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Palladium(II)-assisted activation of thioglycosides†

Samira Escopy, Yashapal Singh * and Alexei V. Demchenko *

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Described herein is the first example of glycosidation of thioglycosides in the presence of palladium(II) bromide. While the activation with $PdBr_2$ alone was proven feasible, higher yields and cleaner reactions were achieved when these glycosylations were performed in the presence of propargyl bromide as an additive. Preliminary mechanistic studies suggest that propargyl bromide assists the reaction by creating an ionizing complex, which accelerates the leaving group departure. A variety of thioglycoside donors in reactions with different glycosyl acceptors were investigated to determine the initial scope of this new reaction. Selective and chemoselective activation of thioglycosides over other leaving groups has also been explored.

Introduction

Improved understanding of the roles of glycans in various biological processes earned this class of molecules a unique stature in contemporary research.[1] To elucidate specific functions of carbohydrates, the availability of analytically pure glycans is essential. However, practically all aspects of the synthesis and purification of complex carbohydrates remain challenging.[2,3] Numerous approaches have been developed for the installation of glycosidic linkages.[4] Among known glycosyl donors, halides,[5] imidates[6] and thioglycosides[7] are the most common. First reported by Fischer in 1916,[8] thioglycosides are very stable compounds and many are already commercially available. However, thioglycosides can be readily activated using thiophilic promoter systems, and are known to fit as building blocks into various strategies for glycan synthesis.[9–11] A significant effort has been dedicated to the development of activators for the glycosidation of thioglycosides[12] including metal salts,[13–16] halogens,[17–22] organosulfur reagents,[23–28] alkylating reagents,[29] photo-activators with or without heavy metal additives,[30–33] and single electron-transfer activators.[34] Nevertheless, many of these approaches have pitfalls, and the quest for better activators continues.

Transition metal catalysis is a relatively new trend in synthesis to replace toxic chemicals and establish greener reaction conditions. This approach has also found its application in glycochemistry.[35–38] Specifically, a new class of glycosyl donors having alkyne-containing aglycones as leaving groups have gained popularity due to their high affinity to non-toxic Au(I), Au(III)[38,39] and other transition metal salts.[40,41] However, these methods require specialized leaving groups that have been specifically purposed to be compatible with these activation conditions. Activation of conventional thioglycosides through the direct coordination of a green post-transition metal salt with the anomeric sulfur was first reported by Pohl *et al.* who employed a sub-stoichiometric amount of $Ph_3Bi(OTf)_2$.[42,43] Subsequently, Sureshan *et al.*[44] demonstrated the direct activation of thioglycosides using a sub-stoichiometric amount of $AuCl_3$ at ambient temperature. Zhu *et al.*[45] also showed that propargyl thioglycosides are activated through the direct coordination of Au(III) to the sulfur atom rather than the remote pathway *via* the alkyne functionality. As a part of our efforts toward the development of novel methods for glycosylation, herein we report first activation of alkyl/aryl thioglycosides with palladium bromide ($PdBr_2$).

Results and discussion

Palladium(II) catalysis is among commonly used methods in organic chemistry, and its application in glycochemistry is also known.[36,46–54] In our previous endeavors, we encountered Pd(II) and Pt(IV) mediated reactions that served as the basis for the development of the temporary deactivation approach,[55,56] metal-complexation directed stereoselective glycosylations,[57,58] and glycosyl donors with switchable stereoselectivity.[59,60] However, the direct utility of these metal salts in activation of thioglycosides did not occur to us, because every time the complexation took place with the involvement of the anomeric sulfur, those thioglycoside complexes appeared deactivated rather than activated. For example, complexes **A–C**, in all of which Pt/Pd atom was coordinated *via* the anomeric sulfur

Department of Chemistry and Biochemistry, University of Missouri – St. Louis, One University Boulevard, St. Louis, MO 63121, USA. E-mail: demchenkoa@umsl.edu, satpal04@gmail.com

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were stable and could not be activated for glycosylation using traditional thioglycoside activators (Fig. 1). In contrast, complexes **D–G**, in which Pt/Pd atom was coordinated away from the anomeric sulfur, could be activated for glycosylation with thioglycoside promoters.

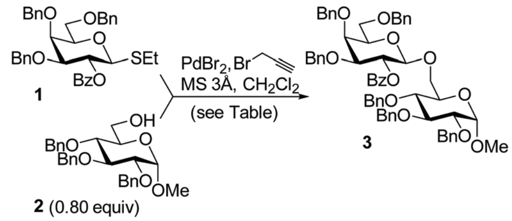
Regardless of their structure, no complexes showed propensity to be activated on their own, without added thioglycoside activators. This is why we were greatly surprised when a reaction between ethylthio galactoside donor **1**[61] and glycosyl acceptor **2**[62] produced disaccharide **3**[63] in the presence of only 20 mol% of $PdBr_2$ (see Table 1, entry 1). The yield of disaccharide **3** was rather modest (12%), and the reaction was very sluggish (72 h), but an important precedent was set, and this result has served as a proof that $PdBr_2$ is capable of activating standard thioglycosides for glycosylation.

