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Study of the Glycosidation Properties of 1-Thiomannosazidopyranosides and 1-Thiomannosaziduronic Acid Esters

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A study of the glycosylation properties of 1-thiomannosazides with a variety of electron-withdrawing substituents in combination with the Ph_2SO/Tf_2O and NIS/TMSOTf reagent systems is presented. Further, assembly of the fully protected trisaccharide **26**, which corresponds to the repeating unit of the enterobacterial common antigen, using both an orthogonal and a chemoselective coupling strategy and based on the outcome of our glycosylation studies, is discussed.

Introduction

N-Acetylmannosamine and *N*-acetylmannosaminuronic acids are constituents of various bacterial capsular polysaccharides and lipopolysaccharides.[1] In most cases, these mannoside residues are connected to the next monosaccharide residue through a 1,2-*cis* linkage.[2] This β-oriented linkage is notoriously difficult to install by chemical synthesis.[3] This is, amongst other reasons, caused by the anomeric effect in the *manno* series, which is enlarged by the Δ2 effect of the axially oriented C-2 function, favoring formation of 1,2-*trans*-oriented linkages. Several methodologies for the synthesis of β-linked mannopyranoside residues have been explored.[4] These include methods in which the O-2 position of β-D-glucopyranosides is oxidized and reduced[5] or displaced in an S_N2-type fashion by an azido nucleophile.[6] Other procedures involve silver silicate mediated S_N2 displacement of α-bromides[7] or intramolecular aglycon delivery[8] as the key step. The finding by Crich and co-workers that activation of 4,6-*O*-benzylidene-protected mannopyranosyl sulfoxide donors with triflic anhydride leading to the formation of β-mannoside linkages proved to be a breakthrough in this field of research.[9] Later studies demonstrated that comparable β-selectivities can be attained using 4,6-*O*-benzylidene-protected 1-thiomannosides in combination with phenylsulfenyl triflate[10] (PhSOTf) or 1-(phenylsulfinyl)piperidine (BSP, **1a**)/triflic anhydride (Tf_2O) as activation systems (Figure 1).[11,12] The β-directing effect of the 4,6-*O*-benzylidene protecting group on β-selective mannosylations was initially explained by increased torsional strain.[13] Recently, Bols and co-workers argued that electronic effects[14] have a major influence on the stereochemical outcome of glycosylation reactions involving 4,6-*O*-benzylidenemannoside donors.[15] The decisive effect of 4,6-*O*-benzylidene protection in mannopyranose donors is further underscored by the finding that variations in the glycosylation procedures and promoter systems only led to minor fluctuations in the stereochemical outcome of the β-mannosylation reaction.[16] In addition, we have published the results of a study of the glycosylation properties of 4,6-*O*-benzylidene-protected 1-phenylthio-D-mannosazidopyranoside donors using diphenyl sulfoxide (Ph_2SO, **1b**)/Tf_2O[17] as the activation system (Figure 1).[18]

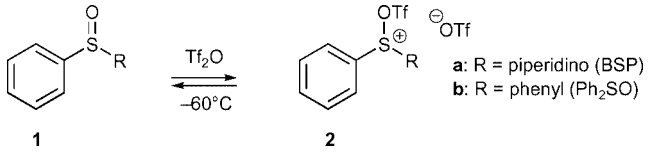

Figure 1. Sulfonium activator systems used for the activation of 1-thioglycosides.

The finding that the deactivating effect of a 4,6-*O*-benzylidene protective group on glycosyl transfer is at least partially governed by electronic effects suggests that the introduction of sufficient electron-withdrawing functionalities in the mannose core may also lead to β-mannosylation.[19] In fact, Schuerch and co-workers demonstrated in 1980 that mannopyranose donors having a strongly electronegative non-participating substituent at C-2 (such as tosyl) and a highly reactive electronegative leaving group at C-1 (such as tosyl or chloride) results in high β-selectivities.[20] Application of this approach is limited by the harsh conditions required for removal of the C-2 tosyl functionality and the moderate selectivities obtained with sterically encumbered acceptor nucleophiles. We recently revealed that installation of a carboxylic acid functionality at the C-5 position of suitably protected 1-thiomannosides strongly favours S_N2-

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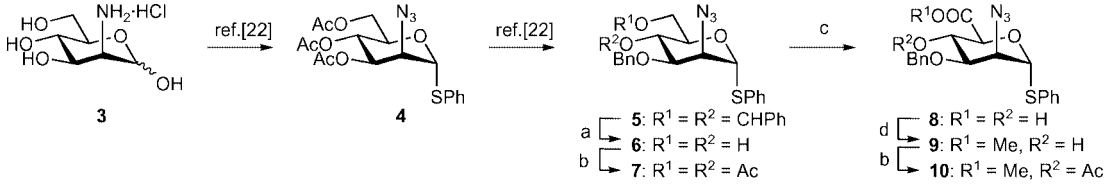
type displacement of the putative α-triflate intermediate resulting in high to exclusive β-selectivities.[21] In line with these studies we have investigated the glycosylation properties, in terms of yield and stereoselectivity, of 1-thio-α-D-mannosazidopyranoside donors **4**, **7** and **10** having electron-withdrawing functionalities on different positions of the pyranoside core. The outcome of these studies and their application in the assembly of the fully protected repeating unit trisaccharide **26** of the enterobacterial common antigen (ECA) are presented here.

Results and Discussion

Donor glycosides **4**, **7** and **10** were obtained starting from commercially available D-mannosamine hydrochloride **3** as follows. Subjection of **3** to diazo transfer, followed by acetylation and finally Lewis acid catalyzed introduction of the anomeric phenylthio group gave tri-*O*-acetylmannosazide **4**.[22] Deacetylation followed by installation of the 4,6-*O*-benzylidene acetal, introduction of the benzyl group at the C-3 position and acidic removal of the benzylidene acetal yielded diol **6** in good yield. Acetylation of diol **6** afforded O-3-benzylated glycoside **7**. Chemo- and regioselective oxidation of the diol **6** using the TEMPO/BAIB {[bis(acetoxy)-iodo]benzene} reagent combination[23] afforded the corresponding mannosaziduronic acid **8** in 65% yield. Methylation of the free carboxylic acid to give **9** and acetylation of the residual C-4 position afforded uronic ester donor **10** (Scheme 1).

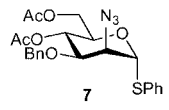
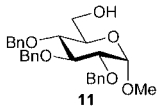
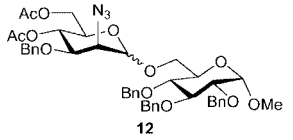
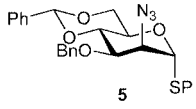
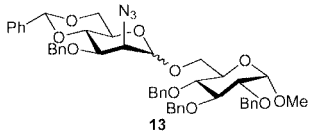
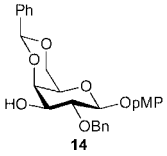
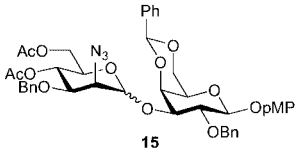
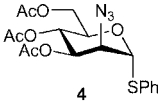
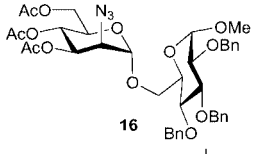
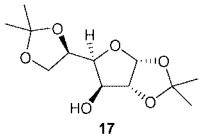
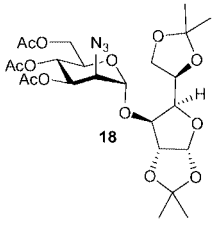
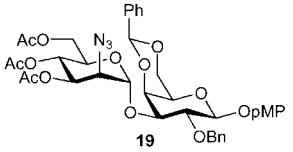
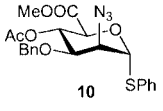
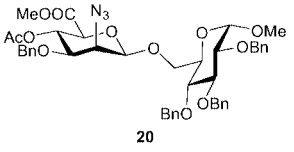
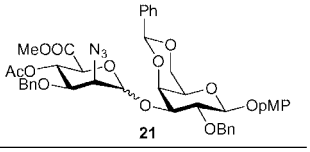
Having our target donor mannosides in hand, we turned our attention to the investigation of their glycosylation properties. Phenyl 4,6-di-*O*-acetyl-2-azido-3-*O*-benzyl-2-deoxy-1-thio-α-D-mannopyranoside (**7**) was condensed, under the influence of in situ generated diphenylsulfonium bis-(triflate) (**2b**), with methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**11**) (Table 1, Entry 1). Donor **7** was preactivated by treatment with 1.4 equiv. of Ph_2SO (**1b**) and 1.4 equiv. of Tf_2O at –60 °C in the presence of the acid scavenger 2,4,6-tri-*tert*-butylpyrimidine (TTBP).[24] After 15 min, during which time the temperature gradually rose to –50 °C, acceptor **11**[25] was added and then the reaction mixture was warmed to room temperature. Disaccharide **12** was isolated in 86% yield as an anomeric mixture (α/β = 1:4).[26] The outcome of this glycosylation procedure in terms of yield and anomeric ratio does not substantially differ from that of the condensation of 4,6-*O*-benzylidene-protected donor **5** with the same acceptor (Entry 2). Condensation of diacetyl donor **7** with secondary alcohol acceptor **14**[27] was executed under the conditions described above giving disaccharide **15** in good yield and with a slight preference for α-anomer formation (Entry 3). This lower α/β ratio agrees with the reported trend that glycosylation of a specific donor with a series of acceptors of decreasing nucleophilicity leads to a change in the anomeric ratio in favour of the α-product.[28] Next, the reactivity of the mannosazide donor was further reduced by replacement of the 3-*O*-benzyl with the 3-*O*-acetyl protective group (**4**). Phenyl 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-1-thio-α-D-mannopyranoside (**4**) was effectively condensed with the highly reactive **11**, the less reactive **17** and the sterically demanding acceptor **14** to give disaccharides **16**, **18** and **19**, respectively (Entries 3–5). In all cases only the α-product was isolated suggesting that the stereochemical outcome of these reactions is independent of the reactivity of the acceptor. These results support earlier observations that 3-*O*-acyl groups in mannopyranose[29] and glucopyranose[30] donors are α-directing as a result of neighbouring-group participation, which proceeds via a six-membered transition state that shields attack at the β-site. Finally, the glycosylation properties of 1-thio-α-mannosaziduronic acid donor **10**, bearing an electron-withdrawing ester moiety at the C-5 position, were investigated. Coupling of donor **10** with primary alcohol **11** gave exclusively β-linked disaccharide **20** in 69% yield. An attempt to glycosylate the secondary alcohol acceptor **14** using the same Ph_2SO/Tf_2O activation protocol did not result in satisfactory product formation. Monitoring of the reaction by TLC analysis showed that the initial preactivation of donor **10** with Ph_2SO/Tf_2O proceeded uneventfully, while addition of the acceptor and warming of the reaction mixture showed, besides the formation of several side-products, partial regeneration of the donor **10**. This indicates that under Ph_2SO/Tf_2O activation conditions the donor glycoside is not always fully converted into the intermediate α-triflate.[31] Changing of the activation system to NIS/TMSOTf[21,32] led to productive coupling of 1-thio-α-mannosaziduronic acid donor **10** with acceptor **14** affording disaccharide **21** in 53% yield as an anomeric mixture (α/β = 1:2).

