The presence of such seeds was further indicated when racemic naphthidine was heated to 215–220 °C, which is well above the melting point of both forms of naphthidine. This destroyed all seed crystals, and when the samples were returned to 203 °C no crystallization occurred over long periods of time. With further cooling (to 175 °C) crystallization occurred, but the samples were completely optically inactive and in the racemic form. Naphthidine melt has a great tendency to supercool, and spontaneous nucleation apparently does not occur in the range of temperature above 197 °C, where the optically active eutectic form is stable. Thus, in contrast to the demonstrated[2] spontaneous production of optical activity in binaphthyl, naphthidine cannot be made to resolve in a truly spontaneous way. Only a bias arising from inadvertent seeding may be amplified by growth of the eutectic form at 203 °C.

Some further variations of experiments arising from knowledge of the phase relationships given in Figure 4 are possible. Above 197 °C and below the melting point of 202 °C, samples of racemic naphthidine should undergo a direct solid-to-solid-state resolution reaction. Eleven samples of racemic preparation were heated to 197 °C, where only the eutectic form is stable. At this temperature the racemization observed up to 195 °C is reversed, resolution occurred, and after 65 h the samples showed rotations of $[\alpha]_D$ +13, −5.5, +25, +26, +29, +32, +39, +36, −3.0, +27, and +20°. Again a bias toward the (+) enantiomer is caused by the presence of adventitious seeds of the eutectic form. If such seeds are annealed out by heating samples at 192 °C for over 5 h (or melted out by heating to 215 °C and solidifying at 175 °C) and the samples then held at 197 °C, no production of optically active samples, nor even the growth of any eutectic crystals, was observed. The spontaneous nucleation of the eutectic form apparently does not occur in solid naphthidine. Also, as mentioned above, it does not occur in supercooled naphthidine melt in the 197–204 °C range.

Acknowledgment. The authors gratefully acknowledge the support of the National Research Council of Canada and the helpful suggestions of Drs. K. R. Wilson and W. M. Johnson.

Registry No.—(*S*)-(+)-Naphthidine, 18531-98-1; (±)-naphthidine, 64282-15-1; (*R*)-(−)-naphthidine, 64235-43-4.

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Synthesis and Epoxidation Kinetics of Some Fused-Ring Cyclopropenes

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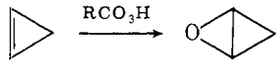
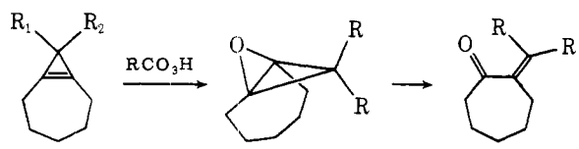
A series of 3,8-disubstituted bicyclo[5.1.0]oct-1(7)-enes was prepared. Measured relative rates of epoxidation were obtained for these allylically substituted fused-ring cyclopropenes. An attempt to fit the partial rate constants of epoxidation to a simple linear free energy dependence revealed a moderate backside interaction of the allylic cyclopropene substituents with the cycloheptane ring.

For many years we[4] have been attempting to delineate the details of cyclopropene epoxidations, since the expected initial product is an oxabicyclobutane. Oxabicyclobutanes

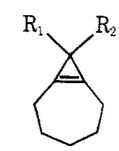


have been postulated as unstable intermediates in many different reactions.[5] They are also interesting theoretical molecules due to a potential antiaromatic interaction of the cyclopropane ring with the neighboring nonbonded electrons on the oxygen atom. Such an interaction mimics the electronic π-type resonance in the yet to be synthesized oxirenes.[6]

Our previous work[4] has studied the epoxidation kinetics and products using simple cyclopropenes. In this work, we sought to epoxidize cyclopropenes that are fused to a seven-membered ring. Not only are the resulting intermediate oxabicyclobutanes unique and novel propellanes,[6b] but we also hoped to establish a quantitative linear free-energy relationship between the epoxidation rate constants and the steric substituent constants of the cyclopropene allylic substituents.



The desired cyclopropenes are compounds **1a–d.** These four compounds form two relevant series. The first series, **1a, 1b,** and **1c,** can be used to probe the steric reaction constant with respect to allylic substituents of different size. The compounds in the second series, **1a, 1b,** and **1d,** all have R_1 = Me with increasing steric bulk for R_2.



1a, R_1 = Me; R_2 = Me
1b, R_1 = Me; R_2 = Et
1c, R_1 = Et; R_2 = Et
1d, R_1 = Me; R_2 = *i*-Pr

Results

All four cyclopropenes were prepared by irradiation of the tosylhydrazone salts of their corresponding ketones, **2a–d.**

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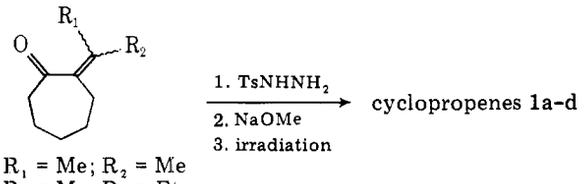
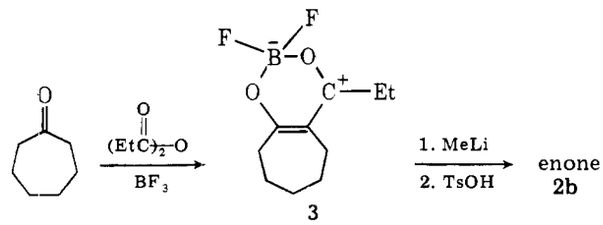


2a, R_1 = Me; R_2 = Me
2b, R_1 = Me; R_2 = Et
2c, R_1 = Et; R_2 = Et
2d, R_1 = Me; R_2 = *i*-Pr

Cyclopropene **1a**[7] and its corresponding enone[8] are known compounds.

The syntheses of the unknown exocyclic enones **2b–d** were relatively straightforward. Enone **2b** was prepared by literature analogies.[9,10] Treatment of cycloheptanone with propionic anhydride–BF_3 forms the stable fluoroborate complex **3**, which on reaction with MeLi and treatment with acid gives enone **2b.**



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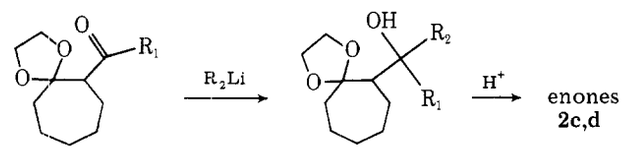
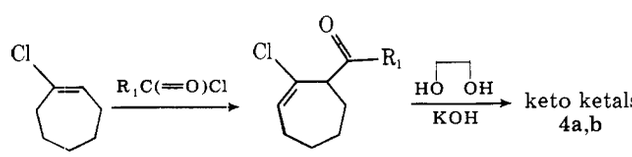
Enones **2c,d** were prepared from their respective keto ketals **4a,b.** The keto ketals were made using literature methods[11] by acylation of cycloheptenyl chloride followed by ketalization with ethylene glycol and base.



