Tetrahedron 66 (2010) 689–697

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

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

Valeria Di Bussolo *, Lorenzo Checchia, Maria Rosaria Romano, Lucilla Favero, Mauro Pineschi, Paolo Crotti *

Dipartimento di Scienze Farmaceutiche, sede Chimica Bioorganica e Biofarmacia, Università di Pisa, Via Bonanno 33, 56126 Pisa, Italy

ARTICLE INFO

Article history:
Received 9 August 2009
Received in revised form
22 October 2009
Accepted 12 November 2009
Available online 17 November 2009

Keywords:
Glycals
Allyl epoxides
Allyl aziridines
Aminolysis

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 **1**α,**1**β,**2**α, and **2**β and *N*-(mesyl)-aziridines **3**α and **3**β 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**,**2**α, and aziridine **3**α (*route* ***a***) and β-*O*-glycosides from epoxides **1**,**2**β, and aziridine **3**β (*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**–**3**α and *route* ***d*** in **1**–**3**β),[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]

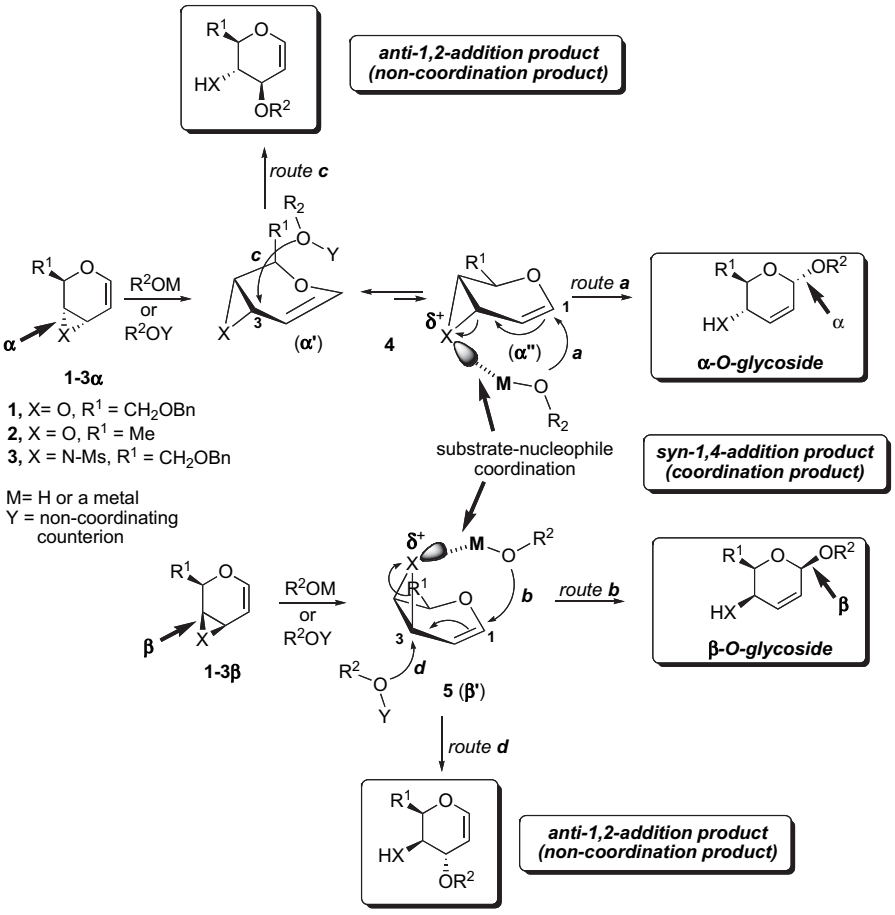
The results obtained with alcohols prompted us to investigate the regio- and stereoselective behavior of epoxides **1**,**2**α,β, and aziridines **3**α,β toward *N*-nucleophiles, such as amines. The aim was to find a simple protocol for the regio- and stereoselective introduction of an *N*-(substituted-amino) 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**,**2**α,β, and the corresponding 4-deoxy-4-(*N*-mesyl-amino)-derivatives **8** and **9** from aziridines **3**α,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

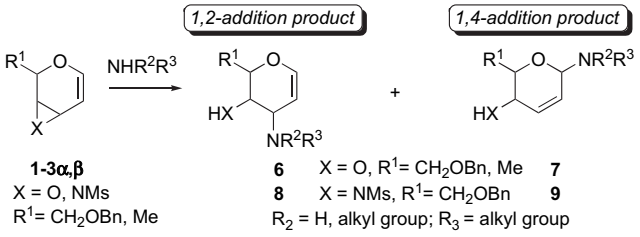
The reactions of epoxides **1**,**2**α,β, and aziridines **3**α,β with primary and secondary aliphatic amines turned out to be particularly interesting, not only because they furnish a simple protocol for the synthesis of the corresponding 1,4- and/or 1,2-*addition products*

* Corresponding authors. Tel.: +39 0502219690; fax: +39 0502219660.
E-mail addresses: valeriadb@farm.unipi.it (V. Di Bussolo), crotti@farm.unipi.it (P. Crotti).

0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.11.059



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]

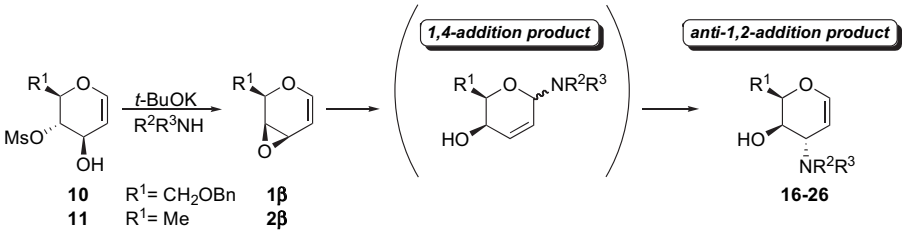
With aziridines **3α** and **3β** and whenever the boiling point of the amine made it possible, the reactions were carried out both by using the amine as the solvent, that is in the presence of a large amount of nucleophile (*protocol A*), and by adding the amine only in a reduced amount (3 equiv) to 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.

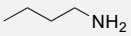
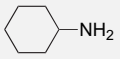
The uncatalyzed reactions of epoxides **1α,β** and **2α,β** with primary and secondary aliphatic amines (*protocol A*) are completely regioselective, with the exclusive formation of the corresponding *anti*-1,2-*addition products*, (3α, 4β)-(**16**–**26**, Table 1) and (3β, 4α)-3-deoxy-3-(*N*-substitued-amino)-glycals (**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*

Table 1
Regio- and stereoselectivity of the addition reactions of primary and secondary aliphatic amines to epoxides **1β** and **2β** (*protocol A*)[a]



Entry	Epoxide	Amine	Time (h)	Addition product (%)		Yield[b] %
1	**1β**		0.5	**16** (>99%)	R^1=CH_2OBn, R^2=Pr, R^3=H	92(72)
2	**1β**		0.5	**17** (>99%)	R^1=CH_2OBn, R^2=Bu, R^3=H	85(51)
3	**1β**		0.5	**18** (>99%)	R^1=CH_2OBn, R^2=Allyl, R^3=H	90(62)
4	**1β**	Et_2NH	1.0	**19** (>99%)	R^1=CH_2OBn, R^2=R^3=Et	88(53)
5	**1β**	Me_2NH	0.5	**20** (>99%)	R^1=CH_2OBn, R^2=R^3=Me	98(75)
6	**1β**	*i*-$PrNH_2$	1.0	**21** (95%)[c]	R^1=CH_2OBn, R^2=*i*-Pr, R^3=H	89(58)
7	**1β**		0.5	**22** (95%)[c]	R^1=CH_2OBn, R^2=C_6H_{11}, R^3=H	89(70)
8	**1β**		0.5	**23** (92%)[c]	R^1=CH_2OBn, R^2=C_3H_5, R^3=H	79(48)
9	**2β**		0.5	**24** (>99%)	R^1=Me, R^2=Pr, R^3=H	90(69)
10	**2β**	Me_2NH	0.5	**25** (>99%)	R^1=R^2=R^3=Me	89
11	**2β**	Et_2NH	1.0	**26** (>99%)	R^1=Me, R^2=R^3=Et	85(69)

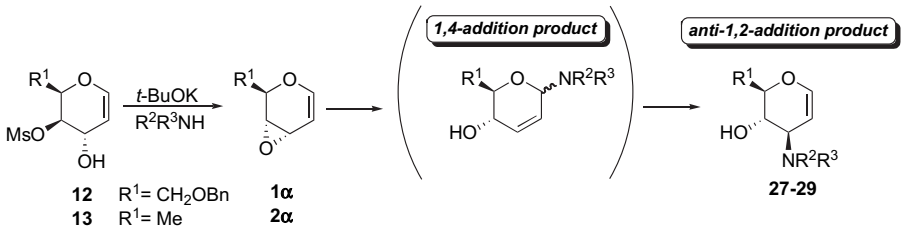
[a] *Protocol A*: amine as the solvent/nucleophile.
[b] Yields calculated on the crude reaction product (yields calculated after purification by flash chromatography or preparative TLC).
[c] A certain amount (5–8%) of the corresponding 1,4-*addition products* was present.

derivative, (3β,4α)-(**30**–**37**) and (3α,4β)-3,4-dideoxy-3-(*N*-substituted-amino)-4-(*N*-mesylamino)-glycals (**46**–**53**) (*anti*-1,2-*addition products*) from **3α** and **3β**, respectively, (Tables 3 and 4).

