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Direct Synthesis of β-Mannosides. Synthesis of β-D-Xyl-(1→2)-β-D-Man-(1→4)-α-D-Glc-OMe: a Trisaccharide Component of the *Hyriopsis schlegelii* Glycosphingolipid. Formation of an Orthoester from a Xylopyranosyl Sulfoxide

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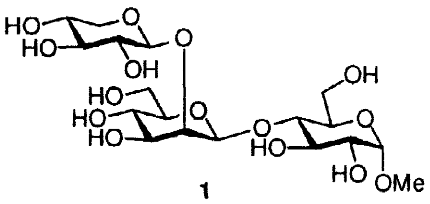
Abstract: A concise synthesis of the title trisaccharide is described in which the key β-mannosylation reaction is achieved directly, with high yield and selectivity, by triflic anhydride mediated coupling of *S*-ethyl 2-*O*-allyl-3-*O*-benzyl4,6-*O*-benzylidene-1-deoxy-1-thia-α-D-mannopyranoside *S*-(*R*)-oxide with methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside. After deallylation of the so-formed disaccharide, β-xylopyranosylation is brought about by reaction with α-tri-*O*-benzoyl xylopyranosyl bromide activated with silver triflate. Attempted xylosylation of cyclohexanol with *S*-phenyl 2,3,4-tri-*O*-benzoyl-1-deoxy-1-thio-β-D-xylopyranoside *S*-oxide, activated by triflic anhydride, and with the corresponding thioglycoside in the presence of benzenesulfenyl triflate both led to the formation of an orthoester rather than the anticipated β-xyloside. Treatment of this orthoester with tin tetrachloride promoted its rearrangement to the β-xyloside. The conformation and configurational assignment of tri-*O*-benzoyl-β-xylopyranosides is discussed. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Carbohydrates; Glycosidation; Stereoselection; Inversion Reactions; orthoesters

The stereoselective chemical synthesis of β-mannopyranosides, a long standing problem in carbohydrate chemistry, has attracted the attention of numerous groups worldwide leading to the development of several diverse and innovative strategies.[1] With the exception of the insoluble silver salt method,[2-5] Schuerch's use of 2-*O*-sulfonyl mannosyl sulfonates,[6,7] and the β-selective alkylation of anomeric metal alkoxides,[8-11] these methods may be classified as indirect requiring either manipulation at C-2 (reduction or inversion) subsequent to glycosylation,[12-19] or tethering of the aglycone to the glycosyl donor prior to coupling.[1,20-25] We have recently developed a new and highly diastereoselective direct entry into β-mannopyranosides which hinges on the *in situ* formation of α-mannosyl triflates[26] from glycosyl sulfoxides, or thioglycosides, and their subsequent participation in S_N2-like displacement reactions with primary, secondary, and tertiary alcohols.[27-30] Here, we describe in full[31] our synthesis of the title trisaccharide (1) which we have conducted with a view to establishing the applicability of the method to the synthesis of complex biomolecules.



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The target trisaccharide (**1**) is a component of the *Hyriopsis schlegelii* glycosphingolipid isolated by Japanese workers in 1981.[32] It has been previously synthesized by Lichtenthaler[33] and, in a protected form, by Takeda[34] who has gone on to incorporate it into a more complete octasaccharide from the same glycosphingolipid.[35] Trisaccharide **1** therefore provides a convenient

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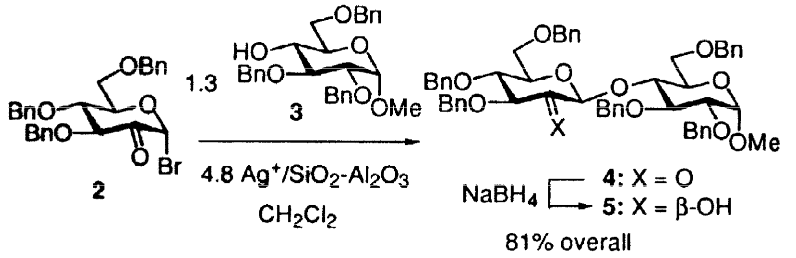
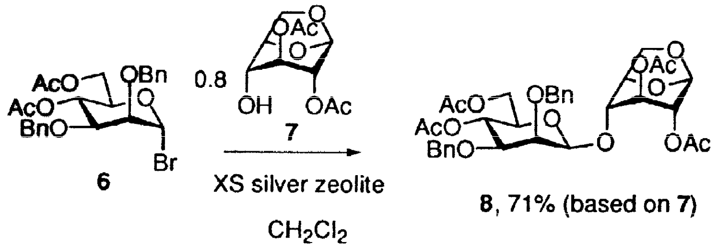
target for comparison of our new chemistry with previous methods. Lichtenthaler and coworkers generated the key β-mannoside linkage in **1** using their ulosyl bromide strategy. They reported that bromide **2** was coupled with the acceptor **3** in dichloromethane using four equivalents of a silver aluminosilicate "catalyst" to give exclusively the β-uloside **4** in 87% yield. Reduction with sodium borohydride then gave the β-mannoside **5** in 81% overall yield for the two steps (Scheme 1). It is noteworthy that closely related reductions of β-2-ulosides do not always give such high selectivity.[36] The Takeda group condensed the bromide **6** with acceptor **7** using a considerable excess of a silver zeolite promoter and reported a yield of 71% for the β-mannoside **8**, based on the limiting reagent (**7**). Based on the glycosyl donor, the yield is calculated to be 57%. Curiously, no mention of the formation of α-anomer corresponding to **8** was given in this report. It is noteworthy that both groups essentially employ variants on the insoluble silver salt method and require multiple equivalents of the promoter. In a further related synthesis Ogawa and co-workers coupled 2,3-di-*O*-allyl-4,6-di-*O*-benzyl-α-D-mannopyranosyl bromide with benzyl 2,3,6-tri-*O*-benzyl-β-D-glucopyranoside using silver silicate in dichloromethane to give a 77% yield of the corresponding β- and α-mannosides in the ratio 1.1:1.[37] This last example nicely demonstrates the fickle nature of the insoluble silver salt method.

Scheme 1

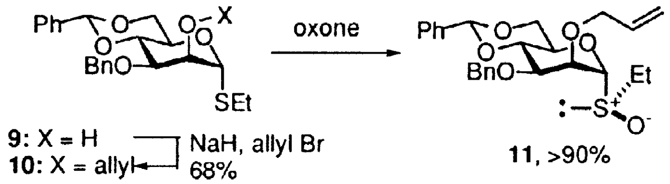


Scheme 2



We began our synthesis with the previously described thioglycoside **9**, which is readily available in two simple steps from *S*-ethyl thiomannopyranoside.[38] Allylation with sodium hydride and allyl bromide provided **10** in 68% yield. Treatment with oxone in aqueous methanol then afforded the sulfoxide **11** in almost quantitative yield (Scheme 3).

