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Synthesis and characterization of a small library of bisglucosides: Influence of the nature of the diol/diphenol used in O-glucosylation

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ABSTRACT

In this paper, the synthesis of different bisglucosides is investigated through the reaction of two acetylated glucose units with a diol (or diphenol) in order to develop a versatile molecular platform for the future development of bio-based polymers. A panel of five diols and one diphenol is initially used in order to examine the influence of their chemical skeleton on the reaction yield and both nature and proportion of formed species. Reaction products are identified using ^{1}H and ^{13}C NMR spectroscopies completed by MALDI-TOF MS technique. The nucleophilicity of these dihydroxy compounds is identified as being the main factor that governs the reaction characteristics. In particular, the best selectivity is obtained with the use of hydroquinone. Inversely, by-products (oligomers, deacetylated compounds) are observed with the diols defined by higher nucleophilicity despite the choice of stereoselective pathway using acyl protecting groups.

1. Introduction

Over the last few decades, the development of biobased polymers arises a great interest in both scientific and industrial communities [1,2]. Different elements support researches in this area such the reduced dependence on petroleum and the implementation of new environmental and safety regulations. Then, the valorization of biobased (macro)molecules appears as a possible solution for reducing the use of toxic precursor compounds [3]. A more recent trend consists in creating innovative molecular building blocks to achieve the creation of custom-made polymers by controlling the chemical structure in order to obtain precise properties for specific use [4]. Among the different existing molecules, carbohydrates are worth of interest because they combine a high degree of functionality with a non-toxic cyclic structure [5]. The former characteristic offers a large range of possible reactions while the latter insures higher physical properties than that observed with aliphatic sequences. As proof of this, carbohydrate derivatives are already present into polymer formulations when high glass transition temperature T_g is required. For instance, they are used to produce thermoset polymeric formulations such as alkyd resins [6], polyurethanes [7] or epoxy resins [8]. Concerning this latter family, Pan et al. worked with commercial sucrose polyesters of fatty acids (SPEFAs) named as Sefose® by Procter & Gamble (P&G) Chemicals [9]. Using a classical peracetic pathway, these researchers produced epoxidized sucrose polyesters of fatty acids (ESPEFAs) and reacted them with cyclic anhydrides [10]. The resulting materials presented higher ultimate performances compared to that of materials derived from native Epoxidized Soybean Oil (ESO) cured with same hardeners. This hierarchy was justified by the presence of cyclic sucrose in ESPEFAs whereas ESO is made with aliphatic molecular segments. Unfortunately, this study was limited to the only family of unsaturated SPEFAs previously developed by P&G.

The boundaries of this concept are likely to be pushed back by the creation of other cyclic molecular cores to achieve the emergence of new performances. Such approach could be carried out through the prior synthesis of a little library of bisglucosides. We studied more particularly the production of this class of molecules through the reaction of a dihydroxy compound with two glucose units. This O-glucosylation process was investigated with various aliphatic diols and a diphenol. Indeed, O-glycosylation is not easy to be performed in organic chemistry because it is often accompanied by parasitic and complex mechanisms [11]. For this reason, different strategies are described in literature involving the pre-activation of the aglycone, Huisgen cycloaddition between alkynes and azides [12–15], olefin cross-metathesis [16], and Sonogashira coupling [17]. The use of protective participating groups (OAc) or non-participating groups (OBn) seems to be essential for conducting selective O-glycosylation. For instance, β-D-glucose pentaacetate

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Abbreviations

$BF_3{\cdot}OEt_2$ Boron trifluoride diethyl etherate
$BGP(OAc)_8$ BisGlucosidePropyl octaacetate
BGX BisGlucosideX
$BGX(OAc)_8$ BisGlucosideX octaacetate
BnD: *cis* 2-butene-1,4-diol
BPA Bisphenol A
ByD 2-butyne-1,4-diol
CHD Cyclohexanediol
DEG Diethylene glycol
DSC Differencial Scanning Calorimetry
$Glc(OAc)_5$ Glucose pentaacetate (α or/and β)
HD Homopolymerization Degree
HQ Hydroquinone
HRMS (ESI) High Resolution Mass Spectrometry (ElectroSpray Ionization)
FT-IR Fourier Transform InfraRed
MALDI-TOF MS Matrix Assisted Laser Desorption/Ionization - Time of flight – Mass Spectrometry
$MGP(OAc)_5$ MonoGlucosidePropyl pentaacetate
$MGX(OAc)_5$ MonoGlucosideX pentaacetate
NMR Nuclear Magnetic Resonance
OAc Acetate group $–O(CO)CH_3$
1,3-PD 1,3-propanediol
PDI PolyDispersity Index
pKa Constant of acidity
RWL: Relative weight loss
T_{deg} Degradation temperature
T_m Melting temperature
TGA ThermoGravimetric Analysis

β-$Glc(OAc)_5$ can be easily synthesized through a simple acetylation. It is also suitable with a one-step glycosylation that can be catalyzed by a Lewis-acid [18]. In literature, some works describe the bisglycosylation reaction between glycosyl peracetates with various diols in dichloromethane (CH_2Cl_2) as solvent and catalyzed by $BF_3{\cdot}OEt_2$ [19,20]. In fact, this catalyst is frequently used for phenol O-glycosylation [21]. It efficiently promotes the conversion of β-$Glc(OAc)_5$ into the corresponding aryl-O-glucosides with high yield and β-stereoselectivity [22]. Other Lewis acids are also employed but they induce the formation of complex mixtures [20] and even lead to lower reaction yield [23].

The nature of the solvent is another factor that has to be considered for performing O-glycosylation reaction. For instance, Mabic et al. described the coupling reaction between 3-methylcatechol and β-$Glc(OAc)_5$ in the presence of $BF_3{\cdot}OEt_2$ as an activator [24]. No coupling is observed when participating solvents are used such as diethyl ether, acetonitrile or tetrahydrofuran (THF). This result is probably the reason why CH_2Cl_2, a non-complexing solvent, is preferred. The configuration of the anomeric center is also dependent on the temperature used for the glucosylation. Temperatures lower than 30 °C favors β-glucoside formation while both anomeric compounds coexist at higher temperatures [25].

Despite these numerous researches, it is important to note that the collection of bivalent glycosides synthesized up to now remains rather limited. Most of the structures are derived from linear diols such as long-chain alkyl "$HO(CH_2)_{12}OH$" [26], alkynes with 2-butyne-l,4-diol [27] and polyethoxy with $HO(CH_2CH_2O)_5H$ [20]. Another researchers investigated the use of phenols [28]. Reported reaction yields are comprised between 11 and 81%. Within this context, we decided to conduct a more global study by building with an only pathway, a library of BisGlucosideX octaacetate with different spacers between two glucose units. Each of them was represented as $BGX(OAc)_8$ in which X would correspond to the diol or diphenol spacer (Fig. 1). The synthesis results were carefully discussed and interpreted on the basis of reliable molecular mechanisms.

2. Results and discussion

2.1. Conditions retained for the synthesis of BisGlucosideX octaacetate $BGX(OAc)_8$

Considering the data already published in literature and summarized hereabove, the synthesis of the $BGX(OAc)_8$ was conducted by reaction of β-$Glc(OAc)_5$ **1a** with a diol or a diphenol (HO-X-OH) **2a-f** in anhydrous CH_2Cl_2 as solvent, catalyzed by $BF_3{\cdot}OEt_2$ and at room temperature (Fig. 1). A molar ratio of the sugar donor/diol (or diphenol) acceptor was set to 1:0.5 in order to promote the formation of $BGX(OAc)_8$.