4a, R_1 = Et
4b, R_1 = *i*-Pr



The structures of the final cyclopropenes **1a–d** are firm, not only because they possess the proper spectral properties, but also because the syntheses involve unambiguous routes. Furthermore, epoxidation of each cyclopropene gave a quantitative yield of enones **2a–d.** Such enone products have been the only products from cyclopropenes of this type when treated with peracid.[4] The detailed stereochemistry of the enone products will be the subject of a separate paper that relates not to the epoxidation of cyclopropenes, but to the fragmentation of oxabicyclobutanes. As a final structure proof ozonolysis of **1d** gave the expected 2-methyl-2-isopropyl-1,3-cyclooctadione, along with a small amount of a lactone (see Experimental Section) formed by a Baeyer–Villiger type of rearrangement.

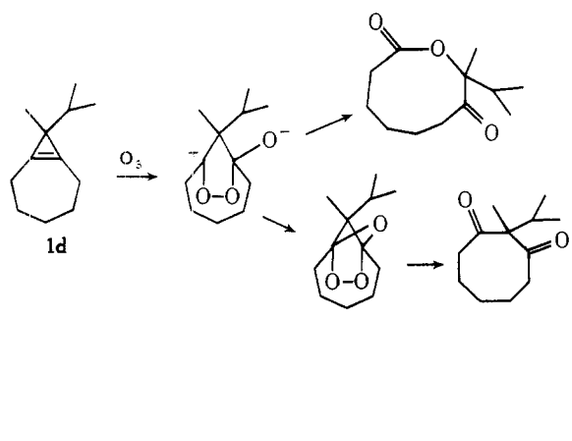


Table I. Relative Rate Constants of Epoxidation[a] of Cyclopropenes[b] 1a–d

Compds	Rel k[c]
1a vs. **1b**	1.97 ± 0.05
1b vs. **1c**	2.68 ± 0.13
	2.98 ± 0.14
1d vs. **1c**	1.27 ± 0.02

[a] *m*-Chloroperbenzoic acid in CCl_4 at 0 °C. [b] ~0.01 M. [c] Errors are standard deviations of the calculated relative k's from a single kinetic run.

Table II. Rate Constants of Epoxidation[a] of Cyclopropenes[b] 1a–d

Compd	Registry no.	k,[c] M^{-1} s^{-1}	Rel k[d]	Rel k[e]
1a, Me, Me	17900-97-9	0.90 ± 0.03	(1.00)	(1.00)
1b, Me, Et	64425-32-7	0.29 ± 0.03[f]	0.32[f]	0.51
1c, Et, Et	64425-33-8	0.16 ± 0.02	0.18	0.18
1d, Me, *i*-Pr	64425-34-9	0.18 ± 0.01	0.20	0.23

[a] *m*-Chloroperbenzoic acid in CCl_4 at 0 °C. [b] ~3×10^{-4} M. [c] Errors are standard deviations with two degrees of freedom from independent runs. Tetramethylcyclopropene has $k = 1.1 \times 10^{-2}$ M^{-1} s^{-1} under the same conditions.[4e] [d] From absolute kinetics in this table. [e] From data in Table I. [f] These numbers may be in error, see text.

The epoxidation kinetic studies were done two ways. Since we are primarily interested in relative rate constants, we performed a series of competitive kinetic experiments in which two cyclopropenes compete for the common peracid.[12] By following the disappearance of the two cyclopropenes, relative second-order rate constants can be obtained.

$$\frac{\ln A/A_0}{\ln B/B_0} = \frac{k_A}{k_B}$$

This method is particularly good for relative k's that are approximately equal to one and produces reliable values even if there may be undetected impurities that destroy peracid. Table I lists these results.

We have also measured absolute kinetics in the standard manner by following the titrimetric disappearance of peracid, see Table II. These absolute values may not be as accurate as the relative rate constant data of Table I because any unrecognized biases in the kinetic method lead to biased rate constants. Table II shows that the competitive relative k's are in good agreement with the absolute kinetics for all compounds except **1b.**

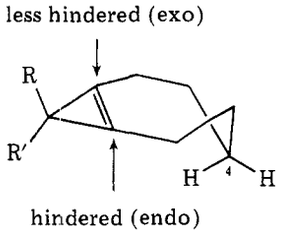
The rate constant for **1b** appears too low in comparison with the other cyclopropenes. There appears to be a reproducible bias in this absolute rate constant. We have chosen to publish this number because, by hindsight, we can find no *chemical* reason to throw out the value. Nevertheless, we have complete confidence in the relative k's that are derived from the data in Table I and will refer to these values in the remaining part of the paper.

Discussion

The inductive effect of the different allylic substituents in the epoxidation of cyclopropenes **1a–d** should be the same because the differences in alkyl substitution occur two carbon atoms removed from the cyclopropene double bond and because σ^* for the differing alkyl substituents are all approximately the same.[13] The rigid position (except for rotational conformers) of the allylic substituents above and below the olefin π system will therefore affect the epoxidation rate constants by primarily a steric effect. Large allylic substituents which cannot rotate out of the way of the entering peracid

should raise the transition-state energy for epoxidation, thereby retarding the rate of epoxidation.

Before a detailed analysis of the relative rate constants is given, it is important to point out an unusual feature of the cyclopropenes. Molecular models of the fused-ring cyclopropenes show that C-3, C-4, and C-5 are not in the plane of the double bond. Atom C-4 is most prominent, which is puckered almost 90° out of the molecular plane. As a result, the endo H on C-4 has a sufficient van der Waals radius that it hinders peracid approach to the endo side of the π system of the

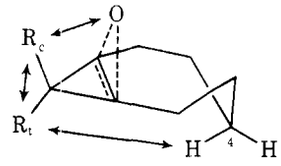


double bond. In fact, models show that the endo side is so hindered that we do not believe that any substantial amount of epoxidation occurs from the endo side.

The endo C-4 hydrogen must absorb at unusually high field in the ^{1}H NMR. Unfortunately, it is only a one-proton absorption which is coupled to five other protons, so that it is not individually seen in the ^{1}H NMR spectrum.

The rate ratio of ~0.5 for **1b/1a** superficially suggests that the ethyl group in **1b** completely blocks epoxidation from the side of the cyclopropene that contains the ethyl group. In conflict with this conclusion is the fact that steric substituent constants, E_s, for Et are only slightly larger than for Me.[14] Even more important is that if the Et completely blocked epoxidation in **1b**, then **1c** with two Et groups should be almost inert to epoxidation from both sides of the double bond. Rather, the rate ratio of **1c/1a** is 0.18, which shows that a simple single linear free-energy relationship cannot be obtained.

