Protective group strategies in carbohydrate and peptide chemistry

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CHAPTER 4

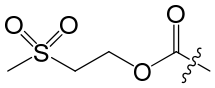
The methylsulfonylethoxymethyl (Msem) as a hydroxyl protecting group in oligosaccharide synthesis

Introduction:

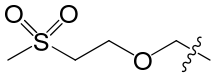
The development of suitable protecting groups is an important objective in synthetic organic chemistry. Although numerous protecting groups for hydroxyl functions are available,[1] the palette of protecting groups that is commonly applied *en route* to an oligosaccharide is quite limited. Benzyl ethers (Bn)[2] and benzoyl (Bz)[3] or pivaloyl (Piv)[4] esters are usually selected as permanent protecting groups, to be removed only at the end of the synthesis of the target oligosaccharide. Among the temporary protecting groups that allow chain elongation by selective deprotection, the levulinoyl (Lev),[5] the 9-fluorenylmethoxycarbonyl (Fmoc),[6] the *p*-methoxybenzyl (PMB) ether,[7] and silyl ethers such as *tert*-butyldimethylsilyl (TBDMS)[8] and *tert*-butyldiphenylsilyl (TBDPS)[9] are most often used. In addition, diol protecting groups, such as the benzylidene acetal,[10] and the

isopropylidene[11] and di-*tert*-butylsilyl ketal[12] are often employed. With the current state of the art in oligosaccharide synthesis it is becoming increasingly clear that the nature of the protecting group at each position on the core of the reacting donor and acceptor glycosides.

Figure 1: The Msc protecting group.



1, Msc



2, Msem

may exert influence on the stereochemical outcome and yield of a glycosylation reaction. Consequently, not only the armed-disarmed concept on the reactivity of glycosyl donors is continuously adjusted and expanded,[13] but also the knowledge of the stereodirecting power of various substituents on the core of the glycosyl donors is progressing.[14] A striking example of the influence of a remote protecting group is presented by the 4,6-*O*-benzylidene protection in mannose donors that allow the easy introduction of the challenging 1,2-cis mannose linkage.[15] On the other hand, the *cis*-directing power of the 4,6-*O*-benzylidene acetal in mannopyranose donors can be overshadowed by the presence of bulky ether or participating acyl groups at the C-3 OH.[16] In this framework alkoxymethyl protecting groups have recently attracted attention.[16,17] A range of alkoxymethyl groups, such as the cyanoethoxymethyl group have been developed in the field of RNA synthesis.[18] Protecting groups at the C-2 hydroxyl of an RNA building block must meet strict requirements to prevent both unwanted removal *en route* to the fully protected oligoribonucleotide and phosphate diester migration at the end of the synthesis. The endeavors on the methylsulfonylethoxycarbonyl (Msc) group **1**, as described in Chapter 2,[19] together with the favorable properties of the cyanoethoxymethyl group in RNA chemistry, in terms of intermediate stability and ease of removal at the end of the oligo nucleotide assembly were an incentive to explore the methylene analogue of the Msc group in oligosaccharide synthesis. In this chapter the methylsulfonylethoxymethyl (Msem, **2**) is introduced for the protection of carbohydrates and its applicability in the synthesis of β−1,3-*O*-mannotriose is demonstrated.

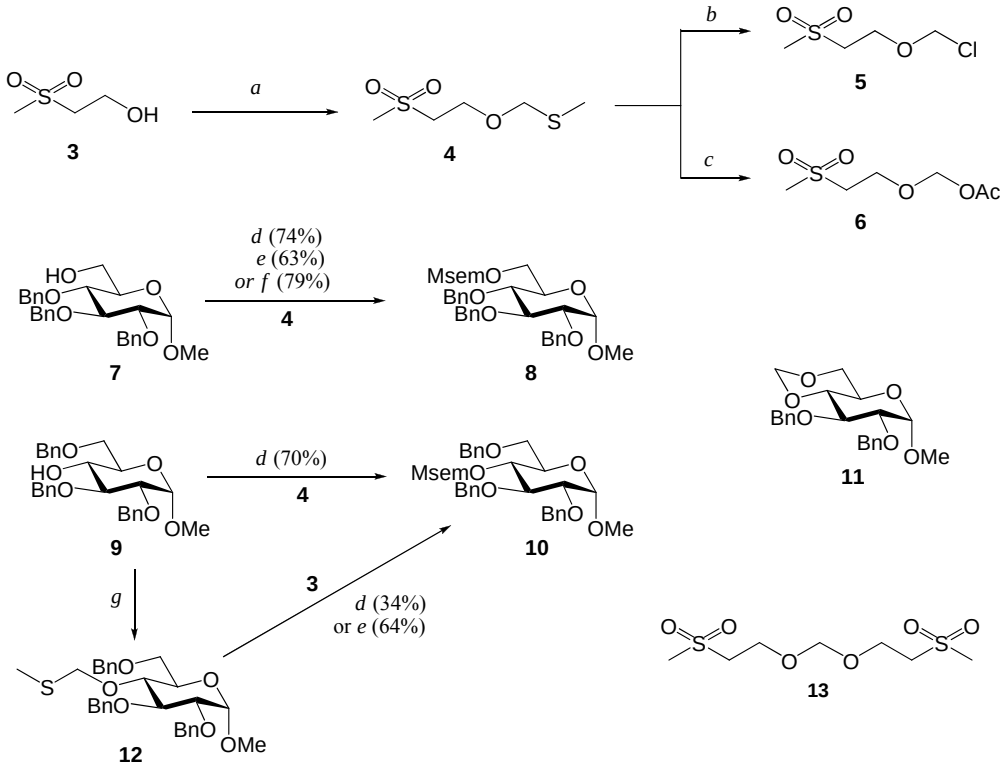
Results and discussion:

The most efficient way to introduce various alkoxymethyl protecting groups relies on the use of thiomethyl intermediates.[5b,20] Therefore it was 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 methylthiomethyl 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). Thiomethyl ether reagent **4** can be used for the introduction of the Msem group at hydroxyl functions using chemistry developed for glycosylations of thioglycosides. Condensation of methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **7** with reagent **4** under the influence of *N*-iodosuccinimide (NIS) and trimethylsilyltriflate (TMSOTf) produced Msem protected **8** in 70% 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 indicate 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, the condensation of methyl glycoside **7** and thiomethyl ether **4** led to the isolation of Msem protected **8** in 63% yield. The yield of this reaction could be increased to 79% by activation of **4** with diphenylsulfoxide (Ph_2SO) in combination with trifluoromethanesulfonic anhydride (Tf_2O) and an excess of tri-*tert*-butylpyrimidine (TTBP) as a proton scavenger. This reaction was accompanied by the formation of side-product **13**.

Since reagent **4** and thioglycosides can both be activated with iodonium or sulfonium ions, orthogonal conditions were sought that are suitable for introduction of the Msem group at hydroxyl functions of thioglycosides. To this end, the thiomethyl ether **4** was transformed into methylsulfonylethoxymethyl chloride **5** by treatment with sulfuryl chloride in DCM. 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, the chloride **5** is not stable under the applied conditions. Since thioglycosides can withstand acidic conditions, attention was shifted to 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 Msem protected **10**, indicating that the Msem can be introduced using acidic conditions, but that the resulting ketal also reacts under these conditions.

Scheme 1: Introduction of the Msem group.



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 ºC to RT, 2 h, 95%; *d*) NIS, TMSOTf, DCM, -20 ºC to RT, 24h; *e*) IDCP, DCM, RT, 2h; *f*) DPS, TTBP, Tf_2O, DCM, -60 ºC, 2h. *g*) NaH, MTM-Cl, DMF, 1h, 73%.

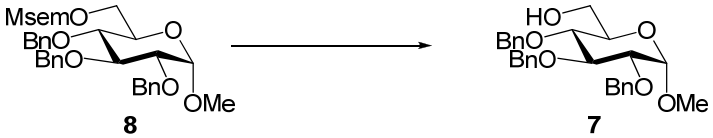
The second approach, in which a hydroxyl function in a monosaccharide is firstly transformed into the methylthiomethyl ether and subsequently into the Msem ether was next pursued. 2,3,4-Tri-*O*-benzyl-α-D-glucopyranoside **9** was converted into fully protected **12** by treatment with sodium hydride and methylthiomethyl chloride (MTM-Cl) in DMF (Scheme 1). Condensation of thiomethyl ether **12** with 2-(methylsulfonyl)ethanol **3** using the NIS/TfOH combination gave methyl 2,3,6-tri-*O*-benzyl-4-*O*-methylsulfonylethoxymethyl-α-D-glucopyranoside **10** in only 34% yield. The low yield can be explained by the unwanted formation of methylene acetal **11**. Employing IDCP (4 equivalents) as a more mildly activating system improved the yield of **10** to 64% but did not completely circumvent the formation of side product **11**. The fluorous analogue of the Msem group could also be constructed under these conditions in combination with ([1H,1H,2H,2H]-perfluorodecyl)sulfonylethanol as a nucleophile. Because of the low reactivity of this alcohol, the side product **11** prevailed in the reaction mixture and the fluorous Msem protected glucose **14** was obtained in unproductive yield.

With two methods at hand for the introduction of the Msem group, the most favorable conditions for cleavage of the Msem group were sought. Therefore, 2,3,4-tri-*O*-benzyl-6-*O*-methylsulfonylethoxymethyl-α-D-glucopyranoside **8** was subjected to conditions that normally effectuate β-elimination. As summarized in Table 1, the Msem group is reasonably stable under basic conditions, and significantly more robust than its carbonate counterpart. The use of 2 equivalents 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) required 3h at elevated temperature (100 ºC) 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). The deblocking of the Msem group with the aid of 5 equivalents of potassium *tert*-butoxide (KOtBu) reached completion after 24 hours at 40 ºC (Table 1, entry 3). Gratifyingly, treatment of **8** with a catalytic amount of tetrabutyl ammonium fluoride (TBAF, 0.1 equivalents) led to the cleavage of the Msem group after 24 hours at room temperature (Table 1, Entry 4).

The feasibility of the Msem group as hydroxyl protecting group in oligosaccharide synthesis was investigated in the context of the construction of 1,2-*cis*-mannosidic bonds. In a seminal study of the group of Crich, it was discovered that glycosylations using 4,6-*O*-benzylidene mannosyl sulfoxides or thiomannosides as glycosyl donors led to the formation

of β-mannosides with high stereoselectivity.[15] Although the presence of 4,6-*O*-benzylidene acetal in several types of mannose donors 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. 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,[21] while 3-*O*-carboxylate esters essentially give pure α–mannosides, presumably *via* neighboring group participation.[16] 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.

Table 1: Conditions for cleavage of the Msem group.

