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The methylsulfonylethoxymethyl (Msem) as a hydroxyl protecting group in oligosaccharide synthesis

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ABSTRACT

The methylsulfonylethoxymethyl (Msem) is introduced as a base-labile, non-participating protecting group in carbohydrate chemistry. Conditions to introduce the Msem on primary and secondary alcohols are described. Removal of the Msem is best achieved using a catalytic amount of tetrabutylammonium fluoride (TBAF), with or without a nucleophilic scavenger. Applicability of the Msem group is illustrated in the assembly of an all 1,3-*cis*-linked mannotrioside.

1. Introduction

The development of new protective group strategies remains a major research objective in synthetic carbohydrate chemistry.[1] The ideal protective group for any given carbohydrate functionality is orthogonal with respect to all other protective groups present in the donor and acceptor glycosides that partake in a glycosylation event. In recent years it has become increasingly clear that protective groups are not necessarily innocent bystanders in a glycosylation event but can influence both reactivity of the donor/acceptor glycoside[2] and the stereochemical outcome and yield of a glycosylation reaction.[3] By carefully selecting the appropriate protective group scheme one can take advantage of this by steering the glycosylation toward the desired interglycosidic linkage. The use of participating groups at the 2-position of donor glycosides is a well-established procedure to obtain 1,2-*trans* glycosidic linkages with high anomeric purity.[1a] Of a more recent date is the discovery that protective groups at positions more distal from the anomeric centre of the donor can also exert remarkable stereochemical control on specific glycosylations.[3] A striking example of the influence of a remote protecting group is represented by 4,6-*O*-benzylidene protected mannopyranose donors, which allow the easy introduction of 1,2-*cis*-mannosidic linkages.[4] Although the presence of 4,6-*O*-benzylidene acetal in several types of mannose donors[5] proved to be effective to obtain β-selective mannosylations, the nature of protective groups at the 3-OH position has also been shown to have a major effect on the α/β-ratio.[6,7] For instance, it has become clear that the bulky 3-*O*-*tert*-butyldimethylsilyl ether reduces the β-selectivity by a steric interaction with the C-2 hydroxyl protecting group,[6] while 3-*O*-carboxylate esters give essentially pure α-mannosides, presumably via neighboring group participation.[3b,7]

We recently reported on the development of the methylsulfonylethoxycarbonyl (Msc, **1**, Fig. 1) functionality as a new orthogonal protective group in the synthesis of glucose containing oligosaccharides.[8] In this work we demonstrated, amongst others, that the Msc group is orthogonal with the levulinoyl (Lev) group and can be easily removed using a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in DMF. At the onset of the here presented work and based on literature precedence[7] we reasoned that the carbonyl character of **1** when introduced onto C-3-OH of 4,6-*O*-benzylidene protected mannopyranose donors would steer

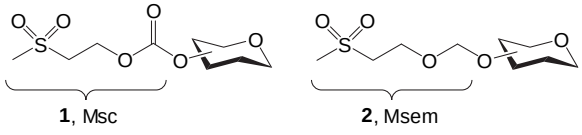

Figure 1. The methylsulfonylethoxycarbonyl (Msc, **1**) and methylsulfonylethoxymethyl (Msem, **2**) protecting groups.

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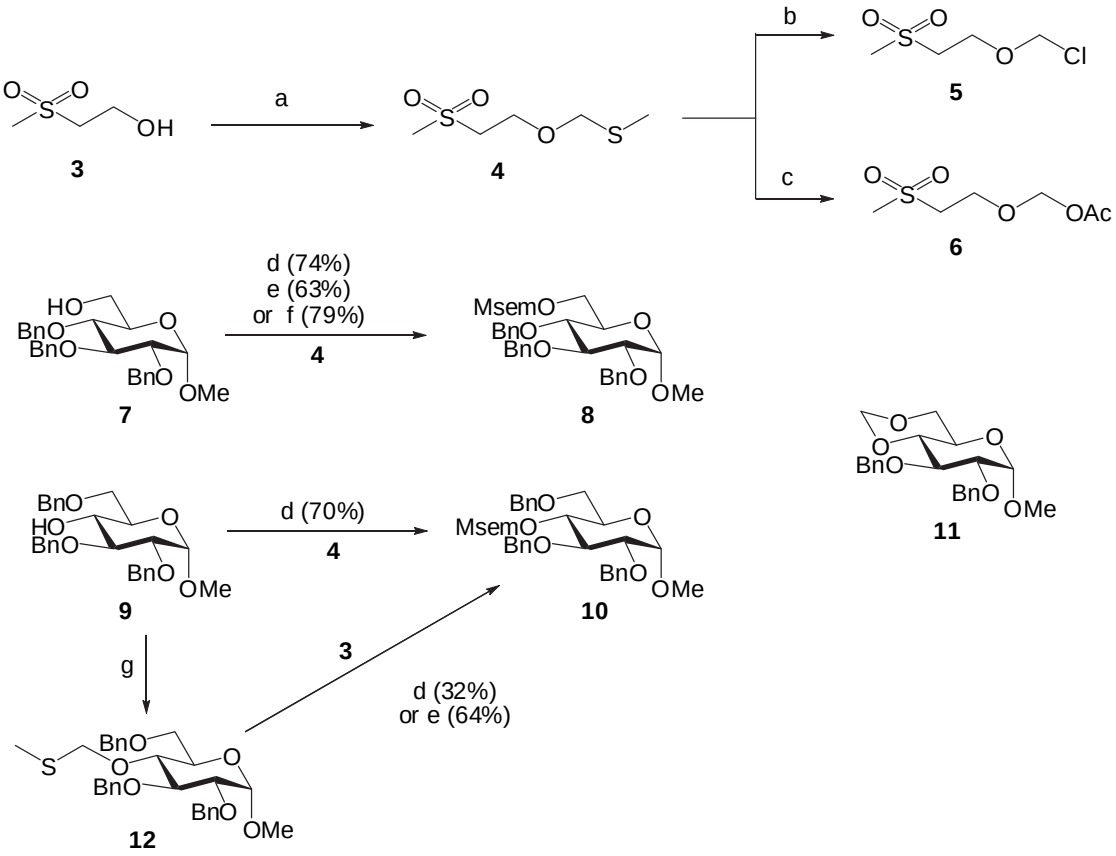
a mannosylation event toward the 1,2-*trans*-linked product. With the aim to install 1,2-*cis*-mannosidic linkages we considered methylsulfonylethoxymethyl (Msem, **2**) as a useful addition to the carbohydrate chemistry protective group palette. In principle, it can be removed by β-elimination in a fashion similar to the removal of Msc **1**. It however lacks the carbonyl and is relatively small and thus we expected little to no interference with the 1,2-*cis* directing effect of the 4,6-*O*-benzylidene moiety in mannoside synthesis. The realization that related alkoxymethyl protective groups such as the cyanoethoxymethyl have proven useful protective groups in RNA oligomer synthesis[9] further strengthened us in our resolve to explore the merits of the Msem functionality as a carbohydrate protective group. We here present our results on the introduction and removal of the Msem group and its use in the construction of a β-1,3-mannan trisaccharide.

2. Results and discussion

The most efficient way to introduce various alkoxymethyl protecting groups is based on the use of thiomethyl intermediates.[9,10] We therefore decided to explore two complementary strategies to introduce the methylsulfonylethoxymethyl (Msem) group on a hydroxyl function. In the first approach, an alkoxymethyl thiomethyl ether reagent is prepared while in the second procedure, the hydroxyl function to be protected is converted into the corresponding thiomethyl ether. First attention was focused on the former approach and to this end commercially available methylsulfonylethanol **3** was converted to thiomethyl ether **4** in 57% yield by treatment with dimethylsulfoxide (DMSO) and acetic anhydride (Ac_2O) in acetic acid (Scheme 1). Condensation of methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **7** with **4** under the influence of *N*-iodosuccinimide (NIS) and trimethylsilyltriflate (TMSOTf)[11] produced Msem-protected **8** in 74% yield (Scheme 1). The preparation of Msem-protected **10** from methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside **9** using reagent **4** and the same activator system demonstrate that this procedure is also suitable to protect secondary hydroxyl functions with the Msem group. Using the milder iodonium di-*sym*-collidine perchlorate (IDCP) as iodonium source,[12] the condensation of methyl glycoside **7** and thiomethyl ether **4** led to the isolation of Msem-protected **8** in 63% yield, whereas activation of **4** with diphenylsulfoxide (Ph_2SO) in combination with trifluoromethanesulfonic anhydride (Tf_2O)[13] and an excess tri-*tert*-butylpyrimidine (TTBP)[14] as a proton scavenger provided **8** in 79% yield.

To investigate whether the Msem group can be introduced under basic conditions methylsulfonylethoxymethyl chloride **5** was prepared by treatment of thiomethyl ether **4** with sulfuryl chloride in DCM. Although it is known that alkyloxymethyl chlorides can be introduced with the aid of tin ketals[15] (vide infra) attention was directed to more stringent conditions. Unfortunately, attempts to introduce the Msem group to the primary hydroxyl in compound **7** with methylsulfonylethoxymethyl chloride **5**, employing either sodium hydride, diisopropylethylamine (DIPEA), 2,6-lutidine or 2,4,6-*syn*-collidine as a base failed and resulted only in the recovery of starting compound **7**. Apparently, chloride **5** is not stable under the applied conditions. The possibility to introduce the Msem under acidic conditions was explored with acetyl acetal **6**, which was produced by reaction of thioether **4** with AcOH under the influence of NIS in 95% yield. Unfortunately the reaction of (2-(methylsulfonyl)ethoxy)methyl acetate **6** and methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside **9** under influence of TfOH or $SnCl_4$ mainly led to the formation of the methylene acetal **11** instead of the desired



Scheme 1. Introduction of the Msem group on glucosyl hydroxyls. Reagents and conditions; (a) AcOH, Ac_2O, DMSO, rt, 48 h, 57%; (b) SO_2Cl_2, DCM, rt, 2 h, 100%; (c) NIS, AcOH, DCM, −20 °C to rt, 2 h, 95%; (d) NIS, TMSOTf, DCM, −20 °C to rt, 24 h; (e) IDCP, DCM, rt, 2 h; (f) DPS, TTBP, Tf_2O, DCM, −60 °C, 2 h; (g) NaH, MTM-Cl, DMF, 1 h, 73%.

Msem-protected **10**, indicating that the Msem can be introduced using acidic conditions, but that the intermediate ketal is sensitive toward these conditions.

The second approach, in which a hydroxyl function in a monosaccharide is firstly transformed into the methylthiomethyl ether and subsequently into the Msem ether was pursued next. 2,3,4-Tri-*O*-benzyl-α-D-glucopyranoside **9** was converted into fully protected **12** by treatment with sodium hydride and methylthiomethyl chloride (MTM-Cl) in DMF (Scheme 1). Condensation of thiomethyl ether **12** with 2-(methylsulfonyl)ethanol **3** using the NIS/TMSOTf combination gave methyl 2,3,6-tri-*O*-benzyl-4-*O*-methylsulfonylethoxymethyl-α-D-glucopyranoside **10** in 20% yield. The low yield can be explained by the predominant formation of methylene acetal **11**. Employing IDCP (4 equiv) as a milder activating system gave **10** in 64% yield but a small amount of side product **11** was also formed in this case.

With two methods at hand for the introduction of the Msem group, we set out to identify the most favorable conditions for cleavage of the Msem group. Therefore, 2,3,4-tri-*O*-benzyl-6-*O*-methylsulfonylethoxymethyl-α-D-glucopyranoside **8** was subjected to conditions that normally effect β-elimination. As summarized in Table 1, the Msem group is reasonably stable under basic conditions, and significantly more robust than its carbonate counterpart (Msc, **1**). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (2 equiv) and reaction for 3 h at elevated temperature (100 °C) were required to completely remove the Msem group (Table 1, entry 1). Addition of thiophenol as the scavenger retarded the time for cleavage considerably (Table 1, entry 2). Complete deblocking of the Msem group with the aid of 5 equiv of potassium *tert*-butoxide (KO^{t}Bu) was achieved after 24 h at 40 °C (Table 1, entry 3). Gratifyingly, treatment of **8** with a catalytic amount of tetrabutylammonium fluoride (TBAF, 0.1 equiv) led to the complete cleavage of the Msem group after 24 h at room temperature (Table 1, entry 4).

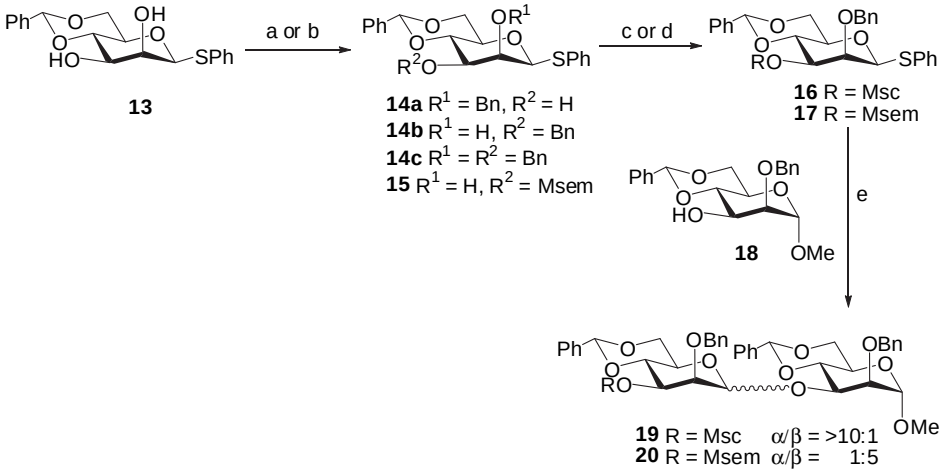
Table 1
Conditions for cleavage of the Msem group

Entry	Conditions	Temperature	Time (h)	Yield
1	DBU (2 equiv), DMF	100 °C	3	91
2	DBU (2 equiv), DMF, PhSH	100 °C	20	93
3	KO^{t}Bu (5 equiv), MeOH	40 °C	24	89
4	TBAF (0.1 equiv), THF	rt	24	94

The feasibility of the Msem acetal as hydroxyl protecting group in oligosaccharide synthesis was investigated in the context of the stereoselective construction of mannosidic bonds. In this respect, the comparison of the here presented Msem group and the methylsulfonylethoxycarbonyl (Msc) group, both relatively small protecting groups and having the methylsulfonylethoxy moiety in common, is relevant (vide supra). To directly compare the influence of the Msem acetal with the Msc carbonate, thiomannosides **16** and **17** were prepared. Benzylation of mannoside **13** under phase transfer conditions[16] provided a separable mixture of the mono benzylated mannosides **14a** and **14b**, and dibenzylated **14c** in a 1.5:4:1 ratio. Mono benzyl ether **14b** was treated with Msc-Cl and pyridine to provide the fully protected MSc-mannoside **16**. Guided by ample literature precedent describing the use of tin ketals to introduce alkoxymethyl ethers,[9a,15] the regioselective alkylation of the 2,3-*O*-dibutylstannylidene of diol **13** with methylsulfonylethoxymethyl chloride **5** was undertaken. A mixture of **13** and dibutyltin oxide in toluene was heated for 2 h and after evaporation of the solvents, the crude product was treated with Msem-Cl **5** in presence of cesium fluoride and tetrabutylammonium bromide (TBABr) in toluene. 3-*O*-Msem protected mannopyranoside **15** was obtained in high yield as the sole regioisomer. Benzylation of this Msem-mannoside could be efficiently effected by treatment of **15** with NaH in the presence of BnBr to give mannoside **17** in 75% yield.

