ORGANIC LETTERS

2007
Vol. 9, No. 22
4479−4482

Stereoselective Synthesis of 2,3-Unsaturated-aza-*O*-glycosides via New Diastereoisomeric *N*-Cbz-imino Glycal-Derived Allyl Epoxides†

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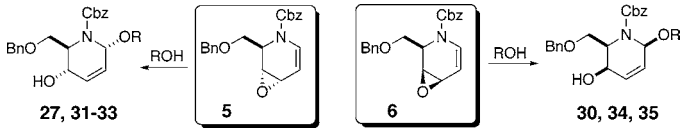
Received July 31, 2007

ABSTRACT



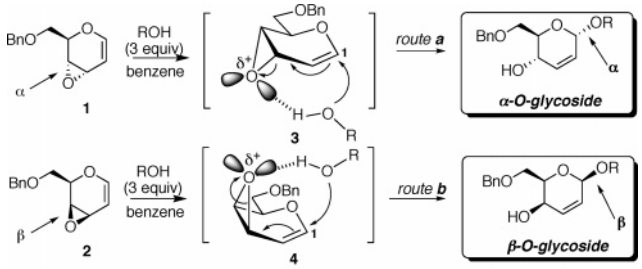
Diastereoisomeric D,L-*N*-Cbz-imino glycal-derived allyl epoxides 5 and 6 have been synthesized, and their addition reactions with alcohols examined. The reactions lead to the corresponding 2,3-unsaturated-aza-*O*-glycosides through a new, completely regioselective 1,4-addition process which proceeds with complete substrate-dependent stereoselectivity.

Recently, we found that the reaction of the diastereoisomeric D-galactal- and D-allal-derived allyl epoxides **1** and **2** with *O*-nucleophiles, such as alcohols and partially protected monosaccharides, led to the corresponding *O*-glycosides and disaccharides through a completely stereoselective 1,4-addition process affording α-*O*-glycosides from **1** and *β*-*O*-glycosides from **2** in a new uncatalyzed substrate-dependent stereospecific glycosylation process.[1] The strict correspondence found between the configuration of the glycosides obtained and that of the starting heterocycle was rationalized by the occurrence of a coordination between the *O*-nucleophile and the oxirane oxygen in the form of a hydrogen bond as shown in **3** and **4** (Scheme 1).

Due to our interest in the synthesis of azasugars from imino glycals,[2] we wanted to verify whether the diastereoisomeric *N*-Cbz-imino glycal-derived allyl epoxides **5** and **6**, the aza analogues of **1** and **2** (Scheme 2), would behave similarly in their reactions with alcohols. At the outset of this work, the glycosylation of alcohols by imino glycals had not been described.[3,4]

However, appropriately substituted imino glycal systems, such as tri-*O*-acetyl imino glucal **7**, react with *C*-nucleophiles, under Lewis acid mediated Ferrier reaction conditions, to give the *β*-anomers **9** with high selectivity (24−72% de).[5] The stereochemical outcome was attributed to a preferential pseudoaxial attack of the nucleophile on the favored con-

Scheme 1. Stereoselective Addition of *O*-Nucleophiles to Allyl Epoxides **1** and **2**



ROH = MeOH, EtOH, *i*-PrOH, *t*-BuOH, benzyl alcohol, dihydrocholesterol, phenol, diacetone-*D*-glucose, 1,2;3,4-di-*O*-isopropylidene-*D*-galactopyranose

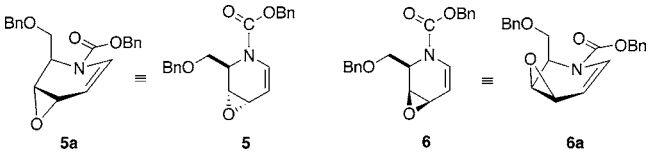
† Dedicated to Professor Franco Macchia in the occasion of his 70th anniversary.

(1) (a) Di Bussolo, V.; Caselli, M.; Romano, M. R.; Pineschi, M.; Crotti, P. *J. Org. Chem.* **2004**, *69*, 7383. (b) *J. Org. Chem.* **2004**, *69*, 8702.

