Linear Synthesis of a Protected H-Type II Pentasaccharide Using Glycosyl Phosphate Building Blocks

Kerry Routenberg Love, Rodrigo B. Andrade, and Peter H. Seeberger*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

seeberg@mit.edu

Received July 30, 2001

A linear synthesis of a fully protected H-type II blood group determinant pentasaccharide utilizing glycosyl phosphate and glycosyl trichloroacetimidate building blocks is reported. Envisioning an automated solid-phase synthesis of blood group determinants, the utility of glycosyl phosphates in the stepwise construction of complex oligosaccharides, such as the H-type II antigen, is demonstrated. Installation of the central glucosamine building block required the screening of a variety of nitrogen protecting groups to ensure good glucosamine donor reactivity and protecting group compatibility. The challenge to differentiate C2 of the terminal galactose in the presence of other hydroxyl and amine protecting groups prompted us to introduce the 2-(azidomethyl)benzoyl group as a novel mode of protection for carbohydrate synthesis. The compatibility of this group with traditionally employed protecting groups was examined, as well as its use as a C2 stereodirecting group in glycosylations. The application of the 2-(azidomethyl)benzoyl group along with a systematic evaluation of glycosyl donors allowed for the completion of the pentasaccharide and provides a synthetic strategy that is expected to be generally amenable to the solid support synthesis of blood group determinants.

Introduction

Carbohydrates play an important role in many cellular processes, such as recognition, adhesion, and signaling between cells.[1] These processes may be initiated by carbohydrates existing as part of a glycoprotein or glycolipid on the cell surface. One class of glycolipids, glycosphingolipids (GSLs), is essential for cellular adhesion and recognition. The Lewis antigens, a group of fucosylated, ceramide containing GSLs, have been implicated in a variety of normal cellular adhesion processes, as well as adhesion associated with different disease states, including many types of metastatic cancer.[2,3]

Lewis blood group oligosaccharides (Figure 1) occur as cell surface carbohydrates on healthy leukocytes.[4] White blood cells, are essential for the repair of tissue in the vicinity of an injury and subsequent defense against possible microbial infection. The recruitment of leukocytes to a site of injury is brought about in a series of signaling steps. In response to the cytokines released by the damaged tissue, the endothelium expresses the two proteins E- and P-selectin on its surface. These selectins recognize carbohydrate ligands containing the Le^x and Le^a sequences, including sialylated and sulfated variants.[4,5]

In addition to their role in the inflammatory response, the Lewis antigens are present on the surface of the endothelium lining of the gastrointestinal tract[6] where they are the point of attachment for pathogenic bacteria.[7] *Heliobacter pylori* was shown to recognize the Le^b antigen in the gastric epithelium, and this interaction is essential for bacterial infection leading to gastric ulcers and adenocarcinoma.[8−10] The H-type II antigenic structure has been implicated in infection of humans with cholera.[11]

Lewis antigens like many other glycosphingolipids,[3] are tumor markers in human cancers including adenocarcinoma,[12,13] colorectal cancer,[14] pancreatic cancer,[15] and breast cancer.[16] Although GSLs are present in both cancerous and normal cellular tissue, their composition and density are altered in tumors.[2] Aberrant glycosylation in tumor cells helps to promote motility and adhesion necessary for tumor-cell invasion and progression.[2]

The widespread biological implications of Lewis antigens have rendered them targets of intense study. Since only small amounts of pure oligosaccharides can be obtained from natural sources due to microheterogeneity, chemical synthesis is the best way to procure appreciable

(1) Varki, A. *Glycobiology* **1993**, *3*, 97.
(2) Hakomori, S.; Zhang, Y. *Chem. Biol.* **1997**, *4*, 97.
(3) Hakomori, S. *Adv. Cancer Res.* **1989**, *52*, 257.
(4) Simanek, E.; McGarvey, G.; Jablanowski, J.; Wong, C.-H. *Chem. Rev.* **1998**, *98*, 833.
(5) Phillips, L.; Nudleman, E.; Gaeta, F.; Perez, M.; Singhal, A.; Hakomori, S.; Paulson, J. *Science* **1990**, *250*, 1130.
(6) Holgersson, J.; Joval, P.-A.; Breimer, M. *J. Biol. Chem.* **1991**, *110*, 120.
(7) Karlsson, K.-A. *Annu. Rev. Biochem.* **1989**, *58*, 309.
(8) Boren, T.; Falk, P.; Roth, K.; Larson, G.; Normark, S. *Science* **1993**, *262*, 1892.
(9) Applemelk, B.; Monteiro, M.; Martin, S.; Moran, A.; Vanderbrouke-Grauls, C. *Trends Microbiol.* **2000**, *8*, 565.
(10) Wang, G.; Ge, Z.; Rasko, D.; Taylor, D. *Mol. Microbiol.* **2000**, *36*, 1187.
(11) Newburg, D. S. *Current Med. Chem.* **1999**, *6*, 117.
(12) Hakomori, S.; Nudelman, E.; Levery, S.; Reiji, K. *J. Biol. Chem.* **1984**, *259*, 4672.
(13) Blaszczyk, M.; Pak, K.; Hereyl, M.; Sears, H.; Steplewski, Z. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 3552.
(14) Nishihara, S.; Hiraga, T.; Ikehara, Y.; Kudo, T.; Iwasaki, H.; Morozumi, K.; Akamatsu, S.; Tachikawa, T.; Hiashi, N. *Glycobiology* **1998**, *9*, 607.
(15) Tempero, M.; Uchida, E.; Takasaki, H., Burnett, D.; Steplewski, Z.; Pour, P. *Cancer Res.* **1987**, *47*, 5501.
(16) Ura, Y.; Dion, A.; Williams, C.; Olsen, B.; Redfield, E.; Ishida, M.; Herlyn, M.; Major, P. *Int. J. Cancer* **1992**, *50*, 57.

10.1021/jo015987h CCC: $20.00
Published on Web 11/06/2001

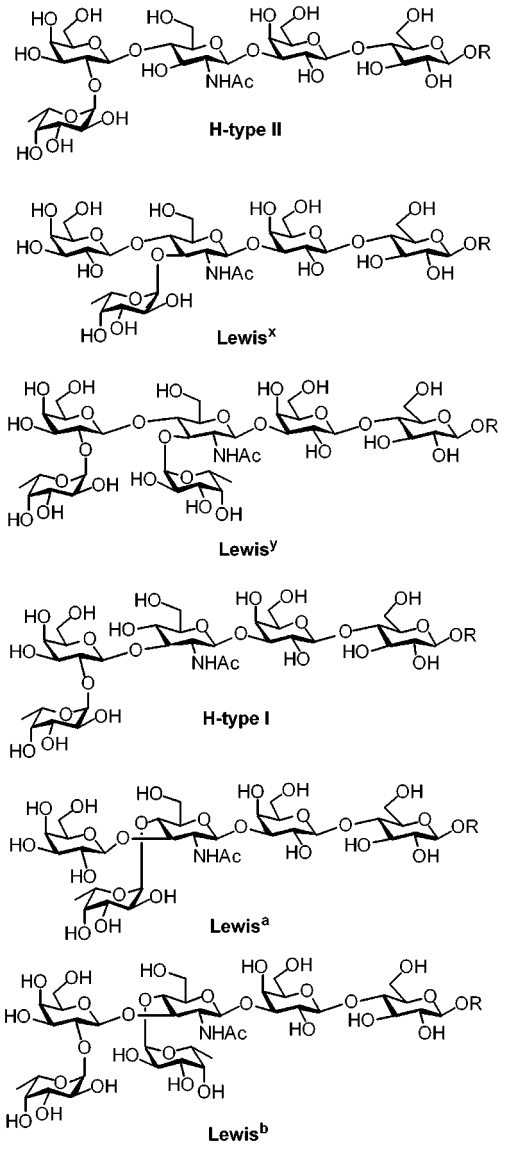


Figure 1. Lewis blood group oligosaccharides (R = ceramide).

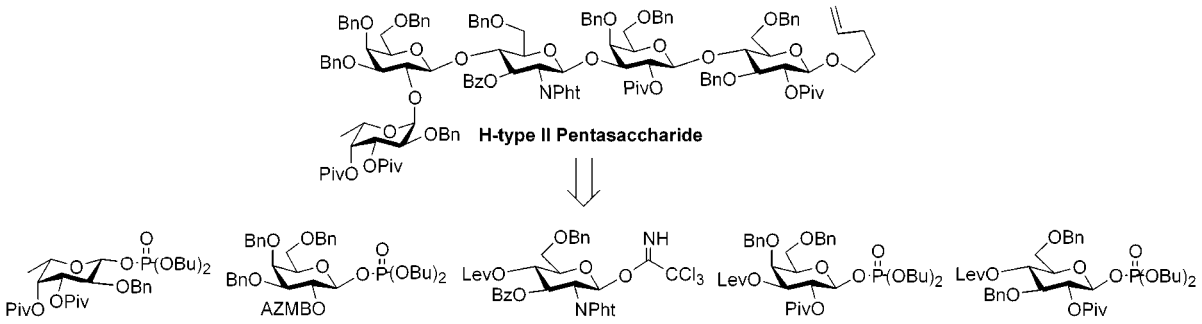
amounts of material for biological investigations. The Lewis blood group antigens have served as a synthetic challenge prompting the development of new methods for oligosaccharide synthesis since the seminal work by Lemieux in the mid 1970s.[17,18] Advances in oligosaccharide chemistry, including the development of novel glycosyl donors and a host of new protecting groups, have since eased the synthesis of complex, branched carbohydrates. Hasegawa reported the first synthesis of the sLe^x antigen in 1991, utilizing thiogylcosides for the installation of glycosidic linkages.[19] Thioglycosides also have been used in combination with selective protection in a one-pot, two-step glycosylation to construct the trimeric antigens in good yield.[20] Kahne and co-workers[21] synthesized the Le^a, Le^b, and Le^x trisaccharides using a single set of sulfoxide donors. Glycosyl phosphites served well in synthesis of the Le^x trisaccharide and SLe^x tetrasaccharides.[22,23] The entire family of tri- and tetrameric Lewis antigens, including SLe^x, were assembled via the glycal assembly method.[24] Schmidt disclosed Lewis antigen syntheses using trichloroacetimidate donors in a block coupling strategy to maximize convergence while exploring a host of amine-protecting groups for construction of the core glucosamine building block, including azide,[25] tetrachlorophthaloyl,[26] dimethylmaleoyl,[27] and trichloroethoxycarbonyl (Troc).[28]

Recently, we addressed the need for efficient glycosylating agents that could be prepared in differentially protected form. Using a one-pot procedure, glycosyl phosphates were readily prepared from glycals and shown to selectively and efficiently form a host of glycosidic linkages.[29−32] The scope of these building blocks in the context of the synthesis of complex carbohydrates in solution and on solid support has yet to be demonstrated. Another factor of crucial importance for the synthesis of complex carbohydrates is the differential protection of hydroxyl and amino groups. The exploration of novel modes of protection that are orthogonal to existing protecting groups and withstand glycosylation conditions is expected to increase synthetic flexibility in the preparation of branched structures.

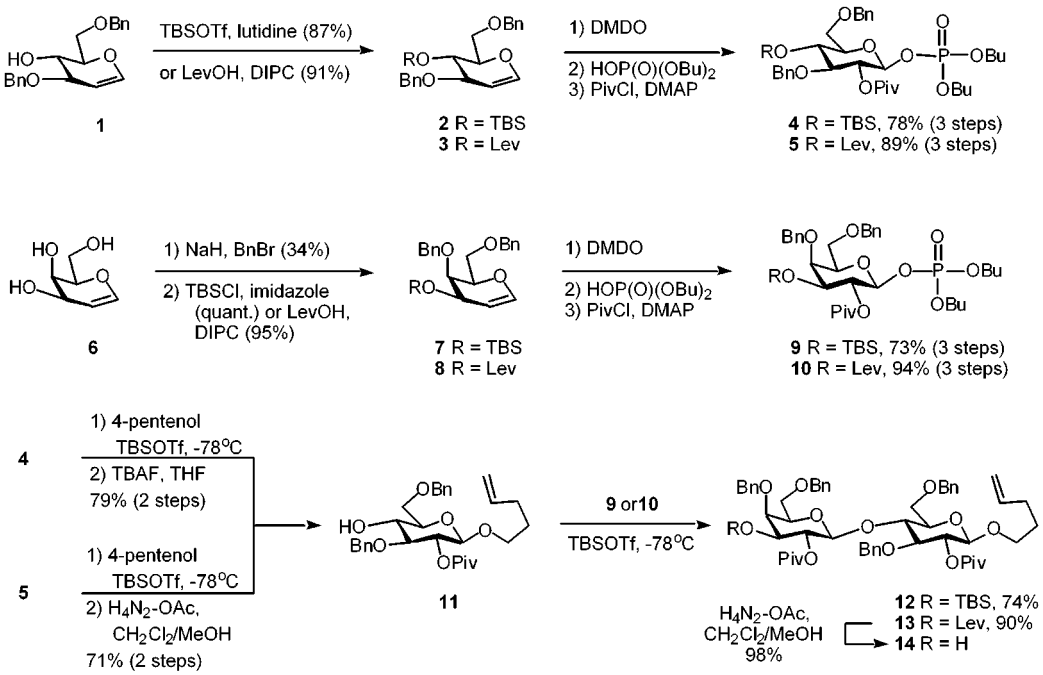
Here we describe the linear solution-phase synthesis of a fully protected H-type II pentasaccharide. Three major challenges were addressed during the course of the synthesis. A strictly linear strategy for the assembly of oligosaccharides from the reducing end was explored in anticipation of an automated solid-phase synthesis method following this paradigm. Second, glycal-derived glycosyl phosphates were utilized for the installation of glycosidic linkages. Finally, a variety of protecting groups for masking the amino group of the central glucosamine moiety were tested; a new 2-(azidomethyl)benzoate ester hydroxyl protecting group was employed as a participating, selectively removable entity. The compatibility of the 2-(azidomethyl)benzoate group with other commonly used protective groups in natural products synthesis, as well as its applicability as a stereodirecting group in glycosylation reactions with glycosyl phosphates, glycosyl