Scheme 3

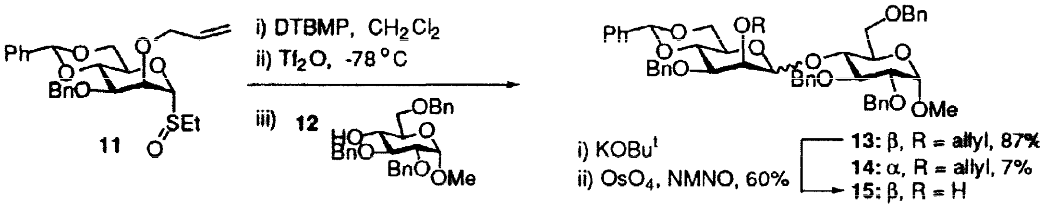


Interestingly, the sulfoxide **11** was formed as a single diastereomer. We have previously observed a similar phenomenon with a range of other *S*-phenyl and *S*-ethyl α-thioglycosides.[29,38] This is to be contrasted with the sulfoxidation of a broad range of β-thioglycosides, all of which are reported to give mixtures of diastereoisomers.[39] Recently, we have succeeded in assigning the configuration at sulfur as (*R*) in three α-glycosyl sulfoxides by X-ray crystallography and chemical correlations and similarly assign **11** by analogy.

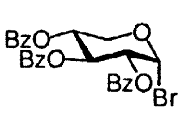
This selectivity is, we believe, a function of the *exo*-anomeric effect which serves to expose one face of the thioglycsoyl *S* to bulk solvent while the other is shielded beneath the pyranose ring; in the β-series, notwithstanding the *exo*-anomeric effect, both faces are exposed to oxidation.[40,41]

The key mannosylation reaction was acheived by activation of sulfoxide **11** with triflic anhydride in dichloromethane at -78 °C in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) followed by addition of 1.9 molar equivalents of the known acceptor **12**.[42] In this manner the β-mannoside **13** was isolated in 87% yield and the corresponding α-anomer (**14**) in 7% yield (Scheme 4). The coupling reaction was therefore highly selective (12:1) and proceeded in excellent yield. The anomeric stereochemistry of **13** was readily assigned from the unusual, somewhat upfield chemical shift of the mannose H-5 (δ ~3.1) which we have previously noted to be a characteristic of 4,6-benzylidene protected β-mannosides.[29] This assignment was confirmed by the $^1J_{CH}$ coupling for the mannosyl anomeric carbon, which was found to be 159.5 Hz.[43] Subsequently, the *O*-allyl protecting group was removed by treatment with potassium *tert*-butoxide followed by catalytic OsO_4 and an excess of *N*-methylmorpholine *N*-oxide (NMNO) as overall oxidant leading to the formation of **15** in 60% yield (Scheme 4).[44] The key stereoselective mannosylation step and selective revealing of the mannose *O*-2 for the final xylosylation was therefore achieved without difficulty. Our simple two step coupling/deprotection protocol is directly comparable with the two step Lichtenthaler approach to a closely analogous disaccharide (Scheme 1, 5) and proceeds with comparable overall yield and selectivity. Both routes are to be contrasted with the Takeda approach which provides **8** directly but in which the mannose *O*-2 and *O*-3 groups are not differentiated (Scheme 2).

Scheme 4



We next turned our attention to the xylosylation reaction. We had anticipated that this step would be essentially trivial and that the use of a xylosyl donor protected with carboxylate esters would proceed with excellent selectivity, through anchimeric assistance, to provide the β-xyloside. Indeed, Lichtenthaler reported the coupling of **5** with α-tri-*O*-benzoylxylosyl bromide (**16**),[45] in the presence of silver triflate, to give exclusively the β-xyloside **17** in 71% yield. Thus, we proceeded to couple **15** with **16** in dichloromethane at -40 °C with activation by silver triflate. A single product **18** was isolated in 68% yield (90% when based recovered substrate), (Scheme 5) and ultimately assigned the β-configuration indicated. However, we were somewhat surprised, even perplexed, to find that the spectral data for the xylose moiety in **18** (Table 1, entry 1) differed considerably from those reported by Lichtenthaler for **17** (Table 1, entry 2), despite the apparently minor change in protecting groups in the mannose segment. This, and the frequent lack of detailed assignment protocols which we encountered while searching the literature for xylosylation protocols, promoted a closer look and the investigation of alternative methods to the one employed in Scheme 5.



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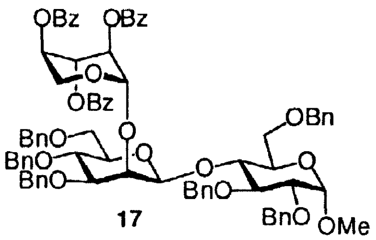

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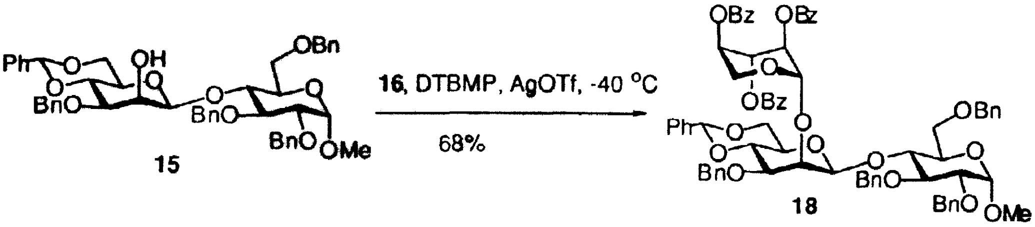
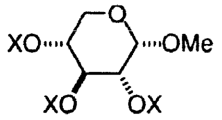
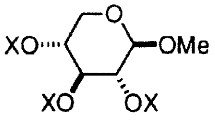
Scheme 5



