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Polymer-Supported Synthesis of a Branched Trisaccharide of the Type IA Group B *Streptococcus* Capsular Polysaccharide: 3-Iodo-4-methoxybenzyl as a New *O*-Protecting Group

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Abstract—The synthesis of a key branched trisaccharide (**1**), of the type IA Group B *Streptococcus* capsular polysaccharide is described. The monomethyl ether of polyethylene glycol (MeO–$(CH_2CH_2O)_n$–H, MPEG) and dioxyxylene [*p*-(O)CH_2–C_6H_4–CH_2(O)–, DOX] have been used as the polymer-support/linker combination. Attempts to use the *p*-methoxybenzyl (PMB) protecting group under glycosylation conditions involving *N*-iodosuccinimide/silver trifuoromethanesulfonate promotion resulted in iodination to form the 3-iodo-4-methoxybenzyl (IPMB) derivative. Subsequently IPMB chloride was independently synthesized and used to introduce this new protecting group. The levulinoyl and the IPMB protecting groups have been used in an orthogonal manner to create 3,4-branching on a galactopyranosyl residue. Due to the enhanced acid stability of the IPMB group over the PMB group, the former group was critical to the success of the synthesis. The final trisaccharide and its intermediates were cleaved from the MPEG polymer-support by scandium(III)trifluoromethanesulfonate and acetic anhydride.

Introduction

The popularity of combinatorial chemistry, and the prospect of automated oligosaccharide synthesis has led to considerable development in the areas of polymer-supported,[1,2] and solid-phase oligosaccharide synthesis.[3] Our interest is to develop efficient and effective methods for the rapid assembly of higher order oligosaccharides by polymer-supported methods. Polymer-supported synthesis on the monomethyl ether of polyethylene glycol (MeO–$(CH_2CH_2O)_n$–H, MPEG) is a powerful tool in organic synthesis.[4] In addition to providing the advantages of solid-phase synthesis, the solubility of MPEG in reaction solvents enables reactions to be performed in a homogenous phase, and to conserve the stereochemical control of solution-phase synthesis. The attractiveness of this method is the ease and the speed of isolation and purification of the polymer-bound product by its precipitation from the solution. Thus, contaminants and excess reagents are removed without tedious and expensive chromatographic purification. Stimulated by the versatility of the combination of MPEG polymer-support and the dioxyxylene [*p*-(O)CH_2–C_6H_4–CH_2(O)–, DOX] linker,[5] we have adopted this approach. The combination [(MPEG)(DOX)OH] has a benzylic ether bond between the polymer and the linker, and one free benzylic hydroxyl for linkage with the growing oligosaccharide chain. We have recently described the novel use of scandium(III)trifluoromethanesulfonate ($Sc(OTf)_3$) and acetic anhydride (Ac_2O), for the cleavage of oligosaccharides bound to PEG via the DOX linker.[6]

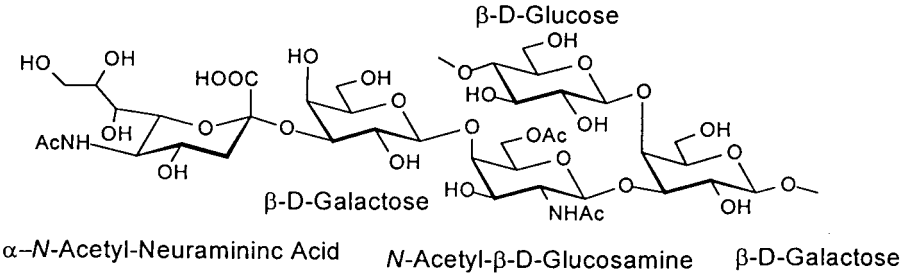

Figure 1. Structure of a single repeat unit of type 1A Group B *Streptococcus* capsular polysaccharide.

Keywords: oligosaccharides; polymer-supported; protecting groups.
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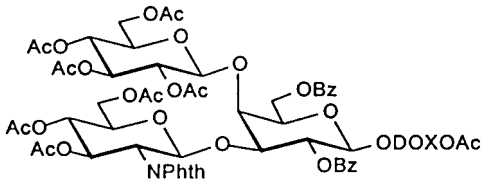

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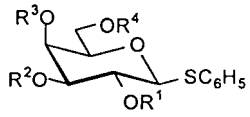
Figure 2. Target branched trisaccharide **1**.



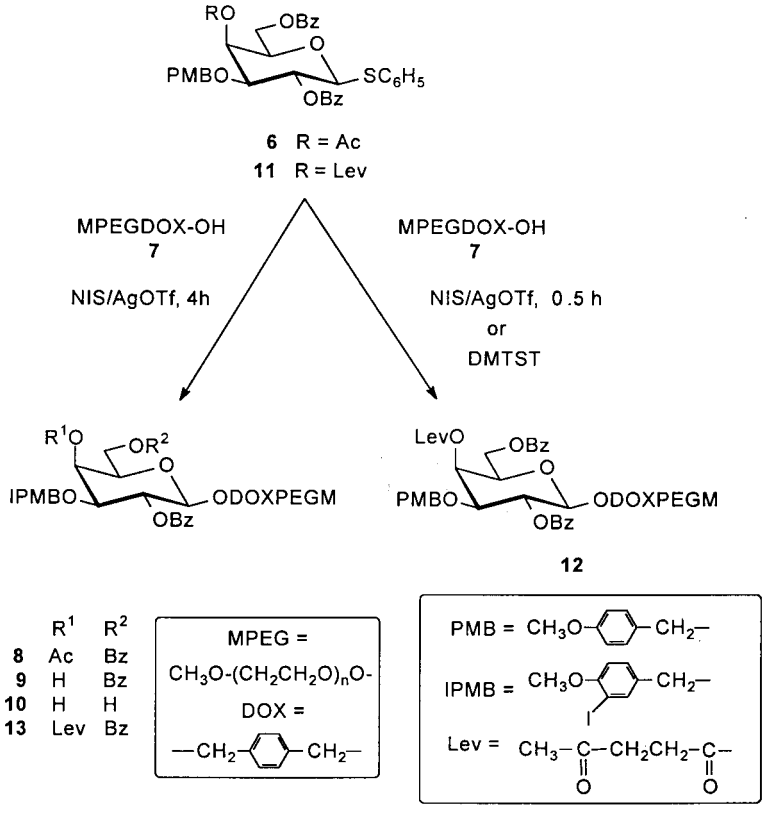
	R^1	R^2	R^3	R^4
2	H	H	H	H
3	H	Bu_2Sn		H
4	H	PMB	H	H
5	Bz	PMB	H	Bz
6	Bz	PMB	Ac	Bz
11	Bz	PMB	Lev	Bz

Figure 3. 4-*O*-Acetyl (**6**) and 4-*O*-Levulinoyl (**11**) building blocks.

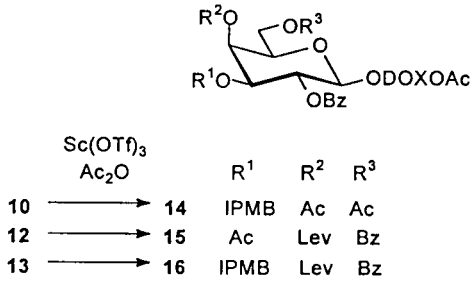
As a part of the process towards the development of vaccines against Group B *Streptococcus* bacteria (Fig. 1), we are involved in a program to synthesize fragments of the serotype specific capsular polysaccharides.[7] We now describe the polymer-supported synthesis of a key branched trisaccharide **1** of type 1A Group B *Streptococcus* capsular polysaccharide (Fig. 2). This requires a galactose building block which can be separately extended at O-3 and O-4. Our first generation building blocks used the acid cleavable isopropylidene ketal protecting group. However, complications from an acyl transfer side reaction and poor O-3/O-4 regioselectivity has led to a search for second generation building blocks.[8] The original formulation of (MPEG)-(DOX) used *O*-benzyl as permanent protecting groups and *O*-acyl as base cleavable protecting groups for chain extension.[5] If *O*-acyl are used for stereochemical control by neighboring group participation then protecting groups cleavable in the presence of acyl and benzyl are required. To date phenylboronate diesters[9] and ketals[8] have been shown to fulfill these criteria. Recently, the combination of *O*-levulinoyl (Lev) and *O*-[9-fluorenylmethoxycarbonyl] (Fmoc) protecting groups has been introduced for this purpose with (MPEG) supported oligosaccharides.[10] In this work we introduce the use of the 3-iodo-4-methoxybenzyl (IPMB) group as a new *O*-protecting group in combination with Lev to achieve the required selectivity.

Results and Discussion

Our strategy was to synthesize a galactopyranosyl building block with persistent benzoyl groups as protecting groups at the O-2 and O-6 positions, and temporary protecting groups at the O-3 and O-4 branching positions. Our initial efforts were focussed on *p*-methoxybenzyl[11] and acetyl groups as the cleavable protecting groups. Treatment of the tetraol **2**[12] with dibutyltin oxide afforded the 3,4-*O*-dibutylstannylene intermediate **3** (Fig. 3).[13] This was reacted with *p*-methoxybenzyl chloride in the presence of cesium fluoride[14] to



Scheme 1.



