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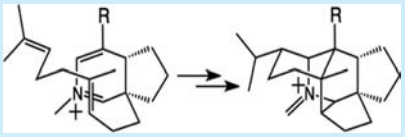
Does Nature Know Best? Pericyclic Reactions in the *Daphniphyllum* Alkaloid-Forming Cation Cascade

Dean J. Tantillo*

Department of Chemistry, University of California—Davis, Davis, California 95616, United States

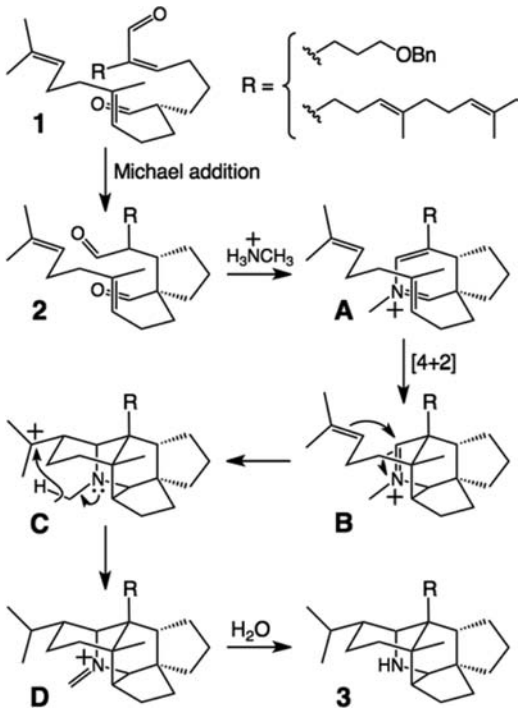
Supporting Information

ABSTRACT: Heathcock's classic cyclization/rearrangement cascade for formation of *Daphniphyllum* alkaloids is subjected to analysis using density functional theory calculations. The results of these calculations are consistent with a two-step pathway involving two pericyclic reactions, a Diels–Alder cycloaddition and an ene reaction.



Undoubtedly one of the most important pieces of work in the history of biomimetic natural product synthesis, both from the standpoint of efficiency in generation of molecular complexity and from the standpoint of inspirational value to contemporary and (potentially) future synthetic chemists, is Heathcock and co-workers' development of cascade polycyclizations to contruct *Daphniphyllum* alkaloids (**1** or **2** → **3**, Scheme 1).[1] This work was summarized in an account published in 1996 titled, "Nature knows best: An amazing reaction cascade is uncovered by design and discovery".[1a] This title points to the mix of synthetic logic, serendipity, and inspiration from nature that characterizes truly amazing synthetic cyclization/rearrangement reactions.[2] Here, the energetic viabiilty of the cascade shown in Scheme 1 is assessed using density functional theory (DFT) calculations.

Scheme 1



The inherent reactivity of a molecule, i.e., the reactivity predicted to predominate in the absence of a catalyst or even in the absence of a solvent (i.e., in the gas phase), has been shown to be relevant to many cyclization/rearrangement reactions promoted by enzymes that generate carbocations.[3] In short, exploration of inherent carbocation reactivity defines the problem(s) that an enzyme must solve (aside from carbocation generation), if any. In many cases, it has been shown that if a carbocation precursor is preorganized into a productive conformation and a carbocation is generated, transformation of a carbocation precursor to the major product requires no activation barrier lowering and no significant changes in substrate conformation.[3] The generality of this principle is extended here to cyclization/rearrangement reactions involving nitrogen-substituted carbocations, i.e., iminium ions, through examination of the conversion of cation **A** to cation **D** (Scheme 1). It is presumed that the biosynthetic reaction involves the R = geranyl system, and polycyclization/rearrangement of **1** with this tail to **3** in the presence of methyl amine and (then) acetic acid has been accomplished in the laboratory (65% yield).[1] The conversion of **2** to **3** with R = $(CH_2)_3OBn$ has also been achieved (75% yield).[1] To simplify the computations, a model system with R = CH_3 was used throughout this study. All results were obtained using the mPW1PW91/6-31+G(d,p)//B3LYP/6-31+G(d,p) + ZPE(B3LYP/6-31+G(d,p)) level of theory,[4] which has been previously validated (through comparisons with other levels of theory and through experimental testing of predictions) for a wide variety of biosynthetically relevant carbocation reactions.[3]

A transition structure for conversion of cation **A** (in a productive conformation) to cation **B** was located (Figure 1) and found by an intrinsic reaction coordinate (IRC) calculation (see the Supporting Information for details)[5] to correspond to a concerted [4 + 2] cycloaddition[6] (aza-Diels–Alder reaction), as proposed by Heathcock and co-workers. This reaction involves asynchronous formation of the two new C–C σ-bonds

