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Regioselective Polymethylation of α-(1→4)-linked Mannopyranose Oligosaccharides

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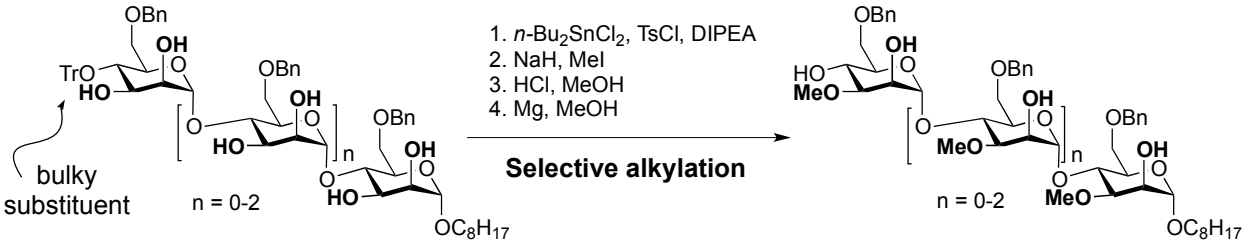


Abstract

An approach has been developed of the regioselective methylation of α-(1→4)-linked mannopyranose oligosaccharides via a four-step methodology. The key reaction involved *n*-Bu_2SnCl_2-mediated activation of *cis*-diols. By tuning protecting groups on the substrates, multiple *cis*-diols in the substrates were functionalized in a consistent and regioselective manner. Using optimized substrates and reaction conditions regioselective methylation of di-, tri- and tetrasaccharide substrates proceeded in isolated yields per *cis*-diol of 95%, 88% and 79%, respectively. The methodology was also applied to functionalize *trans*-diols in α-cyclodextrin.

Introduction

Total synthesis plays an important role in providing compounds that can be used for understanding the biological role of complex organic molecules, both naturally-occurring and synthetic. However, this approach is generally laborious and time-consuming. To overcome this problem, semisynthetic approaches can provide a more rapid solution by using readily available compound skeletons as templates.[1-2] For example, a recent example of semi-synthesis was the installation of a trifluoromethyl moiety onto the drug Lipitor, via direct C–H functionalization.[3]

Although appealing, direct and selective functionalization of carbohydrates, particularly glycans more complicated than monosaccharides, is difficult. Although it is often possible to exploit steric differences to selectively functionalize primary over secondary carbohydrate alcohols, differentiating secondary hydroxyl groups on oligosaccharides is challenging.[4-5] Regioselective acylations have been successfully carried out directly on unprotected disaccharides, *e.g.*, sucrose **1**[6] and lactose **2**[7] (Figure 1), using organotin reagents. However, further functionalization of these molecules is often difficult, as the introduced acyl groups are base-labile and thus prone to migrate under the basic conditions typically used in alkylation reactions.[8] In another example, sulfate groups have been introduced onto unprotected oligosaccharides, however, in low yield, *e.g.*, xylose trisaccharide **3** (Figure 1).[9]

On the other hand, regioselective alkylation reactions appear to be more challenging to carry out on oligosaccharides. Indeed, we were surprised to discover that there are only limited examples of regioselective alkylation of unprotected oligosaccharides, *e.g.*, **4**,[10,†] **5**,[11] **6**[12] (Figure 1). The regioselectivities of the reactions leading to **4** and **5** were achieved by deprotonating the

† Although **4** is not an oligosaccharide, it is classified as such here given its structural similarity to a disaccharide.

most acidic hydroxyl groups with strong bases; lactoside **6** was obtained *via* the organotin-mediated selective activation of vicinal diols.

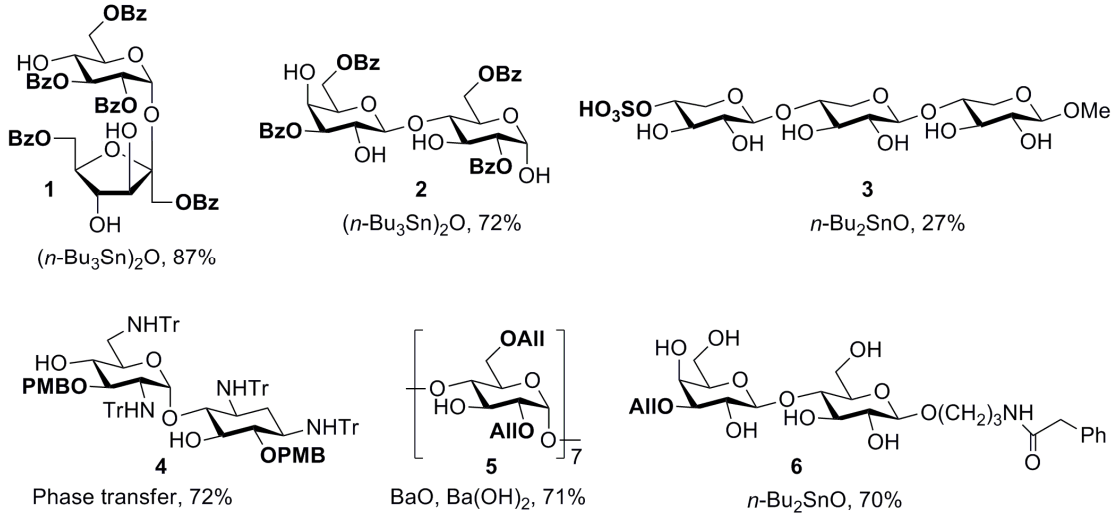


Figure 1. Examples of regioselective acylation, sulfation or alkylation of oligosaccharides.

During studies of the α-(1→4)-mannosyltransferase involved in the biosynthesis of 3-*O*-methyl-mannose polysaccharides (MMPs),[13] we had the need to access a panel of α-(1→4)-linked mannopyranose oligosaccharides with or without methyl groups (**A** and **B**, Figure 2). Although these analogs are structurally similar, traditional routes for their synthesis require different building blocks, and/or multiple functional group interconversions on oligosaccharides. For example, to obtain tetrasaccharides of both analogs (n = 2 for both **A** and **B**), 15 steps are required for **A** and 24 steps for **B** in Figure 2. We were therefore interested to determine if it was possible to access **B** *via* functionalization of **A**. We report here our studies towards achieving this goal.

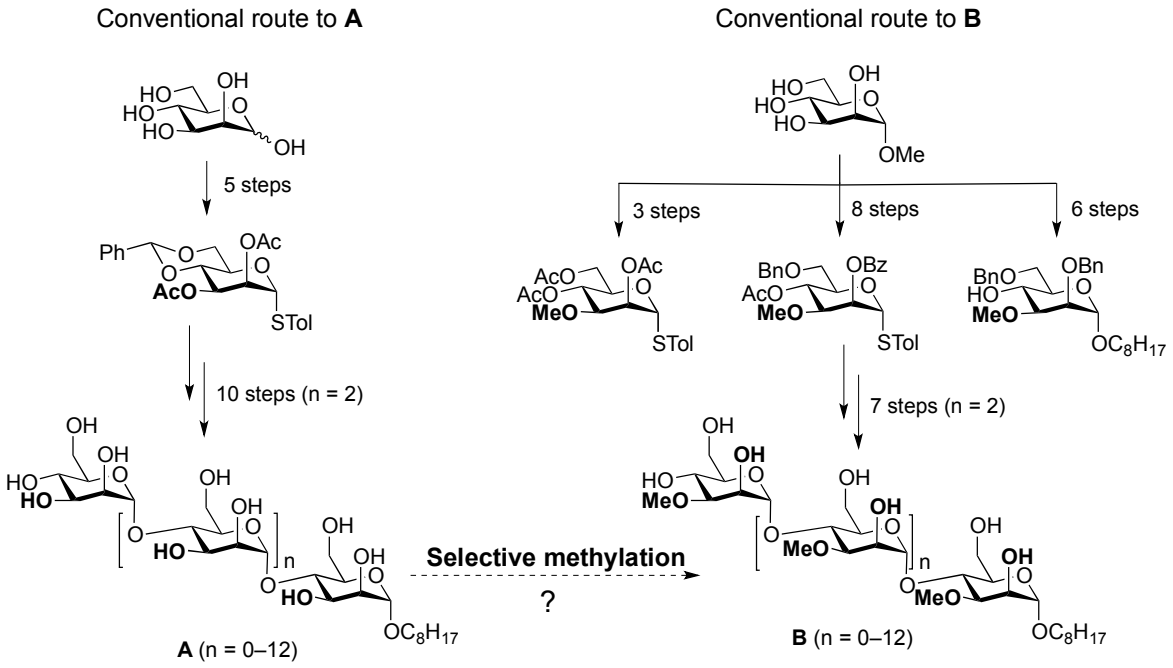
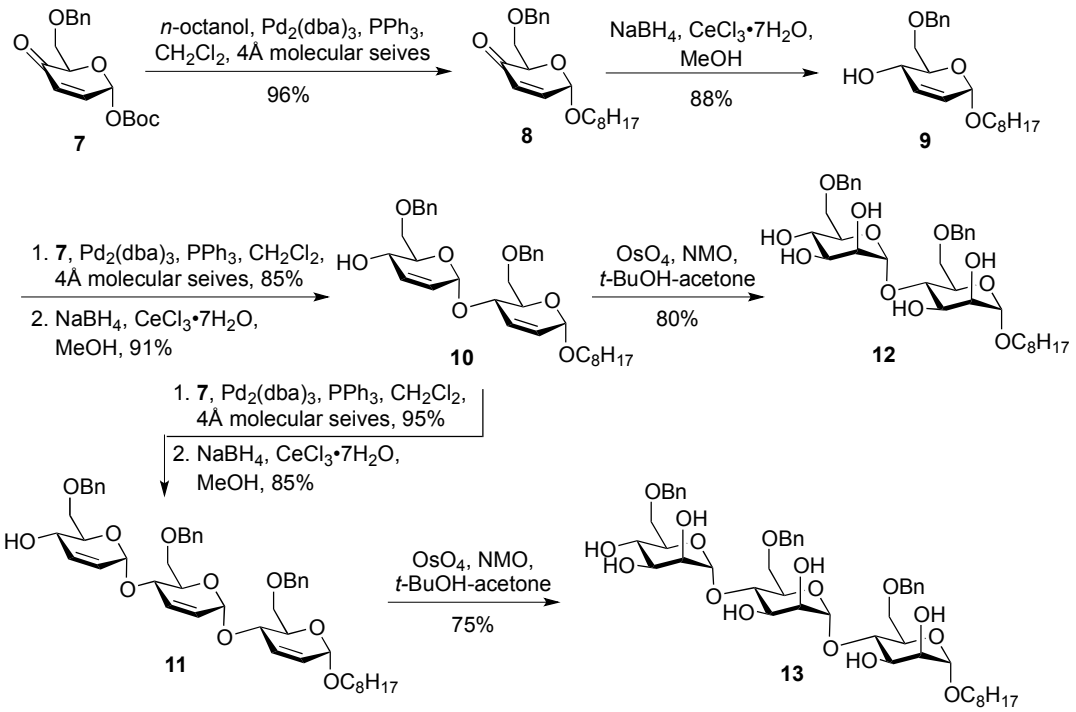


Figure 2. Conventional methods to synthesize analogs **A** and **B** and the approach developed here.

Results and discussion

Initial attempts to regioselectively alkylate α-(1→4)-linked mannopyranose oligosaccharides

We first studied the selective methylation of α-(1→4)-linked mannopyranose di- and trisaccharides. These substrates were synthesized from pyranone **7**, which was obtained in two steps by treatment of (*R*)-2-(benzyloxy)-1-(furan-2-yl)ethanol[14] with *N*-bromosuccinimide followed by reaction with di-*tert*-butyl dicarbonate.[15] With **7** in hand, use of the Pd-catalyzed iterative glycosylation methodology developed by O'Doherty and coworkers (Scheme 1)[16] provided diene **10** and triene **11**. Exhaustive dihydroxylation of the double bonds in **10** and **11** provided the desired disaccharide **12** and trisaccharide **13** in excellent overall yields. The high diasteroselectivity observed in these reactions is consistent with previous report.[16]

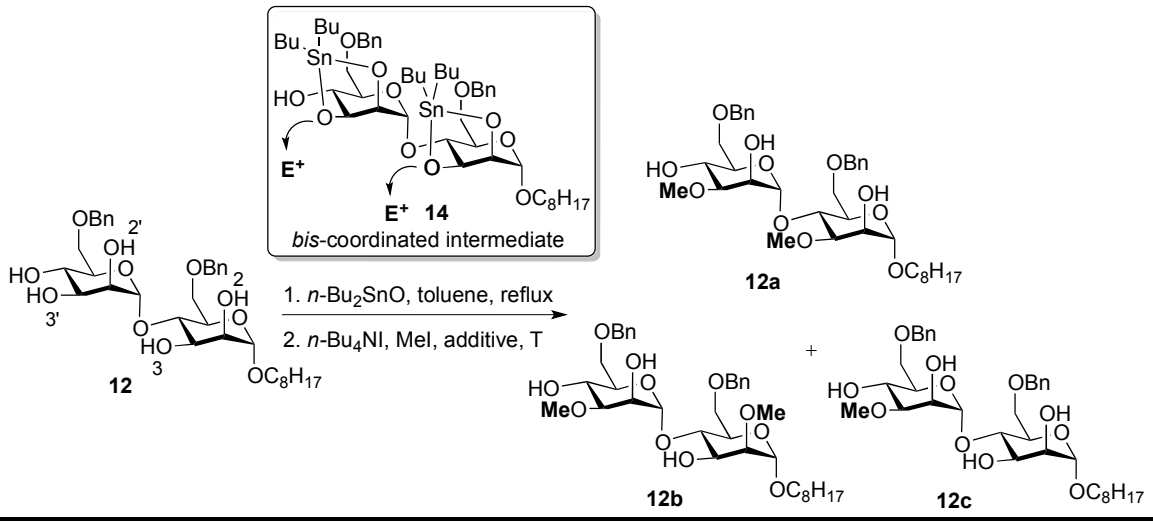


Scheme 1. Synthesis of disaccharide **12** and trisaccharide **13**.

We began by investigating the possibility of direct introduction of two alkyl groups onto disaccharide **12**, at O-3 and O-3′ positions. Because *n*-Bu_2SnO is well known to selectively activate the equatorial hydroxyl groups of *cis*-diols via a cyclic stannylene acetal,[17] we anticipated that using two equivalents of this reagent would result in formation of a bis-coordinated intermediate **14**‡ from disaccharide **12** (Table 1).[17-20] Subsequent addition of the alkylating reagent would lead to the formation of the di-substituted product **12a** (Table 1), with alkylation at both equatorial positions (O-3 and O-3′).

‡ It should be appreciated that stannylene acetals of carbohydrate diols typically adopt structure-dependent higher-order oligomers (*e.g.,* dimers, pentamers) in solution.[17-20] The depiction of **14** as a monomer is a simplified representation of the intermediate, because, if indeed it is formed, its oligomeric structure in solution has not been investigated and is therefore unknown.

Table 1. Direct regioselective alkylation of disaccharide **12**.[a]



Entry	T (°C)	Additive	Products distribution (NMR yield[b])		Recovered
			disubstituted	monosubstituted	**12**
1	40	-	< 5%	15% mixture	80%
2	70	-	**12a** (19%), **12b** (3%)	**12c** (35%), 15% other isomers	28%
3	40	CsF	**12a** (29%), **12b** (45%), 26% other isomers	-	-

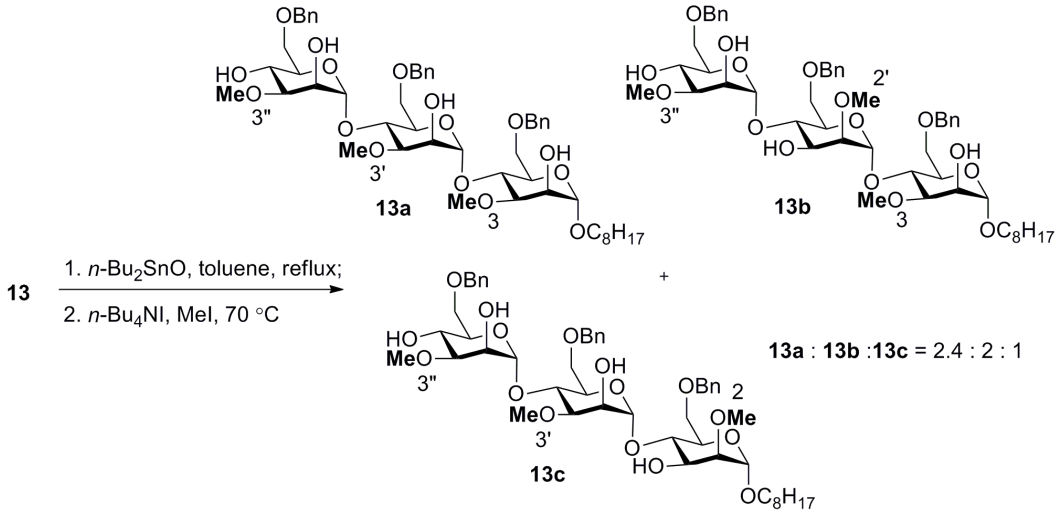
a. Reaction conditions: **12** (1 equiv.), *n*-Bu_2SnO (2 equiv.), *n*-Bu_4NI (2 equiv.), MeI (20 equiv.), additive (4 equiv.), toluene (0.01 M);

b. Yields were obtained by integration of anomeric protons of the products observed in crude ^{1}H NMR spectrum.

To explore this possibility, disaccharide **12** was heated at reflux in toluene with two equivalents of *n*-Bu_2SnO and then treated with methyl iodide at various temperatures (Table 1). Formation of products was monitored by ^{1}H NMR spectroscopy of the crude reaction mixtures, and the yield was determined by integrating the anomeric protons in the newly formed products. Three major products were observed: two disubstituted regioisomers (**12a** and **12b**) as well as a monosubstituted derivative, **12c**. When the alkylation was performed at 40 °C (entry 1, Table 1), 80% of starting material **12** remained. Raising the reaction temperature to 70 °C increased the amount of dimethylated products, **12a** (19%) and **12b** (3%). However, the reaction was incomplete and a number of monomethylated products were produced (entry 2, Table 1). Addition of CsF drove the reaction to completion with the formation of exclusively dimethylated

products (entry 3, Table 1).[21] However, the desired regioisomer **12a** was formed in only 29% yield, while the major product was the undesired isomer **12b** in 45% yield. The remaining mass balance was the other dimethylated isomers, based upon ^{1}H NMR analysis of the crude reaction mixtures. The structures of **12a**, **12b** and **12c** were assigned unambiguously after isolation of the corresponding products and characterization by ^{1}H NMR spectroscopy along with ^{1}H–^{1}H COSY experiments. Regioisomers **12a** and **12b** were distinguished by comparison of the ring protons adjacent to the alkylated hydroxyl groups. Chemical shifts of H-2, H-2′, H-3 and H-3′ of **12** are between 3.94–3.59 ppm. After alkylation H-3 and H-3′ of **12a** are significantly upfield-shifted to 3.46 and 3.33 ppm, respectively, while H-2 and H-2′ slightly downfield-shifted to 4.00 and 4.08 ppm, respectively. This result indicated **12a** is O-3, O-3′-alkylated. In **12b**, H-2 and H-3′ are upfield shifted to 3.37 and 3.33 ppm, indicating substitution taking place at 2-OH and 3′-OH positions. For the major monoalkylated adduct, **12c**, only the signal for H-3′ was deshielded.

Despite the rather modest results obtained with disaccharide **12** as the substrate, we applied the *n*-Bu_2SnO-mediated alkylation conditions to trisaccharide **13** (Scheme 2). With this substrate, tri-substitution took place predominantly. No starting material was detected after the reaction; however, a minimum of five regioisomers were observed. The desired 3, 3′, 3″-trisubstituted **13a** was isolated as the major product but it accounted only for 41% of all the products. Two other identified isomers were: O-3, O-2′, O-3″ tri-*O*-methylated **13b** and O-2, O-3′, O-3″ tri-*O*-methylated **13c**. The structures of the products were established as described above for the reactions with disaccharide **12**.



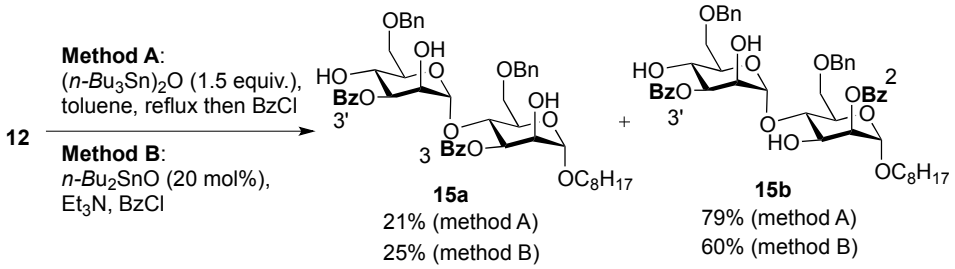
Scheme 2. Direct regioselective alkylation of **13**.

These studies suggest that the degree of alkylation of carbohydrate polyol systems can be controlled with *n*-Bu_2SnO-coordination. However, consistent regioselectivity was difficult to achieve with substrates such as disaccharide **12** and trisaccharide **13**. We therefore decided to explore if regioselectivity could be improved for acylation reactions. We first tested acylation of disaccharide **12**. Because *n*-Bu_2SnO-mediated acylation of *cis*-diols usually activates the equatorial hydroxyl group,[17] we expected to see predominant O-3, O-3′-disubstitution of **12**.

Regioselective acylation of disaccharide 12

Regioselective acylation of **12** was explored using BzCl at room temperature after heating the substrate at reflux with a tin reagent (2 equiv *n*-Bu_2SnO or 1.5 equiv $(n\text{-}Bu_3Sn)_2O$) in toluene. Of the two reagents used, *n*-Bu_2SnO gave only trace amounts of disubstituted products. Isolation was not attempted due to the low yield. In contrast, when $(n\text{-}Bu_3Sn)_2O$ was used, di-*O*-benzoylated products were obtained exclusively (method A, Scheme 3). In addition, only two of the four possible regioisomers were produced. Unexpectedly, the anticipated 3,3′-disubstituted

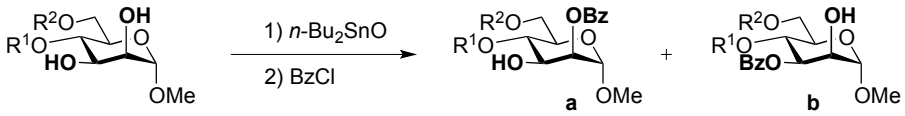
15a was only formed as a minor product (21%, NMR yield). Instead, **15b**, in which O-2 and O-3′ were benzoylated, was the major product, and was produced in a 79% yield as observed from the ^{1}H NMR spectrum of the crude reaction mixture. This regiochemistry was supported by the significant downfield shift of H-2 and H-3′ in the ^{1}H NMR spectrum for **15b** compared to that for **12**. In addition to the method described above, which involved an excess of tin reagent, the reaction was also performed with a catalytic amount of *n*-Bu_2SnO (method B, Scheme 3).[22] However, this catalytic method also produced the 3,3′-disubstituted product **15a** in a low yield (25%, NMR yield). The major product of this reaction was 2,3′-disubstituted **15b**, which was obtained in 60% yield; The remaining 15% were other unidentified disubstituted isomers.



Scheme 3. Regioselective acylation of **12**.

