Dehydrative Glycosylation with Activated Diphenyl Sulfonium Reagents. Scope, Mode of *C*(1)-Hemiacetal Activation, and Detection of Reactive Glycosyl Intermediates

Brian A. Garcia and David Y. Gin*

Contribution from the Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana, Illinois 61801

Received October 6, 1999

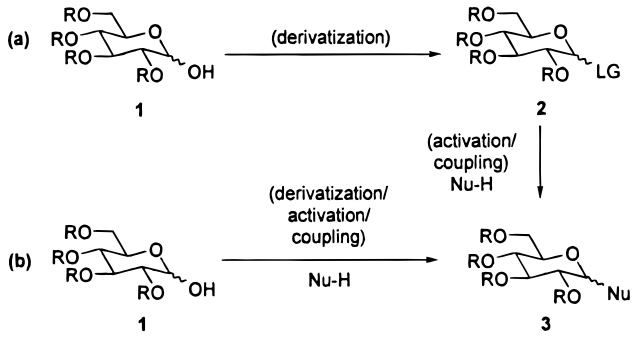
Abstract: The development of a method for direct dehydrative glycosylations with 1-hydroxyglycosyl donors employing the reagent combination of triflic anhydride and diphenyl sulfoxide is described. The one-pot coupling method is a facile process which is applicable to a variety of carbohydrate coupling partners. Oxygen-18-labeling studies are consistent with the first step in carbohydrate activation being the formation of an anomeric oxosulfonium intermediate. This reactive glycosyl species (**35**) is observable in low-temperature NMR experiments when 2,3,4,6-tetra-*O*-methyl-D-mannopyranose is activated as the glycosyl donor. When the dehydrative glycosylation reaction is performed in the presence of the triflic acid scavenger 2-chloropyridine, NMR analysis reveals that the glycosyl oxosulfonium intermediate **35** is converted to the corresponding anomeric 2-chloropyridinium species **36**.

Introduction

The many important roles that complex carbohydrates play in biology have made synthesis of this class of molecules a major focus in synthetic organic chemistry.[1] The key reaction for rational carbohydrate synthesis is the formation of the glycosidic bond as this is the primary means for the controlled assembly of complex oligosaccharides and glycoconjugates from monosaccharide precursors. Most carbohydrate coupling strategies have concentrated on the refinement of the approach outlined in Scheme 1a.[2] Traditionally, the anomeric substituent of a carbohydrate (**1**) is derivatized to become a latent leaving group (LG), and the intermediate glycosyl donor **2** is usually isolated. In a second step the leaving group is then activated in the presence of a nucleophilic glycosyl acceptor (Nu-H) to form the glycosidic bond (**2** → **3**). During the past century, the bulk of the methodology development in this area has concentrated on the invention of new latent leaving groups for the preparation of isolable glycosyl donors **2** that can undergo efficient activation and coupling in the second step of the process.

A far less developed strategy for glycosidic bond formation is a dehydrative coupling strategy shown in Scheme 1b, in which a 1-hydroxy carbohydrate (**1**) can be employed directly as the glycosyl donor. This approach would offer a complementary if not more efficient strategy for glycosylation in that it combines all of the processes of anomeric derivatization, activation, and bond formation into a one-pot procedure for the conversion of **1** to **3**. However, despite the potential advantages of such an approach, this strategy has not been extensively used in complex molecule synthesis due to a number of inherent difficulties. For example, lack of control over the reversibility of the transformation is most evident in the original Fischer glycosylation protocol in which the glycosyl acceptor must also function as the reaction solvent to force the equilibrium toward the glycoside product.[3] Moreover, when dehydrative glycosylations are performed in the absence of a vast excess of glycosyl acceptor, there is the propensity for the hemiacetal donor to self-couple under dehydrating conditions. Over the past several years, a handful of direct dehydrative glycosylation methods have been developed to address these difficulties via the in situ generation of a variety of reactive glycosyl donors.[4] Herein we report details on our efforts in the establishment and understanding of a novel process for direct dehydrative glycosylation that involves a new method for hemiacetal activation using diphenyl sulfonium reagents.

Scheme 1



Results and Discussion

Development of the Dehydrative Coupling Method. Our development of a dehydrative glycosylation reaction arose from

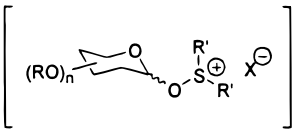
(1) *Synthetic Oligosaccharides. Indispensable Probes for the Life Sciences*; Kovac, P., Ed.; ACS Symposium Series 560; American Chemical Society: Washington, DC, 1994. (b) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683−720.

(2) (a) *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker: New York, 1997; Chapters 12−22. (b) Boons, G.-J. *Tetrahedron* **1996**, *52*, 1095−1121. (c) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380−1419. (d) Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21−123. (e) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503−1531. (f) Sinaÿ, P. *Pure Appl. Chem.* **1991**, *63*, 519−528.

(3) (a) Fischer, E. *Chem. Ber.* **1893**, *26*, 2400−2412. (b) Bochkov, A. F.; Zaikov, G. E. *Chemistry of the O-Glycosidic Bond*; Pergamon: Oxford, 1979.

10.1021/ja993595a CCC: $19.00
Published on Web 04/21/2000

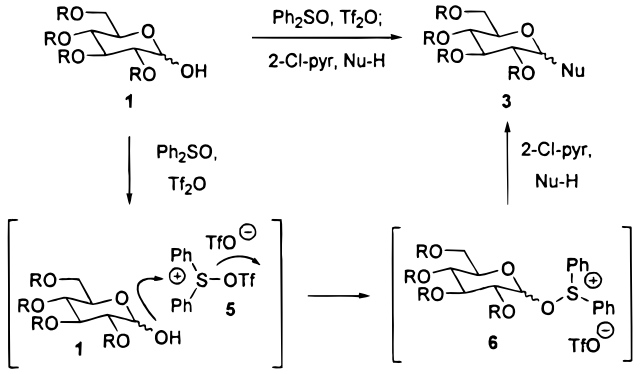
considering the possibility that a reactive anomeric oxosulfonium species (**4**), generated directly from a *C*(1)-hydroxy donor, could



4

function as an efficient glycosylating agent. This hypothesis was indeed confirmed when the reagent combination of triflic anhydride and diphenyl sulfoxide was employed for hemiacetal activation.[5]

Scheme 2



This procedure, outlined in Scheme 2, begins with the addition of triflic anhydride to a solution of the hemiacetal donor **1** and diphenyl sulfoxide at −78 °C. Under these reaction conditions it is presumed that the sulfoxide reagent is converted to diphenyl sulfide bis(triflate) (**5**) in situ. This highly reactive species is believed to activate the hemiacetal donor **1** by *C*(1)-hydroxyl addition to the sulfonium center of **5**, leading to formation of the glycosyl oxosulfonium intermediate **6**. The nucleophilic acceptor subsequently adds to the anomeric center with regeneration of diphenyl sulfoxide to yield the desired product glycoside **3** in an overall one-pot procedure.

In the development of this method, diphenyl sulfoxide was selected as the sulfoxide reagent because it lacks potentially reactive protons adjacent to the sulfur center, thereby precluding oxidation via intramolecular proton transfer.[6] Triflic anhydride was chosen as the sulfoxide activator due to the ability of this reagent to rapidly activate the sulfoxide functionality at low temperatures, as evidenced by the earlier work of Hendrickson,[7] Kahne,[8] and others.[9] An additional advantage of triflic anhydride is that the anionic byproduct of activation, triflate, should truly be a spectator anion and thus should not obstruct glycosidic bond formation with the desired glycosyl acceptor. However, the use of triflic anhydride generates 2 equiv of triflic acid during the course of the coupling process; hence, the inexpensive triflic acid scavenger, 2-chloropyridine,[10] is added after hemiacetal activation to avoid possible acid-mediated decomposition of the newly formed glycoside product.[11] It is also worth noting that an excess (∼2.0−2.8 equiv) of diphenyl sulfoxide is typically employed to ensure rapid and complete hemiacetal activation at low temperature to minimize self-condensation of the donor.

Scope. We have applied this new glycosylation procedure to a host of substrates to afford the glycoside products **7**−**24** (Figure 1). A variety of selectively protected hemiacetal donors are compatible with the dehydrative coupling process, such as gluco-, manno-, and xylopyranose substrates. In addition, furanose donors can be efficiently activated with **5** to form the corresponding furanosides (**19** and **21**). A wide variety of glycosyl acceptors have been shown to be suitable nucleophiles in the coupling, including primary, secondary, and tertiary alcohols, as well as phenols, thiols, electron-rich *C*-aryl nucleophiles, *N*-silyl amides, *N*-silyl pyrimidines, azide, and carboxylic acids.[12] From these examples, it is worth noting that (1) extremely hindered nucleophiles such as *tert*-butyl alcohol and methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside can be glycosylated (**12**, **17**, and **18**) in good yields, (2) the free *N*−*H* of a carbamate functionality tolerates the sulfoxide−triflic anhydride reagent, allowing one access to protected 2-aza-2-deoxy glycosides **10**, and (3) a variety of nitrogen nucleophiles can be employed, including azide, pyrimidines, and amides, to allow direct access to glycosylamine precursors as well as to analogues of nucleosides and glycopeptide linkages.

In all of the glycosylation reactions, 1.5−3 equiv of the acceptor coupling partner is usually employed, so a large excess of the nucleophilic coupling partner is not necessary.[13] For donors possessing a C(2)-participating group such as an ester functionality, the C(1)−C(2)-*trans*-configured glycosides are generated exclusively. For glycosyl donors that do not incorporate such a C(2)-functionality, the anomeric ratio of the glycoside products varies with the nature of the glycosyl acceptor. However, on the basis of low-temperature NMR

(4) Glycosyl halides: (a) Koto, S.; Morishima, N.; Zen, S. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1543−1547. (b) Koto, S.; Morishima, N.; Kusuhara, C.; Sekido, S.; Yoshida, T.; Zen, S. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2995−2999. Glycosyl sulfonates: (c) Leroux, J.; Perlin, A. S. *Carbohydr. Res.* **1978**, *67*, 163−178. (d) Lacombe, J. M.; Pavia, A. A. *J. Org. Chem.* **1983**, *48*, 2557−2563. (e) Koto, S.; Miura, T.; Hirooka, M.; Tomaru, A.; Iida, M.; Kanemitsu, M.; Takenaka, K.; Masuzawa, S.; Miyaji, S.; Kuroyanagi, N.; Yagishita, M.; Zen, S.; Yago, K.; Tomonaga, F. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 3247−3259. (f) Szeja, W. *Synthesis* **1988**, 223−224. Oxophosphonium intermediates: (g) Grochowski, E.; Jurczak, J. *Carbohydr. Res.* **1976**, *50*, C15−C16. (h) Szarek, W. A.; Jarrell, H. C.; Jones, J. K. N. *Carbohydr. Res.* **1977**, *57*, C13−C16. (i) Smith, A. B. III; Rivero, R. A.; Hale, K. J.; Vaccaro, H. A. *J. Am. Chem. Soc.* **1991**, *113*, 2092−2112. (j) Nicolaou, K. C.; Groneberg, R. D. *J. Am. Chem. Soc.* **1990**, *112*, 4085−4086. (k) Chida, N.; Ohtsuka, M.; Nakazawa, K.; Ogawa, S. *J. Org. Chem.* **1991**, *56*, 2976−2983. (l) Roush, W. R.; Lin, X.-F. *J. Am. Chem. Soc.* **1995**, *117*, 2236−2250. Oxo titanium intermediates: (m) Suda, S.; Mukaiyama, T. *Chem. Lett.* **1991**, 431−434. Glycosyl isoureas: (n) Tsutsumi, H.; Ishido, Y. *Carbohydr. Res.* **1981**, *88*, 61−75. Lewis acid catalysis: (o) Inanaga, J.; Yokoyama, Y.; Hanamoto, T. *J. Chem. Soc., Chem. Commun.* **1993**, 1090−1091. (p) Mukaiyama, T.; Matsubara, K.; Hora, M. *Synthesis* **1994**, 1368−1373. (q) Uchiro, H.; Mukaiyama, T. *Chem. Lett.* **1996**, 79−80. (r) Shimomura, N.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2532−2541.

(5) Garcia, B. A.; Poole, J. L.; Gin, D. Y. *J. Am. Chem. Soc.* **1997**, *119*, 7597−7598.

(6) Tidwell, T. T. *Synthesis* **1990**, 857−870.

(7) Hendrickson, J. B.; Schwartzman, S. M. *Tetrahedron Lett.* **1975**, 273−276.

(8) Kahne, D.; Walker, S.; Cheng, Y.; Van Engen, D. *J. Am. Chem. Soc.* **1989**, *111*, 6881−6882.

(9) (a) Coburn, M. D.; Hayden, H. H.; Coon, C. L.; Mitchell, A. R. *Synthesis* **1986**, 490−492. (b) Nenajdenko, V. G.; Vertelezkij, P. V.; Gridnev, I. D.; Shevchenko, N. E.; Balenkova, E. S. *Tetrahedron* **1997**, *53*, 8173−8180. (c) Corey, E. J.; Gin, D. Y.; Kania, R. S. *J. Am. Chem. Soc.* **1996**, *118*, 9202−9203.

(10) Myers, A. G.; Tom, N. J.; Fraley, M. E.; Cohen, S. B.; Madar, D. J. *J. Am. Chem Soc.* **1997**, *119*, 6072−6094.

(11) 2,6-Di-*tert*-butyl-4-methylpyridine can also be used as a triflic acid scavenger in the coupling reaction.

