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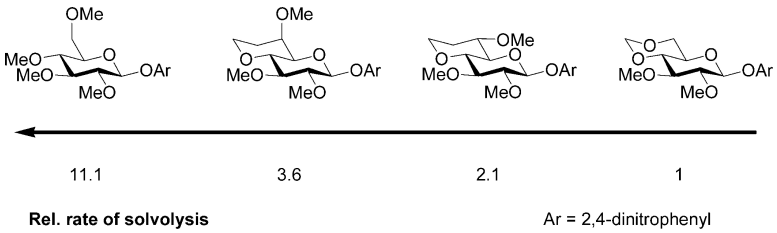

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The Disarming Effect of the 4,6-Acetal Group on Glycoside Reactivity: Torsional or Electronic?

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Abstract: An evaluation of whether the well-known deactivating effect of a 4,6-acetal protection group on glycosyl transfer is caused by torsional or an electronic effect from fixation of the 6-OH in the *tg* conformation was made. Two conformationally locked probe molecules, 2,4-dinitrophenyl 4,8-anhydro-7-deoxy-2,3,6-tri-*O*-methyl-β-D-*glycero*-D-*gluco*-octopyranoside (**18*R***) and the L-*glycero*-D-*gluco* isomer (**18*S***), were prepared, and their rate of hydrolysis was compared to that of the flexible 2,4-dinitrophenyl 2,3,4,6-tetra-*O*-methyl-β-D-glucopyranoside (**21**) and the locked 2,4-dinitrophenyl 4,6-*O*-methylidene-2,3-di-*O*-methyl-β-D-glucopyranoside (**26**). The rate of hydrolysis at pH 6.5 was **21** > **18*R*** > **18*S*** > **26**, which showed that the deactivating effect of the 4,6-methylene group is partially torsional and partially electronic. A comparison of the rate of acidic hydrolysis of the corresponding methyl α-glycosides likewise showed that the probe molecules **17*S*** and **17*R*** hydrolyzed significantly slower than methyl tetra-*O*-methyl-glucoside **19**, confirming a deactivating effect of locking the saccharide in the $^4C_1$ conformation. The experiments showed that the hydroxymethyl rotamers deactivate the rate of glycoside hydrolysis in the order *tg* ≫ *gt* > *gg*.

Introduction

The range of complicated oligosaccharides readily accessible via chemical synthesis has within the past few years exploded as a result of recent developments in carbohydrate synthesis techniques. Among the most spectacular achievements are the promising developments of solid-phase oligosaccharide synthesis[1] and the programmable one-pot glycosylation methods,[2] the latter being an extensive advancement of the so-called "armed−disarmed" principle.

The concept of armed and disarmed glycosyl donors refers to the increased reactivity of benzylated over benzoylated glycosyl donors, a phenomenon observed very early by Paulsen,[3] and which originates from the greater electron-withdrawing capability of ester blocking groups over ether blocking groups. Fraser-Reid and co-workers were the first to name and exploit the armed−disarmed principle, synthetically showing that donors bearing ether protection groups (see **1**, Figure 1) could be activated chemoselectively over donors bearing ester groups[4] (**2**, Figure 1) allowing one-pot synthesis of a trisaccharide via the *O*-pentenyl method.[5]

Fraser-Reid also found that benzylidene protected donor **3** was less reactive than the benzylated donor **4** (Figure 1).[6] A similar order of reactivity is also found for other donors such as mannosyl donors **5** and **6**.[2] Fraser-Reid suggested that the trans fused protection group restricts the molecule from ring flexibility, thereby making it increasingly difficult to reach a half-chair transition state from a chair ground state.[6] This explanation has subsequently been invoked by Ley et al. to account why donors such as **7** containing a vicinal diol protection in the form of a CDA-type acetal was less reactive than donor **8** (Figure 1).[7,8] This modulation of reactivity by cyclic protection groups is termed "torsional disarmament" [6,9] and has been exploited in synthesis to obtain anomeric selectiv-

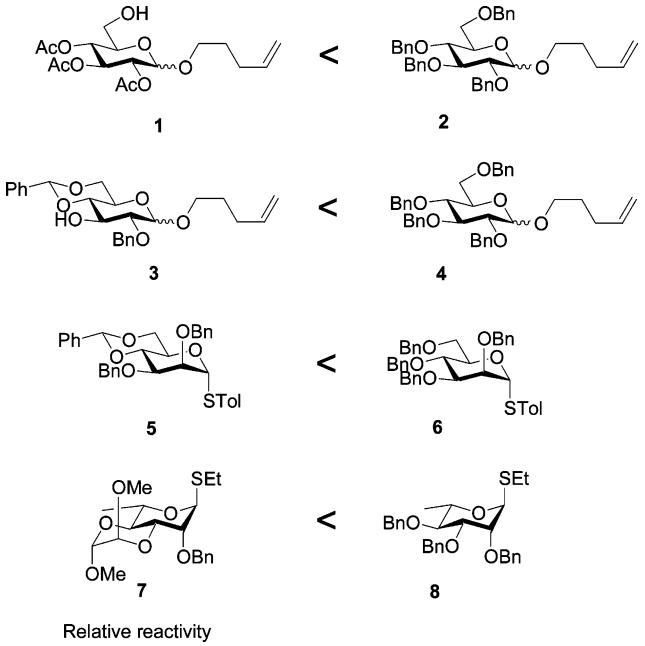

Figure 1. Relative reactivity of various glycosyl donors. Data are from refs 2, 4, 6, and 7.

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(2) Koeller, K. M.; Wong, C.-H. *Chem. Rev.* **2000**, *100*, 4465−4494.
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(4) Mootoo, D. R.; Konradsson, P.; Udodong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583−5584.
(5) Fraser-Reid, B.; Wu, Z.; Udodong, U. E.; Ottosson, H. *J. Org. Chem.* **1990**, *55*, 6068−6070.
(6) Fraser-Reid, B.; Wu, Z.; Andrews, C. W.; Skowronski, E.; Bowen, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 1434−1435.

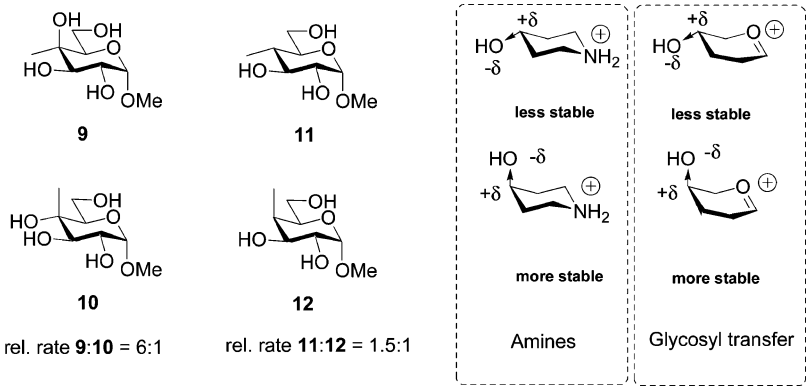

Figure 2. Relative rates of acidic hydrolysis of methyl 4-*C*-methylglycopyranosides **9**−**12** (left, from ref 16). Charge−dipole interaction explanation for the different electronic effects observed in amines (near right) and glycosyl transfer intermediates (far right, from ref 15).

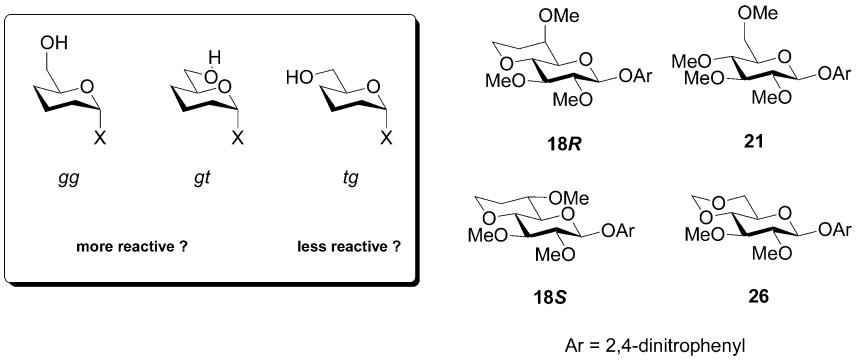

Figure 3. Different reactivities associated with the different hydroxymethyl rotamers based on the anticipated electronic effect (left). Probe glycosides synthesized in this work (right).

ity.[10,11] While such torsional influence on glycosyl transfer is well established, it is also clear that torsional effects in general are quite minor as compared to the electronic effects of the hydroxylic substituents.[12]

In a recent series of papers, we have investigated the substituent effects of the carbohydrate hydroxylic substituents,[13−16] and we find that the axial OH has a much reduced electron-withdrawing power as compared to the equatorial OH. As illustrated for the 4-position of hexopyranosides (Figure 2), compound **9** having an axial OH undergoes acidic hydrolysis 6 times faster than the equatorial isomer **10**. As reference, the nonhydroxylated analogues **11** and **12** hydrolyze at comparatively similar rates.[16] The exact cause of the effect remains unclear, but it is presumably caused by differences in electrostatic effects[17] and/or stereoelectronic effects. A difference in charge−dipole interactions in the two systems has so far been able to account for the observed effect (Figure 2). (Hyperconjugation has also been suggested to explain the effect; see note 14 of ref 15.)