Before trying more acylation conditions, we considered the origin of the regioselectivity. Noticeably, the two diols of **12** (2′,3′-*cis*-diol and 2,3-*cis*-diol) were alkylated with different regioselectivity to produce **15b** as the major product using either method A or method B (Scheme 3). The diol at the non-reducing moiety (2′,3′-*cis*-diol) underwent substitution preferentially at the equatorial 3′-OH group. In contrast, the diol at the reducing end residue (2,3-*cis*-diol) showed the opposite selectivity, resulting in preferential functionalization of the axial 2-OH group.

This latter result is inconsistent with many reported tin-mediated reactions in which functionalization of the equatorial hydroxyl group of *cis*-diols on six-membered rings is preferential.[17] For example, benzoylation of **16**, when carried out in the presence of *n*-Bu_2SnO, produced only **16b** with substitution at the equatorial hydroxyl group (Figure 3).[23] More recently developed methods, using either borinic acid derivatives[24] or Me_2SnCl_2,[25] also give the same selectivity with *cis*-diols. Nevertheless, it should be noted that examples giving different regioselectivity have been previously reported in the case of mannose. As examples, **16–19,** when reacted under the same conditions resulted in different regioselectivities (Figure 3).[23,26-28] These compounds differ only in the protecting groups, suggesting that these substituents play an important role in controlling the regioselectivity.



16: R^1 = H, R^2 = Trityl resin	none	98%
17: R^1, R^2 = benzylidene	major	minor
18: R^1, R^2 = Bn	9-41%	43-67%
19: R^1 = Bn, R^2 = per-benzoyl Man*p* α-(1→6)	32%	63%

Figure 3. Regioselective acylation of 2,3-*cis*-diol of mannose residues.[23,26-28]

To rationalize the selectivity of the acylation reaction of **12**, we compared the steric environment of the two diols. We postulated that the selectivity of the diol at the reducing end (2,3-*cis*-diol) was influenced by the bulky mannose substituent at O-4, which rendered O-3 less accessible for reaction than O-2 (Figure 4A). On the other hand, the diol at the non-reducing end of **12** (2′,3′-*cis*-diol) is not hindered and the acylation occurs on the equatorial O-3′ position preferentially. This rationale also explains the regioselectivity trends observed in **16–19** (Figure 3). With no substituent at O-4, benzoylation occurred exclusively at O-3 to give **16b**.[23] However,

the presence of any substituent at O-4 (**17**,[26] **18**,[27] or **19**[28]) decreased the regioselectivity and significant amounts of O-2 substitution was also observed. Therefore, we hypothesized that introducing a bulky substituent at O-4′ of disaccharide **12** would reverse the selectivity at the non-reducing residue diol, and give an enhanced yield of the O-2 and O-2′ di-*O*-acylated products (Figure 4B).

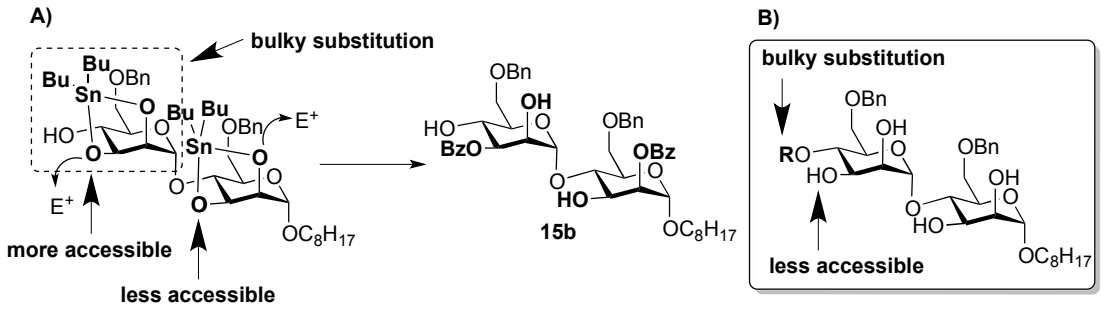
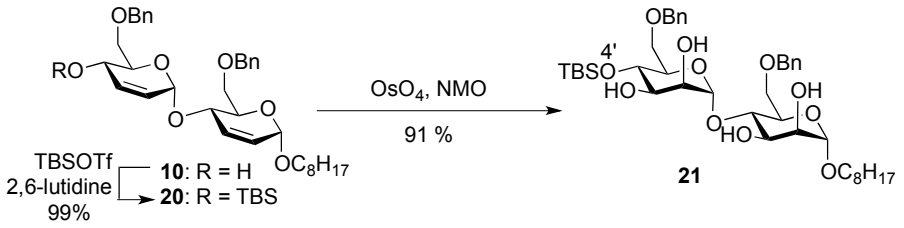


Figure 4. Rationale for the observed regioselectivity of the benzoylation of **12** with *n*-Bu_2SnO.

Substrate modification and optimization of regioselective acylation conditions

To test this hypothesis, a disaccharide modified at O-4′ with a *t*-butyldimethylsilyl (TBS) group (**21**, Scheme 4) was synthesized. The TBS group was introduced by treating alcohol **10** with TBSOTf and the resulting product, **20**, was then dihydroxylated with OsO_4 to provide **21** in 91% yield overall yield. With **21** in hand, the regioselective acylation reaction was examined. We investigated three reported catalytic methods for regioselective acylation of diols, including two tin reagents, Me_2SnCl_2[25] and *n*-Bu_2SnO,[22] as well as a borinic acid derivative $Ph_2BOCH_2CH_2NH_2$.[24] All these methods were reported to efficiently catalyze the regioselective acylation of monosaccharides, but their application to oligosaccharide systems had not been investigated.



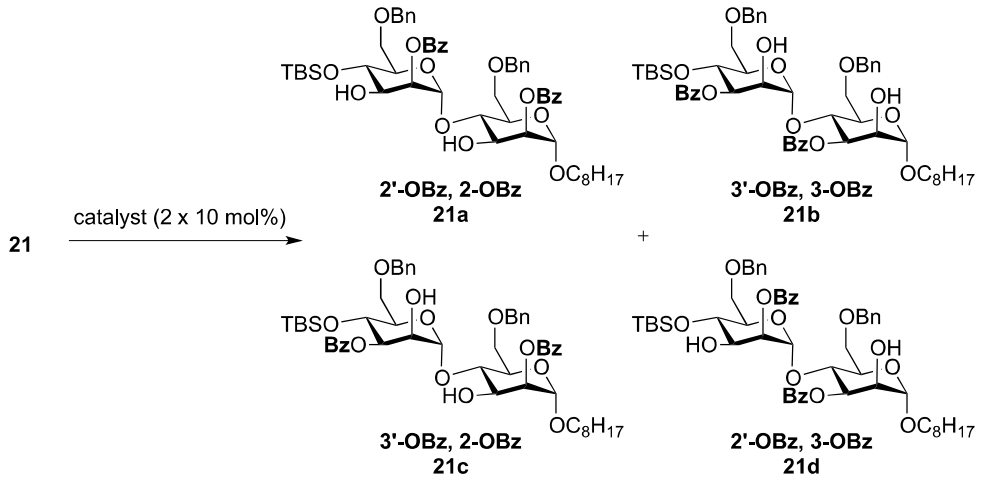
Scheme 4. Preparation of TBS-modified disaccharide **21**.

When **21** was treated with 2.4 equivalents BzCl (1.2 equiv per diol) in the presence of 20 mol% Me_2SnCl_2, *n*-Bu_2SnO or $Ph_2BOCH_2CH_2NH_2$ (10 mol% per diol), both tin reagents gave satisfactory conversions (entries 1 and 2, Table 2). However, the use of $Ph_2BOCH_2CH_2NH_2$ led only to ~10% conversion of **21** (entry 3, Table 2). Using of Me_2SnCl_2 gave 60% of a mixture of mono-*O*-benzoylated products and 40% of di-*O*-benzoylated products (entry 1). Of the disubstituted products, 22% was the expected 2,2′-di-*O*-benzoylated **21a** and 18% was the 3,2′-di-*O*-benzoylated isomer **21d** as determined by ^{1}H NMR spectroscopy. The other two isomers, **21b** and **21c**, were not detected. With *n*-Bu_2SnO, three di-*O*-benzoylated products were formed: 63% of the desired **21a**, 9% of **21c** and 16% of **21d** (entry 2). These results support our hypothesis that a bulky substituent at O-4′ of **21** alters the regioselectivity of the non-reducing end diol to favor substitution at O-2′.

The regioselectivity employing *n*-Bu_2SnO (**21a**:**21d** = 3.9:1) was better than with Me_2SnCl_2 (**21a**:**21d** = 1.2:1), suggesting that the size of the alkyl group in the catalyst also influence acylation regioselectivity. Indeed, replacing Me_2SnCl_2 with the more hindered *n*-Bu_2SnCl_2 gave **21a** as the only observed disubstituted isomer (entry 4, Table 2). However, 57% of the monobenzoylated products remained when this catalyst was used. When the *n*-Bu_2SnCl_2–catalyzed reaction of **21** was repeated with 10 equivalents of BzCl, (5 equiv per diol), an 87% yield of **21a** was produced (entry 5, Table 2). However, when the same amount of BzCl was

employed in reactions using *n*-Bu_2SnO, mainly tribenzoylated products were produced (entry 6, Table 2).

Table 2. Regioselective benzoylation of **21** with different catalysts.[a]



Entry	BzCl amount	Conditions	Products distribution (NMR yield)					Recoverd **21**
			disubstituted				monosubstituted	
			21a	**21b**	**21c**	**21d**		
1	2.4 equiv	Me_2SnCl_2, DIPEA, THF	22	-	-	18	60	-
2	2.4 equiv	*n*-Bu_2SnO, Et_3N, CH_2Cl_2	63	-	9	16	-	-
3	2.4 equiv	$Ph_2BOCH_2CH_2NH_2$, CH_3CN	-	-	-	-	<10	90
4	2.4 equiv	*n*-Bu_2SnCl_2, DIPEA, THF	43	-	-	-	57	-
5	10 equiv	*n*-Bu_2SnCl_2, DIPEA, THF	87	-	6	7	-	-
6	10 equiv	*n*-Bu_2SnO, Et_3N, CH_2Cl_2	tribenzoylated products observed					

[a] Reaction conditions: **21** (1 equiv., 0.1 M), catalyst (20 mol%), base (4 equiv. for entry 1–4, 10 equiv. for entry 5–6,), BzCl (2.4–10 equiv.), room temperature, 3 h.

Encouraged by the success of these preliminary studies, the regioselective benzoylation of **21** catalyzed by *n*-Bu_2SnCl_2 was optimized using various solvents (Table 3). In all solvents, a similar trend in the regioselectivity (**21a** >> **21c**, **21d** > **21b**) was observed, with the exception of pyridine, where the substrate formed a mixture of products containing more than two benzoyl groups. Among all the solvents tested, THF gave the least amount of undesired isomers (entry 1). Lowering the temperature to 0 °C did not improve the selectivity but, as expected, slowed the

reaction (entry 6). Thus, future reactions employed THF as the solvent and were carried out at room temperature.

Table 3. Solvent optimization for regioselective benzoylation of **21**.[a]

Entry	Solvent	T (°C)	Product distribution (%)				
			Disubstituted				Monosubstituted
			21a	**21b**	**21c**	**21d**	
1	THF	RT	87	-	6	7	-
2	CH_2Cl_2	RT	68	-	10	20	-
3	MeCN	RT	61	-	< 4	28	
4	Et_2O	RT	76	-	12	12	-
5	Pyridine	RT			overbenzoylation		
6	THF	0 °C	66	-	8	7	19

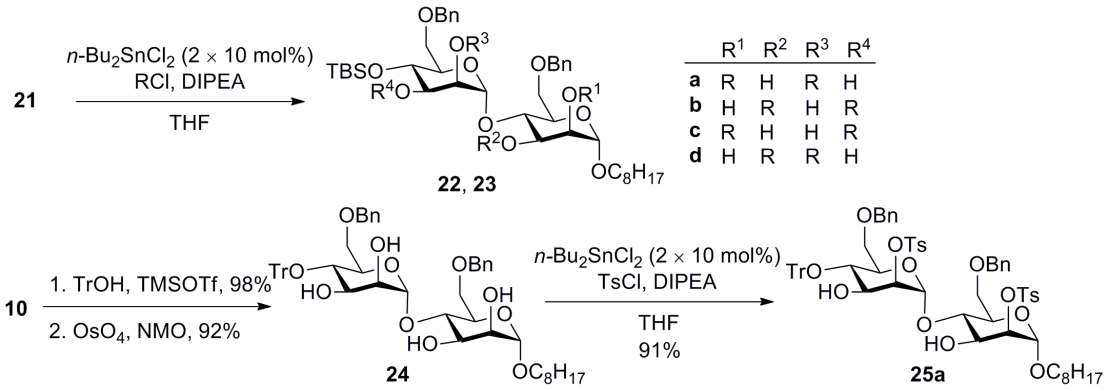
[a] Reaction conditions: **21** (1 equiv.0.1 M), *n*-Bu_2SnCl_2 (20 mol%), DIPEA (10 equiv.), BzCl (10 equiv.), 3 h.

Next, we tested the optimized method with other acylating reagents (Table 4). The relatively unhindered acylation reagent AcCl gave no regioselectivity (entry 1). The bulky PivCl produced a single disubstituted isomer **22a** with the expected 2,2′-disubstitution; however, 51% of the mono-2-*O*-pivaloyated product remained, as well as 36% of starting material **21** (entry 2). Replacing BzCl with *p*-TsCl gave the expected di-*O*-tosylated product **23a** in excellent yield and regioselectivity (entry 3), although the equivalents of TsCl and reaction time had to be increased to drive the reaction to completion. When tosylation was performed with 15 equivalents of TsCl for 24 hours, 89% of **23a** was observed (entry 4).

Having established that the introduction of a sterically-demanding protecting group on O-4′ of **21** successfully switched the regioselectivity of the non-reducing end residue, we next introduced a trityl substituent onto substrate instead of a TBS group (disaccharide **24**, Table 4). This compound was found to be a better substrate than **21**. Regioselective tosylation of **24** efficiently furnished a 91% isolated yield of the desired **25a** (entry 5, Table 4). Only a trace

amount of other isomers was produced from this reaction. Based on these results and for reasons discussed in greater detail below, we shifted our focus to tosylation reactions.

Table 4. Protecting group scope of regioselective acylation.[a]



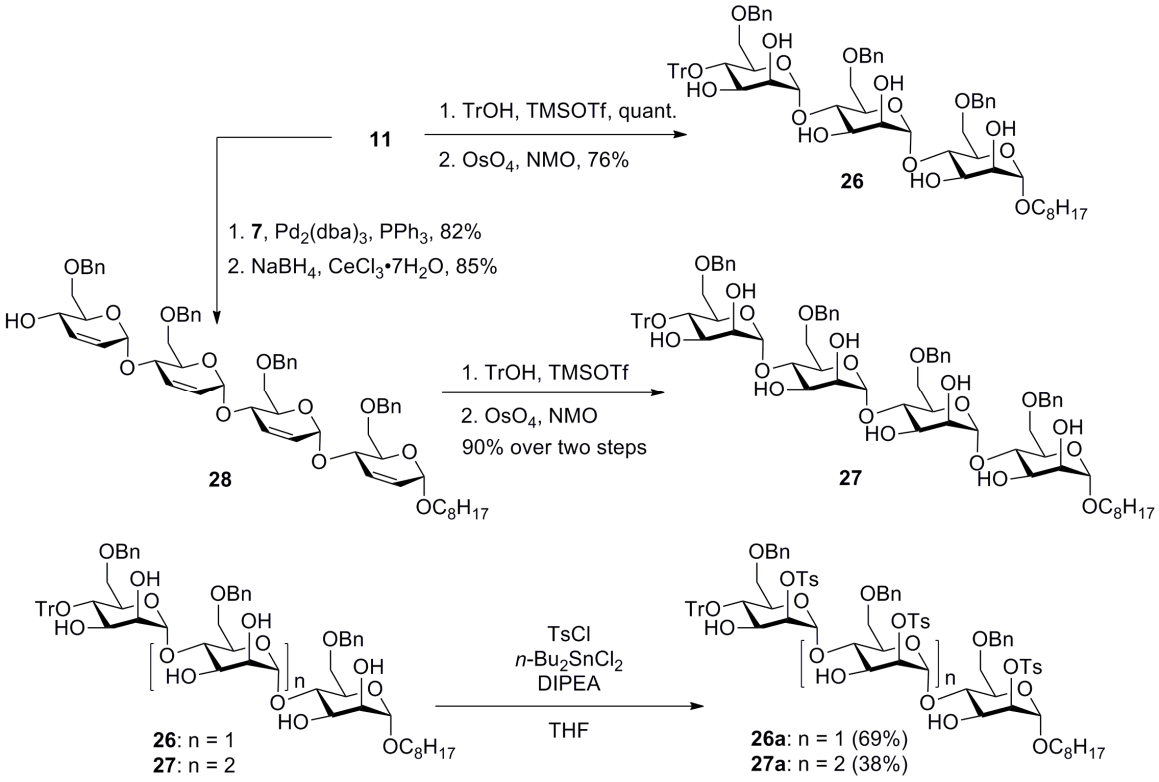
Entry	Substrate	RCl (amount)	Products (NMR yield)		Unreacted starting material
			disubstituted	monosubstituted	
1	**21** (R^1 = TBS)	AcCl (2.4 equiv)	trace	> 80%	10%
2		PivCl (10 equiv)	**22a** (13%)	51%	36%
3		TsCl (10 equiv)	**23a** (62%)	31%	trace
4		TsCl (15 equiv)	**23a** (89%), **23d** (11%)	-	-
5	**24** (R^1 = Tr)	TsCl (10 equiv)	**25a** (96%), **25d** (4%)	-	-

[a] Reaction conditions: substrate (1 equiv., 0.1 M), *n*-Bu_2SnCl_2 (20 mol%), DIPEA (10 equiv.), RCl (2.4–15 equiv.), room temperature, 24h.

Application to tri- and tetrasaccharides substrates

With a set of optimized conditions developed, the methodology was applied to more challenging substrates: trisaccharide **26** and tetrasaccharide **27**, which were obtained from their corresponding triene **11** and tetraene **28**, respectively (Scheme 5). Considering that regioselective acylation of each diol generates two possible regioisomers, trisaccharide **26**, with three diol pairs, would have eight possible tri-*O*-sulfonylated isomers and tetrasaccharide **27** would have 16 possible products. When **26** and **27** were subjected to the optimized regioselective sulfonation conditions, the desired trisubstituted product **26a** and tetrasubstituted product **27a** were obtained

as the major regioisomers in both cases, in 69% and 38% isolated yields, respectively. In both cases, these products were the major regioisomers. Although the isolated yield of the desired regioisomers dropped when the substrates used went from the disaccharide to the tetrasaccharide, the efficiency of the regioselectivity is still remarkable. Tosylation of disaccharide **24** produced a 91% yield of **25a**, corresponding to a 95% sulfonylation selectivity for each diol pair. In the case of the reaction with trisaccharide **26**, a 69% yield of **26a** corresponds to an 88% selectivity for each diol pair. For the reaction with tetrasaccharide **27**, a 38% yield is equivalent to sulfonylating each diol with 79% selectivity.



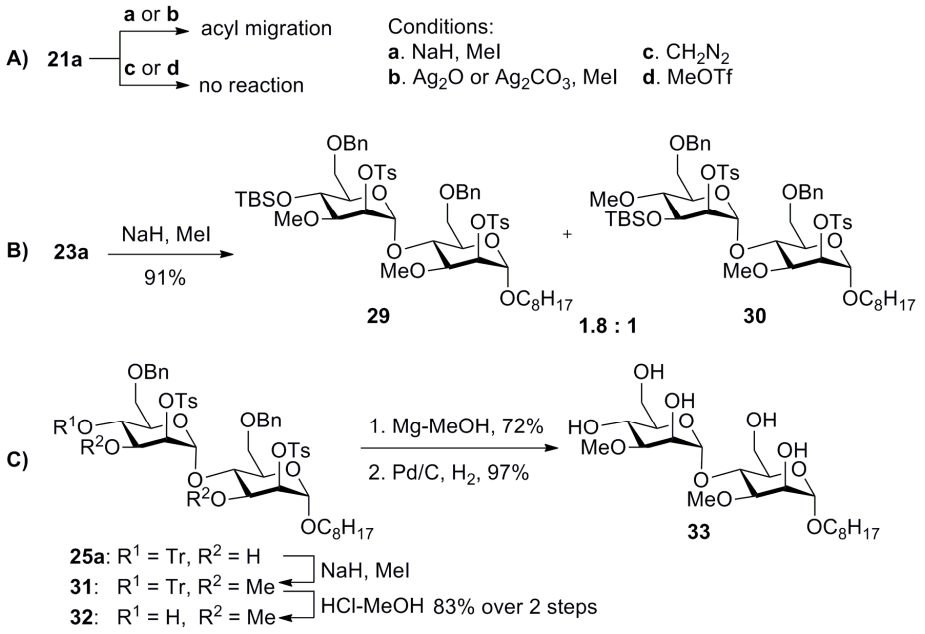
Scheme 5. Regioselective modification of trisaccharide **26** and tetrasaccharide **27**.

Subsequent functionalization of oligosaccharide by alkylation

After successfully introducing multiple protecting groups onto the di-, tri- and tetrasaccharides with good regioselectivity, the ability to further functionalize these compounds

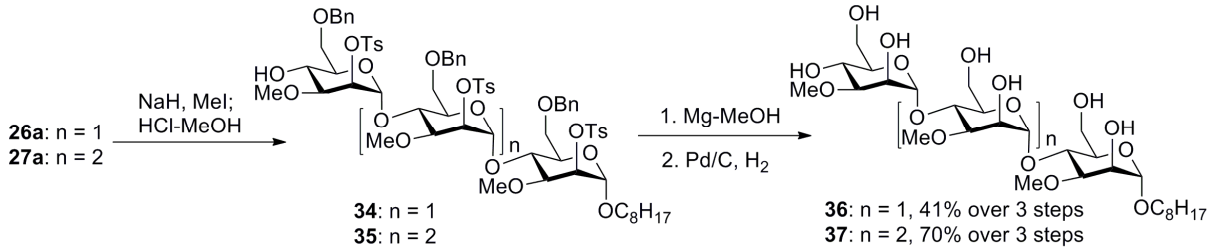
was investigated. Attempts to methylate **21a** using NaH as base resulted in benzoyl group migration (condition a, Scheme 6A), a common problem during alkylation under basic conditions.[8] The use of milder bases such as Ag_2O and Ag_2CO_3 failed to prevent acyl migration (condition b, Scheme 6A).[29-30] In addition, methylation of **21a** using CH_2N_2 and MeOTf also proved unsuccessful (conditions c and d, Scheme 6A).[31-32]

To overcome this acyl migration problem, the substrates with the sulfonyl groups were used.[33] As expected, the tosyl groups of **23a** were stable to alkylation with NaH and MeI. However, in addition to the desired product **29**, an unexpected byproduct, **30** (Scheme 6B), presumably resulting from intramolecular silyl group migration under the basic reaction conditions, was formed. The use of an alternative substrate with a base-stable trityl group on O-4′ (**25a**) avoided this problem, giving the desired di-*O*-methyl disaccharide **31**. The trityl group in **31** was easily removed using HCl in methanol to give **32** in 83% yield over the two steps. Finally, the tosyl groups of **32** were cleaved with magnesium in methanol at reflux.[34] Subsequent hydrogenolysis removed the remaining benzyl groups, furnishing partially methlated disaccharide **33** (Scheme 6C).



Scheme 6. Attempted methylation with disaccharides **21a**, **23a** and **25a**.

Following this approach, the methylated trisaccharide **36** and tetrasaccharide **37** were obtained three steps from **26a** and **27a**, in 41% and 70% overall yields, respectively (Scheme 7).