(12) Glycosylations were performed in a 3:1 (v/v) mixture of toluene/CH_2Cl_2. Many of the reactions in pure toluene did not proceed to completion due to incomplete solubility of the donor at −78 to −40 °C. Reactions performed in pure CH_2Cl_2 proceeded well, but led to slightly diminished yields in some cases compared with the 3:1 v/v toluene/CH_2Cl_2 solvent mixture. Glycosylations performed in both the toluene/CH_2Cl_2 solvent mixture and in pure CH_2Cl_2 led to similar α:β selectivity.

(13) For nonvolatile acceptors, the excess nucleophile can be reisolated with good recovery.

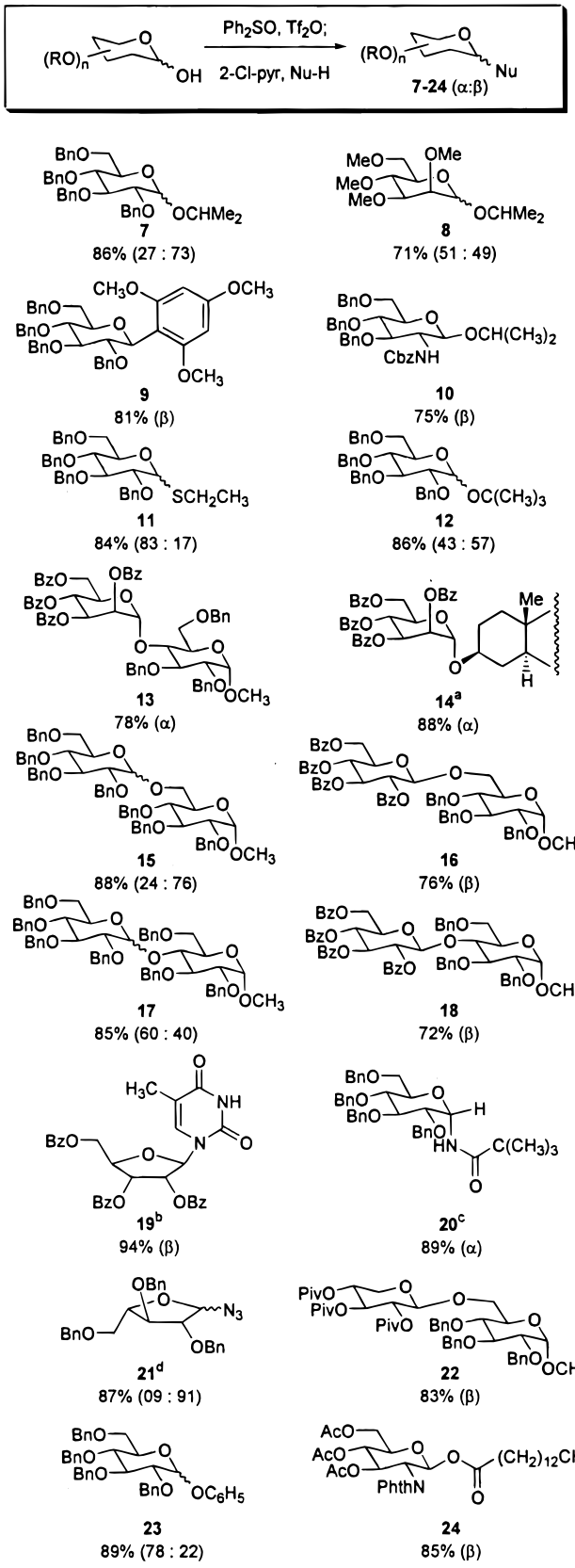
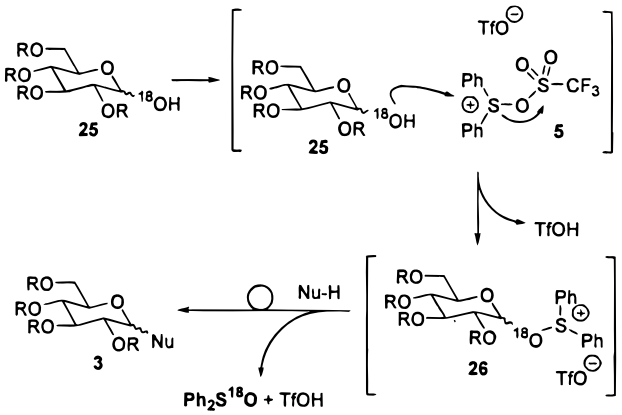


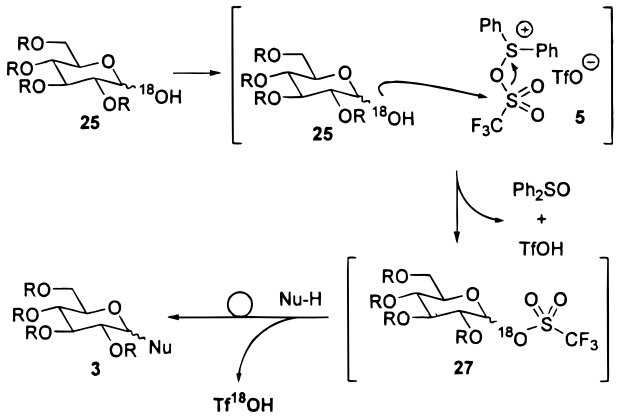
Figure 1. Products of dehydrative glycosylation. Yield (α:*β*). Key: a, acceptor = dihydrocholesterol; b, acceptor = *N*,*N*′-bis(TMS)thymine; c, acceptor = *N*-TMS-2,2,2-trimethylacetamide; d, acceptor = NaN_3.

monitoring of the dehydrative glycosylation of 2-propanol to form the isopropyl mannopyranoside **8**, it appears that the anomeric ratios of the glycoside products are kinetically derived and are not reflective of a thermodynamic product distribution arising from postcoupling anomeric epimerization (vide infra).

Scheme 3



Scheme 4

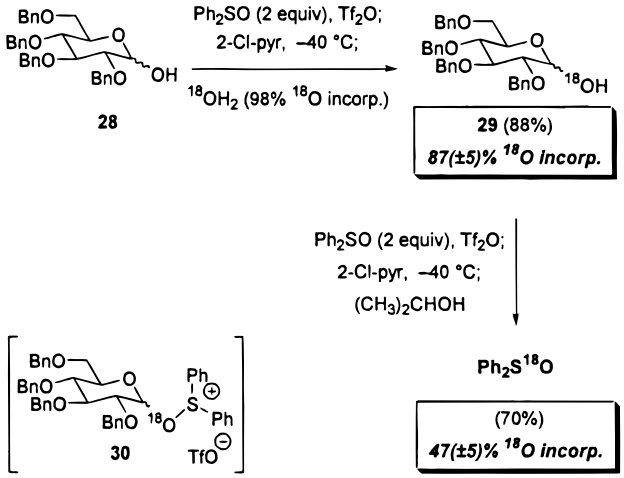


Mode of *C*(1)-Hemiacetal Activation. In the glycosylation reaction, it is proposed (Scheme 3) that activation of diphenyl sulfoxide to form diphenyl sulfide bis(triflate) (**5**) is immediately followed by hemiacetal addition into the *sulfonium* center of **5**. This would lead to the formation of the glycosyl oxosulfonium intermediate **26**, which can then proceed to glycosylate the nucleophilic acceptor. However, an alternate reaction pathway (Scheme 4) could involve addition of the hemiacetal hydroxyl into the *sulfonyl* center of **5**. This would result in the initial expulsion of diphenyl sulfoxide and the immediate formation of the glycosyl triflate **27**, which could then effect glycosylation. In both of these reaction manifolds, a dehydrative glycosylation is carried out and diphenyl sulfoxide is regenerated during the course of the transformation.

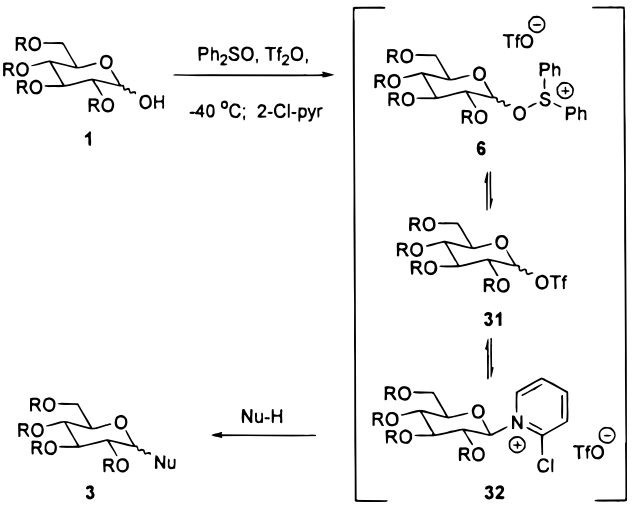
To distinguish between the two carbohydrate activation pathways, an ^{18}O-labeling study was carried out employing a C(1)-^{18}O-labeled hemiacetal donor (**25**). If Scheme 3 is the operative reaction pathway, a net transfer of ^{18}O from the hemiacetal to the sulfoxide reagent would be observed. If, on the other hand, Scheme 4 is operative, ^{18}O would be transferred to the triflic acid (or triflate) byproduct, leaving the diphenyl sulfoxide reagent unlabeled. The preparation of 1-*^{18}OH*-2,3,4,6-tetra-*O*-benzyl-D-glucopyranose was accomplished (Scheme 5) via the glycosylation of $^{18}OH_2$ (98% incorporation) with 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**28**), affording the C(1)-*O*-labeled carbohydrate **29** (87 ± 5% ^{18}O-incorporation).[14] Submission of this donor to our procedure for dehydrative glycosylation of 2-propanol led to the recovery of diphenyl sul-

(14) Content of ^{18}O determined by FAB^+ mass spectrometry.

Scheme 5



Scheme 6



foxide with 47 ± 5% ^{18}O-incorporation. Since 2 equiv of diphenyl sulfoxide reagent was used in the dehydrative coupling procedure, this result indicates near-quantitative ^{18}O-transfer from the hemiacetal hydroxyl of **29** to the sulfoxide reagent. Thus, the operative reaction pathway is considered to be Scheme 3, in which the initial step of carbohydrate activation involves hemiacetal addition to the sulfonium center of **5** to generate the oxosulfonium species **30**.

Detection of Reactive Glycosyl Intermediates. Although the ^{18}O-labeling experiment suggests that the anomeric oxosulfonium intermediate **6** is the first activated carbohydrate species formed (Scheme 6), it is possible that other reactive intermediates are generated in the subsequent stages of the reaction. For example, dissociation of diphenyl sulfoxide from **6** could lead to formation of the glycosyl triflate **31**; moreover, in the presence of a triflic acid scavenger such as 2-chloropyridine, it is possible that the base could add to the anomeric center to generate the glycosyl pyridinium intermediate **32**. Each of these reactive intermediates could effect glycosylation to yield the observed glycoside products.

To determine which intermediates are formed during the glycosylation process, low-temperature NMR spectroscopy was employed to track the course of the reaction. Thus, the first step in our study was to independently synthesize each of the putative intermediates **6**, **31**, and **32** so that they could be unambiguously identified should they be formed during our dehydrative coupling reaction.

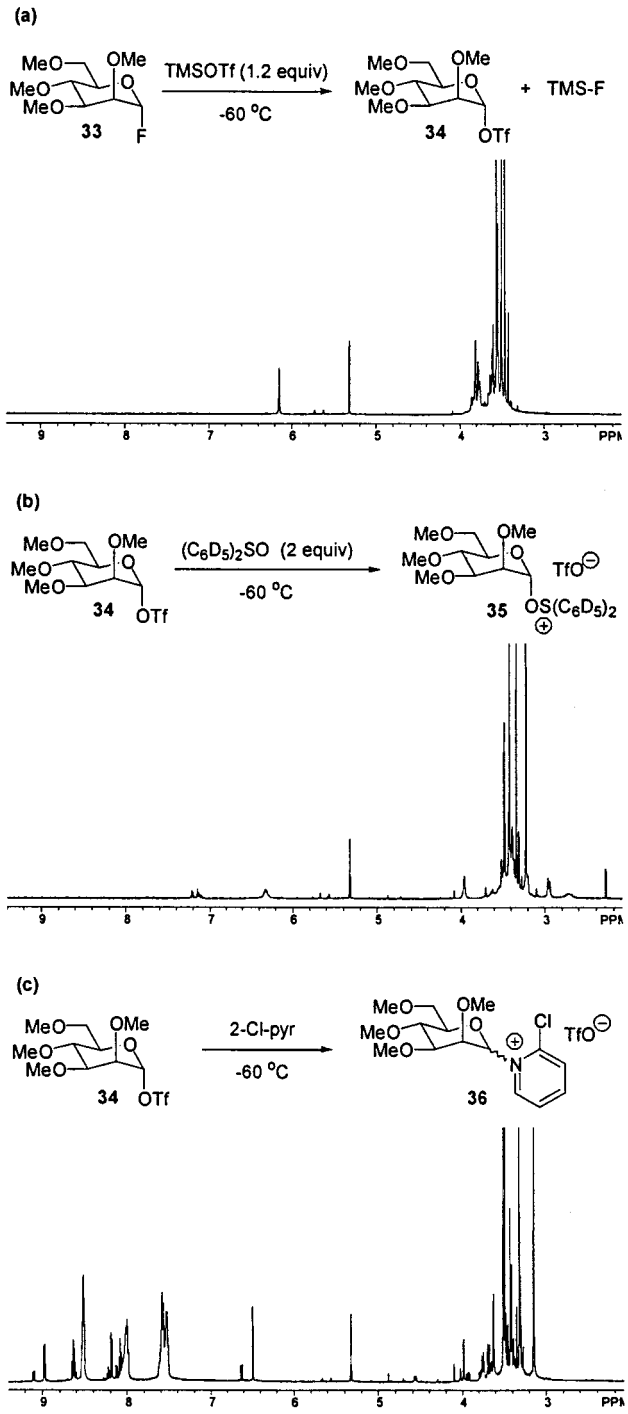


Figure 2. Independent synthesis and ^{1}H NMR characterization of putative glycosyl intermediates: (a) glycosyl triflate **34**; (b) glycosyl oxosulfonium **35**; (c) glycosyl pyridinium **36**.

