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Stereoselective Synthesis of α-Glycosyl Azides by TMSOTf-Mediated Ring Opening of 1,6-Anhydro Sugars

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Access to α-glycosyl azides in modest to high diastereoselectivity by way of $TMSN_3$ ring-opening of 1,6-anhydro sugars mediated by TMSOTf is reported. The reaction tolerates a wide variety of functional groups including alcohol, alkyne, azide and ester groups. The efficient synthesis of a pseudopentasaccharide in five steps from commercially available levoglucosan by way of a "click-click" approach is presented to highlight the interest of the $TMSN_3$ ring-opening reaction.

Introduction

In less than one decade, the concept of "click chemistry" has become a major element in the toolbox of synthetic chemists, especially those working at the interface between biology, material science, and physics.[1,2] The opportunities offered by the simplicity and efficiency of click chemistry are highlighted by the increasing number and diversity of scientific projects based on this strategy. In 2011, less than ten years after its introduction, more than 1400 articles linked to click chemistry were published, double that of 2008. This concept is particularly relevant for the efficient construction of complex molecular systems bearing various functional groups. Not surprisingly, its application in the field of glycosciences for the construction of neoglycoconjugates, glycopolymers, glycoclusters, or glycosylated biomolecules has led to numerous fruitful results to date.[3] Among the set of available click reactions, the Cu^I-catalyzed azide-alkyne cycloaddition (CuAAC)[1,4] is the most extensively utilized because of the numerous advantages of this process including high regio- and chemoselectivity. In addition, the resulting triazoles offer many advantages in terms of stability and biocompatibility. In this context, the efficient preparation of glycosyl azides as valuable carbohydrate building blocks for CuAAC and other reactions exploiting the versatile reactivities of the azido group for *N*-glycoside synthesis is still of great interest.[5,6] Glycosyl azide synthesis generally involves the nucleophilic substitution of anomeric halide by metal azide[5] or alternatively the Lewis acid catalyzed reaction between 1-*O*-acetyl sugar and trimethylsilyl azide ($TMSN_3$).[6] Despite the attractive practical and strategic advantages of this approach, the concept of using 1,6-anhydro sugars (also known as "glycosans") for the synthesis of azido sugars has been only poorly investigated. To the best of our knowledge, the azide nucleophilic ring-opening of 1,6-anhydrohexopyranoses has almost no precedent[7,8] and a general procedure is still to be developed. 1,6-Anhydro sugars offer numerous advantages as glycosylating agents including stability, dual protection of both C-1 and C-6, an unusual conformation ($^1C_4$), a bicyclo[3.2.1] skeleton ensuring high degree of steric-approach control, and the release of a hydroxyl group at C-6 after ring-opening of the anhydro bridge.[9,10] In this paper, we wish to report a new method for the stereoselective synthesis of α-glycosyl azides based on azide nucleophilic ring-opening of 1,6-anhydro sugars and its application to the expeditious synthesis of a pseudopentasaccharide.

Results and Discussion

Exploration of the synthetic scope of this process was first performed with 1,6-anhydro-D-glucose **1**[11] (Table 1). Various experimental parameters were examined such as the nature of the Lewis acid, of the nucleophile and of the solvent. Treatment of **1** with two or more equivalents of sodium azide in the presence of 1 equiv. of trimethylsilyl triflate in acetonitrile led to no conversion. Replacement of sodium azide by $TMSN_3$ afforded the expected glucoside azide **2** in 76% yield and good diastereomeric ratio (4:1) in favour of the α anomer (entry 1). A good balance between short reaction time, high yield and diastereomeric control was first achieved by using 10 equiv. of $TMSN_3$ and 0.5 equiv. of TMSOTf in MeCN at room temperature (entries 1–9). It is noteworthy that small amounts of disaccharides **3** corresponding to the in situ *O*-glycosylation of **2** with **1** may be obtained by using the TMSOTf/$TMSN_3$ system. The maximum yield of **3** (10%) was attained when

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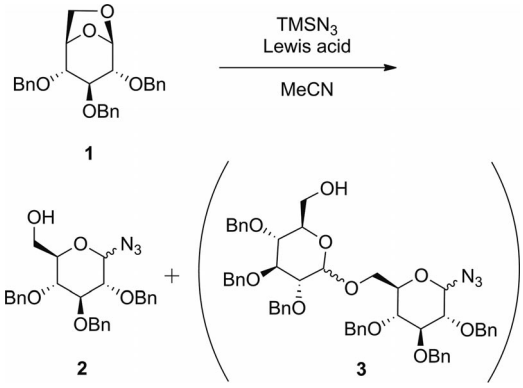
Table 1. Reaction of **1** with Lewis acid and $TMSN_3$.[a]



Entry	RN_3 [equiv.]	Lewis acid[b]	[**1**][c]	*t* [h][d]	Yield [%][e]	α/β[f]
1	2	TMSOTf (1)	0.2	1.15	76	4.1:1
2	10	TMSOTf (1)	0.1	0.3	83	6.4:1
3	20	TMSOTf (1)	0.1	0.75	86	4.4:1
4	20	TMSOTf (1)	0.1	2.25	80	4.0:1
5	20	TMSOTf (1)	0.1	48	89	2.7:1
6	20	TMSOTf (0.1)	0.1	2	75	4.0:1
7	20	TMSOTf (0.5)	0.1	1.5	85	4.3:1
8	2	TMSOTf (5)	0.1	47	33	5.6:1
9	**10**	**TMSOTf (0.5)**	**0.1**	**0.4**	**88**	**10.5:1**
10	20	ZnI_2 (1)	0.1	26[g,h]	76	5.0:1
11	20	$BF_3{\cdot}OEt_2$ (1)	0.1	66[h]	63	1:1.2
12	20	$AlCl_3$ (1)	0.1	66[h]	50	2.8:1
13	20	TBDMSOTf (1)	0.2	0.4	79	8.1:1
14	20	TMSOTf (1)/ $BF_3{\cdot}OEt_2$(1)[j]	0.1	26[g]	87	4.8:1
15	10	TMSOTf (0.5)	0.02	0.9	85	6.0:1
16	10	TMSOTf (0.5)	0.2	0.3	88	3.9:1
17	10	TMSOTf (0.5)	0.1	48[i,h]	97	6.5:1
18	**10**	**TMSOTf (0.5)**	**0.1**	**16**[i,h]	**95**	**8.7:1**
19	10	TMSOTf (0.5)	0.1	1.5[i,h]	84	6.2:1

[a] Unless specified otherwise the reaction was conducted at room temperature, or at 0 °C to room temperature. [b] Number of equivalents in parentheses. [c] Molar concentration of **1**. [d] Reaction time. [e] Isolated yield of **2**. [f] Determined after separation of the anomers on silica gel. [g] Reaction performed in 1,2-dichloroethane. [h] Reaction performed at 40 °C. [i] Reaction performed in toluene (entry 17), in a 3:1 (v/v) mixture of toluene/MeCN (entry 18) or in a 1:1 mixture of toluene/MeCN (entry 19). [j] For synergistic combination of TMSOTf and $BF_3{\cdot}OEt_2$, see ref.[13]

the reaction was performed with 2 equiv. of $TMSN_3$ (entry 1). Prolonged reaction times were found to reduce the stereoselectivity of the reaction (entries 3–5). A screening of various Lewis acids revealed that the nature of the Lewis acid had a strong impact on the diastereomeric ratio and reaction time (entries 9–14). For example, the use of a more sterically demanding trialkylsilyl triflate (TBDMSOTf) led to higher diastereomeric ratio (8.1:1) in favour of the α-glycosyl azide **2** (entry 13), whereas the use of $BF_3{\cdot}OEt_2$ almost abolished the stereoselectivity of the reaction (entry 11).

Changes in the concentration of glycosyl donor **1** was found to strongly affect the stereoselectivity of the reaction (Table 1, entries 9, 15 and 16).[12] The ratio of anomers was found to be the highest at 100 mM (α/β ca. 10.5:1; entry 9), moderate at 20 mM (α/β ca. 6:1; entry 15) and lower at 200 mM (α/β ca. 4:1; entry 16). The use of toluene vs. MeCN as solvent required heating and prolonged reaction times (48 h at 40 °C) and led to a decrease in diastereoselectivity (α/β ca. 6.5:1), but provided **2** in an almost quantitative yield (entry 17). The optimized mixture of toluene/MeCN (3:1) was found to maintain high yield and good stereoselectivity while reducing the reaction time to 16 h (entry 18).

Ring-opening of the anhydro bridge was then evaluated on a series of 1,6-anhydro sugars of different configurations and with diverse protecting group patterns to evaluate the synthetic scope of this process (Figure 1, Table 2). The preparation of the anhydro sugar substrates was performed according to the synthetic sequences presented in Scheme 1 or to known experimental procedures.

