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Iodine Promoted Glycosylation with Glycosyl Iodides: α-Glycoside Synthesis

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Glycosidation of fully acetylated glucopyranosyl iodide with methanol under the influence of iodine gave α-glucoside selectively. Use of less reactive acceptors led to the formation of α/β-mixtures. Glycosylations with fully benzoylated glucosyl iodide yielded β-glucosides only. In contrast, iodine-promoted glycosylation of serine and threonine with 2-azido-2-deoxy-glycosyl iodides, easily obtained in three steps, proceeded smoothly, resulting in only α-linked products in high yield in most cases.

Keywords Glycosyl iodine, Iodine, Glycosylated amino acids, α-glycosylation

INTRODUCTION

Since the pioneering work of Koenigs and Knorr[1] on the activation of glycosyl bromides and chlorides with silver salts, glycosyl halides have become widely employed in carbohydrate chemistry. Although glycosyl chlorides are more stable donors, glycosyl bromides are often the donor of choice due to their

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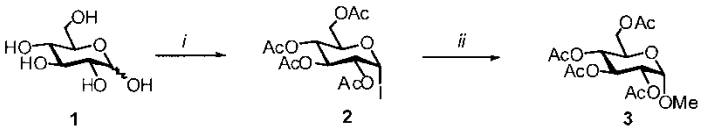
enhanced reactivity.[2] Glycosyl fluorides[3] and iodides have received less attention because the former are less reactive and the latter have generally been considered as too unstable to be useful. However, in the past two decades several laboratories have demonstrated that glycosyl iodides are easily accessible in a variety of ways and display unique properties in glycosylation reactions.[4] Most reports are on the use of "armed" glycosyl iodides as, for example, in the work by Gervay, Hague, and coworkers, who constructed *N*-, *C*- and *O*-glycosides and oligosaccharides either by S_N2 displacement or by an in situ anomerization procedure.[5] More recently, glycosylation reactions with "disarmed" glycosyl iodides, either in the presence or absence of a promotor, have been explored.[6]

Our laboratory has a long-standing interest in the use of iodine as a cheap and easy to handle reagent for the activation of glycosyl donors.[7] From these studies it has emerged that armed thioglycosides and bromides can be easily glycosidated by the action of iodine in a straightforward manner.[8] However, disarmed thioglycosides cannot be activated with iodine alone, and the results with disarmed bromosugars are variable.[7] As glycosyl iodides are more reactive, we investigated the potential to activate disarmed glycosyl iodide donors with iodine. We present here the results of our investigation and demonstrate the utility of this method in the synthesis of glycosylated amino acids.

RESULTS

Fully acetylated α-glucopyranosyl iodide (**2**) was prepared according to the one-pot procedure recently developed in our laboratory, which employs sequential per-*O*-acetylation (Ac_2O/I_2) and glycosyl iodide formation (I_2/hexamethyldisilane).[7] The first attempt to react **2** with a simple acceptor under the influence of iodine resulted in the formation of the α-methyl glucopyranoside **3** as the major product ($\alpha/\beta = 7.5/1$; see Sch. 1).[9–11] Apparently, neighbouring group participation of the acyl function on C-2 does not dominate under these reaction conditions.

Preferential formation of the α-glucoside might be explained by the intermediacy of a β-glucosyl iodide (Fig. 1). The β-form, being thermodynamically less stable[12] and hence more reactive than its α-oriented counterpart, reacts



1 2 3

Scheme 1: Reaction of glucosyl iodide with MeOH under the influence of I_2. Reagents and conditions (*i*) a) Ac_2O, I_2; b) I_2, HMDS, DCM, 5 hr (91% over two steps); (*ii*) MeOH, I_2, DCM, 4 Å MS (35%).

in an S_N2 fashion with methanol to give the α-methyl glucoside. β-Glycosyl iodide formation was not detectable by NMR. In fact, addition of methanol to the glycosyl iodide and iodine in deuterated chloroform only gave a small amount of methyl glycoside after several hours. It appears that the acidic nature of chloroform impedes the reaction with iodine. The addition of molecular sieves to the reaction in DCM proved to be essential for the reaction to proceed smoothly.[13,14]

Extension of this glycosylation method to other acceptors resulted in reduced α-selectivity. For example, reaction of glucosyl iodide **2** with a long-chain alcohol acceptor (**4**) gave an α/β mixture of glycoside **5** with a slight preference for the formation of the α-configured product (see Table 1). Moreover, in the glycosylation of the 6-OH of glucoside **6** with **2**, the β-linked disaccharide **7** was the only isolable glycoside product. The reduced activity of these acceptors compared to methanol may allow the formation of an oxocarbenium intermediate and neighbouring group participation to occur. As benzoyl protecting groups are more disarming,[16] the fully benzoylated glucosyl iodide **8** was prepared by reaction between perbenzoylated glucose and HMDS-I_2. Surprisingly, glycosylation of methanol or 11-bromoundecanol with **8** under the same reaction conditions gave only the β-oriented glucosides.