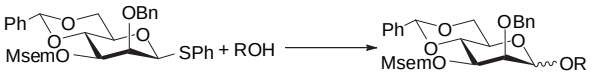
The Ph_2SO/Tf_2O-mediated condensation of 3-*O*-Msc donor **16** with acceptor **18** led to the predominant formation of the α-mannopyranoside linkage in **19** (Scheme 2). This result underlines that, not only carboxylate esters[3b,7] but also carbonates such as the Msc-group at the C-3-hydroxyl of benzylidene mannosides, direct mannosylation reactions toward the α-products. The condensation of 3-*O*-Msem donor **17** with acceptor **18** on the other hand, provided the 1,2-*cis*-linked dimannoside **20** as the major product (Scheme 2). The outcome of this glycosylation indicates that the Msem group does not act as a remote participating group and is sterically minimally intrusive, allowing the selective formation of the β-mannosidic bond in line with recent results from the Crich[17] and Seeberger laboratories.[5e]

The glycosylating properties of 3-*O*-Msem protected mannopyranose **17** were further examined in a set of Ph_2SO/Tf_2O-mediated condensations with a range of different nucleophiles (Table 2).

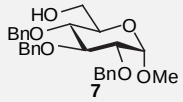
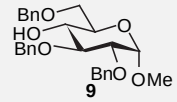
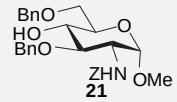
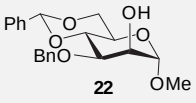
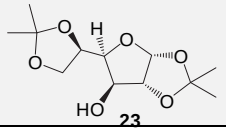


Scheme 2. Coupling of both Msc-protected **16** and Msem-protected **17** with acceptor **18**. Reagents and conditions: (a) BnBr, Bu_4NSO_4, NaOH, DCM, H_2O (**14a**: 17%, **14b**: 44%, **14c**: 11%); (b) (i). Bu_2SnO, toluene, reflux, 2 h: (ii). Msem-Cl, CsF, TBABr, toluene, 18 h, **15**: 81%; (c) Msc-Cl, pyridine, DCM, **16**: 97%; (d) BnBr, TBAI, NaH, DMF, 0 °C, 15 min, **17**: 75%; (e) Ph_2SO, Tf_2O, TTBP, DCM, −78 °C to rt, 2 h, **19**: 78%, **20**: 84%.

Table 2
Glycosylation of donor **17** with various acceptors[a]



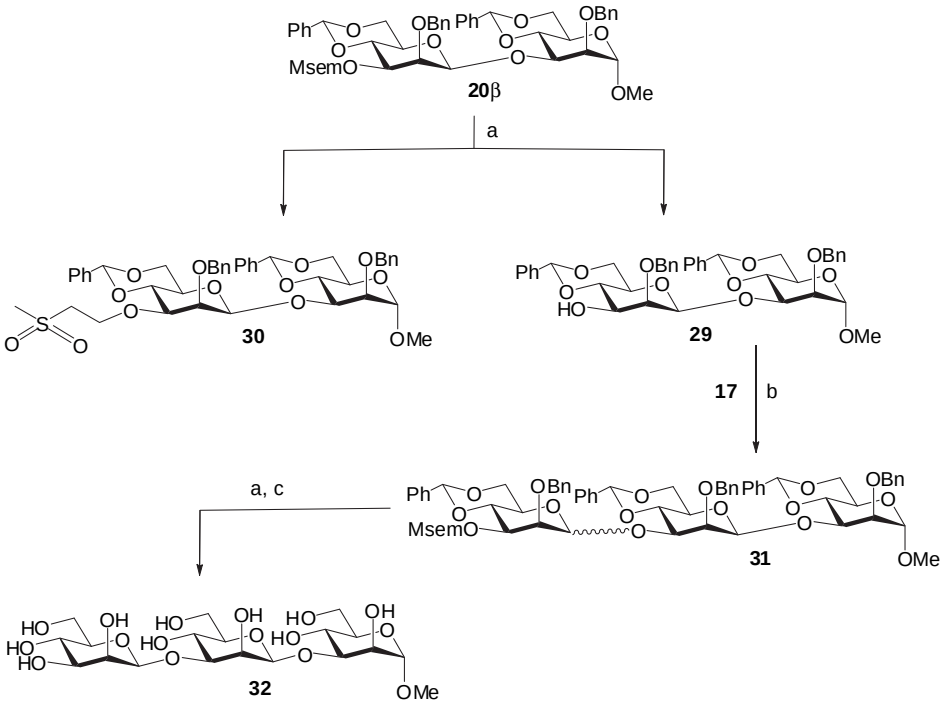
24 R = 7
25 R = 9
26 R = 21
27 R = 22
28 R = 23

Entry	Acceptor (ROH)	Time (h)	Temp.	Yield	α/β
1	 **7**	2	−78 °C to −72 °C	74	4:5
2	 **9**	4	−78 °C to 0 °C	72	1:3
3	 **21**	4	−78 °C to 0 °C	78	1:1
4	 **22**	4	−78 °C to 0 °C	72	1:5
5	 **23**	2	−78 °C to −60 °C	75	1:10

[a] Reagents: TTBP, Ph_2SO, Tf_2O, DCM.

Surprisingly, condensation with primary acceptor **7** furnished the α- and β-isomers of disaccharide **24** in almost equal amounts (Table 2, entry 1).[18] Secondary alcohol **9**, which has previously been shown to be a relatively challenging substrate to β-mannosylate, reacted with donor **17** to provide the α/β-disaccharide **25** in a 1:3 ratio (Table 2, entry 2).[3b,5e,19] When glucosamine acceptor **21**, also a notoriously difficult substrate for the β-mannosylation reaction, was employed, equal amounts of α and β products (**26**) were obtained (Table 2, entry 3).[17,20] Condensation of donor **17** with methyl 4,6-*O*-benzylidine-3-*O*-benzyl-α-D-mannopyranoside **22** on the other hand gave disaccharide **27** with good β-selectivity (α/β=1:5, Table 1, entry 4). The same result, in terms of stereoselectivity and yield was obtained earlier with the corresponding 2-*O*-benzyl acceptor **18** (see Scheme 2). Finally, the use of 1,2:5,6-di-*O*-isopropylidene-3-*O*-α-D-glucofuranose **23** led to the formation of disaccharide **28** in 1:10 α/β ratio (Table 2, entry 6). These experiments show that the glycosylations of **17** can proceed with good to moderate 1,2-*cis* selectivity. It should be noted that the reactivity of the hydroxyl function in the acceptor glycoside plays an important role. Although poor selectivities for acceptors **9**[3b,19] and **21**[5e] have been reported before, the outcome of the mannosylation of primary alcohol **7** stands in sharp contrast to the β-selective mannosylations commonly reported for this acceptor.[4,18] At this moment we cannot offer a conclusive explanation for this unexpected result, but do wish to point out that this result highlights how minor changes in a glycosylation system can result in major changes in the outcome of the reaction.

Finally the assembly of β-1,3-mannotriose **32** was undertaken as depicted in Scheme 3. To this end, the α- and β-anomers of compound **20** were separated by silica gel column chromatography and the Msem group in β-dimer **20** was cleaved by treatment with TBAF to give disaccharide **29** in 60% yield (Scheme 3). Apart from target **29**, a substantial amount of side product **30** was isolated, the formation of which can be explained by Michael addition of the released (methylsulfonyl)ethene to the free C-3-hydroxyl in **29**. Notably this side reaction has not been observed for any other Msem substrate investigated so far. To circumvent the formation of



Scheme 3. The synthesis of β-1,3-mannan **32**. Reagents and conditions; (a) TBAF, piperidine, THF, 24 h, **29**: 88%; (b) TTBP, Ph_2SO, Tf_2O, DCM, −78 °C to rt, 2 h, **31**: 83% (α/β=1:5); (c) $Pd(OH)_2/C$, H_2, 24 h, **32**: 60% over two steps.

side product **30**, piperidine was added to the reaction mixture to scavenge the released vinyl sulfone. In this case disaccharide **29** was obtained in 88% yield. Elongation of **29** by pre-activation of 2 equiv of thioglycoside **17** with Ph_2SO/Tf_2O in the presence of an excess of TTBP furnished trisaccharide **31** in 83% yield, as an anomeric mixture (α/β=1:5). Also in this case, the α- and β-anomers could be separated by silica gel chromatography. Anomerically pure **31** was then deprotected in two steps. First, the Msem group in **30** was removed by treatment with TBAF in the presence of piperidine. Subsequent hydrogenolysis of the remaining benzylidene and benzyl groups using palladium hydroxide on charcoal and hydrogen gas led to the isolation of trisaccharide **32** in 60% yield over two steps.

3. Conclusion

We have reported the development of the methylsulfonylethoxymethyl (Msem) group as a new hydroxyl protecting group that meets the requirements for productive oligosaccharide synthesis. The Msem group can be conveniently introduced at primary and secondary hydroxyl functions of *O*-glycosides with thiomethyl ether reagent **4** and a thiophilic activator. For the installation of the Msem group at the hydroxyl functions of thioglycosides, the conversion of the hydroxyl functions into dibutylstannylidene acetals followed by reaction with Msem-Cl **5** is the method of choice. The methylsulfonylethoxymethyl ether is sterically unbiased, does not provide remote neighboring group participation and is easily removed by a catalytic amount of TBAF in the presence of piperidine as scavenger. The usefulness of the Msem group is illustrated by the synthesis of an all 1,3-*cis*-linked mannotrioside.

4. Experimental

4.1. General method for glycosylations using Ph_2SO/Tf_2O

A solution of the mannopyranosyl donor, diphenylsulfoxide (1.3 equiv) and tri-*tert*-butylpyrimidine (3 equiv) in DCM (0.05 M) was stirred over activated MS 3 Å for 30 min. The mixture was brought to −78 °C before triflic acid anhydride (1.3 equiv) was added. The mixture was allowed to warm to −60 °C in 15 min followed by the addition of the acceptor (1.5 equiv). The reaction mixture was stirred at the temperature described in Table 2. The reaction mixture was quenched with triethylamine (5 equiv), filtered, diluted with DCM and washed with water. The aqueous layer was extracted with DCM thrice, the combined organic layers were dried over $MgSO_4$, filtered, concentrated and purified by size exclusion and silica gel column chromatography.

*4.1.1. ((Methylsulfonylethoxy)methyl)methylsulfane (**4**).* To a solution of methylsulfonylethanol **3** (6.55 g, 52.8 mmol) in DMSO (15 mL, 211 mmol, 4 equiv) was added acetic acid (6 mL, 106 mmol, 2 equiv) and acetic anhydride (9.9 mL, 106 mmol, 2 equiv). The reaction mixture was stirred for 48 h. The mixture was neutralized by careful addition of $NaHCO_{3(s)}$, extracted using a large excess of EtOAc, dried over $MgSO_4$, filtered, concentrated, and purified by silica gel column chromatography to afford **4** (5.54 g, 30.0 mmol, 57%) as a yellow oil. TLC (75% EtOAc in toluene): R_f=0.75; IR (neat, cm^{-1}): 730, 1129, 1286; ^1H NMR (400 MHz, $CDCl_3$) δ=2.15 (s, 3H, $-CH_2SCH_3$), 2.99 (s, 3H, CH_3SO_2-), 3.31 (t, 2H, *J*=5.2 Hz, $MeSO_2CH_2CH_2OCH_2SCH_3$), 3.95 (t, 2H, *J*=5.6 Hz, $MeSO_2CH_2CH_2OCH_2SCH_3$), 4.68 (s, 2H, $MeSO_2(CH_2)_2OCH_2SCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ=13.3 ($-CH_2SCH_3$), 42.0 (CH_3SO_2-), 53.9 ($MeSO_2CH_2CH_2OCH_2SCH_3$), 60.9 ($MeSO_2CH_2CH_2OCH_2SCH_3$), 74.7 ($MeSO_2(CH_2)_2OCH_2SCH_3$); HRMS $[M+NH_4]^+$ calculated for $C_5H_{16}O_3S_2N$ 202.0566, found 202.0566.

*4.1.2. Methylsulfonylethoxymethyl chloride (**5**).* To a solution of ((methylsulfonylethoxy)methyl)methylsulfane **4** (1.39 g, 7.55 mmol) in DCM (25 mL, 0.3 M) was added sulfuryl chloride (0.6 mL, 7.6 mmol, 1 equiv) and the mixture was stirred for 2 h. The solvents were removed in vacuo to give **5**; IR (neat, cm^{-1}): 643, 944, 1112, 1288; ^1H NMR (400 MHz, $CDCl_3$) δ=2.92 (s, 3H, CH_3SO_2-), 3.27 (t, 2H, *J*=5.2 Hz, $MeSO_2CH_2CH_2OCH_2Cl$), 4.07 (t, 2H, *J*=5.6 Hz, $MeSO_2CH_2CH_2OCH_2Cl$), 5.46 (s, 2H, $MeSO_2(CH_2)_2OCH_2Cl$); ^{13}C NMR (100 MHz, $CDCl_3$) δ=42.5 (CH_3SO_2-), 53.9 ($MeSO_2CH_2CH_2OCH_2Cl$), 63.6 ($MeSO_2CH_2CH_2OCH_2Cl$), 81.9 ($MeSO_2(CH_2)_2OCH_2Cl$); HRMS $[M+NH_4]^+$ calculated for $C_4H_{13}ClO_3S_2N$ 190.0299, found 190.0288.

