# Synthesis of Glycosaminoglycan Oligosaccharides − An Unexpected Inhibitory Effect of a Remote *N*-Acetyl Group upon Trichloroacetimidate-Mediated Couplings

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In order to prepare biologically relevant heparan sulfate (HS) tetrasaccharide fragments containing an *N*-acetylated glucosamine at the reducing end, we studied the glycosylation reaction between the 2-azidoglucose trichloroacetimidate disaccharide donor **1** and a range of 4′-OH-uronyl disaccharide acceptors with an *N*-acetylglucosamine at the reducing terminus. Although we tried several condensation conditions, no tetrasaccharide was formed. We show that the failure of these reactions is due to the presence of the *N*-acetyl group, which inhibits the trichloroacetimidate-mediated glycosylation, since the analogous reaction proceeds smoothly once the *N*-acetyl group has been replaced by an azide. In the latter case, we show that the careful optimisation of the solvent system is a powerful way to obtain high yields and α-stereoselectivity in coupling reactions of **1** with the 4-OH of a GlcUA acceptor. Thus, in a THF/$Et_2O$ (9:1) system, we obtained the GlcUA-β-(1→4)-$GlcN_3$-α-(1→4)-GlcUA-β-(1→4)-$GlcN_3$ tetrasaccharide **16α/β** in 90% isolated yield and 92:8 α/β ratio, as compared to 57% yield and 70:30 α/β ratio when $CH_2Cl_2$ was used.


## Introduction

Heparan sulfate (HS) is a member of the glycosaminoglycan (GAG) family. This linear sulfated polysaccharide comprises the repetition of a basic disaccharide in which a uronic acid is 1,4-linked to a 2-deoxy-2-aminoglucose. HS is one of the most heterogeneous biopolymers since various epimerisation and sulfation patterns (sulfoforms) may occur along the chain.[1−3] The uronic acid may be either D-glucuronic (GlcUA) or L-iduronic (IdoUA), while *O*-sulfation may occur at the 2-position of the uronic acid and the 3- and/or 6-positions of the amino sugar. The glucosamine nitrogen may be sulfated, acetylated or, less frequently, unmodified. There is growing evidence that the formation of different HS structures is tightly controlled during biosynthesis, with the presumed goal of generating sequences with biological specificity.[4] In fact, HS chains, either at the cell surface or in the extracellular matrix, interact and regulate the activity of numerous proteins such as growth factors, cytokines, chemokines, viral proteins and coagulation factors.[5,6] Recently, it has been shown that a heparan sulfate antigen, recognized by the monoclonal antibody 10E4, co-distributes precisely with the prion lesions in the brain of scrapie-infected mice. An antigen-positive fragment from heparan sulfate was isolated after partial depolymerisation with heparin lyase III, and its structure was determined, by MS analyses, to be a non-sulfated tetrasaccharide containing an inner *N*-unsubstituted glucosamine and an *N*-acetyl glucosamine at the reducing end.[7] In addition, there is strong evidence that the terminal uronic acid is GlcUA and not IdoUA.[7] The two tetrasaccharides GlcUA−$GlcNH_2$−GlcUA−GlcNAc (**A**) and GlcUA−$GlcNH_2$−IdoUA−GlcNAc (**B**) are thus candidates as the minimum structure recognized by the 10E4 antibody. We felt that as part of an ongoing program aimed at the preparation of libraries of HS fragments,[8] tetrasaccharides **A** and **B** could be interesting biological targets in the development of a strategy for the synthesis of HS fragments containing an *N*-acetylated glucosamine at the reducing end. For the synthesis of compound **A**, our strategy relied upon a Schmidt trichloroacetimidate-mediated coupling between the 2-azido disaccharide donor **1** and the *N*-acetyl glucosamine-containing disaccharide acceptor **2** (Figure 1).

The key point in this approach is to obtain good α-stereoselectivity in the glycosylation reaction between acceptor **2** and donor **1**. The non-participating azide at the 2-position of the donor should allow for a 1,2-cis glycosylation. It has been recently shown that total α-selectivity under such coupling conditions may be obtained when the glucuronyl acceptor is conformationally constrained by a 1,2-*O*-isopropylidene derivative.[9,10] However, this strategy is not applicable when the GlcUA acceptor is already linked to another sugar, as in compound **2**. A quick survey of the literature revealed that, although reactions between donors

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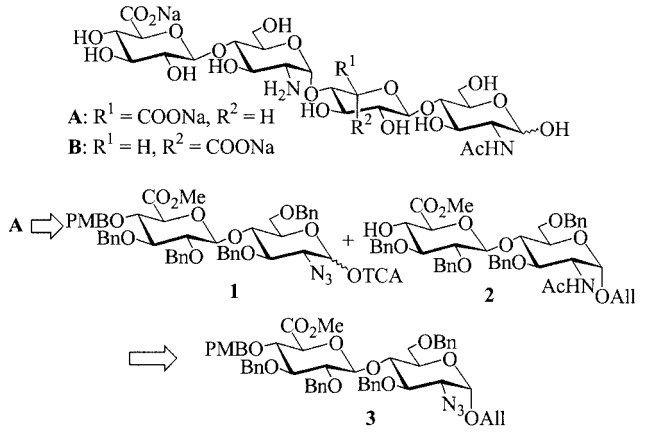
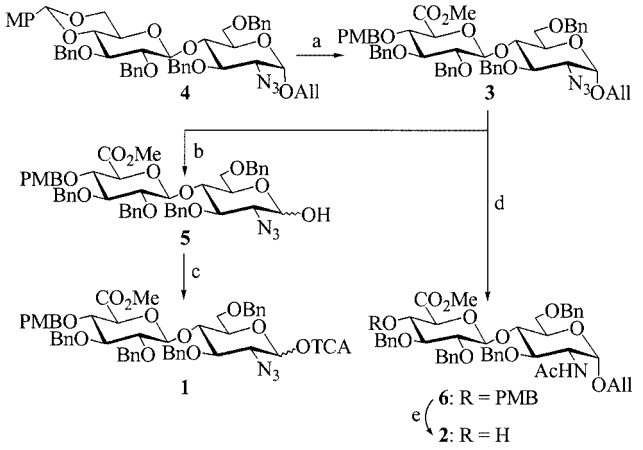



Figure 1. Retrosynthetic strategy for the preparation of GlcUA-containing HS fragments with an *N*-acetyl glucosamine at the reducing end




Scheme 1. Reagents and conditions: a) i. $PhBCl_2$, $Et_3SiH$, 4 Å MS, $Et_2O$, −40 °C, 97%; ii. $(COCl)_2$, DMSO, $CH_2Cl_2$, −78 °C and then $Et_3N$; iii. $Na_2HPO_4$, $NaClO_2$, *t*BuOH/$H_2O$, β-isoamylene, −10 °C to r.t; iv. $Cs_2CO_3$, MeI, DMF, 76%; b) i. $C_8H_{14}(Me_2PhP)_2Ir^IPF_6$, $H_2$,THF, r.t; ii. HgO/$HgCl_2$, acetone/$H_2O$, 9:1, 83% two steps; c) $Cl_3CCN$, DBU, $CH_2Cl_2$, 15 min 88%; d) $PPh_3$, THF/$H_2O$, 9:1, 16 h, r.t; ii. $Ac_2O$, Pyridine, 83%; e) TFA, $CH_2Cl_2$, 15 min, 94%

containing a non-participating azido[11−13] or *O*-benzyl group[14−16] and non-conformationally-locked glucuronyl acceptors may indeed lead to some unwanted β-anomer, this is not the general trend. Indeed, in many cases, the α-anomer was reported to be formed as the sole isolated stereoisomer.[14,15,17−23] We thus felt rather confident that we would be able to find highly α-diastereoselective glycosylation conditions between **1** and **2**. These two compounds will be prepared from the key disaccharide **3**, for which we have recently described an efficient multigram synthesis.[8] This disaccharide building block is central to our strategy for the preparation of GlcUA-containing GAG fragments. The tetrasaccharide formed will comprise the same protecting group pattern at the anomeric and 4′′′-positions, allowing us to perform further iterative chain elongation using sequential addition of disaccharides.

## Results and Discussion

### Preparation of Disaccharide Donor 1 and Disaccharide Acceptor 2

The glucuronic building block **3** was prepared from disaccharide **4** using a slight modification of a protocol that we have recently described (Scheme 1).[8] First, a $PhBCl_2$/$Et_3SiH$-mediated reductive opening of the *p*-methoxybenzylidene moiety of compound **4** was followed by Swern oxidation as described.[8] We then performed the oxidation of the resulting aldehyde to ester **3** using first $NaO_2Cl$-mediated oxidation to the carboxylic acid,[24,25] followed by methylation using methyl iodide and $Cs_2CO_3$ in DMF. We found this oxidation method more reliable than alkaline iodine in methanol, especially when performing the reaction on a larger scale (>1 g). We thus obtained the glucuronic building block **3** from the disaccharide **4** in a good and reproducible overall yield (76%).

From disaccharide **3**, the glucuronic donor **1** was prepared in a few high-yielding steps (Scheme 1). First the anomeric alcohol **5** was obtained using a two-step deallylation comprising allyl to vinyl isomerisation with an $[Ir(C_8H_{14})(PMe_2Ph)_2][PF_6]$ catalyst activated by hydrogen, followed by cleavage of the resulting enol ether using HgO/$HgCl_2$ in a water-acetone mixture.[26] The activation of the anomeric position of **5**, as a trichloroacetimidate, was carried out under standard conditions to give a 3:10 α/β mixture of the required donor **1** in excellent yield.

Ester **3** was also used as a precursor to the disaccharide acceptor **2**. The azido group was readily transformed in 83% yield to the *N*-acetyl derivative **6** by Staudinger[27] reduction and conventional acetylation (Scheme 1). The removal of $Ph_3PO$, after these two steps, was performed using LH-20 size exclusion chromatography, this greatly facilitated the purification of compound **6**, which was otherwise difficult to perform by silica gel chromatography. The cleavage of the *p*-methoxybenzyl group was then achieved with 10% TFA in dichloromethane (DCM)[28] to give the desired disaccharide acceptor **2** in excellent yield (Scheme 1). We found that this method for the cleavage of the *p*-methoxybenzyl group gave superior yields to the use of DDQ.

### Glycosylation Reactions with Disaccharide Acceptors Containing *N*-Acetyl Glucosamine at the Reducing End

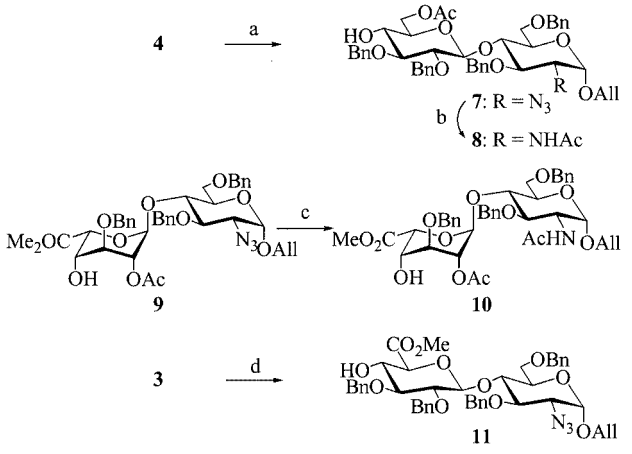
We initially investigated the glycosylation reaction between donor **1** and acceptor **2** under standard conditions, using $CH_2Cl_2$ as solvent and TMSOTf as the promoter at −20 °C or room temperature, but the reactions were sluggish with only trace amounts of the desired tetrasaccharide **13α/β** isolated, as evidenced by mass spectrometry. The typical course of the reaction involved the slow hydrolysis of donor **1** over several hours. Addition of further quantities of promoter — up to one equivalent — served only to speed up this hydrolysis. Thus, after treatment of the reaction mixture, the acceptor could be partly recovered in addition to compound **5**, resulting from donor hydrolysis, and the am-

ide **12**, resulting from the rearrangement of trichloroacetimidate **1**. We then looked at the effects of changing the promoter to $BF_3{\cdot}Et_2O$, TBDMSOTf or $Sn(OTf)_2$ as well as the presence or absence of molecular sieves; in all cases the reactions were unsuccessful.

