Regio- and stereoselective behavior of L-arabinal-derived vinyl epoxide in nucleophilic addition reactions. Comparison with conformationally restricted D-galactal derived analogs

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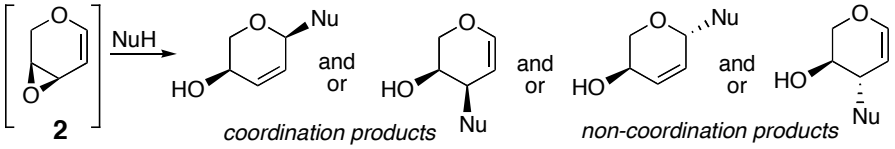

Regio- and stereoselective behavior of L-arabinal-derived vinyl epoxide in nucleophilic addition reactions. Comparison with conformationally restricted D-galactal-derived analogs

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Abstract: The regio- and stereoselectivity of the addition reactions of *O*-, *C*-, *N*- and *S*-nucleophiles to L-arabinal-derived vinyl epoxide **2**, the simplest non-conformationally restricted glycal-derived vinyl epoxide, has been examined and compared with the corresponding, conformationally restricted D-galactal-derived analogs **1β** and **1β-Me**. Results indicated that the *1,4-*/*1,2-regioselectivity* ratio and the related *syn-1,4-*/*anti-1,2-stereoselectivity* observed in glycal-derived vinyl oxiranes is independent of the presence of substituents on the six-membered unsaturated ring, and the absence of conformational freedom: it depends only on the ability of the nucleophile to give a coordination process with the oxirane oxygen in the form of a hydrogen bond or through a coordinating cation.

Keywords: vinyl epoxides; glycals; regioselectivity; stereoselectivity; L-*sugars.*

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1. Introduction

D-Galactal-derived vinlyl epoxide **1β**[1a-c] and the corresponding 6-deoxy analog **1β-Me**[1d] have shown to be, under *protocol B* reaction conditions,[2] excellent glycosyl donors in addition reactions of *O*- (alcohols, phenol and partially protected monosaccharides) and *C*-nucleophiles (alkyl lithium compounds) (NuX, Scheme 1) leading, through a complete 1,4-regio- and syn-stereoselective process, to the exclusive isolation of the corresponding β-*O*- and -*C*-glycosides having at C(4) the same relative configuration (β) as the starting epoxide (*syn-1,4-addition products*). The completely syn-stereoselective result obtained had been rationalized by admitting the occurrence of an oxirane oxygen-nucleophile coordination through a hydrogen bond, in the case of alcohols, or through a metal cation (Li^+) in the case of alkyl lithium compounds (*route **a***, Scheme 1).[1] With an azide ion (*N*-nucleophile)

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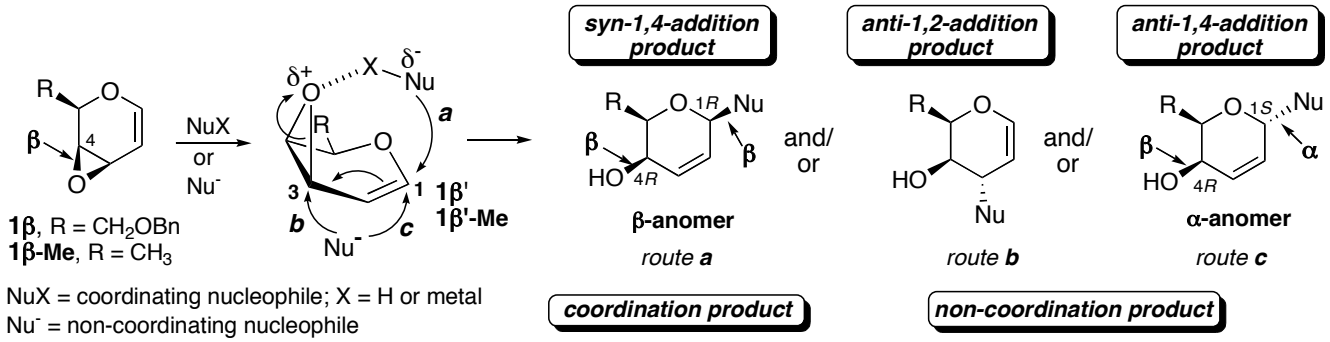
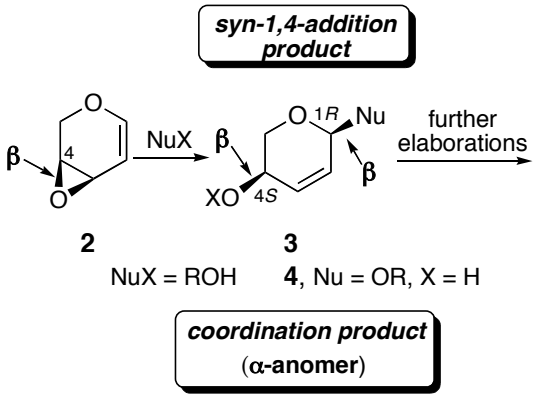
and thiols (*S*-nucleophiles), *anti-1,2-addition products* (*route* ***b***) were obtained as the only reaction products, sometimes accompanied by a small amount of the corresponding *syn-1,4- addition products*, due to the poor ability of the nucleophile to coordinate with the oxirane oxygen.[1a,d] On the basis of this observation, the simplified nomenclature of *coordination products* was given to *syn-1,4-addition products* (*route* ***a***), whereas *anti-1,2-addition products* (*route* ***b***) and the more rarely observed *anti-1,4-addition products* (*route* ***c***), derived by attack of a free, non-coordinated nucleophile at C(3) and C(1), respectively, were simply identified as *non-coordination products* (Scheme 1).[1d,3]



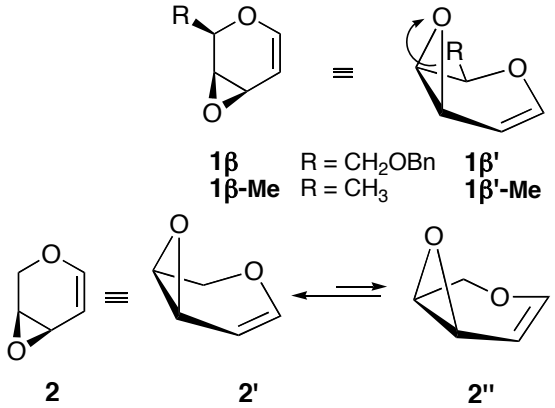
Scheme 1. Regio- and stereoselectivity of the addition of nucleophiles to D-galactal-derived vinyl epoxide **1β** and 6-deoxy analog **1β-Me** under *protocol B* reaction conditions.

However, as epoxides **1β** and **1β-Me** exist as the only conformer **1β'** and **1β'-Me** shown in Scheme 1 with the side chain equatorial,[1d,4] the possibility that the observed complete 1,4-regio- and syn-stereoselective result obtained with alcohols and alkyl lithium compounds were ascribed to the conformational rigidity of the system, could not be ruled out. As a consequence, in order to check if the presence of conformational effects could negatively influence the observed 1,4-regio- and syn-stereoselectivity and to validate our rationalization in a non-conformationally restricted glycal-derived vinyl oxirane, we have now directed our attention to L-arabinal-derived vinyl epoxide **2** and its regio- and stereoselective behavior has been examined in nucleophilic addition reactions under the same reaction conditions previously used for epoxides **1β** and **1β-Me**.[1] In this framework, if epoxide **2** shows with coordinating nucleophiles (NuX) the same chemical behavior as **1β**, it could be used as an effective and simple glycosylating agent for the completely stereoselective construction of corresponding L-series-derived *syn-1,4-addition products* (*coordination products*) **3** as, for an example, alkyl 2,3-dideoxy-α-L-*glycero*-pent-2-enopyranosides **4** when alcohols (NuX = ROH) are used as glycosyl acceptors (Scheme 2).[5] The presence of the double bond makes pyranosides **3** suitable for further elaborations toward L-derivatives of synthetic and of possible biological interest.



Scheme 2. L-Arabinal-derived epoxide **2** and the possible completely 1,4-regio- and syn-stereoselective behavior in addition reaction with coordinating nucleophiles.

