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# Conformational Effects on Glycoside Reactivity: Study of the High Reactive Conformer of Glucose

Ciaran McDonnell,[†] Oscar López,[‡] Paul Murphy,[†] José G. Fernández Bolaños,[‡] Rita Hazell,[§] and Mikael Bols*,[§]

*Contribution from the Department of Chemistry, University College Dublin, Ireland; Department of Chemistry, University of Sevilla, Spain; and Department of Chemistry, Aarhus University, 8000 Aarhus C, Denmark*

Received April 30, 2004; E-mail: mb@chem.au.dk

***Abstract:*** The effect of conformation on glycoside reactivity was investigated by studying the hydrolysis of a selection of 3,6-anhydroglucosides as models for glucose in the highly reactive $^1C_4$ conformation. Methyl 3,6-anhydro-β-D-glucopyranoside was found to hydrolyze 200−400 times faster than methyl glucosides in the $^4C_1$ conformation, while methyl 3,6-anhydro-β-D-galactopyranoside, which is in the $B_{1,4}$ conformation, was less reactive than methyl β-D-galactopyranoside. Methyl (3,6-anhydro-β-D-glucopyranosyl)-(1 → 6)-α-D-glucopyranoside, methyl (3,6-anhydro-α-D-glucopyranosyl)-(1 → 6)-α-D-glucopyranosyl-(1 → 6)-α-D-glucopyranoside, and methyl (3,6-anhydro-β-D-glucopyranosyl)-(1 → 6)-α-D-glucopyranosyl-(1 → 6)-α-D-glucopyranoside were prepared and found to react selectively at the anhydro residue. The finding that $^1C_4$ conformers of glucosides are highly reactive species is in accordance with and supports previous results showing that axial OH groups are less electron withdrawing than equatorial OH groups.

## Introduction

Carbohydrates are among the most common organic molecules on earth, and their chemistry and synthesis of fundamental interest. More than 50% of carbohydrate chemistry deals with the chemistry of the glycosidic bond, and the study of glycosyl transfer reactions is a field of long standing that continues to progress vigorously. The common understanding of glycoside synthesis reactions was much advanced by the demonstrations by the group of Fraser−Reid of the importance of electronic effects in the so-called "armed−disarmed" effects.[1] This understanding was further advanced most notably in the work of Ley[2] and Wong[3] so that today the different reactivities of glycosyl donors effectively can be employed in glycoside synthesis, and much is known about the torsional and electronic effects induced on the saccharide from various protection groups.[4]

A more recent development is a line of investigations dealing with the influence of stereochemistry on the reactivity of glycosides. It has long been known that the rate of acidic hydrolysis of glycosides increase with the amount of axial OH groups in the saccharide ring. This was for many years explained by the theory of Edward, which proposed that the rate increase was caused with relief in the transition state of the sterical strain caused by 1,3 diaxial interactions between the OH and H in the ground state.[5] However recently Bowen et al. suggested, based on molecular mechanics calculations in the gas phase, that the rate increase associated with an axial 4-OH was caused by electrostatic stabilization in the transition state.[6] Miljkovic and co-workers have addressed the reactivity difference of galactosides and glucosides in acetolysis and reached a similar result based on ab initio calculations and experiments.[7] Withers' group has found that the rate of hydrolysis of dinitrophenyl glycosides is caused by inductive effects and shown by using Kirkwood−Westheimer analysis that the rate differences between stereoisomers could be explained by these effects as well.[8] Thus with these three papers a challenge of the Edward hypothesis had begun.

Our group has reached similar results working from a different angle. In the study of hydroxylated piperidines and pyridazines (glycosidase inhibitors), we found that the base strength depended on a predictable manner of the stereochemistry of

[†] University College Dublin.
[‡] University of Sevilla.
[§] Aarhus University.

(1) Mootoo, D. R.; Konradsson, P.; Udodong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583−5584.
(2) Ley, S. V.; Baeschlin, D. K.; Dixon, D. J.; Foster, A. C.; Ince, S. J.; Priepke, H. W. M.; Reynolds, D. J. *Chem. Rev.* **2001**, 53−80.
(3) Zhang, Z.; Ollmann, I. R.; Ye, X.-S.; Wischnat, R.; Baasov, T.; Wong, C.-H. *J. Am. Chem. Soc.* **1999**, *121*, 734−753.
(4) For some other important contributions to this field, see: (a) Friesen R. W.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6656−6660. (b) Veeneman, G. H.; Boom, J. H. v. *Tetrahedron Lett.* **1990**, *31*, 275−278. (c) Roy, R.; Andersson, F.; Letellier, M. *Tetrahedron Lett* **1992**, *33*, 6053−6056. (d) Mehta, S.; Pinto, B. M. *J. Org. Chem.* **1993**, *58*, 3269−3276. (e) Raghavan, S. Kahne, D. *J. Am. Chem. Soc.* **1993**, *115*, 1580−1581. (f) Geurtsen, R.; Holmes, D. S.; Boons, G. J. *J. Org. Chem.* **1997**, *62*, 8145−8154. (g) Hashimoto, S.; Sakamoto, H.; Honda, T.; Abe, H.; Nakamura, S.; Ikegami, S. *Tetrahedron Lett.* **1997**, *38*, 8969−8972. (h) Lahmann, M.; Oscarson, S. *Can. J. Chem.* **2002**, *80*, 889−893.
(5) Edward, J. T. *Chem. Ind.* (London) **1955**, 1102−1104.
(6) Woods, R. J.; Andrews, C. W.; Bowen, J. P. *J. Am. Chem. Soc.* **1992**, *114*, 859−864.
(7) Miljkovic, M.; Yeagly, D.; Deslongchamps, P.; Dory, Y. L. *J. Org. Chem.* **1997**, *62*, 7597−7604.
(8) Namchuk, M. N.; McCarter, J. D.; Becalski, A.; Andrews, T.; Withers, S. G. *J. Am Chem. Soc.* **2000**, *122*, 1270−1277.


**10.1021/ja047476t CCC: $27.50** 

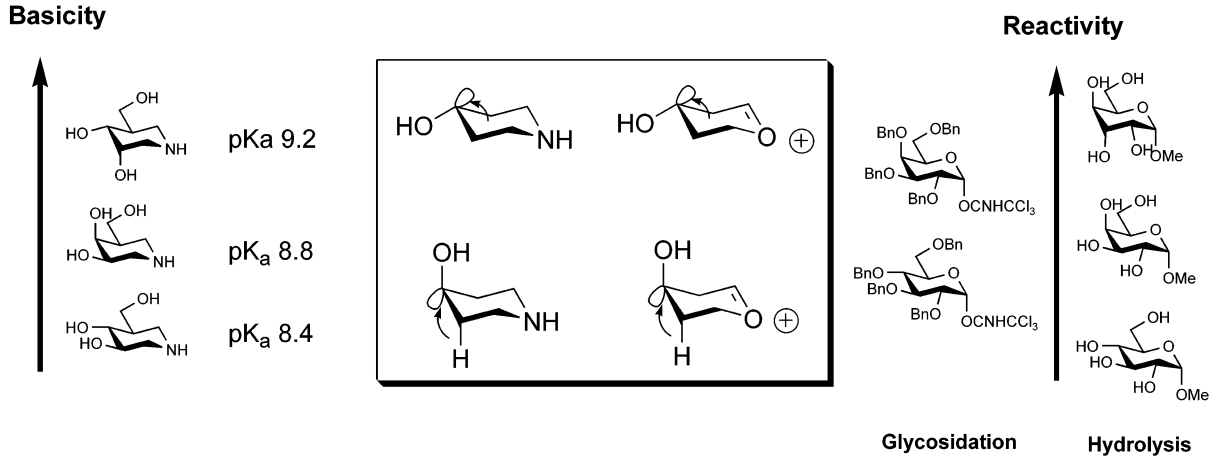



***Figure 1.*** Base strength of isomeric piperidines increase with number of axial OH groups (left). Similarly the reactivity of isomeric glycosyl derivatives increases with axial OH or OR groups (right). An explanation based on hyperconjugation for the different substituent effects of axial and equatorial OH (center, from ref 5, note 14).

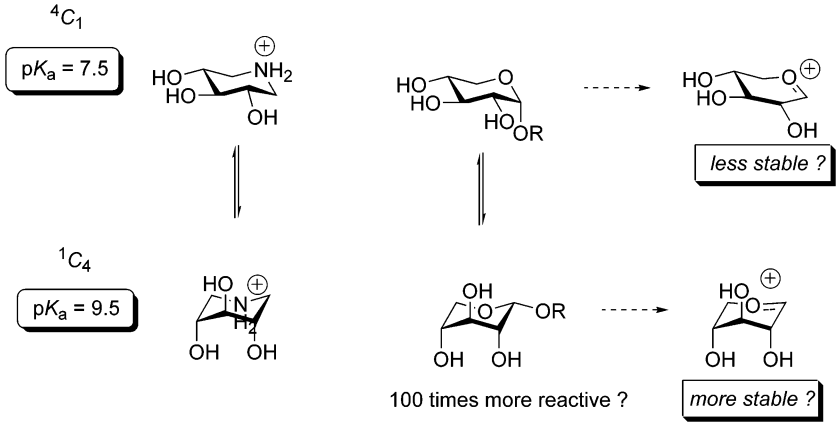


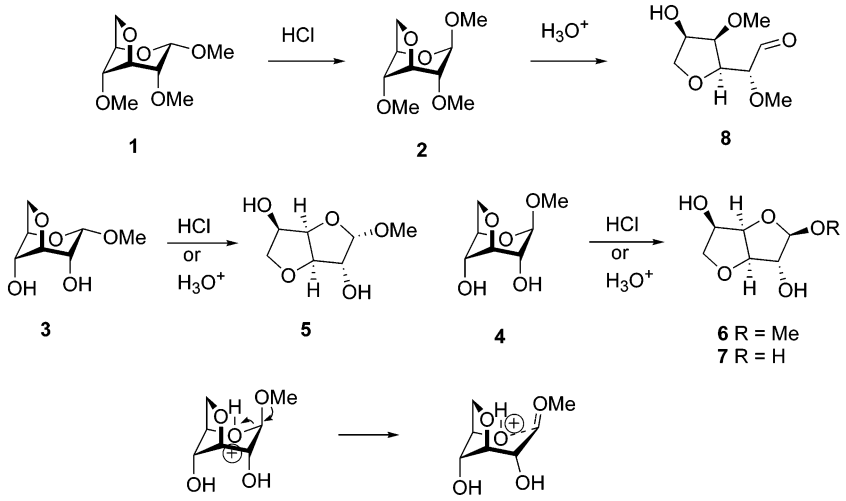

***Figure 2.*** Different chair conformations have different base strengths in the case of piperidines (left) and reactivities in the case of glycosides (right).

the OH substituent.[9] We found that axial hydroxyl groups $\beta$ and $\gamma$ to the basic center were considerably less electron withdrawing than the corresponding equatorial hydroxyl groups (Figure 1). Large differences in electron withdrawing power were also seen for other polar substituents.[9,10] Importantly it was shown that these stereochemical substituent contributions also influence glycoside hydrolysis, since good linear free energy relationships were found between stereochemical substituent constants obtained from amines and the hydrolysis rates of stereoisomeric glycosides.[10,11] Finally the Edward hypothesis was laid to rest by the demonstration that a change of stereochemistry of a methyl group substituent in no way had the same influence on glycoside hydrolysis as an OH group.[12] This is supported by the work of Kirby that also shows that the influence of torsion is much smaller than electronic effects.[13] It should also be noted that although transition state structure and solvation is very different in glycoside synthesis reactions these effects are also observed qualitatively there.[3,14]

An interesting implication of these effects is that they are conformationally dependent and perhaps more appropriately should be termed conformational substituent effects. Thus, the base strength of a hydroxylated piperidine may be markedly different in the two chair forms (Figure 2) and may change conformation as a result of a change of pH.[9] This is also seen in the work of Lankin et al. on fluorinated piperidines, which shows that fluorine prefers the axial position in the protonated piperidine.[15,16] One can calculate the base strength of various piperidine conformers, and for the *trans*,*trans*-3,4,5-piperidinetriol, a $\Delta pK_a$ of 2.0 pH units is calculated between all-equatorial and -axial conformers (Figure 2). Using the parallel already found between glycoside hydrolysis and piperidine base strength, one should accordingly anticipate that glycoside hydrolysis rates should depend on the conformation of the glycoside, and the conformer having more axial hydroxyl groups should be more reactive. On extrapolation of the free energy relationships, the methyl α-xylopyranoside would be anticipated to hydrolyze up to $10^2$ times faster in the $^1C_4$ conformation. If this is correct, it poses many interesting questions such as to which extent certain saccharides hydrolyze from conformers with axial OH groups and whether polysaccharide chains can be selectively cleaved by conformationally flipping a single residue.

