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Chemoselective glycosylations using sulfonium triflate activator systems

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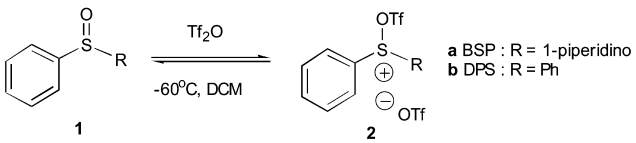
Abstract—A novel chemoselective glycosylation sequence is described that employs the recently developed BSP/Tf_2O and DPS/Tf_2O reagent systems to activate thioglycosides. In the first glycosylation event a relatively armed thioglycoside is activated with the BSP/Tf_2O activator system and condensed with an acceptor thioglycoside to yield the thiodisaccharide, which is activated with the more potent DPS/Tf_2O activator in the next glycosylation event. Quenching of (*N*-piperidino)phenyl(*S*-thiophenyl)sulfide triflate, which is formed upon activation of the first thioglycoside, with triethyl phosphite is crucial for a productive glycosylation.

1. Introduction

The concise and efficient preparation of oligosaccharides and glycoconjugates presents a significant challenge in synthetic organic chemistry. Considerable attention in this field has been devoted to the development of efficient chemoselective and orthogonal synthetic strategies.[1] Ever since the observation of Paulsen, in the early 1970's, that the protecting groups on a glycosyl halide significantly influence the rate of anomeric hydrolysis,[2] and the introduction of the armed–disarmed concept by Fraser–Reid,[3] an array of chemoselective condensation procedures have emerged.[4] Apart from the exploitation of the protecting groups, chemoselective condensations have been achieved by taking advantage of the influence of substituent effects, sugar conformation and configuration, solvent effects, and the nature of the anomeric leaving group.[4a,c] Our contributions in this field have been focussed predominantly on the use of thioglycosides.[5] These present an attractive class of donor glycosides since the thiofunction is stable under most conditions used for protecting group manipulations.[6] An additional important asset in chemoselective condensations comprises the fact that thioglycosides can be activated by a range of activator systems of varying thiophilicity.[7] Recently the Crich laboratory launched 1-benzenesulfinyl piperidine (BSP) in combination with trifluoromethanesulfonic anhydride (Tf_2O) as a novel potent thiophilic activator system (**2a**, Scheme 1).[7b] It



Scheme 1. Sulfonium activator species **2a** and **2b**.

was shown that **2a** could be used for the transformation of both armed and disarmed thioglycosides into the corresponding glycosyl triflates, and their ensuing conversion into various disaccharides. Notably, activator system **2a** could be used to promote the highly stereoselective formation of the β-mannosidic linkage, a feat which is normally difficult to attain. We recently reported that no productive glycosylations were obtained using BSP/Tf_2O reagent **2a** in combination with highly disarmed thioglycosides.[8] In contrast, we found that the analogous diphenyl sulfoxide (DPS)-triflic anhydride combination **2b** could activate these unreactive thiosaccharides. These findings prompted us to explore the possibilities for a novel condensation sequence in which the difference in reactivities of the sulfonium activator systems **2a** and **2b** is exploited to attain chemoselective glycosylations using highly disarmed thioglycosides. The full experimental results of our studies are presented here.

2. Results and discussion

The BSP/Tf_2O activation protocol as developed by Crich,[7b] entails the pre-mixing of the donor thioglycoside and the sulfenyl triflate and subsequent addition of the acceptor.

Keywords: Carbohydrates; Glycosylation; Chemoselective; Triflate.
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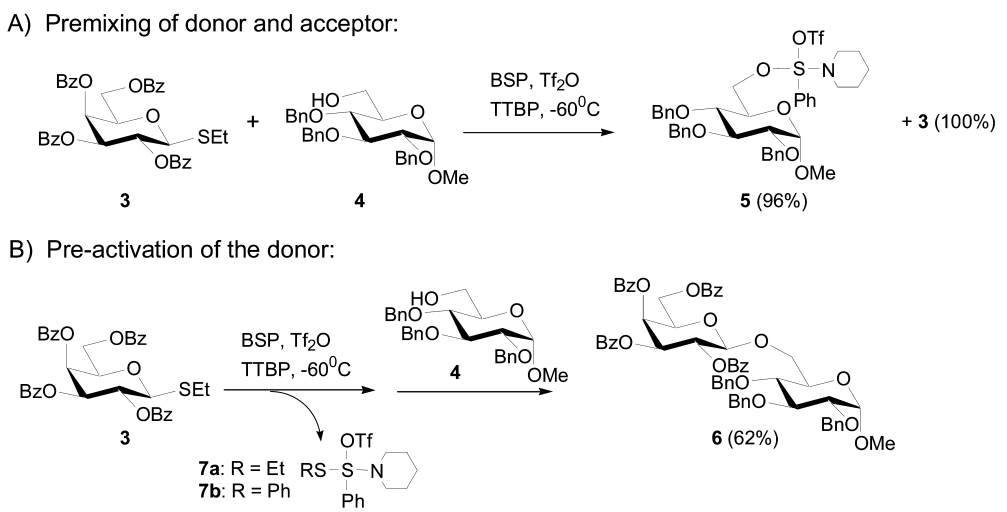
This stepwise protocol was devised to facilitate the intermediate formation of the glycosyl triflate, allowing a more stereoselective condensation reaction. With the objective to attain a chemoselective glycosylation protocol we explored, in a model experiment, whether pre-mixing the donor and acceptor glycosides prior to the addition of the activator would result in a productive glycosylation. Upon treatment of a 1:1 mixture of donor thiogalactoside **3** and glucose acceptor **4**, having an inert anomeric *O*-methyl function, with 1 equiv. of **2a** in the presence of 2,4,6-tri-*tert*-butylpyrimidine (TTBP),[10] we found that the thiofunction of the thiogalactoside remained unaffected (Scheme 2). The acceptor glucoside on the other hand was transformed into the 6-*O*-benzenesulfinyl piperidine triflate adduct **5**, which proved to be remarkably stable and was isolated in a virtually quantitative yield. The outcome of this experiment agrees with the glycosylation procedure of Gin,[9] in which the analogous DPS/Tf_2O activator system **2b** could activate the anomeric hydroxyl function. Thus, the phenyl-1-piperidinosulfide bis(triflate) **2a** can react with both the hydroxyl function in the acceptor glycoside and with the thiofunction of the donor glycoside depending on their relative nucleophilicities. Pre-activation of the donor galactoside **3** with **2a** at low temperature and subsequent addition of the acceptor **4** did lead to the formation of disaccharide **6**. Accordingly, we followed the Crich activation protocol in our explorative BSP/Tf_2O-mediated chemoselective glycosylations.

