Investigation of the reactivity difference between thioglycoside donors with variant aglycon parts

Martina Lahmann and Stefan Oscarson

Abstract: The reactivity of perbenzoylated thioglycosides with various thiol aglycons has been compared and quantified using competitive glycosylation experiments. Methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside was employed as acceptor and DMTST as a promoter. The reactivity was found, as expected, to depend on the electron donating properties of the aglycon. Hence, the most reactive donor, the cyclohexyl thioglycoside, was found to be about three times as reactive as the thioethyl glycoside, which in turn was twice as reactive as the thiomethyl donor. The thiophenyl donor was even less reactive, whereas *p*-halophenyl donors were inert under the glycosylation conditions used — but could be activated using NIS–TfOH as promoter. Furthermore, it was found that galactosyl donors were three to four times more reactive than the corresponding glucosyl derivative. These results allowed the design of an orthogonal coupling between thioglycosides with the same protecting groups (benzoyls) but with different thiol aglycons.

Key words: thioglycosides, orthogonal glycosylations, competititive glycosylations.

Résumé : En se basant sur des expériences de glycosylations compétitives, on a comparé et quantifié la réactivité de thioglycosides perbenzoylés avec diverses thioaglycones. On a utilisé le 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside de méthyle comme accepteur et le DMTST comme promoteur. On a trouvé, tel que prévu, que la réactivité dépend du caractère électrodonneur de l'aglycone. On a donc trouvé que le donneur le plus réactif, le thioglycoside de cyclohexyle, est trois fois plus réactif que le glycoside de thioéthyle qui est lui-même deux fois plus réactif que le donneur thiométhyle. Le donneur thiophényle est encore moins réactif alors que les donneurs *p*-halophényles sont inertes dans les conditions de glycosylation utilisées; ils peuvent toutefois être activés en utilisant le NIS–TfOH comme promoteur. De plus, on a trouvé que les donneurs galactosyles sont de trois à quatre fois plus réactifs que le dérivé glucosyle correspondant. Ces résultats ont permis de mettre au point un couplage orthogonal entre des thioglycosides avec les mêmes groupes protecteurs (benzoyles), mais des thioaglycones différentes.

Mots clés : thioglycosides, glycosylations orthogonales, glycosylations compétitives.

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Introduction

The reactivity of a glycosyl donor in a glycosylation reaction is dependent on its structure and the reaction conditions. This has enabled orthogonal glycosylations and one-pot synthesis of oligosaccharides using less reactive donors as acceptors. To achieve such glycosylations, various approaches have been used employing the reactivity diversity of, for example, various types of glycosyl donors (1, 2) and differently protected glycosyl donors (3–5). In the latter approach, quantification of the influence of the various protecting schemes on the reactivity was performed using model acceptors and competitive glycosylation studies (4, 5). Additionally, the effect of the promoter and solvent on the reactivity must be considered (6).

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Dedicated to the memory of Professor Raymond U. Lemieux.

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Thioglycoside donors have, apart from being stable substances allowing most protective group manipulations but still easily activated by chemoselective promoters (7–9), an additional advantage — their reactivity can be manipulated by the introduction of different thiol aglycons. A few examples of couplings using this approach have been reported (10–12), but no general study of the reactivity differences has been performed. Here, we describe efforts to quantify the reactivity difference between thioglycoside donors differing only in the aglycon moiety using competitive glycosylation studies. In addition, a sample trisaccharide was synthesized to relate the influence of the leaving group to other preparative conditions.

Results and discussion

As glycosyl donors, perbenzoylated thioglycosides with methyl (13), ethyl (13), phenyl (14), halophenyl (13), tolyl (11), benzyl (13), *n*-butyl (13), *n*-hexyl (15, 16), isopropyl (13), *t*-butyl (17), and cyclohexyl (18) aglycon substituents (Fig. 1) have been prepared and used. As a model acceptor, methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**15**) was chosen. Both glucosyl and galactosyl donors were tested. Competitive glycosylations were performed using mainly the ethyl thioglycoside (**Glc-13** or **Gal-13**) as a reference donor

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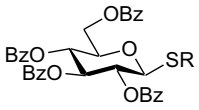
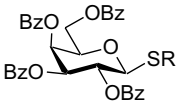
Fig. 1. Thioglycoside donors employed in the study.

