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A New, General Method for the Synthesis of Carbasugar-Sugar Pseudodisaccharides

Kamyar Afarinkia,*,† Mohamed Haji Abdullahi,† and Ian J. Scowen‡

Institute of Cancer Therapeutics and Analytical Center, University of Bradford, Richmond Road, Bradford, BD7 1DP, United Kingdom

k.afarinkia@bradford.ac.uk

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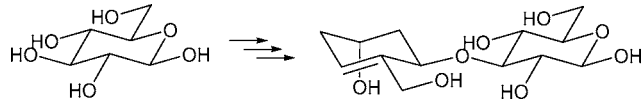
ABSTRACT

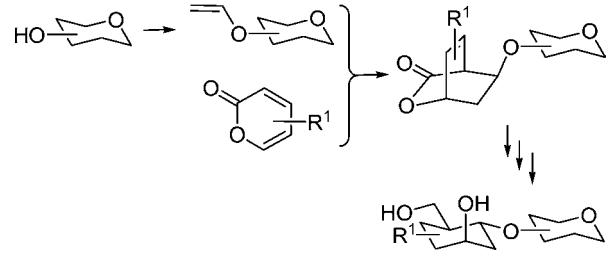


A general synthetic methodology for the synthesis of sugar-carbasugar pseudodisaccharides is described. The methodology is based on the cycloaddition of pyran-2-ones to vinylated sugars and the subsequent manipulation of the cycloadducts to construct the carbasugar component of the pseudodisaccharide.

Synthetic and naturally occurring oligosaccharides containing carbasugars have a plethora of biological activities and have significant applications in biological and medicinal chemistry.[1]

As a result, a good number of synthetic methodologies are available for their synthesis.[1,2] The vast majority of these methods involve synthesis of the carbasugar as a distinct moiety, followed by its coupling to the "true" sugar. However, although quite valid, the obvious disadvantages of this approach are the excessive reliance on functional group protection protocols and an inherent inelegance of using two different chiral sources (one involved in the genesis of carbasugar and one in the form of "true" sugar). Here, we report on a method for the synthesis of pseudodisaccharides that avoids both disadvantages. Building on the methodology we have previously developed for the efficient synthesis of individual carbasugars, we demonstrate a new, general method for the asymmetric construction of a carbasugar unit on a free hydroxyl function of a "true" saccharide (Scheme 1) and show its application to the synthesis of a novel pseudodisaccharide.

Scheme 1. General Method for the Synthesis of Pseudodisaccharides



Following on from pioneering work by Posner,[3] we and others have previously reported extensively on the versatility of the Diels−Alder cycloadditions of 2(*H*)-pyran-2-ones,[4−6] 2(*H*)-pyridones,[7] and 2(*H*)-oxazin-2-ones[8] and

† Institute of Cancer Therapeutics.
‡ Analytical Center.

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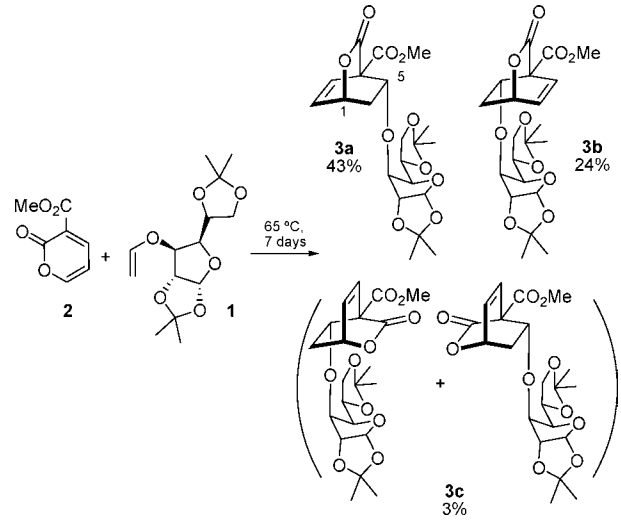
their application in synthesis.[6,9,10] These heterocycles undergo efficient cycloadditions as the diene component to afford functionally rich, bridged bicyclic lactone cycloadducts. Halogen-substituted pyran-2-ones are particularly interesting and useful since they undergo cycloadditions with a very wide range of dienophiles of different electron demand, albeit with modest regio- and stereocontrol.[5] However, significantly improved regio- and stereoselectivity is observed if the pyran-2-one substituent electronically complements that of the dienophile.[3] We have also demonstrated that manipulation of these cycloadducts affords a rapid synthetic access to heavily substituted six-membered rings and, in particular, individual carba- and azasugar moieties. On the basis of this earlier work, we envisaged that cycloadditions of a suitably substituted pyran-2-one to a vinylated sugar would be an advantageous means of accessing pseudodisaccharides. First, the Diels−Alder cycloadducts are functionally rich and, as we have already demonstrated, are ideal springboards for the synthesis of the carbasugar component of a pseudodisaccharide. In addition, cycloadditions can benefit from the induction of chirality by the enantiopure dienophile to afford the required pseudodisaccharides as single enantiomers.