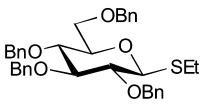
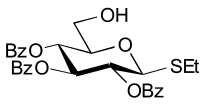
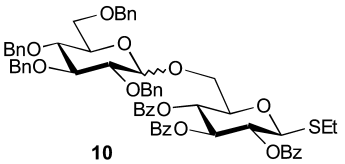
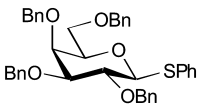
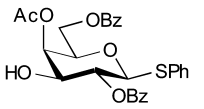
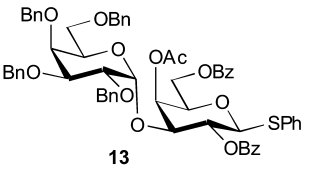
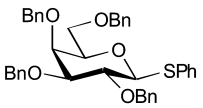
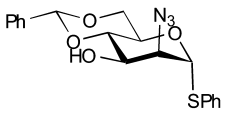
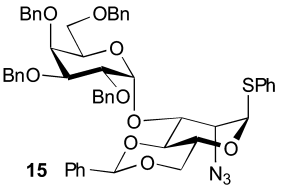
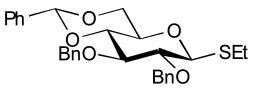
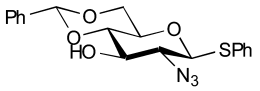
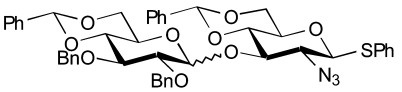
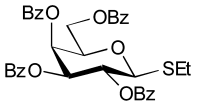
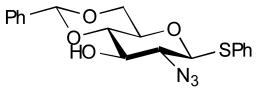
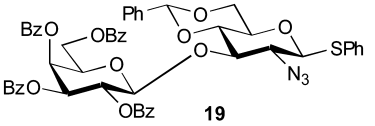
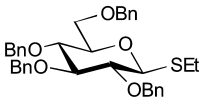
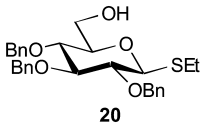
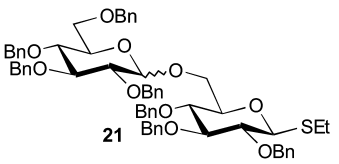
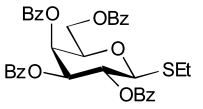
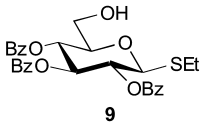
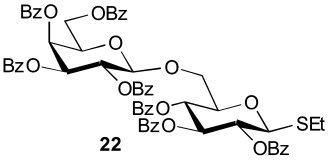
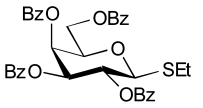
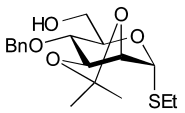
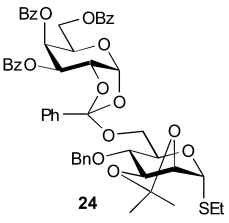
As a first touchstone we investigated the 'classic' condensation of an armed perbenzylated thiodonor with a disarmed perbenzoylated acceptor. Tetrabenzyl thioglucoside **8** was activated by **2a** at −60 °C and condensed with glucoside **9** (Table 1, entry 1). Although the activation and condensation proceeded smoothly as judged by TLC analysis, deterioration of the initially formed disaccharide **10** occurred upon warming of the reaction mixture. It occurred to us that the transiently formed (*N*-piperidino)phenyl(*S*-thioethyl)sulfide triflate **7a** (Scheme 2), generated by the activation of the anomeric phenyl thiofunction with BSP/Tf_2O, is also capable of activating thioglycosides, albeit at higher temperatures. This is supported by the finding of Wong et al.,[11] who use 0.5 equiv. of **2a** to completely activate a highly reactive thiodonor in a chemoselective glycosylation. We therefore set out to exploit the triflate species **7** as an activator for the chemoselective glycosylation of **8** and **9**. Triflate species **7b** was generated by treatment of **2a** with 1 equiv. of thiophenol and used to activate thioglucose **8**. This activation proved to proceed more sluggishly than the BSP/Tf_2O mediated activation of **8** and the ensuing condensation with acceptor **9** led to formation of the thiodisaccharide product **10** in a disappointing yield (44%). Since we were not able to apply the (*N*-piperidino)phenyl(*S*-thiophenyl)sulfide triflate **7b** as an effective activator we returned to the BSP/Tf_2O activator system and decided to scavenge the transiently formed **7** after the condensation event. We selected triethyl phosphite (TEP)[12] as a possible quenching reagent. To investigate the efficacy of TEP as a scavenging reagent we generated triflate species **7b** and treated this with an equimolar amount of TEP prior to the addition of the reactive thioglycoside **8**. In this case the thioacetal function remained intact and the thioglycoside **8** could be quantitatively recovered. Having established that timely addition of the quenching agent TEP prevents decomposition of the thiosaccharide product, we returned to the chemoselective condensation of thiodonor **8** and acceptor **9** (Table 1, entry 1b). Following pre-activation of the glucoside with BSP/Tf_2O at −60 °C and addition of the acceptor the reaction mixture was allowed to warm to −10 °C, after which 1 equiv. of TEP and triethylamine were added to quench (*N*-piperidino)phenyl(*S*-thioethyl)sulfide triflate **7a** and the generated triflic acid, respectively. Thiodisaccharide **10** was now obtained in a satisfactory 78% yield as a mixture of anomers. This successful protocol was next applied to a collection of thiosaccharide donors and acceptors of varying reactivity (Table 1, entries 2–5).

Digalactoside **13** was obtained in a moderate yield of 52% and good α-selectivity by galactosylation of donor **11** with acceptor **12**, which is a relatively strenuous acceptor for both steric and electronic reasons. In a similar manner, armed thiogalactoside **11** was glycosydated with highly disarmed azido thioglucoside **14** to provide the α-linked disaccharide **15** in 73% yield. The conformationally disarmed benzylidene thioglucoside **16** and azido thioglucoside **17** were condensed to give thiosaccharide **18** in an



Scheme 2. Sulfonium activator **2a** can react with both the hydroxyl function of the acceptor (A) and the thiofunction of the donor (B).

Table 1. Chemoselective glycosylations using the BSP/Tf_2O activator system

Entry	Donor	Acceptor	Disaccharide	Product yield (α/β)[a]
1a	 **8**	 **9**	 **10**	1a: 44% (2:1)
1b				1b: 78% (3:1)
2	 **11**	 **12**	 **13**	52% (1:0)
3	 **11**	 **14**	 **15**	73% (1:0)
4	 **16**	 **17**	 **18**	90% (2:1)
5	 **3**	 **17**	 **19**	64% (0:1)
6	 **8**	 **20**	 **21**	0%
7	 **3**	 **9**	 **22**	0%
8	 **3**	 **23**	 **24**	<10%[b]

[a] Anomeric ratio's are determined from the anomeric mixture by ^1H NMR analysis.
[b] Determined in product mixture by NMR analysis.

excellent yield but with a rather disappointing stereoselectivity (α/β 2:1).[7b] Complete chemoselectivity was also achieved when the disarmed perbenzoylated thiogalactoside **3** was glycosylated with glucosazide **17** to give the β-linked dimer **19**. This nicely demonstrates the potential of our chemoselective condensation protocol, since peracylated thioglycosides are mostly employed at the end of a chemoselective glycosylation sequence, because of their low reactivity.[13]

Now that we advantageously applied **2a** for the chemoselective glycosylation of an relatively armed donor and disarmed acceptor we anticipated that the scope of the developed methodology could be extended by decreasing

the difference in reactivity of the donor and acceptor condensation partners. Since the BSP/Tf_2O system is thought to convert the donor thioglycoside in situ to the corresponding anomeric triflate[7b] it should in theory be possible to condense this species with any other thioglycoside, regardless of the reactivity of the acceptor thiofunction, provided that the generated (*N*-piperidino)-phenyl(*S*-thiophenyl)sulfide triflate is timely quenched. However pre-activation of armed donor **8** and reaction with armed acceptor **20** led to an intractable mixture of products and disaccharide **21** was not obtained. The same occurred in the condensations of the disarmed donor **3** with thioglucoside **9** and thiomannoside **23**, although in the latter product mixture little orthoester product (<10%) was detected. Nevertheless, several attempts to optimize these results (longer activation times, lower quenching temperatures) were abortive.

We next focussed on the extension of the chemoselective glycosylation sequence to elongate the obtained thiodisaccharides in a second condensation event. Consequently, we used the more potent DPS/Tf_2O system to activate the disarmed thiodisaccharides and condensed them with a terminal acceptor building block to furnish the target trisaccharides (Scheme 3). Activation of **15** with **2b** and condensation with methyl 2,3,4-tri-*O*-acetyl-α-glucopyranoside (**25**) proceeded uneventfully and gave the expected β-mannose linked trisaccharide **26** in an adequate 64% yield as the sole isomer. Surprisingly, the glycosylation of dimer **19** with the reactive 2,3,4-tri-*O*-benzyl glucose **27** under the same conditions stereoselectively furnished the β-glucoside **28**. This β-selectivity can be explained by the rapid S_N2-like displacement of the intermediate α-triflate, which has also been observed when methanol was used as an acceptor.[14] As a final demonstration the fully protected α-Gal epitope **30**,[15] equipped with an azidopropyl spacer at its reducing end, was assembled by the DPS/Tf_2O mediated condensation of the α-linked digalactoside **13** and the terminal glucosamine building block **29** in 69% yield.

