Acyl Transfer as a Problematic Side Reaction in Polymer-Supported Oligosaccharide Synthesis

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Under a wide variety of glycosylation conditions acyl transfer to the polymer support competed with glycoside formation, including the pivaloyl protecting group. As well as acyl transfer, many glycosylations also led to the formation of polymer-bound β-1,2-linked oligomers of the donor. Using ethyl 2,6-di-*O*-pivaloyl-3,4-*O*-isopropylidene-β-D-galactothiopyranoside as donor under promotion of *N*-iodosuccinimide/silver trifluoromethanesulfonate in the presence of 2-methyl-2-butene, an 82% yield of glycoside was obtained along with pivaloylated polymer. Subsequent work showed that increasing the steric bulk about the alcoholic acceptor in conjunction with this 2-*O*-pivaloyl-protected glycosyl donor completely suppresses this side reaction, giving a nearly quantitative yield of glycoside. This contraintuitive approach of decreasing the reactivity of both the donor and the acceptor to minimize a side reaction is rationalized by assuming that the barrier to acyl transfer is more sensitive to the protecting groups than that of glycosylation. These developments led to a polymer-supported synthesis of the branch point trisaccharide of the group B type 1A *Streptococcus* capsular polysaccharide.

Introduction

As part of our institute's program to design and develop vaccines[2] against group B streptococcal infections the syntheses of fragments of the serotype specific capsular polysaccharides are being undertaken.[3] In particular polymer-supported synthetic methodologies are under development. Such methodologies are in principle amenable to the production of the large number of derivatives and analogues that are critical for vaccine design and development.[4] Furthermore, the possibilities of developing automated methods[5] which could allow for the development of fully synthetic vaccines is alluring.[6] The present strategy uses the soluble monomethyl ether of polyethylene glycol ($MeO-(CH_2CH_2O)_n-OH$, MPEG) as the polymer support[7] and the dioxyxylene (p-$OCH_2-C_6H_4-CH_2O-$, DOX) linker.[8] This combination, **1** ((MPEG)(DOX)OH), has one benzylic ether bond between the polymer and the linker and one free benzylic hydroxyl to link to the growing oligosaccharide chain.

As a primary target a single repeat unit of the type 1A capsular polysaccharide was chosen, Figure 1. The syntheses of oligosaccharides corresponding to this structure were reported from this institute.[9] From a synthetic point of view this pentasaccharide provides two key challenges, namely, the 3,4-branching on the β-D-Gal residue and the NeuNAc(α2,3)Gal terminal linkage. In this paper we concentrates on the β-D-Gal 3,4-branching problem.

Thus, a D-Gal glycosyl donor was needed which could form a β-linkage and allow for chain extension at O-3 and O-4. As a first design, donors based on the ethyl 2,6-di-*O*-acyl-3,4-*O*-isopropylidene-β-D-galactothiopyranoside structures were tested. The 2-*O*-acyl group allows for neighboring group participation to facilitate formation of β-linkages.[10] The 3,4-*O*-isopropylidene group can be cleaved by mild acid, and the resulting diol can in principle be selectively glycosylated at the equatorial O-3 hydroxyl to allow for 3,4-branching.[11] Unfortunately, our first attempts at glycosylating the (MPEG)(DOX)OH with the 2,6-di-*O*-benzoyl donor **2** produced a complex mixture of products, Scheme 1. Most of these products can be traced to a competing acyl transfer from O-2 of the

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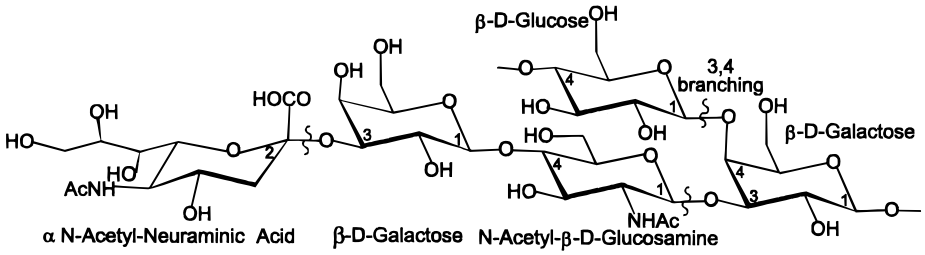


Figure 1. Schematic representation of a single repeat unit of group B *Streptococcus* type 1A capsular polysaccharide. The two key synthetic challenges are also indicated.

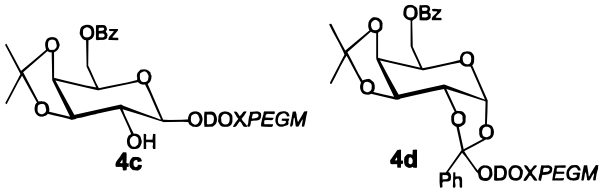
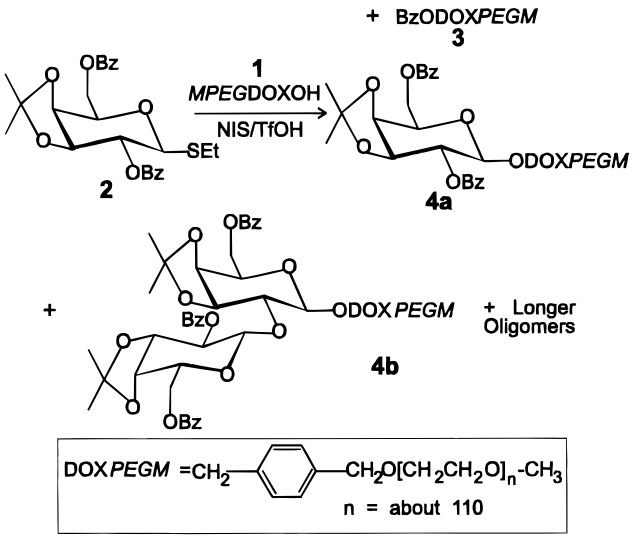


Figure 2. 2-OH glycoside **4c** and orthoester **4d**.

Scheme 1. Complex Reaction Mixture from Reaction of Donor 2 with Polymer-Supported Acceptor 1



glycosyl donor to the acceptor; cf. **3**. The acylated acceptor **3** is a dead end product for polymer-supported synthesis and is especially devastating if the acyl group is used as a cleavable protecting group.

As exemplified by the quote "Unfortunately, many carbohydrate chemists do not seem to be aware of these side-reactions as low yields with O-2 acetylated donors are still frequently reported",[12] this side reaction is poorly understood. Besides the *O*-acylated acceptor in some cases the desired β-glycoside is formed but with the O-2 acyl group missing, i.e., a hydroxyl at O-2; cf. **4c** Figure 2.[13] As well, the unwanted α-isomers with the hydroxyl at O-2 can be part of the product mixture. A second type of side product is 1,2-linked disaccharides.[14] With this knowledge and careful analysis of the ^{1}H NMR spectrum of the polymer-bound reaction mixture, the products that have been identified from the reaction of **1** and **2** are the benzoylated acceptor **3**, (MPEG)(DOX)OBz, the desired β-glycoside **4a** and the β1,2 oligomers **4b**, Table 1. The OH-2 glycoside **4c** is also likely formed as unidentified isopropylidene resonances were found but not assigned. Side products **4b** and **4c** are particularly problematic for polymer-supported schemes as they create erroneous sequences.

This side reaction has been reported for the following leaving groups: halide,[15] 2,3-diphenyl-2-cyclopropen-1-yl,[16] acetate,[17] 1,2-*O*-cyanoethylidene,[18] orthoester,[19] trichloroacetimidate,[20] and alkylthio.[21] The acyl group has been unequivocally shown to originate from O-2 by labeling experiments in two cases.[22] In a solution synthesis such products are removed by chromatography, only affecting the yield of glycoside. In a polymer-supported synthesis where the acceptor alcohol is attached to the polymer all such products are recovered at the end of a glycosylation reaction. To efficiently proceed with polymer-supported methodologies, it is very important to establish the mechanism of this reaction so that conditions can be found to eliminate it.

Following from the results of solution studies the use of the sterically demanding pivaloyl to minimize orthoester formation has been recommended.[23] The relationship between orthoester formation and acyl transfer has never been clearly elucidated. Several early mechanistic studies have suggested that orthoesters are intermedi-

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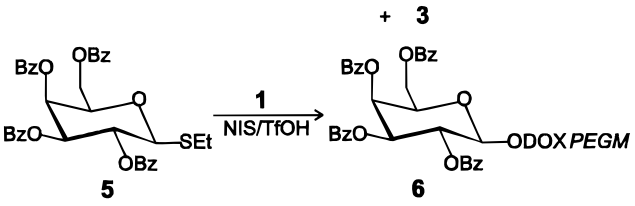
Table 1. Diagnostic ^{1}H NMR Spectral Data for 3, 4a, 4b, 4d, 13a, 13b, and 14[a]

compd	H-1 ($J_{1,2}$)	H-2 ($J_{2,3}$)	DOX-CH_2 (J)	benzoyl$_o$ (J)	isopropylidene
3			5.35 s	8.07 br d (7.6)	
4a		5.33 br t (7.7)	4.83 d (12.3)	8.10 br d (7.4), 8.02 br d (7.8)	1.65 s, 1.36 s
4b		5.25 br t[b] (7.7)	-		1.63 s, 1.36 s
4b		5.17 br t[c] (7.7)	-		shoulders
4d	5.76 d (5.0)	3.89 br d	4.48 d, −	7.99 br d, 7.60 br d	1.43 s, 1.29 s
4d + DBU	5.76 br s	4.19 m	4.65 brs, 4.49 brs	−, 7.63 br d	1.41 s, 1.29 s
13a		5.29 br t (7.8)	4.82 d (12.5)	8.03 br d, 8.00 br d	1.64 s, 1.36 s
13b		5.22[b] (7.8)			shoulders
14			5.12 s	7.93 br d	

[a] See Schemes 1 and 4, Table 2 and Figure 2. Chemical shifts in parts per million and coupling constants in hertz. [b] Disaccharide. [c] Trisaccharide.

Scheme 2. Benzoyl Transfer from Reaction of Donor 5 and 1



ates in neighboring-group-assisted glycosylation reactions which undergo Lewis or Brønsted acid catalysis to the desired 1,2-*trans*-glycoside.[24] In one case kinetic evidence was presented to support this hypothesis.[25] Acyl transfer was postulated as a side reaction of this rearrangement process.[26] This work provides experimental results supplemented by some theoretical studies which give some ideas on how to minimize this side reaction.

Results and Discussion

Model experiments demonstrated that ethyl 2,3,4,6-tetra-*O*-benzoyl-β-D-galactothiopyranoside (**5**)[27] glycosylates (MPEG)(DOX)OH in dichloromethane promoted by *N*-iodosuccinimide and catalytic trifluoromethanesulfonic acid (NIS/TfOH) to give **6**. However, even this preparation leads to about 7% benzoyl transfer product **3**, Scheme 2. Under very similar conditions the corresponding 3,4-*O*-isopropylidene-blocked donor **2** gave the complex mixture (Table 2, entry 1, and Scheme 1). These two results imply that **2** is more prone than **5** toward acyl transfer.

It was essential to determine if this side reaction was a property of the polymer or the donor. Thus, acceptor methyl 4-hydroxymethylbenzoate (**7**) was reacted with **2** under NIS/TfOH conditions, Scheme 3. This reaction produced a complex mixture from which the following products were isolated: the product of benzoate transfer, methyl 4-benzoyloxymethylbenzoate (**8**), the expected β-glycoside **9a**, the α-glycoside **9b**, the reducing sugar **9c**, a β1,2-linked disaccharide (**9d**), and other unidentified products (see Tables 1 and 2 in the Supporting Information for ^{1}H and ^{13}C NMR data). The isolation of donor-derived β1,2-disaccharide **9d** supports the thesis that such side reactions are a general property of neighboring-group-assisted glycosylation reactions. 1D selective NOESY and TOCSY experiments were used for the complete structural elucidation of **9d**. These experiments established connectivities between the β-anomeric proton and the H-2 of the α-linked residue. Also, the α-anomeric proton showed connectivity to a benzoyl ortho proton (not shown), confirming the presence of the benzoate at the reducing terminus. The results of this glycosylation experiment suggest that acyl transfer is a property of donor **2** and not an artifact of the polymer-supported methodology.

Next, the conditions of glycosylation between **1** and **2** were varied to see if factors such as solvent, amounts and nature of the promoters, or temperature could be manipulated to minimize acyl transfer. Pertinent results are presented in Table 2. Entry 1 is the result referred to in Scheme 1. All of the conditions are typical of NIS/TfOH glycosylations except that much more triflic acid (1.4 equiv) was used. This necessity of excess promoter is usual with glycosylations in the presence of PEG derivatives and is ascribed to complexation between the electrophilic promoters and the PEG ether oxygens. Lowering the amount of triflic acid led to formation of predominantly the orthoester **4d**, Figure 2. Its structure was assigned on the basis of the α-anomeric proton resonance at $\delta = 5.76$ ppm and $J = 5.0$ Hz and the upfield-shifted benzoate resonance at $\delta = 7.6$ ppm in the ^{1}H NMR spectrum. The latter resonance did not disappear after treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene, DBU, in methanol, which cleaves benzoyl esters and caused disappearance of the benzoyl resonance at $\delta = 7.99$ ppm. The orthoester was also completely cleaved from the (MPEG)(DOX) by mild acid treatment. It should be noted that all NIS/TfOH reactions are quenched with diisopropylethylamine (DIPEA) before workup and it is likely that the neutral orthoester is formed after this addition.

