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COMMUNICATION

Deuterium-isotope study on the reductive ring opening of benzylidene acetals†

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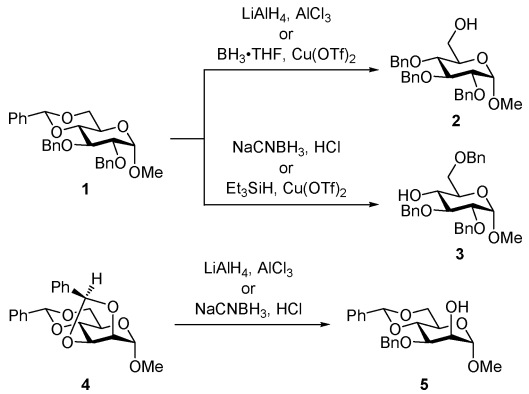
Specific deuterated reference compounds were prepared to probe the stereoselectivity of the reductive ring opening of carbohydrate-based benzylidene-type acetals. AlD_3 revealed a retentive stereoselectivity probably through the rare S_Ni (internal nucleophilic substitution) mechanism. An S_N1-like mechanism occurs in the acid-promoted regioselective BD_3·THF- or Et_3SiD-reductive ring opening.

Regioselective protections of multiple hydroxyls are obligatory steps in the chemical synthesis of complex carbohydrates and natural products.[1] Here, the readily installed and easily manipulated benzylidene-type acetals gained immense importance and widespread use. These base-resistant yet acid-labile functionalities are typically used to block 4- and 6-hydroxyls of hexopyranoses as well as vicinal *cis*-diols to give fused 1,3-dioxane and 1,3-dioxolane backbones, respectively. Aside from protecting two hydroxyl groups simultaneously, they also exhibit significant influence on the stereochemical outcome of chemical glycosylations.[2] Another highly useful advantage is their capability to be reductively opened in a regioselective manner exposing a free hydroxyl and a benzyl-type ether enabling the opportunity for further transformations.

The $LiAlH_4$ and $AlCl_3$ combination is the first reagent set used in the reductive ring opening of cyclic acetals.[3] They generate, depending on mixing proportions, the alane species (*i.e.* $AlHCl_2$, AlH_2Cl and AlH_3) that participate in the actual hydride transfer.[4] In the case of 4,6-*O*-benzylidene-type acetals, the ring opening mediated by alanes occurs at the less hindered and more basic 6-O forming the 4-*O*-benzyl-type derivative (Scheme 1).[5] Not surprisingly, this regioselectivity is also shared by *i*-Bu_2AlH.[6] The $NaCNBH_3$/HCl tandem, later introduced by Garegg, notably favoured the opposite regioselectivity—the ring opening at the 4-O position.[7] In the case of the fused 1,3-dioxolanes, both the alanes and $NaCNBH_3$/HCl gave identical regioselectivity in the benzylidene acetal cleavage that is dependent on the stereochemical orientation of the aromatic group.[8] The so-called 3X (e*X*o gives a*X*ial hydro*X*yls) rule of thumb[1a] was realized as



Scheme 1 Representative examples of the reductive ring opening of benzylidene acetals.

a general tendency during the openings of these 5-membered rings. Cleavage of the 1,3-dioxolanes was also found possible in the presence of the 6-membered counterpart.[9] Over the years, a number of boron-,[10] silicon-,[10f,10h,11] and tin-based[12] hydride reagents in combination with a similarly diverse set of Lewis and Brønsted acids were introduced and applied to reductively open benzylidene-type acetals. Variations in hydride source, ligand, temperature, solvent and the accompanying acid displayed profound effects on the regioselectivity of the ring opening.

The mechanistic aspects of the acid-mediated nucleophilic addition to cyclic acetals resulting in ring opening have been widely investigated. Regioselectivity rests on the stability of the initial complex between the acid and the acetal oxygens and the relative ease with which the nucleophile approaches the acetal carbon. Relating to the C–O bond that would be broken, the nucleophile may form the new covalent bond in either an inversive or retentive manner. It was suggested[13] that the initial complex promotes the formation of ion pairs that vary from being intimate leading to inversive stereoselectivity *via* an S_N2-like mechanism to being separated, presumably through an oxocarbenium ion, enabling stereorandomization in an S_N1-like manner. However, alanes, which are themselves weak Lewis acids, were earlier speculated to resort to internal hydride transfer following initial complexation with the acetal oxygen.[14] This mechanism, which results in stereochemical retention, was dismissed[13] due to insufficient evidence at the time. Recent reports highlighted the influence of solvent and ligand on the relative acid strengths of the Lewis acid and the reducing agent, which subsequently determines the regio- and stereoselectivity of the ring opening.[15]

