before data acquisition was begun (additional probe tuning was advisable after the probe had attained the desired temperature). Spectra were recorded after each estimated 3-5% of total conversion was achieved. Approximately 12 spectra were obtained for each kinetic plot within the first 2 half-lives. The rate constants were obtained by graphing $-\ln(X_{SM})$ vs. time, and the best line was estimated visually. The deviation of individual points along the ordinate was $\leq \pm 0.01$, and the average deviation of points was ± 0.0043. The rate constants listed in table II are averages of 2-3 kinetic runs. Three runs were generally used unless the rates obtained from the first two were within 5%. The data in Table II associated with the rearrangement rates of **11** in acetonitrile-d_3 and ethanol-d_6 were obtained from one kinetic run each. The integrals of the following absorptions were measured to determine the enol ether/ketone ratio: **10**, 4.08 (dt, CH_2O), 4.36 (quintet, OC=CH); 2-allylcyclopentanone, 4.94 (ddt, $=CH_2$), 4.95 (ddt, $=CH_2$), 5.55-5.76 (m, $=CH_2$); **11**, 4.45 (dt, CH_2O); **11** + 1-allyl-2-oxocyclopentanecarbonitrile, 4.8-5.1 ($=CH_2$); **4d**, 5.09 (ddd, $=CH_2$, 5.38 (ddd, $=CH_2$); **5d**, 6.21 (d, = CHOEt). The error in the integrals was less than 2%, and the reproducibility of the integrals was better than ±2%. No products other than the α-allylcyclopentanones were detected in any spectra. The probe temperatures were determined by application of the Van Geet equation[60] to the measured $\Delta\delta$ between the hydroxyl and methylene protons in ethylene glycol. The precision of the temperature measurements is ±1 °C and the reproducibility of the temperatures is ±0.3 °C. Extrapolations were performed through use of a least-squares program when more than two points were to be extrapolated from. The error limits cited for the activation parameters were calculated by propagating the maximum possible error through the calculations used for the parameters. The error in rate was assumed to be the average deviation from the mean, the error in temperature was assumed to be ±1 °C as given by Van Geet,[60] and the transmission coefficent in the Eyring equation was assumed to be unity.

Estimation of the Minimum Rate Ratio of 4b and 4d. Both **9b** and **9d** were oxidized separately and added to solutions of triethylamine in pentane at room temperature as described in the preparation of **4d**. Both reaction mixtures were stirrred, without externally warming the pentane solutions, for 30 min, and then a 50-mL aliquot was removed from both and cooled to −78 °C until their ^{1}H NMR spectra could be taken. The samples were later evaporated quickly and a 200-MHz ^{1}H NMR spectrum was obtained of both reaction mixture residues in benzene-d_6. In each case, the relative amounts of **4** and **5** were estimated by comparison of the integrals of the multiplets at δ 5.9 to the integrals of the doublets at δ 6.2, which are assigned to the allyl methine (**4b** and **4d**) and α-enol ether protons (**5b** and **5d**), respectively. The relative amounts of **4b** to **5b** was estimated to be less than 9:91, and the relative amounts of **4d** to **5d** was estimated to be greater than 95:5 after 50 and 45 min at room temperature, respectively. From these ratio estimates, the relative rate of rearrangement of **4b** and **4d** is estimated to be >45:1.

Acknowledgment. The research at the University of Illinois was supported in part by grants from the National Science Foundation (82-04485) and the National Institutes of Health (GM 13956). The Pittsburgh group thanks the National Institutes of Health (GM-34862) and the Petroleum Research Fund for support and is particularly grateful to Stuart Pharmaceuticals for an unrestricted gift.

Registry No. 1, 3917-15-5; **4d**, 106094-88-6; (*E*)-**5a**, 87698-30-4; (*Z*)-**5a**, 87698-31-5; (*E*)-**5a**-d_5, 106094-97-7; (*Z*)-**5a**-d_5, 106094-98-8; (*E*)-**5b**, 87711-07-7; (*Z*)-**5b**, 87698-14-4; (*E*)-**5c**, 87698-07-5; (*Z*)-**5c**, 87698-08-6; (*E*)-**5d**, 18802-25-0; (*Z*)-**5d**, 18802-26-1; **9a** (isomer 1), 106094-90-0; **9a** (isomer 2), 106094-91-1; **9a**-d_5 (isomer 1), 106094-96-6; **9a**-d_5 (isomer 2), 106095-06-1; **9b** (isomer 1), 106094-92-2; **9b** (isomer 2), 106094-93-3; **9c** (isomer 1), 106094-94-4; **9c** (isomer 2), 106094-95-5; **9d** (isomer 1), 106094-99-9; **9d** (isomer 2), 106095-00-5; **10**, 106094-86-4; **11**, 106094-87-5; **12**, 106095-01-6; **13**, 106094-84-2; **14**, 92127-02-1; **15**, 106094-85-3; (*E*)-**16**, 56175-41-8; (*Z*)-**16**, 56175-40-7; **17**, 106095-03-8; **19**, 106095-04-9; α-chloro-β-(phenylseleno)propyl ethyl ester, 106094-89-7; 2-cyanocyclopentanone, 2941-29-9; 2-methyl-1,3-cyclopentanedione, 765-69-5; cyclopentanone diallyl ketal, 62322-44-5; 2-(2-propenyl)cyclopentanone, 30079-93-7; 1-(2-propenyl)-2-cyclopentanecarbonitrile, 66984-19-8; 2-(*o*-nitrophenylseleno)ethanol, 94650-42-7; 2-methoxyallyl alcohol, 50717-56-1; 3-methoxyallyl alcohol, 106095-02-7; 3-methoxy-4-penten-1-ol, 106095-05-0; 2-carbethoxycyclopentanone, 611-10-9; cyclopentanone, 120-92-3.

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On the Mechanism of Rearrangement of Chorismic Acid and Related Compounds

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Abstract: The thermal reactions of the biochemically important molecule chorismic acid are studied in solution. It undergoes two competitive reactions, one is an unusually facile Claisen rearrangement, and the other an elimination to give *p*-hydroxybenzoic acid and pyruvic acid. Attempts are made to understand the factors responsible for the facility of the Claisen rearrangement by preparation of a variety of analogues of chorismate. Correlations of rate with structure as well as determinations of solvent and isotope effects are undertaken. The data from these experiments lead to the conclusion that chorismic acid and related molecules undergo the rearrangement and, where it occurs, the elimination, by reactions whose transition structures are dissociative in nature, i.e., there is substantial cleavage of the C–O bond linking the sidechain to the ring but little bond formation at the terminus of the sidechain. The roles of radical and zwitterionic structures are discussed, as are the implications of this work for the mechanism of enzyme catalysis of the chorismate to prephenate conversion.

Chorismic acid (**1**) is a key intermediate in the shikimate biosynthetic pathway which bacteria and lower plants use to convert glucose-6-phosphate into a wide variety of primary and secondary metabolites, including phenylalanine, tyrosine, tryptophan, the isoprenoid quinones, and the folate coenzymes.[1] The rearrangement of chorismic acid to prephenic acid (**2**), the first step in the conversion of chorismate to phenylalanine and tyrosine, is the focus of the present paper.

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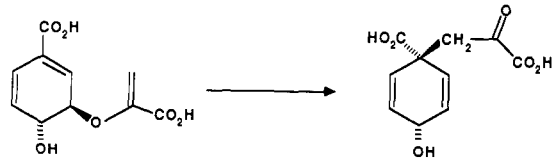

1 2

The conversion of **1** to **2** is apparently a Claisen rearrangement. It is catalyzed in vivo by the enzyme chorismate mutase, which affords a rate enhancement of 2×10^6 at 37 °C.[2] This is, to our knowledge, the only example of a formal pericyclic reaction catalyzed by an enzyme and is of considerable intrinsic interest for that reason. In addition, though, one could imagine that elucidation of the mechanism of catalysis might lead to the rational design of an inhibitor which would presumably have potentially valuable antibacterial and herbicidal properties. Also of importance is the fact that the rearrangement of chorismic acid to prephenic acid is unusually facile, even in the absence of the enzyme. This uncatalyzed reaction has a half-life of 10 min at 75 °C in water at pH 5, which is some 4200 times faster than the rearrangement of allyl vinyl ether in di-*n*-butyl ether at the same temperature.[3] Understanding the inherently fast rearrangement of chorismate is of importance to the general issue of substituent effects on the Claisen rearrangement and could also provide a clue to the mechanism of enzyme catalysis.

The work described in this paper is the result of independent studies at Indiana University and Cornell University. The results and interpretations from the two groups have been kept largely separate, although a final section highlighting areas of agreement and disagreement has been included. A numbering system has been devised for this paper, in which the compounds studied in Indiana are given the prefix I and those studied at Cornell are given the prefix C. Some compounds studied by both groups will appear with two different numbers; this redundant numbering was considered to be easier on the reader trying to locate the structures in the text and easier on the authors trying to correlate their separate contributions.

Results and Discussion—Indiana Group

In order to understand the effect of substituents on the Claisen rearrangement, especially as it relates to the noncatalyzed chorismate–prephenate rearrangement, various allyl enol pyruvates have been prepared and pyrolyzed.

2-Carbomethoxyallyl vinyl ether, **I3a**, rearranges to methyl allyl pyruvate in CCl_4 with $\log k = 11.44\ (.026) - 25754\ (43)/2.303RT$. The activation free energy for this rearrangement is 3.0 kcal/mol less than that for allyl vinyl ether itself in dibutyl ether solvent, all extrapolated to 100 °C. There is a small polar solvent effect on this rearrangement as documented in Table I.

In order to examine the transition-state structure, the secondary deuterium kinetic isotope effects (KIEs) at 61.5 °C were determined by using cyclohexane as the reaction solvent. For the 6,6-dideuterio material **I3b**, $k^H/k^{D_2} = 1/1.10$ where the maximum value for complete bond making (BM) estimated from equilibrium isotope effects (EIE) is 1/1.28.[4] For the 4,4-dideuterio material **I3c**, $k^H/k^{D_2} = 1.122$ where the maximum value for complete bond breaking (BB) estimated from equilibrium isotope effects is 1.46.[4] Therefore, ln BMKIE/ln BMEIE = 0.38 (0.06) and ln BBKIE/ln BBEIE = 0.30 (0.03). For comparison purposes, in the rearrangement of allyl vinyl ether itself in the gas phase, ln BMKIE/ln BMEIE = 0.17 (0.04) and ln BBKIE/ln BBEIE = 0.42 (0.02).[5] The effect of the 2-carbomethoxy substitution is as predicted by Thornton's perpendicular effect,[6] namely, that radical stabilizing groups at C-2 induce more bond making character on the Claisen transition state.

The rate effect of phenyl substitution at C-4, C-5, and C-6 was determined to be ~200, 6.6, and 0.53 times that of the parent material in CCl_4, and a Hammett plot of the *p*-CF_3-, -H-, and -OMe-substituted 2-carbomethoxy-4-phenylallyl vinyl ethers gave a reasonable correlation with σ^+ to give $p^+ = -0.49$ ($r = 0.996$) at 0 °C. A p^+ of −0.53 ($r = 0.988$) was obtained at 29 °C indicating that the reaction is far from the isokinetic temperature. The small negative p is consistent with some positive character at C-4 in the 4-phenyl derivative. While polar solvent rate effects were not examined in these phenyl-substituted cases, there was no evidence for bond heterolysis products from the 4-*p*-anisyl derivative **I3g** when it rearranged in methanol–water at room temperature.

Interesting, however, is that in Me_2SO–D_2O **I3a** rearranges only 2.2 times faster than its saponification product, the sodium carboxylate, **I3ac** at 80 °C. Apparently, the carboxylate anion stabilizes a radical site to the same extent as a carboxylate ester in Me_2SO–water. The carboxylate derivative, however, still rearranges ca. 170 times slower than chorismate itself[2] in aqueous solution. Thus only part of the facility of the chorismate to prephenate 3,3-shift is due to the carboxylate at C-2 of the vinyl ether moiety. Further, Knowles has determined the secondary tritium isotope effects at bond making and breaking sites in chorismate and found a partly dissociative transition state not unlike that in allyl vinyl ether itself.[7] This suggests stabilization of the bond broken moieties in addition to the effect of the carboxylate on the vinyl ether which should reinforce bond making.

To find the source of the extra stabilization various derivatives of allyl vinyl ether were prepared and pyrolyzed—see Table I. 6-Carbomethoxyallyl vinyl ether, **I2**, was stable over long periods of time at 100 °C. The methyl enol pyruvates of a number of allyl alcohols were prepared at 0 °C by a modification of Ganem's method:[8] thus the alcohol was treated with dimethyl diazomalonate with rhodium(II) acetate catalyst, then treated with Eschenmoser's salt in the presence of triethylamine and then treated with methyl iodide; the resulting 2-alkoxy-2-(carbinyltrimethylammonium iodide) malonate was treated with 1.1 equiv of sodium hydroxide in 9:1 Me_2SO–water at 0 °C. The methyl enol pyruvate of *trans*-pentadien-1-ol, **I3m**, rearranged at one-third the rate of **I3a**. The methyl enol pyruvate of 2-cyclohexenol, **I3i**, rearranged at a much slower rate than that of **I3a** ($t_{1/2}$ = 108 h at 80 °C in CCl_4) and with a similar polar solvent effect (Table I). The enol pyruvate of *trans*-cyclohex-3-ene-1,2-diol, **I3j**, was prepared and found to disappear at virtually the same rate as that of **I3i** in both CCl_4 and in Me_2SO–water (9:1). However, the product in CCl_4 could not be identified although methanol was formed in significant quantities. In Me_2SO–water the starting *trans*-diol was formed. On the other hand, elimination of the trimethylammonium salt precursor to the methyl enol pyruvate of 2,4-cyclohexadienol, **I3l**, at 0 °C in 90% Me_2SO–H_2O for 10 min followed by silica gel chromatography at −78 °C gave **I3l** which could be characterized by NMR at low temperatures. At temperatures above −15 °C **I3l** rearranged to methyl 1,4-dihydrophenylpyruvate and underwent elimination to benzene. There is a polar solvent effect on the rate of rearrangement which indicates some zwitterionic character in the transition state. The percent elimination varied between 10 and 20%. It was possible to prepare the enol pyruvate of *trans*-3,5-cyclohexadien-1,2-diol, **I3n**, by percolation of its 2-carbinyl dimethylamine dimethyl malonate derivative through CC-7 silica gel. At 40 °C in CCl_4 its $t_{1/2}$ for 3,3-shift is 39 h, but in Me_2SO–D_2O $t_{1/2}$ is 1.36 h. In all solvents the major initial (>90%) product is methyl 4-hydroxy-1,4-dihydrophenylpyruvate, presumably the trans isomer; however, small amounts of aromatic materials are also formed and are the ultimate products of the reaction. In CCl_4 methyl

(2) Andrews, P. R.; Smith, G. D.; Young, I. G. *Biochemistry* **1973**, *12*, 3492–3498.
(3) Burrows, C. J.; Carpenter, B. K. *J. Am. Chem. Soc.* **1981**, *103*, 6983–6984.
(4) Gajewski, J. J. In *Isotopes in Organic Chemistry*; Buncel, E., Lee, C. C., Eds.; Vol. 7, Chapter 3, in press.
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(6) Thornton, E. R. *J. Am. Chem. Soc.* **1967**, *89*, 2915–2927.
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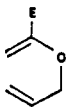
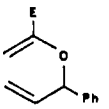
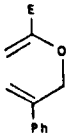
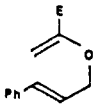
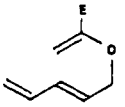
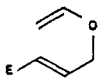
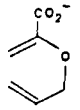
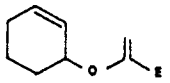
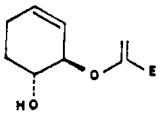
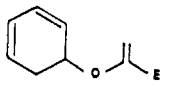
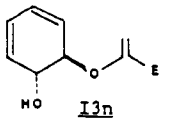
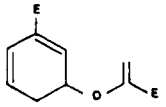
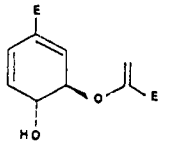
(8) Ganem, B.; Ikota, N.; Muralidharan, V. B.; Wade, W. S.; Young, S. D.; Yukimoto, Y. *J. Am. Chem. Soc.* **1982**, *104*, 6787–6788.

Table I. Half-Lives (h) of Allyl Vinyl Ether Derivatives in Various Solvents[a]

	T, °C	C_6H_{12}	CCl_4	$CHCl_3$	Me_2SO/H_2O (9/1)	CH_3OH
	80		6.03		2.51	
	61.5	64.5	45.76			33.3, 4.61 (33% H_2O)
I3a						
	29.0		1.1 ($rho^+ = -0.53$)			no cleavage in $MeOH/H_2O$ (3/1)
I3f						
	80		0.91			
I3e						
	80		11.33			
I3d						
	80		20.10		6.59	
I3m						
	100		no reaction			
I2						
	80				6.10	
I3ac						
	80		108.55	45	26.53	
I3i						
	80		84.67[e]		25.32 (cleavage only)	
I3j						
	15		17.1 (10% C_6D_{12}) 6.9/1[d]		1.75 6/1[d]	
	−15					0.57 (33% H_2O) 10/1[d]
I3l						
	40		39.1	11.33	1.36	1.93
I3n						
	30			3.63[b] 1/1[d]		
	55				yes[c]	

[a] Products are the 3,3-shift isomers unless stated otherwise. [b] Berchtold, G., private communication. [c] For complete reaction in pure Me_2SO–36 h. [d] Ratio of rearrangement to cleavage. [e] This figure represents a lower limit on the half-life for rearrangement since the products are unknown.

phenyl pyruvate is the final product while in Me_2SO–D_2O the enol form of methyl phenyl pyruvate appears to be the final product. In no case was phenol formed.

The rate and product data indicate the following: 1. An ester group at C-2 of an acyclic allyl vinyl ether accelerates the rate of the Claisen rearrangement by promoting stronger bond making in the transition state. 2. An ester and a carboxylate group at C-2 have comparable effects on the rate of the Claisen rearrangement of allyl vinyl ether in Me_2SO–water. 3. Conjugating groups at C-4 accelerate the rate of the allyl enol pyruvate Claisen rearrangement (see **I3f**). 4. Conjugating groups such as phenyl and vinyl at C-6 (**I3d, I3m**) have a small rate-retarding effect on the allyl enol pyruvate Claisen rearrangement, except in the case of the cyclohexadienyl system (**I3l, I3n**, and dimethyl chorismate). 5. The second double bond in the six-ring has the most dramatic effect in increasing the rate of the Claisen rearrangement of allyl enol pyruvates. 6. *trans*-Hydroxyl and carboxylate substitution on the cyclohexadienyl moiety is rate retarding (dimethyl chorismate vs. **I3n** vs. **I3l**).

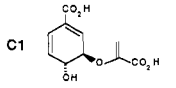
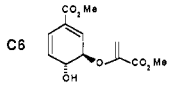
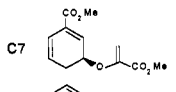
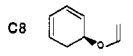
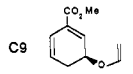
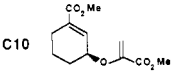
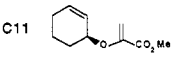
The kinetic data indicate that the enol pyruvate moiety and the cyclohexadienyl moiety are the key factors in lowering the activation free energy for the Claisen rearrangement of chorismate. The former group promotes more bond making, as is clear from comparison of the kinetic isotope effects in **I3a** to those of allyl vinyl ether itself. The cyclohexadienyl group would appear to promote more bond breaking, and Knowles' isotope effects indicate that this is the dominant factor in the noncatalyzed chorismate rearrangement. Just why the cyclohexadienyl moiety provides this driving force, but attachment of a vinyl or phenyl group to C-6 does not, follows from bond dissociation energies. By using the heats of formation for various radicals from the McMillen and Golden review[9] and the known heats of formation of hydrocarbons, the homolytic bond strength of the allyl C–H bond in cyclohexene and in 1,3-pentadiene is 13 kcal/mol less than that of a secondary C–H bond in propane. On the other hand, the C–H bond energy in 1,3-cyclohexadiene is 20 kcal/mol lower. The difference between pentadiene and cyclohexadiene is rationalizable in terms of the instability of cisoid diene systems. Indeed, the heats of formation of 1,4- and 1,3-cyclohexadiene are virtually the same; further, any hyperconjugative stabilization of the cyclohexadienyl radical would appear to enjoy benzene resonance energy. The 7 kcal/mol extra stabilization in the cyclohexadienyl radical cannot be fully transmitted to the chorismate transition state since the kinetic isotope effects indicate roughly only 40% bond breaking. These ideas extend to whatever cyclohexadienyl cation character there might be in the transition state (see below).

There must be some polar character in the transition state judging by the response to polar solvents. However, the magnitude of the rate effects and of the kinetic isotope effects indicates that the transition state is not as polar as that involved in zwitterion or tight ion pair formation. For instance, the change in rate constant for formation of a bona fide zwitterion in the case of a push–pull cyclopropane studied by Cram increased by a factor of 32 000 upon changing the solvent from benzene to DMF.[10] Further, the magnitude of a secondary deuterium kinetic isotope effects in rate-determining tight ion pair formation in solvolysis reactions is typically 70% of the maximum value[11] (not 40% as Knowles observed).

The origin of the elimination products from the cyclohexadienyl materials deserves comment. The parallel response of the rates of rearrangement and of elimination to polar solvents and the lack of elimination in the pyrolysis of **I3i** suggests an intramolecular cyclic process which is facilitated by the same factors that are responsible for the facility of the 3,3-shift.