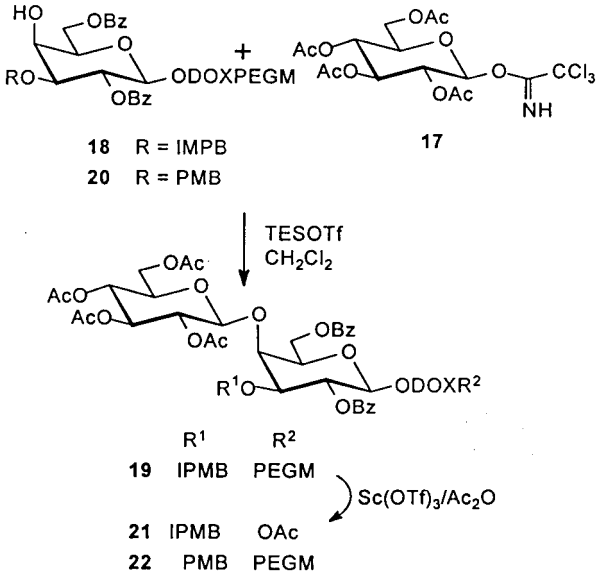
Scheme 2.

produce selectively the 3-*O*-*p*-methoxybenzyl product **4**.[15] Selective benzoylation of the O-2 and O-6 with benzoic anhydride and pyridine did afford the 2,6-di-*O*-benzoate compound **5** in a 50% yield. Also isolated were the 6-*O*-benzoate, 4,6-di-*O*-benzoate and 2,4,6-tri-*O*-benzoate compounds. These compounds were debenzoylated and retreated. Acetylation of **5** afforded the target galactose building block **6** (Fig. 3).

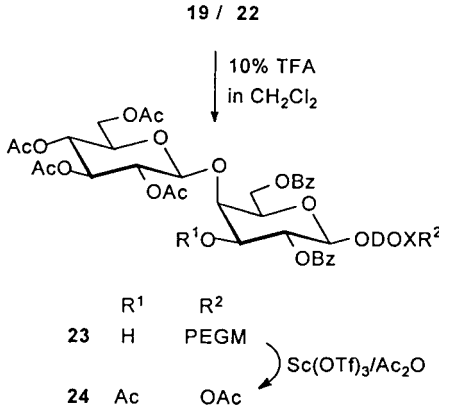
For the synthesis of the trisaccharide MPEG of 5000 molecular weight, was used as the polymer-support with the DOX linker.[5] The first coupling of (MPEG)(DOX)OH **7** with the phenyl thiogalactopyranoside derivative **6** was affected under NIS/silver trifluoromethanesulfonate (AgOTf)[16] promotion at 0–5°C (Scheme 1). According to our earlier investigations, these conditions were the most suitable to avoid the detrimental migration of the benzoyl protecting group at the 2-position of the galactose derivative to the hydroxyl group on the DOX linker.[8] The attempted selective deacetylation at the 4-position of the polymer-bound compound **8**, in the presence of the 2,6-di-*O*-benzoyl protecting groups was problematic. Typically, the selective removal of acetate protecting groups in the presence of benzoate protecting groups is accomplished using 3% HCl in MeOH.[17] However, under these conditions, the simultaneous hydrolysis of the 6-benzoate in compound **8** was observed, and, instead of the desired alcohol **9**, the 4,6-diol **10** was isolated (Scheme 1). At this point, an alternative building block was contemplated and the acetyl group at the 4-position was replaced with a Lev group. The alcohol **5** was transformed into compound **11** by reaction with levulinic acid in the presence of 1,3-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) (Fig. 3). Compound **11** was coupled to the polymer-support under NIS/AgOTf promotion[16] (Scheme 1). Interestingly, depending upon the time of the glycosylation reaction, two different products were isolated. With reaction times of 0.5 h, the expected polymer-bound product **12** was obtained. However, longer reaction times produced a mixture of two compounds. When the reaction was allowed to proceed for 4 h, a single product **13**, was obtained. To our surprise, under the glycosylation conditions, the 4-methoxbenzyl (PMB) protecting group of **12** was iodinated to produce compound **13**. A similar observation of iodination of PMB has been reported but the product was not characterized.[18] Compounds **12** and **13** had very similar NMR spectra, but were differentiated on the basis of the chemical shifts of the aromatic protons of the 4-methoxybenzyl group. As a control experiment, the glycosylation of **7** with **11** was repeated with a non-iodinating promoter, dimethyl(thiomethyl)-sulfonium trifluoromethanesulfonate (DMTST),[19] and the non-iodinated compound **12** was obtained (Scheme 1). For additional proof of structure, and in order to determine the position of iodination, compounds **10**, **12**, and **13**, were cleaved from the polymer support by treatment with scandium(III)trifluoromethanesulfonate ($Sc(OTf)_3$) and acetic anhydride (Ac_2O) to afford **14**, **15** and **16**, respectively (Scheme 2).[6] It is interesting to note that the iodinated-PMB group (IPMB) in **10** and **13** was stable under cleavage conditions. However, the PMB group in **12** was cleaved at room temperature, and the free hydroxyl group at the 3-position was acetylated during treatment with $Sc(OTf)_3/Ac_2O$,[20] to afford **15**.

Complete assignment of the ^1H and ^{13}C NMR signals of the ring, as well as the protecting groups, was accomplished by routine COSY and C–H correlation NMR experiments. The chemical shift of the iodinated carbon atom (C-3 of the IPMB aromatic system) was found to be 85.6 ppm, and was in correspondence with literature values.[21] The position of iodine substitution was further confirmed by TOCSY and HMBC NMR experiments, in particular, HMBC cross-peaks between C-3 and H-2, and C-3 and H-5 of the IPMB aromatic system.

Our attention was next focussed on building block **13**. Selective delevulinoylation of the polymer-bound compound **13** was achieved with a 2% hydrazine hydrate solution in pyridine/acetic acid,[22] to afford **18**. Glycosylation of **18** with trichloroacetimidate donor **17**[23] was performed with TESOTf as promoter,[24] to afford the polymer-bound disaccharide **19** (Scheme 3). Two glycosylations were required for the complete reaction of the polymer-bound galactopyranosyl derivative. It is noteworthy that similar glycosylations of the non-iodinated analog **20** were not as efficient. Disaccharide **19** was cleaved from the polymer with $Sc(OTf)_3/Ac_2O$, and characterized as **21**. The removal of the 3-iodo-4-methoxy benzyl group (IPMB) from **19** was attempted under oxidative conditions, using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ),[11a,11b]



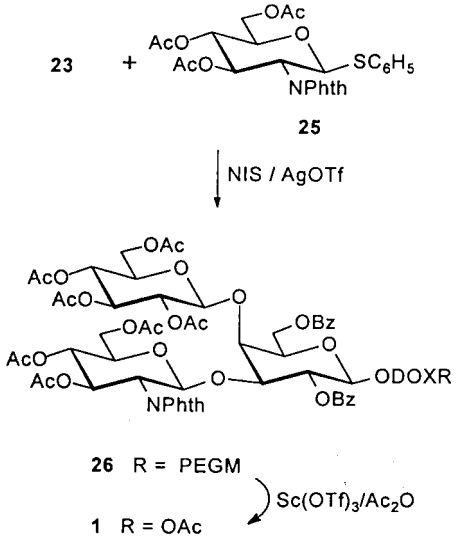
Scheme 3.



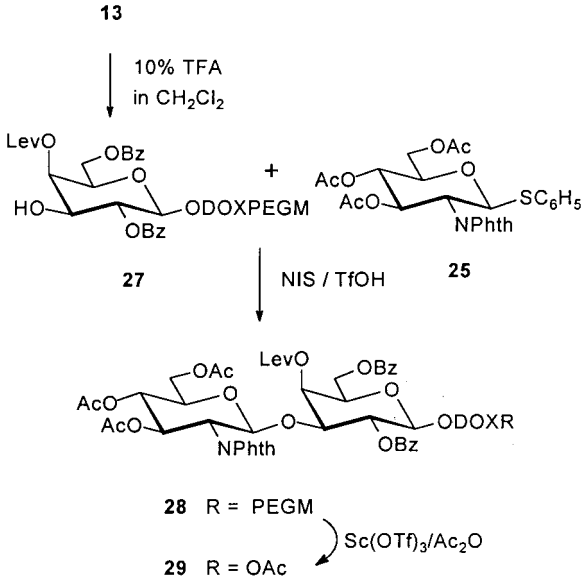
Scheme 4.

as well as cerium(IV) ammonium nitrate (CAN).[25] However, these conditions were not amenable to our substrates linked to the MPEG polymer-support. We attribute these difficulties to the complexation of the reagents to the PEG support as reported for a number of reagents.[26] Further experimentation is necessary to clarify these issues especially in light of the recent report of the successful cleavage of a PEG bound N-PMB group using CAN.[27] The IPMB was removed under acidic conditions, by the treatment of **19** with 10% TFA in dichloromethane,[28] for 24 h (Scheme 4). It is noteworthy that compared to the IPMB group in **19**, the PMB group in the non-iodinated analog **22** was removed with greater ease; the PMB group required 10% TFA treatment for only 12 h. Thus, the acid stability of the IPMB is higher than that of the PMB group. It should be noted that sugar linkages have been reported to be stable in 50% TFA during glycopeptide synthesis.[29] Also, the polymer bound product is precipitated from the 10% TFA solution and is therefore never concentrated in the presence of TFA. Compound **23** was cleaved from the polymer-support with $Sc(OTf)_3/Ac_2O$, and characterized as **24**.

Two sequential glycosylations of **23** with the phenyl thioglycoside **25**,[30] with NIS/AgOTf, afforded the desired



Scheme 5.



Scheme 6.

trisaccharide **26** (Scheme 5). Cleavage of the trisaccharide from the polymer-support, mediated by $Sc(OTf)_3/Ac_2O$, afforded the target trisaccharide **1**. The ^1H and ^{13}C NMR spectra of **1** were completely assigned and are fully consistent with the expected regiochemistry and stereochemistry of the 3,4-branching.

