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Influence of O6 in Mannosylations Using Benzylidene Protected Donors: Stereoelectronic or Conformational Effects?

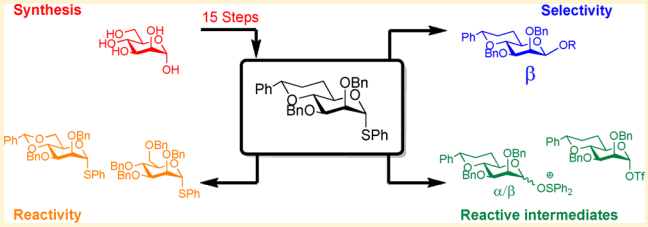
Tobias Gylling Frihed,[†] Marthe T. C. Walvoort,[‡] Jeroen D. C. Codée,[‡] Gijs A. van der Marel,[‡] Mikael Bols,[†] and Christian Marcus Pedersen*[,†]

[†]Department of Chemistry, University of Copenhagen, Universitetsparken 5, 2100 Copenhagen, Denmark

[‡]Leiden Institute of Chemistry, Leiden University, Einsteinweg 55, 2333 CC Leiden, The Netherlands

Supporting Information

ABSTRACT: The stereoselective synthesis of β-mannosides and the underlying reaction mechanism have been thoroughly studied, and especially the benzylidene-protected mannosides have gained a lot of attention since the corresponding mannosyl triflates often give excellent selectivity. The hypothesis for the enhanced stereoselectivity has been that the benzylidene locks the molecule in a less reactive conformation with the O6 trans to the ring oxygen (O5), which would stabilize the formed α-triflate and subsequent give β-selectivity. In this work, the hypothesis is challenged by using the carbon analogue (C7) of the benzylidene-protected mannosyl donor, which is investigated in terms of diastereoselectivity and reactivity and by low-temperature NMR. In terms of diastereoselectivity, the C-7-analogue behaves similarly to the benzylidene-protected donor, but its low-temperature NMR reveals the formation of several reactive intermediate. One of the intermediates was found to be the β-oxosulfonium ion. The reactivity of the donor was found to be in between that of the "torsional" disarmed and an armed donor.



INTRODUCTION

Mannosides play a central role in mammalian biology, where both the α- and the β-anomers are present, e.g., in the core pentasaccharide of *N*-glycoconjugates. It is therefore highly attractive to synthesize glycoconjugates containing mannosides, and amazing progress in synthetic glycoconjugates has been achieved during the past decade in order to decipher the glycocode. The α-mannosides are readily accessible via neighboring group participation and additionally favored due to the anomeric effect. The β-anomer, however, is challenging since both the anomeric effect, the Δ2-effect[1] as well as steric effects disfavor its formation. This synthetic problem has attracted a lot of interest since the early days of oligosaccharide synthesis. The approaches can roughly be divided into direct and indirect methods, where the direct method provides the β-mannoside from a donor and an acceptor without pre- or postmodifications. The indirect methods demand additional steps but are often more efficient in terms of diastereoselectivity.[2] Some examples of indirect approaches are intramolecular aglycon delivery (IAD),[3] 2-O-inversion of the corresponding gluco derivative,[4] stereoselective reduction of the 2-oxo derivative (uloside derivative),[5] or reductive opening of the tricyclic orthoester.[6] Direct methods are, however, preferred, especially in the synthesis of complex compounds, where the number of steps is required to be kept at a minimum. One of the first successful β-mannosylations was based on the classic Königs–Knorr method applying solid silver salts as promoters.[7] The yields are, however, often moderate, and their use in complex oligosaccharide synthesis is limited. For simple glycoside bond formation, anomeric O-alkylation[8] has been found to be useful, but more complex glycoside bonds than 1,6-mannosidic linkages are seldom possible with this method. The influence of the donors reactivity on the β-selectivity was realized by Schuerch[9] and later explored by others;[10] its general use has recently been developed by Kim and co-workers, who systematically studied the influence of electron-withdrawing substituents on the 3, 4, and 6 position, respectively. This demonstrated that not only is the 2-position important, but all the substituents influence the reactivity and hence the outcome of the reaction.[11]

A tremendous improvement of direct β-mannosylation appeared in 1996 from the Crich group,[12] who discovered that when a 4,6-benzylidene-protected donor was preactivated using Kahne's conditions[13] a good to excellent β-selectivity was obtained. Over the years, the reaction has proved to be a general approach for this difficult linkage, and it has gained a lot of attention not only for its use as an applied method but also for the underlying mechanism responsible for the selectivity. Early studies of the reaction using low-temperature NMR revealed that the donor was transformed into the α-triflate under the reaction conditions, and a S_N2-type mechanism was proposed to be responsible for the β-selectivity.[3,5] The decisive role of the triflate ions in terms of selectivity has been demonstrated by the substantial amount of work in the field.[14] The 4,6-tethering of the donor, most often by a benzylidene, is

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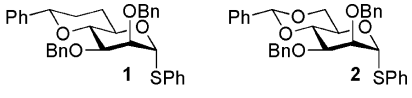
another necessity in the method. The influence of the tethering has been explained by either conformational restriction favoring the β-attack[10,15] or stereoelectronic effects by locking the O6 antiperiplanar (*trans–gauche*) to the ring oxygen (O5), making it more electron poor (disarming the donor). This results in a less stable oxocarbenium ion and hence a more stable covalent triflate intermediate, which results in a S_N2 type reaction.[16] Expanding the ring with one extra atom reduces the β-selectivity dramatically, which supports both hypotheses, i.e., deactivation by either stereoelectronics or strain.[17] Exchange of the O6 with the less electronegative sulfur atom has also been shown to reduce the β-selectivity either by stereoelectronic or torsional effects. The selectivity could, however, be restored by introducing an electron-withdrawing cyano substituent on the benzylidene.[18] The enhanced electron-withdrawing capacity of an antiperiplanar oxygen (*trans–gauche*) has been used to explain the increased stability of the α-triflates when a benzylidene protective group is present. The effect was originally observed in a gluco-model system, where the rate of hydrolysis was hampered by locking the oxygen in different positions (Figure 1).[19] The influence on rate of hydrolysis and thereby the reactivity is clear, but is it responsible for the β-selectivity in mannosides?

Figure 1. Relative rate of hydrolysis of dinitrophenyl (DNP) glycosides.

The reaction mechanism of the preactivated β-mannosides has been extensively investigated during the last two decades, both experimentally and in silico. Kinetic isotope effect studies have supported the S_N2-like mechanism when having mannosyl triflates.[20] The importance of the nucleophile, i.e., the acceptor used in triflate substitution on tetrahydropyrans, has also been investigated, and a S_N2-like mechanism was suggested for strong nucleophiles.[21] Conformational preferences of oxocarbenium ions and the influence on stereochemical outcome have been thoroughly studied on model compounds, and a preference, in the manno system, for a pseudoequatorial 2-O was found. All other hydroxyl groups preferred pseudoaxial arrangement due to electrostatic stabilization (the $^3H_4$ conformation).[22] Is the O6 (when being *trans–gauche*) responsible for the increased β-selectivity obtained with benzylidene-protected mannosyl donors? In this paper, the reaction is studied using a carbon (C7) analogue **1** of the 4,6-benzylidene mannosyl donor **2** in order to answer this question.



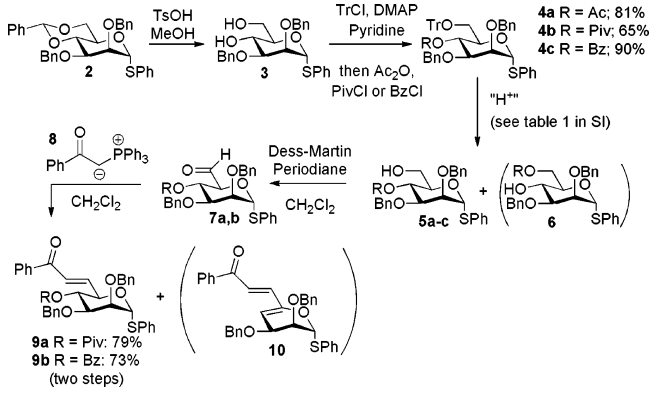
RESULTS

Synthesis. In contrast to previous related studies on the influence of the O6 on the anomeric reactivity in a gluco-model system,[19] it was decided to include the phenyl substituent as part of the bicyclic system resembling the benzylidene; this demanded a new approach for the synthesis. The diol **3** was synthesized from mannose in six steps using standard carbohydrate chemistry.

Protective group manipulations gave the diol **3**, which was tritylated followed by acylation in one-pot to give the compounds **4a–c**. Upon acid-mediated removal of the trityl group, the 4-*O*-acetyl group readily migrated, even in the presence of trifluoroacetic anhydride, to trap the product as the 6-*O*-trifluoroacetyl (entry 3 and 4 in Table 1, Supporting Information).[23] The more bulky esters, the pivaloyl **4b** and the benzoyl **4c**, solved that problem at this stage of the synthesis (entries 5 and 6, Table 1, Supporting Information).

With the access to the alcohols **5a–c**, oxidation to the aldehydes **7a,b** by Dess–Martin periodinane (DMP) could readily be carried out. Wittig olefination of the crude aldehydes gave **9a** and **9b** in overall good yields (Scheme 1). The reaction

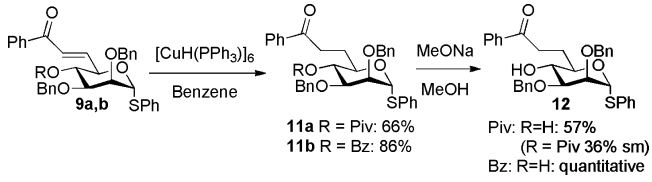
Scheme 1. Synthesis of the Precursor for the C7-Analogue Starting from the Common Mannosyl Donor 3 via Temporary Tritylation of the 6-OH, 4-OH Acylation, 6-O Deprotection, and Oxidation to the Aldehydes, Followed by Wittig Olefination To Give the Alkene 9



with the benzoylated substrate was, however, unpredictable when scaling up the reaction. On a gram scale, the major product turned out to be the benzoyl-eliminated compound **10**.[17,24]

Selective reduction of the olefins was mediated by freshly prepared Stryker's reagent $[CuH(PPh_3)]_6$,[25] which gave good to high yield of the corresponding saturated compounds, Scheme 2. Saponification of the pivaloyl or the benzoyl 4-O-

Scheme 2. Selective Alkene Reduction Using Stryker's Reagent Followed by Deacylation



protective group using Zemplén conditions in MeOH/THF gave the mono-ol **12** ready for ring formation with the ketone. The deprotection of the bulky pivaloyl **11a** was very slow at room temperature. Even at elevated temperatures, 6 days were required to obtain a reasonable conversion. Despite the synthetic challenges, enough of compound **12** could be obtained to investigate the key reaction: ring closure to the C7 donor **1**.

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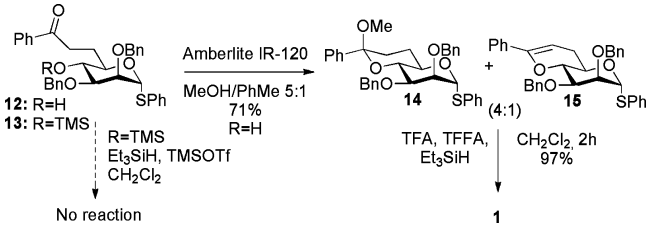
Reductive etherification inspired by Hung and co-workers[26] was attempted, but no conversion of the 4-O-TMS **13** was observed (Scheme 3). Treating **12** with acid in MeOH–toluene, however, gave a mixture of the bicyclic compounds **14** and **15**, which upon reduction gave one major product **1** in 97% yield, Scheme 3. The new donor **1** was carefully analyzed by NMR spectroscopy, and the equatorial position of the phenyl could be confirmed and coupling constants within the sugar ring corresponded to the ones found in the benzylidene donor **2**.

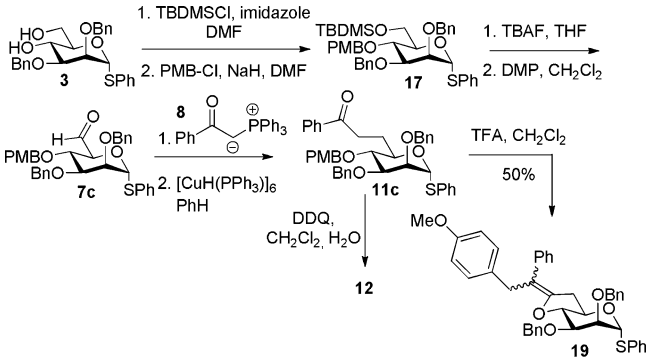
Scheme 3. Ring Closure Followed by Reduction To Give the C7-Analogue 1



With the chemistry developed for the final crucial ring closure, the steps leading to the 4-OH **12** had to be optimized in order to obtain large amounts (grams) of the donor to use in mechanistic studies and glycosylations. The main problem in the synthesis was clearly associated with the (in)stability of the acyl protective groups and their ability as leaving groups.

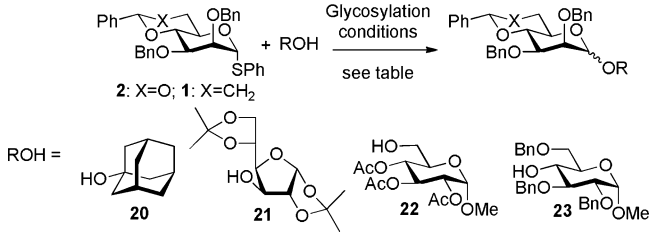
To solve these problems, *p*-methoxybenzyl (PMB) was introduced, as the 4-O protective group, Scheme 4. The diol **3** was first selectively 6-O-silylated using TBDMSCl, followed by alkylation of the 4-OH under basic conditions using PMB-Cl. TBAF-mediated desilylation, 6-OH oxidation by DMP to the aldehydes **7c** and Wittig olefination gave the alkene, which was selectively reduced by Stryker's reagent to give **11c**. Removal of the PMB group using acid surprisingly resulted in a rearrangement to the bicyclic compound **19**; this side reaction could however be avoided using DDQ mediated oxidative deprotection giving **12**, which could be transformed into **1** following the route in Scheme 3.[27]

Scheme 4. Optimized Synthesis of the C7-Analogue 1



Glycosylation. With a solid and scalable synthesis in hand, the glycosylation properties of the donor **1** could be investigated and compared to the standard benzylidene donor **2**. As acceptors, some common alcohols were chosen in order to compare with literature results; 1-adamantanol **20** was chosen as an achiral bulky acceptor, diacetone glucose **21** as a hindered secondary 3-OH, **22** as a primary 6-OH acceptor, and finally **23** as a more challenging secondary 4-OH acceptor, Scheme 5.

Scheme 5. Glycosylation with the C7-Analogue 1 vs the Benzylidene 2



The mannosylations of donor **1** and **2** were first compared using NIS/TfOH as the promoter system, which mainly gave the α-product for both donors; 1:5.7 for the **2** and 1:8.0 for **1**, entries 1 and 2, Table 1. The yield was somewhat better for the benzylidene donor **2**. Changing to the preactivation conditions Ph_2SO/TTBP and Tf_2O with preactivation in 5 min resulted in complete α-selectivity (entry 3) and not the expected β-selectivity (9:1 β:α).[28] Prolonging the preactivation to 30 min significantly improved the selectivity to 6.7:1, clearly underlining the importance of preactivation time, entry 4. When the exact same conditions were applied on the C7-analogue a practically identical selectivity was obtained (5.4:1) though in a slightly lower yield, entry 5. Changing the molecular sieves to 4 Å instead of 3 Å did not significantly alter the selectivity in this example. Performing the mannosylations using the BSP promoter system developed by Crich[29] resulted in complete α-selectivity after 5 min preactivation,[28] but a 6.1:1 β-selectivity after 30 min, entry 7 vs 8. The same result was obtained with the C7-analogue, both in terms of excellent yield and selectivity, entry 9. Mannosylation of the more demanding carbohydrate-based acceptors **21**–**23** were performed as described for the benzylidene donor using the BSP promoter system, but with a preactivation for 30 min since it was found to be crucial for selectivity. Glycosylation of diacetone glucose **21** gave the β-product **26*β*** as the major (4.4:1), a bit lower than the reported >9:1, entry 10. The selectivity with the 6OH acceptor **22** was also slightly lower (6.1:1 vs >9:1), but the yield was slightly higher, entry 11. The reaction with the 4-OH acceptor **23** turned out to give complex mixtures, where one of the major side products was the triflated acceptor. The ratio of anomers was estimated by ^{1}H NMR to be 2:1 (β/α). All glycosides were carefully analyzed by NMR and their anomeric configuration determined from the J_{CH} coupling constant, which followed the trend seen in mannosides, i.e., $J_{CH}\alpha \sim 165-175$ Hz and $J_{CH}\beta \sim 155$ Hz (or ca.10 ppm lower than the α).[30]

Competition Experiments. To get further insight into the reactivity of the C7-analogue donor **1** vs the benzylidene **2**, competition experiments were performed. One equivalent of each donor was activated using 1 equiv of promoter (NIS/TfOH) and was allowed to react with 3 equiv of acceptor, Figure 2.[32,33] To validate the method, a competition between the benzylidene **2** and the perbenzylated mannosyl donor **31** was carried out. From integrals in crude NMR it was estimated that the ratio of reaction was 19:1 in favor of the perbenzylated, determined from the ratio of the remaining donor. The value fits well with the reaction difference obtained by Wong and co-workers by measuring the donor reactivities, where the perbenzylated has a *relative reactivity value* (RRV) of 5000

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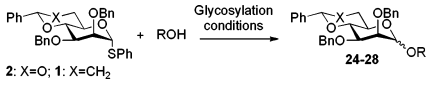
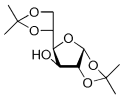
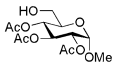
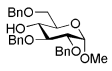
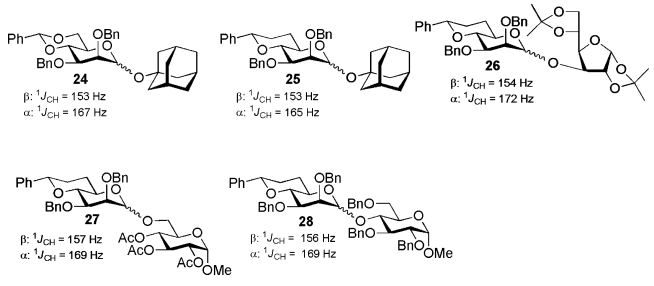
Table 1. Glycosylation between Benzylidene Donor 2 or C7-Analogue 1 and Different Acceptors with Different Activation Methods



