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Enantiopure *cis*- and *trans*-2,5-disubstituted-2,5-dihydrofurans from D-allal- and D-galactal-derived vinyl epoxides

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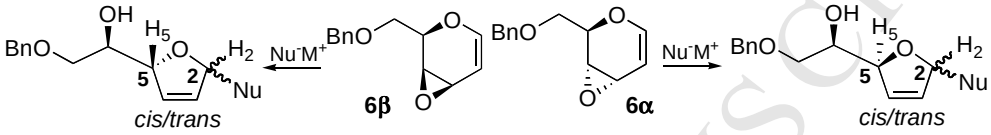

Nu^-M^+ = metal enolates of 1,3-dicarbonyl compounds, lithium anion of benzyl carbamate

Enantiopure *cis*- and *trans*-2,5-disubstituted-2,5-dihydrofurans from D-allal- and D-galactal-derived vinyl epoxides

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Abstract: Upon treatment with the metal enolates of methylene active compounds (dimethyl malonate and dibenzoylmethane) (*C*-nucleophiles) and benzyl carbamate (*N*-nucleophile), D-allal- and D-galactal-derived vinyl epoxides are stereoselectively transformed, in a single step, into diastereoisomeric, highly functionalized, enantiopure *cis*- and *trans*-2,5-disubstituted-2,5-dihydrofurans.

Dedicated to the memory of Professor Franco Macchia (1937-2018).

Keywords: Vinyl epoxides, Glycals, 2,5-Disubstituted-2,5-dihydrofurans, Rearrangement process, Stereoselectivity

1. Introduction

The 2,5-dihydrofuran core represents a privileged heterocyclic system which is present in various compounds showing relevant biological activities. In particular, the 2,5-dihydrofuran moiety can be found as common structural unit in natural products with antibiotic (α-amino acid L-(+)-furanomycin[1a-c] and diterpene (-)-guanacastepene E),[1d] anticancer/cytotoxic (eleutherobin,

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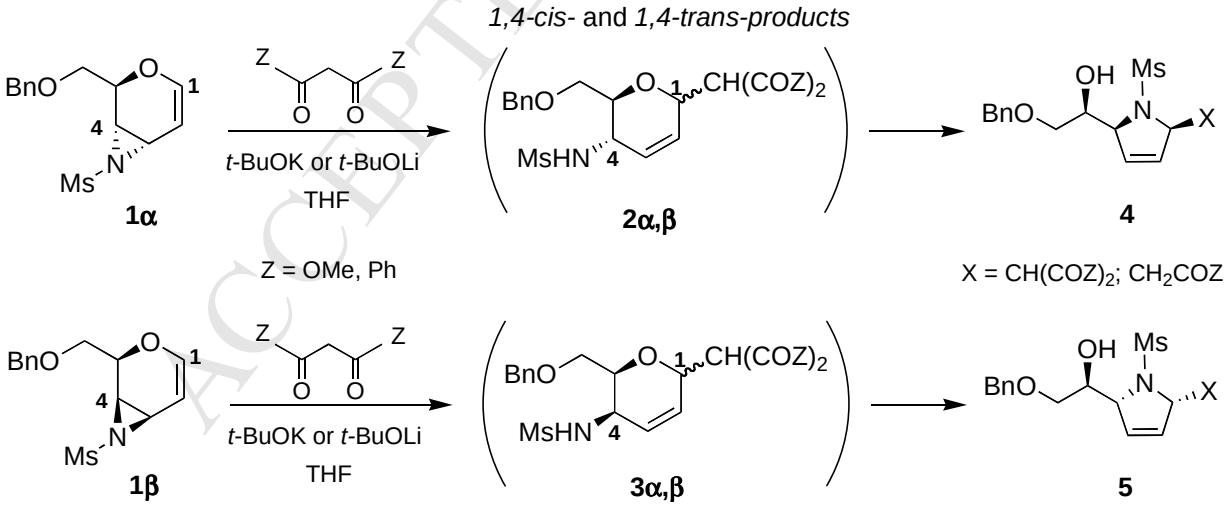
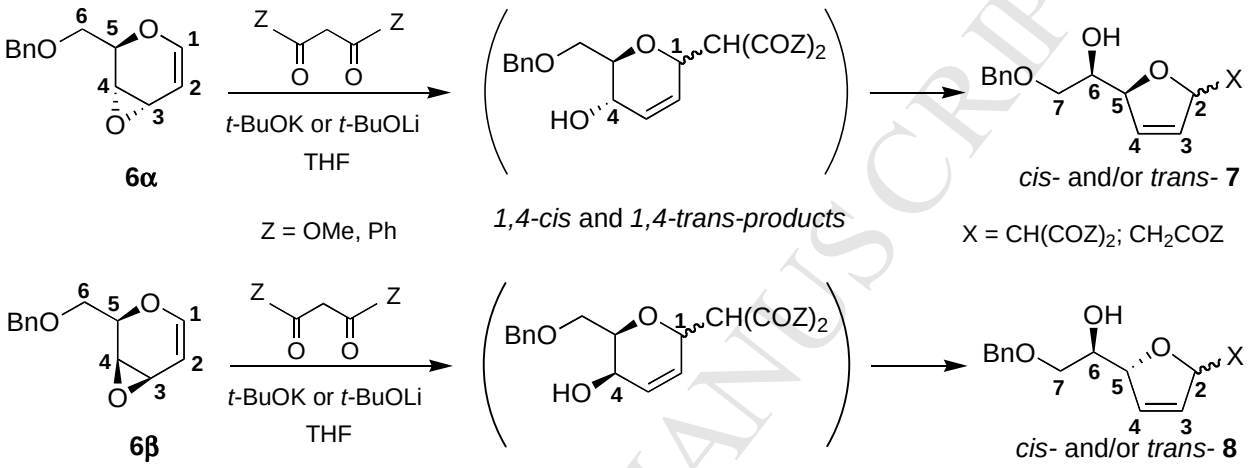
a marine diterpene glycoside)[2] and antileukemic activity (liatrin, a sesquiterpene lactone).[3] Moreover, the 2,5-dihydrofuran system is well represented in capsochrome derivatives,[4] as effective antiproliferative agents, and in the known synthetic antiviral nucleoside stavudine.[5] For these reasons, this system represents an important scaffold in Medicinal Chemistry for the construction of corresponding, biologically active, synthetic products. In this framework, multifunctionalized 2,5-dihydrofurans are particularly useful bulding blocks in organic synthesis due to the numerous synthetic possibilities offered by the transformation of the functional groups present in the side chains and the several functionalizations which can be introduced on the double bond. As a consequence, the construction of 2,5-dihydrofuran rings bearing different substitutions and functionalizations has received much attention.[6-30] However, despite the great effort made in this sense, few efficient methods are available for the obtainment of these systems as pure chiral compounds.

Recently, diastereoisomeric enantiopure *cis*-2,5-disubstituted-2,5-dihydropyrroles **4** and **5** were stereoselectively obtained, in a single step, by glycosylation of metal enolates of methylene active compounds, as dimethyl malonate and dibenzoylmethane, by D-allal- and D-galactal-derived vinyl *N*-mesyl aziridines **1α** and **1β**, respectively. The formation of 2,5-dihydropyrroles **4** and **5** had been demonstrated to be the result of a base-catalyzed rearrangement, with ring contraction, of the corresponding *1,4-cis-* and *1,4–trans-products*, 2,3-unsaturated-α- and -β-*C*-glycosides **2α,β** and **3α,β**, the primary reaction products (Scheme 1).[31a,32a]



Scheme 1. Stereoselective synthesis of enantiopure, highly functionalized *cis*-2,5-disubstituted-2,5-dihydropyrroles **4** and **5** by D-allal- and D-galactal derived vinyl *N*-mesyl aziridines **1α** and **1β**.

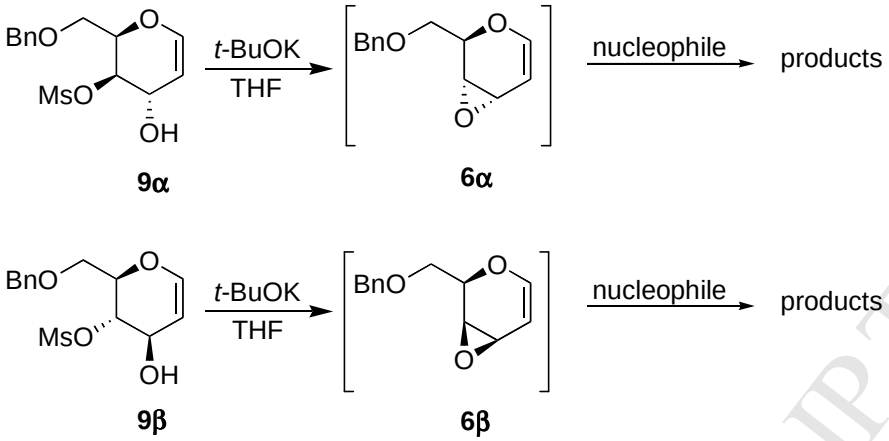
Considering the analogy, these results prompted us to verify if such a process could be applied also to the corresponding D-allal- and D-galactal-derived vinyl epoxides **6α** and **6β**. In this case, enantiomerically pure, highly functionalized *cis*- and/or *trans*-2,5-disubstituted-2,5-dihydrofuran systems as **7** and **8**, could be obtained through a new, simple and innovative process (Scheme 2).



Scheme 2. Envisaged synthesis of 2,5-disubstituted-2,5-dihydrofuran systems **7** and **8** by reactions of vinyl epoxides **6α** and **6β** with metal enolates of methylene active compounds.

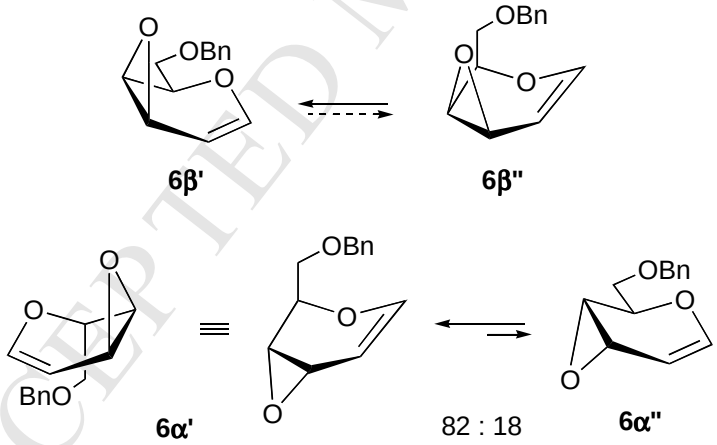
As a consequence, as previously done with aziridines **1α** and **1β**, the behaviour of vinyl epoxides **6α** and **6β**, the glycosyl donors, was initially examined by glycosylation of metal (K^+, Li^+) enolates of dimethyl malonate and dibenzoylmethane (*C*-nucleophiles, the glycosyl acceptors). Subsequently, the behaviour of epoxides **6α** and **6β** with a nitrogen-based glycosyl acceptor, as lithium anion of benzyl carbamate (*N*-nucleophile), was checked, too.

Vinyl epoxides **6α** and **6β** are not stable and can be prepared only *in situ* by base-catalyzed cyclization of the corresponding stable precursor, *trans*-hydroxy mesylate **9α** and **9β**, respectively, and let to react immediately with a nucleophile (Scheme 3).[33]



Scheme 3. Preparation *in situ* of vinyl epoxides **6α** and **6β** by base-catalyzed cyclization of corresponding stable precursor, *trans*-hydroxy mesylate **9α** and **9β**, respectively.

Theoretical computational calculations had indicated that vinyl epoxide **6β** exists in solution as the only conformer **6β'** with the side chain equatorial, whereas epoxide **6α** exists as an 82:18 equilibrium between the corresponding conformers **6α'** and **6α"** with the side chain axial and equatorial, respectively (Scheme 4).[34a]



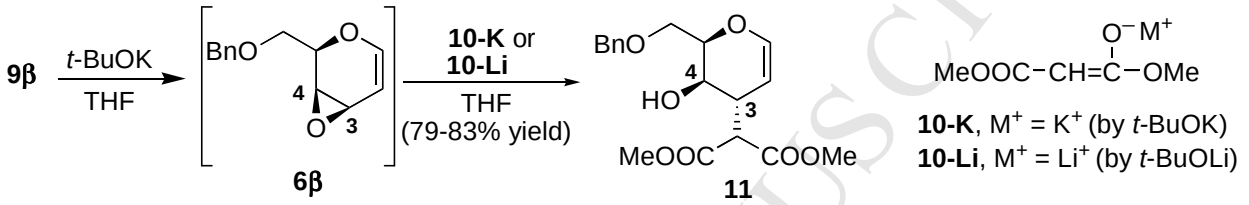
Scheme 4. Theoretical conformational analysis of vinyl epoxides **6α** and **6β**.

2. Results and discussion

*2.1. Reactions of epoxides **6β** and **6α** with metal enolates of dimethyl malonate and dibenzoylmethane*

*2.1.1. Reactions of epoxide **6β** with metal enolates of dimethyl malonate and dibenzoylmethane*

The reaction of epoxide **6β** with potassium enolate of dimethyl malonate (**10-K**), following the typical protocol of addition of a preformed THF solution of the enolate (dimethyl malonate, 3 equiv, and an equimolar amount of *t*-BuOK) to a THF solution of epoxide **6β** afforded a crude product only consisting of the corresponding *3,4-trans-product*[32a] **11** (Scheme 5). No trace of other addition products or rearranged products, as the expected 2,5-dihydrofuran systems, was present in the crude product. The same result was obtained also when the preformed lithium enolate (from *t*-BuOLi) of dimethyl malonate (**10-Li**) was used (Scheme 5 and Table 1, entries 1 and 2).



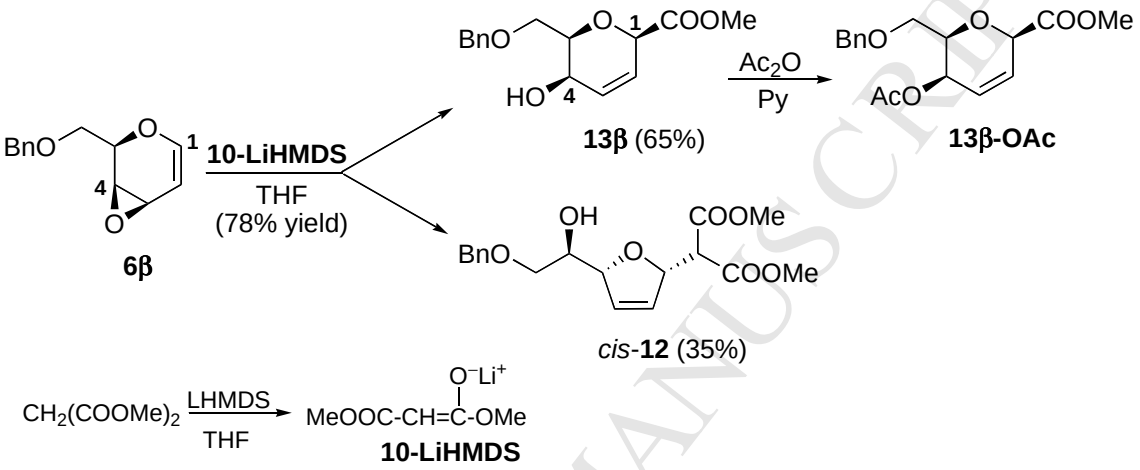
Scheme 5. Reaction of epoxide **6β** with potassium (**10-K)** and lithium enolate **10-Li** prepared by dimethyl malonate/*t*-BuOK and dimethyl malonate/*t*-BuOLi protocol, respectively.

The reason of the unsuccessful obtainment of the expected 2,5-dihydrofuran system was clearly due to the fact that, under the reaction conditions used, no 1,4-adducts were formed, also when more coordinating reaction conditions were used (**10-Li**).[33,35]

In spite of the negative result obtained with *t*-BuOLi as the base, the use of a stronger THF-soluble base, as LHMDS in order to generate **10-LiHMDS**, was attempted. The new protocol guaranteed the presence in the reaction mixture of a higher concentration of the strongly coordinating lithium cation which, reasonably, could favour the formation of *1,4-cis-products*.[32a,33] Moreover, the presence of LHMDS, a base stronger than the previously used ones (*t*-BuOK and *t*-BuOLi), could have a beneficial effect to the rearrangement process of 1,4-adducts, once these products were formed.

The reaction of epoxide **6β** with **10-LiHMDS** (3 equiv, from equal amounts of dimethyl malonate and LHMDS) in anhydrous THF for 4 h at room temperature afforded a crude reaction mixture consisting of two products in a 35:65 ratio which were separated by preparative TLC (Scheme 6 and Table 1, entry 3). Accurate ^{1}H NMR examination of these two products indicated that the minor product was the expected isomerization product, 2,5-dihydrofuran *cis*-**12**, bearing at C(2) the –CH(COOMe)$_2$ residue of enolate **10-LiHMDS**. More intriguing was the determination of the structure of the major product which corresponded to an *1,4-cis-product* of epoxide **6β** in which the –CH(COOMe)$_2$ residue of the starting nucleophile, turned out to be

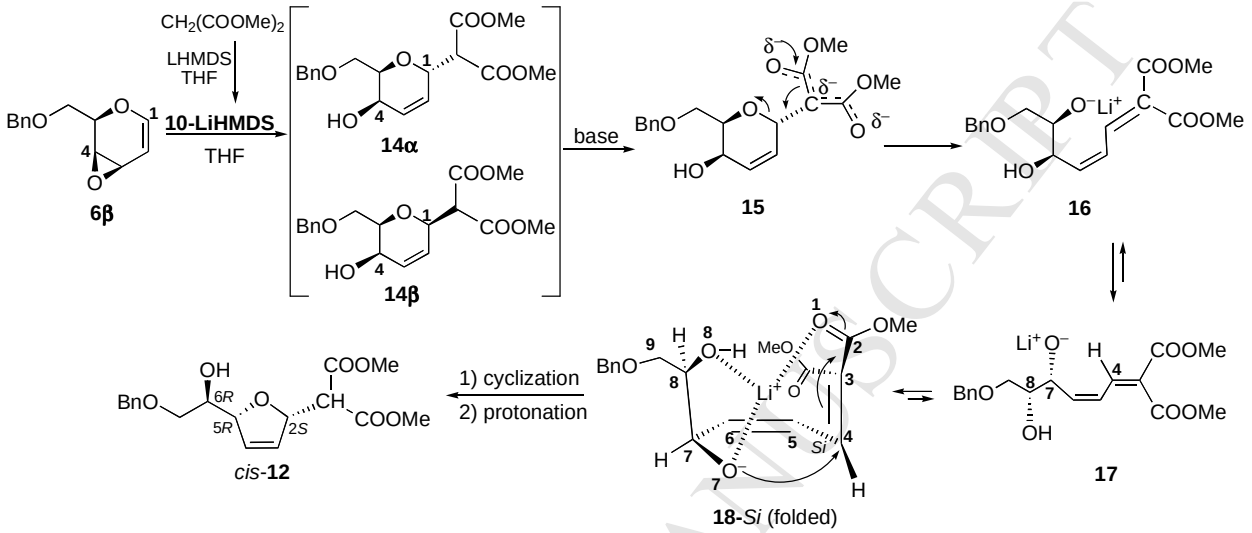
simplified to (methoxycarbonyl)- group (–COOMe). In other words, the –CHCOOMe portion of the nucleophile, enolate **10-LiHMDS**, appeared lost. All ^{1}H NMR evidences allowed the assignation of the structure of methyl β-glycosylcarboxylate derivative **13β** to major reaction product, furtherly confirmed by carrying out the same structural analysis (^{1}H NMR) on the corresponding acetate **13β-OAc** (Scheme 6). A detailed rationalization for the formation of methyl β-glycosylcarboxylate **13β** has been recently published.[36]



Scheme 6. Reaction of epoxide **6β** with lithium enolate **10-LiHMDS** prepared by dimethyl malonate/LHMDS protocol in anhydrous THF.