(9) Jensen, H. H.; Lyngbye, L.; Jensen, A.; Bols, M. *Chem.—Eur. J.* **2002**, *8*, 1218−1226.
(10) Bols, M.; Liang, X.; Jensen, H. H. *J. Org. Chem.* **2002**, *67*, 8970−8974.
(11) Jensen, H. H.; Lyngbye, L.; Bols, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 3447−3449.
(12) Jensen, H. H.; Bols, M. *Org. Lett.* **2003**, *5*, 3419−3421.
(13) Dean, K. E. S.; Kirby, A. J.; Komarov, I. V. *J. Chem. Soc., Perkin Trans. 2* **2002**, 337−341.
(14) Bülow, A.; Meyer, T.; Olszewski, T. K.; Bols, M. *Eur. J. Org. Chem.* **2004**, 323−329.
(15) Lankin, D. C.; Chandrakumar, N. S.; Rao, S. N.; Spangler, D. P.; Snyder, J. P. *J. Am. Chem. Soc.* **1993**, *115*, 3356−3357.
(16) Lankin, D. C.; Grunewald, G. L.; Romero, F. A.; Oren, I. Y.; Snyder, J. P. *Org. Lett.* **2002**, *4*, 3557−3560.

***Scheme 1.*** Hydrolysis of Various 3,6-Anhydrosugars (Top, from Ref 17): Endocyclic Protonation and Cleavage (Bottom)




We therefore in the present work investigate whether it is true that glucose derivatives forced into a $^1C_4$ conformer are much more reactive glycosides. To do that, we have turned our attention to the 3,6-anhydrides. The 3,6-anhydrides are strained molecules but are still good models for glucosides in the $^1C_4$ conformation as the strain is caused by the unfavorable steric interaction between 1,3-diaxial groups, associated with this conformation. There are cases however where the anhydrides are in nonchair conformation, and the anhydrides have one oxygen atom less, possibly making them a semi-deoxygenated species. Indeed, in a classical work, Haworth described 3,6-anhydrides as uniquely reactive compounds,[17] which bode well for the above hypothesis.

One of the interesting observations of Haworth was that the methyl 3,6-anhydro-2,4-di-*O*-methyl-α-D-glucopyranoside (**1**) rapidly changed anomeric configuration to *β*-glucoside **2** on treatment with HCl gas (Scheme 1).[17] He also found that methyl 3,6-anhydro-α-D-glucopyranoside (**3**) and its *β*-isomer **4** under similar nonaqueous conditions were rearranged to the less strained furanosides **5** and **6** with retention of configuration. Even in aqueous acid, **3** converted to **5**, while **6** hydrolyzed to **7**. In aqueous acid, the methylated compounds **1** and **2**, which cannot form furanosides, interestingly formed the open chain aldehyde **8** to relieve strain, and Haworth reported that **1** reacted faster than **2**.[17] So while these derivatives appeared reactive, no quantitative data existed that allowed us to compare them with other glycosides such as glucosides in the $^4C_1$ conformation.

In this paper we have synthesized several different 3,6-anhydrooligosaccharides and investigated their acid-catalyzed hydrolysis. We find that, generally, these compounds are many orders of magnitude more reactive than the relaxed conformers and that they hydrolyze selectively at the anhydro residue.

## Results and Discussion

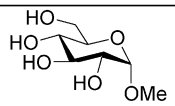
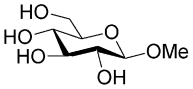
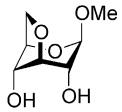
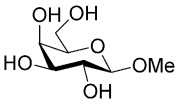
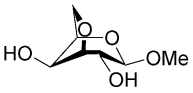
**Kinetic Study of Anhydromonosaccharides.** Since no previous kinetic studies had been done on the hydrolysis of 3,6-anhydroglucosides, we started measuring the hydrolysis rate of anhydroglucoside **4**[17] and anhydrogalactoside **12**[18] in 2 M HCl under which conditions rate constants at 60 °C are known for many glycosides.[19] Under these conditions, **4** is converted into **7** and **12** is converted into 3,6-anhydrogalactose. An interesting difference between these two compounds are that while both are strained bicyclic structures, **4** is in chair and **12** is in boat conformation (as determined by NMR).[18] The first-order rate constants were determined at 21, 31, and 41 °C for **4** and at 60, 70, and 79 °C for **12**, and the Arrhenius equation was used to calculate the rate constants at 60 °C. These values are shown in Table 1 in comparison with known rate constants of glycosides **9**−**11**.[19]

As it is seen, the rate of hydrolysis of **4** is tremendously high, 251 times greater than the rate of hydrolysis of its $^4C_1$ equivalent **10** and 446 times greater than the hydrolysis rate of **9** which is the equivalent with an anomerically stabilized methoxy group. Such a high hydrolysis rate is not entirely anticipated from electronic effects and could also be an effect of the anhydride being semideoxygenated as alluded to above. Second there could be a relief of strain in going from ground state to transition state in this reaction if the compound undergoes endocyclic cleavage (Scheme 1), which is supported by the observations by Haworth of furanosides being formed.[17] Equally remarkable is the contrasting slow hydrolysis rate of anhydrogalactoside **12**. This compound hydrolyzes with only half the rate of methyl *β*-galactoside **11**. Nevertheless, given the boat conformation of **12** and the fact that the compound thereby gets two electron withdrawing equatorial hydroxyl groups, the low reactivity is reasonable. The striking contrast between **4** and **12** shows how important conformation is to glycoside hydrolysis and how much more reactive an all-axially substituted monosacharide becomes. It also shows that release of strain does not itself provide a fast reaction, as the release of **12** from the forced boat conformer is a relatively slow process.

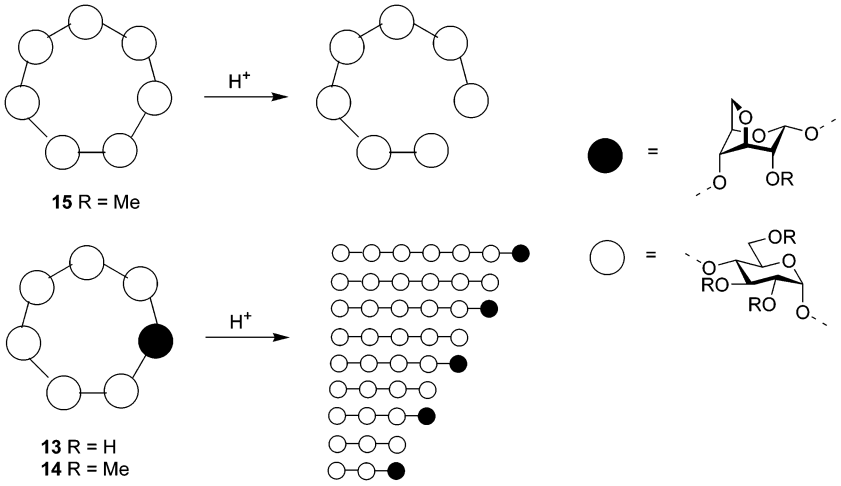
**Anhydrocyclodextrins.** Cyclodextrins with 3,6-anhydro residues are well-known, and from the above it was anticipated that these derivatives would be highly labile toward hydrolysis at the anhydro residues. To investigate that, we synthesized 3,6-anhydro-*β*-cyclodextrin (**13**)[20] and its permethylated analogue (**14**) by treatment of **13** with MeI/NaH in DMSO. Hydrolysis of these two compounds where studied in comparison with

(17) Haworth, W. N.; Owen, L. N.; Smith, F. *J. Chem. Soc.* **1941**, 88−102.
(18) France, C. J.; McFarlane, I. M.; Newton, C. G.; Pitchen, P.; Barton, D. H. R. *Tetrahedron* **1991**, *47*, 6381−6388.
(19) Overend, W. G.; Rees, C. W.; Sequeira, J. S. *J. Chem. Soc.* **1962**, 3429−3440.
(20) Fujita, K.; Yamamura, H.; Imoto, T.; Tabushi, I. *Chem. Lett.* **1988**, 543−546.

***Table 1.*** First-Order Rate Constants for Acidic Hydrolysis of Glycosides (Data for **9**, **10**, and **12** from Ref 19)

| Compound | Structure | $k \times 10^5$ s$^{-1}$ (60 °C) | Relative hydrolysis rate (2M HCl, 60 °C) |
|---|---|---|---|
| **9** |  | 0.708 | 1 |
| **10** |  | 1.26 | 1.8 |
| **4** |  | 316 | 446 |
| **11** |  | 5.13 | 7.2 |
| **12** |  | 2.71 | 3.8 |

***Scheme 2.*** Hydrolysis of Cyclodextrin Derivatives

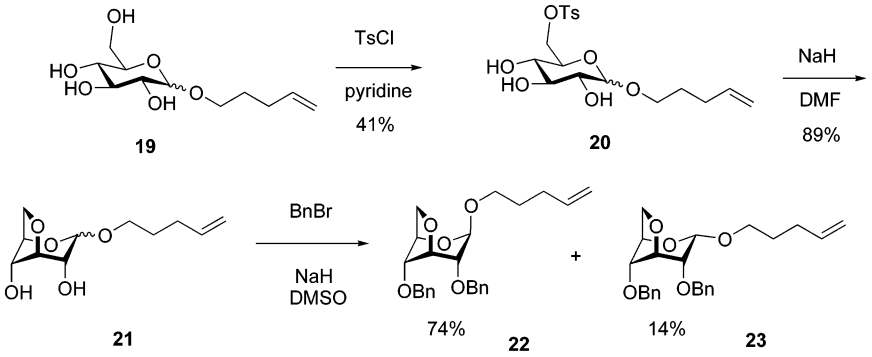



$\beta$-cyclodextrin and permethyl $\beta$-cyclodextrin (**15**) (Scheme 2).[21] Surprisingly, hydrolysis of **13** in 2 M HCl was not found to be faster than that of $\beta$-cyclodextrin itself.[22] At 30 °C little reaction happened, while at 40 °C the reaction progressed very slowly to a mixture of starting material and a hydrolyzed product. Analogously **14** did not hydrolyze at room temperature in 2 M HCl, but treatment for 22 h at 35 °C gave 83% conversion (17% **14** recovered by chromatography) to, according to MALDITOF MS (Figure S4), a mixture of hydrolysis products that consisted of oligosaccharides with 3−7 residues with and without the anhydrosugar (Scheme 2). This hydrolysis mixture is consistent with hydrolysis having occurred to a major extent at two glycosidic linkages. Identical treatment of **15** gave 75% conversion (as based on 25% recovery of **15**) and thus appeared to proceed with an essentially identical rate. However, MS on this hydrolysis product revealed it to consist mainly of the heptamaltoside (Figure S5). As a control experiment, hydrolysis of methyl 3,6-anhydro-2,4-di-*O*-methyl-α-D-glucopyranoside **1**[17] was repeated under comparable conditions, and **1** was found to hydrolyze completely in 1 h in 1 M HCl at 23 °C into aldehyde **8** and is thus clearly much more reactive than **14**.

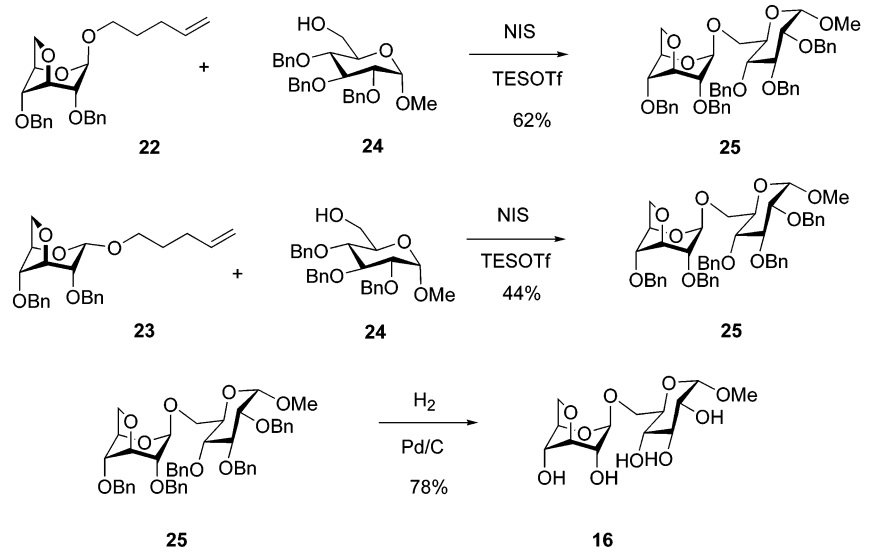
(21) Freudenberg, K.; Meyer-Delius, M. *Chem. Ber.* **1938**, *71*, 1B, 1596−1600.

(22) Hirayama, F.; Kurihara, M.; Utsuki, T.; Uekama, K. *Chem. Commun.* **1993**, 1578−1580.

***Scheme 3.*** Synthesis of Glycosyl Donors **22** and **23**




***Scheme 4.*** Synthesis of Disaccharide **16**




It is clear from these experiments that the anhydro residue does not hydrolyze rapidly in **13** and **14**. It appears that in the hydrolysis of **14** the compound initially hydrolyzes at a random residue. As soon as the cyclodextrin ring is broken, a fast second hydrolysis step occurs at the anhydro residue to give fragments consistent with the masses found. It is not clear why the anhydro glucoside is unreactive in **13** and **14**. A reasonable explanation would be that this residue has been forced away from the $^1C_4$ conformation. However the fact that the anhydrosugar in **13**[20] and other anhydrocyclodextrins[23] have similar $^1$H chemical shifts and couplings as **3** does not support this hypothesis.