*4.1.3. Methylsulfonylethoxymethylacetate (**6**).* To a solution of ((methylsulfonylethoxy)methyl)methylsulfane **4** (1.05 g, 5.7 mmol) in DCM (29 mL, 0.2 M) was added *N*-iodosuccinimide (1.52 g, 6.83 mmol, 1.2 equiv). The mixture was cooled to −20 °C followed by the addition of acetic acid (0.65 mL, 11.4 mmol, 2 equiv). The mixture was allowed to warm to rt and was stirred for 2 h. The reaction mixture was quenched with triethylamine (5 equiv), filtered, diluted with DCM, and washed with $Na_2S_2O_{3(aq)}$. The aqueous layer was extracted with DCM thrice and the combined organic layers were dried over $MgSO_4$, filtered, concentrated, and purified by silica gel column chromatography to afford **6** (1.06 g, 5.41 mmol, 95%). TLC (66% EtOAc in PE): R_f=0.6; IR (neat, cm^{-1}): 489, 961, 1124, 1285, 1740; ^1H NMR (400 MHz, $CDCl_3$) δ=2.12 (s, 3H, CH_3 OAc), 2.98 (s, 3H, CH_3SO_2-), 3.26 (t, 2H, *J*=5.2 Hz, $MeSO_2CH_2CH_2OCH_2OAc$), 4.09 (t, 2H, *J*=5.6 Hz, $MeSO_2CH_2CH_2OCH_2OAc$), 5.27 (s, 2H, $MeSO_2(CH_2)_2OCH_2OAc$); ^{13}C NMR (100 MHz, $CDCl_3$) δ=20.7 (CH_3 OAc), 42.8 (CH_3 CH_3SO_2-), 54.7 (CH_2 $MeSO_2CH_2CH_2OCH_2OAc$), 63.5 (CH_2 $MeSO_2CH_2CH_2OCH_2OAc$), 88.0 (CH_2 $MeSO_2(CH_2)_2OCH_2OAc$); HRMS $[M+Na]^+$ calculated for $C_6H_{12}O_5S_1Na$ 219.0298, found 219.0298.

*4.1.4. Methyl 2,3,4-tri-O-benzyl-6-O-methylsulfonylethoxymethyl-α-D-glucopyranoside (**8**). Method I*: A solution of methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **7** (0.525 g, 1.14 mmol) and ((methylsulfonylethoxy)methyl)methylsulfane **4** (0.314 g, 1.70 mmol, 1.5 equiv) in DCM (23 mL, 0.05 M) was stirred over activated MS 3 Å for 30 min before *N*-iodosuccinimide (0.304 g, 1.36 mmol, 1.2 equiv) was added. The mixture was cooled to −20 °C followed by the addition of trimethylsilyltrifluoromethanesulfonate (10% in DCM, 0.41 mL, 0.23 mmol, 0.2 equiv). The reaction mixture was stirred for 1.5 h. The reaction mixture was quenched with triethylamine (5 equiv), filtered, diluted with DCM, and washed with $Na_2S_2O_{3(aq)}$. The aqueous layer was extracted with DCM thrice, the combined organic layers were dried over $MgSO_4$, filtered, concentrated, and purified by silica gel column chromatography to provide **8** (0.570 g, 0.949 mmol, 84%).

Method II: A solution of methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **7** (0.102 g, 0.22 mmol) and ((methylsulfonylethoxy)methyl)methylsulfane **4** (0.061 g, 0.33 mmol, 1.5 equiv) in DCM (4.5 mL, 0.05 M) was stirred over activated MS 3 Å for 30 min before iodonium di-*sym*-collidine perchlorate (IDCP, 0.412 g, 0.88 mmol, 8 equiv) was added in the dark. The reaction mixture was stirred in the dark for 24 h. The reaction mixture was quenched with $NH_4Cl_{(aq)}$, filtered, diluted with DCM, and washed with $Na_2S_2O_{3(aq)}$. The aqueous layer was extracted with DCM thrice, the combined organic layers were washed with $NH_4Cl_{(aq)}$, $NaHCO_{3(aq)}$ and brine, dried over $MgSO_4$, filtered, concentrated, and purified by silica gel column chromatography to provide **8** (0.070 g, 0.12 mmol, 63%).

Method III: A solution of ((methylsulfonylethoxy)methyl)methylsulfane **4** (0.058 g, 0.31 mmol, 1.5 equiv), diphenylsulfoxide (0.083 g, 0.41 mmol, 1.3 equiv), and tri-*tert*-butylpyrimidine (0.234 g, 0.942 mmol, 3 equiv) in DCM (6.3 mL, 0.05 M) was stirred

over activated MS 3 Å for 30 min. The mixture was brought to −60 °C before triflic acid anhydride (69 μl, 0.41 mmol, 1.3 equiv) was added. The mixture was allowed to warm to −40 °C in 15 min followed by the addition of methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **7** (0.097 g, 0.21 mmol, 1 equiv). The reaction mixture was stirred for 1 h. The reaction mixture was quenched with triethylamine (5 equiv), filtered, diluted with DCM, and washed with water. The aqueous layer was extracted with DCM thrice, the combined organic layers were dried over $MgSO_4$, filtered, concentrated, and purified by silica gel column chromatography to afford **8** (0.099 g, 0.165 mmol, 79%).

TLC (50% EtOAc in PE): R_f=0.4; $[\alpha]_D^{22}$ +43.0 (*c* 1.0, DCM); IR (neat, cm^{-1}): 696, 1026, 1717; ^1H NMR (400 MHz, $CDCl_3$) δ=2.91 (s, 3H, CH_3 Msem), 3.15 (t, 2H, *J*=5.2 Hz, $MeSO_2CH_2CH_2OCH_2-$), 3.38 (s, 3H, OMe), 3.50–3.55 (m, 2H, H-2, and H-4), 3.73–3.77 (m, 3H, H-5, and 2×H-6), 3.88–4.03 (m, 3H, H-3, and $MeSO_2CH_2CH_2OCH_2-$), 4.57–4.63 (m, 3H, H-1, $MeSO_2(CH_2)_2OCH-$, and CH*H* Bn), 4.65–4.70 (m, 2H, $MeSO_2(CH_2)_2OCH-$, and CH*H* Bn), 4.78–4.82 (m, 2H, 2×CH*H* Bn), 4.92 (d, 1H, *J*=11.2 Hz, CH*H* Bn), 4.99 (d, 1H, *J*=10.8 Hz, CH*H* Bn), 7.26–7.37 (m, 15H, H arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ=42.8 (CH_3 Msem), 55.0 ($MeSO_2CH_2CH_2OCH_2-$), 55.2 (CH_3 OMe), 61.8 ($MeSO_2CH_2CH_2OCH_2-$), 66.8 (C-6), 69.7 (C-5), 73.3 (CH_2 Bn), 74.9 (CH_2 Bn), 75.7 (CH_2 Bn), 77.5, 79.8 (C-2 and C-4), 82.0 (C-3), 95.8 ($MeSO_2(CH_2)_2OCH_2-$), 98.1 (C-1), 127.6–128.4 (CH arom), 138.0 (C_q Bn), 138.2 (C_q Bn), 138.6 (C_q Bn); HRMS $[M+Na]^+$ calculated for $C_{32}H_{40}O_9S_1Na$ 623.2285, found 623.2283.

*4.1.5. Methyl 2,3,6-tri-O-benzyl-4-O-methylsulfonylethoxymethyl-α-D-glucopyranoside (**10**). Method I*: A solution of methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside **9** (0.553 g, 1.2 mmol) and ((methylsulfonylethoxy)methyl)methylsulfane **4** (0.330 g, 1.8 mmol, 1.5 equiv) in DCM (24 mL, 0.05 M) was stirred over activated MS 3 Å for 30 min before *N*-iodosuccinimide (0.320 g, 1.435 mmol, 1.2 equiv) was added. The mixture was cooled to −20 °C followed by the addition of trimethylsilyltrifluoromethanesulfonate (10% in DCM, 0.43 mL, 0.239 mmol, 0.2 equiv). The mixture was stirred for 2 h. The reaction mixture was quenched with triethylamine (5 equiv), filtered, diluted with DCM, and washed with $Na_2S_2O_{3(aq)}$. The aqueous layer was extracted with DCM thrice, the combined organic layers were dried over $MgSO_4$, filtered, concentrated, and purified by silica gel column chromatography to afford **10** (0.530 g, 0.74 mmol, 70%).

Method II: A solution of methyl 2,3,6-tri-*O*-benzyl-4-*O*-methylthiomethyl-α-D-glucopyranoside **12** (0.160 g, 0.31 mmol) and methylsulfonylethanol (0.095 g, 0.77 mmol, 2.5 equiv) in DCM (3 mL, 0.1 M) was stirred over activated MS 3 Å for 30 min before *N*-iodosuccinimide (0.102 g, 0.48 mmol, 1.5 equiv) was added. The mixture was cooled to −20 °C followed by the addition of triflic acid (1% in DCM, 0.4 mL, 0.045 mmol, 0.14 equiv). The mixture was allowed to warm to room temperature. The reaction mixture was quenched with triethylamine (5 equiv), filtered, diluted with DCM, and washed with $Na_2S_2O_{3(aq)}$. The aqueous layer was extracted with DCM thrice, the combined organic layers were dried over $MgSO_4$, filtered, concentrated, and purified by silica gel column chromatography to provide **10** (0.062 g, 0.10 mmol, 32%) and **11** (0.029 g, 0.08 mmol, 25%).

Method III: A solution of methyl 2,3,6-tri-*O*-benzyl-4-*O*-methylthiomethyl-α-D-glucopyranoside **12** (0.200 g, 0.381 mmol) and methylsulfonylethanol (0.118 g, 0.95 mmol, 2.5 equiv) in DCM (7.6 mL, 0.1 M) was stirred over activated MS 3 Å for 30 min before iodonium di-*sym*-collidine perchlorate (IDCP, 0.712 g, 1.524 mmol, 4 equiv) was added in dark. The mixture was stirred in the dark for 24 h. The reaction mixture was quenched with $NH_4Cl_{(aq)}$, filtered, diluted with DCM, and washed with $Na_2S_2O_{3(aq)}$. The aqueous layer was extracted with DCM thrice, the combined organic layers were washed with $NH_4Cl_{(aq)}$, $NaHCO_{3(aq)}$ and brine, dried over $MgSO_4$, filtered, concentrated, and purified by silica gel column chromatography to provide **10** (0.146 g, 0.24 mmol, 64%) and **11** (0.024 g, 0.06 mmol, 16%). Compound **10**: TLC (50% EtOAc in PE): R_f=0.4; $[\alpha]_D^{22}$ +70.4 (*c* 1.0, DCM); IR (neat, cm^{-1}): 524, 1027, 1311; ^1H NMR (400 MHz, $CDCl_3$) δ=2.75 (s, 3H, CH_3 Msem), 2.78–2.90 (m, 2H, $MeSO_2CH_2CH_2OCH_2-$), 3.39 (s, 3H, OMe), 3.54 (dd, 1H, *J*=3.6, 9.6 Hz, H-2), 3.60–3.67 (m, 3H, H-4, and 2×H-6), 3.71 (m, 1H, H-5), 3.75 (m, 2H, $MeSO_2CH_2CH_2OCH_2-$), 3.88 (t, 1H, *J*=9.6 Hz, H-3), 4.50 (d, 1H, *J*=12.0 Hz, CH*H* Bn), 4.59–4.68 (m, 5H, H-1, $MeSO_2(CH_2)_2OCH-$, and 3×CH*H* Bn), 4.73–4.78 (m, 2H, $MeSO_2(CH_2)_2OCH-$, and CH*H* Bn), 5.02 (d, 1H, *J*=10.8 Hz, CH*H* Bn), 7.23–7.35 (m, 15H, H arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ=42.6 (CH_3 Msem), 54.6 ($MeSO_2CH_2CH_2OCH_2-$), 55.1 (CH_3 OMe), 62.3 ($MeSO_2CH_2CH_2OCH_2-$), 68.4 (C-6), 69.6 (C-5), 72.9 (CH_2 Bn), 73.2 (CH_2 Bn), 75.1 (C-4), 75.3 (CH_2 Bn), 79.8 (C-2), 81.0 (C-3), 96.2 ($MeSO_2(CH_2)_2OCH_2-$), 97.6 (C-1), 127.5–128.3 (CH arom), 137.7 (C_q Bn), 138.3 (C_q Bn); HRMS $[M+Na]^+$ calculated for $C_{32}H_{40}O_9S_1Na$ 623.2285, found 623.2283.

*4.1.6. Methyl 2,3-di-O-benzyl-4,6-O-methylidine-α-D-glucopyranoside (**11**).* R_f=0.7; $[\alpha]_D^{22}$ +57.8 (*c* 1.0, DCM); IR (neat, cm^{-1}): 696, 1049; ^1H NMR (400 MHz, $CDCl_3$) δ=3.31 (t, 1H, *J*=9.6 Hz, H-4), 3.38–3.44 (m, 4H, H-6, and CH_3 OMe), 3.50 (dd, 1H, *J*=3.6, 9.2 Hz, H-2), 3.72 (m, 1H, H-5), 3.96 (t,1H, *J*=9.2 Hz, H-3), 4.11 (dd, 1H, *J*=4.8, 10.0 Hz, H-6), 4.55 (d, 1H, *J*=4.0 Hz, H-1), 4.60 (d, 1H, *J*=6.0 Hz, CH*H* methylene), 4.65 (d, 1H, *J*=12.0 Hz, CH*H* Bn), 4.80–4.89 (m, 2H, 2×CH*H* Bn), 4.87 (d, 1H, *J*=11.2 Hz, CH*H* Bn), 5.07 (d, 1H, *J*=6.4 Hz, CH*H* methylene), 7.24–7.35 (m, 10H, H arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ=55.3 (CH_3 OMe), 62.4 (C-5), 68.8 (C-6), 73.6 (CH_2 Bn), 75.2 (CH_2 Bn), 78.5 (C-3), 79.3 (C-2), 82.0 (C-4), 93.7 (CH_2 methylene), 99.1 (C-1), 125.8–130.2 (CH arom), 138.0 (C_q Bn), 138.7 (C_q Bn); HRMS $[M+NH_4]^+$ calculated for $C_{22}H_{30}O_6N$ 404.2068, found 404.2067.