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

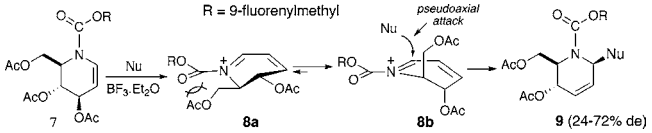
10.1021/ol701836a CCC: $37.00
Published on Web 09/27/2007

Scheme 2. Imino Glycal-Derived Allyl Epoxides **5** and **6**



formation **8b** of the intermediate *N*-acyliminium ion where the $-CH_2OAc$ group was axial (Scheme 3).

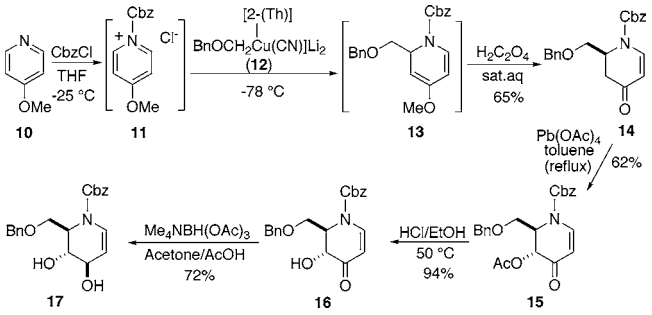
Scheme 3. Addition of *C*-Nucleophiles to Imino Glucal **7**



On the basis of this literature result, it appeared interesting to check not only whether the new imino glycal-derived epoxides **5** and **6** were able to glycosylate alcohols but also whether the facial selectivity of this process was independent of the nature (pseudoaxial or pseudoequatorial) of the nucleophilic attack.

The *trans*-diol **17** necessary for the synthesis of epoxide **6** was prepared in a completely diastereoselective fashion by a racemic application of Comins' enantioselective procedure (Scheme 4).[6] The synthetic protocol is based on the

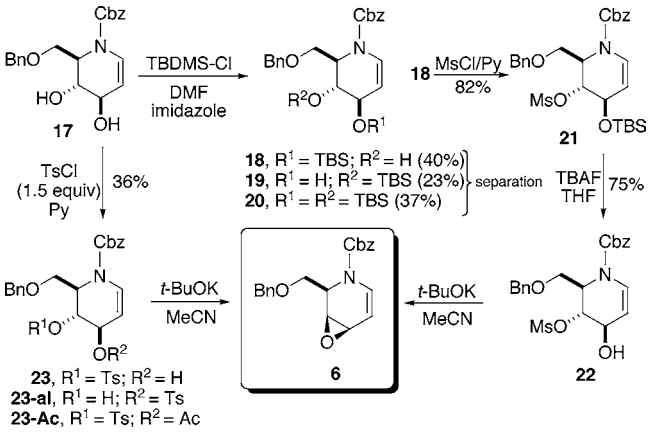
Scheme 4. Stereoselective Synthesis of *trans*-Diol **17**



regioselective addition of cuprate **12** to the C(2) carbon of the pyridinium chloride **11**, generated in situ by reaction of 4-methoxypyridine (**10**) with Cbz-Cl. Acid hydrolysis of the intermediate enol ether **13** afforded the dihydropyridone **14** which was regio- and stereoselectively acetoxylated by $Pb(OAc)_4$, with the formation of α-acetoxy ketone **15** as the only reaction product. Acid hydrolysis of **15** afforded α-hydroxy ketone **16** which was diastereoselectively reduced by $Me_4NBH(OAc)_3$ to the desired *trans*-diol **17**.[6]

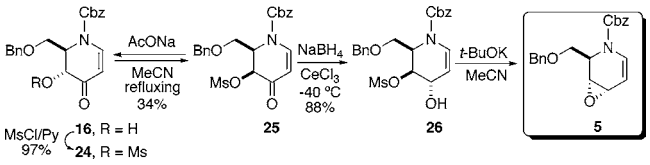
The reaction of **17** with TBDMS−Cl (1.1 equiv) resulted in the formation of a 40:23:37 mixture of 3-OTBS **18**, 4-OTBS **19**, and 3,4-di-OTBS **20** derivatives, which were separated by SiO_2 flash chromatography (Scheme 5).

Scheme 5. Synthesis of Allyl Epoxide **6**



Subsequent treatment of **18** with MsCl yielded mesylate **21**, which was deprotected by TBAF to the *trans*-hydroxy mesylate **22**. Base-catalyzed cyclization (*t*-BuOK/MeCN) of **22** afforded the desired epoxide **6**.[7] Alternatively, treatment of *trans*-diol **17** with TsCl (1.5 equiv) regioselectively afforded the *trans*-hydroxy tosylate **23**,[8] as the only substitution product. Monotosylate **23** is subsequently cyclized under basic conditions to epoxide **6**.

