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# Cycloisomerization of Activated (2*E*,4*Z*)-Heptatrienoate and Its Relevance to Crispatene (Bio)synthesis. A Case of Concerted and Stepwise Uncertainty

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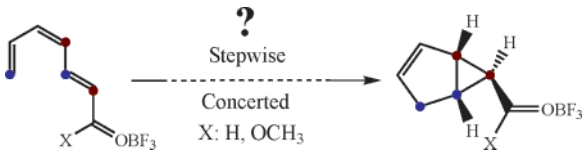


A single transition structure was located on the potential energy surface of the cycloisomerization of protic and Lewis acid activated (2*E*,4*Z*)-heptatrienal and the corresponding methyl ester to provide the bicyclo[3.1.0]hexene derivatives, the central skeleton of the crispatene natural products. A two-dimensional scan of the C−C bond-forming reactions revealed a barrierless cyclopropane closure following the pentadienyl cycloisomerization, with preservation of the stereochemical information.

## Introduction

Among the wealth of organic reactions, concerted reactions have always been challenging to chemists. Their mechanisms are hard to determine experimentally as a result of the lack of intermediates and the complexity of the concomitant changes ocurring in the structure of the molecules. Computational methods have succeeded at shedding some light onto different mechanistic controversies, but they present limitations as well in regard to the size of the molecular system under investigation, the simplifications assumed to perform the calculations,[1] or the interpretation of the results.[2−6]

We have recently been studying the mechanistic features of several (oxo)carbenium ion electrocyclic reactions[7] and found that, for vinylogous systems (e.g., **1m**), the rearrangement of the oxocarbenium ion results in a *tentative* bicyclo[3.1.0]hexene backbone (see Figure 1). Initially, we were unable to explain this behavior because no precedents were available in the literature for such rearrangement. Moreover, after a thorough search, the only transition state located showed exclusively the features of a classical pentadienyl cation electrocyclic ring closure, without offering any hint as to how a putative bicyclic structure could be formed. At first glance, we suspected that the energy minimum related with this peculiar cycloisomerization was *simply* a bicyclic molecule (**int-m** in Figure 1). However, further investigation actually revealed it to be a cyclopentenyl cation whose charge deficiency had been attenuated by the assistance of the $\pi$-electron density of its enol substituent, resulting in a nonclassical carbocation (see Figure 1). The fact that the nonclassical carbonium ion **int-m** was stable and did not evolve toward a cyclopropane ring was enigmatic and led us to consider these findings as computational artifacts, resulting from the assumptions inherent to our calculations (gas-phase structures, limited methodology, etc).

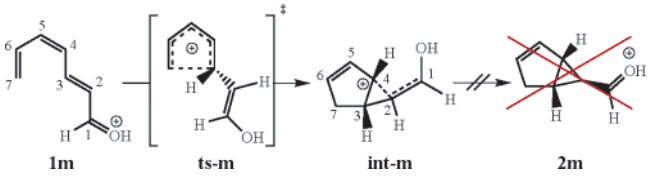


**FIGURE 1.** Cyclization of protonated (2*E*,4*Z*)-heptatrienal **1m**.

Trauner and co-workers recently reported a novel cyclization process that proved itself very useful in synthesizing the central,

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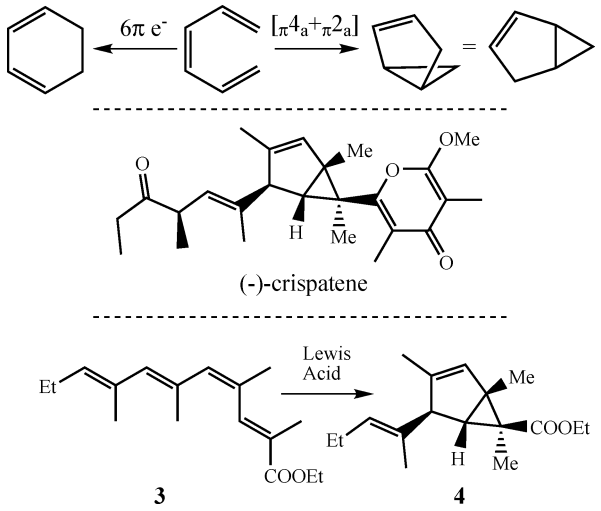


