COMMUNICATION

Stereoselective Synthesis of New Pyran-Dioxane based Polycycles from Glycal Derived Vinyl Epoxide

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Two novel linear fused pyran-dioxane based bi- and tricycles were synthesized with total stereoselectivity from a glycal derived vinyl epoxide; this new straightforward methodology allowed us to prepare a pyran-dioxane-cyclohexane tricycle with a *cis-cisoid-trans* stereochemistry, in agreement with the geometry of many natural products of the same type.

The possibility to easily construct chiral heteropolycyclic structures with a straightforward stereocontrol is extremely appealing, considering their increasing pharmaceutical relevance.[1] In particular, linear fused pyran-dioxane-based polycycles are quite attractive targets,[2] widespread among several natural occurring pharmacologically active biomolecules such as antibiotics anthracyclines,[3] angucyclines[4] and spectinomycin[5] or steroid-based cardiac glycosides.[6] Interestingly, for linear fused pyran-dioxane-cyclohexane tricycles, even if five linkage geometries are possible,[7] only the *cis-cisoid-trans* form is present in natural products (Figure 1).

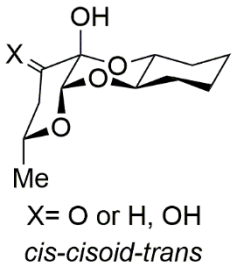
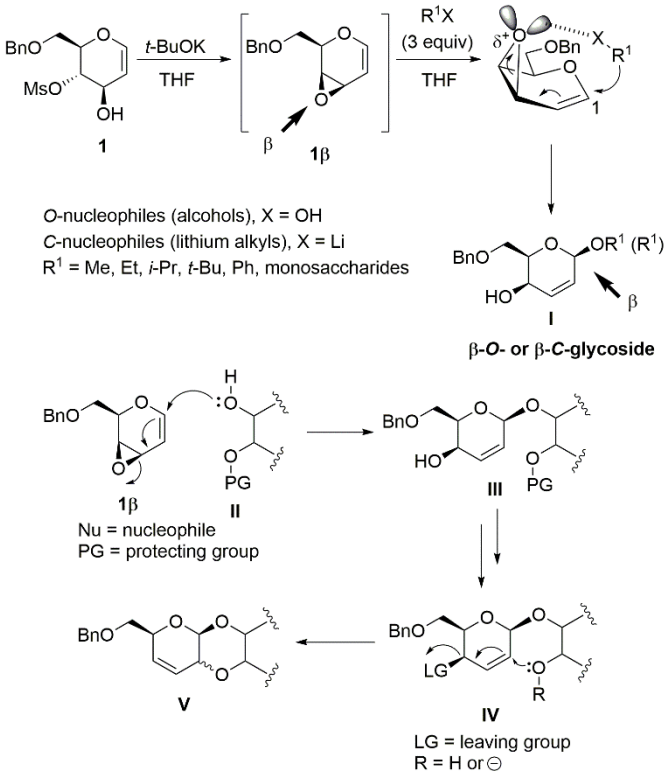


Figure 1. Common linkage geometry for pyran-dioxane-cyclohexane tricycles found in natural products.

Then, considering the intimate connection between structure and possible activity, the overall stereocontrol on the linkage construction, which arises from the specific synthetic pathway chosen, plays the major role. Most of the synthetic efforts towards the preparation of pyran-dioxane based polycycles have been exclusively focused on developing routes to specific biomolecules,[8] with only a few examples of more general approaches to these scaffolds:[9] the first category is quite heterogenous, because it is target-dependent, and it spanned from hetero Diels-Alder followed by epoxidation/epoxide opening,[8a] to a SN_2 on ulosyl halides with successive intramolecular acetalization.[8b] As more general strategy, the use of Michael addition on cyclic enones followed by trans-acetalization represents a very versatile approach to these scaffold.[9b,c] Noteworthy, acetalization reaction seemed to be a common thread as the final ring closing process.[8,9b,c] We previously reported an efficient glycosylation process, using glycal-derived vinyl epoxides **1β** as powerful glycosyl donors (Scheme 1).



Scheme 1. Reactivity and mechanism of epoxide **1β** (above), new intramolecular synthetic strategy (below).

