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Possibility of [1,5] Sigmatropic Shifts in Bicyclo[4.2.0]octa-2,4-dienes

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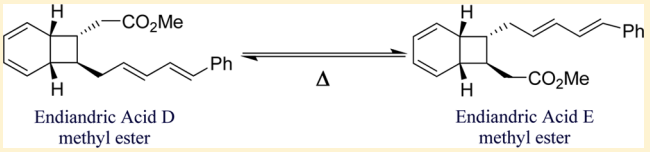
Supporting Information

ABSTRACT: The thermal equilibration of the methyl esters of endiandric acids D and E was subject to a computational study. An electrocyclic pathway via an electrocyclic ring opening followed by a ring flip and a subsequent electrocyclization proposed by Nicolaou [Nicolaou, K. C.; Chen, J. S. *Chem. Soc. Rev.* 2009, *38*, 2993], was computationally explored. The free-energy barrier for this electrocyclic route was shown to be very close to the bicyclo[4.2.0]octa-2,4-diene reported by Huisgen [Huisgen, R.; Boche, G.; Dahmen, A.; Hechtl, W. *Tetrahedron Lett.* 1968, 5215]. Furthermore, the possibility of a [1,5] sigmatropic alkyl group shift of bicyclo[4.2.0]octa-2,4-diene systems at high temperatures was explored in a combined computational and experimental study. Calculated reaction barriers for an open-shell singlet biradical-mediated stepwise [1,5] sigmatropic alkyl group shift were shown to be comparable with the reaction barriers for the bicyclo[4.1.0]hepta-2,4-diene (norcaradiene) walk rearrangement. However, the stepwise sigmatropic pathway is suggested to only be feasible for appropriately substituted compounds. Experiments conducted on a deuterated analogous diol derivative confirmed the calculated (large) differences in barriers between electrocyclic and sigmatropic pathways.



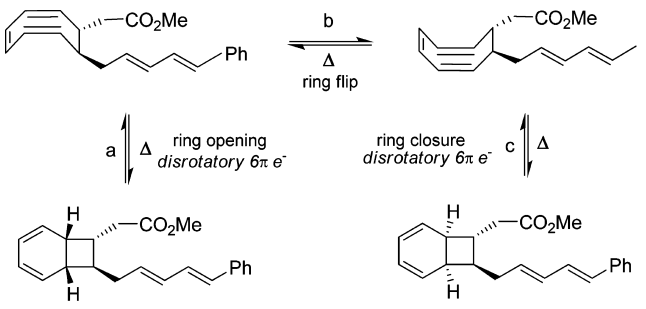
INTRODUCTION

Endiandric acids, phytochemicals that were first discovered by Gatehouse and Black,[1,2] and their derivatives possess various biological activities[3] such as antibacterial,[4−6] antitubercular,[7] and anticancer properties.[6,8] Their biosynthesis via an intricate cascade of pericyclic reactions was proposed by Black[2] and verified experimentally by Nicolaou.[9−13] As part of the biomimetic synthesis, Nicolaou described an unexpected thermal equilibrium between two bicyclo[4.2.0]octa-2,4-diene intermediates, the methyl esters of the natural products endiandric acid D and endiandric acid E (Scheme 1, compounds **1** and **2**, respectively), and proposed a three-step electrocyclic cascade for this equilibrium via (a) an electrocyclic ring opening followed by (b) a ring flip of the resulting cyclooctatriene (COT) and (c) a subsequent electrocyclization.

However, an alternative sigmatropic mechanism for this thermal rearrangement via a [1,5] carbon shift might be possible at high temperatures (Scheme 2).

Most sigmatropic [1,5] hydrogen migrations (Scheme 3, I, R = H) are pericyclic transformations, which typically possess relatively high activation barriers and thus usually require high reaction temperatures.[14−16] Pericyclic reactions are important both from a synthetic and a theoretical point of view,[17,18] due

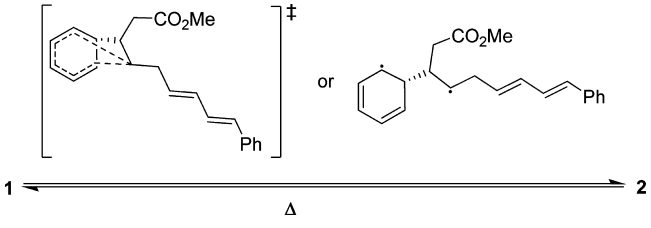
Scheme 1. Thermal Rearrangement of Endiandric Acids D and E: Electrocyclic Route



Endiandric Acid D methyl ester **1**

Endiandric Acid E methyl ester **2**

Scheme 2. Thermal Rearrangement of Endiandric Acids D and E via a Concerted Sigmatropic Route (Transition State on the Left) or a Stepwise Sigmatropic Route (Biradical Intermediate on the Right)



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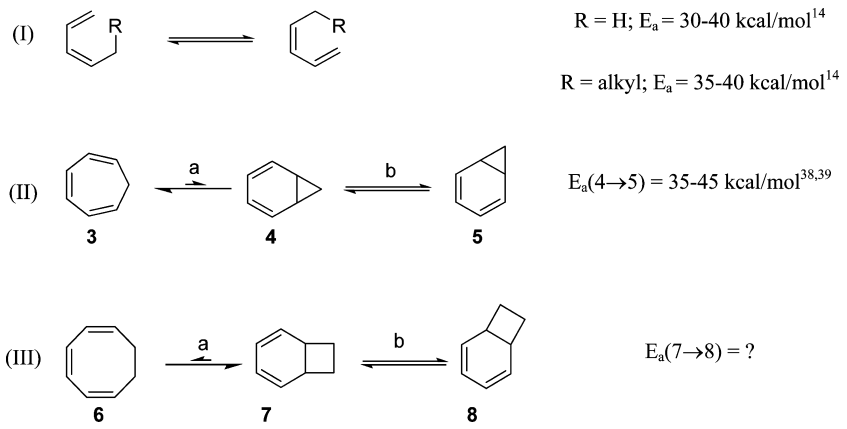
Scheme 3. [1,5] Sigmatropic Rearrangements of (I) 1,3-Dienes; (II) Bicyclo[4.1.0]hepta-2,4-dienes; and (III) Bicyclo[4.2.0]octa-2,4-dienes



to their highly ordered transition states, these concerted transformations usually offer a high degree of selectivity and a high level of mechanistic insight.[19,20] Different types of observed and hypothetical pericyclic processes have been very efficiently categorized depending on the nature of the interacting molecular orbitals. Moreover, consideration of the required symmetry of the implicated orbitals leads to a straightforward prediction of a specific transformation being "favored" or "disfavored".[21−24] However, whether a pericyclic process is a viable reaction pathway, depends on a complex interplay of many factors, and therefore, it is often difficult to make reliable predictions.

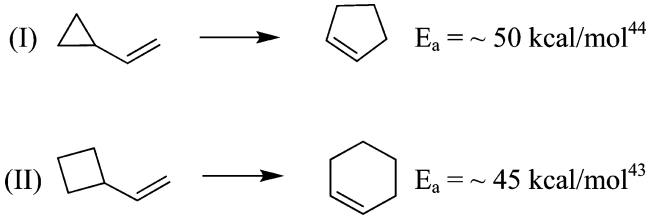
Sigmatropic [1,*n*] carbon migrations (Scheme 3, I, R = alkyl) on the other hand, do not generally involve concerted transition states because the overlap of the orbitals in the transition structure is usually too weak[25] but are believed to occur via intermediate singlet-state biradicals.[26,27] Exceptions, involving pericyclic transition states with good overlap, are the [1,5] sigmatropic migration in 1,3-cyclopentadienes[28,29] and the so-called "walk rearrangements"[30−34] of bicyclo[*n*.1.0]-polyenes for which the thermally allowed process should occur with inversion of configuration at the migrating carbon atom.[27,35,36] Walk rearrangements are [1,5] sigmatropic shifts which involve the migration of a divalent group (O, S, NR, or CR_2) that is part of a three-membered ring in a bicyclic system (Scheme 3, II, for CH_2). These thermally induced processes have been demonstrated in various bicyclo[*n*.1.0]polyene structures.

