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Reversing reactivity: stereoselective desulfurative 1,2-trans-*O*-glycosylation of anomeric thiosugars with carboxylic acids under copper or cobalt catalysis

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ABSTRACT: We have discovered a new mode of reactivity of 1-thiosugars in the presence of Cu(II) or Co(II) for a stereoselective *O*-glycosylation reaction. The process involves the use of a catalytic amount of Cu(acac)₂ or Co(acac)₂ and Ag₂CO₃ as an oxidant in α,α,α -trifluorotoluene (TFT). Moreover, this protocol turned out to have a broad scope, allowing to prepare a wide range of complex substituted *O*-glycoside esters in good to excellent yields with an exclusive 1,2-trans-selectivity. The late-stage modification of pharmaceuticals by this method was also demonstrated. To get a closer insight into the reaction mechanism, cyclic voltammetry (CV) was performed.

Introduction

Sugars are a very important family of biomolecules that play a pivotal role in living organisms. Their inherent structural complexity enables them to interact with myriad of biological receptors.¹ To understand the role of saccharides in biological systems, chemists need to prepare well-defined chemical glycosides. β -Acyl *O*-glycosides (AGs) is one of the common motif found in natural products or bioactive compounds such as phyllanthoside,² neurosporaxanthin,³ cephasinenoside,⁴ macrophyllsode D⁵, celecoxib acyl- β -D-glucuronide metabolite⁶ (Figure 1) and the immunoadjuvant QS-21A⁷. Numerous members of the ellagitannin family also have a 1-acylglycoside unit, such as sanguin H-4 and sanguin H-5.⁸ The use of AGs as surfactants also appeared to be an interesting strategy to increase the lignocellulosic biomass value.⁹ Recently mannosamine lipid esters (Ac₄ManNAz lipid ester, Figure 1) were used as chemical tools for metabolic cell labeling strategy.¹⁰ Moreover, β -1-acyl glucuronides are the major metabolites of most carboxylic acid containing drugs.¹¹ Several β -1-acyl glucosides were also identified as metabolites of bile acids and important bio-markers for patients with hepatic diseases.¹² More importantly, glycoacylation has been pointed out as an attractive pathway to target cancer cells exploiting the Warburg effect.¹³ This antitumor strategy that gained much more attention in the last decades, is based on the use of several glucose-based conjugates to more specifically deliver the attached drug to cancer cells. There have been many examples of glucose-conjugated drugs in preclinical or clinical evaluation (paclitaxel,¹⁴ adriamycin,¹⁵ DNA alkylating agent

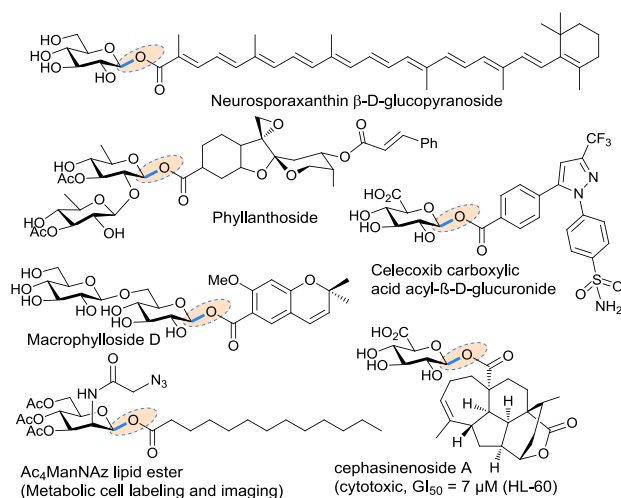


Figure 1. Examples of natural products and bioactive compounds bearing a 1-acyl sugar moiety.

including chlorambucil,¹⁶ platinum¹⁷ and cyclophosphamide¹⁸).

Despite the high added-value of these substrates, a general catalytic-stereoselective acylation method of sugars has not been yet developed. Thus, it has become critical to stereoselectively prepare β -1-acyl glycosides. In vertebrates, acyl *O*-glucuronide are synthesized by the conjugation of carboxylic acids with uridine diphosphate glucuronic acid (UDPGA) mediated by various glucuronosyl transferases (UDPGTs) (Figure 2).¹⁹ From a synthetic point-of-view, usually, these

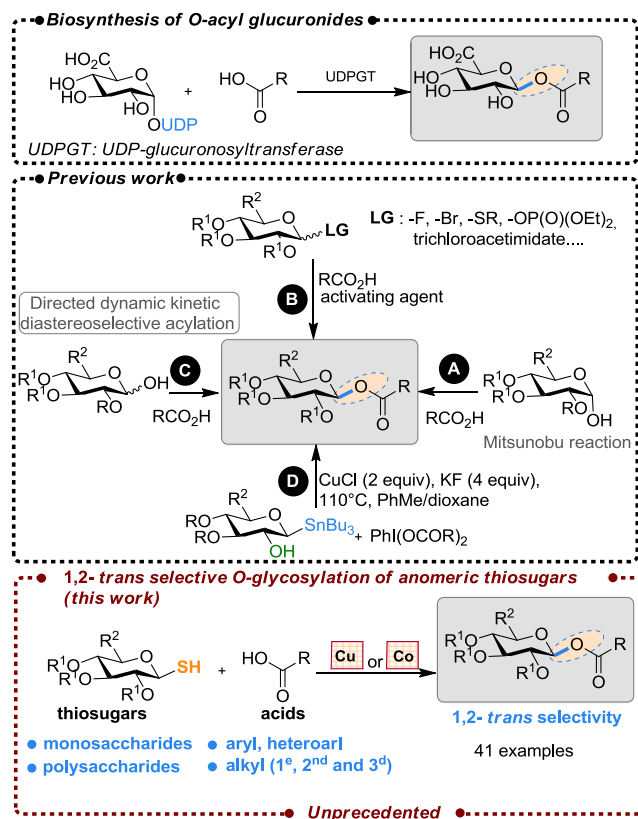


Figure 2. Strategies for *O*-glycosylation to access to acyl-*O*-glycosides.

derivatives were prepared by treating benzoic acid derivatives with sugar lactols through an S_N2 Mitsunobu reaction²⁰ (Figure 2, path A). However a mixture of anomers were obtained in several cases. Some specific acyl glucuronides can be prepared through β-acylation of allyl glucuronate with carboxylic acids catalyzed by HATU²¹ and then mild deprotection after treatment with Pd(PPh₃)₄ in the presence of morpholine. However, the use of glycosyl lactols in all these strategies remains problematic because of the difficulty to prepare well-defined α- or β-anomers. Another way to prepare acyl-*O*-glycosides is the use of glycosyl donors such as glycosyl halides, thioglycosides, glycosyl diethyl phosphates and glycosyl trichloroacetimidates as partners in the glycosylation reaction with carboxylic acids²² (Figure 2, path B). However, these methods suffer from several drawbacks such as the limited scope to non-functionalized substrates, the need for lengthy multisteps preparation of the donor, and the low stereoselectivity of C1 conformation.

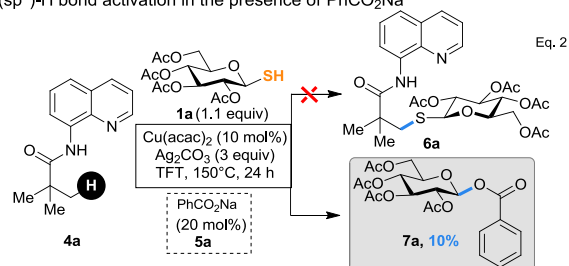
One different approach toward acyl-glycoside is the directed dynamic kinetic stereoselective acylation of anomeric hydroxyl groups by using a chiral catalyst²³ (Figure 2, path C). Recently, Walczak group reported an elegant method to acylate glycosyl stannane donors²⁴ (Path D). This copper-mediated *O*-glycosylation reaction involved the coupling of anomeric stannane nucleophiles with carboxylic acids resulting in exclusive anomeric selectivities. Although this method showed a broad scope, it however requires a multi-steps procedures to prepare the 1-stannylated sugar substrates. Moreover, the toxicity of the organic tin species remain always a major concern. Because of all these drawbacks, developing complementary alternatives are highly desirable for this seemingly simple transformation. In this work we showed for the first time, that thiosugars and acids can be joined together through a

desulfurative 1,2-*trans*-glycosylation process to afford stereoselectively a variety of functionalized acyl- 1,2-*trans*-glycosides. One of the advantages of this approach in addition to the broad scope tolerance, is the availability of thiosugars: these substrates are commercially available or may be synthesized easily from the peracetylated precursors in three-steps.²⁵

During the course of investigating the reactivity of various thiosugars toward C–H activation processes²⁶ we subjected *tetra-O*-acetylated-1-thio-β-D-glucopyranose **1a** and aliphatic amide **4a** to the Cu-catalyzed functionalization of unactivated Csp³–H bonds under previously reported conditions.²⁷ Rather than obtaining the expected Csp³–S bond formation (compound **6a**), an *O*-glycosylation process was serendipitously discovered leading to compound **7a** in 10% yield as a pure β-isomer (Scheme 1).

Scheme 1: Unexpected *O*-glycosylation observed when using β-thioglucose **1a** with benzoic acid **5a**.

Early observation: Unexpected *O*-glycosylation observed when using thiosugar in C(sp³)-H bond activation in the presence of PhCO₂Na



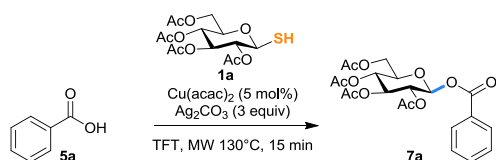
We hypothesized that formation of **7a** resulted from reaction of sodium benzoate, which was used in a catalytic amount (20 mol %), with the β-thioglucose **1a**. We therefore decided to explore the viability of this unusual *O*-glycosylation of thiosugars. Herein, we report the optimization of this reaction which appears as a new method for the 1,2-*trans*-stereoselective *O*-glycosylation of thiosugars.

Results and Discussion

When conducting the reaction of **1a** with 1 equivalent of benzoic acid **5a** in the absence of the amide **4a**, *O*-glycosylation was still observed and the β-*O*-acyl glucoside **7a** was isolated in 29% yield (Table 1, entry 2). The exact structure of **7a**, including its 1,2-diaxial geometry, was determined by 1D and 2D NMR spectroscopy and unambiguously confirmed by crystal structure analysis (Figure S10 in SI). Then, an optimization study was carried out using β-thioglucose **1a** and benzoic acid **5a** as substrates (details can be found in Table S1 in the Supporting Information). To understand the observed *O*-glycosylation reaction and to verify that the outcome was derived from a catalytic process, several control studies were performed (Table 1). These studies led us to identify the best reaction conditions as the use of 5 mol % Cu(acac)₂ and 3 equivalents of Ag₂CO₃ in trifluorotoluene (TFT, 0.1 M) at 130 °C under microwave irradiation for 15 minutes. Under these conditions, the desired phenyl acylglycoside **7a**, was isolated in 79% yield (Table 1, entry 1). Running the reaction in oil bath at 130 °C for 1h instead of microwave irradiation led to the desired product in only 45% yield (entry 3). Moreover, performing the reaction in oil bath at 150°C for 1h furnished **7a** in 74% yield (entry 4). Interestingly, we observed during the optimization that the copper catalyst Cu(acac)₂ can be replaced by Co(acac)₂ without affecting the yield (77% yield, entry 8). We also confirmed that Ag₂CO₃ is required to accomplish *O*-glycosylation; without Ag₂CO₃ (entry 5,6) or

performing the reaction with other bases (K_2CO_3 or Cs_2CO_3) instead of silver carbonate, no reaction occurred (entries 6 and 11). Interestingly, control experiment showed also that this reaction could be performed without catalyst, but **7a** was isolated in a lower yield (52%, entry 7). In addition, reaction with Cu(I) was less efficient and gave product **7a** in a yield similar to the reaction without catalyst (46%, entry 9). We also checked whether the copper salt could act as a Lewis acid by performing the reaction in the presence of a catalytic amount of the Lewis acid $AlCl_3$ (5 mol%) instead of the copper catalyst $Cu(acac)_2$ (entry 10). However under these conditions, only 59% yield of the desired product were obtained, suggesting that this pathway plays only a minor role. Finally, when the reaction was performed in the poorly absorbing toluene solvent, compound **7a** was obtained in a lower yield (67% instead 79% with TFT, entry 12 vs entry 1). This difference maybe is due to the particular properties of trifluorotoluene (dielectric constants and dipole moments) which are more adaptable to the microwave activation mode.

Table 1 Reaction conditions optimization for the *O*-glycosylation of *tetra-O*-acetylated-1-thio- β -D-glucopyranose **1a** with phenylbenzoic acid **5a**.^a

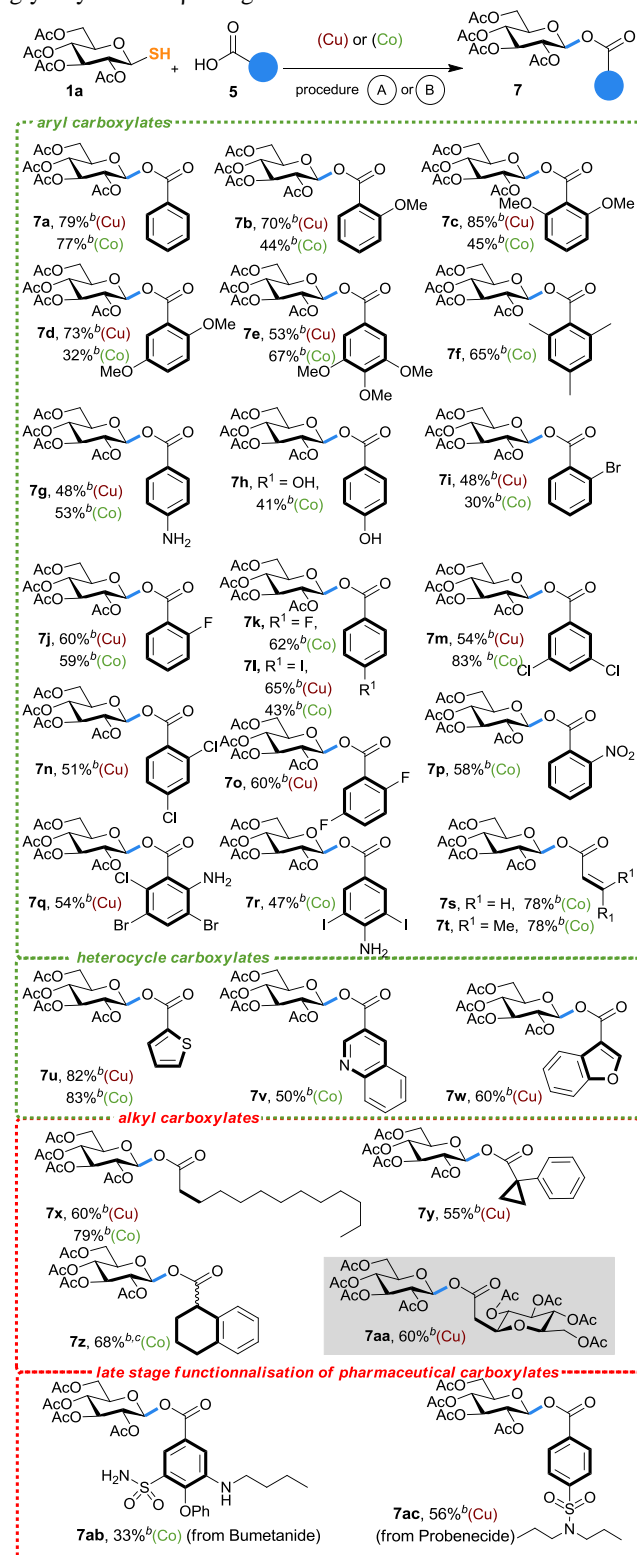


Entry	Deviation from the standard conditions	Yield (%) ^b
1	none	79
2	12 h at 150 °C (oil bath)	29
3	1 h at 130 °C (oil bath)	45
4	1 h at 150 °C (oil bath)	74
5	without Cu-catalyst and Ag_2CO_3	0
6	without Ag_2CO_3	0
7	without Cu-catalyst	52
8	$Co(acac)_2$ instead of $Cu(acac)_2$	77 ^c
9	CuI instead of $Cu(acac)_2$	46
10	$AlCl_3$ (5 mol%) Lewis acid instead of $Cu(acac)_2$	59
11	K_2CO_3 or Cs_2CO_3 instead of Ag_2CO_3	0
12	Toluene instead of TFT	67

TFT = trifluorotoluene ^a Conditions: **1a** (1.5 equiv), **5a** (1 equiv), metal source (5 mol%), base (3 equiv), TFT [0.1 M] were heated in a sealed tube under argon atmosphere. ^b Yield of isolated **7a**. ^c 1h reaction time under thermal heating (at 150 °C).

Prompted by these exciting results, we subsequently investigated the substrate scope for the catalytic *O*-glycosylation of *tetra-O*-acetylated-1-thio- β -D-glucopyranose **1a** with various commercial carboxylic acids **5a-z**, **5aa-ac** using either $Cu(acac)_2$ or $Co(acac)_2$. In most examples, yields arising from Cu- and Co-catalysis are provided, otherwise, in other cases, only one catalyst was used. Overall, the method works well and tolerates a large variety of acid partners (Table 2), and comparable yields were obtained with both copper and cobalt catalysts (Table 2). Benzoic acids having electron-donating groups (**5b-h**) led to the formation of corresponding glycosyl esters **7b-h** in good yields, up to 85%. Delightfully, this protocol was efficient starting from benzoic acids bearing free hydroxyl and amino groups on the aromatic ring (compounds

Table 2. Scope of commercial carboxylic acids **5a-z** in the *O*-glycosylation of β -thioglucose **1a**



[a] Reactions conditions: procedure (A) with Cu : carboxylic acids **5** (1 equiv), *O*-acetylated 1-thio- β -D-glucose **1a** (1.5 equiv), $Cu(acac)_2$ (5 mol %), Ag_2CO_3 (3 equiv), TFT [0.1 M] in a sealed tube under argon at 130 °C under microwave irradiation for 15 min. Procedure (B) with Co: carboxylic acids **5** (1 equiv), *O*-acetylated 1-thio- β -D-glucose **1a** (1.5 equiv), $Co(acac)_2$ (5 or 10 mol %), Ag_2CO_3 (3 equiv), TFT [0.1 M] in a sealed tube under argon at 150 °C for 1 hour under thermal conditions. ^b yield for the isolated product. ^c diastereomeric mixture 1:1 calculated by ¹H NMR.

