (s, 4H, H<sub>a</sub>), 3.23 (br s, 6H, OH), 1.84 – 1.71 (m, 12H, H<sub>e</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 70.9 (C<sub>e</sub>), 70.8 (C<sub>a</sub>), 70.3 (C<sub>d</sub>), 61.2 (C<sub>f</sub>), 45.2 (C<sub>b</sub>), 31.9 (C<sub>c</sub>).

**Compound 29-** A solution of **24** (541 mg, 1.934 mmol, 12 equiv), EDC HCl (309 mg, 1.611 mmol, 10 equiv.) and DMAP (197 mg, 1.611 mmol, 10 equiv.) in dry DMF (3 mL) was firstly prepared. This solution was stirred and warmed (40 °C) until solubilization of compounds. A second solution containing **28** (115 mg, 0.4539 mmol, 1 equiv.) in dry DMF (1 mL) was meantime prepared and heated until solubilization. Once solubilized the second solution was cooled down at room temperature and added to the solution of activated acid. The final solution was stirred overnight at 50 °C under argon then concentrated. The obtained residue was purified by column chromatography on silica gel (CyHex/AcOEt 60:40) to get **29** as a clear white oil (310 mg, 88%). R<sub>f</sub>: 0.45 (CyHex/AcOEt 60:40). APCI-HRMS m/z [M+NH<sub>4</sub>]<sup>+</sup> calculated for C<sub>118</sub>H<sub>170</sub>NO<sub>37</sub>: 2193.1446, found: 2193.1428. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.01 – 7.87 (m, 12H, H<sub>i</sub>), 6.97 – 6.81 (m, 12H, H<sub>j</sub>), 4.65 – 4.55 (m, 6H, CH THP), 4.31 (t, J = 6.5 Hz, 12H, H<sub>f</sub>), 4.10 (t, J = 6.3 Hz, 12H, H<sub>l</sub>), 3.91 (dt, J = 9.9, 6.2 Hz, 6H, H<sub>n</sub>), 3.82 (ddd, J = 11.1, 7.8, 3.4 Hz, 6H, CH THP), 3.56 (dt, J = 9.9, 6.2 Hz, 6H, H<sub>n</sub>), 3.52 – 3.43 (m, 18H, 6 × CH THP, H<sub>d</sub>), 3.38 (s, 12H, H<sub>c</sub>), 3.34 (s, 4H, H<sub>a</sub>), 2.17 – 2.00 (m, 12H, H<sub>m</sub>), 2.02 – 1.87 (m, 12H, H<sub>e</sub>), 1.88 – 1.62 (m, 22H), 1.62 – 1.44 (m, 24H, 12 × CH<sub>2</sub> THP). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 166.4 (C<sub>g</sub>), 162.9 (C<sub>h</sub> or C<sub>k</sub>), 131.6 (C<sub>i</sub>), 122.8 (C<sub>h</sub> or C<sub>k</sub>), 114.2 (C<sub>j</sub>), 99.1 (CH THP), 70.4 (C<sub>a</sub>), 70.0 (C<sub>c</sub>), 68.0 (H<sub>d</sub>), 65.2 (C<sub>l</sub>), 63.9 (C<sub>n</sub>), 62.5 (CH THP), 62.2 (H<sub>f</sub>), 45.8 (C<sub>b</sub>), 30.8 (CH THP), 29.7 (C<sub>m</sub>), 29.3 (C<sub>e</sub>), 25.6 (CH THP), 19.7 (CH THP).

