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A New Access to Dihydrotropones through Ring Expansion of Spirocyclohexadienones: Synthesis and Mechanism†

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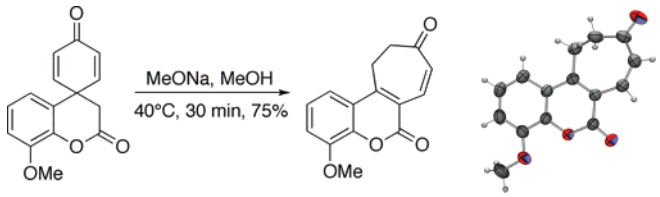

In this paper we report the rearrangement of spirocyclohexadienones into dihydrotropones in basic conditions as a new method for the preparation of seven-membered ring ketones, which are key building blocks for the synthesis of tropoloalkaloids. DFT calculations and deuterium labeling studies support the mechanism we propose for this rearrangement, involving the ring opening of a spirocyclopropane intermediate followed by successive base-catalyzed 1,3-hydrogen shifts. The X-ray structure of the resulting dihydrotropone shows near-perfect planarity and the conjugation gain is likely to be the driving force of the reaction.

Introduction

Substituted carbocyclic seven-membered rings are frequently found in natural and medicinally active compounds (e.g., hinokitiol,[1] thapsigargins,[2] colchicine[3,4]), and several methods for their synthesis are available,[5−7] among them, cycloadditions of allyl cations with 1,3-dienes,[8−10] metal-catalyzed cycloadditions,[11−20] electrochemical oxidations,[21] and radical,[22−24] acidic,[25,26] or thermal[27,28] ring expansion reactions.

We describe here a new method, the rearrangement of spirocyclohexadienones to one-carbon ring expansion products, dihydrotropones, under basic conditions.[29] A mechanism for this reaction is also proposed, which is fully supported by DFT calculations and deuterium labeling studies.

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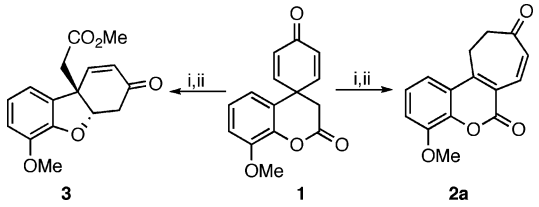
SCHEME 1. Rearrangement and Lactone Ring Opening Products of Spirocyclohexadienone 1 in Basic Conditions[a,b]



[a] Throughout this study, the following naming system is used: (a) for the keto forms; (b) for the enol forms; (c) for the enolate forms (see Table 1 for more details). [b]Conditions: (i) MeONa, MeOH, 40 °C; (ii) HCl 1 M.

Results and Discussion

Reaction Conditions. In basic conditions, we observed conversion of the dienone **1**[30] into two products: a one carbon ring expansion product (**2a**) and a tricyclic ester (**3**) resulting from the lactone ring opening (Scheme 1). These two compounds are obtained in various ratios according to the reaction conditions.

The presence of an efficient protonating agent seems to be essential for the rearrangement of **1** into **2a** to occur. Several systems have been investigated at different temperatures (−78 to 75 °C): (i) in the absence of protonating agent (NaH/THF) no reaction is observed; (ii) in the presence of a stoichiometric quantity of protonating agent (DBU/CH_2Cl_2, potassium phthalimide/THF, lithium *N*-methyltoluenesulfonamide/THF) we observed the suppression of the lactone ring opening, a slow reaction rearrangement, and low yields of **2a** (5−30%); and (iii) when the protonating agent is the solvent (MeONa/MeOH, EtONa/EtOH, *i*-PrONa/*i*-PrOH) we observed a fast reaction and the formation of two compounds—the rearrangement product **2a** and the tricyclic ester **3**. The best results are obtained with MeONa in MeOH at 40 °C for 30 min, the product **2a** being isolated in 75% yield in these conditions.