Changing to the more polar solvent acetonitrile did not change the result, entry 3. Increasing the temperature to room temperature led to recovery of starting acceptor alcohol (MPEG)(DOX)OH, entry 4. Adding the triflic acid at ice-bath temperature and allowing the reaction to warm to room temperature also did not improve the result. Next, the trityl ether (MPEG)(DOX)OTr (**10**) was used as acceptor in the hope that this removal of the proton would minimize acyl transfer. In a previous study the disruption of an intramolecular hydrogen bond of the acceptor alcohol was associated with minimization of acyl transfer.[28] As well, the triflic acid was replaced with silver triflate, but the reactivity resembled the parent hydroxyl with TfOH; cf. entries 6−8 to entries 1−5, and 9. Finally, the first substantial improvement was made by adding

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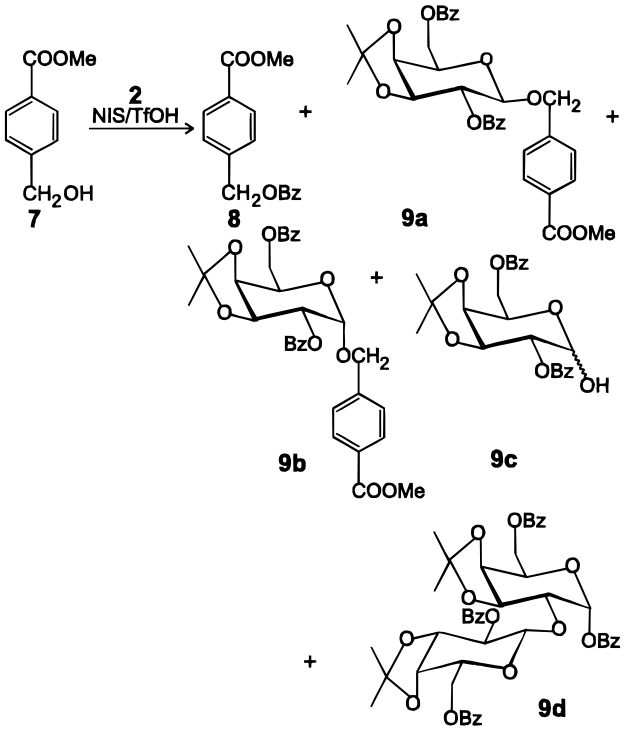
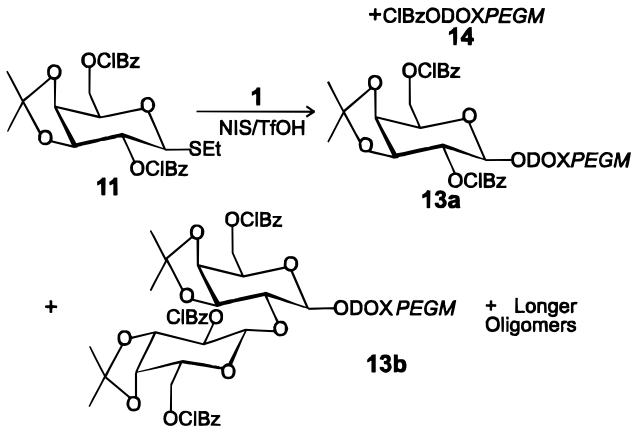
Table 2. Glycosylations of (MPEG)(DOX)OH (1) and (MPEG)(DOX)OTr (10) with Donor 2

entry	donor (equiv)	acceptor (equiv)	promoter (equiv)	temperature, time	solvent, additive	result
1	**2** (1.5)	**1** (1.0)	NIS (5.0), TfOH (1.4)	0−5 °C, 10−15 min	4Å sieves	20% **4a**, **4b**, **3**, and others
2	**2** (1.5)	**1** (1.0)	NIS (5.0), TfOH (0.7)	0−5 °C, 10−15 min	4Å sieves	>90% orthoester **4d**
3	**2** (1.5)	**1** (1.0)	NIS (5.0), TfOH (0.7)	0−5 °C, 10−15 min	4Å sieves	>90% orthoester **4d**
4	**2** (1.5)	**1** (1.0)	NIS (5.0), TfOH (0.7)	20 °C, 10−15 min	4Å sieves	>90% **1**, and 5% **4d**
5	**2** (1.5)	**1** (1.0)	NIS (5.0), TfOH (1.4)	add 0−5 °C to 20 °C, 2.5 h	4Å sieves	20% **4a**, **4b**, **4d**, **3**, and others
6	**2** (1.5)	**10** (1.0)	NIS (5.0), AgOTf (1.1)	20 °C, 2.5 h	4Å sieves	>90% **1** and 5% of **4d**
7	**2** (1.5)	**10** (1.0)	NIS (5.0), AgOTf (1.1)	0−5 °C, 90 h	CH_2Cl_2	>90% **1**, and traces of others
8	**2** (1.5)	**10**	NIS (5.0), AgOTf (1.1)	0−5 to 20 °C 2.5 h	CH_2Cl_2, 2-Me-but	40% **4a**, **4b**, **3**, and traces of others
9	**2** (1.5)	**1** (1.0)	NIS (5.0), AgOTf (1.1)	0−5 to 20 °C 2.5 h	CH_2Cl_2, 2 Me-but	40% **4a**, **4b**, **3**, and traces of others
10	**2** (1.5)	**1**	NIS (2.5), AgOTf (1.1)	20 to 40 °C, h	CH_2Cl_2, 2 Me-but	55% **4a**, **4b**, **3**, and traces of others

Scheme 3. Benzoyl Transfer and 1,2-Disaccharide Formation from Solution Reaction of Donor 2



Scheme 4. Chlorobenzoyl Transfer and 1,2-Disaccharide Formation from Reaction of Donor 11 and 1



2-methyl-2-butene as acid scavenger, but still the glycoside was only formed in 40% yield, entries 8 and 9. Increasing the temperature to 40 °C improved the yield to 55% , entry 10. It should be noted that molecular sieves are often detrimental to NIS/AgOTf-promoted reactions (cf. Table 2, entry 6) and 2-methyl-2-butene is a viable alternative. This optimized condition led to a nearly 3-fold improvement in yield (55% vs 20%) and may prove of value for other glycosylations. However, these conditions are not sufficiently efficient for polymer-supported reactions.

Next, the benzoyl groups were changed to the electronically deactivated 4-chlorobenzoyl **11** or the sterically hindered pivaloyl **12**. With **11** even with the optimized conditions a complex mixture (**13ab**, **14**) was formed, Scheme 4. With donor **12** the first major improvement was made as the only two products isolated were the glycoside **15** and the pivaloylated acceptor (MPEG)-(DOX)OPiv (**16**), in a ratio of 1.2:1 (start at 0 °C and increase to rt). To the best of our knowledge this is the first report of pivaloyl transfer in a glycosylation reaction although an intramolecular pivaloyl migration has been reported recently.[29] Pivalate orthoesters are well known.[30] The pivaloyl group is recommended to prevent orthoester formation during glycosylation reactions.[31] Increasing the temperature to room temperature improved the glycoside to acyl transfer ratio to 5.2:1, corresponding to a 82% yield. Since the pivaloyl group is a permanent protecting group, this last result is synthetically useful. The isopropylidene protecting group was cleaved by treatment with 50% aqueous acetic acid at 60 °C for 16 h to give 3,4-diol **17**.

To further characterize these compounds, the products were cleaved from the polymer using the recently developed conditions of scandium(III) trifluoromethanesulfonate, $Sc(OTf)_3$, and acetic anhydride.[32] These conditions cleave the C−O bond between the benzylic carbon of the DOX and the terminal oxygen of the MPEG. Also, all hydroxyls are acetylated under these conditions. This reaction applied to a small portion of the **15** and **16** mixture gave a mixture of products containing predominantly [4-*O*-acetoxymethyl]benzyl 3,4-di-*O*-acetyl-2,6-di-*O*-pivaloyl-*β*-D-galactopyranoside (**18**) and 4-*O*-acetoxymethylpivaloyloxymethylbenzene (**19**), Scheme 5. Thus, the isopropylidene protecting group was cleaved under these conditions. This reaction may have applications to other synthetic problems. Diol **17** also gave **18** under these conditions. The polymer is recovered as its *O*-acetylated derivative **20**.

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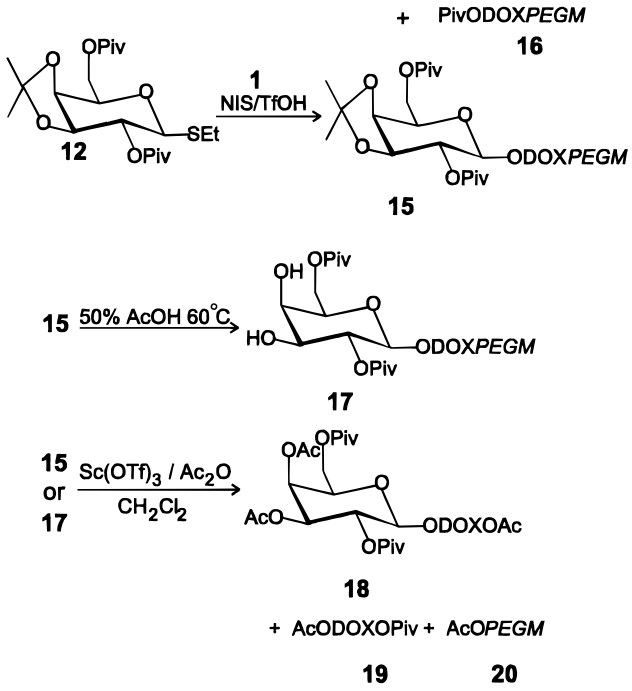
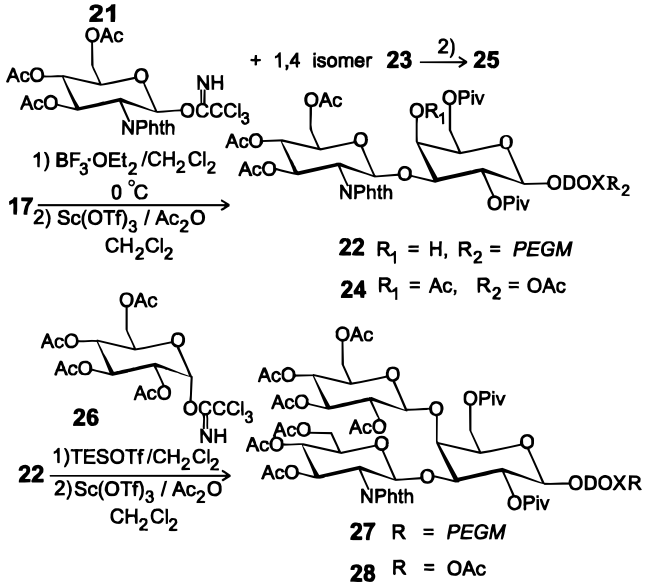
(31) (a) Kunz, H.; Harreus, A. *Liebigs Ann. Chem.* **1982**, 41. (b) Sato, S.; Nunomura, T.; Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1988**, *29*, 4097. (c) Sato, S.; Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1988**, *29*, 5267. (d) Nunomura, S.; Ogawa, T. *Tetrahedron Lett.* **1988**, *29*, 5681.
(32) Mehta, S.; Whitfield, D. M. *Tetrahedron Lett.* **1998**, *39*, 5907.

Scheme 5. Pivaloyl Transfer but No 1,2 Disaccharide Formation from Reaction of Donor 12 and 1



Scheme 6. Formation and Isolation of Branched Trisaccharide 28



Glycosylation of diol **17** with the known glycosyl donor 3,4,6-tri-*O*-acetyl-2-deoxy-2-*N*-phthalimido-*β*-D-glucopyranosyl trichloroacetimidate (**21**)[33] led to a mixture of *β*-1,3-linked (**22**) and *β*-1,4-linked (**23**) polymer-bound disaccharides and unreacted **17** in a ratio of 3.0:1.4:1.0, Scheme 6. Their identities were confirmed by cleavage mediated by $Sc(OTf)_3$ to yield disaccharides **24** and **25**. The synthesis was completed by reaction with known donor 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl-*O*-trichloroacetimidate (**26**)[34] to yield a mixture of products. Cleavage from the polymer mediated by $Sc(OTf)_3$ led to predominantly the 3,4-branched trisaccharide **28**. Apparently the 1,4-linked **23** is less reactive than **22**. The substitution pattern of **28** was established from a NOESY spectrum where cross-peaks between GlcNPhth H-1 and Gal H-3 as well as between Glc H-1 and Gal H-4 were observed. Another characteristic feature of **28** is an unusually upfield-shifted acetyl methyl resonance (1.57 ppm, Table 3). A HMBC spectrum was used to assign this resonance to the O-2 acetyl of the Glc residue (not shown). The HMBC spectrum also provided additional proof of the connectivities.

Since the steric bulk of the donor appeared to be beneficial for minimizing acyl transfer, it was decided to increase the steric bulk about the acceptor by synthesizing the modified DOX linkers α,α′-dimethyldioxyxylene, M2DOX, and α-methyldioxyxylene, MDOX. A limited study of acceptors in the orthoester glycosylation procedure found that increased steric bulk minimized acyl transfer, lending credence to this postulate.[35]

The α,α′-dimethyl linker M2DOX was prepared by a straightforward series of reactions, Scheme 7. The hydroxyl of methyl 4-hydroxymethylbenzoate (**29**), was protected as its *tert*-butyldiphenylsilyl ether **30**, and then **30** was reacted with methyl Grignard reagent to produce the tertiary alcohol **31**. This alcohol was protected as its benzoate **32** followed by cleavage of the silyl ether with tetrabutylammonium fluoride, TBAF, to give the primary alcohol **33** and finally reaction to form the trichloroacetimidate **34** in an overall yield of 22% from **29**. Compounds **31**−**34** all stain purple after spraying with $5\%_{aq}$ H_2SO_4 and heating, which facilitates their identification by TLC. Boron trifluoride etherate promoted etherification of (MPEG)OH produced **35** which was converted to alcohol acceptor **36** by basic hydrolysis. Attempts to glycosylate this acceptor with donor **2** did not go to completion even with repetitive treatments or higher temperatures, presumably due to too much steric hindrance. However, no traces of benzoate **35** were detected, which supports the hypothesis of the importance of steric bulk for minimization of acyl transfer.

To increase the reactivity of the acceptor, the α-monomethyl derivative of DOX, MDOX, was prepared, Scheme 8. A modification of a procedure to produce differently protected trialkylsilyl derivatives of MDOX, cf. **40**, was followed.[36] Thus, the ketoester, ethyl 4-acetylbenzoate (**37**) was reduced nonstereospecifically to the racemic mixture of alcohols **38**. Then **38** was protected as its *tert*-butyldiphenylsilyl ether **39** and the ester reduced with lithium aluminum hydride to the primary alcohol **40**. The alcohol was activated as its trichloroacetimidate **41** in an overall yield of 68% from **37**. Compounds **38**−**41** also stain purple after spraying with $5\%_{aq}$ H_2SO_4 and heating, which facilitates their identification by TLC. Subsequent etherification of (MPEG)OH produced **42**. It should be noted that for this reaction molecular sieves were absolutely necessary as only unreacted (MPEG)OH was isolated in their absence. Acetylation of **42** with acetic anhydride and sodium acetate produced negligible acetyl incorporation as detected by ^1H NMR, suggesting greater than 95% incorporation of the linker. The free alcohol (MPEG)(MDOX)OH (**43**) was liberated by treatment with

(33) Leung, O.-T.; Douglas, S. P.; Pang, H. Y. S.; Whitfield, D. M.; Krepinsky, J. J. *New J. Chem.* **1994**, *18*, 349.
(34) Schmidt, R. R.; Stumpp, M. *Liebigs Ann. Chem.* **1983**, 1249.
(35) Garegg, P. J.; Kvarnström, I. *Acta Chem. Scand. B* **1977**, *31*, 509.
(36) Pilcher, A. S.; Hill, D. K.; Shimshock, S. J.; Waltermire, R. E.; DeShong, P. *J. Org. Chem.* **1992**, *57*, 2492.

