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Origin of Diastereoselectivity in the Tandem Oxy-Cope/Claisen/Ene Reaction: Experimental and Theoretical Studies of the Ring Inversion Mechanism

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Abstract: We report herein a detailed investigation into the reaction mechanism of the oxy-Cope/Claisen/ene reaction. A series of chiral substrates was prepared, subjected to the tandem sequence, and the enantiomeric excess of the final products was evaluated. The observed conservation of enantiomeric excess was taken as evidence that the ring inversion of the intermediary enol ether does not occur. DFT calculations were used to map out the potential energy surface for the reaction and evaluate the relative energies of the ring inversions relative to those of the Claisen and ene reactions. Transition state energies thus obtained were found to support the presence of a high-energy transition state for the ring inversion of **B** to **D** provided $R_1 \neq H$. In addition, the calculations lent further support to the hypothesis that the selectivity of the transannular ene reaction is under Curtin−Hammett control.

Introduction

The pursuit of new methods for the generation of architecturally complex polycyclic molecules is an ongoing challenge for the synthetic organic community. Despite recent advances, however, difficulties remain. In particular, the stereoselective formation of quaternary carbon centers continues to be a significant obstacle.[1] Moreover, with the ever-increasing emphasis being placed on sustainability,[2] the need for efficient, waste-minimizing processes is becoming increasingly important. Consequently, the use of tandem reaction sequences has emerged as a particularly enticing means for the diastereoselective formation of multiple carbon−carbon bonds.[3] Any method which can incorporate both the efficiency of a tandem process and the stereoselective formation of quaternary carbon centers would thus be a significant advancement.

In 2004, we reported the development of a highly diastereoselective tandem oxy-Cope/Claisen/ene reaction as an efficient means of generating decalin skeletons possessing multiple contiguous stereocenters including a quaternary carbon at C9 and a tertiary alcohol at C10 (Figure 1).[4] The pervasiveness of such diterpenoid frameworks in nature makes this reaction cascade an attractive method for the synthesis of numerous natural products.[5] Accordingly, several such total syntheses are underway.[6]

In our original report,[4] an evaluation of the reaction mechanism and the origin of its diastereoselectivity was proposed based on product distributions and a qualitative assessment of the presumed transannular ene transition states. While our reasoning was sufficient to explain the original results, a more rigorous understanding would be advantageous in order to facilitate the expansion of substrate scope and bring into realization the potential for this method. Herein, we report an enhanced view of the reaction mechanism with new experimental findings as well as DFT calculations to expand upon our initial hypotheses.

Results and Discussion

From the reaction mechanism (Figure 2), it is clear that the diastereoselectivity is controlled by the conformational prefer-

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(1) For recent reviews, see: (a) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369. (b) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473. (c) Christoffers, J., Baro, A., Eds. *Quaternary Stereocentres: Challenges and Solutions for Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2005. (d) Ramon, D. J.; Yus, M. *Curr. Org. Chem.* **2004**, *8*, 149. (e) Douglas, C. J.; Overmann, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363. (f) Barriault, L.; Denissova, I. *Tetrahedron* **2003**, *59*, 10105. (g) Christoffers, J.; Baro, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1688. (h) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591. (i) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *110*, 402.

(2) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: New York, 1998.

(3) (a) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2006. (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (c) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195. (d) Ho, T.-L. *Tandem Organic Reactions*; Wiley: New York, 1992.

(4) Sauer, E. L. O.; Barriault, L. *J. Am. Chem. Soc.* **2004**, *126*, 8569.

(5) (a) Myrocin, C: Al-Yahya, M. A.; Muhammad, I.; Mirza, M.; El-Feraly, F. S. *J. Nat. Prod.* **1993**, *56*, 830. (b) Ellestad, G. A.; Kunstmann, M. P.; Mirando, P.; Morton, G. O. *J. Am. Chem. Soc.* **1972**, *94*, 6206. (c) Teucrolivin, A: Bruno, M.; Omar, A. A.; Perales, A.; Piozzi, F.; Rodriguez, B.; Savona, G.; de la Torre, M. C. *Phytochemistry* **1991**, *30*, 275.

(6) (a) Sauer, E. L. O.; Barriault, L. *Org. Lett.* **2004**, *6*, 3329. (b) Morency, L.; Barriault, L. *Tetrahedron Lett.* **2004**, *45*, 6105. (c) Arns, S.; Barriault, L. *J. Org. Chem.* **2006**, *71*, 1809.

(7) Pioneering work of Still demonstrated that the conformation of medium and large macrocycles affords an effective vehicle in which the asymmetric synthesis of stereogenic centers can be achieved. See: (a) Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981. (b) Still, W. C. *J. Am. Chem. Soc.* **1977**, *99*, 4186. (c) Still, W. C. *J. Am. Chem. Soc.* **1979**, *101*, 2493. (d) Still, W. *Curr. Trends Org. Synth., Proc. Int. Conf., 4th* **1983**, 233. (e) Still, W. C.; Murata, S.; Revial, G.; Yoshihara, K. *J. Am. Chem. Soc.* **1983**, *105*, 625. (f) Still, W. C.; Novack, V. J. *J. Am. Chem. Soc.* **1984**, *106*, 1148. (g) Still, W. C.; Romero, A. G. *J. Am. Chem. Soc.* **1986**, *108*, 2105.

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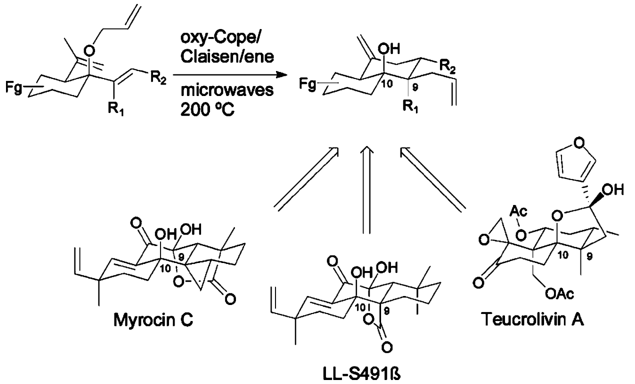

Figure 1. The oxy-Cope/Claisen/ene reaction: applications in total synthesis.