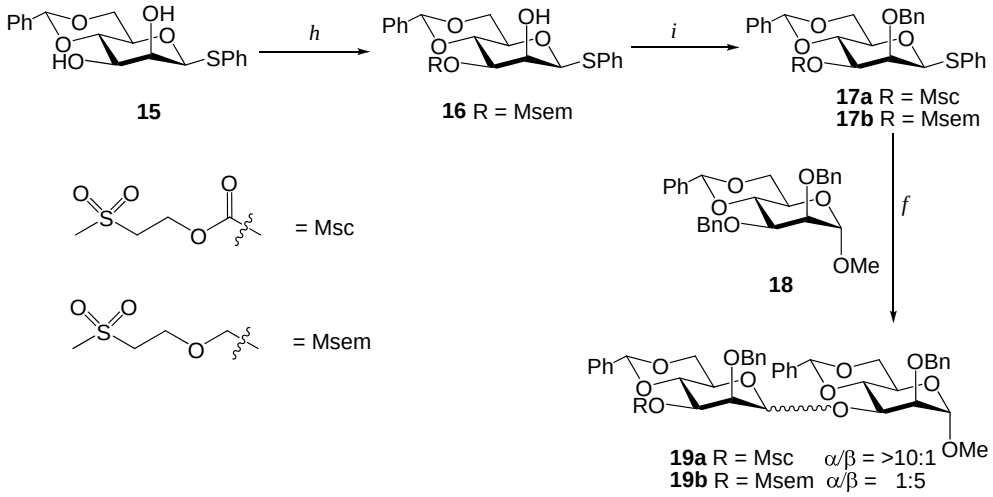


8 **7**

Entry	Conditions	Conc.	Temperature	Time	Yield
1	DBU, DMF	2 eq	100º C	3h	91
2	DBU, DMF, PhSH	2 eq	100º C	20h	93
3	KOtBu, MeOH	5 eq	40º C	24h	89
4	TBAF, THF	0.1 eq	RT	24h	94

In Chapter 2, it was described that the Msc carbonate is an orthogonally removable hydroxyl protecting group that efficiently provides anchimeric assistance during glycosylation reactions. It was shown that the Ph_2SO /Tf_2O mediated condensation of 3-*O*-Msc donor **17a** with acceptor **18** led to the predominant formation of the α-mannopyranoside linkage (Scheme 2). This result underlines that not only carboxylate esters but also carbonates such as the Msc-group at the C-3 hydroxyl of benzylidene mannosides direct mannosylation reactions towards the α products. To investigate the effect of the Msem ether instead of the Msc carbonate in a similar condensation, the synthesis of donor **17b** was required (Scheme 2). Guided by ample literature precedent describing the use of tin ketals to introduce alkoxymethyl ethers, the regioselective alkylation of the 2,3-*O*-dibutylstannylidene of diol **15** with methylsulfonylethoxymethyl chloride **5** was undertaken. A mixture of **15** and dibutyltin oxide in toluene was heated for 2 hours and after evaporation of the solvents, the crude product was treated with Msem-Cl **5**

Scheme 2: Coupling of both Msc protected **17a** and Msem protected **17b** with acceptor **18**.



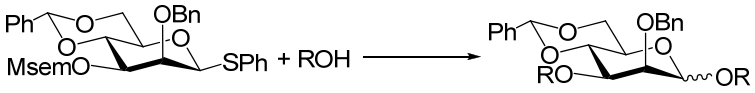
Reagents and conditions; *f*) TTBP, Ph_2SO, Tf_2O, DCM, -78 º C-RT, 2h; *h*) i- Bu_2SnO, tol, Reflux, 2h: ii- Msem-Cl, CsF, TBABr, tol, 18 h, 81% ; *i*) NaH, DMF, 0 ºC, 15 min, 75%.

in the presence of cesium fluoride and tetrabutylammonium bromide (TBABr). 3-*O*-Msem protected mannopyranoside **16** was obtained in high yield as the sole regio isomer. The key

Ph_2SO /Tf_2O mediated condensation of 3-*O*-Msem donor **17b** with acceptor **18** led to the predominant formation of a *cis*-mannopyranoside linkage (α:β = 1:5) (Scheme 2). The outcome of this glycosylation indicates that the Msem group does not act as a remote neighboring group and is sterically minimally intrusive, allowing the selective formation of the β-mannoside bond in line with a comparable study of Codée et al. on the use of [triisopropyl)silyloxy]methyl group.[16a]

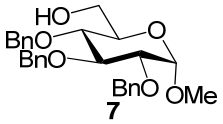
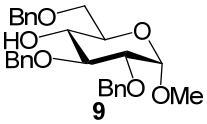
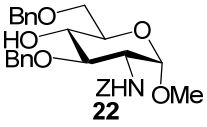
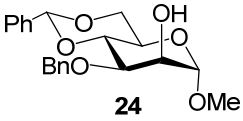
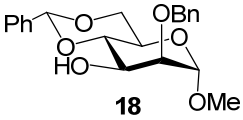
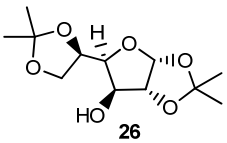
The glycosylating properties of 3-*O*-Msem protected mannopyranose **17b** were further examined in a set of Ph_2SO /Tf_2O-mediated condensation with a range of different nucleophiles (Table 2). Surprisingly, the coupling with primary acceptor **7** furnished the α- and β-isomers of disaccharide **20** in almost equal amounts (Table 2, Entry 1, **20**). Secondary alcohol **9**, which has previously been shown to be a relatively challenging substrate to β-mannosylate, reacted with donor **17b** to provide the α/β-disaccharide in a 1/3 ratio (Table 2, Entry 2, **21**). When glucosamine acceptor **22**, also a notoriously difficult substrate for the β-mannosylation reaction, was employed, equal amounts of α and β products were obtained (Table 2, Entry 3, **23**). Condensation of donor **17b** with methyl 4,6-*O*-benzylidine-3-*O*-benzyl-α-D-mannopyranoside **24**, on the other hand gave disaccharide **25** with good β-selectivity again (α/β = 1:5, Table 1, Entry 4, **25**). The same result, in terms of stereoselectivity and yield was obtained earlier (see Scheme 2) with the corresponding 2-*O*-benzyl acceptor **18**. Executing this reaction for a longer period at -78 ºC led to the same selectivity and a slight increase in yield (Table 2, Entry 5,**19b**). Finally, the use of 1,2:5,6-di-*O*-isopropylidene-3-*O*-α-D-glucofuranose **26** led to the formation disaccharide **27** in 1:10 α/β ratio (Table 2, Entry 6, **27**). These experiments clearly show that the glycosylations of **17b** can proceed with good to moderate 1,2-*cis* selectivity. However, the reactivity of the hydroxyl function in the acceptor glycoside also plays an important role. Although poor selectivities for acceptors **9** and **22** have been reported before,[22,23] the outcome of the mannosylation of primary alcohol **7** stands in sharp contrast to the β-slective mannosylations commonly reported for this acceptor.[14,15a] This result highlights how minor changes in a glycosylation system can result in major changes in the outcome of the reaction, and for this unexpected result there is currently no adequate explanation.

Table 2: Glycosylation of donor **17b** with various acceptors.[f]



17b R = Msem

20 R = 7
21 R = 9
23 R = 22
25 R = 24
19b R = 18
27 R = 26

Entry	Acceptor	Time	Temp.	Yield	α/β
1	 **7**	2h	-78 °C to -72 °C	74	4:5
2	 **9**	4h	-78 °C to 0 °C	72	1:3
3	 **22**	4h	-78 °C to 0 °C	70	1:1
4	 **24**	4h	-78 °C to 0 °C	72	1:5
5	 **18**	4h 18 h	-78 °C to 0 °C -78 °C	75 84	1:5 1:5
6	 **26**	2h	-78 °C to -60 °C	75	1:10

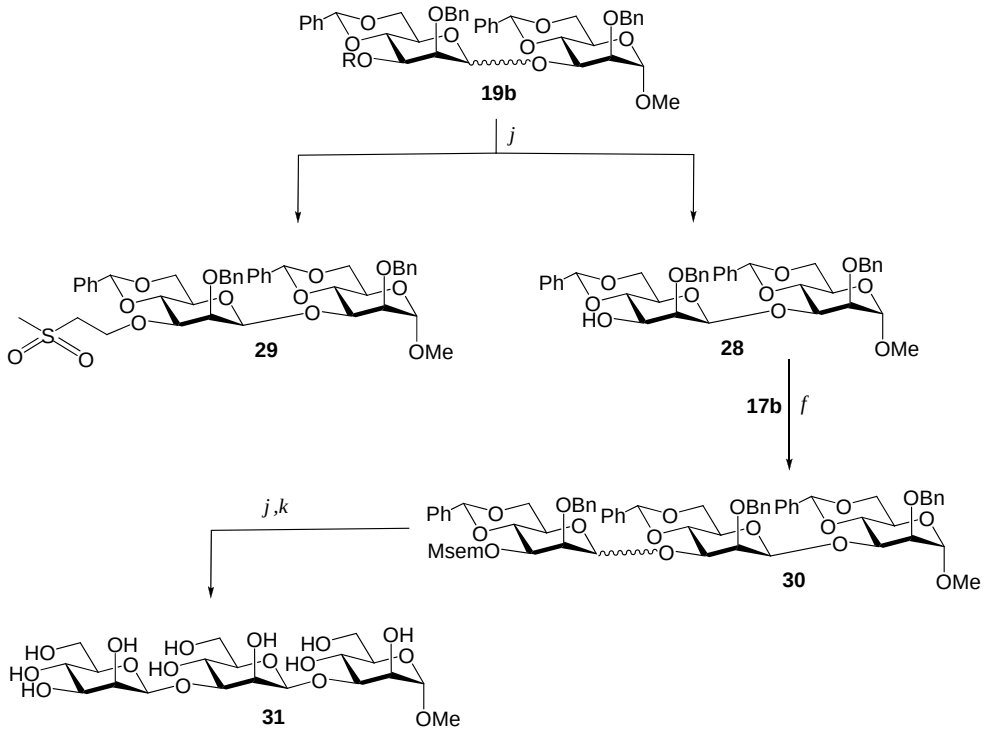
[f] TTBP, Ph_2SO, Tf_2O, DCM.

