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Novel protecting group strategies in the synthesis of oligosaccharides

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Chapter 5

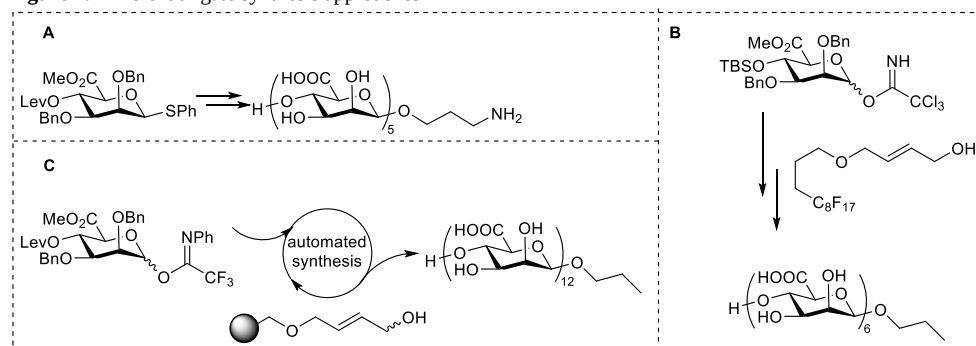
Synthesis of SOMA fragments

Volbeda, A.G.; Van der Vorm, S.; Hogervorst, T.; le Roy, J.; Overkleef, H.S.; Van der Marel, G.A.; Codée, J.D.C. were involved in the research described in this Chapter.

Introduction

Marine animals, plants and algae are an important source of medically and industrially relevant polysaccharides. Brown seaweeds represent a prime example as these provide alginates and fucans, polysaccharides that are being investigated for their biological activity and their attractive physical properties.¹ Alginates are being used in food and cosmetic preparations because of their gelling characteristics, but it has been suggested that they also have immune stimulating activity, through interaction with toll like receptors.^{2,3} Alginate is build up of β -(1-4)-linked D-mannuronic and α -(1-4)-linked L-guluronic acid (ManA and GulA) monosaccharides, and the monomeric composition dictates the properties of the polymer. Modification of these biopolymers, provides semi-synthetic biomaterials with potentially interesting activity. Sulfation of ManA alginates, generates sulfated oligomannuronic alginates, so-called SOMAs, which have been investigated for their glycosaminoglycan (GAG)-like properties, such as anticoagulation activity, but they have also been probed for their anti-cancer, anti-HIV, anti-influenza capacity.^{4,5} The SOMAs used for these studies have been obtained by random sulfation of naturally sourced alginates. For the establishment of structure-activity relationships for this promising class of compounds, synthetic fragments of well-defined length and sulfation pattern would be a very valuable asset. Over the years several syntheses of short alginate fragments have appeared and Figure 1A depicts the different strategies reported to date. Traditional solution phase chemistry has been used to assemble fragments up to five repeating monosaccharides (Figure 1A)^{6,7}, a fluorous supported synthesis (Figure 1B) has led to a ManA hexamer⁸ and an automated solid phase approach has allowed for the generation of fragments with a length of up to 12 monosaccharides (Figure 1C).⁹ In all these syntheses, the unique capacity of mannuronic acid donors to stereoselectively provide the challenging 1,2-*cis* linkages was exploited.^{6,7}

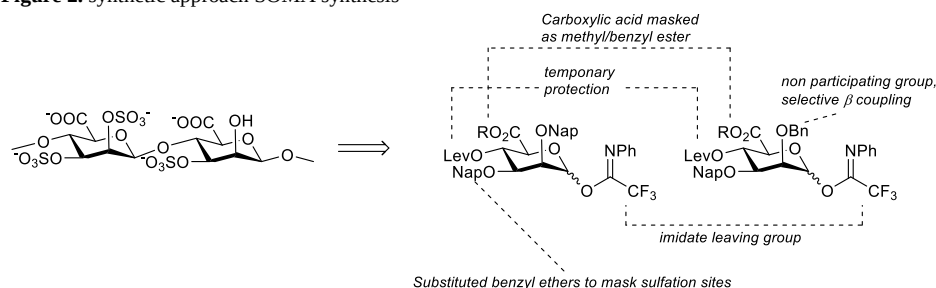
Figure 1. Different alginate synthesis approaches



Building on these precedents, it can be envisaged that the use mannuronic acid donors, bearing a pair of semi-orthogonal protecting groups at the C2 and C3, will allow for the construction of SOMA fragments with pre-defined sulfation patterns. The protecting groups to be used have to meet a selection of stringent criteria, not to compromise the stereoselectivity of the ManA donors. They obviously should not engage in (long-range)

participation since this would lead to the selective formation of 1,2-*trans* ManA linkages. Thus, acyl-type protecting groups are excluded. Bulky silyl ethers are less attractive as these have been shown to cause erosion of stereoselectivity in β -mannosylations reactions.¹⁰ Substituted benzyl ethers, such as the *para*-methoxy benzyl (PMB) and 2-methylnaphthyl (Nap) group, would present an attractive type of masking functionality, as these would maintain all characteristics of the stereoselective 2,3-di-*O*-benzyl ManA donor, yet allow for the regioselective removal to subsequently install the desired sulfate esters. This Chapter describes the development of chemistry required to assemble short SOMAs, building on the use of ManA donors, of which the hydroxyl groups at the C2 and C3 positions are differentiated through the use of Nap and Bn ethers (see Figure 2). In line with the building blocks used by Walvoort *et al.* the donor synthons were equipped with an anomeric *N*-phenyl trifluoroacetimidate latent leaving group and a C-4-*O*-levulinoyl for temporary protection of the alcohol to be elongated during the synthesis.⁹

Figure 2. synthetic approach SOMA synthesis



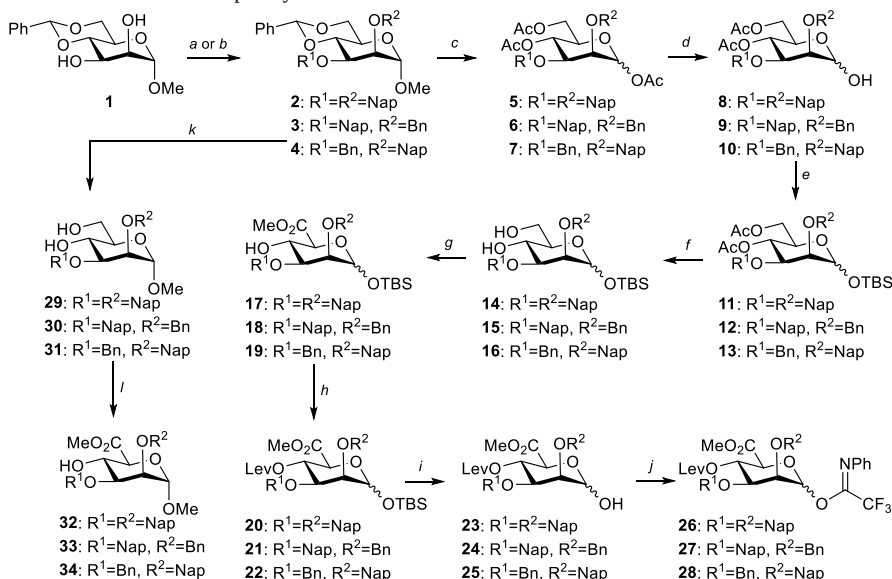
Results and discussion

First, the envisaged protecting group strategy was probed by the assembly of a set of protected ManA dimers and a SOMA disaccharide. Three new donors and acceptors were synthesized from benzylidenemannose **1** as depicted in Scheme 2. This starting compound is readily available and provided ready access to the donors and acceptors to be used in the glycosylations. Starting from compound **1**, the C-2 and C-3 hydroxyls were protected with a 2-methylnaphthyl ether (to give **2**), or the C-3 hydroxyl was regioselectively masked, through the intermediate formation of a stannylene acetal, with either a Nap or a Bn group. The remaining C-2 hydroxyl was then protected with either a Bn (**3**) or a Nap (**4**) ether. The fully protected mannosides were readily transformed into acceptors **32**, **33** and **34**, by acidic removal of the benzylidene acetal, followed by TEMPO/BAIB mediated oxidation of the C-6 hydroxyl and methylation of the newly formed acid.

The set of donor ManA building blocks, comprising donors **26**, **27** and **28**, were also accessed from the benzylidene precursors **2**, **3** and **4**. Thus, acidic cleavage of the anomeric and benzylidene acetals in acetic anhydride, yielded tri-acetates **5**, **6** and **7**. Selective removal of the anomeric acetyl by piperidine and ensuing silylation then afforded lactols **11**, **12** and **13**, which were saponified to give the diols **14**, **15** and **16**. These mannosides were transformed

in their mannuronic acid counterparts **17**, **18** and **19**, through a TEMPO/BAIB mediated oxidation, followed by conversion into the methyl esters. Protection of the C-4 alcohols with a levulinoyl group provided the fully protected ManA **20**, **21** and **22**. Removal of the anomeric silyl group liberated the lactols which were then transformed into donors **26**, **27** and **28**.

Scheme 1. Donor and acceptor synthesis.



Reagents and conditions: a) NapBr, NaH, DMF, 0°C (98%); b) i. $n\text{Bu}_2\text{SnO}$, toluene, reflux; ii. NapBr, CsF, DMF (89%) then NaH, BnBr, DMF (95% for **3**) or BnBr, CsF, DMF (89%) then NaH, NapBr, DMF (94% for **4**); c) pTsOH·H₂O, Ac₂O (**5**: 91%, **6**: 84%, **7**: 66%); d) piperidine, THF (**8**: 79%, **9**: 85%, **10**: 88%); e) TBSCl, imidazole, DCM (**11**: 94%, **12**: 77%, **13**: 86%); f) NaOMe, MeOH (**14**: 94%, **15**: 99%, **16**: 98%); g) i. TEMPO, BAIB, DCM/H₂O; ii. MeI, K₂CO₃, DMF, 0°C (**17**: 81%, **18**: 76%, **19**: 79%); h) LevOH, DIC, DMAP, DCM, 0°C (**20**: 87%, **21**: 96%, **22**: 95%); i) TBAF, AcOH, THF, 0°C (**23**: 98%, **24**: 97%, **25**: 99%); j) ClC(=NPh)CF₃, Cs₂CO₃, acetone, 0°C (**26**: 99%, **27**: 87%, **28**: 98%); k) pTsOH·H₂O, DCM/MeOH (**29**: 88%, **30**: 91%, **31**: 83%); l) i. TEMPO, BAIB, DCM/H₂O; ii. MeI, K₂CO₃, DMF, 0°C (**32**: 55%, **33**: 55%, **34**: 76%).

With the set of donor and acceptor building blocks in hand, a set of glycosylation reactions was performed to assess the selectivity of the reactions and the stability of the Nap-ethers under the conditions used. As summarized in Table 1, all combination of donor and acceptor building blocks provided profitable glycosylation reactions. The combination of donor **27** and acceptor **32** in a TfOH mediated glycosylation reaction at delivered disaccharide **35**, bearing three Nap ethers, in 74% with excellent stereoselectivity. Also, the union of donor **28**, having a Nap ether at C-2 and acceptor **32** proceeded uneventfully, providing dimer **36** in 79% yield. No side reaction originating from the intramolecular attack of the naphthyl on the anomeric center of the activated ManA donor was observed.^{11,12} A similar result was

obtained when donor **26**, bearing two Nap-ethers, was paired with acceptors **33** or **34**. These glycosylations delivered dimannuronic acids **37** and **38** in 85% and 95% yield respectively.

Scheme 2. Glycosylation of donors **26**, **27**, **28** and acceptors **32**, **33** and **34**.

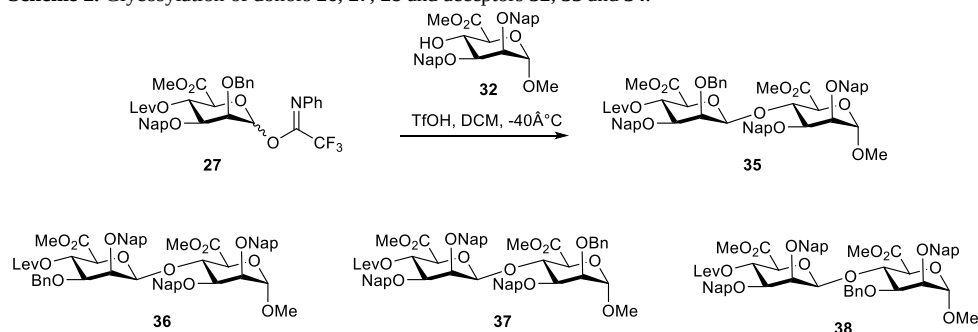


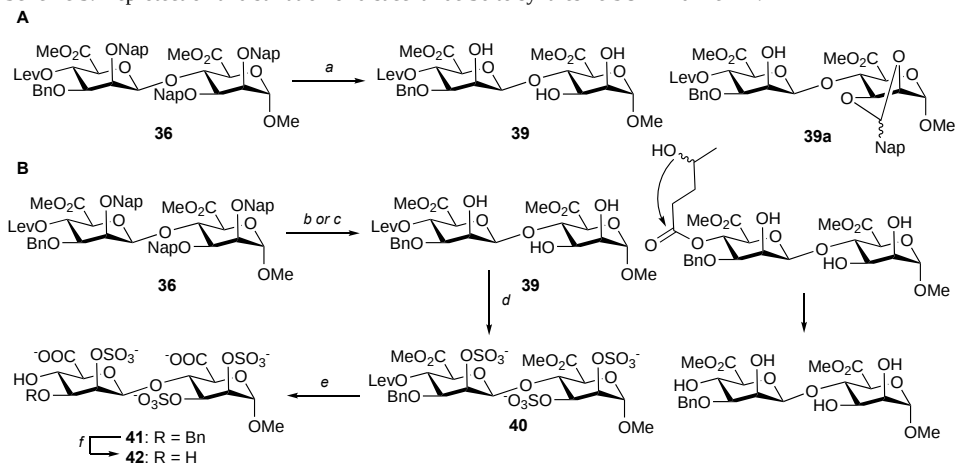
Table 1. Results glycosylation studies

Entry	Donor	Acceptor	TfOH	Product	yield
1	27	32 (1.3 eq.)	0.2 eq.	35	74%
2	28	32 (1.2 eq.)	0.2 eq.	36	79%
3	26	33 (1.3 eq.)	0.2 eq.	37	85%
4	26	34 (1.25 eq.)	0.2 eq.	38	95%

Then the selective removal of the Nap groups was investigated. Initially, oxidative conditions were probed for this purpose.^{13,14} However, when disaccharide **36** was subjected to DDQ, a complex mixture was obtained. Besides the desired triol, undesirable 2,3-naphthylidene formation was observed and the target triol was obtained in a mere 19% (Scheme 3A). Chapter 2 has introduced a new method for the removal of electron rich benzyl ethers using a catalytic amount of HCl in HFIP. When the conditions described in Chapter 2, (3 eq. of HCl (1 eq. per Nap ether) in combination with 5 eq. of triethyl silane (TES) to scavenge the naphthyl cations) were applied to disaccharide **36** (Scheme 3B), rapid removal of the Nap groups was observed via TLC and TLC/MS analysis. However, partial cleavage of the levulinoyl ester was also observed. Likely, the combination of HCl and TES led to reduction of the ketone functionality of the Lev ester, to provide an alcohol group which can attack the nearby carbonyl group to liberate the C-4'-alcohol. To circumvent this side reaction, a more hindered, slightly less reactive hydride donor, tri-*iso*-propylsilane, was examined. The use of this scavenger in combination with 3 eq. HCl in HFIP/DCM resulted in the fast and clean removal of the three Nap-ethers to provide triol **39** in 86% yield. To develop even milder conditions for the removal of multiple Nap ethers from an oligosaccharide, it was attempted to use a catalytic amount of HCl (0.5 eq. per disaccharide substrate, 0.17 eq. for each Nap-ether) acid. Although a slightly longer reaction time was required with respect to the use of stoichiometric amounts of acid, triol **39** was obtained in high yield (86%). The liberated hydroxyls were then decorated with sulfate groups to provide trisulfate **40**. It was observed that concentration of the reaction mixture at elevated temperature, resulted in degradation of the product. Removal of the solvent at room temperature did not jeopardize the integrity of the product and purification of the thus concentrated crude product by LH20 size-exclusion

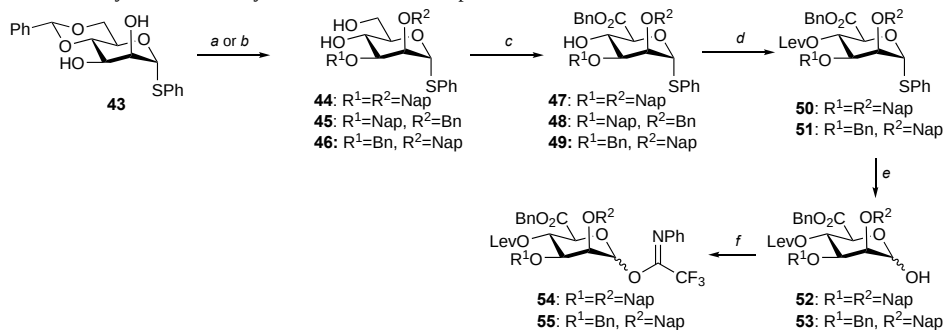
chromatography (using DCM/MeOH as eluent system) provided the trisulfate in quantitative yield. Final saponification of the levulinoyl and methyl esters using an excess of LiOOH (aq), was then followed by removal of the remaining benzyl ether at the C-3' position to deliver SOMA-disaccharide **42**.

Scheme 3. Deprotection and sulfation of disaccharide **36** to synthesize SOMA-dimer **42**.



Reagents and conditions: a) DDQ, DCM/H₂O (19%); b) HCl/HFIP, TES, DCM/HFIP (nd); c) HCl/HFIP, TIS, DCM/HFIP (86%); d) Et₃N·SO₃, DMF, 55°C (quant.); e) LiOH, H₂O₂, THF/H₂O (66%); f) Pd/C, H₂, H₂O (42%).

Aiming for larger SOMA fragments, functionalized with a conjugation handle, a set of ManA thioglycosides was generated as these potentially open the way to a more convergent assembly strategy through the use of chemoselective glycosylation steps. In these synthons, benzyl esters were installed as these can be removed at the end of the synthesis under mild reductive conditions to further streamline the assembly of larger SOMAs. The new building blocks were readily available from 4,6-*O*-benzylidene-1-thio- α -D-mannopyranoside **43**, following chemistry described above. Thus, protection of the C-2 and C-3 acohols with either two Nap-groups or a Nap and Bn-ether, was followed by removal of the benzylidene acetals, chemo- and regioselective oxidation of the primary alcohol and subsequent formation of the benzyl esters (see Scheme 4). This provided ManA thioglycoside acceptors **47**, **48** and **49**. Protection of the C4-OH in **47** and **49** then provided fully protected ManA synthons **49** and **51**. Of note, protection of the C-4-OH generates ManA building blocks that adopt two major conformations in solution: besides the “normal” ⁴C₁ chair conformation they also easily adopt an “inverted” ¹C₄ chair shape. This conformational flexibility leads to significant line broadening in the recorded NMR-spectra of the compounds, necessitating high temperature measurements to obtain NMR spectra with better defined resonances. The fully protected thioglycosides (**50–51**) were hydrolyzed and treated with *N*-phenyltrifluoroacetimidoyl chloride to generate the corresponding imidate donors **54** and **55**.

Scheme 4. Synthesis of benzyl ester donors and acceptors.


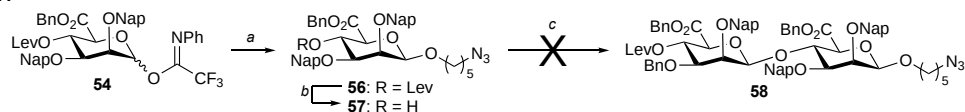
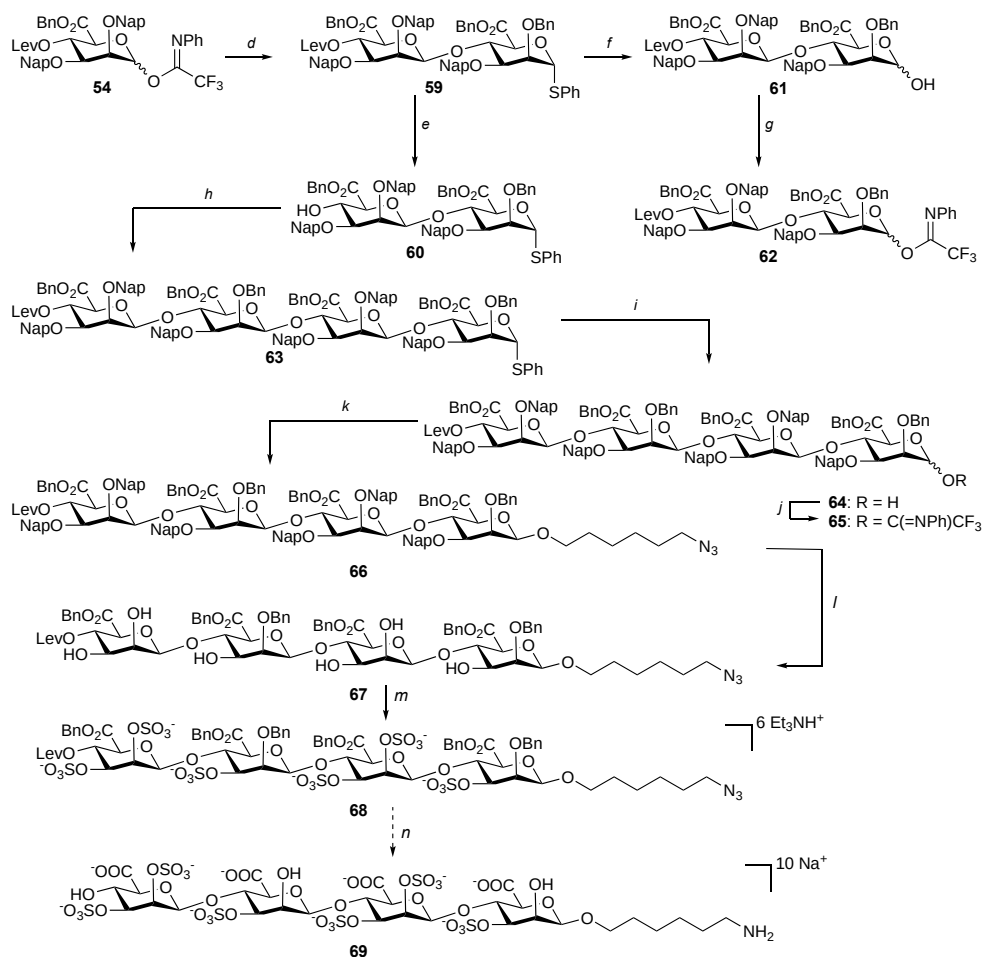
Reagents and conditions: a) i. NapBr, NaH, DMF, 0°C; ii. pTsOH·H₂O, DCM/MeOH (91% for **44**); b) i. Bu₂SnO, toluene, reflux; ii. CsF, NapBr, toluene, 100°C; then BnBr, NaH, DMF, 0°C (88%) or CsF, BnBr, DMF then NapBr, NaH, DMF (86%); iv. pTsOH·H₂O, DCM/MeOH (75% over 3 steps for **45**, 84% for **46**); c) i. TEMPO, BAIB, DCM/H₂O/tBuOH; ii. BnBr, K₂CO₃, DMF, 0°C (**47**: 68%, **48**: 77%, **49**: 56%); d) LevOH, DIC, DMAP, DCM, 0°C (**50**: 82%, **51**: 97%); e) NIS, TFA, DCM, 0°C (**52**: 80%, **53**: 95%); f) ClC(=NPh)CF₃, Cs₂CO₃, acetone, 0°C (**54**: 81%, **55**: 77%).

With the required building blocks in hand, the assembly of SOMA oligomers was started (see Scheme 5). To this end an azide pentanol spacer was first condensed with donor **54** using TMSOTf to provide ManA **56**. Removal of the levulinoyl ester then set the stage to couple the second ManA (Scheme 5A). This reaction however, in sharp contrast to the many successful condensation reactions between various mannuronic acid building blocks (See Figure 1 for a schematic overview) and the dimannuronic acid syntheses described above, did not provide a productive outcome: a complex reaction mixture was obtained, wherefrom the desired disaccharide **58** could not be isolated. Changing the type of ManA donor, the donor/acceptor ratio and the reaction conditions proved to no avail as in each case a complex reaction mixture resulted. The most important difference between the building blocks used here and the previously reported ManA alginate syntheses is the presence of the Nap ethers instead of Bn ethers. Although these protecting groups are very similar they apparently have a major influence on the outcome of the glycosylation reactions. Likely, the electron rich nature (with respect to their Bn-counterparts) of the Nap ethers leads to competitive nucleophilic attack of these functional groups, in an intra- and/or intermolecular fashion, on the activated donor species, to provide the complex reaction mixtures. Apparently, the ManA C-4-OH in this case is not reactive enough to outcompete the Nap ethers and provide a productive glycosylation reaction. This leaves the question why the α -O-methyl mannuronic acid acceptors described above engage in highly efficient glycosylation reactions, while the use of the β -linked mannuronic acids provide complex mixtures. Previously, Zhang *et al.* have described the effect of conformational freedom on the reactivity of guluronic acid-mannuronic acid disaccharide C4'-OH acceptors.¹⁵ In the construction of mixed sequence alginates, they showed that in the condensation of a GulA-ManA-disaccharide donor and a GulA-ManA-dimer acceptor, the nature of the acceptor's "reducing" end moiety played an all-important role. The condensation reaction of the acceptor bearing a β -azidopropanol spacer led to a modest yield of 26%. In contrast, when a disaccharide acceptor was used,

having an α -thiophenol at the reducing end, the yield of the coupling reaction was increased to 91%. It was reasoned that the flexibility of the α -thiophenol disaccharide made this acceptor a better nucleophile by allowing better accommodation of the steric requirements of the crowded glycosylation transition state. Inspired by this result, thioglycoside **48** was probed as an acceptor in a glycosylation reaction with imidate donor **54** (Scheme 5B). This glycosylation reaction proceeded smoothly and the desired disaccharide could now be obtained in 72% yield. Encouraged by this result, dimer **59** was transformed into dimer imidate donor **62** by an anomeric hydrolysis and imidate formation reaction sequence to give dimannuronic acid donor **62**. Removal of the C-4'-levulonoyl ester from dimer **59** provided a disaccharide acceptor **60**. The union of the two latter building blocks under the agency of a catalytic amount of Lewis acid promotor proceeded effectively and tetra-ManA **63** was obtained in 68%. In line with the results of Zhang *et al.*, the effect of the flexible reducing end monosaccharide also here allowed for a productive glycosylation of dimer building blocks. To install a spacer at the reducing end of the tetrasaccharide, the anomeric thiophenyl was again transformed into an *N*-phenyltrifluoroacetimidate to provide donor **65**, which was coupled with azidohexanol to give the fully protected, spacer equipped tetra-mannuronic acid **66**.

With compound **66** in hand, the deprotection conditions described above for the mannuronic acid disaccharide were applied (see Scheme 3). A small molar excess of acid with respect to the tetrasaccharide (1.1 equiv., ± 0.2 equiv. per Nap ether) was used in combination with HFIP and TIS as cation scavenger in DCM to remove the Nap ethers. Using these conditions, all six Nap ethers were cleanly removed to provide the desired hexaol in 94% yield. Sulphation using sulfur trioxide triethylamine complex at 55°C then yielded compound **68**, which could be purified by size exclusion chromatography (DCM/MeOH). The removal of the Lev and benzyl esters was accomplished by LiOH/H₂O₂ mediated saponification, followed by gel filtration. NMR analysis showed removal of the Lev and a reduction of the amount of aromatic resonances. Next, the remaining benzyl ethers and the primary azide were removed by hydrogenolysis. After concentration of the reaction mixture and purification by size exclusion chromatography the desired tetrasaccharide could unfortunately not be obtained in sufficient purity. Because of lack of precursor tetrasaccharide **69**, no further attempts could be made to obtain the final product. Currently, no reason can be provided to explain the failure in obtaining **69** in sufficient yield and purity. It stands in contrast to the successful assembly of dimannuronate **42** and the vast amount of previously accomplished syntheses of various sulfated oligosaccharides,^{14,16,17} that essentially follow a similar protecting group strategy (sulfation, followed by saponification and final hydrogenolysis).

Scheme 5. Construction of tetrasaccharide **68**.

A

B


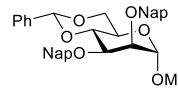
Reagents and conditions: a) 6-azidopentanol, TMSOTf, DCM, -55°C (79%); b) $\text{H}_2\text{NNH}_2 \cdot \text{AcOH}$, pyridine/AcOH, (99%); c) TMSOTf, DCM, -55°C; d) **48**, TMSOTf, DCM, -55°C (72%); e) $\text{H}_2\text{NNH}_2 \cdot \text{AcOH}$, pyridine/AcOH, 0°C (95%); f) NIS, TFA, Et_3N , DCM, 0°C (84%); g) ClC(=NPh)CF_3 , Cs_2CO_3 , acetone, 0°C (70%); h) **62**, TMSOTf, DCM, -55°C (68%); i) NIS, TFA, DCM, 0°C; j) ClC(=NPh)CF_3 , Cs_2CO_3 , acetone, 0°C (83% over 2 steps); k) 6-Azidohexanol, TMSOTf, DCM, -50°C (68%). l) HCl/HFIP , TIS, DCM/HFIP (94%); m) $\text{Et}_3\text{N} \cdot \text{SO}_3$, DMF, 55°C (74%); n) LiOOH , THF/ H_2O , 0°C, then H_2 , $\text{Pd(OH)}_2/\text{C}$, AcOH, THF/ H_2O /tBuOH (n.d.).

Conclusion

This chapter describes a study towards the synthesis of sulfated oligomannuronic acid (SOMA) fragments. First, six new mannuronic acid donors and acceptors were designed and synthesized, bearing a protecting group pattern suited for selective sulfation of the C-2 and/or C-3-hydroxyls. The glycosylating properties of these building blocks were studied in a set of model glycosylations delivering four disaccharides with a varying protecting pattern. One of these disaccharides was transformed into a SOMA fragment, by selective removal of the Nap ethers, sulfation of the liberated hydroxyls and global deprotection. The acidic removal of the Nap ethers using conditions described in Chapter 2, proved superior to the more commonly used oxidative conditions, as these led to significant side reactions. During the assembly of larger SOMA oligosaccharides, it was observed that the union of β -configured Nap-bearing ManA acceptors and ManA donors, also featuring Nap-ethers, posed a significant problem. Notably, the use of more flexible ManA acceptors, bearing an α -thiophenol aglycon, did allow for the construction of larger oligomannuronates, bearing multiple Nap ethers. These results match the finding of Zhang *et al.* that the flexibility of the acceptor nucleophile can have a tremendous impact on the outcome of a glycosylation reaction. They also underscore the need for better insight into the mechanistic details of glycosylation reactions and into the steric requirements of the crowded glycosylation reaction transition states. Finally, a fully protected SOMA tetrasaccharide could be obtained. All six Nap-ethers could be removed from this tetrasaccharide using a catalytic amount of HCl (with respect to the Nap ethers) in HFIP/DCM. The liberated alcohols could be sulfated, but the final deprotection sequence unfortunately did not deliver the desired target SOMA tetrasaccharide in sufficient quantity and purity. The incorporation of a purification/visualization handle, for example mounted on the amino functionalized spacer, may allow for better purification and characterization of synthetic SOMA fragments in the future. Changing the protection of the non-reducing C-4-OH functionality to a benzyl ether (instead of the currently used levulinoyl ester) may streamline the deprotection further.