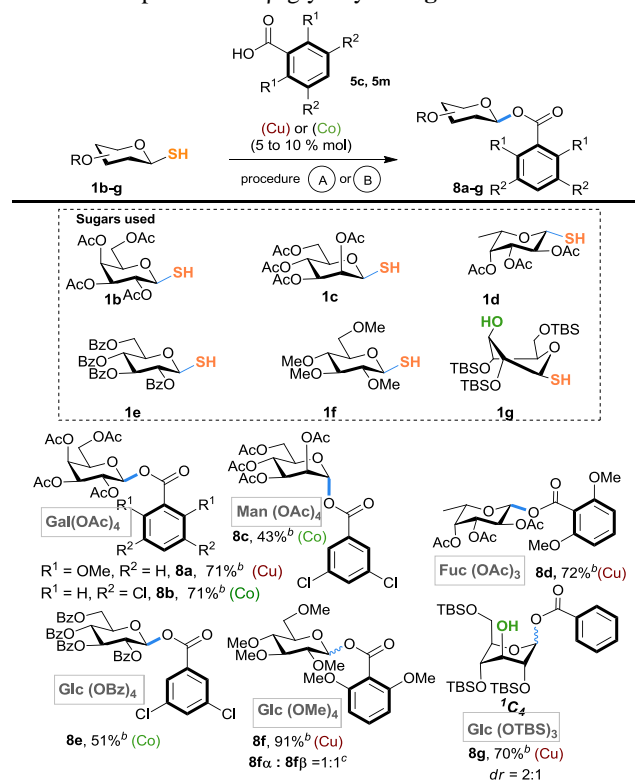
7g, 7h, 7q and **7r**). Likewise, 1-thio- β -D-glucose **1a** was readily coupled with carboxylic acids derivatives bearing electron-withdrawing group (*e.g.*, $-\text{NO}_2$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$) to give the *O*-glycosylated products **7i-r**, which may be useful for further regioselective cross-coupling reaction concerning the halogenated substrates (Table 2). Vinyl carboxylic acids **5s,t** are also well tolerated in this coupling leading to the acrylyl *O*-acyl glycosides **7s,t** in 78% yield. Importantly, heterocyclic acids such as thiophene, quinoline and benzofuran reacted well with **1a**, leading to products **7u-w** in 83%, 50% and 60% yields, respectively. Finally, the synthetic potential of this protocol was well illustrated by its application on substrates containing alkyl groups. Thus, the tridecanoic acid **5x**, cyclopropyl carboxylic acid **5y** as well as tetrahydronaphthalene-1- carboxylic **5z** were good partners leading to glycosyl esters **7x-z** in good to excellent yields (55-79%). Interestingly, the disaccharide ester **7aa** was obtained through this approach in 60% yield when the sugar carboxylic acid **5aa** was used.

After having demonstrated an excellent reactivity with simple substrates, we then examined if the *O*-glycosylation reaction could be extended to drug-like small molecules through a late stage modification process. In this context, Bumetanide (Bumex[®]), a marked-loop diuretic used to treat heart failure, and probenecide (benemide[®]), an uricosuric agent that inhibits the renal excretion, were successfully converted in one step into the corresponding β -acylglucosyl analogues **7ab** and **7ac** in synthetically useful yields (33 % and 56% yields, respectively). These new acyl glycosides may be considered as useful tool metabolites for studying their potential role in drug toxicity. They can be also deacetylated by using literature methods.²⁸

To further demonstrate the generality of this reaction, we applied the optimized conditions to carboxylic acid, **5c** and **5m** and structurally diverse mono-thiosugars **1b-g** (Table 3). This *O*-glycosylation appeared to be not limited to 1-thio- β -D-glucose: thiosugars derived from β -D-galactopyranose (**1b**), and β -D-fucose (**1d**) were also coupled with **5c** or **5m** to provide the corresponding β -*O*-glycosylated esters **8a,b**, **8d** in good yields from either Cu- or Co-catalysts. Of note, the coupling of β -D-mannopyranose (**1c**) led as expected, to the α -*O*-glycosylated ester **3c** in which we observed the inversion of the anomeric configuration. In addition, this methodology tolerates other protecting groups such OBz in the disarmed donor (**1e**) and OMe ether (**1f**). Importantly, in the case of thioGlc(OMe)₄ (**1f**), a 1:1 mixture of both α/β anomers was obtained indicating that the anomeric stereochemistry is controlled by the neighboring participant group at the C2 position. Glycosyl donors protected with tert-butyldimethylsilyl (TBS) group were well known to have superior reactivity and selectivity than other sugar donors.²⁹ This enhanced reactivity/selectivity was correlated to the stereoelectronic effects associated with the conformation change induced by the silyl groups. Inspired by this above literature, we were wondering whether the selectivity in our glycosylation reaction will be impacted by this conformation change. To this end, we prepared the conformationally super armed OTBS-protected thiosugar (**1g**) and we carried out the Cu-catalyzed glycosylation reaction in the presence of phenylbenzoic acid. Interestingly, under our standard conditions the desired ¹C₄ glycoside **8g** was obtained in good 70% yield and 2:1 β -anomeric selectivity although no participating group was installed at C-2 position. This result evidenced the effect of conformation

change on the glycosylation selectivity. One can note that unprotected thiosugars are not tolerated under our reaction conditions.

Table 3. Scope of 1 thio- β -glycosyls **1b-g**^a



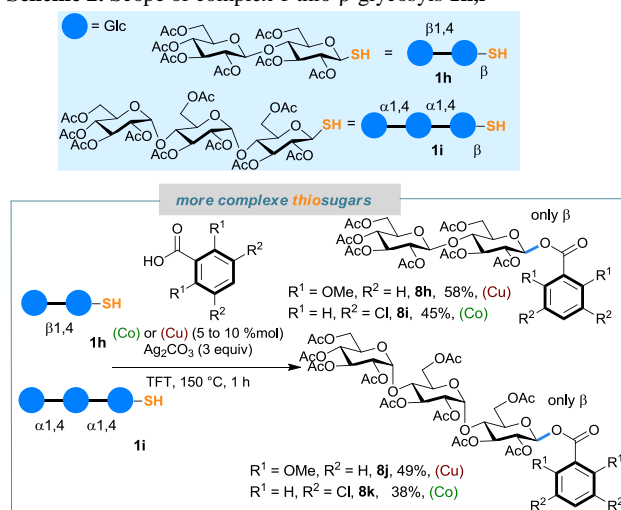
[a] Conditions: procedure (A) with Cu: carboxylic acids **5c** or **5k** (1 equiv), thiosugars **1b-g** (1.5 equiv), Cu(acac)₂ (5 mol %), Ag₂CO₃ (3 equiv), TFT [0.1 M] in a sealed tube under argon at 130 °C under microwave irradiation for 15 min. Procedure (B) with Co: carboxylic acids **5** (1 equiv), *O*-acetylated 1-thio- β -D-glucose **1a** (1.5 equiv), Co(acac)₂ (10 mol %), Ag₂CO₃ (3 equiv), TFT [0.1 M] in a sealed tube under argon at 150 °C for 1 hour. ^b yields of isolated product. ^c diastereomeric mixture 1:1 calculated by ¹H NMR.

Having demonstrated the efficacy of our method with various thiosugars, we next turned our attention to the validation of the method with respect to more complex and biologically relevant saccharides (Scheme 2). We were pleased to find that di- and trisaccharide derivatives cellobiose **1h** and maltotriose **1i**, readily undergo *O*-glycosylation in this transformation. The desired *O*-acyl glycosides **8h,i** were isolated in 58% and 45% yields, respectively. Moreover, the *O*-acyl trisaccharide **8j,k** which are commonly used in bacterial imaging³⁰ were isolated in synthetically useful yields.

To broaden the synthetic applications of this method, we carried out studies on whether the iodinated substrate **7l** could be used as a suitable platform for introducing molecular diversity *via* cross coupling reactions. Thus, the glycosyl ester **9a** bearing both C–O and C–S β -glycosidic bonds was easily prepared through this *O*-glycosylation approach (Scheme 3A) followed by the functionalization of the C–I bond by the coupling with the thioGluNAc **1j** under our previously reported Pd-catalyzed methodology.³¹ We have also shown that this process was effective replacing thiosugar by a commercial NAc-Cys, delivering the glycoamino acid **9b** in 68% yield (Scheme 3B).

With these encouraging results in hand, we next turned our attention to examine the reactivity of other thiols such as alkylthiols instead of thiosugars. Pleasantly, reaction of the commercially available *N*-acetylcysteamine with benzoic acid

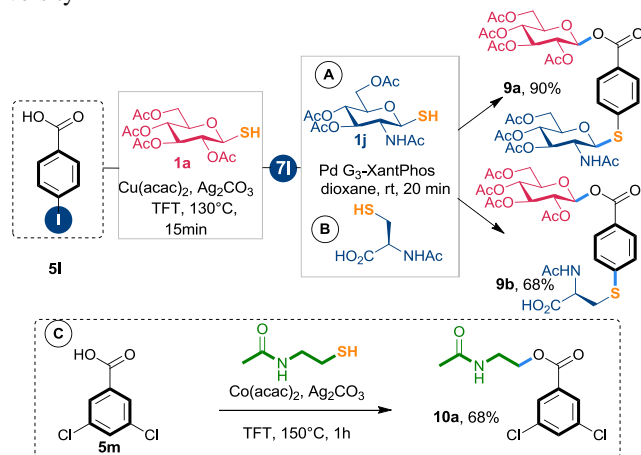
Scheme 2. Scope of complex 1 thio- β -glycosyls **1h,i**^a



[a] Conditions: procedure (A) with Cu: carboxylic acids **5c** or **5m** (1 equiv), thiosugars **1h,i** (1.5 equiv), $\text{Cu}(\text{acac})_2$ (5 mol %), Ag_2CO_3 (3 equiv), TFT [0.1 M] in a sealed tube under argon at 130 °C under microwave irradiation for 15 min. Procedure (B) with Co: carboxylic acids **5** (1 equiv), *O*-acetylated 1-thio- β -D-glucose **1a** (1.5 equiv), $\text{Co}(\text{acac})_2$ (10 mol %), Ag_2CO_3 (3 equiv), TFT [0.1 M] in a sealed tube under argon at 150 °C for 1 hour.^b yields of isolated product.

5m provided the ester product **10a** in a 68 % yield (Scheme 3C). The study of reactivity of a large variety of alkylthiols in this reaction is currently under progress in our group.

Scheme 3. Application of the methodology to molecular diversity

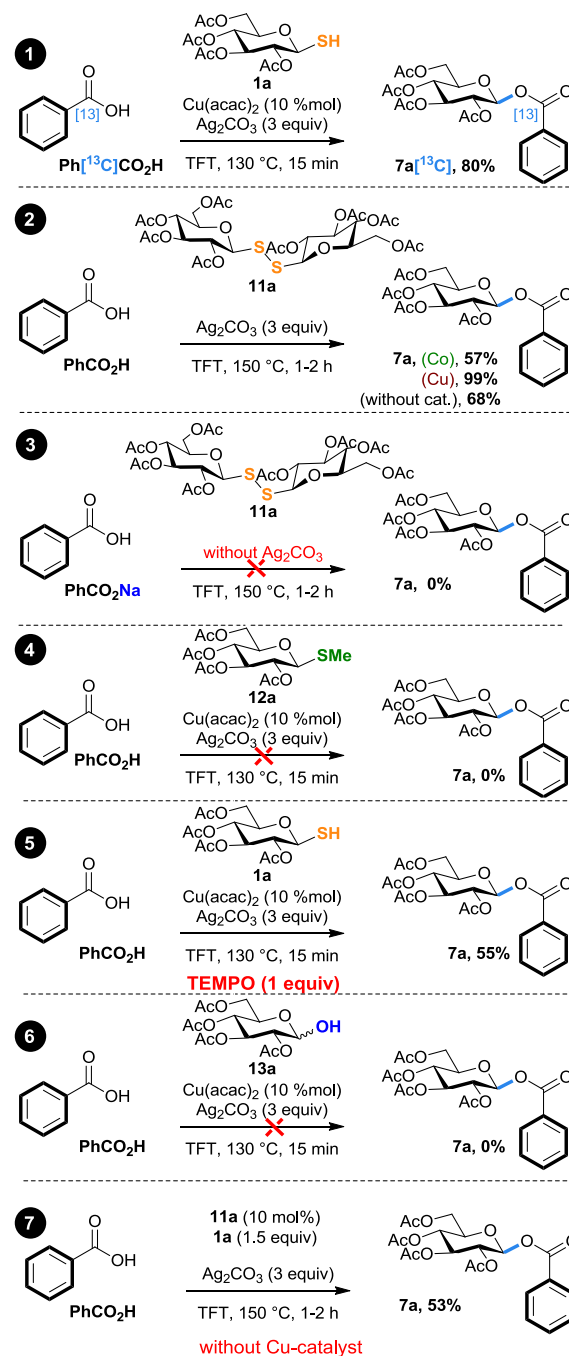


[a] Conditions: path A: *O*-acetylated 1-thio- β -D-glucose **1a** (1.5 equiv), iodophenylbenzoic acid **5l** (1 equiv), $\text{Cu}(\text{acac})_2$ (10 mol %), Ag_2CO_3 (3 equiv), TFT [0.1 M] in a sealed tube under argon at 150 °C for 15 min under MW irradiation. path B: **7j** (1 equiv), **1j** or NHAcCys (1.2 equiv), PdG_3 XantPhos (5 mol %), Et_3N (3 equiv), Dioxane [0.1 M] at rt for 20 min. path C: a commercially available *N*-acetylcysteamine (1.5 equiv), benzoic acid **5m** (1 equiv), $\text{Co}(\text{acac})_2$ (10 mol %), Ag_2CO_3 (3 equiv), TFT [0.1 M] in a sealed tube under argon at 150 °C for 1 hour.

To gain further insight into the origin of this unconventional thiol- to-acid two nucleophiles coupling, we performed the C(13) isotope incorporation experiment conditions by using a ¹³C- α labeled benzoic acid (99 atom % ¹³C) (Scheme 4, eq 1). The incorporation of ¹³C in the phenylglycosyl ester **7a** proves

unambiguously that the ester-group comes from the acid function and not from a decarboxylative/carboxylation sequence with CO_2 arising from the thermal decomposition of silver carbonate.³²

Scheme 4. Mechanistic investigations.



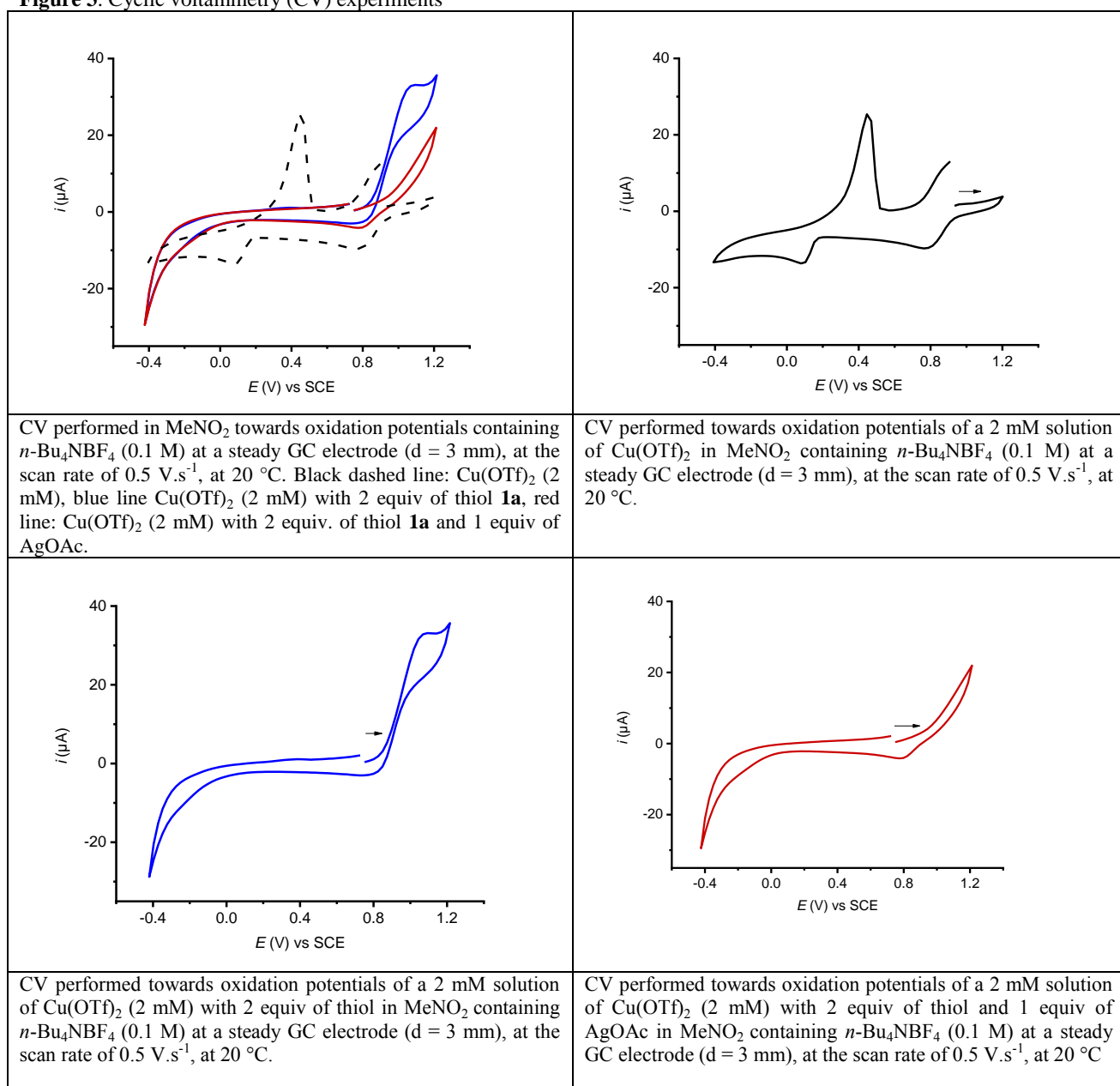
[a] Conditions: *O*-acetylated 1-thio- β -D-glucose **1a** or its dimer **11a** or *S*-methylated **12a** or **13a** (1.5 equiv), benzoic acid **2a** or sodium benzoate (1 equiv), $\text{Cu}(\text{acac})_2$ (5 mol %) or $\text{Co}(\text{acac})_2$ (10 mol %), Ag_2CO_3 (3 equiv), solvent [0.1 M] in a sealed tube under argon.

Because the formation of the disulfide **11a** (Scheme 4, eq.2) was observed during all the reactions (isolated and characterized), we were wondering if **11a** must be regarded as a by-product which may hamper the glycosylation process, or in contrary may be involved in the reaction pathway. In this context, we performed a series of control experiments with the disulfide **11a** (Scheme 4, eq.2). Thus, heating **11a** with benzo-

ic acid **2a** at 150 °C for 1 h in the presence of silver carbonate furnished the desired β -*O*-glycoside **7a** in a 57 % yield when the Co-catalyst was used, and 99 % yield with $\text{Cu}(\text{acac})_2$ as a catalyst (Scheme 4, eq. 2). Interestingly, omitting to add the catalyst led also to the same product **7a** in 68 % yield. This result clearly indicates that disulfide **11a** may be involved in the catalytic cycle. In addition, performing the reaction of **11a** with sodium benzoate in TFT at 150 °C did not furnish **7a** and only the starting material was recovered unchanged (Scheme 4, eq.3). This result indicates that a pathway including a simple nucleophilic substitution is discarded. In another way, the glycosylation reaction was completely inhibited when the thiol function of the sugar was protected (*S*-methyl glucose **12a**) (Scheme 4, eq. 4). It was also found that addition of the radical inhibitor TEMPO, had no significant effect on the reaction, suggesting that a radical species may not be involved in the catalytic cycle (Scheme 4, eq. 5). Finally, the importance of the sulfhydryl ($-\text{SH}$) group was further demonstrated by the

result with glycosyl lactol **13a** as a sugar donor (Scheme 4, eq. 6). Under the standard conditions, no desired product was observed by using **13a**.

