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Disaccharide-Containing Macrocycles by Click Chemistry and Intramolecular Glycosylation

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In this study *o*- and *m*-xylylene moieties in combination with a triazolylmethyl moiety have been successfully employed as a relatively rigid spacer system in intramolecular glycosylation reactions. Phenyl 3,4,6-tri-O-benzyl-2-O-propargyl-1-thio-D-glucopyranoside was employed as a donor, which could be readily connected by 1,3-dipolar cycloaddition (click reaction) to O-(2- or 3-azidomethylbenzyl)-protected

Introduction

Carbohydrate-based molecules play pivotal roles in many physiologically and pathologically important processes including cellular recognition, communication, cell growth regulation, cell differentiation, adhesion, migration, invasion, inflammation, immunological response, tumour metastasis and bacterial and viral infection, and hence the general interest in these compounds, particularly as constituents of glycoconjugates, has greatly increased in recent years.^[1,2] This increasing demand for carbohydrate-containing molecules for biological, pharmaceutical and medicinal studies has led to tremendous efforts to develop novel and facile methods for the synthesis of diverse glycosides.^[3-7] Recently, carbohydrate-containing macrocycles have also received great attention because of their application in bioorganic and supramolecular chemistry as inhibitors of carbohydrate-protein interactions or carbohydrate-RNA interactions in which the embedded carbohydrate structures are involved in binding to the receptor.^[8] They have also found application in host-guest chemistry, in the study of carbohydrate-carbohydrate interactions^[9] or in cyclodextrins or cyclodextrin mimetics, for instance, in glycophanes or their hybrids.^[10] The incorporation of carbohydrates into macrocycles facilitates the modification of their properties particularly by modification of the functional groups of the carbohydrate residue(s).[11,12]

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acceptors to afford, after liberation of the accepting hydroxy groups, the desired donor-spacer-acceptor-linked intermediates. NIS/TMSOTf-promoted glycosylation furnished disaccharide-containing macrocycles. In general, very good results were obtained. The anomeric selectivity is dependent on various factors, the ring size seeming crucial.

Although a large number of synthetic methods for glycoside bond formation are known,[5-7,13,14] regio- and stereocontrol are not always achieved. To accomplish the desirable high selectivity in glycosidation reactions, intramolecular glycosylation has been studied as an attractive method.^[15] In this context it is worth mentioning that glycosyl transfer within the active site of an enzyme formally proceeds intramolecularly: the close proximity between glycosyl donor and acceptor in the active site of an enzyme is gained by specific binding between the enzyme and the substrate, thus leading to a structurally rigid array composed of large rings that enforce (regio- and/or) diastereoselectivity.^[16,17] To enforce a similar in vitro reaction course, various approaches to intramolecular glycoside bond formation have been investigated,^[15-28] which can be categorized into three major classes: (a) leaving group based,^[18] (b) functional substituent based^[19] and (c) rigid spacer based, as shown in Scheme 1.^[20]



Scheme 1. Intramolecular glycoside bond formation. L = leaving group; R = protecting group; S = spacer; Y = acceptor.

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Generally, the functional-substituent-based approach (b), which generates five-membered cyclic transition states, resulted in good anomeric selectivity, yet this selectivity depends on the configuration of the 2-hydroxy group (thus, 2-OH on the β -side gives the β -configuration and vice versa) and also on the spacer type. Larger spacer systems at the 2-OH or any other position of the donor often lead not only to lower anomeric selectivity but also to lower yields. An interesting alternative is spacer-mediated linkage of the glycosyl donor and acceptor by non-reacting centres (c),^[20] which lead, with the help of malonyl,^[23] succinvl,^[24] glutaryl^[25] or peptide spacers,^[26] to carbohydrate-containing macrocyclic systems. A combination of this approach with quite rigid spacers, for instance, m-xylylene,^[16,20a] phthaloyl^[27] or isophthaloyl,^[28] led in many cases to excellent results both in terms of yield and anomeric selectivity.

Herein we combine as rigid spacers *o*- or *m*-xylylene residues with the ease of the triazole-forming click reaction to readily connect a glycosyl donor to an acceptor. The subsequent intramolecular glycosylation reaction gives rise to macrocycles containing the corresponding saccharides. The envisaged proximity of the triazolyl moiety to the anomeric centre will eventually influence the anomeric stereocontrol.

Results and Discussion

Thioglycoside 5, required as a glycosyl donor, was synthesised in good yield from D-glucose via ortho ester 2 in six steps (Scheme 2). The ortho ester^[29a-29c] was prepared by a slightly modified procedure starting from glycosyl bromide 1; bromide 1 was heated in anhydrous acetonitrile at reflux in the presence of triethylamine, methanol and TBAI at 50 °C for 45 min leading to an improved yield. The acetyl groups were removed with sodium methoxide and the resulting free hydroxy groups were benzylated to give ortho ester 2 in good yield; HgBr₂-mediated ring-opening of the ortho ester with thiophenol is known to provide the thioglycoside in relatively low yield.^[29a] However, when the ortho ester protection was removed by treatment with pTsOH and the compound 3 thus obtained was first O-acetyl-protected and then employed in the glycosylation of thiophenol with BF₃·OEt₂ as promoter, compounds 5α and 5β were obtained in good yields. The glycosylation with α isomer 4α proceeded faster than that of β -isomer 4 β . Both diastereomers 5α and 5β were isolated in pure form. The Oacetyl groups of compounds 5α and 5β were easily removed with NaOMe to give the desired thioglycosides 6α and 6β .



Scheme 2. Intramolecular glycosidic bond formation by click reaction with the formation of a 15-membered ring. Reagents and conditions: (a) TBAI, NEt₃, MeOH, CH₃CN, 50 °C, 45 min, 95%; (b) NaOMe, MeOH, 3 h, room temp., 98%; (c) BnBr, DMF, TBAI, 90%; (d) *p*TsOH, acetone, 95%; (e) Ac₂O, Pyr, 99%; (f) PhSH, BF₃·OEt₂, CH₂Cl₂, -10 °C to room temp., 12 h, 70%; (g) NaOMe, MeOH, 99%; (h) HCCCH₂Br, DMF, TBAI, 3 h, room temp., 99%; (i) BnBr, DMF, TBAI, room temp., 8 h, 99% (\rightarrow 9); (j) 70% AcOH (in H₂O), 80 °C, 2 h, 92%; (k) Bu₂SnO, Tol, reflux, 5 h, then PMBCl, NaH, TBAI, 90 °C, 8 h, 90%; (l) *a*,*a*'-dibromo-*o*-xylene, 18-crown-6, NaH, CH₂Cl₂, 0 °C to room temp., 14 h, 90%; (m) NaN₃, DMF, 50 °C, 4 h, 99%; (n) CuI, DIPEA, CH₂Cl₂, room temp., 12 h, 96%; (o) DDQ, CH₂Cl₂, 0 °C, 2 h, 82%; (p) NIS, TMSOTf, CH₂Cl₂, 0 °C to room temp., 2 h, 58%.



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Treatment with propargyl bromide in DMF using NaH (1.5 equiv.) resulted in the formation of 7α and 7β , respectively, in quantitative yields.

Sugar-based azide 13 was obtained from D-glucose in seven high-yielding steps. Treatment of diol 10, obtained in 92% yield from compound 8, with dibutyltin oxide in toluene and then with *p*-methoxybenzyl chloride (PMBCl) in the presence of tetrabutylammonium iodide resulted in selective 6-*O*-PMB protection by chelation with Bu₂SnO. Treatment of compound 11 with α, α' -dibromo-*o*-xylene in the presence of NaH as base and 18-crown-6 as supporting reagent led to 5-*O*-linked derivative 12 in 90% yield. However, direct reaction of 11 with α, α' -dibromo-*o*-xylene in the presence of NaH and in the absence of 18-crown-6 was not selective and provided three spots by TLC. Compound 12 on reaction with sodium azide at 50 °C afforded the desired azide 13 in quantitative yield.

The Cu^I-catalysed Huisgen 1,3-dipolar cycloaddition (click reaction) of an azide and an alkyne has been increasingly used in the field of carbohydrate research for the chemical labelling of biomolecules^[30a] as well as for the preparation of oligosaccharide analogues,^[30b] glycol dendrimers,^[30c] scaffolds^[30d] and micro-arrays.^[30e] Macrocyclic carbohydrates have recently been synthesized by click chemistry of azido and alkyne groups present in sialic acid containing oligosaccharides.^[30f] To explore the concept of intramolecular glycoside bond formation mediated by click reactions, 2-O-propargyl-B-D-glucopyranoside (7B) was initially treated with glycosyl azide 13 to furnish triazole-containing derivative 14 in excellent yield. The PMB protecting group in compound 14 was removed by treatment with 2,3dichloro-5,6-dicyanoquinone (DDQ) in CH₂Cl₂/H₂O. Activation of compound 15 with N-iodosuccinimide (NIS, 2.0 equiv.) and trimethylsilyl trifluoromethanesulfonate (TMSOTf, 0.2 equiv.) in anhydrous CH₂Cl₂ at 0 °C afforded the desired (1-6)-linked triazole-containing disaccharide 16β, as part of a 15-membered macrocycle, as the only

product (Scheme 2). As the yield of **16** β was practically independent of the concentration of **15** in the 0.01–0.1 molar range, oligomerization does not play a major role in the macrocyclization reaction. The β configuration was assigned with the help of NMR spectroscopic data (¹H: 1b-H, $J_{1,2} = 7.6$ Hz; ¹³C: C-1b, $\delta = 101.75$ ppm). The yield of the glycosylation reaction with **15** and NIS/TMSOTf was concentration-dependent because 1.1 equiv. of NIS gave a lower yield of the product than 2 equiv. of NIS. As the reaction with 7α led to the same result, the diastereofacial control in the intramolecular glycosylation step was independent of the glycosyl donor configuration and even at room temperature the β anomer was exclusively generated.