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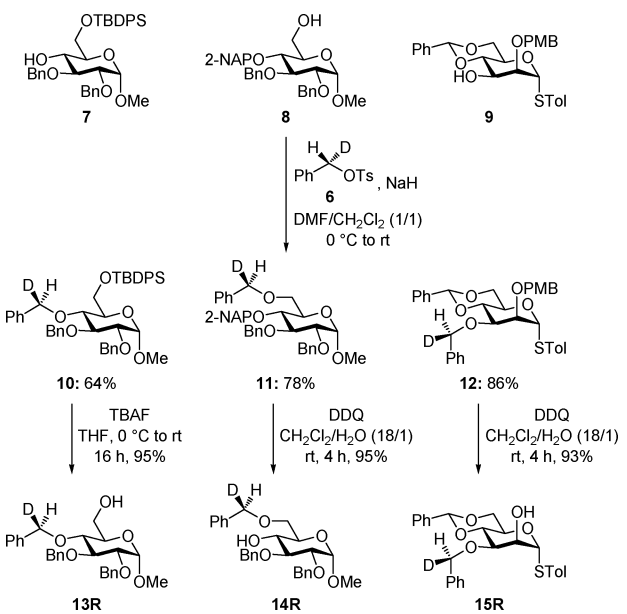
In our preliminary isotope study, the benzylidene acetal in compound **1** was regioselectively opened using either BD_3·THF or Et_3SiD both catalysed by $Cu(OTf)_2$.[10f] Based on the NMR analysis of the products, BD_3·THF generated a deuterated 4-*O*-benzyl derivative with a 5 : 1 diastereomeric ratio whereas Et_3SiD formed the deuterated 6-*O*-benzyl counterpart with apparent stereorandomization (*i.e.* 1 : 1 ratio of diastereomers). The NMR data gathered, however, was inadequate to fully distinguish the configuration of the isomers. Overall, the stereoselective inclinations of the reductive ring opening of benzylidene-type acetals remain highly speculative without the full confirmation of the structure of the deuterated products.

Analysis of the NMR spectra alone cannot be used to ascertain the absolute structure designation of deuterated products in the reductive ring opening of carbohydrate-based benzylidene acetals. We, therefore, decided to synthesize deuterium-labelled reference compounds to probe the stereoselectivity of the nucleophilic attack on the acetal carbon (Scheme 2). The preparations made use of the deuterated tosylate **6** as benzylating reagent *via* Williamson etherification. An approximately 30% ee compound **6** has been reported[16] which is not appropriate for our study. Alternatively, (*S*)-(+)-benzyl-α-d_1 alcohol, generated by the enantioselective reduction of PhCDO with (*R*)-alpine borane (reportedly attainable in 96% ee[17]), was tosylated[18] to provide the desired **6**. Considering the possible ring openings of a 4,6-*O*-benzylidene acetal and the ring cleavage of a 2,3-*O*-benzylidene with an *exo*-oriented phenyl group, the alcohols **7**,[19] **8**,[4b] and **9** were treated with **6**[20] and NaH to generate the deuterated benzyl ethers **10** (64%), **11** (78%), and **12** (86%), respectively. Desilylation of **10** with tetra-n-butylammonium fluoride (TBAF) furnished the target 6-*O*-ring opening reference compound **13R** in 95% yield. Subsequent cleavage of the 2-naphthylmethyl (2-NAP) and *p*-methoxybenzyl (PMB) groups of compounds **11** and **12** gave the individual reference alcohols **14R** (95%) and **15R** (93%), respectively. All the reference compounds are expected to carry the deuterated carbon in the *R*-configuration.



Scheme 2 Preparations of the reference compounds.

The 6-*O*-ring opening of compound **1** was carried out using AlD_3 or BD_3·THF as deuteride source. Inversion of configuration at the acetal carbon would result in the 6-alcohol **13R** whereas retention would lead to **13S** (Fig. 1). Comparison with the ^{1}H NMR spectrum of the undeuterated 6-alcohol **2** identified the 4-*O*-benzylic proton of our reference compound (**13R**) at around 4.61 ppm. The product of AlD_3 treatment only showed a very minor signal for **13R** with a significant peak, ascribed to the 4-*O*-benzylic proton of **13S**, appearing at 4.86 ppm. The reaction is highly stereoselective (**13R**/**13S** = 6/94) providing compelling evidence for a retentive deuteride addition. In previous papers,[10f,10h] we reported the benzylidene 6-*O*-ring opening in compound **1** with BH_3·THF catalysed by various metal triflates in excellent yields. Examination of the stereoselectivity of the BD_3·THF-mediated transformation in tandem with some selected metal triflates as well as TMSOTf revealed notable similarities in the **13R**/**13S** ratios (approx. 1/5). Stereochemical retention is favoured but inversion is more pronounced in contrast to that of AlD_3. The proportion of the diastereomers also appears to be independent of the quantity of added Lewis acid as shown for TMSOTf (0.5 equiv *versus* 1.1 equiv).