The rate-retarding effect of the ring carboxyl may be attributed to its ground-state conjugative stabilization of the reacting double bond with superposition of the usual steric rate retardation by substitution at C-6 of an allyl vinyl ether (if the substituent is not electron donating). The rate-retarding effect of the ring *trans*-hydroxyl may be attributed to hyperconjugative stabilization of the diene (C–OH ↔ C^{+}–$^{-}$OH) and hydrogen bonding in the ground state.[12]

Table II. Relative Rate Constants for Rearrangement and Elimination of Chorismate Analogues

compound	k_{rel} (rearr)[a]	k_{rel} (elim)[a]
C1 	[1]	0.50
C6 	0.78	0.40
C7 	76	66
C8 	~10[b]	~10[b]
C9 	2.4	3.1
C10 	0.002	
C11 	0.09	

[a] All rate constants determined in 2:1 *v:v* methanol/water at 75 °C. [b] Instability of compound **C8** precluded accurate determination of rate constants.

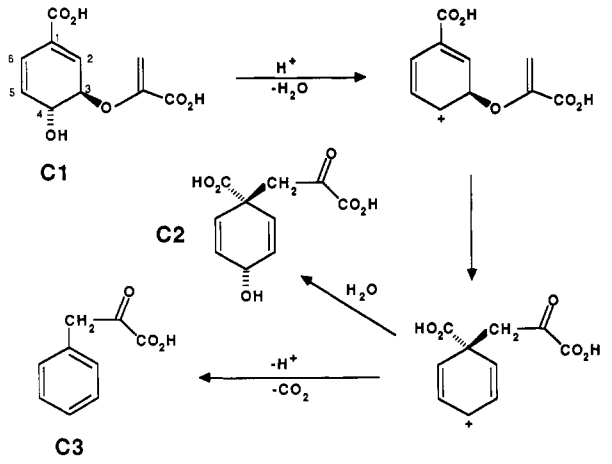
Results and Discussion—Cornell Group

The compounds used by the Cornell group were prepared as follows. Chorismic acid ((−)-**C1**) was obtained from cultures of *Klebsiella pneumoniae* 62-1 according to a procedure based on that of Gibson.[13] Dimethyl chorismate ((−)-**C6**, see Table II and Scheme IV for structures) was obtained from (−)-**C1** by careful diazomethane treatment. Enol pyruvates **C7**, **C10**, and **C11** were obtained from the corresponding known allylic alcohols by a published procedure.[8] Enol ethers **C8**, **C9**, and **C12–C15** were synthesized from the allylic alcohols by mercuric acetate-catalyzed reaction with ethyl vinyl ether.[14] The alcohol precursors to **C12–C14** were prepared from sorbic acid: **C12** by reduction with $LiAlH_4$, **C13** by conversion to methyl sorbate followed by treatment with 2 equiv of MeMgI and $^1/_2$ equiv of $LiBH_4$, and **C14** by reaction with excess methyllithium. The alcohol precursor to **C15** was prepared by addition of the Grignard of chloromethyltrimethylsilane to 2,4-hexadienal.

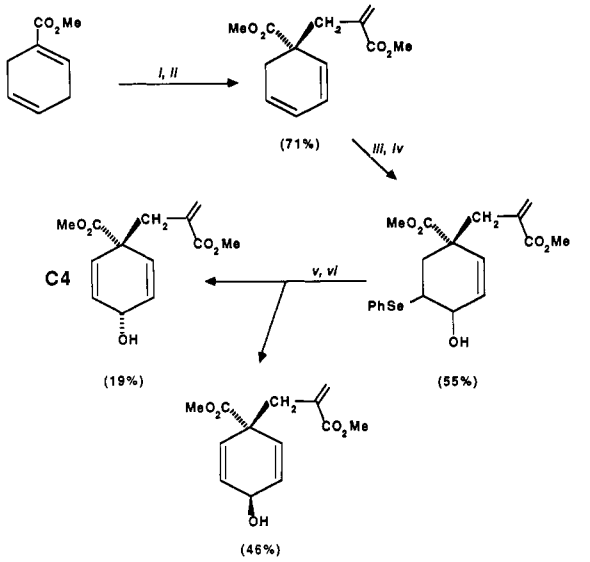
The first hypothesis to be tested by the Cornell group was based on theoretical[15] and experimental[16] evidence suggesting that a [3,3]-sigmatropic rearrangement could be greatly accelerated by a carbocation attached to one of the allylic positions. In the case of chorismic acid (**C1**), protonation of the hydroxyl on carbon 4 might lead to a carbocation by solvolysis. Rapid rearrangement and then either decarboxylation or recapture by water would lead to the observed products (Scheme I). In the enzyme-catalyzed reaction, a suitably positioned carboxyl function in the active site might provide the acid catalysis, and stereoselective recapture of the rearranged cation would then give prephenic acid (**C2**). In

(9) McMillen, D. F.; Golden, D. M. In *Annual Review of Physical Chemistry*; Rabinovitch, B. S., Ed.; 1982; Vol. 33.
(10) (a) Chmurny, A. B.; Cram, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 4237–4244. See also: (b) Huisgen, R. *Acc. Chem. Res.* **1977**, *10*, 117–124. (c) Sauer, J.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779–807.
(11) Shiner, V. J., Jr. *ACS Symp. Ser.* **1975**, *11*, 163.
(12) Hoare, J. H.; Policastro, P. P.; Berchtold, G. A. *J. Am. Chem. Soc.* **1983**, *105*, 6264–6267.
(13) Gibson, F. *Biochemical Prep.* **1968**, *12*, 94–97.
(14) Church, R. F.; Ireland, R. E.; Marshall, J. A. *J. Org. Chem.* **1966**, *31*, 2526–2530.
(15) Carpenter, B. K. *Tetrahedron* **1978**, *34*, 1877–1884.
(16) (a) Breslow, R.; Hoffman, J. M., Jr. *J. Am. Chem. Soc.* **1972**, *94*, 2111–2112. (b) Hansen, H.-J.; Sutter, B.; Schmid, H. *Helv. Chim. Acta* **1968**, *51*, 828–867.

Scheme I. Hypothetical Generation and Rearrangement of a Carbocation from Chorismic Acid



Scheme II. Synthesis of Dimethyl Carboprephenate[a]



[a] Reagents: (i) LiN(*i*-Pr)(*c*-Hx); (ii) $BrCH_2C(CO_2CH_3)=CH_2$; (iii) AgO_2CCF_3/PhSeCl; (iv) K_2CO_3/CH_3OH, H_2O; (v) H_2O_2; (vi) Et_3N/Δ.

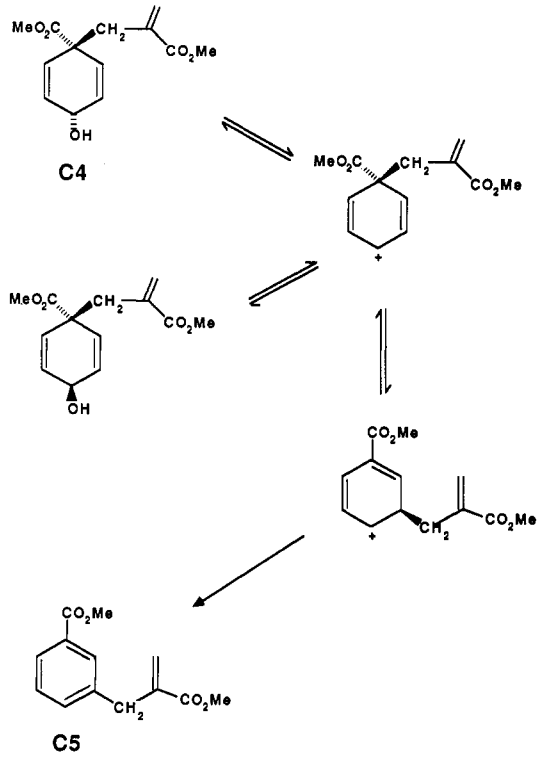
the absence of the enzyme, decarboxylation to phenylpyruvic acid (**C3**, the observed product of rearrangement of chorismic acid at low pH) might be expected to dominate.

Support for this mechanism came from studies on "dimethyl carboprephenate" (**C4**), which was synthesized as shown in Scheme II. Compound **C4** was found to epimerize and to rearrange to **C5** in aqueous methanol (Scheme III). It should be noted that the rearrangement of **C4** occurs in the opposite sense to that of chorismate because, in the case of **C4**, the [3,3]-sigmatropic shift is a Cope rather than a Claisen rearrangement. For chorismate, the direction of reaction is determined by the formation of the new carbonyl function whereas for **C4** it is determined by the irreversible formation of the aromatic product. Both the epimerization and the rearrangement are strongly acid-catalyzed, a fact that can be rationalized by invoking a mechanism very similar to the one proposed for chorismic acid.

Unfortunately, this supporting evidence for the cationic mechanism turned out to be irrelevant for the chemistry of chorismate in vitro.[17] This first became apparent when acid failed

(17) It could, however, still be the mechanism of the enzyme-catalyzed rearrangement. A related carbocation mechanism has been suggested for the acid-catalyzed decarboxylation of prephenate (Hermes, J. D.; Tipton, P. A.; Fisher, M. A.; O'Leary, M. H.; Morrison, J. F.; Cleland, W. W. *Biochemsitry* **1984**, *23*, 6263–6275).

Scheme III. Epimerization and Rearrangement of Dimethyl Carboprephenate via. Carbocation Formation



to catalyze the rearrangement of dimethyl chorismate (**C6**). Later and more convincing evidence came from the observation, originally in the laboratory of Berchtold and co-workers[18] and later at Cornell, that dimethyl 4-desoxychorismate (**C7**) rearranged even faster than chorismic acid itself.

Following the demise of the first hypothesis, a systematic approach was formulated to measure rates of rearrangement and, where it occurred, elimination, in a variety of structural analogues of dimethyl chorismate. The hope was to identify some key structural feature of chorismate that might be responsible for its exceptionally facile rearrangement. Such a discovery might then provide a clue to the mechanism.

The thermal reactions of **C1**, **C6**, and five synthetic analogues (**C7–C11**) were studied in 2:1 v:v $CD_3OD:D_2O$ at 75.0 °C. Results are summarized in Table II.

The data in Table II allow the following conclusions to be drawn about substituent effects, provided one bears in mind two important caveats. First, the pairwise comparison of rates of reaction of compounds in Table II is potentially hazardous unless one refers all rates to a common reference—this will become important in the conclusion section of the present paper. Second, the discussion is most useful if one can assume approximate additivity of substituent effects. Such additivity is almost certainly not quantitative but is likely to be qualitatively correct.

(1) The acidity of **C1** is of little consequence for either rearrangement or elimination (comparing rate constants for **C1** vs. **C6**). (2) The trans hydroxyl group of chorismate retards both rearrangement and elimination (**C6** vs. **C7**). (3) The sidechain carboxyl accelerates both rearrangement and elimination (**C7** vs. **C9**). (4) The ring carboxyl retards both rearrangement and elimination (**C8** vs. **C9** and **C10** vs. **C11**). (5) The 5,6 double bond greatly accelerates both rearrangement and elimination (**C7** vs. **C10**). In order to determine whether the "dihydrobenzene" character of compounds **C1** and **C6–C9** was important for their high reactivity, the acyclic analogue **C13** was prepared. It was found to rearrange with a relative rate constant of 0.45 w.r.t. **C1** or approximately 0.05 w.r.t. **C8**, its closest structural analogue. The extra degree of rotational freedom in **C13** (compared to **C8**)

(18) Berchtold, G. A., personal communication.

Scheme IV. Relative Rate Constants for Rearrangement of Some Acyclic Models for Chorismate

	k_{rel}*
C12: R_1 = H; R_2 = H	0.03
C13: R_1 = H; R_2 = CH_3	0.45
C14: R_1 = CH_3; R_2 = CH_3	8.1
C15: R_1 = H; R_2 = $CH_2Si(CH_3)_3$	> 50

* w.r.t. chorismate = [1]

Table III. Solvent Effects on the Rate Constants for Rearrangement of **C13** and Allyl Vinyl Ether at 75 °C

solvent	E_T (30)	k_{rel} (**C13**)	k_{rel} (allyl vinyl ether)
cyclohexane	30.9	[1]	
di-*n*-butyl ether	33.4		[1]
benzene	34.5	2.6	
diethyl ether	34.6	1.3	
acetone	42.2	3.3	1.4
dimethyl sulfoxide	45.0	5.9	
2-propanol	48.6	16	
ethanol	51.9	20	4.0
methanol	55.5	28	
2:1 methanol/water	58.0	117	58

should reduce its activation entropy[19] by about 4.7 cal/(mol K), giving an expected rate constant for rearrangement of 0.09 w.r.t. **C8**. Thus the cyclic nature of compounds **C1** and **C6–C9** is apparently of little consequence to their rearrangement reactivity.

A hypothesis consistent with all the data would be that both rearrangement and elimination involve heterolytic cleavage of the same C–O bond. The substituent effects in the chorismate analogues would then be explicable by σ induction, while the accelerating effect of the 5,6 double bond would be consistent with stabilization of the cationic fragment by delocalization. (As will be discussed in the conclusion, the need for some caution in accepting this last conclusion becomes apparent when one compares all rates to a common reference. At least part of the effect of the 5,6 double bond is explicable in terms of exceptionally slow rearrangement of **C10** rather than exceptionally fast rearrangement of **C7**.)

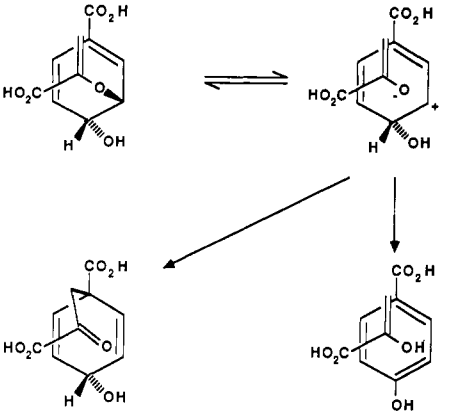
The hypothesis is supported by observation of substituent effects on the acyclic compounds. The relative rate constants for rearrangement of **C12**, **C14**, and **C15** (Scheme IV) are 0.03, 8.1, and >50, respectively, w.r.t. that for **C1** defined as 1.

Some additional support for a dipolar mechanism came from a study of solvent effects on the rate of rearrangement of **C13** and allyl vinyl ether, summarized in Table III. While a rate increase for rearrangement of **C13** in polar solvents was observed, the magnitude of the effect was not significantly greater than that for allyl vinyl ether.

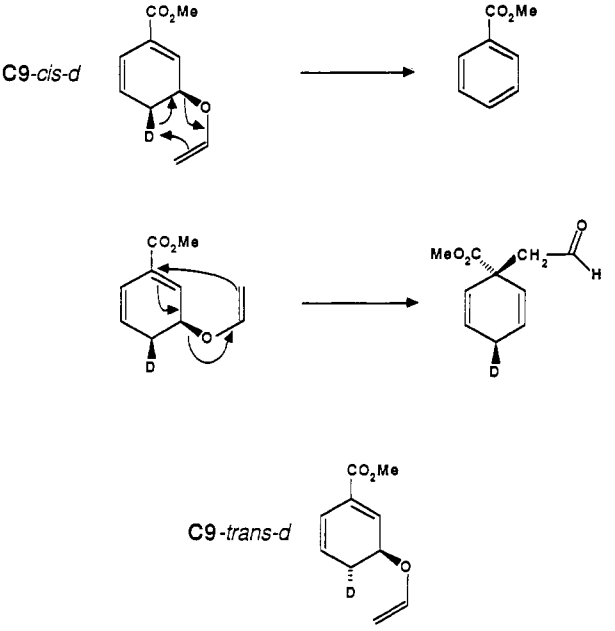
Since the rearrangements of the compounds studied here apparently had some dipolar character in solvents of high E_T, it became intriguing to speculate that the rearrangement and elimination reactions of chorismate might be linked by a common ion pair intermediate (Scheme V). The similar effect of substituents on the rate of rearrangement and elimination revealed in Table II seemed to argue in favor of such a process. Also, secondary tritium isotope effects on the rearrangement have been interpreted in terms of a transition state with considerable C–O cleavage but virtually no C–C bond formation,[7] as would be expected for a dissociative mechanism. On the other hand, attempts to detect ion pair return by racemization of chorismate or to trap ion pairs

(19) Benson, S. W. *Thermochemical Kinetics*, 2nd ed.; Wiley-Interscience: New York, 1976; p 65.

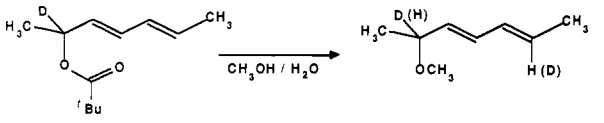
Scheme V. Hypothetical Common Ion Pair for Rearrangement and Elimination of Chorismate



Scheme VI. Pericyclic Mechanisms for Elimination and Rearrangement of the Deuteriated Analogues of **C9**



from **C13** with added nucleophiles were unsuccessful. This was in contrast to the behavior of ester **C16** which reacted in aqueous



C16 **C17**

methanol to give methyl ether **C17**, having the label scrambled between the ends of the diene chain. Thus any ion pair intermediate involved in the reactions of chorismate or its congeners would have to be much "tighter" than that derived from **C16**.

The question of mechanistic linkage between the elimination and rearrangement reactions of chorismate and its analogues was addressed by isotope effect measurements. The compounds selected for this study were **C9**, ***C9-cis-d***, and ***C9-trans-d***. Preliminary studies showed that elimination of ***C9-cis-d*** formed methyl benzoate and CH_2DCHO whereas ***C9-trans-d*** retained the deuterium in the benzoate ester.

Two mechanistic hypotheses consistent with this observation can be considered. In the first, elimination and rearrangement reactions are treated as separate, single-step pericyclic reactions (Scheme VI). In the second, elimination and rearrangement reactions are considered to share formation of an ion pair as a common rate-determining step (cf. Scheme V). Under these

Table IV. Isotope Effects on the Reactions of **C9-*cis*-*d*** and **C9-*trans*-d_6**

compd	Z_r	Z_e	Z_d
C9-*cis*-*d*	1.08 ± 0.04	1.9 ± 0.2	1.41 ± 0.05
C9-*trans*-*d*	1.13 ± 0.07	1.1 ± 0.1	1.12 ± 0.06

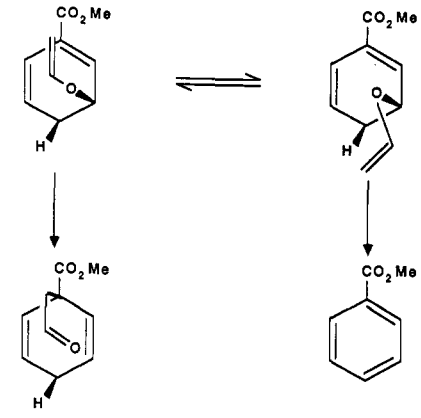
circumstances, the induced kinetic isotope effect (IKIE)[20] operating on the partitioning of the intermediate could lead to an apparent inverse β secondary isotope effect on the rearrangement of **C9-*cis*-*d***. Since the usual hyperconjugation explanation for β secondary isotope effects[21] does not allow for effects <1, such an observation would be good supportive evidence for the intervention of IKIE and hence for mechanistic linkage between the elimination and rearrangement reactions.

The rate constants for the study were determined by ^{1}H NMR at 50 °C, and the isotope effects calculated from them are summarized in Table IV. Z_r, Z_e, and Z_d are defined respectively as the phenomenological isotope effects for appearance of the rearrangement and elimination products and disappearance of the reactant.

The isotope effects for disappearance of the reactant serve as a good place to begin analysis of the data. If a common ion pair were formed in the rate-determining step (as one might expect, and as would seem to be required if one wanted to use the common intermediate as an explanation for the parallel response of rearrangement and elimination reactions to changes in substituent), then the isotope effect on disappearance of reactant ought to be just the β secondary effect. If this were the case, it would be hard to explain the unprecedentedly large value of 1.41 for the disappearance of **C9-*cis*-*d*** and even harder to explain the relative magnitudes of the effects for **C9-*cis*-*d*** and its epimer **C9-*trans*-*d***. If anything, one would expect that the trans diaxial arrangement of the deuterium and the breaking C–O bond would result in a larger β secondary isotope effect for **C9-*trans*-*d***. On the other hand, the larger value of Z_d for **C9-*cis*-*d*** is quite reasonable if one invokes some contribution from the primary isotope effect for breaking the C–D bond in the elimination reaction. This would obviously be the case for the mechanism in which rearrangement and elimination were parallel but unrelated pericyclic processes; it could only be made to work in the ion-pair mechanism if there were a substantial rate constant for internal return of the ion pair. In fact, if one assumes that the isotope effects for return of the ion pair to starting material and advance to the rearrangement product are comparable, then it is possible to calculate that the rate constant for internal return would have to be at least 9 times greater than the rate constant for formation of the rearrangement product in order to explain the observed relative magnitudes of Z_d for **C9-*cis*-*d*** and **C9-*trans*-*d*** while preserving the expected relative magnitudes of the β seconary effect on the dissociation step. Under these circumstances, formation of the ion pair would again not be rate determining, and the main reason for invoking the ion-pair mechanism would be lost. Finally the data show no evidence for an apparent inverse isotope effect on the rearrangement step for **C9-*cis*-*d***, as might have been expected for the ion pair mechanism. Thus, it must be concluded that the data better support a mechanism in which the rearrangement and elimination reactions are unconnected pericyclic processes.