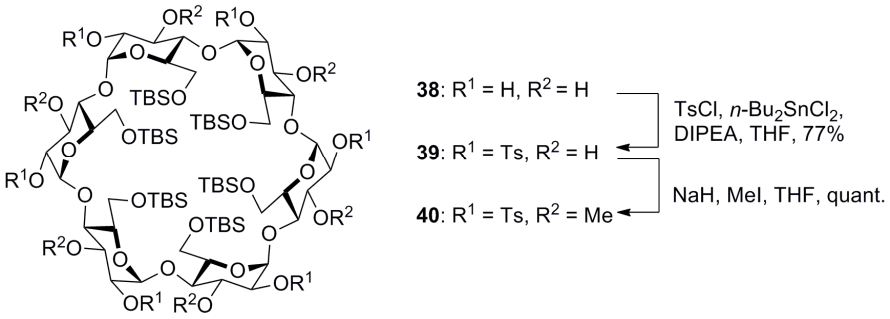


Scheme 7. Methylation of trisaccharide **26a** and tetrasaccharide **27a**.

Application to α-cyclodextrin

To explore the generality of the methodology, it was applied to α-cyclodextrin. Chemical modifications of cyclodextrins are of significant interest and have been widely used to tune their physical properties.[35] However, methods to selectively functionalize the secondary face of these cyclic oligosaccharides are still limited. In particular, derivatives that are functionalized at O-3

positions are difficult to prepare.[36] Noticing of the similarity between the α-(1→4)-linked mannose oligosaccharides described above and the α-(1→4)-linked glucopyranose residues present in α-cyclodextrin, we envisioned our methodology might be able to provide the 3-*O*-alkylated analogs. As expected, the TBS-protected α-cyclodextrin **38**[37] underwent tosylation with high regioselectivity (Scheme 8). The expected fully 2-*O*-tosylated product **39** was obtained in 77% isolated yield. Of the other byproducts produced from this reaction, the major one, isolated in 5% yield, had five of the residues exclusively tosylated at O-2. After protection of all the O-2 positions of cyclodextrin, methyl groups were installed quantitatively onto O-3 of **39** to give **40**. This substrate has *trans*- instead of *cis*-diols, which suggested the approach does not require a *cis*-diol. [§] This methodology thus provides a new method for the selective functionalization of cyclodextrins.



Scheme 8. Regioselective functionalization of α-cyclodextrin.

Conclusion

In conclusion, we demonstrate here a method that can be used to regioselectively functionalize multiple hydroxyl groups in oligosaccharides. Key to the development of this approach was the realization that the regioselectivity of organotin-mediated acylation and

[§] Stannylene-acetal intermediates of *trans*-diols, in particular α-glucopyranosides, have been described.[17-20]

sulfonation of diols can be altered by tuning the size of protecting groups on the substrate. Although such effects can, in retrospect, be identified in previous examples of such functionalizations,[23,26-28] rational optimization of these steric effects appears not to have been carried out previously.

The focus of this paper has been on the selective methylation of *cis*-diols in α-(1→4)-linked mannopyranose oligomers, which are an interesting class of lipid-binding oligosaccharides.[38-40] When coupled with O'Doherty's palladium-catalyzed pyranone glycosylation methodology,[16] we consider this approach to be a viable alternative to more traditional approaches to these targets, which rely on the preparation of a number of selectively protected monosaccharides derivatives.[13,41-47] We also provide examples showing that the method is effective for selectively functionalizing not only *cis*-diols but also *trans*-diols (in α-cyclodextrin) and further work in applying this method to other oligosaccharide systems is ongoing. In particular, the stereochemistry at C-1 and C-4, and the identity of the protecting group at O-6, may influence the selectivity of the process. We note that during the preparation of this manuscript a similar method, also employing *n*-Bu_2SnCl_2 as the catalyst, was reported for the regioselective monosulfonylation of an unprotected disaccharide by Muramatsu.[48] The major difference is that whereas Muramatsu aimed to protect only one of the hydroxyl groups of an oligosaccharide, our approach targets simultaneous functionalization of multiple hydroxyl groups.

Experimental section

General experimental methods: All reagents were purchased from commercial sources and were used without further purification unless noted. All reactions were carried out under a positive pressure of argon or nitrogen at room temperature unless specified and were monitored

by TLC on silica gel 60-F_{254} (0.25 mm). Visualization of the reaction components was achieved using UV fluorescence (254 nm) and/or by charring with acidified anisaldehyde solution in ethanol. Organic solvents were evaporated under reduced pressure and the products were purified by column chromatography on silica gel (230–400 mesh). Optical rotations were measured in a microcell (10 cm, 1 mL) at ambient temperature and are in units of degree·mL/(g·dm). ^{1}H NMR spectra were recorded at 500 MHz or 600 MHz and chemical shifts are referenced to residual $CHCl_3$ (7.26 ppm, $CDCl_3$), $CHDCl_2$ (5.32 ppm, CD_2Cl_2), or CHD_2OD (3.30 ppm, CD_3OD). ^{13}C NMR spectra were recorded at 125 MHz and chemical shifts are referenced to $CDCl_3$ (77.0 ppm) or CD_2Cl_2 (53.8 ppm). Reported splitting patterns are abbreviated as s = singlet, d = doublet, t = triplet, m = multiplet, br = broad, app = apparent. Assignments of NMR spectra were based on two-dimensional experiments (^{1}H–^{1}H COSY, HSQC, and HMBC) and stereochemistry of the anomeric centers of the pyranose rings were confirmed by measuring $^{1}J_{C\text{-}1,H\text{-}1}$ via coupled HSQC experiments. High resolution ESI-MS spectra (time-of-flight analyzer) were recorded on samples suspended in THF or CH_3OH and with added NaCl. Low resolution MALDI-MS (time-of-flight analyzer) used 2,5-dihydroxybenzoic acid (DHB) as matrix.

(2*R*,6*R*)-6-((benzyloxy)methyl)-5-oxo-5,6-dihydro-2*H*-pyran-2-yl *tert*-butyl carbonate (**7**): A reported method was used for the synthesis of **7**.[15] To a stirring ice-cold solution of (*R*)-2-(benzyloxy)-1-(furan-2-yl)ethanol[14] (2.9 g, 13.2 mmol) in mixed THF and H_2O (21 mL, THF–H_2O 4:1) was add $NaHCO_3$•$3H_2O$ (2.3 g, 26.5 mmol) and NaOAc (1.1 g, 13.2 mmol). *N*-bromosuccinimide (2.4 g, 13.2 mmol) was added and the resulting yellow solution was stirred at 0 °C for 1.5 h. The reaction mixture was concentrated to remove THF and then extracted with CH_2Cl_2. After washing with saturated aqueous $NaHCO_3$ and brine, the organic layer was dried

over Na_2SO_4 and concentrated to afford a yellow liquid (3.4 g). This yellow liquid (1.5 g, 5.7 mmol) was then dissolved in CH_2Cl_2 (8 mL) and cooled to −78 °C. Di-*t*-butyl dicarbonate (1.5 g, 6.8 mmol) was added into this solution followed by 4-dimethylaminopyridine (70.8 mg, 0.6 mmol). The solution was stirred for 1 h while warming to room temperature. The resulting black solution was concentrated and the crude residue was purified by chromatography (hexane–EtOAc 9:1) to afford α isomer **7** (919.4 mg, 48% over two steps) as a pale yellow syrup. This reaction also produced the β isomer (212.1 mg, 11%) as yellow syrup. The following data are for α isomer **7** only. R_f 0.57 (hexane–EtOAc 3:1); $[\alpha]_D = -72.2$ (*c* 3.0, $CHCl_3$); IR: 1751.6 (C=O), 1702.3 (Boc C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.27 (m, 5H, Ar), 6.94 (dd, *J* = 10.3, 3.7 Hz, 1H, H-2), 6.48 (d, *J* = 3.7 Hz, 1H, H-1), 6.28 (d, *J* = 10.3 Hz, 1H, H-3), 4.72 (dd, *J* = 4.4, 2.7 Hz, 1H, H-5), 4.60 (s, 2H, 2 × OC*H*$_2$Ph), 3.97 (dd, *J* = 10.9, 4.4 Hz, 1H, H-6a), 3.92 (dd, *J* = 10.9, 2.6 Hz, 1H, H-6b), 1.54 (s, 9H, Boc); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.0 (C-4), 151.7 (Boc C=O), 141.4 (C-2), 137.8 (Ar), 129.1 (C-3), 128.4 (2C, Ar), 127.7 (2C, Ar), 127.7 (Ar), 89.2 (C-1), 83.7 (Boc *t*-Bu), 76.4 (C-5), 73.7 (O*C*H$_2$Ph), 68.5 (C-6), 27.7 (Boc *t*-Bu); HRMS (ESI) calcd $C_{18}H_{22}O_6$ $[M+Na]^+$ 357.1309, found 357.1311.

(2*R*,6*S*)-2-((benzyloxy)methyl)-6-(octyloxy)-2*H*-pyran-3(6*H*)-one (**8**): A solution of CH_2Cl_2 (3 mL) containing **7** (352.9 mg, 1.1 mmol) and 1-octanol (0.5 mL, 3.2 mmol) with 4 Å molecular sieves was stirred at room temperature for 0.5 h before 2.5 mol% tris(dibenzylideneacetone)dipalladium(0) $Pd_2(dba)_3$ (26.8 mg, 0.03 mmol) and 10 mol% triphenylphosphine PPh_3 (28.0 mg, 0.12 mmol) were added. After stirring for 1.5 h, the resulting purple solution was concentrated and the resulting residue was purified by chromatography (hexane–EtOAc 15:1) to afford **8** (351.4 mg, 96%) as a colorless liquid. R_f 0.59 (hexane–EtOAc 3:1); $[\alpha]_D = -32.7$ (*c* 0.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.26 (m, 5H, Ar), 6.91 (dd,

J = 10.2, 3.5 Hz, 1H, H-2), 6.15 (d, *J* = 10.3 Hz, 1H, H-3), 5.33 (d, *J* = 3.5 Hz, 1H, H-1), 4.65–4.60 (m, 3H, H-5, 2 × OC*H*$_2$Ph), 3.95 (dd, *J* = 10.8, 4.8 Hz, 1H, H-6a), 3.92 (dd, *J* = 10.9, 3.0 Hz, 1H, H-6b), 3.88 (dt, *J* = 9.6, 6.8 Hz, 1H, octyl OCH$_2$), 3.62 (dt, *J* = 9.6, 6.6 Hz, 1H, octyl OCH$_2$), 1.70–1.59 (m, 2H, octyl OCH$_2$C*H*$_2$), 1.44–1.21 (m, 10H, octyl CH$_2$), 0.90 (t, *J* = 7.0 Hz, 3H, octyl CH$_3$); ^{13}C NMR (126 MHz, CDCl$_3$) δ 194.4 (C-4), 144.1 (C-2), 138.0 (Ar), 128.3 (2C, Ar), 127.8 (Ar), 127.6 (3C, Ar (2C), C-3), 93.2 (C-1), 74.5 (C-5), 73.7 (O*C*H$_2$Ph), 69.7 (octyl OCH$_2$), 68.7 (C-6), 31.8, 29.7, 29.4, 29.3, 26.2, 22.7 (6C, octyl CH$_2$), 14.1 (octyl CH$_3$); HRMS (ESI) calcd $C_{21}H_{30}O_4$ $[M+Na]^+$ 369.2036, found 369.2040.

(2*R*,3*S*,6*S*)-2-((benzyloxy)methyl)-6-(octyloxy)-3,6-dihydro-2*H*-pyran-3-ol (**9**): To a solution of ketone **8** (343.0 mg, 1.1 mmol) in methanol (2.5 mL) at −78 °C was added $NaBH_4$ (42.3 mg, 1.1 mmol) and $CeCl_3$•$7H_2O$ (392.7 mg, 1.1 mmol). The solution was stirred overnight while warming to room temperature. The mixture was concentrated to remove the methanol and then the residue was redissolved in CH_2Cl_2. After washing with water and brine, the organic layer was dried over Na_2SO_4, and then concentrated. The resulting residue was purified by chromatography (hexane–EtOAc 6:1) to afford alcohol **9** (307.3 mg, 88%) as a colorless syrup. R_f 0.35 (hexane–EtOAc 3:1); $[\alpha]_D$ = +20.0 (*c* 0.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.27 (m, 5H, Ar), 5.94 (d, *J* = 10.2 Hz, 1H, H-3), 5.76 (ddd, *J* = 10.2, 2.7, 2.2 Hz, 1H, H-2), 4.99 (d, *J* = 2.6 Hz, 1H, H-1), 4.65 (d, *J* = 12.0 Hz, 1H, OC*H*$_2$Ph), 4.61 (d, *J* = 12.0 Hz, 1H, OC*H*$_2$Ph), 4.23 (dddd, *J* = 9.2, 5.6, 3.5, 1.8 Hz, 1H, H-4), 3.89–3.83 (m, 1H, H-5), 3.82–3.75 (m, 2H, H-6a, octyl OCH$_2$), 3.72 (dd, *J* = 10.0, 4.9 Hz, 1H, H-6b), 3.50 (dt, *J* = 9.6, 6.6 Hz, 1H, octyl OCH$_2$), 2.67 (d, *J* = 5.9 Hz, 1H, OH-4), 1.67–1.55 (m, 2H, octyl OCH$_2$C*H*$_2$), 1.43–1.22 (m, 10H, octyl CH$_2$), 0.91 (t, *J* = 7.0 Hz, 3H, octyl CH$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.9 (Ar), 133.0 (C-3), 128.5 (2C, Ar), 127.8 (Ar), 127.7 (2C, Ar), 126.2 (C-2), 94.3 (C-1), 73.7 (O*C*H$_2$Ph), 70.7 (C-6), 70.0 (C-5), 68.8

(octyl OCH_2), 65.6 (C-4), 31.9, 29.8, 29.4, 29.3, 26.2, 22.7 (6C, octyl CH_2), 14.1 (octyl CH_3); HRMS (ESI) calcd $C_{21}H_{32}O_4$ $[M+Na]^+$ 371.2193, found 371.2189.

(2*R*,3*S*,6*S*)-2-((benzyloxy)methyl)-6-(((2*R*,3*S*,6*S*)-2-((benzyloxy)methyl)-6-(octyloxy)-3,6-dihydro-2*H*-pyran-3-yl)oxy)-3,6-dihydro-2*H*-pyran-3-ol (**10**): The reaction was performed as described for the synthesis of **8**, with alcohol **9** (611.8 mg, 1.8 mmol) and donor **7** (818.5 mg, 2.6 mmol) in the presence of $Pd_2(dba)_3$ (41.8 mg, 0.05 mmol) and PPh_3 (60.0 mg, 0.23 mmol) in CH_2Cl_2 (6 mL). The crude residue was purified by chromatography (hexane–EtOAc 7:1) to afford a ketone (842.1 mg, 85%) as a colorless syrup. This ketone was then reduced as described for **9**, with $NaBH_4$ (68.6 mg, 1.8 mmol) and $CeCl_3 \cdot 7H_2O$ (656.2 mg, 1.8 mmol) in methanol (6 mL). Chromatographic purification of the crude reaction mixture (hexane–EtOAc 6:1) furnished alcohol **10** (770.3 mg, 91%) as a colorless syrup. R_f 0.38 (hexane–EtOAc 2:1); $[\alpha]_D$ = +35.3 (*c* 0.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.24 (m, 10H, Ar), 6.05 (d, *J* = 10.3 Hz, 1H, H-3), 5.97 (d, *J* = 10.2 Hz, 1H, H-3′), 5.84 (ddd, *J* = 10.3, 2.7, 1.8 Hz, 1H, H-2), 5.68 (ddd, *J* = 10.2, 2.4, 2.4 Hz, 1H, H-2′), 5.20 (d, *J* = 2.4 Hz, 1H, H-1′), 5.03 (d, *J* = 2.1 Hz, 1H, H-1), 4.62–4.41 (m, 5H, H-4, 4 × OC*H*$_2$Ph), 4.26 (dddd, *J* = 10.3, 3.4, 3.4, 1.7 Hz, 1H, H-4′), 4.01 (ddd, *J* = 9.4, 3.6, 3.6 Hz, 1H, H-5), 3.81 (dt, *J* = 9.5, 6.8 Hz, 1H, octyl OCH_2), 3.77–3.73 (m, 2H, H-6a, H-6b), 3.73–3.68 (m, 1H, H-5′), 3.66 (dd, *J* = 9.6, 4.3 Hz, 1H, H-6a′), 3.55 (dd, *J* = 9.6, 5.7 Hz, 1H, H-6b′), 3.50 (dt, *J* = 9.5, 6.6 Hz, 1H, octyl OCH_2), 2.33 (d, *J* = 4.9 Hz, 1H, OH-4′), 1.67–1.57 (m, 2H, octyl $OCH_2C\mathit{H}_2$), 1.40–1.21 (m, 10H, octyl CH_2), 0.90 (t, *J* = 7.0 Hz, 3H, octyl CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.5, 137.6 (2C, Ar), 133.2 (C-3′), 129.3 (C-3), 128.5 (2C, Ar), 128.3 (2C, Ar), 127.9 (Ar), 127.8 (2C, Ar), 127.4 (3C, Ar), 127.3 (C-2), 125.8 (C-2′), 94.3 (C-1), 91.1 (C-1′), 73.7, 73.21 (2C, 2 × O*C*H_2Ph), 70.6 (C-6′), 69.9 (C-5′), 69.7 (C-6), 69.1 (C-5), 68.7

(octyl OCH_2), 67.3 (C-4), 66.0 (C-4′), 31.9, 29.8, 29.4, 29.3, 26.3, 22.7 (6C, octyl CH_2), 14.1 (octyl CH_3); HRMS (ESI) calcd $C_{34}H_{46}O_7$ $[M+Na]^+$ 589.3136, found 589.3136.

(2*R*,3*S*,6*S*)-2-((benzyloxy)methyl)-6-(((2*R*,3*S*,6*S*)-2-((benzyloxy)methyl)-6-(((2*R*,3*S*,6*S*)-2-((benzyloxy)methyl)-6-(octyloxy)-3,6-dihydro-2*H*-pyran-3-yl)oxy)-3,6-dihydro-2*H*-pyran-3-yl)oxy)-3,6-dihydro-2*H*-pyran-3-ol (**11**): The reaction was performed as described for the synthesis of **8**, with alcohol **10** (978.0 mg, 1.73 mmol) and donor **7** (1.02 g, 3.05 mmol) in the presence of $Pd_2(dba)_3$ (69.0 mg, 0.08 mmol) and PPh_3 (80.0 mg, 0.31 mmol) in CH_2Cl_2 (22 mL). The crude residue was purified by chromatography (hexane–EtOAc 9:1) to afford a ketone (1.28 g, 95%) as a pale yellow syrup. $[\alpha]_D$ = +5.1 (*c* 0.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.21 (m, 15H, Ar), 6.83 (dd, *J* = 10.2, 3.5 Hz, 1H, H-2″), 6.18 (d, *J* = 10.3 Hz, 1H, H-3″), 6.11 (d, *J* = 10.3 Hz, 1H, H-3′), 6.05 (d, *J* = 10.3 Hz, 1H, H-3), 5.85 (ddd, *J* = 10.3, 2.7, 1.8 Hz, 1H, H-2), 5.78 (ddd, *J* = 10.3, 2.7, 1.9 Hz, 1H, H-2′), 5.57 (d, *J* = 3.5 Hz, 1H, H-1″), 5.27 (d, *J* = 2.1 Hz, 1H, H-1′), 5.03 (d, *J* = 2.2 Hz, 1H, H-1), 4.63 (dd, *J* = 9.3, 1.3 Hz, 1H, H-4′), 4.60–4.37 (m, 8H, H-4, H-5″, 6 × OC*H*$_2$Ph), 4.02 (ddd, *J* = 9.3, 5.6, 1.8 Hz, 1H, H-5), 3.85–3.75 (m, 4H, H-5′, H-6a, H-6a″, octyl OCH_2), 3.71 (dd, *J* = 10.9, 5.7 Hz, 1H, H-6b), 3.63–3.58 (m, 2H, H-6a′, H-6b″), 3.54 (dd, *J* = 10.8, 1.7 Hz, 1H, H-6b′), 3.50 (dt, *J* = 9.5, 6.6 Hz, 1H, octyl OCH_2), 1.66–1.57 (m, 2H, octyl $OCH_2C\mathit{H}_2$), 1.41–1.22 (m, 10H, octyl CH_2), 0.90 (t, *J* = 7.0 Hz, 3H, octyl CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.0 (C-4″), 143.6 (C-2″), 138.5, 138.0, 137.8 (3C, Ar), 129.2 (2C, C-3, C-3′), 128.3 (2C, Ar), 128.3 (2C, Ar), 128.3 (2C, Ar), 128.2 (C-3″), 127.7 (2C, Ar), 127.6 (2C, Ar), 127.6 (2C, Ar), 127.4 (4C, 3 × Ar, C-2), 127.3 (C-2′), 94.2 (C-1), 91.4 (C-1′), 90.0 (C-1″), 75.0 (C-5″), 73.7, 73.5, 73.2 (3C, 3 × O*C*H$_2$Ph), 69.9 (C-6), 69.7 (C-5′), 69.1 (C-5), 69.0 (C-6′), 68.7 (octyl OCH_2), 68.5 (C-6″), 67.5 (C-4), 67.4 (C-4′), 31.9, 29.8, 29.4, 29.3, 26.3, 22.7 (6C, octyl CH_2), 14.1 (octyl CH_3); HRMS (ESI) calcd $C_{47}H_{58}O_{10}$ $[M+Na]^+$ 805.3922, found 805.3915.

This ketone (208.9 mg, 0.21 mmol) was then reduced as described for **9**, with $NaBH_4$ (8.0 mg, 0.21 mmol) and $CeCl_3$•$7H_2O$ (80.2 mg, 0.21 mmol) in methanol (2.5 mL). Chromatographic purification of the crude reaction mixture (hexane–EtOAc 3:1) furnished alcohol **11** (177.2 mg, 85%) as a colorless syrup. R_f 0.30 (hexane–EtOAc 3:1); $[\alpha]_D$ = +35.6 (*c* 0.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.23 (m, 15H, Ar), 6.07 (d, *J* = 10.1 Hz, 1H, H-3′), 6.05 (d, *J* = 9.3 Hz, 1H, H-3), 5.99 (d, *J* = 10.2 Hz, 1H, H-3″), 5.84 (ddd, *J* = 10.3, 2.7, 1.8 Hz, 1H, H-2), 5.74 (ddd, *J* = 10.3, 2.7, 1.9 Hz, 1H, H-2′), 5.70 (ddd, *J* = 10.2, 2.7, 2.3 Hz, 1H, H-2″), 5.25 (d, *J* = 2.0 Hz, 1H, H-1′), 5.20 (d, *J* = 2.4 Hz, 1H, H-1″), 5.03 (d, *J* = 2.1 Hz, 1H, H-1), 4.60–4.39 (m, 8H, H-4, H-4′, 3 × OCH_2Ph), 4.27 (ddd, *J* = 8.6, 4.4, 1.7 Hz, 1H, H-4″), 4.02 (ddd, *J* = 9.2, 6.0, 1.7 Hz, 1H, H-5), 3.88–3.76 (m, 3H, H-5′, H-6a, octyl OCH_2), 3.74–3.62 (m, 4H, H-5″, H-6a, H-6a′, H-6a″), 3.60 (dd, *J* = 10.8, 2.0 Hz, 1H, H-6b′), 3.55–3.46 (m, 2H, H-6b″, octyl OCH_2), 2.41 (d, *J* = 4.6 Hz, 1H, OH-4″), 1.67–1.55 (m, 2H, octyl $OCH_2C\mathit{H}_2$), 1.40–1.20 (m, 10H, octyl CH_2), 0.90 (t, *J* = 7.0 Hz, 3H, octyl CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.5, 138.4, 137.6 (3C, 3 × Ar), 133.3 (C-3″), 129.9, 129.3 (2C, C-3, C-3′), 128.5 (2C, Ar), 128.3 (2C, Ar), 128.3 (2C, Ar), 127.9 (Ar), 127.8 (2C, Ar), 127.4 (3C, Ar), 127.4 (2C, Ar), 127.4 (Ar), 127.3 (C-2), 126.7 (C-2′), 125.7 (C-2″), 94.2 (C-1), 91.3 (C-1′), 91.0 (C-1″), 73.7, 73.4, 73.2 (3C, 3 × O*C*H_2Ph), 70.7 (C-6″), 69.9 (C-6), 69.8 (2C, C-5′, C-5″), 69.2 (C-6′), 69.1 (C-5), 68.7 (octyl OCH_2), 67.5 (C-4), 66.7 (C-4′), 66.1 (C-4″), 31.9, 29.8, 29.4, 29.3, 26.3, 22.7 (6C, octyl CH_2), 14.1 (octyl CH_3); HRMS (ESI) calcd $C_{47}H_{60}O_{10}$ $[M+Na]^+$ 807.4079, found 807.4070.