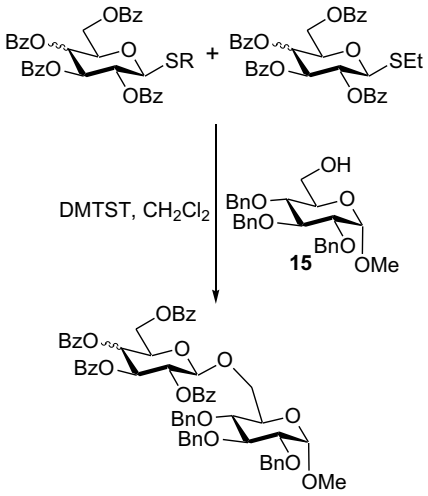


Glc-1 R = *m*-ClPh **8** R = Bn
2 R = *m*-BrPh **9** R = *i*-Pr
3 R = *p*-BrPh **10** R = *t*-Bu
4 R = *p*-ClPh **11** R = cHex
5 R = *n*-Bu **12** R = Me
6 R = *n*-Hex **13** R = Et
7 R = Ph **14** R = Tol



Gal- **6** R = *n*-Hex **12** R = Me
7 R = Ph **13** R = Et
11 R = cHex **14** R = Tol

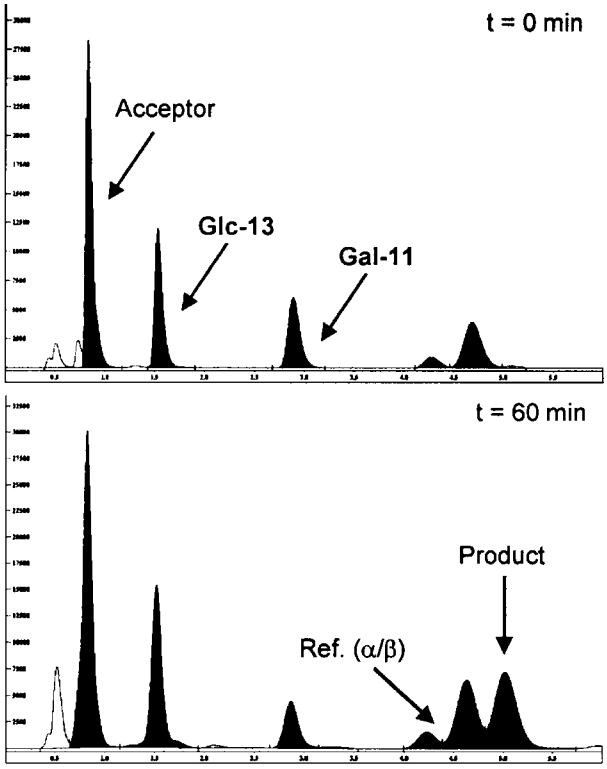
Scheme 1.



and dimethyl(methylthio)sulfonium trifluoromethylsulfonate (DMTST) (19) as a promoter (Scheme 1). The reaction mixtures were analyzed by HPLC (Fig. 2). Since the product is the same in most reactions, the relative reactivity was estimated by comparing the amounts of non-reacted donors. The results are summarized in Table 1.