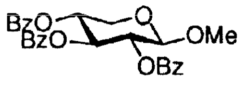
Methyl α- and β-xylopyranosides (**19** and **21**, respectively)[46] were purchased and converted to their perbenzoyl derivatives (**20** and **22**, respectively)[47] in order to provide simple comparison spectra (Table 1). The spectral data for the tribenzoyl β-xyloside **22** were in good agreement with those recorded in the literature by Schraml and coworkers, and by the Paulsen group. Schraml assigned this substance as a 62:38 mixture of the $^4C_1$ and $^1C_4$ conformers (**23** and **24**, respectively) on the basis of a detailed analysis of the coupling patterns,[48] whereas Paulsen and co-workers determined the ratio of **23**:**24** in d_6-acetone to be 74:26 on the basis of earlier NMR data provided by Horton.[47,49] In the crystal **22** adopts a twist-boat conformation (**25**)[49,50] which Schraml was unable to exclude on the basis of his solution NMR work. Paulsen, however, suggests that the NMR data are incompatible with such a conformation in solution. We also prepared the cyclohexyl xylopyranoside **26** by coupling of bromide **16** with cyclohexanol, mediated by silver triflate; its spectral data are presented in Table 1. If the coupling constants, with the obvious exception of $^3J_{1,2}$, in the methyl α-xyloside (**20**) define the pure $^4C_1$ chair conformer for the xylopyranoside series, then it is evident that both **22** and **26** exist largely, but not exclusively, in the $^4C_1$ conformation. This observation is further supported the magnitude of the $^1J_{C1,H1}$ coupling constants of 163 and 159.9 Hz respectively, as contrasted with that (173.3 Hz) of **20**. It is equally clear that in the trisaccharide **18**, the xylopyranoside is in a non-standard conformation, most likely the $^1C_4$ conformer. Thus, the $^3J_{1,2}$ coupling is inconsistent with either an α- or β-xyloside in the $^4C_1$ conformation. The very narrow, poorly resolved multiplets for H1 - H4 are incompatible with this conformation and suggest the inverted chair, or $^1C_4$, conformation. This is corroborated by the $^1J_{C1H1}$ coupling constant of 174.6 Hz which is indicative of an axial glycoside. Thus, the spectral data strongly suggest that the xylose moiety in **18** is a β-xyloside in the inverted chair conformation, as concluded by Lichtenthaler for the corresponding xylose ring in **17**.[33] The discrepancies between the ^{1}H-NMR data found here for **18**, and reported by Lichtenthaler for **17**, particularly the conspicuously unusual chemical shift reported for the anomeric xylose proton in the latter, remain unexplained.



19: X = H
20: X = Bz



21: X = H
22: X = Bz



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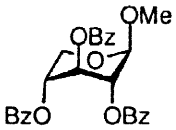

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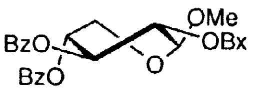

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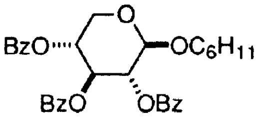

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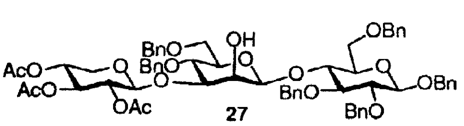
Table 1. Chemical Shifts and Coupling Constants[a] for Xylosides

	Solv	δH1	δH2	δH3	δH4	δH5α	δH5β	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5\alpha}$	$J_{4,5\beta}$	$J_{5\alpha,5\beta}$	δC1	$^1J_{C1H1}$
18	$CDCl_3$	4.90	5.40[b]	5.49[b]	5.06[b]	c	c	<2	c	c	c	c	c	97.6	174.6
17[d]	$CDCl_3$	5.41	5.49	5.54	5.16	3.66[b]	4.82[b]	2.1	3.4	3.8	c	c	c	e	e
20	$CDCl_3$	5.20	5.28	6.20	5.42	3.87	4.10	3.5	9.5		9.4	6.5	9.4	97.1	173.3
22	$CDCl_3$	4.75	5.40	5.80	5.35	4.45	3.74	5.5	8.0	8.0	4.6	8.6	12.1	101.2	163
26	$CDCl_3$	4.95	5.47	5.78	5.32	4.45	3.70	6.7	7.5	8.5	4.7	a	10.3	98.3	159.9
6	$CDCl_3$	5.89	4.68	5.75	5.29	4.11	3.65	4.8	2.5	2.5	7.5	8.0	12.0	96.7	180.0
37	$CDCl_3$	c	c	c	c	c	c	c	c	c	c	c	c	103.6	167.7
19	D_2O	4.55[f]	3.20[f]	3.38[f]	3.34[f]	3.25[f]	3.46[f]	c	c	c	c	c	c	101.8	172.2
21	D_2O	4.23	3.16	3.34	3.53	3.23	3.87	7.8	7.8	7.8	8.0	5.3	11.3	106.3	162.4
1	D_2O	4.37	c	3.13	c	c	c	7.5	10.6	10.6	c	c	c	106.4	164.6
1[d]	D_2O	4.57	3.44	3.52	3.65	3.33	4.03	7.6	9.4	9.1	10.6	5.4	11.5	106.9	e

a: in Hertz; b: could be exchanged; c: unresolved; d: taken from ref 33, see footnote 61; e: not reported; f: ^{1}H-NMR unresolved in D_2O, ^{1}H NMR data in DMSO d_6 taken from ref 46.

The most intriguing aspect of the above study is the difference in conformations between **22** and **26**, on the one hand, and **17** and **18** on the other. Similar shifts in conformation provoked by seemingly even more minor structural changes have been noted by others. In particular, we draw attention to the work of Ogawa in which a series of two mono-xylo and one di-xylosylated tri- and tetramers were prepared (**27** - **29**). In this study,[37] **27** and **28** were both assigned as $^4C_1$ β-xylosides based on the ^{1}H and ^{13}C NMR spectral data, in particular the $^3J_{1,2}$ coupling of 6.9 Hz visible on the (xylose) anomeric proton (δ 4.34) in **27**, and $^1J_{C1H1}$ coupling constant of 153-161 Hz for **28**. On the other hand, in **29** one of the two β-xylosides was found to be in the $^4C_1$, and the other the $^1C_4$ conformation as judged by the presence of a single anomeric carbon with $^1J_{H1,C1}$ of 173 Hz, i.e. exactly as found for **18**. A closely related observation was made by Vliegenthardt and co-workers who found the xylose moiety in **30** to be a $^4C_1$ chair whereas that in the slightly more complex **31** was a $^1C_4$ conformer.[36] Clearly, very minor changes in the aglycone can have significant consequences on the conformation of β-xylopyranoside peresters. The origin of these changes is not readily apparent at the present time.



