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Improvement of the stereoselectivity of the glycosylation reaction with 2-azido-2-deoxy-1-thioglucoside donors

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ABSTRACT

2-Azido-2-deoxy-1-thioglucoside donors with an electron withdrawing group at position 6 were employed to study the stereoselectivity of the glycosylation reaction with several acceptors, ranging from unhindered small primary alcohols to other sugars and steroids, using NIS/TfOH as promoter. *p*-Tolyl 2-azido-3,4-di-O-benzyl-6-O-chloroacetyl-2-deoxy-1-thio-α/β-D-glucopyranoside afforded the higher α-selectivity, showing that a stronger electron withdrawing ester at O-6 influenced the anomeric selectivity towards the 1,2-*cis* glucosides. The anomeric stereoselectivity was highly dependent on the acceptor.

1. Introduction

2-Acetamido-2-deoxyglucosides are present in many natural molecules with important biological roles, such as glycolipids, glycoproteins, peptidoglycans and glucosaminoglycans. In many cases they are present in β-glycosidic bonds; however, in heparin and heparan glycosaminoglycans, *N*-acetyl-D-glucosamine is present as the α-glycoside.[1] This glycosidic bond is also present in the low molecular weight heparins (LMWHs) and ultralow molecular weight heparins (ULMWHs) used as blood anticoagulants.[2,3]

For the synthesis of 1,2-*trans* 2-acetamido-2-deoxyglucosides many procedures have been reported, taking advantage of the neighbouring group participating effect.[4] For the synthesis of 1,2-*cis* 2-acetamido-2-deoxyglucosides other strategies have to be adopted.[5–9] The most common one is to protect the amino functionality by masking it in the form of an azide at the C-2 position of the donor.[4] However, these glycosylations often provide mixtures of α and β anomers.

We have reported that NIS/TfOH mediated glycosylations of ethyl 6-O-acetyl-2,3,4-O-tribenzyl-1-D-thioglucopyranoside afforded higher α-anomeric selectivities when compared with other 6-O-protecting groups. The choice of solvent was also found to be very important and ethyl ether was the solvent that afforded the highest α-selectivities.[10] The 6-O-acetyl group, being electron withdrawing, reduced the reactivity at the anomeric position compared to the tetrabenzylated thioglycoside and favoured the formation of the α-glucosides (1,2-*cis* glucosylation).[10–12] The influence of remote esters in the stereoselectivity of glycosylation reactions has been widely described.[12–17] However, there are several contradictory results showing that there are other factors that play a role in these glycosylation reactions.

In a more recent work, the effect of electron withdrawing groups at positions 4 and 6 on 1,2-*cis* galactosylation, using thiogalactosides as the donors with diverse glycosyl acceptors, was studied.[18] It was concluded that an electron withdrawing protecting group at C-4 in galactose was important for the anomeric stereoselective, and that the chloroacetate groups at C-4 and C-6 provided higher α-selectivity than the corresponding acetate groups. Following the same rationale, we decided to explore the remote influence of the C-6 protecting on the stereoselectivity of the much less studied glycosylation reaction with several 2-azido-2-deoxyglucoside donors.

2. Results and discussion

2.1. Synthesis of the glycosyl donors **5** to **8**

A study of the stereoselectivity of several 2-azido-2-deoxy-thioglucoside donors with different combinations of protecting groups has been reported by Ngoje and Li.[19] The position of the acetate group was varied and it was shown that the acetyl groups at positions 3 and 6 were more likely to direct the reaction towards the formation of the α product and the acetyl group at C-4 favoured the β product formation. However, this study was carried out with only one sugar derived acceptor.

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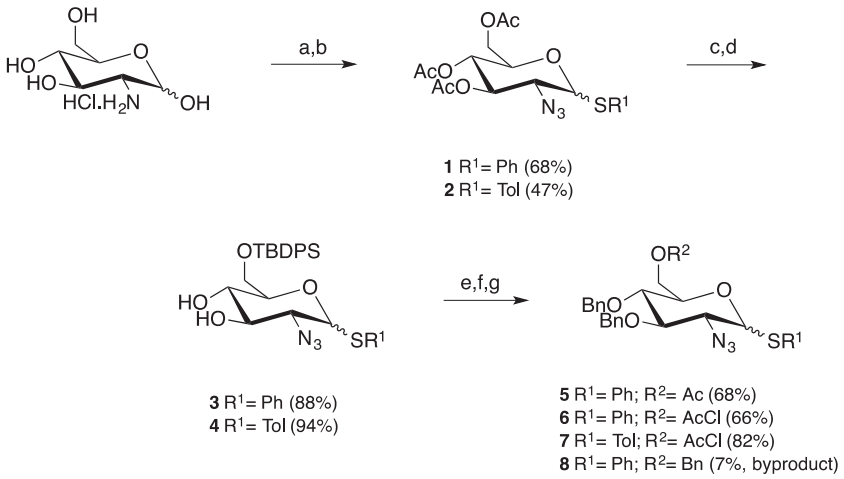


a) (i) K_2CO_3, $CuSO_4.5H_2O$, imidazole-1-sulfonyl azide hydrochloride, MeOH, r.t. (ii) Ac_2O, Py, DMAP, r.t., 82% (over two steps). b) PhSH or TolSH, $BF_3.OEt_2$, CH_2Cl_2, 0°C-r.t. c) NaOMe, MeOH, 0°C-r.t. d) TBDPSCl, Py, DMAP, r.t. e) NaH, BnBr, DMF, 0°C-r.t. f) TBAF, THF, r.t. g) Ac_2O or $ClAc_2O$, Py, DMAP, r.t.

Scheme 1. Synthesis of donors **5–8**.

Park and co-authors described the obtention of excellent α-anomeric selectivities, with two acceptors only the α anomer was obtained, in the TMSOTf-promoted glycosylations of 2-azido-2-deoxy-glucopyranosyl trichloroacetimidates, with an acetate group at C-4 and C-6, when performed at 0 °C in the presence of PhSEt or thiophene.[20] When 2-azido-3,4,6-tri-O-benzyl-2-deoxy-D-glucopyranosyl trichloroacetimidate was used as the donor, poor α-anomeric selectivity was obtained and the addition of thiophene resulted in little improvement (1:2 to 4:1 α/β ratio). This result reinforces the proposal for a positive influence of an electron withdrawing group at the C-6 position for the 1,2-*cis* selectivity of the glycosylation reaction.

Donor **6** has been reported previously.[21,22] It was prepared from 1,6-anhydro-β-D-mannopyranose, in six steps,[23] and was used in the glycosylation reaction with other sugars as acceptors to afford the corresponding α products. Ethyl 2-azido-3,4-O-dibenzyl-6-O-acetyl-2-deoxy-1-D-thioglucopyranoside has been used in the glycosylation reaction with a sugar acceptor.[24] Using NIS-TfOH system as the promoter in 1:4 1,2-dichloroethane/ethyl ether, the α product was obtained in 70% yield.

We have previously shown that the structure of the acceptor had a strong influence on the stereoselectivity of the glycosylation reaction, and when the acceptor was a sugar, the corresponding α products were highly favoured; however, this was not the case for small unhindered alcohols.[18] We decided to explore the influence of the C-6 protecting group on the stereoselectivity of the present glycosylation reaction, and the effect of having different electron withdrawing groups (acetate and chloroacetate) at C-6 was also studied. *S*-phenyl and *S*-tolyl thioglucosides were used as the glycosyl donors.

2-Azido-2-deoxythioglucosides **5–8** were prepared (Scheme 1). From the readily available glucosamine hydrochloride salt,[25] the 1-thiophenyl and 1-thiotolyl per-O-acetylated 2-azido-deoxyglucosides **1** and **2** were obtained in good overall yields for the three consecutive reactions. Deacetylation followed by selective silylation of the primary hydroxyl group afforded **3** and **4** in excellent yields (90% and 98%, respectively). Benzylation of the secondary hydroxyl groups, desilylation and esterification of the 6-OH group either with acetic or chloroacetic anhydride gave donors **5–7**. The 2-azido-per-O-benzyl-2-deoxyglucoside donor **8** was obtained as a by-product of the benzylation of compound **4**, in 7% yield.

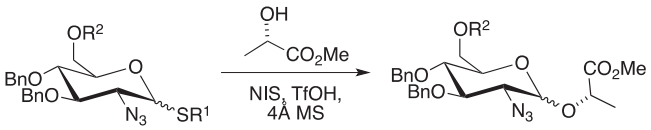
2.2. Optimisation of the glycosylation reaction

To determine the best conditions for the glycosylation reaction in order to obtain the best stereoselectivity, the influence of the protecting group at C-6 (acetyl or chloroacetyl) on the donors, the solvent and the temperature was studied, using the NIS/TfOH promoter system and methyl (*S*)-lactate as the acceptor. These results are described in Table 1.