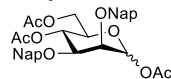
Experimental

General experimental procedures. All solvents used under anhydrous conditions were stored over 4Å molecular sieves except for methanol which was stored over 3Å molecular sieves. ¹H and ¹³C NMR spectra were recorded on a 400/100, 500/125, 600/150, 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, and recorded on a Shimadzu FTIR-8300 or a PerkinElmer universal attenuated total reflectance (UATR; Single Reflection Diamond) Spectrum Two instrument. Solvents used for workup and column chromatography were of technical grade from Sigma Aldrich, Boom, Biosolve or Honeywell and used directly. Unless stated otherwise, solvents were removed by rotary evaporation under reduced pressure at 40 °C. All chemicals were used as received unless stated otherwise. Reactions were monitored by TLC-analysis using Merck 25 DC plastikfolien 60 F254 with detection by spraying with 20% H₂SO₄ in EtOH, (NH₄)₆Mo₇O₂₄·4H₂O (25 g/L) and (NH₄)₄Ce(SO₄)₄·2H₂O (10 g/L) in 10% sulfuric acid or by spraying with a solution of ninhydrin (3 g/L) in EtOH / AcOH (20/1 v/v), or by dipping in anisaldehyde (10 mL in 180 mL EtOH / 10 mL H₂SO₄) followed by charring at approx. 150 °C. Column chromatography was performed on Fluka silicagel (0.04 – 0.063 mm). For LC-MS analysis a Agilent Technologies 1260 Infinity LC system (detection simultaneously at 214 and 254 nm) coupled to a Agilent Technologies 6120 Quadrupole LC/MS, using an analytical Vydac C4 column (Alltech, 50 x 4.60 mm, 5 μm) or a Vydac Diphenyl (Alltech, 150 x 4.60 mm, 5 μm) in combination eluents A: H₂O; B: MeCN and C: 1% aq. TFA. For HPLC, a Gilson HPLC system in combination with eluents A: H₂O (0.1% TFA); B: MeCN as the solvent system using a Vydac C4 HPLC column (Grace, 250 x 10 mm, 5 μm). High resolution mass spectra were recorded by direct injection (2 μL of a 2 μM solution in water/acetonitrile; 50/50; v/v and 0.1% formic acid) on a mass spectrometer (Thermo Finnigan LTQ Orbitrap) equipped with an electrospray ion source in positive mode (source voltage 3.5 kV, sheath gas flow 10, capillary temperature 250 °C) with resolution R = 60000 at m/z 400 (mass range m/z = 150-2000) and dioctylphthalate (m/z = 391.2842) as a “lock mass”. The high resolution mass spectrometer was calibrated prior to measurements with a calibration mixture (Thermo Finnigan). Maldi spectra were recorded on an Ultraflextreme MALDI-TOF (Bruker Daltonics), equipped with Smartbeam-II laser, to measure the samples in reflectron positive ion mode. The MALDI-TOF was calibrated using a peptide calibration standard prior to measurement. 1 μL of 2,5-dihydroxybenzoic acid (2,5-DHB; Bruker Daltonics) matrix (20 mg/mL in ACN/water; 50:50 (v/v)) was applied on a 384-MTP target plate (Bruker Daltonics, Bremen, Germany) and air-dried. Subsequently, 1 μL of compound water solution was spotted on the plate and the spots were left to dry prior MALDI-TOF analysis.

Methyl 4,6-O-benzylidene-2,3-di-O-(2-naphthylmethyl)-α-D-mannopyranoside (2) 2-
 (Bromomethyl)naphthalene (464 mg, 2.1 mmol, 2.1 eq.) was added to a 0°C solution of compound **1** (285 mg, 1.01 mmol) in DMF (5mL) 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 H₂O and extracted with EtOAc. The organic layer was dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by column chromatography (PE/EtOAc, 8:1 → 4:1) yielded the title compound as a yellow oil (560 mg, 0.99 mmol, 98%). TLC: R_f 0.59 (PE/EtOAc, 4/1, v/v); IR (neat): 698, 748, 813, 1053, 1371 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.78-7.81 (m, 5H, CH_{arom}), 7.72-7.74 (m, 2H, CH_{arom}), 7.63-7.66 (m, 1H, CH_{arom}), 7.52-7.54 (m, 3H, CH_{arom}), 7.35-7.47 (m, 8H, CH_{arom}), 5.68 (s, 1H, CHPh), 4.91-4.98 (m, 3H, CH₂ Nap, CHH Nap), 4.79 (d, 1H, *J* = 12.4 Hz, CHH Nap), 4.73 (d, 1H, *J* = 1.2 Hz, H-1), 4.25-4.35 (m, 2H, H-4, H-6), 4.01 (dd, 1H, *J* = 3.2, 10 Hz, H-3), 3.89-3.94 (m, 2H, H-2, H-6), 3.79 (ddd, 1H, *J* = 4.4, 4.8, 9.6 Hz, H-5), 3.28 (s, 3H, CH₃ OMe); ¹³C NMR (CDCl₃, 100 MHz): δ

137.9, 136.3, 135.6, 133.4, 133.2, 133.0 (Cq CHPh, Nap), 129.0, 128.5, 128.4, 128.3, 128.1, 128.1, 128.0, 127.8, 127.8, 127.1, 126.9, 126.3, 126.3, 126.2, 126.2, 126.1, 126.0, 125.8, 125.8 (CH_{arom}), 101.7 (CHPh), 100.6 (C-1), 79.3 (C-4), 76.5 (C-3), 76.2 (C-2), 73.7, 73.1 (CH₂ Nap), 69.0 (C-6), 64.2 (C-5), 54.9 (OMe); HRMS: [M+Na]⁺ calcd. for C₃₆H₃₄O₆Na 585.22476, found 585.22390.

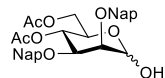
Acetyl 4,6-di-O-acetyl-2,3-di-O-(2-naphthylmethyl)- α -D-mannopyranoside (5) To a solution of compound 2



(12.4 g, 22 mmol) in acetic anhydride (125 mL), pTsOH·H₂O (6.3 g, 33 mmol, 1.5 eq.) was added. The reaction mixture was allowed to stir for 5.5 days at room temperature. The reaction mixture was quenched by pouring it over ice and gradually adding solid NaHCO₃

until all ice had melted and CO₂ evolution had stopped. The aqueous mixture was extracted three times with EtOAc and the combined organic layers were washed once with brine. The organic fraction was dried with MgSO₄, filtered and concentrated *in vacuo*, after which the residue was co-evaporated once with toluene. Column chromatography purification (PE/EtOAc, 9:1 → 2:1) afforded the title compound as an orange oil (11.8 g, 20.1 mmol, 91%, $\alpha >> \beta$). Analytic data for α -anomer of compound 5: TLC: R_f 0.30 (PE/EtOAc, 2/1, v/v); IR (neat): 748, 813, 962, 1051, 1217, 1369, 1732 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): 7.71-7.83 (m, 8H, CH_{arom}), 7.31-7.53 (m, 6H, CH_{arom}), 6.24 (d, 1H, *J* = 1.6 Hz, H-1), 5.56 (t, 1H, *J* = 9.6 Hz, H-4), 4.95 (d, 1H, *J* = 12.6 Hz, CHH Nap), 4.88 (d, 1H, *J* = 12.6 Hz, CHH Nap), 4.66 (d, 1H, *J* = 12.4 Hz, CHH Nap), 4.58 (d, 1H, *J* = 12.4 Hz, CHH Nap), 4.25 (dd, 1H, *J* = 5.2, 11.6 Hz, H-6), 4.14 (dd, 1H, *J* = 2.4, 11.6 Hz, H-6), 3.90-3.94 (m, 1H, H-5), 3.80-3.85 (m, 2H, H-2, H-3), 2.08 (s, 3H, CH₃ Ac), 2.03 (s, 3H, CH₃ Ac), 1.96 (s, 3H, CH₃ Ac); ¹³C NMR (CDCl₃, 400 MHz): δ 171.0, 169.7, 168.7 (C=O Ac), 135.3, 135.1, 133.3, 133.2 (Cq), 128.4, 128.3, 128.0, 127.9, 127.8, 127.2, 127.0, 126.8, 126.5, 126.4, 126.2, 126.1, 125.7, 125.6 (CH_{arom}), 91.9 (C-1), 76.2 (C-3), 72.8 (C-2), 72.7, 72.2 (CH₂ Nap, Nap), 71.6 (C-5), 67.5 (C-4), 62.8 (C-6), 21.0, 21.0, 20.9 (CH₃ Ac); ¹³C-GATED NMR (CDCl₃, 100MHz): δ 91.9 (*J*_{C1,H1} = 174 Hz, C-1 α); HRMS: [M+NH₄]⁺ calcd. for C₃₄H₃₈NO₉ 604.25411, found 604.25468.

4,6-Di-O-acetyl-2,3-di-O-(2-naphthylmethyl)- α/β -D-mannopyranose (8) Compound 5 (255 mg, 0.44 mmol) was

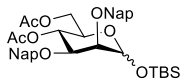


dissolved in 4% piperidine (90 μ L, 0.9 mmol, 2.1 eq.) in THF (2.2 mL). After stirring for 3 days at room temperature H₂O was added and the mixture was extracted with EtOAc. The organic layer was washed once with brine and subsequently dried (MgSO₄), filtered, and

concentrated *in vacuo*. Purification by column chromatography (PE/EtOAc, 8:1 → 1:1) gave the title compound as an yellow oil (188 mg, 0.35 mmol, 79%, $\alpha : \beta = 5 : 1$). TLC: R_f 0.39 (PE/EtOAc, 1/1, v/v); IR (neat): 746, 812, 1049, 1217, 1367, 1732 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.67-7.82 (m, 9.60H, CH_{arom}), 7.34-7.48 (m, 7.20H, CH_{arom}), 5.50 (t, 1H, *J* = 9.6 Hz, H-4 α), 5.43 (t, 0.20H, *J* = 9.6 Hz, H-4 β), 5.29 (s, 1H, H-1 α), 5.18 (d, 0.20H, *J* = 11.6 Hz, CHH Nap β), 4.75-4.87 (m, 2.40H, CH₂ Nap α , CHH Nap β , CHH Nap β), 4.66-4.70 (m, 1.40H, CHH Nap α , CHH Nap β , H-1 β), 4.58 (d, 1H, *J* = 12.4 Hz, CHH Nap α), 4.21 (dd, 1.20H, *J* = 5.2, 12.0 Hz, H-6 α , H-6 β), 4.11-4.14 (m, 1.40H, H-6 α , H-6 β , 1-OH β), 4.03-4.07 (m, 1H, H-5 α), 3.99 (bs, 1H, 1-OH α), 3.95 (dd, 1H, *J* = 2.8, 9.6 Hz, H-3 α), 3.90 (d, 0.20H, *J* = 1.2 Hz, H-2 β), 3.85 (t, 1H, *J* = 2.4 Hz, H-2 α), 3.60 (dd, 0.20H, *J* = 2.8 Hz, H-3 β), 3.50-3.54 (m, 0.20H, H-5 β), 2.01 (s, 0.60H, CH₃ Ac β), 2.00 (s, 0.60H, CH₃ Ac β), 2.00 (s, 3H, CH₃ Ac α), 1.99 (s, 3H, CH₃ Ac α); ¹³C NMR (CDCl₃, 100 MHz): δ 171.1, 171.1, 170.0, 169.9 (C=O Ac), 135.6, 135.6, 135.1, 135.0, 133.3, 133.2, 133.1, 133.0, 133.0 (Cq), 128.5, 128.4, 128.1, 128.1, 128.0, 127.9, 127.8, 127.7, 127.7, 127.7, 127.3, 126.7, 126.5, 126.4, 126.2, 126.2, 126.1, 126.1, 126.0, 126.0, 125.9, 125.6, 125.5 (CH_{arom}), 93.9 (C-1 β), 92.9 (C-1 α), 79.9 (C-3 β), 76.7 (C-3 α), 75.2 (C-2 β), 74.8 (CH₂ Nap β), 74.5 (C-2 α), 72.9 (CH₂ Nap α), 72.6 (CH₂ Nap β), 72.4 (C-5 β), 72.0 (CH₂ Nap α), 69.1 (C-5 α), 68.3 (C-4 α), 67.8 (C-4 β), 63.3 (C-6), 63.0 (C-6 β), 21.0, 21.0,

20.8 (CH₃ Ac); ¹³C-GATED NMR (CDCl₃, 100 MHz): δ 93.9 (*J*_{C1,H1} = 160 Hz, C-1 β), 92.9 (*J*_{C1,H1} = 169 Hz, C-1 α); HRMS: [M+NH₄]⁺ calcd. for C₃₂H₃₆NO₈ 562.24354, found 562.24347.

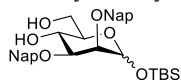
Tert-butyldimethylsilyl 4,6-di-O-acetyl-2,3-di-O-(2-naphthylmethyl)-α/β-D-mannopyranoside (11) TBDMSCl



(3.83 g, 25 mmol, 2 eq.) and imidazole (1.73 g, 25 mmol, 2eq.) were added to a solution of hemiacetal **8** (6.91 g, 12.8 mmol) in dry DCM (65 mL) under an argon atmosphere. After stirring overnight, the reaction was quenched with H₂O and extracted twice with Et₂O.

Combined organic layers were washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by column chromatography (PE/EtOAc, 15:1 → 2:1) yielded the title compound as a yellowish oil (8.39 g, 12.7 mmol, 99%, α : β = 1 : 4). TLC: R_f 0.47 (Pentane/EtOAc, 4/1, v/v); IR (neat): 746, 779, 837, 895, 1052, 1055, 1233, 1368, 1742 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.74-7.89 (m, 9H, CH_{arom}), 7.67-7.69 (dd, 1H, *J* = 1.2, 8.4 Hz, CH_{arom}), 7.63 (s, 1H, CH_{arom}), 7.43-7.54 (m, 5.50H, CH_{arom}), 7.30-7.33 (dd, 1H, *J* = 1.2, 8.4 Hz, CH_{arom} β), 5.57 (t, 0.25H, *J* = 10.0 Hz, H-4 α), 5.47 (t, 1H, *J* = 9.6 Hz, H-4 β), 5.23 (d, 1H, *J* = 12.8 Hz, CHH Nap β), 5.16 (d, 0.25H, *J* = 2.0 Hz, H-1 α), 5.10 (d, 1H, *J* = 12.8 Hz, CHH Nap β), 5.03 (d, 0.25H, *J* = 12.8 Hz, CHH Nap α), 4.88 (d, 0.25H, *J* = 12.8 Hz, CHH Nap α), 4.76-4.79 (m, 1.50H, CH₂ Nap α, H-1 β), 4.59 (d, 1H, *J* = 12.4 Hz, CHH Nap β), 4.46 (d, 1H, *J* = 12.4 Hz, CHH Nap β), 4.18-4.34 (m, 2.50H, H-6 α, H-6 α, H-6 β, H-6 β), 3.97-4.03 (m, 1.50H, H-2 β, H-3 α, H-5 α), 3.70 (t, 0.25H, *J* = 2.4 Hz, H-2 α), 3.53-3.61 (m, 2H, H-3 β, H-5 β), 2.12 (s, 1.50H, CH₃ Ac α), 2.11 (s, 3H, CH₃ Ac β), 2.09 (s, 3H, CH₃ Ac β), 1.03 (s, 9H, CH₃ tBu β), 0.79 (s, 2.25H, CH₃ tBu α), 0.26 (s, 3H, CH₃ Me β), 0.22 (s, 3H, CH₃ Me β), 0.05 (s, 0.75H, CH₃ Me α), -0.04 (s, 0.75H, CH₃ Me α); ¹³C NMR (CDCl₃, 100 MHz): δ 170.7, 170.6, 169.8, 169.7 (C=O Ac), 136.1, 135.5, 135.4, 135.3, 133.1, 133.1, 133.0, 132.9, 132.9 (Cq), 128.2, 128.1, 128.0, 127.8, 127.8, 127.6, 127.6, 126.8, 126.7, 126.4, 126.1, 126.1, 126.0, 126.0, 125.9, 125.9, 125.8, 125.8, 125.6, 125.3 (CH_{arom}), 96.6 (C-1 β), 93.2 (C-1 α), 78.9 (C-3 β), 76.1 (C-3 α), 75.6 (C-2 α), 74.6 (C-2 β), 74.1 (CH₂ Nap β), 73.0 (CH₂ Nap α), 72.6 (C-5 β), 72.2 (CH₂ Nap α), 71.2 (CH₂ Nap β), 69.1 (C-5 α), 68.3 (C-4 β), 68.2 (C-4 α), 63.4 (C-6 β), 63.1 (C-6 α), 25.8 (CH₃ tBu β), 25.3 (CH₃ tBu α), 20.9, 20.7 (CH₃ Ac), 18.0 (Cq tBu β), 17.7 (Cq tBu α), -4.0 (CH₃ Me β), -4.9 (CH₃ Me α), -5.4 (CH₃ Me β), -6.0 (CH₃ Me α); ¹³C-GATED NMR (CDCl₃, 100 MHz): δ 96.6 (*J*_{C1,H1} = 153 Hz, C-1 β), 93.2 (*J*_{C1,H1} = 167 Hz, C-1 α); HRMS: [M+NH₄]⁺ calcd. for C₃₈H₅₀NO₈Si 676.33002, found 676.33046.

Tert-butyldimethylsilyl 2,3-di-O-(2-naphthylmethyl)-α/β-D-mannopyranoside (14) To a solution of compound



11 (8.3 g, 12.6 mmol) in MeOH (63 mL) a catalytic amount of NaOMe (55 mg, 1.0 mmol, 0.1 eq.) was added. After stirring overnight, the reaction mixture was neutralized with

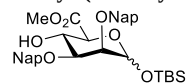
Amberlite H⁺ which was subsequently filtered off. The filtrate was concentrated *in vacuo*

and **14** was obtained as a colourless oil (6.82 g, 11.9 mmol, 94%, α : β = 1 : 3.8). TLC: R_f 0.14 (PE/EtOAc, 2/1, v/v); IR (neat): 745, 779, 814, 835, 1069, 1252, 1362, 3426 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.91 (s, 1H, CH_{arom}), 7.65-7.84 (m, 10.34H, CH_{arom}), 7.45-7.58 (m, 5.30H, CH_{arom}), 7.37 (dd, 1H, *J* = 1.6, 8.4 Hz, CH_{arom}), 5.57 (d, 1H, *J* = 12.4 Hz, CHH Nap β), 5.12 (d, 0.26H, *J* = 1.2 Hz, H-1 α), 5.05 (d, 1H, *J* = 12.4 Hz, CHH Nap β), 4.96 (d, 0.26H, *J* = 12.4 Hz, CHH Nap α), 4.82-4.91 (m, 1.78H, CHH Nap α, CH₂ Nap α, H-1 β), 4.65 (d, 1H, *J* = 12.0 Hz, CHH Nap β), 4.58 (d, 1H, *J* = 12.0 Hz, CHH Nap β), 4.31 (t, 0.26H, *J* = 10.0 Hz, H-4 α), 4.20 (t, 1H, *J* = 9.6 Hz, H-4 β), 3.93-4.06 (m, 3.78H, H-2 β, H-3 α, H-6 α, H-6 α, H-6 β, H-6 β), 3.81-3.85 (m, 0.26H, H-5 α), 3.63-3.65 (m, 0.52H, H-2 α, 4-OH α), 3.53 (bs, 1H, 4-OH β), 3.44 (dd, 1H, 2.8, 9.6 Hz, H-3 β), 3.36-3.41 (m, 1H, H-5 β), 2.88 (bs, 1.26H, 6-OH α, 6-OH β), 1.06 (s, 9H, CH₃ tBu β), 0.78 (s, 2.34H, CH₃ tBu α), 0.28 (s, 3H, CH₃ Me β), 0.24 (s, 3H, CH₃ Me β), 0.05 (s, 0.78H, CH₃ Me α), -0.08 (s, 0.78H, CH₃ Me α); ¹³C NMR (CDCl₃, 100 MHz): δ 136.3, 135.6, 135.4, 135.4, 133.2, 133.0, 133.0, 132.9 (Cq), 128.8, 128.3, 128.2, 128.2, 128.0, 127.9, 127.9, 127.7, 127.0, 126.7, 126.4,

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126.3, 126.1, 126.1, 126.0, 125.9, 125.7, 125.6 (CH_{arom}), 96.8 (C-1 β), 93.3 (C-1 α), 81.5 (C-3 β), 78.8 (C-3 α), 76.0 (C-5 β), 75.9 (C-2 α), 75.2 (C-2 β), 74.5 (CH_2 Nap β), 73.0, 72.6 (CH_2 Nap α), 72.4 (C-5 α), 71.4 (CH_2 Nap β), 67.4 (C-4 β), 67.2 (C-4 α), 62.9 (C-6 β), 62.5 (C-6 α), 25.8 (CH_3 tBu β), 25.4 (CH_3 tBu α), 18.0 (Cq tBu β), 17.7 (Cq tBu α), -3.8 (CH_3 Me β), -4.7 (CH_3 Me α), -5.3 (CH_3 Me β), -6.0 (CH_3 Me α); ^{13}C -GATED NMR (CDCl_3 , 100MHz): δ 96.8 ($J_{\text{C1,H1}} = 153$ Hz, C-1 β), 93.3 ($J_{\text{C1,H1}} = 165$ Hz, C-1 α); HRMS: $[\text{M}+\text{NH}_4]^+$ calcd. for $\text{C}_{34}\text{H}_{46}\text{NO}_6\text{Si}$ 592.30889, found 592.30922.

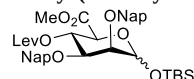
Methyl (*tert*-butyldimethylsilyl 2,3-di-*O*-(2-naphthylmethyl)- α/β -D-mannopyranosyl uronate) (17) Diol 14



(4.58 g, 7.97 mmol) was dissolved in DCM (25 mL) and H_2O (15 mL) was added. To the two phase system TEMPO (250 mg, 1.59 mmol, 0.2 eq.) and BAIB (6.42 g, 19.9 mmol, 2.5 eq.) were added. After stirring vigorously for 6 hours at room temperature, the reaction was

quenched by addition of sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$. 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 (40 mL) and put under an argon atmosphere at 0°C . Methyl iodide (1.5 mL, 23.9 mmol, 3 eq.) and K_2CO_3 (3.30 g, 23.9 mmol, 3 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, 8:1 $\rightarrow$ 2:1) afforded the title compound as a yellow oil (3.9 g, 6.5 mmol, 81%, $\alpha : \beta = 1 : 5$). TLC R_f 0.27 (PE/EtOAc, 4/1, v/v); IR (neat): 745, 781, 814, 837, 1067, 1250, 1362, 1748, 3472 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 7.59-7.83 (m, 10.80H, CH_{arom}), 7.39-7.47 (m, 5H, CH_{arom}), 7.30 (dd, 1H, $J = 1.2, 8.4$ Hz, CH_{arom}), 5.19 (d, 1H, $J = 12.8$ Hz, CHH Nap β), 5.12 (d, 0.20H, $J = 2.0$ Hz, H-1 α), 4.98 (d, 1H, $J = 12.8$ Hz, CHH Nap β), 4.77-4.90 (m, 0.80H, CH_2 Nap α , CH_2 Nap α), 4.75 (s, 1H, H-1 β), 4.67 (d, 1H, $J = 12.4$ Hz, CHH Nap β), 4.63 (d, 1H, $J = 12.4$ Hz, CHH Nap β), 4.37 (t, 1.20H, $J = 9.6$ Hz, H-4 α , H-4 β), 4.20 (d, 0.20H, $J = 9.2$ Hz, H-5 α), 3.83-3.87 (m, 1.20H, H-2 β , H-3 α), 3.79 (s, 3.60H, CH_3 CO_2Me α,β), 3.75 (d, 1H, $J = 9.6$ Hz, H-5 β), 3.56 (t, 0.20H, $J = 2.4$ Hz, H-2 α), 3.41 (dd, 1H, $J = 2.8, 9.6$ Hz, H-3 β), 3.21 (bs, 1H, 4-OH β), 3.10 (bs, 0.20H, 4-OH α), 0.95 (s, 9H, CH_3 tBu β), 0.68 (s, 1.80H, CH_3 tBu α), 0.19 (s, 3H, CH_3 Me β), 0.14 (s, 3H, CH_3 Me β), -0.01 (s, 0.60H, CH_3 Me α), -0.14 (s, 0.60H, CH_3 Me α); ^{13}C NMR (CDCl_3 , 100 MHz): δ 171.0 (C=O CO_2Me α), 170.2 (C=O CO_2Me β), 136.4, 135.8, 135.6, 133.3, 133.3, 133.2, 133.1, 133.1 (Cq), 128.4, 128.3, 128.2, 128.1, 128.0, 128.0, 128.0, 127.8, 127.1, 127.0, 127.0, 126.9, 126.6, 126.4, 126.2, 126.2, 126.1, 126.1, 126.0, 126.0, 125.9, 125.8, 125.7 (CH_{arom}), 97.3 (C-1 β), 93.8 (C-1 α), 80.4 (C-3 β), 77.8 (C-3 α), 75.9 (C-2 α), 75.3 (C-2 β), 75.0 (C-5 β), 74.6, 73.2, 73.1, 72.1 (CH_2 Nap β , α , α , β), 72.0 (C-5 α), 68.8 (C-4 α), 68.4 (C-4 β), 52.6 (CH_3 CO_2Me), 25.9 (CH_3 tBu β), 25.4 (CH_3 tBu α), 18.1 (Cq tBu β), 17.8 (Cq tBu α), -3.9, -5.4 (CH_3 Me); ^{13}C -GATED NMR (CDCl_3 , 100MHz): δ 97.3 ($J_{\text{C1,H1}} = 153$ Hz, C-1 β), 93.8 ($J_{\text{C1,H1}} = 167$ Hz, C-1 α); HRMS: $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{35}\text{H}_{42}\text{O}_7\text{SiNa}$ 625.25920, found 625.25806.

Methyl (*tert*-butyldimethylsilyl 4-*O*-levulinoyl-2,3-di-*O*-(2-naphthylmethyl)- α/β -D-mannopyranosyl uronate) (20)

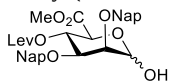


(20) Levulinic acid (2.25 g, 19.4 mmol, 3.0 eq.) and DIC (1.5 mL, 9.7 mmol, 1.5 eq.) were added to a 0°C solution of **17** (3.9 g, 6.47 mmol) in dry DCM (16 mL). A catalytic amount of DMAP (79 mg, 0.65 mmol, 0.1 eq.) was added and the reaction mixture was allowed to

reach room temperature. After 3 hours the reaction mixture was filtered over Celite and the filtrate washed with sat. aq. NaHCO_3 and brine. The organic layer was dried (MgSO_4), filtered, and concentrated *in vacuo*. Column chromatography (PE/EtOAc, 8:1 $\rightarrow$ 2:1) afforded the title compound as an amorphous off-white solid (3.95 g, 5.65 mmol, 87%, $\alpha : \beta = 1 : 5$). TLC: R_f 0.54 (PE/EtOAc, 2/1, v/v); IR (neat): 752, 783, 820, 1030, 1109, 1265, 1368,

1715, 1742, 1753 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 7.68-7.81 (m, 8.80H, CH_{arom}), 7.59-7.63 (m, 2H, CH_{arom}), 7.41-7.48 (m, 5.20H, CH_{arom}), 7.27-7.29 (m, 1H, CH_{arom}), 5.58 (t, 1.20H, $J = 9.6$ Hz, H-4 α , H-4 β), 5.29 (bs, 0.20H, H-1 α), 5.19 (d, 1H, $J = 12.8$ Hz, CHH Nap β), 5.03 (d, 1H, $J = 12.8$ Hz, CHH Nap β), 4.88 (s, 0.40H, CH_2 Nap α), 4.74-4.77 (m, 1.40H, H-1 β , CH_2 Nap α), 4.57 (d, 1H, $J = 12.4$ Hz, CHH Nap β), 4.49 (d, 1H, $J = 12.4$ Hz, CHH Nap β), 4.30 (d, 0.20H, $J = 7.6$ Hz, H-5 α), 3.92 (dd, 0.20H, $J = 3.2$, 8.0 Hz, H-3 α), 3.88 (d, 1H, $J = 2.8$ Hz, H-2 β), 3.84 (d, 1H, $J = 9.6$ Hz, H-5 β), 3.73 (s, 3H, CH_3 CO_2Me β), 3.67 (s, 0.60H, CH_3 CO_2Me α), 3.51-3.54 (m, 1.20H, H-2 α , H-3 β), 2.68 (t, 2H, $J = 6.8$ Hz, CH_2 Lev β), 2.62-2.65 (m, 0.40H, CH_2 Lev α), 2.51-2.58 (m, 2.40H, CH_2 Lev α,β), 2.13 (s, 3.60H, CH_3 Lev α,β), 0.94 (s, 9H, CH_3 tBu β), 0.76 (s, 1.80H, CH_3 tBu α), 0.17 (s, 3H, CH_3 Me β), 0.12 (s, 3H, CH_3 Me β), 0.05 (s, 0.60H, CH_3 Me α), -0.04 (s, 0.60H, CH_3 Me α); ^{13}C NMR (CDCl_3 , 100MHz): δ 206.4 (C=O Lev), 171.7, 168.0 (C=O Lev, CO_2Me), 136.3, 135.5, 133.3, 133.3, 133.1, 133.1 (Cq), 128.2, 128.1, 128.0, 128.0, 127.8, 127.8, 127.0, 126.8, 126.4, 126.3, 126.1, 126.0, 125.8, 125.7 (CH_{arom}), 97.0 (C-1), 78.6 (C-3), 74.6 (C-2), 74.3 (CH_2 Nap), 73.6 (C-5), 71.8 (CH_2 Nap), 69.1 (C-4), 52.7 (OMe), 37.9 (CH_2 Lev), 30.0 (CH_3 Lev), 28.1 (CH_2 Lev), 25.9 (CH_3 tBu), 18.2 (Cq tBu), -3.9, -5.4 (CH_3 Me); ^{13}C -GATED NMR (CDCl_3 , 100MHz): δ 97.0 ($J_{\text{C1,H1}} = 154$ Hz, C-1 β); HRMS: $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{40}\text{H}_{48}\text{O}_9\text{SiNa}$ 723.29598, found 723.29508.