As expected, the reactivity is correlated to the electron withdrawing (donating) capacity of the aglycon substituent. Tolyl and phenyl glycosides were slow (Table 1, entries 1–4, 15, 19, and 20), and an even more pronounced difference was observed with halosubstituted phenyl derivatives, which were inert under the conditions used. The latter donors were, however, easily activated by using NIS–AgOTf as the promoter. Of the alkyl glycosides tested, the methyl derivative showed a rather low reactivity (entries 6 and 7), whereas the *n*-butyl and benzyl glycosides were slightly faster (entries 8 and 10). The *n*-hexyl glycoside was comparable to the ethyl glycoside in reactivity (entries 11 and 12), while the branched alkyl glycosides, isopropyl and cyclohexyl, were the most reactive donors. As can be seen, the cyclohexyl derivative is an interesting effective donor (entries 13, 16, and

Fig. 2. HPLC spectra for entry 21 before addition of promoter and 60 min after addition (see *Experimental*).



18), but has so far not been widely used (20). The *tert*-butyl glycoside disappeared fastest (entry 22), but mainly gave the decomposition product of the donor and very little of the disaccharide product. In contrast, the perbenzylated *tert*-butyl thioglucoside donor was found to be an excellent donor, as was shown also by Stauch and Boons (21) using IDCP as the promoter.

Competition glycosylations between glucosyl and galactosyl donors showed the galactosides to be more reactive (Table 1, entries 5, 9, 14, 17, and 21 compared with entries 2, 3, 6, 12, and 18, respectively). A good correlation between the different derivatives was obtained, with a reactivity difference of about three to four in favour of the galactoside, which is in good agreement with a result of Wong and co-workers (5).

The reactivity difference between thioglycosides differing only in their thiol aglycons is most often to small to allow efficient orthogonal couplings, especially since the removal of a benzoyl group is activating. Often sugars of different reactivity and protecting group patterns as well as with different thiol aglycons are compared (11). *p*-NO_2-Phenyl thioglycosides have been used as inert acceptors, but to function as donors they have to be activated by conversion of the nitro functionality into an acetamido group, and even then the donor capacity is limited except for neuraminic acid donors (22–25). So far, the only report on orthogonal couplings between thioglycosides varying only in the aglycon functionality to give disaccharide donors was performed using steric effects by Boons et al. (12). Couplings between some of the more reactive (cHex, *i*-Pr, Et) perbenzoylated glycosides donors and less reactive acceptors (Ph, Tol, PhX,

Table 1. Relative reactivity of thioglycosyl donors.

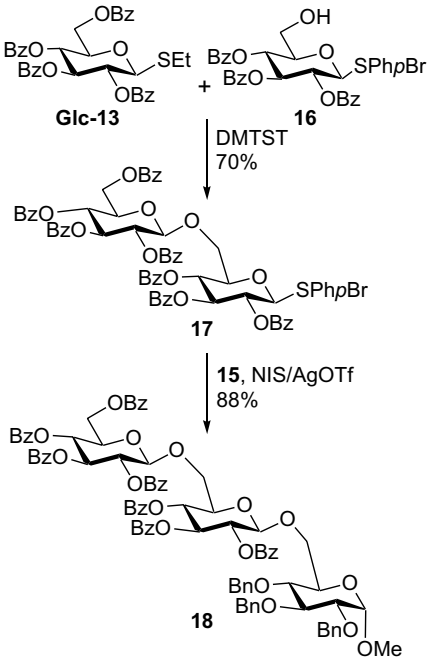
Entry	Donor	Reference donor	Rel. react.[a]
1	Gal-7 (Ph)	Gal-13 (Et)	<0.1
2	Glc-7 (Ph)	Glc-13 (Et)	0.1
3	Glc-14 (Tol)	Glc-13 (Et)	0.1
4	Gal-14 (Tol)	Gal-13 (Et)	0.2
5	Gal-7 (Ph)	Glc-13 (Et)	0.4
6	Glc-12 (Me)	Glc-13 (Et)	0.4
7	Gal-12 (Me)	Gal-13 (Et)	0.5
8	Glc-8 (Bn)	Glc-13 (Et)	0.7
9	Gal-14 (Tol)	Glc-13 (Et)	0.7
10	Glc-5 (*n*-Bu)	Glc-13 (Et)	0.7
11	Gal-6 (*n*-Hex)	Gal-13 (Et)	1.0
12	Glc-6 (*n*-Hex)	Glc-13 (Et)	1.0
13	Glc-9 (*i*-Pr)	Gal-13 (Et)	1.4
14	Gal-12 (Me)	Glc-13 (Et)	1.6
15	Glc-14 (Tol)	Glc-7 (Ph)	1.9
16	Gal-11 (cHex)	Gal-13 (Et)	2.1
17	Gal-6 (*n*-Hex)	Glc-13 (Et)	3.4
18	Glc-11 (*c*-Hex)	Glc-13 (Et)	3.6
19	Glc-12 (Me)	Glc-7 (Ph)	5.8
20	Glc-6 (*n*-Hex)	Glc-7 (Ph)	6.1
21	Gal-11 (cHex)	Glc-13 (Et)	10.3
22	Glc-10 (*t*-Bu)	Glc-13 (Et)	12.5[b]