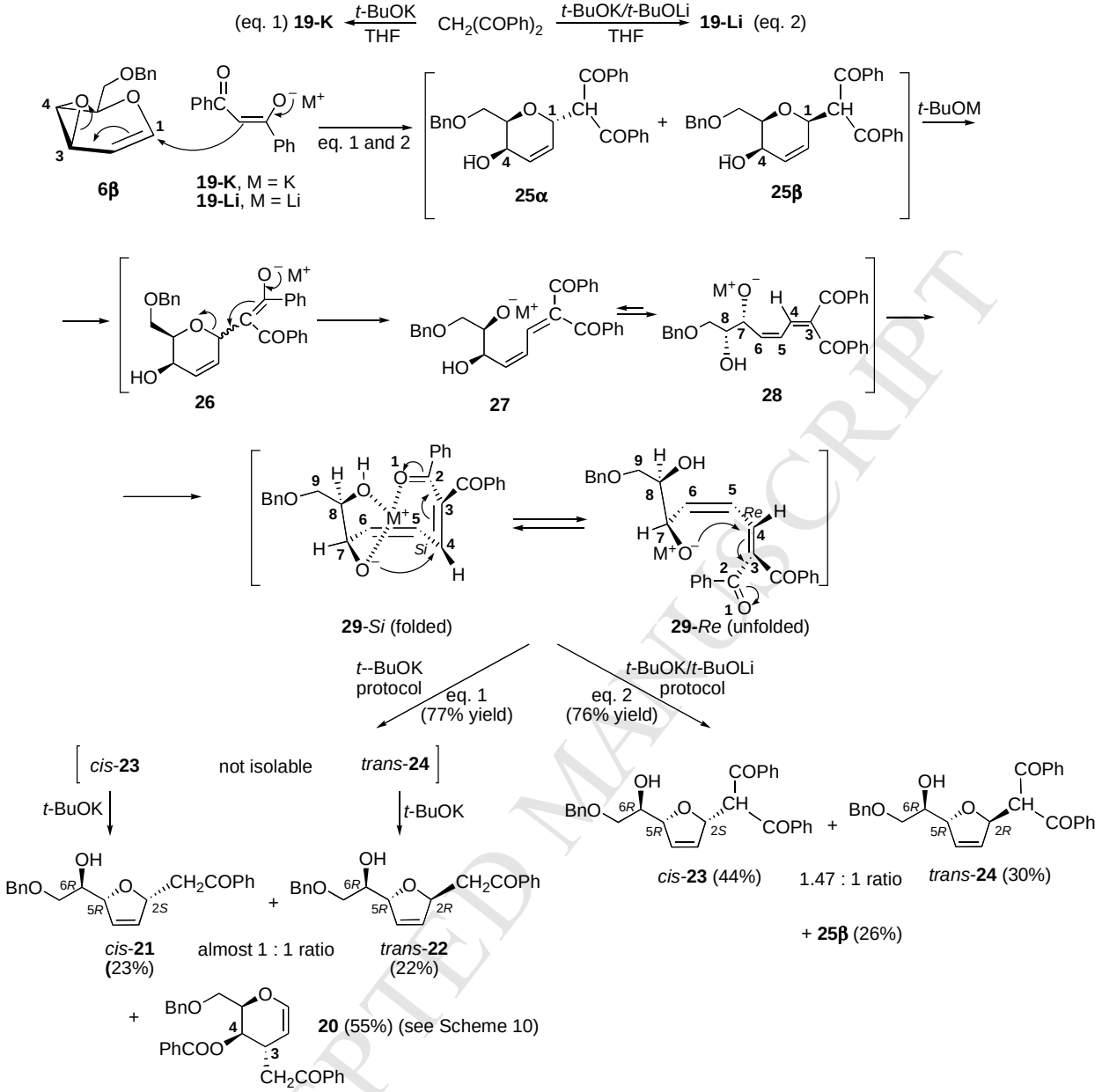
In accordance with previous results (Scheme 1),[31a] 2,5-dihydrofuran *cis*-**12** derives from α-**14α** and β-C-glycoside **14β** (1,4-adducts). the primary reaction products, formed by S_N2' addition of lithium enolate **10-LiHMDS** to vinyl epoxide **6β**. Base-catalyzed deprotonation (a small excess of base is present in the reaction mixture) of the residual acid C-H bond of the –$CH(COOMe)_2$ group of *C*-glycosides **14β** and/or **14α**, generates the corresponding enolate species **15** followed by retro oxa-Michael reaction with the formation of intermediate α,β-γ,δ-unsaturated system **16** (Scheme 7). Acid-base equilibration between the homoallyl alcoholate and the secondary allyl OH group present in **16** leads to the new allyl alcoholate **17**. An intramolecular oxa-Michael addition of the C(7)-O^- alcoholate portion of **17** at C(4) carbon of the α,β-unsaturated system through the folded conformer **18**-*Si*, leads to 2,5-dihydrofuran *cis*-**12**. Actually, in the folded conformer **18**-*Si*, the conjugate system assumes a *s*-cis conformation in order to have a three centers coordination of lithium cation with alcoholate O(7), malonate carbonyl O(1) and secondary hydroxy functionality O(8) oxygens (cation binding). This makes

the nucleophilic C(7)-O$^-$ allyl alcoholate appropriately disposed for a completely facial selective attack, through a favoured *5-exo-trig* mode, on the *Si* face of the α,β-conjugated system, as shown in folded conformer **18**-*Si* to give 2,5-dihydrofuran *cis*-**12**, in a completely *syn*-stereoselective fashion[32b] (Scheme 7).[37]



Scheme 7. Rationalization of the formation of 2,5-dihydrofuran *cis*-**12** by reaction of epoxide **6β** with lithium enolate of dimethyl malonate (**10-LiHMDS**) prepared by LHMDS protocol.

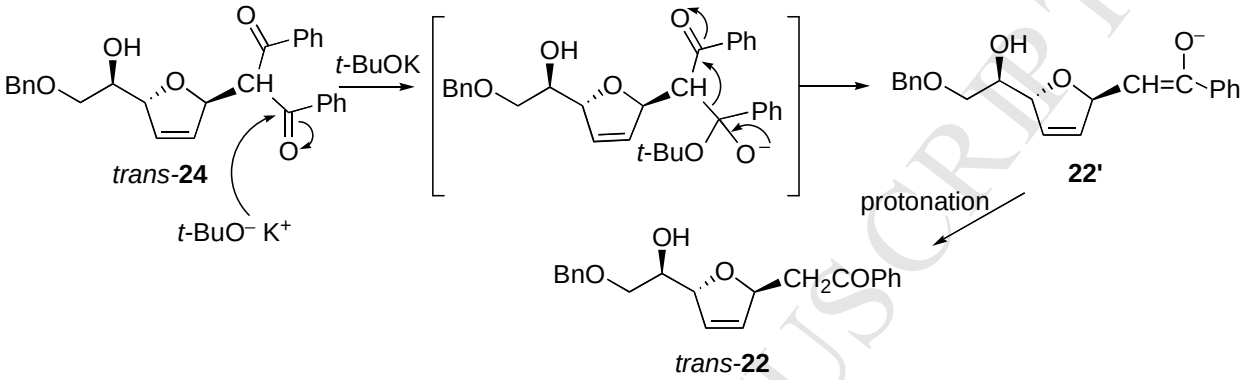
The reaction of potassium enolate of dibenzoylmethane (**19-K**) with epoxide **6β** carried out by using *t*-BuOK as the base both for the formation *in situ* of the epoxide and for the formation of the enolate, led to a crude reaction product consisting of D-gulal-derivative **20** (*3,4-trans-product*)[38] (55%), accompanied by an almost 1:1 mixture of diastereoisomeric rearranged products, 2-(benzoylmethyl)-2,5-dihydrofurans *cis*-**21** (23%) and *trans*-**22** (22%) (eq 1, Scheme 8 and Table 2, entry 1). All products were separated and obtained pure by preparative TLC.[39]



Scheme 8. Reaction of epoxide **6β** with potassium (**19-K**) and lithium enolate **19-Li** prepared by dibenzoylmethane/*t*-BuOK (eq.1) and dibenzoylmethane/*t*-BuOK/*t*-BuOLi protocol (eq.2), respectively.

The formation of 2,5-dihydrofurans *cis*-**21** and *trans*-**22** or, better, of the corresponding 2-(dibenzoylmethyl) derivatives *cis*-**23** and *trans*-**24**, the primary reaction products (eq.1, Scheme 8),[39] can be rationalized as previously admitted for the corresponding reaction of epoxide **6β** with lithium enolate **10-LiHMDS** (Scheme 7). S_N2'addition of enolate **19-K** to epoxide **6β** reasonably leads to a mixture α- **25α** and β-*C*-glycoside **25β** (eq.1, Scheme 8).[40] Subsequent retro oxa-Michael reaction (**26**, **27**), followed by equilibration to alcoholate **28** and intramolecular oxa-Michael reaction, as shown in intermediates **29**-*Si* and **29**-*Re*, leads to not

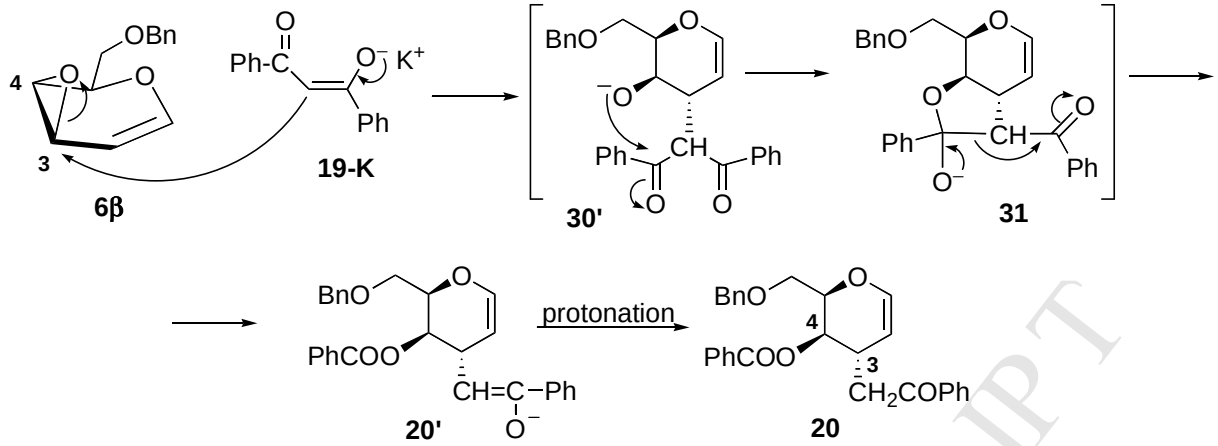
isolable 2,5-dihydrofurans *cis*-**23** and *trans*-**24** (eq. 1, Scheme 8). Actually, a fast mono-debenzoylation process by intermolecular retro-Claisen condensation by *t*-BuOK transforms *cis*-**23** and *trans*-**24** into the corresponding 2-(benzoylmethyl) derivatives *cis*-**21** and *trans*-**22**, the reaction products, as shown in Scheme 9 (for simplicity, only the transformation of *trans*-**24** into corresponding *trans*-**22** is shown).[39]



Scheme 9. Mono-debenzoylation by retro-Claisen condensation of 2,5-dihydrofuran *trans*-**24** with the formation of corresponding 2,5-dihydrofuran *trans*-**22**.

This result indicates that the cyclization step, with ring contraction, is not stereoselective and indifferently occurs at both *Si* and *Re* faces of sp^2 vinyl C(4)-carbon of intermediate α,β-γ,δ-conjugated system **28** through the folded **29**-*Si* and unfolded conformer **29**-*Re* to the point that an almost 1:1 mixture (45%) of the corresponding final mono-benzoylated 2,5-dihydrofurans *cis*-**21** and *trans*-**22** is obtained in the crude reaction product (eq. 1, Scheme 8).[41]

D-Gulal-derivative **20** is obtained by an attack of the nucleophile (potassium enolate **19-K**) at oxirane C(3)-carbon, in a *trans*-diaxial opening fashion of the oxirane ring, to give 3-(dibenzoylmethyl)-derivative **30**, as corresponding alcoholate **30'**. The occurrence of an intramolecular retro-Claisen condensation, as shown in intermediate **31**, is accompanied by *O*-benzoylation of the adjacent alcoholate group with the obtainment of the final all-protected product **20** (Scheme 10).[38,39]



Scheme 10. Rationalization of the formation of D-gulal derivative **20** in the reaction of epoxide **6β** with potassium enolate of dibenzoylmethane (**19-K**)

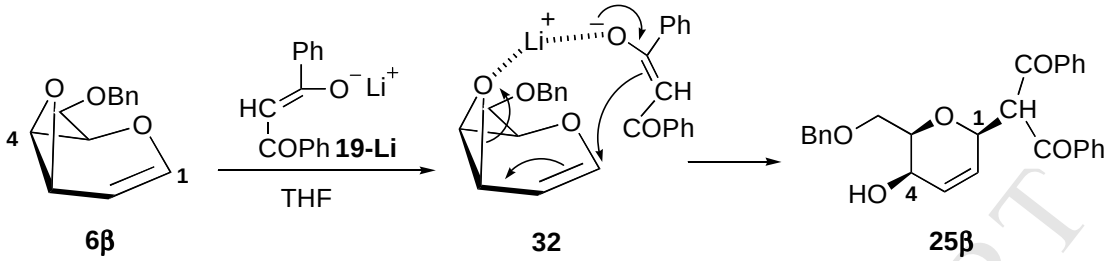
The same reaction of epoxide **6β** was repeated with the corresponding Li-enolate (**19-Li**) by means of the so-called *t*-BuOK/*t*-BuOLi protocol in which *t*-BuOK (1 equiv) is exclusively used to generate epoxide **6β** from *trans*-hydroxy mesylate **9β**, whereas *t*-BuOLi (3 equiv) is exclusively used for the formation of enolate **19-Li** (3 equiv) (eq. 2, Scheme 8). These new conditions would have determined the presence in the reaction mixture of a cation (Li^+), more coordinating than the previously used K^+ (from *t*-BuOK), with beneficial effect both on the regioselectivity of the addition process (increased 1,4-/3,4-adduct ratio) and, as a consequence, on the formation of 2,5-disubstituted-2,5-dihydrofurans with possible *syn*-stereoselectivity (increased corresponding *cis*/*trans* ratio).[42]

Actually, these modified reaction conditions led to a 26:44:30 mixture of β-*C*-glycoside **25β** (*1,4-cis-product*), and 2,5-dihydrofurans *cis*-**23** and *trans*-**24** to indicate that in this case only 1,4-adducts were obtained[33,42] and that no mono-debenzoylation process had occurred at any level.[43] Moreover, as expected, 2,5-dihydrofurans *cis*-**23** and *trans*-**24** are obtained in a satisfactory amount (74%)[42] and a significant, even if slight, *syn*-stereoselectivity is observed (*cis*-**23**/*trans*-**24** ratio = 1.47) (eq. 2, Scheme 8 and Table 2, entry 2) (*vide infra*).

C-glycoside **25β** was separated pure by preparative TLC, whereas 2,5-dihydrofurans *cis*-**23** and *trans*-**24** turned out to be inseparable. Even if obtained in a mixture, accurate ^{1}H NMR analysis made the structural identification of *cis*-**23** and *trans*-**24** possible, with determination of their relative configuration and amount in the crude reaction mixture.

The stereoselective formation of β-*C*-glycoside **25β** can be rationalized by admitting the occurrence of a metal-mediated intermolecular oxirane oxygen-nucleophile (**19-Li**) coordination,

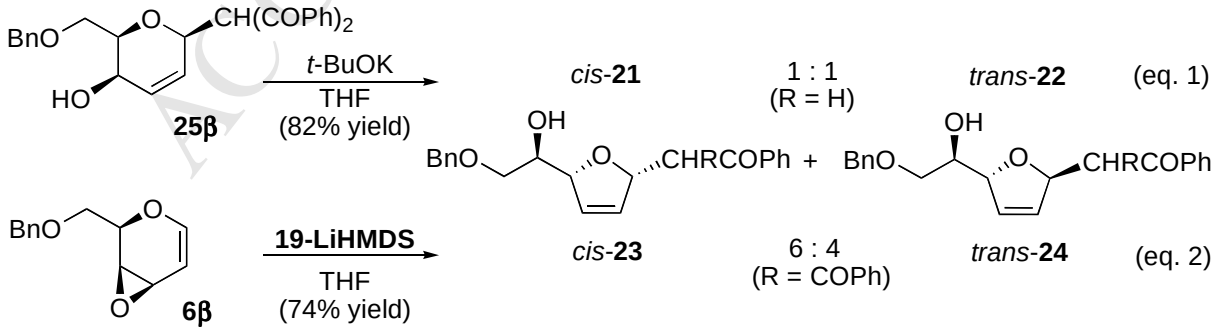
as shown in **32**, followed by, completely stereoselective, nucleophilic attack at C(1)-carbon of epoxide **6β** from the same side as the oxirane oxygen. (Scheme 11).[33,44]



Scheme 11. Rationalization of the formation of β-*C*-glycoside **25β** in the reaction of epoxide **6β** with lithium enolate of dibenzoylmethane (**19-Li**).