Encouraged by this observation, albeit dissatisfied with the rate and the yield of the reaction, we decided to investigate the mode of interaction of $PdBr_2$ with glycosyl donor **1** using NMR. For this purpose, a solution of thiogalactoside **1** in $CDCl_3$ was placed into a standard NMR tube, $PdBr_2$ (1.0 equiv.) was added, and ^{1}H NMR spectrum was recorded after 12 h. As evident from Fig. 2, a new set of signals has appeared along with signals of donor **1**, which were still predominant in the spectrum. This result suggested the formation of **1-PdBr₂**, a complex between Pd(II) and thiogalactoside **1** *via* bidentate coordination. Pd–Metal centre appeared to be coordinated with the anomeric sulfur atom as evident from a downfield shift and division of the *S*-methylene protons that appeared at 2.90 ppm (marked as H^a) and 3.19 ppm (H^b) in **1-PdBr₂**. The second complexation site appeared to be the oxygen atom at C-6, as evidenced by a prominent downfield shift of 6-*O*-benzylic protons to 5.39 ppm (marked as H^c) and 5.80 ppm (H^d) in **1-PdBr₂**.

Some other minor shifts were also been noted, and these observations were fully consistent with the previously reported polydentate complexes of transition metals.[56,57] However, based on the NMR monitoring, nothing really implied that the activation is taking place in this environment. Perhaps, the process is different in the presence of a nucleophile, but it was clear that other, more effective activation modes, need to be engaged to enhance rates and yields of this glycosylation reaction. Analogy with published work[64–66] made us believe that additives such as alkynes may be suitable for this purpose. After preliminary screening, propargyl bromide was chosen as the preferred additive. Glycosylation between donor **1** and acceptor **2** in the presence of catalytic $PdBr_2$ (0.20 equiv.) and C_3H_3Br (1.0 equiv.) in CH_2Cl_2 at rt was more rapid than the previous reaction with $PdBr_2$ alone. When the reaction was stopped after 24 h, disaccharide **3** was isolated in an improved yield of 31% (Table 1, entry 2). Increasing the amount of $PdBr_2$ to 0.50 and 0.80 equiv. showed an increase in yields of disaccharide **3** to 39 and 60%, respectively, in 24 h (entries 3 and 4). When a similar glycosylation reaction was conducted in the presence of a stoichiometric amount of $PdBr_2$, disaccharide **3** was obtained in an excellent yield of 96% (entry 5).

To confirm the active role of propargyl bromide in the latter glycosylation reaction promoted with stoichiometric $PdBr_2$, a

Table 1 $PdBr_2$-mediated glycosidation of donor **1** with glycosyl acceptor **2**



Entry	$PdBr_2$ (equiv)	C_3H_3Br (equiv)	Conditions	Yield of 3
1	0.2	—	72 h, rt	12%
2	0.2	1.0	24 h, rt	31%
3	0.5	1.0	24 h, rt	39%
4	0.8	1.0	24 h, rt	60%
5	1.0	1.0	24 h, rt	96%
6	1.0	—	48 h, rt	76%
7	1.0	—	18 h, 60 °C	77%

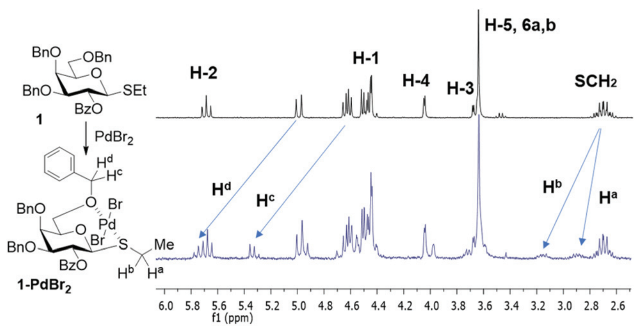


Fig. 2 ^{1}H NMR study of $PdBr_2$ complexation with thioglycoside 1 in $CDCl_3$.

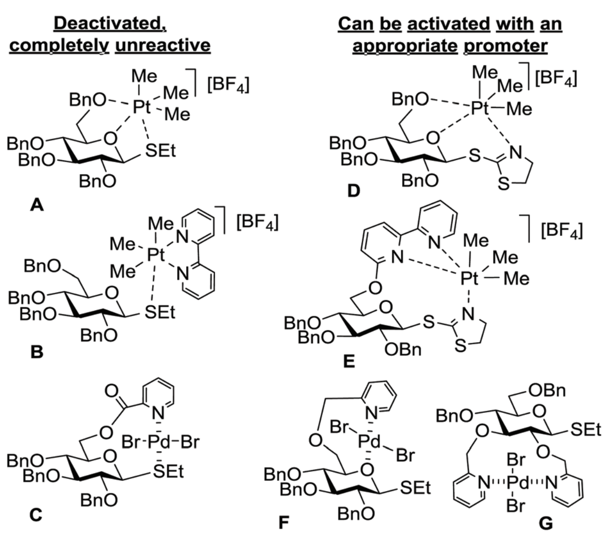


Fig. 1 Representative platinum group metal complexes synthesized in our lab.

similar reaction was conducted in the absence of propargyl bromide. This reaction was notably slower and required 48 h to afford disaccharide **3** in 76% yield (entry 6). Setting up a similar reaction at 60 °C helped to reduce the reaction time to 18 h albeit the yield of disaccharide **3** remained practically the same (77%, entry 7). This preliminary reaction optimization study suggested that the promoter and the additive both are required in a stoichiometric amount to produce disaccharide **3** in an excellent yield and in a reasonable reaction time. We have tried activation with several other palladium(II) salts including PdI_2, $PdCl_2$ and $Pd(OAc)_2$. However, these reactions were notably slower and lead to lower yields of the products.