Entry	Donor	Acceptor (ROH)	Method	Preactivation time[a]	Product	β/α ratio[b] (yield)	Ref. for 2[e]
1	**2**	 **20**	**A**: NIS/TfOH, 3Å MS, 0 °C	0 min.	**24**	1 : 5.7 (91%)	---
2	**1**	**20**	**A**: NIS/TfOH, 3Å MS, 0 °C	0 min.	**25**	1 : 8.0 (62 %)	---
3	**2**	**20**	**B**: Ph_2SO, TTBP, Tf_2O, 3Å MS, -78 °C	5 min.	**24**	0 : 1 (-)[c]	> 9 : 1 (96%)[28]
4	**2**	**20**	**B**: Ph_2SO, TTBP, Tf_2O, 3Å MS, -78 °C	30 min.	**24**	6.7 : 1 (75%)	> 9 : 1 (96%)[28]
5	**1**	**20**	**B**: Ph_2SO, TTBP, Tf_2O, 3Å MS, -78 °C	30 min.	**25**	5.4 : 1 (62%)	---
6	**2**	**20**	**C**: Ph_2SO, TTBP, Tf_2O, 4Å MS, -78 °C	30 min.	**24**	7.0 : 1 (83%)	---
7	**2**	**20**	**D**: BSP, TTBP, Tf_2O, 3Å MS, -60 °C	5 min.	**24**	0 : 1 (-)[c]	> 9 : 1 (88%)[29]
8	**2**	**20**	**D**: BSP, TTBP, Tf_2O, 3Å MS, -60 °C	30 min.	**24**	6.1 : 1 (quant.)	> 9 : 1 (88%)[29]
9	**1**	**20**	**D**: BSP, TTBP, Tf_2O, 3Å MS, -60 °C	30 min.	**25**	6.1 : 1 (quant.)	> 9 : 1 (88%)[29]
10	**1**	 **21**	**D**: BSP, TTBP, Tf_2O, 3Å MS, -60 °C	30 min.	**26**	4.4 : 1 (43%)	> 9 : 1 (77%)[29]
11	**1**	 **22**	**D**: BSP, TTBP, Tf_2O, 3Å MS, -60 °C	30 min.	**27**	6.1 : 1 (78%)	> 9 : 1 (73%)[29]
12	**1**	 **23**	**D**: BSP, TTBP, Tf_2O, 3Å MS, -60 °C	30 min.	**28**	~2:1[d] (~71%)	10 : 1 (90%)[31]

[a]The acceptor was added after the preactivation time. [b]Determined from crude NMR for donor **2** and purified products for donor **1**. [c]Not isolated. [d]The yield and ratio are estimated from NMR. [e]The yields and selectivities are obtained under conditions with 5 min preactivation. BSP = 1-benzenesulfinyl piperidine, MS = molecular sieves, NIS = *N*-iodosuccinimide, Ph_2SO = diphenyl sulfoxide, Tf_2O = triflic anhydride (trifluoromethanesulfonic anhydride), TfOH = triflic acid (trifluoromethanesulfonic acid), TTBP = 2,4,6-tri-*tert*-butylpyrimidine.



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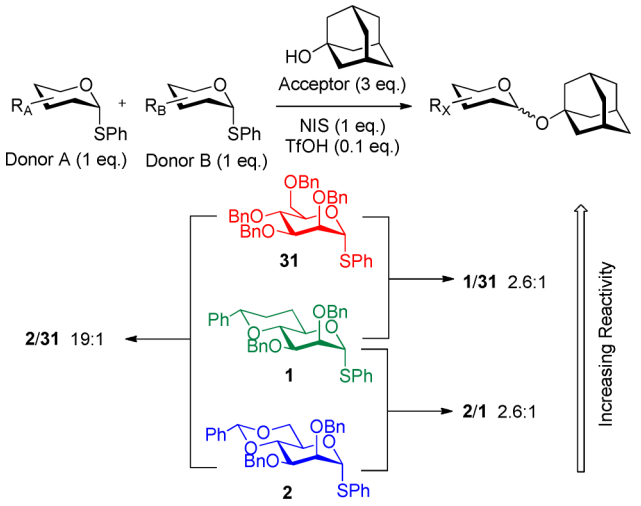

Figure 2. Competitive glycosylation experiments between thiomannosyl donors. Ratios are determined from the ^{1}H NMR of the crude reactions by integration of the H-1 signals of the remaining donors. The reaction was performed in CH_2Cl_2 at −40 °C and allowed to reach 0 °C in 3 h.

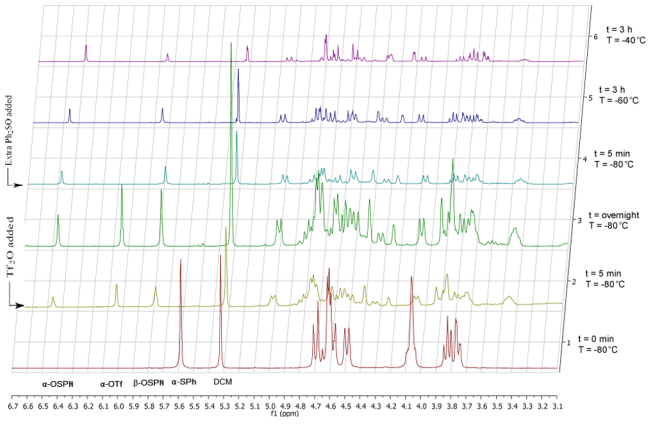

Figure 3. Low-temperature ^{1}H NMR (one experiment) for the activation of **1** with Ph_2SO/Tf_2O (1.3 equiv each) give rise to three new anomeric peaks (δ 5.78, 6.06, and 6.47 ppm) which were stable over time. Addition of extra Ph_2SO (1.7 equiv) resulted in the disappearance of the peak at δ 6.06 ppm while the other peak increased. Warming the sample gradually resulted in the peak at δ 5.78 ppm decreasing while the peak at δ 6.47 increased (−80 °C → −40 °C) (see the Supporting Information for more details).

and the benzylidene 315 (a ratio of ca. 16).[34] When the competition between the two tethered donors was performed a difference between the residue donor integrals of 1:2.6 (**1**/**2**) was observed, indicating that the C7-analogue **1** is slightly more reactive. Competition experiment between the C7-analogue **1** and the armed perbenzylated mannosyl donor **31** resulted in a residue donor ratio of 1:2.6 (**31**/**1**), i.e., the benzyl donor being more reactive. From these experiments it can be concluded that the C7-analogue **1** has a reactivity in between that of the armed donor **31** and the "conformational" disarmed **2**.

Low-Temperature NMR Studies. To further investigate the reactivity of the C7-analogue **1** and get insight into the reactive intermediates at play, low-temperature NMR experiments[35] were carried out. The stability of activated donor over time was also studied by low-temperature ^{1}H NMR, since it reflects the reactivity of the intermediate(s) and hence the donor.

The donor, Ph_2SO (1.3 equiv), and TTBP (2.4 equiv) were dissolved in CD_2Cl_2 and cooled to −80 °C, where a ^{1}H NMR was recorded (t = 0 min) followed by activation with Tf_2O, Figure 3. Spectra were then recorded keeping the temperature at −80 °C at various time (t = 5, 10, and 60 min and 16 h). Surprisingly, three new anomeric peaks, δ 5.78, 6.06, and 6.47 ppm, were instantly formed upon activation and were stable over time at −80 °C. To elucidate the identity of the three new species, extra Ph_2SO (1.7 equiv) was added and a spectrum recorded after 5 min and 3 h. The anomeric peak at δ 6.06 ppm disappeared and the peaks at δ 5.78 and 6.47 ppm increased, indicating that the former peak belongs to an α-anomeric triflate species and the latter two peaks come from an intermediate oxosulfonium species. This indicated that a β-oriented oxosulfonium intermediate had been formed (Scheme 6). To our knowledge, this is the first example of a β-oxosulfonium ion as a reactive intermediate in a glycosylation reaction.

Increasing the temperature, in intervals of 10 °C starting from −80 °C and ending at −40 °C, led to the slow decrease of the anomer peak at δ 5.78 ppm and an increased signal of the anomer at δ 6.47 ppm, i.e., anomerization of the β-oxosulfonium ion into the more stable α-oxosulfonium ion **33*α*** (Figure 3 and Scheme 6). When CD_3OD was added to the mixture of the α- and β-oxosulfonium ions at −80 °C a fast consumption of the oxosulfonium ion at 5.78 ppm was observed; the α-anomer reacted somewhat slower, and at −30 °C it was completely consumed (Figure 3, Supporting Information). From crude ^{1}H NMR the β-anomer was found to be the major product. The slow equilibrium between the two oxosulfonium ions might be hampering the diastereoselectivity in the reaction, and one might suspect that it will be even more predominant with less nucleophilic acceptors. The formation of the oxosulfonium ions could be avoided by using stoichiometric amounts of the diphenyl sulfoxide, which gave a clean, but not complete, formation of the α-triflate (Figure 4, Supporting Information). When the C7-analogue was activated using 1.3 equiv of BSP as the promoter only the formation of the α-triflate was observed (Figure 6, Supporting Information).

From the low-temperature NMR it is clear that the C7-analogue **1** has a surprising preference for forming oxosulfonium ions **33** over triflates **32**, which is opposite that for the benzylidene donor **2**, where the α-triflate was formed exclusively (Figure 8, Supporting Information). α-Oxosulfonium intermediates have been observed previously with other glycosyl donors using the same or a similar promoter system[36] and used as glycosyl donors.[37] β-Oxosulfonium ions have not previously been observed as an intermediate in glycosylation reactions, but other related reactive intermediates have been reported.[38]

Surprisingly, it was observed that whereas the benzylidene donor cleanly furnished the expected α-triflate, the C7-analogue gave a mixture of reactive intermediates (the α-, β-oxosulfonium ions and the α-triflate) when the exact conditions were used. The stability of the two α-triflates (benzylidene and C7-analogue) could also be studied, since their decomposition temperatures are directly related to the reactivity of the donor. To study the stability of the intermediate triflates, both triflates were generated at low temperature after which the temperature of the NMR sample was gradually increased until decomposition set in. The decomposition for the C7-analogue proved to be around −30 °C (Figures 4 and 9, Supporting

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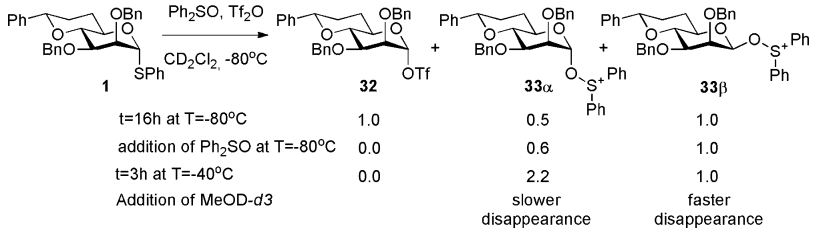
Scheme 6. Relative Ratios of Reactive Intermediates Observed in Low-Temperature NMR Experiments, when Activating the C7-Analogue at −80 °C



Information), where the benzylidene triflate decomposed between −20 and −10 °C, which is in line with the decomposition temperature reported for its 2,3-di-*O*-methyl counterpart.[39] This places the C7-analogue **1**'s reactivity in between the perbenzylated sugar **31** (decompose between −40 and −30 °C)[11] and the benzylidene **2**. This result is in line with the competition experiments described above. The difference, being only around 10−20 °C, is surprising taking the more significant difference in rate of hydrolysis into account in the related gluco derivatives (Figure 1) and the inherently higher reactivity of 6-deoxy sugars.[19]

DISCUSSION

The small differences between the diastereoselectivities of the C7-analogue **1** and the benzylidene donor **2** are surprising. From previous studies it is evident that a fixed *trans*−*gauche* oxygen is more electron withdrawing than an unrestricted or all other staggered positions.[19] It is also well established that a 6-deoxy is more reactive (armed) compared with a 6-hydroxy ether, such as the higher reactivity of rhamnosyl or fucosyl donors (compared to mannosyl or galactosyl donors, respectively).[40] The results in this work suggest that not only the stereoelectronics of C6−O but also the conformational restriction is important for the stereochemical outcome, and the combination. The clearly disarming effect of having a "4,6 tethering" is only partly due to the 6-O being antiperiplanar to the ring oxygen. Torsional effects, as suggested by Fraser-Reid et al.,[41] does probably also play a role. The locked $^4C_1$ ground-state conformation dictates a certain reaction path and limits the number of possible oxocarbenium ion conformations to essentially two; the $B_{2,5}$ and $^3H_4$, which both are in a fast equilibrium with the α-triflate or, depending on the exact glycosylation conditions, the oxosulfonium ions.

From other studies it has been demonstrated that a restricted chair conformation is not enough; a 3,4-tethering[42] does not provide the high β-selectivities and neither does 2,3-tethering, despite the enhanced stability of the respective α-triflates.[43] Conformational flip to the axial-rich conformation, however, does favor α-selectivity in an L-rhamnoside model[44] suggesting the importance of the "ground-state chair" as the starting point. Whitfield[45] has recently suggested, on the basis of computational chemistry, that the C6-OR tend to shield the β-face of the oxocarbenium ion, due to electrostatic interaction, and hence favor the α-product. This is avoided when the O6 and O4 are tethered together. The C1−O5 flexibility is also more restricted by this tethering than, e.g., a 3,4-tethering (such as butane-2,3-diacetal (BDA) protection), which only has a minor influence on the conformation at C1−O5.

From the glycosylation properties of the C7-analogue **1**, in terms of selectivity, reactivity, and the low-temperature NMR studies, a surprisingly small difference from the benzylidene **2** is observed. The effect of having an oxygen antiperiplanar (*trans*−*gauche*) to the ring oxygen is minor when it comes to triflate stability and diastereoselectivity in the glycosylations. Despite being smaller than anticipated, there is, however, an effect that becomes more clear when the system is challenged by more difficult glycosylations involving carbohydrate acceptors. This is exemplified when the 4-OH of a glucoside is glycosylated, which is less nucleophilic and more hindered. The reaction resulted in a complex reaction mixture with a low yield, and the selectivity dropped from around 10:1 (mannosylation using the benzylidene donor **2**) to 2:1. The marginal difference in triflate stability, which is important in the borderline cases such as the glycosylation on the 4-OH, is also confirmed by triflate decomposition observed at low-temperature NMR.

If the antiperiplanar 6-O is not decisive for the increased β-selectivity when having a 4,6-tethering, the strain induced by the tethering together with the limited conformational freedom should be taken into account. With a fixed conformation, the α-triflate is very favored over the β-triflate in mannosides due to the anomeric as well as the Δ2-effect.[1] These effects are amplified by a locked conformation, which thereby stabilizes the α-triflate further and give raise to an increased β-selectivity. The correlation between α-triflate stability and β-selectivity in mannosylation using unrestricted donors has earlier been observed.[46] Crich and Vinogradova[47] prepared a series of 6-deoxy-6-fluoro donors with one, two, and three fluorides. The decomposition of the respective α-triflates increased with roughly 10 degrees for each fluoride attached, and this resulted in an increased β-selectivity. The β-selectivity in the glycosylations decreased when weaker nucleophiles were used. A similar trend was observed by Kim and co-workers[11] when using sulfonyl protective groups on the 3, 4, and 6 positions in a mannosyl donor. It was found that an unrestricted mannosyl donor's β-selectivity could be improved by lowering its reactivity with strongly electron-withdrawing groups; the weakly associated triflate was again crucial for the selectivity. The strongest deactivating effect was found when having a 6-OSO_2Bn protective group followed by the 3 position and the 4 position. The triflate stabilities were again correlated to the β-selectivity.[46] These studies demonstrate that the locked conformation is not decisive for β-mannosylation and the selectivity is related to the overall reactivity of the donor.

A less stabilized oxocarbenium ion results in a tighter triflate and hence a better shielding of the α-site. The oxocarbenium ion can be destabilized by different means, conformational or stereoelectronical, but a fixed conformation maximizes the stereoelectronic effects, i.e., the anomeric and the Δ2 effect in the covalent intermediate, and hence push the equilibrium toward it (illustrated by the α-triflate **30** in Scheme 7). Having a fixed conformation, here restricted by the benzylidene, limits the conformational freedom and results in further stabilization

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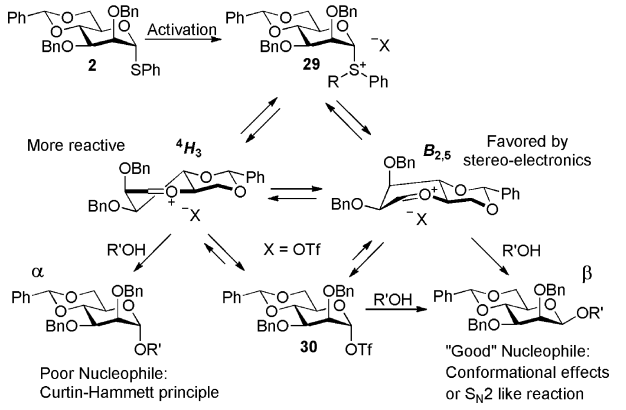
Scheme 7. Suggested Reaction Pathways To Give Either the α- or β-Mannosides



of the intermediate. The enhanced stability of the covalent intermediate is unique for the manno stereochemistry since the optimal stabilization, most often the α-triflate, can be reached due to the combination of the stereoelectronic effects mentioned above. This is not the case with, e.g., gluco stereochemistry, which is only stabilized from the anomeric effect. When having less stable covalent intermediates or less nucleophilic acceptors the competing reaction, i.e., the Curtin–Hammett pathway,[48] involving oxocarbenium intermediates (limited to mainly two species the $^4H_3$ and $B_{2,5}$, where the $^4H_3$ is less stable and therefore more reactive) dominate and the β-selectivity drops (Scheme 7). With more conformational freedom and no restriction the oxocarbenium ion is stabilized (more reactive donor) and the mechanism shifts away from the now less stable covalent intermediate (such as **30** in Scheme 7) resulting in less shielding of the α-side and thereby diminished β-selectivity.

CONCLUSION

In conclusion, we have shown that the C7 carbon analogue **1** indeed is β-selective when using the preactivation procedures developed by Crich. The selectivity is, however, generally lower than the benzylidene donor **2**. The selectivity is therefore not totally dependent on the electron-withdrawing capacity of the 6-O but also on other effects; conformational, stereoelectronical and torsional.

Low-temperature NMR revealed, in contrast to the benzylidene-protected mannosyl donor, that other reactive intermediates than the triflate were formed upon activation. The β-oxosulfonium was observed for the first time as a reactive intermediate in a glycosylation reaction.