(17) Lemieux, R.; Driguez, H. *J. Am. Chem. Soc.* **1975**, *97*, 4063.
(18) Lemieux, R.; Driguez, H. *J. Am. Chem. Soc.* **1975**, *97*, 4069.
(19) Kameyama, A.; Ishida, H.; Kiso, M.; Hasegawa, A. *J. Carbohydr. Chem.* **1991**, *10*, 549.
(20) Tsukida, T.; Yoshida, M.; Kurokawa, K.; Nakai, Y.; Achiha, T.; Kiyoi, T.; Konda, H. *J. Org. Chem.* **1997**, *62*, 6876.
(21) Yan, L.; Kahne, D. *J. Am. Chem. Soc.* **1996**, *118*, 9239.
(22) Lin, C.-C.; Shimazaki, M.; Hack, M.-P.; Aoki, S.; Wang, R.; Kimura, T.; Ritzen, H.; Takayama, S.; Wu, S.-H.; Weitz-Schmidt, G.; Wong, C.-H. *J. Am. Chem. Soc.* **1996**, *118*, 6826.
(23) Kondo, H.; Aoki, S.; Ichikawa, Y.; Halcomb, R.; Ritzen, H.; Wong, C.-H. *J. Org. Chem.* **1994**, *59*, 864.
(24) (a) Danishefsky, S.; Gervay, J.; Peterson, J.; McDonald, F.; Koseki, K.; Oriyama, T.; Griffith, D. *J. Am. Chem. Soc.* **1992**, *114*, 8329. (b) Danishefsky, S.; Gervay, J.; Peterson, J.; McDonald, F.; Koseki, K.; Griffith, D.; Oriyama, T.; Marsden, S. *J. Am. Chem. Soc.* **1995**, *117*, 1940. (c) Danishefsky, S.; Behar, V.; Randolph, J.; Lloyd, K. *J. Am. Chem. Soc.* **1995**, *117*, 5701.
(25) (a) Bommer, R.; Kinzy, W.; Schmidt, R. *Liebigs Ann. Chem.* **1991**, 425. (b) Toepfer, A.; Schmidt, R. *Tetrahedron Lett.* **1992**, *33*, 5161. (c) Windmuller, R.; Schmidt, R. *Tetrahedron Lett.* **1994**, *35*, 7927. (d) Hummel, G.; Schmidt, R. *Tetrahedron Lett.* **1997**, *38*, 1173.
(26) (a) Castro-Palomino, J.; Schmidt, R. *Tetrahedron Lett.* **1995**, *36*, 5343. (b) Lay, L.; Manzoni, L.; Schmidt, R. *Carbohydr. Res.* **1998**, *310*, 157.
(27) (a) Aly, R.; Castro-Palomina, J.; Ibrahim, E.-S.; El-Ashry, E.-S.; Schmidt, R. *Eur. J. Org. Chem.* **1998**, *2305*, 5. (b) Aly, R.; Ibrahim, E.-S.; El-Ashry, E.-S.; Schmidt, R. *Carbohydr. Res.* **1999**, *316*, 121.
(28) Gege, C.; Oscarson, S.; Schmidt, R. *Tetrahedron Lett.* **2001**, *42*, 377.
(29) For a detailed description of necessary considerations when performing solid-phase oligosaccharide synthesis, see: Plante, O. J.; Palmacci, E. R.; Seeberger, P. H. *Science* **2001**, *291*, 1523.
(30) Hewitt, M. C.; Seeberger, P. H. *J. Org. Chem.* **2001**, *66*, 4233.
(31) Plante, O. J.; Andrade, R.; Seeberger, P. H. *Org. Lett.* **1999**, *1*, 211.
(32) Plante, O. J.; Palmacci, E. R.; Andrade, R. B.; Seeberger, P. H. *J. Am. Chem. Soc.* **2001**, *123*, 9545.

Scheme 1. Retrosynthesis of Protected H-Type II Pentasaccharide



Scheme 2. Synthesis of Lactose Disaccharides



trichloroacetimidates, and thioglycosides is discussed. The strategy described here for the synthesis of the H-type II pentasaccharide is representative of the assembly of blood group determinant oligosaccharides in solution and on solid support.

Results and Discussion

Our retrosynthetic analysis of the H-type II pentasaccharide followed a markedly different path from previous routes that had been striving for maximum convergence (Scheme 1). In keeping with our goal of automating solution-phase protocols in a solid-phase paradigm, five glycosyl donors served as building blocks for a sequential synthesis, adding one donor at a time to a growing oligosaccharide chain. Since this solution-phase synthesis was used as a study for future automation, we were cognizant of constraints in solid-phase oligosaccharide chemistry in developing reaction conditions for the incorporation of glycosyl phosphate and trichloroacetimidate donors.[29]

Synthesis of the Lactose Disaccharide. Two glycal-derived glycosyl phosphate donors were required to construct the lactose portion of the molecule (Scheme 2). The first donor, glucosyl phosphate **4**, was derived from readily available 3,6-di-*O*-benzyl glucal **1**.[33] Silylation of **1** yielded differentially protected glycal **2** ready for conversion to the corresponding glycosyl phosphate **4** via the one-pot procedure for phosphate preparation.[31]

Galactose phosphate building block **9** was prepared in a manner analogous to that for glucose donor **4**. Deprotection of peracetylated galactal was followed by regioselective benzylation of the C4 and C6 hydroxyls using benzyl bromide and sodium hydride at 0 °C.[34] Although the yield of the desired galactal was low (34%), three other synthetically useful galactals (tri-*O*-benzyl galactal (21%), 3,6-di-*O*-benzyl galactal (11%), and 3,4-di-*O*-benzyl galactal (10%)) were also obtained from this procedure after silica column chromatography. Protection of the 4,6-di-*O*-benzyl galactal as the silyl ether using TBSCl and imidazole afforded **7** and subsequent conversion to the glycosyl phosphate produced **9** in good yield.

A reducing end building block was prepared by coupling glucose phosphate **4** with 4-penten-1-ol under the agency of TBSOTf. Deprotection with TBAF yielded acceptor **11**, ready for coupling with galactose phosphate **9**. Union of acceptor **11** and galactosyl phosphate **9** furnished disaccharide **12** in good yield. Removal of the silyl ether in **12**, however, proved difficult and could not

(33) Park, T. K.; Kim, I. J.; Hu, S.; Bilodeau, M. T.; Randolph, J. T.; Kwon, O.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1996**, *118*, 11488.
(34) Kessler, H.; Kling, A.; Kottenhahn, M. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 425.

be achieved using standard conditions (TBAF/THF). ^{1}H NMR analysis of the crude product indicated the migration of the pivaloyl ester from the C2 to the C3 hydroxyl of galactose to form an inseparable mixture of disaccharides. A host of other deprotection conditions (TBAF/AcOH, 1% HCl/MeOH, sat. HCl/ether) failed to cleanly liberate disaccharide **12** from the C3 TBS ether.

Reevaluation of the synthetic route in light of difficulties with protecting group removal proved silyl ethers incompatible with both the solution-phase synthesis and subsequent solid-phase automation. Therefore, levulinate esters were chosen as the temporary protecting groups in the synthesis of both building blocks for the lactose portion of the Lewis antigens. Levulinate esters are readily removed in the presence of other esters with hydrazine.

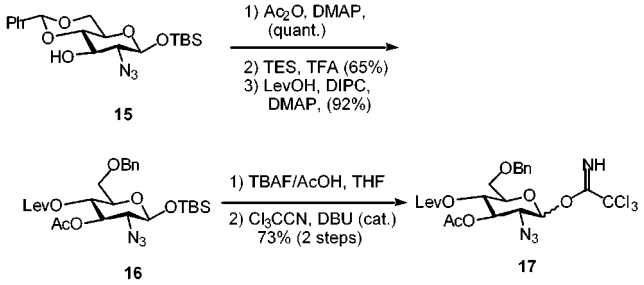
Glycosyl phosphates **5** and **10** were synthesized from glycals substituting the Lev group for the TBS (Scheme 2). Formation of disaccharide **13**, followed by treatment with hydrazine[35] yielded desired lactose disaccharide **14**. With **14** in hand, our focus turned to the construction of the β-(1 → 4) glucosamine linkage bridging the lactose and the antigenic portions of the Lewis oligosaccharides.

Development of a Glucosamine Building Block. The branched nature of the Lewis antigens around the central glucosamine residue mandates a diverse protecting group scheme for this monosaccharide building block. The choice of amine protecting group is essential since it determines the overall protecting group strategy. Previous syntheses of the Lewis antigens relied often on protection of the amine in the form of an azide,[25] owing to the stability of this group to basic conditions required for removal of esters typically used for temporary protection of hydroxyl groups. Following these examples, we initially chose 2-azido glucosamine donor **17** for installation of the β-(1 → 4) glucosamine linkage.

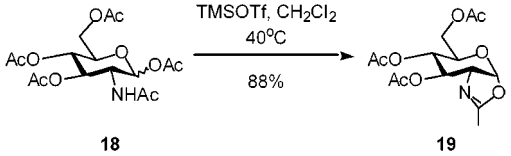
The synthesis commenced with known compound **15**[36] by acetylation of the C3 hydroxyl position and regioselective ring opening of the benzylidene using TES and TFA,[37] followed by protection of the C4 hydroxyl to yield differentially protected monosaccharide **16**. Removal of the anomeric silyl ether and reaction of the lactol with trichloroacetonitrile in the presence of catalytic DBU afforded **17**. Reaction of donor **17** with a series of model compounds using $BF_3{-}OEt_2$ at a range of temperatures was unsuccessful. Increased Lewis acidity of the activator had no effect on the outcome of the glycosylation reaction, but resulted in increased donor decomposition. The lack of success with the C2 azido donor, while disappointing, was not surprising in light of the fact that ester protected 2-azido glucosamines are only weakly active donors.[38] Donor activity can be increased by introduction of allyl and benzyl ethers as hydroxyl protecting groups, but was not possible in this case in light of the required branching pattern.

Since most naturally occurring glucosamines are *N*-acetates, we next investigated glucosamine oxazolines as glycosyl donors for installation of the β-(1 → 4) linkage

Scheme 3. Synthesis of a 2-Azido Glucosamine Donor



Scheme 4. Synthesis of Glucosyl Oxazoline Donor 19



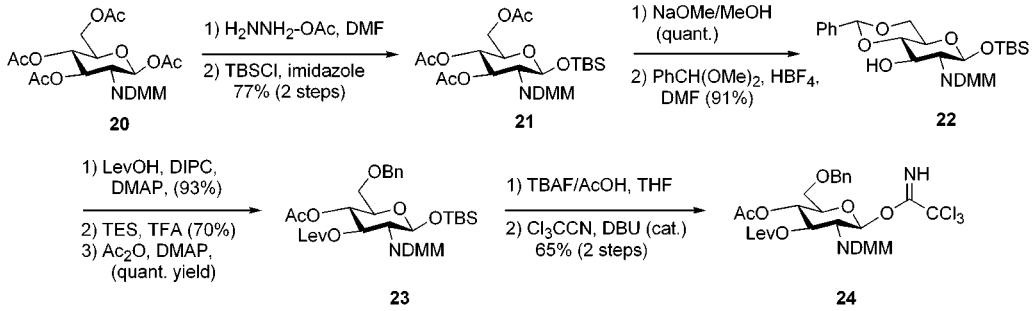
and the *N*-acetate in a single step. While oligosaccharide oxazolines are readily prepared using a variety of methods,[39] their synthetic utility has been limited. Model donor **19** (Scheme 4), derived from peracetylated glucosamine,[39] was activated with triflic acid[40] in the presence of several secondary alcohols as acceptors but yielded no coupling products.

Given the failure of both C2 azido glucosamine donor **17** and glucosyl oxazoline **19** to yield coupling products, additional nitrogen-protecting groups were investigated. Protection of the glucosamine nitrogen with a dimethylmaleoyl (DMM) group was recently reported to effectively mask the glucosamine nitrogen while ensuring *trans* glycosylation products.[27] Installation of the DMM group using dimethyl maleic anhydride, followed by global acetylation produced **20** (Scheme 5). Further elaboration of **20** in a manner analogous to that used in preparing **17** afforded **23**. Conversion of **23** to glycosyl trichloroacetimidate **24** proceeded in modest yield (65%). While **24** proved an acceptable donor in initial model studies, unsatisfactory yields (38% impure product) of trisaccharide **25** were obtained when coupling **24** with lactose acceptor **14** was attempted (Scheme 6). In addition, loss of the DMM group was encountered when coupled products were subjected to benzylation with benzyl bromide and sodium hydride. These factors, along with poor yields reported previously for the removal of DMM from complex oligosaccharides[27b] rendered the DMM group unattractive for amine protection in the context of this synthesis.

