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1-Methyl 1′-cyclopropylmethyl: an acid labile *O*-protecting group for polymer-supported oligosaccharide synthesis

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Abstract—*R*,*S*-1-Methyl 1′-cyclopropylmethanol can be converted to its trichloroacetimidate derivative. Lewis acid catalyzed etherification can then be used to prepare methyl cyclopropylmethyl (MCPM) ethers. Thus, ethyl 2,3,4-tri-*O*-benzyl-6-*O*-(*R*,*S*-1-methyl 1′-cyclopropylmethyl)-1-thio-α/β-D-glucopyranoside was prepared and the linker polymer combination (MPEG)(DOX)OH glycosylated. The MCPM group was cleaved with 10% trifluoroacetic acid in CH_2Cl_2 and the resulting alcohol glycosylated. After protecting group manipulations and cleavage the peracetylated disaccharide GlcNAc(β1→6)GlcOAc was isolated. Similarly the 4,6-*O*-phenylboronate diester of ethyl 1-thio-β-D-galactopyranoside was regioselectively etherified at O-3 and after boronate cleavage the sugar benzoylated to give ethyl 2,4,6-tri-*O*-benzoyl-3-*O*-(*R*,*S*-1-methyl 1′-cyclopropylmethyl)-1-thio-β-D-galactopyranoside. Through a similar sequence of glycosylation of (MPEG)(DOX)OH, MCPM deprotection, glycosylation, functional group manipulation and cleavage the peracylated disaccharide GlcNAc(β1→3)Gal(β1→)DOXOAc was prepared. Finally, the donor 2,6-di-*O*-benzoyl-4-*O*-levulinoyl-3-*O*-(*R*,*S*-1-methyl 1′-cyclopropylmethyl)-1-thio-β-D-galactopyranoside was prepared and elaborated into the trisaccharide GlcNAc(β1→3)[Glc(β1→4)]Gal(β1→)DOXOH. This trisaccharide was elaborated into the pentasaccharide Neu5Ac(α2→3)Gal(β1→4)GlcNAc(β1→3) [Glc(β1→4)]Gal(β1→)DOXOH using GalE-LgtB fusion and CMP-Neu5Ac synthetase/sialyltransferase fusion enzymes. This pentasaccharide is a single repeat unit of the capsular polysaccharide of Group B *Streptococcus* type 1A. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Improved methods for the preparation of oligosaccharides are necessary to meet the growing demand for glycotherapeutics.[1] To this end our research group is investigating methods to simplify oligosaccharide synthesis.[2] In particular, we are interested in preparing oligosaccharides that can be used as antibacterial vaccines.[3] One appealing approach is to use polymer-supported methods that largely avoid the need for expensive chromatography since the experimentalist needs to purify the same polymeric support and not the variable sugar at each synthetic step.[4] Although, a number of supports[5] and linkers[6] have been tested we have concentrated on the combination of the soluble polymer (MPEG), $CH_3O-(CH_2CH_2O)_n-H$[7] and the linker dioxyxylene (DOX), $-(O)-CH_2-Ph-CH_2-(O)-$.[8] This combination (MPEG)(DOX) is stable to most reaction conditions used in oligosaccharide chemistry[9] and has been used with sialidase enzymes to synthesize sialylated oligosaccharides.[10] The polymer bound compounds can be purified by precipitation with *tert*-butyl methylether (TBME) and reprecipitation from absolute ethanol. The (MPEG)(DOX) bound products can be released by hydrogenation[8] or by $Sc(OTf)_3$ in the presence of acetic anhydride to yield easily purifiable peracetylated sugar-DOXOAc products.[11]

For implementation of a chemistry based (MPEG)(DOX) synthetic strategy, a suite of protecting groups with different cleavage conditions is necessary. If acyl groups adjacent to the anomeric center are used to control the stereoselectivity of the glycosylation reactions then protecting groups which can be cleaved in the presence of both the linker DOX and these acyl groups are necessary. Also, the protecting groups must be absolutely stable to glycosylation conditions. For example, experimentation with *tert*-butyl dimethylsilyl ether protected glycosyl donors showed that some silyl ether was cleaved during glycosylation resulting in undesirable extraneous oligosaccharides.[12] To date isopropylidene,[13] benzylidene,[8] phenylboronate diesters,[14] 3-iodo-4-methoxybenzyl[15] and levulinoyl have been successfully used with the (MPEG)(DOX) combination for O-protection. Especially, if branched oligosaccharides are to be synthesized, more protecting groups would be beneficial. Recently, a number of protecting groups have been examined in conjunction with linkers different from DOX for use in MPEG supported oligosaccharide synthesis.[16]

Besides the intrinsic properties of ease of preparation and cleavage other useful properties of protecting groups for glycosyl donors are: (1) small steric size, (2) electron donating (activating) potential, (3) easily characterized by ^1H NMR spectroscopy, (4) cleavable by reagents that are not

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Keywords: polymer support; protecting groups; thioglycosides; cyclopropanes; glycosidation.

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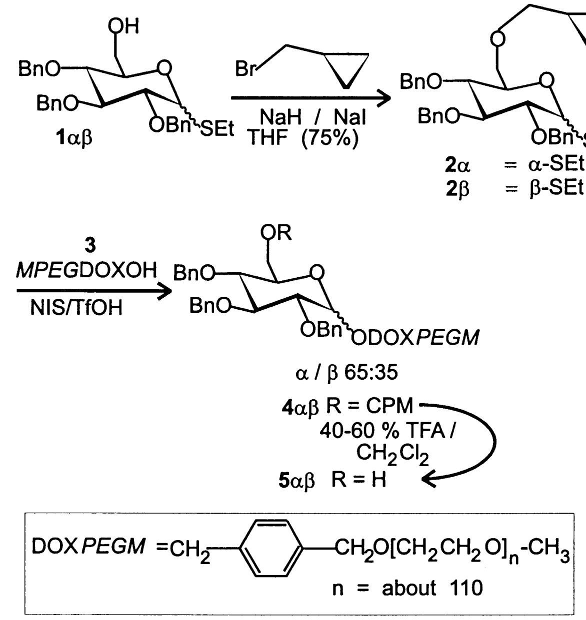

Scheme 1.

very context sensitive, (5) contains few if any electronegative functional groups which may coordinate Lewis acid promotors used in glycosylation reactions. To this end we were intrigued by the reported use of the acid cleavable cyclopropylmethyl ether for the protection of the hydroxyl groups of serine and threonine for solid phase peptide synthesis[17] since this group appears to satisfy all five criteria listed above. (1) It has only four carbons. (2) Ethers are electron donating. In fact, electronic energy calculations suggest that the cyclopropyl group is as efficient an electron donor as phenyl.[18] (3) The characteristic high field ^{1}H NMR resonances of cyclopropyl resonate in a region where few sugar resonances are expected. (4) It is acid cleavable which should not be very sensitive to steric effects. (5) It has very little tendencies to coordinate Lewis acids. Cyclopropylmethyl ether has been used as an *O*-protecting group for phenols too.[19] This communication reports the development of an analogue, 1-methyl 1′-cyclopropylmethyl ether[20] as an *O*-protecting group for polymer-supported oligosaccharide synthesis of a branched trisaccharide. This oligosaccharide is the branchpoint of a single repeat unit of the capsular polysaccharide of Group B *Streptococcus* type 1A[21] and can be converted to the pentasaccharide single repeat unit by the use of bacterial glycosyl transferases.[2]

2. Results and discussion

We first tested cyclopropylmethyl as an *O*-protecting group for polymer-supported oligosaccharide synthesis. To this end we etherified the primary OH-6 of the 1-thioglucose derivative **1αβ**[22] to give the anomeric mixture **2αβ** (75% yield) using standard alkoxide displacement of a primary halide (Scheme 1). Either anomer or in general the anomeric mixture could be used under standard *N*-iodosuccinimide/trifluoromethanesulfonic acid (NIS/TfOH) conditions[23] to glycosylate (MPEG)(DOX)OH, **3**, to yield a 65:35α:β anomeric mixture of polymer bound glycosides **4αβ**. As judged by ^{1}H NMR of **4αβ** the glycosylation reaction went to completion. By testing various concentrations of trifluoroacetic acid (TFA) in dichloromethane it was determined that 40–60% TFA was sufficient to affect cleavage at room temperature. However, under these conditions the DOX linker was partly (40% TFA) or mostly cleaved (60% TFA) too. By conducting the cleavage reaction at 5°C for 16 h in 40% TFA it was possible to isolate alcohol **5αβ** accompanied by only a small amount of DOX cleavage. Thus, cyclopropylmethyl ethers could be used for oligosaccharide synthesis if glycosides more acid stable than DOX are used.

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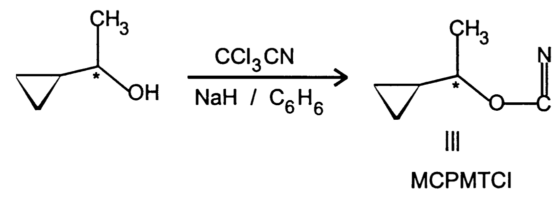

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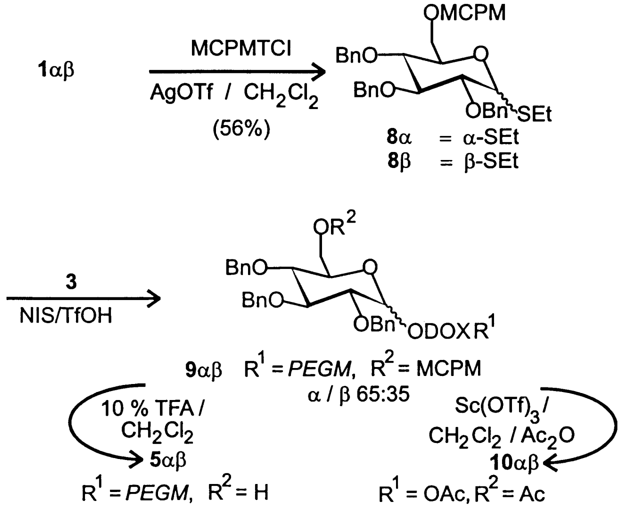
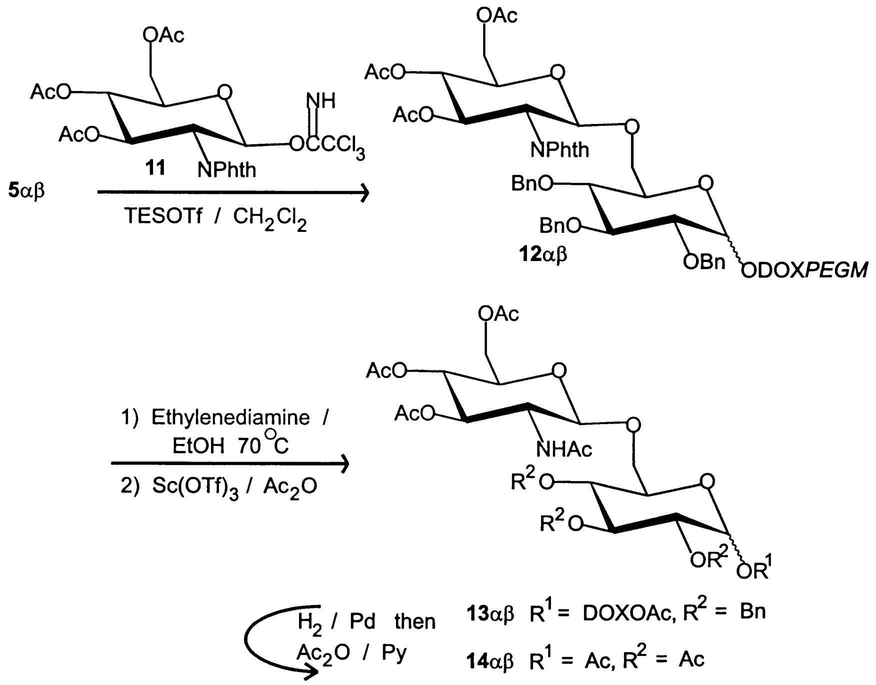
Scheme 2.



Scheme 3.

However, these conditions are unlikely to be general. We therefore decided to examine 1-methyl substituted 1′-cyclopropylmethyl (MCPM) ethers since these should be more acid labile. There is one brief report of the use of this group in peptide synthesis.[20] Since the site of attachment is now a secondary center we thought it unlikely that halide displacement reactions would be efficient. Therefore, we prepared the trichloroacetimidate **7** (MCPMTCI) of racemic alcohol **6** (Scheme 2). It was necessary to use 1 equiv. of the strong base sodium hydride for the reaction to proceed to completion (see Section 4). The resulting reagent is unstable in solution but is stable at −20°C as the pure compound. At room temperature, it is a liquid that can be handled by routine syringe methods.

A variety of Lewis acids were tested for their ability to activate **7**. The best results were obtained with boron trifluoride etherate ($BF_3{\cdot}OEt_2$) and silver trifluoromethanesulfonate (AgOTf) in chlorinated solvents. Thus, **1** could be etherified in a reasonable yield of 56% to give the anomeric mixture **8αβ** (Scheme 3). The yield was lowered



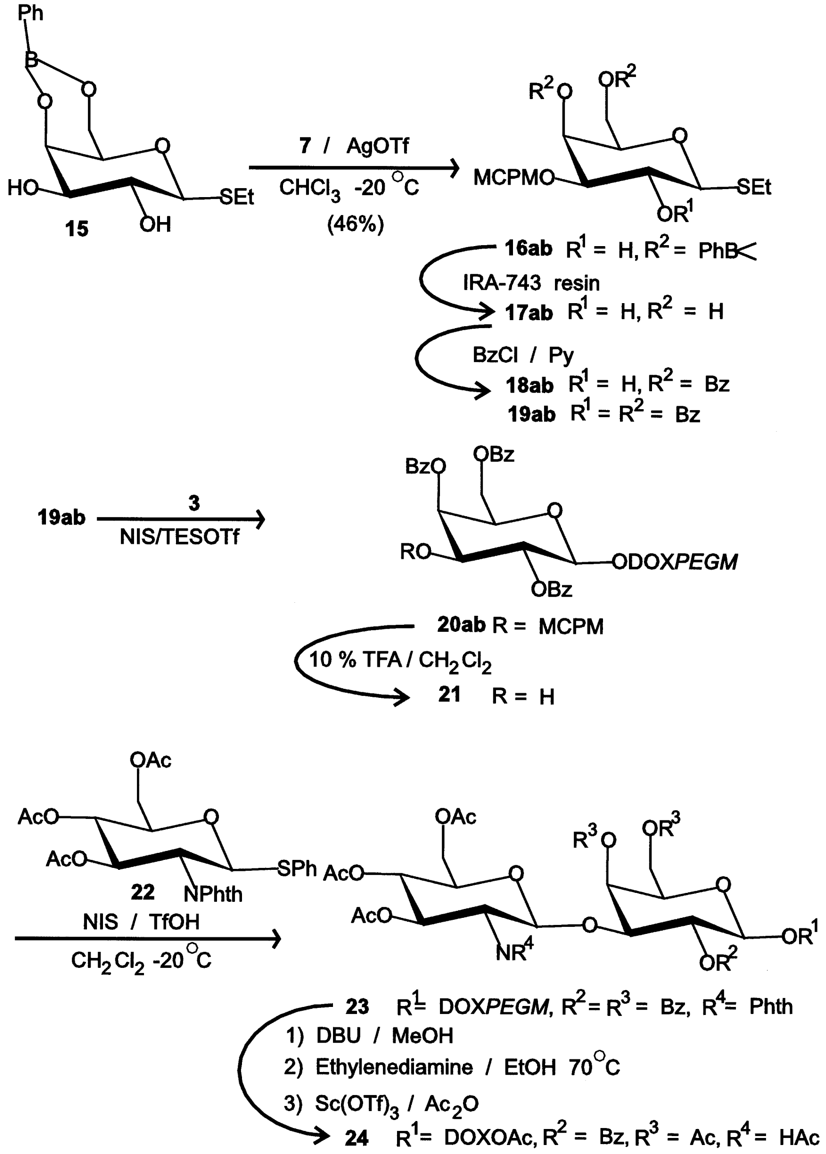
Scheme 4.

by concomitant formation of 2,3,4-tri-*O*-benzyl-1,6-anhydro-β-D-glucopyranose. MCPM ethers **8αβ** are also inseparable diastereomers. In this case, except for the H-6 and MCPM CH resonances, the ^{1}H NMR resonances were not distinguishable (see Section 4). Thioglycosides **8αβ** were readily activated to glycosylate **3** to yield a 65:35α:β anomeric mixture of polymer bound glycosides **9αβ**. Experiments, monitored by ^{1}H NMR, at increasing volume percentages of TFA in CH_2Cl_2 showed that the MCPM ether could be cleaved with as little as 7.5% TFA in CH_2Cl_2 to yield **5αβ**. Thus, MCPM ethers are stable to 5% TFA. This contrasts with *p*-methoxybenzyl ethers which are partly cleaved with 5% TFA. Routinely, we use 10% TFA for 1 h at room temperature to effect cleavage. The polymer is collected by precipitation with TBME and further purified by reprecipitation from absolute ethanol. In the cases examined to date, the DOX linker is stable to these conditions. Interestingly under the $Sc(OTf)_3$ cleavage conditions the MCPM group is also cleaved and the position acetylated cf. **9αβ** to **10αβ**. It should be noted that in the absence of PEG sugars are unstable towards the $Sc(OTf)_3$ cleavage conditions.[11]

In order to demonstrate the usefulness of this process, alcohol **5αβ** was glycosylated with glucosamine derivative **11**[24] under triethylsilyltrifluoromethanesulfonate (TESOTf) activation conditions[25] to cleanly yield disaccharide **12αβ** (Scheme 4). One major advantage of polymer-supported chemistry is the ease of functional group manipulation. Thus, **12αβ** was partly deprotected and cleaved from the polymer in a two step procedure using ethylenediamine[26] to cleave the phthalimide group followed by the combination of $Sc(OTf)_3$ and acetic anhydride to both *O*- and *N*-acetylate as well as effect cleavage from the polymer. The major product **13αβ** was isolated and purified in 20% yield. For polymer-supported reactions only gravimetric recoveries are reported. Thus, yields from cleavage reactions which are based on purified compounds and therefore include all losses due to on polymer steps with less than 100% conversion. In this case eight on polymer steps were used and so each step proceeded on average in just over 80% yield ($80\%^8=17\%$). The benzyl ethers and the DOX glycoside of **13αβ** were removed by hydrogenation and after acetylation and purification the peracetylated disaccharide **14αβ** was isolated.