Next, iodine activation was attempted for the glycosidation of 2-azido-2-deoxyglycosyl iodides, having a nonparticipating neighbouring group on C-2 that has a more disarming effect than acyl protecting groups.[16b] 2-Azido-2-deoxy-sugars have proven practical building blocks for the synthesis of glycopeptides and glycoproteins, a class of molecules ubiquitous in nature.[17]

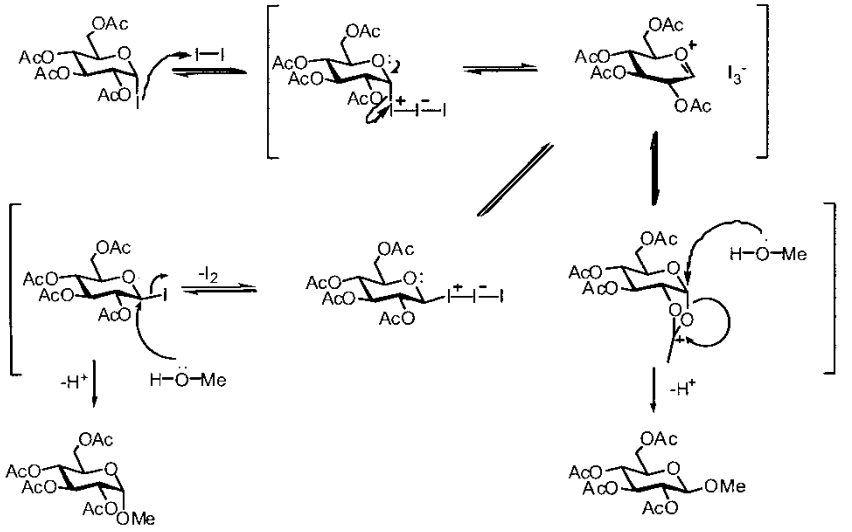
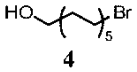
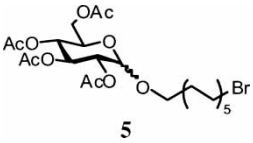
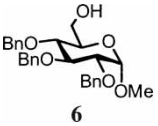
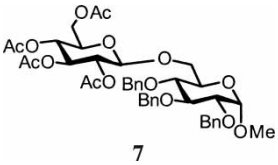
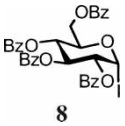
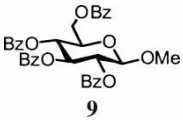
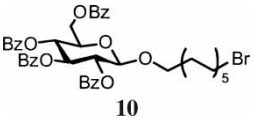


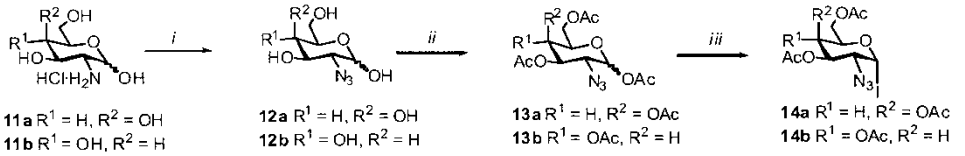
Figure 1: Possible mechanism for iodine activation of glucosyl iodide.[15]

Table 1: Glycosylations with glucosyl iodide. Reaction conditions: Donor (1 eq.), acceptor (MeOH, **4**: 2eq., **6**: 0.8 eq.), I_2 (1.5 eq.), 4 Å MS, DCM.

Donor	Acceptor	Product	Yield
1	 **4**	 **5**	65%, $\alpha/\beta = 1.7/1$
1	 **6**	 **7**	25%, β only
 **8**	MeOH	 **9**	84%, β only
8	**6**	 **10**	76%, β only

Their importance in a variety of biologic processes has inspired numerous synthetic efforts toward α-linked *O*-serinyl and threoninyl 2-acetamido-2-deoxy-glycosides.[18] The methods reported thus far for the formation of the α-glycosidic bond suffer from either low yields or poor α-selectivity, especially in the case of serine.