Octyl 6-*O*-benzyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-α-D-mannopyranoside (**12**): To a solution of **10** (561.8 mg, 0.97 mmol) in *t*-butanol and acetone (4 mL, v/v 1:1) was added OsO_4 (2.5 wt.% in *t*-butanol, 250 uL, 0.02 mmol) and *N*-methyl-morpholine *N*-oxide (NMO, 50% w/v in water, 0.3 mL). After stirring at room temperature overnight, saturated aqueous Na_2SO_3

solution was added. The mixture was concentrated to remove *t*-butanol and then the residue was extracted with CH_2Cl_2 three times. The combined organic layer was concentrated and the resultig residue was purifed by chromatography (CH_2Cl_2–methanol 15:1) to afford **12** (492.3 mg, 80%) as a pale yellow syrup. R_f 0.14 (CH_2Cl_2–methanol 15:1); $[\alpha]_D$ = +59.5 (*c* 1.2, methanol); ^{1}H NMR (498 MHz, CD_3OD) δ 7.34–7.20 (m, 10H, Ar), 5.22 (d, *J* = 1.8 Hz, 1H, H-1′), 4.69 (d, *J* = 1.6 Hz, 1H, H-1), 4.53–4.41 (m, 4H, 4 × OC*H*$_2$Ph), 3.94 (dd, *J* = 3.1, 1.9 Hz, 1H, H-2′), 3.83–3.59 (m, 12H, H-2, H-3, H-3′, H-4, H-4′, H-5, H-5′, 2 × H-6, 2 × H-6′, octyl OCH_2), 3.39 (dt, *J* = 9.6, 6.4 Hz, 1H, octyl OCH_2), 1.61–1.52 (m, 2H, octyl $OCH_2C\mathit{H}_2$), 1.38–1.21 (m, 10H, octyl CH_2), 0.88 (t, *J* = 7.0 Hz, 3H, octyl CH_3); ^{13}C NMR (125 MHz, CD_3OD) δ 139.8, 139.7 (2C, Ar), 129.3 (2C, Ar), 129.3 (2C, Ar), 129.0 (2C, Ar), 128.9 (2C, Ar), 128.6 (Ar), 128.6 (Ar), 103.4 (C-1′, $^1J_{C\text{-}1,H\text{-}1}$ = 171.4 Hz), 101.4 (C-1, $^1J_{C\text{-}1,H\text{-}1}$ = 167.0 Hz), 76.6 (C-4), 74.6, 74.4 (2C, 2 × O*C*H$_2$Ph), 74.4, 73.2, 72.7, 72.5, 72.2, 72.1 (6C, C-2, C-2′, C-3, C-3′, C-5, C-5′), 71.4, 71.4 (2C, C-6, C-6′), 68.8 (octyl OCH_2), 68.7 (C-4′), 33.0, 30.6, 30.4, 30.4, 27.3, 23.7 (6C, octyl CH_2), 14.5 (octyl CH_3); HRMS (ESI) calcd $C_{34}H_{50}O_{11}$ $[M+Na]^+$ 657.3245, found 657.3239.

Synthesis of octyl 6-*O*-benzyl-3-*O*-methyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-3-*O*-methyl-α-D-mannopyranoside (12a), octyl 6-*O*-benzyl-3-*O*-methyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-2-*O*-methyl-α-D-mannopyranoside (12b) and octyl 6-*O*-benzyl-3-*O*-methyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-α-D-mannopyranoside (12c): Compound **12** (0.01–0.04 mmol, 1 equiv.) and *n*-Bu_2SnO (2 equiv.) were heated at reflux in toluene (0.01 M) overnight. The resulting yellowlish solution was cooled to room teperature before MeI (20 equiv.), *t*-Bu_4NI (2 equiv.) and CsF (none for entry 1 and 2, 4 equiv. for entry 3) were added. The mixture was stirred at designated temperature (see Table 1) overnight before concentrated. The crude products were then purifed by chromatography (CH_2Cl_2–methanol 30:1 to 20:1) to

afford an inseparable mixture of **12a** and **12b** as a yellow syrup, as well as separable **12c** as a yellow syrup. R_f 0.51 for **12a** and **12b**, 0.43 for **12c** (CH_2Cl_2–methanol 12:1);

Octyl 6-*O*-benzyl-3-*O*-methyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-3-*O*-methyl-α-D-mannopyranoside (12a): ^{1}H NMR (600 MHz, CD_3OD) δ 7.39–7.18 (m, 10H, Ar), 5.16 (d, *J* = 1.9 Hz, 1H, H-1′), 4.76 (d, *J* = 1.8 Hz, 1H, H-1), 4.53–4.40 (m, 4H, 4 × OC*H*$_2$Ph), 4.08 (dd, *J* = 3.1, 2.1 Hz, 1H, H-2′), 4.00 (dd, *J* = 3.2, 1.9 Hz, 1H, H-2), 3.87–3.55 (m, 9H, H-4, H-4′, H-5, H-5′, 4 × H-6, octyl OCH_2), 3.46 (dd, *J* = 9.2, 3.3 Hz, 1H, H-3), 3.45 (s, 3H, OMe), 3.43–3.40 (m, 1H, octyl OCH_2), 3.41 (s, 3H, OMe), 3.33 (dd, *J* = 9.3, 3.1 Hz, 1H, H-3′), 1.62–1.55 (m, 2H, octyl OCH_2C*H*$_2$), 1.40–1.21 (m, 10H, octyl CH_2), 0.84 (t, *J* = 7.5 Hz, 3H, octyl CH_3); HRMS (ESI) calcd $C_{36}H_{54}O_{11}$ $[M+Na]^+$ 685.3558, found 685.3555.

Octyl 6-*O*-benzyl-3-*O*-methyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-2-*O*-methyl-α-D-mannopyranoside (12b): ^{1}H NMR (600 MHz, CD_3OD) δ 7.39–7.18 (m, 10H, Ar), 5.24 (d, *J* = 1.9 Hz, 1H, H-1′), 4.87 (d, *J* = 1.6 Hz, 1H, H-1), 4.53–4.40 (m, 4H, 4 × OC*H*$_2$Ph), 4.16 (dd, *J* = 3.0, 2.1 Hz, 1H, H-2′), 3.87–3.55 (m, 10H, H-3, H-4, H-4′, H-5, H-5′, 4 × H-6, octyl OCH_2), 3.44 (s, 3H, OMe), 3.44 (s, 3H, OMe), 3.43–3.40 (m, 1H, octyl OCH_2), 3.37 (dd, *J* = 3.5, 1.7 Hz, 1H, H-2), 3.33 (dd, *J* = 9.3, 3.1 Hz, 1H, H-3′), 1.62–1.55 (m, 2H, octyl OCH_2C*H*$_2$), 1.40–1.21 (m, 10H, octyl CH_2), 0.84 (t, *J* = 7.5 Hz, 3H, octyl CH_3); HRMS (ESI) calcd $C_{36}H_{54}O_{11}$ $[M+Na]^+$ 685.3558, found 685.3555;

Octyl 6-*O*-benzyl-3-*O*-methyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-α-D-mannopyranoside (12c): ^{1}H NMR (600 MHz, CD_3OD) δ 7.36–7.19 (m, 10H, Ar), 5.25 (d, *J* = 2.0 Hz, 1H, H-1′), 4.70 (d, *J* = 1.6 Hz, 1H, H-1), 4.54–4.40 (m, 4H, 2 × OCH_2Ph), 4.17 (dd, *J* = 3.0, 2.1 Hz, 1H, H-2′), 3.85–3.60 (m, 11H, H-2, H-3, H-4, H-4′, H-5, H-5′, 4 × H-6, octyl OCH_2),

3.45 (s, 3H, OMe), 3.42–3.38 (m, 1H, octyl OCH_2), 3.35 (dd, J = 9.3, 3.2 Hz, 1H, H-3′), 1.62–1.53 (m, 2H, octyl OCH_2CH_2), 1.38–1.23 (m, 10H, octyl CH_2), 0.89 (t, J = 7.1 Hz, 3H, octyl CH_3); HRMS (ESI) calcd $C_{35}H_{52}O_{11}$ $[M+Na]^+$ 671.3402, found 671.3402.

Octyl 6-*O*-benzyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-α-D-mannopyranoside (**13**): The dihydroxylation reaction was performed as described for the synthesis of **12**, with **11** (243.3 mg, 0.31 mmol), OsO_4 (2.5 wt.% in *t*-butanol, 119 uL, 0.01 mmol), NMO (50% w/v in water, 0.9 mL) in *t*-butanol and acetone (1 mL, v/v 1:1). The crude residue was purified by chromatography (CH_2Cl_2–methanol 12:1) to afford trisaccharide **13** (205.1 mg, 75%) as a colorless foam. R_f 0.61 (CH_2Cl_2–methanol 6:1); $[\alpha]_D$ = +64.8 (*c* 1.0, methanol); ^{1}H NMR (498 MHz, CD_3OD) δ 7.33–7.17 (m, 15H, Ar), 5.25 (d, J = 1.6 Hz, 1H, H-1′/H-1″), 5.23 (d, J = 1.7 Hz, 1H, H-1′/H-1″), 4.71 (d, J = 1.6 Hz, 1H, H-1), 4.52–4.33 (m, 6H, 6 × OCH_2Ph), 3.98 (dd, J = 3.0, 1.9 Hz, 1H, H-2′/H-2″), 3.90 (dd, J = 2.9, 2.2 Hz, 1H, H-2′/H-2″), 3.86–3.60 (m, 17H, H-2, 3 × H-3, 3 × H-4, 3 × H-5, 6 × H-6, octyl OCH_2), 3.38 (dt, J = 9.6, 6.3 Hz, 1H, octyl OCH_2), 1.61–1.52 (m, 2H, octyl OCH_2CH_2), 1.39–1.21 (m, 10H, OCH_2), 0.88 (t, J = 7.0 Hz, 3H, octyl CH_3); ^{13}C NMR (125 MHz, CD_3OD) δ 139.6 (Ar), 139.5 (2C, Ar), 129.3 (2C, Ar), 129.3 (2C, Ar), 129.2 (2C, Ar), 129.0 (2C, Ar), 129.0 (2C, Ar), 128.8 (2C, Ar), 128.6 (Ar), 128.6 (Ar), 128.5 (Ar), 103.3 (C-1′/ C-1″, $^1J_{C\text{-}1,H\text{-}1}$ = 170 Hz), 103.0 (C-1′/ C-1″, $^1J_{C\text{-}1,H\text{-}1}$ = 171 Hz), 101.3 (C-1, $^1J_{C\text{-}1,H\text{-}1}$ = 168.8 Hz), 76.4, 76.2 (2C, C-4, C-4′), 74.5, 74.4 (2C, 2 × OCH_2Ph), 74.3 (C-5″), 74.2 (OCH_2Ph), 73.2, 72.9, 72.8, 72.6, 72.6, 72.5, 72.1, 71.9 (9C, 3 × C-2, 3 × C-3, C-4″, C-5, C-5′), 71.3, 71.3, 71.1 (3C, 3 × C-6), 68.7 (octyl OCH_2), 32.9, 30.5, 30.3, 30.3, 27.2, 23.6 (6C, octyl CH_2), 14.5 (octyl CH_3); HRMS (ESI) calcd $C_{47}H_{66}O_{16}$ $[M+Na]^+$ 909.4243, found 909.4244.

Synthesis of octyl 6-*O*-benzyl-3-*O*-methyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-3-*O*-methyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-3-*O*-methyl-α-D-mannopyranoside (13a), octyl 6-*O*-benzyl-3-*O*-methyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-2-*O*-methyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-3-*O*-methyl-α-D-mannopyranoside (13b) and octyl 6-*O*-benzyl-3-*O*-methyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-3-*O*-methyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-2-*O*-methyl-α-D-mannopyranoside (13c): Compound **13** (33.3 mg, 0.04 mmol) and *n*-Bu_2SnO (31.8 mg, 0.12 mmol, 3 equiv.) were heated at reflux in toluene (4 mL) for 14 h. The resulting yellowish solution was cooled to room teperature before MeI (70 μL, 1.2 mmol), *t*-Bu_4NI (44.0 mg, 0.12 mmol, 3 equiv.) were added. After stirring at 70 °C for 7 h, additional MeI (150 μL, 2.4 mmol) was added and the reaction was stirred overnight. The crude products were purifed by chromatography (CH_2Cl_2–methanol 30:1 to 25:1) to afford three major products: an inseparable mixture (11.7 mg, 34%) of **13a** and **13c**, as well as **13b** (6.0 mg, 17%) both as colorless syrups. R_f 0.64 for **13b**, 0.61 for **13a** and **13c** (CH_2Cl_2–methanol 15:1); **13a** and **13c** were successfully separated after per-acetylation with acetic anhydride (0.1 mL) in pyridine (0.1 mL) and CH_2Cl_2 (1 mL). Chromatography purification gave acetylated **13a** (6.9 mg) and acetylated **13c** (3.5 mg) as colorless syrup.

Octyl 2,4-di-*O*-acetyl-6-*O*-benzyl-3-*O*-methyl-α-D-mannopyranosyl-(1→4)-2-*O*-acetyl-6-*O*-benzyl-3-*O*-methyl-α-D-mannopyranosyl-(1→4)-2-*O*-acetyl-6-*O*-benzyl-3-*O*-methyl-α-D-mannopyranoside (acetylated **13a**): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39–7.16 (m, 15H, Ar), 5.39 (dd, *J* = 3.1, 2.0 Hz, 1H, H-2′), 5.38 (dd, *J* = 3.0, 2.1 Hz, 1H, H-2″), 5.28 (dd, *J* = 3.2, 1.8 Hz, 1H, H-2), 5.25 (d, *J* = 1.8 Hz, 1H, H-1′), 5.19 (app t, *J* = 10.0 Hz, 1H, H-4″), 5.19 (d, *J* = 1.8 Hz, 1H, H-1″), 4.80 (d, *J* = 1.7 Hz, 1H, H-1), 4.64–4.38 (m, 6H, 6 × OC*H*$_2$Ph), 3.90 (app t, *J* =

10.0 Hz, 1H, H-4′), 3.89–3.79 (m, 5H, H-4, H-5, H-5′, H-5″, H-6), 3.76–3.68 (m, 3H, H-6, H-6, octyl OCH_2), 3.67–3.62 (m, 2H, H-3, H-6, H-6), 3.61–3.56 (m, 2H, H-3′, H-3″), 3.46–3.41 (m, 3H, H-6, H-6, octyl OCH_2), 3.41 (s, 3H, OMe), 3.40 (s, 3H, OMe), 3.36 (s, 3H, OMe), 2.11 (s, 3H, Ac), 2.08 (s, 3H, Ac), 2.06 (s, 3H, Ac), 1.99 (s, 3H, Ac), 1.66–1.58 (m, 2H, octyl OCH_2CH_2), 1.40–1.23 (m, 10H, octyl CH_2), 0.89 (t, J = 7.1 Hz, 3H, octyl CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 170.1, 170.0, 169.9 (4C, 4 × OAc), 138.5 (2C, Ar), 138.2 (Ar), 128.3 (2C, Ar), 128.3 (2C, Ar), 128.2 (2C, Ar), 127.8 (2C, Ar), 127.6 (Ar), 127.4 (3C, Ar), 127.4 (2C, Ar), 127.4 (Ar), 99.7 (C-1″), 99.4 (C-1′), 97.5 (C-1), 80.0 (C-3), 79.9 (C-3′), 76.5 (C-3″), 74.5 (C-4), 73.6 (C-4′), 73.6, 73.4, 73.3 (3 × OCH_2Ph), 71.9, 71.0, 70.8 (3C, C-5, C-5′, C-5″), 70.0, 69.9, 69.5 (3C, C-6, C-6′, C-6″), 68.4 (C-4″), 68.3 (octyl OCH_2), 67.7 (2C, C-2, C-2′), 67.4 (C-2″), 57.6, 57.2, 57.1 (3C, 3 × OMe), 31.8, 29.4, 29.4, 29.2, 26.1, 22.7 (6C, octyl CH_2), 21.0, 21.0, 21.0, 21.0 (4C, 4 × Ac), 14.1 (octyl CH_3); HRMS (ESI) calcd $C_{58}H_{80}O_{20}$ $[M+Na]^+$ 1119.5135, found 1119.5114.

Octyl 6-*O*-benzyl-3-*O*-methyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-2-*O*-methyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-3-*O*-methyl-α-D-mannopyranoside (13b): ^{1}H NMR (600 MHz, CD_3OD) δ 7.41–7.13 (m, 15H, Ar), 5.24 (d, J = 2.0 Hz, 1H, H-1″), 5.24 (d, J = 1.7 Hz, 1H, H-1′), 4.76 (d, J = 1.8 Hz, 1H, H-1), 4.53–4.32 (m, 6H, 6 × OCH_2Ph), 4.17 (dd, J = 3.0, 2.1 Hz, 1H, H-2″), 4.01 (dd, J = 3.2, 1.9 Hz, 1H, H-2), 3.86–3.56 (m, 14H, H-3′, H-4, H-4′, H-4″, H-5, H-5′, H-5″,6 × H-6, 1 × octyl OCH_2), 3.48–3.40 (m, 3H, H-2′, H-3, octyl OCH_2), 3.45 (s, 3H, OMe), 3.43 (s, 3H, OMe), 3.42 (s, 3H, OMe), 3.36 (dd, J = 9.2, 3.2 Hz, 1H, H-3″), 1.65–1.52 (m, 2H, octyl OCH_2CH_2), 1.42–1.20 (m, 10H, octyl CH_2), 0.89 (t, J = 7.1 Hz, 3H, octyl CH_3); HRMS (ESI) calcd $C_{50}H_{72}O_{16}$ $[M+Na]^+$ 951.4713, found 951.4708.

Octyl 2,4-di-*O*-acetyl-6-*O*-benzyl-3-*O*-methyl-α-D-mannopyranosyl-(1→4)-2-*O*-acetyl-6-*O*-benzyl-3-*O*-methyl-α-D-mannopyranosyl-(1→4)-3-*O*-acetyl-6-*O*-benzyl-2-*O*-methyl-α-D-mannopyranoside (acetylated **13c**): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39–7.13 (m, 15H, Ar), 5.37 (dd, *J* = 3.1, 2.1 Hz, 1H, H-2″), 5.22 (dd, *J* = 9.6, 3.3 Hz, 1H, H-3), 5.21 (d, *J* = 1.9 Hz, 1H, H-1″), 5.18 (app t, *J* = 9.8 Hz, 1H, H-4″), 5.16 (dd, *J* = 2.9, 2.1 Hz, 1H, H-2′), 4.99 (d, *J* = 1.9 Hz, 1H, H-1′), 4.86 (d, *J* = 1.7 Hz, 1H, H-1), 4.61–4.39 (m, 6H, 6 × OC*H*$_2$Ph), 4.01 (app t, *J* = 9.6 Hz, 1H, H-4), 3.91–3.60 (m, 10H, H-2, H-4′, H-5, H-5′, H-5″, 4 × H-6, 1 × octyl OCH_2), 3.59 (dd, *J* = 9.8, 3.2 Hz, 1H, H-3″), 3.56 (dd, *J* = 9.0, 3.1 Hz, 1H, H-3′), 3.43 (s, 3H, OMe), 3.47–3.39 (m, 3H, 2 × H-6, 1 × octyl OCH_2), 3.37 (s, 3H, OMe), 3.36 (s, 3H, OMe), 2.20 (s, 3H, OAc), 2.10 (s, 3H, OAc), 2.06 (s, 3H, OAc), 1.99 (s, 3H, OAc), 1.66–1.58 (m, 2H, octyl OCH_2C*H*$_2$), 1.40–1.21 (m, 10H, octyl CH_2), 0.89 (t, *J* = 7.0 Hz, 3H, octyl CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7 (OAc), 170.1 (OAc), 170.0 (OAc), 169.9 (OAc), 138.7, 138.4, 138.0, 128.3, 128.2, 128.2, 127.8, 127.6, 127.5, 127.4, 127.4, 127.3 (18C, Ar), 100.2 (C-1′), 99.5 (C-1″), 97.0 (C-1), 79.5 (C-3′), 78.4 (C-2), 76.5 (C-3″), 75.7 (C-4), 73.8 (2C, C-3, C-4′), 73.6, 73.3, 73.3 (3C, 3 × O*C*H_2Ph), 71.9 (C-5″), 71.2 (C-5′), 70.8 (C-5), 69.9, 69.8, 69.5 (3C, C-6, C-6′, C-6″), 68.4 (C-4″), 68.2 (octyl OCH_2), 67.7 (C-2′), 67.6 (C-2″), 59.3, 57.6, 57.2 (3C, 3 × OMe), 31.8, 29.5, 29.4, 29.2, 26.1, 22.7 (6C, octyl CH_2), 21.2, 21.0, 20.9, 20.9 (4C, 4 × Ac), 14.1 (octyl CH_3); HRMS (ESI) calcd $C_{58}H_{80}O_{20}$ $[M+Na]^+$ 1119.5135, found 1119.5117.

Synthesis of octyl 3-*O*-benzoyl-6-*O*-benzyl-α-D-mannopyranosyl-(1→4)-3-*O*-benzoyl-6-*O*-benzyl-α-D-mannopyranoside (**15a**) and **octyl 3-*O*-benzoyl-6-*O*-benzyl-α-D-mannopyranosyl-(1→4)-2-*O*-benzoyl-6-*O*-benzyl-α-D-mannopyranoside** (**15b**): **Method A**: Disaccharide **12** (13.3 mg, 0.02 mmol) and $(n\text{-}Bu_3Sn)_2O$ (175 μL, 0.03 mmol) were heated at

reflux in toluene (1.2 mL) for 15 h. The resulting yellowish solution was cooled to room temperature before BzCl (48 μL, 0.4 mmol) was added. After stirring at room temperature for 6 h, the reaction mixture was concentrated and the crude products were confirmed by ^{1}H NMR spectroscopy to be a mixture of **15a** (21% NMR yield) and **15b** (79% NMR yield). **Method B**: To a solution of **12** (14.1 mg, 0.02 mmol) in CH_2Cl_2 (0.5 mL) was added *n*-Bu_2SnO (1.3 mg, 0.004 mmol), Et_3N (9 μL, 0.06 mmol) followed by BzCl (6.5 μL, 0.05 mmol). The reaction mixture was stirred at room temperature overnight. The crude NMR spectrum indicated a mixture of **15a** (25% NMR) and **15b** (60% NMR) and 15% other regioisomers.