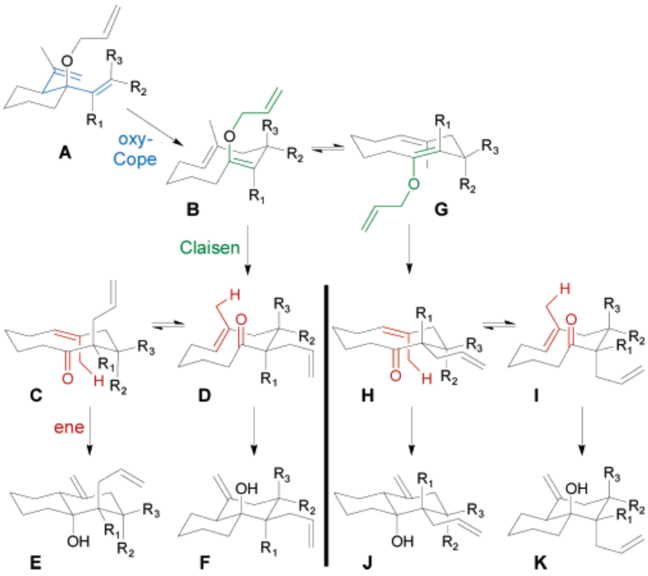

Figure 2. The oxy-Cope/Claisen/ene reaction mechanism.

ences of macrocyclic intermediates **B** and **D**.[7] Our initial findings prompted us to suggest that the ring inversion between **B** and **G** is slow relative to that of the Claisen rearrangement; conversely, the interconversion of **D** and **C** was presumed to be rapid compared to the rate of the transannular ene reactions, thus giving rise to Curtin−Hammett conditions.[8]

Our assertion that intermediates **B** and **G** did not readily interconvert arose from the observation that substrates **1** and **2** gave different products despite converging mechanisms (Figure 3). This result was rationalized by a high-energy barrier for the ring inversion relative to that of the Claisen rearrangement.

A large activation energy for this type of inversion is not without precedence: in 1980, Marshall and co-workers demonstrated that while (*E*)-cyclodecene is conformationally labile via inversion of the disubstituted olefin,[9] the tetrasubstituted olefin in (*E*)-1,2-dimethylcyclodecene fails to invert even at elevated temperatures.[10] We recently reported, however, a tandem oxy-Cope/ene reaction wherein a tetrasubstituted olefin, in the form of an enolate, was observed to rotate through its 10-memebered ring.[11] In light of this conflicting result, the generalization of a high-energy ring inversion for our oxy-Cope/Claisen/ene reaction clearly required further investigation. Of particular concern were those substrates which bore substitution only at R_1: since their products, **E** and **K**, were now enantiomeric (likewise for **F** and **J**), the formation of products resulting from the ring inversion of **B** to **G** was undetectable. Consequently, such substrates could only be assumed to observe the same relative kinetics as seen with substrates **1** and **2**.

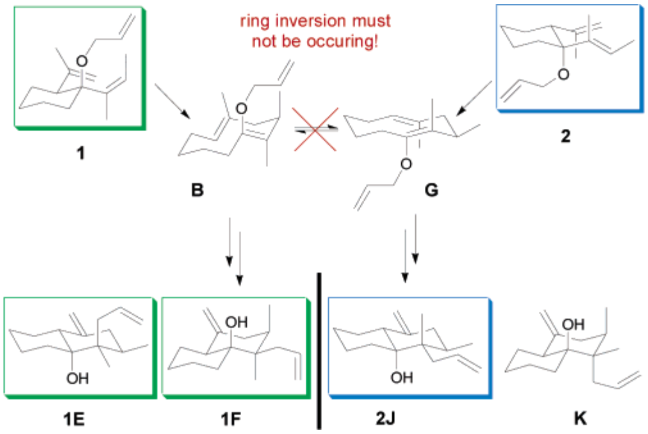

Figure 3. Evidence for a high-energy ring inversion.

In order to determine whether the ring inversion was occurring for such monosubstituted substrates ($R_1 \neq H$, R_2, $R_3 = H$), the use of enantioenriched compounds was envisioned such that any interconversion between **B** and **G** (now *ent*-**B**[12]) could be easily detected as a loss of enantiomeric excess in the final products (Figure 4).

The addition of the *gem*-dimethyl group was desirable since it allowed the enantioenriched compounds to be readily prepared from limonene, while avoiding the addition of any new chiral centers. From ketone **3**,[13] tandem precursors **7**, **8**, and **9** were prepared in both their chiral and racemic forms (Scheme 1).

Subjecting substrates **7**, **8**, and **9** to microwave radiation[14] at 200 °C in toluene for 1.5 h afforded the desired compounds with yields of 85%, 78%, and 91%, respectively (Scheme 2). To our delight, the enantiopurity of the products was completely conserved at 98% in all cases, thus confirming that the interconversion of **B** to *ent*-**B** via inversion of the tetrasubstituted olefin did not compete with the Claisen rearrangement. In addition, it should be noted that the observed diastereoselectivities reflected those obtained previously for the analogous substrate series indicating that the *gem*-dimethyl group does not

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(8) (a) Curtin, D. Y. *Recent Chem. Prog.* **1954**, *15*, 111. (b) Winstein, S.; Holness, N. J. *J. Am. Chem. Soc.* **1955**, *77*, 5562. (c) Eliel, E. L. *Stereochemistry of Carbon Compounds*; McGraw-Hill: New York, 1962. (d) Hammett, L. P. *Physical Organic Chemistry*; McGraw-Hill: New York, 1970; Chapter 5. (e) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83. (f) Seeman, J. I. *J. Chem. Educ.* **1986**, *63*, 42.

(9) Cope, A. C.; Banholzer, K.; Keller, H.; Pawson, B. A.; Whang, J. J.; Winkler, H. J. S. *J. Am. Chem. Soc.* **1965**, *87*, 3644.

(10) Marshall, J. A.; Konicek, T. R.; Flynn, K. E. *J. Am. Chem. Soc.* **1980**, *102*, 3287.

(11) Gauvreau, D.; Barriault, L. *J. Org. Chem.* **2005**, *70*, 1382.

