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N-Nosyl as a stereoselectivity-improving and easily removable group in the O-glycosylation of D-allal and D-galactal-derived allyl aziridines. Stereospecific synthesis of 4-amino-2,3-unsaturated-*O*-glycosides

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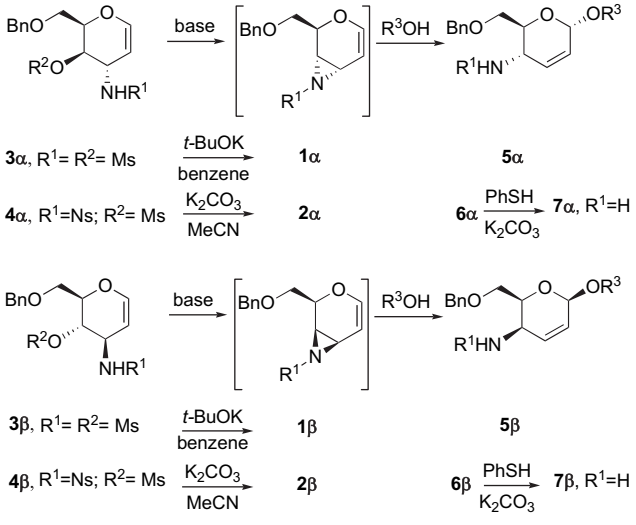
Abstract—The glycosylation of alcohols, phenol, and partially protected monosaccharides with the diastereoisomeric D-allal and D-galactal-derived *N*-nosyl aziridines **2α** and **2β** leads to the corresponding 4-*N*-(nosylamino)-2,3-unsaturated-α-*O*- (**6α**) and β-*O*-glycosides and disaccharides (**6β**), respectively, in a stereospecific substrate-dependent O-glycosylation process. The *N*-(nosylamino) group of **6α** and **6β** can easily be deprotected to give the corresponding 4-amino-2,3-unsaturated-*O*-glycosides **7α** and **7β**, with an increased value to our glycosylation protocol.

1. Introduction

Mono- and oligosaccharides bearing a free amino group (amino sugars) are an important class of sugars, widely present in nature, with important biological properties.[1] Consequently, the realization of effective procedures for the stereo- and regioselective introduction of an amino functionality on a glycosidic structure may be valuable.

We recently found that the D-allal- **1α** and D-galactal-derived *N*-mesyl allyl aziridine **1β** can be successfully used for the completely regio- and highly, or even completely, stereoselective glycosylation with *O*-nucleophiles (alcohols, partially protected monosaccharides, and phenol) to afford the corresponding α-*O*-glycosides **5α** from **1α** and β-*O*-glycosides **5β** from **1β** (Scheme 1).[2] As a consequence of the conjugate addition involved in this glycosylation process, a *N*-mesylamino group, having the same configuration of the starting aziridine, is regioselectively delivered to the C(4) of the newly formed pseudoglycal system present in **5α** and **5β**. As the *N*-mesylamino group is not actually the best choice to have a free amino group by deprotection procedures, it appeared necessary to introduce on the starting aziridine a different *N*-activating group, which could easily be removed after the glycosylation process had taken place. Considering that the simple *N*-acetyl group could not be used because the corresponding *N*-acetyl aziridine had proved not to be sufficiently reactive,[3] our choice fell on aziridines **2α** and **2β**, which bear the *N*-(*o*-nitrobenzenesulfonyl) [*N*-(nosyl)] protecting/activating group, which is easily removable by the $PhSH/K_2CO_3$ protocol, in accordance with a S_NAr reaction mechanism.[4] Application of this protocol to the –NH-nosyl group present in compounds **6α** and **6β**, which derive from the glycosylation process, would give the corresponding free $–NH_2$-containing products **7α** and **7β**, as desired (Scheme 1).



Scheme 1.

Keywords: Allyl aziridines; Glycals; Glycosylation; Amino sugars.
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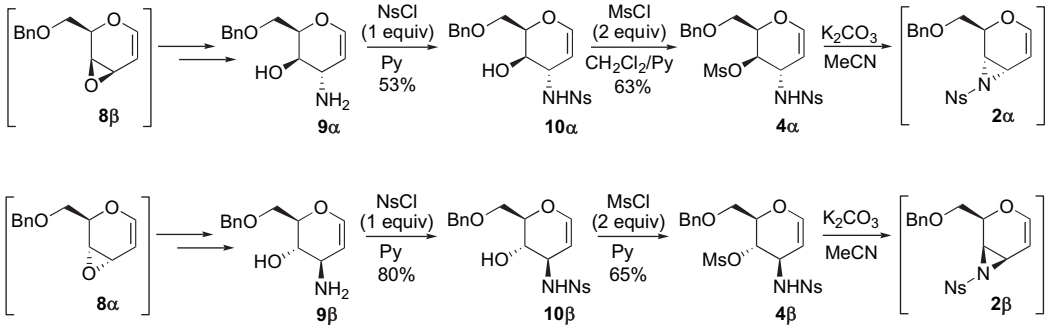
2. Results

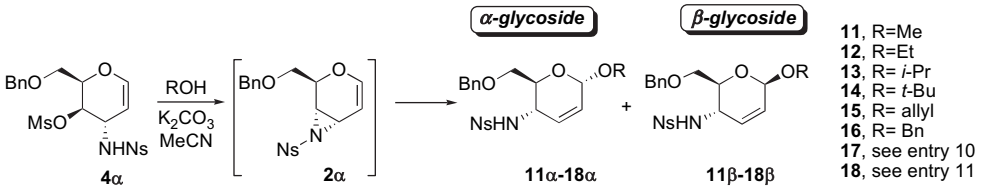
As the *N*-nosyl aziridines **2α** and **2β** are not stable, it was first necessary to prepare their stable precursors, the corresponding *N*-nosyl-*O*-mesylate **4α** and **4β**. The reaction of the diastereoisomeric *trans* amino alcohols **9α** and **9β**, obtained from epoxides **8β**[2a] and **8α**,[2b] respectively, with nosyl chloride (NsCl) (1 equiv) afforded the corresponding *N*-nosyl derivatives **10α** and **10β**, which were treated with MsCl (2 equiv) in CH_2Cl_2/pyridine to give **4α** and **4β**, respectively. Following a previously reported protocol,[5] the cyclization of **4α** and **4β** to the corresponding *N*-nosyl aziridines **2α** and **2β** was carried out with K_2CO_3 (3 equiv) in MeCN, instead of the *t*-BuOK (1 equiv)/benzene protocol, which has been routinely used with the corresponding *N*-mesyl analogues **3α** and **3β**.[2]

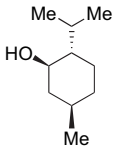
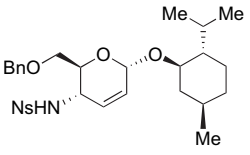
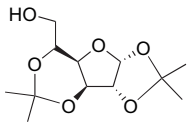
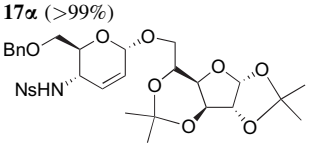
To check the efficiency of aziridines **2α** and **2β** as glycosyl donors, the possible influence of the *N*-nosyl group on the regio- and stereoselectivity, and the applicability of the deprotection procedure on the *N*-(nosylamino)-substituted compounds (**6α** and **6β**) deriving from the glycosylation process, we examined the regio- and stereochemical behavior of aziridines **2α** and **2β** in the reaction with alcohols, partially protected monosaccharides, and phenol (*O*-nucleophiles) (Scheme 2).



