# Major Simplifications in Oligosaccharide Syntheses Arising from a Solid-Phase Based Method: An Application to the Synthesis of the Lewis b Antigen

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**Abstract:** Polymer bound glycals, upon activation by epoxidation, function as competent $\beta$-glycosyl donors. The first glycal is linked through a silyl ether linker to a commercially available divinylbenzene polystyrene copolymer. At the end of the synthesis, soluble oligosaccharide is retrieved from the polymer by fluoridolysis. The method is self-corrective in that failed donors in a coupling step do not reemerge in the next cycle. The method is particularly powerful for creating branched sugars at $C_2$, a common branching site. An application of the solid phase method to a straightforward synthesis of the Lewis b antigen is described. The superiority of a diisopropylsilyl spacer relative to the previously employed diphenyl spacer is established (see compounds **4** and **5**).

## Introduction

Increased awareness of the vital biological roles played by oligosaccharides has led to an ever-expanding interest and appreciation for these structures. These complex biomolecules, in the form of glycoprotein and glycolipid conjugates, carry detailed structural information which serves to mediate a variety of biological events including inflammation,[1] immunological response,[1c,2a−c] metastasis,[2d] fertilization,[2e] and possibly, protein folding.[2f] Furthermore, cell surface carbohydrates act as biological markers for various tumors,[3] and as binding sites to other substances, including pathogens.[4] Not surprisingly, there is increased demand for new, more efficient methods for the chemical synthesis of oligosaccharides and other glycoconjugates (cf. glycolipids and glycopeptides).[5]

A particularly desirable goal would be the development of a generally applicable method for the rapid assembly of such systems with a long term view toward automatability. To begin to address this major challenge, considerable efforts have been directed to the study of solid-phase strategies.[6] Recent advances have demonstrated that useful methodologies for glycosidation in solution are often applicable on a polymer support,[7] and that large, biologically important oligosaccharides can indeed be assembled in solid phase syntheses.[8] However, many of these approaches require laborious manipulation of competing hydroxyl functionality in order to achieve the regio- and stereoselectivities desired. Furthermore, such protecting group manipulations must be carried out in the solid-phase. An intriguing exception from this general consideration can be found in recent work reported by Wong and coworkers in which transferase enzymes were used to prepare a sialyl-Le$^x$ glycopeptide.[9] The Wong method bypasses the need for protecting groups since the transferase enzymes control both regio- and stereoselectivity of glycosidation.[10]

We have been investigating a strategy in which glycals are key building blocks for the synthesis of oligosaccharides and

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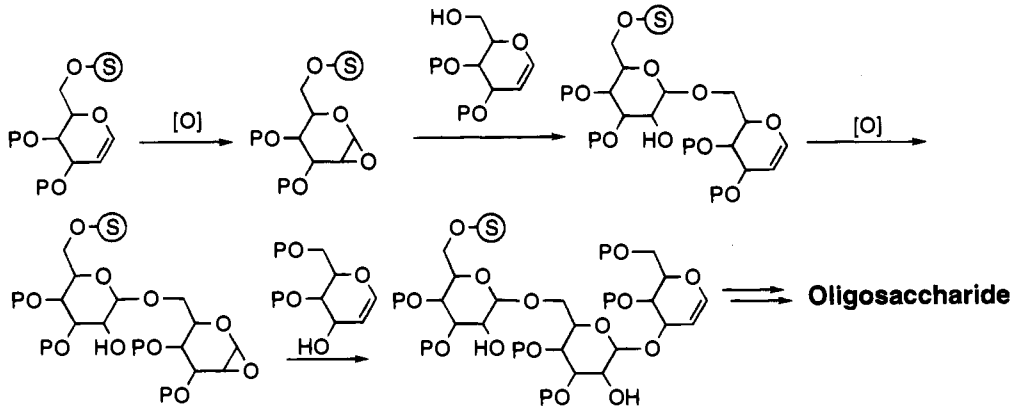
**Scheme 1.** Glycal Assembly of Oligosaccharides Using 1,2-Anhydro Sugars (P = unspecified protecting groups)




glycoconjugates.[11] It was perceived that the glycal assembly paradigm, which has already demonstrated considerable advantages for the solution synthesis of complex carbohydrates,[12] might be particularly well suited for application on a solid support. Thus, the selective exposure of a particular hydroxyl group on a glycal to serve as an acceptor is rather more straightforward than is the case in a fully oxygenated pyranose derivative. Protecting group manipulations, are therefore much simplified in the glycal regime. This feature can be of considerable importance in constructing monosaccharide building blocks for a strategy based on solid-phase methodology. Furthermore, there are a number of mild, efficient methods for the activation of glycals to serve as glycosyl donors. These methods can be mobilized to provide access to various kinds of glycosidic linkages.[13] Through the use of glycals as glycosyl acceptors as well as donors an iterative approach to oligosaccharide formation suggests itself (*vide infra*).

Our initial efforts have focused on the use of our 1,2-anhydrosugar method for glycosidation[11,12c] on a polymer support. The basic strategy involves attachment of a glycal to a polymer support, followed by epoxidation to provide the 1,2-anhydro derivative. This polymer-bound glycosyl donor is treated with a solution of a protected glycal, acting as a glycosyl acceptor, to give a polymer-bound disaccharide glycal. Reiteration of this two-step glycosidation sequence provides larger oligomers which are ultimately retrieved from the support. As we progress, additional advantages to this type of approach will become apparent. The overall logic of our plan is summarized in Scheme 1. It is seen that the method suggested here involves, in anticipation of each coupling event, the generation of a 1,2 epoxide on the support to serve as the glycosyl donor.

*The key feature which makes this possible is the ability to transform a glycal to the 1,2 anhydro donor under mild neutral conditions.* We will also demonstrate a crucial modification of the method such that acceptor is bound to the support and donor (which can be derived from a glycal epoxide)[12a] is introduced in solution. As will be shown, this is a particularly concise and powerful way to introduce a branch at a particular $C_2$ of a hexose in an emerging oligomer.

## Results and Discussion

**Glycal Attachment to a Polystyrene Support.** The basic matrix which we have employed is a commercially available 1% divinylbenzene–styrene copolymer. This type of insoluble resin was the first and only kind which we have thus far explored. Fortunately, it has proven to be equal to the task. The glycal is attached to this resin using a silyl ether linker. Such an attachment mode was chosen in the hope that it would be stable to the reagent conditions required for typical glycosidation reactions. It was further hoped that the desired carbohydrate construct could be retrieved through fluoridolysis.

Two specific silylated polymers have been prepared and investigated (Scheme 2). Each involved a variation of the method reported by Chan and Huang.[14] Lithiation of the copolymer, followed by quenching with diphenyldichlorosilane or diisopropyldichlorosilane provided **1** and **2**, respectively. Each of these silylated polymers reacted with a solution of D-galactal derivative **3** in dichloromethane and Hünig's base to give the corresponding dialkylsilyl-linked glycal-polymer constructs. Diphenylsilyl derivative **4** was obtained with a loading on the order of 0.6 mmol of glycal **3** per gram of **4**, whereas the diisopropylsilyl-linked **5** could be obtained with loadings in excess of 0.9 mmol per gram. It was necessary to catalyze the conversion of **2** to **5** using (dimethylamino)pyridine (DMAP) in order to achieve efficient silylation.