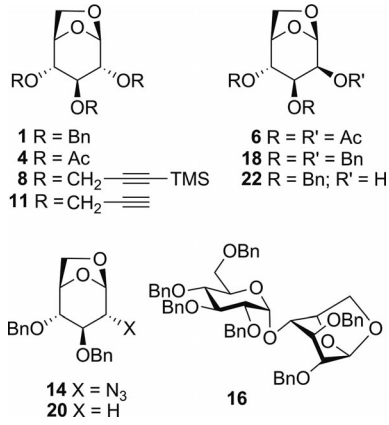
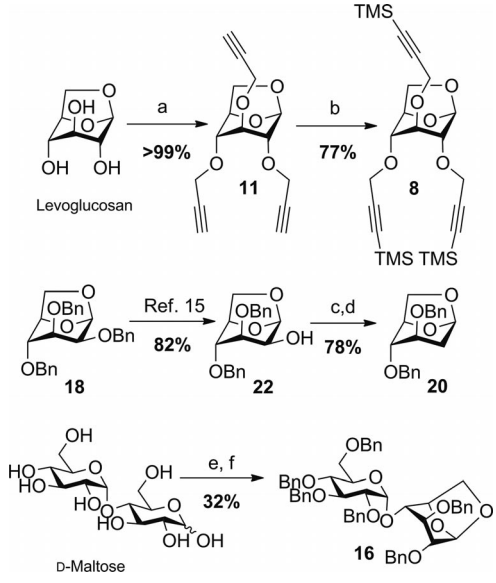
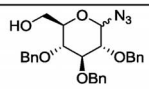
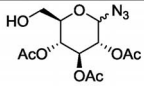
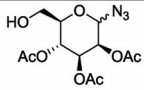
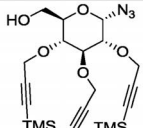
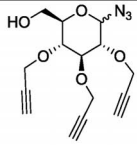
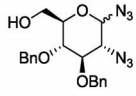
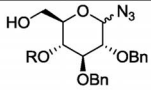
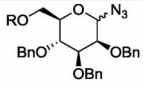
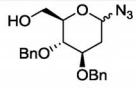
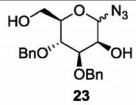


Figure 1. 1,6-Anhydro sugar substrates.



Scheme 1. *Reagents and conditions:* (a) NaH (9 equiv.), propargyl bromide (9 equiv.), DMF, room temp., 39 h; (b) DBU (5 equiv.), AgOTf (0.1 equiv.), TMSCl (10 equiv.), THF, reflux, 20 h; (c) Tf_2O (2 equiv.), pyridine (2.5 equiv.), CH_2Cl_2, –10 °C, 1 h; (d) nBu_4NBH_4 (3 equiv.), toluene, room temp., 2.25 h; (e) 2-chloro-1,3-dimethylimidazolium chloride (3 equiv.), NEt_3 (9 equiv.), H_2O, 0 °C to room temp., 16 h; (f) NaH (12 equiv.), BnBr (10 equiv.), DMF, room temp., 6 h.

Table 2. Synthesis of glycosyl azides.[a,b]

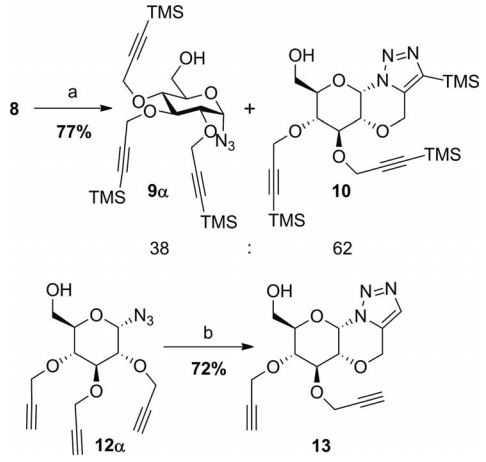
Entry	Cond.[b]	Subs.	Product	α:β[c]	Yield[d]
1	A	**1**		10.5:1	88%
2	B	**1**	**2**	9:1	95%
3	A[j]	**4**		1:1	61%
4	B	**4**	**5**	_[e]	_[e]
5	A[j]	**6**	 **7**	_[e]	_[e]
6	A	**8**		> 20:1	82%
7	B	**8**	**9α**	> 20:1	29%[f]
8	A	**11**		15:1	63%
9	B	**11**	**12**	> 20:1	56%[g]
10	A	**14**	 **15**	3:1	88%
11	A	**16**		4:1	67%
12	B	**16**	**17** R=tetra-*O*-Bn-αGlc	5:1	66%
13	A	**18**		1.8:1	85%[i]
14	B	**18**	**19** R=H → **27α** R=PMB[h]	2:1	86%[i]
15	A	**20**	 **21**	2:1	72%
16	A	**22**	 **23**	1.2:1	82%

[a] The reactions were performed under either conditions A or B. [b] Reaction conditions: 1,6-anhydro sugar/$TMSN_3$/TMSOTf (1:10:0.5) either in MeCN at room temp. (conditions A) or in toluene/MeCN (3:1) at 40 °C (conditions B). [c] Determined after separation of the anomers on silica gel or by NMR spectroscopic analysis of the crude reaction mixture (compound **5**). [d] Isolated yield. [e] Only trace amounts of the desired azide were observed. [f] Compound **10** was also obtained in 48% yield. [g] Tricyclic adduct **13** was also observed in the ^{1}H NMR spectrum of the crude mixture in a 10:1 ratio with respect to **12**. [h] Compound **27α** was obtained in 77% yield by treatment of **19α** with PMB-Cl and NaH in DMF. [i] Isolated yield for compounds **19**. [j] The reaction was carried out at 40 °C.

Tripropargyl derivative **11** was synthesized from levoglucosan under classical Williamson conditions in the presence of NaH and propargyl bromide in almost quantitative yield (Scheme 1). Trisilylated compound **8** was then obtained by treatment of **11** with TMSCl, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and AgOTf. It is noteworthy that the application of classical silylation conditions[14] using a catalytic amount of AgCl or $AgNO_3$ led to incomplete conversion even after several days. Alcohol **22**, obtained by chemoselective monodebenzylation of mannosan **18**,[15] was converted into the corresponding triflate derivative, which was subsequently reduced with nBu$_4$NBH$_4$ to give 2-deoxyglucosan **20**.[16] Per-*O*-benzyl maltosan **16** was prepared by treatment of D-maltose with 2-chloro-1,3-dimethylimidazolinium chloride in the presence of triethylamine[17] followed by benzylation of the remaining free hydroxyl groups. According to the optimization study results (Table 1), the evaluation of the scope of the ring-opening reaction was performed using 10 equiv. of $TMSN_3$ and 0.5 equiv. of TMSOTf in two different solvent systems at two different temperatures [conditions A: MeCN at room temperature; conditions B: toluene/MeCN (3:1) at 40 °C]. The tri-*O*-acetyl analogue of compound **1**, 1,6-anhydro sugar **4**, was first evaluated as a challenging substrate (Table 2, entries 3 and 4). It was anticipated that the presence of three electron-withdrawing groups could strongly disfavour the ring-opening process and the formation of a transient oxocarbenium intermediate. In addition, the possibility of neighbouring group participation of the 2-*O*-acyl protecting group was expected to influence the anomeric stereocontrol during the reaction. Under conditions requiring prolonged reaction time and heating (conditions B), very slow conversion of 1,6-anhydro sugar **4** was observed and only trace amounts of the desired product could be detected by ^{1}H NMR spectroscopic analysis after several days (Table 2, entry 4). Satisfactorily, conditions A afforded the expected azido sugars **5** in 61% yield (entry 3). The complete loss of stereoselectivity at the anomeric position may be rationalized by the possible anchimeric assistance of the C-2 acetoxy group. It is indeed noteworthy that attempts to convert 1,6-anhydromannose **6**,[18] the C-2 epimeric analogue of **4**, into the corresponding azide failed even with prolonged reaction time and higher temperature (entry 5). Other challenging substrates bearing propargyl substituents were evaluated because of their interest in the context of click chemistry (entries 6–9). One serious side reaction expected for these substrates was intramolecular azide-alkyne cycloaddition, leading to the formation of triazole-fused tricyclic compounds.[19]

The reaction temperature and the presence of a silyl group on the *sp*-carbon were found to play an important role on the reaction outcome. TMSOTf-mediated ring opening of 1,6-anhydro sugar **8** at 40 °C in toluene/MeCN (3:1; conditions B) led to the formation of the expected triazole-fused tricyclic compound **10** as the major product along with α-glycosyl azide **9α**, whereas only the desired azide **12α** was obtained from the corresponding unsilylated substrate **11** at room temperature (Scheme 2 and Table 2,

entries 7 and 8). Competing formation of the cycloadduct **10** was almost totally suppressed by lowering the reaction temperature to 20 °C and by using MeCN as solvent (conditions A). Following these experimental conditions, we were able to isolate α-glycosyl azide **9α** in 82% yield (entry 6). Efficient conversion of glucoside azide **12α** into the tricyclic adduct **13** in a good yield of 72% could be realized by heating to reflux in toluene (Scheme 2).



Scheme 2. *Reagents and conditions:* (a) $TMSN_3$ (10 equiv.), TMSOTf (0.5 equiv.), toluene/CH_3CN (3:1), 40 °C, 45 h; (b) toluene, 80 °C, 19 h.

Our procedure was then applied to 2-azido glucosan **14**,[15] with the aim of obtaining bisazide **15** as a potential precursor of aminoglycoside conjugates,[20] and also to per-*O*-benzyl maltosan **16**. The reaction proceeded successfully to provide the expected glycosyl azides in 66–88% yields, albeit with lower diastereoselectivity (Table 2, entries 10–12). The strong influence of the configuration and substitution at C-2 on the stereochemical outcome of the azidation reaction was further demonstrated with mannosan **18**[21] and 2-deoxyglucosan **20**, which provided the expected glycosyl azides in high yields but with significant loss of diastereoselectivity (entries 13–15). Satisfactorily, the reaction could also be performed with partially unprotected substrate, as demonstrated by the efficient conversion of 2-OH-free anhydro sugar **22** into mannosyl azide **23** in 82% yield (entry 16).

