Reductive Cleavage as a Route to Carbohydrate Enolates. Applications to the Synthesis of *C*-Linked Disaccharides

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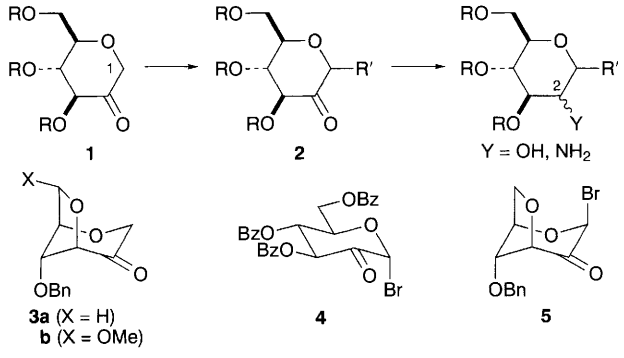
The carbohydrate-derived α-bromo ketones **4** and **5** undergo reductive cleavage using either Zn–Cu or $CeCl_3$–NaI and the resulting enolates are trapped by carbohydrate-based aldehydes **6**, **7** and **14** to give *C*-disaccharide derivatives.

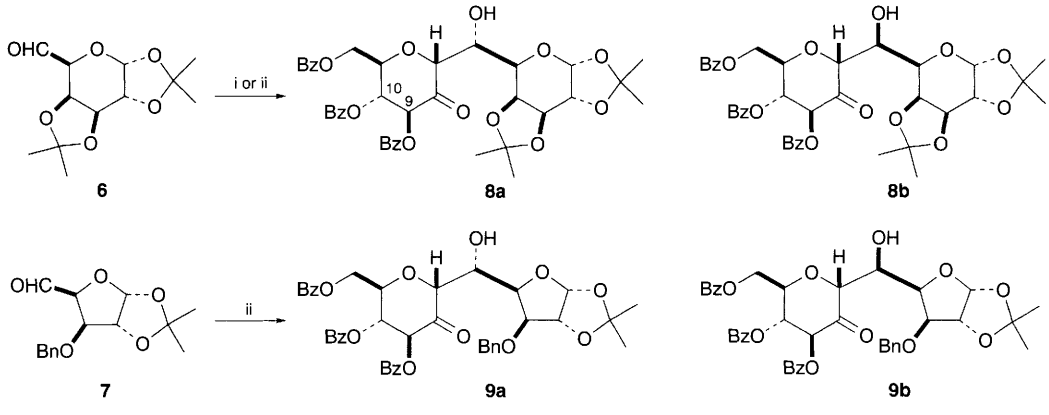
The C-1 alkylation of a nucleophilic sugar to give a *C*-glycoside provides an attractive entry to this important class of carbohydrate derivatives and several approaches towards this objective have been described. However, current solutions do not readily accommodate the presence of a functional group (*e.g.* OR) at C-2 because of problems associated with competing β-elimination leading to glycal formation.[1,2] 2-Keto sugars **1** do offer a potentially general route to *C*-glycosides that can incorporate, for example, a hydroxy or amino group at C-2. Regiospecific enolisation of **1** provides nucleophilic reactivity at C-1 and, following alkylation, the *C*-glycosyl product **2** retains a versatile carbonyl unit at C-2 which is capable of undergoing further manipulation. However, regiocontrolled enolisation of 2-keto sugars is problematic[3] and, while C-1 nucleophiles of this type may be generated by deprotonation of the 1,5:3,6-dianhydro variants **3a** and **3b**, the limitations that we have encountered with the resulting (Li, Na and K) enolates indicate that more flexible solutions are still required.[4]

Reductive cleavage of α-bromo ketones provides an alternative source of enolate reactivity[5] and zinc-based enolates derived from the glycos-2-ulosyl bromide **4** have recently found application in the synthesis of 2-hydroxy-1-*C*-glycosides.[6] We now describe both zinc- and cerium-mediated[7] activation of the α-bromo ketones **4** and **5** and the reactivity of the resulting enolates towards carbohydrate-derived aldehydes **6**, **7** and the nucleoside derivative **14** leading to *C*-linked disaccharides.