Thermal rearrangements of bicyclo[4.1.0]hepta-2,4-diene **4** (or norcaradiene, Scheme 3, II) systems have received a lot of attention in both experimental and computational studies,[17,27,31,32,37−39] as they have been observed to proceed with inversion at the migrating center, indicating an orbital-symmetry forbidden rearrangement.[27,40,41] However, these reactions have been shown not to be concerted and thus not subject to the rules of orbital symmetry conservation.[27]

The experimentally determined activation energies for various substituted norcaradiene walk rearrangements do not differ significantly from those of normal [1,5] alkyl shifts (Scheme 3, II and I with R = alkyl, respectively).[38] This can be rationalized by the fact that the norcaradiene system **4** is usually the less populated valence tautomer in a 6π electrocyclization equilibrium with a less constrained cycloheptatriene **3** (IIa), adding to the overall barrier for the carbon shift. However, a different situation exists for the homologous bicyclo[4.2.0]octa-2,4-diene (Scheme 3, III), where the electrocyclization product **7** is known to be favored over the contorted cyclooctatriene **6** form in most cases (IIIa).[42]

Although there is no prior literature of walk rearrangements in ethylene-bridged cyclic polyene systems, in the context of the well-documented similarity in the reactivity of vinyl cyclopropane and vinyl cyclobutane systems in their formal [1,3] carbon shifts to a cyclopentene and a cyclohexene system, respectively (Scheme 4, I and II, respectively),[43−47] at high

Scheme 4. [1,3] Sigmatropic Rearrangements of (I) Vinyl Cyclopropane and (II) Vinyl Cyclobutane



temperatures, a ring walk-type [1,5] carbon shift in a bicyclo[4.2.0]octa-2,4-diene (Scheme 3, IIIb) system seems to be a viable reaction pathway on the basis of the norcaradiene precedent.

As there is no straightforward way to distinguish experimentally between these two mechanistic schemes (electrocyclic versus sigmatropic) in this particular case, both rearrangement pathways have been comparatively studied from a theoretical point of view.

Additionally, in order to verify theoretical results, an experiment using a model bicyclo[4.2.0]octa-2,4-diene system **9** (Scheme 5) has been devised. Due to the pseudo-C_2 symmetry of this system, the interconverting structures (with respect to their Endiandric acid D and E counterparts) are identical (Scheme 5a). However, this model system is readily accessible as the deuterium labeled analog **9-d$_4$**. The thermal rearrangement of diol **9-d$_4$** would only be unnoticed if it proceeds exclusively via the electrocyclic route. A sigmatropic pathway (or walk rearrangement) would lead to different products with respect to their deuterium substitution patterns (Scheme 5b).

Thus, the aim of this study is 2-fold: unraveling the mechanism of thermal equilibration between endiandric acid methyl esters D/E in particular and more generally exploring

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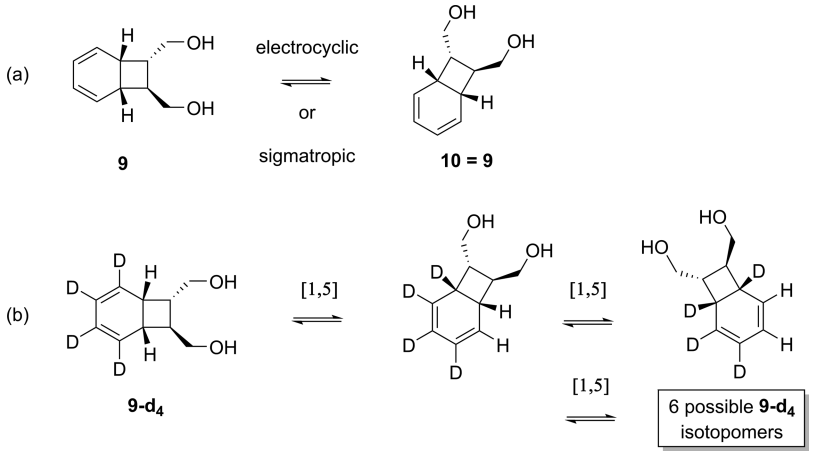
Scheme 5. Thermal Rearrangements of a (a) Model Diol System 9 and its (b) Deuterium-Labeled Analog 9-d_4



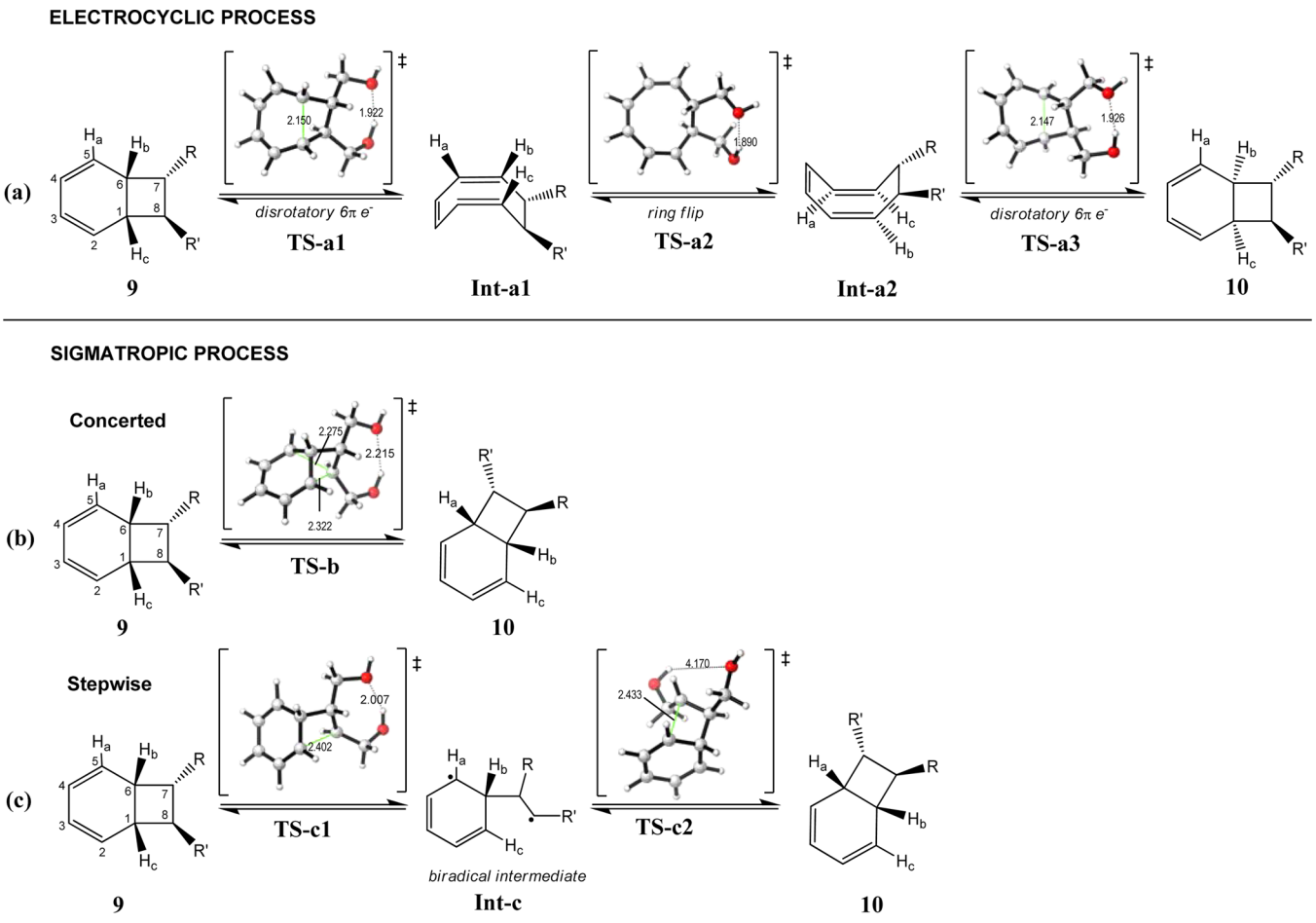


Figure 1. Schematic representation of the electrocyclic and sigmatropic mechanisms for the thermal equilibration of bicyclo[4.2.0]octa-2,4-diene **9**. (a) R = R′ = $-CH_2OH$. (b) M06-2*X*/6-31+G(d,p) geometries for pathway a and UM06-2*X*/6-31+G(d,p) geometries for pathways b and c. (c) Distances in angstroms.

the possibility of [1,5] sigmatropic alkyl shifts (walk rearrangements) in bicyclo[4.2.0]octa-2,4-diene systems at high temperatures through a combined computational and experimental study.