(12) While devoid of any stereocenters, **B** and *ent*-**B** are enantiomeric by virtue of planar chirality. For more information on planar chirality in (*E*)-cycloalkenes, see: (a) Nakazaki, M.; Yamamoto, K.; Naemura, K. *Topp. Curr. Chem.* **1984**, *125*, 1. (b) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley-Interscience: New York, 1994.

(13) Dauben, W. G.; Lorber, M.; Fullerton, D. S. *J. Org. Chem.* **1969**, *34*, 3587.

(14) For reviews on the use of microwaves in organic synthesis, see: (a) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathé, D. *Synthesis* **1995**, 1213. (b) Majetich, G.; Hichs, R. J. *Journal of Microwave Power and Electromagnetic Energy* **1995**, *30*, 27. (c) Loupy, A.; Perreux, L. *Tetrahedron* **2001**, *57*, 9199. (d) Lidström, P.; Tierny, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225. (d) Loupé, A. *Microwaves in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2006.

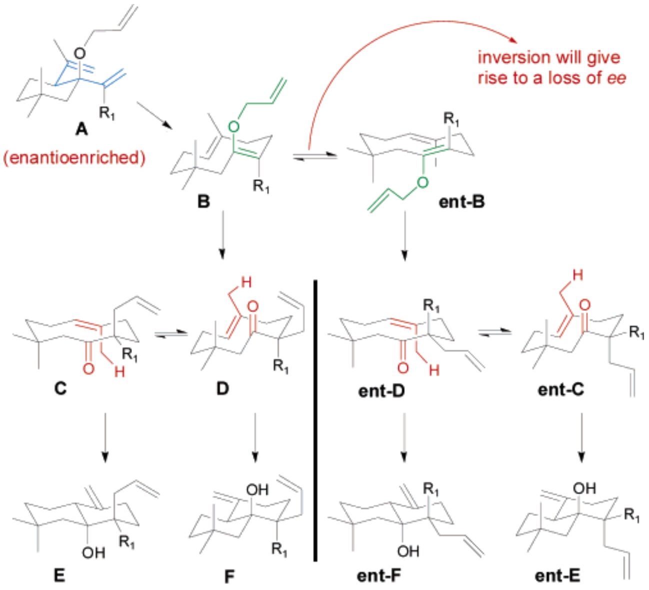

Figure 4. Ring inversion indicated by a loss of enantiomeric excess.

interfere with the relative kinetics of the process to any appreciable extent.[15]

While the above investigation offers conclusive evidence that the ring inversion does not occur for this class of substrates, it provides no information regarding the activation energy for the conversion of **B** to *ent*-**B** relative to that of the Claisen rearrangement. Moreover, no effort has been made to determine the activation energy for the inversion of a tetrasubstituted olefin through a 10-membered ring either experimentally[16] or theoretically.[17] In order to advance the scope of this reaction, it would be beneficial to know how much higher in energy the ring inversion is than the competing Claisen rearrangement. Such information would allow one to assess how reliably the ring inversion, and consequentially, the formation of additional diastereomers could be avoided. To this end, the use of density functional theory calculations was pursued in order to map out the potential energy surface for the tandem reaction sequence.

Substrate **10** was chosen as representative for the previously reported tandem reactions (Scheme 3).[18] For comparison, substrate **11** was also modeled: as part of a related project in our laboratory,[19] its oxy-Cope/Claisen/ene reaction was found to proceed with complete racemization; given that the inversion of intermediate **B** to *ent*-**B** now involves the rotation of a trisubstituted olefin through the ring, its energy profile would provide us with an opportunity to assess the energetic cost associated with the inversion of a tri- versus tetrasubstituted olefin.

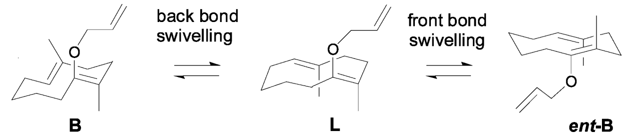

Figure 5. Stepwise ring inversion.

Of particular importance to our theoretical examination of the tandem sequence were the ring inversion transition state energies. It should be noted, however, that the interconversion of **B** to *ent*-**B** is in fact a two-step process, and the rotation of each double bond must be treated separately.[20] Thus, for substrate **10**, the inversion of intermediate **B** to *ent*-**B** goes through partially inverted enol ether, **L** (Figure 5).[21]

Gas-phase relative free energies at 473 K (200 °C) were obtained for intermediates **B**, **L**, and **D**, as well as the Claisen and ring inversion transition states for both substrates **10** and **11**. All energies and geometry optimizations were performed on the Jaguar 6.0 program[22] using Kohn−Sham DFT[23] at the B3LYP level of theory[24] with a 6-311G(d,p) basis set. All of the reported energies include unscaled zero-point energy corrections. Frequency calculations were performed on all stationary points to confirm that minimum energy structures had no imaginary frequencies and that transition states had one and only one imaginary frequency. For the transition state structures, the eigenvector of the imaginary frequency was also examined to evaluate if the mode could bring the "reactant" to the "product". Intrinsic reaction coordinate (IRC) calculations were performed for the ring inversion transition states **B**−**L**‡ and **L**−*ent*-**B**‡ for substrates **10** and **11**.

Due to conformational flexibility in the 10-membered ring and allyl substituent, comprehensive conformer searches were carried out according to the following procedure. First, a conformational search was performed at the semiempirical PM3 level of theory[25] using the default Monte Carlo based conformational search engine of the Spartan 2002 molecular modeling package.[26] Of the 500−1700 structures sampled (the exact number varied between intermediates and substrates depending on the number of rotatable bonds involved), the 10 lowest-energy, distinct conformers obtained were then optimized at the B3LYP/6-31G(d,p) level, the lowest energy of which was further optimized at the B3LYP/6-311G(d,p) level.

Transition states for the **B**−**L**‡ and **L**−*ent*-**B**‡ structures were first found with a simplified model wherein the −Oallyl group

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(15) A lack of interference by the *gem*-dimethyl group is further supported by a study on the ring inversion of an (*E*,*Z*)-cyclononadiene system; the authors found that substitution along the alkyl chain did not influence the relative energy barriers for the ring inversion. Deiters, A.; Müch-Lichtenfeld, C.; Fröhlich, R.; Hoppe, D. *Chem. Eur. J.* **2002**, *8*, 1833.