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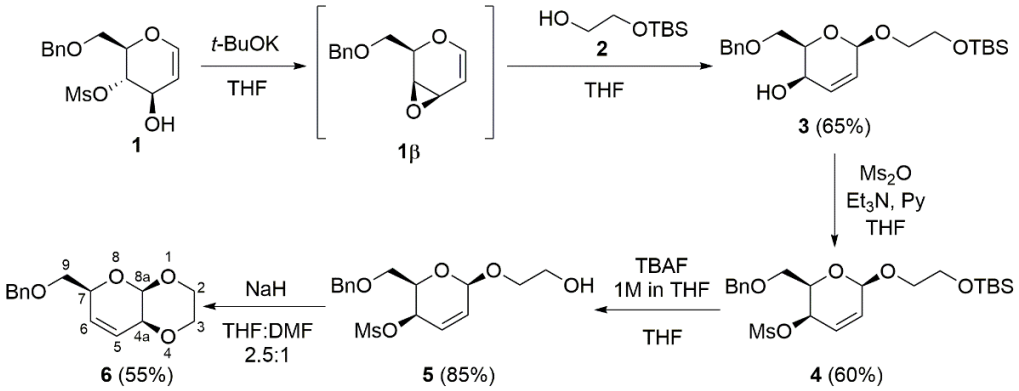
This system, in the presence of alcohols or alkyl lithium reagents as the nucleophiles, affords only 6-*O*-benzyl- protected *O*- and *C*-glycosides (**I**) with the same configuration of the starting epoxide, in an uncatalyzed substrate-dependent stereospecific process. The driving force of this regio- and stereoselective 1,4-addition process is the occurrence of a coordination between the nucleophile and the oxirane oxygen atom in the form of hydrogen bond, in the case of *O*-nucleophile, or through the metal lithium cation, in the case of alkyl lithium reagents.[10] Vinyl epoxide **1β** cannot be isolated and must be prepared *in situ* by cyclization with *t*-BuOK of its precursor, the corresponding *trans*-hydroxymesylate **1**.

In the recent past, this strategy has been successfully applied to the synthesis of promising glycoconjugated molecules of biological interest, making use of monodentate nucleophiles.[11] Herein, we describe a smart application of our completely stereoselective *O*-glycosylation process to an intramolecular version, for the construction of polycyclic systems containing the high value pyran-dioxane moiety. This way, after the stereoselective glycosylation process with a bidentate monoprotected *O*-nucleophile (**II**, Scheme 1), operating the transformation of the allylic alcohol (**III**) into a good leaving group and deprotecting the second nucleophilic functionality, a new SN_2' conjugated addition process on intermediate **IV** should afford a simple intramolecular cyclization reaction towards the desired pyran-dioxane system **V**.



Scheme 2. Synthetic pathway towards bicycle **6**.

As the first 1,2-dihydroxo-nucleophile, we investigated a conformationally free bidentate scaffold: the monoprotected ethylene glycol (as *tert*-butylsilyl ether, TBS, Scheme 2) **2**.[12] The idea was to avoid any additional constraint in the transition state (TS) of the ring closing SN_2', arising from further structural rigidity dictated by the bidentate nucleophile, and then to obtain a clear picture of the more energetically favoured diastereomer (*cis* or *trans*). Compound **2** reacted in anhydrous THF with the *in situ* formed epoxide **1β** in a total regio- and stereoselective manner to obtain the 2,3-unsaturated-β-*O*-glycoside **3**. The formation of the new leaving group in position 4 was realized using methanesulfonic anhydride in THF with both pyridine and triethylamine,[13] to obtain compound **4**, which was readily deprotected from the silyl ether group by the tetrabutylammonium fluoride (TBAF) protocol. Derivative **5** was, finally, subjected to the ring closing SN_2' process: the cyclization was achieved using sodium hydride as the base in a 2.5:1 volumetric mixture of anhydrous THF and DMF; this specific solvent mixture assured a good solubility of the base at room temperature and allowed us to obtain bicycle **6** as a unique diastereomer, with an overall 20% yield over 4 steps (5 considering the *in situ* epoxide formation).

Target bicycle **6** was fully characterized (as well as all the intermediates) by means of 1D and 2D-NMR (full assignment in ESI), high resolution mass (HRMS) and its purity assessed by HPLC (98% at 254 nm). Moreover, its exact stereochemistry was undoubtedly determined by 2D-NOESY map (Figure 2, see ESI for details), thanks also to the known anomeric carbon configuration of compounds of type **I** (Scheme 1).[10] Bicycle **6** was assigned as the *cis* diastereomer (Figure 2) due to the strong NOE effect between the anomeric proton H8a and the new chiral center proton H4a. In addition, the small value of scalar coupling constant $^3J_{H8a\text{-}H4a}$ = 1.7 Hz was in line with the H8a-C8a-C4a-H4a dihedral angle of 48°, measured from the DTF optimized model (Figure 2), corresponding to a calculated ^3J constant of 1.9 Hz.[14] Interestingly, as also appreciable in the structure in Figure 2, dioxane methylene hydrogen atoms H2 were anisochronous (H2eq 3.58 ppm and H2ax 4.20 ppm) with H8a-H2ax being the only inter-ring NOE correlation observed, while methylene H3 were isochronous, (3.80 ppm), mainly because it is too far from other pyran hydrogen atoms.

