A Novel Cyclopropane Ring Fragmentation of Bicyclo[3.1.0]hexene Epoxides to 2,5-Dienals

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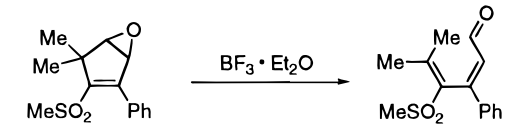
Epoxides of strained cyclic alkenes undergo a variety of ring fragmentation reactions which lead to unsaturated carbonyl compounds.[1] Two of the many known examples are shown in eqs 1 and 2.[2] In this note we report a novel cyclopropane fragmentation of strained bicyclo[3.1.0]hexene epoxides to 2,5-dienals.



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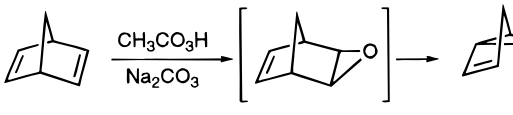
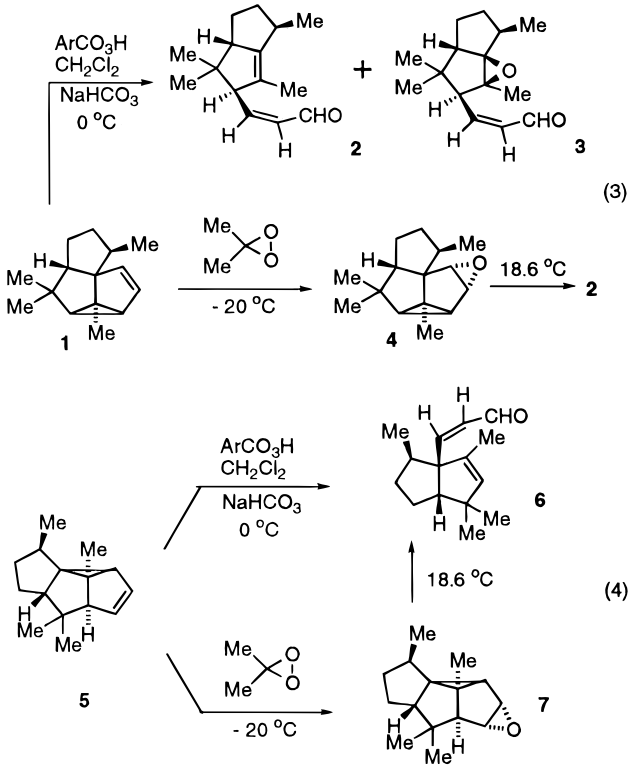


(2)

Angular and linear tetracyclic vinylcyclopropanes **1** and **5** were prepared by intramolecular photoannulation of 1-(1,5-dimethyl-4-hexenyl)-2-methylbenzene as described by Wender and Ternansky.[3] The 60:40 mixture of isomeric olefins was separated by chromatography on silver nitrate-impregnated silica gel. Attempted epoxidation of **1** with *m*-chloroperoxybenzoic acid in the presence or absence of bicarbonate buffer afforded a mixture of dienal **2** (63%) and its epoxidation product **3** (26%). Similar epoxidation of the linear isomer **5** gave rise to dienal **6** (78%). No evidence for the suspected epoxide intermediates could be obtained by TLC and GC analyses during and after the reactions. The *Z* stereochemistry of the 2,3-double bond in the two 2,5-dienal products is assigned on the basis of the coupling interaction between the vicinal vinyl protons in their ^{1}H NMR spectra (for **2**, $J_{2,3} = 11.2$ Hz; for **3**, $J_{2,3} = 11.5$ Hz; for **6**, $J_{2,3} = 12.8$ Hz). Literature values for (*E*)-and (*Z*)-6-(tetrahydropyranyloxy)-2-hexenals are 15.6 and 11.1 Hz, respectively.[4]

The unstable epoxides of **1** and **5** were obtained by epoxidation with dimethyldioxirane[5] in acetone at −20 °C for 10 h. The more sensitive epoxide **4** was invariably produced as a 1:1 mixture with its dienal fragmentation product. The epoxides were characterized by IR, MS, ^{1}H NMR, and ^{13}C NMR spectra. The NMR chemical shifts for the oxiranyl ring protons and carbons are as follows:



for **4**, δ_H 3.16 and 3.46 ($J = 2.9$ Hz), δ_C 65.9 and 67.6; for **7**, δ_H 3.24 and 3.46 ($J = 2.4$ Hz), δ_C 58.2 and 62.8.