An explanation for these rate phenomena can be found by further examination of molecular models. As the allylic substituents are changed, there are three interactions that change in the epoxidation transition state. In addition to potential



interactions between the entering peracid and the cis-substituted cyclopropene allylic substituent, it is evident that there are also potential interactions of the trans cyclopropene allylic substituent with the C-4-endo hydrogen as well as between the two allylic substituents themselves.

These three interactions are not independent. For example, if R_c is Et and R_t is Me, the allylic substituent system forms a butane chain. Peracid–Et interaction is only severe when the butane chain is in a lowest energy anti conformation. Correspondingly, when the butane chain is in a higher energy gauche conformation, the peracid–Et interaction is much reduced. Since these interactions are inversely correlated, there are only approximately two net independent interactions that determine the energy of the epoxidation transition state relative to reactants. Therefore only two observed relative rates are needed to uniquely define the magnitude of these net interactions.

If $\Delta G^{\ddagger}_0$ is the free energy of activation for epoxidation of **1a** from *one side* of the π system, then the rate constant for epoxidation of **1a** from both sides of the π system is

$$k_{1a} = 2\frac{kT}{h}e^{-\Delta G^{\ddagger}_0/RT}$$

For **1c**, there are, as discussed above, two net interactions that raise the free energy of epoxidation above that for **1a**. Let $\Delta\Delta G^{\ddagger}_1$ and $\Delta\Delta G^{\ddagger}_2$ be the two net free-energy increments due to frontside and backside (relative to peracid) interactions. Then

$$k_{1c} = 2\frac{kT}{h}e^{-(\Delta G^{\ddagger}_0+\Delta\Delta G^{\ddagger}_1+\Delta\Delta G^{\ddagger}_2)/RT}$$

For compound **1b**, part of the epoxidation occurs cis to the Me and trans to the Et substituent where the partial rate factor is

$$k_{1b}(\mathrm{Me}) = \frac{kT}{h}e^{-(\Delta G^{\ddagger}_0+\Delta\Delta G^{\ddagger}_2)/RT}$$

Only $\Delta\Delta G^{\ddagger}_2$ is included with $\Delta G^{\ddagger}_0$, since the assumption is that there is only one net independent energy increment of the backside Et group with either the Me or the C-4 ring hydrogen. Similarly, the partial rate constant for epoxidation cis to the Et group in **1b** is

$$k_{1b}(\mathrm{Et}) = \frac{kT}{h}e^{-(\Delta G^{\ddagger}_0+\Delta\Delta G^{\ddagger}_1)/RT}$$

The total expression for k_{1b} is a sum of the partial rate factors

$$k_{1b} = \frac{kT}{h}e^{-(\Delta G^{\ddagger}_0+\Delta\Delta G^{\ddagger}_1)/RT} + \frac{kT}{h}e^{-(\Delta G^{\ddagger}_0+\Delta\Delta G^{\ddagger}_2)/RT}$$

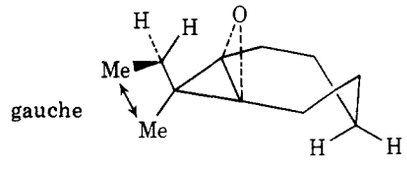
With these assumptions expressions can be written for the relative rate ratios in Table II. Solution of these equations gives

$$k_{1b}/k_{1a} = 0.51 = \tfrac{1}{2}(e^{-\Delta\Delta G^{\ddagger}_1/RT} + e^{-\Delta\Delta G^{\ddagger}_2/RT})$$

$$k_{1c}/k_{1a} = 0.18 = e^{-(\Delta\Delta G^{\ddagger}_1+\Delta\Delta G^{\ddagger}_2)/RT}$$

$\Delta\Delta G^{\ddagger}_1 = 805 \pm 40$ or 126 ± 10 cal/deg mol^{-1} with $\Delta\Delta G^{\ddagger}_2 =$ 126 or 805 cal/deg mol^{-1}, respectively. A distinction between the two solutions cannot be made mathematically, but can be deduced from conformational thermodynamics.

As defined above, $\Delta\Delta G^{\ddagger}_1$ is the frontside free-energy increase when peracid attacks cyclopropene **1b** cis to the Et group. As indicated above, this epoxidation probably occurs with a gauche butane conformation for the two allylic substituents. In the starting cyclopropene, the conformation of



the butane unit is most likely anti with the Et group rotated toward the cyclopropene double bond. The change in free energy of the butane unit between starting material and transition state is then

$$\Delta\Delta G^{\ddagger} = \Delta H^{\ddagger}_{\text{gauche Bu}} - T(R \ln 2)$$

The R ln 2 term is included because there are two degenerate gauche conformations. With an enthalpy of 800 cal/deg mol^{-1} for a gauche butane interaction,[15] $\Delta\Delta G^{\ddagger} = 425$ cal/deg mol^{-1}. This is the minimum possible value for $\Delta\Delta G^{\ddagger}_1$. To this must be added any peracid–Et interaction. As a result, we conclude

that $\Delta\Delta G^{\ddagger}_1$ is the larger value of 805 cal/deg mol^{-1}. The smaller value, $\Delta\Delta G^{\ddagger}_2$ = 126 cal/deg mol^{-1}, corresponds to the net increment interaction of an Et group (compared to Me) with the molecule on the backside when the butane group is in an energy minimum conformation.

The above analysis leads to the reasonable conclusion that the ratio of partial rate factors for **1b** is

$$\frac{k_{1b}(\mathrm{Me})}{k_{1b}(\mathrm{Et})} = e^{-(\Delta\Delta G^{\ddagger}_2 - \Delta\Delta G^{\ddagger}_1)/RT} = \frac{78}{22}$$

Finally, an analysis is needed for why **1d**/**1a** is 0.23. There are various conformational assumptions that can be made about the differences between the Et group in **1b** and the *i*-Pr group in **1d.** Since each assumption is speculation, we prefer to analyze the simplest phenomenological assumption, i.e., that the net effect of the *i*-Pr group in **1d** is some multiple factor, q, of the effect of the Et in **1b.** If so, the partial rate constants for epoxidation of **1d** would be

$$k_{1d}(\mathrm{Me}) = \frac{kT}{h} e^{-(\Delta G^{\ddagger}_0 + q(\Delta\Delta G^{\ddagger}_2))/RT}$$

$$k_{1d}(i\text{-Pr}) = \frac{kT}{h} e^{-(\Delta G^{\ddagger}_0 + q(\Delta\Delta G^{\ddagger}_1))/RT}$$

Then

$$k_{1d}/k_{1a} = 0.23 = \tfrac{1}{2}(e^{-q\Delta\Delta G^{\ddagger}_2/RT} + e^{-q\Delta\Delta G^{\ddagger}_1/RT})$$

Using the previously determined values of $\Delta\Delta G^{\ddagger}_1$ and $\Delta\Delta G^{\ddagger}_2$, q is found to be 3.4 with an estimated standard deviation of ~0.3. Experimentally, this means that the net steric difference between *i*-Pr and Me is about three and a half times as great as the steric difference between Et and Me. This is not at all unreasonable because in standard systems, *i*-Pr has a steric substituent constant, E_s, which is six to nine times greater than Et (E_s for Me = 0).[13,14]

A possible reason why q is 3.4 instead of a larger value as in standard systems is *not* because *i*-Pr presents a smaller steric size, but perhaps because Et presents a larger size than in standard systems. In standard systems, an Et can rotate out of the way of a crowded transition state. In the cyclopropenes **1b,c**, such a movement away from the π double bond only results in a gauche or eclipsing butane-like conformation. In other words, the quaternary allylic cyclopropene center presents sufficient congestion to the regions surrounding the double bond in the epoxidation transition state that substituents of any size have moderately large steric interactions in all conformations.

