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Synthesis of diastereoisomeric 6-deoxy-D-allal- and 6-deoxy-D-galactal-derived allyl epoxides and examination of the regio- and stereoselectivity in nucleophilic addition reactions. Comparison with the corresponding 6-*O*-functionalized allyl epoxides

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Dedicated to the memory of Professor Bruno Macchia (1933–2008)

ABSTRACT

The new 6-deoxy-D-allal- and 6-deoxy-D-galactal-derived allyl epoxides **8α** and **8β** have been stereoselectively prepared and their behaviour as glycosyl donors in addition reactions with nucleophiles examined and compared with that of the corresponding 6-OR (R=Bn, Tr) substituted epoxides. The completely stereoselective substrate-dependent glycosylation process found in the reaction of **8α** and **8β** with *O*-nucleophiles (alcohols and partially protected monosaccharides) and *C*-nucleophiles (alkyl lithium compounds and TMSCN), indicated that a 6-OR group in the side chain is not necessary for determining the selectivity. The reaction of **8α** and **8β** with azide ($TMSN_3$, *N*-nucleophile) made it possible to revise a previously proposed rationalization for the formation of the corresponding *cis*-azido alcohol (*syn*-1,2-addition product).

1. Introduction

The addition reactions of nucleophiles to glycal-derived 6-OR-substituted allyl epoxides **1α**, **1β** (R^2=Bn) and **1β-Tr** (R^2=Tr) had indicated that when the reactions are carried out in the presence of a small amount of the nucleophile (3 equiv), the 1,4-addition product (glycoside) in each case was obtained either as the only addition product or as a mixture with the *anti*-1,2-addition product. The configuration always corresponds to that of the starting epoxide. This behaviour was observed with *O*-nucleophiles (alcohols, phenol and partially protected monosaccharides) and *C*-nucleophiles (alkyl lithium reagents), where the corresponding *O*- and *C*-glycosides were obtained by means of a completely 1,4-regio- and stereoselective process, with exclusive formation of the corresponding α- and β-glycosides from epoxides **1α** and **1β** (or **1β-Tr**), respectively. This reaction represents a new uncatalyzed substrate-dependent stereospecific O-glycosylation and C-glycosylation process (Scheme 1).[1] These results and, in particular, the close correspondence between the configuration of the glycosides obtained (1,4-addition products) and that of the starting epoxide were rationalized by supposing the occurrence of a *coordination* between the nucleophile and the oxirane oxygen in the form of a hydrogen bond, in the case of *O*-nucleophiles, or through the metal (lithium), in the case of alkyl lithium reagents, as shown in structures **5** (from **1α**) and **6** (from **1β** and **1β-Tr**) (Scheme 1). In this way, the nucleophile is appropriately disposed for an entropically favoured attack on C(1) from the same side as the heterocyclic functionality (*route* ***a*** in **5** and *route* ***b*** in **6**), thus accounting for the complete facial selectivity observed.[1] As they are supposed to arise from a coordination process, the 1,4-addition products (glycosides) with the same configuration as the starting glycal-derived epoxide (**1α**, **1β**, **1β-Tr** and title epoxides, vide infra) will be indicated in the following discussion as *coordination products* and in this way are easily distinguished from the other reaction products.

In this rationalization, no role was attributed to the *O*-functionality present in the side chain (–OBn in **1α** and **1β** and –OTr in **1β-Tr**). However, at least in the *cis*-diastereoisomers **1β** and **1β-Tr**, the *O*-functionality at C(6) could take part in the anchorage of the nucleophile on the β face of the allyl oxirane system by *a chelation process*, as tentatively shown in the chelated bidentate structure **7** (Scheme 1), thus playing a decisive role in determining the β-stereoselectivity observed. In the *trans*-diastereoisomer **1α** where, for simple structural reasons, no similar chelation process can occur, the –OBn group has apparently only its inductive electron-withdrawing effect (–I), whose importance on the observed regio- and stereoselectivity was not taken into consideration.[1]

The substitution of the side chain ($–CH_2OBn$ or $–CH_2OTr$) of epoxides **1α**, **1β** and **1β-Tr** with a simple, non-coordinating methyl group, as in the corresponding 6-deoxy-D-allal- and 6-deoxy-D-galactal-derived allyl epoxides **8α** and **8β**, respectively, was thought

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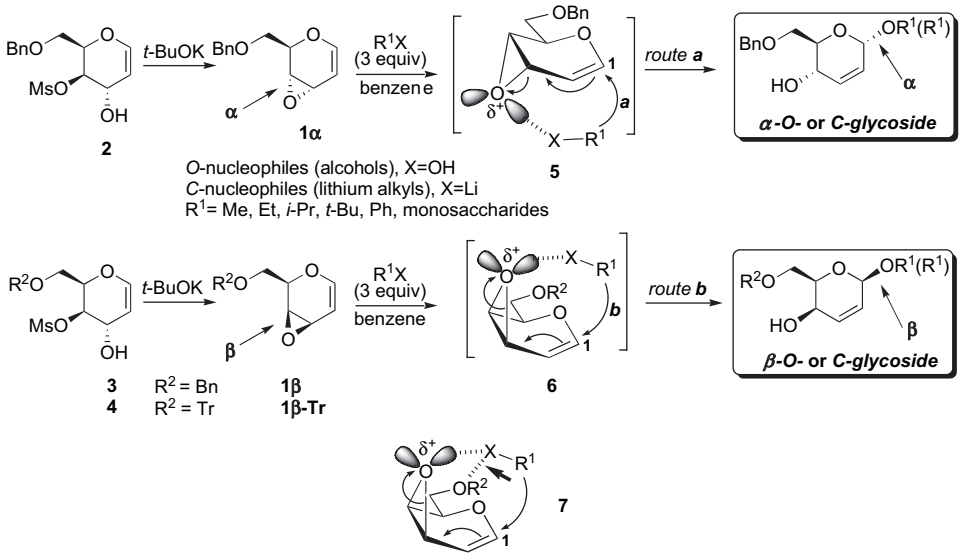
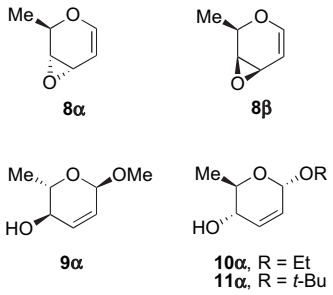


Scheme 1.

to be the simplest way to check whether the presence of the *O*-functionalized side chain is decisive in determining the regio- and stereochemical behaviour in these glycal-derived epoxides (Scheme 2).



Scheme 2.

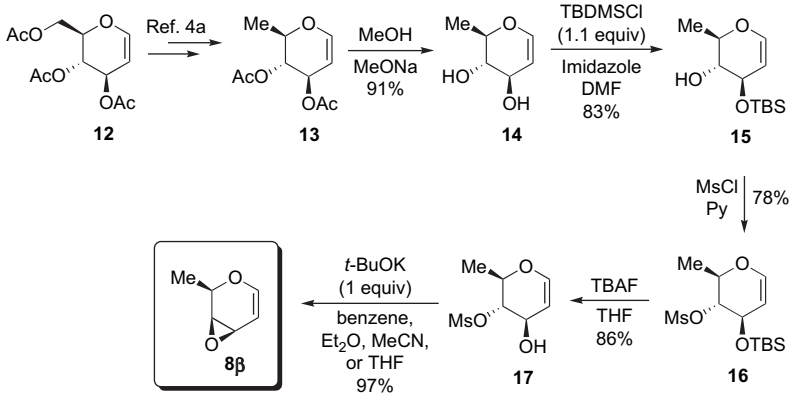
Interest in the 6-deoxy epoxides **8α** and **8β** derived also from the fact that, in the event that they show a regio- and stereoselective behaviour similar to that of the related epoxides **1α**, **1β**, and **1β-Tr**, alkyl 2,3,6-trideoxy-hex-2-enopyranosides, like **9**–**11α**, are valuable synthetic intermediates for the synthesis of fragments of natural products and antibiotics with an antiviral and antitumour activity. These can theoretically be obtained by glycosylation of the corresponding alcohol with **8α**, in the case of **10α** and **11α**, or its enantiomer, in the case of **9α** (Scheme 2).[2] Similar applications could be advantageously found for epoxide **8β**.

2. Results

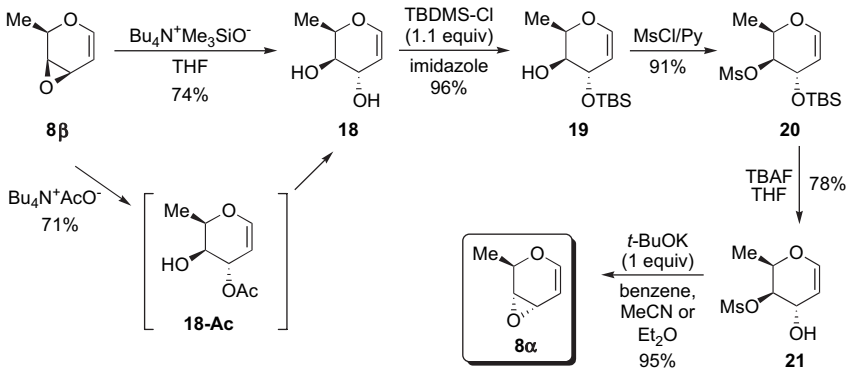
Following a previously described procedure,[4a] the commercially available tri-*O*-acetyl-D-glucal (**12**) was transformed into 6-deoxy-diacetyl-D-glucal (**13**). Saponification (MeONa/MeOH) of **13** afforded *trans*-diol **14** (6-deoxy-D-glucal),[4b,c] which was treated with TBDMS-Cl (1.1 equiv) to give the 3-*O*-TBS-derivative **15**, regioselectively. Compound **15** was subsequently transformed (MsCl/Py) into mesylate **16**. Desilylation (TBAF/THF) of **16** afforded the *trans*-hydroxy mesylate **17**, which was cyclized under basic conditions (*t*-BuOK) to the desired epoxide **8β** (Scheme 3).[5]

The synthesis of the diastereoisomeric epoxide **8α** starts from epoxide **8β** (Scheme 4). Treatment of a THF solution of epoxide **8β** with tetrabutylammonium trimethylsilanolate ($Bu_4N^+Me_3SiO^-$, 4 equiv)[1c] afforded 6-deoxy-D-gulal (**18**),[6,7] in a completely regio- and stereoselective way. Application of the same sequence of reactions previously applied to the distereoisomeric *trans*-diol **14** (from **14** to **17**, Scheme 3) to *trans*-diol **18** afforded, through corresponding compounds **19** and **20**, the *trans*-hydroxy mesylate **21**. Base-catalyzed (*t*-BuOK) cyclization of **21** afforded epoxide **8α**.[5]

A theoretical conformational study was carried out on epoxides **8α** and **8β** and on the corresponding 6-methoxy derivatives **1α-OMe** and **1β-OMe**, as simplified models of epoxides **1α**, **1β** and



Scheme 3.



Scheme 4.