Octyl 3-*O*-benzoyl-6-*O*-benzyl-α-D-mannopyranosyl-(1→4)-3-*O*-benzoyl-6-*O*-benzyl-α-D-mannopyranoside (**15a**): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.23–6.99 (m, 20H, Ar), 5.49 (dd, *J* = 9.6, 3.0 Hz, 1H, H-3), 5.23 (dd, *J* = 9.8, 3.2 Hz, 1H, H-3′), 5.22 (d, *J* = 1.4 Hz, 1H, H-1′), 4.87 (d, *J* = 1.9 Hz, 1H, H-1), 4.61–4.49 (m, 4H, 4 × OC*H*$_2$Ph), 4.38 (app t, *J* = 9.5 Hz, 1H, H-4), 4.20–4.18 (m, 1H, H-2), 4.10 (app td, *J* = 9.6, 4.3 Hz, 1H, H-4′), 4.01–3.71 (m, 6H, H-2′, H-5, H-5′, H-6a, H-6b, octyl OCH_2), 3.69 (dd, *J* = 10.2, 3.6 Hz, 1H, H-6a′), 3.61 (dd, *J* = 10.2, 4.2 Hz, 1H, H-6b′), 3.50–3.43 (m, 1H, octyl OCH_2), 2.71 (d, *J* = 4.3 Hz, 1H, OH-4′), 2.09 (d, *J* = 6.6 Hz, 1H, OH-2), 1.89 (d, *J* = 5.2 Hz, 1H, OH-2′), 1.78–1.58 (m, 2H, octyl OCH_2CH_2), 1.55–1.18 (m, 10H, octyl CH_2), 0.90 (t, *J* = 7.1 Hz, 3H, octyl CH_3); HRMS (ESI) calcd $C_{48}H_{58}O_{13}$ $[M+Na]^+$ 865.3770, found 865.3776.

Octyl 3-*O*-benzoyl-6-*O*-benzyl-α-D-mannopyranosyl-(1→4)-2-*O*-benzoyl-6-*O*-benzyl-α-D-mannopyranoside (**15b**): ^{1}H NMR (600 MHz, CD_3OD) δ 8.23–6.99 (m, 20H, Ar), 5.38 (d, *J* = 2.0 Hz, 1H, H-1′), 5.28 (dd, *J* = 9.7, 3.2 Hz, 1H, H-3′), 5.22 (dd, *J* = 2.8, 1.8 Hz, 1H, H-2), 4.87 (d, *J* = 1.8 Hz, 1H, H-1), 4.61–4.49 (m, 4H, 4 × OC*H*$_2$Ph), 4.25 (dd, *J* = 3.1, 2.0 Hz, 1H, H-2′),

4.23–4.19 (m, 1H, H-3), 4.07 (app t, J = 9.9 Hz, 1H, H-4′), 4.01–3.92 (m, 3H, H-5, H-5′, H-6), 3.90–3.83 (m, 2H, H-4, H-6), 3.79–3.67 (m, 3H, 2 × H-6, octyl OCH_2), 3.49 (app dt, J = 9.7, 6.4 Hz, 1H, octyl OCH_2), 1.78–1.58 (m, 2H, octyl OCH_2CH_2), 1.55–1.18 (m, 10H, octyl CH_2), 0.90 (t, J = 7.1 Hz, 3H, octyl CH_3); HRMS (ESI) calcd $C_{48}H_{58}O_{13}$ $[M+Na]^+$ 865.3770, found 865.3776.

(((2*R*,3*S*,6*S*)-2-((benzyloxy)methyl)-6-(((2*R*,3*S*,6*S*)-2-((benzyloxy)methyl)-6-(octyloxy)-3,6-dihydro-2*H*-pyran-3-yl)oxy)-3,6-dihydro-2*H*-pyran-3-yl)oxy)(tert-butyl)dimethylsilane (**20**): To a solution of alcohol **10** (302.3 mg, 0.53 mmol) in CH_2Cl_2 (6 mL) at −10 °C was added 2,6-lutidine (280 μL, 2.40 mmol) followed by TBSOTf (380 μL, 1.60 mmol). The resulting solution was stirred for 0.5 h before being concentrated. The crude product was purified by chromatography (hexane–EtOAc 12:1) to afford trisaccharide **20** (360.4 mg, 99%) as a colorless syrup. R_f 0.65 (hexane–EtOAc 3:1); $[\alpha]_D$ = +58.8 (*c* 1.1, $CHCl_3$); ^{1}H NMR (498 MHz, $CDCl_3$) δ 7.36–7.20 (m, 10H, Ar), 6.02 (d, J = 10.3 Hz, 1H, H-3), 5.87 (d, J = 10.2 Hz, 1H, H-3′), 5.81 (ddd, J = 10.3, 2.6, 1.9 Hz, 1H, H-2), 5.60 (ddd, J = 10.2, 2.7, 2.1 Hz, 1H, H-2′), 5.21 (d, J = 2.8 Hz, 1H, H-1′), 5.01 (d, J = 2.0 Hz, 1H, H-1), 4.58 (d, J = 12.2 Hz, 1H, OCH_2Ph), 4.53 (d, J = 12.2 Hz, 1H, OCH_2Ph), 4.47 (s, 2H, OCH_2Ph), 4.38 (dd, J = 9.5, 1.2 Hz, 1H, H-4), 4.34 (dd, J = 9.1, 1.4 Hz, 1H, H-4′), 4.02 (ddd, J = 9.0, 6.0, 1.7 Hz, 1H, H-5), 3.84–3.73 (m, 2H, H-6a, octyl OCH_2), 3.71–3.62 (m, 2H, H-5′, H-6b), 3.55 (dd, J = 10.5, 3.7 Hz, 1H, H-6a′), 3.51–3.44 (m, 2H, H-6b′, octyl OCH_2), 1.68–1.52 (m, 2H, octyl OCH_2CH_2), 1.38–1.18 (m, 10H, octyl CH_2), 0.97–0.81 (m, 12H, octyl CH_3, TBS(*t*-Bu)), 0.08 (s, 3H, TBS(Me)), 0.02 (s, 3H, TBS(Me)); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 138.1 (2C, Ar), 134.8 (C-3′), 129.4 (C-3), 128.3 (2C, Ar), 128.2 (2C, Ar), 127.7 (2C, Ar), 127.5 (Ar), 127.4 (2C, Ar), 127.3 (Ar), 127.2 (C-2), 125.1 (C-2′), 94.2 (C-1), 91.6 (C-1′), 73.5, 73.2 (2C, 2 × OCH_2Ph), 71.6 (C-5′), 69.9 (C-6), 69.1 (C-5), 68.6, 68.6 (2C, C-

6′, octyl OCH_2), 67.5 (C-4), 63.8 (C-4′), 31.8, 29.8, 29.4, 29.3, 26.3 (5C, octyl CH_2), 25.7 (TBS(*t*-Bu), 22.7 (octyl CH_2), 17.9 (TBS(*t*-Bu)), 14.1 (octyl CH_3), –4.2, –4.9 (2C, 2 × TBS(Me)); HRMS (ESI) calcd $C_{40}H_{60}O_7Si$ $[M+Na]^+$ 703.4001, found 703.3994.

Octyl 6-*O*-benzyl-4-*O*-*t*-butyldimethylsilyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-α-D-mannopyranoside (**21**): The dihydroxylation reaction was performed as described for the synthesis of **12**, with **20** (588.6 mg, 0.86 mmol), OsO_4 (2.5 wt.% in *t*-butanol, 213 μL, 0.017 mmol), NMO (50% w/v in water, 1.3 mL) in *t*-butanol and acetone (9 mL, v/v 1:1). The crude residue was purified by chromatography (CH_2Cl_2–methanol 30:1) to afford **21** (68.4 mg, 91%) as a colorless syrup. R_f 0.49 (CH_2Cl_2–methanol 15:1); $[\alpha]_D$ = +58.7 (*c* 0.7, $CHCl_3$); ^{1}H NMR (500 MHz, CD_3OD) δ 7.33–7.22 (m, 10H, Ar), 5.24 (d, *J* = 1.9 Hz, 1H, H-1′), 4.71 (d, *J* = 1.5 Hz, 1H, H-1), 4.57–4.41 (m, 4H, 4 × OC*H*$_2$Ph), 3.89 (dd, *J* = 3.1, 2.2 Hz, 1H, H-2), 3.84–3.77 (m, 3H, H-4, H-6a, H-6b), 3.77–3.67 (m, 6H, H-2′, H-3, H-4′, H-5, H-5′, octyl OCH_2), 3.60 (dd, *J* = 8.5, 3.3 Hz, 1H, H-3′), 3.59–3.55 (m, 2H, H-6a′, H-6b′), 3.40 (dt, *J* = 9.6, 6.3 Hz, 1H, octyl OCH_2), 1.65–1.52 (m, 2H, octyl OCH_2C*H*$_2$), 1.41–1.23 (m, 10H, octyl CH_2), 0.89 (t, *J* = 6.9 Hz, 3H, octyl CH_3), 0.86 (s, 9H, TBS(*t*-Bu)), 0.14 (s, 3H, TBS(Me)), 0.05 (s, 3H, TBS(Me)); ^{13}C NMR (126 MHz, CD_3OD) δ 139.7 (Ar), 139.5 (Ar), 129.4 (2C, Ar), 129.4 (2C, Ar), 129.2 (2C, Ar), 128.8 (2C, Ar), 128.7 (Ar), 128.6 (Ar), 103.1 (C-1′, $^1J_{C\text{-}1,H\text{-}1}$ = 171.7 Hz), 101.5 (C-1, $^1J_{C\text{-}1,H\text{-}1}$ = 167.3 Hz), 76.1 (C-4), 74.6 (C-5′), 74.5, 74.4 (2C, 2 × O*C*H$_2$Ph), 73.3 (C-4′), 72.9, 72.7, 72.7, 72.1 (4C, C-2, C-2′, C-3, C-5), 71.4 (C-6), 71.0 (C-6′), 70.5 (C-3′), 68.9 (octyl OCH_2), 33.0, 30.6, 30.4, 30.4, 27.4 (5C, octyl CH_2), 26.7 (TBS(*t*-Bu)), 23.7 (octyl CH_2), 19.2 (TBS(*t*-Bu)), 14.5 (octyl CH_3), –3.4, –4.7 (2C, 2 × TBS(Me)); HRMS (ESI) calcd $C_{40}H_{64}O_{11}Si$ $[M+Na]^+$ 771.4110, found 771.4106.

General procedures for reactions in Table 2: To a solution of **21** (1 equiv., 0.1 M) in the indicated solvent (0.1 M) was added catalyst (20 mol%) and base (4 equiv. for entry 1–4, 10 equiv. for entry 5–6) followed by BzCl (2.4–10 equiv.). The resulting mixture was stirred at room temperature for 3 h before concentrated. The crude products **21a**, **21c** and **21d** were purified by chromatography as indicated below.

Octyl 2-*O*-benzoyl-6-*O*-benzyl-4-*O*-*t*-butyldimethylsilyl-α-D-mannopyranosyl-(1→4)-2-*O*-benzoyl-6-*O*-benzyl-α-D-mannopyranoside (**21a**): The reaction was performed as the general procedure described above. Chromatographic purification (hexane–EtOAc 7:1) gave **21a** as a colorless film. R_f 0.66 (toluene–EtOAc 5:1); $[\alpha]_D$ = +13.9 (*c* 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (dd, *J* = 8.4, 1.3 Hz, 2H, Ar), 8.01 (dd, *J* = 8.4, 1.3 Hz, 2H, Ar), 7.60–7.52 (m, 2H, Ar), 7.44–7.26 (m, 14H, Ar), 5.49 (d, *J* = 1.8 Hz, 1H, H-1′), 5.36 (dd, *J* = 3.4, 1.8 Hz, 2H, H-2, H-2′), 4.97 (d, *J* = 1.8 Hz, 1H, H-1), 4.73–4.54 (m, 4H, 4 × OC*H*$_2$Ph), 4.42 (dd, *J* = 9.6, 3.5 Hz, 1H, H-3), 4.27 (app t, *J* = 9.6 Hz, 1H, H-4), 4.12–4.03 (m, 1H, H-3′), 4.01–3.90 (m, 4H, H-4′, H-5, H-5′, H-6a), 3.88 (dd, *J* = 10.4, 1.5 Hz, 1H, H-6b), 3.76 (dt, *J* = 9.6, 6.8 Hz, 1H, octyl OCH_2), 3.67 (dd, *J* = 10.3, 1.0 Hz, 1H, H-6a′), 3.63 (dd, *J* = 10.3, 5.1 Hz, 1H, H-6b′), 3.49 (dt, *J* = 9.6, 6.6 Hz, 1H, octyl OCH_2), 1.68–1.57 (m, 2H, octyl OCH_2CH_2), 1.44–1.22 (m, 10H, octyl CH_2), 0.91 (t, *J* = 7.0 Hz, 3H, octyl CH_3), 0.87 (s, 9H, TBS(*t*-Bu)), 0.13 (s, 3H, TBS(Me)), 0.05 (s, 3H, TBS(Me)); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.3 (C=O), 66.2 (C=O), 138.6 (Ar), 138.1 (Ar), 133.3 (Ar), 133.2 (Ar), 129.9 (2C, Ar), 129.8 (2C, Ar), 129.7 (Ar), 129.6 (Ar), 128.5 (2C, Ar), 128.4 (2C, Ar), 128.3 (2C, Ar), 128.3 (2C, Ar), 127.5 (3C, Ar), 127.4 (3C, Ar), 97.3 (C-1), 96.9 (C-1′), 75.2 (C-4), 73.5, 73.5 (2C, C-2, C-2′), 73.4, 73.3 (2C, 2 × O*C*H$_2$Ph), 73.2 (C-5′), 70.8 (C-3′), 69.9, 69.6 (2C, C-4′, C-5), 69.5 (C-6), 69.3 (C-6′), 69.2 (C-3), 68.3 (octyl OCH_2), 31.8, 29.4, 29.4, 29.2, 26.2 (5C, octyl CH_2), 25.9 (TBS(*t*-Bu)), 22.7 (octyl CH_2), 18.3 (TBS(Me)), 14.1

(octyl CH_3), –4.0, –4.9 (2C, 2 × TBS(Me)); HRMS (ESI) calcd $C_{54}H_{72}O_{13}Si$ $[M+Na]^+$ 979.4634, found 979.4628.

Octyl 3-*O*-benzoyl-6-*O*-benzyl-4-*O*-*t*-butyldimethylsilyl-α-D-mannopyranosyl-(1→4)-2-*O*-benzoyl-6-*O*-benzyl-α-D-mannopyranoside (**21c**): The reaction was performed as the general procedure described above. Chromatographic purification (hexane–EtOAc 2:1) gave **21c** as a colorless film. R_f 0.14 (toluene–EtOAc 5:1); $[\alpha]_D$ = +17.2 (*c* 0.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15–7.97 (m, 4H, Ar), 7.62–7.17 (m, 16H, Ar), 5.37 (dd, *J* = 8.0, 3.0 Hz, 1H, H-3′), 5.35 (dd, *J* = 3.4, 1.8 Hz, 1H, H-2), 5.32 (d, *J* = 2.7 Hz, 1H, H-1′), 4.97 (d, *J* = 1.7 Hz, 1H, H-1), 4.70–4.49 (m, 4H, 4 × OC*H*$_2$Ph), 4.40 (dd, *J* = 9.5, 3.4 Hz, 1H, H-3), 4.24–4.14 (m, 3H, H-2′, H-4, H-4′), 4.02–3.92 (m, 3H, H-5, H-5′, H-6a), 3.91–3.85 (m, 1H, H-6b), 3.76 (dt, *J* = 9.6, 6.7 Hz, 1H, octyl OCH_2), 3.59 (d, *J* = 3.7 Hz, 2H, H-6a′, H-6b′), 3.48 (dt, *J* = 9.6, 6.7 Hz, 1H, octyl OCH_2), 1.74–1.57 (m, 2H, octyl OCH_2CH_2), 1.47–1.23 (m, 10H, octyl CH_2), 0.92 (t, *J* = 6.9 Hz, 3H, octyl CH_3), 0.76 (s, 9H, TBS(*t*-Bu)), –0.01 (s, 3H, TBS(Me)), –0.05 (s, 3H, TBS(Me); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.3 (C=O), 166.0 (C=O), 138.6 (Ar), 137.9 (Ar), 133.2 (2C, Ar), 130.0 (Ar), 129.9 (2C, Ar), 129.9 (2C, Ar), 129.7 (Ar), 128.4 (2C, Ar), 128.4 (2C, Ar), 128.4 (2C, Ar), 128.3 (2C, Ar), 127.7 (2C, Ar), 127.6 (Ar), 127.3 (3C, Ar), 100.5 (C-1′), 97.4 (C-1), 75.9 (C-4), 75.4 (C-3′), 73.7 (C-5′), 73.4 (O*C*H$_2$Ph), 73.4 (C-2), 73.3 (O*C*H$_2$Ph), 70.3 (C-5), 69.8, 69.7 (2C, C-3, C-4′), 69.6 (C-6), 69.1 (C-6′), 68.3 (octyl OCH_2), 66.6 (C-2′), 31.9, 29.5, 29.4, 29.3, 26.2 (5C, octyl CH_2), 25.7 (TBS(*t*-Bu)), 22.7 (octyl CH_2), 18.0 (TBS(*t*-Bu)), 14.1 (octyl CH_3), –4.2, –4.9 (2C, 2 × TBS(Me)); HRMS (ESI) calcd $C_{54}H_{72}O_{13}Si$ $[M+Na]^+$ 979.4634, found 979.4629.

Octyl 2-*O*-benzoyl-6-*O*-benzyl-4-*O*-*t*-butyldimethylsilyl-α-D-mannopyranosyl-(1→4)-3-*O*-benzoyl-6-*O*-benzyl-α-D-mannopyranoside (**21d**): The reaction was performed as the general procedure described above. Chromatographic purification (hexane–EtOAc 4:1) gave **21d** as a colorless film. R_f 0.43 (toluene–EtOAc 5:1); $[\alpha]_D$ = +42.9 (*c* 0.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (dd, *J* = 8.4, 1.3 Hz, 2H, Ar), 7.81 (dd, *J* = 8.4, 1.3 Hz, 2H, Ar), 7.60–7.22 (m, 16H, Ar), 5.53 (dd, *J* = 9.6, 3.2 Hz, 1H, H-3), 5.25 (d, *J* = 1.8 Hz, 1H, H-1′), 5.14 (dd, *J* = 3.1, 2.0 Hz, 1H, H-2′), 4.89 (d, *J* = 1.8 Hz, 1H, H-1), 4.70–4.53 (m, 4H, 4 × OC*H*$_2$Ph), 4.36 (app t, *J* = 9.6 Hz, 1H, H-4), 4.21 (dd, *J* = 3.1, 2.0 Hz, 1H, H-2), 4.02–3.95 (m, 2H, H-4′, H-5), 3.94–3.89 (m, 2H, H-3′, H-6a), 3.85 (dd, *J* = 10.8, 1.8 Hz, 1H, H-6b), 3.83–3.74 (m, 2H, H-5′, octyl OCH_2), 3.73 (dd, *J* = 10.7, 4.5 Hz, 1H, H-6a′), 3.62 (dd, *J* = 10.6, 1.7 Hz, 1H, H-6b′), 3.49 (dt, *J* = 9.6, 6.7 Hz, 1H, octyl OCH_2), 1.72–1.60 (m, 2H, octyl $OCH_2C\mathit{H}_2$), 1.49–1.24 (m, 10H, octyl CH_2), 0.92 (t, *J* = 6.8 Hz, 3H, octyl CH_3), 0.87 (s, 9H, TBS(*t*-Bu)), 0.07 (s, 3H, TBS(Me)), 0.03 (s, 3H, TBS(Me)); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.6 (C=O), 165.6 (C=O), 138.6 (Ar), 138.3 (Ar), 133.3 (Ar), 133.1 (Ar), 129.8 (2C, Ar), 129.7 (2C, Ar), 129.5 (Ar), 129.4 (Ar), 128.5 (Ar), 128.4 (2C, Ar), 128.30 (2C, Ar), 128.28 (2C, Ar), 128.2 (2C, Ar), 127.6 (2C, Ar), 127.4 (Ar), 127.3 (2C, Ar), 99.5 (C-1), 99.4 (C-1′), 74.9 (C-3), 73.9 (C-5′), 73.5 (O*C*H$_2$Ph), 73.4 (C-4), 73.3 (O*C*H$_2$Ph), 73.0 (C-2′), 70.9, 70.6, 69.6 (3C, C-3′, C-4′, C-5), 69.3 (C-6), 69.2 (C-6′), 69.0 (C-2), 68.3 (octyl OCH_2), 31.9, 29.4, 29.4, 29.3, 26.2 (5C, octyl CH_2), 26.0 (TBS(*t*-Bu)), 22.7 (octyl CH_2), 18.3 (TBS(*t*-Bu)), 14.1 (octyl CH_3), –4.1, –5.0 (2C, 2 × TBS(Me)); HRMS (ESI) calcd $C_{54}H_{72}O_{13}Si$ $[M+Na]^+$ 979.4634, found 979.4628.

Octyl 6-*O*-benzyl-4-*O*-*t*-butyldimethylsilyl-2-*O*-pivaloyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-2-*O*-pivaloyl-α-D-mannopyranoside (22a): The reaction was performed as the general procedure for Table 2 described above. The amounts for each reagent was listed in Table 4. The

reaction mixture were concentrated and examined by crude ^{1}H NMR. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34–7.23 (m, 10H, Ar), 5.27 (d, *J* = 1.8 Hz, 1H, H-1′), 5.04 (dd, *J* = 3.2, 1.7 Hz, 1H, H-2′), 4.98 (dd, *J* = 3.7, 1.8 Hz, 1H, H-2), 4.78 (d, *J* = 2.0 Hz, 1H, H-1), 4.62–4.44 (m, 4H, 4 × OCH_2Ph), 4.22 (dd, *J* = 9.5, 3.5 Hz, 1H, H-3), 4.06 (dd, *J* = 9.5, 3.2 Hz, 1H, H-3′), 4.00–3.35 (m, 10H, H-4, H-4′, H-5, H-5′, 4 × H-6, 2 × octyl OCH_2), 1.72–1.60 (m, 2H, octyl OCH_2CH_2), 1.35–1.24 (m, 10H, octyl CH_2), 0.87 (t, *J* = 6.8 Hz, 3H, octyl CH_3), 1.26 (s, 9H, Piv), 0.83 (s, 9H, TBS(*t*-Bu)), 0.09 (s, 3H, TBS(Me)), 0.00 (s, 3H, TBS(Me).

Synthesis of Octyl 6-*O*-benzyl-4-*O*-*t*-butyldimethylsilyl-2-*O*-toluenesulfonyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-2-*O*-toluenesulfonyl-α-D-mannopyranoside (23a) and Octyl 6-*O*-benzyl-4-*O*-*t*-butyldimethylsilyl-2-*O*-toluenesulfonyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-3-*O*-toluenesulfonyl-α-D-mannopyranoside (23d): To a solution of **23** (50.5 mg, 0.067 mmol) in THF (0.7 mL) was added *n*-Bu_2SnCl_2 (20 mol%, 4.2 mg, 0.0013 mmol) and DIPEA (240 μL, 1.34 mmol) followed by TsCl (190.7 mg, 0.013 mmol). The reaction mixture was stirred at room temperature for 24 h before concentrated. The crude products **23a** and **23d** were purified by chromatography as described below.

