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Stereoselective Synthesis of 4-(*N*-Mesylamino)-2,3-unsaturated-α-*O*-glycosides via a New Glycal-Derived Vinyl α-*N*-(Mesyl)-aziridine

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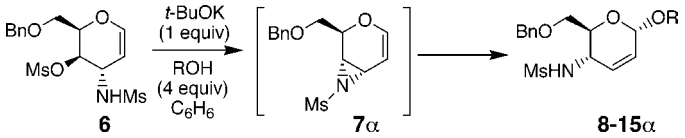
ABSTRACT



***N*-Mesyl aziridine 7α, a new activated vinyl aziridine derived from D-glucal, has been synthesized by cyclization of *trans*-*N*,*O*-dimesylate 6 with *t*-BuOK in anhydrous benzene. The reaction of 7α with alcohols, phenol, and monosaccharides (O-nucleophiles) leads to the corresponding 4-*N*-(mesylamino)-2,3-unsaturated-*O*-glycosides and disaccharides through a completely regioselective 1,4-addition process that proceeds with high or complete α-stereoselectivity.**

Alkyl *O*-glycosides having differently functionalized amino groups in different positions (aminosugars) are an important category of modified carbohydrate units present in numerous oligosaccharides and glycoconjugates.[1] Furthermore, aminosugars are important as essential components of bacterial capsular polysaccharides and as structural elements of aminoglycoside antibiotics with antiviral and antitumor activity.[2] In consideration of the biological importance of natural products containing aminosugars,[3] the development of efficient synthetic routes to these carbohydrates is an attractive goal.

In this framework, our interest has been directed toward the stereoselective introduction of a nitrogen functionality at the C(4) carbon of a glycal system with simultaneous glycosylation to give 2,3,4-trideoxy-4-*N*-(substituted-amino)-hex-2-enopyranosides as valuable, nitrogen-containing, synthetic intermediates since the unsaturation allows further functionalization. Few methods have been reported to date for the synthesis of these synthetically useful compounds: the most convenient of these involves an allyl cyanate-to-isocyanate rearrangement of hex-3-enopyranosides and a palladium-catalyzed allylic substitution by secondary amines of suitable hex-2-enopyranosides.[4]

Recently, we disclosed a new glycosylation process based on the regioselective 1,4-addition of O-nucleophiles (alcohols) and C-nucleophiles (lithium alkyls) to diastereoisomeric vinyl oxiranes **1***β* (**a** and **b**) and **1**α derived from 6-*O*-(benzyl)- (**2a**), 6-(*O*-trityl)-D-glucal (**2b**), and 6-*O*-(benzyl)-D-gulal (**3**), respectively. Corresponding 2,3-unsaturated α-*O*- and *C*-glycosides (from **1**α) and *β*-*O*- and *C*-glycosides (from **1***β*) were obtained in a stereospecific way, whose configuration turned out to depend only on the configuration (α or *β*) of the starting epoxide (Scheme 1).[5] The observation that in this process the C(4)-OH group of addition products comes from the intermediate epoxide led us to pursue the prospect

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(2) (a) Wang, Y.; Kalka-Moll, W. M.; Roehrl, M. H.; Kasper, D. L. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 13478. (b) Choi, Y.-H.; Roehrl, M. H.; Kasper, D. L.; Wang, J. Y. *Biochemistry* **2002**, *41*, 15144. (c) Sears, P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2300.

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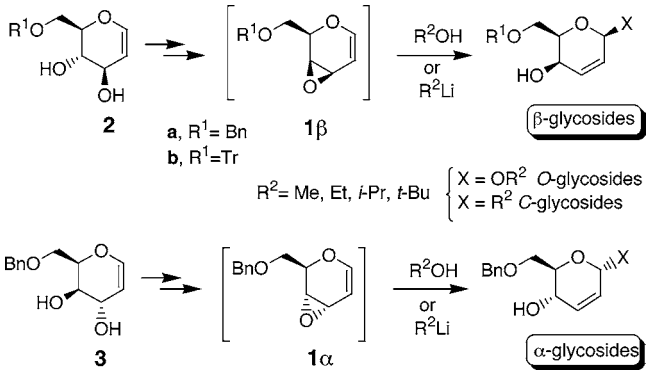
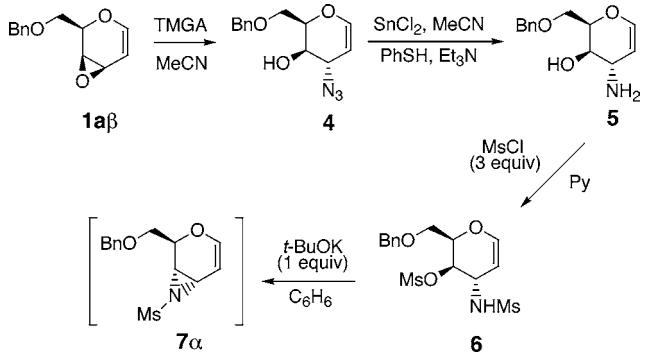
Scheme 1. Stereospecific α- and β-O-Glycosylation and C-Glycosidation by Epoxides **1**α and **1**β, Respectively



of achieving an analogous nitrogen transfer to the C(4) position via a corresponding activated aziridine intermediate.