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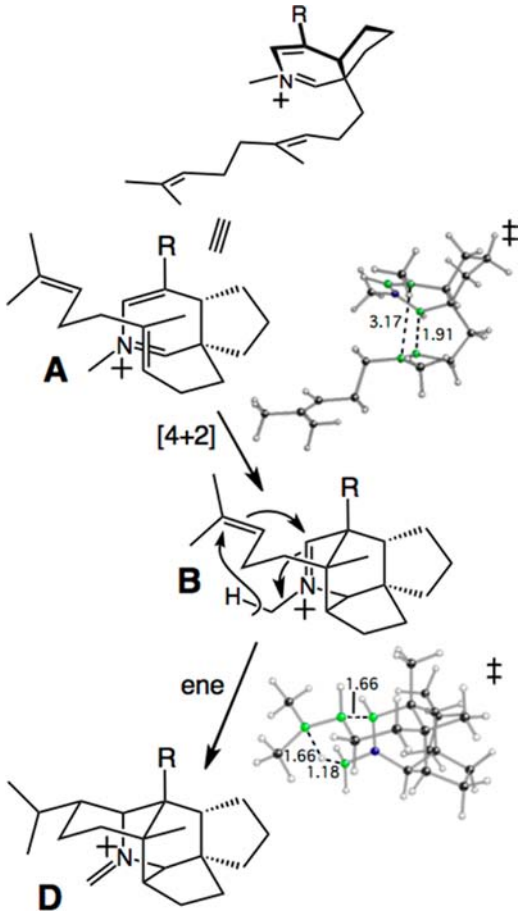

Figure 1. Minina (line drawings) and transition structures (ball-and-stick, carbons involved in bond making/braking highlighted in green, selected distances in Å) involved in the computed pathway.

(1.91 and 3.17 Å in the **A**-to-**B** transition structure), with attack on the iminium carbon occurring earlier along the reaction coordinate.[7] The barrier for this cycloaddition is predicted to be only 7.1 kcal/mol, and the reaction is predicted to be exothermic by 22.2 kcal/mol (due, in large part, to the net trading of a π-bond for two σ-bonds). Thus, this reaction represents a potential biological Diels–Alder reaction for which enzymatic barrier lowering would not be required.[8] Note that the reactant minimum used to compute the cycloaddition barrier corresponds to the conformer that is productive for the **A**-to-**D** cascade (i.e., the conformer directly connected to the **A**-to-**B** transition structure). While an enzyme could enforce the necessary conformation (**A** and its precursors are inherently quite flexible), Heathcock's results demonstrate that such preorganization is not required for a successful reaction, presumably because most conformers are unreactive.

Attempts to locate a minimum corresponding to cation **C** failed. Instead, a transition structure that connects cation **B** directly to cation **D** was found (Figure 1); i.e., instead of a stepwise cyclization/hydride transfer process, an ene reaction is predicted to occur. The direct connection of cations **B** and **D** was confirmed by an IRC calculation (see the Supporting Information for details). This reaction is predicted to have a barrier of 15.0 kcal/mol and an exothermicity of 7.7 kcal/mol (both relative to **B**). Although generally depicted as **B** → **C** → **D**, Heathcock did consider the possibility that the **B**-to-**D** transformation might actually be a concerted ene reaction.[1b] This reaction is joined by the retro-ene reactions of chorismate and isochorismate as rare members of this reaction type in nature.[9] Again, the bond-forming events in this reaction occur asynchronously;[7b−d] note in the **B**-to-**D** transition structure that the new C–C bond is essentially formed (1.66 Å) while the new C–H bond is not (also 1.66 Å).

Overall, the inherently preferred mechanism for the conversion of cation **A** to cation **D** is predicted to involve only two steps, both of which are pericyclic (Figure 1).[6] Both the [4 + 2] cycloaddition and the ene reaction have low predicted barriers and are predicted to be signifcantly exothermic, consistent with barrier lowering by an enzyme *not* being required once **A** is formed in a productive conformation. An amazing reaction cascade, indeed. Once again,[3] Nature appears to make use of inherent reactivity to construct a complex, polycyclic, stereodense molecular framework, one for which an equally efficient nonbiomimetic synthesis seems unlikely, despite the immense reactivity knowledge base accrued over the past century.[10]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01919.

Coordinates and energies for all computed structures and additional computational data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: djtantillo@ucdavis.edu.

Notes

The author declares no competing financial interest.

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■ DEDICATION

This work is dedicated to Clayton Heathcock, whose elegant synthetic and mechanistic work continues to inspire the author and whose undergraduate textbook introduced the author to the wonders of organic chemistry.

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