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Probing the Influence of a 4,6-*O*-Acetal on the Reactivity of Galactopyranosyl Donors: Verification of the Disarming Influence of the *trans-gauche* Conformation of C5-C6 Bonds

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Abstract. The effect of a 4,6-*O*-alkylidene acetal on the rate of acid-catalyzed hydrolysis of methyl galactopyranosides and of spontaneous hydrolysis of 2,4-dinitrophenyl galactopyranosides has been studied through the synthesis and hydrolysis of analogs in which O6 is replaced by a methoxymethylene unit in which the methoxy group adopts either an equatorial or an axial position according to the configuration. Consistent with earlier studies under both acid-catalyzed and spontaneous hydrolysis conditions the alkylidene acetal, or its 7-carba analog, retards hydrolysis with respect to comparable systems lacking the cyclic protecting group. The configuration at C7 in the 7-carba analogs does not influence the rate of acid-catalyzed hydrolysis but has a minor influence on the rate of spontaneous hydrolysis of the 2,4-dinitrophenyl galactosides, confirming earlier studies on the role played by the hydroxymethyl group conformation on glycoside reactivity. The benzylidene acetal is found to stabilize

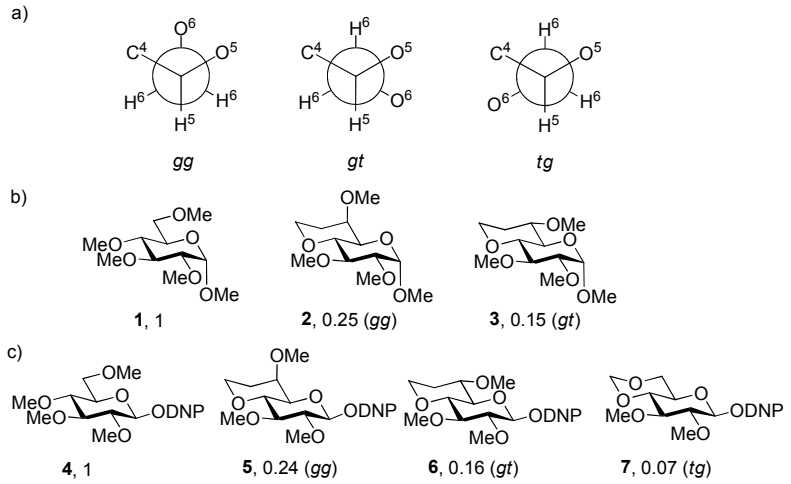
the α-anomer of galactopyranose derivatives relative to monocyclic analogs. Reasons for the α-selectivity of 4,6-*O*-benzylidene-protected galactopyranosyl donors bearing neighboring group-active protecting groups at O2 are discussed.

Introduction

Protecting groups play a major and as yet not always predictable role in controlling the reactivity and stereochemistry of glycosyl donors in their coupling to acceptors to form glycosidic bonds.[1-9] In particular, in recent years, cyclic protecting groups[10] have proven to be especially useful in controlling the stereochemistry of what were previously considered to be difficult glycosylations. Prominent examples include the 4-*O*,5-*N*-oxazolidinones in the sialic acid series,[11-15] the 3,5-*O*-(di-*tert*-butyl)silylene acetals and related groups in the arabinofuranoside series,[16-18] the 2*N*,3*O*-oxazolidinones in the 2-amino-2-deoxyglucopyranose series,[19-21] and the 4,6-*O*-benzylidene acetals in both the gluco-[22-23] and mannopyranoside series.[24-25] In most cases mechanistic understanding lags someway behind application of these mostly serendipitous discoveries owing to the complex nature of glycosylation reactions, but significant progress has been made on the origins of the 4,6-*O*-benzylidene effect in gluco- and mannopyranosylation.[26-28] In this context, the elegant work of the Bols group[29] comparing the reactivity of a series of methyl and dinitrophenyl glucopyranosides (Fig. 1) toward acid-catalyzed and spontaneous[30] hydrolysis, respectively, was seminal. In this work it was found under both sets of conditions (Fig. 1) that bicyclic systems were less reactive than comparable monocyclic systems, from which it was concluded that the fused ring exerts a torsional disarming effect, in line with the earlier conclusion of Fraser-Reid and coworkers.[31-32] It was also found by a comparison of the dinitrophenyl glucoside reactivity that the most disarmed system was the one including O6 in the bicyclic system leading to the conclusion that the *trans-gauche*[33-35] (*tg*) conformation of the C5-C6 bond is the most disarming conformation owing to an electronic effect arising from the locking of the antiperiplanar nature of the C5-O5 and C6-O6 bonds.[29] Comparison of the relative rates of hydrolysis of the dinitrophenyl glucopyranosides affords the conclusion that the electronic effect due to the *tg*

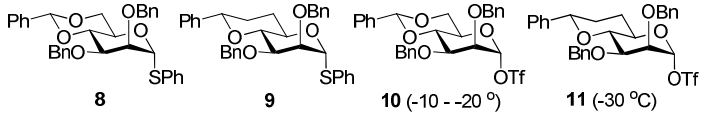
conformation is of greater magnitude than the torsional disarming effect due to the presence of a second ring.[29]

Figure 1. a) Newman projections about the C5-C6 bond defining the *gg*, *gt*, and *tg* conformations in the hexopyranoses, and relative reactivities of b) methyl and c) 2,4-dinitrophenyl glucopyranosides toward acid-catalyzed and spontaneous hydrolysis, in b) 2,5 M $HClO_4$ at 82 °C and c) pH 6.5 aqueous dioxane at 37 °C, according to Bols and coworkers.[29]



More recently, Pedersen and coworkers concluded, following their observation of little or no difference in the β-selectivity of donors **8** and **9** under preactivation conditions at low temperature, that the stereodirecting effect of the benzylidene ring in the mannopyranoside series is not solely due to the electronic effect resulting from the antiperiplanar nature of O5 and O6 but also has a significant torsional component arising from the presence of the fused ring system.[36] Comparison of the decomposition temperatures of the corresponding α-mannosyl triflates **10** and **11** nevertheless revealed the influence of the C6-O6 bond on reactivity.[5,36-37]