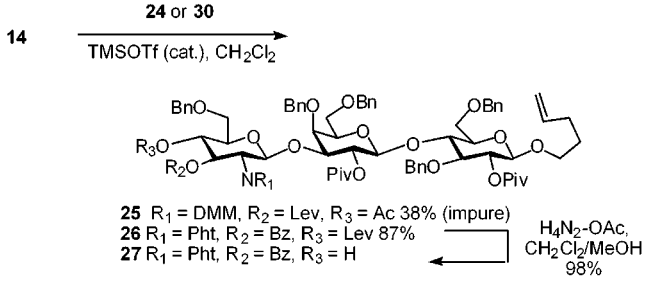
Inadequate performance of donors employing the aforementioned base-stable amine-protecting groups in coupling reactions with lactose acceptor **14** prompted us to consider the use of the phthaloyl group for amine protection. The phthaloyl group is commonly used for the protection of glucosamines in the context of oligosaccharide syntheses; it is readily installed and functions well as a C2 participating group to ensure β-selectivity of glycosylation reactions. Since the phthalimide group is

(35) Zhu, T.; Boons, G.-T. *Tetrahedron Asymm.* **2000**, *11*, 199.
(36) Topefer, A.; Kinzy, W.; Schmidt, R. R. *Liebigs Ann. Chem.* **1994**, 449.
(37) DeNinno, M. P.; Etienne, J. B.; Duplantier, K. C. *Tetrahedron Lett.* **1995**, *36*, 669.
(38) (a) Schmidt, R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212. (b) van Boeckel, C.; Beetz, T.; van Aelst, S. *Tetrahedron* **1984**, *40*, 4097.
(39) (a) Nakabayashi, S.; Warren, C.; Jeanloz, R. *Carbohydr. Res.* **1986**, *150*, C7. (b) Warren, C.; Jeanloz, R. *Carbohydr. Res.* **1980**, *92*, 85. (c) Strivastard, V. *Carbohydr. Res.* **1982**, *103*, 286.
(40) Heskamp, B.; der Marel, G.; van Boom, J. *J. Carbohydr. Chem.* **1995**, *14*, 1265.

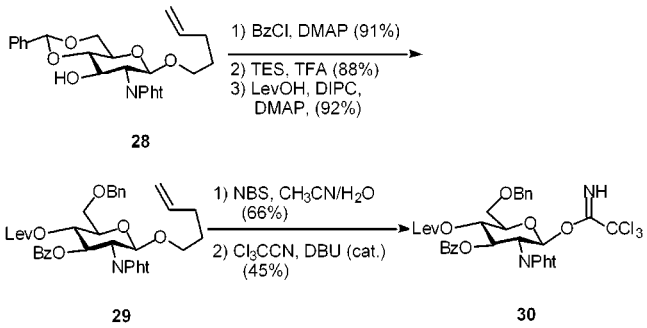
Scheme 5. Synthesis of a Dimethyl Maleoyl-Protected Donor



Scheme 6. Synthesis of H-Type II Core Trisaccharides



Scheme 7. Synthesis of a Pthalimide-Protected Glucosamine Donor

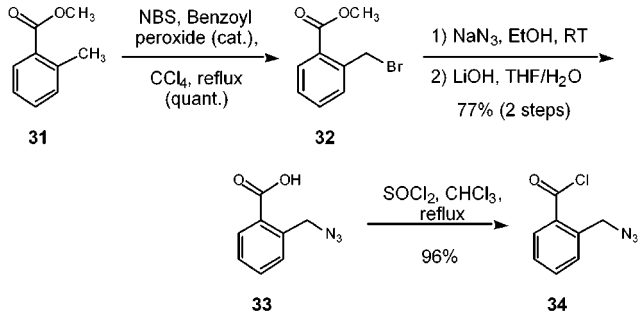


not completely stable under basic conditions, it was not selected initially in anticipation of problems during removal of ester protecting groups. In light of the development of a novel 2-(azidomethyl)benzoyl protecting group (vide infra) the use of base was no longer mandatory during the late stages of the synthesis and allowed for the use of phthaloyl as amine protecting group. Glycosyl trichloroacetimidate building block **30** was prepared using standard protecting group manipulations via known *n*-pentenyl glycoside intermediates[41] (Scheme 7). Glycosylation of lactose acceptor **14** employing glycosyl trichloroacetimidate **30** at −20°C afforded trisaccharide **26** in good yield (87%) albeit an excess of donor **30** (3 equiv) was required. Removal of the C4 levulinate ester using hydrazine acetate readily furnished trisaccharide **27** in 98% yield (Scheme 7).

Completion of the protected H-type II pentasaccharide required addition of a galactosyl donor capable of fashioning the β-(1 → 4) linkage between the galactose and glucosamine building blocks, followed by fucosylation of the C2 position of this newly installed galactose moiety. The nature of the C2 participating group was of crucial importance. Acetate, benzoate, and

(41) Handlon, A. L.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1993**, *115*, 3796.

Scheme 8. Synthesis of 2-(Azidomethyl)benzoyl (AZMB) Chloride



pivaloyl esters were disqualified as participating groups since the basic conditions required for their removal were not compatible with the phthalimide and ester groups present in the existing trisaccharide. The need for a participating group that could be selectively removed in the presence of other esters prompted us to develop the 2-(azidomethyl)benzoyl (AZMB) group[42] for carbohydrate synthesis.

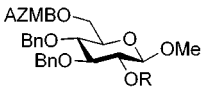
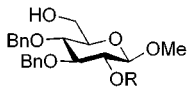
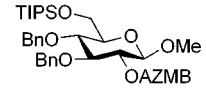
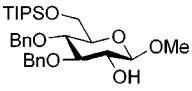
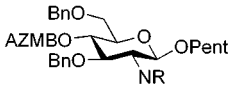
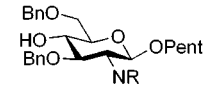
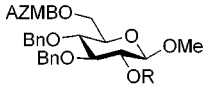
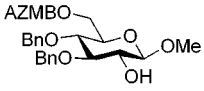
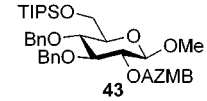
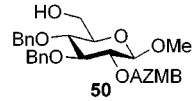
2-(Azidomethyl)benzoyl as an Orthogonal and Participating C2 Protecting Group for Oligosaccharide Assembly. The development of new protecting groups that are stable during glycosylation reactions and can be selectively removed in high yield under conditions orthogonal to other protecting groups are of utmost importance for oligosaccharide synthesis. Traditional modes of hydroxyl protection, such as esters or ethers, rely on varying degrees of basic or acidic conditions for their removal. Protective groups that may be removed using neutral conditions offer an additional dimension of orthogonality to existing groups. "Assisted cleavage" involves the unmasking of a latent functionality, which in turn facilitates the indirect removal of the protecting group.[43] Following this paradigm, reduction of the azide in the 2-(azidomethyl)benzoyl group to the corresponding amine induces intramolecular cyclization and expulsion of the hydroxyl moiety.[42]

Synthesis of the 2-(azidomethyl)benzoyl chloride (AZMB-Cl) commenced with bromination of commercially available methyl 2-methylbenzoate with NBS in the presence of benzoyl peroxide to afford **32** (Scheme 8). Displacement of the bromide with sodium azide, followed by saponification, yielded 2-azidomethyl benzoic acid **33**. Conversion of the **33** to AZMB-Cl **34** was achieved by treatment with

(42) (a) Wada, T.; Ohkabso, A.; Mochizuki, A.; Sekine, M. *Tetrahedron Lett.* **2001**, *42*, 1069. (b) Arasappan, A.; Fuchs, P. L. *J. Am. Chem. Soc.* **1995**, *117*, 177.

(43) Greene, T. W.; Wutz, P. G. M. In *Protecting Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999.

Table 1. Compatibility of AZMB with Commonly Used Hydroxyl and Amine Protecting Groups

Substrate	Product	Yield (%)
		
35 R = Ac **36** R = Lev **37** R = All **38** R = PMB	**39** R = Ac **40** R = Lev **41** R = All **42** R = PMB	92 96 91 91
		86
43	**44**	
		
45 R = Pht **46** R = Troc	**47** R = Pht **48** R = Troc	94 95
		
36 R = Lev **37** R = All **38** R = PMB	**49**	>99[a] 85[b] 90[c]
		90[d]
43	**50**	

Reaction conditions: [a]**36** (1 equiv) and hydrazine acetate (1 equiv) in $MeOH/CH_2Cl_2$ at room temperature for 40 min. [b]**37** (1 equiv); Pd(II)chloride (2.5 equiv), and sodium acetate (7 equiv) in acetic acid (90% aqueous) at 70 °C for 1.5 h. [c]**38** (1 equiv) and TFA (15 equiv.) at room temperature for 1 h. [d]**43** (0.1 M) in a 1:3:3 $TFA/THF/H_2O$ solution.

thionyl chloride. Installation of the AZMB group was achieved quantitatively by reaction of the free hydroxyl group with the AZMB-Cl and a stoichiometric amount of DMAP. Removal of AZMB is equally facile under Staudinger conditions for reduction of the azide (PBu_3 and water).

The compatibility of the AZMB group with traditionally used protecting groups for oligosaccharide synthesis was examined (Table 1). Differentially protected monosaccharides **35**−**38** were used to explore orthogonality with other modes of protection including esters, silyl ethers, *p*-methoxybenzyl (PMB) ethers, and allyl ethers. AZMB was not affected by conditions used for the removal of any of these groups. Similarly, all groups remained intact during AZMB removal from a model monosaccharide. Cleavage of AZMB in the presence of phthaloyl and trichloroethoxycarbonyl (Troc) amine protecting groups afforded high yields of deprotected monosaccharides **47** and **48**. The possibility of AZMB removal in the presence of acetate, levinulate, and phthaloyl groups was particularly notable since these protecting groups were used in preparation of the H-type II pentasaccharide.

In addition to its utility as a temporary protecting group, we intended to demonstrate the ability of the AZMB group to function as a stereodirecting entity during glycosylation reactions utilizing different glycosyl donors. Glycosyl phosphate **52**, thioglycoside **57**, and glycosyl trichloroacetimidate **59** each containing a C2 AZMB group were synthesized. The donors were activated following standard protocols[32,44,45] to fashion disaccharides **54** and **60**. The AZMB group proved stable to activation conditions and exclusively β-linked glycosidic products were obtained. Cleavage of AZMB from disaccharide **54** was carried out to highlight its utility as a removable C2 participating group.

Completion of the H-Type II Pentasaccharide. To achieve the completion of the desired pentasaccharide structure, a galactose unit had to be connected onto the C4 position of the central glucosamine followed by fucosylation of the C2 position of the newly installed galactose. In exploring this chemistry, we initially focused on a simpler trisaccharide model system **66** (Scheme 10) that constitutes the antigenic trisaccharide portion of H-type II without the reducing end lactose.

Given our success using the AZMB group as a C2 participating group with a variety of glycosyl donors, we chose to equip the galactose building block to be connected to the central glucosamine with this protective group. Galactosyl phosphate **61** was prepared via the one-pot procedure from tri-*O*-benzyl galactal.[31] Glycosylation of the C4 position of glucosamine **62** using galactose phosphate **61** proceeded in excellent yield to afford disaccharide **63** (Scheme 10). Removal of the C2 AZMB group did not cause any unexpected problems and furnished disaccharide acceptor **64**.

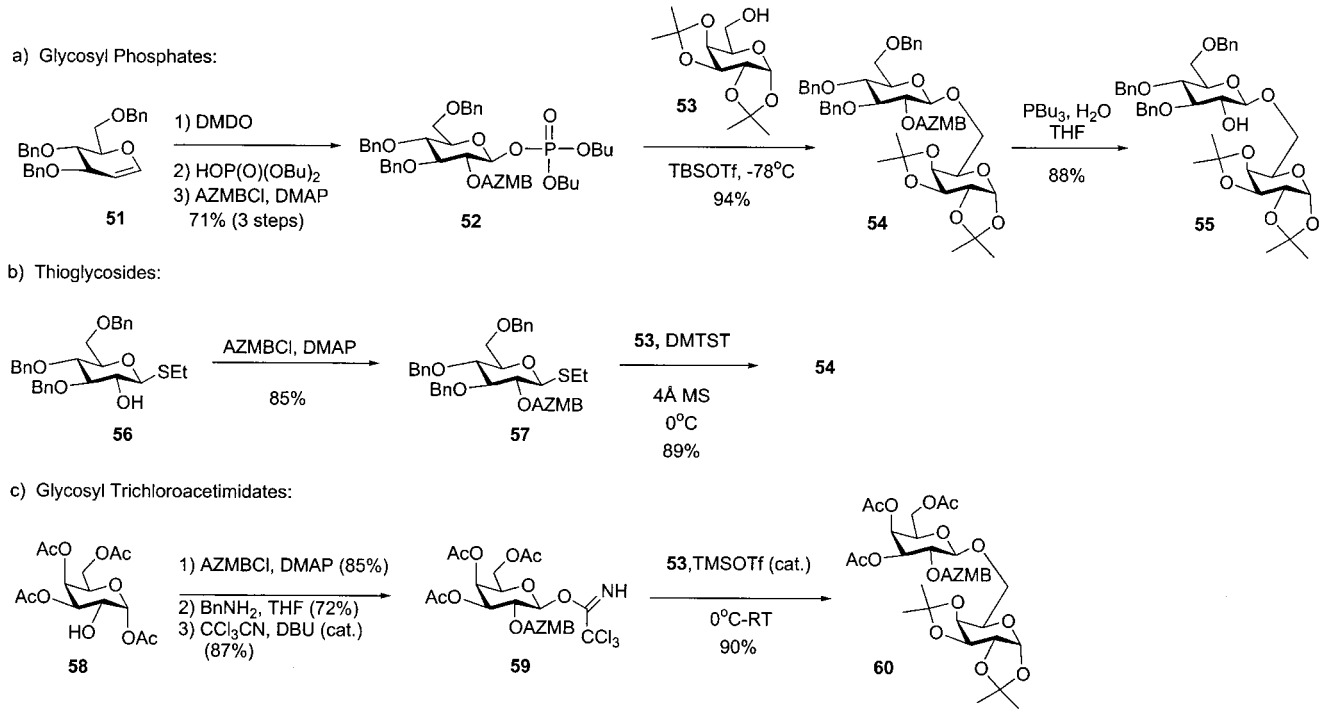
Fucosylation of the C2 hydroxyl of the terminal galactose is the final step for completion of H-type II oligosaccharides. As in most glycoconjugates, Lewis group antigens contain exclusively α-(1,2-*cis*) fucosidic linkages. This *cis* linkage poses a synthetic challenge since C2 participating groups cannot be employed.[46] The use of fucosyl phosphates[32] to establish this difficult linkage was addressed in the context of the Lewis antigen synthesis.