[a]The reactivity factors were calculated as followed: The peak area of the reference donor (D_{ref}) and the test donor (D_{test}) were normalized to the integral of the reference (R_β) (β-anomer): $D^\circ_{ref} = D_{ref^\circ}/R^\circ_\beta$; $D^\circ_{test} = D_{test^\circ}/R^\circ_\beta$; $D^n_{ref} = D_{ref^n}/R^n_\beta$; and $D^n_{test} = D_{test^n}/R^n_\beta$. From these values the amount of unused donor was calculated, as was the yield of product formed from that particular donor: $Y_{ref} = 1 - D^n_{ref}/D^\circ_{test}$. Resulting in the reactivity of the test donor: $R_{test} = Y_{test}/Y_{ref}$.
[b]Donor decomposes.

4-OH, or 6-OH) were carried out, but were found to be ineffective due to concomitant activation of the supposed acceptor. The combination of employing thiocyclohexyl or thioethyl glycosides as donors and thio *p*-Br-phenyl derivative **16** as acceptor, however, led to efficient product formation (Scheme 2). The amount of promoter (DMTST) had to be reduced compared with standard conditions (1.5 equiv instead of 2–4 equiv), which not only slowed down the couplings but also effectively suppressed activation of the acceptor. The *p*-Br-phenyl group of the obtained disaccharide **17** could then be smoothly activated in a NIS–AgOTf-promoted coupling with model acceptor **15** to produce a trisaccharide **18** (26) in high yield (Scheme 2).

In conclusion, a study of the reactivity of thioglycosides with different aglycon moieties has been performed using competitive glycosylations. The results gave a quantitative estimation of the differences between slow-reacting donors with electron withdrawing aglycons and fast-reacting donors with more electron donating aglycons, as well as the reactivity difference between glucosyl and galactosyl donors. A preparative example of a coupling between an ethyl thioglycoside (donor) and *p*-bromophenyl thioglycoside (acceptor), both carrying benzoyl protecting groups, is also described. Although other factors such as choice of solvent and promoter must be taken into account, these results, in combination with earlier investigations regarding the influence of protecting groups, should be of value for designing efficient orthogonal glycosylations between thioglycosides.

Scheme 2.