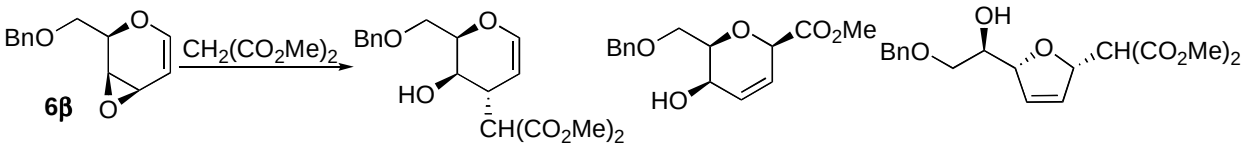
The formation of dihydrofurans *cis*-**23** and *trans*-**24** follows the rationalization previously given for the corresponding reaction of epoxide **6β** with potassium enolate **19-K** (eq. 1 and 2, Scheme 8). In this framework, the presence in the reaction mixture of the more coordinating lithium cation could reasonably favour the occurrence of the folded intermediate conformer **29**-*Si* (M = Li) and, as a consequence, the formation of 2,5-dihydrofuran *cis*-**23** with the slight *syn*-stereoselectivity observed (eq. 2, Scheme 8).[32b]

The obtainment of β-*C*-glycoside **25β** made it possible to have a confirmation of the proposed mechanism of formation of 2,5-dihydrofurans in the reaction of epoxide **6β** with metal enolates of methylene active compounds (Schemes 7 and 8). Actually, the treatment of a THF solution of β-*C*-glycoside **25β** with *t*-BuOK (2 equiv) afforded, after 3 h stirring at room temperature, an almost 1:1 mixture of 2,5-dihydrofurans *cis*-**21** and *trans*-**22** (eq. 1, Scheme 12),[39] a result very similar to the one obtained in the reaction of epoxide **6β** with potassium enolate **19-K** (eq. 1, Scheme 8).

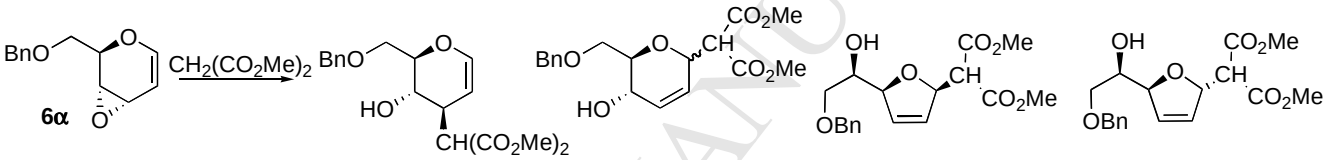


Scheme 12. The treatment of β-*C*-glycoside **25β** with *t*-BuOK (eq. 1) and of epoxide **6β** with lithium enolate **19-LiHMDS** prepared by dibenzoylmethane/LHMDS protocol (eq. 2).

Table 1. Regio- and stereoselectivity of the reactions of epoxides **6β** and **6α** with lithium and potassium enolates of dimethyl malonate.



Reaction conditions	Yield (%)	**11**	**13β**	*cis*-**12**
1) *t*-BuOK/THF	83	only product	–	–
2) *t*-BuOK/*t*-BuOLi THF	79	only product	–	–
3) LHMDS/THF	78	–	65	35

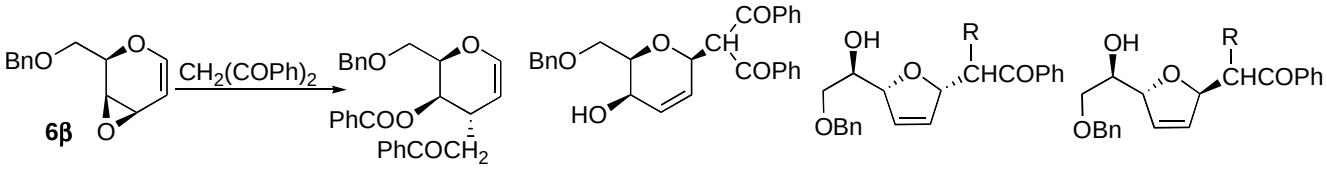


Reaction conditions	Yield (%)	**33**	**34α** + **34β**	*cis*-**35**	*trans*-**36**
4) *t*-BuOK/THF	78	only product	–	–	–
5) *t*-BuOK/*t*-BuOLi THF	75	–	38[a]	31	31[b]
6) LHMDS/THF	complex reaction mixture				

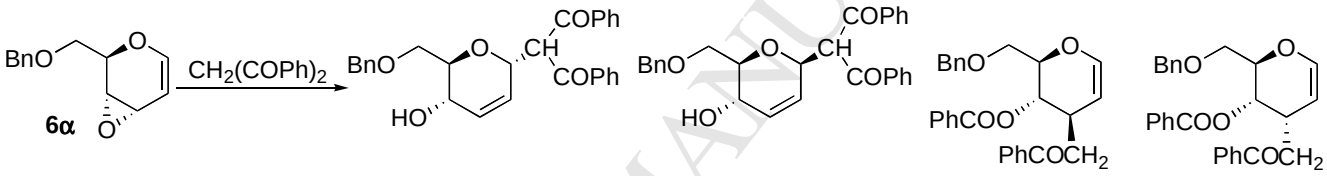
[a] *C*-glycosides **34α** and **34β** was recovered from the reaction mixture only as an inseparable mixture of corresponding acetates **34α-OAc** and **34β-OAc**.

[b] 2,5-Dihydrofuran *trans*-**36** was recovered from the reaction mixture only as corresponding acetate *trans*-**36-OAc**.

Table 2. Regio- and stereoselectivity of the reactions of epoxides **6β** and **6α** with lithium and potassium enolates of dibenzoylmethane.



Reaction conditions	Yield (%)	**20**	**25β**	*cis*-**21**, R = H *cis*-**23**, R = COPh	*trans*-**22**, R = H *trans*-**24**, R = COPh
1) *t*-BuOK/THF	77	55	–	23 (*cis*-**21**)	22 (*trans*-**22**)
2) *t*-BuOK/*t*-BuOLi THF	76	–	26[a]	44 (*cis*-**23**)[b]	30 (*trans*-**24**)[b]
3) LHMDS/THF	74	–	–	60 (*cis*-**23**)[b]	40 (*trans*-**24**)[b]



Reaction conditions	Yield (%)	**38α**	**38β**	**39**	**40**
1) *t*-BuOK/THF	78	68	–	15	17
2) *t*-BuOK/*t*-BuOLi THF	80	–	85	–	15
3) LHMDS/THF		complex reaction mixture			

[a] The treatment of **25β** with *t*-BuOK afforded an almost 1:1 mixture of 2,5-dihydrofurans *cis*-**21** and *trans*-**22**.

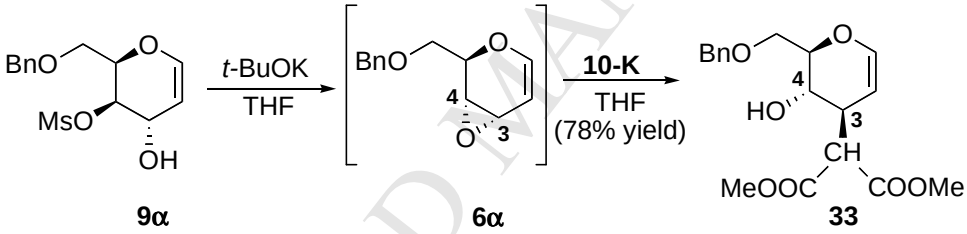
[b] 2,5-Dihydrofurans *cis*-**23** and *trans*-**24** were recovered from the reaction mixture as an inseparable mixture (Scheme 12, eq.1).

Finally, the use of a stronger base was examined. In this way, the reaction of epoxide **6β** with lithium enolate **19-LiHMDS**, prepared by dibenzoylmethane/LHMDS protocol, led to a crude reaction product only consisting of a chemoselective 60:40 mixture of 2,5-dihydrofurans *cis*-**23** and *trans*-**24** (eq. 2, Scheme 12 and Table 2, entry 3).[43] The observed slight *syn*-stereoselectivity (*cis*-**23**/*trans*-**24** ratio = 1.5, similar to that previously observed with **19-Li** (*t*-BuOK/*t*-BuOLi protocol, eq. 2, Scheme 8), even if partially satisfactory, is decidedly inferior to the complete

syn-stereoselective result observed in the reaction of epoxide **6β** with lithium enolate of dimethyl malonate (**10-LiHMDS**) under the same conditions (Scheme 7). The higher basicity of an ester carbonyl oxygen, as present in intermediate **17** from the reaction of **6β** with **10-LiHMDS** (Scheme 7), with respect to a ketonic carbonyl oxygen, as present in intermediate **28** from the corresponding reaction of **6β** with **19-Li** (Scheme 8), could be responsible of the exclusive occurrence of the Li^+-coordinated folded conformer **18**-*Si* and, thus, of the completely *syn*-stereoselective result[32b] found in the reaction of epoxide **6β** with **10-LiHMDS** (Scheme 7).

*2.1.2. Reaction of epoxide **6α** with metal enolates of dimethyl malonate and dibenzoylmethane*

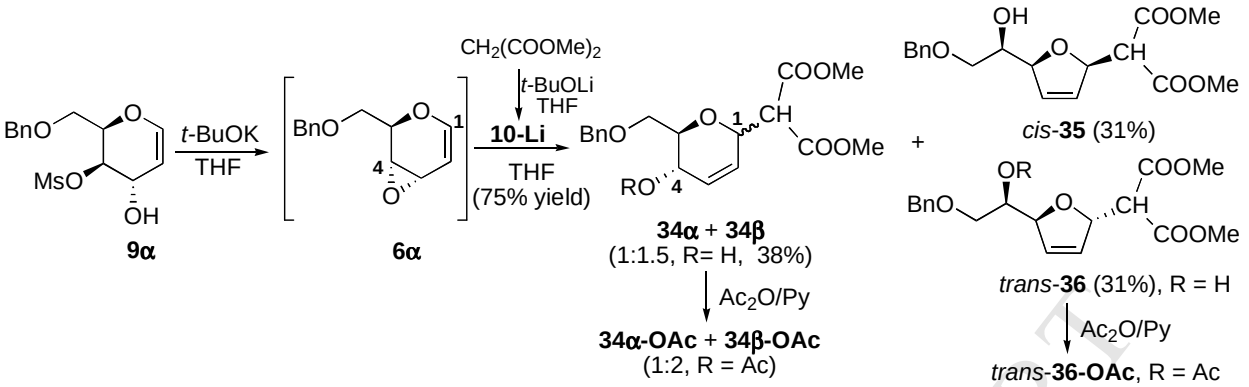
Following the protocol previously used for epoxide **6β**, a THF solution of epoxide **6α** was treated with a preformed THF solution of potassium enolate of dimethyl malonate (**10-K**). The reaction turned out to be completely regio- and *anti*-stereoselective affording D-glucal-derivative **33** (*3,4-trans-product*), as the only reaction product (Scheme 13 and Table 1, entry 4).[45]



9α **6α** **33**

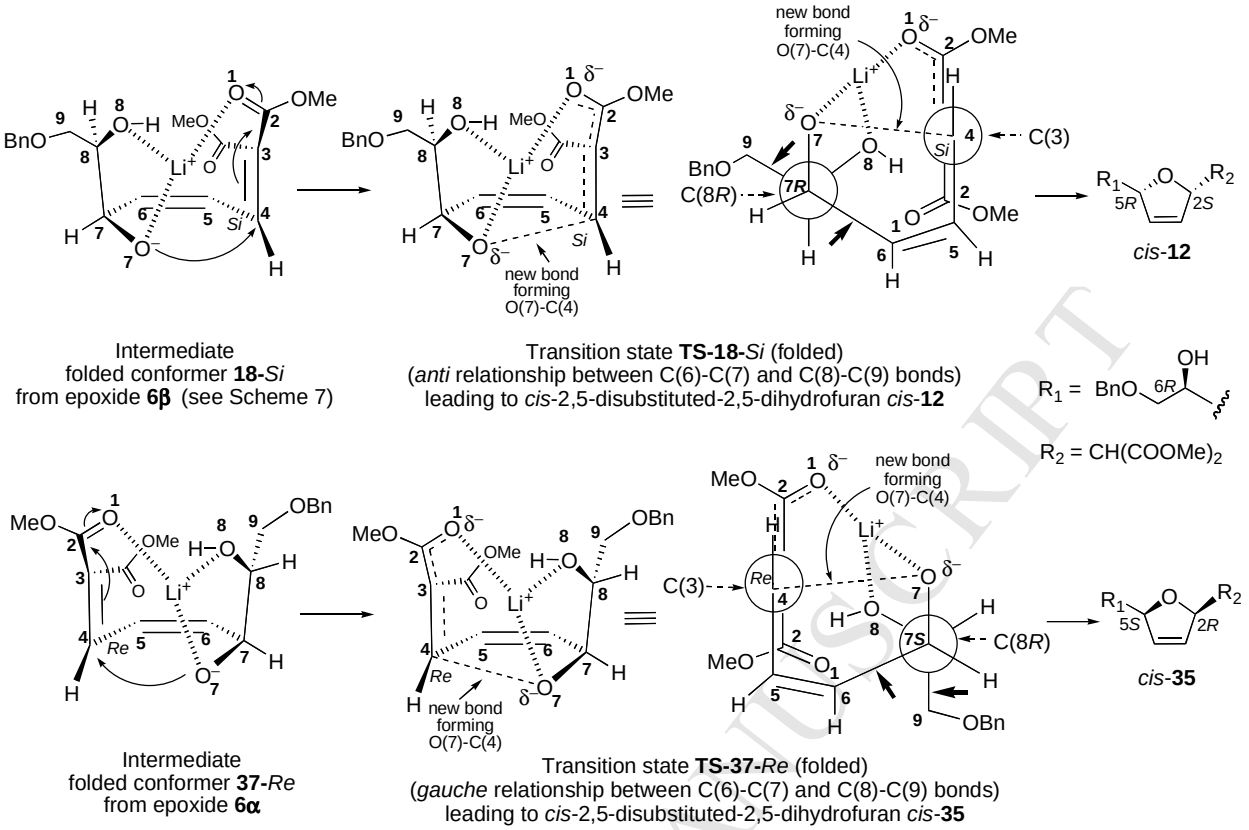
Scheme 13. Reaction of epoxide **6α** with potassium enolate of dimethyl malonate (**10-K**).

As expected, the behaviour of epoxide **6α** drastically changes when *t*-BuOK/*t*-BuOLi protocol was used. Actually, under these reaction conditions, the obtained crude product turned out to be constituted by a 1:1 mixture of 2,5-dihydrofurans *cis*-**35** (31%) and *trans*-**36** (31%), accompanied by a 1:1.5 mixture of diastereoisomeric *1,4-cis*- and *1,4–trans-products*, α- **34α** and β-*C*-glycoside **34β** (38%, ^{1}H NMR) which was subjected to preparative TLC (Scheme 14 and Table 1, entry 5). Only 2,5-dihydrofuran *cis*-**35** was obtained pure and the remaining mixture of *trans*-**36**, **34α** and **34β** was acetylated by Ac_2O/pyridine protocol. Preparative TLC of the obtained crude acetylated mixture afforded pure *O*-Ac-derived dihydrofuran *trans*-**36-OAc**, whereas -*O*Ac-derived α- **34α-OAc** and β-*C*-glycoside **34β-OAc** were recovered as an inseparable 1:2 mixture (Scheme 14).



Scheme 14. Reaction of epoxide **6α** with lithium enolate of dimethyl malonate (**10-Li)** by *t*-BuOK/*t*-BuOLi protocol.

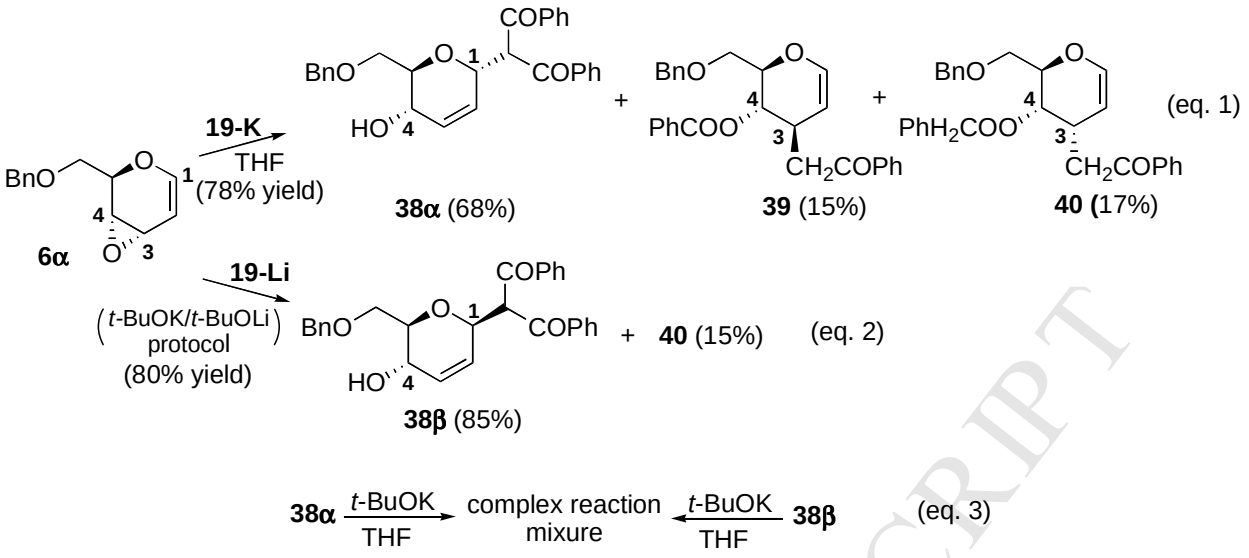
2,5-Dihydrofurans *cis*-**35** and *trans*-**36** derive from a rearrangement of α- **34α** and/or β-*C*-glycoside **34β** through a mechanism similar to the one previously described for the formation of corresponding 2,5-dihydrofuran *cis*-**12** from epoxide **6β** (Scheme 7). The absence of *syn*-stereoselectivity with epoxide **6α** could be due to the different stability of the folded transition states **TS-18**-*Si* (from **6β**) and **TS-37**-*Re* (from **6α**) leading to the corresponding 2,5-dihydrofuran *cis*-**12** and *cis*-**35**, respectively (Schemes 7 and 15).[46] In this framework, an appropriate theoretical study indicated that **TS-18**-*Si*, the folded transition state leading to 2,5-dihydrofuran *cis*-**12** from epoxide **6β**, is 0.89 kcal/mol more stable than **TS-37**-*Re*, the folded transition state leading to 2,5-dihydrofuran *cis*-**35** from epoxide **6α** (Supplementary data).[47] The reason of the observed different stability can reasonably be found in the different relationship between the corresponding residual C(6)-C(7) and C(8)-C(9) bonds: a favourable *anti*-relationship is present in **TS-18**-*Si* whereas a less stable *gauche*-relationship is found in **TS-37**-*Re* (Scheme 15 and Figure 1 in Supplementary data).



Scheme 15. Folded transition states **TS-18**-*Si* and **TS-37**-*Re* involved in the formation 2,5-dihydrofurans *cis*-**12** and *cis*-**35** by the reaction of epoxides **6β** and **6α**, with lithium enolate of dimethyl malonate (**10-Li**), respectively.