During the study of the reaction of **1** with MeONa in MeOH at 40 °C we evidenced two competitive reactions: (i) the rearrangement described above, leading to **2a** after protonation, and (ii) the intermediate formation of the ester **3**,[31] through the nucleophilic opening of the lactone ring followed by a Michael addition of the resulting phenoxide **8** (Scheme 2).

The formation of compound **3** proved to be reversible and the equilibrium is shifted toward the thermodynamic product **2a** (Figure S1, Supporting information). Figure 1 shows that the ester **3** has completely disappeared after 10 min, but the best yields of **2a** are obtained after 30 min at 40 °C. At lower temperatures (−78 to 20 °C), the ester **3** is almost exclusively observed.

When the reaction of **1** with CD_3ONa in CD_3OD at 40 °C is followed by ^1H NMR (Figure S2, Supporting information) it is noteworthy that (i) an equilibrium between three species (**5**, **7c**, and **9**) is immediately established, which is completely shifted toward the delocalized anion **7c** after 30 min and (ii) the deuterium exchange is very fast and all the enolizable positions are completely deuterated after 3 min. The complete incorporation of deuterium into both positions α to the ketone in **5** proves the existence of a dynamic equilibrium between the ester **5** and the open bicyclic phenoxide **9**.[32] Moreover, the reversibility of this process is confirmed by the exclusive formation of the rearrangement product **2a** when the ester **3** is treated with MeONa/MeOH at 40 °C.

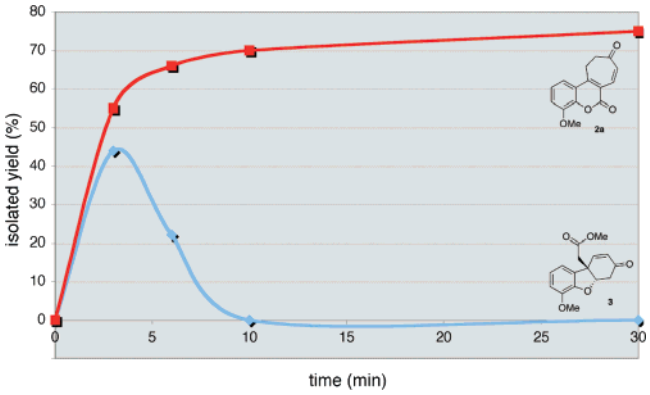


FIGURE 1. Time-dependent formation of compounds **2a** and **3** (MeONa, MeOH, 40 °C).

The rearrangement product **2a**, in the presence of CD_3ONa in CD_3OD at room temperature, is completely deprotonated and immediately forms the enolate **6c**, which then undergoes a slow deuterium exchange, complete after 20 h, leading to the enolate **7c** (Figure S3, Supporting information).

Reaction Mechanism. In light of the results presented above, we propose the following mechanism for this rearrangement (Scheme 3): the deprotonation of the lactone **1**, followed by the intramolecular Michael addition of anion **10** leads to the cyclopropyl derivative **11**, which is transformed into the enolate **12c** by a cyclopropane ring opening.[33] The enolate **12c** is then converted into the final protonated product **2a**.

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(31) Compound **3** can be prepared in a straightforward manner in acidic medium (TFA, MeOH) from spirocyclohexadienone **1** in 87% yield (see the Experimental Section).

(32) Compound **9** is the anionic phenoxide form rather than the neutral phenol form, as indicated by the important shift of the aromatic protons observed in its ^1H NMR spectrum, see: Highet, R. J.; Highet, P. F. *J. Org. Chem.* **1965**, *30*, 902−906.

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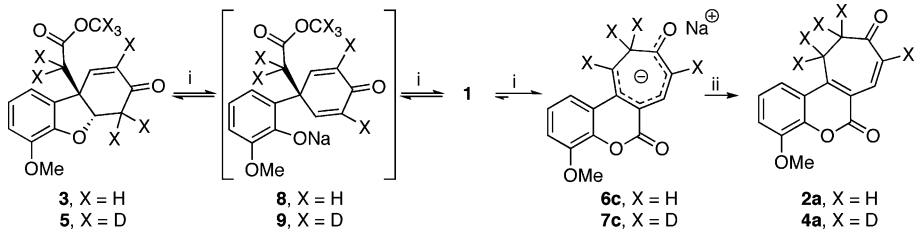
SCHEME 2. Deuterium Labeling Studies during the Rearrangement and Lactone Ring Opening of Spirocyclohexadienone 1 in Basic Conditions[a]



