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Reductive Openings of Benzylidene Acetals Revisited: A Mechanistic Scheme for Regio- and Stereoselectivity

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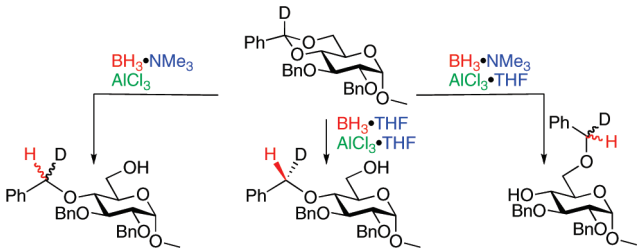

Despite the importance of regioselective reductive openings of cyclic acetals, mechanistic details are scarce. In this study 4,6-*O*-benzylidene acetals were used as model compounds for deciphering the mechanism of regioselective openings using a variety of reducing agents. Competitive isotopic studies aiming at primary and secondary isotope effects, as well as an electron-deficient substrate, were used to evaluate stereo- and regioselectivity. We show that there are three distinctly different mechanistic pathways. In nonpolar solvents, such as toluene, the acetal is activated by the very reactive naked Lewis acid to give a fully developed oxocarbenium ion that is then reduced by the borane, with low stereoselectivity. In THF the reactivity of the Lewis acid is moderated by complex formation with the solvent. These reactions are thus much slower and proceed through an intimate ion pair and thereby show high stereoselectivities. The regioselectivity in these reactions is directed by the interaction between the Lewis acid and the most nucleophilic oxygen of the acetal, thus yielding a free 6-hydroxyl group. Finally, boranes such as $BH_3 \cdot NMe_3$ are activated by Lewis acid, which results in the borane being the most electrophilic species, and consequently the reaction shows inversed regioselectivity to give a free 4-hydroxyl group. These reactions proceed through an oxocarbenium ion and thus show low stereoselectivity.

Introduction

Regioselective reductive openings of cyclic acetals have emerged into a crucial tool for protective group introduction and manipulation, widely used in modern synthetic organic chemistry. The reaction was first performed by Doukas and Fontaine in 1951 to open the acetal diosgenin by the reagent combination $LiAlH_4$ and HCl.[1] The active Lewis acid in this reaction was later established as $AlCl_3$ and the reagent combination $LiAlH_4-AlCl_3$ was intensely explored by Brown et al. for openings of both 1,3-dioxolane and 1,3-dioxane systems and by Lipták et al. to open 4,6-*O*-benzylidene acetals of various carbohydrate derivatives to give 4-*O*-benzyl ethers and free 6-hydroxyl groups.[2] Later on, Garegg and co-workers introduced the milder reagent combination $NaCNBH_3-HCl$,[3] which, interestingly, gave the opposite regioselectivity, i.e. free 4-hydroxyl groups. To get back to the original regioselectivity the Garegg group turned to boranes and found that the reagent combination $BH_3 \cdot NMe_3-AlCl_3$ gave different regioselectivity in different solvents, i.e. free 4-OH in THF and free 6-OH in toluene or dichloromethane/ether mixtures.[4]

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Today, a plethora of reagent combinations is available for regioselective reductive openings of cyclic acetals.[5] Despite the importance of these reactions for organic chemistry in general and carbohydrate chemistry in particular, the rationale for the regioselectivity is not fully understood and details for the reductive steps are scarce.[5b] In an early mechanistic proposal by Garegg[6] the regioselective outcome was explained by the difference in steric bulk between $AlCl_3$ and a proton. However, there are several problems associated with this mechanistic explanation. For example, $BH_3 \cdot NMe_3 - AlCl_3$ in THF gives 6-*O*-benzyl ethers, despite the obvious conclusion that the strongly solvated $AlCl_3 \cdot THF$ would preferably associate with the less sterically hindered O-6 to give 4-*O*-benzyl ethers.

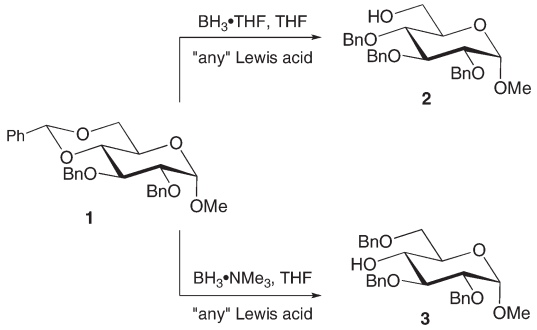
Unlike reductive openings of cyclic acetals, there is a substantial body of experiments performed on acid-mediated additions of carbon nucleophiles to acetals. This reaction was initially introduced by Mukaiyama in 1974[7] and the mechanistic details have later on been thoroughly investigated by several groups. The reaction is usually performed at low temperature, i.e. −78 °C, using the strong Lewis acid $TiCl_4$ in the nonpolar solvent CH_2Cl_2.

In a series of beautiful experiments, Denmark et al. investigated the Lewis acid-catalyzed additions of carbon nucleophiles to cyclic acetals.[8] By using low-temperature NMR experiments they observed the formation of an initial complex between the Lewis acid and the acetal.[9] Further on, Denmark and co-workers showed that this initial complex was not the reactive intermediate. Instead, the complex rapidly equilibrated with intimate and external ion pairs as well as oxocarbenium ions. This led to a stereochemical continuum from high stereoselectivity in the case of intimate ion pairs, i.e. S_N2-like reactions, to stereo randomization in the case of fully developed oxocarbenium ions.

The stereoselectivity of these nucleophilic reactions was thus shown to be dependent on steric effects in the substrate, the acetal configuration, the Lewis acid type, and stoichiometry, as well as solvent, temperature, and nucleophile concentration. Generally, reactions between sterically unhindered acetals and weak Lewis acids proceeded through intimate ion pairs while stronger Lewis acids, cation stabilization, and sterically demanding acetals resulted in the formation of oxocarbenium species. All reactions were performed at low temperatures and only solvents without the ability to form complexes with the Lewis acids were used (i.e., CH_2Cl_2, $CHCl_3$, toluene, nitroethane, and hexane).

However, the situation is completely different in polar solvents, such as THF, that will form complexes with the Lewis acids. For example, $AlCl_3$, a Lewis acid commonly used in the acid-mediated reductive openings of cyclic acetals, forms both mono- and dicoordinated complexes with THF.[10] The dissociation energy is estimated to be 90 kJ/mol for $AlCl_3 \cdot THF$ and 132 kJ/mol for $AlCl_3 \cdot 2THF$.[11] The formation of these complexes moderates the reactivity of the Lewis acid. For example, in the studies of Corcoran, it was found that the addition of even moderate amounts of THF to the acid-mediated additions of carbon nucleophiles resulted in a distinctly lowered reactivity.[12] While reactions in CH_2Cl_2 generally were completed in less than 2.5 h at −78 °C, the addition of 20% THF resulted in reaction times of 6 h at 0 °C. It is thus highly reasonable to assume that the mechanism of Lewis acid-mediated reductions of cyclic acetals, which are usually performed in THF at room temperature, differ from reactions with carbon nucleophiles in nonpolar solvents at low temperatures.