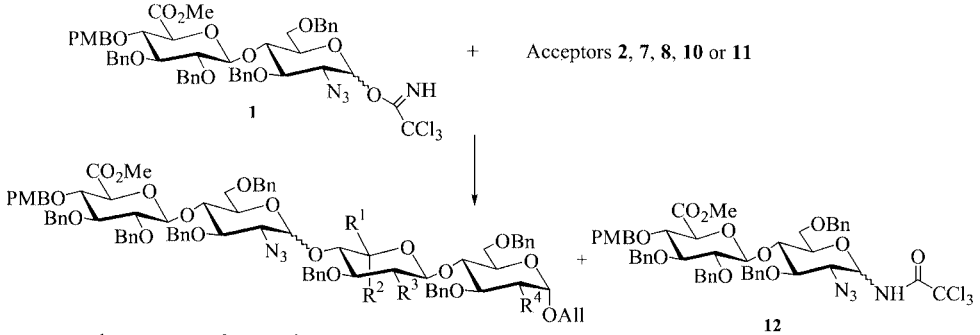
We reasoned that, in compound **2**, the nucleophilicity of the 4′-OH may be reduced by the proximity of the carboxymethyl group that would thus be the cause of the failure of the glycosylation reaction. In order to test this hypothesis, we prepared acceptor **8**, in three steps and 73% overall yield, from the non-oxidised precursor **4** (Scheme 2). Unfortunately, the glycosylation reactions between this new acceptor **8** and donor **1** also failed to generate the desired tetrasaccharide. Irrespective of the promoter and reaction conditions used, only hydrolysis and rearrangement of donor **1** were observed (Scheme 3).

The 4-position of L-iduronyl derivatives has been described as being more reactive than that of their D-glucuronyl counterparts,[9] and we have performed the oligomerisation of an L-iduronyl-containing disaccharide into tetra-, hexa- and octasaccharides in high yields.[29] Thus, in order to compare the reactivity of D-glucuronyl acceptor **2** with a similar L-iduronyl acceptor, we prepared compound **10** from the known disaccharide **9**,[8] using a Staudinger azide reduction and selective *N*-acetylation with acetic anhydride in MeOH (Scheme 2). In addition, the coupling reaction of **1** and **10** would also provide easy access to the biologically important tetrasaccharide **B**. However, when the IdoUA acceptor **10** was treated with the donor **1** and TMSOTf, the desired tetrasaccharide **15** was not obtained (Scheme 3).




Scheme 2. Synthesis of acceptors **7**, **8**, **10** and **11**; reagents and conditions: a) i. PPTS, MeOH, reflux, 10 min, 86%; ii. AcCl, Py, −20 °C, 90%; b) i. $PPh_3$, $THF/H_2O$, 9:1, 16 h. r.t; ii. $Ac_2O$, MeOH, 94%.c) i. $PPh_3$, $THF/H_2O$, 9:1, 16 h. r.t; ii. $Ac_2O$, MeOH, 97%; d) TFA, $CH_2Cl_2$, 15 min, 96%

The above experiments showed unambiguously that the failure of the trichloroacetimidate-mediated coupling of donor **1** with acceptor **2** was not linked to the low reactivity of the 4′-hydroxyl of the glucuronyl moiety. However, since the three disaccharide acceptors **2**, **8** and **10** contain an *N*-acetylated glucosamine at their reducing end, we began to suspect that this acetamido group may exert an inhibitory effect in the trichloroacetimidate-mediated glycosylation, even remote from the reacting centre. A quick survey of the literature shows that numerous successful glycosylation reactions have been performed on *N*-acetyl-containing acceptors.[30−32] In the GAG field, we have already performed the coupling of a trichloroacetimidate with the 3-OH of a 2-acetamidoglucosamine acceptor,[33] while others have successfully performed glycosylation at the 4-OH of a terminal *N*-acetylglucosamine in a tetrasaccharide acceptor,[34] or used a trisaccharide donor containing an *N*-acetylglucosamine at the non-reducing end.[20] Nevertheless, the low reactivity of the 4-OH group in *N*-acetylglucosamine derivatives in some glycosylation reactions has long been known.[35] It has been shown that 4-OH nucleophilicity is variable and linked to the protecting group used for 3-OH. In the case of glycosylation reactions with bromide donors, an acetyl group at the 3-position gives low glycosylation yields, while allyl or benzyl groups allow efficient couplings.[30] More recently, it has been shown that in sulf-




**13α/β**: $R^1 = CO_2Me$, $R^2 = H$, $R^3 = OBn$, $R^4 = NHAc$
**14α/β**: $R^1 = CH_2OAc$, $R^2 = H$, $R^3 = OBn$, $R^4 = NHAc$
**15α/β**: $R^1 = H$, $R^2 = CO_2Me$, $R^3 = OAc$, $R^4 = NHAc$
**16α/β**: $R^1 = CO_2Me$, $R^2 = H$, $R^3 = OBn$, $R^4 = N_3$
**17α/β**: $R^1 = CH_2OAc$, $R^2 = H$, $R^3 = OBn$, $R^4 = N_3$

Scheme 3. Couplings reactions of donor **1** with acceptors **2**, **7**, **8**, **10** and **11**; for reagents, conditions and α/β ratio see Table 1

Table 1. Coupling optimisation studies with donor **1** and acceptors **2**, **8**, **9** and **11** using standard conditions (1.3 equiv. donor, 0.12 M, −30° to −20 °C, 0.1 equiv. promotor and without molecular sieves)

| Entry | Acceptor | Solvent | Ratio | Promotor | Tetrasaccharide | Yield (%) | α/β[a] |
|---|---|---|---|---|---|---|---|
| 1 | 11 | $CH_2Cl_2$ | – | TMSOTf | 16 | 57[b] | 70:30 |
| 2 | 11 | $CH_2Cl_2$[c] | – | TMSOTf | 16 | 55[b] | 70:30 |
| 3 | 11 | $Et_2O$ | – | TMSOTf | 16 | 74 | 68:32 |
| 4 | 11 | THF | – | TMSOTf | 16 | 66 | 93:7 |
| 5 | 11 | THF/$Et_2O$ | 9:1 | TMSOTf | 16 | 90 | 92:8 |
| 6 | 11 | THF/$CH_2Cl_2$ | 8:2 | TMSOTf | 16 | 81 | 88:12 |
| 7 | 11 | THF/$CH_2Cl_2$ | 5:5 | TMSOTf | 16 | 60 | 87:13 |
| 8 | 11 | THF/$Et_2O$ | 9:1 | TBDMSOTf | 16 | 55 | 90:10 |
| 9 | 11 | Dioxane/toluene[d] | 3:1 | TMSOTf | 16 | 45 | 82:18 |
| 10 | 11 | THF/toluene | 9:1 | TMSOTf | 16 | 57 | 84:16 |
| 11 | 7 | $CH_2Cl_2$ | 9:1 | TMSOTf | 17 | 42 | 50:50[e] |
| 12 | 2 | THF/$Et_2O$ | 9:1 | TMSOTf | 13 | No desired reaction under standard conditions | |
| 13 | 8 | THF/$Et_2O$ | 9:1 | TMSOTf | 14 | | |
| 14 | 10 | THF/$Et_2O$ | 9:1 | TMSOTf | 15 | | |

[a] α/β ratio was determined by HPLC after isolation of the tetrasaccharide fraction by LH-20 chromatography (see Exp. Sect. for conditions). [b] Amide yield was determined with respect to donor: 32% and 17% for entries 1 and 2 respectively. [c] Glycosylation reaction performed by inverse procedure. [d] Reaction at 0 °C to avoid solvent freezing. [e] Based on isolated yields after column chromatography.

oxide- [36] or trichloroacetimidate-mediated[37] glycosylations, the reactivity of glucosaminyl 4-OH acceptors, bearing the same group in the 3-position, is markedly influenced by the protecting group of the amino function. Indeed, an acetamido-containing acceptor was shown to be ten times less reactive than its azido counterpart and three times less than the corresponding *N*-phthalimido acceptor. An explanation for this low reactivity has been proposed by Crich and Dudkin, who demonstrated the occurrence of intermolecular hydrogen bonds involving the glucosamine amide group. They showed that these interactions are involved in the low reactivity of *N*-acetyl acceptors since the introduction of a protecting group favouring an intramolecular hydrogen bond enhanced the reactivity by inhibiting the intermolecular one.[36] Although the reacting OH in acceptor **2** is far from the NHAc group, we wondered whether such intermolecular bonds could also explain the absence of reactivity of acceptor **2**. We thus performed glycosylation reactions between donor **1** and acceptor **2** in a THF/$Et_2O$ mixture that should be able to break intermolecular H-bonds, but, once again, no tetrasaccharide was formed (Table 1, entry 12). It appears therefore that intermolecular hydrogen bonding is not responsible for the lack of reactivity of compound **2**.

More recently, Liao and Auzanneau have proposed an alternative explanation for the low reactivity of the 4-OH in *N*-acetamido-containing acceptors which does not exclude that reported previously. They found that the oxygen of the acetamido group may act as a competitive nucleophile in glycosylation reactions, leading to a kinetically favoured imidate.[37] This compound may go on to rearrange to the thermodynamically more stable glycoside, albeit in only 50% yield, thus lowering the overall yield of the glycosylation reaction. In our case, it is possible that the reaction of the donor **1** with acceptor **2** may also lead to a similar imidate, that would be unable to rearrange to the glycoside leading thus to the hydrolysis products **2** and **5** after prolonged exposure to a Lewis acid, when spotted on a TLC plate or upon quenching the reaction. We were unable to isolate this imidate, but we cannot exclude that the product of the condensation of **1** and **2**, characterised by MS analyses as the awaited tetrasaccharide **13**, was in fact an imidate.

In order to ascertain this unforeseen and, to the best of our knowledge, previously unreported remote inhibitory effect of the NHAc group upon these trichloroacetimidate-based glycosylations, we decided to study glycosylation reactions on disaccharide acceptors **7** and **11** in which the NHAc group has been replaced by an azide.

### Glycosylation Reactions with Disaccharide Acceptors Containing 2-Azidoglucose at the Reducing End

Acceptor **11** was prepared in excellent yield by TFA cleavage of the *p*-methoxybenzyl group of the key intermediate **3**. We then investigated the coupling reactions of donor **1** and acceptor **11** and we were pleased to find that, in $CH_2Cl_2$ and with TMSOTf as promoter, the desired tetrasaccharide **16** was formed, albeit in moderate yield (57%) and an α/β ratio of 70:30 (Scheme 3, Table 1, entry 1).[38] In this reaction, all the donor **1** was consumed after 15 min at −30 °C and no further evolution of the reaction was observed by TLC analysis. Along with tetrasaccharide **16**, an α/β mixture of amide **12** (32%) and traces of hydrolysis product **5** were formed. We first attributed the moderate yield of this reaction to the low reactivity of the acceptor that would allow the rearrangement of trichloroacetimidate **1** into the trichloroacetamide by-product **12** to compete with the tetrasaccharide formation. The "inverse procedure" has been reported to give better yields with unreactive acceptors.[39] We thus performed a reaction adding first TMSOTf to the acceptor **11** and then the donor over 5 min. However, no improvements in the yield nor in the α/β ratio were obtained this way (Table 1, entry 2).

As in the case of the NHAc acceptor **2**, we thought that the reactivity of the 4′-OH in **11** could be lowered by the proximity of the C-5 carboxymethyl group. We thus used compound **7** as acceptor in a glycosylation reaction with donor **1** in the same conditions as for acceptor **11** and we obtained the tetrasaccharide **17** in a 42% yield and an α/β ratio of 50:50 (Scheme 3, Table 1, entry 11). This experiment demonstrates clearly that the replacement of the C-5 carboxymethyl function by an acetoxymethyl group in such 4′-OH disaccharide acceptors does not have a marked influence on the yield and stereochemical outcome of the reaction. Similar results have already been observed in the condensation of a 2-azidoglucose trichloroacetimidate donor with a 4′-OH glucosyl disaccharide acceptor protected as a 6′-*O*-TBDMS. In this case, a mixture of α- and β-anomers was obtained from which a 66% yield of the pure α-anomer could be isolated.[40] However, no comparison between the 4-OH glucosyl acceptor and its glucuronyl counterpart was made in this article.