Finally the assembly of β-1,3-mannotriose **31** was undertaken as depicted in Scheme 3. To this end, the α- and β-anomers of compound **19b** were separated by silicagel column chromatography and the Msem group in β-dimer **19b** was cleaved by treatment with the TBAF to give disaccharide **28** in 60% yield (Scheme 3). Apart from target **28**, a substantial amount of side product **29** was isolated, the formation of which can be explained by Michael addition of the released (methylsulfonyl)ethene to the free C-3 hydroxyl in **28**. Notably this side reaction has not been observed for any other Msem substrate investigated so far. To circumvent the formation of side product **29**, piperidine was added to the reaction mixture to scavenge the released vinylsulfone. In this case disaccharide **28** was obtained in 88% yield. Elongation of **28** by preactivation of 2 equivalents of thioglycoside **17b** with Ph_2SO/Tf_2O in the presence of an excess of TTBP furnished trisaccharide **30** 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 **30** was then deprotected in two steps. First, the Msem group in **30** was removed by treatment with TBAF in the presence of piperidine and subsequent hydrogenolysis of the remaining benzylidene and benzyl groups using palladium hydroxide on charcoal and hydrogen gas led to the isolation of trisaccharide **31** in 60% yield over two steps.

Conclusion:

The methylsulfonylethoxymethyl (Msem) group has been introduced as a new hydroxyl protecting group that meets the requirements for productive oligosaccharide synthesis. It can be introduced at primary and secondary hydroxyl functions of *O*-glycosides with thiomethyl ether reagent **4** and a thiophilic activator. For 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 *cis*-linked 1,3-*O*-mannotrioside.

Scheme 3: The synthesis of β-1,3-mannan **30**.



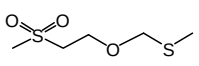
Reagents and conditions; *f*) TTBP, Ph_2SO, Tf_2O, DCM, -78 º C-RT, 2h; *j*) TBAF, piperdine, THF, 24 h; *k*) $Pd(OH)_2/C$, H_2, 24 h.

Experimental:

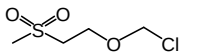
General: Dichloromethane was refluxed with P_2O_5 and distilled before use. Trifluoromethanesulfonic anhydride was distilled from P_2O_5. Traces of water in donor and acceptor glycosides, diphenylsulfoxide and TTBP were removed by co-evaporation with toluene. Molecular sieves 3Å were flame dried before use. All other chemicals (Acros, Fluka, Merck, Fluorous Technologies Inc.) were used as received. Column chromatography was performed on Screening Devices silica gel 60 (0.040-0.063 mm). Size exclusion chromatography was performed on Sephadex LH20 (eluent MeOH/DCM = 1/1). Gel filtration was performed on Sephadex HW40 (0.15 M Et_3NHOAc in H_2O). TLC analysis was conducted on DC-alufolien (Merck, kiesel gel 60, F_{245}). Compounds were visualized by UV absorption (245 nm), by spraying with an aqueous solution of $KMnO_4$ (20%) and K_2CO_3 (10%), by spraying with 20% H_2SO_4 in ethanol or by spraying with a solution of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (25g/L) and $(NH_4)_4Ce(SO_4)_4\cdot 2H_2O$ (10g/L) in 10% $H_2SO_{4\,(aq)}$ followed by charring at ~150 ºC. IR spectra were recorded on a Shimadzu FTIR-8300 and are reported in cm^{-1}. Optical rotations were measured on a Propol automatic

polarimeter. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AV 400 (400 MHz and 100 MHz respectively), AV 500 (500 MHz and 125 MHz respectively) or DMX 600 (600 MHz and 150 MHz respectively). NMR spectra were recorded in $CDCl_3$ unless stated otherwise. Chemical shift are relative to tetramethylsilane and are given in ppm. Coupling constants are given in Hz. All given ^{13}C spectra are proton decoupled. High resolution mass spectra were recorded on a LTQ-Orbitrap (thermo electron).

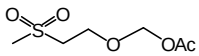
General method for glycosylations using Ph_2SO/Tf_2O: A solution of 1-thio-β-D-mannopyranoside (donor), diphenylsulfoxide (1.3 eq), and tri-*tert*-butylpyrimidine (3 eq) in DCM (0.05 M) was stirred over activated MS3Å for 30 minutes. The mixture was brought to -78 °C before triflic acid anhydride (1.3 eq) was added. The mixture was allowed to warm to -60 °C in 15 minutes followed by the addition of the acceptor (1.5 eq). The reaction mixture was stirred at the temperature described in table 2. The reaction mixture was quenched with triethylamine (5 eq), 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.



((Methylsulfonylethoxy)methyl)methylsulfane (4): To a solution of methylsulfonylethanol **3** (6.55 g, 52.8 mmol) in DMSO (15 ml, 211 mmol, 4 eq) was added acetic acid (6 ml, 106 mmol, 2 eq) and acetic anhydride (9.9 ml, 106 mmol, 2 eq). The reaction mixture was stirred for 48 hours. 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 yellow a oil. TLC (75% EtOAc in toluene): R_f = 0.75; IR (neat, cm^{-1}): 730, 1129, 1286; ^{1}H 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 $C_5H_{16}O_3S_2N$ 202.05661, found 202.05662.

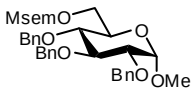


Methylsulfonylethoxymethyl chloride (5): To a solution of ((methylsulofnylethoxy)methyl)methylsulfane **4** (1.39 g, 7.55 mmol) in DCM (25 ml, 0.3 M) was added sulfuryl chloride (0.6 ml, 7.6 mmol, 1 eq) and the mixture was stirred for 2 hours. Next the solvents were removed *in vacuo* to give **5**; IR (neat, cm^{-1}): 643, 944, 1112, 1288; ^{1}H 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 $C_4H_{13}ClO_3S_2N$ 190.02992, found 190.02882.



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 eq). The mixture was cooled to -20 °C followed by the addition of acetic acid (0.65 ml, 11.4 mmol, 2 eq). The mixture was allowed to warm to rt and was stirred for 2 hours. The reaction mixture was quenched with triethylamine (5eq), 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, $C\underline{H}_3SO_2$-), 3.26 (t, 2H, *J* = 5.2 Hz, $MeSO_2C\underline{H}_2CH_2OCH_2OAc$), 4.09 (t, 2H, *J* = 5.6 Hz, $MeSO_2CH_2C\underline{H}_2OCH_2OAc$), 5.27 (s, 2H, $MeSO_2(CH_2)_2OC\underline{H}_2OAc$); ^{13}C NMR (100 MHz, ($CDCl_3$) δ = 20.7 (CH_3 OAc), 42.8 (CH_3 $\underline{C}H_3SO_2$-), 54.7 (CH_2 $MeSO_2\underline{C}H_2CH_2OCH_2OAc$), 63.5 ($CH_2$ $MeSO_2CH_2\underline{C}H_2OCH_2OAc$), 88.0 ($CH_2$ $MeSO_2(CH_2)_2O\underline{C}H_2OAc$); HRMS $[M+Na]^+$ calculated for $C_6H_{12}O_5S_1Na$ 219.02977, found 219.02982.



Methyl 2,3,4-tri-*O*-benzyl-6-*O*-methylsulfonylethoxymethyl-α-D-glucopyranoside (8):

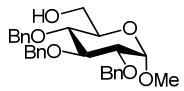
Method I: A solution of methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **7** (0.525 g, 1.14 mmol) and ((methylsulfonylethoxy)methyl)methylsulfane **4** (0.314 g, 1.70 mmol, 1.5 eq) in DCM (23 ml, 0.05 M) was stirred over activated MS3Å for 30 minutes before *N*-iodosuccinimide (0.304 g, 1.36 mmol, 1.2 eq) 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 eq). The reaction mixture was stirred for 1.5 hours. The reaction mixture was quenched with triethylamine (5eq), 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 get **8** (0.570 g, 0.949 mmol, 84%).

Method II: A solution of ((methylsulfonylethoxy)methyl)methylsulfane **4** (0.058 g, 0.31 mmol, 1.5 eq), diphenyl sulfoxide (0.083 g, 0.41 mmol, 1.3 eq), and tri-*tert*-butylpyrimidine (0.234 g, 0.942 mmol, 3 eq) in DCM (6.3 ml, 0.05 M) was stirred over activated MS3Å for 30 minutes. The mixture was brought to -60 °C before triflic acid anhydride (69 µl, 0.41 mmol, 1.3 eq) was added. The mixture was allowed to warm to -40 °C in 15 minutes followed by the addition of methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **7** (0.097 g, 0.21 mmol, 1 eq). The reaction mixture was stirred for 1 hour. The reaction mixture was quenched with triethylamine (5 eq), 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%).

Method III: 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 eq) in DCM (4.5 ml, 0.05 M) was stirred over activated MS3Å for 30 minutes before iodonium di-*sym*-collidine perchlorate (IDCP, 0.412 g, 0.88 mmol, 8 eq) was added in the dark. The reaction mixture was stirred in the dark for 24 hours. 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 get **8** (0.070 g, 0.12 mmol, 63%).

TLC (50% EtOAc in PE): R_f = 0.4; $[\alpha]_D^{22}$: +43.0º (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, $MeSO_2C\underline{H}_2CH_2OCH_2$-), 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 2xH-6), 3.88-4.03 (m, 3H, H-3 and $MeSO_2CH_2C\underline{H}_2OCH_2$-), 4.57-4.63 (m, 3H, H-1, $MeSO_2(CH_2)_2OCH\underline{H}$- and CH<u>H</u> Bn), 4.65-4.70 (m, 2H, $MeSO_2(CH_2)_2OCH\underline{H}$- and CH<u>H</u> Bn), 4.78-4.82 (m, 2H, 2xCH<u>H</u> Bn), 4.92 (d, 1H, *J* = 11.2 Hz, CH<u>H</u> Bn), 4.99 (d, 1H, *J* = 10.8 Hz, CH<u>H</u> Bn), 7.26-7.37 (m, 15H, H arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 42.8 (CH_3 Msem), 55.0 ($MeSO_2\underline{C}H_2CH_2OCH_2$-), 55.2 ($CH_3$ OMe), 61.8 ($MeSO_2CH_2\underline{C}H_2OCH_2$-), 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 ($MeSO_2(CH_2)_2O\underline{C}H_2$-), 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 $C_{32}H_{40}O_9S_1Na$ 623.22852, found 623.22834.



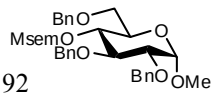
Methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (7) (Cleavage of Msem from 8):

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 eq) and the reaction mixture was heated at 100 ºC for 3 hours. The reaction mixture was neutralized with $NH_4Cl_{(aq)}$, diluted with EtOAc, washed with $NH_4Cl_{(aq)}$, $NaHCO_3$ 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, 0.3 ml, 64 µmol, 1.1 eq) and DBU (1 M in DMF, 116 µl, 116 µmol, 2 eq) and the reaction mixture was heated at 100 ºC for 20 hours. The reaction mixture was neutralized with $NH_4Cl_{(aq)}$, diluted with EtOAc, washed with $NH_4Cl_{(aq)}$, $NaHCO_3$ 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 KOtBu (23 mg, 200 µmol, 5 eq) and the reaction mixture was heated at 40 ºC for 24 hours. The reaction mixture was neutralized with $NH_4Cl_{(aq)}$, diluted with EtOAc, washed with $NH_4Cl_{(aq)}$, $NaHCO_3$ 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 DMF, 57 µl, 5.7 µmol, 0.1 eq) and the reaction mixture was stirred for 24 hours. The reaction mixture was neutralized with $NH_4Cl_{(aq)}$, diluted with EtOAc, washed with $NH_4Cl_{(aq)}$, $NaHCO_3$ 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%).



