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A Synthesis of Carbasugar−Sugar Pseudodisaccharides via a Cycloaddition−Cycloreversion Reaction of 2*H*-Pyran-2-ones

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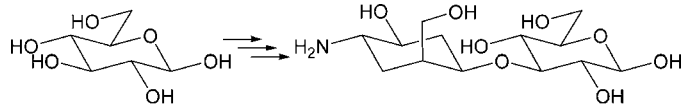
ABSTRACT



Cycloaddition of 3-carbomethoxy-2*H*-pyran-2-one to a vinylated sugar followed by the loss of bridging CO_2 from the cycloadduct affords a cyclohexadiene which can be manipulated to a carbasugar−sugar pseudodisaccharide.

Many diseases are characterized by changes in the makeup and structure of cell surface glycans.[1] Therefore, synthetic routes to glycomimetics are important in preparation of chemical tools for biological investigations of disease, as well as new, "rationally-designed" leads in drug discovery. In this context, synthesis of pseudomonosaccharides, e.g., carbasugars and azasugars, have been extensively investigated.[2] More recently, however, synthetic efforts have focused on pseudodiaccharides, molecules containing a pseudosugar linked to a "true" saccharide.[3] Pseudodiaccharides are considered more useful since additional interactions between the molecules and the receptor/enzyme would be expected to increase the binding affinity and improve selectivity. Indeed, a number of naturally occurring and synthetic pseudodisaccharides are already of medicinal interest.[4]

We have previously reported on the Diels−Alder cycloadditions of 2*H*-pyran-2-ones for the synthesis of carbasugars[5] and other complex molecules.[6] We have also extended the scope of the methodology to the cycloadditions of 1,4-oxazin-2-ones for the preparation of azasugars.[7] More recently, we reported on the application of this method to the synthesis of pseudodisaccharides (Scheme 1, route a). The reaction of 3-carbamethoxy-2*H*-pyran-2-one **1** and vinyl sugar **2** afforded functionally rich cycloadducts **3a** and **3b** (Scheme 2), which were then converted in five chemical steps to carbasugar−

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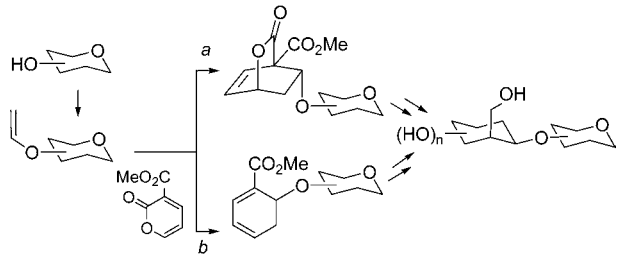
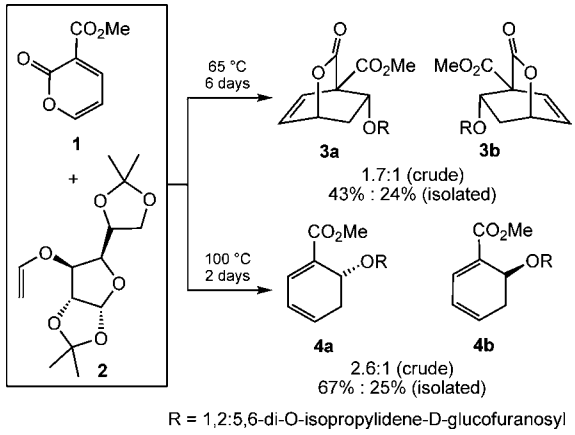
Scheme 1. General Route to Pseudodisaccharides



sugar pseudodisaccharides.[8] The 3-carbomethoxy substituent is a key requirement to promote regio- and endoselectivity in the cycloaddition.[9]

Scheme 2. Cyloaddition of 3-Carbamethoxy-2*H*-pyran-2-one **1** and Vinyl Sugar **2**



This methodology is attractive because it allows the construction of the target molecules in relatively few steps. It also has the advantage of being very general in the sense that any free hydroxyl of a "true" sugar can be vinylated and used to construct the carbasugar moiety.

However, the chemical route involves a potentially inelegant decarboxylative step to remove the carbomethoxy group. Here, we report an alternative route involving cycloaddition of 2*H*-pyran-2-one and an in situ loss of bridging CO_2 to afford a cyclohexadiene and the chemical manipulation of the cyclohexadiene toward the preparation of pseudodisaccharides (Scheme 1, route b).

