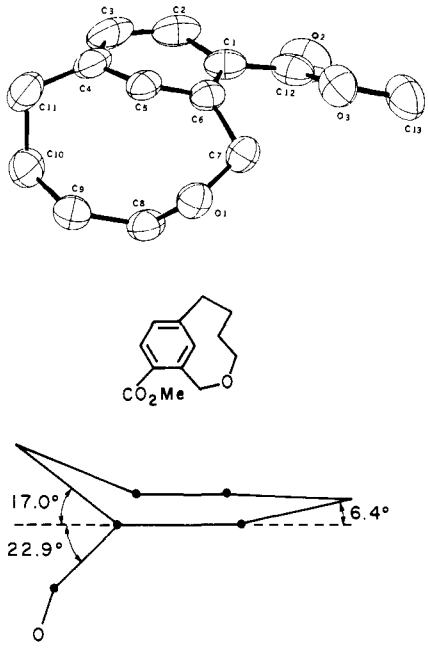

Figure 1. ORTEP drawing of [6]metacyclophane **10** showing the atomic numbering scheme.

9 with DDQ in toluene, while the thermal aromatization (280 °C, 8 h) gives the ester **10** in 50% isolated yield. The methyl ester is a crystalline solid, mp 61.5–62.5 °C. Slow evaporation from CH_2Cl_2/pentane afforded crystals suitable for X-ray analysis, Figure 1 shows an ORTEP drawing of the structure of **10**.[6] Noteworthy is the absence of C(5) substituents in this derivative, common to the two small ring metacyclophane derivatives for which structural data are now available.[7]

Key structural features of this compound are the nonplanarity of the benzene ring which exists in an unsymmetrical boat conformation with bow (C(4)–C(5)–C(6)) and stern (C(1)–C(2)–C(3)) deformations of 17.0° and 6.4°, respectively. Although the sum of these distoritons (23.4°) is significant, it is smaller than that found in the [6]paracyclophane (39°)[8] and the recently reported [5]metacyclophane (38.3°).[7a] Since the six-atom bridge cannot be coplanar with the aromatic ring, there is substantial distortion at the benzylic carbons. This distortion is observed in the angles of 22.9° and 20.1° formed by bond vectors C(7)–C(6) and C(11)–C(4) to the aromatic plane defined by atoms C(1)–C(6)–C(3)–C(4) (Figure 1).

The distortions at the benzylic positions also manifest themselves in the bond angles, of which representative values include C(3)–C(4)–C(11) = 126.1° and C(5)–C(4)–C(11) = 113.2°. Rather severe distortions are found in the six-atom bridge, Although the bond angles at the two benzylic carbons (C(4)–C(11)–C(10) = 108.0°, C(6)–C(7)–O(1) = 109.7°) are near normal, the valence angles at C(9) and C(10) (C(8)–C(9)–C(10) = 120.6° and C(9)–C(10)–C(11) = 119.2°) are significantly expanded.

The thermal extrusion of hydrogen from bridgehead dienes may occur by one of several plausible mechanisms. In addition to a stepwise free radical loss of hydrogen, the enforced boat conformation of the bridgehead diene **2** predisposes the molecule for a 4+2 cycloreversion, Indeed, monitoring the aromatization of diene **7** in benzene over several half-lives revealed that the reaction exhibits clean first-order kinetics. The solution-phase rate constants for aromatization over a 40 °C temperature range (260–300 °C) allowed calculation of the Arrhenius activation energy parameters, ΔE_a^* 40.0 ± 0.6 kcal/mol and $\Delta S^*_{280} = -6.9 \pm 0.9$ eu for the reaction. These values are to be compared with data for aromatization of 1,4-cyclohexadiene, ΔE_a^* 43.8 kcal/mol and $\Delta S^*_{280} = -10.8$ eu.[9] The similarity of activation energy parameters for the two reactions and the failure to intercept radical chain processes argues for a concerted thermal extrusion of hydrogen from bridgehead diene **2** (eq 2).

Acknowledgment. We are grateful to the National Science Foundation for financial support of this work.

Supplementary Material Available: Spectroscopic data for metacyclophanes **6**, **8**, and **10** and tables of positional parameters, anisotropic temperature factors, bond angles, and interatomic distances for metacyclophane **10** (6 pages). Ordering information is given on any current masthead page.