At this stage we decided to investigate the assembly of the fully protected trisaccharide **26** (Scheme 2). In its unprotected form, this trisaccharide, (→3)-α-D-Fuc*p*4NAc-(1→4)-β-D-Man*p*NAcA-(1→4)-α-D-Glc*p*NAc-(1→), is the repeating unit of the polysaccharide that constitutes 70% or more of the enterobacterial common antigen (ECA).[33,34] The synthetic route to trimer **26** was investi-

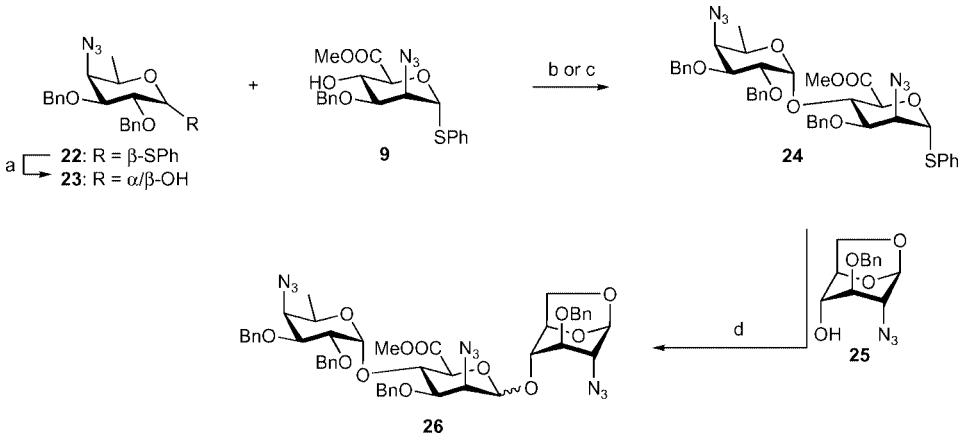


Scheme 1. Synthesis of the donor building blocks. Reagents and conditions: (a) *p*TsOH, MeOH; (b) Ac_2O, pyridine; **7**: 88% (from **4**), **10**: quant.; (c) TEMPO, BAIB, DCM/H_2O (4:1), 65% (from **6**); (d) MeI, K_2CO_3, DMF, 71%.

Table 1. Glycosylation reactions of 2-azido-2-deoxy-1-thio-α-D-mannosides and the corresponding methyl uronates.

Entry	Donor	Acceptor	Activator Yield (α:β)	Disaccharide
1	 **7**	 **11**	Ph_2SO Tf_2O 86% (1:4)	 **12**
2[18]	 **5**	**11**	Ph_2SO Tf_2O 77% (1:3)	 **13**
3	**7**	 **14**	Ph_2SO Tf_2O 82% (3:2)	 **15**
4	 **4**	**11**	Ph_2SO Tf_2O 88% (1:0)	 **16**
5	**4**	 **17**	Ph_2SO Tf_2O 79% (1:0)	 **18**
6	**4**	**14**	Ph_2SO Tf_2O 64% (1:0)	 **19**
7	 **10**	**11**	Ph_2SO Tf_2O 69% (0:1)	 **20**
8		**14**	NIS TMSOTf 53% (1:2)	 **21**

gated starting from the non-reducing end D-fucose residue using both a chemoselective glycosylation[28a] and an orthogonal condensation strategy.[35] In the first instance, known 4-azidothiofucose donor **22**[36] was condensed with 1-thiomannosaziduronic acid ester **9** under the agency of Ph_2SO/Tf_2O to afford, in a chemoselective fashion, α-linked thiodisaccharide **24** in 55% yield. No deterioration of disaccharide **24** in the presence of the transiently formed diphenyl(phenylthio)sulfonium triflate was detected. This is fortunate, because quenching of the reaction with triethyl phosphite (TEP), which we previously reported to be an efficient modulator in chemoselective glycosylation reactions of this type,[28b] would possibly be detrimental to the two azide functionalities in the product disaccharide. We set out to compare this result with an orthogonal glycosylation[37] in which 1-hydroxy donor **23** was condensed with acceptor **9**. To this end, fucose donor **23** was prepared by hydrolysis of the phenylthio function in compound **22** using the NIS/TFA reagent system.[38] Activation of donor **23** with 2.8 equiv. of Ph_2SO and 1.3 equiv. of Tf_2O at –40 °C for 1 h followed by the addition of acceptor **9** gave α-linked thiodisaccharide **24** in 67% yield. Treatment of a



Scheme 2. Synthesis of protected trisaccharide **26**. Reagents and conditions: (a) NIS, TFA, DCM/H_2O (10:1), 73%; (b) **22**, Ph_2SO, Tf_2O, TTBP, DCM, –60 °C then **9**, 55%; (c) **23**, Ph_2SO, Tf_2O, TTBP, DCM, –40 °C then **9**, 67%; (d) **25**, NIS, TMSOTf, DCM, 65% (α/β = 1:2).

mixture of 1-thiodisaccharide donor **24** with 1,6-anhydro acceptor **25**[39] and the NIS/TMSOTf reagent combination finally afforded trisaccharide **26** in 65% yield as a 1:2 (α/β) separable anomeric mixture.

Conclusions

This paper describes the glycosylation properties of 1-thiomannosazidopyranosides bearing electron-withdrawing substituents at different positions of the carbohydrate core. We found that 4,6-di-*O*-acetyl protection of 1-thiomannosazides sufficiently influences the electronic environment around the anomeric centre leading to reasonable β-selectivities, whereas acyl protection at the C-3 position gives exclusive α-glycoside formation. Furthermore, uronic acid ester functionalized mannosazides (e.g., **10**) also showed good to excellent β-selectivities.

Experimental Section

General Procedures: ^1H and ^{13}C NMR spectra were recorded with Bruker DMX-400, AV-400 (both 400/100 MHz) and AV500 (500/125 MHz) spectrometers. Chemical shifts (δ) are given in ppm relative to tetramethylsilane as internal standard. Coupling constants are given in Hz. All ^{13}C spectra are proton-decoupled. Mass spectra were recorded with a PE/SCIEX API 165 instrument with an electrospray interface and Q-Star Applied Biosystems Q-TOF (TOF section) system. Optical rotations were measured with a Propol automatic polarimeter. IR spectra were recorded with a Shimadzu FTIR-8300 spectrometer. Traces of water in the donor and acceptor glycosides, diphenyl sulfoxide and TTBP were removed by coevaporation with toluene. TTBP was synthesized as described by Crich et al.[24] Dichloromethane (DCM, Baker p.a.) was refluxed in the presence of P_2O_5 for 2 h and distilled prior to use. Trifluoromethanesulfonic anhydride was distilled from P_2O_5. Molecular sieves (MS) (3 Å) were flame-dried before use. Solvents used for flash chromatography and TLC were of technical grade and distilled before use. Flash chromatography was performed with Fluka silica gel 60 (0.04–0.063 mm). TLC was conducted with DC-Alufolien (Merck, Kieselgel60, F_{254}) with detection by UV absorption (254 nm) where applicable and by spraying with 20% sulfuric acid in ethanol followed by charring at around 150 °C or by spraying with a solution of $(NH_4)_6Mo_7O_{24}\cdot H_2O$ (25 g/L) and $(NH_4)_4Ce(SO_4)_4\cdot 2H_2O$ (10 g/L) in 10% aqueous sulfuric acid followed by charring at around 150 °C. PE = petroleum ether; pMP = *p*-methoxyphenyl.