The lack of any precedent for oxidative addition of thiols to Cu-catalyst makes a traditional oxidative addition-reductive elimination pathway for this new reaction unlikely. To get a closer insight into the reaction mechanism, cyclic voltammetry (CV) was performed (see SI). $\text{Cu}(\text{OTf})_2$ was selected as $\text{Cu}(\text{II})$ sources and as expected no characteristic oxidation peak could be detected towards oxidation potentials as shown with the dashed line CV (Figure 3). Just after addition of 2 equiv. of thiosugar **1a**, the zero current potential of the solution was shifted by 180 mV towards negative potentials and an oxidation peak at + 1V vs SCE clearly evidenced the formation of $\text{Cu}(\text{I})$ as thiol is not electroactive in this range of potentials (see SI, Figure S1). A similar behavior was observed starting with $\text{Cu}(\text{acac})_2$ but the CV of the metal salt alone is less informative (see SI, Figure S1). The formation of $\text{Cu}(\text{I})$ under

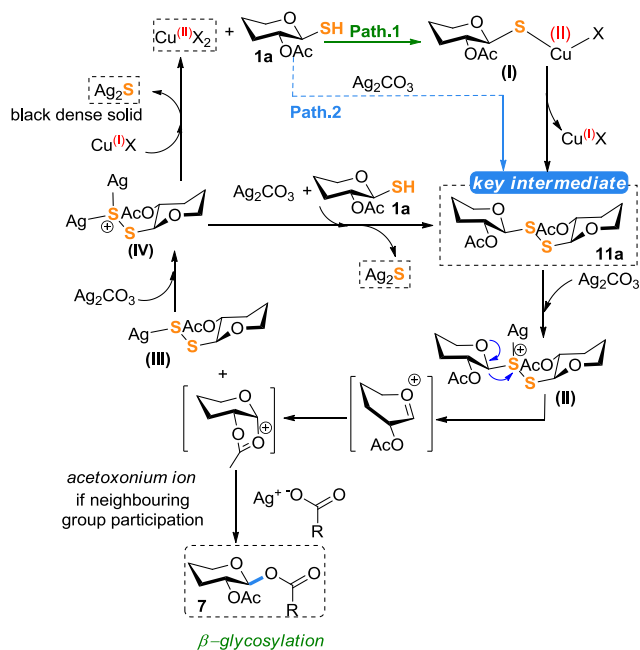


these conditions is in agreement with previous reports in the literature.³³ After addition of 1 equiv of AgOAc, this oxidation peak completely disappears and a black solid precipitated, which was identified to be Ag₂S.³⁴ No further changes could be detected in the presence of a larger excess of **1a** and AgOAc even in the presence of sodium benzoate (see SI, Figure S2). One can be noted that the disulfide is not electroactive in the range of potentials scanned for this study nor in the presence of a stoichiometric amount of Cu(II) (see SI, Figure S3).

Based on all these experiments, we propose the following mechanistic path (Figure 4). The first step involves the oxidation of thiosugar **1a** by the Cu(II) catalyst to give the corresponding disulfide **11a** (Path.1) which has a great affinity for silver. We propose that the strong complexation with silver in complex **(II)** weakened the carbon–sulfur anomeric bond and generated a good leaving group allowing the formation of the acetoxonium ion. The latter is trapped by the carboxylate to give the desired product **7**. Along this process, we propose that a second silver cation was involved to form the sulfonium **(IV)** which can be reduced by Cu(I) to regenerate Cu(II) and one thiol with formation of silver sulfide (Ag₂S) which precipitated out from the solution (see supporting information). The intermediate **(IV)** might regenerate **11a** by reaction with thiosugar **1a** without the need of Cu-catalyst. This step led also to the formation of the silver sulfide (Ag₂S).

Regarding the result obtained in the absence of the catalyst (Table 1, entry 7), we proposed a concomitant pathway (Path.2, Figure 3) mediated by Ag₂CO₃. The disulfide **11a** might be formed in the presence of silver carbonate as an oxidant. Following a strong coordination of a second silver cation (Ag⁺), the complex **(II)** led to the formation of an acetoxonium ion intermediate (if having a neighboring participating group at position 2). In the presence of carboxylate nucleophiles, the 1,2-trans-glycoside ester (**7**) could be formed producing the complex **(III)**. This later evolves to **(IV)** through a second coordination with silver ion, and finally might react with **1a** to regenerate the disulfide key intermediate **11a** and the formation of the Ag₂S. This hypothesis is in agreement with the result highlighted in Scheme 4, Eq.3; when

Figure 4. Proposed mechanism



the reaction of **2a** was performed with the disulfide **11a** in the presence of only Ag₂CO₃ (yield of **7a** = 68%), thus suggesting that this path may be involved in the mechanism. However, when performed with a catalytic amount (10 mol%) of the disulfide **11a** and 1.5 equiv. of **1a** in the presence of **2a** and Ag₂CO₃, without adding the Cu-catalyst (Scheme 4, eq. 7), the reaction proceeded with only 53% yield of **7a** (see supporting information). The improvement observed in the presence of copper salt led us to propose an alternative path for the evolution of **(IV)**. The latter can react with Cu(I) to release Ag₂S regenerating the Cu(II) catalyst.

In conclusion, using an unconventional thiol- to-acid two nucleophiles coupling method for the diastereoselective synthesis of 1,2-trans-O-glycosylated esters through a Cu^(II)- or Co^(III)-catalyzed activation of glycosyl thiols. This approach tolerates a wide range of functional groups, offers a unique strategy to access 1,2-trans-O-glycosylated esters, and streamlines synthesis of pharmaceutically important compounds. Furthermore, efforts to expand the scope of this transformation are undergoing.

EXPERIMENTAL SECTION

General Procedure

The coupling products were all identified by usual physical methods, e.g., ¹H NMR, ¹³C NMR, IR, MS. ¹H and ¹³C NMR spectra were measured in CDCl₃, with a Bruker Avance-300. ¹H chemical shifts are reported in ppm from an internal standard TMS or of residual chloroform (7.26 ppm). The following abbreviations are used: m (multiplet), s (singlet), bs (broad singlet), d (doublet), t (triplet), dd (doublet of doublet), td (triplet of doublet), q (quadruplet), qui (quintuplet), sex (sextuplet). ¹³C chemical shift are reported in ppm from central peak of deuteriochloroform (77.14). IR spectra were measured on a Bruker Vector 22 spectrophotometer and are reported in wave numbers (cm⁻¹). MS were recorded on a Micromass spectrometer. Analytical TLC was performed on Merck precoated silica gel 60F plates. Merck silica gel 60 (0.015–0.040 mm) was used for column chromatography. Melting points were recorded on a Büchi B-450 apparatus (accuracy: up to 100 °C (±0.3 °C); up to 250 °C (±0.5 °C); up to 400 °C

(± 0.8 °C). High resolution mass spectra (HR-MS) were recorded on a Bruker MicroTOF spectrometer, using ESI or APCI with methanol as the carrier solvent. Biotage - microwave reaction vial (2-5 mL, ref.351521) and (10-5 mL, ref.354833) for large scale were used. Nominal and exact m/z values are reported in Daltons. Unless otherwise noted, other materials are obtained from commercial suppliers were used without further purification. Solvents used were used as received without further purification. Thiosugars were prepared following the literature procedure.^{25,31}

General Procedure (A) for Cu-Catalyzed glycosylation with 1-thiosugars

A flame-dried microwave reaction vial (2-5 mL) was charged with Cu(acac)₂ (5 mol%), Ag₂CO₃ (0.53 mmol, 3.0 equiv.), commercial acid carboxylic (0.19 mmol, 1.0 equiv.) and the thiosugar (0.29 mmol, 1.5 equiv.). Then, the reaction mixture was flushed under Argon for 10 minutes. Trifluorotoluene (2 mL) was added and the tube was sealed with a Teflon screwcap, and the mixture was stirred at 130 °C under microwave irradiation until completion. The resulting suspension was cooled to room temperature. The reaction mixture was then filtered through a small pad of Celite and rinsed three times with DCM:MeOH 9:1 (3x10 mL). After concentration under reduced pressure, the residue was purified by silica gel column chromatography to afford the desired product.

1.2 General Procedure (B) for Co-Catalyzed glycosylation with 1-thiosugars

A flame-dried sealed tube was charged with Co(acac)₂ (10 mol%), Ag₂CO₃ (0.53 mmol, 3.0 equiv.), commercial acid carboxylic (0.19 mmol, 1.0 equiv.) and the thiosugar (0.29 mmol, 1.5 equiv.). Then, the reaction mixture was flushed under Argon for 10 minutes. Trifluorotoluene (2 mL) was added and the tube was sealed with a Teflon screwcap, and the mixture was stirred at 150 °C until completion. The resulting suspension was cooled to room temperature. The reaction mixture was then filtered through a small pad of Celite and rinsed three times with EtOAc (3x10 mL). After concentration under reduced pressure, the residue was purified by silica gel column chromatography to afford the desired product.

NMR Data for the glycosyl esters 7a-z, 7aa, 7ab, 7ac, 8af

β-D-Glucopyranose, 2,3,4,6-tetraacetate 1-benzoate [7a]

Compound **7a** was prepared by using both general procedures (A) (reaction time: 15 min), and (B) (reaction time: 1h), with commercial benzoic acid **5a** (23.4 mg, 0.19 mmol, 1.0 equiv.) and **1a** (104.9 mg, 0.29 mmol, 1.5 equiv.), which afforded the product as a white solid (with Cu-catalyst 0.15 mmol, 79% yield, with Co-catalyst 0.142 mmol, 77% yield) after column chromatography EtOAc/Cyclohexane 3:7;

1 mmol scale protocol: A flame-dried microwave reaction vial (10-20 mL) was charged with Cu(acac)₂ (5 mol%), Ag₂CO₃ (3 mmol, 3.0 equiv.), commercial acid carboxylic (1 mmol, 1.0 equiv.) and the thiosugar (1.5 mmol, 1.5 equiv.). Then, the reaction mixture was flushed under Argon for 10 minutes. Trifluorotoluene (10 mL) was added and the tube was sealed with a Teflon screwcap, and the mixture was stirred at 130 °C under microwave irradiation until completion. The resulting suspension was cooled to room tempera-

ture. The reaction mixture was then filtered through a small pad of Celite and rinsed three times with DCM:MeOH 9:1 (3x10 mL). After concentration under reduced pressure, the residue was purified by silica gel column chromatography to afford the desired product **7a** in 75% yield. **TLC** R_f = 0.54 (EtOAc/Cyclohexane, 1:1, SiO₂); **mp**: 132.3 – 134.3 °C ; $[\alpha]_D^{19}$ = - 16.2 (c, 1.00 in CHCl₃); **IR** (neat, cm⁻¹) 2964, 2905, 1759, 1367, 1243, 1066, 1033; **¹H NMR** (300 MHz, CDCl₃) δ (ppm) 8.03 (d, J = 7.6 Hz, 2H), 7.60 (t, J = 7.3 Hz, 1H), 7.45 (t, J = 7.7 Hz, 2H), 5.92 (dd, J = 5.6, 2.5 Hz, 1H), 5.34 (dd, J = 5.7, 3.1 Hz, 2H), 5.25 – 5.10 (m, 1H), 4.32 (dd, J = 12.5, 4.4 Hz, 1H), 4.13 (dd, J = 12.6, 2.3 Hz, 1H), 3.94 (ddd, J = 9.9, 4.5, 2.3 Hz, 1H), 2.06 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 1.98 (s, 3H); **¹³C{¹H} NMR** (75 MHz, CDCl₃) δ (ppm) 170.7 (C_q), 170.2 (C_q), 169.5 (C_q), 169.4 (C_q), 164.6 (C_q), 134.1 (CH), 130.3 (2 x CH), 128.7 (2 x CH), 128.5 (C_q), 92.4 (CH), 72.9 (CH), 72.8 (CH), 70.3 (CH), 68.0 (CH), 61.6 (CH₂), 20.8 (CH₃), 20.7 (3 x CH₃); **HRMS** (ESI) (M + Na)⁺ m/z calculated for C₂₁H₂₄O₁₁Na 475.1211, found 475.1198.

β-D-Glucopyranose, 2,3,4,6-tetraacetate 1-(2-methoxybenzoate) [7b]

Compound **7b** was prepared by using both general procedures (A) (reaction time: 15 min), and (B) (reaction time: 1h), with commercial 2-methoxybenzoic acid **5b** (29.2 mg, 0.19 mmol, 1.0 equiv.) and **1a** (104.9 mg, 0.29 mmol, 1.5 equiv.), which afforded the product as a white solid (with Cu-catalyst 0.133 mmol, 70% yield, with Co-catalyst 0.0836 mmol, 44% yield) after column chromatography EtOAc/Cyclohexane 3:7; **TLC** R_f = 0.36 (EtOAc/Cyclohexane, 1:1, SiO₂); **mp**: 91.9 – 93.0 °C ; $[\alpha]_D^{19}$ = - 12.7 (c, 1.00 in CHCl₃); **IR** (neat, cm⁻¹) 2974, 2920, 1758, 1601, 1492, 1366, 1206, 1079, 1037; **¹H NMR** (300 MHz, CDCl₃) δ (ppm) 7.86 (d, J = 8.2 Hz, 1H), 7.52 (t, J = 7.9 Hz, 1H), 6.99 (t, J = 7.2 Hz, 2H), 5.95 (d, J = 8.0 Hz, 1H), 5.32 (dd, J = 5.4, 3.3 Hz, 2H), 5.23 – 5.14 (m, 1H), 4.31 (dd, J = 12.5, 4.4 Hz, 1H), 4.12 (dd, J = 12.5, 2.1 Hz, 1H), 3.95 – 3.91 (m, 1H), 3.90 (s, 3H), 2.06 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 2.00 (s, 3H); **¹³C{¹H} NMR** (75 MHz, CDCl₃) δ (ppm) 170.8 (C_q), 170.3 (C_q), 169.6 (C_q), 169.5 (C_q), 163.5 (C_q), 160.4 (C_q), 135.1 (CH), 132.7 (CH), 120.4 (CH), 117.6 (C_q), 112.2 (CH), 92.0 (CH), 73.0 (CH), 72.9 (CH), 70.4 (CH), 68.1 (CH), 61.7 (CH₂), 56.0 (CH₃), 20.8 (CH₃), 20.7 (3 x CH₃); **HRMS** (ESI) (M + Na)⁺ m/z calculated for C₂₂H₂₆O₁₂Na 505.1322, found 505.1324.

β-D-Glucopyranose, 2,3,4,6-tetraacetate 1-(2,6-dimethoxybenzoate) [7c]

Compound **7c** was prepared by using both general procedures (A) (reaction time: 15 min), and (B) (reaction time: 1h), with commercial 2,6-dimethoxybenzoic acid **5c** (35.0 mg, 0.19 mmol, 1.0 equiv.) and **1a** (104.9 mg, 0.29 mmol, 1.5 equiv.), which afforded the product as a white solid (with Cu-catalyst 0.185 mmol, 70% yield, with Co-catalyst 0.0855 mmol, 45% yield) after column chromatography EtOAc/Cyclohexane 3:7; **TLC** R_f = 0.32 (EtOAc/Cyclohexane, 1:1, SiO₂); **mp**: 185.7 – 187.2 °C ; $[\alpha]_D^{20}$ = - 4.7 (c, 1.00 in CHCl₃); **IR** (neat, cm⁻¹) 2954, 2841, 1759, 1597, 1477, 1366, 1258, 1235, 1133, 1024; **¹H NMR** (300 MHz, CDCl₃) δ (ppm) 7.30 (d, J = 8.4 Hz, 1H), 6.54 (s, 1H), 6.52 (s, 1H), 6.07 (d, J = 8.2 Hz, 1H), 5.34 – 5.25 (m, 1H), 5.23 – 5.13 (m, 2H), 4.33 (dd, J = 12.4, 4.5 Hz, 1H), 4.19 – 4.10 (m, 1H), 3.90 (ddd, J = 9.9, 4.6, 2.4 Hz, 1H), 3.78 (s, 6H), 2.07 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 2.01 (s,

3H); $^{13}\text{C}\{1\text{H}\}$ NMR (75 MHz, CDCl_3) δ (ppm) 170.8 (C_q), 170.3 (C_q), 169.5 (C_q), 169.3 (C_q), 164.3 (C_q), 157.9 (2 x C_q), 132.1 (CH), 111.3 (C_q), 104.1 (2 x CH), 92.2 (CH), 73.2 (CH), 73.1 (CH), 70.7 (CH), 68.0 (CH), 61.8 (CH_2), 56.1 (2 x CH_3), 20.8 (CH_3), 20.7 (3 x CH_3); HRMS (ESI) ($\text{M} + \text{Na}$) $^+$ m/z calculated for $\text{C}_{23}\text{H}_{28}\text{O}_{13}\text{Na}$ 535.1428, found 535.1431.

β -D-Glucopyranose, 2,3,4,6-tetraacetate 1-(2,5-dimethoxybenzoate) [7d]

Compound **7d** was prepared by using both general procedures (A) (reaction time: 15 min), and (B) (reaction time: 1h), with commercial 2,5-dimethoxybenzoic acid **5d** (35.0 mg, 0.19 mmol, 1.0 equiv.) and **1a** (104.9 mg, 0.29 mmol, 1.5 equiv.), which afforded the product as a white solid (with Cu-catalyst 0.138 mmol, 70% yield, with Co-catalyst 0.060 mmol, 32% yield) after column chromatography EtOAc/Cyclohexane 3:7): TLC R_f = 0.25 (EtOAc/Cyclohexane, 1:1, SiO_2); mp: 126.0 – 127.2 °C ; $[\alpha]_D^{20}$ = - 2.4 (c, 1.00 in CHCl_3); IR (neat, cm^{-1}) 2964, 2929, 1757, 1502, 1367, 1238, 1080, 1039; ^1H NMR (300 MHz, CDCl_3) δ (ppm) 7.39 (d, J = 3.2 Hz, 1H), 7.08 (dd, J = 9.1, 3.2 Hz, 1H), 6.92 (d, J = 9.1 Hz, 1H), 5.93 (dd, J = 5.2, 2.9 Hz, 1H), 5.32 (dd, J = 5.6, 3.2 Hz, 2H), 5.24 – 5.14 (m, 1H), 4.32 (dd, J = 12.5, 4.5 Hz, 1H), 4.13 (dd, J = 12.5, 2.4 Hz, 1H), 3.92 (ddd, J = 10.1, 4.4, 2.1 Hz, 1H), 3.86 (s, 3H), 3.80 (s, 3H), 2.07 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H); $^{13}\text{C}\{1\text{H}\}$ NMR (75 MHz, CDCl_3) δ (ppm) 170.8 (C_q), 170.2 (C_q), 169.6 (C_q), 169.5 (C_q), 163.2 (C_q), 154.9 (C_q), 153.1 (C_q), 121.9 (CH), 117.8 (C_q), 116.1 (CH), 113.9 (CH), 92.1 (CH), 72.9 (2 x CH), 70.4 (CH), 68.1 (CH), 61.7 (CH_2), 56.6 (CH_3), 56.0 (CH_3), 20.9 (CH_3), 20.8 (3 x CH_3); HRMS (ESI) ($\text{M} + \text{Na}$) $^+$ m/z calculated for $\text{C}_{23}\text{H}_{28}\text{O}_{13}\text{Na}$ 535.1428, found 535.1434.

β -D-Glucopyranose, 2,3,4,6-tetraacetate 1-(3,4,5-trimethoxybenzoate) [7e]

Compound **7e** was prepared by using both general procedures (A) (reaction time: 15 min), and (B) (reaction time: 1h), with commercial 3,4,5-trimethoxybenzoic acid **5e** (40.8 mg, 0.19 mmol, 1.0 equiv.) and **1a** (104.9 mg, 0.29 mmol, 1.5 equiv.), which afforded the product as a white solid (with Cu-catalyst 0.100 mmol, 53% yield, with Co-catalyst 0.119 mmol, 67% yield) after column chromatography EtOAc/Cyclohexane 3:7): TLC R_f = 0.40 (EtOAc/Cyclohexane, 1:1, SiO_2); mp: 89.7 – 90.7 °C ; $[\alpha]_D^{20}$ = - 26.1 (c, 1.00 in CHCl_3); IR (neat, cm^{-1}) 3496, 2949, 2841, 1757, 1590, 1504, 1336, 1206, 1126, 1031; ^1H NMR (300 MHz, CDCl_3) δ (ppm) 7.29 (s, 2H), 5.85 (dd, J = 5.6, 2.4 Hz, 1H), 5.37 – 5.30 (m, 2H), 5.26 – 5.12 (m, 1H), 4.34 (dd, J = 12.5, 4.4 Hz, 1H), 4.17 – 4.08 (m, 1H), 3.99 – 3.91 (m, 1H), 3.90 (s, 3H), 3.89 (s, 6H), 2.06 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 1.98 (s, 3H); $^{13}\text{C}\{1\text{H}\}$ NMR (75 MHz, CDCl_3) δ (ppm) 170.7 (C_q), 170.1 (C_q), 169.6 (C_q), 169.5 (C_q), 164.2 (C_q), 153.2 (2 x C_q), 143.2 (C_q), 123.3 (C_q), 107.5 (2 x CH), 92.6 (CH), 72.9 (CH), 72.6 (CH), 70.3 (CH), 68.1 (CH), 61.6 (CH_2), 61.1 (CH_3), 56.4 (2 x CH_3), 20.8 (CH_3), 20.7 (3 x CH_3); HRMS (ESI) ($\text{M} + \text{Na}$) $^+$ m/z calculated for $\text{C}_{24}\text{H}_{30}\text{O}_{14}\text{Na}$ 565.1528, found 565.1534.