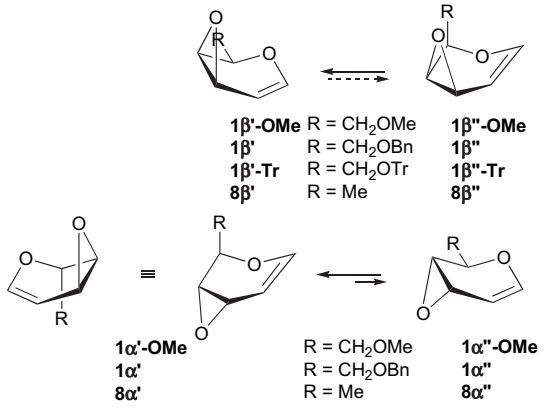
1β-Tr. In **1α-OMe** and **1β-OMe**, the $-CH_2OBn$ and $-CH_2OTr$ side chains of **1α**, **1β** and **1β-Tr** are advantageously replaced by the simpler, less computing-demanding $-CH_2OMe$ group (Scheme 5). The results have indicated that epoxides **1β-OMe** and **8β** exist as a single conformer, **1β′-OMe** and **8β′**, respectively, with the side chain pseudoequatorial. In contrast, epoxides **1α-OMe** and **8α** exist as an equilibrium mixture (~70:30) of the corresponding conformers, **1α′-OMe** and **1α″-OMe**, and **8α′**and **8α″**, respectively, in which **1α′-OMe** and **8α′**, which contain a pseudoaxial side-chain, are the more stable conformers. The results obtained with epoxides **1α-OMe** and **1β-OMe** can reasonably be extended to the configurationally related epoxides **1α**, **1β** and **1β-Tr**, respectively (Scheme 5).[8]

3. Discussion

In order to check the efficiency of 6-deoxy epoxides **8α** and **8β** as glycosyl donors, and for an appropriate comparison of the obtained regio- and stereoselectivity with that of the previously examined 6-OBn- and 6-OTr-substituted allyl epoxides **1α**, **1β** and **1β-Tr**, the chemical behaviour of epoxides **8α** and **8β** was examined in representative reactions with certain *O*-, *C*-, *N*- and *S*-nucleophiles using the same reaction conditions (*protocol A* and/or *protocol B*),[9] as previously used with epoxides **1α**, **1β** and **1β-Tr**.[10]

3.1. *O*-Nucleophiles

The reactions of epoxides **8α** and **8β** with *O*-nucleophiles like simple alcohols as MeOH, EtOH, *i*-PrOH and *t*-BuOH were carried out both under *protocol A* and *protocol B*,[9] whereas the reactions with more complex alcohols like (+)-dihydrocholesterol and partially protected monosaccharides (diacetone-D-glucose and 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose) were carried out only under *protocol B* (Tables 1 and 2).



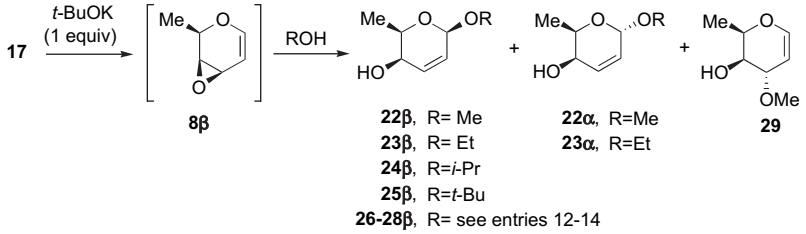
Scheme 5.

The reactions carried out under *protocol A* were completely 1,4-regioselective with an α/β anomeric ratio, which depended on the alcohol used: a mixture of the corresponding α- and β-anomers was obtained with MeOH and EtOH, whereas a completely stereoselective reaction was observed with *i*-PrOH and *t*-BuOH. However, in all cases, that anomer (α or β) having the same configuration as the starting epoxide (α or β, respectively), that is, the corresponding *coordination product*, is the major (in the case of MeOH and EtOH) or the only reaction product (in the case of *i*-PrOH and *t*-BuOH) (Tables 1 and 2). When the reactions with these simple alcohols and with more complex alcohols were carried out under *protocol B*, a completely 1,4-regio- and stereoselective result, with the exclusive formation of the corresponding *coordination product*, was obtained in all cases with epoxide **8β** (Table 1). In this way, epoxide **8β** showed a 1,4-regio- and stereoselectivity (α-/β-anomeric ratio) and, in general, a sensitivity to the reaction conditions (type of alcohol and *protocol A* or *B* used) practically identical to that of the related *O*-functionalized epoxides **1β** and **1β-Tr**.[1a,d] Compared with **1α**,[1c] the same can be said for epoxide **8α** except for the reaction with the more nucleophilic MeOH and EtOH. In these two instances, the reaction outcome unexpectedly turned out to be *insensitive* to the reaction conditions, and almost the same α-/β-anomeric ratio was obtained under both *protocol A* and *B* (about 85:15 and 90:10 in MeOH and EtOH, respectively, entries 1–4, Table 2).

On the whole, the results obtained in the glycosylation of alcohols with **8α** and **8β** (predominance or exclusive formation of the corresponding *coordination product*) are consistent with the occurrence of a hydrogen bond between the oxirane oxygen and *O*-nucleophile (structure **32a**, Scheme 6, where the reaction of epoxide **8β** with MeOH is taken as an example), as previously proposed for epoxides **1α**, **1β** and **1β-Tr** (Scheme 1).[1a,c,d] The result is not affected by the absence of a further *O*-functionality [–OBn or –OTr at C(6)] in the molecule.

The regio- and stereochemical behaviour of epoxide **8β** was also examined with the alkoxide MeONa (*protocol B*). As a consequence of the coordinating ability of Na^+, an almost completely 1,4-regioselective and completely β-stereoselective process was obtained, with the formation of the corresponding *coordination product*, the methyl β-*O*-glycoside **22β** (93%), as the main product, accompanied by only a small amount (7%) of the *anti*-1,2-addition product, the *trans*-methoxy alcohol **29** (Scheme 6). When the reaction was repeated in the presence of 15-crown-5, the sequestering activity of the crown ether reduces the coordinating ability of Na^+. In this case, a 58:42 mixture of **22β** and **29** was obtained (Scheme 6 and entries 9 and 10, Table 1). As found in the case of

Table 1
Glycosylation of alcohols and partially protected monosaccharides by the in situ-formed allyl epoxide **8β** under *protocols A* and *B*



Entry	Glycosyl acceptor (ROH)	Protocol[a]	Time (h)	Product(s)[b]	Yield (%)
1	MeOH	A	0.5	**22β** (65%)+**22α** (35%)	86[c]
2	MeOH	B	1	**22β** (>99%)	91[c]
3	EtOH	A	0.5	**23β** (83%)+**23α** (17%)	90[c]
4	EtOH	B	1	**23β** (>99%)	96[c]
5	*i*-PrOH	A	0.5	**24β** (>99%)	95[c]
6	*i*-PrOH	B	3	**24β** (>99%)	92[d]
7	*t*-BuOH	A	0.5	**25β** (>99%)	91[c]
8	*t*-BuOH	B	3	**25β** (>99%)	88[c]
9	MeONa	B	18	**22β** (93%)+**29** (7%)	90[c]
10	MeONa/15-crown-5	B	18	**22β** (58%)+**29** (42%)	94[c]
11	$Bu_4N^+MeO^-$	B	1	**29** (>99%)	86[d]
12	(+)-Dihydrocholesterol	B	18	**26β** (>99%)	68[d]
13	Diacetone-D-glucose	B	18	**27β** (>99%)	72[d]
14	1,2;3,4-Di-*O*-isopropylidene-α-D-galactopyranose	B	18	**28β** (>99%)	65[d]

[a] See Note 9.
[b] For glycosides **22α** and **22β**, see Ref. 11.
[c] Crude product.
[d] Purified product (flash chromatography or preparative TLC).

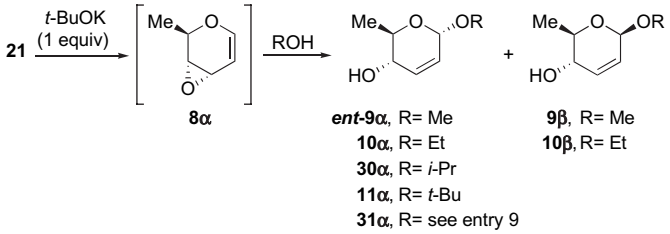
epoxide **1β**,[1d] a completely *anti*-1,2-addition process, with exclusive nucleophilic attack at allylic C(3) oxirane carbon and exclusive formation of *trans*-methoxy alcohol **29**, was observed only when the opening reaction of **8β** was carried out with the non-coordinating tetrabutylammonium methoxide ($Bu_4N^+MeO^-$) as the methoxide-based nucleophile (*protocol B*) (structure **32b**, Scheme 6).[1d] In other words, a free, non-coordinating nucleophile, which reacts with the free non-coordinated epoxide is the necessary condition, in these glycal-derived epoxides, in order to have a completely *anti*-1,2-addition process. As a consequence, *anti*-1,2-addition products, like *trans*-methoxy alcohol **29** in the present case, which are supposed to be formed through an attack by a nucleophile not coordinated to the oxirane oxygen, will be indicated in the following discussion as *non-coordination products* and in this way are easily distinguished from the other reaction products (Scheme 6).[13]

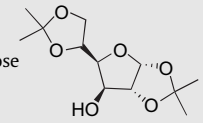
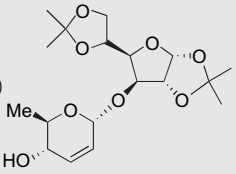
3.2. *C*-Nucleophiles

The reactions of epoxides **8α** and **8β** with alkyl lithium compounds such as MeLi, BuLi, *s*-BuLi and PhLi and an organic solvent-soluble CN^- source like TMSCN (*protocol B*) were completely 1,4-regio- and stereoselective with the exclusive formation of the corresponding *coordination product*, the α-*C*-glycosides **33**–**37α** from **8α** (Table 3) and β-*C*-glycosides **38**–**42β** from **8β** (Table 4), as found in the corresponding reactions of epoxides **1α**[1c,10] and **1β**.[1b,d]

The only difference is given by the reaction of **8β** with *t*-BuLi. In this case, the reaction is not regioselective and the corresponding *coordination product*, β-*C*-glycoside **43β** (75%), is accompanied by a substantial amount of the corresponding *non-coordination product*, *trans*-*tert*-butyl alcohol **44** (*anti*-1,2-addition product, 25%) (Scheme 7, structure **45a**, *route* ***c***, and entry 6, Table 4).

Table 2
Glycosylation of alcohols and partially protected monosaccharide by the in situ-formed allyl epoxide **8α** under *protocols A* and *B*



Entry	Glycosyl acceptor (ROH)	Protocol[a]	Time (h)	Product(s)[b]	Yield (%)
1	MeOH	A	0.5	***ent*-9α** (85%)+**9β** (15%)	88[c]
2	MeOH	B	0.5	***ent*-9α** (83%)+**9β** (17%)	87[c]
3	EtOH	A	0.5	**10α** (93%)+**10β** (7%)	82[c]
4	EtOH	B	1	**10α** (90%)+**10β** (10%)	87[c]
5	*i*-PrOH	A	0.5	**30α** (>99%)	84[c]
6	*i*-PrOH	B	1	**30α** (>99%)	79[d]
7	*t*-BuOH	A	0.5	**11α** (>99%)	86[c]
8	*t*-BuOH	B	1	**11α** (>99%)	70[c]
9	Diacetone-D-glucose 	B	18	**31α** (>99%) 	67[d]

[a] See Note 9.
[b] For glycosides ***ent*-9α** and **9β** (Ref. 11), **10α** (Ref. 3b,c) and **11α** (Ref. 3d), see corresponding references.
[c] Crude product.
[d] Purified product (flash chromatography or preparative TLC).