Scheme 6. Stereoselective Synthesis of *trans*-Hydroxy Mesylate **26** and in Situ Cyclization to Epoxide **5**



For the synthesis of epoxide **5** (Scheme 6), mesylate **24**, obtained by mesylation (MsCl/Py) of α-hydroxy ketone **16**, was partially isomerized by AcONa in refluxing MeCN to a 4:6 mixture of epimer **25** and starting mesylate **24**. After

(3) As they were not necessary to our study as pure enantiomers, epoxides **5** and **6** were prepared in a racemic form. A ciano-substituted epoxide, structurally related to **5**, has been previously described and its reaction with MeOH partially examined: Natsume, M.; Wada, M.; Ogawa, M. *Chem. Pharm. Bull.* **1978**, *26*, 3364.

(4) Theoretical calculations carried out on appropriate, simplified models (**5-Me** and **6-Me**) indicated that epoxides **5** and **6** exist as the only corresponding conformers **5a** and **6a**, respectively, with the $-CH_2OBn$ group axial (Scheme 2) (see Supporting Information).

(5) (a) Dransfield, P. J.; Gore, P. M.; Prokes, I.; Shipman, M.; Slawin, A. M. Z. *Org. Biomol. Chem.* **2003**, *1*, 2723. (b) In a closely related imino glycal system and conditions, the corresponding *β*-attack was up to 99%: Craig, D.; McCague, R.; Potter, G. A.; Williams, M. R. V. *Synlett* **1998**, 55.

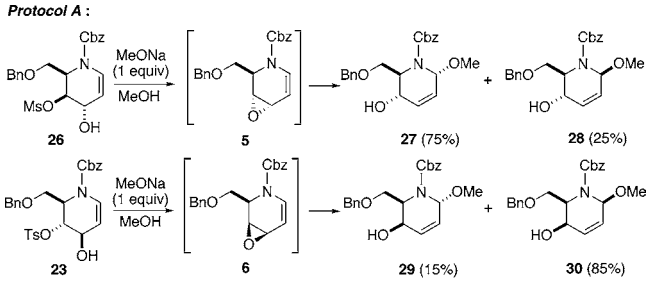
(6) Comins, D. L.; Fulp, A. B. *Tetrahedron Lett.* **2001**, *42*, 6839.

(7) Epoxide **6** turned out to be sufficiently stable in solution to the point that performing the cyclization reaction in CD_3CN allowed the full characterization by ^1H and ^{13}C NMR. Since it was decidedly less stable, it was not possible to register the ^1H NMR spectrum of **5**.

separation by SiO_2 flash chromatography, while the recovered starting mesylate **24** was recycled, the diastereoisomerically pure mesylate **25** was stereoselectively reduced by means of the $NaBH_4/CeCl_3$ protocol,[9] with the exclusive formation of the *trans*-hydroxy mesylate **26**. Cyclization of **26** under basic conditions (*t*-BuOK) afforded the desired epoxide **5**.[7]

In a preliminary examination of the regio- and stereochemical behavior of these new imino glycal-derived allyl epoxides **5** and **6** with alcohols (*O*-nucleophiles), the addition reaction of MeOH was examined by means of protocol A and protocol B. Under protocol A (alcohol as the solvent), the treatment of a MeOH solution of the *trans*-hydroxy mesylate **26** with MeONa (1 equiv) afforded, through the intermediate formation of epoxide **5**, a 75:25 mixture of the anomeric methyl α-*O*-glycoside **27** and *β*-*O*-glycoside **28** (Scheme 7). Under the same conditions, epoxide **6** (from

Scheme 7. Regio- and Stereoselectivity of the Addition of MeOH to Epoxides **5** and **6** under Protocols A and B



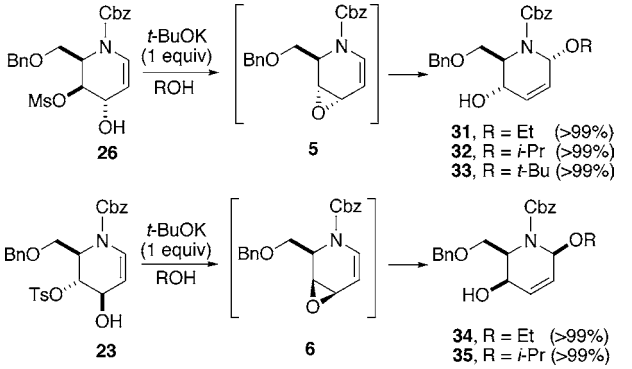
Protocol B : methyl *O*-glycosides **27** and **30** are the only reaction product (>99%).