The glycosyl triflate **31** was the first in our series of putative reactive intermediates to be independently synthesized and characterized. For our NMR experiments, the 2,3,4,6-tetra-*O*-methyl-D-mannopyranosyl sugar (Figure 2) was selected for study for two key reasons. First, we have shown that this hemiacetal is an effective donor in our glycosylation reaction (e.g., **8**, Figure 1). Second, the glycosyl triflate of 2,3,4,6-tetra-*O*-methyl-D-mannopyranose (**34**) has recently been synthesized and characterized by NMR in an elegant study by Crich and Sun[15] to probe the mechanism of the Kahne glycosyl sulfoxide glycosylation method.[16] Thus, this substrate provided a conve-

(15) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1997**, *119*, 11217−11223.

nient starting point for our independent syntheses of the putative reactive intermediates outlined in Scheme 6.

In the Crich study, the method reported for the independent generation of trifluoromethanesulfonyl-2,3,4,6-tetra-*O*-α-D-mannopyranoside (**34**) involved the treatment of the corresponding mannosyl bromide with AgOTf at −78 °C. However, we desired a method to generate **34** that would allow for this species to be further converted to the other putative glycosyl intermediates in the absence of insoluble silver salts. Consequently, we employed an alternate method in which the more stable glycosyl fluoride **33** was treated with a slight excess of TMSOTf as a fluoride scavenger to afford the mannosyl triflate **34** (Figure 2a).[17] Using this reagent, the glycosyl fluoride **33** was smoothly converted to the corresponding mannosyl triflate **34** within 2 h at −60 °C in CD_2Cl_2 (85% conversion) with concomitant formation of TMS−F as a soluble and benign byproduct. The successful preparation of **34** is illustrated in the ^{1}H NMR spectrum in Figure 2a wherein the anomeric proton resonance resides at δ 6.15,[18] a chemical shift which is consistent with that of the Crich study.

With this new method for the low-temperature generation of the glycosyl triflate, the independent synthesis of the glycosyl oxosulfonium species **35** was then addressed. It was reasoned that diphenyl sulfoxide should be an effective nucleophile for displacement of the anomeric triflate functionality in **34**, thereby leading to the facile generation and characterization of the putative glycosyl oxosulfonium species **35**. Thus, to a solution of freshly prepared mannosyl triflate **34** (prepared from **33**) in CD_2Cl_2 was added 2 equiv of the sulfoxide reagent (Figure 2b). In these experiments, bis(pentadeuteriophenyl) sulfoxide[19] was employed to minimize the number of NMR proton resonances that could potentially complicate interpretation. This sulfoxide was added to the solution of **34** to afford complete consumption of the glycosyl triflate within 20 min at −60 °C, leading to the formation of a new intermediate which is considered to be the oxosulfonium species **35**. On the basis of low-temperature COSY and HMQC NMR data,[20] the broad anomeric proton resonance at δ 6.32[21] is consistent with its assignment as the anomeric proton of **35**. In addition, the α-oxosulfonium anomer is shown to be stereoselectively formed as evidenced by NOE enhancement of the C(2)−OCH_3 proton resonance (3.6%) upon irradiation of the anomeric proton resonance (i.e., **35**, Figure 3).

Finally, a similar experiment was conducted for the formation of the glycosyl pyridinium intermediate **36** (Figure 2c). Upon treatment of the mannosyl triflate **34** with 3 equiv of 2-chloropyridine, the glycosyl triflate was completely converted to

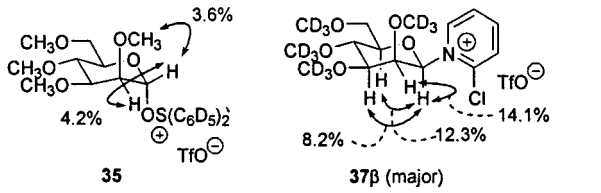


Figure 3. NOE evidence for anomeric configurations of putative glycosyl intermediates.

both anomers of the glycosyl pyridinium species **36** within 20 min at −60 °C. Two resonances at δ 6.63 and 6.49 were assigned by HMQC NMR data[22] to be the *C*(1)-protons of the anomeric mixture of **36** in a ratio of 24:76 (α:*β*), respectively. Interestingly, the *β*-pyridinium diastereomer is found to be the principal anomer in solution on the basis of NOE data.[23] Irradiation of the anomeric proton in the major anomer of the glycosyl pyridinium intermediate **37** (Figure 3) resulted in NOE enhancement of the *C*(3)- and *C*(5)-proton resonances.[24]

The successful independent preparation and NMR characterization of each of the intermediates **34**−**36** provides the basis for possible detection of these reactive species during the course of the coupling reaction (Figure 4). Therefore, the dehydrative glycosylation reaction was performed with 2,3,4,6-tetra-*O*-methyl-D-mannose (**38**) in CD_2Cl_2 (Figure 4a). When a mixture of **38** and $(C_6D_5)_2SO$ at −60 °C was treated with triflic anhydride, complete consumption of the hemiacetal **38** had occurred within 20 min, resulting in the formation of a glycosyl intermediate (Figure 4b). ^{1}H NMR spectral data of this intermediate coincided with the glycosyl oxosulfonium species **35** that we independently synthesized and characterized earlier (cf. Figure 2b). The subsequent stage in the coupling protocol involved the introduction of the triflic acid scavenger 2-chloropyridine (3 equiv). The reaction was allowed to warm to −40 °C, and it was observed (Figure 4c,d) that complete conversion of the oxosulfonium species **35** to both anomers of the glycosyl pyridinium species **36**α and **36*β*** (19:81) proceeded within 2 h.[25] The final step in the coupling transformation involved the introduction of a nucleophilic acceptor, 2-propanol. Upon introduction of the acceptor (Figure 4e,f), the corresponding isopropyl glycoside **8** was formed within 2.5 h at 15 °C in a 54:46 (α:*β*) mixture (anomeric proton resonances at δ 4.91 and 4.41, respectively). This anomeric ratio, which is believed to be kinetically derived,[26] is similar to that obtained earlier (i.e., **8**, Figure 1).

The above experiments thus allow for a clearer definition of the dehydrative coupling process. First, it appears that the initial

(16) For additional studies on the detection of reactive glycosyl intermediates in the Kahne sulfoxide glycosylation method, see: Gildersleeve, J.; Pascal, R. A., Jr.; Kahne, D. *J. Am. Chem. Soc.* **1998**, *120*, 5961−5969.

(17) For the use of substoichiometric quantities of TMSOTf in glycosidic couplings with glycosyl fluorides, see: Hashimoto, S.; Hayashi, M.; Noyori, R. *Tetrahedron Lett.* **1984**, *25*, 1379−1382.

(18) The doublet resonance at δ 5.68 (J = 51 Hz) corresponds to the anomeric proton of traces of unreacted mannosyl fluoride **33**.

(19) Prepared from the treatment of C_6D_6 with aluminum trichloride and thionyl chloride, following a known procedure for the preparation of diphenyl sulfoxide. See: Shriner, R. L.; Struck, H. C.; Jorison, W. J. *J. Am. Chem. Soc.* **1930**. *52*, 2060−2069.

(20) The low-temperature COSY experiment was performed on the 2,3,4,6-tetrakis-*O*-(trideuteriomethyl) analogue of **35**. Thus, it was possible to confidently identify the pyranoside ring protons in the absence of overlapping OCH_3 resonances. HMQC NMR data showed that the proton resonance at δ 6.38 correlated with the C(1) carbon-13 resonance (δ 107.2) in **35**.

(21) The trace resonances at δ 7.45 arise from residual toluene that was employed for azeotropic removal of water from the sulfoxide reagent prior to the reaction.

(22) HMQC NMR data showed that the proton resonances at δ 6.63 and 6.49 correlated with the C(1) carbon-13 resonances (δ 87.35 and 89.58, respectively) in the anomeric mixture of **37**.

(23) Formation of the *β*-anomer of **36** as the major diastereomer may result from the minimization of nonbonding interactions with the sterically demanding pyridinium moiety, or possibly arise as a result of a reverse anomeric effect. For recent discussions on the reverse anomeric effect, see: (a) Jones, P. G.; Kirby, A. J.; Komarov, I. V.; Wothers, P. D. *Chem. Commun*. **1998**, 1695−1696. (b) Vaino, A. R.; Chan, S. S. C.; Szarek, W. A.; Thatcher, G. R. J. *J. Org. Chem.* **1996**, *61*, 4514−4515. (c) Perrin, C. L. *Tetrahedron* **1995**, *51*, 11901−11935.

(24) The mannosyl pyridinium intermediate **37**, in which all of the CH_3 protective groups were replaced with CD_3, was used for the stereochemical assignment of the pyridinium intermediates because it permitted us to clearly assign all of the pyranoside ring protons in the absence of overlapping OCH_3 resonances. Thus, it was possible to confidently identify the enhancement of the C(3) and C(5) protons in the NOE experiment.

(25) From the NMR study, the conversion of **35** → **36** is not instantaneous at −40 °C. Therefore, in the reactions to form glycosides **7**−**24**, it is likely that the extent of conversion to the glycosyl pyridinium intermediate prior to the introduction of the acceptor varies with the nature of the coupling partners.

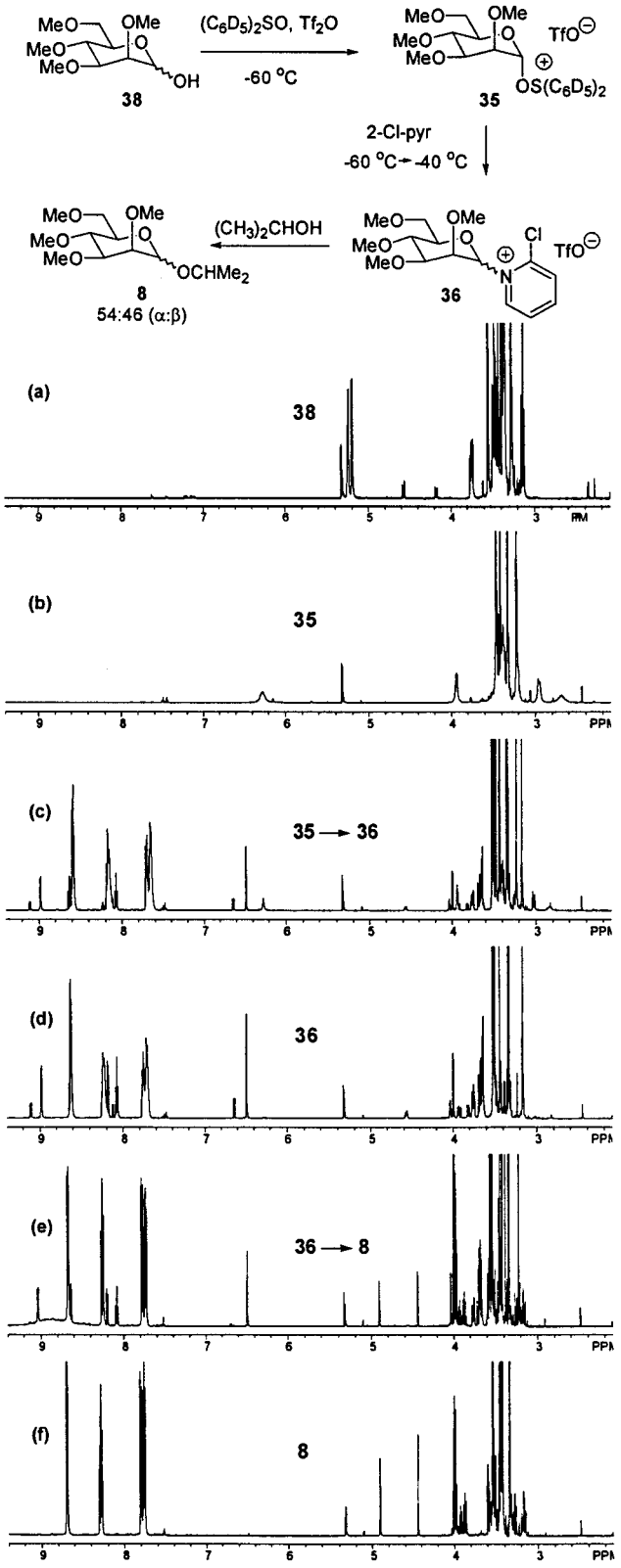
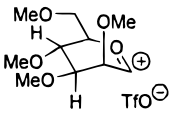


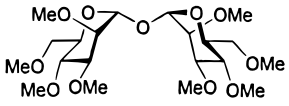
Figure 4. Dehydrative glycosylation monitored by ^{1}H NMR in CD_2Cl_2: (a) hemiacetal **38** and $(C_6D_5)_2SO$ at −60 °C; (b) −60 °C, 20 min after addition of Tf_2O; (c) −40 °C, 20 min after addition of 2-Cl-pyr; (d) −40 °C, 2 h after addition of 2-Cl-pyr; (e) 15 °C, 30 min after addition of 2-propanol; (f) 15 °C, 2.5 h after addition of 2-propanol.

carbohydrate intermediate detected in the activation process is the glycosyl oxosulfonium species **35**, which is consistent with the findings of the ^{18}O-labeling study. Second, it is clear that when 2-chloropyridine is used as the triflic acid scavenger, the glycosyl pyridinium species **36** can accumulate in solution during the course of the reaction. However, one must be aware of the caveat that *simple detection of **36** as the principal species in solution does not necessarily establish it to be the reactive species undergoing coupling to form the product glycoside*. Indeed, the lack of correlation between the anomeric ratios of the glycosyl pyridinium intermediate **36** (19:81, α:*β*) and the isopropyl glycoside product **8** (54:46, α:*β*) suggests that the glycosylation of 2-propanol is unlikely to proceed exclusively through direct invertive displacement of the anomeric pyridinium moieties in **36α*β***. Thus, the actual glycosidic-bond-forming event may proceed, *at least in part*, via other reactive intermediates that were not detected by NMR. Candidates include the glycosyl oxosulfonium **35** and/or the oxocarbenium **39**,[27] which may exist in exceedingly small quantities even after the introduction of 2-chloropyridine.