To further investigate intramolecular glycoside bond formation by the CuI-catalysed click reaction and the formation of 16-membered rings, compound **7** β was first treated with glycosyl azide **18**, obtained from **11** by a similar set of reactions with α, α' -dibromo-*m*-xylene and then with sodium azide, to give triazole-containing carbohydrate **19** (Scheme 3). The removal of PMB from **19** by treatment with DDQ in CH₂Cl₂/H₂O followed by final intramolecular aglycon delivery by activation of compound **20** with NIS (2.0 equiv.) and TMSOTf (0.2 equiv.) in anhydrous CH₂Cl₂ at 0 °C afforded the desired (1–6)-linked triazole-containing disaccharide compounds **21** α and **21** β that could be separated. The β/α selectivity dropped to 3:1 for the formation of the 16-membered macrocyclic rings.

Then we turned our attention to intramolecular glycosylation reactions of acceptors with secondary hydroxy groups. The first studies were performed with 6-*O*-linked glucofuranoses (Scheme 4). To this end, readily available glucofuranose **10**, after regioselective 6-*O*-trityl protection (\rightarrow **22**) followed by 5-*O*-PMB protection (\rightarrow **23**) and finally treatment with *p*TsOH, afforded 6-*O*-unprotected glucofuranose **24** in an overall yield of 88%. 18-Crown-6-supported reaction of **24** with α, α' -dibromo-*o*- or -*m*-xylene (\rightarrow **25** and **30**) followed by treatment with sodium azide afforded 6-*O*-



Scheme 3. Intramolecular glycosidic bond formation by click reaction in the formation of 16-membered rings. Reagents and conditions: (a) α, α' -dibromo-*m*-xylene, 18-crown-6, NaH, CH₂Cl₂, 0 °C to room temp., 14 h, 96%; (b) NaN₃, DMF, 50 °C, 4 h, 99%; (c) **7** β , CuI, DIPEA, CH₂Cl₂, room temp., 10 h, 96%; (d) DDQ, CH₂Cl₂, H₂O, 0 °C, 2 h, 80%; (e) NIS, TMSOTf, CH₂Cl₂, 0 °C, 2 h, 65%, $\beta/\alpha = 3:1$.



Scheme 4. Intramolecular glycosidic bond formation through click reactions to form 15- or 16-membered rings. Reagents and conditions: (a) CPh₃Cl, Pyr, room temp., 10 h, 95%; (b) PMBBr, DMF, TBAI, room temp., 10 h, 97%; (c) PTSA, CH₂Cl₂, MeOH, room temp., overnight, 95%; (d) 18-crown-6, NaH, CH₂Cl₂, 0 °C to room temp., 14 h, 85 (**25**) and 90% (**30**); (e) NaN₃, DMF, 50 °C, 4 h, 99 (**26**) and 98% (**31**); (f) **7** β , CH₂Cl₂, CuI, DIPEA, room temp., 10 h, 95 (**27**) and 98% (**32**); (g) DDQ, CH₂Cl₂, H₂O, 2 h, 88 (**28**) and 85% (**33**); (h) NIS, TMSOTf, 2 h, 80%, α/β = 3:2 (**29**) and 50%, α/β = 2:1 (**34**).

linked azides 26 and 31, respectively, in good yields. The CuI-catalysed click reactions of compound 7β with azides 26 and 31 resulted in nearly quantitative conversion to sugar-containing triazoles 27 and 32, respectively.

DDQ-mediated cleavage of the PMB group in 27 furnished the required 5a-O-unprotected intermediate 28, which, upon treatment with NIS (2.0 equiv.) and TMSOTf (0.2 equiv.) in CH₂Cl₂ at 0 °C, afforded the desired intramolecular glycosylation products 29a, β through the formation of a 15-membered macrocycle in 80% yield as a 3:2 α/β mixture. Separation of the anomers was difficult as both compounds had the same R_f value ($R_f = 0.35$, EtOAc/toluene = 3:7). Similar transformation of 32 into 5a-O-unprotected intermediate 33 and then intramolecular glycosylation with NIS/TMSOTf as activating system led to the 16membered macrocycles 34a, β (that could not be separated) in good yield with an α/β ratio of 2:1.

As the models **28** and **33** for intramolecular glycosylation studies possess high conformational flexibility, not only in parts of the linker, but also in the acceptor moiety, a related system with a conformationally more restricted acceptor moiety was investigated. To this end, readily available *O*- isopropylidene-protected glucofuranose 8 was 3-O-alkylated with α, α' -dibromo-o-xylene to afford bromomethylbenzyl derivative 35, which on reaction with sodium azide in DMF afforded the corresponding azide 36 (Scheme 5). Selective 5,6-O-de-isopropylidenation with aqueous acetic acid $(\rightarrow 37)$ and then regioselective 6-O-benzoylation with benzoyl chloride in CH₂Cl₂/pyridine at -30 °C furnished 5-O-unprotected intermediate 38, which gave on reaction with 2-O-propargyl derivative 7β under 1,3-dipolar cycloaddition (click) reaction conditions donor-acceptor-linked intermediate 39 in excellent yield. Glycosylation under the standard conditions gave only the $\alpha(1-5)$ -linked disaccharide 40 α as part of a 16-membered macrocycle in low yield. Therefore it was not surprising that glycosylation studies with O-protected 41, readily obtained by the click reaction of 7β and 36, did not lead to glycoside bond formation with concomitant loss of the 5a,6a-O-isopropylidene group. The reaction centres do not seem to be well adjusted for intramolecular glycoside bond formation.

After studying the 1,2-O-isopropylideneglucofuranose derivatives as acceptors we investigated pyranoside acceptors, which are generally conformationally more rigid.

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Scheme 5. Intramolecular glycosidic bond formation by click reaction to form a 16-membered ring. Reagents and conditions: (a) 18-crown-6, NaH, CH_2Cl_2 , 0 °C to room temp., 14 h, 90%; (b) NaN₃, DMF, 50 °C, 4 h, 98%; (c) 70% AcOH, room temp., 12 h, 94%; (d) benzoyl chloride, CH_2Cl_2 , Pyr, -30 °C, 2 h, 92%; (e) **7** β , CuI, DIPEA, CH_2Cl_2 , room temp., 12 h, 96%; (f) NIS, TMSOTF, CH_2Cl_2 , 3 h, 20%.

They are also typical of mammalian systems. To this end, known methyl 2,3-di-*O*-benzylglucopyranoside **45** was regioselectively protected with dibutyltin oxide and 4-PMBCl to afford 6-*O*-PMB-protected derivative **46** (Scheme 6). Reaction with α, α' -dibromo-*o*- and -*m*-xylene in the presence of 18-crown-6 and NaH as base furnished 4-*O*-alkylation products **47** and **52**, respectively, which were transformed into azides **48** and **53**. Their click reaction with 2-*O*-prop-



Scheme 6. Intramolecular glycosidic bond formation by click reaction to form 16- and 17-membered rings. Reagents and conditions: (a) PhCH(OMe)₂, DMF, PTSA, 1 h, 50 °C, 95% (\rightarrow 43); (b) BnBr, DMF, TBAI, room temp., 10 h, 95%; (c) TFA, CH₂Cl₂, H₂O, 0 °C, 2 h, 96% (\rightarrow 45); (d) Bu₂SnO, Tol, reflux, 5 h, PMBCl, TBAI, 90 °C, 8 h, 94%; (e) 18-crown-6, NaH, CH₂Cl₂, 0 °C to room temp., 14 h, 95 (47) and 90% (52); (f) NaN₃, DMF, 50 °C, 4 h, 98%; (g) 7 β , CuI, DIPEA, CH₂Cl₂, room temp., 14 h, 96 (49) and 92% (54); (h) DDQ, CH₂Cl₂, H₂O, 2 h, 90 (50) and 86% (55); (i) NIS, TMSOTf, 2 h, 95%, α/β = 1:2 (51) and 80%, α/β = 3:2 (56); (j) H₂, Pd/C, methanol, HCl, 2 d then Ac₂O, Py, 0 °C, 10%.

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argyl-protected donor 7β afforded the donor-acceptorlinked compounds 49 and 54, respectively. DDQ-mediated removal of the PMB group (\rightarrow 50 and 55) followed by glycosylation under standard conditions afforded the (1–6)linked intramolecular glycosylation products 51 α , β and 56 α/β , respectively, in high yields but with modest anomeric preferences (51: $\alpha/\beta = 1:2$, 56: $\alpha/\beta = 3:2$). This and previous results show that the formation of anomers is only marginally influenced, if at all, by anchimeric assistance of the triazolyl moiety, although the N-3 atom could bind to the anomeric carbon to generate a six-membered heterocycle.

Attempts to remove all the *O*-benzyl groups and the linker were carried out with macrocycle **56a** (Scheme 6). Hydrogenolysis with palladium on carbon as catalyst afforded after *O*-acetylation the known methyl isomaltoside **57**, although in low yield. Hence, conditions for the cleavage of the triazolylmethyl moiety have to be further optimized.^[31]

The transformation of glucopyranoside **45** into a 4-*O*unprotected acceptor was performed to study the formation of an intramolecular (1–4)-linkage between two glucopyranose residues. To this end, 4,6-*O*-unprotected glucose derivative **45** was tritylated with trityl (Trt) chloride in pyridine to afford regioselectively the 6-*O*-trityl derivative. The PMB group was then introduced at 4-*O* under standard conditions to furnish the fully *O*-protected intermediate **59**

(Scheme 7). pTsOH-catalysed detritylation led to 6-O-unprotected compound 60 in high overall yield, thus providing a suitable compound for the envisaged studies. Alkylation with α, α' -dibromo-o- and -m-xylene afforded compounds 61 and 66, respectively. Azide introduction (\rightarrow 62 and 67), click reaction with glucopyranosyl donor 7β (\rightarrow 63 and 68) and then DDQ-mediated PMB cleavage furnished the desired precursors 64 and 69, respectively, for the intramolecular glycosylation studies. Treatment with NIS/TMSOTf as promoter afforded the desired 16- and 17-membered macrocycles 65α , β and 70α and 70β , respectively, in high yields. Mixtures of α and β anomers were obtained in both cases (65: 90%, $\alpha/\beta = 3:1$; 70: 82%, $\alpha/\beta = 1:2$). Notably, and in contrast to the formation of 51 and 56, the 16-membered macrocycle was generated mainly with an α -glycosidic linkage whereas the 17-membered macrocycle was generated with a preference for the β product.