An alternate explanation for q = 3.4 does not rely on an unusually congested transition state. Rather, Hancock[14b] has recognized that E_s's for Et and *i*-Pr are less negative than their true steric effect would indicate. The reason is because of a hyperconjugative interaction between the α hydrogen C–H bonds of the substituents and the reaction center in the acid-catalyzed hydrolysis of esters. Such hyperconjugation stabilizes the starting ester and causes the hydrolysis to occur slower than the true steric effect of the substituent would indicate. The effect is greatest for Me because of the three α hydrogens and amounts to a change in E_s of ~0.3 per α hydrogen. Relative to Me (E_s = 0), the corrected E_s's for Et and *i*-Pr are −0.38 and −1.08, respectively. In other words, the true steric effect of *i*-Pr is only 2.84 times greater than Et (relative to Me). This value is similar to our calculated q = 3.4 ± 0.3.

Using q = 3.4, the ratio $k_{1d(Me)}/k_{1d}$(*i*-Pr) is 99:1, which shows a large selectivity for formation of only one oxabicyclobutane.

Conclusion

Four fused-ring cyclopropenes with varying allylic substituents were epoxidized. Relative rate constant ratios show that contrary to standard systems, the steric effect of an allylic Et group is significantly larger than that of a Me group. The reason for the difference may be because in the standard acid-catalyzed hydrolysis of esters, substituents with α hydrogens retard hydrolysis by a hyperconjugative mechanism, thereby causing E_s to contain not only a steric effect, but also an electronic effect.

Experimental Section

General. Instruments were used as follows: melting point, Fisher-Johns; GC, Perkin-Elmer 900, Varian A-90P, Hewlett-Packard 720; UV, Cary 118; IR, Perkin-Elmer 137 or 467; ^{1}H NMR, JEOLCO C-60HL or MH-100; ^{13}C NMR, JEOLCO PFT-100; MS, Perkin-Elmer RMU-6E or Du Pont 21-490B. Elemental analyses were obtained from Chemalytics, Inc., Tempe, Ariz.

2-(Dithiomethoxymethylene)cycloheptanone. Following Corey's procedure for the six-membered ring homologue,[16] 145.2 mL (0.353 mol) of 2.43 M *n*-butyllithium in hexane was added over 0.5 h to 77.7 g (0.352 mol) of 2,6-di-*tert*-butyl-*p*-cresol (DBPC) in 2 L of anhydrous ether at 0 °C under N_2. The white cloudy mixture was warmed to room temperature and 18.50 g (0.165 mol) of cycloheptanone with 60.7 g (0.800 mol) of carbon disulfide were added over 15 min. The bright yellow reaction mixture was stirred at room temperature for 21 h. Then 62.5 g (0.441 mol) of methyl iodide was added and the mixture was stirred at room temperature for an additional 4.5 h. The reaction was poured into 1.5 L of water. The phases were separated and the water solution was extracted twice with ether. Most of the ether was distilled from the combined ether solutions. The organic solution was then dried with Na_2SO_4, filtered, and concentrated. The yellow liquid was cooled to −20 °C and seeded with DBPC. The yellow solid was isolated and recrystallized from pentane. The filtrates containing product and DBPC were then combined, concentrated, and cooled to −20 °C. This process was repeated until a solution was obtained that contained approximately equal amounts (by ^{1}H NMR) of DBPC and product. The DBPC was then distilled under vacuum, bp 66–92 °C (0.25 mm), yielding a dark yellow liquid in the pot which was the desired product, 18.39 g (51%), purity 80–90% by ^{1}H NMR. This crude product was not purified for the next reaction. A sample for analysis was purified by silica gel chromatography and a pure sample was finally obtained by preparative GC (6 ft, 5% Carbowax 20M on Chromosorb W, 140 °C): IR (neat) 1693 cm^{-1}; ^{1}H NMR (CCl_4) 2.70–2.37 (4 H, m), 2.33 (3 H, s), 2.25 (3 H, s), 1.82–1.71 (6 H, m); UV (hexanes) 223 sh (ϵ 3280), 270 (3430), 297 nm sh (2690); MS (70 eV) *m/e* 216 (M$^+$, 43), 203 (10), 202 (12), 201 (100), 173 (13), 169 (30), 125 (33), 93 (37), 85 (28).

Anal. Calcd for $C_{10}H_{16}OS_2$: C, 55.51; H, 7.45. Found: C, 55.54; H, 7.16.

2-Isopropylidenecycloheptanone (2a). A black solution of lithium dimethylcuprate was made by the method of Johnson and Duka[17] with 8.87 g (46.6 mmol) of CuI in 29 mL of dry ether. This solution was added over 40 min under N_2 to 4.55 g (21.1 mmol) of crude 2-(dithiomethoxymethylene)cycloheptanone in 25.0 mL of dry ether at −78 °C. The reaction mixture was stirred at −78 °C for 45 min, and then 16 mL of methanol was cautiously added. The solution was warmed to room temperature and water was added. The mixture was filtered, the phases were separated, and the water solution was acidified with concentrated HCl and extracted three times with ether. The combined organic solutions were dried with Na_2SO_4 and concentrated. The yellow liquid was vacuum distilled to give 2.08 g (65%) of a colorless liquid, bp 101–102 °C (11 mm) [lit.[8] 120–124 °C (17 mm)]. An analytical sample was obtained by preparative GC (10 ft, 20% Carbowax 20M on Chromosorb P, 153 °C): IR (neat) 1678, 1619 cm^{-1}; ^{1}H NMR (CCl_4) δ 2.53–2.18 (4 H, m), 1.81 (3 H, s), 1.76 (3 H, s), 1.72–1.43 (6 H, m); UV (hexanes) 238 (ϵ 7290), 323 nm (70); MS (70 eV) *m/e* 152 (M$^+$, 65), 137 (15), 124 (12), 109 (51), 95 (26), 82 (100), 81 (65), 68 (42), 67 (76).

