Oligosaccharide Synthesis with Glycosyl Phosphate and Dithiophosphate Triesters as Glycosylating Agents

Obadiah J. Plante, Emma R. Palmacci, Rodrigo B. Andrade, and Peter H. Seeberger*

Contribution from the Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Received May 18, 2001

Abstract: Described is an efficient one-pot synthesis of α- and β-glycosyl phosphate and dithiophosphate triesters from glycals via 1,2-anhydrosugars. Glycosyl phosphates function as versatile glycosylating agents for the synthesis of β-glucosidic, β-galactosidic, α-fucosidic, α-mannosidic, β-glucuronic acid, and β-glucosamine linkages upon activation with trimethylsilyl trifluoromethanesulfonate (TMSOTf). In addition to serving as efficient donors for *O*-glycosylations, glycosyl phosphates are effective in the preparation of *S*-glycosides and *C*-glycosides. Furthermore, the acid-catalyzed coupling of glycosyl phosphates with silylated acceptors is also discussed. Glycosyl dithiophosphates are synthesized and are also used as glycosyl donors. This alternate method offers compatibility with acceptors containing glycals to form β-glycosides. To minimize protecting group manipulations, orthogonal and regioselective glycosylation strategies with glycosyl phosphates are reported. An orthogonal glycosylation method involving the activation of a glycosyl phosphate donor in the presence of a thioglycoside acceptor is described, as is an acceptor-mediated regioselective glycosylation strategy. Additionally, a unique glycosylation strategy exploiting the difference in reactivity of α- and β-glycosyl phosphates is disclosed. The procedures outlined here provide the basis for the assembly of complex oligosaccharides in solution and by automated solid-phase synthesis with glycosyl phosphate building blocks exclusively or in concert with other donors.

Introduction

The role of carbohydrates in many biological pathways has become more defined in recent years. The traditional view of carbohydrates as solely sources of energy has been augmented by advances in glycobiology that establish oligosaccharides and glycoconjugates as essential components of information transfer in biological systems.[1] Specific oligosaccharides that participate in both beneficial and pathogenic events have been identified. Oligosaccharide components of human milk are known to protect breast-fed infants from a host of bacterial infections.[2] On the other hand, the cell-surface glycoconjugates found on protozoan parasites (e.g. *Leishmania*) serve to infect human hosts.[3] Finally, particular oligosaccharides such as the globo H hexasacccharide indicate malignant transformation of human breast, prostate, or ovarian cancer cells.[4] A better understanding of the biological capacity of oligosaccharides will eventually lead to the development of novel therapeutics and nutritional supplements targeting these interactions.[5]

The limited availability of complex oligosaccharides remains a major impediment to the study of carbohydrates. The purification of glycoconjugates from natural sources is in most cases extremely difficult due to the microheterogeneity of this class of biopolymers and is practical only on a very small scale (microgram to milligram). The absence of amplification techniques equivalent to the polymerase chain reaction (PCR) that revolutionized nucleic acid research further complicates matters. Currently, there are two synthetic methods available for the preparation of oligosaccharides and glycoconjugates as research tools; however, many challenges remain. Besides the traditional chemical techniques, enzymes have seen more frequent use due to their specificity and efficiency. Enzymatic oligosaccharide synthesis has been scaled up to produce kilogram quantities of complex carbohydrates.[6] While attractive for production on a commercial scale, a shortcoming of this method is the narrow scope of substrates accepted by the enzymes and the need to have access to all glycosyl transferases involved in the preparation of a particular sequence.

Synthetic chemists have been addressing the challenges associated with the preparation of complex carbohydrates for over one hundred years. During this time, numerous versatile building blocks that function as efficient glycosyl donors have been developed.[7] While glycosyl trichloroacetimidates[8] and thioglycosides[9] are the most commonly used methods of glycosylation, glycosyl sulfoxides,[10] *n*-pentenyl glycosides,[11] glycosyl phosphites,[12] glycosyl halides,[13] and anhydrosugars[14] all see wide-

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(2) Kunz, C.; Rudloff, S. *Acta Paediatr.* **1993**, *82*, 903.
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(5) Alper, J. *Science* **2001**, *291*, 2338.
(6) Ichikawa, Y.; Wang, R.; Wong, C.-H. *Methods Enzymol.* **1994**, *247*, 107.
(7) For a review see: Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503.
(8) For a review see: Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21.
(9) For a review see: Garegg, P. J. *Adv. Carbohydr. Chem. Biochem.* **1997**, *52*, 179.
(10) Kahne, D.; Walker, S.; Cheng, Y.; Van Engen, D. *J. Am. Chem. Soc.* **1989**, *111*, 6881.
(11) Fraser-Reid, B.; Konradsson, P.; Mootoo, D. R.; Udodong, U. *J. Chem. Soc., Chem. Commun.* **1988**, 823.

10.1021/ja016227r CCC: $20.00
Published on Web 09/11/2001

spread use. The need for new, readily synthesized, stable, and highly reactive glycosylating agents still persists.

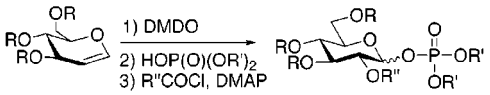
Nucleotide 5′-diphospho sugars (NDPs) serve as substrates for the glycosyl transferases that are responsible for the biosynthesis of oligosaccharides and may thus be considered nature's building blocks.[15] Several approaches to the synthesis of glycosyl phosphates in the form of glycosyl 1-phosphates and NDPs had been reported previously.[16,17] Despite the variety of methods available for the synthesis of glycosyl phosphate mono-, di-, and triesters, the use of these phosphates, and their sulfur analogues, in the chemical synthesis of oligosaccharides has received little attention.[18]

Here, we describe the convenient synthesis of glycosyl phosphate[19] and glycosyl dithiophosphate[20] triesters from glycal precursors. The one-pot synthesis of glycosyl phosphates and derivatives can be performed in high overall yield on a multigram scale and requires minimal chromatographic purification. A panel of activation conditions for these novel glycosylating agents was explored and glycosyl phosphates were found to function as efficient donors for the synthesis of *O*-, *S*-, and *C*-glycosides. Taking advantage of inherent selectivity of glycosyl phosphate mediated reactions, we developed a regioselective glycosylation strategy. Also, an orthogonal glycosylation method involving the activation of phosphate donors in the presence of thioglycosides provides a two-step synthesis of a trisaccharide without the need for intermediate protecting group manipulations. Finally, a unique approach to controlling reactivity of glycosylation reagents by exploiting the inherent reactivity difference between α- and β-phosphates is introduced. This method was successfully applied to the synthesis of a trisaccharide. The procedures outlined here provide the basis for the assembly of complex oligosaccharides in solution and by automated solid-phase synthesis using glycosyl phosphate building blocks.

Results and Discussion

Glycosyl Phosphates. Glycals are attractive starting materials for the preparation of differentially protected building blocks that serve in oligosaccharide assembly. In contrast to other hexoses, glycals possess only three hydroxyl groups that require differentiation by introduction of protective groups when compared to five hydroxyl groups in fully oxygenated sugars. The glycal assembly method has recently been exploited in the synthesis of glycosylated natural products and numerous oligosaccharides both in solution and on the solid support.[14] In the course of these studies it had been demonstrated that other glycosylating agents, such as thioethyl glycosides, can be prepared from glycals.[21] The need for excess thiol reagents and the modest yields of this transformation prompted us to explore the synthesis of other isolable glycosylating agents from glycal precursors.

Scheme 1. Synthesis of Glycosyl Phosphates



Initially we investigated a one-pot procedure for the convenient synthesis of glycosyl phosphates using phosphoric acid diesters in the ring opening of 1,2-anhydrosugars (Scheme 1).[16g,19] Commercially available dibutyl and dibenzyl phosphate diesters quantitatively provided C2−OH glycosyl phosphate triesters[22] upon reaction with 1,2-anhydrosugars at −78 °C. In most cases, glycal epoxidation was complete in 5 min (Figure 1).[23] In situ acylation of the newly generated C2 hydroxyl group afforded fully protected glycosyl phosphates.

Interestingly, when the epoxide opening was carried out in dichloromethane or toluene, β-glycosyl phosphates were obtained with high selectivity. Conversely, the α-glycosyl phosphates predominated when tetrahydrofuran was used as a solvent for the opening of the epoxide. The observed solvent effect was rationalized through the finding that anomerization takes place more rapidly in tetrahydrofuran (Scheme 2). For example, when the ring-opening of 1,2-anhydrosugar **11a** was carried out in CH_2Cl_2 followed by acylation, only β-phosphate **11** was obtained (Scheme 2). Similarly, when the ring-opening was performed in THF and the newly generated C2−OH was immediately acylated, only the β-phosphate was obtained. When the ring-opening was allowed to stir at ambient temperature for 8 h and then acylated, a 1:1 mixture of anomers **11** and **12** was obtained. These results support earlier findings that α-phosphates could be formed from the β-isomers by acid-catalyzed anomerization. The possibility of creating different types of anomeric phosphates proved particularly important with respect to the glycosylation properties of the ensuing species, as discussed below.

The installation of C2 protecting groups other than esters proved challenging. Benzylation employing sodium hydride and benzyl bromide resulted in migration of the phosphate to yield the C2-phosphoryl benzyl glycoside. Milder benzylation conditions involving benzyl bromide/silver(I) oxide also did not meet with success and the incorporation of silyl groups using silyl triflates in the presence of 2,6-lutidine led to phosphate decomposition. Triethylsilyl ethers, on the other hand, were readily prepared by reaction of the C2-hydroxyl group of the glycosyl phosphate with triethylsilyl chloride and imidazole in DMF.

Previous reports of the instability of glycosyl phosphates toward silica gel column chromatography prompted us to simplify the purification of the reaction products.[16d,f] Precipitation of unwanted byproducts was accomplished by the addition

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(13) For the use of glycosyl fluorides see: Mukaiyama, T.; Murai, Y.; Shoda, S. *Chem. Lett.* **1981**, 431. For the use of glycosyl bromides see: (a) Koenigs, W.; Knorr, E. *Chem. Ber.* **1901**, *34*, 957. (b) Lemieux, R. U.; Hayami, J. I. *Can. J. Chem.* **1965**, *43*, 2162. (c) Paulsen, H.; Lockhoff, O. *Chem. Ber.* **1981**, *114*, 3102.

