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# Polymer-Supported Synthesis of Oligosaccharides Using a Diisopropylsiloxane Linker and Trichloroacetimidate Donors

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We describe herein the polymer-supported synthesis of biologically relevant oligosaccharides using a diisopropylsiloxane linker and trichloroacetimidates as glycosyl donors. Siloxane linkers offer important advantages over closely related silyl ethers since even sterically hindered alcohols can be directly loaded onto commercially available polymers, such as soluble polyethylene glycol (PEG), without prior manipulation of the support. Final products can be easily detached by mild fluoridolysis to afford OH-tagged sugar probes. We followed an acceptor-bound approach that fixed the nucleophile on the polymer, and we selected soluble PEG as the support due to higher reactivity of bound sugars and easy reaction monitoring. Following this strategy, the trisaccharide repeating unit of the capsular polysaccharide of *Neisseria meningitidis* (serogroup L) and the disaccharide containing the structural motif of hyaluronic acid were successfully synthesized.

## Introduction

The traditional synthesis of oligosaccharides is a time-consuming process, mainly due to the extensive need for purification steps and protecting-group manipulations. Polymer-supported, synthetic methodologies accelerate oligosaccharide production, facilitating intermediate purifications by the simple washing of the support and, therefore, minimizing the number of chromatographic steps required.[1,2] Additionally, the polymer-supported reactions can ideally be driven to completion by running several reaction cycles with excess reagents. The linker, the connection between the polymer support and the first monosaccharide, is of utmost importance for the entire synthetic process. Its chemical nature determines the reaction conditions that can be used during the oligosaccharide assembly and the cleavage conditions required to release the final product from the support. Moreover, the linker should render the final oligosaccharide with an orthogonal functional group that allows for the creation of glycoconjugates.

Among others, silyl ether linkers have been successfully employed for the polymer-supported synthesis of oligosaccharides.[3,4] Typically, sugar attachment to a solid support through a silyl ether linkage involves the synthesis of silyl halide resin by direct lithiation of polystyrene-like supports and reaction with dialkyldichlorosilane and subsequent silylation with a OH-bearing carbohydrate (see part **A** in Scheme 1).[5–9] Poor efficiencies are found when conducting the loading at relatively hindered OH groups. To solve this problem, Danishefsky and coworkers described a new strategy for the solid-phase synthesis of oligosaccharides using a diisopropylsiloxane linker.[10] The siloxane linkage is formed by first reacting the sugar alcohol with dialkyldichlorosilane in solution prior to the attachment of the resultant chlorosiloxane intermediate to a polymer-bound alcohol (see part **B** in Scheme 1). This approach has been applied to the synthesis of glycopeptides following a donor-bound strategy and employing glycal-derived donors.[10] A siloxane linker has also been employed in the solid-phase synthesis of natural polyketide fragments,[11,12] oligonucleotides[13] and streptogramin antibiotics[14] and for the exploration of hetero-Diels–Alder reactions of dienes with polymer-supported acyl- and arylnitroso dienophiles.[15,16]

Therefore, siloxane linkers[17,18] are attractive alternatives to silyl ethers. They exhibit stability under basic and acidic conditions,[19,20] and no prior manipulation of commercially available polymers is required (Scheme 1, **B**). This advantage is particularly useful for soluble polyethylene glycol (PEG), since the preparation of noncommercially available silyl halide PEG is avoided, and OH-terminated PEG can be directly used. Siloxane linkers can be cleaved readily at the end of the synthesis by exposure to fluoride (Scheme 1, **B**). This treatment affords the original polymer support, which can be recycled for further use, dialkyldifluorosilane as a side product and a OH-functionalized sugar. This OH group, generated by fluoridolysis of the linker, can be considered an orthogonal tag for further manipulation and bioconjugation of the carbohydrate sample.[21] For instance, tosylation and subsequent substitution by azide gives azido-terminated oligosaccharides ready for 1,3-dipolar cycloaddition with alkyne probes or Staudinger reduction to afford amines.

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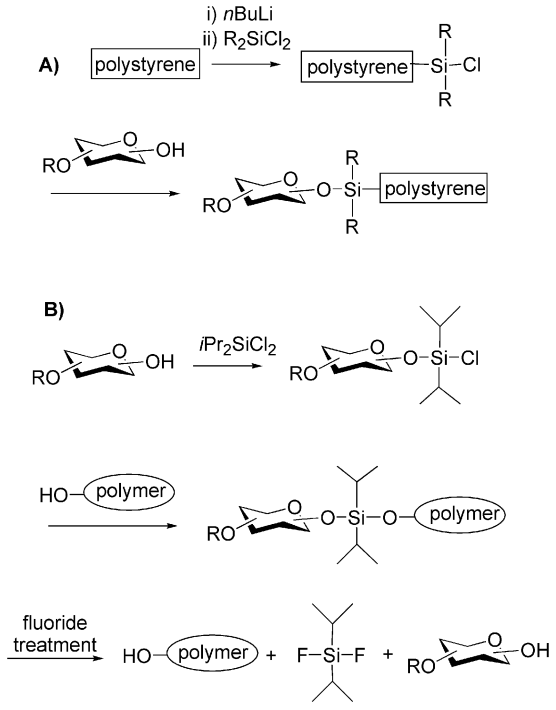
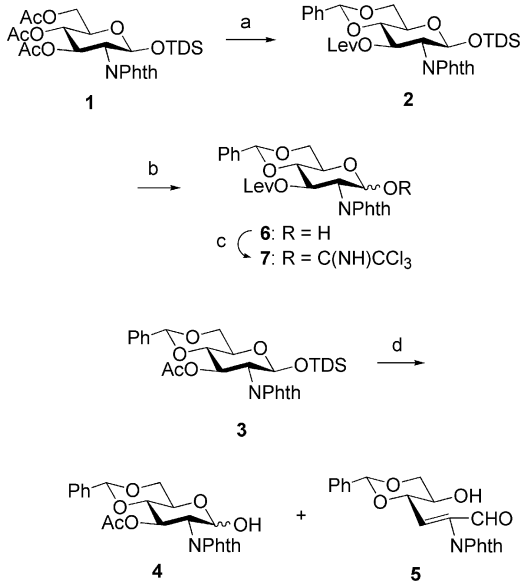



Scheme 1. A): General strategy for sugar attachment to polystyrene resins through a silyl ether linker. B): Alternative approach for sugar loading onto commercially available polymers, both soluble and insoluble supports, using a diisopropylsiloxane linker.

In the framework of a project on the development of polymer-supported syntheses of glycosaminoglycans (GAG), we report herein the synthesis of oligosaccharides using a diisopropylsiloxane linker and trichloroacetimidates as glycosylating agents. To the best of our knowledge, trichloroacetimidates have not been previously used with siloxane linkers, following an acceptor-bound strategy. We chose soluble PEG as the polymer support[22,23] because it combines advantages of solution-phase chemistry with the easy workup of solid-phase synthesis.[24–27] While all reactions are carried out in homogeneous solutions, the polymer is precipitated after each step by the addition of diethyl ether. In this way, excess reagents and other side products are easily removed by washing the PEG precipitate, as in solid-phase synthesis. Specific advantages of soluble polymers as compared to the alternative, insoluble resins include: a) easy monitoring of the reactions using standard techniques and b) higher reactivity of PEG-bound sugars than that of resin-bound sugars. The latter point involves the use of smaller amounts of glycosyl donors to complete glycosylation reactions, which is particularly useful when using valuable, orthogonally protected, building blocks. Potential restrictions are the loss of material during the precipitation, which lowers the overall yield in the assembly of large structures, and the limited temperature range under which PEG is soluble (above –45 °C). Despite these limitations, soluble PEG has been extensively used for oligosaccharide synthesis.

## Results and Discussion

We chose, as our first goal, the synthesis of **13** (Scheme 3), the fully protected, trisaccharide, repeating unit of the capsular polysaccharide of both *Neisseria meningitidis* (serogroup L)[28,29] and *Actinobacillus pleuropneumoniae* (serotype 12).[30] Capsular polysaccharides are commonly important virulence factors, and synthetic oligosaccharide–protein conjugates are promising vaccines, inducing protective antibodies against bacterial infection.[31–34] Thus, the oligosaccharides related to the bacterial capsule are an attractive target. We followed an acceptor-bound strategy, attaching the reducing-end glucosamine to the support through the anomeric position by a diisopropylsiloxane linker. Our approach used as key building blocks the differentially protected monosaccharide **6** and the corresponding trichloroacetimidate **7** (Scheme 2). The levulinoyl (Lev) group served as a temporary protecting group to liberate the glycosyl acceptor in anticipation of chain elongation, while the *N*-phthalimido (NPhth) group ensured the desired β stereochemistry of the glycosidic linkage.