**Synthesis of Anhydrooligosaccharides.** As the cyclodextrin experiments cast doubt on whether the extreme reactivity of the $^1C_4$ conformer is found beyond the monosaccharide level, it was desirable to study hydrolysis of an acyclic oligosaccharide containing a 3,6-anhydride. Such compounds have not been made previously, and it was quickly realized that to prepare such compounds in a practical manner required glycoside synthesis. We synthesized a di- and two trisaccharides containing the 3,6-anhydroglucoside moiety at the terminal end and used two different approaches for this purpose. The disaccharide **16** was synthesized as outlined in Schemes 3 and 4 by glycoside coupling with a 3,6-anhydroglucosyl donor. However, as this turned out only to give the $\beta$-stereochemistry, the trisaccharides **17** and **18** were synthesized by formation of the 3,6-anhydride at the end of the synthesis (Schemes 5 and 6).

In the synthesis of **16** we used a pentenyl glycoside as leaving group. Glucoside **19**[24] ($\alpha$:$\beta$ mixture) was semiselectively tosylated to give 6-*O*-tosyl derivative **20** in 41% yield (Scheme 3). Treatment with NaH in DMF gave a high yield of anhydride **21**, which was benzylated to give the two anomers **22** and **23** that were isolated in 74% and 14% yield after chromatographic separation.

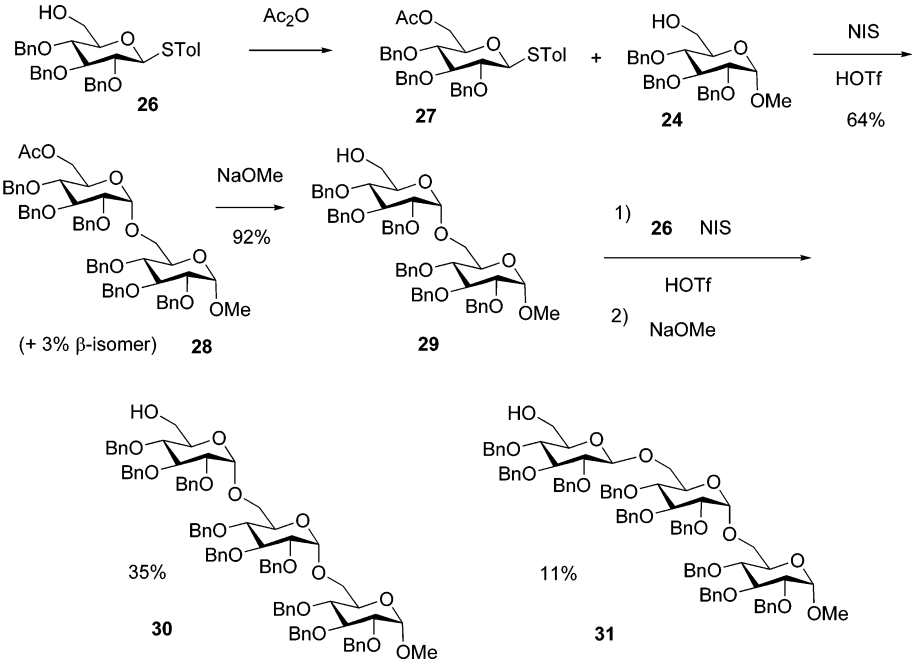
Coupling of **22** or **23** to methyl 2,3,4-tri-*O*-benzyl-$\alpha$-D-glucopyranoside (**24**) using TESOTf/NIS[25] gave the $\beta$-linked disaccharide **25** in 66% and 44% yield, respectively (Scheme 4). No $\alpha$-isomer was isolated or observed. The $\beta$-selectivity in this reaction is intriguing, and the yield is quite high when taking into account that the substituent enters from the crowded endo face. Nevertheless selectivity favors formation of the axial product, which is similar to many glucosidations using donors in $^4C_1$ conformation favoring the $\alpha$-anomer. Compound **25** was uneventfully hydrogenolysed using Pd/C in EtOH and 1 atm of $H_2$ to give **16** in 78% yield (Scheme 4). X-ray structures were obtained of **23** and **25** as well as of the known[25] 1-OMe analogue of **23**, **23a** and are shown in Figure 3. The structure of **25** is of particular interest because it is the first X-ray structure of 3,6-anhydride $\beta$-glycoside to be reported. It is seen that **23** and **23a** are in perfect $^1C_4$ conformations, but in **25** the anhydroglucose is twisted into a half-chair conformation presumably because of sterical conflict between the 1-substituent and the anhydride

(23) Gadelle, A.; Defaye, J. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 78−80.

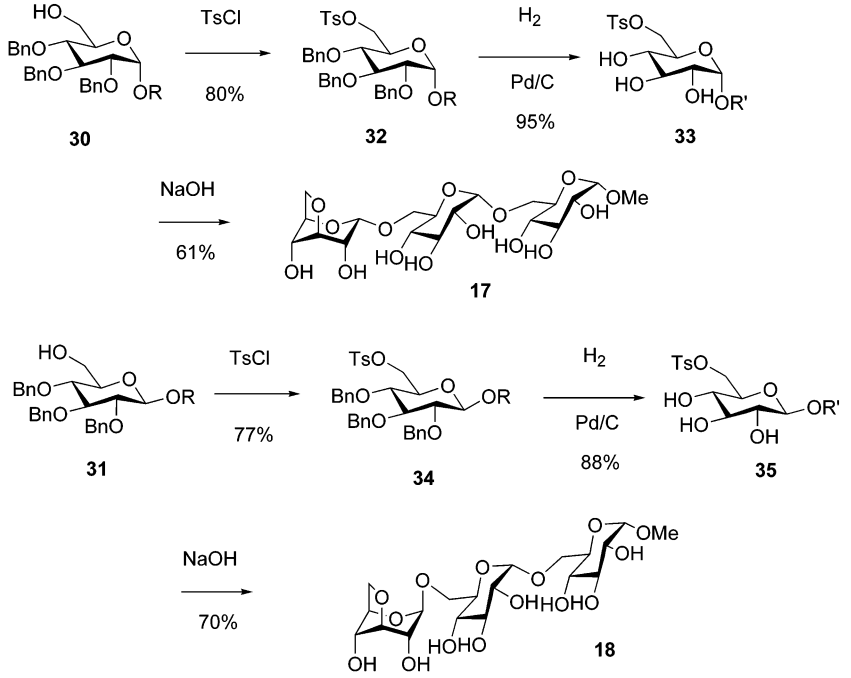
(24) Wilson, B. G.; Fraser-Reid, B. *J. Org. Chem.* **1995**, *60*, 317−320.

(25) Fraser-Reid, B.; Wu, Z.; Udodong, U. E.; Ottosson, H. *J. Org. Chem.* **1990**, *55*, 6068−6070.

***Scheme 5.*** Synthesis of Trisaccharides **30** and **31**




***Scheme 6.*** Synthesis of Trisaccharides **17** and **18**




R = 6-*O*-D-Glc(OBn)$_3$-α-1,6-*O*-D-Glc(OBn)$_3$-α-OMe
R' = 6-*O*-D-Glc-α-1,6-*O*-D-Glc-α-OMe

bridge. This observation makes it even more surprising that the glycosidation with **22** and **23** only gives the *β*-anomer **25**. The fact that **25**, and hence presumably **16** as well, is not in a perfect $^1C_4$ conformation raised some concerns as to the usefulness of the *β*-isomers as models for **13** or **14**. The direct glycosidation method was therefore abandoned in the trisaccharide synthesis because it could not provide the more desirable α-glycosides.

For the trisaccharides, the known tolylthio-2,3,4-tri-*O*-benzyl-*β*-D-glucopyranoside (**26**)[26] was acetylated to 6-acetate **27** and coupled to **24** using the NIS/TfOH promotor system (Scheme 5).[27] This gave the α-linked disaccharide **28** in 64% yield with a small amount of *β*-isomer (3%) being separated chromatographically. After deacetylation with NaOMe/MeOH, the alcohol **29** was obtained in 92% yield. Renewed reaction of **29** with **26** and NIS/TfOH gave, after deacetylation, the α- and *β*-trisaccharides **30** and **31** in 35% and 11% yields, respectively.

(26) Yamago, S.; Kokubo, K.; Hara, O.; Masuda, S.; Yoshida, J. *J. Org. Chem.* **2002**, *67*, 8584−8592.
(27) Veeneman, G. H.; van Leeuwen, S. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 1331−1334.

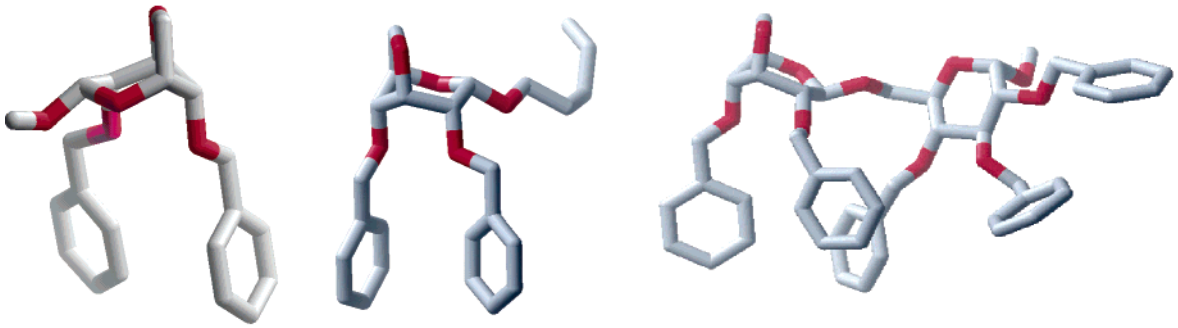
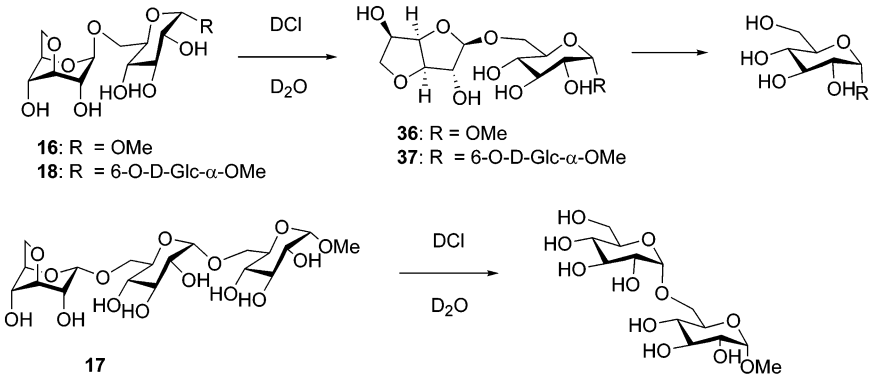


***Figure 3.*** X-ray structures of methyl 3,6-anhydro-2,4-di-*O*-benzyl-α-D-glucopyranoside (**23a**), **23**, and **25**.

***Scheme 7.*** Hydrolysis of **16**−**18**




These trisaccharides were converted into anhydrides as outlined in Scheme 6. Reaction of **30** with TsCl/pyridine gave 6"-tosylate **32** in 80% yield. Hydrogenolysis with $H_2$/Pd proceeded in high yield to unprotected **33** that was treated with NaOH to give the 3,6-anhydride **17** in 61% yield. In an identical sequence of reactions, the β-anomer **31** was converted into **18** (Scheme 6).

**Hydrolysis of Anhydrooligosaccharides.** With the substances **16**−**18** at hand, their reaction with aqueous acid was studied (Scheme 7). This was done in DCl in $D_2O$ at room temperature (26 °C), and the reactions were followed by $^1$H NMR. The reaction of **16** was carried out in 1.3 M DCl. On analysis, this reaction was found to be more complicated than expected. In addition to the cleavage of the disaccharide linkage, a parallel reaction involving the rearrangement of the disaccharide to another species also occurred; this species underwent subsequent hydrolytic cleavage so that after 24 h methyl α-D-glucopyranoside was the only glycoside present. The intermediate had a singlet at 5.03 ppm and triplet at 4.69 ppm (Figure S6), which is close to methyl 3,6-anhydro-β-D-glucofuranoside having a similar singlet (5.01 ppm, H-1) and triplet (4.89 ppm, H-4). The rearrangement product of the parallel reaction is most likely the furanoside **36**. No evidence was seen of cleavage of the methyl glycoside within this time frame.

The rate of conversion of **16** was determined by measuring the rate of decrease in the intensity of the singlet (H-1′, peak 1) at 4.78 ppm in relation to the total of the doublets corresponding to H-1 in substrate, product, and intermediate. This degradation was shown to follow pseudo-first-order kinetics and have a rate constant of $8.8 \times 10^{-4}$ s$^{-1}$ (Table 2).

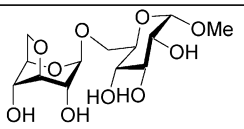
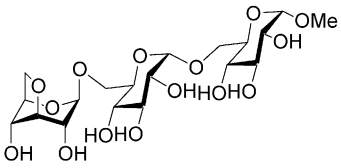
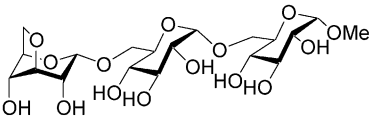
A similar conversion of **18** to what is likely to be furanoside **37** was observed when this quite similar compound was treated with 1.3 M DCl in $D_2O$. Compound **37** had a very similar chemical shift as **36** most notably the triplet at 4.69 ppm (Figure S7). However, no hydrolysis to methyl isomaltoside occurred in this case and within a 24 h period the reaction stopped at **37**. The rate of conversion of **18** or formation of **37** was first-order and gave the rate constant $5.9 \times 10^{-4}$ s$^{-1}$ (Table 2).