(16) The closest systems to ours for which the ring inversion activation energies have been determined experimentally are (a) (*E*)-cyclodecene-1,2,4,4,9,9-d_6: Binsch, G.; Roberts, J. D. *J. Am. Chem. Soc.* **1965**, *87*, 5157. (b) (*E*)-1,2-dimethylcycloalkenes of ring size 12, 13, and 14: Marshall, J. A.; Audia, V. H.; Jenson, T. M.; Guida, W. C. *Tetrahedron* **1986**, *42*, 1703.

(17) Theoretical studies into the ring inversion mechanism have been reported for related systems. See (a) (*E*,*E*)-cyclodecadiene: Yavari, I.; Hosseini-Tabatabaei, M. R.; Nori-Sharhg, D.; Jabbari, A. *J. Mol. Struct. (THEOCHEM)* **2001**, *574*, 9. (b) (*E*,*Z*)-cyclononadiene: see ref 15. (c) (*E*)-1,2-dimethyl-cycloalkenes of ring size 12, 13, and 14: see ref 16b.

(18) The oxy-Cope/Claisen/ene reaction of **10** was reported in our original communication (see ref 4). Its use as a model substrate, rather than **7**, was chosen since removal of the *gem*-dimethyl group both simplified the conformational searches and reduced computational time.

(19) Gauvreau, D. Enantioselective Tandem Oxy-Cope/Ene Reaction. M.Sc. Thesis, University of Ottawa, Ottawa, ON, 2003.

(20) It was suggested by a referee that the conversion of **B** to *ent*-**B** may proceed as a single step. While it is true that such a transition state might exist, the likelihood of it being low enough in energy to compete with a multistep pathway was ruled out after building a molecular model of **B** using a plastic model kit: to simultaneously pass both olefins through the ring forces the methyl and hydrogen substituents to occupy the same space in the already crowded cavity of the 10-membered ring.

(21) Alternatively, the front bond could rotate first, followed by the back double bond, going through the intermediate *ent*-**L**. Since this process is enantiomeric to the one depicted in Figure 5, their energies are equivalent and were therefore not calculated.

(22) *Jaguar 6.0*; Schrodinger LLC: Portland, OR, 2005.

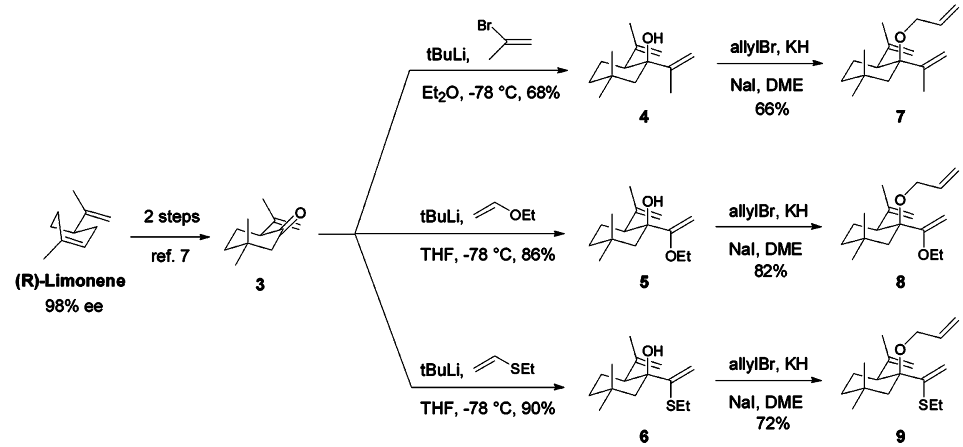
(23) (a) Hohenburg, P.; Kohn, W. *Phys. Rev. B* **1964**, *136*, 864.(b) Kohn, W.; Sham, L. J. *Phys. Rev. A* **1965**, *140*, 1133.

(24) (a) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785. (b) Becke, A. D.; *J. Chem. Phys.* **1993**, *98*, 5648.

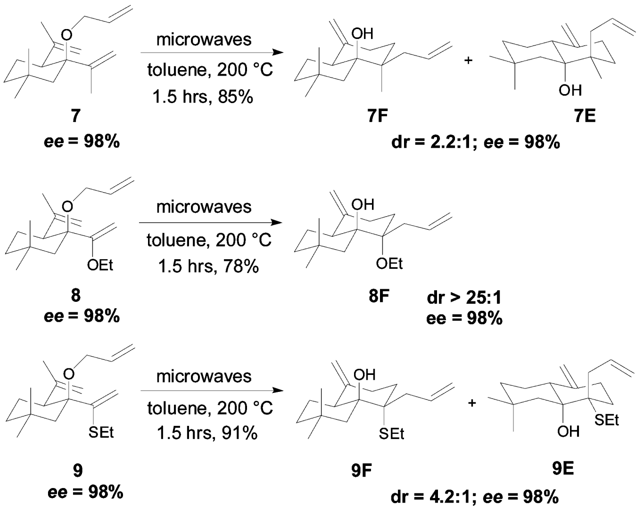
(25) Stewart, J. J. P. *Comput. Chem.* **1989**, *10*, 209.

(26) *Spartan '02*; Wavefunction Inc.: Irvine, CA, 2002.