Epoxide **2** has the same absolute configuration as reference epoxides **1β** and **1β-Me** and theoretical calculations have indicated that it exists as an equilibrium 81:19 of the two corresponding conformers **2'** and **2**" in which the ring conformation of the major conformer **2'** corresponds to that of the unique conformer **1β'** and **1β'-Me** present in the related 5-CH_2OBn and 5-Me substituted epoxides **1β** and **1β-Me**, respectively (Scheme 3).[4]



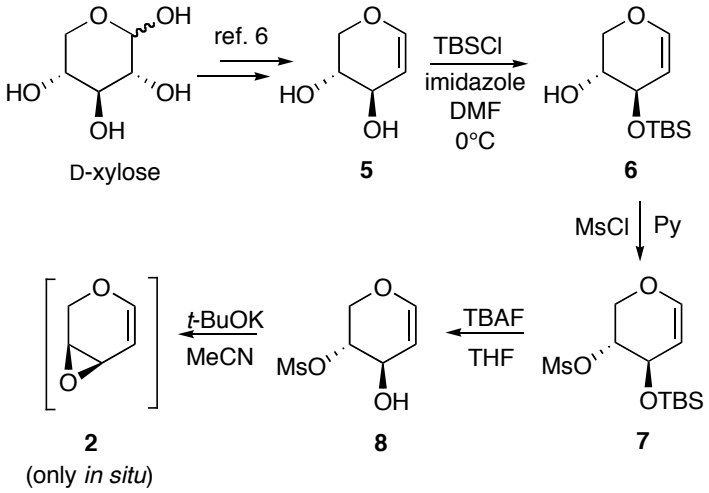
Scheme 3. Conformational equilibrium in vinyl epoxides **1β**, **1β-Me** and **2**.

2. Results and Discussion

2.1. Synthesis of L-arabinal-derived vinyl epoxide 2

The novel epoxide **2** was prepared starting from D-xylal **5**, itself prepared from D-xylose.[6] The treatment of D-xylal **5** with the sterically encumbered TBSCl leads to the mono *O*-TBS derivative **6**

which was transformed into mesylate **7** by the MsCl/Py protocol. Deprotection of **7** with TBAF/THF afforded *trans* hydroxy mesylate **8**, the stable precursor of epoxide **2** (Scheme 4). Epoxide **2** is unfortunately not stable and can be prepared only *in situ* by base-catalyzed cyclization (*t*-BuOK) of *trans* hydroxy mesylate **8** and left to react immediately with the appropriate nucleophile (Scheme 4).

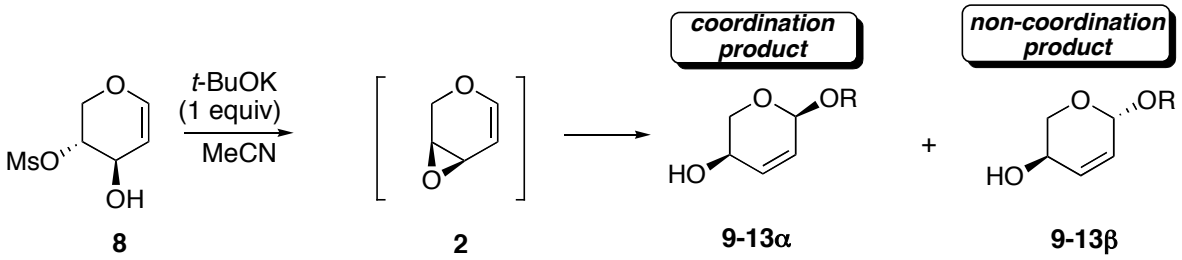


Scheme 4. Synthesis of L-arabinal-derived vinyl epoxide **2**.

2.2. Reaction of epoxide 2 with *O*-Nucleophiles

The addition reactions of simple, low-boiling alcohols, such as MeOH, EtOH, *i*-PrOH, *t*-BuOH, to epoxide **2**, carried out under *protocol A* reaction conditions,[2] turned out to be completely 1,4-regioselective, with exclusive nucleophilic attack at the C(1) carbon of the vinyl system and formation of corresponding alkyl glycosides **9-12**:[7,8] no trace of the corresponding *1,2-addition products* were observed under these conditions (Tabe 1).

Table 1. Glycosylation of alcohols by epoxide **2** under *protocol A* and *B* reaction conditions.



Entry	*O*-nucleophile	Reaction conditions[a]	**α-*O*-glycoside**		**β-*O*-glycoside**
			9α[b]	R= Me	**9β**[b]
1	MeOH	*Protocol A*	47		53
2		*Protocol B*	>99		<1
			10α	R= Et	**10β**
3	EtOH	*Protocol A*	69		31
4		*Protocol B*	>99		<1
			11α[c]	R= *i*-Pr	**11β**[c]
5	*i*-PrOH	*Protocol A*	93		7
6		*Protocol B*	>99		<1
			12α	R= *t*-Bu	**12β**
7	*t*-BuOH	*Protocol A*	>99		<1
			13α[d]	R= Bn	**13β**
8	BnOH	*Protocol B*	>99		<1

[a] See ref. 2.

[b] See ref. 7.

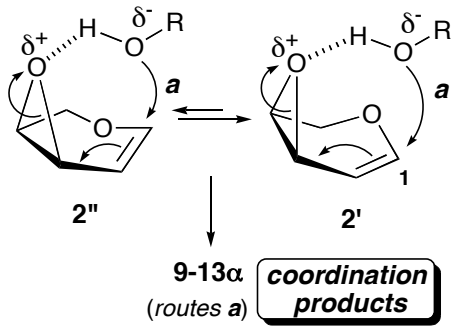
[c] See ref. 8a for corresponding enantiomers ***ent*-11α** and ***ent*-11β**.

[d] See ref. 8 for corresponding enantiomer ***ent*-13α**.

As for the stereoselectivity under *protocol A*, the reactions with the less nucleophilic and more sterically hindered *t*-BuOH, in spite of the presence of a large excess of nucleophile, is completely α-stereoselective with the exclusive formation of the corresponding *t*-butyl α-*O*-glycoside **12α** with the same relative configuration as the starting epoxide (*coordination product*).[5] On the contrary, the reactions with the less hindered MeOH, EtOH and *i*-PrOH are not stereoselective and mixtures of the corresponding anomers, methyl **9α** and **9β** (47:53),[7] ethyl **10α** and **10β** (69:31) and *i*-propyl *O*-glycosides **11α** and **11β** (93:7),[8a] are obtained.[9] Even if not completely stereoselective, it is worth noting that in all cases, with the exception of the reaction with the more nucleophilic MeOH, the corresponding α-anomer (**10-11α**), with the same relative configuration as the starting epoxide (β), is the main product.[5] However, in all cases, when the reactions are repeated under *protocol B* reaction conditions (MeCN as the solvent, Table 1),[2] all the reactions become completely α-stereoselective and the corresponding α-*O*-glycosides **9-11α** (*coordination products*) are the only reaction products.[5]

Protocol B reaction conditions were also used in the glycosylation of benzyl alcohol, as an example of an *O*-nucleophile for which *protocol A* reaction conditions are not possible. A complete α-stereoselective result was obtained with the exclusive formation of the corresponding *coordination product*, benzyl α-*O*-glycoside **13α** (Table 1).[5,8,9]

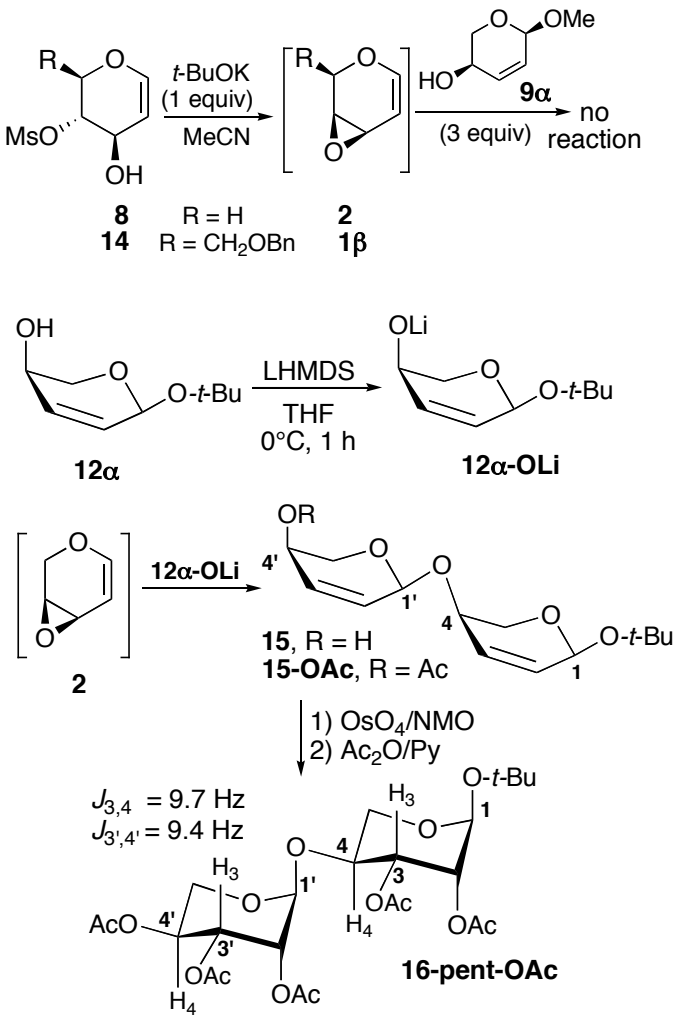
As previously shown for epoxide **1β**, the occurrence of a hydrogen bond between the alcohol (ROH) and oxirane oxygen is considered responsible for the complete 1,4-regio- and syn-stereoselectivity observed with epoxide **2**, conceivably reacting through both the two possible conformers **2'** and **2"** (*routes **a***, Scheme 5).