Dichloromethane, ethyl ether and mixtures of dichloromethane/ethyl ether were tested at different temperatures. When dichloromethane was used as the solvent the anomeric selectivity was relatively low, with all the donors (Table 1, entries 1, 3, 4, 7, 8, 9, 12 and 13). In ethyl ether, the glycosylation reaction did not proceed and the donors were recovered unreacted (Table 1, entries 5 and 10). Previously,[10] we have shown that ethyl ether was the solvent of choice for the glycosylation of ethyl 6-O-acetyl-2,3,4-tribenzyl-1-D-thioglucopyranoside with small and reactive alcohols using NIS/TfOH as the promoter. This result was expected, since ethyl ether is considered as a participating solvent. Greenberg and co-workers reported the use of a solvent mixture of CH_2Cl_2/Et_2O (1:4) with the NIS/TfOH system for obtaining the α-2-azido-2-deoxyglucosides from a tribenzylated 2-azido-2-deoxy-1-thioglucoside.[26] The selectivity reported for the glycosylation using 2-deoxystreptamine as acceptor was 10:1 α/β ratio, in 58% yield. As expected, the use of ethyl ether as cosolvent was fundamental for this selectivity because when the reaction was performed in dichloromethane at –78 °C, the α/β ratio was only 2.5:1.

Using a CH_2Cl_2/Et_2O (1:2) solvent combination and the direct addition of the NIS/TfOH system to the reaction mixture did not afford any improvement and we recovered the unreacted donor. However, when using this solvent combination and adding the NIS/TfOH system in solution to the reaction mixture there was a remarkable improvement of the α-selectivity for almost all of the donors (Table 1, entries 6, 11 and 14). When performing the reaction at a lower temperature, the selectivity lowered from 10.3:1 α/β ratio at –10 °C to 8:1 at –78 °C (Table 1, entries 14 and 15). The influence of the temperature on the stereochemical outcome of the glycosylation reaction is known, and there are reports where higher temperatures afforded higher selectivities.[27–29] It has been proposed that this higher selectivity is due to conformational changes of the oxocarbenium

Table 1
Effect of the solvent, temperature and protecting groups on the stereoselectivity of the glycosylation reaction of donors **5–8** with methyl (*S*)-lactate



5-8 **9-11**

Entry	R^1	R^2	T (°C)	Solvent	Product (Yield, %)	t (min)	α/β
1	Ph	Bn	–10	CH_2Cl_2	**9** (73)	10	1:1
2				CH_2Cl_2:Et_2O (1:2)[a]	**9** (78)	120	2.6:1
3		Ac	r.t.	CH_2Cl_2	**10** (87)	5	3:1
4			–10	CH_2Cl_2	**10** (90)	10	3.5:1
5				Et_2O	**10** (0)[b]	90	-
6				CH_2Cl_2:Et_2O (1:2)[a]	**10** (96)	120	7.3:1
7			–78	CH_2Cl_2	**10** (98)	120	2.5:1
8		AcCl	r.t.	CH_2Cl_2	**11** (96)	5	3.6:1
9			–10	CH_2Cl_2	**11** (85)	10	4.2:1
10				Et_2O	**11** (0)[c]	90	-
11				CH_2Cl_2:Et_2O (1:2)[a]	**11** (84)	120	8.7:1
12			–78	CH_2Cl_2	**11** (87)	120	4.2:1
13	Tol	AcCl	–10	CH_2Cl_2	**11** (93)	10	4:1
14				CH_2Cl_2:Et_2O (1:2)[a]	**11** (99)	120	10.3:1
15			–78	CH_2Cl_2:Et_2O (1:2)[a]	**11** (99)	120	8:1

Reaction conditions: 1 eq. acceptor, 1.27 eq. NIS, cat. TfOH.
[a] Addition of NIS (2 eq.)/TfOH system in solution.
[b] 78% Starting material recovered.
[c] 68% Starting material recovered.

intermediate occurring at higher temperatures. It has been also proposed that the intermediate glycosyl triflates are unstable at higher temperature which favours the SN_1 mechanism, and the ester groups on the donor favour the α selectivity by stabilising the oxocarbenium intermediate.

Other important aspect is that when using these conditions but only one equivalent of NIS, the reaction was incomplete and the initial donor was recovered. This problem was overcome by the addition of two equivalents of NIS.

Finally, the donors **6** and **7** with the 6-chloroacetyl protecting group afforded the highest α anomeric selectivities, a more electronegative group at the 6 position drastically increased the 1,2-*cis* stereoselectivity of the glycosylation reaction,[18] as seen by comparing entries 2, 6, 11 and 14 of Table 1. These are less reactive donors due to the electron withdrawing substituent at C-6.[12] Crich and coworkers studied possible neighbouring group participation in glycosylation reactions for esters in non-vicinal positions in several glycosyl donors[30] and ruled out neighbouring group participation from esters at C-6. Thus, the α-anomeric selectivity obtained with donors **6** and **7** could not be attributed to the direct participation of the ester at C-6, but to stereoelectronic and conformational influences. These electron withdrawing groups will lower the stability of the intermediate carbocationic species and thus, covalent intermediates become more likely. The increased α selectivity could derive from the preferential formation of the β triflate, which is then substituted by the nucleophilic alcohol in an SN_2 manner to afford the α-glucoside. A coherent mechanism for this remote control has not yet been established.[30]

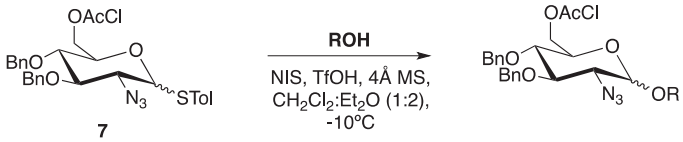
The influence of the anomeric thio group for the stereoselectivity of the glycosylation reaction has been reported in the literature,[31] and in our work the tolyl group afforded the best results, 10.3:1 α/β ratio (Table 1, entry 14).

2.3. Glycosylation reaction between donor **7** with several acceptors

The best conditions, dichloromethane/ethyl ether (1:2) at –10 °C, were employed in the glycosylation reaction between the donor **7** and several acceptors with very diverse structures, from small alcohols such as methyl glycolate, to steroids, sugars and 1-adamantanol (Table 2).

The α anomer was the major product for all the acceptors tested. As observed in our previous study with thiogalactoside donors,[18] the structure of the acceptor has a strong influence on the stereoselectivity of the glycosylation reaction. With donor **7** the best stereoselectivities were obtained with the smaller, less hindered alcohols (Table 2, entries 1, 2 and 6). When the acceptor was dimethyl malate, the product **23** was obtained exclusively as the α anomer (Table 2, entry 6). When the acceptor was a sugar, the α anomer was also exclusively obtained (Table 2, entry 3). For the other acceptors, starting material was recovered and the anomeric selectivity was lower (α/β ratios 6.2:1, 3.2:1, Table 2, entries 4 and 5). It is interesting to note that the stereoselectivities obtained with 1-adamantanol **18** and EPA **20** (epiandrosterone) were very similar to those obtained when phenyl 2,3-O-dibenzyl-4,6-O-dichloroacetyl-1-thiogalactopyranoside was used as the donor (α/β ratios 6.2:1, 3.8:1,

Table 2
Glycosylation of donor **7** with several acceptors



7

Entry	ROH	Product (Yield,%)	t (min)	α/β
1	**12**	**13** (76)	180	12:1
2	**14**	**15** (84)	120	>10:1
3	**16**	**17** (90)	120	1:0
4	**18**	**19** (50)	120	6.2:1
5	**20**	**21** (46)[a]	120	3.2:1
6	**22**	**23** (84)	120	1:0

Reaction conditions: 1 eq. acceptor, 1.27 eq. NIS, cat. TfOH.
[a] 32% Recovery of the starting material **7**.

respectively).[18] This confirms that the nature of the acceptor has indeed a strong influence on the stereoselective outcome of the glycosylation reaction. In another work, the glycosylation reactions of some 2-azido-2-deoxyglucopyranosyl trichloroacetimidates have been reported.[32] When the donor was a 6-O-benzylated 2-azido-2-deoxyglucopyranosyl trichloroacetimidate, mixtures of anomers were obtained with the two described sugar derived acceptors, thioglucosyl 4-alcohols and 1,6-anhydro-α-L-idopyranosyl 4-alcohols. However, the corresponding 6-O-benzoylated glucosyl trichloroacetimidates afforded exclusively the α-anomer in the case of thioglucosyl 4-alcohols as the acceptor, but did not considerably increase the α selectivity with 1,6-anhydro-α-L-idopyranosyl 4-alcohols, which was conformationally strained. The stereoselectivity depended on the acceptor structure.