General Procedure for Glycosidation Reactions with Ph_2SO/Tf_2O: A solution of 1-thiomannopyranoside uronic acid ester (1 equiv.), diphenyl sulfoxide (1.3 equiv.) and tri-*tert*-butylpyrimidine (2.5 equiv.) in DCM (0.05 M) was stirred in the presence of activated MS (3 Å) for 30 min. The mixture was cooled to –60 °C before triflic anhydride (1.3 equiv.) was added. The mixture was then warmed to –50 °C in 15 min and acceptor (1.5 equiv.) in DCM (0.15 M) was added. Stirring was continued and the reaction mixture was warmed to room temperature. The reaction mixture was diluted with EtOAc and washed with water. The aqueous layer was extracted twice with EtOAc. The collected organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash chromatography (EtOAc/PE) and removal of the eluent afforded the corresponding disaccharides.

Phenyl 4,6-Di-*O*-acetyl-2-azido-3-*O*-benzyl-2-deoxy-1-thio-α-D-mannopyranoside (7): Compound **4** (381 mg, 0.9 mmol) was dissolved in MeOH (3 mL) before a catalytic amount of KO*t*Bu was added. After TLC analysis indicated complete reaction, the reaction mixture was neutralized using Amberlite IR120, H^+-form. The reaction mixture was filtered and concentrated under reduced pressure. The crude oil was suspended in acetonitrile (3 mL) followed by addition of benzaldehyde dimethyl acetal (0.15 mL, 1 mmol) and a catalytic amount of *p*-toluenesulfonic acid hydrate. After TLC analysis indicated complete reaction, triethylamine (1 mL) was added and the reaction mixture was concentrated under reduced pressure. The crude oil was dissolved in DMF (3 mL) and cooled to 0 °C. Benzyl bromide (0.14 mL. 1.2 mmol) and sodium hydride (48 mg, 1.2 mmol) were added. After TLC analysis indicated complete conversion, the reaction mixture was dissolved in Et_2O (50 mL) and washed with water. The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude oil was suspended in MeOH (10 mL) and a catalytic amount of *p*-toluenesulfonic acid hydrate was added. The reaction mixture was refluxed for 1 h followed by the addition of triethylamine (1 mL) and concentration under reduced pressure. The crude oil was treated with a mixture of pyridine (5 mL) and acetic anhydride (2 mL). After TLC analysis indicated complete reaction, the reaction mixture was quenched by the addition of MeOH (1 mL), taken

up in Et_2O (50 mL) and washed with water. The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography using EtOAc/PE afforded compound **7** (391 mg, 0.79 mmol, 88% over the five steps) as a colourless oil. TLC: 50% EtOAc/PE. $[\alpha]_D^{22}$ = +12 (*c* = 0.8, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 740, 1001, 1118, 1218, 1373, 2102 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.02 (s, 3 H, CH_3 Ac), 2.03 (s, 3 H, CH_3 Ac), 3.95 (dd, *J* = 9.2 Hz, *J* = 3.6 Hz, 1 H, 3-H), 4.05–4.09 (m, *J* = 2.4 Hz, 2 H, 2-H, 6-H), 4.20 (dd, *J* = 12.4 Hz, *J* = 6.0 Hz, 1 H, 6-H), 4.33–4.38 (m, *J* = 6.0 Hz, *J* = 2.4 Hz, 1 H, 5-H), 4.62 (d, *J* = 12.0 Hz, 1 H, CH*H*Ph), 4.70 (d, *J* = 12.0 Hz, 1 H, C*H*HPh), 5.31 (t, *J* = 9.6 Hz, 1 H, 4-H), 5.48 (d, *J* = 1.6 Hz, 1 H, 1-H), 7.26–7.55 (m, 10 H, H arom) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.7 (CH_3 Ac), 20.8 (CH_3 Ac), 62.2 (C-2), 62.4 (C-6), 67.6 (C-4), 69.9 (C-5), 72.6 (CH_2 Bn), 76.7 (C-3), 85.9 (C-1), 127.9–131.8 (CH arom), 132.7 (C_q SPh), 137.1 (C_q Bn), 169.5 (C=O Ac), 170.7 (C=O Ac) ppm. ESI-MS: *m*/*z* = 472.2 $[M + H]^+$, 489.3 $[M + NH_4]^+$, 494.2 $[M + Na]^+$. HRMS $[M + Na]^+$: calcd. for $C_{23}H_{25}O_6N_3S$ 494.13563; found 494.13583.

Phenyl 2-Azido-3-*O*-benzyl-2-deoxy-1-thio-α-D-mannopyranosiduronic Acid (8): TEMPO (41 mg, 0.26 mmol, 0.2 equiv.) and BAIB (966 mg, 3 mmol, 2.5 equiv.) were added to a vigorously stirred solution of compound **6** (505 mg, 1.3 mmol) in DCM (10 mL) and H_2O (2 mL) . Stirring was continued until TLC indicated complete conversion of the starting material to a lower running spot. The reaction mixture was quenched by the addition of an $Na_2S_2O_3$ solution (10% in H_2O, 25 mL). The mixture was then extracted twice with EtOAc (10 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated. Flash column chromatography using EtOAc/PE and 2% (v/v) AcOH afforded 1-thiomannuronic acid **8** (340 mg, 0.85 mmol, 65%) as a colourless oil. TLC: 50% EtOAc/PE (5% AcOH). ^1H NMR (600 MHz, $CDCl_3$): δ = 3.90 (dd, *J* = 8.4 Hz, *J* = 3.4 Hz, 1 H, 3-H), 3.99 (s, 1 H, 2-H), 4.25 (t, *J* = 8.6 Hz, 1 H, 4-H), 4.64 (d, *J* = 8.4 Hz, 1 H, 5-H), 4.74 (d, *J* = 11.7 Hz, 1 H, CH*H*Ph), 4.84 (d, *J* = 11.7 Hz, 1 H, C*H*HPh), 5.51 (d, *J* = 3.9 Hz, 1 H, 1-H), 7.26–7.59 (m, 10 H, H arom) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 61.1 (C-2), 68.5 (C-4), 71.8 (C-5), 73.4 (CH_2 Bn), 77.9 (C-3), 85.9 (C-1), 127.9–132.2 (CH arom), 132.1 (C_q SPh), 137.2 (C_q Bn), 172.57 (C=O COOH) ppm. ^{13}C-GATED NMR (100 MHz, $CDCl_3$): δ = 85.9 ($J_{C1,H1}$ = 169 Hz, C-1) ppm. ESI-MS: *m*/*z* = 424.0 $[M + Na]^+$, 440.0 $[M + K]^+$, 825.2 $[2 M + Na]^+$. HRMS $[M + Na]^+$: calcd. for $C_{19}H_{19}O_5N_3S$ 424.09376; found 424.09389.

Methyl (Phenyl 2-azido-3-*O*-benzyl-2-deoxy-1-thio-α-D-mannopyranosid)uronate (9): MeI (0.06 mL, 1 mmol, 1.2 equiv.) and K_2CO_3 (200 mg) were added to a stirred solution of compound **8** (340 mg, 0.85 mmol) in DMF (5 mL). The solution was stirred overnight, taken up in EtOAc and washed with H_2O. The aqueous layer was extracted with EtOAc. The collected organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (EtOAc/PE) afforded title compound **9** (245 mg, 0.6 mmol, 71%) as a colourless oil. TLC: 50% EtOAc/PE. $[\alpha]_D^{22}$= +69 (*c* = 1.4, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 740, 1001, 1118, 1218, 1373, 1747, 2102 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.04 (br. s, 1 H, O4-H), 3.71 (s, 1 H, CH_3 COOMe), 3.87 (dd, *J* = 8.0 Hz, *J* = 3.4 Hz, 1 H, 3-H), 3.95 (t, *J* = 3.4 Hz, 1 H, 2-H), 4.31 (dq, *J* = 7.9 Hz, *J* = 2.1 Hz, 1 H, 4-H), 4,60 (d, *J* = 7.9 Hz, 1 H, 5-H), 4.72 (d, *J* = 11.6 Hz, 1 H, CH*H*Ph), 4.78 (d, *J* = 11.6 Hz, 1 H, C*H*HPh), 5.52 (d, *J* = 1.4 Hz, 1 H, 1-H), 7.24–7.51 (m, 10 H, H arom) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.6 (CH_3 COOMe), 61.0 (C-2), 68.3 (C-4), 72.9 (C-5), 73.2 (CH_2 Bn), 77.9 (C-3), 85.4 (C-1), 127.9–131.9 (CH arom), 137.1 (C_q Bn), 169.8 (C=O COOMe) ppm. ESI-MS: *m*/*z* = 453.2 $[M + K]^+$. HRMS $[M + NH_4]^+$: calcd. for $C_{20}H_{21}O_5N_3S$ 433.15457; found 433.15418.