39

Finally, it is clear from the NMR experiments that diphenyl sulfoxide can be expelled from the anomeric center of **35** by 2-chloropyridine prior to addition of the glycosyl acceptor. This observation presents the possibility for catalytic turnover of diphenyl sulfoxide in the hemiacetal activation phase of the reaction. However, this potential catalytic cycle would only be feasible if expulsion of the anomeric sulfoxide moiety is sufficiently rapid so that the rate of hemiacetal activation is fast relative to that of self-condensation of the *C*(1)-hydroxy donor. When activation of the hemiacetal **38** was carried out with 0.2 equiv of $(C_6D_5)_2SO$ in the presence of triflic anhydride (3 equiv) and 2-chloropyridine (1.4 equiv) in CD_2Cl_2, self-condensation was indeed found to be a competitive process. Under these conditions, 56% of the hemiacetal donor **38** is converted to the undesired 1,1′-α,α′-linked disaccharide **40** in the unproductive



40

self-condensation pathway as determined by ^{1}H NMR. Thus, it

(26) It is clear that the 54:46 (α:*β*) ratio obtained is not the thermodynamic anomeric distribution, which is >95:5 (α:*β*). This thermodynamic ratio was established when the glycosyl triflate **34** in CD_2Cl_2 was treated with 2-propanol in the absence of any acid scavenger. This led to the immediate formation of **8** in a ∼1:1 ratio at −60 °C, followed by anomeric epimerization within 30 min at 0 °C to form the α-anomer exclusively. In Figure 4, the glycoside **8** emerges in a constant ratio (54:46; α:*β*) during the course of anomeric bond formation at 15 °C, and this ratio remains unchanged even when the reaction is monitored for an additional hour after the reaction is complete. At higher temperature (i.e., 23 °C), a small amount (∼6%) of anomerization (*β* → α) is observed over the course of 1.5 h. Thus, postcoupling anomeric epimerization is unlikely to be a significant contributor to the observed anomeric ratios.

(27) A dehydrative glycosylation reaction of 2-propanol with **38**, employing the nonnucleophilic acid scavenger 2,4,6-tri-*tert*-butylpyridine, led to the formation of the glycoside product **8** in a 46:54 (α:*β*) anomeric ratio. A similar result was obtained when a mixture of 2,4,6-tri-*tert*-butylpyridine and 2-propanol was introduced directly to a solution of the glycosyl triflate **34** (independently derived from the glycosyl fluoride **33**), affording **8** in an anomeric ratio of 53:47 (α:*β*). The striking similarity in the product ratios in all of these reactions (cf. Figure 4) again alludes to the possibility that the glycosidic-bond-forming event in these transformations may proceed at least in part through a common reactive intermediate such as **39**. Future studies will involve the assessment of the kinetic competency of the reactive glycosyl intermediates.

appears that for the present protocol the use of at least a stoichiometric quantity of diphenyl sulfoxide is needed to ensure rapid and complete activation of the donor at low temperature, allowing for efficient coupling with the desired acceptor.

Conclusion

A method for direct dehydrative glycosylations with 1-hydroxyglycosyl donors employing the reagent combination of triflic anhydride and diphenyl sulfoxide has been developed. The one-pot coupling method is a facile process and appears to be applicable to a wide variety of carbohydrate coupling partners. Oxygen-18-labeling studies indicate that the first step of carbohydrate activation in the coupling process involves the addition of the hemiacetal hydroxyl to the sulfonium center of diphenyl sulfide bis(triflate), leading to the formation of an anomeric oxosulfonium intermediate. The glycosyl oxosulfonium intermediate **35** was detected by low-temperature NMR analysis of the dehydrative glycosylation process. When the reaction is performed in the presence of the triflic acid scavenger 2-chloropyridine, the corresponding anomeric 2-chloropyridinium species **36** accumulates during the course of the reaction. However, on the basis of the anomeric ratio of the glycoside products, the mode of anomeric bond formation is not likely to proceed exclusively through direct invertive displacement of the anomeric pyridinium group in **36**, even though **36** may be the principal species in solution. It is more likely that the actual C(1)-bond-forming event proceeds, at least in part, through an oxocarbenium (**39**) which may exist in the reaction mixture in exceedingly small quantities. In addition, glycosylation experiments with substoichiometric quantities of diphenyl sulfoxide highlight the importance of the sulfoxide reagent in the activation stage of the reaction. In the case of the mannosyl donor **38**, sufficient quantities of the sulfoxide reagent are required for rapid activation of the hemiacetal, thereby minimizing unwanted reaction manifolds such as self-condensation of the hemiacetal donor. These findings should allow for the further development of new sulfoxide/triflic anhydride reagents for glycosylation as well as for hydroxyl activation in general.

Experimental Section

General Procedures. All reactions were performed in flame-dried modified Schlenk (Kjeldahl shape) flasks fitted with a glass stopper or rubber septum under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation below 30 °C at ca. 25 Torr. Flash column chromatography was performed employing 230−400 mesh silica gel. Thin-layer chromatography (analytical and preparative) was performed using glass plates precoated to a depth of 0.25 mm with 230−400 mesh silica gel impregnated with a fluorescent indicator (254 nm).

Dichloromethane, 2-chloropyridine, triethylamine, toluene, and 2-propanol were distilled from calcium hydride at 760 Torr. Diphenyl sulfoxide was purchased from Aldrich and was dried by azeotropic removal of water with toluene prior to use. Trifluoromethanesulfonic anhydride was triply distilled from phosphorus pentoxide. CD_2Cl_2 was stored over CaH_2 (>24 h) and vacuum transferred immediately prior to use in the low-temperature NMR experiments.

Infrared (FTIR) spectra were obtained using a Perkin-Elmer Spectrum BX spectrophotometer referenced to a polystyrene standard. Data are presented as the frequency of absorption (cm^{-1}). Proton and carbon-13 nuclear magnetic resonance (^1H NMR or ^{13}C NMR) spectra were recorded on a Varian Unity 400, a Varian Unity 500, a Varian Unity Inova 500WB, or a Varian Unity Inova 750NB NMR spectrometer. Low-temperature detection of the reactive glycosyl intermediates (Figures 2 and 4) was performed on the Varian Unity Inova 500WB spectrometer. Chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$, δ 7.26; $CHDCl_2$, δ 5.32; C_6HD_5, δ 7.16). Data are presented as follows: chemical shift, multiplicity (*s* = singlet, d = doublet, t = triplet, br s = broad singlet, m = multiplet and/or multiple resonances), integration, and coupling constants in hertz (Hz). Optical rotations were acquired on a JASCO DIP-360 digital polarimeter. Melting points were recorded with a Fisher melting apparatus and are uncorrected. HPLC was performed on a Rainin Dynamax system (model SD-200) with a Dynamax 100 Å SiO column (21.5 mm × 25 cm) and a Dynamax model UV-1 detector (254 nm).

General Procedure for Dehydrative Glycosylation. Isopropyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (7). Trifluoromethanesulfonic anhydride (45 μL, 0.27 mmol, 1.4 equiv) was added to a solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (103 mg, 0.191 mmol, 1 equiv) and diphenyl sulfoxide (108 mg, 0.535 mmol, 2.8 equiv) in a mixture of toluene and dichloromethane (8 mL, 3:1 v/v) at −78 °C. The reaction mixture was stirred at this temperature for 5 min and then at −40 °C for 1 h. 2-Chloropyridine (90 μL, 0.96 mmol, 5.0 equiv) and isopropyl alcohol (44 μL, 0.57 mmol, 3.0 equiv) were added sequentially at −40 °C. The solution was stirred at this temperature for 1 h, then at 0 °C for 30 min, and finally at 23 °C for 1 h before the addition of excess triethylamine (212 μL, 1.53 mmol, 10 equiv). The reaction was diluted with dichloromethane (100 mL) and was washed sequentially with saturated aqueous sodium bicarbonate solution (2 × 100 mL) and saturated aqueous sodium chloride solution (100 mL). The organic layer was dried (sodium sulfate) and concentrated, and the residue was purified by silica gel flash column chromatography (gradient elution: 9% → 10% → 30% ethyl acetate in hexane) to afford **7** (95 mg, 86%; 27:73, α:β) as a white solid.[28] Anal. Calcd for $C_{37}H_{42}O_6$: C, 76.26; H, 7.26. Found (anomeric mixture): C, 76.57; H, 7.57. Analytical samples of each anomer were obtained by preparative TLC (20% ethyl acetate in hexane). α-Anomer: viscous oil; R_f = 0.43 (33% ethyl acetate in hexane); $[\alpha]^{20}_D$ = +28° (*c* = 0.4, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.4−7.1 (m, 20 H), 5.00 (d, 1 H, *J* = 10.8 Hz), 4.88 (d, 1 H, *J* = 3.8 Hz, H 1), 4.83 (d, 1 H, *J* = 10.6 Hz), 4.82 (d, 1 H, *J* = 10.8 Hz), 4.78 (d, 1 H, *J* = 12.0 Hz), 4.65 (d, 1 H, *J* = 12.0 Hz), 4.62 (d, 1 H, *J* = 12.3 Hz), 4.47 (d, 2 H, *J* = 12.1 Hz), 4.00 (t, 1 H, *J* = 9.3 Hz), 3.90 (m, 1 H), 3.85 (ddd, 1 H, *J* = 10.2, 3.4, 2.0 Hz), 3.74 (dd, 1 H, *J* = 10.5, 3.6 Hz), 3.64 (m, 2 H), 3.56 (dd, 1 H, *J* = 9.6, 3.8 Hz), 1.13 (d, 3 H, *J* = 6.3 Hz), 1.18 (d, 3 H, *J* = 6.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.0, 138.3, 138.3, 138.0, 128.5, 128.4, 128.4, 128.2, 128.0, 128.0, 127.9, 127.9, 127.8, 127.7, 127.6, 94.8, 82.2, 79.9, 77.9, 75.7, 75.2, 73.5, 73.2, 70.0, 69.0, 68.5, 23.2, 21.2; FTIR (neat film) 3064, 3030, 2922, 1454, 1364, 1157, 1072, 1040, 1029, 1015 cm^{-1}; HRMS (FAB) *m*/*z* calcd for $C_{37}H_{41}O_6$ (M − H) 581.2903, found 581.2903. β-Anomer: white solid; mp 105 °C (lit. mp 107−108 °C); R_f = 0.33 (33% ethyl acetate in hexane); $[\alpha]^{20}_D$ = +10° (*c* = 0.9, $CHCl_3$) (lit. $[\alpha]^{25}_D$ = +11°, *c* = 1, $CDCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.4−7.1 (m, 20 H), 5.00 (d, 1 H, *J* = 11.0 Hz), 4.95 (d, 1 H, *J* = 10.9 Hz), 4.84 (d, 1 H, *J* = 11.1 Hz), 4.81 (d, 1 H, *J* = 10.8 Hz), 4.73 (d, 1 H, *J* = 10.9 Hz), 4.63 (d, 1 H, *J* = 12.3 Hz), 4.59 (d, 1 H, *J* = 11. Hz), 4.57 (d, 1 H, *J* = 10.8 Hz), 4.50 (d, 1 H, *J* = 7.8 Hz, H 1), 4.05 (m, 1 H), 3.76 (dd, 1 H, *J* = 10.8, 1.8 Hz), 3.70 (m, 1 H), 3.58 (t, 1 H, *J* = 9.64 Hz), 3.48 (m, 1 H), 3.46 (dd, 1 H, *J* = 9.1, 7.9 Hz), 1.34 (d, 3 H, *J* = 6.2 Hz), 1.27 (d, 3 H, *J* = 6.2 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.7, 138.6, 138.4, 138.2, 128.4, 128.3, 128.0, 127.9, 127.8, 127.8, 127.7, 127.6, 127.6, 102.2, 84.9, 82.4, 78.0, 75.7, 75.0, 74.9, 74.9, 73.5, 72.4, 69.2, 23.8, 22.3; FTIR (neat film) 3031, 2904, 1454, 1121, 1104, 1069, 1039 cm^{-1}; HRMS (FAB) *m*/*z* calcd for $C_{37}H_{41}O_6$ (M − H) 581.2903, found 581.2903.