From this result it was concluded that a reduction in ring size, for example, in the transformation of **64** into **65**, will eventually lead to a single anomer, that is, the α anomer. The corresponding 15-membered macrocycle can be easily synthesized by attaching the *o*-xylyl-linker to the 3-hydroxy group of the acceptor. By this approach the formal (5,4)-L-*threo* attachment to the acceptor in intermediate **64** (Scheme 7)^[15] is inverted, as can be seen by comparison with the corresponding target molecule **76** (Scheme 8).



Scheme 7. Intramolecular glycosidic bond formation by click reaction to form 16- and 17-membered rings. Reagents and conditions: (a) TrCl, Pyr, 12 h, 0 °C to room temp., 94% (\rightarrow 58); (b) PMBCl, NaH, DMF, room temp., 10 h, 95%; (c) PTSA, MeOH, CH₂Cl₂, 0 °C, 92%, 2 h; (d) 18-crown-6, NaH, CH₂Cl₂, 0 °C to room temp., 14 h, 90 (61) and 88% (66); (e) NaN₃, DMF, 50 °C, 4 h, 99 (62) and 97% (67); (f) 7 β , CuI, DIPEA, CH₂Cl₂, 14 h, 95 (63) and 96% (68); (g) DDQ, CH₂Cl₂, H₂O, 0 °C, 2 h, 87 (64) and 90% (69); (h) NIS, TMSOTF, CH₂Cl₂, 2 h, 90%, $\alpha/\beta = 3:1$ (65) and 82%, $\alpha/\beta = 1:2$ (70).

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Scheme 8. Intramolecular glycosidic bond formation by click reaction to form a 15-membered ring. Reagents and conditions: (a) BnBr, CH₂Cl₂, NaOH, Bu₄NHSO₄, 60 °C, 48 h, 50 (**71a**), 20 (**71b**) and 10% (mixture of dibenzyl-protected compounds); (b) a,a'-dibromo-*o*-xylene, Pyr/CH₂Cl₂, 18-crown-6, 0 °C, room temp., 18 h, 90%; (c) NaN₃, DMF, 50 °C, 4 h, 99%; (d) 70% AcOH/H₂O, 70 °C, 3 h, 96%; (e) BzCl, CH₂Cl₂, -40 °C, 1 h, 94%; (f) **7** β , CuI, DIPEA, CH₂Cl₂, 14 h, 96%; (g) NIS, TMSOTf, CH₂Cl₂, 55%.

However, from molecular models it can be deduced that this stereochemical change should not negatively influence the result of glycosylation. Thus, 2,3-O-unprotected glucopyranoside 43^[32] was monobenzylated under phase-transfer conditions^[33] to furnish mainly the 2-O-benzyl derivative 71a (together with some 3-O-benzyl derivative 71b). Subsequent reaction with α, α' -dibromo-o-xylene afforded intermediate 72, which was transformed into azide 73. Acid-catalysed debenzylidenation $(\rightarrow 74)$ and then benzovlation with benzoyl chloride in pyridine at -40 °C regioselectively furnished 6-O-benzoyl derivative 75. Click reaction of azide 75 with donor 7β led to the required triazole-containing disaccharide 76 as precursor for the intramolecular glycosylation. NIS/TMSOTf-promoted activation of 76 exclusively afforded, as expected, the $\alpha(1-4)$ -linkage of the 15-membered macrocycle 77a, as indicated by ¹³C NMR spectroscopy (C-1a: δ = 97.72 ppm; C-1b: δ = 97.73 ppm).

Conclusions

The 1,4-substituted triazole-forming click reactions between 2-O-propargyl-substituted glucopyranosyl donors and O-(2- or 3-azidomethylbenzyl)-protected glycosyl acceptors has provided a convenient access to donor-acceptor-ligated intermediates with a quite rigid spacer. Glycosylation reactions led to the desired disaccharides as part of macrocycles generally in good-to-excellent yields, thus confirming the efficiency of this approach to intramolecular glycoside bond formation. Modest-to-excellent anomeric stereocontrol was observed, hence, further studies with different spacer linkage positions, different ring size and possibly different leaving groups or reaction conditions are required to optimize the anomeric stereoselectivity. Note that anchimeric assistance by the neighbouring triazolyl moiety was negligible in the anomeric stereocontrol.

Experimental Section

General: Solvents were purified by standard procedures. Yields refer to chromatographically pure material. Anomeric selectivities are

based on isolated material or on ¹H NMR spectroscopic data. Reactions were monitored by TLC carried out on Merck silica gel (0.2 mm, 60F-254) plastic plates. Compounds were first visualized under UV light and then by using visualizing agent, a solution of (NH₄)₆Mo₇O₂₄·4H₂O (20 g) and Ce(SO₄)₂ (0.4 g) in sulfuric acid (10%, 400 mL), and heating to 120 °C and/or an ethanolic sulfuric acid solution and heat as developing agents. Flash chromatography was performed on MN silica gel 60 (230-400 mesh) at a pressure of 0.2 bar. NMR spectra, including ¹H and ¹³C NMR, DEPT, COSY, HSQC and HMBC spectra, were acquired with a Bruker 400 MHz NMR spectrometer at 300 K; tetramethylsilane (TMS) and the resonance of undeuteriated solvent were used as internal standards (CDCl₃: δ = 7.25 ppm). The multiplicities are indicated as follows: m = multiplet, s = singlet, d = doublet, dd = double of doublets, t = triplet, dt = doublet of triplets, br. s = broad singlet. Mass spectra were recorded with a Bruker ESI-MS mass spectrometer. HRMS were obtained with a Fourier-transform mass spectrometer. Optical rotations were measured at 20 °C with a Büchi Polar-Monitor (1 dm cell) using the sodium D line.

Synthetic methods for all donors, acceptors and intermediates required to investigate the intramolecular glycosylation reactions are given in the Supporting Information.

General Procedure A - Synthesis of Glycosyl Azides: 18-Crown-6 (480 mg, 1.82 mmol) and sodium hydride (300 mg) were added to a solution of free alcohol (5.69 mmol) in anhydrous dichloromethane (30 mL) and then the mixture was stirred for 10 min at -10 °C under an inert atmosphere. α, α' -Dibromo-o- or -m-xylene (11.39 mmol) in dichloromethane (15 mL) was added to the reaction mixture at room temp. and stirring was continued overnight. Progress of the reaction was monitored by TLC and the reaction was continued until the starting material had been consumed. The solution was then filtered through Celite (carefully) and concentrated in vacuo. Chromatography (toluene/ethyl acetate) of the residue afforded the desired compound as a colourless oil. The yields refer to the isolated compounds and varied from 80-90% (excess α, α' -dibromo-*o*- or -*m*-xylene was recovered and reused). The pure product thus obtained was dissolved in anhydrous DMF (10-15 mL) and excess of NaN₃ (4 equiv.) was added. The reaction mixture was stirred at 50 °C for 3-4 h. The solvent was then evaporated under reduced pressure and the crude mass was filtered. Flash chromatography revealed an almost quantitative yield of the glycosyl azide as a colourless oil.

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General Procedure B – Synthesis of Glycosyl Triazole by Copper-Catalysed Click Reaction: Equimolar amounts of the glycosyl alkyne (2.79 mmol) and glycosyl azide (2.79 mmol) were dissolved in anhydrous CH₂Cl₂ (30 mL) and diisopropylethylamine (3.1 mmol) was added. The solution was mixed for 10 min. Copper(I) iodide powder (0.55 mmol) was then added to the reaction mixture at 0 °C and the solution stirred at room temp. for 9–12 h. The progress of the reaction was monitored by TLC using 30% EtOAc/toluene as developing solvent and 5% H₂SO₄ (in ethanol) solution for sugar staining. The mixture was filtered through Celite and concentrated in vacuo. The crude product thus obtained was subjected to flash column chromatography using silica. The desired triazole was obtained as a colourless oil in almost quantitative yield.

General Procedure C – PMB Group Removal: DDQ (1.01 mmol) was added slowly to a stirring solution of the triazole (1.0 mmol) in a mixture of CH₂Cl₂ (27 mL) and distilled water (3.0 mL) at 0 °C and the resulting reaction mixture was stirred at the same temperature for 2 h. The reaction mixture was filtered, extracted with CH₂Cl₂, washed with H₂O (10 mL), the solvent evaporated under reduced pressure, and the residue purified by column chromatography using 40% EtOAc/toluene as eluent to give the desired free alcohol.

General Procedure D - Intramolecular Glycosylation of Triazole-Containing Carbohydrates: Trimethylsilyl trifluoromethanesulfonate (0.3 equiv.) was added through a syringe under argon to a stirring solution of triazole-containing carbohydrate (1.0 mmol) and N-iodosuccinimide (2.0 mmol) in anhydrous dichloromethane (20 mL) at -10 °C under an inert atmosphere. The reaction was stirred for 1-2 h at room temp. if not indicated otherwise. The solution was neutralized with triethylamine at 0 °C, sodium dithionite was added and then stirring was continued until the solution became colourless. The solid was filtered off and the solution was extracted with CH_2Cl_2 (2 × 75mL), washed with H_2O (10 mL), dried with anhydrous Na2SO4 and the solvent removed under vacuo. The residue thus obtained was subjected to flash chromatography (20% EtOAc/toluene) to give the sugar-based macrocycle as a colourless oil. The yields refer to the isolated pure products obtained by column chromatography and the selectivities were determined by NMR analysis of the crude reaction mixtures.