Given these directional electronic effects observed for ring hydroxyl groups, one realizes that the conformation of the hydroxymethyl group of a hexopyranoside may be important for the electronic effect from this group. Normally, the hydroxymethyl group will adopt three staggered conformations, the *tg*, *gt*, and *gg* conformers, and the population of each will depend on the structure of the monosaccharide (Figure 3).[18,19] The *gg* and *tg* conformers have a spatial arrangement that is comparable to having an axial and an equatorial 4-OH in a monosaccharide in relation to O5, that is, galactose versus glucose. Thus, using the charge dipole hypothesis, in the *tg* conformer the C6−O6 bond acts as a dipole with the negative terminus directed away from the electron-deficient center in the transition state and it should be the least reactive, while in the *gg* and *gt* conformers this dipole is perpendicular to the developing positive charge and therefore more favorable. Normally, the *tg* conformer is among the least abundant in a flexible hexopyranoside.[18,19] However, a 4,6-*O*-benzylidene derivative is locked in this deactivating *tg* conformer, and a disarming electronic effect may therefore be anticipated from this group.

We became interested in the origin of this disarming effect during the study of the enhanced reactivity of galactosides over glucosides using probes **9** and **10**.[16] First, the experiments with models **9** and **10** (Figure 2) having bulky methyl groups in the 4-position showed that steric effect had little influence on

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(13) Jensen, H. H.; Lyngbye, L.; Jensen, A.; Bols, M. *Chem.-Eur. J.* **2002**, *8*, 1218−1226.
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(19) Rockwell, G. D.; Grindley, T. B. *J. Am. Chem. Soc.* **1998**, *120*, 10953−10963.

reactivity, indicating that facilitation of bond rotation had a minor influence on reactivity in this part of the molecule. Second, a small unexpected difference in reactivity between probes **11** and **12** was observed (Figure 2), which could be explained by different rotameric populations around the C5/C6 bond, as was supported by the differences in the NMR coupling constants of **11** and **12**. As the size of the deactivating effect observed from having a 4,6-benzylidene in pentenyl glycoside reactions was unclear, a 2-fold decrease in reaction times as measured by TLC,[6] it became questionable whether the observed deactivation was actually caused by a torsional influence or a larger electron-withdrawing effect from O6 and, furthermore, desirable to know how large was actually the deactivating effect of 4,6-benzylidene protection.

To solve this problem, the models **18*R*** and **18*S*** were conceived (Figure 3). These molecules have a torsional restriction similar to that of a 4,6-benzylidene group, but without having O6 in the deactivating *tg* conformer. Comparing the hydrolysis of these molecules with torsionally free analogue **21** and 4,6-methylidene derivative **26**, which has both torsional restriction and *tg* conformation but otherwise similar substituents, would resolve whether electronic or torsional effects are the cause of the benzylidene disarming effect. The dinitrophenyl glycosides allow us to determine first-order rate constants for spontaneous hydrolysis by the method of Withers' and coworkers.[20] We, hence, address a problem about reactions typically conducted on protected glycosides in dichloromethane at low temperatures using Lewis acid promotion by conducting hydrolysis on quite unlike systems. Even though we expect mechanisms in terms of leaving group activation, charge buildups, timing of bond fission and fusion, and solvation to be largely different in the two systems, there are several examples of different carbohydrates behaving remarkably similar. Thus, the order of reactivity in both glycosylation reactions carried out in DCM, acidic hydrolysis of methyl glycosides, and spontaneous hydrolysis of dinitrophenyl glycosides has been found to be fucoside > galactoside > glucoside.[2,20,21] Additionally, the ratios of reactivity have been found to be largely constant.

In the present paper, we report the synthesis of and hydrolysis studies with these models and find that the deactivation associated with having a 4,6-acetal protection is indeed considerable and caused by a roughly equal mixture of torsional and electronic effects.

Results and Discussion

Synthesis. The synthesis of **18*R*** and **18*S*** was carried out as outlined in Scheme 1. Known benzylidene derivative **13**[22] was regioselectively opened using BH_3-THF in CH_2Cl_2 with scandium triflate catalysis,[23] giving the 6-ol **14**[24] exclusively in excellent yield. This reaction was particularly satisfactory because the standard LAH/$AlCl_3$ protocol[25] as well as a procedure employing $PhBCl_2/Et_3SiH$[26] resulted in a mixture of regioisomers that was inseparable by chromatography. Oxidation of the alcohol **14** into the corresponding aldehyde was carried out with Dess−Martin periodinane reagent.[36] It was found to be essential to carry on with the crude aldehyde in the following allylation reaction without extensive chromatographic purification. Allylation was carried out either by the Sakurai reaction using allyltrimethylsilane/$TiCl_4$ or by the Grignard reaction giving, after methylation of the resulting secondary alcohol, the stereoisomers **15*R*/*S*** in 75% or 67% yield, respectively. Both reactions favored the *S*-isomer with the Sakurai reaction being the more selective (selectivity 93:7 versus 63:37 for Grignard), all in accordance with what is known from related cases.[27]

Because in this particular case both isomers were required and because they could be separated chromatographically, we employed the Sakurai reaction to produce **15*S*** and the Grignard reaction to produce **15*R***. The diastereoselectivity of the Sakurai reaction can be rationalized by considering the chelated structure displayed in Scheme 1, which shows the si-face to be more accessible.

The alkene **15*R*** was now subjected to ozonolysis, reduction with $NaBH_4$, and mesylation to give octuloside-8-mesylate **16*R*** in 75% yield. Hydrogenolysis with palladium catalysis of the 4-*O*-benzyl group followed by cyclization with NaH/DMF and NaI as nucleophilic catalyst smoothly gave bicyclic octuloside **17*R*** in 86% yield. After acetolytic cleavage of the methyl glycoside and Zemplén deacetylation, a 1-OH sugar was obtained that after reaction with 2,4-dinitrofluorobenzene gave the β-dinitrophenylglycoside **18*R*** in 53% yield.

Through a similar sequence of reactions, **15*S*** was converted to **18*S***. Ozonolysis, reduction, and mesylation gave **16*S*** in 74% yield. After hydrogenolysis and cyclization, **16*S*** gave 89% yield of **17*S***. This methyl glycoside was similarly by acetolysis, deacetylation, and arylation converted to dinitrophenyl glycoside **18*S*** in 52% yield.

The configuration of C-6 of **17*R*/*S*** and **18*R*/*S*** was assigned on the basis of the width of the ^1H NMR multiplet originating from H7ax, which was easily identified in each of the spectra by being the most upfield shifted proton. This proton couples to four other protons, and the width of this multiplet is the sum of the coupling constants. Because, in the *S* isomers, it will have three large couplings (one geminal and two diaxial) while the *R* isomers only have two large couplings (one geminal and one diaxial coupling), there is a significant difference in width. The width of the H7ax was for the *S* isomers $\sum J$(**17*S***) 42.0 Hz and $\sum J$(**18*S***) 42.4 Hz, and for the *R*-isomers $\sum J$(**17*R***) 31.4 Hz and $\sum J$(**18*R***) 34.4 Hz and thus was evident.

The reference compound **21** was prepared by perchloric acid-catalyzed acetolysis of the known permethylated α-glucoside **19**,[28] giving 1-*O*-acetyl glucoside **20** as an anomeric mixture favoring the α-isomer in 81% combined yield (Scheme 2). After deacetylation and reaction with Sanger's reagent, the β-dinitrophenyl glucoside **21** was obtained in 40% yield.