On the basis of the results obtained, the stereochemical outcome of the ring-opening reactions may be rationalized by considering the stability and the reactivity of the intermediate glycosyl oxocarbenium ion conformers in an S_N1-like mechanism and that the reaction is conducted under kinetic control (Figure 2).[22] Zhu et al. have recently reported the synthesis of α-glycosyl thiols by TMSOTf ring-opening of 1,6-anhydro sugars using $(TMS)_2S$ as the thio-nucleophile source in high stereoselectivity.[23] The authors postulated a concerted S_N2-type process on the basis, *inter alia*, that the presence of a participating neighbouring group at C-2 has no influence on the stereochemical outcome of the reaction. In sharp contrast, a significant (or complete) loss of stereoselectivity was observed for the $TMSN_3$ ring-opening of tri-*O*-acetyl glucosan **4**, 2-deoxy glycosan **20** or tri-*O*-benzyl mannosan **18**. According to Woerpel's model,[22] the α-selectivity observed in the D-*gluco* series may be due to attack of the incoming nucleophile on the diastereotopic face of the most favoured and/or reactive half-chair of the glucosyl cation intermediate along a preferential axial trajectory that leads to the chair product (Figure 2). The highly α-selective ring-opening of tri-*O*-alkyl glucosan substrates (compounds **1**, **8** and **11**) may be rationalized by considering that the intermediate glycosyl cations adopt predominantly the $^4H_3$ conformation **A** in which all the substituents are pseudoequatorial. In addition, the approach of the nucleophile from the stereoelectronically favoured face is not impeded by sugar substituents, in contrast to axial attack on conformers **B**. In pyranosyl oxocarbenium cations, it has been shown that alkoxy groups at C-2 favour equatorial positions, probably due to hyperconjugation between the electron-donating C–H bond and the 2p orbital on the electrophilic carbon atom.[22,24] The lower diastereoselectivity observed in the 2-deoxy D-*gluco* or D-*manno* series (compounds **18**, **20** and **22**) may thus be explained by a reduced stabilization of the $^4H_3$ conformers **C** and/or increased stabilization of the $^3H_4$ conformers **D**. However, the magnitude of selectivity is difficult to anticipate. In addition, alkoxy groups at C-3 and C-4 exhibit a larger preference for the pseudoaxial conformers, mainly to allow stabilization of the electron-depleted anomeric centre.[22,25]

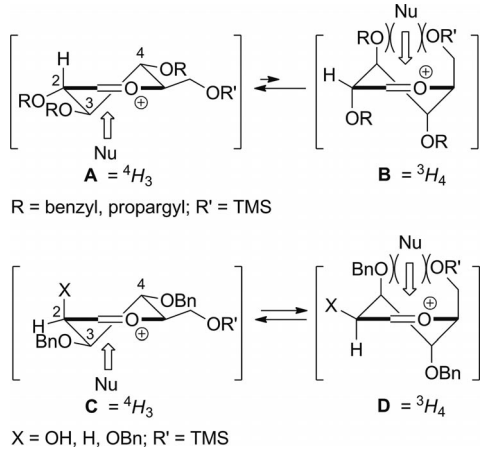
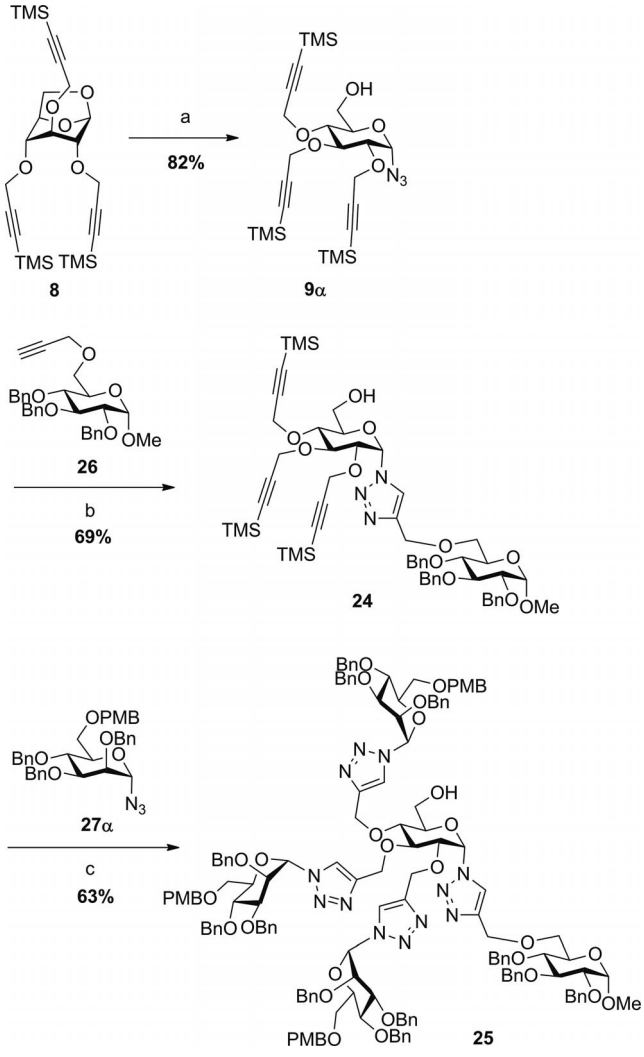


Figure 2. Stereoselective nucleophilic attack on intermediate oxocarbenium ion conformers.

The synthetic potential of the $TMSN_3$ ring-opening strategy was then demonstrated by the rapid synthesis of pseudopentasaccharide **25** in three steps from anhydro sugar **8** following a "click-click" approach[26] (Scheme 3). α-Glucosyl azide **9α**, which was obtained in good yield and high diastereoselectivity from **8** as described above, was treated with methyl 6-*O*-propargyl glucopyranoside **26**[27] in the presence of $CuSO_4$ and sodium ascorbate to yield the corresponding adduct **24**. Compound **24** was then desilylated in situ with tetra-*n*-butylammonium fluoride (TBAF) to form the corresponding disaccharide bearing three terminal alkyne units, with which 6-*O*-PMB α-mannosyl azide **27α**, obtained in two steps from the corresponding anhydro

sugar **18**, was subsequently clicked. This second click reaction, performed in a one-pot process, afforded the desired pseudopentasaccharide **25** with a free primary hydroxyl group in 63% yield (not optimized). Beyond the brevity of the synthesis, another advantage of the $TMSN_3$ ring-opening strategy lies in the release of a hydroxyl group at the C-6 position, which may be further functionalized or orthogonally protected.



Scheme 3. *Reagents and conditions:* (a) $TMSN_3$ (10 equiv.), TMSOTf (0.5 equiv.), CH_3CN, room temp., 16 h; (b) $CuSO_4{\cdot}5H_2O$ (0.5 equiv.), Na ascorbate (1 equiv.), Na_2CO_3 (0.5 equiv.), **26** (1.3 equiv.), THF/H_2O (1:1), room temp., 16 h; (c) TBAF (4 equiv.), $CuSO_4{\cdot}5H_2O$ (0.3 equiv.), Na ascorbate (0.5 equiv.), Na_2CO_3 (0.3 equiv.), **27α** (4.5 equiv.), DMF/H_2O (3.6:1), MW 100 °C, 1 h.

Conclusions

We have reported a new access to α-glycosyl azides by way of $TMSN_3$ ring-opening of 1,6-anhydro sugars in 61 to 95% yield. The reaction has been successfully applied to deactivated substrates bearing up to three electron-withdrawing groups. The level of diastereoselectivity was found to be influenced by the absolute configuration and substitution at C-2 but high diastereoselectivity could nevertheless be achieved in the D-*gluco* series.[28] The α-selectivity observed may be rationalized in part by preferential nucleophilic attack along axial trajectories on the most favoured or reactive half-chair of the glycosyl cation intermediate according to Woerpel's model.[22] The application of this methodology for rapid access to relatively complex oligosaccharides in the context of click chemistry has been demonstrated by the synthesis of a pseudopentasaccharide in five steps from commercially available levoglucosan. Further synthetic applications of this reaction for the preparation of complex neoglycoconjugates are under investigation in our laboratory.[29]

Experimental Section

General Information: THF was dried by passage through an activated alumina column under an atmosphere of argon. CH_2Cl_2 was distilled from CaH_2 under an atmosphere of argon. Pyridine was distilled from KOH under an atmosphere of argon and stored over KOH. The reactions under microwave irradiation were conducted in a Biotage Initiator device. All reactions conducted under anhydrous conditions were performed in standard glassware under an atmosphere of argon. Flash chromatography was performed either on silica gel 60 (230–400 mesh, 0.040–0.063 mm) or using an automatic flash chromatography device. Thin-layer chromatography (TLC) was performed on aluminium sheets coated with silica gel 60 F254. Spots were visualized by staining with aqueous $KMnO_4$ solution or phosphomolybdic acid/cerium stain. NMR spectra were recorded with a 300 MHz or 400 MHz spectrometer with solvent peaks as reference. Carbon multiplicities were assigned on the basis of distortionless enhancement by polarization transfer (DEPT) experiments. The ^1H signals were assigned by 2D experiments (COSY). ESI-HRMS was carried out with a TOF spectrometer. IR spectra (cm^{-1}) were recorded with a Perkin–Elmer Spectrum One spectrophotometer.