SCHEME 1. The Regioselectivity of Reductive Openings of Benzylidene Acetals in THF Is Dependent on the Borane Rather than the Lewis Acid



The reductive opening of methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (**1**) to give either the free 6-OH (i.e., compound **2**) or the free 4-OH (i.e., compound **3**) is often used as a model system for these reactions (Scheme 1). From our own investigations as well as examples from the literature, we found that the regioselectivity in THF is dependent on the type of borane (i.e., BH_3 complexed to NMe_3 or THF) used for the reduction rather than the Lewis acid (e.g., $AlCl_3$, $BF_3 \cdot OEt_2$, $In(OTf)_3$, AgOTf, or $Cu(OTf)_2$).[13−15]

This led us to the conclusion that the selectivity can be found in the activation of certain borane complexes by Lewis acids, and in previous publications we have explored a mechanism based on borane activation.[13] In nonpolar solvents, such as toluene, the unsolvated $AlCl_3$ is by far the strongest Lewis acid and it will form an initial complex with the most nucleophilic acetal oxygen, i.e. O-6 of the model compound **1** (Scheme 2, Path A). The importance of the nucleophilicity of O-6 for the rate and regioselectivity of acid-mediated reductive openings of benzylidene acetals has been discussed in several recent reports[13b,14,15] and is supported by calculations.[16] The situation in THF is

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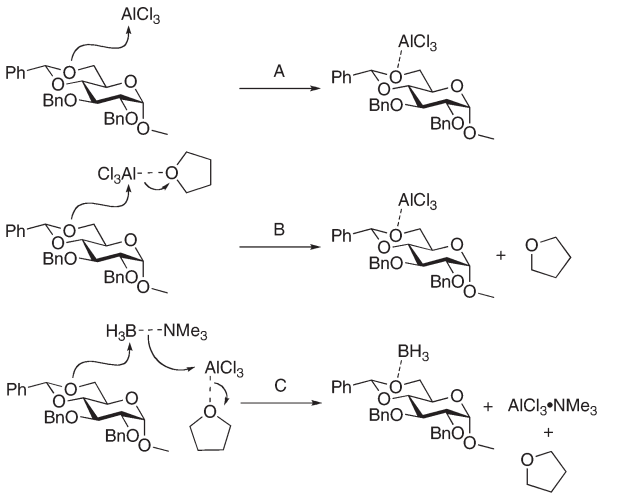
(16) The electrostatic potential for compound **1** was calculated by using density functional theory at the B3LYP/6-31G* level and default settings in Spartan '02 for Macintosh, Wave function, Inc., Irvine, CA. O-4: −32.9040 kcal/mol; O-6: −36.5412 kcal/mol.

SCHEME 2. The Regiochemical Outcome Is Directed by the Relative Nucleophilicity of the Acetal Oxygens Toward the Free Lewis Acid in Toluene (Path A), the Solvated Lewis Acid in THF (Path B), or the Activated Borane (Path C)



slightly different. The strongly solvated $AlCl_3 \cdot THF$ is a stronger Lewis acid compared to $BH_3 \cdot THF$ but both are relatively inactive compared to the naked Lewis acid in nonpolar solvents (Scheme 2, Path B). The reaction in THF is thus slow and might take several hours to reach completion, even at room temperature, whereas reactions in toluene are usually completed within minutes. The regioselectivities in these two cases are both directed by the initial complex between the Lewis acid and the more nucleophilic O-6.

The use of $BH_3 \cdot NMe_3$ as the reducing agent results in the opposite regioselectivity. To deduce the mechanism for this reaction we performed a series of kinetic experiments, ^{11}B NMR spectroscopy, and Hammett plots.[13b] At the beginning of the reaction, only $BH_3 \cdot NMe_3$ was seen in the ^{11}B NMR spectrum. However, over the course of the reaction we observed the build-up of a new peak, which corresponded to a BH_2 group bound to oxygen. We could not detect any traces of $Me_3NBH_2^+$. These data suggest that the borane is cleaved from the amine during the course of the reaction. Interestingly, when we added $AlCl_3$ to a solution of $BH_3 \cdot NMe_3$ in THF, we could not detect any reaction. However, on addition of the acetal, the reaction took place. Our conclusion is that, in the presence of the acetal, $AlCl_3 \cdot THF$ activates $BH_3 \cdot NMe_3$, which renders the borane the most electrophilic species.[13b] Consequently, the regioselectivity is now directed by addition of the borane to the more nucleophilic O-6, giving the opposite product (Scheme 2, Path C). This suggestion is further backed up by similar experiments using $BF_3 \cdot OEt_2$ or metal triflates as the Lewis acid. The complex $AlCl_3 \cdot NMe_3$ is very strong (199 kJ mol^{-1}) compared to the analogous $BF_3 \cdot NMe_3$ (130 kJ mol^{-1}). According to our activation theory, reactions using $BF_3 \cdot OEt_2$ should thus not activate the reaction to the same degree, and indeed we observed a much slower reaction rate using $BF_3 \cdot OEt_2$ compared to $AlCl_3 \cdot THF$.[13c]

To further explore the mechanism and to categorize different reagent combinations, we investigated the reaction kinetics for a number of reductive openings of compound **1**.[13c] Openings to give free 6-OH (i.e., compound **2**), using $BH_3 \cdot THF - AlCl_3 - THF$ or $LiAlH_4 - AlCl_3 - Et_2O$, follow first order kinetics. On the contrary, reactions yielding free 4-OH (i.e., compound **3**),

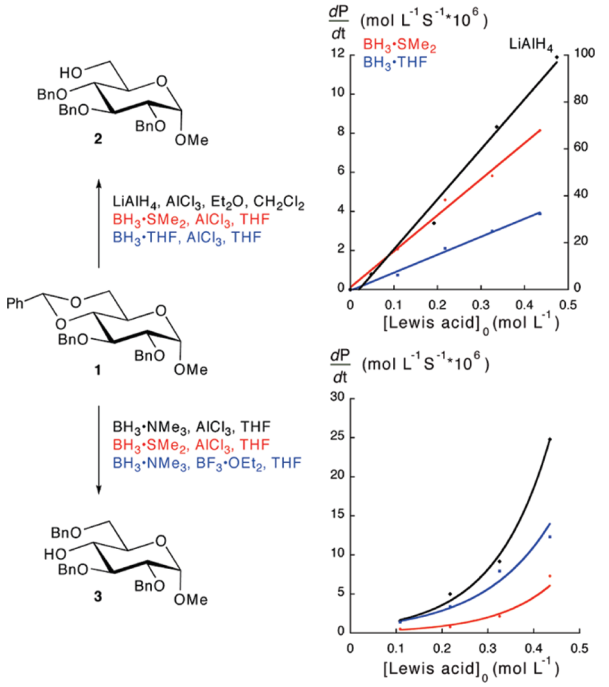


FIGURE 1. Summary of kinetic studies of acetal openings. Reactions opening the acetal to a free 6-hydroxyl group follow first order kinetics (top graph: $LiAlH_4$, black diamonds [right *y*-axis];, $BH_3 \cdot SMe_2$, red circles; and $BH_3 \cdot THF$, blue squares), while reactions to a free 4-hydroxyl group follow higher order kinetics (bottom graph: $BH_3 \cdot NMe_3 - AlCl_3$, black diamonds; $BH_3 \cdot SMe_2 - AlCl_3$, red circles; and $BH_3 \cdot NMe_3 - AlCl_3$, blue squares). Graphs derived from data in ref [13c].