Despite the fact that the results of the isotope effect experiments argue against mechanistic linkage between the two reactions, the transition states for rearrangement and elimination of **C9** must be very similar. The activation parameters are virtually identical ($\Delta H^{\ddagger}$ = 19.9 ● 0.4 kcal/mol, $\Delta S^{\ddagger}$ = −8 ± 1 cal/(mol K) for rearrangement, and $\Delta H^{\ddagger}$ = 20.2 ± 0.3 kcal/mol, $\Delta S^{\ddagger}$ = −8.3 ± 0.8 cal/(mol K) for elimination). The primary isotope effect for elimination in **C9-*cis*-*d*** is very small (1.9), indicating little C–H bond cleavage in the transition state, and the β secondary isotope effect is virtually identical for rearrangement and elimination processes in **C9-*trans*-*d***. Finally, as noted above, substituent and solvent effects are very similar for the two reactions.

Scheme VII. Interconversion of Chairlike Conformations for Rearrangement and Elimination of **C9**



All of this information points to a reaction in which the transition states for elimination and rearrangement involve extensive (but apparently not complete) C–O bond cleavage and very little bond formation at the terminus of the sidechain. So what keeps these very similar transition states from collapsing to a common ion pair? The problem seems all the more puzzling when one recognizes that two chairlike conformations are apparently interconvertible by a simple rotation about the breaking C–O bond (see Scheme VII). In the extreme of complete dissociation the barrier to such a rotation would be zero! On the other hand, an upper limit for this barrier is probably in the range of 3–3.5 kcal/mol (the barrier to rotation about the methyl–oxygen bond in methyl vinyl ether is 3.4 kcal/mol[22]). If the residual barrier to rotation (which in this apparently dipolar reaction could derive at least in part from solvent organization) were 2 kcal/mol or more at the transition structures, then there would be less than 5% crossover between the two manifolds. This would be consistent with the experimental data and is the explanation currently favored by the Cornell group.

Conclusion

There is effectively complete agreement between the Indiana and Cornell groups about the facts of the reactions studied here. There is also substantial agreement about the interpretation, but some differences remain, and these will be highlighted at the end.

We have shown for the first time that the polar medium in which it generally occurs is a significant factor in the facility of the Claisen rearrangement of chorismic acid. Claisen rearrangements that have been previously studied for synthetic or mechanistic purposes have typically been run in relatively nonpolar media or in the gas phase. Thus the rearrangement of dimethyl chorismate (**C6**) is only 18 times faster than that of allyl vinyl ether when both are run in 2:1 methanol:water at 75 °C. Nevertheless, studies on the analogues of chorismate have revealed that there are also important structural effects on the rate of the reaction; these are analyzed below.

A useful way to depict the influence of structure on the rate of Claisen rearrangement is to plot the activation free energy at some fixed temperature and in some fixed solvent (the ones selected for Figure 1 are 75 °C and 2:1 methanol:water) for a series of molecules arranged in order of structural change. In Figure 1, one can envision the effective "construction" of dimethyl chorismate from allyl vinyl ether by sequential alkylation at the sp^3 hybridized carbon, addition of a second double bond in conjugation with that of the allyl moiety, ring closure, addition of an ester to the sidechain, addition of a trans hydroxyl to the ring, and addition of an ester to the ring. The y axis depicts the effect of

(20) Samuelson, A. G.; Carpenter, B. K. *J. Chem. Soc., Chem. Commun.* **1981**, 354–356.

(21) Melander, L.; Saunders, W. H., Jr. *Reaction Rates of Isotopic Molecules*; Wiley-Interscience: New York, 1980; pp 174–180.

(22) Benson, S. W. *Thermochemical Kinetics*, 2nd ed.; Wiley-Interscience: New York, 1976; p 306.

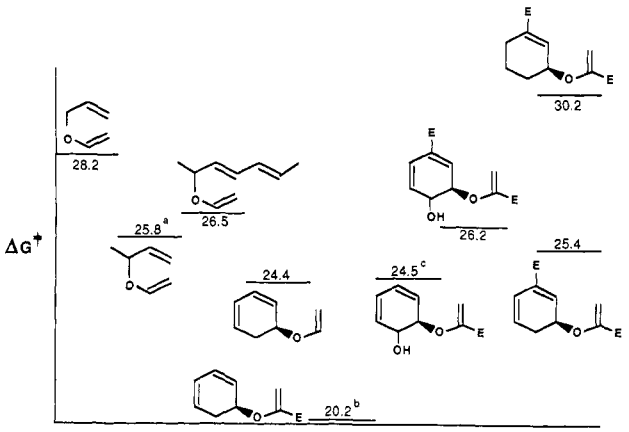


Figure 1. Influence of structure on the free-energy of activation (at 75 °C in 2:1 v:v methanol:water) for Claisen rearrangement of some chorismate analogues. (a) Estimated from the rearrangement of (1-buten-3-yl)vinyl ether in benzonitrile (Frey, H. M.; Montague, D. C. *Trans. Faraday Soc.* **1968**, *64*, 2369) by assuming the same dependence of rate on solvent polarity as observed for allyl vinyl ether. (b) Extrapolated from rate constant measured at −15 °C by assuming a $\Delta S^{\ddagger}$ of −12 cal/(mol K). (c) Extrapolated from rate constant measured at 40 °C by assuming a $\Delta S^{\ddagger}$ of −12 cal/(mol K).

each of these changes on $\Delta G^{\ddagger}$. Also included on this chart are molecules **C7** and **C10**. These last two are particularly important because they reveal that the apparent rate enhancing effect of the 5,6 double bond in chorismate and related cyclohexadienyl enol ethers is, at least in part, due to the exceptionally slow rearrangement of the dihydro compounds to which they are being compared. Comparison of the rates of rearrangement of compounds **13a** and **13i** (Table I) shows particularly clearly that inclusion of the allylic double bond in a cyclohexene ring actually causes rate retardation when a rate enhancement would have been expected on the basis of alkyl substituent effects alone. An explanation suggested by the Cornell group for the sluggish rearrangement of cyclohexenyl enol ethers might be a destabilizing 1,3-diaxial interaction between the sidechain and the syn hydrogen on carbon 5 of the ring. It is the view of the Cornell group that this is enough to explain virtually all of the difference between the rates of rearrangement of cyclohexadienyl and cyclohexenyl enol ethers. The Indiana group, on the other hand, believes that the special stability of the cyclohexadienyl moiety is reflected to some degree in the transition structures for rearrangement of the cyclohexadienyl enol ethers and that this is a major contributor to the rate difference.

The two groups agree that the transition structure for rearrangement of chorismic acid and related compounds is dissociative but not significantly more than for allyl vinyl ether itself. The Cornell group gives heavier emphasis to the dipolar nature of the transition structure and uses this to explain the rate retarding effect of the ring trans hydroxyl. It gives relatively little emphasis to radical structures and radical stabilizing properties of the substituents. The Indiana group gives heavier emphasis to the radical structures and less weight to the dipolar structures. It explains the rate-retarding effect of the trans hydroxyl by invoking hyperconjugation and hydrogen bonding in the ground state.

The implications of this work for the mechanism of enzyme catalysis depend somewhat on the relative importance that one places on the polar and radical contributors to the transition structure. If one believes that the polar character is significant, as the Cornell group does, then one can imagine stabilization of the transition structure by hydrogen bonding or electrostatic interaction with charged groups in the active site of the enzyme. If one views the radical stabilizing properties of the substituents to be more important, as the Indiana group does, then the role for the enzyme is presumably to exert conformational control, as has previously been proposed.[2] In addition, the Indiana group suggests that the enzyme might remove some of the ground-state stabilization exerted by the ring carboxyl and trans hydroxyl,

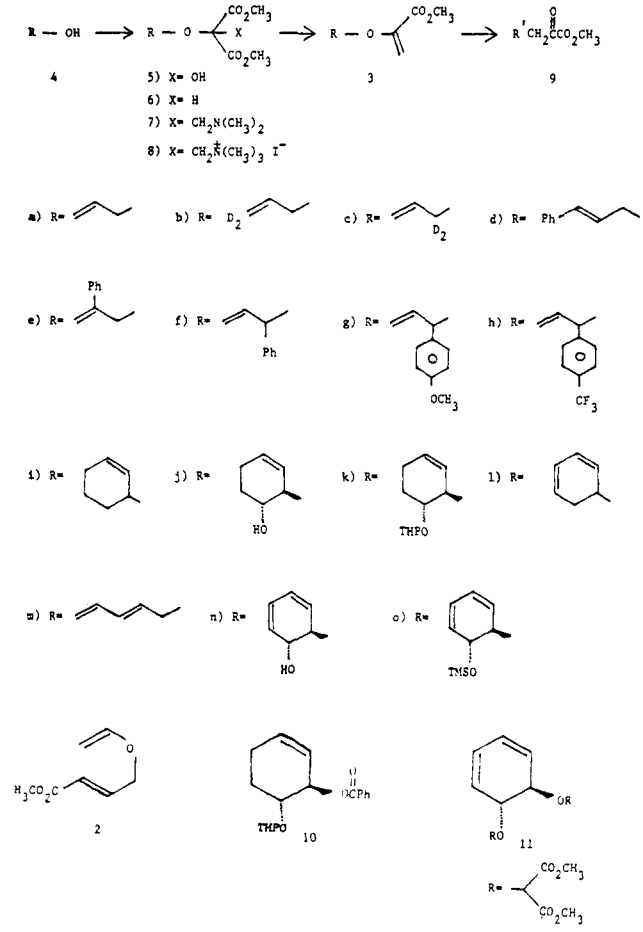


Figure 2. Key to compounds in Experimental Section of Indiana group.

thereby enhancing the rate, as seen in compound **13l**.

Experimental Section—Indiana Group

General Methods. ^{1}H NMR spectra were taken on a Varian T-60, HR-220, EM-390, Varian XL300, and Nic360 machines. Chemical shifts are reported in δ units downfield from internal tetramethylsilane. Infrared spectra were recorded on a P.E. 298 spectrometer. Melting points were determined on a Thomas capillary melting point apparatus and are uncorrected.

Tetrahydrofuran (THF) was dried over lithium aluminum hydride (LAH), ethyl ether was used directly out of Mallinckrodt anhydrous ether cans, methylene chloride, triethylamine, hexamethyl phosphoric triamide (HMPA), and pyridine (Py) were dried over CaH_2, and benzene was dried by distillation from potassium metal. Eschenmoser's salt (*N,N*-dimethylmethyleneammonium iodide) was purchased from Aldrich. Analytical thin-layer chromatography was performed on Polygram Sil G/UV254 precoated plastic sheets. Column chromatography was performed on Merck silica gel 60 and Mallinkrodt CC-7 silica gel.

Kinetic determinations were done by following the disappearance of reactant vs. time, by using NMR integrations as a quantitative measure of concentration. Measurements to determine secondary kinetic isotope effects (KIEs) were performed by using a gas chromatograph equipped with a DB-5 capillary column and a Hewlett-Packard 3390A integrator.

Structures can be found in Figure 2.

6-Carbomethoxy-3-oxa-1,5-hexadiene (12).[23] Freshly recrystallized mercuric acetate (130 mg, 6 equal portions) were added to a solution of methyl 4-hydroxycrotonate[24] (276 mg, 2.38 mmol) in 26 mL of ethyl vinyl ether (freshly distilled from sodium) at 2-h intervals at reflux. The mixture was heated at reflux for 12 h after the last addition. After cooling, the reaction mixture was washed with 10% aqueous sodium carbonate. The ether layer was dried over potassium carbonate, filtered and, concentrated in vacuo. The residue was chromatographed on CC-7 silica gel (9:1 hexane–ether) to give 160 mg (47%) of a colorless liquid:

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NMR (CCl_4, 220 MHz) 6.9 (1 H, dt, J = 16, 4 Hz), 6.4 (1 H, dd, J = 14, 7 Hz), 6.0 (1 H, dt, J = 16, 2 Hz), 4.35 (2 H, dd, J = 4, 2 Hz), 4.13 (1 H, dd, J = 14, 3 Hz), 4.0 (1 H, dd, J = 7, 3 Hz), 3.7 (3 H, s); m/e = 142.0630, calcd 142.0630.

Noncommercially Available Alcohols. 3,3-Dideuterioallyl alcohol (I4b) was prepared[25] with 96.5% of two deuteriums.

1,1-Dideuterioallyl alcohol (I4c) was prepared[26] with 99% of two deuteriums.

2-Phenyl-2-propen-1-ol (I4e).[27] To a stirred solution of dry diisopropylamine (2.33 g, 23 mmol) in anhydrous ether (20 mL) was added n-butyllithium (12.5 mL, 1.92 M in hexane) under nitrogen. After 30 min, a solution of α-methylstyrene oxide[28] (2.1 g, 15.6 mmol) in anhydrous ether (30 mL) was added slowly. The mixture was stirred for 1 day at room temperature and then heated at reflux for 4 h. The reaction was quenched with saturated ammonium chloride, and the layers were separated. The aqueous layer was extracted twice with ether, and the combined ether portions were washed with brine, dried, and evaporated under reduced pressure. The alcohol (0.9 g, 43% yield) was purified by chromatography on silica gel (4:1 hexane–ether): NMR (CCl_4, 90 MHz) 7.3 (5 H, m), 5.3 (2 H, 2 m's), 4.3 (2 H, br s), 2.85 (1 H, br); IR (neat) 3350, 3080, 3040, 3020, 2920, 2860, 1640, 1600, 1050, 1020, 775, 700 cm^{-1}.

1-Aryl-2-propen-1-ols I4f–h were prepared by addition of vinyl Grignard (Alfa) to the appropriate aldehydes and purified by chromatography or distillation; p-(trifluoromethyl)benzaldehyde was obtained by formylation of [p-(trifluoromethyl)phenyl]magnesium bromide with N-formylpiperidine.[29]

2-(Benzoyloxy)-1-[(tetrahydropyranyl)oxy]cyclohex-3-ene (I10). Activated manganese dioxide[30] (4.0 g) was added to a solution of the mixture of monobenzoates derived from *trans*-1,2-dihydroxycyclohex-3-ene[31] (0.8 g, 3.66 mmol) in 80 mL of chloroform with vigorous stirring. After 10 h at room temperature the mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was redissolved in dry methylene chloride. Freshly distilled dihydropyran (0.5 mL, 5.5 mmol) was added, followed by a catalytic amount of pyridinium p-toluenesulfonate (92 mg).[32] The mixture was stirred at room temperature for 4 h, then diluted with ether, and washed once with half saturated brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The product (0.9 g, 80% yield) was isolated by chromatography (silica, 10:90 ether–hexane): IR (neat) 3060, 3020, 2940, 2860, 2830, 1720, 1650, 1600, 1580, 1450, 1350, 1310, 1250, 1100, 1060, 1030, 990, 960, 705 cm^{-1}; NMR (90 MHz, CCl_4) 8.0 (2 H, m), 7.3 (3 H, m), 6.0–5.3 (3 H, 2 m's), 4.8 (1 H, br s), 4.1–3.2 (3 H, 2 m's), 2.1–1.3 (10 H, m).

2-Hydroxy-1-[(tetrahydropyranyl)oxy]cyclohex-3-ene (I4k). A solution of benzoate **I10** (0.9 g, 2.98 mmol) in 10 mL of methanol was stirred with anhydrous lithium hydroxide (0.143 g, 5.96 mmol) for 7 h at room temperature. The solvent was removed, and the residue was partitioned between ether and water. The aqueous layer was extracted 3 times with ether. The combined ether layers were washed with water, dried, and concentrated. The residue was chromatographed (silica, 30:70 ether–hexane) giving the product as a mixture of separable epimers (0.58 g, 98% yield, R_f 0.132, 0.056). For **I4k**: R_f 0.132; IR (neat) 3400, 3020, 2920, 2840, 1650, 1440, 1380, 1340, 1250, 1150, 1130, 1110, 1060, 1020, 970 cm^{-1}; NMR (90 MHz, CCl_4) 5.55 (2 H, br s), 4.60 (1 H, br s), 4.2–3.2 (5 H, m's), 2.2–1.4 (10 H, m). For **I4k**: R_f 0.056; IR (neat) 3400, 3020, 2920, 2860, 2840, 1650, 1450, 1435, 1375, 1350, 1270, 1255, 1195, 1150, 1130, 1110, 1055, 1025, 1015, 975 cm^{-1}; NMR (90 MHz, CCl_4) 5.5 (2 H, m), 4.76 (1 H, br s), 4.1–3.2 (4–5 H, m), 2.2–1.3 (11 H, m).

Cyclohexa-2,4-dien-1-ol (I4l) was prepared according to ref 33. *trans*-2,4-Pentadien-1-ol (I4m) was prepared according to ref 34. *trans*-5,6-Dihydroxy-1,3-cyclohexadiene (I4n) was prepared according to ref 35.

General Procedure for Preparation of I5a–d. Equimolar amounts of alcohols **I4a–d** and dimethyl oxomalonate[36] were stirred at room temperature for 1 day. No further purification was necessary.

1-[(Bis(methoxycarbonyl)hydroxymethyl)oxy]-2-propene (I5a): NMR (CCl_4, 90 MHz) 5.8 (1 H, m), 5.3–5.0 (2 H, m's), 4.55 (1 H, br), 4.1 (2 H, m), 3.8 (6 H, s); IR (neat) 3480, 3080, 3020, 2960, 2890, 1760, 1650, 1340–1000 cm^{-1}.

1-[(Bis(methoxycarbonyl)hydroxymethyl)oxy]-3,3-dideuterioprop-2-ene (I5b): NMR (CCl_4, 90 MHz) 5.85 (1 H, br), 4.6 (1 H, br), 4.15 (2 H, d, J = 5 Hz), 3.8 (6 H, s); IR (neat) 3450, 3010, 2960, 2200, 1750, 1630, 1250, 1140 cm^{-1}.

1-[(Bis(methoxycarbonyl)hydroxymethyl)oxy]-1,1-dideuterioprop-2-ene (I5c): NMR (CCl_4, 90 MHz) 5.85 (1 H, dd, J = 16, 9 Hz), 5.3–5.0 (2 H, m), 4.5 (1 H, br), 3.8 (6 H, s); IR (neat) 3450, 3000, 2950, 2200, 2100, 1750, 1630, 1250, 1120 cm^{-1}.

1-[(Bis(methoxycarbonyl)hydroxymethyl)oxy]-3-phenyl-2-propene (I5d): NMR (CCl_4, 90 MHz) 7.2 (6 H, m), 6.6–6.2 (2 H, m), 4.6–4.2 (3 H, br peak + apparent t), 3.8 (6 H, s); IR (neat) 3450, 3020, 2960, 1750, 1650, 1630, 1600, 1300–980, 750, 700 cm^{-1}.

1-[(Bis(methoxycarbonyl)hydroxymethyl)oxy]-1-phenyl-2-propene (I5f): NMR (CCl_4, 90 MHz) 7.3 (5 H, br s), 6.0 (1 H, m), 5.3–5.0 (3 H, m), 3.8 (3 H, s), 3.5 (3 H, s).

1-[(Bis(methoxycarbonyl)hydroxymethyl)oxy]-1-(p-methoxyphenyl)-2-propene (I5g): NMR (CCl_4, 90 MHz) 7.2 (2 H, d, J = 9 Hz), 6.75 (2 H, d, J = 9 Hz), 5.95 (1 H, m), 5.35–5.05 (3 H, m's), 4.7 (1 H, br s), 3.76 and 3.7 and 3.5 (9 H, 3 singlets).

General Procedure for Conversion of I5 into I6.[37] Thionyl chloride (1.19 equiv) was added under nitrogen to a solution of **I5** (1 equiv) and dry pyridine (1.14 equiv) in THF (12 mL/mmol of **I5**) at −20 °C. The mixture was stirred for 5 more min at −20 °C, 30 min at 0 °C, and then 1 h at room temperature. The mixture was filtered under nitrogen (to remove the precipitated pyridinium hydrochloride), and the filtrate was concentrated in vacuo. The residue was dissolved in dry benzene, and the process of filtration and concentration was repeated. To the well-stirred ice-cooled residue was added cold 9:1 acetic acid–water mixture (16 mL/mmol of **I5**) followed by zinc powder (0.68 g/mmol of **I5**). After stirring for 15 min at 0 °C and 30 min at room temperature, the mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in methylene chloride and successively washed with water, saturated sodium bicarbonate, and brine, and then the methylene chloride solution was dried over sodium sulfate. The product was isolated by chromatography on silica gel.

1-[Bis(methoxycarbonyl)methoxy]-2-propene (I6a): isolated in 76% yield; NMR (CCl_4, 90 MHz) 5.85 (1 H, m), 5.4–5.1 (2 H, m's), 4.4 (1 H, s), 4.1 (2 H, dt, J = 5, 1 Hz), 3.75 (6 H, s); IR (neat) 3080, 3010, 2960, 1750, 1650, 1300–1100 cm^{-1}.

1-[Bis(methoxycarbonyl)methoxy]-3,3-dideuterio-2-propene (I6b): isolated in 62% yield; NMR (CCl_4, 90 MHz) 5.8 (1 H, br), 4.4 (1 H, s), 4.1 (2 H, d, J = 5 Hz), 3.75 (6 H, s); IR (neat) 3010, 2960, 1750, 1620, 1300–1100 cm^{-1}.