Table 3. ^{1}H NMR Spectral Data for 24, 25, and 28[a]

comp	H-1 ($J_{1,2}$)	H-2 ($J_{2,3}$)	H-3 ($J_{3,4}$)	H-4 ($J_{4,5}$)	H-5 ($J_{5,6}$)	H-6 ($J_{5,6'}$)	H-6′ (-$J_{6,6'}$)	Bn-CH$_2$ (-$J_{H,H}$)
24	5.31 d	4.17 dd	5.81 dd	5.17 br t	3.75 br dt 4.35 dd	4.17 dd	5.05 s (2)	
GlcN	(8.0)	(10.8)	(9.0)	(10.1)	(2.4)	(2.7)	(12.1)	
Gal	4.37 d	4.96 dd	3.95 dd	5.38 br d	3.82 br t	4.13 m	4.13 m	4.74 d, 4.46 d
	(7.8)	(9.7)	(3.7)	(<0.5)				(11.9)
ArH	Phth 7.79 m (2), 7.70 m (2); DOX 7.24 d (2), 7.18 d (2) J = 8.0							
Ac	2.13 s (3), 2.12 s (3), 2.07 s (3), 2.01 s (3), 1.82 s (3)							
Piv	1.20 s (9), 1.01 s (9)							
25	5.30 d	4.40 dd	5.92 dd	5.15 br t	3.82 br dt 4.21 m	4.21 m	5.06 s (2)	
GlcN	(8.4)	(10.7)	(9.3)	(10.0)				
Gal	4.33 d	4.81 dd	4.83 dd	4.00 br d	3.64 br dd 4.33 dd	4.26 dd	4.72 d, 4.54 d	
	(7.7)	(10.6)	(2.5)	(<0.5)	(4.0)	(7.7)	(12.0)	(12.4)
ArH	Phth 7.79 br m (2), 7.69 m (2); DOX 7.26 d (2), 7.20 d (2) J = 7.9							
Ac	2.11 s (3), 2.08 s (3), 2.02 s (3), 1.96 s (3), 1.87 s (3)							
Piv	1.20 s (9), 0.85 s (9)							
28	5.33 d	4.24 m	5.89 dd	5.19 br t	3.76 br dt	4.38 dd	4.19 dd	5.04 s (2)
GlcN	(8.3)	(10.7)	(9.1)	(9.9)	(4.4)	(4.2)	(12.3)	
Gal	4.31 d	4.95 dd	4.09 dd	4.11 br d	3.66 br dd	4.17 m	4.17 m	4.64 d, 4.43 d
	(7.8)	(10.1)	(3.4)	(<0.5)	(4.4)	(6.9)		(11.7)
Glc	5.07 d	4.86 dd	5.61 br t	5.11 br t	3.92 br dt	4.26 m	4.26 m	
	(8.1)	(9.5)	(9.7)	(9.7)				
ArH	Phth 8.10 m (1), 7.79 br m (1), 7.71 m (2); DOX 7.23 d (2), 7.18 d (2) J = 8.0							
Ac	2.12 s (3), 2.11 s (3), 2.07 s (6), 2.02 s (3), 2.00 s (3), 1.85 s (3), 1.57 s (3)							
Piv	1.24 s (3), 1.18 s (6), 1.16 s (9)							

[a] See Scheme 6. Chemical shifts in parts per million and coupling constants in hertz.

Table 4. ^{13}C NMR Spectral Data for Oligosaccharides 24, 25, and 28[a]

compd	C-1	C-2	C-3	C-4	C-5	C-6	Bn-CH$_2$
24GlcN	99.8	54.8	70.0	70.8	71.9	61.2	65.9
Gal	97.4	69.9	74.3	69.2	71.2	62.2	68.9
C═O	Piv 178.0, 176.3; Ac 170.9, 170.8, 170.1, 170.0, 169.4; Phth 168.1 br						
ArC	DOX 136.6, 135.5, 128.2, 128.1; Phth 134.2, 131.5, 123.6						
Piv	C 38.8, 38.7;		CH$_3$ 27.1, 26.8				
Ac	21.0, 20.8, 20.64, 20.61, 20.4						
25GlcN	98.2	54.4	70.0	69.1	71.5	61.9	66.0
Gal	98.9	67.7	72.5	74.6	72.2	63.7	68.8
C═O	Piv 178.0, 175.3; Ac 170.9, 170.8, 170.5(2), 170.1, 169.4						
ArC	DOX 137.1, 135.5, 128.3, 128.2; Phth 134.0 br, 131.6 br, 126.8 br						
Piv	C 38.8, 38.7; CH$_3$ 27.2, 26.8						
Ac	21.0, 20.7, 20.6, 20.5, 20.4						
28GlcN	98.8	71.5	71.4	69.8	73.0	61.7	66.0
Glc	99.5	55.0	69.07	69.07	72.5	61.8	68.8
Gal	96.6	71.0	77.5	72.06	72.14	63.5	
C═O	Piv 178.2, 176.4; Ac 170.8, 170.8, 170.5, 170.3, 169.9, 169.7, 169.5(3); Phth 167.6 br						
ArC	DOX 137.0, 135.3, 128.2, 128.1; Phth 134.2 br, 131.5, 124.9, 123.6						
Piv	C 38.9, 38.7;		CH$_3$ 27.1, 26.8				
Ac	21.0, 20.77 (2), 20.75, 20.7, 20.6, 20.5, 19.3						

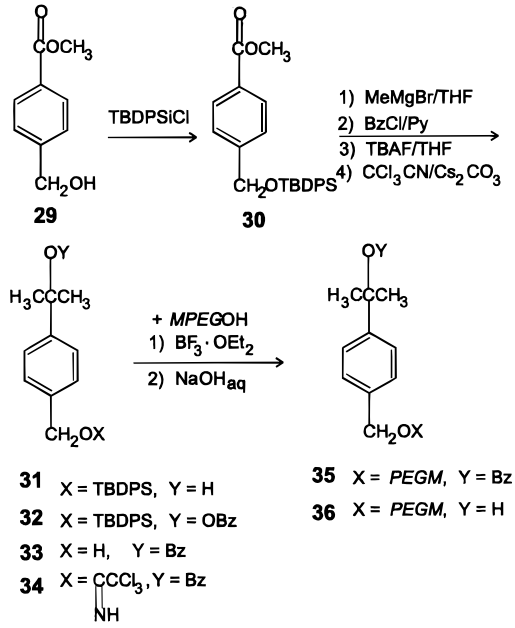
[a] See Scheme 6. Chemical shifts in parts per million.

TBAF. The ^{1}H and ^{13}C NMR spectral data for all linkers are compiled in Tables 3 and 4 of the Supporting Information, respectively.

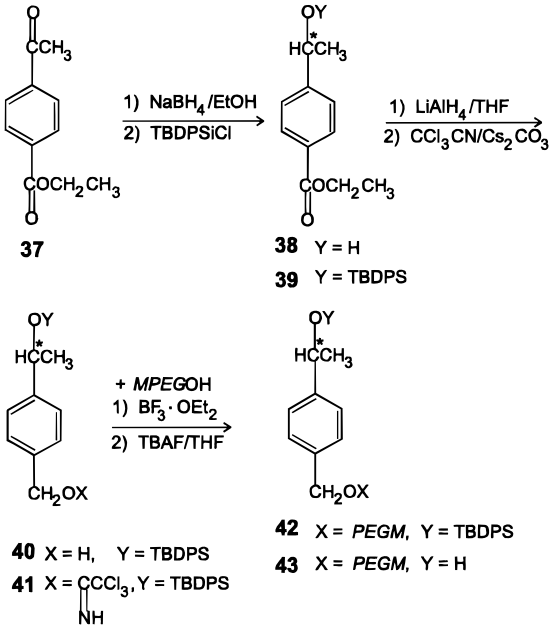
In this case alcohol **43** could be glycosylated successfully under carefully controlled conditions by treatment with donor **2** at −10 to −20 °C using NIS and two additions of TfOH to yield **44ab** and 15% benzoyl transfer product **45**, Scheme 9. The **ab** nomenclature will be used for **44ab** and all subsequent products in which the diastereomers can be distinguished by NMR, Tables 5 and 6. Benzoate **45** had been produced by an alternate less efficient synthesis of **22** (not shown), so its ^{1}H NMR spectrum was known (see the Supporting Information). The combination of NIS/AgOTf and 2-methyl-2-butene at temperatures between 0 and 40 °C in dichloromethane did not work with **43** as acceptor due to formation of a product tentatively identified as the styrene **46** from its ^{1}H NMR spectrum (Table 8, Supporting Information). Reaction temperatures lower than −20 °C or only one addition of TfOH led to the isolation of predominantly the isomeric orthoesters **47ab**. The source of the chirality in **47ab** is not known for certain but is presumed to arise from the diastereomers at the α-methyl benzyl carbon of the MDOX and not from endo/exo isomers at the orthoester carbon since the analogous orthoester with DOX has only one set of resonances in its ^{1}H NMR spectrum. Orthoesters **47ab** could be isomerized to the glycoside **44ab** by treatment with TfOH at −20 to −10 °C, but benzoyl transfer (see product **45**) and some hydrolysis also occurred.

To proceed with the synthesis, the isopropylidene group was cleaved to yield 3,4-diol **48ab**, Scheme 10. The structure of **48ab** was confirmed after cleavage from the polymer with Sc(OTf)$_3$/Ac$_2$O to yield 3,4-di-*O*-acetate **49ab**. Traces of other unidentified products and the expected product from benzoyl transfer, 4-acetoxymethyl (1-(*R*,*S*)-benzoyloxyethyl)benzene (**50**), as well as traces of 4-acetoxymethyl (1-(*R*,*S*)-acetoxyethyl)benzene (**51**) were the only other products isolated. The diacetate **51** could result from unreacted **43**. Isopropylidene **48ab** also led to diacetate **29ab**; cf. **15** to **18**. The ^{13}C NMR spectra of **50** and **51** were unequivocally assigned by use of a long-range ^{13}C−^{1}H correlation, HMBC, experiment. Thus, the aromatic resonances of the MDOX at 142 ± 1 and

Scheme 7. Preparation of α,α′-Dimethyldioxyxylene, M2DOX, Linker



Scheme 8. Preparation of α-Methyldioxyxylene, MDOX, Linker

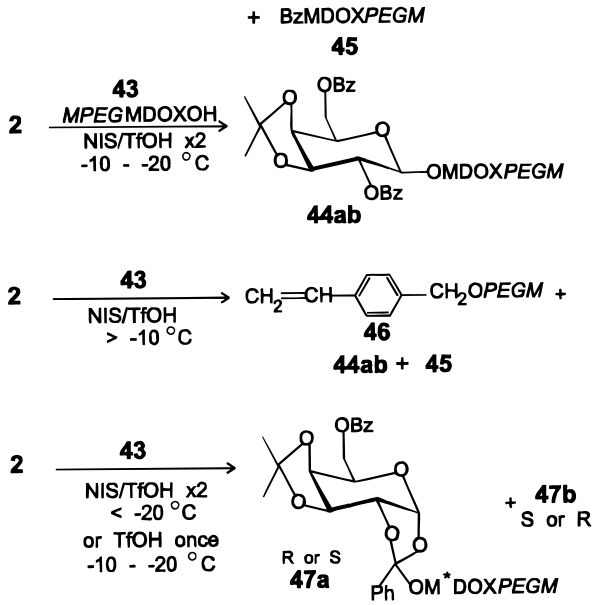


126.5 ± 1 ppm are assigned as *ipso* and *ortho* to the benzylic CH, whereas those at 135.5 ± 1 and 128.5 ± 1 ppm are *ipso* and *ortho* to the benzylic CH_2. These assignments are assumed for all MDOX-containing compounds, Table 6. The isolation and characterization of **50** unequivocally establishes that benzoyl transfer is to the secondary hydroxyl of **43**.

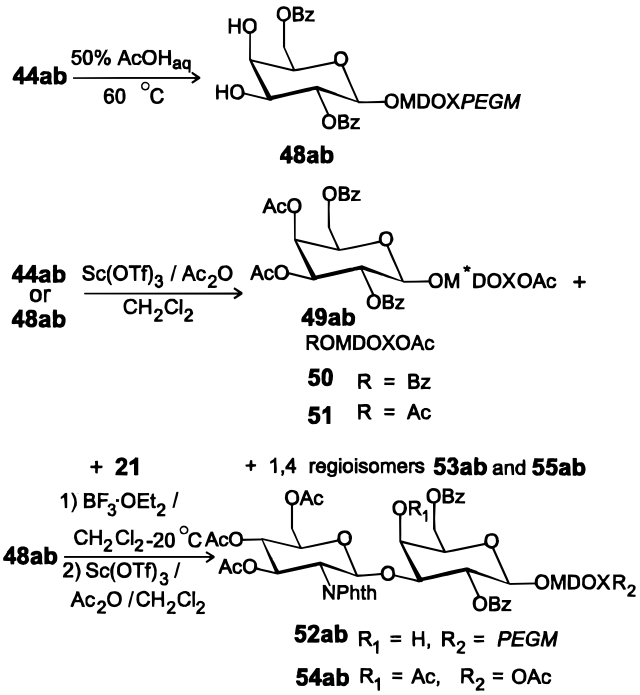
Most of the ^{1}H NMR resonances of **49ab** were doubled; see Figure 3. It proved possible to isolate a small quantity of one isomer by preparative TLC and hence to assign the spectra into two sets of resonances. Molecular modeling of these isomers using the version of MM[37] supplied

(37) Burkert, U.; Allinger, N. L. *Molecular Mechanics*; American Chemical Society: Washington, DC, 1982.