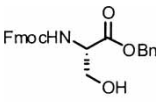
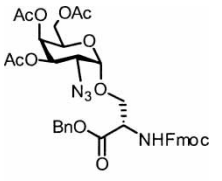
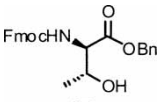
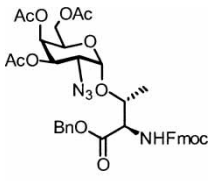
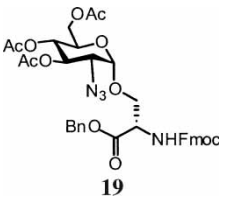
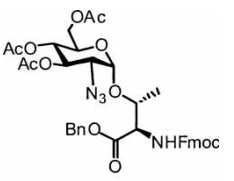
Tri-*O*-acetyl-2-azido-2-deoxy-glycosyl iodide in the *galacto* (**14a**) and *gluco* (**14b**) configuration were obtained in three straightforward steps, starting from the commercially available aminosugars. Thus, introduction of the azide by diazotransfer[19] and standard acetylation was followed by reaction with I_2-HMDS to introduce the anomeric iodide (see Sch. 2).[7]



Scheme 2: Synthesis of 2-azido-2-deoxy-glycosyl iodides. Reagents and conditions: (*i*) TfN_3, $CuSO_4$, K_2CO_3, DCM, H_2O, MeOH, 16 hr. (*ii*) Ac_2O, pyridine, 2 hr (**12a**: 72%, **12b**: 75% over two steps). (*iii*) I_2, HMDS, DCM, 4 hr (**13a**: 71%, **13b**: 78%).

The results of the glycosylation reactions with iodine are summarized in Table 2; all reactions proceeded smoothly in good yield (73–87%). In the case of serine the glycosylation reactions proceeded in a completely α-selective fashion. Similarly, glycosylation of *N*-Fmoc threonine benzyl ester with azidogalactose donor **14a** only gave an α-linked product. However, reaction with azidoglucose donor **14b** yielded an α/β mixture of threoninyl 2-azido-2-deoxy-glucoside. As observed with the fully acylated glucosyl iodide donors, reaction with a less reactive acceptor (threonine) resulted in a poorer α-selectivity. Attempts to enhance the α-selectivity through the use of solvents known to favor α-glycoside formation (i.e., diethyl ether/DCM or 1,4- dioxane/toluene)[20] were unfortunately hampered by the poor acceptor

Table 2: Glycosylations of serine and threonine. Reaction conditions: Donor (1 eq.), acceptor (0.98 eq.), I_2 (1.5 eq.), 4 Å MS, DCM.

Donor	Acceptor	Product	Result
14a	 **15**	 **16**	73%, α only
14a	 **17**	 **18**	74%, α only
14b	14	 **19**	78%, α only
14b	17	 **20**	87%, α/β:2.5/1

solubility. Possibly, remote neighboring group participation of the acetate on C-4 enhances the high α-selectivity observed for the glycosylations with the *galacto*-configured donor.[21]

In conclusion, disarmed glycosyl iodides are readily activated by iodine; however, the nature of the protecting group at C-2 and the reactivity of the acceptor influence the stereochemical outcome of the glycosylation reaction. While glycosylations with acetate protected donors give α-linked products with reactive acceptors, the benzoylated donors only give β-linked product. Neighboring group participation clearly dominates in the latter reaction. Good yields and good α-selectivity were observed in the glycosylation of serine and threonine with a 2-azido-2-deoxy-galactosyl iodide donor. The less reactive 2-azido-2-deoxy-glucosyl donor only gave good α-selectivity with serine. It appears that reduced reactivity of either donor or acceptor favors the formation of an oxycarbenium intermediate and loss of α-selectivity in this case.

EXPERIMENTAL

General Experimental

All reagents were obtained from commercial sources and used without purification. Toluene and dicholoromethane were distilled from calcium hydride and stored over molecular sieves (3 or 4 Å). TLC analysis was conducted on 0.25-mm precoated silica gel plates (Whatman, AL SIL G/UV, aluminium backing) with detection by fluorescence and/or dipping in 4% H_2SO_4 in ethanol, followed by heating. Column chromatography was performed on silica gel 60 (Fluka). ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity Plus spectrometer at 400 MHZ and 100.6 MHz, respectively. Chemical shifts are given in ppm (δ) relative to tetramethylsilane as internal standard. Optical rotations were measured at ambient temperature on a Perkin Elmer 141 polarimeter using the sodium D-line. $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. Compounds **2**,[8] **6**,[22] **15**,[23] and **17**[23] were prepared as recorded in the literature.