1-[Bis(methoxycarbonyl)methoxy]-1,1-dideuterio-2-propene (I6c): isolated in 63% yield; NMR (CCl_4, 90 MHz) 5.8 (1 H, dd, J = 18, 10 Hz), 5.35–5.10 (2 H, m's), 4.4 (1 H, s), 3.75 (6 H, s); IR (neat) 3080, 3010, 2950, 2180, 2090, 1750, 1650, 1350–1100 cm^{-1}.

1-[Bis(methoxycarbonyl)methoxy]-3-phenyl-2-propene (I6d): isolated in 39% yield; NMR (CCl_4, 90 MHz) 7.2 (5 H, m), 6.7–5.8 (2 H, m), 4.5 (1 H, s), 4.2 (2 H, d, J = 5 Hz), 3.7 (6 H, s).

1-[Bis(methoxycarbonyl)methoxy]-1-phenyl-2-propene (I6f): isolated in 16% yield; NMR (CCl_4, 90 MHz) 7.3 (5 H, br s), 5.85 (1 H, m), 5.45–5.15 (2 H, m's), 4.9 (1 H, d, J = 6 Hz), 4.45 (1 H, s), 3.71 and 3.69 (6 H, 2 s); IR (neat) 3040, 3020, 2940, 1740, 1280–1100, 750, 700 cm^{-1}.

General Procedure for the Direct Preparation of I6 from I4.[8,38] A dilute solution ca. 0.5 M of dimethyl diazomalonate[39] (1.25 equiv) in dry benzene was added slowly to a stirred, hot (65 °C) benzene solution of the alcohol **I4** (1 equiv) containing a catalytic amount of rhodium acetate dimer (1 mg). Heating was continued until evolution of nitrogen gas stopped. The solvent was removed under reduced pressure, and the product was isolated by chromatography of the residue on silica gel.

1-[Bis(methoxycarbonyl)methoxy]-2-phenyl-2-propene (I6e): isolated in 59% yield; NMR (CCl_4, 90 MHz) 7.3 (5 H, m), 5.5 and 5.35 (2 H, 2 m's), 4.45 (3 H, br s), 3.7 (6 H, s); IR (neat) 3060, 3040, 2990, 2920,

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1740, 1615, 1280–1100, 770, 690 cm^{-1}.

I6f was isolated in 53% yield by this procedure.

1-[Bis(methoxycarbonyl)methoxy]-1-(*p*-methoxyphenyl)-2-propene (I6g): NMR (CCl_4, 90 MHz) 7.3 (2 H, d, J = 9 Hz), 6.85 (2 H, d, J = 9 Hz), 5.95 (1 H, m), 5.4–5.15 (2 H, m's), 4.85 (1 H, d, J = 5 Hz), 4.4 (1 H, s), 3.85 and 3.83 and 3.75 (9 H, 3 s); IR (neat) 3060, 3000, 2960, 2840, 1750, 1640, 1610, 1300–1100, 830 cm^{-1}.

1-[Bis(methoxycarbonyl)methoxy]-1-[(*p*-trifluoromethyl)phenyl]-2-propene (I6h): isolated in 51% yield; NMR (CCl_4, 90 MHz) 7.55 (4 H, m), 5.8 (1 H, m), 5.5–5.2 (2 H, m's), 5.0 (1 H, d, J = 5 Hz), 4.5 (1 H, s), 3.8 (6.5 H, br s); IR (neat) 3040, 3000, 2950, 1750, 1640, 1615, 1340–1100, 830 cm^{-1}.

1-[Bis(methoxycarbonyl)methoxy]-2-cyclohexene (I6i).[12] Dry benzene (25 mL) was added to a mixture of 2-cyclohexen-1-ol (0.614 g, 6.27 mmol), dimethyl diazomalonate (1.24 g, 7.83 mmol), and rhodium acetate dimer (50 mg), and the mixture was heated at 65 °C under N_2 for 2.5 h. The solution was cooled, filtered, and washed with saturated $NaHCO_3$ and then twice with water. The organic layer was dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was chromatographed (silica gel, 30:70 ether–hexane) to give 1.38 g of a colorless oil (96% yield): IR (neat) 3000, 2900, 1730, 1420, 1270–1100 cm^{-1}; NMR (90 MHz, CCl_4) 5.75 (2 H, m), 4.45 (1 H, s), 3.9 (1 H, m), 3.73 (6 H, s), 2.1–1.4 (6 H, m).

2-[Bis(methoxycarbonyl)methoxy]-1-[(tetrahydropyranyl)oxy]-3-cyclohexene (I6k). Compound **I6k** was prepared from **I4k** in 78% yield by using the same procedure as that for the preparation of **I6i**: IR (neat) 3020, 2940, 2860, 2830, 1740, 1650, 1430, 1385–970 cm^{-1}; NMR (90 MHz, CCl_4) 5.7 (2 H, m), 4.85–4.7 (2 H, m and 2s at 4.83 and 4.7), 4.0–3.2 (10 H, m overlapping with 2s at 3.73 and 3.7), 2.1–1.3 (10 H, m).

1-[Bis(methoxycarbonyl)methoxy]-2,4-cyclohexadiene (I6l). A solution of alcohol **I4l** (2.46 g, 25.6 mmol) and dimethyl diazomalonate (4.0 g, 25.3 mmol) in 100 mL of dry benzene was heated at 65 °C for 1 hour, with a catalytic amount of rhodium acetate (60 mg) under nitrogen. The solution was filtered, washed once with saturated sodium bicarbonate and twice with water, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was chromatographed (CC-7 silica gel, 20:80 ether–hexane) to give 2.115 g of product (36.5% yield) as a colorless oil: IR (neat) 3030, 2940, 2830, 1740, 1640, 1580, 1430, 1400, 1330–1100, 1010, 860, 780 cm^{-1}; NMR (90 MHz, CCl_4) 6.2–5.7 (4 H, m), 4.43 (1 H, s), 4.3–4.1 (1 H, m), 3.7 (6 H, s), 2.6–2.4 (2 H, m).

1-[Bis(methoxycarbonyl)methoxy]-2,4-pentadiene (I6m). Compound **I6m** was obtained in 54% yield following the procedure described in **I6i**: IR (neat) 3075, 2995, 2940, 1740, 1600, 1430, 1280, 1220, 1120, 1000, 900 cm^{-1}; NMR (60 MHz, CCl_4) 6.5–5.6 (3 H, m), 5.26–4.86 (2 H, m), 4.36 (1 H, s), 4.13 (2 H, d, J = 5 Hz), 3.73 (6 H, s).

***trans*-6-Hydroxy-5-[bis(methoxycarbonyl)methoxy]-1,3-cyclohexadiene (I6n) and *trans*-5,6-Bis[bis(methoxycarbonyl)methoxy]-1,3-cyclohexadiene (I11).** An equimolar solution of **I4n** (0.235 g, 2.1 mmol) and dimethyl diazomalonate (0.33 g, 2.1 mmol) in 25 mL of dry benzene was heated at 65 °C with a catalytic amount of rhodium acetate dimer (10 mg) for 1 hour, under nitrogen. The solvent was removed, and the residue was purified by chromatography (CC-7 silica gel, 55:45 ether–hexane) to give 0.35 g of a colorless oil which was a 10:1 mixture of **I6f** and **I11**. For **I6f**: IR (neat) 3490, 3030, 3000, 2940, 2840, 1735, 1600, 1430, 1230, 1120, 1015 cm^{-1}; NMR (360 MHz, $CDCl_3$) 5.84 (4 H, m), 4.755 (1 H, s), 4.696 (1 H, dt, J = 12.6, 1.8 Hz), 4.38 (1 H, dt, J = 12.6, 1.8 Hz), 3.805 and 3.801 (6 H, 2 s), 3.45 (1 H, br). For **I11**: IR (neat) 3020, 2980, 2740, 2830, 1740, 1630, 1430, 1230, 1120, 1015 cm^{-1}; NMR (90 MHz, $CDCl_3$) 5.90 (4 H, s), 4.92 (2 H, s), 4.59 (2 H, s), 3.8 (12 H, s).

General Procedure for Conversion of I6 into I7. A solution of **I6** (1 equiv) in dry methylene chloride was added to solid Eschenmoser salt (1.3 equiv) under nitrogen. Dry triethylamine was added slowly with vigorous stirring. Stirring was continued for 5 h before an excess of 10% aqueous sodium hydroxide was added. The layers were separated, and the aqueous layer was extracted twice with methylene chloride. The combined organic layers were washed with brine and dried over magnesium sulfate. The residue left after removal of drying agent and solvent was filtered through a short pad of silica gel to give nearly pure **I7**.

1-[Bis(methoxycarbonyl)((dimethylamino)methyl)methoxy]-2-propene (I7a): isolated in 77% yield; NMR (CCl_4, 90 MHz) 5.8 (1 H, m), 5.35–5.0 (2 H, m's), 4.1 (2 H, dt, J = 5, 1 Hz), 3.7 (6 H, s), 2.8 (2 H, s), 2.25 (6 H, s); IR (neat) 3080, 2960, 2880, 2860, 2820, 2780, 1750, 1650, 1280–1050 cm^{-1}.

1-[Bis(methoxycarbonyl)((dimethylamino)methyl)methoxy]-3,3-dideuterio-2-propene (I7b): isolated in 90% yield; NMR (CCl_4, 90 MHz) 5.85 (1 H, br), 4.1 (2 H, d, J = 6 Hz), 3.7 (6 H, s), 2.8 (2 H, s), 2.3 (6 H, s); IR (neat) 3000, 2950, 2820, 2780, 1760, 1740, 1250, 1090, 1040 cm^{-1}.

1-[Bis(methoxycarbonyl)((dimethylamino)methyl)methoxy]-1,1-dideuterio-2-propene (I7c): isolated in 83% yield; NMR (CCl_4, 90 MHz) 5.85 (1 H, dd, J = 18, 11 Hz), 5.3–5.0 (2 H, m's), 3.7 (6 H, s), 2.8 (2 H, s), 2.25 (6 H, s); IR (neat) 3080, 2950, 2820, 2780, 2200, 2100, 1760, 1740, 1640, 1260–1140 cm^{-1}.

1-[Bis(methoxycarbonyl)((dimethylamino)methyl)methoxy]-3-phenyl-2-propene (I7d): isolated in 85% yield; NMR (CCl_4, 90 MHz) 7.3 (6 H*, m) (* should integrate to 5 and 6 hydrogens, respectively), 6.6–6.1 (2 H, m), 4.25 (2 H, d, J = 5 Hz), 3.7 (7 H*, s) (* should integrate to 5 and 6 hydrogens, respectively), 2.85 (2 H, s), 2.25 (6 H, s); IR (neat) 3010, 2940, 2800, 2760, 1750, 1730, 1590, 1250, 1100, 1030 cm^{-1}.

1-[Bis(methoxycarbonyl)((dimethylamino)methyl)methoxy]-2-phenyl-2-propene (I7e): isolated in 77% yield; NMR (CCl_4, 90 MHz) 7.4 (5 H, m), 5.4 (2 H, m), 4.55 (2 H, br s), 3.8 (6 H, s), 2.85 (2 H, s), 2.25 (6 H, s); IR (neat) 3080, 3050, 3010, 2940, 2820, 2760, 1760, 1740, 1630, 1250, 1080, 1040, 770, 700 cm^{-1}.

1-[Bis(methoxycarbonyl)((dimethylamino)methyl)methoxy]-1-phenyl-2-propene (I7f): isolated in 79% yield; NMR (CCl_4, 220 MHz) 7.3 (5 H, m), 6.1 (1 H, m), 5.375 (1 H, d, J = 5 Hz), 5.0 (2 H, d), 3.7 (3 H, s), 3.2 (3 H, s), 2.875 (2 H, AB q), 2.3 (6 H, s); IR (neat) 3080, 3060, 3020, 2940, 2810, 2760, 1760, 1740, 1640, 1250, 1090, 1030, 700 cm^{-1}.

1-[Bis(methoxycarbonyl)((dimethylamino)methyl)methoxy]-1-(*p*-methoxyphenyl)-2-propene (I7g): NMR (CCl_4, 90 MHz) 7.23 (2 H, d, J = 9 Hz), 6.76 (2 H, d, J = 9 Hz), 6.06 (1 H, m), 5.3 (1 H, d, J = 4 Hz), 5.1–4.8 (2 H, m's), 3.75 (5 H*, s) (* should integrate to 3 hydrogens), 3.66 (3 H, s), 3.25 (3 H, s), 2.8 (2 H, br s), 2.26 (6 H, s); IR (neat) 3080, 3000, 2950, 2830, 2770, 1760, 1740, 1640, 1610, 1250, 1100, 1040, 830 cm^{-1}.

1-[Bis(methoxycarbonyl)((dimethylamino)methyl)methoxy]-1-(*p*-trifluoromethylphenyl)-2-propene (I7h): isolated in 84% yield; NMR (CCl_4, 90 MHz) 7.6 (4 H, AB q), 6.03 (1 H, m), 5.46 (1 H, d, J = 6 Hz), 5.2–4.9 (2 H, m's), 3.7 (3 H, s), 3.26 (3 H, s), 2.86 (2 H, br s), 2.3 (6 H, s); IR (neat) 3070, 2940, 2810, 2760, 1760, 1740, 1640, 1610, 1320, 1250, 1120, 830 cm^{-1}.

1-[Bis(methoxycarbonyl)((dimethylamino)methyl)methoxy]-2-cyclohexene (I7i): isolated in 96% yield; NMR (90 MHz, CCl_4) 5.67 (2 H, m), 4.27 (1 H, m), 3.68 (6 H, s), 2.76 (2 H, s), 2.23 (6 H, s), 2.1–1.4 (6 H, m); IR (neat) 3010, 2930, 2840, 2800, 2760, 1730, 1640, 1440, 1430, 1250–1020 cm^{-1}.

2-[Bis(methoxycarbonyl)((dimethylamino)methyl)methoxy]-1-[(tetrahydropyranyl)oxy]-3-cyclohexene (I7k): isolated in quantitative yield; NMR (90 MHz, CCl_4) 5.8 (2 H, m), 4.7 (1 H, br s), 4.2–3.2 (10 H, m and s at 3.7), 2.7 (2 H, m), 2.2 (6 H, s), 2.1–1.3 (10 H, m); IR (neat) 3020, 2920, 2860, 2840, 2805, 2760, 2720, 1740, 1650, 1460, 1445, 1430, 1270–950, 780 cm^{-1}.

1-[Bis(methoxycarbonyl)((dimethylamino)methyl)methoxy]-2,4-cyclohexadiene (I7l): isolated in 66% yield; NMR (90 MHz, CCl_4) 5.93–5.6 (4 H, m), 4.6–4.33 (1 H, m), 3.70 (6 H, s), 3.66 (2 H, s), 2.46 and 2.36 (2 H, 2 d, J = 2 Hz), 2.2 (6 H, s); IR (neat) 3030, 2940, 2840, 2810, 2760, 1760, 1730, 1640, 1575, 1425, 1360, 1250, 1085, 1025, 995, 780, 680 cm^{-1}.

1-[Bis(methoxycarbonyl)((dimethylamino)methyl)methoxy]-2,4-pentadiene (I7m): isolated in 75% yield; NMR (60 MHz, CCl_4) 6.56–5.63 (3 H, m), 5.33–4.86 (2 H, m), 4.13 (2 H, d, J = 5 Hz), 3.7 (6 H, s), 2.8 (2 H, s), 2.23 (6 H, s); IR (neat) 3075, 2995, 2940, 2840, 2800, 2760, 1730, 1600, 1430, 1360, 1250, 1095, 1025, 995, 895, 780 cm^{-1}.

***trans*-5-[Bis(methoxycarbonyl)((dimethylamino)methyl)methoxy]-6-(trimethylsilyloxy)-1,3-cyclohexadiene (I7o).** Freshly distilled trimethylsilyl chloride (123.5 mg, 1.136 mmol) was added by syringe to a solution of a mixture of **I6n** and **I11** (110 mg) and triethylamine (114 mg, 1.136 mmol) in 2 mL of dry THF, under nitrogen. The mixture was stirred for 12 h at room temperature, after which the solvent was removed under reduced pressure with protection from moisture. The residue was dissolved in 2 mL of dry methylene chloride and cannulated under a positive nitrogen pressure to a flask containing 0.113 g of Eschenmoser's salt. Triethylamine (66.5 mg, 65.9 mmol) was added, and the mixture was stirred for 3 h at room temperature. The reaction mixture was concentrated down to a small volume and applied to the top of a CC-7 silica column. The column was eluted with 20:80 ether–hexane to give 110 mg of a slightly yellow oil: IR (neat) 3040, 2960, 2820, 2780, 1770, 1750, 1440, 1250, 1095, 1035, 850 cm^{-1}; NMR (360 MHz, $CDCl_3$) 6.25 (1 H, m), 5.87 (2 H, m), 5.75 (1 H, m), 4.76 (1 H, m), 4.5 (1 H, m), 3.775 and 3.750 (6 H, 2 s), 3.0 and 2.84 (2 H, AB q, J = 13.5 Hz), 2.3 (6 H, s), 0.075 (9 H, s).

General Procedure for Quaternization of Amines I7. A solution of the amine and methyl iodide (15 equiv) in methylene chloride or anhydrous ether was stirred for 2 days. The precipitated salt was filtered and recrystallized from methanol–ethyl acetate. Yields exceeded 75% in all cases.

1-[Bis(methoxycarbonyl)((trimethylammonio)methyl)methoxy]-2-propene Iodide (I8a): mp >260 °C; NMR (90 MHz, $(CD_3)_2SO$–$CDCl_3$) 6.0 (1 H, m), 5.5–5.2 (2 H, m), 4.25 (4 H, m), 3.86 (6 H, s), 3.25 (9 H, s).

1-[Bis(methoxycarbonyl)((trimethylammonio)methyl)methoxy]-3,3-dideuterio-2-propene Iodide (I8b): mp >260 °C; NMR (90 MHz, $(CD_3)_2SO$–$CDCl_3$) 5.93 (1 H, br), 4.23 (4 H, overlapping d and s), 3.8 (6 H, s), 3.16 (9 H, s).

1-[Bis(methoxycarbonyl)((trimethylammonio)methyl)methoxy]-1,1-dideuterio-2-propene Iodide (I8c): mp >260 °C; NMR (90 MHz, $(CD_3)_2SO$–$CDCl_3$) 5.96 (1 H, dd, J = 17, 8 Hz), 5.5–5.2 (2 H, m), 4.2 (2 H, s), 3.85 (6 H, s), 3.18 (9 H, s).

1-[Bis(methoxycarbonyl)((trimethylammonio)methyl)methoxy]-3-phenyl-2-propene Iodide (I8d): mp 153 °C dec; NMR (90 MHz, $(CD_3)_2SO$–$CDCl_3$) 7.4 (5 H, m), 6.86–6.1 (2 H, m), 4.53 (2 H, d, J = 6 Hz), 4.35 (2 H, s), 3.96 (6 H, s), 3.5 (9 H, br s).

1-[Bis(methoxycarbonyl)((trimethylammonio)methyl)methoxy]-2-phenyl-2-propene Iodide (I8e): mp 161 °C dec; NMR (90 MHz, $(CD_3)_2SO$–$CDCl_3$) 7.43 (5 H, m), 5.53 and 5.4 (2 H, br s), 4.8 (2 H, br s), 4.23 (2 H, br s), 3.96 (6 H, s), 3.23 (9 H, s).

1-[Bis(methoxycarbonyl)((trimethylammonio)methyl)methoxy]-1-phenyl-2-propene Iodide (I8f): mp 165 °C dec; NMR (90 MHz, $(CD_3)_2SO$–$CDCl_3$) 7.36 (5 H, br s), 6.06 (1 H, m), 6.65 (1 H, d, J = 6 Hz), 5.3–5.0 (2 H, m's), 4.26 (2 H, distorted d), 3.86 (3 H, s), 3.46 (3 H, s), 3.36 (9 H, br s).

1-[Bis(methoxycarbonyl)((trimethylammonio)methyl)methoxy]-1-(*p*-methoxyphenyl)-2-propene Iodide (I8g): mp 169–170 °C dec; NMR (90 MHz, $(CD_3)_2SO$–$CDCl_3$) 7.3 (2 H, d, J = 9 Hz), 6.9 (2 H, d, J = 9 Hz), 6.1 (1 H, m), 5.6 (1 H, d, 6 Hz), 5.15 (2 H, m), 4.2 (2 H, br s), 3.8 (6 H, 2 s), 3.5 (3 H, s), 3.3 (9 H, br s).

1-[Bis(methoxycarbonyl)((trimethylammonio)methyl)methoxy]-1-[(*p*-trifluoromethyl)phenyl]-2-propene Iodide (I8h): mp 177–177.5 °C dec; NMR (360 MHz, $(CD_3)_2SO$–$CDCl_3$) 7.4 (2 H, d, J = 9 Hz), 7.25 (2 H, d, J = 9 Hz), 6.8 (1 H, m), 5.5 (1 H, d, J = 7 Hz), 5.1 (1 H, d, J = 11 Hz), 4.9 (1 H, d, J = 18 Hz), 4.15 (2 H, AB q), 3.6 (3 H, s), 3.22 and 3.0 (12 H, 2 s).

1-[Bis(methoxycarbonyl)((trimethylammonio)methyl)methoxy]-2-cyclohexene Iodide (I8i): mp 164–164.5 dec; NMR (360 MHz, $(CD_3)_2SO$–$CDCl_3$) 5.85 (1 H, m), 5.72 (1 H, m), 4.49 (1 H, m), 4.13 and 4.07 (2 H, AB q, J = 14.5 Hz), 3.84 and 3.832 (6 H, 2 s), 3.2 (9 H, s), 2.1–1.5 (6 H, m).