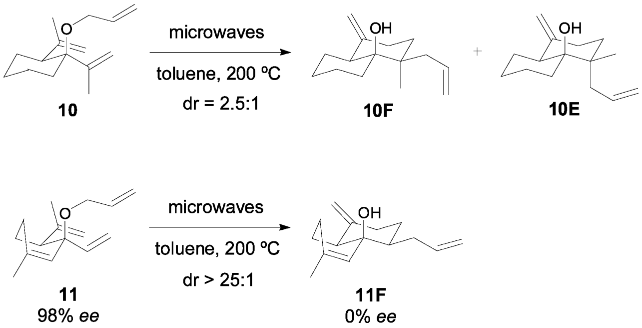
Scheme 1. Preparation of Enantioenriched Tandem Precursors



Scheme 2. Tandem Reaction of Chiral Substrates: Conservation of Enantiomeric Excess



Scheme 3. Tandem Reactions To Be Modeled with DFT Calculations



was replaced by an −OMe group. Once a transition state was found at the B3LYP/6-31G(d,p) level of theory and confirmed to have one imaginary frequency, a Monte Carlo based conformational search was performed on the structure with the coordinates of the two olefins frozen. In this way the conformations of the ring were sampled to search for other possible conformations of the backbone that might lead to a lower energy inversion barrier. The lowest-energy, distinct structure thus obtained was used as a starting point for another transition state search at the B3LYP/6-31G(d,p) level. The −OMe group of the resulting lowest-energy transition state was replaced with an −Oallyl group, and a Monte Carlo based conformational search was performed on the allyl group (all other coordinates were frozen). The lowest-energy, distinct structures were then used as starting structures for transition state searches at the B3LYP/6-31G(d,p) level of theory. The lowest energy transition state structure was then finally optimized at the B3LYP/6-311G-(d,p) level. In some cases, several transition state structures were located that were within 2 kcal/mol energy of one another. However, the differences in these structures involved small conformational changes of peripheral groups, rather than a different core mechanism.

Table 1. Relative Free Energies for Substrates **10** and **11**, Zeroed to **B**

species (**10**)	ΔG (kcal/mol)[a]	species (**11**)	ΔG (kcal/mol)[a]
D	−18.78	**D**	−25.51
B−**D**‡	24.06	**B**−**D**‡	24.32
B	0.00	**B**	0.00
B−**L**‡	17.27	**B**−**L**‡	19.35
L	2.61	**L**	3.27
L−*ent*-**B**‡	163.15	**L**−*ent*-**B**‡	18.09
ent-**B**	0.00	*ent*-**B**	0.00

[a] Gas-phase relative free energy at 473 K calculated at the B3LYP/6-311G(d,p) level of theory.

The potential energy surface for these systems is "complicated" in that they possess many shallow local minima, and the pathways taken between **B** and *ent*-**B** probably include several lower energy processes relating to the interconversion of different conformers. Such processes, however, can reasonably be assumed to be significantly lower in energy than the respective ring inversion transition state energies. Accordingly, our attention was focused on the rate-limiting steps for these processes, **B**−**L**‡ and **L**−*ent*-**B**‡, and the lowest energy conformers for intermediates **B**, **L**, and *ent*-**B**. The results of these calculations are summarized in Table 1 and Figures 6 and 7.

The energy profiles for substrates **10** and **11** showed similar relative energies for the ground-state intermediates **B**, **D**, and **L**, as well as for the transition states of the Claisen rearrangement, **B**−**D**‡, and the first step of the ring inversion, **B**−**L**‡. Not surprisingly, the second step of the ring inversion revealed a significant difference in the activation energy for the rotation of the tetra- and trisubstituted olefins: in the case of **10**, the tetrasubstituted olefin forces a methyl group to pass through the ring (compared to a hydrogen for substrate **11**) at an added cost of 145 kcal/mol.

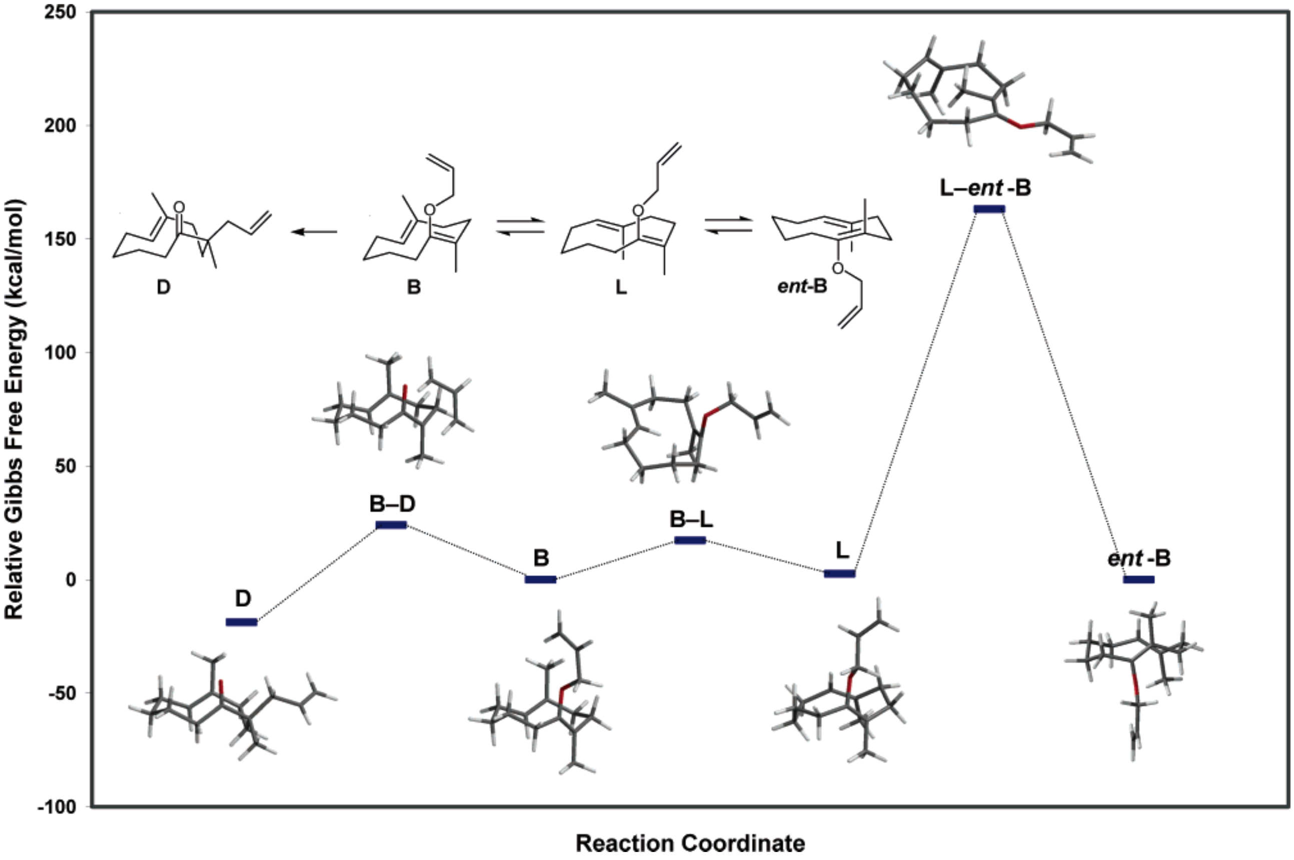
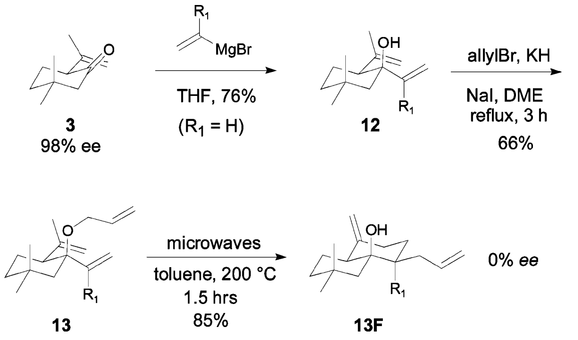