Scheme 2. Reagents and conditions: a) NaOMe, MeOH; $PhCH(OMe)_2$, *p*-TsOH, $CH_3CN$/DMF; LevOH, DCC, DMAP, $CH_2Cl_2$, 82%; b) $(HF)_n$·Pyr, THF, 0 °C → r.t., 77%; c) $Cl_3CCN$, DBU, $CH_2Cl_2$, 88%; d) TBAF, AcOH, THF, 0 °C, 30% **4** + 32% aldehyde **5**; TDS = dimethylthexylsilyl.

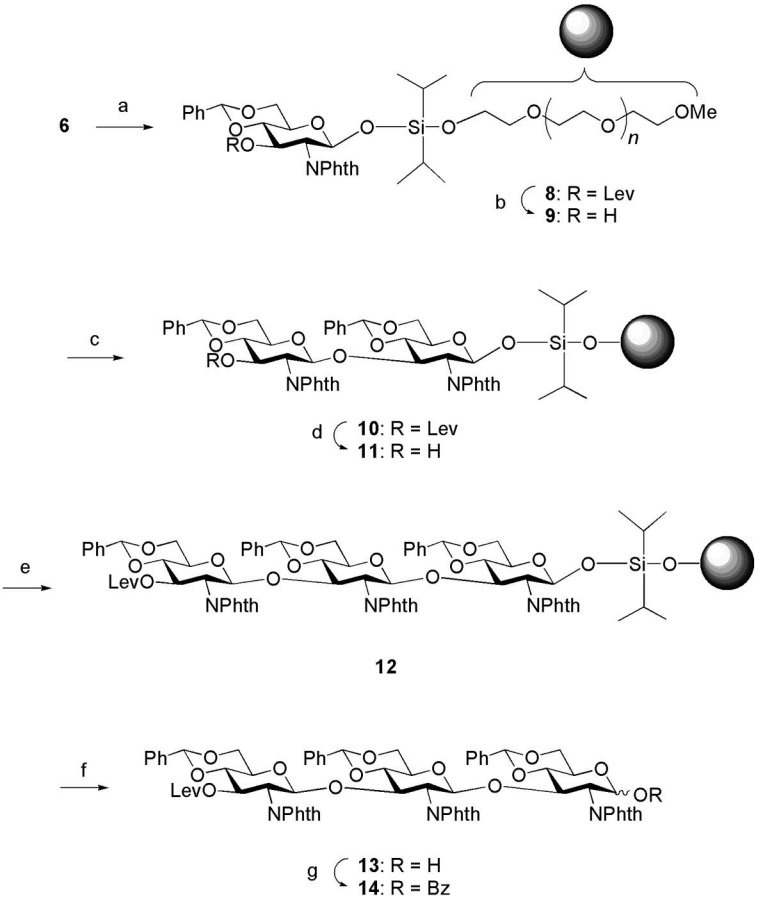
First, the gram-scale synthesis of **7** was undertaken, employing **1**[35] as starting material (Scheme 2). The removal of the three acetates on **1** followed by the formation of the 4,6-benzylidene acetal and subsequent levulinoylation at position 3 afforded monosaccharide **2** in 82% yield over three steps. Turning **2** into trichloroacetimidate **7** first required selective desilylation. The treatment of the closely related, 3-*O*-acetyl monosaccharide **3** with TBAF/AcOH gave the corresponding hemiacetal **4** in low yield (30%, Scheme 2). Aldehyde **5**, derived from 2-H/3-H-acetate elimination, was detected as a side product. The structure of **5**

was unambiguously identified from the characteristic chemical shifts of 1-H and 3-H (9.58 and 7.22 ppm, respectively). Additionally, the treatment of **4** with trichloroacetonitrile in the presence of $K_2CO_3$ also gave aldehyde **5** as the major product. Similar results were recently reported by Mulard and coworkers in the synthesis of a 3-*O*-acyl-2-deoxy-4,6-*O*-isopropylidene-2-trichloroacetamido-D-glucopyranosyl trichloroacetimidate.[36] This side reaction was overcome by the use of $(HF)_n$·Pyr complex in THF followed by trichloroacetimidate formation with catalytic DBU. Taking advantage of this optimization process, donor **7** was obtained in good yield on a multigram scale.

Monosaccharide **6** was attached to the support through the anomeric position (Scheme 3) by a two-stage procedure, which took advantage of the enhanced reactivity of a dialkyldihalosilane relative to its monohalogenated counterpart.[10] This difference in reactivity minimized the formation of the diisopropylsiloxane-linked pseudodisaccharide resulting from two-fold silylation. The exposure of **6** to 1 equiv. of dichlorodiisopropylsilane ($iPr_2SiCl_2$) in the presence of imidazole gave the corresponding chlorosiloxane intermediate, which was directly treated with 1 equiv. of OH-terminated PEG monomethyl ether to yield bound monosaccharide **8** after selective precipitation by the addition of diethyl ether (Scheme 3). The β anomer was exclusively obtained, as deduced by $^1H$ NMR ($J_{1,2}$ = 7.5 Hz). The unreacted polymer sites were capped by reaction with acetic anhydride/pyr. The integration of diagnostic $^1H$ NMR signals (see the Supporting Information) indicated a sugar loading of approximately 55% (1:0.81 mole ratio). The Lev group of **8** was easily removed by treatment with hydrazine monohydrate in $CH_2Cl_2$/Pyr/AcOH to give polymer-supported acceptor **9**, which was efficiently glycosylated with trichloroacetimidate **7** to afford bound disaccharide **10** (Scheme 3). The Lev deprotection and glycosylation sequence was then carried out on **10** to give the bound trisaccharide **12**. Treatment with $(HF)_n$·Pyr complex in THF released trisaccharide **13** in 45% overall yield from polymer **8** (five steps). As expected, **13** was liberated as a reducing sugar (ca. 4:1 β/α). To facilitate structural characterization and NMR assignment, **13** was treated with BzCl in Pyr to yield trisaccharide **14** (≥ 8:1 β/α).

Having demonstrated that the diisopropylsiloxane linker allows for the successful synthesis of trisaccharide **13** using trichloroacetimidates and an acceptor-bound approach, we next turned to the synthesis of more complex hyaluronic acid oligosaccharides.[37–41] Hyaluronic acid is a linear GAG featuring the β-(1→3)-linked, 2-acetamido-2-deoxy-

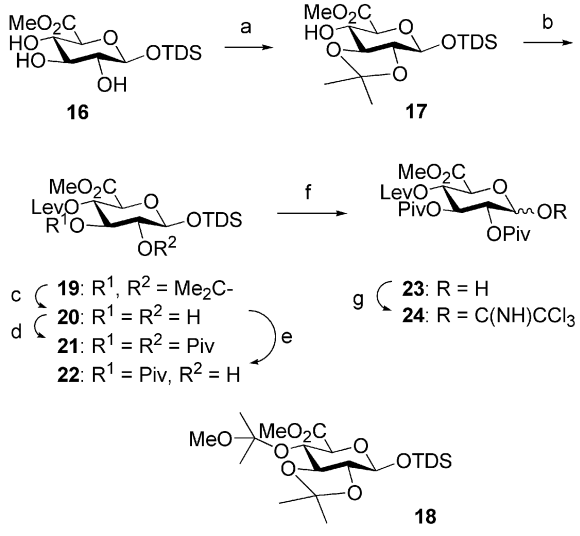



Scheme 3. Reagents and conditions: a) $iPr_2SiCl_2$, imidazole, $CH_2Cl_2$; MeO–$(CH_2CH_2O)_n$–$CH_2CH_2OH$, $CH_2Cl_2$; $Ac_2O$, Pyr, 55% loading; b) $NH_2NH_2$·$H_2O$, Pyr/AcOH, $CH_2Cl_2$; c) **7**, TMSOTf, $CH_2Cl_2$, –10 °C; d) $NH_2NH_2$·$H_2O$, Pyr/AcOH, $CH_2Cl_2$; e) **7**, TMSOTf, $CH_2Cl_2$, –15 °C; f) $(HF)_n$·Pyr, THF, 0 °C, 45% from **8**, five steps; g) BzCl, Pyr.

D-glucose-β-(1→4)-D-glucuronic acid disaccharide as the repeating unit.[42–44] The synthesis of GAG oligosaccharide sequences is crucial for the establishment of specific structure-activity relationships in order to elucidate the role of these complex sugars in nature.[45–53] GAG synthesis is a challenging objective since it generally involves handling electron-poor, uronic acid, building blocks.[54–57] In particular, the synthesis of hyaluronic acid oligosaccharides usually requires the condensation of highly disarmed glucuronic acid building blocks due to the presence of both the electron-withdrawing carboxylic acid and an acyl group at position 2 to control the 1,2-*trans* stereochemistry of the glycosidic bond.

