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# Synthesis of C-Disaccharides *via* Glucal Dimerisation

**Andrew L. J. Byerley, Alan M. Kenwright and Patrick G. Steel***

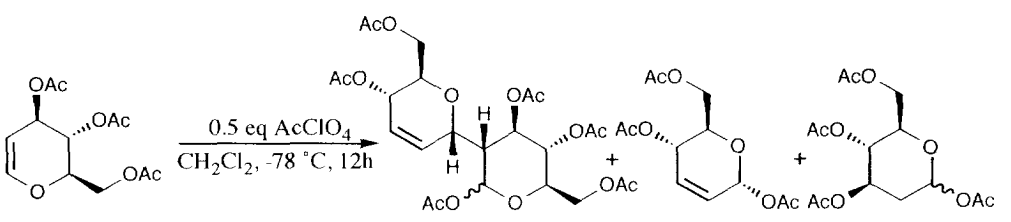
Department of Chemistry, University of Durham, Science Laboratories, South Road, Durham DH1 3LE

email: p.g.steel@durham.ac.uk

***Abstract:*** Treatment of 3-O-acetyl glucal and related species with acetylperchlorate provides good yields of the corresponding C-disaccharides with a high degree of stereocontrol at the new C-C bond.


Owing to their considerable potential in both biological applications and organic synthesis the development of methods for C-glycoside synthesis has become a major area of research.[1] Glycals have been widely utilised as the electrophilic components in many of these processes notably via the "carbon Ferrier rearrangment". Such an approach was pioneered by Ferrier and Prasad who reported the isolation of a dimer in 10% yield from the reaction of tri-O-acetyl-D-glucal (**1**) with $BF_3$•$OEt_2$.[2] In connection with a programmme dedicated to the construction of stereoregular oligomer units based on cyclic ethers we have reexamined this process with a number of cationic polymerisation initiators and in this letter wish to report that 3-O-acyl glucals can be efficiently coupled with high stereoselectivity to provide efficient routes to C-disaccharides.[3]

Our initial experiments focused on the use of the HI / $I_2$ and HI / $ZnI_2$ initiating systems developed by Higashimura and Sawamoto for the living cationic polymerisation of vinyl ethers.[4] However treatment of various glucals with either of these initiators afforded complex polymeric mixtures of broad polydispersity and a low degree of polymerisation indicating that chain transfer processes were highly competitive. We then turned to the use of acetyl perchlorate which has been shown to be an effective initiator for the polymerisation of dihydrofuran.[5] Reaction of tri-O-acetal-D-glucal (**1**) with 0.02 equivalents of this initiator afforded a complex mixture of products from which a significant amount of the dimer (**2**) could be isolated. Repeating this reaction with 0.5 equivalents of acetylperchlorate in dichloromethane at -78°C for 20hours afforded complete conversion of starting material and, after quenching with aqueous $NaHCO_3$, resulted in isolation of an anomeric mixture (3:2) of the corresponding 3,1-dimer (**2**) in 61% isolated yield. Careful analysis of the remainder of the material afforded minor amounts of the Ferrier rearranged product (**3**) (17%) , the 2-deoxyglucose derivative (**4**) (4%), and an unidentified minor isomer (≤1%).




**1** **2** 61% (α/β 3 : 2) **3** 17% **4** 4%

That the major product was isomeric at the anomeric centre was demonstrated by reduction with $Et_3SiH$ in the presence of $BF_3{\bullet}OEt_2$ to afford a single stereoisomer (**5**) in 77% yield. The major anomer from the dimerisation reaction was shown to be the axial acetate by virtue of the coupling to the C-2 proton (J = 3.2Hz). Confirmation that the stereochemistry of the dimer was in agreement with that originally proposed by Ferrier was obtained following extensive nOe studies, Figure 1.[6]