Scheme 9. Optimization of Glycosylation of (MPEG)(MDOX)OH (43), by Donor 1



Scheme 10. Formation and Isolation of 3,4-Diacetate 49ab and Elaboration into 1,3-Linked Disaccharides 54ab



with the Hyperchem program package suggests that the *R*-isomer should have the phenyl group projected toward C-6. A weak cross-peak between a MDOX aromatic proton and a H-6 proton in a NOESY spectrum allows for a tentative assignment of the absolute stereochemistry. This isomer has a ^{1}H chemical shift for H-1 at 4.42, whereas the other isomer has a shift at 4.76 ppm, Table 5. Such a large chemical shift difference is not observed for other chiral secondary aglygons attached to glucose.[38]

(38) (a) Trujillo, M.; Morales, E. Q.; Vázquez, J. T. *J. Org. Chem.* **1994**, *59*, 6637. (b) Morales, E. Q.; Padrón, J. I.; Trujillo, M.; Vázquez, J. T. *J. Org. Chem.* **1995**, *60*, 2537. (c) Padrón, J. I.; Vázquez, J. T. *Chirality* **1997**, *9*, 626.

Table 5. ^{1}H NMR Spectral Data for 49ab, 54ab, 60ab, 64ab, and 66[a]

comp	H-1 ($J_{1,2}$)	H-2 ($J_{2,3}$)	H-3 ($J_{3,4}$)	H-4 ($J_{4,5}$)	H-5 ($J_{5,6}$)	H-6 ($J_{5,6'}$)	H-6′ ($-J_{6,6'}$)	Bn-CH_2 ($-J_{H,H}$)	Bn-CH ($J_{H,H}$)
49a(*R*)	4.42 d (8.1)	5.54 dd (10.7)	5.08 dd (3.4)	5.48 br d (<0.5)	3.96 br t (6.7)	4.58 dd (6.8)	4.32 dd (11.2)	5.00 s	4.87 q (6.5)
ArH	Bz_o 8.02 d (2) J = 7.8, 7.93 d (2) J = 7.2, Bz_p 7.58 m (2), Bz_m 7.45 m (4); MDOX 7.04 br s (4)								
acetyl	2.20 s (3), 2.10 s (3), 1.87 s (3)								
CH_3	1.41 d								
49b(*S*)	4.76 d (7.9)	5.54 dd (10.7)	5.24 dd (3.4)	5.52 br d (<0.5)	4.03 br t (6.5)	4.43 dd (6.9)	4.25 dd (11.2)	5.00 s	4.81 q (6.5)
ArH	Bz_o 8.02 d (2) J = 7.8, 7.97 d (2) J = 7.1, Bz_p 7.58 m (2), Bz_m 7.45 m (4); MDOX 7.25 d (2), 7.19 d (2) J = 7.9								
acetyl	2.17 s (3), 2.06 s (3), 1.90 s (3)								
CH_3	1.32 d								
54aGal	4.2 m	5.12 m	3.82 m (3.4)	5.51 br d (<0.5)	3.82 m (7.5)	4.43 dd (5.3)	4.36 dd (11.5)	4.96 s	4.73 q (6.5)
GlcN	5.29 (8.3)	4.2 m (10.4)	5.60 dd (9.1)	5.29 m	3.73 m	4.2 m	4.2 m		
ArH	Bz_o 8.00 br d (2) J = 7.9, 7.55 m; Phth 7.73 brm (2), 7.55 brm; Bz_p 7.55 m Bz_m 7.45 m, 7.32 br t(2); MDOX 7.10 d (2), 7.07 d (2) J = 8.3								
acetyl	2.19 s (3), 2.09 s (3), 2.03 s (3), 1.96 s (3), 1.74 s (3)								
CH_3	1.25 d (3)								
54bGal	4.56 d (8.0)	5.12 m (10.1)	3.97 dd (3.4)	5.55 br d (<0.5)	3.91 br t	4.2 m	4.2 m	4.92 s	4.65 q (6.5)
GlcN	5.45 d (8.3)	4.2 m (10.7)	5.64 dd (9.1)	5.29 m	3.82 m	4.2 m	4.2 m		
ArH	Bz_o 8.07 br d (2) J = 7.9, 7.66 br d (2) J = 7.9; Phth 7.82 brm (2H), 7.55 brm, Bz_p 7.55 m Bz_m 7.45 m; MDOX 6.90 d (2), 6.82 d (2) J = 7.9								
acetyl	2.15 s (3), 2.05 s (3), 2.03 s (3), 1.98 s (3), 1.76 s (3)								
CH_3	1.12 d (3)								
60aGal	4.08 d (7.7)	4.88 m (9.9)	3.78 dd (3.7)	5.26 br d (<0.5)	3.60 br t 5.9	3.96 dd 7.3	3.89 dd 11.4	4.97 s	4.76 q (6.6)
GlcN	5.26 d (8.1)	4.10 m (10.6)	5.75 m (9.8)	5.11 m (10.1)	3.70 dt (2.6)	4.31 dd	4.12 dd (12.1)		
60bGal	4.45 d (7.7)	4.88 m (9.9)	3.91 dd (3.7)	5.29 br d (<0.5)	3.69 br t	4.06 m	4.06 m	5.01 s	4.72 q (6.6)
GlcN	5.18 d (8.1)	4.10 m (10.6)	5.75 m (9.8)	5.11 m (10.3)	3.65 dt (2.2)	4.29 dd	4.08 m (12.1)		
ArH	Phth 7.74 m (4), 7.65 m (4); MDOX 7.21 d (2), 7.17 d (2) J = 8.1; 7.18 d (2), 7.13 d (2) J=8.1								
acetyl	2.081, 2.077, 2.05, 2.039, 2.037, 2.00, 1.95, 1.94, 1.76, 1.70 10s (3)								
CH_3	1.30 d (3), 1.27 d (3)								
pivaloyl	1.19, 1.16, 1.09, 1.06, 0.94 (36)								
64aGal	4.06 d (7.7)	4.89 dd (10.4)	4.01 dd (3.4)	4.07 br d (<0.5)	3.51 dd	4.2 m	4.2 m	5.09 s	4.84 q (6.4)
GlcN	5.28 d (8.3)	4.2 m (10.7)	5.91 dd (9.3)	5.20 dd (9.8)	3.75 m	4.2 m	4.2 m		
Glc	5.07 d (8.0)	4.94 dd (9.9)	5.649 dd (9.4)	5.14 dd (9.8)	3.94 ddd (4.3)	4.39 dd	4.2 m (12.5)		
ArH	MDOX 7.24 d (2), 7.23 d (2) J=8.3								
acetyl	2.14 s (3), 2.12 s (3), 2.10 s (6), 2.05 s (6), 1.88 s (3), 1.25 s (3)								
CH_3	1.36 d (3)								
64bGal	4.47 d (7.6)	4.96 dd (10.4)	3.93 dd (3.4)	4.10 br d (<0.5)	3.61 dd	4.2 m	4.2 m	5.05 s	4.81 q (6.4)
GlcN	5.35 d (8.2)	4.2 m (10.7)	5.95 dd (9.3)	5.23 dd (9.5)	3.75 m	4.2 m	4.2 m		
Glc	5.09 d (8.0)	4.92 dd (9.9)	5.650 dd (9.4)	5.12 dd (9.8)	3.94 ddd (4.5)	4.41 dd	4.2 m (12.5)		
ArH	Phth 8.13 m (2), 7.82 m (2), 7.74 m (4); MDOX 7.27 d (2), 7.19 d (2) J = 8.3								
acetyl	2.16 s (3), 2.08 s (3), 2.06 s (6), 2.03 s (6), 1.87 s (3), 1.29 s (3)								
CH_3	1.34 d (3)								
pivaloyl	1.2 m								
66α Gal	5.10 m	4.79 dd (10.7)	4.43 m	4.1 m	4.1 m	4.1 m	4.1 m	-	-
GlcN	5.42 d (8.3)	4.2 m	5.82 dd	5.13 dd	3.77 m	4.39 m	4.1 m		
Glc	4.97 d (8.3)	4.78 dd	5.49 dd	5.04 dd	3.84 m	4.1 m	4.1 m		
66β Gal	4.33 d (8.5)	4.69 dd (10.2)	4.1 m	4.1 m	3.62 m	4.1 m	4.1 m		
GlcN	5.37 d (8.3)	4.2 m	5.81 dd (9.9)	5.15 dd	3.73 m	4.38 dd	4.1 m		
Glc	4.97 d (8.3)	4.78 dd	5.49 dd (9.2)	5.04 dd (9.5)	3.84 m	4.1 m	4.1 m		
ArH	Phth 8.04 m (2), 7.72 m (2), 7.66 m (4)								
acetyl	2.08, 2.05, 2.01, 1.98, 1.93, 1.80, 1.18, 1.11								
pivaloyl	1.1−1.2								

[a] See Schemes 10 and 11. Chemical shifts in parts per million and coupling constants in Hertz.

These *R*,*S* assignments are consistent with the assignments for model alkyl β-D-Gal compounds.[39] For both isomers strong cross-peaks are observed between H-1 and the benzylic methine but only weak or absent cross-peaks to the MDOX aromatics, suggesting that the CHO-1---C*HPh(MDOX) bond has the benzylic methine gauche and the phenyl anti to the C-1 methine.

Treatment of **48ab** with trichloroacetimidate **21** produced predominantly one product (**52ab**) along with its 1,4 regioisomer **53ab**, Scheme 10. The 3-*O*-selective

(39) Padrón, J. I.; Morales, E. Q.; Vázquez, J. T. *J. Org. Chem.* **1998**, *63*, 8247.

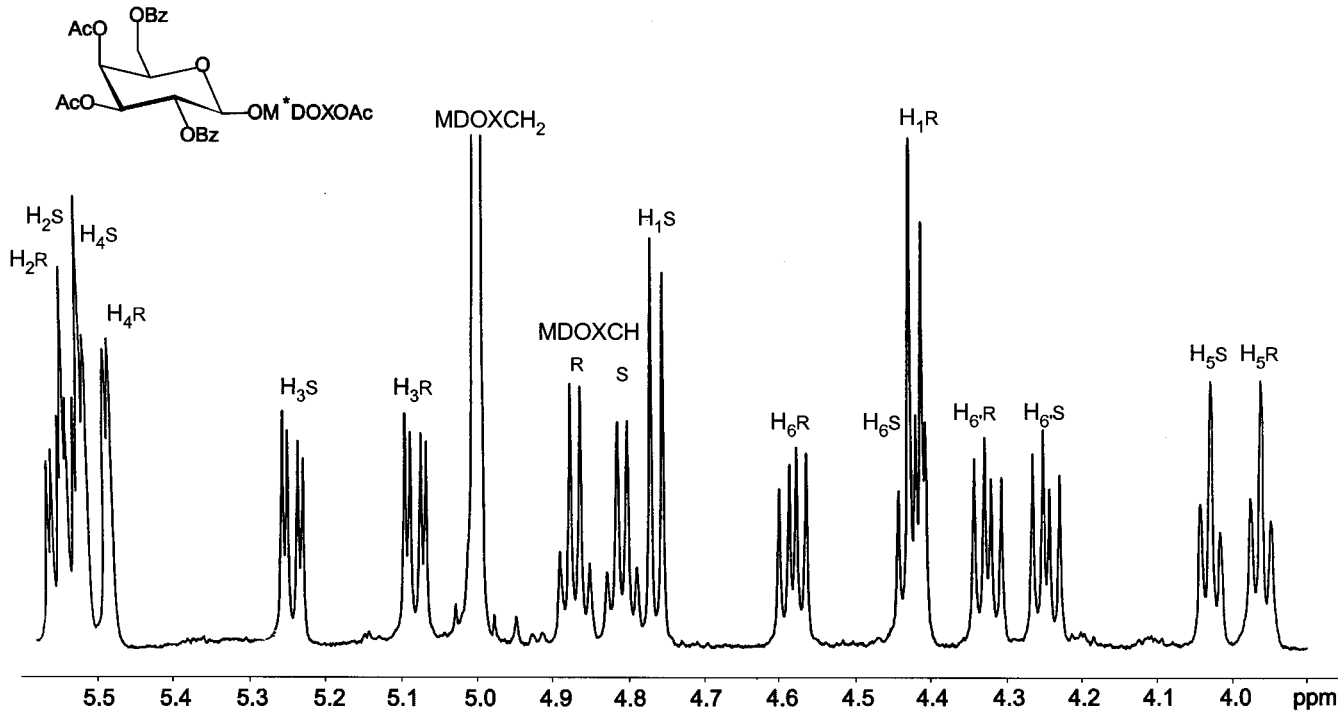


Figure 3. Partial ^{1}H NMR spectrum of diastereomeric glycosides **49ab**.

glycosylation was confirmed by cleaving **52ab** + **53ab** from the polymer using $Sc(OTf)_3/Ac_2O$, which in this case produced the diastereomeric peracetylated MDOXyl disaccharide glycosides **54ab** as the major products along with the regioisomers **55ab** and small amounts of unidentified products. Most of the resonances in the ^{1}H NMR spectrum of **54ab** were doubled due to the diastereomers at the α-methylbenzyl carbon of the MDOX linker, Table 5. The two diastereomers were not equally abundant (55:45), and so it was possible to assign sets of resonances. However, the absolute stereochemistry is not known. The tentative *R,S* assignments follow from those for **49ab**. The downfield shifts of the Gal H-4 (δ = 5.55 and 5.51 ppm) resonances confirmed the O-3 regiochemistry of the glycosylation and the J = 8.3 Hz coupling of the H-1 resonances of the GlcNPhth resonances confirmed the β stereochemistry of the linkage. Since all the easily measured coupling constants are identical the source of this pronounced difference in the two diastereomers of **54ab** is not known. Subtle conformational changes about the glycosidic linkages may be the origin of the induced shifts.

Although preparation of disaccharides **54ab** was possible by this route, the reaction was still not sufficiently efficient for polymer-supported synthesis. Therefore, alcohol **43** was reacted with donor **12**, and in this case only diastereomeric glycosides **56ab** were isolated, Scheme 11. Thus, the contraintuitive approach of decreasing the reactivity of both the donor and the acceptor by increasing the steric bulk leads to conditions that favor glycosylation over acyl transfer. Applying the sequence of hydrolysis of the isopropylidenes to afford diols **57ab** and then subsequent glycosylation with **21** led to the 1,3 disaccharides **58ab** and 1,4 disaccharides **59ab**. The 1,3 to 1,4 selectivity was 2.2 to 1. The structures were confirmed by cleavage from the MPEG using $Sc(OTf)_3/Ac_2O$ to yield **60ab** and **61ab**. Finally, disaccharides **58ab** + **59ab** were glycosylated with known donor **26** to yield **62ab** and 4,3 regioisomers **63ab**, respectively. Subsequent cleavage using $Sc(OTf)_3/Ac_2O$ yielded **64ab** and **65ab**. The overall yield for **64ab** was 12% for three glycosylations and two functional group transformations. This yield is based on 100% derivitization of the MPEG-5000. Comparable solution chemistry is unlikely to proceed in yields higher than 80% for glycosylations or 90% for functional group transformations, i.e., 80 × 80 × 80 × 90 × 90 = 41%. Given that the whole sequence can be done in six working days, once the building blocks are available, this represents a significant development.

