Tetrahedron 72 (2016) 415–419

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Halide-mediated regioselective 6-*O*-glycosylation of unprotected hexopyranosides with perbenzylated glycosyl bromide donors

Dominika Alina Niedbal, Robert Madsen *

Department of Chemistry, Technical University of Denmark, 2800 Kgs. Lyngby, Denmark

ARTICLE INFO

Article history:
Received 22 September 2015
Received in revised form 10 November 2015
Accepted 24 November 2015
Available online 27 November 2015

Keywords:
Glycosylation
Glycosyl bromide
Regioselectivity
Stannane
Stereoselectivity

ABSTRACT

The regio- and stereoselective glycosylation at the 6-position in 2,3,4,6-unprotected hexopyranosides has been investigated with dibutyltin oxide as the directing agent. Perbenzylated hexopyranosyl bromides were employed as the donors and the glycosylations were promoted by tetrabutylammonium bromide. The couplings were completely selective for both glucose and galactose donors and acceptors as long as the stannylene acetal of the acceptor was soluble in dichloromethane. This gave rise to a number of 1,2-cis-linked disaccharides in reasonable yields. Mannose donors and acceptors, on the other hand, did not react in the glycosylation under these conditions.

1. Introduction

The chemical synthesis of oligosaccharides lies at the cornerstone of carbohydrate chemistry due to the immense biological importance of glycans. The area has experienced significant progress over the past three decades with the development of new effective glycosyl donors, promoters and coupling strategies.[1] This has made it possible to synthesize rather large oligosaccharides with more than 20 monosaccharides where each glycosidic linkage is formed with excellent stereocontrol and in good yield.[2] However, the regioselectivity is still controlled by the use of partially protected glycosyl acceptors containing one free hydroxy group. These acceptors are prepared through several protecting group manipulations which add a considerable number of steps to the synthesis of a target molecule. Accordingly, the chemical synthesis of oligosaccharides from monosaccharides is still quite a time-consuming event due to the preparation of building blocks and the transformation of protecting groups.

As a result, there is an increasing interest in the development of regioselective glycosylations with 2,3,4,6-unprotected glycosyl acceptors.[3] Although these acceptors contain both a primary and several secondary hydroxy groups, the direct glycosylation of the primary hydroxy group generally gives poor regioselectivity.[4] Therefore, several directing agents based on tin and boron have been developed in order to steer the donor to only one hydroxy group. These reagents can mediate very regioselective glycosylations to either the primary hydroxy group or to the most reactive secondary alcohol.

Bu_2SnO has been employed in the glycosylation of a number of unprotected β-galacto- and β-glucopyranosides to afford the (1 → 6)-linked disaccharides in good yield.[5] These reactions are believed to proceed through the 4,6-stannylene acetal of the acceptor which enhances the reactivity of the 6-position. On the contrary, Ph_2SnCl_2 mediates the selective glycosylation of the 3-position in 2,3,4,6-unprotected mannosides, glucosides and galactosides.[6] The same selectivity is achieved by transient masking of the 4- and the 6-position with boronic acids in glucosides and galactosides[7] while fully unprotected glucose under these conditions gives glycosylation at position 6 due to temporary blocking of position 1, 2, 3 and 5.[8] Regioselective glycosylation at position 3 in mannosides and galactosides can also be achieved in a borinic acid-catalyzed protocol although protection of position 6 is necessary in this case.[9,10]

However, most of these procedures employ the Koenigs–Knorr glycosylation with peracylated glycosyl bromides and various silver salts as promoters giving rise to the 1,2-trans coupling products. In a few cases peracylated thioglycosides have been used as donors with DMTST[5c] and NIS/Lewis acid[7a,8] as promoters. In addition, the halide ion-catalyzed glycosylation[11] has been utilized with tin reagents for glycosylating methyl β-D-galactopyranoside at position 6 (with perbenzylated glucosyl bromide)[5c] and methyl β-lactoside at position 6′ (with perbenzylated galactosyl bromide).[5d] The latter

* Corresponding author. Tel.: +45 4525 2151; fax: +45 4588 3136; e-mail address: rm@kemi.dtu.dk (R. Madsen).

http://dx.doi.org/10.1016/j.tet.2015.11.059
0040-4020/

two examples are interesting since a cheap glycosylation method is employed and the product is obtained with a 1,2-cis relationship. However, the scope and limitations of this approach have not been thoroughly explored and we therefore decided to investigate the halide ion-catalyzed glycosylation with a range of donors and acceptors under different conditions. Herein, we report full details of the bromide-mediated glycosylation of the 6-position in 2,3,4,6-unprotected hexopyranosides in the presence of Bu_2SnO.