*In our previous disclosure,[11] we reported solely on the use of support–silyl spacer system 1. As will be shown, the systems derived from 2 perform much better, and currently this is the method which is practiced.* In this opening phase of the inquiry, we employed the readily available glycal **3** as the first carbohydrate to be attached to the solid support. We were borrowing from our findings in the solution phase wherein glycals related to **4** and **5** (*cf.* 6-*tert*-butyldimethylsilyl) allowed for stereospecific α-epoxidation with dimethyldioxirane. Furthermore, the epoxide, thus produced, functions as a particularly effective donor for producing β-glycosides.

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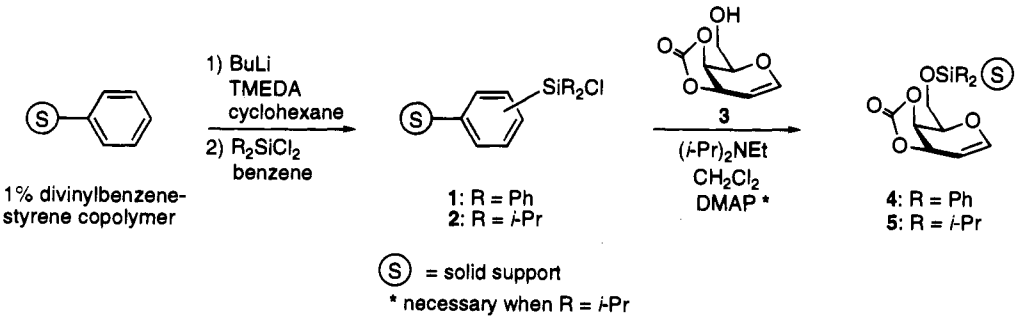
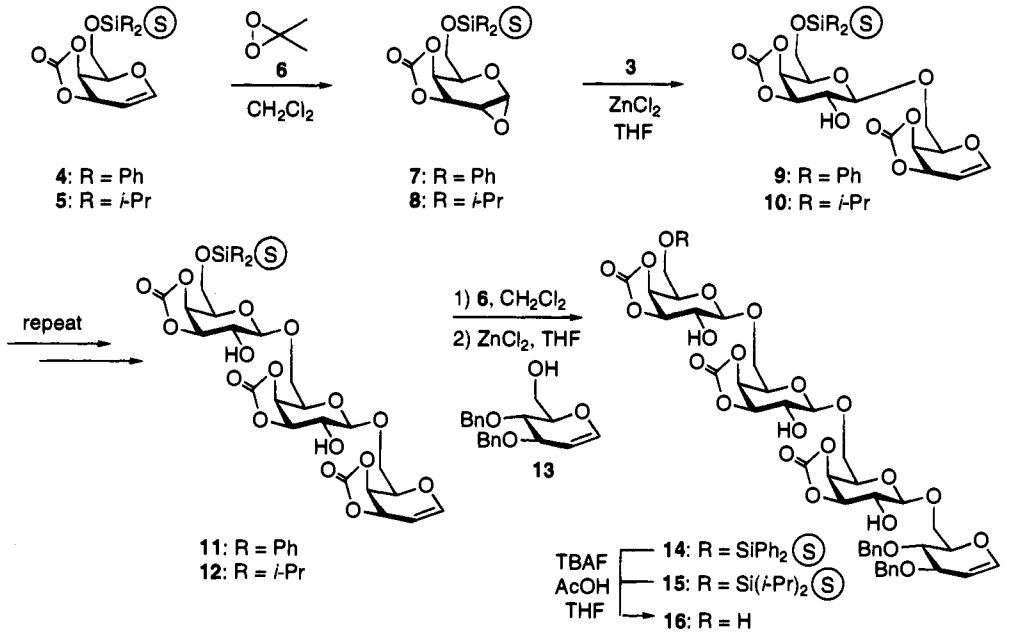
**Scheme 2.** Glycal Attachment to Polystyrene Using a Dialkylsilyl Linkage




**Scheme 3.** Glycal Assembly of a Tetrasaccharide on a Polymer Support




**Synthesis of Oligosaccharides Using Polymer-Bound Glycals.** We first demonstrate the use of **4** and **5** to prepare a tetrasaccharide glycal as shown in Scheme 3. Each polymer-bound glycal was suspended in dichloromethane and exposed to an acetone solution of 3,3-dimethyldioxirane[15] (**6**) at 0 °C. There was thus generated presumed **7** and **8**. The completeness of this epoxidation process could be determined by treating an aliquot of the oxidized material with tetrabutylammonium fluoride (TBAF) and ascertaining the presence of glycal **3** by thin-layer chromatography (TLC). In general, epoxidation of the polymer-bound *monosaccharide* glycal (i.e. the first iteration) requires a large excess of **6** due to the presence of some unknown contaminant seemingly introduced in the loading process. This contaminant is apparently rinsed away in the next extraction, and subsequent dioxirane-mediated epoxidation can be effected using far less oxidant. The oxidizing solution is removed by a simple filtration using dry $N_2$ pressure followed by evacuation.

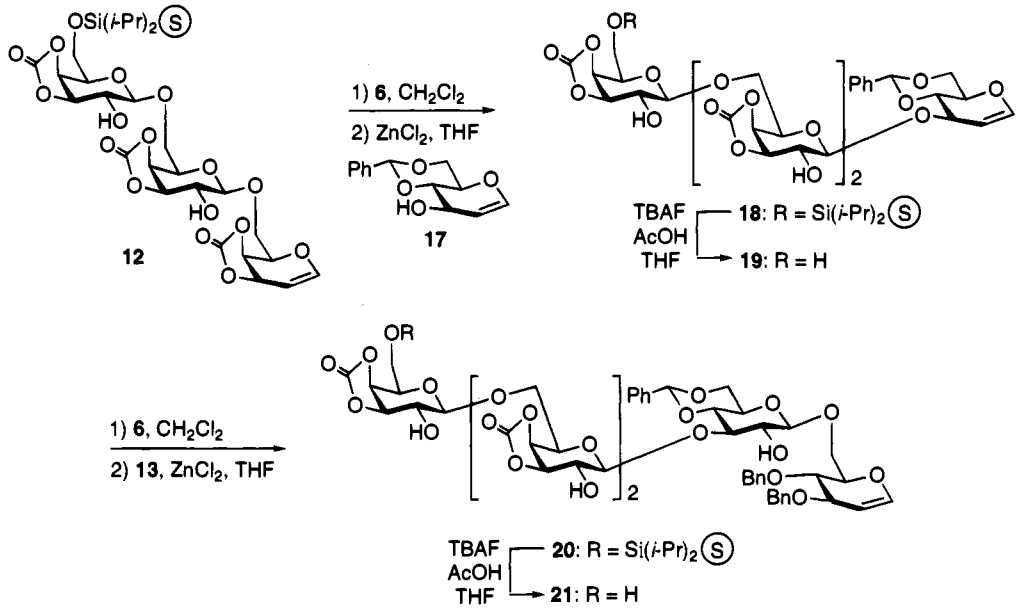
Epoxides **7** and **8** each reacted with a tetrahydrofuran solution of **3** in the presence of anhydrous $ZnCl_2$ to give polymer-bound disaccharides **9** and **10**, respectively. The solid-phase glycosidation procedure, as was practiced in these early studies, involved the use of a 6−10 fold excess of solution-based glycosyl acceptor and 2−3 equiv of promoter at reaction times in excess of 8−10 h. However, shorter reaction times (2−3 h) and less acceptor (4−5 equiv) have also been successful, when examined.[16] At this writing, we have not defined the minimum conditions, which can be tolerated either in terms of time or stoichiometry of acceptor. This will hopefully be done as part of a study to prepare for eventual automation. In present practice, **3** is easily recovered in pure form for future use by aqueous extraction followed by flash chromatography on silica gel. The disaccharide product retrieved from **9** using TBAF indicated a very clean glycosidation event, so that only the $\beta$ anomer was detected by NMR spectroscopy.

