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Carba-D,L-allal- and -D,L-galactal-derived vinyl *N*-nosyl aziridines as useful tools for the synthesis of 4-deoxy-4-(*N*-nosylamino)-2,3-unsaturated-5*a*-carbasugars

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ABSTRACT

The novel carba-D,L-allal- and carba-D,L-galactal-derived vinyl *N*-nosyl aziridines were prepared and the regio- and stereoselective behavior in opening reactions with *O*- and *N*-nucleophiles examined. The carbaglycosylating ability of the novel aziridines, as deduced by the amount of *1,4-addition products* (1,4-regioselectivity) obtained in the acid-catalyzed methanolysis taken as a model reaction, is similar or superior to that observed with the corresponding carba-D,L-allal- and -D,L-galactal-derived vinyl epoxides, respectively. In all *1,2-* and *1,4-addition products* obtained, a –(*N*-nosylamino) group is regio- and stereoselectively introduced at the C(4) carbon of a 1,2- or 2,3-unsaturated carbasugar, susceptible to further elaborations toward aminocyclitol derivatives. The stereoselective synthesis of the corresponding, enantiomerically pure carba-D,L-allal- and -D,L-galactal-derived vinyl *N*-acetyl aziridines is also described.

1. Introduction

Carbasugars, a particular family of cyclitols, are compounds structurally related to carbohydrates with the only difference being the replacement of the endocyclic oxygen with a methylene group.[1] This structural modification is responsible for an increased chemical stability and makes carbasugars valuable mimics of the corresponding carbohydrates.[2]

Within the carbasugar family, aminocyclitols, also regarded as amino carbasugars, can be found in nature in several families of natural and clinically important antibiotics.[3] Moreover, aminocyclitols represent interesting scaffolds in drug discovery. In fact, these structures are present in currently used therapeutic agents,[4] and turn out to be attractive substrates for targeting many key pathways implicated in disorders such as diabetes, viral infections and cancer.[5]

Although the synthesis of amino carbasugars has been investigated and reviewed extensively,[5,6] new versatile methodologies for their preparation still represent an interesting challenge in synthetic carbohydrate chemistry.

Following our experience with vinyl epoxides[7] and *N*-activated aziridines,[7e,8] we herein present a stereoselective synthesis of 2,3-unsaturated-4-(*N*-protected-amino) carbasugars by using carba-D,L-glycal-derived vinyl *N*-nosyl aziridines, as suitable precursors.

Recently, racemic and enantiopure vinyl epoxides **1α** and **1β**,[9] the carba analogs of the previously studied D-allal-and D-galactal-derived vinyl epoxides **2α** and **2β**,[7c-f,h-l] were synthesized and their regio- and stereoselective behavior examined in addition reactions with several *O*-, *C*-, *N*- and *S*-nucleophiles. In particular, by using MeOH as a model *O*-nucleophile, the possibility of considering these epoxides suitable for the stereoselective construction of carba-*O*-glycosides and/or mixed carba-oligo-saccharides was checked. For such an application, a complete or high 1,4-regioselective behavior with associated high stereoselectivity, in the opening reactions, is required. This behavior, defined as carbaglycosylating ability, is determined by the total amount of *1,4-addition products* obtained.[9]

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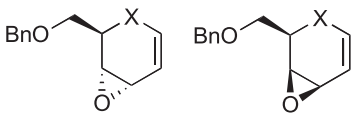
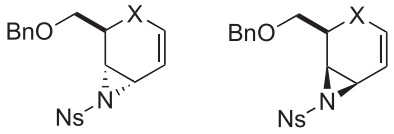
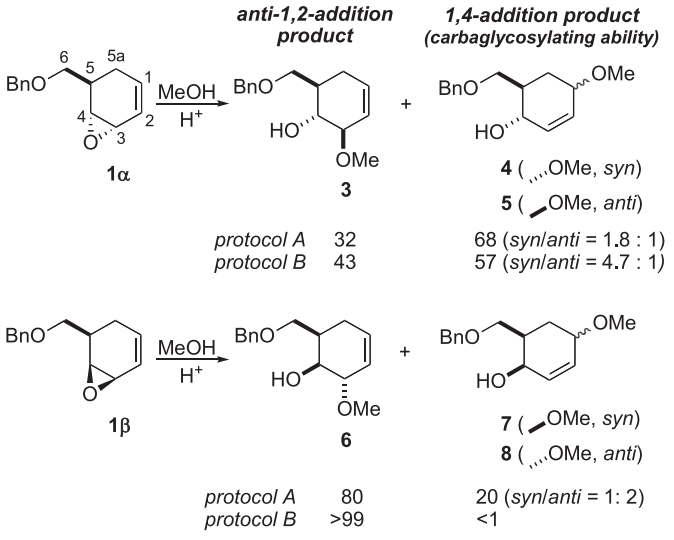