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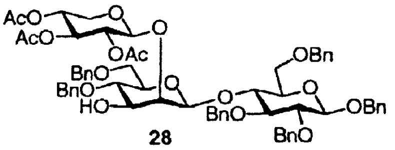

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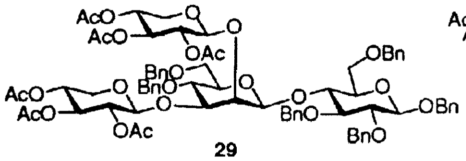

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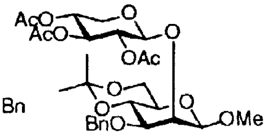

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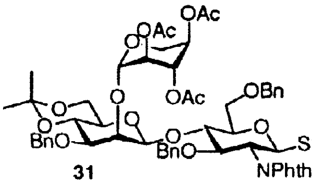

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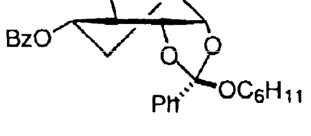
We have also briefly investigated alternative methods of xylosylation, using cyclohexanol as a model glycosyl acceptor. As stated above, coupling of bromide **16** with cyclohexanol mediated by silver triflate in dichloromethane at -40 °C provided the pure β-xyloside **26** in 90% yield. Coupling of the xylopyranose **32** with cyclohexanol following activation in the form of the trichloroacetimidate **33** with promotion by BF$_3$OEt$_2$ provided **26** in 75% yield. Xylopyranosylation by the Schmidt trichloroacetimidate method had been previously reported for the peracetyl congenor of **32**.[36,37,51] Given our success with Kahne's sulfoxide method in mannosylation, we were especially keen to investigate the possibility of its application to xylosylation.[39,52] Toward this end, bromide **16** was treated in dichloromethane with thiophenol in the presence of triethylamine leading to the formation of the phenyl β-thioglycoside **34** in 60% yield. This was then converted to the mixture of diastereomeric sulfoxides **35** in 83% yield by treatment with mCPBA from -78 to -30 °C. In line with the precedent the oxidation of the β-thioglycoside **34** resulted in the formation of **35** as a mixture (~ 3/1) of two diastereomers at *S*, which were separable by silica gel chromatography but whose configurations were not assigned. Activation of the major diastereomeric sulfoxide in dichloromethane at -78 °C, in the presence of DTBMP, with Tf$_2$O followed by addition of cyclohexanol and subsequent quenching at -78 °C led, unexpectedly, not to the formation of the β-xyloside **26** but to a new, unstable cyclohexanol containing product that was assigned as the orthoester **36**. Similarly, activation of the thioglycoside **34** with benzenesulfenyl triflate[29,30] at -78 °C followed by coupling to cyclohexanol produced **36** as the major product. The ^{1}H-NMR spectrum of **36** (Table 1) is characterized by the small ^3J coupling constants around the xylose ring which suggests that it exists predominantly in a non-standard conformation and which rules out any simple α- or β-xyloside. In the ^{13}C-NMR spectrum the anomeric carbon (δ 96.7) is found to have a $^1J_{\mathrm{C1H1}}$ coupling of 180 Hz which is strongly indicative of an axial glycosidic bond. Other noteworthy features of the ^{13}C-NMR spectrum are the presence of only two carbonyl C's, whereas three were readily discernible in all the other xylosides described above, and that of a new quaternary C resonating at δ 121.3 which we assign to the orthoester carbon. The combined spectral data are best explained by the orthoester **36** which exists predominantly in the $^{O}H_5$ conformation indicated in order to retain the axial glycosidic bond, yet minimize steric interactions between the endo-orthoester substituent and ring protons. Half-chair conformers have previously been discussed as viable alternatives to $^1C_4$ chairs for xylopyranosides by Lichtenthaler.[50] The stereochemistry at the orthoester C is assigned arbitrarily on the grounds that the intermediate cation will be more rapidly trapped on the exo-face by the bulky alcohol.[53] Numerous examples of the employment of ester protected β-glycosyl sulfoxides as glycosyl donors have been described by the Kahne group,[39,52] and orthoesters have sometimes been observed as byproducts, even with pivalate esters as protecting groups, but not as major products.[54-56] We also note that a methyl orthoester has been previously isolated as a minor product from such a reaction in this laboratory.[26] Presumably, the non-standard conformation adopted by **36** is reflected to some extent in the transition state for displacement of the anomeric leaving group by the 2-*O*-benzoate and this is facilitated in the more conformationally labile xylose series. Of course, orthoesters are readily rearranged to β-glycosides[57] and such a reaction might be envisaged for the conversion of **36** to **26**. However, previous work by Kochetkov and co-workers with xylosyl orthoesters[58] suggested that, while feasible, such reactions would not be clean. In the event, exposure of **36** to SnCl$_4$ in dichloromethane[59] provided **26** in approximately 50% yield together with several unidentified byproducts. We also note that the coupling of sulfoxide **35** with cyclohexanol at -78 °C followed by warming to 0 °C before quenching provided an approximately 1/1 mixture of orthoester **36** and the β-xyloside **26**, which indicates slow rearrangement of **36** to **26** above -78 °C, presumably catalyzed by DTBMPH$^+$ TfO$^-$.

32: X = α,β-OH
33: X = α-OC(=NH)CCl$_3$
34: X = β-SPh
35: X = β-S(O)Ph



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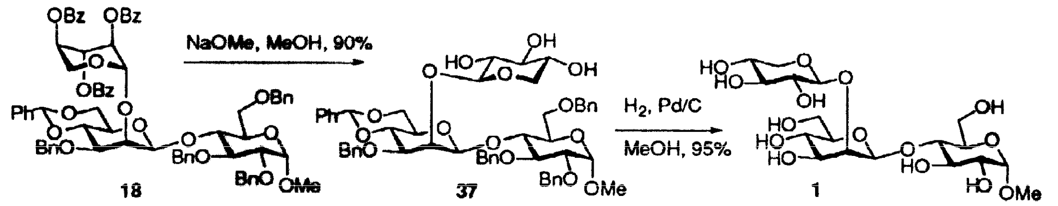
Finally, we returned to the completion of our synthesis. Saponification of **18** under Zemplen conditions provided **37** in 90% yield (Scheme 6). This step also occasioned inversion of the xylose to the $^4C_1$ chair conformer indicated. This change in conformation is not at all apparent from the complex ^{1}H-NMR spectrum, but is readily deduced from the ^{13}C-NMR spectrum, in CDCl$_3$, wherein there is a significant change in the chemical shift of the xylose anomeric carbon on going from **18** (δ 97.6) to **37** (δ 103.4) (Table 1). The $^1J_{C1H1}$ coupling for the xylose anomeric carbon was now 167.7 which is in reasonable agreement with that determined for methyl β-xylopyranoside (**21**) (Table 1) and so nicely confirms the original assignment of the xylose configuration in **18**. The final deprotection was achieved uneventfully by stirring **37** in methanol over Pd/C for three days at room temperature under one atmosphere of hydrogen which cleanly removed all remaining protecting groups and furnished the target molecule (**1**) in 95% isolated yield (Scheme 6). In our hands, **1** was a crystalline, analytically pure monhydrate whose ^{13}C-NMR spectrum and specific rotation corresponded with those reported by Lichtenthaler[33] for the same substance (Table 1).

