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Recent advances in the synthesis of carbohydrate mimics *

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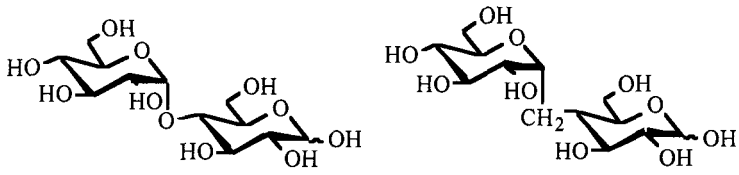
Abstract: C-Disaccharides have been synthesized through a flexible synthetic strategy based on a 8 and 9 *endo-trig* radical cyclization reaction, from two monosaccharides temporarily connected through a tether. Pseudosugars, another class of carbohydrate mimics, have been obtained by a one step rearrangment which converts 5,6-unsaturated glycoside into substituted cyclohexanones, with retention of the stereochemistry of the anomeric centre of the starting sugar.

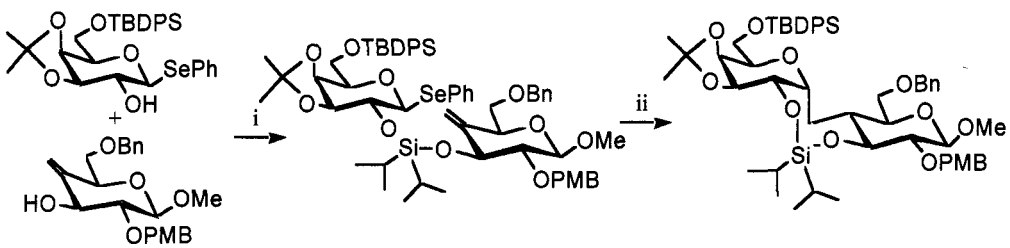
INTRODUCTION

A *C*-disaccharide is a close mimic of a regular disaccharide in which the interglycosidic oxygen atom has been replaced by a methylene group.[1] For example,*C*-maltose is a close mimic of maltose:



Maltose **C- Maltose**

In the last few years, we have developed a general strategy for the stereoselective synthesis of these molecules, based on a 8 or 9 *endo-trig* radical cyclisation from two monosaccharides temporarily connected through a tether.[2] A typical example of this strategy is shown in Scheme 1.



Scheme 1: Reagents and conditions: i) BuLi, THF, 0° C, iPr_2SiCl_2, 4 equiv., -78° C to r.t, DMAP, THF, r.t.(70%); ii) Bu_3SnH, AIBN, toluene, reflux (80%).

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In doing so, three main goals are pursued :

(1) To build a molecular object which is fully resistant to glycosidases, a feature which could be of importance for the development of an oligosaccharide-based drug. On the other hand, such compounds might be competitive inhibitors of glycosidases.

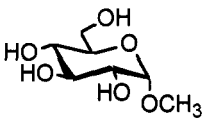
(2) To get information on the potential direct intervention and importance of an interglycosidic oxygen atom on the hydrogen bonding network with a receptor protein.

(3) To evaluate the contribution of the *exo*-anomeric effect on the conformation, and then on the biological activity, of a di- or oligosaccharide.

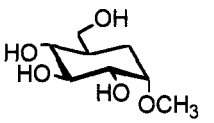
Concerning the first goal, recent studies have indeed demonstrated that oligosaccharides are involved in a steadily increasing number of biological processes and constitute potential active substances for drug development. Several structural modifications have been developed to increase the resistance of oligosaccharides to enzymatic hydrolysis : introduction of *S*-interglycosidic bonds,[3] and the alkylation[4] or acylation[5] of non critical hydroxyl functions. The currently studied introduction of a *C*-interglycosidic bond is another option.

Concerning the third goal, a critical feature with any mimic is that the biological activity must be preserved or increased. The question is thus to evaluate to what extend the replacement of the oxygen atom by a methylene group - which removes the *exo* anomeric effect - affects the conformational properties of the molecule, then the biological activity. In the first part of this lecture, we would like to describe the preparation of a biologically active mixed C,O pentasaccharide.