We chose to use different diols and one diphenol to investigate the effects and limitations of the selected glucosylation conditions (Fig. 2). The diols **2a-e** are based upon different aliphatic skeletons and are likely to present discrepancies in terms of molecular mobility. Indeed, compared to propane-1,3-diol (1,3-PD **2a**), diethylene glycol (DEG **2c**) is characterized by a longer linear sequence including a flexible ether hinge. 2-butyne-1,4-diol ByD (**2d**) and *cis*-2-butene-1,4-diol (BnD **2b**) have rigid unsaturations at the center of their molecular structure. A cycloaliphatic spacer is represented by 1,4-cyclohexanediol (CHD **2e)**

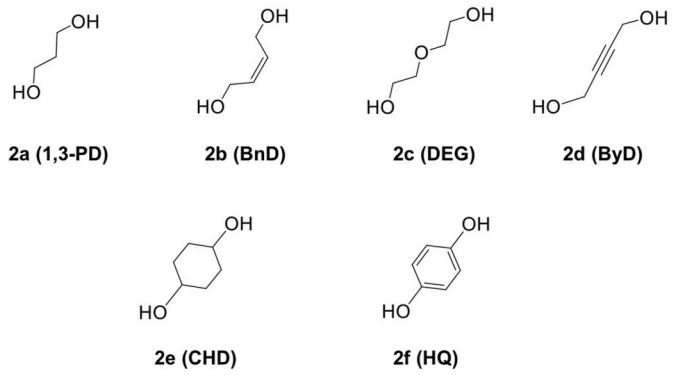


Fig. 2. Panel of dihydroxy compounds (**2a-f**) used in this study for O-glucosylation.

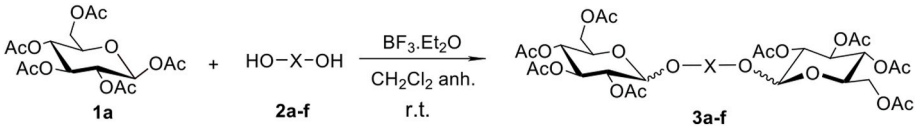


Fig. 1. General glucosylation of diols/diphenol (**2a-f**) with β-$Glc(OAc)_5$ (**1a**) promoted by $BF_3{\cdot}OEt_2$ for the production of BisGlucosideX octaacetate ($BGX(OAc)_8$ with X = aromatic chain, cycloaliphatic, aliphatic of variable length).

while hydroquinone (HQ **2f**) is the only diphenol employed in this work section.

2.2. Synthesis of BisGlucosidePropyl octaacetate BGP(OAc)$_8$

First experiments consisted in investigating the reaction kinetic of β-Glc(OAc)$_5$ **1a** with commercial 1,3-PD **2a** in order to define the time necessary for obtaining the optimal conversion rate of the chemicals used.

2.2.1. Kinetic study

The composition of the reaction mixture was followed over time by thin layer chromatography (TLC) (supporting information Figure S1). These analyses show that the glycosylation of the 1,3-PD leads to a mixture of compounds but can be roughly divided into four fractions. To investigate their chemical composition, samples of the crude reaction mixture were taken at different times *t* and analyzed by ^{1}H NMR spectroscopy. As depicted in Fig. 3, ^{1}H NMR spectroscopy can distinguish the starting ester leaving group of β-Glc(OAc)$_5$ **1a** with the characteristic H_1 proton at 5.7 ppm. The formation of the final product mixture is detected by the presence of different doublets between 4.4 and 4.7 ppm that correspond to β-glucosidic links [29]. For information and in order to remove any form of ambiguity, the peaks at 4.7 ppm are characteristic of β-glucosidic bonds of homopolymerized glucose present in the F4 fraction.

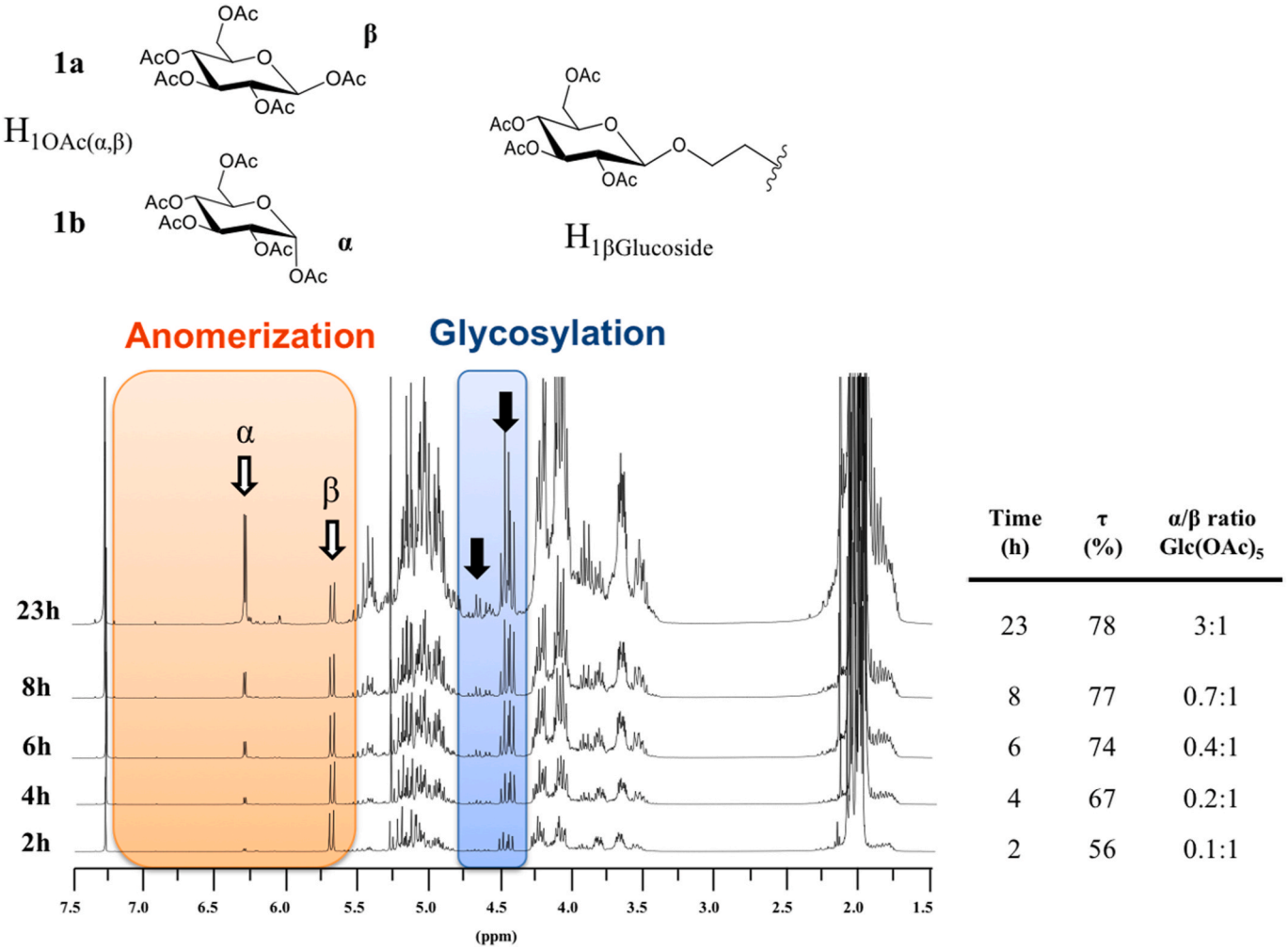
The conversion degree τ of the glucosylation can be evaluated by integration of these different peaks. Indeed, it corresponds to the molar percentage of glucosides that can be calculated at different times using the following formula (1):

$$\tau = \frac{I_{H1\beta G} + I_{H1\alpha G}}{(I_{H1\beta OAc} + I_{H1\alpha OAc} + I_{H1\beta G} + I_{H1\alpha G})} * 100 \quad (1)$$

$I_{H1\alpha OAc}$ and $I_{H1\beta OAc}$ are the intensities of the ^{1}H NMR bands characteristic of the acetylated glucoside under the α and β anomeric forms, respectively. $I_{H1\alpha G}$ and $I_{H1\beta G}$ define the intensities of bands specific of the glucoside under the α and β anomeric forms, respectively.

The exploitation of ^{1}H NMR spectra reveals a fast conversion of about 56% after 2 h and 77% after 8 h. After, the evolution of τ is much reduced between 8 h and 23 h (+1%). In the same period, the anomerization from β-Glc(OAc)$_5$ **1a** to α-Glc(OAc)$_5$ **1b** is more noticeable and the α/β ratio reaches a final value of 3:1. In this same time interval, the anomerization of residual Glc(OAc)$_5$ observed conjointly with the constancy of the conversion rate (≈78%) indicates that the consumption of 1,3-PD **2a** is total. As a result, an average reaction time of 8 h was considered as sufficient for achieving 1,3-PD glucosylation.

