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Stereoselective Synthesis of 4-Amino-2,3-unsaturated-*N*-Cbz-imino-*O*-glycosides via New Diastereoisomeric *N*-Cbz-Imino Glycal-Derived Allyl *N*-Nosyl Aziridines

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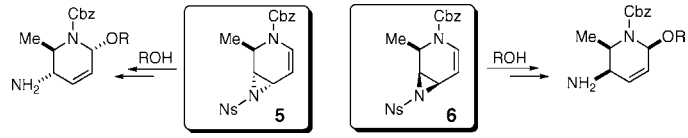
ABSTRACT

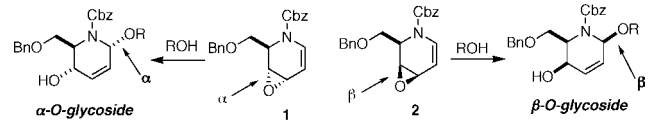


The glycosylation of alcohols by the new diastereoisomeric D,L-6-deoxy-*N*-Cbz-imino glycal-derived allyl *N*-nosyl aziridines 5 and 6 affords, after deprotection of the 4-(*N*-nosylamino) group, the corresponding 2,3-unsaturated-*N*-Cbz-imino-*O*-glycosides bearing a free amino group on C(4) through a completely 1,4-regio- and *substrate-dependent* stereoselective glycosylation process.

Recently, we found that the reaction of the diastereoisomeric D,L-imino galactal- and D,L-imino allal-derived allyl epoxides **1** and **2** with *O*-nucleophiles, such as simple alcohols, led to the corresponding alkyl *O*-glycosides through a completely regio- and stereoselective 1,4-addition process. The stereoselectivity observed depended only on the configuration of the starting heterocycle: α- and *β*-*O*-glycosides were exclusively obtained from epoxides **1** and **2**, respectively, in a first example of a *substrate-dependent* selectivity in nucleophilic addition reactions to imino glycal derivatives (Scheme 1).[1]

To improve the synthetic utilization of imino glycals and their derivatives, the possibility of extending the previous studies on epoxides **1** and **2** to corresponding aziridines, such as the structurally related diastereoisomeric *N*-nosyl aziridines **3** and **4** and/or the related 6-deoxy analogues **5** and **6** was evaluated (Scheme 2). Interest in aziridines **3**−**6** derived from the consideration that if their behavior in the glycosylation of alcohols is similar to that of epoxides **1** and **2** an amino group can theoretically be regio- and stereoselectively (α or *β*) introduced on the C(4) carbon of a stereodefined azapyranoside system with the contemporary formation of previously undescribed alkyl 4-amino-2,3-unsaturated-*N*-Cbz-imino-*O*-glycosides such as **7** and **8**. These compounds are useful precursors for the synthesis, through corresponding alkyl 4-amino-*N*-Cbz-azapyranosides **9** and **10**, of 4-amino-1-deoxy-piperidine azasugars such as **11** and **12** potential glycosidases inhibitors,[2] which, in this way, can be regio- and stereoselectively obtained.[3,4]

Scheme 1. Stereoselective Addition of *O*-Nucleophiles to the *N*-Cbz-Imino Glycal-Derived Allyl Epoxides **1** and **2**



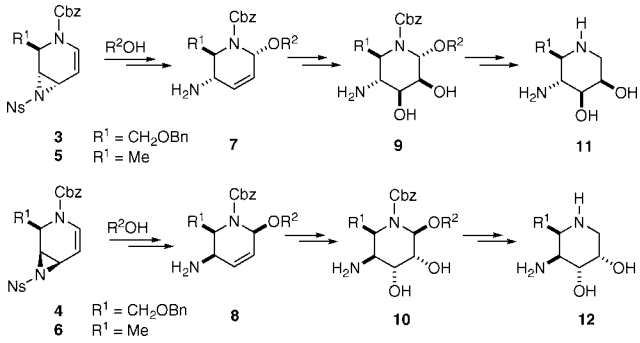
ROH = MeOH, EtOH, *i*-PrOH, *t*-BuOH

(1) Di Bussolo, V.; Fiasella, A.; Romano, M. R.; Favero, L.; Pineschi, M.; Crotti, P. *Org. Lett.* **2007**, *9*, 4479.

