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Note

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Chemoselective cleavage of *para*-methoxy benzyl and 2-naphthylmethyl ethers using a catalytic amount of HCl in hexafluoro-*iso*-propanol

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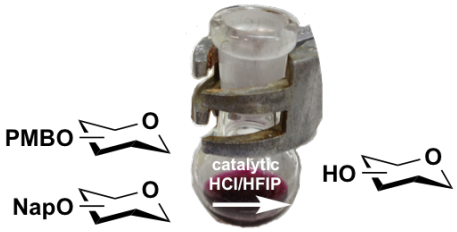


Abstract

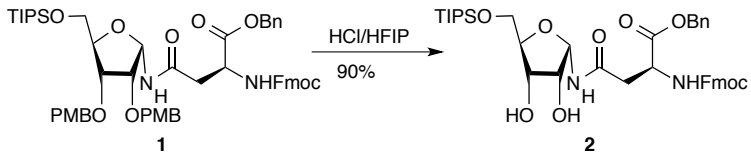
A new, fast, mild and chemoselective deprotection method to cleave p-methoxybenzyl and 2-naphthylmethyl ethers using catalytic amounts of hydrochloric acid in a 1:1 mixture of hexafluoro-*iso*-propanol (HFIP) and methylene chloride (DCM) is described. The scope of the methodology becomes apparent from fourteen examples of orthogonally protected monosaccharides that are subjected to HCl/HFIP treatment. The applicability of the HCl/HFIP method is illustrated by the synthesis of a sulfated β-mannuronic acid disaccharide.

Protecting groups play a pivotal role in synthetic organic chemistry.[1] In oligosaccharide synthesis protecting groups are used to (temporarily) mask hydroxyl

and amino groups to allow for selective modification of other functionalities on the carbohydrate ring. Besides blocking specific functionalities that otherwise would partake in a glycosylation event, the protective group pattern of carbohydrate building blocks also has a profound effect on the outcome of a glycosylation reaction in terms of yield and stereoselectivity. Various types of protecting groups are available to mask carbohydrate hydroxyls, and amongst the most commonly used groups are the benzyl-type ethers. Besides being robust to a wide variety of reaction conditions, the sterically minimally intrusive benzyl-type ethers stand out because of their non-participating nature. Therefore benzyl-type ethers are often the group of choice to protect the C-2-OH when 1,2-*cis* linkages are to be installed. Substituted benzyl ethers, such as the *p*-methoxybenzyl (PMB) and 2-naphthylmethyl (Nap) ether are attractive, electron rich benzyl ethers, as they can be removed en route to the oligosaccharide because using oxidative or acidic cleavage conditions.[2] For their removal, generally strong oxidizing agents, such as ceric ammonium nitrate or 1,2-dichloro-3,4-dicyano-quinone (DDQ), in combination with biphasic reaction media, are used. These conditions can be disadvantageous when dealing with sensitive compounds or solid phase reactions.[2] Alternatively, the PMB and Nap groups can be split off under acidic conditions, using a large molar excess of rather strong Brønsted or Lewis acids such as TFA[3] or HF.pyridine[4], the use of which can jeopardize the integrity of acid labile functionalities in the molecule (acetals, silyl ethers etc.). Recently introduced methods to cleave PMB ethers include the use of $FeCl_3$[5] and $AgSbF_6$/trimethoxybenzene.[6] These methods require relatively long reaction times and have not been employed to remove the more stable Nap ethers. The invention of mild, homogeneous and fast reaction conditions to selectively remove PMB or

Nap ethers will make these groups even more useful in (carbohydrate) synthesis and open up routine application in both solution and solid phase settings.

In search of such a reagent we were drawn to the work of Palladino and Stetsenko, who recently described the use of hydrochloric acid in a fluorinated alcohol, such as hexafluoro-*iso*-propanol (HFIP),[7] to unmask *tert*-butyl protected hydroxyl and carboxylic acid functions in solid phase peptide synthesis.[8,9] The reactivity of this deprotection system arises from the effective hydrogen bonding of the fluorinated alcohol to the chloride leading to the generation of "naked" protons. In the synthesis of poly adenoside diphosphate ribosylated (poly-ADPR) peptides we required mild conditions to transform ribosyl glutamine **1** into building block **2**, suitable for solid phase synthesis (See Scheme 1).



1 **2**

Scheme 1: HCl/HFIP in poly-ADPR synthesis

To this end both PMB ethers at the C2 and C3 positions, installed to allow for the stereoselective construction of the 1,2-*cis* ribosyl linkage, had to be removed. We found that the use of TFA in DCM rapidly cleaved both ethers but also led to substantial epimerization at the anomeric center. The use of oxidative conditions (DDQ in DCM/H_2O) led to the formation of several side products. In contrast, the use of a catalytic amount of HCl in HFIP prevented these side reactions and resulted in the clean removal of the PMB ethers. Encouraged by this profitable outcome we set out to explore the scope and limitations of the latter cleavage method, the result of

which we present here. We have found that a catalytic amount of HCl can be sufficient to cleave both PMB and Nap ethers, while chemoselectivity between these two ethers can also be attained. We demonstrate the applicability of the use of Nap-ethers and their HCl/HFIP mediated removal in the synthesis of a sulfated mannuronic acid disaccharide. The non-participating nature of the Nap-ethers in the building blocks used in this synthesis is crucial for the stereoselective formation of the β-mannuronic acid linkage.[10]

The first substrate we subjected to a catalytic amount of HCl (0.1 equiv) in DCM/HFIP was O-glycoside **3**, carrying a PMB group at C-4 (Table 1, entry 1). Upon addition of a preformed HCl/HFIP mixture to a solution of **3** in DCM/HFIP, the reaction mixture turned dark purple within seconds, indicative for the formation of *para*-methoxybenzyl cationic species. Within minutes all substrate had been consumed and transformed into a single product (**4**). Besides the formation of the desired alcohol, TLC analysis showed the formation of a lipophilic side product. LC-MS analysis of this side product indicated this to be a PMB derived polymer, indicating that the PMB cations, released during the reaction are not scavenged by HFIP, but in stead react with another PMB ether in a Friedel-Crafts manner, resulting in the formation of the polymer.[5,11]

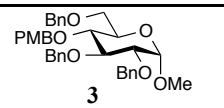
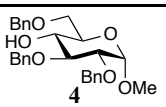
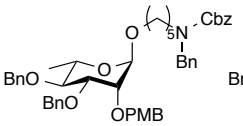
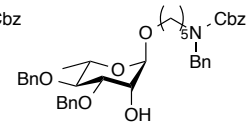
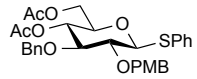
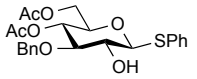
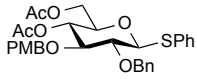
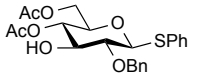
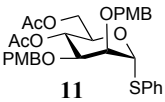
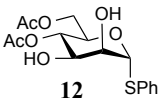
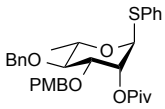
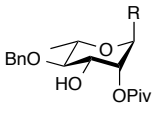
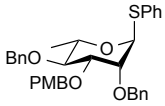
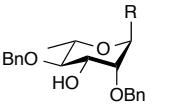
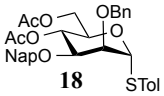
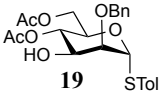
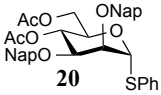
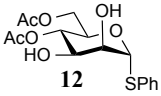
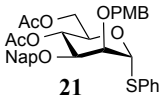
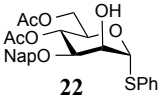
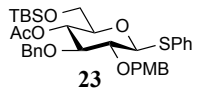
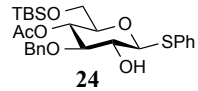
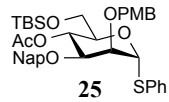
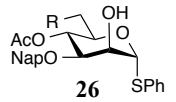
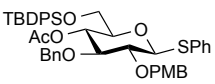
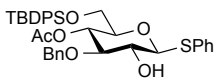
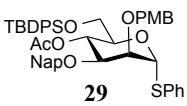
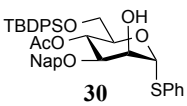
entry	substrate	product	yield
1[a]	 **3**	 **4**	96%
2[a]	 **5**	 **6**	82%
3[a]	 **7**	 **8**	90%
4[a]	 **9**	 **10**	81%
5[a]	 **11**	 **12**	80%
6[b*]	 **13**	 **14**	R = SPh, 85% R = OH (n.d.)
7[b*]	 **15**	 **16, 17**	R = SPh, 75% R = H, 14%
8[b]	 **18**	 **19**	86%
9[c]	 **20**	 **12**	67%
10[a]	 **21**	 **22**	80%
11[d]	 **23**	 **24**	48%
12[d]	 **25**	 **26**	R = OTBS, 63% R = OH, 24%
13[d]	 **27**	 **28**	89%
14[d,e]	 **29**	 **30**	88%

Table 1: Deprotection of PMB and Nap ethers with HCl/HFIP. a) 0.1 eq. HCl/HFIP; b) 1.0 eq. HCl/HFIP, 3.0 eq. TES, *=0ºC; c) 2.0 eq. HCl/HFIP, 5.0 eq. TES; d) 0.1 eq. HCl/HFIP, 1.0 eq. TES; e) 95:5 DCM/TFA 0ºC

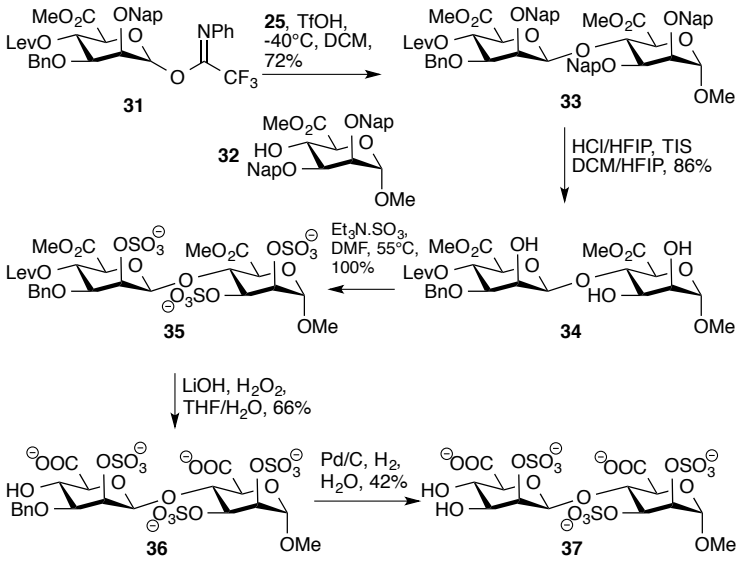
The same conditions (0.1 equiv. HCl DCM/HFIP 1 : 1) also cleanly cleaved the PMB group from the C2-OH in rhamnoside **5** (entry 2), carrying an aminopentanol spacer. The anomeric acetal was completely stable under the conditions used. We next explored various thioglycosides. Glucoside **7**, carrying a single PMB group at C2-OH, was subjected to the deprotection mixture to uneventfully afford alcohol **8**. Likewise, the C3-O-PMB ether was cleanly removed from glucoside **9** to give glucoside **10**. Mannoside **11**, carrying two PMB ethers, was deprotected equally efficient leading to diol **12** in 80% yield (entry 5). When rhamnoside **13** was subjected to the deprotection conditions (0.1 equiv. HCl DCM/HFIP 1 : 1), a complex mixture resulted. Notably, the characteristic purple color was absent and the reaction required hours to reach completion. Besides the desired product **14**, anomeric lactol **14b** was formed in this reaction, indicating that alkylation of the anomeric thiofunction by the PMB cation occurred as a side reaction. Expulsion of the activated aglycon then leads to hydrolysis of the thioglycoside.[12] To circumvent this side reaction, we added triethylsilane (TES) to the reaction mixture to scavenge the released PMB cations. Because we initially reasoned that the addition of a scavenger would necessitate the use of at least an equimolar amount of HCl, we used 1 equivalent of HCl and 3 equivalents of scavenger. These conditions resulted in clean removal of the PMB group from rhamnoside **13** and the isolation of alcohol **14** in 85% yield (entry 6). When the same conditions were used to cleave the PMB group from rhamnoside **15** the desired alcohol **16** was obtained in 75% alongside desulfurized compound **17** (entry 7). Here, activation of the thiofunction in **15** or **16** could not be completely suppressed because of the high reactivity of the rhamnoside, being a 6-deoxy glycoside featuring solely “arming” benzyl ether protecting groups. Of note, the anomeric linkage in *O*-rhamnoside **5**/**6** (entry 2) is completely stable under the acidic conditions.

Since Nap ethers can be removed under acidic conditions, we investigated whether Nap ethers can also be cleaved using the HCl/HFIP cocktail. We subjected mannoside **18** to the catalytic cleavage conditions described above (0.1 equiv. HCl DCM/HFIP 1 : 1). These conditions proved not forceful enough to cleave the Nap ether and the reaction progressed very slow and led to a low yield of the desired alcohol. We therefore raised the amount of acid to an equimolar amount. The addition of triethyl

silane as a scavenger led to the clean and controllable formation of alcohol **19** (entry 8). Similarly, deprotection of bis-Nap ether **20** proceeded uneventfully to give diol **12** (entry 9). Based on these results we reasoned that the difference in reactivity of the PMB and Nap ethers towards the HCl/HFIP combination should allow for the selective removal of a PMB ether in the presence of a Nap ether. The addition of a catalytic amount of HCl to mannoside **21** proved this hypothesis and the PMB ether in **21** was selectively cleaved to give alcohol **22** in good yield (entry 10). We next explored the orthogonality of the PMB ether with respect to commonly used silyl ethers.[1,13] Removal of the PMB ether in **23** and **25** was accompanied by partial cleavage of *tert*-butyldimethylsilyl (TBS) groups at the primary hydroxyl function (entries 11 and 12). Although we were not able to identify conditions that left the TBS ethers untouched it was found during the optimization of these reactions that a catalytic amount of HCl could be used in combination with a stoichiometric amount of scavenger (TES). Besides, the more acid stable *tert*-butyldiphenylsilyl (TBDPS) was stable to this catalytic cleavage cocktail and selective deprotection of the PMB ether in **27** in the presence of a TBDPS ether gave glucosyl alcohol **28** in 89% yield (entry 13). Similarly, the PMB ether in mannoside **29** was selectively deblocked, leaving both the primary TBDPS ether and the secondary napthyl ether unaffected (entry 14). When mannoside **29** was subjected to 5% trifluoroacetic acid in DCM,[1] compound **30** was obtained in 77% yield, where oxidative removal of the C-2-O-PMB using DDQ,[1] resulted in a complex mixture.