■ COMPUTATIONAL METHODOLOGY

All reactants, transition states, intermediates, and products were optimized using three different functionals with a 6-31+G(d,p) basis set:[48,49] the well-established hybrid functional B3LYP,[50,51] Truhlar's meta hybrid exchange-correlation functional M06-2X,[52,53] which accounts for dispersion, and Grimme's B3LYP-D3 approach,[54] which takes into account van der Waals interactions by empirically adding long-range dispersive corrections.[55] Harmonic vibrational frequencies were computed at the same levels of theory and used to provide thermal corrections to the Gibbs free energies and to confirm the nature of the stationary points. The intrinsic reaction coordinate

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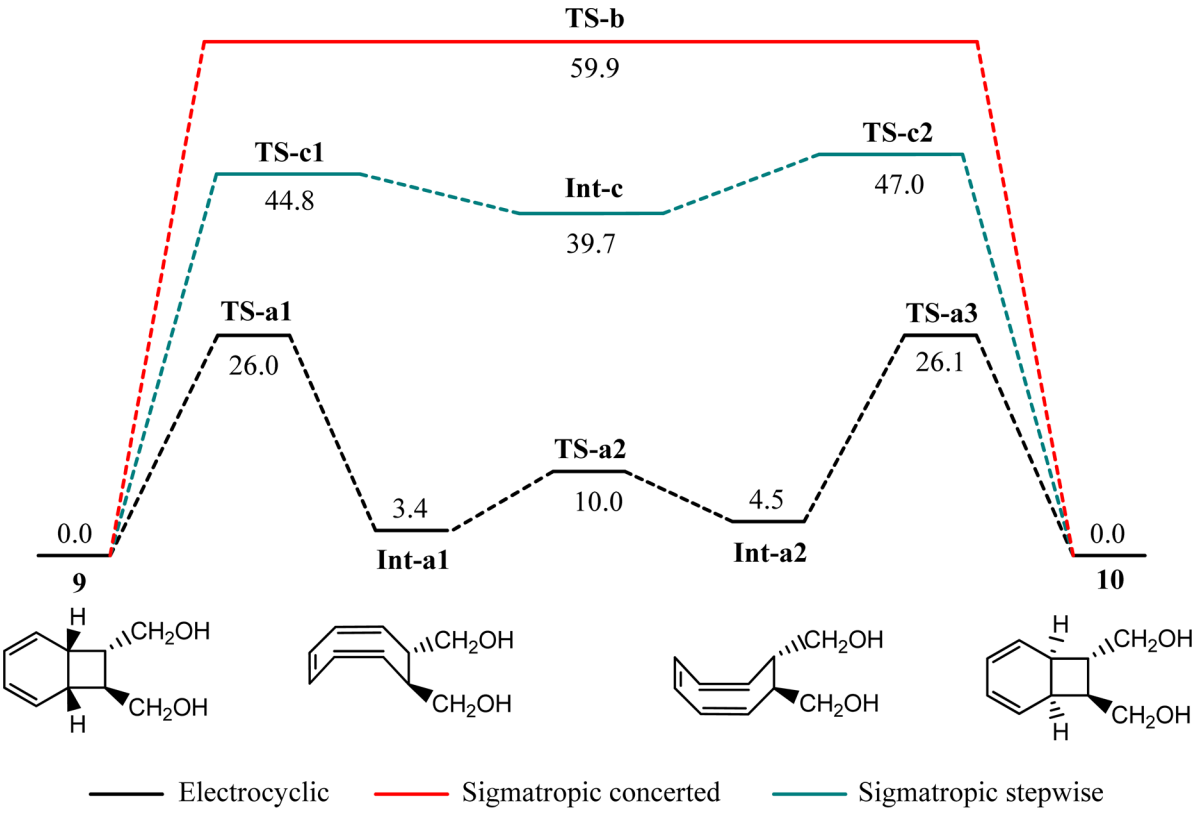

Figure 2. Free-energy profiles for the electrocyclic (M06-2*X*/6-31+G(d,p)) and sigmatropic pathways (UM06-2*X*/6-31+G(d,p)) for the thermal equilibration of bicyclo[4.2.0]octa-2,4-diene **9**. Energies in kilocalories per mol.

(IRC)[56,57] paths were traced to verify the two associated minima connected to each transition state on the potential energy surfaces. In order to investigate the possibility of open-shell transition states and an open-shell biradical intermediate for the sigmatropic processes, HOMO and LUMO initial guesses were mixed to produce unrestricted wave functions for singlet states, and the stability of the wave functions was checked.[58,59] These calculations were carried out with Gaussian 09.[60] In order to assess the diradical character, CASSCF/6-31+G(d,p) calculations were carried out on M06-2X optimized structures.[61] An active space of ROHF molecular orbitals with all valence electrons was targeted with the density matrix renormalization group (DMRG),[62,63] which yielded approximate natural orbitals. On the basis of the natural orbital occupation numbers (NOON), the active space for the subsequent CASSCF calculations was identified: natural orbitals with 0.01 < NOON < 1.99 were regarded as essential for the CASSCF calculations. We refer the reader to ref 64 for an introduction to this procedure, which yields an unbiased initial orbital guess. Both the DMRG and CASSCF calculations were carried out with the free open-source ab initio DMRG code CHEMPS2.[65,66] For the initial DMRG rotation to approximate natural orbitals, $D_{SU(2)}$ = 750 reduced renormalized basis states were retained. In order to obtain Gibbs free CASSCF energies, thermal free energy corrections were taken from the M06-2X optimizations.

RESULTS AND DISCUSSION

Electrocyclic and sigmatropic pathways were computationally explored for the thermal equilibration of three different bicyclo[4.2.0]octa-2,4-diene systems. Computational results were compared with relevant literature data where applicable. The possibility of [1,5] sigmatropic alkyl shifts (walk rearrangements) at high temperatures was also experimentally explored.

1. Thermal Equilibration of Bicyclo[4.2.0]octa-2,4-diene 9. The thermal equilibration of bicyclo[4.2.0]octa-2,4-diene **9** via electrocyclic and sigmatropic (concerted and stepwise) pathways was explored in a combined computational and experimental study.

A. Theoretical Study. Initially, an electrocyclic pathway via an electrocyclic ring opening followed by a ring flip and a subsequent electrocyclization, which was proposed by Nicolaou for endiandric acids D and E,[9−13] was studied computationally for bicyclo[4.2.0]octa-2,4-diene **9** (Figure 1, pathway a).

Orbital symmetry selection rules state that "allowed" sigmatropic reactions occur through concerted pathways, as opposed to "forbidden" processes that are known to thermally occur via stepwise pathways, which go through biradical intermediates.[55c] However, it has been shown that stepwise routes may be favored over concerted ones for some orbital symmetry allowed processes, where substituents stabilize the intermediate biradical.[19,67−69] For this reason, the thermal [1,5] sigmatropic carbon shift under study has been explored through both a concerted and a biradical-mediated stepwise pathway (Figure 1, pathways b and c, respectively).

Electrocyclic Conversion of Bicyclo[4.2.0]octa-2,4-diene 9. Figure 1 depicts a schematic representation along with optimized transition state geometries for the electrocyclic pathway of the thermal equilibration of bicyclo[4.2.0]octa-2,4-diene **9** (pathway a). Furthermore, the free-energy profile is shown in Figure 2. The first step in the electrocyclic process is the ring opening of **9** via C1−C6 bond cleavage through transition state **TS-a1**. This early transition state has a C1−C6

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bond elongation that is relatively small (2.150 Å compared to 1.558 and 3.081 Å for reactant **9** and intermediate **Int-a1**, respectively) and the Gibbs free activation barrier ($\Delta G^{\ddagger}$) for this step is 26.0 kcal/mol at the M06-2*X*/6-31+G(d,p) level of theory. The ring opening leads to a contorted cyclooctatriene intermediate **Int-a1**, which subsequently undergoes a ring flip through transition state **TS-a2**. This second step is characterized by a $\Delta G^{\ddagger}$ of only 6.6 kcal/mol. Finally, electrocyclization through transition state **TS-a3** ($\Delta G^{\ddagger}$ = 26.1 kcal/mol) generates product **10**, which is identical to the starting compound **9** due to symmetry. However, retention of the hydrogen bond during the reaction causes a subtle energy difference between **9** and **10** at some levels of theory, which is also the case for **TS-a1** and **TS-a3** and **Int-a1** and **Int-a3**.