Scheme 5. Completely syn-stereoselective glycosylation of alcohols by epoxide **2** under *protocol B* reaction conditions.

Also the possibility of the construction of a disaccharide by means of epoxide **2** was envisaged. As a first approach, epoxide **2** (the glycosyl donor) was left to react with methyl α-*O*-glycoside **9α** (the glycosyl acceptor), following the usual *protocol B* reaction conditions.[2] No glycosylation occurred and the unreacted glycoside **9α** was the only compound recovered from the crude reaction mixture. The same unsuccessful result was obtained also when the same reaction was repeated by using D-galactal derived epoxide **1β** (prepared *in situ* by base-catalyzed cyclization of *trans* hydroxy mesylate **14**), as the glycosyl donor (Scheme 6).[1a,b,10,11]

However, as epoxide **1β** had demonstrated that the same regio- and completely syn-stereoselective glycosylation process obtained with alcohols could be realized also with the corresponding metal alcoholate,[1a] the preformed lithium alcoholate **12α-OLi**, prepared by reaction of *t*-butyl α-*O*-glycoside **12α** with LHMDS, was used as the glycosyl acceptor and left to react with epoxide **2**. A clean reaction occurred and the 2,3-unsaturated α-1,4-*O*-disaccharide **15** was obtained, as the only reaction product (Scheme 6).

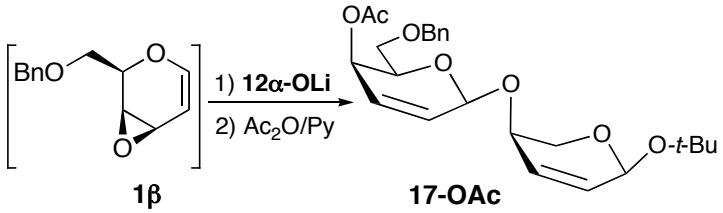


Scheme 6. Synthesis of 1,4-*O*-disaccharides **15, 15-OAc** and **16-pent-OAc**.

Unsaturated disaccharide **15** was acetylated (Ac_2O/Py) and the corresponding *O*-acetyl derivative **15-OAc** was dihydroxylated by catalytic OsO_4/NMO. After acetylation (Ac_2O/Py) of the crude reaction product, the functionalized disaccharide **16-pent-OAc**, containing two units of L-lyxopyranose through an α-1,4-*O*-L-lyxopyranosidic bond, turned out to be the only reaction product (Scheme 6). The structure and configuration of disaccharide **16-pent-OAc** was demonstrated by considerations based on the structure of the starting unsaturated disaccharide **15-OAc**, the complete syn-stereoselectivity of the dihydroxylation process and examination of the corresponding ^{1}H NMR spectrum. In particular, the trans diaxial relationship found between the H_3 and $H_{3'}$ protons with the adjacent H_4 and $H_{4'}$ protons, respectively ($J_{3,4}$ = 9.7 Hz and $J_{3',4'}$ = 9.4 Hz), is consistent only with an α-direction of the dihydroxylation process, that is in a direction opposed to the β-direction of the allyl substituents at the

C(1), C(1'), C(4) and C(4') carbons of the two units of the unsaturated disaccharide **15-OAc**, thus confirming the assigned structure (Scheme 6).[12]

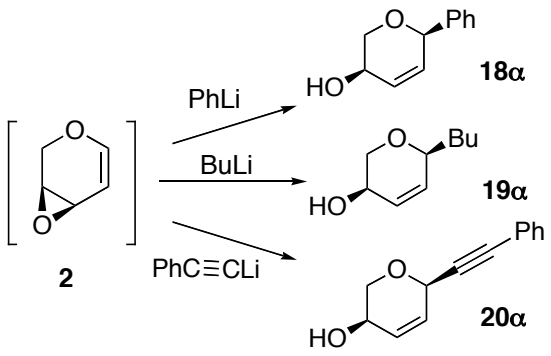
The same reaction was repeated with D-galactal-derived epoxide **1β**, as the glycosyl donor. The reaction proceeded as expected and, after acetylation, the mixed unsaturated β-1,4-*O*-disaccharide **17-OAc** was the only reaction product (Scheme 7).



Scheme 7. Synthesis of β-1,4-*O*-disaccharide **17-OAc**.

2.3. Reactions of epoxide 2 with *C*-Nucleophiles

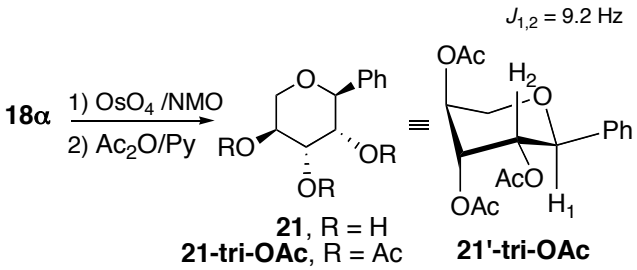
Alkyl lithium compounds having differently hybridized nucleophilic carbons, *i.e* butyllithium (sp^3), phenyllithium (sp^2) and lithium phenylacetylide (*sp*), were taken as samples of *C*-nucleophiles and their behavior examined in their reactions with epoxide **2** (*protocol B*, Scheme 8).



Scheme 8. Reaction of vinyl epoxide **2** with organo-lithium compounds (*C*-nucleophiles).

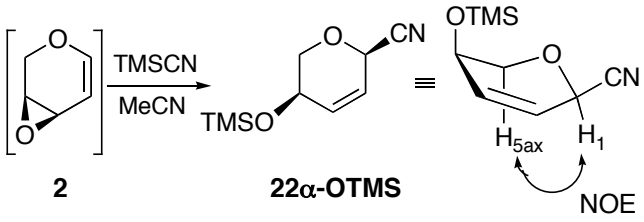
In all cases, only the corresponding *C*-glycosides **18α**,[13] **19α**[13] and **20α**, having the same relative configuration as the starting epoxide (β) were obtained indicating for epoxide **2** a complete 1,4-regio- and stereoselective behavior with formation of only the corresponding *coordination products*.[5] A similar behavior had been previously found with the reference epoxides **1β** and **1β-Me** in the reaction with alkyllithium compounds.[1a,c,d]

As an example of further stereoselective functionalization of these 2,3-unsaturated-*C*-glycosides, phenyl derivative **18α** was dihydroxylated with catalytic OsO_4/NMO. Triol **21** turned out to be the only product, indicating a completely stereoselective behavior. The ^{1}H NMR spectrum of the corresponding tri-*O*-acetyl derivative **21-tri-OAc** showed a large coupling constant value ($J_{1,2}$ = 9.2 Hz) for the anomeric H_1, indicative of its axial nature and of a *trans* diaxial relationship with the adjacent H_2 proton in the more stable conformer **21'-tri-OAc** with the phenyl group equatorial. These structural data clearly indicated that, once again, the dihydroxylation had occurred selectively from the α-face of the starting unsaturated system, that is, from the opposite side with respect to the β-direction of the substituents at C(1) and C(4) (Scheme 9).[12]



Scheme 9. Catalytic dihydroxylation (OsO_4/NMO) of α-*C*-glycoside **18α**.

As previously observed with epoxide **1β-Me**,[1d] the reaction of epoxide **2** with TMSCN in MeCN (*protocol B*) turned out to be completely stereoselective, affording *O*-TMS protected α-glycosyl cyanide **22α-OTMS** (*coordination product*) as the only product. The structure of α-*C*-glycoside **22α-OTMS** was confirmed by the presence of NOE between H_1 and H_{5ax} protons in the ^{1}H NMR spectrum (Scheme 10).

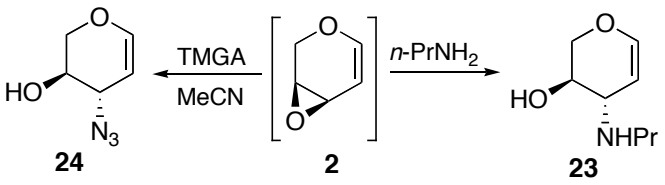


Scheme 10. Reaction of vinyl epoxide **2** with TMSCN.