Having established a robust protocol for the removal of PMB and/or Nap ethers, we moved to explore the reagent system in the context of the assembly of sulfated oligo-β-mannuronic acids (SOMAs)[14]. These molecules have been reported to display a variety of appealing biological activities, including anti-cancer[15], anti-HIV,[16] anti-influenza activity.[17] To firmly establish the activity of SOMAs and decipher structure-activity relationships for this class of molecules well-defined fragments with a well-defined sulfate substitution pattern would be very valuable agents. To site-specifically introduce sulfate groups temporary protecting groups are required to mask the hydroxyl precursors. Substituted benzyl ethers, such as the PMB and Nap ether, represent excellent temporary protecting groups in this regard, because of the advantages mentioned above: they are sterically minimally intrusive and they do not

provide neighboring group participation (from either the C-2 or C-3 position) and building blocks featuring Nap or PMB ethers should perform equally well in glycosylation reactions as building blocks carrying benzyl ethers. Indeed, when mannuronic acid building blocks **31** and **32**, featuring a single Nap ether at C-2 or two Nap ethers at C2 and C-3, respectively, were condensed disaccharide **33** was formed in 72% yield with excellent stereoselectivity. Deprotection of the multiple Nap-ethers using a 10:1 TFA/toluene mixture,[3] resulted in a complex mixture of products due to incomplete Nap removal.



Scheme 2: SOMA synthesis

When this disaccharide was treated with three equivalents of HCl (one for each Nap group) in DCM/HFIP in the presence of five equivalents of TES, fast and clean removal of the Nap ethers was observed. However, we also observed that the keto-function of the levulinoyl ester was partially reduced, leading to a 4-pentenol ester at the C-4' and concomitant removal of this group. To circumvent this side reaction we switched to the use of tri-*iso*-propyl silane (TIS) as a scavenger, and the use of this reagent in conjunction with the HCl/HFIP combination led to the uneventful transformation of disaccharide into triol **34**. Under these conditions both, the α- and β-mannuronic acid linkages, were completely stable. As described above, PMB ethers can be removed using a catalytic amount of HCl in the presence of an excess scavenger. We therefore explored the use of 0.5 equivalents of HCl (0.17 equivalents

per Nap ether) in conjunction with 3.3 equivalents TIS (1.1 equivalent per Nap ether). Under these conditions, the three Nap ethers were rapidly cleaved to give dimer **34** in 82% yield. Of note, when we tried to unmask the Nap ethers in **33** using oxidative conditions (DDQ in DCM/H_2O) a complex mixture resulted, in which a 2,3-naphthylidene side product was formed besides the desired triol. From this reaction disaccharide **34** was isolated in 47% yield.[18] Having triol **34** in hand, we installed the three sulfate groups using $SO_3 \cdot Et_3N$ at elevated temperature (55 ^oC). Ensuing saponification ($LiOH/H_2O_2$) of both the methyl and levulinoyl esters and final debenzylation then gave the target disaccharide **37**.

Conclusion

In summary, a new, fast and homogeneous deprotection method for electron-rich benzyl type ethers is described employing HCl in HFIP. PMB and Nap ethers can be removed with a catalytic amount of acid in a selective manner without affecting other groups. PMB ethers can also be selectively cleaved with respect to Nap ethers by limiting the amount of HCl. The ease of cleavage of these groups under the established conditions is a valuable asset for the utility of the PMB and Nap ethers in synthetic (carbohydrate) chemistry. The mild, fast and homogeneous reactions conditions should allow for their use in a solid phase reaction setting. Also in stereoselective glycosylation reactions that are mediated through external nucleophiles (“moderators”) the use of a protecting group scheme that builds on all-benzyl ether type protecting groups that can be selectively removed, will be very valuable.[19]

Experimental section

General experimental procedures. All chemicals were used as received unless stated otherwise. ^1H and ^{13}C NMR spectra were recorded on a 400/100 MHz, 500/125 MHz, 600/150 MHz or a 850/214 MHz spectrometer. Chemical shifts (δ) are given in ppm relative to tetramethylsilane as internal standard. Coupling constants are given in Hz. All individual signals were assigned using 2D-NMR spectroscopy, HH-COSY, HSQC and HMBC. IR spectra are reported in cm^{-1}. Flash chromatography was performed on silica gel 60 (0.04 – 0.063 mm). TLC-analysis was followed by detection by UV-

absorption (254 nm) where applicable and by spraying with 20% sulfuric acid in ethanol followed by charring at ~150 °C or by spraying with a solution of $(NH_4)_6Mo_7O_{24}\cdot H_2O$ (25 g/l) and $(NH_4)_4Ce(SO_4)_4\cdot{}_2H_2O$ (10 g/l) in 10% sulfuric acid in water followed by charring at 50 °C. LC-MS standard eluents used were A: 100% H_2O, B: 100% acetonitrile, C: 1% TFA in H_2O. The column used was a C18 column (4.6 mmD × 50 mmL, 3µ particle size). All analyses were 13 min, with a flow-rate of 1 ml/min. High-resolution mass spectra were recorded on a LTQ-Orbitrap equipped with an electrospray ion source in positive mode (source voltage 3.5 kV, sheath gas flow 10, capillary temperature 275ºC) with resolution R=60.000 at m/z=400 (mass range = 150-4000) and dioctylphtalate (m/z=391.28428) as "lock mass". HCl/HFIP solution were freshly prepared prior to use.

Methyl 2,3,6-tri-O-benzyl-α-D-glucopyranoside (4) Compound **3**[21] (0.117 g, 0.200 mmol) was dissolved in 1:1 DCM/HFIP (2 mL) and 0.1 mL 0.2M HCl/HFIP was added. After 150 seconds the reaction was quenched by addition of sat. aq. $NaHCO_3$. The mixture was diluted DCM and the organic layer is washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated. Purification by column chromatography (Tol/EtOAc) gave **4** in 96% yield (0.0891 g, 0.19 mmol). TLC R_f 0.35 (Tol/EtOAc, 9/1, v/v); ^{1}H-NMR($CDCl_3$, 500 MHz): δ 7.39 – 7.20 (m, 15H, CH_{arom}), 4.99 (d, 1H, J=11.5 Hz, CH*H* OBn), 4.78 – 4.70 (m, 2H, C*H*H OBn, CH*H* OBn), 4.68 – 4.61 (m, 2H, C*H*H OBn, H-1), 4.55 (q, 2H, J=12.1, 12.1, 12.1 Hz, CH_2 OBn), 3.78 (t, 1H, J=9.2, 9.2 Hz, H-3), 3.74 – 3.64 (m, 3H, H-5, H-6), 3.59 (t, 1H, J=9.2, 9.2 Hz, H-4), 3.52 (dd, 1H, J=9.6, 3.5 Hz, H-2), 3.37 (s, 3H, OMe), 2.37 (s, 1H, 4-OH); ^{13}C-NMR($CDCl_3$, 126 MHz): δ 138.9, 138.2, 138.1 (C_q), 128.6, 128.5, 128.4, 128.2, 128.0, 128.0, 127.9, 127.7, 127.7 (CH_{arom}), 98.3 (C-1), 81.6 (C-3), 79.7 (C-2), 75.5 (CH_2Bn), 73.7 (CH_2Bn), 73.2 (CH_2Bn), 70.9 (C-4), 70.0 (C-50, 69.6 (C-6), 55.3 (CH_3 OMe);

***N*-benzyl-*N*-benzyloxycarbonyl-5-aminopentanyl-3,4-di-*O*-benzyl-2-*O*-*p*-methoxybenzyl-α-L-rhamno-pyranoside (5)** N-benzyl-N-benzyloxycarbonyl-5-aminopentanyl-3,4-di-O-benzyl-α-L-rhamno-pyranoside (0.908 g, 1.39 mmol) was coevaporated twice with anhydrous toluene before being dissolved in DMF (4 mL). The mixture was cooled to 0°C, after which sodium hydride (60% dispersion in

mineral oil, 0.08 g, 2.08 mmol) was added. The mixture was stirred for 10 minutes followed by addition of *para*-methoxybenzylchloride (0.28 mL, 2.08 mmol). After 115 minutes, the reaction was quenched with sat. aq. $NaHCO_3$, diluted with Et_2O and washed with water. The organic layer was dried over $MgSO_4$ and concentrated. Purification by column chromatography (Tol/EtOAc) gave **5** in 75% yield (0.802 g, 1.03 mmol). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.30 (m, 22H, CH_{arom}), 7.17 (s, 1H, CH_{arom}), 6.83 (d, 2H, J=8.6 Hz, CH_{arom}), 5.17 (d, 2H, J=9.4 Hz, CH_2 Cbz), 4.93 (d, 1H, J=10.8 Hz, CH*H* OBn), 4.72 – 4.54 (m, 6H, C*H*H OBn, CH_2 OBn, CH_2 OPMB, H-1), 4.48 (s, 2H, CH_2 Bn), 3.82 – 3.73 (m, 5H, CH_3 OMe, H-2, H-3), 3.66 – 3.50 (m, 3H, H-5, CH_2), 3.33 – 3.10 (m, 1H, H-4, CH_2), 1.66 – 1.37 (m, 5H, CH_2), 1.34 – 1.07 (m, 6H, CH_3 H-6, CH_2); ^{13}C-NMR (CDCl3, 101 MHz): δ 159.3, 138.8, 138.0, 130.6 (C_q), 129.6, 128.7, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.8, 127.7, 127.6, 127.4, 113.9 (CH_{arom}), 98.1 (C-1), 80.7 (C-3), 80.4 (C-4), 75.6 (CH_2Bn), 74.6 (C-2), 72.5, 72.2 (CH_2 PMB/Bn), 68.1 (C-5), 67.3 (CH_2Bn), 55.4 (CH_3 OMe), 50.7, 50.3 (CH_2), 29.3 (CH_2), 23.5 (CH_2), 18.2 (CH_3 C-6); HRMS: $[M+NH_4]^+$ calculated for $C_{48}H_{59}N_2O_8$ 791.42659, found 791.42758.

***N*-benzyl-*N*-benzyloxycarbonyl-5-aminopentanyl-3,4-di-*O*-benzyl-α-L-rhamno-pyranoside (6)** Compound **5** (0.157 g, 0.200 mmol) was dissolved in 1:1 DCM/HFIP (2 mL) and 0.1 mL 0.2M HCl/HFIP was added. After 150 seconds the reaction was quenched by addition of sat. aq. $NaHCO_3$. The mixture was diluted DCM and the organic layer is washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated. Purification by column chromatography (Tol/EtOAc) gave **6** in 82% yield (0.108 g, 0.165 mmol). TLC R_f 0.15 (Tol/EtOAc, 9/1, v/v); IR (neat, cm^{-1}): 694, 731, 910, 984, 1028, 1051, 1069, 1096, 1227, 1304, 1362, 1421, 1452, 1472, 1497, 1695, 1728, 2930; ^{1}H NMR($CDCl_3$, 500 MHz): δ 7.37 – 7.17 (m, 20H, CH_{arom}), 5.17 (d, 2H, J=11.1 Hz, CH_2 Cbz), 4.87 (d, 1H, J=10.9 Hz, CH*H* OBn), 4.75 (s, 1H, H-1), 4.69 – 4.60 (m, 3H, CH_2 OBn), 4,49 (s, 2H, CH_2 OBn), 3.99 (s, 1H, H-2), 3.81 (d, 1H, J=7.0 Hz, H-3), 3.68 (m, 1H, H-5), 3.58 (m, 1H, CH_2) 3.44 (t, 1H, J=9.3, 9.3 Hz, H-4), 3.26 – 3.19 (m, 3H, CH_2), 2.41 (bs, 1H, 2-OH), 1.53 – 1.47 (m, 4H, 2 x CH_2), 1.30 – 1.26 (m, 5H, CH_3-6, CH_2); ^{13}C-NMR (CDCl3, 126 MHz): δ 138.5, 138.1, (C_q), 128.6, 128.6, 128.5, 128.5, 128.1, 128.0, 127.9, 127.9, 127.8, 127.4 (CH_{arom}), 99.0 (C-1), 80.3 (C-3), 80.1 (C-4), 75.5 (CH_2Bn), 72.1 (CH_2), 68.7 (C-2), 67.4 (CH_2), 67.4 (C-5), 67.3 (CH_2 Cbz), 50.6, 50.3

(CH_2Bn), 47.2, 46.2 (CH_2), 29.2 (CH_2), 23.5 (CH_2), 18.0 (CH_3-6). Analytical data are identical to literature precendence.

Phenyl 4,6-di-*O*-acetyl-3-*O*-benzyl-2-*O*-*p*-methoxybenzyl-1-thio-β-D-glucopyranoside (7) Phenyl 4,6-*O*-benzylidene-3-*O*-benzyl-2-*O*-*p*-methoxybenzyl-1-thio-β-D-glucopyranoside (1.76 g, 3.00 mmol) was dissolved in DCM/MeOH (15 mL/ 15 mL) and p-toluenesulfonic acid monohydrate (0.06 g, 0.30 mmol) was added. When TLC analysis showed complete consumption of the starting material, the reaction was neutralized with Et_3N. The crude was dissolved in pyridine (12 mL), cooled to 0°C, followed by addition of 1.3 mL Ac_2O. The reaction was stirred overnight after which it was quenched with EtOH and concentrated. The crude mixture was diluted with EtOAc, washed with 1M HCl, sat. aq. NaCl, dried over $MgSO_4$ and concentrated. Column purification (hexanes/EtOAc) gave compound **7** in 84% yield (1.428 g, 2.52 mmol). ^{1}H-NMR($CDCl_3$, 500 MHz): δ 7.57 (dd, 2H, J=7.6, 1.9 Hz, CH_{arom}), 7.36 – 7.19 (m, 10H, CH_{arom}), 6.86 (d, 2H, J=8.6 Hz, CH_{arom}), 5.03 (t, 1H, J=9.7, 9.7 Hz, H-4), 4.82 (m, 2H, 2x CH*H* OBn/OPMB), 4.67 – 4.57 (m, 3H, H-1, 2x C*H*H OBn/OPMB), 4.20 (dd, 1H, J=12.2, 5.7 Hz, H-6), 4.10 (dd, 1H, J=12.2, 2.2 Hz, H-6), 3.77 (s, 3H, OMe), 3.64 (t, 1H, J=9.1, 9.1 Hz, H-3), 3.60 – 3.49 (m, 2H, H-2, H-5), 2.06 (s, 3H, CH_3 Ac), 1.90 (s, 3H, CH_3 Ac); ^{13}C NMR($CDCl_3$, 126 MHz): δ 170.6, 169.6 (C=O Ac), 159.4, 138.0, 133.2 (C_q), 132.1, 130.0 (CH_{arom}), 129.8 (C_q), 128.9, 128.4, 127.8, 127.7, 113.8 (CH_{arom}), 87.5 (C-1), 83.7 (C-3), 80.2 (C-2), 75.8 (C-5), 75.4, 75.2 (CH_2Bn/PMB), 69.6 (C-4), 62.6 (C-6), 55.2 (CH_3 OMe), 20.7, 20.7 (CH_3 Ac); HRMS: $[M+NH_4]^+$ calculated for $C_{31}H_{38}NO_8S$ 584.23126, found 584.23162.