The conversion of β-Glc(OAc)$_5$ **1a** and the composition of glucoside can be also determined by the exploitation of the intensities of signals characteristic of anomeric carbons in the ^{13}C NMR spectrum (supporting information Figure S2) as described by Sokolov [22]. In particular, ^{13}C NMR confirms in a clearer form the absence of α-glycosidic bonds that are likely to have a chemical shift around 95 ppm in general [29].



Time (h)	τ (%)	α/β ratio Glc(OAc)$_5$
23	78	3:1
8	77	0.7:1
6	74	0.4:1
4	67	0.2:1
2	56	0.1:1

Fig. 3. ^{1}H NMR spectrum (400.1 MHz, $CDCl_3$) for the O-glucosylation of 1,3-PD **2a** (left) and table of the calculated conversion rates at times from 2 to 23 h (right).

2.2.2. Characterization and identification of the different species of the mixture

The different products resulting from 1,3-PD glycosylation were separated by silica gel chromatography into four different fractions, F1, F2, F3 and F4. Then, the chemical structures of the compounds present in each fraction were carefully investigated using different analytical techniques.

- NMR analyses

The NMR coupling made it possible the identification of desired BisGlucosidePropyl octaacetate BGP(OAc)$_8$ **3a** that is the only constituent of fraction F3. This compound is produced in a low yield (21%) with essentially β-isomeric form (Fig. 4). The fraction F2 contains a first by-product identified as MonoGlucosidePropyl pentaacetate (MGP (OAc)$_5$) **4a** (24%; α/β ratio 0:1). F1 consists of residual Glc(OAc)$_5$ (22%) with both anomeric forms (α/β ratio 3:1) **1a,b**. The last fraction F4 is in fact a mixture of different oligomers (33%; α/β ratio 0:1), the nature of which will be defined later in our study by MALDI-TOF MS techniques. Most formed products mainly have the β-configuration (supporting information Figure S3). Such yield of BGP(OAc)$_8$ **3a** was comparable to those reported by Xue et al. for the synthesis of 1,12-dodecyl bisgalactoside [20].

- MALDI-TOF MS analysis

The efficiency of MALDI-TOF MS analyses was already shown in literature for the identification of high mass compounds in product mixtures based on AlkylPolyGlycoside (APG) models [30]. As regards our study, the MALDI-TOF MS spectrum characteristic of the mixture after 23 h of reaction is shown in Fig. 5-a. Each ionized oligomer is detected on the mass spectrum by a signal made of several peaks corresponding to the mass-to-charge ratios *m/z* characteristic of various isotopic forms (Fig. 5-b).

The interest of the MALDI-TOF MS is given by comparing measured monoisotopic $(m/z)_{exp}$ values for $[M_i + Na]^+$ ions with calculated values. Indeed, the mass spectrum of the crude mixture (Fig. 5-a) contains five series of cationized adducts $[M_i + Na]^+$ separated by $\Delta m/z =$ 288 (hexose unit) corresponding to different degrees of glucose homopolymerization (HD). The molar mass M_i of each oligomer can be calculated from the measured value $(m/z)_{exp}$ according to equation (2):

$$M_i = \left(\frac{m}{z}\right)_{exp} \times z - m_{cation} \qquad 2$$

where m_{cation} is the molar mass of Na (23 g.mol^{-1})

The adduct $[M_i + Na]^+ = 759.2$ is interpreted as being representative of the desired bisglucoside BGP(OAc)$_8$ **3a** of molar mass 736.6 g mol^{-1} (Fig. 6). The adducts $[M_i + Na]^+$ registered at 413.3 and 471.3 are characteristic of residual Glc(OAc)$_5$ **1a,b** (390.3 g mol^{-1}) and MGP (OAc)$_5$ **4a** (448.4 g mol^{-1}) respectively. The adducts $[M_i + Na]^+ =$ 717.2 and 429.2 are attributed to the presence of mono- and BisGlucosideX but under deacetylated form. In our work, all calculated $(m/z)_{theo}$

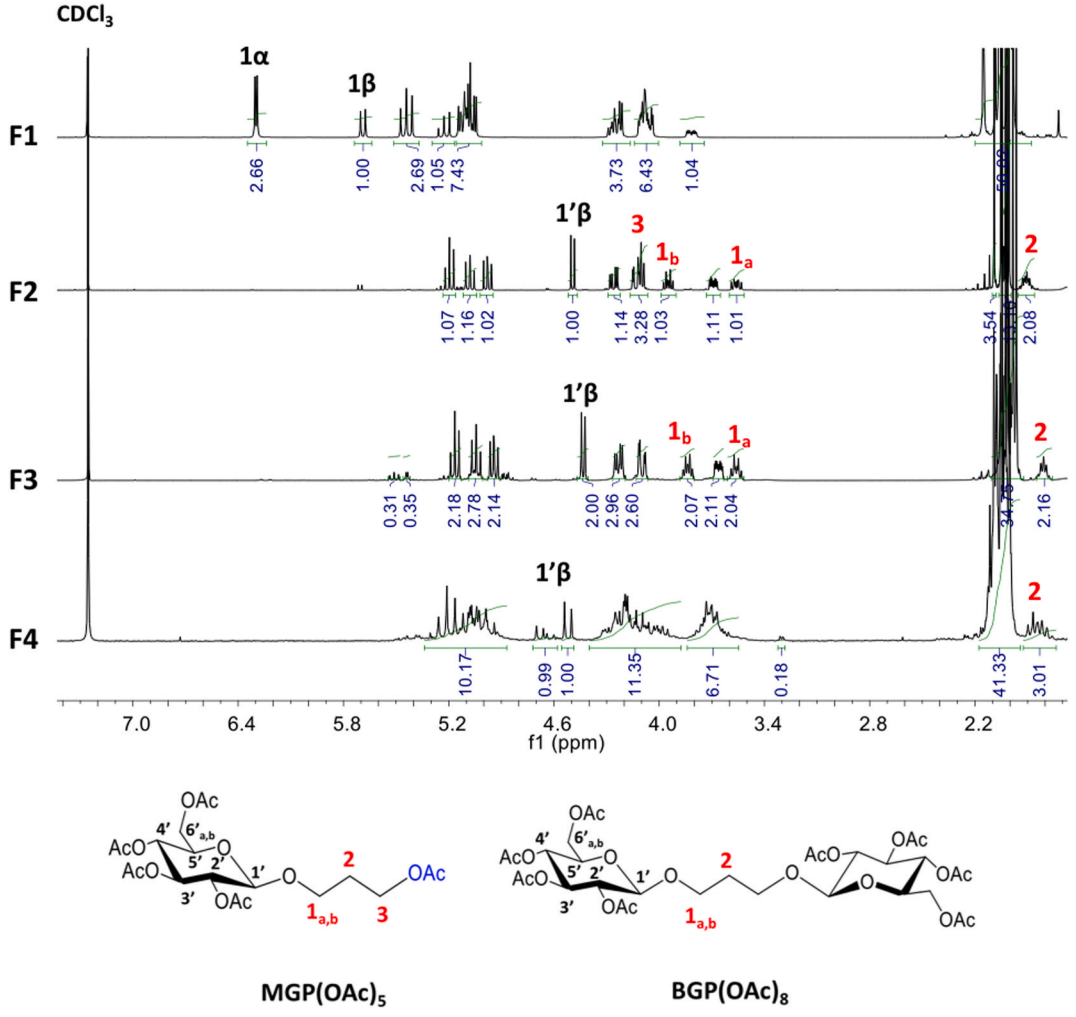


Fig. 4. ^{1}H NMR spectrum ($CDCl_3$) of the different fractions: F1: α,β-Glc(OAc)$_5$ **(1a,b)**; F2: MGP(OAc)$_5$ **(4a)**; F3: BGP(OAc)$_8$ **(3a)** and F4: (A, B, C) mixture.