β -D-Glucopyranose, 2,3,4,6-tetraacetate 1-(2,4,6-trimethylbenzoate) [7f]

Compound **7f** was prepared by using the general procedure (B) (reaction time: 1h), with commercial 2,4,6-trimethylbenzoic acid **5f** (31.5 mg, 0.19 mmol, 1.0 equiv.) and **1a** (104.9 mg, 0.29 mmol, 1.5 equiv.), which af-

forded the product as a white solid (61.2 mg, 65% yield after column chromatography EtOAc/Cyclohexane 3:7); TLC R_f = 0.60 (EtOAc/Cyclohexane, 1:1, SiO_2); mp: 136.2 – 137.5 °C ; $[\alpha]_D^{20}$ = - 8.2 (c, 1.00 in CHCl_3); IR (neat, cm^{-1}) 2969, 2920, 1757, 1612, 1366, 1239, 1167, 1060, 1036; ^1H NMR (300 MHz, CDCl_3) δ (ppm) 6.84 (s, 2H), 5.99 (d, J = 8.1 Hz, 1H), 5.34 – 5.25 (m, 1H), 5.18 (dd, J = 20.4, 9.0 Hz, 2H), 4.32 (dd, J = 12.4, 4.7 Hz, 1H), 4.19 – 4.11 (m, 1H), 3.95 – 3.87 (m, 1H), 2.27 (s, 3H), 2.26 (s, 6H), 2.07 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H); $^{13}\text{C}\{1\text{H}\}$ NMR (75 MHz, CDCl_3) δ (ppm) 170.7 (C_q), 170.3 (C_q), 169.5 (C_q), 169.2 (C_q), 168.1 (C_q), 140.3 (C_q), 135.7 (2 x C_q), 129.1 (C_q), 128.7 (2 x CH), 91.9 (CH), 73.3 (CH), 72.9 (CH), 70.3 (CH), 68.1 (CH), 61.7 (CH_2), 21.3 (CH_3), 20.8 (CH_3), 20.7 (3 x CH_3), 19.9 (2 x CH_3); HRMS (ESI) ($\text{M} + \text{Na}$) $^+$ m/z calculated for $\text{C}_{24}\text{H}_{30}\text{O}_{11}\text{Na}$ 517.1686, found 517.1678; Elemental Analysis calculated: C, 58.29 %; H, 6.12 %; O, 35.59 %, found: C, 58.07 %; H, 6.17 %; O, 35.03 %.

β -D-Glucopyranose, 2,3,4,6-tetraacetate 1-(4-aminobenzoate) [7g]

Compound **7g** was prepared by using both general procedures (A) (reaction time: 15 min), and (B) (reaction time: 1h), with commercial 4-aminobenzoic acid **5g** (26.3 mg, 0.19 mmol, 1.0 equiv.) and **1a** (104.9 mg, 0.29 mmol, 1.5 equiv.), which afforded the product as a white solid (with Cu-catalyst 0.145 mmol, 50% yield, with Co-catalyst 0.1 mmol, 53% yield) after column chromatography EtOAc/Cyclohexane 3:7): TLC R_f = 0.28 (EtOAc/Cyclohexane, 1:1, SiO_2); mp: 138.2 – 140.4 °C ; $[\alpha]_D^{19}$ = - 5.6 (c, 1.00 in CHCl_3); IR (neat, cm^{-1}) 3487, 3384, 2964, 2924, 1758, 1602, 1366, 1210, 1065, 1037; ^1H NMR (300 MHz, CDCl_3) δ (ppm) 7.84 (d, J = 8.7 Hz, 2H), 6.63 (d, J = 8.7 Hz, 2H), 5.88 (dd, J = 6.0, 2.4 Hz, 1H), 5.36 – 5.27 (m, 2H), 5.23 – 5.12 (m, 1H), 4.32 (dd, J = 12.7, 4.2 Hz, 1H), 4.14 (d, J = 2.9 Hz, 1H), 3.92 (ddd, J = 10.3, 4.4, 2.2 Hz, 1H), 2.07 (s, 3H), 2.04 (s, 3H), 2.04 (s, 3H), 1.98 (s, 3H), no NH_2 protons observed; $^{13}\text{C}\{1\text{H}\}$ NMR (75 MHz, CDCl_3) δ (ppm) 170.8 (C_q), 170.2 (C_q), 169.6 (2 x C_q), 164.5 (C_q), 151.9 (C_q), 132.6 (2 x CH), 117.6 (C_q), 114.0 (2 x CH), 92.1 (CH), 72.9 (CH), 72.8 (CH), 70.4 (CH), 68.1 (CH), 61.7 (CH_2), 20.8 (CH_3), 20.7 (3 x CH_3); HRMS (ESI) ($\text{M} + \text{Na}$) $^+$ m/z calculated for $\text{C}_{21}\text{H}_{25}\text{NO}_{11}\text{Na}$ 490.1325, found 490.1327.

β -D-Glucopyranose, 2,3,4,6-tetraacetate 1-(4-hydroxybenzoate) [7h]

Compound **7h** was prepared by using the general procedure (B) (reaction time: 1h), with commercial 4-hydroxybenzoic acid **5h** (26.5 mg, 0.19 mmol, 1.0 equiv.) and **1a**^[25] (104.9 mg, 0.29 mmol, 1.5 equiv.), which afforded the product as a white solid (37.2 mg, 41% yield after column chromatography EtOAc/Cyclohexane 3:7); TLC R_f = 0.28 (EtOAc/Cyclohexane, 1:1, SiO_2); mp: 178.3 – 179.6 °C ; $[\alpha]_D^{19}$ = - 7.3 (c, 1.00 in CHCl_3); IR (neat, cm^{-1}) 3418, 2969, 2910, 1757, 1609, 1367, 1212, 1067, 1038; ^1H NMR (300 MHz, CDCl_3) δ (ppm) 7.93 (dd, J = 7.0, 4.8 Hz, 2H), 6.85 (dd, J = 7.0, 4.8 Hz, 2H), 5.90 (dd, J = 5.8, 2.5 Hz, 1H), 5.39 – 5.27 (m, 2H), 5.26 – 5.11 (m, 1H), 4.33 (dd, J = 12.5, 4.3 Hz, 1H), 4.14 (dd, J = 12.5, 2.4 Hz, 1H), 3.94 (ddd, J = 10.1, 4.4, 2.2 Hz, 1H), 2.07 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H), 1.99 (s, 3H), no OH proton observed; $^{13}\text{C}\{1\text{H}\}$ NMR (75 MHz, CDCl_3) δ (ppm) 170.9 (C_q), 170.3 (C_q), 169.8 (C_q), 169.7 (C_q), 164.3 (C_q), 161.1 (C_q), 132.8 (2 x CH), 120.8 (C_q), 115.6

(2 x CH), 92.3 (CH), 72.9 (CH), 72.8 (CH), 70.4 (CH), 68.1 (CH), 61.7 (CH₂), 20.9 (CH₃), 20.7 (3 x CH₃); **HRMS (ESI) (M + Na)⁺** *m/z* calculated for C₂₁H₂₄O₁₂Na 491.1165, found 491.1174.

β-D-Glucopyranose, 2,3,4,6-tetraacetate 1-(2-bromobenzoate) [7i]

Compound **7i** was prepared by using both **general procedures (A)** (reaction time: 15 min), and **(B)** (reaction time: 1h), with commercial 2-bromobenzoic acid **5i** (38.6 mg, 0.19 mmol, 1.0 equiv.) and **1a** (104.9 mg, 0.29 mmol, 1.5 equiv.), which afforded the product as a white solid (with Cu-catalyst 0.091 mmol, 48% yield, with Co-catalyst 0.057 mmol, 30% yield) after column chromatography EtOAc/Cyclohexane 3:7): **TLC R_f** = 0.47 (EtOAc/Cyclohexane, 1:1, SiO₂); **mp**: 103.3 – 105.2 °C ; **[α]_D²⁰** = - 13.6 (c, 1.00 in CHCl₃); **IR (neat, cm⁻¹)** 2959, 1758, 1590, 1433, 1366, 1235, 1070, 1031; **¹H NMR (300 MHz, CDCl₃) δ (ppm)** 7.93 – 7.83 (m, 1H), 7.75 – 7.61 (m, 1H), 7.38 (dd, *J* = 6.8, 3.5 Hz, 2H), 6.03 – 5.90 (m, 1H), 5.37 – 5.26 (m, 2H), 5.26 – 5.09 (m, 1H), 4.34 (dd, *J* = 12.5, 4.4 Hz, 1H), 4.14 (dd, *J* = 12.6, 2.2 Hz, 1H), 3.93 (ddd, *J* = 12.1, 4.4, 2.1 Hz, 1H), 2.08 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H); **¹³C{¹H} NMR (75 MHz, CDCl₃) δ (ppm)** 170.8 (C_q), 170.2 (C_q), 169.5 (2 x C_q), 163.4 (C_q), 135.1 (CH), 133.9 (CH), 132.5 (CH), 129.5 (C_q), 127.6 (CH), 123.0 (C_q), 92.6 (CH), 73.0 (CH), 72.9 (CH), 70.3 (CH), 67.9 (CH), 61.6 (CH₂), 20.9 (CH₃), 20.8 (CH₃), 20.7 (2 x CH₃); **HRMS (ESI) (M + Na)⁺** *m/z* calculated for C₂₁H₂₃BrO₁₁Na 553.0321, found 553.0327.

β-D-Glucopyranose, 2,3,4,6-tetraacetate 1-(2-fluorobenzoate) [7j]

Compound **7j** was prepared by using both **general procedures (A)** (reaction time: 15 min), and **(B)** (reaction time: 1h), with commercial 2-fluorobenzoic acid **5j** (26.9 mg, 0.19 mmol, 1.0 equiv.) and **1a** (104.9 mg, 0.29 mmol, 1.5 equiv.), which afforded the product as a white solid (with Cu-catalyst 0.114 mmol, 60% yield, with Co-catalyst 0.112 mmol, 59% yield) after column chromatography EtOAc/Cyclohexane 3:7): **TLC R_f** = 0.46 (EtOAc/Cyclohexane, 1:1, SiO₂); **mp**: 116.6 – 118.0 °C ; **[α]_D²⁰** = - 14.0 (c, 1.00 in CHCl₃); **IR (neat, cm⁻¹)** 3496, 2954, 1745, 1613, 1491, 1367, 1240, 1081, 1036 ; **¹H NMR (300 MHz, CDCl₃) δ (ppm)** 7.92 (t, *J* = 7.1 Hz, 1H), 7.56 (dd, *J* = 12.6, 7.2 Hz, 1H), 7.18 (dt, *J* = 19.2, 8.6 Hz, 2H), 5.93 (dd, *J* = 6.0, 0.9 Hz, 1H), 5.38 – 5.26 (m, 2H), 5.26 – 5.11 (m, 1H), 4.32 (dd, *J* = 12.5, 4.3 Hz, 1H), 4.14 (d, *J* = 12.3 Hz, 1H), 4.03 – 3.84 (m, 1H), 2.07 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H); **¹³C{¹H} NMR (75 MHz, CDCl₃) δ (ppm)** 170.7 (C_q), 170.2 (C_q), 169.5 (C_q), 169.4 (C_q), 162.6 (d, *J_{CF}* = 261.0 Hz, C_q), 162.0 (d, *J_{CF}* = 3.8 Hz, C_q), 135.7 (d, *J_{CF}* = 9.0 Hz, CH), 132.5 (CH), 124.3 (d, *J_{CF}* = 3.0 Hz, CH), 117.3 (C_q), 117.3 (d, *J_{CF}* = 21.8 Hz, CH), 92.4 (CH), 73.0 (CH), 72.8 (CH), 70.2 (CH), 68.0 (CH), 61.6 (CH₂), 20.8 (CH₃), 20.72 (3 x CH₃); **¹⁹F NMR (376 MHz, CDCl₃) δ (ppm)** – 108.3 (CF); **HRMS (ESI) (M + Na)⁺** *m/z* calculated for C₂₁H₂₃FO₁₁Na 493.1122, found 493.1126.

β-D-Glucopyranose, 2,3,4,6-tetraacetate 1-(4-fluorobenzoate) [7k]

Compound **7k** was prepared by using the general procedure **(B)** (reaction time: 1h), with commercial 4-fluorobenzoic acid **5k** (26.9 mg, 0.19 mmol, 1.0 equiv.) and **1a** (104.9 mg, 0.29 mmol, 1.5 equiv.), which afforded the product as a white solid

(55.5 mg, 62% **yield** after column chromatography EtOAc/Cyclohexane 3:7); **TLC R_f** = 0.57 (EtOAc/Cyclohexane, 1:1, SiO₂); **mp**: 157.3 – 159.7 °C ; **[α]_D²⁰** = - 11.0 (c, 1.00 in CHCl₃); **IR (neat, cm⁻¹)** 2964, 2924, 1759, 1604, 1509, 1366, 1242, 1067, 1034; **¹H NMR (300 MHz, CDCl₃) δ (ppm)** 8.05 (dd, *J* = 8.8, 5.4 Hz, 2H), 7.13 (t, *J* = 8.6 Hz, 2H), 5.90 (dd, *J* = 4.9, 3.3 Hz, 1H), 5.33 (dd, *J* = 5.6, 3.1 Hz, 2H), 5.27 – 5.09 (m, 1H), 4.32 (dd, *J* = 12.5, 4.4 Hz, 1H), 4.13 (dd, *J* = 12.6, 2.4 Hz, 1H), 3.93 (ddd, *J* = 9.9, 4.5, 2.2 Hz, 1H), 2.07 (s, 3H), 2.04 (s, 3H), 2.04 (s, 3H), 1.98 (s, 3H); **¹³C{¹H} NMR (75 MHz, CDCl₃) δ (ppm)** 170.7 (C_q), 170.2 (C_q), 169.6 (C_q), 169.5 (C_q), 166.5 (d, *J_{CF}* = 254.3 Hz, C_q), 163.7 (C_q), 133.0 (d, *J_{CF}* = 9.0 Hz, 2 x CH), 124.8 (d, *J_{CF}* = 3.0 Hz, C_q), 116.1 (d, *J_{CF}* = 21.8 Hz, 2 x CH), 92.5 (CH), 72.9 (CH), 72.7 (CH), 70.3 (CH), 68.0 (CH), 61.6 (CH₂), 20.8 (CH₃), 20.7 (3 x CH₃); **¹⁹F NMR (376 MHz, CDCl₃) δ (ppm)** – 103.4 (CF); **HRMS (ESI) (M + Na)⁺** *m/z* calculated for C₂₁H₂₃FO₁₁Na 493.1122, found 493.1120.

β-D-Glucopyranose, 2,3,4,6-tetraacetate 1-(4-iodobenzoate) [7l]

Compound **7l** was prepared by using both **general procedures (A)** (reaction time: 15 min), and **(B)** (reaction time: 1h), with commercial 4-iodobenzoic acid **5l** (47.6 mg, 0.19 mmol, 1.0 equiv.) and **1a** (104.9 mg, 0.29 mmol, 1.5 equiv.), which afforded the product as a white solid (with Cu-catalyst 0.123 mmol, 65% yield, with Co-catalyst 0.081 mmol, 43% yield) after column chromatography EtOAc/Cyclohexane 3:7): **TLC R_f** = 0.59 (EtOAc/Cyclohexane, 1:1, SiO₂); **mp**: 149.0 – 151.6 °C ; **[α]_D¹⁹** = - 21.9 (c, 1.00 in CHCl₃); **IR (neat, cm⁻¹)** 2949, 1746, 1586, 1366, 1229, 1085, 1069; **¹H NMR (300 MHz, CDCl₃) δ (ppm)** 7.83 (dd, *J* = 8.5, 2.1 Hz, 2H), 7.73 (dd, *J* = 8.5, 2.0 Hz, 2H), 5.89 (d, *J* = 6.8 Hz, 1H), 5.38 – 5.26 (m, 2H), 5.26 – 5.11 (m, 1H), 4.32 (dd, *J* = 12.6, 4.5 Hz, 1H), 4.13 (dd, *J* = 12.5, 2.1 Hz, 1H), 3.93 (ddd, *J* = 10.0, 4.6, 2.3 Hz, 1H), 2.07 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H), 1.98 (s, 3H); **¹³C{¹H} NMR (75 MHz, CDCl₃) δ (ppm)** 170.7 (C_q), 170.2 (C_q), 169.6 (C_q), 169.5 (C_q), 164.3 (C_q), 138.2 (2 x CH), 131.6 (2 x CH), 128.0 (C_q), 102.4 (C_q), 92.6 (CH), 73.0 (CH), 72.7 (CH), 70.2 (CH), 68.0 (CH), 61.5 (CH₂), 20.8 (CH₃), 20.7 (3 x CH₃); **HRMS (ESI) (M + Na)⁺** *m/z* calculated for C₂₁H₂₃IO₁₁Na 601.0183, found 601.0183.

β-D-Glucopyranose, 2,3,4,6-tetraacetate 1-(3,5-dichlorobenzoate) [7m]

Compound **7m** was prepared by using both **general procedures (A)** (reaction time: 15 min), and **(B)** (reaction time: 1h), with commercial 3,5-dichlorobenzoic acid **5m** (36.7 mg, 0.19 mmol, 1.0 equiv.) and **1a** (104.9 mg, 0.29 mmol, 1.5 equiv.), which afforded the product as a white solid (with Cu-catalyst 0.104 mmol, 55% yield, with Co-catalyst 0.157 mmol, 83% yield) after column chromatography EtOAc/Cyclohexane 3:7): **TLC R_f** = 0.59 (EtOAc/Cyclohexane, 1:1, SiO₂); **mp**: 87.8 – 89.5 °C ; **[α]_D²⁰** = - 12.7 (c, 1.00 in CHCl₃); **IR (neat, cm⁻¹)** 2964, 2920, 1747, 1571, 1426, 1366, 1207, 1073, 1030; **¹H NMR (300 MHz, CDCl₃) δ (ppm)** 7.89 (d, *J* = 2.1 Hz, 2H), 7.57 (t, *J* = 2.1 Hz, 1H), 5.91 (dd, *J* = 5.0, 2.7 Hz, 1H), 5.39 – 5.25 (m, 2H), 5.17 (ddd, *J* = 9.3, 6.0, 3.1 Hz, 1H), 4.30 (dd, *J* = 12.5, 4.5 Hz, 1H), 4.12 (dd, *J* = 12.6, 2.3 Hz, 1H), 3.92 (ddd, *J* = 10.1, 4.6, 2.3 Hz, 1H), 2.06 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 1.99 (s, 3H); **¹³C{¹H} NMR (75 MHz, CDCl₃) δ (ppm)** 170.7 (C_q), 170.2 (C_q), 169.5 (C_q), 169.3 (C_q), 162.5 (C_q), 135.7 (2 x C_q), 133.9 (CH), 131.4 (C_q), 128.6 (2 x CH), 92.9

(CH), 73.0 (CH), 72.6 (CH), 70.3 (CH), 67.9 (CH), 61.5 (CH₂), 20.8 (CH₃), 20.7 (3 x CH₃); **HRMS (ESI) (M + Na)⁺** *m/z* calculated for C₂₁H₂₂Cl₂O₁₁Na 543.0437, found 543.0432.