(14) Seeberger, P. H.; Bilodeau, M. T.; Danishefsky; S. J. *Aldrichim. Acta* **1997**, *30*, 75.

(15) For a review see: Heidlas, J. E.; Williams, K. W.; Whitesides, G. M. *Acc. Chem. Res.* **1992**, *25*, 307.

(16) For the synthesis of glycosyl 1-phosphates see: (a) Inage, M.; Chaki, H.; Kusumoto, S.; Shiba, T. *Chem. Lett.* **1982**, 1281. (b) Schmidt, R. R.; Stumpp, M. *Liebigs Ann. Chem.* **1984**, 680. (c) Pale, P.; Whitesides, G. M. *J. Org. Chem.* **1991**, *56*, 4547. (d) Sabesan, S.; Niera, S. *Carbohydr. Res.* **1992**, *223*, 169. (e) Sim, M. M.; Kondo, H.; Wong, C.-H. *J. Am. Chem. Soc.* **1993**, *115*, 2260. (f) Boons, G.-J.; Burton, A.; Wyatt, P. *Synlett* **1996**, 310. (g) Timmers, C. M.; van Straten, N. C. R.; van der Marel, G. A.; van Boom, J. H. *J. Carbohydr. Chem.* **1998**, *17*, 471. (h) Garcia, B. A.; Gin. D. *Org. Lett.* **2000**, *2*, 2135.

(17) For the chemical synthesis of NDPs see: (a) Moffatt, J. G. *Methods Enzymol.* **1966**, *8*, 136. (b) Hanessian, S.; Lu, P.-P.; Ishida, H. *J. Am. Chem. Soc.* **1998**, *120*, 13296.

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(21) (1) DMDO; (2) EtSH, cat. TFAA.

(22) Referred to as glycosyl phosphates in the remaining text.

(23) Ichikawa, S.; Shuto, S.; Matsuda, A. *J. Am. Chem. Soc.* **1999**, *121*, 10270.

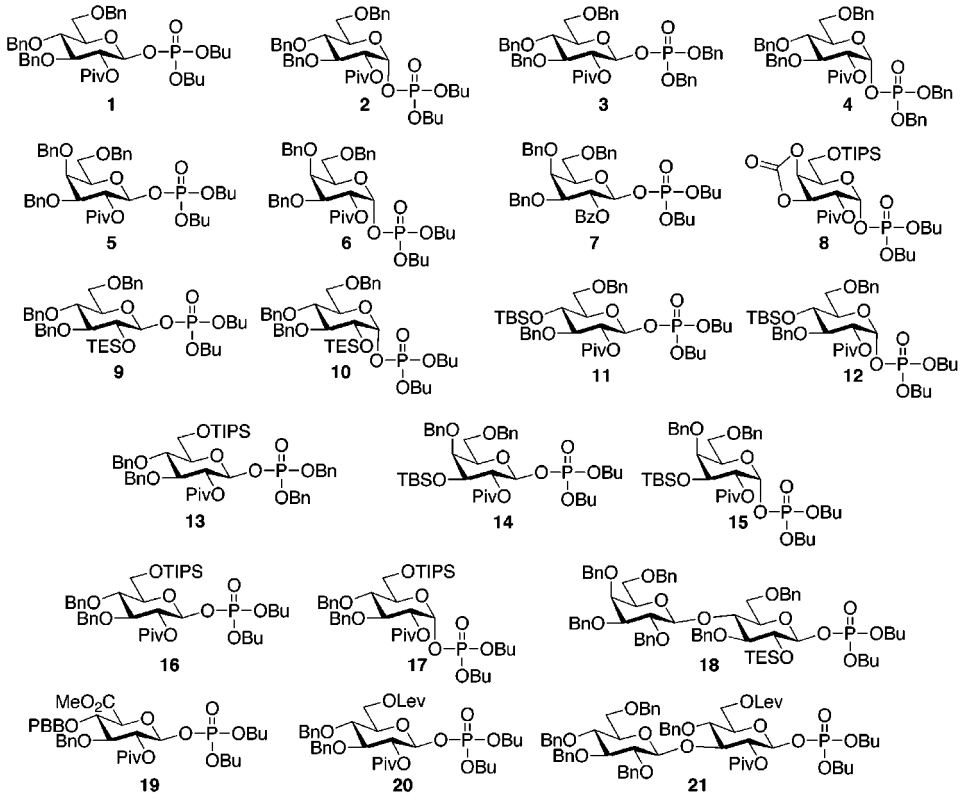
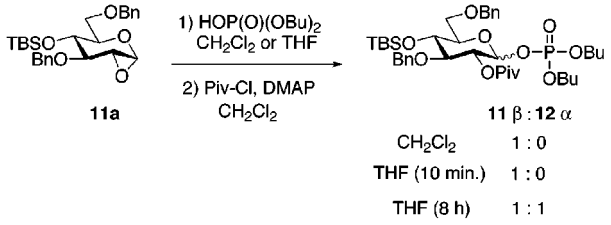


Figure 1. Glycosyl phosphates prepared from glycals.

Scheme 2. Solvent Effect on 1,2-Anhydrosugar Ring-Opening

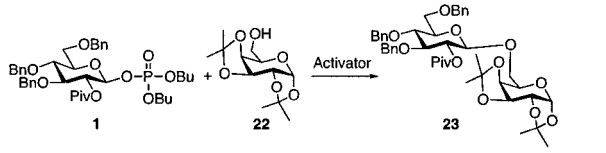


of ethyl acetate/hexane mixtures to the reaction mixture following acylation. Filtration through a pad of silica was sufficient to yield pure glucosyl and galactosyl phosphates (Figure 1). In pure form, α- and *β*-glycosyl phosphates were found to be completely stable to storage for several months at 0 °C.

With a straightforward procedure for the synthesis of gram quantities of glycosyl phosphates in hand, we explored their use as glycosyl donors under the agency of various activators. Trimethylsilyl triflate (TMSOTf) had been reported to activate glycosyl phosphates,[18a] but a thorough analysis of other potential activating reagents had not been described. Screening of a variety of Lewis acids revealed that tin(II) chloride, zinc iodide, zinc triflate, and copper(II) triflate have moderate activity for glycosyl phosphate activation, although product formation was accompanied by side-products (Figure 2). Notably, the silyl triflate reagents TMSOTf and TBSOTf ensured high-yielding glycosylations while the use of BF_3-OEt_2 offered modest results.

Next, the scope of glycosylation reactions employing glycosyl phosphates was explored (Table 1). Glucosyl and galactosyl *β*-phosphates bearing C2-participating groups reacted rapidly with primary and hindered secondary hydroxyls. Whereas the glycosyl *β*-phosphates were sufficiently reactive at −78 °C, the more stable glycosyl α-phosphates, such as **2**, served as competent glycosyl donors only at higher temperatures (−20 → −40 °C). In exploring novel glycosylating agents, it was important for us to establish that linkages commonly encountered in biologically relevant structures can be accessed in good yield. Creation of galactose *β*-(1→4) glucosamine glycosidic linkages common to several Lewis blood group determinants was readily accomplished by coupling of galactosyl phosphate **7** and glucosamine **27**. The efficient glycosylation of electronically and sterically challenging substrates such as **24** and **27** demonstrates the utility of glycosyl phosphates in oligosaccharide synthesis. In addition to their utility for glycoside formation in solution phase, glycosyl phosphates have also proven useful under the solid-phase paradigm.[20] Differentially protected glycosyl phosphates **20** and **21** have been recently used in the automated synthesis of phytoalexin elicitor *β*-glucans.[24]

Deactivated donors such as glucuronic acid phosphate **19** were found to be highly efficient in reactions with primary or



Activator[a]	Solvent	Temp. (C)	Time (h)	Yield (%)
TMSOTf	CH_2Cl_2	-78°	0.25	94
TBSOTf	CH_2Cl_2	-78°	0.25	95
BF_3-OEt_2	CH_2Cl_2	-78°	0.5	81
$SnCl_2$	CH_2Cl_2	0° → rt	5	61
ZnI_2	CH_2Cl_2/THF	0° → rt	5	30

Figure 2. Reagents screened for the activation of glycosyl phosphates. Footnote a: Other activators that were examined but showed no productive couplings included $Mg(OTf)_2$, $SnCl_4$, $TiCl_4$, $ZnCl_2$, $MgCl_2$, $CuCl_2$, $ZrCl_4$, $LaCl_3$, $FeCl_2$, $MgBr_2$ OEt_2, $SnCl_2/AgClO_4$, $MnCl_2$, and CSA.