Next, the secondary O-3 position of D-galactose was selectively protected as its O-3 MCPM ether **16ab** by taking advantage of the easily prepared 4,6-phenylboronate diester of ethyl 1-thio-β-D-galactopyranoside, **15** (Scheme 5).[27] The boronate is easily cleaved with IRA-743 resin to give triol **17ab** in 46% yield from **15**. The MCPM diastereomers were separately identifiable in the ^{1}H and ^{13}C NMR but could not be separated. In this and all subsequent compounds the diastereomer with the most upfield MCPM-CH resonance is arbitrarily assigned as **a**. Attempts to selectively benzoylate **17ab** at the 2,6-positions were unsuccessful as the only diesters isolated were the diastereomeric 4,6-dibenzoates **18a** and **18b** in low yields of 5 and 4%, respectively. Attempts to assign the absolute configuration at the MCPM chiral carbon were unsuccessful. The tribenzoate **19ab** was also prepared. This donor was easily activated to form glycosides **20ab** and the MCPM group readily cleaved with 10% TFA to give alcohol **21**. Glycosylation at −20°C with known donor **22**[28] to give **23** was necessary to prevent migration of the O-2 benzoate which occurred at higher temperatures. Subsequent protecting group manipulations readily led to disaccharide **24**.[14] Surprisingly, the Gal*p* O-2 benzoate was not cleaved during this sequence.

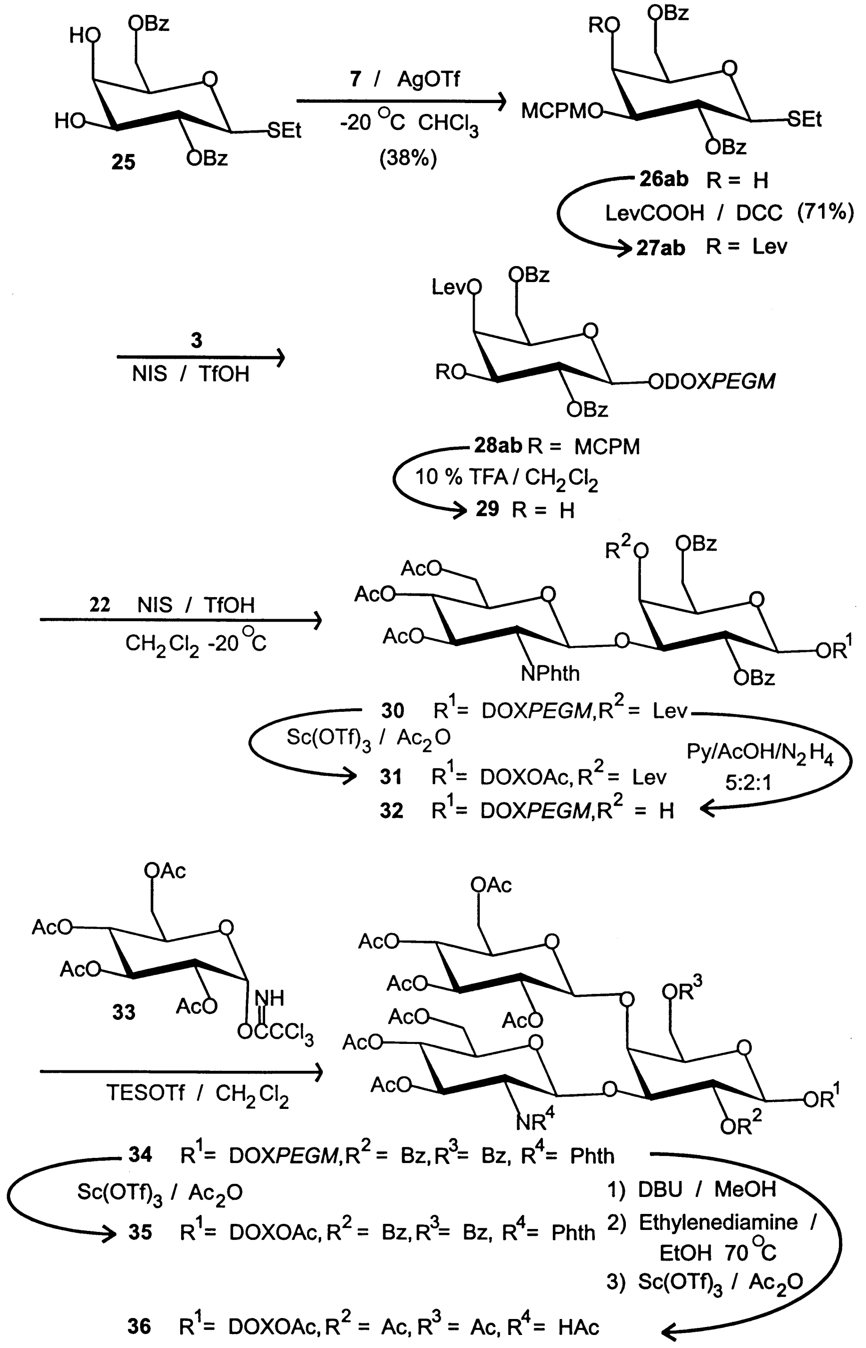
Next, a branched trisaccharide was synthesized using the



Scheme 5.

MCPM group (Scheme 6). Readily available diol **25**[18] was selectively etherified with MCPMTCl to give **26ab** in a moderate yield of 38%. Subsequent levulinoylation produced **27ab** in 71% yield. The MCPM diastereomers of **26ab** or **27ab** were not completely separable but were frequently isolated enriched in one diastereomer thus allowing the assignment of the ^{1}H- and ^{13}C NMR spectra (see Section 4). Glycosylation of the polymer led to **28ab**. Previous experience showed that glycosylation at O-3 followed by O-4 is preferred.[13] Thus, the MCPM ether was cleaved to give **29** and the O-3 alcohol was glycosylated as for **23** to give **30**. To prove the 1,3-regiochemistry disaccharide **30** was cleaved from the polymer to give known β1,3-linked disaccharide **31**.[15] The levulinoyl group of **30** was cleaved with buffered hydrazine to give polymer bound Gal*p* OH-4 disaccharide **32** which was subsequently glycosylated with glucose donor **33** to yield trisaccharide **34**. Trisaccharide **34** could be cleaved to known **35**[15] or treated as for **23** to **24** to give peracylated trisaccharide **36** in 10% yield (almost 80% per step; $80\%^{10}=11\%$). The ^{1}H and ^{13}C NMR were completely assigned and are entirely consistent with the expected regio- and stereochemistry.

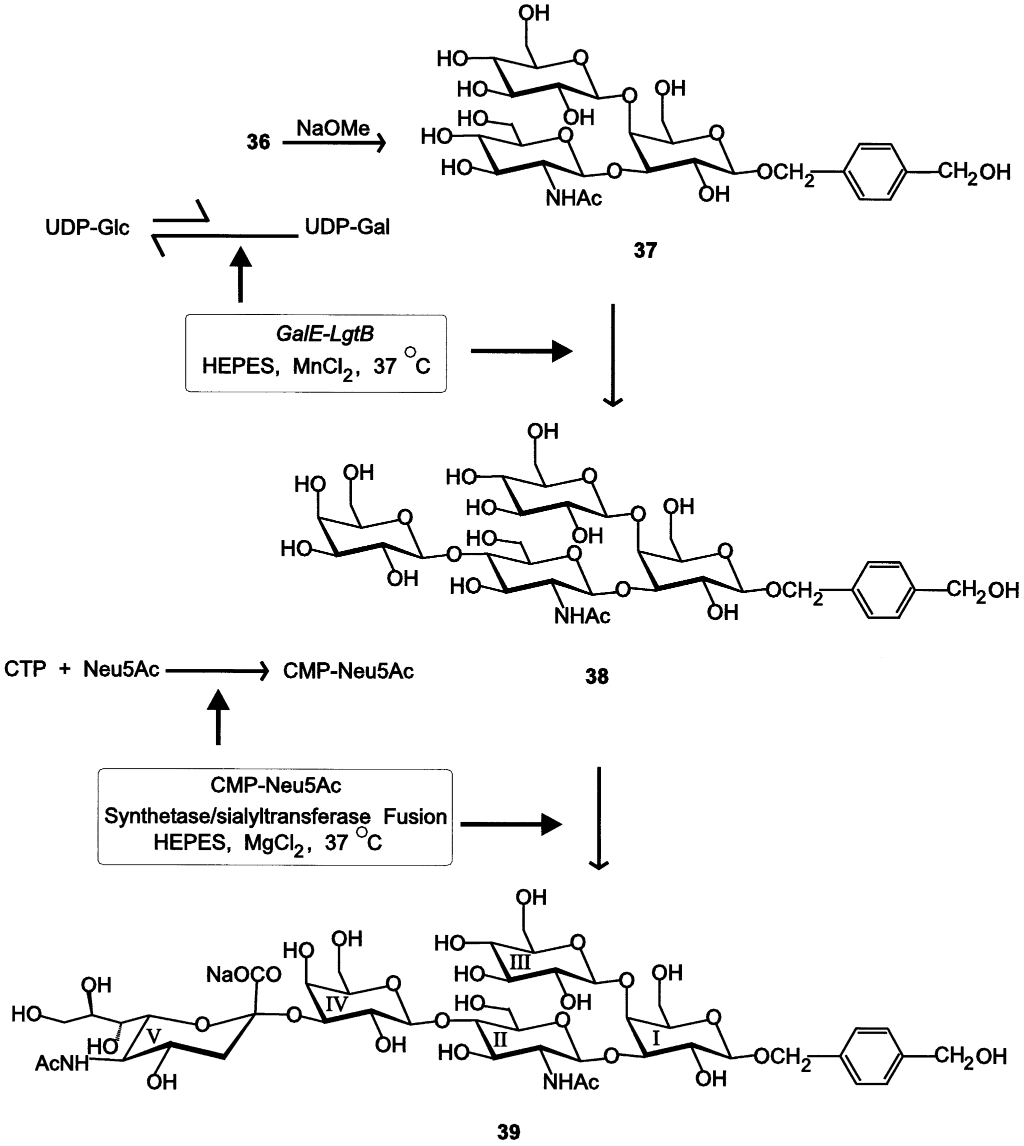
The MCPM group thus allowed for an efficient synthesis of trisaccharide **36** which is a key building block for the synthesis of the pentasaccharide representing a single repeating unit of the type 1A Group B *Streptococcus* capsular polysaccharide. Trisaccharide **36** was deacylated to **37** and then enzymatically glycosylated to yield the type 1A Group B *Streptococcus* single repeat pentasaccharide, **39** (Scheme 7). Trisaccharide **37** was treated with *gluco-galacto* epimerase/β-D-galactose transferase fusion enzyme[2] and uridinediphospho-glucose (UDP-Glc) to generate tetrasaccharide **38**. Subsequent treatment with cytidinemonophosphoneuraminic acid synthetase/α-D-neuraminic acid transferase fusion enzyme,[29] cytidinetriphosphate (CTP) and sialic acid (to generate CMP-Neu5Ac) yielded **39**. After purification by C-18 reverse phase chromatography **39** was characterized by ^{1}H NMR and MS. As well, its properties were compared to other synthetic single repeat units.[30]



Scheme 6.

3. Conclusions

A number of recent publications suggest orthogonal protecting group strategies for polymer-supported oligosaccharide synthesis.[31] Although most remain to be tested in an actual target oriented synthesis. Our reasoning was that one plausible reagent for cleavage of a protecting group in the presence of base labile esters and *O*-benzyl ethers is mild acid. Since some glycosylation reactions involve strong acid conditions it is necessary to carefully choose the acid sensitivity of the proposed protecting group.[32] Most acid promoted cleavage reactions also require a nucleophile and this requirement allows some differentiation since glycosylation reactions are done in the presence of only very weak nucleophiles. In our studies some glycosylation conditions did lead to MCPM cleavage. These all involved reactions at high concentrations of Lewis acids (>1 equiv. to (MPEG)) such as TESOTf in the absence of molecular sieves or added bases. This is comparable to the sensitivity of 4-methoxybenzyl during glycosylation reactions.[33] As exemplified in this work standard NIS/TfOH glycosylation conditions can be used with MCPM in the presence of molecular sieves. Many plausible combinations of glycosyl donors and protecting group strategies need to be tested to fully evaluate the potential of the MCPM group. However, it is clear that MCPM can be successfully used for



Scheme 7.

polymer-supported oligosaccharide chemistry. In fact this report demonstrates its use to synthesize a primary linked disaccharide, a secondary linked disaccharide and a branched trisaccharide.

This trisaccharide represents the branchpoint of type 1A Group B *Streptococcus* capsular polysaccharide and could be converted to the single repeat pentasaccharide using enzymes. The availability of fusion enzymes derived from bacterial enzymes allows the use of relatively inexpensive donors such as UDP-Glc or the in situ generation from relatively inexpensive compounds like CTP and Neu5Ac. The chemical synthesis required only five silica gel chromatographic steps including the three building blocks and the enzymatic synthesis only two C-18 reverse phase purifications which is a great simplification over the traditional stepwise chemical synthesis. With further optimizations the feasibility of commercial production of entirely synthetic oligosaccharide based vaccines becomes more realistic.

4. Experimental

4.1. Materials and general methods

Silica gel (230–400 mesh) was used for flash chromatography. All starting materials were dried overnight in vacuo (10^{-3} mmHg) over KOH or P_2O_5 prior to use, and the solvents were distilled from appropriate drying agents. Optical rotations were measured (λ=589 nm) at room temperature in a 10 cm 1 mL cell. The ^1H and ^{13}C NMR spectra were recorded in deuteriochloroform solution at 500.1 or 600.2 MHz and 125.8 or 150.9 MHz, respectively. ^1H NMR spectra in $CDCl_3$, CD_3OD, C_6D_6 or D_2O were referenced to residual $CHCl_3$ at 7.26 ppm, CHD_2OD at 3.31 ppm, C_6HD_5 at 7.26 ppm or were referenced to internal acetone 2.225 ppm. ^{13}C NMR spectra in $CDCl_3$, CD_3OD, C_6D_6 or D_2O were referenced to the central peaks at 77.0, 35.0 and 129.0 ppm or to internal acetone at 31.07 ppm. Assignments were made by standard ^1H–^1H-COSY and ^{13}C–^1H-COSY experiments. ^1H chemical shifts are reported to two decimal places and ^{13}C shifts to one. In the case of closely separated resonances an additional figure is added to show that they are separately identifiable. The sugar residue nomenclature is shown in Scheme 7. For polymer bound samples the MPEG methylenes were saturated and quantitation was made by comparing integrals to the terminal methyl of the MPEG. Advantage was also taken of gradient enhanced 1D-selective TOCSY and NOESY experiments. Typically 64 transients were used for TOCSY spectra with mixing times from 20 to 150 ms and 6 k transients for NOESY spectra with mixing times of 500 ms.

The mass spectral analysis was done on a forward mass spectrometer. Fast atom bombardment (FAB) MS was performed using Xenon atom at 6 kV as source. Thioglycerol or a mixture of glycerol and thioglycerol were used as FAB matrix. Typically, 10–15 full range, low resolution MS scans were averaged to yield a low resolution mass spectrum. For high resolution MS, the electric sector was scanned over the range of interest. Typically polyethylene glycol or polypropylene glycol was used as an internal mass standard and between 75 and 150 scans were averaged. MALDI-MS spectra were taken on a Voyager-DE STR Biochemistry Workstation. 2,5-Dihydroxybenzoic acid was used as MALDI matrix. Microanalyses were performed by Guelph Chemical Laboratories Ltd., Guelph, Ontario.

