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Stereoselective Synthesis of 2,3-Unsaturated 1,6-Oligosaccharides by Means of a Glycal-Derived Allyl Epoxide and *N*-Nosyl Aziridine†

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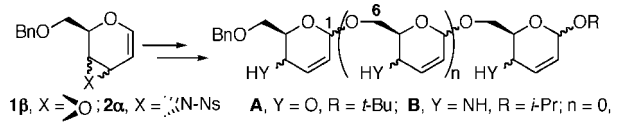
ABSTRACT



***β*-D-*threo*- and 4-deoxy-4-amino-α-D-*erythro*-hex-2-enopyranosyl di- (*n* = 0) and trisaccharides (*n* = 1) of types A and B were synthetized by means of a reiterative, completely stereoselective glycosylation process which makes use of the D-galactal-derived allyl epoxide 1*β* and D-allal-derived allyl *N*-nosyl aziridine 2α, respectively.**

Besides being present in many natural, biologically active compounds (antibiotics, antitumor agents, and cardiac glycosides), oligosaccharides are often found as components of glycoproteins and glycolipids which are important in cell surface recognition and cellular interactions and as blood group determinants and tumor-associated antigens.[1] The interest in these carbohydrates has stimulated the development of several solution- and solid-phase protocols for the synthesis of fully oxygenated natural oligosaccharides.[1,2] By way of contrast, less attention has been given to the synthesis of unsaturated oligosaccharides.[3] In this framework, the presence of the double bond, which allows further functionalization, makes 2,3-unsaturated oligosaccharides very interesting systems for the construction, not only of fully oxygenated, but also of deoxy and dideoxy sugars. [3a]

Recently, we found that the reaction of the diastereoisomeric D-galactal- and D-allal-derived allyl epoxides **1α**[4a] and **1*β***[4b,c] and *N*-nosyl aziridines **2α** and **2*β***[5a] with *O*-nucleophiles, such as alcohols and partially protected monosaccharides (3−4 equiv), led to the corresponding α-*O*-glycosides from **1α** and **2α** and *β*-*O*-glycosides from **1*β*** and **2*β*** in a new uncatalyzed substrate-dependent stereospecific glycosylation process (1,4-addition process). The close 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 or aziridine nitrogen in the form of a hydrogen bond, as shown in **3α″** and **4*β*′** (Scheme 1).[6,7]

† Dedicated to the memory of Professor Bruno Macchia (1933−2008).

(1) (a) Galonic, D. P.; Gin, D. Y. *Nature* **2007**, *446*, 1000, and references therein. (b) Seeberger, P. H.; Werz, D. B. *Nature* **2007**, *446*, 1046.

(2) (a) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed.* **1996**, *35*, 1380. (b) Nicolaou, K. C.; Wissinger, N.; Pastor, J.; DeRoose, F. *J. Am. Chem. Soc.* **1997**, *119*, 449, and references therein.

(3) For recent, effective synthesis of this kind of carbohydrates, see: (a) Babu, R. S.; Zhou, M.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2004**, *126*, 3428. (b) McDonald, F. E.; Zhu, H. Y. H. *J. Am. Chem. Soc.* **1998**, *120*, 4246.

(4) (a) Di Bussolo, V.; Caselli, M.; Romano, M. R.; Pineschi, M.; Crotti, P. *J. Org. Chem.* **2004**, *69*, 7383. (b) Di Bussolo, V.; Caselli, M.; Romano, M. R.; Pineschi, M.; Crotti, P. *J. Org. Chem.* **2004**, *69*, 8702. (c) Di Bussolo, V.; Caselli, M.; Pineschi, M.; Crotti, P. *Org. Lett.* **2003**, *5*, 2173.

(5) (a) Di Bussolo, V.; Romano, M. R.; Pineschi, M.; Crotti, P. *Tetrahedron* **2007**, *63*, 2482. See also: (b) Di Bussolo, V.; Romano, M. R.; Pineschi, M.; Crotti, P. *Org. Lett.* **2005**, *7*, 1299. (c) Di Bussolo, V.; Favero, L.; Romano, M. R.; Pineschi, M.; Crotti, P. *J. Org. Chem.* **2006**, *71*, 1696.