Isopropyl 2,3,4,6-Tetra-*O*-methyl-D-mannopyrannoside (8). Viscous oil. Anal. Calcd for $C_{13}H_{26}O_6$: C, 56.10; H, 9.42. Found (anomeric mixture): C, 55.47; H, 9.57. Analytical samples of each anomer were obtained by preparative TLC (12.5% ethyl acetate in dichloromethane). α-Anomer: viscous oil; R_f = 0.25 (33% ethyl acetate in hexane); $[\alpha]^{23}_D$ = +68° (*c* = 0.5, $CHCl_3$); ^1H NMR (500 MHz, CD_2Cl_2) δ 4.91 (s, 1 H, H 1), 3.88 (hept, 1 H, *J* = 6.02), 3.58−3.28 (m, 20 H), 1.17 (d, 3 H, *J* = 6.23), 1.13 (d, 3 H, *J* = 6.06); ^{13}C NMR (126 MHz, CD_2Cl_2)

(28) (a) Briner, K.; Vasella, A. *Helv. Chim. Acta* **1989**, *72*, 1371−1382. (b) Jansson, K.; Noori, G.; Magnusson, G. *J. Org. Chem.* **1990**, *55*, 3181−3185.

δ 95.46, 81.75, 78.05, 76.77, 72.04, 71.60, 69.26, 60.59, 59.18, 59.12, 57.57, 23.37, 21.40; FTIR (neat film) 2974, 2930, 2825, 1456, 1380, 1193, 1113, 1060, 1063 cm^{-1}; HRMS (FAB) *m/z* calcd for $C_{13}H_{26}O_6$-Na (M + Na$^+$) 301.1627, found 301.1629. β-Anomer: viscous oil; R_f = 0.18 (33% ethyl acetate in hexane); $[\alpha]^{23}_D = -106°$ (c = 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, CD_2Cl_2) δ 4.41 (s, 1 H, H 1), 3.93 (hept, 1 H, J = 6.42), 3.61−3.60 (m, 15H), 3.22 (t, 1 H, J = 9.36), 3.17 (ddd, J = 2.04, 5.05, 9.56), 3.13 (dd, 1 H, J = 3.10, 9.27), 1.21 (d, 3H, J = 6.35), 1.13 (d, 3 H, J = 6.12); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 99.86, 84.69, 78.07, 76.74, 75.86, 72.38, 71.23, 61.59, 60.88, 59.47, 57.43, 53.78, 53.57, 23.84, 21.87; FTIR (neat film) 2974, 2930, 2833, 1468, 1371, 1194, 1111, 1070, 970 cm^{-1}; HRMS (FAB) *m/z* calcd for $C_{13}H_{26}O_6Na$ (M + Na$^+$) 301.1627, found 301.1627.

1-Deoxy-1-(*C*-2′,4′,6′-trimethoxyphenyl)-2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (9).[29] Viscous oil; R_f = 0.40 (10% ethyl acetate in benzene); $[\alpha]^{20}_D = +8°$ (c = 1.0, $CHCl_3$) (lit. $[\alpha]^{25}_D = +5.4°$, c = 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.4−6.9 (m, 20 H), 6.19 (d, 1 H, J = 2.1 Hz), 6.12 (d, 1 H, J = 6.1 Hz), 4.98 (d, 1 H, J = 10.7 Hz), 4.95 (d, 1 H, J = 10.1 Hz), 4.94 (d, 1 H, J = 10.8 Hz), 4.92 (d, 1 H, J = 10.1 Hz), 4.81 (d, 1 H, J = 12.2 Hz), 4.75 (d, 1 H, J = 10.8 Hz), 4.55 (d, 1 H, J = 12.2 Hz), 4.54 (d, 1 H, J = 10.4 Hz), 4.40 (dd, 1 H, J = 9.8, 8.8 Hz), 4.13 (d, 1 H, J = 10.5 Hz, H 1), 3.93 (dd, 1 H, J = 11.7, 3.8 Hz), 3.88 (t, 1 H, J = 9.4 Hz), 3.84 (s, 3 H), 3.80 (s, 3 H), 3.79 (m, 2 H), 3.72 (s, 3 H), 3.59 (m, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.2, 160.8, 159.7, 158.9, 138.8, 138.5, 138.3, 128.3, 128.3, 128.1, 128.1, 128.0, 128.0, 127.9, 127.5, 127.5, 127.3, 127.2, 127.1, 91.6, 90.7, 87.4, 79.9, 79.5, 78.3, 75.8, 75.0, 74.4, 73.0, 72.5, 69.0; FTIR (neat film) 3029, 2936, 1608, 1592, 1205, 1154, 1067, 697 cm^{-1}; HRMS (FAB) *m/z* calcd for $C_{43}H_{47}O_8$ (M + H) 691.3271, found 691.3268. Anal. Calcd for $C_{43}H_{46}O_8$: C, 74.76; H, 6.71. Found: C, 75.15; H, 6.84.

Isopropyl 3,4,6-Tri-*O*-benzyl-2-*N*-benzyloxycarbonyl-2-deoxy-β-D-glucopyranoside (10). R_f = 0.79 (15% ethyl acetate in dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.4−7.2 (m, 20 H), 5.08 (m, 2 H), 4.95 (br s, 1 H, H 1), 4.79 (d, 1 H, J = 11.0 Hz), 4.76 (d, 1 H, J = 11.2 Hz), 4.65 (d, 1 H, J = 11.3 Hz), 4.61 (d, 1 H, J = 12.0 Hz), 4.58 (d, 1 H, J = 11.3 Hz), 4.55 (d, 1 H, J = 12.3 Hz), 4.04 (br s, 1 H), 3.91 (septet, 1 H), 3.74 (dd, 1 H, J = 10.9, 2.2 Hz), 3.68 (dd, 1 H, J = 10.8, 4.7), 3.57 (m, 1 H), 3.52 (m, 1 H), 3.19 (br s, 1 H), 1.22 (d, 3 H, J = 6.1 Hz), 1.06 (d, 3 H, J = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.5, 138.1, 138.1, 136.5, 131.0, 129.3, 128.4, 128.3, 128.3, 128.3, 127.9, 127.8, 127.7, 127.5, 124.7, 95.3, 78.8, 74.9, 74.7, 74.6, 73.3, 71.9, 68.9, 66.4, 58.3, 23.4, 21.8; FTIR (neat film) 3317, 3030, 1695, 1579, 1091 cm^{-1}; HRMS (FAB) *m/z* calcd for $C_{38}H_{42}NO_7$ (M − H) 624.2961, found 624.2961.

1-Deoxy-1-(*S*-ethyl)-2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (11).[30] α-Anomer: white solid; mp 88−89 °C (lit. mp 91 °C); R_f = 0.42 (5% ethyl ether in benzene); $[\alpha]^{20}_D = +108°$ (c = 1.7, $CHCl_3$) (lit. $[\alpha]^{22}_D = +108°$, c = 2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.4−7.2 (m, 20 H), 5.44 (d, 1 H, J = 4.9 Hz, H 1), 4.97 (d, 1 H, J = 11.0 Hz), 4.85 (d, 1 H, J = 10.7 Hz), 4.79 (d, 1 H, J = 10.7 Hz), 4.75 (d, 1 H, J = 11.7 Hz), 4.69 (d, 1 H, J = 11.7 Hz), 4.63 (d, 1 H, J = 12.0 Hz), 4.49 (d, 1 H, J = 10.7 Hz), 4.48 (d, 1 H, J = 12.0 Hz), 4.22 (m, 1 H), 3.87 (m, 2 H), 3.79 (dd, 1 H, J = 10.6, 3.7 Hz), 3.66 (m, 2 H), 2.58 (m, 2 H), 1.30 (t, 1 H, J = 7.4 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.8, 138.4, 138.0, 138.0, 128.5, 128.4, 128.4, 128.4, 128.2, 128.1, 127.9, 127.9, 127.9, 127.7, 127.7, 127.6, 83.1, 82.6, 79.6, 77.5, 75.7, 75.0, 73.5, 72.4, 70.5, 68.6, 23.8, 14.8; FTIR (neat film) 3030, 2955, 1596, 1453, 1363, 1074, 735 cm^{-1}; HRMS (FAB) *m/z* calcd for $C_{36}H_{39}O_5S$ (M − H) 583.2518, found 583.2517. Anal. Calcd for $C_{36}H_{40}O_5S$: C, 73.94; H, 6.89. Found: C, 73.89; H, 6.78. β-Anomer: white solid, mp 88 °C (lit. mp 94 °C); R_f = 0.51 (5% ethyl ether in benzene); $[\alpha]^{20}_D = +9°$ (c = 0.8, $CHCl_3$) (lit. $[\alpha]^{24}_D = +4.7°$, c = 2.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.4−7.1 (m, 20 H), 4.94 (d, 1H, J = 10.9 Hz), 4.93 (d, 1 H, J = 10.1 Hz), 4.85 (d, 1 H, J = 11.1 Hz), 4.82 (d, 1 H, J = 10.8 Hz), 4.74 (d, 1 H, J = 10.1 Hz), 4.61 (d, 1 H, J = 12.2 Hz), 4.57 (d, 1 H, J = 10.8 Hz), 4.56 (d, 1 H, J = 12.1 Hz), 4.47 (d, 1 H, J = 9.9 Hz, H 1), 3.75 (dd, 1 H, J = 10.7, 1.8 Hz), 3.68 (m, 2 H), 3.61 (t, 1 H, J = 9.5 Hz), 3.47 (m, 1 H), 3.45 (t, 1 H, J = 9.3 Hz), 2.77 (m, 2 H), 1.33 (t, 3 H, J = 7.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.5, 138.2, 138.1, 138.0, 128.5, 128.4, 128.4, 128.0, 127.9, 127.8, 127.8, 127.7, 127.6, 86.7, 85.1, 81.8, 79.1, 78.0, 75.8, 75.5, 75.1, 73.4, 69.1, 25.0, 15.2; FTIR (neat film) 3030, 2922, 1453, 1126, 1088, 735 cm^{-1}; HRMS (FAB) *m/z* calcd for $C_{36}H_{39}O_5S$ (M − H) 583.2518, found 583.2517. Anal. Calcd for $C_{36}H_{40}O_5S$: C, 73.94; H, 6.89. Found: C, 73.59; H, 7.02.

***tert*-Butyl 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranoside (12).** Viscous oil. Anal. Calcd for $C_{38}H_{44}O_6$: C, 76.48; H, 7.43. Found (anomeric mixture): C, 76.58; H, 7.36. Analytical samples of each anomer were separated by HPLC (10% ethyl acetate in hexane). α-Anomer: viscous oil; R_f = 0.53 (20% ethyl acetate in hexane); $[\alpha]^{23}_D = +25°$ (c = 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6) δ 7.35−7.06 (m, 25 H), 5.16 (d, 1 H, J = 3.75, H 1), 5.00 (dd, 2 H, J = 11.57), 4.49 (d, 1 H, J = 11.53), 4.47 (d, 1 H, J = 11.68), 4.38 (d, 1 H, J = 12.20), 4.31 (t, 1 H, J = 9.31), 4.27 (ddd, 1 H, J = 1.69, 4.31, 10.02), 3.83 (dd, 1 H, J = 9.03, 9,99), 3.80 (dd, 1 H, J = 4.35, 10.62), 3.68 (dd, 1 H, J = 1.62, 10.39), 3.56 (dd, 1 H, J = 3.63, 9.68), 1.23 (s, 9 H); ^{13}C NMR (126, MHz, C_6D_6) δ 140.36, 139.87, 139.593, 139.589, 128.91, 128.90, 128.82, 128.79, 128.38, 128.36, 128.16, 128.08, 127.98, 127.93, 127.76, 91.97, 82.96, 81.44, 79.26, 75.83, 75.48, 75.36, 73.85,73.35, 71.31, 70.20, 29.09; FTIR 2976, 2929, 2866, 1454, 1366, 1157, 1089, 1073, 1042, 735, 697 cm^{-1}; HRMS (FAB) *m/z* calcd for $C_{38}H_{44}O_6Na$ (M + Na$^+$) 619.3036, found 619.3030. β-Anomer: viscous oil; R_f = 0.53 (20% ethyl acetate in hexane); $[\alpha]^{23}_D = +44°$ (c = 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6) δ 7.41−7.06 (m, 25 H), 5.09 (d, 1 H, J = 11.54), 5.03 (d, 1 H, J = 11.22), 4.88 (d, 1 H, J = 11.22), 4.84 (d, 1 H, J = 11.18), 4.75 (d, 1 H, J = 11.44), 4.56 (m, 2 H, H 1), 4.48 (d, 1 H, J = 3.46, 9.32), 1,27 (s, 9 H); ^{13}C NMR (126 MHz, C_6D_6) δ 140.01, 139.96, 139.76, 139.53, 128.89, 128.85, 128.84, 128.82, 128.45, 128.44, 128.33, 128.24, 128.13, 127.97 127.94, 127.89, 98.84, 85.79, 83.20, 78.90, 75.95, 75.88, 75.44, 75.23, 75.10, 73.78, 70.12,29.36; FTIR (neat film) 3031, 2975, 2904, 2867, 1454, 1364, 1070, 735, 697; HRMS (FAB) *m/z* calcd for $C_{38}H_{44}O_6Na$ (M + Na$^+$) 619.3034, found 619.3030.