3. Conclusions

We have demonstrated that a chloroacetyl group at C-6 in 2-azido-2-deoxyglucosyl donor affords complete or very high α-anomeric selectivities in the glycosylation reaction. This selectivity depends on the glycosyl acceptor used; however, with the less studied small and unhindered acceptors the 1,2-*cis* selectivity was excellent. The temperature also played a role, at –10 °C higher alpha-anomeric selectivities were observed.

The use of *p*-Tolyl 2-azido-3,4-di-O-benzyl-6-O-chloroacetyl-2-deoxy-1-thio-α/β-D-glucopyranoside **7** is a reliable strategy to afford very good to complete α anomeric selectivity on the glycosylation reaction when using more challenging alcohols as the acceptors, employing the classic promoter system NIS/TfOH.

4. Experimental section

4.1. General

^{1}H NMR spectra were obtained at 400 MHz in $CDCl_3$ with chemical shift values (δ) in ppm downfield from tetramethylsilane, and ^{13}C NMR spectra were obtained at 100.61 MHz in $CDCl_3$. Assignments are supported by 2D correlation NMR studies. Medium pressure preparative column chromatography: Silica Gel Merck 60 H. Analytical TLC: Aluminium-backed Silica Gel Merck 60 F254. Reagents and solvents were purified and dried according to Armarego and Chai.[33] Specific rotations ($[\alpha]_D^{20}$): were measured by using a Perkin–Elmer D241 automatic polarimeter. All the reactions were carried out under an inert atmosphere (argon).

4.2. Phenyl 3,4,6-tri-O-acetyl-2-azido-2-deoxy-1-thio-α/β-D-glucopyranoside **1**

$BF_3.OEt_2$ (9.81 mL, 77.4 mmol) was added to a solution of 1,3,4,6-tetra-O-acetyl-2-azido-2-deoxy-α/β-D-glucopyranose[25] (6.42 g, 17.2 mmol) and thiophenol (3.55 mL, 34.4 mmol) in CH_2Cl_2 (60 mL) at 0 °C. The reaction mixture was stirred at r.t. for 48 hours, then diluted with CH_2Cl_2 and washed with sat. aqueous $NaHCO_3$ solution. The aqueous phase was extracted with CH_2Cl_2 and the combined organic phases were dried with $MgSO_4$, filtered and concentrated under vacuum. The crude was purified by flash column chromatography on silica gel (30:70, EtOAc/hexane) to afford **1** (5.40 g, 74%, α/β = 2.5:1) as a colourless viscous foam, and to recover the initial tetraacetate (1.30 g, 20%). The overall yield from D-glucosamine hydrochloride (2 steps) was 68%. **FT-IR** (film) $\upsilon_{máx.}$: 1740 (C = O), 2107 (N_3) cm^{-1}. **^{1}H NMR** ($CDCl_3$): δ 7.60–7.58 (m, Ph), 7.51–7.48 (m, Ph), 7.38–7.28 (m, Ph), 5.64 (d, *J* = 5.6 Hz, H-1 (α)), 5.34 (t, *J* = 10.0, H-3 (α)), 5.10-5.02 (m, H-3 (β), H-4 (α)), 4.92 (t, *J* = 10.0 Hz, H-4 (β)), 4.62-4.57 (m, H-5 (α)), 4.49 (d, *J* = 10.0, H-1 (β)), 4.29 (dd, *J* = 5.2 Hz, *J* = 12.4 Hz, H-6 (α)), 4.23–4.18 (m, H-6 (β)), 4.16-4.01 (m, H-2 (α), H′-6 (α)), 3.71–3.67 (m, H-5 (β)), 3.41 (t, *J* = 10.0, H-2 (β)), 2.105 (Ac (α)), 2.06 (Ac (β)), 2.05 (Ac (α)), 2.04 (Ac (β)), 2.03 (Ac (α)), 2.00 (Ac (β)) ppm. **^{13}C NMR** ($CDCl_3$): δ 170.4, 169.7, 134.1, 132.24, 132.21, 130.1, 129.2, 129.1, 128.0, 86.5 (C-1 (α)), 85.3 (C-1 (β)), 75.7 (C-5 (β)), 74.4 (C-3 (β)), 72.0 (C-3 (α)), 68.7 (C-4 (α)), 68.5 (C-5 (α)), 68.0 (C-4 (β)), 62.6 (C-2 (β)), 62.0 (C-6 (β)), 61.9 (C-6 (α)), 61.6 (C-2 (α)), 20.7 (Ac (β)), 20.66 (Ac (α)), 20.64 (Ac (β)), 20.61 (Ac (α)), 20.5 (Ac (β)) ppm.

4.3. p-Tolyl 3,4,6-tri-O-acetyl-2-azido-2-deoxy-1-thio-α/β-D-glucopyranoside **2**

$BF_3.OEt_2$ (6.57 mL, 51.8 mmol) was added to a solution of 1,3,4,6-tetra-O-acetyl-2-azido-2-deoxy-α/β-D-glucopyranose[25] (3.87 g, 10.4 mmol) and *p*-toluenethiol (2.57 g) at 0 °C. The reaction mixture was stirred at r.t. for 60 hours, then diluted with CH_2Cl_2 and washed with sat. aqueous $NaHCO_3$ solution. The aqueous phase was extracted with CH_2Cl_2 and the combined organic phases were dried with $MgSO_4$, filtered and concentrated under vacuum. The crude was purified by flash column chromatography on silica gel (30:70, EtOAc/hexane) to afford **2** (2.14 g, 47%, α/β = 1.8:1) as a colourless viscous foam, and to recover the initial tetraacetate (1.69 g, 44%). The overall yield from D-glucosamine hydrochloride (2 steps) was 46%. **FT-IR** (film) $\upsilon_{máx.}$: 1747 (C = O), 2109 (N_3) cm^{-1}. **^{1}H NMR** ($CDCl_3$): δ 7.48 (d, *J* = 8.0 Hz, Ph), 7.38 (d, *J* = 7.6 Hz, Ph), 7.14 (t, *J* = 10.8 Hz, Ph), 5.56 (d, *J* = 5.6 Hz, H-1 (α)), 5.33 (t, *J* = 9.6 Hz, H-3 (α)), 5.9–5.01 (m, H-3 (β), H-4 (α)), 4.90 (t, *J* = 10.0 Hz, H-4 (β)), 4.63–4.59 (m, H-5 (α)), 4.42 (d, *J* = 10.0 Hz, H-1 (β)), 4.29 (dd, *J* = 5.2 Hz, *J* = 12.4 Hz, H-6 (α)), 4.22 (dd, *J* = 4.4 Hz, *J* = 12.0 Hz, H-6 (β)), 4.16 (dd, *J* = 2.0 Hz, *J* = 12.4 Hz, H′-6 (β)), 4.08–4.01 (m, H-2 (α), H′-6 (α)), 3.69–3.65 (m, H-5 (β)), 3.36 (t, *J* = 10.0 Hz, H-2 (β)), 2.37 (Me (β)), 2.33 (Me (α)), 2.09 (Ac (β)), 2.05 (Ac (α)), 2.04 (Ac (α)), 2.00 (Ac (β)) ppm. **^{13}C NMR** ($CDCl_3$): δ 170.5, 170.4, 169.8, 169.7, 169.6, 139.3, 138.4, 134.6, 132.8, 130.0, 129.8, 128.5, 126.1, 86.8 (C-1 (α)), 85.7 (C-1 (β)), 75.7 (C-5 (β)), 74.4 (C-3 (β)), 72.0 (C-3 (α)), 68.7 (C-4 (α)), 68.3 (C-5 (α)), 68.0 (C-4 (β)), 62.4 (C-2 (β)), 62.0 (C-6 (β)), 61.9 (C-6 (α)), 61.6 (C-2 (α)), 21.2 (Me), 21.1 (Me), 20.7 (Ac), 20.66 (Ac), 20.61 (Ac), 20.5 (Ac). **HR-MS:** calcd for $C_{19}H_{23}N_3O_7SNa^+$ $[M + Na]^+$: 460.1149; found: 460.1149.