These first experiments showed that in $CH_2Cl_2$ we faced a dual reactivity and diastereoselectivity problem. It has long been known that the solvent used in a glycosylation has a profound impact on the outcome of the reaction.[35,39,41,42] Under $S_N1$ conditions the effect of ethers on the oxycarbenium intermediate generally results in the formation of the thermodynamically more stable glycoside anomer, due to stabilisation of the epimeric oxonium anomer by the reverse anomeric effect.[41,43] We began our optimisation studies by repeating the condensation in $Et_2O$ as the solvent and we were pleased to observe a marked increase in the yield to 74% (Table 1, entry 3). In accordance with the change in solvent polarity,[44] the donor was consumed more slowly in $Et_2O$ than in $CH_2Cl_2$ (30−45 min versus less than 15 min), while the formation of the amide **12** was reduced to around 5%. Thus, as expected, the rearrangement of the imidate was probably inhibited by the disruption of the oxycarbenium/leaving group ion pair by the chelating solvent. However, quite surprisingly, the α/β ratio remained unchanged when using $Et_2O$. We thus turned to THF, a solvent with a higher polarity and donor number than $Et_2O$[44] that may both favour the $S_N1$ pathway and the stability of the oxycarbenium-solvent intermediate. Indeed, the diastereoselectivity of the reaction between donor **1** and acceptor **11** in THF was greatly improved leading to a 93:7 α/β ratio, but the isolated yield of tetrasaccharide **16** α/β dropped to 66%. However, in contrast to the reaction in dichloromethane, this lower yield was not linked to the competitive formation of the amide **12**, whose proportion was low in the reaction mixture. We then decided to study the effect of the addition of a co-solvent to the THF, and conducted the reactions in a THF/$Et_2O$ (9:1) or THF/$CH_2Cl_2$ (8:2) mixture. We were pleased to find that, in both cases, the yields were improved with respect to THF alone while the α/β ratios remained excellent (Table 1, entry 5 and 6). When $Et_2O$ was used as co-solvent, the results were slightly better than with $CH_2Cl_2$, since yields as high as 90% with 92:8 α/β selectivity were obtained with the former while only 81% isolated yield and 88:12 selectivity were obtained with the latter. However, when we diluted the THF with 50% $CH_2Cl_2$, the yield dropped to 60% (Table 1, entry 7). Toluene has been found to be the best solvent in some condensations between a 2-*O*-benzylated glucosyl donor and 4-OH uronic oligosaccharide containing acceptors,[14,15] while dioxane/toluene (3:1) mixtures have been reported to enhance the α/β ratio in thioglycoside-mediated glycosylations.[42] We thus conducted reactions between **1** and **11** in dioxane or THF with toluene as the co-solvent, but this change was not beneficial in our case and only resulted in lower yields similar to that observed with the THF/$CH_2Cl_2$ (1:1) mixture (Table 1, entries 9 and 10). We then decided to study the effect of changing the promoter from TMSOTf to TBDMSOTf, in order to see whether this could still further enhance the diastereoselectivity of the reaction, but this change only resulted in a lower yield (Table 1, entry 8).

We have thus found that the most efficient promoter and reaction solvent for the glycosylation of **11** with **1** are TMSOTf and a THF/$Et_2O$ (9:1) mixture. With these new, optimal conditions we decided to return to our original couplings of donor **1** with the *N*-acetyl-containing acceptors **2**, **8** and **10**. Unfortunately the reactions between donor **1** and acceptors **2**, **8** or **10** were as unsuccessful under these optimised conditions as they had been in pure $CH_2Cl_2$ (Table 1, entries 12, 13 and 14). In order to evaluate if a difference in nucleophilicity between the 4′-OH of *N*-acetyl and azido containing acceptors could explain the difference in reactivity between both groups, we looked at the $^1H$ chemical shifts of their 4′-O*H* (Table 2), but no general tendency can be drawn from these results. This shows once more that the absence of tetrasaccharide formation with acceptors **2**, **8** or **10** is linked to the presence of the *N*-acetyl group.

Table 2. $^1H$ chemical shifts of the 4′-O*H* in acceptors **2** and **7**−**11**

| Compound | δ (ppm) | Amino function |
|---|---|---|
| **2** | 2.87 | NHAc |
| **11** | 2.96 | $N_3$ |
| **8** | 2.81 | NHAc |
| **7** | 2.60 | $N_3$ |
| **10** | 2.87 | NHAc |
| **9** | 2.67[8] | $N_3$ |

## Conclusion

We have demonstrated a complete inhibitory effect of an *N*-acetyl group, even remote from the 4′-OH nucleophilic centre, in the coupling of donor **1** with a range of disaccharide acceptors containing such an *N*-acetyl group, since the analogous coupling proceeds smoothly once the *N*-acetyl moiety is replaced by an azide. Our results are compatible with the formation of an imidate between the donor and the *N*-acetyl group of the acceptors as proposed by Liao and Auzanneau.[37] We have shown that a careful optimisation of the solvent system is a powerful way to obtain high

yields and α-stereoselectivity in coupling reactions with oligosaccharides containing a 4-OH GlcUA acceptor that cannot be conformationally constrained. We have thus obtained the tetrasaccharide **16α/β** in 90% isolated yield and 92:8 α/β ratio. The transformation of tetrasaccharide **16α** into the biologically relevant tetrasaccharide **A** is currently under optimisation in our laboratory and will be reported in due course.

## Experimental Section

**Abbreviations:** DDQ = dichlorodicyanobenzoquinone, PPTS = pyridinium *para*-toluenesulfonate, TMSOTf = trimethylsilyl triflate, TBDMSOTf = *tert*-butyldimethylsilyl triflate, TFA = trifluoroacetic acid.

**General Remarks:** All moisture-sensitive reactions were performed under an argon atmosphere using oven-dried glassware. Evaporation was performed under vacuum with a water bath temperature below 40 °C. All solvents were dried over standard drying agents and freshly distilled prior to use. Flash column chromatography was performed on Silica Gel 60 A.C.C. (6−35 μm). Reactions were monitored by TLC on glass Silica Gel 60 $F_{254}$ plates with detection by UV at 254 nm and by charring with 5% ethanolic $H_2SO_4$. Gel filtration chromatography were performed on LH-20 (Pharmacia) eluting with $CH_2Cl_2$/MeOH, 1:1. Optical rotations were measured on a Jasco DIP 370 digital polarimeter. NMR spectra were recorded at room temperature with Bruker 400 MHz or AC 250 spectrometers. $^{13}C$ NMR were performed at 100 MHz. $Me_4Si$ or solvent signals were used for δ calibration ($CDCl_3$: $^{13}C$ δ = 77.0 ppm). Phase-sensitive COSY were performed by recording 256 or 512 FIDs with 1024 complex data points. Prior to Fourier transform, the data were zero-filled to 1024 points in the F1 dimension and multiplied with a π/3-shifted sinebell function in both dimensions. HSQC were performed by recording 128 FIDs with 1024 complex data points. Prior to Fourier transform, the data were zero-filled to 1024 points in the F1 dimension and multiplied with a π/3-shifted squared sinebell function in both dimensions. Elemental analyses were performed at the CNRS (Gif sur Yvette, France). MS spectra were recorded in the positive or negative mode on a Finnigan MAT 95 S using electrospray ionisation. For the determination of the α/β ratio for tetrasaccharide **16**, size-exclusion chromatography was first performed followed by HPLC analyses of the pooled tetrasaccharide fractions. HPLC was performed using a Nucleosil C18 5μ 200 × 4.6 mm column (Hypersil) and UV detection at 220 and 254 nm. The elution was performed at 0.8 mL/min with a linear water (5% $CH_3CN$)/$CH_3CN$ gradient (10:90 to 5:95 over 10 min) followed by 17 min isocratic elution (95:5).

**Allyl [Methyl 2,3-Di-*O*-benzyl-4-*O*-(4-methoxybenzyl)-β-D-glucopyranosyluronate]-(1→4)-*O*-2-azido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside (3):** Reductive ring opening of **4** and subsequent Swern oxidation gave the corresponding aldehyde as described previously.[8] A solution of $NaH_2PO_4$ (2.42 g, 15.8 mmol, 7.8 equiv.) in water (4.5 mL) was added to a rapidly stirring solution of this aldehyde (1.80 g, 2.03 mmol) and β-isoamylene (2-methyl-2-butene) (23.5 mL, 191 mmol, 94 equiv.) in *tert*-butyl alcohol (9.5 mL). The resulting biphasic mixture was cooled to −10 °C and a solution of $NaO_2Cl$ (1.08 g, 9.8 mmol, 4.8 equiv.) in *tert*-butyl alcohol/$H_2O$, 3:1 (19 mL) was added over 45 min whereupon a yellow colour was observed. The reaction was allowed to warm to room temp. over 16 h after which time no starting material was visible by TLC analysis. The mixture was then re-cooled to 0 °C and a saturated aq. solution of $NaHSO_3$ (40 mL) was added with stirring. The mixture was allowed to warm to room temp. and after 1 h $NaHSO_3$ (20 mL), brine (20 mL) and EtOAc (100 mL) were added. The organic phase was separated and the aqueous layer was extracted with $CHCl_3$ (3 × 50 mL) and EtOAc (3 × 50 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure to yield 1.86 g of the crude acid. TLC (toluene/acetone, 1:1), plate pre-treated by dipping in 2% $Et_3N$/DCM, then dried in vacuo prior to applying samples. $R_f$ = 0.29.

The crude acid from the previous step and $Cs_2CO_3$ (726 mg, 2.23 mmol, 1.1 equiv.) were dissolved in DMF (10 mL) and stirred for 10 min at room temp. To the resulting suspension was added MeI (1.72 g, 754 μL, 12.1 mmol, 6 equiv.) and the reaction stirred for 16 h, after which time no starting material was visible by TLC analysis. The reaction mixture was diluted with diethyl ether (200 mL) and washed with water (10 mL), saturated aq. $NaHCO_3$ (15 mL), 10% aq. $Na_2S_2O_3$ (20 mL) and brine (20 mL). The diethyl ethereal fraction was dried over $MgSO_4$ and concentrated under reduced pressure to afford a yellow oil. Purification by flash chromatography (petroleum ether/EtOAc, 4:1) afforded **3** as a clear, colourless oil (1.41 g, 76%). $C_{52}H_{57}N_3O_{12}$: $M$ = 916.0 g/mol.

**[Methyl 2,3-Di-*O*-benzyl-4-*O*-(4-methoxybenzyl)-β-D-glucopyranosyluronate]-(1→4)-2-azido-3,6-di-*O*-benzyl-2-deoxy-D-glucopyranose (5):** A solution of **3** (1.07 g, 1.17 mmol) in THF (5 mL) was degassed under vacuum and (1,5-cyclooctadiene)bis(methyldiphenylphosphane)iridium(I) hexafluorophosphate catalyst was added (16 mg), followed by further degassing of the mixture. The suspension was stirred for 15 min and then the catalyst was activated with hydrogen at room temperature for 2 min and the solution became nearly colourless. The reaction mixture was degassed again and stirred for 1.5 h. The solvent was then evaporated and the residue was dissolved in acetone/water, 9:1 (20 mL) and HgO (303 mg, 1.41 mmol, 1.2 equiv.) and $HgCl_2$ (349 mg, 1.28 mmol, 1.1 equiv.) were added. After 1 h, the solution was filtered through a pad of celite 545 and the solvent was evaporated. The residue was diluted with EtOAc (150 mL) and washed with $H_2O$ (2 × 50 mL) and saturated aq. $Na_2S_2O_3$ solution (50 mL). The aqueous layer was extracted with EtOAc (2 × 50 mL) and the organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (petroleum ether/EtOAc, 2:1 to 1:1), to yield **5** (846 mg, 83%) as a 2:1 α/β mixture of anomers along with 32 mg (3%) of the starting material **3**.TLC (petroleum ether/EtOAc, 2:1). $R_f$ = 0.25. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.46−7.31 (m, 3 H, *Ph* α and β), 7.37−7.20 (m, 27 H, *Ph* α and β), 7.13 (d, $J_{ortho}$ = 8.8 Hz, 3 H, MeO−*Ph*), 6.82 (d, $J_{ortho}$ = 8.8 Hz, 3 H, MeO−*Ph*), 5.23 (d, $J_{1,2}$ = 3.2 Hz, 1 H, H-1a α), 5.12 (d, $J_{gem}$ = 10.4 Hz, 1 H, C$H_2$Ph α), 5.03 (d, $J_{gem}$ = 10.4 Hz, 0.5 H, C$H_2$Ph β), 4.88−4.47 (m, 9 H, C$H_2$Ph α and β), 4.47−4.40 (m, 2 H, H-1a β, H-1b α and β), 4.34 (d, $J_{gem}$ = 13.5 Hz, 1 H, C$H_2$Ph α), 4.33 (d, $J_{gem}$ = 13.5 Hz, 0.5 H, C$H_2$Ph β), 4.07−3.67 (m, 13.5 H, H-4a, H-6a, H-5a, H-4b, H-3a, H-5b, C$H_3$O−Ph α and β), 3.57 (s, 3 H, COOC$H_3$ β), 3.56 (s, 1.5 H, COOC$H_3$ α), 3.52−3.16 (m, 6 H, H-3b, H-2b, H-2a, OH α and β) ppm. $^{13}C$ NMR (100.0 MHz, $CDCl_3$): δ = 168.4 (*C*=O), 159.1 (*C*-OMe, $CH_3O$−Ph), 138.1−137.3 ($C_{quaternary,arom}$), 129.9−127.3 (*Ph*, $CH_3O$−*Ph*), 113.5 (MeO−*Ph*), 102.6 (C-1b α), 102.5 (C-1b β), 95.8 (C-1a β), 91.6 (C-1a α), 83.6 (C-3b α and β), 81.9 (C-2b α and β), 79.0 (C-3a α and β), 77.7 (C-4b α and β), 77.1 (C-4 α and β), 75.3, 75.1, 75.0, 74.9, 74.8, 74.7, 74.3; 74.2, 74.1 (C-5b α and β), 73.1 ($CH_2$Ph), 70.3 (C-5a α and β), 67.3 (C-6a α and β), 66.8 (C-2a α and β), 63.0 (C-2a α and β), 55.0 (*C*$H_3$O−Ph α and β), 52.1 (COO*C*$H_3$ α and β) ppm. $C_{49}H_{53}N_3O_{12}$ (876): calcd. C 67.17, H 6.10, N 4.80; found C 67.11, H 6.25, N 4.79.