General protocol for glycosidations of glucosyl iodide donors 2 and 8 with I_2: Glucosyl iodide (0.33 mmol) was dissolved in DCM (1 mL), 4 Å MS (150 mg) was added, and the reaction mixture was stirred for 0.5 hr, after which the acceptor (MeOH 2 eq., compound **4** 2 eq., compound **6** 0.8 eq.) and I_2 (1.5 eq.) were added. After TLC (EtOAc/hexane:2/3:v/v) showed the complete conversion of **2** the reaction mixture was diluted with EtOAc (20 mL), filtered, and washed with aq. $Na_2S_2O_3$ (1 M, 2×10 mL) and brine (1×10 mL). Purification by column chromatography (hexane to EtOAc/hexane:2/3:v/v) gave **3** in 35%, **5** in 65%, **7** in 25%, **9** in 84%, and **10** in 76% yield.

Methyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside (3):[24] ^{1}H NMR ($CDCl_3$): δ 5.48 (t, 1H, H4, $J_{3,4}$, $J_{4,5} = 10.2$ Hz), 5.07 (t, 1H, H3, $J_{2,3}$, $J_{3,4} = 10.2$ Hz), 4.96 (d, 1H, H1, $J_{1,2} = 3.7$ Hz), 4.92 (dd, 1H, H2, $J_{1,2} = 3.7$ Hz, $J_{2,3} = 10.2$ Hz), 4.27 (dd, 1H, H6α, $J_{5,6a} = 4.6$ Hz, $J_{6a,6b} = 12.3$ Hz), 4.11 (dd, 1H, H6β, $J_{5,6b} = 2.3$, $J_{6a,6b} = 12.3$ Hz), 3.99 (m, 1H, H5), 3.41 (s, 3H, CH_3OMe), 2.11, 2.08, 2.03, 2.01 (4 × CH_3Ac). The ^{1}H NMR spectrum was in accordance with literature.[24]

11-Bromoundecyl 2,3,4,6-tetra-*O*-acetyl-α/β-D-glucopyranoside (5): ^{1}H NMR ($CDCl_3$): δ 5.22 (t, 1H, H3α, $J_{2,3}$, $J_{3,4} = 9.6$ Hz), 5.13 (t, 0.6H, H3β, $J_{2,3}$, $J_{3,4} = 9.6$ Hz), 5.00 (m, 3H, H2α/β, H4α/β), 4.91 (d, 1H, H1α, $J_{1,2} = 3.8$ Hz), 4.35 (d, 0.6H, H1β, $J_{1,2} = 7.7$ Hz), 4.27 (m, 1.6H, H6αa, H6βa), 4.10 (dd, 0.6H, H6βb, $J_{5,6b} = 2.4$ Hz, $J_{6a,6b} = 12.3$ Hz), 4.06 (dd, 1H, H6αb, $J_{5,6b} = 2.6$ Hz, $J_{6a,6b} = 12.6$ Hz), 3.98–3.94, 3.91–3.89 (2 × m, 1.6 H, CH_2O), 3.76–3.65 (m, 1.6 H, H5α/β), 3.57–3.47 (m, 1.6H, CH_2O), 3.43–3.39 (m, 3H, CH_2Br), 2.09, 2.08, 2.07, 2.04, 2.03 (6 × s, 18H, CH3Ac), 1.88–1.83 (m, 3H, CH_2), 1.65–1.62 (m, 3H, CH_2), 1.43–1.38 (m, 3H, CH_2), 1.29 (bs, 12H, CH_2). ^{13}C NMR ($CDCl_3$): δ 171.1, 170.7, 170.6, 169.6 (4 × C═O, Ac), 102.7 (C1β), 98.1 (C1α), 74.3, 73.5, 72.1, 71.8, 70.8, 70.5, 68.9, 68.4, 67.9, 67.5, 62.1, 61.9 (C2, C3, C4, C5, C6, CH_2O, α and β), 34.0, 32.8, 29.4, 29.33, 29.29, 29.1, 28.7, 28.1, 26.1, 25.8 (10 × CH_2), 20.9, 20.8, 20.7, 20.6 (4 × CH_3Ac). HRMS: calcd. for $C_{25}H_{45}O_{10}BrN$ $[M + NH_4]^+$ 598.2224; found 598.2226.

Methyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl-(1 → 6)-2,3,4-tri-benzyl-α-D-gluco pyranoside (7):[25] ^{1}H NMR ($CDCl_3$): δ 7.37–7.25 (m, 15H, Harom Bn), 5.18 (t, 1H, H3′, $J_{2,3}$, $J_{3,4} = 9.5$ Hz), 5.08 (t, 1H, H4′, $J_{3'4'}$, $J_{4',5'} = 9.5$ Hz), 5.04 (dd, 1H, H2′, $J_{1',2'} = 8.1$ Hz, $J_{2',3'} = 9.5$ Hz), 4.98 (d, 1H, CH_2 Bn, $J_{gem} = 10.8$), 4.86 (d, 1H, CH_2 Bn, $J_{gem} = 10.8$), 4.80 (d, 1H, CH_2 Bn, $J_{gem} = 11.0$), 4.79 (d, 1H, CH_2 Bn, $J_{gem} = 12.2$), 4.65 (d, 1H, CH_2 Bn, $J_{gem} = 11.0$), 4.58 (d, 1H, H1, $J_{1,2} = 3.5$ Hz), 4.53 (d, 1H, CH_2 Bn, $J_{gem} = 10.8$), 4.51 (d, 1H, H1′, $J_{1',2'} = 8.1$ Hz), 4.23 (dd, 1H, H6a′, $J_{5',6a'} = 4.8$ Hz, $J_{6a',6b'} = 12.4$ Hz), 4.11 (dd, 1H, H6b′, $J_{5',6b'} = 2.9$ Hz, $J_{6a',6b'} = 12.4$ Hz), 4.06 (dd, 1H, H6α, $J_{5,6a} = 4.8$ Hz, $J_{6a,6b} = 12.4$ Hz), 3.97 (t, 1H, H3, $J_{2,3}$, $J_{3,4} = 9.3$ Hz), 3.71 (m, 1H, H5), 3.65 (m, 2H, H6β, H5'), 3.51 (dd, 1H, H2, $J_{1,2} = 3.5$ Hz, $J_{2,3} = 9.3$ Hz), 3.43 (t, 1H, H4, $J_{3,4} = J_{4,5} = 9.3$ Hz), 3.36 (s, 3H, CH_3 Ome), 2.05, 2.02, 1.99, 1.95 (4 × s, CH_3 Ac). The ^{1}H NMR spectrum was in accordance with literature.[25]

2,3,4,6-Tetra-*O*-benzoyl-α-D-glucopyranosyliodide (8): Perbenzoylated glucose (1 g, 1.43 mmol) was dissolved in DCM; I_2 (0.22 g, 0.86 mmol) and HMDS (0.18 mL, 0.86 mmol) were added; and the reaction mixture was stirred for 6 hr. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (hexane to EtOAc/hexane:2/3:v/v) to yield **8** in 95% (1.05 g). ^{1}H NMR, ^{1}H-COSY ($CDCl_3$): δ 8.13–7.88 (4 × d, 8H, CHarom Bz), 7.59–7.23 (m, 13H, H1, CHarom Bz),

6.24 (t, 1H, H3, $J_{2,3}$, $J_{3,4} = 9.9$ Hz), 5.92 (t, 1H, H4, $J_{3,4}$, $J_{4,5} = 9.9$ Hz), 4.80 (dd, 1H, H2, $J_{1,2} = 4.4$ Hz, $J_{2,3} = 9.9$ Hz), 4.69 (br.d, 1H H6a), 4.58 (m, 2H, H5, H6b). ^{13}C NMR ($CDCl_3$): δ 171.8, 165.5, 165.1, 165.0 (4 × C═O, Bz), 133.7, 133.6, 133.3, 133.2, 130.1, 130.0, 129.84, 129.78, 129.7, 129.6, 128.5, 128.4, 128.3, 128.2 (CHarom, Bz), 75.3 (C1), 72.9, 72.2, 70.9, 67.6, 61.8 (C2, C3, C4, C5, C6). $[\alpha]_D = +138$ (*c* 1 in $CHCl_3$); this value is in accordance with literature.[25]

Methyl 2,3,4,6 -tetra-*O*-benzoyl-*β*-D-glucopyranoside (9):[27] ^{1}H NMR ($CDCl_3$): δ 8.11–7.82 (m, 8H, CHarom Bz), 7.57–7.32 (m, 12H, CHarom Bz), 5.93 (t, 1H, H4, $J_{3,4}$, $J_{4,5} = 9.7$ Hz), 5.70 (t, 1H, H3, $J_{2,3}$, $J_{3,4} = 9.7$ Hz), 5.54 (dd, 1H, H2, $J_{1,2} = 7.9$ Hz, $J_{2,3} = 9.7$ Hz), 4.78 (d, 1H, H1, $J_{1,2} = 7.9$ Hz), 4.66 (dd, 1H, H6a, $J_{5,6a} = 3.3$ Hz, $J_{6a,6b} = 12.3$ Hz), 4.52 (dd, 1H, H6b, $J_{5,6b} = 5.1$ Hz, $J_{6a,6b} = 12.3$ Hz), 4.18 (m, 1H, H5), 3.56 (s, 3H, CH_3 OMe). The ^{1}H NMR spectrum was in accordance with literature.[26]

