# Synthesis of 6-deoxy-*N*-Cbz-D,L-iminoglycal-derived vinyl epoxides and examination of their regio- and stereoselectivity in nucleophilic addition reactions

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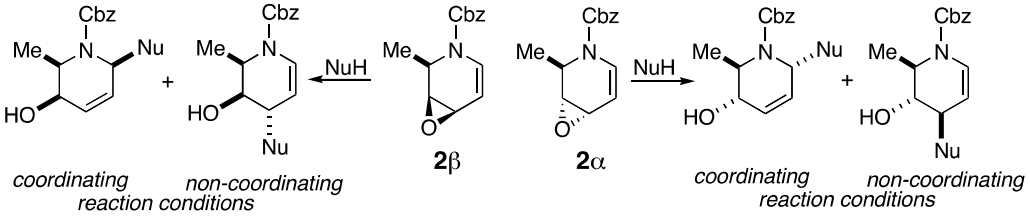

# Synthesis of 6-deoxy-*N*-Cbz-D,L-iminoglycal-derived vinyl epoxides and examination of their regio- and stereoselectivity in nucleophilic addition reactions

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**Abstract:** The regio- and stereoselectivity of the addition reactions of *O*-, *C*-, *N*- and *S*-nucleophiles to 6-deoxy-D,L-iminoallal- and - D,L-iminogalactal-derived epoxides **2α** and **2β** was examined. Results indicated that the *1,4- /1,2-regioselectivity* ratio and the related *syn-1,4-/anti-1,2-stereoselectivity* is closely and directly dependent on the ability of the nucleophile to coordinate with the oxirane oxygen and the configuration of the epoxide. A formal synthesis of a 1,6-dideoxy-piperidine azasugar is also described.

*Keywords: azasugars, vinyl epoxides, stereoselectivity, glycosylation*

## 1. Introduction

Azasugars, the nitrogen analogues of "true" sugars, represent an interesting class of carbohydrate mimics for their ability to inhibit glycosidases and glycosyltransferases with important therapeutic applications in the treatment of a variety of diseases including viral infections, lysosomal storage disorders, cancer and diabetes.[1]

*N*-Cbz Iminoglycal-derived vinyl epoxides **1α** and **1β** were recently prepared and examined in nucleophilic addition reactions as a possible new synthetic tool to azasugars derivatives. Epoxides **1α** and **1β** turned out to be excellent "glycosyl donors", able to glycosylate alcohols in a completely regio- and stereoselective fashion. Actually, the configuration of the alkyl α-*O*- or β-*O*-glycosides (*1,4-addition product*), in each case obtained as the only reaction product, always corresponds to that of the starting epoxide.[2] The complete 1,4-regio- and *syn*-stereoselectivity observed was rationalized by a coordination between the oxirane oxygen and the nucleophile (alcohol) in the form of a hydrogen

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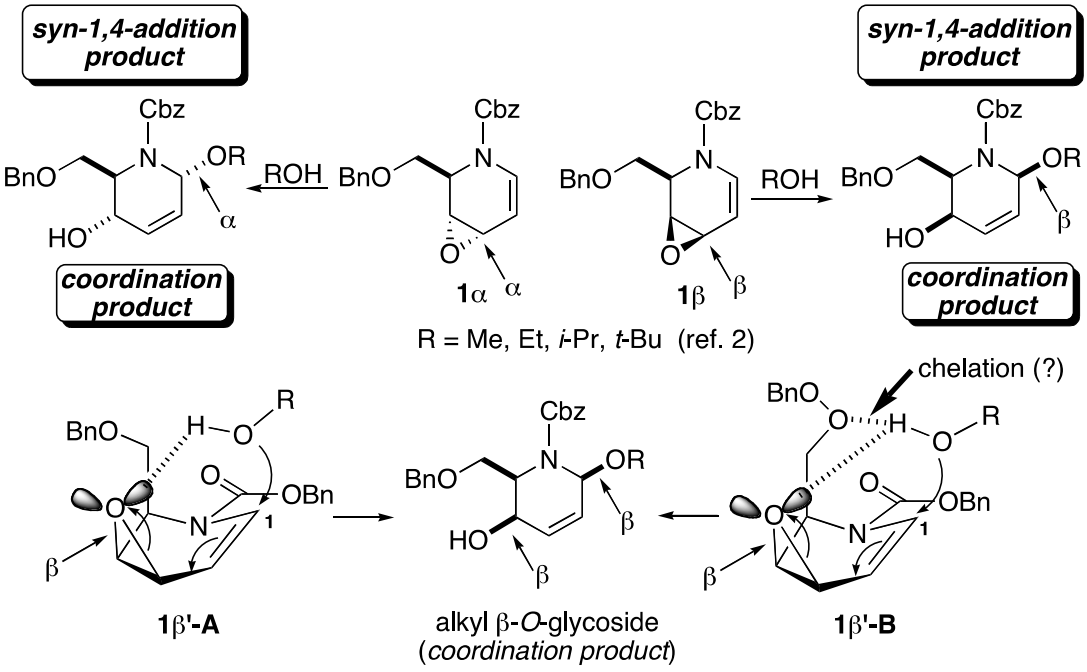
bond, as shown in Scheme 1, for simplicity, only for epoxide **1β** (structure **1β'-A**). Subsequent, entropically favored attack of the coordinated nucleophile on C(1) from the same side, leads to the corresponding *syn-1,4-addition products* (also, significantly named by us *coordination products*).[3]

**Scheme 1**

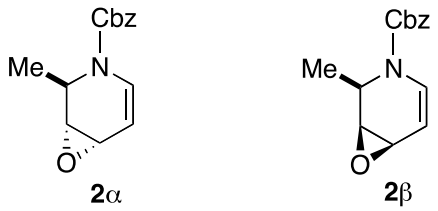



Even if shown not to be influential in other glycal-derived vinyl oxirane systems,[4] the additional chelating ability of the *O*-functionalized side chain (-$CH_2OBn$), reasonably possible in epoxide **1β** as shown in structure **1β'-B** (Scheme 1), cannot be disregarded, particularly considering that epoxide **1β** exists only in the corresponding conformer **1β'** with the side chain axial.[2]

In order to verify the occurrence of such a synergic coordinating effect of the 6-OBn group, vinyl epoxide **2β**, the 6-deoxy analog of **1β**, was synthesized. As our interest in this study derived also from the consideration that the 6-deoxy feature is present in many azasugar-related biologically active compounds,[1b] the diastereoisomeric vinyl epoxide **2α** was prepared, too (Fig. 1). Subsequently, the regio- and stereoselective behavior of both **2α** and **2β**, was examined in nucleophilic addition reactions, primarily with alcohols (*O*-nucleophiles) and then with model *C*-, *N*-, and *S*-nucleophiles. Our aim was to find reaction conditions for the synthesis of corresponding *1,2*- and *1,4-addition products* with,

possibly, high to complete regio- and stereoselectivity, as a new route to differently substituted compounds closely related to 6-deoxy-azasugars.

**Figure 1**

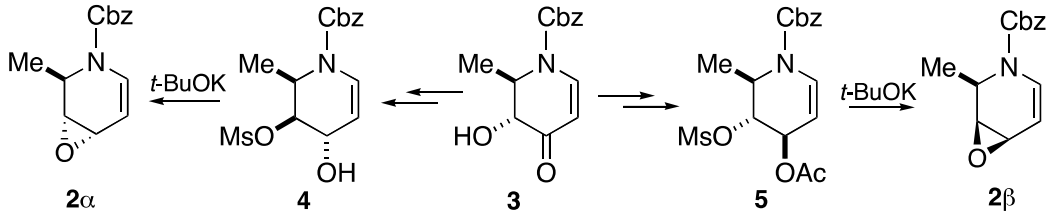



## 2. Results and discussion

### 2.1 Synthesis of epoxides 2α and 2β

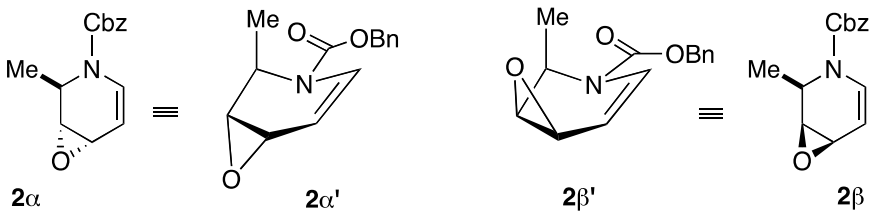
The synthesis of *trans* hydroxy mesylate **4** and *trans* acetoxy mesylate **5**, the stable precursors of 6-deoxy-D,L-iminoallal- **2α** and -D,L-iminogalactal-derived vinyl epoxide **2β**, respectively,[5] has been recently reported,[6] starting from hydroxy ketone **3**,[7] as the common synthetic intermediate (Scheme 2).

**Scheme 2**




As expected, theoretical conformational calculations carried out on the corresponding simplified structures indicated that epoxides **2α** and **2β** exist as the only conformer **2α'** and **2β'**, respectively, with the methyl group axial (Scheme 3).[2]

**Scheme 3**

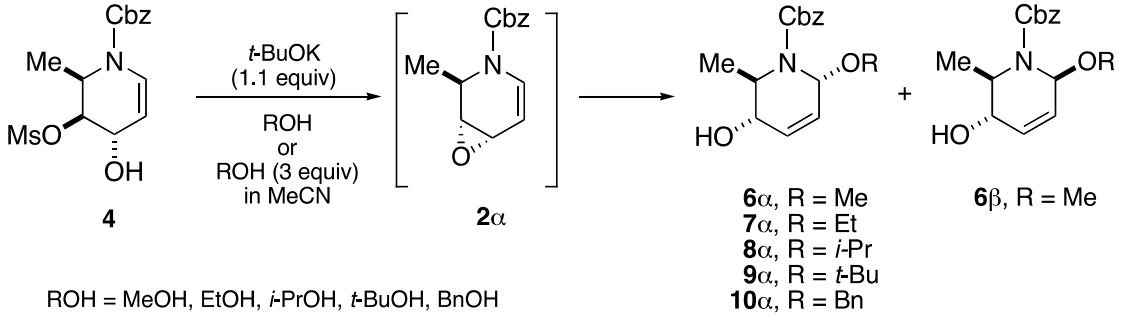



### 2.2. Addition reactions of epoxides 2α and 2β with *O*-, *C*-, *N*-, and *S*-nucleophiles

#### 2.2.1. *O*-Nucleophiles

In spite of the presence of a large amount of nucleophilic molecules, all the reactions of epoxides **2α** and **2β** with simple low-boiling alcohols (MeOH, EtOH, *i*-PrOH, *t*-BuOH and allyl alcohol) under *protocol A* reaction conditions,[8] turned out to be completely 1,4 regio- and *syn*-stereoselective, with the exclusive formation of the corresponding *coordination products* (Tables 1 and 2). The only exception was, in the case of epoxide **2α**, the methanolysis reaction, which afforded an 85:15 mixture of the corresponding anomeric methyl *O*-glycosides **6α** and **6β**. The repetition of the same reaction under *protocol B* reaction conditions[8] led to a completely *syn*-stereoselective result, with the formation of the methyl α-glycoside **6α** as the only addition product (entry 2, Table 1).