**FIGURE 2.** Two potential cyclizations occurring in (3*Z*)-hexatrienes. The structure of (−)-crispatene and the synthesis of its central block **4** (in racemic form) by one-step Lewis acid cycloisomerization of alkyl-substituted (2*E*,4*Z*,6*E*,8*E*)-undecatrienoate **3**.

fused, bicyclic block of natural products related to crispatene in only one step. The reaction is triggered simply by Lewis acid activation of heptatrienoates and yields bicyclo[3.1.0]hexenes under mild conditions (Figure 2).[8,9] Trauner and co-workers described this reaction as an intramolecular [$_\pi$4$_a$ + $_\pi$2$_a$] Diels−Alder with a tether, thus related to the photochemical cyclization of hexatrienes (see Figure 2), although they did not discard an alternative two-step cationic cascade process. The experimental results on the rearrangement of activated heptatrienoates revealed a considerable increase in complexity, which may or may not be achieved in a single step. The similarity of the systems depicted in Figures 1 and 2 prompted us to resume our previous calculations because they seemed to comply with the experimental findings. We decided to include in our study nonprotic Lewis acid activation of both heptatrienal and methyl heptatrienoate.

## Computational Methods

To minimize any of the spurious effects described above, a high-quality, dual-level approach was considered. Nonetheless, it was found that even when employing a very wide basis set in a dual level strategy, the geometries and relative energies of all previously computed structures (those shown in Figure 1) remained mainly unaltered. All the geometries of the stationary points were computed at the B3LYP/6-31++G(d,p) level,[10−12] and the nature of these points was established, obtaining the second derivatives of the energy with respect to the displacement of the atoms (Hessian). An energy refinement was subsequently performed at the B3LYP/6-311++G(3df,2p) level. All the electronic structure calculations were performed with the Gaussian 03 code.[13] Topological analysis of the electron density (AIM) was performed with the AIMPAC program.[14] Natural localized orbitals were computed with NBO 3.1,[15] as implemented in Gaussian 03.

Solvent effects were taken into account with sequential single-point calculations at the gas-phase-optimized B3LYP/6-31++G-(d,p) geometries.

Two different solvation models[16] were considered for comparison: (1) the polarizable continuum model (PCM)[17−19] and (2) a variation of the conductor-like screening model (COSMO;[20] employing the parameters provided by Klamt and co-workers[21]), as implemented in Gaussian 03.[13,22] All PCM and COSMO calculations were performed at the B3LYP/6-311++G(3df,2p)//B3LYP/6-31++G(d,p) level, as for the gas-phase calculations, using the UAKS radii.[23]

## Results

**Proton Activation.** The mechanistic proposal for the cyclization of heptatrienals activated with protic acids has been described in Figure 1. The activated (2*E*,4*Z*)-heptatrienal **1m** undergoes cyclization between positions $C_3$ and $C_7$, yielding a cyclopentenyl cation that, in turn, is readily stabilized by the exocyclic enol, thus creating a bicyclic structure as a result of a homoallylic, anchimerically assisted cation (see Figure 3).[24]

The distorted, cyclopropane-like structure suggests a nonclassical carbonium ion, but the putative allyl cation is strongly localized due to the anchimeric assistance of the enol, as indicated by its bond lengths (1.35 and 1.46 Å for the nonassisted, $C_5-C_6$, and assisted, $C_4-C_5$, bonds, respectively). APT[25] partial charges also reinforce this interpretation, with the charge deficiency being largely supported by $C_1$ and $C_4$ (numbering as in **1m** in Figure 1 throughout the discussion) with partial charges of 0.64 and 1.12 acu, respectively. Despite the strong evidences pointing toward the existence of a chemical bond between $C_2$ and $C_4$, further analysis led to contradictory results. An analysis of the topology of the electron density[14] showed no bond critical point between the nucleus of $C_2$ and

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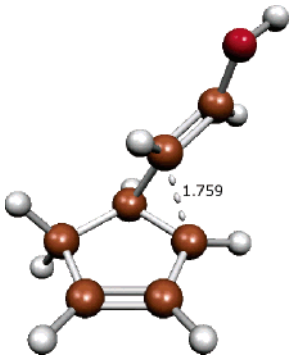


**FIGURE 3.** Homoallylic carbenium ion, characterized as the product of the proton-catalyzed cyclization of (2*E*,4*Z*)-heptatrienal **1m**. The anchimeric charge-transfer interaction is noted with a dashed line, and its *bond length* is provided in angstroms.