The results obtained after acid methanolysis indicated an interesting carbaglycosylating ability for epoxide **1α**, with moderate syn-stereoselectivity, as shown by 68% (1.8:1 *syn*/*anti* ratio) and 57% 1,4-regioselectivity (4.7:1 *syn*/*anti* ratio) under *protocol A* (0.2 N H_2SO_4/MeOH) and synthetically more interesting *protocol B* reaction conditions (MeOH, 6 equiv, in 10^{-2}N TsOH/CH_2Cl_2), respectively.[9a,10] In this framework, diastereoisomeric epoxide **1β** turned out to be a very poor carbaglycosyl donor, as shown by the low 1,4-regioselectivity (20%) observed under the corresponding *protocol A*, and by the complete anti-1,2-regioselectivity (>99%) found under the corresponding *protocol B* reaction conditions. These results and the structures of all the addition products obtained in the acid methanolysis of epoxides **1α** and **1β** (methoxy alcohols **3**–**8**), are shown in Scheme 1.[9a,10]

As an extension of our interest toward glycal-derived systems and their corresponding carba analogues, and looking for new, effective carbaglycosyl donors, our attention was directed to the diastereoisomeric carba-D,L-allal- and -D,L-galactal-derived vinyl *N*-nosyl aziridines **9α-Ns** and **9β-Ns**, the carba analogs of the corresponding, previously studied D-allal- and D-galactal-derived *N*-nosyl aziridines **10α-Ns** and **10β-Ns**.[7e,8c]



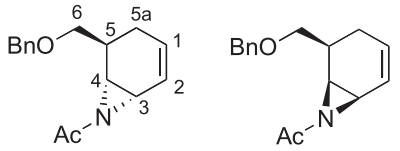
The examination of the regio- and stereoselective behavior in nucleophilic opening reactions could indicate whether aziridines **9α-Ns** and **9β-Ns** are effective carbaglycosyl donors with



Scheme 1. Regio- and stereoselectivity of vinyl carba epoxides **1α** and **1β** in the acid methanolysis under *protocol A* and *protocol B* reaction conditions.

simultaneous, completely regio- and stereoselective introduction of a –(*N*-nosylamino) group at the C(4)-carbon of a 2,3-unsaturated carbasugar system as shown in **11**, with high levels of syn-1,4-stereoselectivity, if possible, when alcohols (ROH) are used as carbaglycosyl acceptors (Scheme 2). The presence of the double bond and the easy deprotection of the –(*N*-nosylamino) group,[8c] could make carbapyranosides **11** suitable for further elaborations toward biologically interesting aminocyclitols,[3–6] through a new synthetic approach (Scheme 2, where only *N*-nosyl aziridine **9α-Ns** is shown, for simplicity).

In this preliminary examination of their regio- and stereoselective behavior in nucleophilic addition reactions, *N*-nosyl aziridines **9α-Ns** and **9β-Ns** were prepared in a racemic form. However, in view of a possible use of these systems for the construction of compounds of biological interest, an enantioselective route to both aziridine systems, in the form of *N*-acetyl analogs, as (3*S*,4*R*,5*S*)-**9α-Ac** and (3*R*,4*S*,5*S*)-**9β-Ac**, has been disclosed, also.



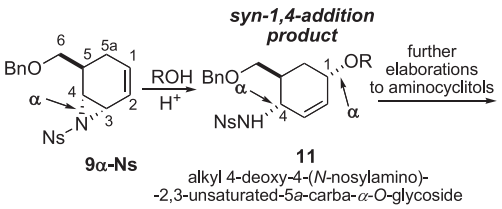
2. Results and discussion

2.1. Synthesis of *N*-nosyl aziridines *9α-Ns* and *9β-Ns* and conformational study

The stereoselective synthesis of vinyl aziridines **9α-Ns** and **9β-Ns** was carried out by means of the same protocol starting from azidolysis of the corresponding epoxide with the opposite configuration **1β** and **1α**, respectively.

For the synthesis of aziridine **9α-Ns**, the azidolysis of epoxide **1β** by NaN_3 in a 1:1 THF/H_2O mixture[11] turned out to be completely 1,2-regio- and anti-stereoselective affording *trans* 3,4-azido alcohol **12** as the only reaction product (Scheme 3).[12]

trans 3,4-Azido alcohol **12** was reduced by polimer-supported PPh_3 (PS-PPh_3, Aldrich)[8b] in a heterogeneous phase (20:1 THF/H_2O) to the corresponding *trans* 3,4-amino alcohol **13**, which was obtained in good yield (96%) and was sufficiently pure to be directly used in the next step. Regioselective *N*-nosylation of the amino group of **13** by a NsCl/NEt_3/CH_2Cl_2 protocol afforded *N*-nosyl derivative **14**. Subsequent *O*-mesylation by MsCl/Py of the free -OH functionality gave *trans* *N*-nosyl-*O*-mesyl derivative **15**. The treatment of mesylate **15** under basic conditions (K_2CO_3/MeCN) gave the cyclization to the desired aziridine **9α-Ns** which was obtained with a good overall yield (69%), through a 5 step sequence, starting from epoxide **1β** (Scheme 3).



Scheme 2. The conceivable behavior of aziridine **9α-Ns** as a carbaglycosyl donor in the acid alcoholysis, with complete 1,4-*syn*-stereoselectivity and simultaneous complete regio- and stereoselective introduction of a –(*N*-nosylamino) group at the C(4) carbon of a 2,3-unsaturated carbasugar.