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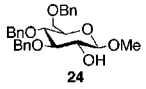
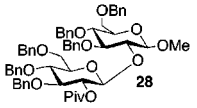
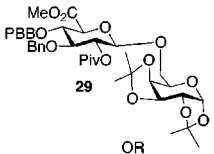
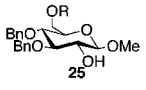
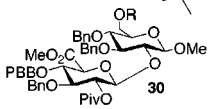
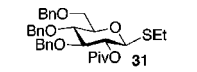
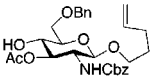
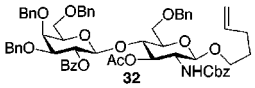
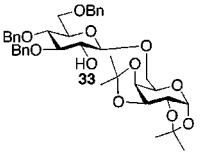
Table 1. Glycosylations with Glycal Derived Glycosyl Phosphates[a]

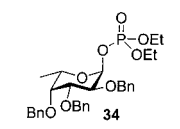
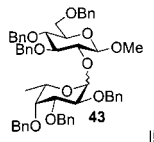
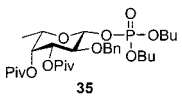
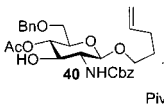
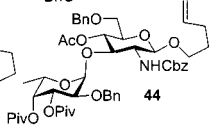
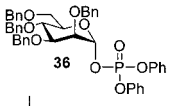
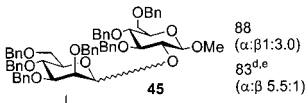
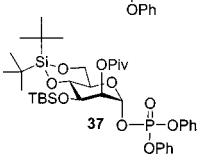
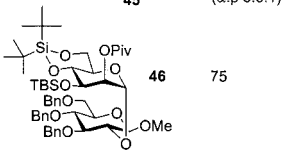
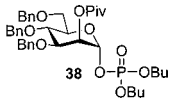
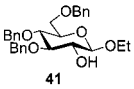
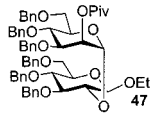
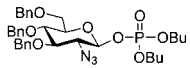
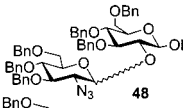
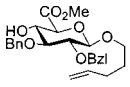
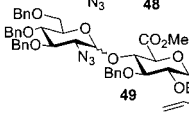
Donor	Acceptor	Product	Yield (%)[a]
1	 **24**	 **28**	83
2	**22**	**23**	87[b]
19	**22**	 **29**	72[b]
19	 **25**	 **30**	84[b,d]
3	EtSH **26**	 **31**	90
7	 **27**	 **32**	96[c]
9	**22**	 **33**	71

[a] All reactions were carried out under the following conditions unless otherwise noted: 1.2 equiv of donor, 1.0 equiv of acceptor, 1.2 equiv of TMSOTf in CH_2Cl_2 at −78 °C for 30 min. [b] −20 °C for 30 min. [c] 1.0 equivof acceptor, 1.7 equiv of donor, and 1.7 equiv of TBSOTf, −50 → −20 °C for 30 min. [d] R = α-azidomethyl benzoate.

secondary alcohols (Table 1).[25] These findings are particularly noteworthy because biologically important polysaccharides including glycosaminoglycans such as heparin and chondroitin are composed of alternating uronic acid and glucosamine monomers. Combined with the straightforward synthesis from readily accessible glucuronic acid glycal precursors, the use of **19** as a glycosylating agent provides a direct entry to complex glycan structures.

The high reactivity observed with the glucose, galactose, and glucuronic acid donors prompted us to explore the properties of glycosyl phosphates prepared from sugars such as fucose, mannose, and glucosamine. Several protocols for the synthesis of these glycosyl phosphates via phosphorylation of lactol precursors were available.[16] Fucosyl phosphate **34** and mannosyl phosphates **36** and **37** were prepared from the corresponding lactols and phosphochloridates in the presence of *N*,*N*-(dimethylamino)pyridine (DMAP).[16d,26,27] The synthesis of glucosamine donor **39** and fucose donor **35** proved more challenging and these glycosylating agents were obtained most efficiently from the anomeric trichloroacetimidates.[16b] Mannosyl phosphate **38** was obtained from the mannosyl 1,2-anhydrosugar that was

Table 2. Glycosylations with Fucosyl, Mannosyl, and Glucosamine Phosphates[a]

Donor	Acceptor	Product	Yield (%, α:β)[a]
 **34**	**24**	 **43**	95[b] (α:β 3:2)
 **35**	 **40** NHCbz	 **44**	97[c]
 **36**	**24**	 **45**	88 (α:β1:3.0) 83[d,e] (α:β 5.5:1)
 **37**	**24**	 **46**	75
 **38**	 **41**	 **47**	82
 **39**	**24**	 **48**	77[d] (α:β 4:1) 61[d,e] (α:β 4:1)
39	 **42**	 **49**	60[d] α:β 1:2.5 60[d,e] α:β 1:1

[a] All reactions were carried out under the following conditions unless otherwise noted: 1.2 equiv of donor, 1.0 equiv of acceptor, 1.2 equiv of TMSOTf in CH_2Cl_2 at −78 °C for 30 min. [b] 1.0 equiv of acceptor, 1.5 equiv of donor, 1.6 equiv of TMSOTf at −20 °C for 10 min. [c] 1.0 equiv of acceptor, 3.0 equiv of donor, 3.0 equiv of TMSOTf −78 → −40 °C. [d] Reaction was performed at −40 °C. [e] CH_3CN was used as the solvent.

derived from 2-*O*-acetyl-mannosyl chloride upon treatment with KO*t*-Bu.[28]

Glycosylations involving the use of donors **34**−**39** are outlined in Table 2. Initially, perbenzylated fucose phosphate **34** was employed with a C2 glucosyl acceptor to determine the degree of stereoselectivity in the absence of participating groups. Activation of **34** at −20 °C furnished coupled product in nearly quantitative yield as an inseparable mixture of diastereomers (95% $\alpha:\beta$ = 3:2) as determined by ^{1}H NMR integration. Previously, glycosylation with other fully benzylated fucose donors (bromides,[29] trichloroacetimidates,[8] fluorides,[30] thioglycosides,[31] and *n*-pentenyl glycosides[32]) had also been reported to give α/β mixtures. While we were encouraged by the high yield of this reaction, a fucosylation method furnishing exclusively the biologically relevant α-linked glycosides was desirable. Donor **35**, bearing C3 and C4 ester groups, allowed for completely α-selective fucosylation in excellent yield (97%). Even though the preparation of fucose donors incorporating

(25) For use of the *p*-bromobenzyl (PBB) protecting group see: Plante, O. J.; Buchwald, S. L.; Seeberger, P. H. *J. Am. Chem. Soc.* **2000**, *122*, 7148.

(26) For prior syntheses of fucosyl phosphates see: (a) Duynstee, H. I.; Wijsman, E. R.; van der Marel, G. A.; van Boom, J. H. *Synlett* **1996**, 313. (b) Nunez, H. A.; O'Connor, J. V.; Rosevear, P. R.; Barker, R. *Can. J. Chem.* **1981**, *59*, 2086.

(27) (a) Hung, S.-C.; Wong, C.-H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2671. (b) Plante, O. J.; Palmacci, E. R.; Seeberger, P. H. *Org. Lett.* **2000**, *2*, 3841.

(28) Du, Y.; Kong, F. *J. Carbohydr. Chem.* **1995**, *14*, 341.

(29) Dejter-Juszynski, M.; Flowers, H. M. *Carbohydr. Res.* **1971**, *18*, 219.

(30) Nicolaou, K. C.; Hummel, C. W.; Bockovich, N. J.; Wong, C.-H. *J. Chem. Soc., Chem. Commun.* **1991**, *10*, 870.

(31) Lonn, H. *Carbohydr. Res.* **1995**, *139*, 105.

(32) Udodong, U. E.; Srinivas, R. C.; Fraser-Reid, B. *Tetrahedron* **1992**, *48*, 4713.

participating C4-ester groups requires longer synthetic routes than perbenzylated donors, two characteristics are noteworthy. Selective α-fucosylations can be effected due to a proposed long-range participation of the C4-ester and the resulting α-product is less prone to hydrolysis under acidic conditions when electron-withdrawing groups are present on the fucose ring.[33]

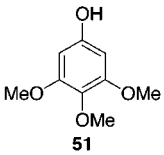
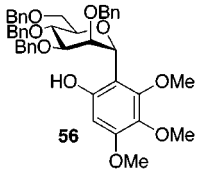
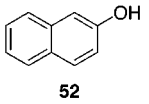
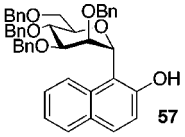
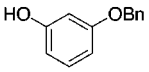
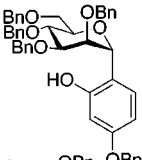
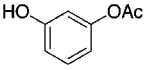
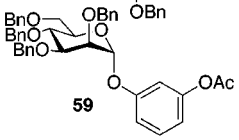
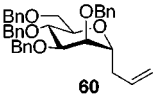
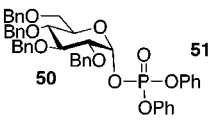
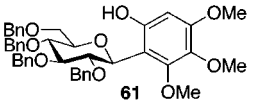
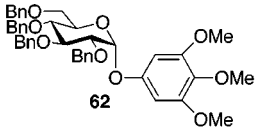
In addition to fucose donors, we were interested in exploring the properties of mannose donors carrying participating and nonparticipating groups on the C2 hydroxyl. Ubiquitous in nature, α-mannosides are major constituents of lipophosphoglycans and are, along with *β*-mannosides, integral components of *N*-linked glycoproteins. Mannose donor **37**, equipped with a C2 participating group, was used in the synthesis of α-mannosides and proved to be a reliable and efficient donor. Depending on the choice of solvent both α- and *β*-enriched mannosides were accessed with perbenzylated donor **36** (Table 2).[34] Coupling of **36** and secondary alcohol **24** preferentially afforded α-mannoside **45** when the reaction was carried out in acetonitrile (*β*:α = 1:5.5). Interestingly, a reversal of the anomeric selectivity (*β*:α = 3:1) was induced when dichloromethane was employed as solvent. Attempts to further increase *β*-selectivity of this reaction by conformationally constraining the glycosyl donor through the use of a 4,6-*O*-benzylidene-protected donor proved unsuccessful. Partial hydrolysis of the cyclic acetal functionality under the acidic reaction conditions required for glycosyl phosphate activation did not allow for the use of the benzylidene constraint.[35,36]

The dramatic solvent effect prevalent in couplings with mannosyl phosphate donors was not observed when glucosamine donor **39**, containing a nonparticipating azide-masked nitrogen, was coupled to glucuronic acceptor **42** (CH_3CN: *β*:α = 1:1; CH_2Cl_2: *β*:α = 1:2.5). Likewise, no change in anomeric selectivity was detected when either acetonitrile or dichloromethane were employed in the coupling of **39** and secondary alcohol **24** (*β*:α = 1:4).