Scheme 6



Experimental[60]

***S*-Ethyl 2-*O*-Allyl-3-*O*-benzyl-4,6-*O*-benzylidene-1-deoxy-1-thia-α-D-mannopyranoside (10)** To a solution of 9[38] (2.42g, 6.0 mmol) in THF (50 mL) was added NaH (0.72 g, 18.0 mmol) at 0 °C. After stirring for 1.3 h at this temperature, allyl bromide (1.26 mL, 14.4 mmol) was added dropwise. The reaction mixture was stirred overnight at reflux temperature, then quenched by addition of saturated NH$_4$Cl solution, then brine, followed by extraction into EtOAc. The organic layers were combined, dried, and, concentrated. Chromatogrphy on silica gel (eluent: hexane/EtOAc = 1 2:1) then afforded **10** (1.80 g, 68%). Based on recovered starting material (822 mg) the yield is 93%. $[\alpha]_D^{20}$ = +131.0 (c = 2.6, CHCl$_3$). ^{1}H NMR (CDCl$_3$, 400 MHz) δ: 1.28 (t, *J* = 6.9 Hz, 3H), 2.61 (m, 2H), 3.92 (m, 3H), 4.22 (m, 3H), 4.72 (d, *J* = 12.0 Hz, 1H), 4.80 (d, *J* = 12.0 Hz, 1H), 5.22 (d, *J* = 10.9 Hz, 1H), 5.29 (br. s, 1H), 5.30 (d, *J* = 17.8 Hz, 1H), 5.63 (s, 1H), 5.95 (m, 1H), 7.37 (m, 8H), 7.50 (m, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ: 14.9, 25.3, 64.4, 68.5, 72.5, 73.0, 76.2, 78.0, 79.2, 83.7, 101.4, 117.9, 125.9, 127.6, 128.1, 128.8, 134.6, 137.5, 138.3. Anal. Calcd for $C_{25}H_{30}0_5S$: C, 67.85; H, 6.83. Found: C, 67.74; H, 6.79.

***S*-Ethyl 2-*O*-Allyl-3-*O*-benzyl-4,6-*O*-benzylidene-1-deoxy-1-thia-α-D-mannopyranoside *S*-(*R*)-Oxide (11).** To a stirred solution of **10** (10.6 g, 24 mmol) in MeOH/H$_2$0 (1:1, 260 mL) in an ice bath was added dropwise oxone (8.8 g, 14 mmol) in water (10 mL). After 0.5 h TLC indicated completion and the reaction mixture was quenched with ice and saturated aqueous Na$_2$SO$_3$ (150 mL), extracted with EtOAc (150 mL x 3). The combined organic layers were dried, and evaporated down to give a reasonably pure, solid product (10.9 g, 100%). Further purification could be achieved by recrystallization from EtOAc, or chromatogaphy on silica gel (eluent: hexane/EtOAc = 4:1). Mp 85 °C; $[\alpha]_D^{20}$ = +39.3 (c = 2.6, CDCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz) δ: 1.41 (t, *J* = 7.5 Hz, 3H), 2.72 (m, 1H), 2.98 (m, 1H), 3.72 (dt, *J* = 4.2, 9.6 Hz, 1H), 3.79 (t, *J* = 9.6, 1H), 4.10 (dd, *J* = 3.1, 9.9 Hz, 1H), 4.30 (m, 4H), 4.44 (d, *J* = 0.5 Hz, 1H), 4.62 (br. s, 1H), 4.75 (d, *J* = 12.1 Hz. 1H), 4.87 (d, *J* = 12.1 Hz, 1H), 5.23 (d, *J* = 9.3 Hz, 1H), 5.34 (d, *J* = 16.7 Hz, 1H), 5.62 (s, 1H), 5.96 (m, 1H), 7.30 (m, 8H), 7.48 (m, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ: 5.82, 43.9, 68.1, 70.0, 72.8, 73.1, 73.2, 75.9, 77.8, 92.7, 101.5, 118.2, 125.9, 127.6, 127.7, 128.2, 128.3, 128.9, 134.2, 137.1, 137.9. Anal. Calcd for $C_{25}H_{30}0_6S$: C, 65.48; H, 6.59. Found: C, 65.17; H, 6.58.

Methyl 2,3,6-Tri-*O*-benzyl-4-*O*-(2-*O*-allyl-3-*O*-benzyl-4,6-*O*-benzylidene-β-D-mannopyranosyl)-(1→4)-α-D-glucopyranoside (13) and the α-Anomer (14). To a stirred solution of **11** (428 mg, 0.93 mmol) and DTBMP (377 mg, 1.83 mmol) in CH_2Cl_2 (25 mL) at -78 °C under an Ar atmosphere was added Tf_2O (173 µL, 1.02 mmol). After 5 min, a solution of **12** (818 mg, 1.76 mmol) in CH_2Cl_2 (10 mL) was added dropwise. The reaction mixture was stirred at -78 °C for 1h then allowed to warm up to 0 °C, followed by quenching with saturated aqueous $NaHSO_3$, washing with brine, and drying (Na_2SO_4). Concentration and chromatography on silica gel (eluent hexane/EtOAc = 20: 1) gave the β-isomer **13** (731 mg, 87%) and the α-isomer **14** (60 mg, 7%). **13** (β-anomer): $[\alpha]_D^{20}$ = -12.1 (c = 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz), δ: 3.05 (m, 1H), 3.32 (dd, *J* = 3.5, 9.7 Hz, 1H) 3.40 (s, 3H), 3.51-3.80 (m, 5H), 3.88-3.96 (m, 2H), 4.00-4.10 (m, 2H), 4.29 (m, 2H), 4.35 (d, *J* = 11.8 Hz, 2H), 4.60-4.70 (m, 4H), 4.76-4.86 (m, 3H), 5.106 (d, *J* = 10.5 Hz, 2H), 5.13 (d, *J* = 11.4 Hz, 1H), 5.28 (d, *J* = 18.4 Hz, 1H), 5.52 (s, 1H), 5.90-6.04 (m, 1H), 7.20-7.50 (m, 25H); ^{13}C ($CDCl_3$, 75 MHz) δ: 55.3, 67.1, 68.2, 68.5, 69.5, 72.4, 73.5 (2C), 74.4, 75.2, 77.0, 77.4, 77.8, 78.6, 78.9, 80.1, 98.3, 101.2 (2C), 116.8, 125.9, 127.3, 127.5, 127.7, 128.0, 128.3, 128.5, 128.8, 135.4,136.5, 137.5, 138.0, 139.3. Anal. Calcd for $C_{51}H_{56}O_{11}.1H_20$: C, 70.97, H, 6.77. Found: C, 70.93; H, 6.64 %). **14** (α-anomer): $[\alpha]_D^{20}$ = +21° (c = 3, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz), δ: 3.39 (s, 3H), 3.55 (dd, *J* = 3.5, 9.5 Hz, 1H), 3.65-3.75 (m, 5H), 3.75-4.00 (m, 7H), 4.10 (m, 1H), 4.18 (m, 1H), 4.50-4.75 (m, 7H), 4.80 (d, *J* = 12.0 Hz, 1H), 5.00 (d, *J* = 10.3 Hz, 1H), 5.06 (d, *J* = 17.3 Hz, 1H), 5.11 (d, *J* = 11.7 Hz, 1H), 5.59 (s, 1H), 5.66 (m, 1H), 7.20-7.55 (m, 25H); ^{13}C ($CDCl_3$, 75 MHz) δ: 55.3, 65.0, 68.6, 68.8, 69.5, 72.7, 72.9, 73.1, 73.5, 75.8, 76.0, 77.0, 77.4, 78.9, 79.9, 81.4, 97.7, 101.3, 101.6, 116.8, 126.0, 126.7, 127.4, 127.6, 127.9, 128.0, 128.2, 128.3, 128.4, 128.7, 134.7, 137.7, 137.9, 138.5.