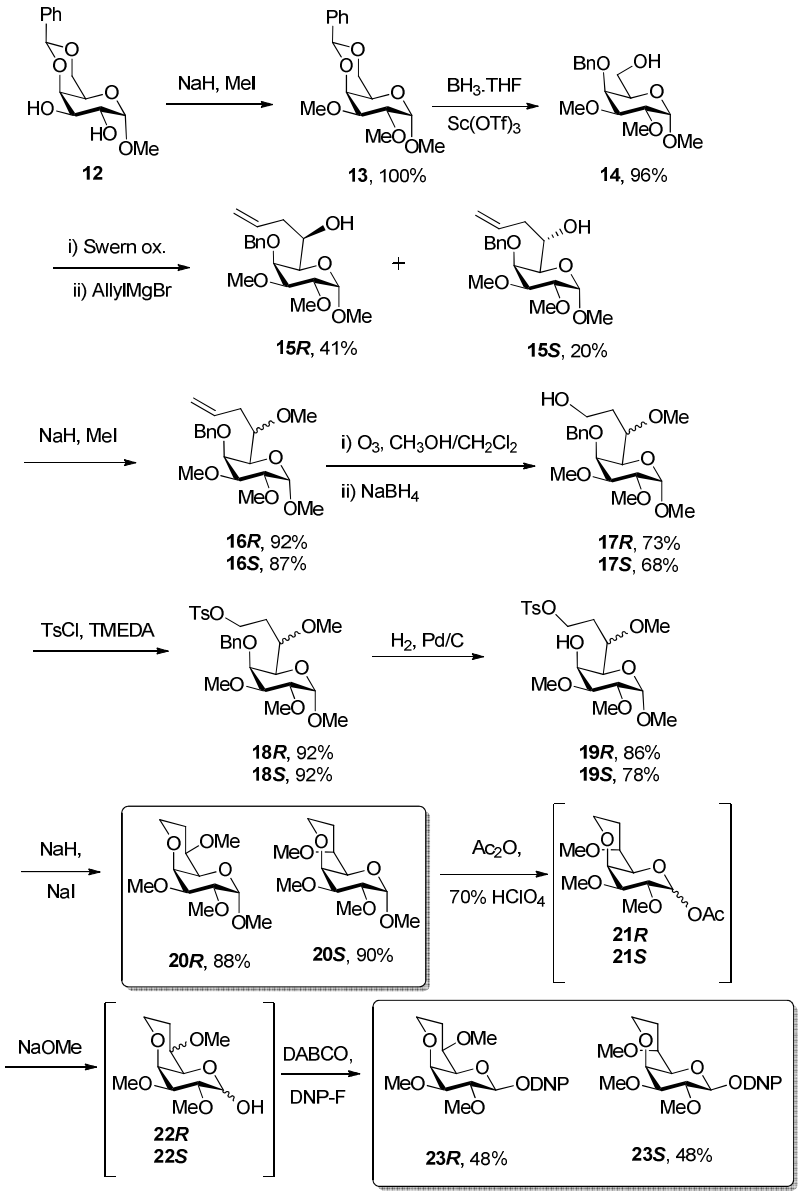
Figure 2. Bicyclic thioglycosides in the mannopyranoside series and decomposition temperatures of the corresponding triflates.[36]



In the galactopyranose series the presence of a 4,6-*O*-benzylidene acetal is typically α-directing in systems carrying ether protection at O2 and O3 except with unhindered reactive acceptors.[38-41] With participating groups at the C2 position 4,6-*O*-benzylidene protected galactopyranosyl donors are commonly found to be β-selective.[42-45] However, a number of reports exist in which such galactosyl donors carrying participating groups at C2 and 4,6-*O*-benzylidene acetals have been shown to favour the formation of the α-glycosides,[46-47] or in which the selectivity has been shown to vary as a function of the promoter.[48-50] With the related 4,6-*O*-di-(*tert*-butyl)silylene acetal protected galactopyranosyl donors α-selectivity is observed whether or not a participating group is present at C2.[51-55] This apparent ability of 4,6-*O*-benzylidene and 4,6-*O*-silylene acetals to direct galactopyranosylation toward selective formation of the α-anomer even in the presence of participating groups at the 2-position has been variously explained as arising from i) stabilization of a galactosyl oxocarbenium ion by O4 and O6 due to the conformation imposed by the presence of the benzylidene acetal,[46] ii) steric factors due to shielding of the β-face of the oxocarbenium ion by the acetal,[54] and iii) stereochemical mismatching[56-57] of donor/acceptor pairs,[48] It has also been noted in some cases that the selectivity is Lewis acid and condition dependent, with the softer BF_3OEt_2 affording higher β-selectivities than the harder TMSOTf.[49] In an attempt to shed light on this issue, by adapting the method of Bols and coworkers,[29] we have studied and report here on the effect of a 4,6-*O*-alkylidene group and carba-analogs thereof on the hydrolysis of 2,4-dinitrophenyl galactopyranosides. As a corollary to these investigations, and following recent observations from our laboratory in the mannopyranose series,[58] we have also studied and report here on the influence of a benzylidene acetal on the anomeric effect in the gluco- and galactopyranosides. Finally, we have investigated and report on the ability of the 4,6-*O*-benzylidene acetal to promote anomerization of *N*-Troc and *N*-trichloroacetyl protected glycosides of galactosamine under standard glycosylation conditions.

