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Synthesis and Structural Verification of the Xylomannan Antifreeze Substance from the Freeze-Tolerant Alaskan Beetle *Upis ceramboides*

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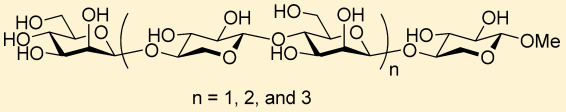
Supporting Information

ABSTRACT: Tetra-, hexa-, and octasaccharide subunits of the [→4)-β-D-Manp-(1→4)-β-D-Xylp-(1→]$_n$ xylomannan motif proposed as the structure of a novel nonprotein, thermal hysteresis-producing antifreeze substance from the freeze-tolerant Alaskan beetle *Upis ceramboides* have been accessed by total chemical synthesis. Comparison of their NMR spectral data with data of the isolate lends strong support to the proposed structure. Synthetic tetrasaccharides representing various linkage isomers considered (α- rather than β-manno, and linkage through mannose O3 rather than O4) show more significant chemical shift differences with the isolate and are therefore excluded from further consideration.



INTRODUCTION

In 2009, Walters and co-workers described the isolation of a thermal hysteresis-producing antifreeze substance from the freeze-tolerant Alaskan beetle *Upis ceramboides*.[1] This new thermal hysteresis factor (THF) is highly unusual insofar as it was shown to be glycan-based and to contain little or no protein,[1] whereas most THFs are protein or glycoprotein-based.[2] On the basis of extensive NMR and mass spectrometric work coupled with both chemical and enzymatic degradative studies, an alternating xylopyranose−mannopyranose glycan [→4)-β-D-Manp-(1→4)-β-D-Xylp-(1→]$_n$ was proposed as the likely structure for this glycan-based THF with both linkage types belonging to the β-(1→4) class. However, as acknowledged by the authors,[1] the linkage isomer [→3)-β-D-Manp-(1→4)-β-D-Xylp-(1→]$_n$, in which the xylopyranose residue is β-linked to the 3-position of the mannopyranose ring rather than to the 4-position, could not be completely excluded on the basis of the spectroscopic evidence available.[1] Similarly, the data did not permit the fully unambiguous assignment of the α-configuration to the mannopyranoside moiety. The alternative possibility that the glycan consists of alternating sections of a mannan and a xylan could also not be excluded on the basis of the data presented.[1] In view of the highly unusual nature of this glycan-based THF and the various ambiguities in its structure, we have undertaken a program of organic synthesis of authentic samples of homogeneous xylomannan oligosaccharides for comparison purposes so as to aid in its structural elucidation. The power of total organic synthesis in the resolution of ambiguous structures is well-known[3] and has proven to be essential in the past for the elucidation of structural motifs necessary for activity of certain antifreeze glycoproteins.[4] We report here on the successful outcome of this synthesis program and on the close similarity of the spectroscopic data of the natural isolate and a homologous series of synthetic oligosaccharides that lends strong support to the proposed structure of the antifreeze glycan-based THF.

RESULTS AND DISCUSSION

We first considered the possibility that the antifreeze glycan might consist of a mixture of xylans and mannans as entertained originally. Comparison of the spectral data reported in the literature for natural β-(1→3)- and β-(1→4)-xylans[5] and for natural[5c,6] and synthetic[7] β-(1→3)- and β-(1→4)-mannans with the xylomannan THF data revealed considerable discrepancies and enabled such structures to be excluded from consideration. The range of candidates for synthesis was therefore narrowed substantially, and attention was focused on the [→4)-β-D-Manp-(1→4)-β-D-Xylp-(1→]$_n$ which was considered to be the most likely structure by Walters and co-workers.[1] Uncertain as to the number of repeating units necessary to mimic the structure of the isolated glycan, and desiring maximum synthetic efficiency, we designed a concise, convergent approach to tetra-, hexa-, and octasaccharyl subunits of [→4)-β-D-Manp-(1→4)-β-D-Xylp-(1→]$_n$, each in the form of the methyl glycosides so as to simplify the NMR spectra. Accordingly, the disaccharides **4** and **5** were assembled from the β-mannosyl donor **1**[8] and the xylopyranosyl acceptors **2**[9] and **3**[10] by our standard methodology[11] involving preactivation of the donor at low temperature with the combination of 1-benzenesulfinyl piperidine (BSP),[12] trifluoromethanesulfonic anhydride (Tf_2O), and the hindered base 2,4,6-tri-*tert*-butylpyrimidine (TTBP) (Scheme 1).[13] With the glycosyl acceptor **5**, itself a thioglycoside, the sulfenyl trap 1-octene was added to the reaction mixture before it was allowed to warm to room temperature to prevent premature activation of the disaccharyl thioglycoside.[7a,14] As anticipated,[11] these reactions were highly β-selective with only a single anomer being isolated in each case. Acidolysis of the reactive *trans*-fused acetonide in **4** and **5** was then followed by benzoylation to give **6** and **7**, which, on treatment with sodium cyanoborohydride and HCl,[15] underwent reductive cleavage of the benzylidene acetal units to

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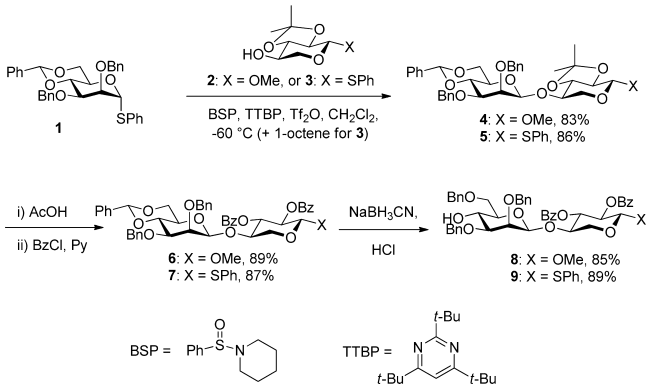
Scheme 1. Synthesis of the Four Disaccharyl Units 6−9



give the corresponding 6′-*O*-benzyl ethers retaining hydroxyl groups at the 4′-positions, **8** and **9** (Scheme 1).

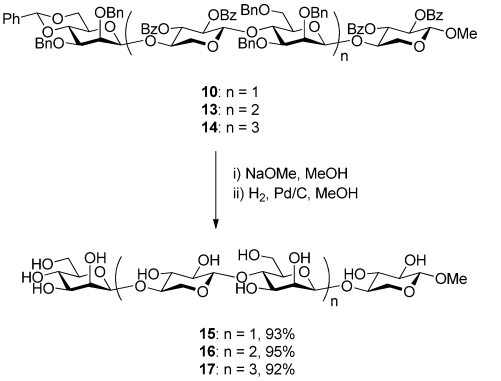
The disaccharide **7** was then coupled to the acceptors **8** and **9**, giving the tetrasaccharides **10** and **11** as single anomers. Subsequent reduction of the benzylidene acetal in **10** by the sodium cyanoborohydride protocol then gave the tetrasaccharyl acceptor **12** (Scheme 2).

Coupling of the tetrasaccharyl donor **11** with the disaccharyl acceptor **8** afforded the hexasaccharide **13**, while similar coupling of the two saccharides **11** and **12** gave the octasaccharide **14** (Scheme 2). In this manner, a homologous series of protected tetra-, hexa-, and octasaccharides for deprotection was assembled efficiently with complete control of anomeric stereochemistry.

Cleavage of the benzoate esters in **10**, **13**, and **14** under Zemplen conditions followed by hydrogenolysis then afforded the pure, homogeneous target tetra-, hexa-, and octasaccharides **15**−**17** (Scheme 3).

The ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra of **15**−**17** were recorded in phosphate buffer (D_2O) at pH 7.5 and 40 °C and assigned by a combination of TOCSY, COSY, HMQC, and HMBC techniques, leading to the chemical shift data presented in Table 1, entries 1−3, for the repeating

Scheme 3. Completion of the Tetra-, Hexa-, and Octasaccharides 15−17



disaccharide units at the core of each structure. All coupling constants were in full agreement with the assigned structures of these synthetic oligosaccharides. It is immediately clear from inspection of the spectra of these three oligosaccharides (Supporting Information) that they differ only in the relative intensity of the signals due to the xylomannan core as compared to those of the monosaccharides at the up- and downstream termini. It is therefore clear that these substances have a regular organized structure, as is expected to be the case for 1→3 and 1→4-glycans in general,[16] and that these simple oligosaccharides are adequate mimics of longer glycans for the purposes of comparison of spectral data.

A graphic representation[17] of the ^{13}C and ^{1}H NMR chemical shift differences between the core residues of the three synthetic xylomannans and the literature data for the antifreeze glycan under comparable conditions[18] (Figures 1 and 2, left-hand column) reveals close homology between the synthetic and isolated material. Thus, in the ^{13}C NMR spectra, only minor differences in chemical shift were found for the two anomeric carbons and for C2 of the mannose unit in **15**−**17** and the isolated glycan (Figure 1, left-hand column). Likewise,

Scheme 2. Convergent Assembly of the Tetra-, Hexa-, and Octasaccharides 10−14

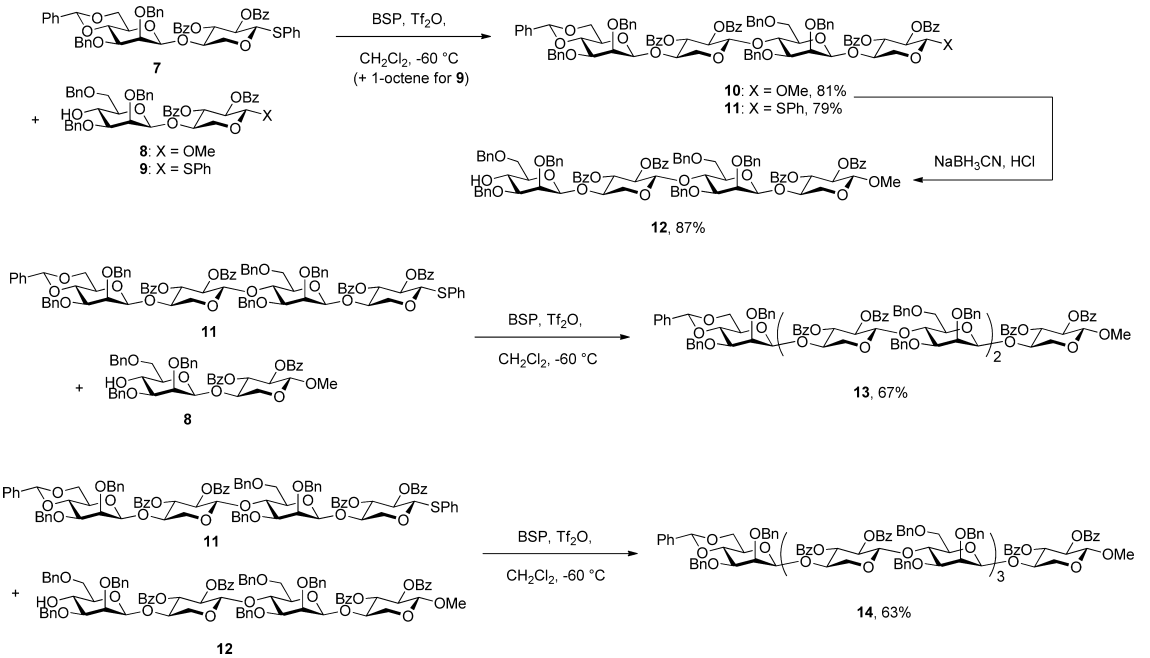


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Table 1. ^{13}C and ^{1}H Chemical Shifts (ppm) for the Repeating Units of Isolated and Synthetic Xylomannans Recorded in D_2O at pH 7.5 and 40 °C