In this preliminary approach to the chemistry of glycal-derived aziridines, the readily accessible *N*-mesyl α-aziridine **7**α (Scheme 2) turned out to be appropriate in order to check

Scheme 2. Stereoselective Synthesis of *N*,*O*-Dimesylate **6** and in Situ Cyclization to *N*-Mesyl Aziridine **7**α



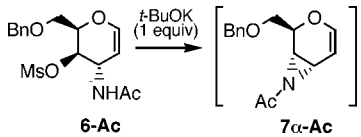
the chemical behavior of this new class of activated aziridines. We now report the stereoselective synthesis of the glycal-derived, activated aziridine **7**α, starting from vinyl β-epoxide **1a**β (Scheme 2), and the corresponding regio- and stereochemical behavior in nucleophilic addition reactions with alcohols (O-nucleophiles).[6]

As previously reported,[7] the reaction of epoxide **1a**β with the noncoordinating tetramethylguanidinazide (TMGA) in MeCN proceeds in a completely 1,2-regioselective and anti-stereoselective way to afford the *trans*-azido alcohol **4** as the only reaction product (Scheme 2). The reduction of **4** with $SnCl_2$ in MeCN in the presence of PhSH/Et_3N led to *trans*-β-amino alcohol **5**,[8] which was protected on both the amino and alcoholic groups with MsCl in Py to give the *trans*-*N*,*O*-dimesylate **6**, the ultimate precursor of vinyl *N*-mesyl aziridine **7**α. As in the case of the corresponding epoxides **1**α and **1**β, aziridine **7**α was not stable enough to be isolated and could only be obtained in situ by base-catalyzed (*t*-BuOK) cyclization of *N*,*O*-dimesylate **6**.[9] However, appropriate ^{1}H NMR (200 MHz) experiments carried out on the sample prepared by adding *t*-BuOK to a C_6D_6 solution of **6** at 5 °C clearly showed that, within 10 min, vinyl aziridine **7**α was present in the reaction mixture together with an almost equivalent amount of the unreacted precursor **6** (50% conversion).[10] The evidence for aziridine formation prompted us to determine the best protocol in order to accomplish an efficient one-pot glycosylation process using this new glycal donor.

In the optimized procedure, *t*-BuOK (1 equiv) was added at room temperature to a solution of *trans*-*N*,*O*-dimesylate **6** in anhydrous benzene containing MeOH (4 equiv) (protocol A). A regioselective S_N2' reaction was obtained with clean formation of the corresponding 4-*N*-(mesylamino)-2,3-unsaturated-α-*O*-methyl glycoside **8**α (entry 1, Table 1) with a high α-stereoselectivity (93%). Under this protocol, the intermediate vinyl aziridine **7**α does not decompose but immediately reacts with the nucleophile (MeOH) present in the reaction mixture.[11]

(5) (a) Di Bussolo, V.; Caselli, M.; Pineschi, M.; Crotti, P. *Org. Lett.* **2002**, *4*, 3695. (b) Di Bussolo, V.; Caselli, M.; Pineschi, M.; Crotti, P. *Org. Lett.* **2003**, *5*, 2173. (c) Di Bussolo, V.; Caselli, M.; Romano, M. R.; Pineschi, M.; Crotti, P. *J. Org. Chem.* **2004**, *69*, 7383.

(6) Actually, the *N*-acetyl-*O*-mesyl deivative **6-Ac** corresponding to *N*,*O*-dimesylate **6** (Scheme 2) was initially prepared as a suitable precursor of the *N*-acetyl aziridine (**7**α-**Ac**) corresponding to **7**α and examined in addition reaction with alcohols.



Unfortunately, **6-Ac** turned out to be completely unreactive with alcohols under protocol B (see text) and was entirely recovered from the reaction mixture. 1,4-Addition products derived from the corresponding aziridine **7**α-**Ac** were obtained, even if in an unsatisfactory yield, only when **6-Ac** was left to react under protocol A (see text) only with MeOH and EtOH.