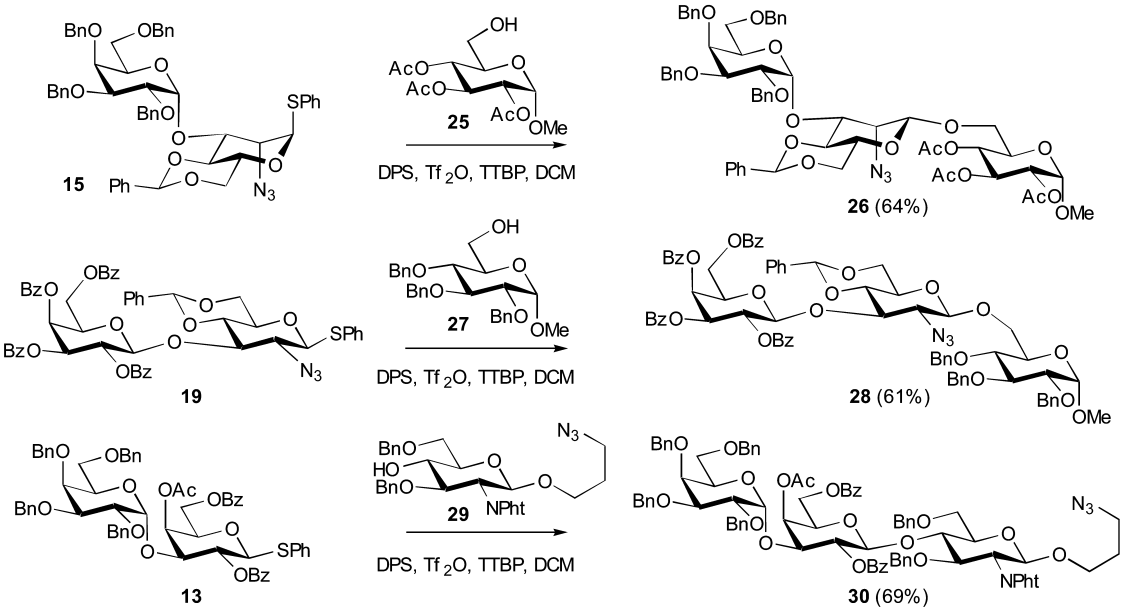
3. Conclusion

A novel chemoselective glycosylation sequence was developed which utilizes thioglycosides and exploits the reactivity difference of the recently developed BSP/Tf_2O and DPS/Tf_2O activator systems. For a productive BSP/Tf_2O mediated chemoselective glycosylation the following requirements have to be fulfilled: (1) the donor glycoside should be pre-activated before addition of the acceptor since the phenyl-1-piperidinosulfide bis(triflate) **2a** can also react with the acceptor hydroxyl function; (2) the donor thioglycoside should be more reactive than the acceptor thioglycoside, to prevent side reactions caused by the transiently formed (*N*-piperidino)phenyl(*S*-thiophenyl/thioethyl)-sulfide triflate **7a/b**; (3) the transiently formed triflate species **7** should be timely quenched with an efficient reagent, here exemplified by the use of triethyl phosphite. The described condensation sequence extends the scope of chemoselective glycosylations towards the use of highly disarmed thioglycosides and can benefit from the advantages inherent to the BSP/Tf_2O mediated glycosylations in the construction of difficult glycosidic linkages. Efforts are currently underway to explore the use of different thio- and seleno-glycosides and to implement the developed methodology in the assembly of more complex oligosaccharides.

4. Experimental

4.1. General methods

Dichloromethane was dried with P_2O_5 and distilled before use. All chemicals (Fluka, Acros, Merck) were used as received. TTBP was synthesized as described by Crich et al.[10] Reactions were performed under an inert atmosphere under strictly anhydrous conditions. Traces of water from the donor and acceptor glycosides, BSP, diphenylsulfoxide and TTBP were removed by co-evaporation with toluene and dichloroethane. Molecular sieves (3 Å) were flame



Scheme 3. DPS/Tf_2O mediated assembly of trisaccharides.

dried before use. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AV 400 (400 and 100 MHz). ^{1}H NMR chemical shifts (δ) in $CDCl_3$ are reported relative to tetramethylsilane. ^{19}F NMR chemical shifts (δ) are reported relative to TFA. Mass spectra were recorded on a PE/SCIEX API 165 equipped with an Electrospray Interface (Perkin–Elmer). Optical rotations were recorded on a Propol automatic polarimeter in $CHCl_3$. Column chromatography was performed on Merck silica gel 60 (0.040–0.063 mm). TLC analysis was conducted on DC-fertigfolien (Schleicher and Schuell, F1500, LS254) or HPTLC aluminum sheets (Merck, silica gel 60, F254). Compounds were visualized by UV absorption (254 nm), and by spraying with 20% H_2SO_4 in ethanol or with a solution of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ 25 g/L.

4.2. General procedure for chemoselective BSP/Tf_2O mediated glycosylations

To a solution of the thiodonor (typically 0.2 mmol, 1.0 equiv.), BSP (1.1 equiv.), TTBP (2.5 equiv.) in dichloromethane (5 mL) was added at −60 °C trifluoromethanesulfonic anhydride (1.1 equiv.). The reaction mixture was stirred for 5 min, after which time a solution of the acceptor thioglycoside (1.1 equiv.) in dichloromethane (1 mL) was added. The mixture was stirred at −60 °C for 1 h, after which it was slowly warmed to −10 °C and quenched by the addition of triethylphosphite (1.0 equiv.) and triethylamine (5 equiv.), followed by saturated aqueous $NaHCO_3$. The organic layer was separated, washed with saturated NaCl solution, dried ($MgSO_4$) and concentrated. Purification by silica gel chromatography (ethyl acetate/petroleum ether) gave the thiodisaccharide.

4.2.1. Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(benzenesulfinylpiperidine triflate)-α-D-glucopyranoside (5). A mixture of ethyl 2,3,4,6-tetra-*O*-benzoyl-1-thio-α-D-galactoside (**3**), methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**4**), BSP and TTBP were dissolved in DCM and the reaction mixture was cooled to −60 °C. Tf_2O was added and the reaction mixture was warmed to room temperature. The mixture was concentrated to a smaller volume and directly purified by silica gel chromatography (100/0/0 to 0/90/10 petroleum ether/ethyl acetate/methanol) to provide tetra-*O*-benzoyl-1-thio-α-D-galactoside (**3**) and the title compound as a white glassy oil as an 1:1 mixture of sulfur diastereoisomers. R_f 0.25 (10% MeOH in EtOAc); ^{1}H NMR (400 MHz, MeOD): δ=7.72–7.27 (m, 20H, H_{arom}), 4.95–4.85 (m, 3H, C*H*H Bn), 4.75–4.67 (m, 5H, H-1, H-6, CH*H* Bn), 4.59 (m, 1H, H-6), 3.95 (t, 0.5H, *J*=9.6 Hz, H-3), 3.92 (t, 0.5H, *J*=9.6 Hz, H-3), 3.87 (m, 1H, H-5), 3.52 (dd, 0.5H, *J*=3.5, 9.6 Hz, H-2), 3.48 (m, 1H, H-4), 3.40–3.24 (m, 4.5H, H-2, CH_2NCH_2), 3.37 (s, 1.5H, OMe), 3.34 (s, 1.5H, OMe), 1.61 (m, 6H, $CH_2{-}CH_2{-}CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=139.7, 139.3, 139.2 (C_q Bn), 131.7, 131.4 (C_q SPh), 135.9–128.7 (CH_{arom}), 124.9 (J_{CF}=317 Hz, CF_3), 99.4, 99.1 (C-1), 82.7, 82.5 (C-3), 81.0, 80.6 (C-2), 77.0 (C-4), 76.5, 76.4, 75.5, 75.4, 74.9 (CH_2 Bn), 73.8 (C-6), 70.5, 70.3 (C-5), 56.1 (OMe), 51.8 (CH_2NCH_2), 26.9, 26.7, 23.6, 23.5 ($CH_2{-}CH_2{-}CH_2$); ^{19}F NMR (188 MHz, CDCl3): δ=0.96; IR (neat): 1263, 731 cm^{-1}; ES-MS: *m*/*z* 656.1 $[M-OTf]^+$.

