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A versatile approach to the synthesis of glycans containing manuronic acid residues†

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Reported herein is a new method for a highly effective synthesis of β -glycosides from manuronic acid donors equipped with the 3-*O*-picoloyl group. The stereocontrol of glycosylations was achieved by means of the H-bond-mediated aglycone delivery (HAD). The method was utilized for the synthesis of a tetrasaccharide linked *via* β -(1 $\rightarrow$ 3)-mannuronic linkages. We have also investigated 3,6-lactonized glycosyl donors that provided moderate to high β -manno stereoselectivity in glycosylations. A method to achieve complete α -manno stereoselectivity with mannuronic acid donors equipped with 3-*O*-benzoyl group is also reported.

Introduction

Uronic acid residues are present in many natural polysaccharides and glycoconjugates found in bacteria, animals and plants. Common examples include pectin, heparin, chondroitin, and hyaluronan polysaccharides among others.¹ As such, many methods for the synthesis of glycosides of uronic acids have been developed.^{2–10} D-Mannuronic acid (ManA) residues (mannuronates) are also commonly found as components in a variety of bacterial glycans¹¹ and also in alginate, a linear (1 $\rightarrow$ 4)-linked co-polymer of β -ManA and its C-5 epimer, α -L-guluronic acid consisting of both homo- and alternating heteromeric regions.¹² Mannose-configured sugars have a strong propensity to form α -linkages, and uncontrolled glycosylations typically produce anomeric mixtures. Among methods developed for the synthesis of β -mannosides,¹³ Crich's method that relies on low reaction temperatures, powerful promoter systems, and the presence of a 4,6-*O*-benzylidene acetal protecting group is arguably the most effective.^{14–18} This method has successfully been used to obtain poly-mannuronates *via* sequential β -mannosylation followed by oxidation of the 6-OH group.^{19,20}

Initially, ManA donors were considered to be very unreactive owing to the C-5 electron-withdrawing group. More recently, their reactivity was found to be similar to that of the respective benzylated (armed) mannosyl donor.²¹ This discovery led to the development of effective and robust method-

ologies for the direct glycosylation with ManA donors. Subsequent studies conducted at Leiden showed that the C-5 carboxylate ester moiety has a stereodirecting role in glycosylations favoring β -mannosides.^{22–24} A very instrumental in advancing this chemistry was the development of a chemo- and regioselective oxidation method using TEMPO/BAIB reagent system.²⁵ The natural abundance, biomedical importance of mannuronates, and a notable improvement in chemical methods have stimulated a notable interest in synthesizing alginates and alginate-like glycan sequences in recent years.^{26–38}

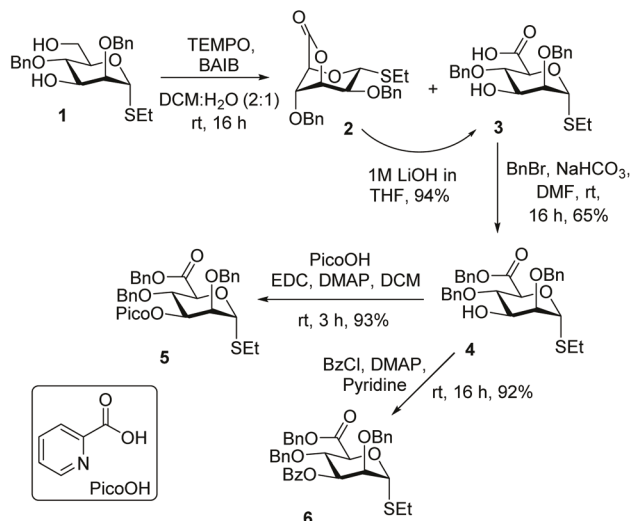
Results and discussion

Our group has introduced the H-bond-mediated Aglycone Delivery (HAD) method for stereocontrolled glycosylation.^{39–41} We and others have demonstrated that highly stereoselective β -mannosylation reactions could be conducted with glycosyl donors equipped with 3-*O*-picoloyl (Pico) group.^{42–44} Since this method does not rely on the 4,6-*O*-benzylidene protection, it was deemed suitable for the synthesis of ManA glycosides. Reported herein is the investigation of the HAD method and other stereodirecting factors in application to the synthesis of mannuronates. First, we prepared a set of suitable ManA donors including the key donor **5** equipped with the 3-Pico group. As depicted in Scheme 1, the synthesis was initiated from known diol **1**⁴⁵ that was obtained *via* a modified synthetic sequence detailed in the ESI.† When compound **1** was subjected to the TEMPO/BAIB oxidation,²⁵ lactone derivative **2** and the desired carboxylic acid derivative **3** were obtained in a ratio of 3.7 : 1. Upon separation of the products, the lactone ring in compound **2** was opened under basic conditions (LiOH) to obtain carboxylic acid **3** in 94% yield. Overall, com-

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Scheme 1 Synthesis of mannuronic acid donors **2**, **5** and **6**.

compound **3** was obtained from **1** in a combined yield of 77% yield. Mild benzylation with benzyl bromide in the presence of NaHCO_3 ⁴⁶ gave the esterified intermediate **4**. The latter was then picoloylated using standard conditions involving coupling with picolinic acid in the presence of EDC and DMAP.⁴² As a result, the desired 3-Pico ManA donor **5** was obtained in 93% yield. For comparison, we also obtained 3-O-benzoylated (3-Bz) donor **6**. This was accomplished by reaction of intermediate **4** with benzoyl chloride in the presence of DMAP in pyridine to afford 3-Bz ManA donor **6** in 92% yield. A portion of lactone **2** was also retained to be tested as a glycosyl donor for comparison.

To investigate whether the remote 3-Pico group in donor **5** would act as the hydrogen bond acceptor for the incoming nucleophile and hence lead to the preferential formation of β -ManA glycosides, we set up a series of glycosylations with standard glycosyl acceptors **7–10**⁴⁷ (Table 1). When donor **5** was reacted with the primary acceptor **7** in the presence of NIS/TfOH promoter system under regular concentration (50 mM of the donor) in 1,2-DCE, disaccharide **11** was obtained in 91% yield with high stereoselectivity ($\alpha/\beta = 1/12$, entry 1, Table 1). This exceeded our initial expectations because the HAD reactions give the highest stereoselectivity under ten-fold dilution conditions (5.0 mM of the donor). However, in this case, the high dilution did not seem to have any effect on the reaction, and disaccharide **11** was produced in a similar yield (88%) and stereoselectivity ($\alpha/\beta = 1/12$, entry 1). No difference in the reaction rates was noted either, both glycosylations were completed in 19 h.

In contrast, exclusive α -ManA stereoselectivity was achieved with mannuronic acid donor equipped with 3-O-benzoyl group. Thus, the glycosidation of 3-Bz donor **6** with acceptor **7** yielded the respective α -linked disaccharide **12** (entry 2). Practically the same outcome in terms of yields (92%) and stereoselectivities (α -only) was obtained in both regular concentration and high dilution experiments. Both experiments

Table 1 Glycosidation of donors **2**, **5** and **6** with glycosyl acceptors **7–10**

			Product (see Table)
		7: $\text{R}_2 = \text{R}_3 = \text{R}_4 = \text{Bn}$, $\text{R}_6 = \text{H}$ (6-OH) 8: $\text{R}_2 = \text{R}_3 = \text{R}_6 = \text{Bn}$, $\text{R}_4 = \text{H}$ (4-OH) 9: $\text{R}_2 = \text{R}_4 = \text{R}_6 = \text{Bn}$, $\text{R}_3 = \text{H}$ (3-OH) 10: $\text{R}_2 = \text{H}$, $\text{R}_3 = \text{R}_4 = \text{R}_6 = \text{Bn}$ (2-OH)	
Entry	Reactants (time)	Product: yield, stereoselectivity (concentration of the donor)	$J_{\text{C1}',\text{H1'}}$, $\delta_{\text{H3'}}$
1	5 + 7 (19 h)	 11: 91%, $\alpha/\beta = 1/12$ (50 mM) 88%, $\alpha/\beta = 1/12$ (5 mM)	157 Hz, 4.97 ppm
2	6 + 7 (20 min)	 12: 92%, $\alpha/\beta > 25/1$ (50 mM) 92%, $\alpha/\beta > 25/1$ (5 mM)	172 Hz, 5.52 ppm
3	2 + 7 (19 h)	 13: 57%, $\alpha/\beta = 1/25$ (50 mM)	161 Hz, 4.68 ppm
4	5 + 8 (19 h)	 14: 79%, $\alpha/\beta = 1/11$ (50 mM) 96%, $\alpha/\beta = 1/20$ (5 mM)	155 Hz, 4.95 ppm
5	6 + 8 (1.5 h)	 15: 85%, $\alpha/\beta > 25/1$ (50 mM) 90%, $\alpha/\beta > 25/1$ (5 mM)	170 Hz, 5.57 ppm
6	2 + 8 (19 h)	 16: 27%, $\alpha/\beta = 1/11$ (50 mM)	172 Hz, 4.63 ppm
7	5 + 9 (19 h)	 17: 74%, $\alpha/\beta = 1/1.3$ (50 mM) 67%, $\alpha/\beta = 1/1.6$ (5 mM)	162 Hz, 5.11 ppm

Table 1 (Contd.)

2, 5 or 6 donor acceptor $\xrightarrow[\text{MS 4 \AA, -30 } ^\circ\text{C} \rightarrow \text{rt}]{\text{NIS/TfOH, 1,2-DCE}}$ Product (see Table)			
7: R ₂ = R ₃ = R ₄ = Bn, R ₆ = H (6-OH) 8: R ₂ = R ₃ = R ₆ = Bn, R ₄ = H (4-OH) 9: R ₂ = R ₄ = R ₆ = Bn, R ₃ = H (3-OH) 10: R ₂ = H, R ₃ = R ₄ = R ₆ = Bn (2-OH)			
Entry	Reactants (time)	Product: yield, stereoselectivity (concentration of the donor)	$J_{\text{C1',H1'}}$, δ H3'
8	6 + 9 (30 min)	 18: 90%, $\alpha/\beta > 25/1$ (50 mM) 83%, $\alpha/\beta > 25/1$ (5 mM)	171 Hz, 5.59 ppm
9	2 + 9 (19 h)	 19: 26%, $\alpha/\beta = 1/2.8$ (50 mM)	160 Hz, 4.68 ppm
10	5 + 10 (20 h)	 20: 88%, $\alpha/\beta < 1/25$ (50 mM) 92%, $\alpha/\beta < 1/25$ (5 mM)	160 Hz, 5.03 ppm
11	6 + 10 (40 min)	 21: 92%, $\alpha/\beta > 25/1$ (50 mM) 91%, $\alpha/\beta > 25/1$ (5 mM)	173 Hz, 5.63 ppm
12	2 + 10 (20 h)	 22: 44%, $\alpha/\beta = 1/4.0$ (50 mM)	160 Hz, 4.59 ppm

were relatively swift and completed in 20 min. The lactonized donor **2** provided excellent β -stereoselectivity in reaction with glycosyl acceptor **7**. The corresponding disaccharide **13** was obtained in 57% yield ($\alpha/\beta = 1/25$, entry 3).