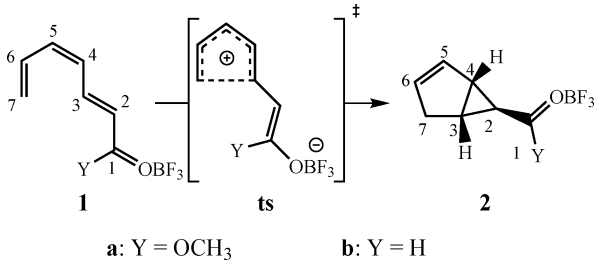


**FIGURE 4.** Cycloisomerization of $BF_3$-activated methyl (2*E*,4*Z*)-heptatrienoate **1a** and (2*E*,4*Z*)-heptatrienal **1b**.

the nucleus of $C_4$, but the Wiberg bond index matrix obtained in the course of Natural Bond Orbital analysis[26] showed a moderate bond order (0.59). Thus, we came to the conclusion that, whereas a considerably strong electrostatic interaction and a certain amount of charge transfer between the allyl cation and the enol moieties exist, the existence of a chemical bond, strictly speaking, could not be ascertained.

**Lewis Acid Activation.** Due to the intriguing difference between the products obtained by our initial computations and the experimental results reported by Trauner and co-workers, we decided to explore both the effect of the activator (proton vs Lewis acid) and the effect of the carbonyl group (aldehyde vs ester). We, therefore, studied the cycloisomerization of $BF_3$-activated methyl (2*E*,4*Z*)-heptatrienoate **1a** and (2*E*,4*Z*)-heptatrienal **1b**, as illustrated in Figure 4.

The computational study performed to attain further insight in the mechanism of the double cyclization with Lewis acid activation proved very challenging as a result of the unusual features the potential energy surface (PES) exhibits. Only one transition structure (see Figure 5) for the cycloisomerization, **1** → **2**, could be located along the reaction coordinate.[8] Intriguingly, the normal mode related to the reaction coordinate in this transition structure shows vectors only for the five-membered ring closure. No evidence of the three-membered ring formation was found after an inspection of the displacement vectors of the only imaginary frequency of **ts-a**. The atoms potentially associated with the three-membered ring remain still, and positions $C_2$ and $C_4$ are not bound (see the transition structure in Figure 5). Several attempts to find an intermediate were unsuccessful, as were the attempts to locate another

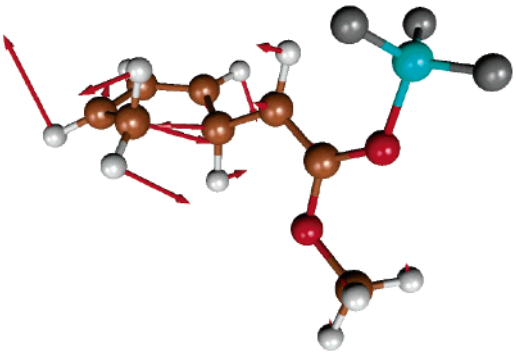

**FIGURE 5.** Displacement vectors associated to the imaginary frequency at the transition structure **ts-a**. Remarkably, carbon atoms $C_2$ and $C_4$ do not approach each other but separate from each other along the reaction coordinate.

transition state where the three-membered ring would form following or preceding the five-membered ring closure. Thus, only the reactant, the five-membered ring formation transition state, and the product minimum were located.

Concerted reactions are characterized by the simultaneous partial formation and/or breaking of bonds in a single transition state. Epitomes of pericyclic reactions usually exhibit symmetry, which implies that bonds are formed/broken exactly to the same extent in the transition state. In these cases, concerted mechanisms are noted as synchronous. Otherwise, when some delay is present between the two concerted bond-forming/breaking events, they are noted as asynchronous.[27] Stepwise reactions, on the other hand, are characterized by the presence of intermediates along the reaction coordinate. The bond-making/breaking events are, therefore, separated in the timeline of the reaction or in the space on the PES. The **1** to **2** mechanism we hereto described cannot be defined as either concerted (because no simultaneous formation of the five- and three-membered rings is observed) or stepwise (due to the lack of intermediates).