***C*-Glycosides.** Along with our efforts to prepare a range of *O*-glycosides, we were interested in exploring the utility of glycosyl phosphates in the synthesis of *C*-glycosides. Decreased susceptibility to hydrolysis in vivo renders *C*-glycosides attractive analogues to naturally occurring sugars.[37] A wide range of *C*-alkyl and *C*-aryl glycosides have been prepared and evaluated as potential pharmaceutical agents.[38] Common methods for the preparation of *C*-glycosides rely on the use of glycosyl donors such as glycosyl trichloroacetimidate, thioglycosides, glycosyl phosphites, and glycosyl fluorides.[38] Coupling of the electrophilic glycosyl donors with electron-rich aromatic systems leads to formation of *C*-aryl glycosides while *C*-alkyl glycosides are formed when silicon-based *C*-nucleophiles are utilized. Other methods for preparing *C*-glycosides involve the use of palladium-mediated couplings, sigmatropic rearrangements, carbene insertions, anomeric anions, and transition metal complexes. Despite considerable interest in this field, current technologies for the synthesis of *C*-glycosides are often hampered by the need for prolonged reaction times and poor stereoselectivity.

Previous work on *β*-*C*-aryl glucoside synthesis suggested an indirect route for anomeric−aryl bond formation via a Fries-like *O*-to-*C* rearrangement.[39,40] Upon coupling with phenolic acceptors, the initially formed *O*-glycoside rearranges to the *C*-glycoside with net retention of configuration at the anomeric center in the presence of a Lewis acid.[41] When glucosyl trichloroacetimidates[39] and fluorides[40] were used, exclusive *β*-*C*-aryl selectivity was observed. We investigated the synthesis of mannosyl and glucosyl *C*-aryl glycosides from glycosyl phosphate donors via a Fries-like rearrangement.[42] Coupling of mannosyl donor **36** with aromatic acceptors **51**−**53** furnished exclusively α-*C*-aryl glycosides **56**−**58** within 1 h at 0 °C (Table 3). Notably, a single regioisomer with regard to the aromatic system was formed when *C*-aryl glycosides **57** and **58** were synthesized. When deactivated phenols such as 3-*O*-acetyl phenol **54** served as glycosyl acceptors, isolation of the α-*O*-glycoside **59** was possible. Coupling **36** and allyltrimethylsilane afforded *C*-alkyl glycoside **60** in high yield (93%). The complete stereospecificity observed in *C*-mannoside formation with perbenzylated donor **36** stands in stark contrast to the formation of anomeric mixtures obtained for *O*-glycoside formation.

Table 3. Formation of *C*-Glycosides with Glycosyl Phosphates[a]

Donor	Acceptor	Product	Yield (%)[a]
36	 **51**	 **56**	85
36	 **52**	 **57**	79
36	 **53**	 **58**	82
36	 **54**	 **59**	73
36	 **55**	 **60**	93
 **50**	**51**	 **61**	57
		 **62**	13[b]

[a] All reactions were carried out under the following conditions unless otherwise noted: 1.2 equiv of acceptor, 1.0 equiv of donor, 1.2 equiv of TMSOTf in CH_2Cl_2 at 0 °C for 1 h. [b] When the reaction of **50** and **51** was carried out at −15 °C for 15 min, **62** was isolated in 79% yield.

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(35) (a) Crich, D.; Sun, S. *J. Org. Chem.* **1996**, *61*, 4506. (b) Weingart, R.; Schmidt, R. R. *Tetrahedron Lett.* **2000**, *41*, 8753.
(36) For the synthesis of the α-mannoside component of Bleomycin A_2 with phosphate donors see: Boger, D. L.; Honda, T. *J. Am. Chem. Soc.* **1994**, *116*, 5647.
(37) For a review see: Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*; Pergamon: New York, 1995; Vol. 13.
(38) For a review see: Postema, M. H. D. *C-Glycoside Synthesis*; CRC Press: London, UK, 1995.
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(41) Kometani, U.; Kondo, H.; Fujimori, Y. *Synthesis* **1988**, 1005.
(42) Palmacci, E. R.; Seeberger, P. H. *Org. Lett.* **2001**, *3*, 1547.

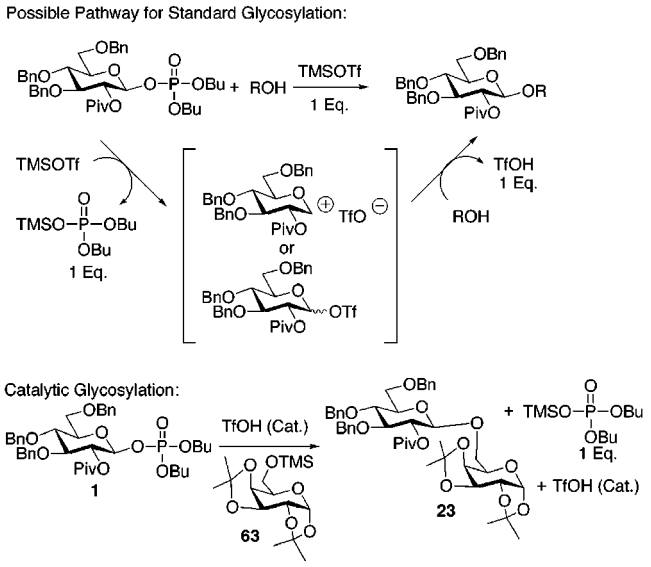


Figure 3. Analysis of TMSOTf-mediated glycosylations.

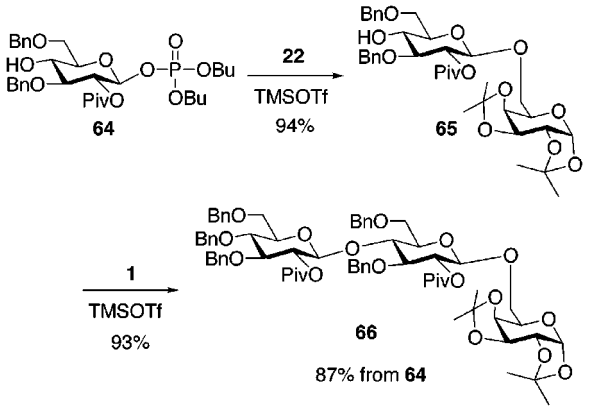
Glucosyl phosphate **50** was employed in the synthesis of *C*-aryl glycosides, however, with reduced yields. Activation of **50** with TMSOTf in the presence of 3,4,5-trimethoxyphenol **51** afforded the α-*O*-glycoside product **62** in good yield (79%) in just 15 min at 0 °C. Prolonged reaction times (2−4 h) and warming of the reaction mixture to room temperature provided the desired *β*-*C*-aryl glucoside **61** in modest 57% yield. No *β*-*O*-glycoside products were formed under any of the reaction conditions explored.

Catalytic Activation. The need for a stoichiometric amount of TMSOTf to efficiently promote the coupling of glycosyl phosphates with *O*- and *C*-nucleophiles prompted us to explore catalytic alternatives. In the screening of reagents for phosphate activation we found that protic acids (TsOH, TfOH, and CSA) were ineffective for this purpose. On the contrary, silyl triflates were excellent activators, affording effective glycosylations with a variety of donors. We propose that a driving force of glycosylations utilizing phosphate donors is the formation of a stoichiometric amount of silyl phosphate as a byproduct. The release of silyl phosphates and phosphites has been observed previously in other systems.[12,43]

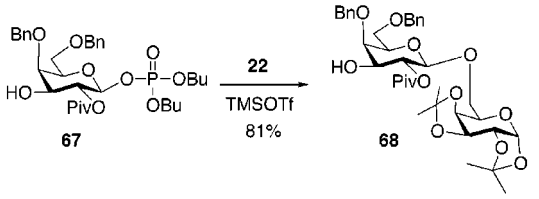
We investigated activation of phosphate donor **1** with catalytic protic acid in the presence of trimethylsilyl-protected acceptor **63** (Figure 3).[44] Varying amounts of triflic acid were added at low temperature (−78 °C) to induce glycosylation. Remarkably, as little as 1 mol % of triflic acid afforded coupled product in excellent yield (91%). This suggests that the in situ generation of catalytic amounts of trimethylsilyl triflate is sufficient for competent glycosylation. Although this analysis does not disprove other mechanistic pathways, the activation of glycosyl phosphates in a catalytic fashion may prove useful in expanding their utility in carbohydrate synthesis.[45]

Regioselective Glycosylations. The necessity of selectively removing protecting groups at each step of an oligosaccharide synthesis is tedious and time-consuming. After establishing the utility of glycosyl phosphates as glycosylating agents, we were interested in the development of a novel orthogonal method that would eliminate the need for intermediate protecting group removal. To carry out the synthesis of oligosaccharides with minimal protecting group transformations, a regioselective glycosylation strategy was envisioned. Fundamental to this approach was the use of a central building block capable of displaying both donor and acceptor properties. The central *β*-glycosyl phosphate building block **64** revealed a C4 hydroxyl group and was prepared from the corresponding 4-*O*-*tert*-butyldimethysilyl glycosyl phosphate by treatment with TBAF.[46]

Scheme 3. Regioselective Glycosylation with C4−OH Glucosyl Phosphate **64**



Scheme 4. Regioselective Glycosylation with C3−OH Galactosyl Phosphate **67**



Activation of donor **64** at −78 °C in the presence of primary alcohol **22** afforded *β*-(1→6)-linked disaccharide **65** bearing a C4-hydroxyl group in excellent yield (94%) as the only coupled product (Scheme 3). Following chromatography, subsequent glycosylation of disaccharide **65** containing a unique C4-hydroxyl with glucosyl phosphate **1** provided trisaccharide **66** in 87% overall yield in only two steps. When both glycosylations were carried out in a one-pot procedure without intermediate purification, trisaccharide **66** was isolated in 72% overall yield. This method may prove useful in the synthesis of naturally occurring glycosphingolipids[47] where a central glucosyl residue is C4-glycosylated and *β*-linked to a lipid via the anomeric position.[48]

To further explore the scope of regioselective glycosylations we prepared *β*-galactosyl phosphate **67** bearing a free hydroxyl group on C3. Activation of **67** in the presence of primary alcohol **22** afforded *β*-(1→6) linked disaccharide **68** in excellent yield (81%) (Scheme 4). Importantly, no other coupled products were observed under these reaction conditions.

After establishing the regioselective glycosylation of donors exposing C3 and C4 hydroxyl groups, we examined the use of

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(44) For glycosylations with TMS-OR acceptors see: (a) Mukaiyama, T.; Matsubara, K. *Chem. Lett.* **1992**, 1041 and references therein. (b) Nashed, E. M.; Glaudemans, C. P. J. *J. Org. Chem.* **1989**, *54*, 6116.