2. Results and discussion

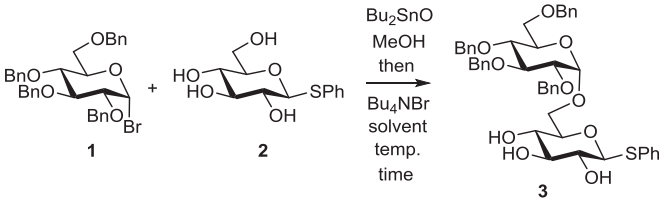
Unprotected phenyl 1-thioglycopyranosides were selected as acceptors for these studies in line with our earlier work[5a,7a] since the regioselective glycosylation would then provide a straightforward route to a number of thioglycoside building blocks that are useful glycosyl donors. For optimizing the reaction conditions both a glucose donor and a glucose acceptor was employed. Tetra-*O*-benzyl-α-D-glucopyranosyl bromide (**1**) was prepared from the corresponding lactol with oxalyl bromide in dichloromethane.[12] Although, bromide **1** in some references has been described as highly unstable, the compound can be purified by silica gel flash chromatography with ethyl acetate/heptane and stored at −15 °C for months.

The regioselective coupling of **1** to phenyl 1-thio-β-D-glucopyranoside (**2**) was performed by treating the latter with 1 equiv of Bu_2SnO in methanol followed by removal of the solvent and drying under high vacuum. The resulting stannylene acceptor complex was then dissolved in dichloromethane with 1.8 equiv of donor **1** and 1.8 equiv of tetra-*n*-butylammonium bromide. After stirring overnight at room temperature the (1 → 6)-linked disaccharide **3** was isolated in 40% yield as the pure α anomer with unreacted donor and acceptor as the only remaining compounds in the mixture (Table 1, entry 1). This indicates that the desired reaction is very stereo- and regioselective under these conditions. However, it is also a rather slow transformation and the coupling was therefore subjected to a further optimization.

The reaction in THF, acetonitrile and trichloroethane produced slightly lower yields than in dichloromethane (entries 2–4). Increasing the reaction temperature gave better conversion in THF while no improvements were observed in acetonitrile and trichloroethane (entries 5–7). However, in THF and acetonitrile the product **3** was obtained as an α/β mixture with a ratio of about 10:1, which renders these conditions unattractive. No conversion occurred in DMF while the stannylene acetal complex was not fully soluble in diethyl ether, dioxane and toluene and therefore only produced a 10–15% yield of **3** in these solvents (results not shown).

Consequently, attention shifted back to dichloromethane where the reaction was repeated in the presence of 4 Å molecular sieves (MS)[13] which increased the yield to 46% (entry 8). When this coupling was performed in the absence of Bu_2SnO the yield dropped to 17% and several byproducts were now clearly visible by TLC (entry 9). This experiment shows that the stannylene acetal is essential to form exclusively the (1 → 6)-linked glycosylation product. Higher or lower temperature gave lower yield in the presence of Bu_2SnO (entries 10 and 11) and room temperature was therefore selected for general use. Interestingly, the amount of Bu_2SnO could be lowered to 10% and the disaccharide **3** was still obtained in a modest yield (entries 12 and 13). The acceptor **2** was not fully soluble in dichloromethane upon pretreatment with only a catalytic amount of Bu_2SnO. This may account for the slightly lower yield under these conditions which is about 15% higher than in the absence of Bu_2SnO (entries 9, 12 and 13). Attempts to replace Bu_2SnO with 10% of Bu_2SnCl_2, Ph_2SnCl_2 or Me_2SnCl_2 gave less than 25% yield of **3** (results not shown). Decomposition of the donor occurred when molecular sieves were replaced with a base such as collidine or lutidine. Replacing the promoter with the stronger activator I_2/DDQ[14] gave essentially the same yield as with Bu_4NBr, but now as a 2:3 α/β mixture (entry 14).

Table 1
Optimization of the regioselective glycosylation



Entry	Solvent	Temp (°C)	Time (h)	Yield (%)[a]
1	CH_2Cl_2	20	18	40
2	THF	20	18	35
3	CH_3CN	20	18	30
4	CH_3CCl_3	20	18	25
5	THF	40	18	45[b]
6	CH_3CN	40	18	30[b]
7	CH_3CCl_3	40	18	18
8[c]	CH_2Cl_2	20	18	46
9[c,d]	CH_2Cl_2	20	18	17
10[c]	CH_2Cl_2	40	8	10
11[c]	CH_2Cl_2	0	18	8
12[c,e]	CH_2Cl_2	20	18	35
13[e]	CH_2Cl_2	20	18	30
14[c,f]	CH_2Cl_2	20	18	48[b]
15[c]	CH_2Cl_2	20	24	50
16[c]	CH_2Cl_2	20	72	56
17[c,e]	CH_2Cl_2	20	24	40
18[c,e]	CH_2Cl_2	20	72	46
19[c,g]	CH_2Cl_2	20	72	45