A somewhat more elaborate synthetic route was required for the preparation of the methylene derivative **26**. Attempting formation of the methylene acetal via Lewis/Brønsted acid-catalyzed reactions[29] on methyl 2,3-di-*O*-methyl-α-D-glucopy-

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(21) Bülow, A.; Meyer, A.; Olszewski, T.; Bols, M. *Eur. J. Org. Chem.* **2004**, *2*, 323−329.
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(24) Guindon, Y.; Girard, Y.; Berthiaume, S. Y.; Gorys, V.; Lemieux, R.; Yoakim, C. *Can. J. Chem.* **1990**, 897−902.
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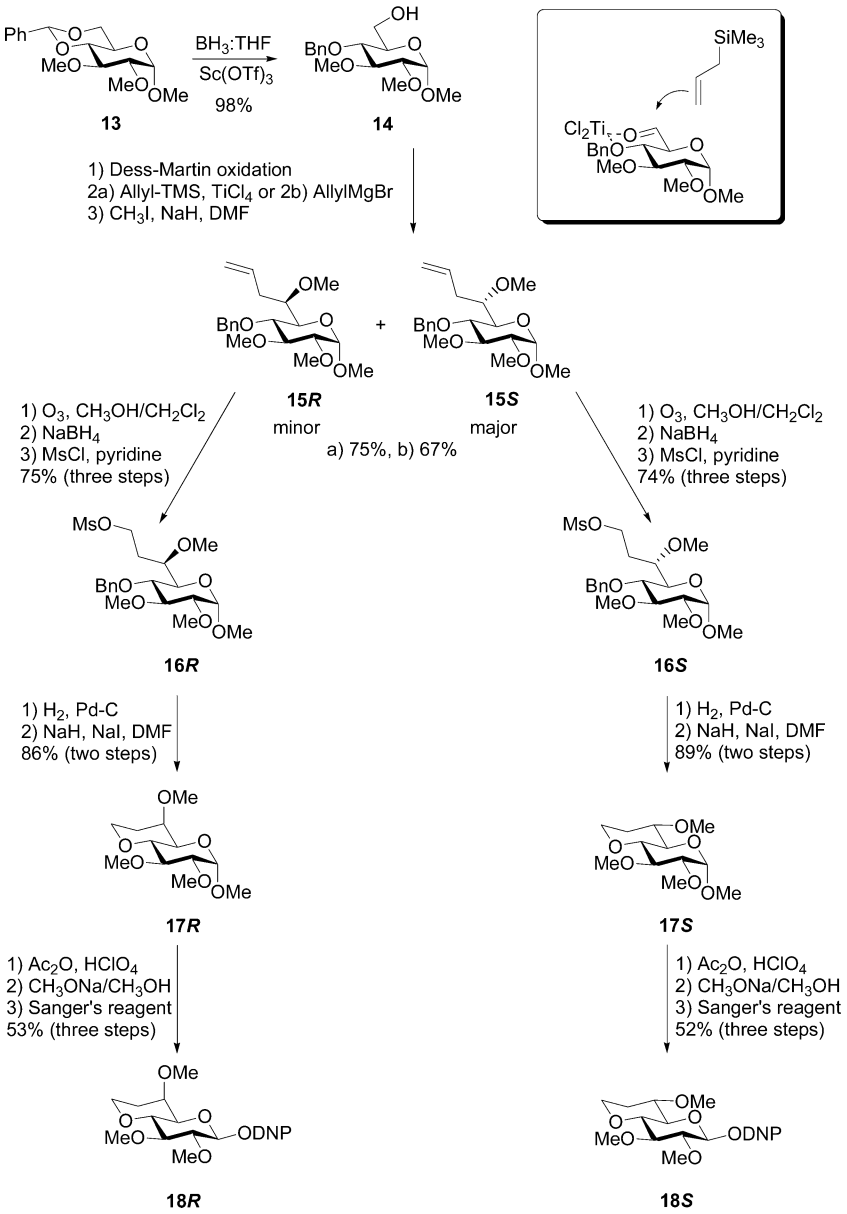
(28) West, E. S.; Holden, R. F. *J. Am. Chem. Soc.* **1934**, *56*, 930−932.

Scheme 1. Synthesis of **18*R*** and **18*S***



ranoside resulted in the undesired di-MOM-protected product. Turning to a procedure using $POCl_3$ in hot DMSO proved successful.[30] The relatively stable methylene acetal, however, was found to undergo cleavage under the subsequent acid-catalyzed acetolysis reaction. A different strategy going through a thioglucoside was therefore investigated.

Accordingly, the known glucose pentaacetate **22** (Scheme 2) was converted to the thioglycoside with *p*-thiocresol and $ZnCl_2$ using a known procedure.[31] The crude tetraacetate was then deacetylated and benzylidene protected using dimethoxytoluene/TsOH in DMF. Methylation of the remaining two alcohols with MeI/NaH and hydrolysis of the benzylidene group with methanolic HCl gave the diol **23** in high overall yield. Attempting methylidene acetal formation using the $POCl_3$/DMSO procedure was counterproductive because the thioglycoside could not tolerate the harsh reaction conditions. We therefore employed Fleet's procedure for the formation of methylidene acetals[32] using methylene bromide, NaOH, and tetrabutylammonium iodide in dioxane, which provided **24** in 34% yield. The thioglycoside was converted to the 1-acetate by means of *N*-iodosuccinimide/acetic acid,[33] giving **25** in 89% yield. Deacetylation followed by reaction with Sanger's reagent in the presence of DABCO then led to **26** in 34% yield.

Hydrolysis Experiments. The rate of hydrolysis was determined under two different sets of conditions. The rate of acidic hydrolysis of methyl glycosides **17*R***, **17*S***, and **19** was determined in 2.56 M $HClO_4$ at 82 °C by following the change in optical rotation (Table 1). The reaction was followed to completion, and from the plot of $(\alpha - \alpha_{end}/\alpha_o - \alpha_{end})$ versus

(29) Gras, J.-L.; Nouguier, R.; Mchich, M. *Tetrahedron Lett.* **1987**, *28*, 6601−6604.
(30) Guiso, M.; Procaccio, C.; Fizzano, M. R.; Piccioni, F. *Tetrahedron Lett.* **1997**, *38*, 4291−4294.
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(33) Veeneman, G. H.; van Leeuwen, S. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 1331−1334.

Scheme 2. Synthesis of **21** and **26**

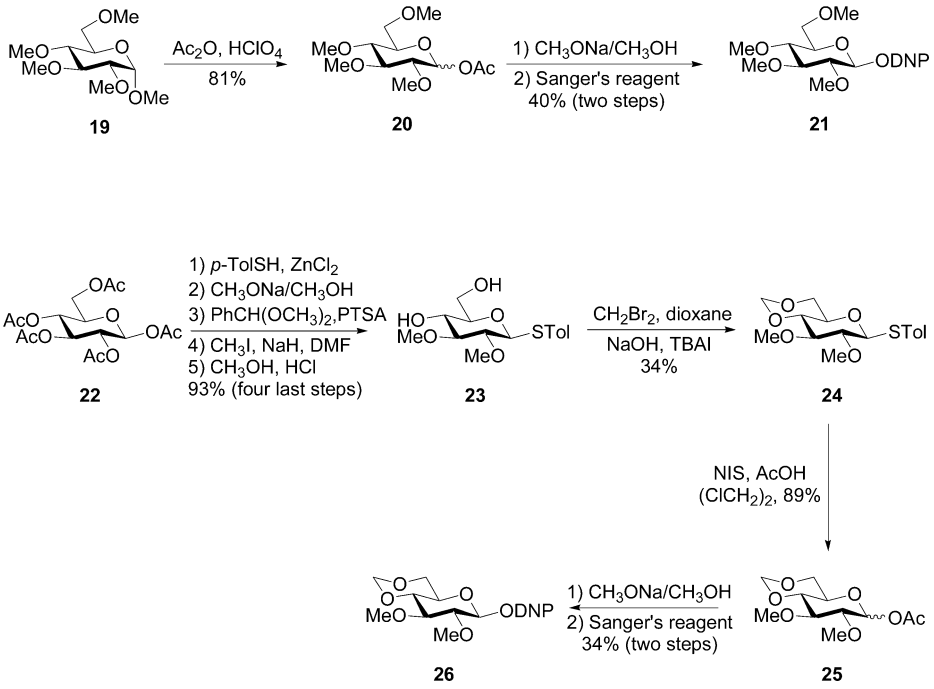
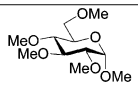
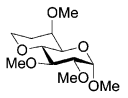
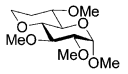


Table 1. First-Order Rate Constants for the Acidic Hydrolysis of Methyl Glycosides

Compound	Structure	$k \times 10^5$ s^{-1} (82 °C)	Relative hydrolysis rate (2.56M $HClO_4$, 82 °C)
19		11±0.56	1
17*R*		2.7±0.25	0.25
17*S*		1.6±0.14	0.15

t (see Supporting Information) the first-order rate constant was successfully determined by fitting the data to an exponential decay curve. The reactions were repeated 2−3 times, and the average rate constants are shown in Table 1.

The rates of spontaneous hydrolysis of dinitrophenyl glycosides **18*R***, **18*S***, **21**, and **26** were determined in a buffer at pH 6.5, 0.4 M KCl containing 25% dioxane to secure full solubility. The progress of the reaction was followed by measuring the change in absorbance at 400 nm (Table 2). Initial velocities were determined at variant substrate concentration and used to check that the reaction was first order and to calculate first-order rate constants. On the basis of values at five different temperatures, Arrhenius plots were constructed (see Supporting Information), and activation energies, entropy, and rate constants at 37 °C were calculated (Table 2). It was ensured that the methylene acetal of **26** was stable under the conditions by checking the product of the hydrolysis by NMR.