(6) A theoretical conformational study carried out on simplified structurally related models has indicated that epoxide **1α**[7] and aziridine **2α** (unpublished results) exist as an equilibrium mixture of the corresponding conformers α′ and α″, whereas the diastereoisomeric epoxide **1*β***[7] and aziridine **2*β***[5c] exist only as the corresponding conformer ***β*′** (Scheme 1).

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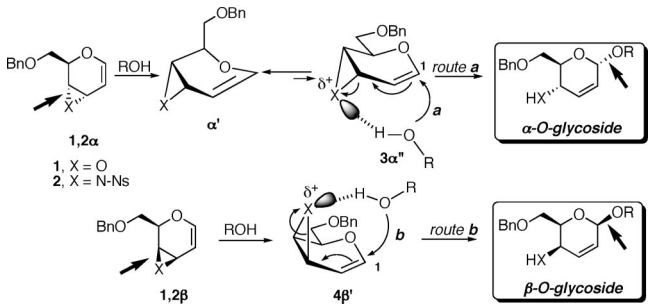
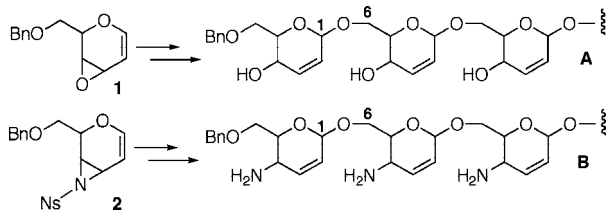
Scheme 1. Stereoselective Addition of *O*-Nucleophiles to Allyl Epoxides **1α** and **1*β*** and Allyl *N*-Nosyl Aziridines **2α** and **2*β***



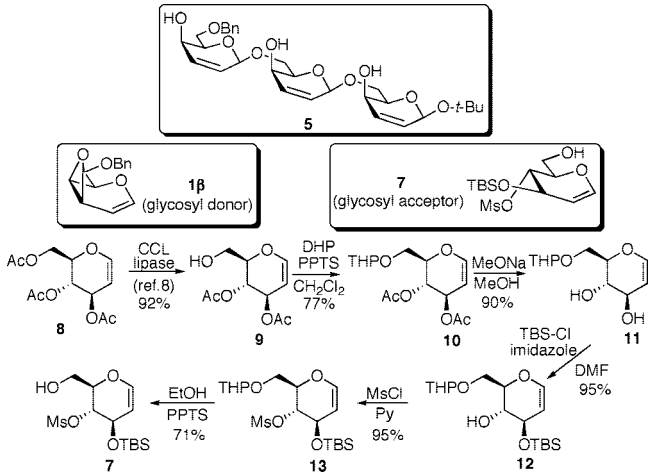
We saw the possibility of adapting the new glycosylation process found with epoxides **1α** and **1*β*** and aziridines **2α** and **2*β***, in a reiterative version for the stereoselective synthesis of 2,3-unsaturated-1,6-oligosaccharides of type **A**, by using a type **1** epoxide, and the corresponding 4-deoxy-4-amino-substituted oligosaccharides of type **B**, by using a type **2** aziridine (Scheme 2). This possibility was checked

Scheme 2. 2,3-Unsaturated-1,6-oligosaccharides (**A** and **B**)