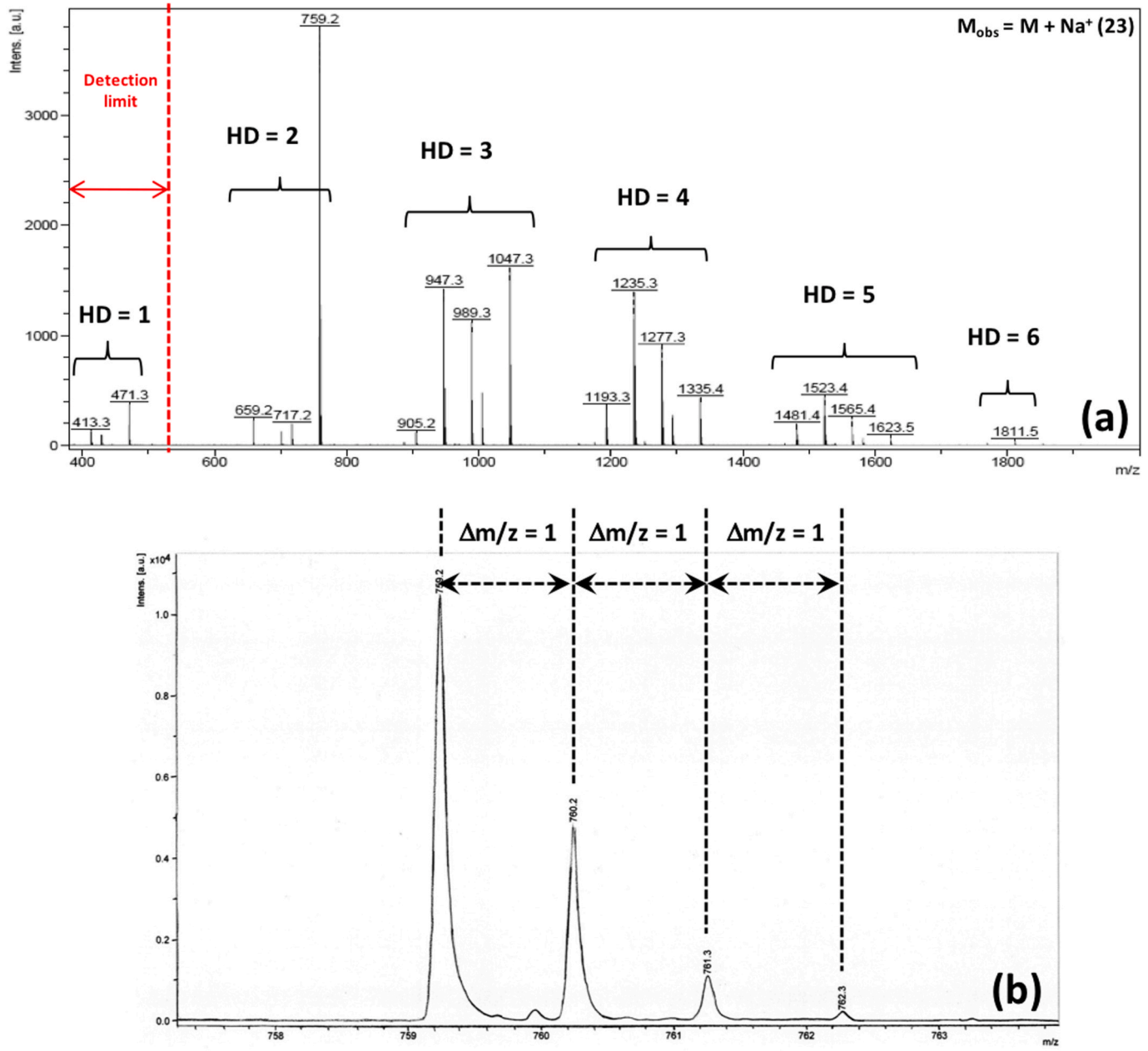


Fig. 5. MALDI-TOF MS spectrum of the crude mixture obtained after 23 h with DCTB as matrix and NaI as cationizing agent (a). Zoom on the isotopic mass of the adduct $[M_i + Na]^+$ (m/z = 759.2) corresponding to $BGP(OAc)_8$ **3a** (736.6 g mol^{-1}) (b).

values for $[M_i + Na]^+$ ions including a possible 2-O deprotection are gathered in supporting information (Table T1) to enable a further comparison with the experimental data $(m/z)_{exp}$ obtained using MALDI-TOF MS. On the basis of these calculations, two major populations, namely, B and C are suspected to be formed during the O-glucosylation of 1,3-PD **2a**. Unfortunately, they cannot be distinguished separately with MALDI-TOF MS experiments because their oligomers have equivalent m/z values (Figures S3 and S4 in supporting information). The further exploitation of the MALDI-TOF MS spectrum makes it possible the identification of the population **A** that defines oligomers characterized by a sequence of peracetylated glucose units but without 1,3-PD building block in their structure (Fig. 6).

It is usually accepted that MALDI-TOF MS is a quantitative analysis of oligomers provided that certain requirements are satisfied such as a polydispersity index PDI (= M_w/M_n) lower than 1.3 [31,32]. If these conditions are fulfilled, the intensity of the adducts detected in the mass spectrum reflects the number of oligomers actually present in the sample. The crude mixture of oligomers obtained in our research presents molecular weights lower than 2000 $g.mol^{-1}$ and low degrees of oligomerization ranging from 1 to 6. In other words, they comply with the criteria for the validity of this technique for quantitative evaluation. Then, the $BGP(OAc)_8$ that is characterized by a peak at 759.2 with the greatest intensity, is the most abundant chemical specie in the mixture by comparison with other oligomers. The relative proportion of $Glc(OAc)_5$ **1a,b** and $MGP(OAc)_5$ **4a** cannot be accurately defined because their corresponding peaks are located too close to the detection limit (>500 $g.mol^{-1}$).