assignments for internal mannopyranoside residues						
glycan	C1 (H1)	C2 (H2)	C3 (H3)	C4 (H4)	C5 (H5)	C6 (H6, 6′)
[→4)-β-D-Manp-(1→4)-β-D-Xylp-(1→]$_n$ (isolated material)[a,b]	100.2 (4.92)	70.1 (4.30)	71.6 (3.98)	76.6 (3.96)	75.1 (3.74)	60.6 (4.09, 3.93)
H[→4)-β-D-Manp-(1→4)-β-D-Xylp-(1→]$_2$OMe (**15**)[c]	98.4 (5.08)	70.9 (4.29)	71.6 (4.01)	76.5 (3.84)	75.3 (3.69)	60.4 (4.18, 3.99)
H[→4)-β-D-Manp-(1→4)-β-D-Xylp-(1→]$_3$OMe (**16**)[c]	98.4 (5.07)	70.9 (4.27)	71.6 (3.99)	76.5 (3.82)	75.3 (3.69)	60.4 (4.16, 3.94)
H[→4)-β-D-Manp-(1→4)-β-D-Xylp-(1→]$_4$OMe (**17**)[c]	98.6 (5.03)	70.8 (4.25)	71.8 (3.98)	76.7 (3.82)	75.5 (3.63)	60.7 (4.16, 3.97)
H[→3)-β-D-Manp-(1→4)-β-D-Xylp-(1→]$_2$OMe (**23**)[c]	98.5 (5.09)	68.4 (4.48)	80.1 (4.14)	65.1 (3.97)	76.5 (3.72)	61.2 (4.21, 4.04)
H[→4)-α-D-Manp-(1→4)-β-D-Xylp-(1→]$_2$OMe (**31**)[c]	102.1 (5.31)	70.2 (4.34)	70.5 (4.09)	78.0 (4.01)	74.8 (3.89)	60.7 (4.18, 4.02)
H[→3)-α-D-Manp-(1→4)-β-D-Xylp-(1→]$_2$OMe (**37**)[c]	101.5 (5.45)	70.1 (4.58)	78.0 (4.28)	67.6 (4.07)	74.8 (3.98)	61.1 (4.20, 4.11)
assignments for internal xylopyranoside residues						
glycan	C1 (H1)	C2 (H2)	C3 (H3)	C4 (H4)	C5 (H5, 5′)	
[→4)-β-D-Manp-(1→4)-β-D-Xylp-(1→]$_n$ (isolated material)[a,b]	101.7 (4.66)	72.8 (3.48)	73.8 (3.73)	76.6 (4.00)	63.0 (4.28, 3.55)	
H[→4)-β-D-Manp-(1→4)-β-D-Xylp-(1→]$_2$OMe (**15**)[c]	103.4 (4.69)	73.0 (3.59)	74.0 (3.84)	76.3 (4.12)	63.1 (4.39, 3.65)	
H[→4)-β-D-Manp-(1→4)-β-D-Xylp-(1→]$_3$OMe (**16**)[c]	103.4 (4.69)	73.0 (3.61)	74.0 (3.84)	76.4 (4.12)	63.1 (4.40, 3.66)	
H[→4)-β-D-Manp-(1→4)-β-D-Xylp-(1→]$_4$OMe (**17**)[c]	103.6 (4.65)	73.3 (3.57)	74.2 (3.85)	76.5 (4.11)	63.2 (4.40, 3.67)	
H[→3)-β-D-Manp-(1→4)-β-D-Xylp-(1→]$_2$OMe (**23**)	100.9 (4.86)	72.8 (3.69)	74.0 (3.87)	76.5 (4.11)	63.0 (4.41, 3.68)	
H[→4)-α-D-Manp-(1→4)-β-D-Xylp-(1→]$_2$OMe (**31**)[c]	104.1 (4.67)	73.2 (3.60)	73.7 (3.85)	76.8 (3.95)	64.5 (4.42, 3.65)	
H[→3)-α-D-Manp-(1→4)-β-D-Xylp-(1→]$_2$OMe (**37**)[c]	101.8 (4.89)	72.9 (3.74)	74.8 (3.97)	77.7 (4.09)	64.2 (4.47 3.78)	

[a]Data taken from Walters and co-workers.[1] [b]Recorded at 800 MHz for ^{1}H and 200 MHz for ^{13}C. [c]Recorded at 500 MHz for ^{1}H and 125 MHz for ^{13}C.

although not identical, the ^{1}H NMR chemical shifts of the internal residues of **15**−**17** differed little from those of the isolated glycan (Figure 2, left-hand column). Most notably though, in the mannopyranose moiety, the largest differences in ^{1}H chemical shift between **15**−**17** and the isolated glycan were found for the anomeric proton and H4, that is, for those protons

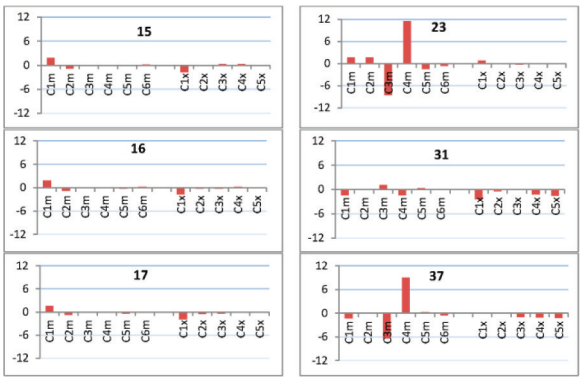

Figure 1. ^{13}C $\Delta\delta$ values for the chemical shifts of **15**−**17**, **23**, **31**, and **37** with the isolated glycan; m = mannopyranoside, x = xylopyranoside.

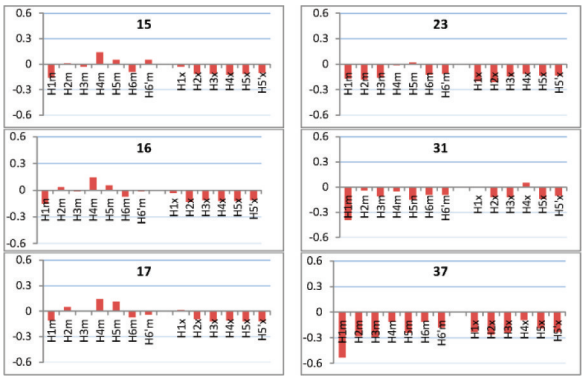

Figure 2. ^{1}H $\Delta\delta$ values for the chemical shifts of **15**−**17**, **23**, **31**, and **37** with the isolated glycan; m = mannopyranoside, x = xylopyranoside.

most closely associated with one of the two interglycosidic linkages.

The differences, albeit small, in chemical shifts between the synthetic xylomannans **15**−**17** and the natural isolate (Figures 1 and 2, left-hand column) prompted the synthesis of three more systems representing the stereoisomeric and positional isomers considered by Walters and co-workers as possible alternative structures.[1] As the close homology of the NMR data for the xylomannans **15**−**17** (Figures 1 and 2, left-hand column and Supporting Information) indicated simple tetrasaccharides to be adequate models of the glycan for spectra purposes, we limited the synthesis of these linkage isomers to the tetrasaccharide level, which we considered a minimal but adequate representations for the purposes of comparison of spectral data with the natural glycan.

In order to prepare a linkage isomer in which the β-xylosyl unit was linked to O3 rather than to O4 of mannnopyranose, we began with the known β-mannosyl donor[7a] **18** protected on O3 with the 2-naphthylmethyl ether. After formation of the disaccharide **19** and replacement of the isopropylidene group with two esters in the usual manner, removal of the naphthylmethyl ether was achieved with DDQ under standard conditions to give **21**. Subsequent coupling of this disaccharide with the β-xylopyranosyl donor **8** gave the tetrasaccharide **22** which on deprotection afforded the linkage isomer **23** (Scheme 4).

A second linkage isomer **31**, in which the mannopyranosyl unit was linked (1→4)-α to the xylopyranosyl residue, was obtained from the known α-mannosyl donor[19] **24** uneventfully as outlined in Scheme 5.

Finally, a third linkage isomer **37**, having the α-configuration at the mannopyranosyl anomeric center and linked via O3 of mannose, was prepared from the α-mannosyl donor[20] **32** by standard methods as illustrated in Scheme 6.

No isomers (positional or stereochemical) of the xylopyranosyl residue were prepared as the original structural assignment of the xylopyranose moiety of the glycan-based THF is considered secure.[1]

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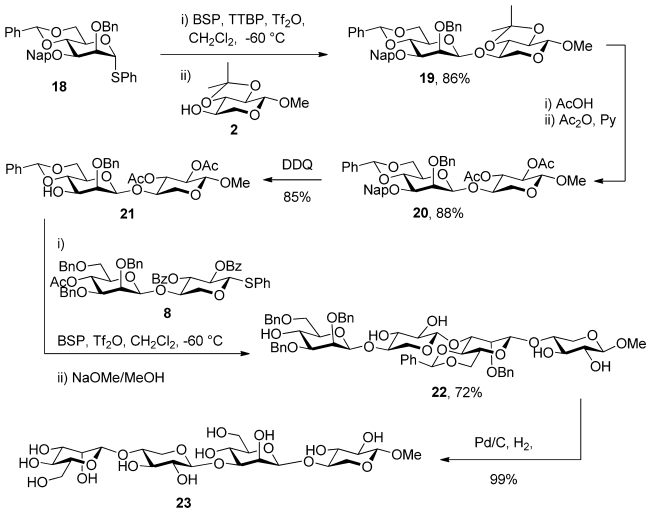
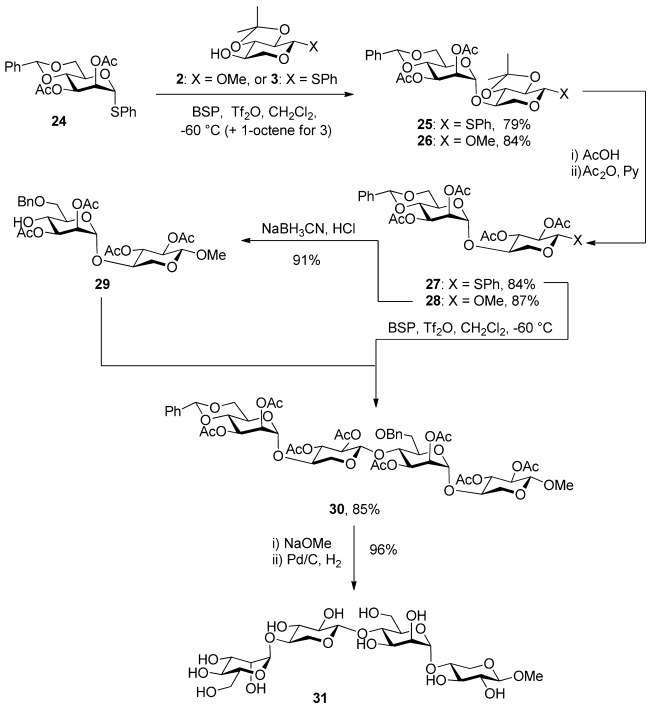
Scheme 4. Synthesis of Linkage Isomer 23

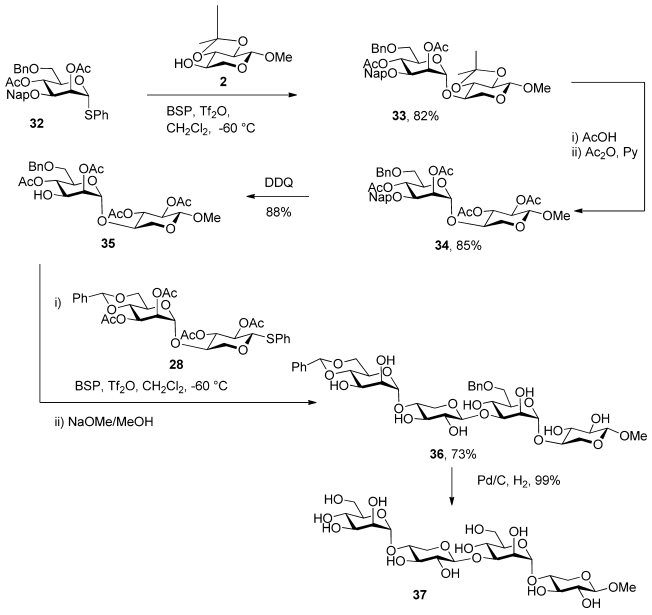


Scheme 5. Synthesis of Linkage Isomer 31



The NMR data for the isomeric tetrasaccharides **23**, **31**, and **37** are presented in Tables 1−3, and the ^{13}C and ^{1}H NMR chemical shift differences between their internal residues and those of the natural isolate are represented graphically in Figures 1 and 2, right-hand column. The ^{13}C NMR spectral data for tetrasaccharide **23** differ significantly from those of the isolated glycan at the level of carbons 3 and 4 of the mannopyranosyl ring, strongly suggesting that the isolate is not linked through C3 of the mannose residue. The ^{1}H and ^{13}C spectral data for tetrasaccharide **31** show good homology with that of the isolated glycan except for the mannose H1, indicating that the isolate is not an α-mannoside. Finally, tetrasaccharide **37**, which differs from the structure proposed for the isolated glycan at both the mannose anomeric center and the linkage position to the mannopyranose ring, shows the largest differences in spectral data with the isolate.