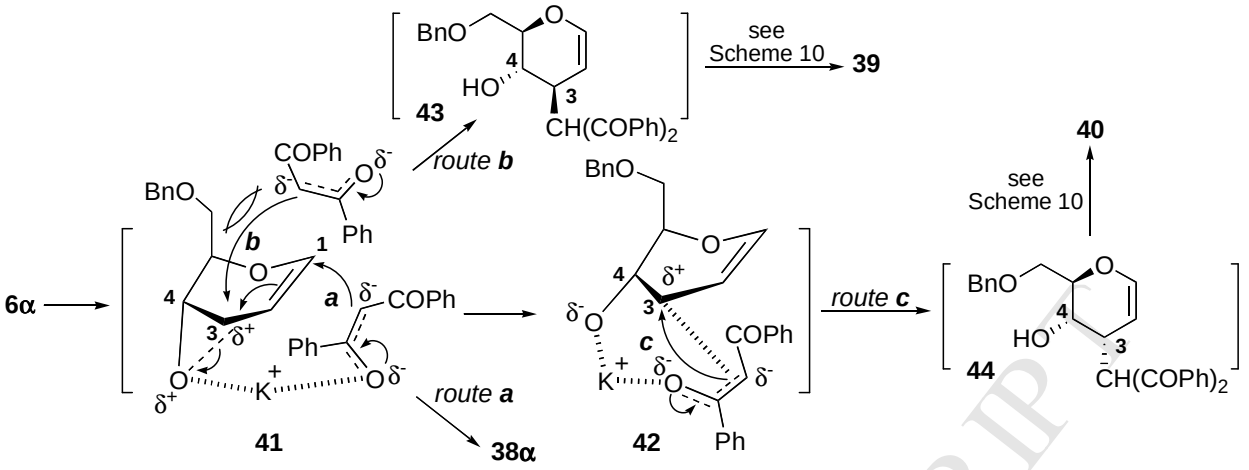
As previously done with epoxide **6β**, also in this case the use of a stronger base was examined. Unfortunately, the treatment of a THF solution of epoxide **6α** with lithium enolate **10-LiHMDS**, by dimethyl malonate/LHMDS protocol, afforded only a complex reaction mixture which was not furtherly examined (Table 1, entry 6).

The reaction of epoxide **6α** with the potassium enolate of dibenzoylmethane (**19-K**) led to a crude reaction mixture mostly consisting of α-*C*-glycoside **38α** (*1,4-cis-product*) (68%) accompanied by small amounts of D-glucal-derivative **39** (*3,4-trans-product*) (15%) and the diastereoisomeric D-allal-derivative **40** (*3,4-cis-product*) (17%) (eq.1, Scheme 16 and Table 2, entry 4).[38]



Scheme 16. Reaction of epoxide **6α** with potassium (**19-K**) (eq. 1) and lithium enolate of dibenzoylmethane (**19-Li**, eq. 2) prepared by *t*-BuOK and *t*-BuOK/*t*-BuOLi protocol, respectively. Treatment of α- **38α** and β-*C*-glycoside **38β** with *t*-BuOK in THF (eq. 3).

The formation of *1,4-cis-product* **38α** is in accordance with the occurrence of a metal ion (K^+)-coordinated syn-1,4-addition process, as shown in intermediate structure **41** (*route **a***, Scheme 17) in which an extended oxirane oxygen-oxirane C(3) carbon is present[33,34b] Nucleophilic attack on allyl C(3)-carbon of **41** can occur also by a free, non-coordinated enolate species, necessarily from the back side because the allyl C(3)-O bond is not broken, by trans-diaxial oxirane ring opening (*route **b***, Scheme 17). In this way, *3,4-trans-product* **43** is obtained as a not isolable intermediate because of the rapid occurrence of the previously described intramolecular retro-Claisen condensation which transforms **43** into 4-*O*-benzoyl-3-benzoylmethyl derivative **39** (Schemes 16, 17 and 10).[48] Moreover, intermediate **41** can evolve, through an internal rearrangment, to the more carbocationic intermediate **42** in which allyl C(3)-O bond is completely broken and C(3)-nucleophile coordination is present, as shown (Scheme 17). Entropically favoured nucleophilic attack on **42** by the coordinated nucleophile, with retention of configuration, affords *3,4-cis-product* **44** (*route **c***).[49] However, as in the case of **43**, 3-dibenzoylmethyl derivative **44** is not isolable because of its transformation, under the reaction conditions, into the isomeric derivative **40**, the reaction product (Scheme 17).[38]



Scheme 17. Rationalization of the formation of *1,4-.cis-product* **38α** (*route **a***), *3,4-.trans-product* **39** (*route **b***) and *3,4-cis-product* **40** (*route **c***) in the reaction of epoxide **6α** with potassium enolate of dibenzoylmethane (**19-K**).

A somewhat similar result was obtained when the same reaction of epoxide **6α** was repeated by means of the *t*-BuOK/*t*-BuOLi protocol. Actually, also under these modified conditions, no corresponding 2,5-dihydrofurans were obtained, but, contrary to expectations based on the presence of the more coordinating Li^+ in the reaction mixture, β-*C*-glycoside **38β** (*1,4-trans-product*) was the main reaction product (85%) accompanied only by D-allal-derivative **40** (15%) (eq. 2, Scheme 16, and Table 2, entry 5).[50,51]

The results obtained in the reactions of epoxide **6α** with metal enolates of dibenzoylmethane (**19-K** and **19-Li**), under different conditions, indicate that the desired corresponding 2,5-dihydrofurans are not formed even though a necessary precursor for the rearrangement process, as *1,4-cis-* **38α** or *1,4–trans-product* **38β** is always the main reaction product (Scheme 16, eq. 1 and 2). As a consequence, in order to force the formation of 2,5-dihydrofurans, THF solutions of α- **38α** and β-*C*-glycoside **38β** were separately treated with *t*-BuOK (2 equiv) for 3 h at room temperature. Unfortunately, only very complex reaction mixtures were obtained in both cases to indicate an intrinsic, unexplained, difficulty of *C*-glycosides **38α** and **38β** to rearrange to 2,5-dihydrofurans (Scheme 16, eq. 3).

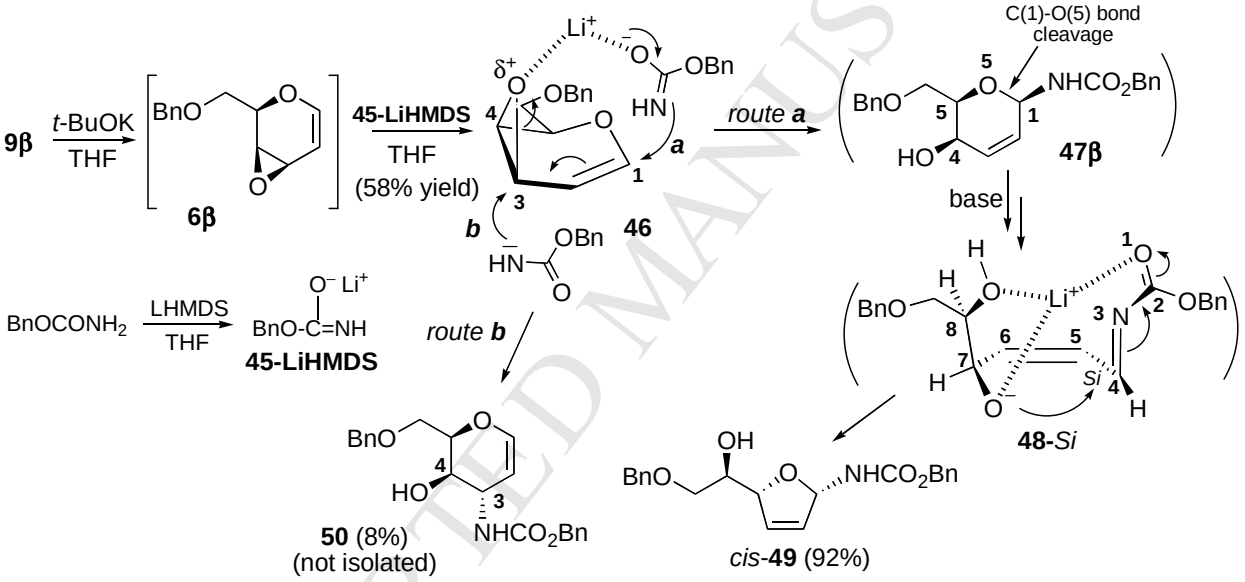
*2.2. Reaction of epoxides **6α** and **6β** with lithium anion of benzyl carbamate*

The possibility to have with epoxides **6α** and **6β** a corresponding rearrangement to 2,5-dihydrofuran systems by the use of a nitrogen-based anion, as the nucleophile, was checked. For

this purpose, benzyl carbamate ($BnOCONH_2$), having an N-H bond sufficiently acid ($K_a=10^{-12}$)[52] to be completely deprotonated by a base both in the preparation of the corresponding lithium anion **45-LiHMDS** and in the rearrangement process was thought appropriate.

*2.2.1. Reaction of epoxide **6β** with lithium anion of benzyl carbamate*

The addition at 0° C of lithium anion of benzyl carbamate **45-LiHMDS** (prepared at –78 °C from benzyl carbamate and LHMDS) to a THF solution of epoxide **6β** afforded after 18 h stirring at room temperature, a crude reaction mixture mostly consisting of 2-(benzyloxycarboxamido)-2,5-dihydrofuran *cis*-**49**, the expected rearrangement product (92%) accompanied by a small amount of D-gulal-derivative **50** (8%) (^{1}H NMR) (Scheme 18 and Table 3, entry 1). Only 2,5-dihydrofuran *cis*-**49** was separated pure by preparative TLC.



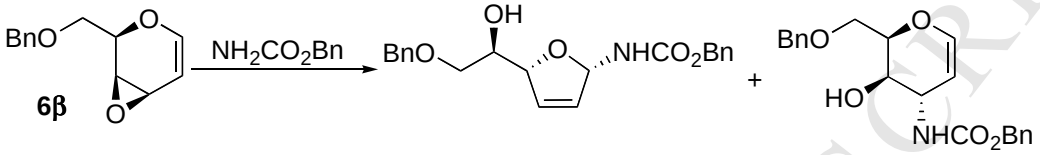
Scheme 18. Reaction of epoxide **6β** with lithium anion of benzyl carbamate (**45-LiHMDS**), prepared by LHMDS protocol.

The presence of 2,5-dihydrofuran *cis*-**49** and the small amount of *3,4-trans-product* **50** indicate that the addition of nitrogen-based lithium anion **45-LiHMDS** is particularly effective in determining 1,4-addition process, reasonably a *syn*-1,4-addition process (*vide infra* for the corresponding reaction of epoxide **6α**). In this way, β-*N*-glycoside **47β** (*1,4-cis-product*)[53] initially obtained as shown in structure **46** (Scheme 18, *route **a***) undergoes a very effective base-catalyzed isomerization to 2,5-dihydrofuran *cis*-**49**, in a nice, completely *syn*-stereoselective fashion,[32b] through the folded intermediate conformer **48**-*Si* whose occurrence is due, in addition to its *anti*-butane-like conformation (see Scheme 15 for the corresponding **18**-*Si*), to the basicity

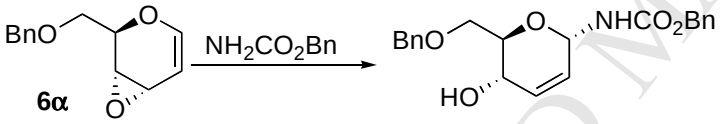
of the carbamate moiety favouring the formation of the shown intramolecular cation binding (Scheme 18).

As for D-gulal derivative **50**, its formation is due to an attack by a free, non-coordinated nucleophile (**45-LiHMDS**) at C(3) oxirane carbon of epoxide **6β**, as shown in **46** (Scheme 18, *route **b***).

Table 3. Regio- and stereoselectivity of the reactions of epoxides **6β** and **6α** with lithium anion of benzyl carbamate.



Reaction conditions	Yield (%)	*cis*-**49**	**50**
1) LHMDS/THF	58	92	8[a]



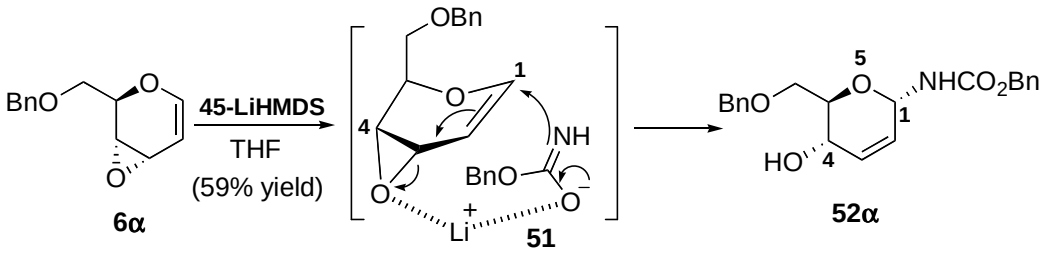
Reaction conditions	Yield (%)	**52α**
2) LHMDS/THF	59	only product[b]

[a] Not isolated.

[b] The treatment of **52α** with *t*-BuOK afforded a 71:29 mixture of 2,5-dihydrofurans *cis*-**53** and *trans*-**54** (Scheme 20).

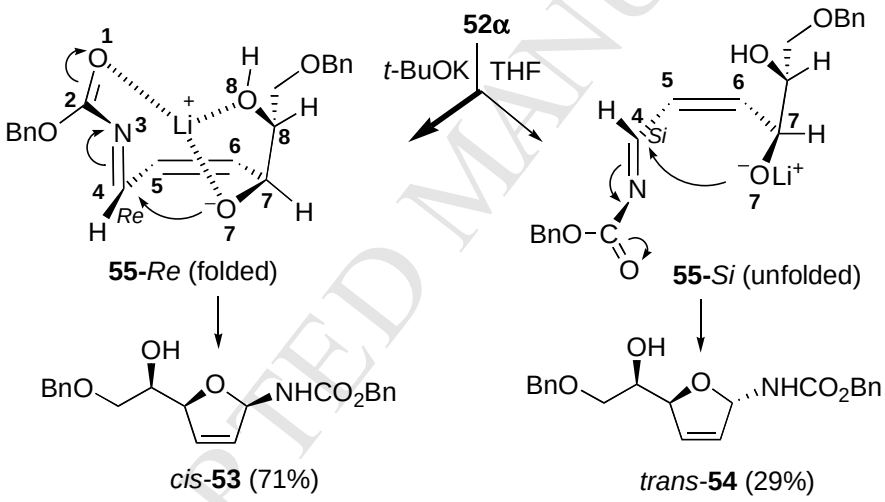
*2.2.2. Reaction of epoxide **6α** with lithium anion of benzyl carbamate*

The same reaction was repeated with epoxide **6α** under the same reaction conditions previously successfully used with epoxide **6β**. In this case, the crude reaction mixture showed the exclusive presence of the corresponding α-*N*-glycoside **52α** (*1,4-cis-product*),[53] as the result of a completely *syn*-stereoselective 1,4-addition process, as shown in structure **51** (Scheme 19 and Table 3, entry 2).



Scheme 19. Reaction of epoxide **6α** with lithium anion of benzyl carbamate (**45-LiHMDS**), prepared by LHMDS protocol.

The possibility of forcing the rearrangement process was tried by treating a THF solution of **52α** with *t*-BuOK (1.5 equiv). After 3 hours stirring at room temperature, a 71:29 mixture of diastereoisomeric 2-(benzyloxycarboxamido)-2,5-dihydrofurans *cis*-**53** and *trans*-**54** was obtained (Scheme 20), then separated by preparative TLC and their structure determined by NMR spectroscopy.

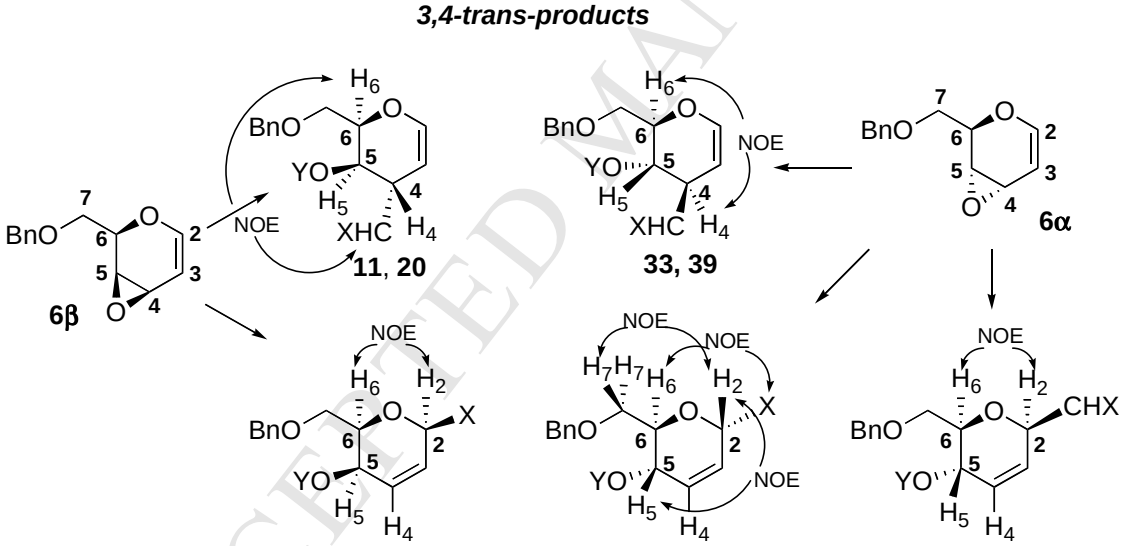


Scheme 20. The treatment of α-*N*-glycoside **52α** with *t*-BuOK.