*4.1.7. Methyl 2,3,6-tri-O-benzyl-4-O-methylthiomethyl-α-D-glucopyranoside (**12**).* To a solution of methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside **9** (0.907 g, 2.1 mmol) in DMF (4.2 mL, 0.05 M) was added methylthiomethyl chloride (0.43 mL, 5.2 mmol, 2.5 equiv). The reaction mixture was brought to 0 °C before sodium hydride (60% in oil, 0.150 g, 3.75 mmol, 1.8 equiv) was added in small portions and the stirring was continued for 1 h. The reaction mixture was diluted with diethyl ether and washed with $NH_4Cl_{(aq)}$, $NaHCO_{3(aq)}$ and brine, dried over $MgSO_4$, filtered, concentrated, and purified by silica gel chromatography to provide compound **12** (0.802 g, 1.5 mmol, 73%). TLC (50% toluene in EtOAc): R_f=0.8; $[\alpha]_D^{22}$ +178.0 (*c* 0.3, DCM); IR (neat, cm^{-1}): 530, 1049; ^1H NMR (400 MHz, $CDCl_3$) δ=1.99 (s, 3H, CH_3 MTM), 3.38 (s, 3H, CH_3 OMe), 3.52 (dd, 1H, *J*=3.6, 9.6 Hz, H-2), 3.57 (t, 1H, *J*=10.0 Hz, H-4), 3.64–3.74 (m, 3H, H-5, and 2×H-6), 3.94 (t, 1H, *J*=9.2 Hz, H-3), 4.56 (m, 2H, 2×CH*H* Bn), 4.60–4.62 (m, 2H, H-1, and CH*H* Bn), 4.68 (d, 1H, *J*=10.8 Hz, C*H*H MeSC*H*H–), 4.74–4.78 (m, 3H, C*H*H MeSC*H*H–, and 2×CH*H* Bn), 4.97 (d, 1H, *J*=10.8 Hz, CH*H* Bn), 7.24–7.37 (m, 15H, H arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ=14.7 (CH_3 MTM), 55.2 (CH_3 OMe), 68.8 (C-6), 69.7 (C-5), 73.3 (CH_2 Bn), 73.4 (CH_2 Bn), 75.6 (CH_2 Bn), 76.1 (C-4), 76.7 (CH_2 MeSCH_2–), 79.9 (C-2), 81.8 (C-3), 97.9 (C-1), 127.6–128.4 (CH arom), 138.0 (C_q Bn), 138.0 (C_q Bn), 138.5 (C_q Bn); HRMS $[M+Na]^+$ calculated for $C_{30}H_{36}O_6S_1Na$ 574.2125, found 574.2120.

*4.1.8. Methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside (**7**) (cleavage of Msem from **8**). Method I*: To a solution of **8** (24 mg, 40 μmol) in DMF (0.8 mL, 0.05 M) was added DBU (1 M in DMF, 80 μl, 80 μmol, 2 equiv) and the reaction mixture was heated at 100 °C for 3 h. The reaction mixture was neutralized with $NH_4Cl_{(aq)}$, diluted with EtOAc, washed with $NH_4Cl_{(aq)}$, $NaHCO_{3(aq)}$ and brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified

by silica gel column chromatography to afford methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside **7** (17 mg, 36 μmol, 91%).

Method II: To a solution of **8** (35 mg, 58 μmol) in DMF (1.2 mL, 0.05 M) was added thiophenol (0.2 M in DMF, 0.32 mL, 64 μmol, 1.1 equiv) and DBU (1 M in DMF, 116 μl, 116 μmol, 2 equiv) and the reaction mixture was heated at 100 °C for 20 h. The reaction mixture was neutralized with $NH_4Cl_{(aq)}$, diluted with EtOAc, washed with $NH_4Cl_{(aq)}$, $NaHCO_{3(aq)}$ and brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by silica gel column chromatography to afford methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside **7** (25 mg, 54 μmol, 93%).

Method III: To a solution of **8** (24 mg, 40 μmol) in MeOH (0.8 mL, 0.05 M) was added KO^{t}Bu (23 mg, 0.2 mmol, 5 equiv) and the reaction mixture was heated at 40 °C for 24 h. The reaction mixture was neutralized with $NH_4Cl_{(aq)}$, diluted with EtOAc, washed with $NH_4Cl_{(aq)}$, $NaHCO_{3(aq)}$ and brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by silica gel column chromatography to afford methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside **7** (16 mg, 35 μmol, 89%).

Method IV: To a solution of **8** (34 mg, 57 μmol) in THF (1.1 mL, 0.05 M) was added TBAF (0.1 M in THF, 57 μl, 5.7 μmol, 0.1 equiv) and the reaction mixture was stirred for 24 h. The reaction mixture was neutralized with $NH_4Cl_{(aq)}$, diluted with EtOAc, washed with $NH_4Cl_{(aq)}$, $NaHCO_{3(aq)}$ and brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by silica gel column chromatography to afford methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside **7** (25 mg, 53 μmol, 94%).

*4.1.9. Phenyl 2-O-benzyl-4,6-O-benzylidene-1-thio-β-D-mannopyranoside (**14a**).* To a solution of phenyl 4,6-*O*-benzylidene-1-thio-β-D-mannopyranoside (**13**) (0.355 g, 1.0 mmol) in DCM (13 mL, 0.08 M) was added benzyl bromide (0.14 mL, 1.18 mmol, 1.2 equiv), tetrabutylammonium sulfonate (0.067 g, 0.20 mmol, 0.2 equiv), and $NaOH_{(aq)}$ (1 M, 5 mL, 5.0 mmol, 5 equiv). The reaction mixture was refluxed at 40 °C for 18 h. The reaction mixture was quenched with $NH_4Cl_{(aq)}$, diluted with EtOAc, and extracted thrice with EtOAc. The combined organic layers were washed with $NH_4Cl_{(aq)}$, $NaHCO_{3(aq)}$ and brine, dried over $MgSO_4$, filtered, concentrated, and purified by silica gel chromatography to provide **14a** (0.196 g, 0.44 mmol, 44%), **14b** (0.071 g, 0.16 mmol, 16%), and **14c** (0.058 g, 0.11 mmol, 11%); compound **14a**: TLC (33% Et_2O in PE): R_f=0.25; $[\alpha]_D^{22}$ −21.2 (*c* 1, DCM); IR (neat, cm^{-1}): 695, 731, 1047, 1089, 2360; ^1H NMR (400 MHz, $CDCl_3$) δ=2.56 (s, 1H, OH-3), 3.37 (m, 1H, H-5), 3.82–3.90 (m, H-3, and H-6), 3.97 (t, 1H, *J*=9.6 Hz, H-4), 4.08 (d, 1H, *J*=2.4 Hz, H-2), 4.29 (dd, 1H, *J*=5.2, 10.8 Hz, H-6), 4.85 (d, 1H, *J*=1.2 Hz, H-1), 4.85–4.97 (m, 2H, 2×CH*H* Bn), 5.53 (s, 1H, CH benzylidene), 7.24–7.37 (m, 15H, H arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ=68.3 (C-6), 71.2 (C-5), 72.8 (C-3), 76.6 (CH_2 Bn), 78.6 (C-4), 80.5 (C-2), 88.8 (C-1), 102.0 (CH benzylidene), 126.1–131.1 (CH arom), 134.7 (C_q SPh), 137.1, 137.8 (C_q CHPh and C_q Bn); CH Gated NMR (100 MHz, $CDCl_3$) δ=88.8 (*J*=153 Hz, C-1); HRMS $[M+Na]^+$ calculated for $C_{26}H_{26}O_5S_1Na$ 473.1393, found 473.1390.

*4.1.10. Phenyl 2-O-benzyl-4,6-O-benzylidene-3-O-methylsulfonyleth oxycarbonyl-1-thio-β-D-mannopyranoside (**16**).* A solution of phenyl 2-*O*-benzyl-4,6-*O*-benzylidene-1-thio-β-D-mannopyranoside **14a** (0.140 g, 0.31 mmol) in DCM (1.5 mL, 0.2 M) was cooled to 0 °C before pyridine (75 μl, 0.93 mmol, 3 equiv) was added. Methylsulfonylethoxycarbonyl chloride (Msc-Cl, in 0.5 mL DCM, 0.116 g, 0.62 mmol, 2 equiv) was added drop wise at 0 °C over the span of 30 min. The mixture was allowed to warm to room temperature. The reaction mixture was quenched with methanol, diluted with DCM, washed with $NaHCO_{3(aq)}$ and brine, dried over $MgSO_4$, filtered, concentrated, and purified by silica gel column chromatography to afford **16** (0.182 g, 0.303 mmol, 97%); TLC (50% EtOAc in PE): R_f=0.2; $[\alpha]_D^{22}$ −42.2 (*c* 1, DCM); IR (neat, cm^{-1}): 523, 630, 699, 1134, 1267, 1752; ^1H NMR (400 MHz, $CDCl_3$) δ=2.75 (s, 3H, CH_3 Msc), 3.15–3.20 (m, 1H, CH*H* $MeSO_2CH$*H*CH_2–), 3.24–3.31 (m, 1H, CH*H* $MeSO_2CH$*H*CH_2O–), 3.48 (m, 1H, H-5), 3.90 (t, 1H, *J*=10.4 Hz, H-6), 4.24 (t, 1H, *J*=9.6 Hz, H-4), 4.30 (dd, 1H, *J*=4.8, 10.4 Hz, H-6), 4.36 (d, 1H, *J*=2.8 Hz, H-2), 4.48 (t, 2H, *J*=6.4 Hz, CH_2 $MeSO_2$-CH_2CH_2–), 4.79 (d, 1H, *J*=11.2 Hz, CH*H* Bn), 4.85 (d, 1H, *J*=11.2 Hz, CH*H* Bn), 4.93–4.97 (m, 2H, H-1, and H-3), 5.53 (s, 1H, CH benzylidene), 7.24–7.42 (m, 15H, H arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ=42.3 (CH_3 Msc), 53.4 (CH_2 $MeSO_2CH_2CH_2O$–), 61.5 (CH_2 $MeSO_2$-CH_2CH_2O–), 68.2 (C-6), 71.3 (C-5), 75.2 (C-4), 76.4 (CH_2 Bn), 77.7 (C-3), 78.1 (C-2), 88.6 (C-1), 101.7 (CH benzylidene), 126–134.0 (CH arom), 134.0 (C_q SPh), 136.9, 137.1 (C_q benzylidene and C_q Bn); CH Gated NMR (100 MHz, $CDCl_3$) δ=88.6 (*J*=154 Hz, C-1); HRMS $[M+Na]^+$ calculated for $C_{30}H_{32}O_9S_2Na$ 623.1380, found 623.1378.

*4.1.11. Phenyl 4,6-O-benzylidene-3-O-methylsulfonylethoxymethyl-1-thio-β-D-mannopyranoside (**15**).* To a solution of phenyl 4,6-*O*-benzylidene-1-thio-β-D-mannopyranoside (**13**) (3.0 g, 8.3 mmol) in toluene (55 mL, 0.15 M) was added dibutyltin oxide (2.18 g, 8.77 mmol, 1.05 equiv) and the reaction mixture was refluxed for 2 h. The solvents were evaporated and the residue was co-evaporated with toluene. The mixture was re-dissolved in toluene (55 mL) followed by the addition of tetrabutylammonium bromide (3.23 g, 10 mmol, 1.2 equiv), cesium fluoride (1.51 g, 10 mmol, 1.2 equiv), and methylsulfonylethoxymethyl chloride (1.86 g, 10.8 mmol, 1.3 equiv) and stirring was continued for 18 h. The reaction mixture was diluted with EtOAc, washed with $NaHCO_{3(aq)}$, and extracted thrice with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, concentrated, and purified by silica gel chromatography to provide **15** (3.48 g, 6.85 mmol, 82%); TLC (66% EtOAc in PE): R_f=0.4; $[\alpha]_D^{22}$ −225.0 (*c* 1, DCM); IR (neat, cm^{-1}): 696, 732, 1020, 1310; ^1H NMR (400 MHz, $CDCl_3$) δ=2.83 (s, 3H, CH_3 Msem), 2.95–3.01 (m, 1H, CH*H* $MeSO_2$-CH*H*CH_2OCH_2–), 3.10–3.17 (m, 1H, CH*H* $MeSO_2CH$*H*CH_2OCH_2–), 3.32 (d, 1H, *J*=2.8 Hz, 2-OH), 3.45 (m, 1H, H-5), 3.85–3.93 (m, 3H, H-3, H-6, and CH*H* $MeSO_2CH_2CH$*H*OCH_2–), 3.98–4.04 (m, 1H, CH*H* $MeSO_2CH_2CH$*H*OCH_2–), 4.10 (t, 1H, *J*=9.6 Hz, H-4), 4.29 (dd, 1H, *J*=4.8, 10.4 Hz, H-6), 4.34 (br s, 1H, H-2), 4.80 (d, 1H, *J*=7.2 Hz, CH*H* $MeSO_2(CH_2)_2CH$*H*O–), 4.86 (d, 1H, *J*=7.2 Hz, CH*H* $MeSO_2$(-$CH_2)_2CH$*H*O–), 4.95 (s, 1H, H-1), 5.53 (s, 1H, CH benzylidene), 7.22–7.42 (m, 10H, H arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ=42.6 (CH_3 Msem), 54.5 (CH_2 $MeSO_2CH_2CH_2OCH_2$–), 61.5 (CH_2 $MeSO_2$-$CH_2CH_2OCH_2$–), 68.2 (C-6), 71.1 (C-5), 71.3 (C-2), 76.0 (C-3), 77.0 (C-4), 87.8 (C-1), 94.5 (CH_2 $MeSO_2(CH_2)_2OCH_2$–), 101.6 (CH benzylidene), 125.9–130.9 (CH arom), 134.2 (C_q SPh), 137.1 (C_q benzylidene); CH Gated NMR (100 MHz, $CDCl_3$) δ=87.8 (*J*=152 Hz, C-1); HRMS $[M+Na]^+$ calculated for $C_{23}H_{28}O_8S_2Na$ 519.1118, found 519.1114.