(2) Afarinkia, K.; Bahar, A. *Tetrahedron: Asymmetry* **2005**, *16*, 1239.

10.1021/ol900742p CCC: $40.75
Published on Web 05/20/2009

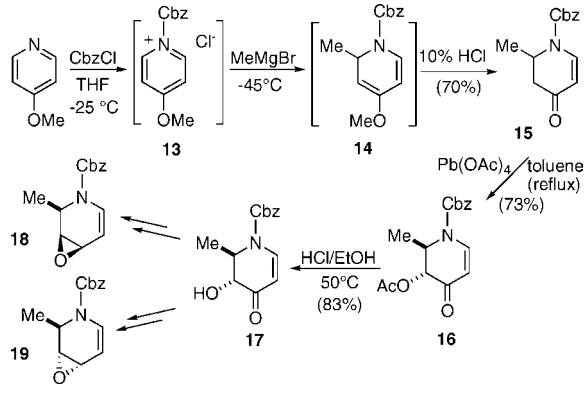
Scheme 2. Synthetic Use of *N*-Cbz-Imino Glycal-Derived Allyl Aziridines **3**−**6**



The experimental feasibility of the above-described amination process was checked by means of the 6-deoxy aziridines **5** and **6**, taken as appropriate models. The decidedly simpler protocol for introduction of a methyl group,[5a−c] compared to a $-CH_2OBn$ side chain,[1,5d] into these iminoglycal systems as well as considerations based on results previously obtained in the glycal system determined our preference for using aziridines **5** and **6** rather than aziridines **3** and **4**.[6]

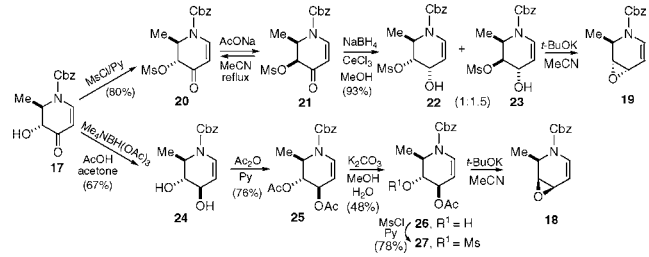
Aziridines **5** and **6** were stereoselectively prepared starting from epoxides **18** and **19**, respectively, which in turn were prepared starting from the common synthetic intermediate, the α-hydroxy ketone **17** (Schemes 3−5).[7]

Scheme 3. Stereoselective Synthesis of α-Hydroxy Ketone **17**, the Precursor of Allyl Epoxides **18** and **19**

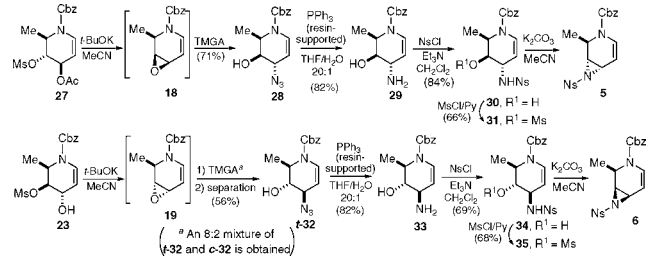


In a racemic application[5c] of Comins' enantioselective procedure,[5a,b] the regioselective addition of MeMgBr to pyridinium chloride **13**, generated in situ by reaction of 4-methoxy pyridine with Cbz−Cl, afforded, after acid hydrolysis of the intermediate enol ether **14**, the dihydropyridone **15** which was acetoxylated by $Pb(OAc)_4$, with the completely regio- and stereoselective formation of α-acetoxy ketone **16**. Acid hydrolysis (HCl/EtOH) of **16** afforded the α-hydroxy ketone **17** (Scheme 3).