It is interesting to note that, in the rearragement process, the formation of 2,5-dihydrofuran *cis*-**53**, reasonably proceeding through the folded conformer **55**-*Re*, is consistently favoured, as expected, over the diastereosimeric 2,5-dihydrofuran *trans*-**54**, formed by the corresponding unfolded conformer **55**-*Si*. Also in this case, the type and strength of the intramolecular coordination of lithium cation with carbamate carbonyl O(1), alcoholate O(7) and secondary alcohol O(8) oxygens**,** occurring in the folded intermediate conformer **55**-*Re*, is able to determine the observed, satisfactory, *syn*-stereoselectivity (Scheme 20).[32b]

2.3. Structures and configurations

The structural and configurational characterization of isolated products and crude reaction mixtures were firmly established by NMR spectroscopy through compared analysis of homonuclear and ^{1}H-^{13}C heteronuclear scalar correlations in the corresponding COSY (COrrelation SpectroscopY), TOCSY (TOtal Correlation SpectroscopY), HSQC (Heteronuclear Single Quantum Correlation) and HMBC (Heteronuclear Multiple Bond Coherence) maps and of dipolar correlations in NOESY (Nuclear Overhauser Effect SpectroscopY) spectra. In this framework, it is very important to keep in mind that the configuration (α or β) at C(5) carbon in the obtained six- (*3,4-cis*- and *3,4-trans-procucts* and *1,4-cis*- and *1,4-trans-products*) and five-membered-heterocyclic systems (*cis*- and *trans*-2,5-disubstituted-2,5-dihydrofurans) is the same as the configuration (α or β) at C(5) carbon of the starting epoxide, **6α** or **6β**, respectively (Schemes 21, 22 and 23).[54]

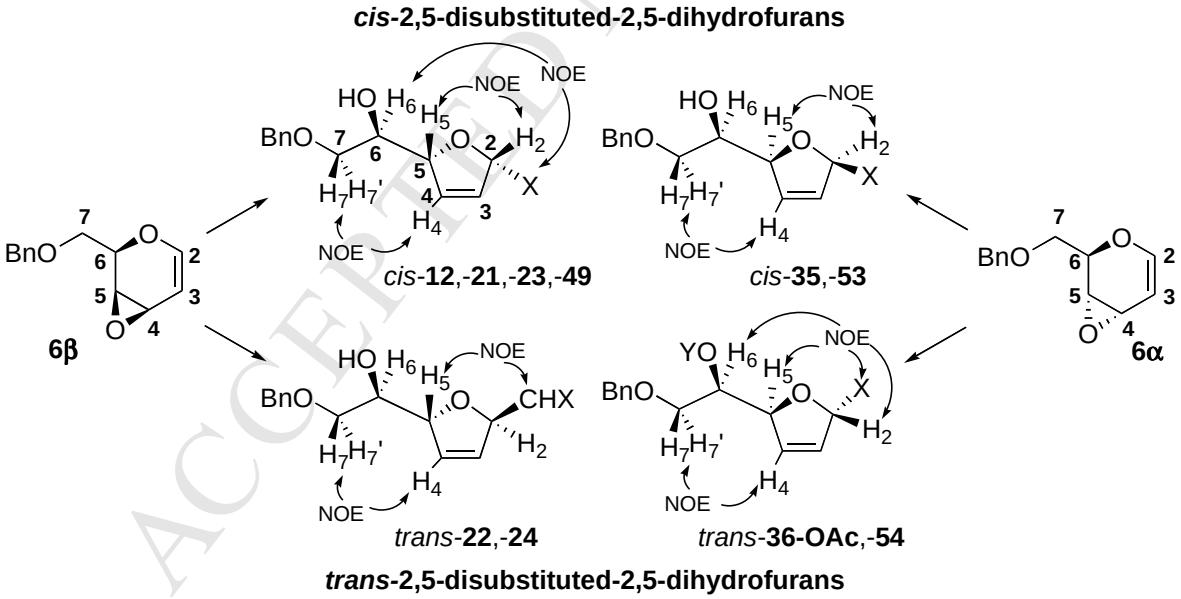


11, 33: X = $(CO_2Me)_2$ Y = H; **13β**: X = CO_2Me, Y = H; **13β-OAc**: X = CO_2Me, Y = Ac;
20: X = HCOPh, Y = PhCO; **25β**: X = $CH(COPh)_2$ Y = H; **34α**: X = $CH(CO_2Me)_2$, Y = H;
34α-OAc: X = $(CO_2Me)_2$, Y = Ac; **34β:** X = $(CO_2Me)_2$, Y = H; **34β-OAc**: X = $CH(CO_2Me)_2$, Y = Ac;
38α: X = $CH(COPh)_2$, Y = H; **38β**: X = $(COPh)_2$, Y = H; **39**: X = HCOPh, Y = PhCO;
52α: X = $NHCO_2Bn$, Y = H.

Scheme 21. NOEs in *3,4-trans-products* and *1,4-cis*- and *1,4-trans-products* from both epoxides **6α** and **6β**. The spatial relationship of methine proton H(5) with two methine protons, vinyl H(4)

and non-vinyl H(6) in the case of *1,4-cis*- and *1,4-trans-products*, and non-vinyl H(6) and H(4) in the case of *3,4-trans-products*, is also shown.

The assessment of five- *vs* six-membered heterocyclic structure relied on the nature of OH scalar couplings, which were detected only in CD_3CN and/or DMSO-d_6. In all 2,5-disubstituted-2,5-dihydrofurans obtained, OH proton showed couplings with methine proton H(6), which was *J*-coupled with non–vinyl methine proton H(5) and methylene protons H(7) and H(7'). On the contrary, in the case of six-membered heterocyclic structures, the corresponding OH proton-coupled methine proton H(5) was *J*-coupled with two methine protons: vinyl H(4) and non-vinyl H(6) protons, in the case of *1,4-cis*- and *1,4–trans-products*, and non-vinyl H(6) and H(4) protons, in the case of *3,4-trans-products*. It is noteworthy that, accordingly to the structural attribution, H(5) proton of five-membered 2,5-dihydrofuran systems was always high-frequencies shifted with respect to H(5) proton in the corresponding six-membered compounds. The same trend was found for the carbon, which is directly connected to it. Furthermore, H(7) and H(7') protons of 2,5-disubstituted-2,5-dihydrofuran compounds originated dipolar interaction with vinyl proton H(4): a similar interaction is not detected in six-membered cyclic structures (Schemes 21 and 22).



cis-**12**: X = $CH(CO_2Me)_2$; *cis*-**21**: X = CH_2COPh; *trans*-**22**: X = HCOPh; *cis*-**23**: X = $CH(COPh)_2$; *trans*-**24**: X = $(COPh)_2$; *cis*-**35**: X = $CH(CO_2Me)_2$; *trans*-**36-OAc**: X = $CH(CO_2Me)_2$, Y = Ac; *cis*-**49**, *cis*-**53**: X = $NHCO_2Bn$; *trans*-**54**: X = $NHCO_2Bn$, Y = H

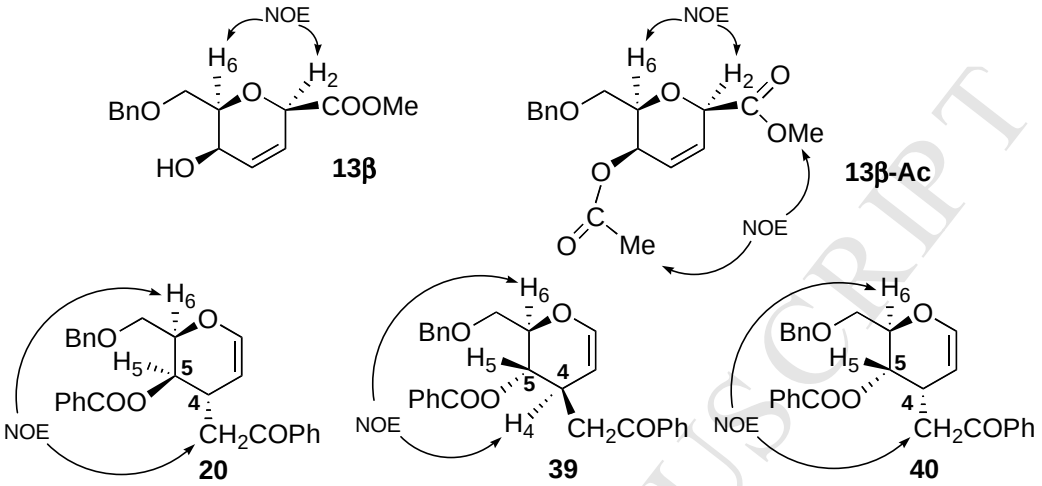
Scheme 22. NOEs in *cis*- and *trans*-2,5-disubstituted-2,5-dihydrofurans from both epoxides **6α** and **6β**. The spatial relationship of proton H(6) with non–vinyl methine proton H(5) and methylene protons H(7) and H(7') is also shown.

The regioisomeric structure of glycal-derived *3,4-trans-products* and *1,4-cis*- and *1,4–trans-products* was ascertained by exploiting the homonuclear scalar couplings starting from the double bond protons, and dipolar interactions produced by substituents present at C(4) and C(6) or C(2) and C(6) for *3,4-trans-products* and *1,4-cis* and *1,4–trans-products*, respectively (Scheme 21). In particular, the following valuable interactions were observed: a) NOE between H(6) proton and CH proton at C(4) in compounds **11** and **20** (*3,4-trans-products* from epoxide **6β**) and between H(6) and H(4) protons in compounds **33** and **39** (*3,4-trans-products* from epoxide **6α**; b) NOE between H(6) and H(2) protons in compounds **13β**, **13β-OAc** and **25β** (*1,4-cis-products* from epoxide **6β**); c) NOE between H(2) and H(7,7'), H(2) and H(5), and H(6) and CH proton at C(2) in compounds **34α**, **34α-OAc**, **38α**, and **52α** (*1,4-cis-products* from epoxide **6α)**; d) NOE between H(6) and H(2) protons in compound **34β**, **34β-OAc** and **38β** (*1,4-trans-products* from epoxide **6α**) (Scheme 21).

The spatial relationship between the two substituents in C(2) and in C(5) of *cis*- and/or *trans*-2,5-disubstituted-2,5-dihydrofurans was established on the basis of the dipolar interactions (NOESY) detected between substituents at C(2) and C(5). In this way, NOE between protons H(2) and H(5), as well, when possible, between H(6) and CH-proton of the substituent chain at C(2) are clearly indicative of a *cis*-arrangement of the involved substituents and as a consequence of the corresponding structure of *cis*-2,5-disubstituted-2,5-dihydrofuran derivative (compounds *cis*-**12**, *cis*-**21**, *cis*-**23** and *cis*-**49** from epoxide **6β** and *cis*-**35** and *cis*-**53** from epoxide **6α**, Scheme 23). In this framework, the presence of NOE between H(5) and CH proton of the side chain at C(2) and between H(2) and H(6) protons are indicative of a *trans*-arrangement of substituents at C(2) and C(5) as a consequence of the corresponding structure of *trans*-2,5-disubstituted-2,5-dihydrofuran derivative (compounds *trans*-**22** and *trans*-**24** from epoxide **6β** and *trans*-**36-OAc** and *trans*-**54** from epoxide **6α**, Scheme 22).

For some compounds, NMR analysis revealed unexpected structural features. In the case of compounds **13β** and **13β-OAc**, only a methoxycarbonyl group directly bound to C(2) carbon was detected on the basis of ^{1}H-^{13}C long range scalar correlation (HMBC) with the endocyclic H(2) proton, adjacent to oxygen. In both compounds, H(2) proton gave rise to a dipolar interaction with H(6) proton, thus defining a *cis*-relationship between substituents at C(2) and

C(6) carbons of the six-membered ring. Moreover, in the case of the acetyl derivative **13β-OAc**, a NOE between methoxy and acetyl protons was found to indicate a *cis*-relationship between all the ring substituents (Scheme 23).



Scheme 23. NOEs in methyl β-glycosylcarboxylate **13β**, correspnding acetate **13β-OAc**, compounds **20** and **39** from epoxides **6β** and **6α**, respectively, and **40** from epoxide **6α.**

The structures of *3,4-trans-products* **20** and **39** and *3,4-cis-product* **40**[38] were even more surprising since the two moieties (PhCO– and $PhCOCH_2$–) deriving from the starting nucleophile [PhCOCH=C(Ph)-O^-] resulted separately connected at two adjacent carbons C(4) and C(5) of the six-membered cyclic system (Scheme 23). As a matter of fact, an additional methylene moiety was detected (–*CH_2*COPh) and the two carbonyl functions (ketone and ester, as revealed by their ^{13}C chemical shifts) showed ^{1}H-^{13}C long range scalar couplings (HMBC) with methylene (C*H_2*COPh) and H(5) protons, respectively. The presence of inter-NOE H(6)-C*H_2*COPh in **20** and **40** and inter-NOE H(6)-H(4) in **39** and all the appropriate considerations about the ring opening process of epoxides **6α** and **6β** (see above) made the assignation of the relative configuration to all substituents in compounds **20**, **39** and **40** possible, as shown in Scheme 23.

3. Conclusions

Highly functionalized, enantiomerically pure 2,5-disubstituted-2,5-dihydrofurans can be obtained by reaction of D-allal- and D-galactal-derived vinyl epoxides **6α** and **6β** with metal

enolates of methylene active compounds, as dimethyl malonate, dibenzoylmethane (*C*-nucleophiles), and lithium anion of benzyl carbamate (*N*-nucleophile). The obtained 2,5-disubstituted-2,5-dihydrofurans are the result of a base-catalyzed rearrangement of corresponding α- and/or β-*C*- and -*N*-glycosides (*1,4-cis* and *1,4-trans-products*), the primary reaction products, with six-membered ring opening followed by ring contraction to five-membered ring. The presence of a sufficiently acid C-H or N-H bond at α-carbon of the glycoside side chain is necessary for the rearrangement process to occur. The relative strength of the intramolecular cation binding occurring in the corresponding folded reaction intermediate conformer and the related *anti*- or *gauche*-butane-like conformation are responsible of the observed stereoselectivity. In this way, a complete or slight *syn*-stereoselectivity is observed when the reaction proceedes only or partially through the folded intermediate conformer, whereas a non-stereoselective result is obtained when the reaction indifferently proceedes through the folded and unfolded intermediate conformer. In this framework epoxide **6β** exclusively leads to corresponding *cis*-2,5-disubstituted-2,5-dihydrofurans with lithium enolate of dimethyl malonate and lithium anion of benzyl carbamate, whereas epoxide **6α** affords, in the same reaction conditions, only 1:1 and 71:29 mixtures of corresponding *cis*- and *trans*-2,5-disubstituted-2,5-dihydrofurans. Due to the weaker intramolecular cation binding involved in the corresponding folded intermediate conformer, the reactions of epoxide **6β** with metal enolates of dibenzoylmethane are not stereoselective and only mixtures of corresponding *cis*- and *trans*-2,5-disubstituted-2,5-dihydrofurans are obtained. The same reaction with epoxide **6α** does not lead to 2,5-dihydrofurans.

4. Experimental

4.1.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. *t*-BuOK, *t*-BuOLi, 1 N LHMDS in THF, dibenzoylmethane, MsCl, Ac_2O, HPLC-grade CH_2Cl_2 and pyridine over molecular sieves were purchased from Aldrich and used without purification. Dimethyl malonate, AcOEt and hexane (Aldrich) were distilled before use. THF (over molecular sieves, Aldrich) and Et_2O were distilled from sodium/benzophenone. D-allal- and D-galactal-derived vinyl epoxides **6α** and **6β** were prepared as previously described.[33a,c-g] Routine ^1H and ^{13}C NMR spectra were recorded at 250 and 62.5 MHz, respectively. ^1H NMR COSY, NOESY and HSQC experiments were performed with a spectrometer operating at 600 MHz. IR spectra were obtained by means of a FTIR spectrophotometer. Elemental analyses were performed at Dipartimento di Farmacia, University of Pisa, by means of Carlo Erba Automated CHN Analyzer model 1106.

*4.2. Reactions of epoxide **6β** with potassium and lithium enolates of dimethyl malonate and dibenzoylmethane*

*4.2.1. Reaction of epoxide **6β** with potassium enolate of dimethyl malonate (**10-K**, by t-BuOK protocol)*

Typical procedure. A solution of dimethyl malonate (0.079 g, 0.60 mmol, 3.0 equiv) in anhydrous THF (1.3 mL) was treated in a Schlenk with *t*-BuOK (0.067 g, 0.60 mmol, 3.0 equiv) and thr reaction mixture was stirred 45 min at room temperature (*Solution A*). In the meantime, a solution of *trans*-hydroxy mesylate **9β** (0.063 g, 0.20 mmol) in anhydrous THF (1.0 mL) was treated in a second Schlenk with *t*-BuOK (0.023 g, 0.20 mmol, 1.0 equiv) and the reaction mixture was stirred at room temperature the time necessary for the cyclization of *trans*-hydroxy mesylate **9β** to epoxide **6β** (15-30 min, TLC) (*Solution B*). *Solution A* was added to *Solution B*. After 24 hours stirring at room temperature, the reaction mixture was partitioned between Et_2O (20 mL) and saturated aqueous NH_4Cl (5 mL) until pH = 4-5 and the organic layer was further washed with brine, dried ($MgSO_4$), and concentrated under vacuum. The reaction mixture was filtered through a silica gel pad eluting first with a 9:1 hexane/AcOEt mixture to remove the

excess of dimethyl malonate, then with AcOEt to obtain a crude consisting of D-gulal derivative **11** (^{1}H NMR) (0.058 g, 83% yield) which was purified by preparative TLC. Elution with a 1:1 hexane/AcOEt mixture afforded pure *dimethyl 2-(1,5-anhydro-6-O-benzyl-2,3-dideoxy-D-xylo-hex-1-enitol-3-yl)propanedioate* (**11**) (0.043 g, 61% yield), as a colourless oil: R_f = 0.41 (1:1 hexane/AcOEt), $[\alpha]_D^{20}$ = –1.8 (*c* 2.0, $CHCl_3$). FTIR (neat) ν 3313, 1731, 1469, 1259, 1179, 1095 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.25-7.39 (m, 5H), 6.47 (dd, 1H, *J* = 6.4, 1.5 Hz), 4.62-4.70 (m, 1H), 4.58 (s, 2H), 3.85-3.96 (m, 2H), 3.81 (d, 1H, *J* = 5.5 Hz), 3.75 (s, 3H), 3.74 (s, 3H), 3.26 (d, 1H, *J* = 10.1 Hz), 2.85-3.00 (m, 2H), 1.57 (**s**, 1H, OH).^{13}C NMR (62.5 MHz, $CDCl_3$) δ 168.3, 167.9, 144.8, 137.5, 128.7, 128.1, 128.0, 98.7, 74.1, 72.4, 70.3, 67.4, 56.5, 52.9, 52.8, 38.2. Anal. Calcd for $C_{18}H_{22}O_7$: C, 61.70; H, 6.33. Found: C, 61.45; H, 6.11.

The same result was observed also when the preformed lithium enolate (from *t*-BuOLi) of dimethyl malonate (**10-Li**) was used. In this case D-gulal derivative **11** was obtained with 79% yield.

*4.2.2. Reaction of epoxide **6β** with lithium enolate of dimethyl malonate (**10-LiHMDS** by LHMDS protocol) in anhydrous THF*

Following the typical procedure, a solution of dimethyl malonate (0.253 g, 1.92 mmol, 3.0 equiv) in anhydrous THF (7.0 mL) was added to 1M LHMDS in THF (1.92 mL, 1.92 mmol, 3.0 equiv) and the reaction mixture was stirred 30 min at room temperature (*Solution A*). A solution of *trans*-hydroxy mesylate **9β** (0.20 g, 0.64 mmol) in anhydrous THF (5.0 mL) was treated with *t*-BuOK (0.072 g, 0.64 mmol, 1.0 equiv) and the reaction mixture was stirred for 15 min at room temperature (*Solution B*). *Solution A* was dropwise added to *Solution A*. After 24 hours stirring at room temperature, usual work-up and filtration (paragraph *4.2.1*) afforded a crude reaction product consisting of a 35:65 mixture of 2-[bis(methoxycarbonyl)methyl]-2,5-dihydrofuran *cis*-**12** and methyl β-glycosylcarboxylate derivative **13β** (^{1}H NMR) (0.151 g, 78% yield) which was subjected to preparative TLC by using a 1:1 hexane/AcOEt mixture, as the eluant. Extraction of the two most intense bands (the faster moving band contained *cis*-**12**) afforded pure 2,5-dihydrofuran *cis*-**12** (0.040 g, 18% yield) and methyl β-glycosylcarboxylate **13β** (0.069 g, 39% yield).[36]

Dimethyl 2-[(1S)-1,4-anhydro-6-O-benzyl-2,3-dideoxy-D-threo-hex-2-enitol-1-C-yl]propanedioate (*cis*-**12**), a colourless oil; R_f = 0.45 (6:4 hexane/AcOEt). $[\alpha]_D^{20}$ = –65.6 (*c* 0.36, $CHCl_3$). FTIR (neat) ν 3308, 1730, 1455, 1259, 1178 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.25-

7.45 (m, 5H), 6.08 (d, 1H, *J* = 6.5 Hz), 5.92 (d, 1H, *J* = 6.5 Hz), 5.30-5.41 (m, 1H), 4.88-4.96 (m, 1H), 4.58 (s, 2H), 3.81 (s, 3H), 3.79 (s, 3H), 3.65-3.86 (m, 2H), 3.58 (d, 2H, *J* = 6.4 Hz), 2.58 (bs, 1H, OH). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 168.0, 167.5, 138.2, 129.4, 129.1, 128.6, 127.9, 127.8, 87.2, 84.0, 73.7, 71.6, 71.5, 57.9, 52.9, 52.8. Anal. Calcd for $C_{18}H_{22}O_7$: C, 61.70; H, 6.33. Found: C, 61.49; H, 6.06.