Scheme 6. Synthesis of Linkage Isomer 37



Overall, we conclude that among the sequences considered for this antifreeze xylomannan the [→4)-β-D-Man*p*-(1→4)-β-D-Xyl*p*-(1→]$_n$ structure favored by Walters and co-workers[1] is the best fit to the available data. This conclusion raises the obvious question as to the origin of the minor chemical shift differences at both the manno- and xylopyranoside anomeric centers and at the mannopyranoside 2-position between the core of the models **15**−**17** and that of the isolate (Table 1, entries 1−4). Short of invoking an actual assignment error in one of the two subunits (such as mannose for talose) by Walters and collaborators,[1] we hypothesize that these might arise from agglomeration of the actual glycan, or from its adoption of a higher order structure not available to the short synthetic models. Alternatively, the small chemical shift differences might simply be the consequence of imperfect reproduction of the original NMR conditions; indeed, the spectra of **15**−**17** showed considerable changes on going from solution in deuteriomethanol to pH 7.5 D_2O buffer, and from 25 to 40 °C, thereby revealing the sensitivity of the spectral data to the acquisition conditions.

EXPERIMENTAL SECTION

General Procedure 1. Synthesis of Disaccharides by the BSP Method (Cmpds 4, 19, 26, and 33). A mixture of phenyl thiomannopyranoside (0.3 mmol), BSP (76 mg, 0.36 mmol), TTBP (112 mg, 0.45 mmol, used only for compounds **4** and **19**), and 4 Å molecular sieves (170 mg) was dried under vacuum for 0.5 h. Freshly distilled dichloromethane (6 mL) was added, and the reaction mixture was stirred for 0.5 h at room temperature under N_2 before it was cooled to −65 °C and stirred for an additional 5 min. Tf_2O (61 μL, 0.36 mmol) was added dropwise and the reaction mixture stirred for 30 min while the temperature was held between −65 and −60 °C, after which a solution of methyl xylopyranoside **2** (67 mg, 0.33 mmol) in dichloromethane (3 mL) was added dropwise and the reaction mixture was stirred for 2.5 h at −60 °C before it was quenched with Et_3N (0.5 mL) and then warmed to room temperature. The reaction mixture was filtered through Celite, concentrated, and purified by chromatography over silica gel.

General Procedure 2. Synthesis of Disaccharyl Thioglycosides (Cmpds 5 and 25). A mixture of phenyl thiomannopyranoside (0.25 mmol), BSP (63 mg, 0.3 mmol), TTBP (93 mg, 0.37 mmol, used only for compound **5**), and 4 Å molecular sieves (150 mg) was dried under vacuum for 0.5 h. Freshly distilled dichloromethane

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Table 2. ^{13}C and ^{1}H Chemical Shifts (ppm) for the Terminal Residues of Synthetic Xylomannans Recorded in D_2O at pH 7.5 and 40 °C[a]

assignments for nonreducing end mannopyranoside residues						
glycan	C1 (H1)	C2 (H2)	C3 (H3)	C4 (H4)	C5 (H5)	C6 (H6, 6′)
H[→4)-β-D-Manp-(1→4)-β-D-Xylp-(1→]$_2$OMe (**15**)	98.6 (5.06)	71.7 (4.25)	71.6 (3.82)	67.1 (3.82)	76.5 (3.63)	61.2 (4.17, 3.97)
H[→4)-β-D-Manp-(1→4)-β-D-Xylp-(1→]$_3$OMe (**16**)	98.2 (5.07)	71.4 (4.25)	72.5 (3.87)	66.9 (3.82)	76.2 (3.66)	61.2 (4.18, 3.97)
H[→4)-β-D-Manp-(1→4)-β-D-Xylp-(1→]$_4$OMe (**17**)	98.7 (5.02)	71.1 (4.23)	71.8 (3.89)	67.2 (3.78)	75.5 (3.62)	61.4 (4.15, 3.95)
H[→3)-β-D-Manp-(1→4)-β-D-Xylp-(1→]$_2$OMe (**23**)	98.2 (5.10)	72.6 (4.28)	68.4 (3.97)	66.9 (3.90)	76.3 (3.70)	61.2 (4.22, 4.04)
H[→4)-α-D-Manp-(1→4)-β-D-Xylp-(1→]$_2$OMe (**31**)	101.7 (5.32)	70.5 (4.30)	70.7 (4.03)	67.1 (3.95)	73.7 (3.86)	61.4 4.16, 4.01)
H[→3)-α-D-Manp-(1→4)-β-D-Xylp-(1→]$_2$OMe (**37**)	100.8 (5.42)	70.4 (4.27)	65.0 (4.15)	66.8 (4.00)	74.8 (3.96)	61.1 (4.20, 4.09)
assignments for reducing end methyl xylopyranoside residues						
glycan	C1 (H1)	C2 (H2)	C3 (H3)	C4 (H4)	C5 (H5, 5′)	OCH_3 (OCH_3)
H[→4)-β-D-Manp-(1→4)-β-D-Xylp-(1→]$_2$OMe (**15**)	104.0 (4.61)	73.3 (3.56)	74.1 (3.84)	76.5 (4.06)	63.3 (4.37, 3.65)	57.5 (3.79)
H[→4)-β-D-Manp-(1→4)-β-D-Xylp-(1→]$_3$OMe (**16**)	103.9 (4.61)	72.9 (3.55)	73.9 (3.83)	76.4 (4.07)	63.0 (4.36, 3.63)	57.3 (3.80)
H[→4)-β-D-Manp-(1→4)-β-D-Xylp-(1→]$_4$OMe (**17**)	104.1 (4.57)	73.1 (3.50)	74.2 (3.83)	76.6 (4.08)	63.3 (4.31, 3.55)	57.5 (3.76)
H[→3)-β-D-Manp-(1→4)-β-D-Xylp-(1→]$_2$OMe (**23**)	103.9 (4.65)	74.0 (3.59)	73.0 (3.85)	76.4 (4.12)	63.0 (4.41, 3.68)	57.4 (3.78)
H[→4)-α-D-Manp-(1→4)-β-D-Xylp-(1→]$_2$OMe (**31**)	103.6 (4.57)	72.4 (3.54)	73.5 (3.84)	77.9 (3.91)	64.5 (4.39, 3.65)	57.7 (3.78)
H[→3)-α-D-Manp-(1→4)-β-D-Xylp-(1→]$_2$OMe (**37**)	103.8 (4.68)	72.8 (3.63)	74.8 (3.82)	77.7 (4.02)	64.3 (4.48, 3.77)	57.3 (3.87)

[a]Recorded at 500 MHz for ^{1}H and 125 MHz for ^{13}C.

Table 3. Coupling Constants (Hz) for the Repeating Units of Synthetic Xylomannans Recorded in D_2O at pH 7.5 and 40 °C[a]

assignments for internal mannopyranoside residues							
glycan	$^{3}J_{H1,H2}$	$^{3}J_{H2,H3}$	$^{3}J_{H3,H4}$	$^{3}J_{H4,H5}$	$^{3}J_{H5,H6}$	$^{2}J_{H6,H6'}$	$^{1}J_{C1,H1}$
H[→4)-β-D-Manp-(1→4)-β-D-Xylp-(1→]$_2$OMe (**15**)	>1.0	2.0	9.7	9.5	*b*	11.5	158.6
H[→4)-β-D-Manp-(1→4)-β-D-Xylp-(1→]$_3$OMe (**16**)	>1.0	2.0	9.5	9.0	*b*	11.5	158.2
H[→4)-β-D-Manp-(1→4)-β-D-Xylp-(1→]$_4$OMe (**17**)	>1.0	2.5	9.5	10.0	*b*	12.0	159.1
H[→3)-β-D-Manp-(1→4)-β-D-Xylp-(1→]$_2$OMe (**23**)	>1.0	2.5	8.0	*b*	*b*	12.5	159.2
H[→4)-α-D-Manp-(1→4)-β-D-Xylp-(1→]$_2$OMe (**31**)	>1.0	1.5	*b*	*b*	*b*	*b*	170.2
H[→3)-α-D-Manp-(1→4)-β-D-Xylp-(1→]$_2$OMe (**37**)	>1.0	3.0	9.5	*b*	*b*	11.0	170.5
assignments for internal xylopyranoside residues							
glycan	$^{3}J_{H1,H2}$	$^{3}J_{H2,H3}$	$^{3}J_{H3,H4}$	$^{3}J_{H4,H5}$	$^{2}J_{H5,H5'}$	$^{1}J_{C1,H1}$	
H[→4)-β-DManp-(1→4)-β-D-Xylp-(1→]$_2$OMe (**15**)	8.0	9.2	9.5	*b*	12.0	164.3	
H[→4)-β-D-Manp-(1→4)-β-D-Xylp-(1→]$_3$OMe (**16**)	7.5	7.5	9.5	*b*	11.7	162.1	
H[→4)-β-D-Manp-(1→4)-β-D-Xylp-(1→]$_4$OMe (**17**)	7.5	7.5	9.0	*b*	11.7	160.6	
H[→3)-β-D-Manp-(1→4)-β-D-Xylp-(1→]$_2$OMe (**23**)	8.0	8.5	9.2	*b*	11.5	155.7	
H[→4)-α-D-Manp-(1→4)-β-D-Xylp-(1→]$_2$OMe (**31**)	7.5	8.7	8.0	*b*	12.0	161.1	
H[→3)-α-D-Manp-(1→4)-β-D-Xylp-(1→]$_2$OMe (**37**)	8.0	8.5	9.5	*b*	11.2	160.4	

[a]Recorded at 500 MHz for ^{1}H and 125 MHz for ^{13}C. [b]Not determined.

(5 mL) was added, and the reaction mixture was stirred for 0.5 h at ambient temperature under N_2 atmosphere, then cooled to −65 °C and stirred for an additional 5 min before the addition of Tf_2O (61 μL, 0.36 mmol). The reaction mixture was stirred for 30 min at −65 to −60 °C, then was cooled to −78 °C and stirred for 5 min before 1-octene (0.3 mL, 2 mmol) was added and stirring continued for 5 min more. A solution of thioxylopyranoside acceptor **3** (77 mg, 0.27 mmol) in dicholoromethane (3 mL) then was added dropwise, and the reaction mixture was stirred for 2.5 h at −60 °C before it was quenched with Et_3N (0.5 mL) and warmed to room temperature. The reaction mixture was filtered through Celite, concentrated, and purified by chromatography over silica gel.

General Procedure 3. Acidolysis of Acetonide Groups and Subsequent Benzoylation (Cmpds 6, 7, 20, 27, 28, and 34). A solution of disaccharide (0.1 mmol) in glacial acetic acid (10 mL) was stirred at 65 °C for 3 h. Upon completion of the reaction, acetic acid was removed in vacuo at 30 °C to give a white residue that was taken up in pyridine (5 mL) and cooled down to 0 °C before it was treated dropwise with benzoyl chloride (47 μL, 0.4 mmol). After stirring for 2 h, the reaction mixture was concentrated in vacuo and the residue was dissolved in EtOAc (25 mL). The organic layer was successively washed with water, saturated aqueous $NaHCO_3$, and brine and dried over Na_2SO_4. The product was purified by chromatography over silica gel.

General Procedure 4. Reductive Cleavage of Benzylidene Acetals (Cmpds 8, 9, 12, and 29). Oligosaccharide (0.1 mmol) was mixed with dry 3 Å molecular sieves (150 mg) and stirred in vacuo for 0.5 h. THF (2 mL) was added, and the reaction mixture was stirred for 5 min before it was cooled to 0 °C followed by the addition of sodium cyanoborohydride (32 mg, 0.5 mmol) (for **12**, 63 mg, 1 mmol). The reaction mixture was stirred at 0 °C for 1 h (for **12** overnight), followed by very slow dropwise addition of dry HCl in diethyl ether (2 N, 1.5 mL) until effervescence ceased, after which the reaction mixture was warmed to room temperature and diluted with chloroform (30 mL). The organic layer was successively washed with water and brine and dried over Na_2SO_4. Chromatographic purification over silica gel afforded the pure product.

General Procedure 5. Synthesis of Oligosaccahrides by the BSP Method (Cmpds 10, 13, 14, 22, 30, and 36). The phenyl thioglycoside (100 μmol) was mixed with BSP (27 mg, 120 μmol) and oven-dried 4 Å molecular sieves (150 mg) and dried under vacuum for 0.5 h before dichloromethane (3 mL) was added under N_2, and the reaction mixture was stirred for 0.5 h at room temperature then cooled to −65 °C and stirred for an additional 5 min. Tf_2O (22 μL, 120 μmol) was added dropwise and the reaction mixture stirred for 30 min between −65 and −60 °C; then it was cooled to −70 °C, and a solution of polysaccharide acceptor (100 μmol) in dichloromethane (2 mL) was added dropwise. The reaction mixture was stirred at

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−60 °C for 2.5 h before it was quenched by addition of Et_3N (500 μL) and warmed to room temperature. The quenched reaction mixture was filtered through Celite, concentrated, and purified by silica gel column chromatography.

