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Origins of Selectivities in the Stork Diels−Alder Cycloaddition for the Synthesis of (±)-4-Methylenegermine

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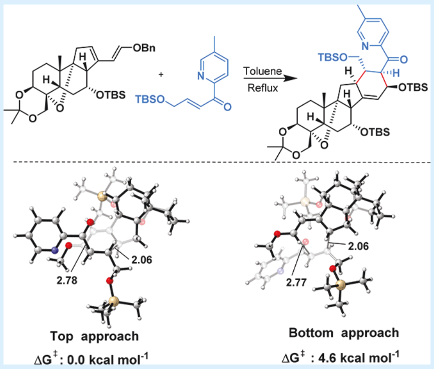
Supporting Information

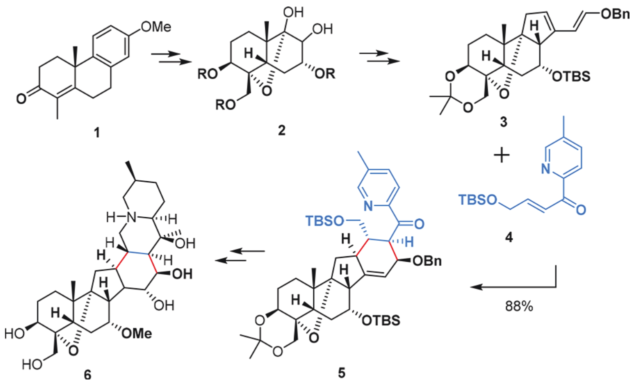
ABSTRACT: The remarkably high stereoselectivity of a Diels−Alder cycloaddition designed by Stork for the synthesis of germine has been examined with theory. We conceived a collaboration with Gilbert Stork, the great synthetic chemist and collaborator. We wished to complement Stork's insights with computations to explain the extraordinary selectivity he designed to introduce four new stereocenters in one step. Stork passed away on October 21, 2017, at age 95, sadly before we finished this work.



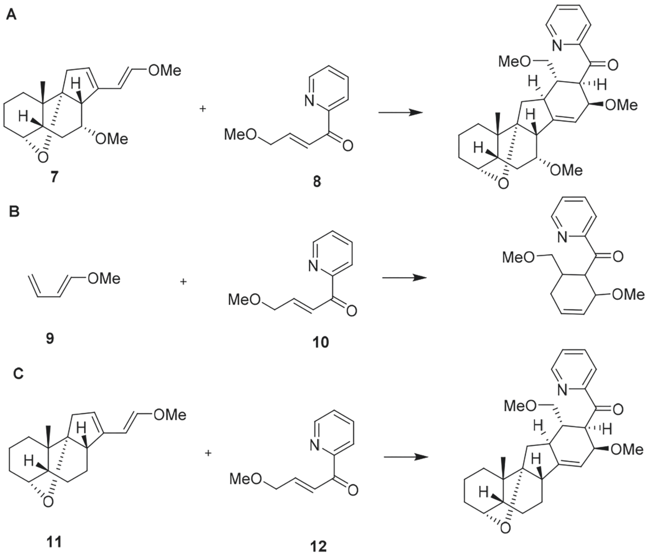
In his last paper, published a few months before his passing, synthetic organic chemist Gilbert Stork reported the Diels−Alder reaction of **3** and **4** as the key step in the synthesis of (±)-4-methylenegermine **6** (Scheme 1).[1] The cycloaddition exhibits remarkably high endo-exo and facial selectivity as well as regioselectivity. Only the Diels−Alder adduct **5** was observed.