Scheme 2.

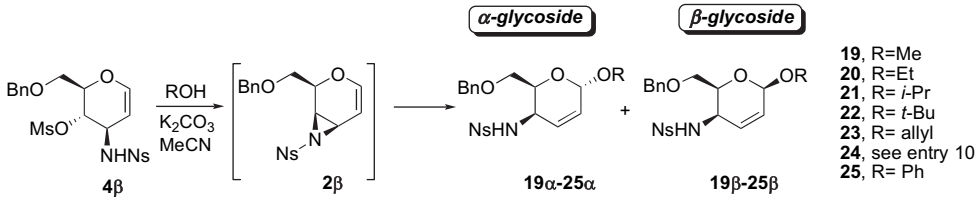
Table 1. Regio- and stereoselectivity of the addition reaction of *O*-nucleophiles to *N*-nosyl aziridine **2α** under protocols A and B[a]



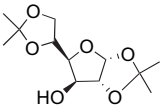
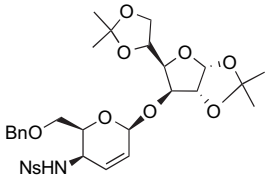
Entry	Glycosyl acceptor (ROH)	Protocol	Time (h)	Product(s)	Yield (%)
1	MeOH	A	3	**11α** (60%) **11β** (40%)	95[b]
2	MeOH	B	3	**11α** (>99%)	68[c]
3	EtOH	A	3	**12α** (73%) **12β** (27%)	89[b]
4	EtOH	B	3	**12α** (>99%)	80[c]
5	*i*-PrOH	A	3	**13α** (>99%)	98[b]
6	*i*-PrOH	B	3	**13α** (>99%)	65[c]
7	*t*-BuOH	A	3	**14α** (>99%)	92[b]
8	CH_2=$CHCH_2OH$	B	3	**15α** (>99%)	63[c]
9	$PhCH_2OH$	B	3	**16α** (>99%)	63[c]
10	 (+)-Menthol	B	3	 **17α** (>99%)	66[c]
11	 1,2;3,5-Di-*O*-isopropylidene-α-D-glucofuranose	B	3	 **18α** (>99%)	60[c]

[a] *Protocol A*: ROH, as the solvent; *protocol B*: MeCN, as the solvent, ROH=2–3 equiv.
[b] Crude product.
[c] Purified product (flash chromatography or preparative TLC).

Table 2. Regio- and stereoselectivity of the addition reaction of *O*-nucleophiles to *N*-nosyl aziridine **2β** under protocols A and B[a]



4β 2β 19α-25α 19β-25β

Entry	Glycosyl acceptor (ROH)	Protocol	Time (h)	Product(s)	Yield (%)
1	MeOH	A	3	**19α** (75%) **19β** (25%)	87[b]
2	MeOH	B	3	**19β** (>99%)	63[c]
3	EtOH	A	3	**20α** (65%) **20β** (35%)	98[b]
4	EtOH	B	3	**20β** (>99%)	71[c]
5	*i*-PrOH	A	3	**21α** (40%) **21β** (60%)	98[b]
6	*i*-PrOH	B	3	**21β** (>99%)	65[c]
7	*t*-BuOH	B	3	**22β** (>99%)	70[c]
8	CH_2=$CHCH_2OH$	B	3	**23β** (>99%)	75[c]
9		B	3		67[c]
	Diacetone-D-glucose			**24β** (>99%)	
10	PhOH	B	3	**25β** (>99%)	80[c]

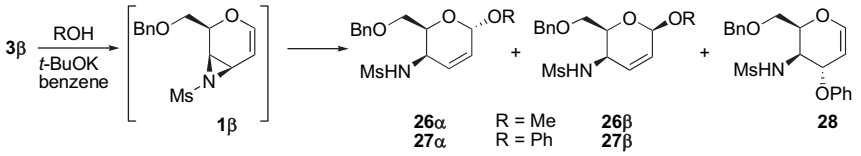
[a] *Protocol A*: ROH, as the solvent; *protocol B*: MeCN, as the solvent, ROH=2–3 equiv.
[b] Crude product.
[c] Purified product (flash chromatography or preparative TLC).

Two conceptually different protocols were used. When possible: (a) a solution of the aziridine precursor, the *N*-nosyl-*O*-mesylate **4α** or **4β** in the alcohol (*O*-nucleophile) was treated with K_2CO_3 (3 equiv) (*protocol A*); (b) the base, K_2CO_3 (3 equiv), was added to an MeCN solution of **4α** or **4β**, containing the *O*-nucleophile (3 equiv) (*protocol B*). Under *protocol A*, the reaction of the in situ-formed aziridine occurred in the presence of a very large amount of nucleophile, whereas under *protocol B*, the nucleophile was present only to a very reduced extent. As glycosyl acceptors, MeOH, EtOH, *i*-PrOH, and *t*-BuOH, were used for both *protocols A* and *B*, whereas allyl alcohol, benzyl alcohol, (+)-menthol, diacetone-D-glucose, 1,2;3,5-diisopropyliden-α-D-glucofuranose, and phenol were used only for *protocol B*. The results obtained are shown in Tables 1 and 2.