The reactivity of the C7-analogue **1** was found to be in between that of the perbenzylated (armed) and the benzylidene **2** ("torsional" disarmed) as determined from α-triflate decomposition. This was further confirmed by competition experiments between the respective donors. Since the O6 is not required the scope of the preactivation procedure is broader and with the optimal conformational restriction other challenging 1,2-cis β-glycosides, such as the β-rhamnosides, should be within reach. Following parameters seems to be of major importance for the β-selectivity: α-triflate stability (by the anomeric and the Δ2 effect), acceptor reactivity and to some extent conformational preference of the activated donor. The O-6 does contribute to the β-selectivity but is not the only decisive factor.

EXPERIMENTAL SECTION

Phenylthio 2,3-Di-*O*-benzyl-α-D-mannopyranoside (3).[49] To a solution of 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (5.00 g, 9.25 mmol) in MeOH/CH_2Cl_2 (4:1, 200 mL) was added *p*-TsOH monohydrate (440 mg, 2.31 mmol, 0.25 equiv), and the reaction mixture was stirred under nitrogen at rt for 18 h. Afterward, the reaction was neutralized with Et_3N and concentrated. The crude was purified by flash column chromatography (EtOAc/petroleum ether 1:10 → 1:1) which gave the desired product phenylthio 2,3-di-*O*-benzyl-α-D-mannopyranoside in 87% (3.64 g) as crystals. The product can be recrystallized from ^{i}PrOH: HRMS (ESI) *m*/*z* calcd for $C_{26}H_{28}O_5SNa^+$ 475.1555, found 475.1557. Spectra were in accordance with literature.[49] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.18 (m, 15H; Ph), 5.49 (s, 1H; H-1), 4.60 (d, ^2J = 12.2 Hz, 1H; CH(H_a)-Ph), 4.51 (dd, ^2J = 11.9, J = 4.6 Hz, 2H; CH_2Ph), 4.40 (d, ^2J = 11.7 Hz, 1H; CH(H_b)-Ph), 4.07–4.01 (m, 2H; H-4, H-5), 3.95 (s, 1H; H-2), 3.86–3.70 (m, 2H; H-6), 3.62 (dd, J = 8.9, J = 2.7 Hz, 1H; H-3), 2.32 (s, 1H; OH-4), 1.83 (t, J = 6.4 Hz, 1H; OH-6). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3 (C_{ipsoBn}), 138.0 (C_{ipsoBn}), 134.4 ($C_{ipsoPhS}$), 132.1 (2 C_{Ph}), 129.5 (2 C_{Ph}), 129.3 (2 C_{Ph}), 128.8 (2 C_{Ph}), 128.8 (2 C_{Ph}), 128.4 (2 C_{Ph}), 128.3 (C_{paraPh}), 128.2 (C_{paraPh}), 127.9 (C_{paraPh}), 86.4 (C-1), 79.9 (C-3), 76.3 (C-5), 74.1 (C-2), 72.6 (CH_2Ph), 72.4 (CH_2Ph), 67.3 (C-4), 62.5 (C-6).

Phenylthio 4-*O*-Acyl-2,3-di-*O*-benzyl-6-*O*-trityl-α-D-mannopyranoside (4a–c). Representative procedure: A solution of phenylthio 2,3-di-*O*-benzyl-α-D-mannopyranoside **3** (3.95 g, 7.31 mmol), trityl chloride (4.48 g, 16.07 mmol, 2.2 equiv), and DMAP (179 mg, 1.46 mmol, 0.2 equiv) in pyridine (15 mL) was stirred under nitrogen at rt for 22 h by which TLC indicated conversion (petroleum ether/EtOAc 2:1). Additional TrCl (2.24 g, 8.10 mmol, 1.1 equiv) was added and the reaction mixture stirred for 1 h. Afterward, acetic anhydride (6.9 mL, 73.06 mmol, 10 equiv) was added, and the mixture was stirred under nitrogen at rt for 6.5 h. Subsequently, the reaction mixture was concentrated, coevaporated with toluene, and diluted with CH_2Cl_2. To remove excess DMAP and pyridine the solution was acidified with 1.0 M HCl, and the phases were separated. Afterward, the organic phase was neutralized with satd aq $NaHCO_3$, washed with brine, dried ($MgSO_4$), and concentrated. The crude was purified by flash column chromatography (petroleum ether/EtOAc 25:1→ 10:1) to give the desired product phenylthio 4-*O*-acetyl-2,3-di-*O*-benzyl-6-*O*-trityl-α-D-mannopyranoside (**4a**) in 81% (4.35 g) as a white foam: $[\alpha]_D^{RT}$ +40 (*c* 1.0, $CHCl_3$); HRMS (ESI) *m*/*z* calcd for $C_{47}H_{44}O_6SNa^+$ 759.2756, found 759.2784; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72–7.67 (m, 2H; PhS), 7.53 (d, J = 8.0 Hz, 6H; Ph), 7.45–7.30 (m, 22H; Ph), 5.73 (s, 1H; H-1), 5.44 (t, $J_{3,4}$ = 9.7 Hz, 1H; H-4), 4.81–4.72 (m, 2H; CH_2Ph), 4.65 (d, ^2J = 12.2 Hz, 1H; CH(H_a)-Ph), 4.54 (d, ^2J = 12.2 Hz, 1H; CH(H_b)-Ph), 4.50–4.42 (m, 1H; H-5), 4.10 (s, 1H; H-2), 3.83 (dd, $J_{3,4}$ = 9.4, $J_{2,3}$ = 1.6 Hz, 1H; H-3), 3.41 (dd, $^2J_{6a,6b}$ =10.1, $J_{5,6a}$ = 6.7 Hz, 1H; H-6a), 3.23 (d, $^2J_{6a,6b}$ = 10.4 Hz, 1H; H-6b), 1.86 (s, 3H; CH_3C=O); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.5 (C=O), 144.0 (3 $C_{ipsoPh\text{-}trityl}$), 138.0 (2 C_{ipsoBn}), 134.4 ($C_{ipsoPhS}$), 131.6 (C_{Ph}), 129.1 (C_{Ph}), 128.9 (C_{Ph}), 128.5 (C_{Ph}), 127.9 (C_{Ph}), 127.8 (C_{Ph}), 127.5 (C_{Ph}), 127.0 (C_{Ph}), 86.8 ($C_{tert\text{-}trityl}$), 85.6 (C-1), 77.3 (C-3), 76.1 (C-2), 72.3 (2 C_{benzyl}), 71.9 (C-5), 71.8 (C_{benzyl}), 68.6 (C-4), 63.4 (C-6), 20.8 ($CH_{3acetyl}$).

*Phenylthio 2,3-Di-O-benzyl-4-O-pivaloyl-6-O-trityl-α-D-mannopyranoside (**4b**).* Pivaloyl chloride (8.3 mg/8.5 mL, 68.94 mmol, 5 equiv). The desired product phenylthio 2,3-di-*O*-benzyl-4-*O*-pivaloyl-6-*O*-trityl-α-D-mannopyranoside was contaminated with Ph_3COH: HRMS (ESI) *m*/*z* calcd for $C_{50}H_{50}O_6SNa^+$ 801.3226, found 801.3222; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (ddd, J = 4.7, J = 2.3, J = 1.3 Hz, 2H; PhS), 7.47–7.44 (m, 6H; Ph), 7.37–7.23 (m, 48H; Ph), 5.71 (d, J = 1.8 Hz, 1H, H-1), 5.36 (t, J = 9.7 Hz, 1H; H-4), 4.69 (s, 2H; CH_2Ph), 4.54 (s, 2H; CH_2Ph), 4.52–4.47 (m, 1H; H-5), 4.06–3.98 (m, 1H; H-2), 3.81 (dd, J = 9.4, 3.0 Hz, 1H; H-3), 3.34 (dd, $^2J_{6a,6b}$ = 10.2, J = 7.4 Hz, 1H; H-6a), 3.07 (dd, $^2J_{6a,6b}$ = 10.2, J = 1.7 Hz, 1H; H-6b), 2.82 (brs, 1H, Ph_3OH), 0.96 (s, 9H; 3 × CH_3);^{13}C NMR (126 MHz, $CDCl_3$) δ 176.7 (C=O), 146.9, 143.9, 138.0 (C_{ipsoBn}), 137.8 (C_{ipsoBn}), 134.6 ($C_{ipsoPhS}$), 131.2 (C_{Ph}), 129.1 (C_{Ph}), 128.9 (C_{Ph}), 128.4

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(C_{Ph}), 128.0 (C_{Ph}), 127.8 (C_{Ph}), 127.7 (C_{Ph}), 127.6 (C_{Ph}), 127.3 (C_{Ph}), 126.8 (C_{Ph}), 86.6($C_{tert\text{-}trityl}$), 85.5 (C-1), 77.8 (C-3), 76.2 (C-2), 72.2 (2 × CH_2Ph), 72.0 (C-5), 68.0 (C-4), 63.2 (C-6), 38.6 ($C_{tert\text{-}pivaloyl}$), 26.9 (3 × $CH_{3pivaloyl}$).

*Phenylthio 4-O-Benzoyl-2,3-di-O-benzyl-6-O-trityl-α-D-mannopyranoside (**4c**).* Benzoyl chloride (4.40 g/3.63 mL, 31.28 mmol, 2 equiv): $[\alpha]_D^{RT}$ + 44 (*c* 1.0, $CHCl_3$); HRMS (ESI) *m*/*z* calcd for $C_{52}H_{46}O_6SNa^+$ 821.2913, found 821.2930; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.5 Hz, 2H; PhS), 7.65−7.58 (m, 3H; Ph), 7.41 (m, 10H; Ph), 7.30 (m, 6H; Ph), 7.24−7.17 (m, 5H; Ph), 7.16−7.09 (m, 9H; Ph), 5.69 (s, 1H; H-1), 5.62 (t, $J_{3,4}$ = 9.6 Hz, 1H; H-4), 4.74 (s, 2H; CH_2Ph), 4.57 (d, *J* = 12.3 Hz, 1H; $CH(H_a)Ph$), 4.54−4.48 (m, 1H; H-5), 4.45 (d, *J* = 12.3 Hz, 1H; $CH(H_b)Ph$), 4.08 (s, 1H; H-2), 3.89 (dd, $J_{3,4}$ = 9.3, *J* = 2.9 Hz, 1H; H-3), 3.40 (dd, *J* = 10.5, *J* = 6.5 Hz, 1H; H-6_a), 3.27−3.19 (m, 1H; H-6_b); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.2 (C═O), 143.8 ($C_{Ph\text{-}ipso}$), 137.9 ($C_{Bn\text{-}ipso}$), 137.7 ($C_{Bn\text{-}ipso}$), 134.3 ($C_{Ph\text{-}ipso}$), 132.9 (C_{Ph}), 131.5 (C_{Ph}), 129.9 ($C_{Ph\text{-}ipso}$), 129.8 (C_{Ph}), 129.1 (C_{Ph}), 128.7 (C_{Ph}), 128.4 (C_{Ph}), 128.3 (C_{Ph}), 128.2 (C_{Ph}), 127.9 (C_{Ph}), 127.7 (C_{Ph}), 127.4 (C_{Ph}), 126.8 (C_{Ph}), 86.75(C_{trityl}), 85.67 (C-1), 75.94 (C-3), 72.34 (C_{Bn}), 72.10 (C-5), 71.68 (C_{Bn}), 69.18 (C-4), 63.40 (C-6).

Phenylthio 4-*O*-Acetyl-2,3-di-*O*-benzyl-α-D-mannopyranoside (5a) and Phenylthio 6-*O*-Acetyl-2,3-di-*O*-benzyl-α-D-mannopyranoside (6). *Procedure 1.* Phenylthio 4-*O*-acetyl-2,3-di-*O*-benzyl-6-*O*-trityl-α-D-mannopyranoside (**4a**) (0.49 g, 0.66 mmol) was dissolved in CH_2Cl_2/MeOH (9:2, 22 mL) and cooled on ice. Subsequently, Amberlite IR-120 was added until the solution was acidic, and the reaction mixture was stirred under nitrogen at rt. The reaction mixture was diluted with CH_2Cl_2, and the resin was filtered and washed twice with CH_2Cl_2. Afterward, the organic phase was neutralized with Et_3N, concentrated, and purified by flash column chromatography (petroleum ether/EtOAc 15:1 → 4:1), which gave the product phenylthio 4-*O*-acetyl-2,3-di-*O*-benzyl-α-D-mannopyranoside (**5a**) as a syrup in 55% yield (180 mg) and phenylthio 6-*O*-acetyl-2,3-di-*O*-benzyl-α-D-mannopyranoside (**6**) in 34% yield (112 mg).

Procedure 2. Phenylthio 4-*O*-acetyl-2,3-di-*O*-benzyl-6-*O*-trityl-α-D-mannopyranoside (**4a**) (0.49 g, 0.66 mmol) was dissolved in benzene (135 mL) and heated under reflux and nitrogen overnight in the presence of anhydrous $CuSO_4$.(10 g). After cooling and concentration, the reaction mixture was poured on a dry silica gel column and purified by flash column chromatography (pure benzene → petroleum ether/EtOAc 15:1 → 4:1), which gave phenylthio 6-*O*-acetyl-2,3-di-*O*-benzyl-α-D-mannopyranoside (**6**) in 55% (186 mg) along with phenylthio 4-*O*-acetyl-2,3-di-*O*-benzyl-α-D-mannopyranoside (**5a**) in 12% yield (40 mg).

Procedure 3. Phenylthio 4-*O*-acetyl-2,3-di-*O*-benzyl-6-*O*-trityl-α-D-mannopyranoside (**4a**) (500 mg, 0.68 mmol) was dissolved in dry CH_2Cl_2 (20 mL) and cooled on ice. Detritylation was affected by the addition of trifluoroacetic acid (78 μL, 1.02 mmol, 1.5 equiv) and trifluoroacetic anhydride (TFFA, 141 μL, 1.02 mmol, 1.5 equiv), and the mixture was stirred overnight under nitrogen at 4 °C. The reaction mixture was neutralized with Et_3N (0.5 mL) by which excess TFAA was removed and the alcohol detrifluoroacetylated by pouring the mixture into MeOH (10 mL). After concentration, the crude was dissolved in CH_2Cl_2, washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude was purified by dry column chromatography[50] (heptane/EtOAc 15:1 → 4:1) which gave the desired product phenylthio 4-*O*-acetyl-2,3-di-*O*-benzyl-α-D-mannopyranoside (**5a**) in 66% yield (223 mg) along with phenylthio 6-*O*-acetyl-2,3-di-*O*-benzyl-α-D-mannopyranoside **6** in 10% yield (35 mg).

Phenylthio 4-*O*-acetyl-2,3-di-*O*-benzyl-α-D-mannopyranoside (**5a**): $[\alpha]_D^{RT}$ +12 (*c* 0.1, $CHCl_3$); HRMS (ESI) *m*/*z* calcd for $C_{28}H_{30}O_6SNa^+$ 517.1661, found 517.1667; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 8.0, 1.5 Hz, 2H; PhS-H_{ortho}), 7.29−7.18 (m, 13H; Ph), 5.51 (d, $J_{1,2}$ = 1.6 Hz, 1H; H-1), 5.30 (t, $J_{3,4}$ = 9.8, $J_{4,5}$ = 9.8, Hz, 1H; H-4), 4.60 (dd, ^2J = 12.4 Hz, 2H; CH_2Ph), 4.46 (dd, ^2J = 12.1 Hz, 2H; CH_2Ph), 4.03 (dt, $J_{4,5}$ = 9.9, $J_{5,6}$ = 3.5 Hz, 1H; H-5), 3.92 (dd, $J_{2,3}$ = 3.0, $J_{1,2}$ = 1.8 Hz, 1H; H-2), 3.76 (dd, $J_{3,4}$ = 9.7, $J_{2,3}$ = 3.1 Hz, 1H; H-3), 3.57 (d, $J_{5,6a}$ = 3.6 Hz, 2H; H-6), 2.27 (s, 1H, 4-OH), 1.99 (s, 3H; CH_3C═O). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9 (C═O), 137.9 (C_{ipsoBn}), 137.7(C_{ipsoBn}), 133.7 ($C_{ipsoPhS}$), 131.6 (C_{Ph}), 129.2 (C_{Ph}), 128.5 (C_{Ph}), 128.4 (C_{Ph}), 128.0 (C_{Ph}), 127.9 (C_{Ph}), 127.8 (C_{Ph}), 127.7 (C_{Ph}), 85.9 (C-1), 76.9 (C-3), 75.7 (C-2), 72.4 (C_{benzyl}), 72.3 (C-5), 72.0 (C_{benzyl}), 68.6 (C-4), 61.7 (C-6), 20.9 ($CH_{3acetyl}$).

Phenylthio-6-O-acetyl-2,3-di-O-benzyl-α-D-mannopyranoside (**6**): $[\alpha]_D^{RT}$ +27 (*c* 0.1, $CHCl_3$); HRMS (ESI) *m*/*z* calcd for $C_{28}H_{30}O_6SNa^+$: 517.1661, found 517.1684. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 8.0, *J* = 1.5 Hz, 2H; PhS-H_{ortho}), 7.26−7.15 (m, 13H; Ph), 5.51 (d, $J_{1,2}$ = 1.1 Hz, 1H; H-1), 4.60−4.38 (m, 4H; 2 CH_2Ph), 4.32 (dd, $^2J_{6a,6b}$ =12.0, $J_{5,6a}$ = 5.8 Hz, 1H; H-6a), 4.25 (dd, $^2J_{6a,6b}$ =12.0, $J_{5,6b}$ = 2.1 Hz, 1H; H-6b), 4.18 (ddd, $J_{4,5}$ = 9.4, $J_{5,6a}$ = 5.8, $J_{5,6b}$ = 1.9 Hz, 1H; H-5), 3.96−3.90 dd, $J_{3,4}$ = 9.6, $J_{4,OH}$ = 2.0, 2H; H-4), 3.90 (dd, $J_{2,3}$ = 2.9, $J_{1,2}$ = 1.5 Hz, 1H; H-2), 3.59 (dd, $J_{3,4}$ = 9.5, $J_{2,3}$ = 3.1 Hz, 1H; H-3), 2.75 (d, $J_{4,OH}$ = 2.2 Hz, 1H; 4-OH), 1.93 (s, 3H; CH_3−C═O). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.3 (C═O), 137.8 (C_{ipsoBn}), 137.7 (C_{ipsoBn}), 134.0 ($C_{ipsoPhS}$), 131.7 ($C_{orthoPhS}$), 129.1 ($C_{orthoPhS}$), 128.6 (C_{Ph}), 128.5 (C_{Ph}), 128.1 (C_{Ph}), 128.0 (C_{Ph}), 127.9 (C_{Ph}), 127.7 (C_{Ph}), 85.7 (C-1), 79.4 (C-3), 75.6 (C-2), 72.0 (C_{benzyl}), 71.9 (C_{benzyl}), 71.6 (C-4), 66.8 (C-5), 63.7 (C-6), 20.9 ($CH_{3\ acetyl}$).