As previously proposed by Codee, van der Marel and co-workers,^{21,23} the intermediate ManA oxacarbenium ion **A** adopts the predominantly axial half-chair $^3\text{H}_4$ conformation depicted in Fig. 1. The axial orientation of the 3-Pico group in donor **5** will favor the HAD pathway as shown for intermediate **B** leading to the formation of the β -linked product. In case of 3-Bz donor **6**, the excellent α -stereoselectivity can be rationalized by the occurrence of a participation of the remote benzoyl group at C-3. This pathway was previously proposed by Crich⁴⁸ for regular mannosides and by us for mannosamine glyco-

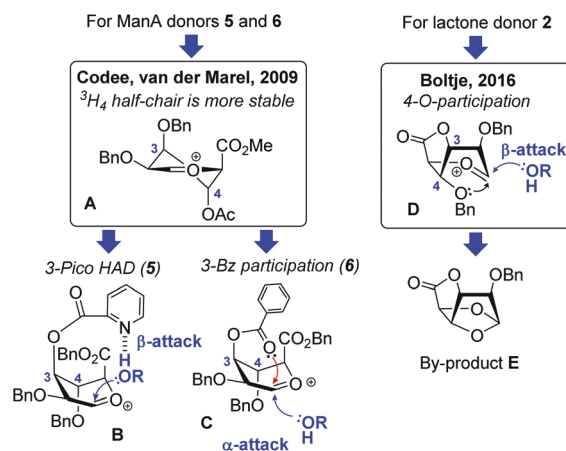


Fig. 1 Mechanistic rationale for stereoselectivity obtained with lactone donor **2** and ManA donors **5** and **6**.

sides,⁴³ as well as by Nifantiev^{49–52} and Kim⁵³ for other sugar series. The axial orientation of the 3-Bz group in the $^3\text{H}_4$ oxacarbenium ion intermediate **C** will favor the participation pathway as shown in Fig. 1. The lactonized donor **2** provided excellent β -stereoselectivity, which could be due to the occurrence of a participation of the remote oxygen at C-4 via intermediate **D** (Fig. 1), as previously proposed by Boltje and co-workers.^{54,55}

To confirm the stereochemical assignment of the products, we conducted a series of NMR experiments. The assignment of the anomeric configuration in sugars of the manno series relies on the measurement of the $J_{\text{C1',H1'}}$ coupling constant. The observed values of 157 and 161 Hz for β -ManA glycosides (entries 1 and 3) were in agreement with those reported for conventional β -mannosides (~ 160 Hz).⁵⁶ The $J_{\text{C1',H1'}}$ coupling constant of 172 Hz measured for α -ManA glycoside (entry 2) was in line with the previously reported values of 170 Hz or greater.⁵⁶ Similarly to our previous studies with mannosamine glycoside,⁴³ we have also noticed that the chemical shift for H-3' of the α -anomer is always shifted downfield in comparison to that of the β -anomer by $\Delta\delta = 0.5\text{--}0.6$ ppm. Thus, chemical shift for H-3' in β -linked disaccharide **11** was 4.97 ppm, whereas the corresponding signal of disaccharide **12** was 5.52 ppm (entries 1 and 2, Table 1). No such definitive trend was noticed for the lactonized products.

We then continued our studies by glycosylation of a series of secondary glycosyl acceptors. When glycosylation of 4-OH acceptor **8** was performed with 3-Pico donor **5** in the presence of NIS/TfOH under regular concentration (50 mM of the donor) in DCE, disaccharide **14** was obtained in 79% yield with commendable β -manno stereoselectivity ($\alpha/\beta = 1/11$, entry 4). The ten-fold dilution experiment (5 mM of donor **5**) produced disaccharide **14** in 96% yield with improved β -manno stereoselectivity ($\alpha/\beta = 1/20$, entry 4). It required 19 h for both glycosylations to complete. When glycosylations of acceptor **8** were performed with 3-Bz donor **6**, disaccharide **15** was obtained with exclusive α -stereoselectivity in 1.5 h. High yields

(85–90%) and complete α -manno stereoselectivity was achieved for both regular concentration and high dilution experiments (entry 5). Glycosidation of lactone **2** with acceptor **8** yielded disaccharide **16** in 27% yield ($\alpha/\beta = 1/11$, entry 6) along with the formation of side product **E** (Fig. 1). The formation of this side product, also observed by Boltje and co-workers,⁵⁴ supports their hypothesis of the reaction pathway proceeding *via* the participation of O-4.

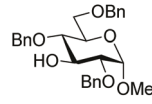
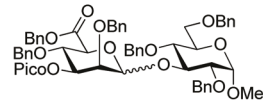
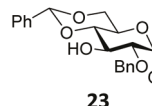
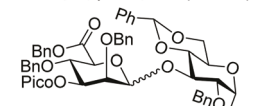
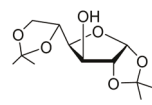
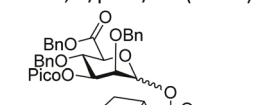
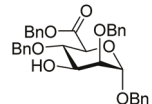
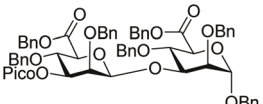
When glycosylation of secondary 3-OH acceptor **9** was performed with donor **5** under regular concentration (50 mM of the donor) in DCE, disaccharide **17** was obtained in 74% yield with a somewhat unexpected poor stereoselectivity ($\alpha/\beta = 1/1.3$, entry 7). Also, the ten-fold dilution experiment (5 mM of the donor) produced disaccharide **17** in 67% yield with poor stereoselectivity ($\alpha/\beta = 1/1.6$, entry 7). It took 19 h for both glycosylations to complete. When glycosylation of acceptor **9** was performed with 3-Bz donor **6**, disaccharide **18** was obtained with exclusive α -stereoselectivity in 30 min. Good yields (83–90%) and complete α -manno stereoselectivity were achieved for both regular concentration and high dilution conditions (entry 8). Glycosidation of lactone **2** with acceptor **9** yielded disaccharide **19** in 26% yield with preferential, albeit unimpressive β -stereoselectivity ($\alpha/\beta = 1/2.8$, entry 9).

When glycosylation of 2-OH acceptor **10** was performed with 3-Pico donor **5** under regular concentration (50 mM of the donor) in DCE, disaccharide **20** was obtained in 88% yield with practically complete β -manno stereoselectivity ($\alpha/\beta < 1/25$, entry 10). The ten-fold dilution experiment (5 mM of donor **5**) produced disaccharide **20** in 92% yield with the same stereoselectivity. It required 20 h for both glycosylations to complete. When glycosylations of acceptor **10** were performed with 3-Bz donor **6**, disaccharide **21** was obtained with exclusive α -stereoselectivity in 40 min. High yields (91–92%) were achieved for both regular and low concentration experiments (entry 11). Glycosidation of lactone **2** with acceptor **10** yielded disaccharide **22** in 44% yield ($\alpha/\beta = 1/4.0$, entry 12).

Being generally satisfied with excellent results achieved for all glycosidations of 3-Pico ManA donor **5** except that with glycosyl acceptor **9**, which gave practically no stereoselectivity (entry 1, Table 2), we endeavored on studying other 3-OH acceptors **23–25**. When glycosylation of 4,6-O-benzylidene-protected acceptor **23**^{57,58} was performed under regular concentration (50 mM of donor **5**) in DCE, disaccharide **26** was obtained in 62% yield with similar β -manno stereoselectivity ($\alpha/\beta = 1/1.3$, entry 2). The ten-fold dilution experiment (5 mM of donor **5**) produced disaccharide **26** in 56% yield with only marginally improved stereoselectivity ($\alpha/\beta = 1/1.9$, entry 2). When glycosylation of diacetone glucose acceptor **24** was performed under regular concentration (50 mM of donor **5**) in DCE, disaccharide **27** was obtained in 59% yield with enhanced, albeit unimpressive β -manno stereoselectivity ($\alpha/\beta = 1/3.4$, entry 3). The ten-fold dilution experiment (5 mM of donor **5**) produced disaccharide **27** in 65% yield ($\alpha/\beta = 1/5.0$, entry 3).

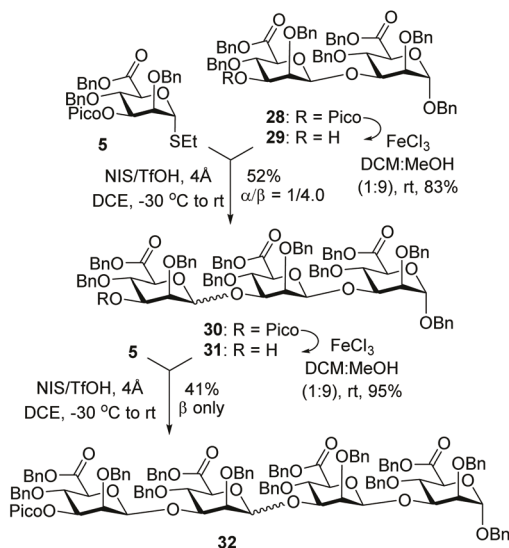
Still puzzled by this poor reaction outcome with various 3-OH glucosyl acceptors, both in terms of yields and stereose-

Table 2 Glycosidation of 3-Pico donor **5** with various 3-OH glycosyl acceptors **9** and **23–25**

Donor 5 + Acceptor (see Table)		NIS/TfOH 1,2-DCE MS 4 Å -30 °C → rt	Product (see Table)
Entry	Acceptor (time)	Product: yield, stereoselectivity (concentration of the donor)	
1	 9 (19 h)	 17 : 74%, $\alpha/\beta = 1/1.3$ (50 mM) 67%, $\alpha/\beta = 1/1.6$ (5 mM)	
2	 23 (19 h)	 26 : 62%, $\alpha/\beta = 1/1.3$ (50 mM) 56%, $\alpha/\beta = 1/1.9$ (5 mM)	
3	 24 (19 h)	 27 : 59%, $\alpha/\beta = 1/3.4$ (50 mM) 65%, $\alpha/\beta = 1/5.0$ (5 mM)	
4	 25 (19 h)	 28 : 83%, $\alpha/\beta = 1/18$ (5 mM)	

lectivities, we assumed that this is due to a donor-acceptor mismatch.⁵⁹ To verify this hypothesis, we synthesized 3-OH mannosyl acceptor **25** (see the ESI for details).† To our delight, glycosylation of mannosyl acceptor **25** with 3-Pico donor **5** performed under ten-fold dilution conditions (5 mM of donor **5**) produced disaccharide **28** in 83% yield with excellent β -manno stereoselectivity ($\alpha/\beta = 1/18$, entry 4). The $J_{C1',H1'}$ coupling constant of 159 Hz confirmed the β -manno configuration achieved in this reaction. With success in obtaining the Man α -(1 → 3) ManA linkage, we extended this finding to the iterative synthesis of a glycan containing β -(1 → 3)-linked ManA residues. It is noteworthy that while many efforts have been made to synthesize 1 → 4 linked ManA glycans found in alginate (*vide supra*), the synthesis of 1 → 3 linked oligomers has received a very scarce attention. Previous known syntheses were achieved by trityl-cyanoethylidene polycondensation by Kochetkov⁶⁰ and automated solution phase synthesis by Pohl.³¹

To achieve the iterative oligosaccharide assembly, pure β -anomer of disaccharide **28** separated chromatographically was taken forward, and the 3-Pico substituent in **28** was chemoselectively removed with FeCl₃ in DCM/MeOH to afford



Scheme 2 Application of 3-Pico donor **5** in the synthesis of ManA tetrasaccharide **32**.

compound **29** as depicted in Scheme 2. Our recent study showed that the Pico group can be removed in a catalytic manner using 30 mol% of iron(III) chloride or copper(II) acetate.⁶¹ In our experience, the reactions performed with Cu(OAc)₂ are generally faster, but in general FeCl₃-catalyzed reactions provide better yields. Hence, the latter reaction conditions have been used in this study. The resulting disaccharide acceptor **29** was subjected to glycosylation with ManA donor **5** to afford trisaccharide **30** in a good yield of 52% albeit incomplete stereoselectivity. Trisaccharide **30** ($\alpha/\beta = 1/4.0$) was then subjected to the Pico group removal using FeCl₃ in DCM/MeOH to afford trisaccharide acceptor **31** in 95% yield. The latter was subjected to final glycosylation with ManA donor **5** to obtain tetrasaccharide **32** in 41% yield. The complete β -manno stereoselectivity was achieved in this step.

