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The Stereodirecting Effect of the Glycosyl C5-Carboxylate Ester: Stereoselective Synthesis of β-Mannuronic Acid Alginates

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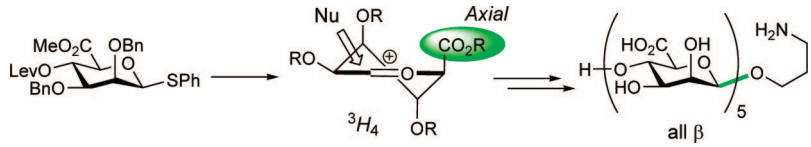

Glycosylations of mannuronate ester donors proceed highly selectively to produce the 1,2-*cis*-linked products. We here forward a mechanistic rationale for this counterintuitive selectivity, based on the remote stereodirecting effect of the C5-carboxylate ester, which has been demonstrated using pyranosyl uronate ester devoid of ring substituents other than the C5- carboxylate ester. It is postulated that the C5-carboxylate ester prefers to occupy an axial position in the oxacarbenium intermediate, thereby favoring the formation of the $^3H_4$ half-chair over the $^4H_3$ conformer. Nucleophilic attack on the $^3H_4$ half-chair intermediate occurs in a β-fashion, providing the 1,2-*cis*-mannuronates with excellent stereoselectivity. The potential of the mannuronate ester donors in the formation of the β-mannosidic linkage has been capitalized upon in the construction of a mannuronic acid alginate pentamer using a convergent orthogonal glycosylation strategy.

Introduction

The stereoselective introduction of glycosidic bonds is the most important transformation in glycochemistry. In spite of enormous efforts, a general procedure for the stereoselective formation of 1,2-*cis* linkages is not available, and their introduction often requires special glycosylation strategies and careful tuning of the reaction parameters.[1,2] Among the several types of 1,2-*cis* linkages, the construction of the β-mannosidic linkage is considered to be one of the greatest challenges[3] since its formation is disfavored on both steric (repulsion by the axial C2-substituent) and electronic (lack of the anomeric effect, destabilization by the Δ-2 effect) grounds. A breakthrough in the formation of β-mannosides was reported by Crich and coworkers, who showed that 4,6-*O*-benzylidene-protected mannosyl sulfoxide and thiomannoside donors preferentially form 1,2-*cis* products in glycosidations.[4] This remarkable stereochemistry is explained by the intermediacy of relatively stable anomeric α-triflates, which are substituted in a S_N2-like manner to provide the β-mannosides. Collapse of the anomeric triflate into the mannosyl oxacarbenium ion, which is presumed to give α-selective condensations, is thought to be disfavored because of the electronically and conformationally disarming effect of the 4,6-*O*-benzylidene group in combination with unfavorable torsional interactions of the C2 and C3 substituents in going from the α-triflate to the oxacarbenium ion.[5,6] On the basis of these results, we reasoned that electron-withdrawing substituents in the mannose core also guide the corresponding mannosylations to give the 1,2-*cis* product. Indeed, we recently showed that glycosylations with disarmed 1-thio-2-azidomannosides[7] and, in particular, 1-thiomannuronate ester donors[8] led to the predominant formation of the 1,2-*cis* products. We here report that the β-selectivity of the mannuronate esters results from the stereodirecting effect of the C5-carboxylate ester and postulate that the observed stereocontrol originates from the oxacarbenium

(1) (a) *Comprehensive Glycoscience*; Kamerling, J. P., Ed.; Elsevier: Oxford, 2007; Vol. 1. (b) *The Organic Chemistry of Sugars*; Levy, D. E., Fügedi, P., Eds.; CRC Press, Boca Raton, FL, 2006. (c) Garegg, P. J. *Adv. Carbohydr. Chem. Biochem.* **2004**, *59*, 69. (d) Codée, J. D. C.; Litjens, R. E. J. N.; van den Bos, J. L.; Overkleeft, H. S.; van der Marel, G. A. *Chem. Soc. Rev.* **2005**, *34*, 769.
(2) Demchenko, A. V. *Synlett* **2003**, 1225.
(3) Gridley, J. J.; Osborn, H. M. I. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1471.
(4) (a) Crich, D.; Sun, S. *J. Org. Chem.* **1996**, *61*, 4506. (b) Crich, D.; Sun, S. *J. Org. Chem.* **1997**, *62*, 1198. (c) Crich, D.; Sun, S. *Tetrahedron* **1998**, *54*, 8321. (d) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1998**, *120*, 435. (e) Crich, D. *J. Carb. Chem.* **2002**, *21*, 667.
(5) (a) Crich, D.; Vinogradova, O. *J. Org. Chem.* **2006**, *71*, 8473–8480. (b) Crich, D.; Li, L. *J. Org. Chem.* **2007**, *72*, 1681.
(6) Crich, D.; Chandrasekera, N. S. *Angew. Chem., Int. Ed.* **2004**, *116*, 5500.
(7) van den Bos, L. J.; Duivenvoorden, B. A.; De Koning, M. C.; Filippov, D. V.; Overkleeft, H. S.; van der Marel, G. A. *Eur. J. Org. Chem.* **2007**, 116.
(8) (a) van den Bos, L. J.; Dinkelaar, J.; Overkleeft, H. S.; van der Marel, G. A. *J. Am. Chem. Soc.* **2006**, *128*, 13066. (b) van den Bos, L. J.; Codée, J. D. C.; Litjens, R. E. J. N.; Dinkelaar, J.; Overkleeft, H. S.; van der Marel, G. A. *Eur. J. Org. Chem.* **2007**, 3963.

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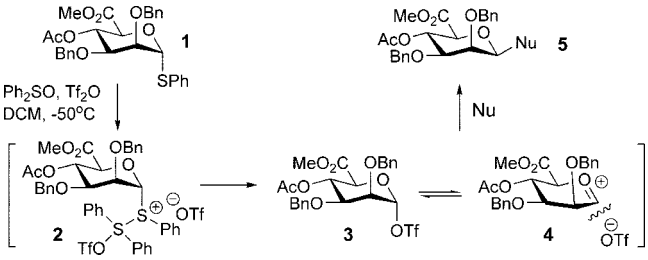
SCHEME 1. Intermediates in the Condensation of Mannuronate Ester 1



ion intermediate. Furthermore, we demonstrate that this reliable stereocontrol can be capitalized upon in the construction of higher mannuronic acid alginate oligomers using a block coupling glycosylation strategy.[1d]

Results and Discussion

To rationalize the β-selectivities observed in the glycosidations of α-(*S*)-phenyl mannuronate ester **1**, we initially reasoned that the equilibrium between the covalent triflate (or the corresponding tight ion pair) **3** and the solvent separated ion pair **4** is shifted toward the covalent triflate because of the strong electron-withdrawing capacity of the C5-carboxylate ester (Scheme 1). To substantiate this hypothesis, we tried to detect the transient intermediate **3** by low-temperature NMR experiments.[4,9] When 1-thiomannuronate ester **1** was treated with diphenylsulfoxide (Ph_2SO, 1.2 equiv) and trifluoromethanesulfonic anhydride (Tf_2O, 1.2 equiv) in CD_2Cl_2 at −50 °C, the temperature required for full activation of 1-thiouronic acids, the starting material disappeared completely. However, several species were formed that did not converge into a single product in time or upon warming. The presence of the C5-carboxylate ester function apparently does not induce the formation of a single triflate species.[10]

To probe whether direct S_N2-like displacement of the activated anomeric α-thiophenyl moiety in **2** is at the basis of the observed selectivity, we examined the glycosylation properties of β-(*S*)-phenyl mannuronate ester **8**. As recorded in Table 1 (entries 1 and 2), this thioglycoside performed identical to α-mannoside **1** in the glycosidation with glucoside **6**, disproving the latter line of thought. Furthermore, the carboxylbenzyl[11] donor **10** and the *N*-phenyl trifluoroacetimidate **13**[12,13] proved equally capable to stereoselectively form the β-mannosidic bond (Table 1, entries 3 and 4), indicating that the stereoselectivity in these mannosylations is independent of the type of donor used and does not rely on the preactivation protocol.

Given the fact that no single anomeric triflate of the mannuronate ester was detected by NMR and that the conformational flexibility of these donors readily allows flattening of the pyranose ring,[14] we reasoned that the putative α-anomeric triflates are not the (sole) intermediate responsible for the observed β-selectivity in the glycosidations of mannuronate esters and that the β-selectivity can also arise from the oxacarbenium intermediate **4**. It is well-established that the nature and orientation of the substituents on the pyranose core have a profound influence on the stability and reactivity of the oxacarbenium ion.[15,16] The effect of both alkyl and heteroatom substituents at C2, C3, and C4 on the stability of pyranosyl cations has been investigated in detail using both experimental[15] and computational techniques.[17] In the most favorable half-chair conformations,[18] alkyl groups prefer to adopt equatorial positions for steric reasons, whereas electron-withdrawing substituents at C3 and C4 preferentially take up axial positions to allow through-space stabilization of the anomeric cation. Hyperconjugative effects are at the basis for the preference of C2-alkoxy groups to assume an equatorial position. For C5, only the effect of alkyl substituents[19] has been examined and little is known about the stereodirecting effects of electron-withdrawing (or donating) groups at this position.

To establish the stereodirecting effect of the C5-carboxylate ester, we "isolated" this substituent and investigated the stereochemical preferences of the stripped pyranosyl uronate ester **16** (Scheme 2 and Table 2). A range of alcohols of increasing size was condensed with **16** and with its "non-oxidized" counterpart **17**, using our standard glycosylation conditions (Scheme 2).[20] The stereodirecting effect of the C5-carboxylate ester is immediately clear from Table 2: uronate ester **16** reacts in a highly 1,5-*cis*-selective fashion when compared to its benzyloxymethyl counterpart **17**. This holds true for all examined nucleophiles. Although the selectivity depends on the steric demands of the nucleophile, the C5 carboxyl ester in **16** is highly 1,5-*cis*-directing. The β-linked products are preferentially formed with both primary and secondary alcohols, and also *tert*-butanol reacts in a 1,5-*cis*-selective fashion. Only with the bulky 1-adamantanol no selectivity is found.[21] In the C5 benzyloxymethylene series (**17**), the same trend is observed: increased steric bulk of the nucleophile leads to a stronger trans preference.[15] The stereochemical outcome of these condensations can be explained with the two diasteromeric half-chair oxacarbenium

(9) (a) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1997**, *119*, 11217. (b) Nokami, T.; Shibuya, A.; Tsuyama, H.; Suga, S.; Bowers, A. A.; Crich, D.; Yoshida, J. *J. Am. Chem. Soc.* **2007**, *129*, 10922.

(10) Although no single α-anomeric triflate was observed, it cannot be excluded that the reaction proceeds via such an intermediate and/or an exploded S_N2-like transition state. See ref 6.

(11) (a) Kim, K. S.; Kim, J. H.; Lee, Y. J.; Lee, Y. J.; Park, J. *J. Am. Chem. Soc.* **2001**, *123*, 8477. (b) Codée, J. D. C.; Kröck, L.; Castagner, B.; Seeberger, P. H. *Chem.—Eur. J.* **2008**, *14*, 3987.

(12) Yu, B.; Tao, H. *Tetrahedron Lett.* **2001**, *42*, 2405.

(13) The corresponding α/β-anomeric acetate and α-trichloroacetimidate were also assessed in the coupling with allylTMS. The former donor proved completely unreactive toward the activation with $BF_3 \cdot OEt_2$ and was recovered after the reaction. The latter donor stereoselectively provided mannuronate **15**, but showed substantial self-condensation, leading to the formation of the anomeric trichloroacetamide.

(14) Even in the condensation of the rigid 4,6-*O*-benzylidene mannosides, in which α-anomeric triflates have convincingly been demonstrated to be intermediates, substantial oxacarbenium ion character developed in the transition state, leading to the coupled products. See ref 6.

(15) (a) Ayala, L.; Lucero, C. G.; Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 1552. (b) Chamberland, S.; Ziller, J. W.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 5322. (c) Lucero, C. G.; Woerpel, K. A. *J. Org. Chem.* **2006**, *71*, 2641.

(16) (a) Jensen, H. H.; Bols, M. *Acc* **2006**, *39*, 259, and references therein. (b) Boutureira, O.; Rodríguez, M. A.; Benito, D.; Matheu, M. I.; Díaz, Y.; Castillón, S. *Eur. J. Org. Chem.* **2007**, 3564.

(17) (a) Woods, R. J.; Andrews, C. W.; Bowen, J. P. *J. Am. Chem. Soc.* **1992**, *114*, 859. (b) Miljković, M.; Yeagley, D.; Deslongchamps, P.; Dory, Y. L. *J. Org. Chem.* **1997**, *62*, 7597. (c) Nukada, T.; Bérces, A.; Wang, L.; Zgierski, M. Z.; Whitfield, D. M. *Carbohydr. Res.* **2005**, *340*, 841.

