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Synthesis of Sulfated Trisaccharide Ligands for the Selectins

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Abstract: In a directed effort to elucidate the molecular factors responsible for selectin-mediated cell adhesion events as a basis for the generation of potent and specific inhibitors of these processes, we have synthesized a variety of sulfated analogs of the trisaccharide recognition epitopes Lewis a [Le^a: Galβ1→3(Fucα1→4)GlcNAc] and Lewis x [Le^x: Galβ1→4(Fucα1→3)GlcNAc]. Our divergent synthetic route allows for the synthesis of gram quantities of these sulfated trisaccharides from common intermediates in 10-20% overall yields and in no more than 15 linear steps. In addition, we have anchored the reducing end of the Le^a and Le^x trisaccharide precursors with a β-allyl aglycone, providing a single anomer of each final product and allowing for further modification into multivalent derivatives. © 1997 Elsevier Science Ltd.

Introduction

Protein-carbohydrate interactions mediate critical events in the immune response as well as in a variety of disease states, including inflammation, tumor metastasis and viral infection.[1] This realization has led to a concerted effort both to identify the physiological determinants of protein-saccharide recognition and to generate potent and specific inhibitors of these processes.[2] Elucidation of physiological determinants will lead to a better understanding of the nature of protein-carbohydrate interactions, and this insight can inspire the development of new therapeutic strategies for the treatment of inflammatory disorders and other mechanistically similar diseases.

One class of saccharide binding proteins termed selectins[3] (E-, P- and L-selectin) is involved in the recruitment of leukocytes from the bloodstream to sites of tissue injury or to secondary lymphoid organs. Recently, a great deal of effort has been directed toward understanding the physiological bases of selectin-mediated cell adhesion events and toward identifying inhibitors of these processes.[2] Despite this effort, much remains unknown about the selectins and their biological ligands. While much of the initial research in the selectin field has been conducted using the tools of molecular and cellular biology, synthesis has recently provided indispensible molecular probes with which to address unanswered questions in this field.

Synthesis (chemical, enzymatic or a combination of both) is particularly important for the elucidation of biologically relevant carbohydrate structure-function relationships. Using cellular systems, it is

difficult to generate sufficient quantities of saccharide derivatives, and because saccharide structure is encoded indirectly by the cell, it is also difficult to make systematic changes in these structures. In addition, biological systems generally produce heterogeneous mixtures of saccharides, complicating data interpretation. Chemical synthesis can solve these problems and also can provide access to a wide variety of non-natural saccharide analogs.

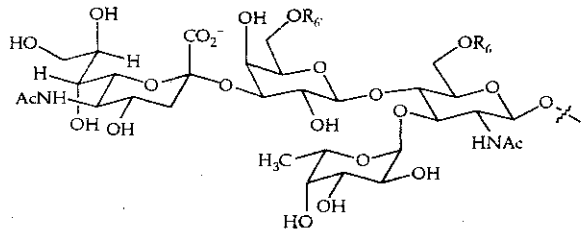
Our research has focused on identifying selectin ligands with the aim of producing high-affinity, specific inhibitors and deconvoluting some of the mysteries of saccharide recognition by the selectins. Herein, we present our approach to the synthesis of a number of monovalent sulfated trisaccharide ligands for the selectins as a prelude to the preparation of a new class of multivalent saccharide arrays.

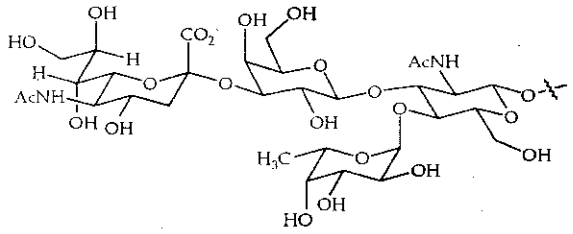
Synthesis of Lewis a and Lewis x Trisaccharides

Although the physiological determinants for selectin recognition remain largely unknown, a number of glycoproteins have been identified as high affinity selectin ligands. These include PSGL-1[4] (P-selectin); ESL-1[5] (E-selectin); and MadCAM-1,[6] CD34[7] and GlyCAM-1[8] (L-selectin). With the exception of ESL-1, all of these ligands are highly *O*-glycosylated, extended polypeptides (mucins), which share the elements of fucosylation and sialylation of terminal residues of polylactosamine saccharide chains. The widespread occurrence of the tetrasaccharide capping groups sialyl Lewis x [sLe^x: NeuAcα2→3Galβ1→4(Fucα1→3)GlcNAc] **1** and sialyl Lewis a[sLe^a: NeuAcα2→3Galβ1→3(Fucα1→4)GlcNAc] **4** (Fig. 1)[9] has led to much speculation that these epitopes or closely related structures may be important for selectin recognition *in vivo*. Sialyl Lewis x and sialyl Lewis a both exhibit fucose and *N*-acetylneuraminic acid (sialic acid) residues on a lactosamine backbone. Conformational and structural studies[10] suggest that sLe^x and sLe^a present their respective sialic acid, galactose and fucose residues in a similar orientation, as represented in Figure 1.

Among the known physiological selectin ligands, the best characterized is the L-selectin ligand GlyCAM-1.[8] It has been demonstrated that in addition to sialylation and possibly fucosylation, sulfation of the saccharide chains of GlyCAM-1 is required for high affinity binding to L-selectin.[11] The identification of the capping groups 6-sulfo sLe^x **2** and 6'-sulfo sLe^x **3** (Fig. 1)[12] prompted us to investigate the role of sulfation on Le^x and Le^a at the 6- and 6'-positions with respect to L-selectin recognition.

Figure 1





1 sialyl Lewis x (sLe^x): $R_6 = R_{6'} = H$

2 6–sulfo sLe^x: $R_6 = SO_3^-$, $R_{6'} = H$

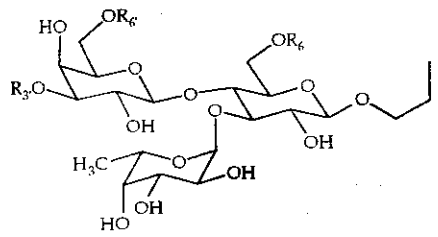
3 6'–sulfo sLe^x: $R_6 = H$, $R_{6'} = SO_3^-$

4 sialyl Lewis a (sLe^a)

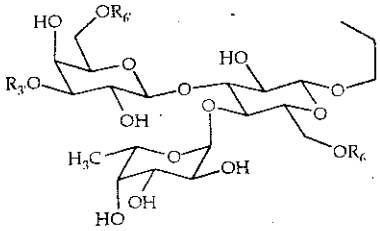
Sialyl Lewis x and sialyl Lewis a represent relatively complicated synthetic targets. Although several chemical[13] and chemoenzymatic[14] approaches to these structures have been described, none provided sufficient flexibility for our purposes: we needed to generate several sulfated derivatives in adequate yields both for biological testing and for further conversion into multivalent derivatives. Chemoenzymatic syntheses, although often high-yielding, require co-factors and enzymes that are expensive or not readily available. In addition, known enzymes do not readily accept substrates which would serve as precursors to various 6'-sulfated derivatives.[15] Alternatively, chemical syntheses allow for the generation of various sulfated analogs; however, they often result in low yields due mainly to the difficulty of chemical sialylation.

To achieve our goal of developing a flexible, high-yielding synthetic route, we simplified the target structures in a way which would facilitate synthesis without sacrificing biological activity. The observation that the sLe^x and sLe^a analogs 3'-sulfo Le^x and 3'-sulfo Le^a occur naturally on selectin-binding cells[16] combined with data from structure-activity studies on numerous synthetic analogs[17] suggests that the main feature of sialic acid necessary for selectin binding is its negatively charged carboxylate group. Given the documented biological data and our need for high material throughput, the target molecules we chose to generate contain a sulfate ester in place of a sialic acid residue, a substitution that greatly simplifies their syntheses. In addition, the replacement of the core glucosamine residue of sLe^x and sLe^a with glucose was found to have little or no effect on selectin recognition.[18] Substitution of the *N*-acetyl group with a hydroxyl group facilitates synthesis by eliminating the need for troublesome nitrogen protecting groups and by improving the solubilities of synthetic intermediates in organic solvents. Therefore, to test the effects of sulfation of Le^a and Le^x on selectin binding, we chose to synthesize the sulfated sLe^x analogs **6**-**11** and sLe^a analogs **13**-**16** (Fig. 2) on the Le^x(Glc)β-OPr (**5**) and Le^a(Glc)β-OPr (**12**) templates (Fig. 2).

Figure 2



Sulfo Lewis x Derivatives



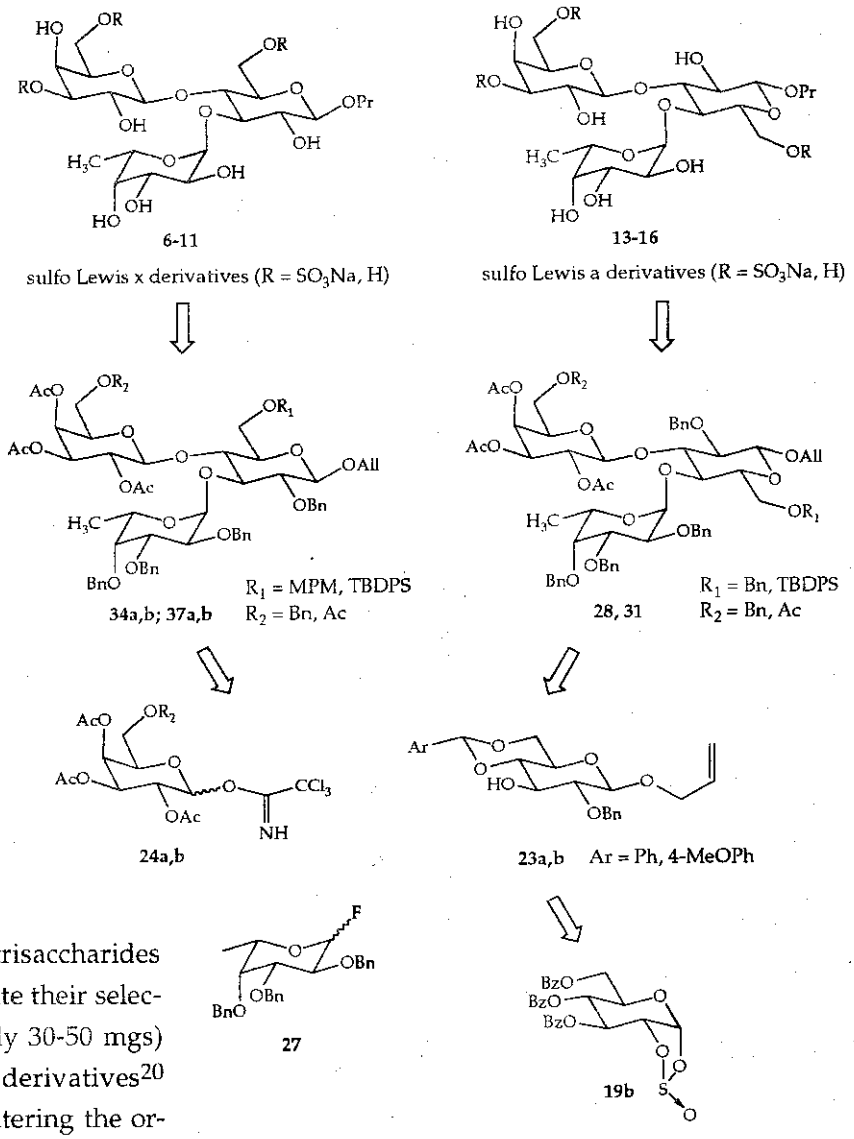
Sulfo Lewis a Derivatives

5 $R_{3'} = R_{6'} = R_6 = H$ [Le^x(Glc)β-OPr]
6 $R_{3'} = R_{6'} = H$, $R_6 = SO_3Na$ [6-sulfo Le^x(Glc)]
7 $R_{3'} = SO_3Na$, $R_6 = R_{6'} = H$ [3'-sulfo Le^x(Glc)]
8 $R_{3'} = R_{6'} = SO_3Na$, $R_6 = H$ [3',6'-disulfo Le^x(Glc)]
9 $R_{3'} = H$, $R_6 = R_{6'} = SO_3Na$ [6',6-disulfo Le^x(Glc)]
10 $R_{3'} = R_6 = SO_3Na$, $R_{6'} = H$ [3',6-disulfo Le^x(Glc)]
11 $R_{3'} = R_{6'} = R_6 = SO_3Na$ [3',6',6-trisulfo Le^x(Glc)]

12 $R_{3'} = R_{6'} = R_6 = H$ [Le^a(Glc)β-OPr]
13 $R_{3'} = R_6 = H$, $R_{6'} = SO_3Na$ [6'-sulfo Le^a(Glc)]
14 $R_{3'} = SO_3Na$, $R_6 = R_{6'} = H$ [3'-sulfo Le^a(Glc)]
15 $R_{3'} = R_{6'} = SO_3Na$, $R_6 = H$ [3',6'-disulfo Le^a(Glc)]
16 $R_{3'} = R_6 = SO_3Na$, $R_{6'} = H$ [3',6-disulfo Le^a(Glc)]

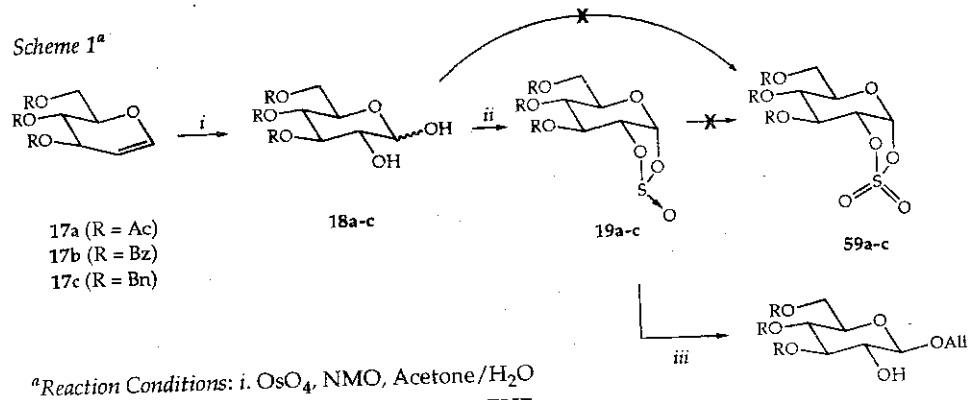
Our divergent strategy was conceived to utilize as many common intermediates as possible en route to the various sulfated trisaccharides. By minimizing protecting group manipulations and maximizing overlap in glycosylation strategies, we planned to increase overall yields and reduce the number of synthetic steps. The sulfated trisaccharide derivatives **6-11** and **13-16** were each envisioned as arising from regioselective sulfation[19] of polyhydroxylated precursors or from sulfation of a single, unprotected hydroxyl group. Sulfation substrates could be generated by selective deprotection of the similar, differentially protected trisaccharides **28, 31, 34** and **37** (Fig. 3). From these key precursors, we generated ten sulfated trisaccharides in sufficient quantities to evaluate their selectin inhibitory activities (typically 30-50 mgs) and to synthesize multivalent derivatives[20] (approximately 0.5-1 gm). By altering the order of introduction of fucose and galactose residues, Lewis a and Lewis x derivatives **28, 31, 34** and **37** can all be generated from a common set of monosaccharide derivatives: galactosyl trichloroacetimidates **24a** and **24b**, fucosyl fluoride **27** and allyl glucopyranosides **23a** and **23b**. The galactose[21] and fucose[22] donors are readily available through established synthetic routes; however, the known approach to substrates such as allyl glucopyranosides **23a** and **23b** employs several difficult and low yielding steps including allylation of the anomeric position and differentiation of *O*-2 and *O*-3. Our investigations therefore began with the search for an efficient route to compounds **23a** and **23b**.

Figure 3



Given the accumulating applications of cyclic sulfates as epoxide equivalents,[23] it was anticipated that compounds **59a-c** (Scheme 1) could act as their epoxide counterparts[24] to yield β-glycosides *via* an S_N2-like reaction at the anomeric center. In order to prepare the required cyclic sulfate precursor diols,

Scheme 1[a]



17a (R = Ac)
17b (R = Bz)
17c (R = Bn)

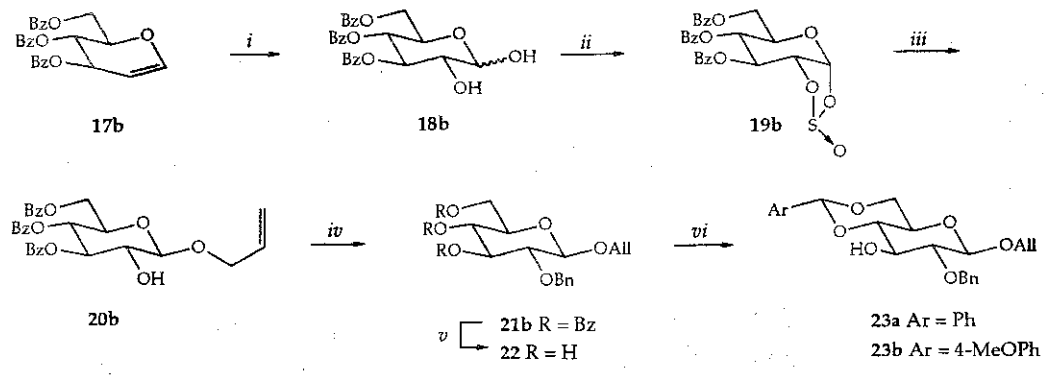
18a-c **19a-c** **59a-c** **20a-c**

[a]*Reaction Conditions*: *i*. OsO_4, NMO, Acetone/H_2O (**18a**: 100%; **18b**: 99%; **18c**: 100%); *ii*. $SO(Im)_2$, THF, -20 °C (**19a**: 87%; **19b**: 88%; **19c**: 80%); *iii*. allyl alcohol, $Ln(OTf)_3$, 3 Å ms, $PhCH_3$, 100 °C.

tri-*O*-acetyl-, tri-*O*-benzoyl- and tri-*O*-benzyl-D-glucal (**17a**, **17b** and **17c**) were treated with osmium tetraoxide under catalytic conditions to give the corresponding diols **18a-c** in quantitative yields and >19:1 preference for the gluco to manno diastereomers in all three cases. Cyclic diols typically react with sulfuryl chloride or sulfuryl diimidazole to form cyclic sulfates directly,[25] but attempts to form the glycosyl derivatives, compounds **59a-c**, under these conditions did not produce the desired products. Reaction of diols **18a-c** with sulfuryl chloride and various amine bases generally provided mixtures of starting diol with glycosyl chlorides. Similarly, reaction of **18a-c** with sulfuryl diimidazole was unsuccessful, resulting mainly in the isolation of unreacted diol. A useful method of preparation of cyclic sulfates is by oxidation of the corresponding cyclic sulfites with $RuCl_3/NaIO_4$,[26] and to this end, cyclic sulfites **19a-c** were prepared by reaction of diol precursors with thionyl diimidazole in THF at -20 °C. These cyclic sulfites, which are more stable than their sulfate analogs due to lesser ring strain and poorer leaving group ability, could be prepared in high yield and purified by flash chromatography on Florisil. Unfortunately, attempts to oxidize sulfites **19a-c** with the catalytic ruthenium system were unsuccessful, possibly due to the use of water as a co-solvent in the oxidation reaction. Given these barriers in the preparation of glycosyl cyclic sulfates, we turned our attention to cyclic sulfites **19a-c** as glycosyl donors.

Cyclic sulfites are generally less useful as electrophiles than their sulfate counterparts. The former are poorer leaving groups and are less strained; consequently, reaction with nucleophiles often results in transesterification at the electrophilic sulfur center. Despite these features, we hypothesized that cyclic sulfites **19a-c** might be active glycosyl donors due to the increased electrophilicity of C-1. In support of this idea, reaction of glycosyl cyclic sulfites with azide and other strong nucleophiles in DMF had been observed.[27] We therefore explored the reactivity of **19a-c** toward hydroxyl nucleophiles. Although these weak nucleophiles were not reactive on their own, we reasoned that selective activation of **19a-c** with Lewis acids could be achieved. Attempted reaction of **19a-c** with alcohol nucleophiles in the presence of a number of commonly employed Lewis acids revealed that several Lewis acids promoted the desired reaction; however, identifying conditions which afforded both the desired stereoselectivity and high yield was more challenging. It was ultimately discovered that the weakly acidic lanthanide(III) triflates[28] facilitated the S_N2-like reaction of glycosyl donors **19a-c** with good stereoselectivity and in high yield. In the optimized procedure, glycosyl cyclic sulfites were reacted with allyl alcohol in the presence of a catalytic amount of ytterbium(III) triflate or holmium(III) triflate. This procedure pro-

Scheme 2[a]



[a]*Reaction Conditions*: *i*. OsO_4, NMO, Acetone, H_2O, 99%; *ii*. $SO(Im)_2$, THF, -20 °C, 88%; *iii*. allyl alcohol,$Yb(OTf)_3$, 3 Å ms, $PhCH_3$, 100 °C, 76% (8:1 β:α); *iv*. benzyl trichloroacetimidate, TfOH, CH_2Cl_2, cyclohexane, 95%; *v*. K_2CO_3, MeOH, 91%; *vi*. $ArCH(OMe)_2$, *p*-TsOH, DMF, 50 °C, reduced pressure (Ar = Ph: 77%, Ar = 4-MeOPh: 84%).

duced *O*-glycosides with stereoselectivities on the order of 8-13:1 and with yields ranging from 75-92%, providing ready access to β-*O*-allyl glucopyranosides differentiated at *O*-2.[29]

Using the cyclic sulfite glycosylation protocol, a synthetic route to the required glucose monomers **23a** and **23b** was then developed (Scheme 2). Although the desired products were available from a variety of protected glucals, it was found that the benzoate protecting groups gave the best yields in the sulfite-forming reaction and in glycosylation when reactions were performed on multi-gram scale. Osmylation of **17b**, cyclic sulfite formation and glycosylation using $Yb(OTf)_3$ proceeded as described, yielding a mixture of anomers (8:1 β:α), which were easily separated to provide β-*O*-allyl glucopyranoside **20b** in 76% yield. Protection of *O*-2 with benzyl trichloroacetimidate/triflic acid,[30] followed by basic methanolysis gave triol **22**, which was converted to the desired glucoside acceptors **23a** and **23b** by standard methods. Using this route, compounds **23a** and **23b** were synthesized in six steps and 44 and 48% yields respectively from tri-*O*-benzoyl-D-glucal **17b**.