The determination of the structure of the only 1,4-*addition product* (*N*-glycosyl amine), in each case obtained in a mixture with the corresponding *anti*-1,2-*addition product*, led to a really unexpected result: the configuration of the anomeric C(1) carbon is *opposite* to that of the starting aziridine. In this way, only 2,3-unsaturated-β-*N*-glycosyl amines **38β**–**45β** from aziridine **3α** and only corresponding 2,3-unsaturated-α-*N*-glycosyl amines **54α**–**61α** from aziridine **3β** (*anti*-1,4-*addition products*) were selectively obtained. To the best of our knowledge, this result appears to be the first example of a completely *anti-stereoselective* and *inversely substrate-dependent* *N*-glycosylation process of amines.[12,13,15] Significantly, the corresponding anomeric *syn*-1,4-*addition products*, having the same configuration as the starting aziridine (*coordination products*, Scheme 1),[6] as constantly found in the reactions of aziridines **3α** and **3β** with alcohols (*directly substrate-dependent* selectivity)[1d,e] are completely absent under all the aminolysis reaction conditions tried (*protocol A* and *B*).[4] Moreover, the reaction outcome with aziridines **3α** and **3β** turned out to be insensitive to the reaction conditions, and almost the same result was obtained under both *protocol A* and *B* (entries 1–4, 7, 8, 10–13, Table 3 and entries 1, 2, 6 and 7, Table 4).

On standing in solution for several hours or days, the *anti*-1,4-*addition products* obtained in the aminolysis reactions of aziridines **3α** and **3β** slowly, and partially, isomerize to the corresponding regioisomeric *anti*-1,2-*addition products*, already present in the

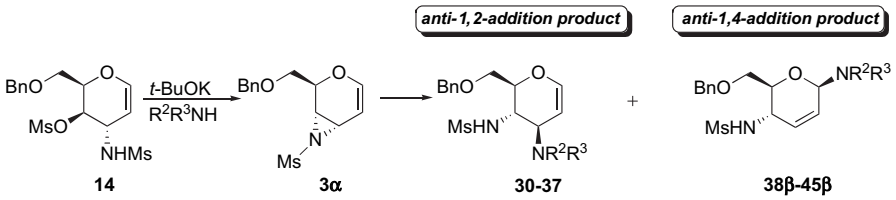
Table 2
Regio- and stereoselectivity of the addition reactions of primary and secondary aliphatic amines to epoxides **1α** and **2α** (*protocol A*)[a]



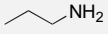
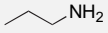
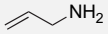
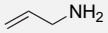
Entry	Epoxide	Amine	Time (h)	Addition product (%)		Yield[b] %
1	**1α**		0.5	**27** (95%)[c]	R^1=CH_2OBn, R^2=Pr, R^3=H	82(51)
2	**1α**	Me_2NH	0.5	**28** (>99%)	R^1=CH_2OBn, R^2=R^3=Me	96(64)
3	**2α**	Me_2NH	0.5	**29** (>99%)	R^1=R^2=R^3=Me	88(63)

[a] *Protocol A*: amine as the solvent/nucleophile.
[b] Yields calculated on the crude reaction product (yields calculated after purification by flash chromatography or preparative TLC).
[c] A certain amount (5%) of the corresponding 1,4-*addition products* was present.

Table 3
Regio- and stereoselectivity of the addition reactions of primary and secondary aliphatic amines to *N*-mesyl aziridine **3α** (*protocol A* and *B*)



14 **3α** **30-37** **38β-45β**

Entry	Amine	Protocol[a]	Time (h)	*anti-1,2*	Addition product(s) (%)	*anti-1,4*	Yield[b] %
1		A	1	**30** (30%)	R^2=Pr, R^3=H	**38β** (70%)	89
2		B	3	**30** (26%)	R^2=Pr, R^3=H	**38β** (74%)	92
3		A	0.5	**31** (20%)	R^2=allyl, R^3=H	**39β** (80%)	89
4		B	3	**31** (14%)	R^2=allyl, R^3=H	**39β** (86%)	70
5	$PhCH_2NH_2$	B	3	**32** (15%)	R^2=$PhCH_2$, R^3=H	**40β** (85%)	97
6	*i*-$PrNH_2$	A	0.5	**33** (15%)	R^2=*i*-Pr, R^3=H	**41β** (85%)	93
7	*t*-Bu-NH_2	A	0.5	**34** (10%)	R^2=*t*-Bu, R^3=H	**42β** (90%)	83
8	*t*-Bu-NH_2	B	3	**34** (10%)	R^2=*t*-Bu, R^3=H	**42β** (90%)	84
9	Me_2NH	A	0.5	**35** (63%)	R^2=R^3=Me	**43β** (37%)	98
10	Et_2NH	A	0.5	**36** (47%)	R^2=R^3=Et	**44β** (53%)	98
11	Et_2NH	B	3	**36** (42%)	R^2=R^3=Et	**44β** (58%)	91
12	Piperidine	A	0.5	**37** (43%)	R^2=R^3=*c*-C_5H_{10}	**45β** (57%)	92
13	Piperidine	B	3	**37** (40%)	R^2=R^3=*c*-C_5H_{10}	**45β** (60%)	82

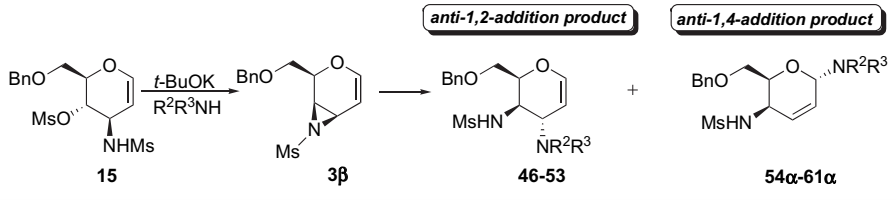
[a] A=*Protocol A*: amine as the solvent/nucleophile; B=*Protocol B*: amine (3 equiv) in anhydrous benzene as the solvent.
[b] Yields calculated on the crude reaction product.

reaction mixture. Experiments appropriately carried out by reducing the reaction time (10 s) have demonstrated that the addition reactions of amines to aziridines **3α** and **3β**, as reported in Tables 3 and 4, are under kinetic control.[16]

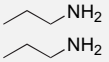
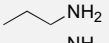
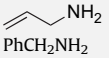
Even if the aminolysis reactions of **3α** and **3β** are not regioselective, there is a clear difference in the *anti*-1,2-*addition product*/*anti*-1,4-*addition product* distribution from the two aziridines: from aziridine **3β**, the *anti*-1,2-*addition products*, the corresponding *N*-(substituted-amino)-glycals, are largely or exclusively obtained (55–99%), whereas from aziridine **3α**, the *anti*-1,4-*addition products*, the corresponding β-*N*-glycosyl amines, are the main reaction products (57–90%) (Tables 3 and 4). In this framework, the less nucleophilic primary amines turned out to favor the formation of the corresponding *anti*-1,4-*addition products*, whereas the more nucleophilic secondary amines showed a clear tendency toward the corresponding *anti*-1,2-*addition products*. As a consequence, a high *anti*-1,4-stereoselectivity (70–90%) is observed in the reactions of aziridine **3α** with primary amines (*n*-$PrNH_2$, allylamine, *i*-$PrNH_2$, *t*-$BuNH_2$, $BnNH_2$), whereas secondary amines (dimethylamine, diethylamine, and piperidine) show little or no regioselectivity (Table 3). Accordingly, in the case of the diastereoisomeric aziridine **3β**, whereas primary amines show a poor regioselectivity, secondary amines determined a complete *anti*-1,2-addition process, with the exclusive formation of the corresponding *anti*-1,2-*addition products* (Table 4).