3, X = H
5, X = D

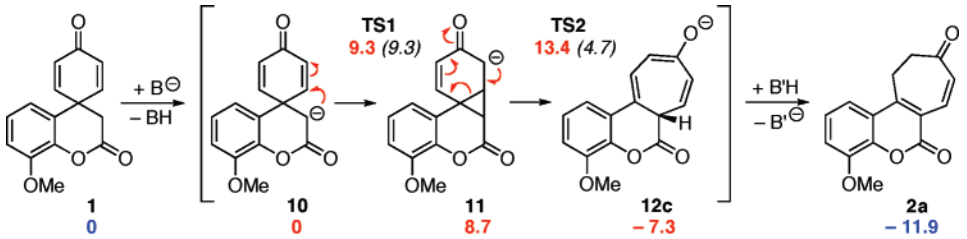
8, X = H
9, X = D

6c, X = H
7c, X = D

2a, X = H
4a, X = D

[a] Conditions: (i) CX_3ONa, CX_3OX, 40 °C; (ii) HCl 1 M.

SCHEME 3. Proposed Mechanism for the Rearrangement of 1 into 2a[a]

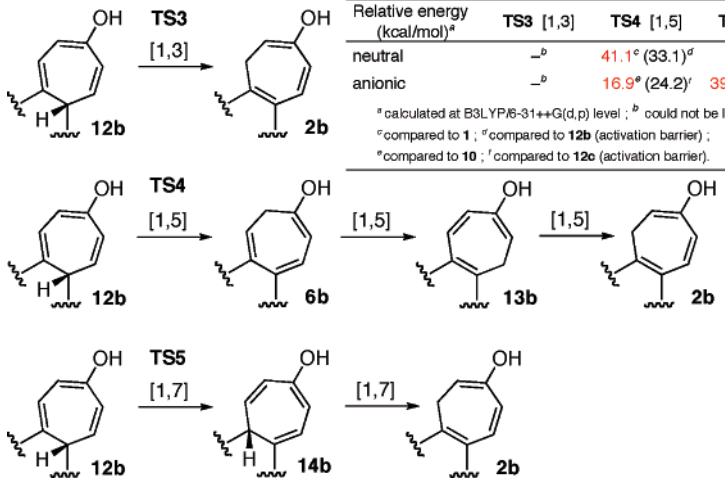


1 0 | **10** 0 | **11** 8.7 | **12c** – 7.3 | **2a** – 11.9

BH = MeOH; B'H = HCl

[a] Calculated relative energies (kcal/mol) of neutral compounds are represented in blue and those of anions and transition states (TS) in red. The activation barriers (kcal/mol) are reported in parentheses.

SCHEME 4. Three Different Possible Pathways for the Conversion of 12b into 2b through Sigmatropic Reactions



Relative energy (kcal/mol)[a]	TS3 [1,3]	TS4 [1,5]	TS5 [1,7]
neutral	–[b]	41.1[c] (33.1)[d]	–[b]
anionic	–[b]	16.9[e] (24.2)[f]	39.2[e] (46.5)[f]

[a] calculated at B3LYP/6-31++G(d,p) level ; [b] could not be located ; [c] compared to **1** ; [d] compared to **12b** (activation barrier) ; [e] compared to **10** ; [f] compared to **12c** (activation barrier).

To support the proposed mechanism, the structures of intermediates and transition states were optimized at the B3LYP level with the 6-31++G(d,p) basis set, using Gaussian 03[34] (Scheme 3). Intrinsic reaction coordinate (IRC) path calculations are in full agreement with a spirocyclopropane intermediate **11**, which rearranges to give a seven-membered ring enolate **12c**. The activation barrier energies for TS1 and TS2 (9.3 and 4.7 kcal/mol, respectively) are not very high, which is consistent with the mild reaction conditions used for this transformation. The driving force of the rearrangement is likely to be the greater extent of conjugation in **2a** than in **1**, confirmed by the near-perfect planarity of the X-ray structure.