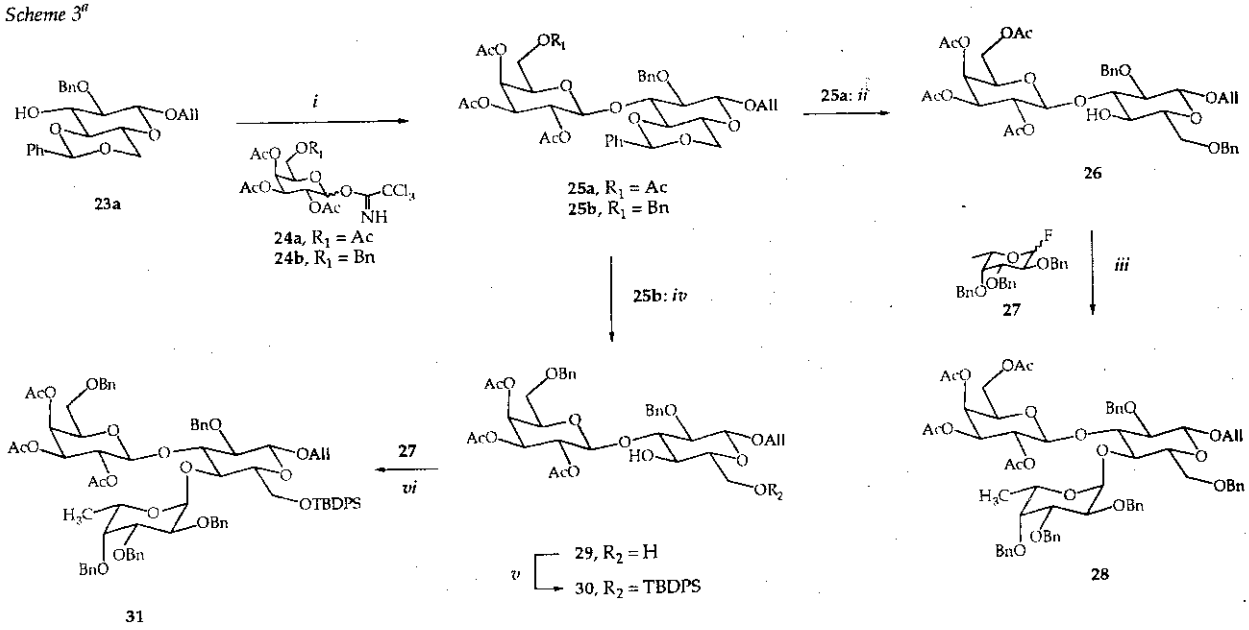
With a successful large-scale synthesis of glucose acceptors in hand, we turned our attention to the construction of Lewis x and Lewis a trisaccharides. In general, Le^a is easier to synthesize than is Le^x. The origins of this difference can be traced to the order of attachment of the galactose and fucose residues. Axial fucoside residues are more labile than other saccharide linkages; consequently, galactose has generally been installed first in syntheses of Le^a and Le^x. Construction of the Le^a template from **23a** or **23b** proceeds naturally by introduction of galactose prior to fucose, requiring no additional protecting group manipulations. To attach galactose first in a route to Le^x, *O*-3 of glucose acceptors **23a** or **23b** must be protected and *O*-4 subsequently deblocked. We surmised that such protecting group machinations could be avoided by designing a glycosylation strategy that allowed for the attachment of either fucose or galactose first. With such a strategy, both Le^a or Le^x could be synthesized by analogous routes with minimal protecting group adjustments.

Important concerns in developing a glycosylation strategy are the reactivities of various glycosyl donors and the stereoselectivities they provide. We reasoned that the greatest control over these param-

eters can be achieved by balancing the reactivities of the leaving group at the anomeric center with the electron-withdrawing properties of the donor protecting groups. For example, construction of a β-galactoside linkage is straightforward when an acetate participating group at *O*-2 of the donor is present; however, ester protecting groups significantly deactivate glycosyl donors, and such substrates have been designated disarmed.[31] To overcome the decreased reactivity of the disarmed donor, we chose to use the highly reactive trichloroacetimidates **24a** and **24b**. Trichloroacetimidates can be activated under homogeneous conditions with non-metallic Lewis acids such as $BF_3{\cdot}OEt_2$ and TMSOTf[32] as well as by protic acids like trifluoromethanesulfonic acid[33] and *p*-toluenesulfonic acid.[34] These conditions favor rapid formation of the desired glycosidic linkage and minimize the contact of acceptors with strong Lewis or protic acids. In contrast to the stability of disarmed donors, the anomeric group of the fucoside monomer is more labile, both because fucose contains no electron withdrawing substituent at the 6-position and because benzyl protecting groups were used. Benzyl groups, which are useful because of their stability and ease of removal, do not strongly deactivate the anomeric position; thus a less reactive, more stable leaving group could be used at the anomeric position. For our purposes, we chose to generate glycosyl fluoride **27**. Fluoride donors are more stable than their bromide or chloride analogs, and are easily prepared and activated under a variety of conditions.[35] By moderating the reactivity of the galactosyl and fucosyl donors, we envisioned either Le^a or Le^x could be synthesized under similar or identical conditions.

With the goal of developing a general strategy, syntheses of Le^a trisaccharides **28** and **31** were initiated (Scheme 3). Schmidt glycosylation of **23a** with 2,3,4,6-tetra-*O*-acetyl galactosyl trichloroacetimidate

Scheme 3[a]



[a]*Reaction Conditions*: *i*. TMSOTf, Et_2O, 0 °C (**25a**: 85%, **25b**: 87%); *ii*. Et_3SiH, CF_3CO_2H, $(CF_3CO)_2O$, CH_2Cl_2, 0 °C, 77%; *iii*. Bu_2SnCl_2, AgOTf, 2,6-di-*tert*-butyl-4-methylpyridine, 4 Å ms, $PhCH_3$, 0 °C, 90% (15:1 α:β); *iv*. *p*-TsOH, $CHCl_3$, MeOH, 79%; *v*. TBDPS-Cl, CH_2Cl_2, pyr, DMAP, 96%; *vi*.Bu_2SnCl_2, AgOTf, 2,6-di-*tert*-butyl-4-methylpyridine, 4 Å ms, $PhCH_3$, 0 °C→rt, 79% (5:1 β:α).

24a or 2,3,4-tri-*O*-acetyl-6-*O*-benzyl galactosyl trichloroacetimidate **24b** in the presence of catalytic trimethylsilyl triflate proceeded readily, providing disaccharides **25a** and **25b** as single anomers in 85 and 87% yields respectively. To reveal *O*-4 for subsequent glycosylation, selective reduction of the benzylidene acetal was planned. A number of methods to promote the reductive cleavage of **25a** and **25b** were attempted including $Et_2O{\cdot}HCl/NaBH_3CN$[36] and $TFA/NaBH_3CN/DMF$,[37] but these reactions were plagued either by poor selectivity or by irreproducibility. While these conditions were being investigated, a report of the selective reduction of benzylidene acetals with trifluoroacetic acid/triethylsilane[38] appeared in the literature. When applied to our system, this protocol provided compound **26** with approximately 10:1 regioselectivity and in 77% isolated yield. To introduce the axial fucoside residue, tin activation methods were explored,[39] and the combination of dibutyltin dichloride and silver triflate[40] with 2,6-di-*tert*-butyl-4-methylpyridine as a proton scavenger proved to be an effective catalyst mixture. Activated fucosyl fluoride **27** should react to favor formation of the desired axial linkage, and in non-polar solvents such as toluene, the desired stereoselectivity was observed. Addition of fucosyl fluoride **27** to a catalyst mixture containing glycosyl acceptor **26** resulted in formation of Le^a trisaccharide **28** in 90% yield as a mixture of diastereomers (15:1 α:β). After removal of the ester protecting groups, the diastereomers could be separated, precluding the need for separation at the glycosylation stage.

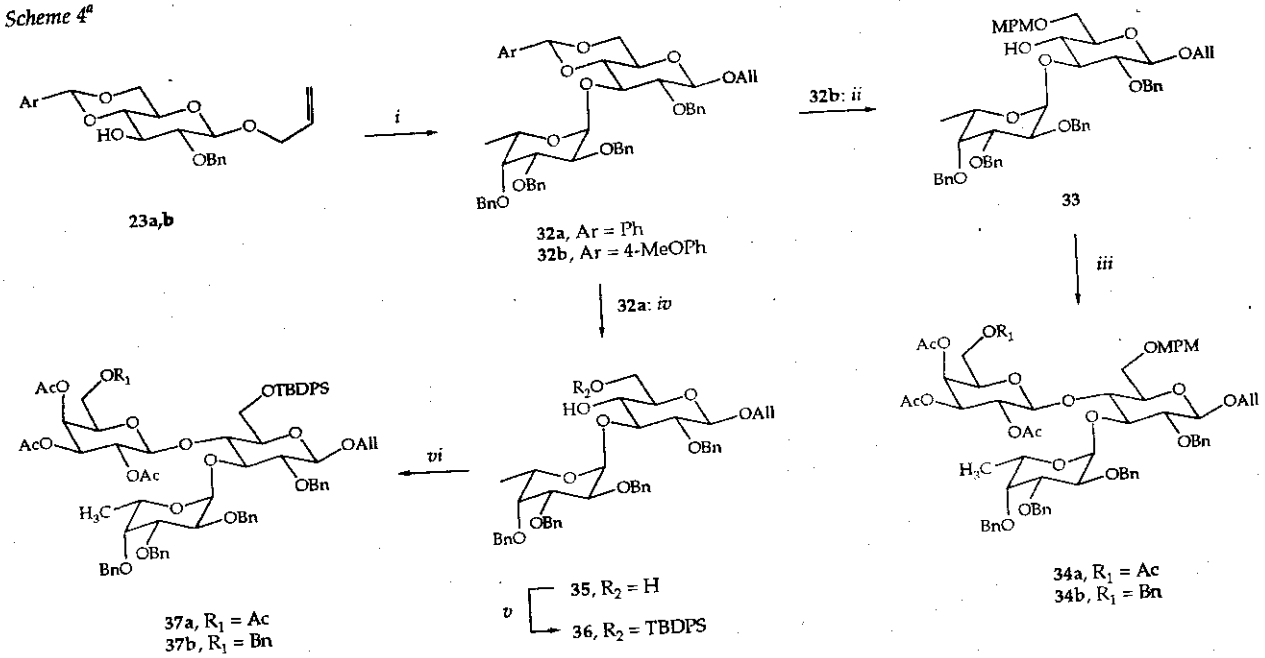
With a route to **28** as the foundation for the synthesis of targets with 3'- and 6'-modifications, an approach to Le^a analogs with *O*-6 of glucose differentiated was required. A strategy employing allyl glucopyranoside acceptor **23b** (Scheme 2) was discarded due to the poor stability of and difficulty in selectively reducing the *p*-methoxybenzylidene acetal as discovered in the synthesis of a similar Le^x derivative (*vide infra*). Selective protection of *O*-6 as a silyl ether, however, could achieve the same objective. To this end, **25b** (Scheme 3) was treated with *p*-toluenesulfonic acid, and the resulting diol **29** protected as the *tert*-butyldiphenylsilyl ether. Disaccharide acceptor **30** was then fucosylated under identical conditions to those used for the synthesis of **28**, yielding Le^a analog **31** in 79% yield as a mixture of anomers (5:1 α:β). Using this approach to trisaccharides **28** and **31**, four Le^a derivatives containing sulfate groups at biologically relevant positions were generated.

To synthesize the Le^x trisaccharide core, we planned to use a variation on our route to Le^a. In this approach, the axial fucoside linkage is formed first, a strategy which has often been avoided due to the reported instability of this glycosidic bond.[41] Still, this plan for trisaccharide construction is the most straighforward, and we anticipated that problems of instability could be avoided by minimizing contact with strong acids and promoting the desired transformations under mild conditions.

From the outset of this synthesis, we found significant differences in the glycosylation reactions with fucosyl fluoride **27** and galactosyl trichloroacetimidates **24a** and **24b**. Glucopyranoside **23b** (Scheme 4) was subjected to fucosylation conditions identical to those utilized in the Le^a synthesis, however, formation of an unknown by-product significantly reduced the isolated yields. This side reaction could, however, be prevented by forming the catalyst in the absence of the disaccharide acceptor with an excess of base and adding a mixture of acceptor **23b** and donor **27** into the pre-formed catalyst mixture. This protocol provided compound **32b** in 74% isolated yield (approximately 9:1 ratio of anomers before separation) without significant side reactions.

Attachment of the galactose residue required exposure of *O*-4, which could be achieved by selective

Scheme 4[a]

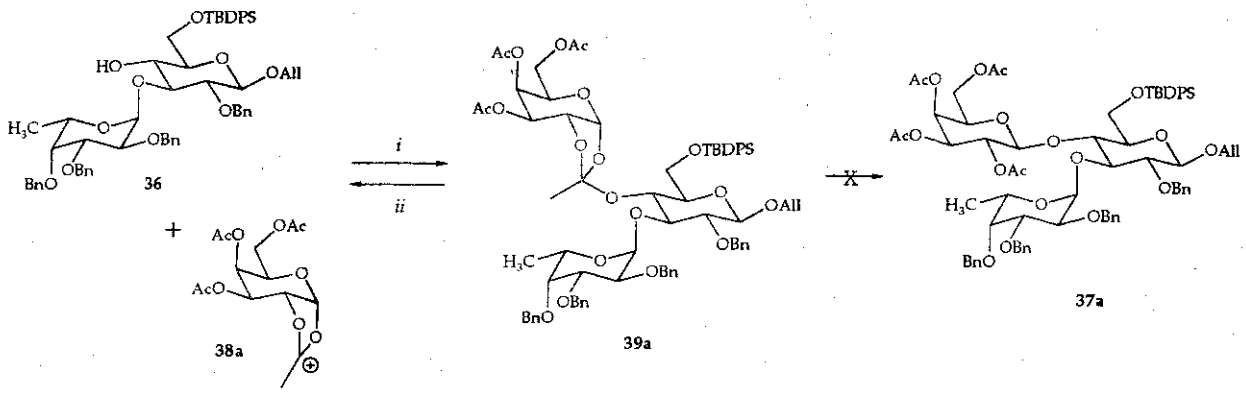


[a]*Reaction Conditions*: *i*. **27**, Bu_2SnCl_2, AgOTf, 4 Å ms, 2,6-di-*tert*-butyl-4-methylpyridine, $PhCH_3$ (**32a**: 76% axial anomer, **32b**: 74% axial anomer); *ii*. $AlCl_3$, $Me_3N{\cdot}BH_3$, 4 Å ms, THF, 0 °C → rt, 67% (+ 22% diol); *iii*. **24a** or **b**, TfOH, Et_2O, 0 °C (**34a**: 95%, **34b**: 96%); *iv*. *p*-TsOH, $CHCl_3$, MeOH, 82%; *v*. TBDPS-Cl, pyr, DMAP, CH_2Cl_2, 95%; vi. **24a** or **b**, TfOH, Et_2O, 0 °C (**37a**: 89%, **37b**: 96%).

reduction of the *p*-methoxybenzylidene acetal of **32b**. A variety of conditions to accomplish this transformation were investigated, including $Et_2O{\cdot}HCl/NaBH_3CN$,[36] TFA/Et_3SiH,[38] TFA/$NaBH_3CN$[37] and TfOH/Et_3SiH. Under all of these conditions, large amounts of the undesired product **35**, arising from hydrolysis of the acetal, were obtained. Successful conversion was achieved through use of a less commonly employed procedure, in which aluminum(III) chloride serves as the Lewis acid and trimethylamine-borane complex as the reducing agent.[42] Interestingly, this result cannot be rationalized by accepted mechanistic models for selective benzylidene acetal reduction,[36] yet the reaction afforded a 67% isolated yield of the desired regioisomer **33** (approximately 13:1 regioselectivity) with 22% of the diol **35** recovered. This desired selectivity, however, could not be attained reproducibly when the reduction was performed on greater than 300 mg of disaccharide acetal; consequently, we sought another approach.

The impracticality of the acetal reduction reaction combined with the observed instability of *p*-methoxybenzylidene acetals **23b** and **32b**, prompted us to devise a different strategy for the differentiation of glucose *O*-6. A sequence similar to that employed in the synthesis of disaccharide acceptor **30** was used to selectively isolate *O*-6. To accomplish this, allyl glucopyranoside **23a** was fucosylated with **27** under the conditions described above. The disaccharide acceptor **36** (Scheme 4) was then prepared by solvolysis of acetal **32a**, followed by selective silylation of the resulting diol **35**, and this sequence could be executed on multi-gram scale. Conditions for the glycosylation of **36** with trichloroacetimidates

Scheme 5[a]

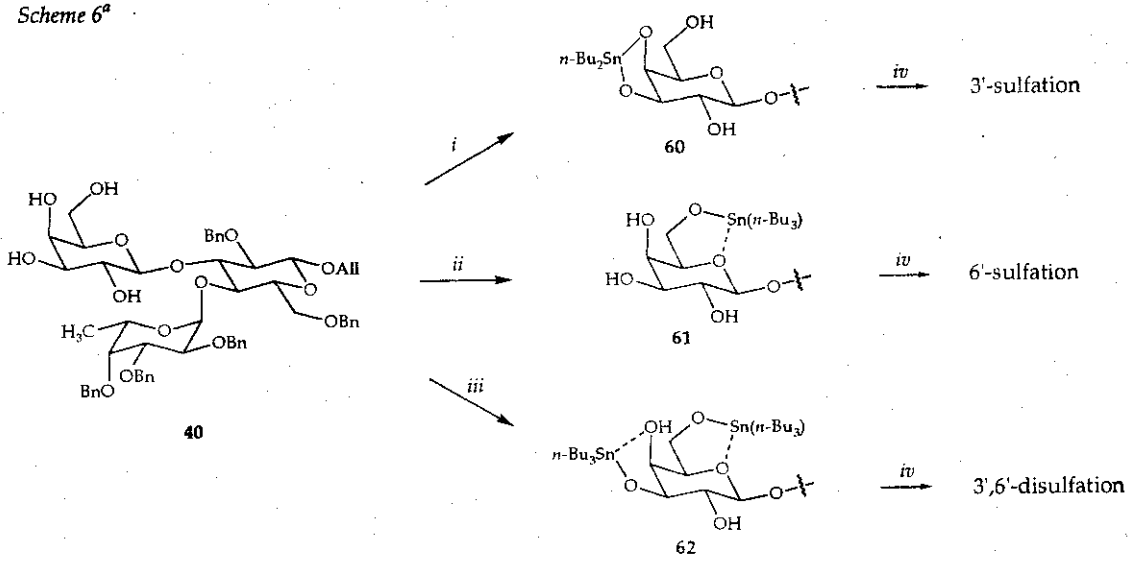


[a]*Reaction Conditions*: *i*. 1.1 eq. **24a**, TMSOTf or TfOH, Et_2O, 0 °C, anhydrous conditions, 50-100 %; *ii*. TfOH, Et_2O, 0 °C, "non-anhydrous" conditions, 93%.

24a and **24b** were then investigated.

We anticipated that glycosylation using trichloroacetimidate donor **24** would occur efficiently with **36** as it had with Le[a] precursor **23a** (Scheme 3); however, we found marked differences between **36** and substrate **23a**. Treatment of **36** with trichloroacetimidate **24a** and catalytic TMSOTf or triflic acid at 0 °C in diethyl ether resulted in production of the desired trisaccharide product, but it was contaminated with trisaccharide orthoester **39a** (Scheme 5), which arises from attack of the oxygen nucleophile on acetoxonium intermediate **38a**. Few references in the literature describe the formation of orthoester by-products in the glycosylation of trichloroacetimidates, and use of these donors is often cited as a way to avoid such side reactions.[31] Yet we obtained between 50 and 100% yields of this unwanted product under the standard glycosylation conditions (TMSOTf, $BF_3{\cdot}OEt_2$, triflic acid). Because orthoester products were not observed in our synthesis of Le[a], their formation may be the result of increased steric interactions encountered in the glycosylation of **36**. The preponderance of orthoester was influenced by the choice of solvent, with non-polar solvents such as toluene producing higher yields of orthoester than more polar solvents such as diethyl ether. Attempts to rearrange the orthoester product with TMSOTf,[43] $BF_3{\cdot}OEt_2$[44] and $SnCl_4$[45] were unsuccessful; however, it was noted that the disaccharide **36** could be isolated in 93% yield upon treatment of orthoester **39a** with catalytic triflic acid. This observation suggested that conditions could be found under which orthoester formation would be reversible and the trisaccharide could be formed. To test this hypothesis, we investigated the use of excess glycosyl donor. Specifically, when **36** was treated with three equivalents of **24a** in the presence of catalytic triflic acid, only traces of orthoester were observed. Using conditions that exploit the reversibility of orthoester formation, trisaccharides **37a** and **37b** could be prepared in 89 and 96% yield respectively. It should be noted that the axial fucoside linkage, which has been reported to be labile, remained intact when subjected to powerful Lewis acids or when treated briefly with triflic acid. With the construction of Lewis a and Lewis x trisaccharide cores completed, it was necessary to implement a strategy for the sulfation of the various interesting positions.