[1,5] Sigmatropic Alkyl Shift of Bicyclo[4.2.0]octa-2,4-diene ***9***. The sigmatropic alkyl group shift could take place via a concerted mechanism, where C1−C8 bond cleavage, rotation of the migrating carbon around the C6−C7 bond and formation of the new bond (C5−C8) take place in a synchronous concerted fashion (Figure 1, pathway b). In transition state **TS-b**, the C1−C8 bond is elongated (C1−C8 distance 2.322 Å) and a slight twist around the C6−C7 bond results in an optimal position to form the new bond (C5−C8 distance 2.275 Å). The activation energy for this concerted sigmatropic process is very high ($\Delta G^{\ddagger}$ = 59.9 kcal/mol, UM06-2*X*/6-31+G(d,p), Figure 2). Alternatively, the sigmatropic alkyl group shift could take place via a biradical-mediated stepwise mechanism (Figure 1, pathway c), where the first step consists of homolytic C1−C8 bond cleavage and subsequent rotation through transition state **TS-c1** to the open-shell singlet biradical intermediate **Int-c**. The transition state for this step has a Gibbs free activation barrier $\Delta G^{\ddagger}$ of 44.8 kcal/mol, which is lower than that for the concerted sigmatropic process but still quite high. The biradical intermediate **Int-c** (Figure 3) has a

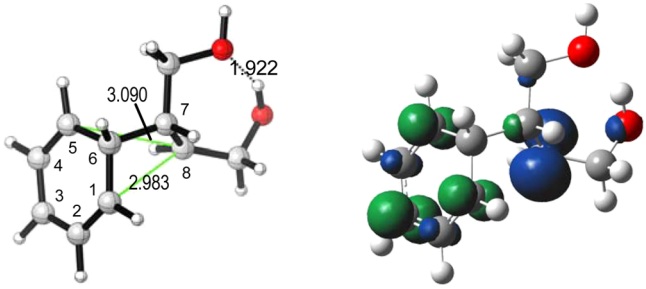

Figure 3. Open-shell singlet biradical intermediate (**Int-c**) in the sigmatropic stepwise process (UM06-2*X*/6-31+G(d,p)) for the thermal equilibration of bicyclo[4.2.0]octa-2,4-diene **9** and its iso-surface (value 0.01 au) of spin density on the right.

C1−C8 distance of 2.983 Å and a C5−C8 distance of 3.090 Å (compared to 2.322 and 2.275 Å for the concerted transition state **TS-b**). The iso-surface of the spin density for biradical intermediate **Int-c** (Figure 3) shows that the unpaired electron in the ring is delocalized not only over C1 and C5, as would be expected, but also over C3, indicating the possibility of a different ring closure leading to an alternative bridged product, namely bicyclo[2.2.2]octa-1,5-diene, which was calculated to be 6 kcal/mol lower in energy than product **10**. This could explain why complex mixtures were observed during the experiments (see next section). Finally, further rotation of the exocyclic radical and ring closure through transition state **TS-c2** ($\Delta G^{\ddagger}$ = 7.3 kcal/mol) generates product **10**.

Relative Gibbs free energies for the pathways under study, calculated with three different functionals (B3LYP, M06-2X, and B3LYP-D3) and a 6-31+G(d,p) basis set are shown in Table 1. It should be noted that calculations with both the B3LYP and the B3LYP-D3 level of theory gave rise to an internal instability of the wave function for the sigmatropic concerted transition state, and analytic frequency calculations are only valid if the wave function has no internal instabilities. Therefore, B3LYP and B3LYP-D3 Gibbs free energies for this transition state are not reported. All relative free energies calculated at the M06-2X level of theory are higher than those at the B3LYP level of theory. However, it can be seen that long-range dispersion effects are very small in these systems, as B3LYP and B3LYP-D3 values are almost equal. As expected, the electrocyclic cascade is clearly preferred over the sigmatropic pathways, which have much higher activation barriers at all levels of theory (26.0 versus 59.9 and 44.8 kcal/mol for the electrocyclic, the concerted sigmatropic and the stepwise sigmatropic pathways, respectively, at the M06-2X level of theory). However, the calculations predict that the activation barriers for the sigmatropic process might be overcome at high temperatures. Within the two sigmatropic pathways, the stepwise pathway is shown to be the most plausible (the activation barrier is 15.1 kcal/mol lower than for the concerted pathway, M06-2*X*/6-31+G(d,p)).

Broken-symmetry unrestricted methodology was used for both sigmatropic pathways, but this led to the restricted solution for the concerted sigmatropic transition state **TS-b**, suggesting a closed-shell system for this pathway, as indicated by expectation values of total spin $\langle S^2 \rangle$ equal to zero (Table 1). The stepwise sigmatropic pathway on the other hand is proposed to go through open-shell transition states and a corresponding open-shell singlet biradical intermediate, as shown by the spin contamination [$\langle S^2 \rangle$ = 0.8335, 1.0372, and 0.7998 for **TS-c1**, **Int-c**, and **TS-c2**, respectively, M06-2*X*/6-31+G(d,p)].

Since only M06-2X calculations gave rise to stable wave functions for all pathways under study, further calculations were done only with the M06-2X level of theory, and the CASSCF calculations in the next subtopic were carried out with M06-2X optimized structures.

CASSCF and DMRG Calculations. Although several sigmatropic shift studies on pericyclic reactions point out that inexpensive methods such as B3LYP predict activation barriers and energies in excellent agreement with experimental data,[38,55c,70−76] the biradical intermediate in the stepwise sigmatropic pathway implies the necessity of a multiconfigurational self-consistent field (MCSCF) method, such as the complete active space self-consistent field (CASSCF) method,[77] which was proven to be valuable for the study of organic reactions.[78−80]

With an initial approximate DMRG calculation in an active space of 66 electrons in 66 ROHF molecular orbitals, which contains all valence electrons, approximate natural orbitals and their occupation numbers were found. Natural orbitals with 0.01 < NOON < 1.99 were regarded as essential for the CASSCF calculations, yielding a common active space of 6 electrons in 6 orbitals.

The converged relative Gibbs free CASSCF(6,6)/6-31+G(d,p) energies of singlet and triplet transition states and intermediates for all pathways under study are shown in Table 1. The triplet energies are much higher than the singlet energies, indicating that all pathways proceed via singlet states;

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Table 1. Relative Gibbs Free Energies (kcal/mol) of Reactants, Transition States, Intermediates, and Products for the Thermal Rearrangement of Bicyclo[4.2.0]octa-2,4-diene diol 9, and Expectation Values of the Total Spin <S^2> (in Parentheses), Calculated at Different Levels of Theory (LOT) with a 6-31+G(d,p) Basis Set[a]

			electrocyclic					sigmatropic				
								concerted	stepwise			
	lot	9	TS-a1	Int-a1	TS-a2	Int-a2	TS-a3	TS-b	TS-c1	Int-c	TS-c2	10
singlet	B3LYP	0.0	22.7	2.4	6.5	3.2	22.9	–[b]	37.7 (0.7865)	32.6 (1.0391)	38.7 (0.8110)	0.1
	B3LYP-D3	0.0	22.1	1.6	6.0	2.6	22.3	–[b]	36.9 (0.8455)	33.4 (1.0390)	38.9 (0.8227)	0.1
	M06-2X	0.0	26.0	3.4	10.0	4.5	26.1	59.9 (0.0000)	44.8 (0.8335)	39.7 (1.0372)	47.0 (0.7998)	0.0
	CASSCF//UM06-2X[c]	0.0	36.8	3.8	11.1	4.5	37.1	65.8	40.6	39.4	44.8	0.0
triplet	CASSCF//UM06-2X[c,d]	54.7	76.0	49.6	55.0	50.0	75.9	146.1	69.7	38.8	72.2	56.6

[a]Unrestricted methodology for the sigmatropic processes. [b]Calculations gave rise to an internal instability of the wave function. [c]CASSCF(6,6)/6-31+G(d,p)//UM06-2X/6-31+G(d,p). [d]Energies relative to singlet reactant **9**.

the biradical intermediate **Int-c** has comparable energies for its singlet and triplet forms. While CASSCF and M06-2X energies are in very good agreement for the sigmatropic pathways, as can be seen by differences of maximum 5.9 kcal/mol, differences of up to 11 kcal/mol were found for the electrocyclic pathway.

The difference in DFT and CASSCF energetics is understandable, since DFT captures dynamic correlation, but not static correlation, and CASSCF captures static correlation but not dynamic correlation. Moreover, CASSCF indicates a closed shell for the singlet and two radical electrons for the triplet in the electrocyclic pathway (see Table 1 of the Supporting Information), implying that single Slater determinants are able to describe these structures, hence energetics from the single Kohn–Sham Slater determinant in DFT calculations are deemed reliable.