4.2. (MPEG) general work-up procedure

(MPEG) bound substrates were worked up by precipitation, by adding TBME (10–20 volumes) to the reaction mixtures cooled in an ice bath. The polymer was recovered by filtration on a coarse sintered glass frit, rinsed with TBME, and reprecipitated from absolute ethanol (about 75 mL per g). The white precipitate was collected by filtration through a medium glass frit, rinsed with ethanol then Et$_2$O, and taken up in CH$_2$Cl$_2$ and filtered through the same glass frit. The filtrate was concentrated and dried in vacuo to afford the polymer-bound product.

4.2.1. (MPEG)(DOX)OH (3). This compound was synthesized according to Ref. 34.

4.2.2. Ethyl 2,3,4-tri-*O*-benzyl-6-*O*-cyclopropylmethyl-1-thio-α/β-D-glucopyranoside 2αβ. Ethyl 2,3,4-tri-*O*-benzyl-1-thio-α/β-D-glucopyranoside[22] (**1αβ**, 750 mg, 1.52 mmol) was dissolved in dry THF (6.0 mL). Then 95% NaH (214 mg, 7.58 mmol) was added. Subsequently, cyclopropylmethyl bromide (441 μL, 4.6 mmol) and sodium iodide (636 mg, 4.55 mmol) were added as a THF (6.0 mL) solution. The mixture was heated to 40°C for 1 h. After concentration the residue was purified by MPLC eluting with hexanes/ethyl acetate 4:1 to yield **2αβ** (621 mg, 75%) α:β 65:35 a small portion was further purified by preparative TLC to yield a small amount of pure α-isomer **2α**: $[\alpha]_D$=30.4 (*c* 8.3, CHCl$_3$); ^{1}H NMR (CDCl$_3$) δ 0.18 (4H, m, C*H*H-Cp), 0.50 (4H, m, CH*H*-Cp), 0.89 (2H, m, C*H*-Cp), 1.29 (3H, t, *J*=7.3 Hz, SCH$_2$C*H*$_3$β), 1.34 (3H, t, *J*=7.3 Hz, SCH$_2$C*H*$_3$α), 2.56 (2H, m, SC*H*$_2$CH$_3$α), 2.75 (2H, m, SC*H*$_2$CH$_3$β), 3.19 (1H, dd, *J*=7.4 Hz, *J*=10.3 Hz, OC*H*HCpα), 3.29 (1H, dd, *J*=7.3 Hz, *J*=10.3 Hz, OC*H*HCpβ), 3.40 (4H, m, CH*H*Cpαβ, H-2β, H-5β), 3.65 (5H, m, H-3β, H-4β, H-6bβ, H-5α, H-6bα), 3.76 (2H, m, H-6aα, H-6β), 3.85 (2H, m, H-2α, H-3α), 4.18 (1H, brd, *J*=8.8 Hz, H-5α), 4.47 (1H, d, $J_{1,2}$=10.3 Hz, H-1β), 4.61 (1H, d, *J*=11.2 Hz, CH*H*Ar), 4.69 (1H, d, *J*=12.2 Hz, CH*H*Ar), 4.70 (2H, d, *J*=10.8 Hz, CH*H*Ar), 4.76 (1H, d, *J*=12.2 Hz, C*H*HAr), 4.80 (2H, d, *J*=10.8 Hz, CH*H*Ar), 4.91 (1H, d, *J*=11.2 Hz, C*H*HAr), 4.93 (2H, d, *J*=10.8 Hz, C*H*HAr), 4.98 (2H, d, *J*=10.8 Hz, C*H*HAr), 5.41 (1H, d, $J_{1,2}$=4.8 Hz, H-1α), 7.31 (26H, m, Ar*H*), 7.39 (4H, m, Ar*H*); ^{13}C NMR (CDCl$_3$) δ 1.0 (*C*H$_2$-Cp), 3.0 (*C*H$_2$-Cp), 3.2 (*C*H$_2$-Cp), 10.4 (*C*H-Cp), 14.8 (SCH$_2$*C*H$_3$α), 15.1 (SCH$_2$*C*H$_3$β), 23.7 (S*C*H$_2$CH$_3$α), 25.1 (S*C*H$_2$CH$_3$β), 68.8 (C-6α), 69.5 (C-6β), 70.5 (C-5α), 72.4, 75.0, 75.7 (*C*H$_2$Ar), 76.1 (O*C*H$_2$Cp), 77.2 (C-4β), 77.5 (C-4α), 79.2 (C-5β), 79.5 (C-3α), 81.8 (C-2β), 82.6 (C-2α), 83.1 (C-1α), 85.1 (C-1β), 86.7 (C-3β), 127.0, 128.0, 137.86, 137.95, 138.5, 138.8 (Ar*C*); MS-FAB+ve 547.3 (M−H$^+$); HRMS C$_{33}$H$_{39}$O$_5$S (M−H$^+$, 547.2504) Calcd 547.2519; Anal. Calcd for C$_{33}$H$_{40}$O$_5$S (548.7446): C 72.23, H 7.34, found: C 72.32, H 7.79.

4.2.3. (MPEG)(DOX)yl 2,3,4-tri-*O*-benzyl-6-*O*-cyclopropylmethyl-α/β-D-glucopyranoside 4αβ. Donor **2αβ** (500 mg, 0.92 mmol), (MPEG)(DOX)OH (**3**, 3.2 g, 0.62 mmol) and powdered molecular sieves 4 Å (about 1 g) were dried together in vacuo. The flask was opened to an argon atmosphere and dichloromethane (17 mL) was added and the mixture cooled in an ice bath. To this mixture was added NIS (910 mg, 4.61 mmol) followed by TESOTf (104 μL, 0.46 mmol). After stirring for 2 h the reaction was quenched with diisopropylethylamine (DIEPA, 200 μL) and standard worked up afforded **4αβ** (3.1 g; 97%): partial ^{1}H NMR (CDCl$_3$) δ 0.20 (m, C*H*H-Cp), 0.51 (m, CH*H*-Cp), 1.06 (m, C*H*-Cp), 4.4–5.0 (m, C*H*$_2$Ar, H-1α, H-1β),7.30 (m, Ar*H*).

4.2.4. *R*,*S*-1-Methyl-1′-cyclopropyl-methyl-*O*-trichloroacetimidate 7. A three-necked RB flask charged with (±)-α-methyl cyclopropylmethanol (**6**, 5.0 mL, 51 mmol), trichloroacetonitrile (25 mL, 10 equiv.), benzene (50 mL) was cooled in an ice bath under an atmosphere of argon. To this solution was added solid 95% NaH (1.35 g, 53 mmol) through the central opening to avoid NaH sticking to the sides of the flask. After 3 h of stirring the reaction was carefully quenched by the dropwise addition of cold water. After the effervescence ceased the mixture was transferred to a separatory funnel and the organic layers separated and then washed again with water. After drying with MgSO$_4$ and filtration the mixture was concentrated. The residue was taken up in cyclohexane, filtered, concentrated and dried in vacuo to yield a colorless oil **7** (8.4 g, 71%): *d*=1.336 g mL^{-1}; ^{1}H NMR (C$_6$D$_6$) δ 0.01 (1H, m, C*H*H-Cp), 0.22 (1H, m, CH*H*-Cp), 0.29 (1H, m, C*H*H-Cp), 0.37 (1H, m, CH*H*-Cp), 0.86 (1H, m, C*H*-Cp), 1.22 (3H, d, *J*=5.9 Hz, OCHC*H*$_3$), 4.52 (1H, dq, *J*=7.3 Hz, *J*=5.9 Hz, OC*H*CH$_3$), 8.17 (1H, s, NH); ^{13}C NMR (C$_6$D$_6$) δ 2.8 (*C*H$_2$-Cp), 3.9 (*C*H$_2$-Cp), 16.7 (*C*H-Cp), 19.3 (*C*H$_3$), 80.5 (O*C*HCH$_3$), 93.0 (CCl$_3$), 162.8 (C=N).

4.2.5. Ethyl 6-*O*-(*R*,*S*-1-methyl 1′-cyclopropylmethyl)-2,3,4-tri-*O*-benzyl-1-thio-α/β-D-glucopyranosides 8αβ. Alcohol (**1**, 970 mg, 1.96 mmol) was dissolved in dichloromethane (25 mL) under an atmosphere of argon. To this solution was added AgOTf (502 mg, 1.96 mmol) and the mixture cooled in an ice salt bath to near 0°C. To the mixture was added imidate (**7**, 0.68 mL, 3.92 mmol) and after stirring for 45 min the reaction was quenched with excess solid NH$_4$HCO$_3$. The solids were removed by filtration through a bed of celite. The filtrate was concentrated and purified by MPLC eluting with TBME/dichloromethane 1:50 to yield a diastereomieric mixture of anomers **8αβ** (620 mg, 56%). A small amount was purified by preparative TLC to yield pure *R*,*S*-**8α**: $[\alpha]_D$=68.8 (*c* 1.7, CHCl$_3$); ^{1}H NMR (CDCl$_3$) δ 0.04 (2H, m, C*H*H-Cp), 0.32 (2H, m, CH*H*-Cp), 0.44 (2H, m, C*H*H-Cp), 0.54 (1H, m, CH*H*-Cp), 0.59 (1H, m, CH*H*-Cp), 0.84 (2H, m, C*H*-Cp), 1.25 (3H, d, *J*=6.0 Hz, OCHC*H*$_3$), 1.26 (3H, d, *J*=6.0 Hz, OCHC*H*$_3$), 1.31 (6H, brt, SCH$_2$C*H*$_3$), 2.55 (2H, m, SC*H*$_2$CH$_3$), 2.67 (1H, m, OC*H*CH$_3$-a), 2.67 (2H, m, SC*H*$_2$CH$_3$), 2.76 (1H, dq, *J*=7.3 Hz, *J*=6.0 Hz, OC*H*CH$_3$-b), 3.29 (2H, m, H-2), 3.60 (1H, dd, J_{56b}=3.9 Hz, J_{6a6b}=10.8 Hz, H-6b-a), 3.68 (2H, brt, H-3), 3.71 (1H, m, H-6b-b), 3.85 (2H, brt, H-3), 3.87 (1H, m, H-6a-a), 3.94 (1H, dd, *J*=<1 Hz, *J*=10.8 Hz, H-6a-b), 4.19 (2H, m, H-5), 4.61 (1H, d, *J*=11.2 Hz, CH*H*Ar), 4.69 (1H, d, *J*=12.2 Hz, CH*H*Ar), 4.70 (2H, d, *J*=10.8 Hz, CH*H*Ar), 4.76 (1H, d, *J*=12.2 Hz, C*H*HAr), 4.80 (2H, d, *J*=10.8 Hz, CH*H*Ar), 4.91 (1H, d, *J*=11.2 Hz, C*H*HAr), 4.93 (2H, d, *J*=10.8 Hz, C*H*HAr), 4.98 (2H, d, *J*=10.8 Hz, C*H*HAr), 5.44 (2H, d, $J_{1,2}$=4.9 Hz, H-1), 7.32 (26H, m, Ar*H*), 7.41 (4H, m, Ar*H*); ^{13}C NMR (CDCl$_3$) δ 0.6 (*C*H$_2$-Cp), 1.0 (*C*H$_2$-Cp), 4.9 (*C*H$_2$-Cp), 5.1 (*C*H$_2$-Cp), 14.8 (SCH$_2$*C*H$_3$), 15.9 (*C*H-Cp), 16.4 (*C*H-Cp), 20.2 (*C*H$_3$), 20.7 (*C*H$_3$), 23.7 (S*C*H$_2$CH$_3$), 66.7, 67.1 (C-6), 70.55, 70.62 (C-5), 72.3, 74.9, 75.7 (*C*H$_2$Ar), 77.5, 77.4 (C-4),79.5 (C-3), 80.6 (O*C*HCH$_3$), 81.1 (O*C*HCH$_3$), 82.7 (C-2), 83.0 (C-1), 127.5, 127.6, 127.7, 127.8, 128.3, 128.0, 137.9, 138.6, 138.7 (Ar*C*); MS-FAB+ve 569.1 (M+Li$^+$), 561.2 (M−H$^+$); HRMS C$_{34}$H$_{42}$O$_5$SK (M+K$^+$, 601.2396) Calcd 601.2390; Anal. Calcd for C$_{34}$H$_{42}$O$_5$S (562.7715): C 72.57, H 7.52, found: C 72.03, H 7.75. and *R*,*S*-**8β**: $[\alpha]_D$=6.5 (*c* 0.6, CHCl$_3$); ^{1}H NMR (CDCl$_3$) δ 0.02 (2H, m, C*H*H-Cp), 0.29 (2H, m, CH*H*-Cp), 0.36 (2H, m, C*H*H-Cp), 0.48 (1H, m, CH*H*-Cp), 0.76 (2H, m, C*H*-Cp), 1.07 (6H, d, *J*=6.0 Hz, OCHC*H*$_3$), 1.29 (6H, brt, SCH$_2$C*H*$_3$), 2.73 (4H, m, SC*H*$_2$CH$_3$), 2.73 (2H, m, OC*H*CH$_3$), 3.39 (4H, m, H-2, H-5), 3.49 (1H, dd, J_{56b}=5.5 Hz, J_{6a6b}=10.6 Hz, H-6b-a), 3.53, 3.55 (2H, 2×brt, H-4), 3.64 (2H, brt, H-3), 3.68 (2H, brs, H-6a-a, H-6b-b), 3.89 (1H, dd, *J*=<1 Hz, *J*=10.6 Hz, H-6a-b), 4.42, 4.41 (2H, 2×d, $J_{1,2}$=9.9 Hz, H-1), 4.60 (1H, d, *J*=10.6 Hz, CH*H*Ar), 4.66 (1H, d, *J*=11.0 Hz, CH*H*Ar), 4.70 (2H, d, *J*=10.3 Hz, CH*H*Ar), 4.80 (4H, m, C*H*HAr), 4.87 (4H, m, CH*H*Ar), 7.26 (26H, m, Ar*H*), 7.33 (4H, m, Ar*H*); ^{13}C NMR (CDCl$_3$) δ 0.8 (*C*H$_2$-Cp), 0.9 (*C*H$_2$-Cp), 4.5 (*C*H$_2$-Cp), 15.3 (SCH$_2$*C*H$_3$), 16.2 (*C*H-Cp), 16.3 (*C*H-Cp), 20.2 (*C*H$_3$), 20.3 (*C*H$_3$), 25.0 (S*C*H$_2$CH$_3$), 67.3 (C-6), 74.9, 75.5, 75.8 (*C*H$_2$Ar), 78.2, 78.1 (C-4), 79.3 (C-2), 80.2 (O*C*HCH$_3$), 80.3 (O*C*HCH$_3$), 81.8 (C-5), 86.7 (C-3), 84.9 (C-1), 127.6, 127.8, 127.9, 128.3, 128.4, 138.0, 138.2, 138.5 (Ar*C*); MS-FAB+ve 569.1 (M+Li$^+$), 561.3 (M−H$^+$); HRMS C$_{34}$H$_{41}$O$_5$S (M−H$^+$, 561.2640) Calcd 561.2674.

4.2.6. (MPEG)(DOX)yl 6-*O*-(*R*,*S*-1-methyl 1′-cyclopropylmethyl)-2,3,4-tri-*O*-benzyl-α/β-D-glucopyranoside 9αβ. (MPEG)(DOX)OH (**3**, 3.0 g, 0.59 mmol) and (**8αβ**, 600 mg, 1.06 mmol) were dried together overnight in vacuo over P$_2$O$_5$. The flask was opened to an argon atmosphere, dichloromethane was added (30 mL) and cooled in an ice bath. To this was added NIS (400 mg, 1.77 mmol) followed by trifluoromethanesulfonic acid (TfOH, 55 mg, 0.21 mmol). After stirring for 20 min the reaction was quenched with DIPEA and after standard workup to give **9αβ** (3.0 g, 99%): partial ^{1}H NMR (CDCl$_3$) δ 0.04 (2H, m, C*H*-Cp), 0.32 (4H, m, C*H*-Cp), 0.42 (4H, m, C*H*-Cp), 0.55 (4H, m, C*H*-Cp), 0.81 (2H, m, C*H*-Cp), 0.86 (8H, m, C*H*-Cp), 1.21, 1.22, 1.24, 1.25 (12H, 4d, C*H*$_3$-Cp), 2.78, 2.84 (4H, m, OC*H*-Cp), 3.86 (brd), 3.94 (brd), 4.01 (brt), 4.5–5.0 (m, H-1αβ, C*H*$_2$Ar), 7.30 (m, Ar*H*).