Cocker and Sinnott[34] have previously reported that hydrolysis of dinitrophenyl β-D-galactopyranoside is pH independent between 1.6 and 8.4. To check whether this was also the case for glycosides bearing OMe, the pH independence of the hydrolysis was checked, by performing the hydrolysis of **18*S*** at pH 5.7 and 7.9 with no significant influence on the rate.

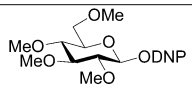
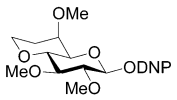
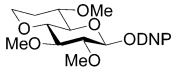
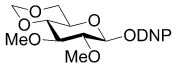
The significant difference between these two reactions is that in the acidic hydrolysis of methyl glycosides a mechanism involving endocyclic protonation is possible, which would generate a rather different transition state. Recent work indicates, however, that in acidic hydrolysis of α-glycopyranosides endocyclic cleavage is negligible.[35] This work likewise shows no significant rate difference between the two cases.

For both reactions, the data clearly show that a torsional disarming effect exists. Methyl glycoside **17*R*** hydrolyzes 4 times slower than **19**, while **17*S*** hydrolyzes 6 times slower than **19** (Table 1). Similarly, the dinitrophenyl glycosides **18*R*** and **18*S*** hydrolyze 4 and 6 times slower than **21**, respectively (Table 2).

Also, the experiments show a clear electronic effect from locking of the hydroxymethyl group in the *tg* conformation. Thus, the least reactive dinitrophenyl glycoside is the methylene derivative **26**. While **26** is about 14 times less reactive than **21** and thus significantly disarmed as compared to **21**, only about a factor of 4 is caused by torsional disarming, and the remaining by electronic effects. It is also noteworthy that the locked *gt* isomers **17*S*** and **18*S*** are consistently 1.5 times less reactive than the *gg* isomers. This observation cannot be explained by the charge−dipole hypothesis as the charge−dipole interaction between C6−O6 and a charged O5 or C1 is identical or virtually identical for the *gt* and *gg* isomers. It is possible that hyperconjugation can be invoked to explain this difference, but due to the limited data it cannot be done with confidence. It is in any case interesting that it is the equatorial isomer that is the least reactive of the two, which is similar to what is seen for OH substituents in the pyranoside ring.

(34) Cocker, D.; Sinnott, M. L. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1391−1393.
(35) Liras, J. L.; Lynch, V. M.; Anslyn, E. V. *J. Am. Chem. Soc.* **1997**, *119*, 8191−8200.

Table 2. First-Order Rate Constants, Energies of Activation, and Activation Entropies for the Solvolysis of Dinitrophenyl Glycosides

Compound	Structure	E_a (kJ/mol)	$\Delta S^{\ddagger}$ (J/molK)	$k \times 10^7$ s^{-1} (37 °C)	Relative hydrolysis rate
21		92.5±4.5	22.8±1.7	19.0	1
18*R*		113.5±2.1	29.5±0.8	4.6	0.24
18*S*		119.1±2.7	30.1±1.0	3.1	0.16
26		107.3±2.5	25.8±0.9	1.3	0.07

Experimental Section

General. Assignment of NMR spectra is based on ^{1}H−^{1}H COSY and DEPT-135 techniques. Column chromatography was carried out on silica gel.

2,4-Dinitrophenyl 2,3,4,6-Tetra-*O*-methyl-*β*-D-glucopyranoside (21). Methyl glucopyranoside **19** (156 mg, 0.62 mmol) was dissolved in acetic anhydride (1.8 mL). To this solution was added concentrated aqueous $HClO_4$ (70%, 5 μL) at room temperature. After 10 min, the reaction was quenched with saturated aqueous $NaHCO_3$ (8 mL) and left to stir for 2 h, after which solid $NaHCO_3$ was added until the solution was found to be neutral. The aqueous solution was subsequently extracted with AcOEt (5 × 8 mL), after which the combined organic extracts were dried ($MgSO_4$) and concentrated. The remaining oil underwent column chromatography (AcOEt/pentane 1:2). This resulted in a mixture of anomers **20** in a combined yield of 141 mg (81%). NMR ($CDCl_3$) δ_C (major anomer, α): 169.3 (*C*(O)CH$_3$), 89.5 (C1), 83.1, 80.9, 78.7, 72.6, 70.8 (C2, C3, C4, C5, C6), 60.8, 60.6, 59.2, 59.0 (O*C*H$_3$), 21.0 (CO*C*H$_3$). (minor anomer, *β*): 169.3 (*C*(O)CH$_3$), 93.9 (C1), 86.5, 82.5, 78.7, 75.2, 70.5 (C2, C3, C4, C5, C6), 60.5, 60.4, 59.2, 59.0 (O*C*H$_3$), 21.1 (CO*C*H$_3$).

A mixture of acetyl glucosides **20** (428 mg, 1.54 mmol) was dissolved in methanol to which had been added a small lump of metallic sodium. This solution was stirred at room temperature until TLC analysis (silica, AcOEt) indicated reaction completion. A lump of dry ice was then added to the solution, after which the solvent was removed under reduced pressure. Toluene was added to the flask and subsequently removed by evaporation under reduced pressure. The resulting substance was dissolved in dry DMF (12 mL), after which DABCO (587 mg, 5.2 mmol) and 2,4-dinitrofluorobenzene (231 μL, 1.9 mmol) were added. This solution was stirred for 5 h at room temperature before the mixture was added to a flask containing AcOEt and H_2O (20 mL of each). The aqueous phase was extracted with AcOEt (2 × 15 mL), and the combined organic layers were dried ($MgSO_4$). After removal of the organic solvent, the resulting oil underwent column chromatography (eluent: AcOEt/pentane 3:7, R_f 0.19), which gave 247 mg (40%) of the desired product (**21**) as a colorless solid. Recrystallization proved possible in Et_2O/pentane. $[\alpha]^{RT}_D$ −53° (*c* 1, $CHCl_3$). NMR ($CDCl_3$) δ_H: 8.73 (d, 1H, J_{meta} 2.8 Hz, Ar*H*), 8.41 (dd, 1H, J_{ortho} 9.2 Hz, Ar*H*), 7.35 (d, 1H, Ar*H*), 5.04 (d, 1H, $J_{1,2}$ 7.8 Hz, H1), 3.67 (s, 3H, OC*H*$_3$), 3.64 (s, 3H, OC*H*$_3$), 3.63−3.66 (m, 1H, H6a), 3.56 (s, 3H, OC*H*$_3$), 3.48−3.58 (m, 2H, H6b, H5), 3.38 (t, 1H, H2), 3.37 (s, 3H, OC*H*$_3$), 3.28 (t, 1H, H3), 3.23 (t, 1H, H4). δ_C: 154.7, 141.4, 139.5, 128.9, 121.6, 117.3 (*Ar*), 100.9 (C1), 86.3, 83.1, 78.8, 75.6, 71.0 (C2, C3, C4, C5, C6), 61.1, 61.0, 60.7, 59.5 (O*C*H$_3$). HRMS(ES): calcd for $C_{16}H_{22}N_2O_{10}Na$, 425.1172; found, 425.1170.

***p*-Tolyl 2,3-Di-*O*-methyl-*β*-D-thioglucopyranoside (23).** *β*-Glucose pentaacetate (**22**) was added to a round-bottomed flask with *p*-thiocresol and heated to 165 °C, after which $ZnCl_2$ was added according to the procedure described in the literature.[31] After the reaction was complete, the resulting mixture was left to cool to room temperature, after which it was treated with ethanol. This resulted in a precipitate that was pure enough for further reaction.