2.4. Reaction of vinyl epoxide 2 with *N*-Nucleophiles

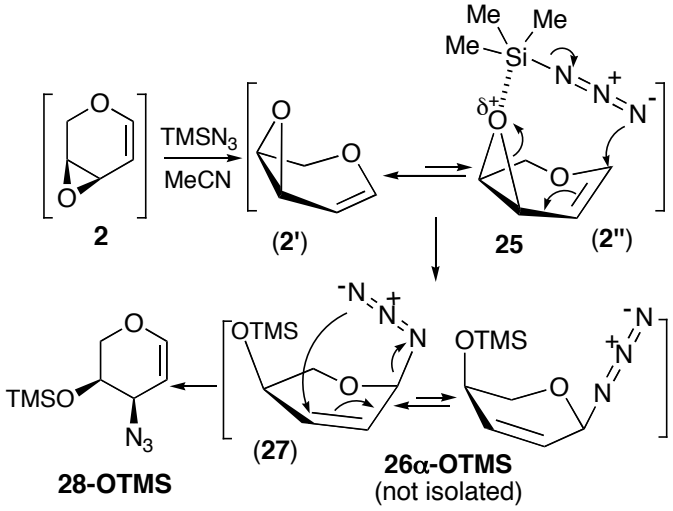
In an attempt to synthesize *N*-glycosides by means of epoxide **2**, the behavior of some *N*-nucleophiles was examined.

The reaction of epoxide **2** with *n*-propylamine (as the solvent/nucleophile, *protocol A*) and tetramethylguanidine azide (TMGA in MeCN, *protocol B*)[14] was not useful to our aim because only the corresponding *anti-1,2-addition product*, the *trans* amino alcohol **23** and *trans* azido alcohol **24**, respectively, were obtained in a completely 1,2-regio- and *anti*-stereoselective fashion, in accordance with the corresponding results previously obtained with epoxides **1β** and **1β-Me** (Scheme 11).[1a,d,15]



Scheme 11. Reaction of vinyl epoxide **2** with *n*-$PrNH_2$ and TMGA.

Decidedly different is the behavior of epoxide **2** with a further source of azide, $TMSN_3$ in MeCN (*protocol B*).[1a,d] In this case, the examination of the crude reaction product clearly showed the presence of two products in an almost 1:1 mixture: the corresponding *1,2*- and *1,4-addition products* (^{1}H NMR spectroscopy). Separation/purification of this mixture by preparative TLC afforded only the *1,2-addition product* which turned out to be *O*-TMS-protected *cis* azido alcohol **28-OTMS**, a *syn-1,2-addition product*. On the contrary, the *1,4-addition product*, initially present in the crude reaction mixture, was not recovered, not allowing the determination of its structure and configuration (Scheme 12).

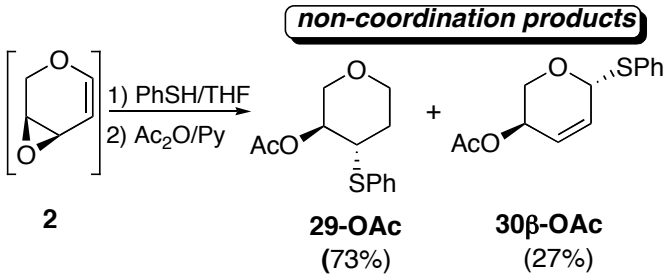


Scheme 12. Reaction of vinyl epoxide **2** with $TMSN_3$.

However, based on our previous experience on the azidolysis of glycal-derived epoxides with $TMSN_3$[1a,d] and considering that a vinyl epoxide such as **2** cannot reasonably give a complete syn-1,2-stereoselective opening process, we thought that the *1,4-addition product* accompanying *cis* azido alcohol **28-OTMS** in the crude reaction mixture (^{1}H NMR spectroscopy) should correspond to *O*-TMS protected α-glycosyl azide **26α-OTMS**. This means that, due to the occurrence of nucleophile-oxirane oxygen coordination as shown in **25** through conformer **2"**, the reaction of epoxide **2** with $TMSN_3$ is completely 1,4-regio- and *syn*-stereoselective with the formation of α-glycosyl azide **26α-OTMS**, the primary reaction product (*coordination product*). Unfortunately α-glycosyl azide **26α-OTMS** is not stable and rapidly isomerizes to *O*-protected *cis*-azido alcohol **28-OTMS**, the stable secondary reaction product, by means of a suprafacial [3,3] sigmatropic rearrangement (shown in **27**) with complete retention of the facial selectivity (Scheme 12). The isomerization process of **26α-OTMS** to **28-OTMS** is operative at any moment (reaction mixture, separation/purification process of the crude product) to the point that α-glycosyl azide **26α-OTMS** cannot be isolated.[1d]

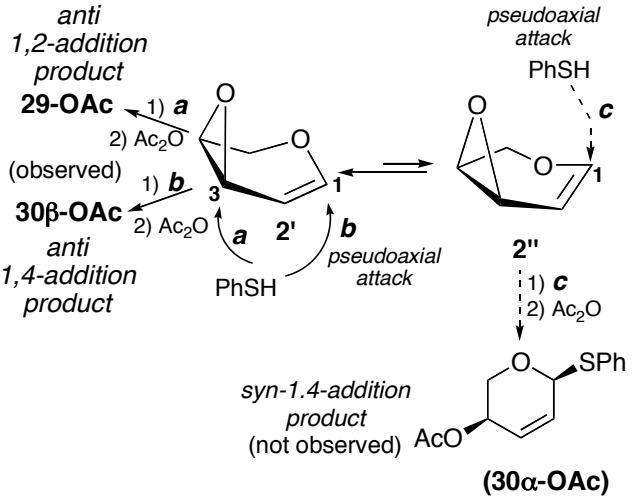
2.5. Reaction of epoxide 2 with PhSH (*S*-Nucleophile) (*protocol B*)

The reaction of epoxide **2** in anhydrous THF with PhSH (*protocol B*), as an example *S*-nucleophile, turned out to be completely anti stereoselective, affording a 73:27 mixture of the two possible regioisomeric *anti-addition products* (*non-coordination products*) which were separated and identified as the corresponding acetates: *trans* 3-phenylthio-4-*O*-acetyl glycal-derivative **29-OAc** (*anti-1,2-addition product*) and 2,3-unsaturated β-phenylthio-glycoside **30β-OAc** (*anti-1,4-addition product*) (Scheme 13).[5] The reduced ability of thiols to hydrogen bond compared to alcohols is the reason why, in this case, no trace of the correspoding *syn-1,4-addition product* was found, thus illustrating the marked difference with alcohols, where the corresponding alkyl *O*-glycosides having the same configuration of the epoxide **2** (*syn-1,4-addition product, coordination products*) are the main or the only addition products (Table 1).[1a,b,d]



Scheme 13. Reaction of vinyl epoxide **2** with PhSH, followed by acetylation.

Phenylthio derivatives *anti-1,2-* **29-OAc** and *anti-1,4-addition product* **30β-OAc** derive from an anti attack of the nucleophile (PhSH) at the oxirane C(3) carbon in a trans diaxial fashion, in the case of **29-OAc** (*route **a***, Scheme 14) and at the vinyl C(1) carbon in a conjugate pseudoaxial fashion, in the case of **30β-OAc** (*route **b***, Scheme 14) with the epoxide reacting through the more stable conformer **2'**.



Scheme 14. Pathways to observed (*routes **a*** and ***b***) and not observed addition products (*route **c)*** in the reaction of epoxide **2** with PhSH, followed by acetylation.

In this framework, α-phenylthio glycoside **30α-OAc**, the *syn-1,4-addition product* (*coordination product*)[5] is not obtained even if, independently of the coordinating ability of the nucleophile (PhSH), it could reasonably be formed through a favorable pseudoaxial attack by the free nucleophile at the C(1) carbon of conformer **2"** (*route **c***, Scheme 14). This observation confirms that in these glycal-derived vinyl oxiranes, the formation of *syn-1,4-addition products* (*coordination products*) is independent of the conformer population in the starting epoxide: it depends only on the occurrence of a nucleophile-oxirane oxygen coordination.