4.2.2. Methyl 6-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-2,3,4-*O*-benzyl-α-D-glucopyranoside (6). Disaccharide **6** was obtained from ethyl tetra-*O*-benzoyl-1-thio-α-D-galactoside (**3**), methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**4**), following the general coupling procedure in 62% as an colourless oil. R_f 0.40 (25% EtOAc in PE); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.09–7.11 (m, 35H, H_{arom}), 5.97 (d, 1H, *J*=2.7 Hz, H-4′), 5.85, (dd, 1H, *J*=8.0, 10.4 Hz, H-2′), 5.60 (dd, 1H, *J*=3.5, 10.4 Hz, H-3′), 4.90 (d, 1H, *J*=10.9 Hz, C*H*H Bn), 4.76 (d, 1H, *J*=8.0 Hz, H-1′), 4.72 (d, 1H, *J*=12.0 Hz, C*H*H Bn), 4.69 (d, 1H, *J*=10.9 Hz, CH*H* Bn), 4.67 (dd, 1H, *J*=6.4, 11.3 Hz, H-6′), 4.58 (d, 1H, *J*=12.0 Hz, CH*H* Bn), 4.56 (d, 1H, *J*=11.2 Hz, C*H*H Bn), 4.51 (d, 1H, *J*=3.5 Hz, H-1), 4.40 (dd, 1H, *J*=6.8, 11.4 Hz, H-6′), 4.38 (d, 1H, *J*=11.2 Hz, CH*H* Bn), 4.25 (m, 1H, H-5′), 4.21 (dd, 1H, *J*=4.2, 12.7 Hz, H-6), 3.90 (t, 1H, *J*=9.2 Hz, H-3), 3.76 (m, 2H, H-5, H-6), 3.40 (dd, 1H, *J*=3.5, 9.6 Hz, H-2), 3.38 (t, 1H, *J*=9.2 Hz, H-4), 3.21 (s, 3H, OMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ=165.9, 165.6, 165.5, 165.1 (C=O, Bz), 138.7, 138.2, 138.0 (C_q Bn), 129.2, 128.9, 128.6, 128.5 (C_q Bz), 133.5–127.4 (CH_{arom}), 101.9 (C-1′), 97.8 (C-1), 81.8 (C-3), 79.8 (C-2), 77.4 (C-4), 75.4, 74.6, 73.3 (CH_2 Bn), 71.6 (C-3′), 71.3 (C-5′), 69.7 (C-2′), 69.5 (C-5), 68.6 (C-6), 68.0 (C-4′), 61.8 (C-6′), 54.9 (OMe); IR (neat): 1724, 1261, 1068 cm^{-1}; $[\alpha]_D^{23}$ +66.8 (*c*=1.0 $CHCl_3$); ES-MS: *m*/*z* 1065.5 $[M+Na]^+$; HRMS calcd for $C_{62}H_{58}O_{15}NH_4$: 1060.4119. Found: 1060.4120.

4.2.3. Ethyl 6-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-glucopyranosyl)-2,3,4-*O*-benzoyl-1-thio-β-D-glucopyranoside (10). BSP (27 mg, 0.13 mmol) was dissolved in DCM (5 mL) and cooled to −60 °C. Tf_2O (20 μL, 0.12 mmol) was added followed by thiophenol (11 μL, 0.11 mmol). The reaction mixture was stirred for 5 min, after which ethyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucoside (**8**, 58 mg, 0.11 mmol) in DCM (1 mL) was added. The mixture was stirred for another 15 min, after which ethyl 2,3,4-tri-*O*-benzoyl-1-thio-β-D-glucopyranoside (**9**) was added and the mixture was allowed to warm to room temperature. Standard work-up and purification gave 50 mg (0.048 mmol, 44%) of the title compound as a 2:1 α/β mixture as an slightly yellow oil. The spectroscopic data were in full accord with those previously reported:[5a] R_f 0.80 (25% EtOAc in PE); α-anomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.09–7.12 (m, 52.5H, H_{arom}), 5.88 (t, 1H, *J*=9.4 Hz, H-3α), 5.86 (t, 0.5H, *J*=9.5 Hz, H-3β), 5.53–5.39 (m, 3H, H-2, H-4), 5.00 (m, 15H, H-1, H-1′, CH_2 Bn), 4.12–3.84 (m, 5H), 3.64–3.39 (m, m, 8.5H, H-5, 2×H-6, H-2′, H-3′, H-4′, H-5′, 2×H6′), 2.75–2.63 (m, 3H, CH_2 SEt), 1.25 (m, 4.5H, CH_3 SEt); ^{13}C NMR (100 MHz, $CDCl_3$): δ=165.7, 165.4, 165.1 (C=O Bz), 138.9, 138.6, 138.1 (C_q Bn), 129.2, 128.9 (C_q Bz), 133.4–127.4 (CH_{arom}) 103.8 (C-1′β), 97.0 (C-1′α), 84.5, 83.6, 82.2, 81.9, 79.9, 78.6, 78.4, 77.6, 74.8, 74.3, 74.2, 70.8, 70.7, 70.1, 70.0, 69.8, 69.5 (C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 75.6, 74.9, 74.7, 73.4, 73.3, 73.2 (CH_2 Bn), 68.9, 68.6, 68.3, 66.8 (C-6, C-6′), 24.2 (CH_2 SEt), 14.7 (CH_3 SEt); IR (neat): 1728, 1257, 1089 cm^{-1}; ES-MS: *m*/*z* 1081.4 $[M+Na]^+$; HRMS calcd for $C_{63}H_{62}O_{13}SNH_4$: 1076.4255. Found: 1076.4265.

Disaccharide **10** was also obtained from ethyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucoside (**8**) and ethyl 2,3,4-tri-*O*-

benzoyl-1-thio-β-D-glucopyranoside (**9**), following the general coupling procedure in 78% as an 3:1 α/β mixture.

4.2.4. Phenyl 3-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-4-*O*-acetyl-2,6-di-*O*-benzoyl-1-thio-β-D-galactopyranoside (13). Disaccharide **13** was obtained from phenyl tetra-*O*-benzyl-1-thio-β-D-galactoside (**11**) and phenyl 4-*O*-acetyl-2,6-di-*O*-benzoyl-1-thio-β-D-galactopyranoside (**12**), following the general coupling procedure in 52% as an colourless oil. R_f 0.80 (33% EtOAc in PE); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.12–7.14 (m, 35H, CH_{arom}), 5.67 (d, 1H, *J*=2.8 Hz, H-4), 5.61 (t, 1H, *J*=9.9 Hz, H-2), 5.22 (d, 1H, *J*=3.2 Hz, H-1′), 4.81 (d, 1H, *J*=10.1 Hz, H-1), 4.76 (d, 1H, *J*=11.4 Hz, C*H*H Bn), 4.65 (s, 2H, CH_2 Bn), 4.64 (d, 1H, *J*=12.2 Hz, C*H*H Bn), 4.48 (m, 2H, H-6, C*H*H Bn), 4.36 (m, 4H, H-6, 3×CH*H* Bn), 4.16 (dd, 1H, *J*=3.0, 9.7 Hz, H-3), 3.93 (m, 3H, H-2′, H-5, H-5′), 3.75 (dd, 1H, *J*=2.6, 10.1 Hz, H-3′), 3.44 (dd, 1H, *J*=7.3, 9.6 Hz, H-6′), 3.23 (bs, 1H, H-4′), 3.20 (dd, 1H, *J*=5.2, 9.6 Hz, H-6′), 1.89 (s, 3H, CH_3 Ac); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.3, 165.9, 164.8 (C=O), 138.6, 138.5, 138.3 (C_q Bn), 133.4 (C_q SPh), 129.5, 129.4 (C_q Bz), 133.2–127.4 (CH_{arom}), 93.3 (C-1′), 87.0 (C-1), 78.7 (C-3′), 75.5 (C-2′), 74.8 (C-5′), 74.7 (C-4′), 74.3, 74.2, 73.1, 73.0 (CH_2 Bn), 72.7 (C-3), 69.9 (C-5), 69.4 (C-6′), 68.9 (C-2), 65.1 (C-4), 62.7 (C-6), 20.4 (CH_3 Ac); IR (neat): 1724, 1093 cm^{-1}; $[\alpha]_D^{23}$ +90.8 (*c*=1.0 $CHCl_3$); ES-MS: *m*/*z* 1068.1 $[M+Na]^+$; HRMS calcd for $C_{62}H_{60}O_{13}SNH_4$: 1062.4098. Found: 1062.4063.