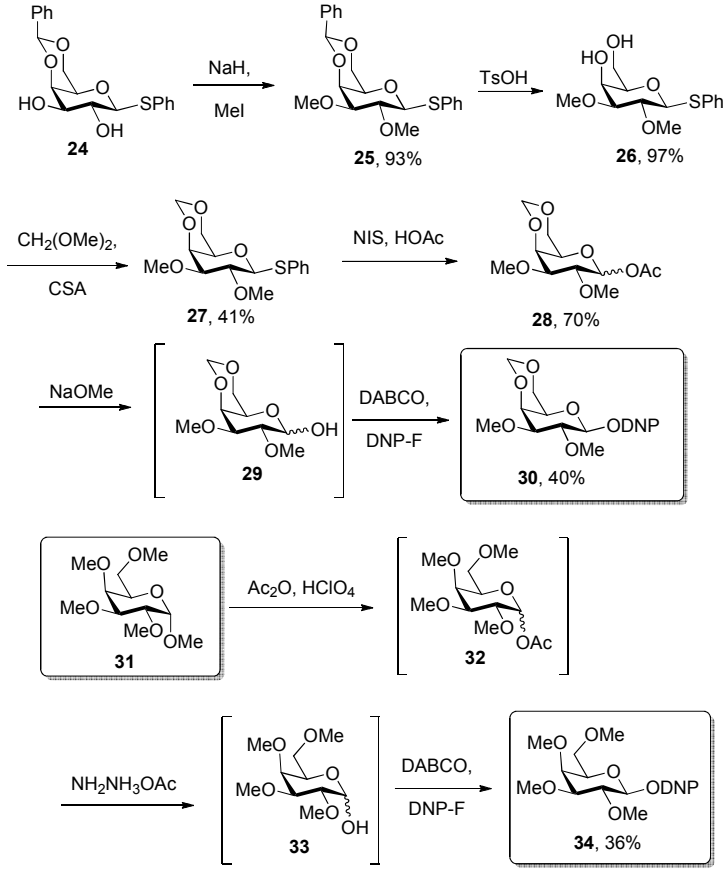
Results

Methylation of methyl 4,6-*O*-benzylidene-α-D-galactopyranoside **12** to give the dimethyl ether **13** was followed by regioselective reductive ring opening of the benzylidene acetal with borane-tetrahydrofuran in the presence of scandium triflate[59] affording the 4-*O*-benzyl ether **14** (Scheme 1). Swern oxidation of the primary alcohol function in **14** gave an aldehyde which, on exposure to allylmagnesium bromide in THF gave a 2:1 mixture of the diastereomeric adducts **15*R*** and **15*S*** in 61% combined yield, whose stereochemistry was assigned retrospectively following conversion to the bicyclic **20*R*** and **20*S***. After chromatographic separation the two diastereomers **15*R*** and **15*S*** were processed in parallel through a series of steps including methyl ether formation, ozonolytic cleavage of the alkene with reductive work-up, tosylation, hydrogenolysis of the benzyl ether moiety, and cyclization with sodium hydride in the presence of sodium iodide to give, ultimately, the bicyclic derivatives **20*R*** and **20*S*** as outlined in Scheme 1. The stereochemistry of **20*R*** rests on the observation of a NOE interaction of the axial hydrogen H6 with the equatorial H4 as well as on the observation of a single ~10 Hz coupling of H6 with an axial hydrogen at H7. Conversely, in isomer **20*S*** there is no NOE between H's 4 and 6, and H6 and H7 do not exhibit *trans*-diaxial coupling in the ^{1}H NMR spectrum. Acetolysis of both **20*R*** and **20*S*** with acetic anhydride and perchloric acid afforded the hemiacetals **21*R*** and **22*S*** which, on saponification and subsequent arylation with 2,4-dinitrofluorobenzene gave, selectively, the β-dinitrophenyl glycosides **23*R*** and **23*S*** (Scheme 1).



Scheme 1. Synthesis of the diastereomeric methyl galactopyranosides **20** and of the dinitrophenyl galactopyranosides **23**.

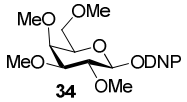
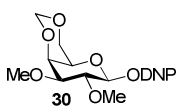
A 2,4-dinitrophenyl 4,6-*O*-methylidene galactopyranoside **30** and the permethylated analog **34** were synthesized by standard methods from the benzylidene-protected thioglycoside **24** and methyl tetra-*O*-methyl-D-galactopyranoside **31**, respectively (Scheme 2).[60-61]

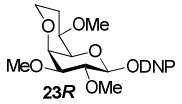
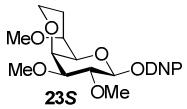


Scheme 2. Synthesis of the dinitrophenyl galactopyranosides **30** and **34**.

The hydrolysis of the 0.05 mM solutions of the dinitrophenyl glycosides **23*R***, **23*S***, **30** and **34** was studied in pH 6.5 phosphate buffer at five different temperatures ranging from 42 to 75 ^{o}C, with spectrophotometric monitoring at 400 nm, and provided the kinetic parameters presented in Table 1.

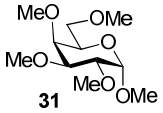
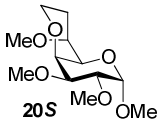
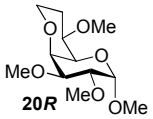
Table 1. Kinetic parameters for the spontaneous hydrolysis of the dinitrophenyl galactopyranosides in pH 6.5 phosphate buffer in order of decreasing relative rate.

Substrate	**Log A**	E_a **(kcal/mol)**	$k \times 10^7$ **s^{-1} (37 °C)**	**Relative rate**	**O5-C5-C6-O6**
 **34**	3.0	24.9±0.22	101	1	-
 **30**	4.7	25.8±0.21	43.3	0.43	60^{o}, *gg*

 **23*R***	4.5	27.0±0.33	25	0.23	60°, *gt*
 **23*S***	4.4	27.2±0.37	18.5	0.17	180°, *tg*

Rate constants for the acid catalysed hydrolysis of the methyl glycosides **20*R***, **20*S***, and **31** were determined polarimetrically in aqueous perchloric acid at 82 °C (Table 2).

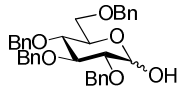
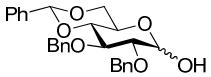
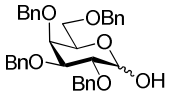
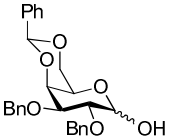
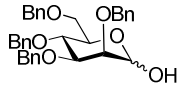
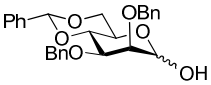
Table 2. Rate Constants for the Acid Catalyzed Hydrolysis of Methyl Galactopyranosides 20*R*, 20*S*, and 31 in order of Decreasing Relative Rate.