The rate of reaction of the trisaccharide **17** was too fast to measure by $^1$H NMR spectroscopy in 1.3 M DCl, so the reaction kinetics were done at 0.13 M DCl. Under these conditions the **17** was rapidly converted to the methyl isomaltoside without any formation of furanoside intermediate being observed. The reaction was first-order in substrate and product, and the rate constant was determined (Table 2).

The anhydrosugars **16**−**18** are all extremely reactive toward aqueous acid and thus behave similarly to **4**. Indeed if, from the Arrhenius data, the hydrolysis rate of **4** in 2 M HCl is calculated at 26 °C, a rate constant of $7.23 \times 10^{-5}$ s$^{-1}$ is obtained, and it is thus clear that the three oligosaccharide analogues actually react even faster than **4**. The reason for this is probably that methanol is a poorer leaving group than the more acidic sugar alcohol. The rearrangements observed for **16** and **18** are similar to those observed by Haworth for the hydrolysis of α-anomer **3**. Curiously Haworth did not observe rearrangement in the β-anomer **4**; an observation we can confirm by NMR. Likewise it is intriguing that it is the α-anomer **17** in which no rearrangement is observed. It therefore appears that whether hydrolysis or rearrangement occurs largely depends on the leaving group. One effect of the leaving group could be, due to the difference in basicity of the exocyclic oxygen, to influence the ratio of exo- and endocyclic protonation and, as only endocyclic protonation can lead to rearrangement, thereby to affect the rearrangement/hydrolysis ratio.

The observation from X-ray that intermediate β-glucoside **25** is in halfchair conformation raises the possibility that β-glyco-

***Table 2.*** First-Order Rate Constants for Acidic Hydrolysis of Glycosides **16**−**18** as Determined by NMR

| Compound | Structure | [DCl] | $k \times 10^4\ s^{-1}$(26 °C) |
|---|---|---|---|
| **16** |  | 1.3 M | 8.8 |
| **18** |  | 1.3 M | 5.89 |
| **17** |  | 0.13 M | 2.85 |

sides **4**, **16** and **18** may be in this conformation as well. In this conformation the molecule still has the 3 and 4 OR/OH groups in axial position and 2-OH in an intermediate position which should also make it much more reactive than the all equatorial $^4C_1$ conformation. On the other hand, all published X-rays of anhydro α-glucosides have shown them to be in $^1C_4$ conformation making it very likely that **17** is in this conformation as well. The reason **17** hydrolyzes faster than **4**, **16**, and **18** therefore may be due to its more perfect conformation.

## Conclusion

It has been experimentally verified that the $^1C_4$ conformers of glucosides are indeed highly reactive species. Oligosaccharides containing the 3,6-anhydroglucopyranoside unit in this conformation were found to undergo selective hydrolysis or rearrangement at that position. One exception is the slow and unspecific hydrolysis of the anhydro-*β*-cyclodextrins. However since the opening of the cyclodextrin ring is followed by immediate specific hydrolysis at the anhydroglucoside, it is proposed that a conformational distortion of the anhydro residue is the cause of its low reactivity in the cyclodextrin ring. The high reactivity of the all-axial conformers opens many interesting questions such as do some glycosides undergo conformational change during hydrolysis or can conformational flipping be used to achieve selective glycoside hydrolysis or transfer? Future research may address these questions.

## Experimental Section

**General Procedure for Determining the Rate of Glycoside Hydrolysis:** A solution of about 5 mg/mL of glycoside in 2 M aq. HCl was added to a cuvette preheated to the desired temperature, and the optical rotation was measured as a function of time until a constant value.

**3,6-Anhydro-D-glucofuranose (7):** A solution of methyl 3,6-anhydro-*β*-D-glucopyranoside (**4**, 76 mg, 0.43 mmol) in 2 M aq. HCl (4 mL) was kept at room temperature for 17 h. Then the solution was neutralized with saturated aqueous $NaHCO_3$ and concentrated to dryness. The residue was purified by column chromatography ($CH_2Cl_2$ → 10:1 $CH_2Cl_2$−MeOH) to give the title compound (67 mg, 95%) in a 1:0.9 α/*β* mixture, as deduced by $^1$H NMR spectroscopy. $^1$H NMR (500 MHz, $D_2O$) *δ* 5.44 (d, 1H, $J_{1,2}$ 3.9 Hz, H-1α), 5.40 (m, 1H, $J_{1,2}$ 1.0 Hz, $J_{1,3}$ 0.5 Hz, H-1*β*), 4.79 (t, 1H, $J_{4,3}$ 4.9 Hz, $J_{4,5}$ 4.9 Hz, H-4*β*), 4.72 (t, 1H, $J_{3,4}$ 5.2 Hz, $J_{4,5}$ 5.2 Hz, H-4α), 4.52 (dd, 1H, $J_{2,3}$ 2.7 Hz, H-3α), 4.44 (m, $J_{3,4}$ 4.9 Hz, $J_{2,3}$ 1.0 Hz, $J_{1,3}$ 0.5 Hz, H-3*β*), 4.37 (ddd, 1H, $J_{5,6a}$ 6.5 Hz, $J_{5,6b}$ 7.4 Hz, H-5*β*), 4.28 (ddd, 1H, $J_{5,6a}$ 6.2 Hz, $J_{5,6b}$ 7.3 Hz, H-5α), 4.14 (m, 1H, H-2*β*), 4.13 (m, 1H, H-2α), 3.94 (dd, 1H, $J_{6a,6b}$ 9.2 Hz, H-6aα), 3.91 (dd, 1H, $J_{6a,6b}$ 8.7 Hz, H-6a*β*), 3.80 (dd, 1H, H-6b*β*), 3.54 (dd, 1H, H-6bα); $^{13}$C NMR (75.5 MHz, $D_2O$) *δ* 103.7 (C-1*β*), 98.8 (C-1α), 86.7 (C-3*β*), 86.4 (C-3α), 83.1 (C-4*β*), 79.3 (C-2*β*), 79.0 (C-4α), 75.6 (C-2α), 71.1 (C-6*β*), 70.7 (C-5*β*), 70.6 (C-5α), 70.4 (C-6α).

**Permethylated-3$^A$,6$^A$-anhydro-*β*-cyclodextrin (14):** Sodium hydride (0.083 g, 3.49 mmol) in dry DMSO (2 mL) under an $N_2$ atmosphere was heated to 50 °C for 45 min. The resulting solution was cooled to room temperature, whereupon **13** (0.065 g, 0.058 mmol) dissolved in dry DMSO (2 mL) was added dropwise over 10 min. The solution was stirred at room temperature for 2 h. Methyl iodide (0.22 mL, 3.49 mmol) was added dropwise over 10 min and left to stir overnight. $CH_2Cl_2$ (15 mL) and MeOH (2 mL) were added to the mixture which was washed with water (4 × 15 mL), dried ($MgSO_4$), and filtered, and solvents were removed in vacuo. Chromatography (20:1 $CH_2Cl_2$−EtOH) gave the title compound **14** as a white solid (0.037 g, 30%); $R_F$ 0.54 (20:1 $CH_2Cl_2$−EtOH); mp 127−130 °C; $[\alpha]_D$ +144° (*c* 0.5 $CHCl_3$); $^1$H NMR ($CDCl_3$, 200 MHz) *δ* 5.52 (d, 1H, *J* 3.6 Hz), 5.24 (d, 1H, *J* 2.6 Hz), 5.16 (d, 1H, *J* 3.3 Hz), 5.03 (d, 1H, *J* 3.3 Hz), 5.00 (d, 1H, *J* 2.9 Hz), 4.96 (d, 1H, *J* 3.3 Hz), 4.87 (d, 1H, *J* 3.3 Hz), 4.55 (t, 1H, *J* 4.5 Hz), 4.36 (bs, 1H), 4.10 (apt t, 2H, *J* 10.0 Hz), 3.66−3.88 (m, 13H), 3.38−3.66 (m, 61H), 3.56 (apt t, 1H), 3.44 (dd, *J* 7.7, 2.9 Hz), 3.36 (bs, 3H), 3.30 (apt t, 3H, *J* 1.8 Hz), 3.23 (bs, 4H), 2.96−3.20 (m, 9H); $^{13}$C NMR ($CDCl_3$, 50 MHz) *δ* 99.1, 98.7, 98.2, 97.9, 97.0, 96.7, 95.7 (each d, 7 × C-1), 81.9, 81.8, 81.5, 81.4, 81.2, 80.9, 80.7, 80.5, 79.3, 78.3, 77.2, 76.4, 72.3, 70.5, 70.2, 70.0,

69.4, 69.2, 68.3, 60.9, 60.8, 60.4, 60.3, 60.2, 59.0, 58.0, 57.9, 57.8, 57.6, 57.4, 24.2, 56.9, 56.8. HRMS-ES: found 1405.6450, requires 1405.6463.

**Hydrolysis of 14:** A solution of **14** (0.117 g, 0.12 mmol) dissolved in 2 M aq. HCl (2.5 mL) was stirred at 35 °C for 22 h. The solution was cooled to room temperature and washed with $CH_2Cl_2$ (4 × 15 mL). The combined organics were dried ($MgSO_4$) and filtered, and solvent was removed in vacuo. Chromatography (20:1 $CH_2Cl_2$−EtOH) yielded **14** (0.02 g, 17%), and a mixture of hydrolysis products (0.079 g) with the same $R_F$ value were isolated; $R_F$ 0.40 (20:1 $CH_2Cl_2$−EtOH); $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 9.80, 9.79, 5.58−5.59 (m), 5.25−5.30 (m), 5.28−5.29 (m), 4.94−4.97 (m), 3.40−3.95 (m), 3.28−3.33 (m), 3.14−3.21 (m); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 202.4, 97.8, 96.1, 95.6, 95.2, 95.2, 89.2, 85.0, 84.1, 83.4, 82.1, 81.8, 81.4, 81.2, 80.7, 79.9, 79.4, 73.0, 72.5, 71.2, 70.7, 70.3, 70.0, 69.8, 69.2, 68.2, 59.8, 59.2, 58.6, 58.2, 57.9, 57.7, 57.4, 57.3. LRMS-MALDI: 1423.6, 1405.5, 1265.3, 1220.3, 1061.2, 1015.2, 857.2, 811.1. LRMS-FAB:1423, 1265, 1219, 1061, 1015, 857, 653.

**Hydrolysis of 15:** A solution of **15** (63 mg, 0.044 mmol) dissolved in 2 M aq. HCl (1.39 mL) was heated at 35 °C for 22 h. The solution was then cooled to room temperature and washed with $CH_2Cl_2$ (4 × 10 mL). The combined organics were dried ($MgSO_4$) and filtered, and $CH_2Cl_2$ was removed in vacuo. Chromatography (20:1 $CH_2Cl_2$−EtOH) yielded **15** (0.016 g, 25%) and the hydrolysis product (0.041 g, 65%); $R_F$ 0.35 (20:1 $CH_2Cl_2$−EtOH); $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 5.59 (d, 2H, *J* 3.3 Hz, 2 × H-1), 5.50 (d, 2H, *J* 3.3 Hz, 4 × H-1), 5.29 (d, 1H, *J* 3.7 Hz, 1 × H-1), 4.56 (d, 1H, *J* 7.3 Hz), 3.59−3.99 (m, 21H), 3.44−3.55 (m, 56H), 3.27−3.34 (m, 21H), 3.12−3.25 (m, 8H); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 96.1, 95.7, 95.2, 89.3, 84.9, 84.2, 82.2, 81.8, 81.2, 80.7, 72.6, 72.2, 71.3, 70.5, 70.2, 69.8, 69.3, 69.1, 68.3, 59.8, 59.2, 59.1, 58.7, 58.5, 58.2, 58.0, 57.8, 57.5. LRMS-MALDI: 1469.1 [M + Na]$^+$. LRMS-FAB: 1469 [M + Na]$^+$.

**Hydrolysis of 1:** A solution of **1** (55 mg, 0.27 mmol) was allowed to stir in 2 M aq. HCl (5.4 mL) at room temperature. TLC showed the starter was completely consumed after 1 h. The product was extracted from the acid with $CH_2Cl_2$ (4 × 15 mL). The combined organic portions were washed with $H_2O$ (30 mL), dried ($MgSO_4$), and filtered, and the solvent was removed at reduced pressure to obtain crude **8**; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ (selected data) 9.74 (s), 4.39 (dd, 1H, *J* 7.7 Hz, 2.2), 3.51, 3.41 (each s, 6H, 2 × OC*H*$_3$); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 201.3, 83.2, 80.1, 77.4, 73.3, 68.0, 58.3, 57.6. LRMS-ES: 245.3 [M + MeOH + Na]$^+$.