General Procedure 6. Global Deprotection of Oligosaccharides by Hydrogenolysis (Cmpds 15, 16, 17, 23, 31, and 37). The protected oligosaccharide (0.02 mmol) was dissolved in methanol (2 mL) and treated with a 25% solution of NaOMe in methanol (0.1 mL) at 0 °C. Upon completion of the reaction, the reaction mixture was neutralized by the addition of Amberlite IR 120 (H^+) followed by filtration through Celite. The filtrate was concentrated under reduced pressure at room temperature to give a white foam that was taken forward without further purification. The saponified oligosaccharide was dissolved in methanol (2 mL) and Pd−C (20 mg), and 1 drop of glacial acetic acid was added to it. The reaction mixture was shaken under 40 psi H_2 at room temperature for 12 h after which it was filtered through Celite and then concentrated under reduced pressure at room temperature to afford the oligosaccharide.

General Procedure 7. Removal of Naphthalylmethyl Ethers with DDQ (Cmpds 21 and 35). To a stirred solution of disaccharide (0.07 mmol) in dichloromethane (10 mL) and water (0.5 mL) was added DDQ (40 mg, 0.18 mmol) at room temperature. The reaction mixture was stirred for 3 h before it was quenched with a saturated aqueous solution of $NaHCO_3$ and diluted with dichloromethane (20 mL). The organic layer was successively washed with water and brine, dried over Na_2SO_4, concentrated, and purified by chromatography over silica gel.

Methyl 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-β-D-mannopyranosyl-(1→4)-2,3-*O*-isopropylidene-β-D-xylopyranoside (4). Obtained by protocol 1 from compounds **1** and **2**. Chromatographic purification with 20% EtOAc in hexanes as eluent afforded disaccharide **4** (151 mg, 83%) as a white foam: $[\alpha]_D^{24}$ −47.8 (c = 1.0, CH_3Cl); ^1H NMR (500 MHz, $CDCl_3$) δ 7.53−7.50 (m, 2H), 7.48−7.45 (m, 2H), 7.41−7.36 (m, 3H), 7.35−7.28 (m, 8H) 5.64 (s, 1H), 4.94 (d, J = 12.5 Hz, 1H), 4.89 (d, J = 12.0 Hz, 1H), 4.76 (d, J = 12.5 Hz, 1H), 4.66 (d, J = 12.0 Hz, 1H), 4.65 (s, 1H), 4.56 (d, J = 7.5 Hz, 1H), 4.28 (dd, J = 4.7, 10.2 Hz, 1H), 4.23 (t, J = 9.7 Hz, 1H), 4.05 (dd, J = 5.2, 12.2 Hz, 1H), 4.02−3.99 (m, 1H), 3.96 (t, J = 10.2 Hz, 1H), 3.91 (d, J = 3.0 Hz, 1H), 3.76 (t, J = 9.2 Hz, 1H), 3.63 (dd, J = 2.7, 9.7 Hz, 1H), 3.54 (s, 3H), 3.42−3.34 (m, 2H), 3.31 (dd, J = 7.5, 9.5 Hz, 1H), 1.44 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (125.9 MHz, $CDCl_3$) δ 138.5, 137.8, 129.1, 128.9, 128.6, 128.4, 128.3, 127.9, 129.8, 126.2, 111.7, 102.6, 101.7 ($^1J_{C-H}$ = 157.6 Hz), 100.3, 79.3, 78.9, 78.3, 76.9, 76.4, 76.3, 75.0, 72.8, 68.9, 67.8, 65.4, 56.7, 27.0, 26.8; ESIHRMS m/z calcd for $C_{36}H_{42}O_{10}Na$ $[M + Na]^+$ 657.2676, found 657.2668.

Phenyl 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-β-D-mannopyranosyl-(1→4)-2,3-*O*-isopropylidene-1-thio-β-D-xylopyranoside (5). Obtained by protocol 2 from compounds **1** and **3**. Chromatographic purification with 20% EtOAc in hexanes as eluent afforded disaccharide **5** (153 mg, 86%) as a white foam: $[\alpha]_D^{24}$ −55.6 (c = 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.57 (dd, J = 3.0, 7.0 Hz, 2H), 7.53−7.50 (m, 2H), 7.46−7.43 (m, 2H), 7.41−7.36 (m, 2H), 7.35−7.29 (m, 12H), 5.63 (s, 1H), 4.92 (d, J = 12.5 Hz, 1H), 4.87 (d, J = 12.0 Hz, 1H), 4.82 (d, J = 9.5 Hz, 1H), 4.76 (d, J = 12.5 Hz, 1H), 4.66 (d, J = 12.5 Hz, 1H), 4.62 (s, 1H), 4.27 (dd, J = 5.0, 10.5 Hz, 1H), 4.22 (t, J = 9.5 Hz, 1H), 4.12 (dd, J = 5.2, 11.7 Hz, 1H), 3.99−3.93 (m, 2H), 3.89 (d, J = 2.5 Hz, 1H), 3.73 (t, J = 9.0 Hz, 1H), 3.61 (dd, J = 3.0, 9.5 Hz, 1H), 3.37−3.31 (m, 2H), 3.20 (t, J = 9.2 Hz, 1H), 1.47 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (125.9 MHz, $CDCl_3$) δ 138.5, 137.8, 133.2, 132, 129.1, 128.9, 128.6, 128.4, 128.3, 127.9, 127.8, 126.2, 111.2, 101.7, 100.1 ($^1J_{C-H}$ = 157.2), 85.4, 81.2, 78.9, 78.3, 76.2, 75.6, 75.5, 75.0, 72.8, 68.8, 67.9, 67.8, 26.9, 26.8; ESIHRMS m/z calcd for $C_{41}H_{44}O_9SNa$ $[M + Na]^+$ 735.2604, found 735.2560.

Methyl 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-β-D-mannopyranosyl-(1→4)-2,3-di-*O*-benzoyl-β-D-xylopyranoside (6). Obtained by protocol 3 from compound **4**. Chromatographic purification over silica gel with 20% EtOAc in hexanes as eluent afforded disaccharide **6** (71 mg, 89%) as a white foam: $[\alpha]_D^{24}$ −38.8 (c = 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, J = 7.0 Hz, 2H), 8.01 (d, J = 7.0 Hz, 2H), 7.56−7.51 (m, 2H), 7.49−7.47 (m, 2H), 7.44−7.37 (m, 9H), 7.35−7.27 (m, 8H), 5.74 (t, J = 8.2 Hz, 1H), 5.46 (s, 1H), 5.36 (dd, J = 6.7, 8.2 Hz, 1H), 4.91 (d, J = 12.0 Hz, 1H), 4.77 (d, J = 12.0 Hz, 1H), 4.71 (d, J = 12.5 Hz, 1H), 4.66 (d, J = 7.0 Hz, 1H), 4.62 (s, 1H), 4.61 (d, J = 11.0 Hz, 1H), 4.21 (dd, J = 4.7, 11.7 Hz, 1H), 4.17−4.13 (m, 1H), 4.03 (t, J = 9.7 Hz, 1H), 4.00 (dd, J = 5.0, 10.5 Hz, 1H), 3.90 (d, J = 3.0 Hz, 1H), 3.61−3.56 (m, 2H), 3.55 (s, 3H), 3.40 (t, J = 10.2 Hz, 1H), 3.23 (dt, J = 5.0, 9.7 Hz, 1H); ^{13}C NMR (125.9 MHz, $CDCl_3$) δ 165.6, 165.5, 138.5, 138.4, 137.5, 133.2, 130.0, 129.9, 129.9, 129.8, 129.5, 128.9, 128.5, 128.4, 128.2, 128.1, 127.6, 127.5, 126.1, 101.9, 101.3, 101.0, 78.3, 77.6, 77.4, 77.2, 76.9, 76.1, 74.6, 72.3, 71.9, 71.1, 68.2, 67.6, 62.8, 56.9; ESIHRMS m/z calcd for $C_{47}H_{46}O_{12}Na$ $[M + Na]^+$ 825.2887, found 825.2873.

Phenyl 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-β-D-mannopyranosyl-(1→4)-2,3-di-*O*-benzoyl-1-thio-β-D-xylopyranoside (7). Obtained by protocol 3 from compound **5**. Chromatographic purification over silica gel with 20% EtOAc in hexanes as eluent afforded disaccharide **7** (72 mg, 87%) as a white foam: $[\alpha]_D^{24}$ −34.8 (c = 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.07−8.02 (m, 4H), 7.57−7.50 (m, 4H), 7.46−7.39 (m, 7H), 7.38−7.32 (m, 9H), 7.31−7.26 (m, 6H), 5.74 (t, J = 7.2 Hz, 1H), 5.42 (s, 1H), 5.39 (t, J = 7.2 Hz, 1H), 5.17 (d, J = 7.0 Hz, 1H), 4.87 (d, J = 12.5 Hz, 1H), 4.74 (d, J = 12.5 Hz, 1H), 4.69 (d, J = 12.5 Hz, 1H), 4.62 (s, 1H), 4.59 (d, J = 12.5 Hz, 1H), 4.42 (dd, J = 4.2, 12.2 Hz, 1H), 4.09−3.97 (m, 3H), 3.87 (d, J = 3.0 Hz, 1H), 3.66 (d, J = 8.0, 12.0 Hz, 1H), 3.55 (dd, J = 3.0, 9.5 Hz, 1H), 3.34 (t, J = 10.2 Hz, 1H), 3.26−3.21 (m, 1H); ^{13}C NMR (125.9 MHz, $CDCl_3$) δ 165.7, 165.6, 138.7, 138.6, 137.8, 133.5, 133.3, 132.9, 130.4, 130.2, 129.9, 129.6, 129.3, 129.1, 128.7, 128.6, 1285, 128.4, 128.3, 127.8, 127.7, 126.3, 101.5, 86.9, 78.5, 77.8, 76.4, 74.9, 74.5, 72.5, 72.1, 70.5, 68.5, 67.8, 65.4; ESIHRMS m/z calcd for $C_{52}H_{48}O_{11}SNa$ $[M + Na]^+$ 903.2815, found 903.2803.

Methyl 2,3,6-Tri-*O*-benzyl-β-D-mannopyranosyl-(1→4)-2,3-di-*O*-benzoyl-β-D-xylopyranoside (8). Obtained by protocol 4 from compound **6**. Chromatographic purification over silica gel with 30% EtOAc in hexanes as eluent afforded disaccharide **8** (68 mg, 85%) as a white foam: $[\alpha]_D^{24}$ −31.2 (c = 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 (dd, J = 1.0, 8.5 Hz, 2H), 7.93 (dd, J = 1.0, 8.0 Hz, 2H), 7.51−7.44 (m, 2H), 7.37−7.27 (m, 16 H), 7.22−7.20 (m, 3H), 5.72 (t, J = 8.2 Hz, 1H), 5.34 (dd, J = 6.7, 8.2 Hz, 1H), 4.82 (d, J = 12.5 Hz, 1H), 4.63−4.58 (m, 3H), 4.52−4.43 (m, 3H), 4.38 (d, J = 12.0 Hz, 1H), 4.27−4.20 (m, 2H), 3.88 (dt, J = 1.5, 9.5 Hz, 1H), 3.84 (d, J = 3.0 Hz, 1H), 3.63−3.56 (m, 3H), 3.52 (s, 3H), 3.40−3.36 (m, 1H), 3.30 (dd, J = 3.0, 9.5 Hz, 1H), 2.65 (br s, 1H); ^{13}C NMR (125.9 MHz, $CDCl_3$) δ 166.0, 165.6, 138.9, 138.2, 138.1, 133.3, 133.2, 130.2, 130.1, 129.9, 129.7, 128.7, 128.6, 128.5, 128.4, 128.3, 128.0, 127.9, 127.5, 102.2, 99.8, 81.3, 75.3, 74.2, 73.9, 73.6, 72.1, 71.4, 71.0, 68.6, 62.9, 57.0; ESIHRMS m/z calcd for $C_{47}H_{48}O_{12}Na$ $[M + Na]^+$ 827.3043, found 827.3055.