Preparation of Tosylhydrazones. Following the general procedure of Closs,[7b] 50 mmol of the enone was dissolved in 15 mL of MeOH and warmed to ~45 °C. Then 50 mmol of tosylhydrazide was added with stirring over several minutes, followed by stirring for periods from one-half to several hours. The mixture was cooled to 0 °C for 12 h and filtered, and the product was recrystallized as desired.

2-Isopropylidenecycloheptanone tosylhydrazone: mp 158–161 °C dec (from CH_2Cl_2) (lit.[7b] 171–172 °C); IR (KBr) 3200, 1681, 1583

cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.78 (2 H, d, J = 8 Hz), 7.45 (1 H, br s), 7.20 (2 H, d, J = 8 Hz), 2.38 (3 H, s), 2.34–2.01 (4 H, m), 1.72–1.25 (6 H, m), 1.62 (3 H, s), 1.47 (3 H, s); UV (MeOH) 225 (ϵ 12 920), 274 nm sh (1610); MS (70 eV) m/e 320 (M^+, 1), 166 (10), 165 (100), 109 (30), 91 (12).

Anal. Calcd for $C_{17}H_{24}N_2O_2S$: C, 63.72; H, 7.55; N, 8.74. Found: C, 63.51; H, 7.55; N, 8.92.

(*Z*)- and (*E*)-2-(2-Butylidene)cycloheptanone tosylhydrazone: mp 152–154 °C dec (from MeOH); NMR ($CDCl_3$) δ 0.50–1.30 (3 H, m), 1.62 (3 H, s), 1.30–1.93 (6 H, m), 1.93–2.47 (6 H, m), 2.44 (3 H, s), 7.17–7.51 (3 H, m), 7.67–8.04 (2 H, m); MS (70 eV) m/e 334 (M^+, 4) 179 (100), 151 (94) 135 (75), 121 (91), 107 (50), 93 (75), 91 (75), 79 (69), 77 (44), 67 (44).

2-(3-Pentylidene)cycloheptanone tosylhydrazone: ^1H NMR ($CDCl_3$) δ 7.82 (2 H, d, J = 8.0 Hz), 7.25 (2 H, d, J = 8.0 Hz), 7.25 (1 H, s), 2.40 (3 H, s), 2.38–1.94 (4 H, m), 2.02 (2 H, q, J = 7.5 Hz), 1.75–1.36 (6 H, m), 1.65 (2 H, q, J = 7.5 Hz), 0.96 (3 H, t, J = 7.5 Hz), 0.60 (3 H, t, J = 7.5 Hz).

(*E*)- and (*Z*)-2-(3-Methyl-2-butylidene)cycloheptane tosylhydrazone: mp 162–164 °C dec (from CH_2Cl_2); IR (KBr) 3208, 1598 cm^{-1}; H NMR ($CDCl_3$) 7.74 (2 H, d, J = 8 Hz), 7.29 (1 H, br s), 7.27 (2 H, d, J = 8 Hz), 2.36 (3 H, s), 2.32–1.93 (5 H, m), 1.66–1.25 (6 H, m), 1.47 (2.25 H, s), 1.07 (0.75 H, s), 0.88 (1.5 H, d, J = 7 Hz), 0.62 (4.5 H, d, J = 7 Hz); UV (MeOH) 225 (ϵ 12 960), 274 nm (1370); MS (70 eV) m/e 349 (M + 1, 0.4), 348 (M^+, 0.4), 194 (15), 193 (100), 178 (23), 151 (57), 95 (14), 91 (15).

Anal. Calcd for $C_{19}H_{28}N_2O_2S$: C, 65.48; H, 8.10; N, 8.04. Found: C, 65.25; H, 7.86; N, 8.24.

Preparation of Cyclopropenes 1a–d. Following the general procedure of Durr,[18] N_2 was bubbled through a solution of 15 mmol of tosylhydrazone (pure or mixture) in 350 mL of purified dioxane for 3 h. Next, 60 mmol of NaOMe was added and stirred under N_2 for 6 h. The solution was irradiated through Pyrex with a 450-W Hanovia medium-pressure mercury-arc lamp. Evolved N_2 was collected and measured. Typically, N_2 evolution would cease after ~8 h with ~50% conversion to N_2. The reaction was poured into ether and washed several times with water. The remaining ether solution was washed with 0.6 M $NaHCO_3$ and dried over Na_2SO_4. The solvent was rotoevaporated to give an oil which was purified by preparative GC. The cyclopropenes could not be sent away for analysis because they react slowly with air.

$\Delta^{1,7}$-8,8-Dimethylbicyclo[5.1.0]octene (1a). GC (10 ft, 10% SE-30 on Chromosorb W, nonacid washed, 81 °C) showed three products. I: cyclopropene **1a**, area ratio ~50%; retention time 15 min; ^1H NMR (CCl_4) δ 2.54–2.18 (4 H, m), 1.94–1.47 (6 H, m), 1.15 (6 H, s) [lit.[7b] δ 1.15 (6 H, s)]. II: 1-(1-propen-2-yl)cycloheptene, area ratio 20%; retention time 31 min; ^1H NMR (CCl_4) δ 5.97 (1 H, t, J = 7 Hz), 4.94 (1 H, s), 4.80 (1 H, s), 2.49–2.11 (4 H, m), 1.85 (3 H, s), 1.94–1.35 (6 H, m). III: 3-isopropylidenecycloheptene, area ratio ~30%; retention time, 35 min; ^1H NMR (CCl_4) δ 6.30 (1 H, d, J = 10 Hz), 5.83–5.48 (1 H, m), 2.57–1.85 (4 H, m), 1.85–1.48 (4 H, m), 1.73 (6 H, s) [lit.[19] ^1H NMR agrees].

$\Delta^{1,7}$-8-Ethyl-8-methylbicyclo[5.1.0]octene (1b): GC, 10 ft 10% SE-30 on Anakrom ABS, 89 °C, retention time 17 min; IR (CCl_4) 1850, 1710 cm^{-1}; ^1H NMR δ 2.51–2.22 (4 H, m), 2.02–1.35 (8 H, m), 1.11 (3 H, s), 0.67 (3 H, t, J = 7.5 Hz); MS (70 eV) m/e 150 (M^+, 42), 135 (70), 121 (93), 107 (88), 92 (100), 79 (86).

$\Delta^{1,7}$-8,8-Diethylbicyclo[5.1.0]octene (1c): GC, 10 ft, 10% SE-30 on Anakrom ABS, 105 °C; IR (neat) 1846 cm^{-1}; ^1H NMR (CCl_4) δ 2.54–2.09 (4 H, m), 2.09–1.24 (6 H, m), 1.56 (4 H, q, J = 7.5 Hz), 0.64 (6 H, t, J = 7.5 Hz); MS (70 eV) m/e 164 (M^+, 53), 149 (15), 136 (14), 135 (100), 121 (22), 107 (33), 93 (63), 91 (28), 81 (28), 79 (48), 67 (30), 55 (30), 41 (36). In addition, 3-(3-pentylidene)cycloheptene was obtained: IR (neat) 3016 cm^{-1}; ^1H NMR (CCl_4) δ 6.20 (1 H, d, J = 12 Hz), 5.49 (1 H, d of t, J = 12, 5 Hz), 2.53–1.80 (4 H, m), 2.06 (4 H, q, J = 7.5 Hz), 1.80–1.28 (4 H, m), 0.96 (6 H, t, J = 7.5 Hz).

