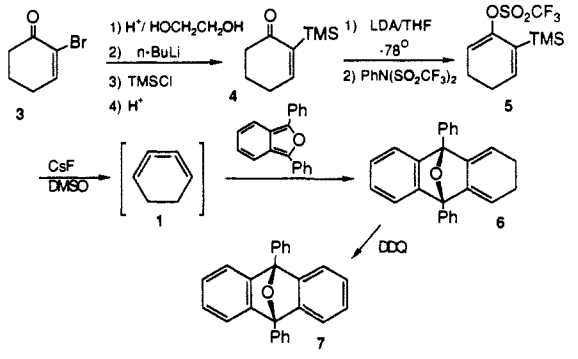
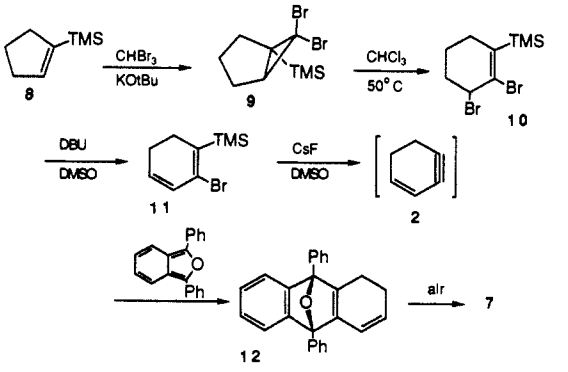
Scheme I



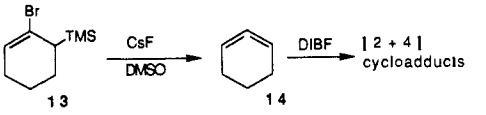
Scheme II



at 25 °C in the presence of diphenylisobenzofuran (DIBF) afforded crystalline adduct **6** in 24% yield after chromatography. The structure of **6** (C_s symmetry) was confidently assigned from spectral data and DDQ oxidation to **7**.[9] Ample literature precedent supports the conclusion that **6** is formed from [2 + 4] cycloaddition of cumulene **1** at its most strained π bond.[1,2,4]

Synthesis of conjugated enyne **2** (Scheme II) follows a similar strategy in the final step. Dibromocarbene addition to **8**, thermal rearrangement to **10**, and treatment of **10** with DBU afforded diene **11** (30% yield from **8**). Treatment with CsF, as above, led to **12** in 30% isolated yield. Air oxidation of **12** gave **7**. Control experiments showed that **11** did not react with DIBF under the reaction conditions. We attribute the formation of **12** to cycloaddition of DIBF with strained enyne **2**.

The fluoride-induced elimination of β-substituted organosilanes has been applied to the preparation of benzyne and strained alkenes,[10] but not to strained cumulenes and enynes. In principal, a similar approach should yield strained allenes; indeed, we find that **13**[11] readily leads to 1,2-cyclohexadiene (**14**), which is trapped by DIBF to yield two stereoisomeric cycloadducts in a ratio identical with that previously reported.[2,12]



We believe that these synthetic approaches should be generally applicable to other ring sizes. Routes to cyclic butatrienes are sparse; this method should make them readily accessible from cyclic enones. Experiments to prepare both smaller and larger homologues are in progress.

Acknowledgment. We are grateful to the National Science Foundation for support of this research through Grant CHE-8722079 and an equipment grant for a 360-MHz NMR spectrometer.