The epoxide of bicyclo[3.1.0]hexene itself is a known compound,[6] and the literature does not indicate any tendency toward fragmentation. Although the preparation of thujene epoxide (**9**) by photosensitized epoxidation of thujene with biacetyl and oxygen has been recorded in the patent literature,[7] this unstable epoxide was characterized only by ^{1}H NMR spectral data in CCl_4. We succeeded in preparing thujene epoxide by dimethyldioxirane epoxidation at room temperature (97%). Its ^{1}H and ^{13}C NMR spectra show absorptions characteristic of the trisubstituted oxirane: δ_H 2.93, δ_C 60.86 and 70.64. Attempts to effect epoxidation of thujene with *m*-chloroperoxybenzoic acid gave complex mixtures. Thujene epoxide underwent thermal fragmentation to the conjugated dienal **11** (8%). However, the major product *p*-cymene (64%) arose from a competing aromatization pathway. (*E*,*E*)-2,5,6-Trimethyl-2,4-heptadienal (**11**) is a known compound resulting from a similar enzyme-catalyzed tandem rearrangement-fragmentation of α-pinene epoxide to the 2,5-heptadienal isomers followed by isomerization to the fully conjugated form.[8−10] However, to our knowledge, complete physical and spectral data for **11** have not been previously reported.

These epoxide to dienal fragmentation reactions occur by simultaneous or successive cleavages of the epoxide C−O bond, the adjacent cyclopropane C−C bond, and an oxygen-bearing C−C bond. The reaction rates were measured in toluene (with and without added *m*-chlo-

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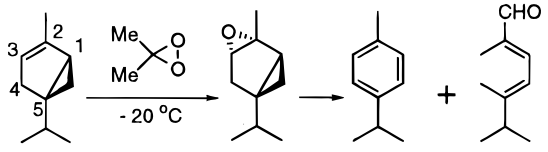
Table 1. Kinetic Data for Fragmentation Reactions of Epoxides 4, 7, and 9 at 18.6 °C (see eqs 3−5)

epoxide	solvent[a]	k (s^{-1})[b]	k_{rel}
4	toluene[c]	$3.8 \pm 0.5 \times 10^{-6}$	27
	acetone	$5.2 \pm 0.7 \times 10^{-6}$	37
	methanol	$1.5 \pm 0.6 \times 10^{-5}$	107
	toluene with *m*-$ClC_6H_4CO_2H$	$1.9 \pm 0.1 \times 10^{-4}$	1357
7	toluene	$1.7 \pm 0.1 \times 10^{-7}$	1.2
	acetone	$1.4 \pm 0.5 \times 10^{-7}$	(1.0)
	methanol	$1.4 \pm 0.4 \times 10^{-5}$	100
	toluene with *m*-$ClC_6H_4CO_2H$	$1.7 \pm 0.3 \times 10^{-5}$	121
9	toluene	$4.1 \pm 0.7 \times 10^{-6}$	29
	acetone	$4.1 \pm 0.9 \times 10^{-6}$	29
	methanol	$3.2 \pm 0.2 \times 10^{-5}$	229
	toluene with *m*-$ClC_6H_4CO_2H$	$3.6 \pm 0.3 \times 10^{-5}$	257

[a] In all cases the solvent is deuterated to greater than 99.9%. [b] The rate is the average of the disappearance of starting material and the formation of the product. [c] Rate measurements taken over 256 h (first half of one half-life).