using $BH_3 \cdot NMe_3 - AlCl_3 - THF$ or $BH_3 \cdot NMe_3 - BF_3 \cdot OEt_2 - THF$, follow higher order kinetics. The higher order dependency with respect to $AlCl_3$ can be explained from the necessity of a second Lewis acid molecule for activation of the initial complex. This mechanism will be further discussed (vide infra). The $BH_3 \cdot SMe_2 - AlCl_3 - THF$ system constitutes a borderline case (dissociation energies: $BH_3 \cdot THF$ 83 kJ/mol; $BH_3 \cdot SMe_2$ 101 kJ/mol; $BH_3 \cdot NMe_3$ 160 kJ/mol) yielding mostly free 6-OH (by a first order reaction) but also free 4-OH (by a higher order reaction). These results are summarized in Figure 1. Due to the very fast reaction rates of both the original (i.e., $NaCNBH_3$) and the modified (i.e., $BH_3 \cdot NMe_3$ in toluene) Garegg conditions, we were not able to investigate the kinetics of these reactions.

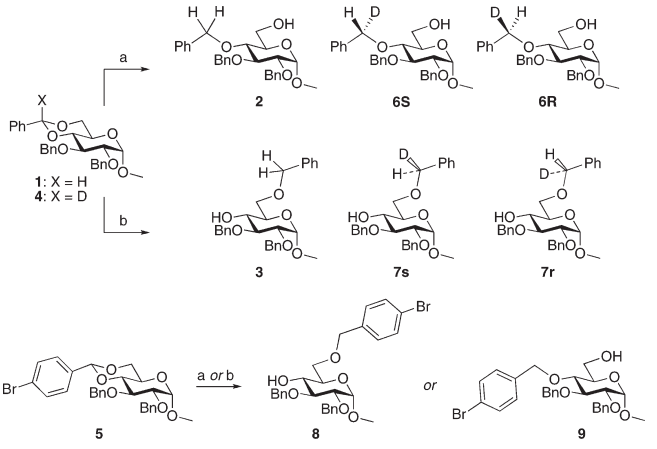
Clearly, reactions using activated and unactivated boranes follow different mechanistic routes and cannot be described by one unifying mechanism, but rather by a mechanistic scheme.

The aims of this investigation are to (i) investigate reactions in nonpolar solvents to position them in the frame of the Denmark mechanistic scheme; (ii) to investigate reactions with unactivated boranes in THF with respect to regio- and stereoselectivity, (iii) to investigate reactions with activated boranes in THF to explore the mechanistic details, and (iv) to categorize the original and the modified Garegg reactions.

Results and Discussion

To explore the stereochemical outcomes of these reductions, as well as secondary isotope effects, we synthesized the deuterium-labeled benzylidene acetal, i.e. methyl 2,3-di-*O*-benzyl-4,6-*O*-(benzylidene-1-*d*)-α-D-glucopyranoside (**4**) from benzaldehyde-α-d_1. In addition, methyl 2,3-di-*O*-benzyl-4,6-*O*-(*p*-bromobenzylidene)-α-D-glucopyranoside (**5**) was synthesized to

SCHEME 3. Reductive Openings of Benzylidene Acetals: (a) Openings To Free 6-OH and (b) Openings To Free 4-OH[a]



[a]Product distributions were determined based on NMR spectroscopy. The stereochemical assignments of **6R** and **6S** were made by 2-dimensional NMR (COSY and NOESY experiments) and confirmed by previously published data.[14] The shift for benzylic proton on **6S** is 4.63 ppm and the benzylic proton on **6R** is 4.86 ppm. The absolute stereochemistry for **7** could not be determined and the r and s designation is arbitrary. The shift for the benzylic proton of **7r** is 4.57 ppm and the benzylic proton of **7s** is 4.53 ppm.[17].

explore electronic effects (Scheme 3). The *p*-bromobenzylidene group was chosen to give a small but measurable electron-withdrawing effect compared to the unsubstituted compound **1** (Hammett $\sigma_{para}(Br) = 0.26$).

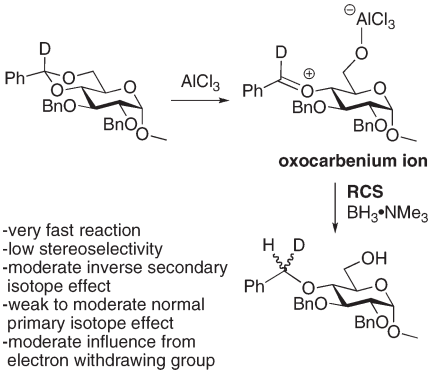
A. Reactions in Nonpolar Solvents. We first investigated the modified Garegg conditions, i.e. $BH_3 \cdot NMe_3 - AlCl_3$ in toluene. The deuterium-labeled compound **4** was thus opened using undeuterated $BH_3 \cdot NMe_3$ and $AlCl_3$ in toluene at room temperature. These reactions were completed in less than 5 min, which further demonstrate the high reactivity of the naked Lewis acid in the nonpolar solvent toluene. The product distribution was determined based on NMR spectroscopy.[17] The results are summarized in Table 1. The reaction gave a stereoisomeric ratio **6S**:**6R** of 42:58, which points to a significant degree of oxocarbenium ion character of the reactive intermediate. To further investigate the mechanism, we performed competitive isotope studies where equimolar mixtures of **1** and **4** were reductively opened using $BH_3 \cdot NMe_3 - AlCl_3$ in toluene and the distribution between **2** and **6S**/**R** was determined by NMR spectroscopy.[17] We thus observed an inverse secondary isotope effect of 0.92. An inverse, rather than a normal, secondary kinetic isotope effect can be explained by either an S_N2-type reaction, where the carbon is more available for the deuterated compound, or a reaction mechanism where the rate-controlling step (RCS) involves a change in hybridization of the former acetal carbon from sp^2 to sp^3. In our case, the latter explanation is the most plausible, taken into consideration the low stereoselectivity observed in the reaction. Primary isotope effects were determined for the opening of **1** using equimolar mixtures of $BH_3 \cdot NMe_3/BD_3 \cdot NMe_3$ under the conditions of entry 1 in Table 1 to give mixtures of **2** and **6**. Reaction for 4 min (34% yield) gave an isotope effect of 2.8, while shorter reaction time (2 min, 29% yield) gave a similar effect (2.6). This primary isotope effect can be explained by a very fast formation of the oxocarbenium ion followed by a slower reductive step. However, since this competitive experiment only shows the relative reaction rates of the reduction of the intermediate oxocarbenium ion, the data are not conclusive for determination of the RCS. Finally, to investigate electronic effects, we performed a competitive study using equimolar mixtures of **1** and the *p*-bromobenzylidene analogue **5** (Scheme 2, Table 1). This reaction gave a **2**:**9** ratio of 58:42, i.e. a modest discrimination for the more electron rich **1** over **5**.