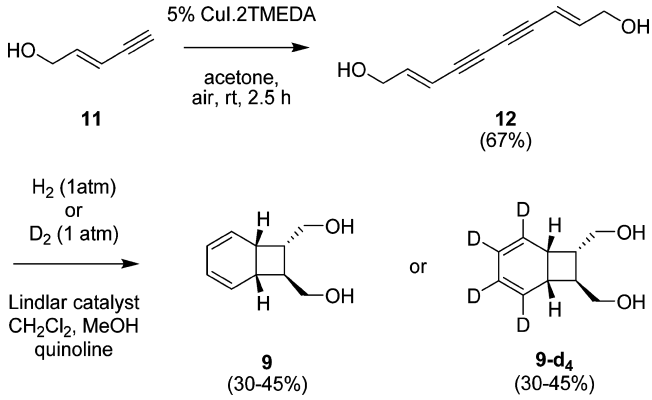
On the other hand, the converged NOON of singlet and triplet transition states and intermediates (Table 1 of the Supporting Information) of the sigmatropic routes, indicate that all sigmatropic transition states have some diradical character, and the sigmatropic stepwise intermediate is a pure diradical. DFT is unable to describe these more exotic electronic structures, indicating the necessity for CASPT2 calculations in order to get accurate energetics.[81,82] However, CASSCF and CASPT2 energies were shown to be comparable for [1,3] sigmatropic rearrangements of bicyclic and tricyclic vinylcyclobutanes,[83] which are described by transition states highly similar in nature to the sigmatropic stepwise transition states in the present study, hence the levels of theory employed are considered to be sufficient. Moreover, CASSCF and M06-2X energies agree reasonably well for both sigmatropic pathways.

DFT calculations had accurately suggested that the stepwise sigmatropic pathway goes through open-shell transition states and a corresponding open-shell singlet biradical intermediate; however, they had incorrectly suggested the concerted sigmatropic pathway to proceed through a closed-shell transition state and therefore it seems to be an artifact of the M06-2X calculations to give rise to stable wave functions for the concerted closed-shell transition state, and therefore, no further calculations will be done on this transition state.

As a conclusion, the electrocyclic cascade is obviously preferred over the sigmatropic pathways; however, the activation barriers for the stepwise sigmatropic processes might be overcome at high temperatures. Moreover, DFT calculations suggested that the stepwise sigmatropic pathway goes through open-shell transition states and a corresponding open-shell singlet biradical intermediate and that the concerted sigmatropic pathway has a closed-shell transition state. NOON from CASSCF calculations on the other hand showed that all sigmatropic transition states have some diradical character, and the sigmatropic stepwise intermediate is a pure diradical.

B. Experimental Study. In order to experimentally investigate the possibility of a [1,5] sigmatropic alkyl shift in a bicyclo[4.2.0]octa-2,4-diene system, the diol derivative **9** was synthesized in two steps from (*E*)-pent-2-en-4-yn-1-ol **11** (Scheme 6). Copper-mediated oxidative Glaser coupling and

Scheme 6. Synthesis of the Bicyclo[4.2.0]octa-2,4-diene diols 9 and 9-d_4



partial hydrogenation of the resulting symmetrical diyne diol **12** was followed in situ by a cascade of an 8π- and a 6π-electrocyclic ring closures as previously described,[2,13] giving the 4π system **9** as the major product, in reasonable yield. When the reaction was run using deuterium gas (99.8% atom D), the expected diol **9-d_4** was obtained as a single isotopomer. This deuterium-labeled system was then used to study the thermal rearrangements.

The methyl esters of endiandric acids D and E are known to interconvert with a half-life of ca. 1.3 h at 70 °C in toluene. Thus, a similar equilibrium is expected to exist in the simpler diol **9**, although the interconverting products are identical in this case. However, for the deuterium-labeled diol **9-d_4**, this equilibrium would be unnoticed only if the rearrangement followed exclusively the electrocyclic ring opening pathway to the 6π cyclooctatriene (COT) valence tautomer, which can

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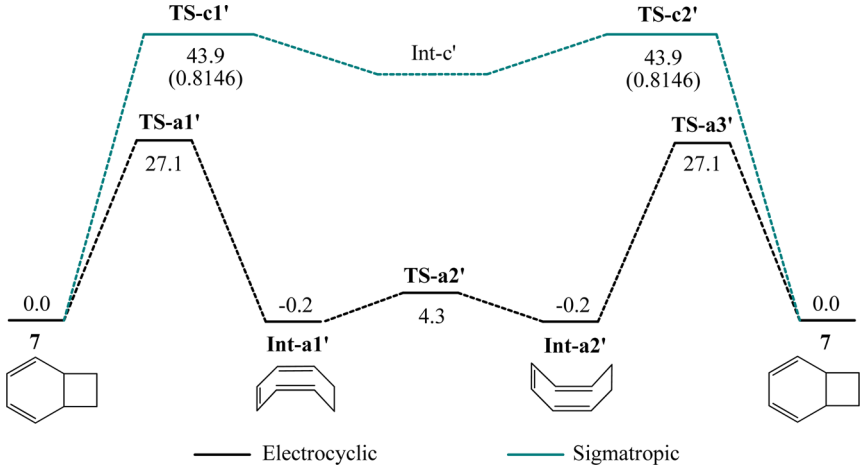

Figure 4. Free-energy profiles for the electrocyclic (M06-2*X*/6-31+G(d,p)) and sigmatropic pathways (UM06-2*X*/6-31+G(d,p)) and expectation values of the total spin $<S^2>$ (in parentheses) in the thermal equilibration of bicyclo[4.2.0]octa-2,4-diene **7**. For the sigmatropic pathway, no stable intermediate could be located, and IRC paths led to an unstable intermediate that disintegrated. All energies in kilocalories per mol.

then ring flip and close again, whereas the alternative single step pathway via a [1,5] sigmatropic alkyl shift or walk rearrangement would result in extensive scrambling of the deuterium labels over the carbons of the six-membered ring (Scheme 5b). The expected isotopomers of diol **9-d$_4$** should be detected easily by the appearance of the diagnostic olefinic resonances in the proton NMR spectrum. However, when a solution of the diol **9-d$_4$** in toluene was heated at 110 °C for 1 h, the starting material was recovered unchanged by NMR analysis. Consequently, at this temperature, the thermal equilibrium previously described by Nicolaou and Black for the endiandric acids does not constitute a walk rearrangement, as previously demonstrated also by computational results.

When dilute solutions of **9-d$_4$** were heated at temperatures between 170 and 195 °C, olefinic resonances did appear in the proton NMR spectra, which were superimposable with those observed for the nonlabeled diol **9** both in $CDCl_3$ and DMSO-d_6. However, assignment to any of the six possible isotopomers was not possible via 1D or 2D NMR experiments. Rigorous chromatographic purification of the reaction mixture obtained after heating for 2 h at 190−195 °C in acetonitrile (sealed tube) gave the unchanged diol **9-d$_4$** as a single isotopomer in about 30% yield. The observed olefinic resonances could therefore not be explained as D-scrambled products but must arise from other thermal reaction products. A similar complex mixture of products was obtained when the nonlabeled diol **9** was subjected to the same conditions, but none of the constituents could be fully identified. Finally, heating diols **9** and **9-d$_4$** at even higher temperatures (up to 230 °C) in ethylene glycol (sealed tube) gave a very fast (<10 min) and complete consumption of the starting material, returning a rather complex and inseparable mixture of products. In contrast to most bicyclo[4.1.0]hepta-2,4-diene (norcaradiene) systems, the bicyclo[4.2.0]octa-2,4-diene system appears to have limited thermal stability. Furthermore, partial analysis by 2D NMR experiments seems to implicate the completely ring-opened acyclic tetraene valence tautomer as the parent structure for most of the observed thermal products, a reaction pathway, which is not available for the norcaradiene systems.

2. Thermal Equilibration of Bicyclo[4.2.0]octa-2,4-diene 7 and Comparison with Literature. The electrocyclic and sigmatropic stepwise pathways were computationally explored for the parent bicyclo[4.2.0]octa-2,4-diene compound **7** (Figure 4) with the M06-2*X*/6-31+G(d,p) level of theory, in order to compare the thermal equilibration of this unsubstituted bicyclo[4.2.0]octa-2,4-diene with the norcaradiene system reported in literature.

