JOC*Note*

Stereoselective Uncatalyzed Synthesis of 2,3-Unsaturated-4-N-substituted-β-*O*-glycosides by Means of a New D-Galactal-Derived *N*-(Mesyl)-aziridine†

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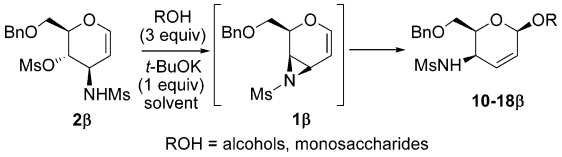
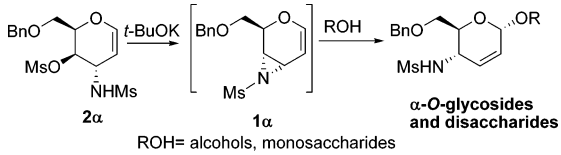


The reaction of the new D-galactal-derived allylic aziridine **1*β*** with *O*-nucleophiles (alcohols and monosaccharides) affords, in a high to complete β-stereoselectivity, the corresponding 2,3-unsaturated-β-*O*-glycosides bearing a β-N-functionality at C(4).

Aminosugars[1] are an important class of monosaccharides, widely distributed in nature, and some of them constitute the essential part of highly effective aminoglycoside antibiotics with antiviral and anticancer activity.[2] Glycal-derived activated allylic aziridines can be valuable synthetic intermediates for the regio- and stereoselective synthesis of 4-amino-derived-2,3-unsaturated glycosides, assuming that a selective glycosylation process (a conjugated addition) could occur under nucleophilic addition reaction conditions. Recently, we synthesized and studied the nucleophilic addition reactions of *O*-nucleophiles to the *N*-(mesyl)-aziridine **1α**, a newly activated D-allal-derived allylic aziridine (Scheme 1).[3,4] The glycosylation of alcohols and monosaccharides with **1α**, obtained by base-catalyzed cyclization of the corresponding stable precursor, the *N*,*O*-dimesylate **2α**,[5] led to the corresponding 2,3-unsaturated-*O*-glycosides and disaccharides through a completely regioselective 1,4-addition

SCHEME 1



process, giving rise to exclusive α-stereoselectivity. Through the use of this methodology, a nitrogen functionality was regio- and stereoselectively introduced at the C(4)-carbon of a pseudoglycal system (Scheme 1).[3]

To evaluate the synthetic utility of this new class of activated allylic aziridines and to check whether the stereoselectivity observed in the glycosylation of alcohols and monosaccharides is substrate-dependent, the diastereoisomeric activated D-galactal-derived allylic aziridine **1*β***[4] was synthesized and its regio- and stereochemical behavior in nucleophilic addition reactions with *O*-nucleophiles was examined.

The stereoselective synthesis of aziridine **1*β*** started from the previously described glycal-derived allylic epoxide **3α** (Scheme 2).[6] The nucleophilic ring opening of epoxide **3α** with tetramethylguanidine azide (TMGA) afforded in a completely regioselective and highly stereoselective way the *trans*-azido alcohol **5** in a 90:10 mixture with the *cis* diastereoisomer **6**. Azido alcohol **5** was separated by flash chromatography and reduced by the $SnCl_2$/PhSH/NEt_3 protocol[7] in MeCN to yield the *trans*-β-amino alcohol **7**, which was not purified, but directly protected with MsCl in pyridine to give the *trans*-*N*,*O*-dimesylate **2*β***, the stable precursor of allylic aziridine **1*β***. Base-catalyzed (*t*-BuOK) cyclization of **2*β*** affords aziridine **1*β***, which is consequently reacted immediately in situ with a nucleophile.[8] Alternatively, the necessary *trans*-azido alcohol **5** was prepared from the more readily available diastereoisomeric allylic epoxide **3*β***.[5] The addition reaction of $TMSN_3$ to epoxide **3*β*** at −20 °C afforded in excellent regio- and stereoselective control the *cis*-azido alcohol **8**, which was oxidized by PCC using microwaves to the azido ketone **9**.[9] The reduction of **9** with $LiAlH_4$ at −20 °C afforded a 20:80 mixture of the starting *cis*-azido alcohol **8** and the desired *trans*-azido alcohol **5**, which was then separated pure by flash chromatography (Scheme 3).[10]

† Dedicated to the memory of Professor Giancarlo Berti.