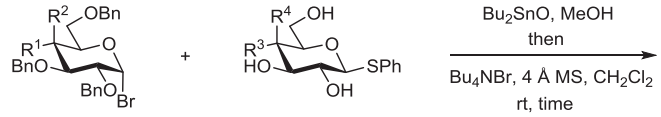
[a] Isolated yield.
[b] Product obtained as an α/β mixture.
[c] 4 Å molecular sieves were also added in the glycosylation.
[d] Reaction performed in the absence of Bu_2SnO.
[e] With 10% of Bu_2SnO.
[f] Bu_4NBr was replaced with I_2/DDQ.
[g] With 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride instead of **1**.

In all these experiments with Bu_2SnO the remaining material in the mixture was unreacted donor and acceptor. Therefore, it was decided to extend the reaction time which produced **3** in 50% yield after 24 h and 56% after 72 h (entries 15 and 16). Both yields were lowered by 10% when only a catalytic amount of Bu_2SnO was employed (entries 17 and 18). Replacing bromide **1** with the corresponding glycosyl chloride also gave a lower yield of **3** due to a slower conversion (entry 19).

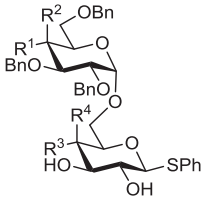
The optimized conditions were then applied for coupling between **1** and galactose acceptor **4** which produced disaccharide **5** in 52% yield after 24 h and 58% after 72 h (Table 2, entries 1 and 2). Again, a decrease of about 10% was observed when the glycosylation was performed with only a catalytic amount of Bu_2SnO (entries 3 and 4). Galactose donor **6** was also prepared and coupled to acceptors **2** and **4** to afford disaccharides **7** and **8**, respectively. The reactions were performed with both stoichiometric and catalytic amounts of Bu_2SnO and the yields were essentially the same as obtained with glucose donor **1** (entries 5–12). All the glycosylations under the optimized conditions gave exclusively the α-linked disaccharides and none of the β-isomers were detected. The regioselectivity was confirmed by HMBC correlations between H-1′ and C-6 in the products.

It was attempted to perform the same couplings with mannose acceptors **9** and **10** (Fig. 1). However, the reactions between the stannylene acetals of these acceptors and donors **1** and **6** only led to decomposed donor and unreacted acceptor after 72 h. The stannylene acetals of **9** and **10** were fully soluble in dichloromethane and the lack of reactivity may therefore be due to the structure of

Table 2
Regioselective glycosylation with glucose and galactose donors and acceptors



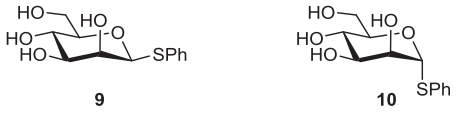
1: R^1 = OBn, R^2 = H
6: R^1 = H, R^2 = OBn
2: R^3 = OH, R^4 = H
4: R^3 = H, R^4 = OH



5: R^1 = OBn, R^4 = OH, R^2 = R^3 = H
7: R^2 = OBn, R^3 = OH, R^1 = R^4 = H
8: R^2 = OBn, R^4 = OH, R^1 = R^3 = H

Entry	Donor	Acceptor	Bu_2SnO (%)	Time (h)	Product	Yield (%)[a]
1	**1**	**4**	100	24	**5**	52
2	**1**	**4**	100	72	**5**	58
3	**1**	**4**	10	24	**5**	42
4	**1**	**4**	10	72	**5**	50
5	**6**	**2**	100	24	**7**	48
6	**6**	**2**	100	72	**7**	57
7	**6**	**2**	10	24	**7**	39
8	**6**	**2**	10	72	**7**	44
9	**6**	**4**	100	24	**8**	44
10	**6**	**4**	100	72	**8**	52
11	**6**	**4**	10	24	**8**	38
12	**6**	**4**	10	72	**8**	47

[a] Isolated yield of α(1 → 6)-linked disaccharides (none of the corresponding β-isomers were detected).