Scheme 6[a]



[a]*Reaction Conditions*: *i*. Bu_2SnO, PhH, reflux; *ii*. 0.5 eq. $(Bu_3Sn)_2O$, PhH, reflux; *iii*. 1.0 eq. $(Bu_3Sn)_2O$, PhH, reflux; *iv*. pyr·SO_3

Synthesis of Sulfated Le^a and Le^x Trisaccharides

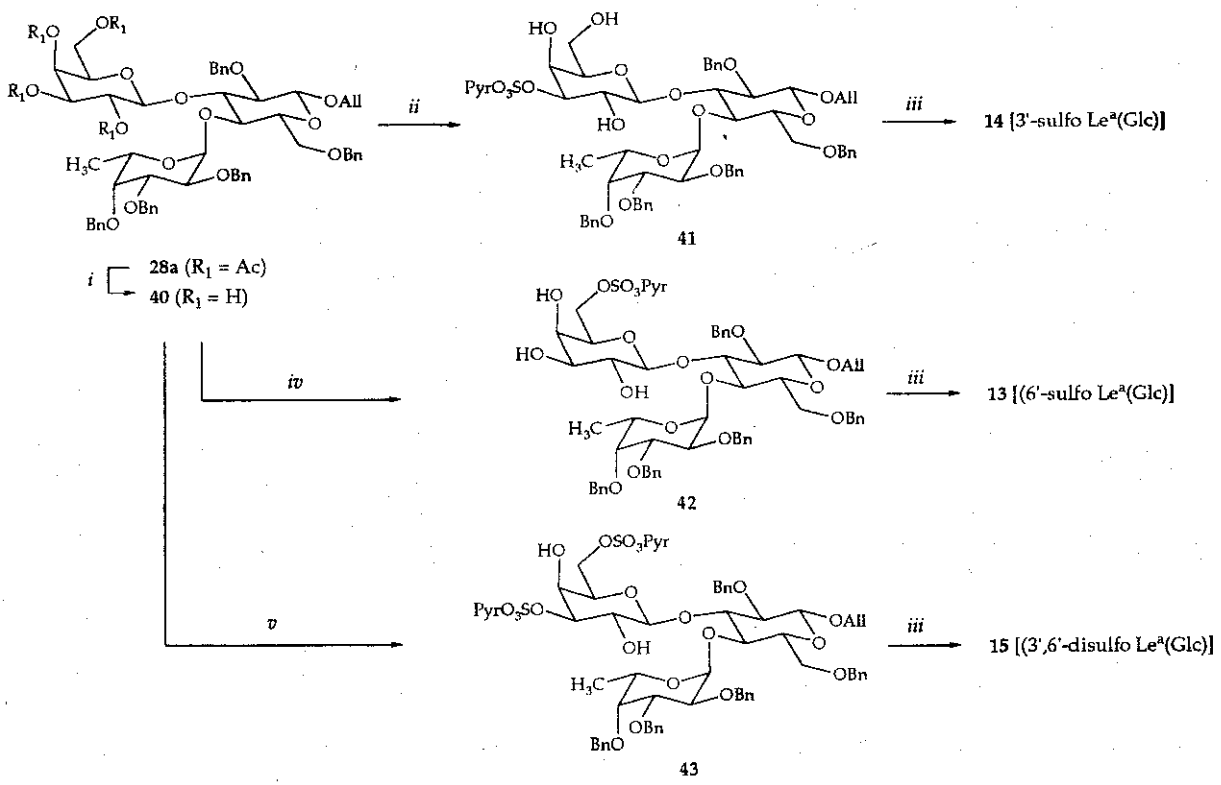
Our design for the synthesis of sulfated Le^a and Le^x derivatives relies on developing conditions for the regioselective introduction of anionic groups late in the synthesis. A key advantage to this strategy is that it reduces the number of protecting group manipulations in the synthesis. At the outset of our work it was known that alkoxystannanes could be used to selectively introduce acyl and alkyl groups at specific positions within polyhydroxylated systems.[46] We planned to capitalize on this observed selectivity to produce sulfated trisaccharides using electrophilic sulfating agents such as pyridine-sulfur trioxide complex.[19] Preparation of a stannylene acetal of unprotected or partially protected galactose residues results in the regioselective activation of the 3-position toward electrophiles, and we envisioned that this mode of activation could be applied to prepare the natural product analogs 3'-sulfo Le^x(Glc) and 3'-sulfo Le^a(Glc). It was also known that treatment of a polyhydroxylated system with bistributyltin oxide increases the nucleophilicity of primary hydroxyl groups,[46a, 47] and we anticipated that this selectivity could be used for the synthesis of various 6- and 6'-sulfated Le^a and Le^x analogs.

Initial sulfation reactions were directed toward the synthesis of the natural product analogs 3'-sulfo Le^x(Glc) and 3'-sulfo Le^a(Glc). Treatment of the partially protected Le^a derivative **40** with dibutyltin oxide resulted in the formation of the presumed stannylene acetal **60** (Scheme 6).[48] Addition of pyr·SO_3 to the reaction mixture resulted in the formation of a single product which, after hydrogenolysis, was unambiguously determined to be 3'-sulfo Le^a(Glc)β-OPr **14** (Fig. 2). These reaction conditions were originally investigated utilizing a 6'-protected galactose residue, however it was subsequently determined that protection of the primary hydroxyl was unnecessary if the sulfation was carried out in benzene. The successful application of this method of activation provides for ready access to the 3'-sulfated derivatives.

To generate 6'-sulfated derivatives, we explored several alternatives. Sulfation of a primary hydroxyl in the presence of secondary hydroxyls can be achieved by reaction with a single equivalent of sulfating agent; however, in the case of compounds like **40**, this reaction proved difficult to effect in high yield. In order to increase the selectivity and yield of the sulfation, it was decided to activate the primary hydroxyl as a tributylstannyl ether. To this end, **40** was treated with 0.5 equivalent of bis-tributyltin oxide, presumably generating stannyl ether **61**. This intermediate reacts with pyr·SO_3 in benzene to produce only the desired monosulfate, with the choice of benzene solvent critical for the suppression of oversulfation.

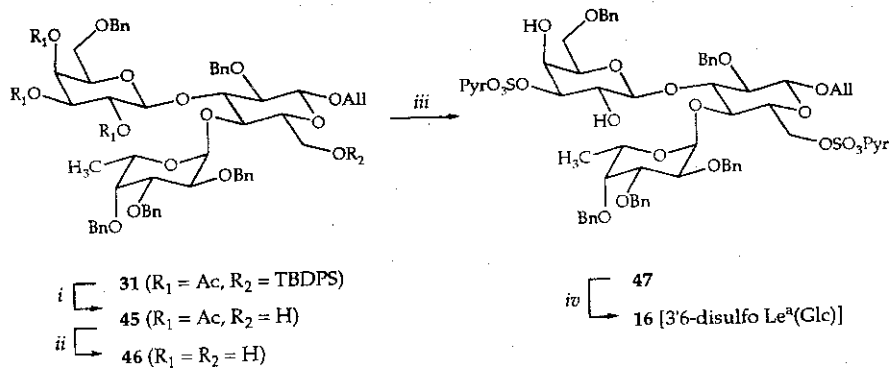
Upon demonstrating that selective activation at either the 3- or 6-positions of an unprotected galactose residue could be accomplished, we explored the activation of both sites simultaneously to generate a 3',6'-disulfated trisaccharide. This approach depends on both the accessibility of the 6'-hydroxyl group and the increased nucleophilicity of galactose *O*-3 relative to *O*-2 and *O*-4. Treatment of **40** with 1.0 equivalent of bis-tributyltin oxide in refluxing benzene led to putative intermediate **62**. Reaction of this tin alkoxide complex with excess pyr·SO_3 in pyridine solvent results in a single product sulfated at *O*-3 and *O*-6. The observed selectivity is mediated by coordination to tin, as treatment of **40** with pyr·SO_3 does not yield similar results. As in the 6'-monosulfation, the choice of solvent was critical in the

Scheme 7[a]



[a]*Reaction Conditions*: *i*. K_2CO_3, MeOH, 91%; *ii*. Bu_2SnO, PhH, reflux; pyr·SO_3; *iii*. $Pd(OH)_2/C$, MeOH, H_2O, 50 psi H_2 (**14**: 96% overall; **13**: 59% overall; **15**: 54% overall); *iv*. 0.5 eq. $(Bu_3Sn)_2O$, PhH, reflux; pyr·SO_3; *v*. 1.0 eq. $(Bu_3Sn)_2O$, PhH, reflux; pyr·SO_3, pyr.

Scheme 8[a]

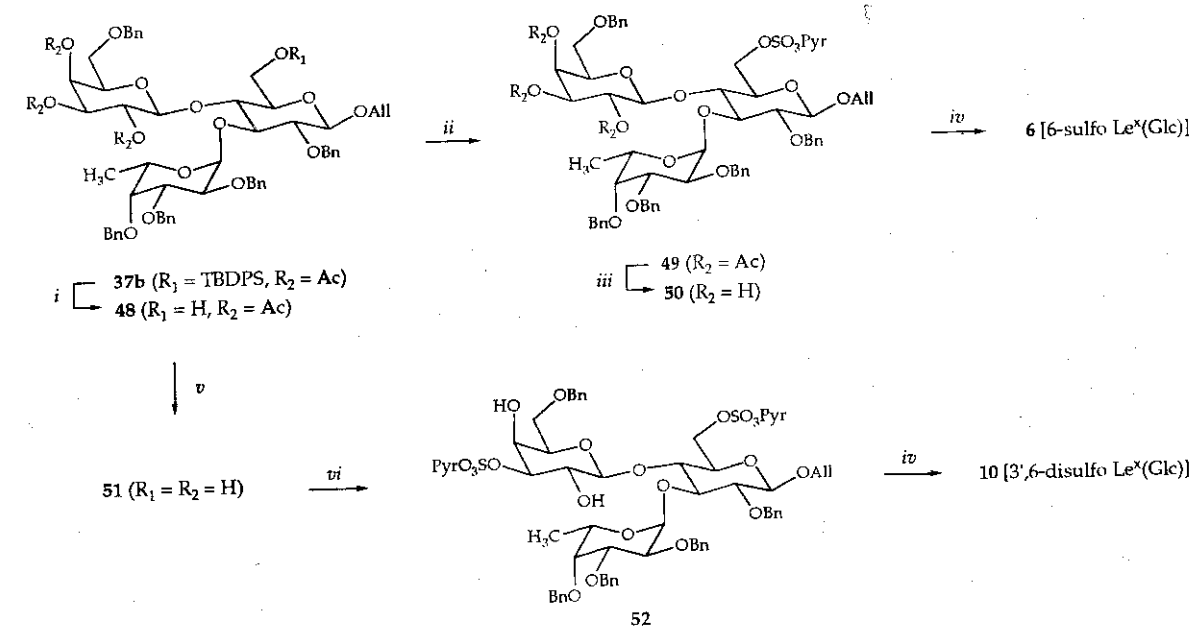


[a]*Reaction Conditions*: *i*. TBAF, THF, 79%; *ii*. K_2CO_3, MeOH, 89%; *iii*. 1.0 eq. $(Bu_3Sn)_2O$, PhH, reflux; pyr·SO_3, pyr, 82%; *iv*. $Pd(OH)_2$/C, MeOH, H_2O, 500 psi H_2, 62%.

disulfation reaction. The target disulfate was only generated in high yield when the reaction was conducted in pyridine; reaction of **62** with pyr·SO_3 was neither selective nor high yielding when conducted in benzene, possible due to the formation of different alkyoxystannyl aggregates, acidic by-products or to the insolubility of the monosulfate intermediates in benzene.

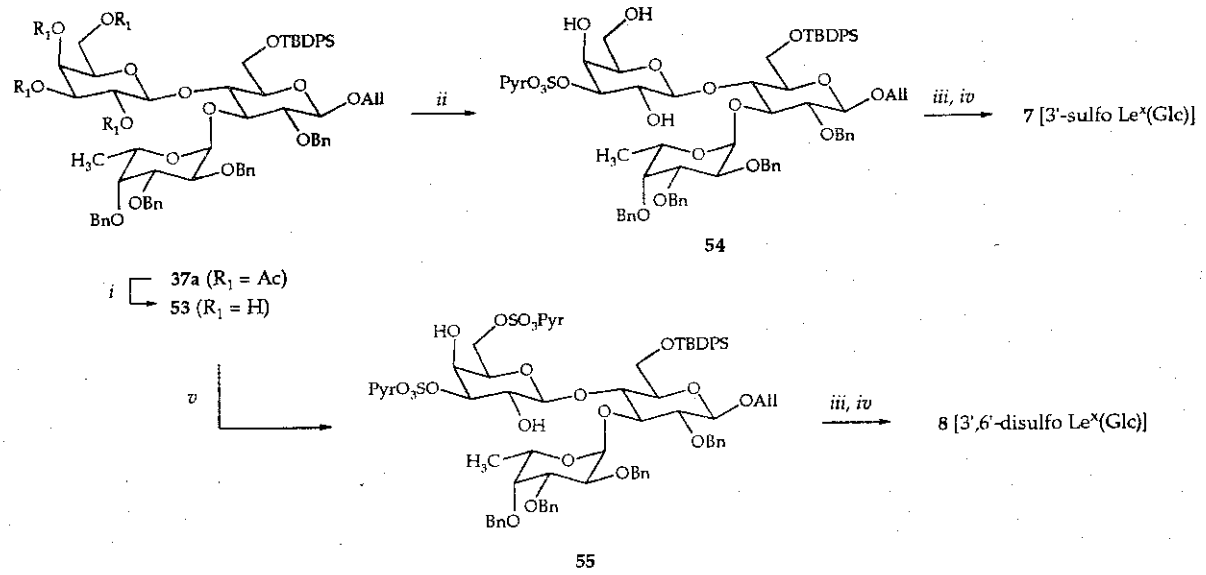
These methods for the selective synthesis of 3'- and 6'-monosulfates as well as 3',6'-disulfates were applied to synthesis of Le^a(Glc) derivatives **13-16** (Scheme 7). From compound **40**, the protected sulfated trisaccharides **41**, **42** and **43** were prepared and deprotected by catalytic hydrogenation over Pearlman's catalyst, yielding the three sulfo Le^a(Glc) derivatives **13**, **14** and **15** as their β-*O*-propyl glycosides. Similarly, the synthesis of 3',6-disulfo Le^a(Glc) **16** was accomplished using differentially protected trisaccharide **31** (Scheme 8). The silyl group of trisaccharide **31** was removed by reaction with

Scheme 9[a]



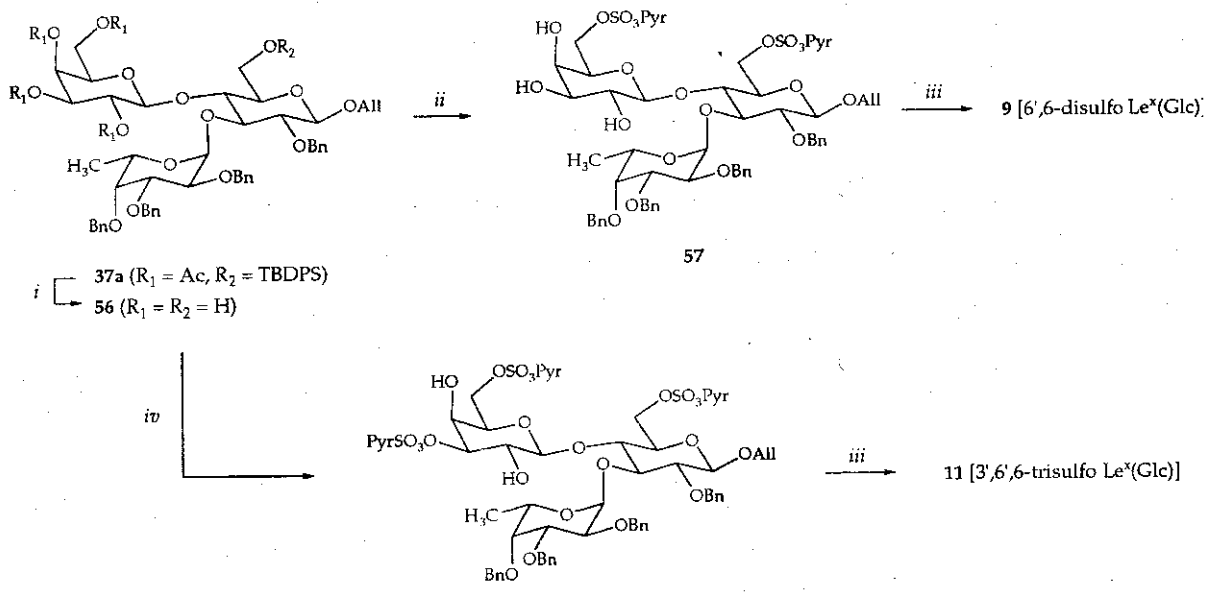
[a]*Reaction Conditions*: *i*. TBAF, THF, 90%; *ii*. pyr·SO_3, pyr, 94%; *iii*. NaOH, H_2O, MeOH, pH = 12, 99%; *iv*. $Pd(OH)_2$/C, MeOH, H_2O, 50 psi H_2 (**6**: 93%, **10**: 98%); *v*. K_2CO_3, MeOH, 97%;*vi*. $(Bu_3Sn)_2O$, PhH, reflux; pyr·SO_3, pyr, 91%.

Scheme 10[a]



[a]*Reaction Conditions*: *i*. K_2CO_3, MeOH, 92%; *ii*. Bu_2SnO, PhH, reflux; pyr·SO_3; *iii*. TBAF, THF; *iv*. $Pd(OH)_2/C$, MeOH, H_2O, 50 psi H_2 (**7**: 81% overall; **8**: 76% overall); *v*. $(Bu_3Sn)_2O$, PhH, reflux; pyr·SO_3, pyr.

Scheme 11[a]



[a]*Reaction Conditions*: *i*. TBAF, THF; K_2CO_3, MeOH, 99%; *ii*. pyr·SO_3, pyr; *iii*. $Pd(OH)_2/C$, MeOH, H_2O, 50 psi H_2 (**9**: 53% overall; **11**: 85% overall); *iv*. $(Bu_3Sn)_2O$, PhH, reflux; pyr·SO_3.

TBAF and the acetates by basic methanolysis to yield tetraol **46**. Disulfation of **46**, using the exact procedure described above for preparation of **43**, afforded 3',6-disulfo Le^a(Glc)β-OPr **16** after hydrogenolysis.

For the synthesis of the six Le^x(Glc) derivatives **6-11**, we applied an analogous sulfation strategy to that described for the production of Le^a derivatives (Schemes 9-11). These procedures differ from those described for the synthesis of **13-16** only in the starting trisaccharides employed. All six derivatives were synthesized from Le^x trisaccharides **37b** (Scheme 9) and **37a** (Schemes 10 and 11). In two cases, no tin reagent was utilized for sulfation. First, 6-sulfo Le^x(Glc) **6** (Scheme 9) was formed by sulfation of a single unprotected hydroxyl group on trisaccharide **48**, ensuring selectivity. The trisaccharide 6',6-disulfo Le^x(Glc) **9** (Scheme 11) could not be prepared by activation of the two primary hydroxyls of trisaccharide **56** with bis-tributyltin oxide, however it could be generated by careful reaction of **56** with excess pyr·SO_3 in pyridine albeit in somewhat poorer yield than in the tin-activated cases.

Conclusion

We have described the synthesis of a number of sulfated analogs of Lewis x and Lewis a designed to test the effects of sulfation on selectin recognition. The route we have developed allows for the synthesis of gram quantities of the target molecules from common intermediates in 10-20% overall yield and with no linear sequence exceeding 15 steps. Our approach provides access to a variety of related structures by utilizing overlapping glycosylation and sulfation strategies and features new methods for β-selective glycosylation of allyl alcohol, prevention of orthoester formation in the Schmidt glycosylation and selective sulfation of polyhydroxylated compounds at several biologically interesting positions. We have already converted some of the described selectin ligands into multivalent derivatives and we anticipate that the biological activities of the monovalent compounds[49] described herein and their multivalent counterparts will contribute to our understanding of biologically and medically important protein-carbohydrate recognition processes.

Acknowledgements

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Experimental Materials and Methods

All non-aqueous reactions were run in oven dried glassware under an inert atmosphere of nitrogen or argon and monitored by thin-layer chromatography (TLC). All materials, unless otherwise noted, were obtained from commercial suppliers and used as provided. Anhydrous reaction solvents were distilled as follows: diethyl ether, tetrahydrofuran and benzene from sodium/benzophenone; toluene from sodium/anthracene; methanol from magnesium metal; and methylene chloride, triethylamine and pyridine from calcium hydride. Analytical TLC was performed on 0.25 mm pre-coated Merck Silica Gel 60 F_{254}, visualizing with ultraviolet light, phosphomolybdic acid stain or *p*-anisaldehyde stain. Flash column chromatography was performed on Merck Silica Gel 60 (230-400 mesh) or Florisil® (200 mesh), using distilled reagent grade hexanes and dichloromethane, and ACS grade ethyl acetate, methanol

and chloroform. Chloroform and dichloromethane were neutralized by filtration through basic alumina immediately prior to use. Infrared spectra were recorded on a Mattson FTIR spectrometer and mass spectra on a VG AutoSpec M (LSIMS) or Kratos MS-80RFA (EI). Melting points were recorded on an Electrothermal® melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-300 or AM-500 spectrometer or on a Varian Unity 500 spectrometer, and are referenced to residual solvent peaks ($CDCl_3$: ^{1}H: δ 7.24, ^{13}C: δ 77.0; CD_3OD: ^{1}H: δ 3.30, ^{13}C: δ 49.0) or to an internal reference of sodium 3-trimethylsilyl-2,2,3,3-d_4 propionate (TSP: ^{1}H: δ –0.012; ^{13}C: δ –0.15). ^{1}H-^{1}H couplings are assumed to be first order, and peak multiplicity is reported as s (singlet), d (doublet), t (triplet), q (quartet) and b (broad).

*3,4,6-Tri-O-benzoyl-α,β-D-glucopyranose (**18b**)*

Tri-*O*-benzoyl-D-glucal **17b** (12.2 g, 26.6 mmol) and 4-methylmorpholine *N*-oxide (3.95 g, 29.3 mmol) were dissolved in acetone (190 mL) and water (23 mL). Osmium tetraoxide (2.5% solution in *t*-butanol, 3.34 mL, 0.27 mmol) was added and the resulting orange mixture stirred for 5 days, after which TLC analysis indicated complete consumption of the glucal. 3-Mercaptopropionic acid (2 mL) was added upon which the solution turned black and stirring was continued for 2 hours. The reaction mixture was filtered through silica gel and concentrated. Purification by flash chromatography (silica, 3:2 EtOAc/hexanes) provided diol **18b** (13.0 g, 99%) as a mixture of α and β anomers. α-Isomer: R_f = 0.27 (3:2 EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05-7.85 (m, 6H), 7.56-7.28 (m, 9H), 5.76 (t, *J* = 9.7, 1H), 5.60 (t, *J* = 9.7, 1H), 5.42 (d, *J* = 3.5, 1H), 4.63-4.52 (m, 2H), 3.38 (dt, *J* = 3.7, 10.5, 1H), 3.89 (dd, *J* = 3.7, 9.7, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.2, 166.4, 165.4, 133.4, 133.3, 133.1, 129.9, 129.8, 129.5, 129.1, 128.9, 128.3, 92.6, 75.3, 71.5, 69.0, 67.8, 63.0; LRMS (LSIMS, 3-NBA): *m/z* 493.1 [M + H$^+$ calc'd for $C_{27}H_{25}O_9$ 493.2].