Fucosylation using dibutyl perbenzylated fucose phosphate[32] resulted as expected in an inseparable mixture of diasteriomers upon reaction with a model acceptor. Similar results had been obtained previously with other fully benzylated fucose donors such as fucosyl bromides,[47] trichloroacetimidates,[36] fluorides,[48] thioglycosides,[49] and *n*-pentenyl glycosides.[50] The problem of stereocontrol during fucosylation was addressed by introduction of a C4 ester protecting group following precedence with other glycosylating agents[47] to create fucosyl phosphate donor **65**.[32] Using model disaccharide **64** as acceptor, fucosylation with **65** (1.6 equiv) under the agency of stoichiometric amounts of TBSOTf provided protected H-type II trisaccharide **66** in excellent yield with complete α-selectivity. It is interesting to note that the corresponding fucosyl trichloroacetimidate donor failed to ensure complete α-selectivity in glycosylation reactions.[51]

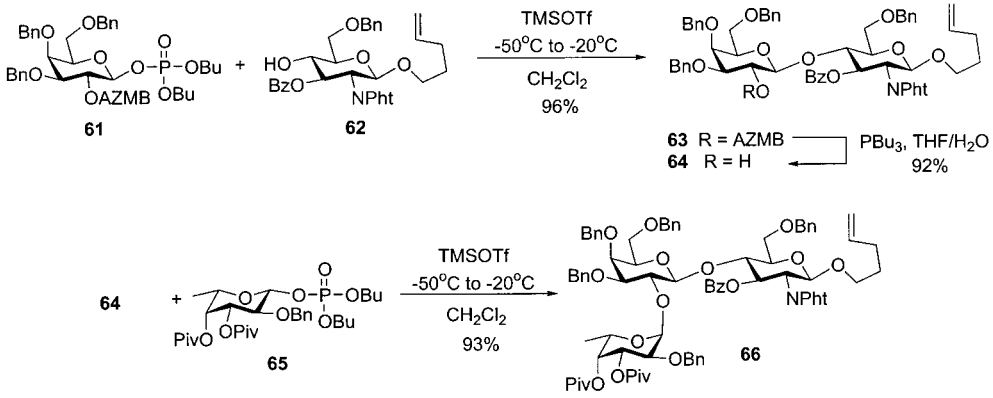
After establishing the feasibility of all synthetic transformations for the construction of the antigenic portion of the oligosaccharide target on a trisaccharide model,

(44) Garegg, P. J. *Adv. Carbohydr. Chem. Biochem.* **1997**, *52*, 179.
(45) Schmidt, R. R. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21.
(46) Flowers, H. M. *Carbohydr. Res.* **1983**, *119*, 75.
(47) Dejter-Juszynski, M.; Flowers, H. M. *Carbohydr. Res.* **1971**, *18*, 219.
(48) Nicolaou, K. C.; Hummel, C. W.; Bockovich, N. J.; Wong, C.-H. *J. Chem. Soc., Chem. Commun.* **1991**, *10*, 870.
(49) Lonn, H. *Carbohydr. Res.* **1995**, *139*, 105.
(50) Udodong, U. E.; Srinivas, R. C.; Fraser-Reid, B. *Tetrahedron* **1992**, *48*, 4713.
(51) Andrade, R. Dissertation, Massachusetts Institute of Technology, 2001.

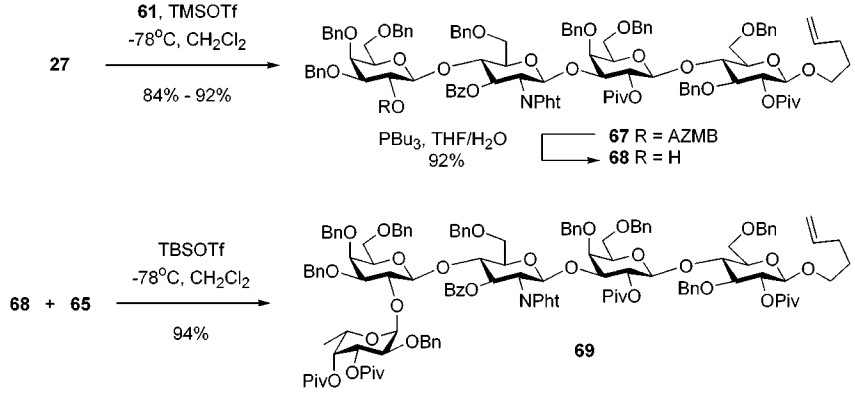
Scheme 9. Compatibility of AZMB with Activation Conditions for Glycosyl Donors and C2 Participation in Glycosylation



Scheme 10. Synthesis of H-Type II Trisaccharide 66



Scheme 11. Completion of the H-Type II Pentasaccharide



we focused our attention on the final steps of the pentasaccharide assembly (Scheme 11). Galactosylation of trisaccharide acceptor **27** afforded tetrasaccharide **67** in 92% yield. Reduction of the azide using Staudinger conditions cleanly removed the AZMB protecting group in **67** to yield desired tetrasaccharide acceptor **68**. Fucosylation of the tetrasaccharide **68** was carried out at low temperatures using phosphate **65** to yield 94% of the desired H-type II pentasaccharide **69** in fully protected form.

Conclusions

In summary, the solution-phase synthesis of a fully protected H-type II pentasaccharide was accomplished using a linear glycosylation strategy as a model for the automated synthesis of this molecule. This synthesis demonstrates the utility of glycal-derived glycosyl phosphates, along with glycosyl trichloroacetimidates, in the synthesis of complex oligosaccharides. Different protecting group patterns for masking the amino group of the central glucosamine moiety were tested. Introduction of a new hydroxyl protecting group, a 2-(azidomethyl)benzoate ester, allowed for the straightforward synthesis of the target pentasaccharide. The synthetic strategy described here for the H-type II pentasaccharide is exemplary for the preparation of blood group determinant oligosaccharides in solution and on solid support.

Experimental Section

General Methods. All chemicals were reagent grade and used as supplied unless otherwise noted. Dichloromethane (CH_2Cl_2), tetrahydrofuran (THF), and toluene were purified by a JT Baker Cycle-Tainer Solvent Delivery System. Analytical thin-layer chromatography was performed on E. Merck silica gel 60 F_{254} plates (0.25 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 Silicycle silica (230−400 mesh). ^{1}H NMR spectra were obtained using a Bruker-400 NMR spectrometer (400 MHz) or a Varian VXR-500 (500 MHz) and are reported in parts per million (δ) relative to $CDCl_3$ (7.27 ppm). Coupling constants (J) are reported in hertz. ^{13}C NMR spectra were obtained using a Bruker-400 NMR spectrometer (100 MHz) or a Varian VXR-500 (125 MHz) and are reported in δ relative to $CDCl_3$ (77.23 ppm) as an internal reference. ^{31}P spectra were obtained using a Varian VXR-300 NMR spectrometer (120 MHz) or a Varian VXR-500 (200 MHz) and are reported in δ relative to H_3PO_4 (0.0 ppm) as an external reference. Optical rotations were measured at 24 °C.

Dibutyl 3,6-Di-*O*-benzyl-4-*O*-levulinyl-2-*O*-pivaloyl-*β*-D-glucopyranosyl Phosphate 5. 3,6-Di-*O*-benzyl-4-*O*-levulinyl-glucal **3** (2.34 g, 5.5 mmol) was azeotroped with toluene (3 × 5 mL) and then dried under vacuum for 1 h. A solution of **3** in CH_2Cl_2 (40 mL) was cooled to 0 °C, and dimethyl dioxirane (103 mL of a 0.08 M solution in acetone, 8.3 mmol) was added. After 20 min, volatiles were removed under vacuum, and the resulting residue was dried for 10 min. The residue was redissolved in CH_2Cl_2 (40 mL) and cooled to −78 °C, and a solution of dibutyl phosphate (1.3 mL, 6.6 mmol) in CH_2Cl_2 (5 mL) was added dropwise over a period of 5 min. After 10 min, the reaction mixture was warmed to 0 °C, and DMAP (2.69 g, 22 mmol) and pivaloyl chloride (1.35 mL, 11 mmol) were added. The solution was left to slowly warm to room temperature and after 2 h was diluted with EtOAc (100 mL) and filtered through a plug of silica gel. The filtrate was concentrated, and the residue was purified by flash silica gel chromatography (25% EtOAc/hexanes) to yield 3.518 g (89%) of **5** as a white solid. $[\alpha]_D$: +0.98° (c = 2.10, CH_2Cl_2); IR (thin film): 2962, 2874, 1745, 1719, 1029 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 7.35−7.22 (m, 10 H), 5.28 (dd, J = 7.8, 7.1 Hz, 1 H), 5.22−5.17 (m, 2 H), 4.65 (d, J = 11.3 Hz, 1 H), 4.57 (d, J = 11.3 Hz, 1 H), 4.49 (dd, J = 13.3, 11.8 Hz, 2 H), 4.07−3.98 (m, 4 H), 3.80−3.72 (m, 2 H), 3.63−3.56 (m, 2 H), 2.67−2.50 (m, 2 H), 2.44−2.36 (m, 1 H), 2.32−2.24 (m, 1 H), 2.12 (s, 3 H), 1.65−1.53 (m, 4 H), 1.42−1.32 (m, 4 H), 1.21 (s, 9 H), 0.92 (t, J = 7.4 Hz, 3 H), 0.87 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): 206.3, 176.8, 171.6, 138.0, 137.9, 128.5, 128.5, 128.0, 127.8, 127.7, 96.7, 80.3, 74.1, 73.8, 73.7, 72.3, 70.3, 69.2, 68.3, 68.1, 39.0, 37.9, 32.3, 32.3, 32.2, 30.0, 28.0, 27.3, 18.8, 13.8, 13.7; ^{31}P NMR (120 MHz, $CDCl_3$): −2.34; ESI-MS: m/z (M + Na)$^+$ calcd 757.3329, obsd 757.3320.

4,6-Di-*O*-benzyl-3-*O*-levulinyl-galactal 8. Levulinic acid (0.77 g, 6.66 mmol) and DMAP (0.856 g, 6.97 mmol) were dissolved in 25 mL of CH_2Cl_2 and cooled to 0 °C. After 10 min, DIPC (0.99 mL, 6.34 mmol) was added with vigorous stirring. After five additional minutes, a solution of 4,6-di-*O*-benzyl galactal (2.07 g, 6.34 mmol) in 25 mL of CH_2Cl_2 was added to the levulinic acid solution via cannula, and the mixture was left to slowly warm to room temperature. After 12 h, the reaction mixture was diluted with EtOAc and flushed through a plug of silica gel. The filtrate was concentrated, and the residue was purified by flash silica gel chromatography (40% EtOAc/hexanes) to afford 2.57 g (95%) of **8** as a white solid. $[\alpha]_D$: −21.09° (c = 2.15, CH_2Cl_2); IR (thin film): 3030, 2916, 2870, 1719, 1645 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 7.36−7.27 (m, 10 H), 6.45 (dd, J = 6.2, 1.4 Hz, 1 H), 5.52−5.49 (m, 1 H), 4.78−4.74 (m, 2 H), 4.55 (d, J = 11.9 Hz, 2 H), 4.46 (d, J = 12.0 Hz, 1 H), 4.29−4.26 (m, 1 H), 4.03−4.01 (m, 1 H), 3.77 (dd, J = 10.3, 7.5 Hz, 1 H), 3.62 (dd, J = 10.3, 4.7 Hz, 1 H), 2.73−2.69 (m, 2 H), 2.58−2.55 (m, 2 H), 2.16 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): 206.5, 172.5, 145.8, 144.4, 138.0, 137.9, 128.7, 128.6, 128.6, 128.5, 128.3, 128.2, 128.0, 127.9, 127.8, 98.6, 75.6, 73.5, 73.2, 70.7, 67.9, 65.7, 38.0, 30.0, 28.2; ESI-MS: m/z (M + Na)$^+$ calcd 447.1784, obsd 447.1758.