Repeating this two-step process of epoxidation with **6** followed by glycosidation with **3** provided trisaccharide glycals **11** and **12** from **9** and **10**, respectively. Each of these polymer-bound trisaccharide glycals was epoxidized using **6** and coupled with glucal-derived **13**. This protocol gave tetrasaccharides **14** and **15**, both of which were then treated with a solution of TBAF and acetic acid (added as a buffer to maintain the cyclic carbonates) in tetrahydrofuran to give **16**. Retrieval from **14** was relatively fast, and could be accomplished in only a few hours at room temperature, the overall yield of **16** from **4** being 32% (~70% per two-step coupling stage). In the case of **15**, complete retrieval required in excess of 12 h at 40 °C. However, there was obtained a 74% overall yield (~90% per coupling stage) of **16**. *We believe that the observed increase in yield*

(15) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847.

(16) For example, in the case of **4**, conversion to **16** using coupling times of 2 h vs 12 h per stage gave 28 and 32% yields, respectively. Furthermore, when **5** was used, a 4−5 fold excess of monosaccharide acceptors **3** and **13** appeared to suffice for efficient coupling yields (>80%). However, when the disaccharide acceptor **22** was examined, a 10−12 fold excess was necessary for good coupling yields (ca. 50−70%), whereas a 4−5 fold excess was far less effective (<30% coupling yield).

**Scheme 4.** Solid-Phase Glycal Assembly Accommodates Both Secondary Alcohol Glycosyl Acceptors and Glucal-Derived Glycosyl Donors




*using the diisopropylsilyl functionalized polymer is due to the superior stability of this linkage, thus avoiding leakage of material from the support during each coupling stage.*[17]

Purification of compound **16**, which was obtained as the only product in its polarity range from the crude reaction, was accomplished by a simple flash chromatography on silica gel. It is well to emphasize that the method practiced here avoids the problem of interior deletions, thereby simplifying final purification. Following each glycosidation event, residual epoxide is hydrolyzed upon workup, apparently producing a 1,2-diol which may be subject to further degradation. The high polarity of byproducts, detectable by TLC analysis of the crude product mixture, is not inconsistent with this possibility. Furthermore, $^1$H NMR analysis of the crude byproduct mixture recovered following chromatography indicates no trace of glycal. The critical feature is that the failure to couple leads to chain termination. There is no reincarnation of donor capacity under the reagent conditions employed for glycal activation. The self-policing nature of the method avoids the need for "capping" after each glycosidation. Such capping is a necessary feature of alternative approaches for reaching large oligosaccharides.[8a]

Each glycosidation in the assembly sequence had occurred with a very high degree of stereoselectivity. $^1$H and $^{13}$C analysis of the tetrasaccharide product was consistent with its being $\beta$-configured in the three glycosidic linkages. No products containing $\alpha$ linkage were detected.

Secondary alcohol glycosyl acceptors are also accommodated by this method (Scheme 4). Compound **12**, following epoxidation with **6**, reacted with D-glucal derivative **17** to give **18**. Tetrasaccharide **19** was retrieved from the support by the action of TBAF on polymer bound **18** in a 66% overall yield based on **5**. Assuming 90% yield per coupling stage in the synthesis of **12**, glycosidation of **17** had occurred in ca. 80% yield. An additional example demonstrating the use of secondary acceptors can be found in our recent report in which 3,6-dibenzyl glucal is used as a solution-based coupling partner with **8** to give a 1,4-linked disaccharide product.[12c]

Compound **18** was oxidized with **6** to give a polymer-bound glucosyl donor. This epoxide reacted with a tetrahydrofuran solution of **13** and $ZnCl_2$ to provide **20**, from which was obtained pentasaccharide **21** in a 39% overall yield from **5**. This glycosidation, which occurred in approximately 60% yield based upon **18**, also occurred with a high degree of stereoselectivity. However, in this particular case, a minor component, believed to be the $\alpha$ product, was detected in the $^1$H NMR spectrum. The ratio of the desired all $\beta$ glycoside product to this unknown component was in excess of 10:1. It is our hope that this apparent erosion from strict $\beta$ selectivity using this glucal-derived donor can be controlled, when important, by appropriate modification of the, as yet unoptimized, conditions.

Additional synthetic convergence can be achieved through the use of disaccharides as solution-phase glycosyl acceptors (Scheme 5). Compound **12**, following epoxidation with **6**, reacted with disaccharide **22**, thereby providing **23**. Treatment of **23** with TBAF gave pentasaccharide **24** in a 58% overall yield from **5** (70% yield from **12**). Disaccharide **22** also reacted with the epoxide derived from **18** to give **25**, from which was obtained hexasaccharide **26** (29% overall yield from **5**, 45% yield from **18**). Since disaccharide **22** has itself been produced via solid-phase synthesis followed by desilylative retrieval,[12c] a convergent approach for assembling large oligo- or polysaccharides is thus suggested.

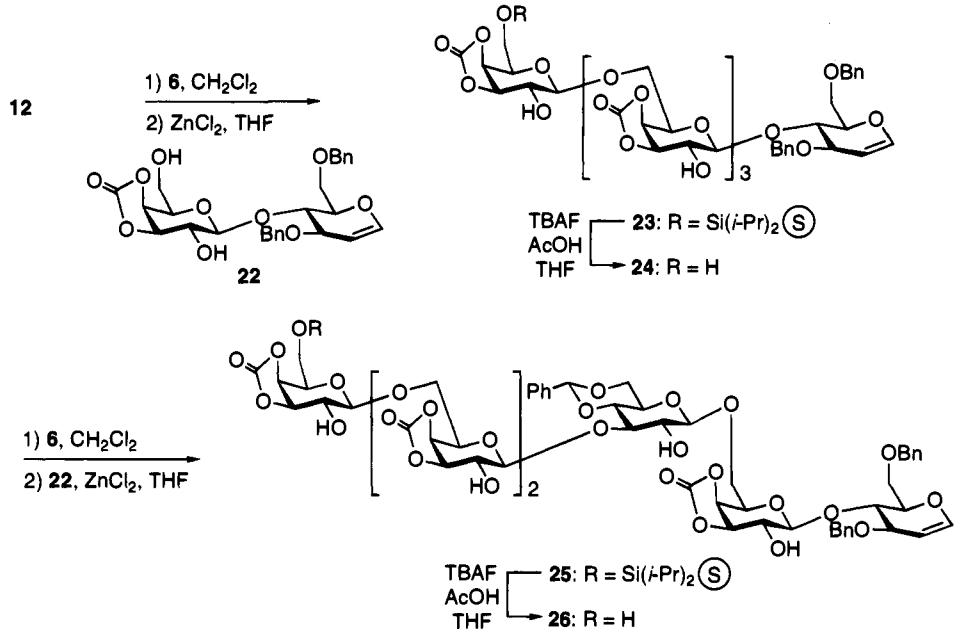
It should be noted that glycosylation of acceptor diol **22** by donors **12** and **18** occurred regioselectively to give the 1,6-linked product. This high selectivity demonstrates an important advantage to this method which employs polymer-bound glycosyl donors for oligosaccharide assembly.

Differing reactivities of various hydroxyl groups present on a solution-based glycosyl acceptor can be exploited. This success suggests a scenario for relief from some of the complexities of protecting group manipulations which are so characteristic of traditional syntheses in this area of chemistry.