Figure 6. Calculated free energy profile for substrate **10**, zeroed to **B** (no ring inversion observed).

Scheme 4. Confirming the Effect of Vinylic Substitution: Racemization When $R_1 = H$



While the existence of a high-energy barrier for this ring inversion was anticipated, its magnitude was not. To the best of our knowledge, this represents the first attempt to determine the activation energy for the inversion of an (*E*)-tetrasubstituted olefin through a 10-memebered ring. In light of the energetic cost associated with this process, it becomes clear that the Claisen rearrangement should be highly favored over the ring inversion for any substrates bearing substitution at R_1, thus preserving the diastereoselectivity of the process.[27]

To test this idea further, enantioenriched **13** was prepared and subjected to the tandem oxy-Cope/Claisen/ene reaction. Having replaced the R_1 methyl substituent with a hydrogen, enol ether intermediate **B** was expected to undergo rapid inversion to *ent*-**B** resulting in a loss of chirality. Indeed, the oxy-Cope/Claisen/ene reaction of **13** was found to proceed with complete racemization (Scheme 4).

Table 2. Relative Free Energies for the Transannular Carbonyl Ene Reaction of Substrate **10**, Zeroed to **D**

species (**10**)	ΔG (kcal/mol)[a]
F	−0.20
D−**F**‡	33.83
D	0.00
D−**C**‡	14.03
C	−0.47
C−**E**‡	34.39
E	0.10

[a] Gas-phase relative free energy at 473 K calculated at the B3LYP/6-311G(d,p) level of theory.

Having successfully modeled the first half of the reaction mechanism, our attention was turned to the latter portion. From the product distributions of our previously reported substrates, as well as a qualitative assessment of the transannular ene transition states, we had suggested that the selectivity of the ene reaction was governed by the Curtin−Hammett principle. To evaluate this hypothesis, the barrier for inversion from **D** to **C** would need to be compared to the transition state energies of the two transannular ene reactions.

While still a two-step process, the ring inversion of **D** to **C** differs in that there is only one (*E*)-olefin required to rotate through the ring; the carbonyl is capable of a simple rotation outside the ring (Figure 8). Consequently, $\Delta G^‡_{DM} \ll \Delta G^‡_{MC}$,

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(27) Given the significant activation energy for the ring inversion of the tetrasubstituted olefin, the feasibility of such a process when enol ether **B** is replaced by an enolate (see ref 11) becomes questionable. Accordingly, an investigation into the mechanism of racemization for the oxy-Cope/ene reaction is underway and will be reported in due course.