3. Discussion

The results obtained indicate that the regio- (only the 1,4-adduct was observed) and stereoselectivity (α-1,4-adduct/β-1,4-adduct ratio) of *N*-nosyl aziridines **2α** and **2β** under *protocol A* closely resembles those previously obtained with the corresponding *N*-mesyl aziridines **1α** and **1β**, respectively.[2] On the contrary, a substantial difference is found under *protocol B* between aziridines **1α** and **1β** and **2α** and **2β**. With aziridines **1α** and **1β**, the reactions were not completely stereoselective in all cases and some amounts, up to 15%, of the anomer with an inverted configuration with respect to the aziridine ring carbons (β-anomer from aziridine **1α** and α-anomer from aziridine **1β**) were detected in many cases.[2] With the present *N*-nosyl-substituted aziridines **2α** and **2β**, complete stereoselectivity is obtained with all the *O*-nucleophiles used and the corresponding α-anomer from **2α** and β-anomer from **2β** are the only reaction products, in the stereospecific O-glycosylation process (Tables 1 and 2). It is significant in this respect to compare the results obtained from the reactions with MeOH and PhOH. In the reaction with MeOH, the *N*-mesyl aziridine **1β** afforded a 85:15 mixture of the corresponding methyl β-**26β** and α-glycoside **26α** (Scheme 3; Table 3 entry 2),[2b] whereas in the reaction with PhOH a 15:45:40 mixture of all the possible addition products (α-1,4-adduct **27α**, β-1,4-adduct **27β**, and *anti* 1,2-adduct **28**) was unexpectedly obtained (Scheme 3; Table 3 entry 9).[2b] The same reactions repeated with the corresponding *N*-nosyl aziridine **2β** gave a completely regio- and stereoselective result in both the cases affording the methyl β-glycoside **19β** (reaction with MeOH) and the phenyl β-glycoside **25β** (reaction with PhOH), as the only respective reaction product (Table 2 entries 2 and 11, or Table 3 entries 6 and 10).

The complete 1,4-regioselectivity and aziridine ring configuration-related stereoselectivity, observed in all the reactions of the *N*-nosyl aziridines **2α** and **2β** with *O*-nucleophiles, can be rationalized, as previously admitted for **1α** and **1β**, by the occurrence of an effective coordination (hydrogen bond) of the *O*-nucleophile with the aziridine nitrogen of **2α** and **2β**, followed by a nucleophilic attack on the nearby C(1) of the allyl aziridine system (*routes **a*** and ***b*** for **2α** and



Scheme 3.

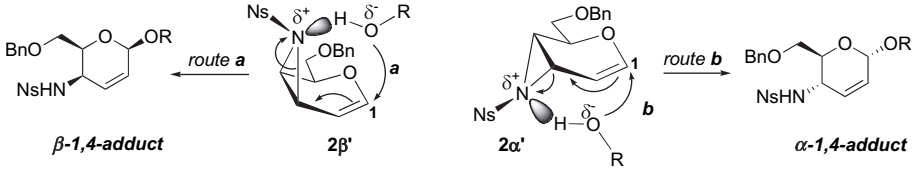
Table 3. Regio- and stereoselectivity of the addition of MeOH and PhOH to *N*-mesyl aziridine **1β** and *N*-nosyl aziridine **2β**

Entry	Aziridine	Generating base and solvent	Glycosyl acceptor	Protocol[a]	Time (h)	Product(s)	Yield (%)
1	**1β**	*t*-BuOK/MeOH	MeOH	A	2	**26α** (69%) **26β** (31%)	92[b,c]
2	**1β**	*t*-BuOK/benzene	MeOH	B	2	**26α** (15%) **26β** (85%)	92[b,c]
3	**1β**	K_2CO_3/MeCN	MeOH	B	2	**26β** (>99%)	97[c]
4	**1β**	*t*-BuOK/benzene 18-crown-6	MeOH	B	2	**26α** (22%) **26β** (78%)	97[b,c]
5	**2β**	K_2CO_3/MeOH	MeOH	A	3	**19α** (75%) **19β** (25%)	87[c]
6	**2β**	K_2CO_3/MeCN	MeOH	B	3	**19β** (>99%)	63[c]
7	**2β**	*t*-BuOK/benzene	MeOH	B	18	**19β** (>99%)	86[d]
8	**2β**	*t*-BuOK/benzene 18-crown-6	MeOH	B	18	**19α** (10%) **19β** (90%)	86[d]
9	**1β**	*t*-BuOK/benzene	PhOH[a]	B	3	**27α** (15%) **27β** (45%) **28** (40%)	90[b,c]
10	**2β**	K_2CO_3/MeCN	PhOH	B	3	**25β** (>99%)	80[d]
11	**2β**	*t*-BuOK/benzene	PhOH	B	1.5	**25β** (>99%)	96[c]
12	**1β**	K_2CO_3/MeCN	PhOH	B	3	**27β** (>99%)	89[c]

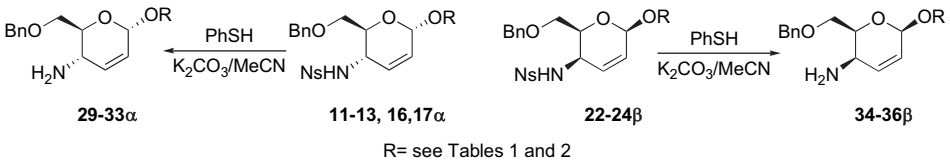
[a] See Tables 1 and 2.
[b] Ref. 2b.
[c] Crude product.
[d] Purified product (flash chromatography or preparative TLC).

2β, respectively, Scheme 4).[2] Additionally, in the present case, the metal ion (K^+) probably plays a role in determining the complete stereoselectivity observed (vide infra).

In this framework, the higher stereoselectivity observed with the *N*-nosyl aziridines **2α** and **2β** than with the *N*-mesyl aziridines **1α** and **1β** could be due to either an intrinsically higher ability to coordinate with the aziridine nitrogen of the *N*-nosyl group than in the mesyl case and/or to the coordinating–chelating ability of K^+, which is present in a decidedly large amount (6 equiv) in the reaction mixture in which aziridines **2α** and **2β** are prepared by the K_2CO_3/MeCN cyclization protocol on the *N*-nosyl-*O*-mesylates **4α** and **4β**, respectively (see above). In order to clarify this point, appropriate experiments were carried out on aziridines **1β** and **2β**, generated in situ by inverted procedures (**1β** by K_2CO_3/MeCN cyclization of **3β** and **2β** by *t*-BuOK/benzene cyclization of **4β**), in their reaction with MeOH and PhOH under *protocol B* (Table 3). While, on the one side, the complete β-stereoselectivity observed under these conditions in the reaction of *N*-mesyl aziridine **1β** with MeOH (entry 3 and comparison with entry 2, Table 3) unequivocally points to the importance of the metal cation (K^+) on the stereoselectivity, on the other hand, the complete β-stereoselectivity obtained with *N*-nosyl aziridine **2β** (entry 7 and comparison with entry 2, Table 3) tends to indicate that the nature of the arylsulfonyl group is also important. This point is confirmed also by the reactions of aziridines **1β** and **2β**, both generated by *t*-BuOK/benzene protocol, carried out in the presence of 18-crown-6, the crown ether specific for K^+: the *N*-nosyl aziridine **2β** affords a better β-stereoselective result than the *N*-mesyl derivative **1β** (Table 3 entries 4 and 8). Similar considerations may be made as regards the results obtained in the reaction with PhOH under different conditions. Particularly significant is the complete 1,4-regio- and β-stereoselectivity obtained with *N*-nosyl aziridine **2β**, when generated by the *t*-BuOK/benzene cyclization protocol (Table 3 entry 11); in the same conditions, the *N*-mesyl aziridine **1β** had previously given a non-regioselective (formation of both 1,2- and 1,4-adduct) and a non-stereoselective result (formation of both α- and β-anomer) (Table 3 entry 9).[2b] At the same time, the *N*-mesyl aziridine **1β**, when



Scheme 4.