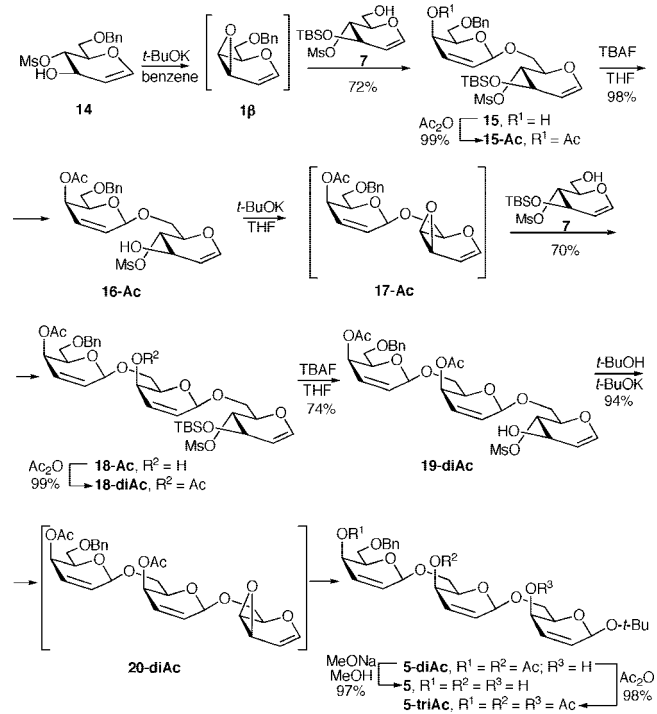


by preparing the type **A** *β*-linked-D-*threo*-hex-2-enopyranosyl-1,6-trisaccharide **5** (Schemes 3 and 4) and the type **B**

Scheme 3. Glycosyl Donor and Glycosyl Acceptor for the Synthesis of Trisaccharide **5**

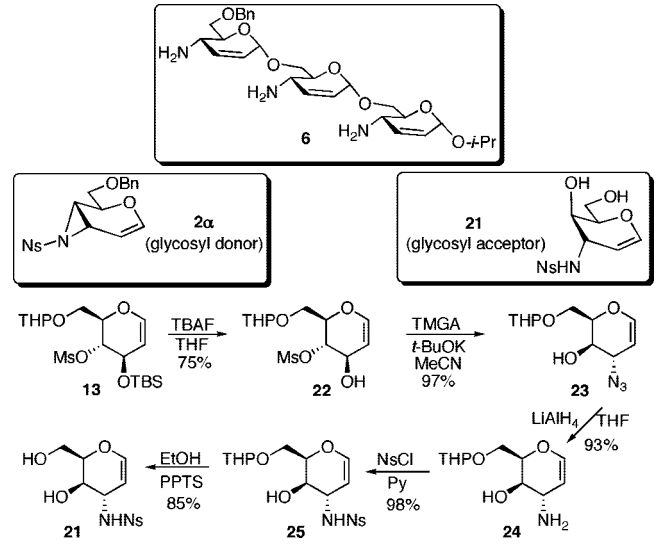


Scheme 4. Stereoselective Synthesis of Trisaccharide **5**



α-linked-4-deoxy-4-amino-D-*erythro*-hex-2-enopyranosyl-1,6-trisaccharide **6** (Schemes 5 and 6).

Scheme 5. Glycosyl Donor and Glycosyl Acceptor for the Synthesis of Trisaccharide **6**



For the synthesis of trisaccharide **5**, epoxide **1*β*** was taken as the initial glycosyl donor and primary alcohol **7** as the permanent glycosyl acceptor. Alcohol **7** was prepared

(7) Crotti, P.; Di Bussolo, V.; Pomelli, C. S.; Favero, L. *Theor. Chem. Acc.*, submitted.