2.6. Conclusion

In conclusion, the results obtained with the non-conformationally restricted epoxide **2** in the glycosylation of alcohols (*O*-nucleophiles), organolithium compounds and TMSCN (*C*-nucleophiles) and $TMSN_3$ (*N*-nucleophile) are substantially similar to those previously obtained with the

conformationally constrained epoxides **1β** and **1β-Me**. In all cases, under *protocol B* reaction conditions, a complete 1,4-regioselectivity and the associated complete *syn*-stereoselectivity with the exclusive isolation of the corresponding *coordination product* was observed.[5] Moreover, epoxide **2** has been effectively used for the stereoselective construction of a 1,4-*O*-disaccharide containing two units of L-lyxopyranose through an α-lyxopyranosidic bond, thus indicating epoxide **2** as a versatile, usefull synthetic tool. The whole results clearly indicate that in glycal-derived vinyl epoxides **1β**, **1β-Me** and **2**, the observed complete 1,4-regio- and syn-stereoselectivity is independent of the presence of a substituent at C(5) of the six-membered unsaturated ring, and, as a consequence, of the absence of conformational freedom: *it depends only* on the ability of the nucleophile to coordinate with the oxirane oxygen in the form of a hydrogen bond or through a coordinating cation.

3. Experimental

3.1. General

All reactions were performed in a flame-dried modified Schlenk (Kjeldahl shape) flask fitted with a glass stopper or rubber septum under a positive pressure of argon. 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. Routine ^1H and ^{13}C NMR spectra were recorded at 250 and 62.5 MHz, respectively. ^1H NMR COSY and NOESY experiments were performed on a spectrometer operating at 600 MHz. Elemental analyses were performed at Dipartimento di Farmacia, Pisa, by means of Carlo Erba Automated CHN Analyzer model 1106. Toluene, Et_2O and THF were distilled from sodium/benzophenone. HPLC grade MeCN, MeOH, EtOH and *i*-PrOH were used without any purification. *t*-BuOH and benzyl alcohol were distilled from sodium. D-Xylal (**5**),[6] *trans* hydroxy mesylate **14**[1a,c] and tetramethylguanidinium azide (TMGA)[14] were prepared as previously described. Alkyl *O*-glycosides **9α**, **9β**,[7] ***ent*-11α**,[8a] ***ent*-11β**,[8a] ***ent*-13α**[8] (D-series) and *C*-glycosides **18α**[13] and **19α**[13] were previously described.

3.2. Synthesis of *trans* hydroxy mesylate 8 (precursor of L-arabinal-derived vinyl epoxide 2)

*3.2.1. 3-O-(t-Butyldimethylsilyl)-D-xylal (**6**).* A solution of D-xylal **5** (6.86 g, 59.10 mmol) in anhydrous DMF (150 mL) was treated with imidazole (6.43 g, 94.56 mmol, 1.6 equiv) and TBSCl (9.76 g, 65.0 mmol, 1.1 equiv) at 0 °C and the reaction mixture was stirred 24 h at room temperature. Dilution with CH_2Cl_2 and evaporation of the washed (saturated aqueous NaCl) organic solvent afforded a crude product (10.22 g, 76% yield) consisting of practically pure TBS-derivative **6** (^1H NMR spectroscopy), as a brown liquid, which was used in the next step without any further purification. An analytical sample of crude **6** was purified by flash chromatography. Elution with an 8:2 hexane/AcOEt mixture afforded pure alcohol **6** as a colourless liquid: R_f = 0.58 (6:4 hexane/AcOEt); FTIR (film) ν 3390, 1650, 1241, 1097 cm^{-1}. ^1H NMR δ ($CDCl_3$) δ 6.45 (d, 1H, *J* =6.1 Hz), 4.79 (ddd, 1H, *J* = 6.5, 4.7, 1.4 Hz), 3.96-4.02 (m, 2H), 3.87-3.95 (m, 1H), 3.66-3.72 (m, 1H), 0.88 (s, 9H), 0.09 (s, 6H). Anal. Calcd for $C_{11}H_{22}O_3Si$: C, 57.34; H, 22.17. Found: C, 57.03; H, 21.84.

3.2.2. 3-O-(t-Butyldimethylsilyl)-4-O-mesyl-D-*xylal (7).* A solution of alcohol **6** (10.0 g, 43.47 mmol) in 1:1 mixture of anhydrous CH_2Cl_2 (47 mL) and anhydrous pyridine (47 mL) was treated dropwise at 0 °C with MsCl (6.7 mL, 86.94 mmol, 2.0 equiv) and the reaction mixture was stirred 18 h at the same temperature. Dilution with Et_2O and evaporation of the washed (brine) organic solvent afforded a crude product (8.0 g, 60% yield) consisting of practically pure mesylate **7** (^{1}H NMR spectroscopy), as a brown liquid, which was used in the next step without any further purification. An analytical sample of crude **7** was subjected to flash chromatography. Elution with an 8:2 hexane/AcOEt mixture afforded pure mesylate **7** as a yellow liquid: R_f = 0.63 (6:4 hexane/AcOEt); FTIR (film) ν 1649, 1360, 1254, 1090 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.47 (dd, 1H, *J* = 6.3, 0.4 Hz), 4.81 (ddd, 1H, *J* = 4.6, 1.4 Hz), 4.60-4.66 (m, 1H), 4.20 (ddd, 1H, *J* = 12.1, 1.4 Hz), 4.10-4.15 (m, 1H), 4.09 (dd, 1H, *J* = 12.1, 1.8 Hz), 3.07 (s, 3H), 0.88 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 145.8, 101.3, 76.0, 63.4, 62.3, 38.9, 25.9, 18.1, -4.26, -4.47. Anal. Calcd for $C_{12}H_{24}O_5SSi$: C, 46.72; H, 7.84. Found: C, 46.39; H, 7.66.

3.2.3. 4-O-Mesyl-D-*xylal (**8**).* A solution of mesylate **7** (2.0 g, 6.49 mmol) in anhydrous THF (200 mL) was treated at 0 °C with 1M TBAF in THF (6.49 mL, 6.49 mmol, 1.0 equiv). After 40 minutes stirring at the same temperature, dilution with Et_2O and evaporation of the washed (brine) organic solution afforded a crude product (1.0 g) consisting of *trans* hydroxy mesylate **8** (^{1}H NMR spectroscopy) which was subjected to flash chromatography. Elution with a 4:6 hexane/AcOEt mixture afforded pure **8** (0.508 g, 40% yield), as a colorless liquid: R_f = 0.08 (6:4 hexane/AcOEt); FTIR (film) ν 3460, 1651, 1245, 1080 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.53 (d, 1H, *J* = 6.2 Hz), 4.89-4.98 (m, 1H), 4.71-4.80 (m, 1H), 4.20-4.27 (m, 1H), 4.15-4.19 (m, 1H), 4.10 (dd, 1H, *J* = 12.3, 2.5 Hz), 3.11 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 146.9, 100.4, 75.8, 63.6, 62.6, 38.8. Anal. Calcd for $C_6H_{10}O_5S$: C, 37.10; H, 10.08. Found: C, 35.94; H, 9.89.

3.3. Glycosylation of alcohols (*O*-nucleophiles) by vinyl epoxide 2

*3.3.1. Reaction of epoxide **2** with EtOH (Protocol A). Typical procedure*. A solution of *trans* hydroxy mesylate **8** (0.094 g, 0.49 mmol) in anhydrous EtOH (3.5 mL) was treated with *t*-BuOK (0.109 g, 0.98 mmol, 2.0 equiv) and the reaction mixture was stirred for 1 h at room temperature. Dilution with Et_2O and evaporation of the washed (brine) organic solution afforded a 69:31 mixture of ethyl α-*O*-glycoside **10α** and ethyl β-*O*-glycoside **10β** (^{1}H NMR spectroscopy) which was subjected to preparative TLC (a 4:6 hexane/AcOEt mixture was used as the eluant). Extraction of the two most

intense bands (the faster moving band contained **10α**) afforded pure ethyl β-*O*-glycoside **10β** (0.009 g, 13% yield) and ethyl α-*O*-glycoside **10α** (0.055 g, 78% yield):

3.3.1.1. Ethyl 2,3-dideoxy-α-L-*glycero-pent-2-enopyranoside* (**10α**), a liquid: R_f = 0.41 (4:6 hexane/AcOEt); $[\alpha]^{20}_D$ -34.6 (*c* 1.62, $CHCl_3$), FTIR (film) ν 3440, 1621, 1451, 1069 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.95-6.06 (m, 1H), 5.77 (ddd, 1H, *J* = 10.2, 2.4, 1.8 Hz), 4.89-4.95 (m, 1H), 4.09-4.29 (m, 1H), 3.64-3.94 (m, 3H), 3.47-3.62 (m, 1H), 1.24 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$) δ 133.0, 128.2, 94.6, 64.3, 64.1, 63.3, 15.5. Anal. Calcd for $C_7H_{12}O_3$: C, 58.31; H, 8.39. Found: C, 58.34; H, 8.06.
3.3.1.2. Ethyl 2,3-dideoxy-β-L-*glycero-pent-2-enopyranoside* (**10β**), a liquid: R_f = 0.29 (4:6 hexane/AcOEt); $[\alpha]^{20}_D$ -72.5 (*c* 0.52, $CHCl_3$), FTIR (film) ν 3440, 1620, 1451, 1065 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.08-6.17 (m, 1H), 5.89 (ddd, 1H, *J* = 10.1, 3.6, 0.4 Hz), 4.95 (dd, 1H, *J* = 3.0, 0.4 Hz), 4.12 (dd, 1H, *J* = 12.2, 2.6 Hz), 3.73-3.91 (m, 3H), 3.46-3.62 (m, 1H), 1.23 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$) δ 129.3, 128.8, 93.2, 64,4, 63.9, 61.7, 15.4. Anal. Calcd for $C_7H_{12}O_3$: C, 58.31; H, 8.39. Found: C, 58.17; H, 8.12.