4.2.7. (MPEG)(DOX)yl 2,3,4-tri-*O*-benzyl-α/β-D-glucopyranoside 5αβ. Glycosides (**9αβ**, 3.0 g, 0.54 mmol) were dissolved in dichloromethane (22.5 mL) under an atmosphere of argon and trifluoroacetic acid (TFA, 2.5 mL) was added. After stirring for 1 h the reaction was cooled in an ice bath and processed by the standard worked to give **5αβ** (2.9 g, 97%): Partial ^{1}H NMR (CDCl$_3$) δ 4.03 (brt, H-3α), 4.5–5.0 (m, H-1α, H-1β, C*H*$_2$Ar), 7.30 (m, Ar*H*).

4.2.8. (4-*O*-Acetoxymethyl)-benzyl 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α/β-D-glucopyranoside 10αβ. A portion of glycosides (**9αβ**, 247 mg, 44 μmol) were dissolved in dichloromethane (2 mL) and acetic anhydride (2 mL). To this mixture was added Sc(OTf)$_3$ (11 mg, 22 μmol) and the stirring continued for 16 h. The polymer was worked up as usual and the combined filtrates concentrated to dryness. The residue was purified by preparative TLC eluting with hexanes/ethyl acetate 50:50 to yield **10αβ** (5 mg, 17%): $[\alpha]_D$=127.5 (*c* 0.38, CHCl$_3$); α:β 65:35; ^{1}H NMR (CDCl$_3$) δ 2.01, 2.04, 2.09 (3×s, C*H*$_3$CO), 3.49 (m, H-2β, H-4β, H-5β, H-2α), 3.50 (brt, $J_{4,5}$=9.9 Hz, H-4α), 3.64 (brt, *J*=8.9 Hz, H-3β), 3.84 (dd, $J_{5,6a}$=4.4 Hz, H-5α), 4.04 (brt, $J_{3,4}$=9.2 Hz, H-3α), 4.15 (dd, $J_{5,6b}$=2.0 Hz, H-6bα), 4.22 (dd, $J_{5,6b}$=4.8 Hz, H-6bβ), 4.24 (dd, $J_{6a,6b}$=12.0 Hz, H-6aα), 4.35 (dd, $J_{6a,6b}$=12.0 Hz, $J_{5,6a}$=2.0 Hz, H-6aβ), 4.48 (d, *J*=12.8 Hz, C*H*HAr), 4.48 (d, $J_{1,2}$=7.8 Hz, H-1β), 4.53 (d, *J*=13.6 Hz, C*H*HAr), 4.54 (d, *J*=12.3 Hz, C*H*HAr), 4.55 (d, *J*=10.9 Hz, C*H*HAr), 4.64 (d, *J*=12.0 Hz, C*H*HAr), 4.66 (d, *J*=12.1 Hz, C*H*HAr), 4.68 (d, *J*=12.0 Hz, C*H*HAr), 4.71 (d, *J*=10.9 Hz, C*H*HAr), 4.77 (d, *J*=11.1 Hz, C*H*HAr), 4.78 (d, $J_{1,2}$=4.0 Hz, H-1α), 4.79 (d, *J*=9.9 Hz, C*H*HAr), 4.83 (d, *J*=11.4 Hz, C*H*HAr), 4.84 (d, *J*=10.9 Hz, C*H*HAr), 4.91 (d, *J*=12.0 Hz, C*H*HAr), 4.92 (d, *J*=10.9 Hz, C*H*HAr), 4.93 (d, *J*=10.9 Hz, C*H*HAr), 5.00 (d, *J*=10.8 Hz, C*H*HAr), 5.09 (s, C*H*$_2$Ar-DOX), 7.30 (m, Ar*H*); ^{13}C NMR (CDCl$_3$) δ 20.9, 21.0 (*C*H$_3$CO), 63.4 (C-6α), 63.6 (C-6β), 66.4 (*C*H$_2$Ar-DOX), 69.3 (C-5α), 69.4 (*C*H$_2$Ar), 71.1 (*C*H$_2$Ar), 73.2 (C-2β), 73.5 (*C*H$_2$Ar), 75.3 (*C*H$_2$Ar), 75.35 (*C*H$_2$Ar), 75.4 (*C*H$_2$Ar), 76.1 (*C*H$_2$Ar), 76.2 (*C*H$_2$Ar), 77.6 (C-2β), 77.8 (C-5α), 80.5 (C-4α), 82.3 (C-3α), 82.6 (C-4β), 85.1 (C-3β), 95.7 (C-1α), 102.5 (C-1β), 127,0, 128.0 136.2, 137.4, 137.6, 137.7, 137.8, 138.0, 138.2, 138.4, 138.6 (Ar*C*), 170.7, 170.8 (CH$_3$*C*O); MS-FAB+ve 653.3 (M−H$^+$); HRMS C$_{39}$H$_{42}$O$_9$Na (M+Na$^+$, 677.2781) Calcd 677.2727.

4.2.9. (MPEG)(DOX)yl 6-*O*-[3,4,6-tri-*O*-acetyl-2-deoxy-2-*N*-phthalimido-β-D-glucopyranosyl]-2,3,4-tri-*O*-benzyl-α/β-D-glucopyranoside 12αβ. Alcohol (**5αβ**, 3.0 g, 0.54 mmol), powdered molecular sieves 4 Å and 3,4,6-tri-

O-acetyl-2-deoxy-2-*N*-phthalimido-β-D-glucopyranosyl-*O*-trichloroacetimidate[24] (**11**, 630 mg, 1.36 mmol) were dried together overnight in vacuo. The flask was opened to an argon atmosphere, dichloromethane (22.5 mL) was added and the mixture cooled in an ice bath. Then TESOTf (96 μL, 0.42 mmol) was added by syringe. After stirring for 2 h, the reaction was quenched with DIPEA (240 μL) and worked up as usual to give **12αβ** (3.08 g, 99%): Partial ^{1}H NMR (CDCl$_3$) δ 2.00, 2.04, 2.06, 2.11 (4×s, C*H*$_3$CO), 5.16 (brt, H-4$^{\rm II}$), 5.32 (d, J=8.8 Hz, H-1$^{\rm II}$α), 5.34 (brt, H-4$^{\rm II}$), 5.45 (d, J=8.8 Hz, H-1$^{\rm II}$), 5.76 ((brt, H-3$^{\rm II}$), 7.02 (m, Ar*H*-DOX), 7.49–7.76 (m, Ar*H*-Phth).

4.2.10. (4-*O*-Acetoxymethyl)-benzyl 6-*O*-[3,4,6-tri-*O*-acetyl-2-deoxy-2-acetamido-β-D-glucopyranosyl]-2,3,4-tri-*O*-benzyl-α/β-D-glucopyranoside 13αβ. To disaccharide (**12αβ**, 2.1 g, 0.35 mmol) was added ethanol (48 mL) followed by ethylenediamine (3.0 mL) and the mixture heated to 70°C and stirred under an atmosphere of argon for 2 h. The mixture was diluted with ethanol (150 mL) and cooled to −20°C to precipitate the polymer. The precipitate was recovered by filtration, rinsed with ethanol followed by diethyl ether and then dissolved in dichloromethane, filtered and concentrated. The residue (2.15 g) was dissolved in dichloromethane (12 mL) cooled in an ice bath under an atmosphere of argon and acetic anhydride (12.0 mL) followed by Sc(OTf)$_3$ (100 mg, 0.2 mmol) were added. The polymer was worked up as usual and the combined filtrates were concentrated to dryness. The residue was purified by MPLC eluting with CH$_2$Cl$_2$/iC$_3$H$_7$OH 20:1 to yield **13αβ** (66 mg, 20%):α:β 1:0.75; ^{1}H NMR (CDCl$_3$) δ 1.82, 1.86, 1.98, 1.99, 2.00, 2.08 (6s, C*H*$_3$CO), 3.48 (m, H-5$^{\rm I}$β, H-4$^{\rm I}$β, H-2$^{\rm I}$β), 3.50 (m, H-4$^{\rm I}$α), 3.51 (m, H-2$^{\rm I}$α), 3.60 (m, H-5$^{\rm II}$αβ), 3.61 (brt, J=8.8 Hz, H-3$^{\rm I}$β), 3.68 (m, H-6b$^{\rm I}$α, H-6b$^{\rm I}$β), 3.80 (m, H-5$^{\rm I}$α), 3.85 (m, H-2$^{\rm II}$β), 3.87 (m, H-2$^{\rm II}$α), 4.01 (m, H-3$^{\rm I}$α, H-6a$^{\rm I}$α), 4.07 (m, H-6a$^{\rm I}$β), 4.10 (m, H-6b$^{\rm II}$αβ), 4.20 (m, H-6a$^{\rm II}$αβ), 4.47 (d, J=8.2 Hz, H-1$^{\rm I}$β), 4.49 (d, J=12.0 Hz, C*H*HAr), 4.52 (d, J=12.4 Hz, C*H*HAr), 4.56 (2 d, J=10.9 Hz, C*H*HAr), 4.64 (d, J=8.1 Hz, H-1$^{\rm II}$α), 4.65 (d, J=11.0 Hz, C*H*HAr), 4.66 (d, J=12.4 Hz, C*H*HAr), 4.67 (d, J=12.0 Hz, C*H*HAr), 4.69 (d, J=10.9 Hz, C*H*HAr), 4.70 (d, J=8.3 Hz, H-1$^{\rm II}$β), 4.75 (d, J=11.0 Hz, C*H*HAr), 4.78 (d, J=10.9 Hz, C*H*HAr), 4.79 (d, J=4.2 Hz, H-1$^{\rm I}$α), 4.81 (d, J=10.9 Hz, C*H*HAr), 4.82 (d, J=10.9 Hz, C*H*HAr), 4.89 (d, J=11.0 Hz, C*H*HAr), 4.912 (d, J=10.9 Hz, C*H*HAr), 4.915 (d, J=11.0 Hz, C*H*HAr), 4.98 (d, J=10.9 Hz, C*H*HAr), 5.03 (brt, J=9.6 Hz, H-4$^{\rm II}$α), 5.04 (brt, J=9.6 Hz, H-4$^{\rm II}$β), 5.08 (s, C*H*$_2$Ar-DOX), 5.09 (s, C*H*$_2$Ar-DOX), 5.24 (brt, J=9.4 Hz, H-3$^{\rm II}$α), 5.25 (brt, J=9.4 Hz, H-3$^{\rm II}$β), 5.29 (d, N*H*$^{\rm II}$β), 5.34 (d, N*H*$^{\rm II}$α), 7.24 (12H, m, Ar*H*), 7.31 (14H, m, Ar*H*), 7.38 (4H, m, Ar*H*); ^{13}C NMR (CDCl$_3$) δ 20.6, 20.7, 21.0 (*C*H$_3$COO), 23.4 (*C*H$_3$CON), 54.5 (C-2$^{\rm II}$α), 54.7 (C-2$^{\rm II}$β), 62.2 (C-6$^{\rm II}$αβ), 66.04 (*C*H$_2$Ar-DOX), 66.06 (*C*H$_2$Ar-DOX), 67.5 (C-6$^{\rm I}$β), 67.7 (C-6$^{\rm I}$α), 68.62 (C-4$^{\rm II}$αβ), 68.60 (*C*H$_2$Ar), 69.9 (C-5$^{\rm I}$α), 70.7 (*C*H$_2$Ar), 72.0 (C-5$^{\rm II}$αβ), 72.3 (C-3$^{\rm II}$β), 72.4 (C-3$^{\rm II}$α), 73.1 (*C*H$_2$Ar), 74.4 (C-2$^{\rm I}$β), 74.7 (*C*H$_2$Ar), 74.8 (*C*H$_2$Ar), 74.9 (*C*H$_2$Ar), 75.7 (2*C*H$_2$Ar), 77.4 (C-5$^{\rm I}$β), 77.9 (C-4$^{\rm I}$β), 79.9 (C-2$^{\rm I}$α), 82.0 (C-3$^{\rm I}$α), 82.2 (C-4$^{\rm I}$α), 84.6 (C-3$^{\rm I}$β), 95.6 (C-1$^{\rm I}$α), 100.51 (C-1$^{\rm II}$α), 100.58 (C-1$^{\rm II}$β), 102.4 (C-1$^{\rm I}$β), 127.0, 128.0, 135.5, 135.6, 137.3, 137.6, 138.1, 138.2, 138.3, 138.4, 138.5, 138.9 (Ar*C*), 169.38, 169.41, 169.45, 169.5, 169.9, 170.7, 170.8, 170.85 (*C*O); MS-FAB+ve 964.1 (M+Na$^+$), 330 (TriAcHexNAc$^+$); HRMS C$_{51}$H$_{59}$NO$_{16}$Na (M+Na$^+$, 964.3667) Calcd 964.3600; Anal. Calcd for C$_{51}$H$_{59}$NO$_{16}$·(H$_2$O)$_{2.5}$ (987.0674): C 62.06, H 6.54, N 1.42 found: C 62.08, H 6.69, N 1.30.

4.2.11. 6-*O*-[3,4,6-Tri-*O*-acetyl-2-deoxy-2-acetamido-β-D-glucopyranosyl]-1,2,3,4-tetra-*O*-acetyl-α/β-D-glucopyranose 14αβ. Disaccharide (**13αβ**, 56 mg, 59 μmol) was dissolved in acetic acid (10 mL) and hyrdrogenated in a Parr apparatus at 50 psi of H$_2$ for 16 h in the presence of 10% Pd on charcoal. The catalyst was removed by filtration through a bed of celite. TLC analysis of the filtrate revealed that the hydrogenation was not complete and so the procedure was repeated. The filtrate was concentrated and the residue was dissolved in pyridine (4 mL) and acetic anhydride (1 mL) was added. After stirring for 16 h at rt the mixture was concentrated and the residue co-concentrated with toluene. The residue was purified by MPLC eluting with hexanes/ethyl acetate 3:1 followed by pure ethyl acetate to yield pure **14αβ** (14 mg, 35%): $[\alpha]_{\rm D}$= 14.2 (*c* 0.82, CHCl$_3$); α:β 1:1.19; ^{1}H NMR (CDCl$_3$) δ 1.94, 1.981, 1.984, 1.987, 1.989, 1.992, 1.998, 2.00(2), 2.01, 2.02, 2.04, 2.06, 2.07, 2.15, 2.16 (16s, C*H*$_3$CO), 3.44 (dd, $J_{6a,6b}$=11.6 Hz, $J_{5,6b}$=4.9 Hz, H-6b$^{\rm I}$α), 3.61 (m, H-6b$^{\rm I}$β, H-6a$^{\rm I}$α), 3.63 (m, H-5$^{\rm II}$αβ), 3.75 (brt, H-5$^{\rm I}$β), 3.84 (brd, $J_{6a,6b}$=12.8 Hz, $J_{5,6a}$=<1.0 Hz, H-6a$^{\rm I}$β), 3.92 (brq, $J_{2,3}$=10.4 Hz, $J_{1,2}$=8.6 Hz, $J_{2,{\rm NH}}$=9.8 Hz, H-2$^{\rm II}$α), 3.99 (brt, H-5$^{\rm I}$α), 4.11 (m, H-2$^{\rm II}$β), 4.12 (brd, $J_{6a,6b}$= 12.8 Hz, $J_{5,6a}$=<1.0 Hz, H-6b$^{\rm II}$αβ), 4.21 (m, H-6a$^{\rm II}$αβ), 4.50 (d, J=8.6 Hz, H-1$^{\rm II}$β), 4.55 (d, J=8.6 Hz, H-1$^{\rm II}$α), 4.93 (brt, $J_{4,5}$=9.8 Hz, $J_{3,4}$=9.8 Hz, H-4$^{\rm I}$β), 4.98 (brt, J= 9.8 Hz, H-3$^{\rm II}$β), 5.019 (dd, $J_{1,2}$=3.7 Hz, $J_{2,3}$=9.8 Hz, H-2$^{\rm I}$α), 5.038, 5.062 (m, H-4$^{\rm II}$α, H-4$^{\rm II}$β), 5.080 (dd, $J_{1,2}$= 8.6 Hz, $J_{2,3}$= 9.8 Hz, H-2$^{\rm I}$β), 5.085 (dd, $J_{3,4}$=9.7 Hz, $J_{4,5}$= 10.4 Hz, H-4$^{\rm I}$α), 5.194 (brt, $J_{2,3}$=10.4 Hz, $J_{3,4}$=9.8 Hz, H-3$^{\rm II}$α), 5.206 (brt, $J_{2,3}$=9.8 Hz, $J_{3,4}$=9.8 Hz, H-3$^{\rm I}$β), 5.44 (brt, $J_{2,3}$=9.8 Hz, $J_{3,4}$=9.7 Hz, H-3$^{\rm I}$α), 5.49 (d, J=8.6 Hz, H-1$^{\rm I}$β), 5.75 (d, $J_{2,{\rm NH}}$=8.6 Hz, N*H*$^{\rm II}$β), 6.20 (d, $J_{2,{\rm NH}}$= 9.8 Hz, N*H*$^{\rm II}$α), 6.25 (d, J=3.7 Hz, H-1$^{\rm I}$α); ^{13}C NMR (CDCl$_3$) δ 20.4–21.0 (*C*H$_3$COO), 22.9, 23.1 (*C*H$_3$CON), 53.3 (C-2$^{\rm II}$β), 54.2 (C-2$^{\rm II}$α), 62.0 (C-6$^{\rm II}$αβ), 66.8 (C-6$^{\rm I}$α), 66.9 (C-6$^{\rm I}$β), 67.9 (C-4$^{\rm I}$β), 68.1 (C-4$^{\rm I}$α), 68.4 (C-4$^{\rm II}$αβ), 69.1 (C-2$^{\rm I}$α), 69.8 (C-3$^{\rm I}$α), 69.9 (C-2$^{\rm I}$β), 70.7 (C-5$^{\rm I}$α), 71.9 (C-5$^{\rm II}$αβ), 72.6 (C-3$^{\rm II}$α, C-3$^{\rm I}$β), 72.9 (C-3$^{\rm II}$β), 75.9 (C-5$^{\rm I}$β), 89.1 (C-1$^{\rm I}$α), 92.3 (C-1$^{\rm I}$β), 101.1 (C-1$^{\rm II}$α), 101.6 (C-1$^{\rm II}$β), 169.2, 169.4, 169.5, 169.6, 169.8, 170.0, 170.1, 170.3, 170.4, 170.6, 170.8, 170.9, 171.0(2), 171.1(2) (*C*O); ^{1}H NMR (CDCl$_3$) δ MS-FAB+ve 678.2 (M+H$^+$), 700.1 (M+Na$^+$); HRMS C$_{28}$H$_{40}$NO$_{18}$ (M+H$^+$, 678.2259) Calcd 678.2244.