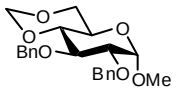
Methyl 2,3,6-tri-*O*-benzyl-4-*O*-methylsulfonylethoxymethyl-α-D-glucopyranoside (10):

Method I: A solution of methyl 2,3,6-tri-*O*-benzyl-4-*O*-methylthiomethyl-α-D-glucopyranoside **9** (0.160 g, 0.31 mmol) and methylsulfonylethanol (0.095 g, 0.77 mmol, 2.5 eq) in DCM (3 ml, 0.1 M) was stirred over activated MS3Å for 30 minutes before *N*-iodosuccinimide (0.102 g, 0.48 mmol, 1.5 eq) 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 eq). The mixture was allowed to warm to room temperature. The reaction mixture was quenched with triethylamine (5 eq), 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, 34%) and side product **11** (0.029 g, .08 mmol, 25%).

Method II: A solution of methyl 2,3,6-tri-*O*-benzyl-4-*O*-methylthiomethyl-α-D-glucopyranoside **9** (0.200 g, 0.381 mmol) and methylsulfonylethanol (0.118 g, 0.95 mmol, 2.5 eq) in DCM (7.6 ml, 0.1 M) was stirred over activated MS3Å for 30 minutes before iodonium di-*sym*-collidine perchlorate (IDCP, 0.712 g, 1.524 mmol, 4eq) was added in dark. The mixture was stirred in the dark for 24 hours. 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 side product **11** (0.024 g, .06 mmol, 16%).

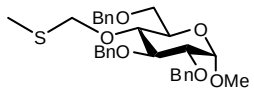
Method III: A solution of methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside **9** (0.553 g, 1.2 mmol) and ((methylsulfonylethoxy)methyl)methylsulfane **4** (0.330 g, 1.8 mmol, 1.5 eq) in DCM (24 ml, 0.05 M) was stirred over activated MS3Å for 30 minutes before *N*-iodosuccinimide (0.320 g, 1.435 mmol, 1.2 eq) 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 eq). The mixture was stirred for 2 hours. The reaction mixture was quenched with triethylamine (5 eq), 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 get **10** (0.530 g, 0.74 mmol, 70%).

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; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.75 (s, 3H, CH_3 Msem), 2.78-2.90 (m, 2H, $MeSO_2C\underline{H}_2CH_2OCH_2$-), 3.39 (s, 3H, OMe), 3.54 (dd, 1H, *J* = 3.6 Hz, *J* = 9.6 Hz, H-2), 3.60-3.67 (m, 3H, H-4 and 2xH-6), 3.71 (m, 1H, H-5), 3.75 (m, 2H, $MeSO_2CH_2C\underline{H}_2OCH_2$-), 3.88 (t, 1H, *J* = 9.6 Hz, H-3), 4.50 (d, 1H, *J* = 12.0 Hz, CH<u>H</u> Bn), 4.59-4.68 (m, 5H, H-1, $MeSO_2(CH_2)_2OCH\underline{H}$- and 3xCH<u>H</u> Bn), 4.73-4.78 (m, 2H, $MeSO_2(CH_2)_2OCH\underline{H}$- and CH<u>H</u> Bn), 5.02 (d, 1H, *J* = 10.8 Hz, CH<u>H</u> Bn), 7.23-7.35 (m, 15H, H arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 42.6 (CH_3 Msem), 54.6 ($MeSO_2\underline{C}H_2CH_2OCH_2$-), 55.1 ($CH_3$ OMe), 62.3 ($MeSO_2CH_2\underline{C}H_2OCH_2$-), 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 ($MeSO_2(CH_2)_2O\underline{C}H_2$-), 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 $C_{32}H_{40}O_9S_1Na$ 623.22852, found 623.22826.

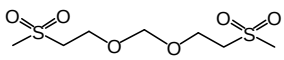


Methyl 2,3-di-*O*-benzyl-4,6-*O*-methylidine-α-D-glucopyranoside (11): A solution of methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside **9** (0.117 g, 25 mmol) in DCM (2.5 ml, 0.1

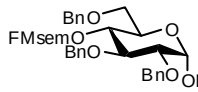
M) was brought to -30 °C before the addition of methylsulfonylethoxymethylacetate **6** (0.099 g, 51 mmol, 2 eq) followed by the addition of tin tetrachloride (45 µl, 380 mmol, 1.5 eq). The TLC analysis showed that compound **10** started to appear after 15 minutes while starting material was still present in addition to a side product. On continuing stirring, the amount of side product increased with the consumption of starting material and compound **10.** After 20 hours all the starting material is gone and the compound **11** (0.062 g, 16 mmol, 63%) is the only product; TLC (50% toluene in EtOAc): 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 Hz, *J* = 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 Hz, *J* = 10.0 Hz, H-6), 4.55 (d, 1H, *J* = 4.0 Hz, H-1), 4.60 (d, 1H, *J* = 6.0 Hz, CHH methylene), 4.65 (d, 1H, *J* = 12.0 Hz, CHH Bn), 4.80-4.89 (m, 2H, 2xCHH Bn), 4.87 (d, 1H, *J* = 11.2 Hz, CHH Bn), 5.07 (d, 1H, *J* = 6.4 Hz, CHH 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 $C_{22}H_{30}O_6N$ 404.20676, found 404.20671.



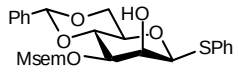
Methyl 2,3,6-tri-*O*-benzyl-4-*O*-methylthiomethyl-α-D-glucopyranoside (12): To a solution of methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside **9** (0.907 g, 2.1 mmol) in DMF (4.2 ml, 0.05 M) was added methylthiomethyl chloride (0.43 ml, 5.2 mmol, 2.5 eq). The reaction mixture was brought to 0° C before sodium hydride (60% in oil, 0.150 g, 3.75 mmol, 1.8 eq) was added in small portions and the stirring was continued for 1 hour. The reaction mixture was diluted with diethyl ether and washed with $NH_4Cl_{(aq)}$, $NaHCO_{3\ (aq)}$ and brine, dried over MgSO4, filtered, concentrated and purified by silica gel chromatography to get 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 Hz, *J* = 9.6 Hz, H-2), 3.57 (t, 1H, *J* = 10.0 Hz, H-4), 3.64-3.74 (m, 3H, H-5 and 2xH-6), 3.94 (t, 1H, *J* = 9.2 Hz, H-3), 4.56 (m, 2H, 2xCHH Bn), 4.60-4.62 (m, 2H, H-1 and CHH Bn), 4.68 (d, 1H, *J* = 10.8 Hz, CHH MeSCHH-), 4.74-4.78 (m, 3H, CHH MeSCHH- and 2xCHH Bn), 4.97 (d, 1H, *J* = 10.8 Hz, CHH 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 $C_{30}H_{36}O_6S_1Na$ 574.21248, found 574.21196.



Di-(2-(methylsulfonyl)ethoxy)methane (13): Collected as by-product during the preparation of the compound **8** (Method II) (14 mg, 54 µmol, 17% w.r.t to the compound **4** used in the reaction). TLC (50% EtOAc in PE): R_f = 0.75; IR (neat, cm^{-1}): 1029, 1277; ^1H NMR (400 MHz, ($CDCl_3$) δ = 3.01 (s, 6H, 2xCH_3 CH_3SO$_2$-), 3.30 (t, 4H, *J* = 5.6 Hz, 2x CH_2 (($MeSO_2CH_2CH_2O)_2CH_2$), 4.02 (t, 4H, *J* = 5.6 Hz, 2x CH_2 (($MeSO_2CH_2CH_2O)_2CH_2$), 4.75 (s, 2H, (($MeSO_2(CH_2)_2O)_2CH_2$); ^{13}C NMR (100 MHz, ($CDCl_3$) δ = 43.1 (2xCH_3 CH_3SO_2-), 54.8 (2xCH_2 (($MeSO_2CH_2CH_2O)_2CH_2$), 61.8 (2xCH_2 (($MeSO_2CH_2CH_2O)_2CH_2$), 95.4 (CH_2 (($MeSO_2(CH_2)_2O)_2CH_2$); HRMS $[M+H]^+$ calculated for $C_7H_{17}O_6S_2$ 261.04611, found 261.04626, $[M+NH_4]^+$ calculated for $C_7H_{20}O_6S_2N$ 278.07266, found 278.07269.

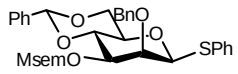


Methyl 2,3,6-tri-*O*-benzyl-4-*O*-([1H,1H,2H,2H]-perfluorodecyl)sulfonylethoxymethyl-α-D-glucopyranoside (14): A solution of methyl 2,3,6-tri-*O*-benzyl-4-*O*-methylthiomethyl-α-D-glucopyranoside **12** (0.145 g, 0.28 mmol) and ([1H,1H,2H,2H]-perfluorodecyl)sulfonylethanol (0.384 g, 0.70 mmol, 2.5 eq) in DCM (5.6 ml, 0.05 M) was stirred over activated MS3Å for 30 minutes before iodonium di-*sym*-collidine perchlorate (IDCP, 0.712 g, 1.52 mmol, 4 eq) was added in the dark. The mixture was stirred in the dark for 24 hours. 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 get **14** (0.036 g, 0.03 mmol, 11%) and the side product **11** (0.033 g, 0.9 mmol, 31%)**;** TLC (50% EtOAc in PE): R_f = 0.9; $[\alpha]_D^{22}$: +23.2º (c = 0.6, DCM); IR (neat, cm^{-1}): 696, 1042; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.54-2.69 (m, 2H, CH_2 RfC<u>H</u>$_2$CH$_2$SO$_2$(CH$_2$)$_2$OCH$_2$O-), 2.75-2.88 (m, 2H, CH_2 Rf(CH$_2$)$_2$SO$_2$C<u>H</u>$_2$CH$_2$OCH$_2$O-), 3.18 (m, 2H, CH_2 RfCH$_2$C<u>H</u>$_2$SO$_2$(CH$_2$)$_2$OCH$_2$O-), 3.39 (s, 3H, OMe), 3.54-3.59 (m, 2H, H-2 and H-4), 3.62-3.66 (m, 2H, 2xH-6), 3.69 (m, 1H, H-5), 3.74 (m, 2H, CH_2 Rf(CH$_2$)$_2$SO$_2$CH$_2$C<u>H</u>$_2$OCH$_2$O-), 3.87 (t, 1H, *J* = 9.6 Hz, H-3), 4.50 (d, 1H, *J* = 12.0 Hz, CH<u>H</u> Bn), 4.60-4.67 (m, 5H, H-1, CH_2 Rf(CH$_2$)$_2$SO$_2$(CH$_2$)$_2$OC<u>H</u>HO- and 3xCH<u>H</u> Bn), 4.73 (d, 1H, *J* = 6.4 Hz, Rf(CH$_2$)$_2$SO$_2$(CH$_2$)$_2$OC<u>H</u>HO-), 4.75 (d, 1H, *J* = 12.4 Hz, CH<u>H</u> Bn), 5.05 (d, 1H, *J* = 10.4 Hz, CH<u>H</u> Bn), 7.26-7.37 (m, 15H, H arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 24.1 (Rf<u>C</u>H$_2$CH$_2$SO$_2$(CH$_2$)$_2$OCH$_2$O-), 46.5 (RfCH$_2$<u>C</u>H$_2$SO$_2$(CH$_2$)$_2$OCH$_2$O-), 53.7 (Rf(CH$_2$)$_2$SO$_2$<u>C</u>H$_2$CH$_2$OCH$_2$O-), 55.3 (CH_3 OMe), 62.1 (Rf(CH$_2$)$_2$SO$_2$CH$_2$<u>C</u>H$_2$OCH$_2$O-), 68.5 (C-6), 69.8 (C-5), 73.3 (CH_2 Bn), 73.6 (CH_2 , Bn), 75.4 (C-2 or C-4), 75.5 (CH_2 Bn), 80.1 (C-2 or C-4), 81.1 (C-3), 96.4 (Rf(CH$_2$)$_2$SO$_2$(CH$_2$)$_2$O<u>C</u>H$_2$O-), 97.9 (C-1), 127.6-128.5 (CH arom), 137.8 (C_q Bn), 137.9 (C_q Bn), 138.6 (C_q Bn); HRMS $[M+Na]^+$ calculated for $C_{41}H_{41}F_{17}O_9S_1Na$ 1055.20920, found 1055.20965.