Phenyl 4,6-di-*O*-acetyl-3-*O*-benzyl-1-thio-β-D-glucopyranoside (8) Compound **7** (0.134 g, 0.236 mmol) was dissolved in 1:1 DCM/HFIP (2 mL) and 0.12 mL 0.2M HCl/HFIP was added. After 15 min the reaction was quenched by addition of sat. aq. $NaHCO_3$. The mixture was diluted DCM and the organic layer is washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated. Purification by column chromatography (Tol/EtOAc) gave **8** in 88% yield (0.093 g, 0.207 mmol). TLC R_f 0.50 (PE/EtOAc, 2/1, v/v); $[\alpha]_D^{20}$ -6.8 (*c* 1, DCM); IR (neat, cm^{-1}): 692, 740, 1026, 1220, 1365, 1739, 2885, 2953, 3375; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.58 – 7.52 (m, 3H, CH_{arom}), 7.36 – 7.24 (m,

13H, CH_{arom}), 4.98 (t, 1H, J=9.8 Hz, H-4), 4.83 (d, 1H, J=11.8 Hz, CH*H* Bn), 4.69 (d, 1H, J=11.8 Hz, C*H*H Bn), 4.51 (d, 1H, J=9.3 Hz, H-1), 4.21 – 4.10 (m, 2H, H-6), 3.62 – 3.51 (m, 3H, H-2, H-3, H-5), 2.65 (s, 1H, 2-OH), 2.07 (s, 3H, CH_3 Ac); ^{13}C-NMR ($CDCl_3$, 126 MHz): δ 170.8, 169.7 (C=O Ac), 138.2 (C_q), 133.3 (CH_{arom}), 131.3 (C_q), 129.1, 128.5, 128.5, 127.9, 127.9 (CH_{arom}), 88.1 (C-1), 82.9 (C-3), 76.2 (C-5), 74.8 (CH_2Bn), 72.5 (C-2), 69.5 (C-4), 62.7 (C-6), 29.8, 20.9 (CH_3 Ac); HRMS: $[M+Na]^+$ calculated for $C_{23}H_{26}O_7SNa$ 469.12915, found 469.12830.

Phenyl 4,6-di-*O*-acetyl-2-*O*-benzyl-3-*O*-*p*-methoxybenzyl-1-thio-β-D-glucopyranoside (9) Phenyl 4,6-*O*-benzylidene-3-*O*-*p*-methoxybenzyl-1-thio-β-D-glucopyranoside (0.443 g, 0.92 mmol) was coevaporated twice with anhydrous toluene before being dissolved in DMF (5 mL). The mixture was cooled to 0°C, after which sodium hydride (60% dispersion in mineral oil, 0.07 g, 1.84 mmol) was added. The mixture was stirred for 10 minutes followed by addition of benzylbromide (0.21 mL, 1.84 mmol). When TLC analysis showed complete consumption of the starting material, the reaction was quenched with sat. aq. $NaHCO_3$. The mixture was diluted with Et_2O, washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated. The crude was dissolved in DCM/MeOH (15 mL/ 15 mL), followed by addition of p-toluenesulfonic acid monohydrate until the pH was acidic. The reaction was stirred for 95 minutes after which it was neutralized with Et_3N and concentrated. The diol was dissolved in 5 mL pyridine, cooled to 0°C and 0.35 mL Ac_2O was added. After overnight stirring, the reaction was quenched with MeOH and concentrated. Column purification (Pent/EtOAc) gave compound **9** in 58% yield (0.301 g, 0.53 mmol). ^{1}H-NMR($CDCl_3$, 500 MHz): δ 7.59 – 7.53 (m, 2H, CH_{arom}), 7.43 – 7.20 (m, 8H, CH_{arom}), 7.15 (d, 2H, J=8.6 Hz, CH_{arom}), 6.84 (d, 2H, J=8.6 Hz, CH_{arom}), 5.02 (t, 1H, J=9.7, 9.7 Hz, H-4), 4.87 (d, 1H, J=10.2 Hz, CH*H* OBn), 4.72 (m, 2H, CH_2 OBn/OPMB), 4.65 (d, 1H, J=9.8 Hz, H-1), 4.58 (d, 1H, J=11.0 Hz, C*H*H OBn/OPMB), 4.21 (dd, 1H, J=12.2, 5.7 Hz, H-6), 4.11 (dd, 1H, J=12.2, 2.1 Hz, H-6), 3.77 (s, 3H, CH_3 OMe), 3.65 (t, 1H, J=9.1, 9.1 Hz, H-3), 3.62 – 3.48 (m, 3H, H-2, H-5), 2.07 (s, 3H, CH_3 Ac), 1.95 (s, 3H CH_3 Ac); ^{13}C NMR($CDCl_3$, 126 MHz): δ 170.7, 169.6 (C=O Ac), 159.3, 137.8, 133.2 (C_q), 132.3 (CH_{arom}), 130.1 (C_q), 129.5, 129.0, 128.5, 128.3, 128.0, 127.9, 113.9 (CH_{arom}), 87.5 (C-1), 83.4 (C-3), 80.6 (C-2), 76.9 (C-5), 75.6, 75.1 (CH_2 OBn/OPMB), 69.8 (C-4), 62.7 (C-

6), 55.3 (CH_3 OMe), 20.9, 20.9 (CH_3 Ac); HRMS: $[M+NH_4]^+$ calculated for $C_{31}H_{38}NO_8S$ 584.23126, found 584.23145.

Phenyl 4,6-di-*O*-acetyl-2-*O*-benzyl-β-D-glucopyranoside (10) Compound **9** (0.107 g, 0.188 mmol) was dissolved in 1:1 DCM/HFIP (2 mL) and 0.1 mL 0.2M HCl/HFIP was added. After 20 min the reaction was quenched by addition of pyridine and the mixture was concentrated. Purification by column chromatography (Tol/EtOAc) gave **10** in 81% yield (0.068 g, 0.152 mmol). TLC: R_f 0.38 (PE/EtOAc, 2/1, v/v); $[\alpha]_D^{20}$ -45.6 (*c* 1, DCM); IR (neat, cm^{-1}): 700, 744, 1028, 1043, 1228, 1371, 1739, 2922, 3477; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.58 – 7.54 (m, 2H, CH_{arom}), 7.37 – 7.26 (m, 8H, CH_{arom}), 4.95 (d, 1H, J=10.9 Hz, H-1), 4.90 (t, 1H, J=9.7, 9.7 Hz, H-4), 4.71 (d, 1H, J=10.9 Hz, CH*H* Bn), 4.64 (d, 1H, J=9.8 Hz, C*H*H Bn), 4.22 (dd, 1H, J=12.2, 5.7 Hz, H-6), 4.14 (dd, 1H, J=12.2, 2.3 Hz, H-6), 3.73 (t, 1H, J=9.0, 9.0 Hz, H-3), 3.60 (ddd, 1H, J=10.0, 5.7, 2.3 Hz, H-5), 3.43 – 3.39 (t, 1H, J=10 Hz, 8.5 Hz, H-2), 2.68 (s, 1H, 3-OH), 2.08 (s, 3H), 2.07 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 170.8, 170.6 (C=O Ac), 137.9 (C_q), 133.3 (C_q), 132.2, 129.1, 128.7, 128.4, 128.3, 127.9 (CH_{arom}), 87.3 (C-1), 80.7 (C-2), 76.5 (C-3), 75.7 (C-5), 75.5 (CH_2Bn), 70.4 (C-4), 62.8 (C-6), 20.9, 20.9 (CH_3 Ac); HRMS: $[M+Na]^+$ calculated for $C_{23}H_{26}O_7SNa$ 469.12915, found 469.12861.

Phenyl 4,6-di-*O*-acetyl-2,3-di-*O*-*p*-methoxybenzyl-1-thio-α-D-mannopyranoside (11) Phenyl 4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside (1.85 g, 5.13 mmol) was coevaporated twice with anhydrous toluene before being dissolved in DMF (13 mL). The mixture was cooled to 0°C, after which sodium hydride (60% dispersion in mineral oil, 0.62 g, 15 mmol) was added. The mixture was stirred for 10 minutes followed by addition of *para*-methoxybenzylchloride (2.16 mL, 15 mmol). When TLC analysis showed complete consumption of the starting material, the reaction was quenched with sat. aq. $NaHCO_3$. The mixture was diluted with EtOAc, washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated. The crude was dissolved in MeOH (50 mL), followed by addition of p-toluenesulfonic acid monohydrate (0.09 g, 0.45 mmol). The reaction was stirred for 95 minutes after which it was neutralized with Et_3N and concentrated. The compound was purified by column chromatography (Pent/EtOAc). The diol was dissolved in 20 mL pyridine, cooled to 0°C and 2.17 mL

Ac_2O was added. After overnight stirring, the reaction was quenched with EtOH and concentrated. Column purification (Pent/EtOAc) gave compound **11** in 64% yield (1.95 g, 3.26 mmol). ^{1}H NMR($CDCl_3$, 399 MHz): δ 7.45 – 7.38 (m, 2H, CH_{arom}), 7.33 – 7.17 (m, 7H, CH_{arom}), 6.85 (m, 4H, CH_{arom}), 5.52 (d, 1H, J=1.6 Hz, H-1), 5.39 (t, 1H, J=9.7, 9.7 Hz, H-4), 4.66 – 4.54 (m, 2H, CH_2PMB), 4.51 – 4.36 (m, 2H, CH_2PMB), 4.31 (ddd, 1H, J=9.6, 6.1, 2.1 Hz, H-6), 4.23 (dd, 1H, J=12.0, 6.1 Hz, H-5), 4.11 (dd, 1H, J=12.0, 2.2 Hz, H-6), 3.97 – 3.91 (m, 1H, H-2), 3.83 – 3.68 (m, 7H, 2x CH_3 OMe, H-3), 2.04 (s, 3H, CH_3 Ac), 2.01 (s, 3H, CH_3 Ac); ^{13}C-NMR($CDCl_3$, 100 MHz): δ 170.7, 169.7 (C=O Ac), 159.4, 133.8 (C_q), 131.6 (CH_{arom}), 129.9, 129.8 (C_q), 129.6, 129.3, 129.1, 127.7, 113.9, 113.8 (CH_{arom}), 85.9 (C-1), 76.5 (C-3), 75.2 (C-2), 71.9, 71.5 (CH_2PMB), 70.0 (C-5), 68.2 (C-4), 63.0 (C-6), 55.3 (CH_3 OMe), 21.0, 20.8 (CH_3 Ac); HRMS: $[M+NH_4]^+$ calculated for $C_{32}H_{40}NO_9S$ 614.24183, found 614.24212.

Phenyl 4,6-di-*O*-acetyl-1-thio-α-D-mannopyranoside (12) Compound **11** (0.112 g, 0.188 mmol) was dissolved in 1:1 DCM/HFIP (2 mL) and 0.12 mL 0.2M HCl/HFIP was added. After 3 min the reaction was quenched by addition of sat. aq. $NaHCO_3$. The mixture was diluted DCM and the organic layer is washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated. Purification by column chromatography (Pent/EtOAc) gave **12** in 79% yield (0.053 g, 0.148 mmol). TLC: R_f 0.21 (PE/EtOAc, 1/1, v/v); $[\alpha]_D^{20}$ +169.0 (*c* 1, DCM); IR (neat, cm^{-1}): 744, 1051, 1232, 1735, 2933, 3300; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.57 – 7.39 (m, 2H, CH_{arom}), 7.39 – 7.19 (m, 3H, CH_{arom}), 5.60 (d, 1H, J=1.4 Hz, H-1), 5.11 (t, 1H, J=9.7 Hz, H-4), 4.46 (ddd, 1H, J=10.0, 5.8, 2.2 Hz, H-5), 4.34 (dd, 1H, J=12.1, 5.9 Hz, H-6), 4.23 (dd, 1H, J=3.5, 1.6 Hz, H-2), 4.08 (dd, 1H, J=12.1, 2.2 Hz, H-6), 3.94 (dd, 1H, J=9.4, 3.4 Hz, H-3), 3.29 (s, 2H, 2-OH, 3-OH), 2.15 (s, 3H, CH_3 Ac), 2.03 (s, 3H, CH_3 Ac); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.9, 171.0 (C=O Ac), 133.3 (C_q SPh), 131.7, 129.2, 127.9 (CH_{arom}), 87.6 (C-1), 72.2 (C-2), 70.8 (C-3), 70.2 C-4), 69.1 (C-5), 62.7 (C-6), 21.1, 20.9 (CH_3 Ac); HRMS: $[M+Na]^+$ calculated for $C_{16}H_{20}O_7SNa$ 379.08219, found 379.08213.

Phenyl 4-*O*-benzyl-2-*O*-Pivaloyl-1-thio-α-L-rhamnopyranoside (14) Compound **13**[2c] (0.156 g, 0.276 mmol) was dissolved in a 1:1 DCM/HFIP mixture (2.8 mL) and TES (0.13 mL, 0.84 mmol) was added. The mixture was cooled to 0°C and 1.4 mL of a

0.2M HCl/HFIP solution was added. After TLC and TLC/MS analysis showed complete conversion of the starting material in a lower running spot, the reaction was quenched with sat. aq. $NaHCO_3$ and diluted with DCM. The aqueous layer was washed with DCM and the combined organic layers were washed with a sat. aq. NaCl solution, dried over $MgSO_4$ and concentrated. Silica gel column purification afforded compound **14** in 85% yield (0.102 g, 0.23 mmol). TLC: R_f 0.55 (PE/EtOAc, 9/1, v/v); $[\alpha]_D^{20}$ -123.0 (*c* 1, DCM); IR (neat, cm^{-1}): 690, 738, 1097, 1151, 1280, 1479, 1730, 2972, 3469; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.50 – 7.42 (m, 2H, CH_{arom}), 7.40 – 7.21 (m, 8H, CH_{arom}), 5.36 (d, 1H, J=1.2 Hz, H-1), 5.33 (dd, 1H, J=3.3, 1.5 Hz, H-2), 4.81 (d, 1H, J=11.2 Hz, CH*H* Bn), 4.74 (d, 1H, J=11.2 Hz, C*H*H Bn), 4.24 (dq, 1H, J=9.5, 6.2, 6.2, 6.2 Hz, H-5), 4.09 (d, 1H, J=10.4 Hz, H-3), 3.38 (t, 1H, J=9.4, 9.4 Hz, H-4), 2.21 (s, 1H, 3-OH), 1.35 (d, 3H, J=6.2 Hz, CH_3-6), 1.23 (s, 9H, CH_3-Piv); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 178.1 (C=O Piv), 138.1 (C_q), 133.9 (C_q), 132.1, 129.2, 128.7, 128.3, 128.2, 127.8 (CH_{arom}), 86.0 (C-1), 81.7 (C-4), 75.2 (CH_2 Bn), 74.0 (C-2), 71.1 (C-3), 68.7 (C-5), 39.2 (C_q Piv), 27.2 (CH_3 Piv), 18.1 (CH_3-6); HRMS: $[M+Na]^+$ calculated for $C_{24}H_{30}O_5SNa$ 453.17062, found 453.17055.