Dibutyl 4,6-di-*O*-benzyl-3-*O*-levulinyl-2-*O*-pivaloyl-*β*-D-galactopyranosyl Phosphate 10. Galactal **8** (0.622 g, 1.46 mmol) was azeotroped with toluene (3 × 3 mL) and then dried under vacuum for 1 h. A solution of **8** in CH_2Cl_2 (15 mL) was cooled to 0 °C, and dimethyl dioxirane (27 mL of a 0.08 M solution in acetone, 2.19 mmol) was added. After 20 min, volatiles were removed under vacuum, and the resulting residue was dried for 10 min. The residue was redissolved in CH_2Cl_2 (40 mL) and cooled to −78 °C, and a solution of dibutyl phosphate (0.35 mL, 1.76 mmol) in CH_2Cl_2 (5 mL) was added dropwise over a period of 5 min. After 10 min, the solution was warmed to 0 °C, and DMAP (0.716 g, 5.86 mmol) and pivaloyl chloride (0.36 mL, 2.93 mmol) were added. After 30 min the reaction mixture was diluted with EtOAc (100 mL) and filtered through a plug of silica gel. The filtrate was concentrated, and the residue was purified by flash silica gel chromatography (30% EtOAc/hexanes) to yield 0.984 g (94%) of **10** as a white solid. $[\alpha]_D$: +16.22° (c = 1.57, CH_2Cl_2); IR (thin film): 2962, 2873, 1742, 1720, 1028 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 7.36−7.26 (m, 10 H), 5.45 (dd, J = 10.4, 7.9 Hz, 1 H), 5.24 (dd, J = 7.8, 7.1 Hz, 1 H), 5.03 (dd, J = 10.5, 3.1 Hz, 1 H), 4.76 (d, J = 11.6 Hz, 1 H), 4.43 (dd, J = 18.6, 11.8 Hz, 2 H), 4.05−3.95 (m, 4 H), 3.76 (dd, J = 6.8, 6.8 Hz, 1 H), 3.59 (dd, J = 7.1, 2.8 Hz, 1 H), 2.70−2.63 (m, 2 H), 2.48−2.43 (m, 2 H), 2.15 (s, 3 H), 1.62−1.57 (m, 4 H), 1.39−1.31 (m, 4H), 1.20 (s, 9 H), 0.91 (t, J = 7.5 Hz, 3 H), 0.88 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): 206.2, 177.1, 172.1, 138.2, 137.7, 128.6, 128.5, 128.3, 128.0, 128.0, 127.9, 96.9, 75.3, 74.1, 73.9, 73.8, 73.6, 69.4, 68.2, 68.1, 68.0, 67.7, 39.0, 37.7, 32.3, 32.2, 32.1, 29.9, 27.9, 27.9, 27.2, 18.8, 13.8, 13.7; ^{31}P NMR (120 MHz, $CDCl_3$): −2.45; ESI-MS: m/z (M + Na)$^+$ calcd 757.3329, obsd 757.3350.

***n*-Pentenyl 4-*O*-*tert*-Butyldimethylsilyl-3,6-di-*O*-benzyl-2-*O*-pivaloyl-*β*-D-glucopyranoside.** Phosphate **4** (0.350 g, 0.47 mmol) was azeotroped with toluene (3 × 3 mL) and dried under vacuum for 1 h. The residue was dissolved in CH_2Cl_2 (5 mL), along with 4-penten-1-ol (58 μL, 0.56 mmol), and the solution was cooled to −78 °C. TBSOTf (108 μL, 0.47 mmol) was added, and after 30 min the reaction mixture was neutralized with Et_3N and concentrated in vacuo. The residue was purified by flash silica gel chromatography (25% EtOAc/hexanes) to yield 262 mg (89%) of *n*-pentenyl 4-*O*-*tert*-butyldimethylsilyl-3,6-di-*O*-benzyl-2-*O*-pivaloyl-*β*-D-glucopyranoside. $[\alpha]_D$: +4.77 (c = 0.73, CH_2Cl_2); IR (thin film): 2947, 2851, 1742, 1140, 1057 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 7.35−7.21 (m, 10 H), 5.85−5.75 (m, 1 H), 5.09 (dd, J = 9.2, 8.0 Hz, 1 H), 5.01 (ddd, J = 18.7, 3.4, 1.6 Hz, 1 H), 4.97−4.94 (m, 1 H), 4.71−4.64 (m, 3 H), 4.54 (d, J = 12.3 Hz, 1 H), 4.43 (d, J = 7.9 Hz, 1 H), 3.88 (dt, J = 9.4, 6.5 Hz, 1 H), 3.78 (dd, J = 9.4, 6.5 Hz, 1 H), 3.65 (app t, J = 9.1 Hz, 1 H), 3.60−3.45 (m, 4 H), 2.13−2.07 (m, 2 H), 1.71−1.60 (m, 2 H), 1.13 (s, 9 H), 0.83 (s, 9 H), −0.04 (s, 3 H), −0.10 (s, 3 H); ^{13}C NMR (100 MHz,

$CDCl_3$) 177.0, 138.3, 138.3, 128.6, 128.3, 127.8, 127.4, 127.1, 115.0, 101.3, 83.5, 77.5, 74.7, 73.6, 71.3, 69.6, 69.1, 39.0, 30.3, 29.1, 27.3, 26.1, 18.2, −3.7, −4.7; ESI-MS: *m*/*z* $(M + Na)^+$ calcd 626.3639, obsd 626.3620.

***n*-Pentenyl 3,6-Di-*O*-benzyl-4-*O*-levulinyl-2-*O*-pivaloyl-*β*-D-glucopyranoside.** Phosphate **5** (0.220 g, 0.306 mmol) was azeotroped with toluene (3 × 3 mL) and dried under vacuum for 1 h. The residue was dissolved in CH_2Cl_2 (5 mL), along with 4-penten-1-ol (29 mg, 0.337 mmol), and the solution was cooled to −78 °C. TBSOTf (70 μL, 0.306 mmol) was added, and after 10 min the reaction mixture was neutralized with Et_3N and concentrated in vacuo. The residue was purified by flash silica gel chromatography (25% EtOAc/hexanes) to yield 160 mg (88%) of *n*-pentenyl 3,6-di-*O*-benzyl-4-*O*-levulinyl-2-*O*-pivaloyl-*β*-D-glucopyranoside. $[\alpha]_D$: −15.66° (*c* = 1.70, CH_2Cl_2); IR (thin film): 2975, 2879, 1743, 1722, 1151 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 7.34−7.21 (m, 10 H), 5.85−5.74 (m, 1 H), 5.12−5.07 (m, 2 H), 5.04−4.99 (m, 1 H), 4.98−4.95 (m, 1 H), 4.63 (d, *J* = 11.3 Hz, 1 H), 4.58−4.52 (m, 3 H), 4.43 (d, *J* = 7.9 Hz, 1 H), 3.88 (dt, *J* = 9.5, 6.4 Hz, 1 H), 3.76 (t, *J* = 9.4 Hz, 1 H), 3.65−3.57 (m, 3 H), 3.47 (dt, *J* = 9.5, 6.8 Hz, 1 H), 2.65−2.52 (m, 2 H), 2.41 (ddd, *J* = 17.3, 7.6, 6.0 Hz, 1 H), 2.29 (dt, *J* = 17.3, 6.4 Hz, 1 H), 2.12 (s, 3 H), 2.12−2.06 (m, 3 H), 1.71−1.63 (m, 2 H), 1.21 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): 206.4, 176.8, 171.8, 138.3, 138.2, 128.5, 128.5, 128.0, 127.8, 127.8, 127.7, 115.1, 101.4, 80.6, 73.8, 73.8, 73.5, 72.5, 71.0, 69.8, 69.4, 39.0, 37.9, 30.2, 30.0, 29.0, 28.0, 27.4; ESI-MS: *m*/*z* $(M + Na)^+$ calcd 633.3034, obsd 633.3018.

***n*-Pentenyl 3,6-Di-*O*-benzyl-2-*O*-pivaloyl-*β*-D-glucopyranoside 11.** Method A: A solution of *n*-pentenyl 4-*O*-*tert*-butyldimethylsilyl-3,6-di-*O*-benzyl-2-*O*-pivaloyl-*β*-D-glucopyranoside (1.75 g, 2.78 mmol) in THF (30 mL) was treated with TBAF (5.56 mL of a 1.0 M solution in THF, 5.56 mmol). After 30 min, the mixutre was diluted with water (50 mL), extracted with EtOAc (3 × 50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (20% EtOAc/hexanes) to yield 1.26 g (89%) of **11**. $[\alpha]_D$: −20.94° (*c* = 1.31, CH_2Cl_2); IR (thin film): 3492, 2922, 1733, 1130, 1071 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 7.38−7.28 (m, 10 H), 5.83−5.74 (m, 1 H), 5.06−4.98 (m, 2 H), 4.96 (dd, *J* = 10.3, 1.7 Hz, 1 H), 4.74 (d, *J* = 11.4 Hz, 1 H), 4.69 (d, *J* = 11.4 Hz, 1 H), 4.63 (d, *J* = 12.1 Hz, 1 H), 4.58 (d, *J* = 12.0 Hz, 1 H), 4.40 (d, *J* = 8.0 Hz, 1 H), 3.85 (dt, *J* = 9.5, 6.5 Hz, 1 H), 3.80−3.70 (m, 3 H), 3.58−3.44 (m, 3 H), 2.69 (d, *J* = 1.3 Hz, 1 H), 2.12−2.06 (m, 2 H), 1.70−1.62 (m, 2H), 1.22 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): 177.0, 138.4, 138.3, 138.0, 128.7, 128.7, 128.0, 128.0, 127.8, 115.1, 101.5, 83.0, 74.6, 74.3, 73.9, 72.8, 72.1, 70.6, 69.3, 39.0, 30.3, 29.0, 27.4; ESI-MS: *m*/*z* $(M + Na)^+$ calcd 535.2666, obsd 535.2645. Method B: A solution of hydrazine acetate (20 mg, 0.27 mmol) in MeOH (0.3 mL) was added to a solution of pentenyl 3,6-di-*O*-benzyl-4-*O*-levulinyl-2-*O*-pivaloyl-*β*-D-glucopyranoside (160 mg, 0.27 mmol) in CH_2Cl_2 (3 mL) and was stirred for 90 min at room temperature. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and concentrated in vacuo. The crude product was purified by flash silica gel chromatography (25% EtOAc/hexanes) to afford 109 mg (81%) of **11**.

***n*-Pentenyl 4,6-Di-*O*-benzyl-3-*O*-levulinyl-2-*O*-pivaloyl-*β*-D-galactopyranosyl-(1 → 4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-*β*-D-glucopyranoside 13.** Monosaccharide **11** (109 mg, 0.22 mmol) and glycosyl phosphate **10** (190 mg, 0.26 mmol) were azeotroped with toluene (3 × 3 mL) and then dried under vacuum for 1 h. Dichloromethane (5 mL) was added, the solution was cooled to −78 °C, and TBSOTf (55 μL, 0.242 mmol) was added. After 30 min, the mixture was neutralized with Et_3N and concentrated in vacuo. The residue was purified by flash silica gel chromatography (25% EtOAc/hexanes) to yield 175 mg (90%) of **13**. $[\alpha]_D$: −11.51° (*c* = 3.95, CH_2Cl_2); IR (thin film): 3027, 2977, 1745, 1723, 1138 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 7.38−7.24 (m, 13H), 7.23−7.19 (m, 4H), 7.16−7.13 (m, 1H), 7.09−7.06 (m, 2H), 5.85−5.74 (m, 1H), 5.35 (dd, *J* = 10.5, 7.9 Hz, 1H), 5.04−4.94 (m, 4H), 4.83 (dd, *J* = 10.5, 3.1 Hz, 1H), 4.74 (app t, *J* = 11.9 Hz, 2H), 4.52−4.44 (m, 4H), 4.36 (d, *J* = 8.0 Hz, 1H), 4.30 (d, *J* = 11.8 Hz, 1H), 4.17 (d, *J* = 11.8 Hz, 1H), 4.04 (app t, *J* = 9.2 Hz, 1H), 3.92 (d, *J* = 2.9 Hz, 1H), 3.86 (dt, *J* = 9.6, 6.4 Hz, 1H), 3.72−3.70 (m, 2H), 3.61 (app t, *J* = 9.1 Hz, 1 H), 3.49−3.41 (m, 2H), 3.37−3.26 (m, 3H), 2.69−2.65 (m, 2H), 2.45 (app t, *J* = 6.3 Hz, 2H), 2.15 (s, 3H), 2.13−2.06 (m, 2H), 1.68−1.63 (m, 2H), 1.18 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): 206.3, 177.0, 176.8, 172.1, 138.9, 138.6, 138.3, 138.1, 138.0, 128.7, 128.6, 128.4, 128.2, 128.2, 128.0, 128.0, 127.9, 127.7, 127.7, 127.1, 115.0, 101.5, 99.7, 81.0, 75.3, 75.2, 74.6, 74.5, 74.3, 73.7, 73.5, 73.3, 72.4, 70.2, 69.1, 68.0, 67.7, 39.0, 38.9, 37.7, 30.2, 29.9, 28.9, 27.9, 27.3; ESI-MS: *m*/*z* $(M + Na)^+$ calcd 1059.5076, obsd 1059.5043.