Phenyl 2,3,6-Tri-*O*-benzyl-β-D-mannopyranosyl-(1→4)-2,3-di-*O*-benzoyl-1-thio-β-D-xylopyranoside (9). Obtained by protocol 4 from compound **7**. Chromatographic purification over silica gel with 30% EtOAc in hexanes as eluent afforded disaccharide **9** (79 mg, 89%) as a white foam: $[\alpha]_D^{24}$ −54.2 (c = 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.05 (dd, J = 1.5, 8.5 Hz, 2H), 7.99 (dd, J = 1.5, 8.5 Hz, 2H), 7.53 (dd, J = 3.0, 6.5 Hz, 2H), 7.51−7.47 (m, 2H), 7.36−7.26 (m, 19H), 7.22−7.19 (m, 3H), 5.76 (t, J = 7.5 Hz, 1H), 5.40 (t, J = 7.2 Hz, 1H), 5.15 (d, J = 7.0 Hz, 1H), 4.81 (d, J = 12.5 Hz, 1H), 4.61 (s, 1H), 4.60 (d, J = 14.0 Hz, 1H), 4.52−4.43 (m, 4H), 4.39 (d, J = 12.0 Hz, 1H), 4.18−4.14 (m, 1H), 3.88 (t, J = 9.5 Hz, 1H), 3.85 (d, J = 3.0 Hz, 1H), 3.70 (dd, J = 7.7, 12.2 Hz, 1H), 3.62−3.55 (m, 2H), 3.42−3.37(m, 1H), 3.30 (dd, J = 2.7, 9.2 Hz, 1H), 2.66 (br s, 1H); ^{13}C NMR (125.9 MHz, $CDCl_3$) δ 165.8, 165.6, 138.9, 138.2, 138.1, 133.4, 133.3, 132.9, 130.3, 130.2, 129.7, 129.3, 128.7, 128.6, 128.5, 128.4, 128.3, 128.0, 127.9, 127.5, 100.2, 87.0, 81.3, 77.5, 77.3, 77.0, 75.3, 74.2, 74.0, 73.9, 73.4, 72.2, 71.4, 71.0, 70.7, 68.6, 65.4; ESIHRMS m/z calcd for $C_{52}H_{50}O_{11}SNa$ $[M + Na]^+$ 905.2972, found 905.2987.

Methyl 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-β-D-mannopyranosyl-(1→4)-2,3-di-*O*-benzoyl-β-D-xylopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-mannopyranosyl-(1→4)-2,3-di-*O*-benzoyl-β-D-xylopyranoside (10). Obtained by protocol 5 from compounds **7** and **8**. Chromatographic purification over silica gel with 30% EtOAc in hexanes as eluent afforded disachharide **10** (127 mg, 81%) as a white

foam: $[\alpha]_D^{24}$ −43.6 (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, J = 7.0 Hz, 2H), 7.93 (d, J = 8.0 Hz, 4H), 7.86 (d, J = 8.0 Hz, 2H), 7.54−7.44 (m, 6H), 7.39−7.32 (m, 18H), 7.29−7.23 (m, 10H), 7.21−7.14 (m, 8H), 5.67 (t, J = 8.2 Hz, 1H), 5.52 (t, J = 9.0 Hz, 1H), 5.43 (s, 1H), 5.30−5.26 (m, 2H), 4.81 (d, J = 12.5 Hz, 1H), 4.81 (d, J = 7.0 Hz, 1H), 4.76 (d, J = 12.5 Hz, 1H), 4.67−4.63 (m, 4H), 4.58−4.55 (m, 3H), 4.49 (s, 1H), 4.43 (s, 1H), 4.35 (d, J = 11.5 Hz, 1H), 4.18−4.13 (m, 3H), 4.07 (d, J = 12.0 Hz, 1H), 4.05−3.99 (m, 1H), 3.97−3.90 (m, 3H), 3.80 (dd, J = 3.2, 9.7 Hz, 2H), 3.54−3.46 (m, 7H), 3.43 (dd, J = 3.0, 9.5 Hz, 1H), 3.36 (t, J = 10.5 Hz, 1H), 3.24−3.20 (m, 1H), 3.15−3.09 (m, 2H); ^{13}C NMR (125.9 MHz, $CDCl_3$) δ 165.7, 165.5, 165.4, 165.2, 138.7, 138.6, 138.5, 138.4, 137.5, 133.2, 133.1, 133.0 129.9, 129.8, 129.7, 129.5, 129.4, 129.3, 128.8, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.5, 127.4, 127.3, 127.1, 126.0, 101.9, 101.3, 100.8, 100.6, 99.3, 80.1, 78.2, 76.8, 76.0, 75.8, 74.6, 74.3, 73.7, 73.2, 73.1, 72.7, 72.2, 72.0, 72.9, 72.3, 68.5, 68.2, 67.5, 63.0, 62.6, 56.7; ESIHRMS m/z calcd for $C_{93}H_{90}O_{23}Na$ $[M + Na]^+$ 1597.5771, found 1597.5748.

Phenyl 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-β-D-mannopyranosyl-(1→4)-2,3-di-*O*-benzoyl-β-D-xylopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-mannopyranosyl-(1→4)-2,3-di-*O*-benzoyl-1-thio-β-D-xylopyranoside (11). Phenyl thioglycoside **7** (88 mg, 100 μmol), BSP (27 mg, 120 μmol), and 4 Å molecular sieves (150 mg) were mixed and dried under vacuum for 0.5 h after which freshly distilled dichloromethane (3 mL) was added and the reaction mixture was stirred for 0.5 h at room temperature under N_2 before it was cooled to −65 °C and stirred for 5 min more. Tf_2O (22 μL, 120 μmol) was added dropwise, and the reaction mixture was stirred for 30 min between −65 and −60 °C then cooled to −78 °C and stirred for 5 min before 1-octene (0.15 mL, 1 mmol) was added. After stirring for 5 min, a solution of the acceptor **9** (90 mg, 50 μmol) in dichloromethane (2 mL) was added dropwise and the reaction mixture stirred for 2.5 h at −60 °C before it was quenched by addition of Et_3N (0.1 mL) and warmed to room temperature. The reaction mixture was filtered through Celite, concentrated, and subjected to chromatographic purification with 30% EtOAc in hexanes as eluent to afford tetrasaccharide **11** (139 mg, 79%) as a light yellow oil: $[\alpha]_D^{24}$ −28.4 (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, J = 7.5 Hz, 2H), 7.95−7.91 (m, 6H), 7.55−7.48 (m, 7H), 7.47−7.43 (m, 3H), 7.40−7.33 (m, 16H), 7,31−7.22 (m, 15H), 7.18−7.12 (m, 6H), 5.71 (t, J = 7.5 Hz, 1H), 5.52 (t, J = 9.0 Hz, 1H), 5.44 (s, 1H), 5.35 (t, J = 7.5 Hz, 1H), 5.28 (dd, J = 7.2, 8.7 Hz, 1H), 5.10 (d, J = 7.5 Hz, 1H), 4.83 (d, J = 12.0 Hz, 1H), 4.81 (d, J = 7.0 Hz, 1H), 4.76 (d, J = 12.5 Hz, 1H), 4.68−4.63 (m, 4H), 4.58 (s, 1H), 4.57 (d, J = 13.0 Hz, 1H), 4.50 (s, 1H), 4.44 (s, 1H), 4.38 (dd, J = 4.0, 12.0 Hz, 1H), 4.34 (d, J = 11.5 Hz, 1H), 4.17 (t, J = 9.5 Hz, 1H), 4.13−4.09 (m, 1H), 4.06 (d, J = 12.0 Hz, 1H), 4.05−4.00 (m, 1H), 3.98−3.89 (m, 3H), 3.80 (dd, J = 3.0, 7.5 Hz, 2H), 3.61 (dd, J = 8.0, 12.0 Hz, 1H), 3.53−3.47 (m, 3H), 3.43 (dd, J = 3.2, 9.2 Hz, 1H), 3.37 (t, J = 10.5 Hz, 1H), 3.25−3.21 (m, 1H), 3.16−3.08 (m, 2H); ^{13}C NMR (125.9 MHz, $CDCl_3$) δ 165.5, 165.3, 165.2, 138.7, 138.5, 138.3, 137.5, 133.2, 133.1, 133.0, 132.7, 132.4, 130.0, 129.8, 129.3, 129.3, 129.0, 128.8, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.5, 127.4, 127.2, 126.0, 101.3, 100.8, 100.6, 99.7, 86.7, 80.1, 78.2, 77.4, 75.9, 75.8, 74.6, 74.3, 73.7, 73.2, 72.9, 72.8, 72.2, 72.0, 70.5, 68.5, 68.2, 67.6, 65.2, 63.0; ESIHRMS m/z calcd for $C_{98}H_{92}O_{22}SNa$ $[M + Na]^+$ 1675.5699, found 1675.5793.

Methyl 2,3,6-Tri-*O*-benzyl-β-D-mannopyranosyl-(1→4)-2,3-di-*O*-benzoyl-β-D-xylopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-mannopyranosyl-(1→4)-2,3-di-*O*-benzoyl-β-D-xylopyranoside (12). Obtained by protocol 4 from compound **10**. Chromatographic purification with 50% EtOAc in hexanes as eluent afforded the tetrasaccharide **12** (137 mg, 87%) as a white foam: $[\alpha]_D^{24}$ 36.2 (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, J = 7.5 Hz, 2H), 8.02−7.93 (m, 4H), 7.91 (d, J = 7.5 Hz, 2H), 7.52 (t, J = 7.2 Hz, 1H), 7.47 (t, J = 7.5 Hz, 1H), 7.43−7.33 (m, 7H), 7.31−7.20 (m, 27H), 7.16−7.14 (m, 6H), 5.75 (t, J = 7.5 Hz, 1H), 5.63 (t, J = 7.7 Hz, 1H), 5.31 (t, J = 6.7 Hz, 1H), 5.16 (t, J = 6.7 Hz, 1H), 4.82 (d, J = 12.0 Hz, 1H), 4.75 (d, J = 11.0 Hz, 1H), 4.73 (d, J = 12.5 Hz, 1H), 4.71 (d, J = 8.0 Hz, 1H), 4.67−4.59 (m, 4H), 4.53 (d, J = 6.0 Hz, 1H), 4.52 (d, J = 5.5 Hz, 1H), 4.49−4.39 (6H), 4.23 (dd, J = 4.0, 12.0 Hz, 1H), 4.17−4.10 (m, 2H), 3.96 (d, J = 9.0 Hz, 1H), 3.92−3.82 (m, 5H), 3.75 (dd, J = 5.5, 11.0 Hz, 1H), 3.63−3.53 (m, 3H), 3.51 (s, 3H), 3.50−3.46 (m, 2H), 3.42−3.38 (m, 2H), 3.34 (dd, J = 2.7, 9.2 Hz, 1H), 2.73 (br s, 1H); ^{13}C NMR (125.9 MHz, $CDCl_3$) δ 165.9, 165.8, 165.4, 139.0, 138.8, 138.5, 138.3, 138.2, 133.4, 133.2, 133.1, 130.4, 130.1, 129.9, 129.8, 128.7, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.6, 127.5, 127.4, 101.5, 100.6, 100.1, 99.6, 82.2, 81.2, 75.9, 75.2, 75.1, 74.6, 74.3, 74.2, 74.1, 74.0, 73.9, 73.6, 73.4, 71.6, 71.3, 71.0, 70.9, 68.8, 68.3, 62.1, 56.8; ESIHRMS m/z calcd for $C_{93}H_{92}O_{23}Na$ $[M + Na]^+$ 1599.5927, found 1599.5914.

Methyl 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-β-D-mannopyranosyl-(1→4)-2,3-di-*O*-benzoyl-β-D-xylopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-mannopyranosyl-(1→4)-2,3-di-*O*-benzoyl-β-D-xylopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-mannopyranosyl-(1→4)-2,3-di-*O*-benzoyl-β-D-xylopyranoside (13). Obtained by protocol 5 from compounds **11** and **8**. Chromatographic purification with 30% EtOAc in hexanes as eluent afforded the hexasaccharide **13** (157 mg, 67%) as a white foam: $[\alpha]_D^{24}$ −32.7 (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, J = 8.0 Hz, 2H), 7.93−7.89 (m, 6H), 7.85 (d, J = 8.0 Hz, 2H), 7.81 (d, J = 7.5 Hz, 2H), 7.54−7.41 (m, 9H), 7.40−7.30(m, 25 H), 7.29−7.23 (m, 17H), 7.21−7.11 (m, 12H), 5.65 (t, J = 8.0 Hz, 1H), 5.48 (t, J = 9.5 Hz, 1H), 5.46 (t, J = 9.5 Hz, 1H), 5.43 (s, 1H), 5.29−5.23 (m, 3H), 4.82−4.70 (m, 4H), 4.68−4.52 (m, 10H), 4.46 (s, 1H), 4.42 (s, 1H), 4.35−4.31 (m, 2H), 4.27 (s, 1H), 4.18−4.09 (m, 4H), 4.08−3.98 (m, 4H), 3.97−3.86 (m, 3H), 3.78 (s, 2H), 3.72 (s, 1H), 3.53−3.49 (m, 3H), 3.48 (s, 3H), 3.47−3.33 (m, 8H), 3.22−3.18 (m, 1H), 3.14−3.02(m, 4H); ^{13}C NMR (125.9 MHz, $CDCl_3$) δ 165.7, 165.6, 165.5, 165.4, 165.2, 138.7, 138.7, 138.6, 138.4, 138.3, 137.5, 133.2, 133.1, 133.0, 132.8, 129.9, 129.8, 129.7, 129.5, 129.4, 129.2, 128.8, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.5, 127.4, 127.3, 127.1, 126.0, 101.9, 101.2, 100.9, 100.8, 100.6, 99.2, 99.0, 80.0, 79.8, 78.2, 75.9, 74.5, 74.4, 74.3, 74.2, 73.7, 73.6, 73.2, 73.1, 73.0, 72.7, 72.1, 72.0, 71.9, 71.3, 68.4, 68.2, 67.5, 62.9, 62.6, 56.8; ESIHRMS m/z calcd for $C_{139}H_{134}O_{34}Na$ $[M + Na]^+$ 2369.8654, found 2369.8691.