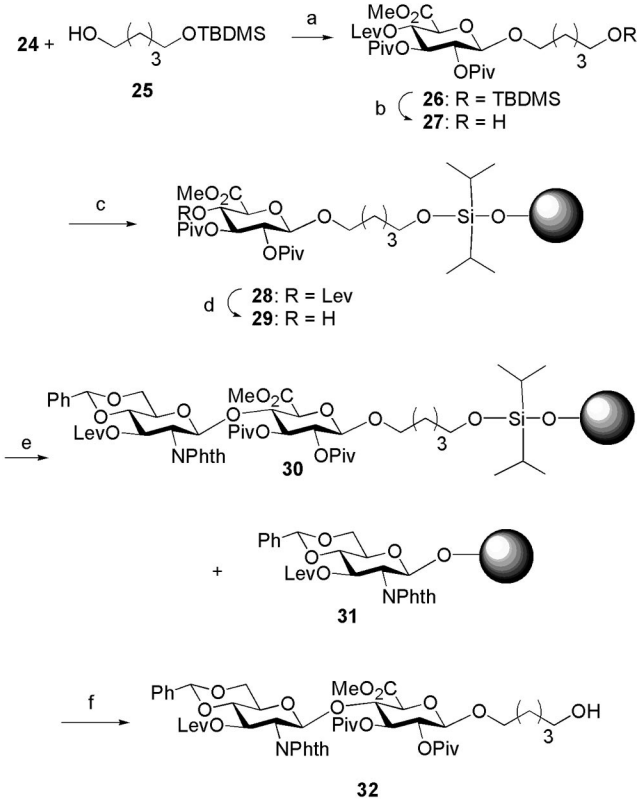
Thus, in addition to the glucosamine monomer **7**, the preparation of a differentially protected, glucuronic acid monosaccharide is essential to the synthesis of hyaluronic acid fragments. Triol **16** (Scheme 4) was prepared from methyl 1,2,3,4-tetra-*O*-acetyl-α,β-D-glucopyranosuronate (**15**)[58] by standard anomeric deacetylation, silylation and subsequent acetate hydrolysis. The key differentiation of OH groups on triol **16** was achieved by selective 2,3-isopropylidene acetal formation under kinetic control.[59] Treatment with 2-methoxypropene and CSA followed by the addition of MeOH gave 2,3-isopropylidene derivative **17** as the main product (50%) together with the 3,4-isopropylidene isomer (36%), which can be easily recycled by acidic hydrolysis. We note that mixed bisacetal **18** was detected by NMR and mass spectroscopy (see the Supporting Information) when the reaction was directly quenched with $Et_3N$ before MeOH addition. A similar bisacetal was recently reported by Gardiner et al. in the synthesis of 1,2-isopropylidene-protected L-*ido* cyanopyranosides.[60] Compound **17** was then transformed in good yield into **21** (Scheme 4) through levulinoylation at position 4 (→**19**),




Scheme 4. Reagents and conditions: a) 2-methoxypropene, CSA, DMF, 0 °C; MeOH, 0 °C, 50%; b) LevOH, DCC, DMAP, $CH_2Cl_2$, 88%; c) DOWEX acidic resin, MeOH; d) PivCl, DMAP, Pyr, 5 d, 78% from **19**, two steps; e) PivCl, DMAP, Pyr, 2 h, quantitative by TLC analysis; f) $(HF)_n$·Pyr, THF, 0 °C → r.t., 89%; g) $Cl_3CCN$, $K_2CO_3$, $CH_2Cl_2$, 85%.

hydrolysis of the 2,3-isopropylidene acetal (→**20**) and extensive pivaloylation at positions 2 and 3 for 5 d. Interestingly, diol **20** was cleanly converted into 3-*O*-pivaloylated derivative **22** with shorter reaction times (2 h), thus opening the way for the preparation of alternative building blocks, orthogonally protected at positions 2 and 3. Compound **21** was then desilylated to give **23**, which was activated as trichloroacetimidate **24** (Scheme 4).

Next, we explored the synthesis of hyaluronic acid disaccharide **32** having a glucuronic acid unit at the reducing end (Scheme 5). Attaching glucuronic acid **23** to the PEG support through the anomeric position, as described above for the synthesis of trisaccharide **13**, would probably lead to anomeric mixture on the support, hampering reaction monitoring and would afford a final product as α/β anomers, complicating released oligosaccharide characterization. Therefore, we envisaged attaching the glucuronic acid unit through the OH group of derivative **27**, bearing a fixed β configuration. This OH group, which can be regenerated by fluoride treatment at the end of the synthesis, is a potential point for further functionalization.




Scheme 5. Reagents and conditions: a) TMSOTf, $CH_2Cl_2$, 0 °C, 70%; b) TBAF, AcOH, THF, 0 °C → r.t., 63% + 18% recovered **26**; c) $iPr_2SiCl_2$, imidazole, $CH_2Cl_2$; MeO–$(CH_2CH_2O)_n$–$CH_2CH_2OH$, $CH_2Cl_2$; $Ac_2O$, Pyr, 54% loading; d) $NH_2NH_2$·AcOH, $CH_2Cl_2$; e) **7**, TMSOTf, $CH_2Cl_2$, 0 °C; f) TBAF, AcOH, THF/$CH_2Cl_2$, 0 °C → r.t., 71% from **28**, three steps.

Monosilylated alcohol **25** (Scheme 5) was obtained from 1,5-pentanediol.[61] Glycosylation of **24** with alcohol **25** followed by desilylation with TBAF/AcOH afforded **27**. Following an analogous sequence of reaction steps as that de-

scribed for the attachment of glucosamine **6**, we reacted $i$Pr$_2$SiCl$_2$ with **27** and, subsequently, with OH-terminated PEG monomethyl ether. After capping the unreacted polymer sites by reaction with acetic anhydride/pyr, the sugar loading (54%; 1:0.86 mole ratio) was deduced from the integration of key $^1$H NMR signals (see the Supporting Information). It is noteworthy that valuable, unbound, glucuronic acid derivatives were transformed into starting **27** by treatment with TBAF/AcOH. We speculate that these derivatives could be silanol formed by hydrolysis of the chlorosiloxane and/or cross-linked pseudodisaccharide derived from double addition on $i$Pr$_2$SiCl$_2$. The Lev group of **28** was easily removed by treatment with hydrazine acetate to give polymer-supported acceptor **29** (Scheme 5). At this stage, we investigated the challenging glycosylation reaction between electron-poor acceptor **29** and donor **7** to produce hyaluronic acid disaccharide **30**. TMSOTf-mediated coupling was carried out at 0 °C. After two glycosylation cycles, the $^1$H NMR spectrum indicated the complete consumption of the glucuronic acid acceptor and formation of bound disaccharide as the main product. However, a second set of minor, NMR, sugar signals was observed and assigned to monosaccharide **31**. This side product derived from the partial release of the sugar acceptor from the polymeric support and the subsequent glycosylation of the generated OH-terminated PEG with donor **7**. Cleavage from the support by TBAF/AcOH led to disaccharide **32** in 71% yield. Bound monosaccharide **31** remained linked to the support (see the Supporting Information) and was easily removed during the workup procedure. Therefore, this side product did not complicate the purification of the final target, although it reduced the applicability of this strategy for the synthesis of longer hyaluronic acid oligosaccharides. Attempts to avoid the partial cleavage of siloxane linker by lowering the reaction temperature or decreasing the TMSOTf amount did not afford any disaccharide. The direct anchoring of the reducing end sugar through the anomeric position, as described for **8**, also failed to reduce partial cleavage.

## Conclusions

We conclude that the combination of a diisopropylsiloxane linker and trichloroacetimidate donors is an attractive approach for the polymer-supported synthesis of oligosaccharides. Accordingly, we have synthesized two biologically relevant oligosaccharides on a PEG support. The use of soluble PEG allowed for direct reaction monitoring by standard analytical techniques. As compared to silyl ethers, the siloxane linker involves a more straightforward sugar loading onto the support, without the prior manipulation of commercially available polymers. Moreover, this linker is stable under the reaction conditions usually required to assemble the oligosaccharide chain and can be selectively cleaved by fluoride treatment at the end of the synthesis. The released, final product contains a OH group that enables further conjugation. However, limitations were encountered when applying this strategy to the synthesis of GAG oligosaccharides. The preparation of these complex carbohydrates is a challenging task, since it usually requires the condensation of electron-poor, disarmed building blocks, involving harsh reaction conditions for glycosylations. A partial cleavage of the diisopropylsiloxane linker was detected during the synthesis of a GAG disaccharide. Therefore, further improvements are required to extend our strategy to the synthesis of large GAG oligomers. In order to address this point, we are now working on the synthesis of glucuronic acid units with electron-donating protecting groups to enhance their glycosylation power, thereby avoiding the use of severe reaction conditions that cleave the linker. Alternatively, the preparation of more stable siloxane linkers is also being considered for GAG synthesis using traditional, disarmed building blocks. We will further report on our progress in future publications.