4.2.12. Ethyl 4,6-*O*-phenylboronate-β-D-galactothiopyranoside 15. A solution of phenylboronic acid (560 mg, 4.58 mmol) in benzene (100 mL) was refluxed in a 2-neck flask fitted with a dropping funnel and Dean–Stark trap. A solution of ethyl 1-thio-β-D-galactopyranoside (1.00 g, 4.58 mmol) in methanol (5 mL) was added dropwise from the funnel and this solution refluxed for 1/2 h, periodically draining the trap and replacing the volume with benzene. The solution was allowed to cool and on standing overnight at room temperature the product crystallized. Three crops were collected totaling (1.31 g, 94%): mp=148.5–149.2°C;

^{1}H NMR (CDCl$_3$) δ 1.22 (t, J=7.4 Hz, 3H, SCH$_2$*C*H_3), 2.65 (m, 2H, S*C*H_2CH$_3$), 2.75 (brs, 1H, O*H*), 2.95 (brs, 1H, O*H*), 3.60 (m, 2H, H-2, H-3), 3.81 (brs, 1H, H-5), 4.12 (d, J=12.2 Hz, 1H, H-6b), 4.20 (d, J=12.3 Hz, 1H, H-6a), 4.33 (m, 2H, H-1, H-4), 7.26 −7.37 (m, 3H, Ar*H*), 7.75 (brd, 2H, Ar*H*); ^{13}C NMR (CDCl$_3$): δ 15.1 (SCH$_2$*C*H$_3$), 23.8 (S*C*H$_2$CH$_3$), 64.7 (C-6), 69.8, 70.4, 72.2, 74.4, (C-2, C-3, C-4, C-5), 85.7 (C-1), 127.6 (2Ar*C*H), 128.3 (Ar*C*B), 131.1 (Ar*C*H), 133.9 (2Ar*C*H).

4.2.13. Ethyl 3-*O*-(*R*,*S*-1-methyl 1′-cyclopropylmethyl)-1-thio-β-D-galactopyranoside 17ab. Ethyl 4,6-*O*-phenylboronate-1-thio-β-D-galactopyranoside (**15**, 1.8 g, 5.8 mmol) was dissolved in, freshly distilled from CaH$_2$, chloroform (15 mL). This solution was cooled to −20°C under an atmosphere of argon and covered in aluminum foil. Then, **7** (1.75 mL, 10.1 mmol) was added followed by AgOTf (651 mg, 2.5 mmol). After stirring for 2 h, the reaction was diluted with cyclohexane (100 mL), filtered through a bed of celite and concentrated to yield **16ab**. The residue was shaken overnight with IRA-743 resin (about 5 g), which had been previously well washed with acetonitrile then methanol, and methanol (about 100 mL). After filtration and evaporation the residue was purified by MPLC eluting with CH$_2$Cl$_2$/CH$_3$OH 93:7 to yield **17ab** (0.78 g, 46%): [α]$_D$=−14.6 (*c* 0.12, CHCl$_3$); ^{1}H NMR (CD$_3$OD) δ 0.14 (2H, m, C*H*H-Cp), 0.44 (4H, m, CH*H*-Cp), 0.55 (2H, m, C*H*H-Cp), 0.90 (2H, m, C*H*-Cp), 1.28 (12H, m, OCHC*H*$_3$, SCH$_2$C*H*$_3$), 2.74 (4H, m, SC*H*$_2$CH$_3$), 3.04 (1H, m, OC*H*CH$_3$-b), 3.16 (1H, m, OC*H*CH$_3$-a), 3.41 (1H, dd, $J_{2,3}$=9.2 Hz, $J_{3,4}$=3.2 Hz, H-3-b), 3.50 (2H, brd, H-5-a,b), 3.56 (1H, $J_{1,2}$=8.2 Hz, $J_{2,3}$=9.2 Hz, H-2-b), 3.57 (1H, dd, $J_{2,3}$=9.2 Hz, $J_{3,4}$=3.2 Hz, H-3-a), 3.61 (1H, $J_{1,2}$=8.2 Hz, $J_{2,3}$=9.2 Hz, H-2-a), 3.68 (2H, dd, $J_{5,6b}$=5.5 Hz, $J_{6a,6b}$=11.5 Hz, H-6b-a,b), 3.74 (2H, dd, $J_{5,6a}$=6.4 Hz, $J_{6a,6b}$=11.5 Hz, H-6a-a,b), 3.98 (1H, brd, H-4-a), 4.05 (1H, brd, H-4-b), 4.33, 4.34 (2H, 2×d, $J_{1,2}$=8.2 Hz, H-1-b, H-1-a); ^{13}C NMR (CD$_3$OD) δ 0.6 (*C*H$_2$-Cp), 1.2 (*C*H$_2$-Cp), 4.3 (*C*H$_2$-Cp), 14.5 (SCH$_2$*C*H$_3$), 16.5 (*C*H-Cp), 17.3 (*C*H-Cp), 19.8 (*C*H$_3$), 20.3 (*C*H$_3$), 23.8 (S*C*H$_2$CH$_3$), 61.6 (C-6-a,b), 67.3 (C-4-b), 68.2 (C-4-a), 69.7 (C-2-a,b), 78.9 (O*C*HCH$_3$-a), 79.5 (C-5-a,b), 80.1 (C-3-a), 80.9 (O*C*HCH$_3$-b), 81.3 (C-3-b), 85.5 (C-1-a,b); MS-FAB+ve 293.2 (M+H$^+$), 231.2 (M−SEt$^+$); HRMS C$_{13}$H$_{25}$O$_5$S (M+H$^+$, 293.1414) Calcd 293.1423.

4.2.14. Ethyl 4,6-di-*O*-benzoyl-3-*O*-(*R*,*S*-1-methyl 1′-cyclopropylmethyl)-1-thio-β-D-galactopyranoside 18ab. Triol (**17ab**, 287 mg, 0.98 mmol) was dissolved in pyridine under an atmosphere of argon and cooled in an ice salt bath to 0°C. To this solution was added benzoyl chloride (0.285 mL, 2.4 mmol). After 5 h at 0°C the reaction was quenched with methanol and concentrated. The residue was dissolved in dichloromethane and washed 3× with cold 0.05 M HCl$_{aq}$ followed by aqueous NaHCO$_3$ and water. The organic layers were dried with MgSO$_4$, filtered and concentrated. The residue was purified by MPLC eluting with hexanes/ethyl acetate 3:1 to yield (**19ab**, 147 mg, 25%) followed by **18a** (24 mg, 5%) and **18b** (20 mg, 4%): **18a** high R_f [α]$_D$=−15.3 (*c* 0.33, CHCl$_3$); ^{1}H NMR (CDCl$_3$) δ 0.08 (1H, m, C*H*H-Cp), 0.34 (1H, m, CH*H*-Cp), 0.42 (1H, m, C*H*H-Cp), 0.64 (1H, m, C*H*H-Cp), 0.80 (1H, m, C*H*-Cp), 1.09 (3H, d, J=6.1 Hz OCHC*H*$_3$), 1.33 (3H, t, J=7.6 Hz, SCH$_2$C*H*$_3$), 2.65 (1H, brs, OH), 2.79 (2H, m, SC*H*$_2$CH$_3$), 3.17 (1H, dq, J=6.1 Hz, J=8.3 Hz, OC*H*CH$_3$), 3.84 (1H, brt, $J_{1,2}$=9.8 Hz, $J_{2,3}$=9.2 Hz, H-2), 3.97 (1H, dd, $J_{2,3}$=9.2 Hz, $J_{3,4}$=3.4 Hz, H-3), 4.08 (1H, brt, H-5), 4.35 (1H, dd, $J_{5,6b}$=5.8 Hz, $J_{6a,6b}$=11.3 Hz, H-6b), 4.51 (1H, dd, $J_{5,6a}$=7.0 Hz, $J_{6a,6b}$=11.3 Hz, H-6a), 4.55 (1H, d, $J_{1,2}$=8.2 Hz, H-1), 5.72 (1H, brd, H-4), 7.44 (4H, m, Bz), 7.55 (2H, m, Bz), 8.00 (2H, d, J=7.1 Hz, Bz), 8.05 (2H, d, J=7.0 Hz, Bz); ^{13}C NMR (CDCl$_3$) δ 0.1 (*C*H$_2$-Cp), 5.6 (*C*H$_2$-Cp), 15.2 (*C*H-Cp), 15.9 (SCH$_2$*C*H$_3$), 20.9 (*C*H$_3$), 24.6 (S*C*H$_2$CH$_3$), 63.0 (C-6), 67.3 (C-4), 69.2 (C-2), 75.1 (C-5), 77.3 (C-3), 78.1 (O*C*HCH$_3$), 86.0 (C-1), 128.4, 128.5, 129.4, 129.6, 129.7, 129.9, 133.2, 133.3 (Ar*C*-Bz), 165.7, 166.2 (*C*O, Bz); **18b** low R_f [α]$_D$=−25.7 (*c* 0.30, CHCl$_3$); ^{1}H NMR (CDCl$_3$) δ 0.07 (1H, m, C*H*H-Cp), 0.26 (1H, m, CH*H*-Cp), 0.39 (2H, m, C*H*H-Cp), 0.88 (1H, m, C*H*-Cp), 1.22 (3H, d, J=6.1 Hz OCHC*H*$_3$), 1.32 (3H, t, J=7.3 Hz, SCH$_2$C*H*$_3$), 2.54 (1H, brs, OH), 2.78 (2H, m, SC*H*$_2$CH$_3$), 3.06 (1H, dq, J=6.1 Hz, J=8.2 Hz, OC*H*CH$_3$), 3.65 (1H, dd, $J_{2,3}$=9.2 Hz, $J_{3,4}$=3.1 Hz, H-3), 3.88 (1H, brt, $J_{1,2}$=9.8 Hz, $J_{2,3}$=9.2 Hz, H-2), 4.06 (1H, brt, H-5), 4.35 (1H, dd, $J_{5,6b}$=5.8 Hz, $J_{6a,6b}$=11.3 Hz, H-6b), 4.48 (1H, dd, $J_{5,6a}$=7.0 Hz, $J_{6a,6b}$=11.3 Hz, H-6a), 4.52 (1H, d, $J_{1,2}$=8.2 Hz, H-1), 5.80 (1H, brd, H-4), 7.42 (4H, m, Bz), 7.54 (2H, m, Bz), 8.01 (2H, d, J=7.3 Hz, Bz), 8.07 (2H, d, J=7.3 Hz, Bz); ^{13}C NMR (CDCl$_3$) δ 1.8 (*C*H$_2$-Cp), 4.1 (*C*H$_2$-Cp), 15.2 (*C*H-Cp), 17.0 (SCH$_2$*C*H$_3$), 19.7 (*C*H$_3$), 24.6 (S*C*H$_2$CH$_3$), 63.0 (C-6), 68.2 (C-4), 69.3 (C-2), 75.3 (C-5), 78.0 (C-3), 79.1 (O*C*HCH$_3$), 86.2 (C-1), 128.39, 128.42, 129.5, 129.6, 129.7, 130.0, 133.2, 133.3 (Ar*C*-Bz), 165.7, 166.2 (*C*O, Bz); MS-FAB+ve 539.2 (M+K$^+$), 439.2 (M−SEt$^+$); HRMS C$_{27}$H$_{32}$O$_7$SNa (M+Na$^+$, 523.1783) Calcd 523.1766; Anal. Calcd for C$_{27}$H$_{32}$O$_7$S (500.6132): C 64.78, H 6.44, found: C 65.24, H 6.76.

4.2.15. Ethyl 2,4,6-tri-*O*-benzoyl-3-*O*-(*R*,*S*-1-methyl 1′-cyclopropylmethyl)-1-thio-β-D-galactopyranoside 19ab. Triol (**17ab**, 0.78 g, 2.6 mmol) was dissolved in pyridine (10 mL) and cooled in an ice bath under an atmosphere of argon. To this solution was added benzoyl chloride (1.81 mL, 6 eq.) and the reaction mixture was left to warm to rt with stirring for 16 h. Methanol was added to quench the reaction. After evaporation, the residue was purified by MPLC eluting with hexanes/ethyl acetate/CH$_2$Cl$_2$ 8:1:1 to yield **19ab** (1.41 g, 90%): [α]$_D$=32.4 (*c* 0.54, CHCl$_3$); ^{1}H NMR (CDCl$_3$) δ −0.06 (2H, m, C*H*H-Cp), 0.22 (3H, m, CH*H*-Cp), 0.33 (2H, m, C*H*H-Cp), 0.46 (1H, m, C*H*H-Cp), 0.54 (1H, m, C*H*-Cp), 0.78 (1H, m, C*H*-Cp), 1.00 (6H, d, J=6.1 Hz, OCHC*H*$_3$), 1.27 (3H, t, J=7.3 Hz, SCH$_2$C*H*$_3$), 2.77 (4H, m, SC*H*$_2$CH$_3$), 2.93 (1H, dq, J=6.1 Hz, J=8.2 Hz, OC*H*CH$_3$-a), 3.04 (1H, dq, J=6.1 Hz, J=8.2 Hz, OC*H*CH$_3$-b), 3.91 (1H, dd, $J_{2,3}$=9.5 Hz, $J_{3,4}$=3.3 Hz, H-3-b), 4.14 (2H, brt, H-5-a,b), 4.22 (1H, dd, $J_{2,3}$=9.5 Hz, $J_{3,4}$=3.3 Hz, H-3-a), 4.39 (2H, dd, $J_{5,6b}$=7.0 Hz, $J_{6a,6b}$=11.6 Hz, H-6b-a,b), 4.53 (1H, dd, $J_{5,6a}$=5.8 Hz, $J_{6a,6b}$=11.6 Hz, H-6a-b), 4.56 (1H, dd, $J_{5,6a}$=5.8 Hz, $J_{6a,6b}$=11.6 Hz, H-6a-a), 4.71 (1H, d, $J_{1,2}$=10.1 Hz, H-1-b), 4.74 (1H, d, $J_{1,2}$=10.1 Hz, H-1-a), 5.47 (1H, brt, $J_{1,2}$=9.5 Hz, $J_{2,3}$=10.1 Hz, H-2-a), 5.51 (1H, brt, $J_{1,2}$=9.5 Hz, $J_{2,3}$=10.1 Hz, H-2-b), 5.80 (1H, brd, H-4-a), 5.91 (1H, brd, H-4-b), 7.45 (12H, m, Bz), 7.56 (6H, m, Bz), 8.03 (8H, m, Bz), 8.11 (4H, m, Bz); ^{13}C NMR

($CDCl_3$) δ 0.0 (*C*H$_2$-Cp), 1.4 (*C*H$_2$-Cp), 4.1 (*C*H$_2$-Cp), 5.3 (*C*H$_2$-Cp), 15.0 (SCH$_2$*C*H$_3$), 15.9 (*C*H-Cp), 16.9 (*C*H-Cp), 20.0 (*C*H$_3$), 20.8 (*C*H$_3$), 24.3 (S*C*H$_2$CH$_3$), 62.95, 62.96 (C-6-a,b), 67.9 (C-4-b), 69.0 (C-4-a), 70.0 (C-2-a), 70.2 (C-2-b), 75.3 (C-5-b), 75.4 (C-5-a), 75.7 (C-3-b), 76.9 (C-3-a), 78.4 (O*C*HCH$_3$-a), 79.9 (O*C*HCH$_3$-b), 84.3 (C-1-a,b), 128.3, 128.41, 128.42, 128.44, 128.51, 128.52, 129.5, 129.9, 129.70, 129.74, 130.0, 130.1, 133.04, 133.07, 133.20, 133.23, 133.27, 133.31 (Ar*C*-Bz), 165.26(2), 165.89, 165.92, 166.1, 166.2 (*C*O-Bz); MS-FAB+ve 643.2 (M+K$^+$), 543.2 (M−SEt$^+$); HRMS $C_{34}H_{36}O_8SNa$ (M+Na$^+$, 627.2075) Calcd 627.2038; Anal. Calcd for $C_{34}H_{36}O_8S$ (604.7216): C 67.53, H 5.33 found: C 67.63, H 5.55.