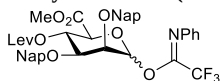
Methyl (4-O-levulinoyl-2,3-di-O-(2-naphthylmethyl)- α/β -D-mannopyranosyl uronate) (23) Acetic acid (70 μL ,



0.7 mmol, 3.5 eq.) was added to a 0°C solution of compound **20** (245 mg, 0.35 mmol) in dry THF (3.5 mL). TBAF (1.0 M solution in THF, 1.0 mL, 1.0 mmol, 3 eq.) was added drop wise over 5 minutes. The reaction mixture was stirred for 4.5 hours at room temperature and

subsequently diluted with EtOAc and washed once with H_2O and brine. The organic layer was dried (MgSO_4), filtered and concentrated *in vacuo*. Purification by column chromatography (Pentane/EtOAc, 8:1 $\rightarrow$ 1:1) furnished the title compound as a yellow oil (216 mg, 0.36 mmol, 98%, $\alpha \gg \beta$). Analytic data is reported for the α -anomer. TLC: R_f 0.17 (PE/EtOAc, 1/1, v/v); IR (neat): 750, 816, 1032, 1123, 1362, 1715, 1742, 3422 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 7.71-7.81 (m, 5H, CH_{arom}), 7.66-7.69 (m, 3H, CH_{arom}), 7.38-7.49 (m, 6H, CH_{arom}), 5.59-5.62 (m, 2H, H-1, H-4), 4.89 (d, 1H, $J = 12.0$ Hz, CHH Nap), 4.78 (d, 1H, $J = 12.0$ Hz, CHH Nap), 4.73 (s, 2H, CH_2 Nap), 4.48 (d, 1H, $J = 5.2$ Hz, H-5), 4.15 (d, 1H, $J = 4.4$ Hz, 1-OH), 3.98 (dd, 1H, $J = 3.2$, 10.4 Hz, H-3), 3.68-3.70 (m, 1H, H-2), 3.61 (s, 3H, CH_3 CO_2Me), 2.37-2.60 (m, 4H, CH_2 Lev), 2.10 (s, 3H, CH_3 Lev); ^{13}C NMR (CDCl_3 , 100 MHz): δ 206.5 (C=O Lev), 171.8, 169.2 (C=O Lev, CO_2Me), 135.7, 135.3, 133.3, 133.2, 133.0 (Cq), 128.2, 128.2, 128.1, 128.0, 127.8, 127.8, 126.8, 126.6, 126.3, 126.2, 126.1, 126.1, 126.0, 126.0, 125.8 (CH_{arom}), 92.7 (C-1), 75.2 (C-2, C-3), 73.1, 72.7 (CH_2 Nap), 71.3 (C-5), 69.7 (C-4), 52.6 (CH_3 CO_2Me), 37.8 (CH_2 Lev), 29.9 (CH_3 Lev), 28.0 (CH_2 Lev); ^{13}C -GATED NMR (CDCl_3 , 100MHz): δ 92.7 ($J_{\text{C1,H1}} = 171$ Hz, C-1 α); HRMS: $[\text{M}+\text{NH}_4]^+$ calcd. for $\text{C}_{34}\text{H}_{38}\text{NO}_9$ 604.25411, found 604.25436.

Methyl (4-O-levulinoyl-2,3-di-O-(2-naphthylmethyl)-1-O-(N-[phenyl]trifluoroacetimidoyl)- α/β -D-mannopyranosyl uronate) (26) Cs_2CO_3 (141 mg, 0.43 mmol, 1.2 eq.) was added to a



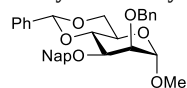
0°C solution of compound **23** (216 mg, 0.36 mmol) and 2,2,2-Trifluoro-N-phenylacetimidoyl chloride (60 μL , 0.4 mmol, 1.1 eq.) in acetone (1.2 mL). After

stirring for 1.5 hours 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 twice with EtOAc. The organic fraction was washed with brine, dried with MgSO_4 , filtered, and concentrated *in vacuo*. The crude compound was purified using column chromatography (PE/EtOAc, 8:1 $\rightarrow$ 1:1) to yield the title compound as a yellow solid (252 mg, 0.356 mmol, 99%, $\alpha : \beta = 6.7 : 1$). TLC: R_f 0.57 α , 0.47 β (PE/EtOAc, 2/1, v/v); IR (neat): 1125, 1153, 1207, 1717, 1748 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 7.56-7.81 (m, 9.20H, CH_{arom}), 7.36-7.50 (m, 6.90H, CH_{arom}), 7.22 (t, 2.30H, $J = 8.0$

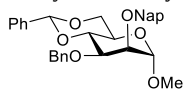
Chapter 5

Hz, NPh), 7.08 (t, 1.15H, $J = 7.6$ Hz, NPh), 6.68 (d, 0.30H, $J = 7.6$ Hz, NPh β), 6.58 (d, 2H, $J = 6.4$ Hz, NPh α), 6.46 (bs, 1H, H-1 α), 6.05 (bs, 0.15H, H-1 β), 5.77 (t, 0.15H, $J = 6.0$ Hz, H-4 β), 5.66 (t, 1H, $J = 7.6$ Hz, H-4 α), 5.00 (d, 0.15H, $J = 12.4$ Hz, CHH Nap β), 4.96 (d, 0.15H, $J = 12.4$ Hz, CHH Nap β), 4.75–4.87 (m, 3.30H, CH₂ Nap α , CH₂ Nap β , CHH Nap α), 4.69 (d, 1H, $J = 12.4$ Hz, CHH Nap α), 4.42 (d, 1H, $J = 7.2$ Hz, H-5 α), 4.16 (bs, 0.15H, H-5 β), 4.09 (bs, 0.15H, H-2 β), 3.95 (dd, 1H, $J = 2.8$, 7.6 Hz, H-3 α), 3.79–3.88 (m, 1.15H, H-2 α , H-3 β), 3.69 (s, 3H, CH₃ CO₂Me α), 3.63 (s, 0.45H, CH₃ CO₂Me β), 2.64–2.67 (m, 2.30H, CH₂ Lev α,β), 2.48–2.60 (m, 2.30H, CH₂ Lev α,β), 2.14 (s, 3H, CH₃ Lev α), 2.13 (s, 0.45H, CH₃ Lev β); ¹³C APT NMR (CDCl₃, 100 MHz, HSQC), only provided for the α -anomer: δ 206.2 (C=O Lev), 171.7, 168.0 (C=O Lev, CO₂Me), 143.2 (Cq NPh), 134.9, 134.9, 133.2, 133.2, 133.2 (Cq), 128.8, 128.7, 128.4, 128.3, 128.1, 128.0, 127.8, 127.2, 127.1, 126.3, 126.3, 126.2, 126.1, 126.0 (CH_{arom} Nap), 124.5, 124.2, 119.4 (CH_{arom} NPh), 94.5 (C-1), 74.8 (C-3), 73.2 (CH₂ Nap), 73.0 (C-2), 72.9 (CH₂ Nap), 72.7 (C-5), 68.9 (C-4), 52.9 (CH₃ CO₂Me), 37.8 (CH₂ Lev), 29.9 (CH₃ Lev), 28.0 (CH₂ Lev); HRMS: [M+Na]⁺ calcd. for C₄₂H₃₈F₃NO₉Na 780.23909, found 780.23981.

Methyl 2-O-benzyl-4,6-O-benzylidene-3-O-(2-naphthylmethyl)- α -D-mannopyranoside (**3**)

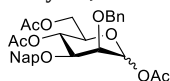


(10.9 g, 43.8 mmol, 1.2 eq.) was added to a solution of compound **1** (10.3 g, 36.6 mmol) in toluene (200 mL) and refluxed overnight under an argon atmosphere. The solution was concentrated to dryness *in vacuo* and DMF (200 mL) was added under argon. Benzyl bromide (9.55 g, 43.2 mmol, 1.18 eq.) and cesium fluoride (6.65 g, 43.8 mmol, 1.2 eq.) were added to the reaction mixture. After stirring overnight, the reaction mixture was quenched with H₂O and extracted with EtOAc. The organic layer was washed with H₂O and brine, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by column chromatography (PE/EtOAc, 8:1 → 2:1) yielded the title compound as a yellow oil (13.7 g, 32.5 mmol, 89%). TLC: R_f 0.22 (PE/EtOAc, 4/1, v/v); IR (neat): 748, 972, 1049, 1373, 1452, 3453 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.78–7.82 (m, 3H, CH_{arom}), 7.70–7.73 (m, 1H, CH_{arom}), 7.50–7.52 (m, 2H, CH_{arom}), 7.43–4.9 (m, 3H, CH_{arom}), 7.36–7.40 (m, 3H, CH_{arom}), 5.63 (s, 1H, CHPh), 4.97 (d, 1H, $J = 12$ Hz, CHH Nap), 4.87 (d, 1H, $J = 12$ Hz, CHH Nap), 4.72 (d, 1H, $J = 1.2$ Hz, H-1), 4.28 (dd, 1H, $J = 4.0$, 12 Hz, H-6), 4.13 (t, 1H, $J = 9.6$ Hz, H-4), 4.05 (dd, 1H, $J = 1.2$, 3.6 Hz, H-2), 3.93 (dd, 1H, $J = 3.6$, 9.6 Hz, H-3), 3.77–3.89 (m, 2H, H-5, H-6), 3.33 (s, 3H, CH₃ OMe), 2.82 (s, 1H, 2-OH); ¹³C NMR (CDCl₃, 400 MHz): δ 137.7, 135.5 (Cq), 133.3, 133.2 (Cq Nap), 129.1, 128.4, 128.1, 127.8, 126.7, 126.3, 126.1, 125.8 (CH_{arom}), 101.8 (CHPh), 101.2 (C-1), 78.9 (C-4), 75.6 (C-3), 73.0 (CH₂ Nap), 69.9 (C-2), 69.0 (C-6), 63.3 (C-5), 55.0 (OMe); HRMS: [M+Na]⁺ calcd. for C₂₅H₂₆O₆Na 445.16216, found 445.16173. The alcohol (10.35 g, 24.5 mmol) was dissolved in DMF (125 mL) and cooled to 0°C. Benzyl bromide (3.2 mL, 27 mmol, 1.1 eq.) and sodium hydride (60% dispersion in oil, 1.08 mg, 27 mmol, 1.1 eq., in three equal parts) were added and the solution left to stir overnight. The reaction mixture was quenched by dropwise addition of MeOH (15 mL) and H₂O (150 mL) and subsequently extracted twice with EtOAc. The organic layer was washed with brine (100 mL) and dried with MgSO₄. 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 (12.0 g, 23.4 mmol, 95%). TLC: R_f 0.67 (PE/EtOAc, 4/1, v/v); IR (neat): 750, 1057, 1099, 1126, 1375, 2909 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.76–7.82 (m, 3H, CH_{arom}), 7.68–7.70 (m, 1H, CH_{arom}), 7.51–7.54 (m, 2H, CH_{arom}), 7.23–7.46 (m, 11H, CH_{arom}), 5.67 (s, 1H, CHPh), 4.92 (d, 1H, $J = 12.8$ Hz, CHH Nap), 4.76–4.94 (m, 3H, CH₂ Bn, CHH Nap), 4.70 (d, 1H, $J = 1.2$ Hz, H-1), 4.24–4.31 (m, 2H, H-4, H-6), 3.99 (dd, 1H, $J = 3.2$, 10 Hz, H-3), 3.85–3.92 (m, 2H, H-2, H-6), 3.74–3.80 (m, 1H, H-5), 3.30 (s, 3H, CH₃ OMe); ¹³C NMR (CDCl₃, 100 MHz): δ 138.2, 137.9, 136.2, 133.4, 133.0 (Cq), 129.0, 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 126.3, 126.2, 126.1, 125.8, 125.7 (CH_{arom}), 101.7 (CHPh), 100.5 (C-1), 79.2 (C-4), 76.3, 76.2 (C-3, C-2), 73.7, 72.9 (CH₂ Bn, Nap), 69.0 (C-6), 64.1 (C-5), 54.9 (OMe); HRMS: [M+NH₄]⁺ calcd. for C₃₂H₃₆NO₆ 530.25371, found 530.25349.

Methyl 3-O-benzyl-4,6-O-benzylidene-2-O-(2-naphthylmethyl)- α -D-mannopyranoside (4)


(5.98 g, 24 mmol, 1.2 eq.) was added to a solution of compound **1** (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 cesium fluoride (3.65 g, 24 mmol, 1.2 eq.) were added to the reaction mixture. After stirring overnight, the reaction mixture was quenched with H₂O and extracted first with Et₂O and then EtOAc, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by column chromatography (PE/EtOAc, 5:1 $\rightarrow$ 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); Spectroscopic data were in accord with those reported previously. IR (neat): 746, 972, 1049, 1373, 1454, 3447 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.48-7.50 (m, 2H, CH_{arom} CHPh), 7.26-7.40 (m, 8H, CH_{arom}), 5.60 (s, 1H, CHPh), 4.84 (d, 1H, *J* = 11.8 Hz, CHH Bn), 4.73 (d, 1H, *J* = 1.2 Hz, H-1), 4.70 (d, 1H, *J* = 11.8 Hz, CHH Bn), 4.27 (dd, 1H, *J* = 4.0, 9.2 Hz, H-6), 4.09 (t, 1H, *J* = 9.2 Hz, H-4), 4.01 (dd, 1H, *J* = 1.2, 3.6 Hz, H-2), 3.77-3.90 (m, 3H, H-3, H-5, H-6), 3.35 (s, 3H, CH₃ OMe), 2.80 (bs, 1H, 2-OH); ¹³C NMR: (CDCl₃, 100 MHz): δ 138.1, 137.7 (Cq Bn, CHPh), 129.0, 128.6, 128.3, 128.0, 127.9, 126.2 (CH_{arom}), 101.7 (CHPh), 101.2 (C-1), 78.9 (C-4), 75.7 (C-3), 73.1 (CH₂ Bn), 70.0 (C-2), 69.0 (C-6), 63.3 (C-5), 55.0 (OMe); HRMS: [M+Na]⁺ calcd. for C₂₁H₂₄O₆Na 395.14651, found 395.14638. The alcohol (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 sodium hydride (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 H₂O and subsequently extracted with EtOAc. The organic layer was washed with brine and dried with MgSO₄. 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); IR (neat): 696, 746, 1051, 1371, 1452 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.74-7.80 (m, 4H, CH_{arom}), 7.50-7.52 (m, 3H, CH_{arom}), 7.41-7.46 (m, 2H, CH_{arom}), 7.23-7.38 (m, 8H, CH_{arom}), 5.66 (s, 1H, CHPh), 4.96 (d, 1H, *J* = 12.4 Hz, CHH Nap), 4.91 (d, 1H, *J* = 12.4 Hz, CHH Nap), 4.83 (d, 1H, *J* = 12.4 Hz, CHH Bn), 4.71 (d, 1H, *J* = 1.2 Hz, H-1), 4.65 (d, 1H, *J* = 12.4 Hz, CHH Bn), 4.25-4.31 (m, 2H, H-4, H-6), 3.96 (dd, 1H, *J* = 3.2, 10 Hz, H-3), 3.87-3.93 (m, 2H, H-2, H-6), 3.75-3.81 (m, 1H, H-5), 3.30 (s, 3H, CH₃ OMe); ¹³C NMR (CDCl₃, 100 MHz): δ 138.8, 137.8, 135.6, 133.3, 133.2 (Cq), 129.2, 129.0, 128.4, 128.4, 128.3, 128.1, 127.8, 127.7, 127.6, 127.1, 126.3, 126.2, 126.2, 126.1 (CH_{arom}), 101.6 (CHPh), 100.6 (C-1), 79.3 (C-4), 76.6 (C-3), 76.2 (C-2), 73.8, 73.3 (CH₂ Bn, Nap), 69.0 (C-6), 64.2 (C-5), 54.9 (OMe); ¹³C-GATED NMR (CDCl₃, 100 MHz): δ 100.6 (*J*_{C1,H1} = 168 Hz, C-1); HRMS: [M+Na]⁺ calcd. for C₃₂H₃₂O₆Na 535.20911, found 535.20818.

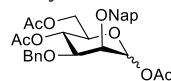
Acetyl 4,6-di-O-acetyl-2-O-benzyl-3-O-(2-naphthylmethyl)- α -D-mannopyranoside (6)


compound **3** (11.5 g, 22.5 mmol) in acetic anhydride (110 mL), pTsOH·H₂O (6.6 g, 35 mmol, 1.5 eq.) was added. The reaction mixture was allowed to stir for four days at room temperature. The reaction mixture was quenched by pouring it over ice and gradually adding

solid NaHCO₃ until all ice had melted and CO₂ evolution had stopped. The aqueous mixture was extracted three times with EtOAc and the combined organic layers were washed once with brine. The organic fraction was dried with MgSO₄, filtered and concentrated *in vacuo*, after which the residue was co-evaporated once with toluene. Column chromatography purification (PE/EtOAc, 9:1 $\rightarrow$ 2:1) afforded the title compound as an orange oil (10.15 g, 18.9 mmol, 84%, $\alpha \gg \beta$). TLC: R_f 0.45 (PE/EtOAc, 2/1, v/v); IR (neat): 700, 745, 820, 955, 1013, 1043, 1217, 1369, 1738 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.78-7.84 (m, 3H, CH_{arom}), 7.70 (s, 1H, CH_{arom}), 7.46-7.49 (m, 2H, CH_{arom}), 7.27-7.39 (m, 6H, CH_{arom}), 6.18 (d, 1H, *J* = 2.0 Hz, H-1), 5.52 (t, 1H, *J* = 9.6 Hz, H-4), 4.68-4.76 (m, 3H, CH₂, CHH Bn/Nap), 4.58 (d, 1H, *J* = 12.4 Hz, CHH Bn/Nap), 4.22 (dd, 1H, *J* = 5.0, 12.4 Hz, H-6), 4.12 (dd, 1H, *J*

= 2.4, 12.4 Hz, H-6), 3.89-3.93 (m, 1H, H-5), 3.83 (dd, 1H, $J = 2.8, 9.6$ Hz, H-3), 3.78 (t, 1H, $J = 2.4$ Hz, H-2), 2.07 (s, 3H, CH₃ Ac), 2.04 (s, 3H, CH₃ Ac), 1.98 (s, 3H, CH₃ Ac); ¹³C NMR (CDCl₃, 100 MHz): δ 170.9, 169.6, 168.7 (C=O Ac), 137.6, 135.2, 133.2, 133.0 (Cq-_{arom}), 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.8, 126.4, 126.3, 126.1, 125.5 (CH_{arom}), 91.8 (C-1), 75.9 (C-3), 72.8 (C-2), 72.6, 71.7 (CH₂ Bn, Nap), 71.4 (C-5), 67.3 (C-4), 62.6 (C-6), 20.9, 20.9, 20.8 (CH₃ Ac); ¹³C-GATED NMR (CDCl₃, 100MHz): δ 91.8 ($J_{C1,H1} = 175$ Hz, C-1 α); HRMS: $[M+NH_4]^+$ calcd. for C₃₀H₃₆NO₉ 554.23846, found 554.23861.

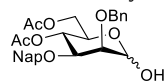
Acetyl 4,6-di-O-acetyl-3-O-benzyl-2-O-(2-naphthylmethyl)- α -D-mannopyranoside (7) To a solution of



compound **4** (7.3 g, 14.2 mmol) in acetic anhydride (70 mL), pTsOH·H₂O (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 NaHCO₃ until all ice had melted and CO₂ evolution had stopped. The aqueous mixture was extracted two times with EtOAc and the combined organic layers were washed once with brine. The organic fraction was dried with MgSO₄, filtered and concentrated *in vacuo*, after which the residue was co-evaporated once with toluene. Column chromatography purification (PE/EtOAc, 6:1 $\rightarrow$ 2:1) afforded the title compound as an orange oil (5.06 g, 9.44 mmol, 66%, $\alpha \gg \beta$). TLC: R_f 0.36 (PE/EtOAc, 2/1, v/v); IR (neat): 733, 955, 1217, 1368, 1740, 2918 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.73-7.82 (m, 4H, CH_{arom}), 7.51 (dd, 1H, $J = 1.6, 8.4$ Hz, CH_{arom}), 7.43-7.47 (m, 2H, CH_{arom}), 7.28-7.33 (m, 3H, CH_{arom}), 7.21-7.27 (m, 2H, CH_{arom}), 6.24 (d, 1H, $J = 1.6$ Hz, H-1), 5.53 (t, 1H, $J = 9.6$ Hz, H-4), 4.92 (d, 1H, $J = 12.4$ Hz, CHH Bn/Nap), 4.87 (d, 1H, $J = 12.4$ Hz, CHH Bn/Nap), 4.52 (d, 1H, $J = 12.0$ Hz, CHH Bn/Nap), 4.44 (d, 1H, $J = 12.0$ Hz, CHH Bn/Nap), 4.24 (dd, 1H, $J = 4.8, 12.0$ Hz, H-6), 4.13 (dd, 1H, $J = 2.4, 12.0$ Hz, H-6), 3.91-3.95 (m, 1H, H-5), 3.78-3.81 (m, 2H, H-2, H-3), 2.08 (s, 3H, CH₃ Ac), 2.05 (s, 3H, CH₃ Ac), 2.04 (s, 3H, CH₃ Ac); ¹³C NMR (CDCl₃, 100 MHz): δ 171.0, 169.7, 168.7 (C=O Ac), 137.9, 135.1, 133.2, 133.2 (Cq-_{arom}), 128.6, 128.5, 128.3, 128.0, 127.9, 127.8, 127.5, 127.0, 126.5, 126.2, 126.1 (CH_{arom}), 92.6 (C-1 β) 91.8 (C-1 α), 76.3 (C-3), 72.7 (C-2), 72.7, 72.1 (CH₂ Bn, Nap), 71.5 (C-5), 67.5 (C-4), 62.7 (C-6), 21.1, 21.0, 20.9 (CH₃ Ac); ¹³C-GATED NMR (CDCl₃, 100MHz): δ 91.8 ($J_{C1,H1} = 175$ Hz, C-1 α); HRMS: $[M+Na]^+$ calcd. for C₃₀H₃₂O₉Na 559.19385, found 559.19279.

4,6-Di-O-acetyl-2-O-benzyl-3-O-(2-naphthylmethyl)- α/β -D-mannopyranose (9) Compound **6** (10.14 g, 18.9

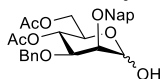


mmol) was dissolved in 4% piperidine (3.75 mL, 38 mmol, 2 eq.) in THF (100 mL). After stirring for 2.5 days at room temperature H₂O was added and the mixture was extracted with EtOAc. The organic layer was washed once with brine and subsequently dried (MgSO₄),

filtered, and concentrated *in vacuo*. Purification by column chromatography (PE/EtOAc, 8:1 $\rightarrow$ 1:1) gave the title compound as an orange oil (8.95 g, 18.1 mmol, 85%, $\alpha : \beta = 3.8 : 1$). TLC: R_f 0.53 (PE/EtOAc, 1/1, v/v); IR (neat): 743, 880, 1042, 1086, 1238, 1371, 1732, 3343 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.78-7.85 (m, 3.78H, CH_{arom}), 7.73-7.75 (m, 1.26H, CH_{arom}), 7.46-7.51 (m, 2.51H, CH_{arom}), 7.25-7.41 (m, 6.56H, CH_{arom}), 5.46 (t, 1H, $J = 9.6$ Hz, H-4 α), 5.38 (t, 0.26H, $J = 9.6$ Hz, H-4 β), 5.27 (d, 1H, $J = 1.6$ Hz, H-1 α), 5.10 (d, 0.26H, $J = 11.6$ Hz, CHH Bn/Nap β), 4.84 (d, 0.26H, $J = 12.4$ Hz, CHH Bn/Nap β), 4.66-4.79 (m, 3.78H, CH₂ Bn/Nap α , CHH Bn β , Nap β , CHH Bn/Nap α , H-1 β), 4.63 (d, 1H, $J = 12.4$ Hz, CHH Bn/Nap α), 4.11-4.22 (m, 2.52H, H-6 α , H-6 α , H-6 β , H-6 β), 4.02-4.06 (m, 1H, H-5 α), 3.95 (dd, 1H, $J = 2.8, 9.6$ Hz, H-3 α), 3.88-3.89 (m, 0.26H, H-2 β), 3.84 (t, 1H, $J = 2.4$ Hz, H-2 α), 3.64 (dd, 0.26H, $J = 2.8, 9.6$ Hz, H-3 β), 3.52-3.56 (m, 0.26H, H-5 β), 3.31 (bs, 1H, 1-OH α), 2.07 (s, 3H, CH₃ Ac α), 2.04 (s, 0.42H, CH₃ Ac β), 2.03 (s, 0.42H, CH₃ Ac β), 2.01 (s, 3H, CH₃ Ac α); ¹³C (CDCl₃, 100 MHz): δ 171.1, 170.0, 169.9 (C=O Ac), 138.2, 137.8, 135.7, 133.4, 133.2, 133.1 (Cq Bn Nap), 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.8, 126.6, 126.5, 126.4, 126.3, 126.1, 125.7, 125.6 (CH_{arom}), 93.8 (C-1

β), 93.1 (C-1 α), 79.9 (C-3 β), 76.7 (C-3 α), 75.5 (C-2 β), 74.9 (CH₂ Bn/Nap β), 74.5 (C-2 α), 73.0 (CH₂ Bn/Nap α), 72.7 (CH₂ Bn/Nap β), 72.5 (C-5 β), 72.1 (CH₂ Bn/Nap α), 69.4 (C-5 α), 68.3 (C-4 α), 67.9 (C-4 β), 63.3 (C-6 α), 63.1 (C-6 β), 21.1, 20.9 (CH₃ Ac); ¹³C-GATED NMR (CDCl₃, 100MHz): δ 93.8 (J_{C1,H1} = 158 Hz, C-1 β), 93.1 (J_{C1,H1} = 169 Hz, C-1 α); HRMS: [M+NH₄]⁺ calcd. for C₂₈H₃₄NO₈ 512.22789, found 512.22750.

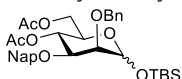
4,6-Di-O-acetyl-3-O-benzyl-2-O-(2-naphthylmethyl)-α/β-D-mannopyranose (10) Compound 7 (5.06 g, 9.44



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 H₂O was added and the mixture was extracted with EtOAc. The organic layer was washed once with brine and subsequently dried (MgSO₄),

filtered, and concentrated *in vacuo*. Purification by column chromatography (PE/EtOAc, 9:1 → 1:1) gave the title compound as a 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); IR (neat): 1042, 1099, 1238, 1369, 1740, 3428 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.73-7.81 (m, 4.92H, CH_{arom}), 7.42-7.49 (m, 3.69H, CH_{arom}), 7.24-7.34 (m, 6.15H, CH_{arom}), 5.46 (t, 1H, J = 10.0 Hz, H-4 α), 5.39 (t, 0.23H, J = 9.6 Hz, H-4 β), 5.27 (s, 1H, H-1 α), 5.18 (d, 0.23H, J = 11.6 Hz, CHH Bn/Nap β), 4.78-4.90 (m, 2.23H, CHH Bn/Nap β, CH₂ Bn/Nap α), 4.67 (m, 0.46H, CHH Bn/Nap β, H-1 β), 4.54-4.60 (m, 1.23H, CHH Bn/Nap β, CHH Bn/Nap α), 4.55 (d, 1H, J = 12.4 Hz, CHH Bn/Nap α), 4.09-4.23 (m, 2.46H, H-6 α, H-6 β, H-6 β, H-6 β), 4.03-4.07 (m, 1H, H-5 α), 3.89 (dd, 1.23H, J = 2.8, 9.6 Hz, H-2 β, H-3 α), 3.82-3.83 (m, 1H, H-2 α), 3.67 (bs, 1H, 1-OH α), 3.55-3.60 (m, 0.46H, H-3 β, H-5 β), 2.03 (s, 3H, CH₃ Ac β), 2.03 (s, 0.69H, CH₃ Ac α), 2.02 (s, 0.69H, CH₃ Ac α), 1.98 (s, 3H, CH₃ Ac β); ¹³C (CDCl₃, 100 MHz): δ 171.2, 171.1, 170.0, 169.9 (C=O Ac), 138.2, 137.6, 135.7, 135.1, 133.2, 133.2, (Cq), 128.9, 128.7, 128.6, 128.4, 128.2, 128.1, 128.0, 128.0, 127.8, 127.7, 127.7, 127.5, 127.4, 126.8, 126.3, 126.2, 126.1, 126.1, 126.0 (CH_{arom}), 93.9 (C-1 β), 93.1 (C-1 α), 80.1 (C-3 β), 76.7 (C-3 α), 75.3 (C-2 β), 74.9 (CH₂ Bn/Nap β), 74.4 (C-2 α), 73.0 (CH₂ Bn/Nap α), 72.7 (CH₂ Bn/Nap β), 72.5 (C-5 β), 72.0 (CH₂ Bn/Nap α), 69.2 (C-5 α), 68.3 (C-4 α), 67.9 (C-4 β), 63.3 (C-6), 63.0 (C-6 β), 21.0, 20.9 (CH₃ Ac); ¹³C-GATED NMR (CDCl₃, 100MHz): δ 93.1 (J_{C1,H1} = 169 Hz, C-1 α); HRMS: [M+NH₄]⁺ calcd. for C₂₈H₃₄NO₈ 512.22789, found 512.22754.

Tert-butyldimethylsilyl 4,6-di-O-acetyl-2-O-benzyl-3-O-(2-naphthylmethyl)-α/β-D-mannopyranoside (12)

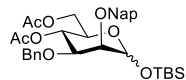


TBDMSCl (5.43 g, 36 mmol, 2.25 eq.) and imidazole (2.45 g, 36 mmol, 2.25 eq.) were added to a solution of hemiacetal 9 (7.9 g, 16 mmol) in DCM (85 mL) under an argon atmosphere. After stirring overnight, the reaction was quenched with H₂O and extracted

twice with EtOAc. Combined organic layers were washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by column chromatography (PE/EtOAc, 15:1 → 2:1) yielded the title compound as a white solid (7.53 g, 12.37 mmol, 77%, α : β = 1 : 2.8). TLC: R_f 0.51 (Pentane/EtOAc, 4/1, v/v); IR (neat): 839, 1044, 1236, 1368, 1744 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.78-7.84 (m, 4.08H, CH_{arom}), 7.72 (s, 0.36H, CH_{arom} α), 7.66 (s, 1H, CH_{arom} β), 7.43-7.49 (m, 5.04H, CH_{arom}), 7.24-7.34 (m, 5.8H, CH_{arom}), 5.41 (t, 0.36H, J = 10.0 Hz, H-4 α), 5.32 (t, 1H, J = 10.0 Hz, H-4 β), 5.06 (d, 0.36H, J = 2.0 Hz, H-1 α), 5.01 (d, 1H, J = 12.4 Hz, CHH Bn/Nap β), 4.81-4.88 (m, 1.36H, CHH Bn/Nap β, CHH Bn/Nap α), 4.60-4.75 (m, 3.08H, CHH Bn/Nap α, CH₂ Bn/Nap α, CHH Bn/Nap β, H-1 β), 4.45 (d, 1H, J = 12.4 Hz, CHH Bn/Nap β), 4.16-4.20 (m, 2.36H, H-6 β, H-6 β, H-6 α), 4.08 (dd, 0.36H, J = 2.2, 12.2 Hz, H-6 α), 3.89-3.92 (m, 0.72H, H-3 α, H-5 α), 3.86 (d, 1H, J = 2.8 Hz, H-2 β), 3.58 (t, 0.36H, J = 2.4 Hz, H-2 α), 3.48-3.53 (m, 2H, H-3 β, H-5 β), 2.06 (s, 1.08H, CH₃ Ac α), 2.04 (s, 3H, CH₃ Ac β), 2.04 (s, 1.08H, CH₃ Ac α), 2.03 (s, 3H, CH₃ Ac β), 0.92 (s, 9H, tBu TBS β), 0.77 (s, 3.24H, tBu TBS α), 0.14 (s, 3H, CH₃ TBS β), 0.11 (s, 3H, CH₃ TBS β), 0.01 (s, 1.08H, CH₃ TBS α), -0.05 (s, 1.08H, CH₃ TBS α); ¹³C (CDCl₃, 100 MHz): δ 170.6, 170.5, 169.7, 169.6 (C=O Ac), 138.6, 138.1, 135.3, 133.1, 133.0, 132.8 (Cq), 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.3, 126.6, 126.1, 126.0, 125.9, 125.8, 125.7, 125.3 (CH_{arom}), 96.5 (C-1 β), 93.2 (C-1 α), 78.8 (C-3

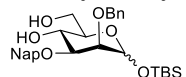
β), 76.0 (C-3 α), 75.7 (C-2 α), 74.7 (C-2 β), 74.0 (CH₂ Bn/Nap β), 72.9 (CH₂ Bn/Nap α), 72.5 (C-5 β), 72.0 (CH₂ Bn/Nap α), 71.0 (CH₂ Bn/Nap β), 69.1 (C-5 α), 68.3 (C-4 β), 68.1 (C-4 α), 63.3 (C-6 β), 63.1 (C-6 α), 25.7 (CH₃ tBu), 25.3 (CH₃ tBu), 20.8 (CH₃ Ac), 20.6 (CH₃ Ac), 17.9 (Cq tBu), 17.6 (Cq tBu), -4.1 (CH₃ Me β), -4.9 (CH₃ Me α), -5.5 (CH₃ Me β), -5.9 (CH₃ Me α); ¹³C-GATED NMR (CDCl₃, 100MHz): δ 96.5 ($J_{C1,H1}$ = 153 Hz, C-1 β), 93.2 ($J_{C1,H1}$ = 168 Hz, C-1 α); HRMS: [M+NH₄]⁺ calcd. for C₃₄H₄₈NO₈Si 626.31437, found 626.31427.