(1) (a) Banoub, J.; Boullanger, P.; Lafont, D. *Chem. Rev.* **1992**, *92*, 1167. (b) van den Bos, L. J.; Codée, J. D. C.; van Boom, J. H.; Overkleeft, H. S.; van der Marel, G. A. *Org. Biomol. Chem.* **2003**, *1*, 4160. (c) Bernfield, M.; Gotte, M.; Park, P. W.; Reizes, O.; Fitzgerald, M. L.; Lincecum, J.; Zako, M. *Annu. Rev. Biochem.* **1999**, *68*, 729. (d) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683.

(2) (a) Kotra, L. P.; Mobashery, S. *Curr. Org. Chem.* **2001**, *5*, 193. (b) Michael, K.; Tor, Y. *Chem.−Eur. J.* **1998**, *4*, 2091. (c) Sears, P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2301.

(3) Di Bussolo, V.; Romano, M. R.; Pineschi, M.; Crotti, P. *Org. Lett.* **2005**, *7*, 1299.

(4) On the basis of the absolute configuration of the corresponding C(3) and C(4) aziridine carbons, aziridines **1α** and **1*β*** are considered to be derived from D-allal and D-galactal, respectively, which present the same absolute configuration at the same carbons.

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

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

(7) Bartra, M.; Romea, P.; Urpi, F.; Vilarrasa, J. *Tetrahedron* **1990**, *46*, 587.

(8) Aziridine **1*β*** turned out to be particularly reactive and unstable: the ^{1}H NMR spectrum of the reaction mixture obtained by treatment of a solution of dimesylate **2*β*** in C_6D_6 with a dried alkaline resin (MP-carbonate) showed the presence of only a limited amount (15%) of aziridine **1*β***, together with products deriving from its extensive decomposition. The use in this experiment of *t*-BuOK (1 equiv) as the base led to a complex reaction mixture containing glycoside **13*β*** (10−15%), the product of the addition of *t*-BuOH, formed in the reaction mixture, to the in situ formed aziridine **1*β***.

(9) The same reaction carried out under standard conditions turned out to be extremely sluggish, to the point that after 36 h at room temperature, the starting azido alcohol **8** was still present (20%). Longer reaction times led only to complex reaction mixtures.

(10) Other reduction protocols ($LiAlH_4$ room temperature, 0 °C, −78 °C, and $NaBH_4$−EtOH) turned out to be decidedly less stereoselective toward the desired *trans*-azido alcohol **5**.

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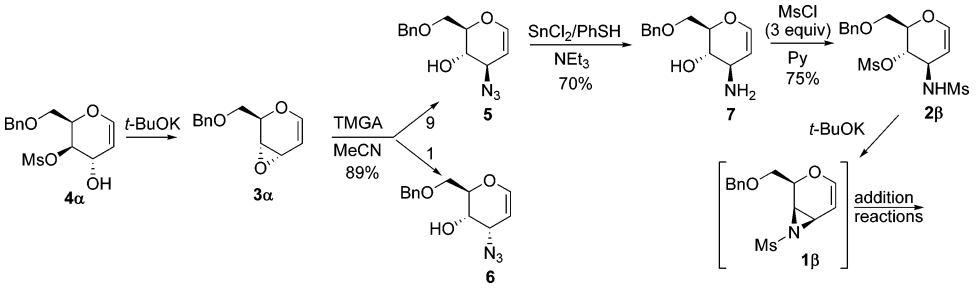
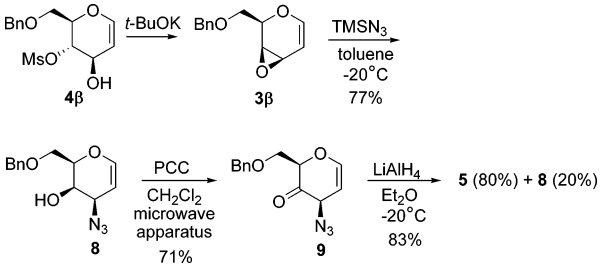


SCHEME 3



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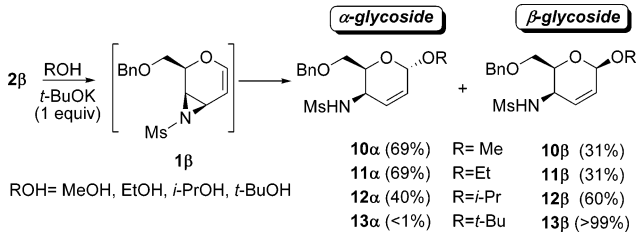