4.4. Phenyl 2-azido-6-O-tert-butyldiphenylsilyl-2-deoxy-1-thio-α/β-D-glucopyranoside **3**

A solution of NaOMe 1N (6.73 mL, 6.73 mmol) in MeOH was added to a stirred solution of **1** (4.75 g, 11.21 mmol) in MeOH (20 mL) at 0 °C. After 3 hours the starting material had been consumed. The reaction mixture was diluted with MeOH and Dowex-H$^+$ resin was added until neutral pH. Filtration and evaporation of the solvents afforded the triol (3.23 g, 97%) as a viscous colourless gum. TBDPSCl (2.36 mL, 9.10 mmol), followed by a catalytic amount of DMAP, were added to a solution of triol (2.46 g, 8.27 mmol) in pyridine (20 mL) at rt. The mixture was stirred overnight, then quenched with H_2O (20 mL), extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated. Purification by flash column chromatography (30:70 AcOEt/hexane) afforded the product **3** (3.88 g, 88%, α/β = 1.8:1) as a white solid. **Alpha anomer: FT-IR** (film) $\upsilon_{máx.}$: 2108 (N_3), 3406 (OH) cm^{-1}. **^{1}H NMR** ($CDCl_3$): δ 7.76–7.72 (m, 4H, Ph), 7.50–7.39 (m, 8H, Ph), 7.28–7.24 (m, 3H, Ph), 5.55 (d, 1H, *J* = 4.9 Hz, H-1), 4.29–4.24 (m, 1H, H-5), 3.96–3.81 (m, 4H, H-2, H-6, H'-6, H-3), 3.73 (t, 1H, *J* = 8.9 Hz, H-4), 2.67 (bs, 2H, OH), 1.00 (s, 9H, *t*-Bu) ppm. **^{13}C NMR** ($CDCl_3$): δ 135.6, 135.5, 133.5, 132.7, 132.6, 132.1, 129.99, 129.94, 129.0, 127.88, 127.81, 127.6, 87.2 (C-1), 73.4 (C-3), 72.9 (C-4), 71.1 (C-5), 64.5 (C-6), 63.4 (C-2), 26.8 ($C(\underline{C}H_3)_3$), 19.2 ($\underline{C}$-Si) ppm. **Beta anomer: FT-IR** (film) $\upsilon_{máx.}$: 2111 (N_3), 3387 (OH) cm^{-1}. **^{1}H NMR** ($CDCl_3$): δ 7.72–7.68 (m, 4H, Ph), 7.46-7.35 (m, 8H, Ph), 7.29–7.23 (m, 3H, Ph), 4.45 (d, 1H, *J* = 10.0 Hz, H-1), 3.98–3.91 (m, 2H, H-6), 3.62 (t, 1H, *J* = 9.1 Hz, H-4), 3.51 (t, 1H, *J* = 9.1 Hz, H-3), 3.40–3.35 (m, 1H, H-5), 3.27 (t, 1H, *J* = 9.4 Hz, H-2),

2.87 (bs, 2H, OH), 1.06 (s, 9H, *t*-Bu) ppm. **^{13}C NMR** ($CDCl_3$): δ 135.6, 135.5, 133.2, 132.8, 132.6, 131.4, 129.95, 129.92, 128.9, 128.2, 127.86, 127.84, 86.2 (C-1), 78.7 (C-5), 77.1 (C-3), 71.3 (C-4), 64.5 (C-2), 64.2 (C-6), 26.8 ($C(\underline{C}H_3)_3$), 19.2 (<u>C</u>-Si) ppm. **HR-MS** (alpha + beta anomers): calcd for $C_{28}H_{33}N_3O_4SSiNa^+$ $[M+Na]^+$: 558.1853; found: 558.1838.

4.5. p-*Tolyl 2-azido-6-O-*tert*-butyldiphenylsilyl-2-deoxy-1-thio-α/β-D-glucopyranoside* ***4***

The same procedure to obtain **3** was applied to compound **2** affording compound **4** as a colourless viscous gum in 94% yield (α/β = 1.8:1) over the two steps. **FT-IR** (film) $\upsilon_{máx.}$: 2108 (N_3), 3385 (OH) cm^{-1}. **^{1}H NMR** ($CDCl_3$): δ 7.74–7.65 (m, Ph), 7.47–7.26 (m, Ph), 7.07-7.01 (m, Ph), 5.44 (d, *J* = 5.1 Hz, H-1 (α)), 4.39 (d, *J* = 10.0 Hz, H-1 (β)), 4.25 (dt, *J* = 4.7 Hz, *J* = 9.4 Hz, H-5 (α)), 3.95–3.83 (m, H-3 (α), H-6 (α), H-6 (β)), 3.78 (dd, *J* = 5.2 Hz, *J* = 10.3 Hz, H-2 (α)), 3.68 (t, *J* = 9.0 Hz, H-4 (α)), 3.61 (t, *J* = 9.1 Hz, H-4 (β)), 3.50 (t, *J* = 9.1 Hz, H-3 (β)), 3.37 (dt, *J* = 4.5 Hz, *J* = 9.1 Hz, H-5 (β)), 3.24 (t, *J* = 9.6 Hz, H-2 (β)), 2.84 (bs, OH), 3.32 (s, Me (β)), 2.29 (s, Me (α)), 1.07 (s, *t*-Bu (β)), 1.06 (s, *t*-Bu (β)) ppm. **^{13}C NMR** ($CDCl_3$): δ 138.5, 137.9, 136.7, 135.6-135.5, 133.8, 132.9–132.6, 129.9–129.7, 127.8–127.7, 87.6 (C-1 (α)), 86.1 (C-1 (β)), 78.7 (C-5 (β)), 77.3 (C-3 (β)), 73.4 (C-3 (α)), 72.8 (C-4 (α)), 71.3 (C-4 (β)), 71.2 (C-5 (β)), 64.4 (C-6 (α)), 64.3 (C-2 (β)), 64.1 (C-6 (β)), 63.5 (C-2 (α)), 26.88 ($C(\underline{C}H_3)_3$ (α)), 26.82 ($C(\underline{C}H_3)_3$ (β)), 21.17 (Me (β)), 21.12 (Me (α)), 19.23 (<u>C</u>-Si) ppm. **HR-MS:** calcd for $C_{29}H_{35}N_3O_4SSiNa^+$ $[M+Na]^+$: 572.2010; found: 572.2001.

4.6. *Phenyl 6-O-acetyl-2-azido-3,4,di-O-benzyl-2-deoxy-1-thio-α/β-D-glucopyranoside* ***5***

To a stirred solution of **3** (3.91 g, 7.30 mmol) and benzyl bromide (1.97 mL, 22.6 mmol) in DMF (15 mL) at 0 °C, portion-wise sodium hydride (0.45 g, 18.6 mmol) was added. After 2 hours, MeOH was added at 0 °C and the reaction mixture was quenched with a saturated aqueous solution and extracted with Et_2O. The combined organic phases were dried with $MgSO_4$, filtered and evaporated under vacuum. Purification by flash column chromatography (10:90 AcOEt/hexane) afforded the dibenzylated product (4.45 g, 85%) as a white solid, and the tribenzylated product **8** (0.31 g, 7%) as a viscous gum. Compound **8**: **FT-IR** (film) $\upsilon_{máx.}$: 2105 (N_3) cm^{-1}. **^{1}H NMR** ($CDCl_3$): δ 7.61–7.59 (m), 7.52–7.48 (m), 7.41–7.16 (m), 5.61 (d, *J* = 5.4 Hz, H-1 (α)), 4.93–4.77 (m), 4.63–4.52 (m), 4.44 (d, *J* = 12.0 Hz), 4.41 (d, *J* = 10.0 Hz, H-1 (β)), 4.38-4.35 (m), 3.95 (dd, *J* = 10.0, 5.4 Hz), 3.85–3.72 (m), 3.65-3.58 (m), 3.53–3.47 (m), 3.37–3.32 (m) ppm. **^{13}C NMR** ($CDCl_3$): δ 137.8, 137.7, 137.6, 133.6, 133.4, 132.0, 129.0, 128.9, 128.5–127.5, 87.2 (C-1 (α)), 85.9 (C-1 (β)), 85.0 (β), 81.8 (α), 79.3 (β), 78.2 (α), 77.5 (β), 75.8 (β), 75.1 (α), 75.0 (β), 73.45 (α), 73.43 (β), 71.8 (α), 68.7 (C-6 (β), 68.2 (C-6 (α), 65.0 (β), 64.1 (α) ppm. **HR-MS:** calcd for $C_{33}H_{33}N_3O_4SNa^+$ $[M+Na]^+$: 590.2084; found: 590.2063.