Compound 16_β: TMSOTf (15 µL, 0.07 mmol) was added through a syringe under argon to a stirring solution of 15 (314 mg, 0.303 mmol) and N-iodosuccinimide (136 mg, 0.606 mmol) in dry dichloromethane (20 mL) at -10 °C under an inert atmosphere. The reaction was stirred for 90 min at room temp. The solution was neutralized with triethylamine at 0 °C, sodium dithionite was added, and then stirring was continued until the solution became colourless. The solid was filtered off and the solution extracted with CH_2Cl_2 (2 × 75 mL), washed with H_2O (10 mL), dried with anhydrous Na₂SO₄ and the solvent removed in vacuo. The residue thus obtained was subjected to flash chromatography (20% EtOAc/toluene) to give sugar-based macrocycle 16β as a colourless oil (163 mg, 58%; β selectivity over 98%). $R_{\rm f} = 0.42$ (35% EtOAc/toluene). $[a]_{D}^{25} = +0.35$ (c = 1, CHCl₃). ¹H NMR (CDCl₃, 400 MHz): $\delta =$ 8.14 (s, 1 H, triazole H), 7.47-7.29 (m, 28 H, Ar-H), 5.92 (d, J = 4.0 Hz, 1 H, 1a-H), 5.53 (d, J = 14.0 Hz, 1 H, N-benzylic H), 5.45 (d, J = 14.0 Hz, 1 H, N-benzylic H), 4.99 (d, J = 12.0 Hz, 1 H, benzylic H), 4.93–4.89 (m, 3 H, benzylic H), 4.82 (d, J = 11.2 Hz, 1 H, benzylic H), 4.77 (d, J = 11.6 Hz, 1 H, benzylic H), 4.68 (d, J = 4.0 Hz, 1 H, 2a-H), 4.65 (d, J = 12.4 Hz, 1 H, benzylic H), 4.63–4.52 (m, 4 H, benzylic H), 4.45 (d, J = 11.6 Hz, 1 H, benzylic H), 4.43 (d, J = 7.6 Hz, 1 H, 1b-H), 4.29 (dd, J = 8.4, 2.8 Hz, 1 H, 4a-H), 4.25 (dd, J = 12.0, 2.0 Hz, 1 H, 6a-H), 4.11 (d, J = 2.8 Hz,

1 H, 3a-H), 4.06 (dt, J = 7.2, 2.0 Hz, 1 H, 5a-H), 3.85 (dd, J = 12.0, 4.8 Hz, 1 H, 6b-H), 3.77 (dd, J = 11.4, 2.0 Hz, 1 H, 6a-H), 3.72–3.67 (m, 2 H, 6a'-H, 5b-H), 3.65 (dd, J = 9.2 Hz, 1 H, 3b-H), 3.49 (m, 1 H, 4b-H), 3.42 (dd, J = 8.4 Hz, 1 H, 2b-H), 1.60 and 1.36 [each s, each 3 H, 2 C(CH₃)₂] ppm. ¹³C NMR (100 MHz): $\delta = 145.70$, 138.38, 138.21, 138.11, 137.65, 137.57, 132.19, 131.71, 130.48, 129.47, 128.89, 128.51, 128.04, 127.99, 127.94, 127.88,

127.79, 127.72, 127.62, 125.11 (Ar-C), 111.94 (*C*Me₂), 104.89 (C-1a), 101.75 (C-1b), 86.48 (C-3b), 81.82 (C-2a, C-3a, merged), 80.25 (C-2b), 78.14 (C-4a), 78.03 (C-5b), 76.54 (C-5a), 75.73 (OCH₂), 74.93 (C-4b merged with OCH₂), 73.47, 72.02, 69.54 (OCH₂Ar), 68.66 (C-6b), 67.89 (C-6a), 66.34 (OCH₂Ar), 51.87 (NCH₂Ar), 26.59 and 26.41 [2 C(*C*H₃)₂] ppm. HRMS (+ mode): calcd. for $C_{54}H_{61}N_3O_{11}$ [M + H]⁺ 926.4228; found 926.4185.

Compounds 21 α , β : Compound **20** (0.2 g, 0.193 mmol) on treatment with NIS (80 mg, 0.38 mmol) and TMSOTf (15 μ L, 0.076 mmol) in dry CH₂Cl₂ for 2 h and workup as described in general procedure D afforded **21** α , β (116 mg, 65%) as a colourless oil. α/β = 1:3.

21*B*: $R_f = 0.35 (30\% \text{ EtOAc/toluene})$. ¹H NMR (CDCl₃, 400 MHz): δ = 7.66 (s, 1 H, Ar-H), 7.38–7.15 (m, 22 H, Ar-H), 6.89 (s, 1 H, Ar-H), 6.86 (d, J = 7.2 Hz, 1 H, Ar-H), 5.74 (d, J = 4.0 Hz, 1 H, 1a-H), 5.62 and 5.49 (each d, each J = 14.8 Hz, each 1 H, N-benzylic H), 4.94 (d, J = 12.4 Hz, 1 H, benzylic H), 4.90 (d, J = 12.0 Hz, 1 H, benzylic H), 4.85 (d, J = 11.6 Hz, 1 H, benzylic H), 4.80 (d, J = 11.2 Hz, 1 H, benzylic H), 4.68 (d, J = 10.8 Hz, 1 H, benzylic H), 4.59 (d, J = 12.0 Hz, 1 H, benzylic H), 4.50 (d, J = 4.0 Hz, 1 H, 2a-H), 4.47 and 4.46 (each d, each J = 12.4 Hz, each 1 H, benzylic H), 4.38 (d, J = 12.0 Hz, 1 H, benzylic H), 4.34–4.29 (m, 4 H, 1b-H merged with 3 benzylic H), 3.99-3.96 (m, 3 H, 3a-H, 4a-H, 5b-H), 3.81-3.79 (m, 2 H, 6a-H), 3.62-3.57 (m, 3 H, 6b-H, 5a-H), 4.53 (dd, J = 9.2 Hz, 1 H, 3b-H), 3.35 (dd, J = 9.2 Hz, 1 H, 4b-H), 3.27 (dd, J = 8.0, 8.4 Hz, 1 H, 2b-H), 1.41 and 1.22 [each s, each 3 H, 2 C(CH₃)₂] ppm. ¹³C NMR (100 MHz): δ = 140.78, 138.46, 138.41, 138.28, 137.70, 135.77, 129.71 (Ar-Cq), 128.49, 128.42, 128.33, 128.23, 127.90, 12.82, 127.80, 127.72, 127.66, 127.63, 127.41, 126.31, 125.91, 125.66 (Ar-C), 111.78 (CMe2), 105.01 (C-1a), 103.68 (C-1b), 86.42 (C-3b), 81.96 (C-2a), 81.86 (C-3a), 79.07 (C-4a), 78.33 (C-2b), 78.28 (C-5a), 75.29 (CH₂Ar), 75.00 (C-5b), 74.71, 73.55, 72.31 (CH₂Ar), 72.08 (C-6a), 71.84 (OCH₂), 69.25 (C-6b), 64.38 (OCH₂), 53.49 (NCH₂Ar), 26.70 and 26.39 [2 $C(CH_3)_2$ ppm. HRMS (+ mode): calcd. for $C_{54}H_{61}N_3O_{11}$ [M + H]⁺ 926.4228; found 926.3905.

Compounds 29α,β: Compound 28 (0.4 g, 0.386 mmol) on treatment with NIS (173 mg, 0.773 mmol) and TMSOTf (30 µL, 0.16 mmol) in dry CH₂Cl₂ (15 mL) for 2 h and workup as described in general procedure D afforded an anomeric mixture of $29\alpha,\beta$ (286 mg, 80%) as a colourless oil. The anomers could not be separated. $\alpha/\beta = 3:2$. $R_{\rm f} = 0.35$ (30% EtOAc/toluene); both anomers have the same $R_{\rm f}$ on TLC. ¹H NMR (CDCl₃, 400 MHz): $\delta = 8.08$ (s, 1 H, triazole H, minor isomer), 7.43-7.06 (m, 25 H, Ar-H, major and minor isomer, triazole H, minor isomer), 5.84 (d, J = 3.6 Hz, 1 H, 1a-H, major isomer), 5.79 (d, J = 3.6 Hz, 1 H, 1a-H, minor isomer), 5.62 (d, J = 14.4 Hz, 1 H, N-benzylic H, major isomer), 5.48 (s, 2 H, NCH_2Ar , minor isomer), 5.39 (d, J = 14.4 Hz, 1 H, N-benzylic H, major isomer), 5.05 (d, J = 13.6 Hz, 1 H, benzylic H, minor isomer), 4.95 (d, J = 4.4 Hz, 1 H, 1b-H, major isomer), 4.93 (d, J = 12.0 Hz, 1 H, benzylic H, major isomer), 4.91 (d, J = 11.2 Hz, 1 H, benzylic H, major isomer), 4.88 (d, J = 10.8 Hz, 1 H, benzylic H, major isomer), 4.85 and 4.83 (each d, each J = 12.4 Hz, each 1 H, benzylic H, major isomer), 4.64 (d, J = 12.8 Hz, 1 H, benzylic H, minor isomer), 4.59–4.52 (m, 3 H, benzylic H, major and minor



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isomer), 4.50 (d, J = 4.0 Hz, 1 H, 2a-H, major isomer), 4.46–4.30 (m, 4 H, 2a-H, 3a-H, minor isomer, 4a-H, major isomer), 4.26 (d, J = 8.0 Hz, 1 H, 1b-H, minor isomer), 4.21 (dd, J = 9.6, 4.0 Hz, 1 H, major isomer), 4.15–4.13 (m, 2 H, 5b-H, major and minor isomer), 3.89 (d, J = 2.8 Hz, 1 H, 3a-H, major isomer), 3.74 (dd, J = 10.8, 1.6 Hz, 1 H, 6'b-H, major isomer), 3.70-3.66 (m, 2 H, 6b-H minor isomer, 4b-H, major isomer), 3.62 (dd, J = 9.2, 1.6 Hz, 6a-H), 3.50-3.32 (m, 3 H, 2b-H, 3b-H, major and minor isomer, 4b-H, minor isomer), 3.20 (m, 1 H, 5a-H, minor isomer), 1.45 and 1.20 [each s, each 3 H, 2 C(CH₃)₂, minor isomer], 1.40 and 1.26 [each s, each 3 H, 2 C(CH₃)₂, major isomer] ppm. ¹³C NMR $(100 \text{ MHz}): \delta = 146.71, 145.41, 138.97, 138.54, 138.30, 138.25,$ 138.06, 137.61, 137.26, 136.93, 133.26, 133.25, 132.56, 132.21, 131.81, 131.44, 129.79, 129.35, 129.28, 129.24, 129.10, 128.56, 128.50, 128.44, 128.42, 128.41, 128.38, 128.35, 128.11, 128.03, 127.94, 127.92, 127.89, 127.86, 127.33, 125.34, 124.32, 123.60 (Ar-C, major and minor isomer), 111.74 (CMe2, major isomer), 111.71 (CMe₂, minor isomer), 104.78 (C-1a, merged for major and minor isomer), 102.53 (C-1b, minor isomer), 94.86 (C-1b, major isomer), 85.59 (C-2b, minor isomer), 84.31 (C-4b, minor isomer), 82.49, 81.99, 81.89, 81.85, 81.46, 81.01, 80.35, 78.08, 78.92, 77.63, 76.48, 75.66, 74.89, 74.69, 74.11, 73.62, 73.49, 72.07, 71.60, 71.59, 71.56, 71.49, 70.70 (C-5a, major isomer), 69.59, 69.27, 68.55, 68.12, 66.64 (C-6, minor isomer), 52.72 (NCH₂, major isomer), 51.79 (NCH₂, minor isomer), 29.72, 26.97, 26.89, 26.43 (2 CH₃, major and minor isomer) ppm. HRMS (+ mode): calcd. for C₅₄H₆₁N₃O₁₁ [M + H]⁺ 926.4228; found 926.3927.

