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Torsional Steering Controls the Stereoselectivity of Epoxidation in the Guanacastepene A Synthesis

Paul Ha-Yeon Cheong,[†] Heedong Yun,[‡] Samuel J. Danishefsky,[‡,§] and K. N. Houk*,[†]

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095-1569, Department of Chemistry, Columbia University, 3000 Broadway, New York, New York 10027, and Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, 1275 York Avenue, New York, New York 10021

houk@chem.ucla.edu

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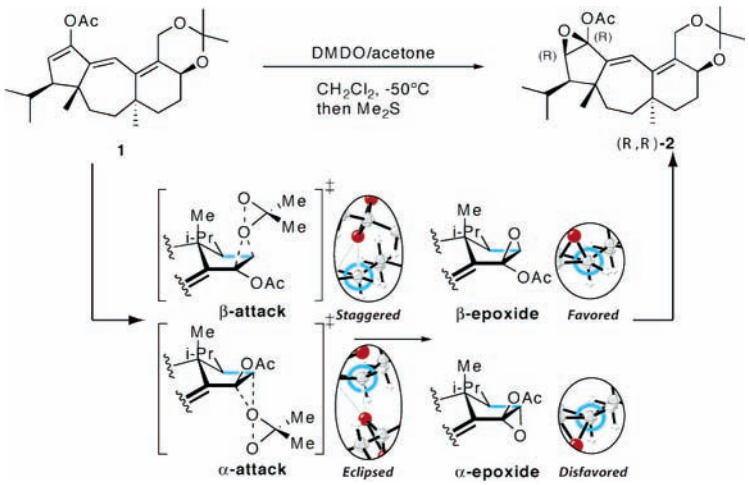
ABSTRACT



The stereoselectivity of the key epoxidation step in the synthesis of guanacastepene A is shown to be controlled by torsional steering. In this particular epoxidation reaction, the transition structure energetic difference is enhanced by the great asynchronicity of the forming C–O bonds that intensifies the torsional interactions.

The stereoselective epoxidation of the guanacastepene A precursor **1** constitutes a key step which provides the correct stereochemistry of the β-acetoxy ketone, as shown above.[1] Cursory inspection of the structure suggests that attack should occur on the α-face, yet exclusive formation of the β-epoxide was observed experimentally. The crystal structure of the hydroxyketone formed from **2** shows that the isopropyl group is in equatorial position, imparting little steric differentiation between the α- and β-faces.[1c] The computational study described here reveals that the origin of stereoselective β-attack in this epoxidation is a strong torsional control of stereoselectivity that we have named torsional steering.[2]

The computed epoxidation transition structures of a model alkene containing all of the substituents of the cyclopentene ring of guanacastepene precursor **1**, computed with density functional theory (B3LYP/6-31G*),[3] are shown in Figure 1.[4]

[†] University of California.
[‡] Columbia University.
[§] Sloan-Kettering Institute for Cancer Research.