(8) Data for new compounds include the following. **5**: ^{1}H NMR ($CDCl_3$, 360 MHz) δ 6.28–6.30 (1 H, t, J = 4.34 Hz), 5.73–5.76 (1 H, t, J = 4.51 Hz), 2.14–2.31 (4 H, symmetrical mult), 0.17 (9 H, s); ^{13}C NMR δ 150.50, 141.23, 133.55, 111.79, 22.58, 21.73, -1.09; UV (hexane) λ_{max} 260 nm (ϵ 2050), 203 (2200). **6**: ^{1}H NMR δ 7.81–7.83 (4 H, d, J = 7.16 Hz), 7.52–7.56 (4 H, t, J = 7.29 Hz), 7.42–7.46 (2 H, t, J = 7.29 Hz), 7.31–7.33 (2 H, dd, J = 3.07, 5.34 Hz), 7.16–7.18 (2 H, dd, J = 3.07, 5.34 Hz), 5.69 (2 H, br s), 2.22–2.24 (4 H, m); ^{13}C NMR δ 146.52, 138.76, 135.27, 128.49, 127.92, 126.80, 126.30, 119.43, 114.28, 88.34, 22.31. Anal. C, H. **10**: ^{1}H NMR δ 4.83 (1 H, br s), 2.37–2.44 (1 H, dd, J = 5.27, 18.38 Hz), 2.18–2.29 (2 H, m), 2.05–2.15 (1 H, dt, J = 3.14, 13.96 Hz), 1.92–2.05 (1 H, m), 1.73–1.77 (1 H, m), 0.23 (9 H, s); ^{13}C NMR δ 143.28, 130.90, 57.14, 33.78, 32.21, 17.32, -0.94. Anal. C, H. **11**: ^{1}H NMR δ 5.83–6.02 (1 H, dt, J = 1.79, 9.72 Hz), 5.83–5.88 (1 H, dt, J = 4.36, 9.72 Hz), 2.22–2.27 (2 H, m), 2.05–2.13 (2 H, m), 0.25 (9 H, s); ^{13}C NMR δ 135.26, 130.92, 129.93, 126.57, 28.53, 21.50, -0.68; UV (hexane) λ_{max} 275 nm (ϵ 4400), 205 (3960). **12**: ^{1}H NMR δ 7.76–7.80 (2 H, d, J = 7.1 Hz), 7.68–7.70 (2 H, d, J = 7.1 Hz), 7.38–7.53 (6 H, m), 7.19–7.26 (2 H, t, J = 7.0 Hz), 6.92–7.01 (2 H, quint, J = 7.5 Hz), 6.17–6.20 (1 H, br d, J = 9.66 Hz), 5.66–5.71 (1 H, dt, J = 4.2, 9.6 Hz), 2.62–2.70 (1 H, ddd, J = 4.82, 7.52, 17.0 Hz), 2.28–2.35 (2 H, m), 2.04–2.16 (1 H, m); ^{13}C NMR δ 151.68, 151.48, 150.56, 147.65, 135.20, 134.69, 128.69, 128.53, 128.20, 127.94, 126.56, 126.06, 125.15, 124.73, 120.14, 120.13, 119.60, 92.46, 92.16, 23.19, 22.66. This compound easily air-oxidizes to **7**.

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(10) For example: (a) Chan, T. H.; Massuda, D. *Tetrahedron Lett.* **1975**, 3385. (b) Chan, T. H.; Massuda, D. *J. Am. Chem. Soc.* **1977**, *99*, 936. (c) Zoch, H. G.; Szeimies, G.; Römer, R.; Germain, G.; Declerca, J. P. *Chem. Ber.* **1983**, *116*, 2285–2310. (d) Trahanovsky, W. S.; Fischer, D. R. *J. Am. Chem. Soc.* **1990**, *112*, 4971. (e) Ito, Y.; Nakatsuka, M.; Saegusa, T. *J. Am. Chem. Soc.* **1982**, *104*, 7069.

(11) Denmark, S. E.; Klix, R. C. *Tetrahedron* **1988**, *44*, 4043.

(12) Wittig, G.; Fritze, P. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 846; *Justus Liebigs Ann. Chem.* **1968**, *711*, 82.

Discovery of a New Fragmentation Reaction[1]

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Fragmentation reactions form one of the major classes of organic transformations, providing the foundation for a variety of strategies for complex molecule synthesis.[2] Decades of research have firmly established that these reactions proceed stereospecifically, in accord with expectations based on molecular orbital analysis.[2] We describe herein a remarkable fragmentation process that provides the basis for a new fragmentation mechanism and for a new mechanistic probe for substitution reactions.

As part of our interest in developing a metathetical approach to medium-ring synthesis (Scheme I: **1** + **2** → **4**), we previously reported[3] that kinetically controlled fragmentation of lactone **3** gives predominantly the (*Z*,*Z*)-cyclodecadiene **4** and lesser amounts of its thermodynamically favored Cope isomers **5**, in accord with a concerted cycloreversion or a stepwise path proceeding through a conformationally relaxed diyl.[4] In an effort

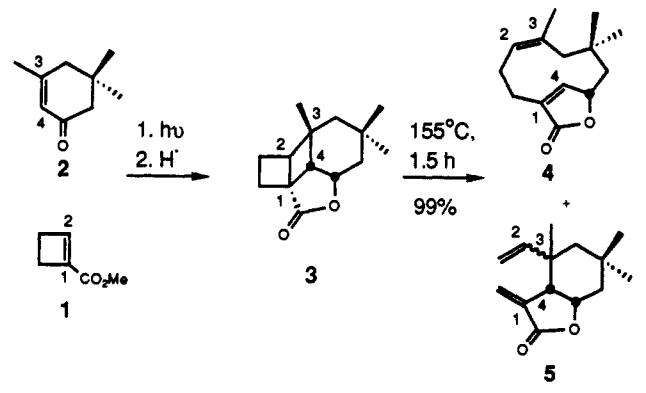
(1) Taken in part from the Ph.D. Thesis of Manly, C. J., Harvard University, 1984.