Probably in this case, the absence of the 6-OBn group and its chelating ability combined with the steric hindrance of the nucleophile (*t*-BuLi) could play a decisive role in determining the different behaviour of epoxide **8β** compared with **1β**[1b] with *t*-BuLi and this is the first example of non-complete 1,4-regioselectivity in the addition of an alkyl lithium compounds to these glycal-derived allyl epoxides.

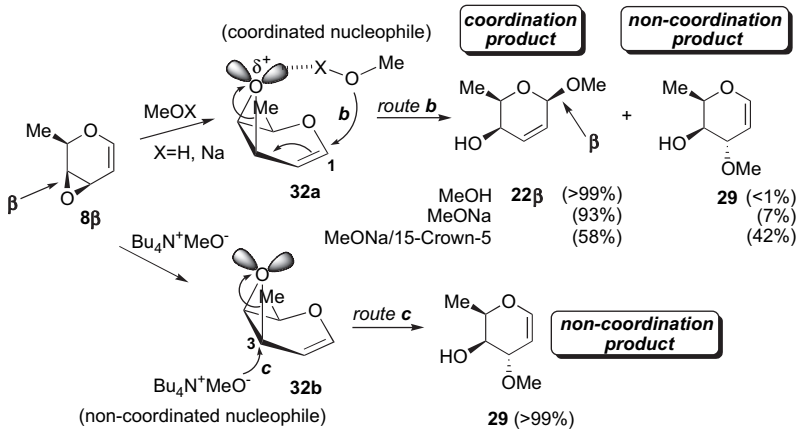
Considering that with TMSCN the actual nucleophile is a corresponding pentacoordinate siliconate, as TMSCN-PS in the present case (Scheme 7),[14] all these results can be rationalized by the occurrence of an effective coordination epoxide-nucleophile through the metal (lithium in the case of alkyl lithium compounds and potassium in the case of TMSCN-PS) and subsequent delivery of the nucleophile to C(1) from the same side of the coordination, as tentatively shown in structures **45b** and **45c** (Scheme 7, *route* ***b***: for simplicity only the behaviour of epoxide **8β** is shown).

3.3. *N*-Nucleophiles (TMGA and $TMSN_3$)

As previously done with the corresponding epoxides **1β** and **1β-Tr**, the azide ion was taken as an effective example of an *N*-nucleophile and tetramethylguanidinium azide (TMGA) and trimethylsilyl azide ($TMSN_3$) were used as organic solvent-soluble azide sources.

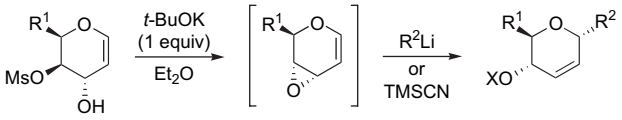
3.3.1. *Trimethylsilyl azide ($TMSN_3$)*

The reaction of epoxide **8β** with $TMSN_3$ at room temperature led to a reaction mixture mostly consisting of the corresponding *syn*-1,2-addition product, the D-galactal-derived *cis*-azido alcohol **50**[16a] (82%), accompanied by the corresponding *coordination product*, the 4-*O*-TMS-derived β-glycosyl azide **48β-OTMS**[16b] (18%) (β-1,4-addition product), which were separated by preparative TLC. This result turned out consistently different from that previously obtained with the structurally related 6-*O*-trityl-substituted



Scheme 6.

Table 3
Glycosylation of alkyl lithium compounds and TMSCN by the in situ-formed allyl epoxides **8α** and **1α** under *protocol B*



21 R[1]=Me **8α**
2 R[1]=CH_2OBn **1α**

33α: R[1]=R[2]= Me, X= H
34α: R[1]= Me, R[2]=Bu, X= H
35α: R[1]=Me, R[2]= Ph, X= H
36α-OTMS: R[1]=Me, R[2]= CN, X= TMS
37α-OTMS: R[1]= CH_2OBn, R[2]=CN, X=TMS

Entry	Epoxide	Glycosyl acceptor	Time (h)	Product[a]	Yield (%)
1	**8α**	MeLi	1	**33α** (>99%)	65[b]
2	**8α**	BuLi	1	**34α** (>99%)	81[c]
3	**8α**	PhLi	1	**35α** (>99%)	75[b]
4	**8α**	TMSCN	2	**36α-OTMS** (>99%)	88[b]
5	**1α**	TMSCN	2	**37α-OTMS** (>99%)	94[c]

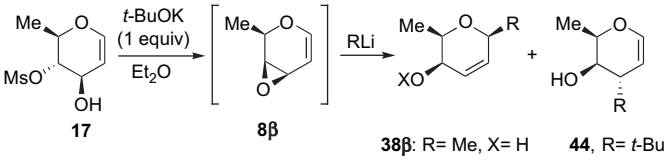
[a] For the acetyl derivative of the enantiomer of **35α**, see Ref. 12a; for the enantiomer and corresponding acetyl derivative of **36α**, see Refs. 12b,c.
[b] Purified product (flash chromatography or preparative TLC).
[c] Crude product.

epoxide **1β-Tr**,[1d,17] particularly as regards the amount (39%) of the corresponding *syn*-1,2-addition product, the D-galactal-derived *cis*-azido alcohol **49**. For this reason, we thought that it would be appropriate to check again the reaction of **1β-Tr** with $TMSN_3$. An 85:15 mixture of *cis*-azido alcohol **49** (*syn*-1,2-addition product) and 4-*O*-TMS-derived β-glycosyl azide **47β-OTMS**[1d] (*coordination product*) was obtained, a result surprisingly different from that previously described,[17] and at the same time, very similar to that presently obtained with **8β** (Scheme 8). The contrasting result found for **1β-Tr** and the observation that in these reactions of both **1β-Tr** and **8β**, the *syn*-1,2-addition product was always accompanied by a certain amount of the corresponding *coordination product*, prompted us to verify whether the rationalization previously given in order to justify the formation of the *cis*-azido alcohol **49** from **1β-Tr** was correct or had to be revised.[1d] For this reason, the *cis*-azido alcohol **49** and the β-glycosyl azide **47β-OTMS** were separated by preparative TLC and **47β-OTMS** was subjected to stability control experiments, by treating a benzene solution of this compound with $TMSN_3$ under the same reaction conditions previously adopted for epoxide **1β-Tr**: an almost complete isomerization of **47β-OTMS** into the *cis*-azido alcohol **49** occurred [**47β-OTMS**/**49**=3:97 (^{1}H NMR)] (Scheme 8). Analogous treatment of a benzene solution of β-glycosyl azide **48β-OTMS** (from the reaction of epoxide **8β** with $TMSN_3$) determined its almost complete isomerization to *cis*-azido alcohol **50** (^{1}H NMR) (Scheme 8).

The examination of this reaction was extended to epoxides **1α** and **8α**. The addition reaction of $TMSN_3$ to epoxide **1α**, in benzene and at room temperature, is almost completely 1,2-regioselective, with the formation of the corresponding *syn*-1,2-addition product, the D-allal-derived *cis*-azido alcohol **55** (92%), accompanied by a small amount (about 8%) of the corresponding 4-OTMS α-glycosyl azide **53α-OTMS** (*coordination product*) (Scheme 9). From the preparative TLC, the *cis*-azido alcohol **55** was obtained pure, whereas, unfortunately, the α-glycosyl azide **53α-OTMS** could not be isolated. For this reason, it was not possible to obtain direct evidence of the existence of an equilibration process **53α-OTMS**→**55**, as in the case of **47β-OTMS**→**49**. However, by repeating the same reaction in C_6D_6 in an NMR tube and registering the spectrum of the reaction mixture at different reaction times, clear evidence of the variation of the **53α-OTMS**/**55** ratio during the reaction time was obtained (from 1:2 after 10 min to 1:8 after 30 min), clearly indicating the occurrence of an isomerization process. Moreover, acetylation of pure *cis*-azido alcohol **55** afforded an almost 8:2 mixture of the acetylated starting compound **55-Ac** and 4-*O*-acetyl-α-glycosyl azide **53α-Ac**, indicating the existence of a rapid equilibrium between configurationally homogeneous 1,2- and 1,4-addition products, also in this system.[18] Attempts to obtain pure **55-Ac** and **53α-Ac** by preparative TLC of the reaction mixture were in vain: extraction of the corresponding well-separated bands afforded only the starting 8:2 **55-Ac**/**53α-Ac** mixture, presumably corresponding to a thermodynamic ratio between the two regioisomers (Scheme 9).

Almost the same results have been obtained with epoxide **8α**, which, under the same reaction conditions ($TMSN_3$, room temperature), led to the corresponding *syn*-1,2-addition product, the D-allal-derived *cis*-azido alcohol **56**[16c,d] (86%), and the corresponding *coordination product*, the 4-*O*-TMS-α-glycosyl azide **54α-OTMS**[16c] (14%). Also in this case, recording the ^{1}H NMR spectra of the reaction mixture at different reaction times (from 10 to 30 min) in C_6D_6, gave clear evidence for the presence of an isomerization process.[19]

Table 4
Glycosylation of alkyl lithium compounds and TMSCN by the in situ-formed allyl epoxide **8β** under *protocol B*

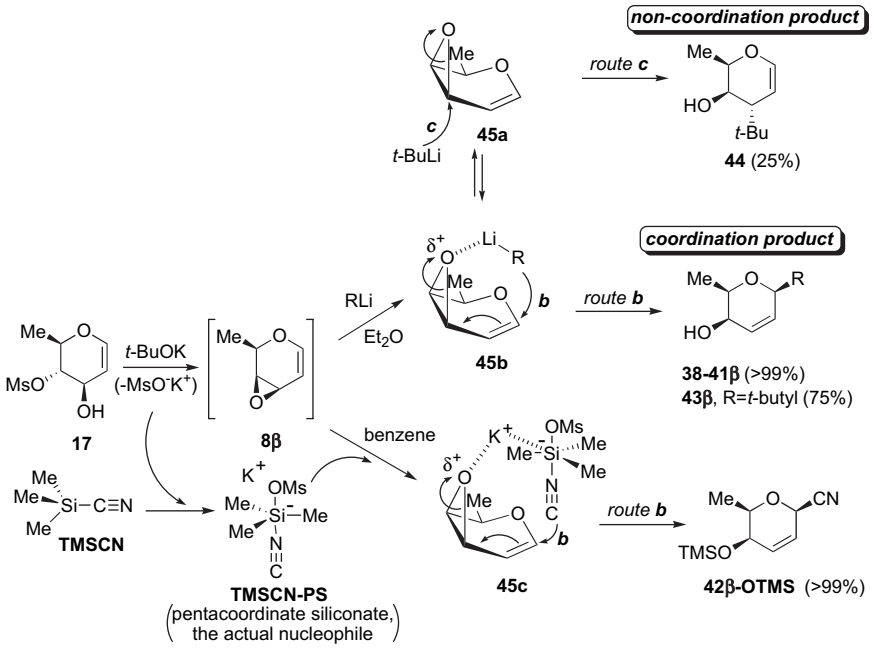


17 **8β**

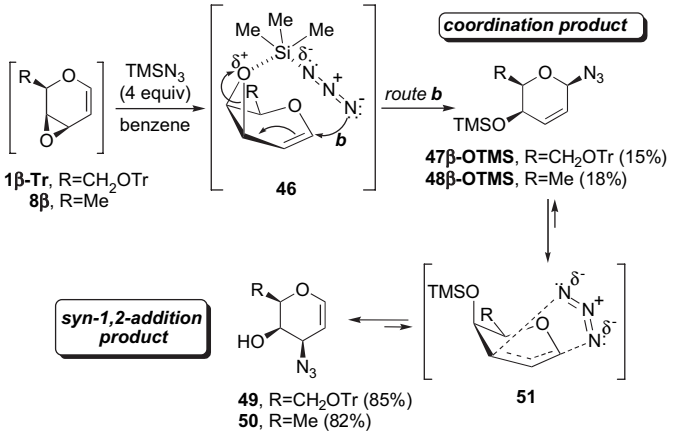
38β: R= Me, X= H **44**, R= *t*-Bu
39β: R= Bu, X= H
40β: R= *s*-Bu, X= H
41β: R= Ph, X= H
42β-OTMS: R= CN, X= TMS
43β: R= *t*-Bu, X= H

Entry	Glycosyl acceptor	Time (h)	Product(s)	Yield (%)
1	MeLi	1	**38β** (>99%)	71[a]
2	BuLi	1	**39β** (>99%)	69[a]
3	*s*-BuLi	1	**40β** (>99%)	78[a]
4	PhLi	1	**41β** (>99%)	74[b]
5	TMSCN	2	**42β-OTMS** (>99%)	86[a]
6	*t*-BuLi	1	**43β** (75%)+**44** (25%)	70[a]

[a] Crude product.
[b] Purified product (flash chromatography or preparative TLC).