Methyl 2,3,6-Tri-*O*-benzyl-4-*O*-(3-*O*-benzyl-4,6-*O*-benzylidene-β-D-mannopyranosyl)-α-D-glucopyranoside (15) To a stirred of solution of **13** (220 mg, 0.26 mmol) in DMS0 (4 mL) was added t-BuO$^-$K$^+$ (175 mg, 1.56 mmol) followed by heating to 85-90 °C for 1h. After cooling the reaction mixture was quenched with water, and extracted with EtOAc. The extracts were washed with brine, dried over Na_2SO_4 and concentrated when ^1H NMR indicated that the reaction was complete. NMNO (152 mg, 1.3mmol) and a catalytic amount of OsO_4 were added. Then 80% aqueous acetone (6 mL) was added to the mixture, followed by stirring overnight. After filtration on Celite, the acetone was removed at water aspirator pressure and the remaining solution was washed by brine, and extracted by EtOAc. The combined organic layers, were dried over Na_2SO_4, concentrated and chromatographed on silica gel (eluent: hexane/EtOAc = 2/1, then 1/2) to give **15** (123 mg, 60%). Mp 80 °C; $[\alpha]_D^{20}$ = +3.68 (c = 1.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz), δ: 2.55 (br. s, 1H), 3.05 (m, 1H), 3.35 (m, 1H), 3.38 (s, 3H), 3.53 (m, 1H), 3.60 (m, 2H), 3.70-3.80 (m, 2H), 3.86-4.10 (m, 5H), 4.39 (d, *J* = 12.3 Hz, 1H), 4.51(br. s, 1H), 4.60-4.82 (m, 8H), 4.85 (d, *J* = 12.0 Hz, 1H), 4.92 (d, *J* = 12.0 Hz, 1H), 5.35 (s, 1H), 7.20-7.60 (m, 25H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 55.2, 66.7, 68.2, 68.5, 69.3, 69.6, 72.2, 73.5 (2C), 75.4, 76.9, 77.0, 78.1, 79.2, 80.3, 98.2, 100.5, 101.4, 125.9, 127.4, 127.6, 127.7, 127.8, 127.9, 128.2, 128.4, 128.5, 128.9, 137.4, 137.5, 138.0, 138.1, 138.9. Anal. Calcd for $C_{48}H_{52}O_{11}$: C, 71.62; H, 6.51. Found: C, 71.56; H, 6.52.

Methyl 2-*O*-(2,3,4-Tri-*O*-benzoyl-β-D-xylopyranosyl)-4-*O*-(3-*O*-benzyl-4,6-*O*-benzylidene-β-D-mannopyranosyl)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (18). A stirred solution of **15** (100 mg, 0.12 mmol) in CH_2Cl_2 (94 mL), powdered molecular sieves (100 mg), and DTBMP (81 mg, 0.39 mmol) was cooled under Ar to -40 °C. After stirring for 0.5 h, a solution of **16** (78 mg, 0.14 mmol) in CH_2Cl_2 (2 mL) was added followed by dropwise addition of AgOTf (62 mg, 0.25 mmol) in toluene (1 mL). The reaction mixture was stirred a further 0.5 h at -40 °C then allowed to warm to 0 °C, before it was filtered on Celite, and washed with 10% aqueous Na_2SO_3 solution, and brine. After drying (Na_2SO_4) and concentration to dryness under vacuum, chromatography on silica gel (eluent: hexane/EtOAc = 3:1) gave **18** (105 mg, 90%, based on 29 mg recovered substrate). Mp 83 °C; $[\alpha]_D^{20}$ = -62° (c = 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ: 2.95 (dt, *J* = 4.2, 9.0 Hz, 1H), 3.02 (t, *J* = 10.1 Hz, 1H), 3.30 (s, 3H), 3.30 (m, 1H), 3.46 (dd, *J* = 3.6, 9.6 Hz, 1H), 3.57 (m, 2H), 3.66 (dd, *J* = 9.9, 2.0 Hz, 1H), 3.74 (t, *J* = 9.1 Hz, 2H), 3.81 (t, *J* = 9.7 Hz, 1H), 3.88 (dd, *J* = 4.3, 10.0 Hz, 1H), 4.01 (t, *J* = 9.3 Hz, 1H), 4.25 (d, *J* = 12.1 Hz, 1H), 4.34 (br. s, 1H), 4.55 (d, *J* = 3.6 Hz, 1H), 4.63 (dd, *J* = 7.2, 12.1 Hz, 2H), 4.72 (d, *J* = 10.8 Hz, 1H), 4.77 (dd, *J* = 8.1, 12.4 Hz, 2H), 4.87 (d, *J* = 12.4 Hz, 1H), 4.94 (s, 1H), 5.01 (br. s, 1H), 5.04 (br. d, *J* = 7.5 Hz, 1H), 5.06 (br. s, 1H), 5.40 (br. s, 1H), 5.45 (s, 1H), 5.49 (br. s, 1H), 7.15-7.55 (m, 33H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.97 (d, *J* = 7.2 Hz, 2H), 8.10 (d, *J* = 7.2 Hz, 2H), 8.17 (d, *J* = 7.1 Hz, 2H); ^{13}C NMR ($CDC1_3$, 75 MHz) δ: 55.2, 58.3, 66.5, 66.8, 66.9, 67.6, 68.3, 69.4, 72.7, 73.6, 74.1, 75.2, 76.6, 78.2, 78.5, 78.9, 79.5, 97.5, 98.8, 101.0, 101.6, 126.0, 126.8, 127.4, 127.5, 127.7, 127.8, 127.9, 128.1, 128.2, 128.2, 128.4, 128.5, 129.0, 129.4, 12 9.9, 130.0, 130.1, 130.3, 133.0, 133.3, 137.5, 138.3, 138.4, 138.9, 164.4, 164.5, 165.7. Anal. Calcd for $C_{74}H_{72}0_{18}$: C, 71.14; H, 5.81. Found: C, 70.96; H, 5.81.