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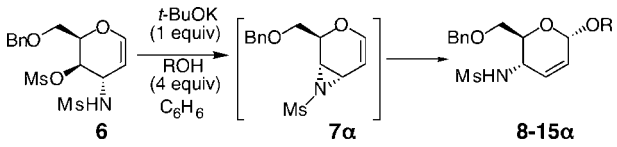
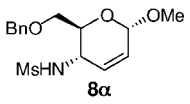
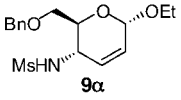
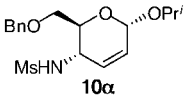
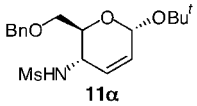
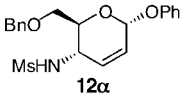
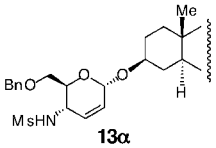
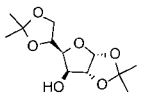
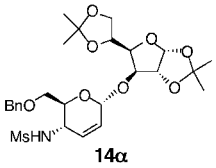
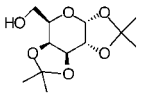
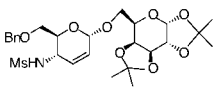
(10) Prolonged reaction times (1 h) at 5 °C afforded a 7:3 mixture of vinyl aziridine **7**α and *tert*-butyl α-*O*-glycoside **11**α (Table 1) derived from 1,4-addition to aziridine **7**α of *t*-BuOH formed in the reaction mixture by deprotonation−cyclization of *N*,*O*-dimesylate **6** by *t*-BuOK.

(11) If MeOH is not initially present in the reaction mixture but is added only after 15 min of stirring of the starting solution of *N*,*O*-dimesylate **6** in the presence of *t*-BuOK, *tert*-butyl α-*O*-glycoside **11**α turned out to be the only product present in the crude reaction mixture (^{1}H NMR).

Table 1. Glycosylation of Alcohols and Phenol by the in Situ-Formed Vinyl Aziridine **7**α (Protocol A)



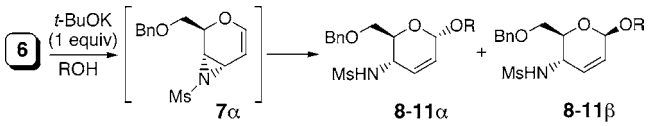
Entry	Glycosyl Acceptor (ROH)	Time (h)	Product[a]	Yield (%)[b]
1	MeOH	3	 **8**α	80
2	EtOH	3	 **9**α	78
3	*i*-PrOH	3	 **10**α	76
4	*t*-BuOH	3	 **11**α	82
5	PhOH	3	 **12**α	75
6	Dihydro-cholesterol	16	 **13**α	76
7		4	 **14**α	74
8		5	 **15**α	72

[a] In all cases, the corresponding β-anomer was detected (^{1}H NMR): entries 1−3 (7%), entry 5 (5%), and entries 4 and 6−8 (less than 1%). [b] Purified product (flash chromatography or preparative TLC).

To verify the scope of this glycosylation method, a number of glycosyl acceptors were employed in coupling reactions with the intermediate aziridine **7**α (Table 1). Under the described protocol (protocol A), simple primary (EtOH) and secondary alcohols (*i*-PrOH) and phenol (entries 2, 3, and 5, Table 1), as well as more hindered O-nucleophiles such as *t*-BuOH, (+)-dihydrocholesterol, 1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose (diacetone D-glucose), and 1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranose (entries 4 and 6−8, Table 1), were glycosylated with good yields. The corresponding 4-*N*-(mesylamino)-2,3-unsaturated-α-glycosides (**9**α−**13**α) and disaccharides (**14**α and **15**α) were obtained with complete 1,4-regioselectivity and high (93−95%, in the case of **9**α, **10**α, and **12**α) or complete α-stereoselectivity (in the case of **11**α and **13**α−**15**α) (Table 1).

In the case of MeOH, EtOH, *i*-PrOH, and *t*-BuOH, the addition reaction was repeated using the alcohol itself as the solvent (protocol B). Under these conditions, the glycosylation reaction was still completely 1,4-regioselective, but the α/β anomeric ratio depended on the alcohol used. For example, the low α-stereoselectivity observed with the less hindered MeOH (α/β = 60/40) increased on passing to the progressively more hindered EtOH (α/β = 75/25) and *i*-PrOH (α/β = 93:7). Only in the case of the encumbered *t*-BuOH was complete α-stereoselectivity observed (Scheme 3).