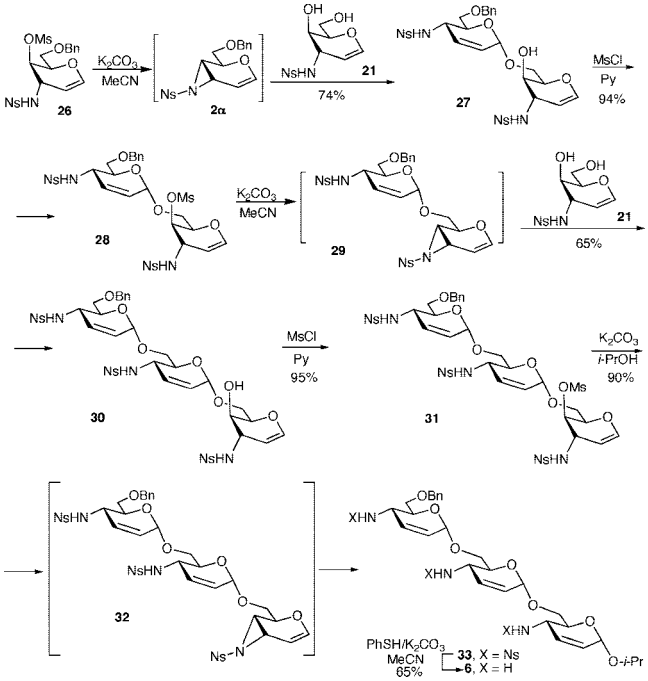
through a simple procedure starting from tri-*O*-acetyl-D-glucal (**8**), as shown in Scheme 3.[8]

The reaction of epoxide **1β** (prepared in situ by base-catalyzed cyclization of *trans*-hydroxy mesylate **14**)[4b] with alcohol **7** afforded, with complete β-stereoselectivity, the β-*O*-glycoside **15**, which was acetylated (**15-Ac**) then deprotected (TBAF/THF) to give the *trans*-hydroxy mesylate **16-Ac**. Base-catalyzed cyclization of **16-Ac**, followed by reaction of the intermediate allyl epoxide **17-Ac** (the new glycosyl donor) with alcohol **7** introduces the third fragment, still with complete β-stereoselectivity, to give the β-*O*-glycoside **18-Ac**, which was acetylated (**18-diAc**). Deprotection of **18-diAc** (TBAF/THF) led to the *trans*-hydroxy mesylate **19-diAc** which, on treatment with *t*-BuOH in the presence of *t*-BuOK, afforded, through the formation of the intermediate allyl epoxide **20-diAc**, the trisaccharide **5-diAc** as the corresponding *tert*-butyl β-*O*-glycoside.[9] Final saponification of the diacetyl derivative **5-diAc** afforded trisaccharide **5** in 33% overall yield (seven steps) (Scheme 4).[10]

Trisaccharide **5** was also prepared without acetylating the synthetic intermediates, but the quality of the crude product of each step and the overall yield [17% (five steps)] were lower (see Scheme 9, Supporting Information).

For the synthesis of trisaccharide **6**, aziridine **2α** was taken as the initial glycosyl donor and 1,3-diol **21** (prepared from the THP-derivative **13**), as the permanent glycosyl acceptor (Scheme 5).

Scheme 6. Stereoselective Synthesis of Trisaccharide **6**

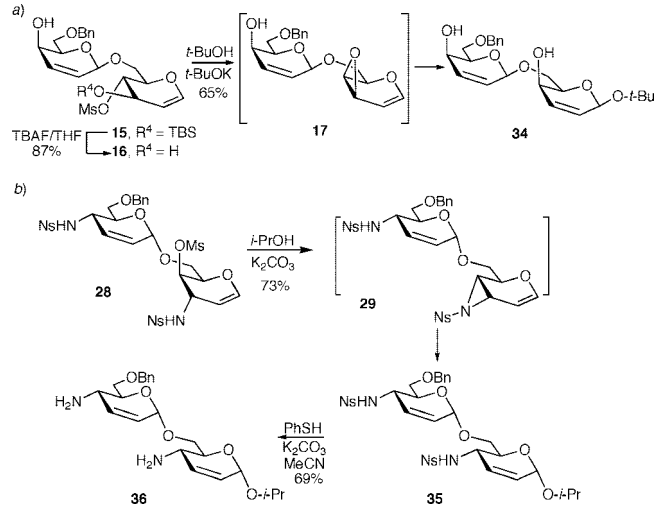


The synthesis of trisaccharide **6** is conceptually similar to that of trisaccharide **5**. In this case, all the glycosylation steps are α-stereoselective because the initial and the intermediate glycosyl donors are α-aziridines (Scheme 6).