General Procedure for the Synthesis of Glycosyl Azides: To a stirred solution of anhydro sugar (231 μmol) in MeCN (conditions A) or in toluene/MeCN (3:1; conditions B) (2.3 mL) were added successively $TMSN_3$ (2.31 mmol, 303 μL) and TMSOTf (116 μmol, 21 μL) at room temp. The mixture was then stirred at room temp. (conditions A) or 40 °C (conditions B). When TLC analysis showed complete conversion of the anhydro sugar, the reaction was quenched with sat. $NaHCO_3$ (25 mL). EtOAc (25 mL) was added, the layers were separated and the organic phase was washed with sat. $NaHCO_3$ (2 × 25 mL), then a few drops of conc. HCl were added along with MeOH (2 mL). After brief shaking, the organic mixture was finally washed with water (25 mL) and brine (25 mL), dried with Na_2SO_4, filtered and concentrated. The crude residue was purified by flash chromatography on silica gel (EtOAc/PE) to afford the desired 1-azidosugars.

1-Azido-2,3,4-tri-*O*-benzyl-D-glucopyranoses (2): Compounds **2** (100 mg, 231 μmol) were synthesized from **1** as described in the general procedure. The resulting crude product was purified to provide **2α** (87.5 mg, 80%) and **2β** (8.4 mg, 8%) as white solids.

Compound 2α: R_f = 0.39 (toluene/acetone, 9:1); m.p. 62.0–64.0 °C. $[\alpha]_D^{26}$ = +95.5 (*c* = 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.47–7.24 (m, 15 H, ArH), 5.17 (d, *J* = 4.1 Hz, 1 H, 1-H), 5.00–4.60 (m, 6 H, CH_2Ph), 3.90 (t, *J* = 9.1 Hz, 1 H, 3-H), 3.83–3.67 (m, 3 H, 5-H, 6-H), 3.59 (dd, *J* = 9.1, 4.2 Hz, 1 H, 2-H), 3.55 (t, *J*

= 9.1 Hz, 1 H, 4-H), 1.57 (br. s, 1 H, OH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 138.6, 138.1, 137.7, 128.8 (2), 128.7 (2), 128.6 (2), 128.4, 128.3 (2), 128.2 (2), 128.12, 128.09 (2), 127.9, 88.1, 81.8, 79.7, 76.7, 76.0, 75.2, 74.0, 73.3, 61.6 ppm. IR (neat): $\tilde{\nu}$ = 3462 (broad, O–H), 2111 (N_3) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{27}H_{29}O_5N_3$ [M + Na]$^+$ 498.200; found 498.199.

Compound 2β: R_f = 0.50 (toluene/acetone, 9:1); m.p. 77.0–79.0 °C. $[\alpha]_D^{29}$ = +2.4 (*c* = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.23 (m, 15 H, ArH), 4.96–4.62 (m, 6 H, OCH_2Ph), 4.67 (d, *J* = 8.7 Hz, 1 H, 1-H), 3.90 (ddd, *J* = 12.0, 5.3, 2.4 Hz, 1 H, 6-Ha), 3.73 (ddd, *J* = 12.0, 7.8, 4.1 Hz, 1 H, 6-Hb), 3.69 (t, *J* = 8.9 Hz, 1 H, 3-H), 3.60 (dd, *J* = 9.4, 8.9 Hz, 1 H, 4-H), 3.45 (ddd, *J* = 9.4, 4.1, 2.5 Hz, 1 H, 5-H), 3.34 (dd, *J* = 9.3, 8.7 Hz, 1 H, 2-H), 1.81 (dd, *J* = 7.8, 5.3 Hz, 1 H, OH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 138.4, 137.9, 137.8, 128.7 (2), 128.63 (2), 128.61 (2), 128.3 (2), 128.21 (2), 128.18, 128.1, 127.9 (3), 90.4, 84.9, 81.9, 77.5, 77.2, 75.9, 75.4, 75.3, 61.8 ppm. IR (neat): $\tilde{\nu}$ = 3439 (broad, OH), 2115 (N_3) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{27}H_{29}O_5N_3$ [M + Na]$^+$ 498.200; found 498.198.

1-Azido-2,3,4-tri-*O*-acetyl-D-glucopyranoses (5): Compound **4** was treated as described in the general procedure and the reaction mixture was stirred for 5 d at 40 °C (conditions A with heating). We were not able to separate the diastereomers. Data for the 1:1 mixture: R_f = 0.33 (toluene/acetone, 8:2). $[\alpha]_D^{27}$ = +67.1 (*c* = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.62 (d, *J* = 4.3 Hz, 1 H, 1α-H), 5.44 (t, *J* = 9.9 Hz, 1 H, 3α- or β-H), 5.26 (t, *J* = 9.9 Hz, 1 H, 3α or β-H), 5.10–4.98 (m, 2 H, 4 α and β-H), 4.96–4.88 (m, 2 H, 2α and β-H), 4.67 (d, *J* = 9.0 Hz, 1 H, 1β-H), 3.94 (ddd, *J* = 10.2, 3.6, 2.2 Hz, 1 H, 5α or β-H), 3.83–3.70 (m, 2 H, 6α or β-H), 3.67–3.54 (m, 3 H, 5α or β-H, 6α or β-H), 2.38 (t, *J* = 7.0 Hz, 2 H, O6α and β-H), 2.10–1.98 (6× s, 18 H, CH_3CO α and β) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 170.6, 170.3, 170.2, 170.1, 170.0, 169.4, 88.0, 86.4, 76.5, 72.6, 71.8, 70.9, 70.5, 69.4, 68.4, 68.3, 61.2, 60.9, 20.8–20.5 (6) ppm. IR (neat): $\tilde{\nu}$ = 3483 (broad, O–H), 2117 (N_3), 1747 (C=O) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{12}H_{17}O_8N_3$ [M + Na]$^+$ 354.091; found 354.089.

1,6-Anhydro-2,3,4-tri-*O*-propargyl-D-glucopyranose (11): To a stirred solution of 1,6-anhydro-D-glucopyranose (1.00 g, 6.17 mmol) in anhydrous DMF (60 mL) was carefully added sodium hydride (60% in oil, 2.22 g, 55.5 mmol) at 0 °C. The mixture was stirred for 20 min until gas release ceased. The flask was then protected from light and propargyl bromide (5.98 mL, 80% in toluene, 55.5 mmol) was added over 2 min, keeping the temperature at 0 °C. The ice-water bath was removed and the mixture, which rapidly became brown, was stirred for 39 h at room temp. The reaction was quenched by addition of MeOH. A saturated solution of NH_4Cl (100 mL) was added and the aqueous mixture was extracted with EtOAc (4× 50 mL). The combined organic phases were washed with brine (2× 30 mL), then dried with Na_2SO_4, filtered and the filtrate was concentrated under vacuum. The resulting residue was purified by flash chromatography (EtOAc/PE, 1:4 to 1:1) to afford **11** (1.70 g, 99.8%) as a green oil. R_f = 0.40 (EtOAc/PE, 3:7). $[\alpha]_D^{29}$ = –52.8 (*c* = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.46 (s, 1 H, 1-H), 4.61 (d, *J* = 5.7 Hz, 1 H, 5-H), 4.39–4.22 (m, 6 H, O-CH_2C≡C), 3.97 (d, *J* = 7.4 Hz, 1 H, 6-Ha), 3.77 (s, 1 H, 3-H), 3.68 (dd, *J* = 7.3, 5.7 Hz, 1 H, 6-Hb), 3.62 (s, 1 H, 2-H), 3.53 (s, 1 H, 4-H), 2.46 (m, 3 H, C≡CH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 100.4, 79.5 (2), 79.4, 76.1, 75.6 (2), 75.3 (2), 75.1, 74.2, 65.5, 57.9, 57.5, 56.8 ppm. IR (neat): $\tilde{\nu}$ = 3283 (sharp, CC–H), 2117 (weak, C≡C) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{15}H_{16}O_5$ [M + Na]$^+$ 299.089; found 299.088.

1,6-Anhydro-2,3,4-tri-*O*-(trimethylsilylpropargyl)-D-glucopyranose (8): A stirred solution of **11** (1.51 g, 5.45 mmol) and silver triflate (140 mg, 0.545 mmol) in anhydrous THF (54 mL) was heated to reflux. DBU (4.07 mL, 27.25 mmol) was added and the mixture was stirred and heated to reflux for 10 min before adding chlorotrimethylsilane (6.92 mL, 54.5 mmol). The mixture was then stirred and heated for 20 h. After cooling to room temp., EtOAc (100 mL) and sat. $NaHCO_3$ (100 mL) were added to the mixture and the phases were separated. The aqueous phase was further extracted with EtOAc (2× 30 mL) and the combined organic phases were successively washed with sat. $NaHCO_3$ (2× 30 mL), 1.0 M HCl (2× 30 mL) and brine (2× 30 mL), then dried with Na_2SO_4, filtered and concentrated. The resulting residue was purified by flash chromatography to afford **8** (2.08 g, 77%) as a pale-green oil. R_f = 0.72 (EtOAc/PE, 1:4). $[\alpha]_D^{22}$ = –28.7 (*c* = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.46 (s, 1 H, 1-H), 4.62 (d, *J* = 5.6 Hz, 1 H, 5-H), 4.39–4.22 (m, 6 H, O-CH_2C≡C), 3.97 (d, *J* = 7.3 Hz, 1 H, 6-Ha), 3.73 (s, 1 H, 3-H), 3.68 (dd, *J* = 7.3, 5.8 Hz, 1 H, 6-Hb), 3.59 (s, 1 H, 2-H), 3.52 (s, 1 H, 4-H), 0.20–0.10 (m, 27 H, TMS) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 101.4, 101.3, 101.2, 100.5, 92.3, 92.2, 91.9, 76.4, 75.8 (2), 74.4, 65.6, 58.7, 58.2, 57.8, –0.1 (9) ppm. IR (neat): $\tilde{\nu}$ = 2178 (weak, C≡C), 1715 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{24}H_{40}O_5Si_3$ [M + Na]$^+$ 515.208; found 515.205.