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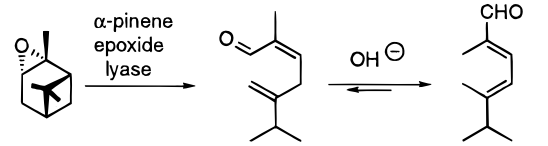

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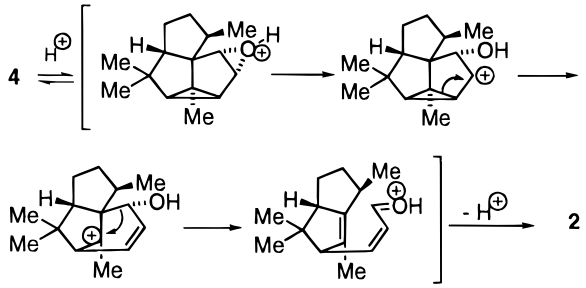
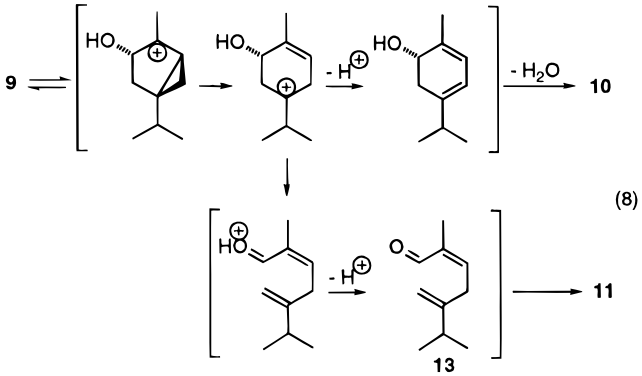
robenzoic acid), acetone, and methanol by ^{1}H NMR spectroscopy to evalute the polarity of the transition state and to determine a probable mechanism for the process. The data in Table 1 show similar slow rates in nonpolar and polar aprotic solvents (toluene and acetone) which increase by 4−100 times in the hydrogen bonding medium of methanol. The 8.8−121-fold rate increases observed in the presence of *m*-chlorobenzoic acid clearly implicate a stepwise mechanism involving protic acid catalysis and cyclopropylcarbinyl and homoallyl carbocation intermediates as shown in eq 7, or alternatively by a concerted fragmentation of a delocalized cyclopropylcarbinyl ion directly to the protonated dienal.



(7)

A similar mechanism for the conversion of thujene epoxide to conjugated dienal **11** and *p*-cymene is proposed in eq 8. In this case, the homoallyl carbocation presumably undergoes competive eliminations and bond cleavage to the observed products. The unstable 2,5-dienal formed undergoes rapid isomerization to the thermodynamically more stable (*E*,*E*)-2,4-dienal. The (*E*,*E*) stereochemistry is assigned to **11** for this reason, and the ^{1}H NMR chemical shifts for the compound are consistent with literature data.[4]



(8)

Experimental Section

General Aspects.[11] ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400 and 100 MHz, respectively. GC analyses were carried out on a 30-m RTX-5 fused silica capillary column using helium as a carrier gas. Complete experimental procedures for the preparation of tetracyclic olefins **1** and **5** based on brief ones given in the literature[3] are presented as supporting information.

Dimethyldioxirane. Solutions of dimethyldioxirane in acetone were generated by a literature procedure.[5b] The concentration (0.05−0.1 M) of the dimethyldioxirane was determined by addition of excess thioanisole and quantitative analysis of the resulting sulfoxide by integration of the ^{1}H NMR spectrum.

[1R-(1α,3aα,5*β*)]-(±)-1,2,3,3a,4,5-Hexahydro-1,4,4,6-tetramethyl-5-[(*Z*)-2-formylethenyl]-6,6a-epoxypentalene (2), [1*R*-(1α,3aα,5b)]-(±)-1,2,3,3a,4,5,6,6a-octahydro-1,4,4,6-tetramethyl-5-[(*Z*)-2-formylethenyl]-6,6a-epoxypentalene (3). A solution of **1** (50 mg, 0.25 mmol) in 10 mL of CH_2Cl_2 was stirred at 0 °C as *m*-CPBA (43.2 mg, 0.25 mmol) was added in one portion. The solution was allowed to warm to rt and stirred for another 10 min when the reaction was complete according to TLC analyses. The reaction mixture was washed with aqueous saturated sodium metabisulfite (10 mL), saturated aqueous Na_2CO_3 (10 mL), and aqueous saturated NaCl (20 mL). The organic layer was dried ($MgSO_4$) and evaporatated at reduced pressure. Purification by flash chromatography using hexane−ether (20:1) provided 34 mg (63%) of dienal **2** and 15 mg (26%) of epoxy aldehyde **3**.