Scheme 3. Glycosylation of Simple Alcohols by the in Situ-Formed Vinyl Aziridine **7**α (Protocol B)



solvent/nucleophile (ROH)			
MeOH	**8**α (60)	R=Me	**8**β (40)
EtOH	**9**α (75)	R=Et	**9**β (25)
i-PrOH	**10**α (93)	R=*i*-Pr	**10**β (7)
t-BuOH	**11**α (>99)	R= *t*-Bu	**11**β (<1)

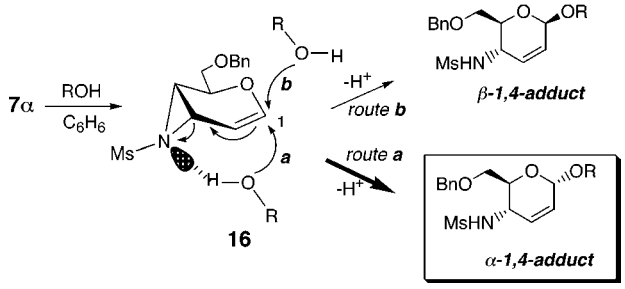
Due to the substantial amount of β-anomer present, the reactions carried out in MeOH and EtOH under protocol B required the separation by preparative TLC of the α- (**8**α and **9**α) and β-glycosides (**8**β and **9**β) whose relative structure and configuration were independently determined by appropriate NOE experiments carried out on the respective H-1 and H-5 protons. This allowed us to assign the α-configuration to the major or only *O*-glycoside present, not only in these (MeOH and EtOH) but also in all other addition reactions (entries 3−8, Table 1).[12]

(12) Contrary to what was observed in the α- and β-*O*-glycosides derived from epoxides **1**α and **1**β, respectively, the chemical shift of the anomeric proton H-1 in the ^{1}H NMR spectra of the diastereoisomeric pairs **8**α and **8**β and **9**α and **9**β is not useful for assigning the relative α- and β-configuration of anomers. However, the chemical shift of the singlet corresponding to the methyl group of the $MeSO_2NH-$ group in the ^{1}H NMR spectrum of both **8**β and **9**β (δ 2.95) is more downfield than that in the corresponding anomers **8**α and **9**α (δ 2.88). As a consequence, the observed value of the chemical shift of the mesyl group for the main or almost unique addition product, typically around δ 2.87−2.90, together with the observation of the constant presence of a slightly downfield singlet signal around δ 2.95−2.98 in the crude addition reaction mixture corresponding to entries 3−8, Table 1, reasonably due to the corresponding β-anomer (5−7% in entries 3 and 5, and less than 1% in entries 4 and 6−8, Table 1) made it possible to assign the α-configuration to the main, or almost unique product, in each addition reaction.

The results obtained indicate that in the case of aziridine **7**α there is a close relationship between the configuration (α) of the three-membered heterocycle (the aziridine ring) and the largely predominant or exclusive direction (α) of the O-glycosylation process, as previously observed for the corresponding epoxide **1**α in related addition reactions.[5c]

The occurrence of an effective coordination (hydrogen bond) between the aziridine nitrogen and the O-nucleophile (ROH) as shown in structure **16** (Scheme 4) can reasonably

Scheme 4. Rationalization of the 1,4-Regio- and α-Stereoselective Addition of Alcohols to Aziridine **7**α



rationalize the results. In this way, the nucleophile alcohol (ROH) is brought onto the α-face of the aziridine system and is suitably arranged for an entropically favored α-directed nucleophilic attack on the C(1) carbon of the unsaturated system, via pseudoaxial attack (*route* ***a***, Scheme 4). Conversely, a *β*-directed attack on C(1) (*route* ***b***, Scheme 4), which corresponds to a less favored pseudoequatorial attack, by a free, noncoordinated O-nucleophile (ROH) should reasonably be less active, particularly in conditions where a small amount of the nucleophile is present (protocol A), as experimentally observed (Table 1 and Scheme 4).

Within this rationalization, it is interesting to note that the α/*β* stereoselectivity observed under protocol B with vinyl α-aziridine **7**α (from α/*β* = 60/40 in MeOH to α/*β* = 75/25 in EtOH, and α/*β* = 93/7 in *i*-PrOH, Scheme 4) is smaller than that observed with the corresponding α-epoxide **1**α under the same O-glycosylating conditions (from α/*β* = 81/19 in MeOH to α/*β* = 93/7 in EtOH and complete α-stereoselectivity in *i*-PrOH).[5c] Reasonably, the inductive and conjugative electron-withdrawing effect of the mesyl group makes the lone pair of the aziridine nitrogen of **7**α less available for hydrogen bonding than the oxirane oxygen lone pair of epoxide **1**α,[13] thus making, in the case of aziridine **7**α, the *β*-directed attack by a noncoordinated nucleophile molecule (ROH) more competitive (*route* ***b***, Scheme 4).

Studies are under way in order to evaluate the regio- and stereochemical behavior of aziridine **7**α with other nucleophiles, such as C-, N-, and S-nucleophiles.

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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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