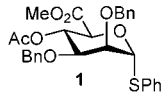
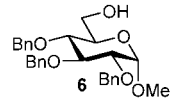
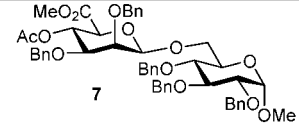
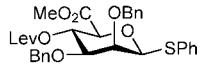
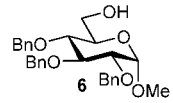
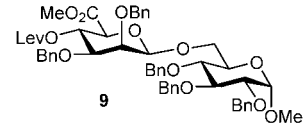
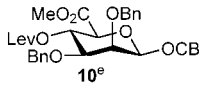
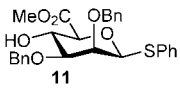
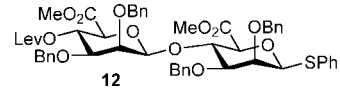
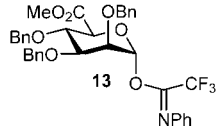
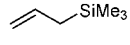
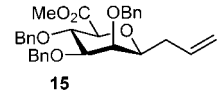
(18) Although the developing double bond character between O5 and C1 can also be accommodated in the pyranose ring by adopting a $^{2,5}B$ or $B_{2,5}$ boat conformation, these conformers will be substantially higher in energy: Shinskina, S. V.; Shishkin, O. V.; Leszczynski, J. *Chem. Phys. Lett.* **2002**, *354*, 428. Also see refs 15 and 22.

(19) Roush, W. R.; Sebesta, D. P.; James, R. A. *Tetrahedron* **1997**, *53*, 8837–8852.

(20) (a) Codée, J. D. C.; van den Bos, L. J.; Litjens, R. E. J. N.; Overkleeft, H. S.; van Boom, J. H.; van der Marel, G. A. *Org. Lett.* **2003**, *5*, 1947. (b) Van den Bos, L. J.; Litjens, R. E. J. N.; van den Berg, R. J. B. H. N.; Overkleeft, H. A.; van der Marel, G. A. *Org. Lett.* **2005**, *7*, 2007.

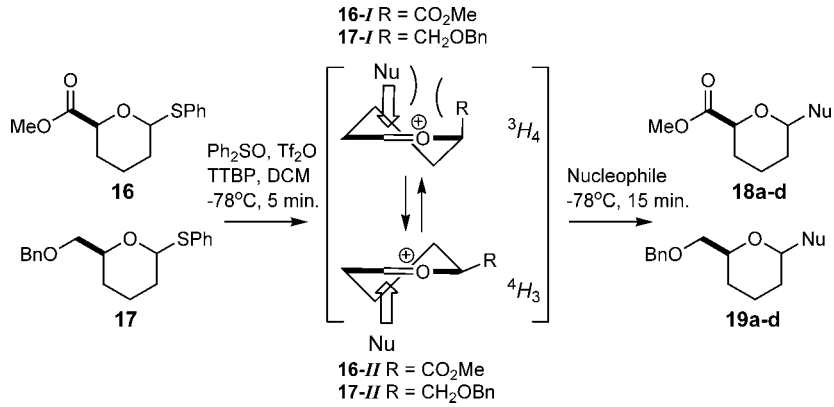
(21) In contrast, 1-adamantanol very reliably provides the β-linked products when used as an acceptor in the benzylidene mannose system, featuring anomeric triflates. See for example ref 4.

TABLE 1. β-Mannosylations Using Various Donors and Promoters

entry	donor	acceptor	conditions	product	yield[a]
1	 1	 6	Ph_2SO, Tf_2O, TTBP[b]	 7	81% (β)[c,d]
2	 8	 6	Ph_2SO, Tf_2O, TTBP[b]	 9	93% (β)[c,d]
3	 10[e]	 11	Tf_2O, *DTBMP*[f]	 12	65% (β)[c,d]
4	 13	 14	TMSOTf (cat.)	 15	74% (β)[c,g]

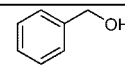
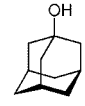
[a] Isolated yields. [b] TTBP = tri-*tert*-butylpyrimidine. [c] The α-anomer could not be detected by TLC analysis and isolated by column chromatography. [d] The stereochemistry of the newly formed glycosidic bond was deduced from the value of the $^1J_{C-H}$ coupling of H-1′ and C-1′. [e] CB = carboxylbenzyl. [f] DTBMP = 2,6-di-*tert*-butyl-4-methyl pyridine. [g] The stereochemistry of the anomeric center was established using NOESY experiments.

SCHEME 2. Oxacarbenium Ions of "Stripped" Uronate Ester 16 and its Benzyloxymethyl Counterpart 17



ions **16-*I*/17-*I*** and **16-*II*/17-*II*** as product-forming intermediates. An incoming nucleophile will attack these cations with a facial selectivity to form the lower-energy chair product as opposed to the twist-boat adduct.[22] If no destabilizing interactions develop in the transition state, oxacarbenium ions **16-*I*/17-*I*** will provide the 1,5-*cis* products, where ions **16-*II*/17-*II*** lead to the corresponding *trans* products. The formation of the 1,5-*cis* products **18a**−**c** arises from the $^3H_4$ oxacarbenium ion **16-*I***, in which the carboxylate ester occupies an axial position. The diminished β-selectivity of the bulky alcohols results from destabilizing interactions between the axially oriented carboxylate and the incoming acceptor, making attack on the $^3H_4$ oxacarbenium ion **16-*I*** (and **17-*I***) less favorable for sterically demanding nucleophiles.[23] The C5-carboxylate ester thus preferentially occupies a *pseudo* axial position in the half-chair oxacarbenium ion intermediate. As such, the positively charged

TABLE 2. Condensations of 16 and 17[a]

entry	nucleophile	product, α:β[b] (yield)[c]	
1		**18a**, 1 : 7.7 (67%)	**19a**, 1 : 1.4 (82%)
2		**18b**, 1 : 3.8 (48%)	**19b**, 1 : 0.60 (61%)
3		**18c**, 1 : 2.9 (52%)	**19c**, 1 : 0.38 (60%)
4		**18d**, 1 : 1.2 (52%)	**19d**, 1 : 0.33 (74%)

[a] Condensations were performed as described in Scheme 2. [b] Determined by NMR spectroscopy of the isolated compounds. [c] Isolated yields.

(22) (a) Stevens, R. V. *Acc. Chem. Res.* **1984**, *17*, 289. (b) Deslongschamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983.
(23) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83.

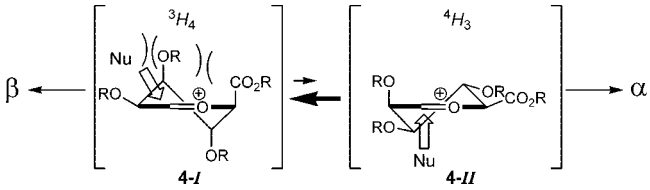


FIGURE 1. Mannuronate ester oxacarbenium ion conformers.

oxacarbenium ion can be stabilized by the through-space interaction with the electron-rich carbonyl function.[24] In addition, the electron-withdrawing effect of the carboxylate ester is minimized in this constellation.[25]

When we now reconsider the mannuronate ester oxacarbenium ions **4-*I*** and **4-*II***, it is clear that all substituents occupy a preferred position in the $^3H_4$ conformer **4-*I*** (Figure 1).[26] The $^4H_3$ conformer on the other hand has all substituents in disfavored positions, thereby destabilizing this intermediate. Although 1,3-pseudo-diaxial interactions of the substituents at C3 and C5 and the incoming nucleophile develop upon attack of the acceptor on **4-*I***, the cooperative stabilization of the ring substituents suffices to allow the stereoselective formation of the β-mannuronic acid bond. It is of interest to note that Woerpel and co-workers have previously established that the mannosyl oxacarbenium also prefers to adopt the $^3H_4$ conformation, having all ring substituents but the C5 group in the most favorable orientation.[15c] A Curtin−Hammet kinetic scenario, in which product formation arises from the higher ground state $^4H_3$ conformer, has been proposed to account for the α-selectivity generally observed in mannosylations. The additional stabilization of the C5-carboxylate ester in oxacarbenium ion **4-*I*** prevents such a Curtin−Hammet reaction scheme to occur.

Next, we turned to the assembly of 1,4-linked β-D-mannuronic alginate oligomers. Alginates are linear, anionic polysaccharides composed of 1,4-linked β-D-mannuronic and α-L-guluronic acids.[27] Small oligomers of these polymers have been shown to have immunomodulating activity by binding to Toll-like receptors (TLRs) 2 and 4.[28] With the dual goal to establish an efficient synthetic route toward these oligomers[8,26] and to explore how the stereochemistry of the mannosylations develops when larger coupling partners are involved,[29] we envisaged a convergent assembly route using both monomer (**8** and **20**) and dimer building blocks (**12** and **21**) as depicted in Scheme 3. The levulinoyl group was selected to temporarily mask the C4 hydroxyl of the oliogomannuronates to be elongated.

To maximize efficiency, we explored the possibility to construct the thiophenyl mannuronic acid dimer building blocks **12** and **21** from thiomannosyl acceptor **11** and thiomannoside donors **8** and **21**, respectively.[30] Preactivation of the donors **20** and **8** was effected using the Ph_2SO/Tf_2O reagent combination and ensuing addition of alcohol **11** led to the formation of the (*S*)-phenyl dimers. Unfortunately, several side products were formed during these reactions, presumably due to activation of the thiomannosyl acceptor and/or the dimer products. Addition of triethylphosphite to scavenge any thiophilic side products of the activator system did not lead to cleaner reactions, and the desired products could only be obtained in moderate yield.[30,31] We therefore switched to an orthogonal glycosylation approach and transformed (*S*)-phenyl mannosides **8** and **20** into carboxylbenzyl (CB) donors **10** and **22**, respectively.[11] Activation of these CB mannuronate esters in the presence of acceptor **11** was achieved using Tf_2O and di-*tert*-butyl methyl pyridine (DTBMP), and the desired dimers **12** and **21** were both obtained in 65% yield, with excellent β-selectivity.

With the monomers (**8** and **20**) and dimer building blocks (**12** and **21**) in hand, we set out to assemble the target oligomers. First, monomeric donor **8** was condensed with azidopropanol at −78 °C to provide the terminal mannuronate ester **23**, carrying an azidopropanol spacer in 76% yield. Hydrazine treatment of **23** liberated the C4-OH, to give the reducing end mannuronate ester **24** in near quantitative yield. Acceptor **24** was then mannosylated with **20** and **8** using our standard Ph_2SO/Tf_2O activation protocol to give the dimers **25** and **26**, in somewhat reduced yields (52 and 46%, respectively). When dimeric donors **21** and **12** were employed in the condensation with **25**, a further drop in yield was observed: trimers **28** and **29** were isolated in 29 and 28%, respectively. In all these condensations, TLC analysis showed complete consumption of the thio donors **8**, **20**, **12**, and **21** in the preactivation step, but incomplete conversion into the coupled products. In our previous studies toward the synthesis of heparin oligosaccharides, we observed a similar behavior of (*S*)-phenyl glucuronate ester donors.[32] This setback was overcome by replacing the Ph_2SO/Tf_2O system with the closely related 1-benzenesulfinyl piperidine (BSP)/Tf_2O couple.[33] Application of the latter activator system in the present case gave a significant improvement in the outcome of the glycosylations, and now the dimers and trimers were obtained in satisfactory yields (**25**: 67%, **26**: 62%, **28**: 74%, and **29**: 51%). To elongate the di- (**26**) and trimannoside (**29**), the levulinoyl groups were removed and the resulting alcohols **27** and **30** were glycosylated with dimer donor **22**. Gratifyingly, both the [2 + 2] and [2 + 3] coupling proceeded efficiently to provide the tetra- and pentamer mannuronate esters **31** and **32** in 67 and 69% yields, respectively. Importantly, the excellent β-selectivity was maintained in all condensations and was not affected by the size of the coupling partners, underscoring the strength of mannuronate ester donors in the construction of the β-mannosidic bond. To complete the synthesis of the set of mannuronic acid alginates, the oligomers were deprotected by saponification and ensuing hydrogenolysis (Scheme 4).

(24) Full neighboring group participation of the C5-carboxylate does not occur. See also: Schmidt, R. R.; Rücker, E. *Tetrahedron Lett.* **1980**, *21*, 1421.

(25) Jensen, H. H.; Lyngbye, L.; Bols, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 3447.