1-Azido-2,3,4-tri-*O*-(trimethylsilylpropargyl)-α-D-glucopyranose (9α): Compound **9α** (232.7 mg, 472 μmol) was synthesized from **8** as described in the general procedure. The resulting crude product was purified to provide **9α** (208.6 mg, 82%) as a pale-green oil. R_f = 0.61 (EtOAc/PE, 15:85). $[\alpha]_D^{20}$ = +119.5 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.59 (d, *J* = 4.0 Hz, 1 H, 1-H), 4.55–4.17 (m, 6 H, OCH_2C≡C), 3.84 (m, 2 H, 6-H), 3.69 (m, 1 H, 5-H), 3.68 (dd, *J* = 9.5, 8.9 Hz, 1 H, 3-H), 3.59 (dd, *J* = 9.5, 4.0 Hz, 1 H, 2-H), 3.49 (dd, *J* = 9.8, 8.9 Hz, 1 H, 4-H), 2.12 (t, *J* = 6.3 Hz, 1 H, OH), 0.2–0.1 (m, 27 H, TMS) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 102.4, 101.8, 101.5, 92.6, 91.7, 91.3, 88.1, 81.4, 80.1, 75.1, 73.0, 61.6, 61.3, 60.7, 60.0, –0.1 (3), –0.2 (6) ppm. IR (neat): $\tilde{\nu}$ = 3542 (broad, O–H), 2177 (weak, C≡C), 2114 (N_3) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{24}H_{41}O_5N_3Si_3$ [M + Na]$^+$ 558.225; found 558.223.

Compound 10: R_f = 0.47 (EtOAc/PE, 2:3). $[\alpha]_D^{26}$ = +72.5 (*c* = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.05 (d, *J* = 4.4 Hz, 1 H, 1-H), 5.19 (d, *J* = 15.5 Hz, 1 H, 7-Ha), 4.82 (d, *J* = 15.5 Hz, 1 H, 7-Hb), 4.43 (s, 2 H, OCH_2C≡C), 4.36 (s, 2 H, OCH_2C≡C), 4.25 (dd, *J* = 5.7, 4.4 Hz, 1 H, 2-H), 4.11 (dd, *J* = 5.7, 4.5 Hz, 1 H, 3-H), 3.92–3.70 (m, 3 H, 4-H, 6-H), 3.64 (ddd, *J* = 9.1, 4.2, 2.6 Hz, 1 H, 5-H), 0.30 (s, 9 H, TMS-triazole), 0.17–0.16 (2× s, 18 H, TMS) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 139.8, 136.9, 101.1, 101.0, 92.9, 92.4, 78.0, 75.5, 74.6, 73.3, 72.8, 61.7, 60.8, 59.4, 58.9, –0.1 (3), –0.2 (3), –1.1 (3) ppm. IR (neat): $\tilde{\nu}$ = 3403 (broad, O–H), 2177 (weak, C≡C) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{24}H_{41}O_5N_3Si_3$ [M + Na]$^+$ 558.225; found 558.223.

1-Azido-2,3,4-tri-*O*-propargyl-α-D-glucopyranose (12α): Compound **11** was treated as described in the general procedure and the reaction mixture was stirred for 3 h at room temp. (conditions A), or for 20 h at 40 °C (conditions B). R_f = 0.63 (toluene/acetone, 3:1). $[\alpha]_D^{20}$ = +181.4 (*c* = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.54 (d, *J* = 4.1 Hz, 1 H, 1-H), 4.49–4.24 (m, 6 H, OCH_2C≡C), 3.85 (br. s, 2 H, 6-H), 3.73 (d, *J* = 9.9 Hz, 1 H, 5-H), 3.72 (t, *J* = 9.3 Hz, 1 H, 3-H), 3.63 (dd, *J* = 9.3, 4.1 Hz, 1 H, 2-H), 3.50 (t, *J* = 9.3 Hz, 1 H, 4-H), 2.49 (m, 3 H, C≡CH), 2.00 (br. s, 1 H, OH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 87.8, 81.0, 80.1, 79.9, 79.5, 79.2, 75.7, 75.6, 74.8, 74.6, 72.9, 61.4, 60.5, 60.1, 59.1 ppm. IR (neat): $\tilde{\nu}$ = 3474 (broad, O–H), 3292 (sharp, CC–H), 2114 (N_3) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{15}H_{17}O_5N_3$ [M + Na]$^+$ 342.106; found 342.103.

Compound 13: A solution of **12α** (43.6 mg, 137 μmol) in toluene (6.5 mL) was heated to reflux for 19 h. The solvent was removed under vacuum and the crude residue was purified by flash chromatography to afford **13** (31.5 mg, 72%) as a colourless oil. R_f = 0.14 (toluene/acetone, 7:3). $[\alpha]_D^{20}$ = +104.2 (*c* = 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.53 (s, 1 H, 8-H), 6.06 (d, *J* = 4.3 Hz, 1 H, 1-H), 5.21 (d, *J* = 15.6 Hz, 1 H, 7-Ha), 4.85 (d, *J* = 15.6 Hz, 1 H, 7-Hb), 4.46 (d, *J* = 2.4 Hz, 2 H, $OCH_2C{\equiv}C$), 4.37 (d, *J* = 2.4 Hz, 2 H, $OCH_2C{\equiv}C$), 4.28 (dd, *J* = 5.8, 4.4 Hz, 1 H, 2-H), 4.14 (dd, *J* = 5.9, 4.8 Hz, 1 H, 3-H), 3.87 (dd, *J* = 12.5, 2.6 Hz, 1 H, 6-Ha), 3.85 (dd, *J* = 9.1, 4.8 Hz, 1 H, 4-H), 3.75 (dd, *J* = 12.5, 4.1 Hz, 1 H, 6-Hb), 3.62 (ddd, *J* = 9.1, 4.1, 2.6 Hz, 1 H, 5-H), 2.66 (br. s, 1 H, OH), 2.53 (t, *J* = 2.4 Hz, 1 H, C≡CH), 2.51 (t, *J* = 2.4 Hz, 1 H, C≡CH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 131.5, 128.1, 79.33, 79.27, 78.2, 75.9, 75.4, 75.3, 74.6, 73.4, 73.0, 61.4, 59.8, 58.7, 58.2 ppm. IR (neat): $\tilde{\nu}$ = 3390 (broad, O–H), 3280 (sharp, CC–H), 2116 (weak, C≡C) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{15}H_{17}O_5N_3$ $[M + Na]^+$ 342.106; found 342.105.

1,2-Diazido-3,4-di-*O*-benzyl-D-glucopyranoses (15): Compounds **15** (88.4 mg, 241 μmol) were synthesized from **14** as described in the general procedure. The resulting crude product was purified to provide **15α** (65.9 mg, 67%) and **15β** (21.0 mg, 21%) as bright-orange oils.

Compound 15α: R_f = 0.20 (EtOAc/PE, 1:4). $[\alpha]_D^{22}$ = +98.3 (*c* = 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.28 (m, 10 H, ArH), 5.40 (d, *J* = 4.1 Hz, 1 H, 1-H), 4.91 (d, *J* = 10.7 Hz, 1 H, OCH_2Ph), 4.88 (d, *J* = 11.1 Hz, 1 H, OCH_2Ph), 4.87 (d, *J* = 10.7 Hz, 1 H, OCH_2Ph), 4.70 (d, *J* = 11.1 Hz, 1 H, OCH_2Ph), 3.88 (dd, *J* = 10.0, 9.3 Hz, 1 H, 3-H), 3.89–3.71 (m, 3 H, 5-H, 6-H), 3.65 (dd, *J* = 9.6, 9.3 Hz, 1 H, 4-H), 3.55 (dd, *J* = 10.0, 4.1 Hz, 1 H, 2-H), 1.73 (br. s, 1 H, OH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 137.7, 137.6, 128.7 (2), 128.6 (2), 128.24 (2), 128.19, 128.14, 128.0 (2), 88.3, 80.4, 77.4, 75.8, 75.2, 73.8, 63.3, 61.3 ppm. IR (neat): $\tilde{\nu}$ = 3452 (broad, O–H), 2106 (N_3) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{20}H_{22}O_4N_6$ $[M + Na]^+$ 433.159; found 433.157.