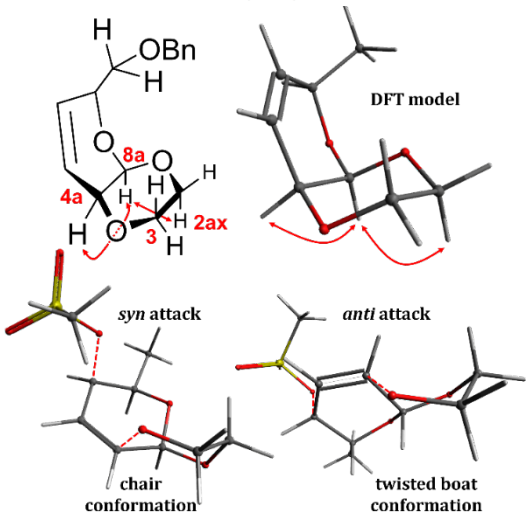
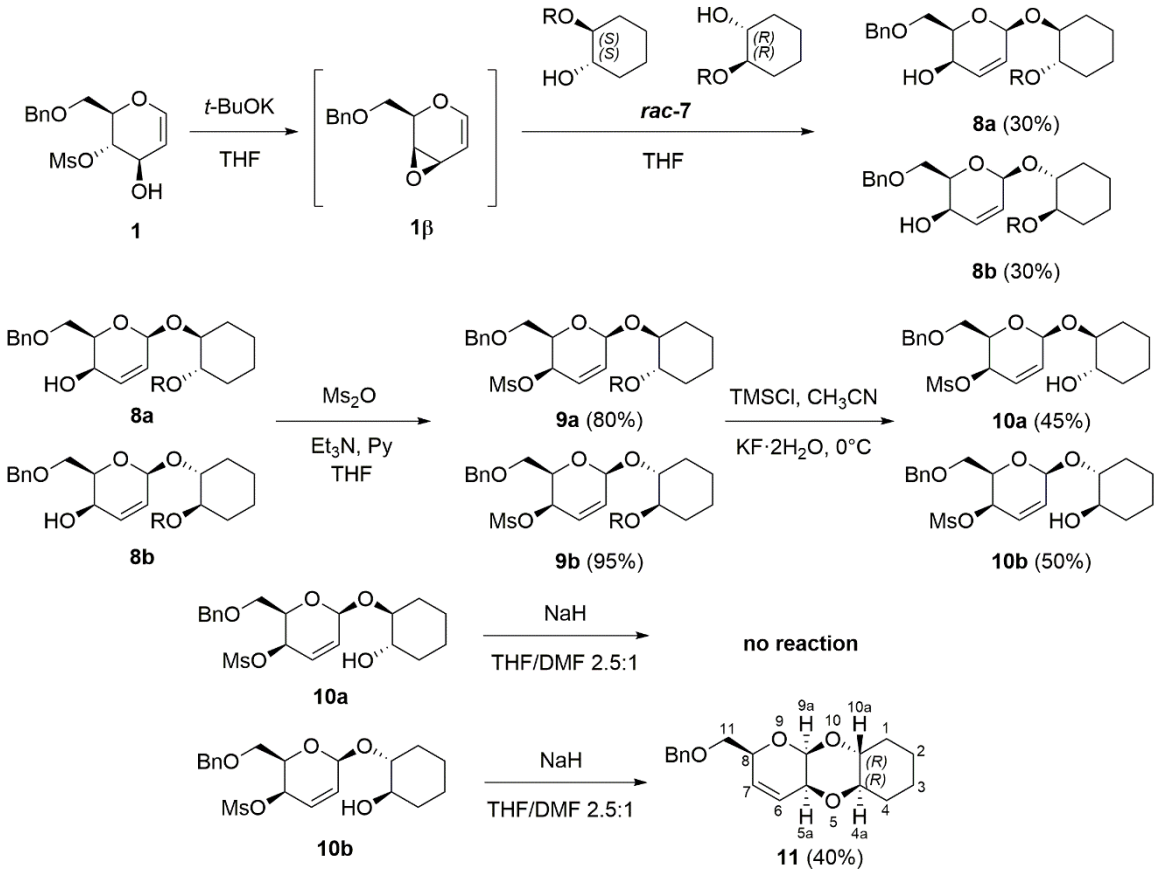


Figure 2. NOESY key correlations (double head red arrows) of bicycle **6** and DFT-optimized model (above), DFT transition states for the *syn* and *anti* ring closing attack of **5** (below).