Methyl (Phenyl 4-*O*-acetyl-2-azido-3-*O*-benzyl-2-deoxy-1-thio-α-D-mannopyranosid)uronate (10): Compound **9** (245 mg, 0.6 mmol) was treated with pyridine/Ac_2O (3:1, 3 mL) solution for 8 h followed by the addition MeOH (2 mL). The reaction mixture was taken up in EtOAc and washed with 2 M HCl and saturated $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (EtOAc/PE) afforded the title compound **10** (274 mg, 0.6 mmol, quant.) as a colourless oil. TLC: 50% EtOAc/PE (5% AcOH). $[\alpha]_D^{22}$= +37 (*c* = 1, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 740, 1001, 1118, 1218, 1373, 1747, 2102 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.05 (s, 3 H, CH_3 Ac), 3.85 (br. s, 4 H, 2-H, CH_3 COOMe), 3.95 (t, *J* = 3.5 Hz, 1 H, 3-H), 4.56 (d, *J* = 2.5, 1 H, 5-H), 4.62 (d, *J* = 11.5 Hz, 1 H, CH*H*Ph), 4.65 (d, *J* = 11.5 Hz, 1 H, C*H*HPh), 5.54 (t, *J* = 3.5 Hz, *J* = 2.5 Hz, 1 H, 4-H), 5.72 (d, *J* = 9.0 Hz, 1 H, 1-H), 7.25–7.66 (m, 10 H, H arom) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.7 (CH_3 Ac), 52.2 (CH_3 COOMe), 57.7 (C-2), 68.2 (C-4), 72.9 (CH_2 Bn), 73.2 (C-5), 74.8 (C-3), 80.7 (C-1), 127.8–132.2 (CH arom), 131.7 (C_q SPh), 136.3 (C_q Bn), 167.9 (C=O COOMe or Ac), 169.5 (C=O Ac or COOMe) ppm. HRMS $[M + H]^+$: calcd. for $C_{22}H_{23}O_6N_3S$ 458.13803; found 458.13934.

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(4,6-di-*O*-acetyl-2-azido-3-*O*-benzyl-2-deoxy-α/β-D-mannopyranosyl)-α-D-glucopyranoside (12): Disaccharide **12** was obtained from donor **7** and acceptor **11** according to the general glycosidation procedure using the Ph_2SO/Tf_2O activator system. Anomers were separated by flash column chromatography: α-anomer: 16 mg, 0.019 mmol, 19%; β-anomer: 55 mg, 0.067 mmol, 67%. TLC: 30% EtOAc/PE. α-Anomer: ^1H NMR (500 MHz, $CDCl_3$): δ = 2.00 (s, 3 H, CH_3 Ac), 2.03 (s, 3 H, CH_3 Ac), 3.33 (s, 3 H, CH_3 COOMe), 3.39 (t, *J* = 9.0 Hz, 1 H, 4-H), 3.49 (dd, *J* = 10.0 Hz, *J* = 4.0 Hz, 1 H, 2-H), 3.61 (d, *J* = 11.5 Hz, 1 H, 6-H), 3.67–3.74 (m, 2 H, 5-H, 5′-H), 3.78 (dd, *J* = 11.5 Hz, *J* = 4.5 Hz, 1 H, 6-H), 3.86 (dd, *J* = 9.5 Hz, *J* = 3.5 Hz, 1 H, 3′-H), 3.89 (d, *J* = 1.5 Hz, 1 H, 2′-H), 3.95 (dd, *J* = 12.0 Hz, *J* = 2.5 Hz, 1 H, 6′-H), 3.99 (t, *J* = 9.0 Hz, 1 H, 3-H), 4.03 (dd, *J* = 12.0 Hz, *J* = 4.5 Hz, 1 H, 6′-H), 4.45 (d, *J* = 11.0 Hz, 1 H, CH*H*Ph), 4.53 (d, *J* = 12.0 Hz, 1 H, CH*H*Ph), 4.61 (d, *J* = 3.5 Hz, 1 H, 1-H), 4.64 (d, *J* = 12.0 Hz, 1 H, C*H*HPh), 4.67 (d, *J* = 11.5 Hz, 1 H, CH*H*Ph), 4.80 (d, *J* = 11.0 Hz, 2 H, CH*H*Ph, C*H*HPh), 4.85 (s, 1 H, 1′-H), 4.92 (d, *J* = 11.5 Hz, 1 H, C*H*HPh), 5.02 (d, *J* = 11.0 Hz, 1 H, C*H*HPh), 5.23 (t, *J* = 9.5 Hz, 1 H, 4′-H), 7.21–7.40 (m, 20 H, H Arom) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.7 (CH_3 Ac), 20.8 (CH_3 Ac), 55.2 (CH_3 OMe), 60.6 (C-2′), 62.1 (C-6′), 66.8 (C-6), 67.2 (C-4′), 68.9 (C-5′), 68.6 (C-5), 71.9 (CH_2 Bn), 73.2 (CH_2 Bn), 74.9 (CH_2 Bn), 75.7 (C-3′), 75.8 (CH_2 Bn), 77.6 (C-4), 79.9 (C-2), 82.0 (C-3), 97.9 (C-1), 98.4 (C-1′), 127.3–128.6 (CH arom), 137.2 (C_q Bn), 137.9 (C_q Bn), 138.1 (C_q Bn), 138.6 (C_q Bn), 169.4 (C=O Ac), 170.7 (C=O Ac) ppm. ^{13}C-GATED NMR (125 MHz, $CDCl_3$): δ = 97.9 ($J_{C1,H1}$ = 171 Hz, C-1), 98.4 ($J_{C1',H1'}$ = 175 Hz, C-1′) ppm. ESI-MS: *m*/*z* = 843.4 $[M + NH_4]^+$. HRMS $[M + H]^+$: calcd. for $C_{45}H_{51}O_{12}N_3$ 826.35455; found 826.35550. β-Anomer: $[\alpha]_D^{22}$ = –17 (*c* = 0.8, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 698, 738, 754, 1004, 1039, 1068, 1132, 1240, 1367, 1743, 2104 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.01 (s, 3 H, CH_3 Ac), 2.03 (s, 3 H, CH_3 Ac), 3.34 (s, 3 H, CH_3 OMe), 3.36 (t, *J* = 9.2 Hz, 1 H, 4-H), 3.38–3.41 (m, 1 H, 5′-H), 3.46 (dd, *J* = 9.6 Hz, *J* = 4.5 Hz, 1 H, 3-H), 3.49 (d, *J* = 8.0 Hz, 1 H, 2-H), 3.51 (m, *J* = 3.6 Hz, 1 H, 6-H), 3.75 (d, *J* = 4.5 Hz, 1 H, 2-H), 4.00 (t, *J* = 9.2 Hz, 1 H, 3-H), 4.07–4.11 (m, 2 H, 6-H, 6′-H), 4.17 (dd, *J* = 12.0 Hz, *J* = 5.2 Hz, 1 H, 6′-H), 4.26 (s, 1 H, 1′-H), 4.53 (d, *J* = 11.6 Hz, 1 H, CH*H*Ph), 4.55 (d, *J* = 12.4 Hz, 1 H, CH*H*Ph), 4.56 (s, 1 H, 1-H), 4.62 (d, *J* = 12.0 Hz,

1 H, C*H*HPh), 4.67 (d, *J* = 12.4 Hz, 1 H, C*H*HPh), 4.77 (d, *J* = 12.0 Hz, 1 H, C*H*HPh), 4.80 (d, *J* = 10.8 Hz, 1 H, CH*H*Ph), 4.87 (d, *J* = 11.6 Hz, 1 H, C*H*HPh), 5.00 (d, *J* = 10.8 Hz, 1 H, C*H*HPh), 5.15 (t, *J* = 9.6 Hz, 1 H, 4′-H), 7.23–7.36 (m, 20 H, H arom) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.7 (CH_3 Ac), 20.7 (CH_3 Ac), 55.1 (CH_3 OMe), 61.3 (C-2′), 62.6 (C-6′), 67.3 (C-4′), 68.7 (C-6), 69.5 (C-5), 71.8 (CH_2 Bn), 72.4 (C-5′), 73.4 (CH_2 Bn), 74.6 (CH_2 Bn), 75.7 (CH_2 Bn), 77.2 (C-3′), 77.6 (C-4), 79.8 (C-2), 81.9 (C-3), 97.8 (C-1), 99.8 (C-1′), 137.2 (C_q Bn), 138.0 (C_q Bn), 138.2 (C_q Bn), 138.6 (C_q Bn), 169.3 (C=O Ac), 170.8 (C=O Ac) ppm. ^{13}C-GATED NMR (100 MHz, $CDCl_3$): δ = 97.8 ($J_{C1,H1}$ = 171 Hz, C-1), 99.8 ($J_{C1',H1'}$ = 158 Hz, C-1′) ppm. ESI-MS: *m*/*z* = 848.4 [M + Na]$^+$. HRMS [M + Na]$^+$: calcd. for $C_{45}H_{51}O_{12}N_3$ 848.33650; found 848.33642.