β-D-Glucopyranose, 2,3,4,6-tetraacetate 1-(2,4-dichlorobenzoate) [7n]

Compound **7n** was prepared by using the general procedure (A) (reaction time: 15min), with commercial 2,3-dichlorobenzoic acid **5n** (36.7 mg, 0.19 mmol, 1.0 equiv.) and **1a** (104.9 mg, 0.29 mmol, 1.5 equiv.), which afforded the product as a amorphous solid (0.097 mmol, 55% **yield** after column chromatography EtOAc/Cyclohexane 4:6); **R_f** (40% EtOAc/Cyclohexane) = 0.50; **[α]_D²⁵** = -37.27 (c 0,011 CH₂Cl₂); **IR (neat, cm⁻¹)** 3460, 1745, 1711, 1584, 1376, 1207, 1071, 1021; **¹H NMR (300 MHz, CDCl₃) δ (ppm)** 7.85 (d, *J* = 8.5 Hz, 1H), 7.49 – 7.45 (m, *J* = 1.4 Hz, 1H), 7.31 (d, *J* = 8.5 Hz, 1H), 5.92 (d, *J* = 7.5 Hz, 1H), 5.29 (t, *J* = 6.6 Hz, 2H), 5.16 (t, *J* = 9.3 Hz, 1H), 4.31 (dd, *J* = 12.5, 4.3 Hz, 1H), 4.15 – 4.07 (m, 1H), 3.95 – 3.88 (m, 1H), 2.05 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H); **¹³C{¹H} NMR (75 MHz, CDCl₃) δ (ppm)** 170.52(C_q), 170.00(C_q), 169.35(C_q), 169.29(C_q), 161.96(C_q), 139.68(C_q), 136.07(C_q), 133.26(CH), 131.41(CH), 127.30(CH), 125.77(C_q), 92.45(CH), 72.86(CH), 72.63(CH), 70.12(CH), 67.73(CH), 61.37(CH₂), 20.66(CH₃), 20.54 (3 x CH₃); **HRMS (ESI) (M + Na)⁺** *m/z* calculated for C₂₁H₂₂O₁₁NaCl₂Na: 543.0437, found 543.0432.

β-D-Glucopyranose, 2,3,4,6-tetraacetate 1-(2,5-difluorobenzoate) [7o]

Compound **7o** was prepared by using the general procedure A (reaction time: 15min), with commercial 2,5-difluorobenzoic acid **5o** (36.7 mg, 0.19 mmol, 1.0 equiv.) and **1a** (104.9 mg, 0.29 mmol, 1.5 equiv.), which afforded the product as a white solid (0.118 mmol, 62% **yield** after column chromatography EtOAc/Cyclohexane 4:6); **R_f** (40% EtOAc/Cyclohexane) = 0.39; **mp**: 105–112 °C; **[α]_D²⁵** = -37.73 (c 0,0053 in CH₂Cl₂); **IR (neat, cm⁻¹)** 1758, 1739, 1496, 1381, 1209, 1185, 1077, 1035; **¹H NMR (300 MHz, CDCl₃) δ (ppm)** 7.64 – 7.55 (m, 1H), 7.30 – 7.21 (m, 1H), 7.16 – 7.10 (m, *J* = 9.3, 4.1 Hz, 1H), 5.91 (d, *J* = 7.4 Hz, 1H), 5.33 – 5.27 (m, *J* = 3.4 Hz, 2H), 5.21 – 5.12 (m, *J* = 9.5 Hz, 1H), 4.30 (dd, *J* = 12.5, 4.4 Hz, 1H), 4.13 (d, *J* = 12.1 Hz, 1H), 3.96 – 3.89 (m, *J* = 9.8 Hz, 1H), 2.06 (s, 3H), 2.03 – 2.00 (m, 9H); **¹³C{¹H} NMR (75 MHz, CDCl₃) δ(ppm)** 170.55(C_q), 170.06(C_q), 169.35(C_q), 169.15(C_q), 161.00(C_q), 160.15(C_q), 159.59(C_q), 156.31(C_q), 122.29(CH), 118.55(CH), 118.21(CH), 92.50(CH), 72.85(CH), 72.59(CH), 70.00(CH), 67.75(CH), 61.40(CH₂), 20.65(CH₃), 20.55(2 x CH₃), 20.48(CH₃); **¹⁹F NMR (376 MHz, CDCl₃) δ (ppm)** -113.91(CF), -117.23 (CF); **HRMS (ESI) (M + Na)⁺** *m/z* calculated for C₂₁H₂₂O₁₁F₂Na: 511.1022, found 511.1028.

β-D-Glucopyranose, 2,3,4,6-tetraacetate 1-(2-nitrobenzoate) [7p]

Compound **7p** was prepared by using the general procedure (B) (reaction time: 1h), with commercial 2-nitrobenzoic acid **5p** (32.1 mg, 0.19 mmol, 1.0 equiv.) and **1a** (104.9 mg, 0.29 mmol, 1.5 equiv.), which afforded the product as a white solid (55.0 mg, 58% **yield** after column chromatography EtOAc/Cyclohexane 3:7); **TLC R_f** = 0.36 (EtOAc/Cyclohexane, 1:1, SiO₂); **mp**: 74.9 – 75.6 °C; **[α]_D²⁰** = -8.5 (c, 1.00 in CHCl₃); **IR (neat, cm⁻¹)** 2954, 2929, 1757,

1536, 1367, 1351, 1242, 1063, 1035; **¹H NMR (300 MHz, CDCl₃) δ (ppm)** 7.96 (d, *J* = 7.4 Hz, 1H), 7.78 – 7.61 (m, 3H), 5.93 (d, *J* = 8.2 Hz, 1H), 5.32 (t, *J* = 9.4 Hz, 1H), 5.16 (dd, *J* = 20.6, 9.1 Hz, 2H), 4.33 (dd, *J* = 12.5, 4.4 Hz, 1H), 4.15 (dd, *J* = 12.0, 1.8 Hz, 1H), 4.02 – 3.82 (m, 1H), 2.11 (s, 3H), 2.08 (s, 3H), 2.04 (s, 3H), 2.01 (s, 3H); **¹³C{¹H} NMR (75 MHz, CDCl₃) δ (ppm)** 170.7 (C_q), 170.2 (C_q), 169.7 (C_q), 169.5 (C_q), 163.9 (C_q), 147.8 (C_q), 133.4 (CH), 132.5 (CH), 130.2 (CH), 126.5 (C_q), 124.3 (CH), 93.1 (CH), 73.0 (CH), 72.8 (CH), 69.9 (CH), 67.8 (CH), 61.5 (CH₂), 20.8 (2 x CH₃), 20.7 (2 x CH₃); **HRMS (ESI) (M + Na)⁺** *m/z* calculated for C₂₁H₂₃NO₁₃Na 520.1067, found 520.1066.

β-D-Glucopyranose, 2,3,4,6-tetraacetate 1-(2-amino, 3,5-dibromo, 6-chlorobenzoate) [7q]

Compound **7q** was prepared by using the general procedure (A) (reaction time: 15 min), with commercial 2-amino-3,5-dibromo-6-chlorobenzoic acid **5q** (63.24 mg, 0.19 mmol, 1.0 equiv.) and **1a** (104.9 mg, 0.29 mmol, 1.5 equiv.), which afforded the product as a white solid (0.09 mmol, 47% **yield** after column chromatography EtOAc/Cyclohexane 4:6); **R_f** (40% EtOAc/Cyclohexane) = 0.38; **mp**: 213–219 °C; **[α]_D²⁵** = -19.6 (c 0,0051 in CH₂Cl₂); **IR (neat, cm⁻¹)** 3371, 2925, 1756, 1730, 1442, 1368, 1245, 1111, 1083, 1032; **¹H NMR (300 MHz, CDCl₃) δ (ppm)** 7.73 (s, 1H), 6.00 (d, *J* = 7.9 Hz, 1H), 5.27 (t, 1H), 5.21 (d, *J* = 9.3 Hz, 1H), 5.15 (d, *J* = 5.8 Hz, 2H), 4.30 (dd, *J* = 12.5, 4.6 Hz, 1H), 4.19 – 4.08 (m, 2H), 3.95 – 3.87 (m, 1H), 2.06 (s, 3H), 2.03 (s, 6H), 2.00 (s, 3H); **¹³C{¹H} NMR (75 MHz, CDCl₃) δ (ppm)** 170.53(C_q), 170.06(C_q), 169.27(C_q), 169.16(C_q), 163.88(C_q), 144.48(C_q), 138.34(CH), 132.37(C_q), 115.83(C_q), 110.31(C_q), 109.00(C_q), 92.71(CH), 73.05(CH), 72.75(CH), 69.99(CH), 67.69(CH), 61.32(CH₂), 20.67(CH₃), 20.54 (3 x CH₃); **HRMS (ESI) (M + Na)⁺** *m/z* calculated for C₂₁H₂₂NO₁₁ClBr₂Na: 679.9140, found 679.9109.

β-D-Glucopyranose, 2,3,4,6-tetraacetate 1-(3,5-diiodo, 4-aminobenzoate) [7r]

Compound **7r** was prepared by using the general procedure (B) (reaction time: 1h), with commercial 4-amino-3,5-diiodobenzoic acid **5r** (74.7 mg, 0.19 mmol, 1.0 equiv.) and **1a** (104.9 mg, 0.29 mmol, 1.5 equiv.), which afforded the product as a white solid (64.4 mg, 47% **yield** after column chromatography EtOAc/Cyclohexane 3:7); **TLC R_f** = 0.52 (EtOAc/Cyclohexane, 1:1, SiO₂); **mp**: 151.8 – 152.5 °C; **[α]_D²⁰** = -3.0 (c, 1.00 in CHCl₃); **IR (neat, cm⁻¹)** 3467, 3359, 2959, 1757, 1610, 1360, 1201, 1060, 1034; **¹H NMR (300 MHz, CDCl₃) δ (ppm)** 8.28 (s, 2H), 5.89 (d, *J* = 7.4 Hz, 1H), 5.34 – 5.26 (m, 1H), 5.22 – 5.10 (m, 2H), 4.31 (dd, *J* = 12.5, 4.3 Hz, 1H), 4.12 (ddd, *J* = 12.5, 1.2, 0.6 Hz, 1H), 3.91 (ddd, *J* = 6.3, 3.8, 1.5 Hz, 1H), 2.08 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H), 1.99 (s, 3H), no NH₂ protons observed; **¹³C{¹H} NMR (75 MHz, CDCl₃) δ (ppm)** 170.7 (C_q), 170.2 (C_q), 169.5 (C_q), 169.4 (C_q), 169.1 (C_q), 161.9 (C_q), 150.7 (2 x C_q), 141.7 (2 x CH), 120.4 (C_q), 92.3 (CH), 72.8 (CH), 72.7 (CH), 70.3 (CH), 67.9 (CH), 61.6 (CH₂), 20.8 (CH₃), 20.7 (3 x CH₃); **HRMS (ESI) (M + Na)⁺** *m/z* calculated for C₂₁H₂₃I₂NO₁₁Na 741.9258, found 741.9264.

β-D-Glucopyranose, 2,3,4,6-tetraacetate 1-acrylate [7s]

Compound **7s** was prepared by using the general procedure (B) (reaction time: 1h), with commercial acrylic acid **5s** (13.8

mg, 0.19 mmol, 1.0 equiv.) and **1a** (104.9 mg, 0.29 mmol, 1.5 equiv.), which afforded the product as a white solid (60.2 mg, 78% **yield** after column chromatography EtOAc/Cyclohexane 3:7); **TLC** R_f = 0.56 (EtOAc/Cyclohexane, 1:1, SiO₂); **mp**: 107.9 – 109.4 °C ; $[\alpha]_D^{20}$ = - 2.7 (c, 1.00 in CHCl₃); **IR** (neat, cm⁻¹) 3457, 2949, 1746, 1368, 1229, 1219, 1079, 1037 ; **¹H NMR** (300 MHz, CDCl₃) δ (ppm) 6.50 (d, J = 17.0 Hz, 1H), 6.11 (dd, J = 17.1, 10.5 Hz, 1H), 5.96 (d, J = 10.5 Hz, 1H), 5.78 (d, J = 8.0 Hz, 1H), 5.36 – 5.03 (m, 3H), 4.30 (dd, J = 12.5, 4.5 Hz, 1H), 4.11 (dd, J = 12.4, 2.3 Hz, 1H), 3.87 (ddd, J = 10.1, 4.6, 2.3 Hz, 1H), 2.08 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H); **¹³C{¹H} NMR** (75 MHz, CDCl₃) δ (ppm) 170.7 (C_q), 170.2 (C_q), 169.5 (C_q), 169.4 (C_q), 163.9 (C_q), 133.7 (CH₂), 127.2 (CH), 92.1 (CH), 72.9 (CH), 72.8 (CH), 70.3 (CH), 68.0 (CH), 61.6 (CH₂), 20.8 (CH₃), 20.7 (3 x CH₃); **HRMS (ESI) (M + Na)⁺ m/z** calculated for C₁₇H₂₂O₁₁Na 425.1060, found 425.1058.

β -D-Glucopyranose, 2,3,4,6-tetraacetate 1-(3-methyl-2-butenate) [7t]

Compound **7t** was prepared by using the general procedure (B) (reaction time: 1h), with commercial 3,3-dimethylacrylic acid **5t** (19.2 mg, 0.19 mmol, 1.0 equiv.) and **1a** (104.9 mg, 0.29 mmol, 1.5 equiv.), which afforded the product as an amorphous solid (64.3 mg, 78% **yield** after column chromatography EtOAc/Cyclohexane 3:7); **TLC** R_f = 0.46 (EtOAc/Cyclohexane, 1:1, SiO₂); $[\alpha]_D^{20}$ = - 4.9 (c, 1.00 in CHCl₃); **IR** (neat, cm⁻¹) 3487, 2964, 1757, 1646, 1434, 1367, 1212, 1081, 1035 ; **¹H NMR** (300 MHz, CDCl₃) δ (ppm) 5.74 (d, J = 8.3 Hz, 1H), 5.67 (s, 1H), 5.32 – 5.21 (m, 1H), 5.14 (dt, J = 9.5, 6.8 Hz, 2H), 4.28 (dd, J = 12.5, 4.4 Hz, 1H), 4.10 (dd, J = 12.5, 2.2 Hz, 1H), 3.84 (ddd, J = 10.0, 4.6, 2.1 Hz, 1H), 2.17 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H), 2.00 (s, 6H), 1.91 (s, 3H); **¹³C{¹H} NMR** (75 MHz, CDCl₃) δ (ppm) 170.7 (C_q), 170.2 (C_q), 169.5 (C_q), 169.4 (C_q), 164.1 (C_q), 161.4 (C_q), 114.7 (CH), 91.3 (CH), 73.0 (CH), 72.7 (CH), 70.4 (CH), 68.0 (CH), 61.6 (CH₂), 27.8 (CH₃), 20.8 (CH₃), 20.7 (4 x CH₃); **HRMS (ESI) (M + Na)⁺ m/z** calculated for C₁₉H₂₆O₁₁Na 453.1373, found 453.1378.

β -D-Glucopyranose, 2,3,4,6-tetraacetate 1-(2-thiophenecarboxylate) [7u]

Compound **7u** was prepared by using both **general procedures** (A) (reaction time: 15 min) with commercial 2-thiophenecarboxylic acid **5u** (24.6 mg, 0.19 mmol, 1.0 equiv.) and **1a** (104.9 mg, 0.29 mmol, 1.5 equiv.), which afforded the product as a white solid (with Cu-catalyst 0.156 mmol, 82% **yield**, with Co-catalyst 0.157 mmol, 83% **yield**) after column chromatography EtOAc/Cyclohexane 3:7); **TLC** R_f = 0.50 (EtOAc/Cyclohexane, 1:1, SiO₂); **mp**: 115.5 – 116.7 °C ; $[\alpha]_D^{20}$ = - 20.8 (c, 1.00 in CHCl₃); **IR** (neat, cm⁻¹) 2959, 1758, 1524, 1416, 1364, 1221, 1065, 1037; **¹H NMR** (300 MHz, CDCl₃) δ (ppm) 7.85 (d, J = 4.1 Hz, 1H), 7.64 (d, J = 4.8 Hz, 1H), 7.18 – 7.04 (m, 1H), 5.92 – 5.81 (m, 1H), 5.36 – 5.27 (m, 2H), 5.25 – 5.11 (m, 1H), 4.32 (dd, J = 12.5, 4.6 Hz, 1H), 4.13 (dd, J = 12.6, 2.3 Hz, 1H), 3.93 (ddd, J = 9.8, 4.5, 2.3 Hz, 1H), 2.07 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 2.00 (s, 3H); **¹³C{¹H} NMR** (75 MHz, CDCl₃) δ (ppm) 170.8 (C_q), 170.2 (C_q), 169.6 (C_q), 169.4 (C_q), 160.1 (C_q), 135.3 (CH), 134.4 (CH), 131.9 (C_q), 128.3 (CH), 92.5 (CH), 72.9 (CH), 72.7 (CH), 70.2 (CH), 68.0 (CH), 61.6 (CH₂), 20.8 (CH₃), 20.7

(3 x CH₃); **HRMS (ESI) (M + Na)⁺ m/z** calculated for C₁₉H₂₂O₁₁Na 481.0781, found 481.0783.

β -D-Glucopyranose, 2,3,4,6-tetraacetate 1-(3-quinolinecarboxylate) [7v]

Compound **7v** was prepared by using the general procedure (B) (reaction time: 1h), with commercial 3-quinolinecarboxylic acid **5v** (33.3 mg, 0.19 mmol, 1.0 equiv.) and **1a** (104.9 mg, 0.29 mmol, 1.5 equiv.), which afforded the product as a white solid (48.2 mg, 50% **yield** after column chromatography EtOAc/Cyclohexane 3:7); **TLC** R_f = 0.27 (EtOAc/Cyclohexane, 1:1, SiO₂); **mp**: 190.0 – 192.2 °C ; $[\alpha]_D^{20}$ = - 23.9 (c, 1.00 in CHCl₃); **IR** (neat, cm⁻¹) 3492, 2959, 1757, 1621, 1367, 1213, 1077, 1034; **¹H NMR** (300 MHz, CDCl₃) δ (ppm) 9.42 (d, J = 2.3 Hz, 1H), 8.84 (d, J = 2.4 Hz, 1H), 8.16 (d, J = 8.5 Hz, 1H), 7.96 (d, J = 7.9 Hz, 1H), 7.92 – 7.81 (m, 1H), 7.64 (t, J = 7.5 Hz, 1H), 6.01 (dd, J = 5.3, 2.6 Hz, 1H), 5.44 – 5.31 (m, 2H), 5.22 (ddd, J = 9.3, 6.2, 2.9 Hz, 1H), 4.34 (dd, J = 12.6, 4.5 Hz, 1H), 4.15 (dd, J = 12.5, 2.4 Hz, 1H), 3.98 (ddd, J = 10.1, 4.6, 2.3 Hz, 1H), 2.07 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H), 1.98 (s, 3H); **¹³C{¹H} NMR** (75 MHz, CDCl₃) δ (ppm) 170.7 (C_q), 170.2 (C_q), 169.5 (C_q), 169.4 (C_q), 163.6 (C_q), 150.3 (C_q), 150.1 (CH), 139.8 (CH), 132.7 (CH), 129.7 (CH), 129.5 (CH), 127.9 (CH), 126.8 (C_q), 121.4 (C_q), 92.7 (CH), 73.0 (CH), 72.7 (CH), 70.3 (CH), 67.9 (CH), 61.6 (CH₂), 20.8 (CH₃), 20.7 (3 x CH₃); **HRMS (ESI) (M + Na)⁺ m/z** calculated for C₂₄H₂₅NO₁₁Na 526.1320, found 526.1328.