Conclusions

In conclusion, a new practical method for the stereoselective synthesis of both α - and β -glycosides of mannuronic acid is reported. The presence of the 3-Pico group on the ManA donor can provide high or complete stereocontrol for β -mannosylation *via* the HAD pathway. The method was utilized for the synthesis of a tetrasaccharide containing ManA residues linked *via* β -(1 $\rightarrow$ 3) linkages. A mismatch between ManA donor and 3-OH glucosyl acceptors that resulted in poor stereoselectivities and yields was also noticed. In contrast, exclusive α -ManA stereoselectivity was achieved in all glycosylations with the mannuronic acid donor equipped with 3-O-benzoyl group. This complete stereoselectivity was rationalized by the occurrence of the remote participation of the 3-Bz substituent. Also investigated was the 6,3-lactonized donor that

was generally β -ManA stereoselective, but many reactions gave low yields due to the propensity to form the 1,4-cyclized side product. Further investigation of the mechanisms and the kinetic profile of these reactions is currently underway in our laboratory.

Experimental

General

Column chromatography was performed on silica gel 60 (70–230 mesh), reactions were monitored by TLC on Kieselgel 60 F254. The compounds were detected by examination under UV light and by charring with 10% sulfuric acid in methanol. Solvents were removed under reduced pressure at <40 °C. CH₂Cl₂ and ClCH₂CH₂Cl (1,2-DCE) were distilled from CaH₂ directly prior to application. Anhydrous DMF was used as is. Molecular sieves (3 Å or 4 Å), used for reactions, were crushed, and activated *in vacuo* at 390 °C during 8 h in the first instance and then for 2–3 h at 390 °C directly prior to application. Optical rotations were measured at 'Jasco P-1020' polarimeter. Unless noted otherwise, ¹H-NMR spectra were recorded in CDCl₃ at 300 or 600 MHz, ¹³C-NMR spectra were recorded in CDCl₃ at 75 or 151 MHz. Two-dimensional heteronuclear *J*-resolved spectra (HETERO2D)⁵⁶ were recorded in CDCl₃ at 600 MHz.

Ethyl 2,4-di-O-benzyl-1-thio- α -D-mannopyranosidurono-6,3-lactone (2). (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl (TEMPO, 100 mg, 0.636 mmol) and bis(acetoxy)iodobenzene (BAIB, 2.56 g, 7.94 mmol) were added to a mixture of ethyl 2,4-di-O-benzyl-1-thio- α -D-mannopyranoside⁴⁵ (**1**, 1.29 g, 3.18 mmol) in CH₂Cl₂/H₂O (30 mL, 2/1, v/v), and the resulting mixture was stirred for 16 h at rt. The reaction was quenched with aq. Na₂S₂O₃ (~3 mL) and the volatiles were removed under reduced pressure. The residue was diluted with EtOAc (~30 mL) and washed with water (2 $\times$ 10 mL). The aqueous layer was separated and extracted with EtOAc (2 $\times$ 30 mL). The organic extracts were combined, dried with Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (CH₃OH–CH₂Cl₂ gradient elution) to give lactone **2** (0.81 g, 2.02 mmol) and acid **3** (0.23 g, 0.55 mmol). Analytical data for **2**: *R*_f = 0.90 (CH₃OH/CH₂Cl₂, 5/95, v/v), *R*_f = 0.65 (ethyl acetate/toluene, 1/4, v/v); [α]_D²² –6.2 (*c* = 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ 7.38–7.29 (m, 10H, aromatic), 4.72 (d, 1H, *J*_{1,2} = 8.9 Hz, H-1), 4.69 (dd, 2H, ²*J* = 11.7 Hz, CH₂Ph), 4.67–4.58 (m, 2H, *J*_{3,4} = 5.9 Hz, H-3, CHPh), 4.47 (d, 1H, ²*J* = 11.7 Hz, CHPh), 4.25 (br d, 1H, H-5), 4.01 (dd, 1H, *J*_{4,5} = 3.0 Hz, H-4), 3.87 (dd, 1H, *J*_{2,3} = 1.5 Hz, H-2), 2.73 (m, 2H, SCH₂CH₃), 1.29 (t, 3H, *J* = 7.5 Hz, SCH₂CH₃) ppm; ¹³C NMR (75 MHz, CDCl₃): δ 170.1, 137.5, 136.4, 128.9 (x2), 128.7, 128.6 (x2), 128.2 (x5), 82.4, 78.1, 75.1, 74.0, 73.5, 72.0, 71.9, 25.2, 15.2 ppm; HR FAB MS [*M* + Na]⁺ calcd for C₂₂H₂₄O₅SN⁺ 423.1242; found 423.1215.

Ethyl 2,4-di-O-benzyl-1-thio- α -D-mannopyranosiduronic acid (3). A 1 M aq. solution of LiOH (5.0 mL) was added to a solution of lactone **2** (0.81 g, 2.02 mmol) in THF (5.0 mL), and the

resulting mixture was stirred at rt for 4 h. After that, the reaction mixture was acidified with 1 N aq. HCl to pH ~3 and the volatiles were removed under reduced pressure. The residue was diluted with EtOAc (~20 mL) and washed with water (10 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL). The organic extracts were combined, dried with Na₂SO₄, concentrated under reduced pressure, and dried *in vacuo* for 2 h to give the acid **3** as a colorless syrup in 94% yield (0.80 g, 1.91 mmol), which corresponds to a combined yield of 77% from compound **1**. Analytical data for **3**: *R*_f = 0.35 (CH₃OH/CH₂Cl₂, 5/95, v/v), *R*_f = 0.15 (ethyl acetate/toluene, 1/4, v/v); [α]_D²² +68.9 (*c* = 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.46–7.33 (m, 10H, aromatic), 5.54 (d, 1H, *J*_{1,2} = 3.5 Hz, H-1), 4.78 (dd, 2H, ²*J* = 11.0 Hz, CH₂Ph), 4.66 (dd, 2H, ²*J* = 11.5 Hz, CH₂Ph), 4.58 (dd, 1H, *J*_{4,5} = 7.2 Hz, H-5), 4.08–3.98 (m, 2H, H-3, 4), 3.86 (dd, 1H, *J*_{2,3} = 3.3 Hz, H-2), 2.81–2.66 (m, 2H, SCH₂CH₃), 1.34 (t, 3H, *J* = 7.4 Hz, SCH₂CH₃) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 173.6, 137.6, 137.3, 128.8 (x2), 128.6 (x2), 128.4, 128.3 (x2), 128.2 (x2), 128.1, 80.4, 77.8, 77.5, 74.2, 72.8, 70.8, 70.7, 25.3, 15.1 ppm; HR FAB MS [*M* + Na]⁺ calcd for C₂₂H₂₆O₆Na⁺ 441.1348; found 441.1375.

Benzyl (ethyl 2,4-di-O-benzyl-1-thio- α -D-mannopyranosid)uronate (4). Benzyl bromide (5.4 mL, 45.0 mmol) and NaHCO₃ (2.27 g, 27.0 mmol) were added to a solution of **3** (1.88 g, 4.50 mmol) in *N,N*-dimethylformamide (DMF, 15 mL), and the resulting mixture was stirred for 16 h at rt. The reaction mixture was diluted with EtOAc (100 mL), washed with water (2 × 15 mL), and the aqueous layer was extracted with EtOAc (80 mL). The organic extracts were combined, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate–hexane gradient elution) to give the title compound as a colorless syrup in 65% yield (1.48 g, 2.91 mmol). Analytical data for **4**: *R*_f = 0.65 (ethyl acetate/hexane, 2/3, v/v); [α]_D²² +53.7 (*c* = 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.37–7.23 (m, 15H, aromatic), 5.46 (d, 1H, *J*_{1,2} = 4.1 Hz, H-1), 5.18 (s, 2H, CH₂Ph), 4.77 (d, 1H, ²*J* = 11.6 Hz, CHPh), 4.68 (d, 1H, ²*J* = 11.2 Hz, CHPh), 4.58–4.52 (m, 3H, H-5, 2 × CHPh), 4.05–3.94 (m, 2H, H-3, 4), 3.79 (dd, 1H, *J*_{2,3} = 3.6 Hz, H-2), 2.65 (m, 2H, SCH₂CH₃), 2.40 (d, 1H, *J* = 6.5 Hz, OH), 1.26 (t, 3H, *J* = 7.4 Hz, SCH₂CH₃) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 169.5, 138.0, 137.5, 135.4, 128.8 (x2), 128.7 (x2), 128.5 (x5), 128.3, 128.2 (x2), 128.0 (x2), 127.9, 80.6, 78.0, 77.8, 74.1, 72.7, 71.7, 70.7, 67.2, 25.3, 15.1 ppm; HR FAB MS [*M* + Na]⁺ calcd for C₂₉H₃₂O₆Na⁺ 531.1817; found 531.1848.