1-[Bis(methoxycarbonyl)((trimethylammonio)methyl)methoxy]-2,4-cyclohexadiene Iodide (I8l): mp > 243 °C; NMR (90 MHz, $(CD_3)_2SO$–$CDCl_3$) 6.26–5.80 (4 H, m), 4.8–4.6 (1 H, m), 4.16 (2 H, s), 3.93 (6 H, s), 3.53 (9 H, s), 2.6–2.45 (~2 H, m overlapping with Me_2SO–d_6 signal).

1-[Bis(methoxycarbonyl)((trimethylammonio)methyl)methoxy]-2,4-pentadiene Iodide (I8m): mp 133–134 °C dec; NMR (360 MHz, $(CD_3)_2SO$–$CDCl_3$) 6.40–6.2 (2 H, m), 5.76 (1 H, dt, J = 14.4, 6.1 Hz), 5.24 (1 H, d, J = 16.97 Hz), 5.12 (1 H, d, J = 10.5 Hz), 4.258 (2 H, d, J = 6.1 Hz), 4.178 (2 H, s), 3.823 (6 H, s), 3.207 (9 H, s).

General Procedure for Thermolysis of I8 in Me_2SO to Enol Pyruvates. A solution of **I8** (200 mg) in wet Me_2SO (1.5 mL of Me_2SO/20 μL of H_2O) was heated at 80 °C for 1 h. The mixture was diluted with water (10 mL) and extracted with ether. The ether extracts were washed with brine and dried over magnesium sulfate. Concentration under reduced pressure gave the desired products **I3** contaminated by a little of the 3,3-shift products (the only exception was **I3d**).

2-(Methoxycarbonyl)-3-oxa-1,5-hexadiene (I3a): NMR (CCl_4, 360 MHz) 5.95 (1 H, m), 5.45 (1 H, dd, J = 18, 2 Hz), 5.26 and 5.23 (2 H, d, J = 2.5 and dd, J = 10, 2 Hz), 4.5 (1 H, J = 2.5 Hz), 4.28 (2 H, complex d), 3.75 (3 H, s); IR (neat) 3070, 3010, 2920, 1730, 1620, 1435, 1320, 1255, 1200, 1165, 1030 cm^{-1}; m/e = 142.0635, calcd 142.0630.

6,6-Dideuterio-2-(methoxycarbonyl)-3-oxa-1,5-hexadiene (I3b): NMR (CCl_4, 360 MHz) 5.95 (1 H, br), 5.28 (1 H, d, J = 2.5 Hz), 4.5 (1 H, d, J = 2.5 Hz), 4.27 (2 H, d, J = 5 Hz), 3.75 (3 H, s).

4,4-Dideuterio-2-(methoxycarbonyl)-3-oxa-1,5-hexadiene (I3c): NMR (CCl_4, 360 MHz) 5.8 (1 H, dd, J = 18, 10 Hz), 5.4 (1 H, dd, J = 18, 2 Hz), 5.3 and 5.27 (2 H, d, J = 2.5, and d, J = 2 Hz), 4.54 (1 H, d, J = 2.5 Hz), 3.79 (3 H, s).

2-(Methoxycarbonyl)-6-phenyl-3-oxa-1,5-hexadiene (I3d): NMR (CCl_4, 90 MHz) 7.25 (5 H, m), 6.7–6.1 (2 H, m), 5.25 (1 H, d, J = 2 Hz), 4.53 (1 H, d, J = 2 Hz), 4.4 (2 H, d, J = 6 Hz), 3.73 (3 H, s).

General Procedure for Hydrolytic Decarboxylative Elimination of I8 to Enol Pyruvates. Aqueous 2 M sodium hydroxide (1.2 equiv) was added to an ice-cooled solution of **I8** in 2 mL of 9:1 Me_2SO–water. The mixture turned cloudy after stirring for 90 min. After dilution with water workup was as described above.

2-(Methoxycarbonyl)-6-phenyl-3-oxa-1,5-hexadiene (I3d): isolated in 85% yield (see spectral data above).

2-(Methoxycarbonyl)-5-phenyl-3-oxa-1,5-hexadiene (I3e): isolated in 85% yield; NMR (CCl_4, 90 MHz) 7.35 (5 H, m), 5.6–5.3 (3 H, 2 br s and d, J = 3 Hz), 4.6 (3 H, br s), 3.75 (3 H, s).

2-(Methoxycarbonyl)-4-phenyl-3-oxa-1,5-hexadiene (I3f): isolated in 85% yield [obtained as 4:1 mixture of **I3f** and its 3,3-shift product, **I9f** (see below)]; NMR (CCl_4, 90 MHz) 7.36 (5 H, br s), 6.06 (1 H, m), 5.4–5.1 (4 H, m's), 4.5 (1 H, d, J = 2 Hz), 3.8 (3 H, s).

2-(Methoxycarbonyl)-4-(*p*-methoxyphenyl)-3-oxa-1,5-hexadiene (I3g): isolated in 85% yield [obtained as 2:1 mixture of **I3g** and its 3,3-shift product, **I9g** (see below)]; NMR (CCl_4, 220 MHz) 7.13 (d, J = 7.5 Hz), 6.75 (d, J = 7.5 Hz), 5.9 (m), 5.25–5.1 (4 H, m), 4.5 (1 H, d, J = 3 Hz), 3.75 (s).

2-(Methoxycarbonyl)-4-[(*p*-trifluormethyl)phenyl]-3-oxa-1,5-hexadiene (I3h): isolated in 80% yield [obtained as 13:1 mixture of **I3h** and its 3,3-shift product, **I9h** (see below); NMR (CCl_4 220 MHz) 7.63 (2 H, d, J = 7.5 Hz), 7.5 (2 H, d, J = 7.5 Hz), 5.9 (1 H, m), 5.4–5.2 (4 H, m's), 4.5 (1 H, d, J = 3 Hz), 3.8 (3 H, s).

1-[[1-(Methoxycarbonyl)ethenyl]oxy]-2-cyclohexene (I3i): isolated in 85% yield; NMR (360 MHz, $CDCl_3$) 5.95 (1 H, m), 5.81 (1 H, m), 5.41 (1 H, d, J = 2.5 Hz), 4.65 (1 H, d, J = 2.16), 4.59 (1 H, m), 3.78 (3 H, s), 2.17–1.58 (6 H, m); IR (neat) 3040, 2950, 1735, 1620, 1440, 1305, 1200, 1170, 1020, 925 cm^{-1}; m/e = 182.0956, calcd 182.0943.

***trans*-1-Hydroxy-2-[[1-(methoxycarbonyl)ethenyl]oxy]-3-cyclohexene (I3j).** A solution of **I3k** (shown below) (45 mg, 0.16 mmol) in 2 mL of ethanol was heated at 55 °C for 3 h with a catalytic amount of pyridinium *p*-toluenesulfonate (10 mg). The solvent was removed; the residue was dissolved in 30% ether–hexane and filtered through a short pad of silica gel. Removal of the solvent under reduced pressure gave the product as a light yellow oil (30 mg, 95% yield): IR (neat) 3420, 3120, 3020, 2940, 2910, 2825, 1720, 1620, 1430, 1380–1020 cm^{-1}; NMR (360 MHz, $CDCl_3$) 5.80 (1 H, m), 5.62 (1 H, m), 5.41 (1 H, d, J = 2.5 Hz), 4.77 (1 H, d, J = 2.5 Hz), 4.40 (1 H, m), 3.94 (1 H, m), 3.78 (3 H, s), 3.35 (1 H, br), 2.20 (2 H, m), 2.00 (1 H, m), 1.70 (1 H, m); m/e (M – H_2O) = 180.0774, calcd 180.0786.

2-[[1-(Methoxycarbonyl)ethenyl]oxy]-1-[(tetrahydropyranyl)oxy]-3-cyclohexene (I3k). A solution of **I7k** (100 mg, 0.26 mmol) and methyl iodide (0.24 mL, 3.9 mmol) in 4 mL of methylene chloride was stirred at room temperature for 12 h. The solvent was removed; the solid residue was dissolved in Me_2SO containing a few drops of water and cooled in an ice bath. Aqueous 2 N sodium hydroxide (0.142 mL, 0.28 mmol) was added, and the mixture was stirred for 90 min. The mixture was diluted with water and extracted with 3 × 5 mL of ether. The combined ether extracts were washed twice with water, dried, filtered, and concentrated to give the product as a colorless oil: IR (neat) 3120, 3020, 2920, 2860, 2830, 1725, 1610, 1430, 1380–970 cm^{-1}; NMR (90 MHz, CCl_4) 6.0–5.5 (2 H, m), 5.3 (1 H, deformed d), 4.85–4.65 (2 H, m and d, J = 2 Hz), 4.15–3.7 (5 H, m with 2 s at 3.73 and 3.70), 3.53–3.3 (1.5 H*, m) (* should integrate to 1 H and 10 H, respectively), 2.3–1.33 (11 H*, m), (* should integrate to 1 H and 10 H, respectively).

1-[[1-(Methoxycarbonyl)ethenyl]oxy]-2,4-cyclohexadiene (I3l). A solution of **I8l** (50 mg, 0.117 mmol) in 1 mL of Me_2SO containing 8 drops of water was cooled to 0 °C in an ice bath, then 76 μL of 2 N sodium hydroxide (0.15 mmol) was added, and the mixture was stirred at 0 °C for 10 min. The mixture was diluted with 2 mL of −78 °C methanol and then chromatographed at −78 °C (CC-7 silica gel, 100 mL of 3:7 ether–pentane precooled to −78 °C was used). The eluate was collected in a −78 °C-cooled flask, and the solvent was removed under vacuum at −65 °C. The residue was dissolved in newly melted deuteriochloroform and transferred to an NMR tube cooled in a dry ice–acetone bath. The NMR spectrum was recorded in a probe cooled to −15 °C. The amount present was estimated to be 3 mg (14% yield) by integration against a weighed amount of mesitylene added to the NMR tube: NMR (360 MHz) 6.15 (1 H, m), 6.03 (1 H, m), 5.90 (2 H, m) 5.426 (1 H, d, J = 2.5 Hz), 4.73 (1 H, m), 4.655 (1 H, d, J = 2.5 Hz), 3.77 (3 H, s), 2.70 (1 H, m), 2.53 (1 H, m).

1-[[1-(Methoxycarbonyl)ethenyl]oxy]-2,4-pentadiene (I3m): isolated in 86% yield; NMR (360 MHz, $CDCl_3$) 6.41–6.29 (2 H, m), 5.90–5.82 (1 H, m), 5.39 (1 H, d, J = 2.5 Hz), 5.25 (1 H, d, J = 16.6 Hz), 5.15 (1 H, d, J = 9.74 Hz), 4.63 (1 H, d, J = 2.88 Hz), 4.38 (2 H, d, J = 5.8 Hz), 3.81 (3 H, s). IR (neat) 3100, 3005, 2960, 2860, 1735, 1625, 1440, 1325, 1200, 1170, 1010, 800 cm^{-1}. m/e = 168.0789; calcd 168.0786.

***trans*-6-Hydroxy-5-[[1-(methoxycarbonyl)ethenyl]oxy]-1,3-cyclohexadiene (I3n).** An aqueous solution of citric acid (20 mg in 1 mL of water) was added to **I7o** (30 mg, 0.081 mmol), and the mixture was stirred vigorously for 10 min. Methylene chloride was added, and with vigorous stirring the mixture was neutralized with 2 N sodium hydroxide. After separation of the layers, the aqueous phase was saturated with sodium chloride and extracted with methylene chloride. The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. Prior

to chromatography, the crude reaction product displayed spectra characteristics of **I7n** [IR (neat) 3470, 3050, 2960, 2830, 2780, 1740, 1440, 1260, 1200, 1140 cm^{-1}; NMR (360 MHz, $CDCl_3$) 6.00–5.80 (4 H, m), 4.75 and 4.49 (2 H, AB q, J = 13.7 Hz), 3.81 and 3.78 (6 H, 2 s), 3.35 and 2.87 (2 H, AB q, J = 14 Hz), 2.265 (6 H, s)]. The residue was applied to the top of a CC-7 silica column (200–320 mesh). The column was successively eluted with 10 mL of 1:9 ether–hexane, 10 mL of 3:7 ether–hexane, and 20 mL of 5:5 ether–hexane. The second and third eluates were combined and concentrated, and the residue was rechromatographed (1 g CC-7 silica, 35:65 ether–hexane) to give 10 mg (60% yield) of the desired product: IR (neat) 3440, 3050, 2960, 2860, 1740, 1625, 1445, 1210, 1175, 1075, 1030 cm^{-1}; NMR (360 MHz, $CDCl_3$) 5.98–5.82 (4 H, m), 5.48 (1 H, d, J = 3.4 Hz), 4.81 (2 H, s), 4.76 (1 H, d, J = 3.4 Hz), 3.82 (3 H, s), 2.8 (1 H, br s, exchangeable with D_2O); NMR (360 MHz, 9:1 $(CD_3)_2SO$–D_2O) 6.05–5.7 (4 H, m), 5.32 (1 H, d, J = 2.9 Hz), 4.83 (1 H, d, J = 2.9 Hz), 4.7 (1 H, d of m, J = 8.77 Hz), 4.35 (1 H, d of m, J = 8.77 Hz), 3.68 (s, not integrated due to presence of a neighboring large water peak); m/e = 196.0746, calcd 196.0735.

Product Characterization. Methyl 2-Oxo-5-hexenoate (I9a): NMR (360 MHz, CCl_4) 5.85 (1 H, m), 5.15 (1 H, d of m, J = 16 Hz), 5.03 (1 H, d of m, J = 11 Hz), 3.87 (3 H, s), 2.96 (2 H, t, J = 7.2 Hz), 2.39 (2 H, q, J = 7.2 Hz).

Methyl 4,4-Dideuterio-2-oxo-5-hexenoate (I9b): NMR (220 MHz, CCl_4) 5.80 (1 H, dd, J = 17, 10 Hz), 5.05 (2 H, m), 3.82 (3 H, s), 2.90 (2 H, br s).

Methyl 6,6-Dideuterio-2-oxo-5-hexenoate (I9c): NMR (220 MHz, CCl_4) 5.75 (1 H, br s), 3.80 (3 H, s), 2.91 (2 H, t, J = 7.5 Hz), 2.3 (2 H, q, J = 7.5 Hz).

Methyl 2-Oxo-2-phenyl-5-hexenoate (I9d): NMR (220 MHz, CCl_4) 7.25–7.10 (5 H, m), 5.90 (1 H, ddd, J = 17, 11, 6 Hz), 5.00 (2 H, m), 3.87 (1 H, q, J = 6 Hz), 3.76 (3 H, s), 3.14 (2 H, 7 lines, ABC pattern).

Methyl 2-Oxo-5-phenyl-5-hexenoate (I9e): NMR (90 MHz, CCl_4) 7.33 (5 H, m), 5.30 (1 H, s), 5.1 (1 H, s), 3.80 (3 H, s), 2.86 (4 H, m).

Methyl 2-Oxo-6-phenyl-5-hexenoate (I9f): NMR (90 MHz, CCl_4) 7.26 (5 H, m), 6.56–6.10 (2 H, m), 3.76 (3 H, s), 2.93 (2 H, distorted t, J = 6 Hz), 2.50 (2 H, distorted q, J = 6 Hz).

Methyl 2-Oxo-6-(*p*-methoxyphenyl)-5-hexenoate (I9g): NMR (220 MHz, CCl_4) 7.16 (2 H, d, J = 7.5 Hz), 6.73 (2 H, d, J = 7.5 Hz), 6.32 (1 H, d, J = 15 Hz), 6.00 (1 H, m), 3.77 (3 H, s), 3.72 (3 H, s), 2.83 (2 H, t, J = 7.5 Hz), 2.44 (2 H, q, J = 7.5 Hz).

Methyl 2-Oxo-6-[(*p*-trifluoromethyl)phenyl]-5-hexenoate (I9h): NMR (360 MHz, $CDCl_3$) 7.54 (2 H, d, J = 8.3 Hz), 7.41 (2 H, d, J = 8.3 Hz), 6.47 (1 H, d, J = 16.2 Hz), 6.31 (1 H, m), 3.88 (3 H, s), 3.06 (2 H, t, J = 7.2 Hz), 2.58 (2 H, q, J = 7.2 Hz).

Methyl (1,2,3,4-Tetrahydrophenyl)pyruvate (I9i): NMR (360 MHz, CCl_4) 5.72 (1 H, m), 5.49 (1 H, m), 3.85 (3 H, s), 2.82 (2 H, d, J = 6.8 Hz), 2.69 (1 H, m), 1.97 (2 H, m), 1.83 (1 H, m), 1.68 (1 H, m), 1.57 (1 H, m), 1.15 (1 H, m).

Methyl (1,4-Dihydrophenyl)pyruvate (I9l): NMR (360 MHz, $CDCl_3$) 5.78 (2 H, m), 5.62 (2 H, m), 3.87 (3 H, s), 3.3 (1 H, m), 2.93 (2 H, d, J = 6.8 Hz), 2.64 (2 H, m). Aromatization of **I9l** with DDQ in benzene gave methyl phenylpyruvate: NMR (90 MHz, CCl_4, mixture of keto and enol forms, integrations approximate) 7.76–7.63 (2 H, m), 7.4–7.1 (4 H, m), 6.4 (2 H, s), 3.98 (4 H, s), 3.86 (3 H, s), 3.73 (1 H, s).

Methyl 2-Oxo-4-vinyl-5-hexenoate (I9m): NMR (360 MHz, $CDCl_3$) 5.75 (2 H, m), 5.07 (4 H, m), 3.86 (3 H, s), 3.38 (1 H, m), 2.985 (2 H, d, J = 7.2 Hz).

Methyl 4-Hydroxy(1,4-dihydrophenyl)pyruvate (I9n): NMR (360 MHz, $CDCl_3$) 5.97 (2 H, m), 5.88 (2 H, m), 4.53 (1 H, m), 3.87 (3 H, s), 3.27 (1 H, m), 2.90 (2 H, d, J = 7.22 Hz).

Kinetic Isotope Effect Measurements. Samples of enol pyruvates **I3a–c** (20 mg) were dissolved in 0.6 mL of reagent grade cyclohexane, and the resulting solutions were placed in three different NMR tubes. The three tubes were heated at the same time in a boiling chloroform bath. At intervals all three tubes were withdrawn and immediately placed in an ice bath. Three aliquots (0.5 μL each) were withdrawn from each tube and injected into a Varian 3700 gas chromatograph equipped with a 30-m long DB-5 capillary column and a Hewlett-Packard 3390A integrator. Helium was used as a carrier gas. The injector port temperature was held at 200 °C, and the oven temperature was 60 °C. Under these conditions no thermal rearrangement of the enol pyruvates was observed. The different integrations were reproducible to within 1% and in the majority of cases were better than 0.5%. In a second experiment the individual rate constants were reproduced to within 2%.

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General Methods. Proton NMR spectra were recorded on a Varian EM-390 (90-MHz) CW spectrometer or on Varian CFT20 (80-MHz) or Bruker WM300 (300 MHz) Fourier transform spectrometers. Absorptions are reported in ppm downfield (δ) from tetramethylsilane (Me_4Si). Proton decoupled ^2H NMR spectra were recorded on a Bruker WM300 Fourier transform spectrometer (46 MHz), by using deuteriated solvent as an internal standard. ^{13}C NMR spectra were recorded at 22.55 MHz on a JEOL JNM-FX90Q Fourier transform spectrometer. For ^{13}C spectra absorptions are reported in ppm downfield (δ) from Me_4Si, by using the solvent $CDCl_3$ as internal standard (δ = 77.0).

Infrared spectra were recorded on a Perkin-Elmer 681 infrared spectrophotometer. Low-resolution mass spectra were obtained on an AEI MS-902 mass spectrometer by using electron impact (EI) ionization at 70 eV or chemical ionization (CI) by using isobutane as the reagent gas. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

Preparative high-pressure liquid chromatography (HPLC) was performed on a Waters PrepLC/System 500 (Prep 500) by using a refractive index detector. Analytical HPLC was performed on a Perkin-Elmer Series 3B solvent delivery system coupled to a LC-75 variable wavelength UV–vis detector and Spectraphysics digital integrator. Solvents were filtered immediately prior to use; the Burdick and Jackson "distilled in glass" hexane was used without further purification, and Mallinckrodt ethyl acetate was distilled before use.

Preparative gas chromatography was performed by using an Aerograph Auto Prep A-700 instrument equipped with a thermal conductivity detector. Helium was used as the carrier gas, and the column was a SE-30.

Materials. Unless otherwise noted, all reagents were commercially available and were used as received. Tetrahydrofuran (THF) was distilled from sodium benzophenone immediately prior to use. Amines and benzene were distilled from calcium hydride. Dry methanol was prepared by distillation from $Mg(OCH_3)_2$ and stored over 3Å sieves. Methylene chloride was distilled from calcium hydride immediately prior to use. Hexamethylphosphoramide (HMPA) was dried with calcium hydride or *n*-butyllithium, vacuum distilled, and stored over 4Å sieves.