*4.1.12. Phenyl 2-O-benzyl-4,6-O-benzylidene-3-O-methylsulfonyle thoxymethyl-1-thio-β-D-mannopyranoside (**17**).* To a solution of phenyl 4,6-*O*-benzylidene-3-methylsulfonylethoxymethyl-1-thio-β-D-mannopyranoside (**15**) (3.3 g, 6.65 mmol) in DMF (33 mL, 0.2 M) was added benzyl bromide (2 mL, 17.0 mmol, 2.5 equiv) and tetrabutylammonium iodide (2.46 g, 6.65 mmol, 1 equiv). The reaction mixture was brought to 0 °C and sodium hydride (60%, 0.266 g, 6.65 mmol, 1 equiv) was subsequently added in small portions. The reaction mixture was allowed to warm to rt and stirring was continued for 2 h. The reaction mixture was quenched with $NH_4Cl_{(aq)}$, diluted with EtOAc, washed with $NH_4Cl_{(aq)}$, $NaHCO_{3(aq)}$,brine, dried over $MgSO_4$, filtered, concentrated and purified by silica gel chromatography to provide **17** (2.91 g, 4.97 mmol, 75%); TLC (50% EtOAc in PE): R_f=0.6; $[\alpha]_D^{22}$ −30.2 (*c* 1, DCM); IR (neat, cm^{-1}): 738, 1089, 1282; ^1H NMR (400 MHz, $CDCl_3$) δ=2.76 (s, 3H, CH_3 Msem), 2.83–2.89 (m, 1H, CH*H* $MeSO_2CH$*H*CH_2OCH_2–), 3.02–3.09 (m, 1H, CH*H*

$MeSO_2CHHCH_2OCH_2-$), 3.42 (m, 1H, H-5), 3.80–3.96 (m, 4H, H-3, H-6, and CH_2 $MeSO_2CH_2CH_2OCH_2-$), 4.16–4.20 (m, 2H, H-2, and H-4), 4.27 (dd, 1H, J=4.8, 10.4 Hz, H-6), 4.71 (d, 1H, J=6.8 Hz, CH*H* $MeSO_2(CH_2)_2OCHH-$), 4.79 (d, 1H, J=6.8 Hz, CH*H* $MeSO_2(CH_2)_2OCHH-$), 4.82 (d, 1H, J=11.2 Hz, CH*H* Bn), 4.91 (s, 1H, H-1), 4.99 (d, 1H, J=10.8 Hz, CH*H* Bn), 5.53 (s, 1H, CH benzylidene), 7.22–7.50 (m, 15H, H arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ=42.5 (CH_3 Msem), 54.4 (CH_2 $MeSO_2CH_2CH_2OCH_2-$), 61.4 (CH_2 $MeSO_2CH_2CH_2OCH_2-$), 68.1 (C-6), 71.4 (C-5), 75.8 (CH_2 Bn), 76.4 (C-3), 77.5, 78.7 (C-2 and C-4), 88.7 (C-1), 94.0 (CH_2 $MeSO_2(CH_2)_2OCH_2-$), 101.4 (CH benzylidene), 125.9–131.1 (CH arom), 134.5 (C_q SPh), 137.2, 137.5 (C_q benzylidene and C_q Bn); CH Gated NMR (100 MHz, $CDCl_3$) δ=88.7 (J=153 Hz, C-1); HRMS $[M+Na]^+$ calculated for $C_{30}H_{34}O_8S_2Na$ 609.1587, found 609.1585.

*4.1.13. Methyl 2-O-benzyl-4,6-O-benzylidene-3-O-(2-O-benzyl-4,6-O-benzylidene-3-O-methylsulfonylethoxy carbonyl-D-mannopyranosyl)-α-D-mannopyranoside (**19**).* Disaccharide **19** (0.178 g, 0.21 mmol) was prepared in 78% yield from donor **16** (0.160 g, 0.27 mmol, 1 equiv) and acceptor **18** (148 g, 40 mmol, 1.5 equiv) according to the general procedure for glycosylations described above. TLC (33% toluene in EtOAc): R_f=0.6; $[\alpha]_D^{22}$ −8.0 (c 0.5); IR (neat, cm^{-1}): 697, 734, 1020, 1066, 1108, 1829; ^{1}H NMR (500 MHz, $CDCl_3$) δ=2.79 (s, 3H, CH_3 Msem), 3.18–3.22 (m, 1H, $MeSO_2CHHCH_2O-$), 3.27–3.33 (m, 1H, $MeSO_2CHHCH_2O-$), 3.38 (s, 3H, CH_3 OMe), 3.80–3.90 (m, 5H, H-2, H-5, H-5′, H-6, and H-6′), 4.05 (m, 1H, H-2′), 4.08–4.16 (m, 2H, H-4′, CH*H* Bn), 4.20–4.29 (m, 5H, H-3, H-4, H-6, H-6′, and CH*H* Bn), 4.37 (d, 1H, J=12.0 Hz, CH*H* Bn), 4.48 (m, 2H, $MeSO_2CH_2$ CH_2O-), 4.76 (d, 1H, J=1.5 Hz, H-1), 4.79 (s, 2H, H-1′, CH*H* Bn), 5.17 (dd, 1H, J=3.5, 10.5 Hz, H-3′), 5.53 (s, 1H, CH benzylidene), 5.61 (s, 1H, CH benzylidene), 7.0–7.5 (m, 20H, H arom); ^{13}C NMR (125 MHz, $CDCl_3$) δ=42.4 (CH_3 Msem), 53.7 ($MeSO_2CH_2CH_2O-$), 55.0 (CH_3 OMe), 61.4 ($MeSO_2CH_2CH_2O-$), 63.8, 64.4, 77.3 (C-2, C-5, and C-5′), 68.7, 68.9 (C-6 and C-6′), 72.6 (CH_2 Bn), 73.5 (CH_2 Bn), 73.8, 79.3 (C-3 and C-4), 75.4 (C-3′), 75.7 (C-2′), 76.0 (C-4′), 99.2, (C-1′), 100.1, (C-1), 101.9 (CH benzylidene), 102.1 (CH benzylidene), 126.2–129.7 (CH arom), 137.2, 137.3, 137.5 (2×C_q benzylidene, and 2×C_q Bn), 153.5 (C=O Msc); CH Gated NMR (125 MHz, $CDCl_3$) δ=99.2 (J=170 Hz, C-1′), 100.1 (J=182 Hz, C-1). HRMS $[M+Na]^+$ calculated for $C_{45}H_{50}O_{15}SNa$ 885.2763, found 885.2768.

*4.1.14. Methyl 2-O-benzyl-4,6-O-benzylidene-3-O-(2-O-benzyl-4,6-O-benzylidene-3-O-methylsulfonylethoxymethyl-D-mannopyranosyl)-α-D-mannopyranoside (**20**).* Disaccharide **20** (0.317 g, 0.37 mmol, α/β=1:5) was prepared in 84% yield from donor **17** (0.26 g, 0.44 mmol, 1 equiv) and acceptor **18** (0.248 g, 0.67 mmol, 1.5 equiv) according to the general procedure for glycosylations described above.

4.1.14.1. α-Anomer. TLC (33% toluene in EtOAc): R_f=0.66; $[\alpha]_D^{22}$ −2.5 (c 0.4, DCM); IR (neat, cm^{-1}): 698, 1067; ^{1}H NMR (400 MHz, $CDCl_3$) δ=2.64 (s, 3H, CH_3 Msem), 2.70–2.77 (m, 1H, $MeSO_2CHHCH_2OCH_2-$), 2.95 (m, 1H, $MeSO_2CHHCH_2OCH_2-$), 3.38 (s, 3H, CH_3 OMe), 3.78–3.89 (m, 8H), 4.05–4.16 (m, 3H) 4.18–4.29 (m, 4H), 4.42 (d, 1H, J=12.4 Hz, CH*H* Bn), 4.59 (d, 1H, J=7.2 Hz, $MeSO_2(CH_2)_2OCHH-$), 4.70–4.77 (m, 4H, H-1′, 2×CH*H* Bn, and $MeSO_2(CH_2)_2OCHH-$), 5.34 (s, 1H, H-1), 5.57 (s, 1H, CH benzylidene), 5.64 (s, 1H, CH benzylidene), 7.02–7.53 (m, 20H, H arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ=42.7 (CH_3 Msem), 54.8 ($MeSO_2CH_2CH_2OCH_2-$), 55.0 (CH_3 OMe), 61.6 ($MeSO_2CH_2CH_2OCH_2-$), 63.9, 64.8, 72.9, 73.9, 76.3, 77.7, 78.1, 79.2 (C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, and C-5′), 68.8, 68.9 (C-6 and C-6′), 72.5 (CH_2 Bn), 73.2 (CH_2 Bn), 94.6 ($MeSO_2(CH_2)_2OCH_2-$), 99.69 (C-1 and C-1′), 101.8 (CH benzylidene), 102.2 (CH benzylidene), 125.3–129.3 (CH arom), 137.5, 137.6, 137.6 (2×C_q benzylidene and 2×C_q Bn); CH Gated NMR (100 MHz, $CDCl_3$) δ=99.69 (J=173 Hz), 99.71 (J=177 Hz); HRMS $[M+Na]^+$ calculated for $C_{45}H_{52}O_{14}SNa$ 871.2970, found 871.2954.

4.1.14.2. β-Anomer. TLC (33% toluene in EtOAc): R_f=0.4; $[\alpha]_D^{22}$ −68.4 (c 1.0, DCM); IR (neat, cm^{-1}): 750, 1088; ^{1}H NMR (400 MHz, $CDCl_3$) δ=2.74 (s, 3H, CH_3 Msem), 2.82 (dt, 1H, J=4.8, 15.2 Hz, $MeSO_2CHHCH_2OCH_2-$), 3.01–3.08 (m, 1H, $MeSO_2CHHCH_2OCH_2-$), 3.14 (m, 1H, H-5′), 3.38 (CH_3 OMe), 3.61 (dd, 1H, J=3.2, 9.6 Hz, H-3′), 3.69–3.92 (m, 7H, H-2, H-2′, H-5, H-6, H-6′, and $MeSO_2CH_2CH_2OCH_2-$), 4.05 (t, 1H, J=9.6 Hz, H-4′), 4.17–4.22 (m, 2H, H-4, and H-6′), 4.27 (dd, 1H, J=4.4, 9.6 Hz, H-6), 4.33 (dd, 1H, J=3.2, 10.4 Hz, H-3), 4.47 (s, 1H, H-1′), 4.56 (d, 1H, J=7.2 Hz, $MeSO_2(CH_2)_2OCHH-$), 4.66–4.76 (m, 4H, 3×CH*H* Bn, and $MeSO_2(CH_2)_2OCHH-$), 4.80 (s, 1H, H-1), 4.96 (d, 1H, J=12.0 Hz, CH*H* Bn), 5.46 (s, 1H, CH benzylidene), 5.63 (s, 1H, CH benzylidene), 7.19–7.51 (m, 20H, H arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ=42.6 (CH_3 Msem), 54.7 ($MeSO_2CH_2CH_2OCH_2-$), 54.9 (CH_3 OMe), 61.2 ($MeSO_2CH_2CH_2OCH_2-$), 64.0 (C-2, C-2′ or C-5), 67.6 (C-5′), 68.5 (C-6′), 68.8 (C-6), 73.1 (CH_2 Bn), 73.6 (C-3), 74.6 (CH_2 Bn), 74.8 (C-3′), 75.2 (C-2, C-2′ or C-5) 76.0 (C-2, C-2′ or C-5), 77.4 (C-4′), 77.6(C-4), 93.9 ($MeSO_2(CH_2)_2OCH_2-$), 99.1 (C-1′), 99.5 (C-1), 101.6 (CH benzylidene), 101.6 (CH benzylidene), 126.0–129.1 (CH arom), 137.4, 137.5, 137.8, 138.4 (2×C_q benzylidene and 2×C_q Bn); CH Gated NMR (100 MHz, $CDCl_3$) δ=99.1 (J=155 Hz, C-1′), 99.5 (J=172 Hz, C-1); HRMS $[M+Na]^+$ calculated for $C_{45}H_{52}O_{14}SNa$ 871.2970, found 871.2967.

*4.1.15. Methyl 2,3,4-tri-O-benzyl-6-O-(2-O-benzyl-4,6-O-benzylidene-3-O-methylsulfonylethoxymethyl-D-mannopyranosyl)-α-D-glucopyranoside (**24**).* Disaccharide **24** (0.171 g, 0.18 mmol, α/β=4:5) was prepared in 74% yield from donor **17** (0.147 g, 0.25 mmol, 1 equiv) and acceptor **7** (0.174 g, 0.38 mmol, 1.5 equiv) according to the general procedure for glycosylations described above.

4.1.15.1. α-Anomer. TLC (33% toluene in EtOAc): R_f=0.65; $[\alpha]_D^{22}$ +52.2 (c 0.5, DCM); IR (neat, cm^{-1}): 697, 1027; ^{1}H NMR (400 MHz, $CDCl_3$) δ=2.74 (s, 3H, CH_3 Msem), 2.77–2.83 (m, 1H, $MeSO_2CHHCH_2OCH_2-$), 2.98–3.05 (m, 1H, $MeSO_2CHHCH_2OCH_2-$), 3.36 (s, 3H, CH_3 OMe), 3.48 (t, 1H, J=9.2 Hz, H-4), 3.51 (dd, 1H, J=3.6, 10.0 Hz, H-2), 3.65 (dd, 1H, J=1.6, 11.2 Hz, H-6), 3.71 (m, 1H, H-5), 3.80–3.90 (m, 6H, H-6, H-2′, H-5′, H-6′, and $MeSO_2CH_2CH_2OCH_2O-$), 3.98–4.04 (m, 2H, H-3, and H-4′), 4.10–4.16 (m, 2H, H-6, and H-3′), 4.57 (d, 1H, J=3.6 Hz, H-1), 4.60 (d, 1H, J=11.2 Hz, CH*H* Bn), 4.68–4.72 (m, 4H, 3×CH*H* Bn, and $MeSO_2(CH_2)_2OCHH-$), 4.75–4.82 (m, 3H, 2×CH*H* Bn, and $MeSO_2(CH_2)_2OCHH-$), 4.90 (d, 1H, J=1.2 Hz, H-1′), 4.93 (d, 1H, J=11.2 Hz, CH*H* Bn), 5.00 (d, 1H, J=10.4 Hz, CH*H* Bn), 5.55 (s, 1H, CH benzylidene), 7.25–7.42 (m, 25H, H arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ=42.8 (CH_3 Msem), 54.8 ($MeSO_2CH_2CH_2OCH_2-$), 55.2 (CH_3 OMe), 61.6 ($MeSO_2CH_2CH_2OCH_2-$), 64.3 (C-5), 66.2 (C-6′), 68.7 (C-6), 69.7 (C-2′or C-5′), 73.3 (CH_2 Bn), 73.4 (CH_2 Bn), 73.6 (C-3 or C-4′), 74.9 (CH_2 Bn), 75.9 (CH_2 Bn), 76.6 (C-2′ or C-5′), 77.4 (C-4), 78.1 (C-3′), 80.0 (C-2), 82.0 (C-3 or C-4′), 94.7 ($MeSO_2(CH_2)_2OCH_2-$), 98.0 (C-1), 99.2 (C-1′), 100.8 (CH benzylidene), 126.1–129.1 (CH arom), 137.5, 137.8, 138.0, 138.1, 138.4 (C_q benzylidene and 4×C_q Bn); CH Gated NMR (100 MHz, $CDCl_3$) δ=97.9 (J=166 Hz, C-1), 99.2 (J=170 Hz, C-1′); HRMS $[M+Na]^+$ calculated for $C_{52}H_{60}O_{14}SNa$ 963.3596, found 963.3595.