Octyl 6-*O*-benzyl-4-*O*-*t*-butyldimethylsilyl-2-*O*-toluenesulfonyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-2-*O*-toluenesulfonyl-α-D-mannopyranoside (23a): Chromatographic purification (hexane–EtOAc 5:1) to give **23a** (47.7 mg, 67%) as a colorless syrup. R_f 0.66 (CH_2Cl_2–methanol 30:1); $[\alpha]_D$ = +27.2 (*c* 0.9, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.3 Hz, 2H, Ar), 7.77 (d, *J* = 8.3 Hz, 2H, Ar), 7.35–7.22 (m, 14H, Ar), 5.09 (d, *J* = 1.8 Hz, 1H, H-1′), 4.80 (d, *J* = 1.7 Hz, 1H, H-1), 4.68 (dd, *J* = 3.1, 2.0 Hz, 1H, C-2′), 4.65 (dd, *J* = 3.4, 1.8 Hz, 1H, H-2), 4.53–4.40 (m, 4H, 4 × OC*H*$_2$Ph), 4.02 (dd, *J* = 8.8, 3.2 Hz, 1H, H-3), 3.78–3.73 (m,

2H, H-3′, H-5′), 3.72–3.65 (m, 3H, H-4, H-5, H-6a), 3.65–3.58 (m, 3H, H-4′, H-6b, octyl OCH_2), 3.56 (dd, J = 10.3, 1.7 Hz, 1H, H-6a′), 3.44 (dd, J = 10.3, 6.8 Hz, 1H, H-6b′), 3.36 (dt, J = 9.6, 6.6 Hz, 1H, octyl OCH_2), 2.43 (s, 3H, ArCH_3), 2.40 (s, 3H, ArCH_3), 1.58–1.48 (m, 2H, octyl OCH_2CH_2), 1.33–1.22 (m, 10H, octyl CH_2), 0.89 (t, J = 7.1 Hz, 3H, octyl CH_3), 0.79 (s, 9H, TBS(*t*-Bu)), 0.06 (s, 3H, TBS(Me)), –0.04 (s, 3H, TBS(Me)); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.3, 145.1, 138.4, 137.8, 133.2, 133.0, 129.9, 129.8, 128.3, 128.2, 128.1, 127.6, 127.5, 127.4 (24C, Ar), 97.4 (C-1′), 97.1 (C-1), 79.4 (C-2′), 79.2 (C-2), 75.8 (C-4), 73.3 (2C, C-5′, OCH_2Ph), 73.2 (OCH_2Ph), 70.0, 69.9 (2C, C-3′, C-5), 69.4 (C-4′), 69.3 (C-6), 69.1 (C-6′), 68.5 (C-3), 68.2 (octyl OCH_2), 31.8, 29.3, 29.2, 29.2, 26.0 (5C, octyl CH_2), 25.8 (TBS(*t*-Bu)), 22.6 (octyl CH_2), 21.7 (ArCH_3), 21.6 (ArCH_3), 18.1 (TBS(*t*-Bu)), 14.1 (octyl CH_3), –4.0, –5.0 (2C, TBS(Me)); HRMS (ESI) calcd $C_{54}H_{76}O_{15}S_2Si$ $[M+Na]^+$ 1079.4287, found 1079.4294.

Octyl 6-*O*-benzyl-4-*O*-*t*-butyldimethylsilyl-2-*O*-toluenesulfonyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-3-*O*-toluenesulfonyl-α-D-mannopyranoside (**23d**): Chromatographic purification to give **23d** as a colorless syrup. R_f 0.37 (CH_2Cl_2–methanol 30:1); $[\alpha]_D$ = +27.5 (*c* 1.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, J = 8.2 Hz, 2H, Ar), 7.76 (d, J = 8.2 Hz, 2H, Ar), 7.42 (d, J = 8.2 Hz, 2H, Ar), 7.39–7.23 (m, 12H, Ar), 7.20 (d, J = 8.1 Hz, 2H, Ar), 4.76 (d, J = 1.7 Hz, 1H, H-1), 4.72 (dd, J = 9.5, 3.1 Hz, 1H, H-3), 4.64 (dd, J = 3.3, 1.7 Hz, 1H, H-2′), 4.61 (d, J = 1.4 Hz, 1H, H-1′), 4.56–4.36 (m, 4H, 4 × OCH_2Ph), 4.04 (br s, 1H, H-2), 3.90 (dd, J = 11.0, 3.6 Hz, 1H, H-6a), 3.76 (t, J = 9.6 Hz, 1H, H-4), 3.73–3.53 (m, 8H, H-3′, H-4′, H-5, H-5′, H-6b, H-6a′, H-6b′, octyl OCH_2), 3.38 (dt, J = 9.6, 6.8 Hz, 1H, octyl OCH_2), 2.48 (s, 3H, ArCH_3), 2.39 (s, 3H, ArCH_3), 2.17 (br d, J = 5.0 Hz, 1H, OH-2), 1.91 (d, J = 6.8 Hz, 1H, OH-3′), 1.64–1.53 (m, 2H, octyl OCH_2CH_2), 1.40–1.24 (m, 10H, octyl CH_2), 0.92 (t, J = 6.7 Hz, 3H, octyl CH_3), 0.86 (s, 9H, TBS(*t*-Bu)), 0.12 (s, 3H, TBS(Me)), 0.03 (s, 3H, TBS(Me)); ^{13}C NMR (126

MHz, $CDCl_3$) δ 145.5, 145.1, 138.3, 138.2, 133.3, 132.8, 130.3, 129.9 (8C, Ar), 128.3 (3C, Ar), 128.3 (3C, Ar), 128.2 (2C, Ar), 128.0 (2C, Ar), 127.9 (2C, Ar), 127.6 (2C, Ar), 127.6 (Ar), 127.5 (Ar), 100.6 (C-1′), 99.2 (C-1), 81.0 (C-3), 79.1 (C-2′), 75.2 (C-4), 73.9 (C-5′), 73.3, 73.2 (2C, 2 × O*C*H_2Ph), 71.2 (C-5), 69.6 (C-6′), 69.6, 69.5, 69.2 (3C, C-2, C-3′, C-4′), 68.6 (C-6), 68.2 (octyl OCH_2), 31.8, 29.4, 29.3, 29.3, 26.1 (5C, octyl CH_2), 26.0 (TBS(*t*-Bu)), 22.7 (octyl CH_2), 21.8, 21.6 (2C, 2 × Ar*C*H_3), 18.3 (TBS(*t*-Bu)), 14.1 (octyl CH_3), –3.9, –5.0 (2C, 2 × TBS(Me)); HRMS (ESI) calcd $C_{54}H_{76}O_{15}S_2Si$ $[M+Na]^+$ 1079.4287, found 1079.4291.

Octyl 6-*O*-benzyl-4-*O*-triphenylmethyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-α-D-mannopyranoside (**24**): TrOTf was prepared *in situ* by adding a CH_2Cl_2 solution of TMSOTf (10% v/v, 1 mL, 0.53 mmol) into stirring ice-cold TfOH (137 mg, 0.53 mmol) in CH_2Cl_2 (4 mL). The bright yellow solution of TrOTf was formed after stirring at 0 °C for 5 min. This fresh-made TrOTf solution was slowly added into a stirring ice-cold solution of alcohol **10** (107 mg, 0.19 mmol) and 2,4,6-collidine (0.11 mL, 0.79 mmol) in CH_2Cl_2 (2 mL) over 0.5 h. Methanol (0.5 mL) was then added and then the reaction mixture was concentrated, and the crude residue was purified by chromatography (hexane–EtOAc 8:1) to afford the expected trityl ether (150.4 mg, 98%) as a colorless syrup. R_f 0.69 (hexane–EtOAc 3:1); $[\alpha]_D$ = +96.8 (*c* 0.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55–7.10 (m, 25H, Ar), 6.01 (d, *J* = 10.3 Hz, 1H, H-3), 5.83 (ddd, *J* = 10.3, 2.7, 1.8 Hz, 1H, H-2), 5.75 (d, *J* = 10.5 Hz, 1H, H-3′), 5.44 (ddd, *J* = 10.5, 2.7, 1.9 Hz, 1H, H-2′), 5.10 (d, *J* = 2.3 Hz, 1H, H-1′), 5.04 (d, *J* = 2.3 Hz, 1H, H-1), 4.69 (d, *J* = 12.2 Hz, 1H, OC*H*$_2$Ph), 4.61 (d, *J* = 12.2 Hz, 1H, OC*H*$_2$Ph), 4.38 (ddd, *J* = 9.5, 2.9, 1.6 Hz, 1H, H-4), 4.34 (s, 2H, OC*H*$_2$Ph), 4.16–4.08 (m, 2H, H-5, H-5′), 3.93–3.88 (m, 2H, H-4′, H-6a), 3.86 (dt, *J* = 9.5, 6.9 Hz, 1H, octyl OCH_2), 3.77 (dd, *J* = 10.9, 6.4 Hz, 1H, H-6b), 3.58–3.47 (m, 3H, H-6a, H-6b, octyl OCH_2), 1.73–1.56 (m, 2H, octyl OCH_2CH_2), 1.45–1.19 (m, 10H, octyl CH_2), 0.92 (t, *J* = 7.0 Hz,

3H, octyl CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.8 (3C, Ar), 138.6 (Ar), 138.2 (Ar), 133.0 (C-3′), 129.5 (C-3), 129.0 (6C, Ar), 128.3 (2C, Ar), 128.2 (2C, Ar), 127.7 (6C, Ar), 127.6 (2C, Ar), 127.5 (2C, Ar), 127.4 (Ar), 127.4 (Ar), 127.2 (C-2), 127.2 (3C, Ar), 124.7 (C-2′), 94.2 (C-1), 91.8 (C-1′), 86.7 (Ph_3C), 73.4, 73.2 (2C, 2 × OCH_2Ph), 70.5 (C-5′), 70.0, 69.3 (2C, C-6, C-6′), 69.2 (C-5), 68.7 (octyl OCH_2), 67.9 (C-4), 66.1 (C-4′), 31.9, 29.9, 29.5, 29.3, 26.3, 22.7 (6C, octyl CH_2), 14.2 (octyl CH_3); HRMS (ESI) calcd $C_{53}H_{60}O_7$ $[M+Na]^+$ 831.4231, found 831.4223. The dihydroxylation of the trityl ether (165.3 mg, 0.20 mmol) was carried out with OsO_4 (2.5 wt.% in *t*-butanol, 40 μL, 0.004 mmol) and NMO (50% w/v in water, 0.3 mL) in *t*-butanol and acetone (2 mL, v/v 1:1). After stirring at room temperature overnight, the resulting saturated aqueous Na_2SO_3 solution was added. The mixture was concentrated to remove *t*-butanol and then the residue was extracted with CH_2Cl_2 three times. The combined organic layer was concentrated and the residue was purifed by chromatography (CH_2Cl_2–methanol 30:1) to afford **24** (187.3 mg, 92%) as a white foam. R_f 0.26 (CH_2Cl_2–methanol 20:1); $[\alpha]_D$ = +33.5 (*c* 0.6, methanol); ^1H NMR (600 MHz, $CDCl_3$) δ 7.43–7.14 (m, 25H, Ar), 4.96 (d, *J* = 4.8 Hz, 1H, H-1′), 4.83 (d, *J* = 1.4 Hz, 1H, H-1), 4.63–4.58 (m, 2H, OC*H*$_2$Ph), 4.37 (d, *J* = 4.8 Hz, 1H, OH-3), 4.33 (d, *J* = 12.0 Hz, 1H, OC*H*$_2$Ph), 4.27 (d, *J* = 12.0 Hz, 1H, OC*H*$_2$Ph), 4.11–4.03 (m, 1H, H-3), 3.95 (app t, *J* = 9.8 Hz, 1H, H-4), 3.92–3.88 (m, 2H, H-5′, H-2), 3.88–3.83 (m, 3H, H-5, H-2′, H-3′), 3.81–3.77 (m, 2H, H-6a, H-6b), 3.69 (dt, *J* = 9.6, 6.8 Hz, 1H, octyl OCH_2), 3.50 (app t, *J* = 5.1 Hz, 1H, H-4′), 3.41 (dt, *J* = 9.6, 6.6 Hz, 1H, octyl OCH_2), 3.36 (dd, *J* = 10.3, 2.8 Hz, 1H, H-6a′), 3.16 (s, 1H, OH-3′), 3.06 (dd, *J* = 10.3, 7.5 Hz, 1H, H-6b′), 2.66 (d, *J* = 2.6 Hz, 1H, OH-2), 2.51 (d, *J* = 3.7 Hz, 1H, OH-2′), 1.59–1.53 (m, 2H, octyl OCH_2CH_2), 1.37–1.22 (m, 10H, octyl CH_2), 0.89 (t, *J* = 7.1 Hz, 3H, octyl CH_3); ^{13}C NMR (126 MHz, CD_3OD) δ 146.0 (3C, Ar), 139.9 (Ar), 139.5 (Ar), 130.3 (3C, Ar), 129.4 (Ar), 129.3 (Ar), 128.87 (3C, Ar), 128.86 (3C, Ar), 128.6 (Ar), 128.5 (Ar), 128.4

(2C, Ar), 101.48, 101.47 (2C, C-1′, $^{1}J_{C\text{-}1,H\text{-}1}$ = 169.0 Hz; C-1, $^{1}J_{C\text{-}1,H\text{-}1}$ = 167.6 Hz), 89.0 (Ph_3C), 77.5 (C-4), 76.2 (C-5′), 74.4 (OCH_2Ph), 73.9 (OCH_2Ph), 73.6, 72.9, 72.4, 72.3, 72.2 (5C, C-2, C-3, C-3′, C-4′, C-5), 72.0 (C-2′), 71.3 (C-6), 70.5 (C-6′), 68.7 (octyl OCH_2), 33.0, 30.6, 30.5, 30.4, 27.4, 23.8 (6C, octyl CH_2), 14.5 (octyl CH_3); HRMS (ESI) calcd $C_{53}H_{64}O_{11}$ $[M+Na]^+$ 899.4341, found 899.4334.

Octyl 6-*O*-benzyl-2-*O*-toluenesulfonyl-4-*O*-triphenylmethyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-2-*O*-toluenesulfonyl-α-D-mannopyranoside (**25a**): To a solution of **24** (36.5 mg, 0.04 mmol) in THF (0.4 mL) was added *n*-Bu_2SnCl_2 (20 mol%, 2.5 mg, 0.008 mmol) and DIPEA (85 μL, 0.48 mmol) followed by TsCl (80.9 mg, 0.42 mmol). The reaction mixture was stirred at room temperature for 24 h before concentrated. The crude product was purified by chromatography (hexane–EtOAc 7:2) to give **25a** (45.0 mg, 91%) as a colorless film. R_f 0.43 (toluene–EtOAc 5:1); ^{1}H NMR (500 MHz, acetone) δ 7.91 (d, *J* = 8.3 Hz, 2H, Ar), 7.87 (d, *J* = 8.3 Hz, 2H, Ar), 7.58–7.24 (m, 29H), 5.32 (d, *J* = 5.4 Hz, 1H, H-1′), 4.92 (d, *J* = 1.7 Hz, 1H, H-1), 4.79 (dd, *J* = 5.4, 2.9 Hz, 1H, H-2′), 4.65 (dd, *J* = 3.5, 1.7 Hz, 1H, H-2), 4.63–4.55 (m, 2H, OCH_2Ph), 4.40–4.33 (m, 2H, OCH_2Ph), 4.10 (dd, *J* = 5.0, 2.9 Hz, 1H, H-3′), 4.02 (dd, *J* = 9.5, 3.4 Hz, 1H, H-3), 3.96 (dd, *J* = 9.8, 6.6 Hz, 1H, H-5′), 3.90 (dd, *J* = 11.0, 1.6 Hz, 1H, H-6a), 3.87–3.79 (m, 2H, H-4, octyl OCH_2), 3.73 (dd, *J* = 10.9, 6.1 Hz, 1H, H-6b), 3.70–3.62 (m, 2H, H-5, H-4′), 3.55 (dt, *J* = 9.8, 6.7 Hz, 1H, octyl OCH_2), 3.41 (dd, *J* = 10.5, 3.0 Hz, 1H, H-6a′), 3.37 (dd, *J* = 10.8, 6.9 Hz, 1H, H-6b′), 2.53 (s, 3H, $ArCH_3$), 2.51 (s, 3H, $ArCH_3$), 1.78–1.67 (m, 2H, octyl OCH_2CH_2), 1.56–1.36 (m, 10H, octyl CH_2), 0.99 (t, *J* = 7.0 Hz, 3H, octyl CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9, 144.9, 144.1, 138.6, 137.6, 133.5, 133.4, 130.0, 129.9, 129.7, 129.6, 129.0, 128.5, 128.4, 128.4, 128.3, 128.2, 128.0, 128.0, 128.0, 127.8, 127.7, 127.7, 127.5, 127.5, 127.4, 127.3.0 (42C, Ar), 97.3 (C-1), 97.0 (C-1′), 88.0 (Ph_3P), 79.4 (C-2), 79.3 (C-2′),

75.3 (C-4), 73.3 (O*C*H$_2$Ph), 73.2 (O*C*H$_2$Ph), 73.1 (C-5′), 71.6 (C-4′), 70.1 (C-5), 69.6 (C-6′), 69.5 (C-6), 69.4 (C-3′), 68.4 (C-3), 68.3 (octyl OCH$_2$), 31.9, 29.4, 29.3, 29.3, 26.1, 22.7 (6C, octyl CH$_2$), 21.7 (Ar*C*H$_3$), 21.7 (Ar*C*H$_3$), 14.2 (octyl CH$_3$). (This compound is not stable in CDCl$_3$. When running the ^{13}C NMR spectrum, a minor byproudct appeared over time, due to decomposition). HRMS (ESI) calcd $C_{67}H_{76}O_{15}S_2$ $[M+Na]^+$ 1207.4518, found 1207.4530.

Octyl 6-*O*-benzyl-4-*O*-triphenylmethyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-α-D-mannopyranoside (**26**): The synthesis was performed as described for **24**. Installation of the trityl group was carried out using **11** (72.5 mg, 0.09 mmol), 2,4,6-collidine (75 μL, 0.56 mmol), TrOH (73.2 mg, 0.28 mmol) and TMSOTf (10% v/v in CH_2Cl_2, 0.5 mL, 0.28 mmol) in CH_2Cl_2 (2 mL). The crude residue was purified by chromatography (hexane–EtOAc 7:1) to afford trityl ether (100 mg, quantitative) as a pale yellow syrup. $[\alpha]_D$ = +78.6 (*c* 0.9, CH_2Cl_2); ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.47–7.10 (m, 30H, Ar), 6.02 (dd, *J* = 10.3, 3.8 Hz, 2H, H-3, H-3′), 5.80 (ddd, *J* = 10.2, 2.8, 1.8 Hz, 1H, H-2), 5.72 (ddd, *J* =10.4, 2.7, 1.9 Hz, 1H, H-2′), 5.71 (d, *J* = 10.3 Hz, 1H, H-3), 5.45 (ddd, *J* = 10.4, 2.6, 1.9 Hz, 1H, H-2″), 5.21 (d, *J* = 2.3 Hz, 1H, H-1′), 5.05 (d, *J* = 2.4 Hz, 1H, H-1″), 4.97 (d, *J* = 2.5 Hz, 1H, H-1), 4.54–4.45 (m, 4H, 4 × OCH$_2$Ph), 4.36–4.30 (m, 2H, H-4, H-4′), 4.27–4.22 (d, *J* = 11.9 Hz, 1H, OCH$_2$Ph), 4.24 (d, *J* = 11.9 Hz, 1H, OCH$_2$Ph), 4.11–4.07 (m, 1H, H-5″), 3.95 (ddd, *J* = 8.5, 6.4, 1.6 Hz, 1H, H-5), 3.88 (ddd, *J* = 7.6, 5.5, 1.6 Hz, 1H, H-5′), 3.84–3.72 (m, 4H, H-4″, H-6a, H-6a′, octyl OCH$_2$), 3.70–3.63 (m, 2H, H-6b, H-6b′), 3.54–3.48 (m, 2H, H-6a″, H-6b″), 3.46 (dt, *J* = 9.5, 6.6 Hz, 1H, octyl OCH$_2$), 1.64–1.48 (m, 2H, octyl OCH$_2$CH$_2$), 1.38–1.21 (m, 10H, octyl CH$_2$), 0.88 (t, *J* = 7.0 Hz, 1H, octyl CH$_3$); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 145.3 (3C; Tr), 139.3, 139.1, 138.8 (3C; Ar), 133.0 (C-3″), 130.5 (C-3′), 129.5 (C-3), 129.3, 128.6, 128.6, 128.5, 128.1, 127.9, 127.9, 127.8, 127.7, 127.7, 127.6 (31C; 30 × Ar, C-2), 127.0 (C-2′), 125.3 (C-2″),

94.5 (C-1), 92.1 (C-1″), 91.7 (C-1′), 87.0 (Tr), 73.7, 73.5, 73.4 (3C; 3 × OCH_2Ph), 71.0 (C-5″), 70.7 (C-6), 70.3 (C-5′), 70.3 (C-6), 69.8 (C-6), 69.6 (C-5), 68.9 (octyl OCH_2), 68.1 (C-4′), 67.8 (C-4), 66.5 (C-4″), 32.2, 30.2, 29.8, 29.7, 26.65, 23.1 (6C; octyl CH_2), 14.3 (octyl CH_3); HRMS (ESI) calcd $C_{66}H_{74}O_{10}$ $[M+Na]^+$ 1049.5174, found 1049.5168. The dihydroxylation of the trityl ether was carried out with OsO_4 (2.5 wt.% in *t*-butanol, 75 μL, 0.006 mmol) and NMO (50% w/v in water, 0.3 mL) in mixed *t*-butanol and acetone (3 mL, v/v 1:1). The crude residue was purified by chromatography (CH_2Cl_2–MeOH 15:1) to afford trisaccharide **26** (79.5 mg, 76%) as a white foam. R_f 0.26 (CH_2Cl_2–methanol 15:1); $[\alpha]_D$ = +63.2 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (500 MHz, CD_3OD) δ 7.46–7.11 (m, 30H, Ar), 5.27 (d, *J* = 1.6 Hz, 1H, H-1′), 5.03 (d, *J* = 5.7 Hz, 1H, H-1″), 4.71 (d, *J* = 1.3 Hz, 1H, H-1), 4.58–4.17 (m, 6H, 6 × OC*H*$_2$Ph), 3.98–3.91 (m, 2H, H-2′, H-2″), 3.91–3.77 (m, 9H, H-3, H-3′, H-3″, H-4, H-4′, H-5, H-5′, H-5″, H-6), 3.76–3.63 (m, 5H, H-2, 3 × H-6, octyl OCH_2), 3.55 (app t, *J* = 4.9 Hz, 1H, H-4″), 3.44–3.37 (m, 2H, H-6a″, octyl OCH_2), 3.30–3.24 (m, 1H, H-6b″), 1.63–1.48 (m, 2H, octyl OCH_2CH_2), 1.43–1.18 (m, 10H, octyl CH_2), 0.90 (t, *J* = 6.9 Hz, 3H, octyl CH_3); ^{13}C NMR (126 MHz, CD_3OD) δ 146.0 (3C, Ar), 139.9, 139.6, 139.5, 130.4, 129.5, 129.4, 129.3, 129.1, 129.0, 128.9, 128.87, 128.7, 128.6, 128.5, 128.4 (33C, Ar), 102.9 (C-1′), 101.7 (C-1″), 101.5 (C-1), 89.1 (Ph_3C), 77.5 (C-4), 76.2, 76.0 (2 × C-5), 74.5, 74.4, 73.9 (3C, 3 × O*C*H_2Ph), 73.6, 73.4, 73.0, 72.8, 72.7, 72.4, 72.3, 72.1, 72.0 (9C, 3 × C-2, 3 × C-3, 2 × C-4, C-5), 71.3 (C-6″), 70.6 (C-6/C-6′), 68.7 (octyl OCH_2), 67.4 (C-6′/C-6), 33.0, 30.6, 30.5, 30.5, 27.4, 23.8 (6C, octyl CH_2), 14.6 (octyl CH_3); HRMS (ESI) calcd $C_{66}H_{80}O_{16}$ $[M+Na]^+$ 1151.5339, found 1151.5333.