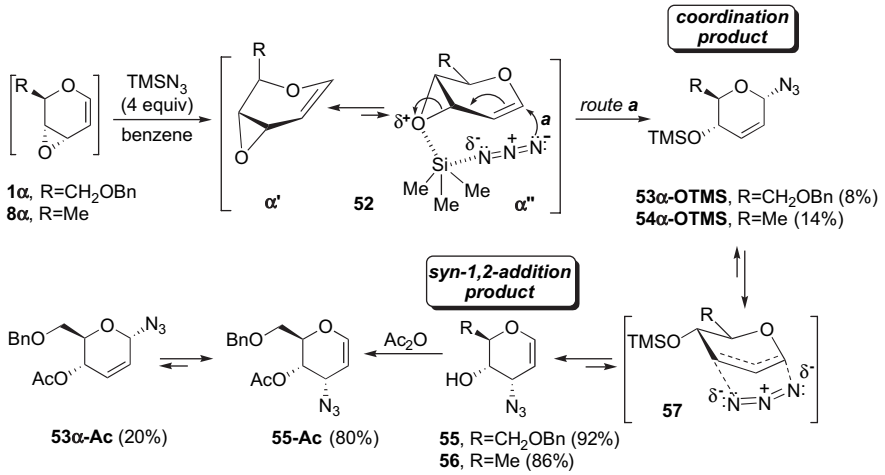


Scheme 7.

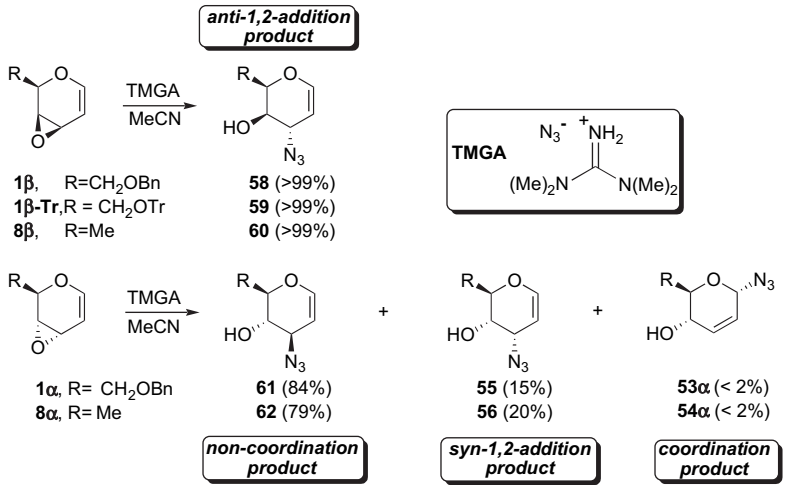


Scheme 8.

In a necessary revision of the previously proposed rationalization in order to justify the formation of the *cis*-azido alcohol **49**,[1d] we conclude that the reaction of $TMSN_3$ with glycal-derived epoxides **1α**, **1β-Tr**, **8α** and **8β** initially leads to the formation of the corresponding *coordination product* (the α-glycosyl azide **53α-OTMS** and **54α-OTMS** from **1α** and **8α** or β-glycosyl azide **47β-OTMS** and **48β-OTMS** from **1β-Tr** and **8β**, respectively) by a coordination between the oxirane oxygen and the TMS-group of the reagent ($TMSN_3$), followed by an attack of the coordinated nucleophile (azido group) on C(1), as exemplified in structures **46**, *route* ***b***, and **52**, *route* ***a*** (Schemes 8 and 9). However, due to the ambident nature of the azido group, the *coordination product*, the primary reaction product, can partially isomerize to the corresponding *syn*-1,2-addition product (*cis*-azido alcohol **55**, **56**, **49** and **50**, respectively), the main reaction product, by a suprafacial [3,3]-sigmatropic rearrangement process, as shown in **51** and **57** (Schemes 8 and 9), leading to an equilibrium mixture of the regioisomeric 1,2- and 1,4-addition products, as is experimentally observed.[16c,20]



Scheme 9.



Scheme 10.

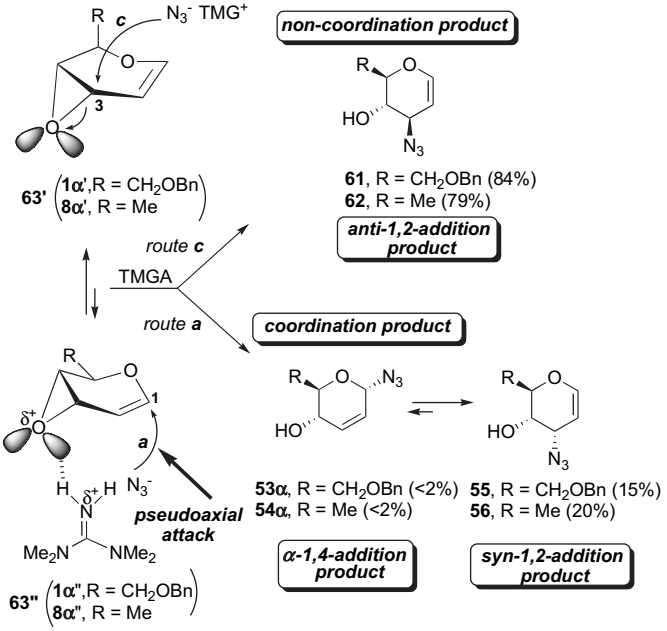
3.3.2. Tetramethylguanidinium azide (TMGA)

The reaction of epoxides **8α** and **8β**, like epoxides **1α**,[10] **1β** and **1β-Tr**,[1d] with TMGA is a further example of how the reactions of these glycal systems are influenced by the presence of chelating or protic species.

Tetramethylguanidinium azide (TMGA) was always considered by us as a non-coordinating source of azide (presence of TMG^+, a supposed non-coordinating counterion, Scheme 10) and, as a consequence, an appropriate reagent for a regioselective non-coordinated 1,2-azidolysis process. The reaction of epoxide **8β** with TMGA is completely regioselective, with the exclusive formation of the corresponding *non-coordination product*, the D-gulal-derived *trans*-azido alcohol **60**, [16c] in accordance with the behaviour of the structurally related epoxides **1β** and **1β-Tr**, which, under the same conditions, afforded the corresponding D-gulal-derived *trans*-azido alcohols **58** and **59**, respectively, as expected (Scheme 10).[1d]

This is not the case with the diastereoisomeric epoxides **8α** and **1α** where the *non-coordination product*, the corresponding D-glucal-derived *trans*-azido alcohols **61** (from epoxide **1α**, 84%) and **62**[16c,d] (from epoxide **8α**, 79%) are unexpectedly accompanied by a small, but significant, amount (almost 15–20%) of the corresponding *syn*-1,2-addition product, the *cis*-azido alcohols **55** (from epoxide **1α**) and **56** (from epoxide **8α**) and traces (<2%) of the corresponding *coordination product*, the α-glycosyl azides **53α** (from **1α**) and **54α** (from **8α**) (^{1}H NMR) (Scheme 10). The presence, even if in traces, of these latter compounds, together with the evidence obtained by an appropriate control experiment,[21] clearly indicate that the small amount of *cis*-azido alcohols **55** and **56** derives from an isomerization process of the corresponding α-glycosyl azides **53α** and **54α**, the respective primary reaction product, as discussed above.

It is our opinion that, in addition to determining the formation of the corresponding *non-coordination product* (*trans*-azido alcohols **61** and **62**, from epoxides **1α** and **8α**, respectively) (*route* ***c***, Scheme 11), TMGA can coordinate, even if to a limited extent, the oxirane oxygen of epoxides **1α** and **8α** by means of the protonated counterion (TMG^+) (hydrogen bond), as shown in structure **63″**. This would give, through the usual entropically favoured attack on C(1) from the same side (*route* ***a***), the corresponding *coordination product*, α-glycosyl azide **53α** (from **1α**) and **54α** (from **8α**). If the non-coordinated process should reasonably occur through the corresponding more stable conformer **1α′** and **8α′**, in which the nucleophilic attack of the azide anion at the allylic C(3) oxirane carbon allows a *trans*-diaxial opening process (*route* ***c***) of the oxirane ring, as shown in structure **63′** (Scheme 11), the coordinated process should reasonably occur through the corresponding conformers **1α″** and **8α″**, in which such a process corresponds to a more favoured *pseudoaxial* attack (*route* ***a***). Subsequent sigmatropic rearrangement process transforms **53α** and **54α**, the primary reaction products, into the corresponding *syn*-1,2-addition product, the *cis*-azido alcohols **55** and **56** (Scheme 11).

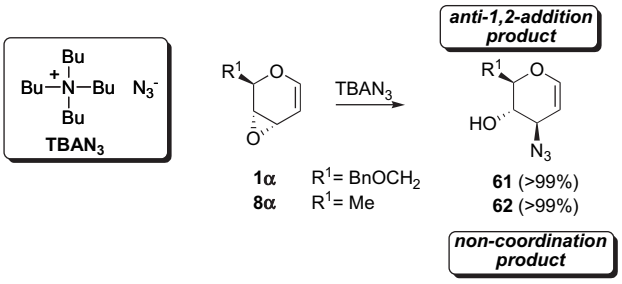


Scheme 11.

Actually, the coordinating/protonating ability of TMGA was not a complete surprise considering that a previous study, which came to our knowledge only after these unexpected results were obtained, clearly indicated that tetramethylguanidinium ion (TMG^+) is capable of forming hydrogen bonds.[22]

As a confirmation of this rationalization, when the azidolysis reaction of **1α** and **8α** was repeated using tetrabutylammonium azide ($TBAN_3$),[23] an azide species having a counterion (TBA^+), which is non-coordinating and non-protic, the crude reaction mixtures became considerably simplified and the corresponding *non-coordination products* **61** (from epoxide **1α**) and **62** (from epoxide **8α**) were the only reaction products (Scheme 12).

