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Stereoselective synthesis of D-galactal-derived *N*-ethoxycarbonyl aziridine, as a new, improved synthetic protocol to glycal-derived *N*-activated vinyl aziridines

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ABSTRACT

A new protocol for the synthesis of D-galactal-derived *N*-ethoxycarbonyl vinyl aziridine **1β-CO$_2$Et**, starting from tri-*O*-acetyl-D-glucal, is described. The new protocol constitutes a simple and fast access, with a satisfactory overall yield (5 steps, 36%), to a D-galactal-derived vinyl aziridine with a clear improvement compared with the previously described procedure leading to the structurally related *N*-nosyl aziridine **1β-Ns** which, starting from the same precursor, proceeded through 13 steps with a low, decidedly unsatisfactory, overall yield (3%).

1. Introduction

Aminosugars, consisting in carbohydrates bearing a free or *N*-protected amino functionality in different ring positions of a glycoside scaffold, are structures widely present in nature,[1] either alone or also as constituents of crucial glycoproteins, glycosaminoglycans and GPI anchors.[2] In particular, 4-aminosugars are found as glycoconjugates in naturally occurring antibiotics, and their presence has been closely related to the activity of this type of antibiotics.[3] Moreover, following the glycodiversification approach, the synthesis of naturally occurring antibiotic analogs with the original sugars replaced by synthetic ones, currently represents an interesting challenge.[4]

Due to the importance of unusual 4-aminosugars, extensive synthetic studies have been carried out toward the production of these compounds and a divergent synthesis of aminosugar libraries has also been proposed.[5,6]

In view of the obtainment of a new synthetic protocol to introduce an *N*-protected amino functionality at C(4)-carbon of a pyranoside system with the simultaneous construction of the glicosydic bond, the use of an *N*-protected vinyl aziridine inserted in a glycal system appeared particularly attractive. Actually, we have recently found that D-allal- and D-galactal-derived *N*-nosyl aziridines **1α-Ns** and **1β-Ns**,[7] prepared *in situ* by cyclization of the corresponding stable precursors *trans N*-nosyl-*O*-mesyl derivatives **2α-Ns** and **2β-Ns**, respectively, are very effective glycosyl donors, able to glycosylate (under *protocol B* reaction conditions)[8] *O*-nucleophiles (alcohols, phenol and partially *O*-protected monosaccharides) in a completely 1,4-regio- and syn-stereoselective fashion.[7] In this way, alkyl 4-*N*-(nosylamino)-2,3-unsaturated-*O*-glycosides **3α-Ns** and **3β-Ns**, having the same configuration as the starting azidridine (*syn-1,4-addition products*, Scheme 1), are obtained in an uncatalyzed, directly *substrate-dependent*, stereospecific glycosylation process with simultaneous, completely regioselective introduction at C(4)-carbon of an α- or β-directed *N*-nosylamino group (−NHNs) from aziridine **1α-Ns** or **1β-Ns**,

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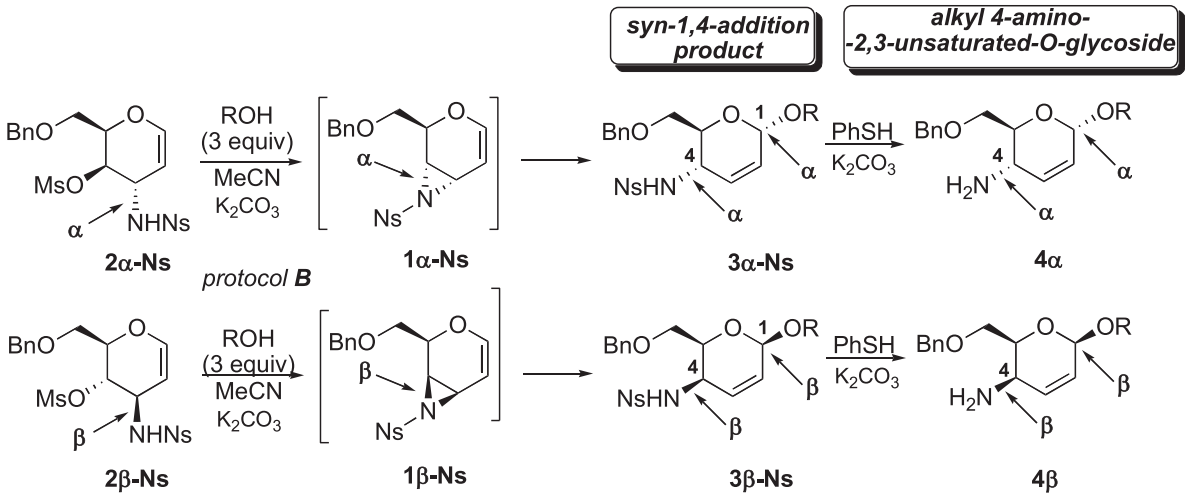

Scheme 1. 1,4-Regio- and syn-stereoselective glycosylation of alcohols by *N*-nosyl aziridines **1α-Ns** and **1β-Ns** (*protocol B* reaction conditions) and stereoselective synthesis of alkyl 4-deoxy-4-amino-2,3-unsaturated-*O*-glycosides **4α** and **4β** (see Ref. 7).