Phenylthio 2,3-Di-*O*-benzyl-4-*O*-pivaloyl-α-D-mannopyranoside (5b). Same procedure as procedure 3 (see above): $[\alpha]_D^{RT}$ +48 (*c* 0.1, $CHCl_3$). HRMS (ESI) *m*/*z* calcd for $C_{31}H_{36}O_6SNa^+$ 559.2130, found 559.2113; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51−7.47 (m, 2H; PhS), 7.42−7.30 (m, 13H; Ph), 5.65 (d, *J* = 1.6 Hz, 1H; H-1), 5.47 (t, *J* = 9.8 Hz, 1H; H-4), 4.71 (dd, *J* = 27.9, 12.3 Hz, 2H; CH_2Ph), 4.63−4.54 (dd, 2H; CH_2Ph), 4.19 (ddd, *J* = 9.9, 4.4, 2.7 Hz, 1H; H-5), 4.05 (dd, *J* = 3.0, 1.8 Hz, 1H; H-2), 3.96 (dd, *J* = 9.7, 3.0 Hz, 1H; H-3), 3.73−3.62 (m, 2H; H-6), 2.57 (s, 1H; 6-OH), 1.28 (s, 9H; 3 × $CH_{3pivaloyl}$);. ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.5 (C═O), 137.7 (2 × $C_{ipso\text{-}benzyl}$), 133.8 ($C_{ipsoPhS}$), 131.6 (C_{Ph}), 129.2 (C_{Ph}), 128.5 (2 C_{Ph}), 128.1 (C_{Ph}), 127.9 (2 C_{Ph}), 127.8 (C_{Ph}), 127.7 (C_{Ph}), 86.0 (C-1), 77.2 (C-3), 75.90 (C-2), 72.5 (C-5), 72.3 (C_{benzyl}), 72.2 (C_{benzyl}), 68.2 (C-4), 61.7 (C-6), 39.0 ($C_{tert\text{-}pivaloyl}$), 27.2 (3 × $CH_{3pivaloyl}$).

Phenylthio 2,3-Di-*O*-benzyl-4-*O*-benzoyl-α-D-mannopyranoside (5c). Same as procedure 3 (see above): $[\alpha]_D^{RT}$ +114 (*c* 0.3, $CHCl_3$); HRMS (ESI) *m*/*z* calcd for $C_{33}H_{32}O_6SNa^+$ 579.1817, found 579.1838; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12−8.06 (m, 2H; PhS), 7.69−7.61 (m, 1H; Ph), 7.51 (m, 4H; Ph), 7.43 (m, 2H; Ph), 7.38−7.24 (m, 11H; Ph), 5.73 (t, $J_{4,5}$ = 9.8 Hz, 1H; H-4), 5.71 (d, $J_{1,2}$ = 1.6 Hz, 1H; H-1), 4.77 (dd, *J* = 31.2, *J* = 12.4 Hz, 2H; CH_2Ph), 4.57 (dd, *J* = 48.2, *J* = 12.2 Hz, 2H; CH_2Ph), 4.31 (dt, $J_{4,5}$ = 9.8, $J_{5,6}$ = 3.4 Hz, 1H; H-5), 4.14 (dd, $J_{2,3}$ = 2.9, $J_{1,2}$ = 1.9 Hz, 1H; H-2), 4.06 (dd, $J_{3,4}$ = 9.6, $J_{2,3}$ = 3.0 Hz, 1H; H-3), 3.76 (d, $J_{5,6}$ = 3.5 Hz, 2H; 2 × H-6), 2.53 (br s, 1H; 4-OH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.4 (C═O), 137.7 ($C_{ipso\text{-}benzyl}$), 137.6 ($C_{ipso\text{-}benzyl}$), 133.8 (C_{ipsoPh}), 133.5−130.0 (in total 5 C_{Ph}), 129.5 (C_{ipsoBz}), 129.3−127.8 (in total 15 C_{Ph}), 86.1 (C-1), 76.7 (C-3), 75.8 (C-2), 72.5 (C-5), 72.4 (C_{benzyl}), 71.9 (C_{benzyl}), 69.1 (C-4), 61.7 (C-6).

(*E*)-Phenylthio 2,3-Di-*O*-benzyl-4-*O*-pivaloyl-6,7-dideoxy-8-*C*-phenyl-α-D-*manno*-oct-6-eno-8-ulo-pyranoside (9a). To a solution of phenylthio 2,3-di-*O*-benzyl-4-*O*-pivaloyl-α-D-mannopyranoside **5b** (969 mg, 1.81 mmol) in dry CH_2Cl_2 (25 mL) was added Dess−Martin periodinane (DMP, 1.15 g, 2.71 mmol, 1.5 equiv), and the reaction mixture was stirred under nitrogen at rt for 22 h. The resulting suspension was diluted with CH_2Cl_2, and satd aq $NaHCO_3$ was added followed by $Na_2S_2O_3$ (560 mg).The mixture was stirred for 2 h to secure complete reduction of excess DMP. Subsequently, the water phase was extracted with CH_2Cl_2 (3×), and the combined organic phases was washed with satd aq $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated to give 973 mg of the crude phenylthio 2,3-di-*O*-benzyl-4-*O*-pivaloyl-α-D-*manno*-hexodialdo-1,5-pyranoside (**7b**). The crude aldehyde **7b** (888 mg, 1.66 mmol) was dissolved in dry CH_2Cl_2 (30 mL), and (benzoylmethylene)-triphenylphosphorane (950 mg, 2.49 mmol, 1.5 equiv) was added. The reaction mixture was stirred under nitrogen at rt for 22 h. Afterward, the reaction mixture was concentrated, and cold Et_2O was added by which some Ph_3P═O precipitated and was removed by filtration through a silica pad. Subsequently, the mixture was concentrated and the crude was purified by dry column chromatography (heptane with 1.5% gradient of EtOAc) which gave the desired

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product (*E*)-phenylthio 2,3-di-*O*-benzyl-4-*O*-pivaloyl-6,7-dideoxy-8-*C*-phenyl-α-D-*manno*-oct-6-eno-8-ulo-pyranoside (**9a**) in 73% yield (838 mg): R_f 0.3 (heptane/EtOAc 5.5:1); $[\alpha]_D^{RT}$ +67 (*c* 0.1, $CHCl_3$), R_f 0.3 (heptane/EtOAc 5:1); HRMS (ESI) *m*/*z* calcd for $C_{39}H_{40}O_6SNa^+$ 659.2443, found 659.2469; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 8.3, *J* = 1.2 Hz, 2H; PhS), 7.46−7.42 (m, 1H; Ph), 7.37−7.31 (m, 4H; Ph), 7.27−7.17 (m, 13H; Ph), 6.92 (dd, $J_{6,7trans}$ = 15.6, *J* = 1.6 Hz, 1H; H-7), 6.75 (dd, $J_{6,7trans}$ = 15.6, $J_{5,6}$ = 4.9 Hz, 1H; H-6), 5.50 (d, *J* = 2.0 Hz, 1H; H-1), 5.38 (t, *J* = 9.5 Hz, 1H; H-4), 4.78 (ddd, $J_{4,5}$ = 9.7, $J_{5,6}$ = 4.9, *J* = 1.3 Hz, 1H; H-5), 4.58 (s, 2H; CH_2Ph), 4.47 (s, 2H; CH_2Ph), 3.95−3.89 (m, 1H; H-2), 3.80 (dd, $J_{3,4}$ = 9.4, *J* = 2.9 Hz, 1H; H-3), 1.10 (s, 9H; 3 × $CH_{3pivaloyl}$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.0 (PhC═O), 177.0 (C═O), 142.1 (C-6), 137.7 (2 × $C_{ipso\text{-}benzyl}$), 137.4 (C_{ipsoPh}), 133.6 ($C_{ipsoPhS}$), 132.8 (C_{Ph}), 131.8 (C_{Ph}), 129.2 (C_{Ph}), 128.9 (C_{Ph}), 128.6 (C_{Ph}), 128.5 (C_{Ph}), 128.0 (C_{Ph}), 127.9 (C_{Ph}), 127.7 (C_{Ph}), 127.2 (C-7), 86.2 (C-1), 77.5 (C-3), 76.0 (C-2), 72.7 (C_{benzyl}), 72.3 (C_{benzyl}), 71.4 (C-5), 70.2 (C-4), 38.9 ($C_{tert\text{-}pivaloyl}$), 27.2 (3 × $CH_{3pivaloyl}$).

(*E*)-Phenylthio 4-*O*-Benzoyl-2,3-di-*O*-benzyl-6,7-dideoxy-8-*C*-phenyl-α-D-*manno*-oct-6-eno-8-ulo-pyranoside (9b) and (*E*)-Phenylthio 2,3-Di-*O*-benzyl-4,6,7-trideoxy-8-*C*-phenyl-α-L-*erythro*-oct-6-eno-8-ulopyranoside (10). Same procedure as above which on small scale gave the desired compound in 73% (838 mg) but on larger scale gave the eliminated product **10** in 97% yield (2.79 g). (*E*)-Phenylthio 4-*O*-benzoyl-2,3-di-*O*-benzyl-6,7-dideoxy-8-*C*-phenyl-α-D-*manno*-oct-6-eno-8-ulo-pyranoside: R_f 0.3 (heptane/EtOAc 5.5:1); $[\alpha]_D^{RT}$ +114 (*c* 0.1, $CHCl_3$); HRMS (ESI) *m*/*z* calcd for $C_{41}H_{36}O_6SNa^+$ 679.2130, found 679.214; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10−8.04 (m, 2H; Ph), 7.84−7.78 (m, 2H; Ph), 7.64 (t, *J* = 7.4 Hz, 1H; Ph), 7.55−7.20 (m, 20H; Ph), 7.08 (dd, $J_{6,7}$ = 15.6, *J* = 1.4 Hz, 1H; H-7), 6.97 (dd, $J_{6,7}$ = 15.6, *J* = 4.7 Hz, 1H; H-6), 5.73 (t, *J* = 9.5 Hz, 1H; H-4), 5.67 (d, *J* = 1.9 Hz, 1H; H-1), 5.06−4.96 (m, 1H; H-5), 4.77 (s, 2H; CH_2Ph), 4.62 (d, *J* = 12.2 Hz, 1H; C(H_a)HPh), 4.51 (d, *J* = 12.2 Hz, 1H; C(H_b)HPh), 4.15−4.10 (m, 1H; H-2), 4.01 (dd, *J* = 9.3, *J* = 2.9 Hz, 1H; H-3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.6 (PhC═O_{ketone}), 165.3 (PhC═O_{ester}), 141.9 (C-6), 137.7 ($C_{Ph\text{-}ipso}$), 137.5 ($C_{Ph\text{-}ipso}$), 137.4 ($C_{Ph\text{-}ipso}$), 133.6 ($C_{Ph\text{-}ipso}$), 133.3−129.9 (4 C_{Ph}), 129.7 ($C_{Ph\text{-}ipso}$), 129.2−127.8 (21 C_{Ph}), 127.0 (C-7), 86.1 (C-1), 76.8 (C-3), 75.8 (C-2), 72.6 (C_{Bn}), 71.9 (C_{Bn}), 71.3 (C-5), 71.2 (C-4). (*E*)-Phenylthio 2,3-di-*O*-benzyl-4,6,7-trideoxy-8-*C*-phenyl-α-L-*erythro*-oct-6-eno-8-ulo-pyranoside (**10**): $[\alpha]_D^{RT}$ +210 (*c* 1.0, $CHCl_3$); mp 122−123 °C; HRMS (ESI) *m*/*z* calcd for $C_{34}H_{30}O_4SNa^+$ 557.1757, found 557.1749; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 8.4 Hz, *J* = 1.4 Hz, 2H; Ph), 7.45 (m, 3H; Ph), 7.38 (m, 2H; Ph), 7.31−7.18 (m, 13H; Ph), 7.12 (d, $J_{6,7}$ = 15.2 Hz, 1H; H-7), 6.99 (d, $J_{6,7}$ = 15.2 Hz, 1H; H-6), 5.61 (d, *J* = 4.9 Hz, 1H; H-1), 5.38 (d, *J* = 3.4 Hz, 1H; H-4), 4.63 (s, 2H; CH_2Ph), 4.54 (s, 2H; CH_2Ph), 4.26 (t, *J* = 3.8 Hz, 1H; H-3), 3.84 (t, *J* = 4.5 Hz, 1H; H2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.2 (PhC═O_{ketone}), 148.7 (C-5), 138.0 ($C_{Ph\text{-}ipso}$), 137.95 ($C_{Ph\text{-}ipso}$), 137.9 (C-6), 137.7 ($C_{Ph\text{-}ipso}$), 133.3 (C_{Ph}), 133.1 (C_{Ph}), 132.6 ($C_{Ph\text{-}ipso}$), 129.2 (C_{Ph}), 128.7 (C_{Ph}), 128.6 (C_{Ph}), 128.4 (C_{Ph}), 128.3 (C_{Ph}), 128.1 (C_{Ph}), 128.0 (C_{Ph}), 127.9 (C_{Ph}), 123.0 (C-7), 110.3 (C-4), 84.1 (C-1), 72.6 (C-2), 72.3 (C_{Bn}), 71.4 (C_{Bn}), 69.3 (C-3).

Stryker's Reagent: $[CuH(PPh_3)]_6$.[51] Schlenk techniques were used for the synthesis of the air-sensitive "copper hydride". Anhydrous copper(II) acetate (3.75 g, 20.64 mmol, prepared from the monohydrate by heating at 105 °C in vacuo) and PPh_3 (10.83 g 41.29 mmol, 2 equiv) were weighed into an dried, argon-filled round-bottomed two-necked flask equipped with a sintered glass. Benzene (45 mL), dried by passing through basic Al_2O_3 and degassed by three freeze−thaw cycles, refilling with argon, was added, followed by diphenylsilane (4.57 mL, 24.77 mmol, 1.2 equiv). The reaction mixture turned from a blue suspension to a green solution within 5 min. The color of the reaction further changed from green to dark red in 1 h. The resulting homogeneous solution was stirred for another 1 h and concentrated under vacuum to approximately one-third of its volume. Anhydrous acetonitrile (45 mL, from a solvent purification system), degassed by three freeze−thaw cycles, was slowly layered onto the benzene solution to promote crystallization of the product. After standing overnight under oxygen-free argon, the red crystals were collected by filtration, washed with degassed acetonitrile (3 × 50 mL), and dried by applying oil pump vacuum. Stryker's reagent was obtained as dark red crystals in 82% and used directly in the next step.

Phenylthio 2,3-Di-*O*-benzyl-4-*O*-pivaloyl-6,7-dideoxy-8-*C*-phenyl-α-D-*manno*-oct-8-ulopyranoside (11a). Schlenk techniques were used for the 1,4-reduction. Freshly made Stryker's reagent (1.90g, 0.97 mmol, 0.37 equiv) was dissolved in dry and degassed benzene (5 mL, dried by passing through basic Al_2O_3 and degassed by three freeze−thaw cycles, refilling with argon). Then (*E*)-phenylthio 2,3-di-*O*-benzyl-4-*O*-*p*-pivaloyl-6,7-dideoxy-8-*C*-phenyl-α-D-*manno*-oct-6-eno-8-ulo-pyranoside (**9a**) (1.68 g, 2.64 mmol) dissolved in dry and degassed benzene (25 mL, see above) was added by cannulation along with degassed water (118 μL). The resulting dark red solution was stirred under argon until completion as indicated by NMR of the crude reaction mixture (30 min). Afterward, the system was opened, and air was bubbled through the solution by which copper-containing degradation products precipitated. The solution was filtered through a bed of Celite and washed with Et_2O followed by concentration in vacuo. The crude was purified by flash column chromatography (heptane/EtOAc 15:1 → 5:1) to give the product as crystals in 86% yield (1.45 g): R_f 0.3 (heptane/EtOAc 5:1); $[\alpha]_D^{RT}$ +62 (*c* 0.8, $CHCl_3$); mp 108.5−108.9 °C; HRMS (ESI) *m*/*z* calcd for $C_{39}H_{42}O_6SNa^+$ 661.2600, found 661.2626. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (dd, *J* = 8.4, *J* = 1.3 Hz, 2H; Ph), 7.87 (dd, *J* = 8.4, *J* = 1.3 Hz, 2H; Ph), 7.67−7.61 (m, 1H; Ph), 7.58−7.54 (m, 1H; Ph), 7.53−7.49 (m, 2H; Ph), 7.46−7.26 (m, 12H; Ph), 7.24−7.17 (m, 5H; Ph), 5.71 (t, *J* = 9.7 Hz, 1H; H-4), 5.69 (d, *J* = 1.7 Hz, 1H; H-1), 4.84−4.77 (m, 2H; CH_2Ph), 4.62 (d, *J* = 12.2 Hz, 1H; C(H_a)HPh)), 4.51 (d, *J* = 12.2 Hz, 1H; C(H_b)HPh)), 4.41 (td, *J* = 9.3, *J* = 2.8 Hz, 1H; H-5), 4.11 (dd, *J* = 2.9, *J* = 1.9 Hz, 1H; H-2), 4.00 (dd, *J* = 9.5, *J* = 3.0 Hz, 1H; H-3), 3.11 (ddd, *J* = 17.9, *J* = 8.2, *J* = 5.1 Hz, 1H; H-7_a), 2.97 (dt, *J* = 17.9, *J* = 7.4 Hz, 1H; H-7_b), 2.24 (tdd, *J* = 9.9, *J* = 7.6, *J* = 2.9 Hz, 1H; H-6_a), 2.03−1.93 (m, 1H; H-6_b); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.4 (PhC═O_{ketone}), 165.8 (PhC═O_{ester}), 137.9 ($C_{Bn\text{-}ipso}$), 137.7 ($C_{Bn\text{-}ipso}$), 136.9 ($C_{Ph\text{-}ipso}$), 134.0−133.8 (2 C_{Ph}), 133.6 ($C_{Ph\text{-}ipso}$), 133.2−127.5 (23 C_{Ph}), 85.7 (C-1), 77.1 (C-3), 75.9 (C-2), 72.6 (C_{Bn}), 72.0 (C-4), 71.8 (C_{Bn}), 70.6 (C-5), 33.6 (C-7), 25.3 (C-6).