**Pent-4′-enyl 6-*O*-Toluenesulfonyl-D-glucopyranoside (20):** To a solution of **19** (1.85 g, 7.45 mmol) in dry pyridine (40 mL) under an $N_2$ atmosphere, *p*-toluenesulfonyl chloride (1.56 g, 8.20 mmol) dissolved in pyridine (20 mL) was added slowly. The resulting solution was stirred at room temperature for 4 days. The pyridine (azeotroped with toluene) was removed under reduced pressure at <40 °C. The resulting residue was dissolved in $CH_2Cl_2$ (50 mL) and was washed successively with satd. aq. $NaHCO_3$ (2 × 50 mL) and satd. aq. $KHCO_3$ (1 × 50 mL), dried ($MgSO_4$), and filtered, and the solvent was removed in vacuo. Chromatography ($CH_2Cl_2$) gave the title compound **20** (1.23 g, 41%) as inseparable diastereomers ($\alpha/\beta$ 1:5); $R_F$ 0.80 (20:1 $CH_2Cl_2$−EtOH); $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 7.71 (m, 2H, *J* 8.4 Hz, ortho-H's), 7.23 (d, 2H, *J* 8.4 Hz, meta-H's), 5.64−5.75 (m, 1H, OCH$_2$CH$_2$CH$_2$C*H*=CH$_2$, both anomers), 5.22 (bs, O*H*), 4.90−4.94 (m), 4.88 (d, 1H, *J* 2.0 Hz, $\alpha$ anomer), 4.67 (d, 1H, *J* 3.7 Hz, $\beta$ anomer), 4.60 (bs, O*H*), 4.53 (d, *J* 3.5 Hz, $\alpha$ anomer), 4.13−4.32 (m), 3.67 (apt t, 1H, *J* 6.7 Hz, $\beta$ anomer), 3.41−3.56 (m), 3.41−3.53 (m), 3.38 (dd, 1H *J* 10.0 Hz, 2.9, $\beta$ anomer), 3.25 (t, 1H, *J* 8.6 Hz, $\alpha$ anomer), 2.34 (s, OC*H*$_3$), 1.93−2.01 (m, OCH$_2$CH$_2$C*H*$_2$CH=CH$_2$), 1.55−1.62 (m, OCH$_2$C*H*$_2$CH$_2$CH=CH$_2$); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 145.1 (s, *ipso* C, both anomers), 138.3 (d, CH$_2$CH$_2$*C*H=CH$_2$, $\beta$ anomer), 138.2 (d, CH$_2$CH$_2$*C*H=CH$_2$, $\alpha$ anomer), 132.9 (s, *ipso* C $\alpha$ anomer), 132.8 (s, *ipso* C, $\beta$), 130.1, 128.2 (each d, aromatic C's), 115.3 (t, OCH$_2$CH$_2$CH$_2$CH=*C*H$_2$, $\alpha$ anomer), 115.2 (t, OCH$_2$CH$_2$CH$_2$CH=*C*H$_2$, $\beta$ anomer), 102.6 (d, C-1, $\beta$ anomer), 98.6 (d, C-1, $\alpha$ anomer), 76.3, 73.5, 73.4, 69.8, 69.7, 69.5, 30.3 (t, OCH$_2$*C*H$_2$CH$_2$CH=CH$_2$, $\alpha$ anomer), 30.2 (t, OCH$_2$*C*H$_2$CH$_2$-CH=CH$_2$, $\beta$ anomer), 28.9 (t, OCH$_2$CH$_2$*C*H$_2$CH=CH$_2$, $\beta$ anomer), 28.6 (t, OCH$_2$CH$_2$*C*H$_2$CH=CH$_2$, $\alpha$ anomer), 21.9 (q, Ph*C*H$_3$). LRMS-ES: 425.9 [M + Na]$^+$.

**Pent-4′-enyl 3,6-anhydro-D-glucopyranoside (21):** A solution of **20** (1.23 g, 3.06 mmol) in EtOH (12 mL) and NaOH (1 M, 12 mL) was stirred at room temperature for 16 h, heated to 45 °C for 2 h, and cooled to room temperature. The reaction was neutralized with solid $CO_2$, and the solvents were removed in vacuo to leave a white solid. The crude product was extracted with boiling acetone (~50 mL), dried ($MgSO_4$), and filtered, and the acetone was removed in vacuo. Chromatography (1:1 toluene−EtOAc) gave the title compound **21** as a clear oil (0.62 g, 89%) of inseparable anomers with a 1:5 $\alpha/\beta$ diastereomeric ratio; $R_F$ 0.23 (1:1 toluene−EtOAc); $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 5.68−5.79 (m, 1H, OCH$_2$CH$_2$CH$_2$C*H*=CH$_2$, both anomers), 5.09 (d, 1H, *J* 4.3 Hz, H-1, $\alpha$ anomer), 4.89−4.98 (m), 4.79 (apt t, 1H, $\alpha$ anomer), 4.55 (apt t, 1H, *J* 5.3 Hz, $\beta$ anomer), 4.38 (dd, 1H, *J* 5.3, 2.9 Hz, $\beta$ anomer), 4.30 (d, 1H, $\alpha$ anomer), 4.25 (d, 1H, $\beta$ anomer, 4.06−4.22 (m), 3.80 (dd, 1H, *J* 10.0, 3.1 Hz, $\beta$ anomer), 3.68−3.79 (m), 2.98−3.58 (m); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 137.0 (d, OCH$_2$CH$_2$CH$_2$*C*H=CH$_2$, $\beta$ anomer), 136.7 (d, OCH$_2$CH$_2$CH$_2$*C*H=CH$_2$, $\alpha$ anomer), 112.2 (t, OCH$_2$CH$_2$CH$_2$CH=*C*H$_2$, $\alpha$ anomer), 114.0 (t, OCH$_2$CH$_2$CH$_2$CH=*C*H$_2$, $\beta$ anomer), 102.0 (d, C-1, $\beta$ anomer), 95.1 (d, C-1, $\alpha$ anomer), 86.8, 86.6, 82.9, 79.1, 76.7, 73.3, 73.3, 71.4, 70.3, 69.7 67.8, 67.0, 29.3 (t, OCH$_2$*C*H$_2$CH$_2$CH=CH$_2$, $\alpha$ anomer), 29.1 (t, OCH$_2$*C*H$_2$CH$_2$CH=CH$_2$, $\beta$ anomer), 27.5 (t, OCH$_2$CH$_2$*C*H$_2$CH=CH$_2$, $\alpha$ anomer), 27.5 (t, OCH$_2$CH$_2$*C*H$_2$CH=CH$_2$, $\beta$ anomer). LRMS-ES: 253.2 [M + Na]$^+$. HRMS-ES: found 253.1049, requires 253.1052 [M + Na]$^+$.

**Pent-4′-enyl 3,6-Anhydro-2,4-di-*O*-benzyl-α-D-glucopyranoside (22) and Pent-4′-enyl 3,6-Anhydro-2,4-di-*O*-benzyl-β-D-glucopyranoside (23):** To a mixture of sodium hydride (0.65 g, 16.2 mmol, 60% dispersed in mineral oil) in dry DMF (10 mL) under an $N_2$ atmosphere, **21** (0.62 g, 2.70 mmol) dissolved in dry DMF (10 mL) was added dropwise. The solution was stirred for 30 min. Benzyl bromide (1.92 mL, 16.2 mmol) was added dropwise over 20 min. The solution was stirred at room temperature for 24 h, poured onto ice−water (50 mL), and extracted with $Et_2O$ (2 × 50 mL), and the combined organic portions were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Chromatography (4:1 pentane−$Et_2O$) gave the title compounds, **22** (0.81 g, 74%) as a white solid and **23** as a white solid. **23** was recrystallized from EtOH to give clear crystals (0.16 g, 14%).

Analytical data for **23**: $R_F$ 0.68 (1:1 pentane−EtOAc); mp 81−82 °C; $[\alpha]_D$ + 125° (*c* 0.5 $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.06−7.23 (m, 10H, aromatic H's), 5.75 (ddt, *J* 17.0, 10.1, 6.8 Hz, OCH$_2$-CH$_2$CH$_2$C*H*=CH$_2$), 4.98 (d, 1H, *J* 2.9 Hz, H-1), 4.97 (dd, 1H, *J* 3.5, 1.6 Hz, OCH$_2$CH$_2$CH$_2$CH=C*H*$_2$), 4.93 (d, 1H, *J* 12.1 Hz, C*H*$_2$Ph), 4.88−4.91 (m, 1H, OCH$_2$CH$_2$CH$_2$CH=C*H*$_2$), 4.72 (d, 1H, *J* 12.3 Hz, C*H*$_2$Ph), 4.49 (d, 1H, *J* 12.1 Hz, C*H*$_2$Ph), 4.47 (d, 1H, *J* 12.3 Hz, C*H*$_2$Ph), 4.30 (t, 1H, *J* 2.7 Hz, H-5), 4.26 (t, 1H, *J* 4.7 Hz, H-4), 3.98 (m, 2H, OC*H*$_2$CH$_2$CH$_2$CH=CH$_2$, H-6a), 3.75 (dd, 1H, *J* 10.3, 2.9 Hz, H-6b), 3.67 (dd, 1H, *J* 4.7, 2.5 Hz, H-3), 3.62 (t, 1H, *J* 3.7 Hz, H-2), 3.43 (td, 1H, *J* 9.6, 6.8 Hz, OC*H*$_2$CH$_2$CH$_2$CH=CH$_2$), 2.08 (m, 2H, OCH$_2$CH$_2$C*H*$_2$CH=CH$_2$), 1.70 (m, 2H, OCH$_2$C*H*$_2$CH$_2$CH=CH$_2$); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 139.2 (d, OCH$_2$CH$_2$CH$_2$C*H*=CH$_2$), 138.5, 138.3 (each s, *ipso* C), 128.5, 128.5, 128.1, 127.9, 127.7 (each d, aromatic C), 115.1 (t, OCH$_2$CH$_2$CH$_2$CH=*C*H$_2$), 98.3 (d, C-1), 76.3, 75.6, 74.8, 74.2, 72.3, 71.9, 69.9, 68.6 (C-2−C-6, O*C*H$_2$CH$_2$CH$_2$CH=CH$_2$ and 2 × *C*H$_2$Ph), 30.4 (t, OCH$_2$*C*H$_2$CH$_2$CH=CH$_2$), 29.0 (t, OCH$_2$-CH$_2$*C*H$_2$CH=CH$_2$); IR (KBr) $\upsilon$ 2964, 2941, 1636, 1497, 1453, 1369,1026, 904 cm$^{-1}$; HRMS-ES: found 433.2007, requires 433.1991 [M + Na]$^+$. X-ray crystallography data: Appendix A2.

Analytical data for **22**: $R_F$ 0.72 (1:1 pentane−EtOAc); mp 46−47 °C; $[\alpha]_D$ +38 (*c* 0.2 $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.17−7.29 (m, 10H, aromatic H's), 5.75 (ddt, *J* 17.0, 10.1, 6.8 Hz, OCH$_2$-

$CH_2CH_2CH{=}CH_2$), 4.94 (m, 1H, *J* 17.0, 3.5, 1.6 Hz, $OCH_2CH_2CH_2CH{=}CH_2$), 4.94 (d, 1H, *J* 2.2 Hz, H-1), 4.89 (m, 1H, *J* 10.1, 2.0, 1.2 Hz, $OCH_2CH_2CH_2CH{=}CH_2$), 4.66 (d, 1H, *J* 11.5 Hz, $CH_2Ph$), 4.61 (d, 1H, *J* 11.8 Hz, $CH_2Ph$), 4.52 (d, 1H, *J* 11.8 Hz, $CH_2Ph$), 4.51 (d, 1H, *J* 11.5 Hz, $CH_2Ph$), 4.30 (t, 1H, $J_{3,4}$ 3.1 Hz, H-3), 4.23 (dd, 1H, *J* 5.1, 2.3 Hz, H-5), 4.01 (d, 1H, $J_{6a,6b}$ 9.8 Hz, H-6a), 3.83 (dd, 1H, *J* 4.5, $J_{4,3}$ 3.1 Hz, H-4), 3.76 (dd, 1H, $J_{6b,6a}$ 9.8 Hz, H-6b), 3.73−3.79 (m, 1H, $OCH_2CH_2CH_2CH{=}CH_2$), 3.56 (bs, 1H, H-2), 3.43 (dt, 1H, *J* 9.6, 6.8 Hz, $OCH_2CH_2CH_2CH{=}CH_2$), 2.08 (m, 2H, $OCH_2CH_2CH_2CH{=}CH_2$), 1.70 (m, 2H, $OCH_2CH_2CH_2CH{=}CH_2$); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 138.3 (d, $OCH_2CH_2CH_2CH{=}CH_2$), 138.1, 137.7 (each s, *ipso* C), 128.7, 128.5, 128.1, 127.9, 127.8, 127.1 (each d, aromatic C), 114.9 (t, $OCH_2CH_2CH_2CH{=}CH_2$), 99.7 (d, C-1), 75.6, 72.8, 72.5, 72.3, 72.2, 71.6, 67.9, 30.5 (t, $OCH_2CH_2CH_2CH{=}CH_2$), 28.9 (t, $OCH_2CH_2CH_2CH{=}CH_2$); IR (KBr) $\upsilon$ 2931, 2886, 1642, 1497, 1453, 1205, 694 $cm^{-1}$. LRMS-ES: 433.2 $[M + Na]^+$. HRMS-ES: found 433.1985, requires 433.1991 $[M + Na]^+$.