In order to probe the orthogonality of the Lev/IPMB protecting group pair, the selective removal of the IPMB group, in the presence of the Lev group was attempted. Treatment of the polymer-bound galactose derivative **13** with 10% TFA in CH_2Cl_2 for 24 h afforded the alcohol **27** (Scheme 6). The Lev group was unaffected under these conditions and the esters did not migrate. Subsequent glycosylation of **27** with phenyl thioglycoside **25**,[30] under NIS/trifluoromethanesulfonic acid (TfOH) promotion,[16] afforded the polymer-bound disaccharide **28**, which was cleaved from MPEG with $Sc(OTf)_3/Ac_2O$, and characterized as the free disaccharide **29**.

The need for acid cleavable protecting groups, particularly, differentially cleavable protecting groups, is well recognized.[31] Recent reports on the use of aminated benzyl ethers and *p*-hydroxybenzyl derived protecting groups are indicative of the desire for selectively removable hydroxyl group protection, for solution, as well as, solid-phase synthesis.[32]

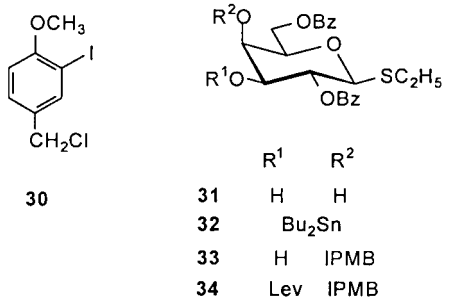
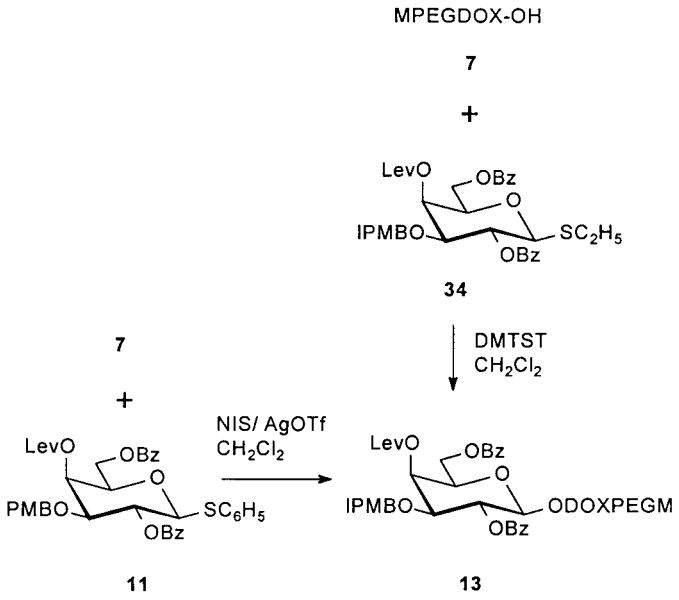


Figure 4. 4-*O*-Levulinoyl and 3-*O*-(3-iodo-4-methoxybenzyl) (**34**) building block.



Scheme 7.

Our observed differences in the properties of the PMB and IPMB ether protecting groups prompted us to investigate the use of IPMB as a novel *O*-protecting group. We describe here the attachment of IPMB group. 3-Iodo-4-methoxybenzyl chloride **30** was synthesized in a manner analogous to that of the 2-iodo compound (Fig. 4).[33] Reaction of chloromethyl methyl ether in glacial acetic acid, with *o*-iodoanisole for 60 h afforded **30**. Treatment of the diol **31**[34] with dibutyltin oxide, followed by cesium fluoride and 3-iodo-4-methoxybenzyl chloride **30** provided **33**, which was levulinoylated at the 4-position to afford **34**. As a control experiment, **34** was coupled to the polymer-support **7** under DMTST promotion ((Scheme 7)). The isolation of polymer-bound substrate **13**, further confirmed the position of iodination to be the 3-position of the PMB group.

In conclusion, this work has described the synthesis of a key branched trisaccharide (**1**), of the type IA Group B *Streptococcus* capsular polysaccharide, by the polymer-supported method, with MPEG and DOX as the polymer-support/linker combination. The IPMB group has been introduced as a new protecting group. The Lev and the IPMB protecting groups are amenable to selective cleavage, and have been used in an orthogonal manner to produce 3,4-branching on the galactopyranosyl residue. The enhanced acid stability of the IPMB group over the PMB group provides a more flexible handle for the use of both these protecting groups on the PEG polymer support, and for more general synthetic applications.

Experimental

Materials and general methods

TLC was performed on Merck Silica gel 60 F_{254} plates and preparative silica gel chromatography on Merck Silica gel 60 (70–230 mesh). For flash chromatography Merck Silica gel 60 (230–400 mesh) was used. Detection was effected by examination under UV light and by charring with 5% sulfuric acid in water. 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. Solutions were concentrated at 1 mmHg pressure in a rotary evaporator. 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 $CDCl_3$ were referenced to residual $CHCl_3$ at 7.24 ppm, and ^{13}C NMR spectra to the central peak of $CDCl_3$ at 77.0 ppm. Assignments were made by standard ^1H–^1H-COSY and ^1H-coupled ^{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. For polymer bound samples the MPEG methylenes were saturated and quantitation was made by comparing integrals to the terminal methyl of the MPEG. Assignments were made by comparison to the spectra of building blocks and cleaved compounds. Advantage was also taken of gradient-enhanced 1D-selective TOCSY and NOESY experiments. Typically 256 transients were used for TOCSY spectra with mixing times from 20 to 150 ms and 4k transients for NOESY spectra with mixing times of 200 to 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, from PerSeptive Biosystems, Framingham, MA, USA. 2,5-Dihydroxybenzoic acid was used as MALDI matrix. Microanalyses were performed by Ms. A. Webb from the analytical services of this department.

(MPEG) general work-up procedure

Typically (MPEG) bound substrates were worked up by precipitation, by adding *tert*-butyl methyl ether (TBME) (10–20 volumes) to the reaction mixtures. The polymer was filtered, rinsed with TBME, and reprecipitated from absolute ethanol (about 50 mL per g). The white precipitate was collected by filtration, rinsed with ethanol then Et_2O, and taken up in CH_2Cl_2 and filtered. The filtrate was evaporated and dried in vacuo to afford the polymer-bound product. Throughout the experimental this procedure will be referred to as standard work up.

Phenyl 2,6-di-*O*-benzoyl-3-*O*-(4-methoxybenzyl)-1-thio-β-D-galactopyranoside (5). Phenyl 1-thio-β-D-galactopyranoside **2**[12] (7.4 g, 27.1 mmol) and dibutyltin oxide (6.8 g, 27.3 mmol) were refluxed in methanol (1.0 L) for 4 h. The solvent was evaporated and the crude stannylene derivative **3** was dried overnight. It was dissolved in *N*,*N*-dimethylformamide (135 mL), and treated with cesium fluoride (5.0 g, 33.0 mmol) and 4-methoxybenzyl chloride (12.0 mL, 81.3 mmol). After 48 h at 30°C, the reaction was concentrated and co-distilled with toluene. The residue was chromatographed with hexane/ethyl acetate/methanol (4:4:1) as eluant to yield phenyl 3-*O*-(4-methoxybenzyl)-1-thio-β-D-galactopyranoside[15] **4** as a white solid (7.0 g, 66%). Triol **4** (1.6 g, 4.1 mmol) was treated with pyridine (30 mL) and benzoic anhydride (2.6 g, 11.5 mmol). The reaction mixture was stirred under argon for 10 days, quenched with methanol and concentrated. The residue was chromatographed with hexane/ethyl acetate (2:1) as eluant. The title compound **5** was obtained as a white solid (1.2 g, 50%). Also isolated were the 2,4,6-tri-*O*-benzoylated, 4,6-di-*O*-benzoylated and the 6-*O*-benzoylated compounds. $[\alpha]_D^{20}=+168.0°$ (*c* 0.5, CH_2Cl_2); ^{13}C NMR ($CDCl_3$): δ 55.0 (O*C*H_3), 64.1 (C-6), 66.5 (C-4), 69.4 (C-2), 71.3 (*C*$H_2C_6H_4$), 76.1 (C-5), 78.5 (C-3), 86.7 (C-1), 113.8 (C3-PMB, C5-PMB), 127.4–133.1 (Ar), 159.4 (C4-PMB), 165.3, 166.4 (2*C*OC_6H_5); ^1H NMR ($CDCl_3$): δ 3.70 (1H, dd, $J_{2,3}$=9.3 Hz, $J_{3,4}$=2.0 Hz, H-3), 3.73 (3H, s, OCH_3), 3.92 (1H, m, H-5), 4.14 (1H, bs, H-4), 4.49 (1H, d, *J*=12.2 Hz, C*H*HC_6H_5), 4.60 (1H, d, *J*=12.2 Hz, C*H*HC_6H_5), 4.64 (1H, dd, $J_{5,6a}$=7.8 Hz, $J_{6a,6b}$=11.2 Hz, H-6a), 4.72 (1H, dd, $J_{5,6b}$=2.9 Hz, $J_{6a,6b}$=11.2 Hz, H-6b), 4.77 (1H, d, $J_{1,2}$=10.3 Hz, H-1), 5.51 (1H, t, $J_{1,2+2,3}$=19.5 Hz, H-2), 6.68 (2H, d, *J*=8.8 Hz, PMB), 7.06–8.08 (17H, Ar); Anal. Calcd for $C_{34}H_{32}O_8S$: C, 67.98; H, 5.37, Found C, 68.03; H, 5.51.