11-Bromoundecyl 2,3,4,6-tetra-*O*-benzoyl-*β*-D-glucopyranoside (10): ^{1}H NMR, ^{1}H-COSY ($CDCl_3$): δ 8.03, 8.01, 7.99, 7.95 (4 × d, 8H, Harom Bz), 7.91–7.82 (m, 12 H, Harom Bz), 5.91 (t, 1H, H3, $J_{2,3}$, $J_{3,4} = 9.7$ Hz), 5.68 (t, 1H, H4, $J_{3,4}$, $J_{4,5} = 9.7$ Hz), 5.53 (dd, 1H, H2, $J_{1,2} = 7.9$ Hz, $J_{2,3} = 9.7$ Hz), 4.84 (d, 1H, H1, $J_{1,2} = 7.9$ Hz), 4.64 (dd, 1H, H6a, $J_{5,6a} = 3.3$ Hz, $J_{6a,6b} = 12.3$ Hz), 4.51 (dd, 1H, H6b, $J_{5,6b} = 5.1$ Hz, $J_{6a,6b} = 12.2$ Hz), 4.15 (m, 1H, H5), 4.11 (m, 1H, CH_2O), 3.53 (m, 1H, CH_2O), 3.40 (m, 2H, CH_2Br), 1.82 (m, 2H), 1.54 (m, 2H), 1.43–1.14 (m, 14H). ^{13}C NMR ($CDCl_3$): δ 165.9, 165.6, 165.0, 164.9 (4 × C═O, Bz), 133.2, 133.0, 132.9, 129.6, 129.5, 129.4, 129.2, 128.6, 128.2, 182.1, 128.0 (CHarom), 101.1 (C1), 72.7, 71.9, 71.7, 70.1, 69.6, 63.0 (C2, C3, C4, C6, CH_2O), 33.9, 32.6, 32.5, 29.3, 29.24, 29.19, 29.15, 28.5, 27.9, 25.9 (10 × CH_2). HRMS: calcd. for $C_{45}H_{53}O_{10}BrN$ $[M + NH_4]^+$ 846.2853; found 846.2861. $[\alpha]_D = +8$ (*c* 1 in $CHCl_3$).

3,4,6-Tri-*O*-acetyl-2-azido-2-deoxy-α-D-galactopyranosyl iodide (14a):[28] 1,3,4,6-Tetra-O-acetyl-2-azido-2-deoxy-galactose, prepared according to the method of Alper et al.,[19] (0.70 g, 3.5 mmol) was dissolved in DCM (3.5 mL); I_2 (0.52 g, 2.07 mmol) and HMDS (0.42 mL, 2.07 mmol) were added; and the reaction mixture was stirred at rt. After 4 hr TLC analysis (EtOAc/hexane:2/3, v/v) revealed complete conversion of the starting material into the galactosyl iodide and the solvent was removed under reduced pressure. Flash column chromatography (hexane to EtOAc/hexane:2/3:v/v) yielded 71% of **14a** (0.89 g). ^{1}H NMR ($CDCl_3$): δ 6.85 (d, 1H, H1, $J_{1,2} = 4.1$ Hz), 5.49 (d, 1H, H4, $J_{3,4} = 3.1$), 5.21 (dd, 1H, H3, $J_{2,3} = 10.6$ Hz, $J_{3,4} = 3.1$ Hz), 4.24 (m, 2H, H5, H6a), 4.14 (m, 1H, H6b), 3.43 (dd, 1H, H2, $J_{1,2} = 4.1$ Hz, $J_{2,3} = 10.6$ Hz), 2.18, 2.08 (3 × s, 9H, 3 × CH_3 Ac). The ^{1}H NMR spectrum was in accordance with literature.[28]

3,4,6-Tri-*O*-acetyl-2-azido-2-deoxy-α-D-glucopyranosyl iodide (14b): Compound **14b** was prepared from 1,3,4,6-tetra-*O*-acetyl-2-azido-2-deoxy-glucose