## Experimental Section

**General Procedures:** PEG monomethyl ether (average molecular weight of 5000 Da) was purchased from Sigma Aldrich. Thin-layer chromatography (TLC) analyses were performed with silica gel 60 $F_{254}$ precoated with aluminum plates (Merck), and the compounds were detected by staining with sulfuric acid/ethanol (1:9) or with anisaldehyde solution [anisaldehyde (25 mL) with sulfuric acid (25 mL), ethanol (450 mL) and HOAc (1 mL)] followed by heating at over 200 °C. Column chromatography was carried out with silica gel 60 (0.2–0.5 mm, 0.2–0.063 mm or 0.040–0.015 mm; Merck). Optical rotations were determined with a Perkin–Elmer 341 polarimeter. $^1$H and $^{13}$C NMR spectra were acquired with Bruker DPX-300 and DRX-500 spectrometers, and chemical shifts are given in ppm ($\delta$) relative to tetramethylsilane. Electrospray mass spectra (ES-MS) were recorded with an Esquire 6000 ESI-Ion Trap from Bruker Daltonics. High resolution FAB mass spectra (HRMS) were recorded by Mass Spectrometry Service, Citius, University of Seville.

**Dimethylthexylsilyl 4,6-*O*-Benzylidene-2-deoxy-3-*O*-levulinoyl-2-phthalimido-β-D-glucopyranoside (2):** Compound **1** (20.0 g, 34.6 mmol) was dissolved in MeOH (280 mL) and NaOMe (2.3 mL, 2.17 M solution in MeOH) was added. After 1 h, Amberlite acidic resin was added, and the mixture was stirred until the pH reached 7. The Amberlite resin was filtered off, and the solvent was removed in vacuo. The residue [TLC (16:1 $CH_2Cl_2$/MeOH) $R_f$ = 0.10] was coevaporated with $CH_2Cl_2$ and toluene and dissolved in acetonitrile/DMF (70:3, 146 mL). Benzaldehyde dimethyl acetal (5.73 mL, 38.1 mmol) and *p*-toluenesulfonic acid (600 mg, 3.2 mmol) were added. After the mixture was stirred at room temperature for 2 h, EtOAc was added, and the mixture was washed with saturated aqueous $NaHCO_3$. The organic phase was dried with $Na_2SO_4$, filtered and concentrated in vacuo. The residue [TLC (4:1 hexane/EtOAc) $R_f$ = 0.30] was dissolved in $CH_2Cl_2$ (175 mL), and levulinic acid (15.4 mL, 150 mmol), 1,3-dicyclohexylcarbodiimide (9.26 g, 44.9 mmol) and DMAP (800 mg) were added. After 1.5 h, the mixture was diluted with $CH_2Cl_2$ and washed with saturated aqueous $NaHCO_3$. The organic phase was dried with $Na_2SO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (2:1 hexane/EtOAc) to give **2** (18.0 g, 82%). TLC (1:1 hexane/EtOAc) $R_f$ = 0.55; $[\alpha]_D^{20}$ = –20.1 ($c$ = 1.17, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.89–7.72 (m, 4 H, NPhth), 7.49–7.36 (m, 5 H, Ph), 5.96 (dd, 1 H, 3-H),

5.64 (d, $J_{1,2}$ = 7.8 Hz, 1 H, 1-H), 5.55 (s, 1 H, PhCHO), 4.38 (dd, $J_{5,6}$ = 4.2, $J_{6,6'}$ = 10.2 Hz, 1 H, 6-H), 4.29 (dd, $J_{2,3}$ = 10.5 Hz, 1 H, 2-H), 3.89–3.74 (m, 3 H, 4-H, 5-H, 6′-H), 2.57–2.41 [m, 4 H, $OCO(CH_2)_2$], 1.92 (s, 3 H, $COCH_3$), 1.42 [m, 1 H, $CH(CH_3)_2$], 0.68–0.63 [4 s, 12 H, $C(CH_3)_2$ and $CH(CH_3)_2$], 0.13–0.00 [2 s, 6 H, $Si(CH_3)_2$] ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 205.7, 171.9, 137.0–123.4 (Ph, NPhth), 101.6, 93.8, 79.6, 69.7, 68.8, 66.3, 57.3, 37.8, 33.8, 29.4, 27.9, 24.5, 19.8, 19.6, 18.3, 18.2, –1.9, –3.8 ppm. HRMS: calcd. for $C_{34}H_{43}O_9NSiNa$ 660.2605 $[M]^+$; found 660.2632.

**4,6-*O*-Benzylidene-2-deoxy-3-*O*-levulinoyl-2-phthalimido-α,β-D-glucopyranose (6):** $(HF)_n$·Pyr complex (6.8 mL) was added to **2** (1.42 g, 2.22 mmol) in dry THF (34 mL) at 0 °C. After stirring for 48 h at 0 °C and then for 8 h at room temperature, the reaction mixture was diluted with $CH_2Cl_2$ and washed with $H_2O$ and saturated aqueous $NaHCO_3$. The organic layer was dried with $Na_2SO_4$ and filtered, and the solvents were removed in vacuo to give a yellow oil. Hexane (15 mL) and EtOAc (5 mL) were added at 0 °C, and a white precipitate formed. The precipitate was filtered and washed with cold hexane to afford **6** (850 mg, 77%) as a white solid: TLC (1:1 hexane/EtOAc) $R_f$ = 0.25; $^1H$ NMR (300 MHz, $CDCl_3$, data for the β anomer): $\delta$ = 7.86–7.69 (m, 4 H, NPhth), 7.49–7.35 (m, 5 H, Ph), 5.97 (dd, 1 H, 3-H), 5.67 (d, $J_{1,2}$ = 8.4 Hz, 1 H, 1-H), 5.56 (s, 1 H, PhCHO), 4.39 (dd, 1 H, 6-H), 4.27 (dd, $J_{2,3}$ = 10.5 Hz, 1 H, 2-H), 3.89–3.76 (m, 3 H, 4-H, 5-H, 6′-H), 2.61–2.39 [m, 4 H, $OCO(CH_2)_2$], 1.89 (s, 3 H, $COCH_3$) ppm. ES-MS: calcd. for $C_{26}H_{25}O_9NNa$ 518.1 $[M]^+$; found 517.7.

***O*-(4,6-*O*-Benzylidene-2-deoxy-3-*O*-levulinoyl-2-phthalimido-α,β-D-glucopyranosyl) Trichloroacetimidate (7):** Trichloroacetonitrile (1.50 mL, 15.1 mmol) and catalytic DBU were added to **6** (750 mg, 1.51 mmol) in dry $CH_2Cl_2$ (10 mL). After stirring at room temperature for 1.5 h, the mixture was concentrated in vacuo. Flash chromatography on silica gel (99:1 $CH_2Cl_2/Et_3N$) afforded **7** (850 mg, 88%) as an α/β mixture. TLC (1:1 hexane/EtOAc) $R_f$ = 0.47; $^1H$ NMR (300 MHz, $CDCl_3$, data for the β anomer): $\delta$ = 8.67 (s, 1 H, NH), 7.90–7.72 (m, 4 H, NPhth), 7.51–7.36 (m, 5 H, Ph), 6.71 (d, $J_{1,2}$ = 8.7 Hz, 1 H, 1-H), 6.08 (dd, 1 H, 3-H), 5.59 (s, 1 H, PhCHO), 4.64 (dd, $J_{2,3}$ = 10.5 Hz, 1 H, 2-H), 4.52 (dd, $J_{5,6}$ = 3.9, $J_{6,6'}$ = 9.6 Hz, 1 H, 6-H), 3.99–3.92 (m, 3 H, 4-H, 5-H, 6′-H), 2.64–2.43 [m, 4 H, $OCO(CH_2)_2$], 1.91 (s, 3 H, $COCH_3$) ppm. ES-MS: calcd. for $C_{28}H_{25}O_9N_2Cl_3Na$ 661.0 $[M]^+$; found 660.5.

**Polymer-Bound Monosaccharide 8:** Dichlorodiisopropylsilane ($iPr_2SiCl_2$, 108 μL, 0.6 mmol) was added dropwise to imidazole (204 mg, 3.0 mmol) in $CH_2Cl_2$ (6 mL), and this mixture was stirred for 5 min before **6** (300 mg, 0.6 mmol) in $CH_2Cl_2$ (9 mL) was added dropwise. The mixture was stirred for 1 h at room temperature and then added dropwise to a solution of PEG monomethyl ether (3.0 g, approximately 0.6 mmol) in $CH_2Cl_2$ (16 mL). After the mixture was stirred for 24 h, diethyl ether (150 mL) was added at 0 °C. The precipitated solid was collected by filtration, washed with cold diethyl ether (150 mL) and dried under high vacuum. The unreacted polymer sites were capped by treating the polymer with acetic anhydride (16 mL) in pyr (32 mL) for 12 h. Diethyl ether (150 mL) was then added at 0 °C. The precipitated solid was collected by filtration, washed with cold diethyl ether (150 mL) and dried under high vacuum to yield polymer **8** (3.2 g) as a white solid. Selected $^1H$ NMR spectroscopic data (500 MHz, $CDCl_3$): $\delta$ = 7.89–7.71 (m, 4 H, NPhth), 7.50–7.33 (m, 5 H, Ph), 5.99 (dd, $J_{2,3}$ = $J_{3,4}$ = 9.7 Hz, 1 H, 3-H), 5.76 (d, $J_{1,2}$ = 7.5 Hz, 1 H, 1-H), 5.55 (s, 1 H, PhCHO), 4.38 (dd, $J_{5,6a}$ = 4.5, $J_{6a,6b}$ = 10.5 Hz, 1 H, 6a-H), 4.29 (dd, 1 H, 2-H), 1.92 (s, 3 H, $COCH_3$) ppm.