TABLE 1. Reductive Openings To Free 6-OH in Toluene

entry	reagent combination	ratio **6S**:**6R**[a]	2° KIE (**2**:**6**)[b]	1° IE (**2**:**6**)[c]	ratio **2**:**9**[d]
1	$BH_3 \cdot NMe_3 - AlCl_3$ − toluene	42:58	0.92	2.8	58:42

[a]**4** was opened with undeuterated reagents. [b]Equimolar mixtures of **1** and **4** were reductively opened using undeuterated reducing agents. [c]**1** was opened using equimolar mixtures of deuterated and undeuterated reagents. [d]Equimolar mixtures of **1** and **5** were opened using undeuterated reducing agents.

SCHEME 4. Mechanistic Details of Reductive Opening To Give a Free 6-OH in Toluene



The low stereoselectivity, in combination with the inverse secondary isotope effect and the low discrimination shown by the electron-withdrawing group suggest that the reaction proceeds with a fast formation of an oxocarbenium ion followed by a rate-controlling reductive step (Scheme 4).

Lewis acid-mediated nucleophilic substitutions of cyclic acetals using $TiCl_4$ in nonpolar solvents, usually CH_2Cl_2, have been investigated by several groups. Mori et al.[18] showed that nucleophilic substitutions, which are similar to the reductive openings using $AlCl_3$ in toluene, proceed through an oxocarbenium ion. Further on, Yamamoto et al. investigated the importance of the nucleophilicity of the carbon nucleophiles used in Lewis acid-mediated nucleophilic substitutions to cyclic acetals.[19] The results indicated that, in nonpolar solvents (CH_2Cl_2) using the strong Lewis acid $TiCl_4$, carbon nucleophiles with low nucleophilicity, i.e. silicon- and boron-substituted compounds, generally react through the oxocarbenium ion pathway while strong nucleophiles, i.e. tributylstannyl derivatives, react through an S_N2 pathway. Denmark and Almstead also

(17) The peaks were overlapping and the areas for each compound were calculated from several ^1H NMR spectra at 400 or 500 MHz in $CDCl_3$ and C_6D_6.

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TABLE 2. Reductive Openings To Free 6-OH

entry	reagent combination	ratio **6S**:**6R**[a]	2° KIE (**2**:**6**)[b]	1° IE (**2**:**6**)[c]	ratio **2**:**9**[d]
1	$BH_3\cdot THF-AlCl_3-THF$	97:3	0.85	2.4	73:27
2	$BH_3\cdot SMe_2-AlCl_3-THF$	97:3			
3	$LiAlH_4-AlCl_3-Et_2O-CH_2Cl_2$	96:4	0.92		

[a]**4** was opened with undeuterated reagents. [b]Equimolar mixtures of **1** and **4** were reductively opened using undeuterated reducing agents. [c]**1** was opened using equimolar mixtures of deuterated and undeuterated reagents. [d]Equimolar mixtures of **1** and **5** were opened using undeuterated reducing agents.

investigated the importance of the nucleophile and came to similar conclusions.[20]

Finally, in an ingeniously designed experiment using a deuterated acetal, Sammakia and Smith showed that nucleophilic addition of allylstannes, mediated by $TiCl_4$ in CH_2Cl_2, proceeds through an oxocarbenium intermediate.[21] Reductive openings using $BH_3\cdot NMe_3-AlCl_3$ in the nonpolar solvent toluene thus represent one extreme in the mechanistic scheme presented by Denmark et al. Since no strong complexes can be formed between toluene and $AlCl_3$, reactions in this solvent give "naked" and very reactive Lewis acids and consequently proceed via fully developed oxocarbenium ions with low stereoselectivity in the reductive step.

To further emphasize the importance of the naked Lewis acid in nonpolar solvents we repeated the reductive opening of the model compound **1** using $AlCl_3\cdot THF$ and $BH_3\cdot NMe_3$ in toluene. Thus, $AlCl_3$ was dissolved in THF, stirred at room temperature for 1 h, and then dried under vacuum to yield $AlCl_3\cdot THF$. Compound **1** was then opened with this reagent to give a 63:37 mixture of **2** and **3**. Thus, by simply using $AlCl_3\cdot THF$ instead of $AlCl_3$ we were able to partly reverse the regioselectivity. To conclude, since $AlCl_3$ is very reactive in nonpolar solvents such as toluene, it will react with the more nucleophilic oxygen of the acetal rather than activate $BH_3\cdot NMe_3$. Thus, the Lewis acid will form an initial complex with the acetal oxygen, and the acetal is opened to an oxocarbenium ion. On the contrary, by complexation with THF, the reactivity is lowered and a viable reaction pathway is a tandem reaction with formation of $AlCl_3\cdot NMe_3$ resulting in reversed regioselectivity as discussed in detail in section C below, as well as a normal complexation with the acetal as described in section B.

B. Reductive Openings Using Unactivated Boranes in THF. Compound **4** was opened by reductive conditions aiming at a free 6-OH (Scheme 3, path a) and the product distribution was determined based on NMR spectroscopy.[17] The results are summarized in Table 2.

The reagent combinations $BH_3\cdot THF-AlCl_3-THF$ and $BH_3\cdot SMe_2-AlCl_3-THF$, as well as the original Lipták conditions using $LiAlH_4-AlCl_3-Et_2O-CH_2Cl_2$, resulted in high stereoselectivities (approximately 97:3). Since the three different reagents result in similar stereoselectivities we assume that they follow a reaction mechanism with a highly ordered reactive intermediate. To further investigate the mechanism, we performed competitive isotope studies where equimolar mixtures of **1** and **4** were reductively opened using $BH_3\cdot THF-AlCl_3-THF$. Reactions were run for different times and the distribution between **2** and **6S**/**R** was determined by NMR spectroscopy.[17] We thus

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(21) (a) Sammakia, T.; Smith, R. S. *J. Am. Chem. Soc.* **1992**, *114*, 10998–10999. (b) Sammakia, T.; Smith, R. S. *J. Am. Chem. Soc.* **1994**, *116*, 7915–7916.

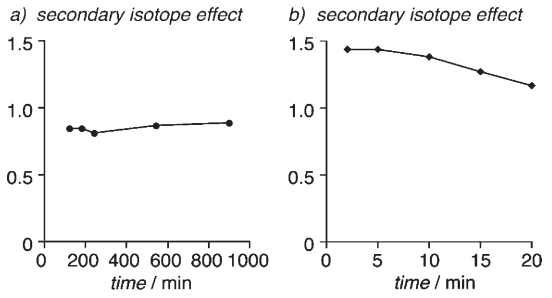
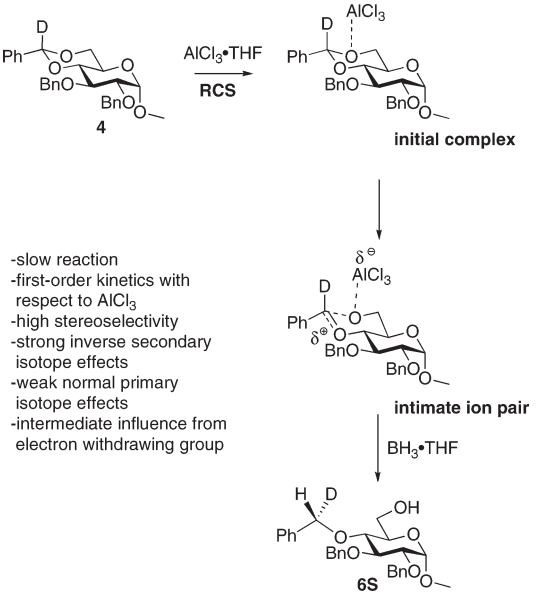


FIGURE 2. Competitive isotope study of reductive opening of equimolar mixtures of **1** and **4** using (a) $BH_3\cdot THF-AlCl_3-THF$ and (b) $BH_3\cdot NMe_3-AlCl_3-THF$.