***p*-Methoxyphenyl 2-*O*-Benzyl-4,6-*O*-benzylidene-3-*O*-(4,6-di-*O*-acetyl-2-azido-3-*O*-benzyl-2-deoxy-α/β-D-mannopyranosyl)-β-D-galactopyranoside (15):** Disaccharide **15** (65 mg, 0.082 mmol, 82%) was obtained from donor **7** and acceptor **14** according to the general glycosidation procedure using the Ph_2SO/Tf_2O activator system. The anomers could not be separated by flash column chromatography. TLC: 30% EtOAc/PE. IR (neat): $\tilde{\nu}$ = 696, 1028, 1035, 1217, 1506, 1733, 2102 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, β-anomer): δ = 1.98 (s, 3 H, CH_3 Ac), 2.05 (s, 3 H, CH_3 Ac), 3.27 (dd, *J* = 9.5 Hz, *J* = 3.6 Hz, 1 H, 3′-H), 3.51 (s, 1 H, 5-H), 3.68 (d, *J* = 9.8 Hz, 1 H, 5′-H), 3.71 (s, 3 H, CH_3 OMe pMP), 3.76 (br. s, 1 H, 2′-H), 3.77 (s, 3 H, CH_3 COOMe), 3.89 (dd, *J* = 10.0 Hz, *J* = 3.4 Hz, 1 H, 3-H), 4.07 (dd, *J* = 12.5 Hz, *J* = 1.2 Hz, 1 H, 6-H), 4.17 (dd, *J* = 10.0 Hz, *J* = 7.8 Hz, 1 H, 2-H), 4.20 (d, *J* = 13.2 Hz, 1 H, 6-H), 4.36 (s, 1 H, 4-H), 4.43 (d, *J* = 12.2 Hz, 1 H, CH*H*Ph), 4.56 (d, *J* = 12.2 Hz, 1 H, C*H*HPh), 4.66 (d, *J* = 11.7 Hz, 1 H, CH*H*Ph), 4.88 (s, 1 H, 1′-H), 4.90 (d, *J* = 7.8 Hz, 1 H, 1-H), 5.07 (d, *J* = 11.7 Hz, 1 H, C*H*HPh), 5.23 (t, *J* = 9.6 Hz, 1 H, 4′-H), 5.59 (s, 1 H, CHPh), 6.81 (d, *J* = 9.1 Hz, 1 H, 2×CH pMP), 7.05 (d, *J* = 9.1 Hz, 1 H, 2×CH pMP), 7.25–7.59 (m, 15 H, H arom) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.8 (CH_3 Ac), 20.9 (CH_3 Ac), 52.7 (CH_3 COOMe), 55.6 (CH_3 OMe pMP), 60.9 (C-2′), 66.7 (C-5), 68.1 (C-4), 68.8 (C-6), 72.2 (CH_2 Bn), 72.9 (C-5′), 75.3 (CH_2 Bn), 75.6 (C-4), 77.1 (C-3), 77.3 (C-3′), 78.9 (C-2), 100.4 (C-1′), 100.7 (CHPh), 103.2 (C-1), 114.4 (CH arom pMP), 118.8 (CH arom pMP), 126.4–128.9 (CH arom), 137.2 (C_q Bn), 137.7 (C_q Bn), 151.3 (C_q pMP), 155.4 (C_q pMP), 167.4 (C=O Ac or COOMe), 169.3 (C=O Ac or COOMe) ppm. ^{13}C-GATED NMR (100 MHz, $CDCl_3$): δ = 100.4 ($J_{C1',H1'}$ = 161 Hz, C-1′), 103.2 ($J_{C1,H1}$ = 163 Hz, C-1) ppm. ESI-MS: *m*/*z* = 913.4 [M + $HNEt_3$]$^+$. HRMS [M + NH_4]$^+$: calcd. for $C_{43}H_{45}O_{13}N_3$ 829.32961; found 829.32829.

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-α-D-mannopyranosyl)-α-D-glucopyranoside (16): Disaccharide **16** (68 mg, 0.088 mmol, 88%) was obtained from donor **4** and acceptor **11** according to the general glycosidation procedure using the Ph_2SO/Tf_2O activator system. TLC: 30% EtOAc/PE. IR (neat): $\tilde{\nu}$ = 698, 734, 819, 999, 1026, 1101, 1132, 1217, 1506, 1747, 2106 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.06 (s, 3 H, CH_3 Ac), 2.07 (s, 3 H, CH_3 Ac), 2.13 (s, 3 H, CH_3 Ac), 3.83 (s, 3 H, CH_3 OMe), 3.45 (t, *J* = 9.2 Hz, 1 H, 4-H), 3.53 (dd, *J* = 9.6 Hz, *J* = 3.6 Hz, 1 H, 3-H), 3.64 (d, *J* = 9.6 Hz, 1 H, 6-H), 3.76–3.80 (m, 1 H, 5-H), 3.81 (dd, *J* = 9.6 Hz, *J* = 4.0 Hz, 1 H, 6-H), 3,82–3.86 (m, 1 H, 5′-H), 3.97–4.03 (m, 3 H, 3-H, 2′-H and 6′-H), 4.09 (dd, *J* = 12.0 Hz, *J* = 4.8 Hz, 1 H, 6′-H), 4.58 (d, *J* = 3.6 Hz, 1 H, 1-H), 4 59 (d, *J* = 11.2 Hz, 1 H, CH*H*Ph), 4.68 (d, *J* = 12.0 Hz, 1 H, CH*H*Ph), 4.78 (d, *J* = 12.0 Hz, 1 H, C*H*HPh), 4.80 (d, *J* = 10.8 Hz, 1 H, CH*H*Ph), 4.88 (d, *J* = 1.6 Hz, 1 H, 1′-H), 4.97 (d, *J* = 11.2 Hz, 1 H, C*H*HPh), 4.99 (d, *J* = 10.8 Hz, 1 H, C*H*HPh), 5.25 (t, *J* = 10.0 Hz, 1 H, 4′-H), 5.31 (t, *J* = 10.0 Hz, 1 H, 3′-H), 7.30–7.43 (15 H, H arom) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.5 (CH_3 Ac), 20.6 (CH_3 Ac), 20.7 (CH_3 Ac), 55.2 (CH_3 OMe), 60.5 (C-2′), 61.8 (C-6′), 65.8 (C-4′), 66.5 (C-6), 68.5 (C-5′), 69.9 (C-5), 70.9 (C-3′), 73.3 (CH_2 Bn), 75.2 (CH_2 Bn), 75.8 (CH_2 Bn), 80.0 (C-4), 81.1 (C-2), 82.1 (C-3), 97.9 (C-1), 98.2 (C-1′), 127.5–128.5 (CH arom), 138.0 (C_q Bn), 138.1 (C_q Bn), 138.5 (C_q Bn), 169.5 (C=O Ac), 169.8 (C=O Ac), 170.6 (C=O Ac) ppm. ^{13}C-GATED NMR (100 MHz, $CDCl_3$): δ = 97.9 ($J_{C1,H1}$ = 164 Hz, C-1), 98.2 ($J_{C1',H1'}$ = 174 Hz, C-1′) ppm. ESI-MS: *m*/*z* = 795.1 [M + NH_4]$^+$. HRMS [M + NH_4]$^+$: calcd. for $C_{40}H_{47}O_{13}N_3$ 795.34471; found 795.34144.

3-*O*-(3,4,6-Tri-*O*-acetyl-2-azido-2-deoxy-α-D-mannopyranosyl)-1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose (18): Disaccharide **18** (45 mg, 0.079 mmol, 79%) was obtained from donor **4** and acceptor **17** according to the general glycosidation procedure using the Ph_2SO/Tf_2O activator system. TLC: 30% EtOAc/PE. IR (neat): $\tilde{\nu}$ = 698, 734, 819, 999, 1026, 1101, 1132, 1217, 1506, 1747, 2106 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (s, 3 H, CH_3 isoprop), 1.32 (s, 3 H, CH_3 isoprop), 1.37 (s, 3 H, CH_3 isoprop), 1.41 (s, 3 H, CH_3 isoprop), 2.06 (s, 3 H, CH_3 Ac), 2.10 (s, 3 H, CH_3 Ac), 2.12 (s, 3 H, CH_3 Ac), 3.97–4.05 (m, 2 H, 5′-H, 6′-H), 4.06 (dd, *J* = 3.0 Hz, *J* = 1.0 Hz, 1 H, 2′-H), 4.07 (dd, *J* = 8.5 Hz, *J* = 2.5 Hz, 1 H, 4-H), 4.12–4.17 (m, 3 H, 6-H, 5′-H and 6′-H), 4.25 (dd, *J* = 12.0 Hz, *J* = 5.5 Hz, 1 H, 6-H), 4.28 (d, *J* = 3.0 Hz, 1 H, 3-H), 4.57 (d, *J* = 3.5 Hz, 1 H, 2-H), 5.19 (d, *J* = 1.0 Hz, 1 H, 1′-H), 5.28 (t, *J* = 9.5 Hz, 1 H, 4′-H), 5.23 (dd, *J* = 10.0 Hz, *J* = 4.0 Hz, 1 H, 3′-H), 5.91 (d, *J* = 3.5 Hz, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.5 (CH_3 Ac), 20.6 (CH_3 Ac), 20.7 (CH_3 Ac), 25.2 (CH_3 isoprop), 26.2 (CH_3 isoprop), 26.8 (2×CH_3 isoprop), 61.2 (C-2′), 62.3 (C-6), 66.0 (C-3′), 67.9 (C-6′), 69.3 (C-5′), 70.4 (C-4′), 72.5 (C-5), 81.3 (C-4), 81.7 (C-3), 83.9 (C-2), 99.1 (C-1′), 105.3 (C-1), 109.5 (C_q isoprop), 112.1 (C_q isoprop), 169.5 (C=O Ac), 169.9 (C=O Ac), 170.7 (C=O Ac) ppm. ^{13}C-GATED NMR (100 MHz, $CDCl_3$): δ = 99.1 ($J_{C1',H1'}$ = 171 Hz, C-1′), 105.3 ($J_{C1,H1}$ = 181 Hz, C-1′) ppm. ESI-MS: *m*/*z* = 596.0 [M + Na]$^+$. HRMS [M + Na]$^+$: calcd. for $C_{24}H_{35}O_{13}N_3$ 596.20621; found 596.20586.