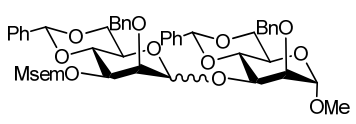


Phenyl 4,6-*O*-benzylidene-3-*O*-methylsulfonylethoxymethyl-1-thio-β-D-mannopyranoside (16): To a solution of phenyl 4,6-*O*-benzylidene-1-thio-β-D-mannopyranoside **(15)** (3.0 g, 8.3 mmol) in toluene (55 ml, 0.15 M) was added dibutyltin oxide (2.18 g, 8.77 mmol, 1.05 eq) and the reaction mixture was refluxed for 2 hours. The solvents were evaporated and the residue was co-evaporated with toluene. The mixture was re-dissolved in toluene (55ml) followed by the addition of tetrabutylammonium bromide (3.23 g, 10 mmol, 1.2 eq), cesium fluoride (1.51 g, 10 mmol, 1.2 eq) and methylsulfonylethoxymethyl chloride (1.86 g, 10.8 mmol, 1.3 eq) and stirring was continued for 18 hours. 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 get **16** (3.48 g, 6.85 mmol, 82%); TLC (66% EtOAc in PE): R_f = 0.4; $[\alpha]_D^{22}$: -225.0º (c = 1, DCM); IR (neat, cm^{-1}): 696, 732, 1020, 1310; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.83 (s, 3H, CH_3 Msem), 2.95-3.01 (m, 1H, CH<u>H</u> MeSO$_2$CH<u>H</u>CH$_2$OCH$_2$-), 3.10-3.17 (m, 1H, CH<u>H</u> MeSO$_2$CH<u>H</u>CH$_2$OCH$_2$-), 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<u>H</u> MeSO$_2$CH$_2$CH<u>H</u>OCH$_2$-), 3.98-4.04 (m, 1H, CH<u>H</u> MeSO$_2$CH$_2$CH<u>H</u>OCH$_2$-), 4.10 (t, 1H, *J* = 9.6 Hz, H-4), 4.29 (dd, 1H, *J* = 4.8 Hz, *J* = 10.4 Hz, H-6), 4.34 (bs, 1H, H-2), 4.80 (d, 1H, *J* = 7.2 Hz, CH<u>H</u> MeSO$_2$(CH$_2$)$_2$CH<u>H</u>O-), 4.86 (d, 1H, *J* = 7.2 Hz, CH<u>H</u>

$MeSO_2(CH_2)_2CH\underline{H}O$-), 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 $MeSO_2\underline{C}H_2CH_2OCH_2$-), 61.5 ($CH_2$ $MeSO_2CH_2\underline{C}H_2OCH_2$-), 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 $MeSO_2(CH_2)_2O\underline{C}H_2$-), 101.6 (CH benzylidene), 125.9-130.9 (CH arom), 134.2 (C_q SPh), 137.1 (C_q CHPh); CH Gated NMR (100 MHz, $CDCl_3$) δ = 87.8 (J = 152 Hz, C-1); HRMS $[M+Na]^+$ calculated for $C_{23}H_{28}O_8S_2Na$ 519.11178, found 519.11140.



Phenyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-methylsulfonylethoxymethyl-1-thio-β-D-mannopyranoside (17b): To a solution of phenyl 4,6-*O*-benzylidene-3-methylsulfonylethoxymethyl-1-thio-β-D-mannopyranoside **(16)** (3.3 g, 6.65 mmol) in DMF (33 ml, 0.2 M) was added benzyl bromide (2 ml, 17.0 mmol, 2.5 eq) and tetrabutylammonium iodide (2.46 g, 6.65 mmol, 1 eq). The reaction mixture was brought to 0 ºC and sodium hydride (60%, 0.266 g, 6.65 mmol, 1 eq) was added subsequently in small portions. The reaction mixture was allowed to warm to rt and stirring was continued for 2 hours. 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 get **17b** (2.91g, 4.97 mmol, 75%); TLC (50% EtOAc in PE): R_f = 0.6; $[\alpha]_D^{22}$: -30.2º (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, $CH\underline{H}$ $MeSO_2CH\underline{H}CH_2OCH_2$-), 3.02-3.09 (m, 1H, $CH\underline{H}$ $MeSO_2CH\underline{H}CH_2OCH_2$-), 3.42 (m, 1H, H-5), 3.80-3.96 (m, 4H, H-3, H-6 and CH_2 $MeSO_2CH_2C\underline{H}_2OCH_2$-), 4.16-4.20 (m, 2H, H-2 and H-4), 4.27 (dd, 1H, J = 4.8 Hz, J = 10.4 Hz, H-6), 4.71 (d, 1H, J = 6.8 Hz, $CH\underline{H}$ $MeSO_2(CH_2)_2OC\underline{H}H$-), 4.79 (d, 1H, J = 6.8 Hz, $CH\underline{H}$ $MeSO_2(CH_2)_2OC\underline{H}H$-), 4.82 (d, 1H, J = 11.2 Hz, $CH\underline{H}$ Bn), 4.91 (s, 1H, H-1), 4.99 (d, 1H, J = 10.8 Hz, $CH\underline{H}$ 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 $MeSO_2\underline{C}H_2CH_2OCH_2$-), 61.4 ($CH_2$ $MeSO_2CH_2\underline{C}H_2OCH_2$-), 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 $MeSO_2(CH_2)_2O\underline{C}H_2$-), 101.4 (CH benzylidene), 125.9-131.1 (CH arom), 134.5 (C_q SPh), 137.2, 137.5 (C_q CHPh and C_q Bn); CH Gated NMR (100 MHz, $CDCl_3$) δ = 88.7 (J = 153 Hz, C-1); HRMS $[M+Na]^+$ calculated for $C_{30}H_{34}O_8S_2Na$ 609.15873, found 609.15848.



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 (19b): Disaccharide **19b** was prepared from donor **17b** (0.26 g, 0.44 mmol, 1 eq) and acceptor **18** (0.248 g, 0.67 mmol, 1.5 eq) according to the general procedure for glycosylations as described above at -78 °C to afford compound **19b** (0.317 g, 0.37 mmol, 84%, α/β = 1:5).

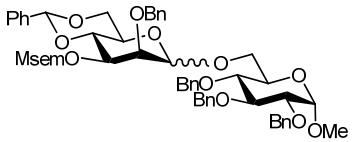
α-anomer:

TLC (33% Toluene in EtOAc): R_f = 0.66; $[\alpha]_D^{22}$: -2.5º (c = 0.4, DCM); IR (neat, cm^{-1}): 698, 1067; ^1H NMR (400 MHz, $CDCl_3$) δ = 2.64 (s, 3H, CH_3 Msem), 2.70-2.77 (m, 1H, $MeSO_2CH\underline{H}CH_2OCH_2$-), 2.95 (m, 1H, $MeSO_2CH\underline{H}CH_2OCH_2$-), 3.38 (s, 3H, CH_3 OMe), 3.78-3.89 (m, 8H, H-2, H-2', H-6, H-6', $MeSO_2CH_2C\underline{H}_2OCH_2$- and two of the H-3, H-4, H-5, H-3', H-4' and H-5'), 4.05-4.16 (m, 3H, H-6 or H-6' and two of the H-3, H-4, H-5,

H-3', H-4' and H-5'), 4.18-4.29 (m, 4H, H-6 or H-6', CHH Bn and two of the H-3, H-4, H-5, H-3', H-4' and H-5'), 4.42 (d, 1H, *J* = 12.4 Hz, CHH Bn), 4.59 (d, 1H, *J* = 7.2 Hz, $MeSO_2(CH_2)_2OCHH$-), 4.70-4.77 (m, 4H, H-1 or H-1', 2xCHH Bn and $MeSO_2(CH_2)_2OCHH$-), 5.34 (s, 1H, H-1 or 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 ($MeSO_2\underline{C}H_2CH_2OCH_2$-), 55.0 ($CH_3$ OMe), 61.6 ($MeSO_2CH_2\underline{C}H_2OCH_2$-), 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 ($MeSO_2(CH_2)_2O\underline{C}H_2$-), 99.69, 99.7(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 (2xC_q benzylidene and 2xC_q Bn); CH Gated NMR (100 MHz, $CDCl_3$) δ = 99.69 (*J* = 173 Hz, C-1), 99.71 (*J* = 177 Hz, C-1'); HRMS $[M+Na]^+$ calculated for $C_{45}H_{52}O_{14}SNa$ 871.29700 found 871.29542.

