Acetals - Exploring reactivity for improved carbohydrate synthesis

Ohlin, Markus

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Acetals

Exploring reactivity for improved carbohydrate synthesis

Markus Ohlin

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Abstract

In my research, I have explored various aspects of acetals and their reactivity. Acetals have a central role in carbohydrate chemistry as an inherent functionality and as versatile protecting groups.The first part of the thesis summarizes results on regioselective reductive openings of benzylidene acetals.

We thus used deuterium substituted benzylidene acetals and boranes, to investigate stereoselectivity and kinetic isotope effects. In addition, we explored the electronic requirements using *p*-bromo benzylidene acetals. Our results show that the regioselective reductive opening reactions of benzylidene acetal rings with boranes, and aluminum trichloride progress via three distinctly different mechanisms. The intermediates range from intimate ion pairs to solvent separated oxocarbenium ions in a mechanistic continuum depending on borane ligand, Lewis acid strength, and solvent polarity.

The second part of thesis is focused on synthetic routes towards daunosamine donors. We thus used the equilibrium between the anomeric hemiacetal and the corresponding aldehyde, and thus improvedthe 1,4-Michael additions of azides, without advanced catalysts. We present an efficient synthesis of a versatile donor which was used to synthesize anthracycline analogs. These anthracyline analogs were tested for anti-tumor activity but initial biological evaluations were inconclusive.

Key words Acetals, Carbohydrate Chemistry, Mechanistic Investigations, Benzylidene Acetals, Kinetic Isotope Effects, Organic Synthesis, Anthracyclines, Daunosamine

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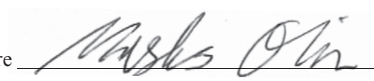
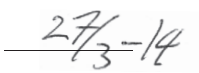
Signature  Date 

Acetals

Exploring reactivity for improved carbohydrate synthesis

Markus Ohlin

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A doctoral dissertation at a university in Sweden is produced as a monograph or as a collection of papers. In the latter case, the introductory part constitutes the formal dissertation, which summarizes the accompanying papers. These have already been published or are manuscripts at various stages.

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“A smooth sea never made for a skilled sailor”

Contents

Abstract

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List of Papers

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1. Richard Johnsson,[†] Markus Ohlin,[†] and Ulf Ellervik
   Reductive Openings of Benzylidene Acetals Revisited: A Mechanistic Scheme for Regio- and Stereoselectivity
   Journal of Organic Chemistry **2010**, *75*, 8003–8011.
   Contribution: Did the majority of the experimental work, data analysis and assisted in writing the paper. [†]These authors contributed equally to this work.

2. Markus Ohlin, Richard Johnsson, Ulf Ellervik
   Regioselective reductive openings of 4,6-benzylidene acetals: synthetic and mechanistic aspects
   Carbohydrate Research **2011,** *346*, 1358–1370.
   Contribution: Did the majority of the writing of the paper.

3. Markus Ohlin, Sophie Manner, Johanna Löfgren, Andrea Persson, Ulf Ellervik
   Short and Efficient Synthesis of a Daunosamine Donor from L-Fucal
   RSC Advances, **2014,** *4,* 12486-12489.
   Contribution: Did the majority of the experimental work and assisted in writing the paper.

   Paper related to, but not included in, this thesis:
   Mihály Herczeg, László Lázár, Markus Ohlin*, Anikó Borbás
   Regioselective Reductive Openings of 4,6-*O*-Benzylidene-Type Acetals using LiAlH4-AlCl3
   Carbohydrate Chemistry: Proven Synthetic Methods, Vol. 2.
   Contribution: Verified reproducibility as checker of the experimental work.

   *To ensure reproducibility, an independent, reasonably skilled artisan (checker) will verify the experimental part involved by repeating the protocol or using the method.

Abbreviations

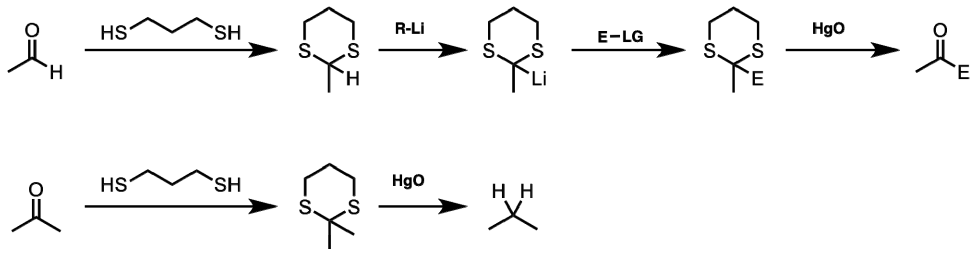
DFT	Density Functional Theory
DIBAL-H	Diisobutylaluminium hydride
DNR	Daunorubicin
DOX	Doxorubicin
EWD	Electron Withdrawing
EPI	Epirubicin
IDA	Idarubicin
KIE	Kinetic Isotope Effect
PG	Protecting Group
RCS	Rate-Controlling Step

1. Introduction to acetals and carbohydrate synthesis

In 2014, most people associate the word "carbohydrate" with nutrition and various diets. Although important, this context is far from the most important - at least not from a scientific perspective. Carbohydrates are the most abundant class of biomolecules in the biosphere and they play many different roles. Carbohydrates may be referred to as biomolecules, organic heterocycles, or sugars. The chemistry of carbohydrates overlaps, to a large extent, with the chemistry of acetals. This thesis describes studies of acetal reactivity with an aim to develop tools for carbohydrate synthesis.

Acetals and acetal derivatives

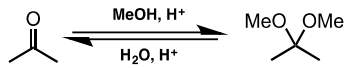
The functionality composed of an sp^3 hybridized carbon, binding a *gem*-diether, derived from an aldehyde or a ketone carbonyl carbon will be referred to as an acetal throughout this thesis. The denotation "ketal", analogous to ketose in carbohydrates, which refers to acetals specifically derived from ketones, will not be used.[1] The central carbon in the acetal group has a formal oxidation state of +1 and can be formed from the condensation reaction with carbonyl functionalities (oxidation state of +1) and alcohols under acid catalysis.[2,3] They can also be prepared under basic conditions with alcohols and *ipso* dihalides. Acetal analogs carrying heteroatoms other than O, *i.e.* aminals, hemiaminals, aminoacetals, or dithioacetals, and thioacetals are not uncommon in organic reaction mechanisms. Aminals can be found *e.g.* as intermediates in the Fischer indole synthesis. The dithioacetals, 1,3-dithianes, are used for *"umpolung"* of carbonyl carbons *i.e.* to reverse the reactivity from electrophilic to nucleophilic. Aldehydes can be substituted via dithioacetals by the Corey-Seebach[4,5] reaction and ketones can be reduced to methylene by the Mozingo reduction as an alternative to Wolff-Kischner or Clemensen reduction (scheme 1).[6]



Scheme 1. *Umpolung* of cabronyl carbons with dithioacetals.

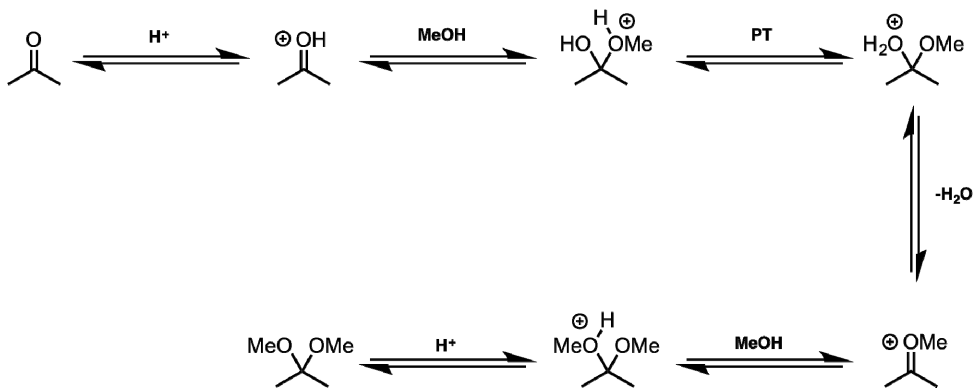
Reactions with acetals

Acetals and hemiacetals are closely related to carbonyls. Acetals can be formed from, or be hydrolyzed to, carbonyl compounds under acid catalysis (scheme 2).



Scheme 2. Acid mediated equilibrium between dimethoxy acetone and acetone

The mechanism for this transformation (scheme 3) may vary depending on reaction conditions. However, it is important to note that each elementary reaction step is in equilibrium and the driving force is the abundance of alcohol or water respectively.

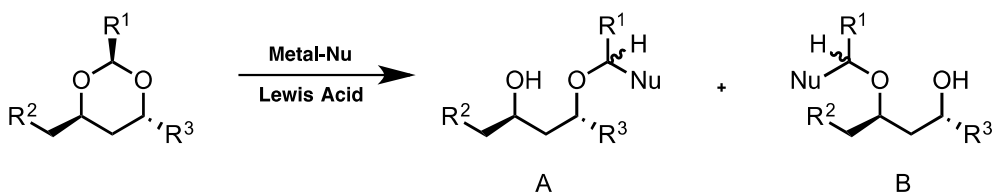


Scheme 3. Mechanism for acid mediated equilibrium between dimethoxy acetone and acetone.

In 1990, Corcoran *et al.* described the nucleophilic addition of cyanide to chiral 1,3-dioxane acetal carbons, catalyzed by Lewis acids.[7] In this reaction, the former acetal carbon is formally reduced from +1 to 0. Corcoran *et al* found that, using $TiCl_4$, a metal complex prone to form a tetrahedral coordination geometry, could be chelated by the neighboring ether and the adjacent acetal oxygen and thus direct the subsequent nucleophilic attack. Under optimized reaction conditions, the ratio was as much as >250:1 in favor of the corresponding regioisomer A (table 1, entry 1; scheme 4) . Interestingly, $ZnBr_2$ reverses the regioselectivity, forming B (entry 2, table 1; scheme 4) .

Further investigations of 1,3-dioxane acetals by Denmark *et al.,* primarily using allyl stannanes as carbon nucleophiles catalyzed by 1:1 mixtures of $TiCl_4$/Ti(i-PrO)$_4$, gave interesting results.[8] The thus studied stereoselective properties, using a racemic mixture of a chiral 1,3-dioxane acetal (entry 3, table 1, scheme 4) without chelation capabilities. The acetal oxygens were electronically equivalent and differed merely by the stereochemistry of the adjacent carbons. A preference for regioisomer B (table 1, scheme 4) was thus observed which Denmark explained by the Lewis acid directed formation of an intimate ion pair intermediate, instead of an oxocarbenium ion, followed by direct displacement via an S_N2-type attack.

Sammakia *et al.* revised the work published by Denmark using a deuterium labeled acetal substrate (table 1, entry 4; scheme 4) .[9] Sammakia argues that the previous studies were inconclusive and that essentially no stereoselectivity was found for nucleophilic additions of allyl stannanes to acetals by $TiCl_4$/Ti(i-PrO)$_4$ catalysis, hence, confirming the presence of an oxocarbenium ion intermediate. However they did not rule out the existence of intimate ion pairs undergoing direct displacements for other systems, *i.e.* weaker nucleophiles and/or Lewis acids.



Scheme 4. Carbon nucleophile additions to 1,3-dioxane acetals.

Table 1. Summary of results from nucleophilic openings of 1,3-dioxane acetals with carbon nucleophiles.

Entry	R^1	R^2	R^3	Lewis Acid	Metal-Nu	A/B	Ref.
1	Bn, Ph	OMe	H	$TiCl_4$	Me_3SiCN	250:1	[7]
2	Bn, Ph	OMe	H	$ZnBr_2$	Me_3SiCN	1:250	[7]
3[a]	$(CH_2)_2CHCH_2$	H	Me	$TiCl_4/Ti(i\text{-}PrO)_4$	$n\text{-}Bu_3SnAllyl$	1:568	[8]
4	C_9H_{19}	H	CH_2D	$TiCl_4/Ti(i\text{-}PrO)_4$	$n\text{-}Bu_3SnAllyl$	1:200	[9]

[a]1,3-dioxane acetal substrate in racemate.

A short history of Carbohydrates

Carbohydrates is a class of compounds which consists of polyhydroxyl aldehydes and ketones. Carbohydrates can be divided into four main categories, monosaccharides, disaccharides, oligosaccharides, and polysaccharides. This work is focused on monosaccharides.

When carbohydrates were studied for the first time in a sensible manner, they were found to have the molecular formulae $C_n(H_2O)_n$, which led the investigators to believe that it was hydrated elemental carbon, hence, the name (*Kohlenhydrat* in German). Chemists like Heinrich Kiliani (1855-1945), Otto Ruff (1871-1939), and, probably more so than any other chemist, Emil Fischer (1852-1919) brought order to the field. In 1874, Van't Hoff and Le Bel presented the theory that the geometry of a carbon center is tetrahedral and could hence be asymmetric.[1] Fischer applied this theory when elucidating the structures of carbohydrates. With just a few simple transformations at hand, optical polarimetry and melting point measurements as analytical methods (besides tasting and smelling), he carried out the Herculean task to elucidate carbohydrate structures. Fischer not only determined their structure, he could eventually synthesize glucose, mannose and fructose from glycerol.[10]

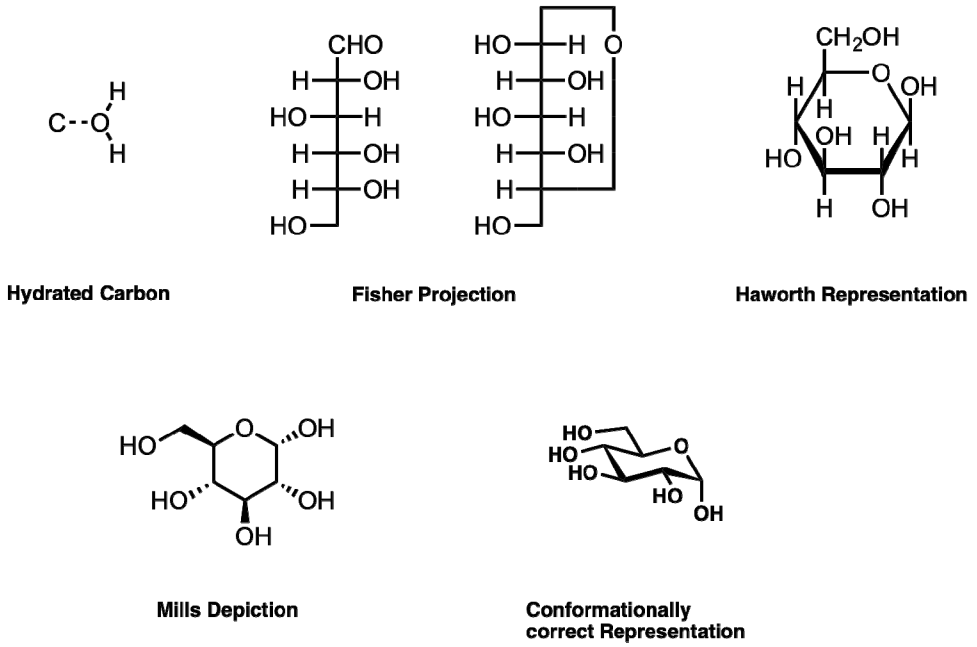


Figure 1. Projections and representations through time exemplified by α-D-Glucose.

Nomenclature

Carbohydrates are often very similar in structure and some differ only in the configuration of one carbon center, *e.g.* D-glucose and D-galactose have R and S configuration at C4 respectively. The highest numbered stereogenic center, *e.g.* C5 in glucose, determines whether the enantiomer is D or L. If a carbohydrate shares configuration for that stereogenic center with the simplest carbohydrate, glyceraldehyde, *i.e.* an R configuration, it is a D sugar. The hemiacetals form an additional stereogenic center upon ring closure at C1. This center, referred to as the anomeric center, can have either an α or a β configuration, determined by the relation to the highest numbered stereogenic center. If a *trans* relationship is seen, the anomer has the α-configuration and *vice versa* (figure 2).

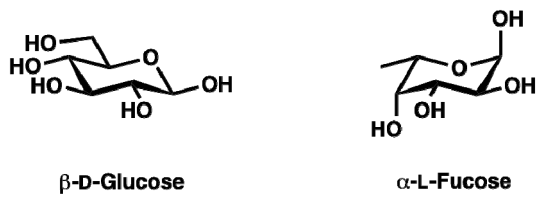


Figure 2. Examples of monosaccharides.

To simplify nomenclature, many carbohydrates carry own names. The systematic name for daunosamine, an accepted trivial name, is 3-Amino-2,3,6-trideoxy-L-lyxo-hexose.[11]

Protecting group chemistry

The ideal synthesis was defined by Hendrickson[12] in 1975 as a synthetic route which: "...creates a complex molecule...in a sequence of only construction reactions involving no intermediary refunctionalizations, and leading directly to the target, not only its skeleton but also its correctly placed functionality." This challenge summarizes much of the driving force behind research aims of modern organic synthetic chemistry. In 2010, Baran[13] presented a method to quantify the level of ideality in order to help artisans of the craft to optimize their synthesis design. This can be a useful tool corresponding to the synthon approach in retro synthetic analysis. Another strategy for achieving a high level of complexity while balancing the "atom economy" is the chiron approach.[14,15] In this methodology, concession steps *i.e.* non-strategic redox manipulations, functional group interconversions and protecting group (PG) manipulations, do not impair the synthetic route to the same extent. Efforts are still made to reduce these steps and hence more work is required to reach ideality using this strategy.

Since carbohydrates are polyhydroxyl compounds, the demand for protecting groups has generated a plethora of more or less selective methodologies to differentiate between similar functionalities. The most common protecting groups used to derivatize carbohydrates are esters, ethers and acetals.[1] Acetals are of particular interest. Carbohydrates form intramolecular hemiacetals spontaneously under most conditions. Protective acetal groups can undergo reactions whilst the hemiacetal remains inert. Two examples of frequently occurring acetals are the benzylidene acetals and the acetonide acetals (figure 3). With respect to "atom-economy", acetals can protect two hydroxyl functionalities where other PGs protect only one. Compare benzyl ether with benzylidene acetals or acetonide acetals with acetate esters.[16] Acetals are inert under a wide range of conditions and they also provide many options for selective protection/deprotection. This will be further discussed in chapter 3.

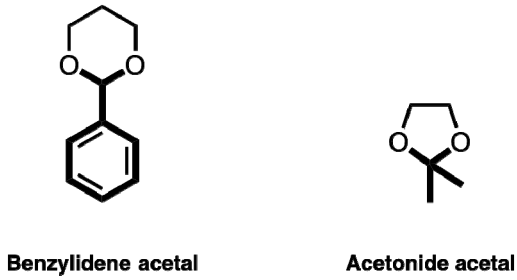
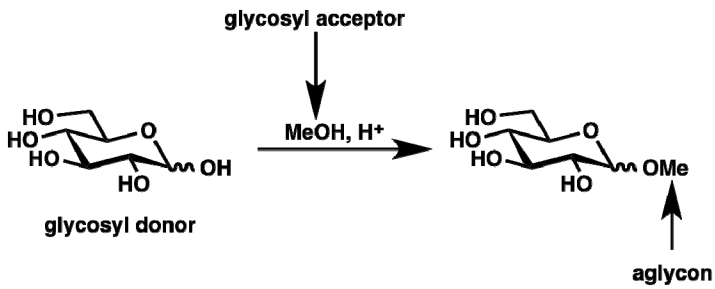


Figure 3. Two acetal protecting groups commonly applied in carbohydrate synthesis.

Glycosylation reactions

The most important types of bioactive natural products are alkaloids, terpenoids and glycosides. The first example of a synthetically prepared glycoside is the Fischer glycosylation of methyl D-glucopyranoside (scheme 5).[17-19] This reaction is typically carried out in an alcoholic media under acid catalysis, similar to Fischer esterification.



Scheme 5. Fischer glycosylation. Synthesis of methyl D-glucopyranoside.

A plethora of different glycosyl donors has been developed and are widely used today. The most important classes of donors are glycosyl halides, thioglycosides, and trichloroacetoamidate donors.[1]

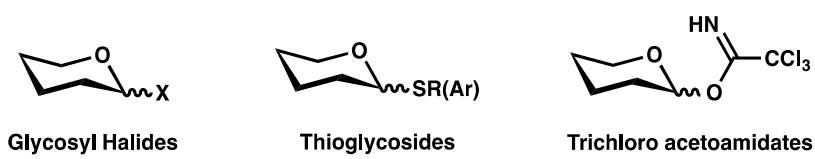
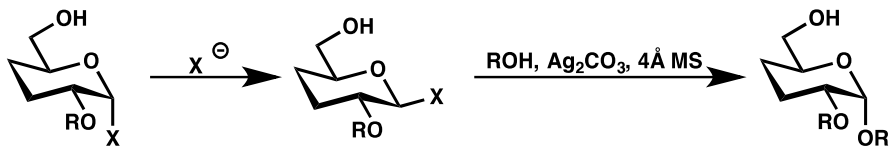


Figure 4. General representation of widely used glycosyl donors.

The most commonly used halide is bromide as it is more reactive than chloride and more stable than iodide. The first example of a glycosylation using a halide donor was carried out with a glycosyl chloride *i.e.* the Koenigs-Knorr reaction.[20] This S_N2 reaction is promoted either by silver salts (*e.g.* Ag_2CO_3, Ag_2O) and molecular sieves (for bromides) or by deprotonation of the acceptor alcohol or phenol. Since the resulting stereochemistry at the anomeric position, *i.e.* the acetal carbon C1 of the glycoside product, is determined by the glycosyl halide, it is crucial to control the formation of the halide. The 1,2 *cis*-halide catalysis is a process for inverting the stereochemistry at C1 *in situ,* from 1,2 *cis* to 1,2 *trans* affording the 1,2 *cis*-glycoside product, typically with an ether substituent at C2 (scheme 6).[21]



Scheme 6. The 1,2 *cis*-halide catalysis generating α-glycosides from α-glycosyl halides.

Thioglycosides can be considered as stable latent donors and can be converted into bromides or activated by promoters such as NIS or NBS with TfOH. Trichloroacetimidates are reactive glycosyl donors. These donors, either with an α or a β configuration, readily forms oxocarbenium ions under Lewis acid catalysis *e.g.* with $BF_3 \bullet OEt_2$.

2. Research Objectives

Acetals are important functional groups in the chemistry of carbohydrates. Although acetals have been thoroughly studied since, there are still on-going method development. Thus further insight into the rules governing the reactions of acetals in general and carbohydrate acetals in particular is required. By exploring the reactivity of acetals encountered in carbohydrate chemistry, new tools can be discovered that makes carbohydrates an even more useful and sustainable source of chiral building blocks for drug discovery. The research objectives of this thesis are:

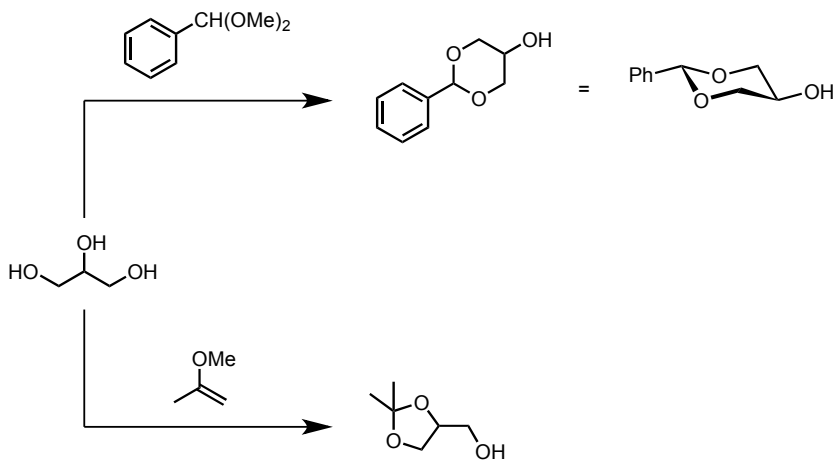
1. What are the mechanisms for regioselective reductive openings of benzylidene acetals?
2. How can synthetic studies improve the tools for discovery of novel anthracycline analogs?
3. What are the biological mechanisms by which the anthracyclines interact with human physiology? Can novel anthracycline analogs, synthesized using the bottom-up approach, help answer these questions?

3. Benzylidene acetals

General introduction

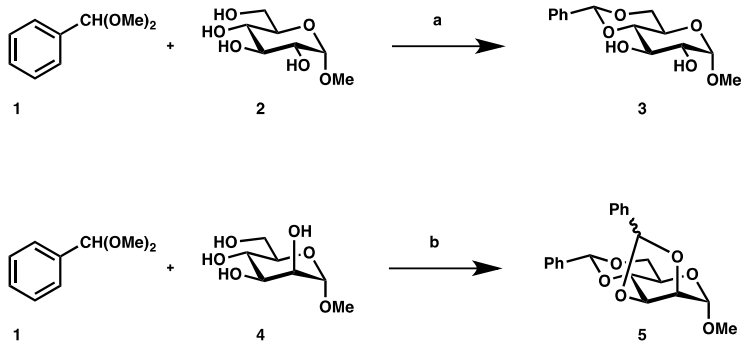
Essentially all reactions involving carbohydrates relies on the foundation of regioselectivity. In order to differentiate between the many hydroxyl functionalities of a carbohydrate, the chemistry of both hydroxyls and acetals must be controlled. Carbohydrates readily form intramolecular hemiacetals, but acetals also serves as versatile protecting groups. A protecting group should be easy to introduce, yet simple to remove. In addition, it must keep the functionality intact and not interfere with other reactions. A crucial property for protecting groups is high regioselectivity. Hence one of the most widely used protecting groups, in carbohydrate synthesis, is the benzylidene acetal.[16]

The benzylidene moiety (PhCH) occurs in different arrangements *e.g.* in stilbene type compounds, Schiff's bases and as benzylidene acetals. Benzylidene acetals selectively protect 1,3-diols over 1,2-diols (scheme 7) since it preferably forms a thermodynamically stable 1,3-dioxane ring rather than the corresponding dioxolane ring.[16]



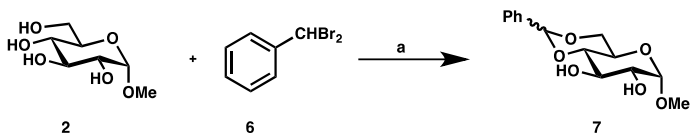
Scheme 7. 1,3 and 1,2 diols can selectively be protected by benzylidene acetals and acetonides respectively.

For glucose, a 4,6-*O*-benzylidene acetal is formed, leaving the 2- and 3-hydroxyl groups unprotected.[22] For 1,2-diols with a cis configuration, *e.g.* mannose, a second 2,3-*O*-benzylidene acetal can be installed (scheme 8). This operation is thermodynamically less preferred and is usually performed under reduced pressure to force the equilibrium towards product formation.