Compound 15β: R_f = 0.35 (EtOAc/PE, 1:4). $[\alpha]_D^{22}$ = –36.6 (*c* = 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.27 (m, 10 H, ArH), 4.90 (d, *J* = 10.7 Hz, 1 H, OCH_2Ph), 4.86 (d, *J* = 11.1 Hz, 1 H, OCH_2Ph), 4.85 (d, *J* = 10.7 Hz, 1 H, OCH_2Ph), 4.68 (d, *J* = 11.1 Hz, 1 H, OCH_2Ph), 4.54 (d, *J* = 9.0 Hz, 1 H, 1-H), 3.90 (br. d, *J* = 12.5 Hz, 1 H, 6-Ha), 3.75 (m, 1 H, 6-Hb), 3.64 (t, *J* = 9.6 Hz, 1 H, 4-H), 3.51 (t, *J* = 9.6 Hz, 1 H, 3-H), 3.43 (ddd, *J* = 9.6, 3.9, 2.5 Hz, 1 H, 5-H), 3.29 (dd, *J* = 9.6, 9.0 Hz, 1 H, 2-H), 1.83 (br. s, 1 H, OH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 137.7 (2), 128.73 (2), 128.66 (2), 128.26, 128.24 (2), 128.20, 128.1 (2), 89.4, 83.4, 77.7, 77.0, 75.9, 75.3, 66.3, 61.5 ppm. IR (neat): $\tilde{\nu}$ = 3468 (broad, O–H), 2106 (N_3) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{20}H_{22}O_4N_6$ $[M + Na]^+$ 433.159; found 433.159.

1,6-Anhydro-2,3,2′,3′,4′,6′-hexa-*O*-benzyl-D-maltopyranose (16): To a solution of D-maltose (1.0 g, 2.78 mmol) and triethylamine (3.37 mL, 25 mmol) in water (56 mL) at 0 °C was added 2-chloro-1,3-dimethylimidazolium chloride (1.41 g, 8.33 mmol). The mixture was stirred for 1 h at 0 °C and then for 15 h at room temperature. The aqueous phase was washed with CH_2Cl_2 (4× 25 mL), the pH was raised to 10 with 10% NaOH solution, and the aqueous phase was further washed with CH_2Cl_2 (3× 25 mL). The water phase was neutralized with 1 M HCl, concentrated and co-evaporated with toluene. The residue was diluted in MeOH, filtered through silica gel and concentrated to afford a pale-green solid. This solid was dissolved in DMF (28 mL) and benzyl bromide (3.3 mL, 27.8 mmol) and sodium hydride (60% in oil, 1.33 g, 33.4 mmol) were successively added. The suspension was stirred for 6 h at room temperature and then quenched with a few drops of MeOH. Water (60 mL) and EtOAc (50 mL) were added and the layers were separated. The aqueous phase was further extracted with EtOAc (2× 50 mL) and the combined organic phases were washed with sat. NH_4Cl (50 mL) and brine (50 mL), dried with Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography to afford pure **16** (777 mg, 32%) as a colourless oil. R_f = 0.23 (EtOAc/PE, 1:4). $[\alpha]_D^{22}$ = +8.9 (*c* = 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.12 (m, 30 H, ArH), 5.49 (s, 1 H, 1-H), 5.03 (d, *J* = 3.6 Hz, 1 H, 1′-H), 4.98 (d, *J* = 10.9 Hz, 1 H, OCH_2Ph), 4.88 (d, *J* = 10.9 Hz, 1 H, OCH_2Ph), 4.83 (d, *J* = 10.9 Hz, 1 H, OCH_2Ph), 4.74 (d, *J* = 6.0 Hz, 1 H, 5-H), 4.70–4.42 (m, 9 H, OCH_2Ph), 4.20–4.02 (m, 2 H, 3′-H, 4′-H), 3.93 (d, *J* = 7.3 Hz, 1 H, 6-Ha), 3.77–3.53 (m, 7 H, 3-H, 4-H, 6-Hb, 2′-H, 5′-H, 6′-H), 3.41 (d, *J* = 2.3 Hz, 1 H, 2-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 139.0, 138.43, 138.38, 138.2, 138.02, 137.97, 128.7–127.5 (30), 100.9, 98.0, 81.9, 79.7, 78.5, 78.0, 77.4, 77.1, 75.8, 75.4, 75.1, 73.6, 72.9, 72.3, 71.6, 71.0, 68.9, 66.0 ppm. HRMS (ESI): *m*/*z* calcd. for $C_{54}H_{56}O_{10}$ $[M + Na]^+$ 887.377; found 887.377.

1-Azido-2,3,2′,3′,4′,6′-hexa-*O*-benzyl-D-maltopyranoses (17): Compound **16** was treated as described in the general procedure and the reaction mixture was stirred for 27 h at room temp. (conditions A) or for 41 h at 40 °C (conditions B).

Compound 17α: R_f = 0.38 (EtOAc/PE, 3:7). $[\alpha]_D^{22}$ = +81.9 (*c* = 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.46–7.00 (m, 30 H, ArH), 5.74 (d, *J* = 3.9 Hz, 1 H, 1′-H), 5.20 (d, *J* = 4.1 Hz, 1 H, 1-H), 5.02–4.39 (m, 12 H, OCH_2Ph), 4.15–3.73 (m, 7 H, 3-H, 4-H, 5-H, 6-H, 3′-H, 5′-H), 3.71–3.61 (m, 2 H, 2-H, 6′-Ha), 3.54–3.43 (m, 2 H, 2′-H, 6′-Hb), 3.37 (dd, *J* = 9.9, 9.0 Hz, 1 H, 4′-H), 3.07 (br. t, *J* = 6.3 Hz, 1 H, OH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 139.0, 138.6, 138.0, 137.9, 137.4, 137.3, 128.9–126.3 (30), 97.7, 87.9, 82.1, 81.6, 79.9, 79.2, 78.3, 75.7, 75.2, 74.3, 73.8, 73.7 (2), 73.0, 72.0, 71.8, 68.9, 60.8 ppm. IR (neat): $\tilde{\nu}$ = 3493 (broad, O–H), 2112 (N_3) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{54}H_{57}O_{10}N_3$ $[M + Na]^+$ 930.394; found 930.394.

Compound 17β: R_f = 0.59 (EtOAc/PE, 3:7). $[\alpha]_D^{20}$ = +31.1 (*c* = 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.47–7.03 (m, 30 H, ArH), 5.67 (d, *J* = 3.9 Hz, 1 H, 1′-H), 4.96–4.74 (m, 6 H, OCH_2Ph), 4.70 (d, *J* = 8.6 Hz, 1 H, 1-H), 4.64–4.40 (m, 6 H, OCH_2Ph), 4.12 (t, *J* = 9.3 Hz, 1 H, 4-H), 3.96–3.87 (m, 3 H, 6-H, 3′-H), 3.86–3.76 (m, 2 H, 3-H, 5′-H), 3.68 (dd, *J* = 10.2, 1.7 Hz, 1 H, 6′-Ha), 3.62–3.37 (m, 5 H, 2-H, 5-H, 2′-H, 4′-H, 6′-Hb), 2.76 (br. s, 1 H, OH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 138.7, 138.6, 138.02, 137.97, 137.6 (2), 128.7–126.2 (30), 97.7, 90.2, 84.9, 82.1, 82.0, 79.2, 78.1, 77.3, 75.7, 75.24, 75.17, 74.1, 73.7 (2), 72.3, 71.7, 68.7, 61.3 ppm. IR (neat): $\tilde{\nu}$ = 3480 (broad, O–H), 2113 (N_3) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{54}H_{57}O_{10}N_3$ $[M + Na]^+$ 930.394; found 930.394.

1-Azido-2,3,4-tri-*O*-benzyl-D-mannopyranoses (19): Compound **18** was treated as described in the general procedure and the reaction mixture was stirred for 1 h at room temp. (conditions A) or for 15.5 h at 40 °C (conditions B).

Compound 19α: R_f = 0.42 (EtOAc/PE, 3:7). $[\alpha]_D^{23}$ = +103.0 (*c* = 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.27 (m, 15 H, ArH), 5.34 (d, *J* = 1.9 Hz, 1 H, 1-H), 4.94 (d, *J* = 11.0 Hz, 1 H, OCH_2Ph), 4.77 (d, *J* = 12.2 Hz, 1 H, OCH_2Ph), 4.71–4.57 (m, 4 H, OCH_2Ph), 4.02 (t, *J* = 9.4 Hz, 1 H, 5-H), 3.92–3.72 (m, 4 H, 3-H, 4-H, 6-H), 3.64 (dd, *J* = 3.3, 1.9 Hz, 1 H, 2-H), 2.02 (br. s, 1 H, OH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 138.3, 138.2, 137.9, 128.63 (2), 128.58 (4), 128.14 (2), 128.08, 128.0 (2), 127.94, 127.89, 127.84 (2), 88.4, 79.2, 75.3, 74.9, 74.6, 74.2, 73.2, 72.7, 62.2 ppm.

IR (neat): $\tilde{\nu}$ = 3468 (broad, O–H), 2111 (N_3) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{27}H_{29}O_5N_3$ [M + Na]$^+$ 498.200; found 498.197.

Compound 19β: R_f = 0.35 (EtOAc/PE, 3:7). $[\alpha]_D^{23}$ = –73.2 (*c* = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47–7.24 (m, 15 H, ArH), 4.93 (d, *J* = 11.0 Hz, 1 H, OCH_2Ph), 4.93 (d, *J* = 11.6 Hz, 1 H, OCH_2Ph), 4.84 (d, *J* = 11.6 Hz, 1 H, OCH_2Ph), 4.67 (d, *J* = 11.0 Hz, 1 H, OCH_2Ph), 4.65 (s, 2 H, OCH_2Ph), 4.45 (s, 1 H, 1-H), 3.98 (dd, *J* = 9.7, 9.5 Hz, 1 H, 4-H), 3.97–3.85 (m, 2 H, 2-H and 6-Ha), 3.78 (m, 1 H, 6-Hb), 3.57 (dd, *J* = 9.5, 2.7 Hz, 1 H, 3-H), 3.42 (ddd, *J* = 9.7, 5.0, 2.7 Hz, 1 H, 5-H), 2.06 (br. s, 1 H, OH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 138.1, 138.03, 137.99, 128.64 (2), 128.61 (2), 128.43 (2), 128.37 (2), 128.27 (2), 128.04, 127.99, 127.93, 127.7 (2), 86.8, 82.8, 78.2, 76.0, 75.5, 74.9, 74.2, 72.5, 62.3 ppm. IR (neat): $\tilde{\nu}$ = 3455 (broad, O–H), 2113 (N_3) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{27}H_{29}O_5N_3$ [M + Na]$^+$ 498.200; found 498.197.