Phenyl 4-*O*-acetyl-2,6-di-*O*-benzoyl-3-*O*-(4-methoxybenzyl)-1-thio-β-D-galactopyranoside (6). Alcohol **5** (100 mg, 0.17 mmol) was treated with pyridine (3 mL) and acetic anhydride (Ac_2O) (3 mL). The reaction was stirred overnight and concentrated. The residue was purified by column chromatography with hexane/ethyl acetate (3:2) as eluant. The title compound **6** was obtained as a white solid (101 mg, 94%). The product was crystallized from ethanol (100%) to afford fluffy white crystals. Mp 165.2°C; $[\alpha]_D^{20}=+97.3°$ (*c* 1.2, CH_2Cl_2); ^{13}C NMR ($CDCl_3$): δ 21.0 (CO*C*H_3), 55.1 (O*C*H_3), 62.9 (C-6), 66.3 (C-4), 69.3 (C-2), 70.7 (*C*$H_2C_6H_4$), 74.8 (C-5), 76.7 (C-3), 87.0 (C-1), 113.6 (C3-PMB, C5-PMB), 127.7–133.3 (Ar), 159.2 (C4-PMB), 165.2, 166.1 (2*C*OC_6H_5), 170.4 (*C*OCH$_3$); ^1H NMR ($CDCl_3$): δ 2.22 (3H, s, COCH_3), 3.71 (1H, dd, H-3), 3.72 (3H, s, OCH_3), 4.04 (1H, m, H-5), 4.36 (1H, d, *J*=12.5 Hz, C*H*HC_6H_5), 4.46 (1H, dd, $J_{5,6a}$=4.9 Hz, $J_{6a,6b}$=11.2 Hz, H-6a), 4.53 (1H, dd, $J_{5,6b}$=8.0 Hz, $J_{6a,6b}$=11.2 Hz, H-6b), 4.60 (1H, d, *J*=12.5 Hz, C*H*HC_6H_5), 4.82 (1H, d, $J_{1,2}$=10.3 Hz, H-1), 5.45 (1H, t, $J_{1,2+2,3}$=20.0 Hz, H-2), 5.67 (1H, d, *J*=2.8 Hz, H-4), 6.61 (2H, d, *J*=8.5 Hz, PMB), 7.03 (2H, d, *J*=8.5 Hz, PMB), 7.06–8.07 (15H, Ar); Anal. Calcd for $C_{36}H_{34}O_9S$: C, 67.28; H, 5.33, Found C, 67.58; H, 5.24.

(MPEG)(DOX)yl 2,6-di-*O*-benzoyl-4-*O*-acetyl-3-*O*-(3-iodo-4-methoxybenzyl)-β-D-galactopyranoside (8). (MPEG)-(DOX)OH **7** (300 mg, 0.06 mmol) and glycosyl donor **6** (60 mg, 0.09 mmol) were dried over drierite/$CaCl_2$ overnight, under vacuum. CH_2Cl_2 (3.0 mL) was added under argon and the reaction flask was cooled to 0°C. *N*-Iodosuccinimide (NIS) (141 mg, 0.6 mmol) was added, followed by silver trifluoromethanesulfonate (AgOTf) (23 mg, 0.09 mmol). The reaction was monitored by TLC for the exhaustion of **6**. The reaction mixture was stirred for 4 h after the colorization of the reaction mixture, and was quenched with diisopropylethylamine (DIPEA). Then standard work up afforded product **8** (290 mg, 97%). ^1H NMR ($CDCl_3$): δ 2.24 (3H, s, COCH_3), 3.38 (3H, s, OCH_3), 3.95 (1H, t, H-5), 4.26 (1H, d, *J*=12.4 Hz, C*H*HC_6H_5), 4.47 (1H, dd, $J_{5,6a}$=6.3 Hz, $J_{6a,6b}$=11.3 Hz, H-6a), 4.5–4.6 (2H, m, C$H_2C_6H_4$-DOX), 4.56 (1H, d, $J_{1,2}$=8.0 Hz, H-1), 4.61 (1H, dd, $J_{5,6b}$=6.9 Hz, $J_{6a,6b}$=11.3 Hz, H-6b), 4.64 (1H, d, *J*=12.7 Hz, C*H*HC_6H_4-DOX), 4.84 (1H, d, *J*=12.7 Hz, C*H*HC_6H_4-DOX), 5.46 (1H, dd, $J_{1,2}$=8.0 Hz, $J_{2,3}$=9.9 Hz, H-2), 5.60 (1H, d, *J*=3.1 Hz, H-4), 6.43 (1H, d, *J*=8.5 Hz, H5-IPMB), 7.04 (1H, d, H6-IPMB), 7.10 (4H, s, DOX), 7.40–7.50 (5H, m, Bz, H2-IPMB), 7.56–7.65 (2H, m, Bz), 7.91 (2H, d, Bz), 8.08 (2H, d, Bz).

Phenyl 2,6-di-*O*-benzoyl-4-*O*-levulinoyl-3-*O*-(4-methoxybenzyl)-1-thio-β-D-galactopyranoside (11). Alcohol **5** (450 mg, 0.75 mmol) was dissolved in anhydrous tetrahydrofuran (THF) (11 mL) and cooled to 0°C. A solution of levulinic acid (0.17 mL, 1.66 mmol) in THF (2 mL) was added, followed by 1,3-dicyclohexylcarbodiimide (DCC) (332 mg, 1.6 mmol) and 4-dimethylaminopyridine (DMAP) (10 mg). The reaction was stirred overnight under argon, quenched with methanol, and filtered through celite and the filtrate evaporated. The residue was purified by column chromatography with hexane/ethyl acetate (2.5:2) as eluant. The title compound **11** was obtained as a white solid (500 mg, 95%). The product was crystallized from hexane/ethyl acetate to afford white crystals. Mp 121.4°C; $[\alpha]_D^{20}=+72.9°$ (*c* 0.5, CH_2Cl_2); ^{13}C NMR ($CDCl_3$): δ 28.1, 38.1 (Lev), 55.1 (O*C*H_3), 63.0 (C-6), 66.5 (C-4), 69.3 (C-2), 70.6 (*C*$H_2C_6H_4$), 74.9 (C-5), 76.5 (C-3), 86.7 (C-1), 113.6 (C3-PMB,C5-PMB), 127.7–133.2 (Ar), 159.2 (C4-PMB), 165.2, 166.1 (2*C*OC_6H_5), 172.1 ($CH_3COCH_2CH_2CO$), 206.2 ($CH_3COCH_2CH_2CO$); ^1H

NMR ($CDCl_3$): δ 2.20 (3H, s, $COCH_3$), 2.67–2.87 (4H, m, $CH_3COCH_2CH_2$), 3.70 (1H, m, $J_{2,3}$=9.7 Hz, $J_{3,4}$=3.2 Hz, H-3), 3.72 (3H, s, OCH_3), 4.05 (1H, m, H-5), 4.33 (1H, d, J=12.2 Hz, $CHHC_6H_5$), 4.48 (1H, dd, $J_{5,6a}$=4.9 Hz, $J_{6a,6b}$=11.5 Hz, H-6a), 4.56 (1H, d, J=12.2 Hz, $CHHC_6H_5$), 4.55 (1H, dd, $J_{5,6b}$=7.6 Hz, $J_{6a,6b}$=11.5 Hz, H-6b), 4.79 (1H, d, $J_{1,2}$=10.1 Hz, H-1), 5.42 (1H, t, $J_{1,2+2,3}$=19.6 Hz, H-2), 5.66 (1H, d, J=3.0 Hz, H-4), 6.61 (2H, d, J=8.5 Hz, PMB), 7.02 (2H, d, J=8.5 Hz, PMB), 7.08–8.06 (15H, Ar); HRMS (FAB) calcd for $C_{39}H_{38}O_{10}SNa$: 721.2083, Found m/z: 721.2127 ($M+Na^+$); Anal. Calcd for $C_{39}H_{38}O_{10}S$: C, 67.03; H, 5.48, Found C, 67.19; H, 5.84.

(MPEG)(DOX)yl 2,6-di-*O*-benzoyl-4-*O*-levulinoyl-3-*O*-(4-methoxybenzyl)-β-D-galactopyranoside (12). A mixture of (MPEG)(DOX)OH **7** (100 mg, 0.02 mmol) and glycosyl donor **11** (20 mg, 0.03 mmol) was dried over drierite/$CaCl_2$, under vacuum overnight. CH_2Cl_2 (1.5 mL) was added under argon and the reaction flask was cooled to 0°C. Dimethyl(methylthio)sulfonium triflate (DMTST) (39 mg, 0.15 mmol) was added. After 5 min the reaction was warmed to room temperature and stirred for 30 min. At this point, TLC indicated exhaustion of **11**. The reaction was cooled to 0°C and quenched with DIPEA. Then standard work up afforded the polymer bound compound **12** (90 mg, 90%). ^{1}H NMR ($CDCl_3$): 2.17 (3H, s, $COCH_3$), 2.71–2.84 (4H, m, $CH_3COCH_2CH_2$), 3.37 (3H, s, OCH_3), 3.59 (H-3), 3.94 (1H, t, H-5), 4.41 (1H, dd, H-6a), 4.48 (1H, d, H-1), 4.82 (1H, d, $CHHC_6H_4$-DOX), 5.42 (1H, t, H-2), 5.59 (1H, d, H-4), 6.58 (2H, d, PMB), 6.99 (2H, d, PMB), 7.07 (4H, m, DOX), 7.43–7.49 (4H, m, Bz), 7.58–7.60 (2H, m, Bz), 7.90 (2H, d, Bz), 8.07 (2H, d, Bz).