13b, synthesized according to the method of Alper et al.,[19] as described for **14a** in a 78% yield. ^{1}H NMR, ^{1}H-COSY ($CDCl_3$): δ 6.78 (d, 1H, H1, $J_{1,2} = 4.2$ Hz), 5.37 (t, 1H, H3, $J_{2,3}$, $J_{3,4} = 9.8$ Hz), 5.16 (t, 1H, H4, $J_{3,4}$, $J_{4,5} = 9.8$ Hz), 4.36 (dd, 1H, H6a, $J_{5,6a} = 4.2$ Hz, $J_{6a,6b} = 12.8$ Hz), 4.13–4.06 (m, 2H, H5, H6b), 3.31 (dd, 1H, H2, $J_{1,2} = 4.2$ Hz, $J_{2,3} = 9.8$ Hz), 2.10, 2.09, 2.06 (3 × s, 3 × 3H, 3 × CH_3 Ac). ^{13}C NMR ($CDCl_3$): δ 170.4, 169.7, 169.6 (3 × C=O), 75.1, 73.6, 72.5, 66.9, 62.0, 60.8 (C1, C2, C3, C4, C5, C6), 20.6, 20.56, 20.52 (3 × CH_3). HRMS: calcd. for $C_{12}H_{20}O_7N_4I$ $[M + NH_4]^+$ 459.0371; found 459.0372. $[\alpha]_D = +155$ (*c* 1 in $CHCl_3$).

General procedure for the glycosylation of Ser and Thr: Compound **14a** or **b** (0.120 g, 0.27 mmol) and Fmoc-Ser-Bn or Fmoc-Thr-Bn (0.26 mmol) were dissolved in DCM (1 mL); 4 Å MS (150 mg) was added; and the reaction mixture was stirred for 0.5 hr. After the addition of I_2 (0.10 g, 0.41 mmol) the reaction was followed by TLC (EtOAc/hexane:2/3:v/v). The reaction mixture was diluted with EtOAc (20 mL), filtered, and washed with aq. $Na_2S_2O_3$ (1 M, 2 × 10 mL) and brine (1 × 10 mL). Purification by column chromatography (hexane to EtOAc/hexane:2/3:v/v) gave **16** in 73%, **18** in 74%, **19** in 78%, and **20** in 87% yield.

***N*-Fmoc-*O*-(3,4,6-Tri-*O*-acetyl-2-azido-2-deoxy-α-*β*-D-galactopyranosyl)-L-serine benzyl ester (16):**[29] ^{1}H NMR ($CDCl_3$): δ 7.79–7.76, 7.64–7.62, 7.43–7.32 (3 × m, 13H, Harom Fmoc, Bn), 5.96 (d, 1H, NH-Ser, $J_{NH,\,H\alpha} = 8.1$ Hz), 5.39 (d, 1H, H4, $J_{3,4} = 2.6$ Hz), 5.25 (m, 3H, H3, CH_2 Bn), 4.88 (d, 1H, H1, $J_{1,2} = 3.5$ Hz), 4.62 (m, 1H, Hα-Ser), 4.41 (d, 2H, CH_2 Fmoc, $J = 7.1$ Hz), 4.25 (t, 1H, Hβ-Ser, $J = 7.0$ Hz), 4.16 (dd, 1H, H6a, $J_{5,6a} = 2.9$ Hz, $J_{6a,6b} = 10.6$ Hz), 4.09–4.00 (m, 4H, 1 × Hβ-Ser, H5, H6b, CH Fmoc), 3.59 (dd, 1H, H2, $J_{1,2} = 3.5$ Hz, $J_{2,3} = 10.9$ Hz), 2.16, 2.08, 1.98 (3 × s, 9H, 3 × CH3 Ac). The ^{1}H NMR spectrum was in accordance with literature.[29]

***N*-Fmoc-*O*-(3,4,6-Tri-*O*-acetyl-2-azido-2-deoxy-α-*β*-D-galactopyranosyl)-L-threonine benzyl ester (18):**[29] ^{1}H NMR ($CDCl_3$): δ 7.79–7.76, 7.64–7.62, 7.43–7.29 (3 × m, 13H, Harom Fmoc, Bn), 5.69 (d, 1H, NH-Thr, $J_{NH,\,H\alpha} = 9.3$ Hz), 5.44 (d, 1H, H4, $J_{3,4} = 2.9$ Hz), 5.31–5.20 (m, 3H, H3, CH_2 Bn), 4.91 (d, 1H, H1, $J_{1,2} = 3.7$ Hz), 4.50–4.21 (m, 6H, Hα-Thr, Hβ-Thr, H5, 2 × H6, CH Fmoc,) 4.08 (d, 2H, CH_2 Fmoc, $J = 6.4$ Hz), 3.59 (dd, 1H, H2, $J_{1,2} = 3.7$ Hz, $J_{2,3} = 10.9$ Hz), 2.16, 2.08, 2.05 (3 × s, 9H, 3 × CH_3 Ac). The ^{1}H NMR spectrum was in accordance with literature.[29]