***p*-Methoxyphenyl 2-*O*-Benzyl-4,6-*O*-benzylidene-3-*O*-(3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-α-D-mannopyranosyl)-β-D-galactopyranoside (19):** Disaccharide **19** (50 mg, 0.064 mmol, 64%) was obtained from donor **4** and acceptor **14** according to the general glycosidation procedure using the Ph_2SO/Tf_2O activator system. TLC: 30% EtOAc/PE. IR (neat): $\tilde{\nu}$ = 698, 734, 819, 999, 1026, 1101, 1132, 1217, 1506, 1747, 2106 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.97 (s, 3 H, CH_3 Ac), 2.03 (s, 3 H, CH_3 Ac), 2.09 (s, 3 H, CH_3 Ac), 3.49 (s, 1 H, 5-H), 3.78 (s, 3 H, CH_3 OMe pMP), 3.86 (dd, *J* = 10.0 Hz, *J* = 3.6 Hz, 1 H, 3-H), 3.93 (d, *J* = 3.2 Hz, 1 H, 6′-H), 4.03–4.06 (m, 2 H, 2-H, 2′-H), 4.08 (dt, *J* = 11.6 Hz, *J* = 1.6 Hz, 1 H, 6-H), 4.14 (dq, *J* = 10.4 Hz, *J* = 2.8 Hz, 1 H, 5′-H), 4.32 (s, *J* = 3.2 Hz, 1 H, 4-H), 4.37 (dd, *J* = 12.4 Hz, *J* = 1.2 Hz, 1 H, 6-H), 4.78 (d, *J* = 10.4 Hz, 1 H, CH*H*Ph), 4.90 (d, *J* = 8.0 Hz, 1 H, 1-H), 5.05 (d, *J* = 1.2 Hz, 1 H, 1′-H), 5.06 (d, *J* = 10.4 Hz, 1 H, C*H*HPh), 5.32 (t, *J* = 10.0 Hz, 1 H, 4′-H), 5.47 (dd, *J* = 10.0 Hz, *J* = 4.0 Hz, 1 H, 3′-H), 5.56 (s, 1 H, CHPh), 6.82 (d, *J* = 9.1 Hz, 1 H, CH arom pMP), 7.05 (d, *J* = 9.1 Hz, 1 H, CH arom pMP), 7.25–7.59 (m, 15H CH arom) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.5 (CH_3 Ac), 20.7 (CH_3 Ac), 20.7 (CH Ac), 55.6 (CH_3 pMP), 61.5 (C-2′), 61.6 (CH_2 Bn), 65.6 (C-4′), 66.3 (C-5), 68.5 (C-5′), 69.2 (C-6), 71.0 (C-3′), 71.1 (C-4), 74.3 (C-3), 76.3 (C-2), 93.8 (C-1′), 101.1 (CHPh), 103.3 (C-1), 114.5 (CH arom pMP), 118.9 (CH arom pMP), 126.4–129.1 (CH arom), 137.5 (C_q Bn), 138.0 (C_q Bn), 151.4 (C_q pMP), 155.5 (C_q pMP), 169.4 (C=O Ac), 169.7 (C=O Ac), 170.6 (C=O Ac) ppm. ^{13}C-GATED NMR (100 MHz, $CDCl_3$): δ = 93.8 ($J_{C1',H1'}$ = 172 Hz, C-1′), 103.3 ($J_{C1,H1}$ = 158 Hz, C-1)

ppm. ESI-MS: *m/z* = 795.4 $[M + NH_4]^+$. HRMS $[M + NH_4]^+$: calcd. for $C_{39}H_{43}O_{14}N_3$ 795.30833; found 795.30491.

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-[methyl (4-*O*-acetyl-2-azido-3-*O*-benzyl-2-deoxy-β-D-mannopyranosyl)uronate]-α-D-glucopyranoside (20): Disaccharide **20** (56 mg, 0.069 mmol, 69%) was obtained from donor **10** and acceptor **11** according to the general glycosidation procedure using the Ph_2SO/Tf_2O activator system. TLC: 30% EtOAc/PE. $[\alpha]_D^{22} = -16$ (c = 1, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 698, 736, 754, 1033, 1070, 1105, 1180, 1224, 2113 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.04 (s, 3 H, CH_3 Ac), 3.31 (s, 3 H, CH_3 OMe), 3.35 (t, J = 9.5 Hz, 1 H, 4-H), 3.44 (dd, J = 10.5 Hz, J = 6.5 Hz, 1 H, 6-H), 3.48 (dd, J = 9.5 Hz, J = 3.5 Hz, 1 H, 2-H), 3.55 (dd, J = 9.0 Hz, J = 3.5 Hz, 1 H, 3′-H), 3.69 (s, 4 H, 2-H and CH_3 CO-OMe), 3.73 (d, J = 9.5 Hz, 1 H, 5′-H), 3.79 (m, J = 8.0 Hz, J = 6.5 Hz, J = 1.5 Hz, 1 H, 5-H), 4.00 (t, J = 9.5 Hz, 1 H, 3-H), 4.10 (dd, J = 8.0 Hz, J = 1.5 Hz, 1 H, 6-H), 4.28 (s, 1 H, 1′-H), 4.53 (d, J = 11.0 Hz, 1 H, CH*H*Ph), 4.54 (s, 1 H, 1-H), 4.61 (d, J = 11.0 Hz, 1 H, CH*H*Ph), 4.62 (d, J = 11.0 Hz, 1 H, C*H*HPh), 4.66 (d, J = 11.0 Hz, 1 H, C*H*HPh), 4.76 (d, J = 11.0 Hz, 1 H, C*H*HPh), 4.79 (d, J = 11.0 Hz, 1 H, C*H*HPh), 4.86 (d, J = 11.0 Hz, 1 H, *CH*HPh), 4.98 (d, J = 11.0 Hz, 1 H, C*H*HPh), 5.31 (t, J = 9.0 Hz, 1 H, 4′-H), 7.23–7.37 (m, 20 H, CH arom) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.7 (CH_3 Ac), 52.7 (CH_3 COOMe), 55.1 (CH_3 OMe), 68.2 (C-4′), 68.8 (C-6), 69.6 (C-5), 72.2 (CH_2 Bn), 73.2 (C-5′), 73.4 (CH_2 Bn), 74.6 (CH_2 Bn), 75.7 (CH_2 Bn), 75.7 (C-3′), 77.6 (C-4), 79.8 (C-2), 81.9 (C-3), 97.6 (C-1), 99.7 (C-1′), 127.6–128.6 (CH arom), 137.1 (C_q Bn), 138.0 (C_q Bn), 138.3 (C_q Bn), 138.4 (C_q Bn), 138.6 (C_q Bn), 167.5 (C=O Ac or COOMe), 169.3 (C=O Ac or COOMe) ppm. ^{13}C-GATED NMR (125 MHz, $CDCl_3$): δ = 97.8 ($J_{C1,H1}$ = 170 Hz, C-1), 99.7 ($J_{C1,H1}$ = 160 Hz, C-1′) ppm. ESI-MS: *m/z* = 829.3 $[M + NH_4]^+$, 834.4 $[M + Na]^+$. HRMS $[M + Na]^+$: calcd. for $C_{41}H_{49}O_{12}N_3$ 834.32084; found 834.32100.