4.2.16. (MPEG)(DOX)yl 3-*O*-(*R*,*S*-1-methyl 1′-cyclopropylmethyl)-2,4,6-tri-*O*-benzoyl-β-D-galactopyranoside 20ab. (MPEG)(DOX)OH (**3**, 4.23 g, 0.82 mmol), powdered molecular sieves 3 Å (about 2 g) and thioglycoside (**19ab**, 1.0 g, 1.65 mmol) were dried in vacuo overnight over P_2O_5. The flask was opened to an argon atmosphere and dichloromethane (25 mL) was added. The reaction mixture was cooled in an ice bath and NIS (558 mg, 2.48 mmol) followed by TESOTf (73 μL, 0.32 mmol) were added. After stirring for 1 h the reaction was quenched with DIPEA (200 μL) and worked up as usual to give **20ab** (4.4 g, 99%): partial ^{1}H NMR ($CDCl_3$) δ −0.05 (2H, m, C*H*H-Cp), 0.20 (3H, m, CH*H*-Cp), 0.31 (2H, m, C*H*H-Cp), 0.41 (1H, m, C*H*H-Cp), 0.52 (1H, m, C*H*-Cp), 0.76 (1H, m, C*H*-Cp), 0.98 (6H, d, J=6.1 Hz, OCHC*H*$_3$), 2.88 (1H, m, OC*H*CH$_3$S), 3.01 (1H, m, OC*H*CH$_3$R), 3.82 (1H, m, H-3S), 4.13 (1H, m, H-3R), 4.62 (1H, d, $J_{1,2}$=8.1 Hz, H-1S), 4.65 (1H, d, $J_{1,2}$=8.1 Hz, H-1R), 4.88 (1H, d, J=12.4 Hz, C*H*HAr-DOX), 4.89 (1H, d, J=12.8 Hz, C*H*HAr-DOX), 5.52 (2H, m, H-2), 5.74 (1H, brd, H-4S), 5.83 (1H, brd, H-4R), 7.12 (8H, m, Ar*H*-DOX), 7.46 (12H, m, Ar*H*-Bz), 7.58 (6H, m, Ar*H*-Bz), 7.99 (4H, brd, Ar*H*-Bz), 8.06 (4H, brd, Ar*H*-Bz), 8.15 (4H, brd, Ar*H*-Bz).

4.2.17. (MPEG)(DOX)yl 2,4,6-tri-*O*-benzoyl-β-D-galactopyranoside 21. Glycoside (**20ab**, 3.59 g, 0.63 mmol) was treated with 10% TFA as for **9ab–5** to afford **21** (3.54 g, 99%): partial ^{1}H NMR ($CDCl_3$) δ 2.82 (1H, brs, OH), 4.12 (1H, dd, $J_{2,3}$=8.8 Hz, $J_{3,4}$=3.0 Hz, H-3), 4.46 (1H, dd, $J_{5,6b}$=5.9 Hz, $J_{6a,6b}$=11.7 Hz, H-6b), 4.53 (2H, s, C*H*$_2$Ar-DOX), 4.64 (1H, dd, $J_{5,6a}$=7.3 Hz, $J_{6a,6b}$=11.7 Hz, H-6a), 4.71 (1H, d, $J_{1,2}$=7.3 Hz, H-1), 4.72, 4.92 (2H, 2×d, J=12.2 Hz, C*H*HAr-DOX), 5.44 (1H, brt, H-2), 5.77 (1H, brd, H-4), 7.21 (4H, m, Ar*H*-DOX), 7.49 (6H, m, Ar*H*-Bz), 7.62 (3H, m, Ar*H*-Bz), 8.01 (2H, brd, Ar*H*-Bz), 8.08 (2H, brd, Ar*H*-Bz), 8.19 (2H, brd, Ar*H*-Bz).

4.2.18. (MPEG)(DOX)yl 3-*O*-[3,4,6-tri-*O*-acetyl-2-deoxy-2-*N*-phthalimido-β-D-glucopyranosyl]-2,4,6-tri-*O*-benzoyl-β-D-galactopyranoside 23. The polymer bound alcohol (**21**, 3.38 g, 0.60 mmol) and phenyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-*N*-phthalimido-1-thio-β-D-glucopyranoside[28] (**22**, 494 mg, 0.94 mmol) were dried in vacuo for 16 h. The flask was opened to an atmosphere of argon and dichloromethane (15 mL) followed by powdered molecular sieves 3 Å (about 2 g) were added. The mixture was cooled to −20°C and NIS (561 mg, 2.49 mmol) followed by trifluoromethanesulfonic acid (TfOH, 40 μL, 0.45 mmol) were added. After stirring for 1.5 h the reaction was quenched with DIPEA (105 μL) and worked up as usual to give **23** (3.6 g, 99%): partial ^{1}H NMR ($CDCl_3$) δ 1.68 (3H, s, C*H*$_3$CO), 1.94 (6H, s, C*H*$_3$CO), 4.03 (m, H-5^{II}), 4.12 (m, H-2^{II}), 4.19 (m, H-6b^{II}), 4.45 (m, H-6a^{II}), 4.64 (m, H-1^{I}), 4.69 (d, J=11.7 Hz, C*H*HAr-DOX), 4.81 (d, J=11.7 Hz, CH*H*Ar-DOX), 5.02 (brt, J=9.8 Hz, H-4^{II}), 5.16 (brt, J=9.8 Hz, H-2^{I}), 5.50 (d, $J_{1,2}$=7.8 Hz, H-1^{II}), 5.57 (brt, J=9.8 Hz, H-3^{II}), 5.78 (brd, J=2.0 Hz, H-4^{I}); 7.03 (4H, brs, Ar*H*-DOX), 7.44 (6H, m, Ar*H*-Bz), 7.58 (3H, m, Ar*H*-Bz), 7.72 (2H, m, Ar*H*-Phth), 7.75 (1H, m, Ar*H*-Phth), 7.83 (1H, m, Ar*H*-Phth), 8.05, 8.06, 8.07 (6H, 3× brd, Ar*H*-Bz).

4.2.19. (4-Acetoxymethyl)-benzyl 3-*O*-[3,4,6-tri-*O*-acetyl-2-deoxy-2-acetamido-β-D-glucopyranosyl]-4,6-di-*O*-acetyl-2-*O*-benzoyl-β-D-galactopyranoside 24. Disaccharide (**23**, 3.61 g, 0.59 mmol) was dissolved in methanol (30 mL) by gentle heating with a heat gun and after cooling DBU (30 drops) was added and the mixture left to stir for 16 h. The polymer was worked up as usual. To the solid was added ethanol (35 mL) followed by ethylenediamine (410 μL, 6.1 mmol) and the mixture heated at 70°C for 2 h. Then ethanol (75 mL) was added and the mixture cooled at −20°C to achieve precipitation. The solid was collected by filtration, rinsed with ethanol and diethyl ether. Then it was dissolved in dichloromethane, filtered, concentrated and dried in vacuo. The solid was dissolved in dichloromethane (15 mL) followed by acetic anhydride (15 mL) and cooled in an ice bath. To this mixture was added $Sc(OTf)_3$ (150 mg, 0.30 mmol) and the mixture left to stir and warm to rt for 16 h. The polymer was worked up as usual and the combined filtrates were concentrated to dryness. The residue was purified by MPLC eluting with CH_2Cl_2/*i*C_3H_7OH 25:1 to yield slightly impure **24** which was further purified on Sephadex LH-20 eluting with $CHCl_3/CH_3OH$ 4:3 to yield pure **24** (94 mg, 19%): $[\alpha]_D$=38.5 (*c* 0.18, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.43, 1.95, 1.98, 2.10, 2.11, 2.12, 2.17 (21H, 7×s, C*H*$_3$CO), 3.51 (1H, brq, $J_{1,2}$=8.1 Hz, $J_{NH,2}$=8.1 Hz, $J_{2,3}$=10.2 Hz, H-2^{II}), 3.60 (1H, ddd, $J_{4,5}$=9.9 Hz, $J_{5,6a}$=2.2 Hz, $J_{5,6b}$=4.0 Hz, H-5^{II}), 3.85 (1H, brt, H-5^{I}), 3.92 (1H, dd, $J_{2,3}$=9.9 Hz, $J_{3,4}$=3.3 Hz, H-3^{I}), 4.06 (1H, dd, $J_{5,6b}$=4.0 Hz, $J_{6a,6b}$=12.1 Hz, H-6b^{II}), 4.15 (1H, dd, $J_{5,6b}$=7.0 Hz, $J_{6a,6b}$=11.4 Hz, H-6b^{I}), 4.22 (1H, dd, $J_{5,6a}$=5.9 Hz, $J_{6a,6b}$=11.4 Hz, H-6a^{I}), 4.23 (1H, dd, $J_{5,6a}$=2.2 Hz, $J_{6a,6b}$=12.1 Hz, H-6a^{I}), 4.54 (1H, d, J=8.1 Hz, H-1^{I}), 4.64 (1H, d, J=12.8 Hz, C*H*HAr-DOX), 4.86 (1H, d, J=12.8 Hz, CH*H*Ar-DOX), 4.88 (1H, d, J=8.2 Hz, H-1^{II}), 5.00 (1H, brt, $J_{3,4}$=9.9 Hz, $J_{4,5}$=9.9 Hz, H-4^{II}), 5.04 (2H, s, C*H*$_2$Ar-DOX), 5.14 (1H, d, N*H*), 5.24 (1H, brt, $J_{2,3}$=10.2 Hz, $J_{3,4}$=9.9 Hz, H-3^{II}), 5.50 (1H, brt, $J_{1,2}$=8.1 Hz, $J_{2,3}$=9.9 Hz, H-2^{I}), 7.15 (4H, m, Ar*H*-DOX), 7.50 (2H, brt, J=7.7 Hz, Ar*H*-Bz), 7.65 (1H, brt, J=7.3 Hz, Ar*H*-Bz), 8.00 (2H, brd, J=7.3 Hz, Ar*H*-Bz); ^{13}C NMR ($CDCl_3$) δ 20.6, 20.7, 21.0 (*C*H$_3$COO), 22.6 (*C*H$_3$CON), 55.3 (C-2^{II}), 61.4 (C-6^{II}), 62.3 (C-6^{I}), 65.9 (*C*H$_2$Ar-DOX), 68.5 (C-4^{II}), 69.4 (C-4^{I}), 69.8 (*C*H$_2$Ar-DOX), 71.2 (C-2^{I}), 71.3 (C-3^{II}), 71.5 (C-5^{I}), 71.6 (C-5^{II}), 99.5 (C-1^{I}), 100.8 (C-1^{II}), 128.0, 128.2 (Ar*C*H-DOX), 128.7 (Ar*C*H-Bz), 129.4 (Ar*C*C-Bz), 129.8, 133.6 (Ar*C*H-Bz), 135.6, 136.7 (Ar*C*C-DOX),165.0 (*C*O-Bz), 169.3, 169.8, 170.2, 170.5, 170.6, 170.7, 171.6 (*C*O-Ac); MS-FAB+ve 860.3 (M+H$^+$), 882.2 (M+Na$^+$); HRMS

$C_{41}H_{49}NO_{19}Na$ (M+Na$^+$, 882.2823) Calcd 882.2796; Anal. Calcd for $C_{41}H_{49}NO_{19}$ (859.8370): C 57.27, H 5.74, N 1.63 found: C 56.80, H 5.71, N 1.62.

4.2.20. Ethyl 2,6-di-*O*-benzoyl-3-*O*-(*R*,*S*-1-methyl 1′-cyclopropylmethyl)-1-thio-β-D-galactopyranoside 26ab. Ethyl 2,6-di-*O*-benzoyl-1-thio-β-D-galactopyranoside[15] (**25**, 2.0 g, 4.6 mmol) was dissolved in, freshly distilled from CaH_2, chloroform (15 mL). This solution was cooled to −20°C under an atmosphere of argon and covered in aluminum foil. Then, *R*,*S*-1-methyl-1-cyclopropylmethyl-*O*-trichloroacetimidate (1.4 mL, 8.1 mmol) was added followed by AgOTf (1.18 g, 4.6 mmol). The reaction was quenched after 1 h with solid NH_4HCO_3, filtered through a bed of celite and concentrated. The residue was taken up in dichloromethane, filtered and concentrated. The residue was purified by MPLC eluting with CH_2Cl_2/CH_3OH 50:1 to yield **26ab** (875 mg, 38%): $[\alpha]_D$=25.3 (*c* 0.23, $CHCl_3$); ^1H NMR ($CDCl_3$) high R_f δ 0.02 (1H, m, C*H*H-Cp), 0.23 (1H, m, C*H*H-Cp), 0.44 (1H, m, C*H*H-Cp), 0.50 (1H, m, C*H*H-Cp), 0.82 (1H, m, C*H*C-Cp), 1.04 (3H, d, *J*=5.9 Hz, C*H*$_3$), 1.18 (3H, t, *J*=7.3 Hz, C*H*$_3$CH$_2$S), 2.68 (2H, m, CH$_3$C*H*$_2$S), 2.75 (1H, brs, O*H*), 2.76 (1H, m, OC*H*CH$_3$), 3.67 (1H, dd, $J_{2,3}$=9.5 Hz, $J_{3,4}$=3.3 Hz, H-3), 3.87 (1H, brt, H-5), 4.11 (1H, brd, $J_{3,4}$=3.3 Hz, H-4), 4.52 (1H, d, $J_{1,2}$=10.3 Hz, H-1), 4.57 (1H, dd, $J_{5,6a}$=5.1 Hz, $J_{6a,6b}$=11.4 Hz, H-6a), 4.65 (1H, dd, $J_{5,6ab}$=7.3 Hz, $J_{6a,6b}$=11.4 Hz, H-6b), 5.38 (1H, dd, $J_{1,2}$=10.3 Hz, $J_{2,3}$=9.5 Hz, H-2), 7.41 (4H, brt, Ar*H*), 7.53 (2H, brt, Ar*H*), 8.01 (4H, m, Ar*H*); low R_f δ 0.02 (1H, m, C*H*H-Cp), 0.22 (1H, m, C*H*H-Cp), 0.37 (1H, m, C*H*H-Cp), 0.46 (1H, m, C*H*H-Cp), 0.78 (1H, m, C*H*C-Cp), 1.28 (6H, m, C*H*$_3$, C*H*$_3$CH$_2$S), 2.81 (2H, m, CH$_3$C*H*$_2$S), 2.78 (1H, brs, O*H*), 3.08 (1H, m, OC*H*CH$_3$), 3.97 (1H, dd, $J_{2,3}$=9.2 Hz, $J_{3,4}$=3.3 Hz, H-3), 3.99 (1H, brt, H-5), 4.19 (1H, brd, $J_{3,4}$=3.3 Hz, H-4), 4.66 (1H, d, $J_{1,2}$=10.3 Hz, H-1), 4.70 (1H, dd, $J_{5,6a}$=5.1 Hz, $J_{6a,6b}$=11.4 Hz, H-6a), 4.78 (1H, dd, $J_{5,6ab}$=7.0 Hz, $J_{6a,6b}$=11.4 Hz, H-6b), 5.52 (1H, dd, $J_{1,2}$=10.3 Hz, $J_{2,3}$=9.2 Hz, H-2), 7.53 (4H, brt, Ar*H*), 7.66 (2H, brt, Ar*H*), 8.15 (4H, m, Ar*H*); ^{13}C NMR ($CDCl_3$) high R_f δ 2.0 (*C*H$_2$-Cp), 4.6 (*C*H$_2$-Cp), 14.9 (*C*H$_3$CH$_2$S), 17.3 (*C*HC-Cp), 20.3 (*C*H$_3$), 24.0 (CH$_3$*C*H$_2$S), 64.0 (C-6), 67.8 (C-4), 69.7 (C-2), 76.1 (C-5), 78.6 (C-3), 81.2 (O*C*HCH$_3$), 83.6 (C-1), 128.4, 129.7 (Ar*C*H), 129.89, 129.93 (Ar*C*C), 133.0, 133.1 (Ar*C*H), 165.3, 166.4 (*C*O); low R_f δ 1.1 (*C*H$_2$-Cp), 4.4 (*C*H$_2$-Cp), 14.9 (*C*H$_3$CH$_2$S), 16.5 (*C*HC-Cp), 21.2 (*C*H$_3$), 23.9 (CH$_3$*C*H$_2$S), 63.9 (C-6), 67.7 (C-4), 69.7 (C-2), 76.1 (C-5), 77.8 (C-3), 79.9 (O*C*HCH$_3$), 83.6 (C-1), 128.4, 129.7 (Ar*C*H), 129.7, 130.0 (Ar*C*C), 133.0, 133.1 (Ar*C*H), 165.3, 166.5 (*C*O); MS-FAB+ve 523.2 (M+Na$^+$); HRMS $C_{27}H_{32}O_7SNa$ (M+Na$^+$, 523.1791) Calcd 523.1766; Anal. Calcd for $C_{27}H_{32}O_7S$ (500.6132): C 64.78, H 6.44 found: C 64.62, H 6.43.