respectively, in a completely stereoselective fashion (Scheme 1).[7,9,10] Considering that alkyl *O*-glycosides **3α-Ns** and **3β-Ns** can be easily deprotected to corresponding 4-deoxy-4-amino-2,3-unsaturated-*O*-glycosides **4α** and **4β** with complete retention of configuration, *N*-nosyl aziridines **1α-Ns** and **1β-Ns** can be considered as effective synthetic tools for the completely regio- and stereoselective introduction of a free amino group at C(4) of a pseudoglycal system (Scheme 1).[7] Moreover, the presence of the unsaturation makes alkyl *O*-glycosides **3α,β-Ns** and **4α,β** susceptible to further elaborations toward more complex structures bearing a free or *N*-protected-amino group with defined regiochemistry and configuration.[11]

Although *N*-nosyl aziridines **1α-Ns** and **1β-Ns** are interesting and synthetically useful, there are problems related to their preparation, particularly as aziridine **1β-Ns** is concerned (Scheme 2). By using tri-*O*-acetyl-D-glucal (**5**), as a useful and not expensive starting material and chiral source, the synthesis of aziridine **1β-Ns** proceeds through the formation of *trans* hydroxy mesylate **6β**, the stable precursor of D-galactal-derived epoxide **7β**[12] and then, through D-gulal-derived *trans* diol **8**, of diastereoisomeric *trans* hydroxy mesylate **6α**, a precursor of D-allal-derived epoxide **7α**.[13] Azidolysis of epoxide **7α** to *trans* azido alcohol **9**,[10b] followed by the usual protocol (reduction of azido group to amino group, *N*-nosylation and *O*-mesylation) leads to *trans* *N*-nosyl-*O*-mesylate **2β-Ns**, the ultimate stable precursor of the desired aziridine **1β-Ns**.[7,14,15] Aziridine **1β-Ns** is not stable and can be prepared only *in situ* by cyclization of **2β-Ns** under basic conditions (*t*-BuOK or K_2CO_3) and left to react immediately with a nucleophile, as shown in Scheme 2, where MeOH is taken as an example of solvent/nucleophile (*protocol A* reaction conditions).[8] Under these conditions, the addition reaction is still completely 1,4-regioselective, but not stereoselective and a 75:25 mixture of methyl α-*O*- **10α** and β-*O*-glycoside **10β** is obtained.[7,9] As a whole, the preparation of *N*-nosyl aziridine **1β-Ns** from tri-*O*-acetyl-D-glucal (**5**) is decidedly long with a low overall yield[16] (13 steps, 3%)[7,10b,12-15] and, as a consequence, requires improvement (Scheme 2).

For these reasons, a study was started to find a new, more convenient protocol which, still starting from tri-*O*-acetyl-D-glucal (**5**), could lead to a stable D-glucal-derived mesylate **2β-PG$_1$**, precursor of a new D-galactal-derived aziridine **1β-PG$_1$** structurally related to *trans*-*N*-nosyl-*O*-mesylate **2β-Ns** and *N*-nosyl aziridine **1β-Ns**, respectively. The generic new aziridine **1β-PG$_1$** and corresponding precursor **2β-PG$_1$** should have easily removable 6-*O*-protecting (PG_2) and *N*-protecting/activating group (PG_1) (Scheme 3).

2. Results and discussion

2.1. Synthesis of 4-*O*-mesyl-3-deoxy-3-*N*-(ethoxycarbonylamino)-D-glucal-derivative *2β-CO$_2$Et*, the stable precursor of D-galactal-derived *N*-ethoxycarbonyl vinyl aziridine *1β-CO$_2$Et*

In the course of literature research into D-glucal-derivatives useful to our study, D-glucal-derived urethane **12**, structurally related to *trans* *N*-nosyl-*O*-mesylate **2β-Ns**, was found to be easily prepared by reaction with chlorosulfonyl isocyanate (CSI)[17,18] of ethyl α-*O*-glycoside **11α**, itself prepared in an 85:15 mixture with diastereoisomeric ethyl β-*O*-glycoside **11β**, by Ferrier rearrangement reaction of tri-*O*-acetyl-D-glucal (**5**) with EtOH/benzene in the presence of $BF_3 \cdot Et_2O$ (Scheme 4).[19]

Urethane **12** appeared decidedly interesting to our purpose, provided that some modifications were necessarily introduced. Actually, the acyl protection of the primary alcohol of **12** had to be replaced with a different, still easily removable protective group, as *t*-butyl-diphenylsilyl group (-OTBDPS), more stable to basic conditions and to nucleophiles, whereas the secondary acetoxy group had to be substituted with a mesyloxy group. In this way, the obtained *trans* *O*-mesyl-*N*-(ethoxycarbonylamino)-derivative **2β-CO$_2$Et** could hopefully act as the ultimate precursor of the new D-galactal-derived *N*-CO_2Et vinyl aziridine **1β-CO$_2$Et** by base-catalyzed intramolecular cyclization process, as shown in Scheme 5 (*vide infra*).

In this framework, the new protocol to D-galactal-derived vinyl aziridine **1β-CO$_2$Et** (see Schemes 4 and 5) was started by repeating the previously described Ferrier reaction consisting in the treatment of a 9:1 benzene/EtOH solution of tri-*O*-acetyl-D-glucal (**5**) with $BF_3 \cdot Et_2O$.[19] Ethyl α-*O*-glycoside **11α** was not separated and the obtained 85:15 mixture of ethyl α- and β-*O*-glycosides **11α** and **11β** (90% yield) was directly subjected to the subsequent reaction with CSI following the previously described protocol (CSI/Et_2O in the