On the whole, the present protocol, which uses *N*-mesyl aziridines **3α** and **3β**, makes possible the simple stereoselective construction of a vicinal *trans*-3,4- (as found in the *anti*-1,2-*addition products*) or distal *trans*-1,4-di-(*N*-substituted-amino) functionality (as found in the *anti*-1,4-*addition products*) in a glycal and

Table 4
Regio- and stereoselectivity of the addition reactions of primary and secondary aliphatic amines to *N*-mesyl aziridine **3β** (*protocol A* and *B*)



15 **3β** **46-53** **54α-61α**

Entry	Amine	Protocol[a]	Time (h)	*anti-1,2*	Addition product(s) (%)	*anti-1,4*	Yield[b] %
1		A	1	**46** (70%)	R^2=Pr, R^3=H	**54α** (30%)	91
2		B	3	**46** (74%)	R^2=Pr, R^3=H	**54α** (26%)	84
3		A	1	**47** (56%)	R^2=allyl, R^3=H	**55α** (44%)	87
4	$PhCH_2NH_2$	B	3	**48** (62%)	R^2=$PhCH_2$, R^3=H	**56α** (38%)	89
5	*i*-$PrNH_2$	A	1	**49** (64%)	R^2=*i*-Pr, R^3=H	**57α** (36%)	95
6	*t*-Bu-NH_2	A	1	**50** (50%)	R^2=*t*-Bu, R^3=H	**58α** (50%)	89
7	*t*-Bu-NH_2	B	3	**50** (55%)	R^2=*t*-Bu, R^3=H	**58α** (45%)	70
8	Me_2NH	A	1	**51** (>99%)	R^2=R^3=Me	**59α** (<1%)	96(72)
9	Et_2NH	A	1	**52** (>99%)	R^2=R^3=Et	**60α** (<1%)	88(61)
10	Piperidine	A	1	**53** (96%)	R^2=R^3=*c*-C_5H_{10}	**61α** (4%)	91(65)

[a] A=*Protocol A*: amine as the solvent/nucleophile; B=*Protocol B*: amine (3 equiv) in anhydrous benzene, as the solvent.
[b] Yields calculated on the crude product (yields calculated after purification by flash chromatography).

pseudoglycal system, respectively. In this way, the corresponding (3β,4α)- and (1β,4α)- (from aziridine **3α**) and (3α,4β)- and (1α, 4β)-di-(*N*-substituted-amino) sub-structural moieties (from **3β**) of interest for the synthesis of biologically active compounds can be stereoselectively synthesized (Tables 3 and 4).[11–13]

3. Discussion

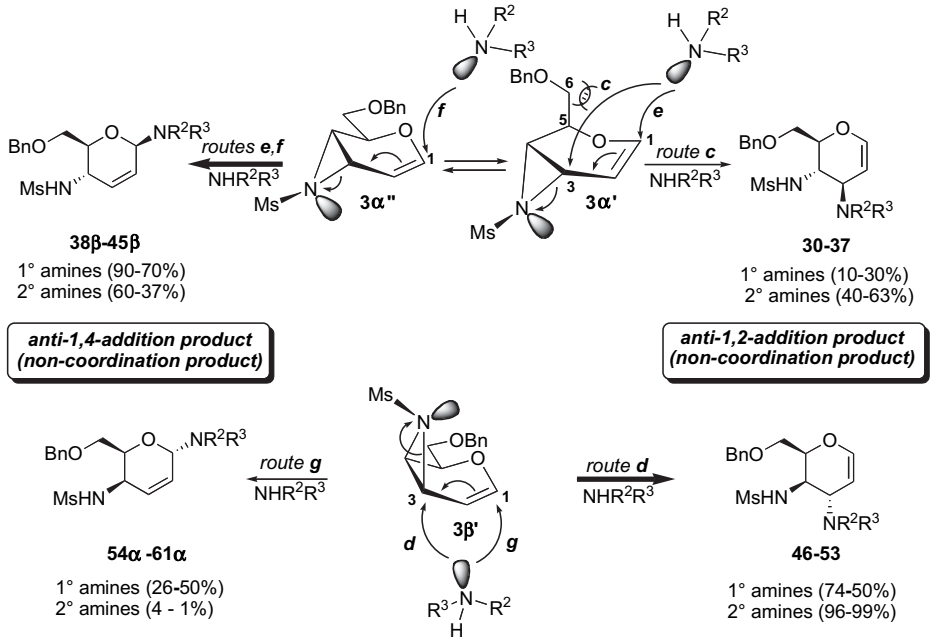
The behavior of epoxides **1,2α,β** in the reactions with amines under *protocol A* is similar to that observed in the corresponding reactions with alcohols under the same conditions, and the different result derives from the decidedly different stability of the primary reaction product. Actually, in both aminolysis and alcoholysis, mixtures of *syn*- and *anti*-1,4-*addition products* are kinetically obtained, but in the case of the alcoholysis, the 1,4-*addition products*, the corresponding alkyl *O*-glycosides are stable and constitute the final reaction products,[1a–c,8] whereas in the aminolysis, an isomerization process occurs on the initially formed 1,4-*addition products* and the corresponding, more stable, *anti*-1,2-*addition products* are the final reaction products (Tables 1 and 2).[15]

The results obtained in the aminolysis of *N*-mesyl aziridines **3α,β** are primarily consistent with the absence of any type of coordination between the nucleophile (amine) and the aziridine nitrogen of **3α,β**. In these conditions, only *anti*-addition processes, made possible also by the marked nucleophilicity of the amine, can occur, and, as a consequence, only products (*non-coordination products*)[6] deriving from a direct, non-coordinated attack of the nucleophile, in an *anti* fashion, on the reactive sites [C(1) and C(3)] of the allylic system can consequently be found: *anti*-1,4-*addition products* by nucleophilic attack on C(1) and *anti*-1,2-*addition products* by corresponding attack on allylic C(3) carbon (Scheme 3).

aziridine **3α**) necessarily arise by a corresponding amine attack on aziridine **3α** through conformer **α′**[2] (*route* ***c***, Scheme 3), but an 1,3-diaxial interaction between the C(5)–C(6) bond and the direction of the nucleophilic attack is present in the opening process. This interaction could be responsible for the reduced amount of *anti*-1,2-*addition products* found in the case of aziridine **3α** (vide infra).

As for the *anti*-1,4-*addition products*, the *N*-glycosyl amines **38β**–**45β** and **54α**–**61α** obtained from aziridines **3α** and **3β**, respectively, steric repulsion between the *N*-mesyl substituted aziridine ring and the attacking nucleophile could be responsible for the conjugated nucleophilic addition to C(1) on the face opposite to that bearing the aziridine ring (Scheme 3). In aziridine **3β**, amine attack on C(1) in an *anti* fashion occurs through the only existing conformer **3β′**[1e] and is favorably *pseudoaxial* (*route* ***g***, Scheme 3), whereas in aziridine **3α**, the corresponding attack can occur in both conformers **3α′** and **3α″** present at the equilibrium in an almost 1:1 ratio.[2] In **3α′**, the conjugated *anti*-attack is *pseudoaxial* (*route* ***e***, Scheme 3), but it suffers from 1,3-diaxial interaction with the axial C(5)-C(6) bond, whereas in conformer **3α″** no strain is present in the corresponding *pseudoequatorial* attack (*route* ***f***, Scheme 3). As a consequence, in **3β**, both *anti*-1,2- and *anti*-1,4-addition process are favored, whereas in aziridine **3α**, due to the possible presence of an 1,3-diaxial interaction, only the *pseudoequatorial anti*-1,4-addition process through conformer **3α″** is favored. All this could determine the prevalence of *anti*-1,4-*addition products* in **3α** and, considering that in the absence of any coordinating and/or steric factors the C(3) allylic carbon should be the preferred reactive terminus,[1] the prevalence of *anti*-1,2-*addition products* in **3β**, thus justifying the different distribution of products observed in the aminolysis of *N*-mesyl aziridines **3α** and **3β**.[17,18]

The behavior of aziridines **3α** and **3β** in the reactions with amines under *protocol A* and *protocol B* is decidedly different from