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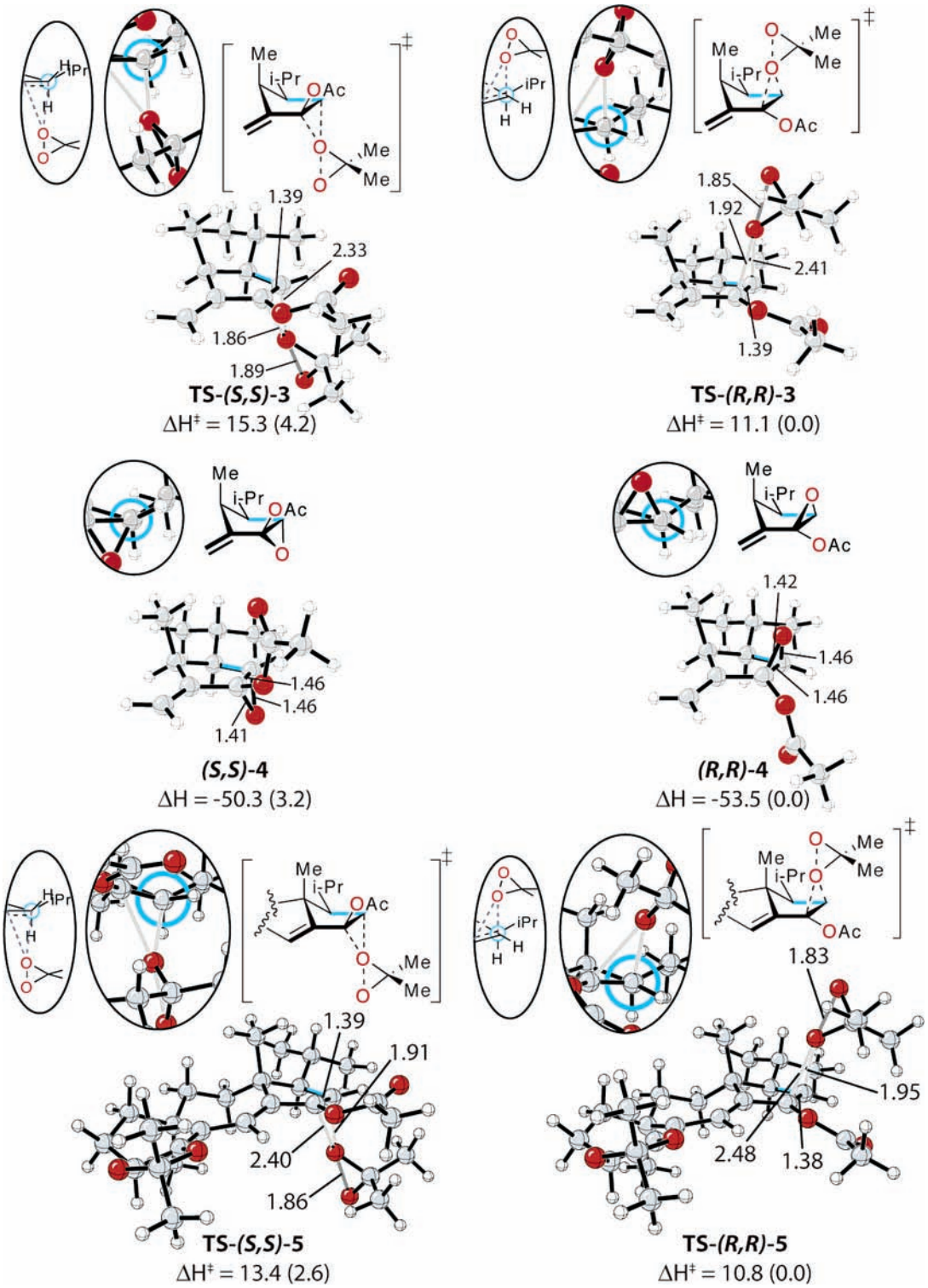


Figure 1. Model transition structures (**TS-(*S*,*S*)-3** and **TS-(*R*,*R*)-3**), model α- and *β*-epoxide products (**(*S*,*S*)-4** and **(*R*,*R*)-4**), and ONIOM transition structures of actual guanacastepene precursor **1** (**TS-(*S*,*S*)-5** and **TS-(*R*,*R*)-5**). The torsion of interest is highlighted in blue in each computed structure, and the corresponding Newman projections are shown in the oval insets. Energy values are in kcal/mol. Values enclosed in parentheses are relative energies in kcal/mol. See Scheme 1 for the ONIOM partition.

The α-epoxidation transition structure **TS-(*S*,*S*)-3**, with the dimethyldioxirane (DMDO) approaching from the sterically less hindered face of the cyclopentene ring, is 4 kcal/mol higher in energy than the analogous *β*-epoxidation process **TS-(*R*,*R*)-3**, in agreement with experimental observations that only the *β*-epoxide is formed.

Both transition structures are very asynchronous; one of the forming C−O bond lengths is ∼1.8 Å, while the other

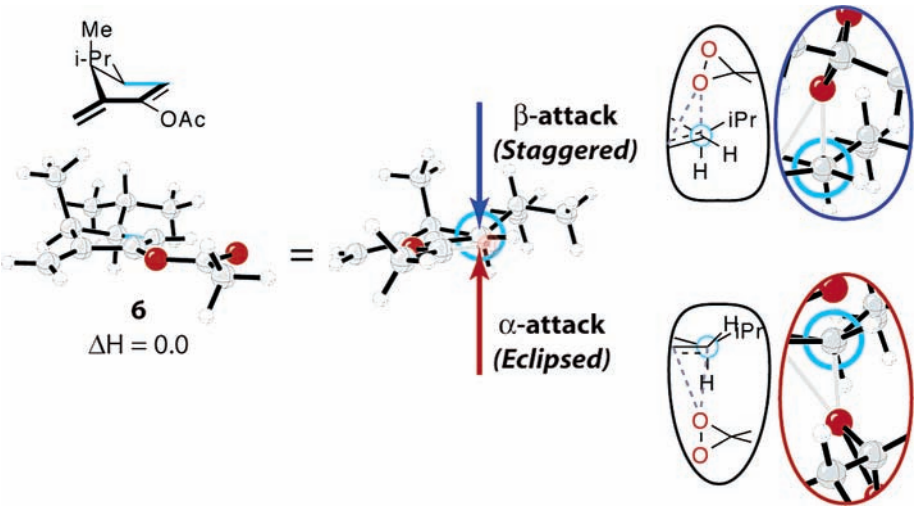


Figure 2. Reactant structure **6** and Newman projection that illustrate the resultant torsional effects for the α- and *β*-epoxidation transition states provided in the insets. Acetoxy oxygen has been rendered transparent in the Newman projection for clarity. The torsion of interest is highlighted in blue in reactant structure **6**.