The crude acetyl thioglucoside (2.14 g, 4.7 mmol) was dissolved in methanol (50 mL) containing a catalytic amount of $NaOCH_3$. This was left to stir until TLC analysis indicated no further development. A minimum of concentrated aqueous HCl was added to the methanolic mixture until the solution was slightly acidic. The resulting mixture was then evaporated to dryness with toluene under reduced pressure. The resulting off-white solid was dissolved in dry DMF (15 mL). α,α-Dimethoxytoluene (1.77 mL, 11.8 mmol) and *p*-toluenesulfonic acid (134 mg, 0.71 mmol) were added to this solution, which was heated to 65 °C. Vacuum was applied via a water aspirator to the reaction setup with 30 min intervals to remove methanol. After 4 h, the reaction was cooled to room temperature and quenched with an aqueous saturated $NaHCO_3$ solution (15 mL), after which AcOEt (20 mL) was added. The phases were separated, and the aqueous phase was extracted with AcOEt (2 × 20 mL), after which the combined organic phases were washed with water (3 × 20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The resulting oil was dissolved in dry DMF (12 mL), after which NaH (617 mg, 14 mmol) and methyl iodide (0.73 mL, 12 mmol) were added. This solution was stirred at room temperature for 90 min before water (15 mL) was carefully added. After extraction with AcOEt (3 × 15 mL), the combined organic phases were washed with water (3 × 15 mL), dried ($MgSO_4$), and concentrated. The remaining oil was stirred in methanol (25 mL) to which had been added concentrated aqueous HCl (0.3 mL). This mixture was left overnight at room temperature after which the reaction mixture was neutralized with solid $NaHCO_3$ and concentrated under reduced pressure. The resulting oil underwent column chromatography in Et_2O (R_f 0.24). This gave 1.38 g (93%) of the desired diol **23**. $[\alpha]^{RT}_D$ −36° (*c* 1, $CHCl_3$). NMR ($CDCl_3$) δ_H: 7.41 (d, 2H, J_{ortho} 8.0 Hz, Ar*H*), 7.12 (d, 2H, Ar*H*), 4.53 (d, 1H, $J_{1,2}$ 10.0 Hz, H1), 3.89 (dd, 1H, $J_{5,6a}$, 3.4 Hz, $J_{6a,6b}$ 11.8 Hz, H6a), 3.75 (dd, 1H, $J_{5,6b}$ 5.4 Hz, H6b), 3.67 (s, 3H, OC*H*$_3$), 3.63 (s, 3H, OC*H*$_3$), 3.47 (t, 1H, *J* 9.4 Hz, H4), 3.33 (ddd, 1H, H5), 3.17 (t, 1H, H3), 3.05 (t, 1H, H2), 2.33 (s, 3H, ArC*H*$_3$). δ_C: 138.1, 132.6, 129.9, 129.5 (*Ar*), 88.0, 87.3 (C1, C5), 82.7 (C3), 79.1 (C2),

70.1 (C4), 62.6 (C6), 61.3, 60.8 (O*C*H$_3$), 21.3 (Ar*C*H$_3$). HRMS(ES): calcd for $C_{15}H_{22}O_5SNa$, 337.1086; found, 337.1088.

***p*-Tolyl 2,3-Di-*O*-methyl-4,6-methylidene-*β*-D-thioglucopyranoside (24).** Diol **23** (592 mg, 1.9 mmol) was dissolved in CH_2Br_2 (3.9 mL) and dioxane (1.95 mL). To this solution were added 50% aqueous NaOH (3.9 mL) and TBAI (70 mg, 0.19 mmol). After this mixture was vigorously stirred for 6 h, Et_2O (15 mL) was added. The aqueous phase was then extracted with ether (2 × 15 mL), after which the combined organic phases were washed with water (25 mL), dried ($MgSO_4$), and concentrated. The remaining oil underwent column chromatography in Et_2O/pentane 1:2 (R_f 0.58). This gave 212 mg (34%) of the desired formaldehyde acetal **24** as a colorless solid. M_p (uncorr.) 102−104 °C. $[\alpha]^{RT}_D$ −39° (*c* 1, $CHCl_3$). NMR ($CDCl_3$) δ_H: 7.40 (d, 2H, J_{ortho} 8.0 Hz, Ar*H*), 7.11 (d, 2H, Ar*H*), 5.03 (d, 1H, J_{gem} 6.0 Hz, acetalH_{eq}), 4.58 (d, 1H, acetalH_{ax}), 4.52 (d, 1H, $J_{1,2}$ 9.6 Hz, H1), 4.19 (dd, 1H, $J_{5,6eq}$ 4.8 Hz, $J_{6eq,6ax}$ 10.4 Hz, H6eq), 3.62 (s, 3H, OCH_3), 3.62 (s, 3H, OCH_3), 3.45 (t, 1H, H6ax), 3.35 (t, 1H, H3), 3.25−3.31 (m, 1H, H5), 3.22 (t, 1H, H4), 3.05 (dd, 1H, $J_{2,3}$ 8.6 Hz, H2), 2.33 (s, 3H, Ar*C*H$_3$). δ_C: 138.2, 133.1, 129.8, 129.2 (*Ar*), 93.6 (acetal*C*), 88.3 (C1), 84.8, 82.6, 80.7, 70.5 (C2, C3, C4, C5), 68.5 (C6), 61.2, 61.0 (O*C*H$_3$), 21.2 (Ar*C*H$_3$). HRMS(ES): calcd for $C_{16}H_{22}O_5SNa$, 349.1086; found, 349.1079.

Acetyl 2,3-Di-*O*-methyl-4,6-methylidene-α/*β*-D-glucopyranoside (25). To a stirred solution of thioglucoside **24** (200 mg, 0.61 mmol) in dry dichloroethane (4 mL) were added NIS (152 mg, 0.68 mmol) and dry glacial acetic acid (106 *μ*L, 1.8 mmol). The mixture was heated to 70 °C for 3 days before it was quenched at room temperature with 5% aqueous solution of $Na_2S_2O_3$ (8 mL). The aqueous phase was additionally extracted with CH_2Cl_2 (2 × 8 mL), after which the combined organic phases were dried ($MgSO_4$) and concentrated. The remaining oil underwent column chromatography (Et_2O/pentane: first 1:3, then 1:2). This gave a mixture of anomeric acetates (**25**) in a yield of 143 mg (89%). NMR ($CDCl_3$) δ_C (major isomer, α): 169.4 (*C*(O)CH$_3$), 93.8 (acetal*C*), 89.7 (C1), 81.1, 80.9, 79.5, 68.5, 64.8 (C2, C3, C4, C5, C6), 61.0, 59.3 (O*C*H$_3$), 21.0 (C(O)*C*H$_3$). (minor anomer, *β*): 169.0 (*C*(O)CH$_3$), 94.1, 93.6 (C1, acetal*C*), 82.7, 82.6, 80.6, 68.3, 66.8 (C2, C3, C4, C5, C6), 60.8, 59.3 (O*C*H$_3$), 21.0 (C(O)*C*H$_3$). HRMS(ES): calcd for $C_{11}H_{18}O_7Na$, 285.0950; found, 285.0950.

2,4-Dinitrophenyl 2,3-Di-*O*-methyl-4,6-methylidene-*β*-D-glucopyranoside (26). A mixture of anomeric acetates **25** (143 mg, 0.55 mmol) was dissolved in methanol (2 mL) to which had been added a catalytic amount of metallic sodium. This solution was stirred until TLC monitoring (Et_2O/pentane 1:1) demonstrated full conversion. The solvent was then removed under reduced pressure. The remaining substance was dissolved in dry DMF (3.2 mL), after which DABCO (208 mg, 1.9 mmol) and 2,4-dinitrofluorobenzene (82 *μ*L, 0.66 mmol) were added. This reaction mixture was stirred at room temperature for 5 h, after which it was poured into a flask containing water and AcOEt (10 mL of each). The aqueous layer was then extracted with AcOEt (2 × 10 mL), after which the combined organic phases were washed with water (2 × 10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. This resulted in an oil that underwent column chromatography (CH_2Cl_2/AcOEt: first 19:1, then 9:1), which gave the desired glucoside **26** (77 mg, 34%) as a solid that could be recrystallized in Et_2O/hexane. R_f (CH_2Cl_2/AcOEt 9:1) 0.32. $[\alpha]^{RT}_D$ −86° (*c* 1, $CHCl_3$). NMR ($CDCl_3$) δ_H: 8.74 (d, 1H, J_{meta} 2.8 Hz, Ar*H*), 8.41 (dd, 1H, J_{ortho} 9.4 Hz, Ar*H*), 7.32 (d, 1H, Ar*H*), 5.18 (d, 1H, J_{1-2} 5.6 Hz, H1), 5.08 (d, 1H, J_{gem} 6.4 Hz, acetalH_{eq}), 4.62 (d, 1H, acetalH_{ax}), 4.21 (dd, 1H, J_{6ax-5} 9.8 Hz, $J_{6ax-6eq}$ 15.8 Hz, H6$_A$), 3.65 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3), 3.38−3.50 (m, 5H, H2, H3, H4, H5, H6$_B$). δ_C: 154.3, 141.7, 139.8, 128.9, 121.8, 117.2 (*Ar*), 101.2 (C1), 93.8 (acetal*C*), 83.3, 82.5, 80.1, 67.0 (C2, C3, C4, C5), 68.2 (C6), 61.5, 61.1 (O*C*H$_3$). HRMS(ES): calcd for $C_{15}H_{18}N_2O_{10}Na$, 409.0859; found, 409.0860.

Methyl 4-*O*-Benzyl-2,3-di-*O*-methyl-α-D-glucopyranoside (14). Acetal **13** (314 mg, 1.0 mmol) was dissolved in dry CH_2Cl_2 (9 mL) to which BH_3−THF complex (1 M, 5 mL, 5.0 mmol) and $Sc(OTf)_3$ (75 mg, 0.15 mmol) were added at room temperature under an atmosphere of nitrogen. This mixture was stirred for 6 h, after which Et_3N (0.14 mL, 1 mmol) and methanol (18 mL) were added. The solvents were removed under reduced pressure, and the remaining substance was put on a short column of silica gel and eluted (Et_2O). This gave 323 mg (98%) of the known desired primary alcohol **14**. This experimental procedure was taken from the literature.[23] The ^{1}H NMR spectrum was identical to that previously reported.[24] NMR ($CDCl_3$) δ_C: 138.2, 128.3, 127.9, 127.7 (Ar), 97.4 (C1), 83.5, 81.9, 77.3, 74.7, 70.7, 61.5 (C2, C3, C4, C5, C6, Ph*C*H$_2$O), 60.9, 58.8, 55.0 (O*C*H$_3$).