Substrate	**$k \times 10^5$ s^{-1} (82 °C)**	**Relative hydrolysis rate**
 **31**	13.5 ± 0.28	1
 **20*S***	10.7 ± 0.22	0.79
 **20*R***	10.5 ± 0.23	0.78

The hemiacetals **35-38** were generated from the corresponding anomeric acetates and their ^{1}H-NMR spectra in $CDCl_3$ monitored at room temperature until equilibration was complete leading to the anomeric ratios presented in Table 3, entries 1-4. The corresponding anomeric ratios for compounds **39**

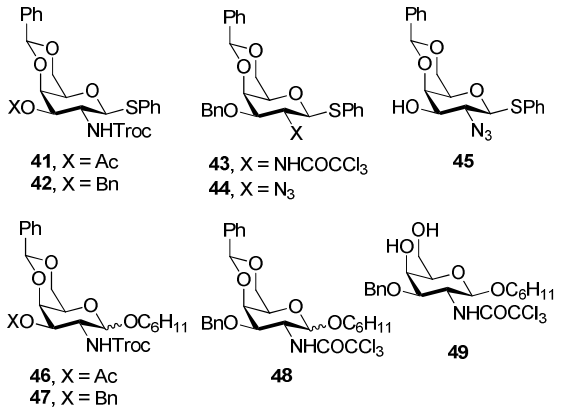
and **40** (Table 3, entries 5 and 6) are taken from the literature[58] and are reproduced here for ease of comparison.

Table 3. Equilibrium Anomeric Ratios for Protected Gluco-, Galacto-, and Mannopyranosides in $CDCl_3$.

Entry	Structure	α:β Ratio	$\Delta,\Delta G_{298K}$ (k.cal.mol^{-1})
1	 **35**	72:28	-0.56
2	 **36**	61:39	-0.27
3	 **37**	71:29	-0.53
4	 **38**	83:17	-0.94
5	 **39**	80:20	-0.82
6	 **40**	54:46	-0.10

The *N*-Troc-3-*O*-acetyl-4,6-*O*-benzylidene-2-amino-2-deoxygalactosyl donor **41** was prepared according to a literature method,[45] while its 3-*O*-benzyl *N*-Troc and *N*-trichloroacetyl analogs **42** and **43** were accessed from the corresponding 2-azido derivative **44**, which itself was obtained by benzylation of the known galactosamine derivative **45**[41] (Fig. 3) as described in the supporting information.

Figure 3. Substrates for and Products from Glycosylation Studies (Table 4)



Coupling reactions of the donors **41**-**43** were then conducted using cyclohexanol as model acceptor in dichloromethane as solvent using *N*-iodosuccinimide and triflic acid as activating agent at a variety of temperatures leading to the formation of the cyclohexyl galactosides **46**-**48** as set out in Table 4. With a view to promoting anomerization, galactoside **47** then was stirred in the presence of 10 mol % of boron trifluoride etherate and an excess of cyclohexanol at -60, -20, 0 ^{o}C, and room temperature; no formation of the α-anomer was observed by NMR spectroscopy even after 2 h at room temperature. When the experiment was repeated with 20 mol % TMSOTf as Lewis acid no change was observed after 2 h at -20 ^{o}C or at room temperature. When the amount of TMSOTf was increased to 95 mol% loss of the benzylidene acetal was observed at room temperature, leading to the diol **49**, albeit without anomerization.

Table 4. Coupling of Donors **41**-**43** with Cyclohexanol.

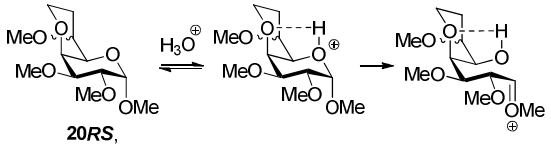
Entry	Donor	Temp (^{o} C)	Time (h)	Product (% yield)	α:β ratio[a]
1	**41**	-78	2	**46** (>95)	6:94
2	**41**	-22	2	**46** (>95)	7:93
3	**41**	0	0.15	**46** (28)	1:10
4	**42**	-78	2	**47** (41)	β-only
5	**42**	rt	0.5	**47** (65)	β-only
6	**43**	-78	2	**48** (36)[b]	β-only

7	**43**	rt	0.5	**48** (33)	1.5:1

a) NMR ratios unless otherwise noted. b) Additionally, 50% of the substrate was recovered unchanged.

Discussion

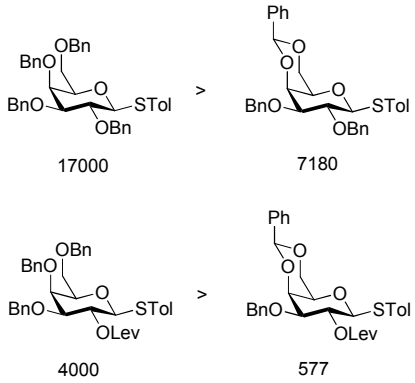
The parallel influence of stereochemistry at C6 on the order of hydrolysis of the methyl glucosides (Fig 1a) and the 2,4-dinitrophenyl glucosides (Fig 1b) led Bols and coworkers to conclude that the acid-catalyzed hydrolysis of the methyl glucosides and the spontaneous hydrolysis of the 2,4-dinitrophenyl glucosides proceeded via comparable mechanisms, i.e., via rate determining steps involving cleavage of the exocyclic glycosidic bond en route to a transient cyclic oxocarbenium ion intermediate.[29] The fact that the acid-catalyzed hydrolysis of the methyl galactopyranosides shows no configuration dependent difference in relative rate between isomers **20*R*** and **20*S*** (Table 2), whereas the 2,4-dinitrophenyl galactosides show the same dependence on configuration *gg>gt>tg* (Table 1) as in the gluco-series (Fig 1) suggests a difference in mechanism for the acid-catalyzed hydrolysis of the methyl galactopyranosides, at the least for the bicyclic analogues **20*R*** and **20*S***. Thus, while the spontaneous hydrolysis of the 2,4-dinitrophenyl galactosides appears to follow the standard mechanism of exocyclic cleavage leading to a cyclic oxocarbenium ion, the acid catalyzed hydrolysis of the methyl galactosides **20*R*** and **20*S*** presumably takes place via protonation on the ring oxygen, with stabilization by hydrogen bonding to O4, and subsequent endocyclic cleavage (Scheme 3). Because of this apparent change to an endocyclic cleavage mechanism, the predominance of exocyclic mechanisms in actual glycosylation reactions with the possible exception of strained systems,[62] and the uncertainty regarding the endo- or exocyclic nature of the mechanism of hydrolysis of the monocyclic system **31**, we do not consider the relative rates of the acid-catalyzed hydrolysis of the methyl galactosides (Table 2) further here.