Methyl 2,6-anhydro-7-O-benzyl-3,4-dideoxy-D-xylo-hept-3-enonate (**13β**), a colourless oil; R_f = 0.42 (6:4 hexane/AcOEt). $[\alpha]_D^{20}$ = –13.7 (*c* 1.34, $CHCl_3$). FTIR (neat) ν 3543, 1736, 1435, 1263, 1229 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.26-7.39 (m, 5H), 6.41 (d, 1H, *J* = 10.3 Hz), 5.96 (ddd, 1H, *J* = 10.4, 5.7, 2.3 Hz), 4.99 (s, 1H), 4.51 (s, 2H), 3.80-3.89 (m, 1H), 3.65-3.79 (m, 5H), 3.54-3.62 (m, 1H), 1.52-1.69 (bs, 1H, OH). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 167.1, 132.2, 128.5, 127.9, 127.7, 127.5, 125.9, 77.9, 76.4, 73.4, 70.3, 62.5, 52.7. Anal. Calcd for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52. Found: C, 64.53; H, 6.19.

*4.2.3. Acetylation of methyl β-glycosylcarboxylate **13β** by Ac_2O/Py protocol*

A solution of methyl β-glycosylcarboxylate **13β** (0.031 g, 0.11 mmol) in dry pyridine (0.6 mL) was dropwise treated with Ac_2O (0.4 mL) at 0 °C. After 18 hours stirring at the same temperature, the reaction mixture was co-evaporated with toluene (several times) to give a reaction product (0.029 g, 82% yield) consisting of *methyl 2,6-anhydro-5-O-acetyl-7-O-benzyl-3,4-dideoxy-D-xylo-hept-3-enonate* (**13β-OAc**),[36] practically pure as a colourless oil: R_f = 0.62 (1:1 hexane/AcOEt). $[\alpha]_D^{20}$ = –54.7 (*c* 0.58, $CHCl_3$). FTIR (neat) ν 1735, 1433, 1227 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.24-7.42 (m, 5H), 6.40 (dd, 1H, *J* = 10.5, 1.1 Hz), 5.86 (ddd, 1H, *J* = 10.3, 5.4, 2.3 Hz), 4.91-5.01 (m, 2H), 4.55 (d, 1H, *J* = 12.1 Hz), 4.44 (d, 1H, *J* = 12.1 Hz), 3.83-3.93 (m, 1H), 3.68 (s, 3H), 3.50-3.60 (m, 2H), 1.92 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 170.5,167.6, 138.1, 133.8, 128.9, 127.8, 127.1, 126.9, 76.3, 76.0, 75.6, 69.2, 64.9, 51.8, 21.3. Anal. Calcd for $C_{17}H_{20}O_6$: C, 63.74; H, 6.29. Found: C, 63.49; H, 6.32.

*4.2.4. Reaction of epoxide **6β** with potassium enolate of dibenzoylmethane (**19-K** by t-BuOK protocol) in anhydrous THF*

Following the typical procedure, a suspension of *t*-BuOK (0.108 g, 0.96 mmol, 3 equiv) in anhydrous THF (3.0 mL) was treated with dibenzoylmethane (0.216 g, 0.96 mmol, 3 equiv) and the reaction mixture was stirred at room temperature for 45 min (*Solution A*). *t*-BuOK (0.036 g, 0.32 mmol, 1.0 equiv) was added to a solution of *trans*-hydroxy mesylate **9β** (0.100 g, 0.32

mmol) in anhydrous THF (3.0 mL) (*Solution B*). After 15 min stirring at room temperature *Solution A* was added dropwise to *Solution B* and the reaction mixture was stirred at room temperature for 18 hours. Usual work-up afforded a crude mixture which was filtered through a silica gel pad eluting first with a 95:5 hexane/AcOEt mixture to remove the excess of dibenzoylmethane, then with AcOEt to obtain a crude product consisting of a 55:23:22 mixture of D-gulal-derivative **20** and 2-(benzoylmethyl)-2,5-dihydrofurans *cis*-**21** and *trans*-**22** (^{1}H NMR) (0.096 g, 77% yield) which was subjected to preparative TLC, by eluting with a 7:3 hexane/AcOEt mixture (three runs). Extraction of the three most intense moving bands afforded D-gulal-derivative **20** (0.047 g, 33% yield) (the fastest one), and 2,5-dihydrofurans *cis*-**21** (0.015 g, 14% yield) (the slowest one) and *trans*-**22** (0.013 g, 12% yield) (^{1}H NMR).

4-O-Benzoyl-6-O-benzyl-2,3-dideoxy-3-C,5-O-[(Z)-ethene-1,2-diyl]-1-C-phenyl-D-lyxo-hexose (**20)**, a colourless oil. R_f = 0.22 (9:1 hexane/AcOEt); $[\alpha]_D^{20}$ = +92.1 (*c* 0.96, $CHCl_3$). FTIR (neat) ν 1708, 1683, 1598, 1450, 1261, 1087, 1024, 798 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.91-8.08 (m, 4H), 7.38-7.65 (m, 6H), 7.17-7.36 (m, 5H), 6.50 (d, 1H, *J* = 5.9 Hz), 5.26-5.32 (m, 1H), 4.83-4.92 (m, 1H), 4.61 (d, 1H, *J* = 12.0 Hz), 4.49 (d, 1H, *J* = 12.0 Hz), 4.23 (t, 1H, *J* = 6.0 Hz), 3.62-3.83 (m, 2H), 3.00-3.26 (m, 2H), 2.91-3.00 (m, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 197.3, 165.8, 143.2, 137.7, 136.9, 133.4, 133.3, 129.9, 129.9, 128.8, 128.6, 128.5, 128.2, 128.0, 127.9, 102.0, 73.8, 72.1, 70.1, 69.0, 44.3, 31.9. Anal. Calcd for $C_{28}H_{26}O_5$: C, 76.00; H, 5.92**.** Found: C, 75.74; H, 5.67.

3,6-Anhydro-8-O-benzyl-2,4,5-trideoxy-1-C-phenyl-D-lyxo-oct-4-enose (*cis*-**21**), a pale yallow oil. R_f = 0.48 (1:1 hexane/AcOEt); $[\alpha]_D^{20}$ = +93.8 (*c* 0.11, $CHCl_3$). FTIR (neat) ν 3485, 1732, 1682, 1452, 1259, 1089, 800, 748, 696 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.93-8.00 (m, 2H), 7.53-7.59 (m, 1H), 7.42-7.51 (m, 2H), 7.29-7.35 (m, 5H), 6.05 (d, 1H, *J* = 7.0 Hz), 5.83 (d, 1H, *J* = 4.6 Hz), 5.31-5.42 (m, 1H), 4.84-4.90 (m, 1H), 4.54 (s, 2H), 3.73-3.82 (m, 1H), 3.50-3.57 (m, 2H), 3.42 (dd, 1H, *J* = 16.1, 6.7 Hz), 3.15 (dd, 1H, *J* = 16.1, 6.7 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 199.6, 138.1, 136.9, 133.5, 131.6, 128.9, 128.8, 128.5, 127.9, 127.8, 127.5, 86.9, 82.8, 73.6, 72.2, 71.6, 45.4. Anal. Calcd for $C_{21}H_{22}O_4$: C, 74.53; H, 6.55. Found: C, 74.38; H, 6.41.

3,6-Anhydro-8-O-benzyl-2,4,5-trideoxy-1-C-phenyl-D-xylo-oct-4-enose (*trans*-**22**), a yellow oil. R_f = 0.39 (1:1 hexane/AcOEt); $[\alpha]_D^{20}$ = +172.4 (*c* 0.58, $CHCl_3$). FTIR (neat) ν 3422, 1721, 1682, 1599, 1452, 1273, 1156, 1094, 1025, 819, 750, 698 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.92-8.01 (m, 2H), 7.52-7.62 (m, 1H), 7.42-7.51 (m, 2H), 7.27-7.39 (m, 5H), 6.08 (d, 1H, *J* = 6.1 Hz), 5.83 (d, 1H, *J* = 5.9 Hz), 5.43 (dd, 1H, *J* = 12.6, 6.8 Hz), 4.91 (t, 1H, *J* = 5.1 Hz), 4.55 (s,

2H), 3.74-3.85 (m, 1H), 3.54-3.62 (m, 1H), 3.46-3.54 (m. 1H), 3.42 (dd, 1H, *J* = 16.4, 6.9 Hz), 3.09 (dd, 1H, *J* = 16.4, 6.9 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 198.2, 138.2, 137.1, 133.5, 131.9, 129.0, 128.8, 128.6, 128.4, 127.9, 127.4, 86.6, 82.8, 73.7, 72.6, 71.4, 45.2. ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 198.6, 138.7, 137.0, 133.5, 131.1, 129.5, 129.0, 128.4, 128.4, 127.9, 127.6, 86.9, 82.5, 72.5, 71.8, 71.4, 44.9. Anal. Calcd for $C_{21}H_{22}O_4$: C, 74.53; H, 6.55. Found: C, 74.16; H, 6.21.

4.2.5. Reaction of epoxide ***6β*** *with lithium enolate of dibenzoylmethane (****19-LiHMDS*** *by LHMDS protocol)*

Following the typical procedure, a solution of dibenzoylmethane (0.080 g, 0.36 mmol, 3 equiv) in anhydrous THF (1.5 mL) was treated with 1M LHMDS in anhydrous THF (0.36 mL, 0.36 mmol, 3 equiv) at -78 °C and the reaction mixture was stirred for 30 min at the same temperature, then at 0 °C for further 30 min (*Solution A*). *t*-BuOK (0.013 g, 0.12 mmol, 1 equiv) was added to a solution of *trans*-hydroxy mesylate **9β** (0.038 g, 0.12 mmol) in anhydrous THF (1.5 mL) and the reaction mixture was stirred 15 min at room temperature (*Solution B*). *Solution A* was added dropwise to *Solution B* at 0 °C and the reaction mixture was stirred at the same temperature for 3 hours. Usual-work-up and filtration (see paragraph *4.2.4*) afforded a crude reaction product consisting of a 60:40 mixture of 2-(dibenzoylmethyl)-2,5-dihydrofurans *cis*-**23** and *trans*-**24** (^{1}H NMR) (0.039 g, 74% yield) which was subjected to preparative TLC by eluting with a 7:3 hexane/AcOEt mixture (three runs). Extraction of the most intense band afforded, again, a 60:40 mixture of 2,5-dihydrofurans *cis*-**23** and *trans*-**24** (0.028 g, 53% yield) which turned out to be inseparable also under other chromatographic conditions appropriately tried. However, accurate ^{1}H NMR analysis of the mixture of 2,5-dihydrofurans *cis*-**23** and *trans*-**24** made the assignement of the corresponding signals to each component of the mixture possible.

2-(Dibenzoylmethyl)-2,5-dihydrofuran cis-**23**: R_f = 0.35 (1:1 hexane/AcOEt); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.03-8.13 (m,2H), 7.84-8.03 (m, 3H), 7.23-7.62 (m, 10H), 6.09 (ddd, 1H, *J* = 6.2, 2.4, 1.5 Hz), 5.84-5.89 (m, 1H), 5.72-5.81 (m, 1H), 5.65 (d, 1H, *J* = 8.5 Hz), 4.78-4.84 (m, 1H), 4.43 (s, 2H), 3.70-3.81 (m, 1H), 3.32-3.43 (m, 2H) 2.41 (bs, 1H, OH).

2-(Dibenzoylmethyl)-2,5-dihydrofuran trans-**24**: R_f = 0.35 (1:1 hexane/AcOEt); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.03-8.13 (m, 2H), 7.84-8.03 (m, 3H), 7.23-7.62 (m, 10H), 6.14 (ddd, 1H, *J* = 6.2, 2.4, 1.5 Hz), 5.83-5.86 (m, 1H), 5.80-5.83 (m, 1H), 5.61 (d, 1H, *J* = 6.9 Hz), 4.68-4.74 (m, 1H), 4.48 (s, 2H), 3.70-3.81 (m, 1H), 3.43-3.48 (m, 2H), 2.32 (bs, 1H, OH).

*4.2.6. Reaction of epoxide **6β** with lithium enolate of dibenzoylmethane (**19-Li** by t-BuOK/t-BuOLi protocol) in anhydrous THF*

Following the typical procedure, a suspension of *t*-BuOLi (0.077 g, 0.96 mmol, 3 equiv) in anhydrous THF (3.0 mL) was treated with dibenzoylmethane (0.214 g, 0.96 mmol, 3 equiv) and the reaction mixture was srirred at room temperature for 45 min (*Solution A*). *t*-BuOK (0.036 g, 0.32 mmol, 1 equiv) was added to a solution of *trans*-hydroxy mesylate **9β** (0.100 g, 0.32 mmol) in anhydrous THF (3.0 mL) and the reaction mixture was stirred 15 min at room temperature (*Solution B*). *Solution A* was added dropwise to *Solution B* and the reaction mixture was stirred at room temperature for 18 hours. Usual work-up and filtration (see paragraph *4.2.4*) afforded a crude reaction product consisting of a 26:44:30 mixture of β-*C*-glycoside **25β** and 2-(dibenzoylmethyl)-2,5-dihydrofurans *cis*-**23** and *trans*-**24** (0.107 g, 76% yield) which was subjected to preparative TLC, by eluting with a 7:3 hexane/AcOEt mixture (three runs). Extraction of the most intense bands afforded β-*C*-glycoside **25β** (0.016 g, 11% yield) and an inseparable mixture of 2,5-dihydrofurans *cis*-**23** and *trans*-**24** (0.064 g, 45% yield).

2-Benzoyl-3,7-anhydro-8-O-benzyl-2,4,5-trideoxy-1-C-phenyl-D-xylo-oct-4-enose (**25β**), a pale yellow liquid. R_f = 0.21 (1:1 hexane/AcOEt); $[\alpha]_D^{20}$ = +75.4 (*c* 0.65, $CHCl_3$). FTIR (neat) ν 3447, 1695, 1597, 1451, 1334, 1269, 1199, 1096, 750, 698 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 7.91-8.01 (m, 3H), 7.20-7.62 (m, 12H), 6.04-6.08 (m, 2H), 5.65 (d, 1H, *J* = 6.4 Hz), 5.15 (d, 1H, *J* = 6.5 Hz), 4.46 (s, 2H), 3.73-3.82 (m, 2H), 3.48-3.63 (m, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 194.5, 194.4, 138.2, 136.8, 136.5, 134.0, 133.7, 131.7, 129.2, 128.9, 128.8, 128.7, 128.5, 127.8, 75.0, 73.7, 70.2, 62.8, 60.4, 53.6. Anal. Calcd for $C_{28}H_{26}O_5$: C, 76.00; H, 5.92. Found: C, 75.93; H, 5.64.

*4.2.7. Treatment of β-C-glycoside **25β** with t-BuOK in anhydrous THF*

A solution of β-*C*-glycoside **25β** (0.016 g, 0.036 mmol) in anhydrous THF (1.0 mL) was treated with *t*-BuOK (0.008 g, 0.072 mmol, 2 equiv) and the reaction mixture was stirred at room temperature for 3 hours. Dilution with Et_2O and evaporation of the washed (brine) organic solution afforded a crude product (0.010 g, 82% yield), consisting of an almost 1:1 mixture of 2-(benzoylmethyl)-2,5-dihydrofurans *cis*-**21** and *trans*-**22** (^1H NMR).

*4.3. Reactions of epoxide **6α** with potassium and lithium enolates of dimethyl malonate and dibenzoylmethane*

*4.3.1. Reaction of epoxide **6α** with potassium enolate of dimethyl malonate (**10-K** by t-BuOK protocol) in anhydrous THF*

Following the typical procedure, a suspension of *t*-BuOK (0.22 g, 0.20 mmol, 3 equiv) in anhydrous THF (1.0 mL) was treated with dimethyl malonate (0.026 g, 0.20 mmol, 3 equiv) and the reaction mixture was stirred at room temperature for 45 min (*Solution A*). *t*-BuOK (0.075 g, 0.066 mmol, 1 equiv) was added to a solution of *trans*-hydroxy mesylate **9α** (0.021 g, 0.066 mmol) in anhydrous THF (1.0 mL) and the reaction mixture was stirred 15 min at room temperature (*Solution B*). *Solution A* was added dropwise to *Solution B* and the reaction mixture was stirred at room temperature for 18 hours. Usual work-up and filtration (see paragraph *4.2.1*) afforded a crude reaction product consisting of D-glucal derivative **33** (0.018 g, 78% yield) which was purified by preparative TLC, by eluting with a 1:1 hexane/AcOEt mixture. Extraction of the most intense band afforded *dimethyl 2-(1,5-anhydro-6-O-benzyl-2,3-dideoxy-D-arabino-hex-1-enitol-3-yl)propanedioate* (**33**) (0.015 g, 65% yield) as a colourless oil: R_f =0.42 (1:1 hexane/AcOEt); $[\alpha]_D^{20}$ = –53.4 (*c* 0.55, $CHCl_3$). FTIR (neat) ν 3505, 1730, 1051, 734, 698 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 7.22-7.47 (m, 5H), 6.34 (dd, 1H, *J* = 6.0, 2.1 Hz), 4.62 (dd, 1H, *J* = 6.0, 2.1 Hz), 4.65 (d, 1H, *J* = 12.0 Hz), 4.55 (d, 1H, *J* = 12.0 Hz), 3.70-3.89 (m, 3H), 3.74 (s, 6H), 3.63 (d, 1H, *J* = 6.2 Hz), 2.92-3.12 (m, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 169.4, 168.9, 144.2, 137.7, 128.7, 128.1, 128.0, 99.9 73.9, 70.1, 67.8, 60.6, 53.6, 52.8, 52.7, 40.5. Anal. Calcd for $C_{18}H_{22}O_7$: C, 61.70; H, 6.33. Found: C, 61.38; H, 6.07.