**Table 1.** Regio- and stereoselectivity of the addition reactions of *O*-nucleophiles to the *in situ*-formed vinyl epoxide **2α** (*protocol A* and *B*).




| Entry | ROH | Protocol[a] | *1,4-addition product* | yield % |
|---|---|---|---|---|
| 1 | MeOH[b] | *A* | **6α/6β** (85:15) | 79[c] |
| 2 | MeOH[b] | *B* | **6α** (>99%)[d] | 86[c] |
| 3 | EtOH | *A* | **7α** (>99%) | 85[c] |

| | | | | |
|---|---|---|---|---|
| 4 | *i*-PrOH | *A* | **8α** (>99%) | 65[c] |
| 5 | *t*-BuOH | *A* | **9α** (>99%) | 68[c] |
| 6 | BnOH | *B* | **10α** (>99%) | 61[e] |

[a] *A = protocol A*: ROH as the solvent-nucleophile; *B = protocol B*: ROH (3 equiv) in MeCN.[8]

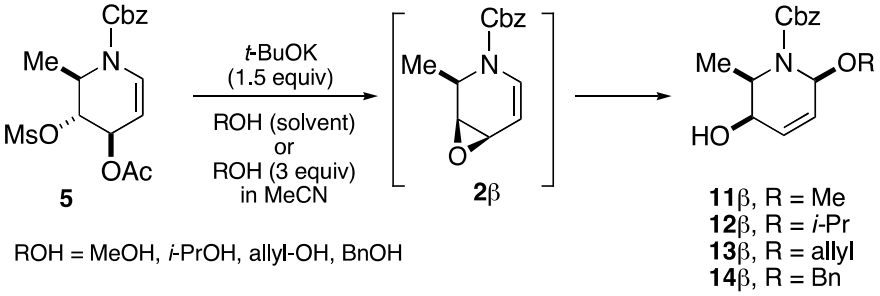
[b] The cyclization of *trans* hydroxy mesylate **4** was performed with MeONa (1.1 equiv).

[c] Crude product.

[d] Methyl α-*O*-glycoside **6α** can be isomerized to methyl β-*O*-glycoside **6β** by treatment with $10^{-5}$ N $H_2SO_4$ in MeOH solution for 60 h at room temperature.

[e] Purified product (preparative TLC).

**Table 2.** Regio- and stereoselectivity of the addition reactions of *O*-nucleophiles to the *in situ*-formed vinyl epoxide **2β** (*protocol A* and *B)*.




| Entry | ROH | Protocol[a] | *1,4-addition product* | yield % |
|---|---|---|---|---|
| 1 | MeOH[b] | *A* | **11β** (>99%) | 76[c] |
| 2 | *i*-PrOH | *A* | **12β** (>99%) | 93[c] |
| 3 | Allyl-OH | *A* | **13β** (>99%) | 66[d] |
| 4 | BnOH | *B* | **14β** (>99%) | 57[d] |

[a] *A = protocol A*: ROH as the solvent-nucleophile; *B = protocol B*: ROH (3 equiv) in MeCN.[8]

[b] The cyclization of *trans* mesyloxy acetate **5** was performed with MeONa (1.1 equiv).

[c] Crude product.

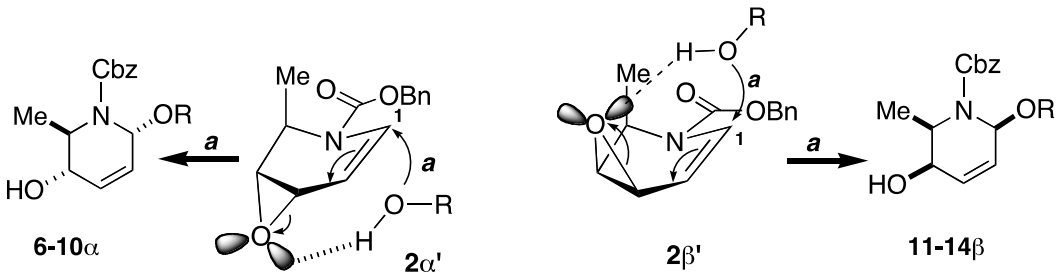
[d] Purified product (flash chromatography or preparative TLC).

*Protocol B* reaction conditions (Tables 1 and 2) were necessarily used in the reaction of epoxides **2α** and **2β** with benzyl alcohol, taken as an example of an *O*-nucleophile for which *protocol A* reaction

conditions were clearly not feasible. In both cases, the corresponding *coordination product*, benzyl α-*O*-glycoside **10α**, from **2α**, and benzyl β-*O*-glycoside **14β**, from **2β**, were the only reaction products.

The results obtained in the glycosylation of alcohols clearly indicated that the regio- and stereochemical behavior of 6-deoxy epoxides **2α** and **2β** is similar to that previously observed with the 6-OBn substituted epoxides **1α** and **1β**. This would indicate that the complete 1,4-regio- and *syn*-stereoselectivity (*route **a***, Scheme 4) found in these imino glycal-derived vinyl oxirane systems is independent of the presence of an *O*-functionality in the C(5)-side chain: it depends only on the configuration of the starting epoxide and the occurrence of a coordination (hydrogen bonding) between the nucleophile and the oxirane oxygen, in an uncatalyzed, directly *substrate-dependent*, glycosylation process.

**Scheme 4**




R = Me, Et, *i*-Pr, *t*-Bu, allyl, Bn

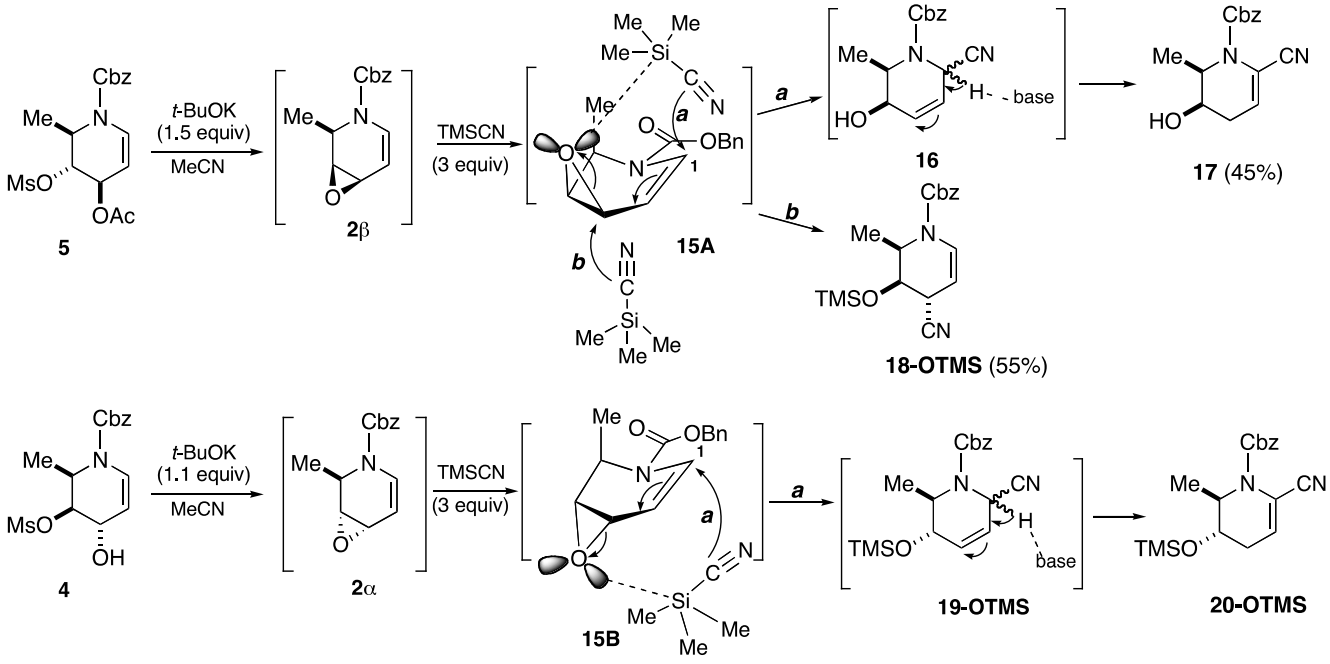
### 2.2.2. *C*-Nucleophiles

The reaction of epoxides **2α** and **2β** with organolithium compounds (BuLi, PhLi), Grignard reagents (MeMgBr), cuprates ($Me_2CuLi$) and aluminum trialkyls ($Me_3Al$) led only to complex reaction mixtures, in which no corresponding *1,2*- and/or *1,4-addition products* could be detected ($^1$H NMR spectroscopy).[9] Better results were obtained with less reactive *C*-nucleophiles, such as $CN^-$ species (from TMSCN) and metal enolates from dimethyl malonate.

The reaction of epoxide **2β** with TMSCN (3 equiv) led to a 45:55 mixture of two regioisomeric unsaturated cyano derivatives, the 4-hydroxy-1-cyano- **17** and 4-*O*-TMS-protected-3-cyano-imino glycal **18-OTMS**. Under the same reaction conditions, the diastereoisomeric epoxide **2α** led only to the corresponding unsaturated 1-cyano-4-OTMS derivative **20-OTMS** (Scheme 5).