(6-*R*) Methyl 6-*C*-Allyl-4-*O*-benzyl-2,3,6-tri-*O*-methyl-α-D-glucopyranoside and (6-*S*) Methyl 6-*C*-Allyl-4-*O*-benzyl-2,3,6-tri-*O*-methyl-α-D-glucopyranoside (15*R* and 15*S*). Sakurai alkylation: To a stirred solution of primary alcohol 14 (438 mg, 1.4 mmol) in CH_2Cl_2 (56 mL) was added freshly prepared Dess−Martin periodinane (893 mg, 2.1 mmol).[36] This mixture was allowed to react for 45 min at room temperature before Et_2O (40 mL) and a saturated aqueous solution of $NaHCO_3$/$Na_2S_2O_3$ (50 mL) were added. Additional stirring for 2 h before phase separation and extraction of the aqueous layer with CH_2Cl_2 (2 × 25 mL), drying ($MgSO_4$), and evaporation resulted in an oil that was directly carried on further.

The crude product from the Dess−Martin procedure was dissolved in dry CH_2Cl_2 (70 mL) and cooled to −78 °C, after which $TiCl_4$ (232 *μ*L, 2.1 mmol) and allyltrimethylsilane (280 *μ*L, 1.75 mmol) were added. This mixture was kept at −78 °C for 2.5 h before the reaction was quenched by adding a saturated aqueous solution of $NaHCO_3$ (50 mL) and hereafter allowed to warm to room temperature. The organic and aqueous phases were separated, and subsequent extraction with CH_2Cl_2 (2 × 30 mL), drying of the combined organic phases ($MgSO_4$), and concentration resulted in an oil that was used for further reaction.

The crude product from the Sakurai reaction was dissolved in dry DMF (3 mL) to which was added NaH (177 mg, 4.2 mmol) and iodomethane (174 *μ*L, 2.8 mmol). This mixture was stirred for 45 min at room temperature before it was carefully added to a flask containing AcOEt/H_2O (15 mL of each). The layers were then separated, and the aqueous phase was extracted with AcOEt (3 × 10 mL). The combined organic phases were washed with H_2O (3 × 10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. This resulted in an oil containing two diastereoisomers which by ^{13}C NMR was estimated to be a 93:7 mixture, **15*S*** being the major product. These diastereoisomers could be separated by column chromatography (Et_2O/pentane: first 1:2, then 1:1) to give **15*R*** and **15*S***, which both appeared as colorless oils, in a combined yield of 382 mg (75% over three steps). Diastereoisomer **15*R*** was found to be the least polar of the two products.

15*S*. $[\alpha]^{RT}_D$ 142° (*c* 1, $CHCl_3$). R_f (Et_2O/pentane 1:1) 0.21. NMR ($CDCl_3$) δ_H: 7.26−7.36 (m, 5H, Ar*H*), 5.74−5.85 (m, 1H, CH_2=C*H*CH$_2$), 5.13 (d, 1H, J_{trans} 16.8 Hz, C*H*$_a$H$_b$=CHCH$_2$), 5.07 (d, 1H, J_{cis}, 10.0 Hz, CH$_a$*H*$_b$=CHCH$_2$), 4.93 (d, 1H, J_{gem}, 11.2 Hz, PhC*H*$_a$H$_b$O), 4.85 (d, 1H, $J_{1,2}$ 3.6 Hz, H1), 4.61 (d, 1H, PhCH$_a$*H*$_b$O), 3.55−3.64 (m, 4H, H3, H4, H5, H6), 3.63 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 3.40 (s, 3H, OCH_3), 3.35 (s, 3H, OCH_3), 3.26 (dd, 1H, $J_{2,3}$ 8.8 Hz, H2), 2.52−2.59 (m, 1H, CH$_2$=CHC*H*$_a$H$_b$), 2.37−2.44 (m, 1H, CH$_2$=CHCH$_a$*H*$_b$). δ_C: 138.7 (*Ar*), 134.7 (CH$_2$=*C*HCH$_2$), 128.6, 127.9, 127.8 (*Ar*), 117.6 (*C*H$_2$=CHCH$_2$), 97.9 (C1), 84.0, 82.1, 77.5, 77.4 (C2, C3, C4, C5), 75.0 (Ph*C*H$_2$O), 70.8 (C6), 61.0, 59.0, 57.9, 55.6 (O*C*H$_3$), 33.8 (CH$_2$=CH*C*H$_2$). HRMS(ES): calcd for $C_{20}H_{30}O_6Na$, 389.1940; found, 389.1938.

15*R*. $[\alpha]^{RT}_D$ 136° (*c* 1, $CHCl_3$). R_f (Et_2O/pentane 1:1) 0.39. NMR ($CDCl_3$) δ_H: 7.18−7.27 (m, 5H, Ar*H*), 5.67−5.77 (m, 1H, CH_2=C*H*CH$_2$), 4.93−4.99 (m, 2H, C*H*$_2$=CHCH$_2$), 4.79 (d, 1H, J_{gem}, PhC*H*$_a$H$_b$O), 4.74 (d, 1H, $J_{1,2}$ 3.6 Hz, H1), 4.55 (d, 1H, PhCH$_a$*H*$_b$O), 3.78 (dd, 1H, $J_{5,6}$ 1.4 Hz, $J_{4,5}$ 10.2 Hz, H5), 3.56 (s, 3H, OCH_3), 3.55 (t, 1H, *J* 9.0 Hz, H3), 3.44 (s, 3H, OCH_3), 3.33−3.38 (m, 1H, H6),

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3.33 (s, 3H, OCH_3), 3.31 (s, 3H, OCH_3), 3.27 (dd, 1H, H4), 3.11 (dd, 1H, H2), 2.25−2.33 (m, 1H, CH_2=CHC$H_a$$H_b$), 2.06−2.13 (m, 1H, CH_2=CHC$H_a$$H_b$). δ_C: 138.4 (*Ar*), 136.0 (CH_2=*C*HCH_2), 128.6, 128.2, 127.9 (*Ar*), 116.7 (*C*H_2=$CHCH_2$), 97.3 (C1), 84.4, 82.3, 80.5, 78.2 (C2, C3, C4, C5), 74.7 (Ph*C*H_2O), 69.8 (C6), 61.2, 59.1, 58.0, 55.1 (O*C*H_3), 34.2 (CH_2=CH*C*H_2). HRMS(ES): calcd for $C_{20}H_{30}O_6Na$, 389.1940; found, 389.1930.

Grignard Alkylation. Primary alcohol **14** (796 mg, 2.6 mmol) was reacted with Dess−Martin periodinane (1.62 g, 3.8 mmol) in CH_2Cl_2 (98 mL) as was previously described. The crude product from this reaction was dissolved in dry Et_2O (11 mL), after which a solution of allylmagnesium bromide was carefully added at 0 °C. The Grignard solution was made by adding allyl bromide (2.2 mL, 26 mmol) to Mg-turnings (930 mg, 38 mmol) in dry Et_2O (22 mL) at such a rate that the solution was kept at a gentle reflux. After the addition was completed, the mixture was heated to reflux for an additional 2 h before it was used for further reaction.

After two-thirds of the freshly prepared Grignard solution had been added to the crude aldehyde, the reaction mixture was left to stir for 3 h at 0 °C before it was quenched by carefully pouring the solution onto aqueous HCl (1.5 M, 20 mL). Extraction of the aqueous phase with CH_2Cl_2 (2 × 20 mL), drying ($MgSO_4$), and concentration gave a crude oil that was further reacted as previously described in DMF (6 mL) with NaH (248 mg, 5.7 mmol) and iodomethane (265 μL, 4.3 mmol). Chromatography in Et_2O/pentane resulted in a combined yield of 626 mg (67%) of two compounds, which were found to be spectroscopically identical to those produced via the Sakurai pathway. The ratio of diastereoisomers was estimated from ^{13}C NMR to be a 37/63 in favor of **15*S***.