1,6-Anhydro-2-deoxy-3,4-di-*O*-benzyl-D-glucopyranose (20): To a stirred solution of **22** (276.6 mg, 808 μmol) in anhydrous CH_2Cl_2 (1.4 mL) at –10 °C under an atmosphere of argon was added dropwise a solution of trifluoromethanesulfonic anhydride (1.0 M in CH_2Cl_2, 1.61 mL, 1.61 mmol) and anhydrous pyridine (163 μL, 2.02 mmol) in anhydrous CH_2Cl_2 (6.1 mL). The addition was performed over 6 min, then the mixture was stirred for 1 h at –10 °C. The reaction was quenched with cold sat. $NaHCO_3$ (25 mL) and CH_2Cl_2 (20 mL) was added. The organic phase was washed with water (2× 25 mL), dried with Na_2SO_4, filtered, concentrated to dryness and further dried under vacuum. The crude mixture was then diluted with toluene (5 mL) under an atmosphere of argon, tetrabutylammonium tetrahydroborate (631 mg, 2.45 mmol) was added and the mixture was stirred at room temp. for 2.25 h. HCl solution (1.0 M, 15 mL) was carefully added until gas release had ceased, then the aqueous mixture was extracted with CH_2Cl_2 (3× 30 mL). The combined organic phases were washed with water and brine (25 mL each), dried with Na_2SO_4, filtered and concentrated to dryness. The crude residue was purified by flash chromatography (EtOAc/PE, 1:4 to 2:3) to afford **20** (206.8 mg, 78%) as a colourless oil. Analytical data of **20** matched those reported.[16]

1-Azido-2-deoxy-3,4-di-*O*-benzyl-D-glucopyranoses (21): Compound **22** was treated as described in the general procedure and the reaction mixture was stirred for 3 h40 at room temp. (conditions A).

Compound 21α: R_f = 0.36 (toluene/acetone, 9:1). $[\alpha]_D^{20}$ = +218.2 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.23 (m, 10 H, ArH), 5.49 (dd, *J* = 3.2, *J* = 1.5 Hz, 1 H, 1-H), 4.95 (d, *J* = 11.1 Hz, 1 H, OCH_2Ph), 4.70 (d, *J* = 11.1 Hz, 1 H, OCH_2Ph), 4.66 (s, 2 H, OCH_2Ph), 3.90 (ddd, *J* = 11.3, 8.9, 4.6 Hz, 1 H, 3-H), 4.86–3.74 (m, 3 H, 5-H, 6-H), 3.55 (t, *J* = 8.9 Hz, 1 H, 4-H), 2.16 (ddd, *J* = 13.2, 4.6, 1.5 Hz, 1 H, 2-Ha), 1.78 (br. s, 1 H, OH), 1.70 (ddd, *J* = 13.2, 11.3, 4.2 Hz, 1 H, 2-Hb) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 138.4, 138.3, 128.61 (2), 128.58 (2), 128.2 (2), 128.0, 127.9, 127.8 (2), 87.4, 77.5, 76.8, 75.1, 73.8, 72.1, 62.0, 34.9 ppm. IR (neat): $\tilde{\nu}$ = 3460 (broad, O–H), 2107 (N_3) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{20}H_{23}O_4N_3$ [M + Na]$^+$ 392.158; found 392.159.

Compound 21β: R_f = 0.47 (toluene/acetone, 9:1). $[\alpha]_D^{20}$ = –27.9 (*c* = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.24 (m, 10 H, ArH), 4.95 (d, *J* = 10.9 Hz, 1 H, OCH_2Ph), 4.74–4.60 (m, 4 H, OCH_2Ph, 1-H), 3.90 (br. d, *J* = 11.8 Hz, 1 H, 6-Ha), 3.78 (m, 1 H, 6-Hb), 3.69 (ddd, *J* = 11.4, 8.7, 4.9 Hz, 1 H, 3-H), 3.53 (dd, *J* = 9.5, 8.7 Hz, 1 H, 4-H), 3.40 (ddd, *J* = 9.5, 4.3, 2.8 Hz, 1 H, 5-H), 2.31 (ddd, *J* = 12.8, 4.9, 2.1 Hz, 1 H, 2-Ha), 1.93 (br. t, *J* = 7.1 Hz, 1 H, OH), 1.60 (dt, *J* = 12.8, 11.2 Hz, 1 H, 2-Hb) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 138.2, 138.1, 128.6 (4), 128.2 (2), 128.1, 128.0, 127.8 (2), 86.6, 79.1, 77.7, 77.4, 75.3, 71.9, 62.2, 36.3 ppm. IR (neat): $\tilde{\nu}$ = 3453 (broad, O–H), 2109 (N_3) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{20}H_{23}O_4N_3$ [M + Na]$^+$ 392.158; found 392.158.

1-Azido-3,4-di-*O*-benzyl-D-mannopyranoses (23): Compound **22** was treated as described in the general procedure and the reaction mixture was stirred for 15 min at room temp. (conditions A).

Compound 23α: R_f = 0.18 (EtOAc/PE, 2:3). $[\alpha]_D^{23}$ = +175.7 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.27 (m, 10 H, ArH), 5.41 (d, *J* = 1.8 Hz, 1 H, 1-H), 4.88 (d, *J* = 10.9 Hz, 1 H, OCH_2Ph), 4.71 (d, *J* = 11.3 Hz, 1 H, OCH_2Ph), 4.69 (d, *J* = 10.9 Hz, 1 H, OCH_2Ph), 4.66 (d, *J* = 11.3 Hz, 1 H, OCH_2Ph), 3.98–3.74 (m, 6 H, 2-H, 3-H, 4-H, 5-H, 6-H), 3.05 (s, 1 H, O2-H), 2.43 (br. s, 1 H, O6-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 138.2, 137.6, 128.8 (2), 128.6 (2), 128.3, 128.1 (2), 128.04 (2), 127.99, 89.3, 79.1, 75.4, 74.0, 73.4, 72.5, 68.5, 61.7 ppm. IR (neat): $\tilde{\nu}$ = 3414 (broad, O–H), 2113 (N_3) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{20}H_{23}O_5N_3$ [M + Na]$^+$ 408.153; found 408.150.

Compound 23β: R_f = 0.36 (EtOAc/PE, 3:7). $[\alpha]_D^{23}$ = –33.6 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.22 (m, 10 H, ArH), 4.91 (d, *J* = 11.0 Hz, 1 H, OCH_2Ph), 4.74 (d, *J* = 11.8 Hz, 1 H, OCH_2Ph), 4.69 (d, *J* = 11.8 Hz, 1 H, OCH_2Ph), 4.68 (d, *J* = 11.0 Hz, 1 H, OCH_2Ph), 4.56 (s, 1 H, 1-H), 4.05 (d, *J* = 3.1 Hz, 1 H, 2-H), 3.98–3.86 (m, 2 H, 4-H, 6-Ha), 3.79 (dd, *J* = 12.0, 4.0 Hz, 1 H, 6-Hb), 3.60 (dd, *J* = 9.2, 3.1 Hz, 1 H, 3-H), 3.41 (ddd, *J* = 9.2, 4.2, 2.6 Hz, 1 H, 5-H), 2.78 (br. s, 1 H, O2-H), 2.33 (br. s, 1 H, O6-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 138.1, 137.5, 128.8 (2), 128.6 (2), 128.3, 128.2 (2), 128.1, 128.0 (2), 87.2, 81.5, 77.8, 75.5, 73.4, 72.1, 69.2, 61.9 ppm. IR (neat): $\tilde{\nu}$ = 3428, 2114 (N_3) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{20}H_{23}O_5N_3$ [M + Na]$^+$ 408.153; found 408.150.