4.1.15.2. β-Anomer. TLC (33% toluene in EtOAc): R_f=0.4; $[\alpha]_D^{22}$ +1.5 (c 0.5, DCM); IR (neat, cm^{-1}): 696, 1026; ^{1}H NMR (400 MHz, $CDCl_3$) δ=2.73 (s, 3H, CH_3 Msem), 2.79–2.85 (m, 1H, $MeSO_2CHHCH_2OCH_2-$), 3.01–3.08 (m, 1H, $MeSO_2CHHCH_2OCH_2-$), 3.29 (m, 1H, H-5′), 3.36 (s, 3H, CH_3 OMe), 3.45 (t, 1H, J=9.6 Hz, H-4), 3.50 (dd, 1H, J=3.6, 9.6 Hz, H-2), 3.55 (dd, 1H, J=5.2, 10.4 Hz, H-6), 3.70 (dd, 1H, J=3.2, 10.0 Hz, H-3′), 3.74–3.87 (m, 4H, H-5, H-2′,

and $MeSO_2CH_2CH_2OCH_2$–), 3.90 (t, 1H, J=10.0 Hz, H-6′), 4.01–4.10 (m, 2H, H-3, and H-4′), 4.14 (dd, 1H, J=1.6, 10.4 Hz, H-6), 4.28 (dd, 1H, J=4.8, 10.4 Hz, H-6), 4.31 (s, 1H, H-1′), 4.51 (d, 1H, J=7.2 Hz, $MeSO_2(CH_2)_2OCHHO$–) 4.54–4.60 (m, 2H, H-1, CH*H* Bn), 4.64–4.69 (m, 2H, CH*H* Bn, and $MeSO_2(CH_2)_2OCHHO$–), 4.73 (d, 1H, J=12.4 Hz, CH*H* Bn), 4.79 (d, 1H, J=12.4 Hz, CH*H* Bn), 4.83 (d, 1H, J=11.2 Hz, CH*H* Bn), 4.87 (d, 1H, J=11.6 Hz, CH*H* Bn), 4.92 (d, 1H, J=12.0 Hz, CH*H* Bn), 5.01 (d, 1H, J=10.8 Hz, CH*H* Bn), 5.53 (s, 1H, CH benzylidene), 7.23–7.44 (m, 25H, H arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ=42.6 (CH_3 Msem), 54.7 ($MeSO_2CH_2CH_2OCH_2$–), 55.1 (CH_3 OMe), 61.2 ($MeSO_2CH_2CH_2OCH_2$–), 67.6 (C-5′), 68.5 (C-6′), 68.6 (C-6), 69.6 (C-2′), 73.3 (CH_2 Bn), 74.7 (CH_2 Bn), 74.7 (C-3′), 74.7 (CH_2 Bn), 75.1 (C-5), 75.7 (CH_2 Bn), 77.6 (C-4), 77.6 (C-4′), 79.8 (C-2), 82.0 (C-3), 93.8 ($MeSO_2(CH_2)_2OCH_2$–), 97.8 (C-1), 101.7 (CH benzylidene), 102.2 (C-1′), 126.0–129.2 (CH arom), 137.4, 138.0, 138.2, 138.3, 138.7 (C_q benzylidene and 4×C_q Bn); CH Gated NMR (100 MHz, $CDCl_3$) δ=97.8 (J=168 Hz, C-1), 102.2 (J=156 Hz, C-1′); HRMS $[M+Na]^+$ calculated for $C_{52}H_{60}O_{14}SNa$ 963.3596, found 963.3603.

*4.1.16. Methyl 2,3,6-tri-O-benzyl-4-O-(2-O-benzyl-4,6-O-benzylidene-3-O-methylsulfonylethoxymethyl-D-mannopyranosyl)-α-D-glucopyranoside (**25**).* Disaccharide **25** (0.135 g, 0.14 mmol, α/β=1:3) was prepared in 72% yield from donor **17** (0.117 g, 0.2 mmol, 1 equiv) and acceptor **9** (0.138 g, 0.3 mmol, 1.5 equiv) according to the general procedure for glycosylations described above.

4.1.16.1. α-Anomer. TLC (33% toluene in EtOAc): R_f=0.45; ^{1}H NMR (400 MHz, $CDCl_3$) δ=2.80 (m, 4H, CH_3 Msem, and $MeSO_2CHHCH_2OCH_2$–), 3.00–3.13 (m, 1H, $MeSO_2CHHCH_2OCH_2$–), 3.41 (s, 3H, CH_3 OMe), 3.55 (m, 1H) 3.76 (m, 6H) 3.84 (m, 4H), 3.98 (m, 2H), 4.09 (m, 1H), 4.20 (d, 1H, J=12.0 Hz, CH*H* Bn), 4.25 (d, 1H, J=12.0 Hz, CH*H* Bn), 4.68 (m, 8H, H-1, 5×CH*H* Bn, and $MeSO_2(CH_2)_2OCH_2$–), 5.17 (d, 1H, J=12.0 Hz, CH*H* Bn), 5.41 (s, 1H, H-1′), 5.54 (s, 1H, CH benzylidene), 7.23–7.43 (m, 25H, H arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ=42.7 (CH_3 Msem), 54.8 ($MeSO_2CH_2CH_2OCH_2$–), 55.4 (CH_3 OMe), 61.5 ($MeSO_2CH_2CH_2OCH_2$–), 68.6, 69.1 (C-6 and C-6′), 73.0 (CH_2 Bn), 73.1 (CH_2 Bn), 73.6 (CH_2 Bn), 74.8 (CH_2 Bn), 65.1, 69.6, 73.4, 76.2, 77.5, 77.8, 79.9, 81.6 (C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 94.4 ($MeSO_2(CH_2)_2OCH_2$–), 97.7 (C-1), 100.5 (C-1′), 101.8 (CH benzylidene), 126.0–129.1 (CH arom), 137.5, 138.0, 138.3, 138.3, 139.4 (C_q benzylidene and 4×C_q Bn); HRMS $[M+Na]^+$ calculated for $C_{52}H_{60}O_{14}SNa$ 963.3596, found 963.3603.

4.1.16.2. β-Anomer. TLC (33% toluene in EtOAc): R_f=0.35; $[\alpha]_D^{22}$ +7.2 (*c* 0.5, DCM); IR (neat, cm^{-1}): 696, 1026; ^{1}H NMR (400 MHz, $CDCl_3$) δ=2.76 (s, 3H, CH_3 Msem), 2.80–2.83 (m, 1H, $MeSO_2CHHCH_2OCH_2$–), 3.05–3.13 (m, 2H, H-5′, and $MeSO_2CHHCH_2OCH_2$–), 3.41 (s, 3H, CH_3 OMe), 3.48–3.58 (m, 3H, H-2, H-3 and H-6′), 3.61–3.68 (m, 3H, H-5, H-6, and H-6), 3.75–3.83 (m, 3H, H-2′, and $MeSO_2CH_2CH_2OCH_2$–), 3.87 (t, 1H, J=9.2 Hz, H-3′), 3.94–4.02 (m, 2H, H-4, and H-4′), 4.09 (dd, 1H, J=5.2, 10.8 Hz, H-6′), 4.46 (d, 1H, J=12.0 Hz, CH*H* Bn), 4.53–4.57 (m, 2H, H-1′, and $MeSO_2(CH_2)_2OCHH$–), 4.60–4.85 (m, 8H, H-1, and 6×CH*H* Bn and $MeSO_2(CH_2)_2OCHH$–), 5.05 (d, 1H, J=10.8 Hz, CH*H* Bn), 5.46 (s, 1H, CH benzylidene), 7.23–7.43 (m, 25H, H arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ=42.8 (CH_3 Msem), 54.6 ($MeSO_2CH_2CH_2OCH_2$–), 55.4 (CH_3 OMe), 61.1 ($MeSO_2CH_2CH_2OCH_2$–), 67.3 (C-5′), 68.5, 68.6 (C-6 and C-6′), 69.7 (C-5), 73.4 (CH_2 Bn), 73.6 (CH_2 Bn), 75.0 (C-3), 75.1 (CH_2 Bn), 75.3 (CH_2 Bn), 76.7 (C-2′), 77.4, 77.9 (C-4 and C-4′), 79.0 (C-2), 80.3 (C-3′), 94.0 ($MeSO_2(CH_2)_2OCH_2$–), 98.4 (C-1), 101.4 (C-1′), 101.6 (CH benzylidene), 126.1–129.2 (CH arom), 137.5, 138.0, 138.3, 138.3, 139.4 (C_q benzylidene and 4×C_q Bn); CH Gated NMR (100 MHz, $CDCl_3$) δ=98.4 (J=170 Hz, C-1), 101.4 (J=156 Hz, C-1′); HRMS $[M+Na]^+$ calculated for $C_{52}H_{60}O_{14}SNa$ 963.3596, found 963.3603.

*4.1.17. Methyl 2-deoxy-3,6-di-O-benzyl-2-(N-carboxybenzyl)-amino-4-O-(2-O-benzyl-4,6-O-benzylidene-3-O-methylsulfonylethoxymethyl-D-mannopyranosyl)-α-D-glucopyranoside (**26**).* Disaccharide **26** (0.177 g, 0.19 mmol, α/β=1:1) was prepared in 78% yield from donor **17** (0.142 g, 0.24 mmol, 1 equiv) and acceptor **21** (0.168 g, 0.36 mmol, 1.5 equiv) according to the general procedure for glycosylations described above.

4.1.17.1. α-Anomer. TLC (33% toluene in EtOAc): R_f=0.5; $[\alpha]_D^{22}$ +58.4 (*c* 0.5, DCM); IR (neat, cm^{-1}): 733, 1311, 1717; ^{1}H NMR (400 MHz, $CDCl_3$) δ=2.78–2.85 (m, 4H, CH_3 Msem, and $MeSO_2CHHCH_2OCH_2$–), 3.03–3.10 (m, 1H, $MeSO_2CHHCH_2OCH_2$–), 3.37 (s, 3H, CH_3 OMe), 3.70–3.83 (m, 6H, H-2, H-4, H-5, H-6, H-6′, and (H-6 or H-6′)), 3.84–3.89 (m, 3H, H-5′, and $MeSO_2CH_2CH_2OCH_2$–), 3.95 (t, 1H, J=9.2 Hz, H-4′), 4.01 (dd, 1H, J=2.8, 10.0 Hz, H-3′), 4.08–4.15 (m, 3H, H-3, H-2′, and (H-6 or H-6′)), 4.21–4.32 (m, 2H, 2×CH*H* Bn), 4.55–4.78 (m, 7H, H-1, 4×CH*H* Bn, and $MeSO_2(CH_2)_2OCH_2$–), 4.92 (d, 1H, J=10.0 Hz, NH), 4.98–5.05 (m, 2H, 2×CH*H* Cbz), 5.36 (s, 1H, H-1′), 5.55 (s, 1H, CH benzylidene), 7.12–7.54 (m, 25H, H arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ=42.8 (CH_3 Msem), 54.4 (C-2′ or C-3), 54.8 ($MeSO_2CH_2CH_2OCH_2$–), 55.3 (CH_3 OMe), 61.6 ($MeSO_2CH_2CH_2OCH_2$–), 67.0 (CH_2 Cbz), 68.6, 69.2 (C-6 and C-6′), 73.0 (CH_2 Bn), 73.6 (CH_2 Bn), 73.8 (CH_2 Bn), 65.3, 70.5, 73.3, 76.0, 77.4, 78.0, 81.1 (C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5-) 94.5 ($MeSO_2(CH_2)_2OCH_2$–), 99.0 (C-1), 100.4 (C-1′), 101.8 (CH benzylidene), 126.2–129.2 (CH arom), 137.6, 137.9, 137.9 (C_q benzylidene and 2×C_q Bn), 155.8 (C=O Cbz); CH Gated NMR (100 MHz, $CDCl_3$) δ=99.0 (J=169 Hz, C-1), 100.4 (J=174 Hz, C-1′); HRMS $[M+H]^+$ calculated for $C_{53}H_{62}NO_{15}S$ 984.38347, found 984.38438, $[M+Na]^+$ calculated for $C_{53}H_{61}NO_{15}SNa$ 1006.3654, found 1006.3659.

4.1.17.2. β-Anomer. TLC (33% toluene in EtOAc): R_f=0.35; $[\alpha]_D^{22}$ +16.4 (*c* 0.5, DCM); IR (neat, cm^{-1}): 522, 1028, 1717; ^{1}H NMR (400 MHz, $CDCl_3$) δ=2.76 (s, 3H, CH_3 Msem), 2.78–2.85 (m, 1H, $MeSO_2CHHCH_2OCH_2$–), 3.06–3.15 (m, 2H, $MeSO_2CHHCH_2OCH_2$–, and H-5′), 3.36 (s, 3H, CH_3 OMe), 3.46 (t, 1H, J=10.0 Hz, H-6′), 3.53 (t, 1H, J=9.6 Hz, H-4), 3.59 (dd, 1H, J=2.8, 10.0 Hz, H-3′), 3.65–3.68 (m, 2H, 2×H-6), 3.83 (m, 4H, H-2′, H-3, and $MeSO_2CH_2CH_2OCH_2$–), 3.95–4.03 (m, 2H, H-2, and H-4′), 4.04–4.12 (m, 2H, H-5, H-6′), 4.50–4.59 (m, 4H, H-1, 2×CH*H* Bn, and $MeSO_2(CH_2)_2OCHH$–), 4.71–4.74 (m, 3H, H-1′, and CH*H* Bn and $MeSO_2(CH_2)_2OCHH$–), 4.80 (m, 2H, NH, and CH*H* Bn), 4.87 (d, 1H, J=12.0 Hz, CH*H* Bn), 5.00–5.12 (m, 3H, CH*H* Bn, and 2×CH*H* Cbz), 5.45 (s, 1H, CH benzylidene), 7.23–7.43 (m, 25H, H arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ=42.9 (CH_3 Msem), 54.6 ($MeSO_2CH_2CH_2OCH_2$–), 55.3 (CH_3 OMe), 61.1 ($MeSO_2CH_2CH_2OCH_2$–), 66.8 (CH_2 Cbz), 67.2 (C-5′), 68.5 (C-6 and C-6′), 70.5 (C-3), 73.5 (CH_2 Bn), 74.3 (CH_2 Bn), 75.0 (C-3), 75.1 (CH_2 Bn), 75.3 (CH_2 Bn), 76.7 (C-2′), 77.8 (C-4′), 77.9 (C-2 and C-5), 78.5 (C-4), 94.0 ($MeSO_2(CH_2)_2OCH_2$–), 98.9 (C-1), 101.6 (CH benzylidene), 101.8 (C-1′), 126.0–129.2 (CH arom), 137.5, 138.0, 138.3, 138.3, 139.4 (C_q benzylidene and 4×C_q Bn), 155.9 (C=O Cbz); CH Gated NMR (100 MHz, $CDCl_3$) δ=98.9 (J=173 Hz, C-1), 101.6 (J=157 Hz, C-1′); HRMS $[M+H]^+$ calculated for $C_{53}H_{62}NO_{15}S$ 984.3835, found 984.3846; $[M+Na]^+$ calculated for $C_{53}H_{61}NO_{15}SNa$ 1006.3654, found 1006.3661.