To a solution of the dibenzylated product (2.42 g, 3.38 mmol) in THF (10 mL) at r.t., TBAF (1.15 g, 4.39 mmol) was added. The reaction mixture was stirred for 3 hours and then water was added. The mixture was extracted with AcOEt (3 × 20 mL), dried ($MgSO_4$) and concentrated to furnish a yellow viscous residue. Purification by flash column chromatography (30:70, AcOEt/hexane) afforded the alcohol (1.43 g, 88%) as a viscous gum. **FT-IR** (film) $\upsilon_{máx.}$: 2107 (N_3), 3462 (O-H) cm^{-1}. **HR-MS**: calcd for $C_{26}H_{27}N_3O_4SNa^+$ $[M+Na]^+$: 500.1614; found: 500.1616. **Alfa Product: ^{1}H NMR** ($CDCl_3$): δ 7.50–7.47 (m, 2H, Ph), 7.40–7.28 (m, 13H, Ph), 5.56 (d, 1H, *J* = 4.9 Hz, H-1), 4.95-4.86 (m, 3H, $C\underline{H}_2$Ph), 4.68(d, 1H, *J* = 11.1 Hz, $C\underline{H}_2$Ph), 4.24 (dt, *J* = 3.2 Hz, *J* = 9.9, 1H, H-5), 3.92–3.83 (m, 2H, H-2, H-3), 3.78–3.71 (m, 2H, H-6, H′-6), 3.65 (dd, 1H, *J* = 8.4 Hz, *J* = 9.8 Hz, H-4), 1.56 (bs, 1H, OH) ppm. **^{13}C NMR** ($CDCl_3$): δ 137.71, 137.60, 133.1, 129.2, 128.17, 128.08, 128.02, 127.95, 87.1 (C-1), 81.7, 77.9, 75.8 ($\underline{C}H_2$Ph), 75.2 ($\underline{C}H_2$Ph), 72.5, 64.2, 61.5 (C-6) ppm. **Beta Product: ^{1}H NMR** ($CDCl_3$): δ 7.54 (m, 2H), 7.36–7.25 (m, 13H), 4.86 (dd, 2H, *J* = 10.8 Hz, *J* = 13.6 Hz, $C\underline{H}_2$Ph), 4.83 (d, 1H, *J* = 11.2 Hz, $C\underline{H}_2$Ph), 4.64 (d, 1H, *J* = 11.0 Hz, $C\underline{H}_2$Ph), 4.46 (d, 1H, *J* = 10.2 Hz, H-1), 3.88 (dd, 1H, *J* = 2.6 Hz, *J* = 12.1 Hz, H-6), 3.69 (dd, 1H, *J* = 4.6 Hz, *J* = 12.1 Hz, H′-6), 3.56–3.49 (m, 2H, H-3, H-4), 3.39–3.31 (m, 2H, H-2, H-5), 1.70 (bs, 1H, OH) ppm. **^{13}C NMR** ($CDCl_3$): δ 137.62, 137.51, 133.5, 131.1, 129.2, 128.57, 128.55, 128.2, 128.1, 127.9, 86.1 (C-1), 84.9, 79.6, 77.3, 75.9 ($\underline{C}H_2$Ph), 75.1 ($\underline{C}H_2$Ph), 65.3, 61.9 (C-6) ppm.

Acetic anhydride (0.55 mL, 5.85 mmol) and a catalytic amount of DMAP were added to a stirred solution of the alcohol (1.396 g, 2.92 mmol) in pyridine (5 mL) at 0 °C. After complete conversion of the starting material, water was added. The mixture was extracted with EtOAc, dried ($MgSO_4$) and concentrated to furnish a viscous residue. Filtration through celite with a mixture of EtOAc/hexane (10/90) afforded the product **5** as a viscous colourless gum (1.38 g, 91%, α/β = 1.4:1). **^{1}H NMR** ($CDCl_3$): δ 7.64–7.57 (m, Ph), 7.57–7.50 (m, Ph), 7.47–7.28 (m, Ph), 5.62 (d, *J* = 5.3 Hz, H-1 (α)), 5.00–4.86 (m), 4.62 (t, *J* = 10.9 Hz), 4.50–4.42 (m), 4.45 (d, *J* = 10.1 Hz, H-1 (β)), 4.33–4.27 (m), 4.25–4.19 (m), 3.98 (dd, *J* = 10.3 Hz, *J* = 5.3 Hz), 3.89 (dd, *J* = 10.2 Hz, *J* = 8.7 Hz), 3.63–3.47 (m), 3.37 (t, *J* = 9.7 Hz), 2.08 (s, Ac), 2.02 (s, Ac) ppm. **^{13}C NMR** ($CDCl_3$): δ 170.56, 170.54, 137.46, 137.40, 137.35, 133.8, 133.0, 132.3, 131.0, 129.12, 128.94, 128.58, 128.52, 128.22, 128.18, 128.15, 128.13, 128.09, 128.01, 127.98, 127.87, 86.9 (C-1 (α)), 85.9 (C-1 (β)), 85.1, 81.8, 78.0, 77.34, 77.24, 77.12, 77.02, 75.97, 75.86, 75.19, 75.13, 70.1, 65.1, 64.1, 62.87, 62.79, 20.83, 20.78 ppm. **HR-MS:** calcd for $C_{28}H_{29}N_3O_5SNa^+$ $[M+Na]^+$: 542.1720; found: 542.1719.

4.7. *Phenyl 2-azido-3,4-di-O-benzyl-6-O-chloroacetyl-2-deoxy-1-thio-α/β-D-glucopyranoside* ***6***

The procedure to obtain **5** was applied to compound **3** using chloroacetic anhydride and affording compound **6** as a colourless viscous gum in 66% (α/β = 1.6:1) yield over the three steps. Characterisation data of compound **6** were identical to those reported in literature.[22]

4.8. p-*Tolyl 2-azido-3,4-di-O-benzyl-6-O-chloroacetyl-2-deoxy-1-thio-α/β-D-glucopyranoside* ***7***

The procedure to obtain compound **5** was applied to compound **4** using chloroacetic anhydride and affording compound **7** as a colourless viscous gum in 82% yield (α/β = 1:1) over the three steps. **FT-IR** (film) $\upsilon_{máx.}$: 1739, 1765 (C═O), 2107 (N_3) cm^{-1}. **^{1}H NMR** ($CDCl_3$): δ 7.45 (d, *J* = 8.1 Hz, Ph), 7.41–7.24 (m, Ph), 7.13–7.11 (m, Ph), 5.50 (d, *J* = 5.1 Hz, H-1 (α)), 4.95 (d, *J* = 10.5 Hz, $C\underline{H}_2$Ph (α)), 4.91–4.81 (m), 4.61-4.55 (m), 4.50–4.43 (m), 4.35–4.30 (m), 4.33 (d, *J* = 10.1 Hz, H-1 (β)), 4.24 (dd, *J* = 11.9 Hz, *J* = 4.6 Hz), 3.98 (s), 3.94-3.83 (m), 3.57–3.41 (m), 3.28 (t, *J* = 9.6 Hz, H-2 (β)), 2.35 (s, Ph$C\underline{H}_3$), 2.33 (s, Ph$C\underline{H}_3$) ppm. **^{13}C NMR** ($CDCl_3$): δ 166.85, 166.80, 139.1, 138.2, 137.42, 137.32, 134.5, 132.7, 129.97, 129.79, 129.0, 128.62, 128.60, 128.30, 128.22, 128.21, 128.19, 128.13, 128.11, 128.07, 126.6, 87.1 (C-1 (α)), 85.9 (C-1 (β)), 85.2, 81.8, 77.7, 77.4, 77.1, 76.76, 76.74, 76.72, 76.02, 75.88, 75.11, 75.04, 69.8, 64.9, 64.35, 64.22, 64.05, 40.64, 40.57, 21.22, 21.15 ppm. **HR-MS:** calcd for $C_{29}H_{30}ClN_3O_5SNa^+$ $[M+Na]^+$: 590.1487; found: 590.1470.

4.9. p-*Tolyl 2-azido-3,4-di-O-benzyl-2-deoxy-1-thio-α/β-D-glucopyranoside*

FT-IR (film) $\upsilon_{máx.}$: 3461 (OH), 2106 (N_3) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.45–7.27 (m, Ph), 7.15–7.11 (m, Ph), 5.48 (d, *J* = 4.6 Hz, H-1(α)), 4.94–4.80 (m, $C\underline{H}_2$Ph), 4.68 (d, *J* = 11.0 Hz, $C\underline{H}_2$Ph (α)), 4.63 (d, *J* = 11.0 Hz $C\underline{H}_2$Ph (β)), 4.38 (d, *J* = 10.2 Hz, H-1 (β)), 4.26 (dt, *J* = 3.2 Hz, *J* = 9.9 Hz, H-5 (α)), 3.90–3.82 (m, H-2 (α), H-3 (α), H-6 (β)), 3.79–3.61 (m, H-4 (α), H-6 (α), H′-6 (α), H′-6 (β)), 3.52 (t, *J* = 9.0 Hz, H-3 (β)), 3.48 (t, *J* = 9.2 Hz, H-4 (α)), 3.37–3.32 (m, H-5 (β)), 3.28 (dd,

J = 9.2 Hz, *J* = 10.1 Hz, H-2 (β)), 2.35 (s, 1H), 2.33 (s, 3H), 1.66 (d, *J* = 0.3 Hz) ppm. **^{13}C NMR** ($CDCl_3$): δ 139.0, 138.3, 137.74, 137.63, 137.53, 134.2, 133.1, 129.99, 129.93, 129.2, 128.59, 128.58, 128.55, 128.53, 128.25, 128.17, 128.06, 128.01, 127.94, 127.93, 126.9, 87.5 (C-1 (α)), 86.1 (C-1 (β)), 84.9 (C-3 (β)), 81.7 (C-3 (α)), 79.6 (C-5 (β)), 78.0 (C-4 (α)), 77.4 (C-4 (β)), 75.9 ($\underline{C}H_2$Ph (β)), 75.77 ($\underline{C}H_2$Ph (α)), 75.16 ($\underline{C}H_2$Ph (α)), 75.13 ($\underline{C}H_2$Ph (β)), 72.4 (C-5 (α)), 65.1 (C-2 (β)), 64.2 (C-2 (α)), 61.9 (C-6 (β)), 61.5 (C-6 (β)), 21.20 ($C\underline{C}H_3$ (β)), 21.16 ($C\underline{C}H_3$ (α)) ppm. **HR-MS:** calcd for $C_{27}H_{29}ClN_3O_4SNa^+$ $[M + Na]^+$: 514.1771; found: 514.1778.