Scheme 3. Possible endocyclic cleavage in the acid-catalyzed hydrolysis of **20*RS***

The hydrolysis of dinitrophenyl glycosides is known to be pH independent over a pH range 1.6 – 8.4 and is considered to proceed via spontaneous exocyclic fragmentation to give the transient glycosyl oxocarbenium in the rate determining step.[30,63] On this basis, from the data presented in Table 1, it is clear that the presence of the additional ring *cis*-fused to the pyranoside ring in **23*R***, **23*S***, and **30** retards formation of the oxocarbenium ion with respect to the simple monocyclic system **34**. This observation is consistent with relative rate values determined by the Wong group for the activation of thioglycosides, which show 4,6-*O*-benzylidene protected thiogalactosides to be less reactive than the corresponding 4,6-di-*O*-benzyl substances (Fig 4).[64-65] Evidently, the *cis*-fusion of a second ring across positions 4- and 5- of the pyranoside is therefore disarming irrespective of the nature, exo- or endocyclic, of the C6-O6 bond. This is a torsional disarming effect and reflects the influence of the fused ring on the ability of the pyranose ring to undergo deformation from the ideal $^4C_1$ conformation in order to accommodate the oxocarbenium ion.

Figure 4. Literature relative Rate Values for the Activation of Thiogalactosides[64-65]



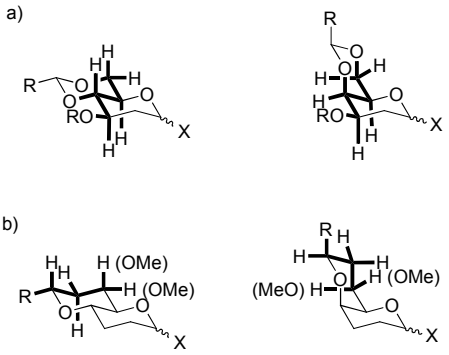
Comparison of the relative rates of spontaneous hydrolysis of the bicyclic systems **23*R***, **23*S***, and **30** (Table 1) reveals the retarding influence of the conformation of the O5-C5-C6-O6 bond on hydrolysis rate to be *tg*>*gt*>*gg*, which is the same as that found earlier by Bols and coworkers in their study on *trans*-fused bicyclic dinitrophenyl glucosides (Fig 1).[29] That **23S**, with the *tg* relationship between O5 and O6, is the least reactive of the series is understood in terms of maximization of the electron-withdrawing effect of the C6-O6 when oriented antiperiplanar to the locus of the positive charge in the

glycosyl oxocarbenium formed in the rate limiting step of hydrolysis.[29,66] The greater reactivity of the *gg*-system **30** can be understood in terms of the optimal positioning of O6 for through space stabilization of the glycosyl oxocarbenium ion,[67] with which it bears the same relationship as the axial O4 bond that is responsible[66,68-69] for the well-known[70-71] greater reactivity of galactopyranosides over glucopyranosides.

Overall, the Bols model (Fig 1)[29] and its application to the galactose series presented here reach the common conclusion that the conformation of the C5-C6 bond has an important influence on the reactivity of glycosyl donors, with the least and most reactive conformations being the *tg* and *gg* conformers, respectively. A second common finding from the two studies is the existence of a Fraser-Reid type torsional component in the disarming effect arising from the fusion of a benzylidene ring across O4 and O6. We do, however, raise a caveat regarding the relative magnitude of this torsional effect especially in the light of the recent findings of Pedersen and coworkers on the importance of the torsional effect in the mannopyranoside series (Fig 2).[36] Although Fraser-Reid and coworkers never precisely identified the exact torsional interaction(s) to which they referred in advancing their model,[31-32] as they involve the cyclic protecting group they must necessarily involve gauche interactions around the C3-C4, C4-C5, and C5-C6 bonds which are distorted from the ideal 60^{o} dihedral angle as the pyranose ring undergoes flattening on formation of the oxocarbenium ion (Fig 5a). In the Bols systems (**2**, **3**, **5**, **6**, **9**, **11**) and in their extension to the galactose series presented here (**23*RS***) an oxygen atom in a 1,3-dioxane is replaced by a methylene group and numerous new potential torsional interactions are brought into play in both the *trans*- and *cis*-fused systems (Fig 5b). The reduced potential for torsional interactions in 1,3-dioxanes as compared to cyclohexanes on distortion from the ideal chair form is borne out by the lower barrier for conformational inversion in 1,3-dioxane (9.0-9.9 kcal.mol^{-1}) than in cyclohexane (10.2 kcal.mol^{-1}),[72-73] and in tetrahydropyran (10.3 kcal.mol-1),[74] even if the twist boat conformer is less highly populated in 1,3-dioxane than in cyclohexane owing to the shorter C-O bonds in 1,3-dioxane which give rise to greater steric interactions across the ring in its twist boat conformers.[72-73] Thus, while the Bols-type systems have value in estimating the influence of the O5-C5-C6-O6 torsion

angle on the reactivity of glycosyl donors, the replacement of an oxygen atom by a methylene group in the 4,6-*O*-alkylidene ring system brings additional C-H bonds into play that are capable of suffering torsional interactions on formation of the oxocarbenium ion. While not all of the bonds involved will be distorted from the ideal staggered conformation on formation of the oxocarbenium ion, some necessarily will be and therefore the Bols-type replacement perforce overestimates the torsional component of the disarming nature of a 4,6-*O*-alkylidene group. These new torsional interactions due to the replacement of O6 by a methylene group provide an adequate rationalization for the unanticipated high β-selectivity observed with the donor **9** (Fig 2) by Pedersen and coworkers.[36]

Figure 5. a) The array of bonds around the 4,6-*O*-alkylidene ring system susceptible to torsional interactions on expulsion of the leaving group X and flattening of the pyranose ring on oxocarbenium ion formation. b) Additional bonds susceptible to torsional interactions on oxocarbenium ion formation following replacement of O7 by a methylene group and the inclusion of a 6-methoxy substituent.