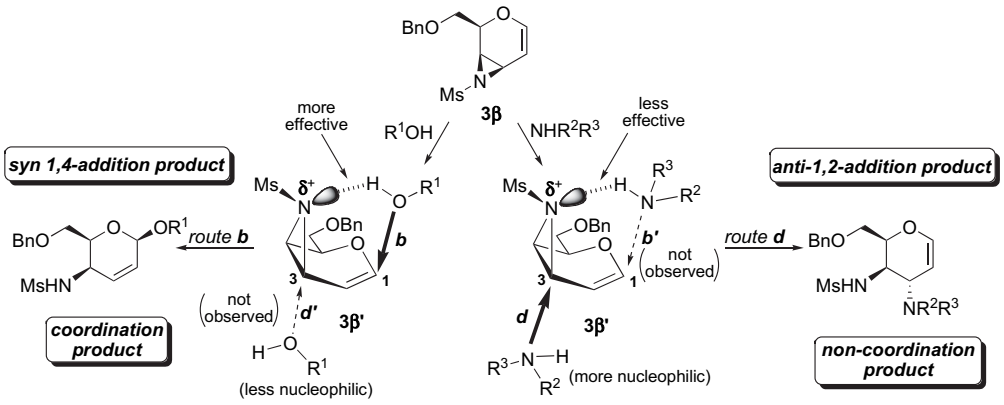
Scheme 3.

Considering the conformational equilibrium present in aziridines **3α,β**[2] and the stereoelectronic factors related to the preferential *trans*-diaxial ring opening of three-membered heterocycles, the *anti*-1,2-*addition products* **46**–**53** (from aziridines **3β**) arise by amine *pseudoaxial* attack on the allylic C(3) carbon of aziridine **3β**, reacting in its corresponding unique conformer **β′**[1e] (*route* ***d***, Scheme 3). Likewise, *anti*-1,2-*addition products* **30**–**37** (from that observed in the corresponding reactions with alcohols under the same conditions: only 1,4-*addition products*, with a consistent prevalence (*protocol A*) or unique presence (*protocol B*) of the corresponding *syn*-1,4-*addition product* (*coordination product*)[6] from the reactions with alcohols (Scheme 1)[1d,e] and mixtures of *anti*-1,2- and *anti*-1,4-*addition products* (*non-coordination products*)[6] from the reaction with amines (Scheme 3).

The reason for such a decidedly different behavior in apparently similar reactions can be found in a combination of the two above-mentioned factors: the different nucleophilicity of amines with respect to alcohols, and the different efficiency of the aziridine nitrogen-nucleophile coordination (hydrogen bond) in the case of alcohols and amines. As shown for simplicity in Scheme 4 only for aziridine **3β**, these two factors make the direct attack on the C(3) carbon (*route* ***d***) particularly favored in the case of amines, which are characterized by a high nucleophilicity and a possibly reduced efficiency of the coordination with the aziridine nitrogen, to the point that the coordination pathway (*route* ***b′***) is not observed at all, and the *anti*-1,2-addition process (*route* ***d***) is the largely observed reaction pathway. With the less nucleophilic alcohols, no direct, uncatalyzed attack on the allylic C(3) carbon (*route* ***d′***) can reasonably take place. In these conditions, only a nucleophilic attack on C(1), largely promoted by the efficient oxirane oxygen–alcohol coordination, in the form of a hydrogen bond, is possible. In this way, the poorly nucleophilic alcohol is brought on the β face and practically 'activated' for a β-directed attack on the nearby C(1) carbon, in a sort of intramolecular, entropically favored, reaction pathway (*route* ***b***, Scheme 4).[19]

corresponding *trans* 4-hydroxy-3-(*N*-substituted-amino) glycals (*anti*-1,2-*addition products*). On the contrary, the aminolysis reactions of the structurally related *N*-mesyl aziridines **3α** and **3β** are under kinetic control and lead to mixtures of the corresponding *trans* 3,4-di-(*N*-substituted-amino) glycals (*anti*-1,2-*addition products*) and *N*-glycosyl amines having a configuration *opposite* to that of the starting aziridine (*anti*-1,4-*addition products*). The composition of the aminolysis reaction mixtures of aziridines **3α** and **3β** depends exclusively of the aziridine and the amine (primary or secondary) and the results obtained have been explained by the nucleophilicity of amines and their reduced ability to form a hydrogen bond with the aziridine nitrogen. When compared with the corresponding results obtained in the alcoholysis, the aminolysis of aziridines **3α** and **3β** probably constitutes the best demonstration of how the presence or the absence of a substrate–nucleophile coordination effect can direct the regio- and stereoselectivity of the nucleophilic addition reactions in these glycal-derived allyl heterocyclic systems.

Theoretical, computational studies are in due progress in our laboratory in order to have, if possible, a more complete rationalization of the regio- and stereochemical behavior of these interesting glycal-derived allyl oxiranes **1,2α,β** and *N*-mesyl aziridines **3α,β** in nucleophilic addition reactions.



Scheme 4.

4. Structures and configurations

The regioisomeric 1,2- or 1,4-*addition product* structure of the products obtained in the aminolysis of epoxides **1,2α,β** and aziridines **3α,β** was simply determined on the basis of the chemical shift of the corresponding vinyl protons in ^{1}H NMR spectra of the addition compounds obtained [δ 6.58–6.35 (1H) and 4.60–4.99 (1H) in 1,2-*addition products* and δ 5.82–6.15 (2H) in 1,4-*addition products*]. Moreover, 1,4-*addition products* also show the presence of the anomeric H(1) proton at δ 4.73–5.30. The *trans* configuration in the *anti*-1,2-*addition products* obtained in the reactions of epoxides **1,2α,β** and aziridines **3α,β** was demonstrated by means of appropriate NOE experiments. As for the *anti*-1,4-*addition products* (*N*-glycosyl amines) obtained in the reactions of aziridines **3α,β** the α (from aziridine **3β**) and β configuration (from aziridine **3α**) were determined on the basis of the presence of NOE between anomeric H(1) and the methyl group of the methansulfonylamino group on C(4) and on the observation that the chemical shift of anomeric H(1) in the α series is constantly at a lower field than in the β series, in accordance with literature data.[12b,c,20]

5. Conclusions

The addition reactions of primary and secondary aliphatic amines to glycal-derived allyl epoxides **1α,β** and **2α,β** are under thermodynamic control and lead to the exclusive formation of the

6. Experimental

6.1. General

All reactions were performed in a flame-dried modified Schlenk (Kjeldahl shape) flasks fitted with a glass stopper or rubber septa under a positive pressure of argon. Flash column chromatography was performed employing 230–400 mesh silica gel (Macherey–Nagel). Analytical TLCs were performed on Alugram SIL G/UV$_{254}$ silica gel sheets (Macherey–Nagel) with detection by 0.5% phosphomolybdic acid solution in 95% EtOH. Benzene, toluene, Et_2O, and THF were distilled from sodium/benzophenone. Epoxides **1,2α,β** and *N*-mesyl aziridines **3α,β** were prepared by cyclization under basic conditions (*t*-BuOK) of the corresponding stable precursors, *trans* hydroxy mesylates **10**–**13**[1a–c] and *trans N,O*-dimesylates **14**[1d] and **15**,[1e] as previously described.

6.2. Reactions of epoxides 1α,1β,2α and 2β with amines under *protocol A* reaction conditions

*6.2.1. Reaction of epoxide **1β** with $PrNH_2$ (protocol A). Typical Procedure*. A solution of *trans* hydroxy mesylate **10** (0.035 g, 0.11 mmol) in $PrNH_2$ (2.2 mL) was treated with *t*-BuOK (0.012 g, 0.11 mmol,

1 equiv) and the reaction mixture was stirred 30 min at room temperature. Dilution with Et_2O and evaporation of the washed (saturated aqueous NaCl) organic solution afforded a crude product (0.028 g, 92% yield) consisting of practically pure 3-deoxy-3-(*N*-propylamino)-D-gulal derivative **16** (^{1}H NMR), which was subjected to flash chromatography. Elution with a 9:1 CH_2Cl_2/MeOH mixture afforded *6-O-(benzyl)-3-deoxy-3-(N-propylamino)-D-gulal* (**16**) (0.022 g, 72% yield), pure as a liquid: R_f=0.23 (9:1 CH_2Cl_2/MeOH); IR (neat) ν 3462, 1645, 1454, 1244, 1097 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.26–7.39 (m, 5H), 6.52 (d, 1H, *J*=6.1 Hz), 4.84 (ddd, 1H, *J*=6.1, 5.0, 1.6 Hz), 4.66 (d, 1H, *J*=11.9 Hz), 4.58 (d, 1H, *J*=11.9 Hz), 3.95–4.04 (t, 1H, *J*=4.0 Hz), 3.78–3.94 (m, 3H), 2.88–2.99 (m, 1H), 2.57–2.73 (m, 2H), 1.88–2.20 (m, 2H, OH and NH), 1.58 (six lines, 2H, *J*=7.3 Hz), 0.90 (t, 3H, *J*=7.3 Hz). ^{13}C NMR δ 145.2, 137.6, 128.7, 128.1, 128.0, 100.0, 74.1, 72.1, 71.4, 69.0, 54.5, 49.4, 23.5, 11.9. Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.12; H, 8.20; N, 5.25.