Scheme 5.

generated by the K_2CO_3/MeCN-promoted cyclization protocol, behaves like the *N*-nosyl aziridine **2β**, affording a completely regio- and stereoselective result (Table 3 entry 12).

The 4-*N*-(nosylamino)-*O*-glycosides **11**–**13α**, **16α**, **17α**, and **22**–**24β** were chosen in order to check the applicability of these pseudoglycals to the deprotection procedure, which makes use of the PhSH/K_2CO_3 protocol.[4] In this way, a solution of the methyl 4-*N*-(nosylamino)-α-*O*-glycoside **11α** (R=Me), taken as an example, in MeCN was treated with PhSH (3 equiv) in the presence of K_2CO_3 (4 equiv) (solution phase conditions): the deprotection reaction is very fast and is completed in 3 h (conversion>99%, TLC and ^{1}H NMR) and the corresponding methyl 4-amino-α-*O*-glycoside **29α** (R=Me) is obtained in pure form (65% yield) after simple preparative TLC or flash chromatography (Scheme 5). However, with the aim of eliminating the purification step, an alternative procedure (solid phase conditions) was tested, by treating a THF solution of glycoside **11α** (R=Me) with a PhSH-supported resin (PS-thiophenol).[6] Unfortunately, under these conditions, the deprotection process turned out to be very slow and after several days and/or addition (2–3 times) of an equal amount of fresh resin, the conversion to **29α** (R=Me) was not complete and a substantial amount (20%) of the starting glycoside **11α** was still present. As a consequence, preparative TLC or flash chromatography was still necessary in order to obtain the pure free amino derivative **29α** (R=Me). Comparison of the two procedures indicated that the solution phase conditions were to be preferred and, consequently, they were adopted in all the other cases [4-*N*-(nosylamino)-*O*-glycosides **12α**, **13α**, **16α**, **17α**, and **22**–**24β**, Scheme 5]. Under these simple conditions, the corresponding 4-amino-*O*-glycosides **30**–**33α** and **34**–**36β** were obtained pure, rapidly (3 h at room temperature), and in good yields (55–75%) (Scheme 5).

4. Conclusion

In conclusion, our original glycosylation protocol of alcohols, partially protected monosaccharides, and phenol by the diastereoisomeric D-allal and D-galactal-derived allyl *N*-mesyl aziridines **1α** and **1β** has now been substantially improved by the use of the corresponding *N*-nosyl aziridines **2α** and **2β**.[2] On passing from the *N*-mesyl to the *N*-nosyl protecting/activating group, the stereoselectivity of all the O-glycosylation reactions increases, to the point that the addition reactions of the new *N*-nosyl-aziridines **2α** and **2β** are completely stereoselective, affording the corresponding 4-*N*-(nosylamino)-2,3-unsaturated-α- (**6α**) and β-*O*-glycosides (**6β**), respectively, in a new uncatalyzed substrate-dependent stereospecific glycosylation process. The *N*-(nosylamino) functionality, regio- and stereoselectively introduced at C(4) of **6α** and **6β**, can be easily deprotected by the simple PhSH/K_2CO_3 protocol to give the corresponding 4-amino-2,3-unsaturated-*O*-glycosides **7α** and **7β**, bearing a free amino group in the same position, with an added value to the final product and to the glycosylation process itself. The obtained results indicate that the use of our O-glycosylation process by means of the *N*-nosyl aziridines **2α** and **2β**, followed by the deprotection protocol, may constitute a simple and valid tool for the stereospecific synthesis of 2,3-unsaturated-4-amino sugars.

5. Experimental

5.1. General

All reactions were performed in flame-dried modified Schlenk (Kjeldahl shape) flasks fitted with a glass stopper or rubber septa under a positive pressure of argon. Air and/or moisture-sensitive liquids and solutions were transferred via syringe. Flash column chromatography was performed with 230–400 mesh silica gel (Macherey–Nagel). Analytical TLC was performed on Alugram SIL G/UV_{254} silica gel sheets (Macherey–Nagel) with detection by 0.5% phosphomolybdic acid solution in 95% EtOH. MeOH, *i*-PrOH, *t*-BuOH, BnOH, and allylic alcohol were distilled from calcium hydride. EtOH (absolute), phenol, (+)-menthol, 1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose (diacetone-D-glucose), and anhydrous MeCN over molecular sieves were purchased from Aldrich and used without purification. 1,2;3,5-di-*O*-isopropylidene-α-D-glucofuranose was prepared as reported.[7] PS-thiophenol resin was purchased from Stepbio. Epoxides **8α**[8a] and **8β**[8b] and *trans* amino alcohol **9α**[2a] and **9β**[2b] were prepared as previously described. In the reaction carried out under *protocol A*, a solution of *trans N*-nosyl-*O*-mesylates **4α** and **4β** in anhydrous MeCN was treated with K_2CO_3 in the presence of the glycosyl acceptor (MeOH, EtOH, *i*-PrOH, *t*-BuOH, phenol, allylic alcohol, BnOH, (+)-menthol, 1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose (diacetone-D-glucose), 1,2;3,5-di-*O*-isopropylidene-α-D-glucofuranose (3 equiv). In the reaction carried out under *protocol B*, *trans N*-nosyl-*O*-mesylates **4α** and **4β** were treated with K_2CO_3 in the glycosyl acceptor (MeOH, EtOH, *i*-PrOH, *t*-BuOH), as the solvent.