**Polymer-Bound Monosaccharide 9:** Compound **8** (2.14 g, approximately 0.22 mmol of sugar) was dissolved in $CH_2Cl_2$ (11 mL) and hydrazine monohydrate (1.52 mL, 0.5 M solution in Pyr/AcOH, 3:2) was added. After stirring at room temperature for 2 h, the reaction mixture was quenched with acetone (4 mL), and diethyl ether (120 mL) was added at 0 °C. The precipitated solid was collected by filtration, washed with cold diethyl ether (120 mL) and dried under high vacuum to give polymer **9** (2.03 g) as a white solid. Selected $^1H$ NMR spectroscopic data (500 MHz, $CDCl_3$): $\delta$ = 7.89–7.72 (m, 4 H, NPhth), 7.53–7.35 (m, 5 H, Ph), 5.64 (d, $J_{1,2}$ = 8.0 Hz, 1 H, 1-H), 5.59 (s, 1 H, PhCHO), 4.71 (dd, $J_{2,3}$ = $J_{3,4}$ = 9.6 Hz, 1 H, 3-H), 4.36 (dd, $J_{5,6a}$ = 4.4, $J_{6a,6b}$ = 10.7 Hz, 1 H, 6a-H) ppm.

**Polymer-Bound Disaccharide 10:** PEG-supported glucosamine **9** (300 mg, approximately 31 μmol of sugar) and glycosyl donor **7** (173 mg, 0.27 mmol), previously coevaporated with toluene and dried under vacuum, were dissolved in $CH_2Cl_2$ (1 mL). TMSOTf (120 μL, 0.1 M solution in $CH_2Cl_2$) was added at –10 °C. After stirring at –10 °C for 40 min, the reaction mixture was quenched with $Et_3N$ (0.4 mL), and then an excess of diethyl ether (100 mL) was added at 0 °C. The precipitated white solid was collected by filtration, rinsed with cold diethyl ether (100 mL) and dried under high vacuum. This glycosidation procedure was repeated once more to give polymer **10** (280 mg). Selected $^1H$ NMR spectroscopic data (500 MHz, $CDCl_3$): $\delta$ = 7.92–7.50 (m, 8 H, NPhth), 7.49–7.31 (m, 10 H, Ph), 5.65 (dd, $J_{2,3}$ = $J_{3,4}$ = 9.6 Hz, 1 H, 3′-H), 5.56 (s, 1 H, PhCHO), 5.51 (d, $J_{1,2}$ = 8.4 Hz, 1 H, 1′-H), 5.43 (s, 1 H, PhCHO), 5.35 (d, $J_{1,2}$ = 8.0 Hz, 1 H, 1-H), 4.91 (dd, $J_{2,3}$ = $J_{3,4}$ = 9.7 Hz, 1 H, 3-H), 4.29 (dd, $J_{5,6a}$ = 4.8, $J_{6a,6b}$ = 10.2 Hz, 1 H, 6a-H or 6′a-H), 4.25–4.11 (m, 3 H, 6a-H or 6′a-H, 2-H, 2′-H), 1.82 (s, 3 H, $COCH_3$) ppm.

**Polymer-Bound Disaccharide 11:** Compound **10** (280 mg, approximately 28 μmol of sugar) was dissolved in $CH_2Cl_2$ (1 mL), and hydrazine monohydrate (180 μL, 0.5 M solution in Pyr/AcOH, 3:2) was added. After stirring at room temperature for 2 h, the reaction mixture was quenched with acetone (0.8 mL), and diethyl ether (100 mL) was added at 0 °C. The precipitated solid was collected by filtration, washed with cold diethyl ether (100 mL) and dried under high vacuum to give polymer **11** (270 mg) as a white solid. Selected $^1H$ NMR spectroscopic data (500 MHz, $CDCl_3$): $\delta$ = 7.73–7.45 (m, 8 H, NPhth), 7.45–7.31 (m, 10 H, Ph), 5.56 (s, 1 H, PhCHO), 5.46 (s, 1 H, PhCHO), 5.35 (m, 2 H, 1-H, 1′-H), 4.91 (dd, $J_{2,3}$ = $J_{3,4}$ = 9.7 Hz, 1 H, 3-H), 4.36 (dd, $J_{2,3}$ = $J_{3,4}$ = 9.7 Hz, 1 H, 3′-H), 4.32–4.12 (m, 4 H, 6a-H, 6′a-H, 2-H, 2′-H) ppm.

**Polymer-Bound Trisaccharide 12:** PEG-supported glucosamine **11** (270 mg, approximately 27 μmol of sugar) and glycosyl donor **7** (147 mg, 0.23 mmol), previously coevaporated with toluene and dried under vacuum, were dissolved in $CH_2Cl_2$ (1 mL). TMSOTf (105 μL, 0.1 M solution in $CH_2Cl_2$) was added at –15 °C. After stirring at –15 °C for 25 min, the reaction mixture was quenched with $Et_3N$ (0.4 mL), and then an excess of diethyl ether (100 mL) was added at 0 °C. The precipitated white solid was collected by filtration, rinsed with cold diethyl ether (100 mL) and dried under high vacuum to give polymer **12** (280 mg) as a white solid. Selected $^1H$ NMR spectroscopic data (500 MHz, $CDCl_3$): $\delta$ = 7.94–7.33 (m, 27 H, NPhth, Ph), 5.58–5.48 (m, 3 H, 3′′-H, PhCHO), 5.38–5.31 (m, 2 H, PhCHO, 1′′-H), 5.27 (d, $J_{1,2}$ = 8.5 Hz, 1 H, 1-H), 5.08 (d, $J_{1,2}$ = 8.5 Hz, 1 H, 1′-H), 4.82 (dd, $J_{2,3}$ = $J_{3,4}$ = 9.9 Hz, 1 H, 3-H), 4.63 (dd, $J_{2,3}$ = $J_{3,4}$ = 9.9 Hz, 1 H, 3′-H), 1.81 (s, 3 H, $COCH_3$) ppm.

***O*-(4,6-*O*-Benzylidene-2-deoxy-3-*O*-levulinoyl-2-phthalimido-β-D-glucopyranosyl)-(1→3)-*O*-(4,6-*O*-benzylidene-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-(1→3)-4,6-*O*-benzylidene-2-deoxy-2-phthalimido-α,β-D-glucopyranose (13):** $(HF)_n$·Pyr complex (720 μL) was added to **12** (150 mg, approximately 14 μmol of sugar) in dry

THF (3.6 mL) at 0 °C. After stirring for 24 h at 0 °C, the reaction mixture was diluted with $CH_2Cl_2$ and washed with $H_2O$ and saturated aqueous $NaHCO_3$. The organic layer was dried with $Na_2SO_4$ and filtered, and the solvents were removed in vacuo. The residue was dissolved in $CH_2Cl_2$ (1 mL), and then an excess of diethyl ether (60 mL) was added at 0 °C. The precipitated white solid was filtered off and washed with cold diethyl ether (60 mL). The filtrate and the washes were combined and concentrated in vacuo. The residue was purified by flash chromatography (160:1 $CH_2Cl_2$/MeOH) to afford **13** (8.1 mg, 45% from **8**, five steps): TLC (160:1 $CH_2Cl_2$/MeOH) $R_f$ = 0.15; $^1H$ NMR (500 MHz, $CDCl_3$, data for the β anomer): $\delta$ = 7.80–7.50 (m, 12 H, NPhth), 7.51–7.38 (m, 15 H, Ph), 5.55 (dd, 1 H, 3′′-H), 5.51 (s, 1 H, PhCHO), 5.46 (s, 1 H, PhCHO), 5.38 (s, 1 H, PhCHO), 5.36 (d, $J_{1,2}$ = 8.5 Hz, 1 H, 1′′-H), 5.11 (d, $J_{1,2}$ = 8.5 Hz, 1′-H), 5.08 (m, 1 H, 1-H), 4.91 (dd, 1 H, 3-H), 4.65 (dd, 1 H, 3′-H), 4.32 (dd, $J_{5,6a}$ = 4.9, $J_{6a,6b}$ = 10.4 Hz, 1 H, 6a-H), 4.20 (m, 1 H, 6a′-H), 4.15–4.06 (m, 3 H, 2′-H, 2′′-H, 6a′′-H), 3.99 (m, 1 H, 2-H), 3.80–3.53 (m, 7 H, 4-H, 4′-H, 4′′-H, 5-H, 6b-H, 6b′-H, 6b′′-H), 3.40 (m, 1 H, 5′-H), 3.34 (m, 1 H, 5′′-H), 3.01 (br. d, 1 H, OH), 2.38–2.24 [m, 4 H, $OCO(CH_2)_2$], 1.81 (s, 3 H, $COCH_3$) ppm. Selected $^{13}C$ NMR spectroscopic data (from HMQC experiment, 125 MHz, $CDCl_3$): $\delta$ = 101.4, 101.2, 101.0 (3 Ph*C*HO), 97.3 (C-1′), 96.9 (C-1′′), 93.5 (C-1), 73.7 (C-3), 69.7 (C-3′′) ppm. HRMS: calcd. for $C_{68}H_{59}N_3O_{21}Na$ 1276.3539 $[M]^+$; found 1276.3524.