**Methyl *O*-[3,6-Anhydro-2,4-di-*O*-benzyl-$\beta$-D-glucopyranosyl]-(1→6)-2,3,4-tri-*O*-benzyl-$\alpha$-D-glucopyranoside (25):** A mixture of **22** or **23** (0.08 g, 0.195 mmol) and **24** (0.113 g, 0.244 mmol), NIS (0.067 g, 0.30 mmol) and activated, crushed 4 Å molecular sieves were subjected to a high vacuum for 4 h. The mixture was dissolved in dry $CH_2Cl_2$ (1 mL) and cooled to −20 °C and treated with TESOTf (8.6 $\mu$L, 0.038 mmol). The reaction was stirred for 45 min at −20 °C, diluted with $CH_2Cl_2$ (1.5 mL), filtered, washed successively with 10% aq. sodium thiosulfate (1 × 2.5 mL), aq. satd. $NaHCO_3$ (1 × 2.5 mL), and dried ($MgSO_4$), and filtered, and the solvent was removed in vacuo. Chromatography (4:1 pentane−EtOAc and 1% triethylamine) gave the title compound **25** (95 mg, 62% with $\beta$ pentenyl and 68 mg, 44% with $\alpha$ pentenyl) as a white solid and recovered **24** (34 mg, 30%); $R_F$ 0.64 (2:1 pentane−EtOAc); mp 78−80 °C; $[\alpha]_D$ −4° (*c* 0.2 $CHCl_3$); $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.13−7.30 (m, 25H, aromatic H's), 5.05 (d, 1H, *J* 2.5 Hz, H-1′), 4.90 (d, 1H, *J* 10.7 Hz, $OCH_2Ph$) 4.75 (d, 1H, *J* 10.7 Hz, $OCH_2Ph$), 4.74 (d, 1H, *J* 10.7 Hz, $OCH_2Ph$), 4.72 (d, 1H, *J* 12.1 Hz, $OCH_2Ph$), 4.65 (d, 1H, *J* 11.5 Hz, $OCH_2Ph$), 4.59 (d, 1H, *J* 11.9 Hz, $OCH_2Ph$), 4.56 (d, 1H, *J* 11.5 Hz, $OCH_2Ph$), 4.54 (d, 1H, *J* 11.5 Hz, $OCH_2Ph$), 4.50 (d, 1H, $J_{1,2}$ 3.1 Hz, H-1), 4.49 (d, 3H, *J* 11.5 Hz, $OCH_2Ph$), 4.27 (t, 1H, *J* 2.9 Hz, H-3′), 4.22 (dd, 1H, $J_{3,2}$ 4.8 Hz, *J* 2.0 Hz, H-5′), 3.99−4.04 (m, 2H), 3.92 (apt t, 1H, *J* 9.2 Hz), 3.85 (dd, 1H, $J_{2,3}$ 4.8 Hz, $J_{2,1}$ 3.1, H-4′), 3.69−3.74 (m, 2H), 3.59−3.63 (m, 2H), 3.40−3.50 (m, 2H) 3.28 (s, 3H, $OCH_3$); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 138.9, 138.4, 138.3, 137.9, 137.6 (each s, *ipso* C's), 128.6, 128.5, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.8, 127.7 (each d, aromatic C), 99.9, 98.1 (each d, C-1, C-1′), 82.2, 81.8, 80.0, 78.1, 75.9, 75.9, 75.2, 73.5, 72.6, 72.4, 71.9, 71.7, 70.0, 67.2, 55.3 (s, $OCH_3$); IR (KBr) $\upsilon$ 2897, 1454, 1262, 1163, 1026 $cm^{-1}$; HRMS-ES: found 811.3452, requires 811.3458 $[M + Na]^+$.

**Methyl 3,6-Anhydro-$\beta$-D-glucopyranoside-(1→6)-$\alpha$-D-glucopyranoside (16):** A solution of **25** (0.069 g, 0.087 mmol) in EtOH (4 mL) in the presence of Pd/C was stirred in an $H_2$ atmosphere at 10 bar in a Parr reactor for 24 h. The reaction was filtered through Celite, and EtOH was removed in vacuo. The resulting residue was dissolved in water (2 mL) and washed with $Et_2O$ (2 × 3 mL). Water was removed at reduced pressure to leave a clear solid (23 mg, 78%); $R_F$ 0.13 (3:1 $CH_2Cl_2$−EtOH); mp 46−48 °C; $[\alpha]_D$ −8.2° (*c* 0.2, $H_2O$); $^1H$ NMR ($D_2O$, 400 MHz) $\delta$ 4.88 (s, 1H, H-1′), 4.73 (d, 1H, $J_{1,2}$ 3.7 Hz, H-1), 4.30 (t, 1H, *J* 2.9 Hz, H-5′), 4.27 (apt t, 1H, H-4′), 4.22 (d, 1H, $J_{6a',6a'}$ 10.3 Hz, H-6a′), 4.15 (apt t, 1H, H-3′), 4.06 (dd, 1H, *J* 11.1, 1.4 Hz, H-6a), 3.89 (dd, 1H, $J_{6b',6a'}$ 10.3 Hz, *J* 2.9 Hz, H-6b′), 3.80 (d, 1H, *J* 3.7 Hz, H-2′), 3.73−3.75 (m, 1H, H-5), 3.58−3.71 (m, 2H, H-3, H-4), 3.51 (dd, 1H, *J* 9.8 Hz, $J_{2,1}$ 3.7 Hz, H-2), 3.39 (apt t, 1H, H-6b), 3.36 (s, 3H, $OCH_3$); $^{13}C$ NMR ($D_2O$, 100 MHz) $\delta$ 102.6 (d, C-1′), 99.4 (d, C-1), 74.3, 73.1, 71.6, 71.6, 71.2, 70.8, 70.6, 69.6, 69.1, 67.2, 55.2 (q, $OCH_3$). HRMS-ES: found 361.1123, requires 361.1111 $[M + Na]^+$.

**4′-Methylphenyl 6-*O*-Acetyl-2,3,4-*O*-tribenzyl-1-thio-$\beta$-D-glucopyranoside (27):** A solution of **26** (1.39 g, 2.50 mmol), acetic anhydride (5 mL), and pyridine (5 mL) in the presence of DMAP was stirred for 2 h. Water (20 mL) was added, and the product was extracted with $CH_2Cl_2$ (2 × 40 mL). The combined organic portions were dried ($MgSO_4$) and filtered, and the solvent was removed in vacuo. Chromatography (10:1 pentane−EtOAc) gave the title compound **27** as a clear oil (1.23 g, 83%); $R_F$ 0.62 (2:1 pentane−EtOAc); $[\alpha]_D$ −18° (*c* 0.9, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.00−7.38 (m, 19H, aromatic H's), 4.84 (d, 1H, *J* 10.4 Hz, $OCH_2Ph$), 4.83 (d, 1H, *J* 11.0 Hz, $OCH_2Ph$), 4.76 (d, 1H, *J* 11.0 Hz, $OCH_2Ph$), 4.75 (d, 1H, *J* 10.2 Hz, $OCH_2Ph$), 4.49 (d, 1H, $J_{1,2}$ 9.8 Hz, H-1), 4.48 (d, 1H, *J* 11.0 Hz, $OCH_2Ph$), 4.27 (dd, 1H, $J_{6a,6b}$ 11.5 Hz, *J* 1.0 Hz, H-6), 4.12 (dd, 1H, $J_{6b,6a}$ 11.5 Hz, *J* 5.1 Hz, H-6b), 3.61−3.65 (m, 1H, H-5), 3.41−3.49 (m, 2H, H-3, H-4), 3.39 (t, 1H, $J_{2,1}$ 9.8 Hz, H-2), 2.23 (s, 3H, $PhCH_3$) 1.95 (s, 3H, $C(O)CH_3$); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 170.7 (s, $C(O)CH_3$), 138.3, 138.0, 137.9, 137.7 (each s, 5 × *ipso* C's), 132.8, 129.7, 129.7, 128.6, 128.5, 128.5, 128.4, 128.3, 128.1, 128.1, 127.9, 127.8 (each d, aromatic C's), 87.8 (d, C-1), 86.8, 80.9, 77.6, 76.9 (each d, C-2−C-5), 75.9, 75.5, 75.1 (each t, 3 × $OCH_2Ph$), 63.4 (t, C-6), 21.2, 20.9 (each q, $C(O)CH_3$ and $PhCH_3$); IR (KBr) $\upsilon$ 3031, 2871, 1741 (C═O), 1362, 1237, 1088 $cm^{-1}$. Anal. Calcd for $C_{36}H_{38}O_6S$: C, 72.21; H, 6.40; S, 5.36. Found: C, 71.86; H, 6.36; S, 5.67. LRMS-ES: 621.2 $[M + Na]^+$.

**Methyl 6-*O*-Acetyl-2,3,4-tri-*O*-benzyl-$\alpha$-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-$\alpha$-D-glucopyranoside (28) and Methyl 6-*O*-Acetyl-2,3,4-tri-*O*-benzyl-$\beta$-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-$\alpha$-D-glucopyranoside (28a):** To a stirred solution of **27** (1.32 g, 2.20 mmol), **24** (1.02 g, 2.20 mmol), and NIS (0.99 g, 4.40 mmol) predried under a high vacuum for 4 h in $CH_2Cl_2$ (2 mL) and $Et_2O$ (10 mL) under an $N_2$ atmosphere at −40 °C, trifluoromethanesulfonic acid (100 $\mu$L) was added. The reaction was stirred for 5 min, satd. aq. $NaHCO_3$ solution (0.1 mL) was added, and the reaction was allowed to warm to room temperature. The reaction was diluted with $CH_2Cl_2$ (25 mL) and washed successively with 10% aq. sodium thiosulfate (2 × 30 mL) and satd. aq. $NaHCO_3$ solution (30 mL). The organic portion was dried ($MgSO_4$) and filtered, and solvent was removed in vacuo. Chromatography (6:1 pentane−EtOAc) gave the title compounds **28** (1.32 g, 64%) and **28a** (0.06 g, 3%) as white solids.

Analytical data of **28**: $R_F$ 0.22 (3:1 pentane−EtOAc); mp 94−97 °C, (lit.[17] mp 80−82 °C); $[\alpha]_D$ +88° (*c* 0.2, $CHCl_3$), (lit.[17] $[\alpha]_D$ +56° (*c* 2.1, $CHCl_3$)); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.16−7.27 (m, 30H, aromatic H's), 4.88 (d, 1H, *J* 2.5 Hz, H-1′), 4.87 (d, 1H, *J* 2.7 Hz, H-1), 4.46−4.91 (m, 12H, 12 × $OCH_2Ph$), 4.11 (d, 2H, *J* 2.9 Hz), 3.91 (t, 1H, *J* 9.3 Hz), 3.90 (t, 1H, *J* 9.3 Hz), 3.78 (dt, 1H, *J* 10.0 Hz, 3.0 Hz), 3.69−3.77 (m, 2H), 3.56 (t, 1H, *J* 9.3 Hz), 3.41−3.45 (m, 2H), 3.35−3.39 (m, 2H), 3.28 (s, 3H, $OCH_3$), 1.90 (s, 3H, $C(O)CH_3$); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 170.8 (s, $C(O)CH_3$), 138.9, 138.7, 138.5, 138.4, 138.2 (each s, 6 × *ipso* C's), 128.5, 128.5, 128.3, 128.2, 128.1, 128.1, 128.0, 127.9, 127.9, 127.8, 127.8, 127.7 (each d, aromatic C's), 98.1, 97.1 (each d, C-1, C-1′), 82.2, 81.7, 80.2, 80.1, 77.9, 75.9, 75.7, 75.1, 75.0, 73.5, 73.0, 72.5, 70.5, 68.8, 66.2, 63.1, 55.3 (q, $OCH_3$), 20.9 (q, $C(O)CH_3$); IR (KBr) $\upsilon$ 3029, 2928, 1740 (C═O), 1453, 1264, 1101 $cm^{-1}$. Anal. Calcd for $C_{57}H_{62}O_{12}$: C, 72.90; H, 6.65. Found: C, 72.50; H, 6.62. HRMS-ES: found 961.4147, requires 961.4139 $[M + Na]^+$.

Analytical data for **28a**: $R_F$ 0.24 (3:1 pentane−EtOAc); mp 116−119 °C; $[\alpha]_D$ +5.6° (*c* 0.5, $CHCl_3$), (lit.[15] $[\alpha]_D$ +29° (*c* 0.5, $CHCl_3$)); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.09−7.28 (m, 30H, aromatic H's), 4.24−4.91 (m, 14H, H-1, H-1′, 6 × $OCH_2Ph$), 4.26 (d, 1H, *J* 7.8 Hz), 4.25 (dd, 1H, *J* 11.9, 2.2 Hz), 4.11 (dd, 1H, *J* 12.1, 4.7 Hz), 4.08 (dd, 1H, *J* 9.3 Hz), 4.04−4.05 (m, 1H), 3.91 (t, 1H, *J* 9.3 Hz), 3.74 (ddd, 1H, *J* 10.2, 4.7, 1.9 Hz), 3.55−3.59 (m, 2H), 3.40−3.48 (m, 2H), 3.37 (ddd, 1H *J* 9.7, 4.5, 2.1 Hz), 3.25 (s, 3H, $OCH_3$), 1.91 (s, 3H, $C(O)CH_3$). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 170.8 (s, $C(O)CH_3$), 138.9, 138.5, 138.4, 138.4, 138.2, 137.9 (each s, 6 × *ipso* C's), 128.6, 128.5, 128.5, 128.5, 128.4, 128.2, 128.2, 128.1, 128.0, 128.0, 128.0, 128.0, 127.9, 127.8, 127.7, 127.7, 127.6 (each d, aromatic C's), 103.9 (d, C-1′), 98.2 (d,

C-1), 84.8, 82.0, 79.9, 78.1, 75.8, 75.8, 75.1, 75.0, 74.9, 73.4, 73.0, 69.9, 68.8, 63.2, 55.3 (q, $OCH_3$), 20.9 (q, C(O)$CH_3$). HRMS-ES: found 961.4152, requires 961.4139 $[M + Na]^+$.