Compound 24: To a solution of **9α** (208.6 mg, 389 μmol) and **26** (258.8 mg, 515 μmol) in THF (1 mL) was added a bright orange-yellow suspension of $CuSO_4{\cdot}5H_2O$ (49 mg, 195 μmol), sodium ascorbate (77 mg, 389 μmol) and Na_2CO_3 (21 mg, 195 μmol) in water (1 mL). The biphasic mixture was vigorously stirred for 16 h at room temperature, then EtOAc (50 mL) was added and the organic phase was washed with water (3× 25 mL). The solvents were evaporated and the residue was dissolved in a mixture of $CH_3CN/H_2O/NH_4OH$ (15:0.5:0.5) and filtered through a pad of silica gel. After concentration of the filtrate, the crude product was purified by flash chromatography (EtOAc/PE, 1:4 to 1:1) to afford pure **24** (278.2 mg, 69%) as a viscous colourless oil. R_f = 0.40 (EtOAc/PE, 1:1). $[\alpha]_D^{24}$ = +55.6 (*c* = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (s, 1 H, 8-H), 7.37–7.22 (m, 15 H, ArH), 6.19 (d, *J* = 5.8 Hz, 1 H, 1-H), 4.98 (d, *J* = 11.0 Hz, 1 H, OCH_2Ph), 4.83 (d, *J* = 10.8 Hz, 1 H, OCH_2Ph), 4.82 (d, *J* = 11.0 Hz, 1 H, OCH_2Ph), 4.78 (d, *J* = 12.2 Hz, 1 H, OCH_2Ph), 4.69 (d, *J* = 12.6 Hz, 1 H, $OCH_2C{\equiv}C$), 4.65 (d, *J* = 12.2 Hz, 1 H, OCH_2Ph), 4.62 (d, *J* = 12.6 Hz, 1 H, $OCH_2C{\equiv}C$), 4.60 (d, *J* = 3.5 Hz, 1 H, 1′-H), 4.58 (d, *J* = 16.4 Hz, 1 H, $OCH_2C{\equiv}C$), 4.54 (d, *J* = 10.8 Hz, 1 H, OCH_2Ph), 4.53 (t, *J* = 9.3 Hz, 1 H, 3-H), 4.46 (d, *J* = 16.4 Hz, 1 H, $OCH_2C{\equiv}C$), 4.41 (d, *J* = 15.8 Hz, 1 H, $OCH_2C{\equiv}C$), 4.36 (d, *J* = 15.8 Hz, 1 H, $OCH_2C{\equiv}C$), 4.22 (d, *J* = 16.6 Hz, 1 H, 7-Ha), 4.14 (d, *J* = 16.6 Hz, 1 H, 7-Hb), 4.04 (dd, *J* = 9.3, 5.8 Hz, 1 H, 2-H), 3.98 (t, *J* = 9.3 Hz, 1 H, 3′-H), 3.86 (ddd, *J* = 12.6, 6.3, 3.2 Hz, 1 H, 6-Ha), 3.82–3.66 (m, 5 H, 4-H, 5-H, 5′-H, 6′-H), 3.66 (ddd, *J* = 12.6, 7.7, 2.3 Hz, 1 H, 6-Hb), 3.59 (t, *J* = 9.3 Hz, 1 H, 4′-H), 3.53 (dd, *J* = 9.3, 3.5 Hz, 1 H, 2′-H), 3.36 (s, 3 H, MeO), 2.08 (br. dd, *J* = 7.8, 6.3 Hz, 1 H, OH), 0.20–0.17 (3× s, 27 H, TMS) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.2, 138.9, 138.3, 138.2, 128.53 (4), 128.45 (2), 128.2 (2), 128.1 (2), 128.0 (3), 127.8, 127.6, 124.9, 102.6, 101.8, 101.4, 98.3, 92.6, 91.7, 91.4, 84.0, 82.2, 82.0, 79.9, 78.6, 77.6, 75.8, 75.2, 75.1, 74.4, 73.5, 70.1, 69.3, 65.0, 61.24,

61.22, 60.5, 60.2, 55.3, –0.1 (6), –0.2 (3) ppm. IR (neat): ṽ = 3465 (O–H), 2177 (weak, C≡C) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{55}H_{75}O_{11}N_3Si_3$ $[M + Na]^+$ 1060.460; found 1060.459.

Compound 25: In a 5 mL microwave vial containing a solution of **24** (63.4 mg, 61 μmol) and **27α** (163.4 mg, 274 μmol) in DMF (2.67 mL) were added successively a bright yellow suspension of $CuSO_4{\cdot}5H_2O$ (4.6 mg, 18.3 μmol), sodium ascorbate (7.0 mg, 35.3 μmol) and Na_2CO_3 (3.1 mg, 29.2 μmol) in water (750 μL), and then a solution of TBAF (1.0 M in CH_2Cl_2, 244 μL, 244 μmol). The resulting suspension was heated under microwave irradiation at 100 °C for 1 h. The solvents were removed under vacuum, using toluene for co-evaporation of the remaining DMF. The residue was diluted in $CH_3CN/H_2O/NH_4OH$ (15:0.5:0.5) and filtered through a pad of silica gel to remove copper traces. After concentration of the filtrate, the crude brown oil was purified by flash chromatography (CH_2Cl_2/MeOH, 99:1) to afford the pure pseudopentasaccharide **25** as a viscous colourless oil (99.7 mg, 63%). R_f = 0.26 (CH_2Cl_2/MeOH, 99:1). $[\alpha]_D^{20}$ = +49.5 (*c* = 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.90 (s, 1 H, 8-H), 7.68 (s, 1 H, 8-H), 7.624 (s, 1 H, 8-H), 7.617 (s, 1 H, 8-H), 7.39–7.14 (m, 60 H, ArH), 7.13–7.05 (m, 6 H, ArH), 6.84–6.75 (m, 6 H, ArH), 6.01 (d, *J* = 3.5 Hz, 1 H, 1′′-H), 5.97 (d, *J* = 3.5 Hz, 1 H, 1′′-H), 5.92 (d, *J* = 5.7 Hz, 1 H, 1-H), 5.91 (d, *J* = 3.5 Hz, 1 H, 1′′-H), 5.07–4.30 (m, 43 H, 12 × OCH_2Ph, 3 × OCH_2PMB, 4×7-H, 1′-H, 3×2′′-H, 3-H), 4.15–3.42 [m, 35 H, 3 × OMe(PMB), 2-H, 4-H, 5-H, 6-H, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H, 3×(3′′-H, 4′′-H, 5′′-H, 6′′-H)], 3.35 (s, 3 H, OMe), 1.75 (br. s, 1 H, OH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.33, 159.29, 145.6, 145.2, 144.6, 144.1, 139.0, 138.5–138.0, 137.8, 137.7, 130.2, 130.0, 129.7–129.4, 128.7–127.5, 125.2, 123.4, 123.2, 122.5, 113.9, 98.3, 85.2, 85.09, 85.04, 83.8, 82.2, 80.0, 78.6, 78.4, 78.3, 77.7, 77.6, 77.4, 75.8, 75.1, 74.9, 74.7, 74.5–73.9, 73.53, 73.49, 73.4, 73.3, 73.13, 73.09, 73.0, 72.72, 72.66, 70.1, 69.3, 68.5–68.2, 66.1, 65.7, 64.9, 60.3, 55.3 ppm. IR (neat): ṽ = 3456 (O–H) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{151}H_{162}O_{29}N_{12}$ $[M + Na]^+$ 2630.146; found 2630.169.

1-Azido-2,3,4-tri-*O*-benzyl-6-(*p*-methoxybenzyl)-α-D-mannopyranose (27α): To a stirred solution of **19α** (521.4 mg, 1.10 mmol) and PMBCl (179 μL, 1.32 mmol) in anhydrous DMF (11 mL) was added NaH (60% in oil, 66 mg, 1.64 mmol) at 0 °C. The mixture was stirred for 19 h and the temperature was allowed to rise to room temp. The reaction was quenched with a few drops of MeOH, the resulting clear solution was concentrated, and the remaining DMF was coevaporated with toluene. The residue was diluted with CH_2Cl_2 (25 mL), the solution was washed with water (2 × 20 mL) and brine (20 mL), dried with Na_2SO_4, filtered and concentrated to dryness. The crude oil was purified by flash chromatography (PE to EtOAc/PE, 1:4) to afford pure **27α** (506.5 mg, 77%) as a colourless oil. R_f = 0.62 (EtOAc/PE, 1:4). $[\alpha]_D^{20}$ = +95.6 (*c* = 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.21 (m, 15 H, ArH), 7.17–7.11 (m, 2 H, ArH), 6.85–6.78 (m, 2 H, ArH), 5.38 (d, *J* = 2.1 Hz, 1 H, 1-H), 4.83 (d, *J* = 10.8 Hz, 1 H, OCH_2Ar), 4.72 (d, *J* = 12.4 Hz, 1 H, OCH_2Ar), 4.67 (d, *J* = 12.4 Hz, 1 H, OCH_2Ar), 4.61 (d, *J* = 11.5 Hz, 1 H, OCH_2Ar), 4.61 (d, *J* = 11.7 Hz, 1 H, OCH_2Ar), 4.56 (d, *J* = 11.7 Hz, 1 H, OCH_2Ar), 4.48 (d, *J* = 10.8 Hz, 1 H, OCH_2Ar), 4.45 (d, *J* = 11.5 Hz, 1 H, OCH_2Ar), 3.99 (t, *J* = 9.5 Hz, 1 H, 4-H), 3.85 (ddd, *J* = 9.5, 4.5, 2.0 Hz, 1 H, 5-H), 3.80–3.74 (m, 5 H, 3-H, 6-Ha, CH_3O), 3.69 (dd, *J* = 11.1, 2.0 Hz, 1 H, 6-Hb), 3.62 (dd, *J* = 3.1, 2.1 Hz, 1 H, 2-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3, 138.4, 138.3, 138.0, 130.4, 129.7 (2), 128.56 (2), 128.54 (2), 128.44 (2), 128.02 (4), 127.95, 127.83 (3), 127.76, 113.8 (2), 88.3, 79.2, 75.2, 74.8, 74.5, 74.1, 73.2, 72.9, 72.6, 68.5, 55.4 ppm. IR (neat): ṽ = 2110 (N_3) cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{35}H_{37}O_6N_3$ $[M + Na]^+$ 618.257; found 618.256.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra for all new compounds.

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