(26) Analogously, in the $^3H_4$ oxacarbenium ion of L-gulose, the C5 epimer of D-mannose, all ring substituents take up their most favorable orientation, and glycosydations of L-gulose proceed with an unusual high preference for the α-anomer: Dinkelaar, J.; van den Bos, L. J.; Hogendorf, W. F. J.; Lodder, G.; Overkleeft, H. S.; Codée, J. D. C.; van der Marel, G. A. *Chem.−Eur. J.* **2008**, *14*, 9400.

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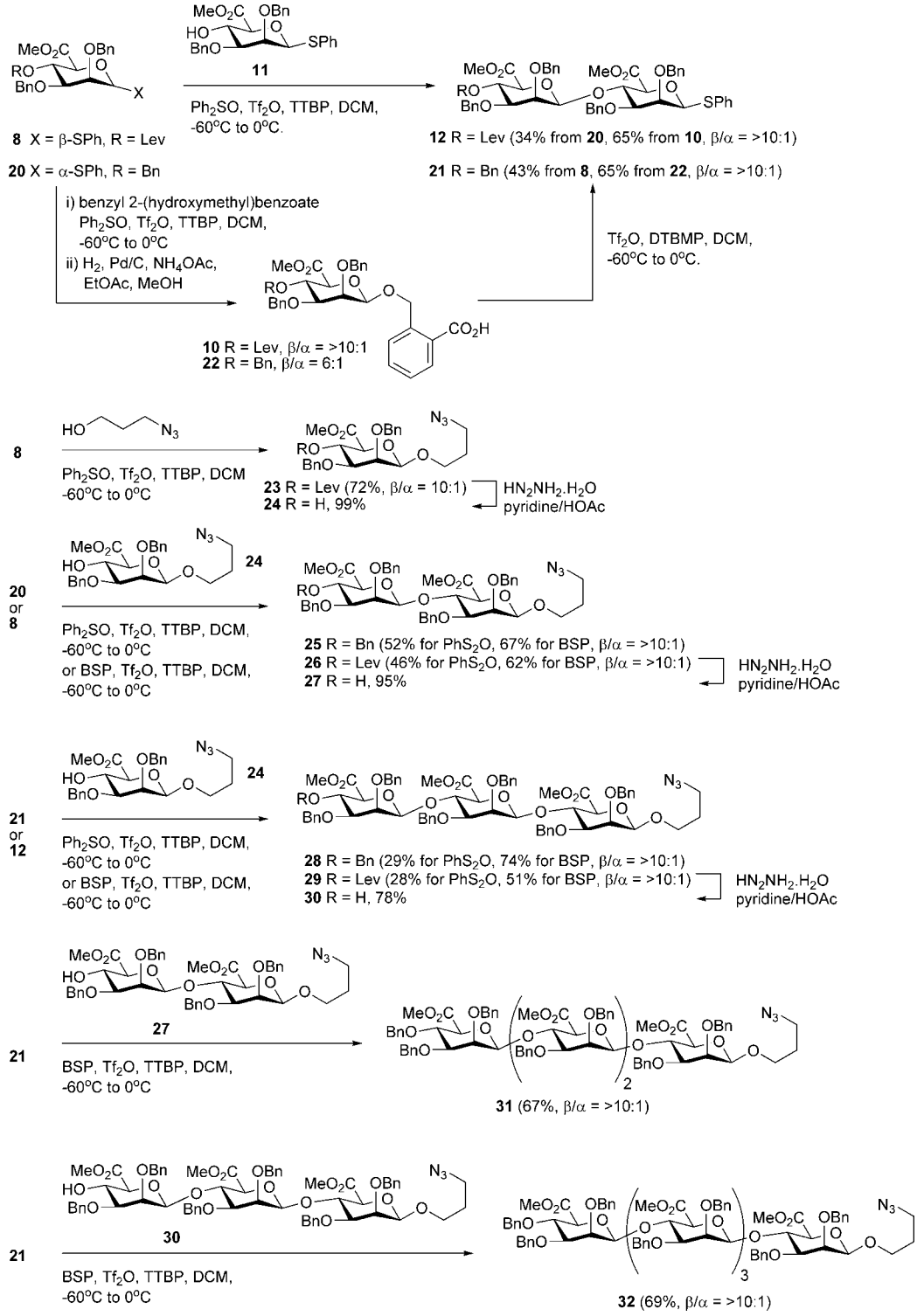
SCHEME 3. Assembly of the Mannuronate Ester Oligomers

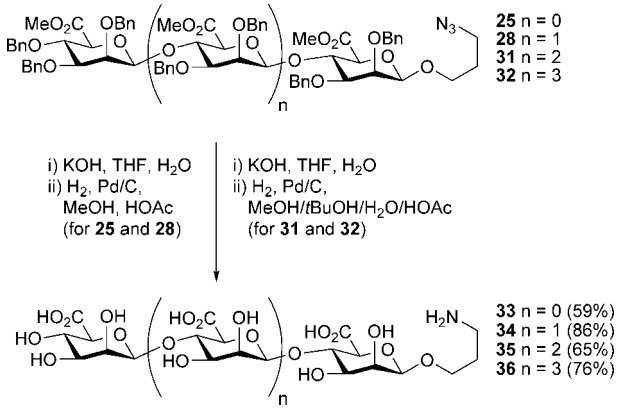


Conclusion

In conclusion, the outcome of the sulfonium ion mediated condensations of pyranosyl uronate **16** indicate that the C5-carboxylate ester exerts a strong stereodirecting effect, promoting the formation of 1,5-*cis* glycosidic bonds. This remote stereodirecting effect can be rationalized with the most stable oxacarbenium ion, having an axially oriented carboxylate ester, as product forming intermediate. The stereocontrol of mannuronate esters is independent of the type of donor employed and agrees well with this postulate.[34,16b] In concert with the other substituents on the ring, the axial C5-carboxylate ester favors the formation of the $^{3}H_{4}$ half-chair over the $^{4}H_{3}$ conformer. Incoming nucleophiles attack the $^{3}H_{4}$ half-chair oxacarbenium ion in a β-fashion, leading to the formation of the counterintuitive 1,2-*cis*-mannosidic bond. The value of the stereodirecting

(34) See for some recent examples of oxacarbenium ion directed stereoselective glycosylations: Zhu, X.; Kawathar, S.; Rao, Y.; Boons, G.-J. *J. Am. Chem. Soc.* **2006**, *128*, 11948. Also see ref 16b.

SCHEME 4. Deprotection of the Mannuronic Acid Oligomers



effect of the C5-glycuronate ester has been demonstrated in the construction of a set of mannuronic acid alginate oligomers. Also when larger coupling partners are involved the mannuronate esters reliably produce the 1,2-*cis* linkage. Current research is aimed at further validation of the mechanistic rationale put forth, the identification of the intermediates observed by NMR, and the role of the counterion in the glycosylations.

Experimental Section

General Procedure for Ph_2SO/BSP-Tf_2O Mediated Glycosylations: The thiodonor, TTBP (3 equiv), and Ph_2SO (1.2 equiv) or BSP (1.2 equiv) were dissolved in DCM (0.05 M donor in DCM) and stirred over molecular sieves (3 Å) for 30 min before being cooled to −60 °C. Tf_2O (1.1 equiv) was added, and the mixture was warmed to −45 °C in 15 min, after which the solution was brought back to −60 °C, and the acceptor was added (0.1 M in DCM). The mixture was allowed to very slowly reach 0 °C (several hours), and Et_3N (5 equiv) was added. The molecular sieves were filtered off, and the mixture was washed with saturated aqueous $NaHCO_3$. The aqueous layer was extracted twice with DCM, and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resulting mixture was purified by silica gel column chromatography and size exclusion chromatography to provide the target compounds.

General Procedure for Levulinoyl Cleavage: The levulinoyl ester was dissolved in pyridine/HOAc (4/1, 0.05 M), and $H_2NNH_2 \cdot H_2O$ (5 equiv) was added. The reaction was stirred for 20 min, after which a few drops of acetone were added. The mixture was diluted with EtOAc, washed with aqueous HCl (1 M), saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated. Column chromatography yielded the pure alcohols.

Low-Temperature NMR Experiment: Thiomannuronic acid **1** (13 mg, 0.025 mmol) and Ph_2SO (6 mg, 1.2 equiv) were dissolved in CD_2Cl_2 (0.5 mL), and the solution was transferred to an argon-flushed NMR tube. The NMR sample was immersed in the NMR probe, which was cooled to −50 °C. After a spectrum was recorded, the sample was removed from the probe and immersed in an acetone bath (−78 °C). Tf_2O (5 μL) was added; the NMR tube was quickly shaken to ensure complete mixing, and the tube was reimmersed in the cold NMR probe (−50 °C). The probe was maintained at this temperature for 30 min and then gradually warmed to −10 °C (steps of 10 °C).

Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(methyl 2,3-di-*O*-benzyl-4-*O*-acetyl-β-D-mannopyranosyl uronate)-α-D-glucopyranoside) (7): The synthesis of the title compound has been reported previously.[8a]

Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(methyl 2,3-di-*O*-benzyl-4-O-levulinoyl-β-D-mannopyranosyluronate)-α-D-glucopyranoside (9): The title compound was synthesized from **8** (98 mg, 0.17 mmol) and **6** (118 mg, 0.26 mmol) as described by the general procedure for Ph_2SO-Tf_2O mediated glycosylations (93%): $[\alpha]_D = +10$ (c = 0.019, DCM); IR (neat) ν (cm^{-1}) 737, 1713, 1744; ^1H NMR (400 MHz) δ 2.53 (m, 2H, CH_2 Lev), 2.71 (t, 2H, J = 6.8 Hz, CH_2 Lev), 3.31 (s, 3H, OCH_3), 3.40 (m, 3H, H-3′, H-6, H-4), 3.50 (dd, 1H, J = 3.6 Hz, J = 9.6 Hz, H-2), 3.70 (m, 4H, CO_2Me, H-5′), 3.77 (m, 2H, H-5, H-5′), 4.01 (t, 1H, J = 9.6 Hz, H-3), 4.13 (m, 2H, H-6, H-1′), 4.29 (d, 1H, J = 12.4 Hz, CH*H*Ph), 4.49 (d, 2H, J = 11.6 Hz, 2 × CH*H*Ph), 4.57 (d, 1H, J = 3.2 Hz, H-1), 4.66 (d, 1H, J = 12 Hz, CH*H*Ph), 4.74−4.89 (m, 4H, 4 × CH*H*Ph), 4.91 (d, 1H, J = 8.0 Hz, CH*H*Ph), 5.02 (d, 1H, J = 10.8 Hz, CH*H*Ph), 5.51 (t, 1H, J = 9.6 Hz, H-4′), 7.17−7.39 (m, 25H, H_{arom}); ^{13}C NMR (100 MHz) δ 27.8 (CH_2 Lev), 29.8 (CH_3 Lev), 37.7 (CH_2 Lev), 52.5 (CH_3 CO_2CH_3), 55.0 (OCH_3), 68.6 (C-6), 69.1 (C-4′), 69.7 (C-5), 71.6 (CH_2 Bn), 72.9 (C-2′), 73.2 (CH_2 Bn), 73.5 (C-5′), 73.5 (CH_2 Bn), 74.6 (CH_2 Bn), 75.6 (CH_2 Bn), 77.5 (C-4), 78.1 (C-3′), 79.8 (C-2), 82.1 (C-3), 97.7 (C-1), 101.5 ($J_{C\text{-}1',H\text{-}1'}$ = 156 Hz, C-1′), 127.4−128.4 (C_{arom}), 137.7 (C_q Bn), 138.0 (C_q Bn), 138.2 (C_q Bn), 138.7 (C_q Bn), 167.8, 171.4 (C═O), 206.1 (C═O); HRMS: [M + Na^+] calcd for $C_{54}H_{60}O_{14}Na$ 955.3875, found 955.3883.