**Compound 30 -** To a solution of compound **29** (238 mg, 0.1094 mmol, 1 equiv.) in a mixture of CH<sub>2</sub>Cl<sub>2</sub> / MeOH 1: 1 (10 mL) was added PTSA (10 mg, 0.0547 mmol, 0.5 equiv.). The reaction was stirred at room temperature for 3 hours and concentrated. The residue was purified by column chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90:10) to give pure compound **30** as a beige solid (150mg, 82%). R<sub>f</sub>: 0.39 (CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90:10). ESI-HRMS m/z [M+Na]<sup>+</sup> calculated for C<sub>88</sub>H<sub>118</sub>NaO<sub>31</sub>: 1693.7549, found: 1693.7547. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.94 (d, J = 8.5 Hz, 12H, H<sub>i</sub>), 6.88 (d, J = 8.7 Hz, 12H, H<sub>j</sub>), 4.31 (t, J = 6.3 Hz, 12H, H<sub>f</sub>), 4.12 (t, J = 6.0 Hz, 12H, H<sub>l</sub>), 3.85 (t, J = 5.8 Hz, 12H, H<sub>n</sub>), 3.49 (t, J = 5.9 Hz, 12H, H<sub>d</sub>), 3.39 (s, 12H, H<sub>c</sub>), 3.35 (s, 4H, H<sub>a</sub>), 2.16 – 1.99 (m, 12H, H<sub>m</sub> or H<sub>e</sub>), 1.99 – 1.87 (m, 12H, H<sub>m</sub> or H<sub>e</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 166.5 (C<sub>g</sub>), 162.8 (C<sub>h</sub> or C<sub>k</sub>), 132.7 (C<sub>i</sub>), 123.0 (C<sub>h</sub> or C<sub>k</sub>), 114.2 (C<sub>j</sub>), 70.3 (C<sub>a</sub>), 70.0 (C<sub>c</sub>), 67.9 (C<sub>d</sub>), 65.5 (C<sub>l</sub>), 62.2 (C<sub>f</sub>), 59.8 (C<sub>n</sub>), 45.8 (C<sub>b</sub>), 32.0 (C<sub>m</sub> or C<sub>e</sub>), 29.24 (C<sub>m</sub> or C<sub>e</sub>).

**Compound 31-** A solution of EDC.HCl (35 mg, 180 μmol, 10 equiv.) and DMAP (22 mg, 180 μmol, 10 equiv.) in dry DMF (500 μL) was previously heated until solubilization of compounds. Then the resulting solution was added to a solution of compound **30** (30 mg, 18 μmol, 1 equiv.) and (S)-N-(2-nitrophenyl) proline (51 mg, 215 μmol, 12 equiv.) in dry DMF (500 μL). The reaction was heated overnight at 50°C under argon and concentrated. The residue was purified by column chromatography on silica gel (CyHex / AcOEt 50:50) to give pure yellow tracer **31** (20 mg, 37%). ESI-HRMS m/z [M+H]<sup>2+</sup> calculated for C<sub>154</sub>H<sub>179</sub>N<sub>12</sub>O<sub>49</sub>: 1490.0936, found: 1490.0945. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.98 – 7.87 (m, 12H, H<sub>i</sub>), 7.62 (dd, J = 8.2, 1.6 Hz, 6H, H ar), 7.31 – 7.18 (m, 6H, H ar), 6.85 – 6.74 (m, 18H, H<sub>j</sub>, H ar), 6.69 (ddd, J = 8.2, 7.2, 1.1 Hz, 6H, H ar), 4.44 – 4.37 (m, 6H, H<sub>p</sub>), 4.32 (t, J = 6.5 Hz, 12H, H<sub>f</sub>), 4.29 – 4.17 (m, 12H, H<sub>n</sub>), 3.97 – 3.79 (m, 12H, H<sub>l</sub>), 3.56 – 3.44 (m, 18H, h<sub>d</sub>, H<sub>s</sub>-), 3.40 (s, 12H, H<sub>c</sub>), 3.36 (s, 4H, H<sub>a</sub>), 3.17 – 3.08 (m, 6H, H<sub>s</sub>-), 2.48 – 2.35 (m, 6H, H<sub>q</sub>'), 2.14 – 1.85 (m, 42H, H<sub>e</sub>, H<sub>m</sub>, H<sub>q</sub>', H<sub>r</sub>).

#### General procedure for supported synthesis of glucan β(1-6) tetrasaccharide:

A solution of soluble polyol core **30** (1 equiv.) and donor **9** (1.5 equiv. up to 2.0 equiv. / hydroxyl group -1.5 equiv. of donor was used for synthesis of supported mono-, di-, and tri- saccharide. 2.0 was then used for tetrasaccharide preparation. -) in dry CH<sub>2</sub>Cl<sub>2</sub> ([donor] = 0.1M) under argon was previously cool down in an ice bath. Then NIS (1.2 equiv. / donor) was added followed by TfOH (0.3 equiv. / donor). The reaction was stirred under argon for 1h at room temperature then neutralized with piperidine (0.5 mL). The mixture was then stirred for 1h and solvents were removed under vacuum to dryness -2.0 mg of “yellow tracer” **31** was added in the crude after first glycosylation. The yellow color was visible all the time during purification on size exclusion and there was no need to add supplementary yellow tracer.