*6.2.2. Reaction of epoxide **1β** with Me_2NH (protocol A).* Following the typical procedure, the treatment of a solution of *trans* hydroxy mesylate **10** (0.041 g, 0.13 mmol) in Me_2NH (2.5 mL) with *t*-BuOK (0.015 g, 0.13 mmol) afforded, after 30 min at room temperature, a crude product (0.034 g, 98% yield) consisting of practically pure 3-deoxy-3-(*N*,*N*-dimethylamino)-D-gulal derivative **20** (^{1}H NMR), which was subjected to flash chromatography. Elution with a 3:7:0.3 hexane/AcOEt/MeOH mixture afforded *6-O-(benzyl)-3-deoxy-3-(N,N-dimethylamino)-D-gulal* (**20**) (0.025 g, 75% yield), pure as a liquid: R_f=0.29 (3:7:0.3 hexane/AcOEt/MeOH); IR (neat) ν 3331, 1655, 1462, 1377, 1095 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.24–7.40 (m, 5H), 6.55 (dd, 1H, *J*=6.3, 0.6 Hz), 4.72 (ddd, 1H, *J*=6.3, 4.9, 1.7 Hz), 4.64 (d, 1H, *J*=12.0 Hz), 4.57 (d, 1H, *J*=12.0 Hz), 4.02 (t, 1H, *J*=4.3 Hz), 3.91–3.95 (m, 1H), 3.86 (dd, 1H, *J*=10.5, 3.5 Hz) 3.79 (dd, 1H, *J*=10.5, 5.1 Hz), 2.47–2.56 (m, 1H), 2.30 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 145.1, 137.7, 128.7, 128.0, 127.9, 98.7, 73.9, 73.1, 71.0, 67.1, 62.1, 42.9. Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.67; H, 8.32; N, 5.13.

*6.2.3. Reaction of epoxide **1α** with $PrNH_2$ (protocol A).* Following the typical procedure, the treatment of a solution of *trans* hydroxy mesylate **12** (0.035 g, 0.11 mmol) in $PrNH_2$ (2 mL) with *t*-BuOK (0.012 g, 0.11 mmol) afforded, after 1 h at room temperature, a crude product (0.025 g, 82% yield) consisting of a 95:5 mixture of 3-deoxy-3-(*N*-propylamino)-D-glucal derivative **27** and corresponding 1,4-addition products (^{1}H NMR), which was subjected to flash chromatography. Elution with a 9:1 CH_2Cl_2/MeOH mixture, containing Et_3N (0.1%) afforded *6-O-(benzyl)-3-deoxy-3-(N-propylamino)-D-glucal* (**27**) (0.016 g, 51% yield), pure as a liquid: R_f=0.40 (9:1 CH_2Cl_2/MeOH); IR (neat) ν 3329, 1651, 1454, 1234, 1097 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.20–7.42 (m, 5H), 6.38 (dd, 1H, *J*=6.1, 1.8 Hz), 4.76 (dd, 1H, *J*=6.1, 1.8 Hz), 4.48–4.71 (m, 2H), 4.65 (d, 1H, *J*=12.1 Hz), 4.58 (d, 1H, *J*=12.1 Hz), 3.61–4.00 (m, 5H), 2.49–2.83 (m, 2H), 1.55 (sextet, 2H, *J*=7.3 Hz), 0.93 (t, 3H, *J*=7.3 Hz). ^{13}C NMR ($CDCl_3$) δ 145.3, 138.0, 128.6, 127.9, 99.4, 77.3, 73.8, 69.6, 58.4, 47.4, 29.8, 18.9, 11.7. Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.09; H, 8.51; N, 5.40.

*6.2.4. Reaction of epoxide **1α** with Me_2NH (protocol A).* Following the typical procedure, the treatment of a solution of *trans* hydroxy mesylate **12** (0.035 g, 0.11 mmol) in Me_2NH (2 mL) with *t*-BuOK (0.012 g, 0.11 mmol) afforded, after 30 min at room temperature, a crude product (0.028 g, 96% yield) consisting of practically pure 3-deoxy-3-(*N*,*N*-dimethylamino)-D-glucal derivative **28** (^{1}H NMR), which was subjected to flash chromatography. Elution with a 3:7:0.3 hexane/AcOEt/MeOH mixture afforded *6-O-(benzyl)-3-deoxy-3-(N,N-dimethylamino)-D-glucal* (**28**) (0.019 g, 64% yield), pure as a liquid: R_f=0.53 (3:7:0.3 hexane/AcOEt/MeOH); IR (neat) ν 3387, 1645, 1361, 1224, 1098 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.18–7.45 (m, 5H), 6.58 (d, 1H, *J*=6.2 Hz), 4.99 (dt, 1H, *J*=6.2, 2.0 Hz), 4.76–4.81 (m, 1H), 4.61 (d, 1H, *J*=11.8 Hz), 4.56 (d, 1H, *J*=11.8 Hz), 4.53–4.64 (m, 1H), 4.18–4.29 (m, 1H), 3.61–3.87 (m, 2H), 2.79–2.84 (m, 1H), 2.98 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 146.9, 137.4, 128.7, 128.1, 99.9, 75.2, 73.8, 70.3, 67.8, 61.7, 38.3. Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.22; H, 8.16; N, 5.57.

*6.2.5. Reaction of epoxide **2β** with $PrNH_2$ (protocol A).* Following the typical procedure, the treatment of a solution of *trans* hydroxy mesylate **11** (0.050 g, 0.24 mmol) in $PrNH_2$ (3.3 mL) with *t*-BuOK (0.027 g, 0.24 mmol) afforded, after 30 min at room temperature, a crude product consisting of 3,6-dideoxy-3-(*N*-propylamino)-D-gulal derivative **24** (0.037 g, 90% yield), which was subjected to flash chromatography. Elution with a 1:1 hexane/AcOEt mixture afforded pure *3,6-dideoxy-3-(N-propylamino)-D-gulal* (**24**) (0.028 g, 69% yield), pure as a liquid: R_f=0.33 (1:1 hexane/AcOEt); IR (neat) ν 3459, 1649, 1451, 1236, 1095 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.44 (d, 1H, *J*=6.1 Hz), 4.85–4.95 (m, 1H), 4.81 (ddd, 1H, *J*=6.1, 4.7, 1.5 Hz), 4.02 (q, 1H, *J*=6.3 Hz), 3.48–3.55 (m, 1H), 2.90–2.97 (m, 1H), 2.66–2.77 (m, 1H), 2.54–2.65 (m, 1H), 1.48 (sextet, 2H, *J*=7.3 Hz), 1.34 (d, 3H, *J*=6.5 Hz), 0.91 (t, 3H, *J*=7.3 Hz). ^{13}C NMR ($CDCl_3$) δ 143.6, 100.0, 70.2, 70.1, 55.1, 46.7, 23.8, 16.7, 11.5. Anal. Calcd for $C_9H_{16}NO_2$: C, 63.13; H, 10.01; N, 8.18. Found: C, 63.45; H, 9.70; N, 8.31.