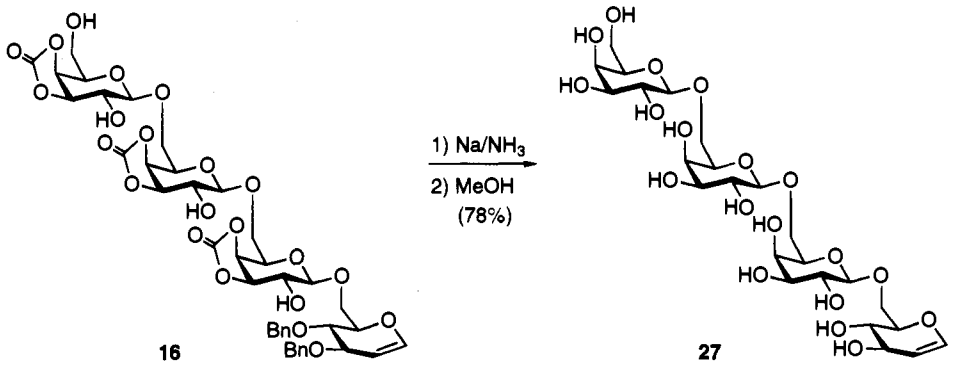
**Removal of Protecting Groups.** Tetrasaccharide glycal **16** was deprotected using a single-pot procedure to give **27** (Scheme 6). Dissolving metal reduction with sodium in refluxing ammonia, followed by quenching with methanol, provided a crude product which was purified by flash-chromatography on

(17) A simple side-by-side experiment comparing the stabilities of **4** and **5** toward methanolysis seems to support this explanation. Thus, a THF suspension of each polymer was treated with methanol and Hunig's base. In the case of **4**, TLC analysis of the solution phase indicated the presence of glycal within 1 min, whereas **5** was apparently stable to these conditions and showed only slight leakage of glycal from the polymer even after 1 h.

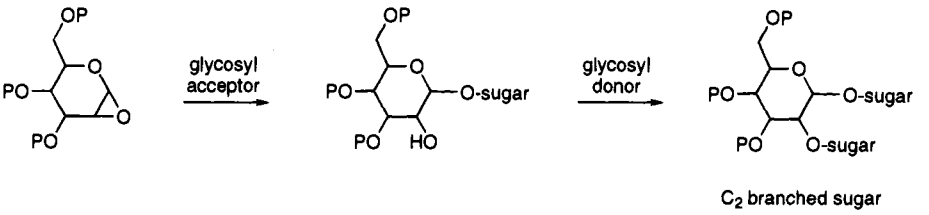
**Scheme 5.** Solid-phase Glycal Assembly Using Disaccharide Acceptors




**Scheme 6.** One-Pot Deprotection of a Tetrasaccharide Assembled on the Polymer Support




**Scheme 7.** A strategy for Assembling 1,2-Linked Oligosaccharides



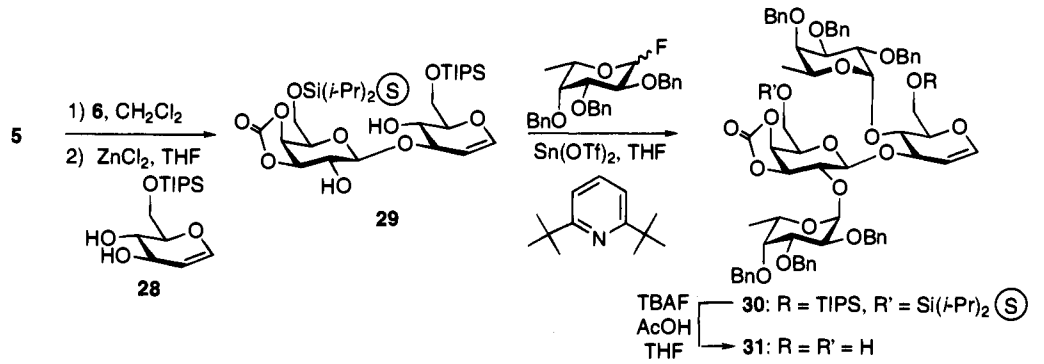

reverse-phase silica gel (78% yield). These reagent conditions should be suitable for the deprotection of each of the oligosaccharides prepared in this study. Examination of the $^1$H NMR spectrum of **27** clearly showed that all glycosidic linkages were of the $\beta$ configuration.

**1,2-Linked Oligosaccharides via Polymer-Bound Anhydro Sugar Derivatives.** The possibility of exploiting the logic of glycal assembly for introducing unique branching at a particular $C_2$ of an oligosaccharide has been considered and reduced to practice in the context of our synthesis of saponins.[12a] The logic is described in Scheme 7. Thus, opening of a glycal-derived epoxide donor with an acceptor generates a unique free alcohol at $C_2$. This can serve as an acceptor viz a viz some glycosylating agent to afford the desired 1,2-linkage. This paradigm obviates the need for any selective operations in exposing a unique $C_2$ acceptor hydroxyl.

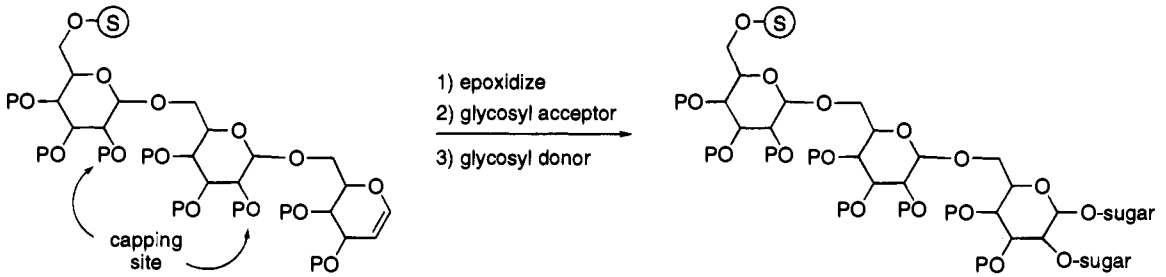
We studied the possibility of implementing this idea in the solid-phase method. We chose to demonstrate this in the context of a synthesis of the Lewis b blood group determinant as shown in Scheme 8. Regioselective glycosylation of **28** provided polymer-bound disaccharide **29**, which was then bisfucosylated to provide tetrasaccharide derivative **30**. Treatment of **30** with TBAF provided **31** in a 40% overall yield from **5**. This example effectively illustrated the potential of the polymer-bound glycal assembly method for the synthesis of complex branched structures. It will again be noted that protecting group manipulations have been sharply minimized.

We note, in principle, the possibility of synthesizing a long oligosaccharide with unique branching at a particular $C_2$ hydroxyl group. The method would involve capping of each hydroxyl generated from glycal assembly upstream (i.e. away from the reducing end). At the desired branch point, epoxide opening is followed by glycosylation at $C_2$ (Scheme 9). Positionally defined multiple branching can be implemented by noncapping of those hydroxyls intended to function as glycosyl acceptors.

**Scheme 8.** Solid-Phase Synthesis of a Lewis b Blood-Group Oligosaccharide




**Scheme 9**




**Summary.** Application of the 1,2-anhydro sugar method for glycal assembly on a polymer support has provided a rapid, high yielding method for the synthesis of oligosaccharides. In all cases, a high degree of $\beta$-selectivity has been observed. In these glycosidations, a wide variety of solution-phase coupling partners (primary and secondary alcohol as well as disaccharide glycosyl acceptors) react with solid-phase epoxides derived from both galactal and glucal units. Applicability to oligosaccharide acceptors bearing uniquely exposed or chemodifferentiated hydroxyl groups (cf. **22**) sets up realistic possibilities for convergent block synthesis. Finally, a seemingly generally viable strategy for the synthesis of branched oligosaccharides has been demonstrated. Applications of the solid-phase method to solve a variety of problems in oligosaccharide and glycoconjugate synthesis is in progress and will be disclosed in due course.