Compounds 34a and 34β: Compound **33** (0.7 g, 0.68 mmol) on treatment with NIS (0.24 g, 1.35 mmol) and TMSOTF (35 μ L, 0.19 mmol) in dry CH₂Cl₂ (20 mL) for 2 h and workup as described in general procedure D afforded **34a**, β as a colourless oil (313 mg, 50%). The two anomers were successfully separated in pure form ($\alpha/\beta = 2:1$) and characterized by their spectroscopic data.

34a: Colourless oil. $R_{\rm f} = 0.68$ (30% EtOAc/toluene). ¹H NMR $(CDCl_3, 400 \text{ MHz}): \delta = 7.43 \text{ (dd}, J = 8.0, 2.0 \text{ Hz}, 2 \text{ H}, \text{Ar-H}), 7.29 \text{---}$ 7.27 (m, 23 H, Ar-H), 5.81 (d, J = 4.0 Hz, 1 H, 1a-H), 5.37 and 5.32 (each d, each J = 14.8 Hz, each 1 H, N-benzylic H), 4.90 and 4.84 (each d, each J = 11.6 Hz, each 1 H, benzylic H), 4.81 (d, J = 10.8 Hz, 1 H, benzylic H), 4.71 and 4.72 (each d, each J = 10.8 Hz, each 1 H, benzylic H), 4.59 (d, J = 12.4 Hz, 1 H, benzylic H), 4.53–4.52 (m, 2 H, 1b-H merged with benzylic H), 4.50 (d, J = 4.0 Hz, 2a-H), 4.49–4.43 (m, 4 H, benzylic H), 4.41 (d, J = 12.4 Hz, 1 H, benzylic H), 4.18-4.11 (m, 2 H, 5b-H, 4a-H), 3.98 (d, J = 2.8 Hz, 1 H, 3a-H), 3.69 (dd, J = 10.8, 2.0 Hz, 1 H, 6a-H),3.65, 3.69 (dd, J = 10.8, 6.4 Hz, 1 H, 6b-H), 3.62 (dd, J = 10.8, 3.6 Hz, 1 H, 6a'-H), 3.57–3.51 (dd, J = 8.4 Hz, 2 H, 3b-H merged with 5b-H), 3.45 (dd, J = 10.0, 5.6 Hz, 1 H, 6b'-H), 3.42–3.38 (m, 2 H, 2b-H, 4b-H), 1.42 and 1.22 [each s, each 3 H, 2 C(CH₃)₂] ppm. ¹³C NMR (100 MHz): δ = 138.91, 137.70, 137.65, 137.42, 137.05, 134.02 and 132.92 (Cq), 131.28, 128.39, 128.22, 127.95, 127.79, 127.77, 127.75, 127.68, 127.24, 127.13, 127.01, 126.98, 126.88, 126.79, 126.74, 126.48, 126.45, 121.96 (Ar-C), 111.11 (CMe₂), 104.63 (C-1a), 86.50 (C-1b), 85.81 (C-3b), 81.32 (C-3a), 80.91 (C-2a), 80.32 (C-2b), 79.59 (C-4a), 78.48 (C-4b), 77.09 (C-5b), 75.05, 74.37, 72.76, 72.71, 72.08 and 71.41 (CH₂Ar, OCH₂Ph, C-6a), 68.41 (C-6b), 68.39 (C-5a), 66.05 (OCH₂Ar), 53.36 (NCH₂Ar), 26.15 and 25.67 [2 C(CH₃)₂] ppm. HRMS (+ mode): calcd. for $C_{54}H_{61}N_3O_{11}$ [M + H]⁺ 926.4228; found 926.3862.

34β: Colourless oil. $R_{\rm f}$ = 0.55 (30% EtOAc/toluene). ¹H NMR (CDCl₃, 400 MHz): δ = 7.42 (d, J = 8.0 Hz, 1 H, Ar-H), 7.28–7.18 (m, 22 H, Ar-H), 7.10 (d, J = 8.0 Hz, 1 H, Ar-H), 6.67 (s, 1 H, Ar-H), 5.80 (d, J = 3.6 Hz, 1 H, 1a-H), 5.67 and 5.23 (each d, each J

= 15.6 Hz, each 1 H, N-benzylic H), 4.84 and 4.80 (each d, each J = 11.2 Hz, each 1 H, benzylic H), 4.76 (d, J = 8.4 Hz, 1 H, 1b-H), 4.74 and 4.73 (each d, each J = 11.2 Hz, each 1 H, benzylic H), 4.65 (d, J = 13.6 Hz, 1 H, benzylic H), 4.60 (d, J = 11.6 Hz, 1 H, benzylic H), 4.58 (d, J = 12.0 Hz, 1 H, benzylic H), 4.53 (d, J =12.4 Hz, 1 H, benzylic H), 4.49 (d, J = 12.4 Hz, 1 H, benzylic H), 4.48–4.45 (m, 2 H, benzylic H), 4.44 (d, J = 3.2 Hz, 2a-H), 4.42 (d, J = 10.8 Hz, 1 H, benzylic H), 4.39 (d, J = 12.4 Hz, 1 H, benzylic H), 4.25 (d, J = 12.4 Hz, 1 H, benzylic H), 3.95–3.91 (m, 3 H, 3a-H, 4a-H, 5b-H), 3.82 (dd, J = 10.4, 4.4 Hz, 1 H, 6a-H), 3.81-3.74(m, 3 H, 5a-H, 3b-H, 6b'-H), 3.55 (dd, J = 8.4, 4.4 Hz, 1 H, 6'a-H), 3.54-3.48 (m, 3 H, 6'b-H, 4b-H, 2b-H), 1.40 and 1.22 [each s, each 3 H, 2 C(CH₃)₂] ppm. ¹³C NMR (100 MHz): δ = 140.54, 138.94, 138.51, 138.26, 138.24, 133.71 and 129.12 (Ar-Cq), 128.41, 128.32, 128.09, 127.81, 127.78, 127.61, 127.54, 127.22, 127.20, 126.87, 125.89, 124.98 (Ar-C), 111.95 (CMe2), 105.09 (C-1a), 96.70 (C-1b), 82.69 (C-2a), 82.20 (C-3a), 81.48 (C-4a), 79.76 (C-2b), 79.17 (C-3a), 78.39 (C-4b), 77.23 (C-5b), 75.52, 75.15, 73.40, 73.03 (CH₂Ar, OCH₂Ph), 72.78 (C-6a), 72.32 (OCH₂), 70.92 (C-5a), 68.97 (C-6b), 53.54 (NCH₂Ar), 26.89 and 26.30 [2 C(CH₃)₂] ppm. HRMS (+ mode): calcd. for $C_{54}H_{61}N_3O_{11}$ [M + H]⁺ 926.4228; found 926.3962.

Compound 40a: Compound 39 (1.0 g, 0.953 mmol) on treatment with NIS (427 mg, 1.90 mmol) and TMSOTf (35 µL, 0.19 mmol) in dry CH₂Cl₂ for 4 h and workup as described in general procedure D afforded 40a as a colourless oil (180 mg, 20%). $R_{\rm f} = 0.54$ (30% EtOAc/toluene). $[a]_{D}^{25} = +0.47$ (c = 1, CHCl₃). ¹H NMR $(CDCl_3, 400 \text{ MHz}): \delta = 8.03 \text{ (d, } J = 8.4 \text{ Hz}, 2 \text{ H}, \text{ Ar-H}), 7.50-7.18$ (m, 23 H, Ar-H), 5.93 (d, J = 3.6 Hz, 1 H, 1a-H), 5.65 and 5.36 (each d, each J = 15.2 Hz, each 1 H, N-benzylic H), 4.96 (d, J =11.6 Hz, 1 H, benzylic H), 4.91 and 4.87 (each d, each J = 10.8 Hz, 1 H, benzylic H), 4.85-4.77 (m, 3 H, benzylic H), 4.71 (d, J =3.6 Hz, 1 H, 2a-H), 4.65 (dd, J = 9.6, 4.8 Hz, 1 H, 6a'-H), 4.59 (d, J = 11.6 Hz, 1 H, benzylic H), 4.57–4.54 (m, 3 H, 1-H merged with benzylic H), 4.52 (d, J = 12.0 Hz, 1 H, benzylic H), 4.44 (d, J =11.6 Hz, 1 H, benzylic H), 4.33-4.28 (m, 2 H, 5a-H, 6b'-H), 4.25 (dd, J = 8.8, 2.8 Hz, 1 H, 4a-H), 4.06 (d, J = 2.8 Hz, 1 H, 3a-H),3.76 (dd, J = 10.8, 1.6 Hz, 1 H, 6a-H), 3.69 (dd, J = 10.8, 4.8 Hz)1 H, 6b-H), 3.64 (m, 1 H, 5b-H), 3.61 (dd, *J* = 9.2 Hz, 1 H, 3b-H), 3.48-3.44 (m, 2 H, 4b-H, 2b-H), 1.50 and 1.32 [each s, each 3 H, $2 C(CH_3)_2$ ppm. ¹³C NMR (100 MHz): $\delta = 165.93$ (C=O), 137.89, 137.80, 137.57, 135.62, 133.09, 132.54, 132.39 (Ar-Cq), 131.44, 129.84, 129.53, 129.37, 129.20, 128.63, 128.49, 128.43, 127.98, 127.97, 127.88, 127.44, 127.39, 127.19, 127.10, 127.00 (Ar-C), 111.41 (CMe2), 104.84 (C-1a), 86.67 (C-1b), 86.01 (C-5b), 81.85 (C-3a), 80.59 (C-2b), 80.20 (C-2a), 79.78 (C-4a), 78.65 (C-4b), 77.27 (C-3b), 75.23, 74.58, 72.96 (CH₂Ar), 69.26 (C-6a), 68.33 (C-6b), 67.33 (OCH₂Ar), 67.24 (C-5a), 66.26 (OCH₂Ar), 50.92 (NCH₂Ar), 26.23 and 25.86 [2 C(CH₃)₂] ppm. HRMS (+ mode): calcd. for $C_{54}H_{59}N_3O_{12}$ [M + H]⁺ 940.4021; found 940.3940.