Methyl 4-*O*-Benzyl-7-deoxy-2,3-di-*O*-methyl-8-*O*-methylsulfonyl-*β*-L-*glycero*-D-*gluco*-octopyranoside (16*S*). At −78 °C, ozone was bobbled through a solution of olefin **15*S*** (993 mg, 2.7 mmol) in methanol/CH_2Cl_2 (2:1, 250 mL) until it turned persistently blue. Pure O_2 followed by N_2 was bobbled through the reaction mixture (5 min) to which then was added $NaBH_4$ (2.06 g, 54 mmol). This solution was stirred and allowed to reach room temperature. After 90 min, an additional amount of $NaBH_4$ (0.52 g, 13.5 mmol) was added and allowed to react for further 1 h before most of the solvent was removed under reduced pressure. To the remaining solution were added AcOEt (30 mL) and hydrochloric acid (1 M) until the aqueous phase was found to be neutral. The aqueous phase was extracted with AcOEt (3 × 20 mL) before the combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated. The remaining crude oil was dissolved in dry pyridine (3 mL). At room temperature was then added methanesulfonyl chloride (262 μL, 3.4 mmol). The reaction mixture was left to stir for 90 min before it was poured into a flask containing AcOEt/H_2O (20 mL of each). The layers were separated before the aqueous phase was extracted with AcOEt (3 × 15 mL), and the combined organic phases washed with diluted HCl (1 M, 3 × 15 mL), dried ($MgSO_4$), and removed under reduced pressure. The remaining oil was put on a short column of silica gel and eluted (Et_2O). This resulted in 901 mg (74%) of the desired mesylate, which appeared as a colorless oil. $[\alpha]^{RT}_D$ 82° (*c* 1, $CHCl_3$). R_f (Et_2O) 0.19. NMR ($CDCl_3$) δ_H: 7.29−7.37 (m, 5H, Ar*H*), 4.97 (d, 1H, J_{gem} 11.2 Hz, PhC$H_a$$H_b$O), 4.86 (d, 1H, $J_{1,2}$ 3.6 Hz, H1), 4.63 (d, 1H, PhC$H_a$$H_b$O), 4.37 (t, 2H, *J* 6.6 Hz, H8), 3.76 (t, 1H, *J* 6.0 Hz, H5), 3.64 (s, 3H, OCH_3), 3.52−3.63 (m, 3H, H3, H4, H6), 3.51 (s, 3H, OCH_3), 3.41 (s, 3H, OCH_3), 3.40 (s, 3H, OCH_3), 3.27 (dd, 1H, $J_{2,3}$ 8.8 Hz, H2), 2.96 (s, 3H, C$H_3$$SO_3$), 2.15−2.23 (m, 1H, H7a), 2.03−2.13 (m, 1H, H7b). δ_C: 138.5, 128.6, 127.9 (*Ar*), 97.9 (C1), 84.0, 82.1, 77.4, 74.3, 72.0 (C2, C3, C4, C5, C6), 74.8 (Ph*C*H_2O), 66.9 (C8), 61.1, 59.1, 58.8, 55.7 (O*C*H_3), 37.6 (*C*H_3-SO_3), 30.4 (C7). HRMS(ES): calcd for $C_{20}H_{32}O_9SNa$, 471.1665; found, 471.1679.

Methyl 4-*O*-Benzyl-7-deoxy-2,3,6-tri-*O*-methyl-8-*O*-methylsulfonyl-α-D-*glycero*-D-*gluco*-octopyranoside (16*R*). Olefin **15*R*** (405 mg, 1.1 mmol) dissolved in methanol/CH_2Cl_2 (2:1, 100 mL) underwent the same series of chemical manipulations and subsequent work-up procedures as described for **15*S***. This gave 375 mg (75%) of mesylate **16*R***, which appeared as a colorless oil. $[\alpha]^{RT}_D$ 125° (*c* 1, $CHCl_3$). R_f (Et_2O) 0.31. NMR ($CDCl_3$) δ_H: 7.17−7.29 (m, 5H, Ar*H*), 4.78 (d, 1H, J_{gem} 11.2 Hz, PhC$H_a$$H_b$O), 4.72 (d, 1H, $J_{1,2}$ 3.6 Hz, H1), 4.52 (d, 1H, PhC$H_a$$H_b$O), 4.21 (dd, 2H, $J_{7a,8}$ 4.8 Hz, $J_{7b,8}$ 7.6 Hz, H8), 3.82 (d, 1H, $J_{4,5}$ 10.0 Hz, H5), 3.56 (s, 3H, OCH_3), 3.50 (m, 2H, H3, H6), 3.43 (s, 3H, OCH_3), 3.32 (s, 3H, OCH_3), 3.31 (s, 3H, OCH_3), 3.15 (t, 1H, H4), 3.09 (dd, 1H, $J_{2,3}$ 9.6, H2), 2.83 (s, 3H, C$H_3$$SO_3$), 1.84−1.92 (m, 1H, H7a), 1.65−1.74 (m, 1H, H7b). δ_C: 138.1, 128.7, 128.3, 128.1 (*Ar*), 97.4 (C1), 84.3, 82.2, 77.8, 75.9, 69.0 (C2, C3, C4, C5, C6), 74.8 (Ph*C*H_2O), 67.4 (C8), 61.2, 59.1, 57.9, 55.2 (O*C*H_3), 37.2 (*C*H_3-SO_3), 29.3. HRMS(ES): calcd for $C_{20}H_{32}O_9SNa$, 471.1665; found, 471.1682.

Methyl 4,8-Anhydro-7-deoxy-2,3,6-tri-*O*-methyl-*β*-L-*glycero*-D-*gluco*-octopyranoside (17*S*). Mesylate **16*S*** (325 mg, 0.73 mmol) was dissolved in methanol (6 mL) and AcOEt (0.5 mL). Palladium on charcoal (10%, 150 mg) was added to the solution together with two drops of concentrated aqueous hydrochloric acid before hydrogen was applied (balloon, 1 atm). After 2 h, the solution was filtered through a bed of Celite and evaporated to dryness with toluene. The remaining oil was dissolved in dry DMF (3 mL) to which were added NaH (380 mg, 0.87 mmol) and NaI (54 mg, 0.36 mmol) at room temperature. The mixture was stirred for 1 h before it was quenched with methanol (0.5 mL) and evaporated to dryness. The remaining substance underwent column chromatography (AcOEt/pentane: first 1:3, then 2:1), which resulted in 170 mg (89%) of the cyclized product **17*S*** that appeared as a colorless oil. $[\alpha]^{RT}_D$ 115° (*c* 1, CH_3OH). R_f (AcOEt) 0.48. NMR ($CDCl_3$) δ_H: 4.87 (d, 1H, $J_{1,2}$ 3.6 Hz, H1), 4.04 (ddd, 1H, $J_{7eq,8eq}$ 1.3 Hz, $J_{7ax,8eq}$ 5.3 Hz, $J_{8eq,8ax}$ 11.9 Hz, H8eq), 3.61 (s, 3H, OCH_3), 3.52 (s, 3H, OCH_3), 3.41−3.54 (m, 3H, H3, H5, H8ax), 3.47 (s, 3H, OCH_3), 3.45 (s, 3H, OCH_3), 3.30 (ddd, $J_{6,7eq}$ 5.0 Hz, $J_{5,6}$ 9.0 Hz, $J_{6,7ax}$ 10.8 Hz, H6), 3.24 (dd, $J_{2,3}$ 9.4 Hz, H2), 2.98 (t, 1H, H4), 2.04−2.11 (m, 1H, H7eq), 1.58 (ddt, 1H, H7ax). δ_C: 97.6 (C1), 81.8, 80.7, 80.0, 78.6, 71.8 (C2, C3, C4, C5, C6), 66.3 (C8), 61.2, 59.1, 57.5, 55.2 (O*C*H_3), 31.2 (C7). HRMS(ES): calcd for $C_{12}H_{22}O_6Na$, 285.1314; found, 285.1315.

Methyl 4,8-Anhydro-7-deoxy-2,3,6-tri-*O*-methyl-α-D-*glycero*-D-*gluco*-octopyranoside (17*R*). Mesylate **16*R*** (375 mg, 0.84 mmol) was dissolved in AcOEt/methanol and underwent a series of chemical manipulations and work-up procedures identical to that described for **17*S***. This gave 188 mg (86%) of the desired product **17*R***. $[\alpha]^{RT}_D$ 89° (*c* 1, $CHCl_3$). R_f (AcOEt/pentane 1:1) 0.16. NMR ($CDCl_3$) δ_H: 4.86 (d, 1H, $J_{1,2}$ 3.2 Hz, H1), 3.41−3.75 (m, 6H, H3,H4, H5, H6, H8ax, H8eq), 3.57 (s, 3H, OCH_3), 3.47 (s, 3H, OCH_3), 3.40 (s, 3H, OCH_3), 3.39 (s, 3H, OCH_3), 3.25 (dd, 1H, $J_{2,3}$ 9.2 Hz, H2), 1.95 (m, 1H, H7eq), 1.68 (dddd, 1H, $J_{7ax,7eq}$ 14.4 Hz, $J_{7ax,8ax}$ 9.0 Hz, $J_{7ax,8eq}$ 6.0 Hz, $J_{7ax,6}$ 2.0 Hz, H7ax). δ_C: 98.3 (C1), 81.6, 81.0, 75.1, 74.2, 69.3 (C2, C3, C4, C5, C6), 62.2 (C8), 61.0, 59.0, 57.1, 55.4 (O*C*H_3), 28.7 (C7). HRMS(ES): calcd for $C_{12}H_{22}O_6Na$, 285.1314; found, 285.1319.