Whereas the mechanism for the conversion of **1** into **12c** is relatively intuitive, the second part of the mechanism presented in Scheme 3, the conversion of the enolate **12c** into the rearrangement product **2a**, is not so obvious. We have formulated two hypotheses: (a) a sigmatropic hydrogen shift and (b) a base-catalyzed 1,3-hydrogen shift.

(a) Sigmatropic Hydrogen Shift. Three pathways can be envisaged for the conversion of **12b** into **2b** through a sigmatropic mechanism: (i) one direct [1,3] hydrogen shift; (ii) three consecutive [1,5] hydrogen shifts; and (iii) two consecutive [1,7] hydrogen shifts (Scheme 4). These sigmatropic shifts can theoretically take place before or after the protonation step, thus both neutral and anionic forms of the possible intermediates must be considered.

In the cycloheptatrienic systems only the suprafacial hydrogen shifts are possible for steric reasons, thus the [1,3] and [1,7] hydrogen shifts are thermally forbidden, whereas the [1,5] hydrogen shift is allowed.[35–39] To evaluate the conditions

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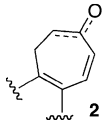
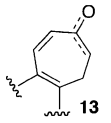
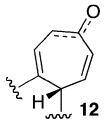
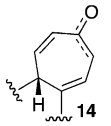
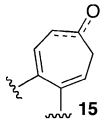
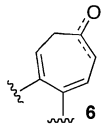
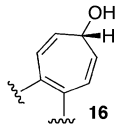
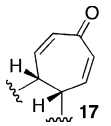
TABLE 1. Calculated Relative Energies of All Possible Intermediates in the Sigmatropic Rearrangement

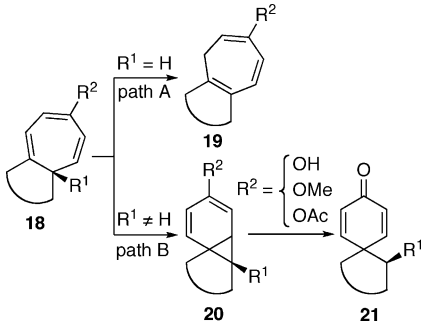
Structure	Relative energy (kcal/mol)[a]		
	keto (**a**)[b]	enol (**b**)[b]	enolate (**c**)[c]
 **2**	– 11.9	– 1.3	– 4.9
 **13**	– 10.3	– 0.9	– 3.4
 **12**	7.6	8.0	– 7.3
 **14**	6.0	5.0	– 13.8
 **15**	– 3.7	– 0.5	– 21.5
 **6**	– 3.7	0.1	– 27.0
 **16**	–	2.7[d]	18.6[d]
 **17**	10.0	–	–

[a] Calculated at the B3LYP/6-31++G(d,p) level. [b] Compared to **1**. [c] Compared to **10**. [d] In this case, alcohol/alcoholate instead of enol/enolate

required for the sigmatropic shift in this rearrangement, we optimized the structures and calculated the energies for all intermediates, as well as for the transition states in the first sigmatropic shift (Scheme 4, Table 1).

We succeeded in locating valid transition states only in three cases, for neutral **TS4n**, anionic **TS4a**, and anionic **TS5a**.[40] The difference of activation barriers between the neutral and anionic forms of **TS4** is almost 9 kcal/mol, so it seems that the sigmatropic rearrangement is more favored in the anionic series. However, in spite of the lower value obtained for **TS4a** (24.2 kcal/mol), this activation barrier is still too high to be compatible with the mild conditions used for this reaction. The activation

SCHEME 5. Influence of the Ring Substituents in the Evolution of Cycloheptatrienic Systems



barrier of the anionic form **TS5a** is higher than that of **TS4a**, as expected for a forbidden sigmatropic shift.

All these calculation data suggest that there is no sigmatropic shift involved in this mechanism; this is further supported by the complete deuterium exchange observed for the two methylene groups in **4a** (Scheme 2), which is not compatible with a sigmatropic shift.

