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Origins of Selectivity in Pericyclic Reaction Cascades for the Synthesis of Gambogin and Lateriflorone

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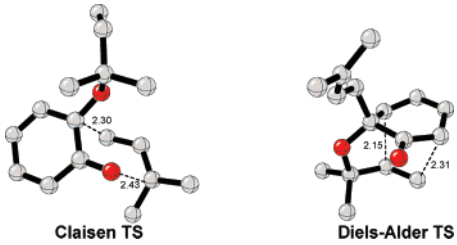
ABSTRACT



Quantum mechanical calculations demonstrate that the second step of a Claisen–Diels–Alder reaction cascade controls regioselectivity that gives advanced intermediates for the synthesis of gambogin and 1-*O*-methyllateriflorone.

Gambogin[1] (**1**) and lateriflorone[2] (**2a**) (Figure 1) are cytotoxic natural products that have tricyclic, caged molecular architectures that have provided a challenge for synthetic chemists. One of our groups recently synthesized 1-*O*-methylforbesione,[3] gambogin,[4] and 1-*O*-methyllateriflorone[5,6] (**2b**) by exploiting a biomimetic pericyclic reaction cascade.

Theodorakis and co-workers used a similar approach to synthesize other lateriflorone derivatives[7,8] such as forbesione and desoxymorellin. In these cases, cascade Claisen−Diels−Alder−Claisen sequences were utilized.[9,10]

To understand the origins of regioselectivity, a simple model system (Scheme 1) was used. All systems in this paper were evaluated using computational methods, namely density

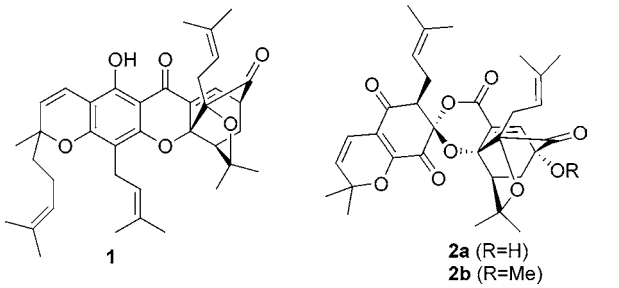


Figure 1. Natural products gambogin (**1**), lateriflorone (**2**), and 1-*O*-methyllateriflorone (**2b**).

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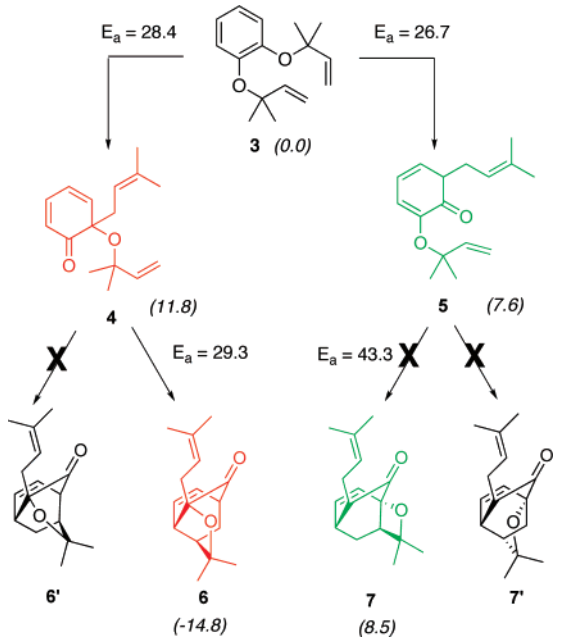
Scheme 1. Possible Pathways in the General Model System