β-anomer:

TLC (33% Toluene in EtOAc): R_f = 0.4; $[\alpha]_D^{22}$: -68.4º (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 Hz, *J* = 15.2 Hz, $MeSO_2CH\underline{H}CH_2OCH_2$-), 3.01-3.08 (m, 1H, $MeSO_2CH\underline{H}CH_2OCH_2$-), 3.14 (m, 1H, H-5'), 3.38 (CH_3 OMe), 3.61 (dd, 1H, *J* = 3.2 Hz, *J* = 9.6 Hz, H-3'), 3.69-3.92 (m, 7H, H-2, H-2', H-5, H-6, H-6' and $MeSO_2CH_2C\underline{H}_2OCH_2$-), 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 Hz, *J* = 9.6 Hz, H-6), 4.33 (dd, 1H, *J* = 3.2 Hz, *J* = 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, 3xCHH Bn and $MeSO_2(CH_2)_2OCHH$-), 4.80 (s, 1H, H-1), 4.96 (d, 1H, *J* = 12.0 Hz, CHH 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 ($MeSO_2\underline{C}H_2CH_2OCH_2$-), 54.9 ($CH_3$ OMe), 61.2 ($MeSO_2CH_2\underline{C}H_2OCH_2$-), 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 ($MeSO_2(CH_2)_2O\underline{C}H_2$-), 99.1 (C-1'), 99.5 (C-1), 101.6 (CH benzylidene), 101.6 (CH bBenzylidene), 126.0-129.1 (CH arom), 137.4, 137.5, 137.8, 138.4 (2xC_q benzylidene and 2xC_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 $C_{45}H_{52}O_{14}SNa$ 871.29700, found 871.29669.



Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-methylsulfonylethoxymethyl-D-mannopyranosyl)-α-D-glucopyranoside (20): Disaccharide **20** was prepared from donor **17b** (0.147 g, 0.25 mmol, 1 eq) and acceptor **7** (0.174 g, 0.38 mmol, 1.5 eq) according to the general procedure for glycosylations as described above to afford compound **20** (0.171 g, 0.18 mmol, 74%, α/β = 4:5).

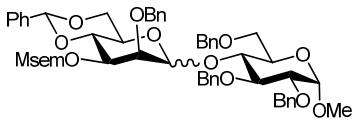
α-anomer:

TLC (33% Toluene in EtOAc): R_f = 0.65; $[\alpha]_D^{22}$: +52.2º (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, $MeSO_2CH\underline{H}CH_2OCH_2$-), 2.98-3.05 (m, 1H, $MeSO_2CH\underline{H}CH_2OCH_2$-), 3.36 (s, 3H, CH_3 OMe), 3.48 (t, 1H, *J* = 9.2 Hz, H-4), 3.51 (dd, 1H, *J* = 3.6 Hz, *J* = 10.0 Hz, H-2), 3.65 (dd, 1H, *J* = 1.6 Hz, *J* = 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 $MeSO_2CH_2C\underline{H}_2OCH_2O$-), 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, CHH Bn), 4.68-4.72 (m, 4H, 3xCHH Bn and $MeSO_2(CH_2)_2OCHH$-), 4.75-4.82 (m, 3H, 2xCHH 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, CHH Bn), 5.00 (d, 1H, *J* = 10.4 Hz, CHH 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 ($MeSO_2\underline{C}H_2CH_2OCH_2$-), 55.2 ($CH_3$ OMe), 61.6 ($MeSO_2CH_2\underline{C}H_2OCH_2$-), 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 ($MeSO_2(CH_2)_2O\underline{C}H_2$-), 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 4xC_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 $C_{52}H_{60}O_{14}SNa$ 963.35960, found 963.35948.

β-anomer:

TLC (33% Toluene in EtOAc): R_f = 0.4; $[\alpha]_D^{22}$: +1.5º (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, $MeSO_2CH\underline{H}CH_2OCH_2$-), 3.01-3.08 (m, 1H, $MeSO_2CH\underline{H}CH_2OCH_2$-), 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 Hz, *J* = 9.6 Hz, H-2), 3.55 (dd, 1H, *J* = 5.2 Hz, *J* = 10.4 Hz, H-6), 3.70 (dd, 1H, *J* = 3.2 Hz, *J* = 10.0 Hz, H-3'), 3.74-3.87 (m, 4H, H-5, H-2', and $MeSO_2CH_2C\underline{H}_2OCH_2$-), 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 Hz, *J* = 10.4 Hz, H-6), 4.28 (dd, 1H, *J* = 4.8 Hz, *J* = 10.4 Hz, H-6), 4.31 (s, 1H, H-1'), 4.51 (d, 1H, *J* = 7.2 Hz, $MeSO_2(CH_2)_2OCH\underline{H}O$-) 4.54-4.60 (m, 2H, H-1, CHH Bn), 4.64-4.69 (m, 2H, CHH Bn and $MeSO_2(CH_2)_2OCH\underline{H}O$-), 4.73 (d, 1H, *J* = 12.4 Hz, CHH Bn), 4.79 (d, 1H, *J* = 12.4 Hz, CHH Bn), 4.83 (d, 1H, *J* = 11.2 Hz, CHH Bn), 4.87 (d, 1H, *J* = 11.6 Hz, CHH Bn), 4.92 (d, 1H, *J* = 12.0 Hz, CHH Bn), 5.01 (d, 1H, *J* = 10.8 Hz, CHH 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 ($MeSO_2\underline{C}H_2CH_2OCH_2$-), 55.1 ($CH_3$ OMe), 61.2 ($MeSO_2CH_2\underline{C}H_2OCH_2$-), 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 ($MeSO_2(CH_2)_2O\underline{C}H_2$-), 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 4xC_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 $C_{52}H_{60}O_{14}SNa$ 963.35960, found 963.36030.



Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-methylsulfonylethoxymethyl-D-mannopyranosyl)-α-D-glucopyranoside (21): Disaccharide **21** was prepared from donor **17b** (0.117 g, 0.2 mmol, 1 eq) and acceptor **9** (0.138 g, 0.3 mmol, 1.5 eq) according to the general procedure for glycosylations as described above to afford compound **21** (0.135 g, 0.14 mmol, 72%, α/β = 1:3).

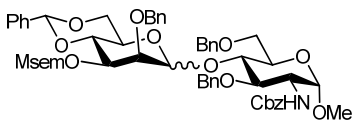
α-anomer:

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 $MeSO_2CH\underline{H}CH_2OCH_2$-), 3.00-3.13 (m, 1H, $MeSO_2CH\underline{H}CH_2OCH_2$-), 3.41 (s, 3H, CH_3 OMe), 3.55 (m, 1H, one of the H-2, H-2', H-3, H-3', H-4, H-4'), 3.76 (m, 6H, (H-5 or H-5'), 2xH-6 and 2xH-6' and one of the H-2, H-2', H-

3, H-3', H-4, H-4'), 3.84 (m, 4H, (H-5 or H-5') and $MeSO_2CH_2C\underline{H}_2OCH_2$- and one of the H-2, H-2', H-3, H-3', H-4, H-4'), 3.98 (m, 2H, two of the H-2, H-2', H-3, H-3', H-4, H-4'), 4.09 (m, 1H, one of the H-2, H-2', H-3, H-3', H-4, H-4'), 4.20 (d, 1H, *J* = 12.0, CH<u>H</u> Bn), 4.25 (d, 1H, *J* = 12.0, CH<u>H</u> Bn), 4.68 (m, 8H, H-1, 5xCH<u>H</u> Bn and $MeSO_2(CH_2)_2OC\underline{H}_2$-), 5.17 (d, 1H, *J* = 12.0 Hz, CH<u>H</u> 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 ($MeSO_2\underline{C}H_2CH_2OCH_2$-), 55.4 ($CH_3$ OMe), 61.5 ($MeSO_2CH_2\underline{C}H_2OCH_2$-), 65.1 (C-5 or C-4), 68.6, 69.1 (C-6 and C-6'), 69.6 (C-2' or C5'), 73.0 (CH_2 Bn), 73.1 (CH_2 Bn), 73.4 (C-3 or C-4'), 73.6 (CH_2 Bn), 74.8 (CH_2 Bn), 76.2 (C-4 or C-5), 77.5 (C-2' or C-5'), 77.8 (C-3'), 79.9 (C-2), 81.6 (C-3 or C-4'), 94.4 ($MeSO_2(CH_2)_2O\underline{C}H_2$-), 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 4xC_q Bn); HRMS $[M+Na]^+$ calculated for $C_{52}H_{60}O_{14}SNa$ 963.35960, found 963.36029.

β-anomer:

TLC (33% Toluene in EtOAc): R_f = 0.35; $[\alpha]_D^{22}$: +7.2º (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, $MeSO_2CH\underline{H}CH_2OCH_2$-), 3.05-3.13 (m, 2H, H-5' and $MeSO_2CH\underline{H}CH_2OCH_2$-), 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 $MeSO_2CH_2C\underline{H}_2OCH_2$-), 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 Hz, *J* = 10.8 Hz, H-6'), 4.46 (d, 1H, *J* = 12.0, CH<u>H</u> Bn), 4.53-4.57 (m, 2H, H-1' and $MeSO_2(CH_2)_2OCH\underline{H}$-), 4.60-4.85 (m, 8H, H-1 and 6xCH<u>H</u> Bn and $MeSO_2(CH_2)_2OCH\underline{H}$-), 5.05 (d, 1H, *J* = 10.8 Hz, CH<u>H</u> 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 ($MeSO_2\underline{C}H_2CH_2OCH_2$-), 55.4 ($CH_3$ OMe), 61.1 ($MeSO_2CH_2\underline{C}H_2OCH_2$-), 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 (C-4 or C-4'), 77.9 (C-4 or C-4'), 79.0 (C-2), 80.3 (C-3'), 94.0 ($MeSO_2(CH_2)_2O\underline{C}H_2$-), 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 4xC_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 $C_{52}H_{60}O_{14}SNa$ 963.35960, found 963.36034.



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 (23): was prepared from donor **17b** (0.142 g, 0.24 mmol, 1 eq) and acceptor **22** (0.168 g, 0.36 mmol, 1.5 eq) according to the general procedure for glycosylations as described above to afford compound **23** (0.177 g, 0.19 mmol, 78%, α/β = 1:1).