Compounds 51a and 51β: Compound **50** (0.76 g, 0.69 mmol) on treatment with NIS (309 mg, 1.38 mmol) and TMSOTF (35 μ L, 0.19 mmol) in dry CH₂Cl₂ for 2 h and workup as described in general procedure D afforded **51a** and **51β** as a colourless oil (0.65 g, 95%). α/β = 1:2. Compounds **51a** and **51β** were successfully separated in pure form and characterized by comparing their spectroscopic data.

51a: Colourless oil. $R_{\rm f} = 0.40$ (30% EtOAc/toluene). $[a]_{\rm D}^{25} = +26.0$ (c = 1, CHCl₃). ¹H NMR (CDCl₃, 400 MHz): $\delta = 7.46$ (dd, J = 7.6, 0.8 Hz, 1 H, Ar-H), 7.44 (s, 1 H, triazole H), 7.32–7.15 (m, 25 H, Ar-H), 7.09 (d, J = 7.6, 1.2 Hz, 1 H, Ar-H), 7.03 (dd, J = 8.0, 2.4 Hz, 2 H, Ar-H), 5.47 (s, 2 H, NCH₂), 5.02 (d, J = 10.8 Hz, 1

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H, benzylic H), 5.00 (d, J = 12.0 Hz, 1 H, benzylic H), 4.97 (d, J= 12.8 Hz, 1 H, benzylic H), 4.81 and 4.80 (each d, each J =11.2 Hz, each 1 H, benzylic H), 4.72 (d, J = 11.2 Hz, 1 H, benzylic H), 4.65 (d, J = 12.0 Hz, 1 H, benzylic H), 4.54 (d, J = 10.0 Hz, 1 H, benzylic H), 4.57 and 4.55 (each d, each J = 12.0 Hz, each 1 H, benzylic H), 4.50 (d, J = 14.0 Hz, 1 H, benzylic H), 4.46 (d, J =3.2 Hz, 1 H, 1b-H), 4.43 (d, J = 12.0 Hz, 1 H, benzylic H), 4.38 (d, J = 10.8 Hz, 1 H, benzylic H), 4.30 (d, J = 12.4 Hz, 1 H, benzylic H), 3.98 (dd, J = 9.2, 8.4 Hz, 1 H, 3b-H), 3.82 (d, J = 3.6 Hz, 1 H, 1a-H), 3.70-3.60 (m, 3 H, 3a-H, 5b-H, 5a-H), 3.53 (dd, J = 10.0, 4.0 Hz, 1 H, 6a-H), 3.46–3.34 (m, 4 H, 2b-H, 2a-H, 4a-H, 6b-H), 3.30 (s, 3 H, OCH₃), 3.15 (dd, J = 10.0, 6.8 Hz, 1 H, 6'a-H), 3.07(dd, J = 10.8, 8.4 Hz, 1 H, 4b-H), 2.40 (d, J = 10.0 Hz, 1 H, 6b'-H) ppm. ¹³C NMR (100 MHz): δ = 147.56, 139.19, 138.53, 138.43, 138.30, 138.10, 135.86, 133.54 (Ar-Cq), 131.14, 130.86, 129.65, 129.03, 128.52, 128.31, 128.29, 128.27, 128.08, 127.99, 127.81, 127.78, 127.53, 122.88 (Ar-C), 97.96 (C-1a), 97.28 (C-1b), 84.00 (C-2a), 82.63 (C-3b), 81.72 (C-3a), 80.24 (C-2b), 77.55 (C-4a), 77.42 (C-4b), 75.68, 75.43, 74.88, 73.31, 73.14, 71.92 (OCH₂Ar), 70.99 (C-5b), 70.12 (C-5a), 69.14 (C-6b), 68.77 (C-6a), 66.67 (OCH₂Ar), 55.19 (OCH₃), 50.60 (NCH₂Ar) ppm. HRMS (+ mode): calcd. for $C_{59}H_{65}N_{3}O_{11}$ [M + H]⁺ 990.4541; found 990.4512.

51β: Colourless oil. $R_{\rm f} = 0.34$ (30% EtOAc/toluene). $[a]_{\rm D}^{25} = -11.3$ $(c = 1, \text{CHCl}_3)$. ¹H NMR (CDCl₃, 400 MHz): $\delta = 7.36$ (s, 1 H, triazole H), 7.31–7.16 (m, 27 H, Ar-H), 7.07 (dd, J = 7.6, 2.0 Hz, 1 H, Ar-H), 5.37 and 5.27 (each d, each J = 14.4 Hz, each 1 H, Nbenzylic H), 4.92 (d, J = 12.4 Hz, 1 H, benzylic H), 4.92 (d, J = 13.2 Hz, 1 H, benzylic H), 4.82-4.75 (m, 3 H, benzylic H), 4.69 (d, J = 10.8 Hz, 1 H, benzylic H), 4.68 and 4.66 (each d, each J =12.0 Hz, each 1 H, benzylic H), 4.64 (d, J = 12.8 Hz, 1 H, benzylic H), 4.52 (d, J = 12.0 Hz, 1 H, benzylic H), 4.49–4.42 (m, 3 H, 1a-H merged with two benzylic H), 4.40 (d, J = 12.0 Hz, 1 H, benzylic H), 4.14 (d, J = 7.2 Hz, 1 H, 1b-H), 4.9 (d, J = 12.8 Hz, 1 H, benzylic H), 3.87 (dd, J = 9.2 Hz, 1 H, 3b-H), 3.64 (dd, J = 11.6, 3.6 Hz, 1 H, 6a-H), 3.60-3.45 (m, 6 H, 6b-H, 6a-H, 4a-H, 5b-H, 3a-H), 3.39 (dd, J = 9.6, 3.2 Hz, 1 H, 2a-H), 3.33–3.28 (m, 3 H, 2b-H, 4b-H, 5a-H), 3.26 (s, 3 H, OCH₃) ppm. ¹³C NMR (100 MHz): δ = 145.97, 138.76, 138.42, 138.35, 138.31, 138.15, 138.02, 131.35 (Ar-Cq), 131.05, 129.42, 128.49, 128.45, 128.42, 128.40, 128.39, 128.05, 128.01, 127.94, 127.87, 127.82, 127.76, 127.72, 127.60, 127.56, 123.28 (Ar-C), 101.76 (C-1b), 98.20 (C-1a), 85.68 (C-3a), 81.96 (C-4b), 81.47 (C-3b), 79.88 (C-2a), 78.78 (C-2b), 77.97 (C-4a), 75.38 (OCH₂Ar), 75.36 (C-5a), 75.25, 74.86, 73.47, 73.26, 71.23 (OCH₂Ar), 70.37 (C-5b), 69.11 and 69.06 (C-6b, C-6a), 66.79 (OCH₂), 55.61 (OCH₃), 52.27 (NCH₂Ar) ppm. HRMS (+ mode): calcd. for $C_{59}H_{65}N_3O_{11}$ [M + H]⁺ 990.4541; found 990.4489.

Compounds 56a and 56β: Compound **55** (0.7 mg, 0.63 mmol) on treatment with NIS (0.3 mg, 1.27 mmol) and TMSOTf (40 μ L, 0.20 mmol) in dry CH₂Cl₂ (30 mL) for 2 h and workup as described in general procedure D afforded **56a** and **56β** as a colourless oil (0.5 mg, 80%). The two compounds were successfully separated in pure form and characterized by their spectroscopic data. The configuration of glycosidation product **56a** was successfully confirmed by treatment with H₂ and Pd/C in methanol for 2 d in the presence of 2 drops of concentrated HCl followed by acetylation using Ac₂O in pyridine. The compound, although obtained in low yield (10%), had spectroscopic data (¹H and ¹³C NMR) that closely matched those of known material **57**.

56a: Colourless oil. $R_f = 0.35$ (30% EtOAc/toluene). $[a]_D^{25} = +47.5$ (c = 1, CHCl₃). ¹H NMR (CDCl₃, 400 MHz): $\delta = 7.47$ (s, 1 H, triazole H), 7.30–7.12 (m, 29 H, Ar-H), 5.61 and 5.14 (each d, each J = 14.8 Hz, each 1 H, *N*-benzylic H), 4.91 (d, J = 13.2 Hz, 1 H,