Tert-butyldimethylsilyl 4,6-di-O-acetyl-3-O-benzyl-2-O-(2-naphthylmethyl)- α/β -D-mannopyranoside (13)



TBDMSCl (1.5 g, 10 mmol, 2 eq.) and imidazole (0.68 g, 10 mmol, 2eq.) were added to a solution of hemiacetal **10** (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 H₂O and extracted twice with EtOAc. Combined organic layers were washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by column chromatography (PE/EtOAc, 15:1 $\rightarrow$ 2:1) yielded the title compound as a 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); IR (neat): 743, 837, 1040, 1233, 1366, 1742 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.73-7.84 (m, 4.88H, CH_{arom}), 7.63 (dd, 1H, J = 1.2, 8.4 Hz, CH_{arom}), 7.52-7.55 (m, 0.22H, CH_{arom}), 7.44-7.49 (m, 2.44H, CH_{arom}), 7.26-7.35 (m, 4.10H, CH_{arom}), 7.18-7.20 (m, 2H, CH_{arom}), 5.47 (t, 0.22H, J = 10.0 Hz, H-4 α), 5.36 (t, 1H, J = 9.8 Hz, H-4 β), 5.17 (d, 1H, J = 12.8 Hz, CHH Bn/Nap β), 5.13 (d, 0.22H, J = 1.6 Hz, H-1 α), 5.05 (d, 1H, J = 12.8 Hz, CHH Bn/Nap β), 4.99 (d, 0.22H, J = 12.4 Hz, CHH Bn/Nap α), 4.83 (d, 0.22H, J = 12.4 Hz, CHH Bn/Nap α), 4.76 (s, 1H, H-1 β), 4.62 (d, 0.22H, J = 12.4 Hz, CHH Bn/Nap α), 4.43 (d, 0.22H, J = 12.4 Hz, CHH Bn/Nap α), 4.46 (d, 1H, J = 12.0 Hz, CHH Nap β), 4.32 (d, 1H, J = 12.0 Hz, CHH Nap β), 4.22-4.26 (m, 2.22H, H-6 α , H-6 β , H-6 β), 4.13 (dd, 0.22H, J = 2.4, 12.0 Hz, H-6 α), 3.94-3.98 (m, 0.22H, H-5 α), 3.90 (dd, 1.22H J = 2.8, 9.2 Hz, H-3 α , H-2 β), 3.64 (t, 0.22H, J = 2.4 Hz, H-2 α), 3.56 (m, 1H, H-5 β), 3.49 (dd, 1H, J = 3.0, 10.0 Hz, H-3 β), 2.10 (s, 0.66H, CH₃ Ac α), 2.09 (s, 3H, CH₃ Ac β), 2.08 (s, 0.66H, CH₃ Ac α), 2.06 (s, 3H, CH₃ Ac β), 1.22 (s, 9H, CH₃ tBu β), 0.82 (s, 1.98H, CH₃ tBu α), 0.20 (s, 3H, CH₃ Me β), 0.17 (s, 3H, CH₃ Me β), 0.04 (s, 0.66H, CH₃ Me α), -0.04 (s, 0.66H, CH₃ Me α); ¹³C (CDCl₃, 100 MHz): δ 170.9, 169.9, 169.9 (C=O Ac), 138.2, 138.0, 136.3, 135.8, 133.3, 133.3, 133.2, (Cq), 128.5, 128.4, 128.3, 128.0, 128.0, 127.9, 127.9, 127.8, 127.7, 127.4, 126.9, 126.8, 126.6, 126.2, 126.2, 126.0, 126.0, 125.8 (CH_{arom}), 96.8 (C-1 β), 93.5 (C-1 α), 79.2 (C-3 β), 76.5 (C-3 α), 75.8 (C-2 α), 74.7 (C-2 β), 74.3 (CH₂ Bn/Nap α), 73.2 (CH₂ Bn/Nap β), 72.8 (C-5 β), 72.3 (CH₂ Bn/Nap α), 71.3 (CH₂ Bn/Nap β), 69.2 (C-5 α), 68.5 (C-4 β), 68.3 (C-4 α), 63.6 (C-6 β), 63.3 (C-6 α), 26.0 (CH₃ tBu β), 25.6 (CH₃ tBu α), 21.1, 21.1, 20.9 (CH₃ Ac), 18.2 (Cq tBu β), 17.9 (Cq tBu α), -3.9 (CH₃ Me β), -4.7 (CH₃ Me α), -5.3 (CH₃ Me β), -5.7 (CH₃ Me α); ¹³C-GATED NMR (CDCl₃, 100MHz): δ 96.8 ($J_{C1,H1}$ = 153 Hz, C-1 β), 93.5 ($J_{C1,H1}$ = 166 Hz, C-1 α); HRMS: [M+NH₄]⁺ calcd. for C₃₄H₄₈NO₈Si 626.31437, found 626.31523.

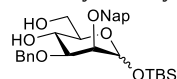
Tert-butyldimethylsilyl 2-O-benzyl-3-O-(2-naphthylmethyl)- α/β -D-mannopyranoside (15)



To a solution of compound **12** (7.5 g, 12.3 mmol) in MeOH (60 ml) a catalytic amount of NaOMe (110 mg, 2.0 mmol, 0.17 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 **15** was obtained as a colourless oil (6.45 g, 12.3 mmol, quant., α : β = 1 : 3.5). TLC: R_f 0.19 (PE/EtOAc, 2/1, v/v); IR (neat): 735, 779, 1070, 1252, 3412 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.76-7.84 (m, 4.12H, CH_{arom}), 7.70 (s, 1H, CH_{arom}), 7.45-7.50 (m, 4.84H, CH_{arom}), 7.37-7.39 (m, 1H, CH_{arom}), 7.26-7.33 (m, 4.40H, CH_{arom}), 5.04 (d, 1.28H, J = 12.0 Hz, CHH Bn/Nap β , H-1 α), 4.74-4.83 (m, 2.84H, CHH Bn/Nap β , CH₂ Bn/Nap α , CHH Bn/Nap α , H-1 β), 4.61-4.65 (m, 1.28H, CHH Bn/Nap β , CHH Bn/Nap α), 4.48 (d, 1H, J = 12.0 Hz, CHH Bn/Nap β), 4.14 (t, 0.28H, J = 9.6 Hz, H-4 α), 4.01 (t, 1H, J = 9.6 Hz, H-4 β), 3.81-3.94 (m, 3.84H, H-6

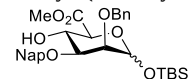
α , H-6 α , H-6 β , H-6 β , H-2 β , H-3 α), 3.70-3.75 (m, 0.28H, H-5 α), 3.58 (t, 0.28H, J = 2.8 Hz, H-2 α), 3.37 (dd, 1H, J = 2.8, 9.6 Hz, H-3 β), 3.29-3.33 (m, 1H, H-5 β), 2.67 (bs, 2.56H, 4-OH α , 4-OH β , 6-OH α , 6-OH β), 0.96 (s, 9H, tBu Me β), 0.78 (s, 2.52H, tBu Me α), 0.17 (s, 3H, CH₃ Me β), 0.15 (s, 3H, CH₃ Me β), 0.02 (s, 0.84H, CH₃ Me α), -0.04 (s, 0.84H, CH₃ Me α); ¹³C (CDCl₃, 100 MHz): δ 138.8, 128.2, 135.5, 135.3, 133.3, 133.2, 133.1 (Cq), 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.6, 127.1, 126.6, 126.3, 126.1, 126.0, 125.7 (CH_{arom}), 96.9 (C-1 β), 93.4 (C-1 α), 81.5 (C-3 β), 78.9 (C-3 α), 76.0 (C-5 β), 75.8 (C-2 α), 75.0 (C-2 β), 74.5 (CH₂ Bn/Nap β), 73.0 (CH₂ Bn/Nap α), 72.3 (CH₂ Bn/Nap α), 72.3 (C-5 α), 71.2 (CH₂ Bn/Nap β), 67.5 (C-4 β), 67.4 (C-4 α), 63.2 (C-6 β), 62.8 (C-6 α), 25.9 (CH₃ tBu β), 25.6 (CH₃ tBu α), 18.1 (Cq tBu β), 17.9 (Cq tBu α), -3.8 (CH₃ Me β), -4.5 (CH₃ Me α), -5.3 (CH₃ Me β), -5.8 (CH₃ Me α); ¹³C-GATED NMR (CDCl₃, 100MHz): δ 96.9 ($J_{C1,H1}$ = 154 Hz, C-1 β), 93.4 ($J_{C1,H1}$ = 166 Hz, C-1 α); HRMS: [M+NH₄]⁺ calcd. for C₃₀H₄₄NO₆Si 542.29324, found 542.29320.

Tert-butyldimethylsilyl 3-O-benzyl-2-O-(2-naphthylmethyl)- α/β -D-mannopyranoside (16) To a solution of



compound **13** (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 **16** 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); IR (neat): 727, 837, 907, 1070, 1252, 3420 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.74-7.86 (m, 5.20H, CH_{arom}), 7.62 (dd, 1H, J = 1.2, 8.4 Hz, CH_{arom}), 7.47-7.51 (m, 2.73H, CH_{arom}), 7.34-7.37 (m, 1.24H, CH_{arom}), 7.28-7.30 (m, 2.73H, CH_{arom}), 7.22-7.25 (m, 1H, CH_{arom}), 5.20 (d, 1H, J = 12.4 Hz, CHH Bn/Nap β), 5.12 (d, 0.24H, J = 1.6 Hz, H-1 α), 4.98 (d, 1H, J = 12.4 Hz, CHH Bn/Nap β), 4.92 (d, 0.24H, J = 12.4 Hz, CHH Bn/Nap α), 4.78-4.82 (m, 1.24H, CHH Bn/Nap α , H-1 β), 4.66 (s, 0.48H, CH₂ Bn/Nap α), 4.49 (d, 1H, J = 12.0 Hz, CHH Bn/Nap β), 4.39 (d, 1H, J = 12.0 Hz, CHH Bn/Nap β), 4.18 (t, 0.24H, J = 9.6 Hz, H-4 α), 4.07 (t, 1H, J = 9.6 Hz, H-4 β), 3.96 (dd, 1H, J = 3.6, 11.6Hz, H-6 β), 3.82-3.94 (m, 2.73, H-6 α , H-6 α , H-6 β , H-2 β , H-3 α), 3.75-3.80 (m, 0.24H, H-5 α), 3.63 (t, 0.24H, J = 2.4 Hz, H-2 α), 3.32-3.38 (m, 2H, H-3 β , H-5 β), 3.18 (bs, 0.24H, 4-OH α), 3.12 (bs, 1H, 4-OH β), 2.62 (bs, 1.24H, 6-OH α/β), 1.02 (s, 9H, CH₃ tBu β), 0.84 (s, 2.16H, CH₃ tBu α), 0.23 (s, 3H, CH₃ Me β), 0.21 (s, 3H, CH₃ Me β), 0.05 (s, 0.72H, CH₃ Me α), -0.04 (s, 0.72H, CH₃ Me α); ¹³C (CDCl₃, 100 MHz): δ 138.1, 137.9, 136.3, 135.6, 133.2, 133.1, 133.0 (Cq), 128.5, 128.4, 128.2, 128.1, 127.9, 127.9, 127.7, 127.6, 126.9, 16.7, 126.4, 126.1, 125.9, 125.7 (CH_{arom}), 96.8 (C-1 β), 93.4 (C-1 α), 81.6 (C-3 β), 78.9 (C-3 α), 76.0 (C-5 β), 75.8 (C-2 α), 75.2 (C-2 β), 74.5 (CH₂ Bn/Nap β), 73.0 (CH₂ Bn/Nap α), 72.4 (C-5 α), 72.3 (CH₂ Bn/Nap α), 71.3 (CH₂ Bn/Nap β), 67.4 (C-4 β), 67.2 (C-4 α), 63.0 (C-6 β), 62.6 (C-6 α), 25.9 (CH₃ tBu β), 25.5 (CH₃ tBu α), 18.0 (Cq tBu β), 17.8 (Cq tBu α), -3.8 (CH₃ Me β), -4.7 (CH₃ Me α), -5.3 (CH₃ Me β), -5.9 (CH₃ Me α); ¹³C-GATED NMR (CDCl₃, 100MHz): δ 96.8 ($J_{C1,H1}$ = 153 Hz, C-1 β), 93.4 ($J_{C1,H1}$ = 166 Hz, C-1 α); HRMS: [M+NH₄]⁺ calcd. for C₃₀H₄₄NO₆Si 542.29324, found 542.29370.

Methyl (tert-butyldimethylsilyl 2-O-benzyl-3-O-(2-naphthylmethyl)- α/β -D-mannopyranosyl uronate) (18)

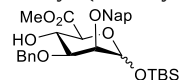


Diol **15** (40 g, 7.6 mmol) was dissolved in DCM (25 mL) and H₂O (13 mL) was added. To the two phase system TEMPO (236 mg, 1.51 mmol, 0.2 eq.) and BAIB (7.08 g, 22 mmol, 2.9 eq.) were added. After stirring vigorously for 6 hours at room temperature, the reaction

was quenched by addition of saturated aqueous Na₂S₂O₃. The mixture was extracted twice with EtOAc. The organic layer was dried with MgSO₄, filtered and concentrated *in vacuo*. The residue was co-evaporated with toluene once. The crude mannuronic acid was then dissolved in DMF (40 mL) and put under an argon atmosphere at 0°C. Methyl iodide (1.4 mL, 22.9 mmol, 3 eq.) and K₂CO₃ (3.16 g, 22.9 mmol, 3 eq.) were added and reaction was stirred overnight. The reaction was quenched with H₂O and extracted twice with EtOAc. The organic layers were collected

and dried with MgSO_4 , filtered and concentrated *in vacuo*. Purification by column chromatography (Toluene/Acetone, 40:1 $\rightarrow$ 10:1) afforded the title compound as a yellow oil (3.2 g, 5.79 mmol, 76%, $\alpha : \beta = 1 : 5.5$). TLC: R_f 0.62 (PE/EtOAc, 2/1, v/v); IR (neat): 698, 781, 839, 1070, 1200, 1252, 1362, 1748, 3447 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 7.81-7.77 (m, 3.90H, CH_{arom}), 7.73 (s, 1H, CH_{arom}), 7.44-7.48 (m, 4.54H, CH_{arom}), 7.38-7.40 (m, 1H, CH_{arom}), 7.27-7.32 (m, 3.72H, CH_{arom}), 5.01 (d, 0.18H, $J = 2.8$ Hz, H-1 α), 5.05 (d, 1H, $J = 12.4$ Hz, CHH Bn/Nap β), 4.65-4.88 (m, 4.72H, CHH Bn/Nap β , CH_2 Bn α , Nap α , Bn/Nap β , H-1 β), 4.32 (dt, 1.18H, $J = 2.0, 9.6$ Hz, H-4 α , H-4 β), 4.18 (d, 0.18H, $J = 9.2$ Hz, H-5 α), 3.82-3.84 (m, 1.18H, H-2 β , H-3 α), 3.80 (s, 3.54H, CH_3 CO_2Me α, β), 3.73 (d, 1H, $J = 9.6$ Hz, H-5 β), 3.53 (t, 0.18H, $J = 2.8$ Hz, H-2 α), 3.41 (dd, 1H, $J = 2.8, 9.6$ Hz, H-3 β), 3.08 (d, 1H, $J = 2.0$ Hz, 4-OH β), 2.96 (d, 0.18H, $J = 2.4$ Hz, 4-OH α), 0.93 (s, 9H, CH_3 tBu β), 0.73 (s, 1.62H, CH_3 tBu α), 0.18 (s, 3H, CH_3 Me β), 0.13 (s, 3H, CH_3 Me β), 0.02 (s, 0.54H, CH_3 Me α), -0.06 (s, 0.54, CH_3 Me α); ^{13}C (CDCl_3 , 100 MHz): δ 170.7 (C=O CO_2Me), 169.9 (C=O CO_2Me β), 138.7, 138.0, 135.5, 133.1, 133.0, 132.9 (Cq), 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.8, 127.7, 127.6, 127.3, 126.9, 126.8, 126.2, 126.0, 125.9, 125.9, 125.8, 125.6 (CH_{arom}), 97.0 (C-1 β), 93.6 (C-1 α), 80.2 (C-3 β), 77.4 (C-3 α), 75.9 (C-2 α), 75.2 (C-2 β), 74.8 (C-5 β), 74.3 (CH_2 Bn/Nap β), 72.9, 72.8 (CH_2 Bn α , Nap α), 72.0 (C-5 α), 71.7 (CH_2 Bn/Nap β), 68.5 (C-4 α), 68.0 (C-4 β), 52.4 (CH_3 CO_2Me β), 52.2 (CH_3 CO_2Me α), 25.7 (CH_3 tBu β), 25.3 (CH_3 tBu α), 17.9 (Cq tBu β), 17.6 (Cq tBu α), -4.1 (CH_3 Me β), -4.8 (CH_3 Me α), -5.6 (CH_3 Me β), -6.0 (CH_3 Me α); ^{13}C -GATED NMR (CDCl_3 , 100MHz): δ 97.0 ($J_{\text{C1,H1}} = 153$ Hz, C-1 β), 93.6 ($J_{\text{C1,H1}} = 168$ Hz, C-1 α); HRMS: $[\text{M}+\text{NH}_4]^+$ calcd. for $\text{C}_{31}\text{H}_{44}\text{NO}_7\text{Si}$ 570.28816, found 570.28804.

Methyl (tert-butylidimethylsilyl 3-O-benzyl-2-O-(2-naphthylmethyl)- α/β -D-mannopyranosyl uronate) (19)

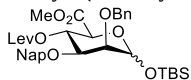


Diol **16** (3.7 g, 7.05 mmol) was dissolved in EtOAc (25 mL) and H_2O (10 mL) was added. To the two phase system TEMPO (220 mg, 1.41 mmol, 0.2 eq.) and BAIB (5.68 g, 17.6 mmol, 2.5 eq.) were added. After stirring vigorously for 4.5 hours at room temperature, the

reaction was quenched by addition of saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$. 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 $\rightarrow$ 2:1) afforded the title compound as a yellow solid (3.11 g, 5.63 mmol, 79%, $\alpha : \beta = 1 : 8.3$). TLC: R_f 0.29 (PE/EtOAc, 4/1, v/v); ^1H NMR (CDCl_3 , 400 MHz): δ 7.74-7.82 (m, 4.48H, CH_{arom}), 7.57-7.60 (dd, 1H, $J = 1.6, 8.4$ Hz, CH_{arom}), 7.44-7.48 (m, 2.48H, CH_{arom}), 7.19-7.35 (m, 5.48H, CH_{arom}), 5.17 (d, 1H, $J = 12.8$ Hz, CHH Bn/Nap β), 5.14 (d, 0.12H, $J = 1.2$ Hz, H-1 α), 4.95 (d, 1H, $J = 12.8$ Hz, CHH Bn/Nap β), 4.89 (d, 0.12H, $J = 12.4$ Hz, CHH Bn/Nap α), 4.81 (d, 0.12H, $J = 12.4$ Hz, CHH Bn/Nap α), 4.76 (s, 1H, H-1 β), 4.72 (d, 0.12H, $J = 12.0$ Hz, CHH Bn/Nap α), 4.65 (d, 0.12H, $J = 12.0$ Hz, CHH Bn/Nap α), 4.51 (s, 2H, CH_2 Bn/Nap β), 4.32 (dt, 1.12H, $J = 2.0, 9.6$ Hz, H-4 α , H-4 β), 4.19 (d, 0.12H, $J = 8.8$ Hz, H-5 α), 3.85 (d, 1H, $J = 3.2$ Hz, H-2 β), 3.74-3.83 (m, 4.48H, H-3 α , H-5 β , CH_3 OMe α, β), 3.56 (t, 0.12H, $J = 2.4$ Hz, H-2 α), 3.38 (dd, 1H, $J = 3.2, 9.6$ Hz, H-3 β), 3.04 (d, 1H, $J = 2.0$ Hz, 4-OH β), 2.93 (d, 0.12H, $J = 2.4$ Hz, 4-OH α), 0.95 (s, 9H, CH_3 tBu β), 0.77 (s, 1.08H, CH_3 tBu α), 0.19 (s, 3H, CH_3 Me β), 0.15 (s, 3H, CH_3 Me β), 0.02 (s, 0.36H, CH_3 Me α), -0.08 (s, 0.36H, CH_3 Me α); ^{13}C (CDCl_3 , 100 MHz): δ 170.9 (C=O CO_2Me α), 170.0 (C=O CO_2Me β), 138.3, 128.1, 136.3, 135.6, 133.2, 133.1, 133.0 (Cq), 128.5, 128.4, 128.2, 128.1, 127.9, 127.9, 127.8, 127.7, 127.6, 127.6, 126.9, 126.7, 126.5, 126.1, 126.1, 125.9, 125.9, 125.8, 125.7 (CH_{arom}), 97.2 (C-1 β), 93.8 (C-1 α), 80.5 (C-3 β), 77.8 (C-3 α), 75.9 (C-2 α), 75.3 (C-2 β), 75.0 (C-5 β), 74.6 (CH_2 Bn/Nap β), 73.1, 72.8 (CH_2 Bn/Nap α), 72.0 (CH_2

Bn/Nap β), 71.9 (C-5 α), 68.6 (C-4 α), 68.2 (C-4 β), 52.5 (CH₃ CO₂Me α,β), 25.9 (CH₃ tBu β), 25.5 (CH₃ tBu α), 18.0 (Cq tBu β), 17.8 (Cq tBu α), -4.0 (CH₃ Me β), -4.7 (CH₃ Me α), -5.5 (CH₃ Me β), -5.9 (CH₃ Me α); ¹³C-GATED NMR (CDCl₃, 100MHz): δ 97.2 ($J_{\text{C1,H1}}$ = 154 Hz, C-1 β), 93.8 ($J_{\text{C1,H1}}$ = 167 Hz, C-1 α).

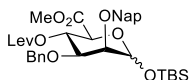
Methyl (tert-butyldimethylsilyl 2-O-benzyl-4-O-levulinoyl-3-O-(2-naphthylmethyl)- α/β -D-mannopyranosyl



uronate) (21) Levulinic acid (2.02 g, 17.4 mmol, 3 eq.) and DIC (1.35 mL, 8.7 mmol, 1.5 eq.) were added to a 0°C solution of **18** (3.2 g, 5.8 mmol) in dry DCM (14 mL). A catalytic amount of DMAP (71 mg, 0.58 mmol, 0.1 eq.) was added and the reaction mixture was

allowed to reach room temperature. After 4 hours, the reaction mixture was filtered over Celite and the filtrate washed with sat. aq. NaHCO₃ and brine. The organic layer was dried (MgSO₄), filtered, and concentrated *in vacuo*. Column chromatography (Toluene/Acetone, 40:1 $\rightarrow$ 10:1) afforded the title compound as an amorphous off-white solid (3.62 g, 5.56 mmol, 96%, $\alpha : \beta = 1 : 5.5$). TLC: R_f 0.47 (PE/EtOAc, 2/1, v/v); IR (neat): 696, 781, 837, 1053, 1152, 1252, 1362, 1717, 1746 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.80-7.82 (m, 3.72H, CH_{arom}), 7.69 (s, 1H, CH_{arom}), 7.45-7.49 (m, 4.72H, CH_{arom}), 7.37 (d, 1H, J = 8.4 Hz, CH_{arom}), 7.25-7.31 (m, 3.72H, CH_{arom}), 5.55 (t, 1.18H, J = 9.6 Hz, H-4 α , H-4 β), 5.28 (s, 0.18H, H-1 α), 5.05 (d, 1H, J = 12.4 Hz, CHH Bn/Nap β), 4.88 (d, 1H, J = 12.4 Hz, CHH Bn/Nap β), 4.73-4.77 (m, 1.72H, CH₂ Bn α , Nap α , H-1 β), 4.64 (d, 1H, J = 12.8 Hz, CHH Bn/Nap β), 4.51 (d, 1H, J = 12.8 Hz, CHH Bn/Nap β), 4.30 (d, 0.18H, J = 6.8 Hz, H-5 α), 3.93 (dd, 0.18H, J = 3.6, 8.4 Hz, H-3 α), 3.82-3.86 (m, 2H, H-2 β , H-5 β), 3.72 (s, 3H, CH₃ CO₂Me β), 3.66 (s, 0.54H, CH₃ CO₂Me α), 3.52-3.55 (m, 1.18H, H-2 α , H-3 β), 2.67 (t, 2.36H, J = 6.8 Hz, CH₂ Lev α , β), 2.55 (t, 2.36H, J = 6.8 Hz, CH₂ Lev α , β), 2.15 (s, 0.54H, CH₃ Lev α), 2.12 (s, 3H, CH₃ Lev β), 0.93 (s, 9H, CH₃ tBu β), 0.80 (s, 1.62H, CH₃ tBu α), 0.17 (s, 3H, CH₃ Me β), 0.11 (s, 3H, CH₃ Me β), 0.02 (s, 0.54H, CH₃ Me α), 0.01 (s, 0.54H, CH₃ Me α); ¹³C (CDCl₃, 100 MHz): δ 206.3 (C=O Lev), 171.6, 167.9 (C=O Lev, CO₂Me), 138.7, 135.4, 133.2, 133.0 (Cq), 128.4, 128.3, 128.2, 128.0, 128.0, 127.9, 127.8, 127.4, 126.8, 126.4, 126.2, 126.2, 126.0, 126.0, 125.7 (CH_{arom}), 96.9 (C-1 β), 93.4 (C-1 α), 78.4 (C-3 β), 76.1 (C-2 α), 75.3 (C-3 α), 74.7 (C-2 β), 74.2 (CH₂ Bn/Nap β), 73.5 (C-5 β), 73.1, 72.7 (CH₂ Bn α , Nap α), 71.8 (CH₂ Bn/Nap β), 71.6 (C-5 α), 69.7 (C-4 α), 69.0 (C-4 β), 52.6 (CH₃ CO₂Me), 37.8 (CH₂ Lev), 28.0 (CH₃ Lev), 28.0 (CH₂ Lev), 25.8 (CH₃ tBu), 25.6 (CH₃ tBu α), 18.1 (Cq tBu), -4.0 (CH₃ Me), -5.4 (CH₃ Me); ¹³C-GATED NMR (CDCl₃, 100MHz): δ 96.9 ($J_{\text{C1,H1}}$ = 153 Hz, C-1 β), 93.4 ($J_{\text{C1,H1}}$ = 167 Hz, C-1 α); HRMS: [M+NH₄]⁺ calcd. for C₃₆H₅₀NO₉Si 668.32494, found 668.32529.

Methyl (tert-butyldimethylsilyl 3-O-benzyl-4-O-levulinoyl-2-O-(2-naphthylmethyl)- α/β -D-mannopyranosyl

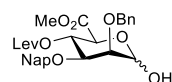


uronate) (22) Levulinic acid (1.08 g, 9.32 mmol, 2.8 eq.) and DIC (0.73 mL, 4.66 mmol, 1.4 eq.) were added to a 0°C solution of **19** (1.84 g, 3.33 mmol) in dry DCM (8.5 mL). A catalytic amount of DMAP (40 mg, 0.3 mmol, 0.1 eq.) was added and the reaction mixture

was allowed to reach room temperature. After 3 hours, the reaction mixture was filtered over Celite and the filtrate washed with sat. aq. NaHCO₃ and brine. The organic layer was dried (MgSO₄), filtered, and concentrated *in vacuo*. Column chromatography (PE/EtOAc, 6:1 $\rightarrow$ 2:1) afforded the title compound as an amorphous off-white solid (2.07 g, 3.18 mmol 95%, $\alpha : \beta = 1 : 10$). TLC: R_f 0.45 (PE/EtOAc, 2/1, v/v); IR (neat): 736, 783, 841, 1055, 115, 1256, 1362, 1722, 1748 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.72-7.81 (m, 4.60H, CH_{arom}), 7.60 (d, 1H, J = 8.4 Hz, CH_{arom}), 7.43-7.48 (m, 2.40H, CH_{arom}), 7.26-7.32 (m, 3.20H, CH_{arom}), 7.17-7.19 (m, 2H, CH_{arom}), 5.56 (t, 1.10H, J = 9.6 Hz, H-4 α , H-4 β), 5.31 (s, 0.10H, H-1 α), 5.17 (d, 1H, J = 12.4 Hz, CHH Bn/Nap β), 5.01 (d, 1H, J = 12.4 Hz, CHH Bn/Nap β), 4.88 (s, 0.20H, CH₂ Bn/Nap α), 4.76 (s, 1H, H-1 β), 4.62 (s, 0.20H, CH₂ Bn/Nap α), 4.44 (d, 1H, J = 12.4 Hz, CHH Bn/Nap β), 4.37 (d, 1H, J = 12.4 Hz, CHH Bn/Nap β), 3.31 (d, 0.10H, J = 7.6 Hz, H-5 α), 3.85-3.92 (m, 2.10H, H-2 β , H-5 β , H-3 α), 3.74 (s, 3H, CH₃ CO₂Me β), 3.67 (s, 0.30H, CH₃ CO₂Me α), 3.55 (t, 0.10H,

$J = 3.2$ Hz, H-2 α), 3.50 (dd, 1H, $J = 2.8, 9.6$ Hz, H-3 β), 2.71 (t, 2H, $J = 6.8$ Hz, CH₂ Lev β), 2.65-2.68 (m, 0.20H, CH₂ Lev α), 2.51-2.57 (m, 2.20H, CH₂ Lev α , β), 2.16 (s, 3H, CH₃ Lev β), 2.04 (s, 0.30H, CH₃ Lev α), 0.95 (s, 9H, CH₃ tBu β), 0.84 (s, 0.90H, CH₃ tBu α), 0.19 (s, 3H, CH₃ Me β), 0.14 (s, 3H, CH₃ Me β), 0.09 (s, 0.30H, CH₃ Me α), 0.01 (s, 0.30H, CH₃ Me α); ¹³C (CDCl₃, 100 MHz): δ 206.3 (C=O Lev), 171.6, 168.0 (C=O Lev, CO₂Me), 138.0, 136.2, 133.3, 133.1 (Cq_{arom}), 128.5, 128.4, 128.2, 128.0, 128.0, 127.9, 127.8, 127.7, 127.6, 126.9, 126.8, 126.7, 126.2, 125.9, 125.7 (CH_{arom}), 97.0 (C-1 β), 93.4 (C-1 α), 78.8 (C-3 β), 76.1 (C-2 α), 75.5 (C-3 α), 74.7 (C-2 β), 74.3 (CH₂ Bn/Nap β), 73.6 (C-5 β), 73.2, 72.8, (CH₂ Bn/Nap α), 71.7 (CH₂ Bn/Nap β), 69.9 (C-4 α), 69.1 (C-4 β), 52.7, 52.5 (CH₃ CO₂Me), 37.9, 37.8 (CH₂ Lev), 29.9 (CH₃ Lev), 28.0 (CH₂ Lev), 25.9, 25.7 (CH₃ tBu), 18.1 (Cq tBu), -3.9, -5.3 (CH₃ Me); ¹³C-GATED NMR (CDCl₃, 100MHz): δ 97.0 ($J_{C1,H1} = 154$ Hz, C-1 β); HRMS: [M+NH₄]⁺ calcd. for C₃₆H₅₀NO₅Si 668.32494, found 668.32532.