*4.3.2. Reaction of epoxide **6α** with lithium enolate of dimethyl malonate (**10-Li** by t-BuOK/t-BuOLi protocol) in anhydrous THF*

Following the typical procedure, a solution of *t*-BuOLi (0.153 g, 1.91 mmol, 3 equiv) in anhydrous THF (6.0 mL) was treated with dimethyl malonate (0.252 g, 1.91 mmol, 3 equiv) and the reaction mixture was stirred at room temperature for 45 min (*Solution A*). *t*-BuOK (0.071 g, 0.636 mmol, 1 equiv) was added to a solution of *trans*-hydroxy mesylate **9α** (0.200 g, 0.636 mmol) in anhydrous THF (6.0 mL) and the reaction mixture was stirred 15 min at room temperature (*Solution B*). *Solution A* was added dropwise to *Solution B* and the reaction mixture was stirred at room temperature for 18 hours. Usual work-up and filtration (see paragraph *4.2.1*) afforded a crude reaction product consisting of an 1:1 mixture of 2-[bis(methoxycarbonyl)methyl]-2,5-dihydrofurans *cis*-**35** (31%) and *trans*-**36** (31%), accompanied by a 1:1.5 mixture of diastereoisomeric α- **34α** and β-*C*-glycoside **34β** (38%, ^1H NMR) (0.167 g, 75% yield) which was subjected to preparative TLC by eluting with a 7:3

hexane/AcOEt mixture (three runs). Extraction of the faster moving band afforded pure *dimethyl 2-[(1R)-1,4-anhydro-6-O-benzyl-2,3-dideoxy-D-erythro-hex-2-enitol-1-C-yl]propanedioate* (*cis*-**35**) (0.035 g, 16% yield), as a colourless oil. R_f = 0.33 (1:1 hexane/AcOEt); $[\alpha]_D^{20}$ = –78.6 (*c* 0.26, $CHCl_3$). FTIR (neat) ν 3461, 1732, 1436, 1256, 1197, 1153, 1070, 1026, 795 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 7.26-7.39 (m, 5H), 6.03 (d, 1H, *J* = 6.5 Hz), 6.00 (d, 1H, *J* = 6.5 Hz), 5.27-5.34 (m, 1H), 4.77-4.83 (m, 1H), 4.57 (d, 1H, *J* = 12.0 Hz), 4.52 (d, 1H, *J* = 12.0 Hz), 3.76-3.82 (m, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.49-3.63 (m, 3H), 2.75 (d, 1H, *J* = 4.4 Hz, OH). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 167.8, 167.4, 138.0, 129.4, 129.2, 128.6, 127.9, 127.8, 87.7, 83.9, 73.6, 72.5, 71.1, 58.0, 52.8, 52.7. Anal. Calcd for $C_{18}H_{22}O_7$: C, 61.70; H, 6.33. Found: C, 61.33; H, 6.01**.**

The extraction of the slower moving band afforded a 40:34:20 mixture of 2,5-dihydrofuran *trans*-**36**, β- **34β** and α-*C*-glycoside **34α** (0.088 g) (^1H NMR) which was dissolved in anhydrous pyridine (3.0 mL) and treated at 0 °C with Ac_2O (1.6 mL). After 18 hours stirring at the same temperature, the reaction mixture was co-evaporated with toluene (several times) affording a crude product (0.095 g) consisting of a corresponding mixture of *O*-acetyl derivatives *trans*-**36-OAc**, **34β-OAc** and **34α-OAc** which was subjected to preparative TLC by eluting with a 7:3 hexane/AcOEt mixture (three runs). Extraction of the faster moving band afforded a 1:2 mixture of α- **34α-OAc** and β-*C*-glycoside **34β-OAc** (0.033 g, 13% yield)), whereas extraction of the slower moving band afforded pure *dimethyl 2-[(1S)-1,4-anhydro-5-O-acetyl-6-O-benzyl-2,3-dideoxy-D-erythro-hex-2-enitol-1-C-yl]propanedioate* (*trans*-**36-OAc**) (0.028 g, 11% yield), as a colourless liquid. R_f = 0.45 (1:1 hexane/AcOEt); $[\alpha]_D^{20}$ = –32.9 (*c* 0.28, $CHCl_3$). FTIR (neat) ν 1750, 1739, 1454, 1437, 1372, 1238, 1082, 1026, 912, 800, 739 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 7.28-7.39 (m, 5H), 6.01-6.07 (m, 1H), 5.92-5.99 (m, 1H), 5.31-5.39 (m, 1H), 4.98-5.09 (m, 2H), 4.55 (d, 1H, *J* = 12.3 Hz), 4.48 (d, 1H, *J* = 12.3 Hz), 3.76 (s, 3H), 3.73 (s, 3H), 3.60-3.67 (m, 2H), 3.57 (d, 1H, *J* = 7.3 Hz), 2.08 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 173.2, 169.0, 168.0, 133.5, 129.5, 128.9, 128.6, 127.8, 127.7, 85.5, 84.7, 74.2, 73.4, 68.5, 57.4, 52.8, 52.7, 21.2. Anal. Calcd for $C_{20}H_{24}O_8$: C, 61.22; H, 6.16. Found: C, 60.94; H, 5.75.

Accurate ^1H NMR analysis of the mixture of *O*-acetylated *C*-glycosides **34α-OAc** and **34β-OAc** made the assignation of the corresponding signals to each component of the mixture possible:

α-C-glycoside **34α-OAc**: R_f = 0.48 (1:1 hexane/AcOEt). ^1H NMR (600 MHz, $CDCl_3$) δ 7.24-7.36 (m, 5H), 6.04 (ddd, 1H, *J* = 10.5, 2.7, 1.6 Hz), 5.87 (dt, 1H *J* = 10.5, 2.2 Hz), 5.29 (m, 1H),

4.87 (m, 1H), 4.58 (d, 1H, *J* = 11.9 Hz), 4.48 (d, 1H, *J* = 11.9 Hz), 3.86 (dt, 1H, *J* = 7.1, 4.4 Hz), 3.77 (d, 1H, *J* = 10.1 Hz), 3.70 (s, 6H), 3.54 (d, 2H, *J* = 4.4 Hz), 1.99 (s, 3H).

β-C-glycoside **34β-OAc**: R_f = 0.48 (1:1 hexane/AcOEt). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24-7.36 (m, 5H), 5.98 (dt, 1H, *J* = 10.4, 1.8 Hz), 5.81 (dt, 1H *J* = 10.4, 2.2 Hz), 5.29 (m, 1H), 4.82 (m, 1H), 4.57 (d, 1H, *J* = 11.9 Hz), 4.53 (d, 1H, *J* = 11.9 Hz), 3.74 (ddd, 1H, *J* = 8.8, 5.7, 2.8 Hz), 3.74 (s, 6H), 3.59 (d, 1H, *J* = 9.0 Hz), 3.59 (dd, 1H, *J* = 11.2, 2.8 Hz), 3.55 (dd, 1H, *J* = 11.2, 5.7 Hz), 1.99 (s, 3H).

*4.3.3. Reaction of epoxide **6α** with potassium enolate of dibenzoylmethane (**19-K** by t-BuOK protocol) in anhydrous THF*

Following the typical procedure, a suspension of *t*-BuOK (0.054 g, 0.48 mmol, 3 equiv) in anhydrous THF (1.5 mL) was treated with dibenzoylmethane (0.108 g, 0.48 mmol, 3 equiv) and the reaction mixture was stirred at room temperature for 45 min (*Solution A*). *t*-BuOK (0.018 g, 0.16 mmol, 1 equiv) was added to a solution of *trans*-hydroxy mesylate **9α** (0.050 g, 0.16 mmol) and the reaction mixture was stirred 15 min at room temperature (*Solution B*). *Solution A* was added dropwise to *Solution B* and the reaction mixture was stirred at room temperature for 18 hours. Usual work-up and filtration (see paragraph *4.2.4*) afforded a crude reaction product consisting of a mixture of α-*C*-glycoside **38α** (68%), D-glucal-derivative **39** (15%), and D-allal-derivative **40** (17%) (^{1}H NMR) (0.055 g, 78% yield) which was subjected to preparative TLC, by eluting with a 7:3 hexane/AcOEt mixture (three runs). Extraction of the faster, intermediate and slower moving bands afforded D-glucal-derivative **39** (0.005 g, 7% yield), D-allal-derivative **40** (0.006 g, 8% yield) and α-*C*-glycoside **38α** (0.026 g, 37% yield).

2-Benzoyl-3,7-anhydro-8-O-benzyl-2,4,5-trideoxy-1-C-phenyl-D-arabino-oct-4-enose (**38α**), a pale yellow oil. R_f = 0.21 (1:1 hexane/AcOEt); $[\alpha]_D^{20}$ = –85.6 (*c* 0.45, $CHCl_3$). FTIR (neat) ν 3456, 1693, 1667, 1596, 1449, 1269, 1100, 736, 688 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.93-8.05 (m, 3H), 7.16-7.65 (m, 12H), 5.99 (ddd, 1H, *J* = 10.5, 2.1, 1.4 Hz), 5.91 (dt, 1H, *J* = 10.5, 2.1 Hz), 5.73 (d, 1H, *J* = 9.1 Hz), 5.32 (dd, 1H, *J* = 4.2, 2.1 Hz), 5.28 (dd, 1H, *J* = 4.2, 2.1 Hz), 4.51 (d, 1H, *J* = 11.8 Hz), 4.39 (d, 1H, *J* = 11.8 Hz), 4.13 (d, 1H, *J* = 5.5 Hz), 3.72 (q, 1H, *J* = 6.6 Hz), 3.21-3.41 (m, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 193.6, 193.5, 142.4, 137.6, 136.9, 136.6, 134.0, 133.6, 132.6, 129.6, 129.1, 128.9, 128.7, 128.5, 127.9, 127.3, 73.8, 73.1, 72.7, 70.9, 65.9, 60.0. Anal. Calcd for $C_{28}H_{26}O_5$: C, 76.00; H, 5.92. Found: C, 75.74; H, 5.67.

4-O-Benzoyl-6-O-benzyl-2,3-dideoxy-3-C,5-O-[(Z)-ethene-1,2-diyl]-1-C-phenyl-D-ribo-hexose (**39**), a colourless liquid. R_f = 0.45 (1:1 hexane/AcOEt). $[\alpha]_D^{20}$ = –72.6 (*c* 0.30, $CHCl_3$).

FTIR (neat) ν 1720, 1684, 1451, 1265, 1108, 1026, 711, 689 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 7.83-8.03 (m, 3H), 7.12-7.64 (m, 12H), 6.41 (dd, 1H, *J* = 5.8, 2.1 Hz), 5.35 (dd, 1H, *J* = 17.4, 8.0 Hz), 4.72 (dd, 1H, *J* = 5.8, 2.1 Hz), 4.53 (d, 1H, *J* = 12.0 Hz), 4.43 (d, 1H, *J* = 12.0 Hz), 4.10-4.26 (m, 1H), 3.67 (d, 2H, *J* = 4.1 Hz), 3.15-3.35 (m, 2H), 3.01 (dd, 1H, *J* = 16.9, 9.7 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 199.4, 168.9, 144.2, 137.7, 133.2, 132.8, 128.7, 128.6, 128.3, 128.1, 128.0, 127.8, 99.9, 77.0, 73.9, 70.0, 67.8, 40.5, 32.1. Anal. Calcd for $C_{28}H_{26}O_5$: C, 76.00; H, 5.92. Found: C, 76.12; H, 5.73.

4-O-Benzoyl-6-O-benzyl-2,3-dideoxy-3-C,5-O-[(Z)-ethene-1,2-diyl]-1-C-phenyl-D-arabino-hexose (**40**), a colourless liquid. R_f = 0.36 (1:1 hexane/AcOEt). $[\alpha]_D^{20}$ = –52.3 (*c* 0.2, $CHCl_3$). FTIR (neat) ν 1719, 1685, 1450, 1264, 1096, 1025 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 7.76-7.97 (m, 3H), 7.15-7.62 (m, 12H), 6.41 (dd, 1H, *J* = 6.2, 2.0 Hz), 5.53 (dd, 1H, *J* = 6.2, 5.1 Hz), 4.74 (ddd, 1H, *J* = 6.2, 3.5, 0.5 Hz), 4.61 (s, 2H), 4.35-4.44 (m, 1H), 3.71 (dd, 2H, *J* = 5.1, 2.5 Hz), 3.32-3.44 (m, 1H), 3.24 (dd, 1H, *J* = 17.0, 6.3 Hz), 2.96 (dd, 1H, *J* = 17.0, 7.5 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 198.1, 168.0, 133.3, 133.2, 133.1, 129.8, 129.7, 128.6, 128.4, 128.2, 127.9, 127.8, 124.9, 100.2, 73.7, 71.9, 71.3, 70.4, 39.3, 31.2. Anal. Calcd for $C_{28}H_{26}O_5$: C, 76.00; H, 5.92. Found: C, 75.81; H, 5.68.

*4.3.4. Reaction of epoxide **6α** with lithium enolate of dibenzoylmethane (**19-Li** by t-BuOK/t-BuOLi protocol) in anhydrous THF*

Following the typical procedure, a suspension of *t*-BuOLi (0.031 g, 0.39 mmol, 3 equiv) in anhydrous THF (1.2 mL) was treated with dibenzoylmethane (0.087 g, 0.39 mmol, 3 equiv) and the reaction mixture was stirred at room temperature for 45 min (*Solution A*). *t*-BuOK (0.015 g, 0.13 mmol, 1 equiv) was added to a solution of *trans*-hydroxy mesylate **9α** (0.041 g, 0.13 mmol) and the reaction mixture was stirred 15 min at room temperature (*Solution B*). *Solution A* was added dropwise to *Solution B* and the reaction mixture was stirred at room temperature for 18 hours. Usual work-up and filtration (see paragraph *4.2.4*) afforded a crude reaction product consisting of a mixture of β-*C*-glycoside **38β** (85%) and D-allal-derivative **40** (15%) (^1H NMR) (0.046 g, 80% yield) which was subjected to preparative TLC, by eluting with a 7:3 hexane/AcOEt mixture (three runs). Extraction of the faster moving band afforded pure D-allal-derivative **40** (0.006 g, 10% yield), whereas extraction of the slower moving band afforded pure *2-benzoyl-3,7-anhydro-8-O-benzyl-2,4,5-trideoxy-1-C-phenyl-D-ribo-oct-4-enose* (**38β**) (0.035 g, 61% yield), as a pale yellow oil. R_f = 0.42 (1:1 hexane/AcOEt); $[\alpha]_D^{20}$ = +105.6 (*c* 0.54, $CHCl_3$). FTIR (neat) ν 3458, 1692, 1669, 1596, 1580, 1448, 1271, 1098, 1069, 908, 732, 689 cm^{-1}. ^1H

NMR (250 MHz, $CDCl_3$) δ 7.89-7.97 (m, 4H), 7.48-7.59 (m, 2H), 7.27-7.47 (m, 7H), 7.17-7.24 (m, 2H), 5.95 (ddd, 1H, *J* = 10.5, 1.8, 1.4 Hz), 5.79-5.86 (m, 1H), 5.50 (d, 1H, *J* = 8.1 Hz), 5.18-5.25 (m, 1H), 4.43 (s, 2H), 4.06-4.14 (m, 1H), 3.43-3.65 (m, 3H), 2.47 (bs, 1H, OH).^{13}C NMR (62.5 MHz, $CDCl_3$) δ 194.3, 193.7, 137.9, 137.1, 136.5, 133.8, 133.4, 130.6, 130.2, 129.1, 128.9, 128.7, 128.6, 128.0, 127.9, 127.7, 77.4, 75.2, 73.8, 71.5, 66.0, 61.3. Anal. Calcd for $C_{28}H_{26}O_5$: C, 76.00; H, 5.92. Found: C, 75.73; H, 5.81.

4.3.5. Treatment of α- ***38α*** *and β-C-glycoside* ***38β*** *with t-BuOK in anhydrous THF*

A solution of β-*C*-glycoside **38β** (0.035 g, 0.079 mmol) in anhydrous THF (1.0 mL) was treated with *t*-BuOK (0.018 g, 0.16 mmol, 2 equiv) and the reaction mixture was stirred at room temperature for 3 hours. Dilution with Et_2O and evaporation of the washed (brine) organic solution afforded a crude product consisting of complex reaction mixture which was not furtherly examined.

The same result was obtained also when the same reaction was repeated with the diastereoisomeric α-*C*-glycoside **38α**, under the same reaction conditions.

4.4. Reaction of epoxides ***6α*** *and* ***6β*** *with lithium anion of benzyl carbamate*

4.4.1. Reaction of epoxide ***6β*** *with lithium anion of benzyl carbamate (****45-LiHMDS*** *by LHMDS protocol) in anhydrous THF*

Following the typical procedure, a solution of benzyl carbamate (0.059 g, 0.39 mmol, 3 equiv) in anhydrous THF (2.5 mL) was treated with 1M LHMDS (0.39 mL, 0.39 mmol, 3 equiv) at -78 °C and the reaction mixture was stirred for 30 min at the same temperature, then at 0 °C for 30 min (*Solution A*). *t*-BuOK (0.018 g, 0.16 mmol, 1.2 equiv) was added to a solution of *trans*-hydroxy mesylate **9β** (0.041 g, 0.13 mmol) in anhydrous THF (3.0 mL) and the reaction mixture was stirred 15 min at room temperature (*Solution B*). *Solution A* was added dropwise to *Solution B* at 0 °C and the reaction mixture was stirred at the same temperature for 3 hours. Usual work-up afforded a reaction product (0.079 g) consisting of a 92:8 mixture of 2-(benzyloxycarboxamido)-2,5-dihydrofuran *cis*-**49** and D-gulal-derivative **50** (^{1}H NMR), with the excess of benzyl carbamate, which was subjected to preparative TLC, by eluting with a 7:3 hexane/AcOEt mixture (three runs). Extraction of the slower moving band afforded pure *benzyl [(1S)-6-O-benzyl-2,3-dideoxy-D-threo-hex-2-enofuranosyl]carbamate* (*cis*-**49**) (0.028 g, 58% yield), as a colourless oil. R_f = 0.21 (1:1 hexane/AcOEt); $[\alpha]_D^{20}$ = +97.6 (*c* 0.45, $CHCl_3$). FTIR

(neat) ν 3446, 3336, 1693, 1518, 1454, 1235, 1049, 1002, 743, 697 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 7.28-7.41 (m, 10H), 6.32 (dd, 1H, *J* = 10.1, 1.5 Hz), 6.02 (dt, 1H, *J* = 5.9, 1.6 Hz), 5.83 (dt, 1H, *J* = 6.0, 2.1 Hz), 5.50-5.60 (m, 1H, NH), 5.12 (d, 2H, *J* = 7.8 Hz), 4.75 (t, 1H, *J* = 2.0 Hz), 4.55 (s, 2H), 3.76-3.82 (m, 1H), 3.54-3.61 (m, 2H), 2.50 (bs, 1H, OH). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 154.8, 137.8, 136.1, 131.0, 128.7, 128.6, 128.4, 128.1, 128.0, 127.9, 85.2, 77.4, 73.7, 71.9, 70.6, 67.1. Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.33; H, 6.28; N, 3.79. Found: C, 68.28; H, 6.27; N, 3.61.