(6) Crystal data for [6]metacyclophane **10**: $C_{13}H_{16}O_3$, triclinic, space group $P\bar{1}$, $a = 6.743$ (4) Å, $b = 12.221$ (6) Å, $c = 7.605$ (4) Å, $\alpha = 91.27$ (4)°, $\beta = 109.91$ (4)°, $\gamma = 100.27$ (4)°, $V = 576.8$ (5) Å^3, $Z = 2$. Intensity measurements were made on a Syntex $P2_1$ diffractometer, Mo Kα radiation $\lambda = 0.71073$ Å, graphite monochromator. Intensities of 2662 reflections with $2\theta \leq 55°$ were meausred; of these 1982 had intensities $I > 3\sigma(I)$. The structure was solved by direct methods (MULTAN 80) and refined by full-matrix least-squares calculations to $R = 0.067$. $R_w = 0.093$ (anisotropic thermal parameters for carbon and oxygen, hydrogen in calculated positions). Tables of positional parameters, anisotropic temperature factors, bond angles, and interatomic distances are included as supplemental information.

(7) (a) X-ray structure of a [9]metacyclophane: Effenberger, F.; Schönwalder, K.-H.; Stezowski, J. J. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 871. (b) X-ray structure of a [5]metacyclophane: Jenneskens, L. W.; Klamer, J. C.; de Boer, H. J. R.; de Wolf, W. H.; Bickelhaupt, F.; Stam, C. H., *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 238.

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The Uncatalyzed Claisen Rearrangement of Chorismate to Prephenate Prefers a Transition State of Chairlike Geometry

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Direct comparison of the transition-state structure of an enzymic reaction with that of the analogous uncatalyzed reaction is usually impossible. First, many enzyme-catalyzed reactions do not proceed at measurable rates in the absence of the catalyst. Second, the chemical participation of active-site amino acids in the enzymic reaction makes the choice of appropriate reaction conditions for the uncatalyzed reaction arbitrary at best. For the Claisen rearrangement of chorismate to prephenate catalyzed by the enzyme chorismate mutase,[1] however, the comparison is easier. There is no evidence for chemical participation by the enzyme, and although the reaction rate is more than a million times faster at the active site than free in solution,[2] the uncatalyzed rearrangement is still a facile process.[3] Here, we address the question of whether this enzyme accelerates the *un*catalyzed pathway that has the lower free energy of activation. Having recently demonstrated[4] that the enzymic reaction proceeds via a transition state of chairlike geometry (Figure 1), we now report the stereochemical course of the nonenzymic rearrangement.

The stereochemical course of several Claisen rearrangements and of the related Cope and oxy-Cope rearrangements has been determined. While in sterically unhindered cases a chairlike transition state can be favored by as much as 6 kcal/mol,[5] geometric constraints can shift the relative energies of the chair and boat transition states so that reaction proceeds partially or com-

(1) Haslam, E. "The Shikimate Pathway"; Wiley: New York, 1974.

(2) Andrews, P. R.; Smith, G. D.; Young, I. G. *Biochemistry* **1973**, *12*, 3492.

(3) The half-life of chorismate in neutral aqueous solution is approximately 25 min at 60 °C.

(4) Sogo, S. G.; Widlanski, T. S.; Hoare, J. H.; Grimshaw, C. E.; Berchtold, G. A.; Knowles, J. R. *J. Am. Chem. Soc.* **1984**, *106*, 2701.

(5) Doering, W. v. E.; Roth, W. R. *Tetrahedron* **1962**, *18*, 67.

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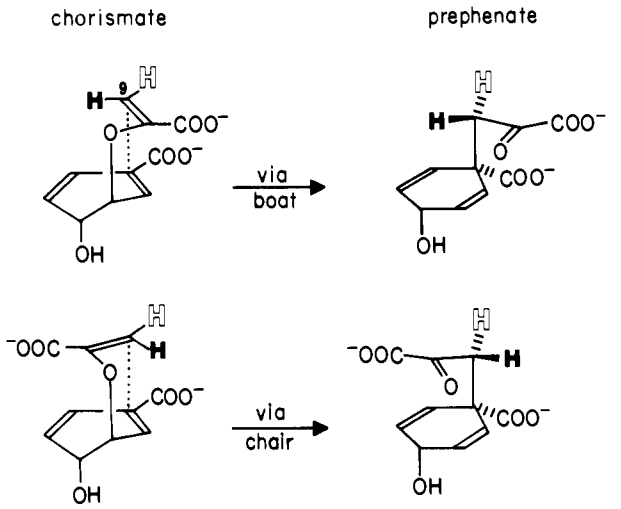