*3.3.2. Reaction of epoxide **2** with EtOH in MeCN (Protocol B). Typical procedure*. A solution of *trans* hydroxy mesylate **8** (0.034 g, 0.18 mmol) in anhydrous MeCN (2.3 mL) was treated with *t*-BuOK (0.020 g, 0.18 mmol, 1.0 equiv) and the reaction mixture was stirred at room temperature until complete cyclization to epoxide **2** had occurred (TLC). EtOH (0.031 mL, 0.54 mmol, 3.0 equiv) was added and the reaction mixture was stirred for 1 h at the same temperature. Dilution with Et_2O and evaporation of the washed (brine) organic solution afforded a yellow oil consisting of ethyl α-*O*-glycoside **10α** (0.020 g, 79% yield), as the only reaction product (^1H NMR spectroscopy).

*3.3.3. Reaction of epoxide **2** with t-BuOH (Protocol A).* Following the typical procedure, the treatment of *trans* hydroxy mesylate **8** (0.028 g, 0.14 mmol) in anhydrous *t*-BuOH (1.0 mL) with *t*-BuOK (0.031 g, 0.28 mmol, 2.0 equiv) afforded, after 1 h stirring at room temperature, a pale yellow liquid consisting of *t-butyl 2,3-dideoxy*-α-L-*glycero-pent-2-enopyranoside* (**12α**) (0.024 g, 90% yield), as the only reaction product: R_f = 0.50 (4:6 hexane/AcOEt); $[\alpha]^{20}_D$ -57.3 (*c* 1.36, $CHCl_3$); FTIR (film) ν 3452, 1615, 1436, 1065 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.97 (d, 1H, *J* = 10.3 Hz), 5.57-5.74 (m, 1H), 5.10-5.22 (m, 1H), 4.08-4.22 (m, 1H), 3.64-3.85 (m, 2H), 1.25 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 132.4, 129.9, 88.4, 75.4, 64.1, 63.2, 28.9. Anal. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.39; H, 9.01.

3.4. Reaction of epoxide 2 and 1β with lithium alcoholate of *t*-butyl α-*O*-glycoside 12α

*3.4.1. Synthesis of 1,4-α-O-disaccharide **15** (protocol B). Formation of the lithium alcoholate of t-butyl α-O-glycoside **12α** (Solution A).* A solution of *t*-butyl α-*O*-glycoside **12α** (0.039 g, 0.228 mmol, 1.8 equiv) in anhydrous THF (0.5 mL) was treated with 1M LHMDS in hexane (0.023 mL, 0.228 mmol, 1.8 equiv) at –78 °C and the reaction mixture was stirred 1 h at the same temperature. *Formation of epoxide **2** (Solution B).* Following the typical procedure, a solution of *trans* hydroxy mesylate **8** (0.025 g, 0.128 mmol) in anhydrous THF (0.5 mL) was treated with *t*-BuOK (0.018 g, 0.154 mmol, 1.2 equiv) and the reaction mixture was stirred at room temperature until complete cyclization to epoxide **2** had occurred (TLC, 15 min). *Solution A* was added dropwise and the resulting reaction mixture was stirred 18 h at room temperature. Dilution with Et_2O and evaporation of the washed (brine) organic solution afforded a crude product (0.055 g) mostly consisting of 1,4-α-*O*-disaccharide **15** (^{1}H NMR spectroscopy) which was subjected to preparative TLC (a 1:1 hexane/AcOEt mixture was used as the eluant). Extraction of the most intense band afforded pure *t-butyl 4-(2',3'-dideoxy-α-*L*-glycero-pent-2'-enopyranosyl)-2,3-dideoxy-*α-L*-glycero-pent-2-enopyranoside* (**15**) (0.022 g, 62% yield), as a colorless oil: R_f = 0.26 (1:1 hexane/AcOEt); $[\alpha]^{20}_D$ -60.3 ($CHCl_3$ c 0.76); FTIR (film) ν 3454, 1655, 1365, 1260, 1049 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 5.91-6.05 (m, 2H), 5.71-5.79 (m, 1H), 5.63-5.70 (m, 1H), 5.18 (bs, 1H), 5.06 (bs, 1H), 4.19-4.31 (m, 2H), 3.73-3.87 (m, 3H), 3.65 (dd, 1H, *J* = 11.7, 8.5 Hz), 1.28 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 133.4, 130.5, 129.3, 127.8, 94.2, 88.6, 70.0, 63.7, 63.3, 61.3, 29.9, 28.9. Anal. Calcd for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20. Found: C, 62.09; H, 7.78. *Acetate* **15-OAc**, yellow oil, R_f = 0.63 (1:1 hexane/AcOEt); $[\alpha]^{20}_D$ -63.1 (c 0.56, $CHCl_3$); FTIR (film) ν 1739, 1649, 1464, 1251, 1066 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 5.90-5.99 (m, 2H), 5.83 (ddd, 1H, *J* = 10.3, 2.3, 1.7 Hz), 5.67 (ddd, 1H, *J* = 10.3, 2.7, 2.0 Hz), 5.23-5.34 (m, 1H), 5.17 (bs, 1H), 5.08 (bs, 1H), 4.19-4.32 (m, 1H), 3.71-3.89 (m, 4H), 2.06 (s, 3H), 1.26 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 170.7, 130.7, 130.5, 129.4, 129.1, 94.0, 88.6, 70.0, 65.1, 61.3, 60.0, 29.9, 28.9, 21.2. Anal. Calcd for $C_{16}H_{24}O_6$: C, 61.52; H, 7.74. Found: C, 61.59; H, 7.41.

*3.4.2. Catalytic dihydroxylation (OsO_4/NMO) of disaccharide **15-OAc**.* A solution of disaccharide **15-OAc** (0.022 g, 0.070 mmol) in 1:1 *t*-BuOH/acetone mixture **(**0.2 mL**)** was added, at 0 °C under stirring and in the dark, to 50% p/v aqueous solution of *N*-methyl morpholine-*N*-oxide (NMO) (0.02 mL). The resulting reaction mixture was treated with 2.5% p/v OsO_4 solution in *t*-BuOH (0.02 ml) and stirred in the dark for 96 h at room temperature. Dilution with Et_2O and evaporation of the filtered (Celite®) organic solution afforded a crude liquid product (0.029 g) which was dissolved in anhydrous pyridine

(0.2 mL) and treated at 0 °C with Ac_2O (0.1 mL). After 18 h stirring at room temperature, co-evaporation of the resulting reaction mixture with toluene afforded pure *t-butyl 4-O-(2',3',4'-tri-O-acetyl*-β-L-*lyxopyranosyl)-2,3-di-O-acetyl*-β-L-*lyxopyranoside* (**16-pent-OAc**), as a pale yellow oil: R_f = 0.22 (1:9 hexane/AcOEt); $[\alpha]^{20}_D$ +16.5 (*c* 0.21, $CHCl_3$), FTIR (film) ν 1740, 1461, 1370, 1218, 1065, 1020 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.31 (dd, 1H, *J* = 9.7, 3.0 Hz), 5.30 (dd, 1H, *J* = 9.4, 3.3 Hz), 5.10-5.21 (m, 1H), 5.07 (t, 1H, *J* = 3.0 Hz), 5.02 (dd, 1H, *J* = 3.3, 2.0 Hz), 4.97 (d, 1H, *J* = 2.0 Hz), 4.92 (d, 1H, *J* = 3.0 Hz), 3.96-4.08 (m, 1H), 3.87 (dd, 1H, *J* = 11.0, 8.9 Hz), 3.86 (dd, 1H, *J* = 10.7, 8.3 Hz), 3.75 (dd, 1H, *J* = 10.7, 6.4 Hz), 3.64 (dd, 1H, *J* = 11.0, 9.2 Hz), 2.12 (s, 3H), 2.11 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 1.22 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 171.1, 170.7, 170.4, 170.3, 170.1, 98.9, 92.4, 73.2, 71.8, 70.8, 69.7, 68.2, 67.2, 61.0, 60.5, 29.9, 28.6, 21.0. Anal. Calcd for $C_{24}H_{36}O_{14}$: C, 52.55; H, 6.62. Found: C, 51.90; H, 6.88.