Again, oligosaccharides **60ab** and **64ab** exhibit remarkable diastereotopic chemical shifts between the two isomers. Figure 4 shows the HSQC partial spectrum of the ring protons and carbons of disaccharides **60ab**. Many resonances show diastereomeric shifts in both the carbon and proton dimensions including the H-6 protons of the terminal GlcNPhth residue which are 10 bonds removed from the MDOX chiral center, Table 5. The *R,S* assignments follow from previous assumptions. The Gal H-1 resonances of the *R*-isomers at 4.05 (**60a**) and 4.06 (**64a**) ppm are unusually upfield and characteristic of these compounds. The connectivities in **64ab** were confirmed by observation of ROESY cross-peaks between GlcNPhth H-1 and Gal H-3 as well as between Glc H-1 and Gal H-4 (not shown). A characteristic of trisaccharides **64ab** is one unusually high-field acetyl methyl resonance 1.25 ppm (**64a**), 1.29 ppm (**64b**). A similar resonance was observed in the analogous trisaccharide derived from DOX **28** and was assigned to the O-2 acetyl of the Glc residue, Table 3. These resonances remained at high field after hydrogenation of **64ab**, which removed the MDOX linker, leading to the reducing trisaccharide **66**α/β, Table 5.

The central question in this work is the cause of the acyl transfer to the glycosyl acceptor. In a previous theoretical study we determined the most important intermediates of the neighboring-group-assisted glycosylation reaction between 2,6-di-*O*-acetyl-3,4-*O*-isopropylidene-1-deoxy-D-galactopyranosyl cation and metha-

Table 6. ^{13}C NMR Spectral Data for Oligosaccharides 49ab, 54ab, 60ab, 64ab, and 66[a]

compd	C-1	C-2	C-3	C-4	C-5	C-6	Bn-CH_2	Bn-CH
49a	98.5	69.8	70.94	67.33	70.85	61.70	66.0	77.5
CH_3	24.0							
49b	99.8	69.5	70.94	67.29	70.90	61.65	65.9	75.9
CH_3	21.0							
C=O	Ac 170.9, 170.3, 170.2, 170.1; Bz 165.94, 165.96, 165.1, 165.0							
ArC	$MDOX_{ip}$ 142.5, 142.0, 135.6, 135.1; $MDOX_o$ 128.4, 128.2, 126.8, 126.4; Bz_p 133.39, 133.35; Bz_o 130.0, 129.7; Bz_{ip} 129.5, 129.4; Bz_m 128.53, 128.48							
Ac	21.02, 20.98, 20.76, 20.72, 20.6, 20.5							
50							66.0	72.6
C=O	Ac 170.9, 170.3							
ArC	DOX_{ipCH} 141.9; DOX_{ipCH2} 135.5; DOX_{oCH2} 128.5; DOX_{oCH} 126.3							
CH_3	22.2							
Ac	21.3, 21.0							
51							66.0	72.0
C=O	Ac 170.9 Bz 165.8							
ArC	DOX_{ipCH} 141.8; DOX_{ipCH2} 135.5; DOX_{oCH2} 128.3; DOX_{oCH} 126.3; Bz_p 133.0; Bz_o 129.6; Bz_m 128.5							
CH_3	22.4							
Ac	21.0							
54aGal	98.1	68.8	77.55	69.4	71.1	62.7	65.0	77.0
GlcN	98.4	54.5	70.3	71.5	71.8	61.4		
54bGal	99.5	68.71	77.41	69.3	71.4	62.8	65.9	75.3
GlcN	98.4	54.5	70.3	71.5	71.8	61.4		
C=O	Ac 170.8 (2), 170.1 (2), 170.0 (4), 169.4 (2); Bz 166.1 (2), 164.5, 164.4; Phth 168.5 br							
ArC	$MDOX_{ip}$ 142.6, 142.0, 135.4, 134.9, $MDOX_o$ 128.9, 128.1, 126.8, 126.2; Bz_p 132.9, 133.2, 133.3; Bz_o 129.8, 129.7, 129.5; Bz_{ip} 129.34, 129.28, 128.8; Bz_m 128.5, 128.4, 128.2; $Phth_o$ 133.9; $Phth_{ip}$ 130.9; $Phth_o$ 123.2 br							
CH_3	22.2, 23.9							
Ac	21.0, 20.8, 20.7, 20.6, 20.3;							
60aGal	97.8	70.95	74.31	69.4	71.1	61.9	66.1	75.0
GlcN	97.3	54.8	69.9	69.0	71.9	61.2		
60bGal	98.7	71.0	74.48	68.9	71.1	62.6	65.9	75.1
GlcN	97.3	54.8	69.9	69.2	71.9	61.0		
C=O	Piv 176.2 (4); Ac 170.8 (2), 170.0 (6), 169.4 (2); Phth −							
ArC	$MDOX_{ip}$ 143.1, 141.4, 135.7, 134.9; $MDOX_o$ 128.2, 128.1, 127.1, 126.1; $Phth_o$ 134.1; $Phth_{ip}$ 131.5; $Phth_o$ 123.6 br							
CH_3	23.4, 21.8							
Ac	21.0, 20.8, 20.6, 20.4							
64aGal	97.6	71.61	74.7	73.02	72.1	64.0	66.0	74.2
GlcN	96.6	55.1	69.8	69.1	72.13	61.8		
Glc	98.9	71.57	73.1	69.08	71.3	61.7		
64bGal	98.4	71.8	74.9	72.4	71.8	63.3	66.2	74.1
GlcN	96.6	55.1	69.8	69.1	72.13	61.8		
Glc	98.8	71.52	73.00	69.08	71.3	61.7		
C=O	Piv 178.2, 176.3; Ac 170.8, 170.5, 170.3, 169.9, 169.7, 169.6, 169.5, 167.5; Phth −							
ArC	$MDOX_{ip}$ 143.5, 141.7, 135.5, 134.5; $MDOX_o$ 128.2, 128.0, 127.3, 126.0; $Phth_o$ 134.2; $Phth_{ip}$ 131.6; $Phth_o$ 124.9 br, 123.6 br							
Piv	31.2, 29.7, 27.2, 26.9							
CH_3	23.2, 21.7							
Ac	21.0, 20.8, 20.7, 20.6, 20.5, 20.4, 19.37, 19.33							
66αGal	90.3	70.8	71.1	73.5	68.4	63.5		
GlcN	96.7	55.2	70.0	69.3	72.2	61.8		
Glc	100.0	71.2	73.0	69.1	71.3	61.9		
66*β*Gal	96.1	73.8	74.3	72.5	72.3	63.5		
GlcN	96.8	55.0	70.0	69.3	72.2	61.8		
Glc	100.0	71.6	73.0	69.1	71.3	61.9		
C=O	Piv 178.1, 177.4; Ac 170.8, 170.5, 1702, 169.6, 169.2; Phth 167.5							
ArC	Phth 134.3, 125.0							
Piv	29.7, 27.1, 26.8							
Ac	20.8, 20.7, 20.6, 20.4, 19.3, 19.2							

[a] See Schemes 10 and 11. Chemical shifts in ppm.

nol.[40] It is valuable to reconsider the theoretical model in light of the current experimental findings and update our understanding of the reaction mechanisms. The most important intermediates and the corresponding energy diagram are shown in Schemes 12 and 13, respectively.

An S_N1 mechanism leads to the reactive intermediate **B**, which can isomerize by an intramolecular ring closure into intermediate **C**. This intramolecular reaction is expected to be very fast with a modest barrier of less than 4 kcal mol^{-1} due to conformational change. The modest conformational barrier can be attributed to the isopropylidene protecting group, which restricts the accessible conformations to the pseudorotational itinerary. Alternatively, **B** can react with the nucleophile in a highly favorable and fast reaction with a minimal barrier to form **H**, the intermediate leading to the wanted *β*-glycoside. The formation of intermediate **G**, leading to the α-glycoside, is significantly less favorable. The formations of **C** and **H** from **B** are competitive, and the intramolecular formation of **C** is expected to be favored for entropic reasons.[41]

Intermediates such as **C** can be isolated and probably play a central role in the reaction mechanism.[42] The reaction of **C** with the nucleophile methanol leads to ion−dipole complexes **D** and **F**, which are in equilibrium in favor of **D**, which is the overall most stable intermediate. It is proposed that **D** can lead to either orthoester formation or acyl transfer. In most mechanistic schemes,

(40) Nukada, T.; Bérces, A.; Zgierski, M. Z.; Whitfield, D. M. *J. Am. Chem. Soc.* **1998**, *120*, 13291.

(41) Paulsen, H. *Adv. Carbohydr. Chem. Biochem.* **1971**, *26*, 127.

(42) Crich, D.; Dai, Z.; Gastaldi, S. *J. Org. Chem.* **1999**, *64*, 5224.

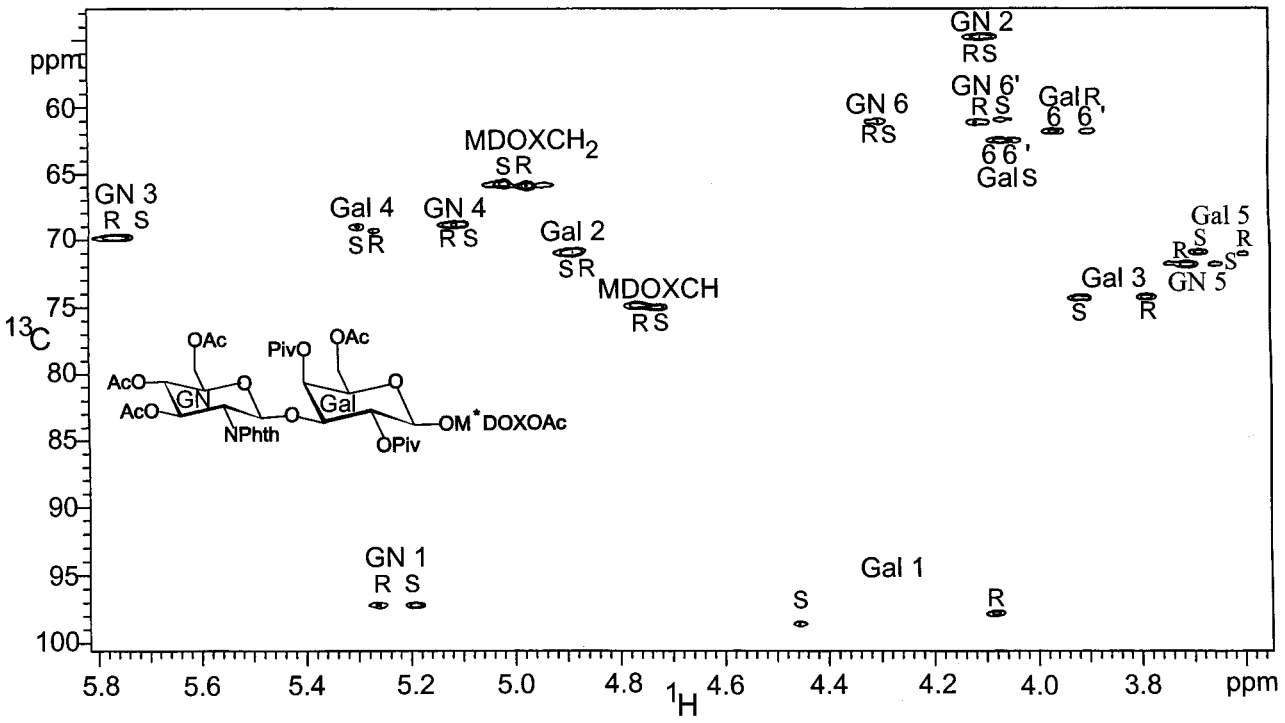
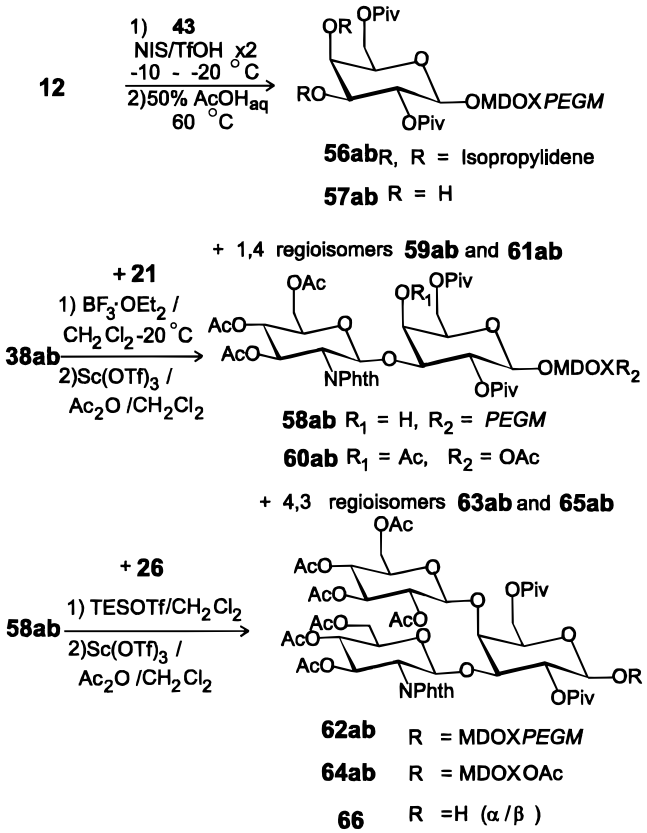


Figure 4. Partial $^{13}C-^{1}H$ correlation spectrum (gHSQC) of diastereomeric disaccharides **60ab**.

Scheme 11. Formation and Isolation of Branched Trisaccharides 64ab and 66



orthoester intermediates such as **D** are drawn with a short C---O bond to the incoming nucleophile in accord with the original proposal.[43] However, our calculated intermediate **D** has a long C---O separation (2.79 Å). Due to the ion:dipole character of these complexes, the dotted lines in Scheme 12 are not chemical bonds in the usual sense and simply indicate the closest points of approach.