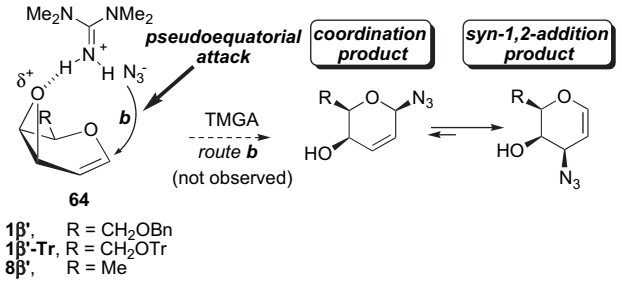
In the framework of the rationalization proposed to justify the formation of the small amount of *syn*-1,2-addition product in the addition reactions of TMGA to epoxides **1α** and **8α**, the absence of the corresponding *syn*-1,2-addition product in the addition reactions of TMGA to the diastereoisomeric epoxides **1β**, **1β-Tr**[1d] and



Scheme 12.

8β could be simply due to conformational and stereoelectronic effects. Epoxides **1β**, **1β-Tr** and **8β** exist only in the corresponding conformer β′[8] and any nucleophilic attack leading to the *coordination product*, then rearranged to the related *syn*-1,2-addition product, corresponds to a less favoured *pseudoequatorial attack* (*route* ***b***), as shown in structure **64** (Scheme 13). This consideration, combined with an evidently reduced ability of TMG^+ to coordination with respect to $TMSN_3$, determines the absence of any *syn*-1,2-addition product in the reactions of epoxides **1β**, **1β-Tr** and **8β** with TMGA.

A comparison of the results obtained with epoxides **1α**, **1β**, **1β-Tr**, **8α** and **8β** in their reactions with azide-based nucleophiles (TMGA, $TBAN_3$ and $TMSN_3$) indicates that it is possible to obtain, in an effective 1,2-regio- and stereoselective fashion, the corresponding 3-deoxy-3-azido glycal (azido alcohol, 1,2-addition product) with a well-defined relative and absolute configuration, depending on the azide-based nucleophile and configuration α or β of the starting epoxide: $TMSN_3$ leads to the corresponding D-allal- (*cis*-azido alcohols **55** and **56**) and D-galactal-derived azido alcohol (*cis*-azido alcohols **49** and **50**), whereas TMGA (or $TBAN_3$) leads to D-glucal- (*trans*-azido alcohols **61** and **62**) and D-gulal-derived azido alcohol (*trans*-azido alcohols **58**–**60**) with α (**1α** and **8α**) and β epoxides (**1β**, **1β-Tr** and **8β**), respectively (Schemes 8–12).



Scheme 13.

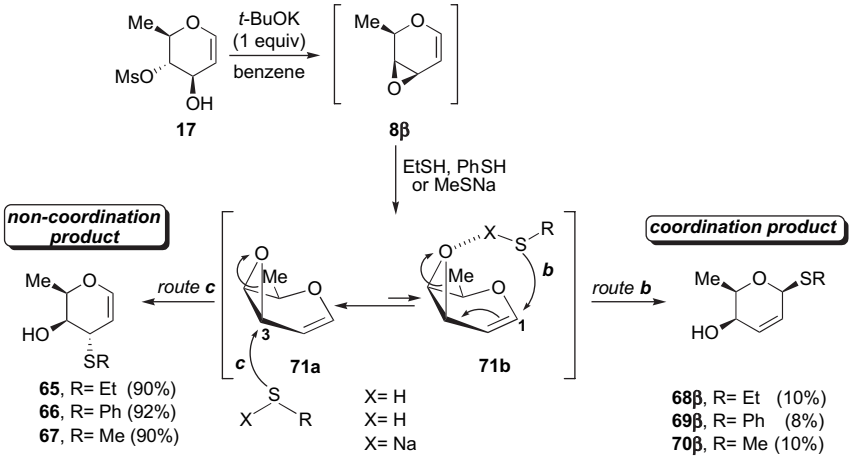
3.4. *S*-Nucleophiles

The regio- and stereoselectivity of the addition reactions of *S*-nucleophiles was examined with epoxides **8β** and **1α** by means of a thiol (EtSH and PhSH) and a thiolate (MeSNa).

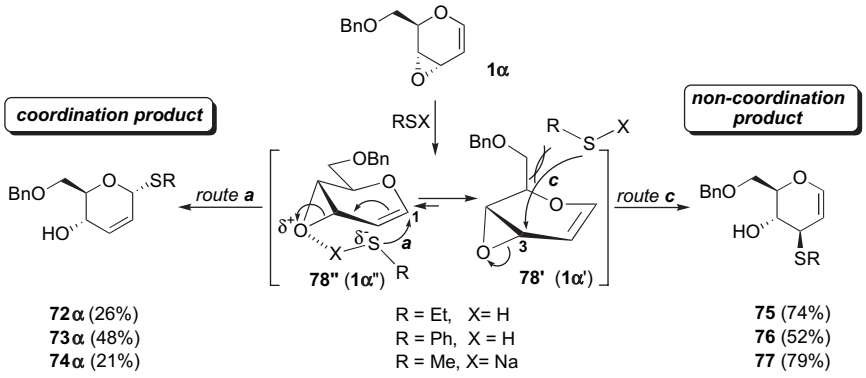
In the case of **8β**, the reactions were largely 1,2-regioselective, with the formation of the corresponding *non-coordination* product, the *trans*-alkyl- or phenylthio alcohols **65**–**67** (90–92%) accompanied only by a small amount (8–10%) of the corresponding *coordination product* (β-1,4-addition product), the alkyl or phenyl β-thioglycosides **68**–**70β** (Scheme 14), showing a behaviour similar to that previously found with the corresponding *O*-trityl substituted epoxide **1β-Tr**.[1d,24]

In the case of epoxide **1α**, the reactions with EtSH and MeSNa are still largely 1,2-regioselective (about 79–74%), but the amount of the corresponding α-thioglycoside (the *coordination product*) significantly increases (21–26%), to the point that with PhSH, an almost 1:1 mixture of the *trans*-phenylthio alcohol **76** (*non-coordination product*) and phenyl α-thioglycoside **73α** (*coordination product*) is obtained (Scheme 15).

As shown in structure **78′** (Scheme 15), the *non-coordination products* (**75**–**77**) derived, as usual, by an attack on the allylic C(3) oxirane carbon from the free, non-coordinated nucleophile (RSX in Scheme 15) on the free, non-coordinated epoxide **1α**, largely present in the reaction mixture as a consequence of the reduced ability of thiols to coordination. In this process, the epoxide should reasonably react through its conformer **1α′**, which allows a more favourable *trans*-diaxial opening pathway (structure **78′**, *route* ***c***, Scheme 15), even if it requires a certain steric and/or torsional strain between the incoming nucleophile and the C(5)–C(6) bond of the side chain. As for the *coordination product*, its formation comes from the presence, which cannot be excluded in the reaction mixture, of a certain amount of the nucleophile coordinated to the epoxide, in the form of a hydrogen bond (EtSH) or through the metal (MeSNa), as shown in **78″**, which allows an entropically favoured α-directed attack of the nucleophile on C(1), with the epoxide reacting through conformer **1α′** in which the coordinated attack corresponds to a *pseudoaxial* attack (*route* ***a***, Scheme 15). In this framework, the unexpectedly high amount (48%) of the corresponding *coordination product*, the phenyl α-thioglycoside **73α**, found in the reaction of epoxide **1α** with PhSH, is reasonably due to a better ability of the more acidic PhSH to coordination.[25]



Scheme 14.



Scheme 15.

4. Structures and configurations

The 1,2- (cis or trans) or 1,4-addition product structure of all compounds described in this work has been determined by their method of preparation, a careful examination of their ^{1}H and ^{13}C NMR spectra and, when possible, by comparison with literature data reported for the same or structurally strictly related compound.[3c,4,6,11,12,16] As for the glycosides (1,4-addition product), the α or β configuration has been determined by means of the following considerations, based on literature data: (a) in *O*-glycosides (Tables 1 and 2), the chemical shift value for the anomeric H-1 proton in the ^{1}H NMR spectra of these compounds is upfield in the α-anomer with respect to the value for H-1 proton in the corresponding β-anomer;[11] (b) in glycosyl azides (Schemes 8 and 9),[16c,d,26] alkyl and phenyl thioglycosides (Schemes 14 and 15),[27] the chemical shift value for the anomeric H-1 proton is downfield in the α-anomer with respect to the value for H-1 proton in the corresponding β-anomer; (c) in *C*-glycosides (Tables 3 and 4) the chemical shift value for C(5) carbon in the ^{13}C NMR spectra of these compounds was taken as a diagnostic tool for the determination of the 1,5-cis (β-anomer) or 1,5-trans relationship (α-anomer) between substituents at C(1) and C(5): in α-anomer, the chemical shift of C(5) is shielded relative to the corresponding β-isomer.[12,28] Moreover, where necessary, appropriate NOE experiments were run in order to confirm the structure and/or configuration assigned.

5. Conclusions

Comparison of the results obtained with the 6-deoxy allyl epoxides **8α** and **8β** with those using the structurally related 6-OBn- and 6-OTr-substituted allyl epoxides **1α**, **1β** and **1β-Tr**, indicates that the regio- and stereochemical behaviour of these epoxides are very similar. For example, except for the reaction with MeOH and EtOH (epoxide **8α**) and with *t*-BuLi (epoxide **8β**), a complete 1,4-regioselectivity and a substrate-dependent stereoselectivity, with exclusive formation of the corresponding *coordination product*, was observed in the reactions (*protocol B*) of epoxides **8α** and **8β** with *O*-nucleophiles (alcohols and partially protected monosaccharides) and *C*-nucleophiles (alkyl lithium compounds and TMSCN). This result parallels what previously found with the corresponding epoxides **1α**, **1β** and **1β-Tr**, and constitutes a further example of a completely stereoselective glycosylation process. As a consequence, the 1,4-regio- and substrate-dependent stereoselectivity originally found with epoxides **1α**, **1β** and **1β-Tr** in their reactions with nucleophiles, that is, the formation of the *coordination product*, does not depend on the presence of the *O*-heterofunctionality in the side chain (–CH_2OBn or –CH_2OTr) and related chelation process, as shown in **4** (Scheme 1), but exclusively on the coordination of the nucleophiles with the oxirane oxygen.

The results obtained in the reaction of epoxides **1α**, **1β-Tr**, **8α** and **8β** with $TMSN_3$ demonstrated the existence of a [3,3]-sigmatropic rearrangement process of the corresponding glycosyl azide (the primary reaction product) into the configurationally related *syn*-1,2-addition product, the corresponding *cis*-azido alcohol. This observation made it possible to correct a previously proposed carbocation-based rationalization for the formation of the *syn*-1,2-addition product in these oxirane systems,[1d] which, in the light of the results obtained in this work, does not appear appropriate any more. 3-Deoxy-3-azido glycals with a well-defined relative (cis/trans) and absolute configuration can be regio- and stereoselectively obtained depending on the azide-based nucleophile ($TMSN_3$, TMGA or $TBAN_3$) and the configuration (α or β) of the epoxide. It was also found that the amount of *coordination product* obtained in the nucleophilic addition reactions of *N*-nucleophiles (TMGA) and *S*-nucleophiles (thiols) is dependent on the *pseudoaxial* or *pseudoequatorial* nature of the corresponding nucleophilic attack.

