Unravelling the stereoselectivity in 6-*exo*-trig radical cyclization of *α*,*β*-unsaturated ester-tethered sugars. A tale of two stereocenters†

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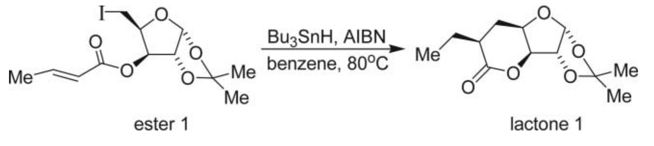
A computational investigation on the origin of the stereoselectivity of 6-*exo*-trig radical cyclization of α,β-unsaturated ester-tethered sugars has revealed that a boat-like transition state, which keeps the ester in a planar conformation, holds the chiral information. Following this model, the stereocenter to which the ester functionality is connected reports the chirality to the newly formed stereocenter *via* a 1,4-transfer mechanism.

Introduction

The intramolecular additions of radical to carbon–carbon double bond to build 5- and 6-membered rings are now widely used in organic chemistry for the construction of carbocycles and heterocycles.[1,2] However, the control of the regio and stereochemistry of radical reactions still pose problems and represents a subject of continuous investigations.[3,4] The regioselectivity in radical cyclizations has been extensively investigated since the seminal works of Beckwith[5] and Houk.[6] Nonetheless, only more recently and with the advancement of computational methods, the origins of the stereoselectivity in radical cyclizations have been better appreciated.[7]

One of our groups reported a number of years ago, the application of 6-*exo*-trig radical cyclization using the Bu_3SnH method to investigate the synthesis of δ-lactones fused to carbohydrates (Scheme 1).[8] The intramolecular radical additions to the α,β-unsaturated esters proceeded in a regio and stereoselective manner and it was observed that the configuration of the newly formed stereocenter is dependent on the structure of the carbohydrate. Herein, we now revisit these results and report a computational investigation towards understanding the origin of the observed stereoselectivity. The participation of the carbohydrate moiety was also examined.



Scheme 1 Radical cyclization of ester **1**.

Results and discussion

Under the reaction conditions, the C–I bond is homolytically cleaved and produces the radical nucleophile. However, for the cyclization reaction to take place, the ester has to adopt the less stable *E* conformation[9] and bring the carbon–carbon double bond closer to the radical center. We found the difference between the *E* and *Z* forms of radical **1** to be 8.0 kcal mol^{-1} (Fig. 1).[10,11] For all purposes, this higher energy structure (**R3**) is considered as the reactive species. Mindful of the small energy gap between *s-trans* and *s-cis* conformations for α,β-unsaturated carbonyl systems and the preference for *s-cis* in the gas phase,[12] the *s-trans* arrangement was also investigated. Indeed, the former was favored by only 0.7 kcal mol^{-1} for the *Z* conformation of the ester.[13]

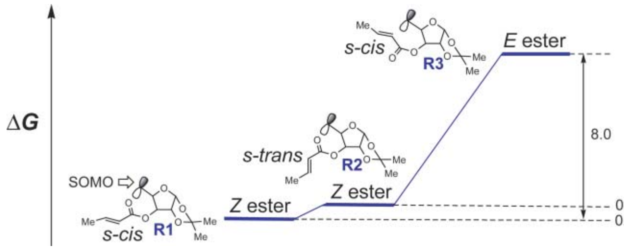


Fig. 1 Relative Gibbs free-energies for conformations of radical reagent **1**. Energy values are given in kcal mol^{-1}.

Since the equilibrium between *s-cis* and *s-trans* conformations can not account for the product ratio,[14] we looked closer at the transition state structures to trace the origin of the stereoselectivity.[15]

To start with, we set out to locate a *pro*-(*S*) TS to account for the only stereoisomer identified in the reaction (Fig. 2). A nearly planar ($\phi_1 = 8.3°$) ester with *s-cis* conformation to form a boat-like structure with the radical center distant 2.30 Å away from the *exo* carbon atom was identified as the first transition state (**TS1**). This product-like TS bears structural similarities with lactone **1**, which was solved by NMR.[8] To generate the stereoisomeric *pro*-(*R*) TS, the conformation was inverted to *s-trans* while the planarity in the ester was maintained in the pursuit of a second boat-like structure. However, this placed the hydrogen attached to the *endo* carbon considerably close to H-3 of the furanose ring. As a result, during