The *trans O*-TMS-cyano derivative **18-OTMS** is a typical *anti-1,2-additon product* (a *non-coordination product* and primary reaction product), formed by direct nucleophilic attack of $CN^-$ at the C(3) allyl oxirane carbon of epoxide **2β** (*route **b*** in **15A**, Scheme 5). On the contrary, unsaturated-1-cyano derivatives **17** and **20-OTMS** are the result of a base-promoted double bond isomerization of the corresponding primary reaction product, the 2,3-unsaturated glycosyl cyanide **16** and **19-OTMS** obtained from **2β** and **2α**, respectively, through corresponding *route **a*** in **15A** and **15B**, as shown in Scheme 5. This indicates for the reagent (TMSCN) a high (in **2β**) and complete 1,4-regioselectivity (in **2α**), but unfortunately, the presence of the unsaturation does not allow the determination of the configuration of the initially formed glycosyl cyanides **16** and **19-OTMS**.[10]

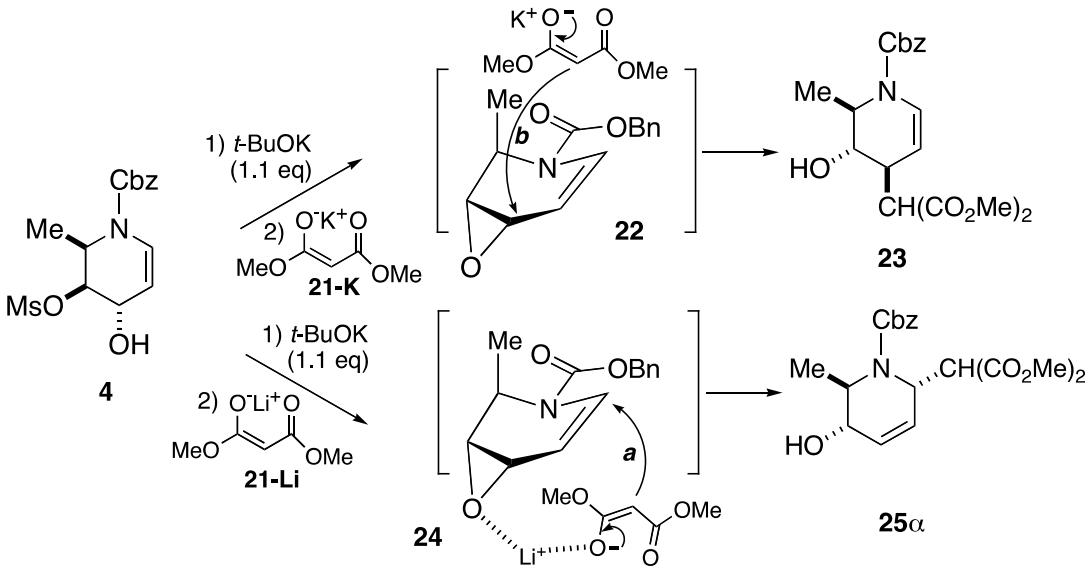
**Scheme 5**




Epoxide **2α** gave an interesting result with metal enolates of dimethyl malonate. The reaction of epoxide **2α** with the potassium enolate of dimethyl malonate (**21-K**, from dimethyl malonate and *t*-BuOK) turned out to be completely regioselective, with the exclusive formation of the corresponding *anti-1,2-addition product*, the *trans* hydroxy-dimethoxycarbonylmethyl derivative **23** (*non-coordination product*) (Scheme 6). Evidently in these conditions, no epoxide-nucleophile coordination through the $K^+$ counterion occurs and the free, non-coordinated nucleophile can attack exclusively the

allyl C(3) carbon of the epoxide reacting in the only existing conformer **2α'** (Scheme 3) through a favoured *trans* diaxial pathway, as shown in **22** (*route **b***, Scheme 6).

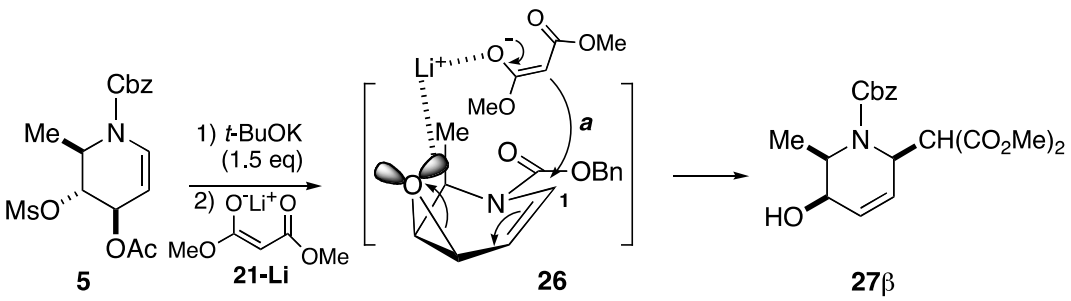
**Scheme 6**




The regioselectivity changed drastically when the corresponding lithium enolate **21-Li** (from dimethyl malonate and *t*-BuOLi) was used (Scheme 6). In these modified conditions, the reaction turned out to be completely 1,4-regio- and *syn*-stereoselective, with exclusive formation of the corresponding *coordination product*, α-*C*-glycoside **25α**. In our opinion, this result derives from an efficient coordination of the nucleophile with the oxirane oxygen through $Li^+$ which develops on the α-face of the oxirane system, followed by attack of the coordinated nucleophile on C(1) with complete facial selectivity, as shown in **24** (*route **a***, Scheme 6).[11]

When the same protocol, based on potassium enolate **21-K**, was applied to the diastereoisomeric epoxide **2β**, a complex reaction mixture was obtained. On the contrary, the reaction of epoxide **2β** with lithium enolate **21-Li** turned out to be completely 1,4-regio- and *syn*-stereoselective, leading to the exclusive formation of β-*C*-glycoside **27β**, the corresponding *coordination product*. Also in this case, an efficient oxirane oxygen-nucleophile coordination, through the metal ion, is considered to be responsible for the directly *substrate-dependent* selectivity observed (structure **26**, *route **a***, Scheme 7).

**Scheme 7**

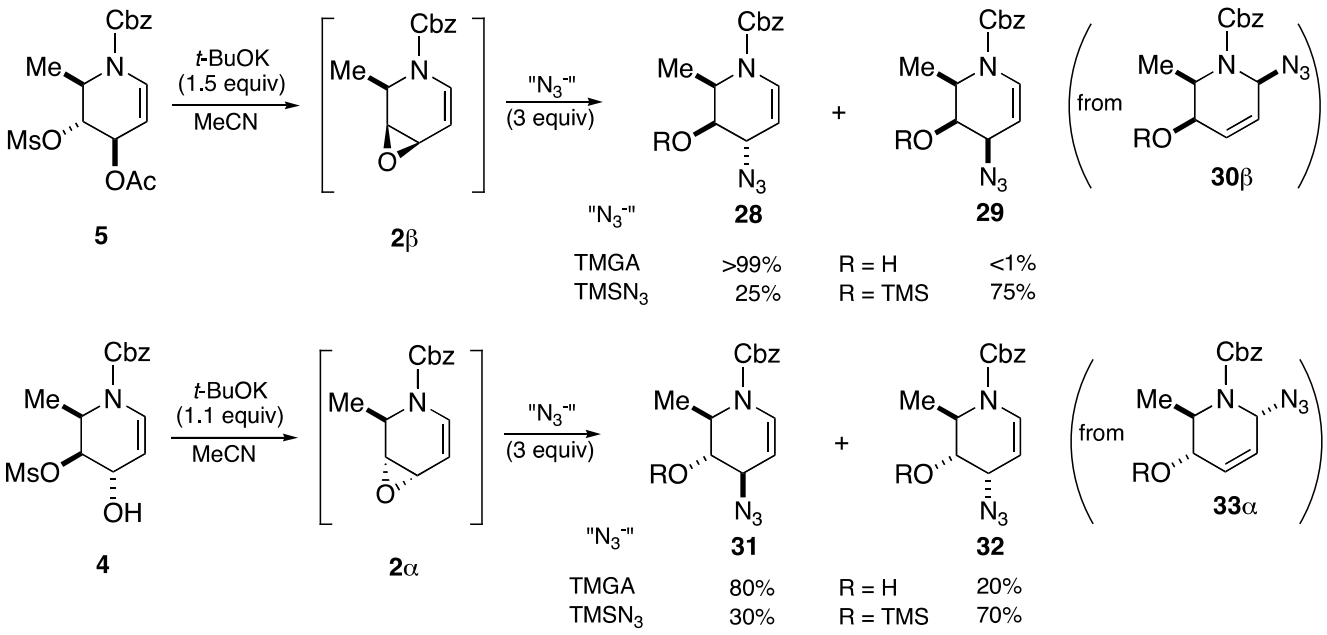



### 2.2.3. *N*-Nucleophiles

The azide ion was taken as a *N*-nucleophile model and two organic solvent-soluble sources of this ion were used, tetramethylguanidinazide (TMGA: $Me_4N_2C{=}NH_2^+N_3^-$) and trimethylsilylazide ($TMSN_3$).

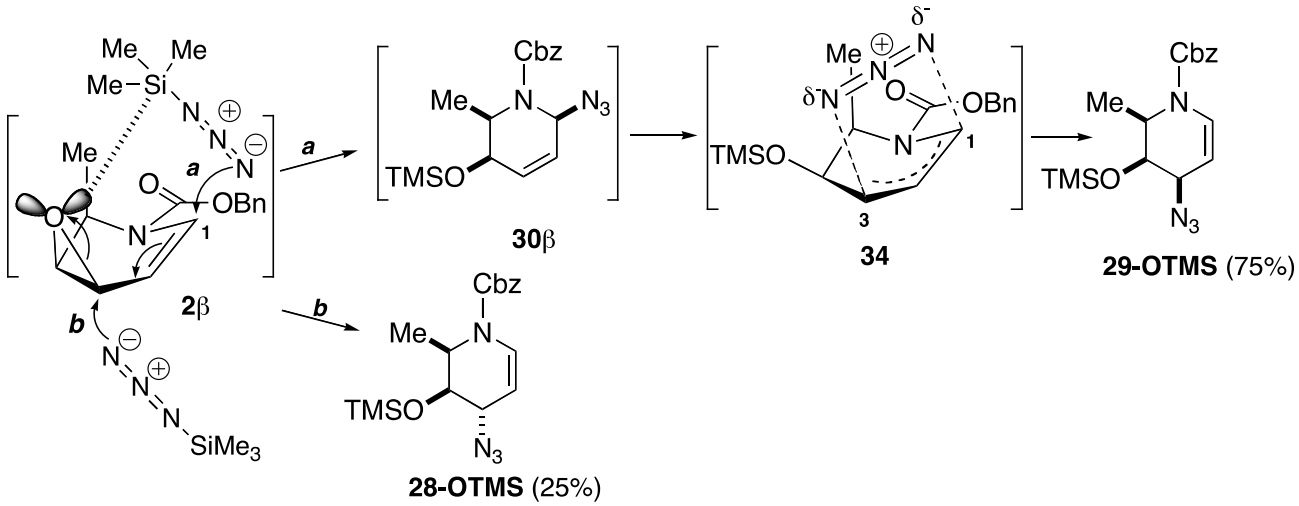
Apart from the reaction of epoxide **2β** with TMGA, which is completely 1,2-regio- and *anti*-stereoselective, with the exclusive formation of *trans* azido alcohol **28**[6] (*non-coordination product*), all the other reactions led to mixtures of the corresponding *anti*- and *syn-1,2-addition products*, the *O*-TMS-protected *trans*- **28-OTMS** and *cis*-azido alcohol **29-OTMS** from **2β** ($TMSN_3$), the *trans*-**31**[6] and *cis*-azido alcohol **32** (TMGA) and the *O*-TMS-protected *trans*- **31-OTMS** and *cis*-azido alcohol **32-OTMS** ($TMSN_3$) from **2α** (Scheme 8).[12]