*6.2.6. Reaction of epoxide **2β** with Et_2NH (protocol A).* Following the typical procedure, the treatment of a solution of *trans* hydroxy mesylate **11** (0.030 g, 0.14 mmol) in Et_2NH (2 mL) with *t*-BuOK (0.016 g, 0.14 mmol) afforded, after 1 h at room temperature, a crude product consisting of 3,6-dideoxy-3-(*N*,*N*-diethylamino)-D-gulal derivative **26** (0.022 g, 85% yield), which was subjected to flash chromatography. Elution with a 1:1 hexane/AcOEt mixture afforded pure *3,6-dideoxy-3-(N,N-diethylamino)-D-gulal* (**26**) (0.018 g, 69% yield), pure as a liquid: R_f=0.44 (1:1 hexane/AcOEt); IR (neat) ν 3559, 1648, 1456, 1229, 1094 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.37 (dd, 1H, *J*=6.3, 1.6 Hz), 4.64 (dd, 1H, *J*=6.2, 3.7 Hz), 4.20 (dd, 1H, *J*=6.4, 2.8 Hz), 3.58–3.65 (m, 1H), 2.99–3.06 (m, 1H), 2.41–2.83 (m, 4H), 1.30 (d, 3H, *J*=6.6 Hz), 1.03 (t, 6H, *J*=7.2 Hz). ^{13}C NMR ($CDCl_3$) δ 144.6, 99.2, 71.7, 68.2, 58.2, 44.0, 29.8, 13.6. Anal. Calcd for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34; N, 7.56. Found: C, 64.90; H, 10.29; N, 7.43.

*6.2.7. Reaction of epoxide **2α** with Me_2NH (protocol A).* Following the typical procedure, the treatment of a solution of *trans* hydroxy mesylate **13** (0.050 g, 0.24 mmol) in Me_2NH (3.3 mL) with *t*-BuOK (0.027 g, 0.24 mmol) afforded, after 30 min at room temperature, a crude product (0.033 g, 88% yield) consisting of *N*,*N*-dimethylamino-derivative **29** and unreacted starting material, which was subjected to preparative TLC (an 1:1 hexane/AcOEt mixture was used as the eluent). Extraction of the slower more intense band afforded pure *3,6-dideoxy-3-(N,N-dimethylamino)-D-glucal* (**29**), as a liquid (0.024 g, 63% yield): R_f=0.14 (1:1 hexane/AcOEt); IR (neat) ν 3342, 1641, 1454, 1226, 1094 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.38 (dd, *J*=6.2, 2.0 Hz), 4.66 (dd, *J*=6.2, 1.8 Hz), 4.07–4.19 (m, 1H), 3.32–3.43 (m, 1H), 3.15–3.24 (m, 1H), 2.24 (s, 6H), 1.36 (d, 3H, *J*=6.3 Hz). ^{13}C NMR δ 147.6, 99.8, 79.2, 70.8, 60.2, 44.1, 39.5, 16.5. Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.46, H, 9.55; N, 8.72.

6.3. Reactions of aziridines 3α and 3β with amines under *protocol A* reaction conditions

*6.3.1. Reaction of aziridine **3α** with $PrNH_2$ (protocol A). Typical procedure.* A solution of *trans N*,*O*-dimesylate **14** (0.031 g, 0.080 mmol) in $PrNH_2$ (1.6 mL) was treated with *t*-BuOK (0.009 g, 0.080 mmol, 1 equiv) and the reaction mixture was stirred at room temperature until the TLC analysis showed the complete disappearance of the starting material (1 h). Evaporation of the solvent

afforded a crude product (0.025 g, 89% yield) consisting of a 70:30 mixture of β-*N*-glycosyl amine **38β** and 3,4-dideoxy-3,4-di-(*N*-substituted-amino)-D-glucal derivative **30** (^{1}H NMR), which was subjected to flash chromatography. Elution with an 8:2 CH_2Cl_2/acetone mixture afforded pure **38β** (0.013 g, 46% yield) and **30** (0.005 g, 16% yield).

*6.3.1.1. N-(Propyl)-[6-O-(benzyl)-2,3,4-trideoxy-4-(N-mesylamino)-β-D-erithro-hex-2-enopyranosyl]-amine (**38β**).* A liquid: R_f=0.31 (8:2 CH_2Cl_2/acetone); IR (neat) ν 3558, 3360, 1653, 1319, 1101 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.27–7.39 (m, 5H), 5.96–6.03 (m, 1H), 5.93 (dt, 1H, *J*=6.2, 1.7 Hz), 5.22–5.26 (m, 1H), 4.58 (d, 1H, *J*=11.7 Hz), 4.56 (d, 1H, *J*=11.7 Hz), 4.46–4.62 (m, 2H), 4.00–4.08 (m, 1H), 3.60 (d, 2H, *J*=5.4 Hz), 2.94–3.15 (m, 2H), 2.76 (s, 3H), 2.59–2.85 (m, 1H), 1.47 (q, 2H, *J*=7.3 Hz), 0.91 (t, 3H, *J*=7.3 Hz). ^{13}C NMR ($CDCl_3$) δ 137.9, 130.4, 129.4, 128.7, 128.1, 80.8, 72.0, 71.4, 69.1, 47.1, 35.9, 29.8, 23.5, 11.9. Anal. Calcd for $C_{17}H_{26}N_2O_4S$: C, 57.60; H, 7.39; N, 7.90. Found: C, 57.45; H, 7.23; N, 7.81.

*6.3.1.2. 6-O-(Benzyl)-3,4-dideoxy-4-(N-mesylamino)-3-(N-propylamino)-D-glucal (**30**).* A liquid: R_f=0.15 (8:2 CH_2Cl_2/acetone); IR (neat) ν 3560, 3345, 1650, 1320, 1098 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.27–7.39 (m, 5H), 6.40 (dd, 1H, *J*=6.1, 1.6 Hz), 4.85 (dd, 1H, *J*=6.1, 2.6 Hz), 4.60 (s, 2H), 3.95–4.05 (m, 1H), 3.84–3.90 (m, 2H), 3.53 (t, 1H, *J*=8.1 Hz), 3.11–3.19 (m, 1H), 3.13 (s, 3H), 2.66–2.76 (m, 1H), 2.44–2.54 (m, 1H), 1.48 (q, 2H, *J*=7.4 Hz), 0.92 (t, 3H, *J*=7.4 Hz). ^{13}C NMR δ 144.0, 137.9, 128.6, 127.9, 102.0, 78.8, 77.3, 69.8, 57.0, 53.6, 48.3, 42.2, 23.6, 12.0 Anal. Calcd for $C_{17}H_{26}N_2O_4S$: C, 57.60; H, 7.39; N, 7.90. Found: C, 57.72; H, 7.50; N, 8.01.

*6.3.2. Reaction of aziridine **3β** with $PrNH_2$ (protocol A).* Following the typical procedure, the treatment of a solution of *trans N,O*-dimesylate **15** (0.023 g, 0.060 mmol) in $PrNH_2$ (1.2 mL) with *t*-BuOK (0.007 g, 0.060 mmol) afforded, after 1 h at room temperature, a crude product (0.019 g, 91% yield) consisting of a 30:70 mixture of the corresponding α-*N*-glycosyl amine **54α** and 3,4-dideoxy-3,4-di-(*N*-substituted-amino)-D-gulal derivative **46** (^{1}H NMR), which was subjected to flash chromatography. Elution with a 4:6 hexane/acetone mixture afforded *6-O-(benzyl)-3,4-dideoxy-4-(N-mesylamino)-3-(N-propylamino)-D-gulal* (**46**) (0.010 g, 49% yield), pure as a liquid: R_f=0.36 (4:6 hexane/acetone); IR (neat) ν 3488, 3360, 1643, 1261, 1093 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.22–7.39 (m, 5H), 6.48 (d, 1H, *J*=6.3 Hz), 4.75–4.89 (m, 1H), 4.47–4.62 (m, 2H), 4.58 (s, 2H), 4.18–4.33 (m, 1H), 3.54–3.80 (m, 3H), 2.99–3.13 (m, 2H), 2.90 (s, 3H), 2.68 (t, 1H, *J*=7.0 Hz), 1.48 (q, 2H, *J*=7.4), 0.91 (t, 3H, *J*=7.4 Hz). ^{13}C NMR ($CDCl_3$) δ 145.4, 137.5, 128.7, 128.0, 100.9, 73.8, 71.1, 69.1, 54.7, 49.4, 29.8, 23.6, 11.8. Anal. Calcd for $C_{17}H_{26}N_2O_4S$: C, 57.60; H, 7.39; N, 7.90. Found: C, 57.53; H, 7.44; N, 8.06.

Even if not recovered from the flash chromatography, the presence of the regioisomeric α-*N*-glycosyl amine **54α**, as a reaction product, was firmly established by ^{1}H NMR examination of the crude reaction mixture: **54α**, ^{1}H NMR δ 5.89 (s, 2H), 5.30 (s, 1H, H-1), 2.74 (s, 3H), 0.90 (t, 3H, *J*=7.4 Hz).