The intriguing aspect of the ring closing SN_2' was the total diastereoselectivity towards the *cis* diastereomer of **6**: in ring closing processes the geometry of the TS and the relative overall ring strain represent a highly relevant contribution to the process energy barrier/s, and to the feasibility of a certain molecular outcome. For bicycle **6**, the TS for the SN_2' *syn* attack (*cis* diastereomer) and *anti* one (*trans* diastereomer) were calculated with Gaussian[15] on a simplified model (methyl substituted in position 9) with DFT-D3 (Figure 2, theory level PW6B95D3/6-311++G(2D,2P)//PW6B95D3/6-311++G(2D,2P), see ESI for details).[16] Interestingly, the two TS shared the same minimum, with *syn* (*cis*) favoured over *anti* (*trans*) with a $\Delta\Delta G^{\ddagger}$ = 54.7 kJ/mol (13.1 kCal/mol), because its TS adopted a chair conformation with respect to a more energetically demanding twisted boat for the *anti* pathway.

As the second 1,2-dihydroxo-nucleophile, we chose a more conformationally rigid cyclic scaffold, intrigued by the possibility to achieve chiral tricyclic compounds closer to various natural derivatives (Scheme 3): a racemic mixture of mono *tert*-butyldimethylsilyl protected 1,2-*trans*-cyclohexandiol, ***rac*-7**, reacted with the *in situ* formed epoxide **1β** to obtain both the diastereomers **8a** and **8b** of the 2,3-unsaturated-β-*O*-glycosides (diastereomeric ratio = 1); these were separated and used in parallel along the synthetic pathway (the absolute configuration was later established on the final target molecule). The synthesis proceeded similarly to the one in Scheme 2 (mesylate formation, removal of the silyl ether protective group) for both the diastereomers, except for the protocol used in the cleavage of the TBS group: while classic TBAF method resulted ineffective (the system is quite more sterically hindered), using



Scheme 3. Synthetic pathway towards tricycle **11** using a racemic mixture of monoprotected 1,2-trans-cyclohexandiol ***rac*-7** as bidentate nucleophile (R = TBS-).

In this case, no counterion to the alkoxide was considered in the calculation (we used a large triple-zeta basis set including diffuse functions 6-311++g(2D,2P)), to extrapolate the pure steric effect of the two possible TS: instead, the inclusion of the counterion determined a further stabilization of the syn pathway, probably due to the efficient coordination of the sodium by at least three oxygen atoms, which resided on the same face. Last, the electronic aspect on the stereochemistry of a SN_2' is commonly exemplified by the attack of the nucleophile electron density to the LUMO of an allylic halide/pseudohalide-type system (usually a π*+σ*), which is usually on the same side of the leaving group, in agreement with the *syn* attack observed.

trimethylsilyl chloride (TMSCl) in presence of $KF{\cdot}2H_2O$ in acetonitrile (0°C to r.t.)[17] was successful. Most importantly, in the last ring closing SN_2' reaction, promoted by sodium hydride, only the **10b** diastereomer determined the formation of tricycle **11** diastereoselectively, while **10a** resulted inert even after 2 days. The tricyclic compound **11** (overall yield 10%) was fully characterized by 1D- and 2D-NMR, HRMS and its purity assessed by HPLC (97% at 254 nm).

The stereochemical analysis of tricycle **11** was realized with a combined NMR/computational approach (Figure 3):

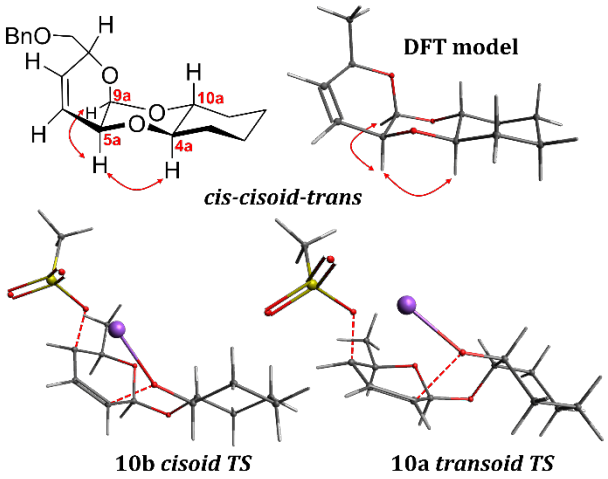


Figure 3. NOESY key correlations (double head red arrows) of tricycle **11** and DFT-optimized model (above), DFT transition states *in vacuo* for the *syn* ring closing attack of the sodium alkoxide intermediates **10a** and **10b** (below).