$\Delta^{1,7}$-8-Isopropyl-8-methylbicyclo[5.1.0]octene (1d): GC, 10 ft, 10% SE-30 on Chromosorb W, nonacid washed; IR (CCl_4) 1845, 1382, 1370 cm^{-1}; ^1H NMR (CCl_4) δ 2.74–2.19 (4 H, m), 2.19–1.21 (7 H, m), 1.08 (3 H, s), 0.74 (6 H, d, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ_{Me_4Si} 134.15, 42.35, 40.41, 35.98, 32.22, 30.70, 26.40, 25.12; UV (hexanes) 210 end absorption (ϵ 1680), 242 nm sh (370).

Boron Difluoride Complex of 2-Propionylcycloheptanone (3). Following the method of Hauser,[9] boron trifluoride gas was bubbled into 133 g (1.78 mol) of propionic acid with mechanical stirring for 20 min. A white semisolid formed. The gas inlet was replaced by a dropping funnel filled with 49.9 g (0.445 mol) of cycloheptanone and 115.7 g (0.890 mol) of propionic anhydride, which was added under N_2 with ice cooling. After 5 h, 1 L of water was added causing the complex to precipitate. The solid was filtered and dried for 48 h in a vacuum drying oven, giving 77.0 g (79.9%) of a yellowish powder. The complex was used without further purification. A sample which was recrystallized from benzene gave the following properties: mp 75–77 °C; IR ($CHCl_3$) 1530, 1500 cm^{-1}; NMR ($CDCl_3$) δ 1.23 (3 H, t, J = 7.5 Hz), 1.5–2.0 (6 H, m), 2.3–2.9 (6 H, m).

Anal. Calcd for $C_{10}H_{15}BF_2O_2$: C, 55.60; H, 6.99. Found: C, 55.69; H, 7.15.

(*Z*)- and (*E*)-2-(2-Butylidene)cycloheptanone (2b). Following the analogy of Smith and Spencer,[10] a 188-mL portion (0.334 mol) of 1.77 M MeLi (Alfa, titrated by Gilman's method[20]) was added dropwise to 36.17 g (0.167 mol) of the borate complex **3** in 360 mL of benzene (passed through activity I alumina). After 0.5 h the reaction was quenched with 300 mL of a ~0.1 M aqueous NH_4Cl. A gelatinous precipitate formed that was removed by suction filtration. Approximately 0.5 g of p-toluenesulfonic acid was added and the solution was heated to reflux and water was azeotropically removed with a Dean–Stark trap over a period of several hours. The solution was washed with three 500-mL portions of water and dried over Na_2SO_4 and the solvent was removed on a rotary evaporator, leaving 33.0 g (120%) of yellow oil, which, by VPC analysis, was found to consist of ~40% of the two enones.

The Z and E isomers were separated and collected by VPC using a 6-ft 20% Carbowax 20M column at 110 °C. The isomer with the longer retention time has: IR (CCl_4) 1668, 1605 cm^{-1}; ^1H NMR (CCl_4) δ 1.02 (3 H, t, J = 7.5 Hz), 1.79 (3 H, s) 1.40–1.86 (9 H, m), 1.86–2.57 (6 H, m); ^1H NMR (PhH) δ 1.93 (3 H, s), 0.82 (3 H, t, J = 7 Hz). The isomer with the shorter retention time has: IR (CCl_4), 1668, 1614 cm^{-1}; ^1H NMR (CCl_4) δ 1.00 (3 H, t, J = 7.5 Hz), 1.71 (3 H, s), 1.35–1.89 (6 H, m), 1.90–2.58 (6 H, m); ^1H NMR (PhH) δ 1.47 (3 H, s), 1.07 (3 H, t, J = 7 Hz). A mixture of the two enones gave: MS (70 eV) m/e 166 (M^+, 100), 151 (26), 137 (56), 123 (39), 109 (80), 96 (50), 81 (62).

1-Chlorocycloheptene. The material was made in 53% yield by the procedure of Braude from PCl_5 and cycloheptanone: bp 66–71 °C (19 mm) [lit. 54–58 °C (14 mm)[21]]; IR (neat) 3042, 1647 cm^{-1}; ^1H NMR (CCl_4) δ 5.84 (1 H, t, J = 6.2 Hz), 2.72–2.33 (2 H, m), 2.33–1.88 (2 H, m), 1.88–1.10 (6 H, m). Also, a 20% conversion of 1,1-dichlorocycloheptane was obtained in this reaction: bp 71–74 °C (8 mm); ^1H NMR (CCl_4) δ 2.74–2.34 (4 H, m), 1.96–1.39 (8 H, m).

Isobutyryl Chloride. Following the procedure of Bosshard[22] et al., a 10.20-g (0.116 mol) portion of isobutyric acid (Eastman) with 8 drops of DMF (Mallinckrodt) was added dropwise at room temperature over 1 h with stirring to 15.05 g (0.126 mol) of distilled thionyl chloride (Eastman) in a 50-ml round-bottom flask. The reaction solution was stirred at 40 °C for 4.5 h. The product was distilled at atmospheric pressure through a 15-cm Vigreux column. Conversion: 9.90 g (80%); bp 90.0–91.5 °C [lit.[23] 90–92 °C]; IR (neat) 1865, 1805, 1768, 1391, 1371 cm^{-1}; ^1H NMR (CCl_4) δ 2.91 (1 H, heptet, J = 6.8 Hz), 1.30 (6 H, d, J = 6.8 Hz).

2-Chloro-3-isobutyrylcycloheptene. A 7.36-g portion (69.1 mmol) of isobutyryl chloride was added over 5 min to 11.53 g (86.5 mmol) of $AlCl_3$ (Fisher) in 52 mL of CH_2Cl_2. The mixture was stirred for 15 min and filtered through glass wool into a three-neck flask under N_2. A 9.00-g portion (69 mmol) of 1-chlorocycloheptene was added dropwise over 10 min at −15 °C under N_2. The reaction mixture was stirred at −20 °C for an additional 10 min and then slowly warmed to +10 °C over 1.5 h. The reaction was quenched by cautiously pouring it into 100 mL of a 3.2 M aqueous HCl with 75 mL of ice. The water layer was extracted twice with CH_2Cl_2. The combined organic solutions were washed once with water and dried with Na_2SO_4. Distillation gave: 6.55 g (47%); bp 74–77 °C (0.64 mm); IR (neat) 3039, 1713, 1646, 1388, 1371 cm^{-1}; ^1H NMR (CCl_4) δ 6.06 (1 H, t, J = 6.5 Hz), 3.75–3.50 (1 H, m), 2.85 (1 H, septet, J = 6.9 Hz), 2.36–1.43 (8 H, m), 1.09 (6 H, d, J = 7.0 Hz); UV (hexanes) 276 nm (ϵ 300); MS (70 eV) m/e 202 (M + 2, 1), 200 (M^+, 2), 93 (11), 71 (66), 43 (100), 41 (18).