benzylic H), 4.87 (d, J = 10.0 Hz, 1 H, benzylic H), 4.79 (d, J =10.8 Hz, 1 H, benzylic H), 4.75 (d, J = 11.6 Hz, 1 H, benzylic H), 4.70 (d, J = 10.8 Hz, 1 H, benzylic H), 4.69 and 4.63 (each d, each J = 11.2 Hz, each 1 H, benzylic H), 4.58 (d, J = 12.0 Hz, 1 H, benzylic H), 4.51 (d, J = 12.0 Hz, 1 H, benzylic H), 4.50 (d, J =14.0 Hz, 1 H, benzylic H), 4.43 (d, J = 12.0 Hz, 1 H, benzylic H), 4.38 (d, J = 4.0 Hz, 1 H, 1b-H), 4.35 (d, J = 11.6 Hz, 1 H, benzylic H), 4.29 (d, J = 12.0 Hz, 1 H, benzylic H), 4.22 (d, J = 11.6 Hz, 1 H, benzylic H), 4.03 (d, J = 3.6 Hz, 1 H, 1a-H), 3.81 (dd, J =9.2 Hz, 1 H, 3b-H), 3.75 (ddd, J = 8.8, 2.0, 1.2 Hz, 1 H, 5a-H), 3.69 (m, 1 H, 5b-H), 4.65 (d, J = 9.2 Hz, 1 H, 3a-H), 3.54--3.48 (m, 1 H, 5b-H), 3.54--3.48 (m, 2 H, 5b-H)3 H, 4b-H, 4a-H, 6a-H), 3.41 (dd, J = 10.8, 2.0 Hz, 1 H, 6b-H), 3.31 (dd, J = 10.0, 3.6 Hz, 1 H, 2a-H), 3.21 (s, 3 H, OCH₃), 3.05 (d, J = 9.6 Hz, 1 H, 3b-H), 2.92–2.88 (m, 2 H, 6b'-H, 2b-H) ppm. ¹³C NMR (100 MHz): δ = 147.09, 139.44, 139.09, 138.82, 138.78, 138.30, 138.12, 135.55 (Ar-Cq), 129.23, 128.67, 128.52, 128.50, 128.38, 128.34, 128.27, 128.14, 128.09, 128.05, 127.94, 127.85, 127.79, 127.77, 127.62, 127.58, 127.54, 127.49, 122.68 (Ar-C), 97.53 (C-1a), 97.37 (C-1b), 83.65 (C-4b), 81.78 (C-3b), 81.78 (C-3a), 79.99 (C-2b), 79.12 (C-2a), 77.70 (C-4a), 75.90, 75.58, 74.89, 74.73, 73.26, 73.12 (OCH₂Ar), 69.97 and 69.94 (C-5b, C-5a), 68.73 (C-6b), 68.43 (C-6a), 66.28 (OCH₂Ar), 55.32 (OCH₃), 54.14 (NCH₂Ar) ppm. HRMS (+ mode): calcd. for C₅₉H₆₅N₃O₁₁ [M + H]⁺ 990.4541; found 990.4548.

56β: Colourless oil. $R_{\rm f} = 0.30$ (30% EtOAc/toluene). $[a]_{\rm D}^{25} = -13.5$ $(c = 1, \text{CHCl}_3)$. ¹H NMR (CDCl₃, 400 MHz): $\delta = 7.61$ (s, 1 H, triazole H), 7.40-7.21 (m, 28 H, Ar-H), 6.93 (s, 1 H, Ar-H), 5.63 and 5.59 (each d, each J = 16.0 Hz, each 1 H, N-benzylic H), 5.08 (d, J = 10.0 Hz, 1 H, benzylic H), 5.06 (d, J = 11.2 Hz, 1 H, benzylic H), 4.95 (d, J = 11.2 Hz, 1 H, benzylic H), 4.92 and 4.90 (each d, each J = 12.0 Hz, each 1 H, benzylic H), 4.89–4.83 (m, 2 H, benzylic H), 4.80 (d, J = 12.0 Hz, 1 H, benzylic H), 4.72 (d, J =12.0 Hz, 1 H, benzylic H), 4.61-4.57 (m, 3 H, benzylic H), 4.54 (d, J = 12.0 Hz, 1 H, benzylic H), 4.53 (d, J = 3.6 Hz, 1 H, 1a-H), 4.50 (d, J = 11.6 Hz, 1 H, benzylic H), 4.29 (d, J = 7.6 Hz, 1 H, 1b-H), 3.96 (dd, J = 9.2 Hz, 1 H, 3b-H), 3.69-3.62 (m, 4 H, 4b-H), 33a-H, 5b-H, 6a'-H), 3.58 (d, J = 11.6 Hz, 1 H, 6b-H), 3.51–3.45 (m, 4 H, 6a-H, 4a-H, 2b-H), 3.40-3.35 (m, 5 H, 2a-H, 5a-H, OCH₃) ppm. ¹³C NMR (100 MHz): δ = 146.57, 139.70, 139.02, 138.52, 138.26, 138.17, 138.14, 135.84 (Ar-Cq), 128.70, 128.56, 128.45, 128.41, 128.02, 128.01, 127.90, 127.72, 127.56, 127.52, 126.82, 123.04 (Ar-C), 104.37 (C-1b), 97.92 (C-1a), 85.44 (C-3a), 82.25 (C-3b, C-2a), 80.22 (C-2b), 78.43 (C-4a), 77.65 (C-4b), 75.60, 75.32 (OCH₂Ar), 75.11 (C-5a), 74.94, 74.87, 73.38, 73.11 (OCH₂Ar), 71.70 (C-6b), 70.49 (C-5b), 68.84 (C-6a), 65.69 (OCH₂), 55.32 (OCH₃), 53.54 (NCH₂Ar) ppm. HRMS (+ mode): calcd. for $C_{59}H_{65}N_{3}O_{11}$ [M + H]⁺ 990.4541; found 990.4479.

Compounds 65α,β: Compound 64 (0.6 g, 0.546 mmol) on treatment with NIS (245 mg, 1.09 mmol) and TMSOTf (25 µL, 0.13 mmol) in dry CH₂Cl₂ (20 mL) for 2 h and workup as described in general procedure D afforded an anomeric mixture of $65\alpha,\beta$ as a colourless oil (486 mg, 90%) The pure isomers could not be separated (α/β = 3:1). $R_{\rm f} = 0.3$ (35% EtOAc/toluene). ¹H NMR (CDCl₃, 400 MHz): δ = 7.61 (s, 1 H, triazole H, minor isomer), 7.45–7.01 (m, 30 H, triazole H, major isomer, Ar-H, major and minor isomer), 5.62 (d, J = 14.4 Hz, 1 H, N-benzylic H, minor isomer), 5.56 (d, J =14.0 Hz, 1 H, N-benzylic H, major isomer), 5.47 (d, J = 14.0 Hz, 1 H, N-benzylic H, major isomer), 5.42 (d, J = 14.4 Hz, 1 H, Nbenzylic H, minor isomer), 5.09 (d, J = 10.8 Hz, 1 H, benzylic H, major isomer), 5.02 (d, J = 12.8 Hz, 1 H, benzylic H, minor isomer), 4.87 (d, J = 10.8 Hz, 1 H, benzylic H, major isomer), 4.86 (d, J = 10.4 Hz, 1 H, benzylic H, minor isomer), 4.81 (d, J = 10.8 Hz, 1 H, benzylic H, minor isomer), 4.79 (d, J = 11.6 Hz, 1 H, benzylic



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H, major isomer), 4.76–4.63 (m, 5 benzylic H for each major and minor isomer, 1 H, benzylic H for minor isomer), 4.61–4.53 (m, 2 H, benzylic H for each major and minor isomer), 4.52–04.50 (m, 1 H, for 1b-H major isomer, J = 5.6 Hz and 1b-H for minor isomer J = 9.2 Hz), 4.48–4.34 (m, 2 benzylic H for each major and minor isomer, 1 H, benzylic H for major isomer), 4.30 (d, J = 4.8 Hz, 1 H, 1a-H, minor isomer), 4.25 (d, J = 12.8 Hz, 1 H, benzylic H, minor isomer), 4.19 (d, J = 3.2 Hz, 1 H, 1a-H, major isomer), 4.10 (d, J = 12.0 Hz, 1 H, benzylic H, minor isomer), 4.06 (dd, J = 12.8, 100)2.4 Hz, 1 H, 6a-H, major isomer), 3.96 (dd, J = 9.2 Hz, 1 H, 3b-H, minor isomer), 3.88 (m, 1 H, 5b-H, minor isomer), 3.86 (m, 1 H, 5a-H, minor isomer), 3.82 and 3.80 (each dd, each J = 9.2 Hz, 3b-H, 3a-H, major isomer), 3.72 (dd, J = 10.4, 5.6 Hz, 4a-H, minor isomer), 3.60-3.40 (m, 13 H, 5b-H, major isomer, 4b-H, major isomer, 3a-H, minor isomer, 5a-H, major isomer, 4a-H, major isomer, 2a-H major isomer, 4b-H, minor isomer, 6b-H, minor isomer, 6b-H, 6a'-H, 6b'-H, major isomer), 3.32-3.31 (m, 4 H, 2a-H of minor isomer merged with OCH_3 of major isomer), 3.28 (s, 3 H, OCH_3 , minor isomer), 3.23 (dd, J = 9.2, 3.6 Hz, 1 H, 2b-H, major isomer) ppm. ¹³C NMR (100 MHz): $\delta = 145.31, 145.30, 139.35,$ 139.31, 139.03, 138.68, 138.38, 138.33, 138.22, 138.13, 138.10, 138.06, 136.72, 133.03, 132.07, 131.81, 131.69, 131.35, 131.23, 129.62, 129.34, 129.19, 128.92, 128.46, 128.41, 128.37, 128.35, 128.32, 128.21, 128.03, 127.99, 127.95, 127.72, 127.60, 127.55, 127.40, 127.38, 127.22, 124.65, 123.47 (Ar-C, major and minor isomer), 101.61 (C-1b, minor isomer), 98.34 (C-1b, major isomer), 97.74, (C-1a, minor isomer), 97.13, (C-1a, major isomer), 85.41, 81.92, 81.91, 80.41, 80.26, 80.25, 78.96, 78.85, 78.19, 77.84, 75.83, 75.33, 75.32, 74.97, 74.90, 74.46, 73.63, 73.38, 73.33, 73.25, 72.08, 71.29, 71.12, 70.44, 69.48, 69.09, 68.83, 66.17 (C-6b, minor isomer), 65.65 (C-6a, major isomer), 55.54 (OCH₃, major isomer), 55.06 (OCH₃, minor isomer), 52.69 (NCH₂Ar, minor isomer), 52.05 (NCH₂Ar, major isomer) ppm. HRMS (+ mode): calcd. for $C_{59}H_{65}N_3O_{11}$ [M + H]⁺ 990.4541; found 990.4547.

Compounds 70a and 706: Compound **69** (250 mg, 0.227 mmol) on treatment with NIS (101 mg, 0.455 mmol) and TMSOTf (25 μ L, 0.13 mmol) in dry CH₂Cl₂ (15 mL) for 2 h and workup as described in general procedure D afforded **70a** and **70β** as a colourless oil (185 mg, 82%, α/β = 1:2). The two compounds were successfully separated in pure form and characterized by their comparative spectroscopic data.