(MPEG)(DOX)yl 2,6-di-*O*-benzoyl-4-*O*-levulinoyl-3-*O*-(3-iodo-4-methoxybenzyl)-β-D-galactopyranoside (13). *(1) Prepared from phenyl 2,6-di-O-benzoyl-4-O-levulinoyl-3-O-(4-methoxybenzyl)-1-thio-β-D-galactopyranoside **11** under AgOTf promotion.* Compound **13** was prepared from (MPEG)(DOX)OH **7** (300 mg, 0.06 mmol) and glycosyl donor **11** (60 mg, 0.09 mmol) with NIS (141 mg, 0.6 mmol) and AgOTf (23 mg, 0.09 mmol) as for compound **8** above. The polymer-bound product **13** was obtained (290 mg, 97%).

*(2) Prepared from ethyl 2,6-di-O-benzoyl-4-O-levulinoyl-3-O-(3-iodo-4-methoxybenzyl)-1-thio-β-D-galactopyranoside **34** under DMTST promotion.* (MPEG)(DOX)OH **7** (150 mg, 0.03 mmol) and glycosyl donor **34** (40 mg, 0.05 mmol) were dried over drierite/$CaCl_2$ overnight in vacuo. CH_2Cl_2 (2.0 mL) was added under argon. DMTST (65 mg, 0.25 mmol) was added at 0°C. After 5 min the reaction was warmed to room temperature and stirred for 30 min. At this point, TLC indicated exhaustion of **34**. The reaction was cooled to 0°C and quenched with DIPEA. Then standard work up afforded the polymer bound compound **13** (90 mg, 90%). ^{1}H NMR ($CDCl_3$): δ 2.19 (3H, s, $CH_3COCH_2CH_2$), 2.71–2.85 (4H, m, $CH_3COCH_2CH_2$), 3.39 (3H, s, OCH_3), 3.95 (1H, t, H-5), 4.63 (1H, d, H-1), 5.44 (1H, t, H-2), 5.61 (1H, d, H-4), 6.45 (1H, d, H5-IPMB), 7.04 (1H, d, H6-IPMB), 7.10 (4H, s, DOX), 7.45–7.50 (4H, m, Bz), 7.52 (1H, s, H2-IPMB), 7.61 (2H, t, Bz), 7.93 (2H, d, Bz), 8.09 (2H, d, Bz).

α-*O*-Acetyl-DOXyl 4,6-di-*O*-acetyl-2-*O*-benzoyl-3-*O*-(3-iodo-4-methoxybenzyl)-β-D-galactopyranoside (14). The polymer-bound galactopyranoside **8** (60 mg, 0.01 mmol) was dissolved in Ac_2O (0.5 mL) with heat. $Sc(OTf)_3$ (3 mg, 0.06 mmol) was added and the reaction was stirred under argon for 2 h. The reaction mixture was cooled to 0°C, excess TBME was added and the mixture was stirred for 15 min in order to precipitate the polymer. The precipitate was filtered, the filtrate was concentrated and purified by preparative TLC with hexane/ethyl acetate (1:1) as eluant to yield the title compound **14** (2 mg, 40%). The precipitated polymer was dissolved in CH_2Cl_2, the solution was concentrated and NMR was performed in order to confirm the complete cleavage of the sugar from the polymer. **14** $[\alpha]_D^{20}$=+2.1° (c 0.1, CH_2Cl_2); ^{13}C NMR ($CDCl_3$): δ 20.8, 20.9, 21.0 ($3COCH_3$), 56.2 (OCH_3), 61.9 (C-6), 65.87 (C-4), 65.92 ($CH_2C_6H_4$-DOX), 69.9 ($CH_2C_6H_4$-DOX), 70.6 ($CH_2C_6H_3$), 70.96 (C-2), 71.01 (C-5), 76.3 (C-3), 85.6 (C3-IPMB), 99.5 (C-1), 110.7 (C5-IPMB), 128.0–136.8 (Ar), 129.9 (C6-IPMB), 131.4 (C1-IPMB), 138.9 (C2-IPMB), 157.7 (C4-IPMB), 165.1 (COC_6H_5), 170.5 ($COCH_3$); ^{1}H NMR ($CDCl_3$): 2.10, 2.12, 2.21 (9H, 3s, $3COCH_3$), 3.60 (1H, dd, $J_{2,3}$=10.3 Hz, $J_{3,4}$=3.4 Hz, H-3), 3.76 (3H, s, OCH_3), 3.83 (1H, t, H-5), 4.23–4.28 (3H, m, $CHHC_6H_3$-IPMB, H-6a, H-6b), 4.52–4.56 (2H, m, H-1, $CHHC_6H_3$-IPMB), 4.64 (1H, d, J=12.7 Hz, $CHHC_6H_4$-DOX), 4.87 (1H, d, J=12.7 Hz, $CHHC_6H_4$-DOX), 5.03 (2H, s, $CH_2C_6H_4$-DOX), 5.44 (1H, t, $J_{1,2+2,3}$=17.6 Hz, H-2), 5.53 (1H, d, J=2.9 Hz, H-4), 6.44 (1H, d, J=8.3 Hz, H5-IPMB), 7.05 (1H, d, J=8.3 Hz, H6-IPMB), 7.16 (4H, dd, DOX), 7.45–7.48 (2H, t, Bz), 7.53 (1H, s, H2-IPMB), 7.61 (1H, t, Bz), 7.92 (2H, d, Bz); HRMS (FAB) calcd for $C_{35}H_{37}O_{12}I$: 799.1227, Found m/z: 799.1243 ($M+Na^+$).

α-*O*-Acetyl-DOXyl 3-*O*-acetyl-2,6-di-*O*-benzoyl-4-*O*-levulinoyl-β-D-galactopyranoside (15). The polymer-bound galactopyranoside **12** (50 mg, 0.01 mmol), was dissolved in CH_2Cl_2 (0.5 mL). Ac_2O (0.5 mL) was added and the reaction was cooled to 0°C. $Sc(OTf)_3$ (3 mg, 0.06 mmol) was added and the reaction was stirred under argon for 2 h. Excess TBME was added and the mixture was stirred for 15 min in order to precipitate the polymer. The precipitate was filtered, the filtrate was concentrated and column chromatographed with hexane/ethyl acetate (1:1) as eluant. The title compound **15** was obtained (4 mg, 52%). The precipitated polymer was dissolved in CH_2Cl_2, the solution was concentrated and NMR was performed in order to confirm the complete cleavage of the sugar from the polymer **15**. $[\alpha]_D^{20}$=−2.2° (c 0.2, CH_2Cl_2); ^{13}C NMR ($CDCl_3$): δ 20.5, 21.0 ($2COCH_3$) 27.9 ($CH_3COCH_2CH_2CO$), 29.7 ($CH_3COCH_2CH_2CO$), 37.9 ($CH_3COCH_2CH_2CO$), 61.7 (C-6), 65.9 ($CH_2C_6H_4$-DOX), 67.4 (C-2), 69.5 (C-4), 70.1 ($CH_2C_6H_4$-DOX), 70.8 (C-3), 71.0 (C-5), 99.5 (C-1), 128.0–136.6 (Ar), 165.1, 166.0 ($2COC_6H_5$), 170.2, 170.8 ($2COCH_3$), 172.0 ($CH_3COCH_2CH_2CO$), 206.0 ($CH_3COCH_2CH_2CO$); ^{1}H NMR ($CDCl_3$): δ 1.90, 2.07, 2.17 (9H, 3s, $3COCH_3$), 2.72–2.78 (4H, m, $CH_3COCH_2CH_2$), 4.06 (1H, t, $J_{4,5+5,6}$=13.3 Hz, H-5), 4.35 (1H, dd, $J_{5,6a}$=6.9 Hz, $J_{6a,6b}$=11.5 Hz, H-6a), 4.59 (1H, dd, $J_{5,6b}$=6.9 Hz, $J_{6a,6b}$=11.5 Hz, H-6b), 4.62 (1H, d, $CHHC_6H_4$-DOX), 4.63 (1H, d, $J_{1,2}$=7.8 Hz, H-1), 4.86 (1H, d, $CHHC_6H_4$-DOX), 5.00 (2H, s, $CH_2C_6H_4$-DOX), 5.17 (1H, dd, $J_{2,3}$=10.2 Hz,

$J_{3,4}$=3.4 Hz, H-3), 5.54 (2H, m, $J_{2,3+3,4}$=18.3 Hz, H-2, H-4), 7.11 (4H, dd, DOX), 7.42–7.46 (4H, m, Bz), 7.55–7.60 (2H, q, Bz), 7.95 (2H, d, Bz), 8.02 (2H, d, Bz); HRMS (FAB) calcd for $C_{43}H_{44}O_{13}Na$: 791.2679, Found *m/z*: 791.2702 ($M+Na^+$).