## Experimental Section

**General Methods.** Chemicals used were reagent grade and used as supplied except where noted. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl under $N_2$. Benzene and dichloromethane ($CH_2Cl_2$) were distilled from calcium hydride under $N_2$. Tetramethylethylenediamine (TMEDA) was distilled from sodium under $N_2$.

Infrared spectra were recorded on a Perkin Elmer 1600 series FTIR. $^1$H NMR spectra were obtained on a Bruker AMX 400 (400 MHz) and are reported in parts per million ($\delta$) relative to acetone-$d_6$ (2.04 ppm) as an internal reference, with coupling constants ($J$) reported in hertz. $^{13}$C NMR spectra were obtained at 100 MHz and are reported in $\delta$ relative to acetone- $d_6$ (20.83 ppm) as an internal reference. High-resolution mass spectra were recorded on a JEOL JMS-DX-303 HF mass spectrometer. Optical rotations were recorded on a Jasco DIP-370 polarimeter using a 1 dm cell at the reported temperatures and concentrations.

Analytical thin-layer chromatography was performed on E. Merck silica gel 60 $F_{254}$ plates (0.25 mm) and E. Merck HPTLC RP-18 $WF_{254s}$ plates (0.20 mm). Compounds were visualized by dipping the plates in a cerium sulfate–ammonium molybdate solution followed by heating. Liquid column chromatography was performed using forced flow of the indicated solvent on Sigma H-Type silica gel (10–40 $\mu$m) for normal phase and EM Science LiChroprep RP-18 (15–25 $\mu$m) for reverse-phase.

**Method for Loading Glycals onto Polystyrene. Synthesis of Polymer-Bound Galactal 5.** A 13.0 g amount of 1% crosslinked divinylbenzene polystyrene copolymer (Fluka), which had been washed and dried as described by Farrall and Frechet,[18] was placed in a 250 mL solid-phase synthesis flask[19] under $N_2$ and suspended in 80 mL of anhydrous cyclohexane. To this suspension was added 20 mL of TMEDA and 80 mL of 2.0 M butyllithium in cyclohexane. The mixture was stirred at 65 °C for 4 h, during which time the polymer turned a dark burgundy color. The lithiated polymer was filtered under $N_2$ pressure and then washed with anhydrous cyclohexane (2 × 100 mL), with stirring 20 min each time before filtering. This polymer was placed under $N_2$ and resuspended in 100 mL of anhydrous benzene before adding 20 mL of diisopropyldichlorosilane. The mixture was stirred at rt for 3 h and then filtered ($N_2$ pressure) and rinsed with dry benzene (3 × 100 mL), with stirring 20 min each time before filtering. This material was dried in vacuo to give silylated polymer **2** as a light brown powder.

Polymer **2** (1.0 g) and DMAP (10 mg) were placed in a 100 mL solid-phase synthesis flask under $N_2$, and a solution of glycal **3** (1.0 g, 5.8 mmol) in 10 mL of anhydrous $CH_2Cl_2$ and 1 mL of diisopropylethylamine was added via cannula. The mixture was stirred at rt for 72 h and then filtered ($N_2$ pressure) and rinsed, with stirring, using anhydrous $CH_2Cl_2$ (2 × 50 mL). The polymer was resuspended in a 1:1:18 mixture of MeOH:diisopropylethylamine:$CH_2Cl_2$ (10 mL) and stirred 1 h at rt. This material was then filtered and stirred with each of the following solvents for 20 min before filtering: $CH_2Cl_2$ (2 × 50 mL), THF (2 × 50 mL), acetone (2 × 50 mL), DMSO (2 × 50 mL), acetone (2 × 50 mL), and THF (50 mL). The polymer was dried in vacuo to give **5** as a light creme powder.

**Method for Retrieval of Glycals from the Polymer Support.** Polymer-bound galactal **5** (50 mg) was placed in a 10 mL solid-phase synthesis flask and suspended in 1 mL of THF before adding 0.1 mL of 1.0 M AcOH in THF and 0.2 mL of 1.0 M TBAF in THF. The mixture was stirred at 40 °C for 18 h, and the polymer was then rinsed, with stirring, using THF (3 × 5 mL). The combined rinsings were concentrated and purified by column chromatography on silica gel (1:19 MeOH:$Et_2O$) to give **3** as a colorless gum (8.0 mg, 46 $\mu$mol). The loading for this batch of polymer-bound glycal was therefore determined to be 0.92 mmol of **3** per gram of **5**.

(18) Farrall, M. J.; Fréchet, J. M. J. *J. Org. Chem.* **1976**, *41*, 3877.

(19) The flask which we use for solid-phase synthesis is a variation of that typically used for reactions on the Merrifield resin. For a description, see: McClure, K. F. Ph. D. Dissertation, Yale University, Dec. 1993. This information is also provided in the supplementary material.

**Method for Synthesis of Polymer-Bound Oligosaccharides from 5. Synthesis of Trisaccharide Glycal 12.** Compound **5** (900 mg) was placed in a 100 mL solid-phase synthesis flask and suspended in 20 mL of anhydrous $CH_2Cl_2$ under $N_2$. The suspension was cooled to 0 °C before adding 50 mL of freshly prepared dimethyldioxirane solution (~0.1 M in acetone). The mixture was stirred at 0 °C for 90 min and then filtered ($N_2$ pressure). The polymer was resuspended in 20 mL of $CH_2Cl_2$ under $N_2$, treated once more at 0 °C with 50 mL of dimethyldioxirane solution, stirred 40 min and filtered ($N_2$ pressure), and dried in vacuo to give **8**. To the polymer-bound epoxide under $N_2$ was added a solution of **3** (1.0 g, 5.8 mmol) in anhydrous THF (10 mL). The suspension was cooled to 0 °C before being treated with 1.0 mL of 1.0 M $ZnCl_2$ (fused) in THF, and the mixture was allowed to slowly warm to rt and stirred for 8 h. The polymer was rinsed, with stirring, using THF (4 × 20 mL) and dried in vacuo to give **10** as a colorless powder.

Compound **10** (800 mg) in a 100 mL solid-phase synthesis flask under $N_2$ was suspended in 10 mL of anhydrous $CH_2Cl_2$ and cooled to 0 °C before being treated with 20 mL of dimethyldioxirane solution. The mixture was stirred at 0 °C for 40 min and then filtered ($N_2$ pressure) and dried in vacuo. The polymer-bound epoxide was placed under $N_2$ and suspended in a solution of **3** (1.0 g) in anhydrous THF (10 mL). The suspension was cooled to 0 °C before being treated with 1.0 M $ZnCl_2$ in THF (1.0 mL). The mixture was allowed to slowly warm to rt and stirred for 8 h. The polymer was rinsed, with stirring, using THF (4 × 20 mL) and dried in vacuo to give **12** as a colorless powder.