***O*-(4,6-*O*-Benzylidene-2-deoxy-3-*O*-levulinoyl-2-phthalimido-β-D-glucopyranosyl)-(1→3)-*O*-(4,6-*O*-benzylidene-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-(1→3)-1-*O*-benzoyl-4,6-*O*-benzylidene-2-deoxy-2-phthalimido-α,β-D-glucopyranose (14):** TLC (3:2 toluene/EtOAc) $R_f$ = 0.26; $^1H$ NMR (500 MHz, $CDCl_3$, data for the β anomer): $\delta$ = 7.83–7.34 (m, 32 H, Ph, NPhth), 6.25 (d, $J_{1,2}$ = 8.9 Hz, 1 H, 1-H), 5.55 (m, 2 H, 3′′-H, PhCHO), 5.47 (s, 1 H, PhCHO), 5.38 (s, 1 H, PhCHO), 5.36 (d, $J_{1,2}$ = 8.4 Hz, 1 H, 1′′-H), 5.13 (d, $J_{1,2}$ = 8.4 Hz, 1 H, 1′-H), 5.06 (dd, $J_{2,3}$ = $J_{3,4}$ = 9.6 Hz, 1 H, 3-H), 4.65 (dd, $J_{2,3}$ = $J_{3,4}$ = 9.7 Hz, 1 H, 3′-H), 4.44 (dd, 1 H, 2-H), 4.37 (m, 1 H, 6a-H), 4.24 (m, 1 H, 6a′-H), 4.15 (dd, 1 H, 2′-H), 4.12–4.05 (m, 2 H, 2′′-H, 6a′′-H), 3.80–3.53 (m, 7 H, 4-H, 4′-H, 4′′-H, 6b-H, 6b′-H, 6b′′-H, 5-H), 3.43 (m, 1 H, 5′-H), 3.35 (m, 1 H, 5′′-H), 2.42–2.24 [m, 4 H, $OCO(CH_2)_2$], 1.82 (s, 1 H, $COCH_3$) ppm. Selected $^{13}C$ NMR spectroscopic data (from HMQC experiment, 125 MHz, $CDCl_3$): $\delta$ = 101.4, 101.24, 101.18 (3 Ph*C*HO), 97.4 (C-1′), 96.8 (C-1′′), 91.1 (C-1), 74.2 (C-3′), 73.5 (C-3), 69.6 (C-3′′) ppm. HRMS: calcd. for $C_{75}H_{63}N_3O_{22}Na$ 1380.3801 $[M]^+$; found 1380.3816.

**Methyl (Dimethylthexylsilyl 2,3-*O*-isopropylidene-β-D-glucopyranoside)uronate (17):** 2-methoxypropene (27 mL, 282 mmol) was added to **16** (4.94 g, 14.1 mmol) in dry DMF (30 mL). The reaction mixture was cooled to 0 °C. A solution of (1*S*)-(+)-camphorsulfonic acid (327 mg, 1.41 mmol) in DMF (5 mL) was added dropwise whilst the mixture was stirred at 0 °C. After 2 h, MeOH (5 mL) was added, and the mixture was stirred for 30 min at 0 °C. $Et_3N$ (1 mL) was added, and the mixture was diluted with EtOAc and washed with $H_2O$. The organic phase was dried with $Na_2SO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (4:1 hexane/EtOAc) to yield **17** (2.74 g, 50%). $[\alpha]_D^{20}$ = –20.4 (*c* = 0.75, $CHCl_3$); TLC (2:1 hexane/EtOAc) $R_f$ = 0.37; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 4.91 (d, $J_{1,2}$ = 7.5 Hz, 1 H, 1-H), 4.10 (dd, $J_{3,4}$ = $J_{4,5}$ = 9.2 Hz, 1 H, 4-H), 3.84–3.81 (m, 4 H, 5-H, $COOCH_3$), 3.55 (dd, 1 H, 3-H), 3.33 (dd, $J_{2,3}$ = 9.3 Hz, 1 H, 2-H), 1.66 [m, 1 H, C*H*$(CH_3)_2$], 1.46–1.45 [2 s, 6 H, $C(CH_3)_2$ isopropylidene acetal], 0.90–0.88 [m, 12 H, $C(CH_3)_2$ and $CH(CH_3)_2$], 0.20 [s, 6 H, $Si(CH_3)_2$] ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 172.4, 113.8, 99.3, 81.5, 80.3, 77.9, 73.2, 55.0, 36.1, 28.8, 27.2, 22.3, 22.1, 20.7, 20.6, 0.0, –0.8 ppm. HRMS: calcd. for $C_{18}H_{34}O_7SiNa$ 413.1972 $[M]^+$; found 413.1965.

**Methyl (Dimethylthexylsilyl 2,3-*O*-isopropylidene-4-*O*-levulinoyl-β-D-glucopyranoside)uronate (19):** Compound **17** (1.87 g, 4.78 mmol), levulinic acid (2.78 g, 23.9 mmol), 1,3-dicyclohexylcarbodiimide (1.48 g, 7.17 mmol) and DMAP (80 mg) were dissolved in $CH_2Cl_2$ (20 mL), and the reaction was stirred at room temperature for 3 h. The mixture was diluted with $CH_2Cl_2$ and washed with saturated aqueous $NaHCO_3$. The organic phase was dried with $Na_2SO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (4:1 hexane/EtOAc) to give **19** (2.04 g, 88%). $[\alpha]_D^{20}$ = –29.0 (*c* = 0.42, $CHCl_3$); TLC (2:1 hexane/EtOAc) $R_f$ = 0.29; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 5.30 (dd, $J_{3,4}$ = 9.9, $J_{4,5}$ = 8.4 Hz, 1 H, 4-H), 4.94 (d, $J_{1,2}$ = 7.5 Hz, 1 H, 1-H), 3.93 (d, 1 H, 5-H), 3.75 (s, 3 H, $COOCH_3$), 3.65 (dd, 1 H, 3-H), 3.47 (dd, $J_{2,3}$ = 9.6 Hz, 1 H, 2-H), 2.77–2.61 [m, 4 H, $OCO(CH_2)_2$], 2.19 (s, 3 H, $COCH_3$), 1.65 [m, 1 H, C*H*$(CH_3)_2$], 1.45–1.44 [2 s, 6 H, $C(CH_3)_2$ isopropylidene acetal], 0.90–0.83 [m, 12 H, $C(CH_3)_2$ and $CH(CH_3)_2$], 0.20 [s, 6 H, $Si(CH_3)_2$] ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 206.1, 171.6, 167.9, 111.7, 96.9, 78.1, 77.2, 74.6, 71.4, 52.7, 37.7, 33.9, 29.9, 27.7, 26.60, 26.57, 24.9, 20.1, 19.9, 18.5, 18.4, –2.2, –3.0 ppm. HRMS: calcd. for $C_{23}H_{40}O_9SiNa$ 511.2339 $[M]^+$; found 511.2341.

**Methyl (Dimethylthexylsilyl 4-*O*-levulinoyl-2,3-di-*O*-pivaloyl-β-D-glucopyranoside)uronate (21):** Compound **19** (7.14 g, 14.6 mmol) was dissolved in MeOH (110 mL), and DOWEX 50WX2 acidic resin (9 g) was added. After 3 h, the DOWEX resin was filtered off, and the solvent was removed in vacuo. The residue was dissolved in pyr (75 mL). Pivaloyl chloride (11.3 mL, 91.8 mmol) and DMAP (1.0 g, 8.19 mmol) were added. After the mixture was stirred at room temperature for 3 d, an additional aliquot of DMAP (1.0 g, 8.19 mmol) was added. After a further 2 d, $CH_2Cl_2$ was added, and the mixture was washed with aqueous HCl (1 N). The organic phase was dried with $Na_2SO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (4:1 hexane/EtOAc) to afford **21** (7.04 g, 78%). $[\alpha]_D^{20}$ = –7.8 (*c* = 0.67, $CHCl_3$); TLC (2:1 hexane/EtOAc) $R_f$ = 0.55; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 5.29 (m, 2 H, 3-H, 4-H), 5.03 (dd, 1 H, 2-H), 4.84 (d, $J_{1,2}$ = 7.5 Hz, 1 H, 1-H), 4.05 (d, $J_{4,5}$ = 9.9 Hz, 1 H, 5-H), 3.77 (s, 3 H, $COOCH_3$), 2.72–2.49 [m, 4 H, $OCO(CH_2)_2$], 2.18 (s, 3 H, $COCH_3$), 1.61 [m, 1 H, C*H*$(CH_3)_2$], 1.17–1.13 [2 s, 18 H, OC-$OC(CH_3)_3$], 0.88–0.83 [m, 12 H, $C(CH_3)_2$ and $CH(CH_3)_2$], 0.20–0.13 [2 s, 6 H, $Si(CH_3)_2$] ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 205.7, 177.3, 176.3, 171.1, 167.2, 95.9, 72.7, 72.3, 71.8, 69.8, 52.7, 38.7, 37.5, 33.7, 29.8, 27.6, 27.2, 27.0, 24.7, 20.0, 19.8, 18.5, 18.4, –2.0, –3.2 ppm. HRMS: calcd. for $C_{30}H_{52}O_{11}SiNa$ 639.3177 $[M]^+$; found 639.3191.