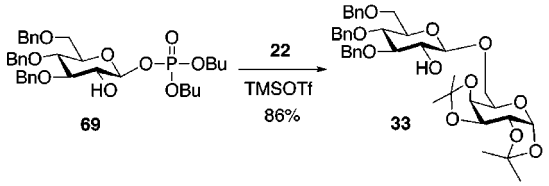
(45) For the benzylation of substrates containing benzylidene functionality with 0.1 equiv of triflic acid as an activator see: Wessel, H. P.; Iversen, T.; Bundle, D. R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2247.

(46) Andrade, R. B.; Plante, O. J.; Melean, L. G.; Seeberger, P. H. *Org. Lett.* **1999**, *1*, 1811.

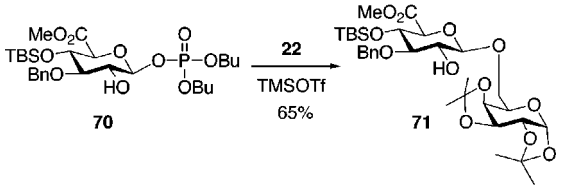
(47) For previous syntheses of glycosphingolipids see: (a) Schmidt, R. R.; Zimmermann, P. *Angew. Chem.* **1986**, *98*, 722. (b) Prabhanjan, H.; Ishida, H.; Kiso, M.; Hasegawa, A. *Carbohydr. Res.* **1991**, *211*, C1−C5.

(48) Varki, A. *Essentials of Glycobiology*; Varki, A., Cummings, R., Esko, J., Freeze, H., Hart, G., Marth, J., Eds.; Cold Spring Harbor Press: Cold Spring Harbor, NY, 1999; pp 115−129.

Scheme 5. Regioselective Glycosylation with C2−OH Glucosyl Phosphate **69**



Scheme 6. Regioselective Glycosylation with C2−OH Glucuronic Acid Phosphate **70**



donors in which the C2 position was unprotected. On the basis of prior observations with donor **9**, we anticipated that any productive coupling events should afford β-linked compounds even without the use of a participating group on C2.[18a] β-Glycosyl phosphate **69**[16g] was prepared and coupled with primary alcohol **22** (Scheme 5). After 10 min at −78 °C, 2-OH disaccharide **33** (86%) was formed as the only product. The exclusive β-selectivity observed in this example is in accordance with earlier reports by Ikegami that described similar stereoselective glycosylations when benzyl ethers were installed on C2 of phosphate donors.[18a] These examples demonstrate that *trans*-glycosidic linkages are readily formed with glycosyl phosphates whereas *cis*-glycosidic linkages are potentially a limitation.

Another example of regioselective glycosylations with C2-OH donor **70** (Scheme 6) also proceeded with complete β-selectivity. Glucuronic acid phosphate **70** was prepared and coupled with **22**. The reaction was significantly more rapid than with donor **19** bearing a C2-ester and afforded disaccharide **71** as the sole coupled product in good yield (65%). The reactivity of **70** as a glycosyl donor is important in light of long reaction times required for most uronic acid donors.

Glycosyl Dithiophosphates. In addition to glycosyl phosphates, we were interested in exploring the synthesis and use of phosphorus analogues as glycosylating agents. A number of phosphate analogues including dimethylphosphinothioates,[49] phosphorimidates,[50] and phosphoramidates[51] had been previously applied to carbohydrate chemistry. We chose to synthesize and evaluate glycosyl dithiophosphate triesters[52] in which the bridging and phosphoryl oxygens are replaced by sulfur atoms. Our choice was based on reasoning that these sites of modification would most greatly influence the stability and reactivity of the donor.

Glycosyl dithiophosphates were prepared in a fashion analogous to that described for glycosyl phosphates. Epoxidation of the glycal with DMDO afforded the 1,2-anhydrosugar that was opened with commercially available *O*,*O*-diethyldithiophosphate

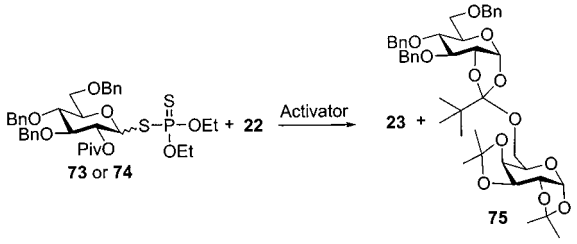
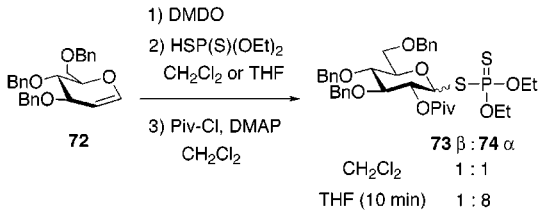


Figure 4. Reagents screened for dithiophosphate activation.

Scheme 7. Synthesis of Glycosyl Dithiophosphates



to afford the C2-OH glycosyl dithiophosphate in good yield (82−88%).[19] The opening with *O*,*O*-diethyldithiophosphate also exhibited a strong solvent dependence regarding the formation of different anomers (CH_2Cl_2: β:α = 1:1; THF: β:α = 1:8) (Scheme 7). Unlike the corresponding glycosyl phosphates, C2-OH glycosyl dithiophosphates were found to be completely stable to silica column chromatography. However, as was the case with glycosyl phosphates, treatment of C2-OH glycosyl dithiophosphates with NaH and benzyl bromide resulted in the formation of C2-thiophosphoryl benzyl glycosides. Acylation of C2-OH glycosyl dithiophosphates successfully furnished fully protected donors **73** and **74**. A major attribute of this method is the efficiency of preparation of glycosyl dithiophosphates (82−88%) when compared to the lower yields (55−75%) reported for the preparation of thioglycosides or *n*-pentenyl glycosides from glycals.[53]

Prior work with 2-deoxy dithiophosphates suggested that thiophilic reagents such as silver salts (AgOTf, $AgClO_4$) and iodonium sources ($I(coll)_2ClO_4$, *N*-iodosuccinimide) may serve as activators for glucosyl dithiophosphate donors.[54] Unexpectedly, low yields (5−38%) were obtained upon reaction of **73** or **74** and **22** in the presence of various promoters (Figure 4). Activation with *N*-iodosuccinimide for 16 h resulted in the formation of the desired β-linked disaccharide **23** (11%) and ortho ester **75** (27%). This finding was unusual considering that the pivaloyl group is widely used to prevent ortho ester formation during glycosylation.

In the search for more efficient promoters of β-selective glycosylations, we explored coupling conditions commonly used for thioglycoside donors (Figure 4). The coupling of either α- or β-glycosyl dithiophosphates with **22** using excess methyl triflate (MeOTf) as an activator in the presence of molecular sieves and 2,6-di-*tert*-butylpyridine (DTBP) proceeded in modest yield (70%). Contrary to results with glycosyl phosphates, no reactivity difference for glycosyl dithiophosphate anomers was found. Hindered secondary acceptors and substrates containing acid-sensitive glycals were glycosylated under MeOTf/DTBP conditions and resulted in coupling yields comparable to those obtained when thioglycosides are subjected to the same conditions.[19]

Application of another thiophilic activator, dimethylthiomethylsulfonium triflate (DMTST),[55] to the coupling of dithio-

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(50) Pan, S.; Li, H.; Hong, F.; Yu, B.; Zhao, K. *Tetrahedron Lett.* **1997**, *38*, 6139.

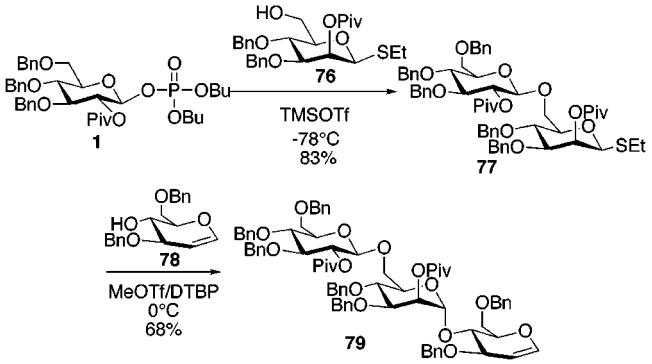
(51) (a) Hashimoto, S.-I.; Sakamoto, H.; Honda, T.; Ikegami, S. *Tetrahedron Lett.* **1997**, *38*, 5181. (b) Hashimoto, S.-I.; Sakamoto, H.; Honda, T.; Abe, H.; Nakamura, S.-I.; Ikegami, S. *Tetrahedron Lett.* **1997**, *38*, 8969. (c) Chen, M.-J.; Ravindran, K.; Landry, D. W.; Zhao, K. *Heterocycles* **1997**, *45*, 1247.

(52) Referred to as glycosyl dithiophosphates in the remaining text.

(53) Seeberger, P. H.; Eckhardt, M.; Gutteridge, C. E.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 10064.

(54) (a) Bielawska, H.; Michalska, M. *J. Carbohydr. Chem.* **1991**, *10*, 107. (b) Laupichler, L.; Sajus, H.; Thiem, J. *Synthesis* **1992**, 1133.

Scheme 8. Orthogonal Glycosylations with Glycosyl Phosphates and Thioglycosides



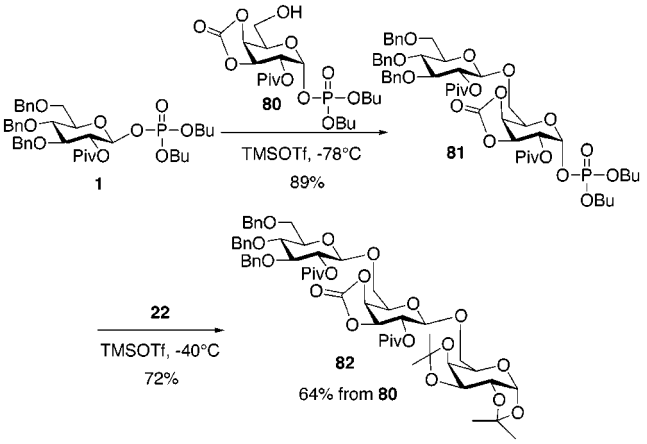
phosphate donor **73** and **22** resulted in the formation of **23** in excellent yield (94%) (Figure 4). The use of DMTST as an activator for glycosyl dithiophosphate donors, in conjunction with their ease of synthesis, should lead to a more widespread use of this class of donors for the synthesis of oligosaccharides.