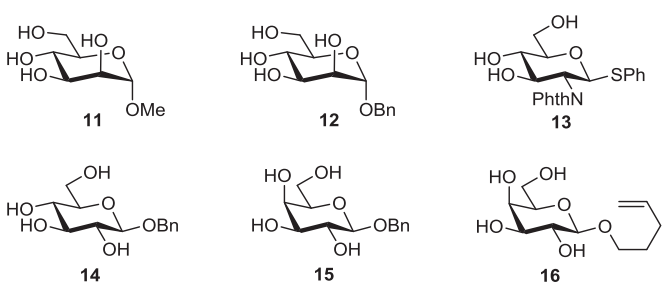


9 **10**

Fig. 1. Unreactive mannose acceptors.

the complexes. We have previously observed that mannose gives a lower yield than glucose and galactose in the regioselective Koenigs–Knorr glycosylation of the corresponding phenyl 1-thioglycosides.[5a] A similar difference between the three monosaccharides was observed in the Bu_2SnO-mediated *tert*-butyldimethylsilylation of the methyl glycosides at position 6.[15] These results may indicate that mannosides are less inclined to form a 4,6-stannylene acetal than glucosides and galactosides, but instead prefer a 2,3-acetal. Furthermore, these acetals can exist as dimers and oligomers in solution[16], which will probably render the stannylene complexes of **9** and **10** unreactive in the halide-mediated glycosylation.

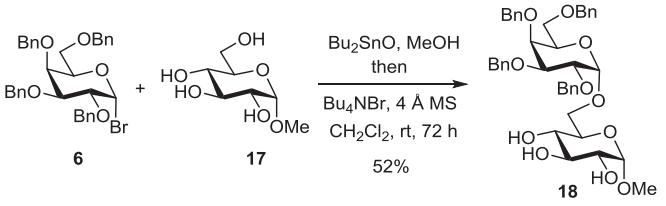
Acceptors **11**–**16** were also prepared (Fig. 2), but unfortunately the stannylene complexes of these were not soluble in



11 **12** **13**
14 **15** **16**

Fig. 2. Insoluble acceptors.

dichloromethane or THF. This was not a limitation with methyl α-D-glucopyranoside (**17**) which was fully dissolved after formation of the tin complex. As a result, glycosylation with donor **6** could be performed and disaccharide **18** was isolated in 52% yield after 72 h (Scheme 1). A mannose donor, i.e. tetra-*O*-benzyl-α-D-mannopyranosyl bromide, was also prepared, but no reaction occurred under the optimized conditions with acceptors **2** and **4**. This is not unexpected since this donor is known to be less reactive than **1** and **6** in the halide-mediated glycosylation.[17]



6 **17** **18**

Scheme 1. Regioselective glycosylation of **17**.

In summary, we have investigated the Bu_2SnO-directed glycosylation of 2,3,4,6-unprotected hexopyranosides with perbenzylated glycosyl bromide donors. Glucose and galactose acceptors can be employed if they are soluble in dichloromethane with Bu_2SnO while no coupling occurred with mannose acceptors. The same was observed with the donors where glucosyl and galactosyl bromides participated in the glycosylation while no conversion took place with the corresponding mannosyl bromide. With glucose and galactose donors and acceptors, the glycosylation occurred regioselectively at position 6 to afford the α-linked disaccharides in decent yields.

3. Experimental section

3.1. General methods

All reactions were performed under an argon atmosphere. Molecular sieves were flame-dried before use. Dichloromethane and tetrahydrofuran were taken from a PureSolv™ solvent purification system. Unprotected phenyl thioglycosides as well as benzyl and pent-4-enyl glycosides were synthesized according to literature procedures.[18] Tetrabutylammonium bromide was recrystallized from ethyl acetate and stored at 60 °C under high vacuum. TLC was performed on aluminum plates coated with silica gel 60. The plates were visualized with UV light or by dipping into a solution of cerium (IV) sulfate (2.5 g) and ammonium molybdate (6.25 g) in sulfuric acid (10%; 250 mL) followed by heating. Column chromatography was carried out with HPLC grade solvents on silica gel 60 (230–400 mesh). IR spectra were measured on a Bruker ALPHA-P FTIR spectrometer. NMR spectra were recorded on a Bruker Ascend instrument with a Prodigy cryoprobe. Chemical shifts were calibrated to the residual solvent signal in $CDCl_3$ (δ_H=7.26 ppm, δ_C=77.16 ppm) or to TMS. Assignment of ^1H and ^{13}C resonances were based on COSY, HSQC, and HMBC experiments. Optical rotations were measured with a Perkin–Elmer 341 polarimeter. High resolution mass spectra were recorded on an Agilent 1100 LC system which was coupled to a Mircromass LCT orthogonal time-of-flight mass spectrometer.