The reaction of aziridine **2α** [prepared in situ by base-catalyzed (K_2CO_3) cyclization of the stable *trans*-*N*-nosyl-*O*-mesylate **26**][5a] with diol **21** afforded the *O*-glycoside **27** with complete regioselectivity (exclusive attack by the primary alcoholic functionality of **21**) and α-stereoselectivity. *O*-Glycoside **27** was transformed (MsCl/Py) into the *trans*-*N*-nosyl-*O*-mesylate **28**, which was cyclized under basic conditions to the intermediate α-aziridine **29**, the new glycosyl donor. The reaction of **29** with diol **21** introduces the third fragment, still with complete regio- and α-stereoselectivity, to give α-*O*-glycoside **30**, which was converted (MsCl/Py) into the *trans*-*N*-nosyl-*O*-mesylate **31**. The treatment of **31** with *i*-PrOH in the presence of K_2CO_3 afforded, through the intermediate α-aziridine **32**, the *N*-nosyl-substituted trisaccharide **33**, as the corresponding isopropyl α-*O*-glycoside (Scheme 6).[11] Deprotection of the *N*-nosyl-protected **33** by the PhSH/K_2CO_3 protocol[5a] afforded the desired free amino group-containing trisaccharide **6** in 25% overall yield (six steps) (Scheme 6).

Alternatively, the protocols described in Schemes 4 and 6 could be directed toward the synthesis of the corresponding disaccharides (equations *a* and *b*, Scheme 7). For this purpose, it was sufficient to subject *trans*-hydroxy mesylate **16**, obtained by deprotection (TBAF/THF) of β-*O*-glycoside **15**, and *trans N*-nosyl-*O*-mesylate **28** to the *t*-BuOH/*t*-BuOK and *i*-PrOH/K_2CO_3 protocol, respectively, in order to obtain,

Scheme 7. Synthesis of Disaccharides **34** and **36** (eqs *a* and *b*)



(8) For the preparation of 3,4-di-*O*-acetyl-D-glucal (**9**), see: Di Bussolo, V.; Favero, L.; Macchia, F.; Pineschi, M.; Crotti, P. *Tetrahedron* **2002**, *58*, 6069.

(9) *t*-BuOH was chosen for the formation of the final *O*-glycoside because, when this alcohol was used as the solvent, a completely β-stereoselective *O*-glycosylation process was obtained, as in the corresponding monomer, epoxide **1β**.[4b]

(10) Trisaccharide **5** was fully characterized also as the corresponding triacetyl derivative **5-triAc** (Scheme 4).

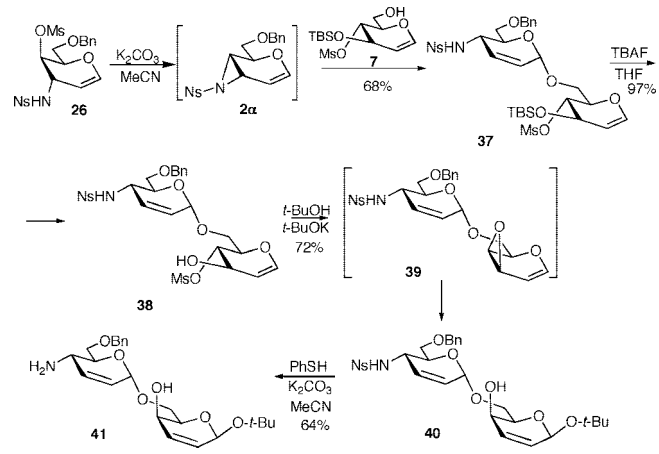
(11) *i*-PrOH was chosen for the formation of the final *O*-glycoside, because when this alcohol was used as the solvent, a completely α-stereoselective *O*-glycosylation process was obtained, as in the corresponding monomer, aziridine **2α**.[5a]

through the intermediate formation of the allyl β-epoxide **17** and allyl α-aziridine **29**, disaccharide **34** as *tert*-butyl β-*O*-glycoside (from **16**) and disaccharide **35** as isopropyl α-*O*-glycoside (from **28**).[9,11] Deprotection of **35** by the usual protocol ($PhSH/K_2CO_3$) afforded the free amino group-containing disaccharide **36**.