NMR clearly showed that the pyran-dioxane rings linkage was again of *cis* stereochemistry, thanks to the strong NOE between anomeric H9a and the new chiral center H5a proton atoms. A first run of DFT-D3 calculation of the TS for the *syn* ring closing process of both **10a** and **10b** diastereomers (as alkoxide) was done *in vacuo* using sodium as the counterion (theory level PW6B95D3/6-31+G(D)//PW6B95D3/6-311++G(2D,2P),[16] the TS did not share the same minimum). In agreement with the experimental observation, even if both the TS's of the two diastereomers (Figure 3) adopted a chair conformation for the central dioxane ring, the overall geometry of the ring closing process of **10b** (towards tricycle **11**) was *cisoid* ($\Delta G^{\ddagger}$= +6.3 kJ/mol) and the one for **10a** (which did not gave any tricyclic outcome) was *transoid* ($\Delta G^{\ddagger}$= +14.3 kJ/mol), with a $\Delta\Delta G^{\ddagger}$ = 8.0 kJ/mol (2 kCal/mol) in favour of the first one.

This represented a double result: the *cisoid* geometry of both the TS of **10b** and, most importantly, of tricycle **11** (in Figure 3 is reported a DTF optimized model) was experimentally confirmed by the NOE correlation between the pyran proton atom H5a and the cyclohexane H4a. This confirmed the *cis-cisoid-trans* geometry, in line with most of the natural compounds of this kind.[5,6,8c,8d] The second consequence was related to the inertness of the **10a** diastereomer in the same ring closing condition, which can be explained through a more energetically demanding pathway for the *transoid* TS, affected by the typical steric issues of axial/equatorial equilibrium of cyclohexane derivatives. To get more insights about the cyclization, we performed a final calculation for the *syn* attack of **10a** and **10b**, both as sodium salt, including the solvent interaction (DMF, same theory level with PCM): noteworthy, the solvent presence determined a stabilization of the sodium salt of **10b** ($\Delta G^{\ddagger}$= +14.3 kJ/mol) with respect to **10a** ($\Delta G^{\ddagger}$= +37.8 kJ/mol), at the expense of a energetically similar TS (6.9 kJ/mol in favour of **10b**), with a $\Delta\Delta G^{\ddagger}$ = 23.5 kJ/mol (5.6 kCal/mol). This result reinforced the conclusion about the hampered cyclization for the **10a** diastereomer.

In conclusion, we synthesized new chiral pyran-dioxane based polycycles with a total stereocontrol over a straightforward and inexpensive synthetic pathway, using 1,2-dihydroxo nucleophiles and thanks to the regio- and stereoselective reactivity of the glycal-derived vinyl epoxide **1β**. The strength of this new methodology is the stepwise diastereoselective nuchelophilic conjugated attacks on sp2 carbons atoms, characterized by a completely different stereocontrol with respect to commonly reported intramolecular acetal/emiacetal formation.[8,9b,c] In particular, using ethylene glycol as the bidentate nucleophile, we prepared bicycle **6**, characterized by the *cis* linkage stereochemistry assessed by NMR and DFT calculation. Finally, using a more rigid nucleophile, such as racemic 1,2-*trans*-cyclohexandiol, we obtained the linear fused tricycle **11**, from the cyclization of the intermediate **10b**, characterized by a *cis-cisoid-trans* stereochemistry, in line with similar natural occurring biomolecules. This new methodology will allow us to embed these polycyclic motifs in several molecular systems of biomedicine application (diagnostic probes, therapeutic agents), to understand their biological activity and their internalization capability.

Author Contributions

D.I., G.B. and S.D.P. synthesis and characterization of intermediates and target molecules; L.F. DFT calculation, S.D.P., M.P. and V.D.B. development of the synthetic pathway; S.D.P NMR and data elaboration; S.D.P and V.D.B. project and manuscript supervision. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

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