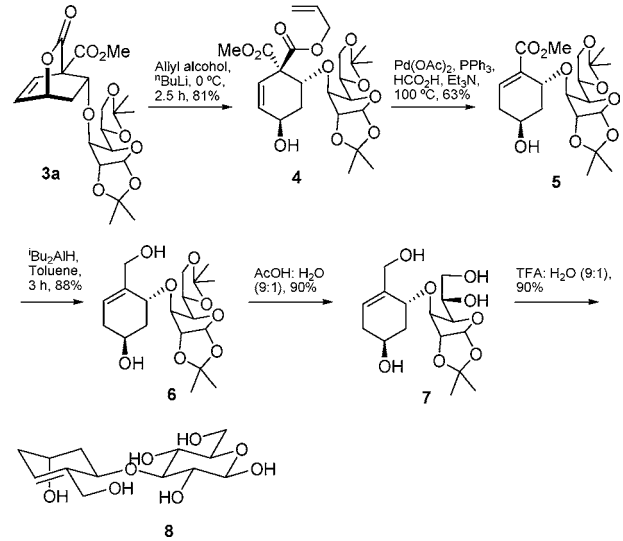
We prepared vinylated glucofuranose **1**[11] from the corresponding glucofuranose in 88% yield, via a palladium-catalyzed trans-etherification. Cycloaddition with commercially available 2-carbomethoxy-2(*H*)-pyran-2-one **2** was carried out in a sealed tube in methylene chloride at 65 °C over 7 days using 2 equiv of the dienophile (Scheme 2). Analysis of the crude reaction mixture by NMR revealed it to contain a mixture of three cycloadducts in the ratio of 3.4(**3a**):2.0(**3b**):0.1(**3c**) as well as a small quantity of unreacted pyrone. Following chromatographic separation on silica gel, the *endo* configuration for cycloadducts **3a** and **3b** and the *exo* configuration for cycloadduct **3c** were established by analysis of the coupling constants in the 400 MHz ^{1}H NMR in accordance to the extensive literature precedent.[3a,5c]

Scheme 2. Cycloaddition of 2-Carbomethoxy-2(*H*)-pyran-2-one to 1,2:5,6-Di-*O*-isopropylideneglucofuranose



At this stage, the absolute configuration of the minor *endo* cycloadduct **3b** was established unequivocally by X-ray crystallography as (1*R*,5*R*) (see Supporting Information). The major *endo* cycloadduct **3a** was an oil; however, as can be seen later, the absolute configuration of this isomer was established retrospectively as (1*S*,5*S*) on the basis of X-ray crystallography on a derivative (Scheme 3). To rationalize this modest diastereofacial selectivity, we must assume that

Scheme 3. Transformation of Cycloadduct **3a** to Pseudodisaccharide **8**



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the approach of the pyrone diene to the vinyl ether is controlled by the steric bulk of the sugar's 5′,6′-*O*-isopropylidene substituent, rather than the 1′,2′-*O*-isopropylidene substituent. This is presumably because the former can exert more steric hindrance due to possible rotation about the C4′−C5′ bond (Figure 1).

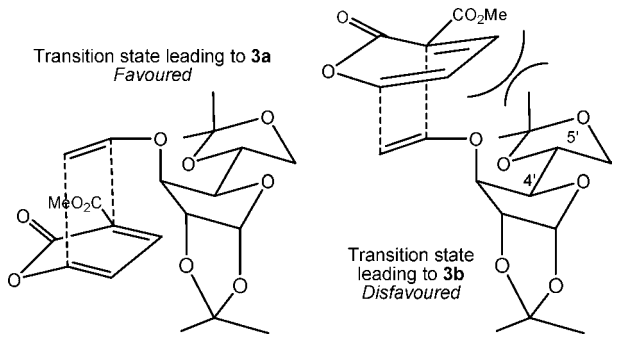
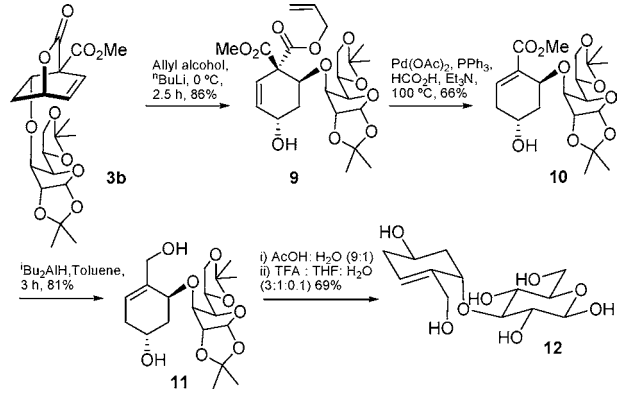


Figure 1. Origins of diastereofacial selectivity.

Treatment of the major *endo* isomer **3a** with lithium allyloxide, freshly prepared by addition of butyllithium to allylalcohol, resulted in transesterification to afford diester **4**. One-pot deallylation/decarboxylation of **4** by treatment with $Pd(OAc)_2$ afforded unsaturated ester **5**.[12] At this stage, the structure of compound **5** was confirmed by X-ray crystallography. Since compound **5** had originated from **3a**, it was now possible to confirm the absolute configuration of **3a** as (1*S*,5*R*).

Treatment of compound **5** with DIBAL-H then afforded allylic alcohol **6**. Stepwise deprotection of acetonide in **6** led to the formation of **7** and then fully deprotected **8**. A similar approach was adapted to prepare compound **12**, starting from the other diastereofacial *endo* isomer **3b** (Scheme 4).

Scheme 4. Transformation of Cycloadduct **3b** to Pseudodisaccharide **12**



In summary, we have provided an example of a new method for the synthesis of carbasugar-"true" sugar pseudodisaccharides. In this method, a free hydroxyl function of a "true" sugar is derivatized to afford an attached carbasugar. Stereoselective transformations allow the synthesis of a range of configurations at the newly constructed carbasugar moiety. We are now in the process of further exemplification of the method and its application to the synthesis of a range of naturally occurring and biologically significant pseudooligosaccharides.

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Supporting Information Available: Experimental procedures and full characterizations of all new compunds. X-ray crystallography data for **3b** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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