Having optimized the reaction conditions, we proceeded to studying differently protected glycosyl donors and acceptors of other sugar series. For the purity of comparison, all reactions were stopped after 24 h, but some yields could be improved if the reactions were kept longer. Glycosylation conducted between glycosyl donor **1** and 6-OH glycosyl acceptor **4**[67] deactivated by benzoyl ester groups afforded disaccharide **5**[68] in a good yield of 75% (Table 2, entry 1). Glycosidation of donor **1** with more hindered, secondary 3-OH glycosyl acceptor **6**[62] and cholesterol **8** produced the corresponding products **7**[63] and **9** in modest yields of 37–43% (entries 2 and 3). A notable drop in the yield of glycosides produced from the secondary hydroxyls compared to the primary ones suggests that the glycosylation rates also depend on the nucleophilicity of glycosyl acceptors. All these reactions were completely β-stereoselective due to the participatory effect of the 2-*O*-benzoyl group in donor **1**.

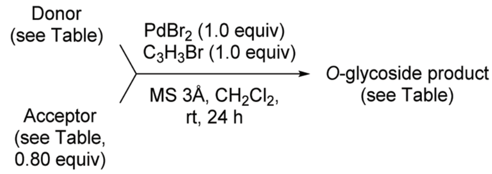
Subsequently, we extended our glycosylation study to glycosyl donors of other series. Glycosidation of per-benzylated galactosyl donor **10**[19,69] with the primary glycosyl acceptor **2** was smooth and efficient. This reaction produced disaccharide **11**[70] in a high yield of 81% albeit with low stereoselectivity (α/β = 1.5/1, entry 4). Glycosidation of mannosyl donor **12**[71] and glucosyl donor **14**[72] with 6-OH acceptor **2** produced very different results. Glycosidation of thiomannoside **12** was relatively slow, which was reflected in a modest yield of 50% for disaccharide **13**[73] (entry 5). However, glycosidation of thioglucoside **14** was much swifter, and disaccharide **15**[70] was produced in a good yield of 80% (entry 6). The drop in the yields of disaccharides **13** and **15** compared to that of **3** (96%) could be due to the relative reactivity of different sugar series.[74,75]

It has also occurred to us that the reactivity of glycosyl donors seems to be the key for success because unreactive glucosamine donor **16**[76] and per-benzoylated (disarmed) glucosyl donor **18**[77] were practically ineffective in glycosidations with glycosyl acceptor **2** under these reaction conditions. As a result, disaccharides **17** and **19**[78] were obtained in 23 and 10% yield, respectively, even after 48 h (entries 7 and 8). In contrast, glycosidation of per-benzylated (armed) glucosyl donor **20**[79] with acceptor **2** was much more effective. Disaccharide **21**[70] was obtained in 61% yield albeit with low stereoselectivity due to the lack of a participating group at C-2 (α/β = 2.0/1, entry 9). A practically identical result was obtained in glycosylation between *S*-tolyl (STol) donor **22**[80] and glycosyl acceptor **2** producing disaccharide **21** in 60% (entry 10). This result indicates that common STol donors can also be activated with $PdBr_2$ in the presence of propargyl bromide, just like their SEt counterparts.

With the acquired knowledge of a very slow activation of the disarmed donor **18** (see entry 8), we hypothesized that the established reaction conditions would allow for chemoselective armed-disarmed activation of thioglycoside building blocks. To verify the viability of this hypothesis we activated armed thioglycoside **20** over disarmed thioglycoside acceptor **23**.[81] Although, we investigated reactions with up to 2.0 equiv. of $PdBr_2$, this chemoselective reaction was slow, which translated into a poor yield of SEt disaccharide **24**[91] (α/β = 2.0/1, entry 11). We then attempted to activate the armed *S*-tolyl donor **22** over the disarmed glycosyl acceptor **25**[82] bearing the same leaving group. Again, a slow reaction even with 2.0 equiv. $PdBr_2$ was observed, and disaccharide **26**[83] was produced in 35% yield (α/β = 2.5/1, entry 12). However, glycosidation of armed SEt thioglycoside **20** with the disarmed *S*-tolyl acceptor **25** was much more effective in the presence of 2.0 equiv. $PdBr_2$, and disaccharide **26** was obtained in a good yield of 73% (α/β = 2.5/1, entry 13). To expand the utility of this approach, we activated the STol leaving group of the resulting disarmed disaccharide **26** in the presence of a more powerful promoter system NIS/TfOH to form trisaccharide **27** in 71% (entry 14). This synthesis represents a conventional two-step armed–disarmed sequence for streamlined oligosaccharide synthesis.[11] Glycosidation of thioglycoside **1** with allyl glycoside acceptor **28** was also attempted to investigate the applicability of this approach in selective activation strategies wherein one class of the leaving group is activated over another. This reaction proceeded smoothly and disaccharide **29** was obtained in a good yield of 78% (entry 15). It should be noted that the latter example represents selective activation, because the allyl group in compound **29** can be activated for subsequent chain elongation.[84,85] In this context, this type of activation reaction cannot be performed in the presence of other thioglycoside activators (except methyl triflate)[86] due to their cross reactivity with olefins.