- Proposed mechanisms

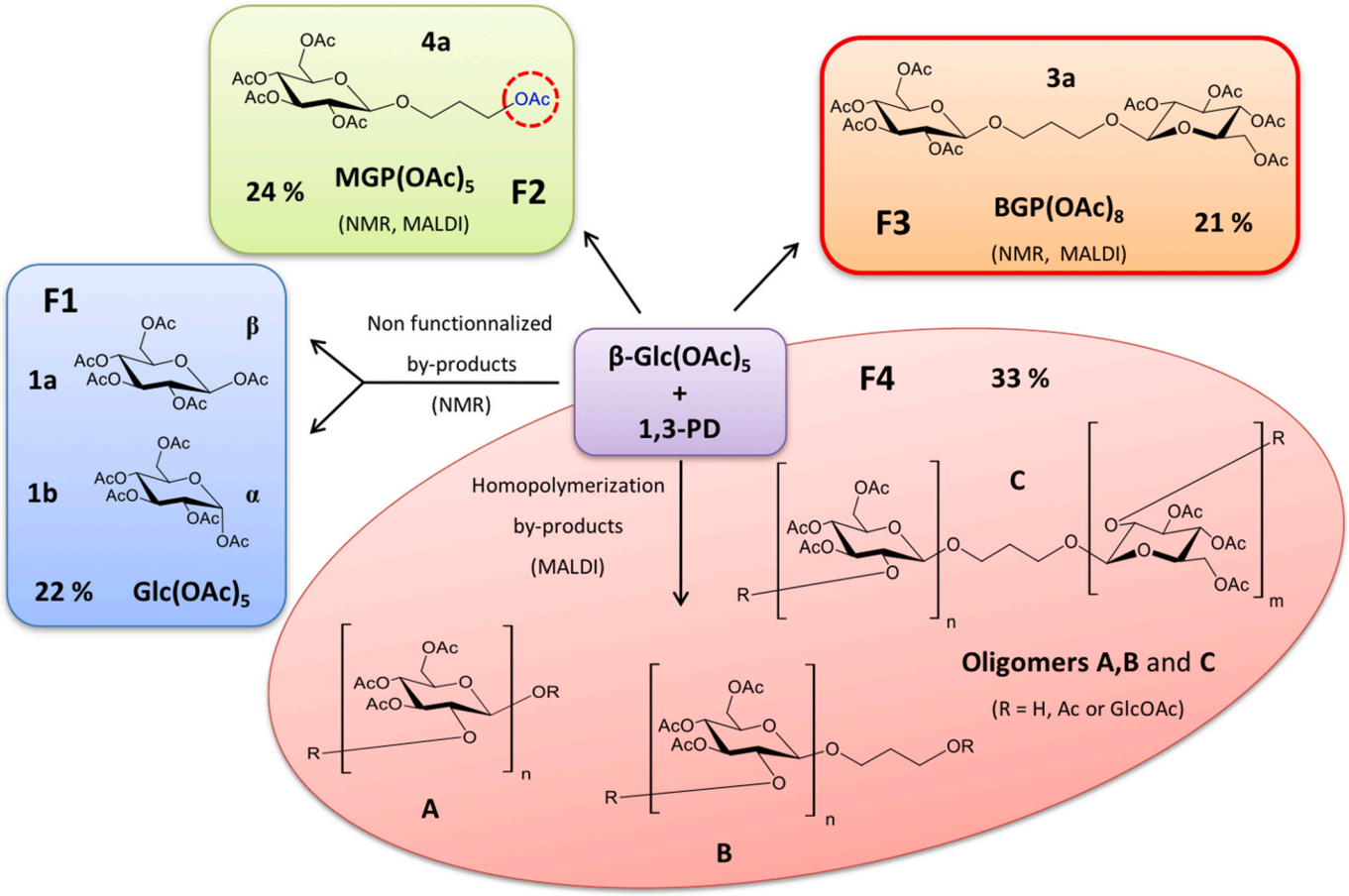


Fig. 6. Overview of the different products obtained by O-glucosylation of 1,3-PD **2a** with β-Glc(OAc)$_5$ **1a** and identified according different techniques.

The observation of MGP(OAc)$_5$ **4a** was coherent with results obtained by Murakami et al. [29]. Indeed, these researchers reported the formation of bromoalkyl acetate as side-product during the glucosylation of bromo-alkanols with the formation of 1,2-orthoester intermediates. This latter topic is particularly well described in Kong's work [33]. By analogy, MGP(OAc)$_5$ **4a** that was isolated is likely the

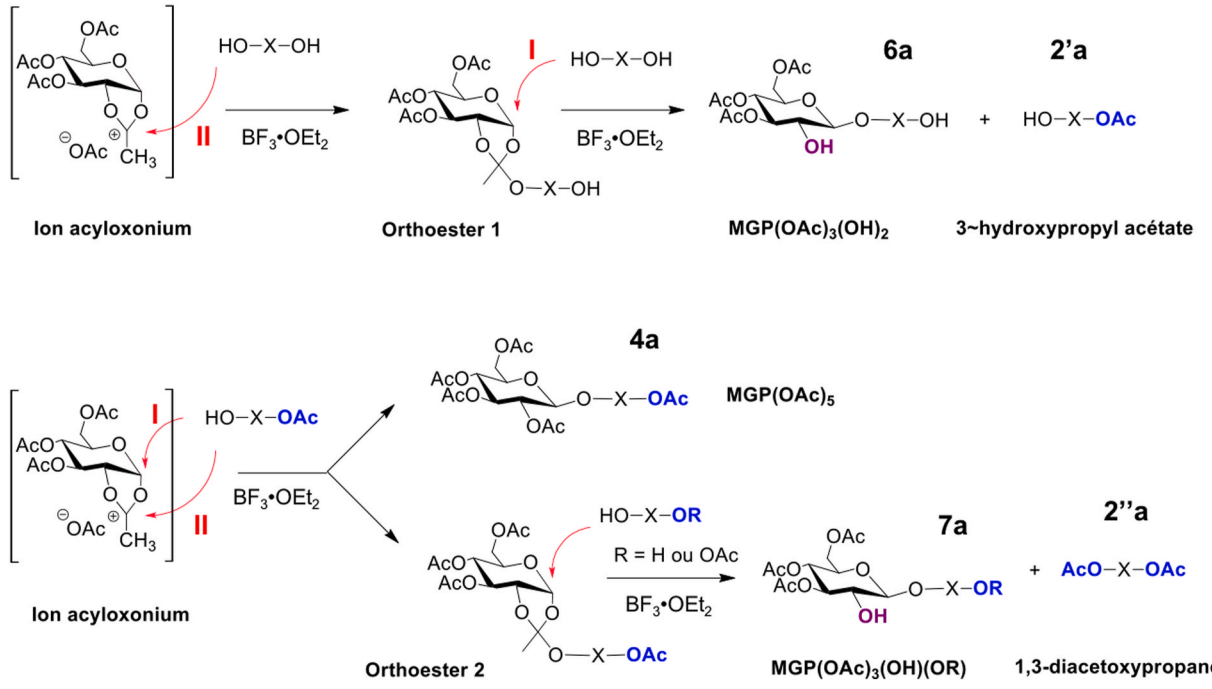


Fig. 7. Intermediate products of the reaction involved in the formation of MGP(OAc)$_5$ **4a**.

result of the conversion of an orthoester **1** into $MGP(OAc)_3(OH)_2$ **6a** and 3-hydroxy-propyl acetate **2′a** (not isolated). Such mechanism is schematically drawn in Fig. 7.

Please note that 3-hydroxy-propyl acetate **2′a** can itself be potentially glycosylated to give the $MGP(OAc)_5$ **4a** in accordance with the results of Banoub et al. and others [34,35]. This mechanism suggests the formation of monoglucosides $MGP(OAc)_3(OH)_2$ **6a** and MGP $(OAc)_3(OH)(OR)$ **7a** that are deacetylated in position 2. It is very likely that these intermediates are responsible of the formation of oligomers.

2.3. Synthesis of the other BisGlucosideX derived from (cyclo)aliphatic diols

Other bisglucosides were synthesized from the respective reaction of aliphatic diols **2b-2e** (Fig. 2) with β-$Glc(OAc)_5$ **1a** using the same chemical pathway as described hereabove with 1,3-PD **2a**. The results issued from their chemical analyses (^1H, ^{13}C NMR and MALDI-TOF MS) are available in supporting information for preserving the clarity of this paper. In all cases, the formation of by-products is observed in addition to the desired bisglucoside production. The respective reaction yields of these compounds are summarized in Table 1. Their proportion in the final mixture appear to be dependent on the nature of the diol used for O-glucosylation. As concerns more particularly the bisglucoside BGX $(OAc)_8$ synthesis, the highest reaction yield value is observed with the use of 2-butyne-1,4-diol **2d** (67%) whereas the reverse case is observed with propane-1,3-diol **2a** (21%). A first possible hypothesis to explain the discrepancies observed between diols used is based on their reactivity, i.e. in our study, their ability to react with peracetylated glucosidic units. This characteristic is directly related to the nucleophilicity of the hydroxyl groups, which is itself influenced by the nature of the chemical skeleton that bears them.

In the present study in which we compare the reactivity of the same family of molecules, (i.e. dihydroxy compounds), the nucleophilicity can be evaluated from the base strength with approximate acid dissociation constant pKa [36–38]. The corresponding values range from 15.1 (for 1, 3-PD **2a**) to 12.5 (for ByD **2d**). It is well known that a sp hybridized carbon as found in (ByD **2d**) is less electron-donating than a sp^2 (BnD **2b**), which in turn is less electron-donating than a sp^3 carbon (1,3-PD **2a**). Such hierarchy is well illustrated by their respective pKa values arranged in ascending order. DEG **2c** presents an oxygen atom in its aliphatic sequence and that has an electron-withdrawing effect. This peculiarity decreases the hydroxyl charge and affects the value of its corresponding pKa (14.4). CHD **2e** presents a pKa value close to that of 1,3-PD **2a** (pKa ≈15) but both diols differ from each other with their respective steric effects.