**Scheme 8**




On the basis of previously obtained evidence from similar systems,[4] *O*-TMS-protected *cis* azido alcohols **29** and **32** cannot be considered to be primary reaction products, as the *trans* diastereoisomers **28** and **31** are the result of a suprafacial [3,3] sigmatropic rearrangement of the azido group [from C(1) to C(3)] by the corresponding glycosyl azide **30β** and **33α** (the actual primary and *coordination product*s) as summarized in Scheme 8 for both epoxides **2α** and **2β**, and thoroughly shown, for simplicity only for epoxide **2β**, in Scheme 9 (*route **a***) by means of transition structure **34**.

**Scheme 9**



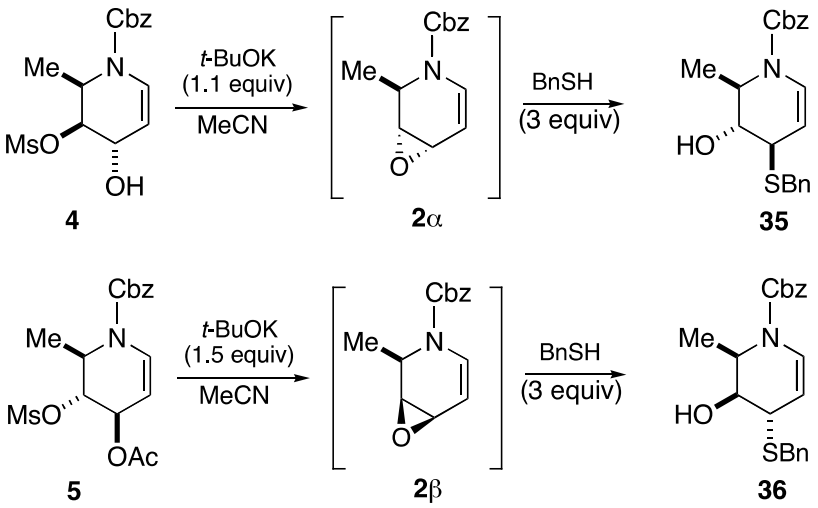
In this framework, results indicate that the behavior of epoxides **2α** and **2β** in these azidolysis conditions is substantially similar and the regio- and stereoselectivity observed is strictly dependent on the different coordinating ability of the two reagents ($TMSN_3$ and TMGA). With the less coordinating TMGA,[4,12] the reactions are, as expected, largely or completely 1,2-regio- and anti-stereoselective.[13] On the contrary, with the more coordinating $TMSN_3$, larger amounts of corresponding *coordination products*, the α- **33α** (from **2α**) and β-glycosyl azide **30β** (from **2β**), are reasonably formed, even if, unfortunately, only as intermediate, not separable, structures which rapidly isomerizes to the corresponding *O*-TMS-protected *cis*-1,2-azido alcohol **32-OTMS** and **29-OTMS**, the actual reaction products.

### 2.2.4. *S*-Nucleophiles

Thiols, like the aromatic thiophenol (PhSH) and the aliphatic benzylmercaptan (BnSH), were taken as typical *S*-nucleophiles and their addition reactions to epoxides **2α** and **2β** were examined only under *protocol B* reaction conditions.

The addition reactions of BnSH to epoxides **2α** and **2β** are completely 1,2-regio- and *anti*-stereoselective, leading to the exclusive formation of the corresponding *trans* hydroxy benzylthio derivatives **35**, from **2α**, and **36**, from **2β** (Scheme 10).

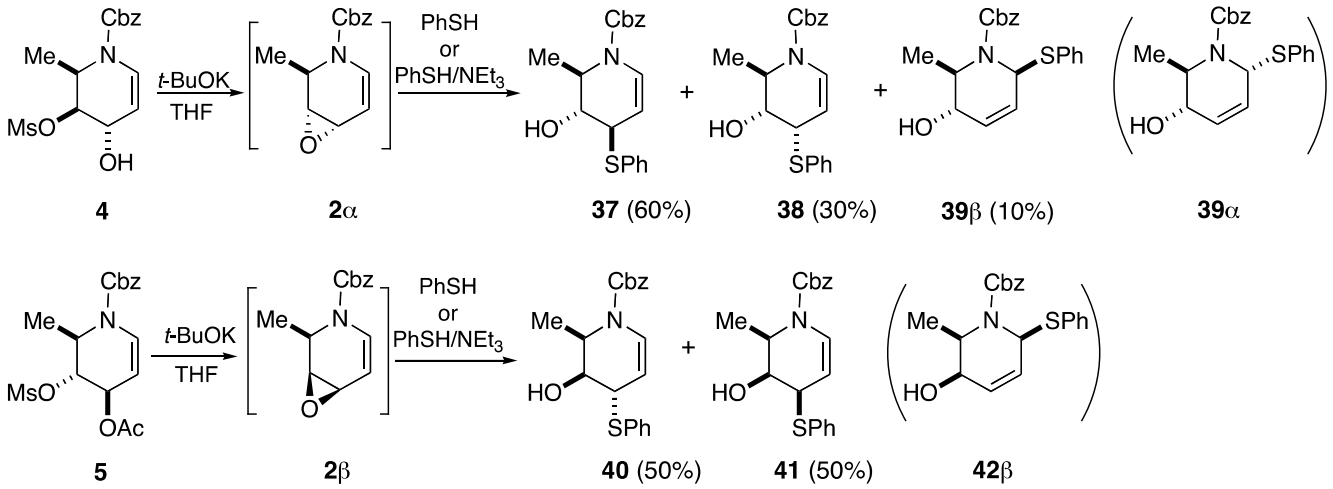
**Scheme 10**




Even if somewhat expected, it is interesting to note how the behavior of epoxides **2α** and **2β** with BnSH (only corresponding *non-coordination products* are obtained) is the opposite of the behavior of the same epoxides with the structurally related benzyl alcohol (only corresponding *coordination products* are obtained, entries 6 and 4,Tables 1 and 2, respectively). Evidently, the absence or decidedly scarce coordinating ability of BnSH with the oxirane oxygen of the epoxides, combined with the higher nucleophilicity of the thiol, prevents the coordinated 1,4-addition process admitted for alcohols (Scheme 4) and makes the direct nucleophilic attack on the oxirane allyl C(3) carbon, the only reaction pathway possible.

When PhSH is used under the same reaction conditions (PhSH, 3 equiv, also in the presence of $NEt_3$, 3 equiv), mixtures of corresponding *anti-1,2-* and *syn-1,2-addition products*, the *trans*- **37** (60%) and the *cis*-hydroxy phenylthio derivative **38** (30%) from epoxide **2α**, and the *trans*- **40** (50%) and *cis*-hydroxy phenylthio derivative **41** (50%) from epoxide **2β**, are obtained (Scheme 11). In the case of epoxide **2α**, a certain amount (10%) of β-phenylthio glycoside **39β** is obtained, too.

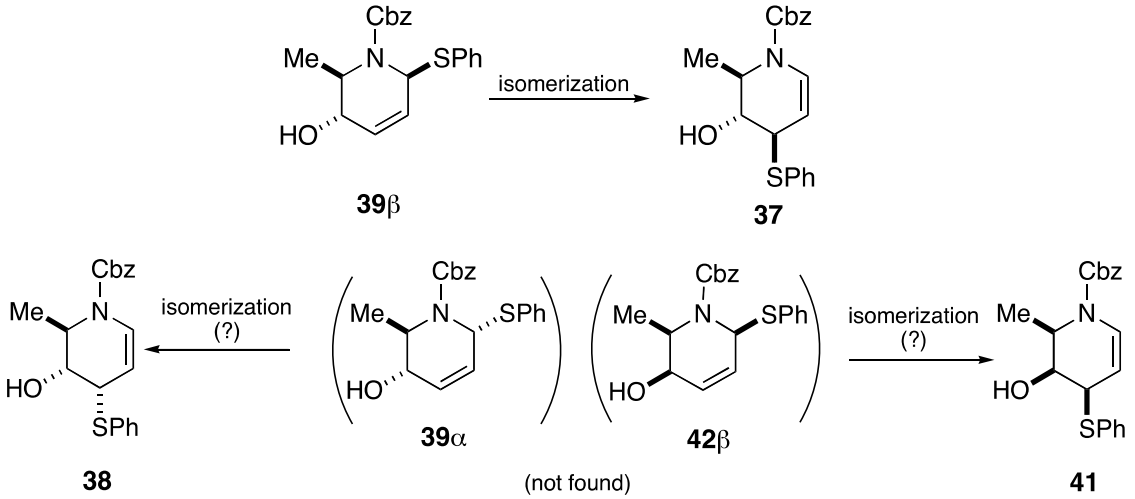
**Scheme 11**




The formation of *anti-1,2-addition products* **37** and **40** (*non-coordination products*) is consistent with the reaction conditions used (slightly basic conditions due to the presence of $Et_3N$ and/or a possible small excess of *t*-BuOK, necessary for the cyclization of the epoxide precursor, Scheme 11). At the same time, this protocol is not compatible, in our opinion, with the formation of the corresponding diastereoisomeric *syn-1,2-addition products* **38** and **41** for which an oxirane ring opening with retention of configuration, a process which reasonably needs acid- or LA-catalyzed reaction conditions, should be necessary.[14]

Actually, the β-phenylthio glycoside **39β**, obtained from the reaction of epoxide **2α,** turned out to be unstable and slowly isomerizes, in a completely regio- and stereoselective fashion, to the corresponding *trans* hydroxy phenylthio derivative **37** (*anti-1,2-addition product*) with complete retention of the initial β configuration (Scheme 12).