The residue was dissolved in a minimum of CH<sub>2</sub>Cl<sub>2</sub> / MeOH 1: 1 v/v then applied on a column chromatography (length: 400 mm, diameter: 35 mm) filled with Sephadex LH20 equilibrated with CH<sub>2</sub>Cl<sub>2</sub> / MeOH 1:1 v/v. and eluted with the same CH<sub>2</sub>Cl<sub>2</sub> / MeOH mixture with a flow of around 2 mL.min<sup>-1</sup> and fraction volumes not exceeding 2 mL. The first colored fractions are kept and checked on a TLC plate for carbohydrate contents (H<sub>2</sub>SO<sub>4</sub>). The protocol was repeated 4 times, starting from 40 mg (0.02394 mmol) of **30** giving after LH20; 91 mg, 134 mg, 170 mg and 205 mg corresponding respectively to supported mono **32** (86%), di **33** (91%), tri **34** (92%) and tetra saccharide **35** (94%). Every supported intermediate oligosaccharide was analyzed on NMR <sup>13</sup>C with special attention around area of 100 ppm to identify formation of anomer carbons.

**Compound 36 -** To a suspension of supported tetrasaccharide **35** (205 mg, 16.12 μmol) in a mixture of dry MeOH / THF 1: 1 (1.5 mL) at 0 °C under argon was added carefully sodium (4 mg). The reaction mixture was stirred at 40 °C overnight under argon. The reaction was then neutralized with Amberlite IR 120 (H<sup>+</sup>) resin, and concentrated. The residue was then solubilized in the minimum of a CH<sub>2</sub>Cl<sub>2</sub> / MeOH 1: 1 mixture then applied on a column chromatography filled with Sephadex

LH20. The compounds were then eluted with a flow rate of CH<sub>2</sub>Cl<sub>2</sub> / MeOH 1: 1 of approximately 2 mL·min<sup>-1</sup> with volume of the fractions not exceeding 2 mL. Fractions were then spotted on TLC plate and eluted with CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90: 10 (revealed with H<sub>2</sub>SO<sub>4</sub> (10% in EtOH)). Tetrasaccharide **36** was obtained as a syrup (76 mg, 43% overall yield). Next eluted is the trisaccharide (13 mg). ESI-HRMS m/z [M+Na]<sup>+</sup> calculated for C<sub>63</sub>H<sub>78</sub>NaO<sub>24</sub>: 1241,4775, found: 1241.4786. <sup>1</sup>H NMR (300 MHz, MeOD) δ 7.96 (d, *J* = 9.0 Hz, 2H, H ar), 7.44 – 7.22 (m, 20H, H ar), 7.01 (d, *J* = 8.9 Hz, 2H), 5.02 – 4.88 (m, 4H, CH Bn), 4.75 – 4.58 (m, 4H, CH Bn), 4.38 – 4.27 (m, 3H, 3 × H<sub>1</sub>), 4.25 (d, *J* = 7.8 Hz, 1H, H<sub>1</sub>), 4.24 – 4.12 (m, 3H, H<sub>9</sub>, 1 × CH<sub>6a</sub>OGlc), 4.14 – 3.99 (m, 3H, H<sub>7a</sub>, 2 × CH<sub>6a</sub>OGlc), 3.86 (s, 3H, OMe), 3.83 – 3.71 (m, 5H, 3 × CH<sub>6b</sub>OGlc, CH<sub>6a</sub>OH, H<sub>7b</sub>), 3.66 (dd, *J* = 12.4, 5.1 Hz, 1H, CH<sub>6b</sub>OH), 3.64 – 3.19 (m, 16H, 4 × H<sub>2</sub>, 4 × H<sub>3</sub>, 4 × H<sub>4</sub>, 4 × H<sub>5</sub>), 2.20 – 2.03 (m, 2H, H<sub>8</sub>). <sup>13</sup>C NMR (75 MHz, MeOD) δ 168.5 (COOMe), 164.6 (C<sub>q</sub> ar), 140.1 (C<sub>q</sub> ar), 140.1 (C<sub>q</sub> ar), 132.6 (C ar), 129.4 (C ar), 129.3 (C ar), 129.3 (C ar), 129.2 (C ar), 129.2 (C ar), 129.1 (C ar), 129.1 (C ar), 128.7 (C ar), 128.6 (C ar), 123.4 (C<sub>q</sub> ar), 115.5 (C ar), 105.2 (C<sub>1</sub>), 105.0 (C<sub>1</sub>), 105.0 (C<sub>1</sub>), 104.4 (C<sub>1</sub>), 79.6 (C<sub>Glc</sub>), 79.6 (C<sub>Glc</sub>), 79.4 (C<sub>Glc</sub>), 79.2 (C<sub>Glc</sub>), 78.5 (3 × C<sub>Glc</sub>), 78.4 (C<sub>Glc</sub>), 77.1 (C<sub>Glc</sub>), 76.1 (C<sub>Glc</sub>), 76.0 (C<sub>Glc</sub>), 75.8 (C<sub>Glc</sub>), 75.8 (C<sub>Glc</sub>), 75.7, 75.7 (2 × CH<sub>2</sub> Bn), 75.4 (C<sub>Glc</sub>), 75.3 (2 × C<sub>Glc</sub>), 75.3 (C<sub>Glc</sub>), 70.3 (C<sub>6</sub>), 70.2 (C<sub>6</sub>), 69.8 (C<sub>6</sub>), 67.6 (C<sub>7</sub>), 66.5 (C<sub>9</sub>), 62.4 (C<sub>6</sub> OH), 52.3 (OMe), 30.7 (C<sub>8</sub>).