Figure 1. Transition-state geometries for the rearrangement of chorismate to prephenate. If the heavier hydrogen isotope on carbon 9 is represented by the solid H, the illustrated chorismate is *Z*, the product of the boat transition state has an *R* methylene center, and that derived from the chair transition has an *S* center.

pletely through a boat.[6-8] In the case of chorismate, it has been calculated that chairlike geometry of the transition state is favored by only 1.3–2.0 kcal/mol,[2,9]

The stereochemistry of the transition state for the rearrangement of chorismate to prephenate can be determined by analyzing the configuration at the methylene carbon of prephenate that derives from chorismate stereoselectively labeled with ^2H and ^3H at carbon-9. For example, the prephenate that is formed from (*Z*)-[9-^{2}H,^{3}H]chorismate will have ^3H in the *pro-S* position if the reaction proceeds through a chairlike transition state and in the *pro-R* position if the transition state is boatlike (Figure 1). Stereoselectively-labeled samples of chorismate containing ^2H and ^3H at carbon-9 were therefore prepared from (*E*)-phospho[3-^{2}H,^{3}H]enolpyruvate and from (*Z*)-phospho[3-^{2}H,^{3}H]enolpyruvate as we described earlier.[10] The labeled chorismate was purified by HPLC[11] was then converted to prephenate by heating[12] at 60 °C for 25 min. The reaction was quenched on ice after approximately 50% conversion, and the prephenate and remaining chorismate were separated by HPLC.

The configuration at the methylene carbon of the isolated prephenate was determined as follows. The isolated prephenate was converted to (*p*-hydroxyphenyl)pyruvate by prephenate dehydrogenase,[13] this reaction being run in the presence of excess phenylpyruvate tautomerase.[15] Phenylpyruvate tautomerase converts (*p*-hydroxyphenyl)pyruvate to the tautomeric enol form by removing the *pro-R* proton, which is subsequently lost to solvent.[16] The proportion of ^3H in the *pro-R* and the *pro-S* positions of prephenate can therefore be determined by measuring the amount of nonvolatile ^3H remaining in the sample as a function of time.[17] To increase the precision of the measurement of ^3H content, some [7-^{14}C]chorismate[18] was included in each incubation and the *ratio* of $^3H/^{14}C$ determined for the starting material and

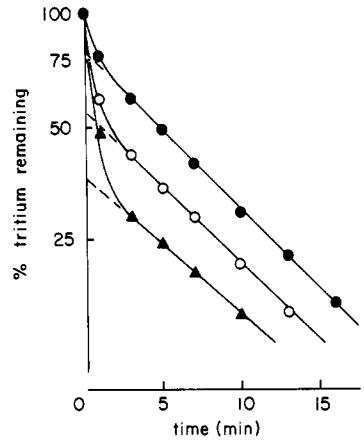

Figure 2. Time course of tritium loss from prephenate deriving from the rearrangement of (*E*)-[9-^{3}H,^{2}H]chorismate (▲), (*Z*)-[9-^{3}H,^{2}H]chorismate (●), and randomly labeled [9-^{3}H]chorismate (○): for details, see the text.

Table I. Percentage of Tritium at the *pro-S* Position on the Methylene Carbon of Prephenate

substrate	product from nonenzymic reaction[a]	predicted for a chair transition[b]	product from enzymic reaction[c]
(*E*)-[9-^{3}H,^{2}H]chorismate[d]	36	34	33
randomly labeled [9-^{3}H]chorismate[e]	55	50	52
(*Z*)-[9-^{3}H,^{2}H]chorismate[d]	79	69	80

[a] This work. The errors in these percentages from the fit of the data to the sum of two exponential processes (see text) are <0.5%. [b] Reference 21. [c] Reference 4, These data are less precise than those for the nonenzymic reaction. [d] Reference 10. [e] Reference 19.

for each sample. The ^3H washout data can be fitted to the sum of two exponential decays expressed as (% ^3H remaining) = $Ae^{-k_1t} + De^{-k_2t}$. The rapid component of the decay corresponds to the tautomerase-catalyzed removal of ^3H from the *pro-R* position of (*p*-hydroxyphenyl)pyruvate that derives from the enzymic decarboxylative oxidation of prephenate. The slow component corresponds to the release of ^3H from the *pro-S* position of (*p*-hydroxyphenyl)pyruvate, which may occur by nonenzymic enolization and via the stereorandom reketonization of tritiated enol followed by the enzyme-catalyzed tautomerization.