**Scheme 12**

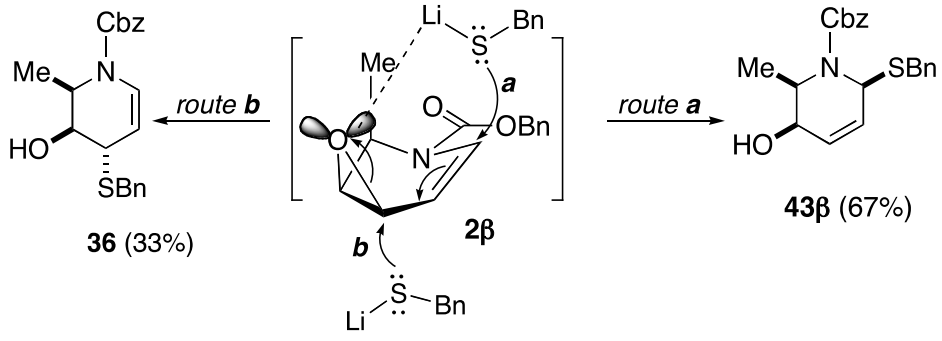


This observation makes it reasonable to think that *cis* hydroxy phenylthio derivatives **38** and **41** (*syn-1,2-addition product*) could be formed by a fast and complete isomerization of the corresponding α-phenylthio glycosides **39α** and **42β** (having the same configuration as the starting epoxide **2α** and **2β**, respectively), the primary reaction products, which, for this reason, cannot be found in the crude reaction mixture (Scheme 12).[15] If this is the case, the *syn-1,2-addition products* **38** and **41** may be reasonably considered as *coordination products*.

Different reaction conditions which could lead to a direct or indirect increased amount of *coordination products* were tried. For this purpose, the addition reactions of BnSH and PhSH to epoxides **2α** and **2β** were repeated by using the corresponding lithium salt, as the nucleophile (BnSLi and PhSLi, prepared *in situ* from equal amounts of BnSH (or PhSH) and *t*-BuLi (3 equiv).

Under these modified reaction conditions, the best result was obtained in the reaction of epoxide **2β** with BnSLi where a 1:2 mixture of the *trans* hydroxy benzylthio derivative **36** (*non-coordination product*) and the corresponding β-benzylthio glycoside **43β** (*coordination product*) was obtained (Scheme 13). This result, decidedly different from the complete *anti*-1,2-regioselectivity observed in the corresponding reaction carried out with the related thiol, BnSH (Scheme 10), and in particular the formation of β-thioglycoside **43β**, is reasonably due to the occurrence of an effective epoxide-nucleophile coordination through the metal ion, which, as usual, is able to modify the regio- and stereoselectivity of the addition reaction towards the corresponding *coordination product* (*route **a***, Scheme 13).

**Scheme 13**




**36** (33%)

**43β** (67%)

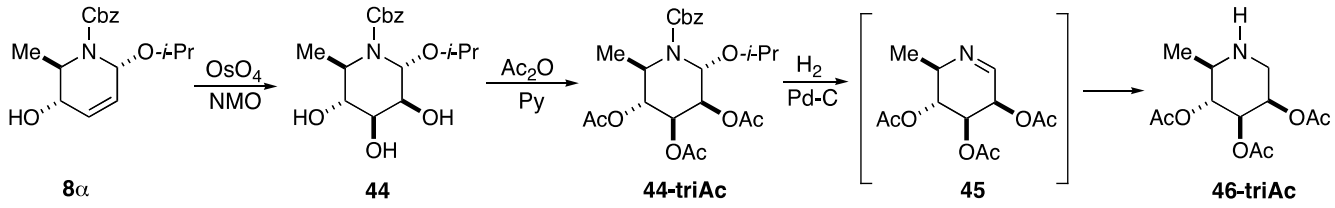
The corresponding reactions of epoxide **2β** with PhSLi and of epoxide **2α** with PhSLi and BnSLi were less satisfactory and did not lead to better results than those previously obtained in the reactions carried out with the corresponding thiols.

### 3. Formal synthesis of the piperidine 1,6-dideoxy-2,3,4-tri-*O*-acetyl-azasugar 46-triAc

*i*-Propyl *O*-glycoside **8α**, taken as an appropriate model, was used for the development of a formal protocol leading to the piperidine azasugar **46**, as shown in Scheme 14.

Catalytic dihydroxylation of *i*-propyl *O*-glycoside **8α** by $OsO_4$/NMO protocol, afforded, in a completely β-stereoselective way, the *i*-propyl *N*-Cbz-α-iminomannopyranoside **44**. The complete β-facial selectivity observed in this reaction is due to the steric hindrance, present on the α-face of **8α** by the two allyl substituents on C(1) and C(4), which directs the electrophilic attack on the opposite β-face, with the formation of **44**, as the only reaction product (*vide infra*) (Scheme 14).

**Scheme 14**



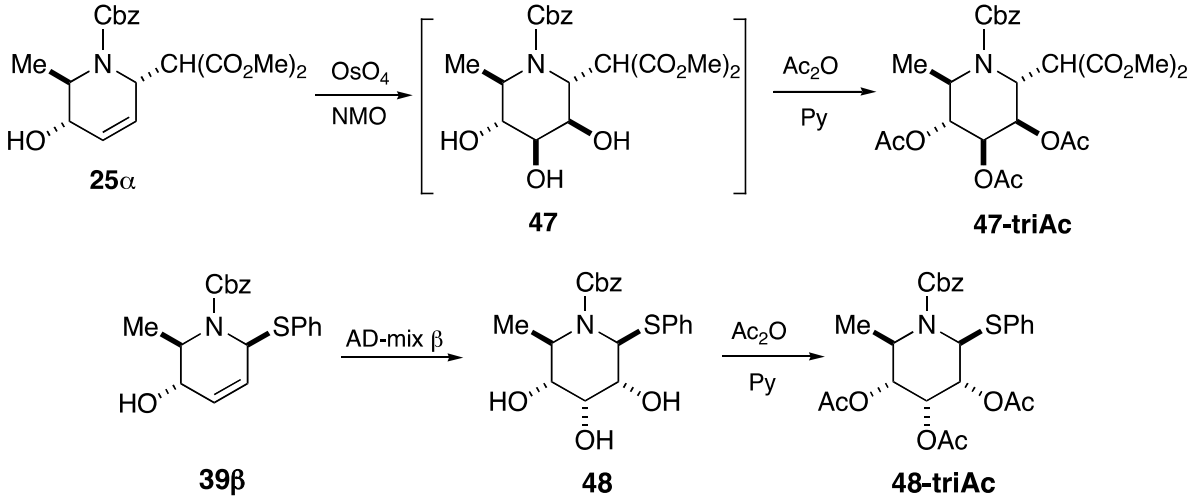

Iminopyranoside **44** was not isolated, but directly transformed ($Ac_2O$/Py) into the less polar triacetyl derivative in order to make the purification by flash chromatography possible. The subsequent catalytic hydrogenolysis of **44-triAc** ($H_2$-10% Pd/C)[16] deprotected the urethane nitrogen, followed by spontaneous elimination of the α-alkoxy group and the formation of intermediate endocyclic imine **45**, which, under the hydrogenating reaction conditions, is reduced to the desired piperidine 1,6-dideoxy-2,3,4-tri-*O*-acetyl-azasugar **46-triAc** (Scheme 14).[17]

### 4. Structures and configurations

The regioisomeric *1,2-* and *1,4-addition product* structure and exact configuration at C(1) or C(3), respectively, of the products obtained in the opening reactions of epoxides **2α** and **2β** were

simply determined by means of $^1$H NMR COSY and NOESY experiments. Only in the case of *C*-glycoside **25α** and *S*-glycoside **39β**, the determination of the anomeric carbon configuration was possible only on the corresponding piperidine-derived triacetate **47-triAc** and **48-triAc**, respectively. In fact, functionalization of the double bond in **25α** and **39β** changes the conformational rigidity towards the half-chair conformer with the methyl group axial, typical of these 2,3-unsaturated systems, into a cyclohexane-type chair conformer, making the configurational determination easier. Triacetates **47-triAc** and **48-triAc** were prepared by acetylation of the corresponding triol **47** and **48**, on their own obtained by catalytic dihydroxylation of **25α** and **39β** by $OsO_4$/NMO and AD-mix β/$MeSO_2NH_2$ protocol,[18] respectively. The complete β- and α-facial selectivity found in the dihydroxylation of α-*C*-glycoside **25α** and β-*S*-glycoside **39β**, respectively, appeared to be strictly dependent on the configuration of the anomeric C(1) carbon: in both cases, the electrophilic addition occurs on the double bond face opposite to the direction of the bulky C(1) substituent (Scheme 15).

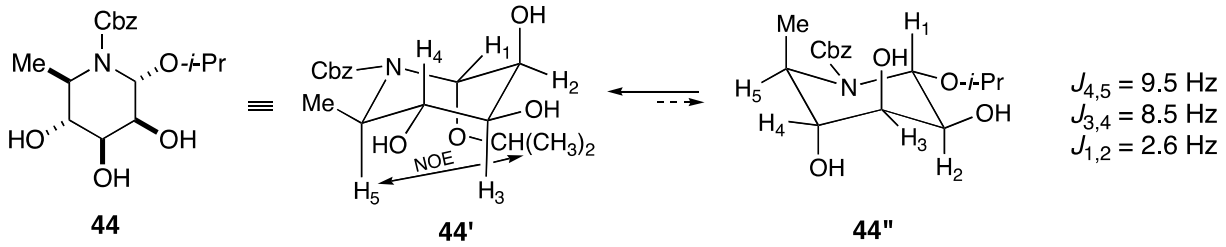
**Scheme 15**




The presence in the piperidine derivative **44** (Scheme 14) of a large H(4)-H(5) coupling constant value ($J_{4,5}$ = 9.5 Hz) indicates the existence of this compound preferentially in the corresponding chair conformer **44'** with the methyl group equatorial (Scheme 16). In such a conformer, the contemporary presence of a large H(3)-H(4) ($J_{3,4}$ = 8.5 Hz) and a small H(1)-H(2) coupling costant value ($J_{1,2}$ = 2.6 Hz) clearly indicates that a complete β-facial selectivity has occurred in the dihydroxylation of α-*O*-glycoside **8α** (Scheme 14). Moreover, the presence of NOE between H(5) and *i*-propyl –CH and

methyl groups is indicative of this group axial and gives further confirmation of the α-*O*-glycoside structure of the starting glycoside **8α** (Schemes 14 and 16).