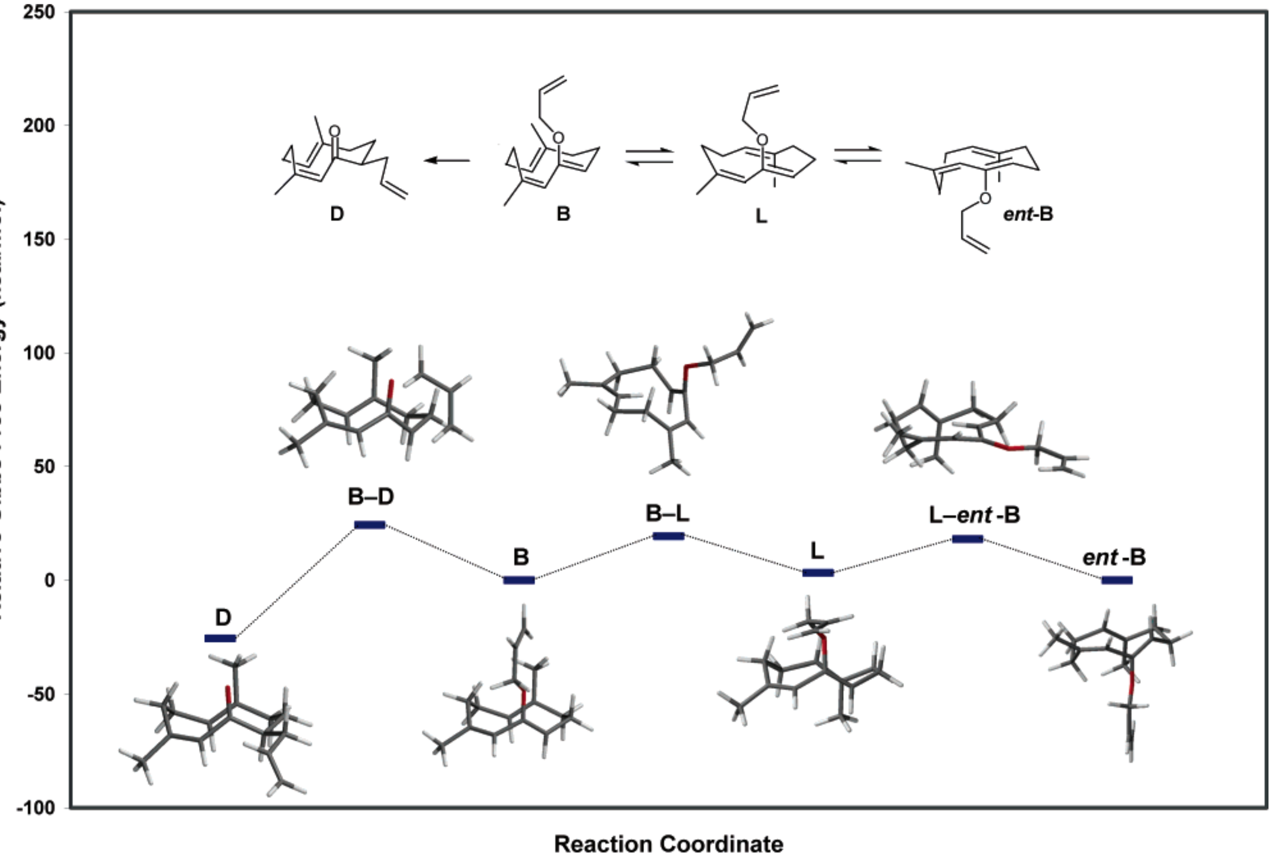


Figure 7. Calculated free energy profile for substrate **11**, zeroed to **B** (ring inversion observed).

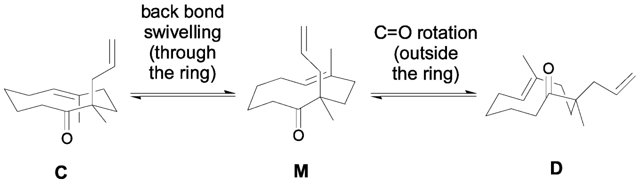


Figure 8. Stepwise conversion of **D** to **C**.

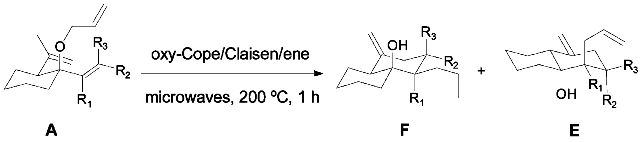
and the rate-limiting step for the interconversion of **D** and **C** is expected to be the transformation of **M** to **C**.

Gas-phase relative free energies at 473 K (200 °C) were calculated for the relevant intermediates and transition states for substrate **10** according to the procedures described above. These results are summarized in Table 2 and Figure 9. The barrier to ring inversion was found to be 14 kcal/mol, about 5 kcal/mol lower than the comparable process of **B** to **L** (Figure 6). This is likely due to an increase in flexibility for intermediate **D** as a result of having only one double bond present in the ring. Both transannular ene reactions were found to have activation energies around 34 kcal/mol, confirming our hypothesis of a comparatively rapid ring inversion.

It is to be noted that the calculations predict the intermediates **C** and **D** to be thermoneutral with the products **E** and **F**. These energetics suggest one should be able to isolate the intermediates **C** and **D**, even though experimentally they have never been observed. The B3LYP exchange-correlation functional has been shown to underestimate the exothermicity of converting a π bond to a σ bond.[28] This could explain the discrepancy between the calculations and the experimental observations. (We note that calculations with the PBE exchange-correlation functional predict that **C** and **D** are 2.19 and 2.67 kcal/mol higher in energy than **F**, respectively, and that **E** is 0.23 kcal/mol less stable than **F**). For our purposes, however, we were interested in the relative energies of transition states **D**−**F**‡ and **C**−**E**‡ rather than the thermodynamics of the corresponding reactions.

For Curtin−Hammett to apply, two conditions must be met: the reaction must be irreversible and the ring inversion rate constant must be at least an order of magnitude greater than

Table 3. Calculated and Observed Product Ratios Assuming Curtin−Hammett Control



entry	substrate	R_1	R_2	R_3	$\Delta\Delta G^‡_{calcd}$ (kcal/mol)[a]	**F/E** – predicted	$\Delta\Delta G^‡_{exptl}$ (kcal/mol)[b]	**F/E** – observed
1	**10**	Me	H	H	0.56	1.8	0.86	2.5
2	**1**	Me	H	Me	−2.13	0.1	−1.13	0.3
3	**2**	Me	Me	H	3.88	62.1	>3.03	>25
4	**14**	SEt[c]	H	H	1.97	8.1	1.09	3.2
5	**15**	OEt[c]	H	H	9.19	17485.2	>3.03	>25

[a] Calculated difference in gas-phase free energies at 473 K for the ene transition states **D**−**F**‡ and **C**−**E**‡. [b] Experimental difference in energy between the ene transition states based on the observed **F**/**E** ratio. [c] To simplify calculations, the ethyl group was reduced to a methyl group.

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(28) Check, C. E.; Gilbert, T. M. *J. Org. Chem.* **2005**, *70*, 9828.

(29) Seeman, J. I.; Farone, W. A. *J. Org. Chem.* **1978**, *43*, 1854.

(30) Molecular mechanics calculations have been used to model the ene reaction of related cyclodecenone systems. In both cases, the authors similarly concluded that the product selectivity was determined by the relative energy of the transition states rather than the population of the ground state conformers. See: (a) Terada, Y.; Yamamura, S. *Tetrahedron Lett.* **1979**, *18*, 1623. (b) Do<crn>sen-Mićović, J; Lorenc, L.; Mihailović, M. L. *Tetrahedron* **1990**, 3659.