For **2**. IR (neat): 1680. ^{1}H NMR: δ 0.95 (3 H, s), 1.03 (3 H, s), 1.04 (3 H, d, J = 6.8 Hz), 1.27 (1 H, m), 1.48 (2 H, m), 1.55 (3 H, s), 2.20 (1 H, m), 2.51 (1 H, app qd, J = 6.8, and 0.7 Hz), 2.91 (1 H, m), 3.60 (1 H, d, J = 6.1 Hz), 5.99 (1 H, ddd, J = 11.2, 8.3, and 0.7 Hz), 6.60 (1 H, dd, J = 11.7 and 11.2 Hz), 10.07 (1 H, d, J = 8.3 Hz). ^{13}C NMR: δ 12.78, 19.90, 24.05, 24.80, 25.49, 31.01, 38.83, 44.47, 59.15, 65.19, 125.77, 129.49, 152.04, 154.06, 191.26. MS (EI, 70 eV) *m*/*z* (relative intensity): 218 (M^+, 11.4). Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.55; H, 10.17.

For **3**. Mp: 49.5−51.0 °C; IR (neat): 3032, 2869, 1680 (C=O), 1363. ^{1}H NMR: δ 0.93 (3 H, s), 0.94 (3 H, s), 1.01 (3 H, d, J = 7.1 Hz), 1.18 (3 H, d, J = 1.8 Hz), 1.71 (1 H, m), 1.90 (1 H, app. sextet, J = 7.2 Hz), 2.11 (2 H, m), 3.24 (1 H, d, J = 11.5 Hz), 6.20 (1 H, dd, J = 11.5 and 8.0 Hz), 6.73 (1 H, t, J = 11.5 Hz), 9.96 (1 H, d, J = 8.0 Hz); ^{13}C NMR: δ 15.72, 18.34, 24.93, 25.71, 27.26, 27.83, 32.65, 42.33, 51.28, 52.17, 70.89, 82.23, 132.45, 150.48, 190.66. MS (EI, 70eV) *m*/*z* (relative intensity): 234 (M^+, 1.7), 123(40.3), 95(100), 41 (100). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 77.17; H, 9.46.

[1R-(1α,3aα,5a*β*,8a*R)]-(±)-1,2,3,3a,4,4a,4b,6b-Octahydro-1,4,4,6a-tetramethyl-5,6-epoxycyclopropa[*cd*]cyclopenta[*c*]pentalene (4).** Olefin **1** (202 mg, 1.0 mmol) was stirred at −20 °C as freshly generated dimethyl dioxirane in acetone (20 mL, 0.072 M, 1.44 mmol)[5b] was added in one portion. The solution was stirred at −20 °C for 10 h, and the reaction was followed by TLC. The reaction mixture was allowed to warm to 0 °C, diluted with pentane (20 mL), and dried ($MgSO_4$). The

(11) Yee, N. K. N.; Coates, R. M. *J. Org. Chem.* **1992**, *57*, 4598.

solvent was carefully removed by rotary evaporation at 0 °C to obtain a 1:1 mixture of epoxide **4** and dienal **2** (186 mg, 85%). The ^{1}H and ^{13}C NMR specra were recorded with the mixture. When this mixture was stored at rt for 24 h, **2** was the only product.

For **4**. ^{1}H NMR: δ 1.04 (3 H, s), 1.07 (3 H, s), 1.13 (3 H, d, J = 7.0 Hz), 1.15 (3 H, s), 1.27 (1 H, m), 1.48 (2 H, m), 2.20 (1 H, m), 2.51 (1 H, app qd, J = 6.8, and 0.7 Hz), 2.91 (1 H, m), 3.16 (1 H, dd, J = 2.9 and 0.9 Hz), 3.46 (1 H, dd, J = 2.9 Hz). ^{13}C NMR: δ 19.07, 19.10, 27.94, 28.72, 30.37, 33.03, 34.02, 36.48, 37.68, 38.45, 47.10, 54.76, 59.45, 65.91, 67.58.