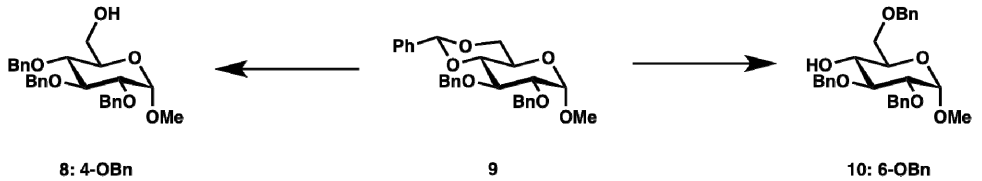
Scheme 8. a) *p*TSA, MeCN, reflux.[23] b) CSA, MeCN, 60 °C, 600 mBar.[22]

Benzylidene acetals can also be introduced under basic conditions yielding a diastereoisomeric mixture (scheme 9). Benzylidene acetals are stable under a large variety of reaction conditions such as pH ≤ 12 in aqueous solution, organolithium, and strongly oxidizing reagents ($KMnO_4$, CrO_3[16]). Removal of the protecting group can easily be carried out by either hydrolysis ($AcOH/H_2O$ – 4:1[24]), with I_2 in MeOH[25,26], or by reductive methods (Pd/C and AcOH or $Pd(OH)_2$ and EtOH[27,28]).



Scheme 9. a) benzal bromide, pyridine.

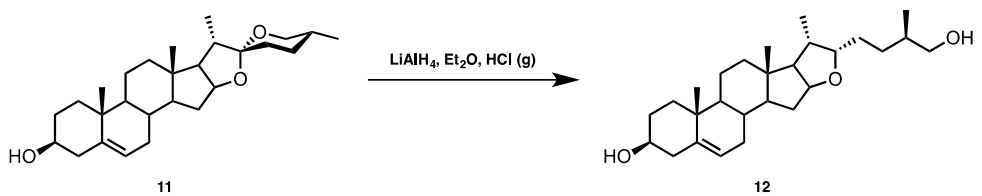
All these features makes the benzylidene acetals versatile protecting groups. The synthetically most useful property might be the ability for reductive cleavage in a highly regioselective fashion, to form a benzyl ether and an alcohol. To facilitate the discussion, methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **8** and corresponding regioisomeric products will further on be referred to as 4-OBn, whereas methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside **10** and corresponding products will be referred to as 6-OBn (scheme 10).



Scheme 10. The benzylidene acetal can be cleaved regioselectively to yield either 4-OBn or 6-OBn as a major product.

Regioselective reductive openings of benzylidene acetals

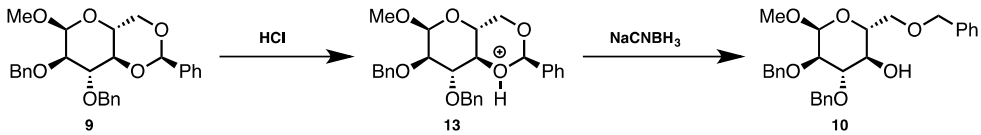
After WWII, an immense effort to find cheaper ways of synthesizing cortisone was commenced. Cortico steroids were used as stress relievers by fighter pilots and as an anti-arthritic agents. Carl Djerassi, the first chemist to synthesize the oral contraceptive, 19-nor-17α-ethynyltestosterone, worked at that time at the Syntex company in Mexico. In attempts to synthesize testosterone and progresterone, he used diosgenin as starting material. Diosgenin is the aglycon of the glycoside sapogenin extracted from the Mexican wild yam. Hence, many new reactions with diosgenin were developed during this time.[29] In 1951, Doukas and Fontain published a method to selectively cleave one C–O bond in the spiro acetal functionality in diosgenin using $LiAlH_4$ with HCl in anhydrous ether (scheme 11).[30]



Scheme 11. First known example of a regioselective reductive opening of an acetal.

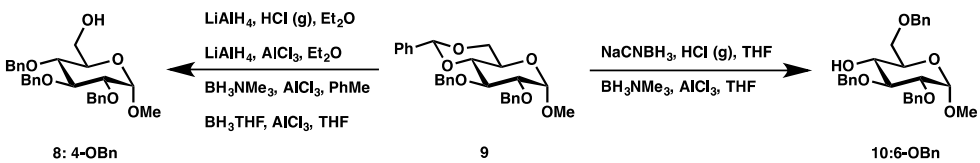
It was later shown that $AlCl_3$, instead of HCl, gave the same regioisomeric mixtures in good yields for a variety of acetals.[31,32] Hence, the theory of *in situ* formation of $AlCl_3$ in the original reagent combination was supported. Later Liptak *et al.* adopted this methodology and applied it to the benzylidene acetals, used as protecting groups for carbohydrates.[33,34] Successfully, a large variety of compounds were exposed to this methodology, all yielding 4-OBn products. In the search for milder conditions, Garegg *et al.*[35,36] were investigating $NaCNBH_3$ as reducing agent, instead of $LiAlH_4$. The aim was to find a method compatible with a wider range of functional groups. They found that $NaCNBH_3$, combined with

HCl in THF, gave the opposite regioselectivity *i.e.* 6-OBn products and hence complemented the Liptak methodology. Garegg credited the reversed regioselectivity to the steric hindrance at O4 which supposedly would hamper $AlCl_3$ from coordination. A proton would not be restricted in this way and would thus coordinate to O4 which was deemed the most Lewis basic oxygen (scheme 12).



Scheme 12. Mechanism presented by Garegg *et al.*

Garegg *et al*. continued investigations on reductive openings and turned their attention to boranes. The reagent combination BH_3•NMe_3 and $AlCl_3$ in THF was found to produce the same products as $NaCNBH_3$ with HCl in THF. They also discovered that the regioselectivity could be altered merely by changing the solvent to toluene. Interestingly, these conditions gave the same selectivity as the Liptak conditions,[37] and BH_3•THF and $AlCl_3$ in THF also gave similar products (scheme 13). The previous theory that the regioselectivity was directed merely by steric properties of the reagents thereby seemed less plausible.

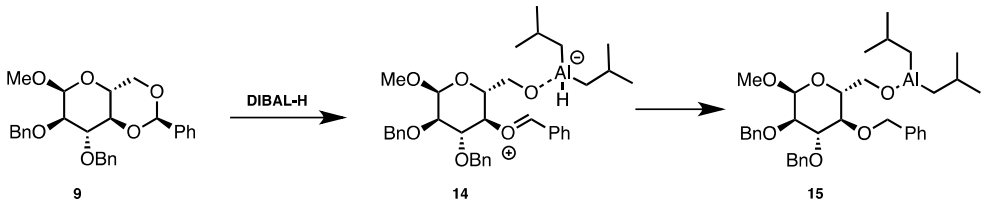


Scheme 13. Methodologies used for regioselective reductive openings of benzylidene acetals.

Reaction mechanisms of regioselective reductive openings of benzylidene acetals

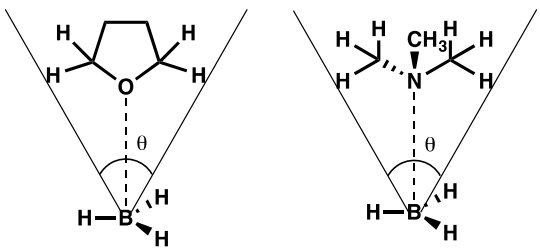
Today there is a large array of methodologies available for regioselective reductive openings of benzylidene acetal rings (se paper II). There are still some major questions unanswered regarding why these different reagent combinations generates different products and the regioselectivity becomes difficult to explain simply by sterical effects. Different changes in reaction conditions, other than steric bulk, reverse the selectivity for some of these reagent combinations. Mikami *et al.*[38] published a paper were they showed that DIBAL-H in DCM, gave the 6-OBn product. Apparently, DIBAL-H acts as both reducing agent and as Lewis

acid catalyst. A plausible mechanism for the reaction is given in scheme 14. Tanaka *et al.*[39,40] later showed that the selectivity could be reversed, either by using other solvents, mixtures of solvents or by running the reaction at different temperatures. The reactivity is obviously of a much more complex nature.



Scheme 14. Plausible mechanism for regioselective reductive openings of benzylidene acetals with DIBAL-H.

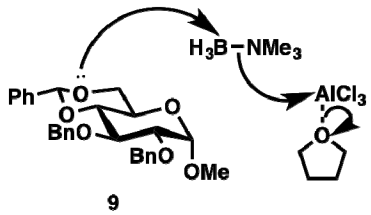
When considering the regioselective reductive openings of benzylidene acetals using boranes in combination with $AlCl_3$ in THF, the regioselectivity is directed by the choice of Lewis base ligand forming the borane complex. For 4,6-*O*-benzylidene acetals, the reagent combination BH_3•THF, $AlCl_3$ in THF yields exclusively the 4-OBn products while the BH_3•NMe_3 complex gives the opposite result. The explanation can not be sterical hindrance since the steric bulk of these complexes are virtually the same. We thus optimized the borane complex structures with density functional theory (DFT) M06 – 6.31**. The Tolman angles θ (scheme 15) could be determined, θ (BH_3·THF) = 90° and θ (BH_3·NMe_3) = 99° respectively. Hence the steric demand posed by these complexes can be considered the same.



Scheme 15. Comparison of steric bulk between BH_3·THF and BH_3·NMe_3.

In 2008, Johnsson *et al.* provided an alternative explanation for the regioselectivity.[41,42] In an extensive investigation of the kinetics of these reactions, they found a second order dependency of $AlCl_3$ for regioselective reductive openings of methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside **9** (scheme 16), using BH_3•NMe_3-$AlCl_3$-THF, aiming for 6-OBn product. They

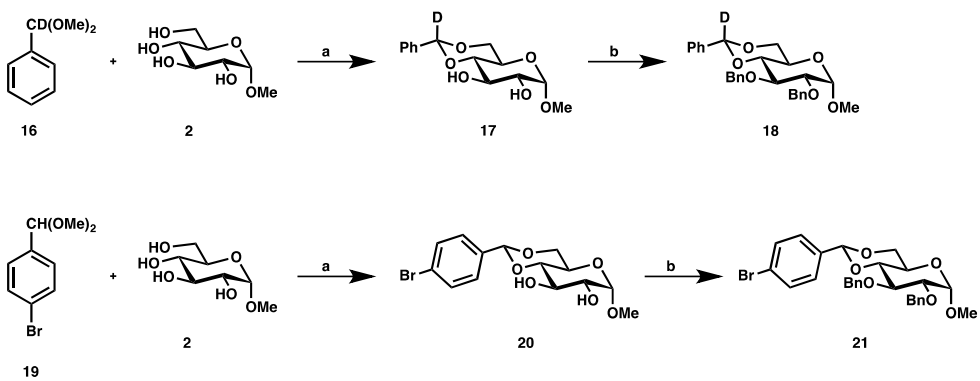
suggested that $AlCl_3$ forms a complex with the amine previously coordinated to borane *in situ*. This would thus render the borane more electrophilic compared to $AlCl_3$•THF (scheme 16). Calculations using DFT B3LYP/6-31G* also confirmed that O6 had a higher electrostatic potential than O4 and hence the borane preferably coordinated to O6. This explanation was further supported by the formation of a new borane complex, detected with ^{11}B–NMR.[42]



Scheme 16. Recomplexation of the borane suggested by Johnsson *et al*.

Mechanistic Investigation

To (i) give a reasonable explanation for the reactivity of the regioselective reductive openings of benzylidene acetals with boranes, (ii) to exclude other possible pathways, and (iii) to further resolve the mechanistic details, we initiated new investigations. Thus, kinetic isotope effects (KIE) and effects of electron withdrawing (EWD) substituents were measured. In addition, isotope labeling experiments were carried out to evaluate the stereoselectivity. The results from these studies are compiled in table 2. In order to accomplish these studies, deuterium labeled benzylidene acetals as well as *p*-bromo benzylidene acetals were synthesized (scheme 18).

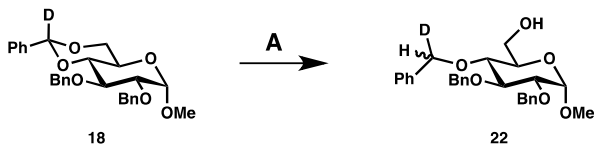


Scheme 18. a) *p*TSA, MeCN, reflux. b) NaH, BnBr, TBAI, DMF, 0 °C – rt.

Stereoselectivity

We did not observe any stereoselectivity, either for the original or the modified Garegg openings to 6-OBn products in THF, or for the BH_3•NMe_3-$AlCl_3$-PhMe reaction combination to 4-OBn products. This indicates that the opposing acetal C–O bond was cleaved prior to reduction. For the Liptak conditions as well as for the BH_3•THF-$AlCl_3$-THF reagent combination, we observed high stereoselectivety for the (S)-configuration, of the deuterium hydrogen methylene formed, using ^{1}H-NMR. This indicates an S_N2-type addition in the reductive step, implying H–C bond formation occurs simultaneously with C–O bond cleavage. These experiments were also carried out with non-labeled benzylidene acetals and deuterium labeled boranes, sodium cyanoborodeuteride and lithium aluminum deuteride and the results were consistent with the previous study. There are obviously three different reaction mechanisms involved *i.e.* mechanisms A, B and C (scheme 19).

Mechanism A: Reaction with BH_3•NMe_3-$AlCl_3$-PhMe



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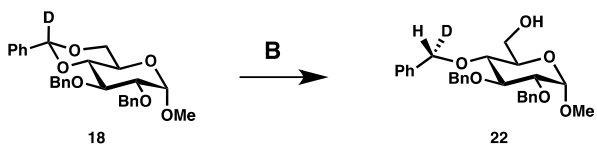
Mechanism B: Reaction with BH_3•THF-$AlCl_3$-THF



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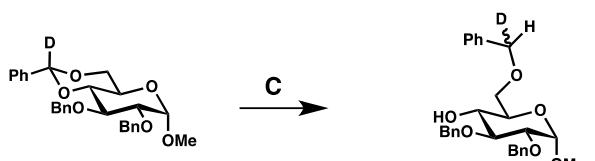
Mechanism C: Reaction with BH_3•NMe_3-$AlCl_3$-THF



18 23

Scheme 19. Reaction schemes exemplifying three different mechanisms A, B and C.

Kinetic isotope studies (KIE)

The KIE's were measured for mechanisms A, B and C. The reactions were quenched early (typically 0 – 10% conversion) to insure that initial rate approximations are valid. Reaction mixtures were purified and the products were analyzed by ^{1}H–NMR (400 MHz). The validity of this method was confirmed by running relevant samples at 600 MHz. Since this is a competitive study KIE = $[P_H]$ / $[P_D]$.

The primary (1°) KIE's were measured using equimolar mixtures of deuterium labeled reducing agents and reducing agents with the natural abundance of hydrogen isotopes. Since this was a competitive study, it only provides information about the reactions where the boranes are involved. In all cases, we observed a KIE for the elementary reaction *i.e.* the reductive step (table 2). The 1° KIE for mechanisms A and B (2.8 and 2.4 respectively) are moderate, but for mechanism C the 1° KIE for the reductive step is high, (4.9). This implies that the transition state is nearly symmetrically located along the reaction coordinate and the structure of the activated complex resembles neither the reactants nor the products. The reaction is thus thermoneutral *i.e.* the reactants and products are close in energy for this elementary reaction.

Secondary (2°) KIE were measured with competitive initial rate studies. A 1:1 mixture (confirmed by ^{1}H–NMR) of deuterium labeled benzylidene acetals and benzylidene acetals with a natural abundance of hydrogen isotopes was prepared and exposed to these reaction conditions. For mechanism A, an inverse 2° KIE was determined to 0.92 which indicates a rehybridization of the adjacent carbon atom from sp^2 to sp^3 in the rate controlling step (RCS), suggesting the formation of an oxocarbenium intermediate in a fast step followed by a slow reduction. The corresponding value for investigations of mechanism B gives a 2° KIE = 0.85 which is consistent with a rehybridization from sp^2 to sp^3 in the RCS. It is also consistent with an S_N2-type reductive step. Large and inverse 2° KIE are found for large substrates undergoing S_N2 reactions via a loose transition state (longer distance between incoming nucleophile and acetal carbon, as well as longer distance between acetal carbon and leaving group). The inversion is lower in energy for carbon centers with a C–D bond due to the out-of-plane bending frequencies that are susceptible to both steric and electronic effects going from reagent to transition state.[43-45] Mechanism C gave a large 2° KIE of 1.4 which is a clear indication of a rehybridization of the acetal carbon from sp^3 to sp^2 forming an oxocarbenium ion in the RCS, in contrast to mechanism A.

Effects of electron withdrawing group

In order to investigate how the capability to stabilize a positive charge would influence the reaction rates, an equimolar mixture (confirmed by ^{1}H–NMR) of benzylidene acetal and *p*-bromo-benzylidene acetal was prepared and competitive initial rate studies were carried out. Virtually no difference could be detected for the product ratio for mechanism A implying a fast C–O bond cleavage to form an oxocarbenium ion prior to reduction. Both mechanisms B and C showed an increased rate for reactions with non-substituted benzylidene acetals compared to *p*-bromo-substituted benzylidene acetals. This effects was further pronounced for mechanism C indicating that the formation of a full oxocarbenium ion is a RCS.

Table 2. Compilation of results from studies of KIE, EWD effects and isotope labeling.

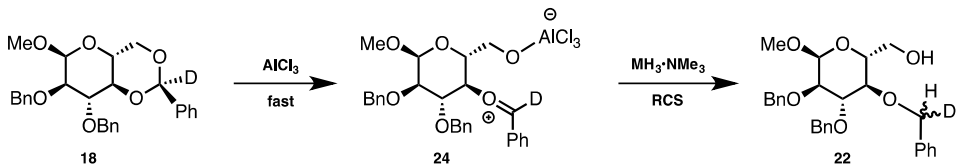
Reagents and conditions	1° KIE	2° KIE	EWD (H/Br)	Stereoselectivity
$BH_3{\cdot}NMe_3$-$AlCl_3$-PhMe	2.8	0.92	58:42	42:58 (S:R)
$BH_3{\cdot}THF$-$AlCl_3$-THF	2.4	0.85	73:27	97:3 (S:R)
$LiAlH_4$-$AlCl_3$-Et_2O/DCM		0.92		96:4 (S:R)
$BH_3{\cdot}SMe_2$-$AlCl_3$-THF				97:3 (S:R)
$BH_3{\cdot}NMe_3$-$AlCl_3$-THF	4.9	1.4	87:13	57:43 (r:s)
$NaCNBH_3$-HCl-Et_2O/THF		1.4		58:42 (r:s)
$BH_3{\cdot}SMe_2$-$AlCl_3$-THF				52:48 (r:s)
$BH_3{\cdot}NMe_3$-$AlCl_3$-THF/H_2O				56:44 (r:s)

Mechanistic Details

We propose the following mechanistic explanations that are consistent with our experimental observations.

Mechanism A

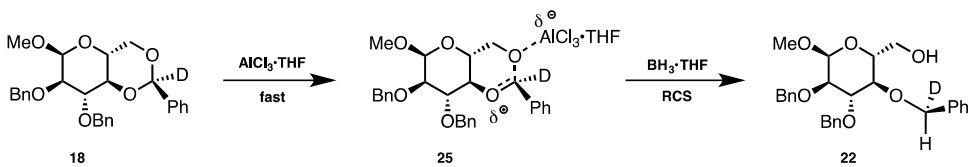
Our results for mechanism A (scheme 20) indicate that the RCS is not the formation of the intermediate oxocarbenium ion, but rather the subsequent reduction. This is in contrary to what would be expected in a fairly non-polar solvent like toluene. If the formation of the oxocarbenium ion would be the RCS, a 2° KIE > 1 would be observed. Essentially no difference in rate was found, between the reactions with non-substituted benzylidene acetal and the *p*-bromo-benzylidene acetal (58:42), in forming a positive charge. This can only be explained by a fast formation of the oxocarbenium ion. No stereochemical distinction was made by the borane between the Re-face or the Si-face of the carbonyl-like carbon of the oxocarbenium ion in the reductive step. This reactive intermediate must hence be a separated ion pair. Our results also suggests that O6 is the most Lewis basic oxygen, since $AlCl_3$ preferably coordinates at this position. This explanation is reasonable considering the expected Lewis acid strength of $AlCl_3$ in toluene compared to $AlCl_3$•THF in THF.



Scheme 20. Mechanism A. Reaction with $BH_3{\cdot}NMe_3$-$AlCl_3$-PhMe.

Mechanism B

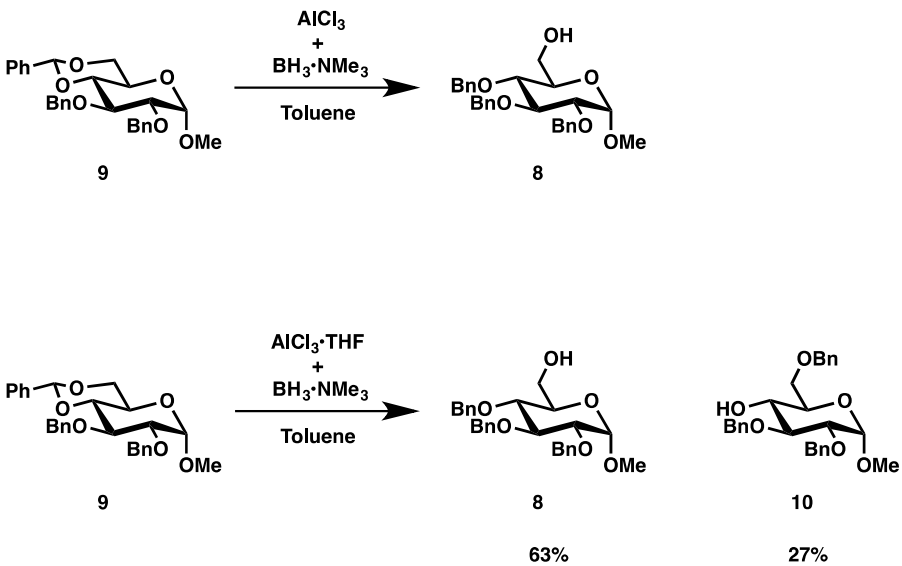
The results from our investigation of mechanism B (scheme 21) show that $AlCl_3$•THF coordinates O6 in a fast step followed by a reductive RCS. The inverse 2° KIE of 0.85 indicates that the reduction is the RCS. It is consistent with a rehybridization from sp^2 to sp^3 as well as an S_N2 reaction. The high stereoselectivety indicates that reduction proceeds via a concerted S_N2–type hydride addition to the acetal carbon with simultaneous bond cleavage of the distal C–O6 bond.[43-45]



Scheme 21. Mechanism B: Reaction with $BH_3{\cdot}THF$-$AlCl_3{\cdot}THF$-THF.

Mechanism C

Mechanism C differs substantially from mechanisms A and B. The reagent combination BH_3•NMe_3, $AlCl_3$ in THF reverses the regioselectivity. The components differs merely by the solvent compared to mechanism A, and by the amine ligand compared to the conditions of mechanism B. Clearly both THF and the amine is required for reversing the regioselectivity. The role of THF was thought to reduce the Lewis acidity of $AlCl_3$ which would allow for competing reactions to take place. We thus tested this theory by running the reaction with BH_3•NMe_3 and $AlCl_3$•THF in toluene (scheme 22). We prepared the $AlCl_3$•THF Lewis acid-base complex by dissolving $AlCl_3$ in THF, stirring it at room temperature for 1 h and then remove the excess of THF under vacuum. The reaction was otherwise run similarly to the reactions of mechanism A. The results showed 27% formation of the 6-OBn regioisomer (scheme 22).

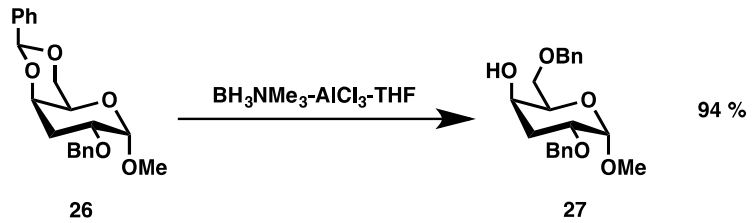


Scheme 22. Reaction with $AlCl_3$ versus $AlCl_3$·THF in Toluene.

This observation confirms what Johnsson *et al.* found.[41,42] Even though toluene provides a drastically different environment, the competing reaction where one equivalent $AlCl_3$•THF complexate the amine coordinated to the borane, is still responsible for 27% of the conversion.

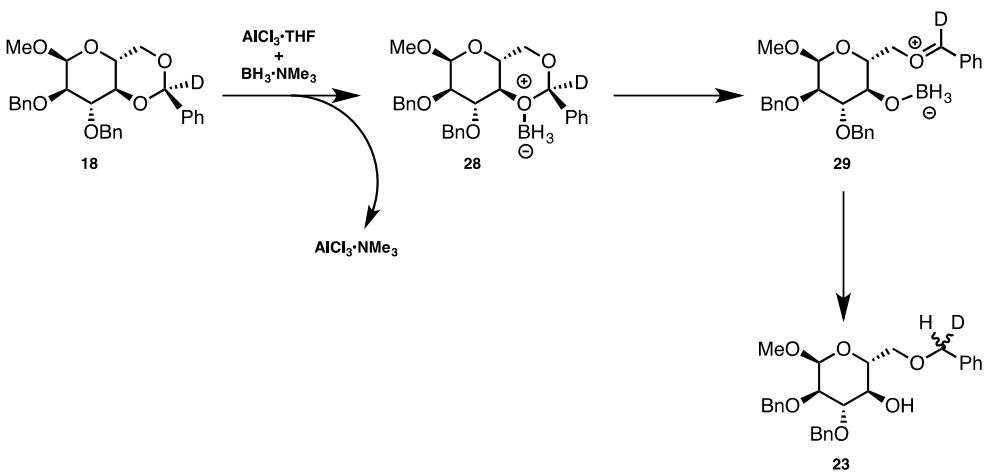
To further test the role of sterical hindrance, methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-deoxy-α-D-galactopyranoside **26**, a compound with less sterical hindrance at O4, was subjected to these reaction conditions (scheme 23). This

reaction gave the corresponding 6-OBn product **27** in a good yield (94%), concluding that sterical hindrance plays an insignificant role in the regioselectivity of these methodologies



Scheme 23. The relevance of sterical hindrance.