*4.1.18. Methyl 3-O-benzyl-4,6-O-benzylidene-2-O-(2-O-benzyl-4,6-O-benzylidene-3-O-methylsulfonylethoxymethyl-D-mannopyranosyl)-α-D-mannopyranoside (**27**).* Disaccharide **27** (0.117 g, 0.14 mmol, α/β=1:5) was prepared in 72% yield from donor **17** (0.112 g, 0.19 mmol, 1 equiv) and acceptor **22** (0.107 g, 0.29 mmol, 1.5 equiv) according to the general procedure for glycosylations described above.

4.1.18.1. α-Anomer. TLC (33% toluene in EtOAc): R_f=0.6; $[\alpha]_D^{22}$ −8.5 (*c* 0.3, DCM); IR (neat, cm^{-1}): 696, 1040, 1312; ^{1}H NMR (400 MHz, $CDCl_3$) δ=2.81.2.87 (m, 4H, CH_3 Msem, and $MeSO_2CHHCH_2OCH_2$–), 3.04–3.11 (m, 1H, $MeSO_2CHHCH_2OCH_2$–), 3.37 (s,

3H, CH_3 OMe), 3.77–3.94 (m, 7H), 3.98 (dd, 1H, *J*=3.2, 10.0 Hz), 4.00–4.17 (m, 4H), 4.27 (m, 2H), 4.42 (d, 1H, *J*=12.0 Hz, CH*H* Bn), 4.51 (d, 1H, *J*=12.0 Hz, CH*H* Bn), 4.67–4.69 (m, 3H, H-1 or H-1′, CH*H* Bn, and $MeSO_2(CH_2)_2OCHH-$), 4.81–4.85 (m, 2H, CH*H* Bn, and $MeSO_2(CH_2)_2OCHH-$), 5.33 (d, 1H, *J*=0.8 Hz, H-1 or H-1′), 5.58 (s, 1H, CH benzylidene), 5.69 (s, 1H, CH benzylidene), 7.23–7.54 (m, 20H, H arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ=42.9 (CH_3 Msem), 54.8 (CH_3 OMe), 54.9 ($MeSO_2CH_2CH_2OCH_2-$), 61.5 ($MeSO_2CH_2CH_2OCH_2-$), 68.6, 68.7 (C-6 and C-6′), 63.9, 64.6, 72.6, 75.4, 76.3, 76.5, 78.3, 79.0 (C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 73.0 (CH_2 Bn), 73.7 (CH_2 Bn), 94.5 ($MeSO_2(CH_2)_2OCH_2-$), 100.3, 101.1 (C-1 and C-1′), 101.4 (CH benzylidene), 101.8 (CH benzylidene), 126.0–129.2 (CH arom), 137.4, 137.5, 137.8, 138.3 (2×C_q benzylidene and 2×C_q Bn); CH Gated NMR (100 MHz, $CDCl_3$) δ=100.3 (*J*=170 Hz), 101.1 (*J*=171 Hz); HRMS $[M+Na]^+$ calculated for $C_{45}H_{52}O_{14}SNa$ 871.2971, found 871.2967.

4.1.18.2. β-Anomer. TLC (33% toluene in EtOAc): R_f=0.35; $[\alpha]_D^{22}$ −61.8 (*c* 1.0, DCM); IR (neat, cm^{-1}): 696, 1084, 1312; ^1H NMR (400 MHz, $CDCl_3$) δ=2.77 (s, 3H, CH_3 Msem), 2.84 (dt, 1H, *J*=3.6, 16.4 Hz, $MeSO_2CHHCH_2OCH_2-$), 3.04–3.11 (m, 1H, $MeSO_2CHHCH_2OCH_2-$), 3.30–3.38 (m, 4H, CH_3 OMe, and H-5′), 3.71–3.82 (m, 5H, H-3, H-5, H-6, and $MeSO_2CH_2CH_2OCH_2-$), 3.88 (t, 1H, *J*=10.4 Hz, H-6′), 3.94–3.98 (m, 2H, H-3, and H-2′), 4.09–4.18 (m, 2H, H-4, and H-4′), 4.23 (m, 1H, H-2), 4.27–4.30 (m, 2H, H-6, and H-6′), 4.53 (d, 1H, *J*=6.8 Hz, $MeSO_2(CH_2)_2OCHH-$), 4.69 (s, 1H, H-1′), 4.72–4.79 (m, 4H, H-1, 2×CH*H* Bn, and $MeSO_2(CH_2)_2OCHH-$), 4.93 (d, 1H, *J*=12.0 Hz, CH*H* Bn), 5.06 (d, 1H, *J*=12.4 Hz, CH*H* Bn), 5.51 (s, 1H, CH benzylidene), 5.55 (s, 1H, CH benzylidene), 7.23–7.39 (m, 20H, H arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ=42.7 (CH_3 Msem), 54.7 ($MeSO_2CH_2CH_2OCH_2-$), 54.9 (CH_3 OMe), 61.1 ($MeSO_2CH_2CH_2OCH_2-$), 64.0 (C-3′ or C-5), 67.8 (C-5′), 68.5 (C-6′), 68.9 (C-6), 71.4 (CH_2 Bn), 74.0 (C-3 or C-2′), 74.3 (C-3′ or C-5), 74.5 (CH_2 Bn), 75.4 (C-3 or C-2′), 75.8 (C-2), 77.5 (C-4′), 78.7 (C-4), 93.8 ($MeSO_2(CH_2)_2OCH_2-$), 99.5 (C-1), 101.2 (C-1′), 101.6 (CH benzylidene), 101.6 (CH benzylidene), 126.0–129.1 (CH arom), 137.3, 137.5, 138.2, 138.8 (2×C_q benzylidene and 2×C_q Bn); CH Gated NMR (100 MHz, $CDCl_3$) δ=99.5 (*J*=167 Hz, C-1), 101.2 (*J*=153 Hz, C-1′); HRMS $[M+Na]^+$ calculated for $C_{45}H_{52}O_{14}SNa$ 871.2970, found 871.2969.

*4.1.19. 1,2:5,6-Di-O-isopropylidene-3-O-(2-O-benzyl-4,6-O-benzylidene-3-O-methylsulfonylethoxymethyl-D-mannopyranosyl)-α-D-glucofuranoside (**28**).* Disaccharide **28** (0.139 g, 0.187 mmol, α/β=1:10) was prepared in 75% yield from donor **17b** (0.147 g, 0.25 mmol, 1 equiv) and acceptor **23** (0.098 g, 0.38 mmol, 1.5 equiv) according to the general procedure for glycosylations described above.

4.1.19.1. α-Anomer. TLC (50% toluene in EtOAc): R_f=0.6; $[\alpha]_D^{22}$ +50.0 (*c* 0.5, DCM); IR (neat, cm^{-1}): 697, 1026; ^1H NMR (400 MHz, $CDCl_3$) δ=1.33 (s, 3H, CH_3 isopropylidene), 1.36 (s, 3H, CH_3 isopropylidene), 1.43 (s, 3H, CH_3 isopropylidene), 1.51 (s, 3H, CH_3 isopropylidene), 2.84–2.88 (m, 4H, CH_3 Msem, and $MeSO_2CHHCH_2OCH_2-$), 3.07–3.10 (m, 1H, $MeSO_2CHHCH_2OCH_2-$), 3.79–3.92 (m, 5H, H-2′, H-5′, H-6′, and $MeSO_2CH_2CH_2OCH_2-$), 4.00 (dd, 1H, *J*=3.2, 10.0 Hz, H-3′), 4.05–4.08 (m, 2H, H-4, and H-6), 4.15–4.20 (m, 2H, H-4′, and H-6), 4.23 (m, 1H, H-5), 4.31–4.35 (m, 2H, H-3′, and H-6), 4.57 (d, 1H, *J*=3.6 Hz, H-2), 4.62 (d, 1H, *J*=7.2 Hz, $MeSO_2(CH_2)_2OCHH-$), 4.66 (d, 1H, *J*=12.4 Hz, CH*H* Bn), 4.76–4.79 (m, 2H, CH*H* Bn, and $MeSO_2(CH_2)_2OCHH-$), 5.30 (s, 1H, H-1′), 5.61 (s, 1H, CH benzylidene), 5.84 (d, 1H, *J*=3.6 Hz, H-1), 7.17–7.47 (m, 10H, H arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ=25.4 (CH_3 isopropylidene), 26.2 (CH_3 isopropylidene), 26.8 (CH_3 isopropylidene), 26.9 (CH_3 isopropylidene), 42.8 (CH_3 Msem), 54.8 ($MeSO_2CH_2CH_2OCH_2-$), 61.6 ($MeSO_2CH_2CH_2OCH_2-$), 65.0 (C-5′), 67.8 (C-6), 68.7 (C-6′), 72.4 (C-5), 73.0 (C-3′), 73.0 (CH_2 Bn), 75.9 (C-2′), 78.0 (C-4′), 80.1 (C-3), 81.4 (C-4), 84.0 (C-2), 94.7 ($MeSO_2(CH_2)_2OCH_2-$), 99.4 (C-1′), 101.7 (CH benzylidene), 105.2 (C-1), 109.5 (C_q isopropylidene), 112.2 (C_q isopropylidene), 125.9–129.2 (CH arom), 137.3, 137.6 (C_q benzylidene and C_q Bn); CH Gated NMR (100 MHz, $CDCl_3$) δ=99.4 (*J*=172 Hz, C-1′), 105.2 (*J*=181 Hz, C-1); HRMS $[M+Na]^+$ calculated for $C_{36}H_{48}O_{14}SNa$ 759.2657, found 759.2660.

4.1.19.2. β-Anomer. TLC (50% toluene in EtOAc): R_f=0.4; $[\alpha]_D^{22}$ −43.0 (*c* 0.5, DCM); IR (neat, cm^{-1}): 697, 733, 1025; ^1H NMR (400 MHz, $CDCl_3$) δ=1.33 (s, 3H, CH_3 isopropylidene), 1.34 (s, 3H, CH_3 isopropylidene), 1.44 (s, 3H, CH_3 isopropylidene), 1.51 (s, 3H, CH_3 isopropylidene), 2.80 (s, 3H, CH_3 Msem), 2.82–2.88 (m, 1H, $MeSO_2CHHCH_2OCH_2-$), 3.08–3.15 (m, 1H, $MeSO_2CHHCH_2OCH_2-$), 3.35 (m, 1H, H-5′), 3.73–3.85 (m, 3H, H-3′, and $MeSO_2CH_2CH_2OCH_2-$), 3.90–3.96 (m, 2H, H-2′, and C-6′), 4.05–415 (m, 3H, 2×H-6, and H-4′), 4.30–4.32 (m, 3H, H-3, H-4, and H-6′), 4.42 (m, 1H, H-5), 4.51 (d, 1H, *J*=4.0 Hz, H-2), 4.55 (d, 1H, *J*=6.8 Hz, $MeSO_2(CH_2)_2OCHH-$), 4.64 (s, 1H, H-1′), 4.70–4.74 (m, 2H, CH*H* Bn, and $MeSO_2(CH_2)_2OCHH-$), 4.88 (d, 1H, *J*=12.0 Hz, CH*H* Bn), 5.56 (s, 1H, CH benzylidene), 5.93 (d, 1H, *J*=3.6 Hz, H-1), 7.15–7.45 (m, 10H, H arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ=25.4 (CH_3 isopropylidene), 26.2 (CH_3 isopropylidene), 26.5 (CH_3 isopropylidene), 26.6 (CH_3 isopropylidene), 42.8 (CH_3 Msem), 54.5 ($MeSO_2CH_2CH_2OCH_2-$), 61.0 ($MeSO_2CH_2CH_2OCH_2-$), 66.0 (C-6), 67.7 (C-5′), 68.3 (C-6′), 72.9 (C-5), 74.4 (C-3′), 74.8 (CH_2 Bn), 75.9 (C-2′), 77.6 (C-4′), 80.3, 80.9 (C-3 and C-4), 82.6 (C-2), 93.9 ($MeSO_2(CH_2)_2OCH_2-$), 100.2 (C-1′), 101.5 (CH benzylidene), 104.8 (C-1), 108.6 (C_q isopropylidene), 111.9 (C_q isopropylidene), 125.2–129.1 (CH arom), 137.2, 137.8 (C_q benzylidene and C_q Bn); CH Gated NMR (100 MHz, $CDCl_3$) δ=100.2 (*J*=154 Hz, C-1′), 104.8 (*J*=181 Hz, C-1); HRMS $[M+Na]^+$ calculated for $C_{36}H_{48}O_{14}SNa$ 759.2657, found 759.2659.