Anal. Calcd for $C_{11}H_{17}ClO$: C, 65.83; H, 8.54. Found: C, 65.70; H, 8.49.

6-Isobutyryl-1,4-dioxaspiro[4.6]undecane (4b). A 12.15-g (60.6 mmol) portion of 2-chloro-3-isobutyrylcycloheptene was added over 5 min to a refluxing mixture of 3.76 g (67.0 mmol) of 85% KOH pellets and 30.14 g (485 mmol) of ethylene glycol in 37 mL of p-dioxane. After refluxing for 40 h, the mixture was added to H_2O and extracted with four portions of Et_2O. The ether solution was dried over $MgSO_4$ and distilled to give 7.27 g (53%), bp 83–85 °C (0.3 mm). An analytical sample was prepared by GC (6 ft, 5% Carbowax 20 M on Chromosorb W, nonacid washed, 105 °C): IR (neat) 1710, 1384, 1310 cm^{-1}; ^1H NMR (CCl_4) δ 3.78 (4 H, s), 3.12–2.92 (1 H, m), 2.65 (1 H, heptet, J = 7 Hz), 2.03–1.19 (10 H, m), 0.99 (6 H, d, J = 7 Hz); UV (hexanes) 286 nm (ϵ 67); MS (70 eV) m/e 226 (M^+, 9), 183 (61), 113 (11), 100 (10), 99 (100), 55 (34), 43 (52).

Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.74; H,

9.91.

(*E*)- and (*Z*)-2-(3-Methyl-2-butylidene)cycloheptanone (2d). A 1.56-g portion (7.0 mmol) of keto ketal **4b** in 9.6 mL of dry pentane was reacted at 0 °C with 8.9 mL (14.4 mmol) of 1.62 M MeLi. The reaction solution was stirred at 0 °C for 4 h and was then cautiously quenched with 20 mL of saturated aqueous NH_4Cl solution. The phases were separated and the water solution was extracted twice with ether. The combined organic solutions were dried with Na_2SO_4, filtered, and concentrated to give the tertiary carbinol as a yellow oil: 1.46 g (86%); IR (neat) 3451 (br), 1654 cm^{-1}; ^1H NMR (CCl_4) δ 4.10–3.45 (4 H, m), 2.5–1.3 (13 H, m), 1.3–0.7 (9 H, m with strong signals at 1.20, 1.00, 0.92, and 0.84). The crude product was directly dehydrated and deketalized.

A solution of 8.3 g (34 mmol) of the crude hydroxy ketal and 23.5 mL of 1.3 M H_2SO_4 in 235 mL of MeOH was refluxed for 1.25 h. The solution was cooled, poured into 360 mL of water, and extracted with four portions of ether.

The yellow ether solutions was dried with Na_2SO_4, and the solvent was removed to give 3.51 g (67%) of crude oil which was used in the tosylhydrazone formation. A portion of the enone mixture was distilled, bp 78–78 °C (0.80 mm), GC chromatographed (10 ft, 20% Carbowax 20 M on Chromosorb P, nonacid washed), and redistilled: IR (neat) 1679, 1617, 1391, 1367 cm^{-1}; ^1H NMR (CCl_4) δ 2.82 (1 H, heptet, J = 6.5 Hz), 2.52–2.09 (4 H, m), 1.80–1.42 (6 H, m), 1.61 (1.5 H, s), 1.57 (1.5 H, s), 1.00 (3 H, d, J = 7 Hz), 0.93 (3 H, d, J = 7 Hz); UV (hexanes) 240 (ϵ 4580), 316 nm (ϵ 70).

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.31; H, 11.52.

2-Chloro-3-propionylcycloheptene. Following the same procedure as for vinylchloro ketone **4b,** 25.96 g (0.195 mmol) of aluminum chloride, 14.34 g (0.155 mmol) of propionyl chloride, and 20.20 g (0.155 mmol) of 1-chlorocycloheptene in 122 mL of methylene chloride were reacted and gave 16.06 g (56%) of distilled product: bp 69–71 °C (0.30 mm); IR (neat) 3038, 1718, 1643 cm^{-1}; ^1H NMR (CCl_4) δ 6.03 (1 H, t, J = 6.5 Hz), 3.49–3.28 (1 H, m), 2.34 (2 H, q, J = 7.0 Hz), 2.33–1.43 (8 H, m), 1.05 (3 H, t, J = 7.0 Hz); MS (70 eV) m/e 188 (M + 2, 1), 186 (M^+, 3), 95 (10), 93 (6), 79 (6), 77 (5), 57 (100), 39 (5).

6-Propionyl-1,4-dioxaspiro[4.6]undecane (4a). Following the procedure for spiro ketone **4b,** 6.17 g (9.35 mmol) of 85% KOH pellets, 41.93 g (0.676 mmol) of ethylene glycol, and 15.75 g (84.5 mmol) of 2-chloro-3-propionylcycloheptene in 50 mL of *p*-dioxane were heated at reflux for 23 h. Workup as before and distillation gave 10.69 g (60%) of the product: bp 85–95 °C (0.70 mm); IR (neat) 1712 cm^{-1}; ^1H NMR (CCl_4) δ 3.78 (4 H, s), 3.00–2.16 (3 H, m), 1.97–1.29 (10 H, m), 0.94 (3 H, 5, J = 7.5 Hz); MS (70 eV) m/e 212 (M^+, 10), 183 (32), 155 (38), 113 (18), 100 (10), 99 (100), 57 (19), 55 (18), 41 (11).

2-(3-Pentylidene)cycloheptanone (2c). Following the procedure for the preparation of enone **2d,** 12.26 g (57.8 mmol) of keto ketal **4a** in 80 mL of purified pentane was reacted at 0 °C with 121 mL (91.6 mmol) of 0.757 M ethyllithium in benzene to give 14.27 g (102%) of a crude oily tertiary carbinol: ^1H NMR (CCl_4) δ 4.18–3.38 (5 H, m), 2.58–1.10 (15 H, m), 0.81 (6 H, t, J = 7.5 Hz). This oil was used without further purification. A 14.27-g (59 mmol) portion of hydroxy ketal was hydrolyzed and eliminated as for enone **2d** with 38 mL of 1.3 M H_2SO_4 in 363 mL of methanol. The crude product (5.92 g, 56%) was distilled, bp 69–80 °C (0.70 mm). An analytical sample was collected by VPC (10 ft, 20% Carbowax 20 M on Chromosorb P, nonacid washed, 160 °C): IR (neat) 1681, 1608 cm^{-1}; ^1H NMR (CCl_4) δ 2.61–1.82 (8 H, m), 1.82–1.35 (6 H, m), 1.18–0.72 (6 H, m); MS (70 eV) m/e 180 (M^+, 93), 152 (14), 151 (96), 137 (51), 123 (45), 110 (34), 109 (25), 95 (41), 81 (100), 79 (22), 69 (20), 67 (63), 55 (59), 41 (59).