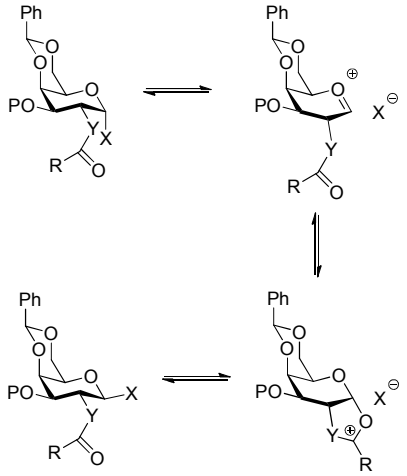


Turning to thermodynamic effects, the data presented in Table 3 clearly illustrate that the inclusion of a 4,6-*O*-benzylidene ring in an otherwise fully benzylated system favors the α- over the β-pyranose form in galactose (Entries 3 and 4), whereas the opposite is true in mannose (Entries 5 and 6), as we have previously reported,[58] and to a lesser extent in glucose (Entries 1 and 2). A similar observation was reported earlier by Koganty and coworkers who noted that 4,6-*O*-benzylidene-*N*-acetylgalactopyranosamine exists completely as the α-anomer in DMSO, whereas the gluco-isomer is an α,β-mixture.[46] Interestingly, this effect is not reflected in the conformational equilibrium of the freely

rotating C5-C6 bond of simple alkyl galactopyranosides where the principle changes between the α- and β-anomers involve differing populations of the predominant *gt* and *tg* conformations.[75] Several reasons can be advanced for the observed effect including i) the restriction of conformational space for the aglycone of the β-isomer by the imposition of the *gt* conformation, and ii) the antiparallel dipoles of the C6-O6 and C1-O1 bonds in the α-anomer of the benzylidene protected system. Whatever the exact reason, it is clear from the data presented in Table 3 that the benzylidene acetal group stabilizes the α-anomer to a greater extent than is seen in fully conformationally labile systems.

Regarding the abnormally high proportions of α-galactopyranoside formation observed by a number of groups[46-49] with donors bearing a 4,6-*O*-benzylidene acetal in spite of the demonstrated[42,48,52] possibility of neighboring group participation from the 2-position, in our hands donors **41**-**43** are β-selective on activation with the NIS/TfOH couple, even at room temperature (Table 4), consistent with work from several other laboratories with a variety of benzylidene-protected 2-aminogalactopyranosyl donors (thioglycosides, fluorides, and trichloroacetimidates) bearing either Troc or trichloroacetyl groups on the amine.[42-45,52] Moreover, repeated attempts at equilibration of the β-glycoside **48** only resulted in cleavage of the benzylidene acetal, leading to the conclusion that the differing selectivities observed by the different groups are likely kinetic in nature. A complete explanation of the selectivity of 4,6-*O*-benzylidene protected galactopyranosyl donors bearing groups capable of neighboring group participcation at the 2-position is beyond the scope of this Article. However, it seems likely that differences in selectivity are due to changes in the key equilibria between the active glycosylating species including cyclic intermediates arising from participation, glycosyl oxocarbenium ions, and even covalent β-glycosyl triflates or analogous species (Scheme 4), such as have recently been observed in the mannuronic acid series.[76-77] Such subtle but important changes are likely to be induced by changes in reaction conditions, including the Lewis acid and its concentration, and the nature of the O3 protecting group such as established by the Huang and Williams groups in the glucose series.[78-79] We also consider it possible that the quantity and nature of the Lewis acid involved may influence the course of the reaction by complexation to the carbonyl oxygen of the participating group at position 2, for example,

leading to silyl imidate formation and thereby limiting participation; such processes have been shown to play a major role in the chemistry of *N*-acetylglucosamine by Auzanneau and coworkers[80-81] following early observation by Pougny and Sinaÿ.[82]



Scheme 4. Equilibria of glycosylation intermediates influenced by reaction conditions and Lewis acid (P = protecting group or glycosyl residue; R = alkyl group, alkoxy group; X = leaving group; Y = NH, O)

Finally, with respect to the role played by the benzylidene acetal in influencing stereoselectivity there is no strong evidence on the basis of X-ray crystallographic structures for steric hindrance of the β-face of 4,6-*O*-benzylidene carrying galactopyranosyl donors by the phenyl ring of the protecting group.[83] However, it is possible that the enforced *gg* conformation of the C5-C6 bond provides additional steric hindrance to β-face attack. With the 4,6-*O*-di-*tert*-butylsilylene protected systems,[54] however, as pointed out by Kiso and coworkers,[52] the crystallographic evidence clearly indicates strong hindrance of the β-face of the donor by a *tert*-butyl group. Additionally, the electropositive nature of silicon with respect to carbon (Pauling electronegativities: C, 2.5, Si, 1.8) assures that the silylene acetal is less electron-withdrawing than the benzylidene acetal and therefore better stabilizes any anomeric oxocarbenium ions and thereby increases their relative proportion in the equilibria of possible glycosylating species. Taken together these two factors adequately explain the significantly greater α-directing influence of the silylene acetal over the benzylidene acetal.

Conclusion

The influence of 7-carba analogs of 4,6-*O*-alkylidene protecting groups on the spontaneous hydrolysis of 2,4-dinitrophenyl galactopyranosides reveals that the *cis*-fused acetals are disarming similarly to their *trans* fused analogs in the gluco- and manno-series, thereby confirming the existence of a torsional component. The same experiments confirm the earlier conclusion of the Bols group that the *tg*-orientation of the C5-C6 bond, which places the C6-O6 bond antiperiplanar to the C5-O5 bond is the most electron-withdrawing conformation. The 7-carba-analogs of the 4,6-*O*-alkylidene protecting groups introduced by the Bols group overestimate the torsional component of the disarming effect of the acetal protecting groups because of the extra torsional interactions they introduce. Under equilibrating conditions a 4,6-*O*-benzylidene acetal increases the proportion of the α-anomer in the galactopyranose series with respect to simple monocyclic systems.

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Supporting Information Available. Full experimental details and copies of ^{1}H and ^{13}C NMR spectra of all compounds. This information is available free of charge via the internet at http://pubs.acs.org.