3.2. Synthesis of glycosyl bromides 1 and 6

Oxalyl bromide (180 μL, 1.3 mmol) was added dropwise to a solution of the corresponding 2,3,4,6-tetra-*O*-benzyl-D-glycopyranose (540 mg, 1.0 mmol) in anhydrous CH_2Cl_2 (10 mL). The reaction was stirred at room temperature for about 3 h until

disappearance of the starting material by TLC (EtOAc/heptane, 2:5). The mixture was then diluted with CH_2Cl_2 and washed with water and brine. The organic layer was dried with Na_2SO_4 and concentrated. The residue was purified by column chromatography (EtOAc/heptane, 2:5) to afford the pure glycosyl bromides as syrups (80% yield of **1** and 74% yield of **6**). NMR data were in accordance with literature values.[12]

3.3. General procedure for tin-mediated regioselective glycosylation

A suspension of the unprotected hexopyranoside (0.5 mmol) and Bu_2SnO (0.5 mmol) in MeOH (3.0 mL) was heated to reflux until a clear solution was obtained (3 h). The solvent was removed in vacuo followed by drying under high vacuum for 6 h to give the stannylene derivative as a colorless foam. The bromide donor (0.9 mmol) and 4 Å molecular sieves (300 mg) were then added to a solution of the stannylene derivative in CH_2Cl_2 (2 mL). The suspension was stirred at room temperature for 15 min. Tetrabutylammonium bromide (0.9 mmol) was then added and the mixture was stirred in the dark for the time indicated. The mixture was diluted with CH_2Cl_2, filtered and concentrated. The crude product was purified by column chromatography (toluene/acetone 3:1) or (CH_2Cl_2/MeOH 95:5 → 90:10) to afford the pure disaccharide.

3.4. Phenyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl-(1 → 6)-1-thio-β-D-glucopyranoside (3)

Colorless oil. R_f 0.54 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D$ +0.8 (*c* 0.3, $CHCl_3$); ν_{max} (film) 3318, 1454, 1114, 1026, 836, 530 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.53–6.98 (m, 25H, Ar), 4.86 (d, *J*=10.9 Hz, 1H, OC*H*$_2$Ph), 4.74 (d, *J*=10.9 Hz, 1H, OC*H*$_2$Ph), 4.69 (d, *J*=10.9 Hz, 1H, OC*H*$_2$Ph), 4.67 (d, *J*=3.3 Hz, 1H, H-1′), 4.66 (d, *J*=10.9 Hz, 1H, OC*H*$_2$Ph), 4.54 (d, *J*=12.1 Hz, 1H, OC*H*$_2$Ph), 4.51 (d, *J*=12.1 Hz, 1H, OC*H*$_2$Ph), 4.43 (d, *J*=9.5 Hz, 1H, H-1), 4.39 (d, *J*=9.7 Hz, 1H, OC*H*$_2$Ph), 4.38 (d, *J*=9.7 Hz, 1H, OC*H*$_2$Ph), 4.02–3.79 (m, 2H, H-3′, H-6a), 3.78–3.35 (m, 9H, H-2′, H-3, H-5, H-5′, H-4, H-4′, H-6b, H-6a′, H-6b′), 3.24 (dd, *J*=9.0, 8.1 Hz, 1H, H-2); δ_C (100 MHz, $CDCl_3$) 138.7, 138.2, 137.9, 137.8, 132.9, 132–127 (Ar), 97.9 (C-1′), 88.1 (C-1), 82.1 (C-3′), 79.7 (C-2′), 77.6 (C-4′), 77.5 (C-3), 77.2 (C-5′), 75.8 (OCH_2Ph) 75.1 (OCH_2Ph), 73.5 (2×OCH_2Ph), 72.1 (C-5), 71.7 (C-2), 70.5 (C-4), 69.0 (C-6′), 68.5 (C-6); HRMS (ESI) calcd for $C_{46}H_{50}O_{10}S$ $[M+Na]^+$ *m*/*z* 817.3022, found 817.2997.