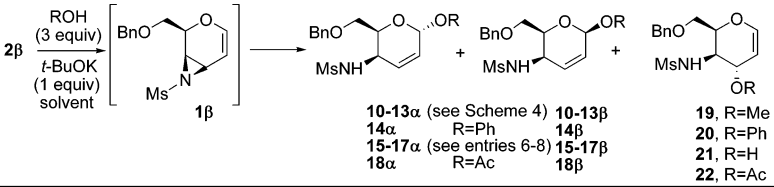
The glycosylation of simple alcohols (MeOH, EtOH, *i*-PrOH, *t*-BuOH) by the in situ formed allylic aziridine **1*β*** (*t*-BuOK cyclization of dimesylate **2*β***), carried out in the alcohol itself as the solvent (protocol A), turned out to be completely 1,4-regioselective, with a stereochemical behavior (the α/*β* anomeric ratio) not only largely dependent on the alcohol used, but also decidedly different from that observed with aziridine **1α** and related allylic oxiranes **3α** and **3*β*** in the same experimental conditions.[3,5,6] In fact, with both MeOH and EtOH a practically identical 31:69 *β*/α selectivity was observed, indicating, for the first time, the same stereochemical behavior for these two alcohols and, more notably, a stereoselectivity (α, in the present case) opposite to the configuration (*β*, in the present case) of the intermediate reactive heterocycle, the aziridine **1*β***, in the present case. Only in the case of the more sterically demanding *i*-PrOH was the usual selectivity, even if inferior to expectations (60%), favoring the anomer (*β*) configurationally homogeneous with the configuration (*β*) of the aziridine obtained, to the point that with *t*-BuOH a complete *β*-stereoselectivity was observed (Scheme 4). In the case of the reactions carried out with MeOH, EtOH, and *i*-PrOH, the corresponding pair of α- and *β*-glycosides were separated and independently characterized.[11]

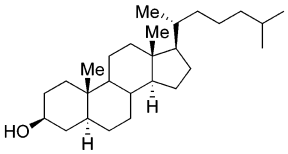
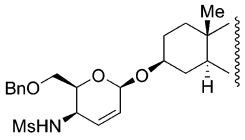
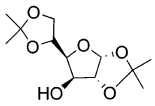
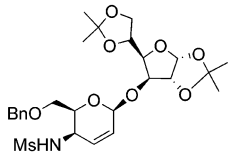
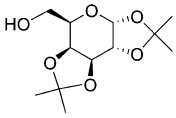
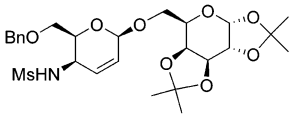
Because we were interested in the use of not only simple alcohols but also more complex alcohols, phenol, and monosaccharides toward a more general preparation of 4-N-substituted-*O*-glycosides, the addition reaction was repeated by treating a benzene solution of aziridine **1*β*** with only a small amount of nucleophile (3−4 equiv) (protocol B, Table 1). Under these conditions, with the only exclusion of phenol, the addition reactions are completely 1,4-regioselective and show a stereoselectivity drastically driven toward the anomer (*β*) having the same configuration (*β*) as the starting aziridine. The nature of the *O*-nucleophile determines only the extent of the generally observed *β*-stereoselectivity. In this framework, whereas MeOH shows only a moderate *β*-stereoselectivity (*β*-anomer/α-anomer = 85:15), showing an inverted behavior with respect to the same reaction carried out under protocol A, EtOH leads to an almost exclusive *β*-stereoselectivity (95%), and a complete *β*-stereoselectivity (>99% of the corresponding *β*-anomer turned out to be present in the crude reaction product) was observed with those *O*-nucleophiles such as *i*-PrOH, *t*-BuOH, dihydrocholesterol, diacetone-D-glucose, and 1,2;3,4-diisopropyliden-D-galactopyranose, which are characterized by an increasing steric demand around the nucleophilic center (entries 1−8, Table 1).