4.2.21. Ethyl 2,6-di-*O*-benzoyl-4-*O*-levulinoyl-3-*O*-(*R*,*S*-1-methyl 1′-cyclopropylmethyl)-1-thio-β-D-galactopyranoside 27ab. Alcohols (**26ab**, 470 mg, 0.94 mmol) were dissolved in dry THF under an atmosphere of argon. To this was added levulinic acid (0.2 mL, 2.0 mmol) followed by dicyclohexylcarbodiimide (387 mg, 1.9 mmol) and DMAP (about 10 mg). The mixture was left to stir for 16 h and filtered through a bed of celite. After evaporation the residue was purified by MPLC eluting with dichloromethane/ethyl acetate 92:8 to yield **27ab** (400 mg, 71%): $[\alpha]_D$=20.9 (*c* 0.34, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.02 (1H, m, C*H*H-Cp-a), 0.08 (1H, m, C*H*H-Cp-b), 0.29 (1H, m, C*H*H-Cp-b), 0.35 (1H, m, C*H*H-Cp-a), 0.54 (2H, m, C*H*H-Cp-a,b), 0.55 (1H, m, C*H*H-Cp-b), 0.60 (1H, m, C*H*H-Cp-a), 0.90 (1H, m, C*H*C-Cp-a), 0.97 (1H, m, C*H*C-Cp-b), 1.12 (3H, d, *J*=6.2 Hz, C*H*$_3$-a), 1.15 (3H, d, *J*=6.2 Hz, C*H*$_3$-b), 1.34 (6H, t, *J*=7.3 Hz, C*H*$_3$CH$_2$S-a,b), 2.26 (6H, s, C*H*$_3$CO-Lev), 2.88 (13H, m, C*H*$_2$C*H*$_2$-Lev-a,b, OC*H*CH$_3$-b, CH$_3$C*H*$_2$S-a,b), 3.05 (1H, m, OC*H*CH$_3$-a), 3.78 (1H, dd, $J_{2,3}$=9.8 Hz, $J_{3,4}$=3.0 Hz, H-3-a), 4.02 (2H, brt, H-5-a,b), 4.07 (1H, dd, $J_{2,3}$=9.8 Hz, $J_{3,4}$=3.0 Hz, H-3-b), 4.35 (2H, dd, $J_{5,6a}$=5.9 Hz, $J_{6a,6b}$=11.7 Hz, H-6a-a,b), 4.51 (2H, m, H-6b-a,b), 4.62 (1H, d, $J_{1,2}$=9.8 Hz, H-1-a), 4.64 (1H, d, $J_{1,2}$=9.8 Hz, H-1-b), 5.33 (1H, dd, $J_{1,2}$=9.8 Hz, $J_{2,3}$=9.8 Hz, H-2-b), 5.35 (1H, dd, $J_{1,2}$=9.8 Hz, $J_{2,3}$=9.8 Hz, H-2-a), 5.52 (1H, brd, $J_{3,4}$=3.0 Hz, H-4-b), 5.65 (1H, brd, $J_{3,4}$=3.0 Hz, H-4-a), 7.43 (8H, brt, Ar*H*), 7.55 (4H, brt, Ar*H*), 8.02 (8H, m, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 0.2 (*C*H$_2$-Cp-b), 1.4 (*C*H$_2$-Cp-a,b), 4.4 (*C*H$_2$-Cp-a), 5.4 (*C*H$_2$-Cp-b), 15.0 (*C*H$_3$CH$_2$S-a,b), 16.0 (*C*HC-Cp-b), 16.8 (*C*HC-Cp-a), 20.1 (*C*H$_3$-a), 20.8 (*C*H$_3$-b), 24.4 (CH$_3$*C*H$_2$S-a,b), 28.1 28.2 (*C*H$_2$*C*H$_2$-Lev-a,b), 29.8 (*C*H$_3$CO-Lev-a,b), 62.7 (C-6-a,b), 67.5 (C-4-b), 68.7 (C-4-a), 69.9 (C-2-b), 70.1 (C-2-a), 74.9 (C-5-b), 75.1 (C-5-a), 75.4 (C-3-b), 76.8 (C-3-a), 78.6 (O*C*HCH$_3$-b), 80.5 (O*C*HCH$_3$-a), 84.1 (C-1-a,b), 128.4, 129.6, 129.7 (Ar*C*H), 129.8, 129.9 (Ar*C*C), 133.0, 133.1 (Ar*C*H), 165.2, 166.1 (*C*O-Bz), 171.9 (*C*OO-Lev), 206.1 (CH$_3$*C*O-Lev); MS-FAB+ve 637.2 (M+K$^+$), 537.2 (M−SEt$^+$); HRMS $C_{32}H_{38}O_9SNa$ (M+Na$^+$, 621.2157) Calcd 621.2134; Anal. Calcd for $C_{32}H_{38}O_9S$ (598.7148): C 64.20, H 6.40 found: C 64.26, H 6.71.

4.2.22. (MPEG)(DOX)yl 2,6-di-*O*-benzoyl-4-*O*-levulinoyl-3-*O*-(*R*,*S*-1-methyl 1′-cyclopropylmethyl)-β-D-galactopyranoside 28ab. (MPEG)(DOX)OH (**3**, 796 mg, 0.16 mmol) and (**27ab**, 186 mg, 0.32 mmol) were dried together in vacuo over P_2O_5. The flask was opened to an argon atmosphere, dichloromethane (4 mL) was added and the mixture cooled to −20°C. To this mixture was added NIS (105 mg, 0.48 mmol) followed by TfOH (10 μL, 0.11 mmol). After stirring for 1 h the reaction was quenched with DIPEA and after standard workup afforded **28ab** (736 mg, 92%): partial ^1H NMR ($CDCl_3$) δ-0.07 (1H, m, C*H*H-Cp), −0.01 (1H, m, C*H*H-Cp), 0.17 (1H, m, C*H*H-Cp), 0.24 (2H, m, C*H*H-Cp), 0.40 (1H, m, C*H*H-Cp), 0.44 (1H, m, C*H*H-Cp), 0.56 (1H, m, C*H*C-Cp), 0.77 (1H, m, C*H*C-Cp), 1.02 (3H, d, *J*=6.0 Hz, C*H*$_3$), 1.06 (3H, d, *J*=6.0 Hz, C*H*$_3$), 2.24 (6H, s, C*H*$_3$CO-Lev), 2.84 (8H, m, C*H*$_2$C*H*$_2$-Lev), 2.87, 2.93 (2H, 2×m, OC*H*CH$_3$), 3.67 (1H, dd, $J_{2,3}$=9.7 Hz, $J_{3,4}$=3.0 Hz, H-3), 3.97 (2H, brt, H-5), 4.42 (1H, dd, $J_{5,6b}$=5.9 Hz, $J_{6a,6b}$=10.8 Hz, H-6b), 4.56, 4.58 (2H, 2×d, $J_{1,2}$=8.8 Hz, H-1), 4.62 (4H, m, H-6a, CH*H*Ar-DOX), 4.87 (2H, d, C*H*HAr-DOX), 5.43 (2H, brt, $J_{1,2}$=8.8 Hz, $J_{2,3}$=9.7 Hz, H-2), 5.50, 5.62 (2H, 2×brd, $J_{3,4}$=3.0 Hz, H-4), 7.13 (8H, m, Ar*H*-DOX), 7.48 (8H, brt, Ar*H*-Bz), 7.61 (4H, brt, Ar*H*-Bz), 8.01 (4H, m, Ar*H*-Bz), 8.09 (4H, m, Ar*H*-Bz).

4.2.23. (MPEG)(DOX)yl 2,6-di-*O*-benzoyl-4-*O*-levulinoyl-β-D-galactopyranoside 29. Glycosides (**28ab**, 736 mg, 0.13 mmol) were dissolved in dichloromethane (9 mL) under an atmosphere of argon and TFA (1 mL) was added. After stirring for 1 h the mixture was cooled in an ice bath and the polymer precipitated with TBME (100 mL). The polymer was worked up as usual to give **29** (657 mg, 89%): partial ^{1}H NMR (CDCl$_3$) δ 2.24 (3H, s, C*H*$_3$CO-Lev), 2.73, 2.90 (4H, m, C*H*$_2$C*H*$_2$-Lev), 3.94 (1H, brd, $J_{2,3}$= 9.8 Hz, H-3), 4.02 (1H, brt, H-5), 4.40 (1H, dd, $J_{5,6b}$= 6.8 Hz, $J_{6a,6b}$=11.7 Hz, H-6b), 4.52 (2H, s, C*H*$_2$Ar-DOX), 4.59 (1H, d, $J_{1,2}$=7.8 Hz, H-1), 4.60 (1H, dd, $J_{5,6a}$=7.9 Hz, $J_{6a,6b}$=11.7 Hz, H-6a), 4.67, 4.87 (2H, 2×d, J=12.6 Hz, C*H*HAr-DOX), 5.33 (1H, brt, $J_{1,2}$=7.8 Hz, $J_{2,3}$=9.8 Hz, H-2), 5.56 (1H, brd, $J_{3,4}$=2.9 Hz, H-4), 7.18 (4H, m, Ar*H*-DOX), 7.48 (4H, brt, Ar*H*-Bz), 7.61 (2H, brt, Ar*H*-Bz), 8.01 (2H, m, Ar*H*-Bz), 8.09 (2H, m, Ar*H*-Bz).

4.2.24. (MPEG)(DOX)yl 3-*O*-[3,4,6-tri-*O*-acetyl-2-deoxy-2-*N*-phthalimido-β-D-glucopyranosyl]-2,6-di-*O*-benzoyl-4-*O*-levulinoyl-β-D-galactopyranoside 30. The polymer bound alcohol (**29**, 1.17 g, 0.21 mmol) and powdered molecular sieves 4 Å (about 500 mg) were dried at 40°C in vacuo for 16 h. After cooling to rt (**22**, 224 mg, 0.42 mmol) was added under an atmosphere of argon followed by dichloromethane (8 mL). The mixture was cooled to −20°C and NIS (190 mg, 0.85 mmol) followed by TfOH (21 μL, 0.24 mmol) were added. After stirring for 1 h the reaction was quenched with DIPEA and worked up as usual to give **30** (1.15 g; 98%): partial ^{1}H NMR (CDCl$_3$) δ 1.78, 2.00, 2.06 (9H, 3×s, C*H*$_3$COO), 2.26 (3H, s, C*H*$_3$CO-Lev), 2.74, 2.94 (4H, m, C*H*$_2$C*H*$_2$-Lev), 4.67, 4.87 (2H, 2×d, J=12.7 Hz, C*H*HAr-DOX), 5.14 (1H, brt, H-4$^{\mathrm{II}}$), 5.32 (1H, brt, H-2$^{\mathrm{I}}$), 5.41 (1H, d, $J_{1,2}$=8.0 Hz, H-1$^{\mathrm{II}}$), 5.60 (1H, brd, $J_{3,4}$=2.9 Hz, H-4$^{\mathrm{I}}$), 5.66 (1H, brt, H-3$^{\mathrm{II}}$), 6.80, 6.92 (2×2H, brd, J=7.8 Hz, Ar*H*-DOX), 7.47 (brm, Ar*H*), 7.60 (brm, Ar*H*), 8.02 (m, Ar*H*-Bz), 8.08 (m, Ar*H*-Bz).

4.2.25. (MPEG)(DOX)yl 3-*O*-[3,4,6-tri-*O*-acetyl-2-deoxy-2-*N*-phthalimido-β-D-glucopyranosyl]-2,6-di-*O*-benzoyl-β-D-galactopyranoside 31. Disaccharide (**30**, 0.94 g, 0.16 mmol) was dissolved in pyridine (12 mL) and cooled in an ice bath. To this solution was added sequentially acetic acid (3.0 mL) followed by hydrazine hydrate (300 μL).[35] After 30 min the polymer was worked up as usual except that the ethanol solution was concentrated to dryness and the residue reprecipitated from fresh ethanol to give **31** (0.77 g, 82%): partial ^{1}H NMR (CDCl$_3$) δ 1.78, 2.02, 2.10 (9H, 3×s, C*H*$_3$COO), 4.86 (1H, d, J=11.7 Hz, C*H*HAr-DOX), 5.11 (1H, brt, H-4$^{\mathrm{II}}$), 5.41 (1H, brt, H-2$^{\mathrm{I}}$), 5.56 (1H, d, $J_{1,2}$= 8.0 Hz, H-1$^{\mathrm{II}}$), 5.65 (1H, brt, H-3$^{\mathrm{II}}$), 6.95, 7.00 (2×2H, brd, J=7.8 Hz, Ar*H*-DOX), 7.47 (brm, Ar*H*), 7.60 (brm, Ar*H*), 8.00 (m, Ar*H*-Bz), 8.09 (m, Ar*H*-Bz).

4.2.26. (4-*O*-Acetoxymethyl)-benzyl 3-*O*-[3,4,6-tri-*O*-acetyl-2-deoxy-2-*N*-phthalimido-β-D-glucopyranosyl]-2,6-di-*O*-benzoyl-4-*O*-levulinoyl-β-D-galactopyranoside 32. A portion of **30** (170 mg, 28 μmol) was cleaved with Sc(OTf)$_3$ as for **10**. The residue was purified by preparative TLC eluting with hexanes/ethyl acetate 50:50 to yield known **32**[18] (5 mg, 17%): $[\alpha]_D$=12.9 (*c* 0.18, CHCl$_3$); MS-FAB+ve 886.2 (M−DOX$^+$).