4.2.5. Phenyl 3-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-mannopyranoside (15). Disaccharide **15** was obtained from tetra-*O*-benzyl-1-thio-β-D-galactoside (**11**) and phenyl 2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-mannopyranoside (**17**), following the general coupling procedure in 73% as an yellow oil. R_f 0.80 (25% EtOAc in PE); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.38–7.03 (m, 30H, H_{arom}), 5.47 (d, 1H, *J*=3.3 Hz, H-1′), 5.45 (s, 1H, C*H*Ph), 5.41 (bs, 1H, H-1), 4.91 (d, 1H, *J*=11.8 Hz, C*H*H Bn), 4.87 (d, 1H, *J*=13.1 Hz, C*H*H Bn), 4.69 (d, 1H, *J*=11.9 Hz, CH*H* Bn), 4.59 (d, 1H, *J*=12.6 Hz, C*H*H Bn), 4.56 (d, 1H, *J*=11.8 Hz, C*H*H Bn), 4.53 (d, 1H, *J*=11.8 Hz, CH*H* Bn), 4.45 (m, 3H, H-3, 2×CH*H* Bn), 4.35 (m, 2H, H-2, H-5), 4.21 (t, 1H, *J*=9.6 Hz, H-4), 4.14 (dd, 1H, *J*=4.8, 10.3 Hz, H-6), 4.00 (m, 3H, H-2′, H-3′, H-5′), 3.87 (bs, 1H, H-4′), 3.79 (t, 1H, *J*=10.3 Hz, H-6), 3.59 (dd, 1H, *J*=6.8, 9.8 Hz, H-6′), 3.46 (dd, 1H, *J*=5.4, 9.8 Hz, H-6′); ^{13}C NMR (100 MHz, $CDCl_3$): δ=138.8, 138.43, 138.38, 137.9, 137.0 (C_q Bn, Ph), 132.9 (C_q SPh), 131.7–126.3 (CH_{arom}), 102.2 (*C*HPh), 98.3 (C-1′), 87.0 (C-1), 79.1 (C-4), 78.0 (C-5′), 75.3 (−2′, 4′), 73.3 (C-3), 74.5, 73.6, 73.5, 71.0 (CH_2 Bn), 70.7 (C-3′), 69.7 (C-6′), 68.3 (C-6), 64.9 (C-2, 5); IR (neat): 2104, 1095 cm^{-1}; $[\alpha]_D^{23}$+66.2 (*c*=1.0 $CHCl_3$); ES-MS: *m*/*z* 930.4 $[M+Na]^+$; HRMS calcd for $C_{53}H_{53}N_3O_9SNH_4$: 925.3846. Found: 925.3853.

4.2.6. Phenyl 3-*O*-(2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α/β-D-glucopyranosyl)-2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-β-D-glucopyranoside (18). Disaccharide **18** was obtained from phenyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-1-thio-β-D-glucoside (**16**) and phenyl 2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-glucopyranoside (**17**), following the general coupling procedure in 90% as an α/β-mixture (2:1) as an colourless oil. R_f 0.50 (20% EtOAc in PE); α-anomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.61–6.99 (m, 25H, H_{arom}), 5.51 (s, 1H, C*H*Ph), 5.49 (d, 1H, *J*=3.9 Hz, H-1′), 5.45 (s, 1H, C*H*Ph), 4.87 (d, 1H, *J*=11.2 Hz, C*H*H Bn), 4.79 (d, 1H, *J*=11.2 Hz, CH*H* Bn), 4.59 (d, 1H, *J*=10.1 Hz, H-1), 4.58 (d, 1H, *J*=12.4 Hz, C*H*H Bn), 4.42 (d, 1H, *J*=12.3 Hz, CH*H* Bn), 4.36 (m, 2H, H-6, H-6′), 4.11 (m, 1H, H-5′), 4.01 (t, 1H, *J*=9.4 Hz, H-3′), 3.94 (t, 1H, *J*=9.3 Hz, H-3), 3.77–3.69 (m, 3H, H-4, H-6, H-6′), 3.57 (t, 1H, *J*=9.0 Hz, H-4′), 3.48 (m, 3H, H-2, H-5, H-2′); ^{13}C NMR (100 MHz, $CDCl_3$): δ=138.7, 137.6, 137.5, 136.8 (C_q Bn, CHPh), 130.2 (C_q SPh), 134.1–126.0 (CH_{arom}), 102.1 (*C*HPh), 101.4 (*C*HPh), 97.5 (C-1′), 87.3 (C-1), 81.8, 81.4, 78.1, 76.2, 70.3, 63.9 (C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 75.2, 72.0 (CH_2 Bn), 69.8, 68.5 (C-6, C-6′), 63.0 (C-2); β-anomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.61–6.99 (m, 25H, H_{arom}), 5.52 (s, 1H, C*H*Ph), 5.39 (s, 1H, C*H*Ph), 4.88 (d, 1H, *J*=7.3 Hz, H-1′), 4.87 (d, 1H, *J*=11.5 Hz, C*H*H Bn), 4.86 (d, 1H, *J*=11.1 Hz, C*H*H Bn), 4.79 (d, 1H, *J*=11.1 Hz, CH*H* Bn), 4.73 (d, 1H, CH*H* Bn), 4.36 (m, 1H, H-6), 4.10 (m, 1H, H-6′), 3.91 (t, 1H, *J*=9.3 Hz, H-3), 3.74–3.59 (m, 3H, H-4, H-3′, H-4′, H-6′), 3.50 (m, 1H, H-2′), 3.41 (m, 2H, H-2, H-5), 3.25 (m, 1H, H-5′); ^{13}C NMR (100 MHz, $CDCl_3$): δ=138.4, 138.3, 137.3, 136.9 (C_q Bn, CHPh), 130.5 (C_q SPh), 133.9–126.0 (CH_{arom}), 102.4, 101.5, 101.0 (*C*H Ph, C-1′), 87.1 (C-1), 82.1, 81.2, 81.1, 79.0, 78.1, 70.6, 65.7 (C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 74.9, 14.7 (CH_2 Bn), 68.7, 68.4 (C-6, C-6′), 64.9 (C-2); IR (neat): 2110, 1089 cm^{-1}; ES-MS: *m*/*z* 816.2 $[M+H]^+$, 838.4 $[M+Na]^+$; HRMS calcd for $C_{46}H_{45}N_3O_9SNH_4$: 833.3220. Found: 833.3233.