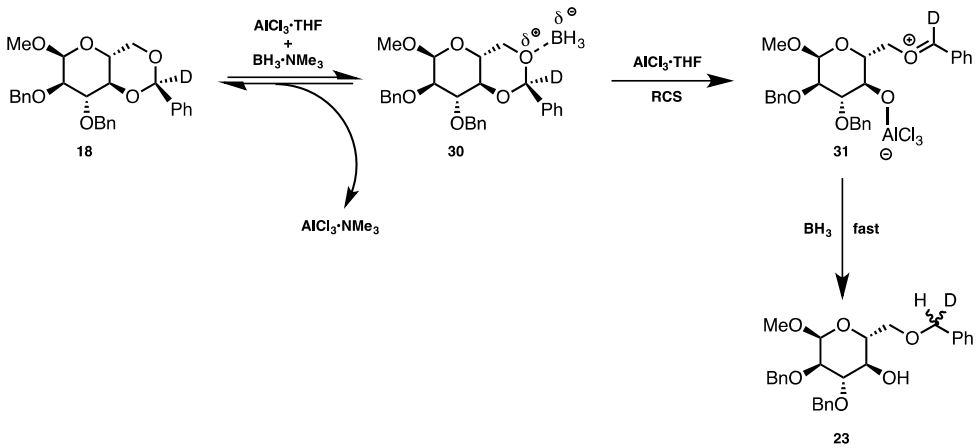
The 2° KIE and the effects from the EWD substituent both indicates that the formation of the oxocarbenium ion intermediate is a RCS, in contrary to the other two mechanisms. This elementary reaction also involves a second equivalent of $AlCl_3$•THF which is in line with the second order dependence, thus ruling out the alternative pathway (scheme 24) where the activated borane coordinates to O4 due to decreased steric bulk. If coordination to O4 would take place, borane would then act as both Lewis acid catalyst and as reducing agent similar to the suggested mechanism for regioselective reductive openings of benzylidene acetals with DIBAL-H *vide supra*.



Scheme 24. Erroneous explanation for the observed results for mechanism C.

If a second equivalent of $AlCl_3$•THF would take part in the formation the oxocarbenium ion by coordination to O6, then the situation would be similar to mechanism B.

A more probable mechanistic suggestion (scheme 25) is that the borane coordinates to O6 and thereby blocks this site from coordination by $AlCl_3$•THF. In a RCS, $AlCl_3$•THF instead coordinates O4 leading to a slow formation of an oxocarbenium ion which is reduced by borane in a fast step.



Scheme 25. Mechanism C: Reaction with BH_3·NMe_3-$AlCl_3$-THF.

Conclusions

In summary, we have provided mechanistic understanding for regioselective reductive openings of benzylidene acetal ring reactions using boranes and aluminum chloride. With deuterium labeled compounds and electron deficient benzylidene acetals, we have gained information regarding important intermediates. We present a mechanistic continuum ranging from solvent separated ion paired oxocarbenium ions to intimate ion pairs. The exact details are directed by the Lewis acid, the reducing agent, and the solvent. We conclude that these reactions progresses via three distinctly different mechanisms.

4. Daunosamine

General introduction

In the southeast corner of Italy, in what today is referred to as *Apulia*, lived an ancient tribe before Roman times called *Daunii* or *Daunians*. In this region, a soil sample was collected in the 1950s from which a colony of *Streptomyces peucetius* bacteria could be grown. These bacteria produced a deep red pigment which was shown to be an antibiotic compound later named daunomycin. Almost simultaneously in France, another team of scientists found a compound with antitumor activity which was named rubidomycin from its ruby red color. Further investigations of these compounds, during the 1960s, showed that they were active against tumors, especially for myelogenous leukemia, but more importantly, that they were the same compound. General consensus regarding the name was found and it is today referred to as Daunorubicin (DNR **32**, figure 5).[46]

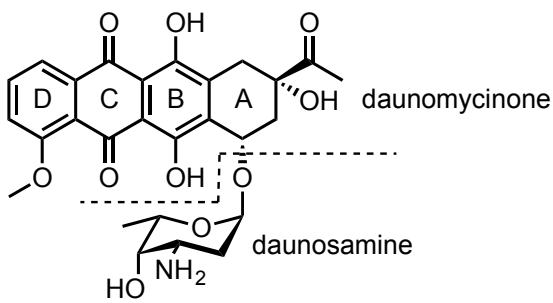


Figure 5. Daunorubicin **32**. The dashed line marks the boundary between the aglycon daunomycinone and the carbohydrate moiety daunosamine.

Mutated strains of *Streptomyces peucetius* bacteria produced new analogs of DNR. One of these analogs had a bluish gray color similar to that of the Adriatic Sea close to where the first soil sample was collected, hence, the name Adriamycin. This analog displayed an increased antitumor activity for some types of cancer

compared to DNR. Today, this compound is referred to as Doxorubicin (DOX **34**) and is probably the most commonly used chemotherapeutic agent.

This family of compounds, the anthracylines, has been expanded to include several analogs (figure 6). Almost exclusively, modifications have been made in the daunomycinone aglycon *e.g.* Idarubicin (IDA **33**) which differs from DNR by lacking the methoxy substituent in ring D. Only a few compounds with modifications in the daunosamine moiety have been synthesized, and shown anti tumor activities comparable to DOX and DNR. One example is Epirubicin (EPI **35**) which differs from DOX by inversed stereochemistry at position 4' of the carbohydrate residue giving the hydroxyl group an equatorial configuration. These compounds were accomplished either by mutations of the DNR producing bacteria, or by semi synthesis.

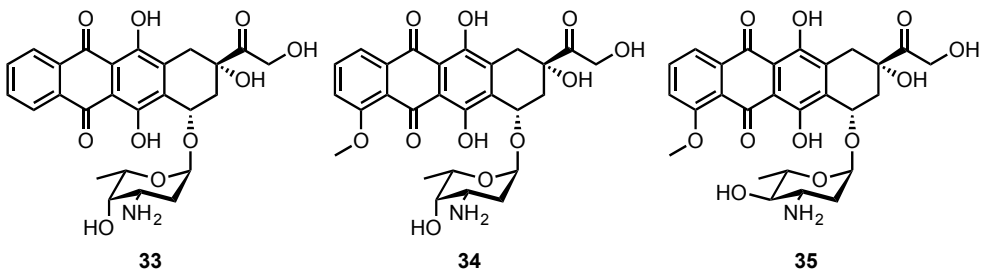


Figure 6. Anthracyclines IDA, DOX and EPI.

There are no well established mechanistic explanations for the biological activity of the anthracyclines. It is suggested that they form a ternary complex with DNA topoisomerase II and DNA, and thus creating DNA strand breaks. It is also possible that they can intercalate DNA, and thus inhibit replication and transcription. The limitations of the anthracylines are due to cardio toxicity and induction of multidrug resistance. Hence, extensive research has focused on solving these problems, although few analogs have matched the activity of the original compounds. SAR studies show that the non-intercalating domain, *i.e.* the daunosamine sugar and the aliphatic ring A, are crucial for the ability of the anthracyclines to bind the DNA minor groove and to inhibit DNA topoisomerase.[47]

Daunosamine have previously been synthesized from both carbohydrate sources as well as *de novo* from petroleum sources. However, daunosamine *per se* can not be used for synthesis of novel anthracycline derivatives. Instead there is a need for a suitable daunosamine donor. Fan *et al.*[48] explored truncated anthracycline analogs by preparing a daunosamine donor **36**. This donor was further on coupled to 1,2,3,4-tetrahydro-naphthalene and 1,2,3,4-tetrahydro-anthracene aglycons (figure 7).

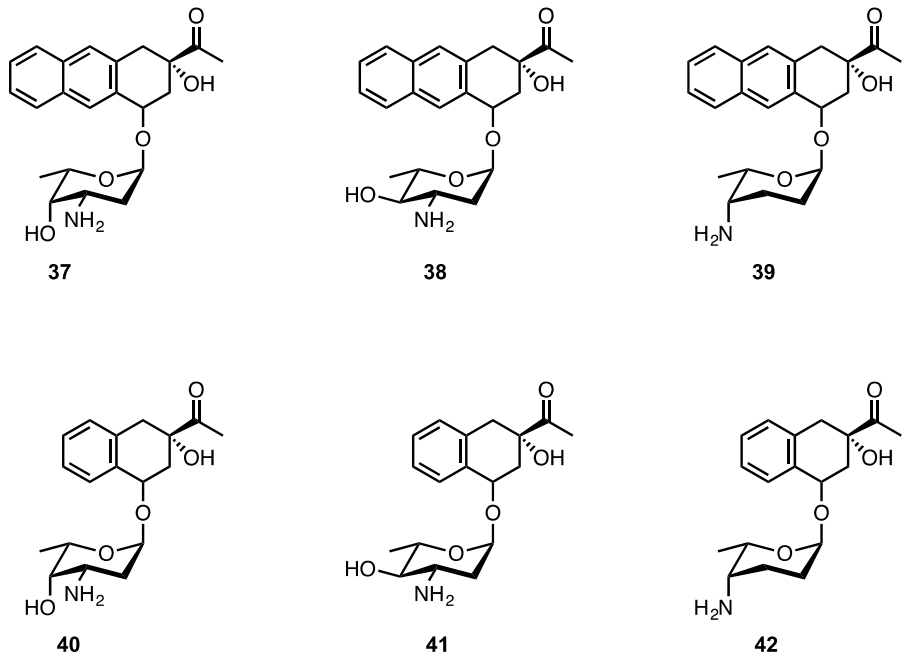


Figure 7. Truncated anthracycline derivatives explored by Fan *et al*.

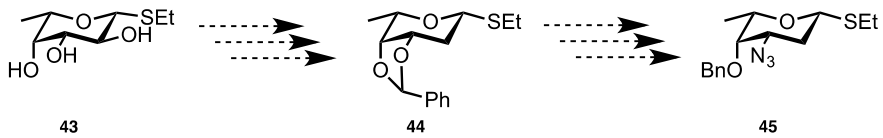
IC_{50} values for compounds **37**, **38**, and **39** were determined for MCF-7 cells and the results were comparable to that of DNR and DOX for the same cell line.[48]

Research aim

One aim of this thesis is to find more active and selective chemotherapeutics, and to study the biological mechanisms by which they interact with normal cells and tumor cells. Novel anthracycline analogs are to be synthesized using the bottom-up approach. We thus initiated studies to i) develop synthetic tools for making anthracycline analogs in a sustainable manner and ii) find the structural properties which makes anthracycline analogs active.

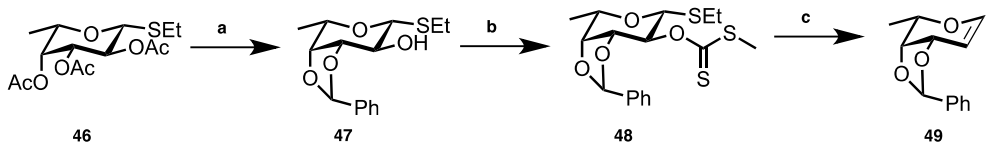
Daunosamine donor

In our pursuit of novel anthracycline analogs, carrying aliphatic as well as aromatic aglycons, we first had to design and evaluate a suitable daunosamine donor. We thus turned our attention to L-fucose, a natural carbohydrate with structural similarities to daunosamine, (scheme 26).



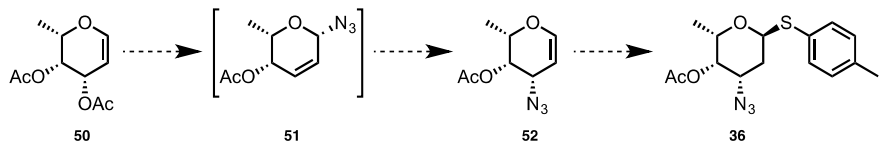
Scheme 26. Initial route towards a daunosamine donor.

Thus ethyl 1-thio-β-L-fucopyranoside **43** was protected with a benzylidene acetal[49] followed by introduction of a xanthate group at O2 (**48**). The subsequent Barton-McCombie reaction did not give the desired deoxy product **44**, instead the fucal **49** was formed in 24% yield (scheme 27).



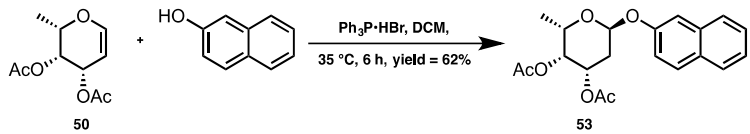
Scheme 27. *Reagents and conditions*: a) i. MeONa, MeOH, r.t., 6h. ii. *p*TSA, MeCN, 50 °C, 600 mBar, 10 h, 74%. b) NaI, CS_2, MeI, THF, 0 °C – r.t., 98%. c) n-Bu_3SnH, AIBN, PhMe, reflux, 8 h, 24%.

Instead, we turned our attention to glycals. Glycals are known to undergo Ferrier type I reactions[50,51] with azide ions to form enopyranosyl azides, which readily undergo [3,3]-sigmatropic rearrangements *in situ* to give 3-azido-3-deoxy glycals.[52-54] Our strategy was to use $Ph_3P{\bullet}HBr$ to glycosylate thiocresol with the 3-azido fucal **52** (scheme 28).[55]



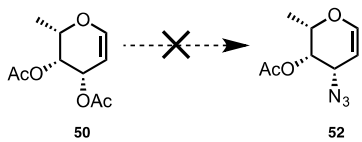
Scheme 28. Glycal route towards donor **36**.

We have previously been successful with this glycosylation protocol where di-*O*-acetyl-L-fucal **50** and 2-naphthol were glycosylated with high α-selectivity in 62% yield of **53** (scheme 29) .



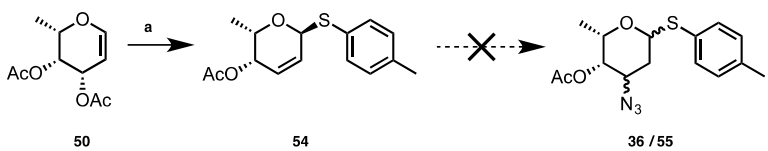
Scheme 29. α-Selective method towards 2-deoxy glycosides.

The conditions for the addition of azide ions, *i.e.* reaction times and catalyst amounts, found in the literature were contradictory.[52-54] We thus subjected L-fucal **50** to BF_3•OEt_2 and NaN_3 in MeCN (scheme 30) and varied reaction times and amount of catalyst. To our surprise, none of these conditions gave the desired glycal **52**.



Scheme 30. Ferrier reaction followed by [3,3]-sigmatropic rearrangement failed.

We thus explored reversed reaction order, *i.e.* glycosylation followed by addition of azide ions (scheme 31). The Ferrier reaction gave 44% of the thiocresyl pseudo fucal **54**.[56] For obvious reasons, the standard procedure to install a substituent using mercury(II) acetate, could not be used. Instead, we subjected **54** to a range of conditions (table 3). Unfortunately, we could not isolate any product. We speculate in that the double bond is resistant to mild acidic conditions, whereas strong acidic conditions results in degradation.



Scheme 31. *Reagents and conditions*: a) HSTol, BF_3•OEt_2, PhMe, 0 °C - r.t., 4 h, 44%.

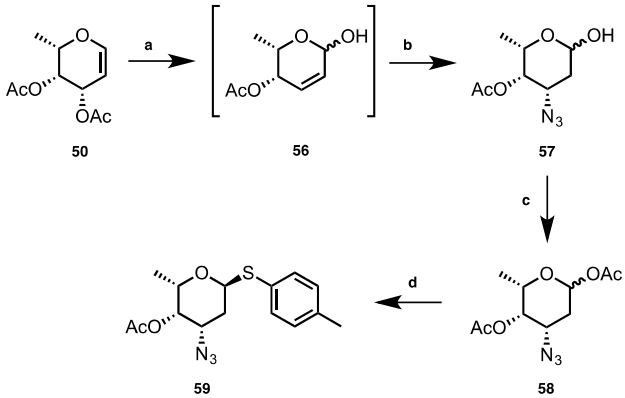
Table 3. Attempts for addition of HN_3 over the alkene **54.**

Entry	Azide	Catalyst	Solvent	Time	Result
1	NaN_3	HOAc	H_2O / MeCN (1:1)	48 h	NR[a]
2	NaN_3	HOAc	H_2O	48 h	NR
3	NaN_3	pTSA	HOAc	48 h	NR
4	NaN_3	Ph_3P-HBr	DCM	3 h	NR
5	TMS-N_3	AcOH /Et_3N	DCM	16 h	NR
6	NaN_3	TFA / 15-C-5	DCM / TFA (1:1)	23 h	degradation
7	NaN_3	TFA / 15-C-5	DCM	3 h	NR
8	TMS-N_3	TFA	DCM	3 h	NR
9	TMS-N_3	TMS-ONO_3	MeCN	24 h	NR
10	AgN_3[b]	HBr / AcOH	DMF	20 h	NR

[a] No reaction. [b] Generated *in situ*.

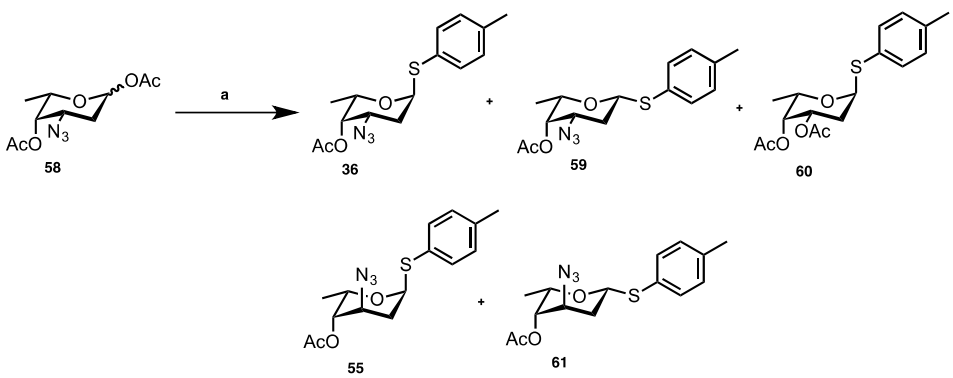
In 1987, Florent et al.[57] published a synthesis of acosaminide starting from di-*O*-acetyl-L-rhamnal. Fan et al.[48] adopted this method in their synthesis of the daunosamine donor, p-tolyl 4-*O*-acetyl-3-azido-2,3,6-trideoxy-1-thio-α-L-lyxohexopyranoside **36**. This method is also based on the Ferrier type I reaction, *i.e.* the addition of water to di-*O*-acetyl-L-rhamnal at 80 °C followed by acid catalyzed addition of azide ions in room temperature for 24 h. After acetylation using standard procedures (pyridine/Ac_2O (1:1) in DCM for 24 h), the glycosylation with thiocresol was catalyzed by $Sc(OTf)_2$ in DCM for 10 h. At this point, an inseparable mixture of four compounds was obtained. Fan *et al.* could only separate the mixture after deacetylation and in order to retrieve **36**, two additional steps were required to invert the configuration at C4.

To our knowledge, this methodology has not been performed with the corresponding fucal. Thus we explored the possibility of applying this method using di-*O*-acetyl-L-fucal **50** (scheme 32) as starting material.



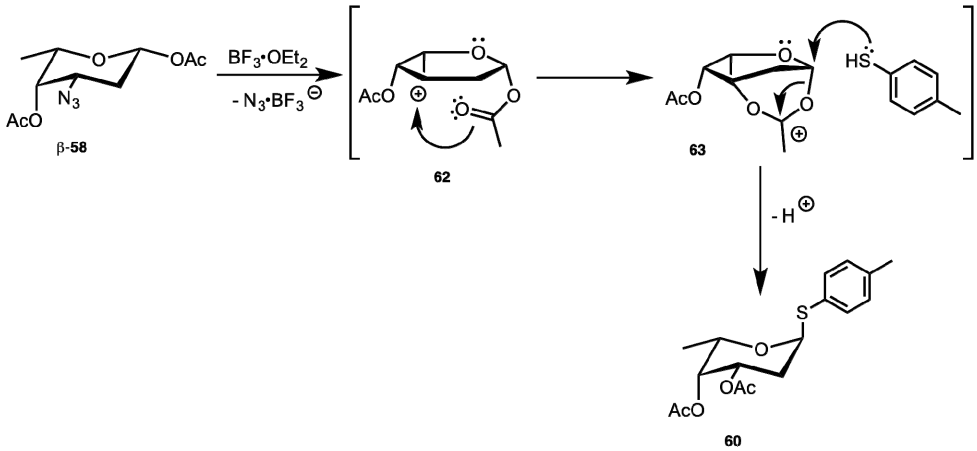
Scheme 32. *Reagents and conditions*: a) H_2O, 100 °C, microwave, 15 min. b) NaN_3, HOAc, 100 °C, microwave, 10 min. (c) Ac_2O, pyridine, rt, 1 h. (d) HSTol, BF_3•OEt_2, DCM, -40 °C, 5 min. 32% overall yield from **50**.

We thus subjected **58** to thiocresol, BF_3•OEt_2 in DCM at room temperature and received a very complex reaction mixture. Apart from the four expected diastereoisomers **36**, **59**, **55**, and **61**, we also isolated compound **60** (scheme 33).



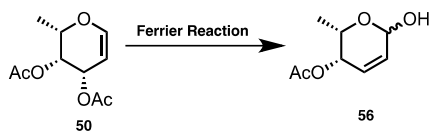
Scheme 33. *Reagents and conditions*: a) HSTol, BF_3•OEt_2, DCM, rt.

The formation of **60** can be explained (scheme 34) by the competing reaction where BF_3•OEt_2 induces bond cleavage between azide and β-**58**, forming the carbocation **62**. The acetoxy group at C1 bridges C3, and forms the activated intermediate **63** that undergoes α-selective glycosylation with thiocresol, leading to **60**.



Scheme 34. Mechanistic explanation for the formation of **60**.

When we lowered the temperature to -40 °C, decreased the reaction time to 5 minutes, and limited the equivalents of both BF_3•OEt_2 and thiocresol to 1.25 and 1.2 respectively, we detected fewer side products. This facilitated purification but the overall yield of the desired **36** remained an unsatisfactory 16%. We identified the formation of the pseudo glycal **56** (scheme 35), formed by heating **50** at 80 °C in H_2O, as a limiting step since competing side reactions converted the product to undesired side products prior to full conversion. Hence, we set out to optimize this reaction.

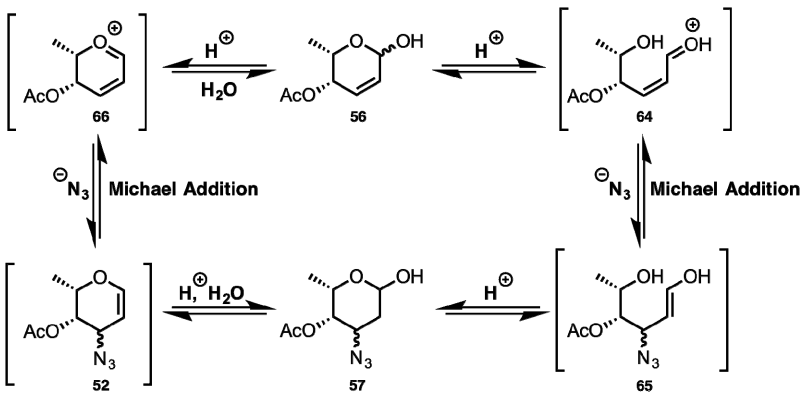


Scheme 35. The Ferrier type I reaction in H_2O.

Refluxing fucal **50** in H_2O gave full conversion after 30 minutes with fewer side products. We then turned to microwave heating in order to test temperatures above boiling point. We initially heated the reaction at 100 °C in a microwave reactor, which gave full conversion after 15 minutes and virtually no side products. The explanation for the often better results possible using microwave irradiation, has been much disputed. One logical explanation is that single mode microwave reactors with external IR sensors, measures the temperature at the surface of the reaction vessel. This might lead to slightly erroneous measurements due to the reversed temperature gradient in the reaction medium, compared to classical refluxing in a round bottom flask with a heating mantle. The ability to convert microwave energy to heat is measured in tan δ which is dependent on temperature.

High absorbing solvents typically has tan δ > 0.5 and low absorbing solvents tan δ < 0.1. Kappe argues that the actual temperature might be slightly higher then the set temperature, especially for highly absorbing solvents, *e.g.* ethylene glycol (tan δ = 1.350; 20 °C) and ethanol (tan δ = 0.941; 20 °C). Water is a low absorbing solvent (tan δ = 0.123; 20 °C) and hence, this effect is smaller in our case.[58] Another attribute credited to microwave heating is the rapid and more evenly distributed heating which causes the temperature gradient to decrease. There are probably many factors involved in the enhancement of the reaction conditions, but a plausible explanation is that the Boltzmann distribution of energy is much more narrow leading to fewer side reactions.

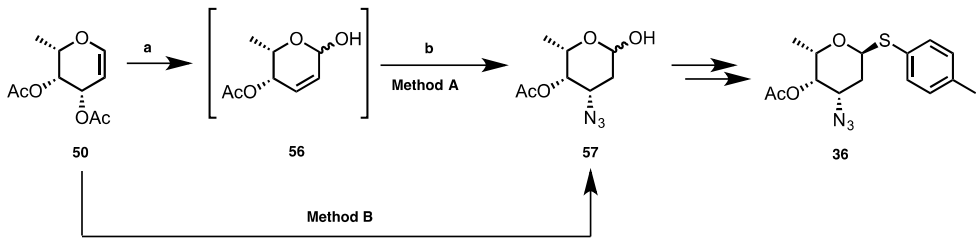
We could then introduce the azide group regioselectively at C3 of the pseudo glycal **56** using NaN_3 and AcOH in H_2O. It is well known that hemiacetals equilibrates with the open aldehyde in acidic aqueous solution, and it is plausible that the addition goes via a 1,4-Michael addition reaction with intermediate **64** (scheme 36). Another possible intermediate is allyloxocarbenium ion **66**. This intermediate could also undergo 1,4-Michael addition and subsequent addition of H_2O to form **57**.



Scheme 36. Possible mechanisms for regioselective addition of azide ions.

We decided to optimize the reaction conditions for the acid catalyzed 1,4-Michael addition of azide to hemiacetal **56** (scheme 37). We again turned to microwave heating and thus mixed **56** with NaN_3 and AcOH in H_2O and heated at 100 °C in a microwave reactor for 10 minutes (method A, table 4). Acetylation and glycosylation then gave **36** in 19% yield. Unfortunately, we found traces of **54** in this material, which we could not separate from **36**. We believe this is due to incomplete conversion of **56** to **57**. We then increased the reaction time to 30 minutes which solved the impurity problem but decreased the yield of **36** to 16%.

A 15 minute reaction gave only a slight improvement (17% yield). Next, we explored a one-pot procedure (method B, table 4) where **50** was mixed with NaN_3 and AcOH in H_2O and heated at 100 °C in a microwave reactor but the results were similar. When we increased the temperature to 120 °C the yield dropped to 8%. Considering the possible mechanistic explanation (scheme 36), an increased concentration of azide ions should force the equilibrium towards **57**. To our satisfaction, heating **50** at 100 °C in a microwave reactor for 15 minutes followed by addition of NaN_3 (4 equiv.) and AcOH and continued heating at 100 °C for 10 minutes yielded 30% of pure **36**. The reaction mixture was close to saturation of azide since the yield only increased to 32% when we used 6 equivalents of azide. Decreasing solvent volume by half might increase the reaction rate. We thus doubled the concentration of **56** which did not increase the yield but showed that we could scale up the reaction, despite limitations in microwave reactor volume.