Methyl-*O*-(2,3,4,6-tetra-*O*-benzoyl-?-D-mannopyranosyl)−(1 → 4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (13). Viscous oil; R_f = 0.56 (11% ethyl acetate in benzene); $[\alpha]^{23}_D = -28°$ (c = 2.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (m, 2 H), 8.09 (m, 2 H), 8.02 (m, 4 H), 7.41 (m, 4 H), 7.25−6.84 (m, 2 H), 6.74 (m, 2 H), 6.65 (t, 1 H, J = 10.2 Hz), 6.40 (dd, 1 H, J = 3.2, 10.0 Hz), 6.24 (dd, 1 H, J = 1.7, 3.3 Hz), 5.93 (d, 1 H, J = 1.7 Hz, H 1), 5.09 (d, 1 H, J = 11.2 Hz), 4.93 (d, 1 H, J = 11.2 Hz), 4.84 (dd, 1 H, J = 2.6, 12.2 Hz), 4.68 (m, 1 H), 4.62 (d, 1 H, J = 3.4 Hz, H 1′), 4.61 (d, 1 H, J = 12.0 Hz), 4.56 (d, 1 H, J = 12.0 Hz), 4.44 (dd, 1 H, J = 3.4, 12.2 Hz), 4.37 (d, 1 H, J = 11.9 Hz), 4.34 (d, 1 H, J = 11.9 Hz), 4.28 (t, 1 H, J = 9.3 Hz), 4.17 (t, 1 H, J = 9.3 Hz), 3.95 (m, 2 H), 3.78 (m, 1 H), 3.47 (dd, 1 H, J = 3.4, 9.5 Hz), 3.20 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.28, 166.23, 166.05, 165.52, 139.5, 139.36, 139.22, 138.22, 133.62, 133.48, 133.38, 133.18, 131.71, 131.21, 130.60, 130.57, 130.43, 130.37, 130.36, 130.17, 130.10, 129.67, 129.66, 129.05, 129.00, 128.98, 128.95, 128.90, 128.76, 128.67, 128.36, 128.25, 128.16, 127.68, 126.03, 100.05, 98.46, 81.82, 81.75, 77.10, 75.69, 74.12, 73.10, 71.49, 71.15, 70.66, 70.65, 70.02, 67.76, 63.12, 55.39, 21.74; FTIR (neat film) 3033, 2904, 1729, 1452, 1265, 1106, 1048, 1027, 710 cm^{-1}; HRMS (FAB) *m/z* calcd for $C_{62}H_{57}O_{15}$ (M − H) 1041.3697, found 1041.3694. Anal. Calcd for $C_{62}H_{58}O_{15}$: C, 71.39; H, 5.60. Found: C, 71.32; H, 5.67.

Dihydrocholesteryl-2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranoside (14). Viscous oil; R_f = 0.50 (20% ethyl acetate in hexanes); $[\alpha]^{23}_D = -22°$ (c = 2.7, $CHCl_3$) 1H NMR (500 MHz, C_6D_6) δ 8.30−8.18 (m, 4 H), 8.00−7.94 (m, 4 H), 7.15−6.65 (m, 12 H), 6.56 (t, 1 H, J = 10.1 Hz), 6.40 (dd, 1 H, J = 9.9, 3.3 Hz), 6.07 (dd, 1 H, J = 3.2, 1.8 Hz), 5.21 (d, 1 H, J = 1.8 Hz, H 1), 4.84 (dd, 1 H, J = 12.2, 9.8 Hz), 4.70 (m, 1 H), 4.47 (dd, 1 H, J = 12.2, 4.8 Hz), 3.49 (m, 1 H), 1.99 (m, 1 H), 1.84 (m, 1 H), 1.70−0.46 (m, 44 H); ^{13}C NMR (126 MHz, C_6D_6) δ 166.25, 166.23, 166.10, 165.99, 150.29, 138.47, 133.72, 133.63, 133.39, 133.27, 131.20, 130.56, 130.54, 130.48, 130.45, 130.36, 130.10, 130.06, 129.20, 128.99, 128.96, 128.77, 128.68, 128.49, 128.45, 128.30,

(29) Stewart, A. O.; Williams, R. M. *J. Am. Chem. Soc.* **1985**, *107*, 4289−4296.

(30) (a) Dasgupta, F.; Garegg, P. J. *Acta Chem. Scand.* **1989**, *43*, 471. (b) Li, Z.; Liu, P.; Li, Z.; Qui, D.; Cai, M. *Synth. Commun.* **1990**, *14*, 2169. (c) Weygand, F.; Ziemann, H. *Liebigs Ann. Chem.* **1962**, *657*, 179−193.

124.65, 122.29, 96.84, 78.56, 72.18, 71.26, 70.06, 68.27, 63.58, 57.16, 57.09, 54.93, 45.42, 43.28, 40.81, 40.27, 37.33, 37.01, 36.58, 36.47, 36.07, 36.04, 32.78, 29.32, 29.03, 28.75, 28.14, 24.94, 24.69, 23.39, 23.14, 21.92, 19.38, 12.79, 12.72; FTIR (neat film) 2934, 2866, 1730, 1452, 1267, 1108, 1070, 710 cm^{-1}; HRMS (FAB) *m/z* calcd for $C_{61}H_{75}O_{10}$ (MH^+) 967.5360, found 967.5373. Anal. Calcd for $C_{61}H_{74}O_{10}$: C, 75.75; H, 7.71. Found: C, 75.56; H, 7.67.

Methyl-*O*-(2,3,4,6-Tetra-*O*-benzyl-D-glucopyranosyl)−(1 → 6)-2,3,4-tri-*O*-benzyl-D-glucopyranoside (15).[31] α-Anomer: white solid, mp 107−108 °C (lit. mp 101 °C); R_f = 0.65 (33% ethyl acetate in hexane); $[\alpha]^{20}_D$ = +49° (*c* = 0.6, $CHCl_3$) (lit. $[\alpha]^{23}_D$ = +57.1°, *c* = 1.97, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.4−7.1 (m, 35 H), 4.98 (d, 1 H, *J* = 3.7 Hz, H 1), 4.96 (d, 1 H, *J* = 11.0 Hz), 4.94 (d, 1 H, *J* = 10.9 Hz), 4.91 (d, 1 H, *J* = 11.0 Hz), 4.82 (d, 1 H, *J* = 11.0 Hz), 4.81 (d, 1 H, *J* = 10.9 Hz), 4.77 (d, 1 H, *J* = 10.9 Hz), 4.71 (d, 1 H, *J* = 11.9 Hz), 4.66 (s, 2 H), 4.64 (d, 1 H, *J* = 11.3 Hz), 4.57 (d, 1 H, *J* = 12.1 Hz), 4.57 (d, 1 H, *J* = 12.0 Hz), 4.55 (d, 1 H, *J* = 3.5 Hz, H 1′), 4.45 (d, 1 H, *J* = 11.0 Hz), 4.42 (d, 1 H, *J* = 12.1 Hz), 3.98 (t, 1 H, *J* = 9.3 Hz), 3.95 (t, 1 H, *J* = 9.3 Hz), 3.79 (m, 3 H), 3.71 (dd, 1 H, *J* = 11.3, 2.7 Hz), 3.65 (m, 3 H), 3.55 (dd, 1 H, *J* = 10.7, 2.2 Hz), 3.54 (dd, 1 H, *J* = 9.7, 3.5 Hz), 3.44 (dd, 1 H, *J* = 9.6, 3.6 Hz), 3.35 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.8, 138.5, 138.4, 138.2, 138.1, 128.4, 128.4, 128.3, 128.3, 128.0, 128.0, 127.9, 127.9, 127.8, 127.7, 127.6, 127.6, 127.6, 127.5, 127.5, 98.0, 97.3, 82.2, 81.7, 80.1, 80.0, 77.8, 77.6, 75.7, 75.5, 75.0, 74.9, 73.4, 72.3, 70.4, 70.2, 68.5, 66.0, 55.1; FTIR (neat film) 3030, 2924, 1453, 1159, 1136, 1028, 736 cm^{-1}; HRMS (FAB) *m/z* calcd for $C_{62}H_{65}O_{11}$ (M − H) 985.4527, found 985.4531. Anal. Calcd for $C_{62}H_{66}O_{11}$: C, 75.43; H, 6.74. Found: C, 75.30; H, 6.78. β-Anomer: white solid; mp 128−130 °C (lit. mp 133−135 °C); R_f = 0.61 (33% ethyl acetate in hexane); $[\alpha]^{20}_D$ = +18.5° (*c* = 1.3, $CHCl_3$) (lit. $[\alpha]^{23}_D$ = +18.6°, *c* = 0.49, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.4−7.1 (m, 35 H), 4.97 (d, 1 H, *J* = 11.0 Hz), 4.96 (d, 1 H, *J* = 10.7 Hz), 4.90 (d, 1 H, *J* = 10.8 Hz), 4.79 (m, 4 H), 4.74 (d, 1 H, *J* = 11.2 Hz), 4.71 (d, 1 H, *J* = 11.1 Hz), 4.65 (d, 1 H, *J* = 12.1 Hz), 4.60 (d, 1 H, *J* = 3.4 Hz, H 1′), 4.58 (d, 1 H, *J* = 10.9 Hz), 4.52 (m, 3 H), 4.34 (d, 1 H, *J* = 7.8 Hz, H 1), 4.18 (dd, 1 H, *J* = 10.6, 2.0 Hz), 3.98 (t, 1 H, *J* = 9.3 Hz), 3.82 (m, 1 H), 3.72 (dd, 1 H, *J* = 11.1, 1.7 Hz), 3.67 (dd, 1 H, *J* = 10.8, 4.9 Hz), 3.62 (t, 1 H, *J* = 9.0 Hz), 3.56 (t, 1 H, *J* = 9.4 Hz), 3.51 (m, 3 H), 3.42 (m, 1 H), 3.32 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.8, 138.4, 138.4, 138.1, 137.9, 128.4, 128.3, 128.2, 128.0, 127.8, 127.8, 127.7, 127.7, 127.6, 127.5, 97.9, 97.2, 82.1, 81.6, 80.1, 79.9, 77.7, 77.5, 75.7, 75.5, 75.0, 74.9, 73.4, 72.3, 70.3, 70.2, 68.4, 66.0, 55.1; FTIR (neat film) 3029, 2945, 1497, 1388, 1068, 739 cm^{-1}; HRMS (FAB) *m/z* calcd for $C_{62}H_{65}O_{11}$ (M − H) 985.4527, found 985.4531. Anal. Calcd for $C_{62}H_{66}O_{11}$: C, 75.43; H, 6.74. Found: C, 75.59; H, 6.79.

Methyl-*O*-(2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl)-(1 → 6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (16). Viscous oil; R_f = 0.40 (33% ethyl acetate in hexane); $[\alpha]^{20}_D$ = +18° (*c* = 1.4, $CHCl_3$) (lit. $[\alpha]^{21}_D$ = +19.6°, *c* = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (m, 1 H), 7.88 (m, 1 H), 7.82 (m, 1 H), 7.6−7.0 (m, 35 H), 5.89 (t, 1 H, *J* = 9.6 Hz), 5.68 (t, 1 H, *J* = 9.69 Hz), 5.60 (dd, 1 H, *J* = 9.6, 7.8 Hz), 4.90 (d, 1 H, *J* = 10.89 Hz), 4.83 (d, 1 H, *J* = 7.8 Hz, H 1), 4.74 (d, 1 H, *J* = 12.1 Hz), 4.69 (d, 1 H, *J* = 11.1 Hz), 4.61 (dd, 1 H, *J* = 12.1, 3.6 Hz), 4.60 (d, 1 H, *J* = 12.1 Hz), 4.51 (m, 3 H, incorporates H 1′), 4.29 (d, 1 H, *J* = 11.1 Hz), 4.15 (d, 1 H, *J* = 10.3 Hz), 4.15 (m, 1 H), 3.89 (t, 1 H, *J* = 9.3 Hz), 3.74 (m, 2 H), 3.43 (dd, 1 H, *J* = 9.6, 3.6 Hz), 3.83 (t, 1 H, *J* = 9.3 Hz), 3.21 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.2, 166.9, 165.2, 165.0, 138.8, 138.2, 138.1, 133.5, 133.3, 133.2, 133.1, 129.9, 129.8, 129.7, 129.6, 129.4, 129.2, 128.8, 128.7, 128.5, 128.4, 128.3, 128.3, 128.3, 128.3, 128.2, 127.9, 127.9, 127.6, 127.5, 127.5, 127.0, 124.8, 101.3, 98.0, 81.9, 79.8, 77.4, 75.6, 74.7, 73.4, 72.9, 72.2, 71.8, 69.8, 69.5, 68.3, 63.3, 55.0; FTIR (neat film) 3032, 2930, 1735, 1731, 1602, 1452, 1267, 1093, 710 cm^{-1}; HRMS (FAB) *m/z* calcd for $C_{62}H_{57}O_{15}$ (M − H) 1041.3697, found 1041.3693. Anal. Calcd for $C_{62}H_{58}O_{15}$: C, 71.39; H, 5.60. Found: C, 71.08; H, 5.40.

(31) (a) Kim, W.-S.; Hosono, S.; Sasai, H.; Shibasaki, M. *Heterocycles* **1996**, *42*, 795−809. (b) Fukase, K.; Hasuoka, A.; Kinoshita, I.; Aoki, Y.; Kusumoto, S. *Tetrahedron* **1995**, *51*, 4923. (c) Koide, K.; Ohno, M.; Kobayashi, S. *Tetrahedron Lett.* **1991**, *48*, 7065−7068.