***p*-Methoxyphenyl 2-*O*-Benzyl-4,6-*O*-benzylidene-3-*O*-[methyl (4-*O*-acetyl-2-azido-3-*O*-benzyl-2-deoxy-α/β-D-mannopyranosyl)uronate]-β-D-galactopyranoside (21):** A solution of donor **10** (41 mg, 0.09 mmol) and acceptor **14** (70 mg, 0.15 mmol, 1.5 equiv.) in DCM (3 mL) was stirred in the presence of activated MS (3 Å) for 30 min before *N*-iodosuccinimide (29 mg, 0.13 mmol, 1.3 equiv.) was added. The mixture was cooled to –40 °C before trimethylsilyl trifluoromethanesulfonate (5 μL, cat.) was added. Stirring was continued and the reaction mixture was warmed to room temperature. When TLC analysis indicated complete reaction, triethylamine (0.2 mL) was added. The reaction mixture was diluted with EtOAc and washed with water. The aqueous layer was extracted twice with EtOAc. The collected organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash chromatography (EtOAc/PE) and removal of the eluent afforded the title compound **21** (40 mg, 0.048 mmol, 53%, α/β = 1:2) as a colourless oil. The anomers could not be separated using flash column chromatography. TLC: 30% EtOAc/PE. IR (neat): $\tilde{\nu}$ = 696, 734, 746, 819, 1045, 1083, 1220, 1365, 1506, 1743, 2108 cm^{-1}. β-Anomer: ^1H NMR (400 MHz, $CDCl_3$): δ = 2.04 (s, 3 H, CH_3 Ac), 3.28 (dd, J = 9.5 Hz, J = 3.6 Hz, 1 H, 3′-H), 3.51 (br. s, 1 H, 5-H), 3.65 (d, J = 9.8 Hz, 5′-H), 3.71 (s, 3 H, CH_3 pMP or COOMe), 3.75 (d, J = 3.6 Hz, 1 H, 2′-H), 3.77 (s, 3 H, CH_3 COOMe or pMP), 3.89 (dd, J = 10.0 Hz, J = 3.4 Hz, 1 H, 3-H), 4.03–4.08 (m, 1 H, 6-H), 4.18 (dd, J = 10.0 Hz, J = 7.8 Hz, 1 H, 2-H), 4.34 (d, J = 13.2 Hz, 1 H, 6-H), 4.37 (s, 1 H, 4-H), 4.45 (d, J = 12.2 Hz, 1 H, CH*H*Ph), 4.58 (d, J = 12.2 Hz, 1 H, C*H*HPh), 4.66 (d, J = 11.7 Hz, 1 H, CH*H*Ph), 4.88 (s, 1 H, 1′-H), 4.87 (s, 1 H, 1′-H), 4.90 (d, J = 7.8 Hz, 1 H, 1-H), 5.08 (d, J = 11.7 Hz, 1 H, C*H*HPh), 5.21 (t, J = 9.6 Hz, 1 H, 4′-H), 5.60 (s, 1 H, C*H*Ph), 6.82 (d, J = 9.1 Hz, 1 H, CH arom pMP), 7.05 (d, J = 9.1 Hz, 1 H, CH arom pMP), 7.25–7.59 (m, 15 H CH arom) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.6 (CH_3 Ac), 52.7 (CH_3 pMP or COOMe), 55.6 (CH_3 COOMe or pMP), 60.9 (C-2′), 66.7 (C-5), 68.2 (C-5), 68.8 (C-6), 72.1 (CH_2 Bn), 73.2 (C-5′), 75.3 (CH_2 Bn), 75.6 (C-4), 77.1 (C-3), 77.3 (C-3′), 78.9 (C-2), 100.4 (C-1′), 100.7 (C*H*Ph), 103.2 (C-1), 114.4 (CH arom pMP), 118.7 (CH arom pMP), 126.4–128.9 (CH arom), 137.2 (C_q Bn), 137.7 (C_q Bn), 138.6 (C_q Bn), 151.4 (C_q pMP), 155.4 (C_q pMP), 167.5 (C=O COOMe or Ac), 169.3 (C=O Ac or COOMe) ppm. ^{13}C-GATED NMR (100 MHz, $CDCl_3$): δ = 100.4 ($J_{C1',H1'}$ = 163 Hz, C-1′), 103.2 ($J_{C1,H1}$ = 161 Hz, C-1) ppm. α-Anomer: ^{13}C-GATED NMR (100 MHz, $CDCl_3$): δ = 93.0 ($J_{C1',H1'}$ = 170 Hz, C-1′), 101.0 ($J_{C1,H1}$ = 161 Hz, C-1) ppm. HRMS $[M + Na]^+$: calcd. for $C_{43}H_{45}O_{13}N_3$ 834.28446; found 834.28513.

4-Azido-2,3-di-*O*-benzyl-4-deoxy-α/β-D-fucopyranose (23): NIS (58 mg, 0.26 mmol, 1 equiv.) and TFA (20 μL, 0.26 mmol, 1 equiv.) were added to a vigorously stirred solution of compound **22**[40] (119 mg, 0.26 mmol) in DCM/H_2O (10:1 v/v, 1 mL). The mixture was stirred for 15 min before $Na_2S_2O_3$ (10% in H_2O, 10 mL) and $NaHCO_3$ (satd. aq., 10 mL) were added. The biphasic mixture was diluted with EtOAc (50 mL) and extracted. The aqueous layers were extracted twice with EtOAc (25 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography using (EtOAc/PE) afforded the title compound **23** (69 mg, 0.19 mmol, 73%) as a colourless oil. TLC: 50% EtOAc/PE. IR (neat): $\tilde{\nu}$ = 609, 1041, 1091, 1222, 2098 cm^{-1}. α -Anomer: ^1H NMR (500 MHz, $CDCl_3$): δ = 1.24 (d, J = 6.5 Hz, 3 H, 6-H), 3.26 (br. s, 1 H, O1-H), 3.74 (d, J = 3.5 Hz, 1 H, 4-H), 3.86 (dd, J = 9.5 Hz, J = 3.5 Hz, 1 H, 2-H), 4.03 (dd, J = 9.5 Hz, J = 3.5 Hz, 1 H, 3-H), 4.18 (q, J = 6.5 Hz, 1 H, 5-H), 4.70 (d, J = 11.5 Hz, 1 H, CH*H*Ph), 4.77 (d, J = 11.5 Hz, 1 H, CH*H*Ph), 4.80 (d, J = 11.5 Hz, 1 H, C*H*HPh), 4.84 (d, J = 11.5 Hz, 1 H, C*H*HPh), 5.18 (d, J = 3.5 Hz, 1 H, 1-H), 7.29–7.42 (m, 10 H, H arom) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.3 (C-6), 64.5 (C-4), 64.6 (C-5), 72.8 (CH_2 Bn), 73.7 (CH_2 Bn), 76.0 (C-2), 77.8 (C-3), 91.6 (C-1), 127.7–128.4 (CH arom), 137.8 (C_q Bn), 137.9 (C_q Bn) ppm. β-anomer: ^1H NMR (500 MHz, $CDCl_3$): δ = 1.31 (d, J = 6.5 Hz, 3 H, 6-H), 3.55 (q, J = 6.5 Hz, 1 H, 5-H), 3.61 (t, J = 9.5 Hz, J = 8.5 Hz, 1 H, 2-H), 3.64 (d, J = 3.5 Hz, 1 H, 4-H), 3.68 (dd, J = 9.5 Hz, J = 3.5 Hz, 1 H, 3-H), 3.70 (br. s, 1 H, O1-H), 4.57 (br. d, J = 8.5 Hz, 1 H, 1-H), 4.76 (d, J = 11.5 Hz, 1 H, CH*H*Ph), 4.82 (d, J = 11.5 Hz, 1 H, CH*H*Ph), 4.83 (d, J = 11.5 Hz, 1 H, C*H*HPh), 4.91 (d, J = 11.5 Hz, 1 H, C*H*HPh), 7.29–7.42 (m, 10 H, H arom) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.4 (C-6), 63.6 (C-4), 69.2 (C-5), 72.9 (CH_2 Bn), 75.2 (CH_2 Bn), 80.2 (C-2), 81.1 (C-3), 97.5 (C-1), 127.7–128.4 (CH arom), 137.7 (C_q Bn), 138.3 (C_q Bn) ppm. ESI-MS: *m/z* = 387.2 $[M + NH_4]^+$, 392.1 $[M + Na]^+$. HRMS $[M + Na]^+$: calcd. for $C_{20}H_{23}O_4N_3$ 392.15808; found 392.15813.

Methyl [Phenyl 2-azido-3-*O*-benzyl-2-deoxy-4-*O*-(4-azido-2,3-di-*O*-benzyl-4-deoxy-α-D-fucopyranosyl)-α-D-mannopyranosid]uronate (24): Chemoselective glycosylation: Disaccharide **24** (42 mg, 0.055 mmol, 55%) was obtained from donor **22** and acceptor **9** according to the general glycosidation procedure using the Ph_2SO/Tf_2O activator system. Orthogonal glycosylation: A solution of donor **23** (55 mg, 0.15 mmol), diphenyl sulfoxide (85 mg, 0.42 mmol, 2.8 equiv.) and tri-*tert*-butylpyrimidine (112 mg, 0.45 mmol, 3 equiv.) in DCM (3 mL) was stirred in the presence of activated MS (3 Å) (100 mg) for 30 min. The mixture was cooled to –60 °C before triflic anhydride (33 μL, 0.20 mmol, 1.3 equiv.) was added. The mixture was warmed to –40 °C in 1 h followed by addition of acceptor **9** (78 mg, 0.17 mmol, 1.1 equiv.) in DCM (1 mL). Stirring was continued and the reaction mixture was warmed to 0 °C. The reaction mixture was taken up in EtOAc (25 mL) and washed with