Orthogonal Glycosylation (Phosphate/Thiodonor). A number of orthogonal glycosylation strategies have been developed for the synthesis of oligosaccharides both in solution and on a solid support.[56] On the basis of our findings that ethanethiol was a suitable acceptor in TMSOTf-mediated glycosyl phosphate glycosylations (Table 1), we envisioned an orthogonal glycosylation strategy employing glycosyl phosphates and thiodonors. We designed a synthesis whereby activation of a phosphate donor with TMSOTf in the presence of a thioglycoside acceptor would lead to formation of a disaccharide thioglycoside. Further elongation of the disaccharide could be accomplished by thioglycoside activation.

In reducing this principle to practice, thioglycoside **76** bearing a free hydroxyl group was selected to function as a central building block (Scheme 8). Activation of **1** with TMSOTf at −78 °C in the presence of **76** furnished disaccharide **77** in good yield. Coupling of **77** with glycal acceptor **78** was affected by MeOTf/DTBP activation to afford trisaccharide **79**. The orthogonality of glycosyl phosphates and thioglycosides provides a convenient two-step method of preparing trisaccharides from a central building block.

Anomer-Controlled Glycosylation. The regioselective and orthogonal glycosylation strategies detailed above had previously been established for glycosyl donors other than glycosyl phosphates. Control of donor reactivity via the anomeric configuration is a strategy that to our knowledge has not previously been explored. As outlined above, we developed conditions that allowed for the synthesis of either α- or *β*-anomers of glycosyl phosphates in excellent yield. Importantly, the more reactive *β*-glycosyl phosphates in the glucose and galactose series were activated at −78 °C while their α-anomeric counterparts were inert under those conditions and required higher temperatures (−40 → −20 °C) for activation. Here we describe an orthogonal glycosylation strategy that takes advantage of the reactivity differences of α- and *β*-glycosyl phosphates.

Scheme 9. Orthogonal Glycosylations Based on Anomeric Configuration



α-Galactosyl phosphate **80** exposing a 6-hydroxyl group was chosen as the central building block for the synthesis of a trisaccharide (Scheme 9). Monomer **80** was prepared from 6-*O*-triisopropylsilyl-3,4-*O*-carbonyl galactal in four steps and 62% overall yield.[57,58] Glycosylation of **80** with *β*-glucosyl phosphate **1** at −78 °C resulted exclusively in *β*-phosphate activation and afforded as anticipated *β*-(1→6)-linked disaccharide α-phosphate **81**. Following chromatography, disaccharide **81** was coupled with **22** at −40 °C to afford trisaccharide **82** in two steps and good overall yield (64%). Anomer-controlled glycosylations with α- and *β*-phosphates provide a novel alternative to existing methods for the synthesis of oligosaccharides.

Summary

In conclusion, we have developed an efficient one-pot synthesis of α- and *β*-glycosyl phosphate and dithiophosphate triesters from glycals via 1,2-anhydrosugars. The resulting glycosyl phosphates have been shown to function as powerful glycosylating agents for the installation of *β*-glucosidic, *β*-galactosidic, α-fucosidic, α-mannosidic, *β*-glucuronic acid, and *β*-glucosamine linkages even with hindered and electron-deficient substrates. In addition to serving as efficient donors for *O*-glycosylations, glycosyl phosphates are effective in the preparation of *S*-glycosides and *C*-glycosides. Not only can glycosyl phosphates be activated by stoichiometric amounts of TMSOTf but the acid-catalyzed coupling of glycosyl phosphates with silylated acceptors is also discussed. Glycosyl dithiophosphates are activated with different thiophiles under basic conditions that are compatible with acceptors containing acid-sensitive functional groups.

To minimize protecting group manipulations, orthogonal and regioselective glycosylation strategies with glycosyl phosphates are reported. An orthogonal glycosylation method involving the activation of a glycosyl phosphate donor in the presence of a thioglycoside acceptor is detailed. Also, an acceptor-mediated regioselective glycosylation strategy is described. Finally, a unique glycosylation strategy exploiting the difference in reactivity of α- and *β*-glycosyl phosphates is disclosed. The protocols developed here demonstrate the versatility of glycosyl phosphates and glycosyl dithiophosphates for the construction of glycosidic linkages. Extension of this work to the automated

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(57) (1) DMDO; (2) $HOP(O)(OBu)_2$, THF; (3) Piv-Cl, DMAP; (4) TBAF, AcOH, room temperature, 15 min (62% overall).

(58) For the synthesis of 6-*O*-TIPS-3,4-di-*O*-carbonyl galactal see: Gervay, J.; Peterson, J. M.; Oriyama, T.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 5465.

solid-phase synthesis of oligosaccharides and glycoconjugates is currently underway in our laboratory.

Experimental Section

Synthesis of β-Glycosyl Phosphates: General Procedure A. Suitably protected glycal (1.0 equiv) was dissolved in CH_2Cl_2 (1 mL/0.10 mmol glycal) and cooled to 0 °C. A 0.08 M solution of dimethyldioxirane in acetone (1.2 equiv) was added and the reaction was stirred for 15 min. After the solvent was removed in vacuo, the residue was dissolved in CH_2Cl_2 (2 mL/0.10 mmol glycal). The solution was cooled to −78 °C for 15 min. A solution of dialkyl phosphate (1.1 equiv) in CH_2Cl_2 (2 mL/0.10 mmol glycal) was added dropwise over 5 min. After addition was complete, the reaction mixture was warmed to 0 °C and DMAP (4 equiv) and pivaloyl chloride (2 equiv) were added. The solution was warmed to room temperature over 1 h. The addition of 40% EtOAc/hexanes afforded a white precipitate that was filtered off through a pad of silica. The eluent was concentrated and purified by flash silica column chromatography (short plug) to afford β-enriched glycosyl phosphates.

Synthesis of α-Glycosyl Phosphates: General Procedure B. Suitably protected glycal (1.0 equiv) was dissolved in CH_2Cl_2 (1 mL/0.10 mmol glycal) and cooled to 0 °C. A 0.08 M solution of dimethyldioxirane in acetone (1.2 equiv) was added and the reaction was stirred for 15 min. After the solvent was removed in vacuo, the residue was redissolved in THF (2 mL/0.10 mmol glycal). The solution was cooled to −78 °C for 15 min. A solution of dialkyl phosphate (1.1 equiv) in THF (2 mL/0.10 mmol glycal) was added dropwise over 5 min. After addition was complete, the reaction mixture was warmed to 0 °C and DMAP (4 equiv) and pivaloyl chloride (2 equiv) were added. The solution was warmed to room temperature over 1 h. The addition of 40% EtOAc/hexanes afforded a white precipitate that was filtered off through a pad of silica. The eluent was concentrated and purified by flash silica column chromatography (short plug) to afford α-enriched glycosyl phosphates.

Synthesis of 2-*O*-Triethylsilyl Glycosyl Phosphates: General Procedure C. Suitably protected glycal (1.0 equiv) was dissolved in CH_2Cl_2 (1 mL/0.10 mmol glycal) and cooled to 0 °C. A 0.08 M solution of dimethyldioxirane in acetone (1.2 equiv) was added and the reaction was stirred for 15 min. After the solvent was removed in vacuo, the residue was redissolved in THF (2 mL/0.10 mmol glycal). The solution was cooled to −78 °C for 15 min. A solution of dialkyl phosphate (1.1 equiv) in THF (2 mL/0.10 mmol glycal) was added dropwise over 5 min. After addition was complete, the reaction mixture was warmed to room temperature and imidazole (3.5 equiv) and triethylsilyl chloride (2.5 equiv) were added. After 2 h at room temperature, the reaction mixture was diluted with EtOAc (50 mL) and washed with saturated $NaHCO_3$(aq), brine, and water. After extraction of the aqueous layers with 2 × 50 mL of EtOAc, the organics were dried over Na_2SO_4, filtered, and concentrated. Purification by flash silica column chromatography afforded 2-*O*-triethylsilylglycosyl phosphates.

Glycosyl Phosphate Couplings: General Procedure D. Glycosyl phosphate donor (1.2 equiv) and acceptor (1.0 equiv) were combined and azeotropically dried with toluene (3 × 5 mL) followed by 1 h under vacuum. The mixture was dissolved in CH_2Cl_2 (2 mL/0.10 mmol acceptor) and cooled to −78 °C for 15 min before trimethylsilyltriflate (1.2 equiv) was added dropwise. After the mixture was stirred for 30 min at −78 °C, triethylamine (2 equiv) was added. The solution was warmed to room temperature and the solvent was removed in a stream of N_2. The resulting mixture was purified by flash silica column chromatography.

Dibutyl 2-*O*-Pivaloyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranoside Phosphate 1. General procedure A with 1,5-anhydro-2-deoxy-3,4,6-tri-*O*-benzyl-D-*arabino*-hex-1-enitol (1.00 g, 2.41 mmol), dimethyldioxirane (36.0 mL, 2.90 mmol), dibutyl phosphate (0.50 mL, 2.5 mmol), pivaloyl chloride (0.59 mL, 4.8 mmol), and DMAP (1.18 g, 9.64 mmol) afforded 1.69 g (91%, 11:1 β:α) of **1** as a colorless oil after flash silica column chromatography (40→50% EtOAc/hexanes). $[\alpha]^{24}_D$ −1.9° (*c* 1.50, CH_2Cl_2); IR (thin film) 2946, 1740, 1454, 1282, 1016 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33−7.25 (m, 13H), 7.16−7.14 (m, 2H), 5.24 (app t, *J* = 7.3 Hz, 1H), 5.17 (app t, *J* = 8.5 Hz, 1H), 4.80−4.75 (m, 2H), 4.70 (d, *J* = 11.0 Hz, 1H), 4.69−4.54 (m, 2H), 4.51 (d, *J* = 11.0 Hz, 1H), 4.08−4.00 (m, 4H), 3.82 (t, *J* = 9.5 Hz, 1H), 3.78−3.70 (m, 3H), 3.64−3.61 (m, 1H), 1.64−1.59 (m, 4H), 1.40−1.34 (m, 4H), 1.20 (s, 9H), 0.96−0.88 (m, 6H);^{13}C NMR (125 MHz, $CDCl_3$) δ 177.2, 138.2, 138.1, 128.7, 128.3, 128.2, 128.1, 128.0, 127.6, 97.0 (d, J_{C-P} = 5.0 Hz), 83.1, 76.2, 75.9, 73.9, 73.3, 68.4, 68.2, 68.1, 39.2, 32.7, 26.9, 19.1, 14.0; ^{31}P NMR (200 MHz, $CDCl_3$) δ -2.2; FAB MS *m*/*z* $(M)^+$ calcd 726.3532, obsd 726.3537.