Phenyl 2,4-di-*O*-benzyl-1-thio-α-L-rhamnopyranoside (16) Compound **15**[2c] (0.108 g, 0.194 mmol) was dissolved in a 1:1 DCM/HFIP mixture (2 mL) and TES (0.09 mL, 0.58 mmol) was added. The mixture was cooled to 0°C and 0.97 mL of a 0.2M HCl/HFIP solution was added. After TLC and TLC/MS analysis showed complete conversion of the starting material in a lower running spot, the reaction was quenched with sat. aq. $NaHCO_3$ and diluted with DCM. The aqueous layer was washed with DCM and the combined organic layers were washed with a sat. aq. NaCl solution, dried over $MgSO_4$ and concentrated. Silica gel column purification afforded compound **16** in 76% yield (0.064 g, 0.147 mmol). TLC: R_f 0.78 (PE/EtOAc, 2/1, v/v); $[\alpha]_D^{20}$ -116.0 (*c* 1, DCM); IR (neat, cm^{-1}): 694, 736, 1026, 1066, 1082, 1583, 2873, 3030, 3061; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.36 – 7.23 (m, 15H, CH_{arom}), 5.56 (s, 1H, H-1), 4.91 (d, 1H, J=11.1 Hz, CH*H* Bn), 4.74 (d, 1H, J=11.7 Hz, CH*H* Bn), 4.67 (d, 1H, J=11.1 Hz, C*H*H Bn), 4.53 (d, 1H, J=11.7 Hz, C*H*H Bn), 4.16 (dq, 1H, J=9.4, 6.2, 6.2, 6.2 Hz, H-5), 4.00 – 3.95 (m, 2H, H-2, H-3), 3.40 (t, 1H, J=9.1, 9.1 Hz, H-4), 2.37 (bs, 1H, 3-OH), 1.34 (d, 3H, J=6.2 Hz, CH_3-6); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 138.5, 137.5, 134.5 (C_q), 131.6, 129.2, 128.7,

128.6, 128.3, 128.2, 128.1, 127.9, 127.5 (CH_{arom}), 85.1 (C-1), 82.5 (C-4), 80.1 (C-2), 75.3 (CH_2Bn), 72.5 (CH_2Bn), 72.2 (C-3), 68.7 (C-5), 18.1 (CH_3-6); HRMS: $[M+Na]^+$ calculated for $C_{26}H_{28}O_4SNa$ 459.16005, found 459.15943.

Tolyl 4,6-di-*O*-acetyl-2-*O*-benzyl-3-*O*-(2-naphthylmethyl)-1-thio-α-D-mannopyranoside (18) Tolyl 4,6-*O*-benzylidene-2-*O*-benzyl-3-*O*-(2-naphthylmethyl)-1-thio-α-D-mannopyranoside (1.37 g, 2.28 mmol) was dissolved in DCM/MeOH (3 mL/ 12 mL) and p-toluenesulfonic acid monohydrate (0.043 g, 0.228 mmol) was added. The reaction was stirred for 5 days after which it was neutralized with Et_3N. The crude was dissolved in pyridine (12 mL), cooled to 0°C, followed by addition of 1.3 mL Ac_2O. The reaction was stirred overnight after which it was quenched with EtOH and concentrated. The crude mixture was diluted with EtOAc, washed with 1M HCl, sat. aq. NaCl, dried over $MgSO_4$ and concentrated. Column purification (PE/EtOAc) gave compound **18** in 70% yield (0.969 g, 1.61 mmol). ^{1}H-NMR($CDCl_3$, 400 MHz): δ 7.87 – 7.79 (m, 3H, CH_{arom}), 7.74 (s, 1H CH_{arom}), 7.53 – 7.48 (m, 1H CH_{arom}), 7.48 – 7.37 (m, 2H CH_{arom}), 7.37 – 7.21 (m, 7H CH_{arom}), 7.12 – 7.05 (m, 2H CH_{arom}), 5.54 – 5.43 (m, 2H, H-1, H-4), 4.84 – 4.51 (m, 4H, CH_2 Bn/Nap), 4.39 – 4.30 (m, 1H, H-5), 4.25 (dd, 1H, J=12.1, 6.0 Hz, H-6), 4.17 – 4.06 (m, 1H, H-6), 4.05 – 3.98 (m, 1H, H-2), 3.84 (dd, 1H, J=9.6, 2.9 Hz, H-3), 2.32 (s, 3H, CH_3 Tol), 2.07 – 2.01 (m, 6H, 2x CH_3 Ac); ^{13}C-NMR($CDCl_3$, 101 MHz): δ 170.8, 169.8 (C=O Ac), 138.0, 137.7, 135.3, 133.3, 133.1 (C_q), 132.2, 129.9 (CH_{arom}), 129.9 (C_q), 128.4, 128.3, 128.0, 127.8, 127.8, 126.5, 126.3, 126.1, 125.7, 118.8 (CH_{arom}), 86.1 (C-1), 77.0 (C-3), 75.5 (C-2), 72.2, 71.8 (CH_2 OBn/ONap), 69.9 (C-5), 68.1 (C-4), 63.0 (C-6), 21.2, 21.0, 20.9 (CH_3 Tol, Ac); HRMS: $[M+NH_4]^+$ calculated for $C_{35}H_{40}NO_7S$ 618.25200, found 618.25193.

Tolyl 4,6-di-*O*-acetyl-2-*O*-benzyl-1-thio-α-D-mannopyranoside (19) Compound **18** (0.117 g, 0.195 mmol) was dissolved in 1:1 DCM/HFIP (2 mL) and 0.09 mL TES was added. The solution was treated with 0.97 mL 0.2M HCl/HFIP. After 33 min the reaction was quenched by addition of sat. aq. $NaHCO_3$. The mixture was diluted DCM and the organic layer is washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated. Purification by column chromatography (hexanes/EtOAc) gave **19** in

86% yield (0.077 g, 0.168 mmol). TLC: R_f 0.56 (PE/EtOAc, 2/1, v/v); $[\alpha]_D^{20}$ +61.6 (*c* 1, DCM); IR (neat, cm^{-1}): 781, 1051, 1101, 1226, 1739, 2924, 3477; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.39 – 7.27 (m, 6H, CH_{arom}), 7.12 (d, 2H, J=8.0 Hz, CH_{arom}), 5.57 (s, 1H, H-1), 5.14 (t, 1H, J=9.9, 9.9 Hz, H-4), 4.74 (d, 1H, J=11.6 Hz, C*H*H Bn), 4.53 (d, 1H, J=11.6 Hz, CH*H* Bn), 4.42 (ddd, 1H, J=9.9, 5.8, 2.0 Hz, H-5), 4.27 (dd, 1H, J=12.1, 5.9 Hz, H-6), 4.12 (dd, 1H, J=12.1, 2.1 Hz, H-6), 4.01 (dd, 1H, J=3.5, 1.1 Hz, H-2), 3.90 (s, 1H, H-3), 2.39 (s, 1H, 3-OH), 2.33 (s, 3H, CH_3 STol), 2.12 (s, 3H, CH_3 Ac), 2.05 (s, 3H, CH_3 Ac); ^{13}C-NMR(CDCl3, 100 MHz): δ ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 170.8 (C=O Ac), 138.2 (C_q), 137.1 (C_q), 132.5, 130.0 (CH_{arom}), 129.6 (C_q), 128.7, 128.3, 128.1 (CH_{arom}), 85.3 (C-1), 79.3 (C-2), 72.4 (CH_2 Bn), 70.3 (C-3), 69.9 (C-4), 69.2 (C-5), 62.9 (C-6), 21.2 (CH_3 STol), 21.1, 20.9 (CH_3 Ac); HRMS: $[M+Na]^+$ calculated for $C_{24}H_{28}O_7SNa$ 483.14480, found 483.14387.

Phenyl 4,6-di-*O*-acetyl-2,3-di-*O*-(2-naphthylmethyl)-1-thio-α-D-mannopyranoside (20) 4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside (1.08 g, 3 mmol) was coevaporated twice with anhydrous toluene before being dissolved in DMF (15 mL). The mixture was cooled to 0°C, after which sodium hydride (60% dispersion in mineral oil, 0.48 g, 12 mmol) was added. The mixture was stirred for 10 minutes followed by addition of 2-naphthylmethylbromide (2.65 g, 12 mmol). When TLC analysis showed complete consumption of the starting material, the reaction was quenched with sat. aq. $NaHCO_3$. The mixture was diluted with EtOAc, the layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated. The crude was dissolved in DCM/MeOH (7.5 mL/ 7.5 mL), followed by addition of p-toluenesulfonic acid monohydrate (0.057 g, 0.3 mmol). The reaction was stirred for overnight after which it was neutralized with Et_3N and concentrated. The compound was purified by column chromatography (Pent/EtOAc). The diol was dissolved in 10 mL pyridine, cooled to 0°C and 1.67 mL Ac_2O was added. After stirring for 6 days, the reaction was quenched with EtOH, diluted with EtOAc and washed with 1M HCl. Column purification (Pent/EtOAc) gave compound **20** in 57% yield (1.09 g, 1.71 mmol). ^{1}H-NMR($CDCl_3$, 400 MHz): δ 7.84 – 7.61 (m, 8H, CH_{arom}), 7.49 – 7.41 (m, 4H, CH_{arom}), 7.41 – 7.32 (m, 4H, CH_{arom}), 7.26 – 7.17 (m, 3H, CH_{arom}), 5.59 (d, 1H, J=1.6 Hz,

H-1), 5.55 (t, 1H, J=9.6, 9.6 Hz, H-4), 4.87 – 4.72 (m, 2H, CH_2 ONap), 4.70 – 4.54 (m, 2H, CH_2 ONap), 4.39 – 4.24 (m, 2H, H-5, H-6), 4.14 (dd, 1H, J=11.8, 1.8 Hz, H-6), 4.09 – 4.01 (m, 1H, H-2), 3.86 (dd, 1H, J=9.6, 3.0 Hz, H-3), 2.02 (m, 6H, 2x CH_3 Ac); ^{13}C-NMR(CDCl3, 101 MHz): δ 170.7, 169.7 (C=O Ac), 135.2, 135.1, 133.5, 133.2, 133.1, 133.0, 133.0 (C_q), 131.5, 129.0, 128.2, 128.2, 127.9, 127.9, 127.7, 127.7, 126.8, 126.4, 126.2, 126.1, 126.0, 125.9, 125.6 (CH_{arom}), 85.8 (C-1), 77.0 (C-3), 75.4 (C-2), 72.2, 71.9 (CH_2 Nap), 70.0 (C-5), 68.0 (C-4), 62.8 (C-6), 20.9, 20.8 (CH_3 Ac); HRMS: $[M+NH_4]^+$ calculated for $C_{38}H_{40}NO_7S$ 654.25200, found 654.25266.

Phenyl 4,6-di-*O*-acetyl-1-thio-β-D-mannopyranoside (12) Compound **20** (0.127 g, 0.199 mmol) was dissolved in 1:1 DCM/HFIP (2.0 mL) and 0.16 mL TES was added. The mixture was treated with 3.0 mL 0.2M HCl/HFIP was added. After 20 min the reaction was quenched by addition of sat. aq. $NaHCO_3$. The mixture was diluted DCM and the organic layer is washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated. Purification by column chromatography (Tol/EtOAc) gave **12** in 68% yield (0.048 g, 0.135 mmol). Spectroscopic data are in full accord with those reported previously.

Phenyl 4,6-di-*O*-acetyl-3-*O*-(2-naphthylmethyl)-2-*O*-*p*-methoxybenzyl-1-thio-α-D-mannopyranoside (21) Phenyl 4,6-O-Benzylidene-3-O-(2-naphthylmethyl)-1-thio- α -D-mannopyranoside (5.17 g, 10.32 mmol) was coevaporated twice with anhydrous toluene before being dissolved in DMF (25 mL). The mixture was cooled to 0°C, after which sodium hydride (60% dispersion in mineral oil, 1.2 g, 30 mmol) was added. The mixture was stirred for 10 minutes followed by addition of *para*-methoxybenzylchloride (4.1 mL, 30 mmol). When TLC analysis showed complete consumption of the starting material, the reaction was quenched with sat. aq. $NaHCO_3$. The mixture was diluted with EtOAc, washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated. After column purification (Pent/EtOAc) the compound was dissolved in DCM/MeOH (15 mL/ 15 mL), followed by addition of p-toluenesulfonic acid monohydrate (0.06 g, 0.30 mmol). The reaction was stirred overnight after which it was neutralized with Et_3N and concentrated. The compound was purified by column chromatography (Pent/EtOAc) to yield the diol in 89% yield (2.97 g, 5.57

mmol). The diol (1.425 g, 2.67 mmol) was dissolved in 15 mL pyridine, cooled to 0°C and 1.5 mL Ac_2O was added. After stirring for 3 days, the reaction was quenched with EtOH and concentrated. The crude was taken up in EtOAc, washed with 1M HCl and sat. aq. NaCl, dried over $MgSO_4$ and concentrated. Column purification (hexanes/EtOAc) gave compound **21** in 75% yield (1.23 g, 1.99 mmol). ^{1}H-NMR($CDCl_3$, 400 MHz): δ 7.83 (m, 3H, CH_{arom}), 7.73 (s, 1H CH_{arom}), 7.48 (m, 1H, CH_{arom}), 7.47 – 7.36 (m, 4H, CH_{arom}), 7.25 (m, 6H, CH_{arom}), 6.78 (d, 2H, J=8.2 Hz, CH_{arom}), 5.55 (s, 1H, H-1), 5.47 (t, 1H, J=9.7, 9.7 Hz, H-4), 4.71 – 4.61 (m, 2H, CH_2 ONap/OPMB), 4.58 (m, 2H, CH_2 ONap/OPMB), 4.37 – 4.21 (m, 2H, H-5, H-6), 4.12 (d, 1H, J=11.7 Hz, H-6), 4.01 (s, 1H, H-2), 3.83 (dd, 1H, J=9.6, 2.9 Hz, H-3), 3.73 (s, 3H, CH_3 OMe), 2.06 – 2.00 (m, 6H, 2x CH_3 Ac); ^{13}C-NMR($CDCl_3$, 101 MHz): δ 170.8, 169.8 (C=O Ac), 159.3, 135.3, 133.7, 133.3, 133.0, 131.5 (C_q), 129.7, 129.1, 128.2, 128.0, 127.8, 127.7, 126.4, 126.3, 126.1, 125.6, 113.8 (CH_{arom}), 85.8 (C-1), 77.0 (C-3), 75.0 (C-2), 71.8, 71.8 (CH_2 ONap/OPMB), 70.0 (C-5), 68.1 (C-4), 62.9 (C-6), 55.3 (CH_3 OMe), 21.0, 20.8 (CH_3 Ac); HRMS: $[M+NH_4]^+$ calculated for $C_{35}H_{40}NO_8S$ 634.24691, found 634.24718.