We have studied theoretically the origins of the remarkable endo-exo and facial selectivity as well as regioselectivity using the simplified model systems shown Scheme 2 and checked our conclusions with the real system as well. Geometry optimizations and frequency calculations were carried out with the B3LYP density functional[2,3] and the 6-31G(d) basis set.[4] Single-point energy calculations were performed at the M06-2X[5−7]/6-311+G(d,p) level with the optimized structures. The SMD model[8] was used to account for the solvation effects of toluene. All of the calculations were performed using Gaussian 09,[9] and the structures were generated by CYLview.[10]

Scheme 1. Diels−Alder Cycloaddition Employed in the Synthesis of (±)-4-Methylenegermine



Scheme 2. Model Reactions Used To Study Computational the Observed Selectivities in the Diels−Alder Cycloaddition Employed in the Synthesis of (±)-4-Methylenegermine



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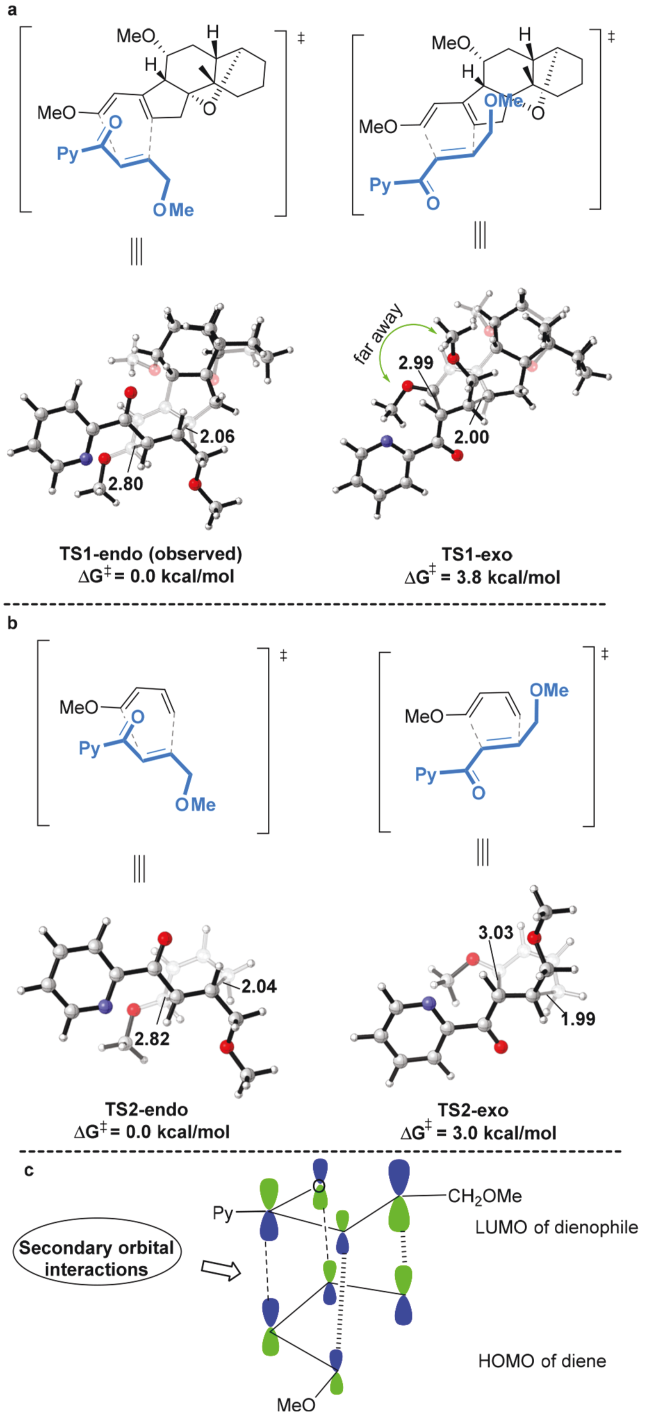

Figure 1. Calculated endo and exo transition structures and their relative Gibbs free energies for (a) the model reaction A and (b) a simple model B at the SMD-M06-2X/6-311+G(d, p)//B3LYP/6-31G(d) level of theory. (c) Secondary orbital interactions stabilizing the endo TS.