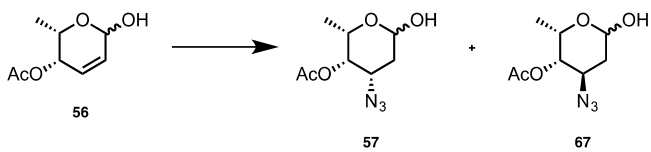


Scheme 37: Optimization of synthesis of **36**. a) H_2O, 100 °C microwave, 15 min. b) NaN_3, HOAc. Method A: sequential reaction. Method B: one-pot reaction.

Table 4. Conditions for optimization

Method	Time	Temp.	Conc.	Equiv. N_3	Yield	Conv.	Comment
A	24 h	rt	0.25 M	1.6	16%		
A	10 min	100 °C	0.25 M	1.6		19%	trace **54**
A	15 min	100 °C	0.25 M	1.6	17%		
A	30 min	100 °C	0.25 M	1.6	16%		
A	10 min	100 °C	0.25 M	4.0	30%		
A	10 min	100 °C	0.25 M	6.0	32%		
A	10 min	100 °C	0.50 M	4.0	29%		
B	20 min	100 °C	0.25 M	1.6		22%	15 mol% **54**
B	25 min	100 °C	0.25 M	1.6		20%	8 mol% **54**
B	30 min	100 °C	0.25 M	1.6		18%	trace **54**
B	10 min	120 °C	0.25 M	1.6	8%		

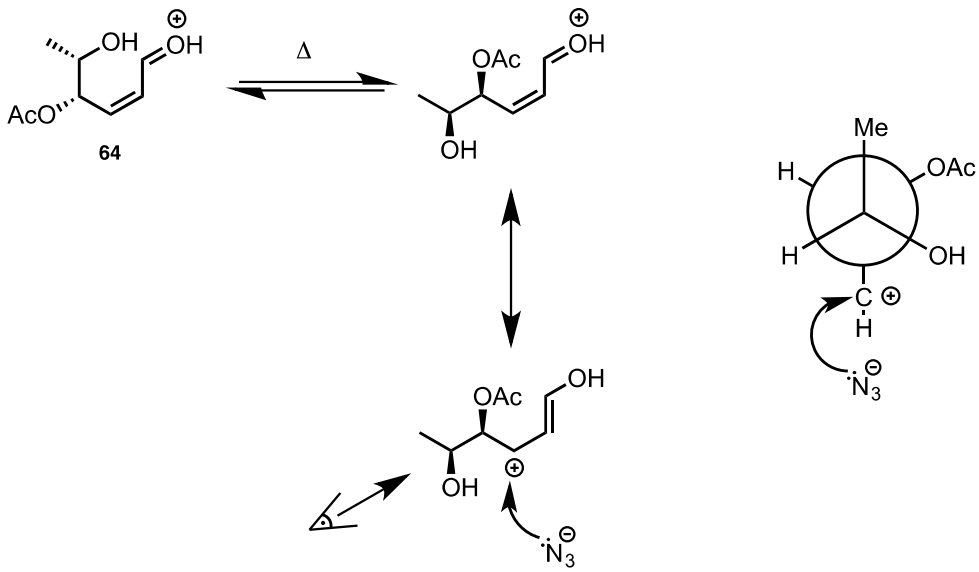
In our study, the stereoselectivity for the azide addition (scheme 38) was 2:1 (**57**/**67**) which is opposite the findings of Renneberg *et al.*[59] They found that generating **56** *in situ* with AcOH, HCl (1 M), THF from methyl 4-*O*-acetyl-2,3,6-trideoxy-α,β-L-threo-hex-2-enopyranoside followed by addition of NaN_3 (1.75 equiv.) and stirring at room temperature for 10 h gave a 1:2.4 ratio of corresponding products.



Scheme 38. Diastereomeric distribution between **57** and **67**.

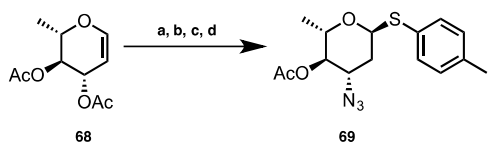
The conclusion we draw from these experiments suggests that long reaction times at low temperatures favor the axial azide, whereas short reaction times at high

temperatures favor equatorial azide. An explanation for this observation could be that high temperatures allows the open α,β-unsaturated aldehyde chain intermediate **64** to adopt other conformations (scheme 39) and hence making one side slightly more accessible than the other. It could also be due to a faster decompositon of **67**. The competing reaction pathway (scheme 36), via allyloxocarbenium ion intermediate **66**, is less probable. The excess H_2O favors the reaction pathway via the open chain aldehyde intermediate.



Scheme 39. Plausible explanation for stereoselective addition of azide.

To explore the scope and limitations of this procedure, we applied the reaction sequence to di-*O*-acetyl-L-rhamnal **68** yielding the corresponding *epi*-daunosamine donor **69** in 28% yield (scheme 40).



Scheme 40. *Reagents and conditions*: a) H_2O, 100 °C, microwave, 15 min. b) NaN_3, HOAc, 100 °C, microwave, 10 min. c) Ac_2O, pyridine, r.t., 1 h. d) HSTol, BF_3•OEt_2, DCM, -40 °C, 5 min. 28% overall yield from **68**.

Conclusions

In summary, we have synthesized a versatile daunosamine donor as well as the corresponding *epi*-daunosamine donor in three synthetic steps from commercially available di-*O*-acetyl-L-fucal **50** (scheme 32) and di-*O*-acetyl-L-rhamnal **68** (scheme 40), respectively. Our aim was a short and simple synthetic route. There are more advanced protocols for stereoselective 1,4-Michael additions of azides to α,β-unsaturated carbonyl compounds (Jacobsen's chiral $[(salen)Al]_2O$ catalyst[60], L-proline methyl ester additive[61]). These type of procedures would not be applicable in our case since they require extensive work-up and purification procedures. Our method requires two work-up procedures and one purification for the entire route. From an economical and environmental standpoint, we argue that this method is more sustainable.

Aromatic daunosides

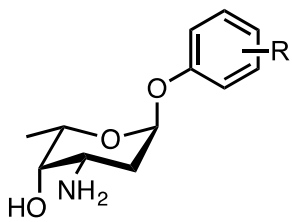
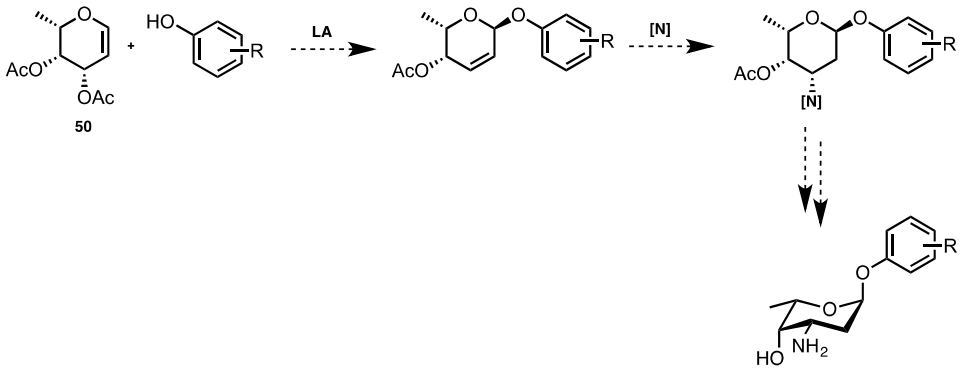


Figure 8. General representation of aromatic daunosides.

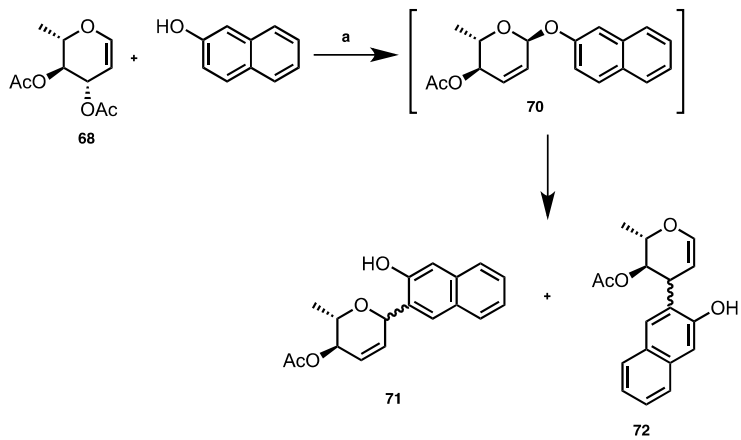
We aimed to investigate the possibility of synthesizing novel anthracyline analogs with a bottom up approach *i.e.* total synthesis starting from a carbohydrate source. To our knowledge, no aromatic daunosides have been synthesized and evaluated in biological systems. We set out to design a general method for synthesis of aromatic daunosides.

Initially, we evaluated a route where the aglycon was introduced in the first step using a Ferrier Type I reaction (scheme 41). Subsequent amination at C3 followed by deprotection would yield aromatic daunosides in four to five steps.



Scheme 41. Synthetic route based on the Ferrier Type I reaction.

We thus evaluated different reaction conditions using a model system with di-*O*-acetyl-L-rhamnal **68** and 2-naphthol (scheme 42). The rationale for using **68** instead of fucal **50** was structural similarities and yet inexpensive starting material. The Lewis acid catalyzed Ferrier Type I reaction between glycals and phenols are notorious for causing rearrangement *in situ* to form C-glycosides and other isomers.[62] In our studies , we made the same observations and isolated a complex reaction mixtures with compounds **71** and **72** as major products (table 5).

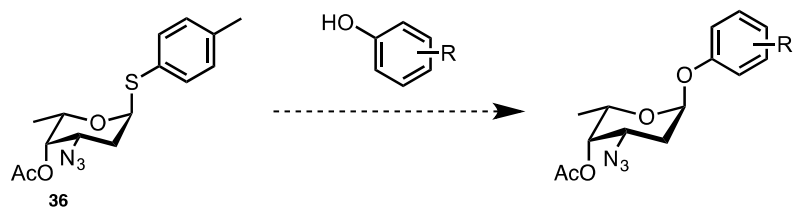


Scheme 42. *Reagents and conditions:* See table 5.

Table 5. Reagents and condition evaluated for a (scheme 42).

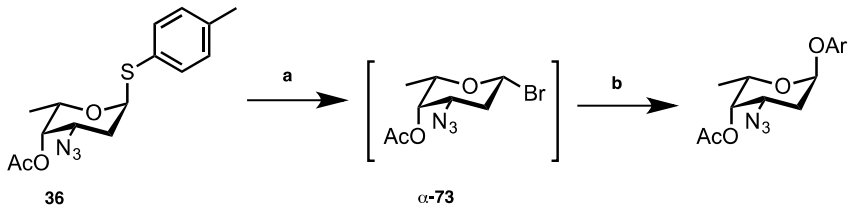
Entry	Lewis Acid	Reaction Media	Temp.	Time
1	$BF_3 \bullet OEt_2$	Toluene	-10 °C	5 h
2	$ZnCl_2$	Al_2O_3 (s)	rt	40 min.
3	H_3PO_4	DCM	rt	35 min.
4	*p*TSA	DCM	rt	2 h
5	*p*TSA	Toluene	rt	20 min.

We then evaluated routes using daunosamine donor **36** (scheme 43). There are numerous procedures for preparation of aromatic 2-deoxy α-glycosides from 1-thio 2-deoxy glycosyl donors. 2-deoxy donors are neither "armed" nor "disarmed" according to the concept brought forth by Fraser-Reid.[63] These thioglycosyl donors are commonly activated using NIS or NBS with TfOH. However, we where not successful with these conditions and we hence turned our attention towards Koenigs-Knorr reactions *i.e.* converting the thioglycosyl donor to glycosyl bromide followed activation using silver salts.[20]



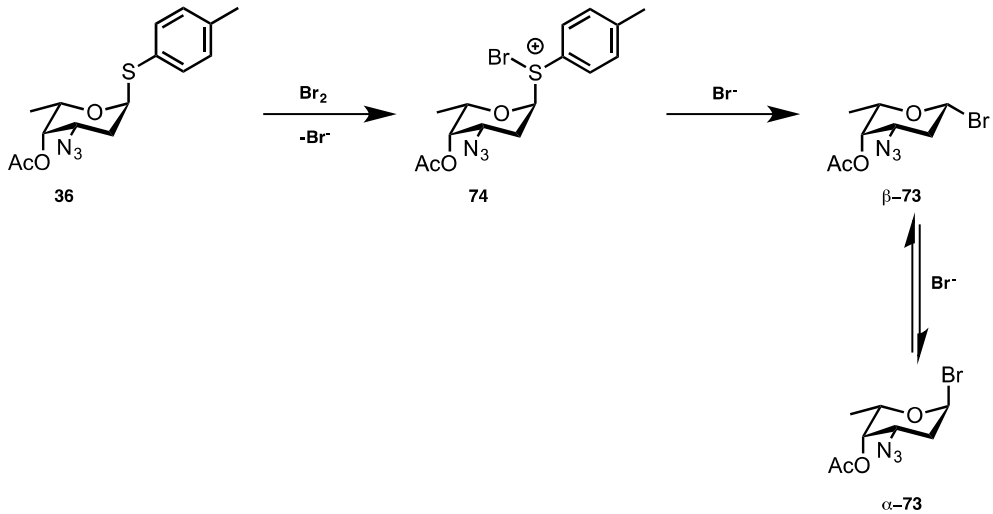
Scheme 43. Synthetic route based on thioglycosyl donor **36**.

Glycosyl bromides are unstable under most conditions and generally have shelf lives of a few days. Generating the glycosyl bromide *in situ* is beneficial also for reasons of stereoselectivity *vide infra*. We thus subjected **36** to bromine in DCM at 0 °C generating the daunosyl bromide **73** prior to mixing with acceptor and Ag_2O (scheme 44).



Scheme 44. *Reagents and conditions*: a) Br_2, DCM, 0 °C, 5 min. b) Ag_2O, ArOH, 4 Å MS, DCM, r.t.

The activation with bromine was rapid and could not be monitored by TLC. We found that a short reaction time (5 minutes) was important for this step. Equally important was to maintain 0 °C, as higher temperatures and longer reaction times generated α,β-aromatic daunoside mixtures with β-daunosides as major products. As the subsequent Koenigs-Knorr proceeds via an S_N2-type reaction, the glycosyl bromide must adopt β-anomeric configuration to get desired α-anomeric product. The equilibrium between α-**73** and β-**73** (scheme 45) accounts for the distribution of α,β-daunosides under thermodynamic control.[21]



Scheme 45. Plausible explanation for presence of β-anomers.

This method proved to be applicable for a variety of phenols and naphthols and hence we set out to synthesize a collection of aromatic daunosides (figure 9). To compare the effect of aromatic daunosides, the structurally similar aliphatic daunosides **81** and **80** were synthesized. This could be achieved with the previously mentioned protocol without modifications.

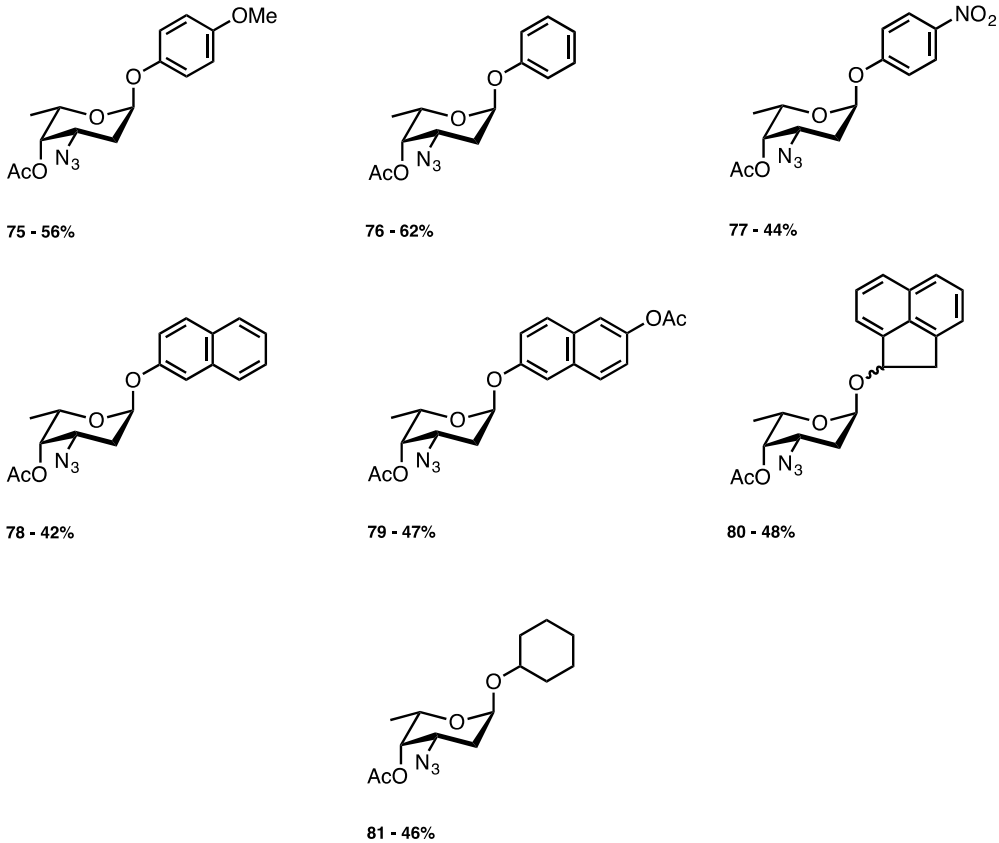
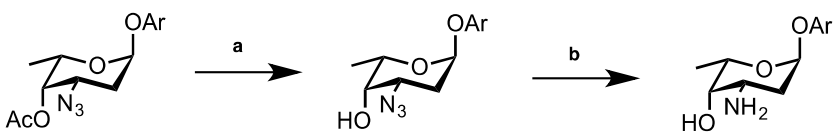


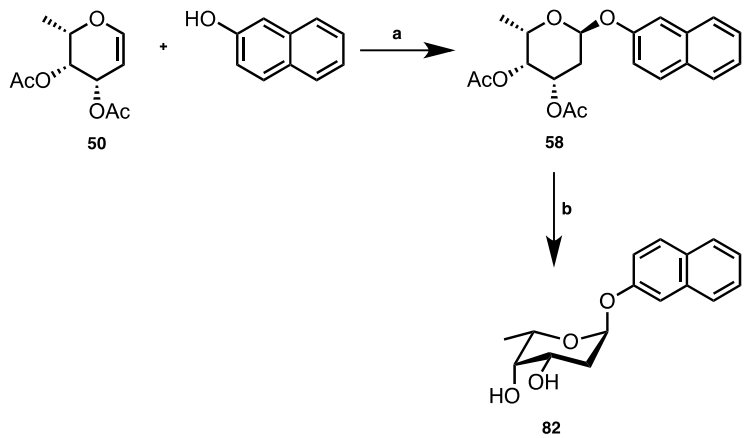
Figure 9. Daunosides synthesized with method described above. Overall yields from **36**.

To obtain the actual daunosamine moiety, deacetylation followed by Staudinger reduction was required. We successfully achieved the reduction of azide using polymer bound Ph_3P which facilitated purification (scheme 46).



Scheme 46. *Reagents and conditions*: a) K_2CO_3, MeOH, r.t., 24 h. b) polymer bound Ph_3P, THF/H_2O - 10:1, 80 °C, 4 h.

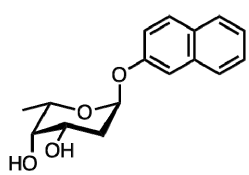
To further expand the structure-activity relationship (SAR) study in general and to evaluate the effect of the amine functionality in particular, we synthesized the hydroxyl analog **82** (scheme 47).



Scheme 47. *Reagents and conditions*: a) $Ph_3P{\bullet}HBr$, DCM, 0 °C, 6 h, 62%. b) MeONa, MeOH, r.t., 3 h, 44%.

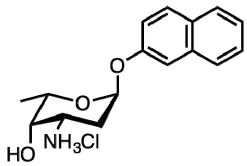
Biological Evaluations

Antiproliferative activity of comound **82** and **87** was measured with a human breast cancer cell line from a 49-year-old female patient with infiltrative ductal cancer (HCC70 cells) and a normal cell line, human adult fibroblast from breast tissue of a 37-year-old patient with infiltrative ductal cancer (CCD-1095Sk cells). Antiproliferative activity of compounds **83**, **84**, **85,** and **86** were measured with two human breast cancer cell lines. One from a 62-year-old woman with ductal breast cancer (JIMT-1), one cell line from a 69-year-old woman with breast adenocarcinoma (MCF-7), and one from human adult female with a ZFN knock out modification (MCF-10A).



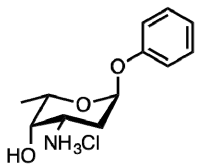
82

Antiproliferative activity of compound **82** was determined by incubating HCC70 and CCD-1095Sk cells with increasing concentrations of compound **82** (5-500 μM) for 96 h. ED_{50} values for compound **82** were calculated as 163 μM and 124 μM for HCC70 and CCD-1095Sk, respectively. Thus, the compound showed moderate cytotoxicity but no selectivity for cancer cells.

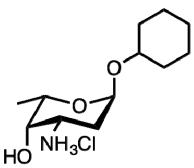


87

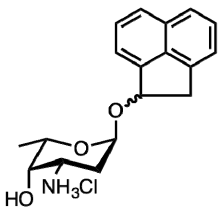
Antiproliferative activity studies of compound **87** initially showed both toxicity and selectivity. After 6 h incubation of 100 μM **87** with HCC70 and CCD-1095Sk cells, < 5% of HCC70 cells and 50% of CCD-1095Sk cells remained.



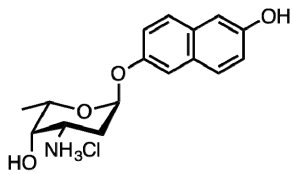
83



84



85



86

Antiproliferative activities of compounds **83**, **84**, **85,** and **86** was determined by incubating JIMT-1, MCF-7 and MCF-10A cells with increasing concentrations of compounds **83**, **84**, **85** and **86** (0.01-100 μM) for 96 h. Unfortunately, no response was observed for these compounds.

Conclusions

Due to ready access of the versatile donor **36**, we could evaluate synthetic routes towards aromatic daunosides as well as aliphatic daunosides. Further on, we used this method to produce a variety of aromatic daunosides. A hydroxyl analog was synthesized to study the effect of the amine of daunosamine. Initial biological evaluations of these compounds showed little or no effects, and further studies are required in order to draw any conclusions regarding their biological activities.

5. Concluding remarks and future perspectives

The focus of the research described in this thesis, has been to understand the reactivity of acetals. Thus we want to improve the applicability of carbohydrates as complex building blocks in the synthesis of pharmaceuticals and materials.

- Research objective 1: What are the mechanisms for regioselective reductive openings of benzylidene acetals?

We have described plausible mechanisms for the regioselective reductive openings of benzylidene acetals, which can generate new methodologies and further improve their use in organic synthesis. To fully grasp the holistic view of acetal reactivity and their properties, further mechanistic investigations poses future research objectives.

- Research objective 2: How can synthetic studies improve the tools for discovery of novel anthracycline analogs?

We have conducted synthetic studies of the reactions yielding a useful daunosamine donor, especially using the 1,4-Michael addition. With knowledge of the mechanism and the use of microwave heating, we could improve conditions for this step without the expense of the environment or atom economy. These findings have improved the synthetic tools for discovering novel anthracycline analogs. The mechanistic understanding of the Ferrier Type I reaction is still limited to assumptions and speculation and needs to be further addressed. To improve the synthesis of 3-amino-2,3-dideoxy-glycosides *e.g.* daunosamine donor **36**, more thorough investigations of the Ferrier reaction mechanism should be performed, especially for the reactions between glycals and azides but also for phenolic additions to glycals to form O-glycosides. If the addition of azide to C1, and the simultaneous displacement of an acetoxy group from C3, followed by a [3,3]-sigmatropic rearrangement can be achieved in a stereo controlled fashion, the probability of preparing compounds like **36** in two steps would increase and the requirements for an ideal synthesis would be fulfilled.[12,13]

- Research objective 3: What are the biological mechanisms by which the anthracyclines interact with human physiology? Can novel anthracycline analogs, synthesized using the bottom-up approach, help answer these questions?

The initial biological evaluations of the novel aromatic daunosides and their analogs has not yet generated enough data to provide certain conclusions. Continued evaluation and investigations of the biological mechanisms are to be undertaken.

6. Populärvetenskaplig sammanfattning (summary in swedish)

År 2014 är ordet "kolhydrater" för de flesta människor förknippat med kost och olika dieter. Det må vara en viktig aspekt, men dock långt från den viktigaste. Kolhydrater utför nämligen en rad viktiga processer i levande organismer.

Av de 200 mest säljande läkemedelsprodukterna på den amerikanska marknaden 2012, har omkring 75 % av dem en aktiva substans som består av små organiska ämnen. Under 1900-talets andra hälft, bestod huvuddelen av dessa molekyler av enkla, styva och tvådimensionella strukturer, molekyler som följer de så kallade Lipinskis regler. Om vi ska hitta nya substanser mot multiresistenta bakterier, virus och cancer måste vi vidga vår uppfattning om vad ett läkemedel är. Möjligheterna är oändliga när man tillverkar organiska molekyler på konstgjord väg för läkemedelsutveckling och produktion, men för att kommersialisera dessa på ett miljö- och socioekonomiskt hållbart sätt, måste utvecklingen begränsas till lättillgängliga aktiva substanser.

Aktiva substanser baserade på kolhydrater har länge varit eftersatt som motiv i läkemedelsdesign, även om deras centrala roll i människans fysiologi är väl etablerad. Ett hinder som ofta framhålls är att komplexitetsnivån för sådana strukturer får till följd att tillverkningen av nya molekyler på konstgjord väg blir en svår, dyr och mödosam process. Selektivitet blir svårt på grund av de många hydroxylgrupperna och det krävs ofta omfattande skyddsgruppskemi. Detta gör det svårt och dyrt att producera kolhydratbaserade läkemedel.

Om verkligt nya och aktiva substanser skall tas fram, måste nya metoder utvecklas. För att uppnå detta, måste vi förstå den underliggande reaktiviteten hos kolhydrater. Hur olika delar av molekylerna reagerar och de mekanismer som styr dessa reaktioner är starkt sammankopplade med möjligheten att använda dessa substanser som farmtida läkemedel.