Procedure. Unless otherwise noted, all reactions were performed under an atmosphere of dry nitrogen or argon. Standard syringe techniques were used to transfer reagents. Flash chromatography refers to rapid medium-pressure chromatography on silica gel (32–63 μ mesh), according to the method of Still.[40] The phrase "worked up in the usual manner" means that the organic solvent extracts were combined, dried over magnesium sulfate, vacuum filtered, and concentrated on a Büchi Rotovapor rotary evaporator at aspirator pressure (ca. 15 torr) with heating supplied by a warm water bath. Last traces of solvent were removed with a Welch Duo-Seal vacuum pump at room temperature. Analytical thin-layer chromatography (TLC) was performed on Merck precoated silica gel 60F-254 plates with fluorescent indicator. Compounds were visualized with UV light, iodine (I_2), or phosphomolybdic acid (PMA) dip.

Dimethyl Diazomalonate. Triethylamine (13.7 mL, 0.10 mol) was added to a solution of tosylazide (18.90 g, 0.096 mol) and dimethyl malonate (11.4 mL, 0.10 mol) in benzene (85 mL) at room temperature and was allowed to stir for 15 h. The mixture was vacuum filtered and concentrated in vacuo to give a yellow oil to which was added hexane (30 mL), and the resulting mixture was vacuum filtered and concentrated in vacuo. Vacuum distillation (58–70 °C, ca. 0.7 torr) gave dimethyl diazomalonate as a yellow oil contaminated with ca. 10% dimethyl malonate (estimated yield 65%). Portions of the mixture were purified by flash chromatography (25% ethyl acetate in hexane): IR (neat) 2135 (s), 1760 (s), 1740 (s), 1690 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.82 (s).

3-[Bis(methoxycarbonyl)methoxy]cyclohexene (C18). To a catalytic amount of rhodium acetate and 2-cyclohexenol (100 μL, 1.01 mmol) dissolved in benzene (1.0 mL) at reflux was added dimethyl diazomalonate (163 mg, 1.03 mmol) in benzene (300 μL), dropwise, over 10 min. The mixture was brought to reflux for 35 min before cooling. The solution was concentrated in vacuo and flash chromatographed (4:1 hexanes:ethyl acetate) to afford 181.9 mg of a clear liquid (79%): IR (neat) 1750 (s), 1435 (m), 1120 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.85 (m, 2 H), 4.65 (s, 1 H), 4.05 (m, 1 H), 3.78 (s, 6 H), 2.2–1.5 (m, 6 H); CIMS, m/e (rel intensity) 149 (100), 81 (85).

3-[1,1-Bis(methoxycarbonyl)-2-(dimethylamino)ethoxy]cyclohexene (C19). To a mixture of **C18** (156 mg, 0.684 mmol) and Eschenmoser's salt (184 mg, 0.996 mmol) suspended in 15 mL of CH_2Cl_2 was added triethylamine (150 μL, 1.1 mmol) at room temperature. The mixture became homogeneous over 5 min and was allowed to stir for 18 h. The reaction mixture was concentrated in vacuo, dissolved in $CHCl_3$ (10 mL), and washed with saturated sodium bicarbonate (2 × 5 mL). The combined aqueous washes were backwashed with $CHCl_3$ (2 × 5 mL). The extracts were worked up in the usual manner to give an oil which was

(40) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

flash chromatographed (4:1 hexanes:ethyl acetate) to afford 162 mg of a clear liquid (83%): IR (neat) 1740 (s), 1435 (w), 1100 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.75 (br s, 2 H), 4.35 (m, 1 H), 3.78 (s, 6 H), 2.90 (s, 2 H), 2.30 (s, 6 H), 2.1–1.5 (br m, 6 H); CIMS, *m/e* (rel intensity) 286 (M + 1, 95), 206 (100).

3-[1-(Methoxycarbonyl)ethenoxy]cyclohexene (C11). A solution of **C19** (108 mg, 0.379 mmol) and CH_3I (240 μL, 3.86 mmol) in CH_2Cl_2 (7.5 mL) was stirred at room temperature for 25 h. This solution was concentrated in vacuo to give a yellow solid that was dissolved in methanol (4.1 mL) and cooled to 0 °C. To this solution was added, over 15 min, aqueous NaOH (0.1 M, 4.1 mL). The resulting solution was stirred at 0 °C for 3 h, and then the methanol was removed in vacuo. The remaining aqueous solution was extracted with $CHCl_3$ (5 × 5 mL). The extracts were worked up in the usual manner to give an oil which was flash chromatographed (7% ethyl acetate in hexanes) yielding 40.2 mg of a clear liquid (58%): IR (neat) 1740 (s), 1620 (s), 1440 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.86 (m, 2 H), 5.41 (d, 1 H, J = 2.5 Hz), 4.65 (d, 1 H, J = 2.5 Hz), 4.50 (m, 1 H), 3.78 (s, 3 H), 2.2–1.5 (br m, 6 H).

***endo*-Bromo-6-oxabicyclo[3.2.1]octa-7-one (C20).** To a solution of 8-*endo*-bromo-6-oxabicyclo[3.2.1]oct-2-en-7-one[41] (399 mg, 1.97 mmol) in ethanol (2.0 mL) was added 10% Pd on carbon (52.6 mg). This suspension was rapidly stirred under an atmosphere of hydrogen for 6 h, filtered through Celite, and concentrated in vacuo giving an orange oil that was flash chromatographed (35% EtOAc in hexanes) affording 368 mg of a white solid (91%): mp 60–63 °C; IR ($CHCl_3$) 1790 (s), 965 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.86 (d, 1 H, J = 3.3 Hz), 4.21 (s, 1 H), 2.95 (d, 1 H, J = 3.4 Hz), 2.14 (m, 1 H), 2.06 (m, 1 H), 1.77 (m, 4 H); CIMS, *m/e* (rel intensity) 205 (M + 1, 99, ^{79}Br), 207 (M + 1, 100, ^{81}Br).

3-Hydroxy-1-cyclohexenecarboxylic Acid, Methyl Ester (C21). To a solution of **C20** (361 mg, 1.76 mmol) in dry methanol (8.0 mL) at room temperature was added a methanol solution of $LiOCH_3$ (0.48 M, 3.8 mmol). The mixture was allowed to stir for 18 h before concentrating in vacuo. Water (5 mL) was added, extracted with $CHCl_3$ (5 × 5 mL), and washed with brine (5 mL). The extracts were worked up in the usual manner to give a yellow oil that was flash chromatographed (35% EtOAc in hexanes) affording 187 mg of **C21** (68%): IR ($CHCl_3$) 2950 (m), 1715 (s), 1650 (w), 1440 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.86 (br s, 1 H), 4.33 (br s, 1 H), 3.73 (s, 3 H), 1.9–1.5 (br m, 6 H); CIMS, *m/e* (rel intensity) (M + 1, 100), 139 (88); EIMS, *m/e* (rel intensity) 156 (M, 19), 97 (100).

3-[Bis(methoxycarbonyl)methoxy]-1-cyclohexenecarboxylic Acid, Methyl Ester (C22). To a catalytic amount of rhodium acetate and **C21** (143 mg, 0.915 mmol) dissolved in benzene (1.0 mL) at reflux was added dimethyl diazomalonate (146 mg, 0.923 mmol) in benzene (300 μL), dropwise, over 5 min. The mixture was kept at reflux for 35 min before cooling. The solution was concentrated in vacuo and flash chromatographed (7:3 hexanes:ethyl acetate) to afford 247 mg of a clear liquid (95%): IR (neat) 1750 (s), 1655 (w), 1440 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.91 (br s, 1 H), 4.67 (s, 1 H), 4.18 (br s, 1 H), 3.80 (s, 3 H), 3.79 (s, 3 H), 3.72 (s, 3 H), 2.25 (m, 2 H), 1.86 (m, 2 H), 1.68 (m, 2 H); CIMS, *m/e* (rel intensity) 287 (M + 1, 1), 139 (100); EIMS, *m/e* (rel intensity) 155 (100), 132 (63), 100 (23).

3-[2-(Dimethylamino)-1,1-bis(methoxycarbonyl)ethoxy]-1-cyclohexenecarboxylic Acid, Methyl Ester (C23). To a mixture of **C22** (247 mg, 0.866 mmol) and Eschenmoser's salt (243 mg, 1.31 mmol) suspended in 20 mL of CH_2Cl_2 was added triethylamine (190 μL, 1.4 mmol) at room temperature. The mixture became homogeneous over 5 min and was allowed to stir for 18 h. The reaction mixture was concentrated in vacuo, dissolved in $CHCl_3$ (20 mL), and washed with saturated sodium bicarbonate (3 × 5 mL). The combined aqueous washes were backwashed with $CHCl_3$ (3 × 5 mL). The extracts were worked up in the usual manner to give an oil which was flash chromatographed (35% EtOAc in hexanes) to afford 291 mg of a clear liquid (97%): IR (neat) 1770 (m), 1720 (s), 1650 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.88 (br s, 1 H), 4.49 (br s, 1 H), 3.80 (s, 3 H), 3.77 (s, 3 H), 3.70 (s, 3 H), 2.89 (s, 2 H), 2.27 (s, 6 H), 2.2 (br m, 2 H), 1.8 (br m, 2 H), 1.6 (br m, 2 H); CIMS; *m/e* (rel intensity) 344 (M + 1, 100).

1-(Methoxycarbonyl)-3-[1-(methoxycarbonyl)ethenoxy]cyclohexene (C10). A solution of **C23** (288 mg, 0.838 mmol) and CH_3I (500 μL, 8.03 mmol) in CH_2Cl_2 (15 mL) was stirred at room temperature for 20 h. This solution was concentrated in vacuo to give a yellow solid that was dissolved in methanol (7.0 mL) and cooled to 0 °C. To this solution was added, over 15 min, aqueous NaOH (0.1 M, 6.7 mL). The resulting solution was stirred at 0 °C for 3 h, and then the methanol was removed in vacuo. The remaining aqueous solution was extracted with $CHCl_3$ (5 × 5 mL). The extracts were worked up in the usual manner to give an oil which was flash chromatographed (4:1 hexanes:ethyl acetate) yielding 140.5 mg of a clear liquid (91%): IR (neat) 1725 (br s), 1655 (w), 1620 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.90 (br s, 1 H), 5.48 (d, 1 H, J = 2.7 Hz), 4.70 (d, 1 H, J = 2.6 Hz), 4.65 (m, 1 H), 3.75 (s, 3 H), 3.72 (s, 3 H), 2.2 (br m, 2 H), 1.8 (br m, 4 H); CIMS, *m/e* (rel intensity) 241 (M + 1, 37), 209 (66), 139 (100).

5-Hydroxy-3-(methoxycarbonyl)-1,3-cyclohexadiene (C24). To a solution of 8-*endo*-bromo-6-oxabicyclo[3.2.1]oct-2-en-7-one (284.7 mg, 1.402 mmol) in THF (1.5 mL) at room temperature was added aqueous NaOH (3.0 mL, 1 M). This solution was stirred for 15 h before the THF was removed in vacuo. To the remaining aqueous solution was added HMPA (3.0 mL) followed by CH_3I (400 μL, 6.43 mmol). The mixture was stirred for 32 h at room temperature before extracting with ether (5 × 5 mL). The extracts were washed with 5% $NaHCO_3$ (5 mL), water (2 × 5 mL), and brine (5 mL). The extracts were worked up in the usual manner to give a yellow liquid that was flash chromatographed (1:1 ethyl acetate:hexanes, with 0.5% Et_3N) to afford 107.6 mg of a clear liquid (50%): IR (neat) 3400 (br m), 1720 (s), 1645 (w), 1590 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.91 (d, 1 H, J = 4.7 Hz), 6.45 (br d, 1 H, J = 9.8 Hz), 5.97 (td, 1 H, J = 3.8, 9.8 Hz), 4.45 (ddd, 1 H, J = 4.8, 7.4, 14.8 Hz), 3.78 (s, 3 H), 2.50 (m, 2 H), 1.65 (d, 1 H, J = 7.7 Hz); CIMS, *m/e* (rel intensity) 155 (M + 1, 100), 137 (100); EIMS, *m/e* (rel intensity) 154 (45), 95 (100), 77 (47).

3-(Methoxycarbonyl)-5-[bis(methoxycarbonyl)methoxy]-1,3-cyclohexadiene (C25). To a catalytic amount of rhodium acetate and **C24** (101 mg, 0.652 mmol) dissolved in benzene (1.0 mL) at reflux was added dimethyl diazomalonate (106 mg, 0.670 mmol) in benzene (300 μL), dropwise, over 1 min. The mixture was brought to reflux for 35 min before cooling. The solution was concentrated in vacuo and flash chromatographed (4:1 hexane:ethyl acetate) to give 97.3 mg of a clear liquid (53%): IR (neat) 1765 (s), 1745 (s), 1720 (s), 1645 (w), 1590 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.86 (br d, 1 H, J = 4.3 Hz), 6.42 (br d, 1 H, J = 9.8 Hz), 5.98 (td, 1 H, J = 4.2, 9.8 Hz), 4.62 (s, 1 H), 4.46 (dt, 1 H, J = 4.3, 8.2 Hz), 3.78 (s, 6 H), 3.77 (s, 3 H), 2.61 (dddd, 1 H, J = 2.0, 4.4, 7.9, 18.8 Hz), 2.48 (dddd, 1 H, J = 2.2, 4.0, 8.5, 18.8 Hz); CIMS, *m/e* (rel intensity) 285 (M + 1, 1), 149 (62), 137 (100).

3-(Methoxycarbonyl)-5-[1-(methoxycarbonyl)ethenoxy]-1,3-cyclohexadiene (C7). To a mixture of **C25** (87 mg, 0.306 mmol) and Eschenmoser's salt (145 mg, 0.789 mmol) suspended in 6.5 mL of CH_2Cl_2 was added triethylamine (120 μL, 0.86 mmol) at room temperature. The mixture became homogeneous over 5 min and was allowed to stir for 21 h. The reaction mixture was concentrated in vacuo, dissolved in $CHCl_3$ (10 mL), and washed with saturated sodium bicarbonate (2 × 5 mL). The combined aqueous washes were backwashed with $CHCl_3$ (2 × 3 mL). The extracts were worked up in the usual manner to give an oil which was dissolved in CH_2Cl_2 (7.5 mL), and CH_3I (250 μL, 4.023 mmol) was added. The resulting solution was stirred at room temperature for 25 h. This solution was concentrated in vacuo to give a yellow solid that was dissolved in methanol (3.2 mL) and cooled to 0 °C. To this solution was added, over 15 min, aqueous NaOH (0.1 M, 3.2 mL). The resulting solution was stirred at 0 °C for 3 h, and then the methanol was removed in vacuo. The remaining aqueous solution was extracted with $CHCl_3$ (5 × 5 mL). The extracts were worked up in the usual manner to give an oil which was flash chromatographed (15% ethyl acetate in hexane, at 4 °C) yielding 43 mg of a solid (59%): mp 51–56 °C; IR (neat) 1725 (s), 1650 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.87 (br d, 1 H, J = 3.7 Hz), 6.44 (br d, 1 H, J = 9.8 Hz), 6.01 (td, 1 H, J = 4.6, 9.7 Hz), 5.47 (d, 1 H, J = 2.8 Hz), 4.92 (dt, 1 H, J = 3.7, 9.4 Hz), 4.68 (d, 1 H, J = 2.9 Hz), 3.68 (s, 3 H), 3.67 (s, 3 H), 2.58 (m, 2 H); CIMS, *m/e* (rel intensity) 239 (M + 1, 46), 137 (100), 103 (57).

3-(Methoxycarbonyl)-5-ethenoxycyclohexadiene (C29). To a solution of **C25** (58 mg, 0.375 mmol) in ethyl vinyl ether (5.0 mL) at room temperature was added mercuric acetate (104 mg, 0.325 mmol), and the solution was allowed to stir for 20 h before addition of acetic acid (5 μL, 0.09 mmol). The resulting solution was stirred for 3 h at room temperature before petroleum ether was added (5 mL) and washed with aqueous KOH (1 M, 2 × 1 mL) and water (2 × 1 mL). The organic solution was dried over Na_2SO_4, vacuum filtered, and concentrated to give an oil that was flash chromatographed (5% ethyl acetate in hexane with 0.5% triethyl amine) yielding 49 mg of a liquid (73%): IR (neat) 1725 (s), 1635 (m), 1615 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.88 (br d, 1 H, J = 4.1 Hz), 6.44 (br d, 1 H, J = 8.0 Hz), 6.16 (dd, 1 H, J = 6.7, 14.1 Hz), 5.99 (td, 1 H, J = 6.4, 9.0 Hz), 4.71 (dt, 1 H, J = 4.1, 8.6 Hz), 4.31 (dd, 1 H, J = 2.0, 14.2 Hz), 4.08 (dd, 1 H, J = 2.0, 6.7 Hz), 3.77 (s, 3 H), 2.51 (m, 2 H); CIMS, *m/e* (rel intensity) 181 (M + 1, 18), 137 (100); UV (methanol) λ 203 nm (ϵ 12 000), 275 nm (ϵ 2300).

4-Hydroxy-5-(phenylselenyl)cyclohexene (C26). The solution resulting from addition of $NaBH_4$ (22 mg, 0.581 mmol) to a suspension of diphenyl diselenide (77 mg, 0.245 mmol) in ethanol (1.0 mL) was added to 1,4-cyclohexadiene monoepoxide (41 mg, 0.429 mmol) in ethanol (1.0 mL) at room temperature and stirred for 23 h. Acetic acid (5%, 3 mL) was added, and the solution was extracted with $CHCl_3$ (4 × 3 mL). The

(41) Ikota, N.; Ganem, B. *J. Am. Chem. Soc.* **1978**, *100*, 351–352.

extracts were worked up in the usual manner to give an oil which was flash chromatographed (15% ethyl acetate in hexanes) yielding 86 mg of a clear liquid (78%): IR (neat) 3420 (br s), 1730 (w), 1660 (m), 1560 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.59 (m, 2 H), 7.30 (m, 3 H), 5.54 (m, 2 H), 3.69 (m, 1 H), 3.21 (dt, 1 H, J = 5, 10 Hz), 2.6 (br m, 2 H), 2.2 (br m, 2 H); CIMS, m/e (rel intensity) 255 (M + 1, 27, ^{80}Se), 253 (M + 1, 11, ^{78}Se), 251 (M + 1, 9, ^{76}Se), 239 (23, ^{82}Se), 237 (100, ^{80}Se), 235 (57, ^{78}Se), 234 (20, ^{77}Se), 233 (24, ^{76}Se).

4-Ethenoxy-5-(phenylselenyl)cyclohexene (C27). To a solution of **C26** (90 mg, 0.356 mmol) in ethyl vinyl ether (4.0 mL) at room temperature was added mercuric acetate (102 mg, 0.321 mmol), and the solution was allowed to stir for 42 h before addition of acetic acid (7 μL, 0.13 mmol). The resulting solution was stirred for 3 h at room temperature before petroleum ether was added (5 mL) and washed with aqueous KOH (1 M, 2 × 1 mL) and water (2 × 1 mL). The organic solution was dried over Na_2SO_4, vacuum filtered, and concentrated to given an oil that was flash chromatographed (5% ethyl acetate in hexane with 0.5% triethyl amine) yielding 70 mg of a liquid (70%): IR (neat) 1730 (w), 1635 (s), 1615 (m), 1580 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.57 (m, 2 H), 7.27 (m, 3 H), 6.30 (dd H, J = 7.6, 15.1 Hz), 5.62 (s, 2 H), 4.22 (dd, 1 H, J = 1.5, 15.1 Hz), 4.07 (dt, 1 H, J = 7.1, 7.1 Hz), 4.00 (dd, 1 H, J = 1.5, 7.6 Hz), 3.59 (dt, 1 H, J = 5.0, 7.1 Hz), 2.66 (m, 2 H), 2.23 (m, 2 H).

4-*exo*-[(Methoxyethoxy)methoxy]-8-*endo*-bromo-6-oxabicyclo-[3.2.1]oct-7-one (C28). To a solution of 4-*exo*-[(methoxyethoxy)methoxy]-8-*endo*-bromo-6-oxabicyclo[3.2.1]oct-2-en-7-one (249 mg, 0.81 mmol) in ethanol (10.0 mL) was added 10% Pd on carbon (37.5 mg). This suspension was rapidly stirred under an atmosphere of hydrogen for 19 h, filtered through Celite, and concentrated in vacuo giving a white solid that was not chromatographed (98%): IR (neat) 1795 (s), 1035 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.85 (m, 1 H), 4.76 (m, 3 H), 4.10 (m, 1 H), 3.70 (m, 2 H), 3.55 (m, 2 H), 3.37 (s, 3 H), 2.94 (br s, 1 H), 1.9 (br m, 2 H); CIMS, m/e (rel intensity) 309 (M + 1, 6, ^{79}Br), 311 (M + 1, 6, ^{81}Br), 89 (100).

4-[(Methoxyethoxy)methoxy]-3-hydroxy-1-cyclohexenecarboxylic Acid, Methyl Ester (C29). To a solution of **C28** (114 mg, 0.37 mmol) in dry methanol (2.0 mL) at room temperature was added a methanol solution of $LiOCH_3$ (1.58 M, 0.8 mmol). The mixture was allowed to stir for 18 h before concentrating in vacuo. Water (10 mL) was added, extracted with $CHCl_3$ (5 × 10 mL), and washed with brine (10 mL). The extracts were worked up in the usual manner to give **C29** which was not purified but used directly in the next reaction: ^1H NMR ($CDCl_3$) δ 6.74 (br s, 1 H), 4.82 (s, 2 H), 4.24 (br s, 1 H), 3.87 (m, 1 H), 3.72 (s, 3 H), 3.70 (m, 2 H), 3.56 (m, 2 H), 3.37 (s, 3 H), 2.5–1.6 (br m, 4 H).