Benzyl (ethyl 2,4-di-O-benzyl-3-O-picoloyl-1-thio- α -D-mannopyranosid)uronate (5). Picolinic acid (0.63 g, 5.09 mmol), EDC (0.98 g, 5.09 mmol) and DMAP (83 mg, 0.68 mmol) were added to a solution of compound **4** (1.72 g, 3.39 mmol) in dry CH₂Cl₂ (50 mL), and the resulting mixture was stirred under argon for 3 h at rt. After that, the reaction mixture was diluted with CH₂Cl₂ (~50 mL) and washed with water (15 mL), sat. aq. NaHCO₃ (15 mL), and water (2 × 15 mL). The organic phase was separated, dried with Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate–hexane gradient elution)

to give the title compound as a colorless syrup in 93% yield (1.94 g, 3.16 mmol). Analytical data for **5**: *R*_f = 0.50 (ethyl acetate/hexane, 1/1, v/v); [α]_D²² +30.6 (*c* = 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 8.78 (m, 1H, aromatic), 7.98 (m, 1H, aromatic), 7.80 (m, 1H, aromatic), 7.48 (m, 1H, aromatic), 7.32–7.14 (m, 15H, aromatic), 5.56–5.49 (m, 2H, *J*_{1,2} = 3.2, *J*_{3,4} = 7.2 Hz, H-1, 3), 5.11 (dd, 2H, ²*J* = 12.2 Hz, CH₂Ph), 4.68 (m, 3H, H-5, 2 × CHPh), 4.59 (m, 2H, 2 × CHPh), 4.44 (dd, 1H, H-4), 4.03 (dd, 1H, *J*_{2,3} = 4.6 Hz, H-2), 2.69 (m, 2H, SCH₂CH₃), 1.29 (t, 3H, *J* = 7.4 Hz, SCH₂CH₃) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 169.1, 163.9, 150.2, 147.5, 137.7, 137.4, 137.1, 135.1, 128.7 (x3), 128.4 (x5), 128.3 (x2), 128.0, 127.9 (x2), 127.8, 127.2, 125.5, 81.3, 77.4, 75.2, 75.0, 74.1, 72.9, 72.5, 72.4, 67.4, 25.3, 15.0 ppm; HR FAB MS [*M* + Na]⁺ calcd for C₃₅H₃₅NO₇Na⁺ 636.2032; found 636.2043.

Benzyl (ethyl 3-O-benzoyl-2,4-di-O-benzyl-1-thio- α -D-mannopyranosid)uronate (6). Benzoyl chloride (0.43 mL, 3.68 mmol) and DMAP (45 mg, 0.37 mmol) were added to a solution of compound **4** (0.94 g, 1.84 mmol) in pyridine (20 mL), and the resulting mixture was stirred under argon for 2 h at rt. After that, the reaction was quenched with MeOH (~5 mL), the volatiles were removed under reduced pressure, and the residue was co-evaporated with toluene. The resulting residue was diluted with CH₂Cl₂ (~30 mL) and washed with water (10 mL), 1 N aq. HCl (10 mL), and water (2 × 10 mL). The organic phase was separated, dried with Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate–hexane gradient elution) to give the title compound as a colorless syrup in 92% yield (1.04 g, 1.70 mmol). Analytical data for **6**: *R*_f = 0.70 (ethyl acetate/hexane, 2/3, v/v); [α]_D²² +24.4 (*c* = 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 8.02–7.99 (m, 2H, aromatic), 7.61–7.56 (m, 1H, aromatic), 7.47–7.42 (m, 2H, aromatic), 7.29–7.14 (m, 15H, aromatic), 5.52 (d, 1H, *J*_{1,2} = 4.9 Hz, H-1), 5.49 (dd, 1H, *J*_{3,4} = 7.4 Hz, H-3), 5.04 (dd, 2H, ²*J* = 12.3 Hz, CH₂Ph), 4.62 (m, 5H, H-5, 2 × CH₂Ph), 4.41–4.37 (dd, 1H, H-4), 4.01 (dd, 1H, *J*_{2,3} = 3.2 Hz, H-2), 2.82–2.62 (m, 2H, SCH₂CH₃), 1.31 (t, 3H, *J* = 7.4 Hz, SCH₂CH₃) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 169.0, 165.4, 137.4 (x2), 134.9, 133.4, 129.8 (x2), 129.5, 128.5 (x4), 128.4, 128.3 (x6), 128.0 (x2), 127.8 (x4), 81.1, 75.2, 75.1, 73.9, 72.4 (x2), 71.8, 67.2, 25.1, 14.9 ppm; HR FAB MS [*M* + Na]⁺ calcd for C₃₆H₃₆O₇Na⁺ 635.2079; found 635.2089.

Synthesis of disaccharides 11–22, 26 and 27

A general procedure for glycosylation. A mixture of a glycosyl donor (0.06 mmol), glycosyl acceptor (0.05 mmol), and freshly activated molecular sieves (4 Å, 100 mg for 50 mM or 200 mg for 5.0 mM reactions) in 1,2-DCE (1.0 mL for 50 mM or 10 mL for 5.0 mM reactions) was stirred under argon for 1 h at rt. The mixture was then cooled to –30 °C, *N*-iodosuccinimide (NIS, 0.12 mmol) and trifluoromethanesulfonic acid (TfOH, 2.0 μ L, 0.02 mmol) were added, and the external cooling was removed, the resulting mixture was allowed to warm to ambient temperature, and stirred at rt for the time specified in tables. After that, the solids were filtered off and washed successively with CH₂Cl₂. The combined filtrate (~30–40 mL) was

washed with water (10 mL), 10% sodium thiosulfate ($\text{Na}_2\text{S}_2\text{O}_3$, 10 mL), and water (2×10 mL). The organic phase was separated, dried with Na_2SO_4 , and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate–hexane or ethyl acetate–toluene gradient elution) to afford respective disaccharide derivatives. Anomeric ratios (or anomeric purity) were determined by comparison of the integral intensities of the relevant signals in the ^1H NMR spectra.

Methyl 6-O-(benzyl 2,4-di-O-benzyl-3-O-picoloyl- α/β -D-mannopyranosyluronate)-2,3,4-tri-O-benzyl- α -D-glucopyranoside (11). The title compound was obtained as a white amorphous solid from glycosyl donor 5 and acceptor 7⁴⁷ in 91% yield ($\alpha/\beta = 1/12$, 50 mM) or 88% yield ($\alpha/\beta = 1/12$, 5.0 mM) under regular and high dilution reaction conditions, respectively. Analytical data for 11: $R_f = 0.45$ (ethyl acetate/toluene, 3/7, v/v); ^1H NMR (300 MHz, CDCl_3): δ 8.75–8.72 (m, 1H, aromatic), 7.87 (m, 1H, aromatic), 7.75–7.69 (m, 1H, aromatic), 7.45–7.40 (m, 1H, aromatic), 7.28–6.97 (m, 30H, aromatic), 5.12 (dd, 2H, $^2J = 12.0$ Hz, CH_2Ph), 4.99–4.92 (m, 2H, $J_{3',4'} = 9.6$ Hz, H-3', CHPh), 4.78 (br s, 1H, CHPh), 4.74 (m, 2H, $2 \times \text{CHPh}$), 4.60–4.43 (m, 7H, $J_{1,2} = 3.5$ Hz, H-1, $6 \times \text{CHPh}$), 4.38 (dd, 1H, $J_{4',5'} = 9.4$ Hz, H-4'), 4.17 (s, 1H, H-1'), 4.07–4.03 (m, 1H, $J_{6a,6b} = 10.0$ Hz, H-6a), 3.93 (dd, 1H, H-3), 3.84 (m, 2H, $J_{2',3'} = 3.2$ Hz, H-2', 5'), 3.72–3.67 (m, 1H, $J_{5,6a} = 1.5$, $J_{5,6b} = 5.3$ Hz, H-5), 3.44–3.40 (m, 1H, $J_{2,3} = 9.7$ Hz, H-2), 3.40–3.36 (m, 1H, H-4), 3.34–3.30 (m, 1H, H-6b), 3.25 (s, 3H, OCH_3) ppm; ^{13}C NMR (151 MHz, CDCl_3): δ 167.8, 164.0, 150.2, 147.5, 138.8, 138.2, 138.0, 137.9, 137.0, 135.3, 128.8 (x2), 128.7 (x4), 128.6 (x2), 128.5 (x5), 128.4 (x2), 128.3 (x5), 128.2 (x2), 128.1 (x3), 127.8 (x4), 127.7, 127.6, 127.1, 125.4, 101.9 ($^1J_{\text{C}1',\text{H}1'} = 157.0$ Hz, C-1'), 97.8 ($^1J_{\text{C}1,\text{H}1} = 171.0$ Hz, C-1), 82.3, 80.0, 77.4, 76.2, 75.9, 75.2, 75.1, 74.9, 74.4, 74.3, 74.1, 73.5, 69.9, 68.8, 67.5, 55.2 ppm; HR-FAB MS $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{61}\text{H}_{61}\text{NO}_{13}\text{Na}^+$ 1038.4041; found 1038.4054.

Methyl 6-O-(benzyl 3-O-benzoyl-2,4-di-O-benzyl- α -D-mannopyranosyluronate)-2,3,4-tri-O-benzyl- α -D-glucopyranoside (12). The title compound was obtained as a colorless amorphous solid from glycosyl donor 6 and acceptor 7⁴⁷ in 92% yield ($\alpha/\beta > 25/1$, 50 mM) and 92% ($\alpha/\beta > 25/1$, 5.0 mM) under regular and high dilution reaction conditions, respectively. Analytical data for 12: $R_f = 0.60$ (ethyl acetate/hexane, 2/3, v/v); ^1H NMR (300 MHz, CDCl_3): δ 8.01 (m, 2H, aromatic), 7.58 (m, 1H, aromatic), 7.44 (m, 2H, aromatic), 7.34–7.05 (m, 30H, aromatic), 5.52 (dd, 1H, $J_{3',4'} = 7.8$ Hz, H-3'), 5.14 (d, 1H, $J_{1',2'} = 3.0$ Hz, H-1'), 5.06 (dd, 2H, $^2J = 12.3$ Hz, CH_2Ph), 4.90 (dd, 2H, $^2J = 10.9$ Hz, CH_2Ph), 4.75 (dd, 2H, $^2J = 10.9$ Hz, CH_2Ph), 4.67 (dd, 2H, $^2J = 12.1$ Hz, CH_2Ph), 4.62 (m, 2H, CH_2Ph), 4.54 (m, 3H, H-1, CH_2Ph), 4.40–4.32 (m, 2H, H-4', 5'), 4.03–3.94 (m, 3H, $J_{2',3'} = 3.1$ Hz, H-2', 3, 6a), 3.76 (m, 2H, H-4, 6b), 3.54–3.46 (m, 2H, H-2, 5), 3.36 (s, 3H, OCH_3) ppm; ^{13}C NMR (151 MHz, CDCl_3): δ 169.3, 165.5, 138.9, 138.3 (x2), 137.9, 137.7, 135.2, 133.4, 129.9 (x2), 129.8, 128.6 (x4), 128.5 (x6), 128.4 (x5), 128.3 (x2), 128.2 (x2), 128.1 (x2), 128.0 (x3), 127.9 (x2), 127.8 (x5), 127.7, 127.6, 98.9 ($^1J_{\text{C}1',\text{H}1'} = 172.0$ Hz, C-1'), 98.0 ($^1J_{\text{C}1,\text{H}1} = 173.1$ Hz, C-1), 82.2, 80.2, 77.8, 75.8, 75.2, 75.1, 75.0, 74.4, 73.5, 73.1, 72.1,

70.1, 67.2, 67.1, 55.3 ppm; HR-FAB MS $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{62}\text{H}_{62}\text{O}_{13}\text{Na}^+$ 1037.4088; found 1037.4099.

