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Aminolysis of glycal-derived allyl epoxides and activated aziridines. Effects of the absence of coordination processes on the regio- and stereoselectivity

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ABSTRACT

The addition of primary and secondary aliphatic amines to glycal-derived allyl epoxides is completely 1,2-regio- and *anti*-stereoselective, whereas mixtures of the corresponding *anti*-1,2- [3–*N*-(substituted-amino) glycals] and *anti*-1,4-*addition products* (*N*-glycosyl amines) are obtained with *N*-(mesyl)-aziridines. In this way, structural moieties, otherwise difficult to synthesize, are obtained by means of a very simple protocol. The regio- and stereoselectivity observed with epoxides is the consequence of an isomerization process, whereas the result obtained with aziridines is explained by the absence of an effective substrate–nucleophile (amine) coordination.

1. Introduction

Recently, we found that the glycal-derived allyl epoxides **1α**,**1β**,**2α**, and **2β** and *N*-(mesyl)-aziridines **3α** and **3β** are very efficient and stereoselective glycosyl donors (Scheme 1).[1–3] Actually, the regio- and stereoselectivity of the glycosylation of *O*-nucleophiles, such as alcohols, partially protected monosaccharides and alcoholate species, turned out to be closely related to the ability of the *O*-nucleophile (R^2OM, M=H, or a metal, Scheme 1) to coordinate the oxirane oxygen or aziridine nitrogen by means of a hydrogen bond (alcohols) or through the metal (metal alcoholate) (structures **4** and **5**, Scheme 1). In the presence of such a coordination and if the nucleophile is present to a very reduced extent (3 equiv) (*protocol B* reaction conditions),[4,5] the corresponding *syn*-1,4-*addition products* (the so-called *coordination products*),[6] whose configuration is the same as the starting epoxide or aziridine, are exclusively obtained: α-*O*-glycosides from epoxides **1**,**2α**, and aziridine **3α** (*route* ***a***) and β-*O*-glycosides from epoxides **1**,**2β**, and aziridine **3β** (*route* ***b***), in a new, uncatalyzed, *directly substrate-dependent*, stereospecific glycosylation process.[7,8]

In contrast, when non-coordinating *O*-nucleophiles (R^2OY, Y=non-coordinating counterion, Scheme 1), such as tetrabutylammonium trimethylsilanolate ($TBA^+Me_3SiO^-$) and tetrabutylammonium methoxide (TBAOMe) are used, the nucleophilic attack occurs exclusively at the C(3) allylic carbon in an *anti* fashion (*route* ***c*** in **1**–**3α** and *route* ***d*** in **1**–**3β**),[9] with the formation of the corresponding *anti*-1,2-*addition products* (the so-called *non-coordination products*),[6,10] never observed with coordinating *O*-nucleophiles.[1,8]

The results obtained with alcohols prompted us to investigate the regio- and stereoselective behavior of epoxides **1**,**2α**,**β**, and aziridines **3α**,**β** toward *N*-nucleophiles, such as amines. The aim was to find a simple protocol for the regio- and stereoselective introduction of an *N*-(substituted-amino) group on the glycal system of these allyl heterocycles. This would lead to 3-deoxy-3-(*N*-substituted-amino) glycals **6** (1,2-*addition products*) and/or 2,3-unsaturated-*N*-glycosyl amines **7** (1,4-*addition products*) from epoxides **1**,**2α**,**β**, and the corresponding 4-deoxy-4-(*N*-mesyl-amino)-derivatives **8** and **9** from aziridines **3α**,**β** (Scheme 2). *N*-glycosyl amines structurally related to **7** and **9** (1,4-*addition products*) are important as intermediates for the synthesis of glycoproteins and glycoconjugates and as constituents of natural products,[11,12] whereas glycals structurally related to **6** and **8** (1,2-*addition products*) are desirable compounds as intermediates for the synthesis of products of pharmaceutical interest.[13]

2. Results and discussion

The reactions of epoxides **1**,**2α**,**β**, and aziridines **3α**,**β** with primary and secondary aliphatic amines turned out to be particularly interesting, not only because they furnish a simple protocol for the synthesis of the corresponding 1,4- and/or 1,2-*addition products*