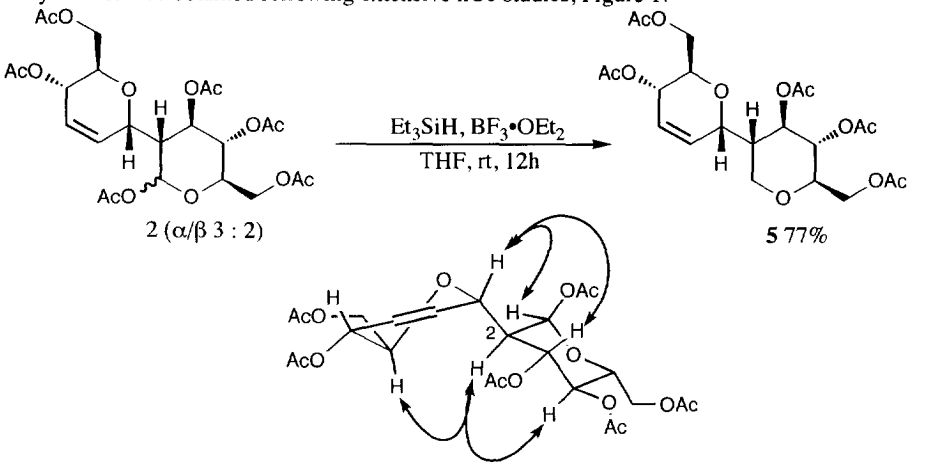
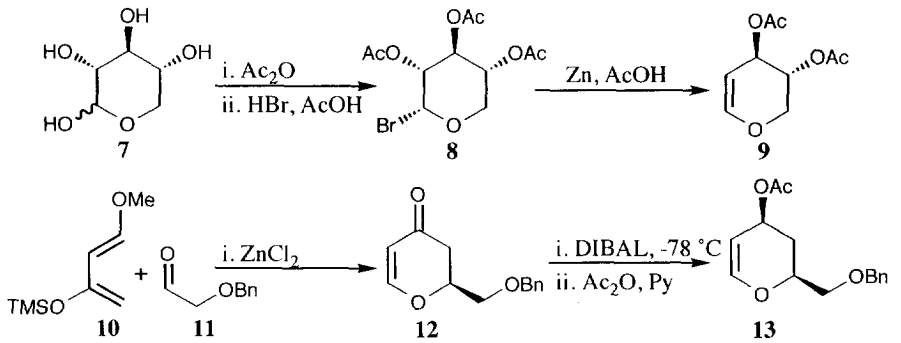



**Figure 1**

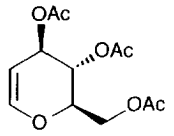
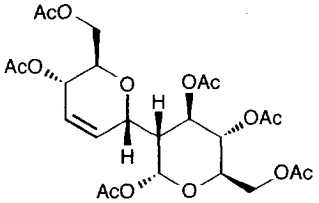
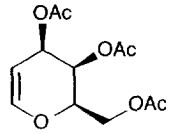
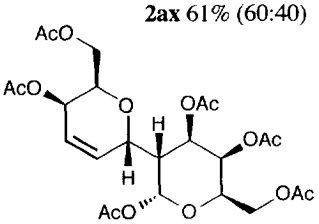
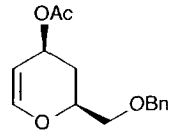
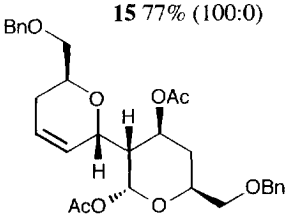
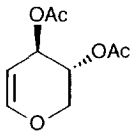
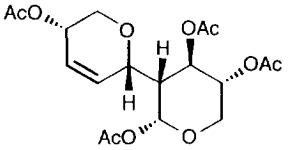
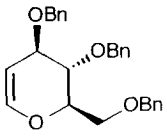
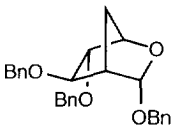
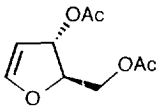
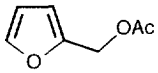
Given that this procedure appeared to be extremely efficient we decided to examine its generality. A range of six membered glucals were prepared, by known chemistry, either from the corresponding hexose via acetylation, bromination and subsequent reductive elimination[7] or *via* heteroatom Diels-Alder reaction between diene (**10**) and aldehyde (**11**) followed by selective reduction and acylation,[8] Scheme 1.