4.10. General glycosylation procedure

A suspension of thioglycoside donor (0.15 mmol), acceptor (0.15 mmol) and 4Å MS in the solvent/mixture of solvents indicated (1 mL) was stirred for 1 h at room temperature then cooled to 0 °C. N-Iodosuccinimide (0.19 mmol) and TfOH (0.9 μL, 0.0102 mmol) were added at 0 °C. When the reaction was complete (TLC), 10% $Na_2S_2O_3$ aqueous solution (2 mL) and saturated aqueous $NaHCO_3$ (1 mL) were added and the reaction mixture was extracted with CH_2Cl_2 (3 × 5 mL), the combined organic phases were dried ($MgSO_4$), filtered and the solvent was removed under vacuum. The crude product was purified by preparative TLC (3:7, EtOAc/Hex). The α/β ratio of the isolated product was measured by ^{1}H NMR (400 MHz, $CDCl_3$) spectra.

4.10.1. Methyl (2S)-2-(2-azido-3,4,6-tri-O-benzyl-2-deoxy-α/β-D-glucopyranosyl)propanoate **9**

FT-IR (film) $\upsilon_{máx.}$: 1752 (C = O), 2108 (N_3) cm^{-1}. **^{1}H NMR** ($CDCl_3$): δ 7.34–7.24 (m, Ph), 7.17–7.14 (m, Ph), 4.98 (d, *J* = 3.6 Hz, H-1 (α)), 4.90 (d, *J* = 10.6 Hz, $C\underline{H}_2$Ph), 4.87 (s, $C\underline{H}_2$Ph), 4.81–4.76 (m, $C\underline{H}_2$Ph), 4.59 (d, *J* = 12.0 Hz, $C\underline{H}_2$Ph), 4.54–4.42 (m, $C\underline{H}_2$Ph), 4.43 (d, *J* = 7.3 Hz, H-1 (β)), 4.10 (dt, *J* = 2.4 Hz, *J* = 10.1 Hz, H-5 (α)), 4.05 (dd, *J* = 9.0 Hz, *J* = 10.3 Hz, H-3 (α)), 3.78–3.72 (m, H-4 (α), H-6 (α)), 3.77 (s, CO_2Me (β)), 3.67 (s, CO_2Me (α)), 3.60 (t, *J* = 9.1 Hz), 3.52 (dd, *J* = 1.9 Hz, *J* = 10.8 Hz, H′-6 (α), 3.43 (t, *J* = 7.9 Hz, H-2 (β)), 3.34 (dd, *J* = 3.6 Hz, *J* = 10.3 Hz, H-2 (α)), 1.50 (d, *J* = 6.9 Hz, $CHC\underline{H}_3$ (β)), 1.46 (d, *J* = 6.7 Hz, $CHC\underline{H}_3$ (α)) ppm. **^{13}C NMR** ($CDCl_3$): δ 172.6, 138.0-137.8, 128.5-128.3, 128.0–127.6, 100.6 (C-1 (β)), 98.8 (C-1 (α)), 83.0 (β), 79.9 (C3 (α)), 78.1 (C-4 (α)), 77.5 (β), 75.5 ($\underline{C}H_2$Ph (β)), 75.3 ($\underline{C}H_2$Ph (α)), 75.05 ($\underline{C}H_2$Ph (β)), 75.04 (β), 74.9 ($\underline{C}H_2$Ph (α), $\underline{C}H_2$Ph (β)), 73.4 ($\underline{C}H_2$Ph (α)), 72.2 (β), 71.3 (C-5 (α), 68.5 (C-6 (β)), 68.0 (C-6 (α), 66.0 (β), 63.1 (C-2 (α), 52.1 ($CO_2\underline{Me}$ (β)), 52.0 ($CO_2\underline{Me}$ (α)), 18.8 ($CH\underline{C}H_3$ (β)), 18.1 ($CH\underline{C}H_3$ (α)) ppm. **HR-MS:** calcd for $C_{31}H_{35}N_3O_7Na^+$ $[M + Na]^+$: 584.2367; found: 584.2362.

4.10.2. Methyl (2S)-2-(6-O-acetyl-2-azido-3,4,di-O-benzyl-2-deoxy-α/β-D-glucopyranosyl)propanoate **10**

FT-IR (film) $\upsilon_{máx.}$: 1741 (C = O), 2107 (N_3) cm^{-1}. **^{1}H NMR** ($CDCl_3$): δ 7.39–7.23 (m, Ph), 4.95 (d, *J* = 3.7 Hz, H-1 (α)), 4.93–4.83 (m, $C\underline{H}_2$Ph), 4.78 (d, *J* = 10.7 Hz, $C\underline{H}_2$Ph (β)), 4.59–4.54 (m, $C\underline{H}_2$Ph), 4.48–4.43 (m), 4.44 (d, *J* = 7.8 Hz, H-1 (β)), 4.33–4.14 (m, H-5 (α), H-6 (α), H′-6 (α), $C\underline{H}CH_3$) 4.07 (dd, *J* = 8.8 Hz, *J* = 10.3 Hz, H-3 (α)), 3.73 (s, CO_2Me (α)), 3.78 (s, CO_2Me (β)), 3.57 (dd, *J* = 8.9 Hz, *J* = 9.8 Hz, H-4 (α)), 3.45–3.41 (m), 3.32 (dd, *J* = 3.7 Hz, *J* = 10.3 Hz, H-2 (α)), 2.03 (Ac (β)), 2.02 (Ac (α)), 1.48 (d, *J* = 6.9 Hz, $CHC\underline{H}_3$ (β)), 1.47 (d, *J* = 6.8 Hz, $CHC\underline{H}_3$ (α)) ppm. **^{13}C NMR** ($CDCl_3$): δ 172.4, 170.6, 137.8 (β), 137.7 (α), 137.6 (α), 137.4 (β), 128.54, 128.51, 128.0, 127.9, 100.6 (C-1 (β)), 98.7 (C-1 (α)), 82.9 (β), 79.8 (C-3 (α)), 77.8 (C-4 (α), 77.1 (β), 75.6 ($\underline{C}H_2$Ph (β)), 75.4 ($\underline{C}H_2$Ph (α)), 75.09 ($\underline{C}H_2$Ph (β)), 75.02 ($\underline{C}H_2$Ph (α)), 74.9 (α), 73.0 (β), 72.4 (β), 69.7 (α), 66.0 (β), 63.1 (C-2 (α), 62.7 (C-6 (β)), 62.5 (C-6 (α)),52.1 ($CO_2\underline{Me}$), 20.8 (Ac), 18.7 ($CH\underline{C}H_3$ (β)), 18.2 ($CH\underline{C}H_3$ (α)) ppm. **HR-MS:** calcd for $C_{26}H_{31}N_3O_8Na^+$ $[M + Na]^+$: 536.2003; found: 536.1998.