(2) For lead references, see: (a) Grob, C. A. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 535. (b) Wharton, P. S.; Hiegel, G. A. *J. Org. Chem.* **1965**, *30*, 3254. (c) Marshall, J. A. *Synthesis* **1971**, 229. (d) Mander, L. N.; Brown, J. M.; Cresp, T. M. *J. Org. Chem.* **1977**, *42*, 3984. (e) Fuchs, P. L.; Clark, D. A. *J. Am. Chem. Soc.* **1979**, *101*, 3567. (f) Eschenmoser, A.; Sternbach, D.; Shibuya, M.; Jaisli, F.; Bonetti, M. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 634. (g) Metivier, P.; Gushurst, A. J.; Jorgensen, W. L. *J. Org. Chem.* **1987**, *52*, 3724.

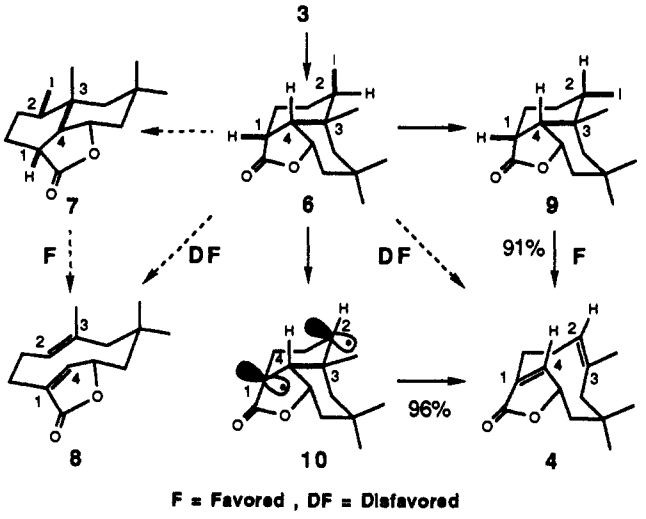
(3) (a) Wender, P. A.; Lechleiter, J. C. *J. Am. Chem. Soc.* **1977** *99*, 267. Wender, P. A.; Lechleiter, J. C. *J. Am. Chem. Soc.* **1980**, *102*, 6340. (b) For studies on cyclobutene diesters, see: Lange, G. L.; Huggins, M. A.; Neidert, E. *Tetrahedron Lett.* **1976**, 4409. (c) For studies on cyclobutene derivatives, see: Wilson, S. R.; Phillips, L. R.; Pelister, Y.; Huffman, J. D. *J. Am. Chem. Soc.* **1979**, *101*, 7373. (d) For extensions to methyl cyclobutene, see: Lechleiter, J. Ph.D. Thesis, Harvard University, 1979. Williams, J. R.; Callahan, J. F. *J. Chem. Soc., Chem. Commun.* **1979**, 404.

0002-7863/90/1512-8579$02.50/0

Scheme I



Scheme II



F = Favored , DF = Disfavored

to extend this method to the synthesis of (*E*,*Z*)-cyclodecadienes, a commonly encountered germacradiene motif,[5] we reasoned that the stereochemical fate of **3** could be recast if a method were devised that allowed nucleophilic cleavage of the C1–C2 bond in **3** with inversion at C2 to give **6** (Scheme II). If the role of the nucleophile could then be reversed to that of a leaving group, fragmentation of **6** would proceed, as dictated by orbital overlap control, from conformer **7** through a boat-like transition state[2,3a] to the (*E*,*Z*)-diene product **8**.