***n*-Pentenyl 4,6-Di-*O*-benzyl-2-*O*-pivaloyl-*β*-D-galactopyranosyl-(1 → 4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-*β*-D-glucopyranoside 14.** A solution of hydrazine acetate (14 mg, 0.19 mmol) in MeOH (0.3 mL) was added to a solution of **13** (175 mg, 0.17 mmol) in CH_2Cl_2 (3 mL), and the resulting solution was stirred for 90 min at room temperature. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and concentrated in vacuo. The crude product was purified by flash silica gel chromatography (25% EtOAc/hexanes) to yield 156 mg (98%) of 14. $[\alpha]_D$: −32.05° (*c* = 0.40, CH_2Cl_2); IR (thin film): 3529, 2969, 1736, 1137, 1064 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 7.36−7.13 (m, 20H), 5.85−5.74 (m, 1H), 5.04−4.92 (m, 5H), 4.76 (d, *J* = 12.1 Hz, 1H), 4.62 (s, 2H), 4.52 (d, *J* = 10.8 Hz, 1H), 4.47 (d, *J* = 12.1 Hz, 1H), 4.41 (d, *J* = 8.0 Hz, 1H), 4.37 (dd, *J* = 8.0 Hz, 1H), 4.35 (d, *J* = 11.8 Hz, 1H), 4.25 (d, *J* = 11.7 Hz, 1H), 4.03 (dd, *J* = 9.4, 9.3 Hz, 1H), 3.86 (dt, *J* = 9.6, 6.4 Hz, 1H), 3.79 (dd, *J* = 8.5, 3.4 Hz, 2H), 3.74 (dd, *J* = 10.7, 1.6 Hz, 1H), 3.59 (dd, *J* = 9.2, 9.2 Hz, 1H), 3.47−3.31 (m, 6H), 2.17 (d, *J* = 10.5 Hz, 1H), 2.12−2.06 (m, 2H), 1.70−1.62 (m, 2H), 1.20 (s, 9H), 1.17 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 176.8, 139.1, 138.3, 138.1, 137.9, 128.7, 128.7, 128.6, 128.2, 128.1, 128.0, 127.9, 127.6, 127.2, 115.0, 101.5, 99.7, 81.1, 76.7, 75.7, 75.5, 75.4, 74.5, 74.1, 73.8, 73.6, 73.3, 72.4, 69.1, 68.1, 67.8, 39.1, 38.9, 30.3, 29.0, 27.4, 27.3; ESI-MS: *m*/*z* $(M + Na)^+$ calcd 961.4714, obsd 961.4744.

***tert*-Butyldimethylsilyl 3-*O*-Acetyl-6-*O*-benzyl-2-deoxy-2-azido-4-*O*-levulinyl-*β*-D-glucopyranoside-3-*O*-benzoyl-6-*O*-benzyl-4-*O*-levulinoyl-2-deoxy-2-phthalimido-*β*-D-glucopyranosyl trichloroacetimidate 30.** To a stirred solution of **29** (1.90 g, 2.83 mmol) in 50 mL of CH_3CN/H_2O (8:1) was added NBS (1.51 g, 8.51 mmol), and the reaction mixture was stirred for 5 h at room temperature. After addition of $Na_2S_2O_3$ (7 mL of a saturated aqueous solution), the reaction mixture was partitioned between EtOAc and water and the aqueous phase was extracted once with EtOAc. The combined organic phases were washed with saturated $NaHCO_3$ and brine and dried over Na_2SO_4. Upon filtration and concentration, the crude product was purified by flash silica gel column chromatography (40% EtOAc/hexanes) to afford 3-*O*-benzoyl-6-*O*-benzyl-4-*O*-levulinoyl-2-deoxy-2-phthalimido-*β*-D-glucopyranoside (1.10 g, 66% yield), which was used immediately in the next step. To a stirred solution of 3-*O*-benzoyl-6-*O*-benzyl-4-*O*-levulinoyl-2-deoxy-2-phthalimido-*β*-D-glucopyranoside (1.10 g, 1.89 mmol) and trichloroacetonitrile (1.89 mL, 18.91 mmol) in 20 mL of CH_2Cl_2 under N_2 was added DBU (60 μL, 0.38 mmol). The reaction mixture was stirred at room temperature for 2 h and then concentrated. The crude product was purified by flash silica gel column chromatography (30% → 40% EtOAc/hexanes with 1% triethylamine) to afford **27** (620 mg, 45% yield). $[\alpha]_D$: +88.2° (*c* = 2.42, CH_2Cl_2); IR (thin film): 2921, 1779, 1720, 1681, 1386 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 8.68 (s, 1H), 7.85 (d, *J* = 7.5 Hz, 1H), 7.82−7.64 (m, 4H), 7.51 (m, 1H), 7.38−7.29 (m, 8H), 6.72 (d, *J* = 9.0 Hz, 1H), 6.17 (dd, *J* = 9.0, 10.5 Hz, 1H), 5.53 (t, *J* = 9.5 Hz, 1H), 4.80 (dd, *J* = 9.0, 10.7 Hz, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 4.59 (d, *J* = 12.0 Hz, 1H), 4.14 (m, 1H), 3.79 (dd, *J* = 3.0, 11.2 Hz, 1H), 3.71 (dd, *J* = 5.0, 11.2 Hz, 1H), 2.59−2.28 (m, 4H), 2.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 206.0, 171.4, 165.8, 160.7, 138.0, 134.4, 133.5, 131.4, 130.0, 128.8, 128.5, 128.2, 127.8, 123.8, 93.8, 74.5, 73.6, 71.2, 69.4, 68.2, 68.2, 53.9, 37.9, 29.6, 28.0; FAB-MS: *m*/*z* $(M + Na)^+$ calcd 767.0936, obsd 767.0932.

***n*-Pentenyl 3-*O*-Benzoyl-6-*O*-benzyl-4-*O*-levulinoyl-2-deoxy-2-phthalimido-*β*-D-glucopyranosyl-(1 → 3)-4,6-di-*O*-benzyl-2-*O*-pivaloyl-*β*-D-galactopyranosyl-(1 → 4)-3,6-**

di-*O*-benzyl-2-*O*-pivaloyl-*β*-D-glucopyranoside 26. To a stirred solution of **14** (77 mg, 0.082 mmol) and **30** (180 mg, 0.248 mmol) in 2.5 mL of CH_2Cl_2 under N_2 at −30 °C was added TMSOTf (8 μL, 0.044 mmol). The reaction was stirred at −30 °C for 5 min and warmed to −15 °C over the course of 10 min. Triethylamine (15 μL) was added, the solution was concentrated, and the crude product purified by flash silica column chromatography (30% → 40% EtOAc/hexanes) to afford **26** (107 mg, 87% yield). $[\alpha]_D$: −5.7° (c = 2.16, CH_2Cl_2); IR (thin film): 2869, 1730, 1387, 1267, 1144 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 7.79 (d, J = 7.0 Hz, 1H), 7.78−7.59 (m, 4H), 7.47 (t, J = 7.0 Hz, 1H), 7.38−7.21 (m, 26H), 7.07 (t, J = 8.0 Hz, 1H), 6.97 (t, J = 8.0 Hz, 1H), 6.14 (dd, J = 9.0, 10.7 Hz, 1H), 5.77 (m, 1H), 5.40 (d, J = 8.0 Hz, 1H), 5.31 (t, J = 9.5 Hz, 1H), 5.10 (dd, J = 5.0, 11.5 Hz, 1H), 5.03 (d, J = 11.0 Hz, 1H), 4.97 (m, 1H), 4.94 (m, 1H), 4.92 (m, 1H), 4.87 (d, J = 10.5 Hz, 1H), 4.70 (d, J = 12.0 Hz, 1H), 4.57−4.42 (m, 2H), 4.43 (d, J = 12.0 Hz, 1H), 4.28 (m, 2H), 4.17 (d, J = 11.5 Hz, 1H), 4.00 (t, J = 9.5 Hz, 2H), 3.94 (m, 1H), 3.86 (dd, J = 3.0, 10.0 Hz, 1H), 3.81 (m, 1H), 3.74 (dd, J = 7.5, 10.5 Hz, 1H), 3.67 (m, 2H), 3.46−3.38 (m, 3H), 3.33−3.27 (m, 3H), 2.62−2.23 (m, 4H), 2.03 (s, 3H), 2.12−2.01 (m, 2H), 1.65−1.59 (m, 2H), 1.14 (s, 9H), 1.09 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): 206.0, 176.6, 176.5, 171.5, 165.6, 139.1, 138.7, 138.3, 138.2, 137.9, 137.8, 134.0, 133.4, 130.0, 129.9, 128.8, 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.6, 127.3, 126.9, 123.7, 114.8, 101.3, 99.4, 98.1, 80.9, 77.6, 76.8, 75.3, 74.6, 74.3, 73.7, 73.5, 72.3, 70.6, 70.2, 69.0, 68.9, 68.4, 68.2, 55.3, 38.8, 38.7, 37.8, 30.1, 29.6, 28.8, 27.9, 27.2, 27.1; FAB-MS: m/z $(M + Na)^+$ calcd 1544.6551, obsd 1544.6523.

***n*-Pentenyl 3-*O*-Benzoyl-6-*O*-benzyl-2-deoxy-2-phthalimido-*β*-D-glucopyranosyl-(1 → 3)-4,6-di-*O*-benzyl-2-*O*-pivaloyl-*β*-D-galactopyranosyl-(1 → 4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-*β*-D-glucopyranoside 27.** To a stirred solution of **26** (54 mg, 0.036 mmol) in 2 mL of CH_2Cl_2 at room temperature under N_2 was added a solution of hydrazine acetate (90 μL, 0.40 M) in MeOH. The reaction mixture was stirred at room temperature for 3 h and concentrated, and the crude product was purified by flash silica column chromatography (50% EtOAc/hexanes) to afford **27** (49 mg, 98% yield). $[\alpha]_D$: −24.4° (c = 1.20, CH_2Cl_2); IR (thin film) 3481, 2868, 1726, 1386, 1272 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 7.87 (d, J = 7.0 Hz, 1H), 7.82−7.59 (m, 4H), 7.48 (t, J = 7.0 Hz, 1H), 7.42−7.20 (m, 26H), 7.08 (t, J = 8.0 Hz, 1H), 6.96 (t, J = 8.0 Hz, 1H), 5.99 (dd, J = 8.5, 11.0 Hz, 1H), 5.78 (m, 1H), 5.37 (d, J = 8.5 Hz, 1H), 5.12 (dd, J = 8.0, 10.0 Hz, 1H), 5.07 (d, J = 11.0 Hz, 1H), 5.01 (m, 1H), 4.95 (m, 1H), 4.87 (d, J = 10.5 Hz, 1H), 4.73 (d, J = 12.0 Hz, 1H), 4.64 (d, J = 12.0 Hz, 1H), 4.62 (d, J = 12.0 Hz, 1H), 4.50 (d, J = 11.0 Hz, 1H), 4.48 (m, 2H), 4.34−4.27 (m, 4H), 4.23 (d, J = 12.0 Hz, 1H), 4.03 (t, J = 9.0 Hz, 1H), 3.99−3.81 (m, 7H), 3.70 (m, 2H), 3.41−3.39 (m, 2H), 3.35−3.29 (m, 3H), 2.13−2.02 (m, 2H), 1.78 (bs, 1H), 1.70−1.59 (m, 2H), 1.16 (s, 9H), 1.13 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): 176.7, 176.6, 167.1, 139.2, 138.8, 138.2, 138.0, 137.7, 134.0, 133.6, 130.0, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.7, 127.3, 126.9, 123.8, 114.9, 101.3, 99.5, 98.0, 81.0, 77.4, 75.4, 75.2, 75.0, 74.7, 74.4, 74.0, 73.9, 73.8, 73.7, 73.6, 72.5, 72.3, 71.9, 70.0, 68.9, 68.4, 68.3, 55.0, 38.9, 38.8, 30.1, 28.9, 27.3, 27.2, 27.1; FAB-MS: m/z $(M + Na)^+$ calcd 1446.6183, obsd 1446.6122.

2-(Azidomethyl)benzoic Acid 33. To a stirred solution of methyl 2-methyl benzoate (4.29 g, 28.56 mmol,) in 100 mL of CCl_4 were added NBS (5.1 g, 28.65) and a catalytic amount of benzoyl peroxide (55 mg, 0.227 mmol). The reaction mixture was refluxed for 24 h and allowed to cool to room temperature. Filtration and concentration afforded crude bromide **32**, which was taken up in 80 mL of anhydrous EtOH before NaN_3 (1.86 g, 28.65 mmol) was added, and the reaction mixture was stirred for 48 h at room temperature under N_2. The reaction was quenched with brine and extracted twice with EtOAc. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash silica column chromatography (2% → 5% → 10% EtOAc/hexanes) to afford 4.58 g (84% for two steps) of methyl 2-(azidomethyl)-benzoate. IR (thin film): 2952, 2109, 1739, 1434, 1263 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 8.01 (d, J = 7.0 Hz, 1H), 7.51 (t, J = 7.5 Hz, 1H), 7.47 (d, J = 7.5 Hz, 1H), 7.38 (t, J = 7.5 Hz, 1H), 4.79 (s, 2H), 3.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 167.1, 137.3, 132.7, 131.6, 129.7, 128.7, 128.1, 53.11, 52.21; FAB-MS: m/z $(M + Na)^+$ calcd 214.0587, obsd 214.0591. To a stirred solution of methyl 2-(azidomethyl)benzoate (15.0 g, 78.45 mmol) in 192 mL of THF/H_2O (10:1) was added LiOH·H_2O (16.2 g, 41.96). The reaction mixture was stirred at room temperature for 60 h, diluted with H_2O, and extracted twice with CH_2Cl_2. The aqueous phase was acidified with 2 N HCl, and the precipitated acid was extracted three times with CH_2Cl_2. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated to afford **33** (13.5 g, 97%) in analytically pure form. Characterization data were consistent with that previously reported.[42]

2-(Azidomethyl)benzoyl Chloride 34. 2-(Azidomethyl)-benzoic acid **33** (10.45 g, 59 mmol) was dissolved in $CHCl_3$ (100 mL), and thionyl chloride (12.9 mL, 177 mmol) was added. The reaction mixture was heated to reflux for 5 h, cooled, and concentrated in vacuo using a base trap. The resulting residue was coevaporated with toluene (3 × 15 mL) to yield 11.15 g of **34** (97%). IR (thin film): 3071, 2962, 2105, 1769, 1201 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 8.33 (dd, J = 8.0, 1.2 Hz, 1 H), 7.70 (td, J = 7.6, 1.3 Hz, 1 H), 7.61 (dd, J = 7.6, 0.5 Hz, 1 H), 7.54 (td, J = 7.9, 1.3 Hz, 1 H), 4.76 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): 138.5, 135.2, 134.7, 131.7, 130.0, 129.7, 128.8, 53.2; ESI-MS: $m/z = (M + Na)^+$ calcd 195.0200, obsd 195.0217.