SCHEME 5. Mechanistic Details of Reductive Opening To Give a Free 6-OH in THF



observed a secondary isotope effect of 0.85, independent of reaction time (Figure 2a). A similar result was obtained for the original Lipták conditions (Table 2, entry 3).

The combination of high stereoselectivities and a strong inverse secondary kinetic isotope effect can be explained by an S_N2-type reaction, where the carbon is more available for the deuterated compound. Primary isotope effects were determined for the opening of **1** using equimolar mixtures of $BH_3\cdot THF$/$BD_3\cdot THF$ under the conditions of entry 1 in Table 2 to give mixtures of **2** and **6**. Reaction for 40 min (11% yield) gave an isotope effect of 2.4, while longer reaction times (60 min, 20% yield) lowered the effect to 1.4. This weak primary isotope effect may indicate that the reductive step is not the rate-controlling step. Finally, to investigate electronic effects, we performed a competitive study using equimolar mixtures of **1** and the *p*-bromobenzylidene analogue **5** (Scheme 3). The reaction was run for 2 h (17% isolated yield) to give a 73:27 ratio of **2**:**9**. Longer reaction times (7.5 h) gave only minor changes (ratio 76:24). Since the reaction is slow, compared to reactions in nonpolar solvents, and shows first-order kinetics with respect to $AlCl_3$, we propose that the rate-controlling step is the formation of an initial complex (Scheme 5). This initial complex is then, in full accordance with Denmark's findings,[9] equilibrated into an intimate ion pair, with low oxocarbenium ion character.

The intimate ion pair is subsequently reduced by the reductive agent, resulting in high stereoselectivity. The major diastereomer is the one expected from a direct attack on the intimate ion pair.

These data then represent the other extreme in the Denmark mechanistic scheme, i.e. the intimate ion pair. Our observations are thus in full accordance with earlier studies, where reactions between sterically unhindered acetals and weak Lewis acids usually proceeded through intimate ion pairs.[8] It is reasonable to assume that the complex $AlCl_3 \cdot THF$ is a substantially weaker Lewis acid compared to $AlCl_3$ in toluene.

C. Reductive Openings Using Activated Boranes in THF. Amine boranes are versatile reducing agents and their reactions have been thoroughly studied in reactions such as hydroboration, reduction of ketones, and hydrolysis. Despite their importance, mechanistic details of the reductive openings of acetals are nonexistent. However, some conclusions can be drawn from the results by Brown and co-workers on acid-catalyzed reduction of ketones.[22] Brown propose three different mechanistic possibilities for reactions using borane−amine complexes in combination with acids: (A) prior dissociation of the borane−amine complex in the presence of acidic solvents, (B) activation of the reducible group by interaction with the acid, or (C) activation of the borane−amine complex by association with the Lewis acid. In a series of experiments Brown et al. observed that the mechanism of reduction of cyclohexanone using $BH_3 \cdot NMe_3$ was drastically different in THF compared to that in acetic acid. This is similar to findings by Jones, who observed the same stereoselectivity in the reduction of 4-*tert*-butylcyclohexanone by diborane or $BH_3 \cdot NMe_3$ in the absence of acid.[23] However, in the presence of $BF_3 \cdot OEt_2$, the stereochemical outcome was essentially the same using diborane but changed dramatically using the $BH_3 \cdot NMe_3$. Similar to our findings, Jones also observed a strong rate enhancement in the acid-catalyzed reactions. Other clues can be found in the hydrolysis reactions of borane−amine complexes, where the hydrolysis of $BH_3 \cdot NMe_3$ follows first order dependency in both acid and borane, which indicates initial association of the acid to the complex.[24] Later investigations of the reactions with amine boranes with carbenium ions showed first order dependency with respect to both the borane−amine complex and the carbenium ion, and a primary kinetic isotope effect of 1.81, which points toward a polar transition state.[25] In an interesting paper by Hung and co-workers, compound **1** was reductively opened using a variety of borane reagents in combination with a catalytic amount of $Cu(OTf)_2$.[14] The regioselectivities were similar to our findings and the reaction rates were closely associated with the nucleophilicity of O-6. Furthermore, the use of $BD_3 \cdot THF$ in combination with $Cu(OTf)_2$ in THF gave a stereoselectivity (i.e., 5:1) in full agreement with our results for unactivated boranes (section B). Reduction using Et_3SiH and a catalytic amount of $Cu(OTf)_2$ gave regioselective opening to a free 4-OH. Interestingly, this reaction showed stereo randomization, similar to openings using activated boranes.

We have earlier proposed a mechanistic explanation for the regioselectivity for the reduction using $BH_3 \cdot NMe_3$,[13b] where the addition of the hydrogen took place in a similar fashion as the mechanistic proposal by Saito et al.[26] This was obviously an oversimplified picture and we now present a more detailed study of the reaction mechanism. Compound **1** was thus opened by conditions aiming at a free 4-OH, as illustrated in Scheme 3, Path b. The distribution between **7r**/**s** was determined by NMR spectroscopy (Table 3).

TABLE 3. Reductive Openings To Free 4-OH in THF

entry	reagent	ratio **7r**:**7s**[a]	2° KIE (**3**:**7**)[b]	1° IE (**3**:**7**)[c]	ratio **3**:**8**[d]
1	$BH_3 \cdot NMe_3-AlCl_3-THF$	57:43	1.4	4.9	87:13
2	$BH_3 \cdot NMe_3-AlCl_3-H_2O-THF$	58:42			
3	$BH_3 \cdot SMe_2-AlCl_3-THF$	52:48			
4	$NaCNBH_3-HCl-Et_2O-THF$	56:44	1.4		

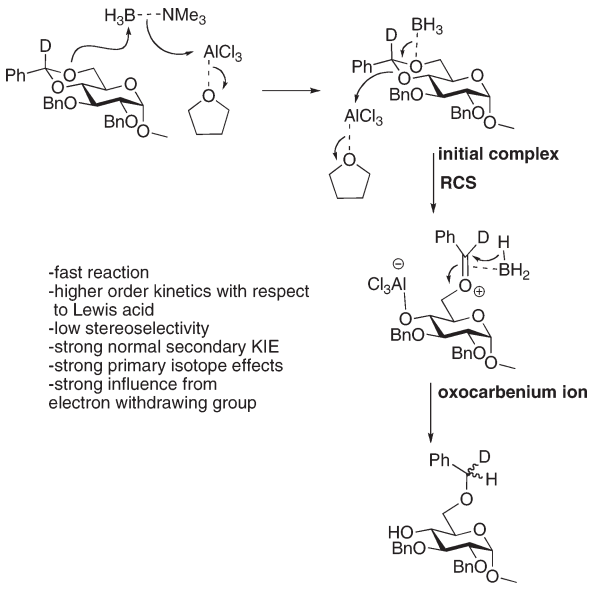
[a] **4** was opened with undeuterated reagents. [b] Equimolar mixtures of **1** and **4** were opened using undeuterated reducing agents. [c] **1** was opened using equimolar mixtures of deuterated and undeuterated reagents. [d] Equimolar mixtures of **1** and **5** were opened using undeuterated reducing agents.