Methyl 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-β-D-mannopyranosyl-(1→4)-2,3-di-*O*-benzoyl-β-D-xylopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-mannopyranosyl-(1→4)-2,3-di-*O*-benzoyl-β-D-xylopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-mannopyranosyl-(1→4)-2,3-di-*O*-benzoyl-β-D-xylopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-mannopyranosyl-(1→4)-2,3-di-*O*-benzoyl-β-D-xylopyranoside (14). Obtained by protocol 5 from compounds **11** and **12**. Chromatographic purification with 40% EtOAc in hexanes as eluent afforded the octasaccharide **14** (196 mg, 63%) as a white foam: $[\alpha]_D^{24}$ −35.1 (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, J = 7.5 Hz, 2H), 7.94−7.89 (m, 8H), 7.86 (d, J = 7.0 Hz, 4H), 7.81 (d, J = 8.5 Hz, 2H), 7.53−7.48 (m, 5H), 7.46−7.43 (m, 3H), 7.38−7.32 (m, 26H), 7.30−7.23 (m, 27H), 7.21−7.17 (m, 7H), 7.16−7.10 (m, 16H), 5.66 (t, J = 8.0 Hz, 1H), 5.54−5.46 (m, 2H), 5.43 (s, 1H), 5.32−5.22 (m, 4H), 4.83−4.69 (m, 8H), 4.67−4.52 (m, 12H), 4.47−4.40 (m, 3H), 4.36−4.31 (m, 3H), 4.27 (s, 1H), 4.26 (s, 1H), 4.18−4.08 (m, 5H), 4.07−3.95 (m, 7H), 3.92−3.86 (m, 3H), 3.82−3.76 (m, 3H), 3.71 (dd, J = 2.7, 11.2 Hz, 2H), 3.54−3.49 (m, 2H), 3.48 (s, 3H), 3.47−3.43 (m, 4H), 3.41−3.32 (m, 6H), 3.19 (dd, J = 3.7, 8.7 Hz, 1H), 3.16−3.06 (m, 5H) 3.03 (t, J = 10.7 Hz, 1H); ^{13}C NMR (125.9 MHz, $CDCl_3$) δ 165.7, 165.6, 165.5, 165.4, 165.2, 138.7, 138.6, 138.4, 138.3, 137.5, 133.2, 133.1, 133.0, 132.8, 129.9, 129.8, 129.7, 129.5, 129.4, 129.2, 128.8 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.6, 127.5, 127.4, 127.3, 127.2, 127.1, 126.0, 101.9, 101.2, 100.9, 100.8, 100.6, 99.2, 99.0, 80.0, 79.9, 78.2, 75.8, 74.6, 74.5, 74.4, 74.3, 74.2, 73.7, 73.6, 73.2, 73.1, 73.0, 72.7, 72.1, 72.0, 71.9, 71.3, 68.4, 68.3, 68.2, 67.5, 62.9, 62.6, 56.8; ESIHRMS m/z calcd for $C_{185}H_{178}O_{45}Na$ $[M + Na]^+$ 3142.1538, found 3142.1489.

Methyl β-D-Mannopyranosyl-(1→4)-β-D-xylopyranosyl-(1→4)-β-D-mannopyranosyl-(1→4)-β-D-xylopyranoside (15). Obtained by protocol 6 from compound **10**. Removal of solvent afforded **15** (11.5 mg 93%) as white amorphous solid: $[\alpha]_D^{24}$ 52.4 (c = 1.0, 1:4 H_2O/MeOH); ESIHRMS m/z calcd for $C_{23}H_{40}O_{19}Na$ $[M + Na]^+$ 643.2061, found 643.2084. For ^{1}H and ^{13}C data, see Tables 1−3.

Methyl β-D-Mannopyranosyl-(1→4)-β-D-xylopyranosyl-(1→4)-β-D-mannopyranosyl-(1→4)-β-D-xylopyranosyl-(1→4)-β-D-mannopyranosyl-(1→4)-β-D-xylopyranoside (16). Obtained by

protocol 6 from compound **13**. Removal of solvent afforded **16** (17.2 mg, 94%) as white amorphous solid: $[\alpha]_D^{24}$ 12.7 (c = 0.5, 1:4 H_2O/MeOH); ESIHRMS m/z calcd for $C_{34}H_{58}O_{28}Na$ $[M + Na]^+$ 937.3012, found 937.3029. For ^1H and ^{13}C data, see Tables 1−3.

Methyl β-D-Mannopyranosyl-(1→4)-β-D-xylopyranosyl-(1→4)-β-D-mannopyranosyl-(1→4)-β-D-xylopyranosyl-(1→4)-β-D-mannopyranosyl-(1→4)-β-D-xylopyranosyl-(1→4)-β-D-mannopyranosyl-(1→4)-β-D-xylopyranoside (17). Obtained by protocol 6 from compound **14**. Removal of solvent afforded **17** (22.1 mg 94%) as white amorphous solid: $[\alpha]_D^{24}$ −16.8 (c = 0.4, 1:4 H_2O:MeOH); ESIHRMS m/z calcd for $C_{45}H_{76}O_{37}Na$ $[M + Na]^+$ 1231.3963, found 1231.3958. For ^1H and ^{13}C data, see Tables 1−3.

Methyl 2-*O*-Benzyl-4,6-*O*-benzylidene-3-*O*-(2-naphthalenylmethyl)-β-D-mannopyranosyl-(1→4)-2,3-*O*-isopropylidine-β-D-xylopyranoside (19). Obtained by protocol 1 from compounds **18** and **2**. Chromatographic purification over silica gel with 20% EtOAc in hexanes as eluent afforded disaccharide **19** (176 mg, 86%) as a light yellow oil: $[\alpha]_D^{24}$ −27.8 (c = 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.85−7.83 (m, 1H), 7.80−7.75 (m, 2H), 7.73−7.69 (m, 1H), 7.56−7.52 (m, 2H), 7.49−7.45 (m, 4H), 7.43−7.39 (m, 4H), 7.37−7.31 (m, 3H), 5.66 (s, 1H), 4.97 (d, J = 12.0 Hz, 1H), 4.91 (d, J = 12.0 Hz, 1H), 4.88 (d, J = 13.0 Hz, 1H), 4.81 (d, J = 13.0 Hz, 1H), 4.62 (s, 1H), 4.55 (d, J = 7.5 Hz, 1H), 4.30−4.24 (m, 2H), 4.04 (dd, J = 5.2, 11.7 Hz, 1H), 4.01−3.95 (m, 2H), 3.92 (d, J = 2.5 Hz, 1H), 3.75 (t, J = 9.2 Hz, 1H), 3.66 (dd, J = 2.7, 10.2 Hz, 1H), 3.53 (m, 3H), 3.41−3.34 (m, 2H), 3.29 (dd, J = 7.7, 9.7 Hz, 1H), 1.43 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (125.9 MHz, $CDCl_3$) δ 138.5, 137.8, 135.9, 133.4, 133.2, 129.1, 129.0, 128.5, 128.4, 128.1, 127.9, 126.6, 126.4, 126.3, 126.2, 125.9, 111.7, 102.6, 101.8, 100.3 ($^1J_{C-H}$ = 157.5 Hz), 79.3, 78.9, 78.0, 76.8, 76.4, 76.1, 75.0, 72.7, 68.9, 67.8, 65.3, 56.7, 27.0, 26.8; ESIHRMS m/z calcd for $C_{40}H_{44}O_{10}Na$ $[M + Na]^+$ 707.2832, found 707.2813.

Methyl 2-*O*-Benzyl-4,6-*O*-benzylidene-3-*O*-(2-naphthalenylmethyl)-β-D-mannopyranosyl-(1→4)-2,3-di-*O*-acetyl-β-D-xylopyranoside (20). Obtained by protocol 3 from compound **19**. Chromatographic purification over silica gel with 20% EtOAc in hexanes as eluent afforded disaccharide **20** (64 mg, 88%) as a light yellow oil: $[\alpha]_D^{24}$ −34.9 (c = 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.84−7.82 (m, 1H), 7.79−7.76 (m, 2H), 7.71−7.69 (m, 1H), 7.53 (dd, J = 2.0, 7.5 Hz, 2H), 7.50−7.46 (m, 4H), 7.42−7.38 (m, 4H), 7.36 (t, J = 7.5 Hz, 2H), 7.32 (d, J = 7.5 Hz, 1H), 5.64 (s, 1H), 5.21 (t, J = 8.7 Hz, 1H), 4.92 (d, J = 12.0 Hz, 1H), 4.87 (dd, J = 7.0, 9.0 Hz, 1H), 4.84 (d, J = 13.0 Hz, 1H), 4.79 (d, J = 12.0 Hz, 1H), 4.78 (d, J = 12.5 Hz, 1H), 4.50 (s, 1H), 4.38 (d, J = 7.0 Hz, 1H), 4.32 (dd, J = 5.0, 10.5 Hz, 1H), 4.21 (t, J = 9.5 Hz, 1H), 4.03 (dd, J = 5.0, 12.0 Hz, 1H), 3.97−3.92 (m, 1H), 3.89 (t, J = 10.0 Hz, 1H), 3.85 (d, J = 3.0 Hz, 1H), 3.62 (dd, J = 3.2, 10.0, Hz, 1H), 3.48 (s, 3H), 3.35−3.28 (m, 2H), 2.05 (s, 3H), 2.01 (s, 3H); ^{13}C NMR (125.9 MHz, $CDCl_3$) δ 170.1, 169.7, 138.5, 137.5, 135.7, 133.2, 132.9, 128.9, 128.5, 128.3, 128.2, 128.1, 127.9, 127.7, 127.6, 126.3, 126.1, 125.9, 125.6, 101.9, 101.5, 100.1, 78.5, 75.9, 74.6, 73.5, 72.2, 72.1, 71.0, 68.5, 67.7, 62.6, 56.8, 20.9, 20.8; ESIHRMS m/z calcd for $C_{41}H_{44}O_{12}Na$ $[M + Na]^+$ 751.2730, found 751.2741.

Methyl 2-*O*-Benzyl-4,6-*O*-benzylidene-β-D-mannopyranosyl-(1→4)-2,3-di-*O*-acetyl- β-D-xylopyranoside (21). Obtained by protocol 7 from compound **20**. Chromatographic purification over silica gel with 40% EtOAc in hexanes as eluent afforded disaccharide **21** (35 mg, 85%) as a white foam: $[\alpha]_D^{24}$ −34.9 (c = 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.48 (dd, J = 2.2, 7.2 Hz, 2H), 7.41−7.30 (m, 8H), 5.54 (s, 1H), 5.24 (t, J = 9.0 Hz, 1H), 4.99 (d, J = 11.5 Hz, 1H), 4.90 (dd, J = 7.2, 8.7 Hz, 1H), 4.64 (s, 1H), 4.57 (d, J = 12.0 Hz, 1H), 4.40 (d, J = 7.0 Hz, 1H), 4.34 (dd, J = 5.0, 10.5 Hz, 1H), 4.11 (dd, J = 5.2, 11.7 Hz, 1H), 4.01−3.96 (m, 1H), 3.87 (d, J = 2.5 Hz, 1H), 3.84−3.77 (m, 3H), 3.50 (s, 3H), 3.41 (dd, J = 9.5, 12.0 Hz, 1H), 3.35−3.31 (m, 1H), 2.43 (d, J = 8.5 Hz, 1H), 2.06 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (125.9 MHz, $CDCl_3$) δ 170.4, 169.9, 138.3, 137.3, 129.4, 128.8, 128.5, 128.2, 126.5, 102.3, 102.2, 100.5, 79.4, 78.6, 75.7, 74.0, 72.3, 71.2, 70.9, 68.7, 67.5, 62.8, 57.1, 21.1, 21.0; ESIHRMS m/z calcd for $C_{30}H_{36}O_{12}Na$ $[M + Na]^+$ 611.2104, found 611.2117.