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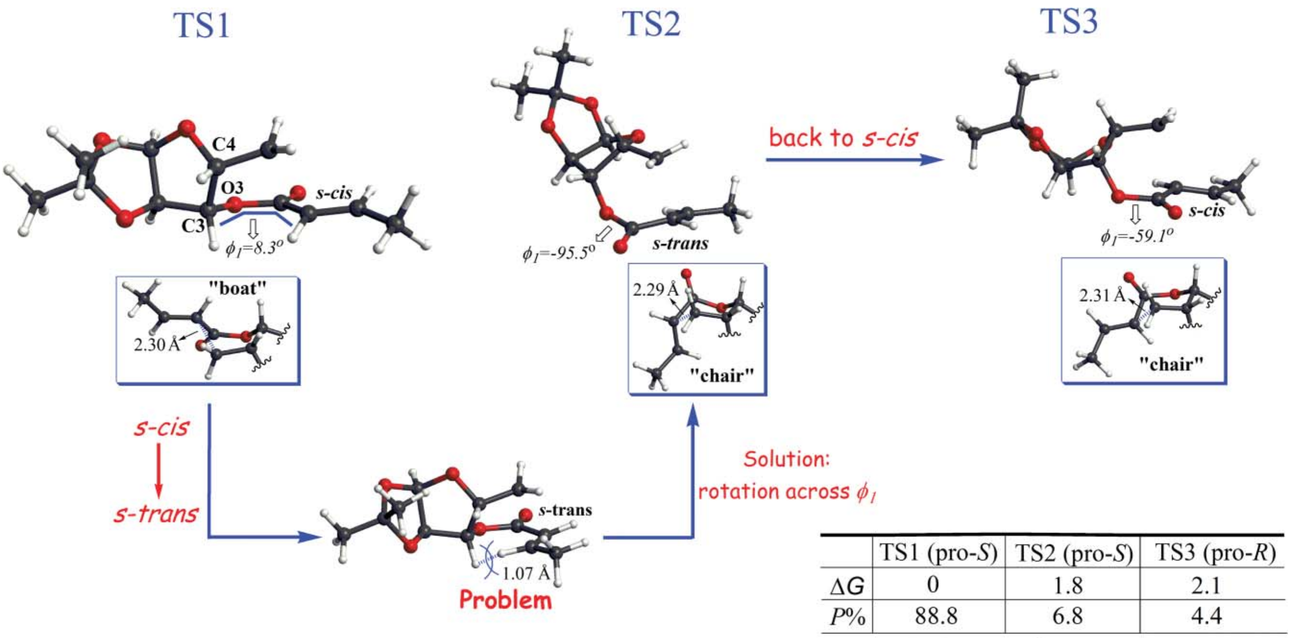
† Electronic supplementary information (ESI) available: Optimized geometries, energies for all computed structures and mimic models for transition states of lactone **2**. See DOI: 10.1039/b923414d



	TS1 (pro-*S*)	TS2 (pro-*S*)	TS3 (pro-*R*)
ΔG	0	1.8	2.1
P%	88.8	6.8	4.4

Energy values in kcal mol^{-1}

Fig. 2 6-*exo* Transition state structures, relative Gibbs free energies and Maxwell-Boltzmann-weighted population (*P*%). The attempt to produce an *s-trans*, *pro*-(*R*) boat-like TS failed as two hydrogens are placed too close and the chair-like **TS2** is obtained instead.[11]

the optimization process a major rotation along ϕ_1 occurred to position C-3 perpendicular to the plane of the unsaturated system and disrupted the ester resonance ($\phi_1 = -95.5°$). This 6-membered ring under construction (**TS2**) has a chair-like conformation and is 1.8 kcal mol^{-1} higher in energy. Still, **TS2** represents yet another *pro*-(*S*) structure. Having tried the combination of an *s-trans* and a planar arrangement, we were left with the option to set back the conformation to *s-cis* to generate a *pro*-(*R*) TS. With $\phi_1 = -59.1°$, the produced chair-like geometry (**TS3**) revealed to be the desired structure and it is 2.1 kcal mol^{-1} higher in energy.

The stereoselectivity of the present 6-*exo*-trig cyclization was calculated by considering Maxwell-Boltzmann statistics on the free-energy differences of the transition states,[15c] which translates into 96 : 4 ratio and is in agreement with experimental result. The boat-like conformation (**TS1**) clearly dominates the transition state equilibrium. The preference for the boat-like pathway arises from the possibility of resonance between the O-3 lone pair electrons and the π bond of the carbonyl group in a nearly planar ($\phi_1 = 8.3°$) arrangement. Conversion into a chair-like conformation implies in the rotation across ϕ_1 torsional angle which no longer allows the orbitals to overlap. Moreover, the rotation to a perpendicular conformation in the ester functionality (as in the case of **TS2**, $\phi_1 = -95.5°$) is energetically more costly (10–13 kcal mol^{-1}) than the penalty associated with the chair-boat difference in cyclohexane (5.7–7.7 kcal mol^{-1}).[16] Thus, the stability promoted by the resonance of the ester more than offsets unfavorable flagpole interactions present in the boat-like transition state.