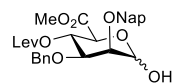
Methyl (2-O-benzyl-4-O-levulinoyl-3-O-(2-naphthylmethyl)- α/β -D-mannopyranosyl uronate) (24) Acetic acid



(0.07 mL, 1.16 mmol, 2 eq.) was added to a 0°C solution of compound **21** (370 mg, 0.57 mmol) in dry THF (5.7 mL). TBAF (1.0 M solution in THF, 0.9 mL, 0.88 mmol, 1.5 eq.) was added drop wise over 5 minutes. The reaction mixture was stirred for 30 minutes at room

temperature and subsequently diluted with EtOAc and washed once with H₂O. The aqueous layer was extracted two more times with EtOAc and the combined organic layers were washed with brine. The organic layer was dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by column chromatography (PE/EtOAc, 4:1 → 1:1) furnished the title compound as a colourless oil (300 mg, 0.55 mmol, 97%, $\alpha : \beta = 17 : 1$). Analytic data is reported for the α -anomer. TLC: R_f 0.18 (PE/EtOAc, 1/1, v/v); IR (neat): 698, 748, 820, 1028, 1123, 1364, 1717, 1742, 3437 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.75-7.81 (m, 4H, CH_{arom}), 7.40-7.47 (m, 3H, CH_{arom}), 7.23-7.30 (m, 5H, CH_{arom}), 5.59 (t, 1H, $J = 6.4$ Hz, H-4), 5.54 (bs, 1H, H-1 α), 4.85 (s, 0.06H, H-1 β), 4.60-4.81 (m, 5H, CH₂ Bn, Nap, 1-OH), 4.47 (d, 1H, $J = 6.4$ Hz, H-5), 3.97 (dd, 1H, $J = 3.2, 6.4$ Hz, H-3), 3.65-3.68 (m, 1H, H-2), 3.58 (s, 3H, CH₃ CO₂Me), 2.65 (t, 2H, $J = 6.4$ Hz, CH₂ Lev), 2.49-2.55 (m, 2H, CH₂ Lev), 2.11 (s, 3H, CH₃ Lev); ¹³C (CDCl₃, 100 MHz): δ 206.5 (C=O Lev), 171.8, 169.2 (C=O Lev, CO₂Me), 138.2, 135.3, 133.2, 133.0 (Cq), 129.1, 128.6, 128.3, 128.1, 128.0, 127.9, 127.7, 127.6, 126.7, 126.4, 126.1, 125.9, 125.7 (CH_{arom}), 93.8 (C-1 β), 92.6 (C-1 α), 75.4, 75.3 (C-2, C-3), 72.9, 72.6 (CH₂ Bn, Nap), 71.7 (C-5), 69.6 (C-4), 52.5 (CH₃ CO₂Me), 37.8 (CH₂ Lev), 29.8 (CH₃ Lev), 28.0 (CH₂ Lev); ¹³C-GATED NMR (CDCl₃, 100MHz): δ 92.6 ($J_{C1,H1} = 170$ Hz, C-1 α); HRMS: [M+NH₄]⁺ calcd. for C₃₀H₃₆NO₉ 559.19385, found 559.19282.

Methyl (3-O-benzyl-4-O-levulinoyl-2-O-(2-naphthylmethyl)- α/β -D-mannopyranosyl uronate) (25) Acetic acid



(0.36 mL, 6.36 mmol, 2 eq.) was added to a 0°C solution of compound **22** (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 H₂O and brine. The organic layer was dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by column chromatography (Pentane/DCM/EtOAc, 4:1:1 → 1:1:2) furnished the title compound as a colourless oil (1.7 g, 3.17 mmol, 99%, $\alpha : \beta = 8.3 : 1$). TLC: R_f 0.18 (PE/EtOAc, 1/1, v/v); IR (neat): 698, 739, 820, 1028, 11.23, 1362, 1717, 1744, 3402 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.72-7.83 (m, 4.48H, CH_{arom}), 7.42-7.49 (m, 3.36H, CH_{arom}), 7.27-7.37 (m, 5.60H, CH_{arom}), 5.63 (t, 0.12H, $J = 7.2$ Hz, H-4 β), 5.55-5.58 (m, 2H, H-1 α , H-4 α), 5.05 (d, 0.12H, $J = 12.0$ Hz, CHH Bn/Nap β), 4.88-4.94 (m, 1.12H, CHH Bn/Nap α , H-1 β), 4.81 (d, 1.12H, $J = 12.4$ Hz, CHH Bn/Nap α , CHH Bn/Nap β), 4.74 (d, 0.12H, $J = 12.0$ Hz, CHH Bn/Nap β), 4.68 (d, 0.12H, $J = 12.0$ Hz, CHH Bn/Nap β), 4.62 (d, 1H, $J = 12.0$ Hz, CHH Bn/Nap α), 4.59 (d, 1H, $J = 12.0$ Hz, CHH Bn/Nap α), 4.47 (d, 1H, $J = 5.2$ Hz, H-5 α), 4.08 (d, 0.12H, $J = 6.8$ Hz,

H-5 β), 3.94 (dd, 1H, J = 3.0, 6.4 Hz, H-3 α), 3.85 (t, 0.12H, J = 2.6 Hz, H-2 β), 3.78 (dd, 0.12H, J = 2.4, 8.0 Hz, H-3 β), 3.68 (s, 0.36H, CH₃ CO₂Me β), 3.65-3.67 (m, 1H, H-2 α), 3.61 (s, 3H, CH₃ CO₂Me α), 3.47 (d, 1H, J = 4.0 Hz, 1-OH α), 2.68-2.72 (m, 0.24H, CH₂ Lev β), 2.63 (t, 2H, J = 6.4 Hz, CH₂ Lev α), 2.39-2.56 (m, 2.24H, CH₂ Lev α,β), 2.17 (s, 0.36H, CH₃ Lev β), 2.14 (s, 3H, CH₃ Lev α); ¹³C (CDCl₃, 100 MHz): δ 206.5 (C=O Lev), 171.7, 169.3 (C=O Lev, CO₂Me), 137.8, 135.7, 135.0 133.2, 133.0 (Cq-_{arom}), 128.6, 128.4, 128.1, 127.9, 127.9, 127.7, 127.3, 126.7, 126.2, 126.1, 126.0, 125.9 (CH_{arom}), 93.9 (C-1 β), 92.6 (C-1 α), 77.9 (C-3 β), 75.3, 75.2 (C-2 α , C-3 α), 73.9 (C-2 β , C-5 β), 73.8, 73.1 (CH₂ Bn β , Nap β), 72.9, 72.6 (CH₂ Bn α , Nap α), 71.7 (C-5 α), 69.6, 69.5 (C-4 α,β), 52.8 (CH₃ CO₂Me β), 52.5 (CH₃ CO₂Me α), 37.7 (CH₂ Lev), 29.8 (CH₃ Lev), 28.0 (CH₂ Lev); ¹³C-GATED NMR (CDCl₃, 100MHz): δ 92.6 ($J_{C1,H1}$ = 170 Hz, C-1 α); HRMS: [M+NH₄]⁺ calcd. for C₃₀H₃₆NO₉ 554.23846, found 554.23850.

Methyl (2-O-benzyl-4-O-levulinoyl-3-O-(2-naphthylmethyl)-1-O-(N-[phenyl]trifluoroacetimidoyl)- α/β -D-mannopyranosyl uronate) (27) Cs₂CO₃ (215 mg, 0.66 mmol, 1.2 eq.) was added to a 0°C solution of compound **24** (300 mg, 0.55 mmol) and 2,2,2-Trifluoro-N-phenylacetimidoyl chloride (92 μ L, 0.61 mmol, 1.1 eq.) in acetone (1.8 mL). After

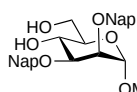
stirring overnight at ambient temperature TLC analysis showed complete conversion of the starting compound to a higher running spot. H₂O was added and the mixture was extracted two times with EtOAc. The organic fraction was washed with brine, dried with MgSO₄, filtered, and concentrated *in vacuo*. The crude compound was purified using column chromatography (PE/EtOAc, 8:1 $\rightarrow$ 2:1) to yield the title compound as a yellow oil (340 mg, 0.48 mmol, 87%, α : β = 6.7 : 1). TLC: R_f 0.63 (PE/EtOAc, 1/1, v/v); IR (neat): 696, 752, 1124, 1153, 1207, 1717, 1749 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.76-7.84 (m, 4.45H, CH_{arom}), 7.39-7.50 (m, 3.60H, CH_{arom}), 7.24-7.33 (m, 8.05H, CH_{arom}), 7.08-7.11 (m, 1.15H, NPh α,β), 6.79 (d, 0.30H, J = 7.6 Hz, NPh β), 6.68 (d, 2H, J = 7.6 Hz, NPh α), 6.44 (bs, 1H, H-1 α), 6.05 (bs, 0.15H, H-1 β), 5.77 (t, 0.15H, J = 6.2 Hz, H-4 β), 5.64 (t, 1H, J = 7.2 Hz, H-4 α), 4.62-4.83 (m, 4.60H, CH₂ Bn α,β , CH₂ Nap α,β), 4.41 (d, 1H, J = 7.2 Hz, H-5 α), 4.05 (bs, 0.15H, H-2 β), 3.97 (dd, 1H, J = 3.0, 7.8 Hz, H-3 α), 3.80-3.85 (m, 0.15H, H-3 β), 3.78 (bs, 1H, H-2 α), 3.67 (s, 3H, CO₂Me α), 3.62 (s, 0.45H, CO₂Me β), 2.70 (t, 2.30H, J = 6.4 Hz, CH₂ Lev α,β), 2.53-2.60 (m, 2.30H, CH₂ Lev α,β), 2.15 (s, 3.45H, CH₃ Lev α,β); ¹³C NMR (CDCl₃, 100 MHz): δ 206.2 (C=O Lev), 171.7, 168.0 (C=O Lev, CO₂Me), 143.2 (Cq NPh), 137.5, 135.0, 133.2, 133.1 (Cq), 128.8, 128.7, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.0, 126.3, 126.2, 126.1, 125.9, 125.5 (CH_{arom}), 124.5, 124.2, 119.4 (CH_{arom} NPh), 94.4 (C-1 α), 74.8 (C-3 α), 73.2 (C-2 α), 73.1, 73.0 (CH₂ Bn, Nap), 72.9 (C-5 α), 71.8 (C-2 β), 69.5 (C-4 β), 68.9 (C-4 α), 52.8 (CH₃ CO₂Me α), 52.6 (CH₃ CO₂Me β), 37.8 (CH₂ Lev), 29.8 (CH₃ Lev), 28.0 (CH₂ Lev); HRMS: [M+Na]⁺ calcd. for C₃₈H₃₆F₃NO₉Na 730.22344, found 730.22384.

Methyl (3-O-benzyl-4-O-levulinoyl-2-O-(2-naphthylmethyl)-1-O-(N-[phenyl]trifluoroacetimidoyl)- α/β -D-mannopyranosyl uronate) (28) 2,2,2-Trifluoro-N-phenylacetimidoyl chloride (0.82 mL, 5.4 mmol, 1.1 eq.) was added drop wise to a 0°C solution of **25** (2.6 g, 4.8 mmol) and Cs₂CO₃ (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. H₂O was added and the mixture was extracted two times with EtOAc. The organic fraction was washed with brine, dried with MgSO₄, filtered, and concentrated *in vacuo*. The crude compound was purified using column chromatography (PE/EtOAc, 8:1 $\rightarrow$ 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): 1123, 1153, 1207, 1717, 1748 cm⁻¹; ¹H NMR (CDCl₃, 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, $J = 6.4$ Hz, H-4 β), 5.61 (t, 1H, $J = 7.6$ Hz, H-4 α), 4.97 (s, 0.24H, CH₂ Bn/Nap β), 4.86 (d, 1H, $J = 12.0$ Hz, CHH Bn/Nap α), 4.80 (d, 1H, $J = 12.0$ Hz, CHH Bn/Nap α), 4.68 (d, 0.12H, $J = 12.4$ Hz, CHH Bn/Nap β), 4.60-4.63 (m, 1.12H, CHH Bn/Nap α , CHH Bn/Nap β), 4.55 (d, 1H, $J = 12.0$ Hz, CHH 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, CH₃ CO₂Me α), 3.64 (s, 0.36H, CH₃ CO₂Me β), 2.69 (t, 2.24H, $J = 6.4$ Hz, CH₂ Lev α,β), 2.46-2.62 (m, 2.24H, CH₂ Lev α,β), 2.17 (s, 3H, CH₃ Lev α), 2.16 (s, 0.36H, CH₃ Lev β); ¹³C (CDCl₃, 100 MHz): δ 206.2 (C=O Lev), 171.6, 168.0 (C=O Lev, CO₂Me), 143.2, 142.5, 142.2, 141.8, 137.9, 137.5, 135.2, 134.9, 133.2 (Cq), 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 (CH₂ 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 (CH₃ CO₂Me α), 52.6 (CH₃ CO₂Me β), 37.7 (CH₂ Lev), 29.8 (CH₃ Lev), 27.9 (CH₂ Lev); ¹³C-GATED NMR (CDCl₃, 100MHz): δ 94.5 ($J_{C1,H1} = 186$ Hz, C-1 α); HRMS: [M+Na]⁺ calcd. for C₃₈H₃₆F₃NO₉Na 730.22344, found 730.22372.

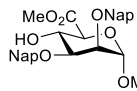
Methyl 2,3-di-O-(2-naphthylmethyl)- α -D-mannopyranoside (29) To a solution of compound 2 (5.4 g, 9.6 mmol)



in MeOH/DCM (1/1, 50 mL) pTsOH·H₂O (1.2 g, 6.25 mmol, 0.65 eq.) was added and allowed to stir overnight. After quenching with sat. aq. NaHCO₃, the mixture was extracted with EtOAc and the layers separated. The organic layer was washed with H₂O and brine, dried with MgSO₄,

filtered and concentrated *in vacuo*. Purification by column chromatography (PE/EtOAc, 7:1 $\rightarrow$ 1:3) afforded the title compound as a yellowish oil (4.0 g, 8.44 mmol, 88%). TLC: R_f 0.20 (Pentane/EtOAc, 1/2, v/v); IR (neat): 748, 812, 1047, 1261, 2922, 3412 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.70-7.80 (m, 8H, CH_{arom}), 7.37-7.51 (m, 6H, CH_{arom}), 4.83 (d, 1H, $J = 12.4$ Hz, CHH Nap), 4.76-4.79 (m, 2H, CHH Nap, H-1), 4.69 (d, 1H, $J = 12.0$ Hz, CHH Nap), 4.63 (d, 1H, $J = 12.0$ Hz, CHH Nap), 4.13 (t, 1H, $J = 9.6$ Hz, H-4), 3.83-3.91 (m, 3H, H-2, H-6, H-6), 3.76 (dd, 1H, $J = 3.2, 9.6$ Hz, H-3), 3.59-3.63 (m, 1H, H-5), 3.30 (s, 3H, CH₃ OMe), 2.85 (bs, 1H, 4-OH), 2.50 (bs, 1H, 6-OH); ¹³C NMR (CDCl₃, 100 MHz): δ 135.6, 135.6, 133.3, 133.3, 133.1, 133.1 (Cq), 128.4, 128.4, 128.0, 128.0, 127.8, 127.8, 126.8, 126.5, 126.3, 126.2, 126.1, 126.1, 126.0, 125.7 (CH_{arom}), 99.4 (C-1), 79.9 (C-3), 73.9 (C-2), 73.0 (CH₂ Nap), 72.3 (C-5), 72.0 (CH₂ Nap), 67.4 (C-4), 62.9 (C-6), 55.0 (OMe); HRMS: [M+NH₄]⁺ calcd. for C₂₉H₃₄NO₆ 492.23806, found 492.23821.

Methyl (methyl 2,3-di-O-(2-naphthylmethyl)- α -D-mannopyranosyl uronate) (32) Diol 29 (2.77 g, 5.84 mmol)



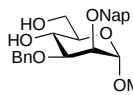
was dissolved in DCM (20 mL) and H₂O (10 mL). To the two phase system TEMPO (228 mg, 1.46 mmol, 0.25 eq.) and BAIB (230 mg, 0.713 mmol, 2.5 eq.) were added. After stirring vigorously for 5 hours at room temperature, the reaction was quenched by addition of sat. aq.

Na₂S₂O₃. The mixture was extracted twice with Et₂O and the layers separated. The organic layer was dried with MgSO₄, 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 K₂CO₃ (2.4 g, 17.5 mmol, 3 eq.) were added and the reaction was stirred overnight. The reaction was quenched with H₂O and extracted two times with EtOAc. The organic layers were collected and dried with MgSO₄, filtered and concentrated *in vacuo*. Purification by column chromatography (Pentane/EtOAc, 10:1 $\rightarrow$ 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): 750, 818, 1059, 1172, 1748, 3480 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.68-7.81 (m, 8H, CH_{arom}), 7.40-7.49 (m, 6H, CH_{arom}), 4.87- 4.90 (m, 2H, H-1 CHH Nap), 4.80-4.84 (m, 2H, CHH Nap, CHH Nap), 4.75 (d, 1H, $J = 12.0$ Hz, CHH Nap), 4.40 (t, 1H, $J = 9.4$ Hz, H-4), 4.14 (d, 1H, $J = 9.4$ Hz, H-5), 3.80-3.84 (m, 2H, H-2, H-3), 3.79 (s, 3H, CH₃ CO₂Me), 3.69 (bs, 1H, 4-OH), 3.37 (s, 3H, CH₃ OMe); ¹³C NMR (CDCl₃, 100 MHz): δ 170.6

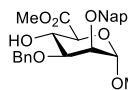
(C=O CO₂Me), 135.8, 135.6, 133.2, 133.1, 132.9, 132.9 (Cq), 128.1, 128.0, 127.8, 127.8, 127.6, 126.5, 126.2, 126.0, 125.9, 125.8, 125.8, 125.6 (CH_{arom}), 99.8 (C-1), 78.6 (C-3), 74.2 (C-2), 72.9, 72.6 (CH₂ Nap), 72.1 (C-5), 68.4 (C-4), 55.3 (CH₃ OMe), 52.5 (CH₃ CO₂Me); ¹³C-GATED NMR (CDCl₃, 100MHz): δ 99.8 (*J*_{C1,H1} = 169 Hz, C-1 α); HRMS: [M+NH₄]⁺ calcd. for C₃₀H₃₄NO₇ 520.23298, found 520.23331.

Methyl 2-O-benzyl-3-O-(2-naphthylmethyl)-α-D-mannopyranoside (30) To a solution of compound **3** (2.84 g, 5.54 mmol) in MeOH/DCM (3/2, 25 mL) pTsOH·H₂O (185 mg, 0.97 mmol, 0.18 eq.) was added and allowed to stir overnight. After quenching with sat. aq. NaHCO₃, the mixture was extracted with EtOAc and the layers separated. The organic layer was washed with H₂O and brine, dried with MgSO₄, filtered and concentrated *in vacuo*. Purification by column chromatography (PE/EtOAc, 4:1 → 1:3) afforded the title compound as a colourless oil (2.16 g, 5.08 mmol, 91%). TLC: R_f 0.22 (Pentane/EtOAc, 1/2, v/v); IR (neat): 698, 737, 814, 1049, 1454, 3404 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.73-7.79 (m, 4H, CH_{arom}), 7.39-7.45 (m, 3H, CH_{arom}), 7.21-7.32 (m, 5H, CH_{arom}), 4.73 (s, 1H, H-1), 4.61-4.71 (m, 4H, CH₂ Bn, Nap), 4.08 (t, 1H, *J* = 10.0 Hz, H-4), 3.72-3.84 (m, 4H, H-2, H-3 H-6, H-6), 3.55-3.59 (m, 1H, H-5), 3.27 (s, 3H, CH₃ OMe), 3.20 (bs, 1H, 4-OH), 2.80 (bs, 1H, 6-OH); ¹³C NMR (CDCl₃, 100 MHz): δ 138.1, 135.7, 133.3, 133.1 (Cq_{arom}), 128.4, 128.3, 128.3, 127.9, 127.8, 127.8, 127.7, 127.6, 126.4, 126.2, 126.1, 126.0, 125.7 (CH_{arom}), 99.3 (C-1), 79.7 (C-3), 74.2 (C-2), 72.8 (CH₂ Bn/Nap), 72.4 (C-5), 72.0 (CH₂ Bn/Nap), 67.2 (C-4), 62.7 (C-6), 54.9 (OMe); ¹³C-GATED NMR (CDCl₃, 100MHz): δ 99.3 (*J*_{C1,H1} = 169 Hz, C-1 α); HRMS: [M+NH₄]⁺ calcd. for C₂₅H₃₂NO₆ 442.22241, found 442.22214.

Methyl (Methyl 2-O-benzyl-3-O-(2-naphthylmethyl)-α-D-mannopyranosyl uronate) (33) Diol **30** (1.27 g, 3.0 mmol) was dissolved in EtOAc (10 mL) and H₂O (5 mL). To the two phase system TEMPO (102 mg, 0.65 mmol, 0.2 eq.) and BAIB (2.62 g, 8.13 mmol, 2.5 eq.) were added. After stirring vigorously for 6 hours at room temperature, the reaction was quenched by addition of sat. aq. Na₂S₂O₃. The mixture was extracted twice with EtOAc. The organic layer was dried with MgSO₄, filtered and concentrated *in vacuo*. The residue was co-evaporated with toluene once. The crude mannuronic acid was then dissolved in DMF (18 mL) and put under an argon atmosphere at 0°C. Methyl iodide (0.6 mL, 9.75 mmol, 3 eq.) and K₂CO₃ (1.35 g, 9.75 mmol, 3 eq.) were added and the reaction was stirred overnight. The reaction was quenched with H₂O and extracted two times with EtOAc. The organic layers were collected, washed with brine and dried with MgSO₄, filtered and concentrated *in vacuo*. Purification by column chromatography (Toluene/Acetone, 20:1 → 7:1) afforded the title compound as a yellow oil (748 mg, 1.65 mmol, 55%). TLC: R_f 0.25 (Toluene/Acetone, 8/1, v/v); IR (neat): 698, 737, 816, 1051, 1125, 1202, 1439, 1746, 3478 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.76-7.82 (m, 4H, CH_{arom}), 7.43-7.47 (m, 3H, CH_{arom}), 7.22-7.35 (m, 5H, CH_{arom}), 4.82 (d, 1H, *J* = 1.6 Hz, H-1), 4.80 (d, 1H, *J* = 12.4 Hz, CHH Bn/Nap), 4.75 (d, 1H, *J* = 12.4 Hz, CHH Bn/Nap), 4.72 (d, 1H, *J* = 12.4 Hz, CHH Bn/Nap), 4.67 (d, 1H, *J* = 12.4 Hz, CHH Bn/Nap), 4.35 (dt, 1H, *J* = 2.4, 9.2 Hz, H-4), 4.10 (d, 1H, *J* = 9.2 Hz, H-5), 3.75-3.81 (m, 5H, CH₃ CO₂Me, H-2, H-3), 3.36 (s, 3H, CH₃ OMe), 3.11 (d, 1H, *J* = 2.4 Hz, 4-OH); ¹³C NMR (CDCl₃, 100 MHz): δ 170.8 (C=O CO₂Me), 138.1, 135.8, 133.3, 133.0 (Cq), 128.4, 128.2, 128.0, 127.9, 127.8, 126.4, 126.2, 125.9, 125.7 (CH_{arom}), 99.9 (C-1), 78.5 (C-3), 74.2 (C-2), 73.0, 72.6 (CH₂ Bn, Nap), 71.8 (C-5), 68.5 (C-4), 55.5 (OMe), 52.7 (CH₃ CO₂Me); HRMS: [M+NH₄]⁺ calcd. for C₂₆H₃₂NO₇ 470.21733, found 470.21690.

Methyl 3-O-benzyl-2-O-(2-naphthylmethyl)- α -D-mannopyranoside (31)

7.4 mmol) in MeOH/DCM (1/1, 40 mL) pTsOH $\cdot$ H₂O (222 mg, 1.17 mmol, 0.15 eq.) was added and allowed to stir over the weekend. After quenching with sat. aq. NaHCO₃, the mixture was extracted with EtOAc and the layers separated. The organic layer was washed with H₂O and brine, dried with MgSO₄, filtered and concentrated *in vacuo*. Purification by column chromatography (PE/EtOAc, 4:1 $\rightarrow$ 1:4) afforded the title compound as a yellow oil (2.63 g, 6.2 mmol, 83%). TLC: R_f 0.25 (PE/EtOAc, 1/2, v/v); IR (neat): 734, 820, 1053, 1454, 2913, 3393 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.72- 7.79 (m, 4H, CH_{arom}), 7.42- 7.48 (m, 3H, CH_{arom}), 7.25-7.32 (m, 5H, CH_{arom}), 4.75-4.83 (m, 3H, H-1, CH₂ Bn/Nap), 4.56 (d, 1H, *J* = 11.8 Hz, CHH Bn/Nap), 4.48 (d, 1H, *J* = 11.8 Hz, CHH Bn/Nap), 4.08 (t, 1H, *J* = 9.6 Hz, H-4), 3.80-3.89 (m, 3H, H-2, H-6, H-6), 3.70 (dd, 1H, *J* = 2.8, 9.6 Hz, H-3), 3.57- 3.61 (m, 1H, H-5), 3.29 (s, 3H, CH₃ OMe), 2.94 (bs, 1H, 4-OH), 2.63 (bs, 1H, 6-OH); ¹³C NMR (CDCl₃, 100 MHz): δ 138.2, 135.6, 133.3, 133.1 (Cq), 128.6, 128.3, 128.0, 127.9, 127.8, 126.8, 126.2, 126.0 (CH_{arom}), 99.4 (C-1), 79.9 (C-3), 74.0 (C-2), 73.0 (CH₂ Bn/Nap), 72.4 (C-5), 72.0 (CH₂ Bn/Nap), 67.3 (C-4), 62.8 (C-6), 54.9 (OMe); HRMS: [M+NH₄]⁺ calcd. for C₂₅H₃₂NO₆ 442.22241, found 442.22236.

Methyl (Methyl 3-O-benzyl-2-O-(2-naphthylmethyl)- α -D-mannopyranosyl uronate) (34)

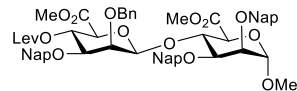
0.285 mmol) was dissolved in DCM (1.0 mL) and H₂O (0.5 mL). To the two phase system TEMPO (9 mg, 0.057 mmol, 0.2 eq.) and BAIB (230 mg, 0.713 mmol, 2.5 eq.) were added.

After stirring vigorously for 6 hours at room temperature, the reaction was quenched by addition of sat. aq. Na₂S₂O₃. The mixture was transferred to a separatory funnel, EtOAc was added and the layers were separated. The organic layer was dried with MgSO₄, filtered and concentrated *in vacuo*. The residue was co-evaporated with toluene once. The crude mannuronic acid was then dissolved in DMF (1.5 mL) and put under an argon atmosphere at 0°C. Methyl iodide (53 μ L, 0.855 mmol, 3.0 eq.) and K₂CO₃ (118 mg, 0.855 mmol, 3.0 eq.) were added and the reaction was stirred overnight. The reaction was quenched with H₂O and extracted three times with EtOAc. The organic layers were collected and dried with MgSO₄, filtered and concentrated *in vacuo*. Purification by column chromatography (PE/EtOAc, 9:1 $\rightarrow$ 2:1) afforded the title compound as a yellow oil (98 mg, 0.217 mmol, 76%). TLC: R_f 0.24 (PE/EtOAc, 2/1, v/v); IR (neat): 698, 737, 1051, 1125, 1201, 1439, 1746, 3476 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.75-7.82 (m, 4H, CH_{arom} Bn/Nap), 7.44-7.49 (m, 3H, CH_{arom} Bn/Nap), 7.26-7.32 (m, 5H, CH_{arom} Bn/Nap), 4.81-4.88 (m, 3H, H-1, CH₂ Bn/Nap), 4.66 (d, 1H, *J* = 11.8 Hz, CHH Bn/Nap), 4.61 (d, 1H, *J* = 11.8 Hz, CHH Nap), 4.35 (t, 1H, *J* = 9.2 Hz, H-4), 4.10 (d, 1H, *J* = 9.2 Hz, H-5), 3.73-3.82 (m, 5H, H-2, H-3, CH₃ CO₂Me), 3.37 (s, 3H, CH₃ OMe), 2.92 (d, 1H, *J* = 2.4 Hz, 4-OH); ¹³C NMR (CDCl₃, 100 MHz): δ 170.8 (C=O CO₂Me), 138.4, 135.6, 133.3, 133.1 (Cq), 128.5, 128.3, 128.0, 127.8, 127.7, 126.8, 126.2, 126.1, 126.0 (CH_{arom}), 100.0 (C-1), 78.7 (C-3), 74.1 (C-2), 73.1 (CH₂ Bn), 72.7 (CH₂ Nap), 71.8 (C-5), 68.6 (C-4), 55.5 (OMe), 52.7 (CH₃ CO₂Me); HRMS: [M+NH₄]⁺ calcd. for C₂₆H₃₂NO₇ 470.21733, found 470.21745.

General procedure for TfOH-mediated glycosylations. A mixture of the donor (1 eq.) and acceptor (1.2 eq.) was co-evaporated with dry toluene twice. While the mixture was under an argon atmosphere, freshly distilled DCM (0.1 M, based on combined amounts of donor and acceptor) was added, followed by the addition of activated molecular sieves (3 Å). The resulting mixture was stirred at room temperature for 30 minutes and then cooled to -40°C. TfOH (0.2 eq.) was added and the reaction was monitored by TLC analysis. After TLC analysis showed the complete consumption of donor material, the reaction was quenched by addition of Et₃N (1 % v/v). The mixture was transferred to a separatory funnel with EtOAc and washed with brine twice. After drying with MgSO₄ and

concentrating *in vacuo*, the crude disaccharide was passed through a column of Sephadex LH-20 (eluted with DCM/MeOH, 1/1, v/v) which gave the purified product.