Phenylthio 4-*O*-Benzoyl-2,3-di-*O*-benzyl-6,7-dideoxy-8-*C*-phenyl-α-D-*manno*-oct-8-ulopyranoside (11b). Same procedure as above using (*E*)-phenylthio 4-*O*-benzoyl-2,3-di-*O*-benzyl-6,7-dideoxy-8-*C*-phenyl-α-D-*manno*-oct-6-eno-8-ulopyranoside (**9b**) (5.00 g, 7.61 mmol) giving the desired product in 66% yield (3.29 g): R_f 0.3 (heptane/EtOAc 4:1); $[\alpha]_D^{RT}$ +8 (*c* 0.5, $CHCl_3$); HRMS (ESI) *m*/*z* calcd for $C_{41}H_{38}O_6SNa^+$ 681.2287, found 681.2322; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (dd, *J* = 8.4, *J* = 1.3 Hz, 2H; Ph), 7.87 (dd, *J* = 8.4, *J* = 1.3 Hz, 2H; Ph), 7.67−7.61 (m, 1H; Ph), 7.58−7.54 (m, 1H; Ph), 7.53−7.49 (m, 2H; Ph), 7.46−7.26 (m, 12H; Ph), 7.24−7.17 (m, 5H; Ph), 5.71 (t, *J* = 9.7 Hz, 1H; H-4), 5.69 (d, *J* = 1.7 Hz, 1H; H-1), 4.84−4.77 (m, 2H; CH_2Ph), 4.62 (d, *J* = 12.2 Hz, 1H; C(H_a)HPh)), 4.51 (d, *J* = 12.2 Hz, 1H; C(H_b)HPh)), 4.41 (td, *J* = 9.3, *J* = 2.8 Hz, 1H; H-5), 4.11 (dd, *J* = 2.9, *J* = 1.9 Hz, 1H; H-2), 4.00 (dd, *J* = 9.5, *J* = 3.0 Hz, 1H; H-3), 3.11 (ddd, *J* = 17.9, *J* = 8.2, *J* = 5.1 Hz, 1H; H-7_a), 2.97 (dt, *J* = 17.9, *J* = 7.4 Hz, 1H; H-7_b), 2.24 (tdd, *J* = 9.9, *J* = 7.6, *J* = 2.9 Hz, 1H; H-6_a), 2.03−1.93 (m, 1H; H-6_b); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.4 (PhC═O_{ketone}), 165.8 (PhC═O_{ester}), 137.9 ($C_{Bn\text{-}ipso}$), 137.7 ($C_{Bn\text{-}ipso}$), 136.9 ($C_{Ph\text{-}ipso}$), 134.0−133.8 (2 C_{Ph}), 133.6 ($C_{Ph\text{-}ipso}$), 133.2−127.5 (23 C_{Ph}), 85.7 (C-1), 77.1 (C-3), 75.9 (C-2), 72.6 (C_{Bn}), 72.0 (C-4), 71.8 (C_{Bn}), 70.6 (C-5), 33.6 (C-7), 25.3 (C-6).

Phenylthio 2,3-Di-*O*-benzyl-6,7-dideoxy-8-*C*-phenyl-α-D-*manno*-oct-8-ulopyranoside (12). Procedure 1 (acyl deprotection): Phenylthio 2,3-di-*O*-benzyl-4-*O*-pivaloyl-6,7-dideoxy-8-*C*-phenyl-α-D-*manno*-oct-8-ulopyranoside (300 mg, 470 mmol) was dissolved in MeOH/THF (5:2, 14 mL) followed by the addition of NaOMe (0.3 mL) until the reaction mixture was slightly basic. The reaction mixture was stirred under nitrogen at rt and followed by TLC (heptane/EtOAc 5:1, R_f 0.21). After 6 days, TLC only showed half conversion but the reaction was acidified by the addition of Amberlite IR-120. Subsequently, concentration and dry column chromatography (heptane with a 1.7% gradient of EtOAc) gave the starting material in

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36% yield (107 mg) and the desired product in 57% yield (148 mg). Procedure 1 was also used for the deprotection of phenylthio 4-*O*-benzoyl-2,3-di-*O*-benzyl-6,7-dideoxy-8-*C*-phenyl-α-D-*manno*-oct-8-ulopyranoside (**11b**) giving the desired product **12** in quantitative yield: $[\alpha]_D^{RT}$ +3.0 (*c* 0.4, $CHCl_3$); HRMS (ESI) *m/z* calcd for $C_{34}H_{34}O_5SNa^+$ 577.2025, found 577.2034; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86−7.74 (m, 2H; Ph), 7.50−7.44 (m, 1H; Ph), 7.36−7.16 (m, 17H; Ph), 5.57 (d, $J_{1,2}$ = 1.0 Hz, 1H; H-1), 4.52 (m, 4H; 2 × CH_2Ph), 4.00 (td, *J* = 9.0, *J* = 2.7 Hz, 1H; H-5), 3.94 (dd, $J_{2,3}$ = 3.0, $J_{1,2}$ = 1.4 Hz, 1H; H-2), 3.83 (t, $J_{3,4}$ = 9.4, $J_{4,OH}$ = 1.9 Hz, 1H; H-4), 3.64 (dd, $J_{3,4}$ = 9.4, $J_{2,3}$ = 3.1 Hz, 1H; H-3), 3.00 (ddd, $J_{7a,7b}$ = 17.9, *J* = 8.8, *J* = 5.4 Hz, 1H; H-7_a), 2.80 (ddd, $J_{7a,7b}$ = 17.9, *J* = 8.5, *J* = 6.3 Hz, 1H; H-7_a), 2.50 (d, $J_{4,OH}$ = 2.3 Hz, 1H; 4-OH), 2.34−2.23 (m, 1H; H-6_a), 1.92 (dtd, *J* = 14.2, *J* = 8.6, *J* = 5.5 Hz, 1H; H-6_b); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.9 (Ph−C═O), 137.8 (2 × $C_{Bn\text{-}ipso}$), 136.9 ($C_{Ph\text{-}ipso}$), 134.0 ($C_{Ph\text{-}ipso}$), 132.9 (C_{Ph}), 131.5 (C_{Ph}), 129.1 (C_{Ph}), 128.6 (C_{Ph}), 128.5 (C_{Ph}), 128.1 (C_{Ph}), 128.0 (C_{Ph}), 127.9 (C_{Ph}), 127.4 (C_{Ph}), 85.2 (C-1), 79.7 (C-3), 75.5 (C-2), 72.4 (C-5), 72.2 (C_{benzyl}), 71.8 (C_{benzyl}), 70.2 (C-4), 34.1 (C-7), 25.4 (C-6).

Phenylthio 2,3-Di-*O*-benzyl-6,7-dideoxy-8-*C*-phenyl-4-*O*-(trimethylsilyl)-α-D-*manno*-oct-8-ulopyranoside (13). To a solution of phenylthio 2,3-di-*O*-benzyl-6,7-dideoxy-8-*C*-phenyl-α-D-*manno*-oct-8-ulopyranoside (**12**) (137 mg, 0.25 mmol) in DMF (3 mL) were added imidazole (50 mg, 0.74 mmol, 3 equiv) and trimethylsilyl chloride (94 μL, 0.74 mmol, 3 equiv). The reaction mixture was stirred under nitrogen at rt for 3 h. Subsequently, the mixture was diluted with EtOAc and H_2O and separated. The water phase was extracted with EtOAc (3×), and the combined organic phases were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude was purified by dry column chromatography (heptane with a 0.9% gradient of EtOAc) giving the desired product in 92% yield (142 mg): R_f 0.3 (heptane/EtOAc 10:1); $[\alpha]_D^{RT}$ +12 (*c* 0.7, $CHCl_3$); HRMS (ESI) *m/z* calcd for $C_{37}H_{42}O_5SSiNa^+$ 649.2425, found 649.2418; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (dt, *J* = 8.5, *J* = 1.5 Hz, 2H; Ph), 7.55−7.49 (m, 1H; Ph), 7.42−7.20 (m, 17H;), 5.57 (d, $J_{1,2}$ = 1.5 Hz, 1H; H-1), 4.65 (s, 2H; CH_2Ph), 4.59 (dd, *J* = 32.1, *J* = 11.9 Hz, 2H; CH_2Ph), 3.97 (td, $J_{5,6}$ = 9.5, $J_{4,5}$ = 2.3 Hz, 1H; H-5), 3.94−3.88 (m, 2H; H-2, H-4), 3.66 (dd, $J_{3,4}$ = 8.8, $J_{2,3}$ = 3.0 Hz, 1H; H-3), 2.98 (ddd, $J_{7a,7b}$ = 17.8, *J* = 9.9, $J_{6b,7a}$ = 4.8 Hz, 1H; H-7_a), 2.74 (ddd, $J_{7a,7b}$ = 17.8, *J* = 9.5, $J_{6a,7b}$ = 5.8 Hz, 1H; H-7_b), 2.38−2.26 (m, 1H; H-6_a), 1.79 (dtd, $J_{6a,6b}$ = 14.4, $J_{5,6}$ = 9.6, $J_{6b,7a}$ = 4.8 Hz, 1H; H-6_b), 0.15 (s, 9H; 3 × CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.7 (C═O), 138.4 ($C_{Bn\text{-}ipso}$), 138.3 ($C_{Bn\text{-}ipso}$), 137.1 ($C_{Ph\text{-}ipso}$), 134.2($C_{Ph\text{-}ipso}$), 132.9 (C_{Ph}), 131.5 (C_{Ph}), 129.1 (C_{Ph}), 128.6 (C_{Ph}), 128.5 (C_{Ph}), 128.1 (C_{Ph}), 127.9 (2 × C_{Ph}), 127.8 (C_{Ph}), 127.7 (C_{Ph}), 127.3 (C_{Ph}), 85.5 (C-1), 80.4 (C-3), 76.6 (C-2), 73.6 (C-5), 72.7 (C_{Bn}), 72.4 (C_{Bn}), 72.3 (C-4), 34.8 (C-7), 25.9 (C-6), 0.9 (3 × C_{TMS}).

Phenylthio 2,3-Di-*O*-benzyl-6-(*tert*-butyldimethylsiloxy)-α-D-mannopyranoside (16).[52] A solution of phenylthio 2,3-di-*O*-benzyl-α-D-mannopyranoside (**3**) (22.20 g, 49.05 mmol) in DMF was cooled to 0 °C. Imidazole (3.51 g, 51.51 mmol, 1.05 equiv) and *tert*-butyldimethylsilyl chloride (7.76 g, 51.51 mmol, 1.05 equiv) were added, and the reaction mixture was warmed to rt under N_2. After being stirred for 3 h, the reaction mixture was quenched with MeOH and concentrated. The residue was taken up in Et_2O and washed two times with water, one time with brine, dried ($MgSO_4$), and concentrated. The crude was purified by dry column chromatography (heptane with a 1.3% gradient of EtOAc) to give the product **15** as a colorless syrup in 78% yield (21.63 g): R_f 0.3 (heptane/EtOAc 7:1); HRMS (ESI) *m/z* calcd for $C_{32}H_{42}O_5SSiNa^+$ 589.2420, found 589.2413; $[\alpha]_D^{RT}$ +24 (*c* 0.4, $CHCl_3$); spectra were in accordance with literature;[9] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.35 (dd, *J* = 8.1, *J* = 1.5 Hz, 2H; Ph), 7.27−7.15 (m, 13H; Ph), 5.51−5.48 (d, $J_{1,2}$ = 1.6 Hz, 1H; H-1), 4.60−4.56 (m, 1H; CH(H_a)Ph), 4.52−4.44 (m, 3H; CH_2Ph; CH(H_b)Ph), 4.04−3.98 (m, 2H; H-4, H-5), 3.91−3.88 (dd, $J_{2,3}$ = 3.1, $J_{1,2}$ = 1.6 Hz, 1H; H-2), 3.85−3.78 (m, 2H; H-6_a, H-6_b), 3.63−3.57 (m, 1H; H-3), 0.83−0.80 (s, 9H; 3 × CH_3), 0.00 (s, 6H; 2 × CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.1 ($C_{Bn\text{-}ipso}$), 138.0 ($C_{Bn\text{-}ipso}$), 134.7 ($C_{PhS\text{-}ipso}$), 131.6 (C_{Ph}), 129.1 (C_{Ph}), 128.7 (C_{Ph}), 128.5 (C_{Ph}), 128.1 (C_{Ph}), 128.0 (C_{Ph}), 127.9 (C_{Ph}), 127.5 (C_{Ph}), 86.0 (C-1), 79.6 (C-3), 75.9 (C-2), 75.9, 73.3, 72.07 (C_{Bn}), 72.0 (C_{Bn}), 68.7, 64.2 (C-6), 26.1 (C_{methyl}), 18.5 ($C_{quart.}$), −5.2 (C_{methyl}).

Phenylthio 2,3-Di-*O*-benzyl-4-*O*-(*p*-methoxybenzyl)-6-(*tert*-butyldimethylsiloxy)-α-D-mannopyranoside (17). A solution of phenylthio 2,3-di-*O*-benzyl-6-(*tert*-butyldimethylsiloxy)-α-D-mannopyranoside (**16**) (1.43 g, 2.53 mmol) and *p*-methoxybenzyl chloride (0.44 mL, 27.79 mmol, 1,1 equiv) in DMF was cooled to −8 °C. Then, NaH (60% in mineral oil, 0.25 g) was added, and the mixture was allowed to stir under N_2 for 1.5 h. The reaction was quenched by addition of MeOH, and the mixture was concentrated and purified by dry column chromatography (heptane with a 0.8% gradient of EtOAc) to give the product **17** as a colorless syrup in 66% yield (1.15 g): R_f 0.3 (heptane/EtOAc 12:1); HRMS (ESI) *m/z* calcd for $C_{40}H_{50}O_6SSiNa^+$ 709.2996, found 709.3000; $[\alpha]_D^{RT}$ +76 (*c* 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46−7.42 (dd, *J* = 8.1, 1.6 Hz, 2H; Ph), 7.39−7.24 (m, 16H; Ph), 6.88−6.85 (m, 2H; Ph), 5.57−5.54 (d, $^2J_{1,2}$ = 1.7 Hz, 1H; H-1), 4.88−4.84 (d, *J* = 10.5 Hz, 1H; CH(H_a)Ph), 4.70−4.61 (m, 4H; 2 × CH_2Ph), 4.60−4.57 (d, ^2J = 10.6 Hz, 1H; CH(H_b)Ph), 4.10−4.05 (m, 1H), 4.01−3.95 (m, 2H; H-2), 3.91−3.87 (m, 1H), 3.86−3.82 (m, 2H; ; H-6_a, H-6_b), 3.82−3.80 (s, 3H; CH_3O), 0.90−0.88 (s, 9H; 3 × CH_3), 0.07−0.06 (s, 3H; CH_3), 0.06−0.05 (s, 3H; CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.4 ($C_{Ph\text{-}ipso}$), 138.5 ($C_{Ph\text{-}ipso}$), 138.2 ($C_{Ph\text{-}ipso}$), 135.0 ($C_{Ph\text{-}ipso}$), 131.6 (C_{Ph}), 131.0 (C_{Ph}), 129.8 (C_{Ph}), 129.0 (C_{Ph}), 128.5 (C_{Ph}), 128.4 (C_{Ph}), 128.0 (C_{Ph}), 127.9 (C_{Ph}), 127.8 (C_{Ph}), 127.7 (C_{Ph}), 127.4 (C_{Ph}), 113.9 (C_{Ph}), 85.7 (C-1), 80.3, 76.7, 75.0 (C_{Bn}), 74.8, 74.37, 72.3 (C_{Bn}), 71.9 (C_{Bn}), 62.8 (C-6), 55.4 (C_{MeO}), 26.1 (C_{methyl}), 18.5 (C_{quart}), −5.0 (C_{methyl}), −5.1 (C_{methyl}).

Phenylthio 2,3-Di-*O*-benzyl-4-*O*-(*p*-methoxybenzyl)-α-D-mannopyranoside (18). To a solution of phenylthio 2,3-di-*O*-benzyl-4-*O*-(*p*-methoxybenzyl)-6-(*tert*-butyldimethylsiloxy)-α-D-mannopyranoside (**17**) (11.50 g, 16.74 mmol) in 200 mL of dry CH_2Cl_2 was added tetra-*n*-butylammonium fluoride (1.0 M in THF, 20.1 mL, 20.1 mmol). The reaction was kept stirred under N_2 for 18 h. Then, the reaction mixture was concentrated, and the residue was purified by dry column chromatography (heptane with a 2.2% gradient of EtOAc) to give the pure compound **18** as a colorless syrup in 99% yield (9.51 g): R_f 0.36 (heptane/EtOAc 2:1); HRMS (ESI) *m/z* calcd for $C_{34}H_{36}O_6SNa^+$ 595.2130, found 595.2124; $[\alpha]_D^{RT}$ +90 (*c* 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46−7.31 (m, 17H; Ph), 6.93 (d, *J* = 8.6 Hz, 2H; Ph), 5.58 (d, $J_{1,2}$ = 1.8 Hz, 1H; H-1), 4.94 (d, ^2J = 10.6 Hz, 1H; CH(H_a)Ph), 4.75 (m, 2H; CH_2Ph), 4.73−4.65 (m, 3H; CH_2Ph, CH(H_b)Ph), 4.18 (m, 1H; H-5), 4.10 (t, $J_{3,4}$ = 9.4 Hz, 1H; H-4), 4.06 (t, *J* = 2.4 Hz, 1H; H-2), 3.95 (dd, $J_{3,4}$ = 9.2, *J* = 3.0 Hz, 1H; H-3), 3.90−3.83 (m, 6H; MeO, 2 × H-6, 6-OH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.4 ($C_{Ph\text{-}ipso}$), 138.2 ($C_{Bn\text{-}ipso}$), 137.9 ($C_{Bn\text{-}ipso}$), 134.0 ($C_{SPh\text{-}ipso}$), 131.9 (C_{Ph}), 130.5 (C_{Ph}), 129.8 (C_{Ph}), 129.2 (C_{Ph}), 128.5 (C_{Ph}), 128.5 (C_{Ph}), 128.0 (C_{Ph}), 127.9 (C_{Ph}), 127.8 (C_{Ph}), 127.8 (C_{Ph}), 127.7 (C_{Ph}), 113.9 (C_{Ph}), 86.1 (C-1), 80.2 (C-3), 76.5 (C-2), 75.0 (C_{Bn}), 74.6 (C-4), 73.4 (C-5), 72.4 (C_{Bn}), 72.3 (C_{Bn}), 62.3 (C-6), 55.4 (C_{MeO}).