**Methyl 2,3,4-Tri-*O*-benzyl-α-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (29):** To a solution of **28** (1.26 g, 1.34 mmol) in toluene (20 mL), methanolic sodium methoxide (20 mL) was added. The reaction was stirred for 3 h, neutralized with solid $CO_2$, and filtered through a pad of Celite, and the solvent was removed in vacuo. Chromatography (3:2 pentane−EtOAc) yielded the title compound **29** as a white solid (1.01 g 92%); $R_F$ 0.43 (1:1 pentane−EtOAc); mp 97−100 °C (lit.[18] mp 109−110 °C); $[\alpha]_D$ +5.6° (*c* 0.5, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.87 (d, 1H, *J* 3.9, H-1), 4.87 (d, 1H, *J* 10.5, OC$H_2$Ph), 4.86 (d, 1H, *J* 3.7, H-1′), 4.84 (d, 1H, *J* 11.0, OC$H_2$Ph), 4.80 (d, 1H, *J* 11.2, OC$H_2$Ph), 4.74 (d, 1H, *J* 9.2 Hz, OC$H_2$Ph), 4.71 (d, 1H, *J* 9.2 Hz, OC$H_2$Ph), 4.64 (d, 1H, *J* 12.1 Hz, OC$H_2$Ph), 4.57 (d, 1H, *J* 11.2 Hz, OC$H_2$Ph), 4.55 (d, 1H, *J* 11.0 Hz, OC$H_2$Ph), 4.49 (d, 1H, *J* 12.1 Hz, OC$H_2$Ph), 3.90 (dt, 2H, *J* 9.2, 3.3 Hz), 3.73 (dd, 1H, *J* 11.2, 4.5 Hz), 3.68−3.74 (m, 1H), 3.53−3.65 (overlapping signals, 5H), 3.42 (t, 1H, *J* 3.5 Hz), 3.40 (t, 1H, *J* 3.7 Hz), 3.37 (dd, 1H, *J* 9.8, 3.5 Hz), 3.28 (s, 3H, OC$H_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 138.9, 138.8, 138.5, 138.4, 138.4, 138.2 (each s, 6 × *ipso* C's), 128.4, 128.4, 128.4, 128.0, 127.9, 127.9, 127.8, 127.7, 127.7, 127.6 (each d, aromatic C's), 98.1, 97.2 (each d, C-1, C-1′), 81.5, 80.2, 77.8, 75.7, 75.5, 75.0, 74.9, 73.4, 72.5, 71.0, 70.5, 66.0, 61.9, 55.2 (q, O$CH_3$); IR (KBr) $\upsilon$ 3462 (O−H), 2909, 1497, 1453, 1089 $cm^{-1}$. Anal. Calcd for $C_{57}H_{62}O_{12}$: C, 73.64; H, 6.74. Found: C, 73.35; H, 6.63. HRMS-ES: found 919.4036, requires 919.4033 $[M + Na]^+$.

**Methyl 2,3,4-Tri-*O*-benzyl-α-D-glucopyranosyl-(1→*6*)-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (30) and Methyl (2,3,4-Tri-*O*-benzyl-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (31):** To a stirred solution of **27** (1.13 g, 1.26 mmol), **29** (0.75 g, 1.26 mmol), and NIS (0.57 g, 2.52 mmol) predried under a high vacuum for 4 h in $CH_2Cl_2$ (2 mL) and $Et_2O$ (10 mL) under an $N_2$ atmosphere at −40 °C, trifluoromethanesulfonic acid (100 μL) was added. The reaction was stirred for 5 min, satd. aq. $NaHCO_3$ solution (0.1 mL) was added, and the reaction was allowed to warm to room temperature. The reaction was diluted with $CH_2Cl_2$ (30 mL) and washed successively with 10% aq. sodium thiosulfate (2 × 30 mL) and satd. aq. $NaHCO_3$ solution (30 mL). The organic portion was dried ($MgSO_4$) and filtered, and solvent was removed in vacuo. Chromatography (4:1 pentane−EtOAc) yielded the acetylated products as a syrup of inseparable diastereomers. The products were dissolved in toluene (10 mL), and methanolic sodium methoxide (10 mL) was added. The reaction was stirred for 2 h, neutralized with solid $CO_2$ and filtered through a pad of Celite, and the solvent was removed in vacuo. Chromatography (3:1 pentane−EtOAc) yielded the title compounds **30** (0.59 g 35%) and **31** (0.18 g, 11%) as clear oils.

Analytical data for **30**: $R_F$ 0.17 (3:1 pentane−EtOAc); $[\alpha]_D$ +96° (*c* 0.5, $CHCl_3$), (lit.[19] $[\alpha]_D$ +89° (*c* 1.0, $CHCl_3$)); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.11−7.26 (m, 45H, aromatic H's), 4.46−4.90 (m, 21H, H-1, H-1′, H-1″, 18 × OC$H_2$Ph), 3.87−3.92 (m, 3H), 3.51−3.92 (m, 11H), 3.31−3.44 (m, 4H), 3.25 (s, 3H, OC$H_3$), 1.50 (bs, 1H, O*H*); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 139.0, 138.9, 138.7, 138.6, 138.5, 138.4, 138.2 (each s, 9 × *ipso* C's), 128.5, 128.5, 128.5, 128.4, 128.4, 128.2, 128.1, 128.1, 128.1, 127.9, 127.9, 127.8, 127.8, 127.7, 127.6, 127.6, 127.6 (each d, aromatic C's), 98.1, 97.2, 97.1 (each d, C-1, C-1′, C-1″), 82.2, 81.7, 81.6, 80.4, 80.3, 77.9, 77.7, 77.5 (each d), 75.8, 75.6, 75.6, 75.1, 75.1, 75.0, 73.5 (each t), 72.5, 72.4, 71.0 (each d), 70.8(t), 70.6(d), 66.0, 65.9, 62.0 (each t), 55.3 (q, O$CH_3$); IR (film) $\upsilon$ 3505 (O−H), 2926, 1498, 1361, 1266 $cm^{-1}$. LRMS-ES: 1351.1 $[M + Na]^+$. HRMS-FAB: found 1351.5938, requires 1351.5970 $[M + Na]^+$.

Analytical data for **31**: $R_F$ 0.20 (3:1 pentane−EtOAc); $[\alpha]_D$ +14.2° (*c* 0.5, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.02−7.25 (m, 45H, aromatic H's), 4.92 (d, 1H, *J* 3.3 Hz, H-1′), 4.53−4.89 (m, 16H, 16 × OC$H_2$Ph), 4.49 (d, 1H, *J* 12.3 Hz, OC$H_2$Ph), 4.46 (d, 1H, *J* 3.5 Hz, H-1), 4.39 (d, 1H, *J* 11.5 Hz, OC$H_2$Ph), 4.25 (d, 1H, *J* 7.8 Hz, H-1″), 3.95 (d, 1H, *J* 10.4 Hz), 3.89 (t, 2H, *J* 9.2 Hz), 3.71−3.83 (m, 3H), 3.65 (dd, 1H, *J* 10.2, 3.4 Hz), 3.53−3.60 (m, 5H), 3.33−3.49 (m, 6H), 3.23 (s, 3H, OC$H_3$), 1.88 (bs, 1H, O*H*); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 139.0, 138.7, 138.6, 138.6, 138.5, 138.3, 138.1 (each s, 9 × *ipso* C's), 128.6, 128.5, 128.5, 128.4, 128.4, 128.1, 128.1, 128.1, 128.0, 128.0, 128.0, 127.9, 127.8, 127.7, 127.6, 127.6 (each d, aromatic C's), 103.9 (d, C-1″), 98.1, 97.3 (each d, C-1, C-1′), 84.7, 82.3, 82.1, 81.6, 80.3, 80.1, 77.9, 77.7, 75.8, 75.5, 75.2, 75.2, 75.1, 74.9, 73.5, 72.4, 70.6, 70.0, 68.9, 66.1, 62.1, 55.2 (q, O$CH_3$); IR (film) $\upsilon$ 3508 (O−H), 2938, 1496, 1454, 1268, 1070 $cm^{-1}$. HRMS-FAB: found 1351.6042, requires 1351.5970 $[M + Na]^+$.

**Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-tosyl-α-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (32):** A solution of **30** (0.53 g, 0.40 mmol) and *p*-toluenesulfonyl chloride (0.75 g, 4.0 mmol) in dry pyridine (10 mL) was stirred for 16 h. Water (10 mL) and $CH_2Cl_2$ (10 mL) were added. The organic portion was washed with water (2 × 10 mL), dried ($MgSO_4$), and filtered, and solvent was removed in vacuo. Chromatography (2:1 pentane−EtOAc) yielded the title compound **32** (0.47 g, 80%) as an oil; $R_F$ 0.43 (2:1 pentane−EtOAc); $[\alpha]_D$ +52.4° (c 0.5, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.79 (d, 2H, *J* 8.3, ortho H's), 7.16−7.40 (m, 47H, aromatic and meta H's), 4.59−5.04 (m, 20H, H-1, H-1′, H-1″, 17 × OC$H_2$Ph), 4.44 (d, 1H, *J* 10.8, OC$H_2$Ph), 4.14−4.17 (m, 2H), 3.94−4.06 (m, 4H), 3.64−3.88 (m, 7H), 3.45−3.53 (m, 5H), 3.38 (s, 3H, OC$H_3$), 2.42 (s, 3H, PhC$H_3$); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 144.8, 138.9, 138.9, 138.7, 138.5, 138.4, 138.3, 138.1, 133.0 (each s, ipso C's), 129.9, 128.5, 128.5, 128.4, 128.4, 128.1, 128.1, 128.0, 127.9, 127.9, 127.8, 127.6, 127.6, 127.5, 127.4, 127.3 (each d, aromatic C's), 98.1, 97.1, 97.1 (each d, C-1, C-1′, C-1″), 82.2, 81.7, 71.4, 80.3, 80.0, 77.8, 76.9 (each d), 75.8, 75.5, 75.1, 75.0, 74.9, 73.5, 72.5, 72.3 (each t), 70.7, 70.6, 68.7 (each d), 68.6, 65.9 (each t), 55.2 (q, O$CH_3$), 21.7 (q, PhC$H_3$); IR (film) $\upsilon$ 3030, 1496, 1453, 1362, 1096 $cm^{-1}$; Anal. Calcd for $C_{34}H_{34}O_5S$: C, 72.04; H, 6.39; S, 2.16. Found: C, 71.68; H, 6.23; S, 2.55. HRMS-FAB: found 1505.6044, requires 1505.6059 $[M + Na]^+$.

**Methyl (2,3,4-Tri-*O*-benzyl-6-*O*-tosyl-α-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (34):** A solution of **31** (0.16 g, 0.12 mmol) and *p*-toluenesulfonyl chloride (0.22 g, 1.2 mmol) in dry pyridine (4 mL) was stirred for 16 h. Water (4 mL) and $CH_2Cl_2$ (4 mL) were added. The organic portion was washed with water (2 × 5 mL), dried ($MgSO_4$), and filtered, and solvent was removed in vacuo. Chromatography (2:1 pentane−EtOAc) yielded the title compound **34** (0.13 g, 77%) as clear oil; $R_F$ 0.47 (2:1 pentane−EtOAc); $[\alpha]_D$ +29.6° (*c* 0.5, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.78 (d, 2H, *J* 8.2 Hz, ortho H's), 7.15−7.38 (m, 47H, aromatic and meta H's), 5.05 (d, 1H, *J* 3.4 Hz, H-1′), 4.69−5.02 (m, 16H, 16 × OC$H_2$Ph), 4.64 (d, 1H, *J* 7.9 Hz, H-1″), 4.58 (d, 1H, *J* 2.9 Hz, H-1), 4.51 (d, 1H, *J* 11.4 Hz, OC$H_2$Ph), 4.49 (d, 1H, *J* 10.7 Hz, OC$H_2$Ph), 3.98−4.18 (m, 5H), 3.45 (m, 13H), 3.35 (s, 3H, OC$H_3$), 2.40 (s, 3H, PhC$H_3$); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ 144.9, 139.0, 138.7, 138.6, 138.2, 138.2, 137.7, 132.9 (each s, ipso C's), 129.9, 128.6, 128.5, 128.5, 128.4, 128.4, 128.2, 128.1, 128.1, 128.0, 127.9, 127.8, 127.7, 127.7, 127.6, 127.5 (each d, aromatic C's), 103.6 (d, C-1″), 98.1, 97.2 (each d, C-1, C-1′), 84.6, 82.2, 81.9, 81.6, 80.3, 80.1, 77.8, 76.9 (each d), 75.8, 75.5, 75.1, 75.0, 74.8, 73.5 (each t), 72.9 (d), 72.4 (t), 70.6, 69.9 (each d), 68.6, 66.0, 66.0 (each t), 55.2 (q, O$CH_3$), 21.8 (q, PhC$H_3$); IR (film) $\upsilon$ 3031, 1497, 1453, 1361, 1071 $cm^{-1}$. Anal. Calcd for $C_{34}H_{34}O_5S$: C, 72.04; H, 6.39; S, 2.16. Found: C, 71.75; H, 6.35; S, 2.03. HRMS-FAB: found 1505.6076, requires 1505.6059 $[M + Na]^+$.