[1R-(1α,3aα,4ab,4bβ,6b*S)]-(±)-1,2,3,3a,4,4a,4b,6a-Octahydro-1,4,4,4b-tetramethyl-5,6-epoxycyclopropa[*cd*]cyclopenta[*c*]pentalene (7) and [1*R*-(1α,3aα,6a*S**)]-(±)-1,2,3,-3a,4,6a-hexahydro-1,4,4,6-tetramethyl-6a-[(*Z*)-2-formylethenyl]pentalene (6).** Epoxidation of **5** (202 mg, 1.0 mmol) with freshly generated dimethyldioxirane in acetone (20 mL, 0.0557 M, 1.11 mmol) was carried out at −20 °C for 2 days. The product epoxide **7** (216 mg, 99%) was isolated as described above for **4**.

For **7**. IR (neat): 3027, 2951, 2868, 1456, 1390, 845. ^{1}H NMR: δ 0.87 (3 H, d, J = 9.3 Hz), 0.93 (3 H, s), 0.96 (3 H, s), 1.17 (3 H, s), 1.48 (2 H, m), 1.73 (4 H, m), 2.01 (1 H, dd, J = 9.0, ans 3.2 Hz), 2.11 (1 H, s), 3.24 (1 H, d, J = 2.7 Hz), 3.46 (1 H, d, J = 2.2 Hz). ^{13}C NMR: δ 16.50, 18.86, 23.47, 23.54, 23.79, 33.15, 35.13, 35.70, 37.75, 50.38, 51.48, 53.58, 55.74, 58.24, 62.80. MS (EI, 70 eV) *m/z* (relative intensity): 218 (M^+, 11.4), 203 (30.0), 161 (48.7), 119 (65.3), 105(70.0), 95 (100.0). Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.58; H, 10.15.

A solution of epoxide **7** (110 mg, 0.50 mmol) in methanol-d_4 (1 mL) was placed in a 15-mL reaction vial with a resealable cap under N_2 and was heated at 135 °C for 8 h. The reaction was followed by TLC. The reaction mixture was diluted with pentane (10 mL), and the solution was washed with brine (1 mL) and dried ($MgSO_4$). Removal of the solvent and purification by chromatography (pentane:ether = 9:1) gave **6** (93 mg, 84%) as a light yellow oil.

For **6**. IR (neat): 2955, 1672, 1456, 1074. ^{1}H NMR: δ 0.99 (3 H, s), 1.03 (3 H, d, J = 7.1 Hz), 1.05 (3 H, s), 1.72 (3 H, d, J = 1.1 Hz), 2.35 (1 H, t, J = 8.6 Hz), 5.13 (1 H, s), 5.84 (1 H, dd, J = 12.8, ans 8.2 Hz), 6.55 (1 H, d, J = 12.8 Hz), 10.18 (1 H, d, J = 8.2 Hz). ^{13}C NMR: δ 13.35, 15.81, 24.45, 27.95, 31.16, 35.71, 44.58, 44.98, 64.55, 67.13, 127.89, 137.68, 140.64, 154.91, 193.63. MS (EI, 70eV) *m/z* (relative intensity): 218 (M^+, 14.6), 161 (49.2), 191 (84.0), 95 (100), 41(67.9). Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.16; H, 9.86.

(1*R*,5*S*)-2-Methyl-5-(1-methylethyl)bicyclo[3.1.0]hex-2-ene (α-thujene) (8). (+)-Sabinene (1.43 g, 10.5 mmol) was isomerized to (−)-thujene according to a literature procedure.[12] Purification by chromatography on $AgNO_3$-impregnated silica gel (15% w/w) with pentane as eluant followed by distillation afforded 1.03 g (83%) of **8** as a colorless liquid (95% purity by NMR analysis). Bp: 159−162 °C. IR (neat): 3027, 2951, 2868, 1456, 1390, 845. ^{1}H NMR: δ 0.29 (1 H, t, J = 4.1 Hz), 0.63 (1 H, dd, J = 8.1, 4.1 Hz), 0.80 (3 H, d, J = 7.0 Hz), 0.86 (3 H, d, J = 7.0 Hz), 0.40−1.05 (3 H, m), 1.43 (3 H, s), 2.93 (1 H, t, J = 1.0). ^{13}C NMR: δ 16.56, 18.00, 19.60, 19.61, 30.36, 30.97, 32.29, 60.86, 70.64. MS (EI, 70 eV) *m/z* (relative intensity): 152 (M^+, 11.4). Anal. Calcd for $C_{10}H_{16}$: C, 78.90; H, 10.59. Found: C, 78.88; H, 10.58.