Octyl 6-*O*-benzyl-2-*O*-toluenesulfonyl-4-*O*-triphenylmethyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-2-*O*-toluenesulfonyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-2-*O*-toluenesulfonyl-

α-D-mannopyranoside (**26a**): To a solution of **26** (29.3 mg, 0.026 mmol) in THF (0.3 mL) was added *n*-Bu_2SnCl_2 (30 mol%, 2.0 mg, 0.008 mmol) and DIPEA (83 μL, 0.47 mmol) followed by TsCl (75.2 mg, 0.39 mmol). The reaction mixture was stirred at room temperature for 24 h before concentrated. Chromatographic purification (hexane–EtOAc 5:2) gave **26a** (28.3 mg, 69%) as a colorless film. $[\alpha]_D$ = +36.2 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.83–7.62 (m, 6H, Ar), 7.37–7.08 (m, 36H, Ar), 5.13 (d, *J* = 1.7 Hz, 1H, H-1′), 5.09 (d, *J* = 3.9 Hz, 1H, H-1″), 4.75 (d, *J* = 1.7 Hz, 1H, H-1), 4.69 (dd, *J* = 3.8, 3.2 Hz, 1H, H-2″), 4.64–4.60 (m, 2H, H-2, H-2′), 4.55–4.39 (m, 4H, 2 × OCH_2Ph), 4.23 (s, 2H, OCH_2Ph), 4.06 (app dt, *J* = 8.4, 3.4 Hz, 1H, H-3), 3.99–3.91 (m, 2H, H-3′, H-5″), 3.86 (ddd, *J* = 9.9, 6.1, 1.6 Hz, 1H, H-5′), 3.78–3.59 (m, 8H, H-3″, H-4, H-4′, H-5, H-6a, H-6b, H-6a′, octyl OCH_2), 3.56 (dd, *J* = 10.7, 6.2 Hz, 1H, H-6b′), 3.43–3.34 (m, 2H, H-4″, octyl OCH_2), 3.33 (dd, *J* = 10.7, 2.2 Hz, 1H, H-6a″), 3.00 (dd, *J* = 10.4, 6.2 Hz, 1H, H-6b″), 2.96 (d, *J* = 7.2 Hz, 1H, OH-3′), 2.71 (d, *J* = 8.0 Hz, 1H, OH-3), 2.42 (s, 3H, ArCH_3), 2.40 (s, 3H, ArCH_3), 2.40 (s, 3H, ArCH_3), 1.59–1.49 (m, 2H, octyl OCH_2CH_2), 1.35–1.22 (m, 10H, octyl CH_2), 0.89 (t, *J* = 6.9 Hz, 1H, octyl CH_3); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 145.8, 145.8, 145.7, 144.6, 138.9, 138.6, 138.1, 133.7, 133.5, 133.4, 130.3, 130.2, 130.1, 129.3, 128.7, 128.6, 128.4, 128.4, 128.3, 128.2, 128.1, 128.0, 128.0, 128.0, 127.9, 127.8 (54C, Ar), 97.8, 97.6, 97.5 (3C, C-1, C-1′, C-1″), 88.3 (Tr), 80.0, 79.9, 79.8 (3C, C-2, C-2′, C-2″), 75.9 (C-4), 75.2 (C-4′), 73.7 (OCH_2Ph), 73.6 (OCH_2Ph), 73.6 (C-5″), 73.5 (OCH_2Ph), 72.1 (C-4″), 71.3 (C-5′), 70.2 (C-5), 69.9 (C-6″), 69.8 (C-3″), 69.7 (C-6′), 69.4 (C-6), 68.9 (C-3′), 68.8 (C-3), 68.6 (octyl OCH_2), 32.2, 29.7, 29.6, 29.6, 26.4, 23.0 (6C, octyl CH_2), 21.79 (2C, 2 × ArCH_3), 21.78 (ArCH_3), 14.3 (octyl CH_3); HRMS (ESI) calcd $C_{87}H_{98}O_{22}S_3$ $[M+Na]^+$ 1613.5604, found 1613.5602.

Octyl 6-*O*-benzyl-4-*O*-triphenylmethyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-α-D-mannopyranoside (**27**): Synthesis was performed as described for **24**. Installation of the trityl group was carried out with **28** (24 mg, 0.02 mmol), 2,4,6-collidine (25 μL, 0.19 mmol), TrOH (23.4 mg, 0.09 mmol) and TMSOTf (10% v/v in CH_2Cl_2, 160 μL, 0.09 mmol) in CH_2Cl_2 (0.6 mL). The crude residue from CH_2Cl_2 extraction was used for next step without further purification. The dihydroxylation of the trityl ether was carried out with OsO_4 (2.5 wt.% in *t*-butanol, 30 μL, 0.002 mmol) and NMO (50% w/v in water, 0.12 mL) in mixed *t*-butanol and acetone (1 mL, v/v 1:1). The crude residue was purified by chromatography (CH_2Cl_2–MeOH 12:1) to afford tetrasaccharide **27** (29.7 mg, 90% over two steps) as a white foam. R_f 0.40 (CH_2Cl_2–methanol 9:1); $[\alpha]_D$ = +63.2 (*c* 0.2, methanol); ^{1}H NMR (600 MHz, CD_3OD) δ 7.45–7.13 (m, 35H, Ar), 5.26 (d, *J* = 1.8 Hz, 1H, H-1′/H-1″), 5.25 (d, *J* = 1.8 Hz, 1H, H-1′/H-1″), 5.04 (d, *J* = 5.5 Hz, 1H, H-1‴), 4.72 (d, *J* = 1.7 Hz, 1H, H-1), 4.58–4.18 (m, 8H, 8 × OCH_2Ph), 3.99 (dd, *J* = 5.5, 3.1 Hz, 1H, H-2‴), 3.96 (dd, *J* = 3.2, 2.0 Hz, 1H, H-2′/H-2″), 3.95–3.90 (m, 2H, H-5‴, H-5′/H-5″), 3.89–3.75 (m, 11H, H-2′/H-2″, 4 × H-3, 3 × H-4, H-5, 2 × H-6), 3.75–3.67 (m, 5H, H-2, H-5′/H-5″, 2 × H-6, octyl OCH_2), 3.58 (d, *J* = 3.4 Hz, 2H, 2 × H-6), 3.54 (app t, *J* = 5.3 Hz, 1H, H-4‴), 3.41 (dt, *J* = 9.7, 6.3 Hz, 1H, octyl OCH_2), 3.38 (dd, *J* = 11.3, 8.2 Hz, 1H, H-6‴), 3.32–3.30 (m, 1H, H-6‴), 1.64–1.54 (m, 2H, octyl OCH_2CH_2), 1.41–1.23 (m, 10H, octyl CH_2), 0.90 (t, *J* = 7.1 Hz, 1H, octyl CH_3); ^{13}C NMR (126 MHz, CD_3OD) δ 146.0, 139.8, 139.7, 139.6, 139.5, 130.4, 129.5, 129.4, 129.4, 129.3, 129.3, 129.1, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4 (42C, Ar), 103.0, 102.9 (2C, C-1′, C-1″, average $^1J_{C\text{-}1,H\text{-}1}$ = 174.6 Hz), 102.1 (C-1‴, $^1J_{C\text{-}1,H\text{-}1}$ = 169.4 Hz), 101.5 (C-1, $^1J_{C\text{-}1,H\text{-}1}$ = 169.3 Hz), 89.1 (Ph_3P), 77.9 (C-4), 76.0, 76.0, 75.9 (3C), 74.5 (2C, 2 × OCH_2Ph), 74.3 (OCH_2Ph), 74.0 (OCH_2Ph), 73.6, 73.4, 73.1, 73.0, 72.8, 72.7, 72.7, 72.4,

72.3, 72.2, 72.0 (15C), 71.4, 71.4, 71.2, 70.8 (4C, 4 × C-6), 68.7 (octyl OCH_2), 33.0, 30.6, 30.4, 30.4, 27.4, 23.8 (6C, octyl CH_2), 14.6 (octyl CH_3); HRMS (ESI) calcd $C_{79}H_{96}O_{21}$ $[M+Na]^+$ 1403.6336, found 1403.6340.

Octyl 6-*O*-benzyl-2-*O*-toluenesulfonyl-4-*O*-triphenylmethyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-2-*O*-toluenesulfonyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-2-*O*-toluenesulfonyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-2-*O*-toluenesulfonyl-α-D-mannopyranoside (**27a**): To a solution of **27** (21.1 mg, 0.015 mmol) in THF (0.3 mL) was added *n*-Bu_2SnCl_2 (40 mol%, 2.0 mg, 0.006 mmol) and DIPEA (65 μL, 0.36 mmol) followed by TsCl (56.2 mg, 0.30 mmol). The reaction mixture was stirred at room temperature for 22 h before concentrated. Chromatographic purification (hexane–EtOAc 3:2) gave **27a** (11.7 mg, 38%) was a colorless film. $[\alpha]_D$ = +35.8 (*c* 0.6, methanol); ^{1}H NMR (600 MHz, CD_3OD) δ 7.88–7.72 (m, 8H, Ar), 7.45–7.07 (m, 43H, Ar), 5.20 (d, *J* = 5.5 Hz, 1H, H-1‴), 5.01 (d, *J* = 1.9 Hz, 1H, H-1′), 4.95 (d, *J* = 1.7 Hz, 1H, H-1″), 4.78 (dd, *J* = 3.2, 2.1 Hz, 1H, H-2′), 4.73 (d, *J* = 1.8 Hz, 1H, H-1), 4.71–4.67 (m, 2H, H-2″, H-2‴), 4.53 (dd, *J* = 3.4, 1.8 Hz, 1H, H-2), 4.46–4.30 (m, 4H, 2 × OCH_2Ph), 4.21 (d, *J* = 12.0 Hz, 1H, OCH_2Ph), 4.16 (d, *J* = 12.0 Hz, 1H, OCH_2Ph), 3.91 (dd, *J* = 9.8, 2.9 Hz, 1H, H-3′), 3.89 (dd, *J* = 9.5, 3.0 Hz, 1H, H-3), 3.79 (brs, 1H, H-3‴), 3.76 (dd, *J* = 9.3, 3.2 Hz, 1H, H-3″), 3.75–3.72 (m, 1H, H-5‴), 3.72–3.68 (m, 1H, H-5′), 3.68 (app t, *J* = 9.5 Hz, 1H, H-4″), 3.65–3.56 (m, 7H, H-4, H-4′, H-5, H-6a, H-6b, H-6a″, octyl OCH_2), 3.57–3.45 (m, 5H, H-4‴, H-5″, H-6b″, H-6a′, H-6b′), 3.35 (dt, *J* = 9.9, 6.3 Hz, 1H, octyl OCH_2), 3.27–3.21 (m, 1H, H-6a‴), 3.20–3.14 (m, 1H, H-6b‴), 2.43 (s, 3H, ArCH_3), 2.39 (s, 3H, ArCH_3), 2.36 (s, 3H, ArCH_3), 2.34 (s, 3H, ArCH_3)), 1.55–1.46 (m, 2H, octyl OCH_2CH_2), 1.35–1.17 (m, 10H, octyl CH_2), 0.86 (t, *J* = 7.0 Hz, 3H, octyl CH_3); ^{13}C NMR (125 MHz, CD_3OD) δ 146.6, 146.5, 146.3, 145.6, 139.8, 139.7, 139.7, 139.4, 135.2, 135.1, 135.0, 131.1, 131.0, 131.0, 130.9, 130.3, 129.5, 129.4, 129.4, 129.4,

129.3, 129.3, 129.0, 128.9, 128.9, 128.8, 128.8, 128.7, 128.6, 128.5, 128.5 (66C, Ar), 100.2 (C-1′), 100.0 (C-1″), 98.5 (C-1), 97.4 (C-1‴), (octyl OCH_2), 33.0, 30.4, 30.4, 30. 89.2 (Ph_3C), 81.4, 81.23, 81.20, 81.17 (4C, C-2, C-2′, C-2″, C-2‴), 76.72 (C-4), 76.68 (C-4′), 75.7 (C-5‴), 74.4 (3C, 3 × OCH_2Ph), 74.0 (OCH_2Ph), 73.1 (C-5′), 73.0 (C-4″), 72.3 (C-5″), 71.0 (C-3‴), 70.9 (C-6″), 70.5 (C-6), 70.4 (2C, C-6′, C-6‴), 70.2 (C-3), 69.9 (C-3″), 69.7 (C-3′), 69.3 4, 27.2, 23.7 (6C, octyl CH_2), 22.1 (ArCH_3), 21.7 (ArCH_3), 21.6 (2C, 2 × ArCH_3), 14.5 (octyl CH_3); HRMS (ESI) calcd $C_{107}H_{120}O_{29}S_4$ $[M+Na]^+$ 2019.6690, found 2019.6684.

(2*R*,3*S*,6*S*)-2-((benzyloxy)methyl)-6-(((2*R*,3*S*,6*S*)-2-((benzyloxy)methyl)-6-(((2*R*,3*S*,6*S*)-2-((benzyloxy)methyl)-6-(((2*R*,3*S*,6*S*)-2-((benzyloxy)methyl)-6-(octyloxy)-3,6-dihydro-2*H*-pyran-3-yl)oxy)-3,6-dihydro-2*H*-pyran-3-yl)oxy)-3,6-dihydro-2*H*-pyran-3-yl)oxy)-3,6-dihydro-2*H*-pyran-3-ol (**28**): The coupling step was performed as described for the synthesis of **8**, with alcohol **11** (219.2 mg, 0.28 mmol) and donor **7** (184.3 mg,0.55 mmol) in the presence of $Pd_2(dba)_3$ (12.9 mg, 0.01 mmol) and PPh_3 (16.0 mg, 0.06 mmol) in CH_2Cl_2 (5 mL). The crude residue was purified by chromatography (hexane–EtOAc 3.5:1) to afford a ketone (208.9 mg, 82%) as pale yellow syrup. $[\alpha]_D$ = +7.7 (*c* 2.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36–7.18 (m, 20H, Ar), 6.82 (dd, *J* = 10.2, 3.5 Hz, 1H, H-2‴), 6.17 (d, *J* = 10.3 Hz, 1H, H-3‴), 6.12 (d, *J* = 10.3 Hz, 1H, H-3″), 6.06 (d, *J* = 10.4 Hz, 1H, H-3′), 6.03 (d, *J* = 10.4 Hz, 1H, H-3), 5.82 (ddd, *J* = 10.3, 2.6, 1.9 Hz, 1H, H-2), 5.78 (ddd, *J* = 10.3, 2.6, 2.0 Hz, 1H, H-2″), 5.73 (ddd, *J* = 10.3, 2.6, 2.0 Hz, 1H, H-2′), 5.56 (d, *J* = 3.5 Hz, 1H, H-1‴), 5.25 (d, *J* = 2.3 Hz, 1H, H-1″), 5.23 (d, *J* = 2.3 Hz, 1H, H-1′), 5.00 (d, *J* = 2.3 Hz, 1H, H-1), 4.64 (dd, *J* = 9.3, 1.3 Hz, 1H, H-4″), 4.46 (dd, *J* = 9.3, 1.3 Hz, 1H, H-4′), 4.56–4.32 (m, 8H, 8 × OCH_2Ph), 4.38 (dd, *J* = 9.4, 1.2 Hz, 1H, H-4), 4.01 (ddd, *J* = 9.1, 6.2, 1.7 Hz, 1H, H-5), 3.85 (ddd, *J* = 9.3, 3.4, 3.4 Hz, 1H, H-5′), 3.82–3.76 (m, 4H, H-5″, H-6a, H-6a‴, octyl OCH_2), 3.68 (dd, *J* = 11.0, 6.2 Hz, 1H, H-6b), 3.63–3.55 (m, 4H,

H-6a′, H-6b′, H-6a″, H-6b‴), 3.50 (dd, *J* = 10.7, 1.8 Hz, 1H, H-6b″), 3.48 (dt, *J* = 9.5, 6.6 Hz, 1H, octyl OCH_2), 1.64–1.54 (m, 2H, octyl OCH_2CH_2), 1.38–1.20 (m, 10H, octyl CH_2), 0.88 (t, *J* = 7.1 Hz, 3H, octyl CH_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 194.0 (C=O), 143.6 (C-2‴), 138.6, 138.3, 137.9, 137.8 (4C; Ar), 129.8, 129.3, 129.3 (3C; C-3, C-3′, C-3″), 128.3, 128.3, 128.3, 128.2, 127.6, 127.6, 127.6, 127.4, 127.4, 127.4, 127.3, 127.2, 126.8 (24C; 20 × Ar, C-2, C-2′, C-2″, C-3‴), 94.1 (C-1), 91.3, 91.3 (2C; C-1′, C-1″), 90.0 (C-1‴), 75.0 (C-5‴), 73.7, 73.5, 73.4, 73.1 (4C; 4 × OCH_2Ph), 70.0 (C-6), 69.8, 69.7 (2C; C-5′, C-5″), 69.4 (C-6′), 69.1 (C-5), 68.9 (C-6″), 68.7 (octyl OCH_2), 68.4 (C-6‴), 67.6 (C-4), 67.2 (C-4″), 67.0 (C-4′), 31.8, 29.8, 29.4, 29.3, 26.2, 22.7 (octyl CH_2), 14.1 (octyl CH_3); HRMS (ESI) calcd $C_{60}H_{72}O_{13}$ $[M+Na]^+$ 1023.4865, found 1023.4856. This ketone (208.9 mg, 0.21 mmol) was then reduced as described for **9**, with $NaBH_4$ (8.0 mg, 0.21 mmol) and $CeCl_3$•$7H_2O$ (80.2 mg, 0.21 mmol) in MeOH (2.5 mL). Chromatography purification (hexane–EtOAc 3:1) furnished alcohol **28** (177.2 mg, 85%) as colorless syrup. R_f 0.37 (hexane–EtOAc 2:1); $[\alpha]_D$ = +32.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.17 (m, 20H, Ar), 6.12–6.03 (m, 3H, H-3, H-3′, H-3″), 6.00 (d, *J* = 10.2 Hz, 1H, H-3‴), 5.84 (ddd, *J* = 10.3, 2.7, 1.8 Hz, 1H, H-2), 5.79–5.69 (m, 3H, H-2′, H-2″, H-2‴), 5.29–5.24 (m, 2H, H-1′, H-1″), 5.22 (d, *J* = 2.6 Hz, 1H, H-1‴), 5.02 (d, *J* = 2.2 Hz, 1H, H-1), 4.58–4.36 (m, 11H, 4 × OCH_2Ph, H-4, H-4′, H-4″), 4.28 (dddd, *J* = 6.2, 3.6, 1.8, 1.8 Hz, 1H, H-4‴), 4.03 (ddd, *J* = 9.3, 6.3, 1.7 Hz, 1H, H-5), 3.91–3.78 (m, 4H, H-5′, H-5″, H-6a, octyl OCH_2), 3.76–3.56 (m, 7H, H-5‴, H-6b, H-6a′, H-6b′, H-6a″, H-6b″, H-6a‴), 3.55–3.46 (m, 2H, H-6b‴, octyl OCH_2), 2.46 (d, *J* = 4.5 Hz, 1H, OH-4‴), 1.66–1.56 (m, 2H, octyl OCH_2CH_2), 1.40–1.21 (m, 10H, octyl CH_2), 0.90 (t, *J* = 7.0 Hz, 3H, octyl CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.6, 138.4, 138.4, 137.6 (4C; Ar), 133.3, 130.0, 129.9, 129.3, 128.5, 128.3, 128.2, 128.0, 127.8, 127.5, 127.4, 127.4, 127.3, 127.3 (20C; Ar), 126.7 (C-2), 126.6 (2C; C-2′, C-2″), 125.7 (C-2‴), 94.1

(C-1), 91.3, 91.2 (C-1′, C-1″), 91.0 (C-1‴), 73.7, 73.4, 73.4, 73.1 (4C; 4 × OCH_2Ph), 70.7 (C-6), 70.1 (C-6), 69.8 (3C; C-5′, C-5″, C-5‴), 69.5 (C-6), 69.2 (C-6), 69.1 (C-5), 68.7 (octyl OCH_2), 67.6 (C-4), 67.0, 66.6 (2C; C-4′, C-4″), 66.0 (C-4‴), 31.9, 29.8, 29.4, 29.3, 26.3, 22.7 (6C; octyl CH_2), 14.1 (octyl CH_3); HRMS (ESI) calcd $C_{60}H_{74}O_{13}$ $[M+Na]^+$ 1025.5022, found 1025.5027.

Synthesis of octyl 6-*O*-benzyl-4-*O*-*t*-butyldimethylsilyl-3-*O*-methyl-2-*O*-toluenesulfonyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-3-*O*-methyl-2-*O*-toluenesulfonyl-α-D-mannopyranoside (29): **and octyl 6-*O*-benzyl-3-*O*-*t*-butyldimethylsilyl-4-*O*-methyl-2-*O*-toluenesulfonyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-3-*O*-methyl-2-*O*-toluenesulfonyl-α-D-mannopyranoside (30):** To a stirring ice-cold solution of alcohol **23a** (9.3 mg, 0.01 mmol) and MeI (10 μL, 0.16 mmol) in DMF (0.7 mL) was added NaH (60% in mineral oil, 6.3 mg, 0.15 mmol). The resulting solution was stirred at 0 °C for 15 min before methanol (0.1 mL) was added. The resulting reaction mixture was diluted with CH_2Cl_2 and washed with brine. The separated organic layer was dried over Na_2SO_4, concentrated and the resulting residue was purified by chromatography (hexane–EtOAc 8:1) to afford an inseparable mixture of **29** and **30** (8.7 mg, 91%, **29**/**30** = 1.8:1) as a colorless syrups. R_f 0.63 (hexane–EtOAc 4:1); Distinguishing between **29** and **30** was assisted by both ^{1}H-^{1}H COSY and 1D-TOCSY NMR spectroscopy.

Octyl 6-*O*-benzyl-4-*O*-*t*-butyldimethylsilyl-3-*O*-methyl-2-*O*-toluenesulfonyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-3-*O*-methyl-2-*O*-toluenesulfonyl-α-D-mannopyranoside (29): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87–7.78 (m, 4H, Ar), 7.36–7.21 (m, 14H, Ar), 5.00 (d, *J* = 2.1 Hz, 1H, H-1′), 4.95 (dd, *J* = 2.9, 2.2 Hz, 1H, H-2′), 4.91 (d, *J* = 1.9 Hz, 1H, H-1), 4.79 (dd, *J* = 3.2, 1.9 Hz, 1H, H-2), 4.55–4.38 (m, 4H, 4 × OC*H*$_2$Ph), 3.75–3.53 (m, 9H); 3.51 (dd, *J* = 9.4, 3.3 Hz, 1H, H-3), 3.41–3.38 (m, 1H, octyl OCH_2); 3.25 (dd, *J* = 8.7, 3.2

Hz, 1H, H-3′), 3.19 (s, 3H, OMe), 3.14 (s, 3H, OMe), 2.44 (s, 3H, ArCH_3), 2.40 (s, 3H, ArCH_3), 1.60–1.53 (m, 2H, octyl OCH_2CH_2), 1.34–1.24 (m, 10H, octyl CH_2), 0.89 (t, J = 7.0 Hz, 3H, octyl CH_3), 0.80 (s, 9H, TBS(*t*-Bu)), -0.02 (s, 3H, TBS(Me)), –0.06 (s, 3H, TBS(Me)); HRMS (ESI) calcd $C_{56}H_{80}O_{15}S_2Si$ $[M+Na]^+$ 1107.4600, found 1107.4594.