*Endo,exo-3,4,6-tri-O-benzoyl-α-D-glucopyranose-1,2-cyclic sulfite (**19b**)*

Diol **18b** (10.0 g, 20.3 mmol) was dissolved in tetrahydrofuran (50 mL) and the solution cooled to -20 °C. A solution of thionyl diimidazole (5.56 g, 30.5 mmol) in THF (80 mL) was then filtered directly into the cold solution of diol under a nitrogen atmosphere. The reaction was stirred at -20 °C for 20 minutes and diluted with hexanes (50 mL). Rapid filtration through a plug of silica gel, eluting with 1:1 ethyl acetate/hexanes, followed by concentration and purification by flash chromatography (Florisil, 1:1 EtOAc/hexanes) provided cyclic sulfite **19b** (9.60 g, 88%) as a white, amorphous solid. *Endo* (minor) isomer: R_f = 0.43 (3:1 hexanes/EtOAc); IR (KBr): 1726, 1452, 1266, 1096 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02-7.93 (m, 6H), 7.60-7.30 (m, 9H), 6.26 (d, *J* = 5.8, 1H), 6.05 (t, *J* = 5.3, 1H), 5.67 (dd, *J* = 5.8, 9.3, 1H), 4.83 (m, 1H), 4.79-4.71 (m, 2H), 4.52 (dd, *J* = 4.7, 12.4, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.9, 165.1, 164.7, 133.7, 133.2, 133.1, 130.0, 129.9, 129.4, 129.3, 128.6, 128.3, 103.4, 76.8, 72.3, 69.6, 67.2, 62.6; LRMS (EI): *m/z* 539.0 [M + H$^+$ calc'd for $C_{27}H_{23}O_{10}S$ 539.1]. *Exo* (major) isomer: R_f 0.39 (3:1 hexanes/EtOAc); IR (KBr): 1726, 1452, 1266, 1095 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05-7.94 (m, 6H), 7.65-7.24 (m, 9H), 6.48 (d, *J* = 4.7, 1H), 5.77 (dd, *J* = 2, 3.5, 1H), 5.56 (m, 1H), 5.18 (m, 1H), 4.66 (dd, *J* = 3.1, 12.1, 1H), 4.49 (dd, *J* = 5.4, 12.1, 1H), 4.14 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.9, 165.0, 164.4, 134.0, 133.8, 133.2, 130.0, 129.9, 129.7, 128.6, 128.5, 128.3, 101.4, 73.0, 68.7, 68.6, 67.7, 63.3; LRMS (EI): *m/z* 539.0 [M + H$^+$ calc'd for $C_{27}H_{23}O_{10}S$ 539.1].

*Allyl 3,4,6-tri-O-benzoyl-β-D-glucopyranoside (**20b**)*

Cyclic sulfite **19b** (9.6 g, 17.8 mmol), ytterbium(III) triflate (2.21 g, 3.56 mmol) and powdered 3 Å molecular sieves (3.32 g) were taken up in toluene (35.6 mL) and freshly distilled allyl alcohol (3.63 mL, 53.4 mmol) was added. The mixture was heated to 100 °C for 12 hours, upon which TLC analysis indicated complete reaction of **19b**. The reaction mixture was diluted with ethyl acetate (50 mL) and filtered through a plug of silica gel, eluting with 200 mL EtOAc. The filtrate was then washed with 1 M HCl (2 x 100 mL), saturated $NaHCO_3$ (2 x 100 mL) and saturated NaCl (1 x 100 mL). The aqueous washings were extracted with EtOAc (2 x 100 mL) and the combined organic extracts dried ($MgSO_4$), filtered, and concentrated. Purification by flash chromatography (silica, 3:1 hexanes/EtOAc) yielded pure **20b** (7.24

g, 76%; 8:1 β:α before separation). R_f = 0.19 (3:1 hexanes/EtOAc); IR (KBr): 3600-3300, 1727, 1451, 1272 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.0-7.85 (m, 6H), 7.55-7.25 (m, 9H), 5.91 (m, 1H), 5.67 (dd, *J* = 9.3, 9.3, 1H), 5.59 (dd, *J* = 9.3, 9.3, 1H), 5.27 (dd, *J* = 1.2, 7.1, 1H), 5.15 (dd, *J* = 1.2, 10.1, 1H), 4.64 (d, *J* = 7.8, 1H), 4.60 (dd, *J* = 3.3, 12.1), 4.48 (dd, *J* = 5.5, 12.1), 4.38 (dd, *J* = 5.3, 12.7), 4.18 (dd, *J* = 6.4, 12.7), 4.07 (m, 1H), 3.88 (m, 1H), 3.25 (d, *J* = 3.5, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 167.5, 166.8, 166.0, 133.8, 133.7, 133.5, 133.4, 130.1, 130.0, 129.5, 128.6, 118.5, 101.9, 75.0, 72.4, 71.8, 70.3, 69.5, 63.1.

*Allyl 3,4,6-tri-O-benzoyl-2-O-benzyl-β-D-glucopyranoside (**21b**)*

Allyl glucopyranoside **20b** (2.09 g, 3.92 mmol) was dissolved in dichloromethane (10 mL) followed by dilution with cyclohexane (20 mL) and addition of benzyl trichloroacetimidate (0.96 mL, 5.88 mmol). Trifluoromethanesulfonic acid (0.105 mL, 0.00119 mmol) was added to this solution and the resulting mixture stirred at room temperature for 3 hours. TLC analysis indicated some remaining unprotected starting material, so excess benzyl trichloroacetimidate (0.32 mL, 1.96 mmol) was added and stirring continued for 1 hour. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with saturated $NaHCO_3$ (3 x 100 mL) and saturated NaCl (1 x 100 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (silica, 3:1 hexanes/EtOAc) yielded **21b** (2.31 g, 95%) as a slightly yellow oil. R_f = 0.33 (3:1 hexanes/EtOAc); ^1H NMR (300 MHz, $CDCl_3$): δ 8.03-7.86 (m, 5H), 7.56-7.04 (m, 15H), 6.01-5.92 (m, 1H), 5.70 (t, *J* = 9.5, 1H), 5.49 (t, *J* = 9.8, 1H), 5.38-5.20 (m, 2H), 4.75-4.40 (m, 6H), 4.26-4.21 (m, 1H), 4.06-4.00 (m, 1H), 3.68 (dd, *J* = 7.7, 9.5, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.1, 165.3, 165.2, 137.5, 133.6, 133.3, 133.0, 129.7, 129.6, 129.4, 128.8, 128.3, 128.1, 127.9, 127.6, 117.8, 102.6, 78.4, 74.1, 73.8, 71.8, 70.5, 69.9, 63.4.

*Allyl 2-O-benzyl-β-D-glucopyranoside (**22**)*

Tri-*O*-benzoate **21b** (2.31 g, 3.71 mmol) was dissolved in methanol (25 mL) followed by addition of sodium methoxide solution (2.5 M in MeOH, 0.148 mL, 0.371 mmol). The reaction was stirred for 12 hours, neutralized with *p*-toluenesulfonic acid (*ca.* 70 mg), and concentrated to an oil. Purification by flash chromatography (silica, 5:4:1 hexanes/EtOAc/MeOH) provided **22** (1.05 g, 91%) as a clear liquid. R_f = 0.27 (5:4:1 hexanes/EtOAc/MeOH); ^1H NMR (300 MHz, CD_3OD): δ 7.25-7.05, (m, 5H), 5.85-5.73 (m, 1H), 5.17 (dq, J = 1.7, 17.3, 1H), 5.01 (dq, J = 1.5, 10.5, 1H), 4.74 (d, J = 11.2, 1H), 4.60 (d, J = 11.2, 1H), 4.31-4.22 (m, 2H), 3.98 (ddt, J = 1.5, 5.9, 13.0, 1H), 3.72 (dd, J = 2.2, 12.0, 1H), 3.52 (dd, J = 5.5, 12.0, 1H), 3.32 (t, J = 8.8, 1H), 3.21-3.00 (m, 3H); ^{13}C NMR (75 MHz, CD_3OD): δ 140.1, 135.6, 129.3, 129.1, 129.0, 128.5, 117.2, 103.7, 83.0, 77.7, 77.6, 75.5, 71.6, 71.0, 62.7.

*Allyl 2-O-benzyl-4,6-O-benzylidene-β-D-glucopyranoside (**23a**)*

Triol **22** (1.22 g, 3.94 mmol) was dissolved in DMF (10 mL) followed by addition of *p*-toluenesulfonic acid in 25 mg increments until the solution became acidic (*ca.* 150 mg). Benzaldehyde dimethylacetal (0.710 mL, 4.73 mmol) was then added and the resulting solution heated to 50 °C under water aspirator pressure for 17 hours. DMF was removed under reduced pressure, and the residue dissolved in ethyl acetate (50 mL). This solution was washed with saturated $NaHCO_3$ (2 x 30 mL) and saturated NaCl (1 x 30 mL). The combined aqueous washings were extracted with EtOAc (2 x 25 mL) and all organic extracts combined and dried ($MgSO_4$). Purification by flash chromatography (silica, 3:1 hexanes/EtOAc) afforded **23a** (1.21 g, 77%) as a white, crystalline solid. R_f = 0.31 (3:1 hexanes/EtOAc); mp 124 °C; IR (KBr): 3496, 3065-2882, 1455, 1104 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.49-7.28 (m, 10H), 5.99-5.91 (m, 1H), 5.51 (s, 1H), 5.37-5.33 (m, 1H), 5.24-5.22 (m, 1H), 4.96 (d, *J* = 11, 1H), 4.74 (d, *J* = 11, 1H), 4.56 (d, *J* = 8, 1H), 4.43-4.39 (m, 1H), 4.33 (dd, *J* = 5, 10, 1H), 4.18-4.13 (m, 1H), 3.85-3.81 (m, 1H), 3.77 (t, *J* = 10, 1H), 3.53 (t, *J* = 9, 1H), 3.44-3.36 (m, 2H), 2.50 (d, *J* = 2, 1H); ^{13}C NMR (125.6 MHz, $CDCl_3$): δ 138.6, 137.4, 134.0, 129.1, 128.5, 128.2, 128.1, 127.8, 126.4, 117.4, 103.1, 101.9, 82.3, 80.8, 74.9, 73.6, 70.6, 68.9, 66.3; HRMS (EI): *m/z* 398.1729 [M^+ calc'd for $C_{23}H_{26}O_6$ 397.9960].

*Allyl 2-O-benzyl-4,6-O-(4-methoxy)benzylidene-β-D-glucopyranoside (**23b**)*

Triol **22** (2.69 g, 8.7 mmol) and *p*-methoxybenzaldehyde dimethylacetal (1.90 g, 10.4 mmol) were dissolved in DMF (17.3 mL) and *p*-toluenesulfonic acid (165 mg) was added. The solution was acidic as

judged by pH paper, and was heated to 50 °C under aspirator pressure for 5 hours. The reaction was cooled to room temperature and saturated $NaHCO_3$ (5 mL) and H_2O (50 mL) were added. The resulting mixture was extracted with EtOAc (4 x 50 mL) and the combined extracts were washed with saturated $NaHCO_3$ (2 x 200 mL) and saturated NaCl (1 x 200 mL). The organic phase was dried (Na_2SO_4), filtered, concentrated and purified by flash chromatography (silica, 5:2 hexanes/EtOAc). The combined product fractions isolated from chromatography were concentrated and the residue crystallized from diethyl ether, providing **23b** (3.1 g, 84%) as a white, crystalline solid.

Allyl (2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)1→3(2-O-benzyl-4,6-O-benzylidene)-β-D-glucopyranoside (25a)

Galactosyl trichloroacetimidate **24a** (2.80 g, 5.18 mmol) and glucopyranoside **23a** (1.87 g, 4.70 mmol) were dissolved in dichloromethane (20 mL) and stirred over activated 4 Å molecular sieves for 1 hour. A freshly prepared 0.1 M solution of TMSOTf in CH_2Cl_2 was added until the reaction appeared pale yellow and was acidic as indicated by pH paper. The reaction was immediately cooled to -78 °C and quenched with triethylamine (0.3 mL). The quenched reaction mixture was diluted with EtOAc (130 mL), washed with saturated aqueous $NaHCO_3$ (25 mL) and saturated NaCl (25 mL), dried (Na_2SO_4), filtered through Celite and concentrated to an oil. Purification by flash chromatography (silica, gradient elution: 20→30% EtOAc in hexanes) afforded **25a** as a white amorphous solid (3.11 g, 85%). R_f = 0.28 (0.5:0.5:2 EtOAc/CH_2Cl_2/hexanes); IR (KBr): 3451, 3031, 2871, 1750, 1454, 1369, 1250, 1222, 1090 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.46-7.18 (m, 10H), 5.95-5.88 (m, 1H), 5.48 (s, 1H), 5.37 (d, *J* = 3, 1H), 5.32-5.29 (m, 1H), 5.26-5.19 (m, 1H), 4.93 (dd, *J* = 3, 10, 1H), 4.84 (dd, *J* = 6, 8, 2H), 4.68 (d, *J* = 10, 1H), 4.52 (d, *J* = 8, 1H), 4.41-4.35 (m, 2H), 4.29 (dd, *J* = 5, 10, 1H), 4.26 (d, *J* = 12, 1H), 4.15-4.11 (m, 1H), 3.93 (t, *J* = 9, 1H), 3.73 (t, *J* = 10, 1H), 3.68 (t, *J* = 9, 1H), 3.59 (t, *J* = 7, 1H), 3.48 (t, *J* = 8, 1H), 3.41 (dd, J = 7, 9, 1H), 3.38-3.32 (m, 2H), 2.04 (s, 3H), 1.94 (s, 3H), 1.80 (s, 3H); ^{13}C NMR (125.6 MHz, $CDCl_3$): δ 160.0, 157.6, 139.9, 134.0, 129.5, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 126.4, 103.1, 101.3, 101.0, 81.5, 80.6, 80.0, 75.4, 73.4, 71.7, 71.3, 70.7, 69.7, 68.6, 67.4, 67.1, 65.9, 34.9, 20.2, 20.1; LRMS (LSIMS, 3-NBA + CsI): *m/z* 909.2 [M + Cs^+, calc'd for $C_{42}H_{48}O_{14}Cs$ 908.9].

Allyl (2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)1→3(2,6-di-O-benzyl)-β-D-glucopyranoside (26)

Disaccharide **25a** (1.79 g, 2.45 mmol) and triethylsilane (2 mL, 12.3 mmol) were dissolved in dichloromethane (8 mL) and the solution cooled to 0 °C. Trifluoroacetic acid (0.95 mL, 12.3 mmol) was added dropwise and the reaction stirred at 0 °C for 3.5 hours. The reaction was quenched with triethylamine (1 mL), diluted with ethyl acetate (50 mL) and poured into saturated $NaHCO_3$ (15 mL). The phases were separated and the organic extract washed with saturated NaCl (1 x 15 mL), dried (Na_2SO_4), filtered through Celite and concentrated. The residue was purified by flash chromatography (silica, gradient elution: 25→35% EtOAc in hexanes) to afford **26** (1.38 g, 77%) as a white amorphous solid. IR (neat): 3478, 3030, 2873, 1753, 1454, 1368, 1226, 1069 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.37-7.26 (m, 10H), 5.95-5.87 (m, 1H), 5.38 (d, *J* = 3, 1H), 5.32-5.26 (m, 2H), 5.19-5.16 (m, 1H), 5.01 (dd, *J* = 3, 10, 1H), 4.97 (d, *J* = 11, 1H), 4.81 (d, *J* = 8, 1H), 4.64-4.57 (m, 3H), 4.45-4.39 (m, 2H), 4.14-4.10 (m, 3H), 3.94 (t, *J* = 7, 1H), 3.87 (dd, *J* = 2, 11, 1H), 3.67 (dd, *J* = 6, 11, 1H), 3.60 (t, *J* = 9, 1H), 3.54 (t, *J* = 9, 1H), 3.50 (s, 1H), 3.44-3.38 (m, 2H), 2.16 (s, 3H), 2.01 (s, 3H), 1.98 (s, 3H), 1.84 (s, 3H), 1.62 (s, 1H); ^{13}C NMR (125.6 MHz, $CDCl_3$): δ 170.1, 170.0, 169.8, 169.1, 138.6, 134.1, 128.4, 128.3, 127.6, 117.3, 102.7, 101.7, 86.1, 81.1, 75.6, 74.6, 73.7, 71.3, 71.2, 70.3, 70.1, 69.4, 67.4, 61.5, 20.4, 20.3; LRMS (LSIMS, 3-NBA + CsI): *m/z* 863.3 [M + Cs^+, calc'd for $C_{37}H_{46}O_{15}Cs$ 862.9].

Allyl (2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)1→3[(2,3,4-tri-O-benzyl-α-L-fucopyranosyl)1→4(2,6-di-O-benzyl)]-β-D-glucopyranoside (28)

Disaccharide **26** (86.9 mg, 0.119 mmol) was combined with silver triflate (96 mg, 0.37 mmol), dibutyltin dichloride (54 mg, 0.19 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (38 mg, 0.19 mmol), and powdered 4 Å molecular sieves (31 mg) under a nitrogen atmosphere. The reaction flask was covered with foil, and cooled to 0 °C. Toluene (0.5 mL) was added to the mixture, and the resulting suspension was stirred for

ten minutes. Fucosyl fluoride **27** (128 mg, 3.03 mmol) was then dissolved in toluene (0.5 mL) and cannulated into the cold catalyst mixture. The reaction was stirred at 0 °C for 15 minutes, followed by addition of triethylamine (0.3 mL). The quenched reaction mixture was filtered through a plug of silica gel eluting with ethyl acetate (*ca.* 30 mL), and the filtrate washed with saturated $NaHCO_3$ (1 x 10 mL) and saturated NaCl (1 x 10 mL). The organic phase was dried (Na_2SO_4), filtered through Celite, and concentrated to a pale yellow oil. The crude oil was purified by flash chromatography (silica, gradient elution: 0.5:0.5:2 to 0.7:0.3:2 EtOAc/CH_2Cl_2/hexanes) to afford trisaccharide **28** (123 mg, 90%, 15:1 α:β) as a mixture of anomers. IR (neat): 3030, 2875, 1753, 1496, 1454, 1368, 1219, 1051 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.42-7.13 (m), 5.99-5.91 (m), 5.33-5.30 (m), 5.25-5.15 (m), 5.09 (d, *J* = 4), 4.98 (dd, *J* = 5, 10), 4.92 (dd, *J* = 3, 10), 4.84-4.72 (m), 4.64 (d, *J* = 12), 4.59 (d, *J* = 10), 4.45 (s), 4.40-4.37 (m), 4.14-4.06 (m), 3.97-3.84 (m), 3.74-3.72 (m), 3.63 (dd, *J* = 2, 11), 3.44-3.36 (m), 2.10 (s), 1.99 (s), 1.97 (s), 1.83 (s), 1.31 (d, *J* = 6); ^{13}C NMR (125.6 MHz, $CDCl_3$): δ 170.0, 169.9, 169.7, 168.7, 138.9, 138.5, 138.3, 138.0, 134.0, 128.6, 128.5, 128.3, 128.2, 128.1, 127.5, 127.4, 127.3, 127.0, 117.3, 102.4, 100.6, 97.5, 83.4, 80.5, 78.8, 76.2, 75.4, 74.7, 74.2, 73.2, 72.4, 72.1, 71.0, 70.3, 70.1, 69.0, 67.7, 67.3, 66.4, 60.5, 20.8, 20.5, 20.4, 16.8; LRMS (LSIMS, 3-NBA + CsI): *m/z* 1279.3 [M + Cs^+, calc'd for $C_{64}H_{74}O_{19}Cs$ 1278.9].

*Allyl (2,3,4-tri-O-acetyl-6-O-benzyl-β-D-galactopyranosyl)1→3(2-O-benzyl-4,6-O-benzylidene)-β-D-glucopyranoside (**25b**)*

Galactosyl trichloroacetimidate **24b** (74.1 mg, 0.145 mmol) and glucopyranoside **23a** (52.5 mg, 0.132 mmol) were combined with powdered 4 Å molecular sieves (20 mg) and dissolved in dichloromethane (0.325 mL). A 0.01M solution of TMSOTf in CH_2Cl_2 was added until the solution was acidic by pH paper. The reaction was then quenched immediately with triethylamine (0.20 mL) followed by saturated aqueous $NaHCO_3$ (2 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 1 mL) and the extracts combined, dried (Na_2SO_4), filtered through Celite, and concentrated to a clear oil. Purification by flash chromatography (silica, 0.7:0.3:2 EtOAc/CH_2Cl_2/hexanes) afforded disaccharide **25b** (83.8 mg, 87%) as an amorphous solid. IR (neat): 3065, 2874, 1751, 1369, 1223, 1087 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.49-7.28 (m, 10H), 5.96-5.88 (m, 1H), 5.53 (s, 1H), 5.33-5.20 (m, 4H), 4.95 (ddd, *J* = 2, 4, 10, 1H), 4.86 (d, *J* = 10, 2H), 4.69 (d, *J* = 10, 1H), 4.55 (d, *J* = 8, 1H), 4.40-4.37 (m, 1H), 4.32 (dd, *J* = 5, 10, 1H), 4.15-4.07(m, 2H), 3.96-3.88 (m, 2H), 3.78 (t, *J* = 10, 1H), 3.68 (t, *J* = 9, 1H), 3.62 (t, *J* = 6, 1H), 3.49 (t, *J* = 9, 1H), 3.41-3.36 (m, 1H), 2.11 (s, 3H), 1.95 (s, 3H), 1.91 (s, 3H), 1.81 (s, 3H); ^{13}C NMR (125.6 MHz, $CDCl_3$): δ 170.0, 169.9, 169.8, 169.2, 138.2, 137.1, 133.5, 128.9, 128.2, 128.1, 127.9, 127.6, 125.9, 117.6, 102.9, 101.1, 100.9, 81.5, 80.6, 79.8, 75.2, 71.1, 70.6, 70.5, 69.5, 68.6, 66.9, 65.9, 60.9, 20.4, 20.3; LRMS (LSIMS, 3-NBA + CsI): *m/z* 861.0 [M + Cs^+, calc'd for $C_{37}H_{44}O_{15}Cs$ 860.9].