While many further steps are still needed to fully understand the main driving forces and the substrate scope of this reaction, our current working hypothesis of the reaction mechanism[87] is as follows. As depicted in Scheme 1, upon complexation with $PdBr_2$, thioglycoside donor will form complex **H** that is fairly stable. Complex **H** forms only partially and probably exists in equilibrium with the glycosyl donor. We observed that it will revert to the starting material in the absence of a nucleophile or upon work-up. This was proven by performing a separate experiment in the absence of a glycosyl acceptor. In the presence of a glycosyl acceptor (R′OH), complex **H** will slowly produce the R′*O*-glycoside product. We hypothesize that in the presence of propargyl bromide additive, complex **H** will undergo oxidative addition to form complex **I** (or similar). The latter is expected to be much more reactive than **H**, and will fall apart with the formation of an oxacarbenium (or acyloxonium if an ester group is present at

Table 2 Broadening the scope of the $PdBr_2$-assisted glycosylation with various donors and acceptors



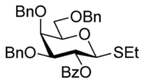
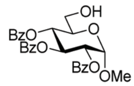
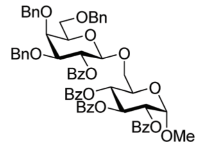
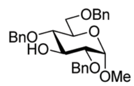
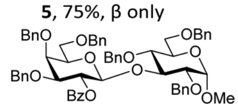
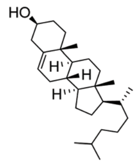
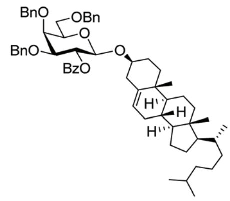
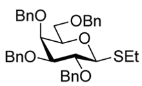
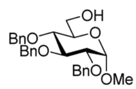
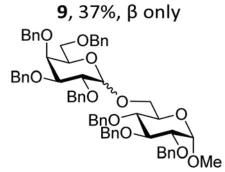
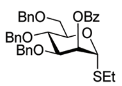
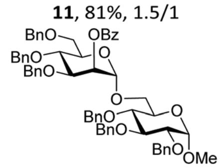
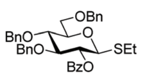
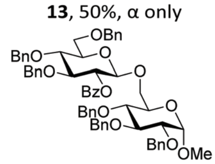
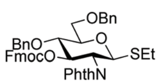
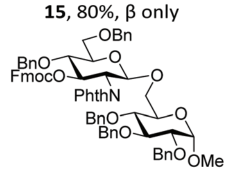
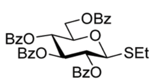
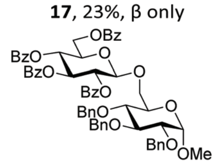
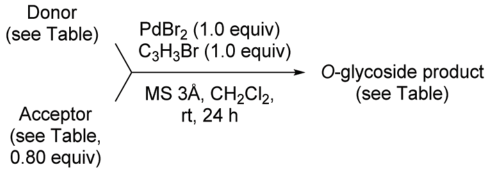
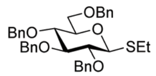
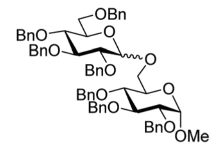
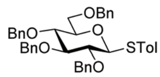
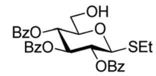
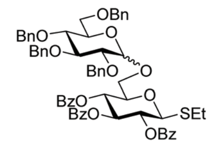
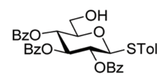
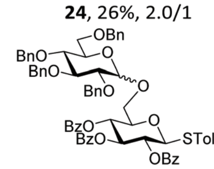
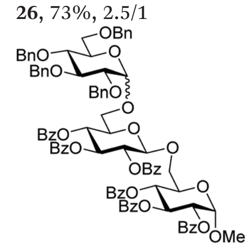
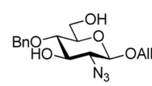
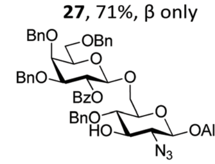
Entry	Donor	Acceptor	Product, yield, α/β ratio
1	 **1**	 **4**	 **5**, 75%, β only
2	**1**	 **6**	 **7**, 43%, β only
3	**1**	 **8**	 **9**, 37%, β only
4	 **10**	 **2**	 **11**, 81%, 1.5/1
5	 **12**	2	 **13**, 50%, α only
6	 **14**	2	 **15**, 80%, β only
7[a]	 **16**	2	 **17**, 23%, β only
8[a]	 **18**	2	 **19**, 10%, β only

Table 2 *(Contd.)*

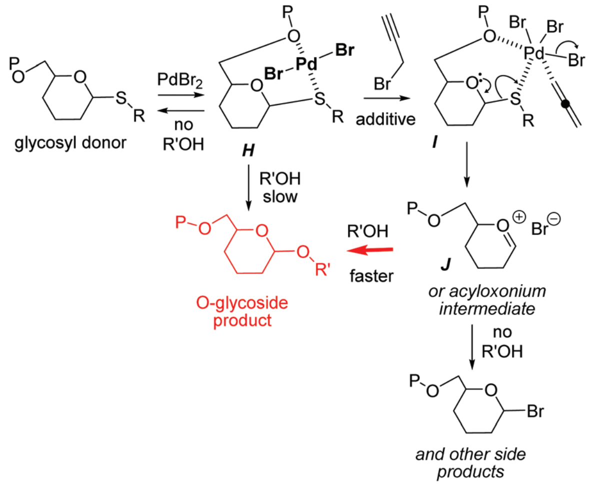


Entry	Donor	Acceptor	Product, yield, α/β ratio
9	 **20**	**2**	 **21**, 61%, 2.0/1
10	 **22**	**2**	**21**, 60%, 2.0/1
11[b]	**20**	 **23**	 **24**, 26%, 2.0/1
12[b]	**22**	 **25**	 **26**, 35%, 2.5/1
13[b]	**20**	**25**	**26**, 73%, 2.5/1
14[c]	**26**	**4**	 **27**, 71%, β only
15	**1**	 **28**	 **29**, 78%, β only

[a] Reaction time 48 h. [b] PdBr$_2$ (2.0 equiv.). [c] Performed in the presence of NIS (2.0 equiv.)/TfOH (0.2 equiv.), 15 min.