**[Methyl 2,3-Di-*O*-benzyl-4-*O*-(4-methoxybenzyl)-β-D-glucopyranosyluronate]-(1→4)-(2-azido-3,6-di-*O*-benzyl-2-deoxy-α,β-D-glucopyranosyluronate)trichloroacetimidate (1):** $CCl_3CN$ (580 μL, 8.8 mmol, 9 equiv.) and DBU (20 μL) were added to a solution of **5** (846 mg, 0.96 mmol) in dry $CH_2Cl_2$ (10 mL). After stirring for 15 min the solvent was evaporated to dryness and the residue was purified by flash chromatography (petroleum ether/EtOAc, 2:1, 1% $Et_3N$) to yield **1** (870 mg, 88%) as a 3:10 α/β mixture of anomers. TLC β/α (petroleum ether/EtOAc, 2:1, 1% $Et_3N$). $R_f$ = 0.73/0.65. IR (thin film): $\tilde{\nu}$ = 3338 ($\nu_{N-H}$), 3090, 3063, 3031, 3000 ($\nu_{C-Harom}$), 2955, 2910, 2813 ($\nu_{C-Haliph}$), 2113 ($\nu_{N3}$), 1750 ($\nu_{C=O}$ COOMe), 1674 ($\nu_{C=NH}$), 1612, 1514, 1497, 1454, 1361, 1284, 1250, 1143, 1068, 1032. $^1$H NMR (400 MHz, $CDCl_3$, selected NMR spectroscopic data for the β anomer): δ = 8.69 (s, 1 H, N*H*), 7.45−7.40 (m, 2 H, *Ph*), 7.40−7.20 (m, 18 H, *Ph*), 7.14 (d, $J_{ortho}$ = 8.4 Hz, 2 H, MeO−*Ph*), 6.83 (d, $J_{ortho}$ = 8.4 Hz, 2 H, MeO−*Ph*), 5.56 (d, $J_{1,2}$ = 8.4 Hz, 1 H, H-1a), 5.06 (d, $J_{gem}$ = 10.8 Hz, 1 H, C$H_2$Ph), 4.85 (d, $J_{gem}$ = 10.8 Hz, 1 H, C$H_2$Ph), 4.80 (d, $J_{gem}$ = 10.8 Hz, 1 H, C$H_2$Ph), 4.76 (d, $J_{gem}$ = 10.8 Hz, 1 H, C$H_2$Ph), 4.72 (d, $J_{gem}$ = 11.0 Hz, 1 H, C$H_2$Ph), 4.69 (d, $J_{gem}$ = 11.0 Hz, 1 H, C$H_2$Ph), 4.68 (d, $J_{gem}$ = 10.5 Hz, 1 H, C$H_2$Ph), 4.60 (d, $J_{gem}$ = 10.8 Hz, 1 H, C$H_2$Ph), 4.64 (d, $J_{gem}$ = 12.4 Hz, 1 H, C$H_2$Ph), 4.56 (d, $J_{1,2}$ = 8.0 Hz, 1 H, H-1b), 4.53 (d, $J_{gem}$ = 10.4 Hz, 1 H, C$H_2$Ph), 4.42 (d, $J_{gem}$ = 12.4 Hz, 1 H, C$H_2$Ph), 4.13 (t, $J_{4,3}$ = $J_{4,5}$ = 9.2 Hz, 1 H, H-4a), 3.87 (dd, $J_{6,5}$ = 3.2, $J_{6,6'}$ = 11.6 Hz, 1 H, H-6a), 3.82 (dd, $J_{4,5}$ = 10.0, $J_{4,3}$ = 9.2 Hz, 1 H, H-4b), 3.79−3.73 (m, 4 H, Ph−OC$H_3$, H-5b), 3.67−3.56 (m, 5 H, H-2a, H-6′a, COOC$H_3$), 3.50 (t, $J_{3,2}$ = $J_{3,4}$ = 9.2 Hz, 1 H, H-3b), 3.48−3.38 (m, 3 H, H-3a, H-5a, H-2b) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 168.7 (*C*=O), 161.2 (*C*=NH), 159.3 (*C*−OMe, $CH_3O$−Ph), 138.3−137.8 ($C_{quaternary,arom.}$), 130.0−127.6 (*Ph*, $CH_3O$−*Ph*), 113.8 (MeO−*Ph*), 102.6 (C-1b), 96.7 (C-1a), 84.0 (C-3b), 82.1 (C-2b), 81.0 (C-3a), 79.2 (C-4b), 76.1 (C-4a), 76.0, 75.7 (*C*$H_2$Ph), 75.3 (C-5a), 75.2, 74.6 (*C*$H_2$Ph), 74.4 (C-5b), 73.3 (*C*$H_2$Ph), 67.0 (C-6a), 65.2 (C-2a), 55.3 (*C*$H_3$O−Ph), 52.4 (COO*C*$H_3$) ppm. $C_{51}H_{53}Cl_3N_4O_{12}$: *M* = 1020.3 g/mol.

**Allyl [Methyl 2,3-Di-*O*-benzyl-4-*O*-(4-methoxybenzyl)-β-D-glucopyranosyluronate]-(1→4)-2-acetamido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside (6):** A solution of **3** (180 mg, 0.19 mmol) and $PPh_3$ (62 mg, 0.236 mmol) in THF/$H_2O$, 9:1 (1 mL) was stirred for 16 h at room temperature. After concentrating to dryness, the residue was dissolved in pyridine (1 mL) and $Ac_2O$ (0.5 mL) was added. The reaction mixture was stirred overnight, the solvent was removed and the residue was purified by gel-filtration chromatography to remove $Ph_3PO$. Fractions containing the product were concentrated and purified by flash chromatography (toluene/acetone, 3:1) to yield **6** (145 mg, 83%). TLC (toluene/acetone, 3:1). $R_f$ = 0.38. $[\alpha]_D^{30}$ = +37 ($CHCl_3$, *c* = 1.0). IR (thin film): $\tilde{\nu}$ = 3275 (3550−3150, $\nu_{O-H}$ and $\nu_{N-H}$), 3088, 3063, 3030, 3000 ($\nu_{C-Harom}$), 2958, 2923, 2851 ($\nu_{C-H\ aliph}$), 1753 ($\nu_{C=O}$ COOMe), 1658 ($\nu_{C=O}$ NHAc), 1550, 1528, 1454, 1438, 1378, 1360, 1313, 1286, 1265, 1214, 1168, 1121, 1068, 1028. $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.38−7.25 (m, 20 H, *Ph*), 7.16 (d, $J_{ortho}$ = 8.8 Hz, 2 H, MeO−*Ph*), 6.82 (d, $J_{ortho}$ = 8.8 Hz, 2 H, MeO−*Ph*), 5.88 (dddd, *J* = 17.0, 10.5, 6.0, 5.0 Hz, 1 H, $CH_2$−C*H*=$CH_2$), 5.26 (dq, *J* = 17.0, 1.5 Hz, 1 H, $CH_2$−CH=C$H_2$), 5.24 (d, $J_{NH,2}$ = 9.2 Hz, 1 H, N*H*), 5.21 (dq, *J* = 10.5, 1.5 Hz, 1 H, $CH_2$−CH=C$H_2$), 4.93 (d, $J_{gem}$ = 12.0 Hz, 1 H, C$H_2$Ph), 4.89 (d, $J_{1,2}$ = 4.0 Hz, 1 H, H-1a), 4.86−4.76 (m, 4 H, C$H_2$Ph), 4.68 (d, $J_{gem}$ = 10.4 Hz, 1 H, C$H_2$Ph), 4.63 (d, $J_{gem}$ = 12.0 Hz, 1 H, C$H_2$Ph), 4.58 (d, $J_{gem}$ = 12.0 Hz, 1 H, C$H_2$Ph), 4.52 (d, $J_{gem}$ = 10.4 Hz, 1 H, C$H_2$Ph), 4.46 (d, $J_{1,2}$ = 7.6 Hz, 1 H, H-1b), 4.42 (d, $J_{gem}$ = 12.0 Hz, 1 H, C$H_2$Ph), 4.22 (ddd, $J_{2,3}$ = 10.8, $J_{2,NH}$ = 9.2, $J_{2,1}$ = 4.0 Hz, 1 H, H-2a), 4.13 (ddt, $J_{gem}$ = 13.0, $J_{a,b}$ = 5.0, $J_{a,cc}$ = $J_{a,ct}$ = 1.5 Hz, 1 H, C$H_2$−CH=$CH_2$), 4.09 (t, $J_{4,3}$ = $J_{4,5}$ = 9.6 Hz, 1 H, H-4a), 3.96 (ddt, $J_{gem}$ = 13.0, $J_{a,b}$ = 6.0, $J_{a,cc}$ = $J_{a,ct}$ = 1.5 Hz, 1 H, C$H_2$−CH=$CH_2$), 3.89 (dd, $J_{6,5}$ = 3.2, $J_{6,6'}$ = 11.2 Hz, 1 H, H-6a), 3.82−3.73 (m, 5 H, $CH_3$O−Ph, H-4b, H-5b), 3.66−3.57 (m, 5 H, H-3a, H-5a, COO$CH_3$), 3.52−3.39 (m, 3 H, H-6′a, H-2b, H-3b), 1.81 (s, 3 H, $CH_3$CONH) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 169.4, 168.6 (*C*=O), 159.0 (*C*−OMe, $CH_3O$−Ph), 139.0−133.7 ($C_{quaternary,arom.}$), 133.5 ($CH_2$−*C*H=$CH_2$), 129.8−127.2 (*Ph*, $CH_3O$−*Ph*), 117.3 ($CH_2$−CH=*C*$H_2$), 113.5 (MeO−*Ph*), 102.6 (C-1b), 96.4 (C-1a), 83.7 (C-3b), 82.0 (C-2b), 79.0 (C-4b), 77.3, 77.1 (C-3a, C-4a), 75.3, 74.9, 74.3 (*C*$H_2$Ph), 74.0 (C-5a), 73.2, 73.0 (*C*$H_2$Ph), 70.6 (C-5b), 68.0 (*C*$H_2$−CH=$CH_2$), 67.2 (C-6a), 55.0 (*C*$H_3$O−Ph), 52.0 (COO*C*$H_3$), 51.6 (C-2a), 23.1 (*C*$H_3$CONH). $C_{54}H_{61}NO_{13}$ (932.1): calcd. C 69.59, H 6.60, N 1.50; found C 69.59, H 6.71, N 1.37. ESI-MS calcd. for $C_{54}H_{61}NNaO_{13}$ [M + Na]: *m*/*z* = 954.4; found 954.3.