Phenyl 4,6-di-*O*-acetyl-3-*O*-(2-naphthylmethyl)-1-thio-α-D-mannopyranoside (22) Compound **21** (0.127 g, 0.202 mmol) was dissolved in 1:1 DCM/HFIP (2 mL) and 0.1 mL 0.2M HCl/HFIP was added. After 5 min the reaction was quenched by addition of sat. aq. $NaHCO_3$. The mixture was diluted DCM and the organic layer is washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated. Purification by column chromatography (Tol/EtOAc) gave **22** in 80% yield (0.080 g, 0.162 mmol). TLC: R_f 0.35 (PE/EtOAc, 2/1, v/v); $[\alpha]_D^{20}$ +132.4 (*c* 1, DCM); IR (neat, cm^{-1}): 742, 1041, 1099, 1224, 1367, 1739, 2893, 3057, 3460; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.88 – 7.82 (m, 3H, CH_{arom}), 7.76 (s, 1H, CH_{arom}), 7.55 – 7.47 (m, 2H, CH_{arom}), 7.50 – 7.37 (m, 3H, CH_{arom}), 7.33 – 7.23 (m, 3H, CH_{arom}), 5.63 (d, 1H, J=1.4 Hz, H-1), 5.35 (t, 1H, J=9.7, 9.7 Hz, H-4), 4.86 (d, 1H, J=12.2 Hz, CH*H* Bn), 4.72 (d, 1H, J=12.2 Hz, C*H*H Bn), 4.37 (ddd, 1H, J=9.9, 5.7, 2.2 Hz, H-5), 4.30 (s, 1H, H-2), 4.24 (dd, 1H, J=12.2, 5.8 Hz, H-6), 4.05 (dd, 1H, J=12.2, 2.3 Hz, H-6), 3.86 (dd, 1H, J=9.3, 3.2 Hz, H-3), 2.85 (s, 1H, 2-OH), 2.01 (s, 6H, 2x CH_3 Ac); ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 170.9, 169.9 (C=O Ac), 134.7 (C_q), 133.3 (C_q), 133.3 (C_q), 133.2, 131.7, 129.2, 128.6, 128.1, 127.9, 127.8, 127.0, 126.5, 126.4,

125.7 (CH_{arom}), 86.9 (C-1), 77.1 (C-3), 72.2 (CH_2 Nap), 69.6 (C-5), 69.5 (C-2), 67.6 (C-4), 62.7 (C-6), 21.0, 20.9 (CH_3 Ac); HRMS: $[M+Na]^+$ calculated for $C_{27}H_{28}O_7SNa$ 519.14480, found 519.14406.

Phenyl 4-*O*-acetyl-3-*O*-Benzyl-2-*O*-*p*-methoxybenzyl-6-*O*-*tert*-butyldimethylsilyl-1-thio-β-D-glucopyranoside (23) Phenyl 3-*O*-Benzyl-2-*O*-*p*-methoxybenzyl-1-thio-β-D-glucopyranoside (2.41 g, 5 mmol) was coevaporated once with anhydrous toluene. The diol was dissolved in DMF (25 mL) and cooled to 0°C. Imidazole (0.35 g, 5.2 mmol) was added followed by TBS-Cl (0.78 g, 5.2 mmol). After 100 minutes the reaction was quenched with MeOH and concentrated. The crude was dissolved in 25 mL pyridine and cooled to 0°C. Ac_2O (1.9 mL) was added and the reaction was stirred for 5 days. The reaction was quenched with EtOH and concentrated. The crude was taken up in EtOAc, washed with 1M HCl and sat. aq. NaCl, dried over $MgSO_4$ and concentrated. Column purification (hexanes/EtOAc) gave compound **23** in 77% yield (2.45 g, 3.83 mmol). ^{1}H-NMR($CDCl_3$, 400 MHz): δ 7.62 – 7.54 (m, 2H, CH_{arom}), 7.38 – 7.18 (m, 10H, CH_{arom}), 6.90 – 6.82 (m, 2H, CH_{arom}), 4.99 (t, 1H, J=9.7, 9.7 Hz, H-4), 4.86 – 4.73 (m, 2H, CH*H* OBn/OPMB), 4.69 – 4.56 (m, 3H, H-1, C*H*H OBn/OPMB), 3.78 (s, 3H, CH_3 OMe), 3.73 – 3.59 (m, 3H, H-3, H-6), 3.52 (t, 1H, J=9.6, 9.1 Hz, H-2), 3.44 (ddd, 1H, J=9.9, 4.8, 3.3 Hz, H-5), 1.90 (s, 3H, CH_3 Ac), 0.90 (s, 9H, CH_3 tBu), 0.89 (s, 3H, CH_3 Me), 0.06 (s, 3H, CH_3 Me); ^{13}C-NMR(CDCl3, 101 MHz): δ 169.6 (C=O Ac), 159.5, 138.3, 133.9 (C_q), 131.9 131.8 (CH_{arom}), 130.2 (C_q), 130.0, 129.0, 128.5, 127.9, 127.8, 127.5, 113.9 (CH_{arom}), 87.6 (C-1), 84.3 (C-3), 80.3 (C-2), 79.2 (C-5), 75.5, 75.1 (CH_2 OBn/OPMB), 70.2 (C-4), 62.9 (C-6), 55.3 (CH_3 OMe), 26.0 (CH_3 tBu), 20.9 (CH_3 Ac), 18.4 (C_q tBu), -5.2, -5.4 (CH_3 Me); $[M+NH_4]^+$ calculated for $C_{35}H_{50}O_7SSiN$ 656.30718, found 656.30769.

Phenyl 4-*O*-acetyl-3-*O*-Benzyl-6-*O*-*tert*-butyldimethylsilyl-1-thio-β-D-glucopyranoside (24) Compound **23** (0.130 g, 0.203 mmol) was dissolved in 1:1 DCM/HFIP (2 mL) and 0.033 mL TES was added. The solution was treated with 0.1 mL of a 0.2M HCl/HFIP solution. After 6 min the reaction was quenched by addition of sat. aq. $NaHCO_3$. The mixture was diluted DCM and the organic layer is washed with

sat. aq. NaCl, dried over $MgSO_4$ and concentrated. Purification by column chromatography (Tol/EtOAc) gave **24** in 48% yield (0.0738 g, 0.142 mmol). TLC: R_f 0.33 (PE/EtOAc, 6/1, v/v); $[\alpha]_D^{20}$ -22.2 (*c* 1, DCM); IR (neat, cm^{-1}): 734, 1026, 1228, 1741, 2856, 2926, 3288; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61 – 7.51 (m, 2H, CH_{arom}), 7.37 – 7.20 (m, 8H, CH_{arom}), 4.93 (t, 1H, J=9.8, 9.8 Hz, H-4), 4.82 (d, 1H, J=11.8 Hz, C*H*H Bn), 4.68 (d, 1H, J=11.8 Hz, CH*H* Bn), 4.50 (d, 1H, J=9.3 Hz, H-1), 3.74 – 3.61 (m, 2H, H-6), 3.60 – 3.43 (m, 3H, H-2, H-3, H-5), 2.46 (s, 1H, 2-OH), 1.96 (s, 3H, CH_3 Ac), 0.90 (s, 9H, CH_3 tBu), 0.07 (s, 3H, CH_3 Me), 0.05 (s, 3H, CH_3 Me); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 169.7 (C=O), 138.4 (C_q), 133.0 (CH_{arom}), 131.6 (C_q), 129.1, 128.6, 128.3, 128.0, 127.9 (CH_{arom}), 88.1 (C-1), 83.3 (C-3), 79.6 (C-5), 74.8 (CH_2 Bn), 72.4 (C-2), 69.9 (C-4), 63.0 (C-6), 26.0 (CH_3 tBu), 21.0 (CH_3 Ac), 18.5 (C_q tBu), -5.1, -5.3 (CH_3 Me); HRMS: $[M+Na]^+$ calculated for $C_{27}H_{38}O_6SSiNa$ 541.20506, found 541.20484.

Phenyl 4-*O*-acetyl-3-*O*-(2-Naphthylmethyl)-2-*O*-*p*-methoxybenzyl-6-*O*-*tert*-butyldimethylsilyl-1-thio-α-D-mannopyranoside (25) Phenyl 3-*O*-(2-Naphthylmethyl)-2-*O*-*p*-methoxybenzyl-1-thio- α -D-mannopyranoside (0.37 g, 0.7 mmol) was coevaporated once with anhydrous toluene. The diol was dissolved in DMF (3.5 mL) and cooled to 0°C. Imidazole (0.05 g, 0.7 mmol) was added followed by TBS-Cl (0.11 g, 0.72 mmol). After 20 minutes the reaction was quenched with MeOH and concentrated. The crude was taken up in Et_2O, washed with H_2O and sat. aq. NaCl, dried over $MgSO_4$ and concentrated. The compound was dissolved in pyridine (3 mL) and cooled to 0°C, followed by addition of 1 mL Ac_2O. The reaction was stirred overnight after which it was quenched with EtOH. The mixture was concentrated, taken up in EtOAc, washed with 1M HCl, sat. aq. $NaHCO_3$ and sat. aq. NaCl, dried over $MgSO_4$ and concentrated. Purification by column chromatography gave compound **25** in 95% yield (0.457 g, 0.66 mmol). ^{1}H-NMR($CDCl_3$, 500 MHz): δ 7.75 – 7.70 (m, 3H, CH_{arom}), 7.66 (s, 1H, CH_{arom}), 7.44 – 7.35 (m, 4H, CH_{arom}), 7.21 – 7.08 (m, 6H, CH_{arom}), 6.69 (d, 2H, J=8.5 Hz, CH_{arom}), 5.43 (s, 1H, H-1), 5.28 (t, 1H, J=9.6, 9.6 Hz, H-4), 4.60 (d, 1H, J=12.4 Hz, CH*H* OPMB/OBn), 4.56 – 4.43 (m, 3H, C*H*H OPMB/OBn, CH_2 OPMB/OBn), 4.10 (bm, 1H, H-5), 3.91 (s, 1H, H-2), 3.76 – 3.67 (m, 2H, H-3, H-6), 3.63 (m, 4H, CH_3 OMe, H-6), 1.94 (s, 3H, CH_3 Ac), 0.86 – 0.77 (m, 9H, CH_3 tBu), -0.05 (s, 6H, 2x CH_3 Me); ^{13}C-NMR($CDCl_3$, 126 MHz): δ 169.9 (C=O Ac), 159.3, 135.5, 134.3,

133.3, 133.0 (C_q), 131.8 (CH_{arom}), 129.9 (C_q), 129.6, 129.0, 128.2, 128.0, 127.8, 127.5, 126.5, 126.2, 126.0, 125.7, 113.8 (CH_{arom}), 85.9 (C-1), 77.2 (C-3), 75.4 (C-2), 73.3 (C-5), 71.7, 71.7 (CH_2 ONap/OPMB), 68.8 (C-4), 63.3 (C-6), 55.2 (CH_3 OMe), 26.0 (CH_3 tBu), 21.1 (CH_3 Ac), 18.4 (C_q tBu), -5.2, -5.3 (CH_3 Me); $[M+NH_4]^+$ calculated for $C_{39}H_{52}O_7SSiN$ 706.32283, found 706.32349.

Phenyl 4-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl-3-*O*-(2-Naphthylmethyl)-1-thio-α-D-mannopyranoside (26) Compound **25** (0.1337 g, 0.194 mmol) was dissolved in 1:1 DCM/HFIP (2 mL) and 0.194 mL TES was added. The solution was treated with 0.095 mL of a 0.2M HCl/HFIP solution. After 3 min the reaction was quenched by addition of sat. aq. $NaHCO_3$. The mixture was diluted DCM and the organic layer is washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated. Purification by column chromatography (Tol/EtOAc) gave **26** in 61% yield (0.07 g, 0.123 mmol). TLC: R_f 0.48 (PE/EtOAc, 7/1, v/v); $[\alpha]_D^{20}$ +92.0 (*c* 1, DCM); IR (neat, cm^{-1}): 740, 777, 835, 1051, 1085, 1228, 1369, 1741, 2854, 2926, 3057, 3640; ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.83 – 7.77 (m, 3H, CH_{arom}), 7.72 (s, 1H, CH_{arom}), 7.45 – 7.42 (m, 4H, CH_{arom}), 7.38 (dd, 1H, J=8.5, 1.6 Hz, CH_{arom}), 7.24 – 7.19 (m, 3H, CH_{arom}), 5.53 (d, 1H, J=1.7 Hz, H-1), 5.23 (t, 1H, J=9.5, 9.5 Hz, H-4), 4.81 (d, 1H, J=12.2 Hz, CH*H* Nap), 4.67 (d, 1H, J=12.2 Hz, C*H*H Nap), 4.27 – 4.22 (m, 1H, H-2), 4.18 (ddd, 1H, J=9.3, 6.2, 2.6 Hz, H-5), 3.79 (dd, 1H, J=9.2, 3.2 Hz, H-3), 3.69 (dd, 1H, J=11.4, 6.2 Hz, H-6), 3.61 (dd, 1H, J=11.4, 2.6 Hz, H-6), 2.74 (s, 1H, 2-OH), 1.96 (s, 3H, CH_3 Ac), 0.82 (s, 9H, CH_3 tBu), -0.03 (s, 3H, CH_3 Me), -0.04 (s, 3H, CH_3 Me); ^{13}C-NMR($CDCl_3$, 125 MHz): δ 170.0 (C=O Ac), 134.9 (C_q), 133.8 (C_q), 133.3 (C_q), 133.2 (C_q), 131.8, 130.5, 129.1, 129.0, 128.6, 128.1, 128.0, 127.9, 127.6, 126.9, 126.5, 126.3, 125.8 (CH_{arom}), 87.2 (C-1), 77.3 (C-3), 72.8 (C-5), 72.0(CH_2 Nap), 69.6 (C-2), 68.3 (C-4), 63.1 (C-6), 26.0 (CH_3 tBu), 21.1 (CH_3 Ac), 18.5 (C_q tBu), -5.2, -5.3 (CH_3 Me); HRMS: $[M+Na]^+$ calculated for $C_{31}H_{40}O_6SSiNa$ 591.22071, found 591.22003.