β -D-Glucopyranose, 2,3,4,6-tetraacetate 1-(3-benzofuran-3-carboxylate) [7w]

Compound **7w** was prepared by using the general procedure A (reaction time: 15 min), with commercial benzofuran-3-carboxylic acid **5w** (31.1 mg, 0.19 mmol, 1.0 equiv.) and **1a** (104.9 mg, 0.29 mmol, 1.5 equiv.), which afforded the product as a white solid (0.114 mmol, 60% **yield** after column chromatography EtOAc/Cyclohexane 4:6); R_f (40% EtOAc/Cyclohexane) = 0.8 ; **mp** 122 - 128 °C ; $[\alpha]_D^{25}$ = -58.33 (c 0,006 CH₂Cl₂); **IR** (neat, cm⁻¹) 2923, 2361, 1738, 1260, 1221, 1072, 1035, 797; **¹H NMR** (300 MHz, CDCl₃) δ (ppm) 8.30 (s, 1H), 8.07 – 8.00 (m, J = 6.0, 3.1 Hz, 1H), 7.56 – 7.52 (m, J = 6.1, 3.1 Hz, 1H), 7.40 – 7.35 (m, J = 6.0, 3.2 Hz, 2H), 5.95 (dd, J = 5.8, 2.3 Hz, 1H), 5.35 (dd, J = 5.9, 2.8 Hz, 2H), 5.25 – 5.16 (m, J = 9.6, 6.5, 3.0 Hz, 1H), 4.34 (dd, J = 12.5, 4.4 Hz, 1H), 4.14 (dd, J = 12.5, 2.0 Hz, 1H), 4.00 – 3.92 (m, 1H), 2.07 (s, 3H), 2.04 (d, J = 2.2 Hz, 6H), 1.99 (s, 3H); **¹³C{¹H} NMR** (75 MHz, CDCl₃) δ (ppm) 170.59(C_q), 170.06(C_q), 169.41(C_q), 169.36(C_q), 160.94(C_q), 155.63(C_q), 152.57(CH), 125.68(CH), 124.58(CH), 124.07(C_q), 121.84(CH), 113.01(C_q), 111.80(CH), 91.85(CH), 72.77(CH), 72.62(CH), 70.11(CH), 67.87(CH), 61.44(CH₂), 20.69(CH₃), 20.58 (3 x CH₃); **HRMS (ESI) (M + Na)⁺ m/z** calculated for C₂₃H₂₄O₁₂Na: 515.1165, found 515.1167.

β -D-Glucopyranose, 2,3,4,6-tetraacetate 1-tridecanecarboxylate) [7x]

Compound **7x** was prepared by using both **general procedures** (A) (reaction time: 15 min), and (B) (reaction time: 1h), with commercial tridecanoic acid **5x** (41.2 mg, 0.19 mmol, 1.0 equiv.) and **1a** (104.9 mg, 0.29 mmol, 1.5 equiv.), which afforded the product as a transparent oil (with Cu-catalyst 0.114 mmol, 65% **yield**, with Co-catalyst 0.15 mmol, 79% **yield**)

after column chromatography EtOAc/Cyclohexane 3:7); **TLC** R_f = 0.46 (EtOAc/Cyclohexane, 1:1, SiO₂); $[\alpha]_D^{20}$ = -3.5 (c, 1.00 in CHCl₃); **IR** (neat, cm⁻¹) 2924, 2854, 1758, 1468, 1366, 1208, 1164, 1082, 1068; **¹H NMR** (300 MHz, CDCl₃) δ (ppm) 5.72 (d, J = 8.3 Hz, 1H), 5.23 (d, J = 9.3 Hz, 1H), 5.20 – 5.04 (m, 2H), 4.29 (dd, J = 12.5, 4.4 Hz, 1H), 4.09 (dd, J = 12.5, 2.2 Hz, 1H), 3.83 (ddd, J = 9.9, 4.6, 2.1 Hz, 1H), 2.34 (t, J = 7.5 Hz, 2H), 2.07 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H), 2.00 (s, 3H), 1.66 – 1.51 (m, 2H), 1.30 (d, J = 7.0 Hz, 2H), 1.27 (s, 2H), 1.24 (s, 14H), 0.86 (t, J = 6.7 Hz, 3H); **¹³C{¹H} NMR** (75 MHz, CDCl₃) δ (ppm) 171.9 (C_q), 170.7 (C_q), 170.2 (C_q), 169.5 (C_q), 169.3 (C_q), 91.7 (CH), 72.9 (CH), 72.8 (CH), 70.3 (CH), 67.9 (CH), 61.6 (CH₂), 34.2 (CH₂), 32.0 (CH₂), 29.7 (3 x CH₂), 29.5 (2 x CH₂), 29.3 (CH₂), 29.1 (CH₂), 24.7 (CH₂), 22.8 (CH₂), 20.8 (CH₃), 20.7 (3 x CH₃), 14.2 (CH₃); **HRMS** (ESI) (M + Na)⁺ m/z calculated for C₂₇H₄₄O₁₁Na 567.2781, found 567.2797.

β -D-Glucopyranose, 2,3,4,6-tetraacetate 1-(1-phenylcyclopropanecarboxylate) [7y]

Compound **7y** was prepared by using the general procedure **A** (reaction time: 15 min), with commercial 1-phenylcyclopropane-1-carboxylic acid **5y** (31.2 mg, 0.19 mmol, 1.0 equiv.) and **1a** (104.9 mg, 0.29 mmol, 1.5 equiv.), which afforded the product as a white solid (52 mg, 55% yield after column chromatography EtOAc/Cyclohexane 4:6); R_f (40% EtOAc/Cyclohexane) = 0.54; mp 154–162 °C; $[\alpha]_D^{25}$ = -13.33 (c 0.006 CH₂Cl₂); **IR** (neat, cm⁻¹) 3250, 1754, 1742, 1629, 1252, 1231, 1082; **¹H NMR** (300 MHz, CDCl₃) δ (ppm) 7.29 (s, 5H), 5.61 (d, J = 8.1 Hz, 1H), 5.17 (d, J = 9.2 Hz, 1H), 5.07 (t, J = 9.6 Hz, 1H), 4.98 (t, J = 8.7 Hz, 1H), 4.26 (dd, J = 12.5, 4.4 Hz, 1H), 4.12 – 4.04 (m, J = 17.0, 4.5 Hz, 1H), 3.83 – 3.77 (m, 1H), 2.07 (s, 3H), 2.00 (s, 3H), 1.98 (s, 3H), 1.96 (s, 3H), 1.77 – 1.69 (m, 1H), 1.60 – 1.52 (m, 1H), 1.26 (d, J = 7.1 Hz, 2H); **¹³C{¹H} NMR** (75 MHz, CDCl₃) δ (ppm) 172.60(C_q), 170.60(C_q), 170.06(C_q), 169.33(C_q), 168.82(C_q), 138.23(C_q), 130.4 (2 x CH), 128.24(2 x CH), 127.54(CH), 92.12(CH), 72.67(CH), 72.62(CH), 69.96(CH), 67.77(CH), 61.45(CH₂), 28.94(C_q), 20.72(CH₃), 20.54(2 x CH₃), 20.46(CH₃), 17.00(CH₂), 16.96(CH₂); **HRMS** (ESI) (M + Na)⁺ m/z calculated for C₂₄H₂₈O₁₁Na: 515.1524, found 515.1523.

β -D-Glucopyranose, 2,3,4,6-tetraacetate 1-(1,2,3,4-tetrahydro-1-naphthalenecarboxylate) [7z]

Compound **7z** was prepared by using the general procedure **(B)** (reaction time: 1h), with commercial 1,2,3,4-tetrahydronaphthalene-1-carboxylic acid **5z** (33.8 mg, 0.19 mmol, 1.0 equiv.) and **1a** (104.9 mg, 0.29 mmol, 1.5 equiv.), which afforded the product as a white solid (65.7 mg, 68% yield after column chromatography EtOAc/Cyclohexane 3:7); diastereomeric mixture mostly visible on ¹³C NMR spectra; **TLC** R_f = 0.53 (EtOAc/Cyclohexane, 1:1, SiO₂); mp: 101.0 – 102.4 °C; $[\alpha]_D^{20}$ = -9.1 (c, 1.00 in CHCl₃); **IR** (neat, cm⁻¹) 2944, 1757, 1455, 1366, 1209, 1073, 1033; **¹H NMR** (300 MHz, CDCl₃) δ (ppm) 7.21 – 7.01 (m, 4H), 5.73 (dd, J = 7.5, 5.2 Hz, 1H), 5.30 – 5.02 (m, 3H), 4.36 – 4.22 (m, 1H), 4.11 (dd, J = 12.6, 1.3 Hz, 1H), 3.95 – 3.69 (m, 2H), 2.91 – 2.61 (m, 2H), 2.24 – 2.12 (m, 1H), 2.08 (s, 3H), 2.02 (s, 3H), 2.00 (d, J = 1.5 Hz, 3H), 1.96 – 1.88 (m, 1H), 1.86 (d, J = 3.9 Hz, 3H), 1.83 – 1.68 (m, 2H); **¹³C{¹H} NMR** (75 MHz, CDCl₃) δ (ppm) 173.0 (C_q), 172.7 (C_q), 170.7 (C_q), 170.2 (C_q), 169.5 (C_q, which is split into 169.3), 137.6 (C_q, which

is split into 137.4), 132.13 (C_q), 129.6 (2 x CH, which is split into 129.5 and 129.4), 127.25 (CH), 126.0 (CH, which is split into 125.9), 92.0 (CH, which is split into 91.8), 72.9 (2 x CH, which is split into 73.0 and 72.8), 70.2 (CH, which is split into 70.1), 68.0 (CH, which is split into 67.9), 61.6 (CH₂), 44.8 (CH, which is split into 43.9), 29.1 (CH₂, which is split into 29.0), 26.5 (CH₂, which is split into 25.8), 20.9 (CH₃, which is split into 20.4), 20.7 (3 x CH₃), 20.2 (CH₂); **HRMS** (ESI) (M + Na)⁺ m/z calculated for C₂₅H₃₀O₁₁Na 529.1680, found 529.1682.

D-glycero-D-gulo-Octonic acid, 3,7-anhydro-2-deoxy-, 2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl ester, 4,5,6,8-tetraacetate [7aa]

Compound **7aa** was prepared by using the general procedure **A** (reaction time: 15 min), with 2-((2S,3S,4R,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)acetic acid **5aa** (75 mg, 0.19 mmol, 1.0 equiv.) and **1a** (104.9 mg, 0.29 mmol, 1.5 equiv.), which afforded the product as a white solid (79 mg, 60% yield after column chromatography EtOAc/Cyclohexane 4:6); R_f (50% EtOAc/Cyclohexane) = 0.28; mp 155 – 162 °C; $[\alpha]_D^{25}$ = -90.00 (c 0.002 CH₂Cl₂); **IR** (neat, cm⁻¹) 1742, 1704, 1365, 1258, 1227, 1149, 1032; **¹H NMR** (300 MHz, CDCl₃) δ (ppm) 5.69 (d, J = 8.2 Hz, 1H), 5.25 (d, J = 9.4 Hz, 1H), 5.16 – 5.04 (m, J = 15.3, 8.9 Hz, 4H), 4.91 (t, J = 9.6 Hz, 1H), 4.30 – 4.19 (m, 2H), 4.11 – 4.06 (m, J = 7.8, 3.5 Hz, 1H), 3.96 – 3.88 (m, 1H), 3.87 – 3.81 (m, J = 9.0, 3.1 Hz, 1H), 3.74 – 3.70 (m, 1H), 3.70 – 3.66 (m, 1H), 3.64 – 3.59 (m, J = 10.1 Hz, 1H), 3.49 – 3.45 (m, J = 8.1, 5.3 Hz, 1H), 2.07 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H), 2.02 (d, J = 3.4 Hz, 9H), 2.01 (s, 3H), 1.99 (s, 3H); **¹³C{¹H} NMR** (75 MHz, CDCl₃) δ (ppm) 170.51(C_q), 170.23(C_q), 170.03(C_q), 169.41(C_q), 169.34(C_q), 167.95(C_q), 91.91(CH), 75.95(CH), 73.96(CH), 73.83(CH), 72.81(CH), 72.53(CH), 71.50(CH), 71.27(C_q), 70.50(C_q), 70.17(C_q), 70.00(CH), 68.25(CH), 67.71(CH), 61.89(CH₂), 61.35(CH₂), 37.17(CH₂), 20.67(3 x CH₃), 20.54(5 x CH₃); **HRMS** (ESI) (M + Na)⁺ m/z calculated for C₃₀H₄₀O₂₀Na: 743.2011, found 743.1990.

2.1 Late stage functionalization of pharmaceutical carboxylates

Procedure for the synthesis of β -D-Glucopyranose, 2,3,4,6-tetraacetate 1-[3-(aminosulfonyl)-5-(butylamino)-4-phenoxybenzoate] [7ab] and its characterization data

Compound **7ab** was prepared by using the general procedure (reaction time: 2h), with commercial Bumetanide (70.0 mg, 0.19 mmol, 1.0 equiv.) and **1a** (104.9 mg, 0.29 mmol, 1.5 equiv.), which afforded the product as a white solid (44.1 mg, 33% yield after column chromatography EtOAc/Cyclohexane 2:8 -> 3:7); **TLC** R_f = 0.35 (EtOAc/Cyclohexane, 1:1, SiO₂); mp: 103.4 – 104.5 °C; $[\alpha]_D^{20}$ = -15.1 (c, 1.00 in CHCl₃); **IR** (neat, cm⁻¹) 3418, 3270, 2959, 2924, 1745, 1436, 1367, 1213, 1034; **¹H NMR** (300 MHz, CDCl₃) δ (ppm) 7.95 (d, J = 1.8 Hz, 1H), 7.51 (d, J = 1.9 Hz, 1H), 7.39 – 7.23 (m, 2H), 7.10 (t, J = 7.3 Hz, 1H), 6.91 (dd, J = 8.6, 2.9 Hz, 2H), 5.96 – 5.84 (m, 1H), 5.39 – 5.27 (m, 2H), 5.27 – 5.12 (m, 1H), 5.06 (s, 2H), 4.32 (dd, J = 12.5, 4.5 Hz, 1H), 4.14 (dd, J = 12.4, 2.5 Hz, 1H), 3.95 (ddd, J = 12.8, 7.6, 3.9 Hz, 2H), 3.10 (dd, J = 12.5, 6.8 Hz, 2H), 2.07 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H), 1.73 – 1.56 (m, 1H), 1.41 – 1.27 (m, 1H), 1.22 – 1.07 (m,

2H), 0.82 (t, $J = 7.3$ Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ (ppm) 170.8 (C_q), 170.2 (C_q), 169.6 (C_q), 169.5 (C_q), 163.5 (C_q), 155.7 (C_q), 142.5 (C_q), 140.7 (C_q), 136.6 (C_q), 130.2 (2 x CH), 126.4 (C_q), 124.0 (CH), 117.1 (CH), 116.8 (CH), 115.5 (2 x CH), 92.8 (CH), 72.9 (CH), 72.6 (CH), 70.3 (CH), 68.0 (CH), 61.6 (CH_2), 43.1 (CH_2), 31.0 (CH_2), 20.8 (CH_3), 20.7 (3 x CH_3), 19.9 (CH_2), 13.8 (CH_3); HRMS (ESI) ($\text{M} + \text{Na}$) $^+$ m/z calculated for $\text{C}_{31}\text{H}_{38}\text{N}_2\text{O}_{14}\text{SNa}$ 717.1936, found 717.1982.

Procedure for the synthesis of β -D-Glucopyranose, 2,3,4,6-tetraacetate 1-[4-[(dipropylamino)sulfonyl]benzoate] [7ac] and its characterization data

Prepared according to the general procedure C, thiosugar **1a** (96 mg, 0.262 mmol), 4-(N,N-dipropylsulfamoyl)benzoic acid (Probenecid) (50 mg, 0.175 mmol), $\text{Cu}(\text{acac})_2$ (4.5mg, 5%, 0.009mmol) and Ag_2CO_3 (145 mg, 0.525 mmol). The mixture was stirred at 130 °C for 15mn in microwaves. The crude product was purified by silica gel chromatography (50% EtOAc/Pentane), and the product was isolated as a white oil (57.15 mg, 53%).

R_f (50% EtOAc/Pentane) = 0.62 ; $[\alpha]_D^{25} = -20.1$ (c 0.0016 CH_2Cl_2) ; IR (neat, cm^{-1}) 1760, 1367, 1243, 1085, 1069 ; ^1H NMR (300 MHz, CDCl_3) δ (ppm) 8.14 (d, $J = 8.3$ Hz, 2H), 7.88 (d, $J = 8.3$ Hz, 2H), 5.94 – 5.89 (m, 1H), 5.36 – 5.32 (m, 2H), 5.22 – 5.14 (m, 1H), 4.31 (dd, $J = 12.5, 4.5$ Hz, 1H), 4.13 (dd, $J = 12.5, 1.8$ Hz, 1H), 4.00 – 3.90 (m, 1H), 3.13 – 3.05 (m, 4H), 2.04 (t, 9H), 1.99 (s, 3H), 1.61 – 1.46 (m, $J = 14.8, 7.4$ Hz, 4H), 0.86 (t, $J = 7.4$ Hz, 6H) ; $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, DMSO) δ (ppm) 170.45(C_q), 169.95(C_q), 169.34(C_q), 169.27(C_q), 163.23(C_q), 145.36(C_q), 131.66(C_q), 130.74(2xCH), 127.17(2xCH), 92.70(CH), 72.89(CH), 72.48(CH), 70.13(CH), 67.85(CH), 61.40(CH_2), 49.90(2x CH_2), 21.89(2x CH_2), 20.61(CH_3), 20.51(3x CH_3), 11.09(2x CH_3); HRMS (ESI) ($\text{M} + \text{H}$) $^+$ m/z calculated for $\text{C}_{27}\text{H}_{38}\text{NO}_{13}\text{S}$: 616.2058, found 616.2061.

β -D-Galactopyranose, 2,3,4,6-tetraacetate 1-(2,6-dimethoxybenzoate) [8a]

Compound **8a** was prepared by using the general procedure A (reaction time: 15 min), with commercial 3,5-dichlorobenzoic acid **5c** (36.7 mg, 0.19 mmol, 1.0 equiv.) and **1b**¹ (104.9 mg, 0.29 mmol, 1.5 equiv.), which afforded the product as a white solid (70.7 mg, 71% yield after column chromatography EtOAc/Cyclohexane 3:7); TLC R_f = (30% EtOAc/Cyclohexane) = 0.91; $[\alpha]_D^{25} = -29.00$ (c 0,0031 CH_2Cl_2); IR (neat, cm^{-1}) 2844, 1746, 1598, 1478,1369, 1232, 1113, 1053; ^1H NMR (300 MHz, CDCl_3) δ (ppm) 7.22 (d, $J = 8.0$ Hz, 1H), 6.48 (d, $J = 8.5$ Hz, 2H), 6.00 (d, $J = 8.3$ Hz, 1H), 5.41 – 5.30 (m, 2H), 5.08 (dd, $J = 10.4, 3.4$ Hz, 1H), 4.12 (d, $J = 5.9$ Hz, 1H), 4.06 (dd, $J = 7.4, 2.0$ Hz, 2H), 3.74 (s, 6H), 2.07 (s, 3H), 2.01 (s, 3H), 1.98 (d, $J = 3.9$ Hz, 3H), 1.94 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ (ppm) 170.30(C_q), 170.16(C_q), 170.01(C_q), 169.20(C_q), 164.29(C_q), 157.67(2 x C_q), 131.82(CH), 103.96 (2 x CH), 92.46(CH), 71.85(CH), 71.14(CH), 68.07(CH), 66.79(CH), 60.90(CH_2), 56.01(2 x CH_3), 29.70(CH_3), 20.63(3 x CH_3), 20.56(CH_3); HRMS (ESI) ($\text{M} + \text{Na}$) $^+$ m/z calculated for $\text{C}_{23}\text{H}_{28}\text{O}_{13}\text{Na}$: 535.1428, found 535.1428.