C-2) intermediate **J**. In the presence of R′OH it will readily produce the R′*O*-glycoside product, but in the absence of the nucleophile, it may produce glycosyl bromide or other by-products. However, the formation of glycosyl bromide is not detected during regular glycosylations with the glycosyl acceptor present from the beginning.

Indeed, a test reaction of **1** with PdBr$_2$ in the presence of propargyl bromide monitored by NMR showed the formation of glycosyl bromide as the main product (see the ESI† for details). In contrast, glycosyl bromide was not observed in the presence of allyl bromide, which supports the important role of propargyl bromide in the activation process. Since no other side products have been isolated from these reactions, the exact fate of the reagents is yet to be determined. By analogy with published work and our own spectroscopic investigation, we postulate that the departed leaving group precipitates as $Pd_6(SEt)_{12}$ or a similar cluster;[88] and allene produces oligomeric brominated alkenes.[89] These products are removed during the standard work-up procedure (see the ESI† for additional details).



Scheme 1 Anticipated $PdBr_2$-promoted reaction pathway in the presence of propargyl bromide additive.

Conclusions

A new method for the activation of thioglycosides has been developed. The activation with $PdBr_2$ can be sluggish, but it accelerates significantly in the presence of propargyl bromide additive that forms a more reactive reaction intermediate, and possibly acts as the leaving group scavenger. A preliminary mechanistic analysis and studying the complexation modes relied on ^{1}H NMR spectroscopy. Upon standardizing the basic reaction conditions, further examination of various thioglycosides has been performed. In most cases, our activation system was effective at room temperature, but the reaction time and the product yield were dependent on the reactivity of the donor and acceptor. Chemoselective and selective activation schemes have been investigated and successfully applied in a two-step synthesis of a trisaccharide. Further optimization of the reaction conditions and its application in automated synthesis of glycans are currently underway in our laboratory.

Experimental

General

All chemicals used were reagent grade and used as supplied. The ACS grade solvents used for reactions were purified and dried in accordance with standard procedures. Column chromatography was performed on silica gel 60 (70–230 mesh), reactions were monitored by TLC on Kieselgel 60 F_{254}. The compounds were detected by examination under UV light and by charring with 10% sulfuric acid in methanol. Solvents were removed under reduced pressure at <40 °C. CH_2Cl_2 was distilled from CaH_2 directly prior to the application. Molecular sieves (3 Å), used for reactions, were crushed and activated *in vacuo* at 390 °C during 8 h in the first instance and then for 2–3 h at 390 °C directly prior to application. Optical rotations were measured at 'Jasco P-2000' polarimeter. Unless noted otherwise, ^{1}H NMR spectra were recorded at 300 MHz, ^{13}C NMR spectra were recorded at 75 MHz. The ^{1}H NMR chemical shifts are referenced to tetramethylsilane (δ_H = 0 ppm) or $CHCl_3$ (δ_H = 7.26 ppm) for ^{1}H NMR spectra for solutions in $CDCl_3$. The ^{13}C NMR chemical shifts are referenced to the central signal of $CDCl_3$ (δ_C = 77.00 ppm) for solutions in $CDCl_3$. The HRMS analysis was performed using Agilent 6230 ESI TOF LC/MS mass spectrometer.

Synthesis of building blocks

Ethyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-1-thio-β-D-galactopyranoside (1) was synthesized as reported previously and its analytical data was in accordance with that previously described.[61]

Methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (2) was synthesized as reported previously and its analytical data was in accordance with that previously described.[62]

Methyl 2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (4) was synthesized as reported previously and its analytical data was in accordance with that previously described.[67]

Methyl 2,4,6-tri-*O*-benzyl-α-D-glucopyranoside (6) was synthesized as reported previously and its analytical data was in accordance with that previously described.[62]

Ethyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-galactopyranoside (10) was synthesized as reported previously and its analytical data was in accordance with that previously described.[19,69]

Ethyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-1-thio-α-D-mannopyranoside (12) was synthesized as reported previously and its analytical data was in accordance with that previously described.[71]

Ethyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (14) was synthesized as reported previously and its analytical data was in accordance with that previously described.[72]

Ethyl 4,6-di-*O*-benzyl-2-deoxy-3-*O*-fluorenylmethoxycarbonyl-2-phthalimido-1-thio-β-D-glucopyranoside (16) was synthesized as reported previously and its analytical data was in accordance with that previously described.[76]

Ethyl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside (18) was synthesized as reported previously and its analytical data was in accordance with that previously described.[77]

Ethyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (20) was synthesized as reported previously and its analytical data was in accordance with that previously described.[79]

Tolyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (22) was synthesized as reported previously and its analytical data was in accordance with that previously described.[80]

Ethyl 2,3,4-tri-*O*-benzoyl-1-thio-β-D-glucopyranoside (23) was synthesized as reported previously and its analytical data was in accordance with that previously described.[81]

Tolyl 2,3,4-tri-*O*-benzoyl-1-thio-β-D-glucopyranoside (25) was synthesized as reported previously and its analytical data was in accordance with that previously described.[82]