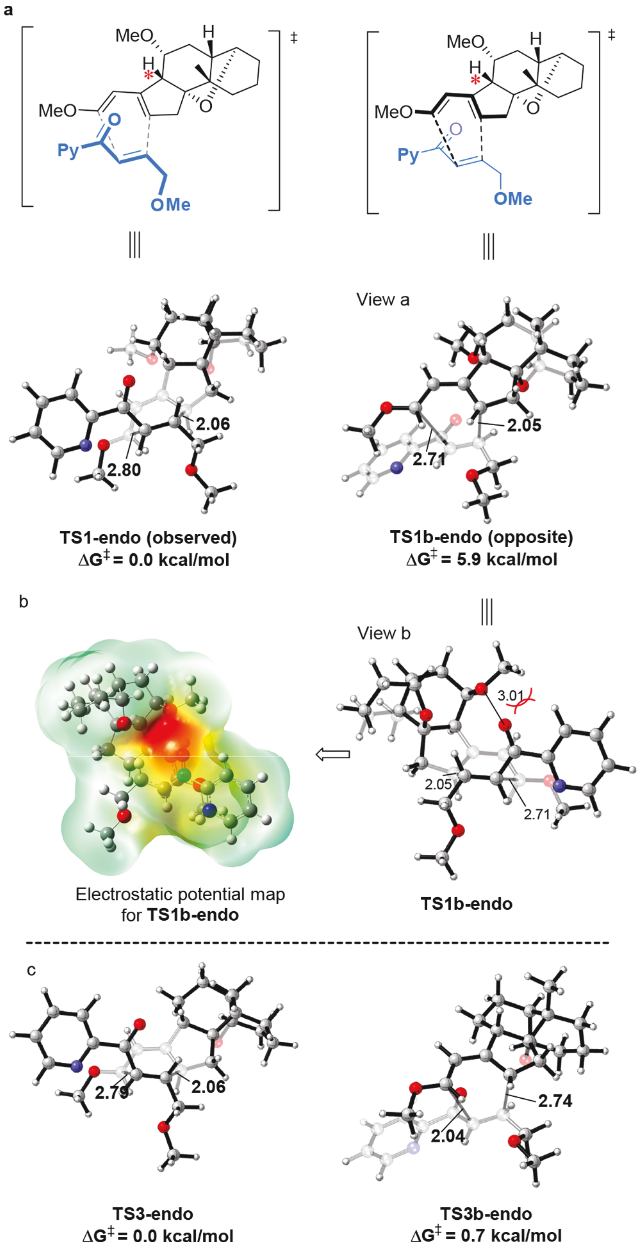

Figure 2. (a) Calculated endo transition structures and their relative Gibbs free energies for the dienophile approach from the top and bottom faces of diene for the model reactions A at the SMD-M06-2X/6-311+G(d, p)//B3LYP/6-31G(d) level of theory. (b) Electrostatic potential map for disfavored TS. (c) Endo transition structures for a simple model C.

We first studied the origins of the endo/exo selectivity. Figure 1a shows the calculated transition structures (TS) leading to endo and exo Diels–Alder products for reaction A. Both TS1-endo and TS1-exo are concerted yet highly asynchronous, each with a shorter forming bond at ∼2.0 Å and a longer forming bond at ∼2.9 Å. TS1-endo is 3.8 kcal/mol more stable than TS1-exo. This gives a ratio of endo/exo product higher than 99:1, consistent with the experimental observation that the endo product is the single product. Stork and co-workers proposed that "*there should be exclusive endo addition because exo addition would lead to very severe interference between the TBSO substituent on the dienophile and the diene.*[1]" The calculated TS-exo structure shows that the two methoxy groups, or TBSO in the actual substrate, have relatively small steric interference (Figure 1a). The calculated endo and exo TSs for model reaction B (Figure 1b) show that the TS2-endo is similarly favored by 3.0 kcal/mol over TS2-exo.[11] We believe that the endo selectivity arises mainly from secondary orbital interactions[12−14] involving orbital overlap of the carbonyl carbon and oxygen orbitals of the dienophile LUMO with the corresponding carbon orbitals of the diene