During the course of our study, we also identified the structure of a 7-*endo*-trig transition state with the ester in a planar conformation. An *s-trans* structure (**TS4**) was located with the radical center 2.36 Å distant from the *exo* carbon and $\phi_1 = -25.9°$ (Fig. 3). Due to steric reasons as it was the case of **TS1**, the stereoisomer of **TS4** with the ester in a planar conformation could not be located.

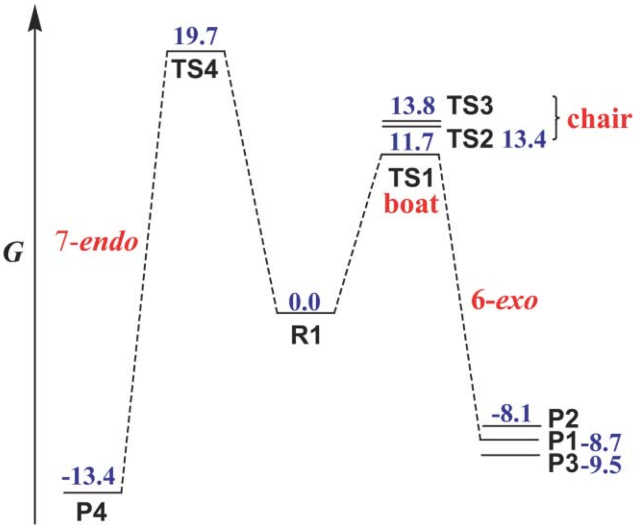


Fig. 3 Free energy profile in different modes of cyclization of radical **1**. Energies are given in kcal mol^{-1}.

Both 6-*exo*-trig and 7-*endo*-trig cyclization modes are favored by Baldwin's rules.[17] However, the activation free energy ($\Delta G^{\ddagger}$) for the 6-*exo* mode (11.7 kcal mol^{-1}) is considerably lower than that associated with the 7-*endo* mode of cyclization (19.7 kcal mol^{-1}). A comparison of the angle of attack of the radical to the double bond for the TS structures shows that the values for 6-*exo* TS structures (108–114°)[18] are close to that observed for the attack of a carbon-centered radical on an alkene in an unstrained intermolecular reaction (109–110°),[19] which contributes to the efficiency of the overlap of the SOMO orbital and the HOMO of the alkene.

For each transition state structure reported, a cyclization product geometry was also computed to check out the thermodynamics of the cyclizations (Fig. 3) and to verify the configuration at the new stereocenter. It was found that the chair-like transition state structures (**TS2** and **TS3**) produced half-chair radical cycles (**P2** and **P3**). Among the 6-membered rings, **P3** is the most stable, whereas **P2** with the ethylidine radical in axial position has the highest energy content. The boat **P1** lies between them. Nonetheless, the product of 7-*endo* cyclization (**P4**) is considerably stable as it could be anticipated for an α-carbonyl radical and represents the lowest energy structure in the rank.

Looking into perspective, it seems that the boat-like transition state (**TS1**) is the key to the stereochemical outcome of the radical cyclization reaction in the fused system. Nonetheless, one can reasonably argue that particular features of lactone **1** related to the sugar moiety have also contributed to some extent to the observed stereoselectivity. Such structural features are as follows: (1) in a cursory inspection, one can promptly spot the *cis* relationship at the carbohydrate junction (C-3 and C-4), (2) a closer look at the computed structures reveals that isopropylidene group, used as a protecting group in the synthesis, locks the furanose ring in a ^3E conformation for all computed structures, and (3) more interestingly, the newly formed stereocenter has the same absolute configuration as C-3 (1,4-*like* relative stereochemistry), where the ester tether is anchored (Fig. 4). The last observation may easily be regarded as just the luck of the draw, but as we are going to show shortly it proved to be rather insightful into the problem.

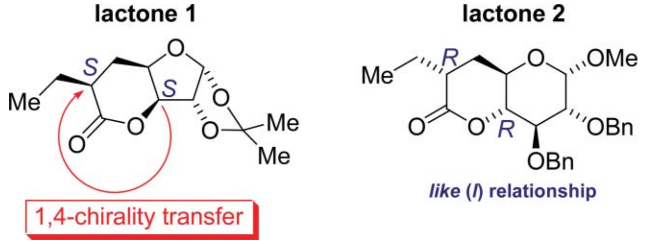


Fig. 4 Absolute configurations of the new stereocenter and that attached to the ester tether of lactones **1** and **2** showing a 1,4-*like* relationship.