Methyl 2,3,6-Tri-*O*-benzyl-β-D-mannopyranosyl-(1→4)-β-D-xylopyranosyl-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-β-D-mannopyranosyl-(1→4)-β-D-xylopyranoside (22). Obtained by protocol 5 from compounds **21** and **7** followed by methanolysis. Chromatographic purification over silica gel with 3% methanol in chloroform as eluent afforded tetrasaccharide **22** (80 mg, 72%) as a light yellow oil: $[\alpha]_D^{24}$ −53.8 (c = 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.50 (dd, J = 2.0, 7.5 Hz, 2H), 7.42−7.37 (m, 5H), 7.35−7.28 (m, 18H), 5.63 (s, 1H), 4.89 (d, J = 11.5 Hz, 1H), 4.88 (d, J = 12.5 Hz, 1H), 4.84 (d, J = 12.5 Hz, 1H), 4.83 (d, J = 12.5 Hz, 1H), 4.76 (d, J = 12.5 Hz, 1H), 4.70 (br s, 1H), 4.64 (d, J = 12.5 Hz, 1H), 4.64 (d, J = 11.5 Hz, 1H), 4.58 (d, J = 11.5 Hz, 1H), 4.54 (d, J = 11.5 Hz, 1H), 4.53 (d, J = 11.5 Hz, 1H), 4.50 (s, 1H), 4.47 (s, 1H), 4.40 (d, J = 7.5 Hz, 1H), 4.32 (dd, J = 5.0, 10.5 Hz, 1H), 4.25−4.22 (m, 2H), 4.16 (t, J = 9.5 Hz, 1H), 3.99−3.95 (m, 2H), 3.94−3.89 (m, 3H), 3.81 (dd, J = 7.5, 10.5 Hz, 1H), 3.75 (dd, J = 4.0, 12.0 Hz, 1H), 3.61−3.56 (m, 3H), 3.55 (s, 3H), 3.54−3.50 (m, 2H), 3.47 (dd, J = 3.0, 9.5 Hz, 1H), 3.43−3.30 (m, 3H), 3.19 (br s 1H), 3.06 (dd, J = 10.0, 11.0 Hz, 1H), 2.48 (br s, 1H); ^{13}C NMR (125.9 MHz, $CDCl_3$) δ 138.3, 138.1, 138.0, 137.7, 137.5, 129.2, 128.9, 128.7, 128.6, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.9, 127.8, 126.3, 103.9, 103.2, 102.3, 101.8, 101.6, 81.0, 80.5, 78.5, 77.9, 76.1, 75.2, 75.1, 74.7, 74.4, 74.3, 74.0, 73.2, 73.0, 72.9, 72.1, 69.7, 68.3, 67.9, 63.8, 63.7, 57.1; ESIHRMS m/z calcd for $C_{58}H_{68}O_{19}Na$ $[M + Na]^+$ 1091.4252, found 1091.4265.

Methyl β-D-Mannopyranosyl-(1→4)-β-D-xylopyranosyl-(1→3)-β-D-mannopyranosyl-(1→4)-β-D-xylopyranoside (23). Obtained by protocol 6 from compound **22**. Removal of the solvent afforded **23** (11.4 mg, 99%) as white amorphous solid: $[\alpha]_D^{24}$ 44.1 (c = 0.5, 1:4 H_2O/MeOH); ESIHRMS m/z calcd for $C_{23}H_{40}O_{19}Na$ $[M + Na]^+$ 643.2061, found 643.2089. For ^1H and ^{13}C data, see Tables 1 and 2.

Phenyl 2,3-Di-*O*-acetyl-4,6-*O*-benzylidene-α-D-mannopyranosyl-(1→4)-2,3-*O*-isopropylidene-1-thio-β-D-xylopyranoside (25). Obtained by protocol 1 from compound **24** and **2**. Chromatographic purification over silica gel with 20% EtOAc in hexanes as eluent afforded disaccharide **25** (122 mg, 79%) as a light yellow oil: $[\alpha]_D^{24}$ −26.5 (c = 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.59−7.56 (m, 2H), 7.47−7.45 (m, 2H), 7.39−7.36 (m, 3H), 7.35−7.32 (m, 3H), 5.58 (s, 1H), 5.43 (dd, J = 1.5, 3.5 Hz, 1H), 5.35 (dd, J = 3.5, 10.5 Hz, 1H), 5.10 (d, J = 1.0 Hz, 1H), 4.81 (d, J = 9.5 Hz, 1H), 4.29 (dd, J = 3.0, 8.5 Hz, 1H), 4.18 (dd, J = 5.0, 12.0 Hz, 1H), 4.04 (t, J = 9.7 Hz, 1H), 3.99 (dt, J = 5.5, 9.0 Hz, 1H), 3.93−3.84 (m, 2H), 3.63 (t, J = 9.0 Hz, 1H), 3.39 (dd, J = 9.2, 11.7 Hz, 1H), 3.23 (t, J = 9.0 Hz, 1H), 2.18 (s, 3H), 2.02 (s, 3H), 1.49 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (125.9 MHz, $CDCl_3$) δ 169.9, 169.7, 136.9, 133.0, 131.6, 129.2, 128.9, 128.3, 128.2, 126.1, 111.6, 101.9, 98.1 ($^1J_{C-H}$ = 169.7 Hz), 85.2, 81.6, 75.9, 75.2, 73.4, 69.7, 68.6, 68.1, 64.4, 26.7, 26.6, 20.9, 20.8; ESIHRMS m/z calcd for $C_{31}H_{36}O_{11}SNa$ $[M + Na]^+$ 639.1876, found 639.1887.

Methyl 2,3-Di-*O*-acetyl-4,6-*O*-benzylidene-α-D-mannopyranosyl-(1→4)-2,3-*O*-isopropylidene-β-D-xylopyranoside (26). Obtained by protocol 2 from compounds **24** and **3**. Chromatographic purification over silica gel with 30% EtOAc in hexanes as eluent afforded disaccharide **26** (136 mg, 84%) as a white foam: $[\alpha]_D^{24}$ −7.6 (c = 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.48−7.46 (m, 2H), 7.39−7.36 (m, 3H), 5.59 (s, 1H), 5.44 (dd, J = 1.5, 3.0 Hz, 1H), 5.38 (dd, J = 3.5, 10.5 Hz, 1H), 5.12 (br s, 1H), 4.56 (d, J = 7.5 Hz, 1H), 4.31 (dd, J = 4.0, 10.0 Hz, 1H), 4.12 (dd, J = 5.0, 12.0 Hz, 1H), 4.08−4.02 (m, 2H), 3.93 (dt, J = 4.0, 9.0 Hz, 1H), 3.88 (t, J = 10.0 Hz, 1H), 3.63 (t, J = 9.0 Hz, 1H), 3.55 (s, 3H), 3.41 (dd, J = 7.7, 12.2 Hz, 1H), 3.34 (t, J = 8.2 Hz, 1H), 2.19 (s, 3H), 2.03 (s, 3H), 1.46 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (125.9 MHz, $CDCl_3$) δ 169.9, 169.8, 136.9, 129.2, 128.3, 126.1, 112.0, 102.5, 102.9, 97.9 ($^1J_{C-H}$ = 170.2 Hz), 79.8, 76.6, 78.0, 73.9, 69.7, 68.6, 68.1, 65.4, 64.3, 56.6, 29.7, 26.6, 20.9; ESIHRMS m/z calcd for $C_{26}H_{34}O_{12}Na$ $[M + Na]^+$ 561.1948, found 561.1959.

Phenyl 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranosyl-(1→4)-2,3-*O*-di-*O*-acetyl-1-thio-β-D-xylopyranoside (27). Obtained by protocol 3 from compound **25**. Chromatographic purification over silica gel with 20% EtOAc in hexanes as eluent afforded disaccharide **27** (55 mg, 84%) as a light yellow oil: $[\alpha]_D^{24}$ −23.2 (c = 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.49−7.47 (m, 2H), 7.46−7.43 (m, 2H), 7.38−7.35 (m, 3H), 7.34−7.32 (m, 3H), 5.57 (s, 1H), 5.36 (dd, J = 3.7, 10.2 Hz, 1H), 5.19−5.16 (m, 2H), 4.93−4.92 (d, J = 7.5 Hz, 1H), 4.89 (d, J = 11.0 Hz, 1H), 4.80 (d, J = 9.0 Hz, 1H), 4.24 (t, J = 11.2 Hz, 1H), 4.23 (t, J = 11.5 Hz, 1H), 4.04 (t, J = 10.0 Hz, 1H), 3.93 (dt, J = 4.5, 9.5 Hz, 1H), 3.83 (t, J = 10.5 Hz,

1H), 3.79 (dt, J = 5.0, 8.5 Hz, 1H), 3.54 (dd, J = 9.0, 11.7 Hz, 1H), 2.17 (s, 3H), 2.12 (s, 3H), 2.11 (s, 3H), 2.01 (s, 3H); ^{13}C NMR (125.9 MHz, $CDCl_3$) δ 169.9, 169.8, 169.7, 169.6, 136.9, 132.6, 132.4, 129.2, 129.1, 128.3, 128.2, 126.1, 101.9, 99.5, 86.4, 76.0, 74.8, 73.3, 70.2, 70.0, 68.4, 67.6, 66.9, 64.5, 20.8, 20.7; ESIHRMS m/z calcd for $C_{32}H_{36}O_{13}SNa$ $[M + Na]^+$ 683.1774, found 683.1785.

Methyl 2,3-Di-*O*-acetyl-4,6-*O*-benzylidene-α-D-mannopyranosyl-(1→4)-2,3-di-*O*-acetyl-β-D-xylopyranoside (28). Obtained by protocol 3 from compound **26**. Chromatographic purification over silica gel with 20% EtOAc in hexanes as eluent afforded disachharide **28** (48 mg, 87%) as a colorless oil: $[\alpha]_D^{24}$ −8.4 (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47−7.43 (m, 2H), 7.38−7.35 (m, 3H), 5.57 (s, 1H), 5.37 (dd, J = 3.5, 10.5 Hz, 1H), 5.17 (br s, 1H), 5.14 (t, J = 8.7 Hz, 1H), 4.92 (d, J = 1.0 Hz, 1H), 4.84 (dd, J = 7.0, 9.0 Hz, 1H), 4.37 (d, J = 7.0 Hz, 1H), 4.25 (dd, J = 4.7, 10.0 Hz, 1H), 4.08−4.02 (m, 2H), 3.93 (dt, J = 4.5, 9.7 Hz, 1H), 3.85−3.78 (m, 2H), 3.49−3.46 (m, 1H), 3.47 (s, 3H), 2.16 (s, 3H), 2.09 (s, 3H), 2.06 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (125.9 MHz, $CDCl_3$) δ 170.0, 169.8, 169.6, 136.9, 129.2, 128.2, 126.1, 101.8, 101.7, 99.5, 76.0, 75.2, 72.8, 71.0, 70.2, 68.4, 67.6, 64.5, 63.6, 56.8, 20.8, 20.6; ESIHRMS m/z calcd for $C_{27}H_{34}O_{14}Na$ $[M + Na]^+$ 605.1846, found 605.1832.

Methyl 2,3-Di-*O*-acetyl-6-*O*-benzyl-α-D-mannopyranosyl-(1→4)-2,3-di-*O*-acetyl-β-D-xylopyranoside (29). Obtained by protocol 4 from compound **28**. Chromatographic purification over silica gel with 40% EtOAc in hexanes as eluent afforded disaccharide **29** (51 mg, 87%) as a colorless oil: $[\alpha]_D^{24}$ −12.1 (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.32 (m, 4H), 7.31−7.28 (m, 1H), 5.13−5.09 (m, 2H), 5.03 (dd, J = 1.5, 3.0 Hz, 1H), 4.91 (br s, 1H), 4.82 (dd, J = 7.2, 9.0 Hz, 1H), 4.63 (d, J = 12.0 Hz, 1H), 4.56 (d, J = 12.0 Hz, 1H), 4.33 (d, J = 7.0 Hz, 1H), 4.12 (dd, J = 5.2, 11.7 Hz, 1H), 3.97 (dt, J = 1.5, 9.5 Hz, 1H), 3.81−3.77 (m, 2H), 3.76−3.73 (m, 2H), 3.45 (s, 3H), 3.42−3.36 (m, 1H), 2.80 (d, J = 3.5 Hz, 1H), 2.09 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 2.04(s, 3H); ^{13}NMR (125.9 MHz, $CDCl_3$) δ 170.8, 180.2, 170.0, 169.8, 137.8, 128.4, 127.8, 127.6, 101.7, 98.8, 75.3, 73.7, 73.0, 72.0, 71.2, 71.1, 69.9, 69.7, 66.9, 63.7, 56.8, 20.9, 20.8, 20.7, 20.6; ESIHRMS m/z calcd for $C_{27}H_{36}O_{14}Na$ $[M + Na]^+$ 607.2003, found 607.1968.