**Allyl (Methyl 2,3-Di-*O*-benzyl-β-D-glucopyranosyluronate)-(1→4)-2-acetamido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside (2):** $CF_3COOH$ (150 μL) was added to a solution of **6** (145 mg, 0.15 mmol) in $CH_2Cl_2$ (1 mL) at room temperature. After stirring for 15 min, the reaction mixture, which had become purple, was neutralised with $Et_3N$ (300 μL) at 0 °C and concentrated. The residue was purified by flash chromatography ( toluene/acetone, 4:1 to 1:1) to yield **2** (114 mg, 94%) as a colourless gum. TLC (toluene/acetone, 3:1): $R_f$ = 0.29. $[\alpha]_D^{30}$ = +43 ($CHCl_3$, *c* = 1.1). IR (thin film): $\tilde{\nu}$ = 3275 (3550−3150, $\nu_{O-H}$ and $\nu_{N-H}$), 3088, 3063, 3030, 3000 ($\nu_{C-Harom}$), 2958, 2923, 2851 ($\nu_{C-Haliph}$), 1753 ($\nu_{C=O}$ COOMe), 1658 ($\nu_{C=O}$ NHAc), 1550, 1528, 1454, 1438, 1378, 1360, 1313, 1286, 1265, 1214, 1168, 1121, 1068, 1028. $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.42−7.20 (m, 20 H, *Ph*), 5.88 (dddd, *J* = 17.0, 10.5, 6.0, 5.0 Hz, 1 H, $CH_2$−C*H*=$CH_2$), 5.26 (br.d, $J_{NH,2}$ = 8.8 Hz, 1 H, N*H*), 5.25 (dq, *J* = 17.0, 1.5 Hz, 1 H, $CH_2$−CH=C$H_2$), 5.20 (dq, *J* = 10.5, 1.5 Hz, 1 H, $CH_2$−CH=C$H_2$), 4.91 (d, $J_{1,2}$ = 4.5 Hz, 0.4 H, H-1a), 4.89 (d, $J_{1,2}$ = 3.5 Hz, 0.6 H, H-1a), 4.84 (s, 2 H, C$H_2$Ph), 4.77 (s, 2 H, C$H_2$Ph), 4.64 (d, $J_{gem}$ = 12.0 Hz, 1 H, C$H_2$Ph), 4.57 (2 d separated by 0.005 ppm, $J_{gem}$ = 12.0 Hz, 1 H, C$H_2$Ph of two NHAc rotamers), 4.42 (d, $J_{1,2}$ = 7.4 Hz, 0.4 H, H-1b of one NHAc rotamers), 4.41 (d, $J_{1,2}$ = 7.4 Hz, 0.6 H, H-1b), 4.35 (d, $J_{gem}$ = 12.0 Hz, 1 H, C$H_2$Ph), 4.29−4.21 (m, 1 H, H-2a), 4.16−4.08 (m, 2 H, H-4a, C$H_2$−CH=$CH_2$), 3.94 (ddt, $J_{gem}$ = 13.0, $J_{a,b}$ = 6.0, $J_{a,cc}$ = $J_{a,ct}$ = 1.5 Hz, 1 H, C$H_2$−CH=$CH_2$), 3.89 (dd, $J_{6,5}$ = 3.5, $J_{6,6'}$ = 11.0 Hz, 1 H, H-6a), 3.80 (t, $J_{4,3}$ = $J_{4,5}$ = 9.2 Hz, 1 H, H-4b), 3.68−3.47 (m, 7 H, H-3b, H-5a, H-5b, CO-OC$H_3$, H-6′a), 3.39−3.28 (m, 2 H, H-2b, H-3b); 2.96 (br. s, 1 H, OH); 1.81 (s, 3 H, C$H_3$CONH) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 169.6, 169.5 (*C*=O), 139.0−137.8 ($C_{quaternary,arom.}$), 133.5 ($CH_2$−*C*H=$CH_2$), 128.4−127.0 (*Ph*, $CH_3O$−*Ph*), 117.3 ($CH_2$−CH=*C*$H_2$), 102.5 (C-1b), 96.4 (C-1a), 83.1 (C-3b), 81.3 (C-2b), 77.4 (C-3a), 76.7 (C-4a), 75.1, 74.9, 73.6 (*C*$H_2$Ph), 73.0 (C-5b), 72.6 (*C*$H_2$Ph), 71.9 (C-4b), 70.6 (C-5a), 68.0 (*C*$H_2$−CH=$CH_2$), 67.3 (C-6a), 52.2 (COO*C*$H_3$), 51.5 (C-2a), 23.1 (*C*$H_3$CONH). $C_{46}H_{53}NO_{12}$ (811.9): calcd. C 68.05, H 6.58, N 1.73, O 23.65; found C 67.71, H 6.63, N 1.66, O 23.73. ESI-MS calcd. for $C_{46}H_{53}NNaO_{12}$ [M + Na]: *m*/*z* = 834.4; found 834.3.

**Allyl (6-*O*-Acetyl-2,3-di-*O*-benzyl-β-D-glucopyranosyl)-(1→4)-2-azido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside (7):** A solution of **4** (390 mg, 0.44 mmol) and PPTS (25 mg, 0.10 mmol) in MeOH (10 mL) was heated for 10 min at reflux. The temperature was then decreased to room temp. and the solution was neutralised with $Et_3N$ (0.1 mL) and concentrated. The residue was purified by flash chromatography (petroleum ether/EtOAc, 4:1 to 1:1) to yield the corresponding diol (290 mg, 86%). Acetyl chloride (19 μL,

0.28 mmol, 1.1 equiv.) was added to a cooled (−20 °C) solution of diol (200 mg, 0.25 mmol) in pyridine (2.0 mL). After 2.5 h, EtOH (1 mL) was added and the mixture was warmed to room temperature. The solvents were then evaporated and the residue was purified by flash chromatography (petroleum ether/EtOAc, 4:1 to 1:1) to afford **7** (188 mg, 90%). TLC (petroleum ether/EtOAc, 3:2): $R_f$ = 0.50. $[\alpha]_D^{30}$ = +19 ($CHCl_3$, *c* = 1.1). IR (thin film): $\tilde{\nu}$ = 3450 (3550−3150, $\nu_{O-H}$), 3089, 3063, 3030, 3010 ($\nu_{C-Harom}$), 2959, 2924, 2866, 2852 ($\nu_{C-Haliph}$), 2109 ($\nu_{N3}$), 1742 ($\nu_{C=O}$ OAc), 1497, 1454, 1364, 1242, 1138, 1119, 1053, 1028. $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.38−7.18 (m, 20 H, *Ph*), 5.88 (dddd, *J* = 17.0, 10.5, 6.0, 5.0 Hz, 1 H, $CH_2-CH=CH_2$), 5.29 (dq, *J* = 17.0, 1.5 Hz, 1 H, $CH_2-CH=CH_2$), 5.18 (dq, *J* = 10.5, 1.5 Hz, 1 H, $CH_2-CH=CH_2$), 5.06 (d, $J_{gem}$ = 10.8 Hz, 1 H, $CH_2$Ph), 4.86 (d, $J_{1,2}$ = 3.6 Hz, 1 H, H-1a), 4.81 (d, $J_{gem}$ = 11.2 Hz, 1 H, $CH_2$Ph), 4.74 (d, $J_{gem}$ = 11.2 Hz, 1 H, $CH_2$Ph), 4.71 (d, $J_{gem}$ = 11.2 Hz, 1 H, $CH_2$Ph), 4.70 (d, $J_{gem}$ = 11.2 Hz, 1 H, $CH_2$Ph), 4.58 (d, $J_{gem}$ = 12.0 Hz, 1 H, $CH_2$Ph), 4.56 (d, $J_{gem}$ = 10.8 Hz, 1 H, $CH_2$Ph), 4.33−4.37 (m, 3 H, H-1b, $CH_2$Ph, H-6b), 4.12 (ddt, $J_{gem}$ = 13.0, $J_{a,b}$ = 5.0, $J_{a,cc}$ = $J_{a,ct}$ = 1.5 Hz, 1 H, $CH_2-CH=CH_2$), 4.05 (dd, $J_{6,5}$ = 2.0, $J_{6,6'}$ = 12.5 Hz, 1 H, H-6′b), 4.01 (t, $J_{4,3}$ = $J_{4,5}$ = 10.0 Hz, 1 H, H-4a), 3.98 (ddt, $J_{gem}$ = 13.0, $J_{a,b}$ = 6.0, $J_{a,cc}$ = $J_{a,ct}$ = 1.5 Hz, 1 H, $CH_2-CH=CH_2$), 3.84 (dd, $J_{6,5}$ = 2.0, $J_{6,6'}$ = 10.8 Hz, 1 H, H-6a), 3.82 (dd, $J_{3,2}$ = 8.8, $J_{3,4}$ = 10.0 Hz, 1 H, H-3a), 3.61 (dt, $J_{5,6}$ = $J_{5,6}$ = 2.0, $J_{5,4}$ = 10.0 Hz, 1 H, H-5a), 3.41 (dd, $J_{6,5}$ = 1.6, $J_{6,6'}$ = 10.8 Hz, 1 H, H-6′a), 3.35−3.29 (m, 2 H, H-4b, H-2a), 3.24 (dd, $J_{2,3}$ = 8.8, $J_{2,1}$ = 7.6 Hz, 1 H, H-2b), 3.18 (dd, $J_{3,4}$ = $J_{3,2}$ = 8.8 Hz, 1 H, H-3b), 3.09−3.05 (ddd, $J_{5,6}$ = 2.0, $J_{5,6'}$ = 4.0, $J_{5,4}$ = 9.6 Hz, 1 H, H-5b), 2.60 (br. s, 1 H, OH), 1.90 (s, 3 H, $OCOCH_3$) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 169.0 (*C*=O), 138.0−137.5 ($C_{quaternary,arom.}$), 133.1 ($CH_2-CH=CH_2$), 128.2−127.3 (*Ph,* $CH_3O-Ph$), 117.7 ($CH_2-CH=CH_2$), 102.3 (C-1b), 96.5 (C-1a), 83.5 (C-3b), 81.9 (C-2b), 77.9 (C-3a), 76.2 (C-4a), 75.2, 74.7, 74.6, 73.3 ($CH_2$Ph), 73.1 (C-5b), 70.3 (C-5a), 69.8 (C-4b), 68.3 ($CH_2-CH=CH_2$), 67.2 (C-6a), 62.9 (C-6b), 62.4 (C-2a), 20.5 ($OCOCH_3$) ppm. $C_{45}H_{51}N_3O_{11}$ (809.9): calcd. C 66.73, H 6.35, N 5.17, O 21.73; found C 66.49, H 6.44, N 4.87, O 21.73. ESI-MS calcd. for $C_{45}H_{51}N_3NaO_{11}$ [M + Na]: *m*/*z* = 832.3; found. 832.5.

**Allyl (6-*O*-Acetyl-2,3-di-*O*-benzyl-β-D-glucopyranosyl)-(1→4)-2-acetamido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside (8):** Compound **7** (200 mg, 0.246 mmol) was treated as described for compound **6**, giving, after flash chromatography (toluene/acetone, 3:1), 184 mg of **8** (94%). TLC (toluene/acetone, 2:1): $R_f$ = 0.45. $[\alpha]_D^{30}$ = +31 ($CHCl_3$, *c* = 1.0). IR (thin film): $\tilde{\nu}$ = 3260 (3550−3150, $\nu_{O-H}$ and $\nu_{N-H}$), 3088, 3061, 3029, 3009 ($\nu_{C-Harom}$), 2938, 2918, 2899, 2859 ($\nu_{C-Haliph}$), 1741 ($\nu_{C=O}$ OAc), 1655 ($\nu_{C=O}$ NHAc), 1576, 1562, 1536, 1496, 1453, 1364, 1313, 1278, 1259, 1239, 1207, 1169, 1143, 1117, 1091, 1052, 1028. $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.28−7.16 (m, 20 H, *Ph*), 5.82 (dddd, *J* = 17.0, 10.5, 6.0, 5.0 Hz, 1 H, $CH_2-CH=CH_2$), 5.22 (d, $J_{NH,2}$ = 7.2 Hz, 1 H, N*H*), 5.20 (dq, *J* = 17.0, 1.5 Hz, 1 H, $CH_2-CH=CH_2$), 5.14 (dq, *J* = 10.5, 1.5 Hz, 1 H, $CH_2-CH=CH_2$), 4.84 (d, $J_{1,2}$ = 3.6 Hz, 1 H, H-1a), 4.82 (d, $J_{gem}$ = 11.0 Hz, 1 H, $CH_2$Ph), 4.80 (d, $J_{gem}$ = 10.0 Hz, 1 H, $CH_2$Ph), 4.77−4.68 (m, 3 H, $CH_2$Ph), 4.59 (d, $J_{gem}$ = 12.0 Hz, 1 H, $CH_2$Ph), 4.53 (d, $J_{gem}$ = 12.0 Hz, 1 H, $CH_2$Ph), 4.37−4.33 (m, 2 H, $CH_2$Ph, H-1b), 4.27 (dd, $J_{6,5}$ = 4.4, $J_{6,6'}$ = 12.0 Hz, 1 H, H-6b), 4.18 (ddd, $J_{2,1}$ = 3.6, $J_{2,NH}$ = 7.2, $J_{2,3}$ = 9.0 Hz, 1 H, H-2a), 4.10−4.02 (m, 3 H, $CH_2-CH=CH_2$, H-6′b, H-4a), 3.89 (ddt, $J_{gem}$ = 13.0, $J_{a,\ b}$ = 6.0, $J_{a,cc}$ = $J_{a,ct}$ = 1.5 Hz, 1 H, $CH_2-CH=CH_2$), 3.84 (dd, $J_{6,5}$ = 3.2, $J_{6,6'}$ = 10.8 Hz, 1 H, H-6a), 3.61 (br. d, $J_{5,4}$ = 10.0, 1 H, H-5a), 3.57 (dd, $J_{3,4}$ = 10.8, $J_{3,2}$ = 9.0 Hz, 1 H, H-3a), 3.48 (dd, $J_{6,5}$ = 1.6, $J_{6,6'}$ = 10.8 Hz, 1 H, H-6′a), 3.36−3.20 (m, 2 H, H-4b, H-3b, H-2b), 3.13 (ddd, $J_{5,6'}$ = 2.2, $J_{5,6}$ = 4.4, $J_{5,4}$ = 9.0 Hz, 1 H, H-5b), 2.81 (br. s, 1 H, OH), 1.86 (s, 3 H, $OCOCH_3$), 1.75 (s, 3 H, $CH_3CONH$) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 171.6, 169.7 (*C*=O), 139.1−137.5 ($C_{quaternary,arom.}$), 133.6 ($CH_2-CH=CH_2$), 128.4−127.3 (*Ph,* $CH_3O-Ph$), 117.3 ($CH_2-CH=CH_2$), 102.3 (C-1b), 96.5 (C-1a), 83.8 (C-3b), 82.1 (C-2b), 77.3 (C-3a), 76.5 (C-4a), 75.3, 74.8, 73.3 ($CH_2$Ph), 73.2 (C-5b), 72.6 ($CH_2$Ph), 70.8 (C-5a), 70.1 (C-4b), 68.1 ($CH_2-CH=CH_2$), 67.6 (C-6a), 63.0 (C-6b), 51.7 (C-2a), 23.2 ($CH_3CONH$), 20.5 ($OCOCH_3$). $C_{47}H_{55}NO_{12}$ (825.9): calcd. C 68.35, H 6.71, N 1.70, O 23.25; found C 67.98, H 6.49, N 1.62, O 23.15. ESI-MS calcd. for $C_{47}H_{55}NNaO_{12}$ [M + Na]: *m*/*z* = 848.4; found 848.3.