(*E*)-Phenylthio 2,3-Di-*O*-benzyl-4-*O*-(*p*-methoxybenzyl)-6,7-dideoxy-8-*C*-phenyl-α-D-*manno*-oct-6-eno-8-ulopyranoside (9c). To a solution of phenylthio 2,3-di-*O*-benzyl-4-*O*-(*p*-methoxybenzyl)-α-D-mannopyranoside (**18**) (4.00 g, 6.98 mmol) in 100 mL of dry CH_2Cl_2 was added Dess−Martin periodinane (4.44 g, 10.48 mmol, 1.5 equiv). The reaction was stirred under N_2 for 5.5 h before the reaction mixture was quenched with satd aqueous $NaHCO_3$ and $Na_2S_2O_3$ (1.65 g). The reaction mixture was stirred for an additional 1 h followed by extraction of the water phase with CH_2Cl_2. The combined organic phases were washed with satd $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. To a solution of crude phenylthio 2,3-di-*O*-benzyl-4-*O*-(*p*-methoxybenzyl)-α-D-*manno*-hexodialdo-1,5-pyranoside **7c** (3.99 g, 6.99 mmol) in dry CH_2Cl_2 (100 mL) was added (benzoylmethylene)triphenylphosphorane (3.19 g, 8.39 mmol, 1.2 equiv). The reaction mixture was stirred for 13 h under N_2 followed by concentration in vacuo and purification by dry column chromatography (heptane with a 1.4% gradient of EtOAc. This gave the product **9c** as a colorless syrup in 74% (3.49 g) over two steps: R_f 0.3 (heptane/EtOAc 5:1); HRMS (ESI) *m/z* calcd for $C_{42}H_{40}O_6SNa^+$ 695.2438, found 695.2430; $[\alpha]_D^{RT}$ +67 (*c* 0.2, $CHCl_3$); ^{1}H NMR (500

MHz, $CDCl_3$) δ 7.82 (dd, J = 8.3, 1.4 Hz, 2H; Ph_{ortho}), 7.47 (m, 1H; Ph), 7.36 (m, 2H; Ph_{ortho}), 7.31−7.16 (m, 15H; Ph), 7.13 (dd, J = 6.4, 2.1 Hz, 3H; 2 × Ph, H-6), 7.07 (m, 1H; H-7), 6.71 (m, 2H; Ph_{ortho}), 5.50 (d, $J_{1,2}$ = 1.8 Hz, 1H; H-1), 4.76 (d, ^2J = 10.4 Hz, 1H; $CH(H_a)Ph$), 4.72 (m, 1H; H-5), 4.65−4.54 (m, 4H; 2 × CH_2Bn), 4.45 (d, ^2J = 10.4 Hz, 1H; $CH(H_b)Ph$), 3.94 (dd, $J_{2,3}$ = 3.0, $J_{1,2}$ = 1.8 Hz, 1H; H-2), 3.83 (dd, $J_{2,3}$ = 3.0, $J_{3,4}$ = 1.9 Hz, 1H; H-3), 3.76 (t, $J_{4,5}$ = 9.4 Hz 1H; H-4), 3.65 (s, 3H; MeO); ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.4 (C═O), 159.4 ($C_{Ph\text{-}ipso}$), 143.9 (C-6), 138.1 ($C_{Bn\text{-}ipso}$), 137.9 ($C_{Bn\text{-}ipso}$), 137.7 ($C_{Bn\text{-}ipso}$), 134.0 ($C_{SPh\text{-}ipso}$), 132.9 (C_{Ph}), 131.8 (C_{Ph}), 130.0 ($C_{Ph\text{-}ipso}$), 129.9 (C_{Ph}), 129.1 (C_{Ph}), 128.7 (C_{Ph}), 128.6 (C_{Ph}), 128.5 (C_{Ph}), 128.5 (C_{Ph}), 128.0 (C_{Ph}), 127.89 (C_{Ph}), 127.87 (C_{Ph}), 127.85 (C_{Ph}), 127.7 (C_{Ph}), 125.8 (C-7), 113.9 (C_{Ph}), 86.0 (C-1), 80.1 (C-3), 78.1 (C-4), 76.6 (C-2), 75.3 (C_{Bn}), 72.5 (C_{Bn}), 72.4 (C_{Bn}), 72.2 (C-5), 55.3 (C_{MeO}).

Phenylthio 2,3-Di-*O*-benzyl-4-*O*-(*p*-methoxybenzyl)-6,7-dideoxy-8-*C*-phenyl-α-D-*manno*-oct-8-ulopyranoside (11c). Schlenk techniques were used for the 1,4-reduction. Freshly made Stryker's reagent (7.38 g, 3.76 mmol, 0.82 equiv) was dissolved in dry and degassed benzene (5 mL, dried by passing through basic Al_2O_3 and degassed by three freeze thaw cycles, refilling with argon). Then (*E*)-phenylthio 2,3-di-*O*-benzyl-4-*O*-(*p*-methoxybenzyl)-6,7-dideoxy-8-*C*-phenyl-α-D-*manno*-oct-6-eno-8-ulopyranoside (**9c**) (3.10 g, 4.61 mmol) dissolved in dry and degassed benzene (35 mL, see above) was added by cannulation along with degassed water (207 mL, 11.52 mol, 2.5 equiv). The resulting dark red solution was stirred under argon until completion as indicated by NMR of the crude reaction mixture (30 min). Afterward, the system was opened, and air was bubbled through the solution by which copper-containing degradation products precipitated. The solution was filtered through a bed of Celite and washed with Et_2O followed by concentration in vacuo. The crude was purified by dry column chromatography (heptane with a 0.91% gradient of EtOAc) to give the product **11c** as a colorless syrup in 99% (3.10 g): R_f 0.3 (heptane/EtOAc 5:1); HRMS (ESI) m/z calcd for $C_{42}H_{42}O_6SNa^+$ 697.2594, found 697.2579; $[\alpha]_D^{RT}$ +93 (c 0.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (dd, J = 8.4, 1.4 Hz, 2H; Ph_{ortho}), 7.52 (m, 1H; Ph), 7.47−7.28 (m, 19H; Ph), 6.89 (m, 2H; Ph_{ortho}), 5.66 (d, $J_{1,2}$ = 1.7 Hz, 1H; H-1), 4.94 (d, ^2J = 10.4 Hz, 1H; $CH(H_a)Ph$), 4.81−4.73 (m, 2H; CH_2Ph), 4.73−4.66 (m, 3H; CH_2Ph, $CH(H_b)Ph$), 4.12 (td, $J_{4,5}$ = 9.3, $J_{5,6}$ = 2.8 Hz, 1H; H-5), 4.04 (dd, $J_{2,3}$ = 3.0, $J_{1,2}$ = 1.8 Hz, 1H; H-2), 3.96 (dd, J = 9.1, $J_{2,3}$ = 3.1 Hz, 1H; H-3), 3.84 (t, $J_{4,5}$ = 9.3 Hz, 1H; H-4), 3.79 (s, 3H; MeO), 2.98 (m, 1H; H-7_a), 2.83 (ddd, J = 17.8, 9.8, 5.5 Hz, 1H; H-7_b), 2.42 (m, 1H; H-6_b), 1.99 (dtd, J = 14.2, 9.6, 4.8 Hz, 1H; H-6_a); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.6 (C═O), 159.3 ($C_{Ph\text{-}ipso}$), 138.3 ($C_{Bn\text{-}ipso}$), 138.0 ($C_{Bn\text{-}ipso}$), 136.9 ($C_{Bn\text{-}ipso}$), 134.40 (C_{Ph}), 134.38 (C_{Ph}), 134.1 ($C_{SPh\text{-}ipso}$), 133.9 (C_{Ph}), 133.7 (C_{Ph}), 132.9 (C_{Ph}), 131.5 (C_{Ph}), 130.5 ($C_{Ph\text{-}ipso}$), 130.2 (C_{Ph}), 129.9 (C_{Ph}), 129.1 (C_{Ph}), 128.8 (C_{Ph}), 128.6 (C_{Ph}), 128.51 (C_{Ph}), 128.49 (C_{Ph}), 128.46 (C_{Ph}), 128.45 (C_{Ph}), 128.04 (C_{Ph}), 127.99 (C_{Ph}), 127.87 (C_{Ph}), 127.84 (C_{Ph}), 127.80 (C_{Ph}), 127.78 (C_{Ph}), 127.3 (C_{Ph}), 113.9 (C_{Ph}), 85.1 (C-1), 80.3 (C-3), 78.2 (C-4), 76.4 (C-2), 75.0 (C_{Bn}), 72.32 (C_{Bn}), 72.28 (C_{Bn}), 72.1 (C-5), 55.3 (C_{MeO}), 34.6 (C-7), 25.7 (C-6).

Phenylthio 4,7-Anhydro-2,3-di-*O*-benzyl-6-deoxy-7,8-ene-8-(*p*-methoxybenzyl)-8-phenyl-α-D-*manno*-octopyranoside (19). Phenylthio 2,3-di-*O*-benzyl-4-*O*-(*p*-methoxybenzyl)-6,7-dideoxy-8-*C*-phenyl-α-D-*manno*-oct-8-ulopyranoside (**11c**) (103 mg, 0.15 mmol) was dissolved in a 10% TFA solution in CH_2Cl_2 (5 mL). The reaction was completed after 5 min (estimated from TLC). The mixture was concentrated in vacuo and purified by dry column chromatography giving the entitled compound **19** as a colorless syrup in 50% (49 mg): HRMS (ESI) m/z calcd for $C_{42}H_{40}O_5SNa^+$ 679.2494, found 679.5109; $[\alpha]_D^{RT}$ +35 (c 0.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (m, 2H; Ph), 7.44−7.27 (m, 18H; Ph), 7.10 (dd, J = 6.5, 2.1 Hz, 2H; Ph), 6.86 (m, 2H; Ph), 5.56 (d, $J_{1,2}$ = 1.6 Hz, 1H; H-1), 4.87 (d, ^2J = 12.0 Hz, 1H; $CH(H_a)Ph$), 4.81−4.71 (q, ^2J = 12.4 Hz, 2H; CH_2Ph), 4.69 (d, ^2J = 12.0 Hz, 1H; $CH(H_b)Ph$), 4.44 (td, $J_{4,5}$ = 9.5, J = 6.7 Hz, 1H; H-5), 4.29 (t, J = 9.7 Hz, 1H; H-4), 4.08 (m, 1H; H-2), 3.97 (dd, $J_{3,4}$ = 9.6, J = 3.3 Hz, 1H; H-3), 3.82 (s, 3H; MeO), 3.54 (d, ^2J = 15.4 Hz, 1H; $CH(H_b)Ph$), 3.37 (d, ^2J = 15.4 Hz, 1H; $CH(H_a)Ph$), 2.28 (m, 2H; H-6); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.0 ($C_{Ph\text{-}ipso}$), 148.7 (C-7), 138.6 ($C_{Bn\text{-}ipso}$), 137.8 ($C_{Bn\text{-}ipso}$), 135.5 ($C_{Ph\text{-}ipso}$), 134.5 ($C_{SPh\text{-}ipso}$), 132.1 ($C_{Ph\text{-}ipso}$), 131.0 (C_{Ph}), 129.3 (C_{Ph}), 129.1 (C_{Ph}), 129.0 (C_{Ph}), 128.5 (C_{Ph}), 128.4 (C_{Ph}), 128.3 (C_{Ph}), 128.2 (C_{Ph}), 128.1 (C_{Ph}), 128.0 (C_{Ph}), 127.8 (C_{Ph}), 127.6 (C_{Ph}), 127.5 (C_{Ph}), 127.3 (C_{Ph}), 113.9 (C_{Ph}), 107.4 (C-8), 86.5 (C-1), 77.6 (C-2), 76.9 (C-3), 76.8 (C-4), 73.0 (C_{Bn}), 72.7 (C_{Bn}), 67.3 (C-5), 55.3 (C_{MeO}), 37.5 (C_{Bn}), 31.2 (C-6).

Phenylthio 2,3-Di-*O*-benzyl-6,7-dideoxy-8-*C*-phenyl-α-D-*manno*-oct-8-ulopyranoside (12). Procedure 2 (DDQ deprotection): To a solution of phenylthio 2,3-di-*O*-benzyl-4-*O*-(*p*-methoxybenzyl)-6,7-dideoxy-8-*C*-phenyl-α-D-*manno*-oct-8-ulopyranoside (2.00 g, 2.96 mmol) dissolved in CH_2Cl_2/H_2O (100 mL, 20:1) was added DDQ (0.81 g, 3.55 mmol, 1.2 equiv), and the reaction was stirred for 2 h. Then, the reaction was quenched by addition of satd $NaHCO_3$, and the mixture was extracted with CH_2Cl_2, washed with satd $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. The crude was purified by dry column chromatography (heptane with a 2.5% EtOAc gradient). This gave the product as a colorless syrup in 89% (1.46 g): R_f 0.26 (heptane/EtOAc 3:1); HRMS (ESI) m/z calcd for $C_{34}H_{34}O_5SNa^+$ 577.2025, found 577.2034; $[\alpha]_D^{RT}$ +8 (c 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86−7.74 (m, 2H; Ph), 7.50−7.44 (m, 1H; Ph), 7.36−7.16 (m, 17H; Ph), 5.57 (d, $J_{1,2}$ = 1.0 Hz, 1H; H-1), 4.52 (m, 4H; 2 × CH_2Ph), 4.00 (td, J = 9.0, J = 2.7 Hz, 1H; H-5), 3.94 (dd, $J_{2,3}$ = 3.0, $J_{1,2}$ = 1.4 Hz, 1H; H-2), 3.83 (t, $J_{3,4}$ = 9.4, $J_{4,OH}$ = 1.9 Hz, 1H; H-4), 3.64 (dd, $J_{3,4}$ = 9.4, $J_{2,3}$ = 3.1 Hz, 1H; H-3), 3.00 (ddd, $J_{7a,7b}$ = 17.9, J = 8.8, J = 5.4 Hz, 1H; H-7_a), 2.80 (ddd, $J_{7a,7b}$ = 17.9, J = 8.5, J = 6.3 Hz, 1H; H-7_a), 2.50 (d, $J_{4,OH}$ = 2.3 Hz, 1H; 4-OH), 2.34−2.23 (m, 1H; H-6_a), 1.92 (dtd, J = 14.2, J = 8.6, J = 5.5 Hz, 1H; H-6_b); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.9 (Ph−C═O), 137.8 (2 × $C_{Bn\text{-}ipso}$), 136.9 ($C_{Ph\text{-}ipso}$), 134.0 ($C_{Ph\text{-}ipso}$), 132.9 (C_{Ph}), 131.5 (C_{Ph}), 129.1 (C_{Ph}), 128.6 (C_{Ph}), 128.5 (C_{Ph}), 128.1 (C_{Ph}), 128.0 (C_{Ph}), 127.9 (C_{Ph}), 127.4 (C_{Ph}), 85.2 (C-1), 79.7 (C-3), 75.5 (C-2), 72.4 (C-5), 72.2 (C_{benzyl}), 71.8 (C_{benzyl}), 70.2 (C-4), 34.1 (C-7), 25.4 (C-6).

Phenylthio 4,8-Anhydro-2,3-di-*O*-benzyl-6,7-dideoxy-8-methoxy-8*R*-*C*-phenyl-α-D-*manno*-octopyranoside (14) and (*Z*)-Phenylthio 4,8-Anhydro-2,3-di-*O*-benzyl-6,7-dideoxy-8-*C*-phenyl-α-D-*manno*-oct-7-enopyranoside (15). To a solution of phenylthio 2,3-di-*O*-benzyl-6,7-dideoxy-8-*C*-phenyl-α-D-*manno*-oct-8-ulopyranoside (**12**) (460 mg, 0.83 mmol) dissolved in dry MeOH/THF (5:1, 15 mL) was added freshly activated Amberlite IR-120H. The reaction mixture was stirred under N_2 at rt for 48 h. When TLC (heptane/EtOAc 5:1) indicated 90% conversion the resin was removed and washed several times with MeOH. The solution was afterward neutralized with a few drops of Et_3N and concentrated. The crude was purified by dry column chromatography (heptane with a 1.0% gradient of EtOAc) to give two products in an overall yield of 71% (333 mg). The starting material **12** could be recovered in 28% yield (129 mg). (*Z*)-Phenylthio 4,8-anhydro-2,3-di-*O*-benzyl-6,7-dideoxy-8-*C*-phenyl-α-D-*manno*-oct-7-enopyranoside (**15**): R_f 0.31 (heptane/EtOAc 5:1); HRMS (ESI) m/z calcd for $C_{34}H_{34}O_4S^+$ 537.2100, found 537.2109; $[\alpha]_D^{RT}$ +13 (c 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (m, 2H; Ph), 7.37−7.15 (m, 18H; Ph), 5.49 (d, $J_{1,2}$ = 1.6 Hz, 1H; H-1), 5.25 (dd, J = 5.0, J = 3.1 Hz, 1H; H-7), 4.84 (d, J = 12.0 Hz, 1H; $CH(H_a)$-PH), 4.66 (m, 3H; Bn), 4.31 (td, J = 9.3, J = 6.7 Hz, 1H; H-5), 4.22 (t, $J_{3,4}$ = 9.6 Hz, 1H; H-4), 3.99 (dd, $J_{2,3}$ = 3.1, $J_{1,2}$ = 1.6 Hz, 1H; H-2), 3.93 (dd, $J_{3,4}$ = 9.6, $J_{2,3}$ = 3.2 Hz, 1H; H-3), 2.37 (m, 2H; H-6). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.6 (C-8), 138.5 ($C_{Ph\text{-}ipso}$), 137.9 ($C_{Ph\text{-}ipso}$), 135.2 ($C_{Ph\text{-}ipso}$), 134.3 ($C_{Ph\text{-}ipso}$), 131.4−124.8 ($C_{Ph\text{-}H}$), 95.3 (C-7), 86.6 (C-1), 77.6 (C-2),77.1 (C-3), 76.7 (C-4), 73.1 (C_{Bn}), 72.8 (C_{Bn}), 67.0 (C-5), 27.6 (C-6). Phenylthio 4,8-anhydro-2,3-di-*O*-benzyl-6,7-dideoxy-8-methoxy-8*R*-*C*-phenyl-α-D-*manno*-octopyranoside (**14**): R_f 0.24 (heptane/EtOAc 5:1); HRMS (ESI) m/z calcd for $C_{35}H_{36}O_5NaS^+$ 591.2181, found 591.2174; $[\alpha]_D^{RT}$ +45 (c 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (dd, J = 8.3, J = 1.4 Hz, 2H), 7.32−7.18 (m, 18H), 5.46 (d, $J_{1,2}$ = 1.5 Hz, 1H; H-1), 4.83 (d, J = 12.2 Hz, 1H; $CH(H_a)$-Ph), 4.72 (m, 1H; $CH(H_a)$-Ph), 4.68 (m, 2H; 2 x $CH(H_b)$-Ph), 4.18 (t, J = 9.8 Hz, 1H; H-4), 4.00 (dd, J = 3.3, $J_{1,2}$ = 1.5 Hz, 1H; H-2), 3.95 (m, 1H; H-5), 3.84 (dd, J = 9.9,

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3.3 Hz, 1H; H-3), 3.03 (s, 3H; MeO), 2.18−2.05 (m, 2H; H-6_a, H-7_a), 1.76 (m, 1H; H-6_b), 1.63 (m, 1H; H-7_b). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.0 ($C_{Ph\text{-}ipso}$),, 138.9 ($C_{Bn\text{-}ipso}$), 138.1 ($C_{Bn\text{-}ipso}$), 134.6 ($C_{Ph\text{-}ipso}$), 131.1−124.8 (20 × Ph-H), 99.7 (C-8 $_{benzylidene}$), 87.1 (C-1), 78.0 (C-2), 76.9 (C-3), 73.1 (C_{benzyl}), 72.9 (C_{benzyl}), 72.0 (C-4), 69.4 (C-5), 49.2 (C_{MeO}), 37.6 (C-7), 25.4 (C-6).