70a: $R_{\rm f} = 0.32$ (30% EtOAc/toluene). $[a]_{\rm D}^{25} = +27.2$ (c = 1, CHCl₃). ¹H NMR (CDCl₃, 400 MHz): δ = 7.73 (s, 1 H, triazole H), 7.30– 7.15 (m, 29 H, Ar-H), 7.12 (s, 1 H, Ar-H), 7.10 and 7.08 (each d, each J = 8.0 Hz, each 1 H, Ar-H), 7.02 (d, J = 8.0 Hz, 1 H, Ar-H), 5.59 and 5.22 (each d, each J = 15.2 Hz, each 1 H, N-benzylic H), 4.98, 4.91, 4.86, 4.82, 4.79 and 4.77 (each d, each J = 12.0 Hz, each 1 H, benzylic H), 4.71-4.65 (m, 1 H, benzylic H), 4.55 (d, J = 12.0 Hz, 1 H, benzylic H), 4.52 (d, J = 4.0 Hz, 1 H, 1a-H), 4.49 (d, J = 4.0 Hz, 1 H, 1b-H), 4.42 (d, J = 12.0 Hz, 1 H, benzylic H), 4.35 and 4.31 (each d, each J = 12.8 Hz, each 1 H, benzylic H), 4.23 (d, J = 12.0 Hz, 1 H, benzylic H), 4.07 and 4.05 (each dd, each J = 9.6 Hz, each 1 H, 3b-H, 3a-H), 3.93 (d, J = 9.6 Hz, 1 H, 4b-H), 3.66 (dd, J = 12.0, 4.0 Hz, 1 H, 6a-H), 3.59–3.50 (m, 2 H, 5b-H, 5a-H), 3.49 (dd, J = 8.8 Hz, 1 H, 6a'-H), 3.45 (d, J =12.0 Hz, 1 H, 6b-H), 3.37-3.30 (m, 3 H, 6b'-H, 2a-H, 4a-H), 3.17-3.12 (m, 4 H, 2b-H, 4a-H), 3.17-3.12 (m, 5 H, OCH₃, 3b-H, 4a-H) ppm. ¹³C NMR (100 MHz): δ = 139.96, 138.66, 138.18, 138.13, 138.06, 137.99, 137.93, 135.65 (Ar-Cq), 128.72, 128.49, 128.45, 128.40, 128.36, 128.26, 128.17, 127.99, 127.96, 127.84, 127.80, 127.66, 127.62, 127.59, 127.36, 127.21, 127.22, 124.04 (Ar-C), 97.72 (C-1b), 97.63 (C-1a), 86.32 (C-5b), 80.99 (C-5a), 78.43 (C-2b), 77.98 (C-2a), 75.89 (C-4a), 75.46 (C-3b), 75.38 (C-3a), 74.88, 74.79,

74.64, 73.45, 73.34 and 72.86 (OCH₂Ar), 69.20 (C-6a), 68.95 (C-6b), 68.74 (C-4b), 65.44 (CH₂Ar), 55.08 (OCH₃), 53.99 (NCH₂Ar) ppm. HRMS (+ mode): calcd. for $C_{59}H_{65}N_3O_{11}$ [M + H]⁺ 990.4541; found 990.4167.

70β: $R_{\rm f} = 0.41$ (30% EtOAc/toluene). $[a]_{\rm D}^{25} = -9.4$ (c = 1, CHCl₃). ¹H NMR (CDCl₃, 400 MHz): δ = 7.70 (s, 1 H, triazole H), 7.32 (m, 23 H, Ar-H), 7.12 (dd, J = 8.0, 1.6 Hz, 2 H, Ar-H), 6.98 (d, J = 8.0 Hz, 1 H, Ar-H), 6.63 (s, 1 H, Ar-H), 5.72 (d, J = 12.0 Hz, 1 H, benzylic H), 5.35 (d, J = 12.8 Hz, 1 H, benzylic H), 5.20 (d, J = 10.8 Hz, 1 H, benzylic H), 8.77-8.74 (m, 4 H, benzylic H), 4.70 (d, J = 12.0 Hz, 1 H, benzylic H), 4.61 (d, J = 12.0 Hz, 1 H, benzylic H), 4.53 (d, J = 12.0 Hz, 1 H, benzylic H), 4.46 (d, J = 4.0 Hz, 1 H, 1a-H), 4.44 (d, J = 8.0 Hz, 1 H, 1b-H), 4.42 (d, J = 12.0 Hz, 1 H, benzylic H), 4.41 (d, J = 12.0 Hz, 1 H, benzylic H), 4.39 (d, J = 12.0 Hz, 1 H, benzylic H), 4.38–4.29 (m, 4 H, 6a-H merged with 3 benzylic H), 3.94-3.88 (m, 2 H, 3b-H, 5a-H), 3.80-3.72 (m, 2 H, 3a-H, 5-H), 3.54 (dd, J = 12.0, 1.6 Hz, 1 H, 6b-H), 3.48-3.36 (m, 4 H, 6a'-H, 4a-H, 2a-H, 6b'-H), 3.35 (d, J = 9.2 Hz, 1 H, 4a-H), 3.27 (s, 3 H, OCH₃), 3.24 (d, J = 4.0 Hz, 1 H, 2a-H) ppm. ¹³C NMR (100 MHz): $\delta = 146.71$, 140.08, 140.01, 138.82, 138.53, 138.13, 138.10, 135.57 (Ar-Cq), 128.41, 128.40, 128.39, 128.38, 128.35, 128.32, 128.31, 128.10, 127.99, 127.97, 127.75, 127.74, 127.69, 127.68, 127.35, 127.34, 125.72, 124.45, 124.03 (Ar-C), 101.28 (C-1b), 98.02 (C-1a), 82.25 (C-3b), 81.28 (C-3a), 80.67 (C-5b), 79.21 (C-2a), 78.74 (C-4b), 78.25 (C-2b), 75.96, 75.73, 75.06, 73.51, 73.39, 72.60 (OCH₂Ar), 71.21 (C-5b), 70.69 (C-4a), 69.72 (C-6a), 69.59 (C-6b), 65.01 (OCH₂), 55.33 (OCH₃), 53.48 (NCH₂Ar) ppm. HRMS: HRMS (+ mode): calcd. for $C_{59}H_{65}N_{3}O_{11}$ [M + H]⁺ 990.4541; found 990.4168.

Compound 77a: Compound 76 (0.4 g, 0.357 mmol) on treatment with NIS (160 mg, 0.715 mmol) and TMSOTf (45 µL, 0.24 mmol) in dry CH₂Cl₂ for 2 h and workup as described in general procedure D afforded 77a as a colourless oil (0.19 g, 55%). $R_{\rm f} = 0.33$ (30% EtOAc/toluene). $[a]_D^{25} = +1.5$ (c = 1, CHCl₃). ¹H NMR $(CDCl_3, 400 \text{ MHz}): \delta = 7.96 \text{ (d, } J = 8.0 \text{ Hz}, 2 \text{ H}, \text{ Ar-H}), 7.50-7.37$ (m, 5 H, Ar-H), 7.34-7.11 (m, 22 H, triazole H, Ar-H), 7.01 (dd, J = 8.4, 2.0 Hz, 1 H, Ar-H), 5.88 and 5.57 (each d, each J =14.8 Hz, each 1 H, N-benzylic H), 4.85 and 4.83 (each d, each J =10.8 Hz, each 1 H, benzylic H), 4.79 (d, J = 10.8 Hz, 1 H, benzylic H), 4.74 (d, J = 11.2 Hz, 1 H, benzylic H), 4.72–4.66 (m, 3 H, 6a-H merged with benzylic H), 4.66 (d, J = 12.0 Hz, 1 H, benzylic H), 4.62 (d, J = 4.0 Hz, 1 H, 1b-H), 4.57 and 4.53 (each d, each J =12.0 Hz, each 1 H, benzylic H), 4.51–4.48 (m, 3 H, 1a-H, benzylic H), 5.45 (d, J = 10.8 Hz, 1 H, benzylic H), 5.43 (d, J = 10.4 Hz, 1 H, benzylic H), 3.76–3.71 (m, 2 H, 5a-H, 3a-H), 3.67 (dd, J = 11.2, 2.0 Hz, 1 H, 6b-H), 3.66-3.57 (m, 3 H, 6b'-H, 5b-H, 4b-H), 3.55 (dd, J = 9.6 Hz, 1 H, 3b-H), 3.49–3.38 (m, 3 H, 2b-H, 2a-H, 4a-H), 3.28 (s, 3 H, OCH₃) ppm. ¹³C NMR (100 MHz): δ = 166.91 (COPh), 145.31, 138.61, 138.36, 138.32, 138.10, 136.02, 134.25, 133.23, 131.93, 130.28, 129.81, 127.51, 129.16, 128.92, 128.86, 128.63, 128.48, 128.45, 128.37, 128.27, 128.00, 127.93, 127.82, 127.72, 127.88, 127.59, 127.48, 123.00 (Ar-C), 97.73 (C-1b), 97.72 (C-1a), 87.12 (C-3a), 86.57 (C-3b), 81.21 (C-2b), 80.95 (C-2a), 80.12 (C-4b), 79.17 (C-4a), 76.77, 75.77, 75.59, 75.06, 73.45, 71.13 (CH₂Ar), 70.39 (C-5a), 67.62 (C-5b), 66.72, 63.73 (C-6b, C-6a), 55.13 (OCH₃), 50.98 (NCH₂Ar) ppm. HRMS (+ mode): calcd. for $C_{59}H_{63}N_3O_{12}$ [M + H]⁺ 1004.4334; found 1004.4298.

Supporting Information (see footnote on the first page of this article): Synthetic methods for all donors, acceptors and intermediates required to investigate the intramolecular glycosylation reactions and the ¹H and ¹³C NMR spectra of all the synthesized compounds.

FULL PAPER

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Disaccharide-Containing Macrocycles



Click Chemistry

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CuAAC reactions between a 2-*O*-propargyl glucopyranosyl donor and *O*-(2- or 3-azidomethylbenzyl) glycosyl acceptors provide a convenient access to donor–acceptorligated intermediates with triazole as a

rigid spacer. Glycosylation led to disaccharides within 15–17-membered macrocycles in good-to-excellent yields, confirming the efficiency of this approach to intramolecular glycoside bond formation.

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R.	R.	Schmidt*	••••••	1–13

Disaccharide-Containing Macrocycles by Click Chemistry and Intramolecular Glycosylation

Keywords: Carbohydrates / Glycosylation / Macrocycles / Nitrogen heterocycles / Click chemistry