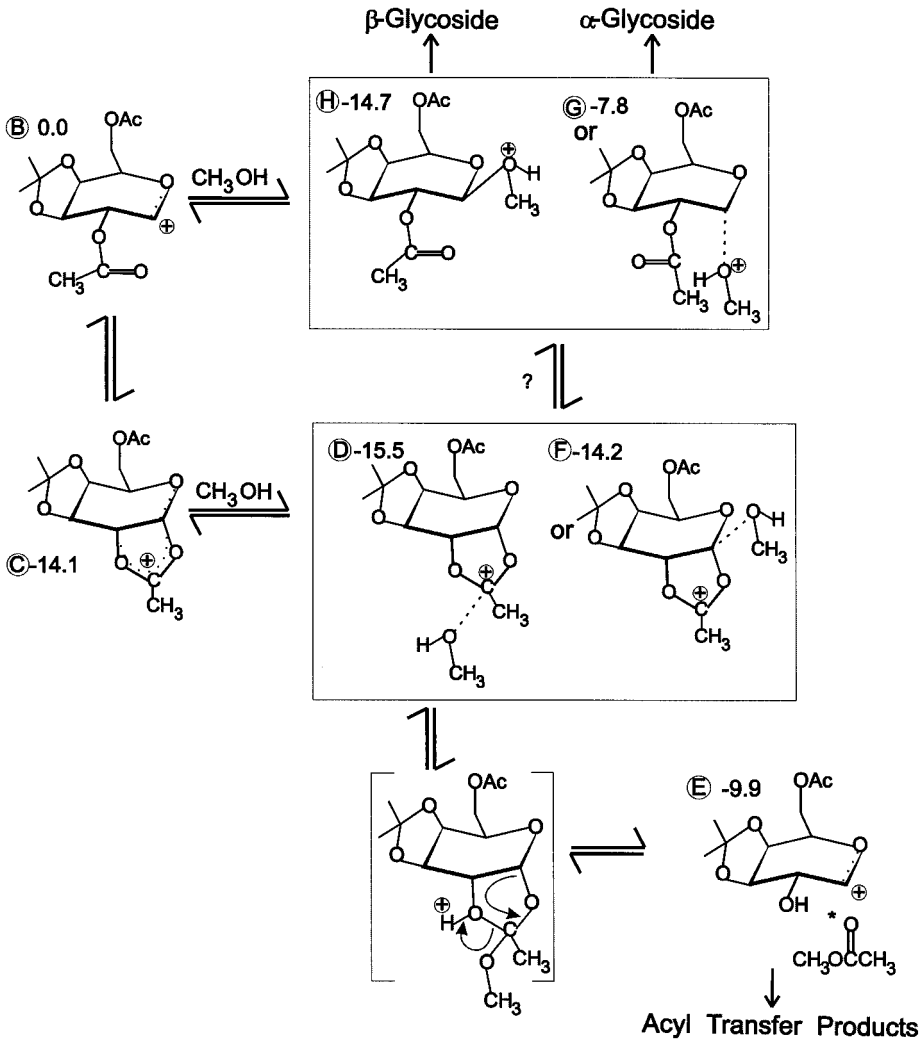
The details of the mechanism of orthoester formation and acyl transfer from **D** is a subject of current theoretical studies. So far, we have established that the transfer of the proton from the nucleophile to O-2 is the most crucial step which leads to the breaking of the C-1---O-1 and O-2---C(=O) bonds. The proton transfer and the orthoester formation (from **D**) both involve significant barriers which are sensitive to electronic and steric factors from the O-2 protecting group and the oxygen nucleophile. The C-1---O-1 bond strength is highly sensitive to the nature of the protecting group at O-2, and proton transfer requires specific geometric orientation. Consequently, the bulky pivaloyl protecting group and the sterically hindered MDOX linker are expected to provide unfavorable conditions for acyl transfer. We also expect that glycosylation is less sensitive to steric hindrance of the nucleophile and the nature of the O-2 protecting group. The successful use of the O-2 pivaloyl group and the MDOX linker is consistent with this hypothesis.

High reaction temperatures and high promoter concentrations were found to favor β-glycoside formation at the expense of orthoesters and acyl transfer. The β-glycoside is the lowest energy product in the calculation not counting decomposition pathways of the acyl transfer. Consequently, higher temperature can be favorable for β-glycosylation, provided that the barrier to acyl transfer is sufficiently high. Higher temperature can also affect the speciation of the promoter (for example, ion pairing), which complicates simple comparisons. According to our mechanism the β-glycoside is formed directly from **B** which is favorably affected by higher promoter concentration.

The explanation regarding the thermodynamic factor to obtain β-glycoside assumes that intermediate **D** or the

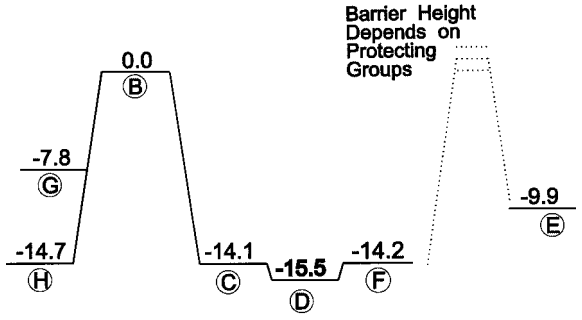
(43) Garegg, P. J.; Kvarnström, I. *Acta Chem. Scand. B* **1976**, *30*, 655.

Scheme 12. Postulated Mechanism for the Formation of Acyl Transfer Products and Glycosides in Neighboring-Group-Assisted Glycosylations of 3,4-*O*-Isopropylidene Donors[a]



[a] The dotted lines in **D**, **F**, and **G** are not bonds and only indicate the nearest points of contact. Energies were calculated using DFT and are in kilocaories per mole relative to solvated isolated cation **B** + solvated methanol. The scheme is modified from ref 40 to include **E**.

Scheme 13. Relative Energies (kcal mol^{-1}) for the Proposed Intermediates in Scheme 12[a]



[a] The dotted lines indicate the barrier to acyl transfer.

corresponding orthoester can be converted to **H**. The textbook explanation of such a mechanism involves an S_N2 mechanism, cf. **F**, which we have previously shown to be a high-energy pathway in accord with earlier suggestions by Dewar.[44] The most straightforward pathway to **H** follows directly from the oxonium intermediate **B** formed in the first step of the S_N1 reaction. The transformation **D** to **H**, however, does not necessarily involve the high-energy intermediate **B**, but another ion−dipole complex. Most likely, the transformation of **D** to **H** involves at least three steps: (i) the breaking of the α-glycosidic bond, (ii) the conformational change of the pyranose ring, (iii) the formation of the β-glycoside bond.

The relatively simple model of Scheme 12 neglects specific solvation and ion-pairing. More complex mechanisms can be considered involving nucleophilic attack on ion pairs, leading to trimolecular intermediates. Also, our results are only directly applicable to this fused ring system. Present efforts are focused on assessing the importance of pyranose ring conformational interconversions by extending this study to more flexible intermediates.

Conclusions

Thus, for the first time the branched trisaccharide corresponding to part of a single repeat unit of the group B *Streptococcus* type 1A capsular polysaccharide has been

(44) Dewar, M. J. S.; Dougherty R. C. *The PMO Theory of Organic Chemistry*; Plenum Publishing Corp.: New York, 1975; p 263.

synthesized by polymer-supported methods. This synthesis required only three chromatographic separations, one for the final product and two for the preparation of building blocks **12** and **26**. Several important observations and developments were made in the process. From a practical synthetic perspective the NIS/AgOTf/2-methyl-2-butene promoter system for thioglycosides is a valuable addition. The versatility of the $ScOTf_3/Ac_2O$ MPEG−DOX cleavage system is a useful improvement to the (MPEG)(DOX) polymer linker combination and should find widespread application. Similarly the observation that isopropylidenes can be directly converted to di-*O*-acetates by this reagent system may have other applications.

The observation that pivaloyl transfers from O-2 of the conformationally restricted 3,4-*O*-isopropylidene protected donors to the acceptor is unprecedented. This transfer suggests that in some way this structural feature promotes this side reaction. Such fused rings have been shown to "torsionally" deactivate other donor systems, and such deactivation is likely operative in these examples.[45]

This work provides a general methodology for preparing modified DOX linkers and is applicable to other linker systems which can be used with both soluble and insoluble PEG derivatives. The application of the $Sc(OTf)_3/Ac_2O$ cleavage conditions to the diastereomeric α-methyl-substituted MDOX glycosides led to the observation of large ^1H NMR chemical shift differences. These diastereotopic shifts are larger than those reported for a large number of *O*-glycosides epimeric at the aglyconic carbon. By finding conditions to eliminate acyl transfer, a method to achieve polymer-supported synthesis of a branched trisaccharide corresponding to a portion of the type 1A capsular polysaccharide of group B *Streptococcus* was created.

Experimental Section

Materials and General Methods. Silica gel (230-400 mesh) was used for flash chromatography. All starting materials were dried overnight *in vacuo* (10^{-3} mmHg) over KOH or P_2O_5 prior to use, and the solvents were distilled from appropriate drying agents. Solutions were concentrated at 1 mmHg of pressure in a rotary evaporator. Optical rotations were measured ($\lambda = 589$ nm) at room temperature in a 10 cm 1 mL cell. The ^1H and ^{13}C NMR spectra were recorded in deuteriochloroform solution at 500.1 or 600.2 MHz and 125.8 or 150.9 MHz, respectively. ^1H NMR spectra in $CDCl_3$ were referenced to residual $CHCl_3$ at 7.24 ppm, and ^{13}C NMR spectra to the central peak of $CDCl_3$ at 77.0 ppm. Assignments were made by standard $^1H-^1H$ COSY and $^{13}C-^1H$ COSY experiments. ^1H chemical shifts are reported to two decimal places and ^{13}C shifts to one. In the case of closely separated resonances an additional figure is added to show that they are separately identifiable. For polymer-bound samples, the MPEG methylenes were saturated and quantitation was made by comparing integrals to the terminal methyl of the MPEG. Assignments were made by comparison to the spectra of building blocks and cleaved compounds. Advantage was also taken of gradient-enhanced 1D selective TOCSY and NOESY experiments. Typically 256 transients were used for TOCSY spectra with mixing times from 20 to 150 ms and 4k transients for NOESY spectra with mixing times of 200−500 ms.

The mass spectral analysis was done on a forward mass spectrometer. Fast atom bombardment (FAB) MS was performed using xenon atom at 6 kV as the source. Thioglycerol or a mixture of glycerol and thioglycerol were used as the FAB matrix. Typically 10−15 full-range, low-resolution MS scans were averaged to yield a low-resolution mass spectrum. For high-resolution MS, the electric sector was scanned over the range of interest. Typically polyethylene glycol or polypropylene glycol was used as an internal mass standard, and between 75 and 150 scans were averaged.

(MPEG)(DOX)OH (**1**) was synthesized according to ref 46.[46]

Ethyl 2,6-Di-*O*-benzoyl-3,4-*O*-isopropylidene-β-D-galactothiopyranoside (2). Ethyl β-D-galactothiopyranoside[47] was converted to its 3,4-*O*-isopropylidene according to ref 48.[48] To a round-bottomed flask containing this 2,6-diol (1.74 g, 6.6 mmol) was added pyridine (20 mL), and the mixture was cooled in an ice bath under an atmosphere of argon. To this mixture were added benzoic anhydride (4.6 g) and 4-dimethylaminopyridine (145 mg), and the mixture was left to stir and warm to rt overnight. The solvents were removed by distillation at high vacuum followed by codistillation with toluene. The residue was taken up in warm 100% ethanol (230 mL) and filtered by gravity through a warm filter paper, and warm water (175 mL) was slowly added. After slow cooling to rt, white needles were separated, collected by filtration, and washed with cold water. The crystals were dissolved in dichloromethane, any residual water was removed in a separatory funnel, and the dichloromethane solution was dried with $MgSO_4$, filtered, and evaporated to yield **2** (2.69 g, 86%): mp 148−149 °C; $[\alpha]_D$ 46.5 (*c*, 0.51, $CHCl_3$); MS FAB +ve 490 ($M + H_2O^+$), 473 (MH^+), 411 ($M - SEt^+$); HRMS $C_{25}H_{29}O_7S$ 473.1661 calcd 473.1634. Anal. Calcd for $C_{25}H_{29}O_7S$ (473.1661): C, 63.40, H, 6.00. Found: C, 63.12, H, 6.25.

(MPEG)(DOX)yl 2,6-Di-*O*-benzoyl-3,4-*O*-isopropylidene-β-D-galactopyranoside (4a) and (MPEG)(DOX)-*O*-benzoate (3) [Table 2, Entry 1]. Donor **2** (71 mg, 0.15 mmol), (MPEG)(DOX)OH (512 mg, 0.1 mmol), and activated 4 Å molecular sieves (about 300 mg) were dried together overnight at high vacuum. Dichloromethane (3 ml) was added and the mixture cooled in an ice−salt bath. After the mixture was stirred for 0.5 h, *N*-iodosuccinimide (NIS; 112 mg, 0.5 mmol) was added followed by trifluoromethanesulfonic acid (TfOH; 200 μL of a dilute solution in CH_2Cl_2,, 0.14 mmol). After being stirred for 15 min, the reaction was quenched with DIPEA (50 μL) and the polymer precipitated with *tert*-butyl methyl ether (TBME; 40 mL). The solid was recovered by filtration and after being rinsed with TBME was recrystallized from absolute ethanol (25 mL). The resulting solid was collected by filtration and after being washed with cold ethanol and diethyl ether was taken up in CH_2Cl_2, filtered, and evaporated to yield the mixture (510 mg) described in Scheme 1 and Tables 1 and 2.

[Table 2, Entry 10]. Donor **2** (55 mg, 0.12 mmol) and (MPEG)(DOX)OH (397 mg, 0.078 mmol) were dried together overnight at high vacuum. Dichloromethane (2.5 ml) was added and the mixture heated in an oil bath to 40 °C. 2-Methyl-2-butene (410 μL of a 1:10 solution in CH_2Cl_2, 0.4 mmol) and NIS (86 mg, 0.5 mmol) were added followed by silver trifluoromethanesulfonate (AgOTf, 22 mg, 0.86 mmol). After being stirred for 40 min, the reaction was cooled in an ice bath and quenched with ammonium bicarbonate (100 mg) and the solid precipitated with TBME (40 mL). The solid was recovered by filtration and after being rinsed with TBME was recrystallized from absolute ethanol (25 mL) containing 0.5% w/v imidazole. The resulting solid was collected by filtration and after washed with cold ethanol and diethyl ether was taken up in CH_2Cl_2, filtered, and evaporated to yield the mixture (380 mg) containing 55% **4a**.