5.1.1. 6-*O*-Benzyl-3-deoxy-3-*N*-(nosylamino)-D-gulal (10α). A solution of amino alcohol **9α** (0.117 g, 0.50 mmol) in anhydrous CH_2Cl_2 (1.7 mL) was treated at room temperature with Et_3N (0.076 mL, 0.55 mmol) and NsCl (0.121 g, 0.55 mmol) and the reaction mixture was stirred 2 h at the same temperature. Dilution with CH_2Cl_2 (30 mL) and evaporation of the washed (saturated aqueous $NaHCO_3$, 1×5 mL, and saturated aqueous NaCl, 1×5 mL) organic solution afforded a crude residue (0.214 g) consisting of the *N*-nosyl derivative **10α**, which was subjected to flash chromatography. Elution with an 1:1 hexane/AcOEt mixture yielded the *N*-nosylate **10α** (0.108 g, 53% yield),

pure as a yellow liquid, $[\alpha]_D^{20}$ +25.2 (*c* 1.04, $CHCl_3$): R_f=0.19 (1:1 hexane/AcOEt); FTIR (neat film) ν 3479, 3350, 1650, 1540, 1450, 1360, 1240, 1150, 1020 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.10–8.18 (m, 1H), 7.82–7.90 (m, 1H), 7.65–7.80 (m, 2H), 7.24–7.43 (m, 5H), 7.00 (d, 1H, *J*= 7.5 Hz), 5.35–5.42 (m, 1H, NH), 4.62 (d, 1H, *J*=12.0 Hz), 4.52 (d, 1H, *J*=12.0 Hz), 4.36 (t, 1H, *J*=3.7 Hz), 3.84–3.92 (m, 1H), 3.74 (unresolved d, 2H, *J*=3.7 Hz), 3.56–3.81 (m, 2H), 3.18 (br s, 1H, OH). ^{13}C NMR ($CDCl_3$) δ 150.0, 133.6, 133.0, 131.0, 128.7, 128.3, 128.0, 125.6, 92.5, 77.4, 74.2, 69.8, 64.4, 51.2. Anal. Calcd for $C_{19}H_{20}N_2O_7S$: C, 54.28; H, 4.79; N, 6.66. Found: C, 54.03; H, 4.65; N, 6.56.

5.1.2. 6-*O*-Benzyl-3-deoxy-3-*N*-(nosylamino)-D-glucal (10β). Following the above described procedure, the treatment of a solution of amino alcohol **9β** (0.310 g, 1.32 mmol) in anhydrous CH_2Cl_2 (4.6 mL) with Et_3N (0.2 mL, 1.45 mmol) and NsCl (0.322 g, 1.45 mmol) afforded, after 3 h stirring at room temperature, a crude residue (0.560 g) consisting of the *N*-nosyl derivative **10β**, which was subjected to flash chromatography. Elution with an 1:1 hexane/AcOEt mixture yielded the *N*-nosylate **10β** (0.448 g, 80% yield), pure as a yellow liquid, $[\alpha]_D^{20}$ +3.8 (*c* 1.07, $CHCl_3$): R_f=0.29 (1:1 hexane/AcOEt); FTIR (neat film) ν 3344, 1650, 1540, 1380, 1230, 1180, 1160, 1100, 1050, 1020 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.17 (dd, 1H, *J*=5.8, 3.5 Hz), 7.91 (dd, 1H, *J*=6.0, 3.4 Hz), 7.70–7.82 (m, 2H), 7.25–7.40 (m, 5H), 6.35 (dd, 1H, *J*=5.9, 1.9 Hz), 5.51 (d, 1H, *J*=7.6 Hz, NH), 4.64 (d, 1H, *J*=12.1 Hz), 4.55 (d, 1H, *J*=12.1 Hz), 4.41 (dd, 1H, *J*=5.9, 2.1 Hz), 3.95–4.10 (m, 1H), 3.74–3.93 (m, 4H), 2.90 (br s, 1H, OH). ^{13}C NMR ($CDCl_3$) δ 146.1, 137.6, 134.4, 133.8, 133.1, 131.4, 128.7, 127.8, 125.5, 99.2, 77.6, 73.9, 69.4, 69.1, 55.4. Anal. Calcd for $C_{19}H_{20}N_2O_7S$: C, 54.28; H, 4.79; N, 6.66. Found: C, 54.35; H, 4.82; N, 6.74.

5.1.3. 6-*O*-Benzyl-3-deoxy-3-*N*-(nosylamino)-4-*O*-mesyl-D-gulal (4α). A solution of the *N*-nosyl derivative **10α** (2.13 g, 5.07 mmol) in anhydrous CH_2Cl_2 (27 mL) was treated at 0 °C with anhydrous pyridine (1.22 mL, 15.21 mmol) and MsCl (0.78 mL, 10.14 mmol) and the reaction mixture was stirred 18 h at 0 °C. Dilution with CH_2Cl_2 (200 mL) and evaporation of the washed (water, 2×15 mL) organic solution afforded a crude residue (2.9 g) consisting of *trans N*-nosyl-*O*-mesyl derivative **4α**, which was subjected to flash chromatography. Elution with a 4:3:3 hexane/CH_2Cl_2/AcOEt mixture yielded the *trans N*-nosyl-*O*-mesylate **4α** (1.26 g, 50% yield), pure as a pale yellow solid, mp 102–105 °C; $[\alpha]_D^{20}$ +89.3 (*c* 0.61, $CHCl_3$): R_f=0.33 (1:1 hexane/AcOEt); FTIR (Nujol) ν 3319, 1647, 1543, 1371, 1251, 1178 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.22–8.31 (m, 1H), 7.61–7.92 (m, 3H), 7.23–7.43 (m, 5H), 6.57 (d, 1H, *J*=5.9 Hz), 5.39 (d, 1H, *J*=4.9 Hz, NH), 4.96–5.03 (m, 1H), 4.63 (td, 1H, *J*=5.9, 1.7 Hz), 4.52 (s, 2H), 4.22 (t, 1H, *J*=6.8 Hz), 3.96–4.05 (m, 1H), 3.74 (dd, 1H, *J*=9.8, 6.0 Hz), 3.64 (dd, 1H, *J*=9.8, 7.5 Hz), 3.03 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 148.2, 137.4, 134.3, 133.4, 132.2, 128.7, 128.3, 125.7, 95.5, 73.9, 73.8, 70.0, 67.4, 47.7, 37.9. Anal. Calcd for $C_{20}H_{22}N_2O_9S_2$: C, 48.19; H, 4.45; N, 5.62. Found: C, 48.31; H, 4.49; N, 5.70.