Compound **37** - To a solution of tetrasaccharide **36** (65 mg, 53.37 μmol) in a mixture of dry THF / MeOH 1: 1 (2 mL) was added palladium on carbon 10% weight (30 mg). The reaction was stirred under a dihydrogen atmosphere at 5 bars for 4 h. The reaction was then filtered off under Celite® and concentrated. The residue was then purified by preparative HPLC (column: C18-Nucleodur (21×250 mm; 5 μm); flow rate: 14 mL·min<sup>-1</sup>; eluents: H<sub>2</sub>O + 0.1% TFA v/v and MeCN + 0.1% TFA) then freeze-dried to afford fully deprotected tetrasaccharide **37** as a white foam (37 mg, 80%). ESI-HRMS m/z [M+Na]<sup>+</sup> calculated for C<sub>35</sub>H<sub>54</sub>NaO<sub>24</sub>: 881.2897, found: 881.2899. <sup>1</sup>H NMR (400 MHz, MeOD) δ 8.02 – 7.84 (m, 2H, H ar), 7.08 – 6.91 (m, 2H, H ar), 4.42 – 4.36 (m, 3H, 3 × H<sub>1</sub>), 4.32 (d, *J* = 7.8 Hz, 1H, H<sub>1</sub>), 4.24 – 4.12 (m, 5H, 3 × CH<sub>6a</sub>OGlc, H<sub>9</sub>), 4.06 (dt, *J* = 10.1, 6.0 Hz, 1H, H<sub>7a</sub>), 3.86 (app. s, 4H, OMe, CH<sub>6a</sub>OH), 3.82 – 3.74 (m, 4H, 3 × CH<sub>6b</sub>OGlc, H<sub>7b</sub>), 3.70 (dd, *J* = 11.8, 5.0 Hz, 1H, CH<sub>6b</sub>OH), 3.56 – 3.43 (m, 3H, 3 × H<sub>5</sub>), 3.42 – 3.17 (m, 13H, 4 × H<sub>2</sub>, 4 × H<sub>3</sub>, 4 × H<sub>4</sub>, 1 × H<sub>5</sub>), 2.16 – 2.05 (m, 2H, H<sub>8</sub>). <sup>13</sup>C NMR (101 MHz, MeOD) δ 168.5 (COOMe), 164.5 (C<sub>q</sub> ar), 132.6 (C ar), 123.3 (C<sub>q</sub> ar), 115.4 (C ar), 104.9 (1 × C<sub>1</sub>), 104.9 (2 × C<sub>1</sub>), 104.4 (1 × C<sub>1</sub>), 77.9 (4 × C<sub>3</sub> or 4 × C<sub>4</sub>), 77.0 (C<sub>5</sub>), 76.9 (C<sub>5</sub>), 76.8 (C<sub>5</sub>), 75.0 (4 × C<sub>2</sub>), 71.6 (C<sub>5</sub>), 71.5 (4 × C<sub>3</sub> or 4 × C<sub>4</sub>), 70.4 (C<sub>6</sub>), 70.3 (C<sub>6</sub>), 70.0 (C<sub>6</sub>), 67.5 (C<sub>7</sub>), 66.4 (C<sub>9</sub>), 62.7 (C<sub>6</sub>OH), 52.4 (OMe), 30.7 (C<sub>8</sub>).