The great tendency of aziridine **1*β***, and in general of three-membered heterocycles (epoxides and aziridines) derived from glycals, to give 1,4-addition products with *O*-nucleophiles[3,5,6] is further demonstrated by the reaction of aziridine **1*β*** with AcONa in DMF, that is to say, under conditions that should reasonably favor a typical S_N2 process. Actually, the corresponding *β*-acetyl glycoside, the acetate **18*β***, turned out to be clearly the main addition reaction product (92%) with only a small amount of the expected 1,2-addition product, the *trans*-mesylamino acetate **22** (8%) (entry 11, Table 1, and Scheme 5). In the same way, the reaction of aziridine **1*β*** with a nucleophile such as MeONa afforded a crude reaction mixture containing both anti-1,2 and *β*-1,4-addition products in a 60:40 ratio (entry 12, Table 1). A selective 1,2-addition process was obtained only by making use of two reagents recently prepared in our laboratory in which the appropriate *O*-nucleophile is the counterion of the noncoordinating tetrabutylammonium cation (Bu_4N^+). In this way, the treatment of a solution of aziridine **1*β*** with tetrabutylammonium methoxide (TBAOMe)[5b] and tetrabutylammonium trimethylsilanolate ($TBAOSiMe_3$)[5b] afforded exclusively the corresponding *trans*-methoxy- (**19**) and *trans*-hydroxymesylamino derivative (**21**), respectively, in a complete 1,2-regio- and anti-stereoselective fashion (entries 9 and 10, Table 1, and Scheme 5). Acetylation of **21** afforded acetate **22**, thus confirming the structure and stereochemistry of the minor product previously obtained in the reaction of aziridine **1*β*** with AcONa.

(11) The α-configuration of glycosides **10**−**12α** and **14α** and the *β*-configuration of glycosides **10**−**17*β*** were established by comparison of the chemical shift of the anomeric proton in both α- and *β*-anomers, which indicates, in accordance with previously reported data, that the value for H-1 in the α-anomer is upfield with respect to the value for the H-1 proton in the corresponding *β*-anomer.[12,13] The *β*-configuration of glycosyl acetate **18*β*** was established by comparison of the chemical shift of the anomeric proton (*δ* 5.79) with literature data for the same proton in structurally related glycosyl acetates (around *δ* 5.75−5.91 for *β*-anomer and *δ* 6.07−6.35 for the corresponding α-anomer).[14]

TABLE 1. Regio- and Stereoselectivity of the Addition Reaction of *O*-Nucleophiles to the in Situ Formed *N*-(Mesyl)-aziridine 1β under Protocol B[a]



entry	glycosyl acceptor (ROH)	solvent	time (h)	product(s)	yield (%)
1	MeOH	benzene	2	**10α** (15%) **10β** (85%)	92[b]
2	EtOH	benzene	2	**11α** (5%) **11β** (95%)	97[b]
3	*i*-PrOH	benzene	2	**12β** (>99%)	78[c]
4	*t*-BuOH	benzene	2	**13β** (>99%)	86[c]
5	PhOH	benzene	3	**14α**(15%) **14β**(45%) **20**(40%)	90[b]
6	Dihydrocholesterol	benzene	16	**15β** (>99%)	78[c]
					
7	Diacetone-D-glucose	benzene	1.5	**16β** (>99%)	77[c]
					
8	1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranose	benzene	2	**17β** (>99%)	73[c]
					
9	$Bu_4N^+MeO^-$	THF	1	**19** (>99%)	96[b]
10	$Bu_4N^+Me_3SiO^-$	THF	1.5	**21** (>99%)	93[b]
11	AcONa	DMF	16	**18β** (92%) **22** (8%)	95[b]
12	MeONa	benzene	3	**10β** (40%) **19** (60%)	92[c]

[a] Protocol B: benzene, THF or DMF as the solvent, ROH = 3−4 equiv. [b] Crude product. [c] Purified product (flash chromatography or preparative TLC).