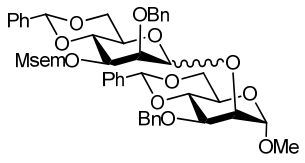
α-anomer:

TLC (33% Toluene in EtOAc): R_f = 0.5; $[\alpha]_D^{22}$: +58.4º (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 $MeSO_2CH\underline{H}CH_2OCH_2$-), 3.03-3.10 (m, 1H, $MeSO_2CH\underline{H}CH_2OCH_2$-), 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 $MeSO_2CH_2C\underline{H}_2OCH_2$-), 3.95 (t, 1H, *J* = 9.2 Hz, H-4'), 4.01 (dd, 1H, *J* = 2.8 Hz, *J* = 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, 2xCH<u>H</u> Bn), 4.55-4.78 (m, 7H, H-1', 4xCH<u>H</u> Bn and $MeSO_2(CH_2)_2OC\underline{H}_2$-), 4.92 (d, 1H, *J* = 10.0 Hz, NH), 4.98-5.05 (m, 2H, 2xCH<u>H</u> 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 ($MeSO_2\underline{C}H_2CH_2OCH_2$-), 55.3 ($CH_3$ OMe), 61.6 ($MeSO_2CH_2\underline{C}H_2OCH_2$-), 65.3 (C-5'), 67.0 ($CH_2$ Cbz), 68.6, 69.2 (C-6 and C-6'), 70.5 (C-2, C-5 or C-4'), 73.0 (CH_2 Bn), 73.3 (C-3'), 73.6 (CH_2 Bn), 73.8 (CH_2 Bn), 76.0 (C-4), 77.4 (C-2, C-5 or C-4'), 78.0 (C-2' or C-3), 81.1 (C-2, C-5 or C-4'), 94.5 ($MeSO_2(CH_2)_2O\underline{C}H_2$-), 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 2xC_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 $C_{53}H_{61}NO_{15}SNa$ 1006.36541, found 1006.36591.

β-anomer:

TLC (33% Toluene in EtOAc): R_f = 0.35 $[\alpha]_D^{22}$: +16.4º (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, $MeSO_2CH\underline{H}CH_2OCH_2$-), 3.06-3.15 (m, 2H, $MeSO_2CH\underline{H}CH_2OCH_2$- 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 Hz, *J* = 10.0 Hz, H-3'), 3.65-3.68 (m, 2H, 2xH-6), 3.83 (m, 4H, H-2', H-3 and $MeSO_2CH_2C\underline{H}_2OCH_2$-), 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, 2xCH<u>H</u> Bn and $MeSO_2(CH_2)_2OCH\underline{H}$-), 4.71-4.74 (m, 3H, H-1' and CH<u>H</u> Bn and $MeSO_2(CH_2)_2OCH\underline{H}$-), 4.80 (m, 2H, NH and CH<u>H</u> Bn), 4.87 (d, 1H, *J* = 12.0 Hz, CH<u>H</u> Bn), 5.00-5.12 (m, 3H, CH<u>H</u> Bn and 2xCH<u>H</u> 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 ($MeSO_2\underline{C}H_2CH_2OCH_2$-), 55.3 ($CH_3$ OMe), 61.1 ($MeSO_2CH_2\underline{C}H_2OCH_2$-), 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 ($MeSO_2(CH_2)_2O\underline{C}H_2$-), 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 4xC_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 $C_{53}H_{62}NO_{15}S$ 984.38347, found 984.38458; $[M+Na]^+$ calculated for $C_{53}H_{61}NO_{15}SNa$ 1006.36541, found 1006.36608.



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 (25): Disaccharide **25** was prepared from donor **17b** (0.112 g, 0.19 mmol, 1 eq) and acceptor **24** (0.107 g, 0.29 mmol, 1.5 eq) according to the general procedure for glycosylations as described above to afford compound **20** (0.117 g, 0.14 mmol, %, α/β = 1:5).

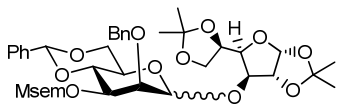
α-anomer:

TLC (33% Toluene in EtOAc): R_f = 0.6; $[\alpha]_D^{22}$: -8.5º (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 $MeSO_2CH\underline{H}CH_2OCH_2$-), 3.04-3.11 (m, 1H, $MeSO_2CH\underline{H}CH_2OCH_2$-), 3.37 (s, 3H, CH_3 OMe), 3.77-3.94 (m, 7H, H-5, H-5', H-6, H-6', $MeSO_2CH_2C\underline{H}_2OCH_2$- and one of the H-2, H-2', H-3, H-3', H-4, H-4'), 3.98 (dd, 1H, *J* = 3.2 Hz, *J* = 10.0 Hz, one of the H-2, H-2', H-3, H-3', H-4, H-4'), 4.00-4.17 (m, 4H, four of the H-2, H-2', H-3, H-3', H-4, H-4'), 4.27 (m, 2H, H-6 and H-6'), 4.42 (d, 1H, *J* = 12.0 Hz, CH<u>H</u> Bn), 4.51 (d, 1H, *J* = 12.0 Hz, CH<u>H</u> Bn), 4.67-4.69 (m, 3H, H-1, CH<u>H</u> Bn and

$MeSO_2(CH_2)_2OCH\underline{H}$-), 4.81-4.85 (m, 2H, $CH\underline{H}$ Bn and $MeSO_2(CH_2)_2OCH\underline{H}$-), 5.33 (d, 1H, *J* = 0.8 Hz, 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 ($MeSO_2\underline{C}H_2CH_2OCH_2$-), 61.5 ($MeSO_2CH_2\underline{C}H_2OCH_2$-), 63.9, 64.6 (C-5 and C-5'), 68.6, 68.7 (C-6 and C-6'), 72.6, 75.4, 76.3, 76.5, 78.3, 79.0 (C-2, C-2', C-3, C-3', C-4 and C-4'), 73.0 (CH_2 Bn), 73.7 (CH_2 Bn), 94.5 ($MeSO_2(CH_2)_2O\underline{C}H_2$-), 100.3 (C-1'), 101.1 (C-1), 101.4 (CH benzylidene), 101.8 (CH benzylidene), 126.0-129.2 (CH arom), 137.4, 137.5, 137.8, 138.3 (2xC_q benzylidene and 2xC_q Bn); CH Gated NMR (100 MHz, $CDCl_3$) δ = 100.3 (*J* = 170 Hz, C-1'), 101.1 (*J* = 171 Hz, C-1); HRMS $[M+Na]^+$ calculated for $C_{45}H_{52}O_{14}SNa$ 871.29700, found 871.29667.

β-anomer:

TLC (33% Toluene in EtOAc): R_f = 0.35; $[\alpha]_D^{22}$: -61.8º (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 Hz, *J* = 16.4 Hz, $MeSO_2CH\underline{H}CH_2OCH_2$-), 3.04-3.11 (m, 1H, $MeSO_2CH\underline{H}CH_2OCH_2$-), 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 $MeSO_2CH_2C\underline{H}_2OCH_2$-), 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, $MeSO_2(CH_2)_2OCH\underline{H}$-), 4.69 (s, 1H, H-1'), 4.72-4.79 (m, 4H, H-1, 2x$CH\underline{H}$ Bn and $MeSO_2(CH_2)_2OCH\underline{H}$-), 4.93 (d, 1H, *J* = 12.0 Hz, $CH\underline{H}$ Bn), 5.06 (d, 1H, *J* = 12.4 Hz, $CH\underline{H}$ 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 ($MeSO_2\underline{C}H_2CH_2OCH_2$-), 54.9 ($CH_3$ OMe), 61.1 ($MeSO_2CH_2\underline{C}H_2OCH_2$-), 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 ($MeSO_2(CH_2)_2O\underline{C}H_2$-), 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 (2xC_q benzylidene and 2xC_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 $C_{45}H_{52}O_{14}SNa$ 871.29700, found 871.29692.



1,2:5,6-Di-*O*-isopropylidene-3-*O*-(2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-methylsulfonylethoxymethyl-D-mannopyranosyl)-α-D-glucofuranoside (27): Disaccharide **27** was prepared from donor **17b** (0.147 g, 0.25 mmol, 1 eq) and acceptor **26** (0.098 g, 0.38 mmol, 1.5 eq) according to the general procedure for glycosylations as described above to afford compound **27** (0.139 g, 0.187 mmol, 75%, α/β = 1:10).

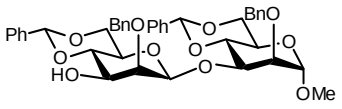
α-anomer:

TLC (50% Toluene in EtOAc): R_f = 0.6; $[\alpha]_D^{22}$: +50º (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 $MeSO_2CH\underline{H}CH_2OCH_2$-), 3.07-3.10 (m, 1H, $MeSO_2CH\underline{H}CH_2OCH_2$-), 3.79-3.92 (m, 5H, H-2', H-5', H-6' and $MeSO_2CH_2C\underline{H}_2OCH_2$-), 4.00 (dd, 1H, *J* = 3.2 Hz, *J* = 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, $MeSO_2(CH_2)_2OCH\underline{H}$-), 4.66 (d, 1H, *J* = 12.4 Hz, $CH\underline{H}$ Bn), 4.76-4.79 (m, 2H, $CH\underline{H}$ Bn and $MeSO_2(CH_2)_2OCH\underline{H}$-), 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 ($MeSO_2\underline{C}H_2CH_2OCH_2$-), 61.6 ($MeSO_2CH_2\underline{C}H_2OCH_2$-), 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 ($MeSO_2(CH_2)_2O\underline{C}H_2$-), 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 $C_{36}H_{48}O_{14}SNa$ 759.26570, found 759.26596.

β-anomer:

TLC (50% Toluene in EtOAc): R_f = 0.4; $[\alpha]_D^{22}$: -43.0º (c = 0.5, DCM); IR (neat, cm^{-1}): 697, 733, 1025; ^{1}H 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, $MeSO_2CH\underline{H}CH_2OCH_2$-), 3.08-3.15 (m, 1H, $MeSO_2CH\underline{H}CH_2OCH_2$-), 3.35 (m, 1H, H-5'), 3.73-3.85 (m, 3H, H-3' and $MeSO_2CH_2C\underline{H}_2OCH_2$-), 3.90-3.96 (m, 2H, H-2' and C-6'), 4.05-415 (m, 3H, 2xH-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, $MeSO_2(CH_2)_2OCH\underline{H}$-), 4.64 (s, 1H, H-1'), 4.70-4.74 (m, 2H, CH<u>H</u> Bn and $MeSO_2(CH_2)_2OCH\underline{H}$-), 4.88 (d, 1H, *J* = 12.0 Hz, CH<u>H</u> 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 ($MeSO_2\underline{C}H_2CH_2OCH_2$-), 61.0 ($MeSO_2CH_2\underline{C}H_2OCH_2$-), 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 ($MeSO_2(CH_2)_2O\underline{C}H_2$-), 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 $C_{36}H_{48}O_{14}SNa$ 759.26570, found 759.26588.

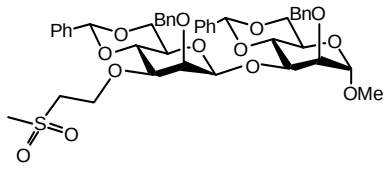


Methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-(2-*O*-benzyl-4,6-*O*-benzylidene-β-D-mannopyranosyl)-α-D-mannopyranoside (28):

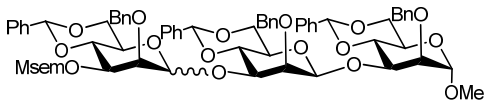
Method I (Without scavenger): To a solution of methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-(2-*O*-benzyl-4,6-*O*-benzylidene3-*O*-methysulfonylethoxymethyl-β-D-mannopyranosyl)-α-D-mannopyranoside **19b(β)** (0.340 g, 0.40 mmol) in THF (4 ml, 0.1 M) was added tetrabutylammonium fluoride (0.05 M/THF, 0.8 ml, 0.04 mmol, 0.1 eq). The reaction mixture was stirred for 24 hours. 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 **28** (0.175 g, 0.248 mmol, 62%) and **29** (0.091 g, 0.111 mmol, 27%).