The opening of compound **4**, using $BH_3 \cdot NMe_3$ activated by $AlCl_3$, gave a 57:43 ratio of **7r**:**7s** (Table 3, entry 1). We have earlier shown that $BH_3 \cdot NMe_3$ can be activated by Lewis acids (i.e., $AlCl_3$ or $BF_3 \cdot OEt_2$) as well as Brønsted acids (i.e., water in combination with $AlCl_3$) and it is well-known that a small amount of water speeds up the reductive openings of benzylidene acetals.[27] Reduction of **4**, using $BH_3 \cdot NMe_3$ activated by $AlCl_3$ and water gave a similar ratio of **7r**:**7s** (Table 3, entry 2). The opening of **4** using $BH_3 \cdot SMe_2-AlCl_3$ gave **6** as the major product (Table 2, 72%). In addition we isolated **7** (11%) in a 52:48 ratio of r:s (Table 3, entry 3). Finally, the original Garegg conditions (Table 2, entry 4) gave similar stereochemical outcome and it is reasonable that $NaCNBH_3$ is activated by the Brønsted acid to give H_2BCN that reacts analogous to BH_3.[28] These data indicate a less ordered reactive intermediate, possibly an oxocarbenium ion, in reactions yielding a free 4-OH. Further on, we performed competitive isotope studies with equimolar mixtures of **1** and **4**, opened by $BH_3 \cdot NMe_3-AlCl_3-THF$ (Table 3, entry 1). Reactions were run for different times and the distribution between **3**, **7s**, and **7r** was determined by NMR spectroscopy.[17] We thus found the isotope effect to be time dependent (Figure 2b) and a normal secondary isotope effect of 1.4 was determined from the kinetic region. Similar experiments using $NaCNBH_3-HCl-THF$ gave comparable isotope effects (Table 3, entry 4). A normal secondary isotope effect indicates that the rehybridization in the transition state goes from sp^3 to sp^2. In this case it would point to formation of an oxocarbenium ion as the rate-controlling step.

Primary isotope effects were determined for the opening of **1** using equimolar mixtures of $BH_3 \cdot NMe_3/BD_3 \cdot NMe_3$. The $BD_3 \cdot NMe_3$ reagent was prepared by mixing $BD_3 \cdot THF$ with an equal amount of NMe_3 in THF prior to the reaction. The primary isotope effects were time dependent and shifted from 4.9 (2 min) to 1.6 (10 min). Several different effects can explain the origin of these rather strong "primary" isotope effects. First, a normal primary kinetic isotope effect can probably be seen from the transfer of the hydride/deuteride. Second, other isotope effects may arise from differences in dissociation constants for $BD_3 \cdot NMe_3$ and $BH_3 \cdot NMe_3$. Similar experiments using 1:1 mixtures of $NaCNBH_3/NaCNBD_3$ indicated an exchange of deuterium in the reducing agent and no primary effects could be

(22) Brown, H. C.; Murray, L. T. *Inorg. Chem.* **1984**, *23*, 2746–2753.
(23) Jones, W. M. *J. Am. Chem. Soc.* **1960**, *82*, 2528–2532.
(24) Ryschkewitsch, G. E. *J. Am. Chem. Soc.* **1960**, *82*, 3290–3294.
(25) Funke, M.-A.; Mayr, H. *Chem.—Eur. J.* **1997**, *3*, 1214–1222.
(26) Saito, S.; Kuroda, A.; Tanaka, K.; Kimura, R. *Synlett* **1996**, 231–233.
(27) (a) Hernández-Torres, J. M.; Achkar, J.; Wei, A. *J. Org. Chem.* **2004**, *69*, 7206–7211. (b) Sherman, A. A.; Mironov, Y. V.; Yudina, O. N.; Nifantiev, N. E. *Carbohydr. Res.* **2003**, *338*, 697–703.
(28) Lane, C. F. *Aldrichim. Acta* **1975**, *8*, 3–10.

SCHEME 6. Mechanistic Details of Reductive Opening To Give a Free 4-OH in THF



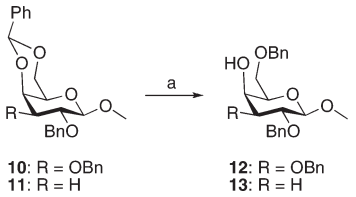
reliably measured, i.e. reactions with HCl gave an isotope effect of 2.7 while DCl lowered the effect to 1.1. A control experiment using only $NaCNBD_3$ (96% D) gave a large proportion (43%) of the unlabeled compound **3**. It is thus reasonable to assume that the Brønsted acid catalyzed the exchange of deuterium for hydrogen in the reducing agent. The reverse reaction with DCl has been reported for $BH_3 \cdot NMe_3$.[29] Finally, to investigate electronic effects, we performed a competitive study using a 1:1 mixture of **1** and the *p*-bromobenzylidene analogue **5**. Short reaction times (4 min) gave an 87:13 ratio of **3**:**8** while longer reaction times (2.5 h) diminished the ratio slightly to 83:17. The rather strong influence of the electron-withdrawing group also points toward a rate-controlling formation of an oxocarbenium ion. We thus propose a mechanistic scheme where the regioselectivity is determined by the fast formation of an initial complex with the borane, activated by the Lewis acid. This initial complex is then transformed into an oxocarbenium ion, aided by a second equivalent of the Lewis acid, in the rate-controlling step. Hence the π-electrons are considered to be donated into the vacant p-orbital of the borane prior to the fast reduction (Scheme 6). The oxocarbenium ion is then reduced with low stereoselectivity to give the free 4-OH.

To exclude the possibility of steric rather than stereoelectronic explanations for these results, we also included reductive openings of two galactose derivatives with different degrees of steric hindrance toward O-4 (Scheme 7).

Opening of methyl 2,3-di-*O*-benzyl-4,6-*O*-(benzylidene)-β-D-galactopyranoside (**10**) using $BD_3 \cdot NMe_3$ and $AlCl_3$ gave, as expected, a free 4-hydroxyl group (i.e compound **12**) with low stereoselectivity, i.e. 61:39 (Supporting Information), similar to earlier results using compound **1**.[3b,4a] Reductive openings of the less sterically hindered **11** using $BH_3 \cdot NMe_3$ and $AlCl_3$ gave mainly opening to free 4-OH (i.e., compound **13**, 94%) with only minor reverse opening (6%). This means that, despite the lowered steric hindrance for O-4, the reaction still proceeds to give free 4-OH rather than 6-OH. Thus, these

(29) Davis, R. E.; Brown, A. E.; Hopmann, R.; Kibby, C. L. *J. Am. Chem. Soc.* **1963**, *85*, 487.