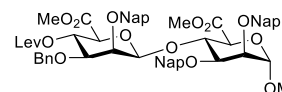
Methyl (methyl 4-O-[methyl 2-O-benzyl-4-O-levulinoyl-3-O-(2-naphthylmethyl)-β-D-mannopyranosyl uronate]-2,3-di-O-(2-naphthylmethyl)-α-D-mannopyranosyl uronate)



(35) Donor **27** (135 mg, 0.19 mmol) and acceptor **32** (123 mg, 0.245 mmol, 1.2 eq.) were condensed using the general protocol for TfOH-mediated

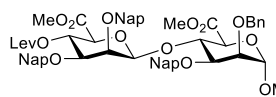
glycosylations to yield disaccharide **35** (145 mg, 0.142 mmol, 74%, $\alpha \ll \beta$) as an off-white foam. TLC: R_f 0.24 (PE/EtOAc, 3/2, v/v); IR (neat): 747, 816, 1051, 1125, 1360, 1717, 1746 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 7.63–7.82 (m, 12H, CH_{arom}), 7.35–7.48 (m, 11H, CH_{arom}), 7.20–7.27 (m, 3H, CH_{arom}), 5.52 (t, 1H, $J = 9.6$ Hz, H-4'), 5.06 (bs, 1H, H-1), 4.91 (d, 1H, $J = 12.4$ Hz, CHH Bn/Nap), 4.63–4.87 (m, 7H, CHH Bn/Nap, CH_2 Nap, CH_2 Bn/Nap, CHH Bn/Nap, H-1'), 4.51–4.54 (m, 2H, CHH Bn/Nap, H-4), 4.27 (d, 1H, $J = 5.2$ Hz, H-5), 4.12 (bs, 1H, H-3), 3.88 (d, 1H, $J = 2.4$ Hz, H-2'), 3.80 (d, 1H, $J = 9.6$ Hz, H-5'), 3.74 (dd, 1H, $J = 2.8, 5.2$, H-2), 3.48–3.53 (m, 10H, CH_3 CO_2Me , $\text{CO}_2\text{Me}'$, OMe, H-3), 2.64 (t, 2H, $J = 6.4$ Hz, CH_2 Lev), 2.53 (t, 2H, $J = 6.4$ Hz, CH_2 Lev), 2.11 (s, 3H, CH_3 Lev); ^{13}C (CDCl_3 , 100 MHz): δ 206.3 (C=O Lev), 171.7, 169.9, 167.8 (C=O CO_2Me , Lev), 138.4, 136.1, 135.8, 135.3, 133.3, 133.2, 133.1, 133.0, 132.9 (Cq), 128.3, 128.2, 128.1, 128.1, 128.0, 127.9, 127.8, 127.7, 127.7, 127.5, 127.4, 127.4, 126.6, 126.5, 126.3, 126.2, 126.1, 126.0, 125.9, 125.9, 125.8, 125.8, 125.8, 125.5 (CH_{arom}), 101.1 (C-1'), 99.7 (C-1), 77.9 (C-3'), 77.0 (C-3), 76.5 (C-4), 75.1 (C-2), 74.2 (CH_2 Bn/Nap), 74.1 (C-2'), 73.5 (C-5'), 73.1, 73.0 (CH_2 Bn/Nap), 71.8 (C-5, CH_2 Bn/Nap), 69.1 (C-4'), 56.2 (OMe), 52.5, 52.3 (CH_3 CO_2Me), 37.8 (CH_2 Lev), 29.9 (CH_3 Lev), 28.0 (CH_2 Lev); ^{13}C -GATED NMR (CDCl_3 , 100MHz): δ 101.1 ($J_{\text{C1,H1}} = 161$ Hz, C-1' β), 99.7 ($J_{\text{C1,H1}} = 167$ Hz, C-1 α); HRMS: $[\text{M}+\text{NH}_4]^+$ calcd. for $\text{C}_{60}\text{H}_{64}\text{NO}_{15}$ 1038.42705, found 1038.42941.

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) (**36**)



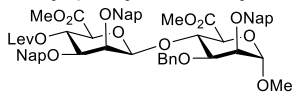
Donor **28** (139 mg, 0.196 mmol) and acceptor **32** (119 mg, 0.237 mmol, 1.2 eq.) were condensed using the general protocol for TfOH-mediated

glycosylations to yield disaccharide **36** (159 mg, 0.156 mmol, 79%, $\alpha \ll \beta$) as an off-white foam. TLC: R_f 0.23 (PE/EtOAc, 3/2, v/v); IR (neat): 750, 820, 1055, 1126, 1364, 1719, 1748 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 7.60–7.80 (m, 12H, CH_{arom}), 7.36–7.50 (m, 9H, CH_{arom}), 7.23–7.36 (m, 3H, CH_{arom}), 7.17–7.19 (m, 2H, CH_{arom}), 5.53 (t, 1H, $J = 9.6$ Hz, H-4'), 5.08 (bs, 1H, H-1), 4.68–4.94 (m, 7H, CH_2 Nap, CH_2 Nap, CH_2 Bn/Nap, H-1'), 4.53 (t, 1H, $J = 5.6$ Hz, H-4), 4.45 (d, 1H, $J = 12.4$ Hz, CHH Bn/Nap), 4.39 (d, 1H, $J = 12.0$ Hz, CHH 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, CH_3 CO_2Me , $\text{CO}_2\text{Me}'$, 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 (CDCl_3 , 100 MHz): δ 206.3 (C=O Lev), 171.7, 169.8, 167.8 (C=O CO_2Me , Lev), 137.8, 136.1, 135.8, 135.7, 133.3, 133.2, 133.2, 133.0, 133.0, 132.9 (Cq), 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 (CH_2 Bn/Nap), 69.2 (C-4'), 56.2 (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 ($J_{\text{C1,H1}} = 156$ Hz, C-1' β), 99.8 ($J_{\text{C1,H1}} = 169$ Hz, C-1 α); HRMS: $[\text{M}+\text{NH}_4]^+$ calcd. for $\text{C}_{60}\text{H}_{64}\text{NO}_{15}$ 1038.42705, found 1038.42936.

Methyl (methyl 4-O-[methyl 4-O-levulinoyl-2,3-di-O-(2-naphthylmethyl)-β-D-mannopyranosyl uronate]-2-O-**benzyl-3-O-(2-naphthylmethyl)-α-D-mannopyranosyl uronate) (37) Donor****26** (140 mg, 0.185 mmol) and acceptor **33** (112 mg, 0.247 mmol, 1.2 eq.) were

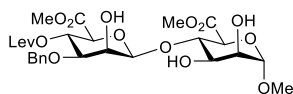
condensed using the general protocol for TfOH-mediated glycosylations to

yield disaccharide **37** (160 mg, 0.157 mmol, 85%, $\alpha << \beta$) as an yellowish foam. TLC: R_f 0.11 (PE/EtOAc, 2/1, v/v); IR (neat): 748, 818, 1053, 1125, 1362, 1717, 1748 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 7.69-7.81 (m, 11H, CH_{arom}), 7.61 (s, 1H, CH_{arom}), 7.55 (dd, 1H, $J = 1.6, 8.4$ Hz, CH_{arom}), 7.39-7.46 (m, 7H, CH_{arom}), 7.31 (dd, 1H, $J = 1.2, 8.4$ Hz, CH_{arom}), 7.19-7.22 (m, 5H, CH_{arom}), 5.56 (t, 1H, $J = 9.6$ Hz, H-4'), 5.04 (bs, 1H, H-1), 5.00 (d, 1H, $J = 12.4$ Hz, CHH Bn/Nap), 4.89 (d, 2H, $J = 12.4$ Hz, CHH Bn/Nap , CHH Bn/Nap), 4.76 (d, 1H, $J = 12.4$ Hz, CHH Bn/Nap), 4.53-4.67 (m, 5H, $\text{CH}_2 \text{ Bn/Nap}$, $\text{CH}_2 \text{ Bn/Nap}$, H-1'), 4.49 (t, 1H, $J = 5.6$ Hz, H-4), 4.26 (d, 1H, $J = 5.6$ Hz, H-5), 4.11 (d, 1H, $J = 2.8$ Hz, H-3), 3.91 (d, 1H, $J = 2.8$ Hz, H-2'), 3.82 (d, 1H, $J = 9.6$ Hz, H-5'), 3.71 (dd, 1H, $J = 2.8, 5.2$ Hz, H-2), 3.54 (s, 3H, $\text{CH}_3 \text{ CO}_2\text{Me}$), 3.49-3.53 (m, 4H, $\text{CH}_3 \text{ OMe}$, H-3'), 3.44 (s, 3H, $\text{CH}_3 \text{ CO}_2\text{Me}$), 2.65 (t, 2H, $J = 6.4$ Hz, $\text{CH}_2 \text{ Lev}$), 2.54 (t, 2H, $J = 6.4$ Hz, $\text{CH}_2 \text{ Lev}$), 2.11 (s, 3H, $\text{CH}_3 \text{ Lev}$); ^{13}C (CDCl_3 , 100 MHz): δ 206.3 (C=O Lev), 171.7, 169.8, 167.8 (C=O CO_2Me , Lev), 138.3, 136.1, 135.9, 135.6, 135.3, 133.3, 133.2, 133.2, 133.0, 133.0, 132.9 (Cq), 128.4, 128.3, 128.2, 128.1, 128.0, 128.0, 127.9, 127.8, 127.7, 127.7, 127.5, 127.0, 126.6, 126.5, 126.3, 126.2, 126.1, 126.0, 125.9, 125.8, 125.8, 125.7 (CH_{arom}), 101.2 (C-1'), 99.7 (C-1), 78.1 (C-3'), 76.9 (C-3), 76.7 (C-4), 75.2 (C-2), 74.2 ($\text{CH}_2 \text{ Bn/Nap}$), 73.9 (C-2'), 73.5 (C-5'), 73.0, 72.9 ($\text{CH}_2 \text{ Bn/Nap}$), 72.0 ($\text{CH}_2 \text{ Bn/Nap}$), 71.9 (C-5), 69.2 (C-4'), 56.2 (OMe), 52.5, 52.2 ($\text{CH}_3 \text{ CO}_2\text{Me}$), 37.8 ($\text{CH}_2 \text{ Lev}$), 29.9 ($\text{CH}_3 \text{ Lev}$), 28.0 ($\text{CH}_2 \text{ Lev}$); ^{13}C -GATED NMR (CDCl_3 , 100MHz): δ 101.2 ($J_{\text{C1,H1}} = 156$ Hz, C-1' β), 99.7 ($J_{\text{C1,H1}} = 168$ Hz, C-1 α); HRMS: $[\text{M}+\text{NH}_4]^+$ calcd. for $\text{C}_{60}\text{H}_{64}\text{NO}_{15}$ 1038.42705, found 1038.42888

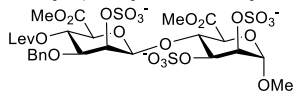
Methyl (methyl 4-O-[methyl 4-O-levulinoyl-2,3-di-O-(2-naphthylmethyl)-β-D-mannopyranosyl uronate]-3-O-**benzyl-2-O-(2-naphthylmethyl)-α-D-mannopyranosyl uronate) (38) Donor****26** (130 mg, 0.172 mmol) and acceptor **34** (96 mg, 0.217 mmol, 1.2 eq.) were

condensed using the general protocol for TfOH-mediated glycosylations to

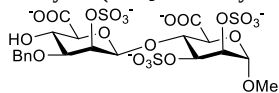
yield disaccharide **38** (167 mg, 0.164 mmol, 95%, $\alpha << \beta$) as an off-white foam. TLC: R_f 0.12 (PE/EtOAc, 2/1, v/v); IR (neat): 750, 820, 1057, 1126, 1364, 1719, 1748 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 7.67-7.80 (m, 12H, CH_{arom}), 7.60 (s, 1H, CH_{arom}), 7.51 (dd, 1H, $J = 1.2, 8.4$ Hz, CH_{arom}), 7.32-7.46 (m, 7H, CH_{arom}), 7.23-7.30 (m, 5H, CH_{arom}), 5.56 (t, 1H, $J = 9.6$ Hz, H-4'), 5.06 (bs, 1H, H-1), 4.90 (d, 1H, $J = 12.8$ Hz, CHH Bn/Nap), 4.83 (d, 1H, $J = 12.8$ Hz, CHH Bn/Nap), 4.69-4.80 (m, 3H, $\text{CH}_2 \text{ Bn/Nap}$, CHH Bn/Nap), 4.57-4.63 (m, 3H, CHH Bn/Nap , CHH Bn/Nap , H-1'), 4.52 (d, 1H, $J = 12.4$ Hz, CHH Bn/Nap), 4.46 (t, 1H, $J = 5.6$ Hz, H-4), 4.26 (d, 1H, $J = 5.6$ Hz, H-5), 4.09 (d, 1H, $J = 2.8$ Hz, H-3), 3.90 (d, 1H, $J = 2.4$ Hz, H-2'), 3.82 (d, 1H, $J = 9.6$ Hz, H-5'), 3.74 (dd, 1H, $J = 2.8, 5.2$ Hz, H-2), 3.61 (s, 3H, $\text{CH}_3 \text{ CO}_2\text{Me}$), 3.49-3.53 (m, 4H, $\text{CH}_3 \text{ OMe}$, H-3'), 3.45 (s, 3H, $\text{CH}_3 \text{ CO}_2\text{Me}$), 2.66 (t, 2H, $J = 6.4$ Hz, $\text{CH}_2 \text{ Lev}$), 2.55 (t, 2H, $J = 6.4$ Hz, $\text{CH}_2 \text{ Lev}$), 2.12 (s, 3H, $\text{CH}_3 \text{ Lev}$); ^{13}C (CDCl_3 , 100 MHz): δ 206.3 (C=O Lev), 171.7, 169.8, 167.8 (C=O CO_2Me , Lev), 138.6, 135.8, 135.8, 135.2, 133.2, 133.2, 133.2, 133.0, 133.0, 133.0 (Cq), 128.4, 128.3, 128.2, 128.2, 128.1, 128.1, 128.1, 128.0, 127.9, 127.9, 127.8, 127.7, 127.7, 127.6, 127.5, 127.4, 127.1, 126.6, 126.5, 126.5, 126.3, 126.2, 126.1, 126.0, 125.9, 125.9, 125.8, 125.8, 125.7 (CH_{arom}), 101.2 (C-1'), 99.8 (C-1), 78.1 (C-3'), 76.9 (C-3), 76.7 (C-4), 75.0 (C-2), 74.1 ($\text{CH}_2 \text{ Bn/Nap}$), 73.8 (C-2'), 73.6 (C-5'), 73.1, 72.8 ($\text{CH}_2 \text{ Bn/Nap}$), 71.9 ($\text{CH}_2 \text{ Bn/Nap}$, C-5), 69.2 (C-4'), 56.2 (OMe), 52.6, 52.2 ($\text{CH}_3 \text{ CO}_2\text{Me}$), 37.8 ($\text{CH}_2 \text{ Lev}$), 29.9 ($\text{CH}_3 \text{ Lev}$), 28.0 ($\text{CH}_2 \text{ Lev}$); ^{13}C -GATED NMR (CDCl_3 , 100MHz): δ 101.2 ($J_{\text{C1,H1}} = 152$ Hz, C-1' β), 99.8 ($J_{\text{C1,H1}} = 169$ Hz, C-1 α); HRMS: $[\text{M}+\text{NH}_4]^+$ calcd. for $\text{C}_{60}\text{H}_{64}\text{NO}_{15}$ 1038.42705, found 1038.42877.

Methyl (methyl 4-O-[methyl 3-O-benzyl-4-O-levulinoyl-β-D-mannopyranosyl uronate]-α-D-mannopyranosyl


uronate) (39) Mannuronic acid disaccharide **36** (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. NaHCO₃. The mixture was diluted DCM and the organic layer is washed with sat. aq. NaCl, dried over MgSO₄ and concentrated. Purification by column chromatography (2:1 pentanes/EtOAc → 19:1 EtOAc/MeOH) yielded the triol **39** 86% yield (0.0421 g, 0.070 mmol). TLC: R_f 0.43 (EtOAc/MeOH, 19/1, v/v); ¹H-NMR (CDCl₃, 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, CHH Bn), 4.65 (d, 1H, *J* = 12.2 Hz, CHH 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, CH₃ CO₂Me), 3.72 – 3.63 (m, 4H, CH₃ CO₂Me, H-3'), 3.43 (s, 3H, CH₃ OMe), 3.28 (bs, 1H, OH), 2.99 (bs, 1H, OH), 2.73 (t, 2H, *J* = 6.5, 6.5 Hz, CH₂ Lev), 2.56 (dt, 2H, *J* = 13.3, 6.5, 6.5 Hz, CH₂ Lev), 2.19 (s, 3H, CH₃ Lev); ¹³C-NMR (CDCl₃, 100 MHz): δ 206.3 (C=O Lev), 171.7, 169.8, 168.1 (C=O Lev, CO₂Me), 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 (CH₂ 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 (CH₃ OMe), 52.9, 52.5 (CH₃ CO₂Me), 37.6 (CH₂ Lev), 29.8 (CH₃ Lev), 27.8 (CH₂ Lev); HRMS: [M+NH₄]⁺ calculated for C₂₇H₄₀NO₁₅ 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) (40) Triol **39** (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 NaCO₃ (0.14 g, 1.67 mmol) in 10 mL H₂O 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 **40** in 100% yield as the triethylammonium salt (0.124 g, 0.108 mmol). TLC: R_f 0.43 (DCM/MeOH, 3/1, v/v); ¹H-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, CHH Bn), 4.45 (d, 1H, *J* = 12.0 Hz, CHH Bn), 4.41 (s, 2H, H-4, H-5), 4.05 (d, 1H, *J* = 9.9 Hz, H-5'), 3.78 (s, 3H, CH₃ CO₂Me), 3.74 (dd, 1H, *J* = 9.8, 2.9 Hz, H-3'), 3.66 (s, 3H, CH₃ CO₂Me), 3.41 (s, 3H, CH₃ OMe), 3.20 (q, 18H, *J* = 7.3, 7.3, 7.2 Hz, 3xCH₂ Et₃N), 2.65 (td, 2H, *J* = 6.5, 6.4, 2.1 Hz, CH₂ Lev), 2.47 (q, 2H, *J* = 6.8, 6.8, 6.6 Hz, CH₂ Lev), 2.10 (s, 3H, CH₃ Lev), 1.28 (t, 27H, *J* = 7.4, 7.4 Hz, 3xCH₃ Et₃N); ¹³C-NMR (MeOD, 214 MHz): δ 207.9 (C=O Lev), 172.7, 170.2, 169.5 (C=O Lev, CO₂Me), 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 (CH₂ Bn), 69.1 (C-4'), 55.2 (CH₃ OMe), 52.4, 52.3 (CH₃ CO₂Me), 47.3 (CH₂ Et₃N), 37.7 (CH₂ Lev), 28.9 (CH₃ Lev), 28.2 (CH₂ Lev), 8.6 (CH₃ Et₃N); HRMS: [M+H]⁺ calculated for C₄₅H₈₁N₃O₂₄S₃ 1144.44591, found 1144.44449.

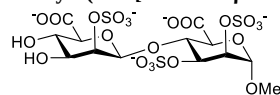
Methyl (4-O-[3-O-benzyl-2-O-sulfo-β-D-mannopyranosyl uronate]-2,3-di-O-sulfo-α-D-mannopyranosyl


uronate) (41) Sulfated disaccharide **40** (0.0567 g, 0.05 mmol) was dissolved in 1:1 THF/H₂O (2 mL) and cooled to 0°C. A 0.5M LiOH/H₂O₂ (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

Chapter 5

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%). $^1\text{H-NMR}$ (D_2O , 600 MHz, $T=313\text{K}$): 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, CHH Bn), 4.86 – 4.78 (m, 3H, H-1, H-2, H-3), 4.54 (d, 1H, $J=11.2$ Hz, CHH 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); $^{13}\text{C-NMR}$ (D_2O , 150 MHz, $T=313\text{K}$): 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: $[\text{M}+\text{Na}]^+$ calculated for $\text{C}_{20}\text{H}_{33}\text{O}_{22}\text{S}_3\text{Na}_2$ 749.06816, found 749.06891.

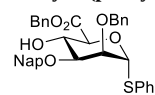
Methyl (4-O-[2-O-sulfo- β -D-mannopyranosyl uronate]-2,3-di-O-sulfo- α -D-mannopyranosyl uronate) (42)



Saponified disaccharide **41** (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 pooled, 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%). $^1\text{H-NMR}$ (D_2O , 600 MHz, $T=313\text{K}$): 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); $^{13}\text{C-NMR}$ (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: $[\text{M}+\text{Na}]^+$ calculated for $\text{C}_{13}\text{H}_{17}\text{O}_{22}\text{S}_3\text{Na}_3$ 712.89589, found 712.89593.

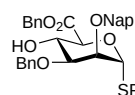
Benzyl (phenyl 2-O-benzyl-3-O-(2-naphthylmethyl)-1-thio- α -D-mannopyranosyl uronate) (48) 4,6-O-



benzylidene-1-thio- α -D-mannopyranoside (7.2 g, 20 mmol) was dissolved in toluene and Bu_2SnO (5.48 g, 22 mmol, 1.1 eq.) was added. The mixture was refluxed overnight, after which CsF (4.56 g, 30 mmol, 1.5 eq.) was added followed by addition of 2-(Bromomethyl)naphthalene (6.63 g, 30 mmol, 1.5 eq.) and the mixture was heated to 100°C . After overnight heating, the mixture was concentrated, coevaporated twice with toluene and dissolved in DMF (100 mL) and cooled to 0°C . The mixture was treated with sodium hydride (60% dispersion in mineral oil, 1.6 g, 40 mmol, 2 eq.), and, after 10 minutes, with Benzyl bromide (4.8 mL, 40 mmol, 2 eq.). After stirring overnight, the reaction was quenched by addition of sat. aq. NaHCO_3 . The mixture was diluted with Et_2O , washed with sat. aq. NaCl , dried over MgSO_4 and concentrated *in vacuo*. The crude was dissolved in MeOH/DCM (50 mL : 50 mL) and pTsOH (0.38 g, 2 mmol, 0.1 eq.) was added. After conversion to a lower running spot, the reaction was neutralized with Et_3N , concentrated and purified by column purification (PE/EtOAc , 4:1 $\rightarrow$ 1:1) yielding diol **45** (7.57 g, 15.1 mmol, 75%). Diol **45** (4.77 g, 9.498 mmol, 1.0 eq.) was dissolved in $t\text{BuOH}/\text{DCM}/\text{H}_2\text{O}$ (4:4:1, 95 mL) and cooled to 0°C . TEMPO (0.30 g, 1.92 mmol, 0.2 eq.) and BAIB (7.64 g, 23.72 mmol, 2.5 eq.) were added and the reaction was stirred vigorously for 230 min. at which it was allowed to warm up to RT. TLC analysis showed conversion of the starting material to a low running spot, and the reaction was quenched with sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$. The mixture was diluted with EtOAc and the

layers were separated. The aqueous layer was acidified and extracted with EtOAc. The combined organic layers were washed with sat. aq. NaCl, dried over MgSO_4 and concentrated *in vacuo*. The resulting oil was coevaporated twice with anhydrous toluene and dissolved in DMF (95 mL). Benzyl bromide (2.26 mL, 18.98 mmol, 2 eq.) was added, followed by K_2CO_3 (2.63 g, 18.98 mmol, 2 eq.). The reaction was stirred over night, after which it was quenched with H_2O . The mixture was diluted with Et_2O and washed with sat. aq. NaCl, dried over MgSO_4 and concentrated *in vacuo*. Column purification (PE/EtOAc, 4:1 $\rightarrow$ 1:1) yielded the title compound (4.44 g, 7.32 mmol, 77%). IR (neat): 966, 1026, 1114, 1440, 1583, 1732, 2870, 1933, 3061, 3394, 3471 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3 , T=328K): δ 7.80 – 7.73 (m, 3H), 7.45 – 7.39 (m, 5H), 7.31 – 7.09 (m, 11H), 5.62 (d, 1H, J = 2.0 Hz, H-1), 5.21 – 5.08 (m, 2H, CH_2 Bn), 4.80 (d, 1H, J = 12.0 Hz, CHH), 4.74 (d, J = 12.0 Hz, 1H, CHH), 4.72 – 4.62 (m, 2H, H-5, CHH), 4.56 (d, 1H, J = 12.1 Hz, CHH), 4.48 (t, 1H, J = 8.6 Hz, H-4), 3.96 (s, 1H, H-2), 3.80 (dd, 1H, J = 8.7, 2.6 Hz, H-3), 3.02 (s, 1H, OH); ^{13}C NMR (126 MHz, CDCl_3 , T=328K): δ 169.6 (C=O), 137.9, 135.7, 135.4, 133.8, 133.5, 133.2 (Cq), 131.8, 129.1, 128.6, 128.5, 128.4, 128.3, 128.3, 128.1, 128.0, 127.9, 127.8, 127.8, 127.6, 126.7, 126.2, 126.0, 125.9 (CH_{arom}), 86.1 (C-1), 78.6 (C-3), 76.3 (C-2), 73.2 (C-5), 72.9 (CH_2 Bn/Nap), 72.6 (CH_2 Bn/Nap), 68.9 (C-4), 67.2 (CH_2 Bn/Nap); HRMS: $[\text{M}+\text{NH}_4]^+$ calcd. $\text{C}_{37}\text{H}_{38}\text{NO}_6\text{S}$ 624.24144, found 624.24128.

Benzyl (phenyl 3-O-benzyl-2-O-(2-naphthylmethyl)-1-thio- α -D-mannopyranosyl uronate) (49) 4,6-O-

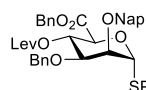


benzylidene-1-thio- α -D-mannopyranoside (3.6 g, 10 mmol) was dissolved in toluene and Bu_2SnO (2.54 g, 10.2 mmol, 1.02 eq.) was added. The mixture was refluxed for 1.5 h, after the mixture was concentrated and coevaporated with toluene, and redissolved in DMF (50 mL).

Benzyl bromide (1.31 mL, 11.0 mmol, 1.1 eq.) and CsF (1.55 g, 10.2 mmol, 1.0 eq.) were added and the mixture was stirred overnight at RT. After overnight stirring, H_2O was added, the mixture was diluted with EtOAc and washed with sat. aq. NaCl, dried over MgSO_4 and concentrated *in vacuo*. Column purification (PE/EtOAc, 8:1 $\rightarrow$ 1:1) yielded alcohol intermediate (3.96 g, 8.8 mmol, 88%). The compound was coevaporated twice with toluene and dissolved in DMF (50 mL) and cooled to 0°C . The mixture was treated with sodium hydride (60% dispersion in mineral oil, 0.42 g, 10.6 mmol, 1.2 eq.), and, after 10 minutes, with Naphthyl bromide (2.14 g, 9.7 mmol, 1.1 eq.). After stirring overnight, the reaction was quenched by addition of H_2O . The mixture was diluted with Et_2O , washed with sat. aq. NaCl, dried over MgSO_4 and concentrated *in vacuo*. Purification by column chromatography yielded protected intermediate (4.43 g, 7.5 mmol, 86%). The mannoside was dissolved in MeOH/DCM (25 mL : 25 mL) and pTsOH (0.084 g, 0.44 mmol, 0.05 eq.) was added. After conversion to a lower running spot, the reaction was neutralized with Et_3N , concentrated and purified by column purification (PE/EtOAc, 9:1 $\rightarrow$ 1:1) yielding diol **46** (3.17 g, 6.5 mmol, 84%). Diol **46** (3.16 g, 6.3 mmol, 1.0 eq.) was dissolved in EtOAc/ H_2O /tBuOH (4:4:1, 40 mL) and cooled to 0°C . AcOH (0.04 mL, 0.7 mmol, 0.1 eq.) was added followed by addition of TEMPO (0.21 g, 1.3 mmol, 0.2 eq.) and BAIB (5.39 g, 16.2 mmol, 2.5 eq.) and the reaction was stirred vigorously for 230 min. at which it was allowed to warm up to RT. TLC analysis showed conversion of the starting material to a low running spot, and the reaction was quenched with sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$. The mixture was diluted with EtOAc and the layers were separated. The aqueous layer was acidified and extracted with EtOAc. The combined organic layers were washed with sat. aq. NaCl, dried over MgSO_4 and concentrated *in vacuo*. The resulting oil was coevaporated twice with anhydrous toluene and dissolved in DMF (50 mL) and cooled to 0°C . Benzyl bromide (1.5 mL, 12.4 mmol, 2 eq.) was added, followed by K_2CO_3 (1.72 g, 12.4 mmol, 2 eq.). The reaction was stirred over night, after which it was quenched with H_2O . The mixture was diluted with Et_2O and washed with sat. aq. NaCl, dried over MgSO_4 and concentrated *in vacuo*. Column purification (PE/EtOAc, 10:1 $\rightarrow$ 5:1) yielded the title compound (2.12 g, 3.5 mmol, 56%). TLC: R_f 0.30 (PE/EtOAc, 4/1, v/v); ^1H NMR (400 MHz, $\text{CDCl}_3/\text{CDCl}_3$): δ 7.88 – 7.65 (m, 5H, CH_{arom}), 7.58 – 7.37 (m, 6H, CH_{arom}), 7.37 – 7.27 (m, 7H, CH_{arom}), 7.25 – 7.11 (m, 4H, CH_{arom}), 5.64 (d, 1H, J = 2.4 Hz, H-1), 5.30

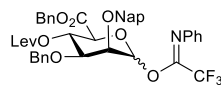
– 5.08 (m, 2H, CH₂ Bn/Nap), 4.93 – 4.53 (m, 5H, 2xCH₂ Bn/Nap, H-5), 4.47 (t, 1H, *J* = 8.7 Hz, H-4), 3.99 (t, 1H, *J* = 2.7 Hz, H-2), 3.73 (dd, 1H, *J* = 8.9, 3.0 Hz, H-3); ¹³C NMR (101 MHz, CDCl₃): δ 169.8 (C=O), 138.0 (Cq), 135.3, 135.2, 133.6, 133.3, 133.1 (Cq), 131.8 (CH_{arom}), 129.1, 128.7, 128.6, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 126.9, 126.2, 126.0 (CH_{arom}), 86.1 (C-1), 78.3 (C-3), 75.7 (C-2), 72.8 (C-5), 72.7 (CH₂ Bn/Nap), 72.5 (CH₂ Bn/Nap), 68.7 (C-4), 67.3 (CH₂ Bn). HRMS: [M+Na]⁺ calcd. for C₃₇H₃₄O₆SNa 629.19683, found 629.19619.

Benzyl (phenyl 3-O-benzyl-4-O-levulinoyl-2-O-(2-naphthylmethyl)-1-thio- α -D-mannopyranosyl uronate) (51)



Compound **49** (2.13 g, 3.5 mmol, 1.0 eq.) was coevaporated with toluene twice, dissolved in DCM (15 mL) and cooled to 0°C. LevOH (0.84 mL, 8.2 mmol, 2.3 eq), DIC (0.6 mL, 3.9 mmol, 1.2 eq) and DMAP (0.04 g, 0.33 mmol, 0.1 eq) were added and the reaction was stirred at RT overnight. After overnight stirring, the mixture was filtrated over Celite® and concentrated *in vacuo*. The residue was dissolved in EtOAc and washed with sat. aq. NaHCO₃ twice, dried over MgSO₄ and concentrated *in vacuo*. Column chromatography (PE/EtOAc 7/1 → 7/3) yielded compound **51** (2.40 g, 3.4 mmol, 97%) as a yellow oil. TLC: R_f 0.26 (PE/EtOAc, 7/3 v/v); ¹H NMR (500 MHz, CDCl₃, T=328K): δ 7.84 – 7.64 (m, 4H, CH_{arom}), 7.58 – 7.36 (m, 7H, CH_{arom}), 7.35 – 7.15 (m, 11, CH_{arom}), 5.79 (d, 1H, *J* = 7.0 Hz, H-1), 5.60 (t, 1H, *J* = 5.4 Hz, H-4), 5.09 – 4.93 (m, 2H, CH₂ Bn/Nap), 4.83 – 4.64 (m, 2H, CH₂ Bn/Nap), 4.57 (d, 1H, *J* = 4.7 Hz, H-5), 4.54 – 4.51 (m, 2H, CH₂ Bn/Nap), 3.87 (dd, 1H, *J* = 6.0, 2.6 Hz, H-3), 3.80 (dd, 1H, *J* = 6.9, 2.3 Hz, H-2), 2.52 (m, 2H, CH₂ Lev), 2.44 – 2.28 (m, 2H, CH₂ Lev), 2.09 (s, 3H, CH₃ Lev); ¹³C NMR (126 MHz, CDCl₃, T=328K): δ 205.8 (C=O Lev), 171.4 (C=O lev), 168.1 (C=O Bn), 137.8 (Cq), 135.4, 135.3, 133.9, 133.4, 133.3 (Cq), 131.6 (CH_{arom}), 131.4, 129.0, 128.6, 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.2, 127.0, 126.9, 126.2, 126.0 (CH_{arom}), 88.8 (C-1), 74.6 (C-2), 74.4 (C-3), 73.1 (C-5), 72.8 (CH₂ Bn/Nap), 72.7 (CH₂ Bn/Nap), 70.2 (C-4), 67.4 (CH₂ Bn), 37.9 (CH₂ Lev), 29.7 (CH₃ Lev), 28.1 (CH₂ Lev). HRMS: [M+Na]⁺ calcd. for C₄₂H₃₆O₆SNa 727.23361, found 727.23328.