A handful of reactions exist that, being at first sight considered concerted processes, have been only rigorously characterized after a thorough examination of their PES.[28−30] In all of them, a bifurcation is observed passing the transition structure, leading to two possible products, the distribution of which could help in the experimental characterization of these mechanisms. We considered the possibility of such peculiar PES, but all our computations suggest that the **1** to **2** reaction mechanism does not show any bifurcation (vide infra) and, as a consequence, determination of the product distribution cannot help discern the mechanistic features through experimental studies.

To unequivocally address which is the pathway of the **1** → **2** transformation, a thorough two-dimensional scan (555 constrained optimizations[31]) of the PES of the **1b** → **2b** cycloisomerization (see Figure 6) was performed, selecting the distance between the termini of both cyclizing systems ($C_3$−

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(31) For the sake of efficiency, the two-dimensional scan was computed at the lower B3LYP/6-31G(d) level. Notwithstanding, this level of theory yielded structures and relative energies very similar to those computed at the much higher level described in the Computational Methods section.

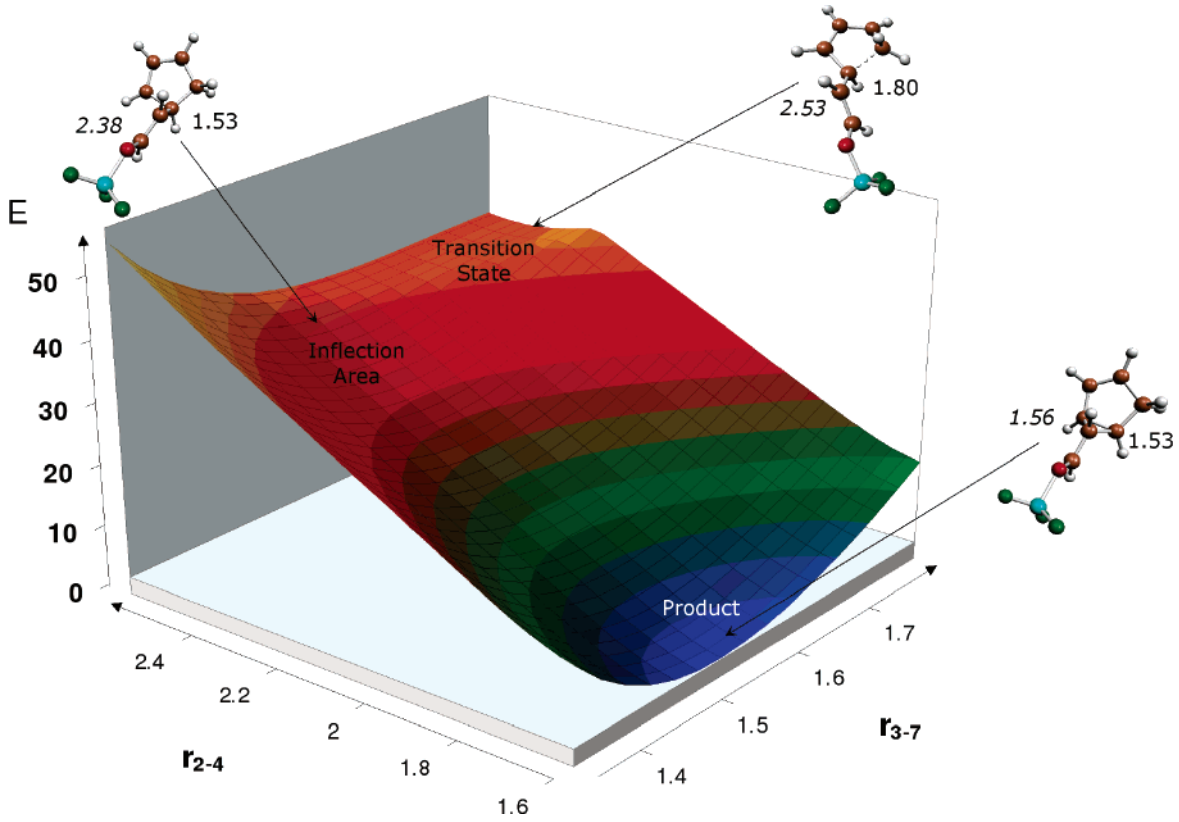


**FIGURE 6.** Gas-phase two-dimensional scan of the PES for the rearrangement of $BF_3$-activated (2*E*,4*Z*)-heptatrienal **1b**, computed at the B3LYP/6-31G(d) level of theory. Relative electronic energy is expressed in kcal/mol and distances in angstroms; C3−C7 and C2−C4 bond distances (Å) are provided in plain text and italics, respectively.

$C_7$ and $C_2-C_4$ for the five- and three-membered rings, respectively) as independent coordinates. The two-dimensional PES confirms that the reaction actually proceeds through just one transition state, which involves the formation of only the five-membered ring (reaction path between the transition state and the inflection area). A slight descent to a plateau is then observed before a dramatic change in the reaction coordinate occurs further downhill. This change, associated to no stationary point, is driven by a gradient with high curvature beyond the plateu region (noted as *inflection area* in Figure 6) and is responsible for the formation of the three-membered ring of the final bicyclic structure. We, therefore, suggest that the double cyclization reaction is not of a concerted nature, at least to the extent organic chemists usually interpret this term, because the reaction transition state shows no signs of concomitant bond formation and both cyclization processes occur at clearly separated regions in the configurational space (which translates into separate events in the time domain).