To summarize, the higher the pKa is, the higher diol reactivity is. But, considering our own data, a high reactivity is not synonym of bisglucoside production with high yield. On the contrary, a lower diol reactivity seems preferable for obtaining a better selectivity. When the pKa value is low as encountered with ByD **2d**, the hydroxyl charge density is reduced. Then, the hydroxyl units are involved into a direct nucleophilic attack on C-1 (Fig. 7 - pathway **I**), which favors the formation of MGX $(OAc)_4(OH)$ (**5a-f**) and then $BGX(OAc)_8$ (**3a-f**). Conversely, with a high pKa value as found with 1,3-PD **2a**, an increased charge density is centered into hydroxyl units. Then, the attack of the carbonyl carbon present in the acyloxonium ion (Fig. 7 - pathway **II**) is privileged with the formation of intermediates orthoesters.

With a pKa value similar to that of 1,3-PD **2a**, CHD **2e** led to the production of BisGlucosideCyclohexyl octaacetate $(BGC(OAc)_8)$ **3e** with a reaction yield close to that of $BGP(OAc)_8$ **3a** (25% against 21%). Nevertheless, the low content of MonoGlucosideCyclohexyl pentaacetate $(MGC(OAc)_5)$ **4e** (12%) seems to indicate that 1,2-orthoesters pathway is not the only one to be involved in this reaction.

Among our results, it is interesting to note that, despite of its nucleophilicity value comparable to that of BnD **2b**, DEG **2c** led to the production of bisglucoside **3c** with a higher efficiency (yield of 45%) than that of $BGBn(OAc)_8$ **3b** (36%). This peculiarity is likely due to the presence of an ether group in the chain (**2c**). This group is likely to have a better interaction with BF_3 than an aliphatic diol bearing unsaturation such as found with **2b** or **2d** diols.

Table 1
$BF_3{\cdot}OEt_2$ catalyzed glucosylation of diols (**2a-e**) with β-$Glc(OAc)_5$ (**1a**).

Entry	Diol	pKa[a]	Yield[b]	
			Bisglucoside	By-products
1	**2a**	15.1	**3a** (21%)	**1** (22%) **4a** (24%) **A, B, C** (33%)
2	**2b**	14.5	**3b** (36%)	**1** (15%) **4b** (13%) **A, B, C** (36%)
3	**2c**	14.4	**3c** (45%)	**1** (22%) **4c** (15%) **A, B, C** (18%)
4	**2d**	12.5	**3d** (67%)[c]	**1** (9%) **4d** (6%) **A, B, C** (18%)
5	**2e**	15	**3e** (25%)	**1** (32%) **4e** (12%) **A, B, C** (31%)

Experimental conditions: molar ratio 1:0.5:1 (β-$Glc(OAc)_5$/HO-X-OH/$BF_3{\cdot}OEt_2$) in CH_2Cl_2, r.t. - 23 h.

[a] Approximative pKa data.

[b] Yields of products isolated after column chromatography based on crude reaction mixture.

[c] Reported yield: 34% [27].

2.4. Synthesis of the BisGlucosideHydroquinone octaacetate (BGH $(OAc)_8$)

The interest of hydroquinone was explored for the synthesis of diphenol-based bisglucosides by following the same experimental procedure as that used previously with (cyclo)aliphatic diols **2a-2e**. The products isolated from the glucosylation mixture were analyzed by means of ^1H NMR and MALDI-TOF MS (see supporting information).

In strong contrast with the analyses previously registered with (cyclo)aliphatic diols, MALDI-TOF MS analysis of the crude product obtained from O-glucosylation with hydroquinone **2f** reveals the only presence of three *m/z* peaks. The first one can be assigned to the residual $Glc(OAc)_5$ **1a,b** (390.3 g mol^{-1}) being ionized by a sodium cation. The other two peaks can be attributed to the monoglucoside MGH $(OAc)_4(OH)$ **5f** (440.4 g mol^{-1}) and desired bisglucoside $BGH(OAc)_8$ **3f** (770.7 g mol^{-1}). Both latter compounds result from direct nucleophilic attack of **2f** on C-1.

The selectivity of the HQ **2f** glycosylation seems quite good without the parasitic formation of orthoesters or 2-O–deacetylated by-products. Once more, this peculiarity can be explained on the basis of nucleophilic considerations. Indeed, HQ presents two hydroxyl groups directly linked to the aromatic ring in para position. The charge delocalization is much reduced than that encountered with the dihydroxy compounds previously investigated. In other words, HQ is less nucleophilic than (cyclo) aliphatic diols **2a-e** as shown by its pKa value close to 10.2.

The extraction of each chemical specie from the mixture would make their respective proportion in the mixture clear. In particular, the desired $BGH(OAc)_8$ **3f** was produced in moderate yield (53%; α/β ratio 0:1). The proportion of MonoGlucosideHydroquinone (MGH $(OAc)_4(OH)$) **5f** was evaluated as being close to 22% (α/β ratio 0:1) while that of residual $Glc(OAc)_5$ **1a,b** was found close to 25% (α/β ratio 1:1). The yield obtained with $BGH(OAc)_8$ **3f** can appear weak but it remains in the same range of order of that observed by Bergeron-Brlek [19] on the synthesis of a bisglucoside from bisphenol A BPA (49%). This similarity is likely a consequence of the pKa values of these diphenols that are evaluated as being rather close (10.2 for HQ against

9.6 for BPA).

2.5. Overall hierarchy

Considering our results and their interpretation, the different diols and phenol studied in this research can be ranked in decreasing order considering the selectivity of their reactivity with glucose via a direct attack on the anomeric carbon C-1 (previously defined as pathway I). The corresponding hierarchy is built as following: aromatic > aliphatic (sp) > ethoxylated > aliphatic (sp^2) > cycloaliphatic > aliphatic (sp^3) (Fig. 8).

The influence of the nucleophilicity of the dihydroxy compounds upon the selectivity of their reaction with glucose units seems now clear. In this present case, nucleophilicity can be correlated to the base strength (pKa value). The best selectivity is obtained with the compound (diphenol) characterized by the lowest pKa value, or in other words, lowest nucleophilicity. This observation seems a direct consequence of its lowest reactivity due to electronic charge delocalization that prevents the formation of by-products.

3. Materials and methods

3.1. Materials

β-glucose pentaacetate (β-Glc(OAc)$_5$), 1,3-propanediol (1,3-PD), hydroquinone (HQ), diethylene glycol (DEG), 2-butyne-1,4-diol (ByD), *cis*-2-butene-1,4-diol (BnD), 1,4-cyclohexanediol (CHD), boron trifluoride diethyl etherate (BF_3·OEt_2; ≥46.5% BF_3 basis) were purchased from Aldrich (France). Anhydrous dichloromethane (CH_2Cl_2), ethyl acetate (EtOAc or EA) were purchased from Analytic Lab. Deuterated chloroform ($CDCl_3$) were purchased from SDS. All these chemicals were used without further purification.

3.2. Techniques

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance I 300 MHz or a Bruker Avance III 400 MHz spectrometers at room temperature with $CDCl_3$ as the solvent. The chemical shifts measured in part per million (ppm) were referenced to the $CDCl_3$ signal peak at 7.26 ppm (^{1}H) and 77.16 ppm (^{13}C). Coupling constants (J) are reported in Hz.

MALDI-TOF MS analyses were performed using a MALDI-TOF MS Bruker Ultra-Flex III (2004) (Bremen, Germany) equipped with a nitrogen laser (337 nm, 30 ns) and a detector. Peptide mixtures were used for external calibration. The ions were accelerated with a potential of 25 kV. The measurements were performed in positive mode POS. The spectra were obtained with trans-2-[3-(4-tertbutylphenyl)-2-methyl-2-propenylidene]malononitrile (DCTB) as matrix and NaI as ionizing salt.

High resolution electrospray ionization mass spectrometry (HRMS-ESI) analyses were obtained using a Bruker MicroTOF QII mass spectrometer. The experiments were carried out in positive ion mode at high resolution.

Thin layer chromatography analyses (TLC) of the reaction mixtures of BGX(OAc)$_8$ were carried out on silica gel plates with a mixture of CH_2Cl_2/EA (7/3; v/v) as eluent. The various compounds were visualized by spraying the TLC plates with a solution of sulfuric acid (10% by volume in ethanol), followed by charring at 150 °C for a few minutes. Spots were compared to standards.

Column chromatographic separations were carried out with a silica gel from VWR (40–63 μm). The various products of the mixtures were isolated with the same eluent as the TLC.