*3.4.3. Synthesis of 1,4–*β*-O-disaccharide* ***17-OAc*** *(protocol B). Formation of the lithium alcoholate of t-butyl* α*-O-glycoside* ***12α*** *(Solution A).* A solution of *t*-butyl α-*O*-glycoside **12α** (0.050 g, 0.290 mmol, 1.8 equiv) in anhydrous THF (0.6 mL) was treated at –78 °C with 1M LHMDS in hexane (0.29 mL, 0.29 mmol, 1.8 equiv) and the reaction mixture was stirred 1 h at the same temperature. *Formation of epoxide* ***1β*** *(Solution B).* Following the typical procedure, a solution of trans hydroxy mesylate **14** (0.050 g, 0.16 mmol) in anhydrous THF (0.6 mL) was treated with *t*-BuOK (0.022 g, 0.19 mmol, 1.2 equiv) and the reaction mixture was stirred until complete cyclization to epoxide **1β** had occurred (15 min, TLC). *Solution A* was added dropwise and the resulting reaction mixture was stirred 18h at room temperature. Typical workup afforded a crude product (0.070 g) consisting of 1,4-β-O-disaccharide **17** (^1H NMR spectroscopy) which was dissolved in anhydrous pyridine (0.6 mL) and treated at 0 °C with Ac_2O (0.3 mL). After 18h stirring at room temperature, co-evaporation of the reaction mixture with toluene afforded a crude product (0.088 g, 99% yield) mostly consisting of acetylated 1,4-β-*O*-disaccharide **17-OAc** (^1H NMR) which was subjected to preparative TLC (a 1:1 hexane/AcOEt mixture was used as the eluant). Extraction of the most intense band afforded pure *t-butyl 4-[6'-O-(benzyl)-2',3-dideoxy*-β-D-*threo-hex-2'-enopyranosyl)-2,3-dideoxy*-α-L-*glycero-pent-2-enopyranoside* (**17-OAc**) (0.054 g, 78% yield), as a colorless liquid: R_f = 0.26 (1:1 hexane/AcOEt); FTIR (film) ν 1741, 1464, 1240, 1179, 1054 cm^{-1}. $[\alpha]^{20}_D$ -74.8 ($CHCl_3$ c 0.18); ^1H NMR ($CDCl_3$) δ 7.27-7.39 (m, 5H), 6.08 (dd, 1H, *J* = 9.6, 4.0 Hz), 6.00 (d, 1H, *J* = 9.9 Hz), 5.91 (d, 1H, *J* = 9.6 Hz), 5.68 (ddd, 1H, *J* = 9.9, 2.2, 1.8 Hz), 5.23 (bs, 1H), 5.17 (d, 1H, *J* = 2.2 Hz), 5.05-5.10 (m, 1H), 4.59 (d, 1H, *J* = 12.2 Hz), 4.48 (d,

1H, *J* = 12.2 Hz), 4.32-4.43 (m, 1H), 3.93-4.01 (m, 1H), 3.85 (d, 2H, *J* = 7.4 Hz), 3.62 (dd, 1H, *J* = 6.2, 1.0 Hz), 1.99 (s, 3H), 1.26 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 171.7, 138.2, 132.9, 130.6, 129.5, 128.6, 127.9, 97.0, 88.6, 79.2, 73.7, 72.9, 69.7, 69.0, 64.0, 61.2, 28.9, 21.0. Anal. Calcd for $C_{24}H_{32}O_7$: C, 66.64; H, 7.45. Found: C, 66.48; H, 7.22.

3.5. Reactions of epoxide 2 with *C*-Nucleophiles

*3.5.1. Reaction of epoxide **2** with lithium phenylacetylide (protocol B). Formation of lithium phenylacetylide (Solution A)*. A solution of phenylacetylene (0.023 mL, 0.22 mmol, 1.4 equiv) in anhydrous THF (1.0 mL) was treated with BuLi (0.11 mL, 0.18 mmol, 1.2 equiv) and the reaction mixture was stirred 1h at room temperature. *Formation of epoxide **2** (Solution B).* Following the tpical procedure, a solution of *trans* hydroxy mesylate **8** (0.030 g, 0.15 mmol) in anhydrous THF (1.6 mL) was treated with *t*-BuOK (0.020 g, 0.185 mmol, 1.2 equiv) and the reaction mixture was stirred until complete cyclization to epoxide **2** had occurred (15 min, TLC). *Solution A* was added dropwise and the resulting reaction mixture was stirred 4 h at room temperature. Typical workup afforded a crude product consisting of practically pure α-*C*-glycoside **20α** (^{1}H NMR spectroscopy) (0.032 g) which was subjected to preparative TLC (a 4:6 hexane/AcOEt mixture was used as the eluant). Extraction of the most intense band afforded pure *(3R, 6R)-6-(2-phenylethynyl)-3,6-dihydro-2H-pyran-3-ol* (**20α**), as a colourless oil: R_f = 0.50 (4:6 hexane/AcOEt); $[\alpha]^{20}_D$ -13.7 (*c* 1.0, $CHCl_3$); FTIR (film) ν 3460, 2120, 1465, 1069 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.45-7.54 (m, 2H), 7.27-7.37 (m, 3H), 5.99 (dd, 1H, *J* = 10.3, 2.5 Hz), 5.66 (dt, 1H, *J* = 10.3, 2.2 Hz), 5.19 (d, 1H, *J* = 2.5 Hz), 4.11-4.21 (m, 1H), 3.78 (d, 1H, *J* = 1.5 Hz), 3.75 (d, 1H, *J* = 3.4 Hz). ^{1}H NMR ($CDCl_3$) δ 132.3, 129.9, 128.9, 128.5, 122.3, 89.5, 83.8, 64.1, 63.3. Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.97; H, 6.03. Found: C, 77.59; H, 5.65.

*3.5.2. Catalytic dihydroxylation (OsO_4 /NMO) of α-C-glycoside **18α*** A solution of α-*C*-glycoside **18α**[13] (0.020 g, 0.114 mmol) in 1:1 *t*-BuOH/acetone mixture (0.3 mL) was added, at 0 °C under stirring and in the dark, to a 50% p/v aqueous solution of *N*-methyl morpholine-*N*-oxide (NMO) (0.08 mL). The resulting reaction mixture was treated with 2.5% p/v OsO_4 solution in *t*-BuOH (0.08 ml) and stirred for 96 h at room temperature. Dilution with Et_2O and evaporation of the filtered (Celite®) organic solution afforded a crude liquid product (0.015 g) which was dissolved in anhydrous pyridine (0.4 mL) and treated with Ac_2O (0.2 mL) at 0 °C. After 18h stirring at room temperature, co-evaporation of the reaction mixture with toluene afforded pure *(2S,3S,4R,5S)-3,4,5-tri-acetoxy-2-*

phenyl-tetrahydro-2H-pyrane (**21-tri-OAc**) (0.022 g, 58% yield), as a pale yellow oil: R_f = 0.17 (1:1 hexane/AcOEt); $[\alpha]^{20}_D$ +19.8 (*c* 0.76, $CHCl_3$); FTIR (film) ν 1739, 1455, 1368, 1211, 1040 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.27-7.48 (m, 5H), 5.41 (t, 1H, *J* = 3.4 Hz), 5.30 (dd, 1H, *J* = 9.7, 3.4 Hz), 4.91-4.96 (m, 1H), 4.60 (d, 1H, *J* = 9.7 Hz), 4.01 (d, 2H, *J* = 1.8 Hz), 2.35 (s, 3H), 2.20 (s, 3H), 2.19 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 170.0, 169.6, 169.4, 137.5, 128.9, 128.7, 128.5, 127.3, 76.5, 69.5, 69.4, 67.5, 65.9, 21.2, 21.1, 20.7. Anal. Calcd for $C_{17}H_{20}O_7$: C, 60.70; H, 5.99. Found: C, 60.37; H, 6.05.