(MPEG)(DOX)yl 2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranoside 6 and (MPEG)(DOX)-*O*-benzoate (3). Donor **5**[27] (545 mg, 0.85 mmol), (MPEG)(DOX)OH (2.9 g, 0.57 mmol), and 4 Å molecular sieves (about 1 g) were dried together overnight

(45) Fraser-Reid, B.; Wu, Z.; Andrews, C. W.; Skowronski, E. *J. Am. Chem. Soc.* **1991**, *113*, 1434.

(46) Krepinsky, J. J.; Douglas, S. P.; Whitfield, D. M. *Methods Enzymol.* **1994**, *242*, 281.

(47) Aberg, P.-M.; Blomberg, L.; Lönn, H.; Norberg, T. *J. Carbohydr. Chem.* **1994**, *13*, 141.

(48) Catelani, G.; Colonna, F.; Marra, A. *Carbohydr. Res.* **1988**, *182*, 297.

at high vacuum. Dichloromethane (12 mL) was added and the mixture cooled in an ice−salt bath to 0 °C. After the mixture was stirred for 1 h, NIS (638 mg, 2.8 mmol) was added followed by TfOH (750 μL of a dilute solution in CH_2Cl_2, 0.28 mmol). After being stirred for 15 min, the reaction was quenched with DIPEA (700 μL) and the polymer precipitated with *tert*-butyl methyl ether (TBME; 150 mL). The solid was recovered by filtration and after being rinsed with TBME was recrystallized from absolute ethanol (175 mL). The resulting solid was collected by filtration and after being washed with cold ethanol and diethyl ether was taken up in CH_2Cl_2, filtered, and evaporated to yield the mixture (2.76 g) of **6** and **3** (7%).

[4-Carbomethoxy]benzyl 2,6-Di-*O*-benzoyl-3,4-*O*-isopropylidene-*β*-D-galactopyranoside (9a), [4-Carbomethoxy]benzyl 2,6-Di-*O*-benzoyl-3,4-*O*-isopropylidene-α-D-galactopyranoside (9b), [4-Carbomethoxy]benzyl-*O*-benzoate (8), and 2-*O*-[2,6-Di-*O*-benzoyl-3,4-*O*-isopropylidene-*β*-D-galactopyranosyl]1,6-di-*O*-benzoyl-3,4-*O*-isopropylidene-α-D-galactopyranose (9d). Donor **2** (278 mg, 0.59 mmol), [4-carbomethoxy]benzyl alcohol (165 mg, 0.39 mmol), and 3 Å molecular sieves (500 mg) were dried together overnight at high vacuum. Then CH_2Cl_2 (10 mL) was added and the mixture cooled in an ice−salt bath to 0 °C. After the mixture was stirred for 0.5 h, NIS (219 mg, 0.98 mmol) was added followed by trifluoromethanesulfonic acid (TfOH, 320 μL of a dilute solution in CH_2Cl_2, 0.20 mmol). After being stirred for 30 min, the reaction was quenched with DIPEA (100 μL) and evaporated to dryness. The residue was purified by flash chromatography on silica gel eluting with 80:15:5 hexanes−ethyl acetate−CH_2Cl_2 to yield in increasing polarity a viscous oil (**8**) (19 mg, 19%), a waxy solid (**9b**) (4 mg, 2%) ($[\alpha]_D$ 215.5 (*c*, 0.02, $CHCl_3$); MS FAB +ve 575 ($M - H^+$), 545 ($M - OCH_3^+$), 411 ($M - C_9H_9O_3^+$); HRMS $C_{32}H_{32}O_{10}Na$ 599.1859, calcd 599.1893), and two fractions which were mixtures. The first was rechromatographed eluting with 88:12 toluene−ethyl acetate to yield an amorphous solid (**9a**) (71 mg, 31%) (mp 123−124 °C; $[\alpha]_D$ −10.7 (*c*, 2.2, $CHCl_3$); MS FAB +ve $C_{32}H_{32}O_{10}$ 575 ($M - H^+$), 545 ($M - OCH_3^+$), 411 ($M - C_9H_9O_3^+$). Anal. Calcd for $C_{32}H_{32}O_{10}$: C, 66.66; H, 5.59. Found: C, 66.56; H, 5.56) and a viscous oil (**9c**) (78 mg, 47%) (MS FAB +ve 451 (MNa^+), 411 ($M - OH^+$); HRMS $C_{23}H_{24}O_8Na$ 451.1361, calcd 451.1369). The second fraction was further purified by preparative TLC eluting two times with 9:1 toluene−ethyl acetate to yield a viscous oil (**9d**) (8 mg, 3%): $[\alpha]_D$ 10.0 (*c*, 0.03, $CHCl_3$); MS FAB +ve $C_{46}H_{46}O_{15}$ 861 ($M + Na^+$), 717 ($M - OBz^+$), 411 ($C_{23}H_{23}O_7^+$); HRMS $C_{46}H_{46}O_{15}Na$ 861.2763, calcd 861.2734.

***O*-Trityl-(MPEG)(DOX) (10).** (MPEG)(DOX)OH (**1**) (2.4 g, 0.47 mmol) was dissolved in CH_2Cl_2 (15 mL), chlorotriphenylmethane (653 mg, 2.4 mmol) followed by 4-dimethylaminopyridine (705 mg, 0.70 mmol) was added, and the mixture was left to stir overnight. The polymer was precipitated by adding TBME (225 mL) and collected by filtration. The solid was recrystallized twice from absolute ethanol (125 mL) to yield **10** (2.3 g, 92 %): ^{1}H NMR 7.51 br d (6H) (J = 8 Hz); 7.28 m (13H); 4.56 s (2H); 4.10 s (2H); 3.38 s (3).

Ethyl 2,6-Di-*O*-[4-chlorobenzoyl]-3,4-*O*-isopropylidene-*β*-D-galactothiopyranoside (11). Donor **11** was prepared as for **2** except that 4-chlorobenzoyl chloride was used as acylating reagent. The product was purified by chromatography on silica eluting with hexanes−ethyl acetate (4:1) to yield an amorphous solid (**11**; 47%): $[\alpha]_D$ 48.0 (*c*, 0.72, $CHCl_3$); MS FAB +ve 541 ($M^{35}Cl_2 + H^+$), 479 ($M^{35}Cl_2 - SEt^+$); HRMS $C_{25}H_{26}O_7{}^{35}Cl_2Na$ 563.0674, calcd 563.0674. Anal. Calcd for $C_{25}H_{26}O_7Cl_2S$ (541.4462): C, 55.46, H, 4.84. Found: C, 55.88, H, 4.85.

Ethyl 2,6-Di-*O*-pivaloyl-3,4-*O*-isopropylidene-*β*-D-galactothiopyranoside (12). Donor **12** was prepared as for **2** except that pivaloyl chloride was used as acylating reagent. The product was purified by chromatography on silica eluting with hexanes−ethyl acetate (9:1) to yield a white solid (**12**; 41%): mp 85−86 °C; $[\alpha]_D$ 29.2 (*c*, 0.53, $CHCl_3$); MS FAB +ve $C_{21}H_{36}O_7S$ 439 ($M + Li^+$), 371 ($M - SEt^+$). Anal. Calcd for $C_{21}H_{36}O_7S$ (432.5752): C, 59.11; H, 8.50. Found: C, 58.90; H, 8.57.

(MPEG)(DOX)yl 2,6-Di-*O*-pivaloyl-3,4-*O*-isopropylidene-*β*-D-galactopyranoside (15) and (MPEG)(DOX)-*O*-pivaloylate (16). Donor **12** (940 mg, 1.0 mmol) and **1** (2.0 g, 0.39 mmol) were dried together overnight at high vacuum. Dichloromethane (9.5 ml) was added and the mixture stirred at rt under an argon atmosphere. 2-Methyl-2-butene (2.0 mL of a 1:10 solution in CH_2Cl_2, 2.0 mmol) and NIS (439 mg, 2.0 mmol) were added followed by AgOTf (110 mg, 0.42 mmol). After being stirred for 3^1/$_2$ h the reaction was cooled in an ice bath and quenched with ammonium bicarbonate and the solid precipitated with TBME (125 mL). The solid was recovered by filtration and after being rinsed with TBME was recrystallized from absolute ethanol (125 mL) containing 0.5% w/v imidazole. The resulting solid was collected by filtration and after being washed with cold ethanol and diethyl ether was taken up in CH_2Cl_2, filtered, and evaporated to yield the mixture of **15** and **16** (4.2:1, 2.07 g).

(MPEG)(DOX)yl 2,6-Di-*O*-pivaloyl-*β*-D-galactopyranoside (17). The mixture of **15** and **16** (1.78 g, 0.33 mmol) was dissolved in 50% $AcOH_{aq}$ (40 mL) and heated at 60 °C for 16 h. The liquids were removed by evaporation followed by coevaporation with toluene. The residue was recrystallized from ethanol (100 mL) and collected by filtration. After being washed with cold ethanol and diethyl ether it was dissolved in CH_2Cl_2, filtered, and evaporated to yield **15** and **16** (1.75 g, 96%).

[4-*O*-Acetoxymethyl]benzyl 3,4-Di-*O*-acetyl-2,6-di-*O*-pivaloyl-*β*-D-galactopyranoside (18) and 4-*O*-Acetoxymethylpivaloyloxymethylbenzene (19). The mixture of **15** and **16** (208 mg; 0.04 mmol) was dissolved in CH_2Cl_2 (1.0 mL) and Ac_2O (1.0 mL) under an atmosphere of argon at rt. To this solution was added $Sc(OTf)_3$ (10 mg, 0.02 mmol) and the stirring continued for 16 h. After the mixture was cooled with an ice bath the polymer was precipitated with TBME (40 mL) and collected by filtration. The filtrate was evaporated. The solid was recrystallized from ethanol (20 mL) and collected by filtration. The filtrate was combined with the residue from TBME and evaporated. The residue was purified by MPLC on silica eluting with 70:30 hexanes−ethyl acetate to yield viscous oil (**19**) (1 mg): $C_{15}H_{20}O_4$ MS FAB +ve 265 (MH^+), 205 ($M - OAc^+$), 163 ($M - OPiv^+$); HRMS $C_{15}H_{20}O_4Na$ 287.1250, calcd 287.1259; and viscous oil **18** (12 mg, 76%) $[\alpha]_D$ −75.0 (*c*, 0.06, $CHCl_3$); MS FAB +ve 595 (MH^+), 415 ($M - DOX^+$); HRMS $C_{30}H_{42}O_{12}Na$ 617.2579, calcd 617.2574.

(MPEG)(DOX)yl 3-*O*-[3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-*β*-D-glucopyranosyl]-2,6-di-*O*-pivaloyl-*β*-D-galactopyranoside (22) and (MPEG)(DOX)yl 4-*O*-[3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-*β*-D-glucopyranosyl]-2,6-di-*O*-pivaloyl-*β*-D-galactopyranoside (23). Diol **17** (1.75 g, 0.3 mmol) and 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-*β*-D-glucopyranosyl-*O*-trichloroacetimidate (**21**) (220 mg, 0.38 mmol) were dried together overnight at high vacuum. Under an atmosphere of argon with cooling in an ice bath CH_2Cl_2 (12 mL) was added followed by $BF_3{\cdot}OEt_2$ (39 μL, 0.32 mmol), and the mixture left to stir for 4 h. The reaction was quenched with DIPEA (50 μL) and the polymer precipitated with TBME (85 mL). After filtration and rinsing with TBME the polymer was recrystallized from ethanol (125 mL). It was collected by filtration and after being rinsed with ethanol and diethyl ether was taken up in CH_2Cl_2, filtered, and evaporated to yield **22**, **23**, and residual **17** (3.0:1.4:1.0, 1.78 g).

[4-*O*-Acetoxymethyl]benzyl 3-*O*-[3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-*β*-D-glucopyranosyl]-4,*O*-acetyl-di-2,6-*O*-pivaloyl-*β*-D-galactopyranoside (24) and [4-*O*-Acetoxymethyl]benzyl 4-*O*-[3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-*β*-D-glucopyranosyl]-3-*O*-acetyl-2,6-di-*O*-pivaloyl-*β*-D-galactopyranoside (25). The mixture of **22**, **23**, and **17** (781 mg) was treated with $Sc(OTf)_3$ as described above for **15**, which after MPLC purification eluting with toluene−ethyl acetate (80:20 to 60:40) yielded **19** (2 mg) and viscous oil **24** (34 mg, 26%) ($[\alpha]_D$ 3.7 (*c*, 0.46, $CHCl_3$); MS FAB +ve 992 ($M + Na^+$), 790 ($M - DOX^+$), 418 ($C_{20}H_{20}NO_9^+$);[49] HRMS $C_{48}H_{59}NO_{20}Na$ 992.3546, calcd 992.3528) and viscous oil **25** (29

(49) Whitfield, D. M.; Pang, H.; Carver, J. P.; Krepinsky, J. J. *Can. J. Chem.* **1990**, *68*, 942.

mg; 23%) ($[\alpha]_D$ −13.4 (*c*, 0.19, $CHCl_3$); MS FAB +ve 992 ($M + Na^+$), 790 ($M - DOX^+$), 418 ($C_{20}H_{20}NO_9^+$); HRMS $C_{48}H_{59}NO_{20}$-Na 992.3597, calcd 992.3528).