Methyl 6-O-(2,4-di-O-benzyl- α/β -D-mannopyranosid-uronate-6,3-lactone)-2,3,4-tri-O-benzyl- α -D-glucopyranoside (13). The title compound was obtained as a colorless amorphous solid from glycosyl donor 2 and acceptor 7⁴⁷ in 57% yield ($\alpha/\beta > 1/25$, 50 mM). Analytical data for 13: $R_f = 0.60$ (ethyl acetate/toluene, 1/4, v/v); ^1H NMR (300 MHz, CDCl_3): δ 7.36–7.26 (m, 25H, aromatic), 5.22 (d, 1H, $J_{1',2'} = 5.0$ Hz, H-1'), 4.95 (d, 1H, $^2J = 10.9$ Hz, CHPh), 4.81 (m, 3H, $3 \times \text{CHPh}$), 4.58 (m, 8H, H-1, 3', $6 \times \text{CHPh}$), 4.13 (dd, 1H, H-2'), 4.06–3.95 (m, 4H, H-3, 4', 5', 6a), 3.85 (m, 1H, $J_{5,6b} = 9.4$ Hz, H-5), 3.62–3.51 (m, 2H, H-2, 4), 3.36 (dd, 1H, H-6b), 3.30 (s, 3H, OCH_3) ppm; ^{13}C NMR (75 MHz, CDCl_3): δ 171.4, 138.9, 138.4 (x2), 137.4, 136.5, 128.9 (x2), 128.7, 128.6 (x3), 128.5 (x6), 128.2 (x2), 128.1 (x6), 128.0 (x2), 127.8 (x2), 127.7, 99.4 ($^1J_{\text{C}1',\text{H}1'} = 160.6$ Hz, C-1'), 97.9 ($^1J_{\text{C}1,\text{H}1} = 176.1$ Hz, C-1), 82.0, 80.1, 78.3, 77.4, 76.4, 75.8, 74.7, 73.5, 72.2, 71.3, 70.9, 70.2, 68.2, 67.8, 55.3 ppm; HR-FAB MS $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{48}\text{H}_{50}\text{O}_{11}\text{Na}^+$ 825.3251; found 825.3267.

Methyl 4-O-(benzyl 2,4-di-O-benzyl-3-O-picoloyl- α/β -D-mannopyranosyluronate)-2,3,6-tri-O-benzyl- α -D-glucopyranoside (14). The title compound was obtained as a colorless amorphous solid from glycosyl donor 5 and acceptor 8⁴⁷ in 79% yield ($\alpha/\beta = 1/11$, 50 mM) or 96% yield ($\alpha/\beta = 1/20$, 5.0 mM) under regular and high dilution reaction conditions, respectively. Analytical data for 14: $R_f = 0.35$ (ethyl acetate/toluene, 3/7, v/v); ^1H NMR (300 MHz, CDCl_3): δ 8.80 (m, 1H, aromatic), 7.90 (m, 1H, aromatic), 7.77 (m, 1H, aromatic), 7.48 (m, 1H, aromatic), 7.45–7.38 (m, 2H, aromatic), 7.33–7.17 (m, 20H, aromatic), 7.15–7.00 (m, 8H, aromatic), 5.16 (d, 1H, $^2J = 10.8$ Hz, CHPh), 5.01 (s, 2H, CH_2Ph), 4.95 (dd, 1H, $J_{3',4'} = 9.8$ Hz, H-3'), 4.79–4.40 (m, 12H, $J_{1,2} = 3.7$, $J_{4',5'} = 9.5$ Hz, H-1, 1', 4', $9 \times \text{CHPh}$), 3.94 (m, 3H, $J_{2',3'} = 3.1$ Hz, H-2', 3, 4), 3.76 (d, 1H, H-5'), 3.66 (m, 1H, H-5), 3.60 (br s, 2H, H-6a, 6b), 3.52 (dd, 1H, $J_{2,3} = 9.2$ Hz, H-2), 3.38 (s, 3H, OCH_3) ppm; ^{13}C NMR (151 MHz, CDCl_3): δ 167.9, 164.0, 150.3, 147.5, 139.5, 138.5, 138.2, 138.0, 137.6, 137.0, 135.3, 128.8 (x2), 128.6 (x4), 128.5 (x2), 128.4, 128.2 (x11), 128.1 (x4), 127.9, 127.7 (x2), 127.6, 127.5, 127.2, 127.1, 125.3, 101.0 ($^1J_{\text{C}1',\text{H}1'} = 155.0$ Hz, C-1'), 98.5 ($^1J_{\text{C}1,\text{H}1} = 171.0$ Hz, C-1), 80.4, 79.3, 77.7, 76.4, 75.6, 75.5, 75.0, 74.9 (x2), 74.5, 73.8, 73.7, 69.7, 68.5, 67.2, 55.5 ppm; HR-FAB MS $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{61}\text{H}_{61}\text{NO}_{13}\text{Na}^+$ 1038.4041; found 1038.4057.

Methyl 4-O-(benzyl 3-O-benzoyl-2,4-di-O-benzyl- α -D-mannopyranosyluronate)-2,3,6-tri-O-benzyl- α -D-glucopyranoside (15). The title compound was obtained as a colorless amorphous solid from glycosyl donor 6 and acceptor 8⁴⁷ in 85% yield ($\alpha/\beta > 25/1$, 50 mM) and 90% ($\alpha/\beta > 25/1$, 5.0 mM) under regular and high dilution reaction conditions, respectively. Analytical data for 15: $R_f = 0.65$ (ethyl acetate/toluene, 1/4, v/v); ^1H NMR (300 MHz, CDCl_3): δ 7.95 (m, 2H, aromatic), 7.55 (m, 1H, aromatic), 7.40–7.05 (m, 32H, aromatic), 5.82–5.26 (m, 2H, $J_{1',2'} = 3.4$, $J_{3',4'} = 7.3$ Hz, H-1', 3'), 5.06–4.90 (m, 3H, $3 \times \text{CHPh}$), 4.83–4.31 (m, 10H, $J_{1,2} = 3.3$ Hz, H-1, 4', 5', $7 \times \text{CHPh}$), 4.20 (dd, 2H, $^2J = 11.9$ Hz, CH_2Ph), 4.05–3.65 (m, 6H, $J_{2',3'} = 2.7$ Hz, H-2', 3, 4, 5, 6a, 6b), 3.55 (dd, 1H, $J_{2,3} = 9.3$ Hz, H-2), 3.39 (s, 3H, OCH_3) ppm; ^{13}C NMR (75 MHz, CDCl_3): δ 169.0, 165.7,

139.0, 138.4, 138.0 (x2), 137.6, 135.0, 133.3, 129.9 (x2), 129.6, 128.6 (x3), 128.5 (x4), 128.4 (x4), 128.2 (x8), 128.0, 127.9 (x2), 127.8, 127.7 (x2), 127.5, 127.4 (x4), 127.3 (x3), 100.2 ($^1J_{\text{C1,H1}} = 170.0$ Hz, C-1'), 97.9 ($^1J_{\text{C1,H1}} = 173.1$ Hz, C-1), 81.6, 80.0, 77.4, 76.2, 75.3, 75.0, 74.2, 73.3, 72.8, 72.7, 72.5, 69.6, 69.2, 67.2, 55.4 ppm; HR-FAB MS $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{62}\text{H}_{62}\text{O}_{13}\text{Na}^+$ 1037.4088; found 1037.4099.

Methyl 4-O-(2,4-di-O-benzyl- α/β -D-mannopyranosid-urono-6,3-lactone)-2,3,6-tri-O-benzyl- α -D-glucopyranoside (16). The title compound was obtained as a colorless amorphous solid from glycosyl donor 2 (50 mM) and acceptor 8⁴⁷ in 27% yield. Analytical data for 16 were in agreement with those previously reported.⁵⁴

Methyl 3-O-(benzyl 2,4-di-O-benzyl-3-O-picoloyl- α/β -D-mannopyranosyluronate)-2,4,6-tri-O-benzyl- α -D-glucopyranoside (17). The title compound was obtained as a colorless amorphous solid from glycosyl donor 5 and acceptor 9⁴⁷ in 74% yield ($\alpha/\beta = 1/1.3$, 50 mM) or 67% yield ($\alpha/\beta = 1/1.6$, 5.0 mM) under regular and high dilution reaction conditions, respectively. Analytical data for 17: $R_f = 0.30$ (ethyl acetate/hexane, 2/3, v/v); ^1H NMR (300 MHz, CDCl_3): ^1H NMR (300 MHz, CDCl_3): δ 8.82 (m, 1H, aromatic), 7.95 (m, 1H, aromatic), 7.86–7.77 (m, 1H, aromatic), 7.52–6.99 (m, 51H, aromatic), 5.62 (dd, 1H, $J_{3\alpha',4\alpha'} = 8.9$ Hz, H-3 α'), 5.51 (d, 1H, $J_{1\alpha',2\alpha'} = 2.3$ Hz, H-1 α'), 5.20–4.98 (m, 6H, $J_{1\beta',2\beta'} = 3.1$ Hz, H-1 β' , 3 β' , 2 $\times$ CH_2Ph), 4.92–4.81 (m, 2H, H-5 α' , CHPh), 4.73–4.18 (m, 18H, H-1 α , 1 β , 3 α , 3 β , 4 α' , 4 β' , 6 α^a , 6 α^b , 5 $\times$ CH_2Ph), 4.10 (dd, H-2 β'), 3.98–3.94 (m, 2H, $J_{2\alpha',3\alpha'} = 3.0$ Hz, H-2 α' , 5 β'), 3.76–3.44 (m, 8H, H-2 α , 2 β , 4 α , 4 β , 5 α , 5 β , 6 β^a , 6 β^b), 3.35 (s, 3H, OCH_3), 3.26 (s, 3H, OCH_3) ppm; ^{13}C NMR (151 MHz, CDCl_3): δ 169.6, 168.1, 164.1, 164.0, 150.2, 150.1, 147.8 (x2), 138.8, 138.5, 138.4 (x2), 138.2, 138.0 (x2), 137.9, 137.5, 136.9 (x2), 135.5 (x2), 129.0 (x2), 128.9 (x2), 128.7 (x2), 128.6 (x2), 128.5 (x7), 128.4 (x4), 128.3 (x3), 128.2 (x4), 128.1 (x3), 128.0, 127.9 (x3), 127.8, 127.7 (x3), 127.6, 127.5 (x3), 127.4, 127.0, 126.9, 126.8, 125.3, 102.0 ($^1J_{\text{C1,H1}} = 162.0$ Hz, C-1'), 99.0, 98.1 ($^1J_{\text{C1,H1}} = 173.1$ Hz, C-1), 97.4, 80.3, 80.2, 78.9 (x2), 78.1, 76.2, 76.1, 75.5, 75.2 (x2), 75.1 (x2), 74.9, 74.8, 74.1, 73.7 (x2), 73.4, 73.2, 72.6, 72.0, 69.9 (x2), 68.7, 68.6, 67.1, 67.0, 55.2 (x2) ppm; HR-FAB MS $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{61}\text{H}_{61}\text{NO}_{13}\text{Na}^+$ 1038.4041; found 1038.4054.