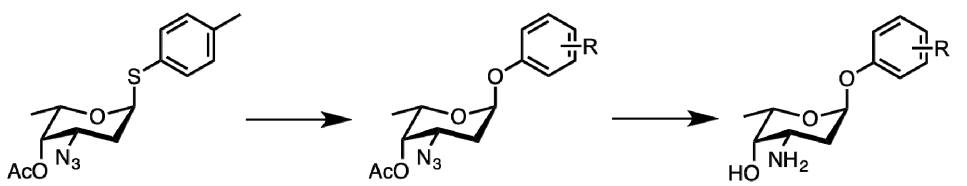
En kolhydratmolekyl, eller sockermolekyl, innehåller i huvudsak två typer av så kallade funktionella grupper: alkoholer och aldehyder. Den senare består av en kolatom med två bindningar till *samma* syre. För att fullt ut kunna förstå den sistnämnda gruppen i sockermolekyler bör man förstå de så kallade acetal- och hemiacetal- grupperna eftersom dessa bildas spontant inom molekylen. Acetalgruppen består av en kolatom med två bindningar till två *olika* syreatomer som i sin tur binder till ytterligare en kolatom vardera. Förutom acetalgruppen som socker bildar med sig själv måste vi också förstår hur acetaler kan skydda andra delar av sockermolekylen.

Målen för forskningen som beskrivs i denna avhandling är 1) att förklara hur öppningar av de så kallade bensylidenacetaler går till och belysa dessa mekanismer i detalj. 2) Undersöka reaktiviteten (hur de reagerar med olika kemiska ämnen) för acetalgruppen inom sockermolekylen för att ta fram nya verktyg som kan utnyttjas vid framställning av nya läkemedel. 3) Undersöka om dessa verktyg kan användas till framställande av nya potentiella botemedel mot cancer, på ett ekonomisk och miljövänligt sätt.

7. Experimental part

General: Known and commercially available compounds were in agreement with previously published data (NMR). Anhydrous DCM was available via a solvent dispensing system (MB SPS-800). THF was distilled from Na (s). Moisture sensitive reactions were carried out under N_2 using dried glassware. NMR spectra were recorded using a Bruker Avance II at 400 MHz (^{1}H) and at 100 MHz (^{13}C), operating at 294 K. Chemical shifts are given in ppm downfield from Me_4Si, with reference to residual $CHCl_3$, 7.26 ppm. Reactions were monitored by TLC using alumina plates coated with silica gel (Merck 60 F_{254}) and visualized using either UV light or by charring with ethanolic H_2SO_4 or staining with a solution of *p*-methoxybenzaldehyde (26 mL), glacial acetic acid (11 mL), concentrated H_2SO_4 (35 mL) and 95% ethanol (960 mL). Microwave heated reactions were performed in sealed tubes with a Biotage™ Initiator Classic microwave instrument using an external surface temperature sensor. Preparative chromatography was performed with an automated Biotage™ Isolera One purification apparatus.

Glycosylation to aromatic daunosides

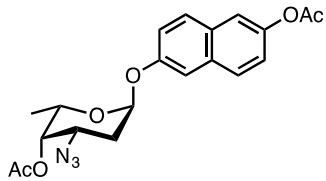


General experimental procedure for aromatic daunosides.

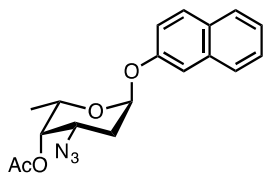
To a solution of **36** (100 mg, 0.31 mmol) in anhydrous DCM (3 mL) cooled to 0 °C was added Br_2 (21.5 µL, 0.42 mmol). After 5 minutes, the solution was added to a mixture of aglycone (0.62 mmol), Ag_2O (76 mg, 0.33 mmol), 4Å MS and anhydrous DCM (1.5 mL). This mixture was stirred at rt and the reaction was monitored by TLC until completion. The reaction mixture was diluted with DCM and filtered through a celite plug (∅ 40 mm x 10 mm). The celite plug was washed with DCM and the combined filtrates were evaporated. The crude product was

chromatographed (SiO_2; n-heptane / Ethyl Acetate) to give protected aromatic daunoside.

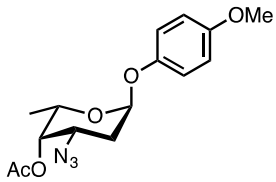
Protected aromatic daunoside (0.145 mmol), K_2CO_3 (0.753) and MeOH (9.5 mL) were mixed and stirred at r.t. After 24 h, Amberlite IR-H^+ (arbitrary amount) was added until pH = 7. The reaction mixture was filtered and the solvents evaporated. The crude product was chromatographed (n-heptane / ethyl acetate) to give the alcohol. The alcohol (0.044 mmol) was mixed with polymer bound Ph_3P (30.1 mg, 0.090 mmol), THF (2 mL) and H_2O (0.2 mL) and heated to 55 °C. After 24 h, the reaction mixture was allowed to reach r.t., diluted with DCM (0.2% Et_3N, 10 mL) and evaporated onto silica gel. The crude product was chromatographed (DCM / MeOH – 10:1, 0.2% Et_3N) to give deprotected aromatic daunoside.



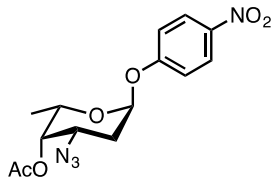
2-(6-*O*-acetyl-naphthyl) 4-*O*-acetyl-3-azido **-2,3,6-trideoxy-α-L-lyxo-hexopyranoside (79).** Yield 47%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, 2H, *J* = 8.6, 7.5, Hz, Ar), 7.49 (dd, 2H, *J* = 14.7, 2.3 Hz, Ar), 7.23-7.18 (m, 2H, Ar), 5.86 (d, 1H, *J* = 2.3 Hz, H-1), 5.24 (d, 1H, *J* = 2.6 Hz, H-4), 4.14-4.10 (m, 2H, H-3/H-5), 2.36-2.19 (m, 2H, H-2/H-2'), 2.35 (s, 3H, $COCH_3$), 2.23 (s, 3H, $COCH_3$), 1.11 (d, 3H, *J* = 6.6 Hz, H-6); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 169.9, 154.2, 147.3, 132.5, 129.3, 128.6, 126.9, 126.5, 119.5, 118.5, 110.4, 95.6, 70.1, 66.3, 54.6, 29.8, 21.3, 20.9, 16.8;



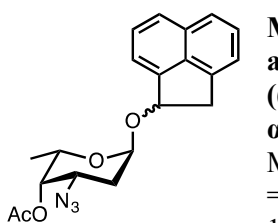
2-naphthyl 4-*O*-acetyl-3-azido-2,3,6-trideoxy-α-L-lyxo-hexopyranoside (78). Yield 42%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.42 (m, 3H, Ar), 7.39-7.35 (m, 3h, Ar), 7.28-7.18 (m, 1H, Ar), 5.88 (d, 1H, *J* = 2.4 Hz, H-1), 5.25 (d, 1H, *J* = 2.4 Hz, H-4), 4.15 (q, 1H, *J* = 7.3 Hz, H-5) 4.13 (ddd, 1H, *J* = 15.3, 8.7, 3.0 Hz, H-3), 2.29 (dt, 1H, *J* = 12.9, 3.4 Hz, H-2), 2.23 (s, 3H, CO_2CH_3), 2.24-2.19 (m, 1H, H-2'), 1.12 (d, 3H, 7.3 Hz, H-6); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 154.3, 134.5, 129.7, 129.7, 127.8, 127.3, 126.6, 124.4, 118.7, 110.4, 95.6, 70.2, 66.3, 54.7, 29.8, 20.9, 16.8.



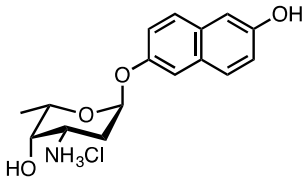
***p*-methoxy-phenyl 4-*O*-acetyl-3-azido-2,3,6-trideoxy-α-L-lyxo-hexopyranoside (75).** Yield 56%; R_f =0.50 (7:3, heptane-EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98, 6.82 (ABq, 2H each, *J* = 9.2 Hz, Ar), 5.59 (d, 1H, *J* = 2.4 Hz, H-1), 5.21 (d, 1H, *J* = 2.4 Hz, H-4), 4.16 – 4.08 (m, 1H, H-5), 4.04 (ddd, 1H, *J* = 12.3, 5.1, 3.0 Hz, H-3), 3.76 (s, 3H, $ArOCH_3$), 2.25 – 2.20 (m, 1H, H-2/H-2'), 2.20 (s, 3H, CO_2CH_3), 2.18 – 2.10 (m, 1H, H-2/H-2'), 1.10 (d, 3H, *J* = 6.6 Hz, H-6); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 155.0 , 150.6, 117.5, 114.7, 96.2, 70.2, 65.9, 55.7, 54.6, 29.8, 20.9, 16.8. HRMS calcd for $C_{15}H_{19}N_3O_5Na$ (M+Na) 344.12169, found 344.12148.



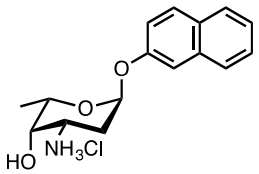
***p*-nitro-phenyl 4-*O*-acetyl-3-azido-2,3,6-trideoxy-α-L-lyxo-hexopyranoside (77).** Yield 44%; R_f = 0.51 (7:3, heptane-EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22, 7.14 (ABq, 2H each, *J* = 9.3 Hz, Ar), 5.82 (d, 1H, *J* = 2.6 Hz, H-1), 5.23 (d, 1H, *J* = 2.3 Hz, H-4), 4.08 – 3.98 (m, 2H, H-5, H-3), 2.34 – 2.23 (m, 1H, H-2/H-2'), 2.21 (s, 3H, CO_2CH_3), 2.20 – 2.14 (m, 1H, H-2/H-2'), 1.10 (d, 3H, *J* = 6.5 Hz, H-6).



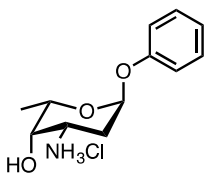
Mixture (1:1) of 1-((1R)-acenaphthenol) 4-*O*-acetyl-3-azido-2,3,6-trideoxy-α-L-lyxo-hexopyranoside and 1-((1S)-acenaphthenol) 4-*O*-acetyl-3-azido-2,3,6-trideoxy-α-L-lyxo-hexopyranoside (80). Yield 48%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, 2H, *J* = 8.5 Hz, Ar), 7.67 (d, 2H, *J* = 8.2 Hz, Ar), 7.59-7.46 (m, 6H, Ar), 7.33 (dd, 2H, *J* = 6.8, 1.3 Hz, Ar), 5.74 (dd, 1H, *J* = 6.9, 1.9 Hz, $ArCH_2R$), 5.65 (dd, 1H, *J* = 7.2, 2.2 Hz, $ArCH_2R$), 5.53 (d, 1H, *J* = 3.3 Hz, H-1), 5.38 (d, 1H, *J* = 3.1 Hz, H-1), 5.20 (br s, 2H, H-4), 4.26 (q, 1H, *J* = 6.5 Hz, H-5), 4.17 (q, 1H, *J* = 6.5 Hz, H-5), 3.88 (ddd, 2H, *J* = 12.6, 7.6, 4.4 Hz, H-3), 3.76 (t, 1H, *J* = 6.6 Hz,), 3.72 (t, 1H, *J* = 6.6 Hz,), 3.34 (d, 2H, *J* = 17.4 Hz,), 2.22 (s, 6H, $COCH_2$), 2.14 (dt, 2H, *J* = 14.3, 3.4 Hz, H-2), 1.99-1.92 (m, 2H, H-2'), 1.25 (d, 3H, *J* = 6.6 Hz, H-6), 1.24 (d, 3H, *J* = 6.6 Hz, H-6); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 143.3, 142.9, 141.8, 141.5, 137.8, 137.6, 131.5, 131.4, 128.3, 128.3, 127.9, 127.8, 125.4, 125.3, 122.9, 121.3, 121.0, 120.0, 119.9, 96.1, 78.8, 78.3, 70.4, 70.3, 65.9, 65.7, 54.6, 54.6, 39.5, 38.6, 30.1, 29.7, 20.9, 16.9, 16.9;



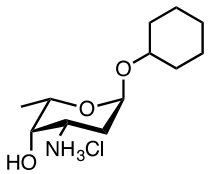
2-(6-hydroxy-naphthyl) 3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranoside (86). Yield 62%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (t, 2H, *J* = 9.5 Hz, Ar), 7.40 (d, 1H, *J* = 2.4 Hz), 7.14 (dd, 1H, *J* = 8.9, 2.5 Hz), 7.06-7.03 (m, 2H, Ar), 5.80 (s, 1H, H-1), 4.09 (q, 1H, *J* = 7.3 Hz, H-5), 3.87 (ddd, 1H, *J* = 12.5, 3.0, 1.5 Hz, H-3), 3.72 (br s, 1H, H-4), 2.21 (dt, 1H, *J* = 12.7, 3.3 Hz,), 2.09 (dd, 1H, *J* = 12.6, 4.6 Hz,), 1.19 (d, 3H, *J* = 6.6 Hz,);



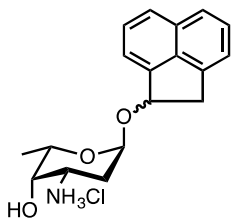
2-naphthyl 4-*O*-acetyl-3-azido-2,3,6-trideoxy-α-L-lyxo-hexopyranoside (87). Yield 70%; ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.78 (d, 2H, *J* = 8.7 Hz, Ar), 7.74 (d, 1H, *J* = 8.2 Hz, Ar), 7.48 (d, 1H, *J* = 2.8 Hz, Ar), 7.45-7.41 (m, 1H, Ar), 7.36-7.32 (m, 1H, Ar), 7.22 (dd, 1H, *J* = 9.0, 2.4 Hz, Ar), 5.83 (d, 1H, *J* = 2.0 Hz, H-1), 4.05 (q, 1H, *J* = 6.6 Hz, H-5), 3.66-3.62 (m, 2H, H-4/H-3), 2.14-2.02 (m, 2H, H-2/H-2'), 1.18 (d, 3H, *J* = 6.6 Hz, H-6). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.4, 134.5, 129.6, 129.0, 127.2, 126.6, 126.0, 123.7, 118.5, 110.2, 100.0, 95.3, 68.4, 67.2, 30.1, 15.7. HRMS calcd for $C_{16}H_{20}NO_3$ (M+H) 274.1443, found 274.1151.



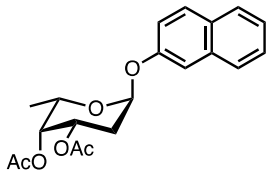
Phenyl 3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranoside (83). Yield 17% R_f = 0.07 (9:3, DCM-EtOH, 0.2% NEt_3). $[\alpha]^{20}_D$ – 131.9 (c 0.0004, MeOH). ^{1}H NMR (400 MHz, MeOD) δ 7.33 – 7.22 (m, 2H), 7.11 – 6.94 (m, 3H), 5.71 (d, 1H, *J* = 2.6 Hz, H-1), 4.03 (dd, 1H, *J* = 13.3, 6.7 Hz, H-5), 3.80 (ddd, 1H, *J* = 12.6, 4.7, 3.0 Hz, H-3), 3.68 (d, 1H, *J* = 2.6 Hz, H-4), 2.17 (td, 1H, *J* = 12.8, 3.5 Hz, H-2/H-2'), 2.04 (dd, 1H, *J* = 12.9, 4.8 Hz, H-2/H-2'), 1.18 (d, 3H, *J* = 6.6 Hz, H-6). HRMS calcd for $C_{12}H_{18}NO_3$ (M+H) 224.1287, found 224.1278.



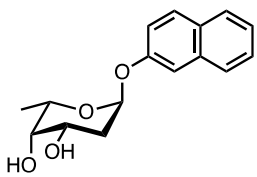
Cyclohexanyl 3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranoside (84). Yield 74%; R_f = 0.08 (10:1, DCM-MeOH, 0.2% NEt_3). $[\alpha]^{20}_D$ -139.5 (c 0.004, MeOH). ^1H NMR (400 MHz, MeOD) δ 5.02 (d, *J* = 3.1 Hz, 1H, H-1), 3.96 (q, *J* = 6.5 Hz, 1H, H-5), 3.60 – 3.51 (m, 1H, $OCHR_2$), 3.49 (s, 1H, H-4), 3.26 (m, 1H, H-3), 1.95 – 1.23 (m, 12H, H-2, H-2', Cy), 1.18 (d, *J* = 6.6 Hz, 3H, H-6); ^{13}C NMR (100 MHz, MeOD) δ 96.0, 75.8, 70.7, 67.7, 48.1, 34.6, 32.7, 32.7, 26.8, 25.2, 25.0, 17.2. HRMS calcd for $C_{12}H_{24}NO_3$ (M+H) 230.1756, found 230.1754.



Mixture (1:0.8) of 1-((R)-acenaphthenol) 3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranoside and 1-((S)-acenaphthenol) 3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranoside (85). Yield 55%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78-7.75 (m, 2H, Ar), 7.65 (d, 2H, *J* = 8.3 Hz, Ar), 7.58-7.47 (m, 6H, *J* = Hz,), 7.32 (d, 2H, *J* = 6.8 Hz, Ar), 5.75 (dd, 1H, *J* = 6.5, 1.8 Hz, ArCHOR), 5.68 (dd, 1H, *J* = 7.2, 2.3 Hz, $ArCH_2R$), 5.49 (d, 1H, *J* = 3.1 Hz, H-1), 5.35 (d, 1H, *J* = 2.9 Hz, H-1), 4.62 (s, 2H, H-4), 4.21 (q, 1H, *J* = 7.2 Hz, H-5), 4.13 (q, 1H, *J* = 6.3 Hz,), 3.78-3.69 (m, 2H, $ArCH_2R$), 3.67 (br s, 2H, $ArCH_2R$), 3.63 (m, 2H, H-3), 2.10 (dq, 2H, *J* = 12.7, 3.6 Hz, H-2), 1.85-1.78 (m, 2H, H-2'), 1.34 (d, 3H, *J* = 6.6 Hz, H-6), 1.33 (d, 3H, *J* = 6.6 Hz,);



2-naphthyl 3,4-di-*O*-acetyl α-L-oliopyranoside (53). Crude **50** (502 mg, 2.35 mmol) was dissolved in anhydrous CH_2Cl_2 (12.0 mL) under N_2 (g). 2-Naphthol (507 mg, 3.52 mmol) was added to the solution, and finally triphenylphosphine hydrogen bromide (42.3 mg, 0.12 mmol) was added. The mixture was heated to 35°C and stirred under N_2 (g) supply for 6 h. The mixture was stirred with $NaHCO_3$ (aq sat.) for 5 min, and subsequently extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, filtered and evaporated to give a brown viscous oil. The crude (1.05 g) was purified by flash chromatography (heptane-EtOAc 8:1 → 1:1) resulting in **53** (517 mg, 62% yield). The α/β ratio was 16:1. $[\alpha]^{20}_D$ = -173.0 ˚C (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.76-7.80 (m, 3H, ArH), 7.42-7.47 (m, 2H, ArH), 7.34-7.39 (m, 1H, ArH), 7.19-7.24 (m, 1H, ArH), 5.88 (d, 1H, *J* = 1.9, 1-H), 5.56 (ddd, 1H, *J* = 12.4, 5.2, 3.0, 3-H), 5.27 (d, 1H, *J* = 2.8, 4-H), 4.22 (q, 1H, *J* = 12.7, 6.8, 5-H), 2.29 (dt, 1H, *J* = 12.6, 3.6, 2ax-H), 2.15 (dd, 1H, *J* = 12.8, 5.2, 2eq-H), 2.22, 2.05 (2s, 6H, 2 CO_2CH_3), 1.12 (s, 3H, 6-H); ^{13}C NMR (100 MHz, $CDCl_3$); δ_C 170.8 (CO_2CH_3), 170.1 (CO_2CH_3), 154.4, 134.5, 129.7, 129.6, 127.8, 127.3, 126.5, 124.3, 118.9, 110.3, 96.0, 69.8, 66.8, 65.9, 32.0, 21.1, 20.9, 16.7. HRMS calcd for $C_{20}H_{22}NaO_6^+$ [M+Na]: 381.1314 found: 381.1314.



2- naphthyl α-L-oliopyranoside (82). 53 (394 mg, 1.1 mmol) was dissolved in MeOH (7.10 mL). NaOMe (0.36 mL, 0.05 M) was added to the mixture. After 2.5 h, the mixture was neutralized with Amberlite R-120 H^+, filtered and evaporated to a light brown oil. The crude material was purified by flash chromatography, followed by recrystallization in $CHCl_3$ and heptane during cooling, resulting in **1** (132 mg, 44% yield). $[\alpha]^{20}_D$ = - 221.8 ˚C (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.73-7.86 (m, 3H, ArH), 7.42-7.48 (m, 2H, ArH), 7.33-7.39 (m, 1H, ArH), 7.18-7.22 (m, 1H, ArH), 5.78 (d, 1H, *J* = 3.3, 1-H), 4.30 (ddd, 1H, *J* = 11.6, 5.2, 3.1, 3-H), 4.07 (dd, 1H, *J* = 13.2, 6.6, 5-H), 3.74 (d, *J* = 2.9, 4-H), 2.19 (dd, 1H, *J* = 13.2, 5.4, 2ax-H), 2.00 (dd, 1H, *J* = 13.2, 3.7, 2eq-H), 1.25 (s, 3H, 6-H), ^{13}C NMR (100 MHz, $CDCl_3$); δ_C 154.6, 134.6, 129.6, 129.5, 127.7, 127.3, 126.5, 124.2, 118.9, 110.4, 96.2, 71.2, 66.8, 66.0, 33.0, 16.9. HRMS calcd for $C_{16}H_{18}NaO_4^+$ [M+Na]: 297.1103 found: 297.1103.

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"By rod and lash the boy was punished, taught to show no pain, no mercy. Constantly tested, tossed into the lab. Left to pit his wits and will against nature's fury. It was his initiation, his time at the university, for he would return to his people a Doctor of Philosophy, or not at all."

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Paper I

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

Richard Johnsson,[†] Markus Ohlin,[†] and Ulf Ellervik*

Organic Chemistry, Lund University, P.O. Box 124, SE-221 00 Lund, Sweden.
[†] These authors contributed equally to this work

ulf.ellervik@organic.lu.se

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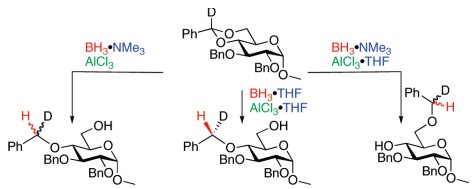

Despite the importance of regioselective reductive openings of cyclic acetals, mechanistic details are scarce. In this study 4,6-*O*-benzylidene acetals were used as model compounds for deciphering the mechanism of regioselective openings using a variety of reducing agents. Competitive isotopic studies 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.

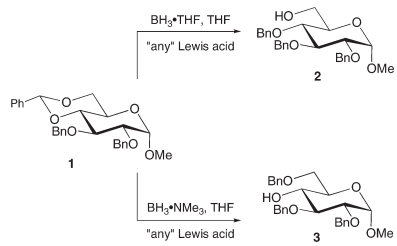
Unlike reductive openings of cyclic acetals, there is a substantial body of experiments performed on acid-mediated additions of carbon nucleophiles to acetals. This reaction was initially introduced by Mukaiyama in 1974[7] and the mechanistic details have later on been thoroughly investigated by several 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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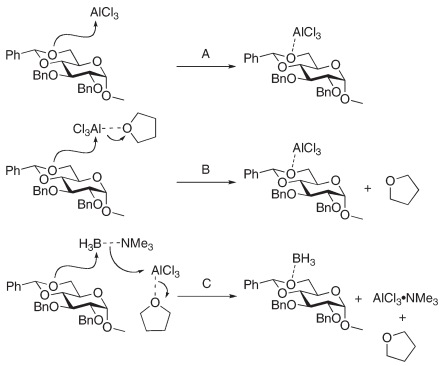
(15) Wang, C.-C.; Luo, S.-Y.; Shie, C.-R.; Hung, S. C. *Org. Lett.* **2002**, *4*, 847–849.

(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**),

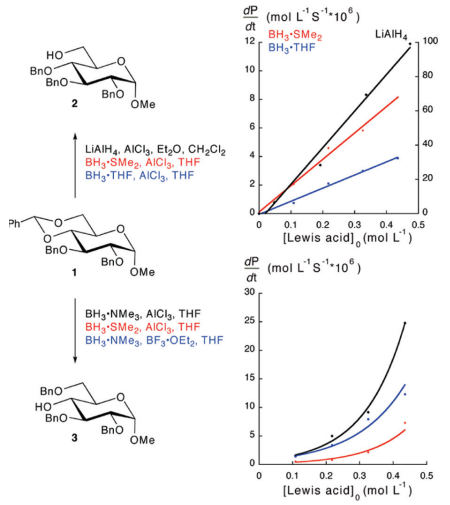


FIGURE 1. Summary of kinetic studies of acetal openings. Reactions opening the acetal to a free 6-hydroxyl group follow first order kinetics (top graph: $LiAlH_4$, black diamonds [right *y*-axis];, $BH_3 \cdot SMe_2$, red circles; and $BH_3 \cdot THF$, blue squares), while reactions to a free 4-hydroxyl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

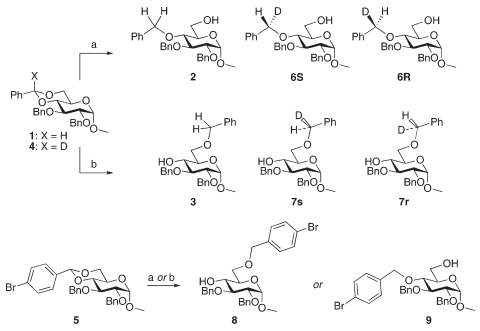
Clearly, reactions using activated and unactivated boranes follow different mechanistic routes and cannot be described by one unifying mechanism, but rather by a mechanistic scheme.

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 $\sigma_{para}(Br) = 0.26$).

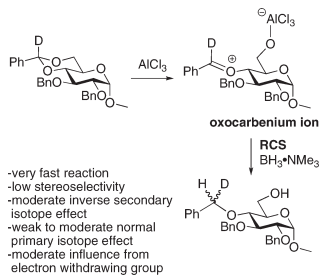
A. Reactions in Nonpolar Solvents. We first investigated the modified Garegg conditions, i.e. $BH_3 \cdot NMe_3 - AlCl_3$ in toluene. The deuterium-labeled compound **4** was thus opened using undeuterated $BH_3 \cdot NMe_3$ and $AlCl_3$ in toluene at room temperature. These reactions were completed 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.

(18) Mori, I.; Ishihara, K.; Flippin, L. A.; Nozaki, K.; Yamamoto, H.; Bartlett, P. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 6107–6115.

(19) Yamamoto, Y.; Nishii, S.; Yamada, J.-i. *J. Am. Chem. Soc.* **1986**, *108*, 7116–7117.

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

(20) Denmark, S. E.; Almstead, N. G. *J. Org. Chem.* **1991**, *56*, 6485–6487.
(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.