Protection of Alcohols with AZMB. General Procedure A. A solution of the alcohol (1.0 equiv) in CH_2Cl_2 (10 mL/mmol alcohol) was stirred at room temperature, and DMAP (2 equiv) was added, followed by a solution of the 2-(methylazido)benzoyl (AZMB) chloride 34 (1.5 equiv) in CH_2Cl_2 (1 mL). After 10 min, the reaction mixture was diluted with CH_2Cl_2 and washed twice with saturated aqueous $NaHCO_3$ and once with water. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by flash silica gel column chromatography.

Cleavage of 2-(Azidomethyl)benzoate Esters. General Procedure B. To a solution of the ester in THF (10 mL/mmol ester) was added water (5 equiv), followed by tributyl phosphine (3 equiv). After 30 min, the reaction mixture was diluted with CH_2Cl_2 and washed once with saturated aqueous $NaHCO_3$ and twice with water. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by flash silica gel column chromatography.

Methyl 2-*O*-Acetyl-6-*O*-(2-(azidomethyl)benzoyl)-3,4-di-*O*-benzyl-*β*-D-glucopyranoside 35. 6-(2-(Azidomethyl)benzoyl)-*O*-3,4-di-*O*-benzyl-*β*-D-glucopyranoside **49** (117 mg, 0.22 mmol) was dissolved in CH_2Cl_2 (2 mL), and DMAP (29 mg, 0.26 mmol) and acetic anhydride (25 μL, 0.26 mmol) were added. After 1 h at room temperature, the reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with saturated aqueous $NaHCO_3$ (20 mL) and water (20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash silica gel column chromatography (30% EtOAc/hexanes) to yield 120 mg of **35** (95%). $[\alpha]_D$: +50.52° (c = 3.62, CH_2Cl_2); IR (thin film): 3031, 2884, 2102, 1747, 1719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 7.99 (app d, J = 7.8 Hz, 1 H), 7.57 (app t, J = 7.5 Hz, 1 H), 7.49 (app d, J = 7.5 Hz, 1 H), 7.42 (app t, J = 7.6 Hz, 1 H), 7.35−7.23 (m, 10 H), 5.04−5.00 (m, 1 H), 4.86−4.74 (m, 4 H), 4.71 (d, J = 11.3 Hz, 1 H), 4.63−4.55 (m, 2 H), 4.45 (dd, J = 11.9, 4.4 Hz, 1 H), 4.34 (d, J = 7.9 Hz, 1 H), 3.75−3.7 (m, 3 H), 3.46 (s, 3 H), 2.00 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): 169.9, 166.4, 138.0, 137.6, 137.5, 133.2, 131.5, 130.0, 128.7, 128.7, 128.5, 128.4, 128.4, 128.3, 128.1, 102.0, 83.2, 77.8, 75.4, 73.2, 63.5, 57.0, 53.2, 21.2; ESI-MS: m/z $(M + Na)^+$ calcd 598.2160, obsd 598.2168.

Methyl 2-*O*-Acetyl-3,4-di-*O*-benzyl-*β*-D-glucopyranoside 39. General procedure B using methyl 2-*O*-acetyl-6-*O*-(2-(azidomethyl)benzoyl)-3,4-*O*-benzyl-*β*-D-glucopyranoside **35** (68 mg, 0.118 mmol), water (10 μL, 0.59 mmol), and PBu_3 (90 μL, 0.355 mmol) afforded **39** (45 mg, 92%) after purification

by flash silica gel column chromatography (25% EtOAc/hexanes). Characterization data were consistent with that previously reported.[54]

Dibutyl 2-*O*-(2-(Azidomethyl)benzoyl)-3,4,6-tri-*O*-benzyl-*β*-D-glucopyranosyl Phosphate 52. 3,4,6-Tri-*O*-benzyl glucal (402 mg, 0.965 mmol) was azeotroped with toluene (3 × 5 mL) and then dried under vacuum for 1 h. A solution of the glucal in CH_2Cl_2 (10 mL) was cooled to 0 °C, and dimethyl dioxirane (20 mL of a 0.08 M solution in acetone, 1.44 mmol) was added. After 20 min, volatiles were removed under vacuum, and the resulting residue was dried for 10 min. The residue was redissolved in CH_2Cl_2 (10 mL) and cooled to −78 °C, before a solution of dibutyl phosphate (0.23 mL, 1.16 mmol) in CH_2Cl_2 (5 mL) was added dropwise over a period of 5 min. After 10 min, the solution was warmed to 0 °C, and DMAP (472 mg, 3.86 mmol) and AZMB chloride (377 mg, 1.93 mmol) were added. After 10 min, the reaction mixture was diluted with EtOAc (100 mL) and filtered through a plug of silica gel. The filtrate was concentrated, and the residue was purified by flash silica gel chromatography (20% EtOAc/hexanes) to yield **52** (547 mg, 71%) as a white solid. $[\alpha]_D$ +17.26° (c = 1.04, CH_2Cl_2); IR (thin film): 2961, 2102, 1729, 1076, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 8.01 (dd, J = 7.9, 1.1 Hz, 1 H), 7.59 (td, J = 7.8, 1.3 Hz, 1 H), 7.55−7.53 (m, 1 H), 7.41−7.30 (m, 9 H), 7.23−7.21 (m, 2 H), 7.15−7.10 (m, 5 H), 5.42−5.33 (m, 2 H), 4.86−4.79 (m, 3 H), 4.73 (d, J = 15.1 Hz, 1 H), 4.65−4.62 (m, 3 H), 4.55 (d, J = 12.0 Hz, 1 H), 4.09−4.03 (m, 2 H), 3.94−3.89 (m, 1 H), 3.83−3.72 (m, 4 H), 3.70−3.65 (m, 1 H), 1.63−1.58 (m, 2 H), 1.39−1.27 (m, 4 H), 1.08−1.03 (m, 2 H), 0.89 (t, J = 7.4 Hz, 3 H), 0.69 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): 164.9, 138.4, 138.0, 137.9, 137.7, 133.3, 131.4, 129.4, 128.7, 128.6, 128.4, 128.2, 128.1, 128.1, 127.9, 96.7, 82.3, 77.6, 75.9, 75.3, 75.3, 73.7, 73.5, 73.4, 68.3, 68.2, 68.1, 53.1, 32.2, 32.1, 32.0, 31.9, 18.7, 18.4, 13.7, 13.5; ^{31}P NMR (120 MHz, $CDCl_3$): −2.21; ESI-MS: m/z $(M + Na)^+$ calcd 824.3283, obsd 824.3299.

2-*O*-(2-(Azidomethyl)benzoyl)-3,4,6-tri-*O*-benzyl-*β*-D-glucopyranosyl-(1 → 6)-1,2;3,4-diisopropylidene-α-D-galactopyranoside 54. Method A: Phosphate **52** (75 mg, 0.094 mmol) and 1,2;3,4-diisopropylidene-α-D-galactopyranoside **53** (21 mg, 0.079 mmol) were coevaporated in toluene (3 × 1 mL) and then dried under vacuum for 1 h. After addition of CH_2Cl_2 (1 mL), the solution was cooled −78 °C, and TBSOTf (20 μL, 0.087 mmol) was added. After 10 min, the mixture was neutralized with Et_3N and concentrated in vacuo. The residue was purified by flash silica gel chromatography (10% EtOAc/hexanes) to yield **53** (75 mg, 94%). $[\alpha]_D$ −22.76° (c = 1.96, CH_2Cl_2); IR (thin film): 3030, 2933, 2102, 1728, 1073 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 7.96 (dd, J = 7.6, 1.1 Hz, 1 H), 7.59−7.53 (m, 2 H), 7.40−7.29 (m, 9 H), 7.22−7.13 (m, 7 H), 5.39 (d, J = 5.0 Hz, 1 H), 5.31−5.27 (m, 1 H), 4.85−4.77 (m, 4 H), 4.70−4.65 (m, 3 H), 4.62−4.58 (m, 2 H), 4.49 (dd, J = 8.4, 2.4 Hz, 1 H), 4.22 (dd, J = 5.0, 2.4 Hz, 1 H), 4.16 (dd, J = 7.9, 1.8 Hz, 1 H), 4.07 (dd, J = 11.1, 4.0 Hz, 1 H), 3.90−3.88 (m, 1 H), 3.84−3.82 (m, 2 H), 3.80−3.79 (m, 2 H), 3.71 (dd, J = 11.1, 7.2 Hz, 1 H), 3.58−3.56 (m, 1 H), 1.27 (s, 3 H), 1.21 (s, 3 H), 1.20 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): 165.5, 138.3, 138.1, 138.0, 132.7, 131.5, 129.0, 128.8, 128.6, 128.4, 128.2, 128.0, 127.8, 109.4, 108.6, 101.5, 96.3, 82.9, 78.2, 75.4, 75.2, 73.8, 73.7, 71.3, 70.7, 70.5, 68.8, 67.6, 53.2, 26.1, 25.8, 25.6, 24.4; ESI-MS: m/z $(M + Na)^+$ calcd 874.3521, obsd 874.3496. Method B: Thiogylcoside 57 (85 mg, 0.13 mmol) and galactopyranoside **53** (41 mg, 0.16 mmol) were coevaporated in toluene (3 × 1 mL) and then dried under vacuum for 1 h. The residue was dissolved in CH_2Cl_2 (1 mL) and activated powdered molecular sieves (4 Å, 200 mg) were added to the solution. The reaction mixture was cooled to 0 °C and NIS (36 mg, 0.16 mmol) was added, followed by triflic acid (2 μL, 0.016). After 10 min, the reaction mixture was neutralized by addition of Et_3N, filtered through a plug of silica, and concentrated in vacuo. The crude product was purified by flash silica gel column chromatography (25% EtOAc/hexanes) to yield **54** (97 mg, 88%).

3,4,6-Tri-*O*-benzyl-*β*-D-glucopyranosyl-(1 → 6)-1,2;3,4-diisopropylidene-α-D-galactopyranoside 55. General procedure B using disaccharide **54** (121 mg, 0.142 mmol), water (13 μL, 0.71 mmol), and PBu_3 (100 μL, 0.426 mmol) yielded **55** (86 mg, 88%) after purification by flash silica gel column chromatography (15% EtOAc/hexanes). Characterization data were consistent with previously reported data.[55]

Dibutyl 2-*O*-(2-(Azidomethyl)benzoyl)-3,4,6-tri-*O*-benzyl-*β*-D-galactopyranoside Phosphate 61. To a stirred solution of tri-*O*-benzyl-D-galactal (505 mg, 1.214 mmol) in 10 mL of CH_2Cl_2 at 0 °C under N_2 was added a solution of dimethyldioxirane in acetone (23 mL, 0.08 M). The reaction mixture was stirred for 15 min at 0 °C, and the volatiles were removed in vacuo. After 1 h under vacuum at 0 °C, 10 mL of CH_2Cl_2 were added, and the reaction mixture was cooled to −78 °C and stirred for 10 min. To the reaction vessel was added a solution of dibutyl phosphate (277 μL, 1.396 mmol) in CH_2Cl_2 (2 mL) dropwise over 5 min and the reaction mixture was warmed to 0 °C over 5 min. After stirring for 10 min at 0 °C, DMAP (445 mg, 3.642 mmol) was added followed by a solution of AZMB chloride (475 mg, 2.428 mmol) in CH_2Cl_2 (2 mL) dropwise over 5 min. The reaction was warmed to room temperature and stirred for 3 h. The reaction mixture was diluted with hexanes to precipitate DMAP salts, filtered, and washed several times with 40% EtOAc/hexanes. The crude product was concentrated and purified by flash silica column chromatography (40% EtOAc/hexanes with 1% triethylamine) to afford of **61** (603 mg, 62% yield). $[\alpha]_D$: +24.2° (c =3.46, CH_2Cl_2); IR (thin film) 2960, 2102, 1729, 1259, 1082 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 8.02 (d, J = 7.7 Hz, 1H), 7.61−7.54 (m, 3H), 7.19−7.04 (m, 16H), 5.72 (dd, J = 8.0, 10.0 Hz, 1H), 5.35 (t, J = 8.0 Hz, 1H), 5.02 (d, J = 11.5 Hz, 1H), 4.83 (d, J = 15.5 Hz, 1H), 4.79 (d, J = 15.0 Hz, 1H), 4.68 (d, J = 8.5 Hz, 1H), 4.66 (d, J = 8.5 Hz, 1H), 4.47 (d, J = 11.5 Hz, 1H), 4.46 (s, 2H), 4.08 (d, J = 1.5 Hz, 1H), 4.07−3.99 (m, 2H), 3.81−3.62 (m, 6H), 1.62−1.56 (m, 2H), 1.38−1.29 (m, 4H), 1.10−1.02 (m, 2H), 0.89 (t, J = 7.5 Hz, 1H), 0.69 (t, J = 7.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 165.1, 138.4, 138.1, 137.7, 137.4, 133.1, 131.4, 129.5, 128.6, 128.4, 128.3, 128.1, 128.0, 127.8, 127.7, 97.0, 79.7, 74.8, 74.4, 73.6, 72.2, 72.0, 68.0, 67.9, 32.1, 32.0, 31.9, 31.8, 18.6, 18.4, 13.7, 13.4; ^{31}P NMR (200 MHz, $CDCl_3$): −2.26; FAB-MS: m/z (M^+) calcd 824.3282, obsd 824.3264.