*Allyl (2,3,4-tri-O-acetyl-6-O-benzyl-β-D-galactopyranosyl)1→3(2,O-benzyl)-β-D-glucopyranoside (**29**)*

Disaccharide **25b** (412 mg, 0.532 mmol) was dissolved in chloroform (3.6 mL) and methanol (1.8 mL). *p*-Toluenesulfonic acid monohydrate (10 mg, 0.053 mmol) was added, and the acidity of the solution monitored by pH paper. After stirring for 4.5 hours, the reaction mixture was diluted with ethyl acetate (25 mL) and washed with saturated $NaHCO_3$ (3 x 25 mL) and saturated NaCl (1 x 25 mL). The organic phase was then dried (Na_2SO_4) and concentrated to an oil. Purification by flash chromatography (silica, 10:4:1 hexanes/EtOAc/MeOH) afforded diol **29** (289 mg, 79%) as a white solid. R_f = 0.11 (1:1 hexanes/EtOAc); IR (neat): 3469, 2914, 2875, 1745, 1370, 1221, 1066 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.34-7.25 (m, 10H), 5.93-5.80 (m, 1H), 5.38 (dd, *J* = 0.6, 3.3, 1H), 5.30-5.22 (m, 1H), 5.16 (dq, *J* = 1.1, 10.3, 1H), 4.98 (dd, *J* = 3.5, 10.5, 1H), 4.89 (d, *J* = 11, 1H), 4.72 (d, *J* = 8.1, 1H), 4.53-4.39 (m, 4H), 4.34 (m, 1H), 4.09 (m, 1H), 4.00 (d, *J* = 1.7, 1H), 3.92-3.82 (m, 2H), 3.75-3.67 (m, 1H), 3.63-3.43 (m, 3H), 3.37-3.26 (m, 2H), 2.07 (s, 3H), 1.95 (s, 3H), 1.73 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 170.2, 170.0, 169.4, 138.4, 133.7, 128.5, 128.4, 128.0, 127.9, 127.6, 127.3, 117.6, 102.5, 101.5, 86.3, 80.4, 76.5, 75.0, 74.6, 73.7, 72.4, 71.2, 70.6, 69.9, 69.1, 67.8, 67.4, 63.0, 20.6, 20.5, 20.5; LRMS (LSIMS, 3-NBA + NaI): *m/z* 711.2 [M + Na^+, calc'd for $C_{35}H_{44}O_{14}Na$ 711.3].

Allyl (2,3,4-tri-O-acetyl-6-O-benzyl-β-D-galactopyranosyl)1→3(2-O-benzyl-6-O-tert-butyldiphenylsilyl)-β-D-

*glucopyranoside (**30**)*

Diol **29** (289 mg, 0.42 mmol), triethylamine (0.176 mL, 1.26 mmol) and *N,N*-dimethylaminopyridine (0.10 mg, 0.084 mmol) were dissolved in dichloromethane (4.2 mL) followed by addition of *tert*-butylchlorodiphenylsilane (0.164 mL, 0.63 mmol). After stirring for 8 hours, TLC analysis indicated complete consumption of starting material, with formation of a major and a minor product. The reaction mixture was diluted with ethyl acetate (20 mL) and washed with 1M HCl (3 x 25 mL), saturated $NaHCO_3$ (3 x 25 mL) and saturated NaCl (1 x 25 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated to an oil. Purification by flash chromatography (silica, 3:2 EtOAc/hexanes) provided disaccharide **30** (353 mg, 96%) as a clear oil. R_f = 0.58 (1:1 hexanes/EtOAc); IR (neat): 3473, 3070, 3032, 2929, 2858, 1753, 1367, 1246, 1221, 1068 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.74-7.71 (m, 4H), 7.39-7.25 (m, 16H), 5.99-5.86 (m, 1H), 5.40 (dd, *J* = 0.7, 2.8, 1H), 5.33-5.23 (m, 2H), 5.19 (dq, *J* = 1.5, 10.3, 1H), 5.02-4.94 (m, 2H), 4.77 (d, *J* = 8.1, 1H), 4.61-4.36 (m, 5H), 4.11 (ddt, *J* = 1.3, 6.1, 12.9, 1H), 4.01 (dd, *J* = 2.0, 11.0, 1H), 3.91-3.84 (m, 2H), 3.73 (d, *J* = 1.5, 1H), 3.65-3.34 (m, 6H), 2.07 (s, 3H), 1.97 (s, 3H), 1.80 (s, 3H), 1.06 (s, 9H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 170.2, 170.0, 169.4, 146.6, 138.5, 137.2, 135.7, 135.6, 134.0, 133.7, 129.5, 129.5, 128.4, 128.4, 128.3, 127.9, 127.9, 127.6, 127.6, 127.5, 127.4, 117.4, 102.2, 101.6, 86.2, 80.7, 77.2, 76.5, 76.3, 74.6, 73.6, 72.3, 71.3, 69.9, 69.2, 69.0, 67.6, 67.5, 63.6, 26.8, 20.6, 20.5, 19.3; LRMS (3-NBA + NaI): *m/z* 949.4 [M + Na^+, calc'd for $C_{51}H_{62}O_{14}SiNa$ 949.2].

*Allyl (2,3,4-tri-O-acetyl-6-O-benzyl-β-D-galactopyranosyl)1→3[(2,3,4-tri-O-benzyl-α-L-fucopyranosyl)1→4(2-O-benzyl-6-O-tert-butyldiphenylsilyl)]-β-D-glucopyranoside (**31**)*

Silver triflate (291 mg, 1.13 mmol), dibutyltin dichloride (172 mg, 0.57 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (232 mg, 1.13 mmol) and 4 Å molecular sieves (105 mg) were weighed into a foil-covered flask under nitrogen. Toluene (1.86 mL) was added and the resulting suspension was cooled to 0 °C and stirred for 15 minutes. A solution of disaccharide **30** (350 mg, 0.38 mmol) and fucosyl fluoride **27** (593 mg, 1.36 mmol) in toluene (0.5 mL) was then cannulated into the catalyst mixture and the reaction allowed to warm to room temperature, with stirring continued for 1.5 hours. Triethylamine (0.1 mL) was added and the mixture diluted with ethyl acetate (25 mL), filtered through a short plug of basic alumina and concentrated to an oil. Purification by flash chromatography (silica, 3.5:1 hexanes/EtOAc) provided trisaccharide **31** (398 mg, 79%) as an inseparable mixture of anomers (5:1 α:β). R_f = 0.29 (2:0.7:0.3 hexanes, EtOAc, CH_2Cl_2); IR (neat): 3064, 3031, 2933, 2858, 1755, 1097 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.74-7.70 (m, 35H), 6.02-5.87 (m, 1H), 5.39 (dd, *J* = 0.7, 2.8, 1H); 5.32 (dq, *J* = 1.7, 17.1, 1H), 5.24-5.20 (m, 3H), 5.16-5.10 (m, 1H), 5.00-4.89 (m, 3H), 4.76-4.72 (m, 2H), 4.65-4.51 (m, 4H), 4.43-4.34 (m, 4H), 4.21 (d, *J* = 12.3, 1H), 4.11-4.02 (m, 3H), 3.97-3.83 (m, 4H), 3.68-3.61 (m, 2H), 3.44-3.30 (m, 2H), 3.27-3.23 (m, 2H), 2.12 (s, 3H), 1.97 (s, 3H), 1.70 (s, 3H), 1.29 (d, *J* = 6.6, 3H), 1.07 (s, 9H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 170.0, 169.7, 169.0, 138.8, 138.8, 138.1, 138.0, 137.3, 136.1, 135.7, 134.0, 133.8, 133.3, 129.7, 129.5, 128.7, 128.5, 128.4, 128.4, 128.3, 128.3, 128.2, 128.2, 128.1, 128.1, 128.0, 127.8, 127.7, 127.6, 127.6, 127.5, 127.5, 127.4, 127.4, 127.1, 117.4, 102.1, 100.7, 97.0, 83.4, 80.5, 78.7, 77.6, 77.3, 77.2, 76.5, 76.5, 75.9, 74.7, 74.3, 74.1, 73.3, 72.9, 71.4, 71.4, 71.3, 69.9, 69.3, 67.7, 66.7, 66.2, 61.9, 27.0, 21.0, 20.6, 20.5, 19.4, 16.9; LRMS (LSIMS, 3-NBA + NaI): *m/z* 1365.2 [M + Na^+, calc'd for $C_{78}H_{90}O_{18}SiNa$ 1365.7].

*Allyl (2,3,4-tri-O-benzyl-α-L-fucopyranosyl)1→3[2-O-benzyl-4,6-O-(4-methoxy)benzylidene]-β-D-glucopyranoside (**32b**)*

Allyl glucopyranoside **23b** (0.56 g, 1.31 mmol) and fucosyl fluoride **27** (1.72 g, 3.93 mmol) were combined, concentrated from anhydrous toluene (3 x 10 mL) and dried under vacuum. Dibutyltin dichloride (0.60 g, 1.97 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (0.81 g, 3.93 mmol), silver triflate (1.01 g, 3.93 mmol) and powdered 4 Å molecular sieves (0.28 g) were weighed into a flame-dried, foil-covered flask under a nitrogen atmosphere and taken up in toluene (8.1 mL). The resulting suspension was stirred for 30 minutes at room temperature followed by slow cannula addition of a solution of **23b** and **27** in toluene (5.0 mL) over 10 minutes. Immediately after addition of **23b** and **27** to the catalyst mixture, triethylamine (2 mL) was added and the mixture filtered through basic alumina. Saturated $NaHCO_3$ (5 mL) was added and toluene removed under reduced pressure. The residue was taken up in EtOAc (100

mL) and washed with saturated $NaHCO_3$ (2 x 100 mL) and saturated NaCl (1 x 100 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated to an oil. Purification by flash chromatography (silica, 3:1 hexanes/EtOAc) afforded **32b** (0.82 g, 74%) as a white, crystalline solid. R_f = 0.29 (3:1 hexanes/EtOAc); ^1H NMR (300 MHz, $CDCl_3$): δ 7.34-7.06 (m, 23H), 6.84-6.80 (m, 2H), 5.91-5.78 (m, 1H), 5.57 (d, *J* = 3.3, 1H), 5.42 (s, 1H), 5.29-5.22 (m, 1H), 5.17-5.12 (m, 1H), 4.97 (d, *J* = 11.8, 1H), 4.68-4.52 (m, 6H), 4.37-4.27 (m, 2H), 4.20 (q, *J* = 6.0, 1H), 4.13-4.04 (m, 1H), 4.00-3.90 (m, 2H), 3.79-3.74 (m, 4H), 3.70-3.58 (m, 2H), 3.49 (bs, 1H), 3.41 (dt, *J* = 4.8, 9.4, 1H), 0.84 (d, *J* = 6.3, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 138.9, 138.7, 138.6, 138.3, 133.6, 130.0, 128.3, 128.1, 127.9, 127.7, 127.5, 127.4, 127.3, 127.2, 126.6, 117.7, 113.5, 103.3, 101.6, 97.4, 83.4, 79.7, 79.3, 77.9, 77.2, 76.3, 76.1, 76.0, 75.6, 74.8, 74.8, 74.1, 73.1, 72.9, 70.7, 68.9, 66.4, 66.1, 55.3, 16.4; LRMS (LSIMS, 3-NBA): *m/z* 845.3 [M + H^+, calc'd for $C_{51}H_{57}O_{11}$ 845.4].

Allyl (2,3,4-tri-O-benzyl-α-L-fucopyranosyl)1→3[2-O-benzyl-6-O-(4-methoxy)benzyl]-β-D-glucopyranoside (**33**)

Disaccharide **32b** (250 mg, 0.30 mmol), trimethylamine-borane (237 mg, 1.78 mmol) and powdered 4 Å molecular sieves (125 mg) were weighed into a flame-dried flask under a nitrogen atmosphere. Tetrahydrofuran (2.5 mL) was added and the resulting suspension stirred under argon for 30 minutes. Aluminum trichloride (130 mg, 1.78 mmol) and 4 Å ms (125 mg) were weighed into a flame-dried flask under a nitrogen atmosphere and the flask cooled to 0 °C. THF (3.4 mL) was slowly added to the cold mixture and resulting suspension stirred at 0 °C for 15 minutes. The mixture of **32b**, $Me_3N{\cdot}BH_3$ and 4 Å ms was then slowly cannulated through a large gauge needle into the $AlCl_3$ solution over 10 minutes. The reaction was stirred at 0 °C for 1.25 hours, then warmed to room temperature with stirring continued for 2 hours. The reaction mixture was filtered through a plug of silica gel and solvent removed under reduced pressure. The residue was taken up in EtOAc (25 mL) and washed with 1 M HCl (4 x 25 mL), saturated $NaHCO_3$ (2 x 25 mL) and saturated NaCl (1 x 25 mL). The organic phase was dried (Na_2SO_4), filtered, concentrated to an oil and purified by flash chromatography (silica, gradient elution: 25→75% EtOAc in hexanes). 6-MPM disaccharide **33** (167 mg, 67%) was isolated as a crystalline solid. The 4-MPM regioisomer was also obtained (12 mg, 5%) along with diol **35** (48 mg, 22%). R_f = 0.34 (3:1 hexanes/EtOAc); mp 87 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.38-7.17 (m, 22H), 6.86-6.82 (m, 2H), 5.97-5.84 (m, 1H), 5.29 (dq, *J* = 1.6, 17.3, 1H), 5.16 (dq, *J* = 1.6, 10.5, 1H), 5.07 (d, *J* = 3.7, 1H), 4.96 (d, *J* = 11.4, 1H), 4.93-4.71 (m, 4H), 4.67-4.61 (m, 3H), 4.55-4.35 (m, 4H), 4.28 (d, *J* = 1.7, 1H), 4.17-3.95 (m, 4H), 3.78 (s, 3H), 3.74 (d, *J* = 2.0, 1H), 3.68-3.53 (m, 3H), 3.44-3.35 (m, 3H), 1.08 (d, *J* = 6.4, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 138.7, 138.2, 134.0, 129.2, 128.4, 128.4, 128.3, 128.2, 128.0, 128.0, 1217.8, 127.7, 127.6, 127.5, 127.4, 127.3, 117.2, 113.7, 102.4, 98.5, 86.7, 79.9, 78.6, 77.4, 75.7, 74.9, 74.7, 74.5, 73.1, 73.0, 70.4, 69.9, 69.5, 67.7, 55.2, 16.5.

Allyl (2,3,4-tri-O-benzyl-α-L-fucopyranosyl)1→3(2-O-benzyl-4,6-O-benzylidene)-β-D-glucopyranoside (**32a**)

Allyl glucopyranoside **23a** (0.624 g, 1.57 mmol) and fucosyl fluoride **27** (1.37 g. 3.14 mmol) were concentrated from anhydrous toluene (3 x 5 mL) and dried under vacuum. Dibutyltin dichloride (0.72 g, 2.36 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (0.97 g, 4.71 mmol), silver triflate (1.21 g, 4.71 mmol) and powdered 4 Å molecular sieves (0.31 g) were weighed into a flame-dried, foil-covered flask under a nitrogen atmosphere and taken up in toluene (8 mL). The resulting suspension was stirred for 45 minutes at room temperature followed by cannula addition of a solution of **23a** and **27** in toluene (7.7 mL). The reaction was stirred for 15 minutes, after which TLC indicated complete consumption of **23a**. Triethylamine (2.5 mL) was added, and the reaction mixture diluted with EtOAc (50 mL), filtered through a plug of basic alumina and concentrated to an oil. Purification by flash chromatography (silica, 5:1 hexanes/EtOAc) provided **32a** (0.96 g, 76%) as a white, crystalline solid. R_f = 0.28 (5:1 hexanes/EtOAc); ^1H NMR (300 MHz, $CDCl_3$): δ 7.30-6.98 (m, 25H), 5.81-5.68 (m, 1H), 5.47 (d, *J* = 3.3, 1H), 5.37 (s, 1H), 5.19-5.02 (m, 2H), 4.89-4.51 (m, 5H), 4.47-4.41 (m, 4H), 4.28-4.19 (m, 2H), 4.11 (q, *J* = 6.7, 1H), 4.09-3.94 (m, 2H), 3.90-3.81 (m, 2H), 3.69-3.49 (m, 3H), 3.38-3.28 (m, 2H), 0.71 (d, *J* = 6.6, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 138.9, 138.7, 138.6, 138.3, 137.4, 133.6, 129.0, 128.3, 127.7, 127.4, 127.4, 127.3, 127.2, 126.6, 126.2, 117.7, 103.3, 101.7, 97.4, 83.4, 79.7, 79.3, 77.9, 75.6, 74.9, 74.8, 74.1, 73.1, 72.9, 70.7, 68.9, 66.4, 66.1, 16.3; LRMS (LSIMS, 3-NBA): *m/z* 813.3 [(M - H)$^+$, calc'd for $C_{50}H_{53}O_{10}$ 813.4].

Allyl (2,3,4-tri-O-benzyl-α-L-fucopyranosyl)1→3(2-O-benzyl)-β-D-glucopyranoside (35)

Disaccharide **32a** (786 mg, 0.96 mmol) was dissolved in chloroform (6.4 mL) and methanol (12.8 mL). *p*-Toluenesulfonic acid monohydrate (18 mg, 0.096 mmol) was then added upon which the solution became acidic as judged by pH paper. The reaction was stirred at room temperature for 24 hours, followed by addition of saturated $NaHCO_3$ (0.25 mL). The neutralized mixture was concentrated to an oil and purified by flash chromatography (silica, 3:2 EtOAc/hexanes). Diol **35** (574 mg, 82%) was isolated as a white solid. R_f = 0.17 (1:1 hexanes/EtOAc); mp 128-9 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.50-7.15 (m, 20H), 5.98-5.86 (m, 1H), 5.35-5.27 (m, 1H), 5.21-5.16 (m, 1H), 5.04-4.87 (m, 4H), 4.81-4.71 (m, 2H), 4.68-4.63 (m, 3H), 4.53 (d, *J* = 1.7, 1H), 4.48 (d, *J* = 7.7, 1H), 4.43-4.33 (m, 1H), 4.17-4.08 (m, 3H), 3.97 (dd, *J* = 2.6, 10.1, 1H), 3.93-3.85 (m, 1H), 3.80-3.69 (m, 2H), 3.60-3.20 (m, 4H), 2.14, t, *J* = 7.8, 1H), 1.10 (d, *J* = 7.0, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 138.7, 138.6, 138.3, 138.2, 133.9, 128.5, 128.4, 128.3, 128.3, 128.1, 128.0, 127.9, 127.7, 127.6, 127.4, 127.3, 117.4, 102.6, 98.7, 87.7, 79.6, 78.4, 75.7, 74.9, 74.6, 73.2, 73.1, 70.7, 70.3, 70.0, 62.9, 16.5; LRMS (LSIMS, 3-NBA): *m/z* 725.3 [(M - H)$^+$, calc'd for $C_{43}H_{49}O_{10}$ 725.4].

Allyl (2,3,4-tri-O-benzyl-α-L-fucopyranosyl)1→3(2-O-benzyl-6-O-tert-butyldiphenylsilyl)-β-D-glucopyranoside (36)

Diol **35** (377 mg, 0.52 mmol), triethylamine (0.22 mL, 1.56 mmol) and *N,N*-dimethylaminopyridine (19 mg, 0.156 mmol) were dissolved in dichloromethane (5.2 mL) followed by addition of *tert*-butylchlorodiphenylsilane (0.20 mL, 0.78 mmol). The reaction was stirred at room temperature for 8 hours, after which TLC analysis indicated complete consumption of **35**. The reaction mixture was diluted with ethyl acetate (30 mL) and washed with 1M HCl (2 x 30 mL), saturated $NaHCO_3$ (2 x 30 mL) and saturated NaCl (1 x 30 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography (silica, 5:1 hexanes/EtOAc) providing **36** (477 mg, 95%) as a clear oil, as well as a trace of the 4-silylated regioisomer. R_f = 0.50 (3:1 hexanes/EtOAc); ^1H NMR (300 MHz, $CDCl_3$): δ 7.75-7.70 (m, 4H), 7.45-7.18 (m, 26H), 6.02-5.89 (m, 1H), 5.35-5.28 (m, 1H), 5.21-5.17 (m, 1H), 5.10 (d, *J* = 3.7, 1H), 5.00-4.60 (m, 8H), 4.47 (d, *J* = 7.9, 1H), 4.43-4.36 (m, 1H), 4.28 (d, *J* = 3.6, 1H), 4.19-4.08 (m, 3H), 4.03-3.96 (m, 2H), 3.91-3.85 (m, 1H), 3.70 (bs, 1H), 3.63-3.50 (m, 2H), 3.45-3.33 (m, 2H), 1.10 (d, *J* = 6.6, 3H), 1.05 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 138.9, 138.7, 138.4, 138.3, 135.7, 135.6, 134.2, 133.6, 133.5, 129.6, 128.4, 128.4, 128.3, 128.2, 128.2, 128.1, 128.0, 127.8, 127.7, 127.6, 127.5, 127.4, 127.2, 127.1, 117.2, 102.3, 98.5, 87.2, 80.7, 78.6, 75.9, 75.6, 74.9, 74.8, 73.1, 73.1, 70.0, 69.6, 67.7, 63.8, 26.8, 19.3, 16.5.