water. The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash chromatography (10% EtOAc/PE) and removal of the eluent afforded the title compound **24** (73 mg, 0.095 mmol, 67%) as a colourless oil. TLC: 30% EtOAc/PE. $[\alpha]_D^{22}$ = +3 (c = 0.3, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 609, 1041, 1091, 1222, 1710, 2098 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.21 (d, J = 6.5 Hz, 1 H, C-6′), 3.45 (dd, J = 10.0 Hz, J = 3.5 Hz, 1 H, 4-H), 3.47 (s, 3 H, CH_3 COOMe), 3.67–3.69 (m, 1 H, 3′-H, 4′-H), 3.77 (dd, J = 9.5 Hz, J = 3.5 Hz, 1 H, 2′-H), 3.83 (q, J = 6.5 Hz, 1 H, 5′-H), 3.93 (t, J = 3.5 Hz, 1 H, 3-H), 4.23 (dd, J = 4.3 Hz, J = 2.0 Hz, 1 H, 2-H), 4.51 (d, J = 11.5 Hz, 2 H, 2×CH*H*Ph), 4.56 (d, J = 11.5 Hz, 1 H, C*H*HPh), 4.61 (d, J = 2.0 Hz, 1 H, 1-H), 4.68 (d, J = 11.5 Hz, 1 H, CH*H*Ph), 4.75 (d, J = 11.5 Hz, 1 H, C*H*HPh), 4.76 (d, J = 11.5 Hz, 1 H, C*H*HPh), 4.77 (d, J = 3.5 Hz, 1 H, 1′-H), 5.62 (d, J = 10.0 Hz, 1 H, 5-H), 7.25–7.67 (m, 20 H, H arom) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.3 (C-6′), 52.1 (CH_3 COOMe), 57.1 (C-4), 64.4 (C-3′ or C-4′), 65.3 (C-5′), 72.9 (CH_2 Bn), 73.1 (CH_2 Bn), 73.8 (CH_2 Bn), 75.0 (C-1), 75.3 (C-2), 75.9 (C-2′), 76.1 (C-3), 77.8 (C-4′ or C-3′), 79.6 (C-5), 99.7 (C-1′), 124.7–134.1 (CH arom), 130.9 (C_q SPh), 136.6 (C_q Bn), 137.9 (C_q Bn), 138.2 (C_q Bn), 168.9 (C=O COOMe) ppm. ^{13}C-GATED NMR (100 MHz, $CDCl_3$): δ = 75.0 ($J_{C1,H1}$ could not be determined), 96.1 ($J_{C1',H1'}$ = 166 Hz, C-1′) ppm. HRMS [M + Na]$^+$: calcd. for $C_{40}H_{42}O_8N_6S$ 789.26770; found 789.26819.

1,6-Anhydro-2-azido-3-*O*-benzyl-4-*O*-{methyl [2-azido-3-*O*-benzyl-2-deoxy-4-*O*-(4-azido-2,3-di-*O*-benzyl-4-deoxy-α-D-fucopyranosyl)-α/β-D-mannopyranosyl]uronate}-2-deoxy-β-D-glucopyranose (26): A solution of donor **24** (38 mg, 0.050 mmol) and acceptor **25** (21 mg, 0.075 mmol, 1.5 equiv.) in DCM (2 mL) was stirred in the presence of activated MS (3 Å) for 30 min before *N*-iodosuccinimide (17 mg, 0.075 mmol, 1.5 equiv.) was added. The mixture was cooled to –40 °C before trimethylsilyl trifluoromethanesulfonate (2 μL, cat.) was added. Stirring was continued and the reaction mixture was warmed to room temperature. When TLC analysis indicated complete reaction, triethylamine (0.2 mL) was added. The reaction mixture was diluted with EtOAc and washed with water. The aqueous layer was extracted twice with EtOAc. The collected organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash chromatography (EtOAc/PE) and removal of the eluent afforded the title compound **26** (32 mg, 0.032 mmol, 65%, α/β = 1:2) as a colourless oil. Anomers were separated using flash column chromatography: α-anomer: 10 mg, 0.010 mmol, 20%; β-anomer: 22 mg, 0.022 mmol, 45%. TLC: 30% EtOAc/PE. α-Anomer: ^1H NMR (400 MHz, $CDCl_3$): δ = 1.20 (d, J = 6.4 Hz, 1 H, 6′′-H), 3.23 (s, 1 H, 2-H), 3.51 (s, 3 H, CH_3 COOMe), 3.72 (s, 1 H, 3-H), 3.74–3.82 (m, 4 H, 6-H, 4′-H, 5′-H and 2′′-H), 3.90–3.92 (m, 2 H, 4-H, 2′-H), 3.91 (t, J = 3.2 Hz, 1 H, 3′′-H), 4.00 (dd, J = 10.0 Hz, J = 3.6 Hz, 1 H, 3′-H), 4.13 (d, J = 7.2 Hz, 1 H, 6-H), 4.19 (t, J = 4.0 Hz, 1 H, 4′′-H), 4.50 (d, J = 12.0 Hz, 1 H, CH*H*Ph), 4.56 (d, J = 12.0 Hz, 1 H, C*H*HPh), 4.63 (d, J = 2.4 Hz, 1 H, 5′′-H), 4.66 (d, J = 12.0 Hz, 1 H, CH*H*Ph), 4.74 (d, J = 12.0 Hz, 1 H, C*H*HPh), 4.76 (d, J = 11.6 Hz, 1 H, CH*H*Ph), 4.80 (d, J = 11.6 Hz, 1 H, C*H*HPh), 4.81 (br. s, 1 H, 1′-H), 4.81–4.83 (m, 3 H, 3×CH Bn), 4.93 (d, J = 5.6 Hz, 1 H, 5-H), 5.32 (d, J = 7.6 Hz, 1 H, 1′′-H), 5.51 (s, 1 H, 1-H), 7.22–7.41 (m, 20 H, CH arom) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.3 (C-6′′), 52.7 (CH_3 COOMe), 59.5 (C-2 or C-2′′), 60.0 (C-2 or C-2′′), 64.5 (C-5′ or C-4′), 65.4 (C-6), 65.6 (C-4′ or C-5′), 72.6 (CH_2 Bn), 72.9 (CH_2 Bn), 73.2 (CH_2 Bn), 73.9 (CH_2 Bn), 74.1 (C-5′′), 74.9 (C-4′′), 75.5, 75.9 (C-3′′, C-4 or C-2′), 76.3 (C-5), 77.5 (C-3′), 77.7 (C-3), 77.8 (C-2′ or C-4), 97.8 (C-1′′), 99.8 (C-1′), 100.6 (C-1), 129.0–130.5 (CH arom), 137.0 (C_q Bn), 137.2 (C_q Bn), 137.9 (C_q Bn), 138.3 (C_q Bn), 169.3 (C=O COOMe) ppm. ^{13}C-GATED NMR (100 MHz, $CDCl_3$): δ = 97.8 ($J_{C1'',H1''}$ = 166 Hz, C-1′′), 99.8 ($J_{C1',H1'}$ = 167 Hz, C-1′), 100.6 ($J_{C1,H1}$ = 168 Hz, C-1) ppm. β-Anomer: $[\alpha]_D^{22}$ = +2 (c = 0.3, $CHCl_3$) ppm. IR (neat): $\tilde{\nu}$ = 609, 1041, 1091, 1222, 1710, 2098 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.19 (d, J = 6.4 Hz, 3 H, 6′′-H), 3.17 (s, 1 H, 2-H), 3.67 (dd, J = 8.7 Hz, J = 3.5 Hz, 1 H, 3′-H), 3.73 (s, 3 H, CH_3 COOMe), 3.74–3.77 (m, 2 H, 4′′-H, 5′′-H), 3.78–3.81 (m, 2 H, 3-H, 6-H), 3.82 (d, J = 3.8 Hz, 1 H, 2′′-H), 3.89 (d, J = 9.3 Hz, 1 H, 5′-H), 3.93 (d, J = 3.8 Hz, 1 H, 3′′-H), 3.96 (s, 1 H, 4-H), 3.98 (d, J = 3.5 Hz, 1 H, 2′-H), 4.15 (d, J = 7.3 Hz, 1 H, 6-H), 4.32 (t, J = 9.0 Hz, 1 H, 4′-H), 4.56–4.61 (m, 5 H, 2×C*H*HPh, 3×CH*H*Ph), 4.63 (d, J = 2.5 Hz, 1 H, 5-H), 4.68 (d, J = 11.8 Hz, 1 H, C*H*HPh), 4.72 (d, J = 11.9 Hz, 1 H, CH*H*Ph), 4.79 (d, J = 11.9 Hz, 1 H, C*H*HPh), 4.81 (s, 1 H, 1′-H), 5.35 (d, J = 3.8 Hz, 1 H, 1′′-H), 5.51 (s, 1 H, 1-H), 7.25–7.36 (m, 20 H, H arom) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.2 (C-6′′), 52.7 (CH_3 COOMe), 58.9 (C-2), 60.6 (C-2′), 64.7 (C-4′′ or C-5′′), 64.8 (C-6), 65.2 (C-5′′ or C-4′′), 71.5 (C-5), 72.0 (CH_2 Bn), 72.5 (C-3′′), 72.6 (CH_2 Bn), 72.8 (CH_2 Bn), 73.1 (C-4′), 73.4 (CH_2 Bn), 75.5 (C-2′′), 75.9 (C-5′), 77.6 (C-4), 77.8 (C-3), 79.7 (C-3′), 96.1 (C-1′), 98.2 (C-1′′), 100.9 (C-1), 127.4–128.5 (CH arom), 137.2 (C_q Bn), 137.9 (C_q Bn), 138.1 (C_q Bn), 167.8 (C=O COOMe) ppm. ^{13}C-GATED NMR (100 MHz, $CDCl_3$): δ = 96.1 ($J_{C1',H1'}$ = 160 Hz, C-1′), 98.2 ($J_{C1'',H1''}$ = 172 Hz, C-1′′), 100.9 ($J_{C1,H1}$ = 175 Hz, C-1) ppm. HRMS [M + Na]$^+$: calcd. for $C_{47}H_{51}O_{12}N_9$ 956.35494; found 956.36039.

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