Method II (With scavenger): To a solution of methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-(2-*O*-benzyl-4,6-*O*-benzylidene3-*O*-methysulfonylethoxymethyl-β-D-mannopyranosyl)-α-D-mannopyranoside **19b(β)** (0.148g, 0.17 mmol) in THF (3.5 ml, 0.05 M) was added pipperdine (35 µl, 0.35 mmol, 2 eq) followed by the addition of tetrabutylammonium fluoride (0.01M, 1.74 ml, 0.1 eq). The reaction mixture was stirred for 24 hours. 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 **28** (0.114 g, 0.160 mmol, 92%). TLC (50% EtOAc in PE): R_f = 0.8; $[\alpha]_D^{22}$: -48.0º (c = 0.6, DCM); IR (neat, cm^{-1}): 535, 698, 1093; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.59 (bs, 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 Hz, *J* = 9.5 Hz, H-6), 4.30 (dd, 1H, *J* = 3.5 Hz, *J* = 10.0 Hz, H-3), 4.44 (s, 1H, H-1'), 4.58-4.62 (m, 2H, 2xCH<u>H</u> Bn), 4.70 (d, 1H, *J* = 12.0 Hz, CH<u>H</u> Bn), 4.79 (s, 1H, H-1), 4.97 (d, 1H, *J* = 11.0 Hz, CH<u>H</u> Bn), 5.20 (bs, 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 (2xC_q benzylidene and 2xC_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 $C_{41}H_{44}O_{11}Na$ 735.27758, found 735.27777.



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 (29): Collected as a side product during the preparation of **28** by the cleavage of Msem without scavenger (0.91 g, 0.111 mmol, 27 %). TLC (50% EtOAc in PE): R_f = 0.6; $[\alpha]_D^{22}$: -33.4º (c = 1.0, DCM); IR (neat, cm^{-1}): 730, 1061; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.79 (s, 3H, CH_3 Mse), 3.01-3.16 (m, 2H, $MeSO_2C\underline{H}_2CH_2$-), 3.36 (m, 1H, H-5'), 3.39 (CH_3 OMe), 3.70-3.80 (m, 3H, H-2', H-6' and $MeSO_2CH_2CH\underline{H}_2$-), 3.80-3.93 (m, 4H, H-2, H-5, H-6 and $MeSO_2CH_2CH\underline{H}_2$-), 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 Hz, *J* = 10.0 Hz, H-6), 4.32 (dd, 1H, *J* = 3.2 Hz, *J* = 10.0 Hz, H-3), 4.39 (s, 1H, H-1'), 4.58 (d, 1H, *J* = 12.4 Hz, CH<u>H</u> Bn), 4.63 (d, 1H, *J* = 11.6 Hz, CH<u>H</u> Bn), 4.74 (d, 1H, *J* = 12.4 Hz, CH<u>H</u> Bn), 4.82 (s, 1H, H-1), 4.96 (d, 1H, *J* = 11.6 Hz, CH<u>H</u> Bn), 5.26 (bs, 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 ($MeSO_2\underline{C}H_2CH_2$-), 63.8 ($MeSO_2CH_2\underline{C}H_2$-), 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 (2xC_q benzylidene and 2xC_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 $C_{44}H_{50}O_{13}SNa$ 841.28643, found 841.28680.



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 (30): Trisaccharide **30** was prepared from donor **17b** (0.172 g, 0.30 mmol, 1.5 eq) and acceptor

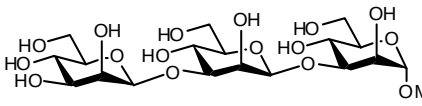
28 (0.144 g, 0.20 mmol, 1 eq) according to the general procedure for glycosylations as described above at -78 ºC yielding compound **35** (0.199 g, 0.17 mmol, 83%, α/β = 1:5).

α-anomer:

TLC (33% Toluene in EtOAc): R_f = 0.66; $[\alpha]_D^{22}$: -2.5º (c = 0.4, DCM); IR (neat, cm^{-1}): 698, 1067; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.59 (s, 3H, CH_3 Msem), 2.72-2.76 (m, 1H, $MeSO_2CH\underline{H}CH_2OCH_2$-), 2.91-2.98 (m, 1H, $MeSO_2CH\underline{H}CH_2OCH_2$-), 3.05-3.10 (m, 1H, H-5') 3.36 (s, 3H, CH_3 OMe), 3.68 (dd, 1H, *J* = 3.2 Hz, *J* = 10.0 Hz, H-3'), 3.75-3.92 (m, 10H, H-2, H-2', H-2'', H-6, H-6', H-6'', $MeSO_2CH_2C\underline{H}_2OCH_2$- and two of the H-3, H-4, H-5, H-3'', H-4'' and H-5''), 4.01-4.36 (m, 10H, H-1', H-4', H-6, H-6', H-6'', C$\underline{H}$ Bn and four of the H-3, H-4, H-5, H-3'', H-4'' and H-5''), 4.39 (d, 1H, *J* = 12.0 Hz, C$\underline{H}$ Bn), 4.56-4.60 (m, 2H, C$\underline{H}$ Bn and $MeSO_2(CH_2)_2OCH\underline{H}$-), 4.73-4.79 (m, 3H, 2xC$\underline{H}$ Bn and $MeSO_2(CH_2)_2OCH\underline{H}$-), 4.85 (s, 1H, H-1), 4.97 (d, 1H, *J* = 12.0 Hz, C$\underline{H}$ Bn), 5.27 (s, 1H, H-1''), 5.55 (s, 1H, CH benzylidene), 5.59 (s, 1H, CH bnzylidene), 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 ($MeSO_2\underline{C}H_2CH_2OCH_2$-), 55.0 ($CH_3$ OMe), 61.5 ($MeSO_2CH_2\underline{C}H_2OCH_2$-), 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 ($MeSO_2(CH_2)_2O\underline{C}H_2$-), 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 (3xC_q benzylidene and 3xC_q Bn); HRMS $[M+Na]^+$ calculated for $C_{65}H_{72}O_{19}SNa$ 1211.42807, found 1211.42847.

β-anomer:

TLC (33% Toluene in EtOAc): R_f = 0.45; $[\alpha]_D^{22}$: -136.4º (c = 1.0, DCM); IR (neat, cm^{-1}): 698, 1092; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.72 (s, 3H, CH_3 Msem), 2.72-2.82 (m, 1H, $MeSO_2CH\underline{H}CH_2OCH_2$-), 2.99-3.00 (m, 1H, $MeSO_2CH\underline{H}CH_2OCH_2$-), 3.10-3.15 (m, 2H, H-5' and H-5"), 3.40 (CH_3 OMe), 3.52 (dd, 1H, *J* = 3.2 Hz, *J* = 10.0 Hz, H-3' or H-3''), 3.71 (m, 1H, H-2' or H-2"), 3.75 (m, 1H, $MeSO_2CH_2CH\underline{H}OCH_2$-), 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 $MeSO_2CH_2CH\underline{H}OCH_2$-), 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 Hz, *J* = 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, $MeSO_2(CH_2)_2OCH\underline{H}$-), 4.64 (d, 1H, *J* = 7.2 Hz, $MeSO_2(CH_2)_2OCH\underline{H}$-), 4.66-4.75 (m, 3H, 3xCH$\underline{H}$ Bn), 4.78 (d, 1H, *J* = 12.0 Hz, C$\underline{H}$ Bn), 4.85 (s, 1H, H-1), 4.96 (d, 1H, *J* = 12.0 Hz, C$\underline{H}$ Bn), 5.04 (d, 1H, *J* = 12.0 Hz, C$\underline{H}$ 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 ($MeSO_2\underline{C}H_2CH_2OCH_2$-), 55.0 ($CH_3$ OMe), 61.3 ($MeSO_2CH_2\underline{C}H_2OCH_2$-), 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 ($MeSO_2(CH_2)_2O\underline{C}H_2$-), 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 (3xC_q Benzylidene and 3xC_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 $C_{65}H_{72}O_{19}SNa$ 1211.42807, found 1211.42842.



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 **30β** (40 mg, 35 μmol) in THF (0.7 ml, 0.05 M) was added pipperdine (7 μl, 70 μmol, 2 eq) followed by the addition of tetrabutylammonium fluoride (0.01M, 0.35 ml, 3.5 μmol, 0.1 eq). The reaction mixture was stirred for 24 hours. 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 get 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. The resulting compound was dissolved in MeOH (1 ml) and H_2O (0.7 ml) before the addition of catalytic amount of $Pd(OH)_2$ on charcoals. The reaction was stirred for 24 hours under an H_2-atmosphere and filtered and purified by Gel filteration to afford the desired trisaccharide **31** (11 mg, 21 μmol, 60%); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 3.30-3.37 (m, 5H, H-5, (H-5' or H-5'') and CH_3 OMe), 3.49 (t, 1H, *J* = 9.6 Hz, H-4' or H-4''), 3.58-3.61 (m, 2H, H-5 and (H-3' or H-3'')), 3.63-3.67 (m, 5H, H-4, (H-4' or H-4"), H-6, H-6' and H-6''), 3.83-3.88 (m, 3H, H-6, H-6', H-6"), 3.91 (dd, 1H, *J* = 2.4 Hz, *J* = 9.6 Hz, H-3' or H-3''), 3.95 (dd, 1H, *J* = 3.0 Hz, *J* = 9.6 Hz, H-3), 3.98 (d, 1H, *J* = 2.4 Hz, H-2' or H-2''), 4.06 (s, 1H, H-2), 4.19 (s, 1H, H-2' or H-2''), 4.73 (s, 1H, H-1), 4.74 (s, 1H, H-1' or H-1''), 4.79 (s, 1H, H-1' or H-1''); ^{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 (C-4 and C-4'), 67.8, 67.9 (C-2 and C-4' or C-4''), 68.7, 71.7 (C-2 and C-2''), 73.3, 73.8 ((C-5' or C-5'') and (C-3' or C-3")), 77.0, 77.3 (C-5'and C-5''), 78.2, 79.8 (C-3' and C-3'') 97.6, 97.7 (C-1' and C-1''), 101.6 (C-1); HRMS $[M+Na]^+$ calculated for $C_{19}H_{34}O_{16}Na$ 541.17391, found 541.17358.

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