Phenylthio 4,8-Anhydro-2,3-di-*O*-benzyl-6,7-dideoxy-8-phenyl-D-*glycero*-α-D-*manno*-octopyranoside (1). A solution of acetal **14** and alkene **15** (1.21 g, 2.13 mmol, from acetal) was dissolved in dry CH_2Cl_2 (20 mL), kept under nitrogen, and cooled to 0 °C. Then, trifluoroacetic anhydride (0.60 mL, 4.26 mmol, 2 equiv) and triethylsilane (1.70 mL, 10.60 mmol, 5 equiv) were added, and the resulting solution was stirred for 5 min. Afterward, trifluoroacetic acid (0.81 mL, 10.60 mmol, 5 equiv) was added dropwise over a period of 2 min. Then the ice bath was removed, and the reaction mixture was left until completion (4 h, judged by TLC). The mixture was diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ and water, dried ($MgSO_4$), and concentrated. The crude was purified by dry column chromatography (heptane with a 1.0% gradient of EtOAc) to give the product **1** as a colorless syrup in 97% (1.15 g): R_f 0.4 (heptane/EtOAc 5:1); HRMS (ESI) m/z calcd for $C_{34}H_{34}O_4SNa^+$ 561.2076, found 561.2090; $[\alpha]_D^{RT}$ +101 (c 0.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47−7.29 (m, 20H; Ph), 5.60 (d, $J_{1,2}$ = 1.4 Hz, 1H: H-1), 4.87 (d, J = 12.4 Hz, 1H; C(H_a)HPh), 4.79 (q, J = 12.3 Hz, 2H; CH_2Ph), 4.73 (d, J = 12.4 Hz, 1H; C(H_b)Ph), 4.61 (dd, $J_{7,8}$ = 2.0 Hz, $J_{7,8}$ = 11.7 Hz, 1H; H-8_{axial}), 4.10 (dd, $J_{1,2}$ = 1.4 Hz, $J_{2,3}$ = 3.1 Hz, 1H; H-2), 4.07 (m, 1H; H-5), 4.05 (m, 1H; H-4), 3.94 (dd, $J_{2,3}$ = 3.1 Hz, 1H; H-3), 2.15 (dt, J = 9.0, J = 2.6 Hz, 2H; H-$6_{equatorial}$, H-$7_{equatorial}$), 1.95 (m, 1H; H-6_{axial}), 1.79 (m, 1H; H-7_{axial}). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.4 ($C_{Ph\text{-}ipso}$), 138.8 ($C_{3\text{-}Bn\ ipso}$), 138.0 ($C_{2\text{-}Bn\ ipso}$), 134.7 ($C_{SPh\text{-}ipso}$), 131.2−125.8 (20 C_{Ph}), 86.90 (C-1), 79.44 (C-4), 79.19 (C-8), 78.13 (C-2), 77.00 (C-3), 73.05 ($C_{3\text{-}Bn}$), 72.84 ($C_{2\text{-}Bn}$), 69.83 (C-5), 33.52 (C-7), 29.31 (C-6).

Glycosylation Procedures. *Method A: NIS/TfOH Method.* Mannosyl donor (100 mg, 185 μmol, 1 equiv) and acceptor (1.1 equiv) were coevaporated twice with toluene. Afterward, the donor and acceptor were dried for 30 min at a Schlenk line along with 3 Å molecular sieves. To the mixture of donor, acceptor, and 3 Å molecular sieves was added 2 mL of dry dichloromethane (0.1 M with respect to donor) at 0 °C under argon, and the reaction mixture was stirred for 1 h. Then, NIS (2.5 equiv) was added followed by a catalytic amount of TfOH (1 drop). The reaction mixture was stirred until completion, as judged by TLC (ca. 5−10 min, heptane/EtOAc 3:1), after which the solution was diluted with dichloromethane and filtered through Celite. Afterward, the filtrate was washed with 10% aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and concentrated. The crude reaction mixture was purified by dry column chromatography on silica gel.

Methods B and C: Ph_2SO/TTBP/Tf_2O Method. Mannosyl donor (100 mg, 185 μmol, 1 equiv), TTBP (1.1 equiv), and Ph_2SO (1 equiv) were coevaporated twice with toluene. Afterward, the donor, TTBP, and Ph_2SO were dried for 30 min on a Schlenk line along with either 3 Å or crushed 4 Å molecular sieves. To the mixture of donor, TTBP, Ph_2SO, and molecular sieves was added 1 mL of dry dichloromethane at −78 °C under argon, and the reaction mixture was stirred for 1 h. Afterward, Tf_2O (2 equiv) was added and the mixture stirred for 30 min (−78 °C) after which the acceptor in 0.5 mL of dichloromethane (1.5 equiv, 0.1 M with respect to donor) was added. After the reaction was complete as judged by TLC (10 min −2 h, heptane/EtOAc 3:1), the temperature was raised to −40 °C, and several drops of Et_3N were added. Then, the mixture was filtered through Celite, concentrated, and purified by dry column chromatography on silica gel to give the α/β products.

Method D: BSP/TTBP/Tf_2O Method. Mannosyl donor (100 mg, 185 μmol, 1 equiv), TTBP (1.1 equiv), and 1-benzenesulfinyl piperidine (BSP, 1 equiv) were coevaporated twice with toluene. Afterward, the donor, TTBP, and BSP were dried for 30 min on a Schlenk line along with 3 Å molecular sieves. To the mixture of donor, TTBP, BSP, and molecular sieves was added 1 mL of dry dichloromethane at −60 °C under argon, and the reaction mixture was stirred for 1 h. Afterward, Tf_2O (2 equiv) was added and the mixture stirred for 30 min (−60 °C) after which the acceptor in 0.5 mL of dichloromethane (1.5 equiv, 0.1 M with respect to donor) was added. After the reaction was complete as judged by TLC (10 min −3 h, heptane/EtOAc 5:1), the temperature was raised to −40 °C and several drops of Et_3N were added. Then, the mixture was filtered through Celite, concentrated, and purified by dry column chromatography on silica gel giving the α/β products.

1-Adamantanyl 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-D-mannopyranoside (24).[53] Method A: β/α 1:5.7. 91% yield (98 mg, starting with 100 mg). Method B: β/α 6.7:1. 75% yield (80 mg, starting with 100 mg). Method C: β/α 7.0:1. 83% yield (89 mg, starting with 100 mg). Method D: β/α 6.1:1. Quantitative yield: 107 mg, starting with 100 mg. HRMS (ESI): m/z calcd for $C_{37}H_{42}O_6Na^+$ 605.287, found 605.2876

1-Adamantanyl 4,8-anhydro-2,3-di-*O*-benzyl-6,7-dideoxy-8-*C*-phenyl-D-*glycero*-α-D-*manno*-octopyranoside (25α): HRMS (ESI) m/z calcd for $C_{38}H_{44}O_5Na^+$ 603.3086, found 603.3098; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (m, 1H; Ph), 7.40−7.27 (m, 14H; Ph), 5.13 (d, $J_{1,2}$ = 1.8 Hz, 1H; H-1), 4.84 (t, J = 12.4 Hz, 2H; CH_2Ph), 4.68 (m, 2H; CH_2Ph), 4.53 (dd, J = 11.2, J = 2.3 Hz, 1H; H-8), 3.92 (m, 1H; H-3), 3.88 (m, 1H; H-4), 3.70 (ddd, J = 11.2, J = 9.0, J = 4.2 Hz, 1H; H-5), 3.62 (dd, J = 3.0, $J_{1,2}$ = 1.8 Hz, 1H; H-2), 2.10 (dd, J = 6.4, J = 3.2 Hz, 3H; $H_{adamantanyl}$), 2.03 (m, 2H; H-6_a, H-7_a), 1.78 (m, 2H; H-6_b, H-7_b), 1.69 (d, J = 2.8 Hz, 6H; $H_{adamantanyl}$), 1.59 (m, 6H; $H_{adamantanyl}$).

1-Adamantanyl 4,8-anhydro-2,3-di-*O*-benzyl-6,7-dideoxy-8-*C*-phenyl-D-*glycero*-β-D-*manno*-octopyranoside (25β): $[\alpha]_D^{RT}$ −11 (c 4.2, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{38}H_{44}O_5Na^+$ 603.3081, found 603.3087. Spectra were in accordance with the literature:[53] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43−7.40 (m, 2H; Ph), 7.28−7.15 (m, 13H; Ph), 4.93 (d, ^2J = 12.7 Hz, 1H; CH(H_a)-Ph), 4.85 (d, ^2J = 12.7 Hz, 1H; CH(H_b)-Ph), 4.60 (d, $J_{1,2}$ = 1.1 Hz, 1H; H-1), 4.53 (d, ^2J = 12.8 Hz, 1H; CH(H_a)-Ph), 4.49 (d, ^2J = 12.8 Hz, 1H; CH(H_b)-Ph), 4.43 (dd, J = 11.5, J = 2.3 Hz, 1H; H-8), 3.77 (t, J = 9.4 Hz, 1H; H-4), 3.64 (dd, $J_{2,3}$ = 3.2, $J_{1,2}$ = 1.0 Hz, 1H; H-2), 3.39 (dd, $J_{3,4}$ = 9.8, $J_{2,3}$ = 3.2 Hz, 1H; H-3), 2.98 (ddd, J = 11.2, J = 9.0, J = 4.2 Hz, 1H; H-5), 2.06 (m, 3H; $C_{adamantanyl}$), 1.98 (m, 2H; H-6, H-7), 1.83 (tdd, J = 12.7, J = 11.3, J = 4.0 Hz, 1H; H-7), 1.72 (m, 6H; $C_{adamantanyl}$), 1.53 (m, 7H; 6 × $C_{adamantanyl}$, C-7); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.6 ($C_{Ph\text{-}ipso}$), 138.9 ($C_{Bn\text{-}ipso}$), 138.8 ($C_{Bn\text{-}ipso}$), 128.8−125.6 (15 × C_{Ph}), 94.5 (C-1), 79.1−78.8 (three peaks; C-3, C-4, C-8), 76.6 (C-2), 74.8 ($C_{quart\text{-}adamantanyl\ next\ to\ O}$), 74.3 ($C_{Bn}$), 72.0 ($C_{Bn}$), 71.6 (C-5), 42.5 ($C_{sec\text{-}adamantanyl}$), 36.3 ($C_{sec\text{-}\ adamantanyl}$), 33.3 (C-7), 30.6 ($C_{tert\text{-}adamantanyl}$), 29.5 (C-6).

Methyl (4,8-Anhydro-2,3-di-*O*-benzyl-6,7-dideoxy-8-*C*-phenyl-D-glycero-D-*manno*-octopyranosyl)-(1→3)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranoside (26α). The product was purified twice by dry column chromatography, but it was not possible to remove unreacted BSP (ratio 1:0.8) which can be seen in the spectra. The peaks from BSP are in accordance with previous published data.[54] Because of the multiple purifications, heptane is present in the spectra: HRMS (ESI) m/z calcd for $C_{40}H_{48}O_{10}Na^+$ 711.3145, found 711.3153; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69−7.63 (dd, J = 8.0, 1.6 Hz, 2H; Ph), 7.37−7.28 (m, 13H; Ph), 5.85−5.82 (d, J = 3.5 Hz, 1H; H-1′), 5.20−5.17 (d, $J_{1,2}$ = 1.3 Hz, 1H; H-1), 4.79−4.71 (m, 3H; 3 × CH(H)Ph), 4.61−4.58 (m, 1H; CH(H)Ph), 4.57−4.53 (m, 2H; H-2′, H-8), 4.29−4.27 (d, J = 2.0 Hz, 1H; H′), 4.10−4.07 (m, 1H; H-6_a′), 4.05−4.03 (dd, J = 3.6, 2.3 Hz, 2H; H′, H-6_b′), 4.03−4.00 (m, 1H; H′), 3.95−3.91 (t, J = 9.3 Hz, 1H; H-4), 3.82−3.78 (m, 2H; H-2, H-3), 3.58−3.53 (m, 1H; H-5), 2.16−2.10 (ddd, J = 16.2, 10.8, 3.3 Hz, 2H; H-6_a, H-7_a), 1.90−1.85 (m, 1H; H-6_a), 1.76−1.72 (m, 1H, H-7_a), 1.50−1.49 (s, 3H; CH_3C), 1.41−1.40 (s, 3H; CH_3C), 1.34−1.33 (s, 3H; CH_3C), 1.32−1.31 (s, 3H; CH_3C). **BSP**: 7.52−7.47 (m, 3H; Ph), 7.37−7.28 (m, 2H; Ph), 3.14−3.10 (dt, J = 7.6, 3.2 Hz, 1H ;), 2.98−2.94 (m, 1H), 1.63−1.58 (m, 6H; 3 x CH_2).^{13}C NMR (126 MHz, $CDCl_3$) δ 143.5 ($C_{Ph\ ipso\ BSP}$), 142.3 ($C_{Ph\text{-}ipso}$), 139.0 ($C_{Ph\text{-}ipso}$), 138.3 ($C_{Ph\text{-}ipso}$), 130.8 ($C_{Ph\ BSP}$), 128.9 ($C_{Ph\ BSP}$), 128.5, 128.4, 128.3, 128.3, 128.1, 127.8, 127.6, 127.5, 127.4, 126.4 ($C_{Ph\ BSP}$), 125.8, 112.2 (C_{acetal}), 109.5 (C_{acetal}), 105.4 (C-1′), 99.8 (C-1), 84.2 (C-2′), 81.6 (C′), 80.1

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(C′), 79.4 (C-4), 79.2 (C-8), 76.7 (C-2). 75.8 (C-3), 73.2 (C′), 73.1 (C_{Bn}), 72.6 (C_{Bn}), 69.4 (C-5), 67.9 (C-6′), 47.1 ($C_{sec.\ BSP}$), 33.3 (C-7), 29.5 (C-6), 27.1(C_{tert}), 26.5 (C_{tert}), 26.1 ($C_{sec\text{-}BSP}$), 25.7 (C_{tert}), 24.1 ($C_{sec\text{-}BSP}$).

Methyl (4,8-anhydro-2,3-di-*O*-benzyl-6,7-dideoxy-8-*C*-phenyl-D-glycero-*β*-D-*manno*-octopyranosyl)-(1→3)-1,2:5,6-di-*O*-isopropyliden-*β*-D-glucofuranoside (26*β*): $[\alpha]_D^{RT}$ −50 (*c* 2.2, CH_2Cl_2); HRMS (ESI) *m*/*z* calcd for $C_{40}H_{48}O_{10}Na^+$ 711.3145, found 711.3163; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.36 (dd, *J* = 8.1, *J* = 1.4 Hz, 2H; Ph), 7.29−7.21 (m, 13H; Ph), 5.83 (d, $J_{1′,2′}$ = 3.7 Hz, 1H: H-1′), 4.82−4.73 (m, 2H; CH_2Ph), 4.65−4.54 (m, 2H; CH_2Ph), 4.46 (dd, *J* = 11.5, *J* = 2.3 Hz, 1H; H-8), 4.43 (d, $J_{1,2}$ = 1.0 Hz, 1H; H-1), 4.40 (d, $J_{4′,5′}$ = 5.0 Hz, 1H; H-5′), 4.33 (d, $J_{1′,2′}$ = 3.8 Hz, 1H; H-2′), 4.26 (dd, $J_{4′,5′}$ = 4.9, $J_{3′,4′}$ = 3.1 Hz, 1H; H-4′), 4.23 (d, $J_{3′,4′}$ = 3.1 Hz, 1H; H-3′), 4.07 (dd, *J* = 8.5, *J* = 6.6 Hz, 1H; H-6′$_a$), 4.01−3.97 (m, 1H; H-6′$_b$), 3.83−3.78 (m, 1H; H-4), 3.76−3.75 (dd, $J_{2,3}$ = 3.1, $J_{1,2}$ = 1.0 Hz, 1H; H-2), 3.45−3.40 (dd, *J* = 9.7, $J_{2,3}$ = 3.1 Hz, 1H; H-3), 3.04−2.98 (ddd, $J_{5,6}$ = 11.1, *J* = 9.1, *J* = 4.3 Hz, 1H; H-5), 2.08−1.98 (m, 2H; H-6$_a$,H-7$_a$), 1.88−1.81 (ddd, *J* = 12.8, $J_{5,6}$ = 11.4, *J* = 8.7 Hz, 1H; H-6$_b$), 1.62−1.52 (m, 1H; H-7$_b$), 1.42 (s, 3H, CH_3C), 1.37 (s, 3H; CH_3C), 1.26 (s, 3H; CH_3C), 1.24 (s, 3H; CH_3C); ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 142.4 ($C_{Ph\text{-}ipso}$), 138.8 ($C_{Ph\text{-}ipso}$), 138.5 ($C_{Ph\text{-}ipso}$), 128.6−125.8 (15 × C_{Ph}), 112.0 (C_{acetal}), 108.7 (C_{acetal}), 105.1 (C-1′), 100.2 (C-1), 83.0 (C-2′), 80.9 (C-4′), 80.8 (C-3′), 79.2 (C-8), 78.9 (C-4), 78.9 (C-3), 76.2 (C-2), 74.8 (C_{Bn}), 74.8 (C-5), 73.4 (C-5′), 72.5 (C_{Bn}), 66.2 (C-6′), 33.2 (C-7), 29.9 (heptane), 29.2 (C-6), 26.9 (C_{Me}), 26.7 (C_{Me}), 26.5 (C_{Me}), 25.5 (C_{Me}).

Methyl (4,8-Anhydro-2,3-di-*O*-benzyl-6,7-dideoxy-8-*C*-phenyl-D-glycero-*β*-D-*manno*-octopyranosyl)-(1→3)-2,3,4-tri-*O*-acetyl-*α*/*β*-D-glucopyranoside (27). The crude was purified by dry column chromatography (heptane with a 1.67% gradient of EtOAc) to give a mixture of *α*/*β* in a 1:6.1 ratio with a overall yield of 78% (108 mg). Only a small amount of the *β*-anomer could be separated for characterization.