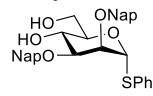
Benzyl (3-O-benzyl-4-O-levulinoyl-3-O-(2-naphthylmethyl)-O-(N-phenyl-trifluoroacetimidoyl)- α / β -D-mannopyranosyl uronate) (55)



Compound **51** (1.40 g, 2.0 mmol, 1.0 eq.) was coevaporated with toluene twice, dissolved in dry DCM (20 mL) and cooled to 0°C. NIS (0.50 g, 2.2 mmol, 1.1 eq) and TFA (0.17 mL, 2.2 mmol, 1.1 eq) were added and the reaction mixture was stirred at 0°C for 15 minutes after which it was allowed to warm up to RT. After 1h, full conversion was observed by TLCMS (masses: 635, product and 731 product + TFA), the reaction was quenched with sat. aq. Na₂S₂O₃ (20 mL) followed by addition of sat. aq. NaHCO₃ (20 mL) and the reaction was stirred for 1 h during which it turned from deep purple to yellow. The mixture was diluted with Et₂O, washed with sat. aq. NaHCO₃, dried over MgSO₄, concentrated *in vacuo* and purified by column chromatography (PE/EtOAc 3/1 to 1/1) which yielded the hemiacetal (1.16 g, 1.9 mmol, 95%) as a yellow oil. Compound **53** (1.16 g, 1.9 mmol, 1.0 eq.) was dissolved in acetone (20 mL) and cooled to 0°C, followed by addition of Cs₂CO₃ (0.78 g, 2.4 mmol, 1.2 eq) and ClC(=NPh)CF₃ (0.48 mL, 3.0 mmol, 1.5 eq) and the reaction was stirred at 0°C for 1.5 h. The mixture was diluted with EtOAc and washed with sat. aq. NaCl (2x), dried over MgSO₄, concentrated *in vacuo* and then purified using column chromatography (PE/EtOAc, 4/1 → 1/1) which yielded compound **55** (1.18 g, 1.5 mmol, 77%) as a yellow oil. TLC: R_f 0.41 (PE/EtOAc, 2/1 v/v); ¹H NMR (500 MHz, CDCl₃, T=328K): δ 7.86 – 7.61 (m, 4H, CH_{arom}), 7.49 – 7.38 (m, 3H, CH_{arom}), 7.31 – 7.16 (m, 12H, CH_{arom}), 7.06 (t, 1H, *J* = 7.5 Hz, CH_{arom}), 6.68 (d, 2H, *J* = 7.5 Hz, CH_{arom}), 6.47 (s, 1H, H-1), 5.65 (t, 1H, *J* = 7.1 Hz, H-4), 5.16 – 5.00 (m, 2H, CH₂ Bn/Nap), 4.89 – 4.72 (m, 2H, CH₂ Bn/Nap), 4.64 – 4.49 (m, 2H, CH₂ Bn/Nap), 4.43 (d, 1H, *J* = 6.8 Hz, H-5), 3.91 (dd, 1H, *J* = 7.4, 2.8 Hz, H-3), 3.84 (t, 2H, *J* = 3.7, 3.1 Hz, H-2), 2.71 – 2.27 (m, 4H, 2xCH₂ Lev), 2.08 (s, 3H, CH₃ Lev); ¹³C NMR (126 MHz, CDCl₃, T=328K): δ 205.7 (C=O Lev), 171.3 (C=O Lev), 167.5 (C=O Bn), 143.4 (Cq), 142.6, 142.3, 137.7, 135.4,

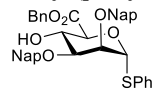
135.2, 135.1, 133.3, 133.2 (Cq), 129.1 (CH_{arom}), 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.5, 127.0, 126.4, 126.2, 126.1, 126.0, 124.4, 124.2, 119.5 (CH_{arom}), 94.8 (C-1), 75.0 (C-3), 73.4 (C-2), 73.3 (C-5), 73.0 (2xCH₂ Bn/Nap), 69.2 (C-4), 67.6 (CH₂ Bn), 37.8 (CH₂ Lev), 29.6 (CH₃ Lev), 28.1 (CH₂ Lev). HRMS: [M+Na]⁺ calcd. for C₄₄H₄₀F₃NO₉Na 806.25474, found 806.25496.

Phenyl 2,3-O-di-(2-naphthylmethyl)-1-thio- α -D-mannopyranoside (44) 4,6-O-benzylidene-1-thio- α -D-

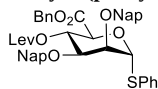


mannopyranoside **43** (8.65 g, 24 mmol) was coevaporated twice with anhydrous toluene before being dissolved in DMF (15 mL). The mixture was cooled to 0°C, after which sodium hydride (60% dispersion in mineral oil, 2.4 g, 60 mmol) was added. The mixture was stirred for 10 minutes followed by addition of 2-naphthylmethylbromide (13.27 g, 60 mmol). When, after overnight stirring, TLC analysis showed complete consumption of the starting material, the reaction was quenched with sat. aq. NaHCO₃. The mixture was diluted with Et₂O and the organic layer was washed with H₂O, dried over MgSO₄ and concentrated *in vacuo*. After a quick column purification/filtration, the crude was dissolved in MeOH/DCM (60 mL : 60 mL) and the mixture was treated with pTsoH (0.5 g, 2.4 mmol, 0.1 eq.). After overnight stirring, the reaction was neutralized with Et₃N and concentrated. Column purification (PE/EtOAc, 4:1 → 1:1) yielded the diol (12.03 g, 21.8 mmol, 91%). TLC: R_f 0.43 (PE/EtOAc, 1/1, v/v); IR (neat): 817, 1039, 1103, 1344, 1508, 2873, 3053, 3354 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 7.88 – 7.62 (m, 8H, CH_{arom}), 7.53 – 7.31 (m, 8H, CH_{arom}), 7.28 – 7.17 (m, 3H, CH_{arom}), 5.54 (s, 1H, H-1), 4.81 (d, 1H, *J* = 12.3 Hz, CHH), 4.74 – 4.62 (m, 3H, CH₂, CHH), 4.23 – 4.15 (m, 1H, H-4), 4.16 – 4.08 (m, 1H, H-5), 4.07 (dd, 1H, *J* = 3.0, 1.6 Hz, H-2), 3.94 – 3.81 (m, 2H, 2x H-6), 3.77 (dd, 1H, *J* = 9.4, 3.0 Hz, H-3), 2.67 (s, 2H, 2x OH); ¹³C NMR (126 MHz, CDCl₃): δ 135.2, 135.2, 133.9, 133.4, 133.3, 133.2 (Cq), 132.1, 132.1, 129.3, 128.6, 128.5, 128.1, 128.1, 127.9, 127.8, 127.0, 126.9, 126.4, 126.3, 126.2, 126.2, 126.1, 125.8 (CH_{arom}), 86.3 (C-1), 79.9 (C-3), 75.7 (C-2), 73.5 (C-5), 72.5, 72.1 (CH₂), 67.5 (C-4), 62.9 (C-6); HRMS: [M+NH₄]⁺ calcd. for C₃₄H₃₆NO₅S 570.23087, found 570.23102.

Benzyl (phenyl 2,3-O-di-(2-naphthylmethyl)-1-thio- α -D-mannopyranosyl uronate) (48) Diol **45** (9.23 g, 16.7

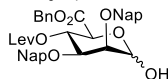


mmol, 1.0 eq.) was dissolved in tBuOH/DCM/H₂O (4:4:1, 152 mL) and cooled to 0°C. TEMPO (3.34 g, 0.52 mmol, 0.2 eq.) and BAIB (13.45 g, 41.75 mmol, 2.5 eq.) were added and the reaction was stirred vigorously for 255 min. at which it was allowed to warm up to RT. TLC analysis showed conversion of the starting material to a low running spot, and the reaction was quenched with sat. aq. Na₂S₂O₃. The mixture was diluted with EtOAc and the layers were separated. The aqueous layer was acidified and extracted with EtOAc. The combined organic layers were washed with sat. aq. NaCl, dried over MgSO₄ and concentrated *in vacuo*. The resulting oil was coevaporated twice with anhydrous toluene and dissolved in DMF (150 mL). Benzyl bromide (3.97 mL, 33.4 mmol, 2 eq.) was added, followed by K₂CO₃ (4.62 g, 33.4 mmol, 2 eq.). The reaction was stirred over night, after which it was quenched with H₂O. The mixture was diluted with Et₂O and washed with sat. aq. NaCl, dried over MgSO₄ and concentrated *in vacuo*. Column purification (PE/EtOAc, 4:1 → 1:1) yielded the title compound (7.41 g, 11.28 mmol, 68%). TLC: R_f 0.59 (PE/EtOAc, 3/1, v/v); IR (neat) 817, 1026, 1099, 1271, 1693, 1747, 2866, 3057, 3423 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.91 – 7.58 (m, 10H, CH_{arom}), 7.55 – 7.35 (m, 10H, CH_{arom}), 7.26 – 7.06 (m, 4H, CH_{arom}), 5.64 (d, 1H, *J* = 2.1 Hz, H-1), 5.32 – 5.08 (m, 2H, CH₂ Bn), 4.89 – 4.77 (m, 2H, CH₂ Nap), 4.75 – 4.62 (m, 3H, CH₂ Nap, H-5), 4.51 (t, 1H, *J* = 8.9 Hz, H-4), 4.00 (t, 1H, *J* = 2.6 Hz, H-2), 3.80 (dd, 1H, *J* = 8.9, 3.0 Hz, H-3); ¹³C NMR (100 MHz, CDCl₃): δ 169.8 (C=O), 135.5 (Cq), 135.2, 135.2, 133.6, 133.3, 133.2, 133.1 (Cq), 131.8 (CH_{arom}), 129.1, 128.7, 128.4, 128.3, 128.2, 128.1, 127.8, 127.7, 126.9, 126.7, 126.2, 126.0, 125.9 (CH_{arom}), 86.1 (C-1), 78.4 (C-3), 75.7 (C-2), 72.9 (CH₂ Nap), 72.8 (C-5), 72.5 (CH₂ Nap), 68.7 (C-4), 67.3 (CH₂ Bn). HRMS: [M+Na]⁺ calcd. for C₄₁H₃₆O₆SN 674.21248, found 674.25715.

Benzyl (phenyl 4-O-levulinoyl-2,3-O-di-(2-naphthylmethyl)-1-thio- α -D-mannopyranosyl uronate) (50)

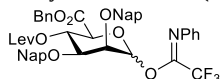
Compound **47** (7.41 g, 11.3 mmol) was coevaporated twice with anhydrous toluene before being dissolved in DCM (30 mL). The mixture was cooled to 0°C, after which LevOH (3.22 mL, 31.6 mmol, 2.8 eq.), DIC (2.47 mL, 15.8 mmol, 1.4 eq.) and DMAP (0.14 g, 1.13 mmol,

0.1 eq.) were added and the reaction was stirred overnight. The mixture was filtered over Celite, washed with sat. aq. NaHCO_3 and sat. aq. NaCl , dried over MgSO_4 and concentrated *in vacuo*. Column purification (PE/EtOAc, 5:1 $\rightarrow$ 2:1) yielded the title compound (6.96 g, 9.22 mmol, 82%). TLC: R_f 0.36 (PE/EtOAc, 3/1, v/v); IR (neat): 896, 1082, 1151, 1361, 1716, 1743, 2870, 2916, 3057 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.80 – 7.51 (m, 10H, CH_{arom}), 7.47 – 7.11 (m, 14H, CH_{arom}), 5.87 (d, 1H, $J = 6.6$ Hz, H-1), 5.65 (t, 1H, $J = 5.2$ Hz, H-4), 5.03 (d, 1H, $J = 12.2$ Hz, CHH), 4.97 (d, 1H, $J = 12.2$ Hz, CHH), 4.75 (d, 1H, $J = 12.1$ Hz, CHH), 4.69 – 4.57 (m, 4H, CHH, CH_2 , H-5), 3.89 (dd, 1H, $J = 5.8$, 2.8 Hz, H-3), 3.80 (d, 1H, $J = 5.7$ Hz, H-2), 2.53 – 2.21 (m, 4H, 2x CH_2 Lev), 2.04 (s, 3H, CH_3 Lev); ^{13}C NMR (126 MHz, CDCl_3 , T=328K): δ 205.8 (C=O Lev), 171.4 (C=O lev), 168.1 (C=O), 135.4, 135.3, 133.9, 133.5, 133.4, 133.3 (Cq), 131.7, 131.4, 129.0, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.8, 127.3, 127.0, 126.9, 126.2, 126.1, 126.0 (CH_{arom}), 83.5 (C-1), 74.7 (C-2), 74.4 (C-3), 73.2 (C-5), 72.8 (CH_2 Nap), 70.2 (C-4), 67.4 (CH_2 Bn), 37.9 (CH_2 Lev), 29.7 (CH_3 Lev), 28.1 (CH_2 Lev). HRMS: $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{46}\text{H}_{43}\text{O}_8\text{S}$ 755.26732, found 755.26848.

Benzyl (4-O-levulinoyl-2,3-O-di-(2-naphthylmethyl)- α/β -D-mannopyranosyl uronate) (52)

Compound **50** (6.96 g, 9.22 mmol) was dissolved in DCM (90 mL) and cooled to 0°C. NIS (2.3 g, 10.1 mmol, 1.1 eq.) was added, followed by addition of TFA (0.78 mL, 10.1 mmol, 1.1 eq.). After 225 min. piperidine (3.0 mL, 30.4 mmol, 3.3 eq.) was added and the mixture was stirred for 30 min.,

allowing to warm up to RT. The mixture was diluted with DCM, and the organic layer was washed with 1M HCl, H_2O and sat. aq. NaCl . The organic layer was dried over MgSO_4 and concentrated *in vacuo*. Column purification (PE/EtOAc, 4:1 $\rightarrow$ 1:1) yielded the hemiacetal as a white foam (4.89 g, 7.38 mmol, 80%). TLC: R_f 0.33 (PE/EtOAc, 3/1, v/v); IR (neat): 1031, 1153, 1361, 1716, 1747, 2872, 2924, 3055, 3458 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 7.81 – 7.59 (m, 8H, CH_{arom}), 7.49 – 7.31 (m, 6H, CH_{arom}), 7.30 – 7.15 (m, 5H, CH_{arom}), 5.65 – 5.57 (m, 2H, H-1, H-4), 5.07 (d, 1H, $J = 12.2$ Hz, CHH), 4.95 (d, 1H, $J = 12.2$ Hz, CHH), 4.87 – 4.68 (m, 2H, CH_2), 4.67 – 4.55 (m, 3H, CH_2 , OH), 4.52 (d, 1H, $J = 5.6$ Hz, H-5), 3.96 (dd, 1H, $J = 6.6$, 2.9 Hz, H-3), 3.69 (dd, 1H, $J = 4.9$, 2.9 Hz, H-2), 2.49 – 2.22 (m, 4H, 2x CH_2 Lev), 2.01 (s, 3H, CH_3 Lev); ^{13}C NMR (101 MHz, CDCl_3): δ 206.5 (C=O Lev), 171.6, 168.8, (2x C=O), 135.6, 135.3, 135.1, 135.0, 134.8, 133.2, 133.1, 133.1, 133.0, 132.9 (Cq), 128.7, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.7, 127.6, 127.2, 126.7, 126.6, 126.5, 126.3, 126.1, 126.1, 126.0, 126.0, 125.9, 125.8, 125.7 (CH_{arom}), 92.5 (C-1), 75.2 (C-2, C-3), 72.9, 72.4 (CH_2), 71.7 (C-5), 69.5 (C-4), 67.4 (CH_2), 37.6 (CH_2 Lev), 29.7 (CH_3 Lev), 27.9 (CH_2 Lev); HRMS: $[\text{M}+\text{NH}_4]^+$ calcd. for $\text{C}_{40}\text{H}_{42}\text{NO}_9$ 680.28541 found 680.28550.

Benzyl (4-O-levulinoyl-2,3-O-di-(2-naphthylmethyl)-O-(N-phenyl-trifluoroacetimidoyl)- α/β -D-mannopyranosyl uronate) (54)

Hemiacetal **52** (4.82 g, 7.27 mmol) was dissolved in acetone and cooled to 0°C. The mixture was treated with $\text{ClC}(=\text{NPh})\text{CF}_3$ (1.35 mL, 8.73 mmol, 1.2 eq.) followed by addition of Cs_2CO_3 (3.55 g, 10.91 mmol, 1.5 eq.). The

reaction was stirred for 6 h, when TLC analysis showed complete reaction, and the mixture was diluted with EtOAc, washed with H_2O , dried over MgSO_4 and concentrated *in vacuo*. Column purification (PE/EtOAc, 4:1 $\rightarrow$ 1:1) yielded the imidate donor (4.93 g, 5.91 mmol, 81%). TLC: R_f 0.43 (PE/EtOAc, 3/1, v/v); IR (neat): 819, 1043, 1151, 1205, 1597, 1714, 1747, 2872, 2922, 3055 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3 , T=328K): δ 7.84 – 7.59 (m, 9H), 7.49

– 7.34 (m, 6H), 7.29 – 7.14 (m, 6H), 7.05 (t, 1H, $J = 7.2$ Hz), 6.60 (d, 2H, $J = 7.3$ Hz), 6.48 (s, 1H), 5.69 (t, 1H, $J = 7.1$ Hz), 5.13 – 5.04 (m, 2H), 4.84 – 4.69 (m, 3H), 4.65 (d, 1H, $J = 12.2$ Hz), 4.44 (d, 1H, $J = 6.7$ Hz), 3.96 (dd, 1H, $J = 7.2, 2.8$ Hz), 3.85 – 3.81 (m, 1H), 2.61 – 2.32 (m, 4H, 2x CH₂ Lev), 2.05 (s, 3H, CH₃ Lev); ¹³C NMR (126 MHz, CDCl₃): δ 205.8 (C=O Lev), 171.4, 167.5 (2x C=O), 143.4, 142.7, 142.4, 135.3, 135.2, 135.1, 133.4, 133.4, 133.3, 133.3 (Cq), 128.8, 128.7, 128.6, 128.6, 128.5, 128.4, 128.3, 128.3, 128.1, 128.1, 127.8, 127.1, 127.0, 126.3, 126.2, 126.2, 126.1, 126.1, 126.0, 125.6, 124.5, 124.2, 119.5 (CH_{arom}), 94.9 (C-1), 75.1 (C-3), 73.5 (C-2), 73.4 (C-5), 73.2 (CH₂), 73.1 (CH₂), 69.2 (C-4), 67.6 (CH₂), 37.8 (CH₂ Lev), 29.7 (CH₃ Lev), 28.1 (CH₂ Lev); HRMS: [M+Na]⁺ calcd. C₄₈H₄₂F₃NO₉Na 856.27039, found 856.27040.

Benzyl (5-azido-pentyl-4-O-Levulinoyl-2,3-O-di-(2-naphthylmethyl)-β-D-mannopyranosyl uronate) (56)

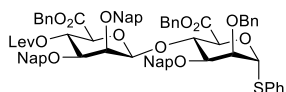
Compound **54** (0.164 g, 0.20 mmol) and 5-azidopentanol (0.039 g, 0.30 mmol, 1.5 eq) were coevaporated with toluene under argon three times, dissolved in dry DCM (2 mL), activated molsieves 3Å were added and the reaction was stirred under an argon atmosphere at RT for 30 min. After 30 min the reaction was cooled to -40 °C, followed by addition of TMSOTf (0.09 mL of a 0.1M TMSOTf/DCM, 0.2 eq.) and the reaction was stirred at -40 °C for 1.5 hours. The reaction was quenched by addition of Et₃N (0.2 mL) at -40°C and was allowed to warm to RT. The mixture was diluted with EtOAc, washed with sat. aq. NaHCO₃, sat. aq. NaCl, dried over MgSO₄, and concentrated *in vacuo*. Column purification (PE/EtOAc 3/1 to 1/1) yielded product **56** (0.124 g, 0.16 mmol 79%) as a white solid. TLC: R_f 0.61 (toluene/EtOAc, 4/1, v/v); ¹H NMR (400 MHz, CDCl₃): δ 7.90 – 7.53 (m, 8H, CH_{arom}), 7.53 – 7.19 (m, 11H, CH_{arom}), 5.64 (t, 1H, $J = 9.4$ Hz, H-4), 5.27 – 4.94 (m, 4H, 2x CH₂ Nap/ Bn), 4.71 – 4.46 (m, 2H, CH₂ Nap/ Bn), 4.41 (s, 1H, H-1), 3.98 (m, 1H, CHH Linker), 3.92 (d, 1H, $J = 2.4$ Hz, H-2), 3.90 (d, 1H, $J = 9.5$ Hz, H-5), 3.51 (dd, 1H, $J = 9.5, 2.8$ Hz, H-3), 3.46 – 3.33 (m, 1H, CHH Linker), 3.21 (m, 2H, CH₂ Linker), 2.65 – 2.19 (m, 4H, 2x CH₂ Lev), 2.05 (s, 3H, CH₃ Lev), 1.85 – 1.52 (m, 4H, 2xCH₂ Linker), 1.52 – 1.35 (m, 1H, CHH Linker), 1.25 (t, $J = 7.1$ Hz, 1H, CHH Linker); ¹³C NMR (101 MHz, CDCl₃): δ 206.3 (C=O Lev), 171.5 (C=O Lev), 167.5 (C=O Bn), 136.0 (Cq), 135.3, 133.1 (Cq), 128.7 (CH_{arom}), 128.6, 128.5, 128.2, 128.0, 127.9, 127.8, 127.2, 126.8, 126.4, 126.2, 126.0, 125.9, 125.8 (CH_{arom}), 101.1 (C-1), 78.3 (C-3), 73.8 (CH₂ Bn/Nap), 73.6 (C-5), 73.0 (C-2), 71.9 (CH₂ Bn/Nap), 70.1 (CH₂ Linker), 69.2 (C-4), 67.5 (CH₂ Bn/Nap), 51.4 (CH₂ Linker), 37.8 (CH₂ Linker), 29.9 (CH₃ Lev), 29.2 (CH₂ Lev), 28.7 (CH₂ Lev), 28.0 (CH₂ Linker), 23.4 (CH₂ Linker). HRMS: [M+Na]⁺ calcd. for C₄₅H₄₇N₃O₉Na 796.32045, found 796.31981.

Benzyl (5-azido-pentyl-2,3-O-di-(2-naphthylmethyl)-β-D-mannopyranosyl uronate) (57)

Compound **56** (0.155 g, 0.20 mmol) was co-evaporated with toluene twice under an argon atmosphere, dissolved pyridine/AcOH (2 mL, 4:1) and H₂NNH₂·AcOH (0.092 g, 1.0 mmol, 5 eq.) was added. The reaction was stirred for 1 hour at RT, after which it was quenched by addition of acetone. The mixture was diluted with EtOAc, washed with 1M HCl (aq), dried over MgSO₄ and concentrated *in vacuo* followed by column chromatography (PE/EtOAc 3/1 to 2/1) which resulted in product **57** (0.128 g, 0.19 mmol, 99%) as a white solid. TLC: R_f 0.81 (PE/EtOAc, 1/1, v/v); ¹H NMR (400 MHz, CDCl₃): δ 7.89 – 7.55 (m, 9H, CH_{arom}), 7.51 – 7.20 (m, 10H, CH_{arom}), 5.35 – 5.18 (m, 2H, CH₂ Bn/Nap), 5.19 – 4.91 (m, 2H, CH₂ Bn/Nap), 4.65 (s, 2H, CH₂ Bn/Nap), 4.47 – 4.36 (m, 2H, H-1, H-4), 4.05 – 3.93 (m, 1H, CHH Linker), 3.94 – 3.90 (m, 1H, H-3), 3.79 (d, 1H, $J = 9.6$ Hz, H-5), 3.51 – 3.33 (m, 2H, H-2, CHH Linker), 3.21 (t, 2H, $J = 6.6$ Hz, CH₂ Linker), 1.62 (m, 4H, 2xCH₂ Linker), 1.45 (dd, 1H, $J = 13.8, 6.0$ Hz, CHH Linker), 1.26 (s, 1H, CHH Linker); ¹³C NMR (101 MHz, CDCl₃): δ 169.1 (C=O), 136.1 (Cq), 135.4, 133.3 (Cq), 128.7 (CH_{arom}), 128.5, 128.4, 128.3, 127.9, 127.8, 127.2, 126.7, 126.5, 126.2, 126.0, 125.9, 125.7 (CH_{arom}), 102.3 (C-1), 80.3 (C-3), 75.3 (C-5), 74.3

(CH₂ Bn/Nap), 73.6 (C-2), 72.1 (CH₂ Bn/Nap), 70.0 (CH₂ Linker), 68.5 (C-4), 67.3 (CH₂ Bn/Nap), 51.4 (CH₂ Linker), 29.3 (CH₂ Linker), 28.7 (CH₂ Linker), 23.4 (CH₂ Linker). HRMS: [M+Na]⁺ calcd. for C₄₀H₄₁N₃O₇Na 698.28367, found 698.28314.

Benzyl (phenyl-4-O-[benzyl 4-O-levulinoyl-2,3-O-di-(2-naphthylmethyl)-β-D-mannopyranosyl uronate]-

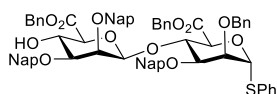


2-O-benzyl-3-O-(2-naphthylmethyl)-1-thio-α-D-mannopyranosyl uronate)

(59) Donor **54** (2.527 g, 3.03 mmol, 1.0 eq.) and acceptor **48** (2.02 g, 3.33 mmol, 1.1 eq.) were coevaporated 3 times under an argon atmosphere. The compounds were dissolved in dry DCM (30 mL) and stirred on activated molecular sieves

for 30 min. The mixture was cooled to -55°C and TMSOTf (6.1 mL of 0.1M TMSOTf/DCM, 0.2 eq.) was added. After 110 min., TLC: indicated complete reaction and the reaction was quenched with Et₃N (1 mL) and allowed to warm up to RT. The mixture was diluted with DCM, washed with sat. aq. NaHCO₃, dried over MgSO₄ and concentrated *in vacuo*. Column purification (hexanes/EtOAc, 6:1 → 2:1) yielded the disaccharide (2.696 g, 2.154 mmol, 72%). TLC: R_f 0.42 (PE/EtOAc, 5/2, v/v); IR (neat) 740, 1026, 1058, 1151, 1363, 1716, 1747, 2868, 3057 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 7.84 – 7.00 (m, 36H, CH_{arom}), 5.80 (d, 1H, *J* = 7.8 Hz, H-1), 5.64 (t, 1H, *J* = 9.3 Hz, H-4'), 5.08 – 4.81 (m, 6H, 3x CH₂), 4.75 – 4.49 (m, 7H, H-1', H-4, H-5, 2x CH₂), 4.38 (s, 2H, CH₂), 4.23 (s, 1H, H-3), 3.91 (s, 1H, H-2'), 3.89 – 3.79 (m, 2H, H-2, H-5'), 3.48 (d, 1H, *J* = 9.2 Hz, H-3'), 2.54 – 2.27 (m, 4H, 2x CH₂ Lev), 2.00 (s, 3H, CH₃ Lev); ¹³C NMR (126 MHz, CDCl₃): δ 205.7 (C=O Lev), 171.3, 169.0, 167.1 (3x C=O), 138.3, 137.9, 136.0, 135.8, 135.4, 135.3, 135.3, 134.1, 133.4, 133.3, 133.1, 133.1 (Cq), 131.5, 131.3, 131.2, 128.9, 128.9, 128.7, 128.5, 128.5, 128.5, 128.4, 128.4, 128.3, 128.3, 128.2, 128.2, 128.1, 128.1, 128.0, 127.9, 127.9, 127.9, 127.8, 127.7, 127.7, 127.6, 127.5, 127.1, 126.9, 126.9, 126.8, 126.7, 126.6, 126.5, 126.4, 126.3, 126.2, 126.1, 126.0, 126.0, 125.9, 125.8, 125.7, 125.6 (CH_{arom}), 101.1 (C-1'), 83.0 (C-1), 78.4 (C-3'), 76.8 (C-4), 75.2 (C-3'), 75.1 (C-2), 74.2 (CH₂), 74.2 (C-2'), 73.8 (C-5), 73.7 (C-5'), 73.3 (CH₂), 72.1, 72.0 (CH₂), 69.3 (C-4'), 67.4, 67.1 (CH₂), 37.8 (CH₂ Lev), 29.6 (CH₃ Lev), 28.1 (CH₂ Lev); HRMS: [M+NH₄]⁺ calcd. C₇₇H₇₄O₁₄SN 1268.48245, found 1268.48297.

Benzyl (phenyl-4-O-[Benzyl 2,3-O-di-(2-naphthylmethyl)-β-D-mannopyranosyl uronate]-2-O-benzyl-3-O-(2-naphthylmethyl)-1-thio-α-D-mannopyranosyl uronate) (60)

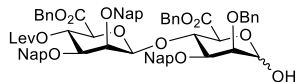


(60) Disaccharide **59** (1.263 g, 1.0 mmol, 1.0 eq.) was dissolved in pyridine/AcOH (10 mL, 4:1) and cooled to 0°C, followed by addition of H₂NNH₂·AcOH (0.46 g, 5 mmol, 5.0 eq.). The reaction was quenched with acetone after 85 min, when TLC analysis

showed complete conversion of the starting material into a higher running spot. The mixture was diluted with EtOAc, washed with aq. 1M HCl, H₂O and sat. aq. NaCl. Column purification (hexanes/EtOAc, 6:1 → 2:1) yielded the title compound (1.098 g, 0.952 mmol, 95%). TLC: R_f 0.65 (PE/EtOAc, 2/1, v/v); IR (neat): 902, 1062, 1122, 1454, 1730, 1743, 2862, 2924, 3053 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 7.88 – 7.55 (m, 14H, CH_{arom}), 7.54 – 7.28 (m, 14H, CH_{arom}), 7.26 – 7.02 (m, 23H, CH_{arom}), 5.78 (d, 1H, *J* = 8.1 Hz, H-1), 5.14 (d, 1H, *J* = 12.3 Hz, CHH), 5.08 (d, 1H, *J* = 12.3 Hz, CHH), 4.94 (d, *J* = 12.3 Hz, 1H, CHH), 4.89 (d, 1H, *J* = 12.2 Hz, CHH), 4.82 (m, 2H, 2x CHH), 4.70 (m, 3H, CH₂, CHH), 4.62 – 4.52 (m, 5H, H-1, H-4, H-5, CH₂), 4.43 – 4.35 (m, 3H, H-4', CH₂), 4.22 – 4.18 (m, 1H, H-3), 3.90 (d, 1H, *J* = 2.8 Hz, H-2'), 3.83 – 3.73 (m, 2H, H-2, H-5'), 3.35 (dd, 1H *J* = 9.4, 2.9 Hz, H-3'), 3.11 (s, 1H, 4-OH); ¹³C NMR (126 MHz, CDCl₃, T=328K): δ 169.0, 169.0 (2x C=O), 138.0, 136.2, 135.8, 135.6, 135.3, 135.3, 134.1, 133.4, 133.4, 133.2, 133.2, 133.2 (Cq), 131.3, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.1, 128.1, 128.0, 128.0, 127.9, 127.8, 127.8, 127.7, 127.6, 127.0, 126.9, 126.7, 126.5, 126.4, 126.2, 126.1, 126.1, 126.0, 126.0, 125.9, 125.8, 125.7, 101.9 (C-1'), 82.9 (C-1), 80.6 (C-3'), 76.9 (C-5), 75.6 (C-3), 75.5 (C-5'), 75.2 (C-2), 74.7 (C-

2'), 74.7 (CH₂), 74.1 (C-4), 73.4 (CH₂), 72.4 (CH₂), 72.2 (CH₂), 68.5 (C-4'), 67.4, 67.2; HRMS: [M+NH₄]⁺ calcd. C₇₂H₆₈NO₁₂S 1170.44567, found 1170.44656.