6. Experimental

6.1. General

IR spectra were obtained using a FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded at 250 and 62.5 MHz, respectively. Mass spectra were recorded with an ESI-MS ThermoFinningan equipment. All reactions were performed in a 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 employing 230–400 mesh silica gel (Macherey-Nagel). Analytical TLC were 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 were distilled from calcium hydride. Benzene, benzene-d_6, toluene, Et_2O and THF were distilled from sodium/benzophenone. EtOH (absolute), anhydrous MeCN and DMF over molecular sieves and all the solution of lithium alkyl compounds were purchased from Aldrich-Fluka. 3,4-Di-*O*-acetyl-6-deoxy-D-glucal (**13**),[4a] epoxides **1β-Tr**[1a] and **1α**[1c] were prepared as previously described. In the reaction carried out under *protocol A*, *trans*-hydroxy mesylate **17** (or **21**) was treated with *t*-BuOK (1 equiv) in the glycosyl acceptor (MeOH, EtOH, *i*-PrOH or *t*-BuOH), as the solvent. In the reaction carried out under *protocol B*, a solution of *trans*-hydroxy mesylate **17** (or **21**) in anhydrous solvent (benzene, Et_2O, MeCN) was treated with *t*-BuOK (1 equiv) and, after 30 min, the glycosyl acceptor (*O*-, *C*-, *N*- or *S*-nucleophile, 3–4 equiv) was added.

6.2. Synthesis of hydroxy mesylates 17 and 21

*6.2.1. 6-Deoxy-D-glucal (**14**)*

A solution of the diacetyl derivative **13**[4a] (1.83 g, 8.55 mmol) in MeOH (23 mL) was treated with MeONa (0.115 g, 2.13 mmol) and the reaction mixture was stirred for 4 h at room temperature. Evaporation of the organic solvent afforded a crude liquid product (1.01 g, 91% yield) consisting primarily of diol **14**,[4b,c] which was used without purification in the subsequent step: R_f=0.26 (3:7 hexane/AcOEt). ^{1}H NMR (CD_3OD) δ 6.21 (dd, 1H, J=5.9, 1.6 Hz), 4.58 (dd, 1H, J=6.0, 2.1 Hz), 4.00 (dt, 1H, J=7.3, 1.9 Hz), 3.57–3.75 (m, 1H), 3.17 (dd, 1H, J=9.8, 7.4 Hz), 1.24 (d, 3H, J=6.3 Hz). ^{13}C NMR (CD_3OD) δ 145.0, 104.7, 76.1, 75.9, 70.6, 17.8. Anal. Calcd for $C_6H_{10}O_3$: C, 55.37; H, 7.74. Found: C, 55.12; H, 7.46.

*6.2.2. 3-O-(tert-Butyldimethylsilyl)-6-deoxy-D-glucal (**15**)*

A solution of diol **14** (1.01 g, 7.77 mmol) in anhydrous DMF (21 mL) was treated at 0 °C with TBDMSCl (1.28 g, 8.54 mmol) in the presence of imidazole (1.06 g, 15.54 mmol) and the resulting reaction mixture was stirred for 16 h at room temperature. Dilution with Et_2O and evaporation of the washed (water) organic solution afforded the silyl ether **15**, pure as a liquid (^{1}H NMR) (1.57 g, 83% yield), which was used directly in the next step without any further purification: R_f=0.48 (8:2 hexane/AcOEt); FTIR (film) ν 3393, 1651, 1244, 1096 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.24 (dd, 1H, J=6.0, 1.3 Hz), 4.60 (dd, 1H, J=6.0, 2.2 Hz), 4.19 (dt, 1H, J=6.7, 1.7 Hz), 3.81–3.98 (m, 1H), 3.53–3.63 (m, 1H), 1.36 (d, 3H, J=6.4 Hz), 0.89 (s, 9H), 0.10 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 143.8, 103.6, 75.0, 74.5, 70.7, 26.0, 18.3, 17.4, −4.1, −4.3. Anal. Calcd for $C_{12}H_{24}O_3Si$: C, 58.97; H, 9.90. Found: C, 58.86; H, 9.78.

*6.2.3. 3-O-(tert-Butyldimethylsilyl)-4-O-mesyl-6-deoxy-D-glucal (**16**)*

A solution of the mono silyl derivative **15** (1.13 g, 4.63 mmol) in a 1:1 mixture of anhydrous CH_2Cl_2 (14 mL) and anhydrous pyridine (10 mL), was treated dropwise, for 2 min, at 0 °C with MsCl (0.71 mL, 1.05 g, 9.26 mmol) and the resulting reaction mixture was stirred for 16 h at the same temperature. Dilution with CH_2Cl_2 and evaporation of the washed (saturated aqueous NaCl) organic solution afforded a liquid crude product (1.46 g, 98% yield), which was subjected to flash chromatography. Elution with an 8:2 hexane/AcOEt mixture afforded mesylate **16** (1.16 g, 78% yield), as a liquid: R_f=0.63 (7:3 hexane/AcOEt); FTIR (film) ν 1649, 1360, 1253, 1175, 1089 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.33 (dd, 1H, J=6.2, 1.2 Hz), 4.72 (dd, 1H, J=6.2, 3.0 Hz), 4.58 (dd, 1H, J=7.2, 5.6 Hz), 4.36–4.42 (m, 1H), 4.09–4.25 (m, 1H), 3.10 (s, 3H), 1.45 (d, 3H, J=6.7 Hz), 0.91 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 143.8, 102.3, 82.3, 72.7, 66.7, 39.1, 25.9, 18.1, 17.0, −4.1, −4.2. Anal. Calcd for $C_{13}H_{26}O_5SSi$: C, 48.42; H, 8.13. Found: C, 48.23; H, 8.04.

*6.2.4. 4-O-Mesyl-6-deoxy-D-glucal (**17**)*

A solution of mesylate **16** (0.45 g, 1.40 mmol) in anhydrous THF (47 mL) was treated at 0 °C with TBAF (1.40 mL of a 1 M solution in THF, 1.40 mmol) and the reaction mixture was stirred at the same temperature for 40 min. Dilution with Et_2O and evaporation of the washed (brine) organic solution afforded a crude product (0.28 g, 98% yield), which was subjected to flash chromatography. Elution with a 1:1 hexane/AcOEt mixture yielded hydroxy mesylate **17** (0.25 g, 86% yield), as a yellow solid, mp 62–64 °C: R_f=0.18 (7:3 hexane/AcOEt); $[\alpha]_D^{20}$ +16.1 (c 1.1, $CHCl_3$); FTIR (Nujol mull) ν 3450, 1649, 1246, 1079 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.36 (d, 1H, J=5.8 Hz), 4.77 (dd, 1H, J=5.8, 1.8 Hz), 4.41–4.53 (m, 2H), 3.86–4.10 (m, 1H), 3.20 (s, 3H), 1.43 (d, 3H, J=6.4 Hz). ^{13}C NMR ($CDCl_3$) δ 145.4, 103.2, 84.6, 73.1, 68.5, 39.5, 17.7. Anal. Calcd for $C_7H_{12}O_5S$: C, 40.38; H, 5.81. Found: C, 40.56; H, 5.65. MS (m/z) 74, 83, 116, 170, 186, 242 $(M+2H_2O)^+$.

*6.2.5. 6-Deoxy-D-gulal (**18**)*

Following a previously described procedure,[1c] a solution of *trans*-hydroxy mesylate **17** (0.67 g, 3.22 mmol) in anhydrous THF (14 mL) was treated with *t*-BuOK (0.36 g, 3.22 mmol). After 30 min stirring at room temperature, the reaction mixture was treated with a solution of tetrabutylammonium trimethylsilanolate [prepared from Bu_4NBr (4.14 g, 12.88 mmol) and Me_3SiOK (1.65 g, 12.88 mmol, 4 equiv)] in anhydrous THF (43 mL). After 48 h stirring at the same temperature, the reaction mixture was concentrated under reduced pressure, then diluted with Et_2O and the resulting mixture was stirred for 30 min at room temperature in the presence of a small amount of Celite. Filtration of the suspension and evaporation of the collected organic solution afforded a crude product consisting of *trans*-diol **18** (^{1}H NMR), which was subjected to flash chromatography. Elution with an 8:2 CH_2Cl_2/acetone mixture afforded diol **18**[6] (0.31 g, 74% yield), as a liquid: R_f=0.2 (8:2 CH_2Cl_2/acetone); FTIR (film) ν 3385, 1647, 1259, 1056 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.57 (d, 1H, J=6.1 Hz), 4.95 (ddd, 1H, J=6.7, 5.5, 1.7 Hz), 4.03 (q, 1H, J=6.7 Hz), 3.96 (dd, 1H, J=5.1, 2.6 Hz), 3.63–3.85 (m, 1H), 1.40 (d, 3H, J=6.7 Hz). ^{13}C NMR δ 147.7, 100.4, 71.2, 70.1, 64.9, 16.5. Anal. Calcd for $C_6H_{10}O_3$: C, 55.37; H, 7.74. Found: C, 55.54; H, 7.89.

In an alternative procedure, the treatment of a solution of hydroxy mesylate **17** (0.030 g, 0.14 mmol) in anhydrous THF (2 mL) with *t*-BuOK (0.016 g, 0.14 mmol) and tetrabutylammonium acetate (Fluka) (0.127 g, 0.42 mmol, 3 equiv) afforded, after 30 min stirring at room temperature, a crude product (0.013 g, 71% yield) consisting of practically pure diol **18**.

*6.2.6. 3-O-(tert-Butyldimethylsilyl)-6-deoxy-D-gulal (**19**)*

Proceeding as previously described for the synthesis of **15**, treatment of a solution of *trans*-diol **18** (0.67 g, 5.15 mmol) in anhydrous DMF (16 mL) at 0 °C with imidazole (0.71 g, 10.40 mmol) and TBDMSCl (0.85 g, 5.66 mmol) afforded silyl ether **19** (1.21 g, 96% yield), as a liquid, which was used in the subsequent step without any further purification; FTIR (film) ν 3385, 1649, 1249, 1096 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.50 (d, 1H, J=6.1 Hz), 4.81 (td, 1H, J=6.1, 1.6 Hz), 4.05 (q, 1H, J=6.7 Hz), 3.90 (dd, 1H, J=5.0, 2.5 Hz), 3.43 (d, 1H, J=10.3 Hz), 1.35 (d, 3H, J=6.7 Hz), 0.88 (s, 9H), 0.11 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 146.0, 101.0, 71.8, 69.7, 65.2, 26.0, 18.2, 16.6, −3.4, −4.6. Anal. Calcd for $C_{12}H_{24}O_3Si$: C, 58.97; H, 9.90. Found: C, 59.06; H, 9.67.

*6.2.7. 3-O-(tert-Butyldimethylsilyl)-4-O-mesyl-6-deoxy-D-gulal (**20**)*

Proceeding as previously described for the synthesis of **16**, treatment of a solution of the silyl derivative **19** (0.46 g, 1.88 mmol) at 0 °C in a mixture of anhydrous CH_2Cl_2 (7.0 mL) and anhydrous pyridine (5 mL) with MsCl (0.29 mL, 0.43 g, 3.76 mmol) afforded a crude reaction product consisting of mesylate **20** (0.55 g, 91% yield), sufficiently pure to be utilized in the next step without any further purification (some attempts at purification by flash chromatography or preparative TLC resulted in an extensive decomposition of the product); FTIR (film) ν 1649, 1358, 1253, 1175, 1087 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.47 (d, 1H, J=6.2 Hz), 4.81 (td, 1H, J=6.3, 1.7 Hz), 4.41–4.23 (m, 3H), 3.05 (s, 3H), 1.37 (d, 3H, J=6.7 Hz), 0.87 (s, 9H), 0.10 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 146.0, 100.0, 78.2, 67.5, 62.8, 38.5, 25.7, 17.9, 16.6, −4.4, −4.5. Anal. Calcd for $C_{13}H_{26}O_5SSi$: C, 48.42; H, 8.13. Found: C, 48.65; H, 8.31.