**Scheme 16**




## 5. Conclusions

The results obtained in the addition reaction of alcohols to 6-deoxy-*N*-Cbz-iminoglycal-derived vinyl epoxides **2α** and **2β** have indicated that the observed complete 1,4-regio- and *syn*-stereoselectivity exclusively depends on the configuration of the epoxide and coordination of the nucleophile with the oxirane oxygen in a direct *substrate-dependent* glycosylation process. In one case, the obtained alkyl 6-deoxy-2,3-unsaturated-*O*-glycoside has been used in a formal synthesis of a 1,6-dideoxy-piperidine azasugars. The reactions of epoxides **2α** and **2β** with further nucleophiles such as *C*- (malonic ester-derived metal enolates), *N*- (TMGA and $TMSN_3$) and *S*-nucleophiles (BnSH and PhSH) have confirmed the great tendency of these epoxides toward high to complete 1,4-regioselectivity with associated *syn*-stereoselectivity (*coordination products*) when the nucleophile is able to coordinate the oxirane oxygen through a metal or by a hydrogen bond. On the contrary, the use of corresponding nucleophiles devoid of any coordinating ability leads to a complete or almost complete 1,2-regio- and *anti*-stereoselectivity (*non-coordination products*), in a nice regioalternating process. In this framework, the coordinating ability of $TMSN_3$, associated with the migratory aptitude of the azido group, is responsible for the unique formation of the corresponding *syn-1,2-addition product*.

## 6. Experimental

### 6.1. General

All reactions were performed in a flame-dried modified Schlenk (Kjeldahl shape) flask fitted with a glass stopper or rubber septum under a positive pressure of argon. Flash column chromatography was performed employing 230-400 mesh silica gel (Macherey-Nagel). Analytical TLC were performed on Alugram SIL G/$UV_{254}$ silica gel sheets (Macherey-Nagel) with detection by 0.5% phosphomolybdic acid solution in 95% EtOH. Toluene, $Et_2O$ and THF were distilled from sodium/benzophenone. HPLC grade MeCN, $Me_2CO$, MeOH, EtOH and *i*-PrOH were used without any purification. Allyl alcohol, *t*-BuOH and benzyl alcohol were distilled from sodium, $Et_3N$ was distilled from $CaH_2$. IR spectra were obtained using a FTIR spectrophotometer. Routine $^1H$ and $^{13}C$ NMR spectra were recorded at 250 and 62.5 MHz, respectively. $^1H$ NMR COSY and NOESY experiments were performed on a spectrometer operating at 600 MHz. Resonances associated with amide rotamers are indicated with *. Tetramethylguanidinium azide (TMGA) was prepared as previuosly described.[19] *Trans* hydroxy mesylate **4**, *trans* acetoxy mesylate **5**, *trans* azido alcohols **28** and **31** and *cis* azido alcohol **32** have been previously described.[6]

### 6.2. Reactions of epoxides 2α and 2β with *O*-Nucleophiles

*6.2.1. Reaction of epoxide **2β** with MeOH (protocol A). Typical Procedure.* A solution of *trans* acetoxy mesylate **5** (0.040 g, 0.10 mmol) in anhydrous MeOH (2 mL) was treated with MeONa (0.008 g, 0.15 mmol, 1.5 equiv) and the reaction mixture was stirred 12 h at room temperature. Dilution with $Et_2O$ and evaporation of the filtered (Celite) organic solution afforded a crude product (0.021 g, 76% yield) consisting of *methyl 2,3,6-trideoxy-N-(benzyloxycarbonyl)-β-D,L-threo-hex-2-eno-azapyranoside* **(11β)** ($^1H$ NMR) practically pure, as a liquid: $R_f$ = 0.15 (7:3 hexane/AcOEt); FTIR (neat) ν 3433, 1701, 1417, 1313 $cm^{-1}$. $^1H$ NMR ($CD_3CN$, 50°C) δ 7.27-7.48 (m, 5H), 5.74 (d, 1H, *J* = 10.7 Hz), 5.66 (d, 1H, *J* = 10.7 Hz), 5.32-5.41 (m, 1H), 5.18 (d, 1H, *J* =11.9 Hz), 5.12 (d, 1H, *J* = 11.9 Hz), 4.47 (quintet, 1H, *J* = 6.9 Hz), 4.24-4.37 (m, 1H), 3.30 (s, 3H), 2.64 (d, 1H, *J* = 6.7 Hz, OH) 1.12 (d, 3H, *J* = 6.9 Hz). $^{13}C$ NMR ($CD_3CN$) δ 156.9, 132.1, 129.6, 129.1, 128.4, 125.4, 80.9, 68.2, 67.0, 56.6, 49.4, 13.3. Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.59; H, 6.74; N, 4.83.

*6.2.2. Reaction of epoxide **2α** with BnOH (protocol B). Typical procedure.* A solution of *trans* hydroxy mesylate **4** (0.020 g, 0.060 mmol) in anhydrous MeCN (0.9 mL) was treated with *t*-BuOK (0.007 g, 0.060 mmol, 1.1 equiv). After 1 h stirring at room temperature, TLC analysis showed that the starting material was consumed by cyclization to epoxide **2α**. BnOH (18 μL, 0.18 mmol, 3.0 equiv) was added and stirring was prolonged for 2 h at the same temperature. Dilution with ether and evaporation of the washed (saturated aqueous NaCl) organic extracts afforded a crude product (0.040 g) consisting of benzyl *O*-glycoside **10α** and an excess of benzyl alcohol which was subjected to preparative TLC (a 7:3 hexane/AcOEt mixture was used as the eluant). Extraction of the slower moving band afforded *benzyl 2,3,6-trideoxy-N-(benzyloxycarbonyl)-α-D,L-erithro-hex-2-eno-azapyranoside* **(10α)** (0.013 g, 61% yield), pure as a liquid; $R_f$ = 0.19 (7:3 hexane/AcOEt); FTIR (neat) ν 3389, 1712, 1551, 1545, 1394, 1335, 1251 $cm^{-1}$. $^1H$ NMR ($CD_3CN$, 50°C) δ 7.10-7.52 (m, 10H), 5.82-6.04 (m, 2H), 5.60-5.75 (m, 1H), 5.23 (d, 1H, *J* = 12.4 Hz), 5.18 (d, 1H, *J* = 12.4 Hz), 4.63 (d, 1H, *J* = 11.5 Hz), 4.56 (d, 1H, *J* = 11.5 Hz), 4.55 (quintet, 1H, *J* = 7.1 Hz), 3.68-3.90 (m, 1H), 2.95 (d, 1H, *J* = 6.9 Hz, OH), 1.20 (d, 3H, *J* = 7.1 Hz); $^{13}C$ NMR ($CD_3CN$) δ 156.4, 139.8, 138.0, 129.5, 129.2, 129.0, 128.7, 128.4, 128.0, 78.8, 71.2, 68.0, 66.8, 53.2, 19.0. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.12; H, 6.28; N, 3.60.

### 6.3. Reactions of epoxides 2α and 2β with *C*-Nucleophiles

*6.3.1. Reaction of epoxide **2β** with TMSCN (protocol B). Typical procedure.* A solution of *trans* acetoxy mesylate **5** (0.022 g, 0.057 mmol) in anhydrous MeCN (2 mL) was treated with *t*-BuOK (0.010 g, 0.085 mmol, 1.5 equiv). After 1h stirring at room temperature, TLC analysis showed that the starting material was consumed. TMSCN (21 μL, 0.17 mmol, 3.0 equiv) was added and stirring was continued for 12 h at the same temperature. Dilution with $Et_2O$ and evaporation of the washed (saturated aqueous $NaHCO_3$, saturated aqueous NaCl) organic solution afforded a crude product (0.022 g) consisting of a 55:45 mixture of 3-cyano- **18-OTMS** and 1-cyano-imino glycal **17** which was subjected to preparative TLC (a 9:1 hexane/AcOEt mixture was used as the eluant). Extraction of the two most intense moving bands (the faster moving band contained **18-OTMS**) afforded pure 3-cyano- **18-OTMS** (0.006 g, 31% yield) and 3-cyano-imino glycal **17** (0.005 g, 32% yield).

*6.3.1.1. 3-Cyano-3,6-dideoxy-4-O-(trimethylsilyl)-N-(benzyloxycarbonyl)-D,L-iminogulal (***18-OTMS***),* a liquid: $R_f$ = 0.32 (9:1 hexane/AcOEt); FTIR (neat) ν 2245, 1714, 1656, 1405, 1338, 1253 $cm^{-1}$. $^1H$ NMR ($CD_3CN$, 50°C) δ 7.23-7.50 (m, 5H), 6.85 (dd, 1H, *J* = 8.1, 2.2 Hz), 5.20 (s, 2H), 4.64-4.80 (m, 1H), 4.24-4.39 (m, 1H), 4.16 (dd, 1H, *J* = 9.7, 4.7 Hz), 3.37 (dt, 1H, *J* = 9.7, 2.4 Hz), 1.03 (d, 3H, *J* = 6.6 Hz), 0.19 (s, 9H). $^{13}C$ NMR ($CD_3CN$) δ 150.6, 137.5, 129.5, 129.2, 128.8, 126.4, 121.4, 115.3, 69.7, 68.6, 52.0, 32.2, 10.6, -0.06. Calcd for $C_{18}H_{24}N_2O_3Si$: C, 62.76; H, 7.02; N, 8.13. Found: C, 62.39; H, 7.15; N, 7.82.

*6.3.1.2. 1-Cyano-3,6-dideoxy-N-(benzyloxycarbonyl)-D,L-iminogalactal (***17***)*, a liquid: $R_f$ = 0.26 (9:1 hexane/AcOEt); FTIR (neat) ν 3360, 2229 $cm^{-1}$. $^1H$ NMR ($CD_3CN$, 50°C) δ 7.23-7.57 (m, 5H), 6.04 (dd, 1H, *J*= 4.6, 3.6 Hz), 5.23 (s, 2H), 4.38-4.51 (m, 1H), 3.85-3.98 (m, 1H), 2.38-2.54 (m, 2H), 1.03 (d, 3H, *J* = 6.8 Hz); $^{13}C$ NMR ($CD_3CN$) δ 153.3, 137.1, 130.3, 129.5, 129.2, 129.1, 115.3, 111.4, 69.0, 65.2, 52.9, 29.5, 13.7. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 65. 81; H, 5.74; N, 9.96.