Another way to prepare hydrolytically stable close mimics is to build up a so called pseudo sugar, in which the *endo* cyclic oxygen atom of a glycoside has been replaced by a methylene group.



methyl α-D-glucopyranoside

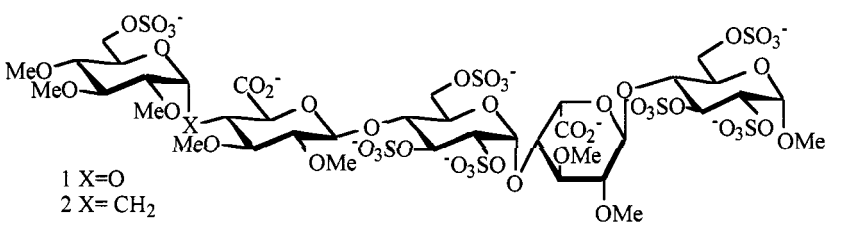


pseudosugar mimic

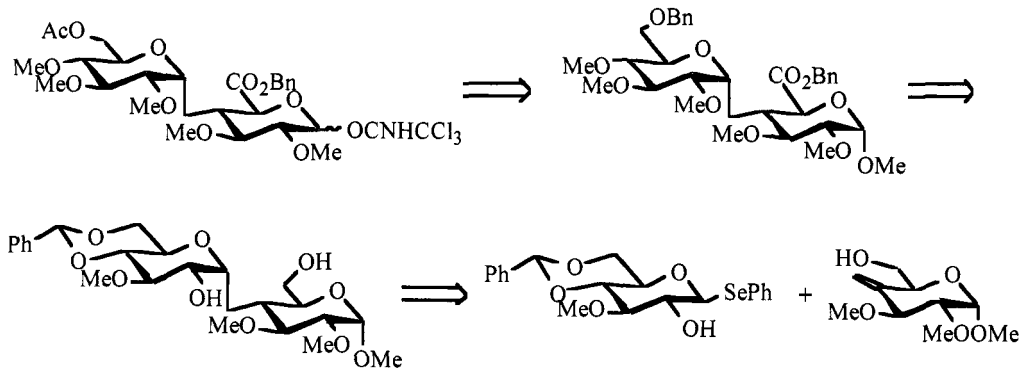
Such a strategy will be described in the second part of this lecture.

INTRODUCING A *C*-INTERGLYCOSIDIC BOND IN A BIOLOGICALLY ACTIVE PENTASACCHARIDE HARDLY AFFECTS ITS BIOLOGICAL PROPERTIES

Among the restricted number of synthetic oligosaccharides clinically investigated is a pentasaccharide that reproduces the exact sequence required in heparin for binding and activation of antithrombin III (AT III),[6] and which is a good candidate as an antithrombotic drug. The availability of a well-established series of biologically active heparin pentasaccharides allowed us to investigate how the introduction of a *C*-disaccharide bond would influence the interaction with the target protein receptor, AT III. The methylated pentasaccharide **1** has already been synthesized[7] and its anti-factor Xa activity evaluated (1180 units/mg) :

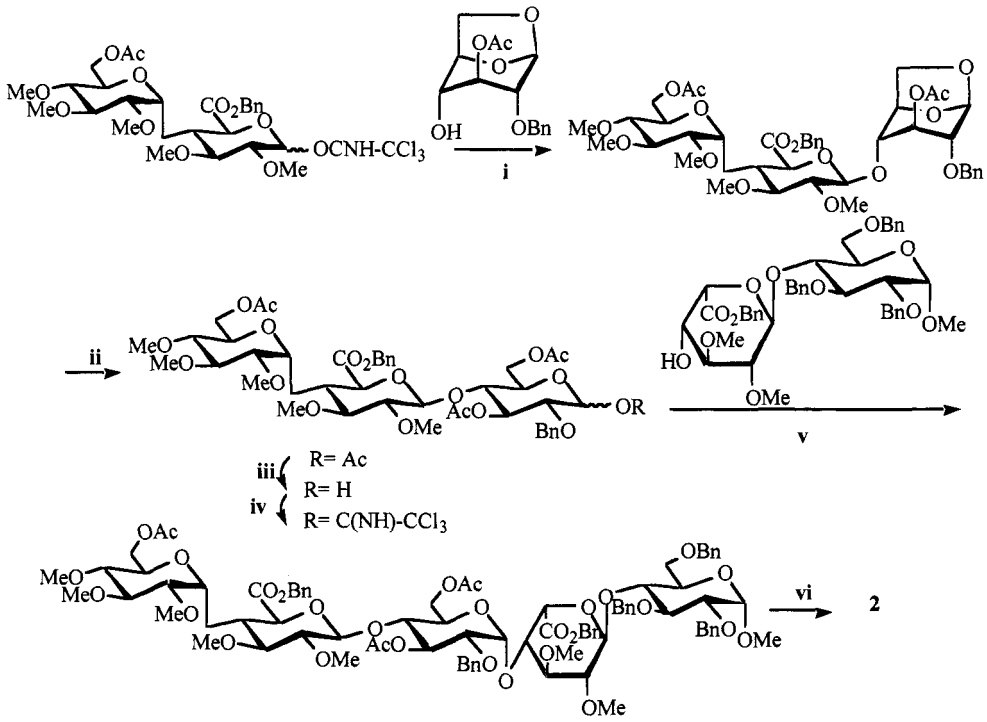


We have synthesized the mixed *C,O*-pentasaccharide **2**.The retrosynthesis of the key *C*-disaccharide trichloroacetimidate is shown in scheme 2.[8] It follows the general route previously delineated.