Methyl-*O*-(2,3,4,6-Tetra-*O*-benzyl-D-glucopyranosyl)−(1 → 4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (17). α-Anomer: viscous oil; R_f = 0.67 (3% ethyl acetate in dichloromethane); $[\alpha]^{20}_D$ = +40° (*c* = 1.1, $CHCl_3$) (lit. $[\alpha]^{23}_D$ = +47.5°, *c* = 0.71, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32−7.06 (m, 35 H), 5.70 (d, 1 H, *J* = 3.6 Hz, H 1), 5.04 (d, 1 H, *J* = 11.5 Hz), 4.88 (d, 1 H, *J* = 10.84 Hz), 4.80 (d, 1 H, *J* = 11.7 Hz), 4.78 (d, *J* = 10.6 Hz), 4.77 (d, 1 H, *J* = 10.9 Hz), 4.70 (d, 1 H, *J* = 12.17 Hz), 4.60 (d, 1 H, *J* = 3.57 Hz, H 1′), 4.59 (d, 1 H, *J* = 11.9 Hz), 4.57 (d, 1 H, *J* = 12.2 Hz), 4.54 (d, 1 H, *J* = 11.9 Hz), 4.52 (d, 1 H, *J* = 12.2 Hz), 4.49 (s, 2H), 4.41 (d, 1 H, *J* = 10.86 Hz), 4.27 (d, 1 H, *J* = 12.1 Hz), 4.09 (t, 1 H, *J* = 8.8 Hz), 4.07 (t, 1 H, *J* = 9.0 Hz), 3.90 (dd, 1 H, *J* = 9.8, 8.6 Hz), 3.84 (m, 2H), 3.67 (m, 3H), 3.59 (dd, 1 H, *J* = 9.2, 3.7 Hz), 3.49 (dd, 1 H, *J* = 9.7, 3.6 Hz), 3.48 (dd, 1 H, *J* = 10.7, 2.9 Hz), 3.38 (dd, 1 H, *J* = 10.66, 1.56 Hz), 3.37 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.9, 138.8, 138.5, 138.2, 138.0, 138.0, 128.5, 128.4, 128.3, 128.3, 128.3, 128.1, 128.0, 127.9, 127.9, 127.7, 127.7, 127.6, 127.5, 127.4, 127.3, 127.1, 126.8, 110.0, 97.8, 96.7, 82.1, 82.1, 80.2, 79.5, 77.8, 76.8, 75.0, 74.4, 73.5, 73.4, 73.3, 73.2, 72.3, 71.0, 69.5, 69.0, 68.2, 55.2; FTIR (neat film) 3028, 2926, 1453, 1156, 1095, 1028, 734 cm^{-1}; HRMS (FAB) *m/z* calcd for $C_{62}H_{65}O_{11}$ (M − H) 985.4527, found 985.4531. β-Anomer: white solid; mp 88−89 °C (lit. mp 87−88 °C); R_f = 0.56 (3% ethyl acetate in dichloromethane); $[\alpha]^{20}_D$ = +20° (*c* = 1.0, $CHCl_3$) (lit. $[\alpha]^{23}_D$ = +24.2°, *c* = 2.23, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49−7.20 (m, 35 H), 5.14 (d, 1 H, *J* = 11.1 Hz), 4.91 (d, 1 H, *J* = 10.8 Hz), 4.85 (d, 1 H, *J* = 11.02 Hz), 4.85 (d, 1 H, *J* = 11.1 Hz), 4.84 (s, 1 H), 4.83 (d, 1 H, *J* = 11.05 Hz), 4.80 (d, 1 H, *J* = 10.6 Hz), 4.80 (d, 1 H, *J* = 11.4 Hz), 4.65 (d, 1 H, *J* = 12.2 Hz), 4.62 (d, 1 H, *J* = 12.0 Hz), 4.62 (d, 1 H, *J* = 3.7 Hz, H 1′), 4.60 (d, 1 H, *J* = 11.0 Hz), 4.48 (d, 1 H, *J* = 12.0 Hz), 4.44 (d, 1 H, *J* = 11.8 Hz), 4.43 (d, 1 H, *J* = 7.9 Hz, H 1), 4.42 (d, 1 H, *J* = 12.0 Hz), 4.01 (dd, 1 H, *J* = 10.0, 9.0 Hz), 3.90 (t, 1 H, *J* = 9.2 Hz), 3.89 (dd, 1 H, *J* = 11.0, 3.3 Hz), 3.88 (dd, 1 H, *J* = 11.0, 3.2 Hz), 3.76 (dd, 1 H, *J* = 11.0, 1.9 Hz), 3.65 (dd, 1 H, *J* = 9.8, 8.8 Hz), 3.64 (dd, 1 H, *J* = 9.8, 2.8 Hz), 3.59 (dd, 1 H, *J* = 11.2, 4.8 Hz), 3.53 (dd, 1 H, *J* = 10.9, 2.0 Hz), 3.51 (t, 1 H, *J* = 8.9 Hz), 3.51 (m, 1 H), 3.41 (dd, 1 H, *J* = 9.0, 7.9 Hz), 3.41 (s, 3H), 3.34 (ddd, 1 H, *J* = 9.8, 4.6, 1.8 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.8, 138.8, 138.8, 138.6, 138.6, 138.1, 128.7, 128.6, 128.6, 128.5, 128.4, 128.3, 128.2, 128.2, 128.0, 128.0, 127.9, 127.8, 127.8, 127.7, 127.5, 127.3, 102.7, 98.6, 85.1, 83.0, 80.6, 79.0, 78.3, 76.9, 76.8, 75.8, 75.6, 75.4, 75.1, 75.0, 73.8, 73.6, 73.5, 70.2, 70.1, 69.2, 68.1, 55.5; FTIR (neat film) 3028, 2926, 1453, 1156, 1095, 1028, 734 cm^{-1}; HRMS (FAB) *m/z* calcd for $C_{62}H_{65}O_{11}$ (M − H) 985.4527, found 985.4531.

Methyl-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)−(1 → 4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (18). Viscous oil; R_f = 0.54 (15% ethyl acetate in benzene); $[\alpha]^{20}_D$ = +1° (*c* = 1.5, $CHCl_3$) (lit. $[\alpha]^{25}_D$ = +1°, *c* = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.0−7.2 (m, 35 H), 5.62 (t, 1 H, *J* = 9.5 Hz), 5.55 (t, 1 H, *J* = 9.6 Hz), 5.46 (dd, 1 H, *J* = 9.6, 8.0 Hz), 5.07 (d, 1 H, *J* = 11.2 Hz), 4.81 (d, 1 H, *J* = 11.1 Hz), 4.78 (d, 1 H, *J* = 8.1 Hz, H 1), 4.76 (d, 1 H, *J* = 12.9 Hz), 4.75 (d, 1 H, *J* = 12.4 Hz), 4.60 (d, 1 H, *J* = 12.2 Hz), 4.56 (d, 1 H, *J* = 3.5 Hz, H 1′), 4.40 (dd, 1 H, *J* 12.1, 3.6 Hz), 4.34 (d, 1 H, *J* = 12.2 Hz), 4.26 (dd, 1 H, *J* = 12.1, 5.0 Hz), 3.96 (t, 1 H, *J* = 9.4 Hz), 3.88 (t, 1 H, *J* = 9.1 Hz), 3.73 (m, 2 H), 3.50 (m, 1 H), 3.46 (dd, 1 H, *J* = 9.5, 3.7 Hz), 3.42 (dd, 1 H, *J* = 10.7, ∼1 Hz), 3.28 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.1, 165.8, 165.1, 164.9, 145.6, 139.3, 138.4, 137.9, 133.4, 133.4, 133.2, 133.0, 131.1, 129.8, 129.7, 129.7, 129.4, 129.1, 128.9, 128.9, 128.5, 128.4, 128.4, 128.3, 128.1, 127.8, 127.4, 127.2, 124.8, 100.4, 98.5, 80.0, 78.8, 77.3, 75.4, 73.6, 73.6, 73.2, 72.3, 71.8; FTIR (neat film) 3032, 2939, 1736, 1731, 1601, 1451, 1265, 1093, 710 cm^{-1}; HRMS (FAB) *m/z* calcd for $C_{62}H_{57}O_{15}$ (M − H) 1041.3697, found 1041.3693. Anal. Calcd for $C_{62}H_{58}O_{15}$: C, 71.39; H, 5.60. Found: C, 71.08; H, 5.73.

2′,3′,5′-Tri-*O*-benzoylthymidine (19). Viscous oil; R_f = 0.13 (33% ethyl acetate in hexanes); $[\alpha]^{23}_D$ = −102° (*c* = 1.7, $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6) δ 8.12 (m, 2 H), 7.88 (m, 2 H), 7.84 (m, 2 H), 7.66 (m, 1 H), 7.56−7.48 (m, 4 H), 7.40−7.26 (m, 5 H), 6.47 (d, 1 H, *J* = 9.6 Hz, H 1), 6.31 (t, 1 H, *J* = 2.6 Hz), 5.55 (m, 1 H), 5.49 (dt, 1 H, *J* = 9.8, 2.7 Hz), 4.33 (dd, 1 H, *J* = 11.0, 5.7 Hz), 4.24 (t, 1 H, *J* = 11.0 Hz),1.95 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.41, 165.11, 164.85, 134.49, 133.84, 133.78, 133.66, 129.98, 129.87, 129.25, 128.86,

128.74, 128.59, 128.52, 128.18, 112.17, 78.55, 69.19, 68.20, 66.74, 64.28, 15.58; FTIR (neat film) 3250 (br), 3030, 1731, 1698, 1694, 1265, 1108, 1094, 709 cm^{-1}; HRMS (FAB) *m/z* calcd for $C_{31}H_{27}N_2O_9$ (MH^+) 571.1717, found 571.1719. Anal. Calcd for $C_{31}H_{26}N_2O_9$: C, 65.26; H, 4.59; N, 4.91. Found: C, 64.90; H, 4.91; N, 4.45.

1-Deoxy-1-(*N*-trimethylacetyl)-2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (20). Viscous oil; $R_f = 0.52$ (33% ethyl acetate in hexane); $[\alpha]^{20}_D = +54°$ ($c = 1.1°$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.2−7.2 (m, 20 H), 6.30 (d, 1 H, $J = 6.6$ Hz), 5.81 (dd, 1 H, $J = 6.6$, 5.6 Hz, H 1), 4.93 (d, 1 H, $J = 10.9$ Hz), 4.80 (d, 1 H, $J = 11.0$ Hz), 4.79 (d, 1 H, $J = 10.3$ Hz), 4.64 (d, 1 H, $J = 12.1$ Hz), 4.55 (m, 2 H), 4.52 (d, 1 H, $J = 10.6$ Hz), 4.48 (d, 1 H, $J = 12.1$ Hz), 3.85 (dd, 1 H, $J =$ 9.2, 5.4 Hz), 3.80 (dd, 1 H, $J = 10.8$, 3.1 Hz), 3.76 (dd, 1 H, $J = 9.6$, 9.0 Hz), 3.68 (dd, 1 H, $J = 10.7$, 2.2 Hz), 3.60 (t, 1 H, $J = 9.0$ Hz), 3.59 (m, 1 H), 1.23 (s, 9 H); NOE 12.11% enhancement of H-2 upon irradiation of H-1; ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.3, 138.3, 137.8, 137.8, 137.1, 128.4, 128.4, 128.3, 128.2, 128.0, 127.9, 127.9, 127.8, 127.7, 127.7, 127.6, 127.6, 81.9, 77.5, 76.7, 75.4, 75.1, 74.6, 73.5, 72.0, 71.0, 68.1, 27.4; FTIR (neat film) 2871, 1672, 1497, 1454, 1084, 1073, 1028, 736, 697 cm^{-1}; HRMS (FAB) *m/z* calcd for $C_{39}H_{46}NO_6$ (M + H) 624.3325, found 624.3325. Anal. Calcd for $C_{39}H_{45}NO_6$: C, 75.09; H, 7.27; N, 2.25. Found: C, 74.86; H, 7.25; N, 2.34.

Azido-2,3,5-tri-*O*-benzyl-L-arabinoside (21). Viscous oil. Anal. Calcd for $C_{26}H_{27}N_3O_4$: C, 70.09; H, 6.11; N, 9.43. Found (anomeric mixture): C, 70.31; H, 6.05; N, 9.17. Analytical samples of each anomer were separated by HPLC. α-Anomer: viscous oil; $R_f = 0.58$ (20% ethyl acetate in hexane); $[\alpha]^{23}_D = -102°$ ($c = 0.7$, $CHCl_3$); ^1H NMR (500 MHz, C_6D_6) δ 7.27−7.46 (m, 27H), 5.24 (d, 1 H, $J = 1.48$, H 1), 4.50 (q, 1 H, $J = 10.37$), 4.40 (d, 1 H, $J = 12.24$), 4.37 (d, 1 H $J =$ 11.99), 4.29 (d, 1 H, $J = 12.21$), 4.26 (d, 1 H, $J = 12.11$), 4.17 (d, 1 H, $J = 11.80$), 4.15 (dd, 1 H, $J = 2.64$, 8.00), 4.09 (d, 1 H, $J = 11.78$), 3.95 (dd, 1 H, $J = 1.61$, 2.52), 3.50 (d, 2 H, $J = 5.61$); ^{13}C NMR (126 MHz, C_6D_6) δ 139.07, 138.67, 138.13, 128.99, 128.93, 128.91, 128.68, 128.45, 128.39, 128.36, 128.25, 128.20, 128.09, 94.94, 88.52, 84.20, 84.06, 73.75, 72.52, 72.39, 70.12; FTIR (neat film) 3031, 2865, 2106, 1454, 1240, 1097, 736, 697 cm^{-1}; HRMS (FAB) *m/z* calcd for $C_{26}H_{27}N_3O_4Na$ (M + Na^+) 468.1899, found 468.1890. β-Anomer: viscous oil; $R_f = 0.48$ (20% ethyl acetate in hexane); $[\alpha]^{23}_D = +111°$ ($c = 0.7$, $CHCl_3$); ^1H NMR (500 MHz, C_6D_6) δ 7.25−7.03 (m, 16 H), 4.89 (d, 1 H, $J = 4.8$, H 1), 4.44 (d, 1 H, $J = 11.86$), 4.40 (d, 1 H, $J =$ 12.13), 4.34 (d, 1 H, $J = 11.75$), 4.29 (s, 2 H), 4.21−4.16 (m, 3 H), 3.84 (t, 1 H, $J = 4.80$), 3.59−3.51 (m, 2 H); ^{13}C NMR (126 MHz, C_6D_6) δ 139.08, 138.89, 138.34, 129.03, 128.91, 128.90, 128.46, 128.37, 128.29, 128.19, 128.09, 90.79, 84.75, 82.74, 81.89, 73.80, 73.00, 72.53, 71.28; FTIR (neat film) 3064, 3031, 2866, 2118, 1496, 1454, 1365, 1250, 1068, 1028, 736, 697 cm^{-1}; HRMS (FAB) *m/z* calcd for $C_{26}H_{27}N_3O_4Na$ (M + Na^+) 468.1899, found 468.1895.