α-*O*-Acetyl-DOXyl 2,6-di-*O*-benzoyl-4-*O*-levulinoyl-3-*O*-(3-iodo-4-methoxybenzyl)-β-D-galactopyranoside (16). Galactopyranoside **13** (200 mg, 0.04 mmol) was dissolved in CH_2Cl_2 (2 mL) and Ac_2O (2 mL) was added. $Sc(OTf)_3$ (15 mg, 0.3 mmol) was added and the reaction mixture was stirred under argon for 3 h. The reaction was cooled to 0°C and treated with excess TBME (100 mL) in order to precipitate the polymer. The polymer was filtered off. The filtrate was concentrated and purified by column chromatography with hexane/ethyl acetate (2.5:2) as eluant, to afford the title compound **16** (20 mg, 50%). The precipitated polymer was dissolved in CH_2Cl_2, the solution was concentrated and NMR was performed in order to confirm the complete cleavage of the sugar from the polymer. **16** $[\alpha]_D^{20}=+15.5°$ (*c* 0.3, CH_2Cl_2); ^{13}C NMR ($CDCl_3$): δ 21.0 ($COCH_3$-DOX), 28.2 ($CH_3COCH_2CH_2CO$), 29.7 ($CH_3COCH_2CH_2CO$), 38.2 ($CH_3COCH_2CH_2CO$), 56.2 (OCH_3), 62.4 (C-6), 65.9 ($CH_2C_6H_4$-DOX), 66.2 (C-4), 69.8 ($CH_2C_6H_3$), 70.1 ($CH_2C_6H_4$), 71.0 (C-2), 71.1 (C-5), 76.4 (C-3), 85.6 (C3-IPMB), 99.3 (C-1), 110.6 (C5-IPMB), 128.0–136.8 (Ar), 129.6 (C6-IPMB), 131.4 (C1-IPMB), 139.0 (C2-IPMB), 157.7 (C4-IPMB), 165.1, 166.2 ($2COC_6H_5$), 170.8 ($COCH_3$-DOX), 172.2 ($CH_3COCH_2CH_2CO$), 206.2 ($CH_3COCH_2CH_2CO$); ^1H NMR ($CDCl_3$): δ 2.10 (3H, s, $COCH_3$-DOX), 2.20 (3H, s, $COCH_3$-Lev), 2.72–2.90 (4H, m, $CH_3COCH_2CH_2CO$), 3.62 (1H, dd, $J_{2,3}$=10.1 Hz, $J_{3,4}$=3.2 Hz, H-3), 3.76 (3H, s, OCH_3), 3.96 (1H, t, $J_{4,5+5,6}$=13.2 Hz, H-5), 4.24 (1H, d, $CHHC_6H_5$), 4.43 (1H, dd, $J_{5,6a}$=6.3 Hz, $J_{6a,6b}$=11.2 Hz, H-6a), 4.52 (1H, d, $CHHC_6H_5$), 4.53 (1H, d, $J_{1,2}$=7.8 Hz, H-1), 4.64 (2H, m, $CH_2C_6H_4$-DOX, H-6b), 5.02 (2H, s, $CH_2C_6H_4$-DOX), 5.44 (1H, t, $J_{1,2+2,3}$=18.0 Hz, H-2), 5.62 (1H, brd, H-4), 6.45 (1H, d, *J*=8.3 Hz, H5-IPMB), 7.04 (1H, d, *J*=8.3 Hz, H6-IPMB), 7.12 (4H, dd, DOX), 7.48 (4H, m, Bz), 7.52 (1H, s, H2-IPMB), 7.61 (2H, t, Bz), 7.93 (2H, brd, Bz), 8.08 (2H, d, Bz); HRMS (FAB) calcd for $C_{43}H_{43}O_{13}INa$: 917.1646, Found *m/z*: 917.1636 ($M+Na^+$); Anal. Calcd for $C_{43}H_{43}O_{13}I$: C, 57.73; H, 4.84, Found C, 57.49; H, 4.91.

(MPEG)(DOX)yl 2,6-di-*O*-benzoyl-3-*O*-(3-iodo-4-methoxybenzyl)-β-D-galactopyranoside (18). Galactopyranoside **13** (700 mg, 0.14 mmol) was treated with a 4:1 solution of pyridine/acetic acid, containing 2% hydrazine hydrate (7 mL). The solution was stirred for 0.5 h, cooled to 0°C, and quenched with excess TBME (500 mL). The reaction was vigorously stirred for 15 min in order to precipitate the polymer. The polymer was filtered and dissolved in hot absolute ethanol (500 mL) and left in the freezer overnight. The white precipitate was collected by filtration, rinsed with Et_2O (2×10 mL) and dried in vacuo to afford the title compound **18** (630 mg, 90%). ^1H NMR ($CDCl_3$): δ 3.38 (3H, s, OCH_3), 4.09 (1H, d, H-4), 4.46 (1H, d, H-1), 5.54 (1H, t, H-2), 6.50 (1H, d, H5-IPMB).

(MPEG)(DOX)yl 2,6-di-*O*-benzoyl-3-*O*-(3-iodo-4-methoxybenzyl)-4-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-β-D-galactopyranoside (19). A mixture of the trichloroacetimidate 17[23] (187 mg, 0.39 mmol) and galactopyranoside **18** (620 mg, 0.13 mmol) was dried over drierite/$CaCl_2$ overnight under vacuum. Anhydrous CH_2Cl_2 (6 mL) was added. It was cooled to −40°C and treated with TESOTf (29 μL, 0.13 mmol). The reaction mixture was stirred for 1 h at −10°C and then for 1 h at 0°C, quenched with DIPEA (two drops). The standard work up afforded the polymer bound disaccharide **19** (610 mg, 98%). The above procedure was repeated to afford the polymer bound disaccharide **19** (600 mg, 97%). ^1H NMR ($CDCl_3$): δ 1.92, 2.03, 2.0, 1.92 (12H, 4s, $4COCH_3$), 3.36 (s, 3H, OCH_3), 4.77 (1H, d, $CHHC_6H_4$-DOX), 4.89 (1H, d, H-1^{II}), 4.98–5.03 (2H, m, H-2^{II}, H-4^{II}), 5.23 (1H, t, H-3^{II}), 5.42 (1H, t, $J_{1,2+2,3}$=17.9 Hz, H-2^{I}), 6.59 (1H, d, *J*=8.3 Hz, aromatic, H5-IPMB), 7.92 (2H, d, Bz); 8.03 (2H, d, Bz).

α-*O*-Acetyl-DOXyl 2,6-di-*O*-benzoyl-3-*O*-(3-iodo-4-methoxybenzyl)-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-β-D-galactopyranoside (21). The polymer bound disaccharide **19** (70 mg, 0.014 mmol) was treated with $Sc(OTf)_3$ (6 mg, 0.01 mmol) in CH_2Cl_2 (1 mL) and Ac_2O (1 mL) as for compound **16** above. The residue was purified by column chromatography with hexane/ethyl acetate (1:1) as eluant. The title compound **21** was obtained (10 mg, 71%). $[\alpha]_D^{20}=-25.0°$ (*c* 0.1, $CHCl_3$); ^{13}C NMR ($CDCl_3$): δ 20.6, 20.7 ($COCH_3$), 56.3 (OCH_3), 61.8 (C-6^{II}), 63.9 (C-6^{I}), 66.0 ($CH_2C_6H_4$-DOX), 68.6 (C-4^{II}), 69.1 ($CH_2C_6H_5$), 71.2 (C-2^{I}), 71.4 (C-2^{II}), 71.7 (C-5^{II}, $CH_2C_6H_5$), 72.2 (C-5^{I}), 72.6 (C-3^{II}), 72.8 (C-4^{I}), 79.6 (C-3^{I}), 99.1 (C-1^{I}), 100.7 (C-1^{II}), 110.8–138.7 (aromatic), 165.0–173.0 ($COCH_3$, COC_6H_5); ^1H NMR ($CDCl_3$): δ 1.99, 2.00, 2.02, 2.06, 2.17, (15H, 5s, $5COCH_3$), 3.55–3.58 (2H, m, H-5^{II}, H-3^{I}), 3.75 (1H, t, $J_{5,6a+5,6b}$=11.8 Hz, H-5^{I}), 3.78 (3H, s, OCH_3), 4.02 (1H, dd, $J_{6a,6b}$=12.1 Hz, H-$6a^{II}$), 4.07–4.12 (2H, m, H-4^{I}, H-$6a^{II}$), 4.41–4.47 (4H, m, H-1^{I}, H-$6a^{I}$, $CH_2C_6H_5$), 4.60 (1H, d, *J*=13.0 Hz, $CHHC_6H_4$-DOX), 4.63 (1H, dd, $J_{5,6a}$=5.3 Hz, $J_{6a,6b}$=11.7 Hz, H-$6a^{I}$), 4.79 (1H, d, *J*=13.0 Hz, $CHHC_6H_4$-DOX), 4.89 (1H, d, $J_{1,2}$=7.9 Hz, H-1^{II}), 4.98 (2H, s, $CH_2C_6H_4$-DOX), 5.02–5.07 (2H, m, H-4^{II}, H-2^{II}), 5.23 (1H, t, $J_{2,3+3,4}$=19.2 Hz, H-3^{II}), 5.42 (1H, t, $J_{1,2+2,3}$=17.8 Hz, H-2^{I}), 6.59 (1H, d, *J*=8.4 Hz, H5-IPMB), 7.05–7.12 (5H, m, DOX, H6-IPMB), 7.42–7.50 (4H, m, Bz), 7.56–7.59 (3H, m, Bz, H2-IPMB), 7.91 (2H, d, *J*=7.7 Hz, Bz), 8.03 (2H, d, *J*=7.7 Hz, Bz); HRMS (FAB) calcd for $C_{52}H_{55}O_{20}INa$: 1149.2228, Found *m/z*: 1149.2275 ($M+Na^+$).

(MPEG)(DOX)yl 2,6-di-*O*-benzoyl-4-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-β-D-galactopyranoside (23). Disaccharide **19** (600 mg, 0.12 mmol) was treated with a 10% TFA solution in CH_2Cl_2 (10 mL) for 24 h. The reaction was cooled to 0°C, quenched with TBME (350 mL), and stirred vigorously for 20 min. in order to precipitate the polymer. The precipitate was filtered and washed well with Et_2O. It was recrystallized in ethanol, overnight. The white precipitate was filtered, rinsed with Et_2O (2×30 mL), collected in CH_2Cl_2 and dried in vacuo to afford the title compound **23** (580 mg, 97%). Compound **23** was characterised as the cleaved compound **24**.