SCHEME 7. Reductive Openings of Galactose Derivatives[a]



[a]Conditions: (a) $BH_3 \cdot NMe_3$, $AlCl_3$, THF.

data render a steric explanation for the regioselectivity less plausible. The analogous reductive opening of compound **10** using unactivated $BD_3 \cdot THF$ and $AlCl_3$ resulted in a free 6-OH group with a high stereoselectivity of 87:13 (Supporting Information), in full accordance with our results described in section B.[2c]

Conclusions

We conclude that the regioselectivity of Lewis acid-catalyzed reductive openings of benzylidene acetals can be directed by the reducing reagent. In the case of unactivated boranes and alanes (e.g., $BH_3 \cdot THF$ or $LiAlH_4$), the regioselectivity is directed by the complexation of the Lewis acid (e.g., $AlCl_3$) with the most electron-rich oxygen of the acetal to give free 6-OH. The stereoselectivities depend on the solvent and represent a mechanistic continuum from an intimate ion pair in THF, resulting in high stereoselectivity, to fully developed oxocarbenium ions in toluene. The latter reaction, which is very fast due to naked Lewis acids, results in stereo randomization. In THF, the Lewis acid is complexed to the solvent (e.g., $AlCl_3 \cdot THF$) and these reactions are thus significantly slower and much more selective compared to reactions in nonpolar solvents. On the contrary, activation of boranes (e.g., $BH_3 \cdot NMe_3$) using Lewis or Brønsted acids results in the borane being the most electrophilic species that will form an initial complex with the most electron-rich oxygen of the acetal. These reactions, which result in free 4-OH, proceed through an oxocarbenium ion, and thus give low stereoselectivity. The mechanistic scheme is summarized in Scheme 8.

These mechanistic details provide a foundation for the design and limitations of new reducing agents for acetals. It is most certainly possible to fine-tune the reactivity and selectivity by a well-designed combination of borane, solvent, Lewis acid, and temperature as indicated by the plethora of reagents presented for this reaction.[13b]

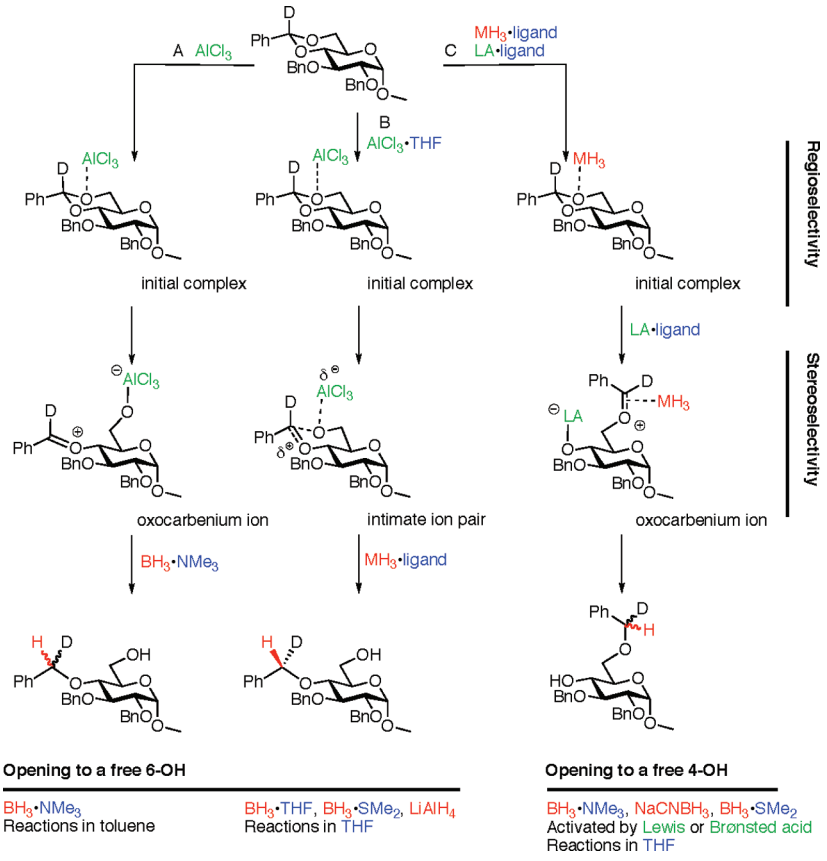
Experimental Section

For general experimental details and detailed experimental conditions see the Supporting Information.

General Procedure for Reductive Openings of Compounds 1, 4, and 5. Compounds **1**, **4**, or mixtures of **1**:**4** or **1**:**5** (0.11 mmol) were dissolved in suitable solvents (THF, CH_2Cl_2:Et_2O, or toluene). The reducing agent ($BH_3 \cdot NMe_3$, $BD_3 \cdot NMe_3$, $BH_3 \cdot SMe_2$, $BH_3 \cdot THF$, $BD_3 \cdot THF$, $LiAlH_4$, $LiAlD_4$, $NaCNBH_3$, or $NaCNBD_3$) was added followed by the acid ($AlCl_3$, HCl, or DCl) and the mixtures were stirred for suitable time periods (2 min to 3.5 h). The mixtures were diluted with ether and washed once with $NaHCO_3$ (sat. aq.) and concentrated from toluene. The residue was chromatographed (SiO_2, toluene/EtOAc 5:1) to give the product.

Methyl 2,3-Di-*O*-benzyl-4,6-*O*-(benzylidene-1-*d*)-α-D-glucopyranoside (4). Benzaldehyde-α-d_1 (0.45 mL, 4.43 mmol) was dissolved in MeOH (4 mL). $CH(OCH_3)_3$ (0.83 mL, 7.59 mmol) was added followed by Amberlite IR-120 H^+ (19 mg). The mixture was heated