Phenyl 4-*O*-acetyl-3-*O*-Benzyl-2-*O*-*p*-methoxybenzyl-6-*O*-*tert*-butyldiphenylsilyl-1-thio-β-D-glucopyranoside (27) Phenyl 3-*O*-Benzyl-2-*O*-*p*-methoxybenzyl-1-thio-β-D-glucopyranoside (1.23 g, 2.55 mmol) was coevaporated twice with anhydrous

toluene. The diol was dissolved in DMF (13 mL) and cooled to 0°C. Imidazole (0.17 g, 2.55 mmol) was added followed by TBDPS-Cl (0.69 mL, 2.66 mmol). After 15 minutes the icebath was removed and the reaction was stirred overnight. The reaction was quenched with MeOH, concentrated, dissolved in Et_2O and washed twice with H_2O. The organic layer was washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated. The crude was dissolved in 15 mL pyridine and cooled to 0°C. Ac_2O (1.2 mL) was added and the reaction was stirred until all starting material was converted in a higher running spot. The reaction was quenched with EtOH and concentrated. The crude was taken up in EtOAc, washed with 1M HCl and sat. aq. NaCl, dried over $MgSO_4$ and concentrated. Column purification (hexanes/EtOAc) gave compound **27** in 78% yield (1.53 g, 2.00 mmol). ^{1}H-NMR($CDCl_3$, 400 MHz): δ 7.75 – 7.64 (m, 5H, CH_{arom}), 7.64 – 7.57 (m, 2H, CH_{arom}), 7.46 – 7.17 (m, 16H, CH_{arom}), 6.92 – 6.83 (m, 2H, CH_{arom}), 5.08 (t, 1H, J=9.6, 9.5 Hz, H-4), 4.80 (m, 2H, CH*H* OBn/OPMB), 4.70 – 4.57 (m, 3H, H-1, C*H*H OBn/OPMB), 3.80 (s, 3H, CH_3 OMe), 3.70 (d, 2H, J=3.7 Hz, H-6), 3.65 – 3.50 (m, 2H, H-2, H-3), 3.46 (dt, 1H, J=10.0, 3.7, 3.7 Hz, H-5) 1.75 (s, 3H, CH_3 Ac), 1.06 (s, 9H, CH_3 tBu); ^{13}C-NMR (CDCl3, 101 MHz): δ 169.5 (C=O Ac), 159.6, 138.3 (C_q), 135.8, 135.8, 134.9 (CH_{arom}), 133.9, 133.3, 133.2 (C_q), 132.0 (CH_{arom}), 130.3 (C_q), 130.1, 129.8, 129.7, 129.1, 128.6, 128.0, 127.9, 127.8, 127.8, 127.6, 114.0 (CH_{arom}), 87.7 (C-1), 84.4 (C-3), 80.5 (C-5), 79.2 (C-2), 75.5, 75.2 (CH_2 Bn/PMB), 69.8 (C-4), 63.1 (C-6), 55.4 (CH_3 OMe), 26.9 (CH_3 tBu), 20.8 (CH_3 Ac), 19.3 (C_q tBu); $[M+NH_4]^+$ calculated for $C_{45}H_{54}O_7SSiN$ 780.33848, found 780.33936.

Phenyl 4-*O*-acetyl-3-O-Benzyl-6-*O*-*tert*-butyldiphenylsilyl-1-thio-β-D-glucopyranoside (28) Compound **27** (0.0798 g, 0.104 mmol) was dissolved in 1:1 DCM/HFIP (1 mL) and 0.017 mL TES was added. The solution was treated with 0.05 mL of a 0.2M HCl/HFIP solution. After 18 min the reaction was quenched by addition of sat. aq. $NaHCO_3$. The mixture was diluted DCM and the organic layer is washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated. Purification by column chromatography (Tol/EtOAc) gave **28** in 90% yield (0.06 g, 0.093 mmol). TLC: Rf 0.37 (PE/EtOAc, 6/1, v/v); $[\alpha]_D^{20}$ -17.2 (*c* 1, DCM); IR (neat, cm^{-1}): 740, 1028, 1112, 1228, 1747, 2929, 2954, 3028, 3496; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.73 – 7.65 (m, 4H, CH_{arom}), 7.62 – 7.56 (m, 2H, CH_{arom}), 7.44 – 7.20 (m, 15H, CH_{arom}), 5.03 (t, 1H, J=9.5,

9.5 Hz, H-4), 4.81 (d, 1H, J=11.8 Hz, C*H*H Bn), 4.67 (d, 1H, J=11.8 Hz, CH*H* Bn), 4.52 (d, 1H, J=9.2 Hz, H-1), 3.73 – 3.68 (m, 2H, H-6), 3.59 – 3.47 (m, 3H, H-2, H-3, H-5), 2.47 (d, 1H, J=1.4 Hz, 2-OH), 1.81 (CH_3 Ac) 1.05 (s, 9H, CH_3 tBu); ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 169.5 (C=O Ac), 138.3 (C_q), 135.8, 135.8, 134.9 (CH_{arom}), 133.3 (C_q), 133.2 (CH_{arom}), 133.0 (C_q), 131.7, 129.8, 129.8, 129.2, 128.6, 128.3, 128.0, 127.9, 127.8, 127.8, 127.8 (CH_{arom}), 88.2 (C-1), 83.3 (C-3), 79.5 (C-5), 74.7 (CH_2 Bn), 72.5 (C-2), 69.4 (C-4), 63.0 (C-6), 26.8 (CH_3 tBu), 20.9 (CH_3 Ac), 19.3 (C_q tBu); HRMS: $[M+Na]^+$ calculated for $C_{37}H_{42}O_6SSiNa$ 665.23636, found 665.23572.

Phenyl 4-*O*-acetyl-3-*O*-(2-Naphthylmethyl)-2-*O*-*p*-methoxybenzyl-6-*O*-*tert*-butyldiphenylsilyl-1-thio-α-D-mannopyranoside (29) Compound **21** (0.416 g, 0.6 mmol) was dissolved in MeOH and a catalytic amount of NaOMe was added. After consumption of the starting material in a lower running spot the mixture was neutralized with Amberlite-H^+ resin, filtered and concentrated. The diol was coevaporated once with anhydrous toluene, dissolved in DMF (5 mL) and cooled to 0°C. Imidazole (0.04 g, 0.6 mmol) was added followed by TBDPS-Cl (0.16 mL, 0.62 mmol). After overnight stirring the reaction was quenched with MeOH and concentrated. The compound was dissolved in pyridine (4 mL) and cooled to 0°C, followed by addition of 2 mL Ac_2O. The reaction was stirred overnight after which it was quenched with EtOH. The mixture was concentrated, taken up in Et_2O, washed with 1M HCl, sat. aq. $NaHCO_3$ and sat. aq. NaCl, dried over $MgSO_4$ and concentrated. Purification by column chromatography gave compound **25** in 50% yield (0.25 g, 0.30 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.86 – 7.77 (m, 3H, CH_{arom}), 7.74 (s, 1H, CH_{arom}), 7.66 (m, 4H, CH_{arom}), 7.52 – 7.16 (m, 17H, CH_{arom}), 6.80 – 6.73 (m, 2H, CH_{arom}), 5.57 (d, 1H, J=1.8 Hz, H-1), 5.44 (t, 1H, J=9.7, 9.7 Hz, H-4), 4.73 – 4.53 (m, 4H, 2x CH_2 ONap/OPMB), 4.29 – 4.20 (m, 1H, H-5), 4.05 – 3.99 (m, 1H, H-2), 3.85 (dd, 1H, J=11.4, 6.2 Hz, H-6), 3.79 (dd, 1H, J=9.4, 3.0 Hz, H-3), 3.75 – 3.64 (m, 4H, CH_3 OMe, H-6), 1.86 (s, 3H, CH_3 Ac), 1.03 (s, 9H, CH_3 tBu); ^{13}C-NMR(CDCl3, 101 MHz): δ 169.7 (C=O), 159.3 (C_q), 135.8, 135.7 (CH_{arom}), 135.5, 134.7, 133.5, 133.4, 133.3, 133.1 (C_q), 131.3 (CH_{arom}), 129.9 (C_q), 129.7, 129.6, 129.6, 129.1, 128.2, 128.0, 127.8, 127.7, 127.6, 127.4, 126.5, 126.2, 126.0, 125.8, 113.8 (CH_{arom}), 86.0 (C-1), 77.2 (C-3), 75.4 (C-2), 73.3 (C-5), 71.8, 71.6 (CH_2 ONap/OPMB), 68.3 (C-4), 63.5 (C-6), 55.3 (CH_3 OMe), 26.8

(CH_3 tBu), 21.0 (CH_3 Ac), 19.3 (C_q tBu); $[M+NH_4]^+$ calculated for $C_{49}H_{56}O_7SSiN$ 830.35413, found 830.35472.

Phenyl 4-*O*-acetyl-6-*O*-*tert*-butyldiphenylsilyl-3-*O*-(2-Naphthylmethyl)-1-thio-α-D-mannopyranoside (30) Compound **29** (0.0825 g, 0.101 mmol) was dissolved in 1:1 DCM/HFIP (1 mL) and 0.1 mL 0.2M HCl/HFIP was added. After 18 min the reaction was quenched by addition of sat. aq. $NaHCO_3$. The mixture was diluted DCM and the organic layer is washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated. Purification by column chromatography (Tol/EtOAc) gave **30** in 88% yield (0.0614 g, 0.0886 mmol). TLC: Rf 0.23 (PE/EtOAc, 6/1, v/v); $[\alpha]_D^{20}$ +71.8 (*c* 1, DCM); IR (neat, cm^{-1}): 740, 821, 1053, 1083, 1228, 1743, 2854, 2927, 3051, 3448; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.84 (d, 3H, J=7.8 Hz), 7.76 (s, 1H), 7.67 – 7.61 (m, 4H), 7.54 – 7.46 (m, 4H), 7.45 – 7.27 (m, 7H), 7.27 – 7.19 (m, 4H), 5.62 (d, 1H, J=1.6 Hz, H-1), 5.34 (t, 1H, J=9.5, 9.5 Hz, H-4), 4.85 (d, 1H, J=12.2 Hz, CH*H* Nap), 4.71 (d, 1H, J=12.2 Hz, C*H*H Nap), 4.31 (s, 1H, H-2), 4.29 – 4.23 (m, 1H, H-5), 3.84 – 3.75 (m, 2H, H-3, H-6), 3.64 (dd, 1H, J=11.5, 2.1 Hz, H-6), 2.74 (s, 1H, 2-OH), 1.85 (s, 3H, CH_3 Ac), 1.01 (s, 9H, CH_3 tBu); ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 169.8 (C=O Ac), 135.9, 135.7, 134.8 (C_q), 134.1 (C_q), 133.5 (C_q), 133.3 (C_q), 133.3 (C_q), 133.3 (C_q), 131.4, 129.7, 129.7, 129.2, 128.6, 128.1, 127.9, 127.8, 127.7, 127.5, 127.0, 126.5, 126.3, 125.8 (CH_{arom}), 87.2 (C-1), 77.3 (C-3), 72.8 (C-5), 71.9 (CH_2 Nap), 69.7 (C-2), 67.8 (C-4), 63.3 (C-6), 26.8 (CH_3 tBu), 21.0 (CH_3 Ac), 19.3 (C_q tBu); HRMS: $[M+Na]^+$ calculated for HRMS: $[M+Na]^+$ calculated for $C_{41}H_{44}O_6SSiNa$ 715.25201, found 715.25149.

Methyl (3-*O*-benzyl-4-*O*-levulinoyl-2-*O*-(2-naphthylmethyl)-1-*O*-(*N*-[phenyl]trifluoroacetimidoyl)-α/β-D-mannopyranosyl uronate) (31) Dibutyltinoxide (5.98 g, 24 mmol, 1.2 eq.) was added to a solution of **methyl 4,6-*O*-benzylidene-α-D-mannopyranoside**[18] (5.65 g, 20 mmol) in toluene (100 mL) and refluxed overnight under an argon atmosphere. The solution was concentrated to dryness *in vacuo* and DMF (100 mL) was added under argon. Benzyl bromide (2.6 mL, 22 mmol, 1.1 eq.) and CsF (3.65 g, 24 mmol, 1.2 eq.) were added to the reaction mixture. After stirring overnight the reaction mixture was quenched with H_2O and extracted first with Et_2O

and then EtOAc, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (PE/EtOAc, 5:1 to 1:2) yielded the title compound as a yellow oil (6.7 g, 18 mmol, 89%). TLC: R_f 0.59 (PE/EtOAc, 1/1, v/v); **Methyl 3-*O*-benzyl-4,6-O-benzylidene-α-D-mannopyranoside** (6.48 g, 17.4 mmol) was dissolved in DMF (90 mL) and cooled to 0°C. 2-(Bromomethyl)naphthalene (4.62 g, 20.9 mmol, 1.2 eq.) and sodiumhydride (60% dispersion in oil, 867 mg, 20.9 mmol, 1.2 eq.) were added and the solution left to stir for 3.5 hours. The reaction mixture was quenched by dropwise addition of H_2O and subsequently extracted with EtOAc. The organic layer was washed with sat. aq. NaCl and dried with $MgSO_4$. After filtration and concentration in vacuo, the crude compound was purified by column chromatography (PE/EtOAc, 9:1 to 4:1) to yield the title compound as a yellow oil (8.41 g, 16.4 mmol, 94%). TLC: R_f 0.62 (PE/EtOAc, 4/1, v/v); To a solution of the compound (7.3 g, 14.2 mmol) in acetic anhydride (70 mL), pTsOH•H_2O (4.0 g, 21.0 mmol, 1.5 eq.) was added. The reaction mixture was allowed to stir for four days at room temperature until TLC analysis showed substantial conversion to the desired product. The reaction mixture was quenched by pouring it over ice and gradually adding solid $NaHCO_3$ until all ice had melted and CO_2 evolution had stopped. The aqueous mixture was extracted two times with EtOAc and the combined organic layers where washed once with sat. aq. NaCl. The organic fraction was dried over $MgSO_4$, filtered and concentrated *in vacuo*, after which the residue was co-evaporated once with toluene. Column chromatography purification (PE/EtOAc, 6:1 to 2:1) afforded the title compound as an orange oil (5.06 g, 9.44 mmol, 66%, α >> β). TLC: R*f* 0.36 (PE/EtOAc, 2/1, v/v); **Methyl 4,6-di-*O*-acetyl-3-*O*-benzyl-2-*O*-(2-naphthylmethyl)-α-D-mannopyranoside** (5.06 g, 9.44 mmol) was dissolved in 4% piperidine (1.85 mL, 18.9 mmol, 2 eq.) in THF (47 mL). After stirring for 3 days at room temperature H_2O was added and the mixture was extracted with EtOAc. The organic layer was washed once with sat. aq. NaCl and subsequently dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (PE/EtOAc, 9:1 to 1:1) gave the hemiacetal as an yellow oil (4.1 g, 8.3 mmol, 88%, α : β = 4.3 : 1). TLC: R_f 0.58 (PE/EtOAc, 1/1, v/v); TBDMSCl (1.5 g, 10 mmol, 2 eq.) and imidazole (0.68 g, 10 mmol, 2eq.) were added to a solution of the hemiacetal (2.45 g, 4.95 mmol) in dry DCM (25 mL) under an argon atmosphere. After stirring for 6.5