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(1*R*,2*S*,3*R*,5*R*)-2-Methyl-5-(1-methylethyl)-2,3-epoxybicyclo[3.1.0]hexane (α-thujene epoxide) (9). Epoxidation of thujene (204 mg, 1.5 mmol) with freshly generated dimethyldioxirane in acetone (30 mL, 0.0557 M, 1.67 mmol) at rt for 4 h gave **9** (221 mg, 97%) as a light yellow oil. IR (neat): 3027, 2951, 2868, 1456, 1390, 845. ^{1}H NMR: δ 0.29 (1 H, t, J = 4.1 Hz), 0.63 (1 H, dd, J = 8.1, 4.1 Hz), 0.80 (3 H, d, J = 7.0 Hz), 0.86 (3 H, d, J = 7.0 Hz), 0.40−1.05 (3 H, m), 1.43 (3 H, s, CH_3), 2.93 (1 H, t, J = 1.0). ^{13}C NMR: δ 16.56, 18.00, 19.60, 19.61, 30.36, 30.97, 31.69, 32.29, 60.86, 70.64. MS (EI, 70 eV) *m/z* (relative intensity): 152 (M^+, 11.4). Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.88; H, 10.58.

Methyl-4-(1-methylethyl)benzene (*p*-cymene 10) and (*E*,*E*)-2,5,6-trimethylhepta-2,4-dienal (11)[7] from the Fragmentation of α-Thujene Epoxide (9). α-Thujene epoxide (76 mg, 0.50 mmol) and benzene (1 mL) were placed in a reaction vial with a resealable cap under N_2. The vial was sealed with a Teflon cap and heated at 135 °C for 8 h. The reaction was followed by TLC. The solution was cooled to 0 °C, diluted with pentane (20 mL), washed with brine (10 mL), and dried ($MgSO_4$). Evaporation of solvents afforded a light yellow oil (75 mg). Purification by chromatography (pentane) gave **10** (43 mg, 64%) and **11** (6 mg, 8%).

For **10**. IR (neat): 1514. ^{1}H NMR: δ 1.22 (6 H, d, J = 6.8 Hz), 2.29 (3 H, s), 2.85 (1 H, septet, J = 6.8), 7.08 + 7.10 (4 H, AA′BB′, J = 8.3, 8.2, 1.9, 1.8, 0.1 Hz). ^{13}C NMR: δ 20.94, 24.11, 33.70, 126.25, 128.97, 135.09, 145.80. MS (EI, 70 eV) *m/z* (relative intensity): 134 (M^+, 11.4). Anal. Calcd for $C_{10}H_{14}$: C, 89.49; H, 10.51. Found: C, 89.51; H, 10.52.

For **11**. IR (neat): 1678. ^{1}H NMR: δ 1.10 (6 H, d, J = 6.8 Hz), 1.85 (3 H, d, J = 0.9 Hz), 1.92 (3 H, d, J = 1.2 Hz), 2.48 (1 H, septet, J = 6.6 Hz), 6.50 (1 H, d of quintets, J = 11.5 and 1.0 Hz), 7.14 (1 H, dq, J = 11.7 and 1.2 Hz), 9.46 (1 H, s). ^{13}C NMR: δ 9.29, 14.81, 22.66, 34.11, 38.11, 118.50, 135.90, 145.94, 157.09, 195.36. MS (EI, 70 eV) *m/z* (relative intensity): 152 (M^+, 20.87). Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.91; H, 10.57.

Kinetic Measurements. Rates in Table 1 were determined by placing the cyclopropyl epoxide (0.10 mmol) and the deuterated solvent (1.0 mL) in an NMR tube under N_2 with tetramethylsilane and benzene as internal standards. Toluene-d_8, acetone-d_6, or methanol-d_4, were employed as solvents. The solution was then placed in the thermostated probe of the NMR spectrometer (18.6 ± 0.2 °C), and spectra were recorded at regular intervals. The disappearance of starting material (cyclopropyl-H) was monitored as a function of time. The concentration of the starting epoxide at various time intervals was calculated from the ratio of intensity of the corresponding NMR signal of the compound to that of the internal standard.

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Supporting Information Available: Experimental procedures and characterization data for tetracyclic olefins **1** and **5** (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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