3.5. Phenyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl-(1 → 6)-1-thio-β-D-galactopyranoside (5)

Colorless oil. R_f 0.55 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D$ +0.6 (*c* 0.4, $CHCl_3$); ν_{max} (film) 3452, 1452, 1141, 1025, 881, 740, 694 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.48–7.00 (m, 25H, Ar), 4.87 (d, *J*=11.7 Hz, 1H, OC*H*$_2$Ph), 4.86 (d, *J*=3.7 Hz, 1H, H-1′), 4.75 (d, *J*=10.7 Hz, 1H, OC*H*$_2$Ph), 4.74 (d, *J*=10.7 Hz, 1H, OC*H*$_2$Ph), 4.70 (d, *J*=11.6 Hz, 1H, OC*H*$_2$Ph), 4.61 (d, *J*=11.9 Hz, 1H, OC*H*$_2$Ph), 4.52 (d, *J*=12.1 Hz, OC*H*$_2$Ph), 4.42 (d, *J*=9.7 Hz, 1H, H-1), 4.41 (d, *J*=12.1 Hz, 1H, OC*H*$_2$Ph), 4.37 (d, *J*=12.1 Hz, 1H, OC*H*$_2$Ph), 4.00–3.68 (m, 5H, H-3′, H-4′, H-5, H-6a, H-6b), 3.68–3.42 (m, 7H, H-2, H-2′, H-3, H-4, H-5′, H-6a′, H-6b′); δ_C (100 MHz, $CDCl_3$) 138.6, 138.2, 137.9, 137.8, 132.5, 132–127 (Ar), 98.0 (C-1′), 88.9 (C-1), 81.9 (C-3′), 79.6 (C-2′), 77.6 (C-5), 77.2 (C-4′), 75.7 (OCH_2Ph), 75.1 (OCH_2Ph) 74.7 (C-3), 73.5 (2×OCH_2Ph), 70.6 (C-5), 70.2 (C-2), 69.2 (C-4), 68.4 (C-6′), 67.8 (C-6); HRMS (ESI) calcd for $C_{46}H_{50}O_{10}S$ $[M+Na]^+$ *m*/*z* 817.3022, found 817.3004.

3.6. Phenyl 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl-(1 → 6)-1-thio-β-D-glucopyranoside (7)

Colorless oil. R_f 0.56 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D$ +0.6 (*c* 0.5, $CHCl_3$); ν_{max} (film) 3372, 2880, 1454, 1345, 1217, 1113, 1090, 967, 834, 749, 692 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.47–7.11 (m, 25H, Ar), 4.83 (d, *J*=11.4 Hz, 1H, OC*H*$_2$Ph), 4.75 (d, *J*=4.1 Hz, 1H, H-1′), 4.74 (d, *J*=11.7 Hz, 1H, OC*H*$_2$Ph), 4.71 (d, *J*=11.7 Hz, 1H, OC*H*$_2$Ph), 4.63 (d, *J*=11.7 Hz, 1H, OC*H*$_2$Ph), 4.56 (d, *J*=11.9 Hz, 1H, OC*H*$_2$Ph), 4.46 (d, *J*=11.5 Hz, 1H, OC*H*$_2$Ph), 4.42 (d, *J*=9.7 Hz, 1H, H-1), 4.38 (d, *J*=11.8 Hz, 1H, OC*H*$_2$Ph), 4.31 (d, *J*=11.8 Hz, 1H, OC*H*$_2$Ph), 3.95 (dd, *J*=9.4, 3.8 Hz, 1H, H-2′), 3.93–3.82 (m, 3H, H-4′, H-5′, H-6a), 3.79 (dd, *J*=9.6, 3.5 Hz, 1H, H-3′), 3.51 (dd, *J*=10.3, 4.7 Hz, 1H, H-6b), 3.47–3.35 (m, 5H, H-3, H-4, H-5, H-6a′, H-6b′), 3.28–3.19 (m, 1H, H-2); δ_C (100 MHz, $CDCl_3$) 138.7, 138.5, 138.1, 137.7, 132.8, 130–127 (Ar), 98.5 (C-1′), 87.7 (C-1), 79.1 (C-3′), 77.6 (C-3), 77.3 (C-4′), 76.3 (C-2′), 74.8 (2×OCH_2Ph), 73.7 (C-5′), 73.5 (OCH_2Ph), 73.1 (OCH_2Ph), 72.0 (C-5), 71.7 (C-2), 69.7 (C-4), 69.1 (C-6′), 68.9 (C-6); HRMS calcd for $C_{46}H_{50}O_{10}S$ $[M+Na]^+$ *m*/*z* 817.3022, found 817.3026.