hours the reaction was quenched with H_2O and extracted twice with EtOAc. Combined organic layers were washed with sat. aq. NaCl, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (PE/EtOAc, 15:1 to 2:1) yielded the silylether as an yellowish oil (2.59 g, 4.25 mmol, 86%, α : β = 1 : 4.5). TLC: R_f 0.49 (PE/EtOAc, 4/1, v/v); To a solution of the anomeric silylether (907 mg, 1.49 mmol) in MeOH (8 ml) a catalytic amount of NaOMe (8 mg, 0.15 mmol, 0.1 eq.) was added. After stirring overnight, the reaction mixture was neutralized with Amberlite H^+ which was subsequently filtered off. The filtrate was concentrated *in vacuo* and ***tert*-butyldimethylsilyl 3-*O*-benzyl-2-*O*-(2-naphthylmethyl)-α/β-D-mannopyranoside** was obtained as a colourless oil (770 mg, 1.47 mmol, 98%, α : β = 1 : 4.2). TLC: R_f 0.48 (PE/EtOAc, 1/1, v/v); Diol (3.7 g, 7.05 mmol) was dissolved in EtOAc (25 mL) and H_2O (10 mL) was added. To the biphasic system TEMPO (220 mg, 1.41 mmol, 0.2 eq.) and BAIB (5.68 g, 17.6 mmol, 2.5 eq.) were added. After stirring vigorously for 4.5 hours at room temperature, the reaction was quenched by addition of sat. aq. $Na_2S_2O_3$. EtOAc (50 mL) was added and the layers separated. The organic layer was dried with $MgSO_4$, filtered and concentrated *in vacuo*. The residue was co-evaporated with toluene once. The crude mannuronic acid was then dissolved in DMF (22 mL) and put under an argon atmosphere at 0°C. Methyl iodide (1.3 mL, 21.15 mmol, 3.0 eq.) and K_2CO_3 (2.92 g, 21.15 mmol, 3.0 eq.) were added and the reaction was stirred overnight. The reaction was quenched with H_2O and extracted twice with EtOAc. The organic layers were collected and dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (PE/EtOAc, 10:1 to 2:1) afforded the mannuronic acid as a yellow solid (3.11 g, 5.63 mmol, 80%, α : β = 1 : 8.3). TLC: R_f 0.29 (PE/EtOAc, 4/1, v/v); Levulinic acid (1.08 g, 9.32 mmol, 2.8 eq.) and DIC (0.73 mL, 4.66 mmol, 1.4 eq.) were added to a 0°C solution of **methyl (*tert*-butyldimethylsilyl 3-*O*-benzyl-2-*O*-(2-naphthylmethyl)-α/β-D-mannopyranosyl uronate)** (1.84 g, 3.33 mmol) in dry DCM (8.5 mL). A catalytic amount of DMAP (40 mg, 0.3 mmol, 0.1 eq.) was added and the reaction mixture was allowed to reach room temperature. After 3 hours the reaction mixture was filtered over Celite and the filtrate washed with sat. aq. $NaHCO_3$ and sat. aq. NaCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Column chromatography (PE/EtOAc, 6:1 to 2:1) afforded the compound as an amorphous

off-white solid (2.07 g, 3.18 mmol 95%, α : β = 1 : 10). TLC: R_f 0.45 (PE/EtOAc, 2/1, v/v); Acetic acid (0.36 mL, 6.36 mmol, 2 eq.) was added to a 0°C solution of compound **Methyl (*tert*-butyldimethylsilyl 3-*O*-benzyl-4-*O*-levulinoyl-2-*O*-(2-naphthylmethyl)-α/β-D- mannopyranosyl uronate)** (2.07 g, 3.18 mmol) in dry THF (30 mL). TBAF (1.0 M solution in THF, 4.8 mL, 4.8 mmol, 1.5 eq.) was added drop wise over 5 minutes. The reaction mixture was stirred for 2.5 hours at room temperature and subsequently diluted with EtOAc and washed once with H_2O and sat. aq. NaCl. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (Pentane/DCM/EtOAc, 4:1:1 to 1:1:2) furnished the hemiacetal as a colourless oil (1.7 g, 3.17 mmol, 99%, α : β = 8.3 : 1). TLC: R*f* 0.18 (PE/EtOAc, 1/1, v/v); Trifluoro-*N*-phenylacetimidoyl chloride (0.82 mL, 5.4 mmol, 1.1 eq.) was added drop wise to a 0°C solution of the hemiacetal (2.6 g, 4.8 mmol) and Cs_2CO_3 (1.9 g, 5.86 mmol 1.2 eq.) in acetone (16 mL). After stirring overnight at ambient temperature TLC analysis showed complete conversion of the starting compound to a higher running spot. H_2O was added and the mixture was extracted two times with EtOAc. The organic fraction was washed with sat. aq. NaCl, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude compound was purified using column chromatography (PE/EtOAc, 8:1 to 1:1) to yield the title compound as a yellow oil (3.39 g, 4.79 mmol, 98%, α : β = 8.3 : 1). TLC: R_f 0.69 α, 0.63 β (PE/EtOAc, 1/1, v/v); IR (neat, cm^{-1}): 1123, 1153, 1207, 1717, 1748; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.71-7.81 (m, 2.24H, CH_{arom}), 7.44-7.50 (m, 3.36H, CH_{arom}), 7.21-7.30 (m, 10.20H, CH_{arom}), 7.11 (t, 1H, *J* = 7.6 Hz, CH_{arom} NPh), 6.67-6.71 (m, 2.24H, CH_{arom} NPh), 6.47 (bs, 1H, H-1 α), 6.04 (bs, 0.12H, H-1 β), 5.74 (t, 0.12H, *J* = 6.4Hz, H-4 β), 5.61 (t, 1H, *J* = 7.6Hz, H-4 α), 4.97 (s, 0.24H, CH2 Bn/Nap β), 4.86 (d, 1H, *J* = 12.0 Hz, C*H*H Bn/Nap α), 4.80 (d, 1H, *J* = 12.0 Hz, CH*H* Bn/Nap α), 4.68 (d, 0.12H, *J* = 12.4 Hz, C*H*H Bn/Nap β), 4.60-4.63 (m, 1.12H, C*H*H Bn/Nap α, CH*H* Bn/Nap β), 4.55 (d, 1H, *J* = 12.0 Hz, CH*H* Bn/Nap α), 4.40 (d, 1H, *J* = 7.2 Hz, H-5 α), 4.14 (bs, 0.12H, H-5 β), 4.07 (bs, 0.12H, H-2 β), 3.89 (dd, 1H, *J* = 3.2, 7.6 Hz, H-3 α), 3.80-3.82 (m, 1.12H, H-2 α, H-3 β), 3.69 (s, 3H, CH_3 CO_2Me α), 3.64 (s, 0.36H, CH_3 CO_2Me β), 2.69 (t, 2.24H, *J* = 6.4 Hz, CH_2 Lev α,β), 2.46-2.62 (m, 2.24H, CH_2 Lev α,β), 2.17 (s, 3H, CH_3 Lev α), 2.16 (s, 0.36H, CH_3 Lev β); ^{13}C-NMR ($CDCl_3$, 100MHz): δ 206.2 (C=O Lev), 171.6, 168.0 (C=O Lev, CO_2Me), 143.2, 142.5, 142.2, 141.8, 137.9, 137.5, 135.2, 134.9, 133.2 (C_q), 128.8,

128.7, 128.5, 128.4, 128.1, 128.0, 128.0, 127.8, 127.7, 127.4, 127.2, 126.2, 126.1, 126.1, 124.5, 124.2, 119.5 (CH_{arom}), 94.5 (C-1 α), 74.8 (C-3 α), 73.3, 73.1, 73.0, 72.9, 72.9, 72.7, 72.6, 71.6 (CH_2 Bn α,β, Nap α,β, C-2 α, C-3 β, C-5 α, C-5 β), 69.5 (C-2 β) (C-4 α), 68.9 (C-4 β), 52.8 (CH_3 CO_2Me α), 52.6 (CH_3 CO_2Me β), 37.7 (CH_2 Lev), 29.8 (CH_3 Lev), 27.9 (CH_2 Lev); ^{13}C-GATED NMR ($CDCl_3$, 100MHz): δ 94.5 ($J_{C1,H1}$ = 186 Hz, C-1 α); HRMS: $[M+Na]^+$ calculated for $C_{38}H_{36}F_3NO_9Na$ 730.22344, found 730.22372.

Methyl (Methyl 2,3-di-*O*-(2-naphthylmethyl)-α-D-mannopyranosyl uronate) (32) 2-(Bromomethyl)naphthalene (464 mg, 2.1 mmol, 2.1 eq.) was added to a 0°C solution of compound **methyl 4,6-*O*-benzylidene-α-D-mannopyranoside**[20] (285 mg, 1.01 mmol) in DMF (5 mL) under an argon atmosphere. Sodium hydride (60% dispersion in oil, 100 mg, 2.5 mmol, 2.5 eq.) was added and the reaction mixture was stirred overnight at room temperature. The reaction was quenched by the dropwise addition of H_2O and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (PE/EtOAc, 8:1 to 4:1) yielded the compound as a yellow oil (560 mg, 0.99 mmol, 98%). TLC: R_f 0.59 (PE/EtOAc, 4/1, v/v); To a solution of **methyl 4,6-*O*-benzylidene-2,3-di-*O*-(2-naphthylmethyl)-α-D-mannopyranoside** (5.4 g, 9.6 mmol) in MeOH/DCM (1/1, 50 mL) pTsOH•H_2O (1.2 g, 6.25 mmol, 0.65 eq.) was added and allowed to stir overnight. After quenching with sat. aq. $NaHCO_3$, the mixture was extracted with EtOAc and the layers separated. The organic layer was washed with H_2O and sat. aq. NaCl, dried with $MgSO_4$, filtered and concentrated *in vacuo.* Purification by column chromatography (PE/EtOAc, 7:1 to 1:3) afforded the diol as a yellowish oil (4.0 g, 8.44 mmol, 88%). TLC: R_f 0.20 (Pentane/EtOAc, 1/2, v/v); The diol (2.77 g, 5.84 mmol) was dissolved in DCM (20 mL) and H_2O (10 mL). To the biphasic system TEMPO (228 mg, 1.46 mmol, 0.25 eq.) and BAIB (230 mg, 0.713 mmol, 2.5 eq.) were added. After stirring vigorously for 5 hours at room temperature, the reaction was quenched by addition of sat. aq. $Na_2S_2O_3$. The mixture was extracted twice with Et_2O and the layers separated. The organic layer was dried with $MgSO_4$, filtered and concentrated *in vacuo*. The residue was co-evaporated with toluene once. The crude mannuronic acid was then dissolved in DMF (30 mL) and put under an argon atmosphere at 0°C. Methyl iodide (1.1 mL, 17.5 mmol, 3 eq.) and K_2CO_3 (2.4

g, 17.5 mmol, 3 eq.) were added and the reaction was stirred overnight. The reaction was quenched with H_2O and extracted two times with EtOAc. The organic layers were collected and dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (Pentane/EtOAc, 10:1 to 3:2) afforded the title compound as a yellow oil (1.6 g, 3.2 mmol, 55%). TLC: R_f 0.24 (Pentane/EtOAc, 2/1, v/v); IR (neat, cm^{-1}): 750, 818, 1059, 1172, 1748, 3480; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.87 – 7.70 (m, 8H, CH_{arom}), 7.55 – 7.43 (m, 6H, CH_{arom}), 4.95 – 4.82 (m, 4H, H-1, CH_2 Nap, CH*H* Nap), 4.77 (d, 1H, J=12.1 Hz, C*H*H Nap), 4.44 (td, 1H, J=9.3, 9.3, 1.9 Hz, H-4), 4.17 (d, 1H, J=9.4 Hz, H-5), 3.86 – 3.82 (m, 5H, H-2, H-3, CH_3 CO_2Me), 3.40 (s, 3H, CH_3 OMe), 3.21 (d, 1H, J=2.5 Hz, 4-OH); ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 170.8 (C=O CO_2Me), 135.8, 135.5, 133.3, 133.2, 133.0, 133.0 (C_q), 128.2, 128.0, 128.0, 127.7, 127.7, 126.8, 126.4, 126.1, 126.1, 126.0, 126.0, 125.9, 125.7 (CH_{arom}), 99.9 (C-1), 78.6 (C-2), 74.0 (C-3), 73.0 (CH_2 Nap), 72.7 (CH_2 Nap), 71.8 (C-5), 68.6 (C-4), 55.5 (CH_3 CO_2Me), 52.7 (CH_3 OMe). ^{13}C-GATED NMR ($CDCl_3$, 100MHz): δ 99.8 ($J_{C1,H1}$ = 169 Hz, C-1 α); HRMS: $[M+NH_4]^+$ calculated for $C_{30}H_{34}NO_7$ 520.23298, found 520.23331.