4.2.7. Phenyl 3-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-β-D-glucopyranoside (19). Disaccharide **19** was obtained from phenyl 2,3,4,5-*O*-benzoyl-1-thio-β-D-galactopyranoside (**3**) and phenyl 2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-glucopyranoside (**17**), following the general coupling procedure in 64% as an slightly yellow oil. R_f 0.50 (25% EtOAc in PE); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.04–7.02 (m, 30H, H_{arom}), 5.93 (d, 1H, *J*=2.7 Hz, H-4′), 5.82 (dd, 1H, *J*=8.1, 10.4 Hz, H-2′), 5.58 (s, 1H, C*H*Ph), 5.57 (dd, 1H, *J*=3.4, 10.6 Hz, H-3′), 5.10 (d, 1H, *J*=8.1 Hz, H-1′), 4.42 (d, 1H, *J*=10.1 Hz, H-1), 4.30 (m, 3H, H-6, H-6′, H-6′), 4.02 (t, 1H, *J*=7.3 Hz, H-5′), 3.80 (t, 1H, *J*=9.1 Hz, H-3), 3.78 (t, 1H, *J*=9.1 Hz, H-6), 3.70 (t, 1H, *J*=9.3 Hz, H-4), 3.41 (m, 2H, H-2, H-5); ^{13}C NMR (100 MHz, $CDCl_3$): δ=165.6, 165.5, 165.4, 165.2 (C=O), 136.8 (Cq CHPh), 133.9–125.9 (CH_{arom}), 130.2, 129.4, 129.2, 129.1 (C_q Bz, SPh), 101.4 (*C*HPh, C-1′), 87.0 (C-1), 81.3 (C-3), 79.2 (C-4), 71.7 (C-3′), 71.4 (C-5′), 70.5 (C-2′), 70.3 (C-5), 68.4 (C-6), 67.8 (C-4′), 64.3 (C-2), 61.2(C-6′); IR (neat): 2111, 1724, 1261, 1091 cm^{-1}; $[\alpha]_D^{23}$ +7.6 (*c*=1.0 $CHCl_3$); ES-MS: *m*/*z* 986.5 $[M+Na]^+$; HRMS calcd for $C_{53}H_{45}N_3O_{13}SNH_4$: 981.3017. Found: 981.3008.

4.2.8. 3,4,6-tri-*O*-benzoyl-α-D-Galactopyranose 1,2-[phenyl {phenyl (3-*O*-benzyl-2,3-*O*-isopropylidene-1-thio-α-D-mannopyranosid-6-yl)} orthoacetate] (24). The title compound was obtained from 2,3,4,5-*O*-benzoyl-1-thio-β-D-galactopyranoside (**3**) and ethyl 3-*O*-benzyl-2,3-*O*-isopropylidene-1-thio-α-D-mannopyranoside (**23**) in a 3:1 mixture of donor **3** and orthoester **24** as an yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ=8.07–7.23 (m, 25H, H_{arom}), 6.03 (d, 1H, J=5.1 Hz, H-1′), 5.79 (dd, 1H, J=2.7, 4.2 Hz, H-4′), 5.74 (s, 1H, H-1), 5.55 (dd, 1H, J=4.2, 6.0 Hz, H-3′), 4.86 (d, 1H, J=11.2 Hz, C*H*H Bn), 4.60 (m, 2H, H-2′, H-6′), 4.51 (m, 2H, H-5′, CH*H* Bn), 4.35 (m, 1H, H-6′), 4.31 (m, 2H, H-2, H-3), 4.26 (m, 1H, H-5), 3.66 (dd, 1H, J=2.1, 10.5 Hz, H-6), 3.55 (dd, 1H, J=6.2, 10.6 Hz, H-6), 3.51 (dd, 1H, J=6.3, 10.3 Hz, H-4), 2.84 (m, 2H, CH_3 SEt), 1.49 (s, 3H, CH_3 isoprop.), 1.37 (s, 3H, CH_3 isoprop.), 1.25 (t, 3H, J=7.2 Hz, CH_3 SEt). ^{13}C NMR (100 MHz, $CDCl_3$): δ=165.9–165.1 (C=O, Bz), 137.9 (C_q Bn), 136.0 (C_q SPh), 129.5, 129.4–129.4 (C_q Bz), 133.4–126.2 (CH_{arom}), 120.2 (C_q orthoester), 109.5 (C_q isoprop.), 98.1 (C-1′), 84.0 (C-1), 78.4, 76.4, 76.2, 73.1, 70.0, 69.2, 68.7, 66.4 (C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 72.8 (CH_2 Bn), 63.2, 62.4 (C-6, C-6′), 27.9, 26.3 (CH_3 isoprop.), 24.4 (CH_2 SEt), 14.9 (CH_3 SEt).

4.3. General procedure for the Ph_2SO/Tf_2O mediated glycosylations

To a solution of the thiodisaccharide (0.1 mmol, 1.0 equiv.), Ph_2SO (2.8 equiv.), TTBP (3.0 equiv.) in dichloromethane (4 mL) was added at −60 °C trifluoromethanesulfonic anhydride (1.4 equiv.). The reaction mixture was stirred for 5 min, after which a solution of the acceptor (1.5 equiv.) in dichloromethane (2 mL) was added. The mixture was stirred at −60 °C for 1 h, after which it was slowly warmed to room temperature and quenched by the addition of saturated aqueous $NaHCO_3$. The organic layer was washed with brine, dried ($MgSO_4$), filtered and concentrated. The glycosides were isolated by silica gel chromatography (ethyl acetate/ petroleum ether).

4.3.1. Methyl 6-*O*-[3-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-2-azido-4,6-*O*-benzylidene-2-deoxy-β-D-mannopyranosyl]-2,3,4-tri-*O*-acetyl-α-D-glucopyranoside (26). Trisaccharide **26** was obtained from **15** and **25**, following the general Ph_2SO/Tf_2O coupling procedure in 64% yield as a colourless oil. R_f 0.50 (50% EtOAc in PE); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.35–7.01 (m, 25H, H_{arom}), 5.49 (dd, 1H, J=9.3, 9.9 Hz, H-3), 5.41 (bs, 2H, H-1″, C*H*Ph), 4.95 (dd, 1H, J=9.3, 10.3 Hz, H-4), 4.90 (d, 1H, J=4.0 Hz, H-1), 4.89 (d, 1H, C*H*H Bn), 4.88 (d, 1H, C*H*H Bn), 4.86 (dd, 1H, J=4.4, 6.5 Hz, H-2), 4.70 (d, 1H, CH*H* Bn), 4.57 (d, 1H, C*H*H Bn), 4.55 (bs, 1H, H-1′), 4.52 (d, 2H, J=11.7 Hz, CH*H* Bn, C*H*H Bn), 4.42 (d, 1H, J=13.0 Hz, CH*H* Bn), 4.42 (d, 1H, J=11.6 Hz, CH*H* Bn), 4.26 (dd, 1H, J=4.9, 10.5 Hz, H-6′), 4.17 (dd, 1H, J=1.3, 3.4 Hz, H-2′), 4.08 (m, 1H, H-3′), 4.07 (m, 1H, H-4′), 4.01 (m, 1H, H-5), 3.98 (m, 3H, H-2″, H-3″, H-5″), 3.94 (dd, 1H, J=2.0, 10.8 Hz, H-6), 3.88 (bs, 1H, H-4″), 3.81 (t, 1H, J=10.4 Hz, H-6′), 3.54 (dd, 1H, J=6.8, 9.6 Hz, H-6″), 3.50 (dd, 1H, J=7.6, 11.1 Hz, H-6), 3.44 (dd, 1H, J=5.6, 9.7 Hz, H-6″), 3.38 (s, 3H, OMe), 3.34 (m, 1H, H-5′), 2.07 (s, 3H, Ac), 2.01 (s, 3H, Ac), 1.97 (s, 3H, Ac); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.1, 170.0, 169.9 (C=O), 138.8, 138.4, 138.0, 137.0 (C_q Bn, CHPh), 129.3–126.2 (CH_{arom}), 102.1 (*C*HPh), 100.5 (C-1′), 98.4 (C-1″), 96.4 (C-1), 78.2 (C-4′), 78.1, 75.3, 70.5 (C-2″, C-3″, C-5″), 75.1 (C-4″), 74.5 (C-3′), 74.6, 73.6, 73.5, 71.1 (CH_2 Bn), 70.9 (C-2), 70.0 (C-3), 69.5 (C-6″), 69.1 (C-4), 68.8 (C-6), 68.4 (C-6′), 68.1 (C-5), 67.3 (C-5′), 64.3 (C-2′), 55.3 (OMe), 20.7, 20.6 (CH_3 Ac); IR (neat): 2106, 1749, 1223, 1035 cm^{-1}; $[\alpha]_D^{23}$ +9.2 (c=0.60 $CHCl_3$); ES-MS: m/z 1141.9 $[M+Na]^+$; HRMS calcd for $C_{69}H_{67}N_3O_{18}NH_4$: 1135.4763. Found: 1135.4790.