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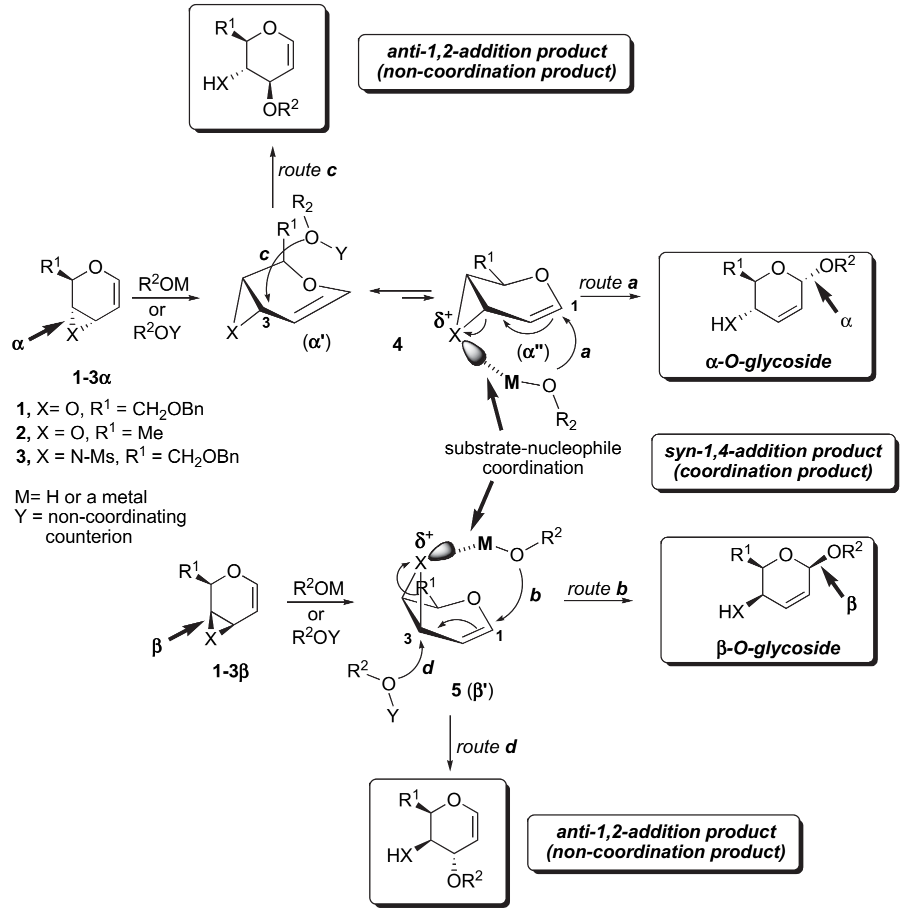
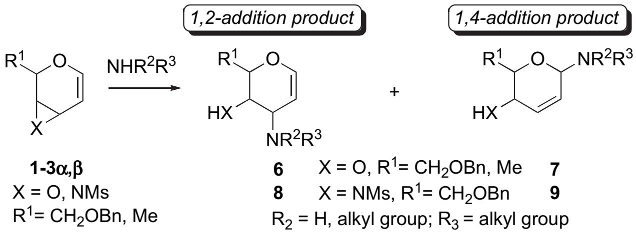


Scheme 1.



Scheme 2.

(Tables 1–4), but also because they have revealed some significant differences in the reactivity and the regio- and stereochemical behavior of these allyl heterocycles with respect to that previously observed with alcohols.[1]

With aziridines **3α** and **3β** and whenever the boiling point of the amine made it possible, the reactions were carried out both by using the amine as the solvent, that is in the presence of a large amount of nucleophile (*protocol A*), and by adding the amine only in a reduced amount (3 equiv) to a benzene solution of the aziridine (*protocol B*).[4] With epoxides **1α,β** and **2α,β**, *protocol A* reaction conditions were effective for the formation of the corresponding addition products, whereas the reactions carried out under *protocol B* turned out to be sluggish, and complex reaction mixtures were usually obtained. However, no catalyst was added in any case to the reaction mixture in order to promote the addition reaction.

The uncatalyzed reactions of epoxides **1α,β** and **2α,β** with primary and secondary aliphatic amines (*protocol A*) are completely regioselective, with the exclusive formation of the corresponding *anti*-1,2-*addition products*, (3α, 4β)-(**16**–**26**, Table 1) and (3β, 4α)-3-deoxy-3-(*N*-substitued-amino)-glycals (**27**–**29**, Table 2), from **1,2β** and **1,2α**, respectively, characterized by the presence of a *trans* 3,4-(*N*-substituted-amino)-alcohol moiety. While the regiochemical behavior is the same, the reactivity of α- and β-epoxides is decidedly different: epoxides **1,2β** show a good reactivity and afford a satisfactory yield of the corresponding *anti*-1,2-*addition products* with different types of amines (Table 1), whereas epoxides **1,2α** with the opposite configuration show a reactivity unexpectedly limited to few amines (Table 2).

The finding, in some cases (entries 6–8, Table 1 and entry 1, Table 2), of small amounts of the corresponding 1,4-*addition products* in the crude reaction mixture (^{1}H NMR spectroscopy) could be an indication of the presence of an isomerization process controlling the final result of the addition reaction. In fact, appropriate experiments carried out by stopping the reaction at different times (30 s, 1, 5, and 30 min) clearly indicated that the aminolysis reaction of epoxides **1,2α,β** is under thermodynamic control and the final *anti*-1,2-*addition product*, the only reaction product in each case obtained, is the consequence of an isomerization process by the corresponding 1,4-*addition product* (apparently a mixture of α- and β-anomers, ^{1}H NMR spectroscopy), the primary (kinetic) reaction product. Unfortunately, due to their rapid isomerization and instability under any chromatographic conditions attempted, the 1,4-*addition products* could not be isolated (Tables 1 and 2).

The corresponding reactions of aziridines **3α** and **3β**, carried out under both *protocol A* and *B*,[4] are not regioselective, and lead to mixtures of the corresponding 1,2- and 1,4-*addition products*.[14] Accurate ^{1}H NMR spectroscopy analysis indicated that the 1,2-*addition product* in each case obtained is the corresponding *trans*