*6.3.3. Reaction of aziridine **3β** with Me_2NH (protocol A).* Following the typical procedure, the treatment of a solution of *trans N,O*-dimesylate **15** (0.031 g, 0.080 mmol) in Me_2NH (1.6 mL) with *t*-BuOK (0.009 g, 0.080 mmol) afforded, after 1 h at room temperature, a crude product (0.026 g, 96% yield) essentially consisting of 3,4-dideoxy-3,4-di-(*N*-substituted-amino)-D-gulal derivative **51** (^{1}H NMR), which was subjected to flash chromatography. Elution with a 1:1 CH_2Cl_2/AcOEt mixture containing Et_3N (0.1%) afforded *6-O-(benzyl)-3,4-dideoxy-4-(N-mesylamino)-3-(N,N-dimethylamino)-D-gulal* (**51**) (0.019 g, 72% yield), pure as a liquid: R_f=0.20 (1:1 CH_2Cl_2/AcOEt); IR (neat) ν 3283, 1643, 1323, 1098 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.23–7.42 (m, 5H), 6.52 (d, 1H, *J*=6.1 Hz), 4.73 (ddd, 1H, *J*=6.1, 5.3, 1.7 Hz), 4.61 (d, 1H, *J*=11.9 Hz), 4.54 (d, 1H, *J*=11.9 Hz), 4.60 (d, 1H, *J*=3.8 Hz, NH), 4.22–4.32 (m, 1H), 3.65–3.78 (m, 3H), 2.91 (s, 3H), 2.53–2.59 (m, 1H), 2.34 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 145.5, 137.7, 128.7, 128.2, 128.1, 99.1, 73.9, 72.0, 68.9, 62.2, 49.8, 43.0. 41.9. Anal. Calcd for $C_{16}H_{24}N_2O_4S$: C, 56.45; H, 7.11; N, 8.23. Found: C, 56.40; H, 7.45; N, 8.16.

6.4. Reactions of aziridines 3α and 3β with amines under *protocol B* reaction conditions

*6.4.1. Reaction of aziridine **3α** with $BnNH_2$ (protocol B). Typical procedure.* A solution of *trans N,O*-dimesylate **14** (0.030 g, 0.077 mmol) in anhydrous benzene (1 mL) was treated with *t*-BuOK (0.009 g, 0.080 mmol) in the presence of $BnNH_2$ (0.025 mL, 0.23 mmol, 3 equiv) and the resulting reaction mixture was stirred at room temperature until the TLC analysis showed the complete disappearance of the starting material and the formation of a product (3 h). Dilution with Et_2O and evaporation of the washed (saturated aqueous NaCl) organic solution afforded a crude product (0.030 g, 97% yield) consisting of an 85:15 mixture of β-*N*-glycosyl amine **40β** and the corresponding regioisomeric 3,4-dideoxy-3,4-di-(*N*-substituted-amino)-D-glucal derivative **32** (^{1}H NMR) (Table 3), which was subjected to flash chromatography. Elution with an 5:3:2 CH_2Cl_2/hexane/AcOEt mixture afforded pure *N-(benzyl)-[6-O-(benzyl)-2,3,4-trideoxy-4-(N-mesylamino)-β-D-erithro-hex-2-enopyranosyl]amine* (**40β**), pure as a liquid (0.019 g, 62% yield): R_f=0.23 (5:3:2 CH_2Cl_2/hexane/AcOEt); IR (neat) ν 3451, 3325, 1647, 1320, 1099 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.15–7.44 (m, 10H), 6.00 (dd, 1H, *J*=6.2, 0.8 Hz), 5.93 (dt, 1H, *J*=6.2, 1.5 Hz), 5.30 (s, 1H), 4.58 (d, 1H, *J*=11.9 Hz), 4.55 (d, 1H, *J*=11.9 Hz), 4.46–4.51 (m, 1H), 4.03–4.12 (m, 1H), 3.86 (s, 2H), 3.57–3.64 (m, 2H), 2.76 (s, 3H), 2.09–2.52 (br s, 2H). ^{13}C NMR ($CDCl_3$) δ 144.1, 140.1, 137.8, 130.5, 129.3, 128.6, 128.4, 128.0, 127.3, 127.2, 80.8, 73.7, 71.9, 71.4, 49.1, 46.5, 41.7. Anal. Calcd for $C_{21}H_{26}N_2O_4S$: C, 62.66; H, 6.51; N, 6.96. Found: C, 62.69; H, 6.16; N, 7.15.

Even if not recovered from the flash chromatography, the presence of the corresponding regioisomeric 3,4-dideoxy-3,4-di-(*N*-substituted-amino)-D-glucal derivative **32** as a reaction product, was firmly established by ^{1}H NMR examination of the crude reaction mixture: **32**, ^{1}H NMR δ 6.42 (dd, 1H, *J*=6.2, 1.4 Hz), 4.88 (dd, 1H, *J*=6.2, 2.5), 3.04 (s, 3H).

*6.4.2. Reaction of aziridine **3β** with $BnNH_2$ (protocol B).* Following the above described typical procedure, the treatment of a solution of *trans N,O*-dimesylate **15** (0.030 g, 0.077 mmol) in anhydrous benzene (1 mL) with *t*-BuOK (0.009 g, 0.080 mmol) in the presence of $BnNH_2$ (0.025 mL, 0.23 mmol, 3 equiv) afforded, after 3 h stirring at room temperature, a crude product (0.028 g, 89% yield) consisting of a 38:62 mixture of α-*N*-glycosyl amine **56α** and the corresponding regioisomeric 3,4-dideoxy-3,4-di-(*N*-substituted-amino)-D-gulal derivative **48**, which was subjected to flash chromatography. Elution with a 5:3:2 CH_2Cl_2/hexane/AcOEt mixture afforded *N-(benzyl)-[6-O-(benzyl)-2,3,4-trideoxy-4-(N-mesylamino)-α-D-threo-hex-2-enopyranosyl]amine* (**56α**), pure as a liquid (0.008 g, 25% yield): R_f=0.25 (5:3:2 CH_2Cl_2/hexane/AcOEt); IR ν (neat) 3487, 3302, 1645, 1319, 1104 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.20–7.41 (m, 10H), 5.92 (s, 2H), 5.36 (s, 1H), 4.63 (d, 1H, *J*=11.7 Hz), 4.54 (d, 1H, *J*=11.7 Hz), 4.54–4.62 (m, 1H), 3.91 (s, 2H), 3.57–3.74 (m, 2H), 3.77–3.85 (m, 1H), 2.75 (s, 3H), 2.01–2.09 (br s, 2H). ^{13}C NMR ($CDCl_3$) δ 145.6, 139.2, 138.4, 130.3, 129.7, 128.8, 128.1, 127.9, 127.4, 127.2, 82.7, 74.1, 72.3, 70.1, 48.2, 45.4, 41.9. Anal. Calcd for $C_{21}H_{26}N_2O_4S$: C, 62.66; H, 6.51; N, 6.96. Found: C, 62.27; H, 6.39; N, 6.57.

Even if not recovered from the flash chromatography, the presence of the corresponding regioisomeric 3,4-dideoxy-3,4-di-(*N*-substituted-amino)-D-gulal derivative **48** as a reaction product,

was firmly established by ^{1}H NMR examination of the crude reaction mixture: **48**, ^{1}H NMR δ 6.48 (d, 1H, J=6.3 Hz), 4.79 (dt, 1H, J=6.3, 1.8), 3.02 (s, 3H).

Acknowledgements

This work was supported by the Università di Pisa and MIUR (Ministero dell'Istruzione, della Università e della Ricerca), Roma. Professor Gloria Uccello-Barretta and Dr. Federica Balzano of the Dipartimento di Chimica e Chimica Industriale of the University of Pisa are gratefully acknowledged for NOE experiments. P.C. gratefully acknowledges Merck Research Laboratories for the generous financial support deriving from the 2005 ADP Chemistry Award.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2009.11.059.