Allyl (2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)1→4[(2,3,4-tri-O-benzyl-α-L-fucopyranosyl)1→3(2-O-benzyl-6-O-tert-butyldiphenylsilyl)]-β-D-glucopyranoside (37a)

Disaccharide **36** (245 mg, 0.25 mmol) and galactosyl trichloroacetimidate **34a** (313 mg, 0.64 mmol) were combined and concentrated from anhydrous benzene (4 x 10 mL) and dried under vacuum for 24 hours. The residue was dissolved in diethyl ether (2.5 mL) and cooled to 0 °C, upon which a white precipitate (trichloroacetimidate) formed. To the cooled solution, 0.10 mL of a cold triflic acid solution (22 μL/mL in diethyl ether) was added and the reaction stirred at 0 °C for 1 hour. The reaction was quenched with triethylamine (0.1 mL) and diluted with ethyl acetate (25 mL). The mixture was then transferred to a separatory funnel and washed with saturated $NaHCO_3$ (3 x 30 mL), 1M HCl (2 x 30 mL) and saturated NaCl (1 x 30 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated to an oil. Purification by flash chromatography (silica, 3:1 hexanes/EtOAc) followed by crystallization of the isolated product from methanol afforded trisaccharide **37b** (291 mg, 89%) as a white crystalline solid. R_f = 0.33 (2:1 hexanes/EtOAc); mp 145.5-147 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.80-7.70 (m, 4H), 7.50-7.00 (m, 26H), 5.94-5.82 (m, 1H), 5.73 (d, *J* = 3.1, 1H), 5.32-5.03 (m, 5H), 4.96-4.72 (m, 7H), 4.59 (d, *J* = 6.3, 2H), 4.45-4.22 (m, 4H), 4.13-3.91 (m, 8H), 3.79-3.73 (m, 2H), 3.64 (t, *J* = 9.1, 1H), 3.15 (d, *J* = 9.6, 1H), 2.02 (s, 3H), 1.98 (s, 3H), 1.81 (s, 3H), 1.80 (s, 3H), 1.29 (d, *J* = 6.4, 3H), 1.10 (s, 9H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 169.9, 169.8, 169.7, 168.5, 139.0, 139.0, 138.7, 138.1, 136.0, 135.2, 133.9, 133.4, 132.0, 130.0, 129.9, 128.4, 128.2, 128.0, 127.6, 127.5, 127.2, 127.1, 127.0, 126.9, 126.9, 126.2, 117.2, 102.6, 99.8, 97.9, 83.0, 80.2, 76.9, 75.8, 75.3, 74.0, 73.7, 73.3, 73.2, 72.5, 70.9, 70.3, 69.7, 69.1, 66.7, 65.9, 61.1, 60.1, 26.8, 20.6, 20.5, 20.5, 20.4,

19.4, 16.8; LRMS (LSIMS, 3-NBA): *m/z* 1293.4 [(M - H)$^+$, calc'd for $C_{73}H_{85}O_{19}Si$ 1293.6].

*Allyl (2,3,4-tri-O-acetyl-6-O-benzyl-β-D-galactopyranosyl)1→4[(2,3,4-tri-O-benzyl-α-L-fucopyranosyl)1→3(2-O-benzyl-6-O-tert-butyldiphenylsilyl)]-β-D-glucopyranoside (**37b**)*

Disaccharide **36** (249 mg, 0.26 mmol) and galactosyl trichloroacetimidate **34b** (279 mg, 0.52 mmol) were combined and concentrated from anhydrous benzene (4 x 5 mL) and dried under vacuum for 24 hours. The residue was dissolved in diethyl ether (2.6 mL) and cooled to 0 °C, upon which a white precipitate (trichloroacetimidate) formed. To the cooled solution, 0.10 mL of a cold triflic acid solution (23 μL/mL in diethyl ether) was added and the reaction stirred at 0 °C for 10 minutes. The reaction was quenched with triethylamine (1 mL) and diluted with ethyl acetate (25 mL). The mixture was then transferred to a separatory funnel and washed with saturated $NaHCO_3$ (2 x 30 mL), 1 M HCl (2 x 30 mL) and saturated NaCl (1 x 30 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated to an oil. Purification by flash chromatography (silica, 3:1 hexanes/EtOAc) provided trisaccharide **37b** (333 mg, 96%) as an amorphous solid. R_f = 0.35 (2:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77-7.71 (m, 4H), 7.42-6.98 (m, 31H), 5.93-5.80 (m, 1H), 5.70 (d, *J* = 3.1, 1H), 5.45 (d, *J* = 2.9, 1H), 5.29-5.02 (m, 5H), 4.96-4.80 (m, 4H), 4.75-4.54 (m, 4H), 4.47-4.32 (m, 4H), 4.27-4.19 (m, 2H), 4.08-3.88 (m, 6H), 3.73-3.60 (m, 4H), 3.39 (t, *J* = 8.5, 1H), 3.13 (d, *J* = 9.6, 1H), 1.98 (s, 3H), 1.80 (s, 3H), 1.74 (s, 3H), 1.26 (d, *J* = 6.4, 3H), 1.08 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 169.8, 169.6, 168.6, 139.0, 138.8, 138.8, 138.1, 137.3, 136.1, 135.3, 134.0, 133.4, 132.1, 130.0, 129.9, 128.5, 128.4, 128.2, 128.2, 128.0, 127.8, 127.6, 127.6, 127.5, 127.2, 127.0, 126.2, 117.3, 102.7, 100.0, 97.7, 83.0, 80.3, 77.6, 77.2, 76.8, 76.4, 75.7, 75.4, 74.1, 73.6, 73.3, 73.1, 73.0, 71.4, 71.2, 69.8, 69.4, 67.3, 66.5, 65.9, 61.1, 26.8, 20.6, 20.5, 19.4, 16.8; LRMS (LSIMS, 3-NBA): *m/z* 1342.5 [M$^+$, calc'd for $C_{78}H_{90}O_{18}Si$ 1342.7].

*Allyl (β-D-galactopyranosyl)1→3[(2,3,4-tri-O-benzyl-α-L-fucopyranosyl)1→4(2,6-di-O-benzyl)]-β-D-glucopyranoside (**40**)*

Trisaccharide **28a** (123 mg, 0.107 mmol) was dissolved in methanol and treated with excess potassium carbonate. After the starting materiàl was consumed as determined by TLC, the reaction was filtered through cellulose, and concentrated to an oil. The oil was purified by flash chromatography (silica, 10% methanol in dichloromethane) to afford **40** (94.9 mg, 91%) as a single diastereomer. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42-7.20 (m, 25H), 6.00-5.87 (m, 1H), 5.34-5.27 (m, 1H), 5.21-5.17 (m, 1H), 5.07 (d, *J* = 3 Hz, 1H), 4.93-4.88 (m, 2H), 4.82-4.76 (m, 2H), 4.70-4.53 (m, 6H), 4.47-4.36 (m, 6H), 4.12-3.82 (m, 7H), 3.74-3.37 (m, 9H), 3.13 (bs, 1H), 2,80 (bs, 1H), 2.59 (bs, 1H), 1.26 (bs, 1H), 1.15 (d, *J* = 6, 3 H).

*Allyl (3-O-sulfo-β-D-galactopyranosyl)1→3[(2,3,4-tri-O-benzyl-α-L-fucopyranosyl)1→4(2,6-di-O-benzyl)]-β-D-glucopyranoside (**41**)*

Dibutyltin oxide (16.1 mg, 0.0647 mmol) was combined with trisaccharide tetraol **40** (50.7 mg, 0.0226 mmol) and benzene (2 mL). The reaction was fitted with a Dean-Stark apparatus, and the solvent concentrated to *ca.* 1 mL by slow distillation. An additional portion of benzene (1.5 mL) was added to the reaction vessel, and the reaction solvent again concentrated by distillation to *ca.* 0.75 mL. The solution was cooled to room temperature and pyridine-sulfur trioxide complex (7.6 mg, 0.0475 mmol) was added. After stirring for twenty minutes, excess pyr·SO_3 was quenched with methanol (1 mL) and the mixture concentrated under reduced pressure. The resulting residue was purified by flash chromatography (silica gel, gradient elution: 5→20% MeOH in $CHCl_3$) to afford **41** as an amorphous solid. IR (neat): 3485, 3030, 2859, 1497, 1454, 1098, 1053 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD): δ 7.44-7.43 (m, 2H), 7.34-7.11 (m, 28H), 5.97-5.89 (m, 1H), 5.31-5.27 (m, 1H), 5.15-5.13 (m, 1H), 4.99 (d, *J* = 3, 1H), 4.95 (d, *J* = 8, 1H), 4.89-4.81 (m, 2H), 4.71-4.42 (m, 15H), 4.37-4.30 (m, 3H), 4.23-4.19 (m, 1H), 4.11-4.02 (m, 1H), 3.93-3.89 (m, 3H), 3.84-3.73 (m, 4H), 3.69-3.66 (m, 1H), 3.61-3.59 (m, 1H), 3.50-3.47 (m, 2H), 1.19 (d, *J* = 6, 3H); LRMS (LSIMS, 3-NBA): *m/z* 1187.4 [M + Ca^{2+}, calc'd for $C_{63}H_{71}O_{18}SCa$].

*Propyl (3-O-sulfo-β-D-galactopyranosyl)1→3(α-L-fucopyranosyl)1→4-β-D-glucopyranoside (**14**)*

Monosulfate **41** (55.0 mg, 0.0472 mmol) was dissolved in a 2:1 mixture of methanol in water (0.4 mL),

and 20% $Pd(OH)_2/C$ (55 mg, Pearlman's catalyst) was added. Hydrogenolysis on a Parr shaker at 50 psi H_2 for 12 hours resulted in complete removal of the benzyl protecting groups and reduction of the allyl aglycone. The reaction mixture was filtered through a 1 cm plug of cellulose (methanol eluent) and the filtrate subjected to cation exchange chromatography (Sephadex-sp C-25; 0.5 x 6.0 cm; H_2O; Na^+). Concentration afforded the sodium salt of **14** (28.8 mg, 96%) as a white powder. IR (KBr): 3426, 2936, 2517, 1250, 1161, 1075, 1040 cm^{-1}; ^1H NMR (500 MHz, D_2O): δ 4.99 (d, J = 4, 1H), 4.93 (d, J = 8, 1H), 4.85 (q, J = 7, 1H), 4.47 (d, J = 8, 1H), 4.32 (dd, J = 3, 10, 1H), 4.27 (d, J = 3, 1H), 4.01 (t, J = 9, 1H), 3.97 (dd, J = 2, 12, 1H), 3.90-3.73 (m, 7H), 3.69-3.61 (m, 4H), 3.55-3.50 (m, 2H), 1.62 (sx, J = 7, 2H), 1.18 (d, J = 7, 3H), 0.91 (t, J = 7, 3H); ^{13}C NMR (125.6 MHz, D_2O): δ 103.4, 103.3, 99.2, 81.7, 80.4, 76.7, 75.6, 75.4, 73.5, 73.3, 73.2, 70.5, 70.4, 69.2, 68.1, 68.0, 62.6, 61.2, 23.4, 16.6, 10.8; LRMS (LSIMS, 3-NBA, negative ion mode): m/z 609.1 [M^-, calc'd for $C_{21}H_{37}O_{18}S$ 609.0].

*Allyl (6-O-sulfo-β-D-galactopyranosyl)1→3[(2,3,4-tri-O-benzyl-α-L-fucopyranosyl)1→4(2,6-di-O-benzyl)]-β-D-glucopyranoside (**42**)*

Trisaccharide tetraol **40** (22.1 mg, 0.0226 mmol) and bis(tributyltin) oxide (12.8 μL, 0.0249 mmol) were combined in benzene (2 mL) and reaction was fitted with a Dean-Stark apparatus. The reaction mixture was concentrated to *ca.* 0.7 mL by slow distillation over 2 hours and cooled to room temperature. To the cooled solution, pyridine-sulfur trioxide complex (7.6 mg, 0.0475 mmol) was added, and after stirring for twenty minutes, methanol (1 mL) was added and the reaction mixture concentrated under reduced pressure. The resulting residue was purified by flash chromatography (silica, gradient elution: 5→20% MeOH in $CHCl_3$) to afford **42** as an amorphous solid.

*Propyl (6-O-sulfo-β-D-galactopyranosyl)1→3(α-L-fucopyranosyl)1→4-β-D-glucopyranoside (**13**)*

Monosulfate **42** was dissolved in methanol (1 mL), and 20% $Pd(0H)_2/C$ added. The mixture was shaken under 50 psi H_2 for 10 hours, followed by filtration through a plug of cellulose (methanol eluent). Cation exchange chromatography (Sephadex-sp C-25; 0.5 x 6.0 cm; H_2O; Na^+) provided **13** (8.5 mg, 59% for two steps) as a white powder. ^1H NMR (500 MHz, D_2O): δ 4.89 (d, J = 4, 1H), 4.80 (q, J = 7, 1H), 4.75 (d, J = 8, 1H), 4.38 (d, J = 8, 1H), 4.08 (ABX, J_{AB} = 10.5, J_{AX} = 8.6, 1H), 4.06 (ABX, J_{AB} = 10.5, J_{BX} = 3.8, 1H), 3.93-3.86 (m, 3H), 3.83-3.71 (m, 5H), 3.67 (dd, J = 4, 10, 1H), 3.60-3.52 (m, 3H), 3.48-3.44 (m, 2H), 3.40 (t, J = 8, 1H), 1.54 (sx, J = 7, 2H), 1.10 (d, J = 7, 3H), 0.82 (t, J = 7, 3H); ^{13}C NMR (125.6 MHz, D_2O): δ 103.8, 103.3, 99.4, 80.7, 76.6, 75.5, 73.7, 73.6, 73.4 (B), 73.3, 72.2, 70.4, 69.4, 69.3, 68.8, 68.0, 61.0, 23.4, 16.7, 10.8; LRMS (LSIMS, 3-NBA, negative ion mode): m/z 609.2 [M^-, calc'd for $C_{21}H_{37}O_{18}S$ 609.2].

*Allyl (3,6-di-O-sulfo-β-D-galactopyranosyl)1→3[(2,3,4-tri-O-benzyl-α-L-fucopyranosyl)1→4(2,6-di-O-benzyl)]-β-D-glucopyranoside (**43**)*

Trisaccharide tetraol **40** (32.0 mg, 0.0327 mmol) and bis(tributyltin) oxide (17.5 μL, 0.0344 mmol) were combined in benzene (2 mL) and the reaction fitted with a Dean-Stark apparatus. The reaction mixture was concentrated to *ca.* 0.7 mL by slow distillation over 2 hours. Remaining benzene was removed under a stream of argon, and pyridine (0.125 mL) was added. Addition of pyridine-sulfur trioxide complex (15.8 mg, 0.993 mmol) followed by stirring for 20 minutes, resulted in the formation of a single product as judged by TLC. Methanol was added and the reaction mixture concentrated to an oil. The resulting residue was filtered through a plug of silica gel (20% MeOH in $CHCl_3$) and carried on without further purification.

*Propyl (3,6-di-O-sulfo-β-D-galactopyranosyl)1→3(α-L-fucopyranosyl)1→4-β-D-glucopyranoside (**15**)*

Crude disulfate **43** was dissolved in a 2:1 mixture of methanol/water and 20% $Pd(OH)_2/C$ (35 mg) was added. Shaking under 50 psi H_2 for 3 days resulted in the formation of a single product as judged by TLC, and the hydrogenated mixture was filtered through cellulose (methanol eluent) and concentrated. The crude solid was purified by anion exchange chromatography (Dowex 1X2-400 anion exchange resin; 100 mL 0→0.25 M triethylammonium bicarbonate; 0.5 x 6.0 cm), and then passed through cation exchange resin (Sephadex-sp C-25; 0.5 x 6.0 cm; H_2O; Na^+) to afford **15** (12.9 mg, 54% for two steps) as the disodium salt. ^1H NMR (500 MHz, D_2O): δ 4.96 (d, J = 4, 1H), 4.94 (d, J = 8, 1H), 4.86 (q, J =

6, 1H), 4.46 (d, J = 8, 1H), 4.33 (dd, J = 3, 10, 1H), 4.30 (d, J = 3, 1H), 4.20 (ABX, J_{AB} = 10.6, J_{AX} = 4.6, 1H), 4.16 (ABX, J_{AB} = 10.6, J_{BX} = 7.7, 1H), 4.01 (t, J = 9, 1H), 3.96 (dd, J = 2, 12, 1H), 3.91-3.79 (m, 6H), 3.74 (dd, J = 4, 10, 1H), 3.70-3.60 (m, 3H), 3.56-3.48 (m, 2H), 1.62 (sx, J = 7, 2H), 1.17 (d, J = 3, 3H), 0.90 (t, J = 7, 3H). LRMS (ESI, H_2O : CH_3CN, negative ion mode): $m/2z$ 344.0 [M^{2-}, calc'd for $C_{21}H_{36}O_{21}S_2$ $m/2z$ 344.0]

*Allyl (2,3,4-tri-O-acetyl-6-O-benzyl-β-D-galactopyranosyl)1→3[(2,3,4-tri-O-benzyl-α-L-fucopyranosyl)1→4(2-O-benzyl)]-β-D-glucopyranoside (**45**)*

Trisaccharide **31** (131 mg, 0.098 mmol) was dissolved in tetrahydrofuran (0.98 mL) and a 1 M solution of tetrabutylammonium fluoride (0.176 mL, 0.176 mmol) in THF was added. The reaction was stirred at room temperature for 24 hours, with TLC analysis indicating complete consumption of starting material. The reaction mixture was diluted with ethyl acetate (10 mL) and washed with 1 M HCl (3 x 10 mL), saturated $NaHCO_3$ (3 x 10 mL) and saturated NaCl (1 x 10 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated. Purification by flash chromatography (silica, 3:2 hexanes/EtOAc) afforded **45** (79 mg, 79%) as a white solid. R_f = 0.30 (1:1 hexanes/EtOAc); IR (neat): 3064, 3032, 2931, 2875, 1755, 1367, 1219, 1095, 1049 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.40-7.10 (m, 25H), 6.00-5.87 (m, 1H), 5.41 (d, J = 6.4, 1H), 5.31 (dq, J = 1.5, 18.6, 1H), 5.23-5.10 (m, 3H), 5.03 (d, J = 3.5, 1H), 4.97-4.89 (m, 3H), 4.83 (d, J = 11.2, 1H), 4.72-4.64 (m, 4H), 4.61-4.56 (m, 2H), 4.45-4.34 (m, 4H), 4.26 (d, J = 12.3, 1H), 4.14-4.08 (m, 2H), 3.93-3.82 (m, 4H), 3.74-3.61 (m, 3H), 3.46-3.27 (m, 4H), 2.08 (s, 3H), 1.97 (s, 3H), 1.76 (s, 3H), 1.28 (d, J = 6.4, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 169.9, 169.6, 168.9, 138.7, 138.6, 138.0, 137.7, 137.3, 133.7, 128.7, 128.7, 128.5, 128.5, 128.4, 128.4, 128.4, 128.3, 128.3, 128.2, 128.1, 127.8, 127.6, 127.5, 127.1, 117.7, 102.5, 100.6, 97.9, 83.3, 80.5, 78.3, 77.4, 77.2, 76.9, 76.5, 76.1, 75.7, 74.8, 74.2, 73.4, 72.7, 72.6, 71.4, 71.3, 70.6, 69.2, 67.7, 66.8, 66.6, 61.3, 20.9, 20.6, 16.8; LRMS (LSIMS, 3-NBA + NaI): m/z 1127.3 [M + Na^+, calc'd for $C_{62}H_{72}O_{18}Na$ 1127.5].

*Allyl (6-O-benzyl-β-D-galactopyranosyl)1→3[(2,3,4-tri-O-benzyl-α-L-fucopyranosyl)1→4(2-O-benzyl)]-β-D-glucopyranoside (**46**)*

Trisaccharide **45** (45 mg, 0.041 mmol) was dissolved in methanol (0.27 mL) and potassium carbonate (1 mg, 0.005 mmol) was added. Stirring at room temperature for 4 hours resulted in cleavage of the acetate esters, and the reaction mixture was neutralized with acidic ion exchange resin (Amberlyst). Concentration and purification by flash chromatography (silica, 5:4:1 hexanes/EtOAc/MeOH) afforded **46** (33 mg, 89%) as a white solid. R_f = 0.40 (5:4:1 hexanes/EtOAc/MeOH); IR (KBr): 3357, 3064, 3032, 2866, 1454, 1365, 1093 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.41-7.22 (m, 25H), 5.99-5.86 (m, 1H), 5.31 (dd, J = 1.5, 17.3, 1H), 5.21 (dd, J = 1.1, 10.5, 1H), 5.10 (d, J = 3.3, 1H), 4.94-4.77 (m, 4H), 4.72-4.67 (m, 4H), 4.57-4.54 (m, 2H), 4.46-4.35 (m, 4H), 4.14-4.04 (m, 2H), 3.98-3.90 (m, 4H), 3.86-3.69 (m, 4H), 3.64-3.44 (m, 6H), 3.29 (m, 1H), 2.79 (bs, 1H), 2.58-2.50 (m, 2H), 1.16 (d, J = 6.3, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 138.9, 138.7, 137.9, 137.9, 137.8, 133.8, 128.7, 128.5, 128.5, 128.4, 128.4, 128.3, 128.1, 128.0, 127.8, 127.7, 127.4, 127.4, 127.2, 117.9, 117.7, 102.6, 102.2, 98.3, 82.1, 79.6, 79.2, 78.1, 76.3, 75.6, 75.0, 74.8, 74.7, 74.3, 73.4, 72.8, 72.4, 72.1, 70.5, 68.9, 68.3, 67.0, 61.4, 17.0; LRMS (LSIMS, 3-NBA + NaI): m/z 1001.1 [M + Na^+, calc'd for $C_{56}H_{66}O_{15}Na$ 1001.6].

*Allyl (6-O-benzyl-3-O-sulfo-β-D-galactopyranosyl)1→3[(2,3,4-tri-O-benzyl-α-L-fucopyranosyl)1→4(2-O-benzyl-6-O-sulfo)]-β-D-glucopyranoside (**47**)*

Trisaccharide tetraol **46** (68 mg, 0.075 mmol) and bis(tributyltin) oxide (40 μL, 0.079 mmol) were combined in benzene (5 mL) in a Dean-Stark apparatus. The reaction was refluxed for 1 hour, concentrating to approximately 0.5 mL, and cooled to room temperature. Remaining benzene was removed under a stream of argon and the residue dissolved in pyridine (0.30 mL). Pyridine-sulfur trioxide complex (28 mg, 0.173 mmol) was added and the mixture stirred at room temperature for 20 minutes. Methanol was added and the solution concentrated to an oil. Disulfate **47** (76 mg, 82%) was isolated as an amorphous solid by flash chromatography (silica, 20% MeOH in $CHCl_3$).