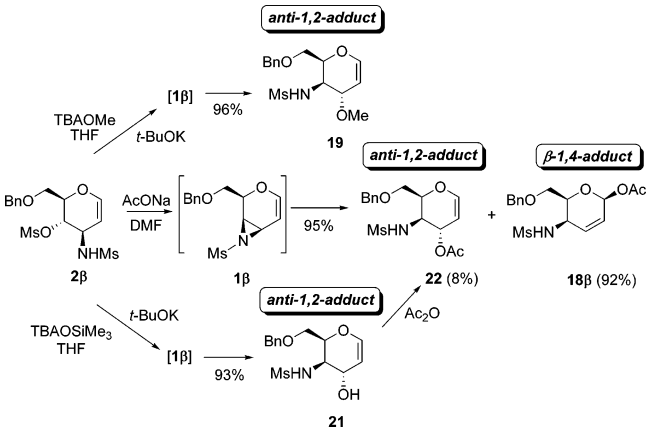
With the only exception of these two last reactions, which are completely 1,2-regio- and anti-stereoselective (see above), the addition reactions of *O*-nucleophiles to aziridine **1*β***, at least in conditions of a reduced amount of nucleophile present (protocol B, Table 1), show a complete 1,4-regioselectivity and a stereoselectivity (*β*) that appear to be driven by the configuration of the aziridine. As in the case of the other previously examined aziridine and epoxides derived from the glycal system,[3,5,6] the occurrence of a suitable coordination in the form of a hydrogen bond between the reactive substrate, the aziridine **1*β*** reacting in the only stable conformation **1*β′***,[15] and the *O*-nucleophile appears to be adequate to rationalize the observed results. In this way, the nucleophile is advantageously brought to the *β* face of the aziridine system and is well-disposed for

(12) Achmatowicz, O., Jr.; Bielski, R. *Carbohydr. Res.* **1977**, *55*, 165.

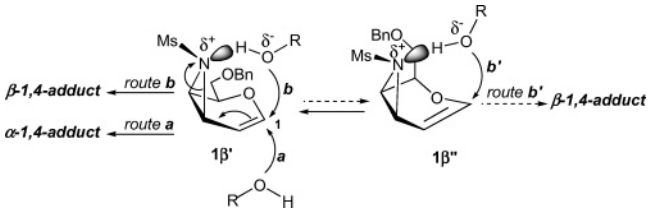
(13) In the case of the reaction of aziridine **1*β*** with *t*-BuOH, (+)-dihydrocholesterol, diacetone-D-glucose, and 1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranose (protocol B), a signal could be detected at *δ* 5.06, 4.99−5.03, 5.13−5.17, 4.99−5.03 in the ^{1}H NMR spectrum of the respective crude reaction mixture, reasonably due to the corresponding isomeric α-anomer **13α**, **15**−**17α** (less than 1%), respectively.

(14) (a) Horton, D.; Hughes, J. B.; Jewell, J. S.; Philips, K, D.; Turner, W. N. *J. Org. Chem.* **1967**, *32*, 1073. (b) Liu, F.-W.; Zhang, Y.-B.; Liu, H.-M.; Song, X.-P. *Cabohydr. Res.* **2005**, *304*, 489. (c) Vaghefi, M. M.; Bernacki, R. J.; Dalley, N. K.; Wilson, B. E.; Robins, R. K. *J. Med. Chem.* **1987**, *30*, 1383. (d) Capon, B.; Lee, Y. *J. Org. Chem.* **1991**, *56*, 4428.

SCHEME 5



SCHEME 6



an entropically favored β-directed attack on the nearby C(1) carbon, as shown in Scheme 6 (*route* ***b***), which determines the typical 1,4-regio- and β-stereoselectivity observed.[16]

Even if favored by the coordination, the pseudoequatorial nature of this type of nucleophilic attack (*route* ***b***), together with the reduced ability of the aziridine nitrogen to give rise to hydrogen bonds[3] and the impossibility for the aziridine **1*β*** to adopt the alternative conformation **1*β″***,[15,17] makes the attack on the C(1) from an external nucleophile through a pseudoaxial attack (*route* ***a***) decidedly competitive, particularly in the presence of a large excess of nucleophile (protocol A), to the point that with the more nucleophilic MeOH and EtOH, a stereoselectivity in favor of the α-anomer is observed under these conditions (Schemes 4 and 6). Phenol is the only *O*-nucleophile that partially escapes this rationalization, and an unusual mixture of all the three possible addition products (the corresponding α-anomer **14α**, β-anomer **14*β***, and anti-1,2-adduct **20**) was unexpectedly obtained under protocol B reaction conditions (entry 5, Table 1).[18]

A comparison of the results obtained with D-galactal-derived aziridine **1*β*** with previously studied D-allal-derived aziridine **1α** in their reactions with *O*-nucleophiles, under protocol B, indicates that, in these glycal-derived vinyl aziridine systems, the configuration β or α of the aziridine ring and the related coordination effects are responsible for the complete or almost complete β- or α-stereoselectivity, respectively, observed in the completely regioselective conjugate addition of *O*-nucleophiles.[19]

Studies are in progress to examine the chemical behavior of this new class of activated aziridines with nucleophiles other than *O*-nucleophiles, such as *C*-, *N*-, and *S*-nucleophiles.