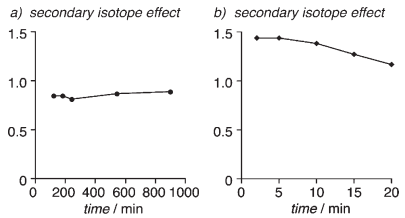
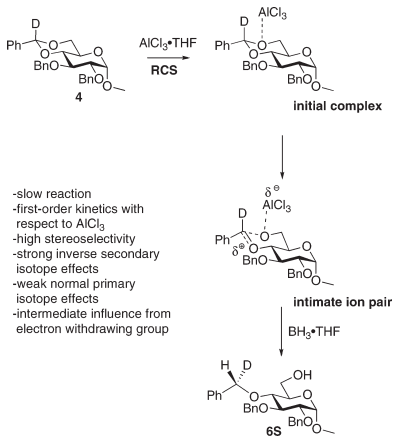


FIGURE 2. Competitive isotope study of reductive opening of equimolar mixtures of **1** and **4** using (a) $BH_3\cdot THF-AlCl_3-THF$ and (b) $BH_3\cdot NMe_3-AlCl_3-THF$.

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

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(24) Ryschkewitsch, G. E. *J. Am. Chem. Soc.* **1960**, *82*, 3290–3294.
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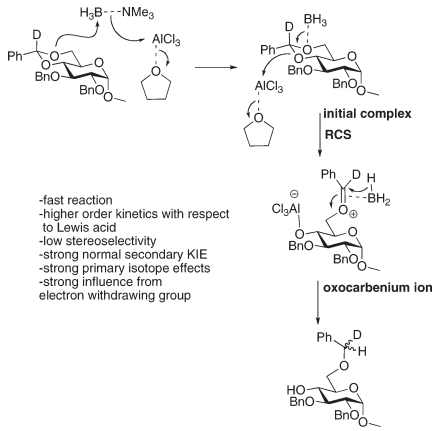
(27) (a) Hernández-Torres, J. M.; Achkar, J.; Wei, A. *J. Org. Chem.* **2004**, *69*, 7206–7211. (b) Sherman, A. A.; Mironov, Y. V.; Yudina, O. N.; Nifantiev, N. E. *Carbohydr. Res.* **2003**, *338*, 697–703.
(28) Lane, C. F. *Aldrichim. Acta* **1975**, *8*, 3–10.

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



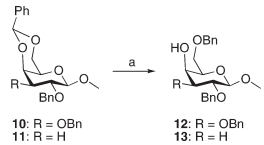
reliably measured, i.e. reactions with HCl gave an isotope effect of 2.7 while DCl lowered the effect to 1.1. A control experiment using only $NaCNBD_3$ (96% D) gave a large proportion (43%) of the unlabeled compound **3**. It is thus reasonable to assume that the Brønsted acid catalyzed the exchange 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]

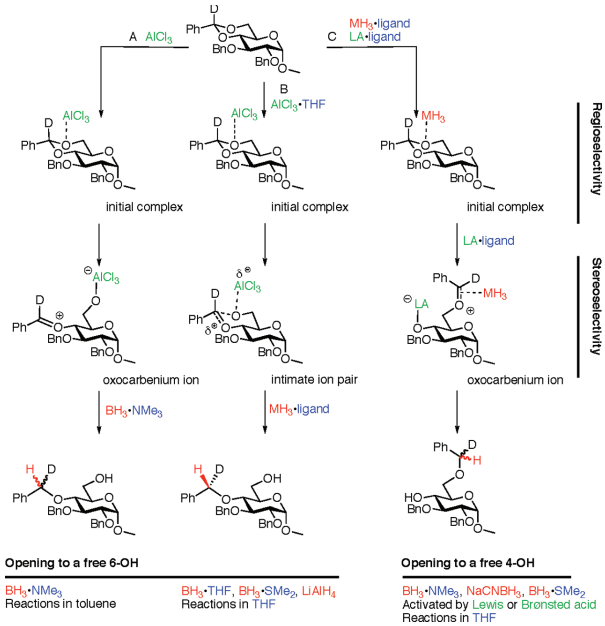
Experimental Section

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, $CDCl_3$). ^{1}H 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, $CDCl_3$). ^{1}H 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, $CHCl_3$). ^{1}H 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, $CHCl_3$). ^{1}H 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.

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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.

Paper II

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Regioselective reductive openings of 4,6-benzylidene acetals: synthetic and mechanistic aspects

Markus Ohlin, Richard Johnsson [†], Ulf Ellervik [*]

Center for Analysis and Synthesis, Lund University, PO Box 124, SE-221 00 Lund, Sweden

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Dedicated to Professor András Lipták on the occasion of his 75th birthday

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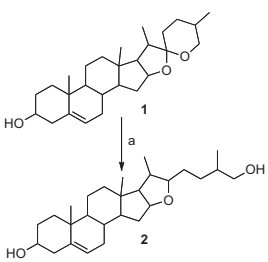
Boranes
Lewis acid
Mechanism

ABSTRACT

The use of benzylidene acetals as protecting groups in carbohydrate chemistry is utterly important. The main advantage of benzylidene acetal is the ability for regioselective openings. 4,6-benzylidene acetal can be opened selectively under reductive conditions to yield either free 4-OH or 6-OH. There are a plethora of methods available for regioselective openings, but only a few of these are widely used. In recent years, the mechanism has been investigated for borane mediated openings and it seems likely that the regioselectivity is determined by borane, rather than Lewis acid. When borane is activated by Lewis acids, borane is the most electrophilic species that consequently coordinates to the most nucleophilic oxygen of the acetals, usually O-6. This results in the formation of 6-*O*-benzyl ethers. If borane is not activated, Lewis acid is the most electrophilic species that thus adds to O-6 and hence generates the 4-*O*-benzyl ether.

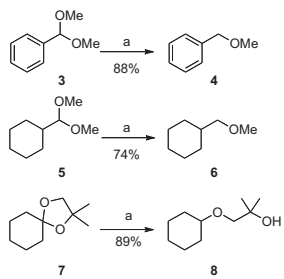
1. Introduction

In December 1951, Doukas and Fontaine published the first example of a regioselective reductive opening of a cyclic acetal. They thus subjected diosgenin (**1**), a steroidal precursor in the semisynthesis of progesteron and other steroids, to lithium aluminum hydride and, in the presence of hydrogen chloride gas in anhydrous ether the acetal opened to give dihydrodiosgenin (Scheme 1).[1]



Scheme 1. Opening of diosgenin. Reagents: (a) $LiAlH_4$, Et_2O, HCl.

A couple of years later Eliel and Rerick reasoned that the reagent in the reduction might be lithium aluminum hydride–aluminum chloride, and subsequently subjected a number of acetals (e.g., **3**, **5,** and **7**) to these conditions and thus isolated the corresponding ethers in good yields (Scheme 2).[2,3] The best yields were observed using a ratio of $AlCl_3$ to $LiAlH_4$ of 4:1 and a ratio of $LiAlH_4$ to acetal of 1:2.



Scheme 2. Examples of reductive acetal openings. Reagents: (a) $LiAlH_4$, Et_2O, $AlCl_3$.

* Corresponding author. Tel.: +46 46 222 8220; fax: +46 46 222 8209.
E-mail address: ulf.ellervik@organic.lu.se (U. Ellervik).
† Present address: Department of Chemistry, McGill University, Montréal, Québec, Canada H3A 2K6.

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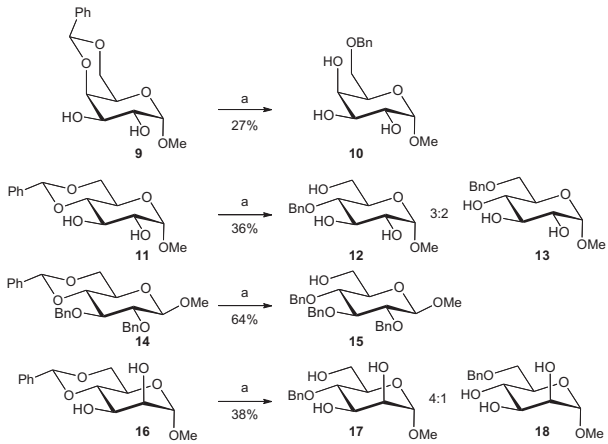
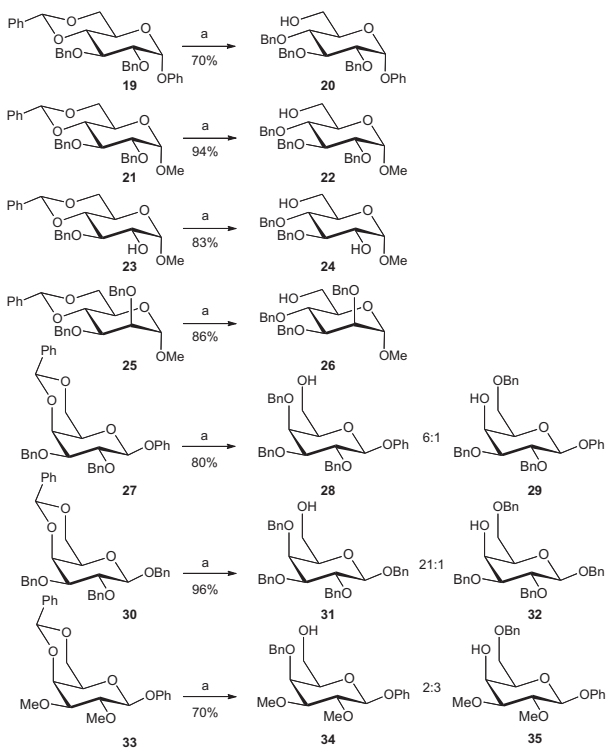


Scheme 3. Acetal openings presented by Bhattacharjee and Gorin. Reagents and conditions: (a) $LiAlH_4$, $AlCl_3$, CH_2Cl_2–Et_2O, reflux.



Scheme 4. Acetal openings presented by Lipták et al. Reagents and conditions: (a) $LiAlH_4$, $AlCl_3$, CH_2Cl_2–Et_2O, reflux.

In 1969 Bhattacharjee and Gorin transferred the use of reductive openings of benzylidene acetals to carbohydrate chemistry. A slightly modified method, that is, an equimolar mixture of $AlCl_3$ and $LiAlH_4$ in refluxing CH_2Cl_2–Et_2O (1:3) was used to open a number of different acetals as summarized in Scheme 3.[4]

The chemo-, stereo- and regioselectivities of reductive openings of benzylidene acetals were then intensively explored by Lipták et al.[5] Some of the results are summarized in Scheme 4. In general, this reagent combination gave regioselective openings to the 4-*O*-benzyl protected compounds in good yields and the results from these investigations indicate that the regioselectivity is not dependent on the anomeric configuration, the aglycon, or substitution at O-2. However, in the case of galactose derivatives, regioisomeric mixtures were usually the result. In addition free hydroxyl groups influenced the regioselectivity and yields.

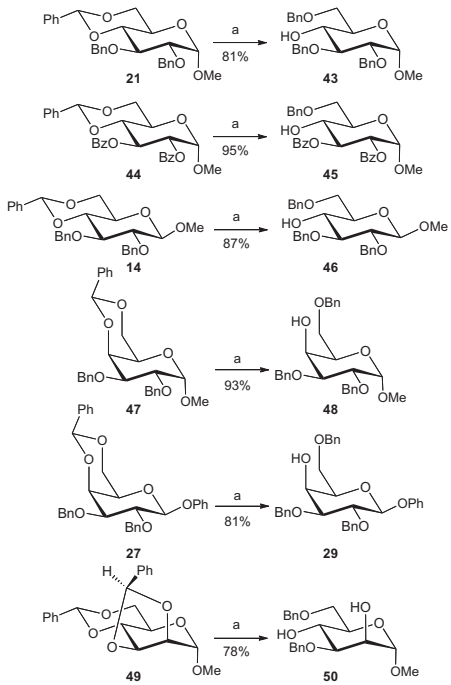
Another series of experiments by Lipták et al. showed very interesting results, as summarized in Scheme 5.[6] Reductive openings of these double benzylidene protected compounds with 1 equiv of the reagent opened only the dioxolane ring. Ring opening of the *exo*-isomer (**36**) gave the 3-*O*-benzyl derivative (**37**, 97%) whereas the *endo*-isomer (**39**) gave the 2-*O*-benzyl compound (**40**, 64%). Compound **37** could then be opened to the 3,4-di-*O*-benzyl derivative **38** with more equivalents of the reagent under reflux. Similar treatment of **40** gave a mixture of 2,4- and 2,6-*O*-benzyl ethers (2.9:1).

Thus, apart from the obvious conclusion that five-membered acetals (dioxolanes) are easier to open compared to six-membered ones (dioxanes), it seems likely that these openings depend on steric factors.

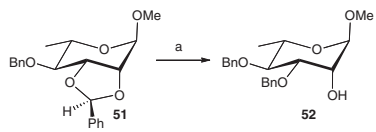
In 1981 Garegg et al. published the first paper on reductive openings of benzylidene acetals using the reagent combination $NaCNBH_3$–HCl–THF.[7] The main reason for their work was to find chemoselective conditions, that is, conditions that would not reduce other functionalities such as esters. Interestingly this procedure gives mainly 6-*O*-benzyl ethers and is thus complementary to the $LiAlH_4$–$AlCl_3$ procedure. Some representative examples are given in Scheme 6.[7,8]

In order to get back to the Lipták regioselectivity (i.e., openings to 4-*O*-benzyl ethers) under mild conditions, the Garegg group turned their attention to borane–trimethylamine.[9] First, rhamnoside **51** was tested and this compound gave the same product as earlier experiments using $LiAlH_4$–$AlCl_3$ as indicated in Scheme 7. The reaction gave the same product both in THF and in toluene. However, the yield was significantly lower in toluene (31% vs 85%).

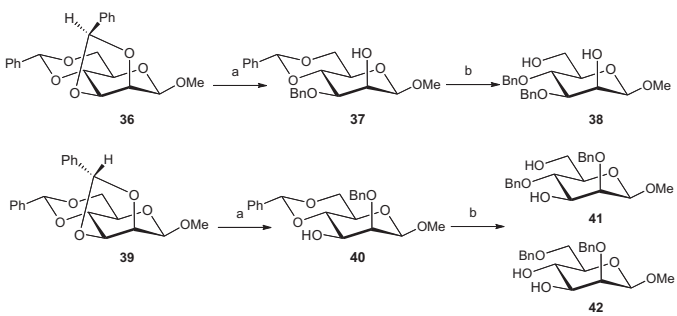
The results for dioxane rings were more interesting (Scheme 8) and reactions in THF gave openings to a 6-*O*-benzyl group whereas reactions in toluene gave the opposite regioselectivity. The



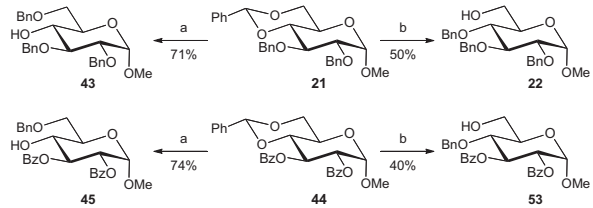
Scheme 6. Examples of reductive openings by Garegg et al. Reagents and conditions: (a) $NaCNBH_3$, HCl, THF, 0 °C.



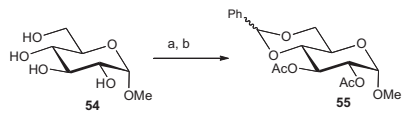
Scheme 7. Reductive opening of a dioxolane ring. Reagents: (a) $BH_3{\cdot}NMe_3$, $AlCl_3$, THF or toluene.



Scheme 5. Acetal openings presented by Lipták et al. Reagents and conditions: (a) $LiAlH_4$, $AlCl_3$, CH_2Cl_2–Et_2O, rt; (b) $LiAlH_4$, $AlCl_3$, CH_2Cl_2–Et_2O, reflux.



Scheme 8. Reagents and conditions: (a) $BH_3{\cdot}NMe_3$, $AlCl_3$, THF, rt, hours; (b) $BH_3{\cdot}NMe_3$, $AlCl_3$, toluene, rt, minutes.



Scheme 9. Formation of a diasteromeric mixture using α,α-dibromotoluene (benzal bromide) in pyridine. Reagents: (a) benzal bromide, pyridine; (b) Ac_2O, pyridine.

generally lower yield for the toluene method is not due to poor regioselectivity, but rather to degradation.

Since the introduction of reductive opening of benzylidene acetals a number of reagents have been introduced, as discussed in the methodology section below.

2. Methodology

The benzylidene acetals can be formed from the unprotected sugar by at least three commonly used methods. The most straightforward is the use of zinc chloride and benzaldehyde. Zinc chloride is added to Benzaldehyde and stirred for 15–20 min and then sugar is added to form benzylidene acetal over a couple of hours.[10] A nowadays more common method is transacetalization using benzaldehyde dimethyl acetal (α,α-dimethoxytoluene) under acidic conditions (usually *p*-toluenesulfonic acid or camphorsulfonic acid) in DMF[11] or MeCN,[12] a reaction that usually gives very high yields. Finally, it is possible to form the benzylidene acetal under basic conditions using α,α-dibromotoluene (benzal bromide) in combination with a base. However, the disadvantage with this method is the possible formation of a diastereomeric mixture (Scheme 9).

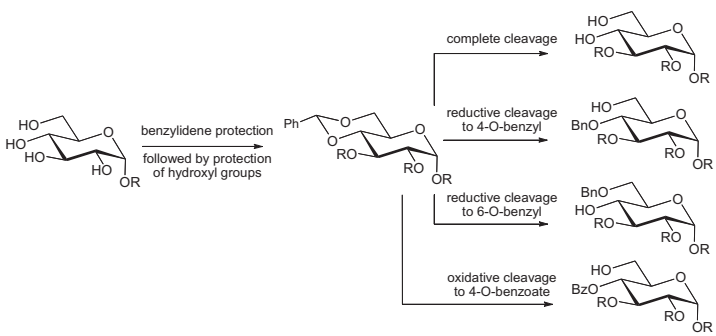
The benzylidene protected sugar can then be opened using different methods (Scheme 10). The acetal can be completely removed by for example mild acidic hydrolysis (usually 80% acetic acid in water),[13] iodine in methanol,[14,15] or by hydrogenolysis (Pd/C in acetic acid or $Pd(OH)_2$ in ethanol).[16,17]

The benzylidene acetals can also be regioselectively opened under oxidative conditions, for example, by *N*-bromosuccinimide in CCl_4 under basic conditions (usually $BaCO_3$) to give a 4-*O*-benzoate and bromine in position 6.[18] The addition of water gives the corresponding free 6-OH.[19] A similar transformation is also possible by using ozone.[20] However, the most versatile methods involving benzylidene acetals are regioselective openings under reductive conditions as described below.

2.1. Regioselective reductive openings of benzylidene acetals

Since the introduction of regioselective reductive openings of benzylidene acetals it has evolved into a crucial method in carbohydrate synthesis. A search of the literature indicates an increasing interest both in the use of the method as well as method development (Fig. 1).

The opening of methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (**21**) has evolved into a standard in the comparison of different methods. A search of the literature for reductive openings applied to this compound resulted in 58 different methods. The methods are summarized in Figure 2. The isolated yields of the 6-*O*-benzyl compound (**43**) are shown in grey whereas the yields of the 4-*O*-benzyl compound (**22**) are shown in black. While most techniques result in regioisomeric mixtures a few methods give excellent selectivity.



Scheme 10. Formation and reactions of 4,6-benzylidene acetals.

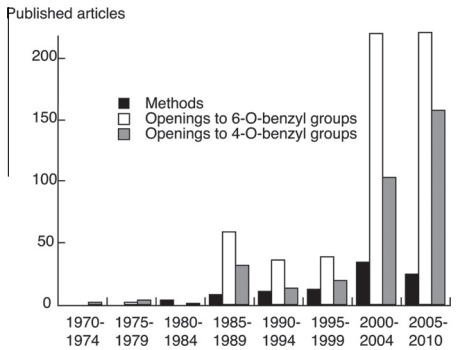


Figure 1. Published articles concerning method development for regioselective reductive openings of benzylidene acetals (black), reductive openings yielding 6-*O*-benzyl ethers (unfilled), and reductive openings to 4-*O*-benzyl ethers (grey) 1970–2010.

The most common methods for openings to 6-*O*-benzyl compounds are: $NaCNBH_3$–HCl–THF–ether, $BH_3{\cdot}NMe_3$–$AlCl_3$–THF, and Et_3SiH–Lewis acid. The most commonly used methods for openings to 4-*O*-benzyl compounds are: $BH_3{\cdot}$THF–$AlCl_3$–THF and $LiAlH_4$–$AlCl_3$–ether. The methods are discussed in detail below.

2.2. The Liptak method ($LiAlH_4$–$AlCl_3$)

The $LiAlH_4$–$AlCl_3$ method was extensively studied by Lipták et al. and optimized to give openings of **21** in 94% yield within 2 h.[4] The major change, compared to the original methods, was increased equivalents of the reagents. The research group also showed that for glucose and mannose derivatives, the product was exclusively the 4-*O*-benzyl ether in good yields. However, for galactose derivatives, 6-*O*-benzyl ethers were also isolated (5–12%).

2.3. The original Garegg method ($NaCNBH_3$–HCl–Ether)

Garegg et al. introduced the $NaCNBH_3$–HCl–ether method to reductively open benzylidene acetals to the 6-*O*-benzyl ether.[7,8] Sugar and $NaCNBH_3$ are dissolved in THF (dry, MS3Å is added) and HCl in dry ether is added until the mixture reaches pH 2–3 (checked by pH paper). This method is mild and both esters and amides are tolerated, but with an increasing number of unprotected hydroxyls the yields are lowered and in some cases only degradation is observed.[35,36] The method has been further developed by use of other acids, such as TfOH[37] or MsOH.[38] In both cases the acids were changed to facilitate the addition. Ether saturated with HCl is very difficult to handle. Johansson and Samuelson used TFA in DMF and opened *p*-methoxy benzylidene acetals to 4-*O*-benzyl ethers in 85% yield. However TFA is too weak to open unsubstituted benzylidene acetals.[39,40] In the same study, the authors used $NaCNBH_3$ in combination with TMSCl in acetonitrile and they thus observed reverse openings, that is, the formation of the 4-*O*-benzyl ether in 76% yield. Interestingly, when Ghosh et al. repeated the reaction using a different substrate, the regioselectivity was the opposite and 6-*O*-benzyl ether was isolated in 60% yield.[41] So far, the best results for formation of the 6-*O*-benzyl ether (**43**) from compound **21** (95% yield) is the use of $NaCNBH_3$ in combination with I_2 in MeCN.[21] This method was developed for the same reason as above, to find a reagent combination that was easier to handle (comparing to moisture sensitive triflates or HCl). The method also gave excellent yields when esters were used as protecting groups (90–97%). Molecular iodine could activate thioglycoside donors, but the authors showed that this method works in combination with thioethyl and thiocresyl aglycons (74–94%). Interestingly, the method was not compatible with acetamides and no reaction was detected on *N*-acetylglucoseamine.

2.4. The modified Garegg conditions ($BH_3{\cdot}NMe_3$–$AlCl_3$)

Garegg et al. also introduced the reagent combination $BH_3{\cdot}NMe_3$–$AlCl_3$.[9] When the reaction is performed in THF, the reaction yields 6-*O*-benzyl ethers while reactions in toluene give 4-*O*-benzyl ethers. In the original article, the reactions were performed with molecular sieves present, but later studies have shown that the presence of small amounts of water do not hamper the reaction, but rather increase the rates.[42]

$BH_3{\cdot}NMe_3$ has been used in combination with other Lewis acids, such as $Cu(OTf)_2$ and in CH_2Cl_2 the 6-*O*-benzyl ether was isolated in 40% yield.[36] The same research group also showed that an increase of the molar percent of $Cu(OTf)_2$ only marginally increased the yield for 6-*O*-benzyl ether but increased the amount of the 4-*O*-benzyl ether significantly.[22] When $BF_3{\cdot}OEt_2$ was used as Lewis acid, in combination with $BH_3{\cdot}NHMe_2$ it was shown that the substituent in position 3 as well as the solvent (CH_2Cl_2 or MeCN) affected the regioselectivity.[28] Acetonitrile gave more of the 6-*O*-benzyl ether in all cases, except for the model compound **21** that actually gave 55% of the 4-*O*-benzyl ether **22** and 40% of the 6-*O*-benzyl ether **43**. However, when CH_2Cl_2 was used as solvent, 4-*O*-benzyl ether was always the major product. Fügedi and Daragics recently showed that TMSOTf appears to be the best acid for this reaction.[23] They showed that the model compound **21** was opened in 84% yield to the corresponding 4-*O*-benzyl ether **22**. $BH_3{\cdot}NMe_3$ works fine in combination with amides,[28] esters[28,9] and even with unprotected hydroxyls.[28,35] An interesting application was recently published by Tanaka and Fukase, where they used $BH_3{\cdot}NMe_3$ and $BH_3{\cdot}NHMe_2$ in combination with $BF_3{\cdot}OEt_2$ in a micro fluid system to produce a large amount of the desired product in high yields.[43]

2.5. The $BH_3{\cdot}$THF method

Methods with $BH_3{\cdot}$THF as the hydride source are the ones that have gained the most attention concerning method development.[22,23,26,32,31,34] The best yielding reduction of the model compound **21** to get the 4-*O*-benzyl ether **22** is in combination with $CoCl_2$ as Lewis acid in THF, a reaction that gives quantitative conversion in 10 min.[34] The method also gave excellent yields of galactose and mannose derivatives.

As expected, different acids result in a different reaction time. For example, $CoCl_2$ (3 equiv) gave complete conversion in 10 min,[34] whereas TMSOTf the product (0.15 equiv) gave 96% after 1 h. $BF_3{\cdot}OEt_2$ (3 equiv) resulted in 91% conversion in 240 h.[23]

Most of the common protective groups, such as esters,[23,26,32,31,34] amides,[23,32] silyls,[23,32] azids[22,23,26,31] carbonates,[23] and thio donors,[22,23,26,32,31,34] are well tolerated by the $BH_3{\cdot}$THF reagent combination. It also works well with unprotected hydroxyl groups.