4-[(Methoxyethoxy)methoxy]-3-[bis(methoxycarbonyl)methoxy]-1-cyclohexenecarboxylic Acid, Methyl Ester (C30). To a catalytic amount of rhodium acetate and **C29** (85 mg, 0.327 mmol) dissolved in benzene (1.2 mL) at reflux was added dimethyl diazomalonate (81 mg, 0.511 mmol) in benzene (350 μL), dropwise, over 1 h. The mixture was kept at reflux for 45 min before cooling. The solution was concentrated in vacuo and flash chromatographed (45% ethyl acetate in hexanes) to afford 115 mg of a clear liquid (50% from starting lactone): IR (neat) 1770 (s), 1750 (s), 1720 (s), 1660 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.83 (br s, 1 H), 4.93 (s, 1 H), 4.79 (q, 2 H, J = 7.1 Hz), 4.18 (br s, 1 H), 3.86 (m, 1 H), 3.80 (s, 3 H), 3.79 (s, 3 H), 3.75 (s, 3 H), 3.72 (m, 2 H), 3.52 (m, 2 H), 3.37 (s, 3 H), 2.4 (br m, 2 H), 2.01 (m, 1 H), 1.65 (m, 1 H); CIMS, m/e (rel intensity) 391 (M + 1, 1), 385 (10), 161 (100).

4-[(Methoxyethoxy)methoxy]-3-[1-(methoxycarbonyl)ethenoxy]-1-cyclohexenecarboxylic Acid, Methyl Ester (C31). To a mixture of **C30** (73 mg, 0.187 mmol) and Eschenmoser's salt (98 mg, 0.618 mmol) suspended in 2.0 mL of CH_2Cl_2 was added triethylamine (110 μL, 0.79 mmol) at room temperature. The mixture became homogeneous over 5 min and was allowed to stir for 28 h. The reaction mixture was diluted with $CHCl_3$ (30 mL) and washed with water (3 × 5 mL). The extracts were worked up in the usual manner to give an oil which was dissolved in CH_2Cl_2 (3.5 mL), and CH_3I (275 μL, 4.42 mmol) was added. The resulting solution was stirred at room temperature for 22 h. This solution was concentrated in vacuo to give a white foam that was dissolved in methanol (3.0 mL) and cooled to 0 °C. To this solution was added, over 15 min, aqueous NaOH (0.1 M, 1.8 mL). The resulting solution was stirred at 0 °C for 4 h, and then the methanol was removed in vacuo. The remaining aqueous solution was diluted with water (6.0 mL) and extracted with $CHCl_3$ (5 × 5 mL). The extracts were worked up in the usual manner to give an oil which was flash chromatographed (35% ethyl acetate in hexane) yielding 47 mg of **C31** (72%): IR (neat) 1725 (s), 1660 (w), 1620 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.76 (br s, 1 H), 5.48 (d, 1 H, J = 2.8 Hz), 4.81 (s, 2 H), 4.80 (d, 1 H, J = 2.9 Hz), 4.61 (m, 1 H), 3.98 (m, 1 H), 3.77 (s, 3 H), 3.72 (s, 3 H), 3.71 (m, 2 H), 3.54 (m, 2 H), 3.37 (s, 3 H), 2.4 (br m, 2 H), 2.05 (m, 1 H), 1.78 (m, 1 H); CIMS, m/e (rel intensity) 137 (10), 115 (100), 89 (91).

4-Hydroxy-3-[1-(methoxycarbonyl)ethenoxy]-1-cyclohexenecarboxylic Acid, Methyl Ester (C32). A solution of $TiCl_4$ in pentane (0.9 M, 350 μL) was added, dropwise, to **C31** (46 mg, 0.133 mmol) in CH_2Cl_2 (1.0 mL) at −30 °C and allowed to stir at this temperature for 30 min before addition of aqueous ammonia (10%, 10 mL). The mixture was extracted with CH_2Cl_2 (5 × 10 mL) and worked up in the usual manner. Flash chromatography (35% ethyl acetate in hexanes) gave 13 mg of starting **C31** (29%) and 16 mg of **C32** (46%): IR (neat) 3440 (br m), 1720 (s), 1655 (w), 1620 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.74 (br s, 1 H), 5.56 (d, 1 H, J = 2.7 Hz), 4.87 (d, 1 H, J = 2.7 Hz), 4.47 (br d, 1 H, J = 4.3 Hz), 3.96 (m, 1 H), 3.80 (s, 3 H), 3.77 (s, 3 H), 2.55 (m, 1 H), 2.40 (m, 1 H), 2.10 (m, 1 H), 1.70 (m, 1 H); CIMS, m/e (rel intensity) 257 (M + 1, 2), 155 (100), 103 (32), 97 (39).

8-*endo*-Bromo-6-oxabicyclo[3.2.1]oct-2-en-7-one-*exo*-4-*d* (C33). A mixture of 4-*exo*-bromo-8-*endo*-bromo-6-oxabicyclo[3.2.1]oct-2-en-7-one (838 mg, 2.97 mmol) and $NaBD_3CN$ (393 mg, 5.97 mmol) in HMPA (3.0 mL) was heated to 95 °C for 1.5 h. After having been cooled to room temperature, water (30 mL) was added, and the solution was extracted with ether (6 × 30 mL). The combined organic extracts were washed with water (3 × 30 mL) and brine (2 × 30 mL), CH_2Cl_2 (100 mL) was added, dried over $MgSO_4$, vacuum filtered, and concentrated in vacuo. The resulting oil was flash chromatographed (20% ethyl acetate in hexanes) to give 570 mg of a 1:2 mixture of **C33**: 8-*endo*-bromo-7-oxabicyclo[3.2.1]oct-2-en-8-one-*exo*-4-*d*, which was separated by preparative HPLC (10% ethyl acetate in hexane, retention time = 36.5 min) to yield 147 mg of a white solid (25%): IR (KBr) 3040 (w), 2910 (w), 1785 (s), 1630 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.93 (ddd, 1 H, J = 1.4, 7.2, 9.3 Hz), 5.79 (ddd, 1 H, J = 1.1, 3.3, 9.3 Hz), 4.86 (dd, 1 H, J = 1.2, 1.4 Hz), 4.37 (s, 1 H), 3.27 (d, 1 H, J = 7.2 Hz), 2.58 (br s, 1 H); ^2H NMR ($CHCl_3$) δ 2.64; CIMS, m/e (rel intensity) 204 (M + 1, 100, ^{79}Br), 206 (M + 1, 95, ^{81}Br).

3-(Methoxycarbonyl)-5-ethenoxy-1,3-cyclohexadiene-*trans*-6-*d* (C9-*trans*-*d*). To a solution of **C33** (147 mg, 0.722 mmol) in THF (750 μL) at 0 °C was added aqueous NaOH (1.5 mL, 1 N). This solution was stirred for 21 h at room temperature before the THF was removed in vacuo. The remaining aqueous solution was cooled to 0 °C, and HMPA (1.5 mL) was added followed by CH_3I (250 μL, 4.0 mmol). The mixture was allowed to warm to room temperature and was stirred for 20 h at room temperature before water (25 mL) was added. The mixture was extracted with ether (5 × 20 mL). The extracts were washed with water (3 × 20 mL) and brine (2 × 20 mL) and then worked up in the usual manner to give an oil (52 mg) that was dissolved in ethyl vinyl ether (2.0 mL). To this, at room temperature, was added mercuric acetate (104 mg, 0.325 mmol), and the mixture was allowed to stir for 20 h before addition of acetic acid (10 μL, 0.2 mmol). The resulting solution was stirred for 3.5 h at room temperature before petroleum ether was added (10 mL) and washed with aqueous KOH (1 M, 2 × 2 mL) and water (2 mL). The organic solution was dried over Na_2SO_4, vacuum filtered, and concentrated to give an oil that was flash chromatographed (5% ethyl acetate in hexane) yielding 26 mg of a liquid (20%): IR (neat) 1725 (s), 1640 (m), 1620 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.87 (br d, 1 H, J = 4.0 Hz), 6.44 (br d, 1 H, J = 9.6 Hz), 6.31 (dd, 1 H, J = 6.6, 14.2 Hz), 5.99 (dd, 1 H, J = 4.2, 9.7 Hz), 4.71 (dd, 1 H, J = 3.7, 9.4 Hz), 4.28 (dd, 1 H, J = 2.0, 14.2 Hz), 4.08 (dd, 1 H, J = 2.0, 6.7 Hz), 3.77 (s, 3 H), 2.51 (m, 1 H); ^2H NMR ($CHCl_3$) δ 2.50; CIMS m/e (rel intensity) 136 (38), 74 (100).

4-*exo*-Hydroxy-8-*endo*-bromo-6-oxabicyclo[3.2.1]oct-7-one (C34). To a solution of 8-*endo*-bromo-6-oxabicyclo[3.2.1]oct-2-ene-4,7-dione[41] (37 mg, 0.170 mmol) in methanolic $CeCl_3$ (0.4 M, 425 μL) at room temperature was added $NaBH_4$ (7 mg, 0.17 mmol) in 2 portions. After 5 min water (1 mL) was added, and the solution was extracted with ether (5 × 1 mL). The extracts were worked up in the usual manner to give a mixture of **C34** and the endo alcohol **C35** which was separated by flash chromatography (35% ethyl acetate in hexanes) giving 16 mg of **C35** (42%) and 17 mg of **C34** (47%): ^1H NMR ($CDCl_3$) δ 6.15 (dd, 1 H, J = 7.4, 9.3 Hz), 5.88 (ddd, 1 H, J ≈ 1.7, 3.4, 9.2 Hz), 4.73 (ddd, 1 H, J = 1.5, 1.5, 3.0 Hz), 4.58 (s, 1 H), 4.45 (td, 1 H, J = 3.3, 5.6 Hz), 3.30 (d, 1 H, J = 7.3 Hz), 2.13 (d, 1 H, J = 5.7 Hz). In a similar fashion, using $NaBD_4$, the corresponding deuteriated allylic alcohol was obtained in 38% yield: ^1H NMR ($CDCl_3$) δ 6.15 (dd, 1 H, J = 7.4, 9.3 Hz), 5.88 (dd, 1 H, J = 1.7, 9.2 Hz), 4.73 (s, 1 H), 4.58 (s, 1 H), 3.30 (d, 1 H, J = 7.3 Hz), 2.13 (s, 1 H); ^2H NMR ($CHCl_3$) δ 4.40.

4-*endo*-Hydroxy-8-*endo*-bromo-6-oxabicyclo[3.2.1]oct-2-en-7-one-*exo*-4-*d* (C35-*d*). To a solution of 8-*endo*-bromo-6-oxabicyclo[3.2.1]-oct-2-ene-4,7-dione (1.75 g, 8.06 mmol) in THF (75 mL) at −10 °C was added $Li(t\text{-}BuO)_3AlD$ in THF (ca. 0.67 M, 18 mL) over 5 min. After 10 min acetic acid (5%, 200 mL) was added, and the solution was extracted with CH_2Cl_2 (5 × 150 mL). The combined organic solutions were washed with saturated $NaHCO_3$ (150 mL) and worked up in the usual manner to give a solid that was flash chromatographed to give 1.58

g of **C35-*d*** (89%): ^{1}H NMR ($CDCl_3$) δ 6.13 (dd, 1 H, J = 7.2, 9.3 Hz), 5.88 (dd, 1 H, J = 1.5, 9.5 Hz), 4.99 (s, 1 H), 4.35 (s, 1 H), 3.28 (d, 1 H, J = 7.0 Hz), 1.4 (s, 1 H); ^{2}H NMR ($CHCl_3$) δ 4.44.

8-*endo*-Bromo-6-oxabicyclo[3.2.1]oct-2-en-7-one-*endo*-4-*d* (C36). To a solution of **C34** (423 mg, 1.92 mmol) in pyridine (3.0 mL) at 0 °C was added methanesulfonyl chloride (145 μL, 1.87 mmol) over 3 min. The solution was allowed to stir at 0 °C for 20 h before addition of water (5 mL) and extraction with ethyl acetate (5 × 5 mL). The combined organics were washed with 10% HCl (5 mL) and worked up in the usual manner to give a solid that was dissolved in HMPA (6.5 mL). To this solution was added $NaBH_4$ (505 mg, 8.04 mmol), and the mixture was heated to 120 °C for 3 h. After having been cooled to room temperature, water (75 mL) was added, and the solution was extracted with ether (5 × 75 mL). The combined organic extracts were washed with water (3 × 75 mL) and brine (2 × 75 mL), CH_2Cl_2 (200 mL) was added, dried over $MgSO_4$, vacuum filtered, and concentrated in vacuo. The resulting oil was flash chromatographed (20% ethyl acetate in hexanes) to give 280 mg of a 1:2 isomeric mixture, which was separated by preparative HPLC (10% ethyl acetate in hexane, retention time = 36.5 min) to yield 81 mg of a white solid (23%): IR (KBr) 1785 (s), 1640 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.93 (ddd, 1 H, J = 2.3, 7.2, 9.3 Hz), 5.79 (ddd, 1 H, J = 1.5, 9.3 Hz), 4.83 (d, 1 H, J = 1.3 Hz), 4.37 (s, 1 H), 3.27 (d, 1 H, J = 7.2 Hz), 2.63 (br s, 1 H); ^{2}H NMR ($CHCl_3$) δ 2.59; CIMS, m/e (rel intensity) 204 (M + 1, 100, ^{79}Br), 206 (M + 1, 97, ^{81}Br).

3-(Methoxycarbonyl)-5-ethenoxycyclohexadiene-*cis*-6-*d* (C9-*cis*-*d*). To a solution of **C36** (154 mg, 0.7564 mmol) in THF (800 μL) at 0 °C was added aqueous NaOH (1.6 mL, 1 N). This solution was stirred for 21 h at room temperature before the THF was removed in vacuo. The remaining aqueous solution was cooled to 0 °C, and HMPA (1.5 mL) was added followed by CH_3I (250 μL, 4.0 mmol). The mixture was allowed to warm to room temperature and was stirred for 20 h at room temperature. Water (25 mL) was added, and the mixture was extracted with ether (5 × 20 mL). The extracts were washed with water (3 × 20 mL), and brine (2 × 20 mL). The extracts were worked up in the usual manner to give an oil (52 mg) that was dissolved in ethyl vinyl ether (2.0 mL). To this, at room temperature, was added mercuric acetate (97 mg, 0.31 mmol), and the mixture was allowed to stir for 20 h before addition of acetic acid (10 μL, 0.2 mmol). The resulting solution was stirred for 3.5 h at room temperature before petroleum ether was added (10 mL) and washed with aqueous KOH (1 M, 2 × 2 mL) and water (2 mL). The organic solution was dried over Na_2SO_4, vacuum filtered, and concentrated to give an oil that was flash chromatographed (5% ethyl acetate in hexane) yielding 30 mg of a liquid (23%): IR (neat) 1725 (s), 1640 (m), 1620 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.87 (br d, 1 H, J = 4.1 Hz), 6.45 (td, 1 H, J = 1.7, 9.6 Hz), 6.23 (dd, 1 H, J = 6.7, 14.2 Hz), 5.99 (dd, 1 H, J = 4.0, 9.7 Hz), 4.70 (dd, 1 H, J = 4.0, 8.3 Hz), 4.30 (dd, 1 H, J = 2.0, 14.2 Hz), 4.08 (dd, 1 H, J = 2.0, 6.7 Hz), 3.77 (s, 3 H), 2.49 (m, 1 H); ^{2}H NMR ($CHCl_3$) δ 2.53; CIMS, m/e (rel intensity) 138 (19), 137 (10), 75 (100).

Chorismic Acid (C1). Chorismic acid was isolated from a mutant strain of *Klebsiella pneumoniae* (ATCC no. 25306) by the procedure of Gibson et al.[13] and Haslam et al.[42] It was purified by recrystallization from ethyl acetate/hexane: ^{1}H NMR (acetone-d_6) 6.95 (m, 1 H), 6.29 (dt, J = 9.0, 2.0 Hz, 1 H), 5.99 (dd, 1 H, J = 10.2, 3.1 Hz, 1 H), 5.45 (d, J = 1.5 Hz, 1 H), 4.98 (dd, J = 10.2, 2.5 Hz), 4.89 (d, J = 1.5 Hz), 4.65 (dt, J = 11.7, 1.5 Hz, 1 H).

Dimethyl Chorismate (C6). Dimethyl chorismate was synthesized by the method of Haslam et al.[42] reacting chorismic acid with diazomethane. A solution of diazomethane was prepared as follows. In a 50-mL Erlenmeyer flask was placed KOH pellets (approximately 3 g, 0.05 mol) which were subsequently dissolved in water (ca. 15 mL). Ether (15 mL) was added, and the mixture was stirred in an ice bath. To it was slowly added *N*-methyl-*N*-nitrosourea (1 g). When all the urea had dissolved, the mixture was poured through a plastic funnel into a separatory funnel (free from scratches and with a Teflon stopcock), and the layers were separated. The yellow ethereal layer containing the diazomethane was stored over KOH pellets in a 25-mL Erlenmeyer flask in an ice bath while it was titrated and used. Titration was accomplished by reacting 2 mL of the diazomethane solution, by using a gas tight syringe fitted with a Teflon needle, with a known excess amount of benzoic acid (ca. 140 mg) dissolved in 10 mL of ether which was then back titrated with a 0.111 M solution of NaOH by using a phenolphthalein indicator. Chorismic acid (315 mg, 1.4 mmol) was dissolved in ether (20 mL) in a 50-mL, round-bottom flask under nitrogen at −78 °C. Diazomethane solution (2 equiv, 2.8 mmol) was added via the same syringe. The solution turned yellow upon addition and was then warmed to room temperature. The solution was concentrated, and the yellow oil was taken up in a small amount of ether for purification by preparative TLC: solvent, $CHCl_3$:methanol, 98:2, R_f 0.45; ^{1}H NMR (acetone-d_6) 6.90 (m, 1 H), 6.32 (dt, J = 9, 2 Hz, 1 H), 6.02 (dd, J = 10, 3 Hz, 1 H), 5.46 (d, J = 1.5 Hz, 1 H), 5.02 (dd, J = 10, 3 Hz, 1 H), 4.91 (d, J = 1.5, 1 H), 4.70 (dt, J = 12, 1.5 Hz, 1 H), 3.89 (s, 3 H), 3.80 (s, 3 H).

***trans*,*trans*-3,5-Heptadienone (C37).** Sorbic acid (5.0 g, 0.04 mol) was weighed into a 500-mL, three-necked flask and dissolved in ca. 200 mL of dry ether. The flask was fitted with a condenser and a 125-mL addition funnel and placed under argon. A solution of methyllithium in ether (100 mL of a 0.8 M solution, 0.08 mol) was transferred via cannula to the addition funnel. The methyllithium was added slowly to the solution of sorbic acid with stirring. The solution immediately turned cloudy white. After the addition of 1 equiv, it then turned light brown. When addition was completed, the solution was stirred for an additional 30 min. It was then quenched by transferring it to a stirred solution of ice water via cannula. The mixture was poured into a separatory funnel, and the layers were separated. The ethereal layer was washed once with saturated sodium bicarbonate and once with brine and dried ($MgSO_4$). The solution was filtered and concentrated to give a mixture of the desired ketone and tertiary alcohol. Distillation of the residue through a 20-cm Vigreux column failed to separate the ketone instead giving a 1:1 mixture of the ketone and the tertiary alcohol. Purification was accomplished by flash chromatography: solvent, 30% diethyl ether in pentane, 6-cm diameter column, 20-mL fractions analyzed by TLC R_f 0.41 UV; mixed fractions were rechromatographed. Combining and concentrating all the appropriate fractions gave 0.9 g (18%) of a pale yellow oil: 90-MHz ^{1}H NMR ($CDCl_3$) 7.20–6.67 (m, 1 H), 6.25–5.65 (m, 3 H), 2.01 (s, 3 H), 1.75 (d, J = 5 Hz, 3 H).

***trans*, *trans*-3,5-Heptadien-2-ol (C38) from 3,5-Heptadienone.** Lithium aluminum hydride (75 mg, 2 mmol) was weighed into a 50-mL, round-bottom flask and slurried in ether. The flask was fitted with a reflux condenser and placed under argon. An ethereal solution of the 3,5-heptadienone (100 mg, 0.91 mmol in ca. 5 mL of ether) was added to the flask through the condenser via a syringe. The solution began to distill almost immediately upon addition. After addition was completed, the solution was refluxed for 30 min and cooled in ice water. It was quenched by the addition of 0.5 mL of water, 0.5 mL of 2 M NaOH solution, and 1.5 mL of water. The solution was then filtered through Celite and dried ($MgSO_4$). The solution was filtered, and the solvent was stripped off on a rotary evaporator. The pale yellow oil remaining was used crude with no further purification: ^{1}H NMR ($CDCl_3$) 6.13 (dd, J = 15.5, 11 Hz, 1 H), 6.00 (m, 1 H), 5.84–5.51 (m, 2 H), 4.30 (m, 1 H), 1.72 (dd, J = 7, 1 Hz, 3 H), 1.25 (d, J = 7 Hz, 3 H).

***trans*,*trans*-3,5-Heptadien-2-ol (C38) from Methyl Sorbate.** The alcohol was also prepared by the method of Comins et al.[43] The procedure was followed directly by using methyl sorbate (2.5 g, 19.8 mmol), CH_3MgBr (12 mL of a 3.3 M solution in ether, 39.6 mmol), $LiBH_4$ (0.23 g, 9.9 mmol), or $NaBH_4$ (0.75 g, 19.8 mmol) with 18-crown-6 (5.23 g, 19.8 mmol) in THF (100 mL). The alcohol was purified by flash chromatography: solvent, 30% ethyl acetate in hexane, 4-cm column diameter, 25-mL fractions, TLC R_f 0.37.