The question of which mechanistic definition should be applied to this cycloisomerization is still open. It cannot be considered a stepwise process because no intermediate is found along the reaction path, and it is not a concerted mechanism because the timing of the bond-formation process is such that *the second bond-forming event only starts after the first one is fully completed*. The PES suggests the mechanism is an extreme case of both concepts: on one hand it can be seen as a limit case of asynchrony for concerted processes, where the *concerted* nature of the reaction is only granted by the lack of intermediates between reactants and products but where the bond-forming events are clearly separated in two independent *steps*. Being this the case, the reaction could also be interpreted as an extremely asynchronous $[_4\pi_a + _2\pi_a]$ Diels−Alder reaction. On the other hand, it can also be seen as a stepwise reaction with a infinitesimally shallow intermediate (corresponding with the near-zero slope of the inflection area found after the transition state). We consider, however, that the present case exceeds both mechanistic definitions, and the reaction actually proceeds through the ill-defined frontier region: a pentadienyl cation cyclization reaction of **1** is followed by the barrierless capture of the carbonium ion by an enol to afford the bicyclo[3.1.0]-hexene derivative **2**.

Usually concerted processes are considered to keep better *organization* in terms of the stereochemical course of reactions. Organic chemists intuitively associate synthetically valuable stereocontrolled reactions with pericyclic, concerted processes and stereorandom with ionic, stepwise mechanisms. There are, however, examples in the literature showing how often we underestimate the stereocontrol certain ionic reactions can achieve.[32,33]

In this case, the reaction stereocontrol stems from the fact that the three-membered ring cyclization occurs through a barrierless pathway. This prevents conformational scrambling, and the chiral information is transferred from the stereogenic $C_2-C_3$ double bond to the cyclopropane, yielding only one of the possible diastereomers (see Figure 6). The thermodynamic data provided in Table 1 show no significant role for the ester group, other than raising the activation energy for the process relative to the trienal counterpart. Furthermore, a second

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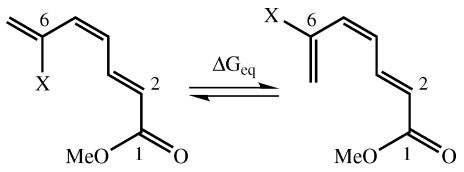
**TABLE 1. Thermodynamic Data for the Cyclization of Molecules 1m, 1a, and 1b[a]**