Scheme 4. Stereoselective Synthesis of Allyl Epoxides **18** and **19**



Scheme 5. Stereoselective Synthesis of *trans*-*N*-Nosyl-*O*-mesylates **31** and **35**, the Precursors of Aziridines **5** and **6**



For the synthesis of **19**, α-hydroxy ketone **17** was transformed (MsCl/Py) into the corresponding mesylate **20** which was epimerized (AcONa/MeCN, 90 °C, 4 days) to a 60:40 mixture of the diastereoisomeric mesylate **21** and the starting mesylate **20**. The inseparable mixture of mesylates **20** and **21** was reduced ($NaBH_4/CeCl_3$),[8] in a completely stereoselective fashion, to a corresponding mixture of *cis*-hydroxy mesylate **22** and *trans*-hydroxy mesylate **23** which were separated by flash chromatography (Scheme 4).[9] The

(3) Dihydroxylation of the double bond of *O*-glycosides **7** and **8** should reasonably occur in the opposite direction to the substituents on C(1) and C(4) and lead to azapyranosides **9** and **10**, respectively, which can be transformed into the corresponding 4-amino-1-deoxy-azasugars **11** and **12** by deprotection of the *N*-Cbz group. See, for example: Tschamber, T.; Backenstrass, F.; Neuburger, M.; Zehnder, M.; Streith, J. *Tetrahedron* **1994**, *50*, 1135.

(4) A *β*-stereoselective introduction of a −NHAc group on C(4) of an iminosugar precursor has been recently described: Toumieux, S.; Compain, P.; Martin, O. R. *J. Org. Chem.* **2008**, *73*, 2155.

(5) (a) Comins, D. L.; Joseph, S. P.; Goehring, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 4719. (b) Comins, D. L.; Goehring, R. R.; Joseph, S. P.; O'Connor, S. *J. Org. Chem.* **1990**, *55*, 2574. (c) Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1986**, *27*, 4549. (d) Comins, D. L.; Fulp, A. B. *Tetrahedron Lett.* **2001**, *42*, 6839.

(6) We have previously observed that replacing the $-CH_2OBn$ group on the C(5) of a glycal-derived allyl oxirane system with the simpler methyl group has no influence on the completely regio- and stereoselective glycosylation of *O*-nucleophiles or on the conformational equilibrium of these systems: Di Bussolo, V.; Favero, L.; Romano, M. R.; Pineschi, M.; Crotti, P. *Tetrahedron* **2008**, *64*, 8188, and references therein. The same behavior can reasonably be expected with the 6-deoxy aziridines **5** and **6** and the related 6-OBn-substituted aziridines **3** and **4**. As a consequence, the results which are obtained with aziridines **5** and **6** can reasonably be extended to aziridines **3** and **4** too.

(7) As in the case of epoxides **1** and **2**, aziridines **5** and **6** were prepared in a racemic form. However, the same synthetic procedure can reasonably be used for a corresponding enantioselective synthesis, provided that the methyl introduction step is carried out in an asymmetric fashion.[5a]

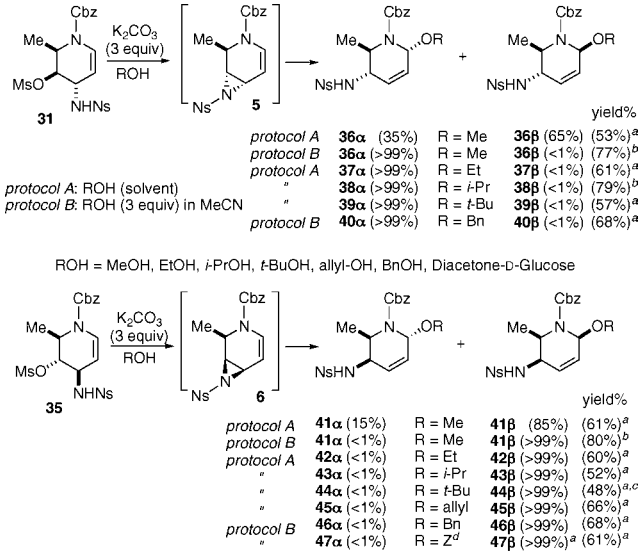
(8) Luche, J.-L.; Gemal, A. L. *J. Am. Chem. Soc.* **1979**, *101*, 5848.