*6.3.2. Reaction of epoxide* ***2α*** *with the potassium enolate of dimethylmalonate (protocol B). Typical procedure.* A solution of dimethylmalonate (20 μL, 0.18 mmol, 3.0 equiv) in anhydrous THF (0.5 mL) was treated with *t*-BuOK (0.020 g, 0.18 mmol, 3.0 equiv) (*Solution A*). A solution of *trans* hydroxy mesylate **4** (0.022 g, 0.060 mmol) in anhydrous THF (1.0 mL) was treated with *t*-BuOK (0.007 g, 0.066 mmol, 1.1 equiv) and the reaction mixture was stirred at room temperature for 40 min (*Solution B*). *Solution B* was added dropwise to *Solution A* cooled at 0°C and the resulting reaction mixture was stirred 12 h at room temperature. Dilution with $Et_2O$ and evaporation of the washed (saturated aqueous $NaHCO_3$, saturated aqueous NaCl) organic solution afforded a crude product (0.066 g) consisting of the *anti-1,2-addition product* **23** and an excess of the nucleophile, which was subjected to preparative TLC (a 7:3 hexane/AcOEt mixture was used as the eluant). Extraction of the slower moving band afforded *3-[(dimethoxycarbonyl)methyl]-3,6-dideoxy-N-(benzyloxycarbonyl)-D,L-iminoglucal* (**23**) (0.019 g, 84% yield), pure as a liquid: $R_f$ = 0.16 (7:3 hexane/AcOEt); FTIR (neat) ν 3415, 1737, 1661, 1482, 1251, 1033, 1020, 800 $cm^{-1}$. $^1H$ NMR ($CD_3CN$) δ 7.28-7.47 (m, 5H), 6.80 (d, 1H, *J* = 8.6 Hz), 5.19 (s, 2H), 4.68-4.79 (m, 1H), 4.10-4.24 (m, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 3.61-3.72 (m, 1H), 3.50 (d, 1H, *J* = 11.5 Hz), 3.12 (d, 1H, *J* = 4.5 Hz, OH), 2.72-2.35 (m, 1H), 1.14 (d, 3H, *J* = 6.9 Hz); $^{13}C$ NMR

($CD_3CN$) δ 169.3, 168.9, 154.2, 137.6, 129.5, 129.1, 128.8, 125.0, 103.7, 69.9, 68.2, 55.3, 53.4, 53.3, 53.2, 39.9, 15.9. Calcd for $C_{19}H_{23}NO_7$: C, 60.47; H, 6.14; N, 3.71. Found: C, 60.09; H, 5.93; N, 3.44.

*6.3.3. Reaction of epoxide **2α** with lithium enolate of dimethylmalonate (protocol B).* Following the typical procedure, a solution of dimethylmalonate (20 μL, 0.18 mmol, 3.0 equiv) in anhydrous toluene (0.5 mL) was treated with *t*-BuOLi (0.015 g, 0.18 mmol, 3.0 equiv) (*Solution A*). A solution of *trans* hydroxy mesylate **4** (0.022 g, 0.06 mmol) in anhydrous toluene (0.5 mL) was treated with *t*-BuOK (0.008 g, 0.07 mmol, 1.1 equiv) and the reaction mixture was stirred for 40 minutes at room temperature (*Solution B*). *Solution B* was dropwise added to *Solution A* cooled at 0°C and the resulting reaction mixture was stirred 12 h at room temperature. Usual work-up afforded a crude product (0.042 g) consisting of the *syn-1,4-addition product* **25α** and an excess of the nucleophile, which was subjected to flash chromatography. Elution with a 6:4 hexane/AcOEt mixture with 0,1% of $Et_3N$ afforded *dimethyl 2,3,6-trideoxy-N-(benzyloxycarbonyl)-α-D,L-erithro-hex-2-eno-azapyranosyl malonate* (**25α**) (0.011 g, 48% yield), pure as a liquid: $R_f$= 0.22 (6:4 hexane/AcOEt); FTIR (neat) ν 3445, 1732, 1661, 1415, 1310 $cm^{-1}$. $^1H$ NMR ($CD_3CN$, 50°C) δ 7.29-7.42 (m, 5H), 6.03 (dd, 1H, *J* = 10.2, 4.6 Hz), 5.93 (dd, 1H, *J* = 10.2, 3.7 Hz), 5.15 (s, 2H), 4.74-4.84 (m, 1H), 4.52 (d, 1H, *J* = 6.7 Hz), 3.94-4.05 (m, 1H), 3.84-3.93 (m, 1H), 3.67 (s, 3H), 3.65 (s, 3H), 3.24 (d, 1H, *J* = 8.3 Hz, OH), 1.12 (d, 3H, *J* = 6.7 Hz); $^{13}C$ NMR ($CD_3CN$) δ 169.8, 168.9, 157.8, 137.7, 129.4, 129.1, 128.8, 128.1, 68.2, 67.1, 56.2, 55.6, 53.4, 53.2, 41.5, 17.6. Calcd for $C_{19}H_{23}NO_7$: C, 60.47; H, 6.14; N, 3.71. Found: C, 60.12; H, 6.09; N, 3.42.

### 6.4. Reaction of epoxides 2α and 2β with *S*-Nucleophiles

*6.4.1. Reaction of epoxide **2β** with BnSH (protocol B). Typical procedure.* A solution of *trans* acetoxy mesylate **5** (0.030 g, 0.078 mmol) in anhydrous MeCN (0.90 mL) was treated with *t*-BuOK (0.013 g, 0.117 mmol, 1.5 equiv). After 1 h stirring at room temperature, when TLC analysis showed the complete cyclization of the starting material into epoxide **2β**, BnSH (27 μL, 0.23 mmol, 3.0 equiv) was added and stirring was prolonged for 6 h at the same temperature. Dilution with $Et_2O$ and evaporation of the washed (saturated aqueous $NaHCO_3$, saturated aqueous NaCl) organic solution afforded a crude product (0.063 g) consisting of benzylthio derivative **36** and an excess of BnSH which was subjected to preparative TLC (a 7:3 hexane/AcOEt mixture was used as the eluant). Extraction of the slower moving

band afforded *3-(benzylthio)-3,6 dideoxy-N-(benzyloxycarbonyl)-D,L-iminogulal* (**36**) (0.016 g, 56% yield), pure as a liquid: $R_f$ = 0.39 (7:3 hexane/AcOEt); FTIR (neat) ν 3474, 3063, 3030, 1710, 1645, 1410, 526 $cm^{-1}$. $^1H$ NMR ($CD_3CN$, 50°C) δ 7.18-7.45 (m, 10H), 6.73 (dd, 1H, *J* = 8.2, 1.1 Hz), 5.17 (s, 2H), 4.79 (dd, 1H, *J* = 8.2, 2.1 Hz), 4.35 (quintet, 1H, *J* = 6.7 Hz), 3.89 (d, 1H, *J* = 12.8 Hz), 3.81 (d, 1H, *J* = 12.8 Hz), 3.70-3.81 (m, 1H), 3.46 (d, 1H, *J* = 4.3 Hz, OH), 3.25 (dt, 1H, *J* = 4.3, 2.1 Hz), 1.05 (d, 3H, *J* = 6.7 Hz); $^{13}C$ NMR ($CD_3CN$) δ 153.4, 139.9, 137.6, 130.0, 129.5, 129.4, 129.1, 128.8, 127.8, 125.1, 106.8, 71.2, 68.3, 52.8, 44.1, 34.7, 10.8. Calcd for $C_{21}H_{23}NO_3S$: C, 68.27; H, 6.27; N, 3.79. Found: C, 68.06; H, 6.01; N, 3.48.

*6.4.2. Reaction of epoxide **2α** with PhSH (protocol B).* Following the typical procedure, treatment of a solution of *trans* hydroxy mesylate **4** (0.030 g, 0.088 mmol) in anhydrous THF (1 mL) with *t*-BuOK (0.011 g, 0.097 mmol, 1.1 equiv) and PhSH (27 μL, 0.26 mmol, 3.0 equiv) afforded, after 12 h stirring, a crude liquid product (0.056 g) consisting of a 60:30:10 mixture of *anti-1,2-* **37**, *syn-1,2-* **38**, and *anti-1,4-addition product* **39β** ($^1H$ NMR) which was subjected to preparative TLC (a 7:3 hexane/AcOEt was used as the eluant). The extraction of the most intense bands afforded pure **37** (0.013 g, 42% yield), **38** (0.007 g, 22% yield), and **39β** (0.006 g, 19% yield).

*6.4.2.1. 3-(Phenylthio)-3,6-dideoxy-N-(benzyloxycarbonyl)-D,L-imino glucal (**37**)*, $R_f$ = 0.25 (7:3 hexane/AcOEt): FTIR (neat) ν 3430, 1705, 1640, 1415, 1333, 1020 $cm^{-1}$; $^1H$ NMR ($CD_3CN$, 50°C) δ 7.23-7.51 (m, 10H), 6.80 (d, 1H, *J* = 8.4 Hz), 5.19 (s, 2H), 4.73 (d, 1H, *J* = 8.4 Hz), 4.29 (dq, 1H, *J* = 13.1, 3.0 Hz), 4.05-4.11 (m, 1H), 3.74-3.85 (m, 1H), 3.19 (d, 1H, *J* = 5.0 Hz, OH), 1.08 (d, 3H, *J* = 6.9 Hz). $^{13}C$ NMR ($CD_3CN$) δ 154.1, 137.6, 135.7, 130.1, 129.5, 129.1, 128.9, 128.0, 125.0, 103.9, 68.3, 67.5, 49.2, 45.5, 15.6. Calcd for $C_{20}H_{21}NO_3S$: C, 67.58; H, 5.96; N, 3.94. Found: C, 67.33; H, 5.51; N, 3.59.