27α. R_f 0.39 (heptane/EtOAc 2:1). The *α*-anomer could not be separated from the *β*-anomer. In the mixture of both anomers the *α*-anomer was found to resonate ^{1}H NMR (500 MHz, $CDCl_3$) at *δ* 4.80 (d, $J_{1,2}$ = 1.60 Hz, 1H; H-1) and in ^{13}C NMR (126 MHz, $CDCl_3$) at *δ* 99.23 (C-1, $J_{C1,H1}$ = 169.3 Hz).

27β: R_f 0.38 (heptane/EtOAc 2:1); HRMS (ESI) *m*/*z* calcd for $C_{41}H_{48}O_{13}Na^+$ 771.2987, found 771.3002; $[\alpha]_D^{RT}$ +3 (*c* 0.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.46 (m, 2H; Ph), 7.36−7.26 (m, 13H; Ph), 5.51 (dd, *J* = 10.3, *J* = 9.2 Hz, 1H; H-3′), 4.99−4.93 (m, 3H; CH(H$_a$)Ph, H-1′, H-4′), 4.89−4.84 (m, 2H; CH(H$_b$)Ph, H-2′), 4.60 (q, ^2J = 12.6, 2H; CH_2Ph), 4.52 (dd, $J_{7ax,8}$ = 11.4, $J_{7eq,8}$ = 2.3 Hz, 1H; H-8), 4.43 (d, $J_{1,2}$ = 1.1 Hz, 1H; H-1), 4.07−4.00 (m, 2H; H-5′, H-6$_a$′), 3.96 (d, $J_{2,3}$ = 3.2 Hz, 1H; H-2), 3.86 (t, *J* = 9.5 Hz, 1H; H-4), 3.51−3.45 (m, 2H; H-3, H-6$_b$′), 3.38 (s, 3H; MeO), 3.09 (ddd, *J* = 11.0, *J* = 9.1, *J* = 4.2 Hz, 1H; H-5), 2.15 (dd, *J* = 12.1, 3.6 Hz, 1H; H-6$_{eq}$), 2.09 (s, 3H; CH_3CO), 2.05 (dt, *J* = 4.2, *J* = 2.6 Hz, 1H; H-7$_{eq}$), 2.03 (s, 3H; CH_3CO), 2.02 (s, 3H; CH_3CO), 1.95−1.86 (m, 1H; H-6$_{ax}$), 1.64 (m, 1H; H-7$_{ax}$). ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 170.4 (C═O), 170.2 (C═O), 170.1 (C═O), 142.5 ($C_{ipso\ Ph}$), 138.8 ($C_{ipso\ Ph}$), 128.6 (C_{Ph}), 128.4 (C_{Ph}), 128.28 (C_{Ph}), 128.27 (C_{Ph}), 127.7 (C_{Ph}), 127.6 (C_{Ph}), 127.5 (C_{Ph}), 127.4 (C_{Ph}), 125.8 (C_{Ph}), 102.3 (C-1, $J_{C1,H1}$ = 156.6 Hz), 96.6 (C-1′, $J_{C1′,H1′}$ = 175.1 Hz), 79.2 (C-8), 78.9 (C-4), 78.5 (C-3), 76.0 (C-2), 74.9 (C_{Bn}), 72.3 (C_{Bn}), 72.2 (C-5), 71.1 (C-2′), 70.3 (C-3′), 69.4 (C-4′), 68.6 (C-6′), 68.6 (C-5′), 55.4 (C_{MeO}), 33.3 (C-7), 29.3 (C-6), 20.9 (C_{acetyl}), 20.88 (C_{acetyl}), 20.85 (C_{acetyl}).

Methyl (4,8-Anhydro-2,3-di-*O*-benzyl-6,7-dideoxy-8-*C*-phenyl-D-glycero-*β*-D-*manno*-octopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-*α*/*β*-D-glucopyranoside (28). With the 4-OH as acceptor slightly changed conditions were used. Donor (95 mg, 0.18 mmol), TTBP (110 mg, 0.44 mmol, 2.5 equiv), BSP (37 mg, 0.18 mmol, 1 equiv), Tf_2O (59 *μ*L, 0.35 mmol, 2 equiv), and acceptor (123 mg, 0.26 mmol, 1.5 equiv). The glycosylation gave a mixture of ≈2:1 *α*/*β* anomers in 71% yield, which was estimated from NMR. The major byproduct was methyl 2,3,6-tri-*O*-benzyl-4-*O*-trifluoromethanesulfonyl-*α*-D-glucopyranoside (36 mg). The anomers could not be clearly separated from each other, the triflated acceptor and the acceptor itself. It was possible to estimate the *α*/*β* mixture from ^{1}H NMR after partial purification (*β*/*α* ≈2:1). Furthermore, spectra of the *α*-anomer were also obtained but were contaminated with BSP in 1:3 (*α*-anomer/BSP). The *β*-anomer was contaminated with the *α*-anomer and acceptor.

28α: R_f 0.50 (heptane/EtOAc 5:2); HRMS (ESI) *m*/*z* calcd for $C_{56}H_{60}O_{10}Na^+$ 915.4079, found 915.4060; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.66 (m, 2H), 7.40−7.20 (m, 26H), 7.15 (m, 2H), 5.23 (d, $J_{1,2}$ = 1.8 Hz, 1H; H-1), 5.07 (d, *J* = 11.5 Hz, 1H; CH(*H*)Ph), 4.79 (m, 1H; CH(*H*)Ph), 4.68 (m, 1H; CH(*H*)Ph), 4.63−4.56 (m, 5H; H-1′, 2 × CH_2Bn), 4.51−4.47 (m, 2H; H-8, CH(*H*)Ph), 4.44 (d, *J* = 12.0 Hz, 1H; CH(*H*)Ph), 4.23 (d, *J* = 11.9 Hz, 1H; CH(*H*)Ph), 3.88 (m, 1H; H-4), 3.86−3.82 (m, 2H; H-3′, H-4′), 3.76 (dd, $J_{2,3}$ = 2.9 Hz, $J_{1,2}$ = 1.8 Hz, 1H; H-2), 3.75−3.69 (m, 4H; H-3, H-5′, 2 × H-6′), 3.58 (m, 1H; H-5), 3.54 (dd, $J_{2′,3′}$ = 9.6 Hz, $J_{1′,2′}$ = 3.5 Hz, 1H; H-2′), 3.40 (s, 3H; CH_3O), 1.99 (ddd, *J* = 13.3 Hz, *J* = 5.6 Hz, *J* = 3.0 Hz, 2H; H-7$_{eq}$), 1.90 (dq, *J* = 11.1 Hz, *J* = 3.6 Hz, 2H; H-6$_{eq}$), 1.77 (ddd, *J* = 24.3 Hz, *J* = 12.5 Hz, *J* = 4.1 Hz, 2H; H-6$_{ax}$), 1.67−1.46 (m, 1H; H-7$_{ax}$). **BSP**: 7.55−7.45 (m, 3H), 7.40−7.20 (m, 12H), 3.15−3.08 (m, 3H), 3.02−2.92 (m, 3H), 1.67−1.46 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 143.5 ($C_{Ph\ ipso\ BSP}$), 142.6 ($C_{Ph\text{-}ipso}$), 139.2 ($C_{Bn\text{-}ipso}$), 138.9 ($C_{Bn\text{-}ipso}$), 138.7 ($C_{Bn\text{-}ipso}$), 138.3 ($C_{Bn\text{-}ipso}$), 138.00 ($C_{Bn\text{-}ipso}$), 130.79 ($C_{Ph\ BSP}$), 128.9 ($C_{Ph\ BSP}$), 128.6 (C_{Ph}), 128.60 (C_{Ph}), 128.56 (C_{Ph}), 128.50 (C_{Ph}), 128.47 (C_{Ph}), 128.41 (C_{Ph}), 128.35 (C_{Ph}), 128.31 (C_{Ph}), 128.25 (C_{Ph}), 128.2 (C_{Ph}), 128.1 (C_{Ph}), 127.68 (C_{Ph}), 127.67 (C_{Ph}), 127.64 (C_{Ph}), 127.6 (C_{Ph}), 127.5 (C_{Ph}), 127.4 (C_{Ph}), 127.3 (C_{Ph}), 127.0 (C_{Ph}), 126.4 (C_{Ph}), 125.8 (C_{Ph}), 101.6 (C-1, $J_{C,H}$ = 169 Hz), 97.9 (C-1′, $J_{C,H}$ = 170 Hz), 81.6, 80.1 (C-2′), 79.4 (C-8), 79.1, 78.0, 77.7, 75.2 (C_{Bn}), 73.7 (C_{Bn}), 73.4 (C_{Bn}), 73.3 (C_{Bn}), 73.0 (C_{Bn}), 69.9, 69.4 (C-6′), 55.4 (C_{MeO}), 47.1 ($C_{sec.\ BSP}$), 33.6 (C-7), 29.9 (C-6), 26.3 ($C_{sec.\ BSP}$), 24.1 ($C_{sec.\ BSP}$).

Methyl 2,3,6-Tri-*O*-benzyl-4-*O*-trifluoromethanesulfonyl-*α*-D-glucopyranoside: R_f 0.55 (heptane/EtOAc 5:2); HRMS (ESI) *m*/*z* calcd for $C_{29}H_{31}O_8SF_3Na^+$ 619.1584, found 619.1586; $[\alpha]_D^{RT}$ 21 (*c* 2.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.32−7.18 (m, 15H; Ph), 4.95 (t, *J* = 9.6 Hz, 1H; H-4), 4.87 (d, *J* = 10.2 Hz, 1H; CH(H_a)Ph), 4.76 (d, *J* = 10.2 Hz, 1H CH(H_b)Ph), 4.67 (d, *J* = 12.0 Hz, 1H CH(H_a)Ph), 4.50 (m, 2H; CH_2Ph), 4.47 (s, 1H; H-1), 4.40 (d, *J* = 12.0 Hz, 1H CH(H_b)Ph), 3.98 (t, *J* = 9.4 Hz, 1H; H-3), 3.89 (ddd, *J* = 10.0, 3.6, 2.1 Hz, 1H; H-5), 3.60 (m, 2H; 2 x H-6), 3.52 (dd, *J* = 9.6, 3.5 Hz, 1H; H-2), 3.31(s, 3H; CH_3O); ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 137.8 (C_{Bn}), 137.6 (C_{Bn}), 137.5 (C_{Bn}), 128.7 (C_{Ph}), 128.5 (C_{Ph}), 128.4 (C_{Ph}), 128.3 (C_{Ph}), 128.1 (C_{Ph}), 128.0 (C_{Ph}), 127.9 (C_{Ph}), 127.8 (C_{Ph}), 122.3, 119.8, 117.2, 114.7 (q, F_3CSO_2R), 98.0 (C-1), 81.5 (C-4), 80.2 (C-2), 78.1 (C-3), 75.6 (C_{Bn}), 73.8 (C_{Bn}), 73.8 (C_{Bn}), 67.9 (C-5), 67.7 (C-6), 55.9 (C_{MeO}).

Phenylthio 2,3,4,6-Tetra-*O*-benzyl-*α*-D-mannopyranoside (31).[55] To a 0 °C solution of phenylthio-*α*-D-mannopyranoside (0.50 g, 1.84 mmol) in DMF (15 mL) was added NaH (60% in mineral oil, 0.59 g 14.7 mmol, 8 equiv), and the mixture was stirred for 30 min. Then, benzyl bromide (0.98 mL, 8.26 mmol, 4.5 equiv) was added and the ice bath removed. The reaction was left until completion (3 h, estimated by TLC). Methanol was added to quench the reaction, and the mixture was afterward concentrated, poured into water, and extracted with EtOAc (3×). The combined organic layers were washed with brine, dried ($MgSO_4$), concentrated, and purified by dry column chromatography (heptane with a 1.3% gradient of EtOAc) to give the product as a yellow syrup in 87% yield (1.01 g): R_f 0.45 (heptane/EtOAc 6:1); ESI *m*/*z* calcd for $C_{40}H_{40}O_5SNa$ 655.2494, found 655.2514; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.44 (m, 2H; PhS), 7.36−7.20 (m, 23H; Ph), 5.61 (d, $J_{1,2}$ = 1.8 Hz, 1H; H-1), 4.90 (d, *J* = 10.8 Hz, 1H; CH(H_a)Ph), 4.31 (d, *J* = 12.3 Hz, 1H; CH(H_a)Ph), 4.64 (m, 2H; CH_2Ph), 4.61 (m, 2H; CH_2Ph), 4.54 (d, *J* = 10.8 Hz, 1H; CH(H_b)Ph), 4.49 (d, *J* = 12.0 Hz, 1H; CH(H_b)Ph), 4.28 (ddd, *J* = 9.9, 5.1, 1.9 Hz, 1H; H-5), 4.07 (t, *J* = 9.6 Hz, 1H; H-4), 4.00 (dd, $J_{2,3}$ = 3.1 Hz, $J_{1,2}$ = 1.8 Hz, 1H; H-2), 3.86 (m, 2H; H-3, H-6$_b$), 3.75 (dd, *J* = 10.9 Hz, *J* = 1.9 Hz 1H; H-6$_b$); ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 138.6 ($C_{Bn\text{-}ipso}$), 138.5 ($C_{Bn\text{-}ipso}$), 138.3 ($C_{Bn\text{-}ipso}$), 138.1 ($C_{Bn\text{-}ipso}$), 134.6 ($C_{SPh\text{-}ipso}$), 131.8 (C_{Ph}), 129.1 (C_{Ph}), 128.6 (C_{Ph}), 128.5 (C_{Ph}), 128.5 (C_{Ph}), 128.4 (C_{Ph}), 128.11 (C_{Ph}), 128.06 (C_{Ph}), 128.0 (C_{Ph}), 127.9

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(C_{Ph}), 127.84 (C_{Ph}), 127.76 (C_{Ph}), 127.6 (C_{Ph}), 127.5 (C_{Ph}), 85.9 (C-1), 80.3 (C-3), 76.4 (C-2), 75.3 (C_{Bn}), 75.1 (C-4), 73.4 (C_{Bn}), 72.9 (C-5), 72.3 (C_{Bn}), 72.0 (C_{Bn}), 69.3 (C-6).

Competitions Experiments. General procedure for competitive NIS/TfOH-promoted glycosylation: The donors (ca. 01 mmol, 1 equiv each) and 1-adamantanol (acceptor, 3 equiv) were coevaporated with toluene (2×) and placed under vacuum for 30 min together with activated molecular sieves (3 Å). Then, freshly distilled CH_2Cl_2 (donor conc 0.05 M) was added, and the mixture was stirred under argon at rt for 30 min. Subsequently, NIS (1 equiv) was added, and the mixture was cooled to −40 °C followed by the addition of TfOH (0.1 equiv, 0.1 m stock solution in distilled CH_2Cl_2). Then, the reaction mixture was slowly warmed to 0 °C in about 3 h after which Et_3N (0.1 mL) was added. The reaction mixture was diluted with EtOAc, washed with satd aq $Na_2S_2O_3$ and brine, dried ($MgSO_4$), and concentrated. NMR of the crude mixture was used to determine the consumption of donors.

Phenylthio 2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranoside vs Phenylthio 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (31 vs 2). Perbenzylated donor **31** (63 mg, 1.0 mmol) and benzylidene donor **2** (54 mg, 0.1 mmol) were used in a competitive glycosylation using 1-adamantanol (46 mg, 3.0 mmol) following the general procedure described above. The experiment yielded a 1:19 (perbenzyl vs benzylidene donor) mixture of starting material determined from crude NMR. Diagnostic peaks used for determination of the donor ratio: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.63 (d, J = 1.8 Hz, 1H; α-SPh H-1 of perbenzyl), 5.53 (d, J = 1.4 Hz, 19.2H; α-SPh H-1 of benzylidene). ^{13}C NMR (126 MHz, $CDCl_3$) δ 87.2 ($^2J_{C1,H1}$ = 167.3 Hz, C-1 of α-SPh benzylidene), 85.8 ($^2J_{C1,H1}$ = 167.0 Hz, C-1 of α-SPh perbenzyl).

Phenylthio 2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranoside vs Phenylthio 4,8-Anhydro-2,3-di-*O*-benzyl-6,7-dideoxy-8-phenyl-D-*glycero*-α-D-*manno*-octopyranoside (31 vs 1). Perbenzylated donor **31** (63 mg, 1.0 mmol) and C7-analogue donor **1** (54 mg, 0.1 mmol) were used in a competitive glycosylation using 1-adamantanol (46 mg, 3.0 mmol) following the general procedure described above. The experiment yielded a 1:2.6 (perbenzyl vs C-7 benzylidene analogue donor) mixture of starting material determined from crude NMR. Diagnostic peaks used for determination of the donor ratio: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.63 (d, J = 1.8 Hz, 1H; α-SPh H-1 of perbenzyl), 5.55 (d, J = 1.5 Hz, 1H; α-SPh H-1 of C7-analogue). ^{13}C NMR (126 MHz, $CDCl_3$) δ 86.9 ($^2J_{C1,H1}$ = 166.4 Hz, C-1 of α-SPh C7-analogue), 85.8 ($^2J_{C1,H1}$ = 167.0 Hz, C-1 of α-SPh perbenzyl).

Phenylthio 4,8-Anhydro-2,3-di-*O*-benzyl-6,7-dideoxy-8-phenyl-D-*glycero*-α-D-*manno*-octopyranoside vs Phenylthio 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (1 vs 2). C7-analogue donor **1** (54 mg, 1.0 mmol) and benzylidene donor **2** (54 mg, 0.1 mmol) were used in a competitive glycosylation using 1-adamantanol (46 mg, 3.0 mmol) following the general procedure described above. The experiment yielded a 1:2.6 (C7-analogue vs benzylidene donor) mixture of starting material determined from crude NMR. Diagnostic peaks used for determination of the donor ratio: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.55 (d, J = 1.5 Hz, 1H; α-SPh H-1 of C7-analogue), 5.53 (d, J = 1.4 Hz, 2.6H; α-SPh H-1 of benzylidene). ^{13}C NMR (126 MHz, $CDCl_3$) δ 87.2 ($^2J_{C1,H1}$ = 167.3 Hz, C-1 of α-SPh benzylidene), 86.9 ($^2J_{C1,H1}$ = 166.4 Hz, C-1 of α-SPh C7-analogue).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Characterization data, low-temperature NMR studies, competition experiments, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: cmp@chem.ku.dk.

Notes

The authors declare no competing financial interest.

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