Methyl 3-O-(benzyl 3-O-benzoyl-2,4-di-O-benzyl- α -D-mannopyranosyluronate)-2,4,6-tri-O-benzyl- α -D-glucopyranoside (18). The title compound was obtained as a colorless amorphous solid from glycosyl donor 6 and acceptor 9⁴⁷ in 90% yield ($\alpha/\beta > 25/1$, 50 mM) and 83% ($\alpha/\beta > 25/1$, 5 mM) under regular and high dilution reaction conditions, respectively. Analytical data for 18: $R_f = 0.55$ (ethyl acetate/toluene, 1/4, v/v); ^1H NMR (300 MHz, CDCl_3): δ 7.97 (m, 2H, aromatic), 7.56 (m, 1H, aromatic), 7.42–7.01 (m, 32H, aromatic), 5.59 (dd, 1H, $J_{3',4'} = 8.9$ Hz, H-3'), 5.53 (d, 1H, $J_{1',2'} = 2.3$ Hz, H-1'), 5.07 (dd, 2H, $^2J = 12.4$ Hz, CH_2Ph), 4.86 (m, 1H, $J_{4',5'} = 8.7$ Hz, H-5', CHPh), 4.73 (d, 1H, $^2J = 11.8$ Hz, CHPh), 4.60 (d, 1H, $^2J = 5.6$ Hz, CHPh), 4.57–4.28 (m, 8H, $J_{1,2} = 3.5$ Hz, H-1, 4', 6 $\times$ CHPh), 4.27–4.11 (m, 2H, H-3, CHPh), 3.93 (dd, 1H, $J_{2',3'} = 3.1$ Hz, H-2'), 3.82–3.52 (m, 4H, H-4, 5, 6a, 6b), 3.46 (dd, 1H, $J_{2,3} = 9.7$ Hz, H-2), 3.25 (s, 3H, OCH_3) ppm; ^{13}C NMR (151 MHz, CDCl_3): δ

169.7, 165.7, 138.4, 138.3, 137.9 (x2), 137.8, 135.4, 133.2, 129.9 (x2), 128.6 (x2), 128.5 (x6), 128.4 (x2), 128.3 (x3), 128.2 (x5), 128.0 (x2), 127.8 (x4), 127.6, 127.5 (x3), 127.4 (x3), 126.8 (x2), 99.0 ($^1J_{\text{C1,H1}} = 171.0$ Hz, C-1'), 98.1 ($^1J_{\text{C1,H1}} = 173.1$ Hz, C-1), 78.9, 78.8, 78.2, 76.3, 75.2, 74.4, 74.2, 73.6, 73.5, 73.4, 72.6, 72.0, 69.8, 68.5, 67.0, 55.2 ppm; HR-FAB MS $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{62}\text{H}_{62}\text{O}_{13}\text{Na}^+$ 1037.4088; found 1037.4106.

Methyl 3-O-(2,4-di-O-benzyl- α/β -D-mannopyranosid-urono-6,3-lactone)-2,4,6-tri-O-benzyl- α -D-glucopyranoside (19). The title compound was obtained as a colorless amorphous solid from glycosyl donor 2 and acceptor 9⁴⁷ in 26% yield ($\alpha/\beta = 1:2.8$, 50 mM) under regular dilution reaction conditions. Analytical data for 19: $R_f = 0.45$ (ethyl acetate/toluene, 1/4, v/v); ^1H NMR (300 MHz, CDCl_3): δ 7.33–7.21 (m, 25H, aromatic), 5.67 (d, 1H, $J_{1',2'} = 5.3$ Hz, H-1'), 4.96 (d, 1H, $^2J = 10.9$ Hz, CHPh), 4.76 (br s, 1H, CHPh), 4.73–4.62 (m, 4H, H-3', 3 $\times$ CHPh), 4.57 (m, 2H, CH_2Ph), 4.51 (m, 1H, CHPh), 4.48–4.42 (m, 3H, $J_{1,2} = 3.8$ Hz, H-1, CH_2Ph), 4.14–4.02 (m, 3H, $J_{4',5'} = 2.3$ Hz, H-2', 3, 4'), 3.94 (d, 1H, H-5'), 3.67 (m, 4H, H-4, 5, 6a, 6b), 3.51 (dd, 1H, $J_{2,3} = 9.3$ Hz, H-2), 3.30 (s, 3H, OCH_3) ppm; ^{13}C NMR (75 MHz, CDCl_3): δ 171.9, 139.0 (x2), 137.9, 137.8, 136.5, 129.9, 128.8 (x2), 128.6 (x2), 128.5 (x7), 128.3 (x2), 128.2 (x2), 128.1 (x2), 128.0 (x3), 127.8 (x2), 127.7, 127.4, 100.5 ($^1J_{\text{C1,H1}} = 160.0$ Hz, C-1'), 98.4 ($^1J_{\text{C1,H1}} = 175.2$ Hz, C-1), 83.4, 77.8, 77.4, 76.4, 73.8, 73.7, 73.2, 71.9, 71.5 (x2), 69.8, 69.7, 68.8, 68.2, 55.1 ppm; HR-FAB MS $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{48}\text{H}_{50}\text{O}_{11}\text{Na}^+$ 825.3251; found 825.3274.

Methyl 2-O-(benzyl 2,4-di-O-benzyl-3-O-picoloyl- α/β -D-mannopyranosyluronate)-3,4,6-tri-O-benzyl- α -D-glucopyranoside (20). The title compound was obtained as a colorless amorphous solid from glycosyl donor 5 and acceptor 10⁴⁷ in 88% yield ($\alpha/\beta = 1/24$, 50 mM) or 92% yield ($\alpha/\beta = 1/25$, 5.0 mM) under regular and high dilution reaction conditions, respectively. Analytical data for 20: $R_f = 0.48$ (ethyl acetate/toluene, 3/7, v/v); ^1H NMR (300 MHz, CDCl_3): δ 8.83 (m, 1H, aromatic), 7.98 (m, 1H, aromatic), 7.82 (m, 1H, aromatic), 7.51 (m, 1H, aromatic), 7.37–7.02 (m, 30H, aromatic), 5.31–5.15 (m, 2H, CH_2Ph), 5.03 (dd, 1H, $J_{3',4'} = 9.9$ Hz, H-3'), 4.97–4.80 (m, 5H, H-1, 1', 3 $\times$ CHPh), 4.70 (m, 3H, 3 $\times$ CHPh), 4.58–4.43 (m, 5H, $J_{4',5'} = 9.7$ Hz, H-4', 2 $\times$ CH_2Ph), 4.01 (m, 2H, $J_{2',3'} = 3.2$ Hz, H-2', 3), 3.91 (d, 1H, H-5'), 3.82–3.66 (m, 5H, H-2, 4, 5, 6a, 6b), 3.38 (s, 3H, OCH_3) ppm; ^{13}C NMR (151 MHz, CDCl_3): δ 167.9, 163.9, 150.3, 147.7, 138.3 (x2), 138.2, 138.1, 137.8, 137.0, 135.3, 128.9 (x3), 128.7 (x3), 128.5 (x4), 128.3 (x3), 128.2 (x3), 128.1 (x5), 127.9 (x6), 127.8, 127.7, 127.5, 127.1, 125.4, 102.6 ($^1J_{\text{C1,H1}} = 160.0$ Hz, C-1'), 99.8 ($^1J_{\text{C1,H1}} = 171.0$ Hz, C-1), 82.1, 78.9, 78.4, 76.4, 76.1, 75.1 (x2), 75.0, 74.4 (x3), 73.7, 70.3, 68.6, 67.4, 55.4 ppm; HR-FAB MS $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{61}\text{H}_{61}\text{NO}_{13}\text{Na}^+$ 1038.4041; found 1038.4053.

Methyl 2-O-(benzyl 3-O-benzoyl-2,4-di-O-benzyl- α -D-mannopyranosyluronate)-3,4,6-tri-O-benzyl- α -D-glucopyranoside (21). The title compound was obtained as a colorless amorphous solid from glycosyl donor 6 and acceptor 10⁴⁷ in 92% yield ($\alpha/\beta > 25/1$, 50 mM) and 91% ($\alpha/\beta > 25/1$, 5.0 mM) under regular and high dilution reaction conditions, respectively. Analytical data for 21: $R_f = 0.65$ (ethyl acetate/toluene, 1/4, v/v); ^1H NMR

(300 MHz, CDCl₃): δ 8.01 (m, 2H, aromatic), 7.58 (m, 1H, aromatic), 7.47–7.00 (m, 32H, aromatic), 5.63 (dd, 1H, $J_{3',4'} = 8.0$ Hz, H-3'), 5.16 (d, 1H, $J_{1',2'} = 3.1$ Hz, H-1'), 5.03 (m, 3H, 3 $\times$ CHPh), 4.89–4.38 (m, 11H, H-1, 5', 9 $\times$ CHPh), 4.36 (dd, 1H, $J_{4',5'} = 7.8$ Hz, H-4'), 4.13–3.87 (m, 3H, $J_{2',3'} = 3.1$ Hz, H-2, 2', 3), 3.83–3.56 (m, 4H, H-4, 5, 6a, 6b), 3.30 (s, 3H, OCH₃) ppm; ¹³C NMR (151 MHz, CDCl₃): δ 169.2, 165.5, 138.5, 138.4, 138.1, 137.9, 137.8, 135.3, 133.4, 129.9 (x2), 129.7, 128.6 (x5), 128.5 (x2), 128.4 (x3), 128.3 (x2), 128.2 (x3), 128.0 (x3), 127.9 (x3), 127.8 (x4), 127.7 (x3), 127.6 (x2), 127.4 (x2), 96.8 ($^1J_{C1',H1'} = 173.0$ Hz, C-1'), 95.9 ($^1J_{C1,H1} = 173.1$ Hz, C-1), 80.8, 77.7, 76.1, 76.0, 75.1, 75.0, 74.9, 74.0, 73.6, 73.4, 72.8, 72.2, 70.3, 68.7, 67.1, 55.1 ppm; HR-FAB MS [$M + H$]⁺ calcd for C₆₂H₆₂O₁₃Na⁺ 1037.4088; found 1037.4099.

Methyl 2-O-(2,4-di-O-benzyl- α/β -D-mannopyranosid-urono-6,3-lactone)-3,4,6-tri-O-benzyl- α -D-glucopyranoside (22). The title compound was obtained as a colorless amorphous solid from glycosyl donor 2 and acceptor 10⁴⁷ in 44% yield ($\alpha/\beta = 1/4.0$) under regular concentration (50 mM). Analytical data for 22: $R_f = 0.65$ (ethyl acetate/toluene, 1/4, v/v); ¹H NMR (300 MHz, CDCl₃): δ 7.34–7.09 (m, 25H, aromatic), 5.50 (d, 1H, $J_{1',2'} = 5.2$ Hz, H-1'), 4.90 (m, 3H, $^2J = 12.4$ Hz, $J_{1,2} = 2.3$ Hz, H-1, CH₂Ph), 4.69 (d, 1H, $^2J = 10.3$ Hz, CHPh), 4.63–4.43 (m, 7H, H-3', 3 $\times$ CH₂Ph), 4.28 (d, 1H, $^2J = 12.4$ Hz, CHPh), 4.10–3.99 (m, 3H, H-2', 3, 4'), 3.91 (d, 1H, $J_{4',5'} = 2.5$ Hz, H-5'), 3.85–3.80 (m, 1H, H-2), 3.77–3.66 (m, 4H, H-4, 5, 6a, 6b), 3.40 (s, 3H, OCH₃) ppm; ¹³C NMR (75 MHz, CDCl₃): δ 171.4, 139.4, 138.2, 138.1, 137.2, 136.3, 128.9 (x2), 128.6 (x2), 128.5 (x4), 128.4 (x4), 128.2 (x2), 128.1 (x4), 127.9 (x2), 127.8, 127.7, 127.1, 126.7 (x2), 100.4 ($^1J_{C1',H1'} = 160.0$ Hz, C-1'), 98.8 ($^1J_{C1,H1} = 175.2$ Hz, C-1), 81.3, 78.9, 78.6, 77.0, 76.3, 75.0, 74.5, 73.6, 72.1, 71.5, 70.3, 70.0, 68.5, 68.1, 55.0 ppm; HR-FAB MS [$M + H$]⁺ calcd for C₄₈H₅₀O₁₁Na⁺ 825.3251; found 825.3276.