4.3.2. Methyl 6-*O*-[3-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-2-azido-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranosyl]-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (28). Trisaccharide **28** was obtained from **19** and **27**, following the general Ph_2SO/Tf_2O coupling procedure in 61% yield as a colourless oil. R_f 0.55 (33% EtOAc in PE); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.07–7.18 (m, 40H, H_{arom}), 5.94 (bd, 1H, J=3.5 Hz, H-4), 5.83 (dd, 1H, J=8.0, 10.4 Hz, H-2″), 5.58 (dd, 1H, J=10.5, 3.4 Hz, H-3″), 5.57 (s, 1H, C*H*Ph), 5.06 (d, 1H, J=8.0 Hz, H-1″), 4.97 (d, 1H, J=11.0 Hz, C*H*H Bn), 4.87 (d, 1H, J=11.0 Hz, C*H*H Bn), 4.80 (d, 1H, J=11.0 Hz, CH*H* Bn), 4.76 (d, 1H, J=11.0 Hz, C*H*H Bn), 4.63 (d, 1H, J=11.0 Hz, CH*H* Bn), 4.46 (d, 1H, J=3.5 Hz, H-1), 4.50 (d, 1H, J=11.0 Hz, CH*H* Bn), 4.41 (dd, 1H, J=5.8, 11.1 Hz, H-6″), 4.31 (m, 1H, H-6″), 4.28 (m, 1H, H-6′), 4.20 (d, 1H, J=8.1 Hz, H-1′), 4.09 (t, 1H, J=7.2 Hz, H-5″), 4.02 (dd, 1H, J=1.8, 10.8 Hz, H-6), 3.97 (t, 1H, J=9.2 Hz, H-3), 3.78 (m, 1H, H-6′), 3.75 (m, 1H, H-5), 3.70 (m, 1H, H-4′), 3.68 (m, 1H, H-3), 3.65 (dd, 1H, J=4.4, 10.9 Hz, H-6), 3.50 (dd, 1H, J=7.4, 11.0 Hz, H-2), 3.44 (t, 2H, J=9.1 Hz, H-2′, H-4), 3.31 (s, 3H, OMe), 3.29 (m, 1H, H-5′); ^{13}C NMR (100 MHz, $CDCl_3$): δ=165.7, 165.6, 165.5, 165.3 (C=O), 138.8, 138.3, 138.1, 137.0 (C_q Bn), 133.5–125.9 (CH_{arom}), 129.1, 129.0, 128.8, 128.6 (C_q Bz), 102.8 (C-1′), 101.9 (C-1″), 101.3 (*C*HPh), 98.1 (C-1), 82.0 (C-3), 79.8 (C-2), 79.5 (C-3′), 79.3 (C-4′), 77.7 (C-4), 75.6, 74.7, 73.4 (CH_2 Bn), 71.7 (C-3″), 71.3 (C-5″), 70.2 (C-2″), 69.7 (C-5), 68.7 (C-6), 68.4 (C-6′), 67.8 (C-4″), 66.5 (C-5′), 65.8 (C-2′), 61.3 (C-6″), 55.2 (OMe); IR (neat): 2112, 1728, 1265, 1093, 1070 cm^{-1}; $[\alpha]_D^{23}$ +14.8 (c=0.70 $CHCl_3$); ES-MS: m/z 1340.5 $[M+Na]^+$; HRMS calcd for $C_{75}H_{71}N_3O_{19}NH_4$: 1335.5026. Found: 1335.5004.

4.3.3. 3-Azido-1-*O*-(2,6-di-*O*-benzyl-2-deoxy-phthalimido-β-D-glucopyranosyl)-propanol (29). Ethyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxyphthalimido-1-thio-β-D-glucopyrano-side and 3-azidopropanol (3 equiv.) were condensed following the general coupling protocol in 84% yield. The product (215 mg, 0.38 mmol) was treated with TfOH (96 μL, 1.14 mmol) in the presence of triethyl silane (0.20 mL, 1.26 mmol) in DCM at −78 °C. After 20 min the reaction was quenched by the subsequent addition of MeOH and triethylamine. After the reaction mixture was washed with saturated aqueous $NaHCO_3$, dried and concentrated the mixture was purified by column chromatography to provide the title compound **29** (127 mg, 0.22 mmol, 58%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.79–6.92 (m, 14H, H_{arom}), 5.14 (d, 1H, J=8.3 Hz, H-1), 4,75 (d, 1H, J=12.2 Hz, C*H*H Bn), 4.64 (d, 1H, J=12.0 Hz, C*H*H Bn), 4.58 (d, 1H, J=12.0 Hz, CH*H* Bn), 4.53 (d, 1H, J=12.2 Hz, CH*H* Bn), 4.24 (dd, 1H, J=8.4, 10.8 Hz, H-3), 4.15 (dd, 1H, J=8.4, 10.8 Hz, H-2), 3.81 (m, 4H, H-4, H-6, O–CH_2–CH_2), 3.66 (m, 1H, H-5), 3.45 (m, 1H, H-6), 3.11 (m, 2H, CH_2N_3), 1.66 (m, 2H, CH_2–CH_2–CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ=138.0, 137.6 (C_q Bn), 133.8, 128.4, 128.0, 127.7, 127.6, 127.3, 123.2 (CH_{arom}), 131.4 (C_q, Pht), 98.2 (C-1), 78.6 (C-3), 74.2 (CH_2 Bn), 74.2 (C-5), 74.0 (C-4), 73.6 (CH_2 Bn), 70.3

(O–CH_2–CH_2), 55.2 (C-2), 47.8 (CH_2N_3), 28.7 (OCH$_2$–CH_2–CH_2). ES-MS: *m/z* 595.3 $[M+Na]^+$.