α-*O*-Acetyl-DOXyl 3-*O*-acetyl-2,6-di-*O*-benzoyl-4-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-β-D-galactopyranoside (24). Disaccharide **23** (50 mg, 0.01 mmol) was

treated with $Sc(OTf)_3$ (3 mg) in Ac_2O (1 mL) as for compound **14**. The residue was purified by preparative thin layer chromatography with hexane/ethyl acetate (2:3) as eluant. The title compound **24** was obtained (4 mg, 60%). ^{13}C NMR ($CDCl_3$): δ 20.57, 20.60, 20.63, 20.7, 20.8, 21.0 (6CO*C*H_3), 61.7 (C-6^{II}), 63.7 (C-6^{I}), 66.0 (*C*$H_2C_6H_4$-DOX), 68.4 (C-4^{II}), 69.5 (*C*$H_2C_6H_4$-DOX), 69.6 (C-2^{I}), 71.4 (C-2^{II}), 71.8 (C-5^{II}), 72.2 (C-5^{I}), 72.5 (C-3^{II}), 73.2 (C-3^{I}), 74.2 (C-4^{I}), 99.0 (C-1^{I}), 101.3 (C-1^{II}), 128.1–140.8 (aromatic), 165.0–173.0 (*C*OCH$_3$, *C*OC_6H_5); ^1H NMR ($CDCl_3$): δ1.98, 2.01, 2.02, 2.06, 2.21 (18H, 5s, 6COC*H*$_3$), 3.59 (1H, m, H-5^{II}), 3.90 (1H, t, $J_{5,6a+5,6b}$= 11.2 Hz, H-5^{I}), 3.97 (1H, dd, $J_{5,6a}$=2.3 Hz, $J_{6a,6b}$=12.2 Hz, H-6a^{II}), 4.08 (1H, dd, $J_{5,6a}$=4.5 Hz, $J_{6a,6b}$=12.2 Hz, H-6b^{II}), 4.23 (1H, t, $J_{3,4+4,5}$=2.6 Hz, H-4^{I}), 4.46 (1H, dd, $J_{5,6a}$=6.8 Hz, $J_{6a,6b}$=11.6 Hz, H-6a^{I}), 4.55 (1H, d, $J_{1,2}$=7.9 Hz, H-1^{I}), 4.59 (1H, d, $J_{1,2}$=8.0 Hz, H-1^{II}), 4.62 (1H, d, J=12.7 Hz, C*H*HC_6H_4-DOX), 4.65 (1H, dd, $J_{5,6b}$=5.2 Hz, $J_{6a,6b}$=11.6 Hz, H-6b^{I}), 4.81 (1H, d, J=12.7 Hz, C*H*HC_6H_4-DOX), 4.99 (2H, s, C$H_2C_6H_4$-DOX), 5.03–5.08 (3H, m, H-3^{I}, H-2^{II}, H-4^{II}), 5.23 (1H, t, $J_{2,3+3,4}$=19.2 Hz, H-3^{II}), 5.44 (1H, t, $J_{1,2}$=7.9 Hz, $J_{2,3}$=10.0 Hz, H-2^{I}), 7.07–7.12 (4H, m, DOX), 7.41–7.47 (4H, m, Bz), 7.57 (2H, t, Bz), 7.92 (2H, d, J=7.3 Hz, Bz), 8.03 (2H, d, J=7.3 Hz, Bz); HRMS (FAB) calcd for $C_{46}H_{50}O_{20}Na$: 945.2792, Found *m/z*: 945.2745 (M+Na$^+$).

(MPEG)(DOX)yl 2,6-di-*O*-benzoyl-4-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-3-(3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-β-D-galactopyranoside (26). A mixture of phenyl (3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido)-1-thio-β-D-glucopyranoside 25[30] (125 mg, 0.24 mmol) and disaccharide **23** (600 mg, 0.12 mmol) was dried over P_2O_5 overnight under vacuum. Anhydrous CH_2Cl_2 (6 mL) was added. The reaction mixture was cooled to 0°C and treated with NIS (270 mg, 1.2 mmol) and AgOTf (62 mg, 0.24 mmol). The reaction mixture was stirred for 1 h at 0°C and quenched with DIPEA (two drops). Then standard work up afforded the polymer bound trisaccharide **26** (575 mg, 89%). The above procedure was repeated to afford the polymer bound trisaccharide **26** (550 mg, 86%). Compound **26** was characterized as the cleaved compound **1**.

α-*O*-Acetyl-DOXyl 2,6-di-*O*-benzoyl-4-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-3-(3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-β-D-galactopyranoside (1). Trisaccharide **26** (550 mg, 0.1 mmol) was treated with $Sc(OTf)_3$ (25 mg, 0.05 mmol) in CH_2Cl_2 (1 mL) and Ac_2O (1 mL) as for compound **16** above. The residue was purified by column chromatography with hexane/ethyl acetate (1:1) as eluant. The title compound **1** was obtained (14 mg, 13%). $[\alpha]_D^{20}$=+2.0° (*c* 0.2, CH_2Cl_2); ^{13}C NMR ($CDCl_3$): δ 20.03–20.73 (CO*C*H_3), 54.4 (C-2^{III}), 61.5 (C-6^{I}), 61.6 (C-6^{III}), 63.8 (C-6^{II}), 65.7 (*C*$H_2C_6H_4$-DOX), 68.4 (C-4^{III}), 68.7 (*C*$H_2C_6H_4$-DOX), 68.7 (C-4^{II}), 69.9 (C-3^{III}), 70.6 (C-2^{I}), 71.4 (C-2^{II}), 71.4 (C-5^{III}), 71.3 (C-5^{II}), 71.9 (C-5^{I}), 72.9 (C-3^{II}), 73.9 (C-4^{I}), 79.6 (C-3^{I}), 98.6 (C-1^{I}), 99.02 (C-1^{III}), 99.7 (C-1^{II}), 128.0–133.7 (aromatic), 165.0–173.0 (*C*OCH$_3$, *C*OC_6H_5); ^1H NMR ($CDCl_3$): δ 1.80, 1.90, 2.02, 2.06, 2.09, 2.15 (24H, 6s, 8COC*H*$_3$), 3.80 (H-5^{II}), 3.81 (H-5^{I}), 3.85 (H-5^{III}), 3.92 (1H, dd, $J_{2,3}$=10.3 Hz, H-3^{I}), 4.09 (H-6a^{III}), 4.13 (1H, dd, H-6a^{I}), 4.20 (1H, dd, $J_{5,6a}$=3.9 Hz, $J_{6a,6b}$=11.7 Hz, H-6b^{I}), 4.32 (H-2^{III}), 4.34 (H-4^{I}), 4.35 (H-1^{I}), 4.45 (H-6a^{II}), 4.51 (H-6b^{III}), 4.52 (1H, d, C*H*HC_6H_4-DOX), 4.64 (H-6b^{II}), 4.66 (1H, d, CH*H*C_6H_4-DOX), 4.97 (2H, s, C$H_2C_6H_4$-DOX), 5.05 (H-2^{II}), 5.13 (H-4^{II}), 5.16 (H-1^{II}), 5.20 (H-4^{III}), 5.24 (H-2^{I}), 5.47 (1H, t, $J_{2,3+3,4}$=18.6 Hz, H-3^{II}), 5.49 (1H, d, $J_{1,2}$=8.3 Hz, H-1^{III}), 5.68 (1H, t, $J_{2,3+3,4}$=19.5 Hz, H-3^{III}), 6.95 (4H, m, DOX), 7.20–8.10 (14H, aromatic). MS (MALDI) calcd for $C_{64}H_{67}NO_{28}Na$: 1320.37, Found *m/z*: 1320.66 (M+Na$^+$) and MS (FAB) calcd for $C_{64}H_{67}NO_{28}K$: 1336.35, Found *m/z*: 1336.1 (M+K$^+$), *m/z* 1118.1 (M-DOX$^+$).

(MPEG)(DOX)yl 2,6-di-*O*-benzoyl-4-*O*-levulinoyl-3-*O*-(3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-β-D-galactopyranoside (28). A mixture of 25[30] (60 mg, 0.12 mmol) and **27** (300 mg, 0.06 mmol, prepared from **13** as for **23**) was dried over P_2O_5 under vacuum overnight. Anhydrous CH_2Cl_2 (3 mL) was added. The reaction mixture was treated with NIS (67 mg, 0.3 mmol) and triflic acid (3.0 μL, 0.036 mmol). The reaction mixture was stirred for 2 h at room temperature and quenched with DIPEA (two drops). Then standard work up afforded the polymer bound disaccharide **28** (290 mg, 97%). Compound **28** was characterized as the cleaved compound **29**.