**Synthesis of Tetrasaccharide Glycal 16.** Compound **12** (100 mg) in 3 mL of $CH_2Cl_2$ was epoxidized using 5 mL of dioxirane solution, dried in vacuo, and then treated with a solution of **13** (0.15 g, 0.46 mmol) in THF (1.5 mL) and $ZnCl_2$ (1.0 M in THF, 0.15 mL) to give **15** as a colorless powder (120 mg). Retrieval from the support was accomplished using TBAF (0.2 mL) and AcOH (0.1 mL) in THF (1 mL) to give a crude product, which was purified by silica gel chromatography (1:19 MeOH:$CH_2Cl_2$) to give **16** (44 mg, 49 μmol, 74% overall yield from **5**): $R_f$ = 0.34 (15:85 MeOH:$Et_2O$); $[\alpha]^{22}_D$ = −33.5° (*c* 1.7, MeOH); FTIR (thin film) 3447 (OH), 2936, 2892, 1799 (C=O), 1690, 1648, 1370, 1172, 1138, 1071, 1032, 753, 700; $^1$H NMR (400 MHz, acetone-$d_6$) δ 7.39−7.24 (m, 10 H, Ar*H*), 6.38 (dd, 1 H, *J* = 1.1 Hz, *J* = 6.2 Hz, $H_1$ glucal), 5.32 (br s, 1 H, OH), 5.14 (br s, 1 H, OH), 5.03−4.97 (m, 3 H, 3 × $H_4$ galactose), 4.94 (dd, 1 H, *J* = 2.8 Hz, *J* = 6.2 Hz, $H_2$ glucal), 4.87−4.80 (m, 4 H, 3 × $H_3$ galactose, C*H*Ph), 4.75 (d, 1 H, *J* = 5.8 Hz, $H_1$ galactose), 4.74 (d, 1 H, *J* = 11.4 Hz, C*H*Ph), 4.68 (d, 1 H, *J* = 11.8 Hz, C*H*Ph), 4.66 (d, 1 H, *J* = 6.2 Hz, $H_1$ galactose), 4.60 (d, 1 H, *J* = 6.6 Hz, $H_1$ galactose), 4.58 (d, 1 H, *J* = 11.8 Hz, C*H*Ph), 4.25−4.20 (m, 2 H), 4.18−4.13 (m, 2 H, $H_3$ glucal), 4.12−4.00 (m, 4 H), 3.90−3.73 (m, 6 H, 3 × $H_{6,6a}$ galactose), 3.72 (ψt, 1 H, J = 5.3 Hz, $H_2$ galactose), 3.68 (ψt, 1 H, J = 6.2 Hz, $H_2$ galactose), 3.64 (ψt, 1 H, J = 5.8 Hz, $H_2$ galactose), 2.91 (br s, 1 H, OH), 2.82 (br s, 1 H, OH); $^{13}$C NMR (acetone-$d_6$) δ 164.11, 145.94, 145.86, 136.00, 130.79, 120.07, 119.64, 119.61, 119.25, 93.77, 93.51, 93.04, 91.84, 70.73, 70.10, 69.62, 68.23, 66.96, 66.78, 66.53, 66.39, 66.20, 64.93, 63.49, 62.38, 62.36, 62.10, 61.86, 52.52; HRMS (FAB) *m/z* 913.2377 (M + Na), calcd for $C_{41}H_{46}O_{22}Na$ 913.2378.

**Synthesis of Tetrasaccharide Glycal 19.** Compound **12** (300 mg) in 10 mL of $CH_2Cl_2$ was reacted with 20 mL of dioxirane solution to give the epoxide, which reacted with **17** (380 mg, 1.6 mmol) and $ZnCl_2$ (1.0 M in THF, 0.4 mL) in THF (4 mL) to give **18** (335 mg). Compound **18** (100 mg) provided **19** (31 mg, 39 μmol, 66% overall yield from **5**): $R_f$ = 0.44 (15:85 MeOH:$CH_2Cl_2$); $[\alpha]^{22}_D$ = −49.2° (*c* 1.5, MeOH); FTIR (thin film) 3443 (OH), 2895, 1799 (C=O), 1692, 1643, 1380, 1260, 1238, 1174, 1128, 1075, 1031, 958, 758, 702; $^1$H NMR (400 MHz, acetone-$d_6$) δ 7.59−7.55 (m, 2 H, Ar*H*), 7.43−7.37 (m, 3 H, Ar*H*), 6.44 (dd, 1 H, *J* = 1.4 Hz, *J* = 6.2 Hz, $H_1$ glucal), 5.72 (s, 1 H, C*H*Ph), 5.15 (br s, 1 H, OH), 5.10 (br s, 1 H, OH), 5.00 (dd, 1 H, *J* = 1.8 Hz, *J* = 7.6 Hz, $H_4$ galactose), 4.97 (dd, 1 H, *J* = 1.9 Hz, *J* = 7.6 Hz, $H_4$ galactose), 4.90−4.74 (m, 6 H, $H_2$ glucal, $H_1$, 3 × $H_3$, $H_4$ galactose), 4.72 (d, 1 H, *J* = 5.9 Hz, $H_1$ galactose), 4.66 (m, 1H, *J* = 1.8 Hz, *J* = 7.4 Hz, $H_3$ glucal), 4.50 (d, 1 H, *J* = 6.4 Hz, $H_1$ galactose), 4.30 (m, 1 H, *J* = 10.6 Hz, *J* = 15.7 Hz), 4.18 (m, 1 H, *J* = 1.9 Hz, *J* = 5.4 Hz, *J* = 7.3 Hz), 4.08−3.95 (m, 5 H), 3.92−3.72 (m, 6 H), 3.71 (ψt, 1 H, *J* = 5.6 Hz, $H_2$ galactose), 3.66 (ψt, 1 H, *J* = 5.7 Hz, $H_2$ galactose), 3.58 (ψt, 1 H, *J* = 5.8 Hz, $H_2$ galactose), 3.01 (br s, 1 H, OH), 2.90 (br s, 1 H, OH); $^{13}$C NMR (acetone-$d_6$) δ 146.07, 145.96, 145.78, 136.47, 129.90, 120.65, 119.95, 118.21, 93.55, 93.19, 92.77, 90.56, 70.31, 70.09, 69.98, 69.78, 66.55, 66.43, 63.86, 63.59, 62.69, 62.40, 62.17, 60.76, 59.72, 59.66, 59.00, 52.52; HRMS (FAB) *m/z* 799.1978 (M + H), calcd for $C_{34}H_{39}O_{22}$ 799.1933.