4.3.4. 3-Azido-1-*O*-{4-*O*-[3-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-4-*O*-acetyl-2,6-di-*O*-benzoyl-β-D-galactopyranosyl]-3,6-di-*O*-benzyl-2-deoxy-2-phtalimido-β-D-glucopyranosyl}propanol (30). Trisaccharide **30** was obtained from **13** and **29**, following the general Ph_2SO/Tf_2O coupling procedure in 69% yield as a colourless oil. R_f 0.60 (33% EtOAc in PE); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.10–6.83 (m, 44H, H_{arom}), 5.54 (m, 2H, H-2′, H-4′), 5.14 (d, 1H, *J*=3.3 Hz, H-1″), 5.00 (d, 1H, *J*=8.5 Hz, H-1), 4.91 (d, 1H, *J*=12.4 Hz, C*H*H Bn), 4.78 (d, 1H, *J*=8.1 Hz, H-1′), 4.74 (d, 1H, *J*=11.4 Hz, C*H*H Bn), 4.63 (s, 2H, CH_2 Bn), 4.62 (d, 1H, *J*=11.8 Hz, C*H*H Bn), 4.55 (d, 1H, *J*=12.0 Hz, C*H*H Bn), 4.51 (d, 1H, *J*=12.4 Hz, CH*H* Bn), 4.44 (d, 1H, *J*=11.8 Hz, C*H*H Bn), 4.42 (d, 1H, *J*=11.8 Hz, CH*H* Bn), 4.35 (d, 1H, *J*=12.0 Hz, CH*H* Bn), 4.29 (m, 3H, 2×CH*H* Bn, H-3), 4.22 (dd, 1H, *J*=6.5, 11.3 Hz, H-6′), 4.13 (m, 2H, H-6′, H-2), 4.05 (dd, 1H, *J*=8.5, 9.9 Hz, H-4), 3.99 (dd, 1H, *J*=3.4, 10.2 Hz, H-3′), 3.91 (dd, 1H, *J*=3.3, 10.2 Hz, H-2″), 3.85 (bt, 1H, *J*=6.9 Hz, H-5″), 3.75 (m, 1H, O–C*H*H–CH_2), 3.67 (m, 2H, H-5′, H-6), 3.58 (m, 2H, H-6, H-3″), 3.41 (m, 1H, H-5), 3.38 (m, 2H, H-6″, O–CH*H*–CH_2), 3.25 (dd, 1H, *J*=1.2, 2.6 Hz, H-4″), 3.21 (dd, 1H, *J*=5.9, 9.4 Hz, H-6″), 3.08 (m, 2H, CH_2N_3), 1.81 (s, 3H, CH_3 Ac), 1.64 (m, 2H, CH_2CH_2-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.2, 166.0, 164.6 (C=O), 138.7, 138.4, 138.1, 138.0 (C_q Bn), 131.5 (C_q Pht), 129.3, 129.7 (C_q Bz), 133.7–123.2 (CH_{arom}), 100.8 (C-1′), 98.3 (C-1), 94.1 (C-1″), 78.8 (C-3″), 78.3 (C-4), 76.9 (C-3), 75.5 (C-2″), 74.8 (C-4″), 74.7 (C-5), 74.5, 73.5, 73.3, 73.2, 73.1 (CH_2 Bn), 72.3 (C-3′), 71.4 (C-2′), 71.0 (C-5′), 69.8 (C-5″), 69.2 (C-6″), 67.8 (C-6), 65.9 (O–CH_2–CH_2), 65.0 (C-4′), 61.7 (C-6′), 55.7 (C-2), 48.0 (CH_2N_3), 28.8 (CH_2–CH_2–CH_2), 20.4 (CH_3 Ac); IR (neat): 2096, 1712, 1068 cm^{-1}; $[\alpha]_D^{23}$ +39.2 (*c*=0.75, $CHCl_3$); ES-MS: *m/z* 1529.8 $[M+Na]^+$.

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References and notes

1. Boons, G.-J. *Tetrahedron* **1996**, *52*, 1095–1121.
2. (a) Paulsen, H.; Richter, A.; Sinnwell, V.; Stenzel, W. *Carbohydr. Res.* **1974**, *38*, 312–315. (b) Paulsen, H. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 155–224.
3. Mootoo, D. R.; Konradsson, P.; Udodong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583–5584.
4. (a) Douglas, N. L.; Ley, S. V.; Lücking, U.; Warriner, S. L. *J. Chem. Soc. Perkin Trans. 1* **1998**, 51–65. (b) Baeschlin, D. K.; Green, L. G.; Hahn, M. G.; Hinzen, B.; Ince, S. J.; Ley, S. V. *Tetrahedron: Asymmetry* **2000**, 173–197. (c) Zhang, Z.; Ollmann, I. R.; Ye, X.-S.; Wischnat, R.; Baasov, T.; Wong, C.-H. *J. Am. Chem. Soc.* **1999**, *121*, 734–753. (d) Burkhart, F.; Zhang, Z.; Wacowich-Sgarbi, S.; Wong, C.-H. *Angew. Chem. Int. Ed.* **2001**, *40*, 1274–1277. (e) Mong, K.-K. T.; Wong, C.-H. *Angew. Chem. Int. Ed.* **2002**, *41*, 4087–4090. (f) Fridman, M.; Solomon, D.; Yogev, S.; Baasov, T. *Org. Lett.* **2002**, *4*, 281–283.
5. (a) Veeneman, G. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 275–278. (b) Veeneman, G. H.; van Leeuwen, S. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 1331–1334. (c) Zuurmond, H. M.; van der Marel, G. A.; van Boom, J. H. *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 301–302. (d) Duynstee, H. I.; de Koning, M. C.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron* **1999**, *55*, 9881–9898. (e) Sliedrecht, L. A. J. M.; Zegelaar-Jaarsveld, K.; van der Marel, G. A.; van Boom, J. H. *Synlett* **1993**, 335–337.
6. Garegg, P. J. *Adv. Carbohydr. Chem. Biochem.* **1997**, *52*, 179–205.
7. (a) Crich, D.; Smith, M. *Org. Lett.* **2000**, *2*, 4067–4069. (b) Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2001**, *123*, 9015–9020. (c) Kartha, K. P. R.; Aloui, M.; Field, R. A. *Tetrahedron Lett.* **1996**, *37*, 5175–5178. (d) Ercegovic, T.; Meijer, A.; Magnusson, G.; Ellervik, U. *Org. Lett.* **2001**, *3*, 913–915. (e) See Refs. 4c,5.
8. Codée, J. D. C.; Litjens, R. E. J. N.; Den Heeten, R.; Overkleeft, H. S.; van Boom, J. H.; van der Marel, G. A. *Org. Lett.* **2003**, *5*, 1519–1522.
9. (a) Garcia, B. A.; Poole, J. L.; Gin, D. Y. *J. Am. Chem. Soc.* **1997**, *119*, 7597–7598. (b) Garcia, B. A.; Gin, D. Y. *J. Am. Chem. Soc.* **2000**, *122*, 4269–4279. (c) Nguyen, H. M.; Poole, J. L.; Gin, D. Y. *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 414–417. (d) Codée, J. D. C.; van den Bos, L. J.; Litjens, R. E. J. N.; Overkleeft, H. S.; van Boom, J. H.; van der Marel, G. A. *Org. Lett.* **2003**, *5*, 1947–1950.
10. Crich, D.; Smith, M.; Yao, Q.; Picione, J. *Synthesis* **2001**, 323–326.
11. Mong, K.-K. T.; Lee, H.-K.; Durón, S. G.; Wong, C.-H. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 797–802.
12. Sliedregt, L. A. J. M.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **1994**, *35*, 4015–4018.
13. Peracylated thioglycosides have been employed for the chemoselective condensation with relatively more disarmed thioglycosides. See for example: (a) Zhu, T.; Boons, G.-J. *Org. Lett.* **2001**, *3*, 4201–4203. (b) See Ref. 8.
14. (a) Crich, D.; Cai, W. *J. Org. Chem.* **1999**, *64*, 4926–4930. (b) See Ref. 8.
15. For previous syntheses of the α-Gal epitope see: (a) Garegg, P.; Oscarson, S. *Carbohydr. Res.* **1985**, *136*, 207–213. (b) Schaubach, R.; Hemberger, J.; Kinzy, U. *Liebigs Ann. Chem.* **1991**, 607–614. (c) Reddy, G. V.; Jain, R. K.; Bhatti, B. S.; Matta, K. L. *Carbohydr. Res.* **1994**, *263*, 67–77. (d) Vic, G.; Tran, C. H.; Scigelova, M.; Crout, D. H. G. *Chem. Commun.* **1997**, 167–170. (e) Nilsson, K. G. I. *Tetrahedron Lett.* **1997**, *38*, 133–136. (f) Fang, J.; Li, J.; Chen, X.; Zhang, X.; Wang, J.; Guo, Z.; Zhang, W.; Yu, L.; Brew, K.; Wang, P. G. *J. Am. Chem. Soc.* **1998**, *120*, 6635–6638. (g) Hanessian, S.; Huynh, H. K.; Reddy, G. V.; Duthaler, R. O.; Katopodis, A.; Streiff, M. B.; Kinzy, W.; Oehrlein, R. *Tetrahedron* **2001**, *57*, 3281–3290. (h) See Ref. 9d.