As suggested by one of the referees, in the light of Herndon's studies,[11] we investigated the possibility to convert **2a** into **13a** by two successive thermal [1,5] hydrogen shifts. However, heating **2a** in *p*-xylene at 140 °C for 16 h led only to the partial conversion of **2a** into **13a** and from the mixture of these two compounds (ratio **2a**/**13a** = 3/1) **13a** was isolated in 11% yield. Longer reaction time (3 days) resulted in extensive decomposition. These results are in agreement with an extended delocalized system in our case, a high activation barrier for the thermal [1,5] hydrogen shifts, and support the greater stability (1.6 kcal/mol) calculated for **2a** compared to **13a**.

However, from the results of Table 1, it is noteworthy that, with one exception (structures **14**), the keto form is always more stable than the enol, the difference of energies being very important for **2** and **13**. This is in agreement with the experimental results[41] showing that the cycloheptadienone is the major form in this keto−enol equilibrium. Moreover, the energies of compounds **12**, **14**, and **17**, bearing ring junction hydrogen atoms, are unusually high, for both keto and enol forms. This is a consequence of the significant geometrical change induced by the presence of these hydrogen atoms, which prevents the conjugation between the 7-membered ring and the other two rings.

(b) Base-Catalyzed 1,3-Hydrogen Shift. Several examples of this type of transformation are described in cycloheptatrienic systems, catalyzed by triethylamine,[42−45] 1,8-diazabicyclo[5.4.0]-undec-7-ene,[27,28] or potassium *tert*-butoxide.[46,47] The mechanism and regioselectivity have been studied for cycloheptatrienes bearing electron-withdrawing groups.[48−52] There are also a few examples of thermal,[53−57] photochemical,[58] or acid-catalyzed[57,58]

(39) Okajima, T.; Imafuku, K. *J. Org. Chem.* **2002**, *67*, 625−632.

(40) In the search for the transition states **TS3n**, **TS3a**, and **TS5n**, several initial structures were tested. In some cases, local maximums were found (one negative frequence), but the IRC calculations did not lead to the expected reactants or products. This is probably due to the constraints induced by the cyclic form of the system.

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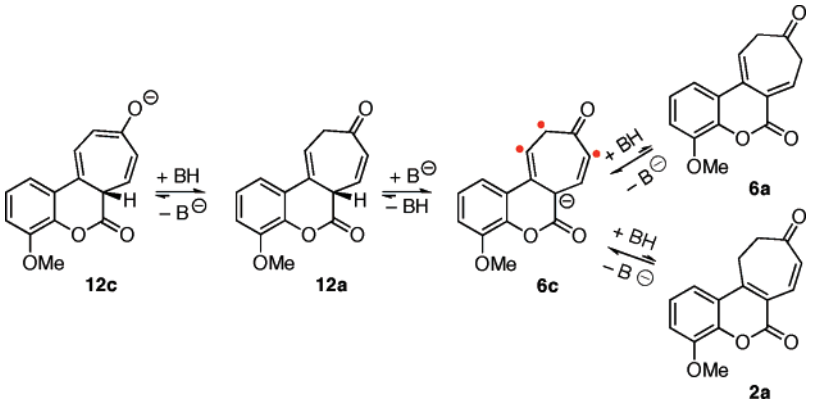
SCHEME 6. Proposed Mechanism for the Conversion of 12c to 6c[a]



[a] The red dots represent the positions completely deuterated when the reaction is carried out in CD_3OD.

1,3-hydrogen shifts. In most cases, the hydrogen atom shifts from a ring-junction position to the nearest unsubstituted position (path A, Scheme 5).[27,28,42−44,56−58] In the case where cycloheptatriene **18** has $R^1 \neq H$ (path B, Scheme 5), the 1,3-shift is very unfavored. The system evolves toward the spirodienone **21**[43,53−55] if an oxygenated substituent is present at R^2 or remains in the less constrained norcaradiene form **20**[59] in the other cases. To sum up the above, the pathways and the final products are determined by the stability given by the substituents present on the molecule.