*6.4.2.2. 3-(Phenylthio)-3,6-dideoxy-N-(benzyloxycarbonyl)-D,L-iminoallal (**38**)*, $R_f$ = 0.18 (7:3 hexane/AcOEt): FTIR (neat) ν 3450, 1710, 1645, 1463, 1409, 1333, 1265 $cm^{-1}$; $^1H$ NMR ($CD_3CN$, 50°C) δ 7.23-7.51 (m, 10H), 6.90 (d, 1H, *J* = 8.4 Hz), 5.20 (s, 2H), 4.96-5.06 (m, 1H), 4.28 (unresolved q, 1H, *J* = 7.3 Hz), 4.01-4.11 (m, 1H), 3.70-3.79 (m, 1H), 3.29 (d, 1H, *J* = 5.5 Hz, OH), 1.33 (d, 3H, *J* = 7.3 Hz). $^{13}C$ NMR ($CD_3CN$) δ 152.0 136.8, 135.7, 129.4, 128.8, 128.6, 128.3, 128.0, 127.1, 124.8,

102.6, 70.5, 67.5, 52.1, 45.3, 14.3. Calcd for $C_{20}H_{21}NO_3S$: C, 67.58; H, 5.96; N, 3.94. Found: C, 67,19; H, 5.57; N, 3.63.

*6.4.2.3. Phenyl 2,3,6-trideoxy-1-thio-N-(benzyloxycarbonyl)-β-D,L-erithro-hex-2-eno-azapyranoside (**39β**)*, $R_f$ = 0.11 (7:3 hexane/AcOEt): FTIR (neat) ν 3425, 1712, 1644, 1415, 1337, 1260, 1037 $cm^{-1}$; $^1H$ NMR ($CD_3CN$, 50°C) δ 7.08-7.43 (m, 10H), 6.02 (dd, 1H, *J* = 9.7, 3.9 Hz), 5.88-5.97 (m, 1H), 5.83-5.90 (m, 1H), 5.19 (d, 1H, *J* = 12.1 Hz), 5.14 (d, 1H, *J* = 12.1 Hz), 4.52 (q, 1H, *J* = 7.2 Hz), 3.83-3.94 (m, 1H), 2.94 (d, 1H, *J* = 6.8 Hz, OH), 1.23 (d, 3H, *J* = 7.2 Hz). $^{13}C$ NMR ($CD_3CN$) δ 156.0, 137.7, 134.1, 131.6, 130.3, 129.9, 129.4, 128.9, 128.0, 125.5, 124.1, 68.9, 68.1, 66.6, 53.3* and 53.8*, 18.3. Calcd for $C_{20}H_{21}NO_3S$: C, 67.58; H, 5.96; N, 3.94. Found: C, 67.26; H, 5.61; N, 3.58.

### 6.5. Formal synthesis of the piperidine 1,6-dideoxy-2,3,4-tri-*O*-acetyl-azasugar 46-triAc

*6.5.1. Dihydroxylation of i-propyl α-O-glycoside **8α** by $OsO_4$/NMO protocol.* A solution of *i*-propyl *O*-glycoside **8α** (0.167 g, 0.57 mmol) in a 1:1 *t*-BuOH/acetone mixture (1.15 mL) was added, at 0°C under stirring and in the dark, to a 50% p/v aqueous solution of *N*-methyl morpholine-*N*-oxide (NMO) (0.31 mL). The resulting reaction mixture was treated with 2.5% p/v $OsO_4$ solution in *t*-BuOH (0.62 mL) and stirring was prolonged 12 h at room temperature. Dilution with AcOEt and evaporation of the filtered (Celite) organic solution afforded *i-propyl 6-deoxy-N-(benzyloxycarbonyl)-α-D,L-azamannopyranoside* (**44**) (0.137 g, 70% yield) practically pure, as a liquid: $R_f$ = 0.12 (1:1 hexane/AcOEt); FTIR (neat) ν 3420, 1707, 1643, 1410, 1333, 1020 $cm^{-1}$. $^1H$ NMR ($CD_3CN$, 50°C) δ 7.24-7.47 (m, 5H), 5.52 (d, 1H, *J* = 2.6 Hz), 5.11 (d, 1H, *J* = 12.5 Hz), 5.04 (d, 1H, *J* = 12.5 Hz), 3.80 (dd, 1H, *J* = 2.6, 0.6 Hz), 3.78 (seven lines, 1H, *J* = 6.2 Hz), 3.57-3.64 (m, 1H), 3.47 (t, 1H, *J* = 8.3 Hz), 3.23-3.39 (m, 1H), 1.48 (d, 3H, *J* = 6.8 Hz), 1.12 (d, 3H, *J* = 6.2 Hz), 1.10 (d, 3H, *J* = 6.2 Hz); $^{13}C$ NMR ($CD_3CN$) δ 157.0, 138.1, 129.3, 128.7, 128.6, 86.1, 73.9, 72.7, 69.2, 67.2, 65.1, 51.6, 23.3, 21.4, 15.9. Calcd for $C_{17}H_{25}NO_6$: C, 60.15; H, 7.43; N, 4.13. Found: C, 59.75; H, 7.11; N, 3.97. *Triacetate* **44-triAc**: a liquid, $R_f$ = 0.27 (7:3 hexane/AcOEt); FTIR (neat) ν 1725, 1652, 1419, 1233, 1070 $cm^{-1}$. $^1H$ NMR ($CD_3CN$) δ 7.27-7.43 (m, 5H), 5.58 (d, 1H, *J* = 2.1 Hz), 4.98-5.21 (m, 5H), 3.80 (quintet, 1H, *J* = 5.9 Hz), 3.54-3.70 (m, 1H), 2.02 (s, 3H), 1.92 (s, 3H), 1.84 (s, 3H), 1.44 (d, 3H, *J* = 6.8 Hz), 1.17 (d, 3H, *J* = 5.9 Hz), 1.14 (d, 3H, *J* = 5.9 Hz). $^{13}C$ NMR ($CD_3CN$) δ 171.0, 170.9, 170.7, 156.5, 137.7,

129.5, 129.1, 128.9, 83.3, 71.9, 71.4, 70.8, 70.5, 67.8, 49.7, 23.6, 23.1, 21.2, 20.9, 20.7, 15.3. Calcd for $C_{23}H_{31}NO_9$: C, 59.33; H, 6.72; N, 3.01. Found: C, 59.12; H, 6.34; N, 2.79.

*6.5.2. N-Deprotection of triol **44-triAc** by $H_2$/Pd-C protocol.* A solution of triacetyl derivative **44-triAc** (0.087 g, 0.187 mmol) in absolute EtOH (2.6 mL) was stirred, under hydrogen saturated atmosphere in appropriate apparatus, for 30 minutes in the presence of 10% Pd/C (0.010 g, 0.0187 mmol). Dilution with absolute EtOH and evaporation of the filtered (Celite) organic solution afforded a crude product (0.043 g), which was subjected to preparative TLC (a 1:9 $CH_2Cl_2$/acetone mixture was used as the eluant). Extraction of the slower moving band afforded *1,6-dideoxy-2,3,4-tri-O-acetyl-D,L-azamannopyranose* (**46-triAc**) (0.014 g, 28% yield), pure as a liquid: $R_f$ = 0.12 (1:1 hexane/AcOEt); $^1$H NMR ($CD_3CN$) δ 5.30 (bs, 1H), 4.86-4.97 (m, 2H), 3.09 (dd, 1H, *J* = 14.6, 2.6 Hz), 2.89 (d, 1H, *J* = 14.6 Hz) 2.68-2.82 (m, 1H), 2.14 (s, 3H), 2.09 (s, 1H), 2.05 (s, 3H), 1.98 (s, 3H), 1.12 (d, 3H, *J* = 6.5 Hz); $^{13}$C NMR ($CD_3CN$) δ 171.3, 171.0, 170.2, 74.0, 73.6, 71.0, 47.8, 44.7, 22.2, 21.2, 21.0, 18.2. Calcd for $C_{12}H_{19}NO_6$: C, 52.72; H, 7.01; N, 5.13. Found: C, 52.37; H, 6.77; N, 4.78.

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**Supplementary data**

Supplementary data associated with this article can be found, in the online version, at…...

**References and notes**


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3. Accordingly, *anti-1,2-* and *anti-1,4-addition products*, which are supposed to derive from an attack by a free, non-coordinated nucleophile, are named *non-coordination products*.

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5. Epoxides **2α** and **2β** are not stable and can be prepared only *in situ* by cyclization under basic conditions (*t*-BuOK) of the corresponding stable precursor, the *trans* hydroxy mesylate **4** and *trans* acetoxy mesylate **5**, respectively (Scheme 2), and immediately left to react with the selected nucleophile.

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7. Hydroxy ketone **3** was prepared by a racemic application of Comins' enantioselective synthetic strategy. See: (a) Comins, D. L.; Joseph, S. P.; Goehring, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 4719-4728. (b) Comins, D. L.; Goehring, R. R.; Joseph, S. P.; O'Connor, S. *J. Org. Chem.* **1990**, *55*, 2574-2576. (c) Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1986,** *27*, 4549-4552. (d) Comins, D. L.; Fulp, A. B. *Tetrahedron Lett.* **2001**, *42*, 6839-6841.

8. Reaction conditions. *Protocol A*: the nucleophile is also the solvent of the reaction; *protocol B*: only 3-4 equiv of nucleophile are present in MeCN, THF, or toluene, as the solvent.

9. Most likely, the urethane *N*-Cbz protecting group negatively competes with the oxirane ring of epoxides **2α** and **2β** in the reaction with the organometallic compound.

10. The slightly alkaline reaction conditions (*t*-BuOK necessary for the formation of the epoxide) and the acidity of anomeric H(1) proton of glycosyl cyanides **15** and **19** are responsible for the isomerization process (Scheme 5).

11. In this reaction, *t*-BuOLi is used only for the generation of the corresponding enolate species, whereas for the generation *in situ* of epoxide **2α** from the stable precursor **4**, *t*-BuOK is necessarily used and cannot be substituted. Actually, when *t*-BuOLi was used both for the generation *in situ* of epoxide **2α** and lithium enolate **21-Li**, a complex reaction mixture was obtained.

12. For the use of TMGA and $TMSN_3$ in the azidolysis of glycal-derived vinyl epoxides, see ref. 4 and: a) Di Bussolo, V.; Caselli, M.; Romano, M. R.; Pineschi, M.; Crotti, P. *J. Org. Chem*. **2004**, *69*, 8702-8708. b) Di Bussolo, V.; Frau, I.; Pineschi, M.; Crotti, P. *Synthesis*, in press.

13. The absence of the corresponding *syn-1,2-addition product* in the reaction of epoxide **2β**, may be due to steric hindrance to the necessary oxirane oxygen-nucleophile coordination (hydrogen bond) occurring between the *cis* axial methyl group and the bulky tetramethylguanidinium ion ($Me_4N_2C{=}NH_2^+$).

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