For the initial cleavage step in the above plan, several Lewis acid/nucleophile combinations were examined. Of these, trimethylsilyl iodide[6] was found to be particularly effective, allowing for the conversion of **3** to iodide **6**[7a] in 91% yield. As this represented the first study of the stereochemistry of this process, the structure of **6** was securely established by X-ray crystallography.[7b]

While it was originally thought that the silyl enol ether intermediate[8] in the above reaction would fragment under the conditions of its formation, this proved to be untenable. Consequently, fragmentation of the more reactive lactone enolate was investigated. Upon treatment with LDA (1.2 equiv in THF, 5 min) at −78 °C followed by warming to room temperaure (ca. 15 min), lactone **6** smoothly underwent fragmentation but gave, in contrast to conventional mechanistic expectations, only the (*Z*,*Z*)-cyclodecadiene **4** in 96% yield. The stereochemistry of lactone **4** was established in part through NOE analysis[9] and by X-ray crystallography of its diol reduction product.[7b,c] It is synthetically noteworthy that cyclodecadiene **4** was not accompanied by its Cope isomers (**5**) as is found in the thermolysis of lactone **3**.[3a]

The unprecedented stereochemical outcome of the above reaction prompted an examination of the fragmentation behavior of the iodide epimer of **6**. This iodide (**9**) was obtained from **6** (66% yield), but only under forcing conditions (NaI, acetone, reflux, >24 h), as expected for substitution at a neopentyl center. The epimeric relationship of iodides **6** and **9** was established by their independent conversion to a common product[10] upon treatment with *n*-Bu_3SnH. When iodide **9** was submitted to the previous fragmentation conditions, (*Z*,*Z*)-cyclodecadiene **4** was again obtained in high yield (91%). Thus, while iodide **9** behaves conventionally, its epimer (**6**) suffers stereochemical amnesia under the fragmentation conditions. In both fragmentation reactions, the lactone enolate is the first-formed intermediate as only monodeuterated, stereochemically intact starting material is recovered when either iodide is treated with LDA in THF at −78 °C and quenched with MeOD. When either reaction is warmed and quenched after partial fragmentation, no trace of iodide epimerization is observed. Thus, if one or more intermediates between **6** and **4** are formed, they do not accumulate. The use of only 0.5 equiv of LDA in the fragmentation of **6** resulted in the isolation of only 0.5 equiv of **4** and 0.5 equiv of **6**. This stoichiometry tends to exclude a radical chain process. In order to determine comparative rates of fragmentation, a 1:1 mixture of iodides **6** and **9** was treated with LDA and warmed for 4 min at −25 °C. Fragmentation of the enolate of **9** was found to be faster but only by a factor of 8.7. Finally, the anomalous behavior of iodide **6** is not attributable to photocatalysis, since its reaction in the absence of light proceeds identically.

These data suggest that the fragmentation of **6** could involve an intriguing single electron transfer (SET) or an enolate-accelerated heterolysis mechanism, each having exciting implications for substitution reactions.[11] Thus, the enolate of **6** possesses a C1-donor–C2-acceptor (nucleophile–electrophile) system capable

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(7) (a) Satisfactory analyses and spectroscopic data were obtained for all new compounds. (b) Supplementary material. (c) A suitable crystal of **4** could not be obtained. However, DIBAH reduction of **4** provided a 1,4-diol that was suitable for X-ray analysis (supplementary material).

(8) Rigorous exclusion of water results in the formation of a hydrolytically unstable enol ether as determined by NMR.

(9) Irradiation of the C3-methyl gave an 8% enhancement of the C2-hydrogen, and a 5% enhancement was found in the methyl group resonance when the C2-hydrogen was irradiated.

(10) This common, iodide reduction product is the same as that obtained from the metal ammonia reduction of lactone **3** (Wender, P. A.; Lechleiter, J. C. *J. Am. Chem. Soc.* **1978**, *100*, 4321).

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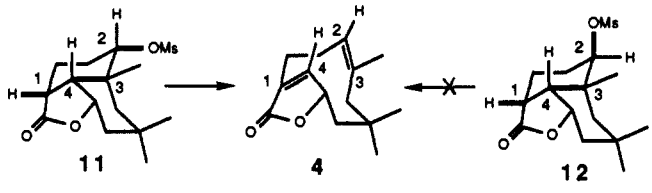
of undergoing an internal redox (substitution) reaction. With little nuclear motion, transfer of an electron (in the limiting case)[12] from the enolate HOMO to the C-I σ^* would produce diyl **10** directly or indirectly through its expectedly short-lived (10^{-8}-10^{-10} s)[13] C-I radical anion precursor. Alternatively, enolate-accelerated heterolysis of the C I bond could produce a zwitterion, differing from **10** only in electron distribution.[12] In either case, the stereochemical information stored in the original C-I bond would be lost at this point as the resulting C2 center in **10** would rapidly invert or be planar.[14] As generated in this least motion path, **10** is in a conformation suitable for direct orbital overlap controlled fragmentation[2-4] to the (*Z*,*Z*)-cyclodecadiene **4**. The conversion of **6** to diyl **10** finds analogy in substitution reactions proceeding by SET. For such reactions, diradical formation is followed by cage combination, while in the current case, the analogous diyl combination is frustrated by the energetic cost of closure to the strained bicyclo[2.2.0]hexane subunit.[15]