**Synthesis of Pentasaccharide 21.** Compound **18** (80 mg) in 3 mL of $CH_2Cl_2$ was reacted with 5 mL of dioxirane solution to give the epoxide, which was dried in vacuo. This material was suspended in a solution of **13** (0.15 g, 0.46 mmol) in THF (1 mL) under $N_2$ and cooled to −23 °C ($CCl_4$−dry ice bath) before adding $ZnCl_2$ (1.0 M in THF, 0.1 mL). This mixture was allowed to slowly warm to rt and stirred 8 h to give **20** (88 mg), from which was obtained **21** (19 mg, 17 μmol, 39% overall yield from **5**): $R_f$ = 0.52 (1:9 MeOH:$CH_2Cl_2$); $[\alpha]^{22}_D$ = −25.2° (*c* 1.0, MeOH); FTIR (thin film) 3415 (OH), 2923, 1800 (C=O), 1691, 1649, 1453, 1370, 1276, 1174, 1070, 1029, 754, 700; $^1$H NMR (400 MHz, acetone-$d_6$) δ 7.58−7.55 (m, 2 H, Ar*H*), 7.43−7.27 (m, 13 H, Ar*H*), 6.40 (dd, 1 H, *J* = 1.2 Hz, *J* = 6.1 Hz, $H_1$ glucal), 5.62 (s, 1 H, PhC*H*$O_2$), 5.13 (d, 1 H, *J* = 4.2 Hz, OH), 5.08 (d, 1 H, *J* = 4.0 Hz, OH), 5.03−4.94 (m, 4 H, $H_2$ glucal, 3 × $H_4$ galactose), 4.89−4.73 (m, 6 H), 4.71 (d, 1 H, *J* = 5.8 Hz, $H_1$ pyranose), 4.69 (d, 1 H, *J* = 12 Hz, PhC*H*), 4.59 (d, 1 H, *J* = 12.7 Hz, PhC*H*), 4.54 (d, 1 H, *J* = 7.8 Hz, $H_1$ pyranose), 4.50 (d, 1 H, *J* = 6.5 Hz, $H_1$ pyranose), 4.26 (dd, 1 H, *J* = 4.9 Hz, *J* = 10.2 Hz), 4.22−3.87 (m, 11 H), 3.82 (m, 7 H), 3.63−3.53 (m, 3 H), 3.49 (m, 1 H, *J* = 4.7 Hz, *J* = 9.7 Hz); $^{13}$C NMR (acetone-$d_6$) δ 146.06, 146.00, 145.82, 135.90, 130.94, 130.82, 129.95, 120.63, 120.10, 120.07, 119.91, 119.68, 119.59, 119.27, 118.16, 95.73, 93.65, 93.25, 93.09, 92.50, 91.94, 71.66, 70.85, 70.42, 69.85, 68.30, 67.36, 66.63, 66.52, 66.44, 66.00, 65.05, 63.65, 63.14, 62.91, 62.59, 62.38, 62.30, 61.86, 59.80, 59.72, 58.98, 58.13, 52.51, 45.95; HRMS (FAB) *m/z* 1163.3210 (M + Na), calcd for $C_{54}H_{60}O_{27}Na$ 1163.3220.

**Disaccharide 22:** $[\alpha]^{22}_D$ = −21.8° (*c* 1.1, MeOH); FTIR (thin film) 3406 (OH), 2873, 1801 (C=O), 1649, 1454, 1368, 1240, 1166, 1071, 741, 699; $^1$H NMR (400 MHz, acetone-$d_6$) δ 7.38−7.22 (m, 10 H, Ar*H*), 6.39 (dd, 1 H, *J* = 1.2 Hz, *J* = 6.2 Hz, $H_1$ glucal), 5.20 (d, 1 H, J = 4.3 Hz, $OH_2$'), 4.99 (dd, 1 H, *J* = 1.9 Hz, *J* = 7.3 Hz, $H_4$ galactose), 4.87 (dd, 1 H, *J* = 3.4 Hz, *J* = 6.2 Hz, $H_2$ glucal), 4.84 (d, 1 H, *J* = 6.7 Hz, $H_1$ galactose), 4.80 (d, 1 H, *J* = 5.8 Hz, *J* = 7.3 Hz, $H_3$ galactose), 4.68 (d, 1 H, *J* = 11.8 Hz, C*H*Ph), 4.63 (d, 1 H, *J* = 11.8 Hz, C*H*Ph), 4.55 (s, 2 H, C$H_2$Ph), 4.20 (dd, 1 H, *J* = 4.8 Hz, *J* = 6.7 Hz), 4.15 (m, 1 H), 4.12 (m, 1 H), 4.07 (dd, 1 H, *J* = 5.1 Hz, *J* = 7.1 Hz), 4.00 (m, 1 H, *J* = 1.9 Hz, *J* = 6.6 Hz), 3.93 (dd, 1 H, *J* = 5.1 Hz, *J* = 10.9 Hz), 3.79−3.70 (m, 3 H), 3.64 (m, 1 H, *J* = 4.4 Hz, $H_2$ galactose); $^{13}$C NMR (acetone-$d_6$) δ 145.96, 135.99, 131.11, 130.48, 120.10, 119.93, 119.41, 119.27, 119.03, 93.16, 91.98, 70.74, 67.94, 66.66, 65.81, 64.86, 64.64, 64.09, 63.37, 61.97, 59.83, 52.29; HRMS (FAB) *m/z* 515.1944 (M + H), calcd for $C_{27}H_{31}O_{10}$ 515.1918.

**Synthesis of Pentasaccharide 24.** Compound **12** (100 mg) in 3 mL of $CH_2Cl_2$ was reacted with 5 mL of dioxirane solution to give the epoxide, which reacted with **22** (320 mg, 0.62 μmol) and $ZnCl_2$ (1.0 M in THF, 0.1 mL) in THF (1.5 mL) to give **23** (130 mg), which provided **24** (42 mg, 38 μmol, 58% overall yield from **5**): $R_f$ = 20 (1:9 MeOH:$CH_2Cl_2$); $[\alpha]^{22}_D$ = −37.6° (*c* 2.1, MeOH); FTIR (thin film) 3447 (OH), 2931, 1799 (C=O), 1649, 1372, 1172, 1070, 1032, 754, 701; $^1$H NMR (400 MHz, acetone-$d_6$) δ 7.40−7.25 (m, 10 H, Ar*H*), 6.39 (dd, 1 H, *J* = 1.0 Hz, *J* = 6.2 Hz, $H_1$ glucal), 5.25 (br s, 1 H, OH), 5.23 (br s, 1 H, OH), 5.18 (br s, 1 H, OH), 5.11 (br s, 1 H, OH), 5.02 (m, 2 H, 2 × $H_4$ galactose), 4.97 (m, 2 H, 2 × $H_4$ galactose), 4.89−4.80 (m, 6 H, $H_2$ glucal, $H_1$, 4 × $H_3$ galactose), 4.78 (δ, 1 H, *J* = 5.8 Hz, $H_1$ galactose), 4.70 (d, 1 H, *J* = 5.9 Hz, $H_1$ galactose), 4.68 (d, 1 H, *J* = 11.6 Hz, C*H*Ph), 4.64 (d, 1 H, *J* = 12 Hz, C*H*Ph), 4.63 (d, 1 H, *J* = 6.1 Hz, $H_1$ galactose), 4.58 (d, 1 H, *J* = 12.1 Hz, C*H*Ph), 4.54 (d, 1 H, *J* = 12.1 Hz, C*H*Ph), 4.31−4.18 (m, 5 H), 4.10 (m, 1 H, *J* = 1.8 Hz, *J* = 6.5 Hz), 4.08−3.98 (m, 4 H), 3.92−3.71 (m, 9 H), 3.64 (ψt, 1 H, *J* = 6.0 Hz, $H_2$ galactose), 3.61 (ψt, 1 H, *J* = 5.8 Hz, $H_2$ galactose), 3.01 (br s, 1 H, OH); $^{13}$C NMR (acetone-$d_6$) δ 146.11, 145.98, 145.94, 135.94, 130.92, 130.40, 120.12, 120.05, 119.66, 119.49, 119.27, 119.17, 93.58, 93.17, 93.00, 92.83, 91.72, 70.98, 70.04, 69.72, 69.62, 67.82, 66.78, 66.47, 66.40, 65.06, 64.63, 64.08, 63.47, 63.38, 62.50, 62.42, 62.11, 62.08, 62.01, 60.10, 59.86, 59.47, 59.05, 52.54; HRMS (FAB) *m/z* 1101.2670 (M + Na), calcd for $C_{48}H_{54}O_{28}Na$ 1101.2700.