Methyl (methyl 4-O-[methyl 3-*O*-benzyl-4-*O*-levulinoyl-2-*O*-(2-naphthylmethyl)-β-D-mannopyranosyl uronate]-2,3-di-*O*-(2-naphthylmethyl)-α-D-mannopyranosyl uronate) (33) Imidate donor **31** (0.74 g, 1.05 mmol) and acceptor **32** (0.632 g, 1.26 mmol, 1.2 eq were co-evaporated twice with anhydrous toluene. The residue was dissolved in dry DCM (21 mL) and 3Å molecular sieves were added. The solution was stirred at room temperature for 30 minutes before it was cooled to -45°C and stirred at that temperature for 30 minutes. Triflic acid (0.02 mL, 0.216 mmol) was added and and the reaction was allowed to stir for 30 min, after which time Et_3N was added (0.2 mL). The mixture was diluted with EtOAc, washed with sat. aq. NaCl, the organic phase was dried over $MgSO_4$ and concentrated in vacuo. Purification using column chromatography (4:1 → 2:1 hexanes/EtOAc) yielded the disaccharide as a white foam (0.80 g, 0.78 mmol, 72%). TLC: R_f 0.23 (PE/EtOAc, 3/2, v/v); IR (neat, cm^{-1}): 750, 820, 1055, 1126, 1364, 1719, 1748; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.60-7.80 (m, 12H, CHarom), 7.36-7.50 (m, 9H, CHarom), 7.23-7.36 (m, 3H, CHarom), 7.17-7.19 (m, 2H, CHarom), 5.53 (t, 1H, *J* = 9.6 Hz, H-4'), 5.08 (bs, 1H, H-1), 4.68-4.94 (m, 7H, CH2 Nap, CH2 Nap, CH2 Bn/Nap, H-1'), 4.53 (t, 1H, *J* = 5.6 Hz, H-4), 4.45 (d, 1H, *J* = 12.4 Hz, C*H*H Bn/Nap), 4.39 (d, 1H, *J* = 12.0 Hz, CH*H* Bn/Nap), 4.28 (d, 1H, *J* = 5.6 Hz, H-5), 4.14 (bs, 1H, H-3), 3.89 (d, 1H, *J* = 2.8 Hz, H-2'), 3.83 (d, 1H, *J* = 9.6 Hz, H-5'), 3.76 (dd, 1H, *J* = 2.8, 5.2 Hz, H-2), 3.52-3.54 (m, 9H, 2x CH_3 CO_2Me, OMe), 3.46 (dd, 1H, *J* = 2.8, 9.6 Hz, H-3'), 2.68 (t, 2H, *J* = 6.4 Hz, CH_2 Lev), 2.51-2.55 (m, 2H, CH_2 Lev), 2.13 (s, 3H, CH_3 Lev); ^{13}C-APT NMR ($CDCl_3$, 100 MHz): δ 206.3 (C=O Lev), 171.7, 169.8, 167.8 (C=O CO2Me, Lev), 137.8, 136.1, 135.8, 135.7, 133.3, 133.2, 133.2, 133.0, 133.0, 132.9 (C_q), 128.4, 128.4, 128.1, 128.1, 128.0, 128.0, 128.0, 127.9, 127.8, 127.7, 127.7, 127.6, 127.0, 126.6, 126.2, 126.1, 126.0, 126.0, 125.9, 125.9, 125.8, 125.7, 125.6 (CH_{arom}), 101.2 (C-1'), 99.8 (C-1), 78.1 (C-3'), 76.9 (C-3), 76.7 (C-4), 75.2 (C-2), 74.2 (CH_2 Bn/Nap), 73.9 (C-2'), 73.5 (C-5'), 73.0, 72.9 (CH_2 Bn/Nap), 72.0 (CH_2 Bn/Nap), 71.9 (C-5), 71.8 (CH2 Bn/Nap), 69.2 (C-4'), 56.2 (CH_3 OMe), 52.5, 52.3 (CH_3 CO_2Me), 37.8 (CH_2 Lev), 29.9 (CH_3 Lev), 27.9 (CH_2 Lev); ^{13}C-GATED NMR ($CDCl_3$, 100MHz): δ 101.2 ($J_{C1,H1}$ = 156 Hz, C-1' β), 99.8 ($J_{C1,H1}$ = 169 Hz, C-1 α); HRMS: $[M+NH_4]^+$ calculated for $C_{60}H_{64}NO_{15}$ 1038.42705, found 1038.42936.

Methyl (methyl 4-O-[methyl 3-*O*-benzyl-4-*O*-levulinoyl-β-D-mannopyranosyl uronate]-α-D-mannopyranosyl uronate) (34) Mannuronic acid disaccharide **33** (0.0825 g, 0.0807) was dissolved in 1:1 DCM/HFIP (2 mL). Triisopropylsilane (0.082 mL, 0.4 mmol) was added and the mixture was treated with 1.2 mL 0.2M HCl/HFIP. After stirring for 10 minutes, the reaction was quenched with sat. aq, $NaHCO_3$. The mixture was diluted DCM and the organic layer is washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated. Purification by column chromatography (2:1 pentanes/EtOAc → 19:1 EtOAc/MeOH) yielded the triol **34** 86% yield (0.0421 g, 0.070 mmol). TLC: R_f 0.43 (EtOAc/MeOH, 19/1, v/v); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.40 – 7.29 (m, 5H, CH_{arom}), 5.47 (t, 1H, J=8.7, 8.7 Hz, H-4'), 4.83 – 4.74 (m, 3H, H-1, H-1', OH), 4.71 (d, 1H, J=12.2 Hz, C*H*H Bn), 4.65 (d, 1H, J=12.2 Hz, CH*H* Bn), 4.21 – 4.06 (m, 3H, H-5, H-2, H-2'), 4.06 – 3.94 (m, 3H, H-3, H-4, H-5'), 3.77 (s, 3H, CH_3 CO_2Me), 3.72 – 3.63 (m, 4H, CH_3 CO_2Me, H-3'), 3.43 (s, 3H, CH_3 OMe), 3.28 (bs, 1H, OH), 2.99 (bs, 1H, OH), 2.73 (t, 2H, J=6.5, 6.5 Hz, CH_2 Lev), 2.56 (dt, 2H, J=13.3, 6.5, 6.5 Hz, CH_2 Lev), 2.19 (s, 3H, CH_3 Lev); ^{13}C-NMR($CDCl_3$, 100 MHz): δ 206.3 (C=O Lev), 171.7, 169.8, 168.1 (C=O Lev, CO_2Me), 137.5 (C_q), 128.4, 127.9, 127.7 (CH_{arom}), 100.9 (C-1), 100.4 (C-1'), 79.9 (C-4), 77.3 (C-3'), 72.0 (CH_2 Bn), 71.9 (C-5'), 69.5 (C-2), 69.3 (C-3), 69.1 (C-5), 67.9 (C-4'), 67.4 (C-2'), 55.4 (CH_3 OMe), 52.9, 52.5 (CH_3 CO_2Me), 37.6 (CH_2 Lev), 29.8 (CH_3 Lev), 27.8 (CH_2 Lev); HRMS: $[M+NH_4]^+$ calculated for $C_{27}H_{40}NO_{15}$ 618.23925, found 618.23972.

Methyl (methyl 4-O-[methyl 3-*O*-benzyl-4-*O*-levulinoyl-2-*O*-sulfo-β-D-mannopyranosyl uronate]-2,3-di-*O*-sulfo-α-D-mannopyranosyl uronate) (35) Triol **34** (0.061 g, 0.101 mmol) was co-evaporated twice with DMF and dissolved in DMF. Sulfur trioxide triethylamine complex (0.276 g, 1.52 mmol) was added and the temperature is raised to 55°C. The septum is replaced with a stopper and the flask is sealed, allowed to stir overnight at 55°C. After TLC analysis showed conversion of the starting material in a lower running spot, the mixture was cooled to 0°C and $NaCO_3$ (0.14 g, 1.67 mmol) in 10 mL H_2O was added and stirred for 30 minutes at 0°C. The mixture was concentrated at 25°C and purified using size exclusion chromatography (eluted with DCM/MeOH, 1/1, v/v) to yield sulfated disaccharide in 100% yield as the triethylaminium salt (0.124 g, 0.108 mmol). TLC: R_f 0.43 (DCM/MeOH, 3/1, v/v); ^{1}H-

NMR (MeOD, 850 MHz): δ 7.38 (d, 2H, J=7.6 Hz, CH_{arom}), 7.30 (t, 2H, J=7.6, 7.6 Hz, CH_{arom}), 7.23 (t, 1H, J=7.4, 7.4 Hz, CH_{arom}), 5.16 – 5.09 (m, 2H, H-1', H-4'), 5.01 – 4.97 (m, 2H, H-1, H-2'), 4.94 – 4.86 (m, 2H, H-2, H-3), 4.84 (d, 1H, J=12.0 Hz, C*H*H Bn), 4.45 (d, 1H, J=12.0 Hz, CH*H* Bn), 4.41 (s, 2H, H-4, H-5), 4.05 (d, 1H, J=9.9 Hz, H-5'), 3.78 (s, 3H, CH_3 CO_2Me), 3.74 (dd, 1H, J=9.8, 2.9 Hz, H-3'), 3.66 (s, 3H, CH_3 CO_2Me), 3.41 (s, 3H, CH_3 OMe), 3.20 (q, 18H, J=7.3, 7.3, 7.2 Hz, 3xCH_2 Et_3N), 2.65 (td, 2H, J=6.5, 6.4, 2.1 Hz, CH_2 Lev), 2.47 (q, 2H, J=6.8, 6.8, 6.6 Hz, CH_2 Lev), 2.10 (s, 3H, CH_3 Lev), 1.28 (t, 27H, J=7.4, 7.4 Hz, 3xCH_3 Et_3N); ^{13}C-NMR (MeOD, 214 MHz): δ 207.9 (C=O Lev), 172.7, 170.2, 169.5 (C=O Lev, CO_2Me), 138.9 (C_q), 128.6, 128.5, 128.5, 128.5, 127.9 (CH_{arom}), 100.1 (C-1), 99.6 (C-1'), 77.4 (C-3'), 76.8 (C-4 or C-5), 74.9 (C-2), 74.2 (C-2'), 73.4 (C-3 and C-5'), 71.9 (C-4 or C-5), 71.4 (CH_2 Bn), 69.1 (C-4'), 55.2 (CH_3 OMe), 52.4, 52.3 (CH_3 CO_2Me), 47.3 (CH_2 Et_3N), 37.7 (CH_2 Lev), 28.9 (CH_3 Lev), 28.2 (CH_2 Lev), 8.6 (CH_3 Et_3N); HRMS: $[M+H]^+$ calculated for $C_{45}H_{81}N_3O_{24}S_3$ 1144.44591, found 1144.44449.

Methyl (4-O-[3-*O*-benzyl-2-*O*-sulfo-β-D-mannopyranosyl uronate]-2,3-di-*O*-sulfo-α-D-mannopyranosyl uronate) (36) Sulfated disaccharide **35** (0.0567 g, 0.05 mmol) was dissolved in 1:1 THF/H_2O (2 mL) and cooled to 0°C. A 0.5M LiOH/H_2O_2 (0.74 mL, 5 eq. per ester) solution was added and the reaction was allowed to warm up to room temperature. After overnight stirring, the reaction was neutralized with 1M HCl (aq). The mixture was concentrated *in vacuo* and purified using HW-40 size-exclusion chromatography (eluted with NH_4OAc) to give the oligosaccharide after lyophilization. The compound was taken up in a small amount of H_2O and passed through a column of Dowex 50 WX-4 (Na^+ form) to yield the saponified disaccharide after lyophilization (23.8 mg, 28.9 µmol, 66%). ^{1}H-NMR (D_2O, 600 MHz, T=313K): δ 7.54 – 7.49 (m, 2H, CH_{arom}), 7.45 – 7.41 (m, 2H, CH_{arom}), 7.40 – 7.36 (m, 1H, CH_{arom}), 5.12 (d, 1H, J=3.8 Hz, H-1'), 5.05 (d, 1H, J=2.8 Hz, H-2'), 4.91 (d, 1H, J=11.2 Hz, C*H*H Bn), 4.86 – 4.78 (m, 3H, H-1, H-2, H-3), 4.54 (d, 1H, J=11.2 Hz, CH*H* Bn), 4.33 (s, 1H, H-4), 4.21 (d, 1H, J=7.0 Hz, H-5), 3.77 (t, 1H, J=9.7, 9.7 Hz, H-4'), 3.70 (d, 1H, J=9.9 Hz, H-5'), 3.65 (dd, 1H, J=9.7, 2.9 Hz, H-3'), 3.49 (s, 3H, CH_3 OMe); ^{13}C-NMR (D_2O, 150 MHz, T=313K): δ 176.5, 175.8 (2x COO^-), 138.3 (C_q), 130.7, 129.8, 129.6, 129.4, 129.0 (CH_{arom}), 99.4 (C-1), 98.5 (C-1'), 80.0 (C-3'), 77.7 (C-5'), 76.8 (C-4), 75.6 (C-2'), 75.2 (C-

2), 74.9 (C-3), 74.7 (C-5), 72.1 (CH_2 Bn), 68.5 (C-4'), 56.6 (CH_3 OMe); HRMS: $[M+Na]^+$ calculated for $C_{20}H_{33}O_{22}S_3N_2$ 749.06816, found 749.06891.

Methyl (4-O-[2-*O*-sulfo-β-D-mannopyranosyl uronate]-2,3-di-*O*-sulfo-α-D-mannopyranosyl uronate) (37) Saponified disaccharide **36** (3.98 mg, 4.84 µmol) was dissolved in H_2O (1.5 mL) and purged with argon for 5 minutes. Pd/C (10% palladium on carbon, 8.3 mg) was added and the resulting black suspension was purged with argon for 5 minutes. A hydrogen balloon was applied and the suspension was purged for 5 minutes after which it was allowed to stir overnight at room temperature. The mixture was filtered through a Whatmann-filter and concentrated *in vacuo*. This procedure was repeated followed by HW-40 size-exclusion chromatography (eluted with NH_4OAc). The product fractions were puled, concentrated, dissolved in a small amount of H_2O and passed through a column of Dowex 50 WX-4 (Na^+ form) to yield the fully deprotected disaccharide as a white solid after lyophilization (1.49 mg, 2.03 µmol, 42%). ^{1}H-NMR (D_2O, 600 MHz, T=313K): δ 5.10 (d, 1H, J=3.3 Hz, H-1'), 4.86 – 4.77 (m, 3H, H-1, H-2, H-3), 4.73 (d, 2H, J=3.3 Hz, H-2'), 4.29 (s, 1H, H-4), 4.17 (d, 1H, J=7.3 Hz, H-5'), 3.76 – 3.66 (m, 3H, H-3', H-4', H-5'), 3.47 (s, 3H CH_3 OMe); ^{13}C-NMR (D_2O, 150 MHz): δ 176.5, 175.8 (2x COO^-), 99.2 (C-1), 98.6 (C-1'), 79.2 (C-2'), 77.6 (C-3'), 76.6 (C-4), 75.3 (C-2), 74.8 (C-3), 74.6 (C-5), 73.1 (C-5'), 69.8 (C-4'), 56.5 (CH_3 OMe); HRMS: $[M+Na]^+$ calculated for $C_{13}H_{17}O_{22}S_3Na_3$ 712.89589, found 712.89593.

ASSOCIATED CONTENT

Supporting Information Available. ^{1}H and ^{13}C spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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