(Carboxylbenzyl 2,3-di-*O*-benzyl-4-*O*-levulinoyl-β-mannopyranosyluronic acid) methyl ester (10). Thiomannuronic acid **8** (914 mg, 1.58 mmol) and 2-hydroxymethyl benzoic acid benzyl ester (1.14 g, 4.73 mmol) were coupled as described in the general procedure for Ph_2SO-Tf_2O mediated glycosylations. The resulting (benzyl carboxylbenzyl 2,3-di-*O*-benzyl-4-*O*-levulinoyl-β-mannopyranosyluronic acid) methyl ester was purified by column chromatography (100% PE to 98/2 toluene/EtOAc) and taken up in EtOAc/MeOH (0.05 M, 1/3). NH_4OAc (3 equiv) and Pd/C (catalytic amount) were added, and the mixture was degassed and purged with H_2. The mixture was stirred overnight under a H_2 atmosphere, after which the Pd/C was filtered off and the mixture was concentrated. The product was purified by column chromatography (100% PE to 80/20/1 PE/EtOAc/AcOH) to provide the title compound (66% over 2 steps): $[\alpha]_D = -36$ (c = 0.75, $CHCl_3$); IR (neat) ν (cm^{-1}) 729, 1271, 1686, 1714, 1734; ^1H NMR (400 MHz) δ 2.15 (s, 3H, CH_3 Lev), 2.54 (m, 2H, CH_2 Lev), 2.71 (m, 2H, CH_2 Lev), 3.61 (m, 4H, CH_3 CO_2Me, H-3), 3.96 (s, H-2), 3.99 (d, 1H, J = 8.0 Hz, H-5), 4.47 (d, 1H, J = 12.0 Hz, C*H*HPh), 5.53 (d, 1H, J = 12.0 Hz, CH*H*Ph), 4.69 (s, 1H, H-1), 4.83 (d, 1H, J = 12.4 Hz, C*H*HPh), 4.93 (d, 1H, J = 12.4 Hz, CH*H*Ph), 5.06 (d, 1H, J = 13.2 Hz, C*H*HPh), 5.36 (d, 1H, J = 13.2 Hz, C*H*HPh), 5.63 (t, 1H, J = 8.4 Hz, H-4), 7.22−7.49 (m, 12H, H_{arom}), 7.66 (d, 1H, J = 7.6 Hz), 8.05 (d, 1H, J = 7.6 Hz), 9.9 (br s, 1H, CO_2H); ^{13}C NMR (125 MHz) δ 27.8 (CH_2 Lev), 29.7 (CH_3 Lev), 37.7 (CH_2 Lev), 52.4 (CH_3 CO_2Me), 69.1 (C-4), 69.9 (CH_2 Bn), 71.7 (CH_2 Bn), 73.1, 73.2 (C-2 and C-5), 73.4 (CH_2 Bn), 77.3 (C-3), 100.5 (J_{C1-H1} = 158 Hz, C-1), 126.8 (C_q CB), 127.1, 127.2, 127.4, 127.5, 127.6, 127.7, 127.9, 128.1, 128.2, 131.2, 133.1 (CH_{arom}), 137.7 (C_q Bn), 138.1 (C_q Bn), 140.4 (C_q CB), 168.0 (C═O), 171.5 (C═O), 171.7 (C═O), 206.4 (C═O, Lev); HRMS [M + Na^+] calcd for $C_{34}H_{36}O_{11}NNa$ 643.2155, found 643.2155.

Phenyl (methyl 2,3-di-*O*-benzyl-4-*O*-(methyl 2,3-di-*O*-benzyl-4-*O*-levulinoyl-β-D-mannopyranosyl uronate)-1-thio-β-D-mannopyranosyl uronate) (12): CB-Mannoside **10** (800 mg, 1.29 mmol), thiomannoside **11** (929 mg, 1.93 mmol), and di-*tert*-butylmethylpiridine (DTBMP, 662 mg, 3.35 mmol) were dissolved in DCM (0.05 M, 25 mL) and stirred over molecular sieves (3 Å) for 30 min before being cooled to −60 °C. Tf_2O (0.24 mmol, 1.43 mmol) was added, and the mixture was allowed to very slowly reach 0 °C (several hours). Et_3N (5 equiv) was added; the molecular sieves were filtered off, and the mixture was washed with saturated aqueous $NaHCO_3$. The aqueous layer was extracted twice with DCM, and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resulting mixture was purified by silica gel column chromatography to provide the thiodisaccharide (65%): $[\alpha]_D = -68$ (c = 1, DCM); IR (neat) ν (cm^{-1}) 729, 1060, 1361, 1717, 1744; ^1H NMR (400 MHz) δ 2.14 (s, 3H, CH_3 Lev), 2.54 (m, 2H, CH_2 Lev), 2.67 (m, 2H, CH_2 Lev), 3.46 (dd, 1H, J =

2.8 Hz, J = 9.6 Hz, H-3′), 3.51 (s, 3H, CH_3 CO_2Me), 3.64 (m, 4H, CH_3 CO_2Me, H-3), 3.72 (d, 1H, J = 10.0 Hz, H-5′), 3.81 (d, 1H, J = 2.8 Hz, H-2′), 3.85 (d, 1H, J = 9.6 Hz), 4.06 (d, 1H, J = 2.0 Hz, H-2), 4.40−4.52 (m, 3H, H-4, CH_2 Bn), 4.66−4.80 (m, 7H, H-1, H-1′, 5 × C*H*HPh), 4.97 (d, 1H, J = 12.0 Hz, CH*H*Ph), 5.43 (t, 1H, J = 9.6 Hz, H-4′), 7.19−7.54 (m, 25H, H_{arom}); ^{13}C NMR (100 MHz) δ 27.8 (CH_2 Lev), 29.8 (CH_3 Lev), 37.7 (CH_2 Lev), 52.3 (CH_3 CO_2Me), 52.4 (CH_3 CO_2Me), 68.9 (C-4′), 73.1 (CH_2 Bn), 73.3 (C-5′), 74.3 (CH_2 Bn), 74.9 (C-2′), 75.1 (CH_2 Bn), 77.5 (C-2), 77.7 (C-4, C-5), 78.4 (C-3′), 81.2 (C-3), 81.2 (J_{C1-H1} = 154 Hz, C-1), 102.5 ($J_{C1'-H1'}$ = 159 Hz, C-1′), 127.2, 127.3, 127.5, 127.7, 127.9, 128.1, 128.2, 128.3, 128.9, 130.7 (CH_{arom}), 135.2 (C_q SPh), 137.8 (C_q Bn), 138.0 (C_q Bn), 138.6 (C_q Bn), 138.7 (C_q Bn), 167.7 (C═O), 168.3 (C═O), 171.5 (C═O), 206.1 (C═O, Lev); HRMS [M + Na^+] calcd for $C_{53}H_{56}O_{14}NaS$ 971.3289, found 971.3293.

(2,3,4-Tri-*O*-benzyl-α/*β*-mannopyranosyluronic acid methyl ester)-1-(*N*-phenyl)-2,2,2-trifluoroacetimidate (13): 2,3,4-Tri-*O*-benzyl-α-mannopyranosyluronic acid methyl ester (**20**)[8] (3.0 g, 5.3 mmol) was dissolved in DCM/H_2O (0.2 M, 10/1) and treated with *N*-iodosuccinimide (NIS) (1.2 g, 5.3 mmol) and TFA (0.41 mL, 5.3 mmol) for 15 min, after which the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ and $Na_2S_2O_3$. The layers were separated, and the aqueous layer was extracted once with DCM. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification of the crude oil by column chromatography (80/20 PE/EtOAc 75/25 PE/EtOAc) gave the pure lactol (1.55 g, 3.23 mmol 61%). The lactol (330 mg, 0.690 mmol) was dissolved in acetone (4 mL), containing 5 drops of water. Trifluoroacetimidoyl chloride[35] and K_2CO_3 (190 mg, 1.38 mmol) were added, and the reaction mixture was stirred until TLC analysis indicated complete cenversion of the starting material. The reaction mixture was filtered and concentrated. Purification of the crude oil by column chromatography (100% toluene to 92.5/7.5 toluene/EtOAc) gave the pure imidate (α/β = 5:1, 434 mg, 0.668 mmol, 98%): IR (neat) ν (cm^{-1}) 736, 1101, 1708, 1749; ^{1}H NMR (400 MHz) major anomer (α) δ 3.66 (s, 3H, CH_3 CO_2Me), 3.81 (br s, 1H, H-2), 3.88 (dd, 1H, J = 3.2 Hz, J = 8.4 Hz, H-3), 4.29 (t, 1H, J = 8.4 Hz, H-4), 4.38 (d, 1H, J = 8.4 Hz, H-5), 4.53−4.83 (m, 6H, 3 × CH_2 Bn), 6.34 (br s, 1H, H-1), 6.75 (d, 2H, J = 8.0 Hz, CH_{arom}*N*Ph), 7.06 (t, 1H, J = 8.8 Hz, CH_{arom}*N*Ph), 7.25−7.33 (17H, CH_{arom}); ^{13}C NMR (125 MHz) major anomer (α) δ 52.5 (CH_3 CO_2Me), 72.7 (2 × CH_2 Bn), 73.2 (C-2), 73.8 (C-5), 74.6 (CH_2 Bn), 75.8 (C-4), 77.4 (C-3), 94.8 (J_{C1-H1} = 178 Hz, C-1), 115.8 (q, $^1J_{C-F}$ = 285 Hz, CF_3), 119.3 (CH_{arom}*N*Ph), 124.3 (CH_{arom}*N*Ph), 126.9, 127.3, 127.5, 127.7, 127.8, 127.9, 128.2, 128.3, 128.6, 128.8, 129.1, 129.2, 129.7, 129.9 (CH_{arom}), 137.4 (C_q Bn), 137.6 (C_q Bn), 137.7 (C_q Bn), 143.2 (C_q NPh), 142.4 (q, $^2J_{C-F}$ = 36 Hz, *C*═N), 168.7 (C═O); β-anomer ^{1}H NMR (400 MHz) diagnostic peaks 3.63 (s, CH_3 CO_2Me), 5.93 (br s, 1H, H-1); ^{13}C NMR (125 MHz) diagnostic peaks 52.2 (CH_3 CO_2Me), 94.4 (J_{C1-H1} = 166 Hz, C-1); HRMS [M + Na^+] calcd for $C_{36}H_{34}F_3O_7NNa$ 672.2185, found 672.2191.

(Allyl 1-deoxy-2,3,4-tri-*O*-benzyl-*β*-mannopyranosyluronic acid) methyl ester (15): (2,3,4-Tri-*O*-benzyl-α/β-mannopyranosyluronic acid methyl ester)-1-(*N*-phenyl)-2,2,2-trifluoroacetimidate (**13**) (110 mg, 0.169 mmol) and allylTMS (0.11 mL, 0.68 mmol) were dissolved in DCM (3.4 mL) and cooled to −60 °C. TMSOTf (6 μL, 3.4 μmol) was added, and the mixture was allowed to warm to −20 °C in 2 h, after which the reaction was quenched by the addition of Et_3N. The mixture was concentrated and the product purified by column chromatography (95/5 toluene/EtOAc to 90/10 toluene/EtOAc) to give the pure C-mannoside **15** (62 mg, 0.122 mmol, 73%): $[\alpha]_D$ = −36 (*c* 1); IR (neat) ν (cm^{-1}) 736, 1101, 1749; ^{1}H NMR (400 MHz) δ 2.29 (m, 1H, C*H*HCH═CH_2), 2.48 (m, 1H, CH*H*CH═CH_2), 3.35 (t, 1H, J = 6.8 Hz, H-1), 3.60 (dd, 1H, J = 2.8 Hz, J = 9.2 Hz, H-3), 3.70 (s, 3H, CH_3 CO_2Me), 3.76 (d, 1H, J = 2.8 Hz, H-2), 3.81 (d, J = 10.0 Hz, H-5), 4.23 (t, 1H, J = 9.2 Hz, H-4), 4.66 (2H, CH_2Ph), 4.73 (d, 1H, J = 11.6 Hz, CH*H*Ph), 4.77 (d, 1H, J = 11.6 Hz, CH*H*Ph), 4.85 (d, 1H, J = 12.4 Hz, CH*H*Ph), 5.01 (m, 3H, CH_2CH═C*H*$_2$, CH*H*Ph), 5.63 (m, 1H, CH_2C*H*═CH_2), 7.21−7.38 (m, 15H, H_{arom}); ^{13}C NMR (100 MHz) δ 35.4 (*C*H_2CH═CH_2), 52.3 3 (CH_3 CO_2Me), 72.6 (CH_2 Bn), 74.4 (CH_2 Bn), 74.4 (C-2), 75.2 (CH_2 Bn), 76.3 (C-4), 79.1 (C-5), 79.3 (C-1), 84.5 (C-3), 117.5 (CH_2CH═*C*H_2), 127.4, 127.6, 127.7, 128.0, 128.2, 128.3, 128.5 (CH_{arom}), 134.1 (CH_2*C*H═CH_2), 138.2 (C_q Bn), 138.5 (C_q Bn), 169.2 (C═O); HRMS [M + Na^+] calcd for $C_{31}H_{34}O_7Na$ 525.2253, found 525.2240.

Couplings of 16 and 17. 16 and **17** were condensed with benzyl alcohol (BnOH, 4 equiv), isopropanol (4 equiv), *tert*-butanol (4 equiv), and 1-adamantanol (4 equiv) as described by the general procedure for Ph_2SO-Tf_2O mediated glycosylations. The acceptor alcohols were added as a stock solution (5 M in DCM), which were dried over molecular sieves. Activation of the thiopyranosides was achieved at −78 °C for 5 min. The reactions were quenched after 15 min at −78 °C to prevent possible anomerization. Purification of the products was achieved by column chromatography. If complete separation of both anomers was achieved, they were separately isolated. If separation was not possible, the α/β-mixtures were isolated and analyzed.