3.7. Phenyl 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl-(1 → 6)-1-thio-β-D-galactopyranoside (8)

Colorless oil. R_f 0.54 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D$ +0.9 (*c* 0.5, $CHCl_3$); ν_{max} (film) 3423, 1453, 1113, 1025, 868, 743, 693 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.49–7.04 (m, 25H, Ar), 4.88 (d, *J*=3.7 Hz, 1H, H-1′), 4.83 (d, *J*=11.4 Hz, 1H, OC*H*$_2$Ph), 4.74 (d, *J*=11.8 Hz, 1H, OC*H*$_2$Ph), 4.70 (d, *J*=11.8 Hz, 1H, OC*H*$_2$Ph), 4.64 (d, *J*=11.7 Hz, 1H, OC*H*$_2$Ph), 4.61 (d, *J*=11.8 Hz, 1H, OC*H*$_2$Ph), 4.46 (d, *J*=11.4 Hz, 1H, OC*H*$_2$Ph), 4.39 (d, *J*=9.5 Hz, 1H, H-1), 4.37 (d, *J*=11.6 Hz, 1H, OC*H*$_2$Ph), 4.30 (d, *J*=11.7 Hz, 1H, OC*H*$_2$Ph), 3.96 (dd, *J*=9.4, 3.7 Hz, 1H, H-2′), 3.93–3.82 (m, 4H, H-2, H-4′, H-5′, H-6a), 3.78 (dd, *J*=9.6, 2.7 Hz, 1H, H-3′), 3.68 (dd, *J*=10.9, 5.3 Hz, 1H, H-6b), 3.59–3.37 (m, 5H, H-3, H-4, H-5, H-6a′, H-6b′); δ_C (100 MHz, $CDCl_3$) 138.6, 138.6, 138.1, 137.9, 132.8, 133–127 (Ar), 98.7 (C-1′), 88.6 (C-1), 78.9 (C-3′), 77.2 (C-2′), 76.2 (C-4′), 74.8 (C-3), 74.7 (C-5′), 73.8 (OCH_2Ph), 73.5 (OCH_2Ph), 72.9 (2×OCH_2Ph), 70.1 (C-5), 69.7 (C-2), 69.2 (C-4), 69.0 (C-6′), 67.8 (C-6); HRMS (ESI) calcd for $C_{46}H_{50}O_{10}S$ $[M+Na]^+$ *m*/*z* 817.3022, found 817.3012.

3.8. Methyl 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl-(1 → 6)-α-D-glucopyranoside (18)

Colorless oil. R_f 0.51 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D$ +5 (*c* 0.6, $CHCl_3$); ν_{max} (film) 3381, 1452, 1114, 1024, 965, 546 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.36–6.13 (m, 20H, Ar), 4.85 (d, *J*=11.5 Hz, 1H, OC*H*$_2$Ph), 4.77 (d, *J*=12.0 Hz, 1H, OC*H*$_2$Ph), 4.73 (d, *J*=11.5 Hz, 1H, OC*H*$_2$Ph), 4.71 (d, *J*=2.5 Hz, 1H, H-1′), 4.65 (d, *J*=11.6 Hz, 1H, OC*H*$_2$Ph), 4.64 (d, *J*=3.5 Hz, 1H, H-1), 4.58 (d, *J*=12.0 Hz, 1H, OC*H*$_2$Ph), 4.48 (d, *J*=11.6 Hz, 1H, OC*H*$_2$Ph), 4.40 (d, *J*=11.8 Hz, 1H, OC*H*$_2$Ph), 4.30 (d, *J*=11.8 Hz, 1H, OC*H*$_2$Ph), 3.96 (dd, *J*=9.4, 3.8 Hz, 1H, H-2′), 3.90–3.80 (m, 4H, H-2, H-3, H-3′, H-6a), 3.67–3.58 (m, 2H, H-4, H-4′), 3.52–3.31 (m, 5H, H-5, H-5′, H-6b, H-6a′, H-6b′), 3.29 (s, 3H, OCH_3); δ_C (100 MHz, $CDCl_3$) 138.6, 138.5, 138.3, 137.6, 133–127 (Ar), 99.1 (C-1), 98.8 (C-1′), 79.1 (C-3′), 76.2 (C-2), 74.8 (C-3), 74.7 (C-4′), 74.3 (OCH_2Ph), 73.8 (OCH_2Ph), 73.6 (OCH_2Ph), 73.1 (OCH_2Ph), 72.3 (C-5), 72.0 (C-5′), 70.0 (C-2′), 69.4 (C-4), 69.3 (C-6′), 69.2 (C-6); HRMS (ESI) calcd for $C_{41}H_{48}O_{11}$ $[M+Na]^+$ *m*/*z* 739.3094, found 739.3082.

Acknowledgements

We thank The Novo Nordisk Foundation for financial support.

Supplementary data

Supplementary data (^{1}H and ^{13}C NMR spectra of all compounds) associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2015.11.059.