**Synthesis of Hexasaccharide 26.** Compound **18** (120 mg) in 3 mL of $CH_2Cl_2$ was reacted with 5 mL of dioxirane solution to give the epoxide, which was suspended in a solution of **22** (0.36 g, 0.70 $\mu$mol) in THF (1.5 mL) under $N_2$ and cooled to −23 °C ($CCl_4$–dry ice bath) before adding $ZnCl_2$ (1.0 M in THF, 0.15 mL). This provided **25** (140 mg), from which was obtained **26** (26 mg, 19 $\mu$mol, 29% overall yield from **5**): $R_f$ = 0.31 (1:9 MeOH:$CH_2Cl_2$); $[\alpha]^{22}_D$ = −45.9° (*c* 0.9, MeOH); FTIR (thin film) 3427 (OH), 2924, 1799 (C=O), 1648, 1373, 1173, 1070, 1030, 753, 701; $^1$H NMR (400 MHz, acetone-$d_6$) $\delta$ 7.56–7.53 (m, 2 H, Ar*H*), 7.44–7.20 (m, 13 H, Ar*H*), 6.39 (d, 1 H, *J* = 6.1 Hz, $H_1$ glucal), 5.56 (1 H, PhC*H*$O_2$), 5.28 (br s, 1 H, OH), 5.18 (br s, 1 H, OH), 5.13 (br s, 1 H, OH), 5.02–4.98 (m, 2 H, 2 × $H_4$ galactose), 4.98–4.94 (m, 2 H, 2 × $H_4$ galactose), 4.90–4.74 (m, 6 H), 4.76–4.64 (m, 4 H), 4.63–4.33 (m, 3 H), 4.49 (d, 1 H, *J* = 6.6 Hz, $H_1$ pyranose), 4.29 (dd, 1 H, *J* = 5.6 Hz, *J* = 7.4 Hz), 4.23–4.10 (m, 5 H), 4.08 (m, 1 H, *J* = 1.8 Hz, *J* = 6.7 Hz), 4.02–3.92 (m, 5 H), 3.83–3.64 (m, 11 H), 3.63–3.54 (m, 2 H), 3.46 (m, 1 H), 3.38 (m, 1 H, J = 4.9 Hz, J = 9.7 Hz); $^{13}$C NMR (acetone-$d_6$) $\delta$ 145.09, 146.00, 145.90, 136.08, 131.10, 130.51, 129.96, 120.61, 120.18, 120.07, 119.89, 119.56, 119.52, 119.33, 119.19, 118.20, 95.31, 93.60, 93.24, 92.96, 92.57, 92.21, 71.74, 70.51, 69.80, 68.22, 66.69, 66.64, 66.49, 66.43, 66.10, 65.59, 65.51, 64.68, 63.62, 63.28, 63.04, 62.58, 62.55, 62.36, 62.33, 59.90, 59.01, 58.01, 52.53, 46.47; HRMS (FAB) *m/z* 1351.3520 (M + Na), calcd for $C_{61}H_{68}O_{33}Na$ 1351.3540.

**Synthesis of 27.** To a −78 °C solution of sodium (~20 mg) in $NH_3$ (~6 mL) under $N_2$ was added, via cannula, a solution of tetrasaccharide glycal **16** (25 mg, 28 mmol) in THF (0.3 mL). The mixture was allowed to warm to reflux, stirred for 30 min, and then quenched with anhydrous MeOH (2 mL). The $NH_3$ was allowed to evaporate, and the residue was concentrated to give crude **27**, which was purified by column chromatography on C-18 reverse-phase silica gel ($H_2O$). Lyophilization provided **27** as a colorless powder (14 mg, 78%): $R_f$ = 0.82 (RP-18, $H_2O$); $[\alpha]^{22}_D$ = +2.4° (*c* 1.0, $H_2O$); FTIR (KBr) 3426 (OH), 2919, 2850, 1654, 1463, 1233, 1073, 778; $^1$H NMR (400 MHz, $D_2O$) $\delta$ 6.42 (dd, 1 H, *J* = 1 Hz, *J* = 6.1 Hz, $H_1$ glucal), 4.84 (dd, 1 H, *J* = 2.4 Hz, *J* = 6.1 Hz, $H_2$ glucal), 4.49 (d, 1 H, *J* = 7.8 Hz, $H_1$ galactose), 4.47 (d, 1 H, *J* = 7.9 Hz, $H_1$ galactose), 4.45 (d, 1 H, *J* = 8.0 Hz, $H_1$ galactose), 4.25 (m, 1 H, *J* = 2.1 Hz, *J* = 5.5 Hz, $H_3$ glucal), 4.23 (s, 1 H), 4.09–3.87 (m, 11 H), 3.83–3.72 (m, 3 H), 3.71–3.63 (m, 4 H), 3.57–3.50 (m, 3 H); $^{13}$C NMR ($D_2O$) $\delta$ 146.24, 106.09, 106.01, 105.95, 105.90, 79.82, 77.87, 76.64, 76.47, 75.43, 75.29, 75.25, 73.45, 73.40, 71.86, 71.82, 71.41, 71.34, 71.06, 70.88, 63.72; HRMS (FAB) *m/z* 655.2059 (M + Na), calcd for $C_{24}H_{40}O_{19}Na$ 655.2061.

**Synthesis of 31.** Full experimental detail for the synthesis of **31** can be found in ref 12c. Compound **30** (100 mg) provided **31** (18 mg, 15 $\mu$mol, 40% overall yield from **5**): $[\alpha]^{23}_D$ = −82.5° (*c* 0.4, $CH_2Cl2$); FTIR (thin film) 3467.0 (OH), 3029.6, 2923.6, 1807.2 (C=O), 1647.3, 1496.0, 1453.5, 1358.1, 1240.2, 1095.6, 1049.2, 738.5, 697.2; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.40–7.25 (m, 30 H, Ar*H*), 6.18 (d, 1 H, *J* = 6.0 Hz, $H_1$ glucal), 5.26 (d, 1 H, *J* = 3.5 Hz, $H_1$ fucose), 5.09 (d, 1 H, *J* = 3.7 Hz, $H_1$ fucose), 4.96 ($\psi$t, 2 H, *J* = 10.8 Hz, PhC$H_2$), 4.90–4.56 (m, 13 H), 4.43 (m, 1 H), 4.15–4.06 (m, 4 H), 3.97 (m, 1 H, *J* = 8.3 Hz, *J* = 2.4 Hz), 3.87–3.65 (m, 10 H), 3.64 (d, 1 H), 3.57 (d, 1 H), 2.69 (br, 1 H, OH), 2.52 (br, 1 H, OH), 1.11 (d, 3 H, *J* = 7.0 Hz, C$H_3$ fucose), 1.09 (d, 3 H, *J* = 7.0 Hz, C$H_3$ fucose); $^{13}$C NMR ($CDCl_3$) $\delta$ 153.37, 145.75, 138.60, 138.52, 138.19, 137.61, 128.55, 128.52, 128.44, 128.24, 128.16, 128.07, 127.62, 127.56, 127.45, 98.71, 98.38, 97.65, 97.34, 79.26, 78.87, 78.67, 78.01, 77.79, 77.65, 76.37, 76.10, 74.92, 74.40, 74.16, 73.95, 72.86, 72.64, 72.53, 67.43, 67.29, 61.31, 60.90, 16.65, 16.53; HRMS (FAB) *m/z* 1189.4757 (M + Na), cacld for $C_{67}H_{74}O_{18}Na$ 1189.4772.

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**Supplementary Material Available:** $^1$H and $^{13}$C NMR spectra for compounds **16**, **19**, **21**, **22**, **24**, **26**, **27**, and **31** (24 pages). A picture of the solid state synthesis flask is attached to the first spectra. This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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