Experimental Section

Reaction of Aziridine 1*β* with MeOH in Anhydrous Benzene. Typical Procedure (Protocol B). A solution of *trans*-*N*,*O*-dimesylate **2*β*** (0.034 g, 0.086 mmol) in anhydrous benzene (1 mL) was treated with *t*-BuOK (0.010 g, 0.086 mmol, 1 equiv) in the presence of MeOH (0.014 mL, 0.34 mmol, 4 equiv), and the reaction mixture was stirred at room temperature for 2 h. The solution was partitioned between Et_2O (8 mL) and brine (3 mL), and the aqueous layer was further extracted with Et_2O (2 × 5 mL). Evaporation of the combined organic extracts afforded a clean crude product (0.026 g, 92% yield) consisting of a 85:15 mixture of methyl glycosides **10*β*** and **10α** (^{1}H NMR) (see Supporting Information).

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Supporting Information Available: General information and experimental details, spectral and analytical data of all compounds prepared in this study, and conformational study of aziridine **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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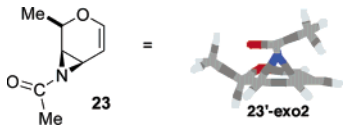
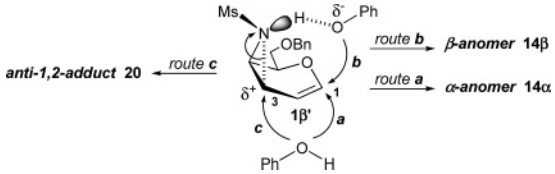
(15) Theoretical conformational studies, in a vacuum and in the presence of the solvent, carried out for simplicity on the 6-deoxy-*N*-acetyl aziridine **23**, which is structurally related to aziridine **1*β***, revealed that aziridine **23** exists only in the ring conformation **23′-exo2** with the methyl group equatorial and with a preference (>98%) for the *N*-acetyl group in the exo position (see the Supporting Information). The results obtained with aziridine **23** can reasonably be extended to aziridine **1*β*** and allow us to consider aziridine **1*β*** as existing only in the corresponding conformation **1*β′*** (Scheme 6), corresponding to **23′-exo2**, as stated in the text.



(16) To check the influence of the chelation ability of K^+ on the β-stereoselective results obtained under protocol B, the reactions with MeOH and *i*-PrOH were repeated in benzene in the presence of 18-Crown-6 and in THF, substituting the *t*-BuOK with a basic resin (MP-carbonate). The stereoselective results obtained under these modified protocol B reaction conditions [**10α**:**10*β*** anomeric ratio = 22:78 (crown ether) and 20:80 (basic resin) with MeOH and >99% β-*O*-glycoside **12*β*** with *i*-PrOH in both conditions] may indicate that K^+ has little or no influence on the β-stereoselectivity observed under typical protocol B reaction conditions [see, for comparison, entries 1 (MeOH) and 3 (*i*-PrOH), Table 1].

(17) In conformation **1*β″***, the corresponding coordination-driven nucleophilic attack on C(1) (*route* ***b′***) would correspond to a more favored pseudoaxial attack (Scheme 6).

(18) In addition to the reasonable presence of both α- and β-anomers **14α** (15%) and **14*β*** (45%) (see *routes* ***a*** and ***b***, respectively, and discussion in the text), the unexpected presence of the anti-1,2-adduct **20** (40%) in this reaction could be attributed to the acidity of phenol, which determines, in the reaction mixture, a more pronounced protonation of the aziridine nitrogen with concomitant polarization of the aziridine C(3)−N bond in the direction of the C(3) allylic carbon. Subsequent nucleophilic attack on C(3) by a free, noncoordinated PhOH, necessarily occurring in an anti fashion (*route* ***c***), leads to the *trans*-phenoxy sulfonamide **20**, as experimentally found.



(19) In accordance with the pseudoaxial or pseudoequatorial nature of the corresponding coordination-driven nucleophilic attack on C(1), the α-stereoselectivity previously observed with aziridine **1α** under protocol A[3] is larger than the β-stereoselectivity presently obtained with aziridine **1*β***, under the same conditions.