*4.1.20. Methyl 2-O-benzyl-4,6-O-benzylidene-3-O-(2-O-benzyl-4,6-O-benzylidene-β-D-mannopyranosyl)-α-D-mannopyranoside (**29**).* To a solution of methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-(2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-methysulfonylethoxymethyl-β-D-mannopyranosyl)-α-D-mannopyranoside (**20β**) (0.148 g, 0.17 mmol) in THF (3.5 mL, 0.05 M) was added piperidine (35 μl, 0.35 mmol, 2 equiv) followed by the addition of tetrabutylammonium fluoride (0.01 M in THF, 1.74 mL, 0.1 equiv). The reaction mixture was stirred for 24 h. The reaction mixture was quenched with $NH_4Cl_{(aq)}$, diluted with EtOAc, washed with $NH_4Cl_{(aq)}$, $NaHCO_{3(aq)}$, brine, dried over $MgSO_4$, filtered, concentrated, and purified by silica gel chromatography to give **29** (0.114 g, 0.160 mmol, 92%). TLC (50% EtOAc in PE): R_f=0.8; $[\alpha]_D^{22}$ −48.0 (*c* 0.6, DCM); IR (neat, cm^{-1}): 535, 698, 1093; ^1H NMR (500 MHz, $CDCl_3$) δ=2.59 (br s, 1H, OH-3′), 3.12 (m, 1H, H-5′), 3.35 (CH_3 OMe), 3.63–3.71 (m, 2H, H-5′, and H-6′), 3.71 (d, 1H, *J*=4.0 Hz, H-2′), 3.79–3.88 (m, 4H, H-2, H-5, H-6, H-4′), 4.11–4.15 (m, 2H, H-4, and H-6′), 4.25 (dd, 1H, *J*=4.0, 9.5 Hz, H-6), 4.30 (dd, 1H, *J*=3.5, 10.0 Hz, H-3), 4.44 (s, 1H, H-1′), 4.58–4.62 (m, 2H, 2×CH*H* Bn), 4.70 (d, 1H, *J*=12.0 Hz, CH*H* Bn), 4.79 (s, 1H, H-1), 4.97 (d, 1H, *J*=11.0 Hz, CH*H* Bn), 5.20 (br s, 1H, CH benzylidene), 5.57 (s, 1H, CH benzylidene), 7.16–7.49 (m, 20H, H arom); ^{13}C NMR (125 MHz, $CDCl_3$) δ=54.8 (CH_3 OMe), 64.0 (C-2 or C-5), 66.6 (C-5′), 68.5 (C-6′), 68.7 (C-6), 70.0 (C-3′), 72.6 (C-3), 72.9 (CH_2 Bn), 74.3 (C-2 or C-5), 74.5 (CH_2 Bn), 77.1 (C-4 and C-2′), 79.7 (C-4′), 98.0 (C-1′), 99.4 (C-1), 101.4 (CH benzylidene), 101.8 (CH benzylidene), 126.1–128.9 (CH arom), 137.2, 137.4, 137.5, 138.0 (2×C_q benzylidene and 2×C_q Bn); CH Gated NMR (100 MHz, $CDCl_3$) δ=98.0 (*J*=158 Hz, C-1′), 99.4 (*J*=168 Hz, C-1); HRMS $[M+H]^+$ calculated for $C_{41}H_{45}O_{11}$ 713.29564, found 713.29657; $[M+Na]^+$ calculated for $C_{41}H_{44}O_{11}Na$ 735.2776, found 735.2778.

*4.1.21. Methyl 2-O-benzyl-4,6-O-benzylidene-3-O-(2-O-benzyl-4,6-O-benzylidene-3-O-methylsulfonylethyl-D-mannopyranosyl)-α-D-mannopyranoside (**30**).* The title compound was obtained as a side product in the reaction of **20β** with TBAF without piperidine as a scavenger. TLC (50% EtOAc in PE): R_f=0.6; $[\alpha]_D^{22}$ −33.4 (*c* 1.0, DCM);

IR (neat, cm^{-1}): 730, 1061; ^1H NMR (400 MHz, $CDCl_3$) δ=2.79 (s, 3H, CH_3 Mse), 3.01–3.16 (m, 2H, $MeSO_2CH_2CH_2-$), 3.36 (m, 1H, H-5′), 3.39 (CH_3 OMe), 3.70–3.80 (m, 3H, H-2′, H-6′, and $MeSO_2CH_2CH_2-$), 3.80–3.93 (m, 4H, H-2, H-5, H-6, and $MeSO_2CH_2CH_2-$), 4.04 (t, 1H, J=8.8 Hz, H-4′), 4.08–4.20 (m, 2H, H-4, and H-6′), 4.29 (dd, 1H, J=4.4, 10.0 Hz, H-6), 4.32 (dd, 1H, J=3.2, 10.0 Hz, H-3), 4.39 (s, 1H, H-1′), 4.58 (d, 1H, J=12.4 Hz, CH*H* Bn), 4.63 (d, 1H, J=11.6 Hz, CH*H* Bn), 4.74 (d, 1H, J=12.4 Hz, CH*H* Bn), 4.82 (s, 1H, H-1), 4.96 (d, 1H, J=11.6 Hz, CH*H* Bn), 5.26 (br s, 1H, CH benzylidene), 5.63 (s, 1H, CH benzylidene), 7.19–7.50 (m, 20H, H arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ=43.1 (CH_3 Mse), 54.9 (CH_3 OMe), 55.3 ($MeSO_2CH_2CH_2-$), 63.8 ($MeSO_2CH_2CH_2-$), 64.0 (C-2 or C-5), 67.0 (C-5′), 68.6 (C-6′), 68.8 (C-6), 72.6 (C-3), 72.9 (CH_2 Bn), 74.2 (CH_2 Bn), 74.4 (C-2 or C-5), 74.9 (C-2′), 77.2 (C-4), 77.3 (C-4′), 77.7 (C-3′), 99.1 (C-1′), 99.4 (C-1), 101.2 (CH benzylidene), 101.8 (CH benzylidene), 126.0–129.0 (CH arom), 137.2, 137.5, 137.6, 138.2 (2×C_q benzylidene and 2×C_q Bn); CH Gated NMR (100 MHz, $CDCl_3$) δ=99.1 (J=160 Hz, C-1′), 99.5 (J=167 Hz, C-1); HRMS $[M+Na]^+$ calculated for $C_{44}H_{50}O_{13}SNa$ 841.2864, found 841.2868.

*4.1.22. Methyl 2-O-benzyl-4,6-O-benzylidene-3-O-[2-O-benzyl-4,6-O-benzylidene-3-O-(2-O-benzyl-4,6-O-benzylidene-3-O-methylsulfonylethoxymethyl-D-mannopyranosyl)-β-D-mannopyranosyl]-α-D-mannopyranoside (**31**).* Trisaccharide **31** (0.199 g, 0.17 mmol, α/β=1:5) was prepared in 83% yield from donor **17** (0.172 g, 0.30 mmol, 1.5 equiv) and acceptor **29** (0.144 g, 0.20 mmol, 1 equiv) according to the general procedure for glycosylations described above.

4.1.22.1. α-Anomer. TLC (33% toluene in EtOAc): R_f=0.66; $[\alpha]_D^{22}$ −2.5 (*c* 0.4, DCM); IR (neat, cm^{-1}): 698, 1067; ^1H NMR (400 MHz, $CDCl_3$) δ=2.59 (s, 3H, CH_3 Msem), 2.72–2.76 (m, 1H, $MeSO_2CHHCH_2OCH_2-$), 2.91–2.98 (m, 1H, $MeSO_2CHHCH_2OCH_2-$), 3.05–3.10 (m, 1H, H-5′) 3.36 (s, 3H, CH_3 OMe), 3.68 (dd, 1H, J=3.2, 10.0 Hz, H-3′), 3.75–3.92 (m, 10H) 4.01–4.36 (m, 10H), 4.39 (d, 1H, J=12.0 Hz, CH*H* Bn), 4.56–4.60 (m, 2H, CH*H* Bn, and $MeSO_2(CH_2)_2OCHH-$), 4.73–4.79 (m, 3H, 2×CH*H* Bn, and $MeSO_2(CH_2)_2OCHH-$), 4.85 (s, 1H), 4.97 (d, 1H, J=12.0 Hz, CH*H* Bn), 5.27 (s, 1H), 5.55 (s, 1H, CH benzylidene), 5.59 (s, 1H, CH benzylidene), 5.63 (s, 1H, CH benzylidene), 7.03–7.51 (m, 30H, H arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ=42.8 (CH_3 Msem), 54.8 ($MeSO_2CH_2CH_2OCH_2-$), 55.0 (CH_3 OMe), 61.5 ($MeSO_2CH_2CH_2OCH_2-$), 64.0, 64.8, 67.4, 72.9, 72.9, 74.2, 76.2, 76.5, 78.0, 78.2, 78.2, 78.6 (C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′, C-2″, C-3″, C-4″, and C-5″), 68.6, 68.8 (C-6, C-6′, and C-6″), 72.6 (CH_2 Bn), 72.7 (CH_2 Bn), 75.0 (CH_2 Bn), 94.8 ($MeSO_2(CH_2)_2OCH_2-$), 98.7, 99.1, 99.8 (C-1, C-1′, and C-1″), 101.7 (CH benzylidene), 101.8 (CH benzylidene), 102.0 (CH benzylidene), 126.1–129.3 (CH arom), 137.5, 137.6, 137.6 (3×C_q benzylidene and 3×C_q Bn); HRMS $[M+Na]^+$ calculated for $C_{65}H_{72}O_{19}SNa$ 1211.4281, found 1211.4285.

4.1.22.2. β-Anomer. TLC (33% toluene in EtOAc): R_f=0.45; $[\alpha]_D^{22}$ −136.4 (*c* 1.0, DCM); IR (neat, cm^{-1}): 698, 1092; ^1H NMR (400 MHz, $CDCl_3$) δ=2.72 (s, 3H, CH_3 Msem), 2.72–2.82 (m, 1H, $MeSO_2CHHCH_2OCH_2-$), 2.99–3.00 (m, 1H, $MeSO_2CHHCH_2OCH_2-$), 3.10–3.15 (m, 2H, H-5′, and H-5″), 3.40 (CH_3 OMe), 3.52 (dd, 1H, J=3.2, 10.0 Hz, H-3′ or H-3″), 3.71 (m, 1H, H-2′ or H-2″), 3.75 (m, 1H, $MeSO_2CH_2CHHOCH_2-$), 3.82–3.95 (m, 8H, H-2, H-5, H-6, H-2′ or H-2″), (H-3′ or H-3″), H-6′, H-6″, and $MeSO_2CH_2CHHOCH_2-$), 4.01 (m, 1H, H-4′ or H-4″), 4.08 (m, 1H, H-4′ or H-4″), 4.15–4.22 (m, 3H, H-4, H-6′, and H-6″), 4.28 (dd, 1H, J=3.6, 9.2 Hz, H-6), 4.34–4.38 (m, 2H, H-3, and (H-1′ or H-1″), 4.43 (s, 1H, H-1′ or H-1″), 4.49 (d, 1H, J=6.8 Hz, $MeSO_2(CH_2)_2OCHH-$), 4.64 (d, 1H, J=7.2 Hz, $MeSO_2(CH_2)_2OCHH-$), 4.66–4.75 (m, 3H, 3×CH*H* Bn), 4.78 (d, 1H, J=12.0 Hz, CH*H* Bn), 4.85 (s, 1H, H-1), 4.96 (d, 1H, J=12.0 Hz, CH*H* Bn), 5.04 (d, 1H, J=12.0 Hz, CH*H* Bn), 5.46 (s, 1H, CH benzylidene), 5.48 (s, 1H, CH benzylidene), 5.58 (s, 1H, CH benzylidene), 7.15–7.48 (m, 30H, H arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ=42.5 (CH_3 Msem), 54.7 ($MeSO_2CH_2CH_2OCH_2-$), 55.0 (CH_3 OMe), 61.3 ($MeSO_2CH_2CH_2OCH_2-$), 64.0, 74.2, 74.2, 74.4 (C-2, C-3 C-2′, and C-5), 67.5, 67.8 (C-5′ and C-5″), 68.5, 68.6 (C-6′ and C-6″), 68.8 (C-6), 72.7 (CH_2 Bn), 72.8 (C-3), 74.3 (CH_2 Bn), 74.5 (CH_2 Bn), 74.6 (C-2″), 75.2 (C-3″), 77.0, (C-4″), 77.3 (C-4), 77.4 (C-4′), 93.7 ($MeSO_2(CH_2)_2OCH_2-$), 98.1, 98.4 (C-1′ and C-1″), 99.2 (C-1), 101.5 (CH benzylidene), 101.7 (CH benzylidene), 101.7 (CH benzylidene), 125.3–129.7 (CH arom), 137.3, 137.4, 137.5, 137.5, 138.3, 138.6 (3×C_q benzylidene and 3×C_q Bn); CH Gated NMR (100 MHz, $CDCl_3$) δ=98.1 (J=153 Hz, C-1′ or C-1″), 98.1 (J=155 Hz, C-1′ or C-1″), 99.2 (J=167 Hz, C-1); HRMS $[M+Na]^+$ calculated for $C_{65}H_{72}O_{19}SNa$ 1211.4281, found 1211.4284.

*4.1.23. Methyl 3-O-[3-O-(β-D-mannopyranosyl)-β-D-mannopyranosyl]-α-D-mannopyranoside (**31**).* To a solution of methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-[2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-(2-*O*-benzyl-4,6-*O*-benzylidene3-*O*-methysulfonylethoxymethyl -β-D-mannopyranosyl)-β-D-mannopyranosyl] α-D-mannopyranoside **31β** (40 mg, 35 μmol) in THF (0.7 mL, 0.05 M) were added piperidine (7 μl, 70 μmol, 2 equiv) and tetrabutylammonium fluoride (0.01 M in THF, 0.35 mL, 3.5 μmol, 0.1 equiv). The reaction mixture was stirred for 24 h. The reaction mixture was quenched with $NH_4Cl_{(aq)}$, diluted with EtOAc, washed with $NH_4Cl_{(aq)}$, $NaHCO_{3(aq)}$, brine, dried over $MgSO_4$, filtered, concentrated, and purified by silica gel chromatography to provide methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-[2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-(2-*O*-benzyl-4,6-*O*-benzylidene-β-D-mannopyranosyl)-β-D-mannopyranosyl]-α-D-mannopyranoside. This trimer was dissolved in MeOH (1 mL) and H_2O (0.7 mL) before the addition of catalytic amount of Pd $(OH)_2$ on charcoal. The mixture was stirred for 24 h under an H_2-atmosphere, filtered, and purified by gel filtration (HW-40), to afford trisaccharide **32** (11 mg, 21 μmol, 60%); ^1H NMR (600 MHz, $CDCl_3$) δ=3.30–3.37 (m, 5H) 3.49 (t, 1H, J=9.6 Hz), 3.58–3.61 (m, 2H), 3.63–3.67 (m, 5H), 3.83–3.88 (m, 3H), 3.91 (dd, 1H, J=2.4, 9.6 Hz), 3.95 (dd, 1H, J=3.0, 9.6 Hz), 3.98 (d, 1H, J=2.4 Hz), 4.06 (s, 1H), 4.19 (s, 1H), 4.73 (s, 1H), 4.74 (s, 1H), 4.79 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ=53.7 (CH_3 OMe), 61.8, 61.9 (C-6, C-6′, and C-6″), 66.1, 66.2, 67.8, 67.9, 68.7, 71.7, 73.3, 73.8, 77.0, 77.3, 78.2, 79.8 (C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′, C-2″, C-3″, C-4″, C-5″), 97.6, 97.7, 101.6 (C-1, C-1′, and C-1″); HRMS $[M+Na]^+$ calculated for $C_{19}H_{34}O_{16}Na$ 541.1739, found 541.1736.

Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.06.007. These data include MOL files and InChIKeys of the most important compounds described in this article.

References and notes

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