***trans*,*trans*-4-Methyl-3-oxa-1,5,7-nonatriene (C13).** The procedure of Ireland et al.[14] for the synthesis of vinyl ethers was followed directly by using 3,5-heptadien-2-ol. The compound was purified by flash chromatography: solvent, 10% ether in pentane, TLC R_f 0.79. Additional purification was accomplished by bulb-to-bulb distillation under vacuum at room temperature by using a dry ice–acetone bath (−78 °C) to cool the receiving flask: ^{1}H NMR ($CDCl_3$) 6.31 (dd, J = 12.5, 5 Hz, 1 H), 6.15 (dd, J = 12, 9 Hz, 1 H), 6.02 (m, 1 H), 5.70 (m, 1 H), 5.49 (dd, J = 14, 7.5 Hz, 1 H), 4.31 (m, 1 H), 4.28 (dd, J = 12.5, 2.5 Hz, 1 H), 3.99 (dd, J = 5, 2.5 Hz, 1 H), 1.75 (dd, J = 1.5, 7.5 Hz, 3 H), 1.31 (d, J = 6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 150.3, 131.6, 131.1, 130.6, 130.2, 88.6, 76.1, 21.0, 18.1. Anal. Calcd for $C_9H_{14}O$: C, 78.20; H, 10.22. Found: C, 78.32; H, 9.94.

***trans*,*trans*-2,4-Hexadienol (C39).** Lithium aluminum hydride (0.38 g, 0.01 mol) was weighed into a 50-mL, round-bottom flask equipped with a stirbar and then slurried with 25 mL of ether. The flask was fitted with a reflux condenser, and a 10-mL ethereal solution of sorbic acid (1.12 g, .01 mol) was added via syringe through the top of the condenser. The solution was heated to reflux for 1 h and then cooled to room temperature. The reaction was quenched by the addition of water (0.4 mL), 4 M NaOH solution (0.4 mL), and water (1.2 mL). The solution was then vacuum filtered through a size C frit containing a small amount of Celite and dried over $MgSO_4$. The solution was concentrated, and the colorless oil was purified by flash chromatography: solvent, 30% ethyl acetate in hexane, 4-cm diameter column, 20-mL fractions, R_f 0.29. Concentration of the chromatographic fractions yielded 0.9 g (95%) of

(42) Ife, R. J.; Ball, L. F.; Lowe, P.; Haslam, E. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1776–1783.

(43) Comins, D. L.; Herrick, J. J. *Tetrahedron Lett.* **1984**, *25*, 1321–1324.

a colorless oil: 90-MHz ^{1}H NMR ($CDCl_3$) 6.5–5.3 (m, 4 H), 4.14 (br d, J = 6 Hz, 2 H), 1.74 (d, J = 5.4 Hz, 3 H).

***trans,trans*-3-Oxa-1,5,7-nonatriene (C12).** The procedure of Ireland et al.[14] for the synthesis of vinyl ethers was followed directly by using 2,4-hexadienol. The product was purified by flash chromatography: solvent, 10% ethyl acetate in hexane; TLC R_f 0.61; yield 60%; 300-MHz ^{1}H NMR ($CDCl_3$) 6.44 (dd, J = 13.7, 6.6 Hz, 1 H), 6.23 (dd, J = 15.8, 10.7 Hz, 1 H), 6.05 (m, 1 H), 5.80–5.56 (m, 2 H), 4.30–4.15 (m, 3 H), 4.00 (dd, J = 7.6, 2.5 Hz, 1 H), 1.75 (br d, J = 6.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 151.4, 133.6, 130.6, 130.5, 124.8, 86.9, 68.6, 18.0. Anal. Calcd for $C_8H_{12}O$: C, 77.36; H, 9.75. Found: C, 77.08; H, 9.63.

***trans,trans*-2-Methyl-3,5-heptadien-2-ol (C40).** 2-Methyl-3,5-heptadien-2-ol was acquired as a byproduct from the reaction of sorbic acid and methyllithium to form 3,5-heptadienone. It was separated from the ketone by flash chromatography: solvent, 30% ether in pentane, TLC R_f 0.2; 300-MHz ^{1}H NMR ($CDCl_3$) 6.16 (dd, J = 15, 10 Hz, 1 H), 6.01 (m, 1 H), 5.67 (m, 2 H), 1.74 (dd, J = 6.5, 1 Hz, 3 H), 1.32 (s, 6 H).

***trans,trans*-4,4-Dimethyl-3-oxa-1,5,7-nonatriene (C14).** The procedure of Ireland et al.[14] for synthesis of vinyl ethers was followed directly by using 2-methyl-3,5-heptadien-2-ol. The product was purified by flash chromatography: solvent, 10% ethyl acetate in hexane, TLC R_f 0.66; 300-MHz ^{1}H NMR ($CDCl_3$) 6.33 (dd, J = 12.7, 6.1 Hz, 1 H), 6.23–5.98 (m, 2 H), 5.85–5.67 (m, 1 H), 5.58 (d, J = 14.2 Hz, 1 H), 4.39 (dd, J = 12.7, 1.0 Hz, 1 H), 3.98 (dd, J = 6.1, 1.0 Hz, 1 H), 1.77 (dd, J = 7.1, 1.0 Hz, 3 H), 1.36 (s, 6 H); ^{13}C NMR ($CDCl_3$) 147.3, 135.0, 130.8 (2 carbons), 130.2, 90.1, 77.7, 26.8, 18.1.

***trans,trans*-1-(Trimethylsilyl)-3,5-heptadien-2-ol (C41).** The Grignard reagent from (trimethylsilyl)methyl chloride was prepared as follows. Magnesium turnings (0.25 g, 10 mmol) were placed in a 100-mL, round-bottom flask in 5–10 mL of diethyl ether. The flask was equipped with a Claisen adapter fitted with a condenser and an addition funnel. The system was placed under argon. The (trimethylsilyl)methyl chloride (1.23 g, 10 mmol) was dissolved in 10 mL of ether and placed into the addition funnel. Approximately 25% of the Me_4SiCH_2Cl solution was added to the flask, and the mixture was stirred. If the reaction did not begin, a test tube reaction was started with a freshly crushed piece of magnesium and a drop of Me_4SiCH_2Cl in a small amount of ether. When the test tube solution turned cloudy, its contents were added to the reaction flask where in ca. 5 min the solution began to turn cloudy. The heat was removed, and the remaining solution of the Me_3SiCH_2Cl was added slowly so as to maintain a gentle reflux. When most of the magnesium had reacted, the solution was cooled to room temperature. 3,5-Heptadienal (0.96 g, 10 mmol) was dissolved in ca. 20 mL of ether and placed into the addition funnel. The aldehyde was used without any further purification. The aldehyde solution was added at a rate to promote reflux. When the addition was complete, the solution was heated to 40 °C and refluxed overnight. It was quenched with the addition of 20 mL of water. The layers were separated, and the aqueous phase was extracted once with ether. The ether layers were combined and washed with water, sodium thiosulfite solution, and brine. The solution was dried over $MgSO_4$ and filtered, and the solvent was removed. The residue was purified by flash chromatography: solvent, 25% ether in pentane, 3-cm diameter column, 20-mL fractions. Fractions with TLC R_f 0.38 were collected and stripped of solvent to give 1-(trimethylsilyl)-3,5-heptadien-2-ol (540 mg, 3 mmol) in 30% yield: ^{1}H NMR ($CDCl_3$) 5.9–6.2 (m, 2 H), 5.67 (m, 1 H), 5.54 (dd, J = 8, 15 Hz, 1 H), 4.3 (m, 1 H), 1.73 (d, J = 8, 3 H), 0.8 (m, 2 H), −0.01 (s, 9 H).

***trans,trans*-4-[(Trimethylsilyl)methyl]-3-oxa-1,5,7-nonatriene (C15).** The procedure of Ireland et al.[14] was followed by using 1-(trimethylsilyl)-3,5-heptadien-2-ol (1.10 g, 3.1 mmol). The product was purified by flash chromatography: solvent, 10% ether in pentane, 3-cm diameter column, 15-mL fractions. Fractions with TLC R_f 0.8 were stripped of solvent and further purified by high-vacuum bulb-to-bulb distillation from a 30 °C bath to a −78 °C trap to give a 71% yield of product (0.8 g, 2.2 mmol): ^{1}H NMR (C_6D_6) 6.30 (dd, J = 14.9, 7.4 Hz, 1 H), 5.85–6.13 (m, 2 H), 5.35–5.61 (m, 2 H), 4.48 (dd, J = 14.9, 1.5 Hz, 1 H), 4.23 (m, 1 H), 4.04 (dd, J = 7.4, 1.5 Hz, 1 H), 1.52 (br d, J = 7.4 Hz, 3 H), 1.12 (m, 2 H), 0.04 (s, 9 H). Anal. Calcd for $C_{12}H_{22}OSi$: C, 68.49; H, 10.55. Found: C, 68.14; H, 10.20.

***trans,trans*-3,5-Heptadien-2-ol-2-*d* (C38-*d*).** The procedure followed was the same as that used for 3,5-heptadien-2-ol from methyl sorbate, except using $LiAlD_4$ instead of $LiAlH_4$ or $LiBD_4$ or $NaBD_4$ with 18-crown-6 instead of $LiBH_4$. Since acidic workup produced deuterium scrambling between the 2 and 5 positions, the Grignard reactions were quenched by pouring into ice water and stirring until the ice melted. The mixture was extracted into ether (3 × 30 mL) with some difficulty, and the ether layers were washed with brine and dried over $MgSO_4$. The solution was filtered and purified as for the unlabeled compound: 300-MHz ^{1}H NMR ($CDCl_3$) 6.25 (dd, J = 15.5, 11.4 Hz, 1 H), 6.02 (m, 1 H), 5.70 (m, 1 H), 5.59 (d, J = 15.5 Hz, 1 H), 1.74 (dd, J = 7.8, 1.0 Hz, 3 H), 1.26 (s, 3 H); ^{2}H NMR ($CHCl_3$) 4.30 (s).

***trans,trans*-3,5-Heptadien-2-ol Trimethylacetate Ester (C16).** 3,5-Heptadien-2-ol (49.4 mg, 0.44 mmol) was dissolved in THF under argon in a 50-mL, round-bottom flask equipped with a stir bar. It was cooled to ca. 0 °C in an ice water bath. To it was added *n*-butyllithium (0.33 mL of a 1.3 M solution in hexane, 0.44 mmol) via syringe. The solution was stirred at 0 °C for 1 h. Pivalic anhydride (164 mg, 0.18 mL, 0.88 mmol) was added to the solution via syringe, and the solution was stirred for an additional hour. The reaction was quenched by the addition of water (1 mL). The solution was poured into an ether–water mixture, and the layers were separated, and the aqueous phase was extracted twice more with ether. The organic layers were combined and washed with brine and dried over $MgSO_4$. The solution was filtered and concentrated. The ester was purified by flash chromatography: solvent, 10% ethyl acetate in hexane, TLC R_f 0.61 or 10% ether in pentane, TLC R_f 0.69, 2-cm diameter column, 2-mL fractions. The appropriate fractions were combined and concentrated to give a yellow oil which was further purified by bulb-to-bulb distillation under high vacuum at ca. 30 °C by using a dry ice–acetone trap to cool receiving flask to −78 °C. Isolated product was a clear vs. pale yellow oil in 65% yield: 300-MHz ^{1}H NMR ($CDCl_3$) 6.16 (dd, J = 15.5, 10.4 Hz, 1 H), 5.99 (m, 1 H), 5.71 (m, 1 H), 5.50 (dd, J = 15.5, 6.8 Hz, 1 H), 5.32 (m, 1 H), 1.73 (dd, J = 7.8, 1 Hz, 3 H), 1.26 (d, J = 6.8 Hz, 3 H), 1.17 (s, 9 H); ^{13}C NMR ($CDCl_3$) 173.9, 131.5, 130.6 (2 C), 130.5, 40.1, 27.0, 26.4, 20.0.

Dimethyl 1-[2-Carboxylato-2-propenyl]-1,2-dihydrobenzoate (C42). To a −78 °C solution of lithium isopropylcyclohexylamide (6 mmol) in THF (30 mL) containing HMPA (1 mL) was added methyl 3,6-dihydrobenzoate (neat, 0.8 mL, 6.25 mmol). The resulting dark red solution was stirred 3 min and then transferred via cannula to a stirred solution of methyl 2-(bromomethyl)acrylate (0.95 mL, 7.8 mmol) in THF (40 mL) at −78 °C. Upon completion of addition, the reaction mixture was quenched with acetic acid (1 mL) and poured into water, and the organic layer was separated. The aqueous phase was extracted with ether (3 × 30 mL), and the combined organic layers were washed with 3 M HCl (2 × 30 mL) and saturated $NaHCO_3$ and then dried ($MgSO_4$). Solvent evaporation left an oil which was flash chromatographed (1:9 ethyl acetate:hexanes) to afford 1.049 g (71%) of **C42** as a pale yellow oil: IR (neat) 1730, 1440, 1280, 1205, 1150 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.16 (d, 1 H, J = 1.4 Hz), 5.95–5.65 (m, 4 H), 5.43 (d, 1 H, J = 1.4 Hz), 3.66, 3.59 (2 s, 6 H), 2.68, 2.55 (AB q, 2 H, J = 13.1 Hz), 2.55 (dd, 1 H, J = 18.0, 5.2 Hz), 2.30 (dd, 1 H, J = 18.0, 5.2 Hz); CIMS (isobutane), m/e (rel intensity) 237 (M + 1, 100), 205 (32), 177 (72).

Dimethyl 1-[2-Carboxylato-2-propenyl]-*trans*-3-(phenylseleno)-4-hydroxycyclohex-5-ene-1-carboxylate (C43). A mixture of finely ground silver trifluoroacetate (121 mg, 0.55 mmol) and PhSeCl (85 mg, 0.44 mmol) in CH_2Cl_2 was stirred at room temperature for 15 min and then cooled to −78 °C. To it was quickly added diester **C42** (100 mg, 0.42 mmol) in CH_2Cl_2 (2 mL), and the mixture was warmed to room temperature over 5 h. A saturated solution of K_2CO_3 in 4:1 H_2O:CH_3OH (10 mL) was added followed by concentrated NH_4OH (4 mL). After the silver salts had dissolved, the organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to an oil. Purification by flash chromatography (1:4 ethyl acetate:hexanes) afforded **C43** (96 mg, 55%) as a 3:1 mixture of diastereomers: IR (neat) 3500, 1725, 1630, 1580, 1480, 1430, 1290, 1200, 1160 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.65–7.5 (m, 2 H), 7.35–7.20 (m, 3 H), 6.18 (d, 0.75 H, J = 1.1 Hz), 6.12 (d, 0.25 H, J = 1 Hz), 5.9–5.6 (m, 2 H), 5.44 (s, 0.75 H), 5.32 (s, 0.25 H), 3.97 (d, 1 H, J = 9.3 Hz), 3.69, 3.61 (2 s, 6 H), 3.25–3.1 (m, 1 H), 2.73–2.53 (m, 4 H), 2.32 (d, 0.5 H, J = 12 Hz), 2.03 (t, 0.5 H, J = 12 Hz); CIMS (isobutane), m/e 410 (M + 1, 5), 393 (18), 391 (10), 203 (100).

Dimethyl 1-[2-Carboxylato-2-propenyl]-*trans*-3-(phenylseleninyl)-4-hydroxycyclohex-5-ene-1-carboxylate (C44). To a solution of selenide **C43** (377 mg, 0.92 mmol) in CH_2Cl_2 (40 mL) at 5 °C was added a solution of 30% H_2O_2 (1 mL, 9.9 mmol) in THF (10 mL). After having been stirred 2.5 h at 5 °C, the reaction mixture was washed with saturated aqueous K_2CO_3 (2 × 10 mL), and the combined aqueous layers were back-extracted with CH_2Cl_2 (2 × 10 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated to afford selenoxide m (373 mg, 95%) as a solid mixture of four diastereomers.

Dimethyl Carboprephenate C4 and 4-Epicarboprephenate (C45). A mixture of selenoxides **C44** (365 mg, 0.85 mmol) and diethylamine (0.2 mL, 1.93 mmol) in CH_2Cl_2 (10 mL) was added to hexane (40 mL) at reflux. After 2 h, the solvents were removed, and the resulting yellow oil was purified by flash chromatography (1:4 ethyl acetate:hexanes) to afford pure 4-epicarboprephenate (36 mg) as a solid along with several mixed fractions containing **C4**. These were combined and rechromatographed by using 5:15:80 1-butyl alcohol:$CHCl_3$:hexanes to yield additional 4-epicarboprephenate (61 mg, total yield 46%) and **C4** (35 mg,

16%). Carboprephenate exhibited the following spectral characteristics: IR (neat) 3400, 1730, 1630, 1440, 1290, 1240, 1200, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.11 (d, 1 H, J = 1.2 Hz), 5.94 (dd, 2 H, J = 10.5, 3.8 Hz), 5.87 (dd, 2 H, J = 10.5, 1.0 Hz), 4.29 (br s, 1 H), 3.64 (s, 6 H), 2.72 (s, 2 H); CIMS (isobutane), m/e (rel intensity) 253 (M + 1, 2), 203 (100).

Kinetics. The tubes used in the NMR kinetic studies were 7-in. No. 528PP 5-mm o.d. NMR tubes with approximately 3 in. of a 6-mm o.d. Pyrex tubing fused to the end. They were soaked in a concentrated ammonia solution for a minimum of 1 h and then oven dried (ca. 100 °C) for at least 12 h. Deuteriated solvents used were reagent grade quality with no further purification. Prior to each quantitative kinetic run on a new compound an approximate reaction half-life was determined as follows: a small amount (ca. 5 mg) of the compound was dissolved in the appropriate solvent (0.5 mL), degassed (vide infra), and sealed. It was then heated (75 °C unless otherwise noted) in an oil or water bath. ^1H NMR spectra were taken at various times and an approximate reaction half-life (and products) was noted.

All quantitative NMR studies were performed on a Bruker WM300 (300 MHz) Fourier transform spectrometer. For the quantitative studies, a solution of the compound was prepared and distributed among the appropriate number of NMR tubes. The tubes were degassed by 5 freeze–pump–thaw cycles, by using liquid nitrogen. When the solvent was aqueous methanol, a dry–ice/acetone bath, which caused the sample to become viscous but not to freeze, was used in place of liquid nitrogen. While in the dry–ice/acetone bath, the sample was exposed to a manifold that had been evacuated with a mercury diffusion pump. While the sample was being warmed, the manifold would be reevacuated. After degassing and sealing, the sample was heated in a Neslab Exacal EX-200 constant temperature bath (filled with watger or ethylene glycol), a Tamson Holland regulated temperature bath (silicone oil), or in the probe of the Bruker WM300. The temperature of the baths was noted on a NBS standardized total immersion thermometer by using the standard stem correction.[44] The NMR probe temperature was measured by using a Fluke 2190A digital thermometer (copper/constantan thermocouple). Samples were removed from the bath at the appropriate times and quenched (−78 °C or 0 °C bath), and an NMR spectrum was obtained. In some cases, the sample was then returned to the bath to obtain further data points. The proton relaxation times (τ) were measured by using an inverse-recovery delay program (Bruker software). Once τ was determined for all the protons in the reaction mixture, a value of 5 times the largest τ was used as the relaxation delay between pulses. The relative concentrations were determined by comparison of the integration values for the compound of interest against an internal standard or against the sum of starting material and product(s). The integrals of each resonance were plotted five times and measured with a ruler. An average value and standard deviation (σ) were then calculated. The weighted values ($1/\sigma^2$) were used to determine rate constants. Activation parameters were determined by nonlinear least-squares fit of the data to the Arrhenius or Eyring equations.

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Acyclic Stereocontrol in Catalyzed Intramolecular Diels–Alder Cyclizations Leading to Octahydronaphthalenecarboxaldehydes

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Abstract: Diels–Alder cyclizations of 2-methyl-2,8,10-undecatrienals (I) were effected at −23 to −13 °C in the presence of alkylaluminum chlorides to afford the endo products II and III in high yield. An OTBS grouping at C-7 exhibited high diastereocontrol in favor of the syn isomer III whereas a C-4 methyl substituent showed complete preference for the anti isomer (IV → V). On the other hand, C-7 methoxy, benzyloxy, or methoxymethyl substituents displayed no diastereomeric preference. Methyl substitution at C-6 in the trienal likewise played a negligible role in diastereocontrol. Both *syn*- and *anti*-4,6-dimethyl-2,8,10-undecatrienal cyclizations were controlled by the C-4 methyl substituent. The major stereochemical trends of this study were predicted from molecular modeling calculations performed on the boat–chair conformation of the product via Still's Model program. These findings are directly applicable to synthetic work on the hydronaphthalene subunit of the macrocyclic natural products chlorothricin and kijanimicin.

In the course of synthetic studies on the macrocyclic antitumor antibiotics chlorothricolide, kijanolide, and tetronolide (Figure 1)[1] we found that 7-alkoxy-2,8,10-undecatrienals such as I (Table I) undergo facile endo selective Lewis acid catalyzed Diels–Alder cyclization to give trans fused octahydronaphthalene aldehydes II and III related to chlorothricolide.[2,3] Interestingly, the TBS ether (I, R^2 = *tert*-butyldimethylsilyl) afforded mainly the syn[4]

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