6-Benzyloxy tetrahydropyran-2-carboxylic acid methyl ester (18a): The product was obtained from **16** (37 mg, 0.15 mmol) and benzylalcohol as an α/β-mixture (α/β = 1:7.7, 74%): IR (neat) ν (cm^{-1}) 997, 1738; ^{1}H NMR (400 MHz) δ 1.51−2.12 (m, 6.8 H, H-3, 4, 5 α+β), 3.77 (s, 3.1 H, CH_3 CO_2Me α+β), 4.08 (dd, 1H, J = 2.4 Hz, J = 10.0 Hz, H-6 β), 4.46 (dd, 0.13H, J = 2.4 Hz, J = 10.0 Hz, H-6 α), 4.52 (d, 1H, J = 9.2 Hz, H-2 β), 5.53 (d, 0.13 H, J = 12.0 Hz, CH*H*Ph α), 4.62 (d, 1H, J = 12.0 Hz, CH*H*Ph β), 4.76 (d, 0.13 H, J = 12.0 Hz, CH*H*Ph α), 4.95 (d, 1 H, J = 12.0 Hz, CH*H*Ph β), 5.08 (s, 0.13H, H-2 α); 7.26−7.35 (m, 5.7H, H_{arom}); ^{13}C NMR (125 MHz) δ 17.7 (α), 21.2 (β), 27.7 (β), 28.2 (α), 29.1 (α), 30.5 (β) (C-3, C-4, C-5), 52.1 (CH_3 CO_2Me α+β), 68.5 (C-6 α), 69.0 (CH_2 Bn α), 70.0 (CH_2 Bn β), 74.4 (C-6β), 97.0 (C-1α), 100.8 (C-1β), 127.6, 127.8, 127.9, 128.3, 128.4 (CH_{arom} α+β), 137.7 (C_q Ph β), 138.4 (C_q Ph α), 171.3 (C═O, β), 172.3 (C═O, α); HRMS [M + Na^+] calcd for $C_{14}H_{18}O_4Na$ 273.1103, found 273.1098.

6-Isopropyloxy tetrahydropyran-2-carboxylic acid methyl ester (18b): The product was obtained from **16** (87 mg, 0.35 mmol) and isopropanol as an α/β-mixture (α/β = 1:3.8, 48%): IR (neat) ν (cm^{-1}) 1037, 1755; ^{1}H NMR (400 MHz) δ 1.12 (d, 0.78H, CH_3 *i*Pr α), 1.14 (d, 3H, CH_3 *i*Pr β), 1.21 (d, 0.78H, CH_3 *i*Pr α), 1.26 (d, 3H, CH_3 *i*Pr β), 1.38−1.95 (m, 7.6H, H-3, 4, 5 α+β), 3.75 (3.8 H, CH_3 CO_2Me α+β), 3.93 (m, 0.26H, CH *i*Pr α), 4.06 (m, 2H, CH *i*Pr β, C-6 β), 4.46 (d, 0.26H, J = 11.6 Hz, H-6 α), 4.53 (d, 1H, J = 9.2 Hz, H-2 β), 5.07 (s, 0.26H, H-1α); ^{13}C NMR (125 MHz) δ 17.7 (α), 21.9 (β), 27.7 (β), 28.3 (α), 29.6 (α), 31.0 (β) (C-3, 4, 5), 21.3 (CH_3 *i*Pr α), 21.6 (CH_3 *i*Pr β), 23.3 (CH_3 *i*Pr α), 23.5 (CH_3 *i*Pr β), 52.0 (CH_3 CO_2Me α+β), 68.1 (C-6α), 68.4 (CH_3 *i*Pr α), 70.0 (CH_3 *i*Pr β), 74.7 (C-6β), 95.0 (C-2α), 100.1 (C-2α), 171.2 (C═O); HRMS [M + Na^+] calcd for $C_{10}H_{18}O_4Na$ 225.1103, found 225.1099.

6-*tert*-Butyloxy tetrahydropyran-2-carboxylic acid methyl ester (18c): The products were obtained from **16** (62 mg, 0.25 mmol) and *tert*-butanol as pure anomers (α/β = 1:2.9, 52%); IR (neat) ν (cm^{-1}) 1038, 1740; α-anomer, ^{1}H NMR (400 MHz) δ 1.24 (s, 9H, *t*Bu), 1.51−1.95 (m, 6H, H-3, 4, 5), 3.75 (s, 3H, CH_3 COOMe), 4.57 (d, 1H, J = 10.4 Hz, H-6), 5.25 (s, 1H, Hz, H-2); ^{13}C NMR (125 MHz) δ 17.9, 28.2, 31.0 (C-3, C-4, C-5), 28.4 (CH_3 *t*Bu), 52.0 (CH_3 CO_2Me), 68.7 (C-6), 74.5 (C_q *t*Bu), 91.9 (C-2), 172.9 (C═O); β-anomer, ^{1}H NMR (400 MHz) δ 1.27 (s, 9H, *t*Bu), 1.49−1.96 (m, 6H, H-3, 4, 5), 3.75 (s, 3H, CH_3 COOMe), 4.04 (dd,1H, J = 2.4 Hz, J = 10.8 Hz, H-6), 4.63 (dd, 1H, J = 2.0 Hz, J = 10.8 Hz, H-2); ^{13}C NMR (125 MHz) δ 22.2, 27.5, 31.8 (C-3, C-4, C-5), 28.7 (CH_3 *t*Bu), 52.0 (CH_3 CO_2Me), 74.6 (C-6), 75.2

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(C_q *t*Bu), 96.8 (C-2), 171.2 (C═O); HRMS [M + Na^+] calcd for $C_{10}H_{18}O_4Na$ 239.1254, found 239.1254.

6-Adamantyloxy tetrahydropyran-2-carboxylic acid methyl ester (18d): The product was obtained from **16** (48 mg, 0.19 mmol) and 1-adamantanol as an α/*β*-mixture (α/*β* = 1:1.2, 52%), containing Ph_2SO and 1-adamantanol: ^{1}H NMR (400 MHz) *δ* 1.33−2.13 (m, 46.2H, H-3, 4, 5, CH and CH_2 adamantanol, α+*β*), 3.73 (s, 3H, CH_3CO_2Me α), 3.74 (s, 3.6H, CH_3CO_2Me *β*), 4.05 (dd, 1.2H, *J* = 2.4 Hz, *J* = 10.8 Hz, H-6 *β*), 4.60 (dd, 1H, *J* = 2.4 Hz, *J* = 10.8 Hz, H-6 α), 4.75 (d, 1.2H, *J* = H2 *β*), 5.39 (s, 1H, H-2 α); ^{13}C NMR (100 MHz) *δ* 17.8 (α), 22.1 (*β*), 27.5 (*β*), 28.3 (α), 30.8 (α), 31.7 (*β*) (C-3, 4, 5), 30.5 (CH Ada), 36.3 (CH_2 Ada), 42.4 (CH_2 Ada), 51.9 (CH_3CO_2Me α+*β*), 68.5 (C-6 α), 73.5 (C_q Ada α), 74.4 (C_q Ada *β*), 74.5 (C-6 *β*), 90.2 (C-2 α), 94.5 (C-2 α), 171.2 (C═O *β*), 172.8 (C═O α); HRMS [M + Na^+] calcd for $C_{17}H_{26}O_4Na$ 317.1729, found 317.1724.

6-Benzyloxymethyl-2-benzyloxytetrahydropyran (19a): The product was obtained from **17** (94 mg, 0.30 mmol) and benzylalcohol as an α/*β*-mixture (α/*β* = 1:1.4, 82%): IR (neat) *ν* (cm^{-1}) 739, 1037, 1454; ^{1}H NMR (400 MHz) *δ* 1.23−1.89 (m, 14.1H, H-3, 4, 5, α+*β*), 3.44−3.53 (m, 3.35H, 2 × H-7α, H-7*β*), 3.59 (m, 2.7H, H-6*β*, H-7*β*), 4.03 (m, 1H, H-6α), 4.78 (m, 2.35H, H-1*β*, C*H*HPh α), 4.53−4.65 (m, 6.05H, 2 × C*H*HPh α, 3 × C*H*HPh *β*), 4.76 (d, 1H, *J* = 12.0 Hz,C*H*HPh α), 4.76 (d, 1.35H, *J* = 12.0 Hz,C*H*HPh *β*), 4.96 (m, 1H, H-1α), 7.22−7.37 (m, 23.5H, H_{arom}); ^{13}C NMR (100 MHz) *δ* 17.7 (α), 21.7 (*β*), 27.4 (*β*), 27.5 (α), 29.5 (α), 31.0 (*β*) (C-3, C-4, C-5), 68.1 (C-6 α), 68.3 (CH_2 Bn α), 69.8 (CH_2 Bn *β*), 73.2, 73.3, 73.4, 73.5 (C-7α, C-7*β*,CH_2 Bn α, CH_2Bn *β*), 75.4 (C-6 *β*), 96.5 (C-2 α), 100.9 (C-2 *β*), 126.9, 127.4, 127.5, 127.6, 127.8, 127.9, 128.3, 128.4 (CH_{arom} α+*β*), 137.9, 138.4 (C_q Ph α+*β*); HRMS [M + Na^+] calcd for $C_{20}H_{24}O_3Na$ 335.1623, found 335.1618.

6-Benzyloxymethyl-2-isopropyloxytetrahydropyran (19b): The product was obtained from **17** (101 mg, 0.32 mmol) and isopropanol as an α/*β*-mixture (α/*β* = 1:0.6, 61%): IR (neat) *ν* (cm^{-1}) 741, 1037, 1454; ^{1}H NMR (400 MHz) *δ* 1.12 (m, 4.8H, CH_3 *i*Pr α+*β*), 1.23 (m, 4.8H, CH_3 *i*Pr α+*β*), 1.32−1.92 (m, 9.6H, H-3, 4, 5, α+*β*), 3.40−3.50 (m, 2.6H, 2 × H-7α, H-7*β*), 3.57 (m, 0.6H, H-7*β*), 3.66 (m, 0.6H, H-6*β*), 3.91−4.07 (m, 2.6H, H-6α, CH *i*Pr α+*β*), 4.50 (d, 0,6H, *J* = 8.4 Hz, H-1*β*), 4.54−4.62 (m, 3.2H, 2 × C*H*HPh α, 2 × C*H*HPh *β*), 4.99 (s, 1H, H-1α), 7.14−7.33 (m, 8H, H_{arom}); ^{13}C NMR (100 MHz) *δ* 17.7 (α), 21.4 (CH_3 *i*Pr α), 21.8 (CH_3 *i*Pr *β*), 22.0 (*β*), 27.5 (*β*), 27.6 (α), 30.0 (α), 31.6 (*β*) (C-3, C-4, C-5), 67.5 (CH *i*Pr *β*), 67.8 (CH *i*Pr *β*), 69.8 (C-6 α), 73.2, 73.4, 73.6 (C-7α, C-7*β*,CH_2 Bn α, CH_2Bn *β*), 75.4 (C-6 *β*), 94.7 (C-2 α), 100.1 (C-2 *β*), 127.4, 127.5, 128.2, 128.3 (CH_{arom} α+*β*), 138.5 (C_q Ph α+*β*); HRMS [M + Na^+] calcd for $C_{16}H_{24}O_3Na$ 287.1623, found 287.1619.