Methyl 2-O-benzyl-3-O-(benzyl 2,4-di-O-benzyl-3-O-picoloyl- α/β -D-mannopyranosyluronate)-4,6-O-benzylidene- α -D-glucopyranoside (26). The title compound was obtained as a colorless amorphous solid from glycosyl donor 5 and acceptor 23^{47,57,58} in 62% yield ($\alpha/\beta = 1/1.3$, 50 mM) or 56% yield ($\alpha/\beta = 1/1.9$, 5.0 mM) under regular and high dilution reaction conditions, respectively. Analytical data for α/β -26: $R_f = 0.40$ (ethyl acetate/toluene, 3/7, v/v); ¹H NMR (300 MHz, CDCl₃): δ 8.78 (m, 1H, aromatic), 7.92–7.88 (m, 1H, aromatic), 7.79–7.74 (m, 1H, aromatic), 7.53–6.82 (m, 26H, aromatic), 5.19–5.03 (m, 3H, H-1', 3', CHPh), 4.94 (d, 1H, CHPh), 4.70–4.32 (m, 9H, H-1, 4', 5', 3 $\times$ CH₂Ph), 4.27–4.18 (m, 2H, H-3, 6a), 4.16 (dd, 1H, $J_{1',2'} = 2.9$ Hz, H-2'), 3.87–3.77 (m, 2H, H-5, CHPh), 3.69–3.48 (m, 3H, H-2, 4, 6b), 3.35 (s, 3H, OCH₃) ppm; ¹³C NMR (75 MHz, CDCl₃): δ 169.6, 168.0, 164.1, 163.9, 150.2, 150.1, 147.8, 147.5, 138.5, 138.1, 137.9, 137.8, 137.7 (x2), 137.4, 137.3, 137.0, 135.5, 135.3, 129.4, 128.9, 128.8 (x4), 128.6 (x3), 128.5 (x2), 128.4 (x3), 128.3 (x2), 128.2 (x4), 128.1 (x2), 128.0 (x2), 127.8 (x2), 127.7 (x2), 127.6, 127.4 (x2), 127.1, 126.3, 126.2 (x2), 125.4, 102.0, 101.6, 101.1, 99.0, 98.5, 98.4, 82.4, 80.1, 79.6, 77.4, 76.6, 75.4, 75.1, 74.9, 74.8, 74.7, 74.3, 73.7, 71.7, 69.0, 67.3, 67.1, 62.4, 61.9, 55.4 (x2) ppm; HR-FAB MS [$M + Na$]⁺ calcd for C₅₄H₅₃NO₁₃Na⁺ 946.3415; found 946.3429.

3-O-(Benzyl 2,4-di-O-benzyl-3-O-picoloyl- α/β -D-mannopyranosyluronate)-1,2,5,6-di-O-isopropylidene- α -D-glucofuranose (27). The title compound was obtained as a colorless amorphous solid from glycosyl donor 5 and commercial acceptor 24 in 59% yield ($\alpha/\beta = 1/3.4$, 50 mM) or 65% yield ($\alpha/\beta = 1/5$, 5.0 mM) under regular and high dilution reaction conditions, respectively. Analytical data for 27: $R_f = 0.35$ (ethyl acetate/toluene, 3/7, v/v); ¹H NMR (300 MHz, CDCl₃): δ 8.79 (m, 1H, aromatic), 7.88 (m, 1H, aromatic), 7.78 (m, 1H, aromatic), 7.50 (m, 1H, aromatic), 7.36–7.03 (m, 15H, aromatic), 5.94 (dd, 1H, $J_{1,2} = 3.7$ Hz, H-1), 5.28–5.15 (m, 2H, CH₂Ph), 5.11 (dd, 1H, $J_{3',4'} = 9.8$ Hz, H-3'), 4.84 (d, 1H, $^2J = 12.2$ Hz, CHPh), 4.77 (s, 1H, H-1'), 4.69 (d, 1H, $^2J = 10.8$ Hz, CHPh), 4.59–4.44 (m, 5H, H-2, 4', 5', 2 $\times$ CHPh), 4.33 (m, 2H, H-3, 6a), 4.17–3.95 (m, 4H, $J_{2',3'} = 3.1$ Hz, H-2', 4, 5, 6b), 1.41 (3 s, 12H, 2 $\times$ CMe₂) ppm; ¹³C NMR (75 MHz, CDCl₃): δ 167.6, 164.1, 150.2, 147.3, 137.7 (x2), 137.0, 135.2, 128.7 (x4), 128.6, 128.5 (x2), 128.3 (x2), 128.2 (x2), 127.9 (x2), 127.8 (x2), 127.2, 125.4, 112.1, 111.9, 109.7, 108.7, 105.4, 105.1, 100.1, 85.2, 83.0, 81.7, 80.5, 76.4, 75.3, 75.2, 74.9, 74.6, 74.0, 73.3, 67.5, 66.1, 27.0, 26.9, 26.8, 26.7, 26.4, 25.3 ppm; HR-FAB MS [$M + Na$]⁺ calcd for C₄₅H₄₉NO₁₃Na⁺ 834.3102; found 834.3110.

Synthesis of Mannuronans

Benzyl O-(benzyl 2,4-di-O-benzyl-3-O-picoloyl- β -D-mannopyranosyluronate)-(1 $\rightarrow$ 3)-(benzyl 2,4-di-O-benzyl- α -D-mannopyranosid)uronate (28). A mixture containing mannosyl donor 5 (47 mg, 0.077 mmol), mannosyl acceptor 25 (39 mg, 0.070 mmol), and molec. sieves (4 Å, 200 mg) in 1,2-DCE (5.0 mL) was stirred under argon for 1 h at rt. The mixture was then cooled to –30 °C, NIS (35 mg, 0.154 mmol) and TfOH (3.0 μ L, 0.031 mmol) were added, the external cooling was removed, and the resulting mixture was stirred for 16 h at rt. After that, the solids were filtered off through a pad of Celite, rinsed successively with CH₂Cl₂, and the combined filtrate was concentrated under reduced pressure. The residue was redissolved in CH₂Cl₂ (~20 mL) and washed with water (8 mL), 10% aq. Na₂S₂O₃ (8 mL) and water (2 $\times$ 8 mL). The organic phase was separated, dried with Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate–toluene gradient elution) to obtain the title compound as a colorless syrup in 83% yield ($\alpha/\beta = 1/18$). For the purpose of the glycan synthesis, the mixture was subjected to second purification by column chromatography to afford pure β -anomer of 28. Analytical data for 28: $R_f = 0.45$ (ethyl acetate/toluene, 1/4, v/v); ¹H NMR (300 MHz, CDCl₃): δ 8.79 (m, 1H, aromatic), 7.90 (m, 1H, aromatic), 7.77 (m, 1H, aromatic), 7.52–7.44 (m, 1H, aromatic), 7.76–6.86 (m, 35H, aromatic), 5.29–5.00 (m, 6H, $J_{1,2} = 3.4$ Hz, H-1, 3', 2 $\times$ CH₂Ph), 4.86–4.39 (m, 12H, $J_{4',5'} = 9.7$ Hz, H-1', 4', 5, 9 $\times$ CHPh), 4.28 (dd, 1H, $J_{4,5} = 6.8$ Hz, H-4), 4.15–4.03 (m, 2H, H-3, CHPh), 4.03 (dd, 1H, $J_{2',3'} = 2.9$ Hz, H-2'), 3.86 (d, 1H, H-5'), 3.75 (dd, 1H, H-2) ppm; ¹³C NMR (75 MHz, CDCl₃): δ 169.3, 167.8, 163.8, 150.1, 147.4, 138.1, 137.9 (x2), 137.8, 137.1, 136.9, 135.7, 135.2, 128.7 (x2), 128.6 (x8), 128.5 (x6), 128.3 (x7), 128.1, 128.0 (x2), 127.9 (x2), 127.8 (x2), 127.7 (x2), 127.4, 127.1,

125.4, 100.6 ($^1J_{\text{C1',H1'}} = 159.0$ Hz, C-1'), 96.9 ($^1J_{\text{C1,H1}} = 171.3$ Hz, C-1), 78.1, 76.1, 75.1, 75.0, 74.7, 74.5, 74.2, 74.0, 73.9, 72.8, 72.5, 70.0, 67.3, 67.1, 60.5, 21.2, 14.3 ppm; HR-FAB MS [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{67}\text{H}_{63}\text{NO}_{14}\text{Na}^+$ 1128.4146; found 1128.4163.

Benzyl O-(benzyl 2,4-di-O-benzyl- β -D-mannopyranosyluronate)-(1 $\rightarrow$ 3)-(benzyl 2,4-di-O-benzyl- α -D-mannopyranosid)uronate (29). FeCl_3 (1.0 mg, 0.006 mmol) was added to a solution of compound **28** (21 mg, 0.019 mmol) in $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (1.0 mL, 1/9, v/v) and the resulting mixture was stirred for 10 min at rt. The volatiles were removed under reduced pressure. The residue was diluted with CH_2Cl_2 (~10 mL) and washed with water (5 mL), sat. aq. NaHCO_3 (5 mL) and water (5 mL). The organic phase was separated, dried with Na_2SO_4 , and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate–hexane gradient elution) to obtain the title compound in 83% yield (15 mg, 0.015 mmol). Analytical data for **29**: $R_f = 0.60$ (ethyl acetate/hexane, 2/3, v/v); ^1H NMR (300 MHz, CDCl_3): δ 7.34–7.15 (m, 35H, aromatic), 5.26–5.22 (m, 2H, H-1, CHPh), 5.16–5.03 (m, 3H, 3 $\times$ CHPh), 4.93 (d, 1H, $^2J = 11.9$ Hz, CHPh), 4.86–4.40 (m, 11H, $J_{1',2'} = 2.1$ Hz, H-1', 5, 9 $\times$ CHPh), 4.28 (dd, 1H, H-4), 4.17 (dd, 1H, $J_{3,4} = 6.3$ Hz, H-3), 3.92 (dd, 1H, $J_{4',5'} = 8.6$ Hz, H-4'), 3.79–3.76 (m, 2H, $J_{2,3} = 3.1$ Hz, H-2, 5'), 3.63–3.51 (m, 2H, $J_{2',3'} = 3.6$, $J_{3',4'} = 8.9$ Hz, H-2', 3'), 2.47 (d, 1H, $J = 9.6$ Hz, OH) ppm; ^{13}C NMR (75 MHz, CDCl_3): δ 169.5, 168.4, 138.1 (x3), 137.2, 135.6, 135.3, 128.6 (x6), 128.5 (x9), 128.4 (x4), 128.3 (x7), 128.2 (x2), 128.0 (x5), 127.9, 127.8, 127.7, 100.9, 97.0, 77.8, 77.7, 76.4 (x2), 74.7, 74.6, 74.5, 73.8, 73.1, 72.8, 72.7, 70.1, 67.2 (x2), 60.5 ppm; HR-FAB MS [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{61}\text{H}_{60}\text{O}_{13}\text{Na}^+$ 1023.3932; found 1023.3951.