Octyl 6-*O*-benzyl-3-*O*-*t*-butyldimethylsilyl-4-*O*-methyl-2-*O*-toluenesulfonyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-3-*O*-methyl-2-*O*-toluenesulfonyl-α-D-mannopyranoside (30): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87–7.78 (m, 4H, Ar), 7.36–7.21 (m, 14H, Ar), 4.85 (br d, J = 1.9 Hz, 2H, H-1, H-1′), 4.78–4.76 (m, 2H, H-2, H-2′), 4.55–4.38 (m, 4H, 4 × OCH_2Ph), 3.94 (dd, J = 8.9, 2.7 Hz, 1H, H-3′), 3.75–3.53 (m, 5H); 3.47–3.42 (m, 2H, H-3, H-6a′); 3.41–3.38 (m, 1H, octyl OCH_2); 3.39 (s, 3H, OMe-4′), 3.35 (app t, J = 8.7 Hz, 1H, H-4′), 3.20 (s, 3H, OMe-3), 2.43 (s, 3H, ArCH_3), 2.40 (s, 3H, ArCH_3), 1.60–1.53 (m, 2H, octyl OCH_2CH_2), 1.34–1.24 (m, 10H, octyl CH_2), 0.89 (t, J = 7.0 Hz, 3H, octyl CH_3), 0.94 (s, 9H, TBS(*t*-Bu)), 0.13 (s, 3H, TBS(Me)), 0.12 (s, 3H, TBS(Me)); HRMS (ESI) calcd $C_{56}H_{80}O_{15}S_2Si$ $[M+Na]^+$ 1107.4600, found 1107.4594.

Octyl 6-*O*-benzyl-3-*O*-methyl-2-*O*-toluenesulfonyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-3-*O*-methyl-2-*O*-toluenesulfonyl-α-D-mannopyranoside (**32**): To a stirring ice-cold solution of alcohol **25a** (56.3 mg, 0.05 mmol) and MeI (24 μL, 0.38 mmol) in THF (0.6 mL) was added NaH (60% in mineral oil, 24 mg, 0.6 mmol). The resulting solution was stirred at 0 °C for 20 min before methanol (1 mL) was added. Then a methanolic solution of HCl (0.1 mL, 10% v/v) was added and the reaction mixture was stirred for 0.5 h. The yellowish solution was concentrated and redissolved in CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, followed by saturated Na_2SO_3 and brine. The separated organic layer was dried over Na_2SO_4, concentrated

and the resulting residue was purified by chromatography (hexane–EtOAc 2.5:1) to afford **32** (38.2 mg, 83% over two steps) as a colorless syrup. R_f 0.31 (hexane–EtOAc 2:1); $[\alpha]_D$ = +6.2 (*c* 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.3 Hz, 2H, Ar), 7.82 (d, *J* = 8.3 Hz, 2H, Ar), 7.38–7.23 (m, 14H, Ar), 5.15 (d, *J* = 1.7 Hz, 1H, H-1′), 4.96–4.92 (m, 2H, H-1, H-2′), 4.81 (dd, *J* = 3.0, 2.0 Hz, 1H, H-2), 4.54–4.44 (m, 4H, 4 × OC*H*$_2$Ph), 3.82–3.64 (m, 7H, H-4′, H-4, H-5, H-5′, H-6, H-6, octyl OCH_2), 3.62–3.52 (m, 3H, H-3, H-6, H-6), 3.42 (dt, *J* = 9.7, 6.7 Hz, 1H, octyl OCH_2), 3.39 (dd, *J* = 9.5, 3.0 Hz, 1H, H-3′), 3.25 (s, 3H, OMe), 3.21 (s, 3H, OMe), 2.63 (brs, 1H, OH-4′), 2.46 (s, 3H, ArC*H*$_3$), 2.44 (s, 3H, ArC*H*$_3$), 1.65–1.54 (m, 2H, octyl OCH_2CH_2), 1.37–1.25 (m, 10H, octyl CH_2), 0.91 (t, *J* = 6.9 Hz, 3H, octyl CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.9, 144.8, 138.4, 138.0, 134.0, 133.7, 129.8, 129.7, 128.4, 128.3, 128.1, 127.9, 127.7, 127.5, 127.4 (24C, Ar), 99.6 (C-1′), 97.3 (C-1), 79.4 (C-3), 78.4 (C-3′), 74.2 (C-2), 73.9 (C-2′), 73.6 (O*C*H$_2$Ph), 73.5 (C-4), 73.4 (O*C*H$_2$Ph), 72.0 (C-5), 71.0 (C-5′), 70.2, 69.4 (2C, C-6, C-6′), 68.3 (octyl OCH_2), 67.4 (C-4′), 57.1, 56.8 (2C, 2 × OMe), 31.8, 29.4, 29.3, 29.2, 26.1, 22.7 (6C, octyl CH_2), 21.7 (Ar*C*H$_3$), 21.6 (Ar*C*H$_3$), 14.1 (octyl CH_3); HRMS (ESI) calcd $C_{50}H_{66}O_{15}S_2$ $[M+Na]^+$ 993.3735, found 993.3736.

Octyl 3-*O*-methyl-α-D-mannopyranosyl-(1→4)-3-*O*-methyl-α-D-mannopyranoside (**33**): A solution of **32** (25.5 mg, 0.03 mmol) and Mg (39.9 mg, 1.66 mmol) was heated in dry methanol (1 mL) at reflux overnight. The solution was cooled to room temperature and then 1M HCl (5 mL) was added. The resulting mixture was extracted with CH_2Cl_2 and washed with brine. The organic layer was then concentrated and purified by chromatography (CH_2Cl_2–methanol 30:1) to afford a partially deprotected disaccharide (12.5 mg, 72%) as a colorless syrup. R_f 0.30 (CH_2Cl_2–methanol 20:1); ^{1}H NMR (500 MHz, CD_3OD) δ 7.36–7.11 (m, 10H, Ar), 5.15 (d, *J* = 1.6 Hz, 1H, H-1′), 4.75 (d, *J* = 1.5 Hz, 1H, H-1), 4.54–4.38 (m, 4H, 4 × OC*H*$_2$Ph), 4.08 (dd, *J* = 2.9, 2.1 Hz,

1H, H-2′), 4.00 (dd, *J* = 3.1, 1.9 Hz, 1H, H-2), 3.85–3.78 (m, 2H, H-4, H-6), 3.78–3.65 (m, 6H, H-4′, H-5, H-5′, H-6, H-6, octyl OCH_2), 3.62 (dd, *J* = 10.7, 5.5 Hz, 1H, H-6), 3.48–3.44 (m, 1H, H-3), 3.45 (s, 3H, OMe), 3.44–3.39 (m, 1H, octyl OCH_2), 3.41 (s, 3H, OMe), 3.33 (dd, *J* = 9.1, 3.0 Hz, 1H, H-3′), 1.64–1.55 (m, 2H, octyl OCH_2CH_2), 1.41–1.24 (m, 10H, octyl CH_2), 0.89 (t, *J* = 6.9 Hz, 3H, octyl OCH_3); ^{13}C NMR (126 MHz, CD_3OD) δ 139.8 (Ar), 139.7 (Ar), 129.34 (2C, Ar), 129.30 (2C, Ar), 129.0 (2C, Ar), 128.9 (2C, Ar), 128.6 (Ar), 128.6 (Ar), 103.7 (C-1′), 101.4 (C-1), 83.3 (C-3), 82.2 (C-3′), 75.3 (C-4), 74.6 (C-5), 74.6 (OCH_2Ph), 74.4 (OCH_2Ph), 72.3 (C-5′), 71.4, 71.3 (2C, C-6, C-6′), 68.9 (octyl OCH_2), 68.1 (C-2′), 67.7 (C-2), 67.5 (C-4′), 57.3, 56.7 (2C, 2 × OMe), 33.0, 30.5, 30.4, 30.4, 27.4, 23.7 (6C, octyl CH_2), 14.5 (octyl CH_3); HRMS (ESI) calcd $C_{36}H_{54}O_{11}$ $[M+Na]^+$ 685.3558, found 685.3551. Hydrogenolysis of this disaccharide (9.8 mg, 0.01 mmol) was performed in with Pd–C (5 wt.%, 10 mg) in methanol (0.5 mL) under H_2 atmosphere for overnight. The catalyst was removed by filtration through Celite. The filtrate was then concentrated and the residue was purified by chromatography (CH_2Cl_2–methanol 9:1) to afford **33** (6.9 mg, 97%) as a colorless syrup. R_f 0.11 (CH_2Cl_2–methanol 9:1); $[\alpha]_D$ = +82.5 (*c* 0.04, methanol); The NMR spectra were identical to those previously reported.[13]

Octyl 6-*O*-benzyl-3-*O*-methyl-2-*O*-toluenesulfonyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-3-*O*-methyl-2-*O*-toluenesulfonyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-3-*O*-methyl-2-*O*-toluenesulfonyl-α-D-mannopyranoside (34): Installation of the methyl groups was performed as described for the synthesis of **32**, with alcohol **26a** (16.5 mg, 0.01 mmol), NaH (60% in mineral oil, 7.8 mg, 0.20 mmol) and MeI (8 μL, 0.12 mmol) in THF (0.5 mL), at 0 °C for 1h. The trityl group was removed by addtion of a methanolic solution of HCl (0.1 mL, 10% v/v). The crude product was purifed by chromoatography to affored **34** (10.2 mg, 73%) as coloreless syrup. $[\alpha]_D$ = +9.4 (*c* 0.3, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89–7.77 (m, 6H, Ar), 7.36–

7.19 (m, 21H, Ar), 5.10 (d, J = 1.7 Hz, 1H, H-1″), 5.06 (d, J = 1.9 Hz, 1H, H-1′), 4.95–4.91 (m, 2H, H-2′, H-2″), 4.90 (d, J = 1.8 Hz, 1H, H-1), 4.80 (dd, J = 3.0, 2.0 Hz, 1H, H-2), 4.51–4.36 (m, 6H, 6 × OCH_2Ph), 3.77 (app t, J = 9.7 Hz, 1H, H-4″), 3.72 (app t, J = 9.7 Hz, 1H, H-4′), 3.71–3.61 (m, 6H, H-4, H-5, H-5′, H-5″, H-6, octyl OCH_2), 3.61–3.49 (m, 6H, H-3, 5 × H-6), 3.46 (dd, J = 9.3, 3.0 Hz, 1H, H-3′), 3.40 (dt, J = 9.8, 6.6 Hz, 1H, octyl OCH_2), 3.36 (dd, J = 9.5, 3.1 Hz, 1H, H-3″), 3.25 (s, 3H, OMe), 3.24 (s, 3H, OMe), 3.20 (s, 3H, OMe), 2.63 (d, J = 1.6 Hz, 1H, OH-4″), 2.45 (s, 3H, $ArCH_3$), 2.41 (s, 3H, $ArCH_3$), 2.41 (s, 3H, $ArCH_3$), 1.62–1.51 (m, 2H, octyl OCH_2CH_2), 1.35–1.23 (m, 10H, octyl CH_2), 0.89 (t, J = 7.0 Hz, 3H, octyl CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.0, 144.9, 144.8, 138.3, 138.3, 138.0, 134.0, 134.0, 133.6, 129.9, 129.8, 129.8, 128.4, 128.3, 128.2, 128.1, 127.9, 127.7, 127.6, 127.5, 127.5, 127.4 (36C, Ar), 99.5 (2C, C-1′, C-1″), 97.3 (C-1), 79.2 (C-3′), 79.0 (C-3), 78.4 (C-3″), 74.4 (C-4), 74.1, 74.1, 73.9 (3C, C-2, C-2′, C-2″), 73.7, 73.4, 73.4 (3C, 3 × OCH_2Ph), 73.1 (C-4′), 72.2, 71.9, 71.2 (3C, C-5, C-5′, C-5″), 70.2, 69.6, 69.3 (3C, C-6, C-6′, C-6″), 68.4 (octyl OCH_2), 67.4 (C-4″), 57.1, 56.8, 56.7 (3C, 3 × OMe), 31.8, 29.4, 29.3, 29.2, 26.0, 22.7 (6C, octyl CH_2), 21.7, 21.6, 21.6 (3C, 3 × ArCH_3), 14.1 (octyl CH_3); HRMS (ESI) calcd $C_{71}H_{90}O_{22}S_3$ $[M+Na]^+$ 1413.4978, found 1413.4964.

Octyl 6-*O*-benzyl-3-*O*-methyl-2-*O*-toluenesulfonyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-3-*O*-methyl-2-*O*-toluenesulfonyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-3-*O*-methyl-2-*O*-toluenesulfonyl-α-D-mannopyranosyl-(1→4)-6-*O*-benzyl-3-*O*-methyl-2-*O*-toluenesulfonyl-α-D-mannopyranoside (35): Installation of the methyl groups was performed as described for the synthesis of **32**, with alcohol **27a** (10.5 mg, 5.3 μmol), NaH (60% in mineral oil, 8.2 mg, 0.21 mmol) and MeI (14 μL, 0.22 mmol) in THF (0.4 mL), at 0 °C for 0.5h. The trityl group was removed by addtion of a methanolic solution of HCl (0.1 mL, 10% v/v). The crude product was

purifed by chromoatography to affored **35** (8.3 mg, 87%) as coloreless syrup. $[\alpha]_D$ = +14.5 (*c* 0.6, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 7.88–7.77 (m, 8H, Ar), 7.38–7.17 (m, 28H, Ar), 5.11 (d, *J* = 1.4 Hz, 1H, H-1‴), 5.05 (d, *J* = 1.7 Hz, 1H, H-1′), 5.02 (d, *J* = 1.5 Hz, 1H, H-1″), 4.95–4.92 (m, 3H, H-2′, H-2″, H-2‴), 4.90 (d, *J* = 1.7 Hz, 1H, H-1), 4.80 (dd, *J* = 2.9, 2.0 Hz, 1H, H-2), 4.52–4.31 (m, 8H, 8 × OCH_2Ph), 3.77 (br app t, *J* = 9.6 Hz, 1H, H-4‴), 3.73 (app t, *J* = 9.8 Hz, 1H, H-4″), 3.73–3.56 (m, 10H, H-4, H-4′, H-5, H-5′, H-5″, H-5‴, 3 × H-6, octyl OCH_2), 3.57–3.43 (m, 8H, H-3, H-3′, H-3″, 5 × H-6), 3.40 (dt, *J* = 9.8, 6.9 Hz, 1H, octyl OCH_2), 3.37 (dd, *J* = 9.5, 3.1 Hz, 1H, H-3‴), 3.27 (s, 6H, 2 × OMe), 3.22 (s, 3H,OMe), 3.20 (s, 3H, OMe), 2.63 (br s, 1H, OH-4‴), 2.45 (s, 3H,$ArCH_3$), 2.42 (s, 3H, $ArCH_3$), 2.41 (s, 6H, 2 × $ArCH_3$), 1.61–1.52 (m, 2H, octyl OCH_2CH_2), 1.36–1.23 (m, 10H, octyl CH_2), 0.89 (t, *J* = 7.0 Hz, 3H, octyl CH_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 145.0, 144.9, 144.8, 138.3, 138.3, 138.2, 137.9, 134.0, 134.0, 133.9, 133.6, 129.9, 129.8, 129.7, 128.3, 128.2, 128.1, 127.9, 127.6, 127.6, 127.6, 127.5, 127.4, 127.4, 127.4 (48C, Ar), 99.5 (2C, C-1″, C-1‴), 99.4 (C-1′), 97.2 (C-1), 79.1 (C-3), 78.9 (C-3″), 78.8 (C-3′), 78.4 (C-3‴), 74.6 (C-4), 74.0, 74.0, 74.0, 73.9 (4C, C-2, C-2′, C-2″, C-2‴), 73.8 (C-4′), 73.6 (OCH_2Ph), 73.5 (2C, 2 × OCH_2Ph), 73.4 (OCH_2Ph), 73.1 (C-4″), 72.2 (C-5′), 72.1 (C-5″), 71.9 (C-5‴), 71.2 (C-5), 70.2, 69.7, 69.5, 69.2 (4C, C-6, C-6′, C-6″, C-6‴), 68.4 (octyl OCH_2), 67.4 (C-4‴), 57.0 (OMe), 56.7 (OMe), 56.62 (OMe), 56.61 (OMe), 31.8, 29.3, 29.3, 29.2, 26.0, 22.6 (6C, octyl CH_2), 21.7 ($ArCH_3$), 21.6 (3C, 3 × $ArCH_3$), 14.1 (octyl CH_3); HRMS (ESI) calcd $C_{92}H_{114}O_{29}S_4$ $[M+Na]^+$ 1833.6221, found 1833.6199.

Synthesis of Octyl 3-*O*-methyl-α-D-mannopyranosyl-(1→4)-3-*O*-methyl-α-D-mannopyranosyl-(1→4)-3-*O*-methyl-α-D-mannopyranoside (36): Deprotection was performed as for **33**. Removal of tosyl group was carried out with Mg (30 mg) in MeOH (2 mL)

for 2 overnights. The crude product was purifed by chromatography (CH_2Cl_2–methanol 15:1) to afford a partially deprotected triasaccharide (4.9 mg, 64%) as a colorless syrup. The benzyl groups of this tetrasaccharide (4.5 mg) was then removed by hydrogenolysis with Pd–C (5 wt.%, 5 mg) in methanol (1.5 mL) under H_2 atmosphere for 3 overnights. The catalyst was removed by filtration through Celite. The filtrate was then concentrated and purified by chromatography to afford **36** (2.8 mg, 88%) as a colorless film. $[\alpha]_D$ = +57.8 (*c* 0.2, MeOH); HRMS (ESI) calcd $C_{29}H_{54}O_{16}$ $[M+Na]^+$ 681.3304, found 681.3298. The ^1H NMR spectra was identical to the previously reported.[13]

Octyl 3-*O*-methyl-α-D-mannopyranosyl-(1→4)-3-*O*-methyl-α-D-mannopyranosyl-(1→4)-3-*O*-methyl-α-D-mannopyranosyl-(1→4)-3-*O*-methyl-α-D-mannopyranoside (37): Deprotection was performed as for **33**. Removal of tosyl group was carried out with Mg (20 mg) in MeOH (1 mL) for overnight. The crude product was purifed by chromatography (CH_2Cl_2–methanol 15:1) to afford a partially deprotected tetrasaccharide (5.3 mg, quantitative) as a colorless syrup. The benzyl groups of this tetrasaccharide was then removed by hydrogenolysis with Pd–C (5 wt.%, 13 mg) in methanol (1.5 mL) under H_2 atmosphere for 3 overnights. The catalyst was removed by filtration through Celite. The filtrate was then concentrated to afford **37** (2.7 mg, 80%) as a colorless film. $[\alpha]_D$ = +35.1 (*c* 0.3, MeOH); HRMS (ESI) calcd $C_{36}H_{66}O_{21}$ $[M+Na]^+$ 857.3989, found 857.3993.The ^1H NMR spectra was identical to the previously reported.[13]

Hexakis(6-*O*-*t*-butyldimethylsilyl-2-*O*-toluenesulfonyl)-α-cylcodextrin (39): To a solution of **38**[37] (50.7 mg, 0.03 mmol) in THF (0.3 mL) was added *n*-Bu_2SnCl_2 (6.4 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (190 μL, 1.08 mmol) followed by toluenesulfonyl chloride (177.0

mg, 0.90 mmol). The reaction mixture was stirred at room temperature for six days and then purified by chromatography (hexane–EtOAc 3:1 to 1:1) to afford **39** (60.6 mg, 77%) as a colorless film. R_f 0.77 (CH_2Cl_2–methanol 30:1); $[\alpha]_D$ = +54.0 (*c* 0.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.3 Hz, 2H, Ar), 7.36 (d, *J* = 8.1 Hz, 2H, Ar), 5.13 (d, *J* = 3.5 Hz, 1H, H-1), 4.28 (dd, *J* = 9.9, 3.5 Hz, 1H, H-2), 3.95 (ddd, *J* = 9.9, 8.5, 3.3 Hz, 1H, H-3), 3.91 (dd, *J* = 11.5, 2.9 Hz, 1H, H-6a), 3.71 (app t, *J* = 9.0 Hz, 1H, H-4), 3.64 (d, *J* = 11.0 Hz, 1H, H-6b), 3.56 (dd, *J* = 9.3, 2.7 Hz, 1H, H-5), 3.07 (d, *J* = 3.3 Hz, OH-3), 2.49 (s, 3H, $ArCH_3$), 0.89 (s, 9H, TBS(*t*-Bu)), 0.03 (s, 6H, 2 × TBS(Me)); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.1 (1C, Ar), 133.0 (1C, Ar), 129.6 (2C, Ar), 128.4 (2C, Ar), 99.3 (C-1), 81.2 (C-4), 79.7 (C-2), 71.7 (C-5), 70.1 (C-3), 61.8 (C-6), 25.9 (TBS(*t*-Bu)), 21.8 (Ar*C*H_3), 18.3 (TBS(*t*-Bu)), –5.1, –5.2 (2C, 2 × TBS(Me)); HRMS (ESI) calcd $C_{114}H_{180}O_{42}S_6Si_6$ $[M+2(NH_4)]^{2+}$ 1308.4783, found 1308.4761.

Hexakis(6-*O*-*t*-butyldimethylsilyl-3-*O*-methyl-2-*O*-toluenesulfonyl)-α-cylcodextrin (40): To a stirring ice-cold solution of alcohol **39** (30.6 mg, 0.01 mmol) and MeI (15 μL, 0.22 mmol) in THF (0.5 mL) was added NaH (60% in mineral oil, 17 mg, 0.43 mmol). The resulting solution was stirred at 0 °C for 1 h before methanol (1 mL) was added. The reaction mixture was then concentrated and the residue was purified by chromatography (hexane–EtOAc 3:1) to afford **40** (34.3 mg, quantitative) as a pale yellow syrup. R_f 0.66 (hexane–EtOAc 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.3 Hz, 2H, Ar), 7.35 (d, *J* = 8.1 Hz, 2H, Ar), 4.83 (d, *J* = 3.2 Hz, 1H, H-1), 4.07 (dd, *J* = 9.6, 3.2 Hz, 1H, H-2), 3.89 (dd, *J* = 11.4, 2.5 Hz, 1H, H-6a), 3.65–3.49 (m, 4H, H-3, H-4, H-5, H-6b), 3.45 (s, 3H, OMe), 2.48 (s, 3H, Ar*CH*$_3$), 0.84 (s, 9H, TBS(*t*-Bu)), -0.02 (s, 3H, TBS(Me)), –0.03 (s, 3H, TBS(Me); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.0 (Ar), 133.5 (Ar), 129.6 (2C, Ar), 128.5 (Ar), 100.1 (C-1), 80.9 (C-3), 79.2 (C-4), 78.7 (C-2), 72.8 (C-5), 61.9 (OMe),

61.8 (C-6), 25.8 (TBS(*t*-Bu)), 21.8 (ArCH_3),18.2 (TBS(*t*-Bu)), –5.0, –5.2 (2C, 2 × TBS(Me)); HRMS (ESI) calcd $C_{120}H_{192}O_{42}S_6Si_6$ $[M+NH_4]^+$ 2683.0166, found 2683.0076.

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Supporting Information

NMR spectra for compounds **7–40**. This material is available free of charge via the Internet at http://pubs.acs.org.

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