6-Benzyloxymethyl-2-*tert*-butyloxytetrahydropyran (19c): The products were obtained from **17** (94 mg, 0.30 mmol) and *tert*-butanol as pure anomers (α/*β* = 1:0.38, 60%): IR (neat) *ν* (cm^{-1}) 741, 1101, 1479; α-anomer, ^{1}H NMR (400 MHz) *δ* 1.25 (s, 9H, CH_3 *t*Bu), 1.40 (m, 1H), 1.50−1.68 (m, 4H), 1.87 (m, 1H, H-3, 4, 5), 3.38−3.46 (m, 2H, 2 × H-7), 4.13 (m, 1H, H-6), 4.53 (d, 1H, *J* = 12.4 Hz, C*H*HPh), 4.57 (d, 1H, *J* = 12.4 Hz, CH*H*Ph), 5.17 (d, 1H, *J* = 2.8 Hz, H-1), 7.24−7.32 (m, 5H, H_{arom}); ^{13}C NMR (100 MHz) *δ* 17.7, 27.9, 31.3 (C-3, C-4, C-5), 28.8 (CH_3 *t*Bu), 67.4 (C-6), 73.2, 73.8 (C-7, CH_2 Bn), 91.5 (C-1), 127.3, 127.4, 128.2 (CH_{arom}), 138.6 (C_q Ph); *β*-anomer, ^{1}H NMR (400 MHz) *δ* 1.27 (s, 9H, CH_3 *t*Bu), 1.21 (m, 1H), 1.42−1.61 (m, 4H), 1.87 (m, 1H, H-3, 4, 5), 3.47 (dd, 1H, *J* = 5.2 Hz, *J* = 10.0 Hz, H-7), 3.55 (d, 1H, *J* = 6.0 Hz, *J* = 10.0 Hz, H-7), 3.64 (m, 1H, H-6), 4.53 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.59 (d, 1H, *J* = 12.4 Hz, CH*H*Ph), 4.61 (dd, 1H, *J* = 2.4 Hz, *J* = 9.6 Hz, H-1), 7.25−7.32 (m, 5H, H_{arom}); ^{13}C NMR (100 MHz) *δ* 22.4, 27.4, 32.5 (C-3, C-4, C-5), 28.8 (CH_3 *t*Bu), 73.4 (CH_2 Bn), 73.6 (C-7), 75.3 (C-6), 96.6 (C-2), 127.4, 127.5, 128.3 (CH_{arom}), 138.5 (C_q Ph); HRMS [M + Na^+] calcd for $C_{17}H_{26}O_3Na$ 301.1780, found 301.1775.

6-Benzyloxymethyl-2-adamantyloxytetrahydropyran (19d): The products were obtained from **17** (94 mg, 0.30 mmol) and 1-adamantanol as pure anomers (α/*β* = 1:0.33, 74%): IR (neat) *ν* (cm^{-1}) 736, 1078, 1439; α-anomer, ^{1}H NMR (400 MHz) *δ* 1.33 (m, 1H), 1.50−1.69 (m, 10H), 1.79−1.95 (m, 7H, H-3, 4, 5 + 6 × CH_2 Ada), 2.10 (br s, 3H, 3 × CH Ada), 3.39−3.48 (m, 2H, 2 × H-7), 4.17 (m, 1H, H-6), 4.53 (d, 1H, *J* = 12.4 Hz, C*H*HPh), 4.57 (d, 1H, *J* = 12.4 Hz, CH*H*Ph), 5.30 (d, 1H, *J* = 2.8 Hz, H-1), 7.22−7.36 (m, 5H, H_{arom}); ^{13}C NMR (100 MHz) *δ* 17.7, 27.9, 31.3 (C-3, C-4, C-5), 30.6 (CH Ada), 36.4 (CH_2 Ada), 42.7 (CH_2 Ada), 67.4 (C-6), 73.3, 73.9 (C-7, CH_2 Bn), 90.0 (C-1), 127.3, 128.2 (CH_{arom}), 138.6 (C_q Ph); *β*-anomer, ^{1}H NMR (400 MHz) *δ* 1.26 (m, 1H), 1.41−1.65 (m, 10H), 1.79−1.89 (m, 7H, H-3, 4, 5 + 6 × CH_2 Ada), 2.10 (br s, 3H, 3 × CH Ada), 3.47 (dd, 1H, *J* = 4.4 Hz, *J* = 9.6 Hz, H-7), 3.55 (d, 1H, *J* = 6.4 Hz, *J* 10.0 Hz, H-7), 3.64 (m, 1H, H-6), 4.53 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.59 (d, 1H, *J* = 12.4 Hz, CH*H*Ph), 4.72 (dd, 1H, *J* = 2.8 Hz, *J* = 8.8 Hz, H-1), 7.24−7.35 (m, 5H, H_{arom}); ^{13}C NMR (100 MHz) *δ* 22.4, 27.4, 32.5 (C-3, C-4, C-5), 30.7 (CH Ada), 36.3 (CH_2 Ada), 42.7 (CH_2 Ada), 73.4 (CH_2 Bn), 73.7 (C-7), 76.7 (C-6), 94.8 (C-2), 127.4, 127.5, 128.3 (CH_{arom}), 138.5 (C_q Ph); HRMS [M + Na^+] calcd for $C_{23}H_{32}O_3Na$ 379.2249, found 379.2244.

Phenyl (methyl 2,3-di-*O*-benzyl-4-*O*-(methyl 2,3,4-tri-*O*-benzyl-*β*-D-mannopyranosyl uronate)-1-thio-*β*-D-mannopyranosyl uronate) (21): The title compound was synthesized form CB-Mannoside **22** (800 mg, 1.29 mmol) and thiomannoside **11** (929 mg, 1.93 mmol) as described for **12**: $[\alpha]_D = -55$ (*c* 1, DCM); IR (neat) *ν* (cm^{-1}) 737, 1063, 1749; ^{1}H NMR (400 MHz) *δ* 3.49 (dd, 1H, *J* = 2.8 Hz, *J* = 9.6 Hz, H-3′), 3.53 (s, 3H, CH_3CO_2Me), 3.64 (m, 4H, CH_3CO_2Me, H-3), 3.79 (d, 1H, *J* = 10.0 Hz, H-5′), 3.83 (d, 1H, *J* = 2.8 Hz, H-2′), 3.86 (d, 1H, *J* = 9.6 Hz), 4.05 (d, 1H, *J* = 2.0 Hz, H-2), 4.19 (t, 1H, *J* = 9.6 Hz, H-4′), 4.51 (t, 1H, *J* = 9.6 Hz, H-4), 4.56 (s, 2H, CH_2 Bn), 4.60−4.64 (m, 2H, 2 × C*H*HPh), 4.64 (s, 1H, H-1′), 4.73 (d, 1H, *J* = 10.8 Hz, CH*H*Ph), 4.78−4.86 (m, 4H, H-1, 3 × C*H*HPh), 4.96 (d, 1H, *J* = 12.0 Hz, CH*H*Ph), 4.98 (d, 1H, *J* = 12.0 Hz, CH*H*Ph), 7.20−7.46 (m, 30H, H_{arom}); ^{13}C NMR (100 MHz) *δ* 52.5 (CH_3CO_2Me), 52.9 (CH_3CO_2Me), 72.3 (CH_2 Bn), 73.8 (CH_2 Bn), 74.9 (CH_2 Bn), 77.5 (2 × CH_2Bn), 75.6 (C-5′), 75.8 (C-2′), 76.1 (C-4′), 77.8 (C-4), 77.9 (C-2),78.3 (C-5), 81.7 (C-3), 81.9 (C-3′), 89.4 (J_{C1-H1} = 154 Hz, C-1), 103.3 ($J_{C1'-H1'}$ = 156 Hz, C-1′), 127.2, 127.3, 127.4, 127.5, 127.6, 127.7, 128.0, 128.1, 128.2, 128.3, 128.5, 128.9, 129.0, 129.2, 130.2, 130.7, 130.8 (CH_{arom}), 135.3 (C_q SPh), 137.8 (C_q Bn), 138.0 (2xC_q Bn), 138.1 (C_q Bn), 138.3 (C_q Bn), 138.6 (C_q Bn), 138.8 (C_q Bn), 168.8 (C═O), 169.1 (C═O); HRMS [M + NH_4^+] calcd for $C_{55}H_{60}O_{12}NS$ 958.3831, found 958.3841.

(Carboxylbenzyl 2,3,4-tri-*O*-benzyl-*β*-mannopyranosyluronic acid) methyl ester (22): The title compound was synthesized from **20**[8] (1.72 g, 3.0 mmol) and 2-hydroxymethyl-benzoic acid benzyl ester (2.2 g, 9.1 mmol) as described for **10** (α/*β* = 1:6, 65% over 2 steps): IR (neat) *ν* (cm^{-1}) 731, 1278, 1680, 1715, 1734; *β*-anomer, ^{1}H NMR (400 MHz) *δ* 3.57 (dd, 1H, *J* = 2.4 Hz, *J* = 9.2 Hz, H-3), 3.66 (s, 3H, CH_3CO_2Me), 3.92 (d, 1H, *J* = 8.8 Hz, H-5), 3.98 (s, 1H, H-2), 4.30 (t, 1H, *J* = 8.8 Hz), 4.48 (d, 1H, *J* = 11.6 Hz, C*H*HPh), 4.64 (m, 2H, H-1, CH*H*Ph), 4.86 (m, 2H, 2 × C*H*HPh), 5.00 (d, 1H, *J* = 12.4 Hz, CH*H*Ph), 5.07 (d, 1H, *J* = 14.4 Hz, C*H*HPh), 5.34 (d, 1H, *J* = 14.0 Hz, C*H*HPh), 7.21−7.60 (m, 17H, H_{arom}), 7.65 (d, 1H, *J* = 7.6 Hz), 8.05 (d, 1H, *J* = 8.0 Hz), 9.0 (br s, 1H, CO_2H); ^{13}C NMR (100 MHz) *δ* 52.3 (CH_3CO_2Me), 70.0 (CH_2 Bn), 61.6 (CH_2 Bn), 73.7 (C-2), 73.9 (CH_2 Bn), 74.9 (CH_2 Bn), 75.0 (C-5), 75.8 (C-4), 80.9 (C-3), 101.5 (J_{C1-H1} = 159 Hz, C-1), 126.9 (C_q CB), 127.1, 127.4, 127.5, 127.6, 127.7, 127.8, 127.9, 128.1, 128.2, 129.7, 131.3, 133.1 (CH_{arom}), 137.9 (C_q Bn), 138.0 (C_q Bn), 138.3 (C_q Bn), 140.5 (C_q CB), 168.9 (C═O), 171.9 (C═O); HRMS [M + Na^+] calcd for $C_{36}H_{36}O_9Na$ 635.2251, found 635.2248.

3-Azidopropyl (methyl 2,3-di-*O*-benzyl-4-*O*-levulinoyl-*β*-D-mannopyranosyl uronate) (23): The title compound was synthesized from **8** (3.2 g, 5.6 mmol) and 3-azidopropanol (1.13 g, 11.2

mmol) as described by the general procedure for Ph_2SO-Tf_2O mediated glycosylations at −78 °C (α/β = 1:10, 72%): $[\alpha]_D$ = −56 (*c* 1); IR (neat) ν (cm^{-1}) 741, 1153, 1719, 1755, 2097; ^1H NMR (400 MHz) δ 1.88 (m, 2H, $CH_2CH_2CH_2$), 2.16 (s, 3H, CH_3 Lev), 2.54 (m, 2H, CH_2 Lev), 2.71 (m, 2H, CH_2 Lev), 3.38 (t, 2H, *J* = 6.8 Hz, CH_2N_3), 3.53 (m, 2H, H-3, O-$CHHCH_2$), 3.71 (s, 3H, CO_2Me), 3.87 (m, 2H, H-2, H-5), 4.03 (m, 1H, O−$CHHCH_2$), 4.41 (d, 1H, *J* = 12.4 Hz, $CHHPh$), 4.43 (s, 1H, H-1), 4.53 (d, 1H, *J* = 12.4 Hz, $CHHPh$), 4.80 (d, 1H, *J* = 12.8 Hz, $CHHPh$), 4.91 (d, 1H, *J* = 12.4 Hz, $CHHPh$), 5.53 (t, 1H, *J* = 9.6 Hz), 7.24−7.42 (m, 10H, H_{arom}); ^{13}C NMR (100 MHz) δ 27.9 (CH_2 Lev), 29.0 (CH_2 $CH_2CH_2CH_2$), 29.8 (CH_3 Lev), 37.7 (CH_2 Lev), 48.2 (CH_2N_3), 52.6 (CO_2CH_3), 66.9 (O-CH_2CH_2), 69.1 (C-4), 73.1, 73.5 (C-2 and C-5), 73.8 (CH_2 Bn), 78.0 (C-3), 101.5 (J_{C1-H-1} = 158 Hz, C-1), 127.5, 127.7, 128.0, 128.3 (C_{arom}), 137.7 (C_q Ph), 138.2 (C_q Ph), 167.9 (C═O), 171.5 (C═O), 206.2 (C═O Lev); HRMS [M + Na^+] calcd for $C_{29}H_{35}O_9N_3Na$ 592.2271, found 592.2261.