4.2.27. (4-*O*-Acetoxymethyl)-benzyl 3-*O*-(3,4,6-tri-*O*-acetyl-2-deoxy-2-*N*-acetamido-β-D-glucopyranosyl-)-4-*O*-[2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl]-6-*O*-acetyl-2-*O*-benzoyl-β-D-galactopyranoside 36. Disaccharide (**31**, 0.77 g, 0.13 mmol) was glycosylated with 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl-*O*-trichloroacetimidate[36] (**33**) as described in Ref. 13 to yield **34** and then cleaved with Sc(OTf)$_3$ as described above for **10** to yield known trisaccharide **35** after purification by preparative TLC eluting with CH$_2$Cl$_2$/*i*C$_3$H$_7$OH 25:1 followed by Sephadex LH-20 chromatography eluting with chloroform/methanol 4:3. Alternatively **34** (0.93 g, 0.16 mmol) was treated as described for **23** to **24** to yield after MPLC eluting with hexanes/ethyl acetate/ethanol 6:6:1 **36** (18 mg, 10%): ^{1}H NMR (CDCl$_3$) δ 1.42 (3H, s, C*H*$_3$CON), 1.96, 1.99, 2.016, 2.021, 2.077, 2.084, 2.088, 2.11, 2.19 (27H, 9×s, C*H*$_3$COO), 3.61 (1H, m, H-5$^{\mathrm{III}}$), 3.67 (2H, m, H-5$^{\mathrm{I}}$, H-2$^{\mathrm{II}}$), 3.75 (1H, m, H-5$^{\mathrm{II}}$), 3.86 (1H, dd, $J_{2,3}$=10.4 Hz, $J_{3,4}$= 3.1 Hz, H-3$^{\mathrm{I}}$), 4.00 (1H, brd, $J_{6a,6b}$=12.2 Hz, H-6b$^{\mathrm{I}}$), 4.14 (1H, dd, $J_{5,6b}$=3.7 Hz, $J_{6a,6b}$=12.2 Hz, H-6b$^{\mathrm{III}}$), 4.22 (3H, m, H-6b$^{\mathrm{I}}$, H-6a$^{\mathrm{III}}$, H-4$^{\mathrm{I}}$), 4.34 (1H, dd, $J_{5,6b}$=4.3 Hz, $J_{6a,6b}$=11.6 Hz, H-6a$^{\mathrm{I}}$), 4.39 (1H, dd, $J_{5,6b}$=4.9 Hz, $J_{6a,6b}$= 12.2 Hz, H-6a$^{\mathrm{II}}$), 4.43 (1H, d, $J_{1,2}$=8.0 Hz, H-1$^{\mathrm{I}}$), 4.60 (1H, d, J=12.8 Hz, C*H*HAr-DOX), 4.78 (1H, d, J=12.8 Hz, CH*H*Ar-DOX), 4.81 (1H, d, $J_{1,2}$=8.0 Hz, H-1$^{\mathrm{II}}$), 4.93 (1H, dd, $J_{1,2}$=8.0 Hz, $J_{2,3}$=9.8 Hz, H-2$^{\mathrm{III}}$), 5.01 (2H, s, C*H*$_2$Ar-DOX), 5.02 (1H, m, H-4$^{\mathrm{II}}$), 5.11 (1H, brt, $J_{3,4}$=9.8 Hz, $J_{4,5}$=9.8 Hz, H-4$^{\mathrm{III}}$), 5.16 (3H, m, N*H*, H-1$^{\mathrm{III}}$, H-3$^{\mathrm{II}}$), 5.41 (2H, brt, H-2$^{\mathrm{I}}$, H-3$^{\mathrm{III}}$), 7.12 (4H, m, Ar*H*-DOX), 7.49 (2H, brt, J=7.3 Hz, Ar*H*-Bz), 7.63 (1H, brt, J=7.3 Hz, Ar*H*-Bz), 7.97 (2H, brd, J=7.2 Hz, Ar*H*-Bz); ^{13}C NMR (CDCl$_3$) δ 20.6–21.0 (*C*H$_3$COO), 22.5 (*C*H$_3$CON), 55.4 (C-2$^{\mathrm{II}}$), 61.8 (C-6$^{\mathrm{III}}$), 61.9 (C-6$^{\mathrm{II}}$), 63.8 (C-6$^{\mathrm{I}}$), 65.9 (*C*H$_2$Ar-DOX), 68.3 (C-4$^{\mathrm{II}}$), 68.8 (C-4$^{\mathrm{III}}$), 68.9 (*C*HHAr-DOX), 71.0 (C-2$^{\mathrm{I}}$), 71.3 (C-5$^{\mathrm{III}}$), 71.5 (C-3$^{\mathrm{II}}$), 71.9 (C-2$^{\mathrm{III}}$), 72.1 (C-5$^{\mathrm{I}}$, C-5$^{\mathrm{II}}$), 72.8 (C-3$^{\mathrm{III}}$), 73.8 (C-4$^{\mathrm{I}}$),79.6 (C-3$^{\mathrm{I}}$), 98.9 (C-1$^{\mathrm{I}}$), 99.3 (C-1$^{\mathrm{III}}$), 101.3 (C-1$^{\mathrm{II}}$), 128.0, 128.1 (Ar*C*H-DOX), 128.7, 129.5, 129.7 (Ar*C*H-Bz), 133.7 (Ar*C*C-Bz), 135.3, 137.1 (Ar*C*C-DOX), 164.8 (*C*O-Bz), 169.36, 169.45, 169.9, 170.25, 170.36(2), 170.5, 170.66, 170.7 (*C*OO, *C*ON); MS-FAB+ve 1148.3 (M+H$^+$), 968 (M−DOX$^+$), 331 (Ac$_4$Hex$^+$), 330 (Ac$_3$HexNAc$^+$); HRMS C$_{53}$H$_{66}$O$_{27}$N (M+H$^+$, 1148.4047) Calcd 1148.3803.

4.2.28. (4-*O*-Acetoxymethyl)-benzyl 3-*O*-(2-deoxy-2-*N*-acetamido-β-D-glucopyranosyl-)-4-*O*-[β-D-glucopyranosyl]-β-D-galactopyranoside 37. Trisaccharide (**36**, 16 mg, 14 μmol) was dissolved in methanol (5 mL) and 1 M sodium methoxide (0.5 mL) was added. After stirring for 16 h the mixture was neutralized with RexynH$^+$ resin, filtered and concentrated to yield **37** (9 mg, 97%): $[\alpha]_D$= −33.1 (*c* 0.25, CH$_3$OH); ^{1}H NMR (D$_2$O) δ 2.01 (C*H*$_3$CON), 3.29 (1H, dd, $J_{1,2}$=8.6 Hz, $J_{2,3}$=9.2 Hz, H-2$^{\mathrm{III}}$), 3.41 (1H, brt, $J_{3,4}$=9.8 Hz, $J_{4,5}$=9.8 Hz, H-4$^{\mathrm{III}}$), 3.43 (1H, m, H-5$^{\mathrm{III}}$), 3.45 (1H, m, H-5$^{\mathrm{II}}$), 3.50 (1H, brt, $J_{2,3}$=8.6 Hz, $J_{3,4}$=9.2 Hz, H-3$^{\mathrm{III}}$), 3.52 (1H, brt, $J_{3,4}$=9.2 Hz, $J_{4.5}$=9.2 Hz, H-4$^{\mathrm{II}}$), 3.56 (1H, brt, $J_{3,4}$=9.2 Hz, $J_{4,5}$=9.9 Hz, H-3$^{\mathrm{II}}$), 3.67 (1H, brt, J=6.1 Hz, H-5$^{\mathrm{I}}$), 3.68 (1H, m, H-2$^{\mathrm{I}}$), 3.69 (1H, m, H-6b$^{\mathrm{III}}$), 3.70 (1H, m, H-3$^{\mathrm{I}}$), 3.71 (1H, m, H-2$^{\mathrm{II}}$), 3.73 (1H, m, H-6b$^{\mathrm{II}}$), 3.78 (2H, m, H-6a$^{\mathrm{I}}$, H-6b$^{\mathrm{I}}$), 3.92 (2H, brdd, H-6a$^{\mathrm{II}}$, H-6a$^{\mathrm{III}}$), 4.37 (1H, dd, $J_{3,4}$=2.4 Hz, H-4$^{\mathrm{I}}$), 4.45 (1H, d, $J_{1,2}$=7.9 Hz, H-1$^{\mathrm{I}}$), 4.65 (2H, s, C*H*$_2$Ar-DOX), 4.68 (1H, d, $J_{1,2}$=7.9 Hz, H-1$^{\mathrm{II}}$), 4.74 (1H, d, J= 11.6 Hz, C*H*HAr-DOX), 4.88 (1H, d, $J_{1,2}$=7.9 Hz, H-1$^{\mathrm{III}}$), 4.92 (1H, d, J=11.6 Hz, CH*H*Ar-DOX), 7.42 (2H, d, J= 7.9 Hz, Ar*H*-DOX), 7.47 (2H, d, J=7.9 Hz, Ar*H*-DOX);

^{13}C NMR (D$_2$O) δ 23.1 (*C*H$_3$CON), 56.6 (C-2$^{\mathrm{II}}$), 61.4 (C-6$^{\mathrm{I}}$), 61.6 (C-6$^{\mathrm{II}}$, C-6$^{\mathrm{III}}$), 64.5 (*C*H$_2$Ar-DOX), 70.4 (C-4$^{\mathrm{III}}$), 70.7 (C-3$^{\mathrm{III}}$), 71.0 (C-2$^{\mathrm{I}}$), 71.9 (*C*HHAr-DOX), 74.5 (C-2$^{\mathrm{III}}$, C-3$^{\mathrm{II}}$), 75.0 (C-5$^{\mathrm{I}}$), 75.7 (C-4$^{\mathrm{I}}$), 76.5 (C-5$^{\mathrm{III}}$), 76.7 (C-4$^{\mathrm{II}}$, C-5$^{\mathrm{II}}$), 82.9 (C-3$^{\mathrm{I}}$), 102.6 (C-1$^{\mathrm{I}}$), 102.9 (C-1$^{\mathrm{III}}$), 103.9 (C-1$^{\mathrm{II}}$), 128.5, 129.8 (Ar*C*H-DOX), 136.9, 141.1 (Ar*C*C-DOX), 175.7 (CH$_3$*C*ON); MS-FAB+ve 688.2 (M+Na$^+$).

4.2.29. Sodium (4-*O*-acetoxymethyl)-benzyl (5-acetamido-3,5-dideoxy-D-*glycero*-α-D-*galacto*-nonulopyranosylonate-3-*O*-β-D-galactopyranosyl-4-*O*-2-deoxy-2-*N*-acetamido-β-D-glucopyranosyl-)-4-*O*-[-3-*O*-β-D-glucopyranosyl]-β-D-galactopyranoside 39. A fusion enzyme UDP-galactose 4-epimerase/β (1→4)Galactosyltransferase (*GalE-LgtB*, 0.5 units, 3000 μmL) was added to a solution of 2 mM acceptor trisaccharide (**37**, 9.0 mg, 136 μL of 10 mM), 10 mM MnCl$_2$ (70 μL of 1 M), and 1 mM UDP-Glc (340 μL of 20 mM) in 50 mM HEPES buffer (350 μL of 1 M, pH 7.5). The reaction was performed at 37°C for a total of 2 h while two additional portions of 1 mM UDP-Glc (340 μL of 20 mM) were added in 30 min intervals. The formation of **38** (R_f 0.45) was monitored by TLC (MeOH/CHCl$_3$/0.5%CaCl$_2$; 45:45:10). Chromatography of the crude reaction mixture on a C-18 reverse-phase column (water/MeOH 95:5 to 90:10) afforded **38** which was used directly. The reaction was performed in a total volume of 5.0 mL, and the following reagents were added sequentially: acceptor **38**, CTP (14.4 mg) and sialic acid (8.5 mg). The pH was adjusted to 7.0 with 1N NaOH, and 100 mM HEPES (350 μL of 1 M, pH 7.4), 20 mM MgCl$_2$ (700 μL of 100 mM), and 0.2 mM dithiothreitol (14 μL of 100 mM) were added. The reaction was allowed to proceed at 37°C after the addition of the CMP-Neu5Ac synthetase/sialyltransferase fusion enzyme (1.6 units, 250 μL). The reaction progress, i.e. the formation of material having R_f 0.1, was monitored by TLC (MeOH/CHCl$_3$/0.5%CaCl$_2$; 45:45:10). After a total reaction time of 3 h, the crude product was chromatographed on a C-18 reverse-phase column by elution with water followed by 99:1 water/MeOH to yield pure pentasaccharide **39** (5.8 mg, 38%). Before spectroscopic analysis an aqueous solution of the pentasaccharide was passed through a short column of Chelex-100 (Na$^+$ form) and lyophilized, to insure the uniformity of cations present: $[\alpha]_D$=10.2 (*c* 0.31, H$_2$O); ^{1}H NMR (D$_2$O) δ 1.80 (1H, brt, $J_{3ax,3eq}$=12.0 Hz, $J_{3ax,4}$=12.0 Hz, H-3$_{ax}$), 2.01, 2.03 (6H, 2×s, C*H*$_3$CON), 2.76 (1H, dd, $J_{3ax,3eq}$=12.0 Hz, $J_{3eq,4}$=4.5 Hz, H-3$_{eq}$), 3.29 (1H, dd, $J_{1,2}$=8.0 Hz, $J_{2,3}$=9.0 Hz, H-2$^{\mathrm{III}}$), 3.38 (1H, brt, $J_{3,4}$=10.0 Hz, $J_{4,5}$=9.5 Hz, H-4$^{\mathrm{III}}$), 3.44 (1H, m, H-5$^{\mathrm{III}}$), 3.53 (1H, brt, $J_{2,3}$=9.0 Hz, $J_{3,4}$=10.0 Hz, H-3$^{\mathrm{III}}$), 3.57 (1H, brt, $J_{1,2}$=8.0 Hz, $J_{2,3}$=9.5 Hz, H-2$^{\mathrm{IV}}$), 3.58 (1H, m, H-5$^{\mathrm{II}}$), 3.59 (1H, brd, H-7$^{\mathrm{V}}$), 3.64 (2H, m, H-6$^{\mathrm{V}}$, H-9b$^{\mathrm{V}}$), 3.68 (1H, m, H-5$^{\mathrm{IV}}$), 3.69 (1H, m, H-4$^{\mathrm{V}}$), 3.71 (2H, m, H-3$^{\mathrm{II}}$, H-2$^{\mathrm{I}}$), 3.73 (4H, m, H-6b$^{\mathrm{III}}$, H-6a$^{\mathrm{IV}}$, H-6b$^{\mathrm{IV}}$, H-4$^{\mathrm{II}}$, H-5$^{\mathrm{I}}$), 3.75 (1H, m, H-3$^{\mathrm{I}}$), 3.76 (2H, m, H-6a$^{\mathrm{I}}$, H-6b$^{\mathrm{I}}$), 3.80 (1H, m, H-2$^{\mathrm{II}}$), 3.85 (1H, m, H-5$^{\mathrm{V}}$), 3.86 (1H, m, H-6b$^{\mathrm{II}}$), 3.87 (1H, m, H-9a$^{\mathrm{V}}$), 3.90 (1H, m, H-8$^{\mathrm{V}}$), 3.91 (1H, dd, $J_{6a,6b}$=11.0 Hz, $J_{5,6a}$=<1 Hz, H-6a$^{\mathrm{III}}$), 3.96 (1H, brd, $J_{3,4}$=3.0 Hz, H-4$^{\mathrm{IV}}$), 4.00 (1H, brd, $J_{6a,6b}$=11.5, H-6a$^{\mathrm{II}}$), 4.11 (1H, dd, $J_{2,3}$=9.5 Hz, $J_{3,4}$=3.0 Hz, H-3$^{\mathrm{IV}}$), 4.37 (1H, brd, $J_{3,4}$=2.4 Hz, H-4$^{\mathrm{I}}$), 4.46 (1H, d, $J_{1,2}$=7.0 Hz, H-1$^{\mathrm{I}}$), 4.55 (1H, d, $J_{1,2}$=8.0 Hz, H-1$^{\mathrm{IV}}$), 4.65 (2H, s, C*H*$_2$Ar-DOX), 4.69 (1H, d, $J_{1,2}$=7.5 Hz, H-1$^{\mathrm{II}}$), 4.77 (1H, d, *J*=12.0 Hz, C*H*HAr-DOX), 4.89 (1H, d, $J_{1,2}$=8.0 Hz, H-1$^{\mathrm{III}}$), 4.93 (1H, d, *J*=12.0 Hz, CH*H*Ar-DOX), 7.42 (2H, d, *J*=7.5 Hz, Ar*H*-DOX), 7.47 (2H, d, *J*=7.5 Hz, Ar*H*-DOX); ^{13}C NMR (D$_2$O) δ 22.8, 23.0 (2×*C*H$_3$CON), 40.4 (C-3$^{\mathrm{V}}$), 52.4 (C-5$^{\mathrm{V}}$), 56.1 (C-2$^{\mathrm{II}}$), 61.0 (C-6$^{\mathrm{II}}$), 61.3 (C-6$^{\mathrm{I}}$), 61.6 (C-6$^{\mathrm{III}}$), 61.8 (C-6$^{\mathrm{IV}}$), 63.3 (C-9$^{\mathrm{V}}$), 64.3 (*C*H$_2$Ar-DOX), 68.2 (C-4$^{\mathrm{IV}}$), 68.9 (C-7$^{\mathrm{V}}$), 69.1 (C-4$^{\mathrm{V}}$), 70.1 (C-2$^{\mathrm{IV}}$), 70.6 (C-4$^{\mathrm{III}}$), 70.8 (C-2$^{\mathrm{I}}$), 71.8 (*C*HHAr-DOX), 72.5 (C-8$^{\mathrm{V}}$), 72.9 (C-3$^{\mathrm{II}}$), 73.6 (C-6$^{\mathrm{V}}$), 74.3 (C-2$^{\mathrm{III}}$),74.9 (C-5$^{\mathrm{IV}}$), 75.49 (C-5$^{\mathrm{II}}$), 75.50 (C-4$^{\mathrm{I}}$), 75.9 (C-5$^{\mathrm{I}}$), 76.2 (C-3$^{\mathrm{IV}}$), 76.4 (C-5$^{\mathrm{III}}$), 76.6 (C-3$^{\mathrm{III}}$), 78.9 (C-4$^{\mathrm{II}}$), 83.1 (C-3$^{\mathrm{I}}$), 100.6 (C-2$^{\mathrm{V}}$), 102.5 (C-1$^{\mathrm{I}}$), 102.8 (C-1$^{\mathrm{III}}$), 103.3 (C-1$^{\mathrm{IV}}$), 103.9 (C-1$^{\mathrm{II}}$), 128.4, 129.7 (Ar*C*H-DOX), 136.9, 141.0 (Ar*C*C-DOX), 174.6 (C-1$^{\mathrm{V}}$), 175.6, 175.8 (2×CH$_3$*C*ON); MS-MALDI+ve 1141.4 (MH+Na$^+$); HRMS C$_{45}$H$_{69}$N$_2$O$_{30}$Na$_2$ (M+2Na$^+$, 1163.3792) Calcd 1163.3809.

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