***n*-Pentenyl 2-*O*-(2-(Azidomethyl)benzoyl)-3,4,6-tri-*O*-benzyl-*β*-D-galactopyranosyl-(1 → 4)-3-*O*-benzoyl-6-*O*-benzyl-2-deoxy-2-phthalimido-*β*-D-glucopyranosyl-(1 → 3)-4,6-di-*O*-benzyl-2-*O*-pivaloyl-*β*-D-galactopyranosyl-(1 → 4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-*β*-D-glucopyranoside 67.** To a stirred solution of **27** (31 mg, 0.022 mmol) and galactosyl phosphate **61** (66 mg, 0.127 mmol) in 2.5 mL of CH_2Cl_2 under N_2 at −60 °C was added TMSOTf (23 μL, 0.127 mmol). The reaction was stirred at −60 °C for 5 min and allowed to warm to −50 °C over 5 min. Triethylamine (30 μL) was added, the solution was concentrated, and the crude product was purified by flash silica column chromatography (10% EtOAc/toluene) to afford **67** (41.2 mg, 92% yield). $[\alpha]_D$: −11.5° (c = 1.95, CH_2Cl_2); IR (thin film): 2870, 2102, 1733, 1077 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 7.83 (d, J = 7.5 Hz, 1H), 7.78 (d, J = 7.5 Hz, 1H), 7.62−7.58 (m, 6H), 7.42−7.02 (m, 44H), 6.92 (t, J = 7.0 Hz, 1H), 6.10 (t, J = 9.0 Hz, 1H), 5.77 (m, 1H), 5.51 (t, J = 9.5 Hz, 1H), 5.34 (d, J = 8.5 Hz, 1H), 5.07 (t, J = 8.0 Hz, 1H), 5.02 (d, J = 11.5 Hz, 1H), 4.96 (d, J = 11.0 Hz, 1H), 4.92 (d, J = 15.0 Hz, 1H), 4.90 (d, J = 17.5 Hz, 1H), 4.83 (m, 2H), 4.76 (d, J = 15.0 Hz, 1H), 4.69 (d, J = 12.0 Hz, 1H), 4.60 (d, J = 8.0 Hz, 1H), 4.57 (d, J = 12.5 Hz, 1H), 4.44 (m, 3H), 4.36 (t, J = 7.5 Hz, 1H), 4.32−4.27 (m, 4H), 4.21−4.05 (m, 4H), 4.05 (s, 2H), 3.98 (t, J = 9.0 Hz, 1H), 3.57 (d, J = 10.5 Hz, 1H), 3.44−3.36 (m, 5H), 3.32−3.26 (m, 3H), 3.08 (m, 1H), 3.02

(52) Schmidt, R. R.; Wegmann, B.; Jung, K.-H. *Liebigs Ann. Chem.* **1991**, 121.
(53) Nashed, M., A.; Slite, C. W.; Kiso, M.; Anderson, L. *Carbohydr. Res.* **1980**, *82*, 237.
(54) Plante, O. J.; Buchwald, S. J.; Seeberger, P. H. *J. Am. Chem. Soc.* **2000**, *122*, 7148.
(55) Love, K. R.; Seeberger, P. H. *Synthesis* **2001**, 317.

(t, J = 8.5 Hz, 1H), 2.92 (m, 1H), 2.12−2.01 (m, 2H), 1.68−1.59 (m, 2H), 1.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): 176.7, 176.6, 165.0, 164.9, 139.2, 138.8, 138.7, 138.4, 138.3, 138.0, 138.0, 137.9, 137.7, 133.9, 133.0, 132.9, 131.0, 130.0, 129.8, 129.6, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 127.6, 127.6, 127.5, 127.3, 126.9, 114.9, 101.3, 101.2, 99.5, 97.9, 81.0, 80.0, 76.6, 75.5, 75.1, 74.7, 74.6, 74.5, 74.4, 73.7, 73.6, 73.5, 73.3, 72.8, 72.4, 72.3, 72.2, 71.7, 71.5, 71.3, 68.9, 68.3, 67.8, 67.0, 55.6, 53.1, 38.9, 38.8, 30.2, 28.9, 27.3, 27.2, 25.7; FAB-MS: m/z $(M + Na)^+$ calcd 2037.8552, obsd 2037.8478.

***n*-Pentenyl 3,4,6-Tri-*O*-benzyl-*β*-D-galactopyranosyl-(1 → 4)-3-*O*-benzoyl-6-*O*-benzyl-2-deoxy-2-phthalimido-*β*-D-glucopyranosyl-(1 → 3)-4,6-di-*O*-benzyl-2-*O*-pivaloyl-*β*-D-galactopyranosyl-(1 → 4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-*β*-D-glucopyranoside 68.** General procedure B using tetrasaccharide **67** (45 mg, 0.022 mmol), water (4 μL, 0.225 mmol), and PBu_3 (30 μL, 0.112 mmol) after purification by flash silica gel column chromatography (30% EtOAc/hexanes) afforded **68** (40 mg, 96%). $[\alpha]_D$: −18.1° (c 1.35, CH_2Cl_2); IR (thin film): 3387, 2868, 2360, 1733, 1070 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): 7.79 (d, J = 8.5 Hz, 1H), 7.67−7.58 (m, 4H), 7.41−7.13 (m, 41H), 7.11 (d, J = 7.0 Hz, 1H), 7.07 (t, J = 7.5 Hz, 1H), 6.93 (t, J = 7.5 Hz, 1H), 6.55 (dd, J = 9.0, 11.0 Hz, 1H), 5.77 (m, 1H), 5.39 (d, J = 8.0 Hz, 1H), 5.11 (t, J = 10.0 Hz, 1H), 5.04 (d, J = 10.5 Hz, 1H), 4.99 (d, J = 18.5 Hz, 1H), 4.93 (d, J = 12.5 Hz, 1H), 4.90 (d, J = 9.5 Hz, 1H), 4.86 (d, J = 10.5 Hz, 1H), 4.74 (d, J = 8.0 Hz, 1H), 4.72 (d, J = 8.0 Hz, 1H), 4.64 (d, J = 9.0 Hz, 1H), 4.60 (d, J = 9.0 Hz, 1H), 4.52 (d, J = 11.5 Hz, 1H), 4.47 (d, J = 13.0 Hz, 1H), 4.44 (d, J = 12.5 Hz, 1H), 4.39 (d, J = 12.0 Hz, 1H), 4.37 (d, J = 8.5 Hz, 1H), 4.33−4.27 (m, 6H), 4.18 (d, J = 12.0 Hz, 1H), 4.17 (d, J = 7.0 Hz, 1H), 4.06−3.99 (m, 6H), 3.88−3.80 (m, 4H), 3.79 (d, J = 1.5 Hz, 1H), 3.68 (s, 2H), 3.46−3.38 (m, 3H), 3.36−3.22 (m, 2H), 3.21 (dd, J = 2.5, 9.7 Hz, 1H), 2.97 (d, J = 8.0 Hz, 1H), 2.79 (s, 1H), 2.73 (q, J = 4.5 Hz, 1H), 2.10−2.01 (m, 2H), 1.67−1.59 (m, 3H), 1.14 (s, 9H), 1.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): 176.8, 176.7, 165.1, 139.3, 139.0, 138.9, 138.3, 138.1, 137.9, 137.8, 133.0, 130.0, 129.9, 128.7, 128.6, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.5, 127.4, 126.9, 114.9, 104.0, 101.4, 99.6, 98.2, 81.8, 81.1, 75.6, 75.3, 74.8, 74.6, 74.5, 74.4, 73.8, 73.7, 73.6, 73.3, 73.0, 72.5, 72.4, 72.1, 72.0, 71.8, 71.7, 69.0, 68.4, 67.1, 55.6, 39.0, 38.9, 30.2, 29.0, 27.3, 27.2; FAB-MS: m/z $(M + Na)^+$ calcd 1878.8120, obsd 1878.8152.

***n*-Pentenyl 2-*O*-Benzyl-3,4-di-*O*-pivaloyl-α-L-fucopyranosyl-(1 → 2)-3,4,6-tri-*O*-benzyl-*β*-D-galactopyranosyl-(1 → 4)-3-*O*-benzoyl-6-*O*-benzyl-2-deoxy-2-phthalimido-*β*-D-glucopyranosyl-(1 → 3)-4,6-di-*O*-benzyl-2-*O*-pivaloyl-*β*-D-galactopyranosyl-(1 → 4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-*β*-D-glucopyranoside 69.** To a stirred solution of tetrasaccharide acceptor **68** (12.1 mg, 0.0065 mmol) and fucosyl phosphate **65** (39.7 mg, 0.0645 mmol) in 1.5 mL of CH_2Cl_2 under N_2 at −55 °C was added TBSOTf (15 μL, 0.0645 mmol). The reaction was stirred at this temperature for 10 min. Triethylamine (60 μL) was added, the solution was concentrated, and the crude product purified by flash silica column chromatography (10% EtOAc/toluene) to afford **69** (13.9 mg, 94%). $[\alpha]_D$: −32.7° (c = 1.16, CH_2Cl_2); IR (thin film): 2930, 2869, 1732, 1387, 1268 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): 7.81−7.57 (m, 4H), 7.71 (d, J = 8.5 Hz, 1H), 7.35−6.90 (m, 49H), 6.02 (dd, J = 9.0, 11.0 Hz, 1H), 5.77 (m, 1H), 5.60 (d, J = 3.5 Hz, 1H, H_e-1), 5.39 (d, J = 8.5 Hz, 1H, H_c-1), 5.36 (dd, J = 3.0, 10.5 Hz, 1H), 5.28 (d, J = 3.0 Hz, 1H), 5.15 (dd, J = 7.5, 10.2 Hz, 1H), 5.09 (d, J = 11.0 Hz, 1H), 5.05−4.99 (m, 2H), 4.91 (d, J = 8.0 Hz, 1H), 4.87 (d, J = 11.0 Hz, 1H), 4.72 (d, J = 12.0 Hz, 1H), 4.71 (d, J = 14.0 Hz, 1H), 4.68 (d, J = 12.0 Hz, 1H), 4.59 (d, J = 12.5 Hz, 1H), 4.57 (d, J = 12.5 Hz, 1H), 4.52 (d, J = 12.5 Hz, 1H), 4.48−4.41 (m, 3H), 4.38 (d, J = 7.5 Hz, 1H, H_d-1), 4.35 (d, J = 8.0 Hz, 1H, H_b-1), 4.33−4.30 (m, 4H), 4.29 (d, J = 7.5 Hz, 1H, H_a-1), 4.20 (d, J = 11.5 Hz, 1H), 4.18−4.11 (m, 4H), 4.03−3.96 (m, 5H), 3.83−3.78 (m, 3H), 3.74−3.65 (m, 4H), 3.49 (t, J = 6.5 Hz, 1H), 3.46−3.38 (m, 4H), 3.32−3.28 (m, 3H), 3.24 (dd, J = 4.5, 9.0 Hz, 1H), 3.05 (dd, J = 5.0, 9.0 Hz, 1H), 2.68 (t, J = 9.0 Hz, 1H), 2.14−2.01 (m, 2H), 1.66−1.59 (m, 2H), 1.27 (d, J = 6.5 Hz, 3H), 1.18 (s, 9H), 1.16 (s, 9H), 1.14 (s, 9H), 1.09 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): 177.8, 177.6, 176.7, 176.6, 165.2, 139.4, 138.9, 138.8, 138.4, 138.3, 138.2, 138.0, 137.7, 134.0, 132.3, 130.4, 130.0, 128.7, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.4, 127.3, 126.9, 126.3, 123.8, 114.9, 101.3 (C_a-1), 100.2 (C_d-1), 99.7 (C_b-1), 98.5 (C_c-1), 97.1 (C_e-1), 83.6, 81.1, 77.6, 77.4, 75.6, 75.3, 75.2, 74.5, 74.3, 73.7, 73.6, 73.5, 73.4, 73.2, 72.7, 72.5, 72.4, 72.2, 71.8, 71.5, 71.4, 70.8, 70.4, 70.3, 68.9, 68.6, 68.4, 67.7, 67.4, 65.2, 55.4, 39.2, 38.9, 38.8, 30.2, 29.9, 28.9, 27.4, 27.3, 27.2, 15.5; ESI-MS: m/z $(M + 2Na)^{2+}$ calcd 1153.0106, obsd 1153.0107.

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 NIH (Biotechnology Training Grant for K.R.L.); and NSF (Predoctoral Fellowship for R.B.A.) 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, ^{13}C NMR, and ^{31}P NMR spectral data for all described compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO015987H