Scheme 2

This compound has then been transformed into the target molecule through a sequence presented in scheme 3.[9]

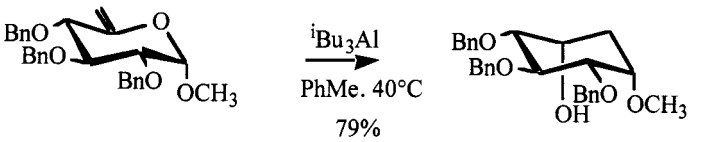


Scheme 3: Reagents and conditions: i) TMSOTf, CH_3CN, -37°C, 88% ii) H_2SO_4, AcOH, Ac_2O, -20°C, 100%; iii) NH_3NH_2OAc, DMF, 90%; iv) CCl_3CN, DBU, CH_2Cl_2, 94%; v) TMSOTf, CH_2Cl_2, -20°C, 79%; vi) 1. H_2, Pd/C, CH_2Cl_2, MeOH, 99%, 2. NaOH, H_2O, MeOH, 0°C, 77%, 3. SO_3. Et_3N, DMF, 55°C, 85%

It has been found that such a structural modification only slightly affected the affinity of the compound for AT III, as well as the active factor Xa activity (880 anti Xa/mg). This compound represents the first example of a new class of anti-factor Xa pentasaccharides containing a *C*-interglycosidic bond.

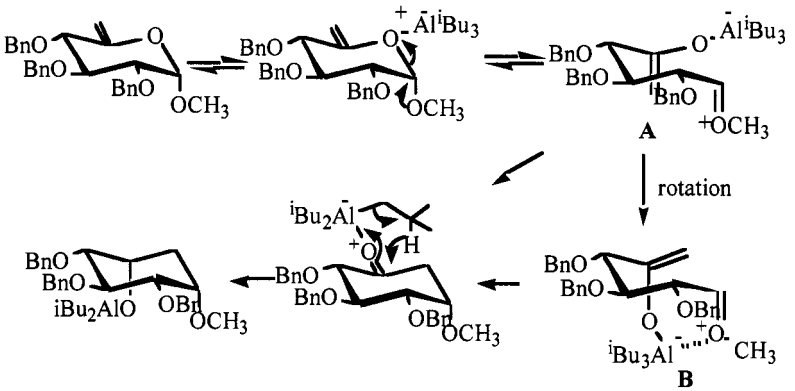
ONE-STEP STEREOSELECTIVE CONVERSION OF A SUGAR DERIVATIVE INTO A PSEUDO-SUGAR.

It is appealing to invent reactions to transform a carbohydrate derivative into a substituted cyclohexane derivative. We have discovered[10] that reaction of a carbohydrate vinyl acetal (6-deoxy-hex-5-exopyranoside) with an excess of triisobutylaluminum at 40 °C resulted in the transposition of an oxygen atom on the ring with the exocyclic carbon atom (Scheme 4)



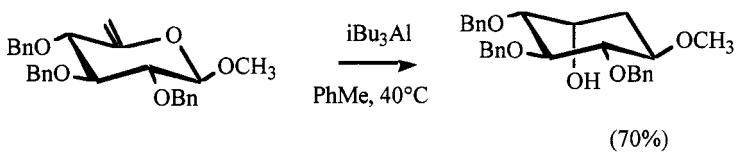
Scheme 4

A postulated mechanism of this transposition is presented in Scheme 5.



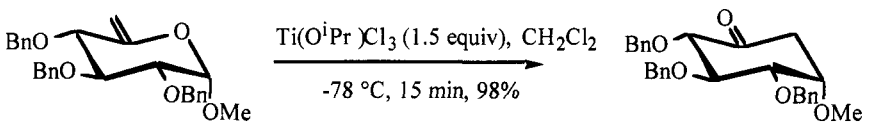
Scheme 5.

When the reaction was applied to a β-methyl glucoside, the stereochemical information of the anomeric centre was again retained, as shown in Scheme 6.



Scheme 6

This novel reaction complements the Ferrier-II reaction,[11] which inherently requires an *exo* cleavage to eject the aglycon. We then turned our attention to the case of titanium (IV) derivatives and found that the Lewis acid $Ti(OiPr_2)Cl_3$[12] resulted in an almost quantative rearrangement, as shown in Scheme 7.



Scheme 7

In comparison with the previously disclosed triisobutylaluminum mediated rearrangement, this Ti (IV) version involves much milder reaction conditions (-78°C) and does not result in the reduction of the keto function.

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