2,4-Dinitrophenyl 4,8-Anhydro-7-deoxy-2,3,6-tri-*O*-methyl-α-L-*glycero*-D-*gluco*-octopyranoside (18*S*). Concentrated aqueous $HClO_4$ (70%, 20 μL) was added to acetic anhydride (7.8 mL) at room temperature. A portion of this (2.8 mL) was poured onto methyl glycoside **17*S*** (255 mg, 0.97 mmol). This solution was stirred for 15 min before the reaction was quenched with a saturated aqueous $NaHCO_3$ solution (15 mL). Stirring for 2 h at room temperature before neutralization with solid $NaHCO_3$, extraction with AcOEt (3 × 20 mL), drying ($MgSO_4$), and concentration resulted in a crude oil that was sufficiently pure for further reaction. The mixture of crude acetates was stirred in methanol (8 mL) to which had been added a tiny piece of metallic sodium until TLC analysis (AcOEt) indicated consumption of all starting material. A small lump of dry ice was then added to the reaction flask before all solvent was carefully removed under reduced pressure. The remaining material was dissolved in dry DMF (5.8 mL) before 2,4-dinitrofluorobenzene (147 μL, 1.2 mmol) and DABCO (371

mg, 3.3 mmol) were added at room temperature. After being stirred for 5 h, the reaction mixture was poured into a flask containing H_2O and AcOEt (30 mL of each). After extraction of the aqueous phase with AcOEt (3 × 20 mL), the combined organic extracts were washed with H_2O (3 × 20 mL), dried ($MgSO_4$), and concentrated. The remaining oil underwent column chromatography (eluent: AcOEt/pentane, 3:7, R_f 0.11), yielding 210 mg (52%) of the desired aryl glycoside **18*S*** as a colorless solid. Recrystallization proved possible in hexane/Et_2O. $[\alpha]^{RT}_D$ −112° (*c* 1, $CHCl_3$). NMR ($CDCl_3$) δ_H: 8.76 (d, 1H, J_{meta} 2.8 Hz, Ar*H*), 8.42 (dd, 1H, J_{ortho} 9.2 Hz, Ar*H*), 7.44 (d, 1H, Ar*H*), 5.08 (d, 1H, $J_{1,2}$ 7.2 Hz, H1), 4.04−4.08 (m, 1H, H8eq), 3.65 (s, 6H, OC*H*$_3$), 3.47 (dt, $J_{7eq,8ax}$ 1.9 Hz, *J* 12.4 Hz, H8ax), 3.32−3.45 (m, 2H, H2, H6), 3.39 (s, 3H, OC*H*$_3$), 3.33, 3.21, 3.12 (t, *J* 9.0 Hz, H3, H4, H5), 2.11−2.15 (m, 1H, H7eq), 1.53−1.64 (m, 1H, H7ax). δ_C: 154.6, 141.5, 139.5, 129.0, 121.8, 117.4 (*Ar*), 101.2 (C1), 83.5, 83.1, 78.8, 78.3, 76.9 (C2, C3, C4, C5, C6), 66.2 (C8), 61.5, 61.3, 58.2 (O*C*H$_3$), 31.2 (C7). HRMS(ES): calcd for $C_{17}H_{22}N_2O_{10}Na$, 437.1172; found, 437.1169.

2,4-Dinitrophenyl 4,8-Anhydro-7-deoxy-2,3,6-tri-*O*-methyl-*β*-D-*glycero*-D-*gluco*-octopyranoside (18*R*). Methyl glycoside **17*R*** (116 mg, 0.44 mmol) was stirred for 15 min in acetic anhydride containing $HClO_4$ (1.3 mL) prepared as described for the synthesis of **18*S***. Work-up procedures and further chemical manipulations were carried out as in the synthesis of **18*S***. This eventually resulted in 98 mg (53%) of the desired aryl glycoside **18*R***. $[\alpha]^{RT}_D$ −49° (*c* 1, $CHCl_3$). R_f (AcOEt/pentane 1:1) 0.22. NMR ($CDCl_3$) δ_H: 8.74 (d, 1H, J_{meta} 2.8 Hz, Ar*H*), 8.41 (dd, 1H, J_{ortho}, 9.6 Hz, Ar*H*), 7.35 (d, 1H, Ar*H*), 5.12 (d, 1H, $J_{1,2}$ 7.2 Hz, H1), 3.71−3.79 (m, 4H, H4, H6, H8ax, H8eq), 3.64 (s, 3H, OC*H*$_3$), 3.63 (s, 3H, OC*H*$_3$), 3.44 (dd, 1H, $J_{2,3}$ 8.6 Hz, H2), 3.38 (dd, 1H, $J_{5,6}$ 2.8 Hz, $J_{4,5}$ 9.6 Hz, H5), 3.36 (s, 3H, OC*H*$_3$), 3.28 (t, 1H, H3), 1.96−2.00 (m, 1H, H7eq), 1.69−1.77 (m, 1H, H7ax). δ_C: 154.6, 141.5, 139.8, 128.7, 121.9, 117.3 (*Ar*), 101.5 (C1), 83.9, 82.8, 74.5, 73.9, 73.9 (C2, C3, C4, C5, C6), 62.2 (C8), 61.3, 60.9, 59.9 (O*C*H$_3$), 29.4 (C7). HRMS(ES): calcd for $C_{17}H_{22}N_2O_{10}Na$, 437.1172; found, 437.1173.

Procedure for Determining the Rate of Glycoside Hydrolysis in Acidic Media. A solution (26 mM) of glycoside (**19**, **17*R***, or **17*S***) in perchloric acid (2.56 M by titration with NaOH(ai)) was prepared. This was added to a cuvette preheated to the desired temperature (82 °C). The polarimeter was reset whereupon the cuvette was positioned in the apparatus. The optical rotation was measured as a function of time at sodium's D-line. The measurements went on until the rotational value had stabilized (20−166 h). At this point, the α(inf) was determined. The solution of hydrolyzed glycoside underwent MS(ES) analysis, which only revealed the presence of the hemiacetal corresponding to the glycoside starting material. The same procedure was then repeated 2−3 times for each of the three glycosides.

The measurements for each determination were fitted as $A(t) = (\alpha(t) - \alpha(\text{inf}))/(\alpha(0) - \alpha(\text{inf}))$ to a curve of the type $y(t) = y_o + a \cdot \exp(-bt)$. Good fits were obtained in every case ($R^2 = 0.9994-0.9999$). The rate constant was obtained as the value of the constant *b* in the equation.

Procedure for Determining the Rate of Hydrolysis of Dinitrophenyl Glycopyranoside. A solution (2.4 mM) of the dinitrophenyl glycopyranoside (**21**, **18*R***, **18*S***, or **26**) in 1,4-dioxane was prepared, as well as a phosphate buffer (pH 6.5, 25 mM) containing 0.4 M KCl. These were preheated to the desired temperature, and the following volumes were transferred into several cuvettes: buffer 1.500 mL and glycoside solution 0.500 mL (for the reference sample was used 0.500 mL of 1,4-dioxane). The solution was mixed thoroughly on a vortex mixer. After a 5 min delay (to ensure temperature equilibration), the rate of hydrolysis was measured spectrophotometrically at 400 nm over a time span of 3 h. The hydrolysis of each compound at each temperature was carried out 5−7 times to get reliable results. Each measurement was carried out at four different substrate concentrations (0.6, 0.3, 0.15, and 0.075 mM).

The rate constant was calculated from the slope of a plot of absorbance versus time. Arrhenius plots were produced from the rate constants for five different temperatures, and the activation energy, E_a, was calculated from the slope and the activation entropy, $\Delta S^{\ddagger}$, was found at the *y*-axis intercept.

Conclusion

A series of probe molecules for the delineation of the effects of a 4,6-acetal on glycoside reactivity were efficiently prepared through multistep synthetic paths. Kinetic results from acid-catalyzed glycoside hydrolysis of three methyl glycosides and spontaneous dinitrophenyl glycoside hydrolysis confirmed the existence of a disarming torsional effect. It was furthermore shown that electronic effects also play a substantial role in the disarming effect of the 4,6-acetal group. It is therefore concluded that the deactivating effect of a 4,6-benzylidene group is not exclusively "torsional disarmament" but also to a roughly equal extent an electronic effect associated with locking the hydroxymethyl group in the *tg* conformation. A small electronic difference between the *gg* and the *gt* isomers **18*R*** and **18*S*** was also observed, with the latter being the less reactive glycoside. The results show once more the very crucial influence electronic effects have on carbohydrate reactivity.

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Supporting Information Available: Progress curves for the acidic hydrolysis of methyl glycosides and Arrhenius plot for the solvolysis of dinitrophenyl glycosides. This material is available free of charge via the Internet at http://pubs.acs.org.

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