***N*-Fmoc-*O*-(3,4,6-Tri-*O*-acetyl-2-azido-2-deoxy-α-*β*-D-glucopyranosyl)-L-serine benzyl ester (19):**[30] ^{1}H NMR ($CDCl_3$): δ 7.78–7.76, 7.64–7.62, 7.43–7.30 (3 × m, 13H, CHarom Fmoc, Bn), 5.95 (d, 1H, NH-Ser, $J_{NH,H\alpha} = 8.2$ Hz), 5.41 (t, 1H, H3α, $J_{2,3} = J_{3,4} = 10.3$ Hz), 5.27 and 5.22 (2 × d, 2 × 1H, CH2 Bn, $J_{gem} = 12.1$ Hz), 4.99 (t 1H, H4, $J_{3,4} = J_{4,5} = 10.3$ Hz), 4.84 (d, 1H, H1, $J_{1,2} = 3.5$ Hz), 4.63 (m, 1H, Hα-Ser), 4.42 (d, 2H, CH_2 Fmoc, $J = 7.0$ Hz),

4.25–4.00 (m, 5H, 2 × Hβ-Ser, CH Fmoc, 2 × H6), 3.95 (m, 1H, H5), 3.25 (dd, 1H, H2, $J_{1,2} = 3.5$ Hz, $J_{2,3} = 10.3$ Hz), 2.11, 2.05, 2.04 (3 × s, 9H, 3 × CH3 Ac). The ^{1}H NMR spectrum was in accordance with literature.[30]

***N*-Fmoc-*O*-(3,4,6-Tri-*O*-acetyl-2-azido-2-deoxy-α–*β*-D-glucopyranosyl)-L-threonine benzyl ester (20):** ^{1}H NMR ($CDCl_3$): δ 7.78–7.75, 7.64–7.59, 7.41–7.29 (3 × m, 13H, CHarom Fmoc, Bn), 5.72 (d, 1H, NH-Thr, $J_{NH,H\alpha} = 9.8$ Hz), 5.64 (d, 0.4 H, NH-β, $J_{NH,H\alpha} = 9.5$ Hz), 5.42 (t, 1H, H3α, $J_{2,3} = J_{3,4} = 9.8$ Hz), 5.29–5.13 (m, 3H, CH2 Bn α/β), 4.99 (t 1H, H4α, $J_{3,4}$, $J_{4,5} = 9.8$ Hz), 4.90 (m, 1H, H3β, H4β), 4.84 (d, 1H, H1α, $J_{1,2} = 3.7$ Hz), 4.60–4.32, 4.27–4.18, 4.08–3.99 (3 × m, 13H, 2 × Hα-thr, 2 × Hβ-thr, 2 × CH Fmoc, 2 × CH2 Fmoc, H5α, 2 × H6α, 2 × H6β), 3.37 (m, 0.8 H, H2β, H5β), 3.27 (dd, 1H, H2α, $J_{1,2} = 3.7$ Hz, $J_{2,3} = 10.6$ Hz), 2.11, 2.09, 2.07, 2.06, 2.02, 2.00 (6 × s, 14H, 6 × CH3 Ac), 1.35–1.32 (m, 5H, 2 × CHγ-Thr). ^{13}C NMR ($CDCl_3$): δ 170.5, 169.6 (3 × C═O Ac, C═O Thr), 156.8 (C═O Fmoc), 143.8, 141.2 (Cq-arom Fmoc), 128.65, 128.59, 128.51, 128.4, 127.7, 127.6, 127.1, 125.3, 119.9 (CHarom Bn, FMoc), 103.3 (C1β), 98.7 (C1α), 74.8, 71.7, 70.3, 68.5, 67.9, 67.7, 67.6, 67.4, 63.2, 61.8, 61.1, 58.7 (C2, C3, C4, C5, C6, CH_2 Fmoc, CH_2 Bn, Cα-Thr, Cβ-Thr), 47.0 (CH Fmoc), 20.7, 20.63, 20.57 (3 × CH_3 Ac), 18.6 (CHγ-Thr). HRMS: calcd. for $C_{37}H_{39}O_{12}$ $[M + H]^+$ 731.2564; found 731.2577.

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