Allyl 2-azido-4-*O*-benzyl-2-deoxy-β-D-glucopyranoside (28). A mixture containing 3,6-di-*O*-acetyl-2-azido-4-*O*-benzyl-2-deoxy-α-D-glucopyranosyl bromide[90] (1.77 g, 4.0 mmol), allyl alcohol (0.50 mL, 6.0 mmol) and molecular sieves (4 Å, 2.0 g) in acetonitrile (20 mL) under argon was cooled to −40 °C. Mercury(II) cyanide (1.01 g, 4.0 mmol) was added, the external cooling was removed, the resulting mixture was allowed to warm to rt, and stirred for additional 2.5 h at rt. After that, the solids were filtered off through a pad of Celite and washed successively with DCM. The combined filtrate (~150 mL) was concentrated under reduced pressure and dried *in vacuo*. The crude residue was dissolved in MeOH (40 mL), a 1 M solution of NaOMe in MeOH was added dropwise to pH ~ 9, and the resulting mixture was stirred for 22 h at rt. After that, the reaction mixture was neutralized with Dowex (H^+). The resin was filtered off and rinsed successively with MeOH. The combined filtrate (~80 mL) was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate–hexanes gradient elution). Fractions containing **β-28** were combined, concentrated under reduced pressure, and the residue was recrystallized from ethyl acetate–hexanes to afford the title compound as white crystals in 55% yield (0.74 g, 2.2 mmol). Also eluted from the column was **α-28** that was obtained in 12% yield. Analytical data for **β-28**: R_f = 0.35 (ethyl acetate/hexane, 2/3, v/v); $[\alpha]_D^{21}$ −15.7 (c = 1, $CHCl_3$); m.p. 121–122 °C (ethyl acetate–hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.88 (m, 1H, 6-OH), 2.39 (s, 1H, 3-OH), 3.29–3.35 (m, 2H, H-2, 5), 3.47–3.53 (m, 2H, H-3, 4), 3.73–3.80 (m, 1H, H-6a), 3.87–3.93 (m, 1H, H-6b), 4.12 (dd, 1H, $OCH_2{}^aCH{=}$), 4.35–4.41 (m, 2H, $J_{1,2}$ = 8.1 Hz, H-1, $OCH_2{}^bCH{=}$), 4.71 (dd, 2H, CH_2Ph), 5.23 (dd, 1H, J = 10.7 Hz, $CH{=}CH_2{}^a$), 5.32 (dd, 1H, J = 17.0 Hz, $CH{=}CH_2{}^b$), 5.90–5.99 (m, 1H, $CH{=}CH_2$), 7.17–7.59 (m, 5H, aromatic) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 61.7, 66.1 (×2), 70.6, 74.8, 75.1 (×2), 101.0, 118.0, 128.1 (×2), 128.2, 128.6 (×2), 133.2, 137.8 ppm; HR-FAB MS [M + Na]$^+$ calcd for $C_{16}H_{21}N_3O_5Na$ 358.1379, found 358.1401.

Synthesis of *O*-glycosides

General procedure for $PdBr_2$–C_3H_3Br assisted glycosidation of thioglycosides. A mixture of thioglycoside precursor (30 mg, 0.05–0.04 mmol), glycosyl acceptor (0.04–0.03 mmol) and freshly activated molecular sieves (3 Å, 90 mg) in dry CH_2Cl_2 (1.0 mL) was stirred under argon for 1 h at rt. After that, propargyl bromide (C_3H_3Br, 0.05 mmol) followed by palladium bromide ($PdBr_2$, 0.05–0.01 mmol) were added and the reaction mixture was stirred for 24 h. The solids were filtered off through a pad of Celite and rinsed successively with CH_2Cl_2. The combined filtrate (~20 mL) was washed with H_2O (2 × 5 mL). The organic phase was separated, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate–hexanes gradient elution) to afford a glycoside derivative in yields listed in tables. Anomeric ratios (if applicable) were determined by comparison of the integral intensities of relevant signals in ^{1}H NMR spectra.

Methyl 6-*O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (3) was obtained from thioglycoside **1** and glycosyl acceptor **2** by the general glycosylation method in 96% yield as a clear film. Analytical data for **3** was in accordance with that reported previously.[63]

Methyl 6-*O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (5) was obtained from thioglycoside **1** and glycosyl acceptor **4** by the general glycosylation method in 75% yield as a white amorphous solid. Analytical data for **5** was in accordance with that reported previously.[68]

Methyl 3-*O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl)-2,4,6-tri-*O*-benzyl-α-D-glucopyranoside (7) was obtained from thioglycoside **1** and glycosyl acceptor **6** by the general glycosylation method in 43% yield as a clear film. Analytical data for **7** was in accordance with that reported previously.[63]