Compound **38** - Tetrasaccharide **37** (20 mg, 23 μmol) was solubilized in propargyl alcohol (2mL) previously dried over molecular sieves 4 Å. The mixture was then cooled down at 0 °C in an ice bath then sodium (2mg) was added. After the end of the dihydrogen release, the mixture was heated at 90°C for 90 minutes under argon. The reaction was neutralized with Amberlite IR 120 (H<sup>+</sup>) resin, filtered off and propargyl alcohol was evaporated under vacuum. The resulting tetrasaccharide was purified by preparative HPLC (column: C18-Nucleodur (21×250 mm; 5 μm); flow rate: 14 mL·min<sup>-1</sup>; eluents: H<sub>2</sub>O + 0.1% TFA v/v and MeCN + 0.1% TFA) then freeze-dried to afford tetrasaccharide **38** as a white foam (12 mg, 58%). APCI-HRMS m/z [M+NH<sub>4</sub>]<sup>+</sup> calculated for C<sub>37</sub>H<sub>58</sub>NO<sub>24</sub>: 900.3343, found: 900.3351. <sup>1</sup>H NMR (400 MHz, MeOD) δ 8.00 (d, *J* = 8.8 Hz, 2H, H ar), 7.06 (d, *J* = 8.9 Hz, 2H, H ar), 4.92 (d, *J* = 2.4 Hz, 2H, CH<sub>2</sub>), 4.45 – 4.37 (m, 3H, 3 × H<sub>1</sub>), 4.33 (d, *J* = 7.8 Hz, 1H, H<sub>1</sub>), 4.29 – 4.14 (m, 5H, 3 × CH<sub>6a</sub>OGlc, H<sub>9</sub>), 4.09 (dt, *J* = 10.4, 6.0 Hz, 1H, H<sub>7a</sub>), 3.92 – 3.86 (m, 1H, CH<sub>6a</sub>OH), 3.85 – 3.76 (m, 4H, 3 × CH<sub>6b</sub>OGlc, H<sub>7b</sub>), 3.70 (dd, *J* = 11.9, 5.0 Hz, 1H, CH<sub>6b</sub>OH), 3.56 – 3.45 (m, 3H, 3 × H<sub>5</sub>), 3.43 – 3.19 (m, 13H, 4 × H<sub>2</sub>, 4 × H<sub>3</sub>, 4 × H<sub>4</sub>, 1 × H<sub>5</sub>), 2.97 (t, *J* = 2.4 Hz, 1H, C≡CH), 2.20 – 2.08 (m, 1H, H<sub>8</sub>). <sup>13</sup>C NMR (151 MHz, MeOD) δ 167.0 (CO ester), 164.9 (C<sub>q</sub> ar), 132.8 (C ar), 122.8 (C<sub>q</sub> ar), 115.6 (C ar), 105.0 (C<sub>1</sub>), 104.9 (C<sub>1</sub>), 104.9 (C<sub>1</sub>), 104.5 (C<sub>1</sub>), 78.0 – 77.9 (4 × C<sub>3</sub> or 4 × C<sub>4</sub>), 77.1 (C<sub>5</sub>), 77.0 (C<sub>5</sub>), 76.9 (C<sub>5</sub>), 76.2 (C≡CH), 75.1–75.0 (4 × C<sub>2</sub>, 1 × C<sub>5</sub>), 71.7 (C<sub>3</sub> or C<sub>4</sub>), 71.7 (C<sub>3</sub> or C<sub>4</sub>), 71.6 (C<sub>3</sub> or C<sub>4</sub>), 71.6 (C<sub>3</sub> or C<sub>4</sub>), 70.5 (C<sub>6</sub>), 70.4 (C<sub>6</sub>), 70.0 (C<sub>6</sub>), 67.5 (C<sub>7</sub>), 66.5 (C<sub>9</sub>), 62.7 (C<sub>6</sub>OH), 53.0 (CH<sub>2</sub>), 30.7 (C<sub>8</sub>).

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