Figure 2 shows the time course of ^3H loss from prephenate derived from the two stereoselectively labeled samples of chorismate and from randomly labeled material.[19] Values for the percentage of ^3H label in the *pro-R* and *pro-S* positions of prephenate obtained from fitting the results to a double exponential are given in Table I, The values obtained for the *enzymic* conversion of the chorismate samples used earlier[4,10] are shown for comparison. For (*E*)-chorismate, 36% of the ^3H was found in the *pro-S* position of prephenate. This figure agrees, within experimental error, with the 33% ^3H in the *pro-S* position found for the chairlike transition state of the enzyme-catalyzed process. For (*Z*)-chorismate, 79% of the ^3H is found in the *pro-S* position of prephenate, which agrees well with the value of 80% found for

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(10) Grimshaw, C. E.; Sogo, S. G.; Copley, S. D.; Knowles, J. R. *J. Am. Chem. Soc.* **1984**, *106*, 2699.
(11) On a Zorbax SAX column (Du Pont), with a gradient (10–133 mM) of sodium phosphate buffer, pH 7.0.
(12) In 20 mM *N*-ethylmorpholine-2-(*N*-morpholino)ethanesulfonate buffer, pH 7.5, containing EDTA (1 mM).
(13) The partially purified[14] chorismate mutase–prephenate dehydrogenase (0.13 units/mL) was used, in 150 mM sodium phosphate buffer, pH 7.0, containing NAD^+ (2 mM), at 29 °C.
(14) Addadi, L.; Jaffe, E. K.; Knowles, J. R. *Biochemistry* **1983**, *22*, 4494.
(15) Bovine kidney enzyme (2.3 units/mL), from Sigma.
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(17) Samples (75–165 μL) were removed from the incubation and quenched by the addition of sodium borohydride (44 μmol, per 1 mL of sample). After the removal of successive additions of H_2O (1 mL) in vacuo, the residue was dissolved in H_2O (0.2 mL) and subjected to scintillation counting.
(18) Prepared enzymically from shikimate 3-phosphate and phospho[1-^{14}C]enolpyruvate by using 3-phosphoshikimate-1-carboxyvinyl transferase and chorismate synthase.[14]
(19) This sample was prepared by allowing the equilibrium of solvent ^3H with the protons of carbon-9 of 5-enolpyruvoylshikimate 3-phosphate catalyzed by 3-phosphoshikimate-1-carboxyvinyl transferase.[20]
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the enzymic reaction.[21] We conclude, therefore, that the thermal rearrangement of chorismate to prephenate follows the same stereochemical course as the enzymic reaction and proceeds through a transition state of chairlike geometry.

Acknowledgment. We are grateful to Dr. J. Hermes for assistance, to D. Hansen for discussions, to the National Institutes of Health for a Research Grant (J.R.K.) and a Public Health Service National Research Service Award (S.D.C.), and to Merck, Sharp and Dohme for support.

Registry No. Chorismate, 617-12-9; *trans*-prephenate, 97645-23-3; (*E*)-[9-^{3}H,^{2}H]chorismate, 89437-80-9; (*Z*)-[9-^{3}H,^{2}H]chorismate, 89496-34-4.

(21) From independent analysis of the stereochemical location of ^{3}H at carbon-3 of the labeled phosphoenolpyruvate used (Grimshaw, C. E., unpublished work) and from the known isotope effect in the reaction catalyzed by 3-phosphoshikimate-1-carboxylvinyl transferase,[20] we predicted that our (*E*)-chorismate sample would yield prephenate having a 66:34 distribution at the prochiral positions of the methylene carbon, and the (*Z*)-chorismate sample would yield a 69:31 distribution in the location of ^{3}H, if the reaction were completely stereospecific. While the results from Figure 2 suggest a bias to high values of the percentage of ^{3}H at the *pro-S* position (the cause of which is unknown), the agreement between the results for the enzymic and nonenzymic reactions (Table I) makes the assignment of transition-state geometry unambiguous.