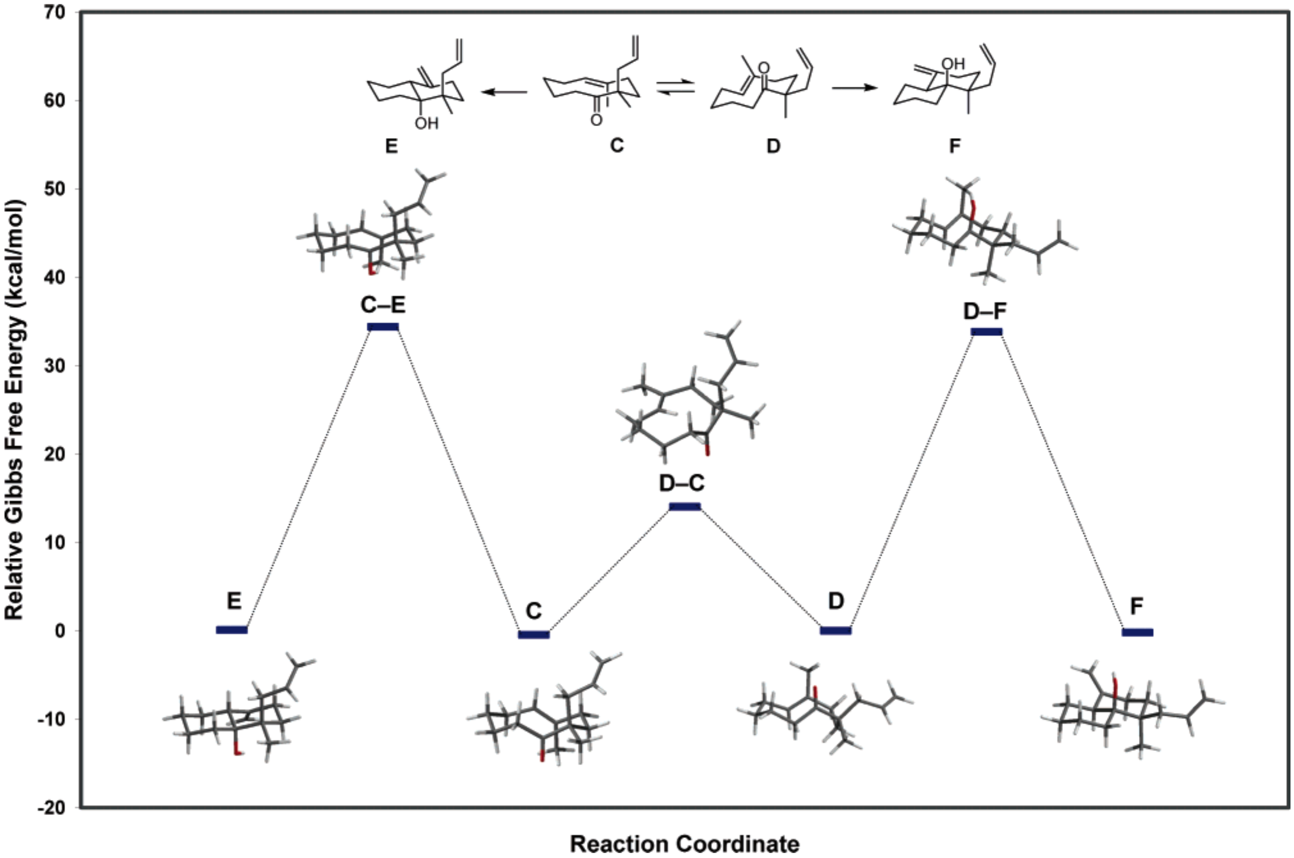

Figure 9. Calculated free energy profile for the transannular carbonyl ene reaction of substrate **10**, zeroed to **D**.

that of the Claisen rearrangement ($k_{\text{inversion}} \geq 10k_{\text{ene}}$).[29] The irreversibility of our reaction was proven experimentally by resubjecting the minor product (**10E**) to the reaction conditions for 1 h: none of the major isomer was detected by crude NMR. Although we lack kinetic data, the ~20 kcal/mol difference in energy between the inversion and ene transition states suggests that the second condition is also met. If we therefore assume Curtin−Hammett conditions are in effect, we should be able to predict the product ratio from the calculated transition state energies for the two ene reactions using eq 1. Indeed, the calculated values predict a 1.8:1 ratio of products, in close agreement with the observed 2.5:1 ratio.[30]

$$[\mathrm{F}]/[\mathrm{E}] = \exp[(\Delta G_{\mathrm{CE}}{}^{\ddagger} - \Delta G_{\mathrm{DF}}{}^{\ddagger})/RT] \qquad (1)$$

Interested in whether the calculated product ratios of other substrates could be similarly fit to their experimental data, we began modeling the two competing ene transition states for a selection of our previously tested compounds.[4] In all cases, the predicted ratios closely mirror the observed ratios with less than a kcal/mol difference in energy between the predicted and experimentally determined $\Delta\Delta G^{\ddagger}$ values (Table 3). Notably, substrate **1** (entry 2) is accurately predicted to favor product **1E**, rather than the thermodynamic product, **1F**.[31] Likewise, the formation of a single observable isomer for substrates **2** and **15** is accurately predicted (entries 3 and 5). These ratios, together with the energy profile obtained for **10**, strongly suggest that Curtin−Hammett conditions are in effect.

Conclusion

The tandem oxy-Cope/Claisen/ene reaction is a powerful method for the stereoselective formation of contiguous stereogenic centers along a *trans*-decalin framework. Fundamental to its utility, however, is the ability to accurately predict and control its product distributions. This requirement can only be met by a clear understanding of the reaction mechanism. The experimental evidence presented in this paper, along with the DFT calculations of key intermediates and transition states, has provided insight into the factors which govern the selectivity of this reaction. Most notably, the occurrence of a ring inversion from **B** to **G** (or *ent*-**B**, when $R_2 = R_3 = H$) was found to be entirely dependent on whether a tri- or tetrasubstituted double bond was present in the enol ether intermediate. As a result, controlling the substitution at R_1 allows one to determine whether products **J** and **K** will be accessible. Finally, the ene reaction and the interconversion between intermediates **C** and **D** was evaluated. DFT calculations supported our original hypothesis of a facile interconversion between **C** and **D**, and a variety of substrates were found to be following Curtin−Hammett conditions.

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(31) The ground state free energies were found to slightly favor the minor product, **1F**, by 0.14 kcal/mol.

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Supporting Information Available: Experimental procedures, spectroscopic data, and copies of ^{1}H and ^{13}C NMR for all new compounds; details regarding the assignment of stereochemistry for all tandem products including 2D NMR spectra where appropriate; Cartesian coordinates, calculated frequencies, and total energies for all calculated intermediates and transition states. This material is available free of charge via the Internet at http://pubs.acs.org.

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