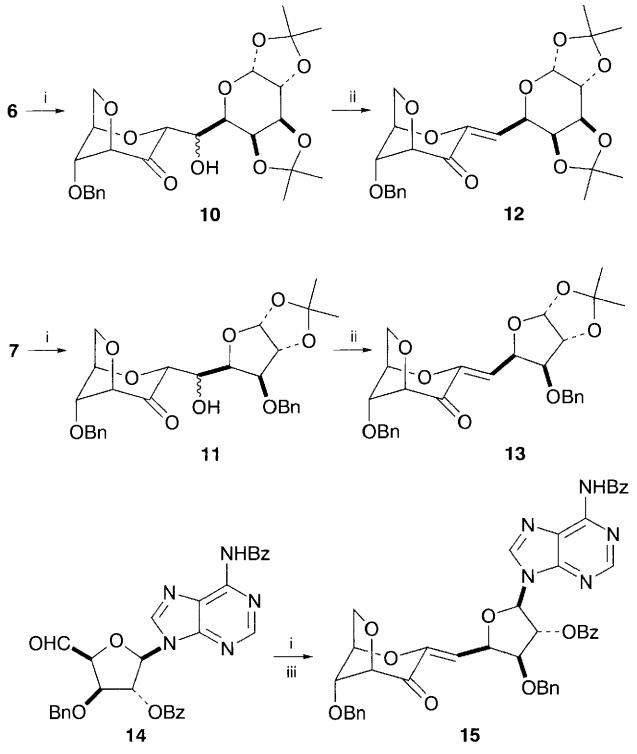
The zinc enolate, resulting from activation of ulosyl bromide **4** with Zn–Cu, reacts smoothly with the D-galactose-derived aldehyde **6**[8] to give an 8:1 mixture of the aldol adducts, *C*-disaccharides **8a** and **8b** in essentially quantitative yield (Scheme 1).† The α-stereocontrol observed in this process is noteworthy, given that this zinc enolate shows a negligible level of α/β selectivity with simpler aldehydes (HCHO or MeCHO).[6] $CeCl_3$–NaI[7] in THF provides an alternative method for reductive activation of ulosyl bromide **4** and reaction of the resulting cerium species with aldehyde **6** gave the α-adducts **8a** and **8b** (as a 1:1 mixture, 53%). Cerium-mediated reaction of ulosyl bromide **4** with the furanoside aldehyde **7**[9] was also α-selective leading to *C*-disaccharides **9a** and **9b** (as a 2:1 mixture, 58% yield).†

The reactivity of enolates obtainable from the sterically more demanding 3,6-anhydro-bridged ulosyl bromide **5**‡ have also been examined. Accordingly, cerium-mediated activation of **5** (a procedure that proved to be more efficient than use of zinc) and trapping with aldehydes **6** and **7** gave aldol adducts **10** (as a 4:1 mixture of diastereomers at C-6, 46% from **6**) and **11** (as a 10:1 mixture of diastereomers at C-5, 40% from **7**), respectively (Scheme 2). While it was possible to separate these diastereomeric mixtures, dehydration of the crude product in each case gave a single enone **12** (62% from **10**) and **13** (34% from **11**), respectively.§ Enone **13** has recently been used in the synthesis of the C_{11}-glycosyl component of the herbicidins[10] and, as part of this study, we have also examined the nucleoside-based aldehyde **14**¶ as an aldol substrate. The extreme sensitivity of aldehyde **14** towards basic conditions precluded the use of enolates derived from **3a**, but reaction of the cerium enolate obtained from bromide **5** gave a 1:1 diastereomeric mixture of aldol adducts which were immediately dehydrated to give enone **15**§ (20% overall from **14**).





Scheme 1 *Reagents and conditions*: i, **4**, Zn–Cu, THF, −35 °C; ii, **4**, $CeCl_3$, NaI, THF, room temp.



Scheme 2 *Reagents and conditions*: i, **5**, $CeCl_3$, NaI, THF, room temp.; ii, DCC, $Cu^{I}I$, PhMe, reflux; iii, $MeO_2CNSO_2NEt_3$, PhH, reflux

In summary, both zinc- and cerium-mediated reductive cleavage of carbohydrate-based α-bromo ketones provides a useful source of nucleophilic reactivity at C-1 that has potential for the synthesis of a range of *C*-disaccharides, given the accessibility of glycos-2-ulosyl bromides.[11] Further work is underway to address the range of C-2 functionality that may be incorporated following alkylation at C-1 and to shed further light on the factors controlling the stereoselectivity attainable in the aldol step. This does vary with the method of activation (Zn or Ce) used and, in the cerium series, not only is the nature of the nucleophilic component unclear but we have found the isomer distribution of aldol products to be markedly sensitive to the concentration of the cerium species present.[12]

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Footnotes

† The structures of **8a,b** and **9a,b** are based on ^{1}H NMR analysis, assignment of the *C*-glycosyl 'anomeric' configuration (α *vs.* β) was established by NOE studies, and in the case of **8a**, also by CD data of the corresponding enolone ester, readily formed by base-induced 9,10-elimination of benzoic acid.

‡ Bromide **5** was prepared by bromination (NBS, −20 °C, THF) of the Bu^tMe_2Si enol ether derived from **3a**.[4]

§ Enones **12**, **13** and **15** were isolated as single isomers but alkene geometry has not been assigned.

¶ Aldehyde **14** was prepared in six steps from 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-xylofuranose ($ClCH_2COCl$, pyridine; TFA, H_2O; PhCOCl, pyridine; *N*-benzoyl adenine, $Me_3SiNHSiMe_3$, Me_3SiCl, $SnCl_4$, MeCN; $HSCH_2CH_2NH_2$, pyridine; Me_2SO, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, TFA, pyridine). Essentially quantitative epimerisation (at C-4′) was observed when **14** was exposed to silica gel and all attempts to achieve a base-mediated aldol reaction involving **14** resulted in decomposition.

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