(MPEG)(DOX)yl 3-*O*-[3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-*β*-D-glucopyranosyl]-4-*O*-[2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl]-2,6-di-*O*-pivaloyl-*β*-D-galactopyranoside (27) and [4-*O*-Acetoxymethyl]benzyl 3-*O*-[3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-*β*-D-glucopyranosyl]-4-*O*-[2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl]-2,6-di-*O*-pivaloyl-*β*-D-galactopyranoside (28). The mixture of **22** and **23** (974 mg, 0.16 mmol) was dried at high vacuum overnight with 2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl-*O*-trichloroacetimidate **26** (160 mg, 0.33 mmol). After the mixture was cooled in an ice bath under an atmosphere of argon, CH_2Cl_2 (5 mL) was followed by TESOTf (25 μL; 0.11 mmol) and the mixture left to warm to rt and stir for 1¼ h. The reaction was quenched with DIPEA (50 μL) and the polymer precipitated with TBME (80 mL). After filtration and rinsing with TBME the polymer was recrystallized from ethanol (100 mL). It was collected by filtration and after being rinsed with ethanol and diethyl ether was taken up in CH_2Cl_2, filtered and evaporated to yield a mixture containing **27** (0.99 g). This was dissolved in CH_2Cl_2 (4 mL) and Ac_2O (4 mL). To this solution was added $Sc(OTf)_3$ (40 mg; 0.08 mmol). After the mixture was stirred for 16 h at rt, the polymer was precipitated with TBME (90 mL) and collected by filtration. The polymer was recrystallized from ethanol (75 mL), and the combined filtrates were evaporated to dryness. The residue was purified by MPLC on silica eluting with 60:40 ethyl acetate−hexanes to yield a viscous oil (**28**) (23 mg; 11%): $[\alpha]_D$ −24.6 (*c*, 0.07, $CHCl_3$); MS FAB +ve $C_{60}H_{75}NO_{28}$ 1078 ($M - DOX^+$); MS MALDI +ve 1280.3 ($M + Na^+$).

α,α′-Dimethyl(DOX)(PEG)yl-*O*-benzoate (35). The monomethyl ether of poly(ethylene oxide) 5000, (MPEG)OH (2.0 g, 0.4 mmol) was dissolved in CH_2Cl_2 (10 mL), and **34** (0.32 g, 0.8 mmol) dissolved in CH_2Cl_2 (2 mL) was added along with molecular sieves 3 Å (1 g) under an atmosphere of argon. After the mixture was in an ice bath, $BF_3{\cdot}OEt_2$ (55 μL, 0.14 mmol) was added dropwise to the mixture. The reaction mixture was allowed to slowly warm to rt over 4 h and then recooled in an ice bath. The reaction was quenched with diisopropylethylamine (DIPEA) (6 drops) and the polymer precipitated with *tert*-butyl methyl ether (TBME) (200 mL). The solid was recovered by filtration and after being rinsed with TBME was recrystallized from EtOH (100 mL). The product was recovered by filtration and after being rinsed with EtOH and Et_2O was taken up in CH_2Cl_2, filtered, and evaporated to yield **35** (2.1 g, 99%). A small portion was acetylated by being dissolving in acetic anhydride (0.7 mL) and stirred with KOAc (5 mg) for 16 h. The acetylated polymer was recovered by precipitation with TBME followed by recovery by filtration and recrystallization from EtOH. ^1H NMR analysis of the product suggested >95% derivitization.

α,α′-Dimethyl(DOX)(PEG)ol (36). Ester **35** (1.96 g, 0.37 mmol) was dissolved in 0.5 M $NaOH_{aq}$ (20 mL) and the mixture left to stir for 16 h. After neutralization with 1 M HCl_{aq} the water was evaporated and residual water removed by coevaporation with toluene several times. The residue was taken up in CH_2Cl_2, filtered, and evaporated and the residue recrystallized from EtOH (150 mL). The product was recovered by filtration and after being rinsed with EtOH and Et_2O it was taken up in CH_2Cl_2, filtered and evaporated. This last process was repeated again to yield **36** (1.65 g, 87%).

α-Methyl(DOX)(PEG)-*O*-*tert*-butyldiphenylsilyl Ether (42). Diether **42** was prepared as for **35** from (MPEG)OH (7.5 g, 1.5 mmol) and trichloroacetimidate **41** (2.42 g, 4.5 mmol) except that after the first treatment ^1H NMR analysis indicated that the reaction was only 70−75% complete. Therefore, the polymer was retreated with **41** (1.61 g, 3.0 mmol) to yield **42** (7.0 g, 91%).

α-Methyl(DOX)(PEG)ol (43). Silyl ether **42** (5.1 g, 1.0 mmol) was dissolved in dry THF (100 mL) under an argon atmosphere to which was added 4 Å molecular sieves (1 g) and 1 M TBAF in THF (2 mL, 2 mmol). The mixture was heated at 40 °C for 3 h. After the mixture was cooled in an ice bath, the polymer was precipitated with TBME (200 mL) and recovered by filtration. The residue was recrystallized twice from ethanol to yield **43** (4.73 g, 92%). A small portion was acetylated by being dissolved in acetic anhydride (0.7 mL) and stirred with KOAc (5 mg) for 16 h. The acetylated polymer was recovered by precipitation with TBME followed by recovery by filtration and recrystallization from EtOH. ^1H NMR analysis of the product indicated >95% derivatization.

1-Methyl(DOX)(PEG)yl-2,6-di-*O*-benzoyl-3,4-*O*-isopropylidene-*β*-D-galactopyranoside (44ab). Thioglycoside **2** (224 mg, 0.47 mmol), **43** (975 mg, 0.19 mmol) and activated 3 Å molecular sieves (500 mg) were placed in a 100 mL round-bottomed flask and dried *in vacuo* in a desiccator containing P_2O_5. The desiccator was opened to argon and the flask maintained under an argon atmosphere. To the flask was added CH_2Cl_2 (5 mL), and it was cooled in an ethylene glycol−water cooling bath with the temperature maintained between −20 and −15 °C by a cold finger. To this stirred mixture was added NIS (107 mg, 0.48 mmol) followed by TfOH (17 μL, 0.19 mmol). After 1.5 h another aliquot of TfOH (17 μL, 0.19 mmol) was added and the stirring continued for another 1 h. The reaction was quenched with DIPEA (100 μL) and the polymer precipitated with TBME (100 mL). After recovery of the solids by filtration through a coarse glass frit the residue was dissolved in warm EtOH and filtered through the same glass frit. The filtrate was placed in a −20 °C freezer and after precipitation was recovered by filtration with a medium glass frit and rinsed with EtOH and Et_2O. The residue was dissolved in CH_2Cl_2 and filtered through the same glass frit. The filtrate was evaporated to yield **44ab** (859 mg, 81%).

1-Methyl(DOX)(PEG)yl-2,6-di-*O*-benzoyl-*β*-D-galactopyranoside (48ab). Polymer-bound diol **48ab** was prepared as for **17** to yield **48ab** (813 mg, 97%).

[4-*O*-Acetoxymethyl-(1-(*R*,*S*)-ethyloxy)]phenyl-3,4-di-*O*-acetyl-2,6-di-*O*-benzoyl-*β*-D-galactopyranoside (49ab). The mixture containing **44ab** was treated as for **15**−**18**. The residue was purified by MPLC eluting with 2:1 hexanes−ethyl acetate to yield in increasing order of polarity 4-acetoxymethyl-(1-(*R*,*S*)-benzoyloxyethyl)benzene (**50**) (2 mg, 20%), 4-acetoxymethyl-(1-(*R*,*S*)-acetoxyethyl)benzene (**51**) (<1 mg) and (**49ab**) (8.8 mg, 31%): $[\alpha]_D$ −15.9 (*c* 0.24, $CHCl_3$); MS FAB +ve 649 ($M + H^+$), 455 ($M - MDOX^+$); HRMS $C_{35}H_{36}O_{12}Na$ ($M + Na^+$) 671.2103, calcd 671.2104. A small portion was repurified by preparative TLC eluting with 3:1 hexanes−ethyl acetate and isolating the least polar band yielded predominantly **49a** (<1 mg): $[\alpha]_D$ −59.4 (*c* 0.02, $CHCl_3$).

1-Methyl(DOX)(PEG)yl-3-*O*-(3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-*β*-D-glucopyranosyl)-2,6-di-*O*-benzoyl-*β*-D-galactopyranoside (52ab) and 1,4 regioisomer (52ab). Disaccharide **52ab** was prepared as for **22** + **23** to yield a mixture of **52ab** and **53ab** (1.32 g, 92%).

[4-*O*-Acetoxymethyl-(1-(*R*,*S*)-ethyloxy)]phenyl-3-*O*-(3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-*β*-D-glucopyranosyl)-4-*O*-acetyl-2,6-di-*O*-benzoyl-*β*-D-galactopyranoside (54ab). Polymer-bound mixtures **52ab** and **53ab** (350 mg, 0.06 mmol) were treated with $Sc(OTf)_3$ as for **44ab** above. The residue (55 mg) was purified by chromatography eluting with ethyl acetate−hexanes (50:50) to yield four fractions in increasing order of polarity (**50** (5 mg), **51** (2 mg), a mixture of monosaccharides and disaccharides (9 mg), and **54ab** (5 mg, 8%)): $[\alpha]_D$ 38.8 (*c* 0.32, $CHCl_3$); MS ES +ve $C_{53}H_{53}NO_{20}$ 1046 ($M + Na^+$), 1024 ($M + H^+$), 830 ($M - MDOX^+$).

1-Methyl(DOX)(PEG)yl-2,6-di-*O*-pivaloyl-3,4-*O*-isopropylidene-*β*-D-galactopyranoside (56ab). Glycoside **56ab** was prepared as for **44ab** except thioglycoside **12** was used as donor to yield **56ab** (83 %).

1-Methyl(DOX)(PEG)yl-2,6-di-*O*-pivaloyl-*β*-D-galactopyranoside (57ab). Diol **57ab** was prepared as for **48ab** to yield **57ab** (95 %).

1-Methyl(DOX)(PEG)yl-3-*O*-(3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-*β*-D-glucopyranosyl)-2,6-di-*O*-pivaloyl-*β*-D-galactopyranoside (58ab) and 1,4 regioisomer (59ab). Diol **57ab** was glycosylated as for **33ab** except the temperature was maintained at −15 to −20 °C to yield a 2.2:1.0 mixture of **58ab** and **59ab** and only traces of unreacted **57ab**.

[4-*O*-Acetoxymethyl-(1-(*R*,*S*-ethyloxy)]phenyl-3-*O*-(3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-*β*-D-glucopyranosyl)-4-*O*-acetyl-2,6-di-*O*-pivaloyl-*β*-D-galactopyranoside (60ab) and [4-*O*-Acetoxymethyl-(1-(*R*,*S*)-ethyloxy)]-phenyl-4-*O*-(3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-*β*-D-glucopyranosyl)-3-*O*-acetyl-2,6-di-*O*-pivaloyl-*β*-D-galactopyranoside (61ab). Polymer-bound mixture **58ab**s and **59ab** (285 mg, 0.048 mmol) were treated with $Sc(OTf)_3$ as for **52ab** above. The residue was purified by chromatography eluting with ethyl acetate−hexanes (50:50) to yield two fractions in increasing order of polarity (**60ab** (3.2 mg, 7%) ($[\alpha]_D$ −103.7 (*c* 0.03, $CHCl_3$); MS-FAB +ve 1022 ($M + K^+$), 1006 ($M + Na^+$), 790 ($M - MDOX^+$), 418 ($C_{20}H_{20}NO_9^+$);[49] HRMS $C_{49}H_{61}NO_{20}Na$ ($M + Na^+$) 1006.3662, calcd 1006.3685. Anal. Calcd for $C_{49}H_{61}NO_{20}$ (983): C, 59.44, H, 6.13, N, 1.44. Found: C, 60.07, H, 6.51; N, 1.38) and a mixture of **59ab** and **60ab** (8.9 mg, 19%)). The latter was further purified by preparative TLC eluting with 70:30 toluene−ethyl acetate to yield **60ab** (1 mg) as a 75:25 mixture of diastereomers: $[\alpha]_D$ 2.9 (*c* 0.12, $CHCl_3$); MS-FAB +ve 1006 ($M + Na^+$), 790 ($M - MDOX^+$); HRMS $C_{49}H_{61}NO_{20}Na$ ($M + Na^+$) 1006.3618, calcd 1006.3685.

[4-*O*-Acetoxymethyl-(1-(*R*,*S*)-ethyloxy)]phenyl-3-*O*-(3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-*β*-D-glucopyranosyl)-4-*O*-[2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl]-2,6-di-*O*-pivaloyl-*β*-D-galactopyranoside (64ab). Trisaccharide **64ab** was prepared as for **28** above. The residue was purified by MPLC on silica eluting with a gradient of 70:30 to 50:50 toluene−ethyl acetate to yield a viscous oil (**64ab**) (32 mg; 15%) $[\alpha]_D$ −20.4 (*c*, 0.48, $CHCl_3$); MS FAB +ve 1078 ($M - MDOX^+$); HRMS $C_{61}H_{77}NO_{28}Na$ ($M + Na^+$, 1294.4624), calcd 1294.4520. Anal. Calcd for $C_{61}H_{77}NO_{28}$ (1271): C, 57.28, H, 6.01, N, 1.11. Found: C, 57.53; H, 6.38; N, 0.83) and a more polar fraction (probably **65ab**) (10 mg) which also gave a MS FAB +ve peak at 1294 but was not possible to purify to homogeneity.

3-*O*-(3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-D-glucopyranosyl)-4-*O*-[2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl]-2,6-di-*O*-pivaloyl-*β*-D-galactopyranoside 66α/*β*. Trisaccharide **64ab** (13 mg, 0.01 mmol) was dissolved in acetic acid (2 mL) and ethyl acetate (2 mL) and placed in a screw cap test tube. To this tube was added palladium black (15 mg), and the tube was placed in a cotton-filled Parr bottle and hydrogenated on a Parr apparatus at 45 psi of H_2 for 16 h. The solids were removed by filtration through celite and rinsed well with methanol. The filtrates were evaporated, and the residue was purified on a preparative TLC plate eluting two times with 60:40 toluene−ethyl acetate to yield **66**α/*β* (5 mg, 46%): $[\alpha]_D$ −4.6 (*c*, 0.17, $CHCl_3$); MS FAB +ve $C_{50}H_{65}NO_{26}$ 1134 ($M + K^+$), 1118 ($M + Na^+$), 1078 ($M - OH^+$).

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Supporting Information Available: Synthetic procedures for linker precursors **30**−**34** and **38**−**41** as well as their ^1H and ^{13}C NMR spectral data, ^1H and ^{13}C NMR spectral data are provided for compounds **2**, **6**−**9**, **11**, **12**, **15**, **17**−**19**, **22**−**24ab**, **44ab**−**47ab**, **50**−**53ab**, **56ab**−**59ab**, and **61ab**, and copies of the spectra of **8**, **9b**−**d**, **15**, **16**, **18**, **19**, **24**, **25**, **28**, **32**, **33**, **34**, **38**, **39**, **42**, **43**, **45**, **49ab**, **50**, **51**, **54ab**, **61ab**, and **66**. This material is available free of charge via the Internet at http://pubs.acs.org.

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