*Propyl (3-O-sulfo-β-D-galactopyranosyl)1→3[(α-L-fucopyranosyl)1→4(6-O-sulfo)]-β-D-glucopyranoside (**16**)*

Disulfate **47** (76 mg, 0.061 mmol) and 20% $Pd(OH)_2/C$ (75 mg) were combined in 2:1 methanol/

water (1.5 mL) and the resulting mixture stirred under 500 psi H_2 for 24 hours. TLC analysis indicated several product spots, so the catalyst was removed by filtration through a plug of celite (1:1 MeOH/H_2O) and the filtrate concentrated. The residue was redissolved in 1:1 methanol/water and fresh catalyst (75 mg) added. Stirring under 500 psi H_2 for 20 hours resulted in complete conversion to a single product spot. Filtration through celite (1:1 MeOH/H_2O) provided a white solid which was purified by flash chromatography (silica, 5:4:1 $CHCl_3$/MeOH/H_2O), followed by cation exchange chromatography (Sephadex-sp C-25; 0.5 x 6.0 cm; H_2O; Na^+). The disodium salt of **16** (28 mg, 62%) was isolated as a white powder. R_f = 0.16 (5:4:1 $CHCl_3$/MeOH/H_2O); ^1H NMR (500 MHz, D_2O, 37 °C): δ 5.01 (d, J = 4.1, 1H), 4.91 (d, J = 7.9, 1H), 4.84 (q, J = 6.6, 1H), 4.48 (d, J = 8.1, 1H), 4.35-4.29 (m, 3H), 4.25 (d, J = 3.3, 1H), 4.00 (t, J = 9.0, 1H), 3.88-3.81 (m, 2H), 3.79-3.77 (m, 2H), 3.73-3.58 (m, 7H), 3.52 (dd, J = 8.1, 9.3, 1H), 1.60 (sx, J = 6.6, 2H), 1.17 (d, J = 6.6, 3H), 0.89 (t, J = 7.4, 3H); ^{13}C NMR (125.7 MHz, D_2O, 37 °C): δ 105.1, 105.0, 100.8, 83.3, 81.6, 77.3, 76.9, 75.9, 75.3, 74.8, 74.6, 72.1, 72.0, 70.7, 69.8, 69.7, 68.9, 64.2, 25.0, 18.2, 12.4; LRMS (3-NBA, negative ion mode): *m/z* 711.1 [M^{2-} + Na^+, calc'd for $C_{21}H_{36}O_{21}NaS_2$ 711.2].

*Allyl (2,3,4-tri-O-acetyl-6-O-benzyl-β-D-galactopyranosyl)1→4[(2,3,4-tri-O-benzyl-α-L-fucopyranosyl)1→3(2-O-benzyl)]-β-D-glucopyranoside (**48**)*

Trisaccharide **37b** (82 mg, 0.061 mmol) was dissolved in tetrahydrofuran (0.61 mL) and a 1 M solution of tetrabutylammonium fluoride (0.11 mL, 0.11 mmol) in THF was added. After stirring at room temperature for 3 hours, solvent was removed and the residue taken up in ethyl acetate (5 mL). The solution was washed with saturated $NaHCO_3$ (2 x 5 mL) and saturated NaCl (1 x 5 mL), then dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (silica, 1:1 hexanes/EtOAc) afforded **48** (61 mg, 90%) as a white solid. R_f = 0.22 (1:1 hexanes/EtOAc); ^1H NMR (300 MHz, $CDCl_3$): δ 7.34-6.98 (m, 25H), 5.87-5.74 (m, 1H), 5.67 (d, J = 3.5, 1H), 5.46 (dd, J = 1.0, 3.0, 1H), 5.22 (dq, J = 1.7, 17.1, 1H), 5.12 (dq, J = 1.3, 10.5, 1H), 5.08-4.89 (m, 4H), 4.77-4.57 (m, 6H), 4.49-4.39 (m, 4H), 4.32-4.22 (m, 2H), 4.07-3.81 (m, 9H), 3.69-3.62 (m, 2H), 3.53-3.47 (m, 1H), 3.38 (t, J = 8.7, 1H), 3.22-3.19 (m, 1H), 2.00 (s, 3H), 1.94 (s, 3H), 1.74 (s, 3H), 1.24 (d, J = 6.4, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 169.9, 169.6, 168.8, 138.8, 137.4, 133.7, 128.5, 128.4, 128.4, 128.2, 128.1, 128.0, 127.8, 127.6, 127.5, 127.2, 127.0, 126.3, 117.6, 102.8, 100.4, 97.6, 82.9, 80.3, 77.5, 75.8, 75.4, 74.2, 73.7, 73.4, 73.3, 73.1, 73.0, 71.6, 71.1, 70.6, 69.3, 67.4, 66.6, 65.9, 60.6, 20.6, 20.6, 16.8; LRMS (LSIMS, 3-NBA + NaI): *m/z* 1127.3 [M + Na^+, calc'd for $C_{62}H_{72}O_{18}Na$ 1127.5].

*Allyl (2,3,4-tri-O-acetyl-6-O-benzyl-β-D-galactopyranosyl)1→4[(2,3,4-tri-O-benzyl-α-L-fucopyranosyl)1→3(2-O-benzyl-6-O-sulfo)]-β-D-glucopyranoside (**49**)*

Trisaccharide **48** (61 mg, 0.0552 mmol) was dissolved pyridine (0.55 mL) and pyridine-sulfur trioxide complex (53 mg, 0.331 mmol) was added. After stirring for 40 minutes, TLC indicated complete reaction of **48**. Methanol (5 mL) was added and solvent removed. Purification by flash chromatography (silica, 20% MeOH in $CHCl_3$) afforded **49** (66 mg, 94%) as a white solid.

*Allyl (6-O-benzyl-β-D-galactopyranosyl)1→4[(2,3,4-tri-O-benzyl-α-L-fucopyranosyl)1→3(2-O-benzyl-6-O-sulfo)]-β-D-glucopyranoside (**50**)*

Sulfated trisaccharide **49** (40 mg, 0.0316 mmol) was dissolved in methanol (1 mL) and water (0.5 mL). The pH of the solution was adjusted to approximately 12, as judged by pH paper, by addition of 1 M NaOH. After stirring for 12 hours, the reaction mixture was neutralized by addition of 1 M HCl and concentrated. Purification by flash chromatography (silica, 30% MeOH in $CHCl_3$) provided **50** (34 mg, 99%) as a white solid.

*Propyl (β-D-galactopyranosyl)1→4[(α-L-fucopyranosyl)1→3(6-O-sulfo)]-β-D-glucopyranoside (**6**)*

Compound **50** (54 mg, 0.0499 mmol) was dissolved in 2:1 methanol/water (1.5 mL) and $Pd(OH)_2$/C (55 mg) was added. The mixture was stirred under 500 psi H_2 for 12 hours, after which TLC indicated a single product. Filtration through cellulose (methanol eluent) and concentration afforded a crude solid which was purified by flash chromatography (silica, 5:4:1 $CHCl_3$/MeOH/H_2O). Cation exchange chromatography (Sephadex-sp C-25; ; 0.5 x 6.0 cm; H_2O; Na^+) followed by dialysis (100 MWCO vs. 1 L H_2O;

2 x 24 hours) of the isolated product provided the sodium salt of **6** (29.5 mg, 93%) as a white powder. ^{1}H NMR (500 MHz, D_2O, 37 °C): δ 5.40 (1H, d, J = 4.0), 4.77 (1H, bq, J = 6.7), 4.49 (1H, d, J = 7.8), 4.46 (1H, d, J = 8.0), 4.34-4.29 (2H, m), 3.94-3.87 (3H, m), 3.85-3.80 (1H, m), 3.77-3.67 (6H, m), 3.64-3.56 (3H,m), 3.49 (1H, dd, J = 8.1, 9.1), 3.44 (1H, app dd, J = 7.8, 9.8), 1.58 (2H, sx, J = 7.3), 1.15 (3H, d, J = 6.7), 0.88 (3H, t, J = 7.4); ^{13}C NMR (125 MHz, D_2O, 37 °C): δ 107.8, 107.2, 104.1, 82.8, 80.7, 80.1, 78.7, 78.3, 78.2, 78.0, 77.8, 76.9, 75.0, 74.2, 73.9, 72.2, 71.8, 67.2, 27.8, 20.9, 15.4; LRMS (LSIMS, 3-NBA, negative ion mode): m/z 609.0 [M^-, calc'd for $C_{21}H_{37}O_{18}S$ 609.2].

Allyl (6-O-benzyl-β-D-galactopyranosyl)1→4[(2,3,4-tri-O-benzyl-α-L-fucopyranosyl)1→3(2-O-benzyl)]-β-D-glucopyranoside (**51**)

Trisaccharide **37b** (204 mg, 0.152 mmol) was dissolved in tetrahydrofuran (1.5 mL) and a 1 M solution of tetrabutylammonium fluoride (0.274 mL, 0.274 mmol) in THF was added. This mixture was stirred at room temperature for 2.5 hours, at which time TLC analysis indicated conversion to a single product. Solvent was removed under a stream of argon and the residue taken up in methanol (3 mL). Potassium carbonate (5 mg, 0.038 mmol) was added and after stirring for 1 hour, silica gel (*ca.* 2 g) was added and the mixture concentrated to dryness. The dry silica gel was transferred to a column and subjected to flash chromatography (silica, 10% MeOH in $CHCl_3$), yielding **51** (144 mg, 97%) as a white solid. R_f = 0.43 (9:1 $CHCl_3$/ MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ 7.34-7.02 (m, 25H), 5.90-5.79 (m, 1H), 5.59 (d, J = 3.9, 1H), 5.24 (dq, J = 1.7, 17.3 1H), 5.09 (dq, J = 1.3, 10.5, 1H), 4.97-4.92 (m, 2H), 4.86-4.83 (m, 1H), 4.75 (m, 2H), 4.64-4.45 (m, 8H), 4.35 (ddt, J = 1.7, 5.2, 13.0, 1H), 4.19 (dd, J = 2.8, 10.3, 1H), 4.07 (ddt, J = 1.5, 5.8, 12.8, 1H), 3.98-3.74 (m, 9H), 3.64 (t, J = 6.4, 1H), 3.57-3.35 (m, 4H), 1.19 (d, J = 6.4, 3H); ^{13}C NMR (75.4 MHz, CD_3OD): δ 140.4, 140.3, 139.8, 139.6, 135.5, 129.4, 129.3, 129.2, 129.1, 129.1, 128.9, 128.8, 128.6, 128.5, 128.5, 128.4, 128.3, 128.1, 127.6, 117.3, 104.0, 103.8, 98.8, 84.5, 80.6, 79.9, 74.7, 74.6, 74.3, 74.3, 73.9, 73.4, 72.9, 71.1, 70.3, 69.7, 67.6, 61.3, 16.9; LRMS (LSIMS, 3-NBA): m/z 977.3 [(M - H)$^+$, calc'd for $C_{56}H_{65}O_{15}$ 977.5].

Allyl (3-O-sulfo-β-D-galactopyranosyl)1→4[(2,3,4-tri-O-benzyl-α-L-fucopyranosyl)1→3(2-O-benzyl-6-O-sulfo)]-β-D-glucopyranoside (**52**)

Tetraol **51** (130 mg, 0.133 mmol) and bis(tributyltin) oxide (71 μL, 0.140 mmol) were combined in benzene (6 mL) and the mixture refluxed in a Dean-Stark trap for 3.5 hours. Over the course of the reaction, the solvent was concentrated to approximately 0.5 mL, upon which it was cooled to room temperature. The remaining solvent was evaporated under a stream of argon and the residue dissolved in pyridine (1.33 mL). Addition of pyridine-sulfur trioxide complex (53 mg, 0.333 mmol) followed by stirring for 9 minutes led to the formation of a single product as judged by TLC. Methanol (2 mL) was added and the solution was concentrated under reduced pressure. Purification by flash chromatography (silica, 25% MeOH in $CHCl_3$) afforded disulfate **52** (159 mg, 91%) as a white solid.

Propyl (3-O-sulfo-β-D-galactopyranosyl)1→4[(α-L-fucopyranosyl)1→3(6-O-sulfo)]-β-D-glucopyranoside (**10**)

Disulfate **52** (23.4 mg, 0.18 mmol) and Pearlman's catalyst (25 mg) were combined in a 2:1 methanol/water solution (0.75 mL) and the mixture stirred under 500 psi H_2 for 16 hours. The mixture was filtered through cellulose (1:1 MeOH/H_2O) and subjected to cation exchange chromatography (Sephadex-sp C-25; 0.5 x 6.0 cm; H_2O, Na^+). The isolated product was then dialyzed (100 MWCO vs. 1 L H_2O; 2 x 24 hours) and concentrated to yield the disodium salt of disulfate **10** (13 mg, 98%) as a white powder. ^{1}H NMR (500 MHz, D_2O, 35 °C): δ 5.37 (1H, d, J = 4.0), 4.70 (1H, bq, J = 6.6), 4.54 (1H, d, J = 7.8), 4.42 (1H, d, J = 8.1), 4.31-4.23 (3H, m), 4.20 (1H, bd, J = 3.3), 3.90-3.86 (2H, m), 3.81-3.76 (1H, m), 3.73-3.64 (6H, m), 3.59-3.51 (3H, m), 3.45 (1H, dd, J = 8.2, 9.1), 1.55 (2H, sx, J = 7.2), 1.11 (3H, d, J = 6.6), 0.83 (3H, t, J = 7.4); ^{13}C NMR (125 MHz, D_2O, 32 °C): δ 107.2, 106.2, 103.4, 85.2, 81.9, 79.5, 79.5, 77.6, 77.3, 77.2, 77.0, 77.0, 74.2, 74.2, 73.1, 71.6, 71.4, 70.9, 26.8, 19.8, 18.6; LRMS (LSIMS, 3-NBA, negative ion mode): m/z 710.9 [M^{2-} + Na^+, calc'd for $C_{21}H_{36}O_{21}NaS_2$ 711.2].

Allyl (β-D-galactopyranosyl)1→4[(2,3,4-tri-O-benzyl-α-L-fucopyranosyl)1→3(2-O-benzyl-6-O-tert-butyldiphenylsilyl)]-β-D-glucopyranoside (**53**)

Trisaccharide **37a** (34 mg, 0.0262 mmol) was combined with methanol (0.53 mL) in a round bottom flask upon which the trisaccharide crystallized. Potassium carbonate (0.9 mg, 0.0066 mmol) was added and the mixture stirred at room temperature for 12 hours, resulting in a clear solution. Silica gel (*ca.* 1g) was added and the resulting suspension concentrated to dryness. The dry powder was transferred to a column and chromatographed (silica, 5% MeOH in $CHCl_3$), yielding tetraol **53** (27 mg, 92%) as a white solid. R_f = 0.25 (1:1 hexanes/EtOAc); ^1H NMR (300 MHz, CD_3OD): δ 7.81-7.72 (m, 4H), 7.44-7.03 (m, 26H), 5.98-5.85 (m, 1H), 5.67 (d, *J* = 3.9, 1H), 5.27 (dq, *J* = 1.7, 17.3, 1H), 5.14 (dq, *J* = 1.6, 10.4, 1H), 5.08-4.98 (m, 2H), 4.89-4.83 (m, 5H), 4.72 (d, *J* = 12.0, 1H), 4.60-4.49 (m, 4H), 4.40-4.33 (m, 3H), 4.19 (dd, J = 2.7, 10.3, 1H), 4.09-3.91 (m, 5H), 3.78 (d, *J* = 3.3, 1H), 3.67 (dd, *J* = 4.2, 11.6, 1H), 3.60-3.36 (m, 5H), 1.20 (d, *J* = 6.6, 3H), 1.08 (s, 9H); ^{13}C NMR (75.4 MHz, CD_3OD): δ 140.4, 140.3, 139.2, 137.2, 136.7, 135.5, 135.2, 134.2, 130.8, 129.3, 129.3, 129.2, 128.9, 128.6, 128.5, 128.4, 128.2, 127.6, 117.3, 116.8, 103.7, 103.6, 98.9, 84.8, 80.7, 79.9, 77.6, 77.2, 76.9, 76.4, 75.1, 74.7, 74.5, 73.5, 72.8, 70.8, 70.1, 67.8, 63.5, 62.8, 27.5, 16.9; LRMS (LSIMS, 3-NBA): *m/z* 1127.3 [M + H^+, calc'd for $C_{65}H_{79}O_{15}Si$ 1127.6].

Allyl (3-O-sulfo-β-D-galactopyranosyl)1→4[(2,3,4-tri-O-benzyl-α-L-fucopyranosyl)1→3(2-O-benzyl-6-O-tert-butyldiphenylsilyl)]-β-D-glucopyranoside (**54**)

Tetraol **53** (17 mg, 0.012 mmol) and dibutyltin oxide (3 mg, 0.012 mmol) were combined in benzene (1.0 mL) and the mixture refluxed in a Dean-Stark trap for 3 hours. Over the course of the reaction, the solvent was concentrated to approximately 0.3 mL, after which the flask was cooled to room temperature. Pyridine-sulfur trioxide complex (2 mg, 0.12 mmol) was added to the cooled solution and stirring for 5 minutes resulted in quantitative conversion to a single product as judged by TLC. Methanol (1 mL) was added and the solvent removed under reduced pressure. Purification by flash chromatography (silica, 5% MeOH in $CHCl_3$) yielded monosulfate **54**, however, it was contaminated with some tin by-products. The impure mixture was carried on as isolated.

Propyl (3-O-sulfo-β-D-galactopyranosyl)1→4(α-L-fucopyranosyl)1→3-β-D-glucopyranoside (**7**)

Impure monosulfate **54** was dissolved in tetrahydrofuran (0.174 mL) and a 1 M solution of tetrabutylammonium fluoride 87 μL, 0.0872 mmol) in THF was added. The reaction was stirred for 2 hours, then filtered through a plug of silica gel (methanol) and concentrated. The residue was taken up in a 2:1 mixture of methanol/water (0.75 mL) and $Pd(OH)_2/C$ (15 mg) was added. After stirring under 500 psi H_2 for 14 hours, the mixture was filtered through cellulose (1:1 MeOH/H_2O) and concentrated. Purification by flash chromatography (silica, 5:4:1 $CHCl_3$/MeOH/H_2O) followed by cation exchange chromatography (Sephadex-sp C-25; 0.5 x 6.0 cm; H_2O; Na^+) provided a white solid which was dialyzed (100 MWCO vs. 1 L H_2O; 2 x 24 hours) to afford pure **7** (5.9 mg, 81% for three steps) as a white powder. ^1H NMR (500 MHz, D_2O, 37 °C): δ 5.44 (1H, d, *J* = 4.0), 4.77 (1H, bq, *J* = 6.8), 4.53 (1H, d, *J* = 7.8), 4.47 (1H, d, *J* = 8.1), 4.31 (1H, app dd, *J* = 3.3, 9.9), 4.26 (1H, app d, *J* = 3.3), 4.00-3.93 (2H, m), 3.90-3.70 (8H, m), 3.65-3.55 (4H, m), 3.50 (1H, dd, *J* = 8.3, 9.0), 1.61 (2H, sx, *J* = 7.2), 1.18 (3H, d, *J* = 6.7), 0.90 (3H, t, *J* = 7.4); ^{13}C NMR (125 MHz, D_2O, 37 °C): δ 104.9, 104.7, 101.4, 83.1, 80.0, 78.1, 77.6, 77.6, 76.5, 75.4, 75.1, 74.8, 72.0, 70.7, 69.6, 69.6, 64.2, 62.6, 24.7, 17.8, 12.4; LRMS (LSIMS, 3-NBA, negative ion mode): *m/z* 609.1 [M^-, calc'd for $C_{21}H_{37}O_{18}S$ 609.2].

Allyl (3,6-di-O-sulfo-β-D-galactopyranosyl)1→4[(2,3,4-tri-O-benzyl-α-L-fucopyranosyl)1→3(2-O-benzyl-6-O-tert-butyldiphenylsilyl)]-β-D-glucopyranoside (**55**)

Tetraol **53** (27 mg, 0.0239 mmol) and bis(tributyltin) oxide (13 μL, 0.0251 mmol) were combined in benzene (3 mL) and the mixture refluxed in a Dean-Stark trap for 3 hours. Over the course of the reaction, the reaction volume was reduced to approximately 0.5 mL, upon which the solution was allowed to cool to room temperature. Remaining solvent was removed under a stream of argon and the residue dissolved in pyridine (0.24 mL). Pyridine-sulfur trioxide complex (9.5 mg, 0.0598 mmol) was added and

the mixture stirred for 15 minutes, followed by addition of methanol (1 mL). Solvent was removed under reduced pressure and the residue purified by flash chromatography (silica, 30% MeOH in $CHCl_3$). The isolated product contained some tin by-products as well as a small amount of a more polar compound, so disulfate **55** was carried on as a mixture.

Propyl (3,6-di-O-sulfo-β-D-galactopyranosyl)1→4(α-L-fucopyranosyl)1→3-β-D-glucopyranoside (8)

Crude disulfate **55** was dissolved in tetrahydrofuran (0.239 mmol) and a 1 M solution of tetrabutylammonium fluoride (0.239 mL, 0.239 mmol) in THF was added. After stirring for 50 minutes at room temperature, the mixture was filtered through silica gel (methanol) and concentrated. The residue was dissolved in a 2:1 mixture of methanol/water and $Pd(OH)_2/C$ was added. Stirring under 500 psi H_2 for 14 hours did not achieve complete reaction, so the mixture was filtered through celite (1:1 MeOH/H_2O) and concentrated. The residue was dissolved in 1:1 MeOH/H_2O and fresh catalyst was added. After an additional 16 hours of stirring under 500 psi H_2, TLC analysis indicated complete conversion to a polar product. The reaction mixture was then filtered through cellulose (H_2O) and concentrated. Purification by flash chromatography (silica, 5:4:1 $CHCl_3$/MeOH/H_2O), cation exchange chromatography (Sephadex-sp C-25; 0.5 x 6.0 cm; H_2O; Na^+) and dialysis (100 MWCO vs. 1 L H_2O; 2 x 24 hours) afforded the disodium salt of **8** (13.4 mg, 76% for three steps) as a white powder. ^1H NMR (500 MHz, D_2O, 40 °C): δ 5.38 (1H, d, J = 4.0), 4.74 (1H, bq, J = 6.6), 4.51 (1H, d, J = 7.9), 4.42 (1H, d, J = 8.1), 4.30 (1H, app dd, J = 3.4, 9.8), 4.27 (1H, app d, J = 3.4), 4.16-4.09 (2H, m), 3.97-3.91 (2H, m), 3.87-3.76 (5H, m), 3.73-3.69 (2H, m), 3.62-3.53 (3H, m), 3.48 (1H, dd, J = 8.1, 9.1), 1.58 (2H, sx, J = 7.2), 1.14 (3H, d, J = 6.7), 0.87 (3H, t, J = 7.4); ^{13}C NMR (125 MHz, D_2O, 37 °C): δ 108.0, 107.4, 104.3, 85.9, 83.4, 81.2, 80.4, 79.3, 78.2, 78.0, 77.9, 75.1, 75.1, 74.2, 73.0, 72.4, 72.3, 65.8, 28.0, 21.1, 15.4; LRMS (LSIMS, 3-NBA, negative ion mode): m/z 711.1 [M^{2-} + Na^+, calc'd for $C_{21}H_{36}O_{21}NaS_2$ 711.2].