**Methyl 4-*O*-Levulinoyl-2,3-di-*O*-pivaloyl-α,β-D-glucopyranosuronate (23):** $(HF)_n$·Pyr complex (5 mL) was added to **21** (1.10 g, 1.78 mmol) in dry THF (25 mL) at 0 °C. After stirring for 24 h at 0 °C and then for 10 h at room temperature, the reaction mixture was diluted with $CH_2Cl_2$ and washed with $H_2O$ and saturated aqueous $NaHCO_3$. The organic layer was dried with $Na_2SO_4$ and filtered, and the solvents were removed in vacuo to yield **23** (754 mg, 89%) as an α/β mixture: TLC (2:1 hexane/EtOAc) $R_f$ = 0.15. $^1H$ NMR (300 MHz, $CDCl_3$, data for the α anomer): $\delta$ = 5.65 (dd, 1 H, 3-H or 4-H), 5.57 (d, 1 H, 1-H), 5.22 (dd, 1 H, 3-H or 4-H), 4.88 (dd, $J_{1,2}$ = 3.6, $J_{2,3}$ = 10.2 Hz, 1 H, 2-H), 4.61 (d, $J_{4,5}$ = 10.2 Hz, 1 H, 5-H), 3.77 (s, 3 H, $COOCH_3$), 3.40 (br. s, 1 H, OH), 2.70–2.48 [m, 4 H, $OCO(CH_2)_2$], 2.19 (s, 3 H, $COCH_3$), 1.18–1.16 [2 s, 18 H, $OCOC(CH_3)_3$] ppm. ES-MS: calcd. for $C_{22}H_{34}O_{11}Na$ 497.2 $[M]^+$; found 497.2.

***O*-(Methyl 4-*O*-levulinoyl-2,3-di-*O*-pivaloyl-α,β-D-glucopyranosyluronate) Trichloroacetimidate (24):** Trichloroacetonitrile (1.59 mL, 15.9 mmol) and $K_2CO_3$ (242 mg, 1.75 mmol) were added to **23** (754 mg, 1.59 mmol) in dry $CH_2Cl_2$ (7 mL). After stirring at room temperature for 3 h, the mixture was filtered off and concentrated in vacuo. Flash chromatography on silica gel (4:1 hexane/EtOAc) afforded **24** (834 mg, 85%) as an α/β mixture.

**α Anomer:** TLC (2:1 hexane/EtOAc) $R_f$ = 0.45; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 8.74 (s, 1 H, NH), 6.67 (d, $J_{1,2}$ = 3.3 Hz, 1 H, 1-H), 5.71 (dd, $J_{2,3} = J_{3,4}$ = 9.9 Hz, 1 H, 3-H), 5.33 (dd, 1 H, 4-H), 5.20 (dd, 1 H, 2-H), 4.53 (d, $J_{4,5}$ = 10.2 Hz, 1 H, 5-H), 3.77 (s, 3 H, $COOCH_3$), 2.74–2.50 [m, 4 H, $OCO(CH_2)_2$], 2.19 (s, 3 H, $COCH_3$), 1.17–1.14 [2 s, 18 H, $OCOC(CH_3)_3$] ppm.

**β Anomer:** TLC (2:1 hexane/EtOAc) $R_f$ = 0.26; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 8.77 (s, 1 H, NH), 6.04 (d, $J_{1,2}$ = 7.2 Hz, 1 H, 1-H), 5.40–5.37 (m, 3 H, 2-H, 3-H, 4-H), 4.26 (d, $J_{4,5}$ = 9.0 Hz, 1 H, 5-H), 3.77 (s, 3 H, $COOCH_3$), 2.72–2.52 [m, 4 H, $OCO(CH_2)_2$], 2.19 (s, 3 H, $COCH_3$), 1.16–1.15 [2 s, 18 H, $OCOC(CH_3)_3$] ppm. ES-MS: calcd. for $C_{24}H_{34}O_{11}NCl_3Na$ 640.1 $[M]^+$; found 640.1.

**Methyl [*O*-(*tert*-Butyldimethylsilyl)-5-hydroxypentyl 4-*O*-levulinoyl-2,3-di-*O*-pivaloyl-β-D-glucopyranoside]uronate (26):** Acceptor **25** (741 mg, 3.39 mmol) and glucuronic acid trichloroacetimidate **24** (700 mg, 1.13 mmol) were combined in a flask, coevaporated with toluene and dried under vacuum. The starting materials were dissolved in $CH_2Cl_2$ (7 mL) and further dried by stirring over activated molecular sieves (650 mg) for 30 min. TMSOTf (10 μL, 57 μmol) was added at 0 °C. After 15 min, the reaction was quenched with $Et_3N$ (1 mL) and filtered, and the solvent was removed under reduced pressure. Purification by flash chromatography (hexane/EtOAc, 4:1) yielded **26** (536 mg, 70%). TLC (3:1 hexane/EtOAc) $R_f$ = 0.39; $[\alpha]_D^{20}$ = –9.3 ($c$ = 0.42, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 5.29 (dd, $J_{2,3} = J_{3,4}$ = 9.5 Hz, 1 H, 3-H), 5.23 (dd, $J_{4,5}$ = 9.5 Hz, 1 H, 4-H), 5.02 (dd, $J_{1,2}$ = 8 Hz, 1 H, 2-H), 4.54 (d, 1 H, 1-H), 4.04 (d, 1 H, 5-H), 3.87 (m, 1 H, $OCH_2$), 3.75 (s, 3 H, $COOCH_3$), 3.56 (m, 2 H, $OCH_2$), 3.45 (m, 1 H, $OCH_2$), 2.68–2.45 [m, 4 H, $OCO(CH_2)_2$], 2.16 (s, 3 H, $COCH_3$), 1.58–1.30 (m, 6 H, $CH_2$), 1.14–1.11 [2 s, 18 H, $OCOC(CH_3)_3$], 0.87 [s, 9 H, $SiC(CH_3)_3$], 0.03 [2 s, 6 H, $Si(CH_3)_2$] ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 177.3, 176.3, 171.1, 167.4, 101.0, 72.6, 71.5, 70.6, 70.3, 69.8, 62.9, 52.9, 38.73, 38.68, 37.5, 32.5, 29.7, 29.2, 27.6, 27.1, 27.0, 26.0, 22.1, 18.3 ppm. HRMS: calcd. for $C_{33}H_{58}O_{12}SiNa$ 697.3595 $[M]^+$; found 697.3651.

**Methyl (5-hydroxypentyl 4-*O*-levulinoyl-2,3-di-*O*-pivaloyl-β-D-glucopyranoside)uronate (27):** Monosaccharide **26** (380 mg, 0.56 mmol) was dissolved in anhydrous THF (5 mL). Glacial HOAc (39 μL, 0.68 mmol) and TBAF (1 M in THF, 0.68 mL, 0.68 mmol) were added at 0 °C, and the mixture was stirred at room temperature for 12 h. The mixture was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$. The organic layer was dried with $MgSO_4$ and filtered, and the solvents were removed in vacuo. Purification by flash chromatography on silica gel (hexanes/EtOAc, 1:1) afforded **27** (200 mg, 63%) and unreacted starting material (70 mg, 18%). TLC (1:1 hexane/EtOAc) $R_f$ = 0.2; $[\alpha]_D^{20}$ = –20.5 ($c$ = 0.83, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 5.21 (m, 2 H, 3-H, 4-H), 4.97 (dd, 1 H, 2-H), 4.50 (d, $J_{1,2}$ = 7.8 Hz, 1 H, 1-H), 4.00 (d, $J_{4,5}$ = 9.3 Hz, 1 H, 5-H), 3.82 (m, 1 H, $OCH_2$), 3.70 (s, 3 H, $COOCH_3$), 3.54 (m, 2 H, $OCH_2$), 3.42 (m, 1 H, $OCH_2$), 2.65–2.43 [m, 4 H, $OCO(CH_2)_2$], 2.11 (s, 3 H, $COCH_3$), 1.55–1.29 (m, 6 H, $CH_2$), 1.09–1.06 [2 s, 18 H, $OCOC(CH_3)_3$] ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 205.8, 177.3, 176.4, 171.1, 167.3, 101.0, 72.5, 71.4, 70.6, 70.1, 69.7, 62.5, 52.9, 38.70, 38.67, 37.4, 32.3, 29.7, 29.1, 27.5, 27.0, 26.9, 22.1 ppm. HRMS: calcd. for $C_{27}H_{44}O_{12}Na$ 583.2730 $[M]^+$; found 583.2753.