Dibutyl 2-*O*-Pivaloyl-3,4,6-tri-*O*-benzyl-α-D-glucopyranoside Phosphate 2. General procedure B with 1,5-anhydro-2-deoxy-3,4,6-tri-*O*-benzyl-D-*arabino*-hex-1-enitol (0.192 g, 0.462 mmol), dimethyldioxirane (8.7 mL, 0.69 mmol), dibutyl phosphate (0.100 mL, 0.508 mmol), pivaloyl chloride (85.0 μL, 693 μmol), and DMAP (0.169 g, 1.39 mmol) afforded 0.169 g (59%, 1:4 β:α) of **2** as a colorless oil after flash silica column chromatography (40→50% EtOAc/hexanes). $[\alpha]^{24}_D$ +50.5° (*c* 0.63, CH_2Cl_2); IR (thin film) 2960, 2872, 1736, 1454, 1282 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35−7.27 (m, 13 H), 7.18−7.15 (m, 2H), 5.85 (dd, *J* = 1.8, 6.4 Hz, 1H), 4.99−4.97 (m, 1H), 4.83−4.80 (m, 3H), 4.63 (d, *J* = 11.5 Hz, 1H), 4.56−4.50 (m, 3H), 4.10−4.02 (m, 5H), 3.86−3.79 (m, 2H), 3.68 (d, *J* = 11.0 Hz, 1H), 1.86−1.61 (m, 4H), 1.44−1.36 (m, 4H), 1.24 (s, 9H), 0.97−0.91 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.7, 138.3, 138.1, 138.0, 128.6, 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 127.7, 127.6, 94.7 (d, J_{C-P} = 5.5 Hz), 79.5, 75.6, 75.4, 73.7, 72.7, 72.6, 68.2, 68.0, 67.9, 67.8, 39.0, 32.5, 32.4, 27.3, 18.8, 13.8; ^{31}P NMR (200 MHz, $CDCl_3$) δ −2.5; FAB MS *m*/*z* $(M)^+$ calcd 726.3532, obsd 726.3537.

Dibutyl 3,4,6-Tri-*O*-benzyl-2-*O*-triethylsilyl-D-glucopyranoside Phosphates 9 and 10. General procedure C with 1,5-anhydro-2-deoxy-3,4,6-tri-*O*-benzyl-D-*arabino*-hex-1-enitol (0.295 g, 0.495 mmol), dimethyldioxirane (9.0 mL, 0.70 mmol), dibutyl phosphate (0.108 mL, 0.545 mmol), imidazole (50.0 mg, 0.740 mmol), and triethylsilyl chloride (0.10 mL, 0.59 mmol) afforded 359 mg (79%, 2:1, β:α) of **9** and **10** as colorless oils after flash silica column chromatography (30→40%EtOAc/hexanes).

Dibutyl 3,4,6-tri-*O*-benzyl-2-*O*-triethylsilyl-β-D-glucopyranoside phosphate 9: $[\alpha]^{24}_D$ −8.3° (c 4.39, CH_2Cl_2); IR (thin film) 2976, 2870, 1460, 1130 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37−7.25 (m, 13H), 7.12−7.09 (m, 2H), 5.02 (dd, *J* = 6.0, 7.5 Hz, 1H), 4.93−4.86 (m, 2H), 4.75 (d, *J* = 11.0 Hz, 1H), 4.61−4.50 (m, 2H), 4.13−4.08 (m, 3H), 3.75−3.67 (m, 4H), 3.61−3.58 (m, 1H), 3.55 (app t, *J* = 8.6 Hz, 1H), 1.69−1.60 (m, 4H), 1.45−1.38 (m, 4H), 1.00−0.89 (m, 15H), 0.68 (app q, *J* = 8.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.0, 138.3, 138.2, 128.7, 128.6, 128.2, 128.1, 128.0, 127.6, 127.5, 99.5 (d, J_{C-P} = 6.4 Hz), 85.8, 77.9, 75.8, 75.6, 75.5, 75.4, 75.2, 73.8, 68.8, 68.0, 67.9, 32.6, 32.5, 19.0, 14.0, 13.9, 7.2, 5.3; ^{31}P NMR (200 MHz, $CDCl_3$) δ −1.4; FAB MS *m*/*z* $(M)^+$ calcd 756.3822, obsd 756.3822.

Dibutyl 3,4,6-tri-*O*-benzyl-2-*O*-triethylsilyl-α-D-glucopyranoside phosphate 10: $[\alpha]^{24}_D$ +44.1° (*c* 1.50, CH_2Cl_2); IR (thin film) 2976, 2870, 1460, 1130 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37−7.26 (m, 13H), 7.10−7.09 (m, 2H), 5.65 (dd, *J* = 2.5, 6.3 Hz, 1H), 4.93 (d, *J* = 11.5 Hz, 1H), 4.83−4.79 (m, 2H), 4.62 (d, *J* = 12.0 Hz, 1H), 4.51−4.47 (m, 2H), 4.12−3.98 (m, 5H), 3.84−3.70 (m, 4H), 3.65 (d, *J* = 10.0 Hz, 1H), 1.70−1.60 (m, 4H), 1.45−1.34 (m, 4H), 1.02−0.89 (m, 15H), 0.67 (app q, *J* = 8.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.9, 138.3, 138.0, 128.6, 128.5, 128.2, 128.0, 127.9, 127.7, 127.6, 97.9 (d, J_{C-P} = 8.1 Hz), 82.2, 75.8, 75.3, 73.8, 73.4, 73.3, 72.5, 68.3, 67.8, 67.6, 67.5, 32.5, 32.4, 18.9, 18.8, 13.8, 7.0, 5.1; ^{31}P NMR (200 MHz, $CDCl_3$) δ −2.3; FAB MS *m*/*z* $(M)^+$ calcd 756.3822, obsd 756.3823.

3,4,6-Tri-*O*-benzyl-2-*O*-pivaloyl-β-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranoside 23. General procedure D with donor **1** (57.5 mg, 77.0 μmol), acceptor **22** (13.3 mg, 51.0 μmol), and TMSOTf (14.0 μL, 77.0 μmol) afforded 37.2 mg (94%) of **23** as a colorless oil after flash silica column chromatography (25% EtOAc/hexanes). $[\alpha]^{24}_D$ −45.2° (*c* 2.34, CH_2Cl_2); IR (thin film) 3029, 2978, 2933, 2904, 1741, 1134, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39−7.24 (m, 13H), 7.19−7.15 (m, 2H), 5.49 (d, *J* = 5.0 Hz, 1H), 5.10 (app t, *J* = 8.5 Hz, 1H), 4.79−4.69 (m, 3H), 4.64 (d, *J* = 8.0 Hz, 1H), 4.58−4.53 (m, 3H), 4.46 (d, *J* = 8.0 Hz, 1H), 4.29−4.25 (m, 2H), 4.10−4.07 (m, 1H), 3.97−3.94 (m, 1H), 3.76−3.69 (m, 4H), 3.63−3.59 (m, 1H), 3.53−3.50 (m, 1H), 1.51 (s, 3H), 1.43 (s, 3H), 1.32 (s,

3H), 1.31 (s, 3H), 1.21 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.1, 138.5, 138.4, 128.7, 128.6, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 109.5, 108.8, 101.8, 96.6, 83.6, 78.1, 75.7, 75.2, 73.9, 73.3, 71.5, 70.9, 69.0, 67.4, 39.1, 27.5, 26.4, 26.3, 25.4, 24.7; FAB MS *m*/*z* $(M)^+$ calcd 776.3772, found 776.3770.

***n*-Pentenyl 2-*O*-Benzoyl-3,4,6-tri-*O*-benzyl-*β*-D-galactopyranosyl-(1→4)-3-*O*-acetyl-6-*O*-benzyl-2-deoxy-2-benzyloxycarbonylamino-*β*-D-glucopyranoside 32.** General procedure D with donor **7** (63.4 mg, 84.0 μmol), acceptor **27** (24.2 mg, 49.1 μmol), and TBSOTf (20.9 μL, 84.0 μmol) at −50 °C followed by 30 min at −20 °C afforded 50.0 mg (96%) of **32** as a colorless oil after flash silica column chromatography (30%→50% EtOAc/hexanes). $[\alpha]^{24}_D$ +29.3° (*c* 1.10, CH_2Cl_2); IR (thin film) 3029, 2872, 1726, 1540, 1453, 1367, 736; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, J = 7.0 Hz, 1H), 7.70 (t, J = 7.5 Hz, 1H), 7.57−7.27 (m, 28H), 5.87−5.85 (m, 1H), 5.62 (dd, J = 8.0, 10.0 Hz, 1H), 5.22 (s, 2H), 5.11 (d, J = 11.5 Hz, 1H), 5.10−5.04 (m, 2H), 4.92−4.90 (m, 1H), 4.74 (d, J = 12.5 Hz, 1H), 4.70 (d, J = 12.0 Hz, 1H), 4.63 (d, J = 12.5 Hz, 1H), 4.57 (s, 2H), 4.56 (d, J = 11.5 Hz, 1H), 4.38 (d, J = 12.0 Hz, 1H), 4.33 (d, J = 7.5 Hz, 1H), 4.13 (d, J = 2.5 Hz, 1H), 4.00 (app t, J = 9.0 Hz, 1H), 3.91 (dt, J = 3.0, 6.5 Hz, 1H), 3.84−3.77 (m, 3H), 3.71−3.59 (m, 6H), 3.46−3.44 (m, 2H), 2.22−2.12 (m, 2H), 1.98 (s, 3H), 1.77−1.66 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 165.0, 156.1, 138.7, 138.4, 138.2, 137.8, 136.7, 133.2, 130.1, 130.0, 128.6, 128.5, 128.4, 128.1, 127.8, 127.7, 127.6, 115.0, 102.0, 100.8, 79.8, 74.7, 74.6, 73.7, 73.4, 73.1, 72.4, 72.3, 71.5, 69.1, 68.1, 66.8, 55.9, 30.1, 28.7, 20.9; FAB MS *m*/*z* $(M)^+$ calcd 1049.4561, obsd 1049.4528.