β -D-Galactopyranose, 2,3,4,6-tetraacetate 1-(3,5-dichlorobenzoate)[8b]

Compound **8b** was prepared by using the general procedure (reaction time: 1h), with commercial 3,5-dichlorobenzoic acid **5m** (36.7 mg, 0.19 mmol, 1.0 equiv.) and **1b** (104.9 mg, 0.29 mmol, 1.5 equiv.), which afforded the product as a white solid (70.7 mg, 71% yield after column chromatography EtOAc/Cyclohexane 3:7); TLC R_f = 0.58 (EtOAc/Cyclohexane, 1:1, SiO_2); mp: 67.6 – 69.5 °C ; $[\alpha]_D^{20} = -10.4$ (c, 1.00 in CHCl_3); IR (neat, cm^{-1}) 3087, 1739, 1572, 1368, 1208, 1081, 1030; ^1H NMR (300 MHz, CDCl_3) δ (ppm) 7.92 (s, 2H), 7.58 (s, 1H), 5.89 (d, $J = 8.3$ Hz, 1H), 5.57 – 5.37 (m, 2H), 5.16 (dd, $J = 10.4, 3.5$ Hz, 1H), 4.23 – 3.99 (m, 3H), 2.19 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ (ppm) 170.5 (C_q), 170.2 (C_q), 170.1 (C_q), 169.5 (C_q), 162.5 (C_q), 135.7 (2 x C_q), 133.9 (CH), 131.4 (C_q), 128.6 (2 x CH), 93.4 (CH), 72.0 (CH), 70.7 (CH), 67.8 (CH), 66.9 (CH), 61.1 (CH_2), 20.8 (3 x CH_3), 20.7 (CH_3); HRMS (ESI) ($\text{M} + \text{Na}$) $^+$ m/z calculated for $\text{C}_{21}\text{H}_{22}\text{Cl}_2\text{O}_{11}\text{Na}$ 543.0437, found 543.0433.

β -D-Mannopyranose, 2,3,4,6-tetraacetate 1-(3,5-dichlorobenzoate) [8c]

Compound **8c** was prepared by using the general procedure (reaction time: 1h), with commercial 3,5-dichlorobenzoic acid **5m** (36.7 mg, 0.19 mmol, 1.0 equiv.) and **1c** (104.9 mg, 0.29 mmol, 1.5 equiv.), which afforded the product as a white solid (42.8 mg, 43% yield after column chromatography EtOAc/Cyclohexane 3:7); TLC R_f = 0.58 (EtOAc/Cyclohexane, 1:1, SiO_2); mp: 80.0 – 81.5 °C ; $[\alpha]_D^{20} = +26.3$ (c, 1.00 in CHCl_3); IR (neat, cm^{-1}) 3087, 2959, 1750, 1572, 1369, 1271, 1095, 1051; ^1H NMR (300 MHz, CDCl_3) δ (ppm) 7.91 (d, $J = 1.7$ Hz, 2H), 7.67 – 7.56 (m, 1H), 6.31 (s, 1H), 5.49 – 5.35 (m, 3H), 4.32 (dd, $J = 12.6, 5.3$ Hz, 1H), 4.12 (dd, $J = 9.3, 3.4$ Hz, 2H), 2.21 (s, 3H), 2.09 (s, 6H), 2.04 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ (ppm) 170.7 (C_q), 170.1 (C_q), 169.8 (C_q), 169.6 (C_q), 161.8 (C_q), 135.9 (2 x C_q), 134.0 (CH), 131.6 (C_q), 128.4 (2 x CH), 92.2 (CH), 71.4 (CH), 68.9 (CH), 68.3 (CH), 65.4 (CH), 62.1 (CH_2), 20.9 (CH_3), 20.8 (3 x CH_3); HRMS (ESI) ($\text{M} + \text{Na}$) $^+$ m/z calculated for $\text{C}_{21}\text{H}_{22}\text{Cl}_2\text{O}_{11}\text{Na}$ 543.0437, found 543.0444.

β -D-Fucopyranose, 2,3,4,6-tetraacetate 1-(2,6-dimethoxybenzoate) [8d]

Compound **8d** was prepared by using the general procedure (reaction time: 15 min), with commercial 2,6-dimethoxybenzoic acid **5c** (27.75 mg, 0.152 mmol, 1.0 equiv.) and **1d** (70.0 mg, 0.228 mmol, 1.5 equiv.), which afforded the product as a white oil (50 mg, 72 % yield after column chromatography (1% MeOH/DCM); TLC R_f = (50% EtOAc/Cyclohexane) = 0.63 ; $[\alpha]_D^{25} = -16.68$ (c 0.0016 CH_2Cl_2); IR (neat, cm^{-1}) 1575, 1598 ,1257 ,1056 ,726 ; ^1H NMR (300 MHz, CDCl_3) δ (ppm) 7.29 (t, $J = 8.4$ Hz, 1H), 6.54 (d, $J = 8.5$ Hz, 2H), 6.05 (d, $J = 8.3$ Hz, 1H), 5.45 – 5.33 (m, 1H), 5.29 (d, $J = 3.3$ Hz, 1H), 5.15 (dd, 1H), 4.16 – 4.07 (m, 1H), 3.80 (s, 6H), 2.16 (s, 3H), 2.08 (s, 3H), 2.00 (s, 3H), 1.31 – 1.24 (m, $J = 6.5, 1.9$ Hz, 3H) ; $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ (ppm) ^{13}C NMR (75 MHz, CDCl_3) δ (ppm) 170.55(C_q), 170.04(C_q), 169.30(C_q), 164.43(C_q), 157.69(2 x C_q), 131.67(CH), 111.59(2 x CH), 103.95(CH), 92.50(CH), 71.59(CH), 70.50(CH), 70.10(CH), 68.24(CH), 55.99(2 x CH_3), 20.66(CH_3), 20.61(CH_3), 20.57(CH_3), 15.98(CH_3); HRMS (ESI) ($\text{M} + \text{H}$) $^+$ m/z calculated for $\text{C}_{21}\text{H}_{27}\text{O}_{11}$: 455.15479, found 455.1542.

β-D-Glucopyranose, 2,3,4,6-benzoate 1-(3,5-dichlorobenzoate) [8e]

Compound **8e** was prepared by using the general procedure (reaction time: 1h), with commercial 3,5-dichlorobenzoic acid **5m** (36.7 mg, 0.19 mmol, 1.0 equiv.) and **1e** (176.3 mg, 0.29 mmol, 1.5 equiv.), which afforded the product as a white solid (75.1 mg, 51% yield after column chromatography EtOAc/Cyclohexane 3:7); **TLC** R_f = 0.84 (EtOAc/Cyclohexane, 1:1, SiO₂); **mp**: 100.9 – 101.5 °C ; $[\alpha]_D^{20}$ = + 8.9 (c, 1.00 in CHCl₃); **IR** (neat, cm⁻¹) 3067, 2969, 1722, 1602, 1452, 1316, 1091, 1086, 1026; **¹H NMR** (300 MHz, CDCl₃) δ (ppm) 8.05 (d, *J* = 7.3 Hz, 2H), 7.94 (dd, *J* = 7.5, 4.1 Hz, 4H), 7.90 (s, 1H), 7.89 (s, 2H), 7.87 (s, 1H), 7.56 (d, *J* = 7.3 Hz, 1H), 7.54 – 7.51 (m, 2H), 7.51 – 7.47 (m, 1H), 7.44 (dd, *J* = 7.3, 2.8 Hz, 2H), 7.37 (d, *J* = 7.3 Hz, 3H), 7.32 (d, *J* = 7.8 Hz, 3H), 7.28 (s, 1H), 6.27 (d, *J* = 7.9 Hz, 1H), 6.06 (t, *J* = 9.4 Hz, 1H), 5.84 (dd, *J* = 13.5, 5.8 Hz, 2H), 4.69 (dd, *J* = 12.3, 2.7 Hz, 1H), 4.52 (dd, *J* = 12.3, 4.7 Hz, 1H), 4.47 – 4.36 (m, 1H); **¹³C{¹H} NMR** (75 MHz, CDCl₃) δ (ppm) 166.2 (C_q), 165.8 (C_q), 165.2 (2 x C_q), 162.6 (C_q), 135.6 (3 x C_q), 133.8 (2 x CH), 133.7 (2 x CH), 133.5 (CH), 133.3 (CH), 131.5 (C_q), 130.0 (4 x CH), 129.9 (4 x CH), 129.6 (C_q), 128.7 (2 x C_q), 128.6 (5 x CH), 128.5 (4 x CH), 93.4 (CH), 73.5 (CH), 72.7 (CH), 71.0 (CH), 69.0 (CH), 62.7 (CH₂); **HRMS** (ESI) (M + Na)⁺ *m/z* calculated for C₄₁H₃₀Cl₂O₁₁Na 791.1063, found 791.1062.

α-D-Glucopyranose, 2,3,4,6-tetra-O-methyl 1-(2,6-dimethoxybenzoate) [α-8f]

Compounds **α-8f** and **β-8f** were prepared by using the procedure (A) (reaction time: 15 min) with commercial 2,6-dimethoxybenzoic acid **5c** (91.46 mg, 0.502 mmol, 1.0 equiv.) and **1f** (190.0 mg, 0.753 mmol, 1.5 equiv.), which afforded the product as a yellow oil in a mixture of α : β (1:1 ratio) (184 mg, 91%). After purification through column chromatography EtOAc/Cyclohexane 5:5), both anomers were isolated and characterized:

Anomer α-8f: 45% yield, **TLC** R_f = (50% EtOAc/Cyclohexane) = 0.4 ; $[\alpha]_D^{25}$ = 123.07 (c 0.0016 CH₂Cl₂); **IR** (neat, cm⁻¹) 1752, 1597, 1476, 1257, 1091, 730; **¹H NMR** (300 MHz, CDCl₃) δ (ppm) 7.28 (t, *J* = 8.4 Hz, 1H), 6.54 (d, *J* = 8.4 Hz, 2H), 5.72 (d, *J* = 7.8 Hz, 1H), 3.77 (d, *J* = 15.4 Hz, 6H), 3.68 – 3.67 (m, *J* = 1.9 Hz, 1H), 3.65 (s, 3H), 3.63 (d, *J* = 3.8 Hz, 1H), 3.57 (s, 3H), 3.55 (s, 3H), 3.50 – 3.45 (m, 1H), 3.41 (s, 3H), 3.29 (dd, *J* = 10.5, 6.1 Hz, 2H), 3.25 – 3.18 (m, 1H); **¹³C{¹H} NMR** (75 MHz, CDCl₃) δ (ppm) 164.90(C_q), 157.40(C_q), 131.28(CH), 112.52(C_q), 103.83(2 x CH), 94.65(CH), 86.42(CH), 82.65(CH), 78.78(CH), 75.73(CH), 70.75(C_q), 60.81(CH₃), 60.29(CH₃), 60.15(CH₃), 59.30(CH₃), 55.85(2 x CH), 29.63(CH₂); **HRMS** (ESI) (M + H)⁺ *m/z* calculated for C₁₉H₂₉O₉; 401.1806, found 401.1766.

β-D-Glucopyranose, 2,3,4,6-tetra-O-methyl 1-(2,6-dimethoxybenzoate) [β-8f]

Anomer β-8f: 45% yield, **TLC** R_f = (50% EtOAc/Cyclohexane) = 0.52 ; $[\alpha]_D^{25}$ = 235.72 (c 0.0016 CH₂Cl₂); **IR** (neat, cm⁻¹) 1745, 1596, 1476, 1257, 1097, 990; **¹H NMR** (300 MHz, CDCl₃) δ (ppm) 7.28 (s, 1H), 6.54 (d, *J* = 8.4 Hz, 2H), 6.49 (d, *J* = 3.5 Hz, 1H), 3.95 – 3.86 (m, *J* = 12.9, 5.4 Hz, 1H), 3.80 (s, 6H), 3.62 (s, 2H), 3.61 (s, 3H), 3.55 (s, 3H), 3.49 (s, 3H), 3.40 (s, 3H), 3.39 (d, *J* = 3.5 Hz, 1H), 3.36 (d, *J* = 3.6 Hz, 1H), 3.32 – 3.26 (m, *J* = 9.5 Hz, 1H); **¹³C{¹H} NMR** (75 MHz, CDCl₃) δ (ppm) 164.78(C_q),

157.81(C_q), 131.38(CH), 112.44(C_q), 104.02(2 x CH), 89.96(CH), 83.05(CH), 80.52, (CH) 78.82(CH), 72.41(CH), 70.67(C_q), 60.73(CH₃), 60.45(CH₃), 59.14(CH₃), 58.24(CH₃), 55.91(2 x CH), 29.65(CH₂); **HRMS** (ESI) (M + H)⁺ *m/z* calculated for C₁₉H₂₉O₉; 401.1806, found 401.1766.

D-Glucopyranose, 2,4,6-tri-O-[tert-butyldimethylsilyl] 1-benzoate [8g]

Compound **8g** was prepared by using the general procedure A (reaction time: 15 min), with commercial benzoic acid **5a** (1.0 equiv.) and **1g** (1.2 equiv.), which afforded the product as a colourless oil in a mixture of two isomers 2:1 ratio (36 mg, 70% yield after column chromatography EtOAc/Cyclohexane 3:7); **TLC** R_f = 0.33 (EtOAc/Cyclohexane, 95:5, SiO₂); **¹H NMR** (300 MHz, CDCl₃) δ (ppm) 8.08 (m, 2H, H-2, H-6), 7.59 (m, 1H, H-4), 7.47 (dt, *J* = 15.1, 7.6 Hz, 2H, H-3, H-5), 6.33 (d, *J* = 3.4 Hz, 0.3H, H-1'), 6.09 – 5.99 (m, 0.7H, H-1'), 4.08 – 3.93 (m, 2H,), 3.85 (d, *J* = 2.7 Hz, 2H,), 3.81 – 3.58 (m, 2H,), 3.24 (d, *J* = 4.1 Hz, 0.7H, OH), 2.82 (d, *J* = 2.7 Hz, 0.3H, OH), 0.98 (s, 3H, CH₃), 0.89 (dd, *J* = 4.4, 2.3 Hz, 21H, 7XCH₃), 0.82 (s, 3H, CH₃), 0.21 (d, *J* = 15.0 Hz, 3H, CH₃), 0.18 – 0.14 (m, 6H, 2XCH₃), 0.12 (d, *J* = 2.0 Hz, 3H, CH₃), 0.09 (d, *J* = 4.5 Hz, 3H, CH₃), 0.05 (s, 3H, CH₃). **¹³C{¹H} NMR** (75 MHz, CDCl₃) δ (ppm) 164.23 (C=O), 132.25 (Ph), 129.02 (Ph), 128.83 (C1), 128.76 (Ph), 127.46 (Ph), 127.25(Ph), 93.57 (C1'), 91.77 (C1'), 74.85, 74.66, 74.00, 71.98, 71.65, 71.50, 70.58, 63.35 (C6'), 63.19 (C6'), 25.18 (SiC(CH₃)₃), 24.97 (SiC(CH₃)₃), 24.77 (SiC(CH₃)₃), 17.40 (SiC(CH₃)₃), 17.23 (SiC(CH₃)₃), 16.93 (SiC(CH₃)₃), -5.03 (SiCH₃), -5.08 (SiCH₃), -5.18 (SiCH₃), -5.30 (SiCH₃), -5.42 (SiCH₃), -6.46 (SiCH₃). **HRMS** (ESI) (M + Na)⁺ *m/z* calculated for C₃₁H₆₂NO₇Si₃⁺ 644.3832, found 644.3834.

β-D-Cellobiose, 2,2',3,3',4',6,6'-heptaacetate 1-(2,6-dimethoxybenzoate) [8h]

Compound **8h** was prepared by using the general procedure A (reaction time: 15 min), with commercial 2,6-dimethoxybenzoic acid **5c** (18.58 mg, 0.102mmol, 1.0 equiv.) and **1h** (99.85 mg, 0.153 mmol, 1.5 equiv.), which afforded the product as a yellow oil (43.3 mg, 53% yield after column chromatography 2% MeOH/DCM); **TLC** R_f = (50% MeOH/DCM) = 0.29; $[\alpha]_D^{25}$ = -43.75 (c 0.0032 CH₂Cl₂); **IR** (neat, cm⁻¹) 3400, 1759, 1738, 1364, 1212, 1114, 1042 ; **¹H NMR** (300 MHz, CDCl₃) δ (ppm) 7.22 (d, *J* = 6.5 Hz, 1H), 6.47 (d, *J* = 8.4 Hz, 2H), 5.96 (d, *J* = 8.1 Hz, 1H), 5.26 – 5.18 (m, *J* = 8.9 Hz, 1H), 5.14 – 5.03 (m, 2H), 4.99 (d, *J* = 9.6 Hz, 1H), 4.87 (t, *J* = 8.4 Hz, 1H), 4.51 – 4.43 (m, 2H), 4.30 (dd, *J* = 12.4, 4.5 Hz, 1H), 4.13 (dd, *J* = 12.2, 4.5 Hz, 1H), 4.03 – 3.97 (m, *J* = 12.6 Hz, 1H), 3.86 – 3.80 (m, *J* = 6.7 Hz, 1H), 3.79 – 3.75 (m, 1H), 3.73 (s, 6H), 3.64 – 3.57 (m, *J* = 9.8 Hz, 1H), 2.06 (s, 3H), 2.04 (s, 3H), 1.98 (s, 6H), 1.97 (s, 3H), 1.95 (s, 3H), 1.93 (s, 3H); **¹³C{¹H} NMR** (75 MHz, CDCl₃) δ (ppm) 169.52(C_q), 169.27(C_q), 169.22(C_q), 168.71(C_q), 168.46(C_q), 168.29(C_q), 168.01(C_q), 163.08(C_q), 156.73(2 x C_q), 130.85(CH), 110.30(C_q), 102.97(2 x CH), 99.61(CH), 90.96(CH), 74.93(CH), 72.74(CH), 71.92(CH), 71.61(CH), 70.99(CH), 70.60(CH), 69.81(CH), 66.85(CH), 60.69(CH₂), 60.59(CH₂), 54.99(2 x CH₃), 19.81(CH₃), 19.63(CH₃), 19.53(5 x CH₃); **HRMS** (ESI) (M + Na)⁺ *m/z* calculated for C₃₅H₄₄O₂₁Na: 823.2273, found 823.2275.