**Scheme 1**

All these substrates reacted under similar conditions to afford anomeric mixtures of the desired dimer[9] together with varying amounts of the Ferrier rearranged products, Table 1. There is a general requirement for an efficient leaving group at at C-3 since analogous treatment of tri-O-benzyl-D-glucal (**19**) produced the bicylic acetal (**20**).[10] Extension to furanoid systems also proved less successful. Reaction of the dihydrofuran (**21**), prepared in three steps from thymidine,[11] with acetyl perchlorate under identical conditions afforded only acetoxymethylfuran (**22**).

**Table 1: Dimerisation of Glucals with $AcClO_4$, $CH_2Cl_2$, -78 °C**

| Run | Glucal | Major Product [%yield (α :β)] | $Et_3SiH$ / $BF_3$•$OEt_2$ Reduction [Product, %Yield] |
|---|---|---|---|
| 1 |  **1** |  **2ax** 61% (60:40) | **5** 77% |
| 2 |  **14** |  **15** 77% (100:0) | **16** 58% |
| 3 |  **13** |  **17** 59% (94:6) | — |
| 4 |  **9** |  **18** 21% (100:0) | — |
| 5 |  **19** |  **20** 45% | — |
| 6 |  **21** |  **22** 83% | — |

The reaction presumably proceeds, Figure 2, *via* generation of the unsaturated oxacarbenium ion (**23**) through Lewis acid mediated loss of acetate. This species is then alkylated by a second equivalent of the glucal to produce a second oxacarbenium ion intermediate (**24**) which is preferentially trapped by acetate. The formation of higher oligomers is minimised by the higher nucleophilicity of acetate compared with the starting glycal. Support for this hypothesis arises from the fact that if the reaction is quenched with methanol there is no evidence for the production of the methyl glycoside. Moreover, if the simple Ferrier product (**3**) is isolated and resubjected to the reaction conditions with a further equivalent of glucal the dimer is again produced.

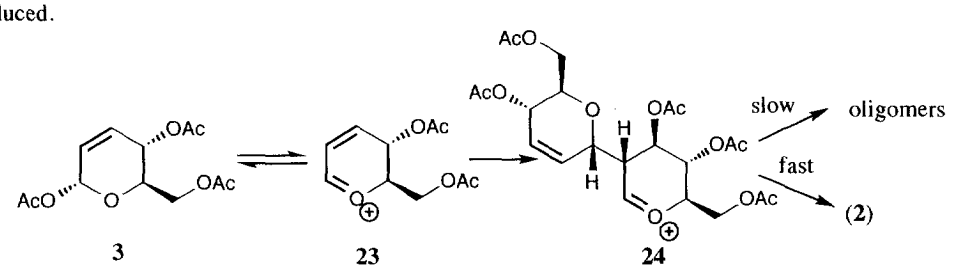



**Figure 2**

A consequence of this is that a heterocoupling of two different glucal residues becomes feasible. This and the extension to the preparation of higher C-oligosaccharides are currently under investigation and will be reported in due course.

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9. All new compounds were fully characterised giving satisfactory spectral and analytical data. All yields refer to pure isolated products.
10. This structure was determined by a series of NMR experiments [$^{1}$H, $^{13}$C, $^{1}$H-COSY, nOe, one bond and long range HETCOR]. To the best of our knowledge this rearrangemnt of a glucal derivative is unprecedented. The highly functionalised cyclopentane product has great potential in synthesis eg. as a precursor to carbocyclic nucleosides. The scope of this process and synthetic applications of the products are currently under study and the results obtained will be reported in due course.
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