Allyl (β-D-galactopyranosyl)1→4[(2,3,4-tri-O-benzyl-α-L-fucopyranosyl)1→3(2-O-benzyl)]-β-D-glucopyranoside (56)

Trisaccharide **37a** (32 mg, 0.0238 mmol) was dissolved in tetrahydrofuran (0.238 mL) and a 1 M solution of tetrabutylammonium fluoride (0.043 mL, 0.043 mmol) in THF was added. After stirring at room temperature for 2.5 hours, solvent was removed under a stream of argon and the residue taken up in methanol (1 mL). Potassium carbonate (0.8 mg, 0.00595 mmol) was added and after stirring for 1 hour, silica gel (*ca.* 1 g) was added. The resulting suspension was concentrated to dryness, transferred to a column and purified by flash chromatography (silica, 10% MeOH in $CHCl_3$), affording **56** (23 mg, 99%) as a white solid. R_f = 0.31 (9:1 $CHCl_3$/MeOH); ^1H NMR (300 MHz, CD_3OD): δ 7.40-7.03 (m, 20H), 5.92-5.81 (m, 1H), 5.63 (d, J = 3.9, 1H), 5.25 (dq, J = 1.7, 17.3, 1H), 5.13-4.80 (m, 5H), 4.69 (d, J = 1.7, 1H), 4.59-4.45 (m, 6H), 4.37 (ddt, J = 1.7, 5.1, 12.9, 1H), 4.16 (dd, J = 2.8, 10.3, 1H), 4.08 (ddt, J = 1.5, 5.9, 13.0, 1H), 4.01-3.89 (m, 7H), 3.80 (d, J = 1.5, 1H), 3.71-3.64 (m, 1H), 3.54-3.35 (m, 5H), 1.19 (d, J = 6.4, 3H); ^{13}C NMR (75.4 MHz, CD_3OD): δ 140.4, 140.3, 139.3, 135.5, 129.3, 129.1, 128.6, 128.5, 128.4, 128.2, 127.6, 117.3, 104.0, 103.7, 98.9, 84.6, 80.6, 79.8, 77.6, 77.2, 77.0, 76.9, 76.4, 74.9, 74.7, 74.5, 74.0, 73.4, 73.0, 71.1, 70.1, 67.8, 63.4, 61.2, 16.9; LRMS (LSIMS, 3-NBA + NaI): m/z 911.2 [M + Na^+, calc'd for $C_{49}H_{60}O$ Na 911.4].

Allyl (6-O-sulfo-β-D-galactopyranosyl)1→4[(2,3,4-tri-O-benzyl-α-L-fucopyranosyl)1→3(2-O-benzyl-6-O-sulfo)]-β-D-glucopyranoside (57)

Compound **56** (30 mg, 0.0337 mmol) was dissolved in pyridine (0.337 mmol) and pyridine-sulfur trioxide complex (11.3 mg, 0.0708 mmol) was added. Stirring at room temperature resulted in incomplete reaction of **56**, with TLC analysis indicating one major product as well as several minor products. Additional pyr·SO_3 (2.1 mg, 0.135 mmol) was added and stirring continued for 15 minutes. Addition of methanol (1 mL) followed by concentration under reduced pressure afforded a white solid which contained the desired product **57**, and which was carried on without purification.

Propyl (6-O-sulfo-β-D-galactopyranosyl)1→4[(α-L-fucopyranosyl)1→3(6-O-sulfo)]-β-D-glucopyranoside (9)

The crude reaction mixture containing **57** was combined with $Pd(OH)_2/C$ (40 mg) in a 2:1 mixture of methanol/water and the resulting suspension stirred under 500 psi H_2 for 12 hours. TLC indicated incomplete reaction, so the mixture was filtered through celite (1:1 methanol/water) and concentrated. The residue was redissolved in 1:1 MeOH/H_2O and fresh catalyst (40 mg) added. Stirring under 500 psi H_2 for an additional 12 hours resulted in complete reaction, and filtration through cellulose (H_2O) and concentration afforded a crude white solid. Purification by flash chromatography (silica, 5:4:1 $CHCl_3$/MeOH/H_2O), cation exchange chromatography (Sephadex-sp C-25; 0.5 x 6.0 cm; H_2O; Na^+) and dialysis (100 MWCO vs. 1 L H_2O; 2 x 24 hours) provided the disodium salt of **9** (13 mg, 53% for two steps) as a white powder. ^1H NMR (500 MHz, D_2O, 37 °C): δ 5.35 (1H, d, J = 4.1), 4.74 (1H, bq, J = 6.9), 4.48 (1H, d, J = 8.1), 4.44 (1H, d, J = 8.1), 4.35-4.25 (2H, m), 4.09 (2H, d, J = 6.9), 3.92-3.68 (9H, m), 3.62 (1H, app dd, J = 4.0, 10.0), 3.60-3.53 (1H, m), 3.50-3.41 (2H, m), 1.56 (2H, sx, J = 7.3), 1.13 (3H, d, J = 6.8), 0.85 (3H, t, J = 7.4); ^{13}C NMR (125 MHz, D_2O, 37 °C): δ 107.0, 106.8, 103.8, 82.6, 79.3, 78.2, 77.9, 77.4, 77.2, 77.2, 77.1, 76.0, 74.3, 73.3, 73.1, 71.8, 71.6, 71.1, 27.3, 20.4, 14.7; LRMS (LSIMS, 3-NBA, negative ion mode): m/z 711.1 [M^{2-} + Na^+, calc'd for $C_{21}H_{36}O_{21}NaS_2$ 711.2].

Allyl (3,6-di-O-sulfo-β-D-galactopyranosyl)1→4[(2,3,4-tri-O-benzyl-α-L-fucopyranosyl)1→3(2-O-benzyl-6-O-sulfo)]-β-D-glucopyranoside (58)

Trisaccharide **56** (34 mg, 0.0382 mmol) and bis(tributyltin) oxide (31 μL, 0.0611 mmol) were combined in benzene (5 mL) and the mixture refluxed in a Dean-Stark trap for 4 hours. Over the course of the reaction, the solvent volume was reduced to about 0.5 mL, upon which the solution was cooled to room temperature. Remaining solvent was evaporated under a stream of argon and the residue dissolved in pyridine (0.255 mL). Pyridine-sulfur trioxide (21 mg, 0.134 mmol) was added and the reaction stirred for 30 minutes. TLC indicated incomplete reaction so excess pyr·SO_3 (9 mg, 0.0573 mmol) was added and stirring continued for 1 hour. Methanol (1 mL) was added and the solution concentrated and filtered through a plug of silica gel (methanol). **58** was carried on as a crude mixture.

Propyl (3,6-di-O-sulfo-β-D-galactopyranosyl)1→4[(α-L-fucopyranosyl)1→3(6-O-sulfo)]-β-D-glucopyranoside (11)

Crude **58** was dissolved in 1:1 methanol/water (1 mL) and $Pd(OH)_2/C$ (50 mg) was added. Stirring under 500 psi H_2 for 10 hours resulted in incomplete hydrogenolysis, so the mixture was filtered through celite (1:1 MeOH/H_2O) and concentrated. The residue was redissolved in 1:1 MeOH/H_2O (1 mL), fresh catalyst (50 mg) was added and the mixture stirred under 500 psi H_2 for an additional 7 hours. Filtration through celite (H_2O) followed by anion exchange chromatography (DEAE-Sephadex A-25; 100 mL 0→0.25M $Et_3NH_2CO_3$; 0.5 x 6.0 cm), cation exchange chromatography (Sephadex-sp C-25; 0.5 x 6.0 cm; H_2O; Na^+) and dialysis (100 MWCO vs. 1 L H_2O; 2 x 24 hours) afforded pure **11** (27 mg, 85% for two steps) as a white powder. ^1H NMR (500 MHz, D_2O, 32 °C): δ 5.34 (1H, d, J = 3.9), 4.71 (1H, bq, J = 6.5), 4.53 (1H, d, J = 7.8), 4.41 (1H, d, J = 8.0), 4.33-4.23 (4H, m), 4.11-4.05 (2H, m), 3.89-3.62 (8H, m), 3.57-3.51 (2H, m), 3.46 (1H, dd, J = 8.1, 9.0), 1.54 (2H, sx, J = 7.3), 1.10 (3H, d, J = 6.6), 0.82 (3H, t, J = 7.4); ^{13}C NMR (125 MHz, D_2O, 32 °C): δ 107.4, 106.7, 103.8, 85.2, 82.7, 79.7, 78.5, 78.3, 77.7, 77.4, 77.3, 74.5, 74.5, 73.6, 72.2, 71.8, 71.7, 71.5, 27.4, 20.5, 14.9; LRMS (LSIMS, 3-NBA, negative ion mode): m/z 813.2 [M^{3-} + 2Na^+, calc'd for $C_{21}H_{35}O_{24}Na_2S_3$ 813.2].

References and Notes

1. a) Rosen, S. D.; Bertozzi, C. R. *Curr. Opin. Cell Biol.* **1994**, *6*, 663-673. b) Carlos, T. M.; Harlan, J. M. *Blood* **1994**, *84*, 2068-2101. c) Tedder, T. F.; Steeber, D. A.; Pizcueta, P. *J. Exp. Med.* **1995**, *181*, 2259-2264.
2. a) Borman, S. *Chemical and Engineering News* **1992**, 25-28. b) Bertozzi, C. R. *Chemistry and Biology* **1995**, *2*, 703-708. c) Bertozzi, C. R.; Fukuda, S.; Rosen, S. D. *Biochemistry* **1995**, *34*, 14271-14278. d) Kogan, T. P.; Dupré, B.; Keller, K. M.; Scott, I. L.; Huong, B.; Market, R. V.; Beck, P. J.; Voytus, J. A.; Revelle, B. M.; Scott, D. *J. Med. Chem.* **1995**, *38*, 4976-4984. e) Sears, P.; Wong, C.-H. *Proc. Nat. Acad. Sci. USA* **1996**, *93*, 12086-12093.

3. Varki, A. *Proc. Nat. Acad. Sci. USA* **1994**, *91*, 7390-7397.
4. Sako, D.; Chang, X.-J.; Barone, K. M.; Vachino, G.; White, H. M.; Shaw, G.; Veldman, G. M.; Bean, K. M.; Ahern, T. J.; Furie, B.; Cumming, D. A.; Larsen, G. R. *Cell* **1993**, *75*, 1179-1186.
5. Patel, T. P.; Goelz, S. E.; Lobb, R. R.; Parekh, R. B. *Biochemistry* **1994**, *33*, 14815-14824.
6. a) Berg, E. L.; McEvoy, L. M.; Berlin, C.; Bergatze, R. F.; Butcher, E. C. *Nature* **1993**, *366*, 695-698. b) Briskin, M. J.; McEvoy, L. M.; Butcher, E. C. *Nature* **1993**, *363*, 461-464.
7. Baumheuter, S.; Singer, M. S.; Henzel, W.; Hemmerich, S.; Renz, M.; Rosen, S. D.; Lasky, L. A. *Science* **1993**, *262*, 436-438.
8. Lasky, L. A.; Singer, M. S.; Dowbenko, D.; Imai, Y.; Henzel, W. J.; Grimley, C.; Fennie, C.; Gillett, N.; Watson, S. R.; Rosen, S. D. *Cell* **1992**, *69*, 927-938.
9. a) Tyrell, D.; James, P.; Rao, N.; Foxall, C.; Abbas, S.; Dasgupta, F.; Nashed, M.; Hasegawa, A.; Kiso, M.; Asa, D.; Kidd, J.; Brandley, B. K. *Proc. Nat. Acad. Sci. USA* **1991**, *88* 10372-10376. b) Berg, E. L.; Magnani, J.; Warnock, R. A.; Robinson, M. K.; Butcher, E. C. *Biochem. Biophys. Res. Commun.* **1992**, *184*, 1048-1055. c) Foxall, C.; Watson, S. R.; Dowbenko, D.; Fennie, C.; Lasky, L. A.; Kiso, M.; Hasegawa, A.; Asa, D.; Brandley, B. K. *J. Cell Biol.* **1992**, *117*, 895-902.
10. a) Kogelberg, H.; Frenkiel, T. A.; Homans, S. W.; Lubineau, A.; Feizi, T. *Biochemistry* **1996**, *35*, 1954-1964. b) Kurutz, J. W.; Kiessling, L. L. *Glycobiology* **1997**, *7*, 337-347.
11. Imai, Y.; Lasky, L. A.; Rosen, S. D. *Nature* **1993**, *361*, 555-557.
12. a) Hemmerich, S.; Bertozzi, C. R.; Leffler, H.; Rosen, S. D. *Biochemistry* **1994**, *33*, 4820-4829. b) Hemmerich, S.; Rosen, S. D. *Biochemistry* **1994**, *33*, 4830-4835.
13. For representative chemical syntheses, see: a) Kameyama, A.; Ishida, H.; Kiso, M.; Hasegawa, A. *J. Carbohydr. Chem.* **1991**, *10*. 549-560. b) Nicolaou, K. C.; Hummel, C. W.; Iwabuchi, Y. *J. Am. Chem. Soc.* **1992**, *114*, 3126-3128. c) Jain, R. K.; Vig, R.; Rampal, R.; Chandrasekaran, E. V.; Matta, K. L. *J. Am. Chem. Soc.* **1994**, *116*, 12123-12124. d) Iida, M.; Endo, A.; Fujita, S.; Numata, M.; Matsuzaki, Y.; Sugimoto, M.; Numomura, S.; Ogawa, T. *Carbohydr. Res.* **1995**, *260*, C15-C19. e) Danishefsky, S. J.; Gervay, J.; Peterson, J. M.; McDonald, F. E.; Koseki, K.; Griffith, D. A.; Oriyama, T.; Marsden, S. P. *J. Am. Chem. Soc.* **1995**, *117*, 1940-1953.
14. For representative chemoenzymatic syntheses, see: a) Ball, G. E.; O'Neill, R. A.; Schultz, J. E.; Lowe, J. B.; Weston, B. W.; Nagy, J. O.; Brown, E. G.; Hobbs, C. J.; Bednarski, M. D. *J. Am. Chem. Soc.* **1992**, *114*, 5449-5451. b) Scudder, P. R.; Shailubhai, K.; Duffin, K. L.; Streeter, P. R.; Jacob, G. S. *Glycobiology* **1994**, *4*, 929-933. c) Halcomb, R. L.; Huang, H.; Wong, C.-H. *J. Am. Chem. Soc.* **1994**, *116*, 11315-11322.
15. Chandrasekaran, E. V.; Jain, R. K.; Larsen, R. D.; Wlasichuk, K.; Matta, K. L. *Biochemistry* **1995**, *34*, 2925-2936.
16. a) Yuen, C.-T.; Lawson, A. M.; Chai, W.; Larkin, M.; Stoll, M. S.; Stuart, A. C.; Sullivan, F. X.; Ahern, T. J.; Feizi, T. *Biochemistry* **1992**, *31*, 9126-9131. b) Yuen, C.-T.; Bezouska, K.; O'Brien, J.; Stoll, M. S.; Lemoine, R.; Lubineau, A.; Kiso, M.; Hasegawa, A.; Bockovich, N. J.; Nicolaou, K. C.; Feizi, T. *J. Biol. Chem.* **1994**, *269*, 1595-1598.
17. Yoshida, M.; Uchimura, A.; Kiso, M.; Hasegawa, A. *Glyconjugate J.* **1993**, *10*, 3-15.
18. a) Brandley, B. K.; Kiso, M.; Abbas, S.; Nikrad, P.; Srivasatava, O.; Foxall, C.; Oda, Y.; Hasegawa, A. *Glycobiology* **1993**, *3*, 633-639. b) Nelson, R. M.; Dolich, S.; Aruffo, A.; Cecconi, O.; Bevilacqua, M. P. *J. Clin. Invest.* **1993**, *91*, 1157-1166.
19. Regioselective sulfation of a stannylene acetal has been reported by others as well, see: a) Guilbert, B.; Davis, N. J.; Flitsch, S. L. *Tetrahedron Lett.* **1994**, *35*, 6563-6566. b) Lubineau, A.; Lemoine, R. *Ibid.* 8795-8796.
20. a) Brüning, J.; Kiessling, L. L. *Tetrahedron Lett.* **1996**, *37*, 2907-2910. b) Manning, D. D.; Hu, X.; Beck, P.; Kiessling, L. L. *J. Am. Chem. Soc.* in press.
21. Schmidt, R. R.; Stumpp, M. *Liebigs Ann. Chem.* **1983**, 1249-1256.
22. Nicolaou, K. C.; Caulfield, H. K.; Kataoka, H.; Stylanides, N. A. *J. Am. Chem. Soc.* **1990**, *112*, 3693-3695.
23. a) Gao, Y.; Sharpless, K. B. J. Am. Chem. Soc. 1988, 110, 7538-7539. b) Lohray, B. B. *Synthesis* **1992**,

1035-1052.
24. a) Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661-6666. b) Gordon, D. M.; Danishefsky, S. J. *Carbohydr. Res.* **1990**, *206*, 361-366.
25. a) Hanessian, S.; Vatele, J. M. *Tetrahedron Lett.* **1981**, *37*, 3579-3582. b) Tewson, T. J. *J. Org. Chem.* **1983**, *48*, 3507-3510. c) Berridge, M. S.; Franceschini, M. P.; Rosenfeld, E.; Tewson, T. J. *J. Org. Chem.* **1990**, *55*, 1211-1217.
26. Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968.
27. a) Guiller, A.; Gagnieu, C. H.; Pacheco, H. *Carbohydr. Res.* **1988**, *180*, 233-242. b) Meslouti, A. E.; Beaupére, D.; Demailly, G. Uzan, R. *Tetrahedron Lett.* **1994**, *35*, 3913-3916.
28. Forsberg, J. H.; Spaziano, V. T.; Balasubramanian, T. M.; Liu, G. K.; Kinsley, S. A.; Duckworth, C. A.; Poteruca, J. J.; Brown, P. S.; Miller, J. L. *J. Org. Chem.* **1987**, *52*, 1017-1021.
29. Sanders, W. J.; Kiessling, L. L *Tetrahedron Lett.* **1994**, *35*, 7335-7338.
30. Wese., H.-P.; Iversen, T.; Bundle, D. R. *J. Chem. Soc. Perkins I* **1985**, 2247-2250.
31. Mootoo, D. R.; Konradsson, P.; Udodong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583-5584.
32. a) Schmidt, R. R. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 212-235. b) Schmidt, R. R. in *Comprehensive Organic Synthesis*, Pergamon Press: Oxford, 1991; vol. 6, pp. 33-64. c) Halcomb, R. L.; Boyer, S. H.; Danishefsky, S. J. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 338-340.
33. Myers, A. G.; Gin, D. Y.; Rogers, D. H. *J. Am. Chem. Soc.* **1994**, *116*, 4697-4718.
34. Schmidt, R. R.; Michel, J. *Angew. Chem. Int. Ed. Eng.* **1980**, *19*, 731-732.
35. Matsumoto, T.; Maeta, H.; Suzuki, K.; Tsuchihashi, G.-I. *Tetrahedron Lett.* **1988**, *29*, 3567-3570.
36. Garegg, P. J.; Hultberg, H.; Wallin, S. *Carbohydr. Res.* **1982**, *108*, 97-101.
37. Johansson, R.; Samuelsson, B. *J. Chem. Soc. Perkins I* **1984**, 2371-2374.
38. DeNinno, M. P.; Etienne, J. B.; Duplantier, K. C. *Tetrahedron Lett.* **1995**, *36*, 669-672.
39. Mukaiyama, T.; Murai, Y.; Shoda, S.-I. *Chem. Lett.* **1981**, 431-432.
40. Maeta, H.; Matsumoto, T.; Suzuki, K. *Carbohydr. Res.* **1993**, *249*, 49-56.
41. For examples of Le^x syntheses where fucose is introduced first, see a) Danishefsky, *et al.* ref. 13a. b) Sprengard, U.; Kretzschmar, G.; Bartnik, E.; Hüls, C.; Kunz, H. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 990-992.
42. Ek, M.; Garegg, P. J.; Hultberg, H.; Oscarson, S. *J. Carbohydr. Chem.* **1983**, *2*, 305-311.
43. Gass, J.; Strobl, M.; Loibner, A.; Kosma, P.; Zähringer, U. *Carbohydr. Res.* **1993**, *244*, 69-84.
44. Hanessian, S.; Banoub, J. *Carbohydr. Res.* **1981**, *93*, C6-C9.
45. Banoub, J.; Bundle, D. R. *Can. J. Chem.* **1979**, *57*, 2091-2097.
46. a) David, S.; Hanessian, S. *Tetrahedron* **1985**, *41*, 643-663. b) Glen, A.; Leigh, D. A.; Martin, R. P.; Smart, J. P.; Truscello, A. M. *Carbohydr. Res.* **1993**, *248*, 365-369.
47. a) Ogawa, T.; Matsui, M. *Tetrahedron* **1981**, *37*, 2363-2369. b) Kawana, M.; Kuzuhara, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3317-3320.
48. The alkoxystannanes described in this manuscript were not isolated, but their formation is rationalized by precedent (ref.'s 46a and 47a). In addition, the sulfation reactions are not selective in the absence of the tin reagents.
49. a) Manning, D. D.; Bertozzi, C. R.; Pohl, N. L.; Rosen, S. D.; Kiessling, L. L. *J. Org. Chem.* **1995**, *60*, 6254-6255. b) Sanders, W. J.; Katsumoto, T. R.; Bertozzi, C. R.; Rosen, S. D.; Kiessling, L. L. *Biochemistry* **1996**, *35*, 14862-14867.

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