**Allyl (Methyl 2-*O*-Acetyl-3-*O*-benzyl-α-L-idopyranosyluronate)-(1→4)-2-acetamido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside (10):** Compound **9**[8] (136 mg, 0.18 mmol) was treated as described for compound **6**, giving, after flash chromatography (toluene/acetone, 3:1), 128 mg of **10** (97%). TLC (toluene/acetone, 3:1): $R_f$ = 0.25. $[\alpha]_D^{30}$ = +15 ($CHCl_3$, *c* = 1.0). IR (thin film): $\tilde{\nu}$ = 3275 (3550−3150, $\nu_{O-H}$ and $\nu_{N-H}$), 3095, 3063, 3030, 3004 ($\nu_{C-Harom}$), 2955, 2922, 2864, 2851 ($\nu_{C-Haliph}$), 1739 ($\nu_{C=O}$ OAc), 1660 ($\nu_{C=O}$ NHAc), 1604, 1550, 1536, 1498, 1454, 1446, 1373, 1316, 1235, 1211, 1169, 1156, 1102, 1041. $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.42−7.12 (m, 15 H, *Ph*), 5.87 (dddd, *J* = 17.0, 10.5, 6.0, 5.0 Hz, 1 H, $CH_2-CH=CH_2$), 5.35 and 5.34 (2 d, $J_{NH,2}$ = 10 Hz, 1 H, N*H*, 2 rotamers), 5.25 (dq, *J* = 17.0, 1.5 Hz, 1 H, $CH_2-CH=CH_2$), 5.20 (br. d, *J* = 10.5 Hz, 1 H, $CH_2-CH=CH_2$), 5.16 (br. s, 1 H, H-1b), 4.99 (d, $J_{5,4}$ = 2.0 Hz, 1 H, H-5b), 4.96 (br. s, 1 H, H-2b), 4.82 (d, $J_{1,2}$ = 3.6 Hz, 1 H, H-1a), 4.72 (d, $J_{gem}$ = 11.2 Hz, 1 H, $CH_2$Ph), 4.67 (d, $J_{gem}$ = 12.0 Hz, 1 H, $CH_2$Ph), 4.65 (d, $J_{gem}$ = 11.2 Hz, 1 H, $CH_2$Ph), 4.52 (s, 2 H, $CH_2$Ph), 4.45 (d, $J_{gem}$ = 12.0 Hz, 1 H, $CH_2$Ph), 4.33 (td, $J_{2,1}$ = 3.6, $J_{2NH}$ = $J_{2,3}$ = 10.0 Hz, 1 H, H-2a), 4.14 (br. dd, $J_{gem}$ = 13.0, $J_{a,b}$ = 5.0 Hz, 1 H, $CH_2-CH=CH_2$), 4.06 (t, $J_{4,3}$ = $J_{4,5}$ = 9.6 Hz, 1 H, H-4a), 3.96 (br. s, 1 H, H-4b), 3.94 (br. dd, $J_{gem}$ = 13.0, $J_{a,b}$ = 6.0 Hz, 1 H, $CH_2-CH=CH_2$), 3.79−3.75 (m, 2 H, H-5a, H-6a), 3.72 (t, $J_{3,2} \approx J_{3,4}$ = 2.8 Hz, 1 H, H-3b), 3.67−3.62 (m, 2 H, H-3a, H-6′a), 3.45 (s, 3 H, $COOCH_3$), 2.87 (br. s, 1 H, OH), 2.05 (s, 3 H, $OCOCH_3$), 1.75 (s, 3 H, $CH_3CONH$) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 169.4, 169.3 169.0 (*C*=O), 138.0−137.2 ($C_{quaternary,arom.}$), 133.4 ($CH_2-CH=CH_2$), 128.2−127.0 (*Ph,* $CH_3O-Ph$), 117.3 ($CH_2-CH=CH_2$), 97.6 (C-1b), 96.5 (C-1a), 78.1 (C-3a), 74.9 (C-4a), 74.5 (C-3b), 73.0, 72.0, ($CH_2$Ph), 71.0 (C-5b), 68.2 (C-4b), 68.1 ($CH_2-CH=CH_2$), 68.0 (C-6a), 67.7 (C-5b), 67.1 (C-2b), 51.8 (C-2a), 51.7 ($COOCH_3$), 23.0 ($OCOCH_3$), 20.7 ($CH_3CONH$) ppm. $C_{41}H_{49}NO_{13}$ (763.8): calcd. C 64.47, H 6.47, N 1.83; found C 64.19, H 6.44, N 1.73. ESI-MS calcd. for $C_{41}H_{49}NNaO_{13}$ [M + Na]: *m*/*z* = 786.3; found 786.3.

**Allyl (Methyl 2,3-Di-*O*-benzyl-β-D-glucopyranosyluronate)-(1→4)-2-azido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside (11):** Compound **3** (285 mg, 0.31 mmol) was treated as described for the preparation of compound **2**. Flash chromatography (petroleum ether/EtOAc, 4:1 to 1:1 ) gave **11** (235 mg, 96%) as a colourless oil. TLC (petroleum ether/EtOAc, 2:1): $R_f$ = 0.4. $[\alpha]_D^{30}$ = +45 ($CHCl_3$, *c* = 1.0). IR (thin film): $\tilde{\nu}$ = 3466 (3550−3150, $\nu_{O-H}$), 3086, 3063, 3030, 3010 ($\nu_{C-Harom}$), 2955, 2922, 2851 ($\nu_{C-Haliph}$), 2108 ($\nu_{N3}$), 1751 ($\nu_{C=O}$ COOMe), 1607, 1584, 1497, 1453, 1360, 1261, 1245, 1210, 1161, 1118, 1066, 1027. $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.45−7.20 (m, 20 H, *Ph*), 5.98 (dddd, *J* = 17.0, 10.5, 6.0, 5.0 Hz, 1 H, $CH_2-CH=CH_2$), 5.40 (dq, *J* = 17.0, 1.5 Hz, 1 H, $CH_2-CH=CH_2$), 5.28 (dq, *J* = 10.5, 1.5 Hz, 1 H, $CH_2-CH=CH_2$), 5.13 (d, $J_{gem}$ = 10.5 Hz, 1 H, $CH_2$Ph), 4.96 (d, $J_{1,2}$ = 3.6 Hz, 1 H, H-1a), 4.88 (s, 2 H, $CH_2$Ph), 4.69 (d, $J_{gem}$ = 12.0 Hz, 1 H, $CH_2$Ph), 4.68 (d, $J_{gem}$ = 10.5 Hz, 1 H, $CH_2$Ph), 4.69 (m, 2 H, $CH_2$Ph), 4.42 (d,

$J_{1,2}$ = 7.6 Hz, 1 H, H-1b), 4.37 (d, $J_{gem}$ = 12.0 Hz, 1 H, C$H_2$Ph), 4.24−4.06 (m, 3 H, H-4a, C$H_2$−CH=CH$_2$), 3.94−3.83 (m, 3 H, H-6a, H-3a, H-4b), 3.70 (dd, $J_{5,6}$ = $J_{5,6}$ = 1.5, $J_{5,4}$ = 9.6 Hz, 1 H, H-5a), 3.59 (s, 3 H, COOC$H_3$), 3.57 (d, $J_{5,4}$ = 8.5 Hz, 1 H, H-5b), 3.50 (dd, $J_{6',5}$ = 1.5, $J_{6,6'}$ = 10.8 Hz, 1 H, H-6′a), 3.42 (dd, $J_{2,1}$ = 3.6, $J_{2,3}$ = 10.4 Hz, 1 H, H-2a), 3.37 (dd, $J_{2,1}$ = 7.6, $J_{2,3}$ = 9.6 Hz, 1 H, H-2b), 3.32 (t, $J_{3,4}$ = $J_{3,2}$ = 9.6 Hz, 1 H, H-3b), 2.90 (br. s, 1 H, OH) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 169.4 (*C*=O), 138.3−137.5 ($C_{quaternary,arom.}$), 133.1 (CH$_2$−*C*H=CH$_2$), 128.3−127.1 (*Ph,* CH$_3$O−*Ph*), 117.7 (CH$_2$−CH=*C*H$_2$), 102.4 (C-1b), 96.6 (C-1a), 83.1 (C-3b), 81.4 (C-2b), 77.9 (C-3a), 76.8 (C-5a), 75.0, 74.9, 74.7 (*C*H$_2$Ph), 73.7 (C-5b), 73.1 (*C*H$_2$Ph), 71.4 (C-4b), 70.3 (C-4a), 68.4 (*C*H$_2$−CH=CH$_2$), 67.2 (C-6a), 62.4 (C-2a), 52.2 (COO*C*H$_3$) ppm. $C_{44}H_{49}N_3O_{11}$ (795.9): calcd. C 66.39, H 6.21, N 5.28, O 22.11; found C 66.51, H 6.29, N 5.06, O 21.88.