References and notes

1. (a) Zhu, X.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 1900–1934; (b) Smoot, J. T.; Demchenko, A. V. *Adv. Carbohydr. Chem. Biochem.* **2009**, *62*, 161–250.
2. (a) Calin, O.; Eller, S.; Seeberger, P. H. *Angew. Chem., Int. Ed.* **2013**, *52*, 5862–5865; (b) Ishiwata, A.; Ito, Y. *J. Am. Chem. Soc.* **2011**, *133*, 2275–2291; (c) Joe, M.; Bai, Y.; Nacario, R. C.; Lowary, T. L. *J. Am. Chem. Soc.* **2007**, *129*, 9885–9901; (d) Fraser-Reid, B.; Lu, J.; Jayaprakash, K. N.; López, J. C. *Tetrahedron: Asymmetry* **2006**, *17*, 2449–2463.
3. Böttcher, S.; Thiem, J. *Curr. Org. Chem.* **2014**, *18*, 1804–1817.
4. (a) Uriel, C.; Gómez, A. M.; López, J. C.; Fraser-Reid, B. *Org. Biomol. Chem.* **2012**, *10*, 8361–8370; (b) Yu, B.; Li, B.; Xing, G.; Hui, Y. *J. Comb. Chem.* **2011**, *3*, 404–406; (c) Kanie, O.; Barresi, F.; Ding, Y.; Labbe, J.; Otter, A.; Fosberg, L. S.; Ernst, B.; Hindsgaul, O. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2720–2722.
5. (a) Maggi, A.; Madsen, R. *Eur. J. Org. Chem.* **2013**, 2683–2691; (b) Kaji, E.; Harita, N. *Tetrahedron Lett.* **2000**, *41*, 53–56; (c) Garegg, P. J.; Maloisel, J.-L.; Oscarson, S. *Synthesis* **1995**, 409–414; (d) Cruzado, C.; Bernabe, M.; Martin-Lomas, M. *Carbohydr. Res.* **1990**, *203*, 296–301; (e) Murase, T.; Kartha, K. P. R.; Kiso, M.; Hasegawa, A. *Carbohydr. Res.* **1989**, *195*, 134–137.
6. Muramatsu, W.; Yoshimatsu, H. *Adv. Synth. Catal.* **2013**, *355*, 2518–2524.
7. (a) Fenger, T. H.; Madsen, R. *Eur. J. Org. Chem.* **2013**, 5923–5933; (b) Nishino, T.; Ohya, Y.; Murai, R.; Shirahata, T.; Yamamoto, D.; Makino, K.; Kaji, E. *Heterocycles* **2012**, *84*, 1123–1140.
8. Kaji, E.; Yamamoto, D.; Shirai, Y.; Ishige, K.; Arai, Y.; Shirahata, T.; Makino, K.; Nishino, T. *Eur. J. Org. Chem.* **2014**, 3536–3539.
9. Gouliaras, C.; Lee, D.; Chan, L.; Taylor, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 13926–13929.
10. Reference 9 also contains one example where methyl 3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-mannopyranoside is selectively glycosylated at position 6 of the mannose residue in the presence of the borinic acid catalyst.
11. Lemieux, R. U.; Hendriks, K. B.; Stick, R. V.; James, K. *J. Am. Chem. Soc.* **1975**, *97*, 4056–4062.
12. The quality of oxalyl bromide proved important for fast and clean formation of **1** and it is recommended to use a freshly distilled sample. Previous syntheses of **1** with oxalyl bromide have also included DMF in the reaction, but in our hands the bromination worked equally well in the absence of the amide. See also: (a) Matwiejuk, M.; Thiem, J. *Eur. J. Org. Chem.* **2011**, 5860–5878; (b) Presser, A.; Kunert, O.; Pötschger, I. *Monatsh. Chem.* **2006**, *137*, 365–374; (c) Grayson, E. J.; Ward, S. J.; Hall, A. L.; Rendle, P. M.; Gamblin, D. P.; Batsanov, A. S.; Davis, B. G. *J. Org. Chem.* **2005**, *70*, 9740–9754; (d) Wessel, H.-P.; Bundle, D. R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2251–2260.
13. Lemieux, R. U.; Driguez, H. *J. Am. Chem. Soc.* **1975**, *97*, 4069–4075.
14. Kartha, K. P. R.; Aloui, M.; Field, R. A. *Tetrahedron Lett.* **1996**, *37*, 8807–8810.
15. Bredenkamp, M. W. *S. Afr. J. Chem.* **1995**, *48*, 154–156.
16. Grindley, T. B. *Adv. Carbohydr. Chem. Biochem.* **1998**, *53*, 17–142.
17. Rachaman, E. S.; Eby, R.; Schuerch, C. *Carbohydr. Res.* **1978**, *67*, 147–161.
18. (a) Schmidt, T. H.; Madsen, R. *Eur. J. Org. Chem.* **2007**, 3935–3941; (b) Clausen, M. H.; Jørgensen, M. R.; Thorsen, J.; Madsen, R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 543–551; (c) Pedretti, V.; Veyrières, A.; Sinaÿ, P. *Tetrahedron* **1990**, *46*, 77–88.