Methyl-*O*-(2,3,4-tri-*O*-pivaloyl-β-D-xylopyranosyl)-(1 → 6)-2,3,4-tri-*O*-benzyl-D-glucopyranoside (22). $R_f = 0.14$ (11% ethyl acetate in hexane); $[\alpha]^{23}_D = -8.7$ ($c = 1.8$, $CHCl_3$); ^1H NMR (400 MHz, C_6D_6) δ 7.28−7.20 (m, 6 H), 7.16−7.00 (m, 9 H), 5.34 (t, 1 H, $J = 9.0$ Hz), 5.21 (dd, 1 H, $J = 7.1$, 9.1 Hz), 4.98 (m, 1 H), 4.95 (d, 1 H, $J = 11.4$ Hz), 4.91 (d, 1 H, $J = 11.5$ Hz), 4.71 (d, 1 H, $J = 11.5$ Hz), 4.59 (d, 1 H, $J = 3.3$ Hz, H 1′), 4.57 (d, 1 H, $J = 11.4$ Hz), 4.47 (d, 1 H, $J =$ 12.1 Hz), 4.40 (d, 1 H, $J = 12.1$ Hz), 4.23 (d, 1 H, $J = 7.2$ Hz, H 1), 4.18 (t, 1 H, $J = 9.2$ Hz), 3.94 (m, 2 H), 3.77 (dd, 1 H, $J = 5.6$, 10.6 Hz), 3.48 (m, 2 H), 3.20 (s, 3 H), 2.82 (dd, 1 H, $J = 9.5$, 11.5 Hz), 1.18 (s, 9 H), 1.10 (s, 9 H), 1.05 (s, 9 H); ^{13}C NMR (100 MHz, C_6D_6) δ 177.29, 176.99, 176.55, 140.04, 139.58, 139.48, 128.89, 128.80, 128.37, 128.36, 128.32, 128.28, 128.13, 128.05, 128.88, 102.06, 98.49, 82.56, 81.26, 78.80, 75.88, 75.15, 73.12, 72.49, 71.69, 70.97, 69.73, 69.10, 62.76, 55.47, 39.18, 39.15, 39.08, 27.72, 27.66, 27.53; FTIR (neat film) 2971, 1742, 1480, 1455, 1279, 1143, 1074, 698 cm^{-1}. Anal. Calcd for $C_{48}H_{64}O_{13}$: C, 67.90; H, 7.60. Found: C, 67.93; H, 7.62.

Phenyl 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranoside (23).[32] Viscous oil. Anal. Calcd for $C_{40}H_{40}O_6$: C, 77.90; H, 6.54. Found (anomeric mixture): C, 77.79; H, 6.63. Analytical samples of each anomer were separated by HPLC. α-Anomer: viscous oil; $R_f = 0.75$ (33% ethyl acetate in hexane); $[\alpha]^{20}_D = +86°$ ($c = 0.6$, $CHCl_3$) (lit. $[\alpha]^{20}_D = +83°$, $c = 3.0$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.42−7.00 (m, 25 H), 5.51 (d, 1 H, $J = 3.5$ Hz, H 1), 5.09 (d, 1 H, $J = 10.9$ Hz), 4.93 (d, 1 H, $J = 10.9$ Hz), 4.87 (d, 1 H, $J = 11.8$ Hz), 4.82 (d, 1 H, $J = 12.1$ Hz), 4.71 (d, 1 H, $J = 12.1$ Hz), 4.62 (d, 1 H, $J = 11.9$ Hz), 4.52 (d, 1 H, $J = 10.7$ Hz), 4.42 (d, 1 H, $J = 12.0$ Hz), 4.24 (t, 1 H, $J = 9.2$ Hz), 3.91 (m, 1 H), 3.82 (dd, 1 H, $J = 10.0$, 8.8 Hz), 3.76 (m, 2 H), 3.59 (dd, 1 H, $J = 10.8$, 2.1 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.6, 138.7, 138.1, 137.9, 137.7, 129.3, 128.4, 128.3, 128.3, 128.2, 127.9, 127.8, 127.8, 127.8, 127.6, 127.5, 122.2, 116.7, 95.3, 81.9, 79.6, 75.7, 75.0, 73.3, 73.2, 70.7, 68.1; FTIR (neat film) 3088, 2922, 1597, 1495, 1225, 1099, 1046, 1028, 697 cm^{-1}; HRMS (FAB) *m/z* calcd for $C_{41}H_{41}O_6$ (M + H) 629.2903, found 629.2906. β-Anomer: white solid; mp 85−86 °C (lit. mp 84.5−86 °C); $R_f = 0.75$ (33% ethyl acetate in hexane); $[\alpha]^{20}_D = -11°$ ($c = 0.5$, $CHCl_3$) (lit. $[\alpha]^{25}_D = -11.8°$, $c =$ 1.2, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.37−7.05 (m, 25 H), 5.05 (d, 1 H, $J = 11.0$ Hz), 5.01 (m (X of ABX), 1 H, $J_{H1,H2} = 7.57$ Hz, H 1) 4.96 (d, 1 H, $J = 11.0$ Hz), 4.84 (m, 3 H), 4.60 (d, 1 H, $J =$ 12.0 Hz), 4.57 (d, 1 H, $J = 10.2$ Hz), 4.53 (d, 1 H, $J = 12.1$ Hz), 3.80 (dd, 1 H, $J = 10.8$, 1.9 Hz), 3.77 (m, 2 H), 3.71 (m, 1 H), 3.69−3.60 (m, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.4, 138.1, 138.0, 137.8, 129.4, 128.3, 128.3, 128.2, 128.1, 127.8, 127.7, 127.7, 127.6, 127.6, 127.5, 127.4, 122.5, 116.7, 101.5, 84.5, 81.9, 77.5, 75.7, 75.0, 74.9, 74.9, 73.4, 68.7; FTIR (neat film) 3030, 2968, 1495, 1453, 1229, 1070, 1028, 696 cm^{-1}; HRMS (FAB) *m/z* calcd for $C_{41}H_{41}O_6$ (M + H) 629.2903, found 629.2906.

Myristoyl-3,4,6-tri-*O*-acetyl-2-deoxy-2-*N*-phthalamido-β-D-glucopyranoside (24). Viscous oil; $R_f = 0.65$ (50% ethyl acetate in hexanes); $[\alpha]^{23}_D = +40°$ ($c = 3$, $CHCl_3$); ^1H NMR (500 MHz, C_6D_6) δ 7.46 (dd, 1 H, $J = 4.8$, 3.3 Hz,), 7.12 (d, 1 H, $J = 8.9$ Hz, H 1), 6.82 (dd, 1 H, $J = 5.5$, 3.0 Hz), 6.27 (dd, 1 H, $J = 10.7$, 9.3 Hz), 5.44 (dd, 1 H, $J = 10.1$, 9.4 Hz), 4.88 (dd, 1 H, $J = 10.4$, 8.7 Hz), 4.28 (dd, 1 H, $J = 12.7$, 3.9 Hz), 3.97 (dd, 1 H, $J = 12.4$, 1.9 Hz), 3.402 (ddd, 1 H, $J = 10.3$, 2.3, 1.5 Hz), 1.90 (dt, 2 H, $J = 7.4$, 2.2 Hz), 1.71 (s, 3 H), 1.62 (s, 3 H), 1.48 (s, 3 H), 1.36−0.80 (m, 25 H); ^{13}C NMR (126 MHz, C_6D_6) δ 17107, 170.4, 170.3, 169.6, 128.7, 128.5, 128.4, 128.3, 90.6, 73.4, 71.5, 68.8, 61.5, 54.9, 34.3, 32.7, 30.5, 30.5, 30.4, 30.3, 30.2, 30.0, 29.8, 29.4, 25.1, 23.5, 20.6, 20.5, 20.2, 20.2, 14.7; FTIR (neat film) 2926, 2854, 1756, 1723, 1386, 1227, 1082, 1045, 722 cm^{-1}; HRMS (FAB) *m/z* calcd for $C_{34}H_{47}NO_{11}Na$ (MNa^+) 668.3046, found 668.3047. Anal. Calcd for $C_{34}H_{47}NO_{11}$: C, 63.24; H, 7.34; N, 2.17. Found: C, 63.36; H, 7.49; N, 2.22.

General Procedure for the Detection of Reactive Glycosyl Intermediates. Trifluoromethanesulfonyl 2,3,4,6-Tetra-*O*-methyl-D-mannopyrannoside (34). To a solution of 2,3,4,6-tetra-O-methyl-α-D-mannopyranosyl fluoride (**33**) (15 mg, 0.063 mmol, 1.0 equiv) in CD_2Cl_2 (0.8 mL) in a 5 mm NMR tube at −78 °C was added TMSOTf (19 μL, 0.095 mmol, 1.5 equiv). The reaction was briefly agitated (∼2−3 s; Fisher Vortex Genie 2) and was placed in the NMR probe at −60 °C. The conversion of **33** to **34** was monitored at this temperature over the course of 2 h (85% conversion; Figure 2a).

Bis(pentadeuteriophenyl)sulfonium 2,3,4,6-Tetra-*O*-methyl-α-D-mannopyranoside (35). To a freshly prepared solution of glycosyl triflate **34** (vide supra) at −78 °C was added a solution of bis-(pentadeuteriophenyl) sulfoxide (40 mg, 0.19 mmol, 3.0 equiv) in CD_2-Cl_2 (0.2 mL). After the solution was briefly agitated, the reaction was placed in the NMR probe at −60 °C. The conversion of **34** to **35** was complete within 20 min at this temperature (Figure 2b).

1-Deoxy-2,3,4,6-tetra-*O*-methyl-D-mannopyranosyl 2-Chloropyridinium Triflate (36). To a freshly prepared solution of glycosyl triflate **34** (vide supra) at −78 °C was added 2-chloropyridine (24 μL, 0.25 mmol, 4.0 equiv). After the solution was briefly agitated, the reaction was placed in the NMR probe at −60 °C. The conversion of **34** to **36** was complete within 20 min at this temperature (Figure 2c).

Dehydrative Glycosylation with 2,3,4,6-Tetra-*O*-methyl-D-mannopyranose (38) To Form the Isopropyl 2,3,4,6-Tetra-*O*-methyl-D-Mannopyranoside (8). To a solution of 2,3,4,6-tetra-*O*-methyl-D-mannopyranose (**38**) (8.0 mg, 0.034 mmol, 1.0 equiv) and bis(pentadeuteriophenyl) sulfoxide (14 mg, 0.068 mmol, 2.0 equiv) in CD_2Cl_2 (1 mL) at −78 °C in a 5 mm NMR tube was added triflic anhydride (8 μL, 0.05 mmol, 1.4 equiv). After the solution was briefly agitated, the

(32) (a) Briner, K.; Vasella, A. *Helv. Chim. Acta* **1990**, *73*, 1764−1778. (b) Koto, S.; Morishima, N.; Araki, M.; Tsuchiya, T.; Zen, S. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1895−1896.

reaction was placed in the NMR probe at −60 °C. The conversion of **38** to **35** was complete within 20 min at this temperature (Figure 4b). The reaction was removed from the NMR probe, cooled to −78 °C, and 2-chloropyridine was added (10 μL, 0.102 mmol, 3.0 equiv). After the solution was briefly agitated, the reaction was placed in the NMR probe at −60 °C and then warmed to −40 °C. Conversion of **35** to the glycosyl pyridinium intermediate **36** was monitored via ^{1}H NMR at −40 °C and was found to be complete within 30 min at this temperature (Figure 4d). The reaction was removed from the NMR probe and cooled to −78 °C, and 2-propanol (8 μL, 0.1 mmol, 3.0 equiv) was added. After the solution was briefly agitated, the reaction was placed in the NMR probe at −40 °C and then warmed to 15 °C. Conversion to the isopropyl glycoside (**8**) was monitored via ^{1}H NMR at 15 °C and was found to be complete within 2.5 h at this temperature (Figure 4f).

Acknowledgment. This research was supported by the National Institutes of Health (Grant GM-58833), the Arnold and Mabel Beckman Foundation (BYI), Glaxo Wellcome Inc., and the Alfred P. Sloan Foundation. We also thank Ms. Jennifer Poole and Ms. Jannine Haberman for their assistance in the preparation of glycosides **10**, **16**, and **18**. NMR spectra were obtained in the Varian Oxford Instrument Center for Excellence in NMR Laboratory, funded in part by the W.M. Keck Foundation, the National Institutes of Health (Grant PHS 1 S10 RR10444), and the National Science Foundation (Grant NSF CHE 96-10502). The assistance of Drs. Vera Mainz, Feng Lin, and Paul Molitor of the VOICE NMR Spectroscopy Lab at the University of Illinois is recognized.

Supporting Information Available: ^{1}H NMR data of **34**−**37**, COSY NMR data of **35** and **37**, HMQC NMR data of **35** and **37**, and NOE NMR data of **35** and **37** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA993595A