The free-energy profiles for both pathways of the thermal equilibration of bicyclo[4.2.0]octa-2,4-diene **7** are shown in Figure 4. These look fairly similar to the free-energy profiles for bicyclo[4.2.0]octa-2,4-diene **9**, again suggesting a clear preference for the electrocyclic cascade. While the bicyclo[4.2.0]octa-2,4-diene **9** was found to be more stable than its contorted cyclooctatriene intermediate, as anticipated in the introduction, this is not true for the bicyclo[4.2.0]octa-2,4-diene **7**, which was found to be as stable as its contorted cyclooctatriene intermediate, as was also recently reported by Houk.[55a] Consequently, the sigmatropic pathway is shown to be less likely for bicyclo[4.2.0]octa-2,4-diene **7** when compared to the bicyclo[4.2.0]octa-2,4-diene **9**. Furthermore, no stable singlet intermediate could be located for the unsubstituted bicyclo[4.2.0]octa-2,4-diene **7**, whereas an open-shell singlet biradical intermediate was found for bicyclo[4.2.0]octa-2,4-diene **9**, which can be attributed to the difference in stability for primary and secondary radicals. Nonetheless, the parent bicyclo[4.2.0]octa-2,4-diene compound **7** could undergo a "one step nonconcerted" sigmatropic shift,[38,84] which proceeds without the formation of an intermediate.

The Gibbs free activation barrier for the electrocyclic route found here is very close to the ones reported earlier by Huisgen[42b] and recently by Houk[55a] ($\Delta G^{\ddagger}$ = 27.1 ± 0.2 kcal/mol). Furthermore, although no stable singlet intermediate could be located for the parent bicyclo[4.2.0]octa-2,4-diene compound **7**, appropriate substituents can favor the stepwise sigmatropic pathway, as demonstrated in the previous section for bicyclo[4.2.0]octa-2,4-diene **9**. The calculated barriers for the sigmatropic bond cleavage ($\Delta G^{\ddagger}$ = 43.9 kcal/mol) are within the range of experimental and predicted activation barriers for [1,5] alkyl shifts in bicyclo[4.1.0]hepta-2,4-dienes, which range from 35 to 45 kcal/mol.[38,39]

As a conclusion, even though the electrocyclic cascade is more plausible, comparable barriers for the [1,5] alkyl shifts of bicyclo[4.2.0]octa-2,4-dienes and bicyclo[4.1.0]hepta-2,4-dienes strongly suggest that the sigmatropic stepwise pathway

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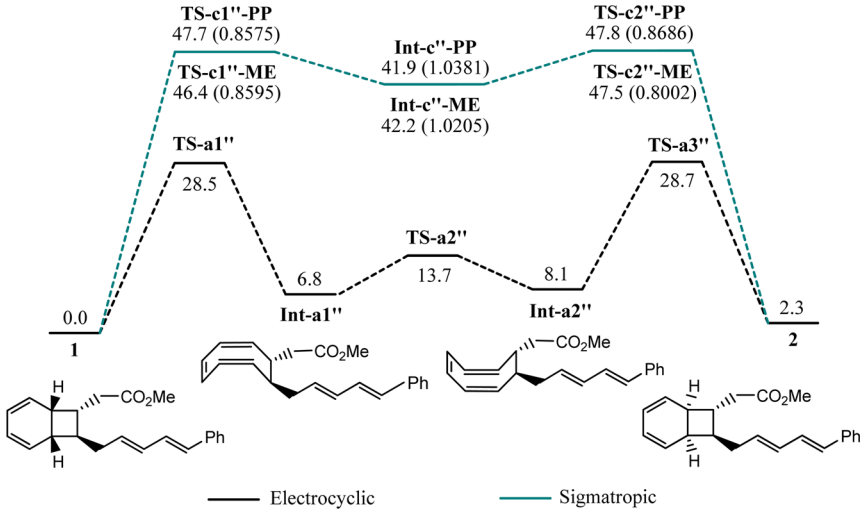

Figure 5. Free-energy profiles for the electrocyclic (M06-2*X*/6-31+G(d,p)) and sigmatropic pathways (UM06-2*X*/6-31+G(d,p)) and expectation values of the total spin <S^2> (in parentheses) in the thermal equilibration of endiandric acid methyl esters D/E (**1**/**2**). For the sigmatopic pathways, PP indicates the breaking of the C−C bond close to the phenyl pentadienyl group and ME indicates the breaking of the C−C bond close to the methyl ester group. All energies in kilocalories per mol.

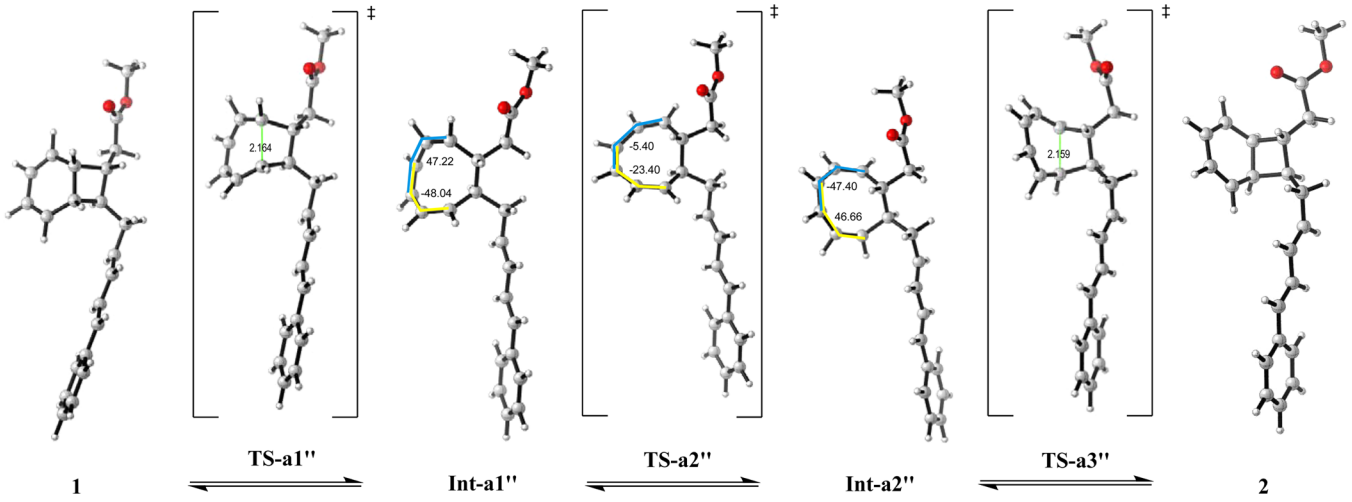

Figure 6. Electrocyclic cascade (M06-2*X*/6-31+G(d,p)) for the thermal equilibration of endiandric acid methyl esters D/E (**1**/**2**). Some critical distances (green, angstroms) and dihedral angles (yellow and blue, in degrees) are shown.

is feasible at higher temperatures for appropriately substituted compounds.

3. Thermal Equilibration of Endiandric Acid Methyl Esters D/E (1/2). Finally, the electrocyclic and sigmatropic stepwise pathways were computationally explored for the thermal equilibration of endiandric acid methyl esters D/E (**1**/**2**). The free-energy profiles shown in Figure 5 reveal relative Gibbs free energies that are only slightly higher than those for the thermal equilibration of the diol derivate **9** and expectation values of total spin <S^2> that are comparable to those for the diol derivate **9**, suggesting a clear preference for the electrocyclic cascade. Although the sigmatropic pathway might be feasible at high temperatures. The energetically favorable electrocyclic pathway along with optimized transition state and intermediate geometries is shown in Figure 6. A thorough conformational search was done on the phenyl pentadienyl group and the methyl ester group of methyl ester **1**, and the most stable conformer is shown in Figure 6. All other transition states and intermediates originated from this conformation. Endiandric acid methyl esters **1**/**2** were found to be more stable with respect to their contorted cyclooctatriene (COT) intermediate, compared to the diol derivate **9**, this favors the sigmatropic pathways. Moreover, substituents made it possible to locate a stable singlet intermediate for the stepwise sigmatropic pathway, whereas no stable intermediate could be located for the unsubstituted bicyclo[4.2.0]octa-2,4-diene **7**. Therefore, the stepwise sigmatropic pathway may be plausible at higher temperatures for both the diol derivate **9** and the endiandric acid methyl esters **1**/**2**. Expectation values of total spin <S^2> from DFT calculations indicate that the sigmatropic pathway goes through open-shell transition states and a corresponding open-shell singlet biradical intermediate (Figure 5). Similarly, NOON from CASSCF calculations on the diol derivate **9** had shown that the sigmatropic transition states have some diradical character, and the sigmatropic intermediate is a pure diradical. It was also previously shown for the sigmatropic transition states of the diol derivate **9** that CASSCF and M06-2X energies are in very good agreement. Since the relative Gibbs free energies (M06-2X) for the thermal equilibration of methyl esters **1**/**2** are comparable to those of

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the diol derivate **9** for all pathways, CASSCF calculations were not performed on the sigmatropic pathways of methyl esters **1**/**2**, due to the large size of the system. However, this system is assumed to be comparable to the diol derivate **9**, which was shown to proceed via singlet states for all pathways and have a sigmatropic pathway with diradical character.