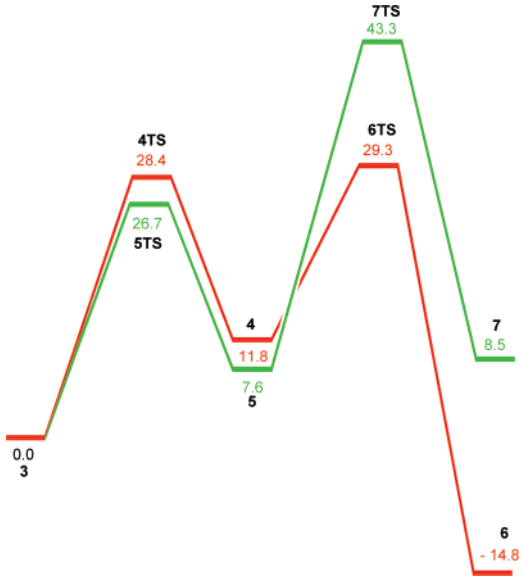


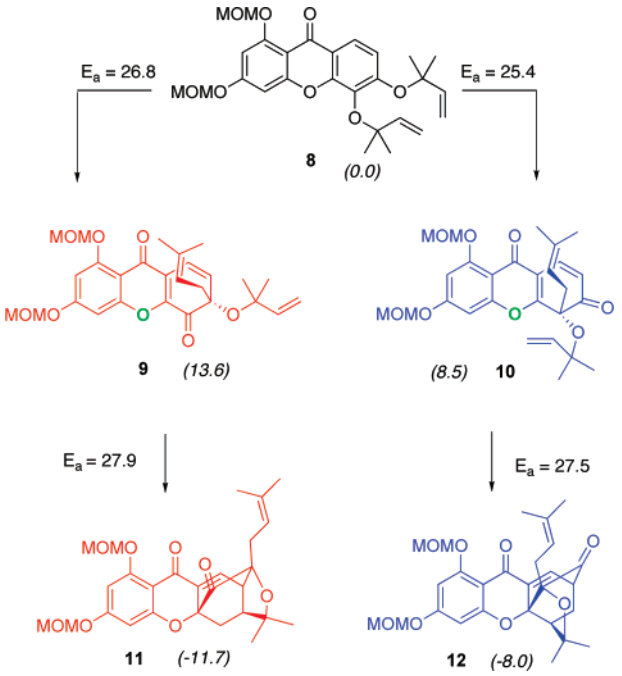
Figure 2. Energy profile of model system.

functional theory (DFT) at the B3LYP/6-31G(d) level, computed using Gaussian 03.[11] There are only two possible products of the Claisen rearrangement, since removing the substituents encountered in the real system gives 2-fold symmetry. The four products shown represent favored products (red) and unfavored products (green and black) in both the gambogin and lateriflorone systems. The black Diels−Alder adduct (**6′** and **7′**) structures could not even be located on the potential energy surface due to geometric strain. An energy profile for the model system is shown in Figure 2. Both Claisen intermediates of the model system are of similar energy, and there is a small preference for the formation of the alkoxy-substituted dienone **5**. However, the nonobserved pathway was found to have a high-energy Diels−Alder transition state and product, rendering this pathway unfeasible due to the strain in **7**, which possesses a four-membered ring.

The aryl ethers **8** and **13** (Schemes 2 and 3) were used to synthesize gambogin and lateriflorone via the Claisen−Diels−Alder cascade. Compound **8** produces **11** and **12** in a 1:3 ratio, while **13** produces **16** and **17** in a 1.1:1 ratio.

Each of the starting materials has four possible Claisen rearrangement possibilities (Figure 3). All four pathways were calculated for both starting materials. Theodorakis[9] proposed that differences in resonance stabilization of the oxygen (marked as green in Scheme 2) and the carbonyl

Scheme 2. Possible Pathways from **8** to an Advanced Intermediate for the Synthesis of Gambogin



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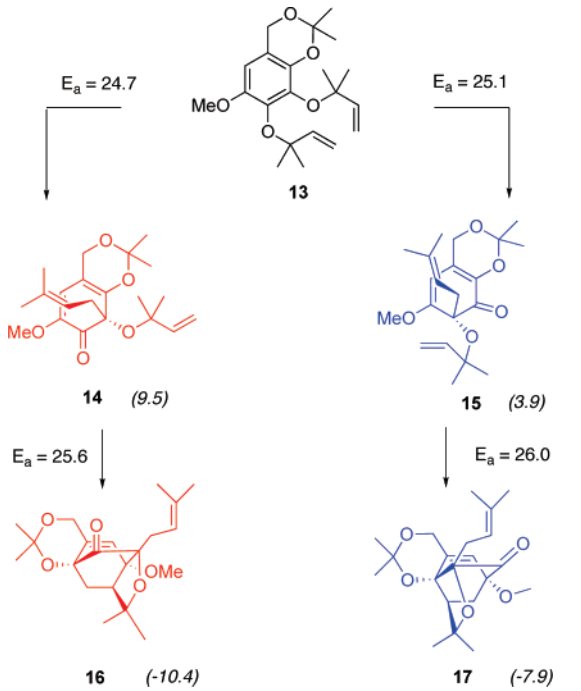
Scheme 3. Possible Pathways from **13** to an Advanced Intermediate for the Synthesis of 1-*O*-Methyllateriflorone



groups of the products led to selectivity. The computations indicate that these Claisen transition states and intermediates all have similar energies; all four are predicted to occur with reasonably low activation barriers of 25−29 kcal/mol. Therefore, the energetics of the Diels−Alder reaction actually determine which products are favored. The Claisen step is reversible, and the irreversible Diels−Alder step determines the product ratio.