References and notes

1. (a) Di Bussolo, V.; Caselli, M.; Romano, M. R.; Pineschi, M.; Crotti, P. *J. Org. Chem.* **2004**, *69*, 7383–7386; (b) Di Bussolo, V.; Caselli, M.; Romano, M. R.; Pineschi, M.; Crotti, P. *J. Org. Chem.* **2004**, *69*, 8702–8708; (c) Di Bussolo, V.; Favero, L.; Romano, M. R.; Pineschi, M.; Crotti, P. *Tetrahedron* **2008**, *64*, 8188–8201; (d) DiBussolo, V.; Romano, M. R.; Pineschi, M.; Crotti, P. *Org. Lett.* **2005**, *7*, 1299–1302; (e) Di Bussolo, V.; Favero, L.; Romano, M. R.; Pineschi, M.; Crotti, P. *J. Org. Chem.* **2006**, *71*, 1696–1699.
2. A theoretical conformational study carried out on epoxides **2α** and **2β** and simplified models structurally related to epoxides **1α** and **1β** and aziridines **3α**, and **3β** has indicated that epoxides **1α**[3] and **2α**[3] and aziridine **3α** (see Supplementary data) exist as an equilibrium mixture (about 65:35 in the case of **1α** and **2α** and almost 1:1 in the case of **3α**) of the corresponding conformers α′ and α″, whereas the corresponding diastereoisomeric epoxides **1β**[3] and **2β**[3] and aziridine **3β**[1e] exist as the corresponding single conformer β′ (Scheme 1). The unique conformer β′ has the side chain pseudoequatorial as conformer α″, whereas conformer α′ has the side chain pseudoaxial.
3. Crotti, P.; Di Bussolo, V.; Pomelli, C. S.; Favero, L. *Theor. Chem. Accounts* **2009**, *122*, 245–256.
4. *Protocol A* reaction conditions: the epoxide **1,2α,β** or the aziridine **3α,β** in the solvent-nucleophile (alcohol or amine). *Protocol B* reaction conditions: the epoxide **1,2α,β** or the aziridine **3α,β** in a non-nucleophilic solvent (anhydrous MeCN or benzene) is treated with the nucleophile (alcohol or amine, 3 equiv).[5]
5. Epoxides **1,2α,β** and aziridines **3α,β** are not stable and can be prepared only in situ by cyclization under basic conditions (*t*-BuOK) of the corresponding stable precursor [*trans* hydroxy mesylates **10**–**13** for the epoxides (Tables 1 and 2) and *trans N,O*-dimesylates **14**–**15** for the aziridines (Tables 3 and 4)] and made to react immediately with a nucleophile.[1]
6. The '*coordination product*' and '*non-coordination product*' nomenclature indicates addition products deriving from a nucleophile–substrate (epoxide or aziridine) coordination or non-coordination process, respectively.[1c]
7. The nucleophilic attack on C(1) from the same side as the substrate–nucleophile coordination (*route* ***a***, a *pseudoaxial* attack, in **1**–**3α** and *route* ***b***, a *pseudoequatorial* attack, in **1**–**3β**) is entropically favored with respect to a corresponding attack from the opposite side by a non-coordinated nucleophile (Scheme 1).
8. With simple alcohols (MeOH, EtOH, *i*-PrOH. *t*-BuOH), the reactions of epoxides **1,2α,β** and aziridines **3α,β** were repeated using the alcohol/nucleophile as the solvent (*protocol A* reaction conditions).[4] In these conditions, the addition reactions were still completely 1,4-regioselective, but not completely stereoselective and mixtures of the corresponding anomeric alkyl α-*O*- and β-*O*-glycosides were obtained with increasing amount of the corresponding *coordination product* on passing from MeOH to EtOH and *i*-PrOH. With the more sterically hindered and less nucleophilic *t*-BuOH, a completely regio- and stereoselective reaction toward the corresponding *coordination product* was observed.[1]
9. *Routes* ***c*** and ***d*** (Scheme 1) correspond to a preferred *trans* diaxial opening of the oxirane ring.
10. Corresponding *trans* 3,4-diols and 3-methoxy-4-hydroxy derivatives are obtained from epoxides **1,2α,β**,[1a–c] and corresponding 3-hydroxy- and 3-methoxy-4-*N*-mesylamino derivatives are obtained from aziridine **3β**[1e] by their reaction with $TBA^+Me_3SiO^-$ and TBAOMe, respectively.
11. Norris, P. *Curr. Top. Med. Chem.* **2008**, *8*, 101–113 and references therein.
12. (a) Zhang, G.; Shen, J.; Cheng, H.; Zhu, L.; Fang, L.; Luo, S.; Muller, M. T.; Lee, G. E.; Wei, L.; Du, Y.; Sun, D.; Wang, P. G. *J. Med. Chem.* **2005**, *48*, 2600–2611; (b) Ichikawa, Y.; Hirata, K.; Ohbayashi, M.; Isobe, M. *Chem.—Eur. J.* **2004**, *10*, 3241–3251; (c) Gallant, M.; Link, J. T.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 343–349; (d) Argoudelis, A. D.; Baczynskj, L.; Kuo, M. T.; Laborde, A. L.; Sebek, O. K.; Truesdell, S. E.; Shilliday, F. B. *J. Antibiot.* **1987**, *40*, 750–760; (e) Watanabe, K. A.; Fox, J. J. *Chem. Pharm. Bull.* **1973**, *21*, 2213–2216.
13. (a) Lu, Y.; Gervay-Hague, J. *Carbohydr. Res.* **2007**, *342*, 1636–1650; (b) Li, J.; Zheng, M.; Tang, W.; He, P.-L.; Zhu, W.; Li, T.; Zuo, J.-P.; Liu, H.; Jiang, H. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5009–5013; (c) Liu, K.-G.; Yan, S.; Wu, Y.-L.; Yao, Z.-J. *Org. Lett.* **2004**, *6*, 2269–2272; (d) Masuda, T.; Shibuya, S.; Arai, M.; Yoshida, S.; Tomozawa, T.; Ohno, A.; Yamashita, M.; Honda, T. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 669–673; (e) Sun, X.-L.; Sato, N.; Kai, T.; Furhuata, K. *Carbohydr. Res.* **2000**, *323*, 1–6.
14. When it was possible, the 1,2- and 1,4-*addition products* present in the aminolysis reaction mixtures of aziridines **3α** and **3β** were separated by flash chromatography. In other cases, these products, clearly present in the crude reaction mixtures (^{1}H NMR spectroscopy), could not be recovered pure from the chromatographic process due to their instability under the separation/purification conditions or because not separable under the chromatographic conditions used (flash chromatography or preparative TLC).
15. Ferrier, R. J.; Zubkov, O. A. In *Organic Reactions*; Overman, L. E., Ed.; John Wiley: Hoboken, NJ (USA), 2003; Vol. 62, pp 569–736; see, in particular, the '2,3-Unsaturated Glycosyl Azides and *N*-Glycosides' paragraph, pp 610–614.
16. The *anti*-1,2-*addition product*/*anti*-1,4-*addition product* ratio obtained after 10 s reaction time is identical to that observed after 30 min or 1 h (Tables 3 and 4). The only difference in the reaction after 10 s is that a consistent amount (70–75%) of the unreacted stable precursor of the aziridine, the *trans N,O*-dimesylate **14** (for **3α**) or **15** (for **3β**), is still present.
17. Some model reactions were repeated by using the corresponding *N*-(nosyl)-aziridines **3α**–**Ns** and **3β**–**Ns**[18] instead of *N*-(mesyl)-aziridines **3α** and **3β**. The regio- and stereoselectivity obtained in these reactions indicated that the behavior of *N*-(nosyl)-aziridines **3α**–**Ns** and **3β**–**Ns** is similar to that of *N*-(mesyl)-aziridines **3α** and **3β**. However, the use of aziridines **3α**–**Ns** and **3β**–**Ns** makes possible the removal of the nosyl residue from the addition product and the obtainment of the corresponding free amino group-containing product (see Supplementary data and Ref. 18).
18. Di Bussolo, V.; Romano, M. R.; Pineschi, M.; Crotti, P. *Tetrahedron* **2007**, *63*, 2482–2489.
19. A similar, appropriately modified, rationalization can be applied to aziridine 3α.
20. (a) Zhang, G.; Shen, J.; Cheng, H.; Zhu, L.; Fang, L.; Lou, S.; Mulle, M. T.; Lee, G. E.; Wei, L.; Du, Y.; Sun, D.; Wang, P. G. *J. Med. Chem.* **2008**, *48*, 2600–2611; (b) Somsák, L.; Felföldi, N.; Kónya, B.; Hüse, C.; Telepó, K.; Bokor, E.; Czifrák, K. *Carbohydr. Res.* **2008**, *343*, 2083–2093; (c) Das, T. M.; Rao, C. P.; Kolehmainen, E. *Carbohydr. Res.* **2001**, *334*, 261–269.