5.1.4. 6-*O*-Benzyl-3-deoxy-3-*N*-(nosylamino)-4-*O*-mesyl-D-glucal (4β). Following the above described procedure, the treatment of a solution of the *N*-nosyl derivative **10β** (0.63 g, 1.50 mmol) in anhydrous CH_2Cl_2 (8 mL) with anhydrous pyridine (0.36 mL, 4.5 mmol) and MsCl (0.23 mL, 3.0 mmol) afforded, after 18 h stirring at 0 °C, a crude residue (1.05 g) consisting of the *trans N*-nosyl-*O*-mesyl derivative **4β**, which was subjected to flash chromatography. Elution with a 4:3:3 hexane/CH_2Cl_2/AcOEt mixture yielded the *trans N*-nosyl-*O*-mesylate **4β** (0.38 g, 51% yield), as a pale yellow solid, mp 39–41 °C; $[\alpha]_D^{20}$ −54.5 (*c* 0.52, $CHCl_3$): R_f=0.32 (1:1 hexane/AcOEt); FTIR (Nujol) ν 3310, 1653, 1541, 1466, 1351 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.11–8.21 (m, 1H), 7.85–7.94 (m, 1H), 7.71–7.83 (m, 2H), 7.21–7.45 (m, 5H), 6.33 (dd, 1H, *J*=6.0, 1.7 Hz), 5.88 (d, 1H, *J*=8.9 Hz, NH), 4.97 (dd, 1H, *J*=7.9, 6.8 Hz), 4.66 (d, 1H, *J*=11.7 Hz), 4.55 (d, 1H, *J*=11.7 Hz), 4.12–4.41 (m, 3H), 3.84 (dd, 1H, *J*=11.5, 3.1 Hz), 3.77 (dd, 1H, *J*=11.5, 4.0 Hz), 3.21 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 146.3, 137.4, 134.3, 134.2, 133.4, 130.9, 128.6, 128.2, 128.0, 125.7, 97.9, 76.1, 75.6, 73.8, 68.1, 51.9, 39.6. Anal. Calcd for $C_{20}H_{22}N_2O_9S_2$: C, 48.19; H, 4.45; N, 5.62. Found: C, 47.98; H, 4.39; N, 5.56.

5.1.5. Glycosylation of alcohols, partially protected monosaccharides, and phenol in anhydrous MeCN by the in situ-formed allyl aziridines 2α and 2β (*protocol B*).

5.1.5.1. Reaction of aziridine 2α with MeOH in anhydrous MeCN. Typical procedure (*protocol B*): a solution of *trans N*-nosyl-*O*-mesylate **4α** (0.032 g, 0.064 mmol) in anhydrous MeCN (3.6 mL) was treated with K_2CO_3 (0.026 g, 0.192 mmol, 3 equiv) in the presence of MeOH (0.008 mL, 0.192 mmol, 3 equiv) and the reaction mixture was stirred at room temperature for 3 h. The solution was partitioned between Et_2O (15 mL) and brine (5 mL), and the aqueous layer was further extracted with Et_2O (2×10 mL). Evaporation of the combined organic extracts afforded a clean crude product (0.027 g, 97% yield) consisting of practically pure methyl glycoside **11α** (^1H NMR), which was subjected to flash chromatography. Elution with an 1:1 hexane/AcOEt mixture afforded pure methyl 6-*O*-(benzyl)-2,3,4-trideoxy-4-*N*-(nosylamino)-α-D-*erythro*-hex-2-enopyranoside (**11α**) (0.019 g, 68% yield), as a yellow liquid, $[\alpha]_D^{20}$ +104.2 (*c* 0.80, $CHCl_3$): R_f=0.30 (1:1 hexane/AcOEt); FTIR (neat film) ν 3329, 1732, 1541, 1456, 1363, 1288, 1170, 1072 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.06–8.16 (m, 1H), 7.80–7.89 (m, 1H), 7.72 (td, 1H, *J*=7.5, 1.8 Hz), 7.65 (td, 1H, *J*=7.5, 1.8 Hz), 7.23–7.40 (m, 5H), 5.75 (dt, 1H, *J*=10.1, 2.6 Hz), 5.51 (d, 1H, *J*=10.1 Hz), 5.39 (d, 1H, *J*=9.4 Hz, NH), 4.85–4.93 (m, 1H, H-1), 4.52 (s, 2H), 4.24–4.40 (m, 1H), 3.81–3.92 (m, 1H), 3.65–3.80 (m, 2H), 3.42 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 147.9, 138.2, 134.4, 133.9, 133.1, 131.0, 130.1, 128.3, 128.2, 127.9, 127.7, 125.6, 95.2, 73.7, 69.4, 68.8, 56.1, 48.9. Anal. Calcd for $C_{20}H_{22}N_2O_7S$: C, 55.29; H, 5.10; N, 6.45. Found: C, 55.35; H, 5.24; N, 6.51.

5.1.5.2. Reaction of aziridine 2α with 1,2;3,5-di-*O*-isopropylidene-α-D-glucofuranose in anhydrous MeCN (*protocol B*). Following the above described typical procedure, the treatment of a solution of *trans N*-nosyl-*O*-mesylate **4α** (0.035 g, 0.070 mmol) in anhydrous MeCN (4 mL) with K_2CO_3 (0.029 g, 0.210 mmol, 3 equiv) in the presence of 1,2;3,5-di-*O*-isopropylidene-α-D-glucofuranose (0.036 g, 0.140 mmol, 2 equiv) afforded, after 3 h stirring at room temperature, a crude product consisting of a mixture of

disaccharide **18α** and unreacted monosaccharide (^{1}H NMR), which was subjected to flash chromatography. Elution with a 9:1 CH_2Cl_2/AcOEt mixture afforded 3-*O*-[6-*O*-benzyl-2,3,4-trideoxy-4-*N*-(nosylamino)-α-D-*erythro*-hex-2-enopyranosyl]-1,2;3,5-di-*O*-isopropylidene-α-D-glucofuranose (**18α**) (0.028 g, 60% yield), as a yellow liquid, $[\alpha]_D^{20}$ +95.9 (*c* 1.58, $CHCl_3$): R_f=0.29 (7:3 hexane/acetone); FTIR (neat film) *ν* 3290, 1732, 1541, 1456, 1373, 1242, 1168, 1076, 1026 cm^{-1}. ^{1}H NMR ($CDCl_3$) *δ* 8.09 (dd, 1H, *J*=7.2, 2.0 Hz), 7.84 (dd, 1H, *J*=7.5, 1.6 Hz), 7.70 (td, 1H, *J*=7.4, 1.7 Hz), 7.63 (td, 1H, *J*=7.4, 1.6 Hz), 7.23–7.40 (m, 5H), 5.97 (d, 1H, *J*=3.7 Hz), 5.76 (dt, 1H, *J*=10.1, 2.6 Hz), 5.52 (d, 1H, *J*=10.1 Hz), 5.34 (d, 1H, *J*=9.2 Hz, NH), 5.04 (br s, 1H, H-1), 4.56 (d, 1H, *J*=3.7 Hz), 4.49 (s, 2H), 4.26–4.43 (m, 2H), 4.18 (d, 1H, *J*=3.8 Hz), 3.73–3.96 (m, 4H), 3.69 (unresolved d, 2H, *J*=2.9 Hz), 1.48 (s, 3H), 1.33 (s, 9H). ^{13}C NMR ($CDCl_3$) *δ* 147.9, 138.2, 134.5, 133.9, 133.2, 131.1, 130.1, 128.5, 128.3, 127.9, 127.7, 125.6, 112.3, 106.5, 101.0, 92.2, 84.1, 79.6, 75.1, 73.7, 71.4, 69.4, 68.8, 68.6, 48.7, 27.4, 26.7, 24.2. Anal. Calcd for $C_{31}H_{38}N_2O_{12}S$: C, 56.18; H, 5.78; N, 4.23. Found: C, 56.35; H, 5.85; N, 4.41.