The method here described for the synthesis of 2,3-unsaturated-1,6-oligosaccharides (trisaccharides **5** and **6** and disaccharides **34** and **36**) appears to be very efficient with regard to the complete stereo- and regioselectivity observed in each glycosylation step and nice with regard to the overall yield (25−33% for six to seven steps). Moreover, it is interesting to note that the two protocols described for the construction of this class of oligosaccharides, one based on the D-galactal-derived allyl epoxide **1*β*** and the other based on the D-allal-derived allyl aziridine **2α**, can reasonably be mixed to give 1,6-oligosaccharides containing alternating −OH and $-NH_2$ groups at C(4), in which the stereoselectivity (α or β) of each glycosylation process is simply determined by the configuration (α or β) of the starting and intermediate allyl epoxide or aziridine system.[4,5] This point is nicely demonstrated by the synthesis of disaccharide **41**. In this case, aziridine **2α** was reacted with alcohol **7** (the glycosyl acceptor previously used for the synthesis of disaccharide **34** and trisaccharide **5**) affording the new *O*-glycoside **37**, with complete α-stereoselectivity. By means of the usual protocol (TBAF/THF), α-*O*-glycoside **37** was transformed into the *trans*-hydroxy mesylate **38**, which, on treatment with *t*-BuOH in the presence of *t*-BuOK, afforded, through the intermediate formation of β-epoxide **39**, disaccharide **40** as the corresponding *tert*-butyl β-*O*-glycoside (Scheme 8).[9] Deprotection of **40** by the $PhSH/K_2CO_3$ protocol afforded the corresponding free amino group-containing disaccharide **41** in 30% overall yield (four steps).

The synthetic value and utility of our protocol for the construction of 2,3-unsaturated-1,6-oligosaccharides such as **5**, **6**, **34**, **36**, and **41** is also confirmed by the observation that little is present in the literature on this subject. Actually, 4-amino-substituted-2,3-unsaturated-1,6-oligosaccharides such as trisaccharide **6**, the corresponding disaccharide **36** and the "mixed" disaccharide **41** are not present at all, at the moment, in literature, whereas, as regards 2,3-unsaturated-1,6-oligosaccharides such as the β-linked (*threo* configuration) trisaccharide **5** and the corresponding disaccharide **34**, there is only a recent paper by O'Doherty reporting the synthesis of structurally related α-linked (*erythro* configuration) di- and trisaccharides.[3a]

Scheme 8. Synthesis of Disaccharide **41**



Studies are in progress in order to identify conditions for the stereo- and/or regioselective functionalization of the double bond present in disaccharides **34**, **36**, and **41**, trisaccharides **5** and **6**, and the corresponding monosaccharides.[12]

Acknowledgment. This work was supported by the University of Pisa and MIUR, Roma. We thank Prof. Gabriele Renzi (Università di Camerino) for the determination of the molecular weight of oligosaccharides **5**, **5-triAc**, **6**, **34**, and **36**. P.C. gratefully acknowledges Merck Research Laboratories for the generous financial support deriving from the 2005 ADP Chemistry Award.

Supporting Information Available: Experimental details and spectral and analytical data for all reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) The choice of the 6-OBn protecting group on the terminal unsaturated unit of type **A** and **B** oligosaccharides was based on the assumption that its removal should occur only after functionalization of the double bond. Moreover, in type **B** oligosaccharides the cleavage of the benzyl ether should be carried out on the corresponding *N*-acetyl derivatives, rather than on the free amino group-containing compounds.