trans-hydroxy mesylate **23** was the stable ultimate precursor of epoxide **19**.[10] For the synthesis of epoxide **18**, α-hydroxy ketone **17** was stereoselectively reduced [$Me_4NBH(OAc)_3$][1,5d] to *trans*-diol **24** and subsequently transformed into the corresponding diacetate **25**. Regioselective saponification (0.053 N K_2CO_3 in 16:1 MeOH/H_2O) of **25** afforded, after 5 h at −30 °C, a crude product mostly consisting of *trans*-hydroxy acetate **26** (57%) accompanied by a certain amount of the starting diacetate **25** (38%) and diol **24** (5%).[11] After separation, *trans*-hydroxy acetate **26** was transformed into the *trans* mesyloxy acetate **27**, the stable ultimate precursor of epoxide **18** (Scheme 4).[10,12]

For the synthesis of aziridine **5**, epoxide **18**, obtained by cyclization (*t*-BuOK/MeCN) of *trans*-mesyloxy acetate **27**, was subjected to azidolysis by tetramethylguanidinium azide (TMGA) affording *trans*-azido alcohol **28** in a completely 1,2-regio- and anti-stereoselective way. Reduction of **28** by resin-supported PPh_3[13] in THF led to the corresponding *trans*-amino alcohol **29**, which was regioselectively nosylated at the amino group by *o*-nitrobenzenesulfonyl chloride (NsCl)/Et_3N/CH_2Cl_2 protocol with the formation of the corresponding *N*-nosyl derivative **30**. Subsequent mesylation (MsCl/Py) of **30** at the residual hydroxy functionality afforded the *trans*-*N*-nosyl-*O*-mesylate **31**, the stable ultimate precursor of *N*-nosyl aziridine **5** (Scheme 5).[10] The same protocol applied to epoxide **19**, obtained by cyclization (*t*-BuOK/MeCN) of *trans*-hydroxy mesylate **23**, yielded through the corresponding synthetic intermediates ***t*-32**−**34**,[14] the diastereoisomeric *trans*-*N*-nosyl-*O*-mesylate **35**, the precursor of aziridine **6** (Scheme 5).[7,10]

In an examination of the regio- and stereochemical behavior of the new imino glycal-derived allyl *N*-nosyl aziridines **5** and **6** with *O*-nucleophiles, the addition reactions with simple, low-boiling alcohols such as MeOH, EtOH, *i*-PrOH, *t*-BuOH, and allylic alcohol were examined by using the nucleophile (alcohol) as the reaction solvent (*protocol A* reaction conditions).[15] In spite of the presence of a large amount of nucleophilic molecules, the reactions turned out to be completely 1,4-regio- and stereoselective with nucleophilic attack on the C(1) carbon of the allyl system and exclusive formation of the corresponding alkyl 4-(*N*-nosylamino)-2,3-unsaturated-*N*-Cbz-imino-*O*-glycosides **37**−**39α** (from **5**) and **42**−**45*β*** (from **6**) with the same configuration as the starting aziridine.[16] The only exception was given by the methanolysis reactions, which afforded mixtures of the corresponding anomeric methyl *O*-glycosides **36α** and **36*β*** from **5** and **41α** and **41*β*** from **6**. In the reaction mixture from aziridine **6**, the anomer (**41*β***) with configuration the same as the starting aziridine was the main product (**41*β***:**41α** = 85:15), whereas from aziridine **5** an inverted result was obtained and methyl *β*-*O*-glycoside **36*β*** having a configuration opposite to that of the starting aziridine turned out to be the main product (**36*β***:**36α** = 65:35) (Scheme 6).[17] However, in both cases,