β-D-Cellobiose, 2,2',3',3',4',6,6'-heptaacetate 1-(3,5-dichlorobenzoate) [8i]

Compound **8i** was prepared by using the general procedure B (reaction time: 1h), with commercial 3,5-dichlorobenzoic acid **5m** (36.7 mg, 0.19 mmol, 1.0 equiv.) and **1h** (187.8 mg, 0.29 mmol, 1.5 equiv.), which afforded the product as a white solid (69.1 mg, 45% **yield** after column chromatography EtOAc/Cyclohexane 3:7); **TLC** R_f = 0.41 (EtOAc/Cyclohexane, 1:1, SiO₂); **mp**: 162.2 – 164.0 °C ; $[\alpha]_D^{20}$ = - 10.7 (c, 1.00 in CHCl₃); **IR** (neat, cm⁻¹) 2949, 1757, 1745, 1368, 1230, 1215, 1168, 1037; **¹H NMR** (300 MHz, CDCl₃) δ (ppm) 7.87 (d, *J* = 2.2 Hz, 2H), 7.58 (t, *J* = 2.2 Hz, 1H), 5.87 (d, *J* = 7.8 Hz, 1H), 5.34 – 5.21 (m, 2H), 5.11 (dt, *J* = 18.9, 9.7 Hz, 2H), 4.98 – 4.90 (m, 1H), 4.56 – 4.46 (m, 2H), 4.37 (dd, *J* = 12.5, 4.5 Hz, 1H), 4.13 (dd, *J* = 12.2, 4.2 Hz, 1H), 4.06 (dd, *J* = 12.5, 2.4 Hz, 1H), 3.93 – 3.79 (m, 2H), 3.68 (ddd, *J* = 9.7, 4.6, 2.3 Hz, 1H), 2.11 (s, 3H), 2.10 (s, 3H), 2.06 (s, 3H), 2.04 (s, 3H), 2.01 (s, 3H), 2.00 (s, 3H), 1.99 (s, 3H); **¹³C{¹H} NMR** (75 MHz, CDCl₃) δ (ppm) 170.6 (C_q), 170.4 (2 x C_q), 169.7 (C_q), 169.6 (C_q), 169.5 (C_q), 169.2 (C_q), 162.4 (C_q), 135.7 (2 x C_q), 133.9 (CH), 131.5 (C_q), 128.6 (2x CH), 100.9 (CH), 92.8 (CH), 76.0 (CH), 73.8 (CH), 73.0 (CH), 72.3 (CH), 72.2 (CH), 71.7 (CH), 70.4 (CH), 67.9 (CH), 61.8 (CH₂), 61.7 (CH₂), 21.0 (CH₃), 20.8 (CH₃), 20.7 (5 x CH₃); **HRMS (ESI) (M + Na)⁺** *m/z* calculated for C₃₃H₃₈Cl₂O₁₉Na 831.1277, found 831.1299.

β-D-Glucopyranose, O-2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl-(1→4)-O-2,3,6-tri-O-acetyl- α -D-glucopyranosyl-(1→4)-, 2,3,6-triacetate 1-(2,6-dimethoxybenzoate) [8j]

Compound **8j** was prepared by using the general procedure A (reaction time: 15 min), with commercial 2,6-dimethoxybenzoic acid **5c** (10.2 mg, 0.056 mmol, 1.0 equiv.) and **1i**^[25] (79.0 mg, 0.084 mmol, 1.5 equiv.), which afforded the product as a white solid (25.6 mg, 42% **yield** after column chromatography (1% MeOH/DCM); **TLC** R_f = R_f (50% EtOAc/Cyclohexane) = 0.17; **mp**: 92-101 °C ; $[\alpha]_D^{25}$ = +28.88 (c 0,0045 CH₂Cl₂); **IR** (neat, cm⁻¹) 3260,2978, 1757, 1641, 1369, 1297, 1115, 1044; **¹H NMR** (300 MHz, CDCl₃) δ (ppm) 7.22 (d, *J* = 6.6 Hz, 1H), 6.47 (d, *J* = 8.5 Hz, 1H), 6.03 (d, *J* = 7.9 Hz, 1H), 5.37 – 5.33 (m, *J* = 4.0 Hz, 2H), 5.29 (d, *J* = 4.4 Hz, 2H), 5.25 (dd, *J* = 6.9, 3.5 Hz, 2H), 5.02 – 4.95 (m, *J* = 9.0, 4.4 Hz, 2H), 4.80 (dd, *J* = 10.5, 3.9 Hz, 1H), 4.69 (dd, *J* = 10.3, 4.0 Hz, 1H), 4.43 – 4.38 (m, 2H), 4.32 (dd, *J* = 12.1, 4.0 Hz, 1H), 4.19 (dd, *J* = 12.5, 3.4 Hz, 1H), 4.08 (d, *J* = 7.1 Hz, 1H), 4.03 – 3.99 (m, *J* = 7.4 Hz, 1H), 3.92 – 3.85 (m, *J* = 8.5 Hz, 4H), 3.73 (s, 6H), 2.09 (d, *J* = 3.9 Hz, 6H), 2.04 (s, 3H), 2.01 (s, 3H), 1.97 (s, 9H), 1.96 – 1.93 (m, 9H); **¹³C{¹H} NMR** (75 MHz, CDCl₃) δ (ppm) 170.79(2 x C_q), 170.64(2 x C_q), 170.50(C_q), 170.19(C_q), 169.93(C_q), 169.78(2 x C_q), 169.60(2 x C_q), 164.14(C_q), 157.91(C_q), 132.00(CH), 104.12(2 x CH), 96.00(CH), 95.84(CH), 91.84(CH), 75.60(CH), 73.63(CH), 73.30(CH), 72.70(CH), 71.89(CH), 71.58(CH), 70.59(CH), 70.22(CH), 69.54(CH), 69.14(CH), 68.67(CH), 68.09(CH), 63.00(CH₂), 62.47(CH₂), 61.57(CH₂), 56.15(2 x CH₃), 29.85(C_q), 21.00(CH₃), 20.81(CH₃), 20.73(8 x CH₃); **HRMS (ESI) (M + Na)⁺** *m/z* calculated for C₄₇H₆₀O₂₉Na: 1111.3118, found 1111.3125.

β-D-Glucopyranose, O-2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl-(1→4)-O-2,3,6-tri-O-acetyl- α -D-

glucopyranosyl-(1→4)-, 2,3,6-triacetate 1-(3,5-dichlorobenzoate) [8k]

Compound **8k** was prepared by using the general procedure B (reaction time: 1h), with commercial 3,5-dichlorobenzoic acid **5m** (36.7 mg, 0.19 mmol, 1.0 equiv.) and **1i** (270.8 mg, 0.29 mmol, 1.5 equiv.), which afforded the product as a white solid (80.6 mg, 38% **yield** after column chromatography EtOAc/Cyclohexane 1:1); **TLC** R_f = 0.25 (EtOAc/Cyclohexane, 1:1, SiO₂); **mp**: 125.4 – 126.7 °C ; $[\alpha]_D^{20}$ = + 64.0 (c, 1.00 in CHCl₃); **IR** (neat, cm⁻¹) 2964, 2934, 1756, 1572, 1433, 1367, 1205, 1024; **¹H NMR** (300 MHz, CDCl₃) δ (ppm) 7.88 (s, 2H), 7.58 (s, 1H), 5.97 (d, *J* = 7.7 Hz, 1H), 5.44 – 5.35 (m, 4H), 5.33 (d, *J* = 4.4 Hz, 1H), 5.29 (d, *J* = 4.6 Hz, 1H), 5.17 – 5.09 (m, 1H), 5.05 (d, *J* = 9.9 Hz, 1H), 4.86 (dd, *J* = 10.3, 4.1 Hz, 1H), 4.75 (dd, *J* = 10.3, 3.9 Hz, 1H), 4.47 (d, *J* = 11.6 Hz, 2H), 4.28 (ddd, *J* = 20.8, 12.4, 3.6 Hz, 2H), 4.21 – 4.12 (m, 1H), 4.10 – 4.00 (m, 2H), 3.93 (dd, *J* = 11.1, 6.0 Hz, 3H), 2.15 (s, 6H), 2.10 (s, 3H), 2.06 (s, 3H), 2.04 (s, 6H), 2.03 (s, 3H), 2.01 (s, 3H), 1.99 (s, 6H); **¹³C{¹H} NMR** (75 MHz, CDCl₃) δ (ppm) 170.8 (2 x C_q), 170.7 (C_q), 170.6 (C_q), 170.5 (C_q), 170.0 (2 x C_q), 169.8 (C_q), 169.7 (C_q), 169.6 (C_q), 162.4 (C_q), 135.7 (2 x C_q), 133.9 (CH), 131.5 (C_q), 128.6 (2 x CH), 96.2 (CH), 95.8 (CH), 92.4 (CH), 74.9 (CH), 73.6 (CH), 73.2 (CH), 72.6 (CH), 71.8 (CH), 70.9 (CH), 70.6 (CH), 70.2 (CH), 69.5 (CH), 69.3 (CH), 68.7 (CH), 68.0 (CH), 62.7 (CH₂), 62.4 (CH₂), 61.5 (CH₂), 21.1 (3 x CH₃), 20.8 (7 x CH₃); **HRMS (ESI) (M + Na)⁺** *m/z* calculated for C₄₅H₅₄Cl₂O₂₇Na 1119.2127, found 1119.2125.

2. Application of the methodology for molecular complexity

β-D-Glucopyranose, 2,3,4,6-tetraacetate 1-[4-[[3,4,6-tri-O-acetyl-2-(acetylamino)-2-deoxy- β -D-glucopyranosyl]thio]benzoate] [9a]

According to A. Bruneau *et al.* procedure^[31], a sealed tube is charged with Xantphos Pd-G3 precatalyst (2 mol%), *N*-acetyl-1-thio- β -D-aminoglucopyranose **1j** (27.2 mg, 0.075 mmol, 1.0 equiv.), (2*R*,3*R*,4*S*,5*R*,6*S*)-2-(acetoxymethyl)-6-((4-iodobenzoyl)oxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate **7i** (43.4 mg, 0.075 mmol, 1 equiv.). After Argon flushing, dioxane (0.3 mL, 0.25M) is added. Upon stirring the reaction mixture, NEt₃ (0.01 mL, 0.075 mmol, 1 equiv.) is added to the medium. The reaction mixture was stirred at room temperature under Argon during 2h, which afforded the product **9a** as a white solid (54.9 mg, 90% **yield** after column chromatography EtOAc/Cyclohexane 5:5 -> 8:2); **TLC** R_f = 0.07 (EtOAc/Cyclohexane, 1:1, SiO₂); **mp**: 248.9 – 249.4 °C ; $[\alpha]_D^{19}$ = - 8.5 (c, 1.00 in CHCl₃); **IR** (neat, cm⁻¹) 2939, 1740, 1595, 1434, 1367, 1213, 1084, 1043; **¹H NMR** (300 MHz, CDCl₃) δ (ppm) 7.92 (d, *J* = 8.5 Hz, 2H), 7.48 (d, *J* = 8.5 Hz, 2H), 5.89 (d, *J* = 7.9 Hz, 1H), 5.73 (d, *J* = 9.2 Hz, 1H), 5.36 – 5.30 (m, 2H), 5.30 – 5.13 (m, 2H), 5.13 – 4.99 (m, 2H), 4.32 (dd, *J* = 12.6, 4.4 Hz, 1H), 4.23 – 4.09 (m, 3H), 3.93 (ddd, *J* = 9.7, 4.5, 2.2 Hz, 1H), 3.81 (ddd, *J* = 10.0, 5.6, 2.6 Hz, 1H), 2.10 (s, 3H), 2.07 (s, 3H), 2.04 (s, 6H), 2.03 (s, 6H), 1.98 (s, 3H), 1.95 (s, 3H), no NH proton observed; **¹³C{¹H} NMR** (75 MHz, CDCl₃) δ (ppm) 171.2 (C_q), 170.7 (2 x C_q), 170.3 (C_q), 170.2 (C_q), 169.6 (C_q), 169.5 (C_q), 169.4 (C_q), 164.1 (C_q), 141.9 (C_q), 130.6 (2 x CH), 129.6 (2 x CH), 126.9 (C_q), 92.5 (CH), 85.6 (CH), 76.1 (CH), 73.5 (CH), 72.9 (CH), 72.7 (CH), 70.2 (CH), 68.4 (CH), 68.0 (CH), 62.5 (CH₂), 61.6 (CH₂), 53.4 (CH), 23.4 (CH₃), 20.9 (CH₃), 20.8 (2 x CH₃), 20.7 (4 x CH₃);

HRMS (ESI) (M + Na)⁺ m/z calculated for C₃₅H₄₃NO₁₉SNa 836.2048, found 836.2033.

L-Cysteine, *N*-acetyl-*S*-[4-[[2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl]oxy]carbonyl]phenyl]- **[9b]**

According to A. Bruneau *et al.* procedure^[31], a sealed tube is charged with Xantphos Pd-G3 precatalyst (4 mol%), *N*-Acetyl-*L*-Cysteine (17 mg, 0.10 mmol, 1.0 equiv.), (2*R*,3*R*,4*S*,5*R*,6*S*)-2-(acetoxymethyl)-6-((4-iodobenzoyl)oxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate **7I** (50 mg, 0.086 mmol, 1 equiv.). After Argon flushing, dioxane (1 mL) is added. Upon stirring the reaction mixture, NEt₃ (0.129 mmol) is added to the medium. The reaction mixture was stirred at 60 °C during 20 min, which afforded the product **9b** as a beige solid (35.5 mg, 67% yield after column chromatography MeOH/DCM 1:9); **R_f** (5% MeOH/DCM) = 0.29 ; **mp**: 152-160 °C; [α]_D²⁵ = -50.00 (c 0,002 CH₂Cl₂); **IR** (neat, cm⁻¹) 1752, 1738, 1595, 1235, 1214, 1087, 1054, 1033 ; **¹H NMR** (300 MHz, DMSO) δ (ppm) 7.77 (d, *J* = 8.3 Hz, 2H), 7.66 – 7.61 (m, 1H), 7.42 (d, *J* = 8.4 Hz, 2H), 6.16 (d, *J* = 8.2 Hz, 1H), 5.53 (t, *J* = 9.6 Hz, 1H), 5.17 – 5.09 (m, 1H), 5.03 (t, *J* = 9.7 Hz, 1H), 4.33 – 4.25 (m, *J* = 9.2 Hz, 1H), 4.20 (dd, *J* = 12.2, 4.8 Hz, 1H), 4.02 (d, *J* = 12.4 Hz, 1H), 3.59 – 3.50 (m, 1H), 3.36 – 3.21 (m, 2H), 2.08 (s, 3H), 2.00 (d, *J* = 1.2 Hz, 6H), 1.98 (s, 3H), 1.95 (s, 3H); **¹³C{¹H} NMR** (75 MHz, DMSO) δ(ppm) 172.88(C_q), 170.87(C_q), 170.31(2 x C_q), 170.09(2 x C_q), 164.14(C_q), 147.14(C_q), 130.25(2 x CH), 126.48(2 x CH), 124.07(C_q), 92.06(CH₂), 72.02(2 x CH), 70.48(CH), 68.06(CH), 61.71(CH₂), 53.90(CH), 34.92(CH₂), 22.97(CH₃), 20.81(CH₃), 20.69(CH₃), 20.62(CH₃), 20.54(CH₃).; **HRMS (ESI) (M + Na)⁺ m/z** calculated for C₂₆H₃₁NO₁₄NaS: 636.1363, found 636.1370.

3. Extension of the methodology for molecular diversity

3.1 Procedure for the synthesis of 2-acetamidoethyl 3,5-dichlorobenzoate [10a] and its characterization data

Compound **10a** was prepared by using the general procedure (reaction time: 1h), with commercial 3,5-dichlorobenzoic acid **5m** (36.7 mg, 0.19 mmol, 1.0 equiv.) and commercial *N*-acetylcysteamine (34.3 mg, 0.29 mmol, 1.5 equiv.), which afforded the product as a white solid (35.8 mg, 68% yield after column chromatography EtOAc/Cyclohexane 1:1 -> 7:3); **TLC R_f** = 0.13 (EtOAc/Cyclohexane, 1:1, SiO₂); **mp**: 139.0 – 139.5 °C ; [α]_D²⁰ = - 5.1 (c, 1.00 in CHCl₃); **IR** (neat, cm⁻¹) 3293, 3078, 1728, 1642, 1570, 1432, 1385, 1362, 1274; **¹H NMR** (300 MHz, CDCl₃) δ (ppm) 7.90 (d, *J* = 1.9 Hz, 2H), 7.56 (t, *J* = 2.0 Hz, 1H), 5.99 – 5.77 (m, 1H, NH proton), 4.43 (t, *J* = 5.3 Hz, 2H), 3.66 (dd, *J* = 10.9, 5.5 Hz, 2H), 2.03 (s, 3H); **¹³C{¹H} NMR** (75 MHz, CDCl₃) δ (ppm) 170.7 (C_q), 164.5 (C_q), 135.6 (2 x C_q), 133.2 (CH), 132.7 (C_q), 128.2 (2 x CH), 64.8 (CH₂), 39.0 (CH₂), 23.4 (CH₃); **HRMS (ESI) (M + Na)⁺ m/z** calculated for C₁₁H₁₁NO₃Cl₂Na 298.0014, found 298.0025.

Synthesis of the starting thiosugars **1g**

β-*D*-Glucopyranose, 2,4,6-tris-*O*-[(1,1-dimethylethyl)dimethylsilyl]-1-thio-**1g**

NaOMe (0.5 M sol. in MeOH, 6 ml, 1.5 eq) was added to a solution thiosugar **1a** (750 mg, 2 mmol) in MeOH (28 ml) and stirred at RT for 30 min under Ar atmosphere. The solution was neutralized using Dowex® 50WX8 100-200 (H), filtered, concentrated and used without further purification.

To the polyhydroxy product in anhydrous DMF (14 ml), TBDMSCl (3 g, 20 mmol, 10 equiv.) and imidazole (3.3 g, 48 mmol, 24 equiv.) were added and stirred at RT for overnight under Ar atmosphere. TLC showed no more starting material and also showed products with different number of TBS protecting groups (three and four according to HRMS (ESI+)). The reaction was quenched with MeOH (10ml) then extracted with pentane (3x 15 ml). The pentane layers were collected and dried over MgSO₄, filtered, concentrated under reduced pressure then purified by column chromatography using (1-2% EtOAc in pentane). Out of all fractions, only one pure fraction was obtained as colorless oil (72 mg) in 7% yield.

R_f = 0.67 (using 10% EtOAc in cyclohexane); [α]_D¹⁵ = -10 (c, 0.5 in CHCl₃); **IR** (neat, cm⁻¹) 2956.90, 2926.87, 2855.56, 1258.66, 1151.15, 835.71, 777.26, 670.96; **¹H NMR** (400 MHz, CDCl₃) δ 4.71 (dd, *J* = 8.6, 5.3 Hz, 1H, H-1), 3.94 (dd, *J* = 10.3, 4.9 Hz, 1H, H-6), 3.86 (dd, *J* = 10.3, 6.6 Hz, 1H, H-6'), 3.72 (t, *J* = 5.6 Hz, 1H, H-4), 3.68 (d, *J* = 5.4 Hz, 1H, H-2), 3.67 – 3.62 (m, 1H, H-3), 3.60 (dd, *J* = 6.8, 5.0 Hz, 1H, H-5), 3.11 (d, *J* = 4.7 Hz, 1H, OH), 2.42 (d, *J* = 8.5 Hz, 1H, SH), 0.94 (s, 6H, 2XCH₃), 0.92 (s, 9H, 3XCH₃), 0.90 (s, 12H, 4XCH₃), 0.18 (s, 3H, CH₃), 0.16 (s, 3H, CH₃), 0.14 (d, *J* = 2.8 Hz, 6H, 2XCH₃), 0.09 (s, 6H, 2XCH₃); **¹³C{¹H} NMR** (101 MHz, CDCl₃): δ 79.96 (C1), 78.32 (C3), 77.55 (C2), 77.22 (C4), 72.78 (C5), 65.21 (C6), 26.44 (SiC(CH₃)₃), 26.23 (SiC(CH₃)₃), 26.01 (SiC(CH₃)₃), 18.64 (SiC(CH₃)₃), 18.41 (SiC(CH₃)₃), 18.27 (SiC(CH₃)₃), -3.18 (SiCH₃), -3.27 (SiCH₃), -3.47 (SiCH₃), -3.57 (SiCH₃), -5.20 (SiCH₃), -5.23 (SiCH₃). **HRMS (ESI) (M + NH₄)⁺ m/z** calculated for C₂₄H₅₈NO₅SSi₃⁺ 556.3338, found 556.3353.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Full optimization table, NMR spectra of all synthesized compounds and HPLC chromatograms.

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ABBREVIATIONS

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1,2 trans-selective O-glycosylation of anomeric thiosugars