The thermo-oxidative stability of each bisglucoside was examined using a Q50 thermogravimetric analyzer (TGA) from TA Instruments® (New Castle, DE, USA). The experiments consisted in registering the weight loss of the sample as a function of temperature from ambient up to 600 °C with a heating rate of 10 °C.min^{-1} under air flow (25 mL min^{-1}). A relative weight loss (RWL) value of 5% was chosen as a reasonable criterion to evaluate the thermal degradation temperature T_{deg} of each bisglucoside.

Differential scanning calorimetric experiment (DSC) were registered using a Mettler Toledo DSC Star One (Greifensee, Switzerland), under air and with a heating rate of 5 °C.min^{-1}. Before analysis, the sample was cooled down from ambient to 0 °C with a ramp of −3 °C.min^{-1} and maintained at this constant temperature during 15 min to insure thermal equilibrium. The thermogram characteristic of each bisglucoside analysis presented an endotherm. Then, the value of the corresponding melting temperature T_m was taken at the inception of the endothermic peak.

3.3. Synthesis

3.3.1. Standard O-glucosylation protocol

β-Glc(OAc)$_5$ **1a** (3.00 g, 7.68 mmol) and diol or diphenol (HO-X-OH) **2** (3.84 mmol) were mixed in anhydrous CH_2Cl_2 (50 mL). Then BF_3·OEt_2

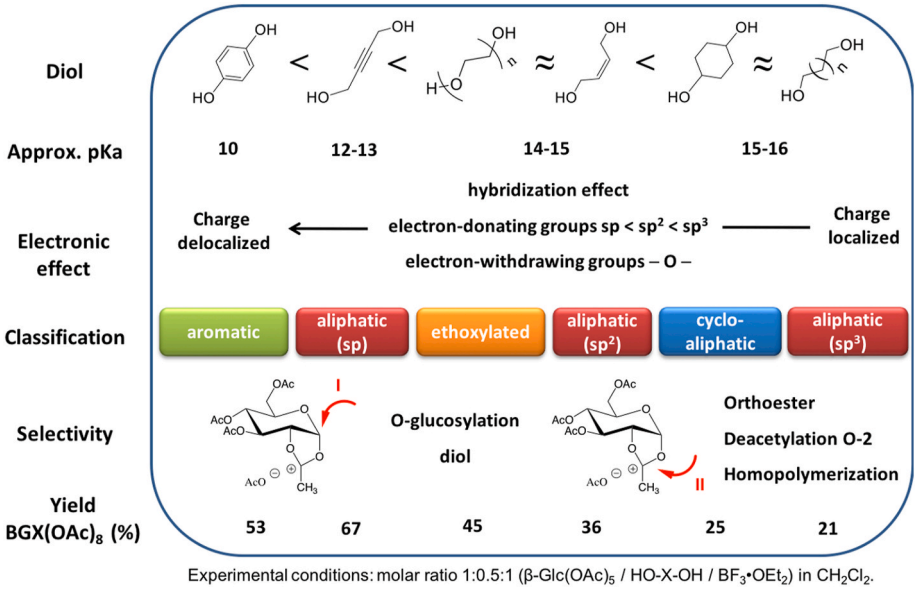


Fig. 8. Influence of diol/diphenol nucleophilicity on O-glucosylation mechanisms.

(0.950 mL, 7.68 mmol) was added dropwise. The molar ratio β-Glc $(OAc)_5$/HO-X-OH/BF_3·OEt_2 is 1:0.5:1. The mixture was stirred at room temperature for 23 h under inert atmosphere (nitrogen), and then quenched by saturated aq. $NaHCO_3$. The organic layer was separated, washed successively with aq. $NaHCO_3$ and (once) with brine solution, dried over $MgSO_4$, and concentrated. BGX$(OAc)_8$ and other products are isolated by column chromatography (eluent CH_2Cl_2/EA, 7/3) or by recrystallization (ethanol), depending on the nature of the BGX$(OAc)_8$.

Remarks. The glucosylation reactions were also carried out for different quantities up to 15 g. The products were obtained in similar yields and selectivity.

3.3.2. β-BisGlucosidePropyl octaacetate (β-BGP$(OAc)_8$) (3a)

Compound (**3a**) 1,3-bis(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyloxy)propane.

The reaction was carried out as described in the standard protocol using 0.292 g (3.84 mmol) 1,3-PD **2a**. The product **3a** was isolated after purification by column chromatography.

Yield: 0.594 g (21%).

R_f: 0.59 (CH_2Cl_2/EtOAc; 7/3)

DSC (5 °C.min^{-1}), T_m: 146 °C.

TGA (10 °C.min^{-1} – RWL = 5%), T_{deg}: 234 °C.

^{1}H NMR ($CDCl_3$, 400.1 MHz): δ (ppm) = 5.18 (t, J = 9.5, 2H, H-3′); 5.06 (t, J = 9.7, 2H, H-4′); 4.96 (t, J = 9.6, 2H, H-2′); 4.45 (d, J = 7.9, 2H, H-1′β); 4.25 (dd, J = 4.8, 12.3, 2H, H-6′b); 4.11 (dd, J = 2.3, 12.3, 2H, H-6′a); 3.86 (dt, J = 5.6, 10.0, 2H, H-1b); 3.68 (m, 2H, H-5′); 3.58 (dt, J = 6.7, 9.7, 2H, H-1a); 1.99–2.07 (4s, 24H, CH_3CO); 1.83 (m, 2H, H-2).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) = 170.60, 170.21, 169.38, 169.22 (O–C═O); 101.03 (C-1′β); 72.82 (C-3′); 71.84 (C-5′); 71.43 (C-2′); 68.47 (C-4′); 66.61 (C-1); 61.98 (C-6′); 29.90 (C-2); 20.57–20.70 (CH_3CO).

HRMS (ESI): *m/z* calculated for $C_{31}H_{44}O_{20}$ $[M+Na]^+$: 759.2324; Found: 759.2315.

3.3.3. β-BisGlucosideCyclohexane octaacetate (β-BGC$(OAc)_8$)

1,4-bis(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyloxy)cyclohexane (mixture of *cis* and *trans*) (**3e**)

The reaction was carried out as described in the standard protocol using 0.446 g (3.84 mmol) CHD **2e**. The product **3e** was isolated after purification by column chromatography.

Yield: 0.746 g (25%).

R_f: 0.62 (CH_2Cl_2/EtOAc; 7/3)

DSC (5 °C.min^{-1}), T_m: 180 °C.

TGA (10 °C.min^{-1} – RWL = 5%), T_{deg}: 283 °C.

^{1}H NMR ($CDCl_3$, 400.1 MHz): δ (ppm) = 5.17 (t, J = 10.0, 2H, H-3′); 5.03 (t, J = 9.0, 2H, H-4′); 4.93 (t, J = 9.3, 2H, H-2′); 4.53 (d, J = 9.3, 2H, H-1′β); 4.23 (dd, J = 4.0, 11.3, 2H, H-6′b); 4.08 (dd, J = 12.2, 2H, H-6′a); 3.68 (m, 2H, H-1); 3.68 (m, 2H, H-5′); 1.30–1.94 (m, 8H, H-2); 1.98–2.05 (4s, 24H, CH_3CO).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) = 170.72, 170.41, 169.50, 169.27 (O–C═O); 99.85, 98.32 (C-1′β); 76.50 (C-1); 72.96 (C-3′); 71.84 (C-5′); 71.64 (C-2′); 68.68 (C-4′); 62.21 (C-6′); 26.42, 27.34, 28.39, 28.87 (C-2); 20.73–20.84 (CH_3CO).

HRMS (ESI): *m/z* calculated for $C_{34}H_{48}O_{20}$ $[M+Na]^+$: 799.2637; Found: 799.2629.

3.3.4. β-BisGlucosideButene octaacetate (β-BGBn$(OAc)_8$)

(*Z*)-1,4-bis(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyloxy)-2-butene (**3b**)

The reaction was carried out as described in the standard protocol using 0.339 g (3.84 mmol) BnD **2b**. The product **3b** was isolated after purification by column chromatography.