*6.2.8. 4-O-Mesyl-6-deoxy-D-gulal (**21**)*

Proceeding as previously described for the synthesis of **17**, the treatment at 0 °C of a solution of mesylate **20** (0.72 g, 2.23 mmol) in anhydrous THF (60 mL) with 1 M TBAF in THF (2.23 mL) afforded a crude reaction product (0.45 g, 97% yield) consisting of hydroxy mesylate **21**, which was subjected to flash chromatography.

Elution with a 95:5 CH_2Cl_2/acetone mixture afforded hydroxy mesylate **21** (0.36 g, 78% yield), as a slightly yellow solid: mp 76–78 °C; $[\alpha]_D^{20}$ +55.7 (*c* 0.8, $CHCl_3$); FTIR ν (Nujol mull) 3447, 1648, 1246, 1081 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.60 (d, 1H, *J*=6.2 Hz), 4.96 (td, 1H, *J*=6.2, 1.4 Hz), 4.57–4.61 (m, 1H), 4.11–4.26 (m, 2H), 3.08 (s, 3H), 1.41 (d, 3H, *J*=6.6 Hz). ^{13}C NMR ($CDCl_3$) δ 146.9, 99.4, 78.3, 67.9, 61.9, 38.5, 16.3. Anal. Calcd for $C_7H_{12}O_5S$: C, 40.38; H, 5.81. Found: C, 40.12; H, 5.47. MS (*m*/*z*) 74, 83, 116, 170, 186, 242 $(M+2H_2O)^+$.

6.3. Glycosylation of alcohols by the in situ-formed allyl epoxides 8α and 8β, in the alcohol as the solvent/nucleophile (*protocol A*)

*6.3.1. Reaction of epoxide **8α** with MeOH as the solvent/nucleophile (protocol A)*

Typical procedure. A solution of *trans*-hydroxy mesylate **21** (0.092 g, 0.44 mmol) in anhydrous MeOH (5 mL) was treated with *t*-BuOK (0.050 g, 0.44 mmol) and the reaction mixture was stirred at room temperature for 30 min. The solution was partitioned between Et_2O (15 mL) and brine (10 mL), and the aqueous layer was further extracted with Et_2O (2×10 mL). Evaporation of the combined and washed (saturated aqueous NaCl) organic extracts afforded a crude reaction product (0.056 g, 88% yield) consisting of an 85:15 mixture of methyl *O*-glycosides ***ent*-9α** and **9β** (^1H NMR), which was subjected to preparative TLC (a 1:1 hexane/AcOEt mixture was used as the eluant). Extraction of the two most intense bands (the faster moving band contained **9β**) afforded ***ent*-9α** (0.031 g, 49% yield) and **9β** (0.006 g, 9% yield).

*6.3.1.1. Methyl 2,3,6-trideoxy-α-D-erythro-hex-2-enopyranoside (**ent-9α**).*[11] Liquid, R_f=0.25 (1:1 hexane/AcOEt); $[\alpha]_D^{20}$ +99.5 (*c* 0.6, $CHCl_3$); FTIR (film) ν 3418, 1629, 1448, 1051 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.92 (d, 1H, *J*=10.2 Hz), 5.72 (dt, 1H, *J*=10.1, 2.3 Hz), 4.77–4.84 (m, 1H, H-1), 3.58–3.90 (m, 2H), 3.40 (s, 3H), 1.32 (d, 3H, *J*=6.1 Hz). ^{13}C NMR ($CDCl_3$) δ 133.8, 127.1, 95.6, 70.1, 68.4, 56.1, 18.4. Anal. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 58.64; H, 8.21.

*6.3.1.2. Methyl 2,3,6-trideoxy-β-D-erythro-hex-2-enopyranoside (**9β**).*[11] Liquid, R_f=0.23 (1:1 hexane/AcOEt); FTIR (film) ν 3448, 1629, 1454, 1069 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.98 (d, 1H, *J*=11.9 Hz), 5.77 (d, 1H, *J*=12.9 Hz), 5.04 (d, 1H, *J*=1.2 Hz, H-1), 3.85–3.99 (m, 1H), 3.59–3.71 (m, 1H), 3.46 (d, 3H, *J*=7.2 Hz), 1.38 (d, 3H, *J*=6.4 Hz). ^{13}C NMR ($CDCl_3$) δ 132.0, 129.0, 97.6, 74.4, 68.6, 55.1, 18.4. Anal. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 58.23; H, 8.15.

*6.3.2. Reaction of epoxide **8β** with MeOH as the solvent/nucleophile (protocol A)*

Following the typical procedure, the treatment of a solution of *trans*-hydroxy mesylate **17** (0.060 g, 0.29 mmol) in anhydrous MeOH (4.5 mL) with *t*-BuOK (0.032 g, 0.29 mmol) for 1 h at room temperature afforded a crude product (0.036 g, 86% yield) consisting of a 65:35 mixture of methyl *O*-glycosides **22β** and **22α** (^1H NMR), which was subjected to flash chromatography. Elution with a 1:1 hexane/AcOEt mixture afforded pure methyl *O*-glycosides **22β** (0.017 g, 41% yield) and **22α** (0.006 g, 14% yield).

*6.3.2.1. Methyl 2,3,6-trideoxy-α-D-threo-hex-2-enopyranoside (**22α**).*[11] Liquid, R_f=0.27 (1:1 hexane/AcOEt); $[\alpha]_D^{20}$ +70.0 (*c* 0.4, $CHCl_3$); FTIR (film) ν 3425, 1626, 1449, 1064 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.20 (dd, 1H, *J*=9.8, 5.3 Hz), 5.90 (dd, 1H, *J*=9.8, 3.0 Hz), 4.87 (d, 1H, *J*=3.0 Hz, H-1), 4.13 (qd, 1H, *J*=6.6, 2.1 Hz), 3.52–3.66 (m, 1H), 3.45 (s, 3H), 1.32 (d, 3H, *J*=6.6 Hz). ^{13}C NMR ($CDCl_3$) δ 130.3, 128.0, 95.5, 66.3, 63.8, 55.4, 16.1. Anal. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 58.12; H, 8.09.

*6.3.2.2. Methyl 2,3,6-trideoxy-β-D-threo-hex-2-enopyranoside (**22β**).*[11] Liquid, R_f=0.29 (1:1 hexane/AcOEt); $[\alpha]_D^{20}$ −143.2 (*c* 0.5, $CHCl_3$); FTIR (film) ν 3440, 1627, 1450, 1069 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.16 (ddd, 1H, *J*=10.1, 5.0, 1.5 Hz), 5.82 (unresolved d, 1H, *J*=10.1 Hz), 4.98 (d, 1H, *J*=1.5 Hz, H-1), 3.61–3.80 (m, 2H), 3.51 (s, 3H), 1.32 (d, 3H, *J*=6.4 Hz). ^{13}C NMR δ 131.5, 130.9, 99.1, 71.6, 64.9, 55.7, 16.8. Anal. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 58.53; H, 8.21.

6.4. Glycosylation of alcohols and partially protected monosaccharides in anhydrous benzene by the in situ-formed allyl epoxides 8α and 8β (*protocol B*)

*6.4.1. Reaction of epoxide **8α** with MeOH in anhydrous benzene (protocol B)*

Typical procedure. A solution of *trans*-hydroxy mesylate **21** (0.025 g, 0.12 mmol) in anhydrous benzene (2 mL) was treated with *t*-BuOK (0.013 g, 0.12 mmol). After 30 min stirring at room temperature, MeOH (20 μL, 0.48 mmol) was added and the reaction mixture was stirred for further 30 min at the same temperature. The solution was partitioned between Et_2O (10 mL) and saturated aqueous NaCl (3 mL), and the aqueous layer was extracted with Et_2O (2×5 mL). Evaporation of the combined organic extracts afforded a clean crude product (0.015 g, 87% yield) consisting of an 83:17 mixture of methyl *O*-glycosides ***ent*-9α** and **9β** (^1H NMR).

*6.4.2. Reaction of epoxide **8β** with 1,2;3,4-di-O-isopropylidene-α-D-galactopyranose (protocol B)*

Following the typical procedure, the treatment of a solution of *trans*-hydroxy mesylate **17** (0.033 g, 0.16 mmol) in anhydrous benzene (2.6 mL) with *t*-BuOK (0.018 g, 0.16 mmol) and 1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranose (0.16 g, 0.64 mmol, 4 equiv) afforded, after 18 h stirring at room temperature, a crude product (0.18 g) consisting of glycoside **28β** and the excess of the glycosyl acceptor (^1H NMR), which was subjected to preparative TLC (a 6:4 hexane/AcOEt mixture was used as the eluant). Extraction of the slower moving band afforded *3-O-(2,3,6-trideoxy-β-D-threo-hex-2-enopyranosyl)-1,2;3,4,-di-O-isopropylidene-α-D-galactopyranose (**28β**)*, as a liquid (0.039 g, 65% yield): $[\alpha]_D^{20}$ −61.7 (*c* 0.6, $CHCl_3$); FTIR (film) ν 3445, 1643, 1454, 1245, 1097 cm^{-1}. ^1H NMR δ 6.13 (ddd, 1H, *J*=10.1, 5.1, 1.3 Hz), 5.90 (d, 1H, *J*=10.0 Hz), 5.54 (d, 1H, *J*=5.0 Hz), 5.12 (d, 1H, *J*=1.2 Hz, H-1), 4.60 (dd, 1H, *J*=7.9, 2.4 Hz), 4.30 (dd, 1H, *J*=4.9, 2.4 Hz), 4.20 (dd, 1H, *J*=7.8, 1.7 Hz), 3.93–4.07 (m, 2H), 3.54–3.82 (m, 3H), 1.53 (s, 3H), 1.44 (s, 3H), 1.32 (s, 6H), 1.29 (d, 3H, *J*=6.5 Hz). ^{13}C NMR δ 131.5, 131.3, 109.7, 109.6, 98.9, 96.6, 71.7, 71.6, 70.9, 70.8, 68.8, 68.1, 65.0, 26.5, 26.2, 25.2, 24.7, 16.9. Anal. Calcd for $C_{18}H_{28}O_8$: C, 58.05; H, 7.58. Found: C, 58.43; H, 7.65. MS (*m*/*z*) 130, 203, 224, 260, 278, 390 $(M+H_2O)^+$.

6.5. Reactions of epoxides 8α and 8β with alkyl lithium compounds (*C*-nucleophiles) (*protocol B*)

*6.5.1. Reaction of epoxide **8β** with MeLi in anhydrous Et_2O (protocol B)*

Typical procedure. A solution of *trans*-hydroxy mesylate **17** (0.050 g, 0.24 mmol) in anhydrous Et_2O (3 mL) was treated with *t*-BuOK (0.029 g, 0.26 mmol) and the reaction mixture was stirred for 30 min at room temperature. After cooling to 0 °C, MeLi (0.45 mL of a 1.6 M solution in Et_2O, 0.72 mmol) was added and the reaction mixture was stirred 1 h at the same temperature. Dilution with Et_2O and evaporation of the washed (saturated aqueous NaCl) organic solution afforded a crude product (0.022 g, 71% yield) essentially consisting of β-*C*-glycoside **38β** (^1H NMR), which was subjected to flash chromatography. Elution with a 1:1 hexane/

AcOEt mixture yielded pure *(2S,5R,6R)-5-hydroxy-2,6-dimethyl-2H-5,6-diihydropyran (**38β**)* (0.012 g, 39% yield), as a liquid: R_f=0.45 (1:1 hexane/AcOEt); FTIR (film) ν 3427, 1643, 1446, 1375, 1085 cm^{-1}. ^1H NMR δ 6.02 (ddd, 1H, J=10.0, 7.4, 2.3 Hz), 5.81 (dd, 1H, J=10.0, 1.2 Hz), 4.09–4.27 (m, 1H), 3.54–3.75 (m, 2H), 1.29 (d, 3H, J=5.8 Hz), 1.26 (d, 3H, J=6.3 Hz). ^{13}C NMR δ 135.4, 127.3, 73.9, 71.8, 65.2, 21.3, 17.0. Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.43; H, 9.67.