*3.5.3. Reaction of epoxide **2** with TMSCN (protocol B).* A solution of *trans* hydroxy mesylate **8** (0.040 g, 0.21 mmol) in anhydrous CH_3CN (1.0 mL) was treated with *t*-BuOK (0.028 g, 0.247 mmol, 1.2 equiv) and the reaction mixture was stirred until complete cyclization to epoxide **2** had occurred (15 min, TLC). TMSCN (0.11 mL, 0.80 mmol, 4.0 equiv) was added and the resulting reaction mixture was stirred 30 min at room temperature. Dilution with Et_2O and evaporation of the washed (saturated aqueous $NaHCO_3$ and saturated aqueous NaCl) ether extracts afforded a crude liquid product (0.029 g) mostly consisting of *O*-TMS protected α-glycosyl cyanide **22α-OTMS** (^1H NMR spectroscopy) which was subjected to preparative TLC (a 1:1 hexane/AcOEt mixture was as used as the eluant). Extraction of the most intense band afforded pure *4-O-trimethylsilyl-2,3-dideoxy*-α-L-*glycero-pent-2-enopyranosyl cyanide* (**22α-OTMS**), as a colourless oil: R_f = 0.26 (6:4 hexane/AcOEt); $[\alpha]^{20}_D$ +45.4 (*c* 0.27, $CHCl_3$); FTIR (film) ν 2250, 1445, 1269, 1089 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.99 (ddd, 1H, *J* = 10.7, 3.2, 1.5 Hz), 5.72 (ddd, 1H, *J* = 10.7, 3.2, 1.8 Hz), 4.89 (dd, 1H, *J* = 5.5, 2.4 Hz), 4.24-4.36 (m, 1H), 3.93 (dd, 1H, *J* = 11.2, 5.5 Hz), 3.53 (dd, 1H, *J* = 11.2, 8.7 Hz), 0.13 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 134.7, 128.1, 122.7, 121.7, 67.3, 65.4, 61.5, 29.9, 0.1. Anal. Calcd for $C_9H_{15}NO_2Si$: C, 54.78; H, 7.76; N, 7.10. Found: C, 54.39; H, 7.58; N, 6.81.

3.6. Reactions of epoxide 2 with *N*-Nucleophiles

*3.6.1. Reaction epoxide **2** with $TMSN_3$ (protocol B).* A solution of *trans* hydroxy mesylate **8** (0.040 g, 0.206 mmol) in anhydrous MeCN (1.0 mL) was treated with *t*-BuOK (0.028 g, 0.25 mmol, 1.2 equiv) and the reaction mixture was stirred 15 min at room temperature. $TMSN_3$ (0.11 mL, 0.80 mmol, 4.0 equiv) was added and the resulting reaction mixture was stirred 18 h at the same temperature. Dilution with Et_2O and evaporation of the washed (brine) organic solution afforded a crude product (0.048 g) consisting of a 60:40 mixture of α-*N*-glycoside **26α-OTMS** and *cis* 1,2-azido derivative **28-OTMS** (^1H NMR spectroscopy) which was subjected to preparative TLC (a 7:3 hexane/AcOEt mixture was

used as the eluant). Extraction of the most intense band afforded pure *3-azido-3-deoxy-4-O-(trimethylsilyl)*-L-*arabinal* (**28-OTMS**), as a colourless liquid: R_f = 0.86 (4:6 hexane/AcOEt); $[\alpha]^{20}_D$ -198.0 (*c* 0.99, $CHCl_3$); FTIR (film) ν 2100, 1643, 1250 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.44 (dd, 1H, *J* = 6.0, 0.8 Hz), 4.74 (dd, 1H, *J* = 6.0, 5.3 Hz), 4.08-4.17 (m, 1H), 3.85-3.92 (m, 1H), 3.83-3.84 (m, 1H), 3.80-3.82 (m, 1H), 0.19 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 147.3, 96.9, 67.8, 65.7, 56.2, 0.1. Anal. Calcd for $C_8H_{15}N_3O_2Si$: C, 45.04; H, 7.08; N, 19.70. Found: C, 45.12; H, 6.91; N, 19.45.

Acknowledgments

This work was supported by the Università di Pisa and MIUR (Ministero dell'Istruzione, della Università e della Ricerca, Roma) which are sincerely acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at…...

References

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2. Reaction conditions. *Protocol A*: the epoxide is dissolved in a solvent/nucleophile; *protocol B*: the nucleophile (3 equiv) is added to the epoxide dissolved in a non-nucleophilic solvent (MeCN, THF, toluene).

3. *Anti-1,4-addition products* (*route* ***c***, Scheme 1) are commonly obtained in a mixture with corrresponding *syn-1,4-addition products* in the glycosylation of alcohols by glycal-derived epoxides **1β**,[1a,b] **1β-Me**[1d] and epoxide **2** (vide infra and Table 1) carried out under *protocol A* reaction conditions.[2]

4. Crotti, P.; Di Bussolo, V.; Pomelli, C.S.; Favero, L. *Theor. Chem. Acc.* **2009**, *122*, 245-256.

5. It is important to point out that, due to nomenclature rules for glycosides, the same relative configuration (β) of the starting epoxide and corresponding obtained glycosides, that is the structural condition necessarily present in the addition products for the application of the *syn-1,4-addition product* (*coordination product*) simplified nomenclature, is found in (1*R*,4*R*)-β-anomers from epoxides **1β** and **1β-Me** (Scheme 1) and in (1*R*,4*S*)-α-anomers from epoxide **2** (Scheme 2). Accordingly, corresponding *anti-1,4-addition products* (*non-coordination products*) have an opposite configuration at C(1).

6. Matsuo, K.; Shindo, M. *Tetrahedron* **2011**, *67*, 971-975 and references therein.

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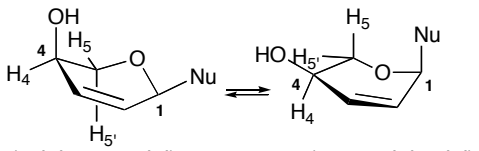
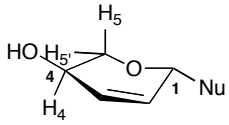
8. For ***ent*-11α**, ***ent*-11β**, and ***ent*-13α**, see: a) Fava, C.; Galeazzi, R.; Mobbili, G.; Orena, M. *Tetrahedron: Asymmetry* **2001***, 12,* 2731-2741. For only ***ent*-13α**, see: b) Naz, N.; Al-Tel, T. H.; Al-Abed, Y.; Voelter, W.; Ficker, R.; Hiller, W. *J. Org. Chem*. **1996**, *61*, 3250-3255.

9. With respect to substituents at C(1) and C(4), the different conformer population present in 2,3-unsaturated anomers derived from epoxide **2** (α-anomers exist as an axial-equatorial/equatorial-axial equilibrium between conformers, whereas only the diequatorial conformer is present in corresponding β-anomers) makes H_4 proton in ^{1}H NMR spectra (δ 4.00-4.40 ppm) of all 2,3-unsaturated-α-anomers (**9-13α**, **15**, **18-20α**, **22α-OTMS**, **31α**) as a not resolved multiplet and in the three β-anomers obtained (alkyl *O*-glycosides **9β**, **10β** and **11β**) as a doublet-doublet. As a consequence, this spectral data, in addition to appropriate NOE experiments, turned out to be an useful tool in order to assign the configuration to the anomeric centre of the obtained glycosides.



(axial-equatorial) α-anomer (equatorial-axial)



β-anomer (diequatorial)

10. Epoxide **1β** had been successfully used in the synthesis of oligosaccharides by means of an effective reiterative protocol: Di Bussolo, V.; Checchia, L.; Romano, M. R.; Pineschi, M.; Crotti, P. *Org. Lett.* **2008**, *10*, 2493-2496.

11 Considering that previous and present results have indicated epoxides **1β** [1a,b,10] and **2** (Table 1) as excellent glycosyl donors toward primary, secondary and tertiary alcohols, the negative results obtained with methyl α-*O*-glycoside **9α** (a secondary alcohol), as the glycosyl acceptor, were unexpected and an appropriate rationalization is not available.

12. A similar substrate-dependent facial selectivity had been previously observed in the

dihydroxylation of disaccharides prepared by means of the reiterative process[10] developed in our laboratory: Checchia, L. PhD Thesis, University of Pisa, School of Graduate Studies "Scienza del Farmaco e delle Sostanze Bioattive", 2009, p. 90-91.

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15. The behavior of epoxide **2** in the aminolysis with *n*-$PrNH_2$ is similar to that of epoxides **1β** and **1β-Me** in the same reaction. For a more detailed discussion of the aminolysis of **1β** and **1β-Me**, see: Di Bussolo, V.; Checchia, L.; Romano M. R.; Favero, L.; Pineschi, M.; Crotti, P. *Tetrahedron* **2010**, *66,* 689-697.