References

(1) Fraser-Reid, B.; Lopez, C. *Top. Curr. Chem.* **2011**, *301*, 1-9.
(2) Gomez, A. M. *Top. Curr. Chem.* **2011**, *301*, 31-68.
(3) Shiao, T. C.; Roy, R. *Top. Curr. Chem.* **2011**, *301*, 69-108.
(4) Kim, K. S.; Suk, D.-H. *Top. Curr. Chem.* **2011**, *301*, 109-140.
(5) Aubry, S.; Sasaki, K.; Sharma, I.; Crich, D. *Top. Curr. Chem.* **2011**, *301*, 141-188.
(6) Premathilake, H. D.; Demchenko, A. V. *Top. Curr. Chem.* **2011**, *301*, 189-222.
(7) Wu, C.-Y.; Wong, C.-H. *Top. Curr. Chem.* **2011**, *301*, 223-252.
(8) Codée, J. D. C.; Christina, A. E.; Walvoort, M. T. C.; Overkleeft, H. S.; van der Marel, G. A. *Top. Curr. Chem.* **2011**, *301*, 253-290.
(9) Codée, J. D. C.; Ali, A.; Overkleeft, H. S.; van der Marel, G. A. *CR Chimie* **2011**, *14*, 178-193.
(10) Litjens, R. E. J. N.; van den Bos, L. J.; Codée, J. D. C.; Overkleeft, H. S.; van der Marel, G. *Carbohydr. Res.* **2007**, *342*, 419-429.
(11) Tanaka, H.; Nishiura, Y.; Takahashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 7124-7125.
(12) Crich, D.; Li, W. *J. Org. Chem.* **2007**, *72*, 2387-2391.
(13) Farris, M. D.; De Meo, C. *Tetrahedron Lett.* **2007**, *48*, 1225-1227.
(14) Hsu, C.-H.; Chu, K.-C.; Lin, Y.-S.; Han, J.-L.; Peng, Y.-S.; Ren, C.-T.; Wu, C.-Y.; Wong, C.-H. *Chem. Eur. J.* **2010**, *16*, 1754-1760.
(15) Kancharla, P. K.; Navuluri, C.; Crich, D. *Angew. Chem. Int. Ed.* **2012**, *51*, 11105-11109.

(16) Zhu, X.; Kawatkar, S. P.; Rao, Y.; Boons, G.-J. *J. Am. Chem. Soc.* **2006**, *128*, 11948-11957.
(17) Ishiwata, A.; Akao, H.; Ito, Y. *Org. Lett.* **2006**, *8*, 5525-5528.
(18) Crich, D.; Pedersen, C. M.; Bowers, A. A.; Wink, D. J. *J. Org. Chem.* **2007**, *72*, 1553-1565.
(19) Benakli, K.; Zha, C.; Kerns, R. J. *J. Am. Chem. Soc.* **2001**, *123*, 9461-9462.
(20) Boysen, M.; Gemma, E.; Lahmann, M.; Oscarson, S. *Chem. Comm.* **2005**, 3044-3046.
(21) Manabe, S.; Ishii, K.; Ito, Y. *Eur. J. Org. Chem.* **2011**, 497-516.
(22) Crich, D.; Cai, W. *J. Org. Chem.* **1999**, *64*, 4926-4930.
(23) Bousquet, E.; Khitri, M.; Lay, L.; Nicotra, F.; Panza, L.; Russo, G. *Carbohydr. Res.* **1998**, *311*, 171-181.
(24) Crich, D.; Sun, S. *J. Org. Chem.* **1996**, *61*, 4506-4507.
(25) Crich, D.; Sun, S. *J. Org. Chem.* **1997**, *62*, 1198-1199.
(26) Crich, D. *Acc. Chem. Res.* **2010**, *43*, 1144-1153.
(27) Huang, M.; Garrett, G. E.; Birlirakis, N.; Bohé, L.; Pratt, D. A.; Crich, D. *Nat. Chem.* **2012**, *4*, 663-667.
(28) Huang, M.; Retailleau, P.; Bohé, L.; Crich, D. *J. Am. Chem. Soc.* **2012**, *134*, 14746-14749.
(29) Jensen, H. H.; Nordstrom, M.; Bols, M. *J. Am. Chem. Soc.* **2004**, *126*, 9205-9213.
(30) Cocker, D.; Sinnott, M. L. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1391-1393.
(31) Fraser-Reid, B.; Wu, Z. C.; Andrews, W.; Skowronski, E. *J. Am. Chem. Soc.* **1991**, *113*, 1434-1435.
(32) Andrews, C. W.; Rodebaugh, R.; Fraser-Reid, B. *J. Org. Chem.* **1996**, *61*, 5280-5289.
(33) Bock, K.; Duus, J. O. *J. Carbohydr. Chem.* **1994**, *13*, 513-543.
(34) Rao, V. S. R.; Qasba, P. K.; Balaji, P. V.; Chandrasekaran, R. *Conformation of Carbohydrates*; Harwood Academic Publishers: Amsterdam, 1998.
(35) Grindley, T. B. In *Glycoscience: Chemistry and Chemical Biology*; Fraser-Reid, B., Tatsuta, K., Thiem, J., Eds.; Springer: Berlin, 2001; Vol. 1, p 3-51.
(36) Gylling Frihed, T.; Walvoort, M. T. C.; Codée, J. D. C.; van der Marel, G. A.; Bols, M.; M., P. C. *J. Org. Chem.* **2013**, *78*, 2191-2205.
(37) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1997**, *119*, 11217-11223.
(38) Crich, D.; de la Mora, M.; Vinod, A. U. *J. Org. Chem.* **2003**, *68*, 8142-8148.
(39) Mogemark, M.; Elofsson, M.; Kihlberg, J. *J. Org. Chem.* **2003**, *68*, 7281-7288.
(40) Crich, D.; Yao, Q. *J. Am. Chem. Soc.* **2004**, *126*, 8232-8236.
(41) Tanaka, H.; Takeuchi, R.; Jimbo, M.; Kuniya, N.; Takahashi, T. *Chem. Eur. J.* **2013**, *9*, 3177-3187.
(42) Zhu, T.; Boons, G.-J. *Angew. Chem. Int. Ed.* **1999**, *38*, 3495-3497.
(43) Tully, S. E.; Mabon, R.; Gama, C. I.; Tsai, S. M.; Liu, X.; Hsieh-Wilson, L. C. *J. Am. Chem. Soc.* **2004**, *126*, 7736-7737.
(44) Wang, Z.; Zhou, L.; El-Boubbou, K.; Ye, X.-s.; Huang, X. *J. Org. Chem.* **2007**, *72*, 6409-6420.
(45) Lv, X.; Cheng, S.; Wei, G.; Du, Y. *Carbohydr. Res.* **2010**, *345*, 2272-2276.
(46) Yule, J. E.; Wong, T. C.; Gandhi, S. S.; Qiu, D.; Riopel, M. A.; Koganty, R. R. *Tetrahedron Lett.* **1995**, *36*, 6839-6842.
(47) Chen, L.; Kong, F. *Tetrahedron Lett.* **2003**, *44*, 3691-3695.
(48) Bélot, F.; Jacquinet, J.-C. *Carbohydr. Res.* **2000**, *325*, 93-106.
(49) Vibert, A.; Lopin-Bon, C.; Jacquinet, J.-C. *Chem. Eur. J.* **2009**, *15*, 9561-9578.
(50) Imamura, A.; Ando, H.; Ishida, H.; Kiso, M. *J. Org. Chem.* **2009**, *74*, 3009-3023.
(51) Kumagai, D.; Miyazaki, M.; Nishimura, S.-I. *Tetrahedron Lett.* **2001**, *42*, 1953-1956.
(52) Imamura, A.; Ando, H.; Korogi, S.; Tanabe, G.; Muraoka, O.; Ishidaa, H.; Kiso, M. *Tetrahedron Lett.* **2003**, *44*, 6725-6728.
(53) Imamura, A.; Ando, H.; Ishida, H.; Kiso, M. *Org. Lett.* **2005**, *7*, 4415-4418.
(54) Imamura, A.; Ando, H.; Ishida, H.; Kiso, M. *Heterocycles* **2008**, *76*, 883-908.
(55) Imamura, A.; Kimura, A.; Ando, H.; Ishida, H.; Kiso, M. *Chem. Eur. J.* **2006**, 8862-8870.
(56) Spijker, N. M.; van Boeckel, C. A. A. *Angew. Chem. Int. Ed.* **1991**, *30*, 180-183.