Benzyl O-(benzyl 2,4-di-O-benzyl-3-O-picoloyl- α/β -D-mannopyranosyluronate)-(1 $\rightarrow$ 3)-O-(benzyl 2,4-di-O-benzyl- β -D-mannopyranosyluronate)-(1 $\rightarrow$ 3)-(benzyl 2,4-di-O-benzyl- α -D-mannopyranosid)uronate (30). A mixture containing mannosyl donor **5** (22 mg, 0.036 mmol), disaccharide acceptor **29** (33 mg, 0.033 mmol), and molec. sieves (4 Å, 200 mg) in 1,2-DCE (5.0 mL) was stirred under argon for 30 min at rt. The mixture was then cooled to -30 °C, NIS (16 mg, 0.072 mmol) and TfOH (1.3 μL , 0.014 mmol) were added, the external cooling was removed, and the resulting mixture was stirred for 16 h at rt. After that, the solids were filtered off through a pad of Celite, rinsed successively with CH_2Cl_2 , and the combined filtrate was concentrated under reduced pressure. The residue was redissolved in CH_2Cl_2 (~20 mL) and washed with water (8 mL), 10% aq. $\text{Na}_2\text{S}_2\text{O}_3$ (8 mL) and water (2 $\times$ 8 mL). The organic phase was separated, dried with Na_2SO_4 , and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate–toluene gradient elution) to obtain the title compound as a colorless syrup in 52% yield (14 mg, 0.010 mmol, $\alpha/\beta = 1/4.0$). Analytical data for **30**: $R_f = 0.60$ (ethyl acetate/toluene, 1/4, v/v); ^1H NMR (600 MHz, CDCl_3): δ 8.80 (m, 1H, aromatic), 7.90 (m, 1H, aromatic), 7.77–7.75 (m, 1H, aromatic), 7.47 (m, 1H, aromatic), 7.36–6.89 (m, 50H, aromatic), 5.30 (d, 1H, $J_{1,2} = 4.7$ Hz, H-1), 5.24 (d, 1H, $^2J = 12.3$ Hz, CHPh), 5.12–4.98 (m, 6H, H-3'', 5 $\times$ CHPh), 4.89–4.77 (m, 4H, 2 $\times$ CH_2Ph), 4.69–4.16 (m, 18H, H-1',

1'', 2', 3', 4, 4', 4'', 5, 5 $\times$ CH_2Ph), 4.03 (m, 1H, H-3), 3.83–3.68 (m, 4H, H-2, 2'', 5', 5'') ppm; ^{13}C NMR (75 MHz, CDCl_3): δ 169.3, 168.2, 167.7, 163.8, 150.2, 147.4, 138.4, 138.2, 138.1, 137.9 (x2), 137.8, 137.3, 137.0, 135.8, 135.4, 135.1, 129.2, 128.8 (x2), 128.7 (x8), 128.6 (x7), 128.5 (x6), 128.4 (x6), 128.3 (x9), 128.2 (x2), 128.1, 128.0 (x6), 127.9 (x2), 127.8 (x2), 127.6 (x2), 127.5, 125.4 (x2), 102.0 ($^1J_{\text{C1',H1'}} = 159.2$ Hz, C-1'), 97.6 ($^1J_{\text{C1'',H1''}} = 163.3$ Hz, C-1''), 96.9 ($^1J_{\text{C1,H1}} = 170.1$ Hz, C-1), 78.6, 78.2, 77.4, 76.1, 75.2, 75.1, 74.9, 74.6, 74.4, 74.2, 73.7, 72.9, 72.0, 70.2, 67.4, 67.2, 67.1 ppm; HR-FAB MS [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{94}\text{H}_{89}\text{NO}_{20}\text{Na}^+$ 1575.5909; found 1575.5932.

Benzyl O-(benzyl 2,4-di-O-benzyl- α/β -D-mannopyranosyluronate)-(1 $\rightarrow$ 3)-O-(benzyl 2,4-di-O-benzyl- β -D-mannopyranosyluronate)-(1 $\rightarrow$ 3)-(benzyl 2,4-di-O-benzyl- α -D-mannopyranosid)uronate (31). FeCl_3 (0.4 mg, 0.003 mmol) was added to a solution of compound **30** (14 mg, 0.01 mmol) in $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (1 mL, 1/9, v/v) and the resulting mixture was stirred for 15 min at rt. The volatiles were removed under reduced pressure. The residue was diluted with CH_2Cl_2 (~10 mL) and washed with water (5 mL), sat. aq. NaHCO_3 (5 mL), and water (5 mL). The organic phase was separated, dried with Na_2SO_4 , and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate–hexane gradient elution) to obtain the title compound in 95% yield (13 mg, 0.01 mmol). Analytical data for **31**: $R_f = 0.60$ (ethyl acetate/hexane, 2/3, v/v); ^1H NMR (300 MHz, CDCl_3): δ 7.37–7.10 (m, 50H, aromatic), 5.31–3.85 (m, 28H, H-1, 1', 1'', 3, 4, 4', 4'', 5, 10 $\times$ CH_2Ph), 3.79–3.63 (m, 5H, H-2, 2', 3', 5', 5''), 3.43–3.33 (m, 2H, H-2'', 3''), 2.33 (d, 1H, $J = 10.1$ Hz, OH) ppm; ^{13}C NMR (75 MHz, CDCl_3): δ 169.4, 168.2, 168.1, 138.3, 138.2 (x3), 138.1 (x2), 137.3, 135.7, 135.3, 135.2, 128.8 (x2), 128.7 (x5), 128.6 (x13), 128.5 (x4), 128.4 (x6), 128.3 (x5), 128.1 (x2), 128.0 (x3), 127.9 (x4), 127.8 (x2), 127.7 (x2), 127.3, 127.0, 102.0, 98.1, 96.8, 78.6, 78.2, 77.8, 77.4, 75.2, 75.1, 75.0 (x2), 74.9, 74.6 (x2), 74.4, 73.7, 73.4, 72.9, 72.8, 72.4, 72.3, 70.2, 67.3 (x2), 67.1 ppm. HR-FAB MS [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{88}\text{H}_{86}\text{O}_{19}\text{Na}^+$ 1469.5661; found 1469.5680.

Benzyl O-(benzyl 2,4-di-O-benzyl-3-O-picoloyl- β -D-mannopyranosyluronate)-(1 $\rightarrow$ 3)-O-(benzyl 2,4-di-O-benzyl- α/β -D-mannopyranosyluronate)-(1 $\rightarrow$ 3)-O-(benzyl 2,4-di-O-benzyl- β -D-mannopyranosyluronate)-(1 $\rightarrow$ 3)-(benzyl 2,4-di-O-benzyl- α -D-mannopyranosid)uronate (32). A mixture containing mannosyl donor **5** (153 mg, 0.249 mmol), trisaccharide acceptor **31** (55 mg, 0.038 mmol), and molec. sieves (4 Å, 450 mg) in 1,2-DCE (5.0 mL) was stirred under argon for 30 min at rt. The mixture was then cooled to -30 °C, NIS (370 mg, 1.646 mmol) and TfOH (14.6 μL , 0.164 mmol) were added, the external cooling was removed, and the resulting mixture was stirred for 16 h at rt. After that, the solids were filtered off through a pad of Celite, rinsed successively with CH_2Cl_2 , and the combined filtrate was concentrated under reduced pressure. The residue was redissolved in CH_2Cl_2 (~20 mL) and washed with water (8 mL), 10% aq. $\text{Na}_2\text{S}_2\text{O}_3$ (8 mL), and water (2 $\times$ 8 mL). The organic phase was separated, dried with Na_2SO_4 , and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate–toluene

gradient elution) to obtain the title compound as a colorless syrup in 41% yield (31 mg, 0.015 mmol). Analytical data for **32**: R_f = 0.55 (ethyl acetate/toluene, 1/4, v/v); ^1H NMR (600 MHz, CDCl_3): δ 8.80 (m, 1H, aromatic), 7.92 (m, 1H, aromatic), 7.77 (m, 1H, aromatic), 7.47 (m, 1H, aromatic), 7.35–6.79 (m, 65H, aromatic), 5.29–4.96 (m, 12H, H-1, 1', 5 $\times$ CH_2Ph), 4.90–4.54 (m, 12H, H-1'', 3', 3'', 9 $\times$ CHPh), 4.51–4.33 (m, 7H, H-2'', 4'', 5, 2 $\times$ CH_2Ph), 4.29–4.17 (m, 4H, H-4, 3 $\times$ CHPh), 4.02–3.85 (m, 4H, H-1'', 2', 3, 4'), 3.80–3.61 (m, 6H, H-2, 3'', 4'', 5', 5'', 5'''), 3.50 (dd, 1H, $J_{1'',2''}$ = 2.9 Hz, H-2'') ppm; ^{13}C NMR (75 MHz, CDCl_3): δ 169.4, 168.2, 168.0, 167.7, 163.8, 150.3, 147.5, 138.4, 138.3, 138.2, 138.1, 137.9 (x2), 137.8, 137.6, 137.3, 137.0, 135.8, 135.4, 135.3, 135.1, 129.2, 128.9, 128.8, 128.7 (x6), 128.6 (x20), 128.5 (x3), 128.4 (x4), 128.3 (x8), 128.2 (x2), 128.1 (x4), 128.0 (x5), 127.9 (x5), 127.8 (x2), 127.7, 127.6, 127.5, 126.9, 125.4, 102.0 ($J_{\text{C}1',\text{H}1'} = 159.2$ Hz, C-1'), 97.9 ($J_{\text{C}1'',\text{H}1''} = 159.2$ Hz, C-1''), 97.9 ($J_{\text{C}1'',\text{H}1''} = 163.3$ Hz, C-1''), 96.9 ($J_{\text{C}1,\text{H}1} = 170.1$ Hz, C-1), 78.5, 78.3, 77.9, 77.4, 76.1, 75.3, 75.2, 75.1 (x2), 74.9, 74.8 (x2), 74.6, 74.5 (x2), 74.4, 74.2, 74.1, 73.7, 72.9 (x2), 72.8, 72.7, 72.3, 70.2, 67.5, 67.3, 67.2, 67.1 ppm; HR-FAB MS $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{121}\text{H}_{115}\text{NO}_{26}\text{Na}^+$ 2021.7639; found 2021.7686.

Conflicts of interest

There are no conflicts to declare.

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