Scheme 6. Regio- and Stereoselectivity of the Glycosylation of Alcohols and Monosaccharides by Aziridines **5** and **6** Under *Protocols A* and/or *B*



a Purified product (preparative TLC or flash chromatography). b Crude product. c See footnote 16. d Z = 3-(1,2;4,5-di-*O*-isopropylidene-β-D--glucofuranosyl)-.

when the reactions were repeated by using a few nucleophile (alcohol) equivalents in anhydrous MeCN (*protocol B* reaction conditions),[15] a complete stereoselectivity was observed, and the corresponding methyl *O*-glycoside with the configuration the same as the starting aziridine (**36α** from **5** and **41*β*** from **6**) was the only reaction product. *Protocol B* reaction conditions were necessarily used also in the glycosylation of benzyl alcohol by **5** and **6** and diacetone-D-glucose (a partially protected monosaccharide) by **6**, as examples of *O*-nucleophiles for which *protocol A* reaction conditions are clearly not feasible. In all cases,

(9) *Cis*-hydroxy mesylate **22** is recycled by oxidation (PCC, AcONa, CH_2Cl_2) to α-mesyloxy ketone **20** (89% yield).

(10) Epoxides **18** and **19** and *N*-nosyl aziridines **5** and **6** are not stable and can be prepared only in situ by cyclization under basic conditions (*t*-BuOK for epoxides and K_2CO_3 for aziridines) of the corresponding stable precursor and made to react immediately with a nucleophile.

(11) The recycling of diacetate **25** and diol **24** makes the overall yield of the desired *trans*-hydroxy acetate **26** more acceptable.

(12) In a preliminary examination of their ability as glycosyl donors in the reaction with alcohols, the new 6-deoxy epoxides **18** and **19** showed a regio- and stereoselective behavior completely identical to that of the corresponding 6-OBn-substituted epoxides **1** and **2** (see Supporting Information).[1] This constitutes a nice confirmation of what was previously admitted about the presence of a methyl or a $-CH_2OBn$ group on C(5) of an imino glycal system.[6]

(13) Zou, W.; Sandbhor, M.; Bhasin, M. *J. Org. Chem.* **2007**, *72*, 1226.

(14) The azidolysis of epoxide **19** by TMGA is not completely stereoselective, leading to an 8:2 mixture of *trans*-azido alcohol ***t*-32** and diastereoisomeric *cis*-azido alcohol ***c*-32**. Separation by flash chromatography afforded pure *trans*-azido alcohol ***t*-32**.

(15) In the reaction carried out under *protocol A*, a solution of *trans*-*N*-nosyl-*O*-mesylate **31** (or **35**) in the glycosyl acceptor (alcohol) is treated with K_2CO_3 (3 equiv). In the reaction carried out under *protocol B*, a solution of *trans*-*N*-nosyl-*O*-mesylate **31** (or **35**) in anhydrous MeCN containing the glycosyl acceptor (3 equiv) is treated with K_2CO_3 (3 equiv).

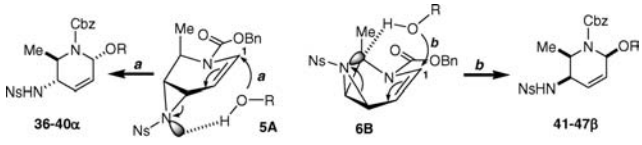
(16) In the reaction of aziridine **6** with *t*-BuOH, the corresponding *β*-*O*-glycoside **44*β*** is accompanied by a certain amount (about 20%) of an unidentified nonaddition product (see Supporting Information).

(17) The result obtained with aziridine **5** in the presence of a large amount of MeOH could be due to a certain intrinsic tendency of iminoglycal systems towards a *product-dependent* selectivity.[1]

the corresponding 4-(*N*-nosylamino)-α-*O*-glycoside (**40α**) from **5** and 4-(*N*-nosylamino)-*β*-*O*-glycoside (**46*β*** and **47*β***) from **6** were the only reaction products (Scheme 6).[18,19]