For most protecting groups TMSOTf[23] is the best Lewis acid, except for perbenzylated compounds, where $CoCl_2$[34] usually gives improved yields, and unprotected compounds where Bu_2BOTf is the better Lewis acid.[32]

In general, reductions using $BH_3{\cdot}$THF results in the formation of 4-*O*-benzyl ethers. However, Hernández-Torres et al. have shown that in reductive openings of *p*-methoxybenylidene acetals, using Bu_2BOTf as Lewis acid, the regioselectivity can be changed if the reaction is performed at −78 °C instead of 0 °C.[44] In these experiments, unsubstituted benzylidene acetals were not reactive until

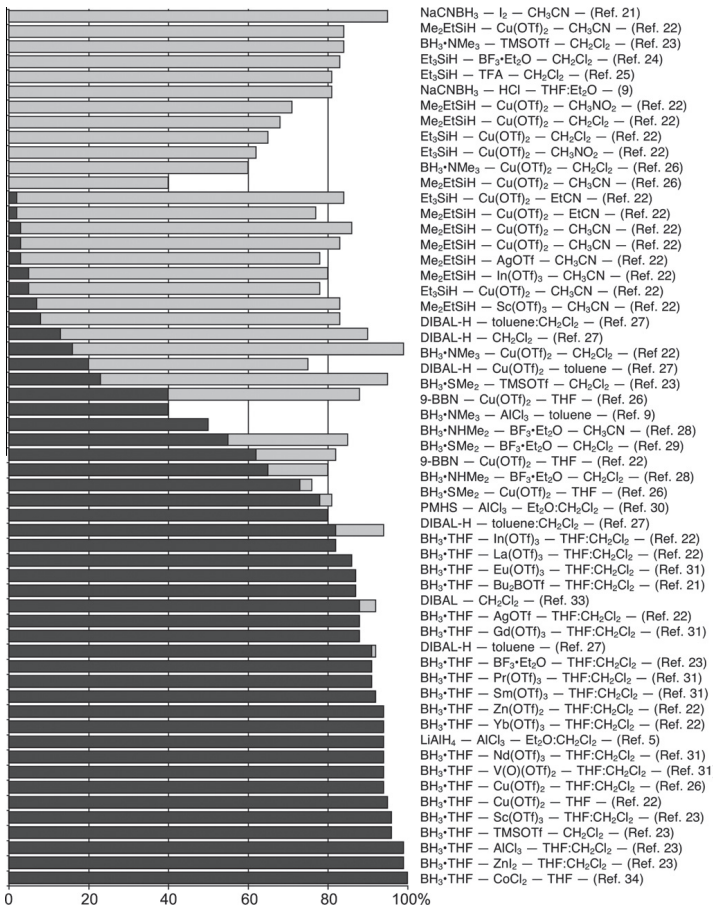
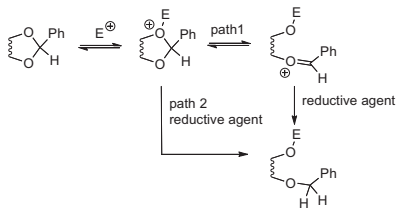


Figure 2. Regioselective openings of methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (**21**) to give methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (**43**, grey) or methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**22**, black). (See above mentioned references for further information.)

heated to −30 °C and at that temperature the product was solely the 4-*O*-benzyl ether. The authors also conclude that water is not a problem since it will be consumed by excess borane and the addition of molecular sieves is thus unnecessary. An interesting adaptation is to use sonication to decrease the time. For example, compound **21** was opened in 99% yield in 5 min in comparison to 94% after 45 min without sonication.[45]

2.6. The Et_3SiH method

Silanes have also been used with success as a hydride source in reductive openings of acetals. In one of the first publications triethyl silane (TES) was used in combination with TFA in openings of compounds carrying either ethers or esters as protecting groups, including *N*-acetylglucoseamine to give 6-*O*-benzyl ethers in good yields (80–98%).[25] Interestingly, the benzyl and acetyl protected galactosides did not react at all. Shie et al. studied the use of silanes in combination with a variety of metal triflates and in different solvents.[22,26] However, only a few of the tested triflates gave conversion to the desired product. The best combination was Me_2EtSiH with $Cu(OTf)_2$ as Lewis acid in acetonitrile, which resulted in 84% yield. Other Lewis acids that have been tested are $EtAlCl_2$[46] and TfOH.[47] An interesting modification was the use of PS-DES, a polystyrene supported silane that in combination with TfOH gave the 6-*O*-benzyl ether in excellent yield.[47] However, the most versatile method seems to be TES in combination with I_2 as Lewis acid.[48] This combination is mild and accepts common protecting groups such as ethers, esters, allyl as well as thioglycoside donors. All of the above methods generated the 6-*O*-benzyl ether in more than 80% yield. To the best of our knowledge the only Lewis acid that in combination with a silane results in formation of 4-*O*-benzyl compounds is $PhBCl_2$.[47] An innovative use of the regioselective



Scheme 11. General mechanistic pathway suggested by Garegg.

opening of silanes was explored by Boons and co-workers in a one-pot synthesis of trisaccharides.[49] A trichloroacetimidate donor and an acceptor with a benzylidene acetal were stirred at 0 °C with TfOH present to first bring about the glycosylation. The reaction mixture was then cooled to −78 °C and Et_3SiH was added for the reductive opening. The temperature was then increased to 0 °C and a second trichloroacetimidate donor was added to give the trisaccharide.

3. Mechanism

Despite the immense importance of regioselective reductive openings of acetals for organic chemistry in general and for carbohydrate chemistry in particular, the underlying principles for the regioselectivity was not until recently understood.[50] For long, the predominant explanation was the one suggested by Garegg including two major mechanistic possibilities as indicated in Scheme 11.[51] In this model the Lewis acid was first coordinated to one of the oxygen atoms, followed by either formation of an oxocarbenium ion (path 1) and subsequent reduction, or direct reduction of the formed complex (path 2). In either case, the Lewis acid has to coordinate to the oxygen that will become a free HO-group. Garegg then reasoned that the main difference between the original $LiAlH_4$–$AlCl_3$ system and $NaCNBH_3$–HCl combination was the difference in steric bulk between the two Lewis acids used, that is, $AlCl_3$ versus a proton. The more sterically demanding $AlCl_3$ would thus preferentially coordinate to the less hindered primary O-6 in 4,6-benzylidene acetals. In contrary, Brønsted acids would protonate O-4 to form a more stable oxocarbenium ion at C-6. The concept is shown in Scheme 12.

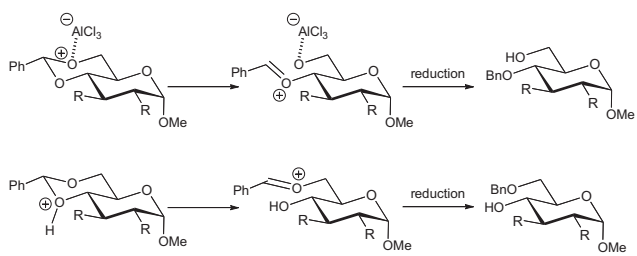
The major problem with this very simplified mechanistic model is to explain the different regioselectivities shown by BH_3·THF and BH_3·NMe_3 in combination with $AlCl_3$ in THF. $AlCl_3$ forms both mono- and di-coordinated complexes with THF and it is reasonable that these complexes would be very bulky and thus preferentially coordinate to the less sterically hindered O-6 to give a free 6-hydroxyl group. However, the two reductive agents give opposite regioselectivities, which thus rule out a steric explanation for the regioselectivity. This observation is not limited to $AlCl_3$ but seems to be general. Thus, 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·OEt_2, $In(OTf)_3$, AgOTf, or $Cu(OTf)_2$) (Scheme 13).[26,31,50,52,53]

In addition, openings of less sterically hindered substrates indicate that the origin for the selectivity must be stereoelectronical rather than steric. Thus, openings of substrate **56** (Scheme 14) gave interesting results. Clearly, the steric constraints in position 4 compared to position 6 must be similar in this compound. However, reductive openings using either $NaCNBH_3$–HCl–Et_2O[54] or BH_3·NMe_3–$AlCl_3$–THF[50] gave mainly openings to the 6-*O*-benzyl ether **57**. Reactions using BH_3·THF gave the opposite regioselectivity.

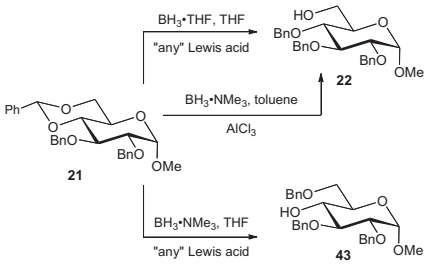
To categorize different reagent combinations, the reaction kinetics were determined for a number of reductive openings of compound **21**.[53] Openings to give 4-*O*-benzyl ethers (i.e., compound **22**), using BH_3·THF–$AlCl_3$–THF or $LiAlH_4$–$AlCl_3$–Et_2O, were shown to follow first-order kinetics. On the contrary, reactions yielding 6-*O*-benzyl ethers (i.e., compound **43**), using BH_3·NMe_3–$AlCl_3$–THF or BH_3·NMe_3–BF_3·OEt_2–THF, follow higher order kinetics. The BH_3·SMe_2–$AlCl_3$–THF system constitutes a borderline case yielding mostly 4-*O*-benzyl (by a first-order reaction) but also 6-*O*-benzyl (by a higher order reaction). These results are summarized in Figure 3. Due to the very fast reaction rates of both the original (i.e., $NaCNBH_3$) and the modified (i.e., BH_3·NMe_3 in toluene) Garegg conditions, the kinetics of these reagent combinations were not determined.

Altogether, these data render a steric explanation for the regioselectivity less plausible and it is obvious that these reactions cannot be explained by a simple mechanism, but rather by a mechanistic scheme with several different routes.

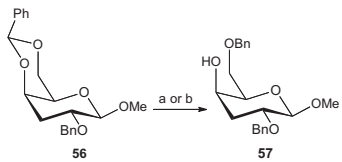
In a series of recent publications Lewis acid activation of certain borane complexes has been studied.[50,53,55] For example, BH_3·NMe_3 can be activated by $AlCl_3$ in combination with an acetal, which renders borane to be the most electrophilic species. The regioselectivity of reductive openings of benzylidene acetals can thus be explained by addition of the most electrophilic species to the most nucleophilic oxygen, that is, O-6. Thus, three different pathways can be discussed. In non-polar solvents, such as toluene, the unsolvated Lewis acid is by far the strongest Lewis acid and it will form an initial complex with O-6, followed by reduction (Scheme 15, Path A). In polar solvents, such as THF, the situation is completely different. The Lewis acid is thus strongly solvated and the reaction rate is slow. However, the Lewis acid will again interact with the more nucleophilic O-6, to yield the same product as in non-polar solvents (Path B). Activated borane complexes show inverse regioselectivity due to the addition of borane to O-6 (Path C). The three different cases will be discussed in detail below.



Scheme 12. Summary of early mechanistic explanations for reductive openings of benzylidene acetals.



Scheme 13. The regioselectivity of reductive openings of benzylidene acetals depends on the type of borane as well as the solvent.



Scheme 14. Reductive opening of a 3-deoxy sugar. Reagents: (a) $NaCNBH_3$–HCl–Et_2O; (b) $BH_3{\cdot}NMe_3$–$AlCl_3$–THF.

3.1. Reductive openings in non-polar solvents

On contrary to reductive openings of cyclic acetals, there is extensive knowledge on the mechanism of acid-mediated additions of carbon nucleophiles to acetals. Mukaiyama initially introduced this reaction in 1974[56] and the mechanistic details have later on been thoroughly investigated by several groups. The reaction is usually performed at low temperature, that is, −78 °C, using the strong Lewis acid $TiCl_4$ in non-polar solvents, such as CH_2Cl_2, $CHCl_3$, toluene, or hexane.

In a series of experiments Denmark et al. investigated the Lewis acid catalyzed additions of carbon nucleophiles to cyclic acetals and observed, at low temperature, the formation of an initial complex between the Lewis acid and the acetal.[57,58] This initial complex was 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, that is, S_N2-like reactions, to stereo randomization in the case of fully developed oxocarbenium ions. 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.

To explore the mechanistic details of reductive openings of 4,6-benzylidene acetals a deuterium labeled analog, that is, methyl 2,3-di-*O*-benzyl-4,6-*O*-(benzylidene-1-d)-α-D-glucopyranoside (**58**) was synthesized.[50] In addition, methyl 2,3-di-*O*-benzyl-4,6-*O*-(*p*-bromobenzylidene)-α-D-glucopyranoside (**59**) was synthesized to explore electronic effect. The *p*-bromobenzylidene group was chosen to give a small but measurable electron withdrawing effect compared to the unsubstituted compound **1**.

Compound **58** was then reductively opened using the modified Garegg conditions, that is, $BH_3{\cdot}NMe_3$–$AlCl_3$ in toluene at room temperature. These reactions were completed in less than 5 min, which demonstrate the high reactivity of the naked Lewis acid in the non-polar solvent. The reaction gave a stereoisomeric ratio **60S**:**60R** of

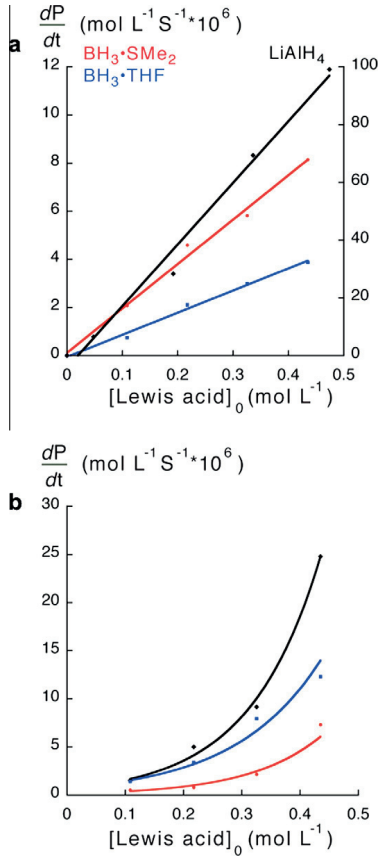
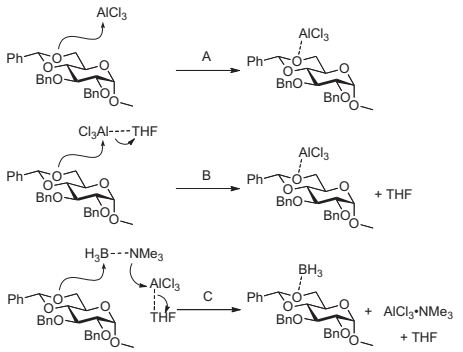


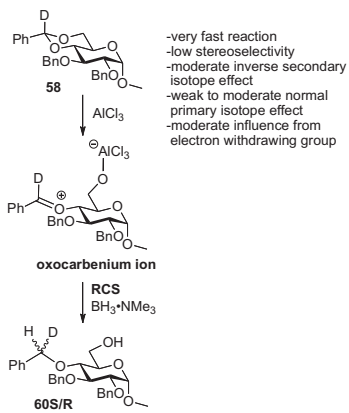
Figure 3. Summary of kinetic studies of acetal openings. (a) Openings of compound **21** to a free 6-hydroxyl group follow first-order kinetics ($LiAlH_4$—black diamonds [right *y*-axis], $BH_3{\cdot}SMe_2$—red circles, and $BH_3{\cdot}THF$—blue squares. (b) Reactions to a free 4-hydroxyl group follow higher order kinetics ($BH_3{\cdot}NMe_3$–$AlCl_3$—black diamonds, $BH_3{\cdot}NMe_3$–$BF_3{\cdot}OEt_2$—blue squares, and $BH_3{\cdot}SMe_2$–$AlCl_3$—red circles). Graphs derived from data in Ref. 53. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

42:58, which point to a significant degree of oxocarbenium ion character of the reactive intermediate. To further investigate the mechanism, competitive isotope studies were performed. These experiments showed an inverse secondary isotope effect of 0.92, which can be explained by either an S_N2 type reaction 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. Taking into consideration the low stereoselectivity, the latter explanation is the most plausible. Finally, this reaction only showed a modest discrimination for the more electron rich **21** over **59**.

Since no strong complexes can be formed between toluene and $AlCl_3$, reactions in this solvent give 'naked' and very reactive Lewis acids. Altogether, these data suggest that the reaction proceeds with fast formation of an oxocarbenium ion followed by a rate-controlling reductive step (Scheme 16). Reductive openings



Scheme 15. The regiochemical outcome of reductive openings of 4,6-benzylidene acetals 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).



Scheme 16. Mechanistic details of reductive opening to give a free 6-OH in toluene.

using $BH_3{\cdot}NMe_3$–$AlCl_3$ in the non-polar solvent toluene thus represent one extreme in the mechanistic scheme presented by Denmark et al.

3.2. Reductive openings using unactivated boranes in polar solvents

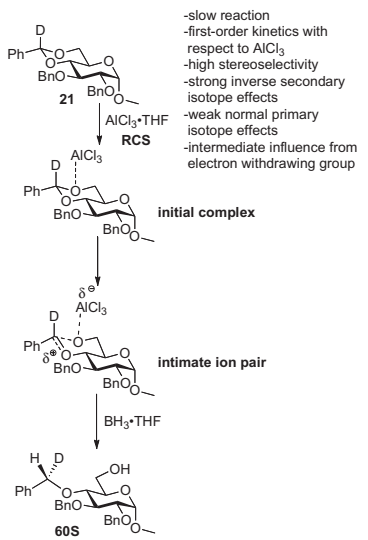
In polar solvents, such as THF, the Lewis acids form complexes with the solvent. For example $AlCl_3$, a Lewis acid commonly used in the acid mediated reductive openings of cyclic acetals, forms both mono- and di-coordinated complexes with THF.[59,60] The dissociation energy of $AlCl_3{\cdot}THF$ is estimated to 90 kJ/mol and for $AlCl_3{\cdot}2THF$ to 132 kJ/mol.[61,62] The formation of these complexes moderates the reactivity of 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.[63] 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. The effect of even minute amounts of THF for the reaction outcome was also shown by the reductive opening of the model compound **21** using $AlCl_3{\cdot}THF$ and $BH_3{\cdot}NMe_3$ in toluene. Thus a 63:37 mixture of **22** and **43** was formed compared to exclusive formation of **22** using $AlCl_3$ in toluene.

It is thus highly reasonable 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 non-polar solvents at low temperatures.

While reactions in unpolar solvents are too fast to reliably measure kinetic effects, reactions in polar solvents are well suited for this. Thus, the reagent combinations $BH_3{\cdot}THF$–$AlCl_3$–THF and $LiAlH_4$–$AlCl_3$–Et_2O–CH_2Cl_2 were evaluated and showed first-order kinetics with respect to Lewis acid. The $BH_3{\cdot}SMe_2$–$AlCl_3$–THF system constitutes a borderline case, yielding both 4-*O*-benzyl (**22**, by a first-order reaction) and 6-*O*-benzyl (**43**, by a higher order reaction) compounds.

Experiments using deuterated starting materials or deuterated reductive agents gave further insight into the reaction mechanism.[50] All three reagent combinations thus gave high stereoselectivities (approx. 97:3). Since the three different reagents result in similar stereoselectivities, and they all show first-order kinetics, it is reasonable to assume that they follow a reaction mechanism with a highly ordered reactive intermediate. Further on, inverse secondary isotope effects in the range of 0.85–0.92 were observed in these reactions.

The combination of high stereoselectivities and strong inverse secondary kinetic isotope effects can be explained by an S_N2 type reaction, where the carbon is more available for the deuterated compound. These reactions also showed weak, time dependent, primary isotope effects as well as moderate influence from an electron withdrawing substituent in the aromatic system. Since the reaction is slow, compared to reactions in non-polar solvents, and show first-order kinetics with respect to the Lewis acid, the rate-controlling step is probably the formation of an initial complex (Scheme 17). This initial complex is then, in full accordance



Scheme 17. Mechanistic details of reductive opening to give a free 6-OH in THF.

with Denmarks findings,[57,58] 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 (**60S**) 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, that is, the intimate ion pair and in full accordance with earlier studies, where reactions between sterically unhindered acetals and weak Lewis acids usually proceeded through intimate ion pairs.[57] It is reasonable to assume that the complex $AlCl_3$·THF is a substantially weaker Lewis acid compared to $AlCl_3$ in toluene.

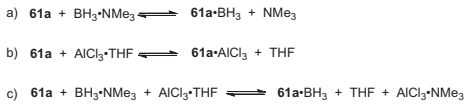
3.3. Reductive openings using activated boranes in polar solvents

While reactions yielding free 6-OH (e.g., BH_3·THF–$AlCl_3$–THF, $LiAlH_4$–$AlCl_3$–Et_2O–CH_2Cl_2, and BH_3·NMe_3–$AlCl_3$–toluene) are easily interpreted using the Denmark mechanistic scheme, reactions yielding a free 4-OH (e.g., $NaCNBH_3$–HCl–Et_2O–THF and BH_3·NMe_3–$AlCl_3$–THF) are not that easily explained. In order to shed light on these reactions, a model system based on a phenolic-benzylic acetal was used (Scheme 18).[55]

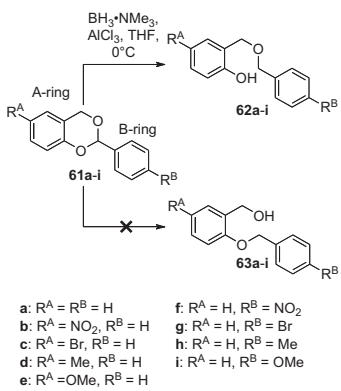
These acetals were opened under reductive conditions. In all cases double benzylic ethers (compounds **62a–i**) were isolated as single products, which indicate that the Lewis acid must have coordinated to the phenolic oxygen. The electrostatic potential of the oxygen atoms in compounds **61a–i** were calculated using density functional theory at the B3LYP/6-31G* level and throughout the series, benzylic oxygen showed the highest electrostatic potential. Benzylic oxygen is thus both the more basic and also the less sterically hindered oxygen atom—but not the one chosen by the Lewis acid in reductive openings using BH_3·NMe_3. There are two alternative explanations for these observations. One possibility is that the regiochemistry is directed by the relative energies of the two oxocarbenium ions. However, Hammett plots indicated that the build-up of a positive charge of the acetal carbon is more important than the charge of the phenolic oxygen, which in turn implies a diminished importance of the oxocarbenium ion pathway. Another explanation is that the outcome of these reactions is directed by initial coordination of the borane, followed by coordination of the Lewis acid, and subsequent reduction.

Boranes are weak Lewis acids, compared to $AlCl_3$. However, as indicated earlier, in THF the Lewis acid $AlCl_3$ form different complexes with much lowered reactivity as the result. One possible explanation for the shown regioselectivity is activation of the borane by the Lewis acid, a concept suggested, but not further investigated by Brown.[64] To investigate this option we estimated the energies for the formation of different complexes as shown in Scheme 19. The dissociation energies for known complexes,[61,62,65] in combination with calculated data for the formation of complexes of **61a** with the electrophiles (i.e., BH_3 and $AlCl_3$), indicate that reactions (a) and (b) are thermodynamically unfavorable (by 32 and 45 kJ/mol, respectively) whereas reaction (c) is thermoneutral.[55] The driving force is the formation of the highly stabilized $AlCl_3$·NMe_3.

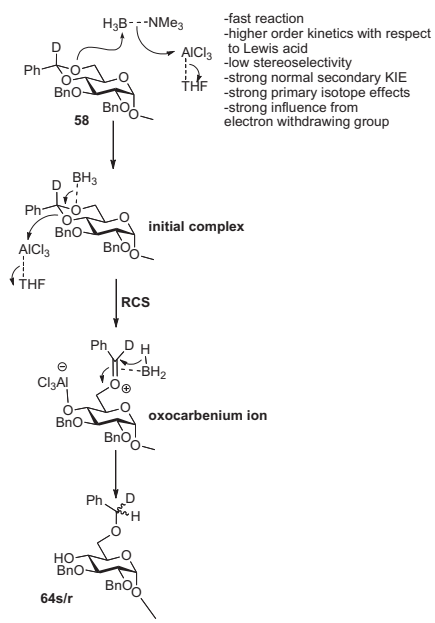
Activation of boranes can also explain the higher order kinetics, with respect to the Lewis acid, exhibited in these reactions. Thus, 1 equiv of the Lewis acid is used to activate the borane–amine complex and another equivalent is needed for the activation of the acetal in the reductive step. This explanation was further supported by ^{11}B NMR studies.[55] Addition of $AlCl_3$ to a solution of BH_3·NMe_3 in THF, gave no visible changes in the ^{11}B NMR spectra. However, on addition of the acetal, the reaction took place and the build-up of a new peak, which corresponded to a BH_2 group bound to oxygen,



Scheme 19. Possible reactions between reactive species in the mixture. While reactions (a) and (b) are thermodynamically unfavorable, reaction (c) is thermoneutral.



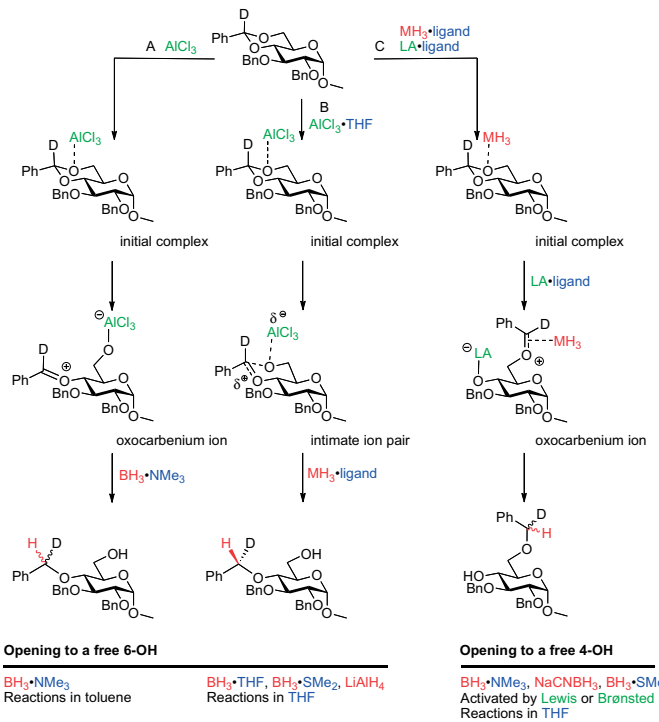
Scheme 18. Reductive opening of phenolic-benzylic acetals.



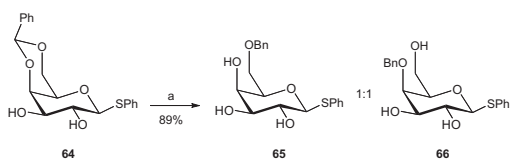
Scheme 20. Mechanistic details of reductive opening to give a free 4-OH in THF.

was observed. No traces of $Me_3NBH_2^+$ were detected in these studies. These data suggest that the borane is cleaved from the amine during the course of the reaction. The activation theory was later on backed up by activation of $BH_3{\cdot}NMe_3$ by $BF_3{\cdot}OEt_2$ or metal triflates as 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}). Reactions using $BF_3{\cdot}OEt_2$ should thus not activate the reaction to the same degree, and indeed a much slower reaction rate was observed using $BF_3{\cdot}OEt_2$ compared to $AlCl_3{\cdot}THF$.[53] Activation of borane reagents thus offers an explanation to regioselective openings of 4,6-benzylidene protected carbohydrates. It is reasonable that $NaCNBH_3$ is activated by the Brønsted acid to give H_2BCN, a reagent that reacts similar to BH_3 in THF.