6.5.2. *Reaction of epoxide **8α** with MeLi in anhydrous Et_2O (protocol B)*

Following the typical procedure, treatment of a solution of *trans*-hydroxy mesylate **21** (0.050 g, 0.24 mmol) in anhydrous Et_2O (3 mL) with *t*-BuOK (0.029 g, 0.26 mmol) and 1.6 M CH_3Li in Et_2O (0.45 mL, 0.72 mmol, 4 equiv) afforded, after 1 h stirring at 0 °C, a crude product essentially consisting of *(2R, 5S, 6R)-5-hydroxy-2,6-dimethyl-2H-5,6-dihydropyran (**33α**)* (0.020 g, 65% yield), pure, as a liquid: R_f=0.45 (1:1 hexane/AcOEt); $[\alpha]_D^{20}$ +43.3 (*c* 1.3, $CHCl_3$); FTIR (film) ν 3427 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.79 (s, 2H), 4.30 (q, 1H, J=6.8 Hz, H-1), 3.68–3.81 (m, 2H), 1.28 (d, 6H, J=6.7 Hz). ^{13}C NMR ($CDCl_3$) δ 133.2, 128.5, 71.5, 68.3, 66.8, 30.5, 18.2. Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.78; H, 9.59. MS (*m*/*z*) 91, 102, 112, 122, 129 $(M+H)^+$.

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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.2008.06.039.

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2. Methyl *O*-glycoside **9α** is the intermediate for the formal synthesis of D ring of calicheamicin γ_1^I;[3a] ethyl *O*-glycoside **10α** is the 2,3-unsaturated glycoside necessary for the synthesis of (−)-methyl ravidosaminide;[3b,c] *tert*-butyl *O*-glycoside **11α** is the key intermediate for the synthesis of the antifungal agent GM222712.[3d]
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5. Epoxides **8α** and **8β** are not isolable, and can only be prepared in situ by cyclization of the corresponding stable precursors, the *trans*-hydroxy mesylates **17** and **21**, respectively, and left immediately to react with a nucleophile.
6. For a recently described synthesis of 6-deoxy-D-gulal (**18**), see: Engstrom, K. M.; Mendoza, M. R.; Navarro-Villalobos, M.; Gin, D. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1128–1130.
7. Alternatively, *trans*-diol **18** could be prepared by reaction of epoxide **8β** with commercially available tetrabutylammonium acetate ($Bu_4N^+AcO^-$). In this reaction, contrary to expectations, *trans*-diol **18** was the only reaction product: a saponification process on the primary reaction product, the monoacetate **18-Ac**, reasonably occurred under the slightly alkaline reaction conditions (Scheme 3).
8. It is interesting to note that the unique (**1β′-OMe**, **1β′**, **1β′-Tr** and **8β′**) and the more stable conformer (**1α′-OMe**, **1α′** and **8α′**) present at the equilibrium in epoxides **1β-OMe**, **1β**, **1β-Tr**, **8β**, **1α-OMe**, **1α** and **8α** contain the same ring conformation, with the oxirane and the endocyclic oxygen on the same side of the molecular plane. Corresponding conformers **1β″-OMe**, **1β″**, **1β″-Tr** and **8β″** (not present) and **1α″-OMe**, **1α″** and **8α″** (less stable) have the two oxygens on the opposite side of the molecular plane. All the results obtained in this theoretical conformational study are the subject of a manuscript from our laboratory: Crotti, P.; Di Bussolo, V.; Pomelli, C. S.; Favero, L. *Theor. Chem. Acc.*, submitted for publication.
9. In the reaction carried out under *protocol A*, *trans*-hydroxy mesylate **17** (or **21**) was treated with *t*-BuOK (1 equiv) in the glycosyl acceptor (MeOH, EtOH, *i*-PrOH or *t*-BuOH), as the solvent. In the reaction carried out under *protocol B*, a solution of *trans*-hydroxy mesylate **17** (or **21**) in an anhydrous solvent (benzene, Et_2O, MeCN or THF) was treated with *t*-BuOK (1 equiv). After the TLC analysis showed that the starting material was completely consumed (15–30 min), the glycosyl acceptor (*O*-, *C*-, *N*- or *S*-nucleophile, 3–4 equiv) was added.
10. For the completeness of the comparison between the 6-deoxy- (**8α** and **8β**) and 6-OR-substituted allyl oxirane systems (**1α**, **1β** and **1β-Tr**), also some previously unreported results with TMSCN, $TMSN_3$, TMGA and thiols from epoxide **1α** are described, too: see entry 5, Table 3 (TMSCN), Scheme 9 ($TMSN_3$), Schemes 10–13 (TMGA), Scheme 15 (thiols) and related discussion. All the other results from epoxide **1α** [alcohols and partially protected monosaccharides (*O*-nucleophiles) and alkyl lithium compounds (*C*-nucleophiles)][1c] and all the results from epoxides **1β** and **1β-Tr** have been previously described.[1a,b,d]
11. Achmatowicz, O., Jr.; Szechner, B. *Carbohydr. Res.* **1976**, *50*, 23–33. See also: Achmatowicz, O., Jr.; Bukowski, P.; Szechner, B.; Zwierzchowska, Z.; Zamojski, A. *Tetrahedron* **1971**, *27*, 1973–1996.
12. (a) Ramnauth, J.; Poulin, O.; Rakhit, S.; Maddaford, S. P. *Org. Lett.* **2001**, *3*, 2013–2015; (b) Hayashi, M.; Kawabata, H.; Nakayama, S.-Z. *Chirality* **2003**, *15*, 10–16; (c) Pudlo, P.; Thiem, J.; Vill, V. *Chem. Ber.* **1990**, *123*, 1129–1135.
13. The proposed oxirane oxygen–nucleophile coordination appears at the moment as the only rationalization able to justify the regio- and stereoselectivity obtained both with coordinating and non-coordinating nucleophiles. However, at least in principle, the occurrence of other effects cannot be ruled out.
14. On the basis of the evidences found by Woerpel,[15] the required activation of TMSCN by a nucleophile, with the formation of a pentacoordinate siliconate such as TMSCN-PS, the actual reacting species (Scheme 7), could arise by the reaction of TMSCN with $MeSO_3^-K^+$, formed in the base-catalyzed cyclization of *trans*-hydroxy mesylate **17** to the epoxide **8β**. The same can be said for the corresponding reaction of epoxides **8α**, **1α** and **1β-Tr**. In the case of **1β-Tr**, the rationalization previously proposed in order to justify the complete regio- and stereoselectivity observed in its reaction with TMSCN should be appropriately modified.[1d]
15. Shenoy, S. R.; Smith, D. M.; Woerpel, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 8671–8677 and references therein.
16. (a) Among the four diastereoisomeric 6-deoxy azido alcohols, *cis*-azido alcohol **50** has not been previously described. (b) For the 4-OBz derivative of the enantiomer of **48β**, see: Kirschning, A.; Domann, S.; Dräger, G.; Rose, L. *Synlett* **1995**, 767–769. For the 4-OAc or 4-OBz derivative of **54**, **56**, **60** and **62**, see: (c) Boivin, J.; Montagnac, A.; Monneret, C.; Pais, M. *Carbohydr. Res.* **1980**, *85*, 223–242; (d) Boivin, J.; Pais, M.; Monneret, C. *Carbohydr. Res.* **1980**, *79*, 193–204.
17. The previously described result for the reaction of epoxide **1β-Tr** with $TMSN_3$ indicated a 16:39:45 mixture of *trans*-azido alcohol **59** (*anti*-1,2-addition product), *cis*-azido alcohol **49** (*syn*-1,2-addition product) and 4-OTMS-derived β-glycosyl azide **48β-OTMS** (β-1,4-addition product, *coordination product*).[1d]
18. The **55-Ac**/**53α-Ac** ratio slightly decreased on standing in solution ($CDCl_3$): after two days **55-Ac**/**53α-Ac**=67:33.
19. The *syn*-1,2-addition product (**56**)/*coordination product* (**54α-OTMS**) ratio increased from about 1.25:1 after 10 min to about 5.3:1 after 30 min.
20. For examples of [3,3]-sigmatropic rearrangement by the azido group, see: (a) Heyns, K.; Hohlweg, R. *Chem. Ber.* **1978**, *111*, 1632–1645; (b) Paulsen, H.; Heiker, F. R. *Carbohydr. Res.* **1982**, *102*, 83–98; (c) Takasu, H.; Tsuji, Y.; Sajiki, H.; Hirota, K. *Tetrahedron* **2005**, *61*, 11027–11031.
21. The reaction of epoxide **1α** with TMGA was repeated in CD_3CN in an NMR tube. The ^1H NMR spectra of the reaction mixture registered at different reaction times indicated the presence of a mixture of *trans*-azido alcohol **61**, as the main reaction product (84%), accompanied by a mixture (overall 16%) of *cis*-azido alcohol **55** and α-glycosyl azide **53α** in a ratio, which increased with the reaction times from **55**/**53α**=6:1 after 5 min to 40:1 after 50 min. After 2 h, ^1H NMR analysis indicated only the presence of *trans*-azido alcohol **61** (85%) and *cis*-azido alcohol **55** (15%).
22. Bonner, O. D. *J. Phys. Chem.* **1979**, *83*, 1218–1220.
23. Moss, R. A.; Terpinski, J.; Cox, D. P.; Denny, D. Z.; Krogh-Jespersen, K. *J. Am. Chem. Soc.* **1985**, *107*, 2743–2748.
24. The addition reactions of EtSH and MeSNa to epoxide **1β-Tr** are completely 1,2-regioselective with the exclusive formation of the corresponding *non-coordination product*. In the case of PhSH, a small amount (15%) of the corresponding phenyl β-thioglycoside, the *coordination product*, was obtained.[1d]
25. As previously admitted for the corresponding reaction with TMGA, the larger amount of *coordination product* (α-thioglycoside, 1,4-addition product) found in the reaction with thiols of epoxide **1α** with respect to **8β** (Schemes 14 and 15) and **1β-Tr**[1d,24] is due to the possibility for **1α** to react through conformer **1α′**, in which the coordinated attack on C(1) corresponds to a more favourable *pseudoaxial* attack (structure **78″**, *route **a***, Scheme 15). As they exist in only conformer **1β′-Tr** and **8β′**[8], respectively, the same attack in **1β-Tr** and **8β**

corresponds to a less favourable *pseudoequatorial* attack (structure **71b**, *route* ***b***, Scheme 14, where only epoxide **8β** is shown), thus justifying the smaller amount of 1,4-addition product obtained in the reaction of these allyl β oxirane systems with *S*-nucleophiles.

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28. (a) Stothers, J. B. *Carbon-13 NMR Spectroscopy*; Academic: New York, NY, 1973; Chapter 3; (b) Orsini, F.; Pelizzoni, F. *Carbohydr. Res.* **1993**, *243*, 183–189.