Experimental

All organic solvents were distilled before use. Organic solutions were dried over $MgSO_4$, before concentration, which was performed under reduced pressure at <40°C (bath temperature). NMR spectra were recorded at 300 MHz or 400 MHz (Varian) (^{1}H) or at 75 MHz or 100 MHz (^{13}C), respectively, in $CDCl_3$. For the ^{1}H NMR spectra, TMS was used as internal standard (δ = 0); the ^{13}C NMR spectra were referenced to the chloroform signal (δ = 77.17). Silica gel MERCK 60 (0.040–0.063) was used for flash chromatography. For the competition reactions, several stock solutions were prepared in dry CH_2Cl_2. The HPLC reference was dissolved together with the acceptor. The DMTST solution was left for one day at 4°C to stabilize the solution. The activity of the promoter solution was checked before (and after) each set of competition experiments performing a standard coupling experiment following the coupling procedure for competition experiments but using two equivalents of the reference donor (thioethyl glucoside) instead. All vials and sample tubes were dried and stored in an desiccator before use. For taking aliquots to prepare the reaction mixtures, glass pipettes with fixed volumes (50 μL, 500 μL) were used. The HPLC solvents (CH_3CN–H_2O (83:17), containing 0.1% TFA) were filtered (0.45 μm pores) before use. The reaction mixtures were analyzed on an analytical reversed phase column [column: RP C-18 (Rocket, 33 mm, ID 7 mm, beads size 3 μ, Alltima C18) pH 2.0–7.5] with UV detection (215 nm). During the analysis a low stream of helium was bubbled through the solvents. Once the coupling product was isolated and characterized by proton and carbon NMR. To check for the occurrence of decomposition products, the reactions were followed by TLC (toluene–EtOAc, 3:1; silica-gel F_{254} (E. Merck)) with detection by UV-light and (or) charring with 8% sulphuric acid. MALDI-TOF spectra were

recorded on a Bruker Biflex III with 2′,4′,6′-trihydroxyacetophenone monohydrate (THAP) as the matrix.

Typical preparation of the donors

The peracetylated sugar (2.5 mmol, 1.0 equiv) was dissolved in dry CH_2Cl_2 (2 mL per mmol sugar). Thiol (1.2–1.5 equiv) and $BF_3{\cdot}Et_2O$ (1.5–2 equiv) were successively added. When the reaction was complete (TLC: toluene–EtOAc, 3:1) the reaction mixture was quenched with Et_3N (2.5 equiv), evaporated, and redissolved in CH_2Cl_2, then washed with brine, dried, and concentrated. The crude product was filtered through a plug of silica gel (toluene–EtOAc, 9:1) and after crystallization (95% ethanol or pentane–Et_2O) the β-compounds were obtained. After removal of the acetates with NaOMe, the crude material was benzoylated in pyridine.

Competitive glycosylation experimental procedure

A mixture of the glycoside donor (10 μmol, 1.0 equiv, 1 mmol in CH_2Cl_2), the reference donor (10 μmol, 1.0 equiv, 1 mmol in CH_2Cl_2), the HPLC reference compound (5 μmol, 0.5 equiv, α/β 17:83, 0.5 mmol in CH_2Cl_2), the acceptor (20 μmol, 2.0 equiv, 2 mmol in CH_2Cl_2), and molecular sieves (4 Å) was stirred at room temperature for 30 min. An HPLC sample (5 μL) was taken, centrifuged, and analyzed. DMTST (10 μmol, 1.0 equiv., 1 mmol in CH_2Cl_2) was added and HPLC samples (20 μL) were taken at regular intervals (first set: 30 min, 1 h, 2 h, 4 h, 24 h; second set: 1 h, 3 h), centrifuged, and analyzed. All couplings were carried out as a double experiment at the same time to minimize errors.

4-Bromophenyl 2,3,4-tri-*O*-benzoyl-1-thio-β-D-glucopyranoside (16)

4-Bromophenyl 1-thio-β-D-glucopyranoside (680 mg, 1.92 mmol), dissolved in pyridine (5 mL), was stirred with TBDMSCl (350 mg, 2.3 mmol) and DMAP (cat.) at room temperature over night ($CHCl_3$–MeOH, 9:1). Then benzoyl chloride (2 mL) was added and the mixture was left stirring for additional 2 h (toluene–EtOAc, 6:1). After aqueous work-up, the raw material was purified by silica gel flash-chromatography (pentane–Et_2O, 3:1) to yield 4-bromophenyl 2,3,4-tri-*O*-benzoyl-6-*O*-*tert*-butyldimethylsilyl-1-thio-β-D-glucopyranoside (1.34 g, 1.72 mmol, 90%). ^{1}H NMR δ: 8.3–7.1 (m, 19H), 5.9 (t, *J* = 9.3 Hz, 1H), 5.5 (t, *J* = 9.6 Hz, 1H), 5.4 (t, *J* = 9.9 Hz, 1H), 5.0 (d, *J* = 9.6 Hz, 1H, H-1), 4.0–3.8 (m, 3H), 0.9 (s, 9H, *t-Bu*Si), 0.0 (2s, 6H, Me_2Si). ^{13}C NMR δ: 165.9, 165.1, 165.1 (Ph*C*O), 134.5, 133.8, 133.4, 132.1, 130.3, 129.9, 129.8, 128.5, 128.5, 128.3 (aromatic C), 122.8 (*C*-Br), 85.8 (C-1), 79.7, 74.5, 70.6, 69.1, 62.7, 25.9 (*t-Bu*Si), 18.4 (*t-Bu*Si), –5.2, –5.3 (Me_2Si).