**Allyl [Methyl 2,3-di-*O*-benzyl-4-*O*-(4-methoxyphenyl)-β-D-glucopyranosyluronate]-(1→4)-(2-azido-3,6-di-*O*-benzyl-2-deoxy-D-glucopyranosyl)-(1→4)-*O*-(methyl 2,3-di-*O*-benzyl-β-D-glucopyranosyluronate)-(1→4)-2-azido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside (16):** A solution of TMSOTf (10%, 76 μL of a 0.55 mM in $CH_2Cl_2$) was added to a cooled solution (−30 °C) of **11** (240 mg, 0.301 mmol) and **1** (431 mg, 0.422 mmol, 1.4 equiv.) in THF/Et$_2$O, 9:1 (500 μL). The solution was stirred for 2 h at this temperature, and then neutralised with Et$_3$N (100 μL). The solvent was evaporated and the residue was purified by flash chromatography (toluene/EtOAc, 20:1 to 6:1) to give 413 mg **16α** (83% isolated yield) and 36 mg **16β** (7% isolated yield). Data for **16 α**: TLC (toluene/EtOAc, 6:1 ): $R_f$ α 0.42. $[\alpha]_D^{30}$ = +39 ($CHCl_3$, *c* = 1.0). IR (thin film): ṽ = 3084, 3063, 3030, 3004 ($\nu_{C-Harom}$), 2954, 2923, 2865, 2852 ($\nu_{C-Haliph}$), 2109 ($\nu_{N3}$), 1750 ($\nu_{C=O}$ COOMe), 1610, 1585, 1513, 1497, 1453, 1438, 1361, 1249, 1216, 1141, 1090, 1064, 1027. $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.50−7.21 (m, 40 H, *Ph*), 7.19 (d, $J_{ortho}$ = 8.4 Hz, 2 H, CH$_3$O−*Ph*), 6.88 (d, $J_{ortho}$ = 8.4 Hz, 2 H, CH$_3$O−*Ph*), 5.97 (dddd, *J* = 17.0, 10.5, 6.0, 5.0 Hz, 1 H, CH$_2$−C*H*=CH$_2$), 5.57 (d, $J_{1,2}$ = 4.0 Hz, 1 H, H-1c), 5.39 (dq, *J* = 17.0, 1.5 Hz, 1 H, CH$_2$−CH=C*H*$_2$), 5.28 (dq, *J* = 10.5, 1.5 Hz, 1 H, CH$_2$−CH=C*H*$_2$), 5.19 (d, $J_{gem}$ = 10.4 Hz, 1 H, C$H_2$Ph), 5.12 (d, $J_{gem}$ = 10.4 Hz, 1 H, C$H_2$Ph), 4.84 (d, $J_{1,2}$ = 4.0 Hz, 1 H, H-1a), 4.81 (d, $J_{gem}$ = 11.5 Hz, 1 H, C$H_2$Ph), 4.76−4.37 (m, 11 H, C$H_2$Ph), 4.52 (d, $J_{gem}$ = 11.0 Hz, 1 H, C$H_2$Ph), 4.46 (d, $J_{gem}$ = 11.0 Hz, 1 H, C$H_2$Ph), 4.41 (d, $J_{1,2}$ = 7.5 Hz, 1 H, H-1d), 4.35 (d, $J_{gem}$ = 12.0 Hz, 1 H, C$H_2$Ph), 4.27 (d, $J_{gem}$ = 12.0 Hz, 1 H, C$H_2$Ph), 4.25 (d, $J_{1,2}$ = 8.0 Hz, 1 H, H-1b), 4.21 (br. dd, $J_{gem}$ = 13.0, $J_{a,b}$ = 5.0 Hz, 1 H, C$H_2$−CH=CH$_2$), 4.14−4.01 (m, 4 H, C$H_2$−CH=CH$_2$, H-4a, H-4c, H-4b), 3.98 (dd, $J_{6,5}$ = 1.6, $J_{6,6'}$ = 11.2 Hz, 1 H, H-6a), 3.90−3.80 (m, 7 H, H-6c, H-4d, H-3a, Ph−OC$H_3$, H-3c), 3.77 (d, $J_{5,4}$ = 9.6 Hz, 1 H, H-5b), 3.73 (d, $J_{5,4}$ = 10.0 Hz, 1 H, H-5d), 3.65 (br. d, $J_{5,4}$ = 10.5 Hz, 1 H, H-5a), 3.61 (s, 3 H, COOC$H_3$), 3.58−3.38 (m, 7 H, H-6′a, H-5c, H-3b, H-3d, H-6′c, H-2b, H-2d), 3.38 (dd, $J_{2,1}$ = 4.0, $J_{2,3}$ = 10.4 Hz, 1 H, H-2a), 3.37 (dd, $J_{2,1}$ = 4.0, $J_{2,3}$ = 10.4 Hz, 1 H, H-2c), 3.18 (s, 3 H, COOC$H_3$) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 168.4, 167.9 (*C*=O), 159.1 (*C*−OCH$_3$, MeO−*Ph*), 138.1−137.3 ($C_{quaternary,arom.}$), 133.1 (CH$_2$−*C*H=CH$_2$), 129.9−126.9 (*Ph,* CH$_3$O−*Ph*), 117.7 (CH$_2$−CH=*C*H$_2$), 113.54 (CH$_3$O−*Ph*); 102.5 (C-1d); 102.3 (C-1b); 97.2 (C-1c), 96.6 (C-1a), 83.8, 83.7 (C-3d, C-3b), 82.2 (C-2d), 81.7 (C-2b), 79.0 (C-4d), 77.9 (C-3a), 77.0 (C-3c), 76.9, 76.5 (C-4a, C-4c), 75.3, 75.0, 74.9, 74.7, 74.6, 74.5, 74.3, 74.2 (*C*H$_2$Ph), 74.1 (C-4b), 73.4, 73.3 (C-5b, C-5d), 70.6 (C-5c), 70.3 (C-5a), 68.4 (*C*H$_2$−CH=CH$_2$), 66.9, 66.8 (C-6c, C-6a), 62.4 (C-2c), 62.3 (C-2a), 55.0 (*C*H$_3$O-Ph), 52.0, 51.7 (COO*C*H$_3$) ppm. $C_{93}H_{100}O_{22}N_6$ (1653.8): calcd. C 67.54, H 6.09, N 5.08; found C 67.39, H 6.12, N, 4.95.

**Data for 16β:** TLC (toluene/EtOAc, 6:1): $R_f$ β 0.34. $[\alpha]_D^{30}$ = +3 ($CHCl_3$, *c* = 1.0). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.41−7.15 (m, 36 H, *Ph*), 7.15−7.06 (m, 6 H, *Ph*, CH$_3$O−*Ph*), 6.78 (d, $J_{ortho}$ = 8.8 Hz, 2 H, CH$_3$O−*Ph*), 5.89 (dddd, *J* = 17.0, 10.5, 6.0, 5.0 Hz, 1 H, CH$_2$−C*H*=CH$_2$), 5.31 (dq, *J* = 17.0, 1.5 Hz, 1 H, CH$_2$−CH=C*H*$_2$), 5.19 (dq, *J* = 10.5, 1.5 Hz, 1 H, CH$_2$−CH=C*H*$_2$), 5.02 (d, $J_{gem}$ = 11.5 Hz, 1 H, C$H_2$Ph), 5.01 (d, $J_{gem}$ = 10.0 Hz, 1 H, C$H_2$Ph), 4.99 (d, $J_{gem}$ = 11.0 Hz, 1 H, C$H_2$Ph), 4.87 (d, $J_{1,2}$ = 3.6 Hz, 1 H, H-1a), 4.79 (d, $J_{gem}$ = 11.0 Hz, 1 H, C$H_2$Ph), 4.73 (d, $J_{gem}$ = 11.0 Hz, 1 H, C$H_2$Ph), 4.68−4.58 (m, 6 H, C$H_2$Ph), 4.57 (d, $J_{gem}$ = 10.5 Hz, 1 H, C$H_2$Ph), 4.53 (d, $J_{gem}$ = 10.5 Hz, 1 H, C$H_2$Ph), 4.42 (d, $J_{1,2}$ = 7.6 Hz, 1 H, H-1c), 4.35−4.23 (m, 4 H, C$H_2$Ph, H-1d, H-1b), 4.12 (br. dd, $J_{gem}$ = 13.0, $J_{a,b}$ = 5.0 Hz, 1 H, C$H_2$−CH=CH$_2$), 4.08 (d, $J_{gem}$ = 12.0 Hz, 1 H, C$H_2$Ph), 4.08−3.95 (m, 4 H, C$H_2$−CH=CH$_2$, H-4a, H-4c, H-4b), 3.83 (dd, $J_{6,5}$ = 2.5, $J_{6,6'}$ = 11.0 Hz, 1 H, H-6a), 3.79 (dd, *J* = 9.0, $J_{6,5}$ = 9.0 Hz, 1 H, H-3a), 3.84−3.73 (m, 5 H, H-3c, H-4d, Ph−OC$H_3$), 3.67 (dd, $J_{6,5}$ = 3.0, $J_{6,6'}$ = 10.5 Hz, 1 H, H-6c), 3.649 (s, 3 H, COOC$H_3$), 3.64 (d, $J_{5,4}$ = 3.5 Hz, 1 H, H-5d), 3.61 (d, $J_{5,4}$ = 3.5 Hz, 1 H, H-5d), 3.56 (br. d, $J_{5,4}$ = 9.0 Hz, 1 H, H-5a), 3.53 (s, 3 H, COOC$H_3$), 3.45 (br. d, $J_{6,6'}$ = 10.5 Hz, 1 H, H-6′c), 3.38 (t, $J_{3,2}$ = $J_{3,4}$ = 9.0 Hz, 1 H, H-3d), 3.34−3.21 (m, 6 H, H-6′a, H-2a, H-2c, H-3b, H-2d, H-2b), 3.16 (br. d, $J_{5,4}$ = 9.0 Hz, 1 H, H-5c) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 168.7, 167.4 (*C*=O), 159.1 (*C*−OCH$_3$, MeO−*Ph*), 138.8−137.3 ($C_{quaternary,arom.}$), 133.0 (CH$_2$−*C*H=CH$_2$), 129.8−127.0 (*Ph,* CH$_3$O−*Ph*), 117.8 (CH$_2$−CH=*C*H$_2$), 113.5 (CH$_3$O−*Ph*), 102.4 (C-1d), 102.3 (C-1b), 101.7 (C-1c), 96.5 (C-1a), 83.6 (C-3d, C-3b), 81.9 (C-2d), 81.7 (C-2b), 80.8, 79.2, 78.9, 77.9, 76.1, 75.4, 75.1, 74.9, 74.7, 74.4, 74.1; 73.7, 73.2 (C-5b, C-5d), 72.7, 70.3; 68.4 (*C*H$_2$−CH=CH$_2$), 67.2; 66.9, 66.1 (C-6c, C-6a), 62.3 (C-2c, C-2a), 55.0 (*C*H$_3$O−Ph), 52.4, 52.1 (COO*C*H$_3$) ppm. $C_{93}H_{100}O_{22}N_6$ (1653.8): calcd. C 67.54, H 6.09, N 5.08; found C 67.48, H 6.21, N 4.85.

**[Methyl 2,3-di-*O*-benzyl-4-*O*-(4-methoxybenzyl)-β-D-glucopyranosyluronate]-(1→4)-2-azido-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranose trichloroacetamide (12):** TLC β anomer (toluene/acetone, 7:1): $R_f$ = 0.33. IR (thin film): (ṽ = 3300 (3450−3250, $\nu_{N-H}$), 3084, 3064, 3031, 3004 ($\nu_{C-Harom}$), 2957, 2924, 2865, 2852 ($\nu_{C-Haliph}$), 2114 ($\nu_{N3}$), 1753 ($\nu_{C=O}$ COOMe), 1728 ($\nu_{C=O}$ CONHCCl$_3$), 1612, 1585, 1514, 1496, 1454, 1439, 1360, 1282, 1249, 1216, 1176, 1138, 1089, 1063, 1030. $^1$H NMR (400 MHz, $CDCl_3$) (β anomer): δ = 7.34−7.40 (m, 2 H, *Ph*), 7.38−7.15 (m, 18 H, *Ph*), 7.09 (d, $J_{ortho}$ = 8.8 Hz, 2 H, CH$_3$O−*Ph*), 7.04 (d, $J_{1,NH}$ = 9.5 Hz, 1 H, N*H*), 6.77 (d, $J_{ortho}$ = 8.8 Hz, 2 H, CH$_3$O−*Ph*), 5.04 (d, $J_{gem}$ = 10.4 Hz, 1 H, C$H_2$Ph), 4.84 (t, $J_{1,NH}$ = $J_{1,2}$ = 9.5 Hz, H-1a), 4.79 (d, $J_{gem}$ = 11.0 Hz, 1 H, C$H_2$Ph), 4.75 (d, $J_{gem}$ = 11.0 Hz, 1 H, C$H_2$Ph), 4.70 (d, $J_{gem}$ = 11.0 Hz, 1 H, C$H_2$Ph), 4.65 (d, $J_{gem}$ = 11.0 Hz, 1 H, C$H_2$Ph), 4.63 (d, $J_{gem}$ = 10.4 Hz, 1 H, C$H_2$Ph), 4.59 (d, $J_{gem}$ = 10.4 Hz, 1 H, C$H_2$Ph), 4.52 (d, $J_{gem}$ = 12.0 Hz, 1 H, C$H_2$Ph), 4.46 (d, $J_{gem}$ = 10.4 Hz, 1 H, C$H_2$Ph), 4.38 (d, $J_{1,2}$ = 7.2 Hz, 1 H, H-1b), 4.31 (d, $J_{gem}$ = 12.0 Hz, 1 H, C$H_2$Ph), 4.04 (t, $J_{4,3}$ = $J_{4,5}$ = 9.5 Hz, 1 H, H-4a), 3.79 (dd, $J_{6,5}$ = 2.4, $J_{6,6'}$ = 11.2 Hz, 1 H, H-6a), 3.74 (t, $J_{4,3}$ = $J_{4,5}$ = 10.0 Hz, 1 H, H-4b), 3.73 (s, 3 H, Ph−OC$H_3$), 3.66 (d, $J_{5,4}$ = 10.0 Hz, 1 H, H-5b), 3.54 (s, 3 H, CO-OC$H_3$), 3.51−3.44 (m, 2 H, H-6′a, H-3a), 3.39−3.30 (m, 3 H, H-3b, H-2a, H-2b), 3.26 (br. d, $J_{5,4}$ = 9.5 Hz, 1 H, H-5a) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 168.4 (*C*=O), 161.7 (NH−*C*=O), 159.0 (*C*−OMe, MeOPh), 138.0−137.1 ($C_{quaternary,arom.}$), 129.8−127.4 (*Ph,* CH$_3$O−*Ph*), 113.8 (MeO−*Ph*), 102.3 (C-1b), 92.0 (*C*Cl$_3$), 83.6, 81.8, 81.6 (C-3a), 75.7 (C-4b), 75.3, 75.0, 74.4, 74.2, 73.1, 67.0 (C-6a), 65.2 (C-2a), 55.0 (*C*H$_3$O−Ph), 52.1 (CO-O*C*H$_3$) ppm. ESI-MS calcd. for $C_{51}H_{53}N_4O_{12}Cl_3$ [M + Na]: *m/z* =

1041.3/1403.3; found 1041.3/1043.3. $C_{51}H_{53}Cl_3N_4O_{12}$: $M$ = 1020.3 g/mol.