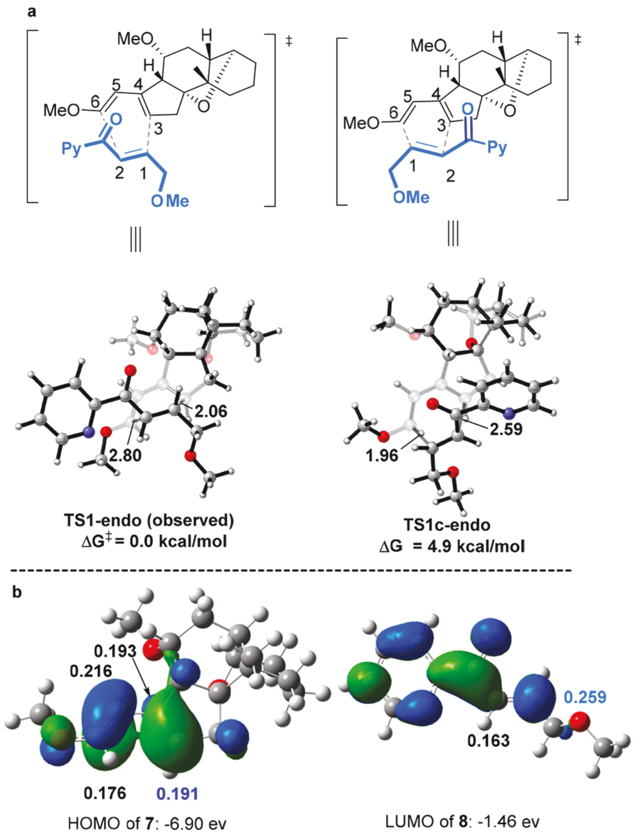

Figure 3. (a) Calculated regioselectivity determining transition structures and their relative Gibbs free energies for the model reaction A at the SMD-M06-2X/6-311+G(d, p)//B3LYP/6-31G(d) level of theory. (b) HOMO and LUMO of diene and dienophile in reaction A.

HOMO (Figure 1c). This type of interaction has been found to give ambimodal reactions in other cases.[15−19]

We next investigated the facial selectivities of reactions A and C. The dienophile can approach from the top or bottom faces of the diene. Stork and co-workers hypothesized that "*the dienophile would approach the more accessible face of the diene, i.e., cis to the starred hydrogen.*[1]" Figure 2a shows that the transition structure for the bottom approach (**TS1b-endo**) is 5.9 kcal/mol higher in energy than the top approach (**TS1-endo**). This means that only the product from the top approach (near the "starred H") transition structure will be observed as predicted. A closer inspection of the transition structures reveals that the O⋯O distance between the oxygen of methoxy group in diene and the oxygen of carbonyl group in dienophile is only 3.01 Å, an interatomic distance that is shorter than the sum of the van der Waals radii (3.04 Å). Thus, **TS1b-endo** is destabilized by O⋯O lone pair repulsion, which is clearly shown in the calculated electrostatic potential map (Figure 2b). Indeed, the replacement of the methoxy group in 7 with a hydrogen atom (reaction C) reduces the energy difference to 0.7 kcal/mol (Figure 2c), corroborating that the O⋯O lone pair repulsion is a key factor in facial selectivity. When Stork's actual substrates are computed, the energy difference is 4.6 kcal/mol (see TOC).

Finally, we investigated the regioselectivity. In the major product, the most nucleophilic site of the diene and electrophilic site of the dienophile are united. The transition state (**TS1c-endo**) for the attack at the dienophile C-1 terminus by the C-6 terminus of the diene is 4.9 kcal/mol higher in energy than by the C-3 terminus (**TS1-endo**) (Figure 3a). The computed molecular orbital coefficients of the diene and dienophile are presented in Figure 3b. Due to the presence of a methoxy group at the C-6 terminus, the C-3 terminus of diene possesses a larger coefficient than the C-6 terminus in the HOMO. For dienophile **8**, the larger orbital coefficient resides on the C-1 terminus in the LUMO as a result of the conjugation with carbonyl. The regioselectivity can be understood through frontier molecular orbital theory (FMO) with **TS1-endo** having the more favorable FMO interactions.[20−24]

The origins of the remarkably high endo-exo and facial selectivity as well as regioselectivity observed in this Diels−Alder cycloaddition have been explored to honor the remarkable insights by Gilbert Stork in his monumental design of the germine synthesis.[1]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02548.

Figures S1 to S3, optimized geometries of all computed species (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

We would like to dedicate this study to the memory of Gilbert Stork, who was a master molecule maker and one of the towering synthetic organic chemistry minds of our time.

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