**Polymer-Bound Monosaccharide 28:** $i$Pr$_2$SiCl$_2$ (41 μL, 0.23 mmol) was added dropwise to imidazole (78 mg, 1.14 mmol) in $CH_2Cl_2$ (2 mL), and this mixture was stirred for 5 min before **27** (128 mg, 0.23 mmol) in $CH_2Cl_2$ (2 mL) was added dropwise. The mixture was stirred for 1 h at room temperature and then added dropwise to PEG monomethyl ether (1.14 g, approximately 0.23 mmol) in $CH_2Cl_2$ (5 mL). After the mixture was stirred for 24 h, diethyl ether (120 mL) was added at 0 °C. The precipitated solid was collected by filtration, washed with cold diethyl ether (120 mL) and dried under high vacuum. The unreacted polymer sites were capped by treating the polymer with acetic anhydride (6 mL) in pyr (12 mL) for 12 h. Diethyl ether (120 mL) was then added at 0 °C. The precipitated solid was collected by filtration, washed with cold diethyl ether (120 mL) and dried under high vacuum to yield polymer **28** (1.24 g) as a white solid. Selected $^1$H NMR spectroscopic data (500 MHz, $CDCl_3$): $\delta$ = 5.31 (dd, 1 H, 3-H or 4-H), 5.26 (dd, 1 H, 3-H or 4-H), 5.05 (dd, $J_{2,3}$ = 8.5 Hz, 1 H, 2-H), 4.57 (d, $J_{1,2}$ = 7.5 Hz, 1 H, 1-H), 4.06 (d, $J_{4,5}$ = 9.5 Hz, 1 H, 5-H), 2.71–2.46 [m, 4 H, $OCO(CH_2)_2$], 2.18 (s, 3 H, $COCH_3$), 1.17–1.14 [2 s, 18 H, $OCOC(CH_3)_3$] ppm.

**Polymer-Bound Monosaccharide 29:** Compound **28** (400 mg, approximately 40 μmol of sugar) was dissolved in $CH_2Cl_2$ (4 mL), and hydrazine acetate (197 μL, 0.66 M solution in MeOH) was added. After stirring at room temperature for 2 h, the reaction mixture was quenched with acetone (1 mL), and diethyl ether (60 mL) was added at 0 °C. The precipitated solid was collected by filtration, washed with cold diethyl ether (60 mL) and dried under high vacuum to give polymer **29** (360 mg) as a white solid. Selected $^1$H NMR spectroscopic data (500 MHz, $CDCl_3$): $\delta$ = 5.09 (dd, $J_{2,3} = J_{3,4}$ = 9.0 Hz, 1 H, 3-H), 4.95 (dd, 1 H, 2-H), 4.50 (d, $J_{1,2}$ = 7.8 Hz, 1 H, 1-H), 1.15–1.13 [2 s, 18 H, $OCOC(CH_3)_3$] ppm.

**Polymer-Bound Disaccharide 30:** PEG-supported glucuronic acid **29** (360 mg, approximately 36 μmol of sugar) and glycosyl donor **7** (139 mg, 0.22 mmol), previously coevaporated with toluene and dried under vacuum, were dissolved in $CH_2Cl_2$ (3 mL). TMSOTf (102 μL, 0.11 M solution in $CH_2Cl_2$) was added at 0 °C. After stirring at 0 °C for 30 min, the reaction mixture was quenched with $Et_3N$ (0.3 mL), and excess diethyl ether (80 mL) was added at 0 °C. The precipitated white solid was collected by filtration, rinsed with cold diethyl ether (80 mL) and dried under high vacuum. Precipitation from diethyl ether was repeated until no low-molecular-weight byproducts were detected by TLC and DOSY NMR experiments.[62] This glycosidation procedure was repeated once more to give polymer **30** (320 mg). Selected $^1$H NMR spectroscopic data for PEG-bound disaccharide (500 MHz, $CDCl_3$): $\delta$ = 7.86–7.72 (m, 4 H, NPhth), 7.44–7.32 (m, 5 H, Ph), 5.88 (dd, $J_{2,3} = J_{3,4}$ = 9.5 Hz, 1 H, 3′-H), 5.48 (s, 1 H, PhCHO), 5.31 (d, $J_{1,2}$ = 8.2 Hz, 1 H, 1′-H), 5.14 (dd, $J_{2,3} = J_{3,4}$ = 9 Hz, 1 H, 3-H), 4.86 (dd, $J_{1,2}$ = 8.4 Hz, 1 H, 2-H), 4.42 (dd, 1 H, 6′a-H), 4.36 (d, 1 H, 1-H), 4.27 (dd, 1 H, 4-H), 4.11 (dd, 1 H, 2′-H), 1.86 (s, 3 H, $COCH_3$), 1.22–1.12 [2 s, 18 H, $OCOC(CH_3)_3$] ppm.

**Methyl [5-Hydroxypentyl 4-*O*-(4,6-*O*-benzylidene-2-deoxy-3-*O*-levulinoyl-2-phthalimido-β-D-glucopyranosyl)-2,3-di-*O*-pivaloyl-β-D-glucopyranoside]uronate (32):** Polymer **30** (274 mg, approximately 26 μmol of sugar) was dissolved in THF/$CH_2Cl_2$ (3:2, 5 mL). Glacial HOAc (17 μL, 0.29 mmol) and TBAF (1 M in THF, 0.29 mL, 0.29 mmol) were added at 0 °C, and the mixture was stirred at room temperature for 12 h. Diethyl ether (50 mL) was added at 0 °C. The precipitated solid was filtered off and washed with cold diethyl ether (50 mL). The filtrate and the washes were combined,

washed with saturated aqueous $NaHCO_3$, dried with $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography (80:1 $CH_2Cl_2$/MeOH) afforded disaccharide **32** (17 mg, 71% from polymer **28**, three steps). TLC (80:1 $CH_2Cl_2$/MeOH) $R_f$ = 0.19; $[a]_D^{20}$ = –47.9 ($c$ = 1.17, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.90–7.75 (m, 4 H, NPhth), 7.47–7.37 (m, 5 H, Ph), 5.92 (dd, $J_{2,3}$ = $J_{3,4}$ = 9.5 Hz, 1 H, 3′-H), 5.52 (s, 1 H, PhCHO), 5.36 (d, $J_{1,2}$ = 8 Hz, 1 H, 1′-H), 5.18 (dd, $J_{2,3}$ = $J_{3,4}$ = 9 Hz, 1 H, 3-H), 4.90 (dd, 1 H, 2-H), 4.46 (dd, $J_{5,6a}$ = 4 Hz, $J_{6a,6b}$ = 10.5 Hz, 1 H, 6′a-H), 4.41 (d, $J_{1,2}$ = 7 Hz, 1 H, 1-H), 4.32 (dd, $J_{4,5}$ = 9.3 Hz, 1 H, 4-H), 4.16 (dd, 1 H, 2′-H), 3.81–3.66 (m, 8 H, 4′-H, 5′-H, 6′b-H, 5-H, $COOCH_3$, $OCH_2$), 3.61 (m, 2 H, $OCH_2$), 3.36 (m, 1 H, $OCH_2$), 2.53–2.38 [m, 4 H, $OCO(CH_2)_2$], 1.90 (s, 3 H, $COCH_3$), 1.54–1.31 (m, 6 H, $CH_2$), 1.25–1.16 [2 s, 18 H, $OCOC(CH_3)_3$] ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 205.6, 176.7, 176.6, 171.8, 167.8, 136.8–123.4 (Ph, NPhth), 101.6 (Ph*C*HO), 101.0 (C-1), 97.2 (C-1′), 79.2, 74.5, 74.4, 71.8, 71.3, 69.8, 69.4, 68.6, 66.3, 62.7, 55.2, 53.0, 38.8, 38.7, 37.7, 32.3, 29.4, 29.1, 27.8, 27.3, 27.1, 22.1 ppm. HRMS: calcd. for $C_{48}H_{61}O_{18}NSiNa$ 962.3786 $[M]^+$; found 962.3820.

**Supporting Information** (see also the footnote on the first page of this article): Spectroscopic data for **4**, **5**, **18** and **22** and copies of selected NMR spectra.

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