| | gas phase | | | | $CH_2Cl_2$ | |
|---|---|---|---|---|---|---|
| | $\Delta E$ | $\Delta E_0$ | $\Delta H$ | $\Delta G$ | $\Delta G_{COSMO}$ | $\Delta G_{PCM}$ |
| | | | Proton Activation | | | |
| **1m** | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| **ts-m** | 20.04 | 19.38 | 18.72 | 20.35 | 16.40 | 16.90 |
| **int-m** | 8.21 | 9.17 | 8.40 | 10.44 | 4.35 | 4.73 |
| | | | Lewis Acid Activation | | | |
| **1a** | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| **ts-a** | 38.81 | 38.13 | 37.29 | 39.51 | 31.45 | 33.09 |
| **2a** | 0.53 | 2.16 | 1.16 | 3.74 | 1.91 | 2.22 |
| **1b** | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| **ts-b** | 35.96 | 35.33 | 34.52 | 35.77 | 24.45 | 26.12 |
| **2b** | 2.76 | 4.29 | 3.32 | 5.68 | 3.75 | 3.69 |

[a] Relative thermodynamic magnitudes (electronic energy, electronic energy plus the ZPVE, enthalpy, and Gibbs free energy at 298 K) of the stationary points computed at the B3LYP/6-311++G(3df,2p)//B3LYP/6-31++G(d,p) level of theory. Nonexplicit solvent effects have been taken into consideration through the PCM and its conductor-like variation (COSMO; see Section 2).

bidimensional scan of **1a** was also performed yielding a PES whose topology closely resembles that of aldehyde **1b**. Thus, it can be concluded that both substrates can potentially undergo the same cycloisomerization, provided they are activated with Lewis acids (potential side reactions, such as acid-induced *Z* → *E* isomerization, could drive the process toward different products notwithstanding).

All the conclusions extracted from the study of these model systems should also apply to the synthesis of the crispatene core **4**, starting from a more-substituted acyclic precursor **3**. The location of methyl groups along the polyenic structure of the precursor must enforce this unprecedented cycloisomerization. In particular, because the reactive geometry of the polyene chain involves the *s*-cis conformation at the $C_5-C_6$ bond, we studied the effect of the methyl group at $C_6$ on the conformational equilibrium. Calculations of both conformers of methyl (2*E*,4*Z*)-heptatrienoate **1a** and its 6-methyl analogue $\mathbf{1a}_{6-Me}$ were performed, which revealed the key role of this methyl group facilitating the pentadienyl cation cycloisomerization (Figure 7). The *s*-cis conformation in **1a** lies 4.05 kcal/mol above the *s*-trans global minimum, and methylation at C6 renders these two conformations of $\mathbf{1a}_{6-Me}$ nearly degenerate in energy (the *s*-trans being only 0.28 kcal/mol more stable than the *s*-cis counterpart). Thus, the methylation pattern found in crispatene seems to be far from accidental, reinforcing the potential biomimetic nature of the route developed by Trauner and coworkers.[8,9]




**1a** X = H $\Delta G_{eq}$ = 4.05 kcal/mol
$\mathbf{1a}_{6\text{-Me}}$ X = Me $\Delta G_{eq}$ = 0.28 kcal/mol

**FIGURE 7.** Model systems to account for the effect of the C6-methyl substitution on the $C_5-C_6$ *s*-cis/*s*-trans conformational equilibrium of the acyclic precursor of crispatene.

## Conclusion

The mechanistic features of the cycloisomerization of protic and Lewis acid activated (2*E*,4*Z*)-heptatrienal and methyl (2*E*,4*Z*)-heptatrienoate to provide bicyclo[3.1.0]hexene derivatives, the skeleton of crispatenes, has been studied. Departing from the classical definitions of these terms, the reaction is neither strictly concerted nor stepwise but somehow intermediate to both. This ambiguous character is inferred from the analysis of the reaction coordinate linking the only transition state located on the PES and the reactant and product wells. The barrierless cyclization forming the cyclopropane moiety preserves the chiral information of the stereogenic $C_2-C_3$ double bond by preventing any conformational scrambling. Further analysis of the structural features of crispatene and its reaction path reveals an essential role for the methyl group at $C_6$ for the cycloisomerization to occur.

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**Supporting Information Available:** Two-dimensional scan of molecule **1a**, Cartesian coordinates, and energies. This material is available free of charge via the Internet at http://pubs.acs.org.

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