Cyclohexyl 2,3,4-Tri-*O*-benzoyl-β-D-xylopyranoside (26). A solution of cyclohexanol (20 mg, 0.2 mmol) in CH_2Cl_2 (3 mL) was stirred with powdered molecular sieves (20 mg) and cooled under Ar to -40 °C. After stirring for 0.5 h, a solution of **16** (50 mg, 0.1 mmol) in CH_2Cl_2 (3 mL) was added followed, dropwise, by a solution of AgOTf (50 mg, 0.2 mmol) in toluene (1 mL). After stirring for a further 0.5 h at -40 °C the reaction mixture was allowed to warm to 0 °C before it was filtered on Celite, then washed with aqueous Na_2SO_3 and brine. After drying on Na_2SO_4 and concentration, chromatography on silica gel (eluent: hexane/EtOAc 8/1) gave **26** as a white solid (46.5 mg, 90%). Mp 61 °C; $[\alpha]_D$ = -37.5 (c = 0.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.10-2.00 (m, 10H), 3.70 (m. 2H), 4.45 (dd, *J* = 4.7, 10.3 Hz, 1H), 4.95 (d, *J* = 6.7 Hz, 1H), 5.32 (m, 1H), 5.47 (dd, *J* = 6.6, 7.5 Hz, 1H), 5.78 (t, *J* = 8.5 Hz, 1H), 7.30-7.40 (m, 6H), 7.45-7.60 (m, 3H), 7.90-8.05 (m, 6H); ^{13}C NMR ($CDC1_3$, 75 MHz) δ: 23.4, 23.7, 25.4, 31.3, 33.2, 61.2, 69.2, 70.4, 70.6, 98.3, 128.3, 129.1, 129.4, 129.7, 133.1, 133.2, 133.2, 165.0, 165.4, 165.5. HRMS: Calcd for $C_{18}H_{20}0_4$: 300.1362, found: 300.1358 (M^+ - $2xPhCO_2H$). Anal. Calcd for $C_{32}H_{32}0_8$: C, 70.58; H, 5.92. Found: C, 70.29; H, 5.93.

***S*-Phenyl 2,3,4-Tri-*O*-benzoyl-1-deoxy-1-thio-β-D-xylopyranoside (34).** PhSH (0.5 mL) was added dropwise at room temperature to a stirred solution of **16** (1.00 g, 1.9 mmol) and Et_3N (2 mL) in CH_2Cl_2 (15 mL). After stirring overnight the reaction was diluted with aqueous NaOH (3 M). The organic phase was decanted and washed with aqueous $NaHCO_3$, then brine, and dried over Na_2SO_4 before concentration to driness. Chromatography on silica gel (eluent: hexane/EtOAc 10/1) gave **34** as a white solid (635 mg, 60%). Mp 63 °C; $[\alpha]_D^{20}$ = -26.5° (c = 2.1, $CHC1_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 3.85 (dd, *J* = 11.2, 6.5 Hz, 1H), 4.75 (dd, *J* = 11.2, 4.7 Hz, 1H), 5.30 (m, 2H), 5.50 (t, *J* = 7.5 Hz, 1H), 5.80 (t, *J* = 7.5 Hz, 1H), 7.25-7.50 (m, 9H), 7.50-7.65 (m, 3H), 7.90-8.10 (m, 8H); ^{13}C NMR ($CDC1_3$, 75 MHz) δ: 63.4, 68.6, 70.0, 70.4, 86.3, 128.1, 128.4, 128.9, 129.1, 129.9, 130.0, 132.5, 133.1, 133.4, 133.5, 165.1, 165.2, 165.5. Anal. Calcd for $C_{32}H_{26}0_7S$: C, 69.30; H, 4.73. Found: C, 68.80; H, 4.77.

***S*-Phenyl 2,3,4-Tri-*O*-benzoyl-1-deoxy-1-thio-β-D-xylopyranoside *S*-Oxide (35).** A stirred solution of **34** (400 mg, 0.72 mmol) in CH_2Cl_2 (10 mL) was cooled to -78 °C under Ar and treated dropwise with a solution of mCPBA (174 mg, 1 mmol) in CH_2Cl_2 (2 mL). After warming to room temperature and evaporation to driness chromatography on silica gel (eluent: hexane/EtOAc 6/1) gave **35** as an ~ 3:1 mixture of two isomers (340 mg, 83%). Anal. Calcd for $C_{32}H_{26}0_8S$: C, 67.36; H, 4.59. Found: C, 67.08; H, 4.67. Careful chromatography enabled separation into a major isomer (260 mg) and a minor isomer (80 mg) whose configurations were not established. **35**, Major isomer. Mp 140 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ: 3.90 (dd, *J* = 11.3, 7.5 Hz, 1H), 4.55 (dd, *J* = 11.3, 3.8 Hz, 1H), 4.82 (d, *J* = 7.5 Hz, 1H), 5.25 (m, 1H), 5.85 (m, 2H), 7.20-7.60 (m, 12H), 7.75 (d, J = 9.4 Hz, 2H), 7.90 (d, J = 9.0 Hz, 2H), 7.95 (d, J = 9.0 Hz, 2H), 8.05 (d, J = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 65.8, 65.9, 67.8, 70.1, 94.0, 125.1, 128.2, 128.3, 128.4, 128.6, 128.8, 129.0, 129.8, 129.9, 131.5, 133.5, 139.9, 165.1, 165.2, 165.5. Minor isomer ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.85 (dd, J = 11.3, 7.5 Hz, 1H), 4.60 (d, J = 7.5 Hz, 1H), 4.65 (dd, J = 11.3, 4.0 Hz, 1H), 5.40 (m, 1H), 5.68 (t, J = 7.5 Hz, 1H), 5.90 (t, J = 7.5 Hz, 1H), 7.25-7.65 (m, 12H), 7.65-7.80 (m, 2H), 7.85-8.10 (m, 6H).