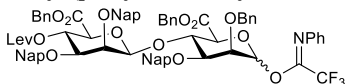
Benzyl (phenyl-4-O-[benzyl 2,3-O-di-(2-naphthylmethyl)-β-D-mannopyranosyl uronate]-2-O-benzyl-3-O-(2-naphthylmethyl)-α/β-D-mannopyranosyl uronate) (61)



To a solution of compound **59** (1.798 g, 1.436 mmol, 1.0 eq.) in DCM (15 mL) at 0°C, was added NIS (0.36 g, 1.580 mmol, 1.1 eq.) and TFA (0.12 mL, 1.580 mmol, 1.1

eq.) after which the reaction mixture turned dark purple. After 3h, the reaction was quenched with Et₃N (0.4 mL), 15 mL sat. aq. Na₂S₂O₃ was added and the reaction was stirred for 30 min. after which the color changed from purple to colorless. The mixture was diluted with DCM and washed with sat. aq. NaHCO₃. The aqueous layer was extracted 2x with DCM, and the combined organic layers were washed with sat. aq. NaCl, dried over MgSO₄ and concentrated *in vacuo*. Column purification (hexanes/EtOAc) yielded the hemiacetal (1.41 g, 1.22 mmol, 84%). TLC: R_f 0.33 (PE/EtOAc, 3/1, v/v); IR (neat): 731, 1055, 1122, 1361, 1716, 1747, 2875, 3030, 3057 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 7.86 – 7.57 (m, 12H), 7.49 (dd, 1H, *J* = 8.5, 1.8 Hz), 7.47 – 7.02 (m, 23H), 5.68 – 5.43 (m, 2H), 5.11 – 4.75 (m, 6H), 4.75 – 4.42 (m, 8H), 4.20 (dd, 1H, *J* = 5.4, 2.8 Hz), 3.91 (d, 1H, *J* = 2.9 Hz), 3.82 (d, 1H, *J* = 9.2 Hz), 3.44 (dd, 1H, *J* = 9.4, 3.0 Hz), 3.23 (d, 1H, *J* = 5.3 Hz), 2.63 – 2.22 (m, 4H), 2.00 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 205.9, 171.4, 169.3, 167.2, 138.5, 136.2, 136.1, 135.9, 135.5, 135.5, 135.4, 133.5, 133.4, 133.4, 133.2, 133.2, 133.1, 128.7, 128.6, 128.6, 128.5, 128.5, 128.4, 128.4, 128.4, 128.3, 128.3, 128.3, 128.2, 128.2, 128.2, 128.1, 128.0, 128.0, 128.0, 127.9, 127.8, 127.7, 127.5, 126.9, 126.8, 126.8, 126.7, 126.6, 126.6, 126.5, 126.4, 126.4, 126.3, 126.2, 126.1, 126.1, 126.0, 126.0, 125.9, 125.9, 125.8, 125.8, 125.7, 125.6, 101.3, 101.1, 94.1, 93.0, 92.9, 78.6, 78.4, 78.1, 76.8, 76.8, 76.4, 75.9, 75.5, 74.7, 74.5, 74.5, 74.4, 74.3, 73.7, 73.7, 73.4, 73.3, 73.1, 72.8, 72.5, 72.5, 72.4, 72.1, 72.0, 70.1, 69.3, 67.4, 67.3, 67.1, 60.4, 37.9, 37.9, 29.7, 28.2, 21.0, 14.3; HRMS: [M+NH₄]⁺ calcd. C₇₁H₇₀NO₁₅ 1176.47400, found 1176.47406.

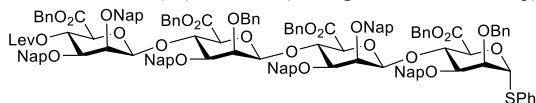
Benzyl (phenyl-4-O-[benzyl 2,3-O-di-(2-naphthylmethyl)-β-D-mannopyranosyl uronate]-2-O-benzyl-3-O-(2-naphthylmethyl)-O-(N-phenyl-trifluoroacetimidoyl)-α/β-D-mannopyranosyl uronate) (62)



Hemiacetal **61** (0.871 g, 0.751 mmol, 1.0 eq.) was dissolved in acetone and cooled to 0°C. The mixture was

treated with ClC(=NPh)CF₃ (0.14 mL, 0.901 mmol, 1.2 eq.) followed by addition of Cs₂CO₃ (0.367 g, 1.126 mmol, 1.5 eq.). The reaction was stirred for 110 min., after which it was diluted with EtOAc, washed with H₂O, dried over MgSO₄ and concentrated *in vacuo*. Column purification (PE/EtOAc, 6:1 → 2:1) yielded the imidate donor (0.696 g, 0.522 mmol, 70%). TLC: R_f 0.53 (PE/EtOAc, 2/1, v/v); IR: 732, 817, 1051, 1151, 1205, 1323, 1597, 1716, 1749, 2873, 3034, 3059 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.83 – 7.59 (m, 14H), 7.51 (dd, 1H, *J* = 8.5, 1.6 Hz), 7.49 – 6.97 (m, 30H), 6.68 (d, 2H, *J* = 7.8 Hz), 6.47 (s, 1H), 5.63 (t, 1H, *J* = 9.3 Hz), 5.09 – 4.83 (m, 7H), 4.75 – 4.37 (m, 10H), 4.22 (dd, 1H, *J* = 5.8, 2.8 Hz), 3.90 (d, 1H, *J* = 2.8 Hz), 3.88 – 3.79 (m, 2H), 3.45 (dd, 1H, *J* = 9.4, 2.8 Hz), 2.60 – 2.22 (m, 4H), 2.03 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 205.8, 171.4, 168.6, 167.9, 167.5, 167.2, 167.2, 143.7, 143.4, 143.0, 142.7, 138.4, 138.1, 137.9, 136.1, 135.9, 135.5, 135.5, 135.4, 135.3, 135.2, 135.2, 135.1, 133.4, 133.4, 133.2, 133.2, 128.8, 128.7, 128.6, 128.6, 128.6, 128.6, 128.5, 128.4, 128.4, 128.4, 128.3, 128.3, 128.3, 128.2, 128.1, 128.1, 128.1, 128.0, 128.0, 128.0, 127.9, 127.8, 127.8, 127.7, 127.7, 127.1, 127.0, 126.9, 126.7, 126.6, 126.4, 126.4, 126.3, 126.2, 126.2, 126.1, 126.1, 126.0, 125.9, 125.8, 125.8, 125.7, 124.4, 124.3, 119.7, 119.5, 115.1, 101.6, 101.5, 78.6, 76.7, 76.1, 75.9, 75.1, 74.8, 74.5, 74.4, 74.4, 74.4, 74.4, 73.8, 73.6, 73.5, 73.5, 73.4, 73.2, 73.1, 72.8, 72.6, 72.2, 69.3, 69.2, 67.6, 67.5, 67.4, 67.3, 67.1, 60.4, 53.4, 37.9, 37.8, 29.7, 29.6, 28.2, 28.1, 21.0, 14.3; HRMS: [M+NH₄]⁺ calcd. C₇₉H₇₄F₃N₂O₁₅ 1347.50358, found 1347.50430.

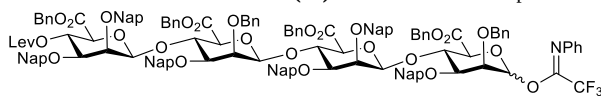
Tetrasaccharide (63) Donor **62** (0.527 g, 0.396 mmol, 1.0 eq.) and acceptor **60** (0.502 g, 0.440 mmol, 1.1 eq.) were



coevaporated 3 times with anhydrous toluene under an N₂ atmosphere. The mixture was dissolved in DCM (4 mL) and stirred on activated molecular sieves for 30 min. at RT. The mixture

was cooled to -65°C and treated with TMSOTf (0.8 mL of 0.1M TMSOTf/DCM, 0.2 eq.). When TLC analysis indicated complete consumption of the donor, the reaction was quenched with Et₃N (0.3 mL) and allowed to warm up to RT. The mixture was diluted with DCM, washed with sat. aq. NaHCO₃, dried over MgSO₄ and concentrated *in vacuo*. Purification by size exclusion chromatography (LH20, eluted with DCM/MeOH, 1/1, v/v), yielded the title tetrasaccharide as a white foam (0.617 g, 0.269 mmol, 68%). TLC: R_f 0.52 (PE/EtOAc, 5/4, v/v); IR (neat): 742, 1026, 1103, 1153, 1361, 1720, 1747, 2875, 2926, 3034, 3055 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 7.88 – 6.94 (m, 77H), 5.77 (d, 1H, J = 7.3 Hz), 5.54 (t, 1H, J = 9.6 Hz), 5.05 – 4.23 (m, 38H), 4.15 (s, 1H), 3.97 – 3.55 (m, 8H), 3.55 – 3.18 (m, 3H), 2.61 – 2.14 (m, 4H), 1.99 (s, 3H); ¹³C NMR (126 MHz, CDCl₃): δ 205.8 (C=O Lev), 171.4, 169.1, 168.3, 168.0, 167.3 (5x C=O), 139.2, 138.1, 136.8, 136.6, 136.6, 136.2, 135.9, 135.7, 135.5, 135.4, 135.3, 135.3, 134.2, 133.5, 133.5, 133.4, 133.2, 133.2, 133.1, 133.1, 133.0 (Cq), 131.3, 128.8, 128.7, 128.7, 128.6, 128.6, 128.5, 128.5, 128.4, 128.4, 128.4, 128.3, 128.2, 128.2, 128.1, 128.1, 128.0, 128.0, 128.0, 127.9, 127.9, 127.9, 127.8, 127.8, 127.7, 127.7, 127.6, 127.5, 127.3, 126.9, 126.8, 126.6, 126.5, 126.4, 126.3, 126.3, 126.2, 126.1, 126.1, 126.0, 126.0, 125.9, 125.9, 125.9, 125.9, 125.7, 125.7, 125.7, 125.6 (CH_{arom}), 102.3, 102.2, 101.1 (3x C-1), 83.1 (C-1), 79.3, 79.1, 78.8, 78.0, 77.8, 76.5, 76.4, 75.5, 75.4, 74.7, 74.5, 74.3, 73.7, 73.3, 73.1, 72.8, 72.3, 71.9, 69.3 (C-4'''), 67.2, 67.1, 67.1, 66.9, 37.9 (CH₂ Lev), 29.6 (CH₃ Lev), 28.1 (CH₂ Lev); HRMS: [M+H]⁺ calcd. C₁₄₃H₁₂₉O₂₆S 2294.85210, found 2294.85237.

Tetrasaccharide imidate donor (65) To a solution of compound **63** (0.345 g, 0.156 mmol, 1.0 eq.) in DCM (1.5

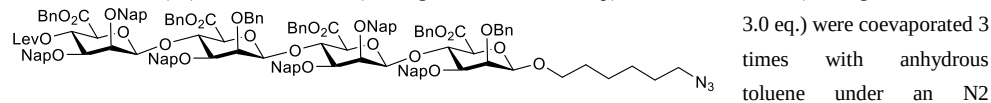


mL) at 0°C, was added NIS (0.04 g, 0.180 mmol, 1.2 eq.) and TFA (0.014 mL, 0.180 mmol, 1.2 eq.) after which the reaction

mixture turned dark purple. After 35 min, the reaction was quenched with Et₃N (0.04 mL), 3 mL sat. aq. Na₂S₂O₃ was added and the reaction was stirred for 30 min. after which the color changed from purple to colorless. The mixture was diluted with DCM and washed with sat. aq. NaHCO₃. The aqueous layer was extracted 2x with DCM, and the combined organic layers were washed with sat. aq. NaCl, dried over MgSO₄ and concentrated *in vacuo*. Column purification (hexanes/EtOAc) yielded the hemiacetal as a difficult to concentrate foam. R_f 0.30 (PE/EtOAc, 2/1, v/v); HRMS: [M+NH₄]⁺ calcd. C₁₃₇H₁₂₈NO₂₇ 2219.87020, found 2219.87251. The hemiacetal (**63**) was dissolved in acetone (1 mL) and cooled to 0°C. Then, ClC(=NPh)CF₃ (0.03 mL, 0.18 mmol, 1.2 eq.) was added, followed by Cs₂CO₃ (0.074 g, 0.23 mmol, 1.5 eq.), after which the reaction was allowed to stir overnight. TLC analysis indicated complete conversion of the hemiacetal, after which the mixture was diluted with EtOAc, washed with H₂O and sat. aq. NaCl, dried over MgSO₄ and concentrated *in vacuo*. Column purification (Hexanes/EtOAc, 4:1 → 1:1) yielded the imidate donor (0.298 g, 0.125 mmol, 83% over 2 steps). R_f 0.57 (PE/EtOAc, 2/1, v/v); IR (neat): 752, 1157, 1212, 1365, 1724, 1745, 2849, 3059 cm⁻¹; ¹H NMR (500 MHz, CDCl₃, T=328K): δ 7.89 – 6.94 (m, 96H, CH_{arom}), 6.67 (d, 2H J = 7.5 Hz), 6.46 (s, 1H, H-1), 5.54 (t, 1H, J = 9.7 Hz, H-4'''), 5.04 – 4.24 (m, 39H), 4.24 – 4.13 (m, 1H), 3.86 – 3.74 (m, 5H), 3.74 – 3.56 (m, 4H), 3.56 – 3.39 (m, 2H), 3.36 – 3.24 (m, 2H), 2.51 – 2.18 (m, 4H, 2x CH₂ Lev), 2.00 (s, 3H, CH₃ Lev); ¹³C NMR (126 MHz, CDCl₃, T=328K): δ 205.9 (C=O Lev), 171.4, 168.6, 168.3, 168.0, 167.4 (5x C=O), 143.8, 143.0, 142.7, 139.3, 138.0, 136.8, 136.7, 136.6, 136.3, 135.9, 135.7,

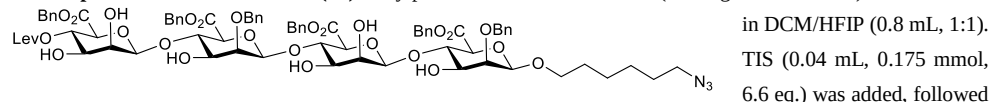
135.5, 135.5, 135.3, 135.2, 133.5, 133.5, 133.5, 133.5, 133.2, 133.2, 133.1, 133.1 (Cq), 129.4, 129.2, 128.7, 128.6, 128.5, 128.5, 128.4, 128.4, 128.3, 128.3, 128.2, 128.2, 128.2, 128.1, 128.1, 128.0, 127.9, 127.8, 127.8, 127.7, 127.6, 127.4, 126.8, 126.8, 126.7, 126.5, 126.4, 126.4, 126.3, 126.2, 126.1, 126.1, 126.1, 126.0, 126.0, 126.0, 125.9, 125.9, 125.8, 125.7, 125.7, 124.3, 119.7 (CH_{arom}), 102.3, 102.3, 101.5 (3x C-1), 95.0 (C-1), 79.3, 79.3, 78.8, 78.0, 77.8, 76.5, 76.4, 75.6, 75.5, 75.4, 75.1, 74.7, 74.4, 74.3, 73.7, 73.6, 73.2, 72.8, 72.1, 71.9 (4x C-2, 4x C-3, 3x C-4, 4x C-5, 9x CH₂), 69.3 (C-4'''), 67.2, 67.1, 66.9 (CH₂), 37.9 (CH₂ Lev), 29.7 (CH₃ Lev), 28.2 (CH₂ Lev); HRMS: [M+Na]⁺ calcd. C₁₄₅H₁₂₈F₃NO₂₇Na 2395.85518, found 2395.85657.

Tetrasaccharide (66) Imidate donor **65** (0.298 g, 0.125 mmol, 1.0 eq.) and 6-azidoheptanol (0.054 g, 0.375 mmol,



The mixture was dissolved in DCM (1 mL) and stirred on activated molecular sieves for 30 min. The mixture was cooled to -50°C, followed by addition of TMSOTf (0.25 mL of 0.1M TMSOTf/DCM, 0.2 eq.). The reaction was stirred for 80 min., quenched with Et₃N and allowed to warm up to RT. The mixture was diluted with DCM, washed with sat. aq. NaHCO₃, dried over MgSO₄ and concentrated *in vacuo*. Purification by size exclusion chromatography (LH-20, eluted with DCM/MeOH, 1/1, v/v) followed by column purification (Hexanes/EtOAc) yielded the tetrasaccharide (0.197 g, 0.085 mmol, 68%). TLC: R_f 0.6 (PE/EtOAc, 2/1, v/v); IR (neat): 749, 819, 1059, 1124, 1274, 1363, 1455, 1746, 2095, 2933, 3056 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 7.83 – 6.95 (m, 72H), 5.47 (t, 1H, J = 9.8 Hz), 5.08 – 4.18 (m, 38H), 3.92 – 3.44 (m, 16H), 3.43 – 3.36 (m, 1H), 3.36 – 3.12 (m, 7H), 2.48 – 2.27 (m, 4H), 2.02 (s, 3H), 1.59 (s, 8H), 1.42 – 1.27 (m, 7H); ¹³C NMR (126 MHz, CDCl₃): δ 206.2, 171.5, 168.2, 168.2, 168.1, 167.9, 167.3, 139.1, 138.7, 136.8, 136.6, 136.5, 136.5, 136.2, 135.5, 135.3, 133.4, 133.3, 133.1, 133.0, 132.9, 128.7, 128.6, 128.6, 128.6, 128.5, 128.5, 128.4, 128.4, 128.3, 128.2, 128.1, 128.1, 128.0, 127.9, 127.9, 127.8, 127.8, 127.7, 127.5, 127.3, 126.7, 126.6, 126.4, 126.3, 126.3, 126.2, 126.1, 126.0, 125.9, 125.8, 125.8, 125.7, 125.6, 102.5, 102.2, 102.0, 79.0, 78.4, 77.8, 77.7, 76.0, 75.1, 75.0, 74.8, 74.6, 73.8, 73.4, 73.1, 72.9, 72.8, 72.3, 71.6, 70.1, 69.0, 67.2, 67.0, 66.9, 66.7, 51.4, 37.8, 29.8, 29.6, 29.5, 28.9, 28.8, 28.0, 26.6, 25.7; HRMS: [M+Na]⁺ calcd. C₁₄₃H₁₃₅N₃O₂₇Na 2349.92086, found 2349.92411.

Semi deprotected tetrasaccharide (67) Fully protected tetrasaccharide **66** (0.062 g, 0.0266 mmol) was dissolved

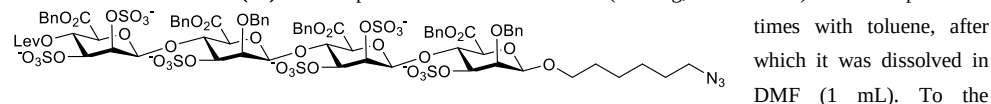


by addition of HCl/HFIP (0.33 mL of 0.2M HCl/HFIP, 2.5 eq.). After 100 min., an additional portion HCl/HFIP (0.13 mL of 0.2M HCl/HFIP, 1.0 eq.) was added and the reaction was quenched with sat. aq. NaHCO₃ (4 mL) after 30 min. The mixture was diluted with DCM, and the layers were separated. The aqueous layer was extracted with DCM and the combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. Column purification (Hexanes/DCM 2:1 → 1:1 → DCM/MeOH 15:1) yielded the semi deprotected tetrasaccharide (0.0372 g, 0.025 mmol, 94%). TLC: R_f 0.61 (DCM/MeOH, 9/1, v/v); IR (neat): 698, 751, 1041, 1104, 1364, 1455, 1744, 2096, 2933, 3475 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 7.37 – 7.27 (m, 30H, CH_{arom}), 5.26 – 4.99 (m, 8H, 4x CH₂), 4.87 (d, J = 12.3 Hz, 1H, CHH), 4.80 (s, 1H, H-1), 4.75 – 4.59 (m, 3H, CHH, CH₂), 4.49 – 4.36 (m, 2H), 4.22 – 4.13 (m, 2H), 4.05 – 3.57 (m, 9H), 3.50 – 3.27 (m, 6H), 3.23 (t, J = 6.9 Hz, 2H, linker CH₂), 2.71 – 2.22 (m, 4H, 2x CH₂ Lev), 2.13 (s, 3H, CH₃ Lev), 1.60 – 1.49 (m, 4H), 1.43 – 1.11 (m, 6H); ¹³C NMR (126 MHz, CDCl₃): δ 206.8 (C=O Lev), 172.3, 169.1, 167.9, 167.4, 167.3 (C=O), 138.8, 138.7, 135.5, 135.0, 135.0, 134.9, 134.9, 134.8 (Cq), 129.4, 129.2,

Chapter 5

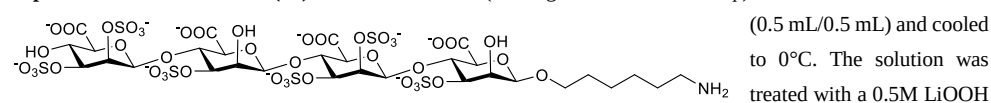
129.1, 128.9, 128.9, 128.8, 128.7, 128.4, 128.2, 128.1, 128.0, 127.7, 127.7 (CH_{arom}), 102.1, 101.2, 100.5, 99.4 (4x C-1), 80.3, 79.3, 79.1, 76.6, 76.1 (4x C-3, C-5), 75.1 (CH₂), 74.0 (CH₂), 73.5, 73.4, 72.4, 72.2, 71.9, 71.5, 70.6, 70.1, 69.7, 69.4, 69.4 (4x C-4, 4x C-2, 3x C-5), 68.3 (CH₂), 68.1 (CH₂), 68.0 (CH₂), 67.8 (CH₂), 67.3 (CH₂), 51.5 (CH₂), 38.1 (CH₂ Lev), 29.9 (CH₃ Lev), 29.3 (CH₂), 28.9 (CH₂), 28.0 (CH₂), 26.6 (CH₂), 25.8 (CH₂); HRMS: [M+NH₄]⁺ calcd. C₇₇H₉₁N₄O₂₇ 1503.58652, found 1503.58865.

Sulfated tetrasaccharide (68) Semi deprotected tetrasaccharide **67** (0.024 g, 0.016 mmol) was coevaporated 3



solution, Et₃N·SO₃ (0.09 g, 0.49 mmol, 30 eq.) was added and the solution was heated to 55°C. The septum was replaced with a stopper and sealed, after which the reaction was stirred at 55°C overnight. The reaction was cooled to 0°C, and quenched with NaHCO₃ (0.045 g, 0.54 mmol, 33 eq.) in 1 mL H₂O, and the mixture was stirred for 1h after which the solvents were removed *in vacuo* at 22°C. The crude compound was taken up in a small volume of DCM/MeOH and applied on a Sephadex LH-20 column and eluted with DCM/MeOH (1:1), resulting in the sulfated tetrasaccharide (0.0304 g, 0.012 mol, 74%); IR (neat): 699, 750, 807, 1040, 1217, 1365, 1455, 1747, 2096, 2942, 3474 cm⁻¹; ¹H NMR (500 MHz, MeOD) δ 7.63 – 7.12 (m, 30H, CH_{arom}), 5.39 – 4.92 (m, 17H), 4.82 – 3.91 (m, 15H), 3.63 – 3.38 (m, 6H), 3.21 (t, J = 6.9 Hz, 2H), 3.14 (q, J = 7.3 Hz, 36H, 18x CH₂ Et₃N), 2.75 – 2.27 (m, 4H, 2x CH₂ Lev), 2.10 (s, 3H, CH₃ Lev), 1.64 – 1.44 (m, 4H, CH₂ linker), 1.31 (d, J = 8.8 Hz, 6H, CH₂ linker), 1.24 (t, J = 7.3 Hz, 54H, 18x CH₃ Et₃N); ¹³C NMR (126 MHz, MeOD) δ 209.2 (C=O Lev), 173.4 (C=O Lev), 169.9, 169.9, 169.8, 169.7 (4x CO₂Bn), 140.5, 137.4, 136.6 (Cq), 129.8, 129.6, 129.6, 129.5, 129.4, 129.1, 128.3 (CH_{arom}), 100.8, 100.7, 100.5, 100.5 (4x C-1), 78.5, 77.7, 77.5, 77.4, 76.7, 76.6, 75.8, 73.7, 68.7, 68.7, 68.4, 68.3, 68.2, 68.2, 52.4, 49.5, 49.3, 49.2, 49.0, 48.8, 48.7, 48.5, 47.8, 38.6, 30.7, 29.9, 29.6, 29.2, 27.6, 26.7, 9.3. ESI-MS: m/z [M+2H]⁴⁺ calc. for C₇₇H₈₃N₃O₄₅S₆ 490.8, found 490.8.

Deprotected tetrasaccharide (69) Tetrasaccharide **68** (0.031 g, 0.012 mmol, 1.0 eq.) was dissolved in H₂O/THF



solution (0.6 mL, 5.0 eq. per ester) and the reaction was allowed to stir overnight during which at warmed up to RT. After overnight stirring, the reaction was neutralized with 1M HCl and concentrated at 25°C. The crude was purified by gel filtration (HW40 eluted with NH₄HCO₃) and passed through a Dowex Na⁺ column. NMR analysis indicated removal of the Lev and several benzyl esters. The tetrasaccharide was dissolved in H₂O/THF/tBuOH (3 mL, 3:1.3:1.3), 2-3 drops of AcOH were added and the solution was purged with N₂ for 5 minutes. Pd(OH)₂/C (20 mg) was added, after which the solution was purged with N₂ for 5 minutes, H₂ for 5 minutes after which the reaction was kept under a H₂ atmosphere overnight. The mixture was passed through a Whatmann filter, rinsed several times with H₂O/THF/tBuOH and H₂O, after which it was concentrated at 25°C. The compound was purified by gel filtration (HW40 eluted with NH₄HCO₃), lyophilized 4 times and passed through a Dowex Na⁺ column. (2.22 mg, 1.46 μmol, 12% over 2 steps). ¹H NMR (D₂O, 850 MHz): δ 5.08 – 5.02 (m, 2H), 4.98 (s, 1H), 4.90 (s, 1H), 4.58 – 4.48 (m, 5H), 4.40 – 4.33 (m, 4H), 4.18 – 4.01 (m, 6H), 3.99 – 3.92 (m, 3H), 3.89 – 3.81 (m, 3H), 3.67 (s, 2H), 3.15 – 3.08 (m, 2H), 3.03 – 2.92 (m, 2H), 1.76 – 1.70 (m, 2H), 1.70 – 1.57 (m, 4H), 1.40 (s, 3H); ¹³C NMR (D₂O, 214 MHz): δ 173.7, 173.7, 100.6, 100.5, 78.4, 78.3, 77.7, 77.4, 77.4, 77.0, 76.7, 76.5, 76.5, 76.3, 75.9, 75.8, 75.5, 74.7, 69.6, 67.3, 62.7, 45.5, 40.3, 29.1, 27.4, 25.9, 23.1, 22.4.

Notes and references

- (1) Black, W. A. P.; Cornhill, W. J.; Dewar, E. T. *J. Sci. Food Agric.* **1952**, *3*, 542–550.
- (2) Ramsey, D. M.; Wozniak, D. J. *Mol. Microbiol.* **2005**, *56*, 309–322.
- (3) Flo, T. H.; Ryan, L.; Latz, E.; Takeuchi, O.; Monks, B. G.; Lien, E.; Halaas, O.; Akira, S.; Skjåk-Bræk, G.; Golenbock, D. T.; Espevik, T. *J. Biol. Chem.* **2002**, *277*, 35489–35495.
- (4) Wang, W.; Wang, S.; Guan, H. **2012**, 2795–2816.
- (5) Zhao, H.; Liu, H.; Chen, Y.; Xin, X.; Li, J.; Hou, Y.; Zhang, Z.; Zhang, X.; Xie, C.; Geng, M.; Ding, J. *Cancer Res.* **2006**, *66*, 8779–8787.
- (6) Codée, J. D. C.; van den Bos, L. J.; de Jong, A. R.; Dinkelaar, J.; Lodder, G.; Overkleeft, H. S.; van der Marel, G. A. *J. Org. Chem.* **2009**, *74*, 38–47.
- (7) van den Bos, L. J.; Dinkelaar, J.; Overkleeft, H. S.; van der Marel, G. a. *J. Am. Chem. Soc.* **2006**, *128*, 13066–13067.
- (8) Tang, S.-L.; Pohl, N. L. B. *Org. Lett.* **2015**, *17*, 2642–2645.
- (9) Walvoort, M. T. C.; van den Elst, H.; Plante, O. J.; Kröck, L.; Seeberger, P. H.; Overkleeft, H. S.; van der Marel, G. A.; Codée, J. D. C. *Angew. Chemie Int. Ed.* **2012**, *51*, 4393–4396.
- (10) Crich, D.; Sun, S. *J. Org. Chem.* **1997**, *62*, 1198–1199.
- (11) Crich, D.; Cai, W.; Dai, Z. *J. Org. Chem.* **2000**, *65*, 1291–1297.
- (12) Adero, P. O.; Furukawa, T.; Huang, M.; Mukherjee, D.; Retailleau, P.; Bohé, L.; Crich, D. *J. Am. Chem. Soc.* **2015**, *137*, 10336–10345.
- (13) Crich, D.; Vinogradova, O. *J. Org. Chem.* **2007**, *72*, 3581–3584.
- (14) Hu, Y.; Zhong, Y.; Chen, Z.-G.; Chen, C.; Shi, Z.; Zulueta, M. M. L.; Ku, C.-C.; Lee, P.-Y.; Wang, C.-C.; Hung, S.-C. *J. Am. Chem. Soc.* **2012**, *134*, 20722–20727.
- (15) Zhang, Q.; van Rijssel, E. R.; Walvoort, M. T. C.; Overkleeft, H. S.; van der Marel, G. A.; Codée, J. D. C. *Angew. Chemie Int. Ed.* **2015**.
- (16) Jayson, G. C.; Hansen, S. U.; Miller, G. J.; Cole, C. L.; Rushton, G.; Avizienyte, E.; Gardiner, J. M. *Chem. Commun.* **2015**, *51*, 13846–13849.
- (17) Arlov, Ø.; Aachmann, F. L.; Sundan, A.; Espevik, T.; Skjåk-Bræk, G. *Biomacromolecules* **2014**, *15*, 2744–2750.