2-(2′,3′,4′,6′-Tetra-*O*-benzyl-α-D-mannopyranosyl)-3,4,5-trimethoxyphen-1-ol 56. Diphenyl 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl phosphate **36** (35 mg, 45 μmol) was coevaporated with toluene and dissolved in CH_2Cl_2 (2.0 mL), and the solution was cooled to 0 °C. 3,4,5-Trimethoxyphenol **51** (25.0 mg, 136 μmol) was added, followed by the addition of TMSOTf (10.0 μL, 55.0 μmol). The reaction mixture was allowed to warm to ambient temperature over 1 h. Triethylamine (Et_3N, 15 μL) was added and the solvent was removed in vacuo. Purification by flash silica column chromatography (5:1 hexanes:EtOAc) afforded 27.0 mg (85%) of **56** as a colorless oil. $[\alpha]^{24}_D$ +12.7° (*c* 1.82, CH_2Cl_2); IR (thin film) 3364, 2933, 1621, 1495, 1362, 1100 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.38−7.26 (m, 13H), 7.21−7.10 (m, 6H), 6.27 (s, 1H), 4.92 (d, J = 11.0 Hz, 1H), 4.82 (d, J = 0.9 Hz, 1H), 4.70 (app s, 2H), 4.64 (d, J = 12.2 Hz, 1H), 4.62 (d, J = 12.0 Hz, 1H), 4.57 (d, J = 11.0 Hz, 1H), 4.54−4.50 (m, 2H), 4.17 (app t, J = 9.8 Hz, 1H), 3.90 (app d, J = 1.9 Hz, 1H), 3.82 (s, 3H), 3.79−3.71 (m, 6H), 3.70 (s, 3H), 3.57−3.54 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9, 153.7, 150.2, 138.6, 138.5, 138.4, 138.2, 134.6, 128.8, 128.6, 128.6, 128.5, 128.5, 128.2, 128.2, 127.9, 127.9, 127.8, 127.8, 127.7, 127.6, 107.6, 97.0, 84.2, 79.7, 77.0, 76.8, 75.5, 74.4, 73.6, 72.4, 68.8, 61.1, 60.9, 56.0. FAB MS *m*/*z* $(M + Na)^+$ calcd 729.3010 obsd 729.3034.

3,6-Di-*O*-benzyl-2-*O*-pivaloyl-*β*-D-glucopyranosyl-(1*β*6)-1,2:3,4-di-*O*-isopropylidene-→-D-galactopyranoside 65. General procedure D with donor **64** (63.7 mg, 100. μmol), acceptor **22** (31.2 mg, 0.120 mmol), and TMSOTf (12.0 μL, 0.100 mmol) afforded 64.6 mg (94%) of **65** as a colorless oil after flash silica column chromatography (30% EtOAc/hexanes). $[\alpha]^{24}_D$ −37.2° (*c* 5.11, CH_2Cl_2); IR (thin film) 3507, 2978, 1740, 1318, 1071 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.27 (m, 10H), 5.49 (d, J = 4.9 Hz, 1H), 5.06 (dd, J = 8.2, 9.8 Hz, 1H), 4.74 (d, J = 11.3 Hz, 1H), 4.70 (d, J = 11.3 Hz, 1H), 4.62 (d, J = 11.9 Hz, 1H), 4.59−4.56 (m, 2H), 4.48 (d, J = 7.9 Hz, 1H), 4.29 (dd, J = 2.4, 4.9 Hz, 1H), 4.24 (dd, J = 1.8, 8.2 Hz, 1H), 4.06 (dd, J = 5.2, 10.4 Hz, 1H), 3.95−3.92 (m, 1H), 3.77−3.73 (m, 4H), 3.62−3.55 (m, 2H), 3.51−3.49 (m, 1H), 1.51 (s, 3H), 1.44 (s, 3H), 1.33 (s, 3H), 1.32 (s, 3H), 1.23 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0, 138.4, 137.9, 128.6, 128.0, 127.9, 127.7, 109.3, 108.7, 101.7, 96.4, 82.8, 74.5, 74.4, 73.9, 72.6, 72.0, 71.3, 70.7, 70.2, 68.9, 67.2, 38.9, 27.3, 26.3, 26.1, 25.2, 24.5; ^{31}P NMR (120 MHz, $CDCl_3$) δ −3.3; ESI MS *m*/*z* $(M + Na)^+$ calcd 709.3194, obsd 709.3161.

4,6-Di-*O*-benzyl-2-*O*-pivaloyl-*β*-D-galactopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranoside 68. General procedure D with donor **67** (40.8 mg, 64.0 μmol), acceptor **22** (18.3 mg, 70.4 μmol), and TMSOTf (11.8 μL, 64.0 μmol) at −78 °C for 10 min followed by 30 min at −0 °C afforded 38.3 mg (79%) of **68** as a colorless oil after flash silica column chromatography (35% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39−7.27 (m, 10H), 5.48 (d, J = 5.0 Hz, 1H), 4.97 (dd, J = 8.0, 9.9 Hz, 1H), 4.72−4.69 (m, 2H), 4.58−4.47 (m, 3H), 4.45 (d, J = 8.0 Hz, 1H), 4.27 (dd, J = 2.5, 5.0 Hz, 1H), 4.21 (dd, J = 1.7, 8.0 Hz, 1H), 4.03 (dd, J = 4.7, 10.4 Hz, 1H), 3.94−3.89 (m, 2H), 3.70−3.58 (m, 5H), 2.40 (d, J = 9.6 Hz, 1H), 1.48 (s, 3H), 1.43 (s, 3H), 1.31 (app s, 6H), 1.23 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.2, 138.2, 137.8, 128.7, 128.7, 128.3, 128.1, 109.3, 108.7, 101.5, 96.4, 76.6, 75.6, 73.7, 73.5, 73.4, 73.4, 71.3, 70.7, 70.6, 69.0, 68.2, 67.2, 39.1, 27.3, 26.3, 26.1, 25.2, 24.5.

Dibutyl 3,4,6-Tri-*O*-benzyl-2-*O*-pivaloyl-*β*-D-glucopyranosyl-(1→6)-3,4-*O*-carbonyl-2-*O*-pivaloyl-α-D-galactopyranoside Phosphate 81. General procedure D with donor **1** (76.3 mg, 105 μmol), acceptor **80** (48.3 mg, 0.100 mmol), and TMSOTf (19.4 μL, 105 μmol) afforded 89.0 mg (89%) of **81** as a colorless oil after flash silica column chromatography (40% EtOAc/hexanes). $[\alpha]^{24}_D$ +6.7° (*c* 2.56, CH_2Cl_2); IR (thin film) 2962, 1817, 1740, 1138, 1068 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.25 (m, 13H), 7.17−7.16 (m, 2H), 5.67−5.64 (m, 1H), 5.12 (d, J = 8.5 Hz, 1H), 5.06−5.02 (m, 2H), 4.77 (d, J = 10.7 Hz, 1H), 4.75 (d, J = 11.0 Hz, 1H), 4.69 (d, J = 11.0 Hz, 1H), 4.58 (d, J = 11.9 Hz, 1H), 4.55−4.46 (m, 3H), 4.44 (d, J = 7.9 Hz, 1H), 4.09−3.99 (m, 5H), 3.86−3.84 (m, 1H), 3.74−3.66 (m, 4H), 3.56−3.52 (m, 1H), 1.67−1.61 (m, 4H), 1.44−1.40 (m, 4H), 1.22 (s, 9H), 1.19 (s, 9H), 0.95−0.91 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.1, 176.1, 153.3, 138.1, 138.0, 128.7, 128.6, 128.1, 128.0, 127.9, 127.6, 102.3, 94.1, 83.2, 77.8, 75.3, 75.2, 73.7, 73.2, 71.9, 71.5, 69.4, 68.9, 68.4, 66.9, 39.0, 32.3, 27.3, 27.2, 18.8, 13.8, 13.7; ^{31}P NMR (120 MHz, $CDCl_3$) δ −3.3; ESI MS *m*/*z* $(M + Na)^+$ calcd 1021.4321, obsd 1021.4356.

Acknowledgment. Financial support from the donors of the Petroleum Research Fund, administered by the American Chemical Society (ACS-PRF 34649-G1), for partial support of this research; the Mizutani Foundation for Glycoscience; the Kenneth M. Gordon Scholarship Fund (Fellowship for O.J.P.); the NIH (Biotechnology Training Grant for O.J.P.); Pfizer (ACS Division of Organic Chemistry-Pfizer Fellowship for O.J.P.); NSF (Predoctoral Fellowship for R.B.A.); Merck (Predoctoral Fellowship for E.R.P.); and Boehringer-Ingelheim (Predoctoral Fellowship for E.R.P.) is gratefully acknowledged. Funding for the MIT-DCIF Inova 501 was provided by NSF (Award No. CHE-9808061). Funding for the MIT-DCIF Avance (DPX) 400 was provided by NIH (Award No. 1S10RR13886-01). Funding for the MIT-DCIF Mercury 300 was provided by NSF (Award No. CHE-9808061) and NSF (Award No. DBI-9729592).

Supporting Information Available: Detailed experimental procedures and compound characterization data, including ^{1}H NMR and ^{13}C NMR spectral data for all described compounds and five additional schemes (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA016227R