(57) Bohé, L.; Crich, D. *Trends. Glycosci. Glycotech.* **2010**, *22*, 1-15.
(58) Sharma, I.; Bohé, L.; Crich, D. *Carbohydr. Res* **2012**, *357*, 126-131.
(59) Wang, C. C.; Luo, S. Y.; Shie, C. R.; Hung, S. C. *Org. Lett.* **2002**, *4*, 847-849.
(60) Liptak, A.; Jodal, I.; Herangi, J.; Nanagi, P. *Acta Chim. Hung.* **1983**, *113*, 415-422.
(61) Matwiejuk, M.; Thiem, J. *Eur. J. Org. Chem.* **2011**, 5860-5878.
(62) Satoh, H.; Manabe, S.; Ito, Y.; Luthi, H. P.; Laino, T.; Hutter, J. *J. Am. Chem. Soc.* **2011**, *133*, 5610-5619.
(63) Namchuk, M. N.; McCarter, J. D.; Becalski, A.; Andrews, T.; Withers, S. G. *J. Am. Chem. Soc.* **2000**, *122*, 1270-1277.
(64) Zhang, Z.; Ollmann, I. R.; Ye, X.-S.; Wischnat, R.; Baasov, T.; Wong, C.-H. *J. Am. Chem. Soc.* **1999**, *121*, 734-753.
(65) Koeller, K. M., Wong, C. H., *Chem. Rev.* **2000**, *100*, 4465-4493.
(66) Jensen, H. H.; Bols, M. *Acc. Chem. Res.* **2006**, *39*, 259-265.
(67) Yang, M. T.; Woerpel, K. A. *J. Org. Chem.* **2009**, *74*, 545-553.
(68) Miljkovic, M.; Yeagley, D.; Deslongchamps, P.; Dory, Y. L. *J. Org. Chem.* **1997**, *62*, 7597-7604.
(69) Smith, D. M.; Woerpel, K. A. *Org. Biomol. Chem.* **2006**, *4*, 1195-1201.
(70) Edward, J. T. *Chem. Ind.* **1955**, 1102-1104.
(71) Foster, A. B.; Overend, W. G. *Chem. Ind.* **1955**, 566-567.
(72) Eliel, E. L. *Acc. Chem. Res.* **1970**, *3*, 1-8.
(73) Kellie, G. M.; Riddel, F. G. *Top. Stereochem.* **1974**, *8*, 225-269.
(74) Lambert, J. B.; Mixan, C. E.; Johnson, D. H. *J. Am. Chem. Soc.* **1973**, *95*, 4634-4639.
(75) Padrón, J. I.; Morales, E. Q.; Vázquez, J. T. *J. Org. Chem.* **1998**, *63*, 8247-8258.
(76) Walvoort, M. T. C.; Lodder, G.; Mazurek, J.; Overkleeft, H. S.; Codée, J. D. C.; van der Marel, G. A. *J. Am. Chem. Soc.* **2009**, *131*, 12080-12081.
(77) Walvoort, M. T. C.; Moggré, G.-J.; Lodder, G.; Overkleeft, H. S.; Codée, J. D. C.; van der Marel, G. A. *J. Org. Chem.* **2011**, *76*, 7301-7315.
(78) Zeng, Y.; Wang, Z.; Whitfield, D.; Huang, X. *J. Org. Chem.* **2008**, *73*, 7952-8049.
(79) Williams, R. J.; McGill, N. W.; White, J. M.; Williams, S. J. *J. Carbohydr. Chem.* **2010**, *29*, 236-263.
(80) Liao, L.; Auzanneau, F.-I. *J. Org. Chem.* **2005**, *70*, 6265-6273.
(81) Cheng, A.; Hendel, J. L.; Colangelo, K.; Bonin, M.; Auzanneau, F.-A. *J. Org. Chem.* **2008**, *73*, 7574-7579.
(82) Pougny, J. R.; Sinaÿ, P. *Carbohydr. Res.* **1976**, *47*, 69-79.
(83) Gururaja, T. L.; Venugopalan, P.; Levine, M. J. *J. Chem. Crystallogr.* **1998**, *28*, 747-759.

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