D-Gulal derivative **50** was not recovered from the preparative TLC. However, an accurate examination of the ^1H NMR spectrum of the crude reaction mixture firmly established its presence and made the assignation of corresponding signals possible, as here reported:
D-gulal derivative **50**: ^1H NMR (250 MHz, $CDCl_3$) δ 7.28-7.41 (m, 10H), 6.59 (d, 1H, *J* = 5.6 Hz, H_1), 5.15-5.21 (m, 1H), 3.94-4.05 (m, 1H), 2.91 (bs, 1H, OH).

*4.4.2. Reaction of epoxide **6α** with lithium anion of benzyl carbamate (**45-LiHMDS** by LHMDS protocol) in anhydrous THF*

Following the typical procedure, a solution of benzyl carbamate (0.082 g, 0.54 mmol, 3 equiv) in anhydrous THF (1.8 mL) was treated with 1M LHMDS (0.54 mL, 0.54 mmol, 3 equiv) at -78 °C and the reaction mixture was stirred for 30 min at the same temperature, then at 0 °C for further 30 min (*Solution A*). *t*-BuOK (0.020 g, 0.18 mmol, 1 equiv) was added to a solution of *trans*-hydroxy mesylate **9α** (0.057 g, 0.18 mmol) in anhydrous THF (1.8 mL) and the reaction mixture was stirred 15 min at room temperature (*Solution B*). *Solution A* was added dropwise to *Solution B* at 0 °C and the reaction mixture was stirred at the same temperature for 3 hours. Usual work-up afforded a crude reaction product (0.110 g) consisting of α-*N*-glycoside **52α** and excess of benzyl carbamate which was subjected to preparative TLC, by eluting with a 7:3 hexane/AcOEt mixture (three runs). Extraction of the most intense band afforded *benzyl [(1S)-6-O-benzyl-2,3-dideoxy-D-threo-hex-2-enopyranosyl]carbamate* (**52α**) (0.039 g, 59% yield), as a white solid; m.p. 99-100 °C. R_f = 0.16 (1:1 hexane/AcOEt). $[\alpha]_D^{20}$ = −14.9 (*c* 0.67, $CHCl_3$). FTIR (nujol) ν 3467, 3319, 1691, 1522, 1259, 1084, 1019, 797 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 7.28-7.42 (m, 10H), 5.96-6.04 (m, 1H), 5.70-5.76 (m, 1H), 5.65-5.70 (m, 1H), 5.59-5.65 (m, 1H), 5,09-5.22 (m, 2H), 4.58 (d, 2H, *J* = 2.2 Hz), 4.18-4.26 (m, 1H), 3.77-3.84 (m, 1H), 3.57-3.69 (m, 2H), 2.93-3.03 (m, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 155.5, 137.5, 133.5, 128.8, 128.7, 128.7, 128.5, 128.3, 128.2, 128.1, 127.9, 79.5, 74.1, 71.4, 69.6, 67.3, 66.7. ^{13}C NMR (62.5 MHz, CD_3CN) δ 154.9, 139.7, 138.0, 134.9, 134.7, 129.5, 129.3, 129.0, 128.8,

128.7, 128.4, 75.3, 73.8, 72.7, 71.1, 67.2, 64.0. Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.27; N, 3.79**.** Found: C, 68.01; H, 5.89; N, 3.41.

*4.4.3. Treatment of α-N-glycoside **52α** with t-BuOK in anhydrous THF*

A solution of α-*N*-glycoside **52α** (0.063 g, 0.17 mmol) in anhydrous THF (1.0 mL) was treated with *t*-BuOK (0.038 g, 0.34 mmol, 2 equiv) and the reaction mixture was stirred at room temperature for 1 hour. Dilution with Et_2O and evaporation of the washed (brine) organic solution afforded a crude product (0.049 g, 78% yield), consisting of a 71:29 mixture of 2-(benzyloxycarboxamido)-2,5-dihydrofurans *cis*-**53** and *trans*-**54** (^{1}H NMR) with a small amount of unreacted α-*N*-glycoside **52α**, which was subjected to preparative TLC, by eluting with a 7:3 hexane/AcOEt mixture (three runs). Extraction of the two most intense bands (the faster moving band contained *cis*-**53**) afforded pure diastereoisomeric 2,5-dihydrofurans *cis*-**53** (0.025 g, 40% yield) and *trans*-**54** (0.008 g, 12% yield).

Benzyl [(1R)-6-O-benzyl-2,3-dideoxy-D-erythro-hex-2-enofuranosyl]carbamate (*cis*-**53**), a pale yellow oil. R_f = 0.23 (1:1 hexane/AcOEt); $[\alpha]_D^{20}$ = – 46.8 (*c* 0.22, $CHCl_3$). FTIR (neat) ν 3401, 3298, 1707, 1515, 1455, 1414, 1262, 1097, 1031, 802 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.29-7.49 (m, 10H), 6.30 (d, 1H, *J* = 9.5 Hz), 6.12 (d, 1H, *J* = 6.1 Hz), 5.82 (d, 1H, *J* = 5.9 Hz), 5.42-5.57 (m, 1H), 5.05-5.24 (m, 2H), 4.68-4.80 (m, 1H), 4.55 (s, 2H), 3.78-3.92 (m, 1H), 3.63 (dd, 1H, *J* = 9.6, 4.0 Hz), 3.53 (dd, 1H, *J* = 9.7, 5.9 Hz), 2.43-2.56 (m, 1H). ^{13}C NMR (62.5 MHz, CD_3CN) δ 155.7, 132.4, 132.3, 129.3, 129.2, 128.9, 128.7, 128.4, 128.5, 128.3, 127.9, 86.6, 73.6, 73.1, 73.0, 72.3, 67.0. Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.27; N, 3.79. Found: C, 68.15; H, 6.05; N, 3.85.

Benzyl [(1S)-6-O-benzyl-2,3-dideoxy-D-erythro-hex-2-enofuranosyl]carbamate (*trans*-**54**), a colourless oil. R_f = 0.12 (1:1 hexane/AcOEt); $[\alpha]_D^{20}$ = −19.6 (*c* 0.23, $CHCl_3$). FTIR (neat) ν 3546, 3393, 1713, 1518, 1462, 1413, 1259, 1083, 1012, 792 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.28-7.39 (m, 10H), 6.33-6.42 (m, 1H), 6.25 (dt, 1H, *J* = 5.9, 1.5 Hz), 5.80 (ddd, 1H, *J* = 6.0, 2.2, 1.5 Hz), 5.15-5.22 (m, 1H), 5.09-5.15 (m, 2H), 4.82-4.89 (m, 1H), 4.58 (d, 1H, *J* = 11.7 Hz), 4.53 (d, 1H, *J* = 11.7 Hz), 3.67-3.78 (m, 1H), 3.54-3.67 (m, 2H). ^{13}C NMR (62.5 MHz, CD_3CN) δ 151.1, 133.2, 133.1, 129.5, 129.3, 129.0, 128.9, 128.7, 128.6, 128.5, 127.8, 86.6, 73.8, 73.5, 73.2, 72.6, 67.1. Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.27; N, 3.79. Found: C, 68.04; H, 5.93; N, 3.39.

4.5. NMR measurements

^{1}H and ^{13}C measures were carried out by means of Varian INOVA 600 spectrometer at 600 MHz for ^{1}H and at 150 MHz for ^{13}C, respectively, in the appropriate deuterated solvent ($CDCl_3$, CD_3CN and/or DMSO-d_6) by using TMS as the external standard. Temperature has been controlled to ± 0.1 °C by Varian control system. For all the 2D spectra, the minimum spectral width has been used in both the dimensions. COSY(COrrelation SpectroscopY) spectra have been recorded by using a relaxation daly of 1 s, 128 increments of 4-16 scans**,** each with 4K data points. For 2D-TOCSY (TOtal Correlation SpectroscopY) spectra, a mixing time of 80 ms has been used, with 256 increments of 4-16 scans**,** each with 4K data points. 2D NOESY (Nuclear Overhauser Effect SpectroscopY) measures have been carried out by using 1 s mixing time. Relaxation dalay was maintained at 2 s: 256 increments of 16-32 scans each with 4K data points. g-HSQC (gradient-Heteronuclear Single Quantum Correlation) and HMBC (Heteronuclear Multiple Bond Coherence) spectra have been recorded with 32-128 increments of 32 scans, by using a relaxation daly of 1 s. HMBC experiment has been optimized for 8 Hz ^{1}H-^{13}C long-range coupling constant. No decoupling during acquisition has been used.

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Appendix A: Supplementary data

Supplementary data related to this article can be found at…...

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32. a) The previously used *syn*- and *anti-1,2-addition product* and *syn*- and *anti-1,4-addition product* terminology for addition products obtained with epoxides **6α** and **6β** by S_N2 and S_N2' pathway, respectively (ref. 33a,b), has been changed into *3,4-cis*- and *3,4–trans-product* and *1,4-cis*- and *1,4–trans-product*, respectively. b) As for the formation of 2,5-dihydrofurans by cyclization of the corresponding α,β-γ,δ-unsaturated system, the use of "*syn*-stereoselective" or "*syn*-stereoselectivity" terminology refers to an intermediate cyclizing structure in which the two terminal portions, –CH(OH)-CH_2OBn and –$CH(COOMe)_2$, –$CH(COPh)_2$ or –NHCOOBn of the reacting species are on the same side with respect to the new forming bond (Schemes 7, 8, 15, 18 and 20).

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35. Actually, in accordance with the evidences found in the case of the rearragement process leading to 2,5-dihydropyrroles from aziridines **1α** and **1β**, it is reasonable, as envisaged in Scheme 2, that the intermediate formation and presence of corresponding 1,4-adducts in the reaction mixture, independently on their α- or β-configuration, is necessary in order to trigger the isomerization process to 2,5-dihydrofurans by epoxides **6α** and **6β** (see ref. 31a).

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37. Appropriate experiments, carried out on the corresponding isolated product, have indicated that 2,5-dihydrofurans *cis*-**12**, *cis*-**21**, *trans*-**22**, *cis*-**35**, *trans*-**36-OAc**, *cis*-**49**,

cis-**53** and *trans*-**54** are completely stable under the reaction conditions used for their formation and, consequently, that the cyclization step is not reversible.

38. Correctly speaking, only the not isolated primary reaction products **30** (Scheme 10), **43** (Scheme 17, *route* ***b***) and **44** (Scheme 17, *route* ***c***) could be considered as *3,4-trans*- (**30** and **43**) and *3,4-cis-product* (**44**). However, the same simplified nomenclature could reasonably be extended to the corresponding final reaction product **20** (Schemes 8 and 10), **39** and **40** (Schemes 16 and 17) whose presence is strictly related to the formation of **30**, **43** and **44**, respectively (Schemes 10 and 17).

39. All the obtained compounds (**20**, *cis*-**21** and *trans*-**22**, Scheme 8, eq 1) showed the presence of a 2-(benzoylmethyl)- substituting chain ($-CH_2COPh$) instead of the 2-(dibenzoylmethyl)-substituent [$-CH(COPh)_2$], as expected on the basis of the structure of the nucleophile. This simplification of the residue of the nucleophile in the products is due to a retro-Claisen condensation on the corresponding, initially formed, 2-(dibenzoylmethyl)- derivatives **30**, *cis*-**23** and *trans*-**24** (the primary reaction products), which are not found in the crude reaction mixture because not stable under the alkaline reaction conditions (Schemes 8-10 and eq. 1, Scheme 12).

40. Interestingly, the alkaline reaction conditions (*t*-BuOK) do not determine mono debenzoylation of *C*-glycosides **25α** and **25β**, but deprotonation of the residual acid *C*-H bond of the (dibenzoylmethyl)- group to give the corresponding enolate species **26** (Scheme 8).

41. The observed lack of facial selectivity in the formation of 2,5-dihydrofurans *cis*-**21** and *trans*-**22** was decidedly unexpected. Evidently, the possible occurrence of an intramolecular cation binding through potassium cation in folded conformer **29**-*Si*, as tentatively shown in Scheme 8 (M = K), is not sufficient to direct the facial selectivity in the cyclization process, as when the more coordinating lithium cation is involved as in the case of formation of 2,5-dihydrofuran *cis*-**12** (Scheme 7, intermediate **18**-*Si*).

42. In the reactions of glycal-derived epoxides **6α** and **6β** with *O*- and *C*-nucleophiles, the corresponding *1,4-cis-product*/*3,4-trans-product* ratio was demonstrated to be increased

by favouring the occurrence of a coordination between the nucleophile and the oxirane oxygen (see ref. 33). As a consequence, having reasonably admitted that the obtained 2,5-dihydrofurans derive from the corresponding *1,4-cis*- and/or *1,4-trans-products* (Schemes 7 and 8), if the amount of these addition products is increased, also the amount of the rearranged products (corresponding 2,5-dihydrofuran derivatives) could be correspondently increased in the final crude reaction mixture.

43. It is interesting to note that when *t*-BuOK is not directly involved in the formation of the enolate species and in the rearrangement process, mono-debenzoylation, by retro-Claisen condensation, does not occur and 2-(dibenzoylmethyl)-2,5-dihydrofurans *cis*-**23** and *trans*-**24** are the reaction products (eq. 2, Schemes 8 and 12).

44. On the basis of the previously observed behaviour of epoxide **6β** in nucleophilic addition reactions in the presence of a chelating cation as Li^+ (ref. 33), β-*C*-glycoside **25β** could largely be the main 1,4-adduct in the reaction of **6β** with enolate **19-Li** (Scheme 8, eq. 2, first step, and Scheme 11), accompanied by only a very small amount of α-*C*-glycoside **25α**. However, the possibility of a non-stereoselective formation of β- **25β** and α-*C*-glycoside **25α**, with the latter more readily converted into 2,5-dihydrofurans, cannot be ruled out.

45. Evidently, the exclusive presence in the reaction mixture of the less coordinating K^+ is not sufficient, in ths case, to determine the formation of corresponding *1,4-cis-product*. As a consequence, the expected rearranged product(s), the corresponding 2,5-dihydrofuran(s), cannot be obtained.

46. Evidently, both folded **37**-*Re* (presence of an intramolecular cation binding, Scheme 15) and corresponding unfolded intermediate conformer (absence of an intramolecular cation binding, not shown), leading to 2,5-dihydrofuran *cis*-**35** and *trans*-**36**, respectively, are likewise involved in the case of epoxide **6α**.

47. The theoretical study was performed on two simplified models, **TS-18-OMe**-*Si* and **TS-37-OMe**-***Re*** corresponding to **TS-18**-***Si*** and **TS-37**-*Re*, respectively, in which the BnO-group present in **TS-18**-*Si* and **TS-37**-*Re* has been substituted with the simpler, less

calculation demanding MeO- group (see Scheme 15 and Figure 1 in Supplementary data).

48. The low amount of *3,4-trans-product* **39** obtained in the reaction could be due to the occurrence of 1,3-syn-diaxial repulsion between nucleophile (enolate **19-Li**) and benzyloxymethyl group, as shown in *route **b***, Scheme 17.

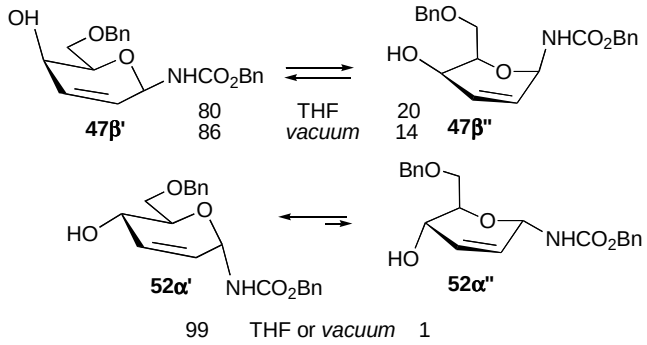
49. The proposed mechanism of formation of *3,4-cis-product* **40**, through not isolable intermediate **44** (Scheme 17, *route **c***), is based on the "ion-dipole pair" mechanism for the ring opening reactions of 2-aryl oxiranes under acid conditions. See: a) Crotti P, Dell'Omodarme G, Ferretti M, Macchia F.. *J. Am. Chem .Soc.* 1987; 109: 1463-1469 and b) Crotti P, Di Bussolo V, Macchia F, Favero L, Pineschi M, Lucarelli L, Roselli G, Renzi G. *J. Phys. Org. Chem.* 2005; 18: 321-328 and references therein.

50. The obtainment of *1,4-trans-product* **38β**, as the only 1,4-adduct by the reaction of epoxide **6α** under *t*-BuOK/*t*-BuOLi protocol, is in contrast with the 1,4-syn-stereoselective behaviour commonly observed in nucleophilic addition reactions to glycal-derived epoxides **6α** and **6β** under chelating reaction conditions (presence of the strongly coordinating Li^+ in the reaction mixture, see ref. 33). A satisfactory explanation of this unusual behaviour of epoxide **6α** is not at the moment available.

51. As previously observed in the corresponding reaction with lithium enolate **10-LiHMDS**, the reaction of epoxide **6α** with lithium enolate **19-LiHMDS** by dibenzoylmethane/LHMDS protocol afforded only a complex reaction mixture which was not furtherly examined. (Table 2, entry 6).

52. Approximate value, see: Ripin DH, Evans DA. *Chem. 206,* Harvard, at http://evans.rc.fas.harvard.edu/pdf/evans_pKa_table.pdf

53. Theoretical calculations have indicated that intermediate *1,4-cis-product* **47β** exists, in THF and in *vacuum*, as 80:20 and 86:14 equilibrium, respectively, between conformers **47β'**(pseudoequatorial $-NHCO_2Bn$) and **47β"** (pseudoaxial $-NHCO_2Bn$), whereas *1,4-cis-product* **52α** practically exists as the only conformer **52α'**(pseudoaxial $-NHCO_2Bn$) (**52α'**: **52α"**= 99:1) both in THF and in *vacuum* (see Supplementary data).



The consistent presence of corresponding "pseudoequatorial" conformer **47β'** makes **47β** not isolable because readily transformed into 2,5-dihydrofuran *cis*-**49** via C(1)-O(5) bond cleavage due to *exo*-anomeric effect (Scheme 18). The exclusive presence of corresponding "pseudoaxial" conformer **52α'** makes **52α** less prone to isomerization to the point that it is recovered as the only reaction product (Scheme 19).

54. In order to simplify the discussion in the "*Structures and configurations*" paragraph (Schemes 21-23), the numbering of six-membered heterocycles (*1,4-cis*- and *1,4-trans-products* and *3,4-cis*- and *3,4-trans-products*) has been modified in order to have the same number given to corresponding carbons in six-membered and five-membered heterocycles (2,5-disubstituted-2,5-dihydrofurans).