trans-hydroxy tosylate **23**) afforded an 85:15 mixture of the corresponding methyl *β*-*O*-glycoside **30** and α-*O*-glycoside **29**. The pairs of glycosides **27** and **28** and **29** and **30** were separated by preparative TLC and structurally characterized (^{1}H NMR and FTIR).[10,11]

In both cases, the glycosylation reactions were completely 1,4-regioselective, with exclusive attack of the nucleophile (MeOH) on the C(1) carbon of the allyl system. The reactions were not completely stereoselective: a mixture of α- and *β*-glycosides was obtained in both cases. However, as previously observed in the corresponding reactions of **1** and **2**, also with epoxides **5** and **6**, the predominant methyl *O*-glycoside had the same configuration as the starting epoxide: α-*O*-glycoside **27** from **5** and *β*-*O*-glycoside **30** from **6**. When the same reactions were carried out under protocol B [MeONa (1.1 equiv), MeOH (3 equiv) in anhydrous MeCN], the methanolysis of epoxides **5** and **6** became completely regio- and stereoselective, with exclusive formation of the α-*O*-glycoside **27** from **5** and the *β*-*O*-glycoside **30** from **6** (Scheme 7).

O-Glycosyl acceptors other than MeOH, such as EtOH, *i*-PrOH, and *t*-BuOH, were also utilized in couplings with epoxides **5** and **6**. Except for the reaction of **6** with *t*-BuOH, which led to a complex reaction mixture under protocol A, the reactions of epoxides **5** and **6** were completely regio- and stereoselective with exclusive formation of the corresponding alkyl *O*-glycoside (**31**−**33** from **5** and **34**−**35** from **6**) with configuration the same as the starting epoxide (Scheme 8). Similar high stereocontrol was not regularly

Scheme 8. Regio- and Stereoselectivity of the Addition of EtOH, *i*-PrOH, and *t*-BuOH (Protocol A) to Epoxides **5** and **6**



observed under protocol A with the related glycal-derived epoxides **1** and **2**.

The complete 1,4-regio- and stereoselectivity observed in the reactions of **5** and **6** with alcohols (MeOH, under protocol B, and EtOH, *i*-PrOH, and *t*-BuOH, under protocol A, Schemes 7 and 8) was rationalized, as previously with epoxides **1** and **2**, by hydrogen bonding between the oxirane oxygen 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 conformer **6a**,[3] respectively, suitably arranged for an entropically favored attack on the corresponding C(1) carbon, from the same side as the oxirane ring: an α-directed attack in **5a** (*route **a***, a pseudoequatorial attack) and a *β*-directed attack in **6a** (*route **b***, a pseudoaxial attack) (Scheme 9).[12] This meant that with epoxides **5** and **6** the selectivity of the *O*-glycosylation of alcohols *did not depend* on the pseudoaxial or pseudoequatorial nature of the nu-

(8) The monotosylate **23** was obtained in an unsatisfactory yield (36%), reasonably due to the concomitant formation of the very reactive regioisomeric allyl tosylate **23-al**, which rapidly decomposes in the reaction medium, determining the loss of the corresponding portion of the starting diol **17**. The structure of **23** was confirmed by NOE experiments on the corresponding acetate **23-Ac**.

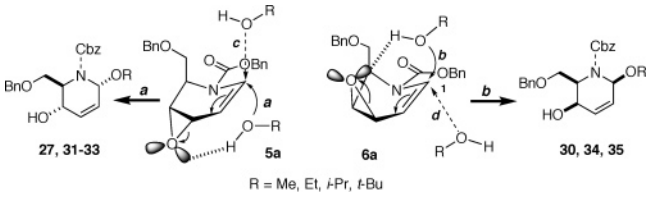
(9) Luche, J.-L.; Gemal, A. L. *J. Am. Chem. Soc*. **1979**, *101*, 5848.

(10) The characterization by NMR spectroscopy of many of the compounds obtained was hampered by the presence of rotamers around the N−CO bond. This necessitated the use of variable-temperature NMR spectroscopy to complete structural assignments.