3-Azidopropyl (methyl (2,3-di-*O*-benzyl-β-D-mannopyranoside)uronate) (24): Mannuronic acid **23** (2.28 g, 4.0 mmol) was delevulinoylated as described by the general procedure for levulinoyl cleavage (99%). Spectroscopic data were identical to those reported previously.[8a]

3-Azidopropyl (methyl 2,3-di-*O*-benzyl-4-*O*-(methyl 2,3,4-tri-*O*-benzyl-β-D-mannopyranosyl uronate)-β-D-mannopyranoside uronate) (25): The title compound was synthesized from **20** (106 mg, 0.19 mmol) and **24** (70 mg, 0.15 mmol) as described by the general procedure for BSP-Tf_2O mediated glycosylations (67%): $[\alpha]_D$ = −33 (*c* 1, DCM); IR (neat) ν (cm^{-1}) 739, 1064, 1747, 2097; ^1H NMR (400 MHz) δ 1.84 (m, 2H, $CH_2CH_2CH_2$), 3.32 (t, 1H, *J* = 6.8 Hz, CH_2N_3), 3.48 (m, 2H, O-$CHHCH_2$, H-3), 3.55 (s, 3H, CH_3 CO_2Me), 3.61 (m, 4H, H-3, CH_3 CO_2Me), 3.75 (d, 1H, *J* = 9.5 Hz, H-5), 3.82 (d, 1H, *J* = 3.0 Hz, H-2), 3.85 (d, 1H, *J* = 2.4 Hz, H-2), 3.88 (d, 1H, *J* = 8.4 Hz, H-5), 3.99 (m, 1H, O-$CHHCH_2$), 4.18 (t, 1H, *J* = 9.6 Hz, H-4), 4.42 (t, 1H, *J* = 9.5 Hz, H-4), 4.46 (s, 1H, H-1), 4.52−4.62 (m, 4H, 2 × CH_2 Bn), 4.69 (s, 1H, H-1), 4.71−4.85 (m, 6H, 3 × CH_2 Bn), 7.19−7.40 (m, 25H, H_{arom}); ^{13}C NMR (100 MHz) δ 28.9 (CH_2 $CH_2CH_2CH_2$), 48.1 (CH_2N_3), 52.0 (CH_3 CO_2Me), 52.2 (CH_3 CO_2Me), 66.7 (O-CH_2CH_2), 71.7 (CH_2 Bn), 72.3 (CH_2 Bn), 73.7 (CH_2 Bn), 74.0 (C-2), 74.3 (C-5), 74.4 (CH_2 Bn), 75.0 (C-5), 75.0 (CH_2 Bn), 75.2 (C-2), 75.6 (C-4), 77.3 (C-4), 79.1 (C-3), 81.3 (C-3), 101.6 (J_{C1-H1} = 156 Hz, C-1), 102.5 (J_{C1-H1} = 155 Hz, C-1), 127.2, 127.3, 127.4, 127.5, 127.6, 127.7, 127.9, 128.0, 128.1, 128.3 (CH_{arom}), 137.9 (C_q Bn), 138.0 (C_q Bn), 138.3 (C_q Bn), 138.5 (C_q Bn), 138.8 (C_q Bn), 168.6 (2 × C═O); HRMS [M + NH_4^+] calcd for $C_{52}H_{610}O_{13}N_4$ 949.4230, found 949.4241.

3-Azidopropyl (methyl 2,3-di-*O*-benzyl-4-*O*-(methyl 2,3-di-*O*-benzyl-4-*O*-levulinoyl-β-D-mannopyranosyl uronate)-β-D-mannopyranoside uronate) (26): The title compound was synthesized from **20** (80 mg, 0.14 mmol) and **24** (83 mg, 0.18 mmol) as described by the general procedure for BSP-Tf_2O mediated glycosylations (62%). Spectroscopic data were identical to those reported previously.[8a]

3-Azidopropyl (methyl 2,3-di-*O*-benzyl-4-*O*-(methyl 2,3-di-*O*-benzyl-β-D-mannopyranosyl uronate)-β-D-mannopyranoside uronate) (27): Dimannuronic acid **26** (65 mg, 0.069 mmol) was delevulinoylated as described by the general procedure for levulinoyl cleavage (95%). Spectroscopic data were identical to those reported previously.[8a]

3-Azidopropyl (methyl 2,3-di-*O*-benzyl-4-*O*-(methyl 2,3-di-*O*-benzyl-4-*O*-(methyl 2,3,4-tri-*O*-benzyl-β-D-mannopyranosyl uronate)-β-D-mannopyranosyl uronate)-β-D-mannopyranoside uronate) (28): The title compound was synthesized from **21** (100 mg, 0.11 mmol) and **24** (75 mg, 0.16 mmol) as described by the general procedure for BSP-Tf_2O mediated glycosylations (74%): $[\alpha]_D$ = −55 (*c* 1, DCM); IR (neat) ν (cm^{-1}) 739, 1059, 1749, 2095; ^1H NMR (400 MHz) δ 1.86 (m, 2H, $CH_2CH_2CH_2$), 3.33 (t, 1H, *J* = 6.8 Hz, CH_2N_3), 3.44 (m, 4H, H-3, CH_3 CO_2Me), 3.47−3.55 (m, 5H, H-3, O-$CHHCH_2$, CH_3 CO_2Me), 3.57 (m, 4H, H-3, CH_3 CO_2Me), 3.73 (m, 3H, H-2, 2 × H-5), 3.78−3.84 (m, 3H, 2 × H-2, H-5), 4.01 (m, 1H, O-$CHHCH_2$), 4.16 (t,1H, *J* = 9.6 Hz, H-4), 4.32 (t, 1H, *J* = 9.5 Hz, H-4), 4.41 (t, 1H, *J* = 9.5 Hz, H-4), 4.44 (s, 1H, H-1), 4.49−4.61 (m, 7H, H-1, 6 × $CHHPh$), 4.69−4.85 (m, 10H, H-1, 9 × $CHHPh$), 7.18−7.40 (m, 35H, H_{arom}); ^{13}C NMR (100 MHz) δ 29.0 (CH_2 $CH_2CH_2CH_2$), 48.2 (CH_2N_3), 52.0 (2 × CH_3 CO_2Me), 52.3 (CH_3 CO_2Me), 66.7 (O-CH_2CH_2), 71.7 (CH_2 Bn), 72.3 (CH_2 Bn), 72.7 (CH_2 Bn), 73.8 (CH_2 Bn), 74.3 (CH_2 Bn), 74.4 (CH_2 Bn), 75.0 (CH_2 Bn), 74.2, 74.4, 74.4, 75.0, 75.1, 75.2, 75.6 (3 × C-2 and 3 × C-5), 76.0 (C-4), 77.2 (C-4), 77.4 (C-4), 79.2 (C-3), 79.6 (C-3), 81.3 (C-3), 101.6 (J_{C1-H1} = 155 Hz, C-1), 102.3 (J_{C1-H1} = 157 Hz, C-1), 102.7 (J_{C1-H1} = 155 Hz, C-1), 127.2, 127.4, 127.5, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3 (CH_{arom}), 138.0 (C_q Bn), 138.2 (C_q Bn), 138.4 (C_q Bn), 138.7 (C_q Bn), 138.8 (C_q Bn), 138.9 (C_q Bn), 168.6 (3 × C═O); HRMS [M + NH_4^+] calcd for $C_{73}H_{83}O_{19}N_4$ 1319.56460, found 1319.56664, [M + Na^+] calcd for $C_{73}H_{79}O_{19}N_3$ 1324.5200, found 1324.5217.

3-Azidopropyl (methyl 2,3-di-*O*-benzyl-4-*O*-(methyl 2,3-di-*O*-benzyl-4-*O*-(methyl 2,3-di-*O*-benzyl-4-*O*-levulinoyl-β-D-mannopyranosyl uronate)-β-D-mannopyranosyl uronate)-β-D-mannopyranoside uronate) (29): The title compound was synthesized from **21** (362 mg, 0.38 mmol) and **24** (225 mg, 0.48 mmol) as described by the general procedure for BSP-Tf_2O mediated glycosylations (51%). Spectroscopic data were identical to those reported previously.[8]

3-Azidopropyl (methyl 2,3-di-*O*-benzyl-4-*O*-(methyl 2,3-di-*O*-benzyl-4-*O*-(methyl 2,3-di-*O*-benzyl-β-D-mannopyranosyl uronate)-β-D-mannopyranosyl uronate)-β-D-mannopyranoside uronate) (30): Trimannuronic acid **29** (71 mg, 0.054 mmol) was delevulinoylated as described by the general procedure for levulinoyl cleavage (78%): $[\alpha]_D$ = −67 (*c* 1, DCM); IR (neat) ν (cm^{-1}) 727, 1055, 1747, 2097; ^1H NMR (500 MHz) δ ^1H NMR (400 MHz) 1.85 (m, 2H, $CH_2CH_2CH_2$), 2.98 (br s, 1H, 3″-OH), 3.27 (dd, 1H, *J* = 2.5 Hz, *J* = 9.5 Hz, H-3), 3.34 (t, 1H, *J* = 6.5 Hz, CH_2N_3), 3.47 (s, 3H, CH_3 CO_2Me), 3.50−3.62 (m, 10H, 2 × H-3, H-5, O-$CHHCH_2$, 2 × CH_3 CO_2Me), 3.73−3.88 (m, 5H, 3 × H-2, 2 × H-5), 4.01 (m, 1H, O-$CHHCH_2$), 4.17 (t, 1H, *J* = 9.5 Hz, H-4), 4.36 (t, 1H, *J* = 9.0 Hz, H-4), 4.42 (t, 1H, *J* = 9.0 Hz, H-4), 4.45 (s, 1H, H-1), 4.52−4.58 (m, 4H, 4 × $CHHPh$), 4.62 (s, H-1), 4.64 (d, 1H, *J* = 13.5 Hz, $CHHPh$), 4.72 (s, 1H, H-1), 4.72−4.83 (m, 7H, 7 × $CHHPh$), 7.18−7.38 (m, 30H, H_{arom}); ^{13}C NMR (125 MHz) δ 29.0 (CH_2 $CH_2CH_2CH_2$), 48.2 (CH_2N_3), 52.1 (CH_3 CO_2Me), 52.2 (CH_3 CO_2Me), 52.3 (CH_3 CO_2Me), 66.8 (O-CH_2CH_2), 68.1 (C-4), 71.7 (CH_2 Bn), 72.3 (CH_2 Bn), 73.8 (CH_2 Bn), 74.5 (CH_2 Bn), 74.1, 74.4, 74.7, 75.0, 75.1, 75.7, (3 × C-2 and 3 × C-5), 77.1 (C-4), 77.2 (C-4), 79.3 (C-3), 79.7 (C-3), 80.3 (C-3), 101.7 (C-1), 102.3 (C-1), 102.5 (C-1), 127.1, 127.2, 127.3, 127.4, 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.4 (CH_{arom}), 137.9 (C_q Bn), 138.3 (C_q Bn), 138.6 (C_q Bn), 138.7 (C_q Bn), 168.5 (C═O), 168.6 (C═O), 169.8 (C═O); HRMS [M + NH_4^+] calcd for $C_{66}H_{77}O_{19}N_4$ 1229.51765, found 1229.51990, [M + Na^+] calcd for $C_{66}H_{73}O_{19}N_3$ 1234.4730, found 1234.4753.

3-Azidopropyl (methyl 2,3-di-*O*-benzyl-4-*O*-(methyl 2,3-di-*O*-benzyl-4-*O*-(methyl 2,3-di-*O*-benzyl-4-*O*-(methyl 2,3,4-tri-*O*-benzyl-β-D-mannopyranosyl uronate)-β-D-mannopyranosyl uronate)-β-D-mannopyranosyl uronate)-β-D-mannopyranoside uronate) (31): The title compound was synthesized from **21** (124 mg, 0.13 mmol) and **27** (74 mg, 0.088 mmol) as described by the general procedure for BSP-Tf_2O mediated glycosylations (67%): $[\alpha]_D$ = −56 (*c* 1, DCM); IR (neat) ν (cm^{-1}) 738, 1057, 1747, 2096; ^1H NMR (400 MHz) δ 1.86 (m, 2H, $CH_2CH_2CH_2$), 3.42 (t, 1H, *J* = 6.8 Hz, CH_2N_3), 3.40 (s, 3H, CH_3 CO_2Me), 3.41 (s, 3H, CH_3 CO_2Me), 3.41−3.58 (m, 11H, 4 × H-3, O-$CHHCH_2$, 2 × CH_3CO_2Me), 3.69−3.75 (m, 5H, 2 × H-2, 3 × H-5), 3.80−3.84 (m, 3H, 2 × H-2, H-5), 4.02 (m, 1H, O-$CHHCH_2$), 4.15 (t,1H, *J* = 9.6 Hz, H-4), 4.30 (m, 2H, 2 × H-4), 4.40 (t, 1H, *J* = 9.6 Hz, H-4), 4.44 (s, 1H, H-1), 4.49−4.54 (m, 5H, 5 × $CHHPh$), 4.58−4.60 (m, 3H, 2 × H-1, $CHHPh$), 4.68−4.83 (m, 12H, H-1, 11 × $CHHPh$), 7.22−7.40 (m, 45H, H_{arom}); ^{13}C NMR (100 MHz)

δ 29.0 (CH_2 $CH_2CH_2CH_2$), 48.2 (CH_2N_3), 52.0 (2 × CH_3 CO_2Me), 52.1 (CH_3 CO_2Me), 52.3 (CH_3 CO_2Me), 66.8 (O-CH_2CH_2), 71.7 (CH_2 Bn), 72.3 (CH_2 Bn), 72.5 (CH_2 Bn), 73.9 (CH_2 Bn), 74.4 (CH_2 Bn), 74.5 (CH_2 Bn), 75.0 (CH_2 Bn), 74.2, 74.4, 74.5, 74.5, 75.0, 75.2, 75.9, 76.0 (4 × C-2 and 4 × C-5), 75.6 (C-4), 77.1 (C-4), 77.3 (C-4), 77.4 (C-4), 79.2 (C-3), 79.6 (C-3), 79.7 (C-3), 81.4 (C-3), 101.7 (J_{C1-H1} = 155 Hz, C-1), 102.3 (J_{C1-H1} = 157 Hz, C-1), 102.5 (J_{C1-H1} = 158 Hz, C-1), 102.7 (J_{C1-H1} = 155 Hz, C-1), 127.2, 127.3, 127.4, 127.5, 127.6, 127.7, 127.9, 128.0, 128.1, 128.2, 128.3 (CH_{arom}), 138.0 (C_q Bn), 138.2 (C_q Bn), 138.3 (C_q Bn), 138.6 (C_q Bn), 138.8 (C_q Bn), 138.9 (C_q Bn), 168.6 (C═O), 168.6 (C═O), 168.7 (C═O); HRMS [M + NH_4^+] calcd for $C_{94}H_{105}O_{25}N_4$ 1689.7096, found 1689.7075.