**Methyl 6-*O*-Tosyl-α-D-glucopyranosyl)-(1→6)-α-D-glucopyranosyl-(1→6)-α-D-glucopyranoside (33):** A mixture of **32** (0.45 g, 0.30 mmol) in EtOAc (50 mL) and MeOH (50 mL) and diluted HCl (1 drop) was stirred in a Parr hydrogenator for 2 h under a hydrogen atmosphere of 30 psi in the presence of Pd/C. The contents were filtered

through a pad of Celite, and the solvents were removed in vacuo to leave the title compound **33** as a yellow oil (0.19 g, 95%); $R_F$ 0.13 (3:1 EtOAc−MeOH); $[\alpha]_D$ +117.0° (*c* 0.5, MeOH); $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 7.85 (d, 2H, *J* 8.2 Hz, *ortho* H's), 7.49 (d, 2H, *J* 8.2 Hz, *meta* H's), 4.89 (d, 1H, *J* 3.7 Hz, H-1″), 4.79 (d, 1H, *J* 3.7 Hz, H-1′), 4.74 (d, 1H, *J* 3.5 Hz, H-1), 4.31−4.35 (m, 1H), 4.24 (dd, 1H, *J* 10.8, 5.2 Hz), 3.62−4.02 (m, 10H), 3.24−3.50 (m, 6H), 3.47 (s, 3H, OC*H*$_3$), 2.51 (s, 3H, PhC*H*$_3$); $^{13}$C NMR (300 MHz, $CD_3OD$) $\delta$ 145.1, 133.0 (each s, *ipso* C's), 129.7, 127.8 (each d, aromatic C's), 99.9, 99.9, 98.2 (each d, C-1, C-1′, C-1″), 73.9, 73.6, 72.3, 72.0, 70.6, 70.5, 70.3, 69.8, 69.6 (each d), 69.5, 66.4, 66.0 (each t, C-6, C-6′, C-6″), 54.5 (q, O*C*H$_3$), 20.3 (q, $C_6H_4CH_3$); IR (film) $\upsilon$ 3407 (O−H), 2924, 1451, 1358, 1176, 1033 cm$^{-1}$. LRMS-ES: 695.1 $[M + Na]^+$. HRMS-ES: found 695.0837, requires 695.1833 $[M + Na]^+$.

**Methyl 6-*O*-Tosyl-$\beta$-D-glucopyranosyl-(1→6)-$\alpha$-D-glucopyranosyl-(1→6)-$\alpha$-D-glucopyranoside (35):** A mixture of **34** (0.12 g, 0.08 mmol) in EtOAc (20 mL) and MeOH (20 mL) and diluted HCl (1 drop) was stirred in a Parr hydrogenator for 2 h under a hydrogen atmosphere of 30 psi in the presence of Pd/C. The contents were filtered through a pad of Celite, and the solvents were removed in vacuo to leave the title compound **35** as a yellow oil (0.05 g, 88%); $R_F$ 0.16 (3:1 EtOAc−MeOH); $[\alpha]_D$ +62.0° (*c* 0.5, MeOH); $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 7.81 (d, 2H, *J* 8.4 Hz, *ortho* H's), 7.45 (d, 2H, *J* 8.4 Hz, *meta* H's), 4.84 (d, 1H, *J* 3.4 Hz, H-1′), 4.68 (d, 1H, *J* 3.7 Hz, H-1), 4.33 (dd, 1H, *J* 10.8, 1.8 Hz), 4.29 (d, 1H, *J* 7.8 Hz, H-1″), 3.95 (dd, 1H, *J* 11.3, 1.8 Hz), 3.95 (dd, 1H, *J* 11.1, 5.4 Hz), 3.82−3.87 (m, 1H), 3.58−3.78 (m, 5H), 3.27−3.54 (m, 6H), 3.42 (s, 3H, OC*H*$_3$), 3.18 (t, 1H, *J* 9.2 Hz), 3.14 (apt t, 1H), 2.46 (s, 3H, PhC*H*$_3$); $^{13}$C NMR (75 MHz, $CD_3OD$) $\delta$ 145.1, 132.9 (each s, *ipso* C's), 129.8, 127.8 (each d, aromatic C's), 103.2 (d, C-1″), 99.9, 98.5 (each d, C-1, C-2), 76.3, 73.9, 73.7, 73.5, 72.2, 72.1, 71.3, 70.5, 70.4, 70.2, 69.7 (each d), 69.5, 68.5, 66.3 (each t, C-6, C-6′, C-6″), 20.4 (q, PhC*H*$_3$); IR (film) $\upsilon$ 3405 (O−H), 1664, 1387, 1175 cm$^{-1}$. LRMS-ES: 695.2 $[M + Na]^+$. HRMS-ES: found 695.0841, requires 695.1833 $[M + Na]^+$.

**Methyl 3,6-Anhydro-$\alpha$-D-glucopyranosyl-(1→6)-$\alpha$-D-glucopyranosyl-(1→6)-$\alpha$-D-glucopyranoside (17):** A solution of **33** (0.195 g, 0.29 mmol) in 1 M NaOH solution (12 mL) was stirred at 70 °C for 8 h. The reaction was neutralized with solid $CO_2$, and the water was removed by lyophylisation. The resulting crude material and a catalytic amount of DMAP were dissolved in pyridine (5 mL) and acetic anhydride (5 mL) and stirred for 5 h. The reaction was quenched by the addition of water (10 mL), and the product was extracted with EtOAc (2 × 10 mL). The combined organic portions were dried ($MgSO_4$) and filtered, and solvent was removed in vacuo for 8 h. The resulting material was stirred in methanolic $NH_3$ (3 mL) for 5 h, and the solvents were removed in vacuo to give the title compound **17** as a yellow oil (91 mg, 61%); $R_F$ 0.09 (3:1 EtOAc−MeOH); $[\alpha]_D$ +45.3° (*c* 0.5, $H_2O$); $^1$H NMR (300 MHz, $D_2O$) $\delta$ 5.23 (d, 1H, *J* 2.8 Hz, H-1″), 5.01 (d, 1H, *J* 3.8 Hz, H-1′), 4.86 (d, 1H, *J* 3.8 Hz, H-1), 4.46 (bs, 1H), 4.38 (t, 1H, *J* 2.6 Hz), 4.15 (dd, 1H, *J* 12.0, 5.3 Hz), 4.05−4.10 (m, 2H), 3.99−4.02 (m, 2H), 3.95 (ddd, 1H, *J* 10.2, 5.1, 2.0 Hz), 3.87 (ddd, 1H, *J* 10.0, 4.7, 1.7 Hz), 3.76−3.80 (m, 2H), 3.72 (t, 1H, *J* 9.4 Hz), 3.64 (apt t, 1H, *J* 4.0, 3.6 Hz), 3.62 (dd, 1H, *J* 5.8, 3.8 Hz), 3.52−3.57 (m, 2H), 3.49 (s, 3H, OC*H*$_3$); $^{13}$C NMR (75 MHz, $D_2O$) $\delta$ 100.3, 98.7, 97.9 (each d, C-1, C-1′, C-1″), 98.7, 76.4, 74.4, 73.9, 72.4, 72.2, 72.0, 71.7, 71.0, 70.5, 70.4, 70.4 (each d), 69.6, 69.1, 66.6 (each t, C-6, C-6′, C-6″), 56.1 (q, O*C*H$_3$). LRMS-ES: 523.1 $[M + Na]^+$. HRMS-ES: found 523.1635, requires 523.4382 $[M + Na]^+$.

**Methyl (3,6-Anhydro-$\beta$-D-glucopyranosyl)-(1→6)-$\alpha$-D-glucopyranosyl-(1→6)-$\alpha$-D-glucopyranoside (18):** A solution of **35** (50 mg, 0.074 mmol) in 1 M aq. NaOH solution (5 mL) was stirred at 70 °C for 8 h. The reaction was neutralized with solid $CO_2$, and the water was removed by lyophylisation. The resulting crude material and catalytic DMAP were dissolved in pyridine (3 mL) and acetic anhydride (3 mL) and stirred for 5 h. The reaction was quenched by the addition of water (10 mL), and the product was extracted with EtOAc (2 × 10 mL). The combined organic portions were dried ($MgSO_4$) and filtered, and solvent was removed in vacuo for 8 h. The resulting material was stirred in methanolic $NH_3$ (2 mL) for 5 h, and the solvents were removed in vacuo to give the title compound **18** as a yellow oil (26 mg, 70%); $R_F$ 0.13 (3:1 EtOAc−MeOH); $[\alpha]_D$ +112.3° (*c* 0.5, $H_2O$); $^1$H NMR (300 MHz, $D_2O$) $\delta$ 4.83 (d, 2H, *J* 3.7 Hz, H-1′) 4.82 (bs, 1H, H-1″), 4.71 (d, 1H, *J* 3.7 Hz, H-1), 4.26 (t, 1H, *J* 3.0 Hz), 4.21 (dd, 1H, *J* 5.3, 3.0 Hz), 4.18 (d, 1H, *J* 10.4 Hz), 4.10 (dd, 1H, *J* 5.5, 3.7 Hz), 4.00 (dd, 1H, *J* 11.4, 2.0 Hz), 3.87 (dd, 1H, *J* 11.2, 4.4 Hz), 3.83 (dd, 1H, *J* 10.2, 2.8 Hz), 3.74−3.78 (m, 2H), 3.71 (ddd, 1H, *J* 10.2, 4.4, 1.8 Hz), 3.64 (bs, 1H), 3.62, (t, 1H, *J* 2.6 Hz), 3.53 (d, 1H, *J* 9.2 Hz), 3.47 (dd, 1H, *J* 3.7, 2.2 Hz), 3.44−3.46 (m, 1H), 3.40 (t, 1H, *J* 9.0 Hz), 3.37 (dd, 1H, *J* 10.0, 9.0 Hz), 3.35 (dd, 1H, *J* 10.0, 9.2 Hz), 3.31 (s, 1H, OC*H*$_3$); $^{13}$C NMR (300 MHz, $D_2O$) $\delta$ 103.5, 100.3, 98.8 (each d, C-1, C-1′, C-1″), 75.2, 74.4, 74.0, 72.6, 72.5, 72.4, 72.2, 71.8, 71.7, 71.0, 70.7, 70.5 (each d), 70.0, 68.0, 66.2 (each t, C-6, C-6′,C-6″), 56.1 (q, O*C*H$_3$). LRMS-ES: 523.2 $[M + Na]^+$.

**Standard Procedure for the Determination of the Rate and Specificity of Acid Glycoside Hydrolysis of 16, 17, and 18:** To a sample of **16**, **17**, or **18** (0.005 g) shaken with $D_2O$ (2 × 2 mL) and dried each time on a high-vacuum for 6 h a standard sample of either 1.296 M (**16** and **18**) or 0.1296 M (**17**) DCl (0.60 mL) was added. This was placed directly into the NMR (Varian 400 MHz) at 26 °C. $^1$H NMRs were taken every 10 min until the starter had been consumed. Each reaction was left in the NMR for 24 h, and a final $^1$H NMR was taken. After **16** had been fully consumed, a sample of methyl-$\alpha$-D-glucopyranoside was added (0.005 g in 0.2 mL of 1.296 M DCl) to determine the specificity of cleavage. The reaction profiles were determined by monitoring the changes in the intensities of specific peaks of $^1$H NMR spectra. All plots were constructed using Psi plot 6.0, where applicable, linear regression was used to determine rate constants.

**X-ray Work:** In all cases data collection was done on a Siemens SMART diffractometer with a CCD detector using $\omega$ rotation scans with narrow frames. The crystals were kept at 120 K during data collection. The structures were solved by direct methods using the SIR97 program package. Refinement was done using a locally modified ORFLS program. All crystals were thin needles of moderate or poor diffracting power. **23a**, $C_{21}H_{24}O_5$, is monoclinic, *C*2, with $a = 39.105(8)$ Å, $b = 5.6150(10)$ Å, $c = 16.609(3)$ Å, $\beta = 97.007(5)°$, $V = 3619.5(13)$ Å$^3$, and $Z = 8$. Final R = 0.035, Rw = 0.036 for 4865 significant reflections, and 470 parameters.

**23**, $C_{25}H_{30}O_5$, is monoclinic, $P2_1$, with $a = 13.295(2)$ Å, $b = 5.6635(8)$ Å, $c = 14.117(2)$ Å, $\beta = 99.446(5)°$, $V = 1048.5(3)$ Å$^3$, $Z = 2$. Final R = 0.044, Rw = 0.041 for 2961 reflections, and 271 parameters.

**25**, $C_{48}H_{52}O_{10}$, is monoclinic, $P2_1$, with $a = 10.168(3)$ Å, $b = 9.673(3)$ Å, $c = 23.850(7)$ Å, $\beta = 100.382°$, $V = 2068.8(11)$ Å$^3$, $Z = 2$. Final R = 0.066, Rw = 0.068 for 3306 reflections, and 523 parameters.

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**Supporting Information Available:** Included as Supporting Information is the rate constants for hydrolysis of **4** and **12** at three temperatures (Table S1), logarithmic plots of the hydrolytic decay of **16**−**18** (Figures S1−S3), mass spectra of cyclodextrin hydrolysis products (Figures S4 and S5), and $^1$H NMR spectra of the hydrolysis of **16** and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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