To shed further light on the mechanism of reductive openings using activated boranes the deuterated compound **58** was reductively opened by the following reagents: $BH_3{\cdot}NMe_3$–$AlCl_3$–THF, $BH_3{\cdot}SMe_2$–$AlCl_3$–THF, and $NaCNBH_3$–HCl–Et_2O–THF. In all cases these openings gave stereoisomeric mixtures ranging from 52:48 to 57:43. In addition, these reactions showed a normal secondary isotope effect of 1.4. 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 the formation of an oxocarbenium ion as the rate-controlling step. Reductive openings using $BH_3{\cdot}NMe_3$–$AlCl_3$–THF also showed strong, but time dependent primary isotope effects, ranging from 4.9 to 1.6. No primary isotope effects could be determined from the reactions with $NaCNBH_3$, due to exchange of deuterium with the acid. Finally, a competitive study using a 1:1 mixture of **21** and the *p*-bromobenzylidene analog **59** gave a 87:13 ratio. The rather strong influence of the electron withdrawing group also points toward a rate-controlling



Scheme 21. Mechanistic proposal for reductive openings of 4,6-*O*-benzylidene acetals. Scheme originally published in Ref. 50.



Scheme 22. Reagents and conditions: (a) $BH_3{\cdot}THF$, Bu_2BOTf, THF–CH_2Cl_2, 0 °C.

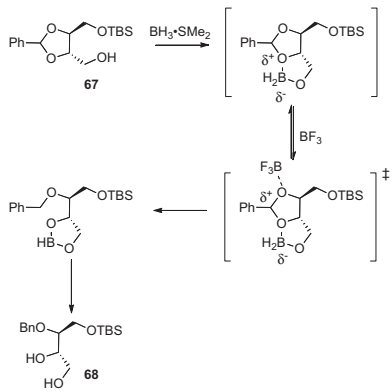
formation of an oxocarbenium ion. It is thus reasonable to assume that the regioselectivity is determined by the fast formation of an initial complex with borane, activated by Lewis acid. This initial complex is then transformed into an oxocarbenium ion, aided by a second equivalent of Lewis acid, in the rate-controlling step (Scheme 20). The oxocarbenium ion is then reduced with low stereoselectivity to give the free 4-OH.

It is known that $BH_3{\cdot}NMe_3$ can be activated by Lewis acids (e.g., $AlCl_3$ or $BF_3{\cdot}OEt_2$) as well as Brønsted acids (e.g., water in combination with $AlCl_3$) and several studies indicate that a small amount of water speed up the reductive openings of benzylidene acetals.[38,42] Consequently, aprotic conditions, that is, the use of acid scavengers, severely decelerated the reduction rate.[38] To further investigate the importance of water in the reduction, the kinetics of the reduction of compound **1** using the water–$BH_3{\cdot}NMe_3$–$AlCl_3$ system was investigated.[53] Interestingly, equimolar amounts of $AlCl_3$ and water completely quenched the reaction, while a 3:1 ratio gave a rate enhancement of approximately four times. However, the addition of even more $AlCl_3$ lowered the reaction rate and at 8 equiv of $AlCl_3$, the rates were similar to reaction without water. These observations can be rationalized by the reactions of water with $AlCl_3$. In a series of experiments, Gálová showed that the conductivity of a solution of $AlCl_3$ in THF reached a maximum at a molar ratio of $AlCl_3$–water of 1:2, which corresponds to the formation of the charged species $AlCl_2(H_2O)_4^+$ and $AlCl_4^-$.[66] It is reasonable to assume that the formed aluminum complexes can act as proton sources that activate either the borane or the acetal. Further on, Brown and Murrey showed that the rate of hydrolysis of $BH_3{\cdot}NMe_3$ in aqueous diglyme is almost negligible but that the complex can be activated by proton sources, such as acetic acid or mineral acids.[64] Protons are thus probably strong activators of $BH_3{\cdot}NMe_3$, which explains the enhanced reaction rates. At high molar ratios of $AlCl_3$, other complexes are formed, and the effects of the added water are insignificant. It is reasonable that minute amounts of water present in reagents and solvents generally enhance the reaction rates in reductive openings using borane complexes. Reduction of **58**, using $BH_3{\cdot}NMe_3$ activated by $AlCl_3$ and water gave a similar stereoisomeric ratio as reaction without water.[44]

3.4. A mechanistic scheme for regioselective openings of 4,6-benzylidene acetals

The regioselectivity of Lewis acid catalyzed reductive openings of benzylidene acetals is directed both by the reducing reagent and the solvent. 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 4-*O*-benzyl ethers. The reaction represents a mechanistic continuum from an intimate ion pair in THF to fully developed oxocarbenium ions in toluene. Reactions in polar solvents such as THF are slow, compared to reactions in non-polar solvents, and generally results in high stereoselectivity. On contrary, reactions in unpolar solvents such as toluene are very fast due to naked Lewis acids, and results in stereo randomization. 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 acetal. These reactions, which result in 6-*O*-benzyl ethers, proceed through an oxocarbenium ion, and thus give low stereoselectivity. The different mechanistic patways are summarized in Scheme 21.

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.



Scheme 23. Mechanism proposed by Saito.

3.5. Future investigations

Despite recent advances in the understanding of regioselective reductive openings of benzylidene acetals there are still several unanswered questions. One question is the regioselectivity shown in openings of five-membered benzylidene acetals, that is, dioxolanes such as **36** (Scheme 5).

It is also apparent that free hydroxyl groups in the substrate influence the regioselective outcome. For example, with two free hydroxyl groups the reagent combination $BH_3{\cdot}THF$, Bu_2BOTf gave a 1:1 mixture of the two regioisomers **65** and **66** (Scheme 22).[35] With the use of $BH_3{\cdot}THF$, $CoCl_2$, THF the same reaction also gave significant hydrolysis to the 4,6-di-OH in the case of free hydroxyl groups.[37]

Saito et al. investigated reductive openings of simple benzylidene acetals using $BH_3{\cdot}SMe_2$ and $BF_3{\cdot}OEt_2$ and found that the free hydroxy group directs the borane.[67] Thus, an oxyborane was formed and the Lewis acid then brought the reaction to completion. Without Lewis acid no reaction took place. Saito presented a mechanism where the regioselctivity is directed by an oxyborane intermediate (Scheme 23). However, the reaction details for reductive openings of carbohydrates derivatives with free hydroxyl groups need to be studied.

4. Conclusions

The use of benzylidene acetals for selective protection of hydroxyl groups is essential in carbohydrate synthesis and the interest for using and developing new methods is increasing. The 4,6-benzylidene acetal can be opened selectively, by a number of methods to yield either free 4-OH or free 6-OH. Although there is an abundance of methods, only a few are widely used. The two most important aspects when choosing a method are functional group compatibility and regioselectivity. Figure 2 constitutes a guide, which clearly shows the advantages of some methods in terms of selectivity. In the recent years the mechanism has been investigated and it seems likely that 4-*O*-benzyl ethers are formed by coordination of Lewis acids to the most nucleophilic oxygen in the acetals, which usually is O-6. However, in the case of activated boranes, such as $BH_3{\cdot}NMe_3$, borane turns into the most electrophilic species and the regioselectivity is directed by coordination of borane to the same oxygen.

Acknowledgments

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Paper III

RSC Advances

COMMUNICATION

Short and efficient synthesis of a daunosamine donor from L-fucal†

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Markus Ohlin, Sophie Manner, Johanna Löfgren, Andrea Persson and Ulf Ellervik*

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Anthracyclines, *e.g.* daunorubicin, doxorubicin, and idarubicin, consist of a tetracycline moiety linked *via* a glycosidic bond to a sugar residue, usually the aminosugar daunosamine. The anthracyclines are efficient chemotherapeutic agents against cancer, but their use is limited due to cardiotoxicity and induction of multidrug resistance. In the search for new anthracycline analogs, a daunosamine donor that can be used to glycosylate suitable aglycons is of utmost importance. Here, we present a short and efficient synthesis of the versatile donor *p*-tolyl 4-*O*-acetyl-3-azido-2,3,6-trideoxy-1-thio-α-L-lyxo-hexopyranoside in 3 steps from commercially available L-fucal with an overall yield of 32%. The same procedure can be used to synthesize the donor *p*-tolyl 4-*O*-acetyl-3-azido-2,3,6-trideoxy-1-thio-α-L-arabino-hexopyranoside in 28% overall yield from L-rhamnal, for the synthesis of epirubicin analogs.

Introduction

Daunorubicin was isolated from *Streptomyces peucetius* in the early 1960s and has, together with a few additional anthracyclines, reached the clinical market as an efficient chemotherapeutic agent against cancer.[1,2] Anthracyclines consist of a tetracycline moiety linked *via* a glycosidic bond to a sugar residue, usually the aminosugar daunosamine. The clinically most important anthracyclines are daunorubicin (DNR), doxorubicin (DOX) and idarubicin (IDA) (Fig. 1).

The anthracyclines show high affinity for DNA and RNA, and are suggested to act by forming a ternary complex with DNA topoisomerase II and DNA, and thus creating DNA strand breaks, but also by intercalating DNA and by that inhibiting replication and transcription. The detailed mechanisms are not yet known. Unfortunately, the use of anthracylines is limited due to cardiotoxicity and induction of multidrug resistance.[1]

Center for Analysis and Synthesis, Chemical Center, Lund University, P.O. Box 124, SE-221 00 Lund, Sweden. E-mail: ulf.ellervik@chem.lu.se; Fax: +46 46 2220209; Tel: +46 46 2228220

† Electronic supplementary information (ESI) available: Copies of ^{1}H and ^{13}C NMR spectra. See DOI: 10.1039/c4ra01056f

In the search for new, more effective compounds with moderate general toxicities, a large number of anthracycline analogs have been developed by semi-synthetic methods, although very few have matched the activity of the original compounds. The non-intercalating domain, *i.e.* the daunosamine sugar and the aliphatic ring, has been shown to be crucial for the ability of the anthracyclines to bind the DNA minor groove and to inhibit DNA topoisomerase.[3] So far, most analogs have been variations of the anthraquinone skeleton and there are few examples of truncated compounds.

One problem, in the search for new analogs, has been the lack of versatile daunosamine donors that can be produced in reasonable quantities. In 2007, Fan and coworkers published a valuable daunosamine donor.[4] Starting from 3,4-di-*O*-acetyl-L-rhamnal, a fairly straightforward synthesis in 7 steps gave the daunosamine donor **1α/β** (*p*-tolyl 4-*O*-acetyl-3-azido-2,3,6-trideoxy-1-thio-α,β-L-lyxo-hexopyranoside) in an overall yield of 21% (α : β 2 : 1). The donor was used in the synthesis of

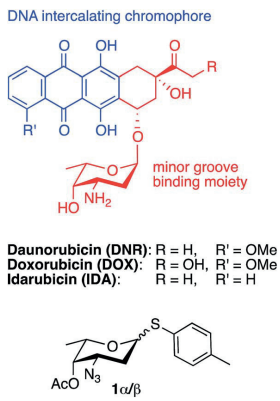


Fig. 1 Structures of anthracyclines and the daunosamine donor **1**.

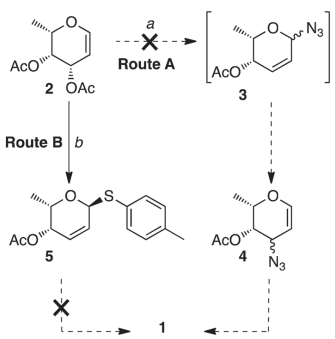
daunorubicin analogs with truncated daunomycinone aglycones, *i.e.* tetrahydro-naphthalene or tetrahydro-anthracene derivatives. The thioglycoside donors were activated with silver hexafluorophosphate and used for α-selective glycosylations in good yields. Finally, the azide moieties were converted to the corresponding amines by Staudinger reduction, and thereby proving the usefulness of the donor.[4]

Here we report a short and efficient synthesis of **1α** starting from commercially available 3,4-di-*O*-acetyl-L-fucal (3,4-di-*O*-acetyl-1,5-anhydro-2-deoxy-L-lyxo-hex-1-enitol, **2**).[5] The rationale for using **2** as starting material for the daunosamine donor is the correct stereochemistry of two of the three relevant stereocenters (*i.e.* C-4 and C-5).

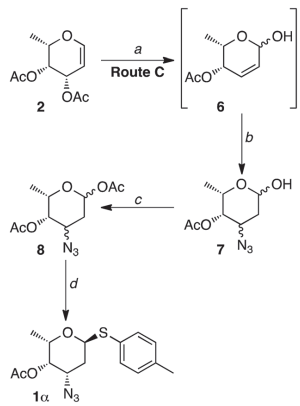
Results and discussion

We explored three different routes from **2** to **1**, all based on the Ferrier type 1 reaction, *i.e.* the addition of nucleophiles to the anomeric position to yield 2,3-unsaturated glycosides (Schemes 1 and 2).

It is known that glycals can react with sodium azide/$BF_3 \cdot OEt_2$ in acetonitrile to give enopyranosyl azides, in a standard Ferrier type 1 reaction (Scheme 1, route A). The enopyranosyl products then undergo [3,3] sigmatropic rearrangements to give 3-azido-3-deoxy glycals. Usually the 3-azido regioisomer is the major product under thermodynamic control.[6–9] Even though the regioisomeric distribution can be predicted for a variety of glycals (D-glucal, D-allal, L-rhamnal and D-xylal), the stereochemical outcome is less predictable. In 1980, Guthrie and coworkers showed that additions to tri-*O*-acetyl-D-allal and -D-glucal gave similar product distributions, *i.e.* a 2 : 1 ratio of axial : equatorial azide.[7] Later, Paulsen *et al.* described a similar reaction using D-xylal which further favored the axial product, *i.e.* a 4 : 1 ratio of axial : equatorial azide.[8] To the best of our knowledge there are no examples of this reaction with L-fucal and we thus subjected **2** to these conditions, aiming for **4**. To our surprise, no 3-azido-3-deoxy fucal (**4**) was formed. We



Scheme 1 Attempted routes A and B, reagents and conditions: (a) NaN_3, $BF_3 \cdot OEt_2$, CH_3CN, r.t., 2 h. (b) HSTol, $BF_3 \cdot OEt_2$, PhMe, 0 °C to r.t., 4 h, 44%.



Scheme 2 Route C, reagents and conditions: (a) H_2O, 100 °C, microwave, 15 min. (b) NaN_3, HOAc, 100 °C, microwave, 10 min. (c) Ac_2O, pyridine, r.t., 1 h. (d) HSTol, $BF_3 \cdot OEt_2$, DCM, −40 °C, 5 min. 32% overall yield from **2**.

speculate in that the enopyranosyl azide (**3**) is the preferred product in this case.

Next, we evaluated the possibility of reversing the reaction sequence *i.e.* introducing the thiocresyl (*p*-methyl-thiophenyl) moiety prior to the azido functionality (Scheme 1, route B). By using thiocresol as nucleophile in the first Ferrier type 1 reaction we isolated the thiocresyl pseudo fucal **5** in moderate yield (44%).[10] Further on, we explored conditions for introduction of the azido functionality: NaN_3/HOAc/H_2O, NaN_3/pTSA/HOAc, NaN_3/TFA/DCM, $TMSN_3$/TFA/DCM, and AgN_3/HBr/HOAc/DMF. Unfortunately, none of these reaction conditions gave the desired product. The C2–C3 double bond is seemingly inert toward mild acidic conditions. Under stronger acidic conditions, the material decomposed. In contrast, the addition of azide ions to the corresponding pseudo fucal (**6**, *vide infra*) worked well. We speculate that this reaction is limited to unsaturated hemiacetals, where the open form constitutes an α,β-unsaturated aldehyde intermediate that can be attacked by the nucleophile, in a Michael addition reaction.

Finally, we decided to test a protocol similar to the one used by Florent[11] and Fan (Scheme 2, route C).[4] Thus, we formed the corresponding pseudo fucal **6** by reaction in water at 80 °C for 3 h. The pseudo fucal was not isolated but instead subjected to NaN_3/AcOH/H_2O in r.t. for 24 h to give the hemiacetal **7**, which was subsequently acetylated using standard conditions (pyridine/acetic anhydride). The reaction mixture was coevaporated with toluene to get crude **8**.

Initial glycosylation attempts of compound **8** towards donor **1α/β** using $BF_3 \cdot OEt_2$ at r.t. resulted in a complicated mixture of products. Apart from **1α**, we also isolated compound **9** (Chart 1). This material is most probably formed by internal transfer of the anomeric acetyl group. To avoid the formation of **9**, the temperature was lowered to −40 °C and the amounts of thiocresol and $BF_3 \cdot OEt_2$ were decreased to 1.2 and 1.25 equivalents,

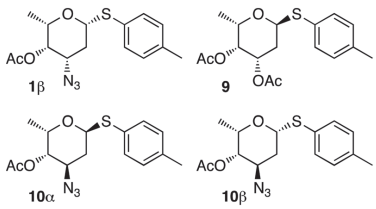


Chart 1 Sideproducts in the synthesis of **1**.

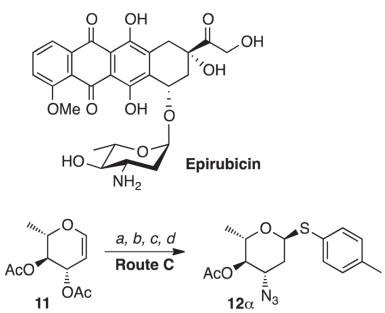
respectively. In addition, the reaction time was shortened and the reaction was quenched after 5 minutes. Consequently, fewer side-products were formed, which simplified the purification. In addition, during these conditions, the glycosylation was found to be highly α-selective and only trace amounts of **1β** was detected.

With optimized glycosylation conditions we returned to the Ferrier reaction. The problems seemed to be long reaction times, with associated decomposition of the product. Thus, we turned to microwave heating and performed the first step, *i.e.* the formation of the pseudo fucal **6**, in a microwave reactor at 100 °C for 15 min, followed by addition of NaN_3/HOAc, and further microwave heating for 10 minutes to obtain **7**. The crude reaction mixture was worked up, acetylated and glycosylated to give 19% of **1** over three steps. Unfortunately this material was contaminated with a small amount of compound **5**, which could not be separated from **1**. The presence of **5** indicated that the addition of azide to **6** was incomplete, and therefore we prolonged the reaction times. As expected, after 30 minutes, no traces of **5** could be observed, but the overall yield was lowered to 16%, mainly due to decomposition. Next, we tried a one-pot reaction where compound **2** was dissolved in H_2O/HOAc/NaN_3 and heated in a microwave reactor at 100 °C. With a total reaction time of 20 minutes, the conversion was raised to 22% but accompanied by a substantial amount of **5** (ratio **1** to **5** was 1 : 0.15). Without acid catalysis (acetic acid) the ratio **1** : **5** was further increased to 1 : 0.64. Finally, we increased the amount of NaN_3 from 2 to 4 or 6 equivalents, which gave compound **1α** in 30% and 32% yield respectively, without any trace of **5**.

Under these optimized conditions we could only detect trace amounts of β-glycosides (**1β** or **10β**, Chart 1). However, the addition of the azide ion to the pseudo fucal is not satisfactorily stereoselective and our reaction conditions gave a 2 : 1 ratio (**1α** : **10α**). In a similar reaction sequence starting from **6**, generated *in situ*, using 1.75 equivalents of NaN_3 in THF at r.t. for 10 hours, Renneberg *et al.* observed a 1 : 2.4 ratio (equatorial : axial) in the addition of azide.[12] Shorter reaction times and elevated temperatures seemingly reverses the selectivity.

To broaden the scope of this synthetic procedure, we isolated the corresponding donor for epirubicin, *i.e. p*-tolyl 4-*O*-acetyl-3-azido-2,3,6-trideoxy-1-thio-α-L-arabino-hexopyranoside[4] (**12α**) in 28% overall yield from L-rhamnal (Scheme 3).

Our optimized synthetic procedure is only limited by the microwave reactor size. We have run the reaction in a 2 g scale with similar yields.



Scheme 3 Route C, reagents and conditions: (a) H_2O, 100 °C, microwave, 15 min. (b) NaN_3, HOAc, 100 °C, microwave, 10 min. (c) Ac_2O, pyridine, r.t., 1 h. (d) HSTol, $BF_3{\cdot}OEt_2$, DCM, −40 °C, 5 min. 28% overall yield from **11**.

Conclusions

In summary, we have investigated three different routes to the versatile daunosamine donor **1α**. In the optimized procedure, **1α** can be produced in three synthetic steps with one final chromatographic separation in an overall yield of 32%. The synthetic sequence can be performed in one day. The donor **12α** was synthesized in 28% overall yield from L-rhamnal, using the same procedure.

Experimental

General methods

Known and commercially available compounds were in agreement with previously published data (NMR). Anhydrous DCM was available *via* a solvent dispensing system (MB SPS-800). Moisture sensitive reactions were carried out under N_2 using dried glassware. NMR spectra were recorded on a Bruker Avance II at 400 MHz (^{1}H) and at 100 MHz (^{13}C), operating at 294 K. Chemical shifts are given in ppm downfield from Me_4Si, with reference to residual $CHCl_3$, 7.26 ppm. Reactions were monitored by TLC using alumina plates coated with silica gel (Merck 60 F_{254}) and visualized using either UV light or by charring with ethanolic H_2SO_4 or staining with a solution of *p*-methoxybenzaldehyde (26 mL), glacial acetic acid (11 mL), concentrated H_2SO_4 (35 mL) and 95% ethanol (960 mL). Microwave heated reactions were performed in sealed tubes with a Biotage™ Initiator Classic microwave instrument using an external surface temperature sensor. Preparative chromatography was performed with an automated Biotage™ Isolera One purification apparatus.

***p*-Tolyl 4-*O*-acetyl-3-azido-2,3,6-trideoxy-1-thio-α-L-lyxo-hexopyranoside (1).** **2** (ref. 5) (507 mg, 2.37 mmol) was mixed with water (10 mL) and heated in a microwave reactor at 100 °C for 15 minutes and allowed to reach r.t. before addition of AcOH (1.5 mL, 26.2 mmol) and NaN_3 (926 mg, 14.2 mmol). The

reaction mixture was heated in a microwave reactor at 100 °C for 10 minutes, allowed to reach r.t. and poured into sat. aq. $NaHCO_3$ (10 mL). The resulting mixture was extracted with DCM (4 × 20 mL). The organic phases were dried (Isolute phase separator), combined and evaporated. The crude residue was stirred with pyridine (3.0 mL) and acetic anhydride (2.5 mL) at r.t. After 1 h, the reaction mixture was coevaporated with toluene several times. The crude residue was mixed with *p*-thiocresol (248 mg, 2.00 mmol), dissolved in anhydrous DCM (6 mL) and cooled to −40 °C. After 10 minutes $BF_3{\cdot}OEt_2$ (0.28 mL, 2.21 mmol) was added dropwise. After 5 minutes, sat. aq. $NaHCO_3$ (10 mL) was added and the reaction mixture was allowed to reach r.t. The aqueous phase was extracted with DCM (4 × 20 mL). The organic phases were dried (Isolute phase separator), combined and evaporated. The crude product was chromatographed (KP-Sil 50 g column; solvent system: 100 : 0 A–B (23 CV), linear gradient to 95 : 5 A–B (16 CV), 95 : 5 A–B (14 CV) where A: petroleum ether and B: Et_2O; flow-rate: 50 mL min^{-1}; UV detection at 254 nm) to give **1α** (241 mg, 32%). Analytical data were in agreement with previously published results.[4]

***p*-Tolyl 4-*O*-acetyl-2,3,6-trideoxy-1-thio-α-L-threo-hex-2-enopyranoside (5).** $BF_3{\cdot}OEt_2$ (0.075 mL, 0.60 mmol) was added to a solution of **2** (ref. 5) (129 mg, 0.60 mmol) and *p*-thiocresol (80 mg, 0.64 mmol) in toluene (6 mL) at 0 °C. After 5 h sat. aq. $NaHCO_3$ was added, the phases were separated and the aqueous phase was extracted with DCM. The combined organic phases were coevaporated with toluene. The crude product was chromatographed (KP-Sil 10 g column; solvent system = 100 : 0 A–B (10 CV), linear gradient to 95 : 5 A–B (110 CV), where A = heptane and B = EtOAc; flow-rate = 25 mL min^{-1}; UV detection at 254 nm) to give **5** (74 mg, 44%), as a white solid. $[\alpha]_D^{20}$ +0.03 (*c* 1.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.41, 7.11 (ABq, 2H each, J = 16.0 Hz, Ar), 6.20 (ddd, 1H, J = 9.9, 3.4, 0.4 Hz, H-2), 6.05 (ddd, 1H, J = 9.8, 5.4, 1.7 Hz, H-3), 5.76 (dd, 1H, J = 3.3, 1.7 Hz, H-1), 5.03 (dd, 1H, J = 5.5, 2.5 Hz, H-4), 4.54 (dq, 1H, J = 6.6, 2.4 Hz, H-5), 2.33 (s, 3H, Ar-CH_3), 2.10 (s, 3H, CO_2CH_3), 1.27 (d, 3H, J = 6.8 Hz, H-6). ^{13}C NMR ($CDCl_3$): δ 170.7, 137.6, 131.9, 131.6, 131.5, 129.8, 125.0, 84.2, 65.7, 65.4, 21.2, 21.0, 16.1. HRMS calcd for $C_{15}H_{18}O_3SNa$ (M + Na): 301.0874; found: 301.0878.

***p*-Tolyl 3,4-di-*O*-acetyl-2,6-dideoxy-1-thio-α-L-lyxo-hexopyranoside (9).** Isolated in initial glycosylations of **8** towards **1**. Analytical data in full agreement with published data.[13]

***p*-Tolyl 4-*O*-acetyl-3-azido-2,3,6-trideoxy-1-thio-α-L-xylo-hexopyranoside (10α).** Isolated in the synthesis of **1**. ^{1}H NMR ($CDCl_3$): δ 7.37, 7.10 (ABq, 2H each, J = 8.0 Hz, Ar), 5.45 (dd, 1H, J = 6.0, 3.3 Hz, H-1), 4.73 (dd, 1H, J = 4.1, 1.9 Hz, H-4), 4.66 (dq, 1H, J = 6.6, 2.0 Hz, H-5), 3.93 (q, 1H, J = 4.2 Hz, H-3), 2.50 (ddd, 1H, J = 14.8, 6.2, 4.1 Hz, H-2), 2.32 (s, 3H, Ar-CH_3), 2.14 (s, 3H, CO_2CH_3), 2.03 (dt, 3H, J = 14.8, 3.3 Hz, H-2′), 1.17 (d, 3H, J = 6.6 Hz, H-6). ^{13}C NMR ($CDCl_3$): δ 170.3, 137.3, 132.6, 131.4, 129.8, 82.6, 70.4, 62.9, 56.1, 30.9, 21.2, 21.0, 16.1. HRMS calcd for $C_{15}H_{19}N_3O_3SNa$ (M + Na): 344.1045; found: 344.1044.

***p*-Tolyl 4-*O*-acetyl-3-azido-2,3,6-trideoxy-1-thio-α-L-arabino-hexopyranoside (12α).** Synthesized as compound **1**, starting from **11** (525 mg, 2.45 mmol) to give **12α** (217 mg, 28%). Analytical data were in agreement with previously published results.[4]

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