Cholesteryl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl (9) was obtained from thioglycoside **1** and cholesterol **8** by the general glycosylation method in 37% yield as a white amorphous solid. Analytical data for **9**: R_f = 0.70 (ethyl acetate/hexane, 2/3, v/v); $[\alpha]_D{}^{22}$ +0.6 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ, 0.64 (s, 3H), 0.84–0.90 (m, 14H), 0.96–1.10 (m, 8H), 1.25 (s, 3H), 1.31–1.55 (m, 10H), 1.74–2.11 (m, 5H), 3.44 (m, 1H), 3.60–3.66 (m, 4H, H-3′, 5′, 6a′, 6b′), 3.99 (d, 1H, $J_{4',5'}$ = 2.2 Hz, H-4′), 4.47–4.50 (m, 3H, 3 × CHPh), 4.56 (d, 1H, $J_{1',2'}$ = 7.9 Hz, H-1′), 4.62–4.68 (m, 2H, 2 × CHPh), 4.98 (d, 1H, ^2J = 11.7 Hz, CHPh), 5.19 (d, J = 5.0 Hz, 1H), 5.59 (dd, 1H, $J_{2',3'}$ = 8.0 Hz, H-2′), 7.13–7.60 (m, 18H, aromatic), 8.01 (d, 2H, J = 7.8 Hz, aromatic) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.9, 18.6, 19.2, 20.9, 22.5, 22.6, 22.8, 23.7, 24.2, 27.9, 28.2, 29.4, 29.7, 31.7, 31.8, 35.7, 36.1, 36.6, 37.2, 38.7, 39.4, 39.7, 42.2, 50.0, 56.0, 56.6, 68.7, 71.5, 72.1, 73.5 (×2), 74.3, 76.5, 79.3, 79.9, 100.2, 121.5, 127.5 (×2), 127.6, 127.8 (×2), 127.9 (×2), 128.1 (×2), 128.2 (×2), 128.4 (×4), 129.7, 130.0, 132.8, 137.6, 137.8, 138.2, 138.4, 140.7, 165.3 ppm; HR-FAB MS [M + Na]$^+$ calcd for $C_{61}H_{78}O_7Na$ 945.5645, found 945.5662.

Methyl 6-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-galactopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (11) was obtained from thioglycoside **10** and glycosyl acceptor **2** by the general glycosylation method in 81% yield (α/β = 1.5/1) as a colorless syrup. Analytical data for **11** was in accordance with that reported previously.[70]

Methyl 6-*O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (13) was obtained from thioglycoside **12** and glycosyl acceptor **2** by the general glycosylation method in 50% yield as a colorless syrup. Analytical data for **13** was in accordance with that reported previously.[73]

Methyl 6-*O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (15) was obtained from thioglycoside **14** and glycosyl acceptor **2** by the general glycosylation method in 80% yield as a clear film. Analytical data for **15** was in accordance with that reported previously.[70]

Methyl 6-*O*-(4,6-di-*O*-benzyl-2-deoxy-3-*O*-fluorenylmethoxycarbonyl-2-phthalimido-β-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (17) was obtained from thioglycoside **16** and glycosyl acceptor **2** by the general glycosylation method as a clear film in 23% yield. Analytical data for **17**: R_f = 0.50 (ethyl acetate/hexane, 2/3, v/v); $[\alpha]_D^{21}$ +10.0 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.14 (s, 3H, OCH_3), 3.26 (dd, 1H, $J_{4,5}$ = 9.2 Hz, H-4), 3.36 (dd, 1H, $J_{2,3}$ = 3.7 Hz, H-2), 3.63–3.67 (m, 2H, H-5, 6a), 3.74–3.91 (m, 6H, 3, 4′, 5′, 6a′, 6b′, OCOCH$_2$C*H*), 3.99 (dd, 1H, OCOC*H*$_2$[a]), 4.09–4.16 (m, 3H, 6b, OCOC*H*$_2$[b], C*H*Ph), 4.34 (d, 1H, $J_{1,2}$ = 3.4 Hz, H-1), 4.39 (d, 1H, ^2J = 10.1 Hz, C*H*Ph), 4.45 (dd, 1H, $J_{2',3'}$ = 8.7 Hz, H-2′), 4.54–4.73 (m, 7H, 7 × C*H*Ph), 4.83 (d, 1H, ^2J = 10.7 Hz, C*H*Ph), 5.39 (d, 1H, $J_{1',2'}$ = 8.4 Hz, H-1′), 5.70 (dd, 1H, $J_{3',4'}$ = 8.8 Hz, H-3′), 7.01–7.70 (m, 37H, aromatic) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 46.3, 54.8 (×2), 68.6, 69.2, 70.2, 73.3, 73.4, 74.7, 74.9, 75.6 (×2), 79.6, 81.8, 97.8, 98.1, 113.8, 119.8 (×2), 123.3 (×2), 124.9, 125.1, 127.1 (×2), 127.5 (×2), 127.6 (×5), 127.7 (×6), 127.8 (×2), 127.9 (×2), 128.0 (×4), 128.2 (×5), 128.3 (×4), 128.4 (×2), 133.8 (×2), 137.6, 137.7, 138.0, 138.1, 138.6, 140.9, 141.0, 142.8, 143.2, 154.6, 167.2, 168.1 ppm; HR-FAB MS [M + Na]$^+$ calcd for C$_{71}$H$_{67}$NO$_{14}$Na 1180.4460, found 1180.4550.

Methyl 6-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (19) was obtained from thioglycoside **18** and glycosyl acceptor **2** by the general glycosylation method in 10% yield as a clear film. Analytical data for **19** was in accordance with that reported previously.[78]

Methyl 6-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (21) was obtained from thioglycosides **20** or **22** and glycosyl acceptor **2** by the general glycosylation method in 61 and 60% yield (α/β = 2.0/1) as a colorless syrup. Analytical data for **21** was in accordance with that reported previously.[70]

Ethyl 6-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-glucopyranosyl)-2,3,4-tri-*O*-benzoyl-1-thio-β-D-glucopyranoside (24) was obtained from thioglycoside **20** and glycosyl acceptor **23** by the general glycosylation method in 26% yield (α/β = 2.0/1) as a colorless syrup. Analytical data for **24** was in accordance with that reported previously.[91]

Tolyl 6-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-glucopyranosyl)-2,3,4-tri-*O*-benzoyl-1-thio-β-D-glucopyranoside (26) was obtained from thioglycosides **20** or **22** and glycosyl acceptor **25** by the general glycosylation method in 73 or 35% yield (α/β = 2.5/1) as a colorless syrup. Analytical data for **26** was in accordance with that reported previously.[83]