Orthoester 36. A. From sulfoxide 35. A solution of 35 (50 mg, 0.09 mmol) and DTBMP (36 mg, 0.18 mmol) in CH_2Cl_2 (6 mL) was cooled to -78 °C with stirring under Ar and treated with Tf_2O (17 μL, 0.1 mmol) and after 5 min at -78 °C., with cyclohexanol (20 μL, 0.18 mmol). Stirring was continued for 1 h at -78 °C before the reaction mixture was quenched by addition of aqueous $NaHCO_3$. After warming to room temperature the reaction mixture was filtered on Celite and washed with brine. Examination of the crude extracts by ^{1}H NMR spectroscopy revealed formation of one very major product (>90%), identified as **36**. Preparative TLC on silica gel (eluent: hexane/EtOAc 8/1) provided a pure sample of the unstable, oily orthoester for characterization purposes. When the reaction mixture was allowed to warm to 0 °C before quenching ^{1}H-NMR spectroscopy of the crude extracts indicated an ~ 1/1 mixture of **36** and **26**. **B.** From thioglycoside 34. To a stirred solution of AgOTf (67.5 mg, 0.27 mmol) in CH_2Cl_2 at -78 °C was added under Ar, a solution of PhSCl (46 mg, 0.31 mmol) in CH_2Cl_2 (2 mL) followed after 10 min by dropwise addition of a solution of 34 (50 mg, 0.09 mmol) and DTBMP (55.4 mg, 0.27 mmol) in CH_2Cl_2. After a further 5 min at -78 °C, cyclohexanol (18 mg, 0.18 mmol) in CH_2Cl_2 (2 mL) was added. After stirring for 1 h at -78 °C the reaction mixture was allowed to come to room temperature before quenching with aqueous $NaHCO_3$ (2 drops). Drying on Na_2SO_4, and concentration provided a crude preparation which, on examination by ^{1}H NMR spectroscopy was revealed to contain a 4-5:1 mixture of 36 and 26. 36: ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.05-1.85 (m, 10H), 3.38 (m, 1H), 3.65 (dd, J = 8.1, 12.0 Hz, 1H), 4.11 (m, $w_{1/2}$ = 25 Hz, 1H), 4.68 (m, $w_{1/2}$ = 12 Hz, 1H), 5.29 (dd, J = 7.4, 2.5 Hz, 1H), 5.75 (t, J = 2.5 Hz, 1H), 5.89 (d, J = 4.8 Hz, 1H), 7.30-7.55 (m, 7H), 7.55-7.65 (m, 2H), 7.73 (d, J = 6.7 Hz, 2H), 7.97 (d, J = 7.7 Hz, 2H), 8.08 (d, J = 8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 24.2 (2C), 25.3, 33.1, 33.4, 59.3, 68.0, 68.8, 72.8, 96.7, 121.3, 126.4, 128.0, 128.3, 128.3, 128.5, 128.9, 129.2, 129.8, 129.9, 133.3, 133.6, 136.4, 164.7, 165.3. No attempt was made to characterize further this unstable oil.

Methyl 2-*O*-(β-D-Xylopyranosyl)-4-*O*-(3-*O*-benzyl-4,6-*O*-benzylidene-β-D-mannopyranosyl)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (37). A NaOMe solution was prepared by adding Na (23 mg, 1 mmol) to MeOH (10 mL) and added to a mixture of **18** (289 mg, 0.23 mmol) in dry MeOH (5 mL) under Ar. After stirring overnight, evaporation, and chromatography on silica gel (eluent: EtOAc/hexane 3/2) gave **37** (217 mg, 97%). Mp 76-80 °C; $[\alpha]_D^{20}$ = -50° (c = 0.1, $CDCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.25 (br. s, 1H), 1.74 (br. s, 2H), 3.04 (m, 2H), 3.31 (m, 2H), 3.37 (s, 3H), 3.48-3.75 (m, 10H), 3.80-3.98 (m, 4H), 4.05 (dd, J = 4.8, 10.5 Hz, 1H), 4.19 (dd, J = 2.3, 11.8 Hz, 1H), 4.32 (d, J = 12.0 Hz, 1H), 4.40 (br. s, 1H), 4.60 (m, 2H), 4.63 (d, J = 5.6 Hz, 1H), 4.70 (d, J = 12.1 Hz, 1H), 4.76 (d, J = 12.0 Hz, 1H), 4.78 (br. s, 1H), 4.80 (d, J = 11.5 Hz, 2H), 4.86 (d, J = 10.6 Hz, 1H), 5.51 (s, 1H), 7.15-7.50 (m, 25H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 55.5, 63.3, 66.9, 68.2, 68.3, 69.0, 69.2, 71.4, 72.7, 73.3, 73.6., 74.8, 76.1, 76.4, 77.9, 78.5, 78.9, 79.6, 96.2, 101.1, 101.3, 103.6, 126.0, 127.5, 127.6, 127.7, 127.9, 128.1, 128.2, 128.4, 128.6, 128.9, 137.3 (2C), 137.9, 138.0, 139.0. Anal. Calcd for $C_{53}H_{60}O_{15}.0.5H_2O$: C, 67.29; H, 6.50. Found: C, 67.22; H, 6.89.

Methyl 2-*O*-(β-D-Xylopyranosyl)-4-*O*-(β-D-mannopyranosyl)-α-D-glucopyranoside (1). To a stirred solution of **37** (97 mg, 0.10 mmol) in dry MeOH (15 mL) was added Pd/C (30mg) and the reaction mixture stirred under hydrogen (1 atm, balloon) for 3 days. Filtration and evaporation then gave **1** as a clean, white solid (50 mg, 94%); Mp 212 °C; $[\alpha]_D^{20}$ = +20.0 (c = 0.1, H_2O); ^{1}H NMR (D_2O, 400 MHz)[61] δ: 3.14 (t, J

= 10.5 Hz, 1H), 3.23 (s, 3H), 3.23-3.36 (m, 5H), 3.41-3.56 (m, 4H), 3.61-3.86 (m, 6H), 4.11 (d, J = 3.5 Hz, 1H), 4.38 (d, J = 7.5 Hz, 1H), 4.80 (br. s, 1H), glucose H-1 is obscured by the HOD signal at δ 4.70; ^{1}H NMR (DMSO-d_6 + 5% D_2O, 400 MHz) anomeric resonances δ: 4.35 (d, J = 7.0 Hz, 1H), 4.51 (d, J = 4.2 Hz, 1H), 4.58 (br. s, 1H); ^{13}C NMR (D_2O, 75 MHz) δ: 57.4, 62.5, 62.8, 67.4, 69.2, 71.6, 72.5, 73.3, 74.0, 74.1, 75.6, 77.7, 78.8, 80.1, 81.1, 101.3, 102.5, 106.4. Anal. Calcd for $C_{18}H_{32}0_{15}.1H_20$: C, 42.69; H, 6.76. Found: C, 42.68; H, 6.45.

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