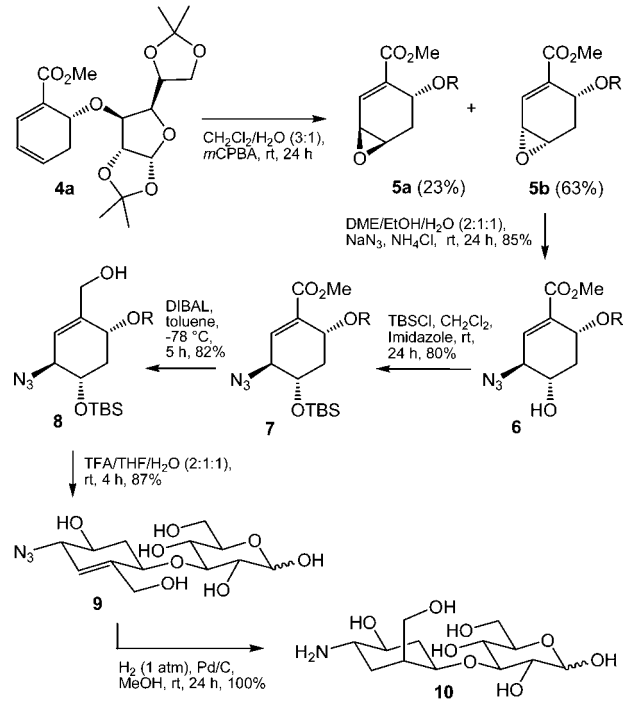
As previously reported,[8] the Diels−Alder cycloaddition between **1** and **2** in dichloromethane in a sealed tube at 65 °C slowly progressed over 7 days to regio- and stereoselectively afford bridged bicyclic lactones **3a** and **3b** (Scheme 2). During these studies, however, we noticed an unexpected role played by the temperature of the reaction. An attempt to increase the rate of the reaction by increasing the temperature to 100 °C afforded, instead, cyclohexadienes **4a** and **4b**, obtained from the loss of bridging CO_2. Reactions conducted between 60 and 100 °C afforded mixtures of the four compounds.

The structure of compound **4a** was subsequently confirmed by X-ray crystallography (Supporting Information). The formation of an isolable cyclohexadiene from the reaction of 3-carbomethoxy-2*H*-pyran-2-one is precedented in the literature.[10] However, this is the first crystal structure of a cyclohexadiene obtained by cycloaddition−cycloreversion. Compound **4a** is exceptionally stable. It withstands temperatures of up to 120 °C, can be isolated by chromatography in multigram quantity, and is air stable over a period of months, although treatment with acids leads to rapid decomposition.

The disparity between the ratio of **3a**/**3b** and **4a**/**4b** was unexpected. Heating pure **3a** at 100 °C exclusively afforded **4a**. Therefore, we assume that the rates of the loss of bridging CO_2 from the cycloadducts **3a** and **3b** are not the same.

The loss of bridging CO_2 removes many of the stereochemical features from the molecule and at first sight might appear undesirable. However, stereochemical information can be reintroduced into the cyclohexadiene component via the pendant sugar moiety. Treatment of compound **4a** with *m*-CPBA afforded a mixture of two epoxides **5a** and **5b** in a ratio of 1:2.7 (Scheme 3) The absolute configuration of

Scheme 3. Chemical Manipulation of Cyclohexadiene **4a**



the major stereoisomer **5a** was confirmed by X-ray crystallography (Supporting Information). Presumably, this dias-

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tereoselectivity suggests that epoxidation is significantly controlled by intramolecular H-bonding between the peracid and an oxygen atom in one of the many ether linkages contained in the sugar moiety. Ring-opening of this epoxide with sodium azide exclusively afforded azide **6**. Other regio- and stereoisomers were not detectable in the crude reaction mixture within the limits of detection by NMR. This is in agreement with that reported in a similar system.[11]

Reduction of compound **6** with DIBAL-H gave a complex reaction mixture. However, after it was converted to its silyl ether, compound **7**, treatment with DIBAL-H afforded allylic alcohol **8** in good yield (Scheme 3). Full deprotection of **8**, to afford **9**, followed by reduction of the alkene and azide functions by hydrogenation then afforded carbasugar−sugar pseudodisaccharide **10** as an anomeric mixture. The relative configuration of the carbasugar moiety in **10** was unequivocally established by NOESY.

In summary, we have provided a new method for the synthesis of carbasugar-"true" sugar pseudodisaccharides. In this method, any vinyl-sugar undergoes a cycloaddition with 3-carbamethoxy-2*H*-pyran-2-one followed by loss of CO_2 to afford a cyclohexadiene that can then undergo chemical transformations toward target molecules.

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Supporting Information Available: Experimental procedures and full characterizations of all new compunds. X-ray crystallography data for **4a** and **5a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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