α-*O*-Acetyl-DOXyl 2,6-di-*O*-benzoyl-4-*O*-levulinoyl-3-*O*-(3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-β-D-galactopyranoside (29). Polymer-bound disaccharide **28** (270 mg, 0.06 mmol) was treated with $Sc(OTf)_3$ (15 mg, 0.3 mmol) in CH_2Cl_2 and Ac_2O as for compound **16** above. The residue was purified by column chromatography with hexane/ethyl acetate (1:1) as eluant. The title compound **29** was obtained (10 mg, 16%). ^{13}C NMR ($CDCl_3$): δ 20.4, 20.6, 21.0 (3CO*C*H_3), 28.1 ($CH_3COCH_2CH_2CO$), 29.8 (*C*$H_3COCH_2CH_2CO$), 38.2 ($CH_3COCH_2CH_2CO$), 54.4 (C-2^{II}), 61.5 (C-6^{II}), 62.7 (C-6^{I}), 65.9 (*C*$H_2C_6H_4$-DOX), 68.8 (C-4^{II}), 69.4 (*C*$H_2C_6H_4$-DOX), 69.7 (C-4^{I}), 70.2 (C-3^{II}), 70.8 (C-2^{I}), 71.5 (C-5^{I}), 71.8 (C-5^{II}), 77.2 (C-3^{I}), 98.4 (C-1^{II}), 98.8 (C-1^{I}), 128.0–133.7 (aromatic), 165.0–173.0 (*C*OCH$_3$, *C*OC_6H_5); ^1H NMR ($CDCl_3$): δ 1.70, 2.0, 2.06, 2.23, 2.26 (15H, 5s, 5COC*H*$_3$), 2.78 ($CH_3COCH_2CH_2CO$), 3.78 (1H, m, H-5^{II}), 3.96 (2H, m, H-3^{I}, H-5^{I}), 4.12 (1H, H-6a^{II}), 4.22 (1H, H-2^{I}), 4.30 (1H, H-6b^{II}), 4.41 (1H, H-1^{I}), 4.44–4.58 (2H, H-6a^{I}, H-6b^{I}, C*H*HC_6H_4-DOX), 4.72 (1H, d, CH*H*C_6H_4-DOX), 4.98 (2H, s, C$H_2C_6H_4$-DOX), 5.13 (H-4^{II}), 5.31 (H-2^{I}), 5.43 (1H, d, $J_{1,2}$=8.3 Hz, H-1^{II}), 5.61 (H-4^{I}), 5.68 (1H, t, $J_{2,3+3,4}$=19.5 Hz, H-3^{II}), 6.96 (4H, m, DOX), 7.28–8.18 (14H, aromatic). MS(MALDI-TOF) calcd for $C_{55}H_{55}NO_{21}Na$: 1089.03, Found *m/z*: 1088.42 (M+Na$^+$).

3-Iodo-4-methoxybenzyl chloride (30). Chloromethyl methyl ether (2.0 mL, 0.027 mmol) was dissolved in glacial acetic acid (35 mL) and treated with *o*-iodoanisole (1.5 mL, 0.012 mmol). The reaction mixture was stirred at 55°C for 60 h. The mixture was poured over ice, extracted into CH_2Cl_2 and washed with water. The organic extract was dried over sodium sulphate, filtered and concentrated. The residue was purified by column chromatography with hexane/ethyl acetate (5:1) as eluant to afford the title compound **30** (2.5 g, 74%). The product was recrystallized from hexane/ethyl acetate to afford needle shaped crystals;

mp 47.3°C. ^{13}C NMR ($CDCl_3$): δ 45.0 (CH_2), 56.4 (OCH_3), 85.9 (C-3), 110.7 (C-5), 130.0 (C-6), 131.6 (C-1), 139.7 (C-2), 158.2 (C-4); ^{1}H NMR ($CDCl_3$): δ 3.89 (3H, s, OCH_3), 4.52 (2H, s, CH_2), 6.81 (1H, d, J=8.3 Hz, H-5), 7.34 (1H, d, J=8.3 Hz, H-6), 7.81 (1H, s, H-2); Anal. Calcd for C_8H_8OClI: C, 34.00; H, 2.85, Found C, 34.22; H, 2.91.

Ethyl 2,6-di-*O*-benzoyl-3-*O*-(3-iodo-4-methoxybenzyl)-1-thio-β-D-galactopyranoside (33). A mixture of **31**[34] (200 mg, 0.42 mmol) and dibutyltin oxide (104 mg, 0.42 mmol) were refluxed in toluene (20 mL) for 7 h. The solvent was evaporated and the crude stannylene derivative **32** was dried in vacuo. It was dissolved in dry *N*,*N*-dimethylformamide (2.0 mL), and treated with cesium fluoride (76 mg, 0.42 mmol) and 3-iodo-4-methoxybenzyl chloride **30** (356 mg, 1.26 mmol). The reaction was stirred at 55°C for 7 h, cooled to room temperature, quenched with excess methanol, and concentrated. The residue was chromatographed with hexane/ethyl acetate (2:1) as eluant. The title compound **33** was obtained as a white solid (170 mg, 60%). $[\alpha]_D^{20}$=+30.1° (*c* 0.8, CH_2Cl_2); ^{13}C NMR ($CDCl_3$): δ 14.9 (SCH_2CH_3), 24.0 (SCH_2CH_3), 56.2 (OCH_3), 63.6 (C-6), 66.6 (C-4), 69.5 (C-2), 70.6 ($CH_2C_6H_3$), 76.0 (C-5), 79.2 (C-3), 83.6 (C-1), 85.7 (C3-IPMB), 110.7 (C5-IPMB), 128.4–133.1 (Ar), 139.0 (C2-IPMB), 157.9 (C4-IPMB), 165.3, 166.4 ($2COC_6H_5$); ^{1}H NMR ($CDCl_3$): δ 1.22 (3H, t, SCH_2CH_3), 2.64 (1H, bs, OH), 2.64–2.76 (2H, m, J=14.7 Hz, SCH_2CH_3), 3.69 (1H, dd, $J_{2,3}$=9.3 Hz, $J_{3,4}$=2.5 Hz, H-3), 3.70 (3H, s, OCH_3), 3.90 (1H, m, H-5), 4.17 (1H, bs, H-4), 4.43 (1H, d, J=12.2 Hz, $CHHC_6H_3$), 4.55 (1H, d, $J_{1,2}$=10.3 Hz, H-1), 4.59 (1H, d, J=12.2 Hz, $CHHC_6H_3$), 4.62 (1H, dd, H-6a), 4.69 (1H, dd, $J_{5,6b}$=5.4 Hz, $J_{6a,6b}$=11.7 Hz, H-6b), 5.51 (1H, t, $J_{1,2+2,3}$=19.1 Hz, H-2), 6.52 (1H, d, J=8.3 Hz, H5-IPMB), 7.12 (1H, dd, J=8.3 Hz, H6-IPMB), 7.47 (4H, m, Bz), 7.59 (3H, m, H2-IPMB, Bz), 8.0 (2H, d, J=7.8 Hz, Bz), 8.07 (2H, d, J=7.8 Hz, Bz); HRMS (FAB) calcd for $C_{30}H_{31}O_8ISNa$: 701.0649, Found *m*/*z*: 701.0661 ($M+Na^+$).

Ethyl 2,6-di-*O*-benzoyl-4-*O*-levulinoyl-3-*O*-(3-iodo-4-methoxybenzyl)-β-D-thio-galactopyranoside (34). Compound **33** (135 mg, 0.2 mmol) was dissolved in anhydrous THF (4 mL) and cooled to 0°C. A solution of levulinic acid (0.04 mL, 0.4 mmol) in THF (1 mL) was added, followed by DCC (82 mg, 0.4 mmol) and DMAP (3.0 mg). The reaction was stirred overnight under argon. It was quenched with methanol and filtered through celite. The residue was purified by column chromatography with hexane/ethyl acetate (2:1) as eluant. The title compound **34** was obtained as a white solid (130 mg, 84%). $[\alpha]_D^{20}$=+30.1° (*c* 0.8, CH_2Cl_2); ^{13}C NMR ($CDCl_3$): δ 14.9 (SCH_2CH_3), 24.3 (SCH_2CH_3), 28.1 ($CH_3COCH_2CH_2CO$), 29.8 ($CH_3COCH_2CH_2CO$), 38.2 ($CH_3COCH_2CH_2CO$), 56.2 (OCH_3), 62.5 (C-6), 66.6 (C-4), 69.2 (C-2), 70.1 ($CH_2C_6H_3$), 74.8 (C-5), 77.5 (C-3), 84.0 (C-1), 85.6 (C3-IPMB), 110.6 (C5-IPMB), 128.4–136.8 (Ar), 129.6 (C6-IPMB), 139.1 (C2-IPMB), 157.7 (C4-IPMB), 165.2, 166.2 ($2COC_6H_5$), 172.2 ($CH_3COCH_2CH_2CO$), 206.2 ($CH_3COCH_2CH_2CO$); ^{1}H NMR ($CDCl_3$): δ 1.24 (3H, t, J=14.7 Hz, SCH_2CH_3), 2.19 (3H, s, $COCH_3$-Lev), 2.71–2.90 (6H, m, $CH_3COCH_2CH_2CO$, SCH_2CH_3), 3.72 (1H, dd, $J_{2,3}$=9.8 Hz, $J_{3,4}$=3.4 Hz, H-3), 3.77 (3H, s, OCH_3), 4.04 (1H, t, $J_{4,5+5,6}$=14.0 Hz, H-5), 4.28 (1H, d, J=12.2 Hz, $CHHC_6H_3$), 4.40 (1H, dd, $J_{5,6a}$=5.9 Hz, $J_{6a,6b}$=11.2 Hz, H-6a), 4.54 (1H, d, J=12.2 Hz, $CHHC_6H_3$), 4.58 (1H, dd, $J_{5,6b}$=6.8 Hz, $J_{6a,6b}$=11.2 Hz, H-6b), 4.61 (1H, d, $J_{1,2}$=10.3 Hz, H-1), 5.41 (1H, t, $J_{1,2+2,3}$=19.5 Hz, H-2), 5.68 (1H, d, $J_{3,4+4,5}$=2.9 Hz, H-4), 6.47 (1H, d, J=8.3 Hz, H5-IPMB), 7.05 (1H, dd, J=8.3 Hz, J=2.0 Hz, H6-IPMB), 7.47 (4H, m, Bz), 7.54 (1H, d, J=2.0 Hz, H2-IPMB), 7.59 (2H, m, Bz), 7.98 (2H, d, Bz), 8.06 (2H, d, Bz).; HRMS (FAB) calcd for $C_{35}H_{37}O_{10}ISNa$: 799.1050, Found *m*/*z*: 799.1066 ($M+Na^+$); Anal. Calcd for $C_{35}H_{37}O_{10}IS$: C, 54.13; H, 4.80, Found C, 54.47; H, 4.86.

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