CONCLUSION

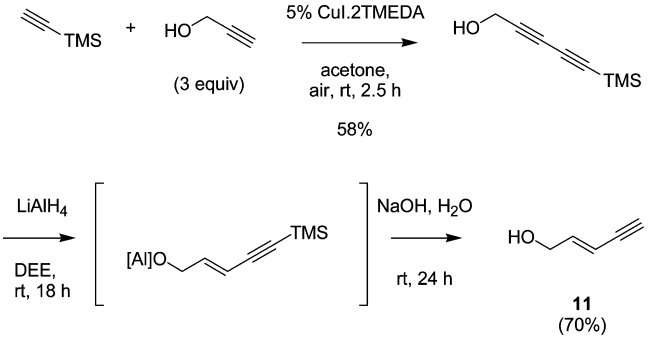
The mechanism of thermal equilibration between endiandric acid methyl esters D/E in particular and more generally the possibility of [1,5] sigmatropic alkyl shifts (walk rearrangements) in bicyclo[4.2.0]octa-2,4-diene systems at high temperatures have been explored in a combined computational and experimental study, pointing to the following conclusions: (a) an electrocyclic cascade is clearly preferred over the sigmatropic pathways; the calculated free-energy barriers for this route, which was previously proposed by Nicolaou, are shown to be very close to the one for bicyclo[4.2.0]octa-2,4-diene reported by Huisgen. (b) The activation barriers for the sigmatropic process might be overcome at high temperatures. Calculated barriers for the sigmatropic stepwise pathway were shown to be comparable with the reaction barriers for the bicyclo[4.1.0]-hepta-2,4-diene (norcaradiene) walk rearrangement. Nevertheless, this stepwise pathway is only feasible for appropriately substituted compounds. (c) DFT calculations suggested that the stepwise sigmatropic pathway goes through open-shell transition states and a corresponding open-shell singlet biradical intermediate, whereas a proposed concerted sigmatropic pathway has a closed-shell transition state. CASSCF calculations showed that all sigmatropic transition states have some diradical character, and the sigmatropic stepwise intermediate is a pure diradical. Therefore, the closed-shell concerted sigmatropic transition state **TS-b** that was located with DFT is not a true transition state.

Experimental NMR analysis on the thermal rearrangement of the deuterium-labeled diol (**9-d$_4$**), for which the electrocyclic and sigmatropic rearrangements would lead to different interconverting isotopomeric products, showed that in this model system, [1,5] sigmatropic alkyl shifts do not occur with a significant reaction rate at temperatures up to 195 °C. Higher temperatures could not be explored because of the limited thermal stability of this bicyclic system. Our results indicate that [1,5] sigmatropic shifts should be energetically comparable processes both in bicyclo[4.2.0]octa-2,4-diene and bicyclo[4.1.0]hepta-2,4-diene compounds, but they have so far only been observed in the latter.

EXPERIMENTAL SECTION

General Methods. Reactions were monitored by thin layer chromatography (TLC) using UV254 precoated silicagel plates (0.25 mm thickness). The TLC plates were visualized using an anisaldehyde (5% anisaldehyde in ethanol with 1% sulfuric acid) or a PMA (5% phosphomolybdic acid in ethanol) solution. Flash column chromatography was performed using silica gel (0.063−0.200 mm particle size). ^{1}H NMR and ^{13}C NMR spectra were recorded on a 300 MHz instrument at 300 and at 75 MHz, respectively. Chemical shifts (δ) are reported in units of parts per million (ppm), referenced relative to the residual ^{1}H or ^{13}C peaks of the used solvent as internal standards (chloroform-*d*: δ_H 7.26 and δ_C 77.16; dimethyl sulfoxide-d_6: δ_H 2.49 and δ_C 39.50). The following abbreviations were used to explain the multiplicities: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet; br, broadened; band, several overlapping signals; AB, AB system with strongly skewed signals. Where given and if appropriate, assignments of resonances were confirmed by standard COSY(GPQF) and HSQC(EDETGP) 2D NMR experiments. Infrared spectra (IR) were recorded on a FTIR spectrometer and reported in wave numbers (cm^{-1}). Samples were prepared as a thin film (neat) on the KBr plate. Mass spectra (MS) were recorded on an ESI-single quadrupole detector type VL. High-Resolution Mass Spectra (HRMS) were recorded on an accurate-mass quadrupole time-of-flight mass spectrometer. Reported melting point ranges were determined after iterative crystallization until a stable value was obtained.

Materials. All chemicals and solvents were purchased and used without any further purification, except dichloromethane, which was distilled from CaH_2 prior to use. (*E*)-pent-2-en-4-yn-1-ol **11** is a commercially available compound but is prohibitively expensive and not readily available from standard suppliers. However, it was easily prepared in two steps from ethynyl trimethylsilane.



(E)-Pent-2-en-4-yn-1-ol ***11***. A solution of 2-propyn-1-ol (463 mg, 8.3 mmol) and ethynyl trimethylsilane (50 mg, 0.51 mmol) in acetone (15 mL) was added to a vigorously stirred solution of copper(I)iodide (169 mg, 0.89 mmol) and tetramethylethylenediamine (207 mg, 1.78 mmol) in acetone (20 mL), in a reaction flask that was open to air. The resulting mixture was stirred open to air for 5 min, and then a solution of ethynyl trimethylsilane (450 mg, 4.58 mmol) and prop-2-yn-1-ol (250 mg, 4.5 mmol) in acetone (15 mL) was added dropwise over 20 min. The reaction was stirred for another 2 h, the bulk of the acetone was removed under reduced pressure, and the residue was diluted with methyl-*tert*-butylether (100 mL). The organic layer was washed with a saturated aqueous solution of ammonium chloride (3 × 10 mL), water (10 mL), and brine (10 mL), dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by chromatography on silica, eluting with 30% methyl-*tert*-butylether in light petroleum (bp 40−60 °C), to give 5-trimethylsilanyl-penta-2,4-diyn-1-ol (450 mg, 58%) as a clear colorless liquid.

A solution of the alcohol obtained above in diethyl ether (7.0 mL) was added dropwise over 5 min to a suspension of lithium aluminumhydride (333 mg, 8.87 mmol) in diethyl ether (7.0 mL) that was vigorously stirred at 0 °C. The resulting mixture was warmed to room temperature and stirred for 18 h. Then, the reaction mixture was cooled to 0 °C, and water (0.33 mL) was added carefully, followed by a 15% aqueous solution of sodium hydroxide (0.33 mL) and water (1.0 mL). The resulting white suspension was stirred vigorously for 24 h, and then filtered over a pad of silica, which was thouroughly washed with methyl-*tert*-butylether. The filtrate was concentrated to give (*E*)-pent-2-en-4-yn-1-ol **11** (170 mg, ∼70%) as a volatile, clear colorless liquid which contained residual trimethyl silanol and solvent but was used in the next step without further purification. The compound showed proton NMR data that were consistent with data reported for this compound, previously synthesized using different methods.[85−88]

(2E,8E)-Deca-2,8-diene-4,6-diyne-1,10-diol ***12***. The crude alcohol **11** (170 mg) was dissolved in acetone (3 mL) and then added over 5 min to a solution of copper(I)iodide (28 mg, 0.15 mmol) and tetramethylethylenediamine (35 mg, 0.30 mmol) in acetone (3 mL) that was stirred open to air at room temperature. After stirring for another 2 h, the bulk of the acetone was removed under reduced pressure, and the dark residue (∼0.5 mL) was directly subjected to chromatography over silica, eluting with a 3:1 mixture of methyl-*tert*-butylether and light petroleum (bp 40−60 °C), to give (2*E*,8*E*)-deca-2,8-diene-4,6-diyne-1,10-diol **12** (114 mg, 67%) as an off-white solid.