3-Azidopropyl (methyl 2,3-di-*O*-benzyl-4-*O*-(methyl 2,3-di-*O*-benzyl-4-*O*-(methyl 2,3-di-*O*-benzyl-4-*O*-(methyl 2,3,4-tri-*O*-benzyl-β-D-mannopyranosyl uronate)-β-D-mannopyranosyl uronate)-β-D-mannopyranosyl uronate)-β-D-mannopyranosyl uronate)-β-D-mannopyranoside uronate) (32): The title compound was synthesized from **21** (116 mg, 0.12 mmol) and **30** (100 mg, 0.082 mmol) as described by the general procedure for BSP-Tf_2O mediated glycosylations (69%): $[\alpha]_D = -63$ (*c* 1, DCM); IR (neat) ν (cm^{-1}) 735 1057, 1747, 2097; ^{1}H NMR (500 MHz) δ 1.86 (m, 2H, $CH_2CH_2CH_2$), 3.37 (t, 1H, *J* = 7.0 Hz, CH_2N_3), 3.41 (s, 3H, CH_3 CO_2Me), 3.43 (s, 3H, CH_3 CO_2Me), 3.45 (s, 3H, CH_3 CO_2Me), 3.43−3.62 (m, 6H, 5 × H-3, O-CHHCH$_2$), 3.56 (s, 3H, CH_3 CO_2Me), 3.61 (s, 3H, CH_3 CO_2Me), 3.70−3.79 (m, 6H), 3.84−3.87 (m, 3H, 5 × H-2, 5 × H-5), 4.04 (m, 1H, O-CHHCH$_2$), 4.18 (t, 1H, *J* = 9.0 Hz, H-4), 4.30 (m, 3H, 3 × H-4), 4.44 (t, 1H, *J* = 8.5 Hz, H-4), 4.47 (s, 1H, H-1), 4.52−4.63 (m, 10H, 3 × H-1, 7 × CHHPh), 4.71−4.80 (m, 10H, H-1, 9 × CHHPh), 4.83−4.86 (m, 6H, 6 × CHHPh), 7.23−7.43 (m, 55H, H_{arom}); ^{13}C NMR (150 MHz) δ 28.9 (CH_2 $CH_2CH_2CH_2$), 48.1 (CH_2N_3), 52.0 (3 × CH_3 CO_2Me), 52.1 (CH_3 CO_2Me), 52.3 (CH_3 CO_2Me), 66.7 (O-CH_2CH_2), 71.6 (CH_2 Bn), 72.3 (CH_2 Bn), 72.4 (CH_2 Bn), 72.5 (CH_2 Bn), 73.8 (CH_2 Bn), 74.4 (CH_2 Bn), 74.5 (CH_2 Bn), 75.1 (CH_2 Bn), 75.0 (CH_2 Bn), 74.2, 74.4, 75.0, 75.2, 75.9, 75.9, 76.0, (5 × C-2 and 5 × C-5), 75.6 (C-4), 77.2 (3 × C), 79.2 (C-3), 79.7 (3 × C-3), 81.4 (C-3), 101.7 (J_{C1-H1} = 1565 Hz, C-1), 102.3 (J_{C1-H1} = 157 Hz, C-1), 102.5 (J_{C1-H1} = 155 Hz, 2 × 1), 102.7 (J_{C1-H1} = 154 Hz, C-1), 127.1, 127.2, 127.3, 127.4, 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3 (CH_{arom}), 138.0 (C_q Bn), 138.2 (C_q Bn), 138.3 (C_q Bn), 138.6 (C_q Bn), 138.8 (C_q Bn), 138.9 (C_q Bn), 168.5 (C═O), 168.6 (C═O); HRMS [M + 2NH_4^+] calcd for $C_{115}H_{131}O_{31}N_5$ 1039.4425, found 1039.4438.

General Procedure for Deprotection of the Mannuronic Acid Oligomers: The fully protected mannuronic acid oligomers were dissolved in THF (0.025 M) and aqueous KOH (0.45 M, (*n* + 1) equiv, in which *n* is the number of ester groups). The biphasic mixture was homogenized by the addition of a little extra THF (<half the total volume). The mixture was stirred for 1 h, before being quenched by the addition of Amberlite-H^+. The resin was filtered off and the solvent evaporated. The crude product was taken up in MeOH/HOAc (10/1, ∼0.01 M for **25** and **28**) or MeOH/*t*BuOH/H_2O/HOAc (6/5/4/0.15, ∼0.01 M, for **31** and **32**) and Pd/C (catalytic amount) was added. The heterogeneous mixture was degassed, purged with H_2, and stirred (48 h) under a H_2 atmosphere, after which the Pd/C was filtered off and the mixture was concentrated. The product was purified by gel filtration (HW-40, 0.15 M Et_3NHOAc in H_2O) to provide the fully deprotected products (**33**: 59% over 2 steps; **34**: 86% over 2 steps; **35**: 65% over 2 steps; **36**: 76% over 2 steps).

3-Aminopropyl (4-*O*-(β-D-mannopyranosyluronate)-β-D-mannopyranoside uronate)triethylammonium salt (33): The target compound was synthesized from **26** (70 mg, 0.077 mmol) as described above and isolated as its monotriethyl ammonium salt (21 mg, 0.045 mmol, 59%): ^{1}H NMR (400 MHz) δ 1.26 (t, 9H, *J* = 7.6 Hz, CH_3, Et_3N), 1.97 (m, 2H, $CH_2CH_2CH_2$), 3.11 (m, 2H, CH_2NH_3), 3.28 (q, 6H, *J* = 7.6 Hz, CH_2, Et_3N), 3.64−3.76 (m, 5H), 3.81−3.97 (m, 4H), 4.03 (d, 1H, *J* = 2.8 Hz), 4.62 (s, 1H, H-1), 4.71 (s, 1H, H-1); ^{13}C NMR (100 MHz) δ 8.2 (CH_3, Et_3N), 26.7 (CH_2 $CH_2CH_2CH_2$), 37.7 (CH_2NH_2), 46.7 (CH_2 Et_3N), 67.5 (O-CH_2-CH_2), 68.5, 69.8, 70.1, 70.8, 71.5, 72.6, 75.9, 76.0, 78.3, 99.9 (C-1), 100.1 (C-1), 175.5 (C═O), 175.8 (C═O); HRMS [M + H^+] calcd for $C_{15}H_{26}O_{13}N$ 428.1401, found 428.1397.

3-Aminopropyl (4-*O*-(4-*O*-(β-D-mannopyranosyluronate)-β-D-mannopyranosyluronate)-β-D-mannopyranosideuronate)triethylammonium salt (34): The target compound was synthesized from **29** (50 mg, 0.038 mmol) as described above and isolated as its monotriethyl ammonium salt (20 mg, 0.033 mmol, 86%): ^{1}H NMR (400 MHz) δ 1.26 (t, 18H, *J* = 7.6 Hz, CH_3, Et_3N), 1.90 (m, 2H, $CH_2CH_2CH_2$), 3.05 (m, 2H, CH_2NH_3), 3.11 (q, 12H, *J* = 7.6 Hz, CH_2, Et_3N), 3.55−3.69 (m, 7H), 3.75−3.90 (m, 5H), 3.95 (br s, 2H), 4.54 (s, 1H, H-1), 4.58 (s, 1H, H-1), 4.65 (s, 1H, H-1); ^{13}C NMR (100 MHz) δ 8.24 (CH_3 Et_3N), 26.7 ($CH_2CH_2CH_2$), 37.7 (CH_2NH_2), 46.7 (CH_2 Et_3N), 67.5 (O-CH_2−CH_2), 68.5, 69.8, 70.0, 70.4, 71.4, 72.6, 75.9, 76.0, 78.1, 78.2, 99.9 (C-1), 100.0 (C-1), 100.1 (C-1), 175.2 (C═O), 175.4 (C═O), 176.0 (C═O); HRMS [M + H^+] calcd for $C_{21}H_{34}O_{19}N$ 604.1725, found 604.1717.

3-Aminopropyl (4-*O*-(4-*O*-(4-*O*-(β-D-mannopyranosyluronate)-β-D-mannopyranosyluronate)-β-D-mannopyranosyluronate)-β-D-mannopyranosideuronate)triethylammonium salt (35): The target compound was synthesized from **32** (40 mg, 0.024 mmol) as described above to give the title compound (17 mg, 0.016 mmol): ^{1}H NMR (400 MHz) δ 1.26 (t, 27H, *J* = 7.6 Hz, CH_3, Et_3N), 1.90 (m, 2H, $CH_2CH_2CH_2$), 3.07 (m, 2H, CH_2NH_3), 3.10 (q, 18H, *J* = 7.6 Hz, CH_2, Et_3N), 3.48−3.69 (m, 10H), 3.74−3.92 (m, 7H), 3.95 (brs, 3H), 4.55 (s, 1H, H-1), 4.57 (s, 1H, H-1), 4.58 (s, 1H, H-1), 4.65 (s, 1H, H-1); ^{13}C NMR (100 MHz) δ 26.6 ($CH_2CH_2CH_2$), 37.7 (CH_2NH_2), 67.5 (O-CH_2-CH_2), 68.5, 69.8, 69.9, 70.4, 71.3, 71.4, 75.9, 77.8, 78.0, 78.2, 99.8 (C-1), 100.0 (2 × C-1), 100.1 (C-1), 175.2 (C═O), 175.3 (C═O); HRMS [M + H^+] calcd for $C_{27}H_{42}O_{25}N$ 780.2046, found 780.2044.

3-Aminopropyl (4-*O*-(4-*O*-(4-*O*-(4-*O*-(β-D-mannopyranosyluronate)-β-D-mannopyranosyluronate)-β-D-mannopyranosyluronate)-β-D-mannopyranosyluronate)-β-D-mannopyranosideuronate)triethylammonium salt (36): The target compound was synthesized from **33** (54 mg, 0.026 mmol) as described above, and passed through a small Amberlite Na^+ column to give the title compound (27 mg, 0.020 mmol): ^{1}H NMR (400 MHz) δ 1.26 (t, 6H, *J* = 7.6 Hz, CH_3, residual Et_3N), 1.91 (m, 2H, $CH_2CH_2CH_2$), 3.14 (m, 2H, CH_2NH_3), 3.18 (q, 4H, *J* = 7.6 Hz, CH_2, residual Et_3N), 3.56−4.02 (m, 22H), 4.62−4.72 (m, 5H, 5xH-1); ^{13}C NMR (100 MHz) δ 26.6 ($CH_2CH_2CH_2$), 37.7 (CH_2NH_2), 67.5 (O-CH_2-CH_2), 68.5, 69.8, 69.9, 70.4, 71.3, 72.6, 75.9, 77.8, 78.0, 78.1, 99.8 (C-1), 99.9 (3 × C-1), 100.1 (C-1); HRMS [M + H^+] calcd for $C_{33}H_{50}O_{31}N$ 956.2361, found 956.2360.

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Supporting Information Available: Additional experimental details for the synthesis of **8**, **11**, **16**, and **17** and NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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