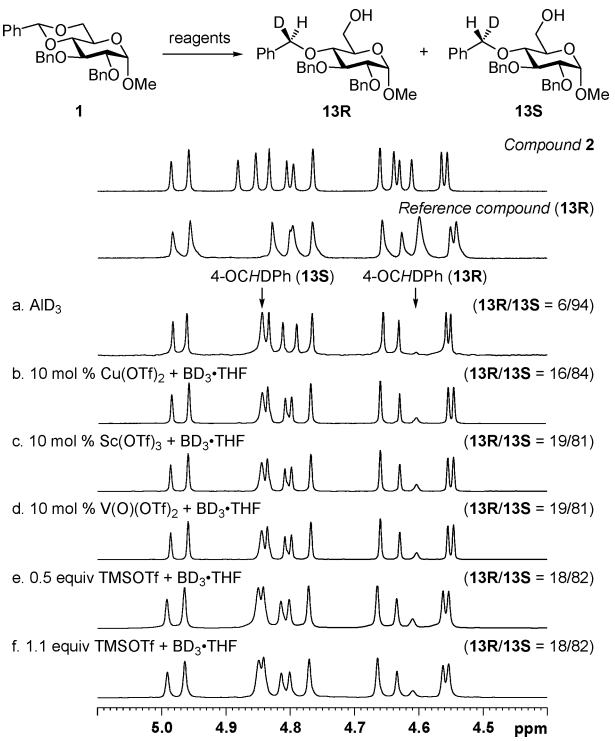


Fig. 1 ^{1}H NMR spectra for the 6-*O*-ring opening of compound **1**.

The 4-*O*-ring opening of the benzylidene acetal in compound **1** was then carried out using Et_3SiD in the presence of $Cu(OTf)_2$,[10f] BF_3·Et_2O,[11c] or CF_3COOH.[11a] In this transformation, the reference compound **14R** corresponds to retentive substitution whereas **14S** represents inversion. The identified signal relating to the 6-*O*-benzylic proton in the ^{1}H NMR spectrum of **14R** in comparison to that of the 4-alcohol **3** appears at 4.50 ppm. As illustrated in Fig. 2, the diastereomers **14R** and **14S** are generated in nearly equal amounts in all cases (**14S** is measured from the resonance

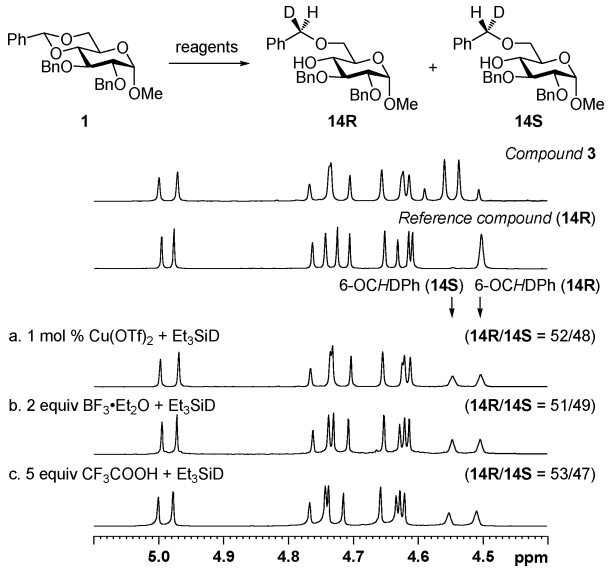


Fig. 2 ^{1}H NMR spectra for the 4-*O*-ring opening of compound 1.

at 4.55 ppm). The data clearly demonstrates stereorandomization that is independent of the nature of the acid used.

The stereoselectivity of the ring opening of the 1,3-dioxolane in compound **16** was next probed (Fig. 3). With the *exo* orientation of the phenyl ring, the reductive ring opening is predicted to favour the formation of the 2-alcohol **17**[1b] instead of the 3-alcohol counterpart. Thus, the diastereomers **15R** (retentive reduction) and **15S** (inversive reduction) are the possible products upon reduction with AlD_3. The resonance at 4.71 ppm, indicated by the reference compound (**15R**), fully coincides with the major peak of the ring-opening product. Comparison with the minor signal at around 4.86 ppm attributed to **15S** (in reference to the ^{1}H NMR spectrum of compound **17**) gave a 91/9 ratio (**15R**/**15S**) clearly favouring the retentive introduction of the deuteride.