Methyl 2,3-Di-*O*-acetyl-4,6-*O*-benzylidene-α-D-mannopyranosyl-(1→4)-2,3-di-*O*-acetyl-β-D-xylopyranosyl-(1→4)-6-*O*-benzyl-2,3-di-*O*-acetyl-α-D-mannopyranosyl-(1→4)-2,3-di-*O*-acetyl-β-D-xylopyranoside (30). Obtained by protocol 5 from compounds **27** and **29**. Chromatographic purification over silica gel with 30% EtOAc in hexanes as eluent afforded tetrasaccharide **30** (96 mg, 85%) as a colorless oil: $[\alpha]_D^{24}$ −18.3 (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47−7.44 (m, 2H), 7.43−7.41 (m, 2H), 7.40−7.36 (m, 6H), 5.58 (s, 1H), 5.38 (dd, J = 3.5, 10.5 Hz, 1H), 5.25 (dd, J = 3.0, 9.7 Hz, 1H), 5.17 (dd, J = 1.5, 3.0 Hz, 1H), 5.11 (t, J = 9.0 Hz, 1H), 5.00−4.95 (m, 3H), 4.89 (s, 1H), 4.83 (dd, J = 7.5, 9.0 Hz, 1H), 4.76 (d, J = 12.0 Hz, 1H), 4.70 (dd, J = 7.0, 8.0 Hz, 1H), 4.49 (d, J = 12.0 Hz, 1H), 4.37 (d, J = 7.0 Hz, 1H), 4.34 (d, J = 7.5 Hz, 1H), 4.23 (dd, J = 4.0, 10.0 Hz, 1H), 4.07−4.02 (m, 3H), 3.95−3.88 (m, 2H), 3.84 (t, J = 10.0 Hz, 1H), 3.81−3.67 (m, 4H), 3.65 (d, J = 10.0 Hz, 1H), 3.45 (s, 3H), 3.44−3.39 (m, 1H), 3.26 (dd, J = 9.5, 12.0 Hz, 1H), 2.16 (s, 3H), 2.13 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H), 2.01 (s, 3H), 1.96 (s, 3H); ^{13}NMR (125.9 MHz, $CDCl_3$) δ 170.0, 169.8, 169.6, 169.4, 137.7, 136.8, 129.2, 128.6, 128.3, 128.1, 127.9, 126.0, 101.8, 101.7, 100.4, 99.3, 98.6, 77.3, 77.2, 77.0, 76.7, 75.9, 75.1, 74.7, 73.7, 73.4, 72.9, 72.7, 71.7, 71.1, 71.0, 70.3, 70.1, 68.4, 67.7, 67.5, 64.5, 63.6, 63.4, 56.8, 20.9, 20.8, 20.7, 20.6; ESIHRMS m/z calcd for $C_{53}H_{66}O_{27}Na$ $[M + Na]^+$ 1157.3689, found 1157.3663.

Methyl α-D-Mannopyranosyl-(1→4)-β-D-xylopyranosyl-(1→4)-α-D-mannopyranosyl-(1→4)-β-D-xylopyranoside (31). Obtained by protocol 6 from compound **30**. Removal of solvent afforded **31** (11.4 mg 92%) as white amorphous solid: $[\alpha]_D^{24}$ 24.5[c = 1, H_2O/MeOH(1/4)]; ESIHRMS m/z calcd for $C_{23}H_{40}O_{19}Na$ $[M + Na]^+$ 643.2061, found 643.2079. For ^{1}H and ^{13}C data, see Tables 1−3.

Methyl 2,4-Di-*O*-acetyl-6-*O*-benzyl-3-*O*-(2-naphthalenylmethyl)-α-D-mannopyranosyl-(1→4)-2,3-*O*-isopropylidene-β-D-xylopyranoside (33). Obtained by protocol 1 from compounds **32** and **2**. Chromatographic purification over silica gel with 25% EtOAc in hexanes as eluent afforded disaccharide **33** (167 mg, 82%) as a colorless oil: $[\alpha]_D^{24}$ −22.7 (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85−7.80 (m, 3H), 7.73 (s, 1H), 7.52−7.46 (m, 2H), 7.38 (dd, J = 1.5, 8.5 Hz, 1H), 7.35−7.31 (m, 5H), 5.53 (br s, 1H), 5.25 (t, J = 10.2 Hz, 1H), 5.18 (s, 1H), 4.83 (d, J = 12.0 Hz, 1H), 4.59−4.52 (m, 4H), 4.15 (dd, J = 5.5, 12.0 Hz, 1H), 4.06−4.03 (m, 1H), 3.87 (dd, J = 3.2, 9.7 Hz, 1H), 3.84−3.80 (m, 1H), 3.60 (t, J = 9.0 Hz, 1H), 3.58−3.53 (m, 2H), 3.52 (s, 3H), 3.36−3.32 (m, 2H), 2.17 (s, 3H), 1.92 (s, 3H), 1.48 (s, 3H), 1.45 (s, 3H); ^{13}NMR (125.9 MHz, $CDCl_3$) δ 170.3, 169.8, 137.8, 135.3, 133.2, 132.9, 129.2, 128.8, 128.3, 128.1, 127.9, 127.7, 127.6, 126.5, 126.2, 126.0, 125.7, 112.0, 102.4, 97.5 ($^1J_{C-H}$ = 170.6 Hz), 79.6, 74.7, 74.4, 73.6, 71.3, 70.5, 69.4, 68.1, 67.9, 65.5, 56.4, 26.7, 26.4, 21.1, 20.9; ESIHRMS m/z calcd for $C_{37}H_{44}O_{12}Na$ $[M + Na]^+$ 703.2730, found 703.2756.

Methyl 2,4-Di-*O*-acetyl-6-*O*-benzyl-3-*O*-(2-naphthalenylmethyl)-α-D-mannopyranosyl-(1→4)-2,3-di-*O*-acetyl-β-D-xylopyranoside (34). Obtained by protocol 3 from compound **33**. Chromatographic purification over silica gel with 25% EtOAc in hexanes as eluent afforded disaccharide **34** (61 mg, 85%) as a colorless oil: $[\alpha]_D^{24}$ −15.8 (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87−7.81 (m, 3H), 7.74 (s, 1H), 7.52−7.47 (m, 2H), 7.38 (d, J = 8.5 Hz, 1H), 7.35−7.29 (m, 5H), 5.24 (t, J = 10 Hz, 1H), 5.20 (br d, J = 2.7 Hz, 1H), 5.13 (t, J = 9.0 Hz, 1H), 4.96 (s, 1H), 4.86 (dd, J = 7.2, 9.2 Hz, 1H), 4.77 (d, J = 12.0 Hz, 1H), 4.56 (d, J = 12.5 Hz, 1H), 4.54−4.53 (m, 2H), 4.31 (d, J = 7.5 Hz, 1H), 4.21 (dd, J = 5.0, 11.5 Hz, 1H), 3.84−3.78 (m, 3H), 3.56−3.49 (m, 2H), 3.46 (s, 3H), 3.34 (dd, J = 10.0, 11.5 Hz, 1H), 2.13 (s, 3H), 2.09 (s, 3H), 2.06 (s, 3H), 1.90 (s, 3H); ^{13}C NMR (125.9 MHz, $CDCl_3$) δ 170.6, 170.1, 169.9, 138.0, 135.3, 133.5, 133.2, 128.6, 128.4, 128.3, 127.9, 127.0, 126.4, 126.2, 126.0, 102.1, 99.6, 76.7, 74.3, 73.8, 73.4, 71.6, 71.4, 70.9, 69.5, 68.5, 68.1, 64.2, 57.0, 21.2, 21.1, 21.0, 20.9; ESIHRMS m/z calcd for $C_{38}H_{44}O_{14}Na$ $[M + Na]^+$ 747.2629, found 747.2641.

Methyl 2,4-Di-*O*-acetyl-6-*O*-benzyl-α-D-mannopyranosyl-(1→4)-2,3-di-*O*-acetyl-β-D-xylopyranoside (35). Obtained by protocol 7 from compound **34**. Chromatographic purification over silica gel with 40% EtOAc in hexanes as eluent afforded disaccharide **35** (36 mg, 88%) as a white foam: $[\alpha]_D^{24}$ −11.4 (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.29 (m, 5H), 5.13 (t, J = 9.0 Hz, 1H), 5.11 (t, J = 10.0 Hz, 1H), 5.01 (d, J = 1.0 Hz, 1H), 4.90 (dd, J = 1.5, 3.5 Hz, 1H), 4.85 (dd, J = 7.5, 9.5 Hz, 1H), 4.63 (d, J = 12.0 Hz, 1H), 4.49 (d, J = 12.5 Hz, 1H), 4.33 (d, J = 7.0 Hz, 1H), 4.17 (dd, J = 5.5, 11.5 Hz, 1H), 3.96 (br d, J = 8.0 Hz, 1H), 3.85−3.78 (m, 2H), 3.57−3.51 (m, 2H), 3.47 (s, 3H), 3.36 (dd, J = 10.0, 11.5 Hz, 1H), 2.23 (br s, 1H), 2.14 (s, 3H), 2.12 (s, 3H), 2.06 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (125.9 MHz, $CDCl_3$) δ 171.2, 170.4, 170.3, 169.7, 137.7, 128.4, 127.8, 127.8, 101.9, 98.8, 76.0, 73.5, 73.0, 72.3, 71.2, 70.1, 69.5, 68.4, 64.0, 56.8, 21.0, 20.9, 20.8, 20.7; $C_{27}H_{36}O_{14}Na$ $[M + Na]^+$ 607.2003, found 607.2023.

Methyl 4,6-*O*-Benzylidene-α-D-mannopyranosyl-(1→4)-β-D-xylopyranosyl-(1→3)-6-*O*-benzyl-α-D-mannopyranosyl-(1→4)-β-D-xylopyranoside (36). Obtained by protocol 5 from compounds **28** and **35** followed by methanolysis. Chromatographic purification over silica gel with 5% methanol in chloroform as eluent afforded disaccharide **36** (59 mg, 74%) as a white foam: $[\alpha]_D^{24}$ −21.7 (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, CD_3OD) δ 7.48−7.43 (m, 3H), 7.41−7.35 (m, 7H), 5.58 (s, 1H), 5.58 (s, 1H), 5.40−5.33 (m, 1H), 5.30−5.23 (m, 1H), 5.18 (s, 1H), 5.14−5.09 (m, 2H), 5.03−4.93 (m, 2H), 4.90 (s, 1H), 4.83 (t, J = 7.7 Hz, 1H), 4.78−4.67 (m, 2H), 4.51 (t, J = 6.5 Hz, 1H), 4.33 (d, J = 7.2 Hz, 1H), 4.27−4.22 (m, 2H), 4.09−3.99 (m, 4H), 3.96−3.88 (m, 2H), 3.85−3.69 (m, 6H), 3.53−3.39 (m, 4H), 3.37−3.26 (m, 1H), 2.18 (s, 3H), 2.15 (s, 3H), 2.14 (s, 3H), 2.11 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (125.9 MHz, CD_3OD) δ 138.5, 138.1, 128.7, 128.2, 127.9, 127.6, 126.3, 104.7, 103.9, 103.3, 102.2, 78.9, 78.1, 78.0, 76.8, 75.8, 75.7, 73.8, 73.6, 73.3, 71.5, 71.2, 70.1, 69.7, 69.1, 68.5, 68.2, 64.7, 64.6, 64.5, 56.1; $C_{53}H_{66}O_{27}Na$ $[M + Na]^+$ 821.2844, found 821.2857.

Methyl α-D-Mannopyranosyl-(1→4)-β-D-xylopyranosyl-(1→3)-α-D-mannopyranosyl-(1→4)-β-D-xylopyranoside (37). Obtained by protocol 6 from compound **36**. Removal of solvent afforded **37** (11.7 mg, 99%) as white amorphous solid: $[\alpha]_D^{24}$ 32.1 (c = 0.5, 1:4

H_2O/MeOH); ESIHRMS m/z calcd for $C_{23}H_{40}O_{19}Na$ $[M + Na]^+$ 643.2061, found 643.2082. For ^1H and ^{13}C data, see Tables 1−3.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^1H, ^{13}C, and 2D NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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