Yield: 1.036 g (36%).

R_f: 0.54 (CH_2Cl_2/EtOAc; 7/3)

DSC (5 °C.min^{-1}), T_m: 127 °C.

TGA (10 °C.min^{-1} – RWL = 5%), T_{deg}: 221 °C.

^{1}H NMR ($CDCl_3$, 400.1 MHz): δ (ppm) = 5.66 (m, 2H, H-2); 5.19 (t, J = 9.5, 2H, H-3′); 5.06 (t, J = 9.7, 2H, H-4′); 4.95 (t, J = 8.9, 2H, H-2′); 4.49 (d, J = 8.0, 2H, H-1′β); 4.32 (m, 2H, H-1b); 4.25 (dd, 2H, H-6′b); 4.18 (m, 2H, H-1a); 4.10 (dd, 2H, H-6′a); 3.68 (m, 2H, H-5′); 1.97–2.06 (4s, 24H, CH_3CO).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) = 170.61, 170.21, 169.39, 169.28 (O–C═O); 128.71 (C-2); 99.43 (C-1′β); 72.76 (C-3′); 71.80 (C-5′); 71.20 (C-2′); 68.29 (C-4′); 64.47 (C-1); 61.79 (C-6′); 20.69 (CH_3CO).

HRMS (ESI): *m/z* calculated for $C_{32}H_{44}O_{20}$ $[M+Na]^+$: 771.2324; Found: 771.2311.

3.3.5. β-BisGlucosideDiEthyleneGlycol octaacetate (β-BGDEG$(OAc)_8$)

1,5-bis(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyloxy)-3-oxapentane (**3c**)

The reaction was carried out as described in the standard protocol using 0.408 g (3.84 mmol) DEG **2c**. The product **3c** was isolated after purification by column chromatography.

Yield: 1.326 g (45%).

R_f: 0.30 (CH_2Cl_2/EtOAc; 7/3)

DSC (5 °C.min^{-1}), T_m: 117 °C.

TGA (10 °C.min^{-1} – RWL = 5%), T_{deg}: 267 °C.

^{1}H NMR ($CDCl_3$, 400.1 MHz): δ (ppm) = 5.18 (t, J = 9.5, 2H, H-3′); 5.05 (t, J = 9.7, 2H, H-4′); 4.95 (t, J = 9.6, 2H, H-2′); 4.56 (d, J = 8.0, 2H, H-1′β); 4.23 (dd, J = 4.7, 12.3, 2H, H-6′b); 4.11 (dd, J = 2.3, 12.3, 2H, H-6′a); 3.90 (dt, J = 4.2, 10.7, 2H, H-1b); 3.68 (m, 2H, H-5′); 3.67 (m, 2H, H-1a); 3.59 (m, 4H, H-2); 1.97–2.05 (4s, 24H, CH_3CO).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) = 170.74, 170.35, 169.51, 169.41 (O–C═O); 100.95 (C-1′β); 72.91 (C-3′); 71.91 (C-5′); 71.37 (C-2′); 70.46 (C-2); 69.23 (C-1); 68.51 (C-4′); 62.05 (C-6′); 20.70–20.84 (CH_3CO).

HRMS (ESI): *m/z* calculated for $C_{32}H_{46}O_{21}$ $[M+Na]^+$: 789.2429; Found: 789.2417.

3.3.6. β-BisGlucosideButyne octaacetate (β-BGBy$(OAc)_8$)

1,4-bis(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyloxy)-2-butyne (**3d**)

The reaction was carried out as described in the standard protocol using 0.331 g (3.84 mmol) ByD **2d**. The product **3d** was isolated after purification by column chromatography.

Yield: 1.922 g (67%).

R_f: 0.62 (CH_2Cl_2/EtOAc; 7/3)

DSC (5 °C.min^{-1}), T_m: 121 °C.

TGA (10 °C.min^{-1} – RWL = 5%), T_{deg}: 267 °C.

^{1}H NMR ($CDCl_3$, 400.1 MHz): δ (ppm) = 5.21 (t, J = 9.4, 2H, H-3′); 5.08 (t, J = 9.7, 2H, H-4′); 4.97 (t, J = 9.5, 2H, H-2′); 4.70 (d, J = 7.9, 2H, H-1′β); 4.38 (m, 4H, H-1); 4.25 (dd, J = 4.5, 12.4, 2H, H-6′b); 4.12 (dd, J = 2.3, 12.4, 2H, H-6′a); 3.72 (m, 2H, H-5′); 1.98–2.06 (4s, 24H, CH_3CO).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) = 170.67, 170.27, 169.45, 169.42 (O–C═O); 98.39 (C-1′β); 81.84 (C-2);72.76 (C-3′); 71.98 (C-5′); 71.15 (C-2′); 68.33 (C-4′); 61.83 (C-6′); 56.22 (C-1); 20.66–20.80 (CH_3CO).

HRMS (ESI): *m/z* calculated for $C_{32}H_{42}O_{20}$ $[M+Na]^+$: 769.2167; Found: 769.2150.

3.3.7. β-BisGlucosideHydroquinone octaacetate (β-BGH$(OAc)_8$)

1,4-bis(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyloxy)benzene (**3f**)

The reaction was carried out as described in the standard protocol using 0.423 g (3.84 mmol) HQ **2f**. The product **3f** was isolated after purification by column chromatography or by recrystallization (ethanol).

Yield: 1.570 g (53%).

R_f: 0.64 (CH_2Cl_2/EtOAc; 7/3)

DSC (5 °C.min^{-1}), T_m: 185 °C.

TGA (10 °C.min^{-1} – RWL = 5%), T_{deg}: 311 °C.

^{1}H NMR ($CDCl_3$, 400.1 MHz): δ (ppm) = 6.92 (s, 4H, H-1); 5.27 (t, J = 9.2, 2H, H-3′); 5.23 (t, J = 9.3, 2H, H-2′); 5.15 (t, J = 9.3, 2H, H-4′); 4.98 (d, J = 7.5, 2H, H-1′β); 4.28 (dd, J = 5.1, 12.3, 2H, H-6′b); 4.16 (dd, J = 2.5, 12.3, 2H, H-6′a); 3.81 (m, 2H, H-5′); 2.02–2.07 (4s, 24H, CH_3CO).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) = 170.64, 170.34, 169.49, 169.38 (O–C═O); 152.97 (C-2); 118.57 (C-1); 99.96 (C-1′β); 72.82 (C-3′); 72.18 (C-5′); 71.34 (C-2′); 68.41 (C-4′); 62.02 (C-6′); 20.73–20.82 (CH_3CO).

HRMS (ESI): *m/z* calculated for $C_{34}H_{42}O_{20}$ $[M+Na]^+$: 793.2167; Found: 793.2153.

4. Conclusions

This article demonstrates that the production of bisglucosides through O-glucosylation of a dihydroxy compound is not a trivial topic at all. Indeed, depending on the nature of the diol/diphenol used, different by-products can be formed in addition to the desired bisglucoside. On the basis of our results, the nucleophilicity of the dihydroxy compound related to the value of its pKa seems an important factor to control the reaction yield and the potential formation of side-products. Among the different molecules investigated, the hydroquinone-based monomer is identified as the most promising compound for the production of bisglucosides. Indeed, due to its low nucleophilicity, its reaction with acetylated glucose units is characterized by a good selectivity without glucose homopolymerization. Even if the reaction yield is limited, the purification process is easy to perform and the overall production remains economical. Reminding that this research was initially supported by the wish of producing biobased monomers, that based on hydroquinone is undeniably promising. Indeed, β-BGH $(OAc)_8$ presents a high thermostability (T_{deg} > 300 °C) through the presence of an aromatic cycle set at the core of the bisglucoside chemical skeleton. Moreover, this critical temperature is somewhat 120 °C higher than the melting temperature. Thus, this temperature gap seems large enough to make the conduction of further functionalization in the molten state possible i.e. without the use of any solvent.

Author contributions

This research was led within the context of Stéphane Patry's Ph-D thesis under the scientific direction of Prof. Jean-Pierre Habas. Dr Mike Robitzer was helpful for the understanding the different reaction mechanisms and contributed to the supervision of this work.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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