To a cooled (0°C) solution of 4-bromophenyl 2,3,4-tri-*O*-benzoyl-6-*O*-*tert*-butyldimethylsilyl-1-thio-β-D-glucopyranoside (1.28 g, 1.65 mmol) in CH_2Cl_2 (50 mL), was slowly added $BF_3{\cdot}Et_2O$ (520 μL, 4.1 mmol). After 2 h, the reaction mixture was diluted with CH_2Cl_2, washed consecutively with H_2O, $NaHCO_3$, and brine, then dried and concentrated. The crude product was purified by silica gel flash-chromatography (toluene → toluene–EtOAc, 6:1) to yield **16** (0.94 g, 1.42 mmol, 86%). ^{1}H NMR δ: 8.0–7.8 (m, 6H), 7.6–7.1 (m, 13H), 5.9 (t, *J* = 9.6 Hz, 1H), 5.4 (t, *J* = 9.6 Hz, 2H), 5.0 (d, *J* = 9.6 Hz, 1H, H-1), 3.9–3.7 (m, 3H). ^{13}C NMR δ: 166.1, 165.8, 165.1 (Ph*C*O), 135.0, 133.8, 133.5, 133.4, 132.2, 130.0, 129.9, 129.8, 128.6, 128.5, 128.5, 128.4 (aromatic C), 123.1 (*C*-Br), 85.8 (C-1), 79.0, 73.9, 70.5, 69.2, 61.5. MALDI-TOF MS calcd. for $C_{33}H_{27}BrO_8S$: 662.06 [M(^{79}Br)], 664.06 [M(^{81}Br)]; found: 685.05 [M(^{79}Br) + Na]$^+$, 687.06 [M(^{81}Br) + Na]$^+$, 701.03 [M(^{79}Br) + K]$^+$, 703.02 [M(^{81}Br) + K]$^+$.

4-Bromophenyl (2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzoyl-1-thio-β-D-glucopyranoside (17)