Methyl 2,3,4,6-tetra-*O*-benzyl-α/β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (27). A mixture of thioglycoside **26** (0.016 mmol), glycosyl acceptor **4** (0.015 mmol) and freshly activated molecular sieves (3 Å, 52 mg) in dry CH$_2$Cl$_2$ (1.0 mL) was stirred under argon for 1 h at rt. After that, NIS (0.03 mmol) followed by TfOH (0.3 μL, 0.003 mmol) were added, and the reaction mixture was stirred for 15 min at rt. The solids were filtered off through a pad of Celite and rinsed successively with CH$_2$Cl$_2$. The combined filtrate (~20 mL) was washed with sat. aq. Na$_2$S$_2$O$_3$ (5 mL), sat. aq. NaHCO$_3$ (5 mL) and brine (2 × 5 mL). The organic phase was separated, dried with MgSO$_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate–hexanes gradient elution) to afford the title compound in 71% yield (0.011 mmol) as a white amorphous solid. Selected analytical data for α-**27**: R_f = 0.45 (ethyl acetate/hexane, 2/3, v/v); ^{1}H NMR (300 MHz, CDCl$_3$): δ 3.03 (s, 3H, OCH$_3$), 3.39 (dd, 1H, $J_{2'',3''}$ = 3.3 Hz, H-2″), 3.50–3.87 (m, 9H, H-3″, 4″, 5″, 6a, 6a′, 6a″, 6b′, 6b″), 4.01–4.09 (m, 3H, 5, 5′, 6b), 4.33–4.69 (m, 7H, H-1″, 6 × C*H*Ph), 4.78–4.85 (m, 2H, H-1, C*H*Ph), 4.88–5.00 (m, 3H, H-1′, 2, C*H*Ph), 5.31 (dd, 1H, $J_{4,5}$ = 9.0 Hz, H-4), 5.48–5.54 (m, 2H, H-2′, 4′), 5.83 (dd, 1H, $J_{3',4'}$ = 9.6 Hz, H-3′), 5.98 (dd, 1H, $J_{3,4}$ = 9.7 Hz, H-3), 7.11–7.51 (m, 38H, aromatic), 7.74–7.98 (m, 12H, aromatic) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 54.1, 66.2, 67.1, 67.4, 67.5 (×2), 68.4, 68.8, 69.2, 70.9, 71.2, 71.9, 72.0, 72.4, 73.8, 74.5, 95.4, 96.4, 100.3, 112.9, 126.5, 126.6 (×2), 126.7 (×6), 126.8 (×2), 126.9, 127.0 (×6), 127.2 (×5), 127.3 (×3), 127.4, 127.8 (×2), 127.9, 128.0 (×2), 128.1, 128.2 (×2), 128.5 (×2), 128.6 (×2), 128.8, 128.9 (×3), 131.0, 132.0 (×2), 132.1(×4), 132.3 (×4), 132.4, 136.9, 137.0, 137.1, 137.2, 137.2, 137.5, 137.8, 138.0, 164.1, 164.2 (×2), 164.7 (×2), 164.8 ppm; HR-FAB MS [M + Na]$^+$ calcd for C$_{89}$H$_{82}$O$_{22}$Na 1525.5196, found 1525.5174.

Allyl 6-*O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl)-2-azido-4-*O*-benzyl-2-deoxy-β-D-glucopyranoside (29) was obtained from thioglycoside **1** and glycosyl acceptor **28** by the general glycosylation method in 78% yield as a white amorphous solid. Analytical data for **29**: R_f = 0.55 (ethyl acetate/hexane, 2/3, v/v); $[\alpha]_D^{21}$ +11.8 (c = 1, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): δ 3.17–3.26 (m, 2H, H-2, 5), 3.36–3.42 (m, 2H, H-3, 4), 3.57–3.66 (m, 5H, H-3′, 5′, 6a, 6a′, 6b′), 3.76 (dd, 1H, OC*H*$_2$[a]CH═), 3.98–4.03 (m, 2H, H-4′, OC*H*$_2$[b]CH═), 4.12–4.18 (m, 2H, H-1, 6b), 4.39–4.70 (m, 7H, H-1′, 6 × C*H*Ph), 4.96 (d, 1H, ^2J = 11.6 Hz, C*H*Ph), 5.09 (dd, 1H, J = 10.0 Hz, CH═C*H*$_2$[a]), 5.16 (dd, 1H, J = 17.7 Hz, CH═C*H*$_2$[b]), 5.61–5.74 (m, 2H, H-2′, C*H*═CH$_2$), 7.14–7.56 (m, 23H, aromatic), 7.96 (d, 2H, J = 7.7 Hz, aromatic) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 65.9 (×2), 67.4, 68.4, 69.5, 71.5, 71.6, 72.2, 73.5, 73.6, 74.4 (×2), 74.6, 75.2, 79.8, 100.3, 101.3, 117.4, 118.5, 127.6 (×4), 128.1 (×4), 128.2 (×2), 128.3 (×5), 128.4 (×3), 129.8 (×3), 130.0, 130.2, 132.9, 133.1, 134.0, 137.5, 137.7, 137.8, 138.3, 165.1 ppm; HR-FAB MS [M + Na]$^+$ calcd for C$_{50}$H$_{53}$N$_3$O$_{11}$Na 894.3578, found 894.3587.

Conflicts of interest

There are no conflicts to declare.

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