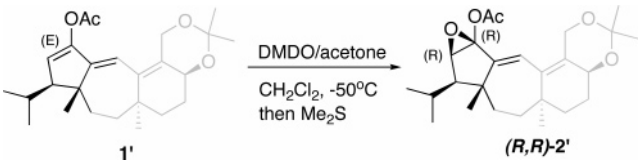
forming C−O bond length is ∼2.4 Å. This high asynchronicity is the result of electron donation from the acetoxy group and the conjugated alkene.

The inherent stability difference between the transition structures is due to the difference in torsional strain between bonds linking the forming epoxide to the rest of the skeleton, as shown in the Newman projections (insets) in Figure 1. The α-epoxidation transition structure **TS-(*S*,*S*)-3** exhibits substantial eclipsing, in contrast to the substantially more staggered *β*-epoxidation transition structure **TS-(*R*,*R*)-3**. Such torsional control of electrophilic or nucleophilic reactions has been observed in many reactions.[2]

The chair product **(*S*,*S*)-4**, which arises from the α-epoxidation, is also higher in energy by 3 kcal/mol than the boat product **(*R*,*R*)-4**, from *β*-epoxidation. Bicyclo[3.1.0]-hexane systems are known to prefer the boat conformation over the chair due to torsional interactions with the bridgeheads.[5] In the case of parent 6-oxabicyclo[3.1.0]hexane, this preference is computed to be 4.0 kcal/mol.[5d] As shown in the corresponding insets, the difference between the eclipsing in **(*S*,*S*)-4** and **(*R*,*R*)-4** is reduced as compared to the transition state.

To assess the effect that the rest of **1** may have on the transition structures, activation barriers for the actual guanacastepene precursor were also computed with the ONIOM method.[3] Density functional theory (B3LYP/6-31G*) was used for the cyclopentene ring of interest, while the PM3 semiempirical method was used for the rest of the target molecule, as shown in Scheme 1.

Scheme 1. ONIOM Partition As Described in Text[a]



[a] Black region was modeled with B3LYP/6-31G*, while the gray region was modeled by PM3.

The *β*-epoxidation transition structure **TS-(*R*,*R*)-5** is shown to be more stable by ∼2.5 kcal/mol than the analogous α-epoxidation transition structure **TS-(*S*,*S*)-5**. The slight lowering of the energetic difference is attributed to stabilizing $CH^{\delta+}—^{\delta-}O$ electrostatic interactions between the substituents of the cyclopentene ring and the approaching DMDO in **TS-(*S*,*S*)-5**.

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We have also investigated the effect of entropy and solvation on the stereoselectivity of this reaction. In all cases, the β-epoxidation transition structures were more stable than the analogous α-epoxidation transition structures. The free energy difference for the model transition structure **TS-(*S*,*S*)-3** and **TS-(*R*,*R*)-3** is 3.9 kcal/mol, while the analogous difference between the ONIOM transition structures **TS-(*S*,*S*)-5** and **TS-(*R*,*R*)-5** is 2.6 kcal/mol. Single-point PCM solvation energy calculations have been performed using the HF/6-31+G(d,p) basis set and UAKS radii with CH_2Cl_2 as the solvent. Solvation energy decreases the computed stereoselectivity by 2.6 kcal/mol for the model transition structures and 1.6 kcal/mol for the ONIOM transition structures. This decrease in computed stereoselectivity is the result of greater electrostatic stabilization of the later, and hence more zwitterionic, α-epoxidation transition structures. In the products **(*S*,*S*)-4** and **(*R*,*R*)-4** where the difference in zwitterionic character should be minimal, the difference in solvation energy is also minimal (0.8 kcal/mol).

Torsional steering, as the effect has been called, is a general factor involved in additions of nucleophiles, radicals, and electrophiles to multiple bonds, including carbonyls, imines, and alkenes.[2] The importance of such an effect was first identified by Felkin in the discussion of nucleophilic additions to cyclohexanones,[6] but it is now clear that it governs stereoselectivity in a wide variety of situations.[2] It can actually be identified in the conformation of the alkene reactant, shown in Figure 2. The effect influences the relative energies of diastereomeric conformations that involve torsional factors not present in the reactants, but which become significant in the products of the reaction. This effect has been reported previously,[2] but the current example in the guanacastepene synthesis is especially striking.

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Supporting Information Available: Cartesian and internal redundant coordinates, energies, thermodynamic corrections for all reported structures, and complete ref 3. This material is available free of charge via the Internet at http://pubs.acs.org.

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