4.10.3. Methyl (2S)-2-(2-azido-3,4,di-O-benzyl-6-O-chloroacetyl-2-deoxy-α/β-D-glucopyranosyl)propanoate **11**

FT-IR (film) $\upsilon_{máx.}$: 1742 (C = O), 2106 (N_3) cm^{-1}. **^{1}H NMR** ($CDCl_3$): δ 7.41–7.23 (m, Ph), 4.96–4.84 (m, $C\underline{H}_2$Ph), 4.93 (d, *J* = 3.4 Hz, H-1 (α)), 4.79 (d, *J* = 10.7 Hz, $C\underline{H}_2$Ph (β)), 4.62–4.56 (m, $C\underline{H}_2$Ph), 4.46–4.39 (m), 4.45 (d, *J* = 7.9 Hz, H-1 (β)), 4.34–4.21 (m), 4.07 (dd, *J* = 8.8 Hz, *J* = 10.3 Hz, H-3 (α)), 4.03–3.93 (m), 3.78 (s, CO_2Me (β)), 3.73 (s, CO_2Me (α)), 3.56 (dd, *J* = 8.9 Hz, *J* = 9.9 Hz, H-4 (α)), 3.48–3.41 (m), 3.31 (dd, *J* = 3.7 Hz, *J* = 10.3 Hz, H-2 (α)), 1.47 (d, *J* = 6.8 Hz, $CHC\underline{H}_3$) ppm. **^{13}C NMR** ($CDCl_3$): δ 172.4, 166.8, 137.6, 137.5, 128.5, 128.1-128.0, 100.5 (C-1 (β)), 98.7 (C-1 (α)), 82.9 (β), 80.0 (C-3 (α), 77.3 (C-4 (α), 76.6 (β), 75.6 (β), 75.5 (α), 75.0 (α), 74.9, 72.8 (β), 72.4 (β), 69.5 (α), 65.9 (β), 64.1 (C-6 (β)), 64.0 (C-6 (α)), 63.1 (C-2 (α), 52.1 (CO_2Me), 40.67 ($CO\underline{C}H_2Cl$ (α)), 40.65 ($CO\underline{C}H_2Cl$ (β)), 18.7 ($CH\underline{C}H_3$ (β)), 18.2 ($CH\underline{C}H_3$ (β)) ppm. **HR-MS:** calcd for $C_{26}H_{30}ClN_3O_8Na^+$ $[M + Na]^+$: 570.1614; found: 570.1603.

4.10.4. Methyl 2-(2-azido-3,4,di-O-benzyl-6-O-chloroacetyl-2-deoxy-α/β-D-glucopyranosyl)acetate **13**

FT-IR (film) $\upsilon_{máx.}$: 1759 (C =O), 2110 (N_3) cm^{-1}. **^{1}H NMR** ($CDCl_3$): δ 7.40–7.26 (m, Ph), 5.02 (d, *J* = 3.5 Hz, H-1 (α)), 4.96–4.84 (m, $C\underline{H}_2$Ph), 4.81 (d, *J* = 10.6 Hz, $C\underline{H}_2$Ph (β)), 4.60 (d, *J* = 11.1 Hz, $C\underline{H}_2$Ph (α)), 4.55 (d, *J* = 12.0 Hz, $C\underline{H}_2$Ph (β)), 4.45 (d, *J* = 6.5 Hz, H-1 (β)), 4.38 (dd, *J* = 3.6 Hz, *J* = 10.2 Hz, H-6 (α)), 4.31–4.25 (m), 4.18 (d, *J* = 16.6 Hz), 4.07–3.94 (m), 3.78 (s, CO_2Me (β)), 3.77 (s, CO_2Me (α)), 3.55 (dd, *J* = 8.8 Hz, *J* = 10.0 Hz, H-4 (α)), 3.44 (dd, *J* = 3.6 Hz, *J* = 10.2 Hz, H-2 (α)) ppm. **^{13}C NMR** ($CDCl_3$): δ 169.5, 166.8, 137.5, 137.3, 128.58, 128.55, 128.16, 128.13, 128.0, 101.2 (C-1 (β)), 97.8 (C-1 (α)), 80.2 (C-3 (α)), 77.2 (C-4 (α)), 75.6 ($\underline{C}H_2$Ph (α)), 75.0 ($\underline{C}H_2$Ph (α)), 72.8 (β), 69.6 (C-5 (α)), 65.9 (β), 64.3 ($O\underline{C}H_2CO_2$Me (α)), 64.0 (C-6 (α)), 63.3 (C-2 (α)), 52.1 ($CO_2\underline{C}H_3$ (α)), 40.6 ($CO\underline{C}H_2Cl$ (α)) ppm. **HR-MS:** calcd for $C_{25}H_{28}ClN_3O_8Na^+$ $[M + Na]^+$: 556.1457; found: 556.1441.

4.10.5. Methyl (2R)-tert-butyldimethylsilyl-3-(2-azido-3,4,di-O-benzyl-6-O-chloroacetyl-2-deoxy-α/β-D-glucopyranosyl)-2,3-dihydroxypropanoate **15**

FT-IR (film) $\upsilon_{máx.}$: 1743 (C = O), 2107 (N_3) cm^{-1}. **^{1}H NMR** ($CDCl_3$): δ 7.69–7.26 (m, Ph), 7.69–7.61 (m, Ph), 7.45–7.28 (m, Ph), 7.22–7.19 (m, Ph), 5.10 (d, *J* = 3.5 Hz, H-1 (α)), 4.93 (d, *J* = 10.4 Hz, $C\underline{H}_2$Ph (α)), 4.86 (d, *J* = 11.3 Hz, $C\underline{H}_2$Ph (α)), 4.83 (d, *J* = 10.4 Hz, $C\underline{H}_2$Ph (α)), 4.57 (d, *J* = 11.3 Hz, $C\underline{H}_2$Ph (α)), 4.46 (dd, *J* = 3.8 Hz, *J* = 6.6 Hz, $C\underline{H}CH_2$OTBDPS), 4.40 (d, *J* = 8.1 Hz, H-1 (β)), 4.28–4.23 (m), 4.14.4.15 (m), 4.02–3.90 (m), 3.75 (s, CO_2Me (α)), 3.54 (dd, *J* = 8.9 Hz, *J* = 9.8 Hz, H-4 (α)), 3.38 (dd, *J* = 3.5 Hz, *J* = 10.3 Hz, H-2 (α)), 1.04 (s, *t*-Bu) ppm. **^{13}C NMR** ($CDCl_3$): δ 169.6, 166.8, 137.65, 137.63, 135.6-135.5, 132.8, 132.7, 129.9, 129.8, 128.6, 128.5, 128.4, 128.1, 128.0, 127.88, 127.85, 127.78, 127.75, 96.3 (C-1 (α)), 80.0 (α), 75.63 ($O\underline{C}HCH_2$OTBDPS (α)), 75.60 ($\underline{C}H_2$Ph (α)), 74.8 ($\underline{C}H_2$Ph (α)), 69.2 (α), 64.4 ($OCH\underline{C}H_2$OTBDPS (α)), 64.0 (C-6 (α)), 63.07 (C-2 (α)), 52.3 ($CO_2\underline{C}H_3$ (α)), 40.5 ($CO\underline{C}H_2Cl$ (α)), 26.7 (*t*-Bu (α)), 19.1 (C-Si (α)) ppm. **HR-MS:** calcd for $C_{42}H_{48}ClN_3O_9SiNa^+$ $[M + Na]^+$: 824.2741; found: 824.2739.

4.10.6. Methyl 3-O-tert-butyldiphenylsilyl-(2R)-2-O-[2-azido-3,4,di-O-benzyl-6-O-chloroacetyl-2-deoxy-α-D-glucopyranosyl-(1→6)-2,3,4-tri-O-benzyl-1-O-α-D-glucopyranosyl]-2,3-dihydroxypropanoate **17**

FT-IR (film) $\upsilon_{máx.}$: 1752 (C = O), 2108 (N_3) cm^{-1}. **^{1}H NMR** ($CDCl_3$): δ 7.72–7.69 (m, 3H), 7.46–7.44 (m, 2H), 7.39–7.20 (m, 30H), 5.21 (d, 1H, *J* = 3.5 Hz, H-1 (2)), 5.03–4.83 (m, 6H, $C\underline{H}_2$Ph), 4.92 (d, 1H, *J* = 2.8 Hz, H-1 (1)), 4.75 (d, 1H, *J* = 10.7 Hz, $C\underline{H}_2$Ph), 4.70 (d, 1H, *J* = 11.5 Hz, $C\underline{H}_2$Ph), 4.59–4.52 (m, 3H, $C\underline{H}_2$Ph, $C\underline{H}CH_2$OTBDPS), 4.22 (dd, 1H, *J* = 2.0 Hz, *J* = 12.0 Hz, H-6 (1)), 4.14–4.03 (m, 3H, H′-6 (1), H-3 (2), $CHC\underline{H}$H′OTBDPS), 4.00–3.90 (m, 3H, H-3 (1), H-5 (2), $CHCH\underline{H}$′OTBDPS), 3.87 (s, 2H, $CO\underline{C}H_2Cl$), 3.74–3.71 (m, 5H, H-5 (1), H-6 (2), CO_2Me), 3.66–3.60 (m, 2H, H-2 (2), H-4 (2)), 3.52–3.46 (m, 2H, H-4 (1), H′-6 (2)), 3.28 (dd, 1H, *J* = 3.5 Hz, *J* = 10.3 Hz, H-2 (1)),

1.04 (s, 9H, t-Bu) ppm. **^{13}C NMR** ($CDCl_3$): δ 170.3, 166.8, 138.7, 138.5, 138.3, 137.66, 137.53, 135.65, 135.59, 133.08, 132.93, 129.76, 129.74, 128.60, 128.54, 128.52, 128.39, 128.33, 128.29, 128.26, 128.24, 128.17, 128.15, 128.12, 128.06, 128.03, 127.81, 127.78, 127.63, 127.51, 127.2, 97.9 (C-1 (2)), 94.7 (C-1 (1)), 81.7 (C-3 (2)), 80.1 (C-3 (1)), 79.5 (C-2 (2)), 77.4 (C-4 (1)), 77.3 (C-4 (2)), 75.8 ($\underline{C}H_2Ph$), 75.5 ($\underline{C}H_2Ph$), 75.0 ($\underline{C}H_2Ph$), 74.8 ($\underline{C}H_2Ph$), 74.6 ($\underline{C}HCH_2OTBDPS$), 72.1 ($\underline{C}H_2Ph$), 70.2 (C-5 (2)), 68.9 (C-5 (1)), 66.1 (C-6 (2)), 64.8 ($CH\underline{C}H_2OTBDPS$), 64.1 (C-6 (1)), 63.5 (C-2 (1)), 52.0 ($CO_2\underline{Me}$), 40.6 ($CO\underline{C}H_2Cl$), 26.8 ($SiC(\underline{C}H_3)_3$), 19.2 ($Si\underline{C}(CH_3)_3$) ppm.