5.1.5.3. Reaction of aziridine 2β with MeOH in anhydrous MeCN (*protocol B*). Following the above described typical procedure, the treatment of a solution of *trans N*-nosyl-*O*-mesylate **4β** (0.031 g, 0.062 mmol) in anhydrous MeCN (3.5 mL) with K_2CO_3 (0.026 g, 0.186 mmol, 3 equiv) in the presence of MeOH (0.008 mL, 0.186 mmol, 3 equiv) afforded, after 3 h stirring at room temperature, a crude product (0.024 g, 90% yield) consisting of practically pure methyl glycoside **19β** (^{1}H NMR), which was subjected to flash chromatography. Elution with an 1:1 hexane/AcOEt mixture afforded pure methyl 6-*O*-(benzyl)-2,3,4-trideoxy-4-*N*-(nosylamino)-β-D-*threo*-hex-2-enopyranoside (**19β**) (0.017 g, 63% yield), as a yellow liquid, $[\alpha]_D^{20}$ −136.7 (*c* 0.90, $CHCl_3$): R_f=0.28 (1:1 hexane/AcOEt); FTIR (neat film) *ν* 3354, 1541, 1456, 1417, 1396, 1168, 1120, 1053 cm^{-1}. ^{1}H NMR ($CDCl_3$) *δ* 8.09–8.16 (m, 1H), 7.81–7.88 (m, 1H), 7.60–7.76 (m, 2H), 7.24–7.39 (m, 5H), 5.73 (s, 2H), 5.71 (d, 1H, *J*=7.7 Hz, NH), 5.00 (d, 1H, *J*=1.7 Hz, H-1), 4.45 (s, 2H), 3.88–4.09 (m, 2H), 3.68 (dd, 1H, *J*=10.1, 5.6 Hz), 3.62 (dd, 1H, *J*=10.1, 6.3 Hz), 3.47 (s, 3H). ^{13}C NMR ($CDCl_3$) *δ* 147.9, 138.1, 135.4, 133.7, 133.1, 131.0, 130.5, 128.9, 128.6, 127.9, 125.5, 98.4, 73.6, 73.5, 69.7, 55.6, 48.7. Anal. Calcd for $C_{20}H_{22}N_2O_7S$: C, 55.29; H, 5.10; N, 6.45. Found: C, 55.17; H, 4.89; N, 6.32.

5.1.5.4. Reaction of aziridine 2β with 1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose (diacetone-D-glucose) in anhydrous MeCN (*protocol B*). Following the above described typical procedure, the treatment of a solution of *N*-nosyl-*O*-mesylate **4β** (0.028 g, 0.056 mmol) in anhydrous MeCN (3.2 mL) with K_2CO_3 (0.023 g, 0.168 mmol, 3 equiv) in the presence of diacetone-D-glucose (0.029 g, 0.112 mmol, 2 equiv) afforded, after 3 h stirring at room temperature, a crude product consisting of a mixture of disaccharide **24β** and unreacted monosaccharide (^{1}H NMR), which was subjected to flash chromatography. Elution with a 7:3 hexane/acetone mixture afforded 3-*O*-[6-*O*-benzyl-2,3,4-trideoxy-4-*N*-(nosylamino)-β-D-*threo*-hex-2-enopyranosyl]-1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose (**24β**) (0.025 g, 67% yield), as a yellow liquid, $[\alpha]_D^{20}$ −33.6 (*c* 0.33, $CHCl_3$): R_f=0.16 (7:3 hexane/acetone); FTIR (neat film) *ν* 3358, 1541, 1413, 1261, 1070 cm^{-1}. ^{1}H NMR ($CDCl_3$) *δ* 8.09–8.16 (m, 1H), 7.79–7.87 (m, 1H), 7.69 (td, 1H, *J*=7.4, 2.0 Hz), 7.62 (td, 1H, *J*=8.6, 3.0 Hz), 7.23–7.41 (m, 5H), 5.84–5.95 (m, 3H), 5.71 (d, 1H, *J*=10.2 Hz), 5.32 (d, 1H, *J*=1.3 Hz, H-1), 4.61 (d, 1H, *J*=3.8 Hz), 4.41 (s, 2H), 4.25–4.35 (m, 2H), 4.19 (dd, 1H, *J*=6.8, 3.3 Hz), 3.89–4.11 (m, 4H), 3.61 (d, 2H, *J*=5.9 Hz), 1.50 (s, 3H), 1.39 (s, 3H), 1.34 (s, 3H), 1.32 (s, 3H). ^{13}C NMR ($CDCl_3$) *δ* 148.0, 137.9, 133.6, 132.9, 130.5, 130.4, 130.3, 128.6, 128.0, 127.8, 125.5, 112.2, 109.1, 105.3, 96.2, 83.8, 80.5, 77.8, 73.7, 73.6, 72.8, 69.3, 67.0, 48.3, 27.1, 27.0, 26.5, 25.5. Anal. Calcd for $C_{31}H_{38}N_2O_{12}S$: C, 56.18; H, 5.78; N, 4.23. Found: C, 56.27; H, 5.91; N, 4.31.

5.1.6. Glycosylation of alcohols by the in situ-formed allyl aziridines 2α and 2β, in alcohol as the solvent/nucleophile (*protocol A*).