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Mp 152−153 °C (recryst. from methyl-*tert*-butylether and light petroleum). IR ν_{max}: 3284(s), 2894, 2207(vw). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.18 (4H, ddd, J = 5.4, 4.3, and 1.9 Hz, 2 × CH_2OH), 4.17 (2H, t, J = 5.4 Hz, 2 × OH), 4.98 (2H, dt, J = 15.6 and 1.9 Hz, 2 × CH═CHCH$_2$), 5.60 (2H, dt, J = 15.6 and 4.3 Hz, 2 × CH═CHCH$_2$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 60.8 (2CH$_2$), 73.5 (2C), 80.3 (2C), 106.1 (2CH), 149.1 (2CH). MS(ESI): m/z 145.1 (MH$^+$ − H$_2$O). HRMS (ESI) calcd. For $C_{10}H_9O$ (m/z M + H$^+$ − H$_2$O), 145.0648; found, 145.0643 and calcd. For $C_{10}H_{11}O_2$ (m/z M − H+, negative mode), 161.0608; found, 161.0603.

(8-Hydroxymethyl-bicyclo[4.2.0]octa-2,4-dien-7-yl)-methanol **9**. Lindlar's catalyst (palladium, 5% on calcium carbonate, poisoned with lead (purchased from Aldrich chemical company), 102 mg) was added to a solution of diol **12** (50.0 mg, 0.308 mmol) and quinoline (0.050 mL) in dichloromethane (9.0 mL) and methanol (1.0 mL). The resulting suspension was degassed and placed under an atmosphere of hydrogen gas. The reaction progress was closely monitored by thin layer chromatography. The starting material was usually quickly converted into the monohydrogenated product (5−10 min), which was then slowly transformed into a number of products, but mainly the diol **9** (0.5−4 h). The reaction mixture was degassed upon consumption of the monohydrogenated intermediate (as judged by TLC) and filtered over a short pad of silica, which was washed with methyl-*tert*-butylether. The filtrate was concentrated in vacuo, and the residue was purified by chromatography over silica, eluting with 2.5% methanol in chloroform. The obtained product was further purified by chromatography over silica, eluting with a 2:1 mixture of methyl-*tert*-butylether and light petroleum (bp 40−60 °C). This afforded the pure diol **12** (23.5 mg, 45%) as a very viscous, clear colorless oil [in some runs, lower yields were obtained (down to 30%)]. IR ν_{max}: 3318(s), 2922(s), 1461, 1376, 1028. ^{1}H NMR (300 MHz, CDCl$_3$): δ 2.67−2.74 (3H, band, 3 × cyclobutane−CH), 3.13−3.20 (1H, m, ═CH—CHcyclobutane), 3.45−3.51 (1H, m, CHHOH), 3.76 (1H, dd, J = 10.2 and 3.6 Hz, CHHOH), 3.79−3.85 (2H, m, CH_2OH), 5.53 (1H, dd(br), J = 9.7 and 3.8 Hz, CH═CH—CH═CH), 5.60 (1H, dd(br), J = 9.5 and 3.9 Hz, CH═CH−CH═CH), 5.72 (1H, dd, J = 9.5 and 5.5 Hz, CH═CH—CH═CH), 5.87 (1H, ddd(br), J = 9.7, 5.5, and 1.7 Hz, CH═CH—CH═CH). ^{13}C NMR (75 MHz, CDCl$_3$): δ 32.5 (CH), 33.0 (CH), 51.1 (CH), 52.5 (CH), 62.8 (CH$_2$), 65.5 (CH$_2$), 122.3 (CH), 124.3 (CH), 125.5 (CH), 126.1 (CH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.25 (1H, app. quintet, J = ∼7.2 Hz, C7′-H), 2.59 (1H, (app. q)d, J = ∼8.5 and 6.9 Hz, C8′-H), 2.66 (1H, ddd, J = 11.1, 8.1, and 5.3 Hz, C6′-H), 3.02 (1H, app.t(br), J = ∼9.5 Hz, C1′-H), 3.34 (2H, app.t, J = ∼5.7 Hz, C1-H_2OH), 3.48 (1H, d(AB)dd, J = 10.4, 6.7, and 4.5 Hz, C1″-HHOH), 3.55 (1H, d(AB)dd, J = 10.4, 8.7, and 5.3 Hz, C1″-HHOH), 4.35 (1H, app.t, J = ∼4.9 Hz, C1″-H$_2$OH), 4.48 (1H, app.t, J = ∼5.3 Hz, C1−H$_2$OH), 5.55 (1H, d(AB)d, J = 9.7 and 4.4 Hz, C5′-H), 5.56−5.61 (1H, m, C2′-H), 5.62 (1H, d(AB)d, J = 9.7 and 4.9 Hz, C4′-H), 5.80 (1H, dd(app.t), J = 9.9, 4.9, and 1.5 Hz, C3′-H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 32.1 (CH), 32.2 (CH), 48.4 (CH), 51.3 (CH), 61.2 (CH$_2$), 63.5 (CH$_2$), 121.3 (CH), 123.5 (CH), 126.1 (CH), 127.2 (CH). MS(ESI): m/z 167.1 (M + H$^+$, 26), 149.1 (M+H$^+$-H$_2$O, 100). HRMS (ESI): calcd. For $C_{10}H_{15}O_2$ (m/z M + H$^+$), 167.1067; found, 167.1066.

[2,3,4,5-$^2H_4$]-(8-Hydroxymethyl-bicyclo[4.2.0]octa-2,4-dien-7-yl)-methanol **9-d$_4$**. The general procedure for the synthesis of bicyclic diol **9** was followed, but deuterium gas (99.8% atom D) was used instead of hydrogen gas. Starting from 50 mg of diol **12** (0.295 mmol), chromatography as described for compound **9** gave the deuterium-labeled bicyclic diol **9-d$_4$** (18.0 mg, 34%) as a clear viscous oil. IR ν_{max}: 3336(s), 2922(s), 1462, 1376, 1025. ^{1}H NMR (300 MHz, CDCl$_3$): δ 2.67−2.74 (3H, band, 3 × CH), 3.14−3.19 (1H, m, ═CD—CH), 3.45−3.51 (1H, m, CHHOH), 3.76 (1H, dd, J = 10.2 and 3.6 Hz, CHHOH), 3.79−3.85 (2H, m, CH_2OH). ^{13}C NMR (75 MHz, CDCl$_3$): δ 32.5 (CH), 33.0 (CH), 51.1 (CH), 52.5 (CH), 62.8 (CH$_2$), 65.5 (CH$_2$). MS(ESI): m/z 171.1 (MH$^+$, 58), 153.1 (MH$^+$ − H$_2$O, 100). HRMS (ESI): calcd. For $C_{10}D_4H_{11}O_2$ (m/z M + H$^+$), 171.1318, found, 171.1323.

Thermal Equilibration Experiments. A solution of the diol **9** or the diol **9-d$_4$** (2 to 5 mg per run) in acetonitrile (2.0 mL) was neutralized with ∼1 mg of sodium bicarbonate and purged with argon. The solution was then stirred in a closed reaction vessel under microwave heating (CEM Discover). The reaction temperature and vessel pressure were monitored by external surface sensors. Reactions in acetonitrile were maintained at temperatures between either 170−175 °C or 190−195 °C for 1−6 h [which was the highest temperature that could be achieved in this solvent (p_{max} = 17.0 bar)]. Reactions were monitored by TLC and NMR, and the reaction mixtures were increasingly complex with reaction temperature and time. The starting materials were isolated unchanged from the reaction mixtures by careful chromatography over silica, eluting with 2% methanol in chloroform. The obtained products (0.5−2.5 mg, 25−50%) showed ^{1}H NMR spectra which were indistinguishable from those of the starting materials **9** or **9-d$_4$**. The same experiments performed in ethylene glycol, which allows reaction temperatures higher than 200 °C, gave similar results. However, no trace of starting material remained after heating to 230 °C (20 min) in these experiments, as judged by TLC and NMR.

■ ASSOCIATED CONTENT

Supporting Information

Cartesian coordinates and energies of M06-2X/6-31+G(d,p) optimized geometries, imaginary and low frequencies of transition states. Full reference 59. Natural orbital occupation numbers (NOON) of transition states and intermediates for the thermal rearrangement of **9** (CASSCF(6,6)/6-31+G(d,p)//UM06-2X/6-31+G(d,p)) and discussion. NMR spectra for compounds **9**, **9-d$_4$**, **11**, **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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