In our study, the intermediate **12c** is a particular form of **18**, with $R^1 = H$ and $R^2 = O^-$. Following path A, the enolate **12c** is protonated and the resulting compound **12a** forms the enolate **6c** by deprotonation at the ring-junction position. This deprotonation represents the first step of the base-catalyzed hydrogen shift. In the second step, the delocalized enolate **6c** can be protonated at several positions to give either the compounds **12a**, **6a**, or **2a**, which are in equilibrium via **6c** as a common intermediate (Scheme 6).

This equilibrium is completely shifted toward the enolate **6c**, which is the only species visible in the NMR spectrum. The complete incorporation of deuterium in the positions marked with red dots in Scheme 6 supports the existence of successive base-catalyzed 1,3-hydrogen shifts leading to the enolate **6c**, which is the most stable of all anionic intermediates (Table 1). The protonation of **6c** leads exclusively to the isomer **2a**, the most stable compound among **2a**, **6a**, and **12a** (Table 1).

The deuterium-labeling results indicate that the mechanism of the rearrangement involves base-catalyzed 1,3-hydrogen shifts. This conclusion is supported by the calculations data.

Conclusion

In this paper we report the rearrangement of spirocyclohexadienones into dihydrotropones in basic conditions as a new method for the preparation of seven-membered-ring ketones, which are key building blocks for the synthesis of tropoloalkaloids. We gained insight into the mechanism that we proposed for this rearrangement by DFT calculations of the possible intermediates and transition states as well as by deuterium labeling. All these data allowed us to choose between two possible paths and thus conclude that the mechanism involves a base-catalyzed 1,3-hydrogen shift in the cycloheptatrienic system obtained from the opening of a fused cyclopropane intermediate.

Experimental Section

General Remarks. Starting materials and reagents were purchased from a commercial supplier and used without further purification with the exception of MeOH, which was distilled over Mg and I_2.

Synthesis of Methyl 2′-(4-Methoxy-7-oxo-5a,6,7,9a-tetrahydrodibenzo[*b*,*d*]furan-9a-yl)acetate (3). To a solution of 8-methoxyspiro[chroman-4,1′-cyclohexa[2′,5′]diene]-2,4′-dione (**1**)[30] (20 mg, 0.078 mmol) in methanol (0.5 mL) was added trifluoroacetic acid (0.1 mL, 1.3 mmol). After being stirred for 16 h at room temperature, the mixture was concentrated in vacuo. Preparative silica gel TLC (heptane/ethyl acetate 50/50) afforded 20 mg of methyl 2′-(4-methoxy-7-oxo-5a,6,7,9a-tetrahydrodibenzo[*b*,*d*]furan-9a-yl) acetate (**3**) as a pale yellow oil (87%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.94 (dd, J = 7.7, 7.8 Hz, 1H), 6.86 (d, J = 7.7 Hz, 1H), 6.83 (d, J = 7.8 Hz, 1H), 6.57 (dd, J = 10.3, 2 Hz, 1H), 6.02 (d, J = 10.3 Hz, 1H), 5.13 (m, 1H), 3.88 (s, 3H), 3.69 (s, 3H), 3.09 (d, J = 14.3 Hz, 1H), 3.13 (dd, J = 17.7, 2.8 Hz, 1H), 6.03 (dd, J = 17.7, 4.2 Hz, 1H), 2.90 (d, J = 15 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.0, 170.3, 146.9, 146.3, 145.1, 131.4, 127.6, 122.6, 115.0, 112.7, 86.0, 56.2, 52.2, 47.4, 41.5, 38.5; IR ($CDCl_3$) 1199, 1280, 1492, 1680, 1731 cm^{-1} ; MS (ESI) m/z 311(M + Na)$^+$; HRMS (ESI) m/z calcd for $C_{16}H_{16}O_5Na^+$ 311.0895, found 311.0878.