**Allyl [Methyl 2,3-di-*O*-benzyl-4-*O*-(4-methoxyphenyl)-β-D-glucopyranosyluronate]-(1→4)-(2-azido-3,6-di-*O*-benzyl-2-deoxy-α,β-D-glucopyranosyl)-(1→4)-*O*-(6-*O*-acetyl-2,3-di-*O*-benzyl-β-D-glucopyranosyl)-(1→4)-2-azido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside (17):** A solution of TMSOTf (6%, 10 μL of a 0.55 mM solution in $CH_2Cl_2$) was added to a cooled solution (−30 °C) of **7** (65 mg, 0.082 mmol) and **1** (100 mg, 0.098 mmol, 1.2 equiv.) in $CH_2Cl_2$ (200 μL). The solution was stirred for 2 h at this temperature, and then neutralised with $Et_3N$. The solvent was evaporated and the crude reaction mixture was passed through a gel-filtration chromatography column (LH-20) with $CH_2Cl_2$/MeOH, 1:1 as eluent to afford a 50:50 α/β mixture of the corresponding tetrasaccharides. Flash column chromatography (toluene/EtOAc, 9:1 to 6:1) afforded 28 mg **17α** and 28 mg **17β** (42% overall). Data for **17α**: TLC (toluene/EtOAc, 6:1): $R_f$ α 0.66. $[\alpha]_D^{30}$ = +26 ($CHCl_3$, $c$ = 1.0). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.40−7.35(m, 2 H, *Ph*), 7.34−7.12 (m, 38 H, *Ph*), 7.07 (d, $J_{ortho}$ = 8.4 Hz, 2 H, $CH_3O-Ph$), 6.76 (d, $J_{ortho}$ = 8.4 Hz, 2 H, $CH_3O-Ph$), 5.86 (dddd, $J$ = 17.0, 10.5, 6.0, 5.0 Hz, 1 H, $CH_2-CH=CH_2$), 5.53 (d, $J_{1,2}$ = 4.0 Hz, 1 H, H-1c), 5.28 (dq, $J$ = 17.0, 1.5 Hz, 1 H, $CH_2-CH=CH_2$), 5.17 (br. d, $J$ = 10.5 Hz, 1 H, $CH_2-CH=CH_2$), 5.08 (d, $J_{gem}$ = 10.8 Hz, 1 H, $CH_2Ph$), 5.01 (d, $J_{gem}$ = 10.8 Hz, 1 H, $CH_2Ph$), 4.92 (d, $J_{gem}$ = 10.8 Hz, 1 H, $CH_2Ph$), 4.86 (d, $J_{1,2}$ = 3.5 Hz, 1 H, H-1a), 4.79−4.71 (m, 6 H, $CH_2Ph$), 4.70−4.53 (m, 7 H, $CH_2Ph$), 4.48 (d, $J_{gem}$ = 12.5 Hz, 1 H, $CH_2Ph$), 4.45 (d, $J_{gem}$ = 12.5 Hz, 1 H, $CH_2Ph$), 4.39 (d, $J_{1,2}$ = 7.2 Hz, 1 H, H-1d), 4.35 (d, $J_{gem}$ = 12.8 Hz, 1 H, $CH_2Ph$), 4.32 (d, $J_{gem}$ = 12.8 Hz, 1 H, $CH_2Ph$), 4.29 (d, $J_{1,2}$ = 7.2 Hz, 1 H, H-1b), 4.20 (dd, $J_{6,5}$ = 1.6 Hz $J_{6,6'}$ = 10.0 Hz, 1 H, H-6b), 4.10 (br. dd, $J_{gem}$ = 13.0, $J_{a,b}$ = 5.0 Hz, 1 H, $CH_2-CH=CH_2$), 4.03−3.94 (m, 3 H, H-4c, H-4a, $CH_2-CH=CH_2$), 3.85−3.74 (m, 6 H, H-6a, H-6′b, H-6c, H-4d, H-3a, H-3c), 3.72 (s, 3 H, $Ph-OCH_3$), 3.65−3.54 (m, 4 H, H-5d, H-5c, H-5a, H-4b), 3.50 (s, 3 H, $COOCH_3$), 3.46 (t, $J_{3,2}$ = $J_{3,4}$ = 9.0 Hz, 1 H, H-3b), 3.39−3.32 (m, 4 H, H-3d, H-6′c, H-2d, H-6′a), 3.30 (dd, $J_{2,1}$ = 3.5, $J_{2,3}$ = 10.0 Hz, 1 H, H-2c), 3.29 (dd, $J_{2,1}$ = 7.2, $J_{2,3}$ = 9.0 Hz, 1 H, H-2b), 3.24 (dd, $J_{2,1}$ = 4.0, $J_{2,3}$ = 10.5 Hz, 1 H, H-2c), 3.27−3.21 (m, 1 H, H-5b), 1.63 (s, 3 H, $OCOCH_3$) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 170.1, 168.4 ($C$=O), 159.0 ($C-OCH_3$, $MeO-Ph$), 138.4−137.2 ($C_{quaternary,arom.}$), 133.0 ($CH_2-CH=CH_2$), 129.8−127.1 (*Ph,* $CH_3O-Ph$), 117.7 ($CH_2-CH=CH_2$), 113.54 ($CH_3O-Ph$), 102.7 (C-1d), 101.8 (C-1b), 97.7 (C-1c), 96.5 (C-1a), 84.2 (C-3b), 83.7 (C-3d), 82.8 (C-2b), 81.6 (C-2d), 78.9 (C-4d), 77.6, 77.5 (C-3a, C-3c), 75.3−73.0 ($CH_2Ph$, H-4a, H-4c), 71.9 (C-5b), 71.2 (C-4b), 70.2 (C-5a), 68.3 ($CH_2-CH=CH_2$), 67.0 (C-6c), 66.8 (C-6a), 63.0 (C-6b), 62.4 (C-2a), 62.2 (C-2c), 55.0 ($CH_3O-Ph$), 52.0 ($COOCH_3$), 20.2 ($OCOCH_3$) ppm. $C_{94}H_{102}N_6O_{22}$ (1667.8): calcd. C 67.69, H 6.16, N 5.04; found C 67.11, H 6.22, N 4.71;. ESI-MS calcd. for $C_{94}H_{102}N_6NaO_{22}$ [M + Na]: $m/z$ = 1689.7 (94%), 1690.7 (100%); found 1689.8 (90%), 1690.8 (100%).

**Data for 17β:** TLC (toluene/EtOAc, 6:1): $R_f$ β 0.51. $[\alpha]_D^{30}$ = +45.4 ($CHCl_3$, $c$ = 1.0). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.39−7.35 (m, 2 H, *Ph*, $CH_3O-Ph$), 7.35−7.16 (m, 38 H, *Ph*), 7.07 (d, $J_{ortho}$ = 8.8 Hz, 2 H, $CH_3O-Ph$), 6.77 (d, $J_{ortho}$ = 8.8 Hz, 2 H, $CH_3O-Ph$), 5.87 (dddd, $J$ = 17.0, 10.5, 6.0, 5.0 Hz, 1 H, $CH_2-CH=CH_2$), 5.29 (dq, $J$ = 17.0, 1.5 Hz, 1 H, $CH_2-CH=CH_2$), 5.17 (dq, $J$ = 10.5, 1.5 Hz, 1 H, $CH_2-CH=CH_2$), 5.05 (d, $J_{gem}$ = 11.2 Hz, 1 H, $CH_2Ph$), 5.00 (d, $J_{gem}$ = 10.4 Hz, 1 H, $CH_2Ph$), 4.93 (d, $J_{gem}$ = 11.6 Hz, 1 H, $CH_2Ph$), 4.86 (d, $J_{1,2}$ = 3.6 Hz, 1 H, H-1a), 4.76 (d, $J_{gem}$ = 11.2 Hz, 1 H, $CH_2Ph$), 4.72 (d, $J_{gem}$ = 11.2 Hz, 1 H, $CH_2Ph$), 4.68−4.54 (m, 10 H, $CH_2Ph$), 4.45 (d, $J_{gem}$ = 10.4 Hz, 1 H, $CH_2Ph$), 4.42 (d, $J_{1,2}$ = 8.0 Hz, 1 H, H-1c), 4.30 (d, $J_{gem}$ = 12.0 Hz, 1 H, $CH_2Ph$), 4.29 (d, $J_{gem}$ = 12.0 Hz, 1 H, $CH_2Ph$), 4.28 (d, $J_{gem}$ = 11.0 Hz, 1 H, $CH_2Ph$), 4.25 (d, $J_{1,2}$ = 7.5 Hz, 1 H, H-1d), 4.19−4.13 (m, 3 H, H-1b, $2CH_2Ph$), 4.11 (ddt, $J_{gem}$ = 13.0, $J_{a,b}$ = 5.0, $J_{a,b}$ = 1.5 Hz, 1 H, $CH_2-CH=CH_2$), 4.01−3.93 (m, 3 H, H-4b, H-4a, $CH_2-CH=CH_2$), 3.82 (dd, $J_{6,6'}$ = 3.0, $J_{6,5}$ = 12.8 Hz, 1 H, H-6a), 3.79 (dd, $J_{3,4}$ = 8.5, $J_{3,4}$ = 10.0 Hz, 1 H, H-3a), 3.75 (dd, $J_{6,6'}$ = 3.5, $J_{6,5}$ = 11.0 Hz, 1 H, H-6c), 3.73−3.71 (m, 5 H, H-3c, H-4d, Ph-$OCH_3$), 3.67 (dd, $J_{4,5}$ = 9.6, $J_{4,3}$ = 8.8 Hz, 1 H, H-4c), 3.62 (d, $J_{5,4}$ = 9.6 Hz, 1 H, H-5d), 3.59−3.56 (m, 2 H, H-5a, H-6a), 3.51 (s, 3 H, $COOCH_3$), 3.40−3.36 (m, 3 H, H-6′a, H-6′b, H-6′c), 3.32−3.28 (m, 5 H, H-2c, H-2a, H-5c, H-3b, H-2b), 3.26−3.22 (m, 1 H, H-5c), 3.22 (dd, $J_{2,1}$ = 7.5, $J_{2,3}$ = 9.0 Hz, 1 H, H-2d), 3.03 (ddd, $J_{5,6}$ = 1.5, $J_{5,6'}$ = 3.0, $J_{5,4}$ = 10.0, 1 H, H-5b), 1.85 (s, 3 H, $OCOCH_3$) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 170.3, 168.4 ($C$=O), 159.0 ($C-OCH_3$, $MeO-Ph$), 138.4−137.0 ($C_{quaternary,arom.}$), 133.1 ($CH_2-CH=CH_2$), 129.3−126.8 (*Ph,* $CH_3O-Ph$), 117.7 ($CH_2-CH=CH_2$), 113.5 ($CH_3O-Ph$), 102.4 (C-1d), 102.0 (C-1b), 101.3 (C-1c), 96.5 (C-1a), 83.6 (C-3b), 82.7 (C-3d), 81.9, 81.8 (C-2b, C-2d), 841.2, 78.9, 77.7, 77.0, 76.2, 75.3, 75.0, 74.8, 74.3, 73.2, 72.8, 72.3, 70.3; 68.3 ($CH_2-CH=CH_2$), 67.0 (C-6c, C-6a), 66.2 (C-6b), 62.3 (C-2a, C-2c), 55.0 ($CH_3O-Ph$), 52.1 ($COOCH_3$), 20.4 ($OCOCH_3$) ppm. $C_{94}H_{102}N_6O_{22}$ (1667.8): calcd. C 67.69, H 6.16, N 5.04; found, C 67.67, H 6.51, N 4.42. ESI-MS calcd. for $C_{94}H_{102}N_6NaO_{22}$ [M + Na]: $m/z$ = 1689.7 (94%), 1690.7 (100%); found 1689.7 (93%), 1690.7 (100%).

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