SCHEME 8. Mechanistic Proposal for Reductive Openings of 4,6-*O*-Benzylidene Acetals



in a microwave to 75 °C for 30 min, filtered, and concentrated to give the corresponding α,α-dimethoxy acetal. The α,α-dimethoxy acetal was dissolved in MeCN (10 mL) followed by addition of methyl α-D-glucopyranoside (723 mg, 3.72 mmol) and *p*TSA (29 mg, 0.15 mmol). The mixture was stirred at rt and then refluxed for 21 h. NEt_3 (2 mL) was added and the mixture was concentrated. The residue was chromatographed (SiO_2, toluene/EtOAc 1:2) to give methyl 4,6-*O*-(benzylidene-1-*d*)-α-D-glucopyranoside (365 mg, 35%). $[\alpha]^{20}_D$ +112.0 (*c* 0.4, $CDCl_3$). ^1H NMR ($CDCl_3$) δ 7.48−7.50 (m, 2H, Ar), 7.35−7.39 (m, 3H, Ar), 4.79 (d, 1H, J = 3.9 Hz, H-1), 4.29 (dd, 1H, J = 9.6, 4.3 Hz, H-6), 3.92 (t, 1H, J = 9.2 Hz, H-3), 3.71−3.84 (m, 2H, H-5, H-6), 3.62 (dd, 1H, J = 9.0, 3.7 Hz, H-2), 3.49 (t, 1H, J = 9.3 Hz, H-4), 3.45 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 137.1, 129.4, 128.5, 126.4, 101.7 (t, J = 24.8 Hz), 99.9, 81.0, 73.0, 71.9, 69.0, 62.5, 55.7. HRMS calcd for $C_{14}H_{17}DO_6Na$ (M + Na) 306.1064, found 306.1065. Methyl 4,6-*O*-(benzylidene-1-*d*)-α-D-glucopyranoside (362 mg, 1.28 mmol) and TBAI (49 mg, 0.13 mmol) were dissolved in DMF (10 mL) and the mixture was cooled to 0 °C under N_2. After 15 min, NaH (381 mg, 60% in oil) was added, and after an additional 30 min benzyl bromide (0.38 mL, 3.19 mmol), then the mixture was stirred for 105 min. NH_4Cl (sat. aq.) was added and the mixture was extracted two times with ether. The combined organic phases were washed once with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed (SiO_2, toluene/EtOAc 4:1) to give **4** (578 mg, 97%). $[\alpha]^{20}_D$ −25.0 (*c* 1.0, $CDCl_3$). ^1H NMR ($CDCl_3$) δ 7.48−7.50 (m, 2H, Ar), 7.28−7.41 (m, 13H, Ar), 4.84, 4.91 (ABq, 1H each, J = 11.2 Hz, $PhCH_2$), 4.70, 4.86 (ABq, 1H each, J = 12.2 Hz, $PhCH_2$), 4.59 (d, 1H, J = 3.7 Hz, H-1), 4.27 (dd, 1H, J = 10.1, 4.7 Hz, H-6), 4.05 (t, 1H, J = 9.3 Hz, H-3), 3.80−3.86 (m, 1H, H-5), 3.71 (t, 1H, J = 10.2 Hz, H-6), 3.60 (t, 1H, J = 9.4 Hz, H-4), 3.56 (dd, 1H, J = 9.3, 3.7 Hz, H-2), 3.41 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 138.9, 138.3, 137.5, 129.1, 128.6, 128.44, 128.35, 128.3, 128.2, 128.1, 127.7, 126.2, 101.0 (t, J = 24.7 Hz), 99.4, 82.2, 79.3, 78.7, 75.5, 73.9, 69.2, 62.5, 55.5. HRMS calcd for $C_{28}H_{29}DO_6Na$ (M + Na) 486.2003, found 486.2003.

Methyl 2,3-Di-*O*-benzyl-4,6-*O*-(*p*-bromobenzylidene)-α-D-glucopyranoside (5). *p*-Bromobenzaldehyde (513 mg, 2.77 mmol) was dissolved in MeOH (4 mL). $CH(OCH_3)_3$ (0.52 mL, 4.74 mmol) was added followed by Amberlite IR-120 H^+ (11 mg). The mixture was heated in a sealed tube to 75 °C for 3 h, filtered, and concentrated to give the corresponding α,α-dimethoxy acetal. The α,α-dimethoxy acetal was dissolved in MeCN (7 mL) followed by addition of methyl α-D-glucopyranoside (456 mg, 2.35 mmol) and *p*TSA (36 mg, 0.21 mmol). The mixture was stirred at rt for 30 min and then refluxed for 24 h. NEt_3 (2 mL) was added and the mixture was concentrated. The residue was chromatographed (SiO_2, toluene/EtOAc 1:2) to give methyl 4,6-*O*-(*p*-bromobenzylidene)-α-D-glucopyranoside (164 mg, 19%). $[\alpha]^{23}_D$ +75.3 (*c* 0.7, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 7.50, 7.37 (ABq, 2H each, J = 8.4 Hz, Ar), 5.49 (s, 1H, $ArCH[OR]_2$), 4.80 (d, 1H, J=3.9 Hz, H-1), 4.29 (dd, 1H, J=9.5, 4.0 Hz, H-6), 3.92 (t, 1H, J=9.2 Hz, H-3), 3.71−3.82 (m, 2H, H-5, H-6), 3.63 (dd, 1H, J = 8.9, 3.7 Hz, H-2), 3.49 (t, 1H, J = 9.2 Hz, H-4), 3.46 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 136.2, 131.6, 128.2, 123.5, 101.3, 99.9, 81.0, 73.1, 71.9, 69.0, 62.4, 55.8. HRMS calcd for $C_{14}H_{17}O_6BrNa$ (M + Na) 383.0106, found 383.0100. Methyl 4,6-*O*-(*p*-bromobenzylidene)-α-D-glucopyranoside (112 mg, 0.31 mmol) and TBAI (12 mg, 0.03 mmol) were dissolved in DMF (3 mL), then the mixture was cooled to 0 °C under N_2. After 17 min NaH (95 mg, 60% in oil) was added and after an additional 34 min benzyl bromide (0.09 mL, 0.77 mmol), then the mixture was stirred for 2 h. NH_4Cl (satd.) was added and the mixture was extracted two times with ether. The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was chromatographed (SiO_2, toluene/EtOAc 4:1) to give **5** (42 mg, 25%). $[\alpha]^{22}_D$ −36.8 (*c* 0.8, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 7.51 (d, 2H, J=1.9, Ar), 7.28−7.40 (m, 12H, Ar), 5.49 (s, 1H, $ArCH[OR]_2$), 4.87, 4.84 (ABq, 1H each, J = 11.3 Hz,

$PhCH_2$), 4.85 (d, 1H, $J = 12.2$ Hz, $PhCH_2$), 4.70 (d, 1H, $J = 12.2$ Hz, $PhCH_2$), 4.59 (d, 1H, $J = 3.7$ Hz, H-1), 4.25 (dd, 1H, $J = 10.0$, 4.7 Hz, H-6), 4.02 (t, 1H, $J = 9.3$ Hz, H-3), 3.80 (dt, 1H, $J = 9.9$, 4.7 Hz, H-5), 3.68 (t, 1H, $J = 10.2$ Hz, H-6), 3.57 (t, 1H, $J = 9.4$ Hz, H-4), 3.55 (dd, 1H, $J = 9.3$, 3.7 Hz, H-2), 3.40 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 138.8, 138.2, 136.6, 131.5, 128.6, 128.5, 128.3, 128.1, 127.97, 127.95, 127.8, 123.2, 100.7, 99.4, 82.2, 79.4, 78.7, 75.5, 73.9, 69.2, 62.4, 55.5. HRMS calcd for $C_{28}H_{29}O_6BrNa$ (M + Na) 563.1045, found 563.1028.

Acknowledgment. The Swedish Research Council, Lund University, The Lennander Foundation, and The Crafoord Foundation supported this work

Supporting Information Available: Experimental details, compound characterization data, and NMR spectra of reaction mixtures. This material is available free of charge via the Internet at http://pubs.acs.org.