As a further test of the above analysis, the fragmentation of mesylates **11** and **12** was examined. Since the mesylate group retains the superior leaving-group ability of an iodide but is less easily reduced, an SET based fragmentation would be unlikely for these compounds. In accord with this expectation, mesylate **11**, under the above conditions, gave only (*Z*,*Z*)-diene **4** (84%) and starting material, while the epimeric mesylate (**12**) proved unreactive, even at 25 °C for 1.5 h.



In summary, a fragmentation reaction is reported that proceeds in a stereochemical sense completely opposite that expected from the conventional mechanism. Preliminary evidence is consistent with this process occurring by a novel SET pathway or an anion-accelerated heterolysis. Either pathway represents a novel example of a frustrated substitution in which the nucleophile is positioned suitably close to an electrophilic center to transfer an electron or to induce heterolysis but closure of the resulting diyl or zwitterion is frustrated by a faster fragmentation. As it relates to synthesis, this novel fragmentation creates new opportunities for regulating the stereochemistry and mode selectivity of fragmentation reactions as evidenced by the efficient and selective formation of cyclodecadienes from readily available lactones.

Acknowledgment. This work was supported by a grant (CA31845) from the National Institutes of Health. The assistance of Dr. Gil Shoham with the X-ray structure determination of iodide **6** is gratefully acknowledged.

Supplementary Material Available: Spectroscopic data (NMR, IR, and MS) for compounds **6**, **9**, and **4** and tables of X-ray crystallographic data for compound **6** and the diol derivative of **4** (5 pages); listing of observed and calculated structure factors for compounds **6** and **4** (14 pages). Ordering information is given on any current masthead page.

(12) This zwitterion could undergo direct fragmentation or internal return to give **9** and thence fragmentation. For a relevant theoretical analysis, see: Hwang, J.-K.; King, G.; Creighton, S.; Warshel, A. *J. Am. Chem. Soc.* **1988**, *110*, 5297. A chain process involving SET can also be involved in the formation of **10** or **4**.

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Observation of an Isotope Effect in the Chorismate Synthase Reaction

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Received July 6, 1990

Chorismate synthase (EC 4.6.1.4) catalyzes the seventh step on the shikimate pathway, the conversion of 5-enolpyruvylshikimate 3-phosphate (**1**, EPSP) to chorismate (**2**) (Scheme I).[1] The reaction involves the removal of the *pro-R* hydrogen on C-6 and loss of phosphate in what is formally a 1,4-elimination to generate a diene.[2,3] The overall anti stereochemistry of the elimination has led to a reluctance to postulate a concerted mechanism, and consequently several other mechanisms of varying plausibility have been proposed. These include, inter alia, an X-group mechanism,[3] a 1,3-suprafacial shift of phosphate to C-1 followed by an E2 elimination,[1] and a carbonium ion mechanism where loss of phosphate precedes C-H bond breaking.[4] Each of these mechanisms avoids the problem that concerted anti 1,4-eliminations are historically disfavored. This conclusion comes from studies on model systems[5] and from molecular orbital considerations.[6] However, these objections to a concerted process are not soundly based in the context of an enzyme-catalyzed reaction where the orientation of catalytic groups may well play a decisive role.

The first step toward elucidating the actual mechanism of the enzyme-catalyzed reaction is to establish the timing of the two bond-breaking steps, at C-3 and C-6. This is experimentally accessible if bond breaking at either position is partly rate determining and proceeds with an associated isotope effect. In this communication we report the observation of a primary kinetic isotope effect for cleavage of the carbon-hydrogen bond at C-6. This result is surprising in the light of a preliminary study, which failed to detect an isotope effect.[7]

The synthesis of (6*R*)-[6-^{2}H]EPSP is outlined in Scheme II. (6*R*)-[6-^{2}H]shikimic acid (**5**) (and enantiomer) was synthesized from (*Z*)-[3-^{2}H]acrylic acid[8] and (*E*,*E*)-1,4-diacetoxybutadiene by the route of Raphael and Smissman.[9] The resulting (±)-shikimic acid had 94 ± 2% deuterium cis to the C-5 hydroxyl group and 5 ± 2% in the trans position.[10] The minor deuteriated

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† University of Cambridge.
‡ University of Glasgow.

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