Synthesis of 4-Methoxy-10,11-dihydrocyclohepta[*c*]chromene-6,9-dione (2a). A solution of 8-methoxyspiro[chroman-4,1′-cyclohexa[2′,5′]diene]-2,4′-dione (**1**)[30] (20 mg, 0.078 mmol) in

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methanol (0.6 mL)/THF (0.3 mL) is added at 40 °C to a solution of sodium methoxide, freshly prepared from sodium (13 mg, 0.56 mmol) and methanol (0.6 mL). After being stirred for 30 min at 40 °C, the reaction is quenched with 1 M hydrochloric acid (2 mL), stirred for 10 min, and extracted with dichloromethane (3 × 5 mL). Concentration in vacuo of the combined organic layers followed by preparative silica gel TLC (heptane/ethyl acetate 70/30) afforded 15 mg of 4-methoxy-10,11-dihydrocyclohepta[*c*]chromene-6,9-dione (**2a**) (75%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, J = 12.9 Hz, 1H), 7.39 (d, J = 8.35 Hz, 1H), 7.30 (dd, J = 8.35, 8.04 Hz, 1H), 7.18 (d, J = 8.04 Hz, 1H), 6.40 (d, J = 12.8 Hz, 1H), 4.01 (s, 3H), 3.20 (dd, J = 5.5, 6.0 Hz, 2H), 2.83 (dd, J = 5.6, 6.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.8, 159.7, 155.8, 148.0, 143.4, 135.6, 132.0, 124.7, 121.5, 119.4, 116.7, 115.0, 56.6, 41.2, 22.7; IR ($CDCl_3$) 1469, 1662, 1710 cm^{-1} ; MS (ESI) *m*/*z* 279 (M + Na)$^+$; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{12}O_4Na^+$ 279.0633, found 279.0616.

Synthesis of 4-Methoxy-7,8-dihydrocyclohepta[*c*]chromene-6,9-dione (13a). A solution of 4-methoxy-10,11-dihydrocyclohepta-[*c*]chromene-6,9-dione (**2a**) (22 mg, 0.086 mmol) in *p*-xylene (1 mL) is heated at 140 °C for 16 h then concentrated in vacuo, and the resulting mixture (ratio **2a**/**13a** = 3/1) is purified by preparative silica gel TLC (eluting with heptane/ethyl acetate 40/60) to afford 2.5 mg of 4-methoxy-7,8-dihydrocyclohepta[*c*]chromene-6,9-dione (**13a**) (11%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, J = 12.8 Hz, 1H), 7.28 (m, 2H), 7.14 (dd, J = 7.0, 2.1 Hz, 1H), 6.65 (d, J = 12.8 Hz, 1H), 4.01 (s, 3H), 3.17 (m, 2H), 2.84 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 200.9, 160.6, 147.7, 142.5, 142.1, 136.3, 132.5, 129.3, 124.4, 119.1, 115.0, 113.3, 56.3, 44.1, 20.9; IR ($CDCl_3$) 1473, 1671, 1707 cm^{-1} ; MS (ESI) *m*/*z* 279 (M + Na)$^+$; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{12}O_4Na^+$ 279.0633, found 279.0631.

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Computational Methods

Geometry optimization and vibrational frequency calculations were performed at the Density Functional Theory (DFT) level by using the Gaussian 03 program suite.[34] Becke's three-parameter exchange functional (B3)[60,61] was employed in conjunction with the Lee−Yang−Parr correlation functional (LYP),[62] as implemented in Gaussian 03[34] at a 6-31++G(d,p) basis set level. Geometries were optimized without constraint, and vibrational frequencies were then computed to characterize each structure as a minimum or transition structure (TS), via the number of imaginary frequencies (zero for minima and one for saddle points, respectively). After locating a TS, an intrinsic reaction coordinate (IRC)[63−66] calculation was carried out to identify its respective reactant and product.

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Supporting Information Available: Spectral characterization of compounds **3**, **2a**, and **13a**, equilibrium between different intermediates and deuterium labeling followed by NMR, detailed data for the X-ray structure of compound **2a**, theoretical data for calculated compounds, intermediates, and transition states, and a movie generated from the IRC calculations showing the first part of the mechanism. This material is available free of charge via the Internet at http://pubs.acs.org.

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