Construction of Linearly Fused Tricyclopentanoids by Intramolecular [6 + 2] Cycloadditions of Fulvenes with Enamines

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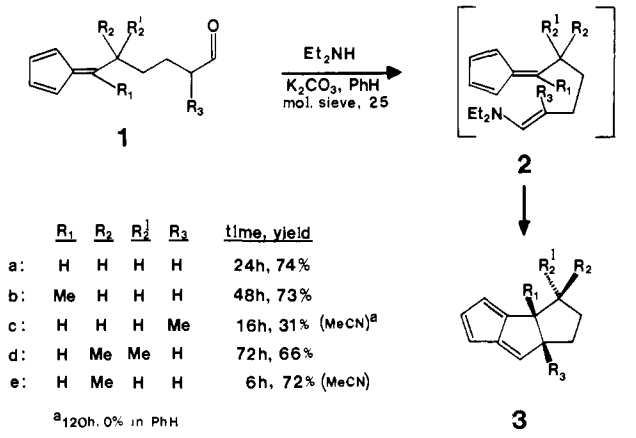
The synthesis of linearly fused tricyclopentanoids is a popular subject for the demonstration of modern synthetic methods.[1] Among the two-score methods applied to the preparation of hirsutene and its more elaborate relatives,[2] those reported by the groups of Little and Curran involve the simultaneous annulation of two new five-membered rings onto a preexisting cyclopentane.[3] We have developed a similar strategy based upon intramolecular [6 + 2] cycloadditions. We previously reported the [6 + 4] cycloadditions of dienamines to fulvenes,[4] as well as intramolecular analogues.[5] The electrophilicity of the 6-position of a fulvene toward nucleophilic dienamines suggested to us that the intramolecular [6 + 2] reaction of a fulvene with an enamine might succeed through the intervention of a zwitterionic intermediate.[6] Here we report the successful realization of this plan.

The new reaction sequence for conversion of **1** to **3** is shown in Scheme I.[7] Fulvenes substituted at the exocyclic 6-position by 6-(ω-formylalkyl) groups are converted into the corresponding enamines,[8] which undergo the intramolecular [6 + 2] cycloaddition and spontaneous loss of diethylamine to form tricyclopentanoid

Scheme I



1

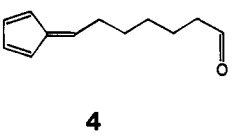
	R_1	R_2	R_2^1	R_3	time, yield
a:	H	H	H	H	24h, 74%
b:	Me	H	H	H	48h, 73%
c:	H	H	H	Me	16h, 31% (MeCN)[a]
d:	H	Me	Me	H	72h, 66%
e:	H	Me	H	H	6h, 72% (MeCN)

[a] 120h, 0% in PhH

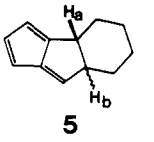
2 **3**

fulvenes. The yields given are for the overall conversion of **1** to **3**.

The reaction is actually a cycloaddition analogue of Hafner's elegant electrocyclic synthesis of dihydropentalenes,[9] It is also related to the strategy used in Büchi's β-vetivone synthesis,[10] where addition of a cuprate to the 6-position of fulvene generates a cyclopentadienide which attacks a ketone to form a spiro [6.5] system. Whereas the tricyclopentanoids are formed exclusively as the cis isomers (see below), the higher homologue, **4**, gives a ~2:1 ratio of cis and trans products, **5**.



4



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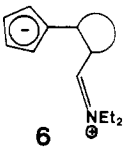

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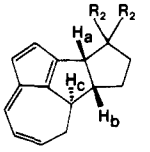

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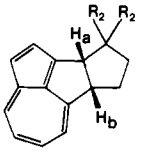

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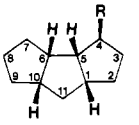
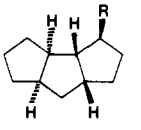


9

a: R=H
b: R=Me



10

a: R=H
b: R=Me

The reaction is subject to steric hindrance, as evidenced by the failure of **1c** to give any adduct under normal conditions. However, in the more polar solvent, acetonitrile, even this reaction proceeds readily, albeit in modest yield. Similarly, the reaction of **1e** is rapid in acetonitrile. These results suggest that these [6 + 2] cycloadditions involve zwitterionic intermediates, **6**. It is possible that the formation of **6** is reversible, but only *cis*-**6a-e** cyclizes, since the trans-fused adducts will be considerably more strained than the cis. The exclusive formation of **3e** from **1e** can also be rationalized as a result of equilibration of **6** to give the most stable intermediate before the second cyclization, or by steric control of the first step of the reaction sequence,

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(6) Although we have found that enamines do react with dimethylfulvene, we have been unable to characterize the products, which rapidly decompose.
(7) All new compounds were characterized by 300-MHz NMR and high-resolution mass spectrometry. The conversion of **1** to **3** also occurs with base catalysis. With potassium *tert*-butoxide, formation of **3a** occurs in several minutes at 25 °C, but the product is rapidly destroyed under these conditions. Triethylamine converts **1** to **3** at a rate about ten times slower than the reaction with diethylamine.
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