To probe the boat-like TS as a model to explain the stereoselectivity of the 6-*exo*-trig radical cyclization in the fused system under investigation and rule out any thinking related to the constrained furanose system of ester **1**, we analyzed the radical cyclization of a second carbohydrate-tethered α,β-unsaturated ester and applied the same rationality. In contrast, lactone **2**[8,20] possesses a *trans*-junction in a pyranose ring and does not have the isopropylidene group to restrict the conformation (Fig. 4). The critical difference, though, lies in the configuration of the carbon where the ester is attached. In fact, our suspicions about the involvement of C-3 emerged from a thorough analysis of the transition states and particularly the manipulation of models in the attempt to create a second boat-like TS as depicted in Fig. 2. In lactone **2**, the configuration of the stereocenter to which the ester is attached is inverted in relation to lactone **1**. As a result, the configuration of the newly formed stereocenter is also inverted. It is worth noting that the groups and the resulting order of priority for configuration assignment in the lactone ring is the same. Hence, it is evident that the stereochemical information is communicated to the new stereocenter through the center to which the ester is attached according to a 1,4-chirality transfer mechanism. All in all, this clearly demonstrates the leading role of the boat-like TS as a model for this radical cyclization.

The effect of the ester conformation on the stereochemistry of cyclizations has been reported previously. Investigations on intramolecular Diels–Alder (IMDA) reactions have shown a preference for products derived from transition states in which the amide or ester-containing ring system tends to adopt a boat-like conformation.[21,22] Tantillo and co-workers[22] in a computational study confirmed experimental observations for this preference and further examined the origin of the stereoselectivity based on a boat-like model. In the realm of radical cyclizations, Fang and co-workers[23] located only boat-like transition states for the 6-*exo*-trig cyclization of 3-butenyl iodoalkanoates and the preference for 3,4-*cis*-lactones was explained straightforwardly by the lower energy of *cis*-oriented transition states. This fact contrasts to the general preference for chair-like transition states upon 6-*exo* radical cyclizations[3b] and also corroborates the conformational role of the ester to favor boat-like transition states.

Concluding remarks

In conclusion, we have shown that the radical cyclization of the tethered α,β-unsaturated esters is governed by a boat-like transition state and that the stereochemical outcome is dependent on the configuration of the stereocenter to which the ester is connected following a 1,4-*like* chirality transfer mechanism. Though the chair-like transition state is the generally invoked model for the formation of 6-membered rings in radical cyclizations, the ester functionality imposes a planar conformation in a boat-like transition state, which is energetically favored. This model can be applied to similar ester or amide-tethered systems to predict the stereochemistry of radical cyclizations including radical cascades.[24] Furthermore, the told "tale" provides another strike for the ester-controlled boat-like transition state model and highlights the potentiality of the concept to different reaction classes.

Computational details

All gas phase structures were computed using DFT UB3LYP[25] as implemented in the GAMESS[26] suite of programs. Previous reports have shown that this level of theory is reasonably accurate for the evaluation of molecular geometries and energies associated with radical reactions.[27,28] In view of the popularity enjoyed by hybrid methods and for the sake of computational cost, a mixed basis set was employed for geometry optimizations and frequency analyses of all species. We denote this mixed basis set as MIX and it comprises 6-31G(d,p) for the atoms at the reaction center and nearby, and 3-21G(d,p) for the atoms at the periphery (Fig. 5).

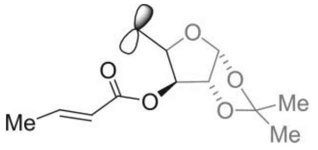


Fig. 5 Mixed basis set applied in geometry optimization. The black region was modelled with 6-31G(d,p), while gray region was modelled with 3-21G(d,p).

Further single-point energy using 6-31G(d,p) basis set for all atoms was also computed to get more accurate results.[29] For the TS structures, we also checked single points with 6-311++G(2d,2p).[11] The geometry of all ground state structures was fully optimized and in the case of transition states, a "loose" geometry convergence criterion was set to rms gradient below 0.0005 hartree/au. Tests showed that further optimization did not result in significant improvements in the geometry or energy. Spin contamination ($\langle S^2 \rangle$) values never exceeded 0.79, which is close to the theoretical expected value of 0.75. All species were verified by vibrational frequency analysis in order to ascertain that the computed transition states represented first-order saddle points. The total energies were corrected by zero-point vibrational energy (ZPE) and the respective thermal contributions at 353 K.

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