5.1.6.1. Reaction of aziridine 2α with MeOH as the solvent/nucleophile. Typical procedure (*protocol A*): a solution of *trans N*-nosyl-*O*-mesylate **4α** (0.040 g, 0.080 mmol) in anhydrous MeOH (4.4 mL) was treated with K_2CO_3 (0.033 g, 0.240 mmol, 3 equiv) and the reaction mixture was stirred at room temperature for 2 h. The solution was partitioned between Et_2O (15 mL) and brine (5 mL), and the aqueous layer was further extracted with Et_2O (2×10 mL). Evaporation of the combined washed (brine) organic extracts afforded a crude reaction product (0.033 g, 95% yield) consisting of a 60:40 mixture of methyl glycosides **11α** and **11β** (^{1}H NMR), which was subjected to preparative TLC using a 6:4 CH_2Cl_2/*i*-Pr_2O mixture, as the eluant (3 runs). Extraction of the two most intense bands (the faster moving band contained **11β**) afforded pure **11α** (0.016 g, 46% yield) and methyl 6-*O*-benzyl-2,3,4-trideoxy-4-*N*-(nosylamino)-β-D-*erythro*-hex-2-enopyranoside (**11β**) (0.011 g, 31% yield), as a yellow liquid, $[\alpha]_D^{20}$ +24.1 (*c* 0.98, $CHCl_3$); FTIR (neat film) *ν* 3325, 1537, 1452, 1417, 1357, 1261, 1167, 1080 cm^{-1}. ^{1}H NMR ($CDCl_3$) *δ* 8.05 (dd, 1H, *J*=7.8, 1.3 Hz), 7.84 (dd, 1H, *J*=7.9, 1.2 Hz), 7.68 (td, 1H, *J*=7.7, 1.4 Hz), 7.49 (td, 1H, *J*=7.7, 1.3 Hz), 7.24–7.42 (m, 5H), 5.82 (d, 1H, *J*=11.0 Hz), 5.72 (dd, 1H, *J*=11.0, 3.8 Hz), 5.58 (d, 1H, *J*=9.3 Hz, NH), 4.88–4.93 (m, 1H, H-1), 4.47 (s, 2H), 4.04–4.19 (m, 1H), 3.63–3.88 (m, 2H), 3.57 (dd, 1H, *J*=9.9, 5.1 Hz), 3.41 (s, 3H). ^{13}C NMR ($CDCl_3$) *δ* 148.0, 138.3, 134.7, 133.8, 133.1, 131.3, 129.5, 128.6, 127.9, 126.9, 125.5, 95.6, 75.1, 73.5, 69.9, 55.6, 48.1. Anal. Calcd for $C_{20}H_{22}N_2O_7S$: C, 55.29; H, 5.1; N, 6.45. Found: C, 55.12; H, 5.36; N, 6.32.

5.1.6.2. Reaction of aziridine 2β with MeOH as the solvent/nucleophile (*protocol A*). Following the above described typical procedure, the treatment of a solution of *trans N*-nosyl-*O*-mesylate **4β** (0.033 g, 0.066 mmol) in anhydrous MeOH (3.7 mL) with K_2CO_3 (0.027 g, 0.198 mmol, 3 equiv) afforded, after 2 h stirring at room temperature a crude product (0.025 g, 87% yield) consisting of a 75:25 mixture of methyl glycosides **19α** and **19β** (^{1}H NMR), which proved to be inseparable under any chromatographic conditions.

5.1.7. Deprotection of 4-*N*-nosyl-*O*-glycoside 11α by the PhSH/K_2CO_3 protocol. Typical procedure: a solution of 4-*N*-nosyl-*O*-glycoside **11α** (0.016 g, 0.037 mmol) in

anhydrous MeCN (0.9 mL) was treated with K_2CO_3 (0.020 g, 0.148 mmol, 4 equiv) in the presence of PhSH (0.011 mL, 0.111 mmol, 3 equiv) and the resulting reaction mixture was stirred 3 h at room temperature. The solution was diluted with AcOEt (20 mL). The organic solution was filtered through a short Celite pad and evaporated to afford a crude product consisting of a mixture of 4-amino-*O*-glycoside **29α** and PhSH (^{1}H NMR), which was subjected to preparative TLC using an 1:1:0.1 CH_2Cl_2/AcOEt/MeOH mixture, as the eluant. Extraction of the slower moving band afforded methyl 6-*O*-(benzyl)-2,3,4-trideoxy-4-amino-α-D-*erythro*-hex-2-enopyranoside (**29α**) (0.006 g, 65% yield), as a yellow liquid, $[\alpha]_D^{20}$ +46.2 (*c* 0.49, $CHCl_3$): R_f=0.12 (1:1:0.1 CH_2Cl_2/AcOEt/MeOH); FTIR (neat film) *ν* 3360, 3296, 1454, 1396, 1261, 1097, 1057 cm^{-1}. ^{1}H NMR ($CDCl_3$) *δ* 7.27–7.41 (m, 5H), 5.88 (d, 1H, *J*=10.1 Hz), 5.74 (dt, 1H, *J*=10.1, 2.4 Hz), 4.87–4.93 (m, 1H, H-1), 4.69 (d, 1H, *J*=12.2 Hz), 4.55 (d, 1H, *J*=12.2 Hz), 3.71–3.77 (m, 2H), 3.54–3.66 (m, 1H), 3.38–3.52 (m, 1H), 3.44 (s, 3H), 1.36–1.56 (m, 2H, NH_2). ^{13}C NMR ($CDCl_3$) *δ* 135.4, 128.6, 127.9, 125.5, 95.4, 73.6, 72.8, 70.3, 55.8, 47.1. Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.61; H, 7.78; N, 5.34.

5.1.8. Deprotection of 4-*N*-nosyl-*O*-glycoside 11α by the PS-thiophenol resin protocol.[6] A solution of 4-*N*-nosyl-*O*-glycoside **11α** (0.030 g, 0.070 mmol) in anhydrous THF (0.2 mL) was treated with Cs_2CO_3 (0.072 g, 0.22 mmol) and PS-thiophenol resin (0.040 g, 0.08 mmol). This amount of resin had been previously treated by shaking for 30 min in a sealed vial with 1.6 mL of a 0.7 M solution of PPh_3 in anhydrous deoxygenated THF. The resin was filtered on a sintered glass, washed with anhydrous THF (30 mL), and used immediately without drying. The reaction mixture was shaken in a sealed vial at room temperature for 8 h. Additional PS-thiophenol resin was added (0.040 g, 0.08 mmol) and the reaction mixture was shaken again for 16 h. The reaction mixture was filtered and the solid was washed several times with CH_2Cl_2 (20 mL). Evaporation of the combined organic extracts afforded a crude product consisting of an 80:20 mixture of 4-amino-*O*-glycoside **29α** and unreacted 4-*N*-nosyl-*O*-glycoside **11α** (^{1}H NMR), which was subjected to preparative TLC using an 1:1 hexane/AcOEt mixture, as the eluant. Extraction of the two most intense bands (the slower moving band contained **29α**) afforded pure **29α** (0.012 g, 70% yield) and **11α** (0.004 g, 15% yield).

In other runs, even if operating under the same experimental conditions, the starting 4-*N*-nosyl-*O*-glycoside **11α** was recovered completely unreacted.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.12.069.

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