*4.10.7. 1-O-Adamantanyl-2-azido-3,4,di-O-benzyl-6-O-chloroacetyl-2-deoxy-α/β-D-glucopyranoside **19***

FT-IR (film) $\upsilon_{máx.}$: 1763, 1743 (C = O), 2104 (N_3) cm^{-1}. **^{1}H NMR** ($CDCl_3$): δ 7.41–7.23 (m, Ph), 5.29 (d, *J* = 3.7 Hz, H-1 (α)), 4.93–4.84 (m), 4.77 (d, *J* = 10.8 Hz, CH_2Ph (β)), 4.58 (d, *J* = 10.8 Hz, CH_2Ph (α)), 4.57 (d, *J* = 11.0 Hz, H-1 (β)), 4.38–4.29 (m, H-6 (α), H′-6 (α)), 4.20 (dd, *J* = 5.3 Hz, *J* = 11.6 Hz, β), 4.13 (ddd, *J* = 2.4 Hz, *J* = 4.3 Hz, *J* = 10.0 Hz, H-5 (α), 4.08 (dd, *J* = 8.7 Hz, J = 10.2 Hz, H-3 (α)), 4.02–3.92 (m, $COC\underline{H}_2Cl$), 3.51 (dd, *J* = 8.8 Hz, *J* = 9.9 Hz, H-4 (α)), 3.48–3.39 (m, β) 3.17 (dd, *J* = 3.6 Hz, *J* = 10.3 Hz, H-2 (α)), 2.16 (bs, $C\underline{H}(CH_2)_3$), 1.88–1.76 (m), 1.67–1.57 (m) ppm. **^{13}C NMR** ($CDCl_3$): δ 166.9, 137.8 (β), 137.5 (α), 128.6–128.5, 128.13, 128.10, 128.0, 127.9, 95.1 (C-1 (β)), 91.0 (C-1 (α)), 83.3 (β), 79.9 (C-3 (α)), 77.9 (C-4 (α)), 77.1 (β), 75.7 ($O\underline{C}(CH_2)_3$), 75.5 ($\underline{C}H_2Ph$ (β)), 75.2 ($\underline{C}H_2Ph$ (α)), 75.1 ($\underline{C}H_2Ph$ (α)), 74.9 ($\underline{C}H_2Ph$ (β)), 72.4 (β), 68.4 (C-5 (α)), 66.4 (β), 64.7 (C-6 (β)), 64.6 (C-6 (α)), 63.1 (C-2 (α), 42.36 (β), 42.30 (α), 40.6 ($CO\underline{C}H_2Cl$), 36.1, 30.68 ($\underline{C}H(CH_2)_3$ (β)), 30.62 ($\underline{C}H(CH_2)_3$ (α)) ppm. **HR-MS:** calcd for $C_{32}H_{38}ClN_3O_6Na^+$ $[M + Na]^+$: 618.2341; found: 618.2335.

*4.10.8. 3-O-(2-azido-3,4,di-O-benzyl-6-O-chloroacetyl-2-deoxy-α/β-D-glucopyranosyl)-epiandrosterone **21***

FT-IR (film) $\upsilon_{máx.}$: 1742, 1762 (C = O), 2107 (N_3) cm^{-1}. **^{1}H NMR** ($CDCl_3$): δ 7.46–7.43 (m, Ph), 7.41-7.24 (m, Ph), 7.13 (d, *J* = 7.9 Hz, Ph), 5.30 (d, *J* = 3.6 Hz, H-1 (α)), 4.94–4.82 (m), 4.78 (d, *J* = 10.8 Hz, $C\underline{H}_2Ph$ (β)), 4.61–4.55 (m), 4.48 (dd, *J* = 11.9, *J* = 1.9 Hz), 4.39–4.29 (m), 4.24 (dd, *J* = 11.9, *J* = 4.6 Hz), 4.22–4.18 (m), 4.14 (ddd, *J* = 10.1 Hz, *J* = 4.5 Hz, *J* = 2.5 Hz), 4.08 (dd, *J* = 10.3 Hz, *J* = 8.7 Hz, H-3 (α)), 4.03–3.89 (m), 3.54-3.39 (m), 3.28 (dd, *J* = 10.0, *J* = 9.3 Hz, H-5 (α)), 3.17 (dd, *J* = 10.3, *J* = 3.6 Hz, H-2 (α)), 2.35 (s), 2.19-2.13 (m), 1.92–1.75 (m), 1.67–1.57 (m) ppm. **^{13}C NMR** ($CDCl_3$): δ 166.99, 166.79, 139.1, 137.9, 137.51, 137.48, 137.32, 137.31, 134.5, 129.8, 128.66, 128.60, 128.56, 128.52, 128.51, 128.29, 128.19, 128.18, 128.14, 128.10, 128.06, 128.02, 127.94, 126.6, 95.1 (C-1 (β)), 91.1 (C-1 (α)), 85.9 (α), 85.1 (α), 83.3 (β), 80.0 (α), 78.0 (α), 77.1 (β), 76.75, 76.71, 76.2, 76.0, 75.8, 75.5, 75.25, 75.12, 75.04, 74.95, 72.4 (β), 68.5 (α), 66.4 (β), 64.85 (α), 64.74 (β), 64.67, 64.2, 63.1 (α), 42.36, 42.31, 40.6, 36.16, 36.11, 30.68, 30.62, 21.2 ppm. **HR-MS:** calcd for $C_{41}H_{53}ClNO_7^+$ $[M\text{-}N_2 + H]^+$: 706.3511; found: 706.3465.

*4.10.9. Dimethyl (2S)-2-O-(2-azido-3,4,di-O-benzyl-6-O-chloroacetyl-2-deoxy-α-D-glucopyranosyl)-2-hydroxysuccinate **23***

FT-IR (film) $\upsilon_{máx.}$: 1740 (C = O), 2108 (N_3) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.39–7.26 (m, 10H, Ph), 5.05 (d, *J* = 3.8 Hz, 1H, H-1), 4.91–4.85 (m, 3H, $C\underline{H}_2Ph$), 4.60 (d, *J* = 11.2 Hz, 1H, $C\underline{H}_2Ph$), 4.54 (t, *J* = 6.5 Hz, 1H, $C\underline{H}CH_2CO_2Me$), 4.35–4.24 (m, 3H, H-5, H-6, H'-6), 4.04–3.93 (m, 3H, H-3, $COC\underline{H}_2Cl$), 3.75 (s, 3H, CO_2Me), 3.73 (s, 3H, CO_2Me), 3.55 (t, *J* = 9.2 Hz, 1H, H-4), 3.30 (dd, *J* = 10.4, 3.8 Hz, 1H, H-2), 2.85 (d, *J* = 6.6 Hz, 2H, $CHC\underline{H}_2CO_2Me$) ppm. **^{13}C NMR** ($CDCl_3$): δ 170.8, 170.2, 166.9, 137.6, 137.5, 128.55, 128.53, 128.06, 128.04, 128.00, 100.0 (C-1), 79.9 (C-3), 77.3 (C-4), 75.4 ($\underline{C}H_2Ph$), 75.3 ($\underline{C}HCH_2CO_2Me$), 74.9 ($\underline{C}H_2Ph$), 69.7 (C-5), 64.0 (C-6), 63.2 (C-2), 52.5 ($CO_2\underline{Me}$), 52.2 ($CO_2\underline{Me}$), 40.7 ($CO\underline{C}H_2Cl$), 37.6 ($CO\underline{C}H_2CO_2Me$) ppm.

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Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.carres.2016.03.021.

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