A solution of donor **Glc-13** (100 mg, 156 μmol) and acceptor **16** (100 mg, 150 μmol) in dry CH_2Cl_2 (5 mL) was stirred with powdered molecular sieves (4 Å, 200 mg) under argon for 1 h, then DMTST (54 mg, 209 μmol dissolved in 500 μL CH_2Cl_2) was added. The reaction, followed by TLC (toluene–EtOAc, 6:1), was quenched after 4 h by addition of Et_3N (100 μL) and the mixture was diluted with CH_2Cl_2 (20 mL), filtered, and concentrated. The residue was subjected to silica gel column chromatography (pentane–Et_2O, 1:1 followed by toluene–EtOAc, 20:1) to obtain **17** (130 mg, 105 μmol, 70%) as a white solid. ^{1}H NMR δ: 8.0–7.7 (m, 14H), 7.5–6.9 (m, 25H), 5.9 (t, *J* = 9.6 Hz, 1H), 5.8 (t, *J* = 9.4 Hz, 1H), 5.6 (t, *J* = 9.9 Hz, 1H), 5.5 (dd, *J* = 7.7, 9.9 Hz, 1H), 5.3 (t, *J* = 9.6 Hz, 1H), 5.2 (t, *J* = 9.9 Hz, 1H), 4.9 (d, *J* = 7.7 Hz, 1H, H-1′), 4.8 (d, *J* = 9.9 Hz, 1H, H-1), 4.6 (dd, *J* = 3.3, 12.1 Hz, 1H), 4.4 (dd, *J* = 4.4, 12.1 Hz, 1H), 4.0 (m, 3H), 3.9 (dd, *J* = 7.1, 11.5 Hz, 1H). ^{13}C NMR δ: 166.1, 165.9, 165.7, 165.4, 165.2, 165.0 (Ph*C*O), 134.8, 133.6, 133.5, 133.4, 133.3, 132.2, 130.7, 130.0, 129.9, 129.8, 129.6, 129.3, 129.2, 128.9, 128.7, 128.5, 128.4, 128.3, 125.4, 123.0 (aromatic C), 101.5 (C-1′), 85.6 (C-1), 78.2, 74.1, 73.0, 72.5, 71.9, 70.5, 69.6, 68.7, 65.0. MALDI-TOF MS calcd. for $C_{67}H_{53}BrO_{17}S$: 1240.22 [M(^{79}Br)], 1242.42 [M(^{81}Br)]; found: 1263.25 [M(^{79}Br) + Na]$^+$, 1265.25 [M(^{81}Br) + Na]$^+$, 1279.24 [M(^{79}Br) + K]$^+$, 1281.25 [M(^{81}Br) + K]$^+$.

Methyl (2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-(1→6)-(2,3,4-tri-*O*-benzoyl-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (18) (26)

A solution of donor **17** (40 mg, 32 μmol) and acceptor **15** (18 mg, 39 μmol) in dry CH_2Cl_2 (2 mL) was stirred with powdered molecular sieves (4 Å, 100 mg) under argon for 1 h. The mixture was cooled (0°C) and NIS (11 mg, 49 μmol) and AgOTf (cat.) were added. The reaction, followed by TLC (toluene–EtOAc, 6:1), was quenched after 30 min by addition of Et_3N (50 μL), the mixture was then diluted with CH_2Cl_2 (20 mL), filtered, and concentrated. The residue was subjected to silica gel column chromatography (toluene → toluene–EtOAc, 10:1) to yield **18** (42 mg, 28 μmol, 88%). ^{1}H NMR δ: 8.0–7.7 (m, 14H), 7.5–6.9 (m, 36H), 5.8 (t, *J* = 10 Hz, 1H), 5.7 (t, *J* = 10 Hz, 1H), 5.6 (t, *J* = 10 Hz, 1H), 5.4 (m~dd, *J* = 10 Hz, *J* = 8 Hz, 2H), 5.3 (t, *J* = 10 Hz, 1H), 5.0 (d, *J* = 7.8 Hz, 1H,), 4.9 (d, *J* = 11 Hz), 4.7 (d, *J* = 12 Hz, 1H), 4.6 (d, *J* = 11 Hz, 1H), 4.5 (m, 3H), 4.4 (d, *J* = 8 Hz, 1H), 4.3 (m, 2H), 4.1 (d, *J* = 11 Hz, 1H), 4.0 (m, 2H), 3.8 (m, 4H), 3.5–3.3 (m, 4H), 3.3 (s, 3H) ppm. ^{13}C NMR δ: 166.1, 165.8, 165.4, 165.1, 164.9 (Ph*C*O), 139.7–137.5, 133.5–127.4 (aromatic C), 101.5, 100.8 (C-1′, C-1″), 98.2 (C-1), 81.9, 79.8, 75.5, 74.5, 74.4, 73.5, 72.8,

72.4, 72.1, 71.8, 69.7, 69.6, 69.4, 68.6, 67.6, 63.0, 55.4 (O*Me*). MALDI-TOF MS calcd. for $C_{89}H_{80}O_{23}$: 1516.51 $[M]^+$; found: 1539.53 $[M + Na]^+$.

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