In the synthetic path to gambogin, there are two plausible regioisomeric intermediates, **9** and **10**, that can give favorable Diels−Alder products. As in the model system, the slightly more favorable Claisen intermediates do not give stable Diels−Alder adducts. Of the two observed adducts, **11** and **12**, **11** is lower in energy, but **12** is the major product (Figure 4). There is a 3:1 ratio of **12**:**11**, which corresponds to a 0.6 kcal/mol difference in energies. The quantity calculated as the energy difference between the transition states (**11TS** and **12TS**) was 0.4 kcal/mol.

Analogously, there are also two possible products in the synthesis of the advanced intermediate of lateriflorone, **16**

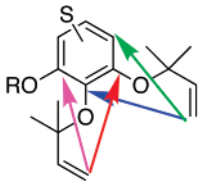


Figure 3. Possible Claisen processes. Observed pathways are in red and blue. Nonobserved pathways are in pink and green.

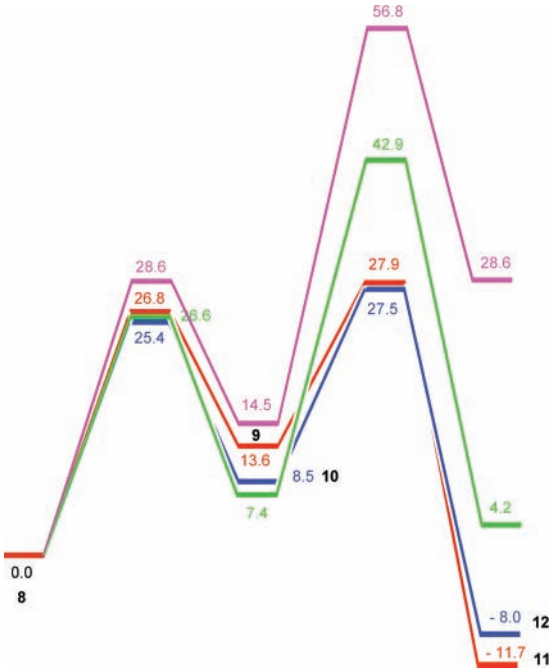


Figure 4. Energy profile for gambogin system.

and **17**. Experimentally, there is almost no energy difference with a 1.1:1 ratio of products formed (0.06 kcal/mol).

Computationally (Scheme 3 and Figure 5), there is a 0.4

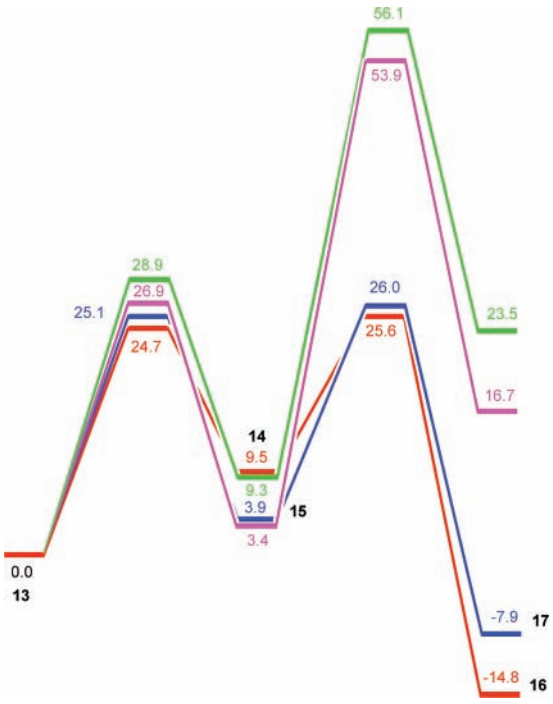


Figure 5. Energy profile for lateriflorone system.

kcal/mol lower activation energy for the major product, overestimating the preference for formation of **16**.

In conclusion, two similar kinetically controlled Claisen−Diels−Alder cascade processes have been investigated using DFT. In both instances, the Claisen rearrangement is a reversible and relatively unselective process, while the Diels−Alder reaction is only favored for five-membered ring formation.

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Supporting Information Available: Cartesian coordinates and Gaussian output files for transition and ground states. This material is available free of charge via the Internet at http://pubs.acs.org.

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