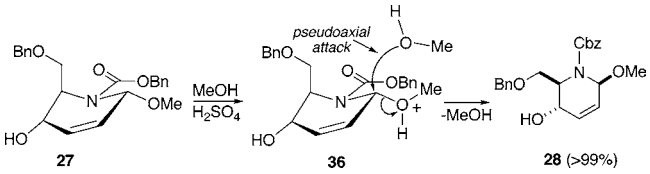
(11) The structures and configurations of methyl *O*-glycosides **27**−**30** were determined by means of their ^{1}H NMR spectra and appropriate NOE experiments. A confirmation of the structures assigned was obtained by examination of the OH-stretching band in the IR spectra of these compounds in dilute CCl_4 solution. With the exception of **28** which showed only a free OH, all the other *O*-glycosides (**27**, **29**, and **30**) showed a strong intramolecular hydrogen bond, a result which was completely in agreement with an appropriate theoretical conformational study carried out on simplified models (**27**−**30-OMe**) of these compounds. This study indicated also that the corresponding conformer with the $-CH_2OBn$ group axial is largely the more stable one (see Supporting Information).

(12) The failure of the addition of *t*-BuOH to **6** could be due to an unfavorable steric interaction between the attack direction along *route **b*** and the syn axial $-CH_2OBn$ side chain (Scheme 9).

Scheme 9. *Substrate-Dependent* Selectivity in the Glycosylation of Alcohols by Allyl Epoxides **5** and **6**



Scheme 10. Epimerization of methyl α-*O*-glycoside **27** into methyl *β*-*O*-glycoside **28**



cleophilic attack on C(1) of the corresponding imino glycal system, as could be expected on the basis of previous results (*product-dependent* selectivity, Scheme 3). Rather *it depended only* on the configuration of the epoxide and the correlated direction of the oxirane oxygen−alcohol coordination, in a sort of a *substrate-dependent* selectivity.[13]

A simple confirmation of how, at least in the reaction of **5** with alcohols,[12] the oxirane oxygen−alcohol coordination and related nucleophilic attack goes in the opposite way to the natural tendency of the imino glycal system to undergo preferential pseudoaxial nucleophilic attack at C(1) is obtained by treating the methyl α-*O*-glycoside **27** (the *substrate-dependent* selectivity anomer from **5** and MeOH) with a 10^{-5} N H_2SO_4−MeOH solution. A clean reaction occurs with complete epimerization of **27**[11] to **28**, the *product-dependent* selectivity anomer, by pseodoaxial attack of MeOH on the intermediate protonated species **36** (Scheme 10).[14,15]

In the framework of the proposed rationalization (Scheme 9), only in an excess of the more nucleophilic MeOH (protocol A) can a configurationally opposite attack by the free, noncoordinated nucleophile (*route* ***c*** and ***d***, R = Me) become competitive, as was experimentally observed with both epoxides **5** and **6**. In all other cases, the reduced nucleophilicity of the alcohol, probably associated with a more marked tendency of the imino glycal system of **5** and **6** to coordination, is sufficient to afford a completely stereoselective result, even in the presence of a large amount of the nucleophile (protocol A).

In our opinion, the present results offer the best demonstration of the occurrence and importance of an oxirane oxygen−alcohol coordination in directing the stereoselectivity of the addition reaction of alcohols to the present imino glycal- and related glycal-derived allyl epoxides.

Acknowledgment. This work was supported by the University of Pisa and MIUR, Roma. P.C. gratefully acknowledges Professor Daniel L. Comins for helpful details with regard to the synthesis of diol **17** and Merck Research Laboratories for the generous financial support deriving from the 2005 ADP Chemistry Award.

Supporting Information Available: Experimental details, spectral and analytical data for all reaction products, and theoretical conformational analysis for **5**, **6**, and **27**−**30**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Particularly significant is the result from epoxide **5**, where a *product-dependent* selectivity of the glycosylation process would have led to the corresponding *β*-anomer instead of the observed α-anomer. In **6**, the *product-* and the *substrate-dependent* selectivity lead to the same compound, the corresponding *β*-anomer.

(14) Alternatively, the intermediate occurrence of an *N*-acyliminio carbocation, pseudoaxially attacked by MeOH, cannot be excluded.

(15) Analogously, under the same reaction conditions, **29** completely epimerizes to **30**, whereas **28** and **30** are stable.