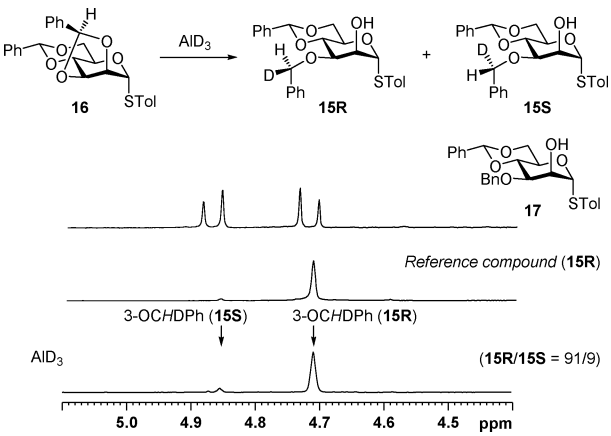
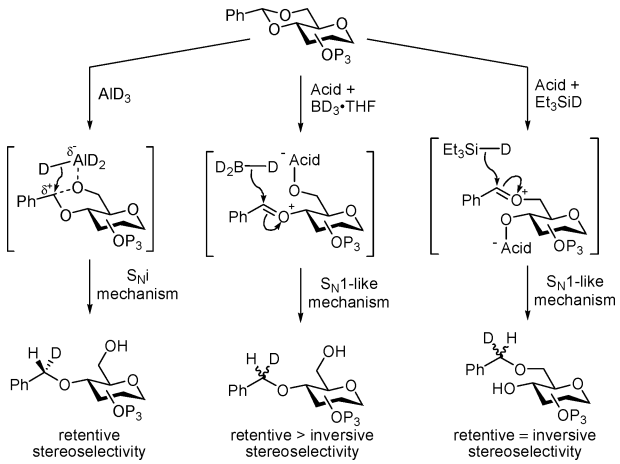


Fig. 3 ^{1}H NMR spectra for the 2-*O*-ring opening of compound **16**.

With the reference compounds and their corresponding ^{1}H NMR data, the stereoselectivity of the reductive ring opening of benzylidene acetals is now evident. The AlD_3-mediated ring opening possesses retentive stereoselectivity for acetals with both 1,3-dioxane and 1,3-dioxolane backbones. By applying our NMR data, the previously reported[15c] inversive ring opening of a deuterated derivative of compound **1** with the $LiAlH_4/AlCl_3$ tandem was found to agree with our result; the original interpretation was based on a wrong stereochemical assignment. The highly retentive deuteride addition by AlD_3 led us to suggest the mechanism following the rarely observed internal nucleophilic substitution (S_Ni). As depicted in Scheme 3, AlD_3 weakly coordinates with the less hindered and more nucleophilic 6-O and subsequently transfers a deuteride to the acetal carbon on the same side of the departing 6-O. The same mechanism is also expected for the reductive ring opening by *i*-Bu_2AlH. The BD_3·THF cleavage of the benzylidene acetal also displayed a preference for a retentive deuteride addition with relatively minor inversion. Together with the requirement for a Lewis acid, the NMR data precludes the S_N2-like substitution suggested for intimate ion pairs[13,15c] or a mechanism similar to that of AlD_3. We propose that the acid complexation with 6-O generated a separated ion pair with an oxocabenium ion involving O-4. The stereochemical bias is probably caused by asymmetric induction of the nearby chiral center (4-C of the sugar) leading to more retention rather than inversion. The reduction carried out by Et_3SiD together with an acid appears to include an oxocarbenium ion intermediate. Full stereorandomization suggests deuteride addition in an S_N1-like fashion. The acid may in principle interact with either acetal oxygen granting more preference for 6-O; but, in this case, the resultant 4-*O*-benzyl cation cannot be reduced as Et_3SiD is bulky and not very reactive. On the other hand, the silane can readily approach either side of the 6-*O*-benzyl cation formed by the initial acid complexation with 4-O.



Scheme 3 Mechanisms of the benzylidene ring opening.

In conclusion, the deuterated reference compounds we prepared were successfully utilized to clarify the stereoselectivity of the reductive benzylidene ring opening. The data we presented can supplement further selectivity and mechanistic analysis of this type of reaction.

Acknowledgements

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20 Subsequent NMR analysis of the corresponding benzylic proton of compound **14R** gave a diastereomeric ratio of 97/3. This would translate to an enantiomeric excess of 94% for compound **6** ignoring any possible racemization during the predicted inversive etherification step.