Analogously to the same reaction on the related epoxides **1** and **2**, the complete 1,4-regio- and stereocontrol observed in the glycosylation of alcohols by aziridines **5** and **6** can be explained by a possible coordination (hydrogen bonding) between the aziridine nitrogen and the *O*-nucleophile. In this way, the nucleophile (alcohol) is guided to the α-face in the case of **5**, reacting through conformer **5A**, or the *β*-face in the case of **6**, reacting through the corresponding conformer **6B**,[20] respectively, suitably arranged for an entropically favored attack on the C(1) carbon, from the same side as the aziridine ring (*routes **a*** and ***b***, Scheme 7). The corresponding 4-(*N*-nosylamino)-2,3-unsaturated-*O*-glycosides (**36**−**40α** from **5** and **41**−**47*β*** from **6**), with configuration the same as the starting aziridine, were consequently obtained (*substrate-dependent* selectivity).

Scheme 7. Rationalization of the *Substrate-Dependent* Selectivity in the Glycosylation of Alcohols and Monosaccharides by Allyl Aziridines **5** and **6**

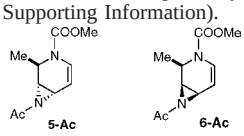


R = Me, Et, *i*-Pr, *t*-Bu, allyl, benzyl, 3-(1,2;4,5-di-*O*-isopropylidene-β-D-glucofuranosyl)-

(18) In the reaction of aziridine **6** with diacetone-D-glucose, *β*-*O*-glycoside **47*β*** is obtained as a mixture of corresponding D,L-diastereoisomers (see Supporting Information).

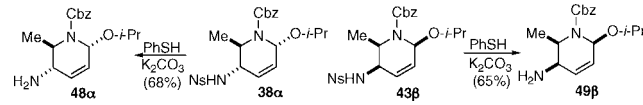
(19) The structures and configurations of *O*-glycosides **36**−**40α**, **36*β***, **41**−**47*β***, and **41α** were determined by means of their ^{1}H NMR spectra and appropriate NOE experiments.

(20) Theoretical calculations, carried out on appropriate, simplified models (**5-Ac** and **6-Ac**), indicated that aziridines **5** and **6** exist as the only corresponding conformer **5A** and **6B**, respectively, with the methyl group axial (Scheme 7) (see Supporting Information).



To check the possibility of deprotecting selectively the *N*-nosylamino functionality of glycosides **36**−**40α** and **41**−**47*β*** without affecting the carbamate moiety, the usual PhSH/K_2CO_3 protocol[21] was applied to *i*-propyl *O*-glycosides **38α** and **43*β***, taken as suitable models for the reaction. A clean reaction occurred with the exclusive formation of the corresponding 4-amino derivatives **48α** and **49*β***, in a short reaction time (2 h) and respectable yield (65−68%, calculated after purification from the excess of PhSH) (Scheme 8).[22]

Scheme 8. Deprotection of 4-(*N*-Nosylamino)-*O*-glycosides **38α** and **43*β*** to Corresponding 4-Amino-*O*-glycosides **48α** and **49*β***



In conclusion, we have demonstrated the possibility of introducing a free amino group on the C(4) of a 2,3-unsaturated-*N*-Cbz-imino-*O*-glycoside, starting from corresponding allyl *N*-nosyl aziridines. In the only 4-amino-*O*-glycoside obtained in each case, the configuration around C(4) and anomeric C(1) is the same and corresponds to that of the starting aziridine in a new version of a *substrate-dependent* selectivity applied to an *N*-Cbz-imino glycal-derived system.

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Supporting Information Available: Experimental details, spectral and analytical data for all reaction products, and theoretical conformational analysis for aziridines **5-Ac** and **6-Ac**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Di Bussolo, V.; Romano, M. R.; Pineschi, M.; Crotti, P. *Tetrahedron* **2007**, *63*, 2482, and references therein.

(22) Considering the mildness of the reaction conditions and the efficiency demonstrated on *O*-glycosides **38α** and **43*β***, the deprotection protocol (PhSH/K_2CO_3) can reasonably be applied to all the other 4-(*N*-nosylamino)-*O*-glycosides synthesized (Scheme 6).