Ozonolysis of $\Delta^{1,7}$-8-Isopropyl-8-methylbicyclo[5.1.0]octene (1d). A 0.1147-g (0.70 mmol) sample of cyclopropene **1d** with 15 mL of spectrograde methylene chloride (Mallinckrodt) was placed in a 25 × 200 mm side-arm test tube. The solution was cooled to −78 °C and ozone (Welsbach T-408 Ozonator) was bubbled through the solution until the solution turned blue. The excess ozone was purged with oxygen and 0.64 g (10.3 mmol) of dimethyl sulfide (Me_2S) was added at −78 °C. The reaction sat at −78 °C for 15 min, then was warmed to room temperature and sat another 15 min. The solvent and excess Me_2S were evaporated and pentane was added. The product solution was washed with water and dried with Na_2SO_4. Concentration left 0.11 g (80%) of a yellow oil. Two products were collected by GC (6 ft, 5% Carbowax 20 M on Chromosorb W, nonacid washed). The major product, conversion ~60%, identified as the expected 2-isopropyl-2-methylcycloocta-1,3-dione, had the following spectra data: IR (CCl_4) 1713, 1687, 1395, 1378 cm^{-1}; ^1H NMR (CCl_4) δ 2.56 (1 H, septet, J = 6.7 Hz), 2.51–2.13 (4 H, m), 1.98–1.40 (6 H, m), 1.16 (3 H, s), 0.79 (6 H, d, J = 6.8 Hz); MS (70 eV) m/e 196 (M^+, 17), 99 (13), 98 (55), 97 (14), 83 (100), 71 (22), 55 (73), 41 (38). The minor product, conversion ~20%, identified as 2-isopropyl-2-methyl-3-oxacyclonona-1,4-dione had the following spectral data: IR (CCl_4) 1740, 1720, 1395, 1381 cm^{-1}; ^1H NMR (CCl_4) δ 2.89–1.50 (11 H, m), 1.52 (3 H, s), 0.99 (3 H, d, J = 6.7 Hz), 0.79 (3 H, d, J = 6.7 Hz); MS (70 eV) m/e 212 (M^+, 0.3), 126 (37), 99 (39), 98 (63), 83 (19), 80 (25), 70 (40), 69 (57), 56 (18), 55 (100).

Products from Epoxidation of Cyclopropenes 1a–d. All product runs were done in CCl_4 at 0 °C with ~0.05 M cyclopropene and 0.05 M 85% *m*-chloroperbenzoic acid. After 2–11 h, the organic solution was washed with 0.6 M of $NaHCO_3$, dried over Na_2SO_4, and concentrated. Analysis by ^1H NMR and GC (Carbowax) showed the respective enones **2a–d** as the major or sole products. Minor signals in the ^1H NMR were attributed to further oxidation of the primary enone products.

Absolute Kinetics. The procedure used was essentially the same as described earlier by Friedrich and Fiato.[4e]

Competitive Kinetics. A mixture of approximately 0.01 M in each cyclopropene, A and B, along with 0.01 M undecane or decane as an internal standard was prepared in CCl_4 (Eastman Spectro ACS) in a 5-mL volumetric flask. The flask was kept at 0 °C. From 10- to 100-μL portions of 0.13 M *m*-chloroperbenzoic acid in CCl_4 (saturated) were added and the flask was shaken. Ten minutes after each addition, aliquots of the solution were analyzed by GC with a flame ionization detector (15 ft, 10% Carbowax 20 M on Chromosorb P, nonacid washed, 120 °C). The areas of the two cyclopropenes were divided by the area of the internal standard. The normalized cyclopropene areas were fitted to the following equation to find the best value of k_A/k_B. A general least-squares program was used which provides weighting for each observable. The data was also visually examined by a plot of ln A_t vs. ln B_t, on which was indicated the calculated slope and intercept.

$$\frac{\ln (A_t/A_0)}{\ln (B_t/B_0)} = \frac{k_A}{k_B}$$

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Registry No.—**2a,** 23438-72-4; **2a** tosylhydrazone, 17826-99-2; (*E*)-**2b,** 64425-35-0; (*E*)-**2b** tosylhydrazone, 64425-36-1; (*Z*)-**2b,** 64425-37-2; (*Z*)-**2b** tosylhydrazone, 64425-38-3; **2c,** 64425-39-4; **2c** tosylhydrazone, 64425-40-7; (*E*)-**2d,** 64425-41-8; (*E*)-**2d** tosylhydrazone, 64425-42-9; (*Z*)-**2d,** 64425-43-0; (*Z*)-**2d** tosylhydrazone, 64425-44-1; **3,** 64440-65-9; **4a,** 64425-45-2; **4a** tertiary carbinol derivative, 64425-52-1; **4b,** 64425-46-3; **4b** tertiary carbinol derivative, 64425-53-2; 2-(dithiomethoxymethylene)cycloheptanone, 61539-01-3; 2,6-di-*tert*-butyl-*p*-cresol, 128-37-0; cycloheptanone, 502-42-1; 1-(1-propen-2-yl)cycloheptene, 64425-47-4; 3-isopropylidenecycloheptene, 53147-82-3; boron trifluoride, 7637-07-2; propionic anhydride, 123-62-6; 1-chlorocycloheptene, 13294-30-9; 1,1-dichlorocycloheptane, 32617-34-8; isobutyryl chloride, 79-30-1; 2-chloro-3-isobutyrylcycloheptene, 64425-48-5; ethylene glycol, 107-21-1; 2-chloro-3-propionylcycloheptene, 64425-49-6; propionyl chloride, 79-03-8; 2-isopropyl-2-methylcycloocta-1,3-dione, 64425-50-9; 2-isopropyl-2-methyl-3-oxacyclonona-1,4-dione, 64425-51-0; methyllithium, 917-54-4; ethyllithium, 811-49-4.

References and Notes

(1) Taken primarily from the Ph.D. thesis of R. A. Leckonby, University of Rochester, 1976.
(2) Taken in part from the Masters thesis of D. M. Stout, University of Rochester, 1971. D. Stout performed the first synthesis of compound **1b.**
(3) Y.-S. Lam performed the competitive kinetics experiments.
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Synthesis of Epoxides with Electronegative Substituents. Photometric Substrates for Epoxide Hydrase

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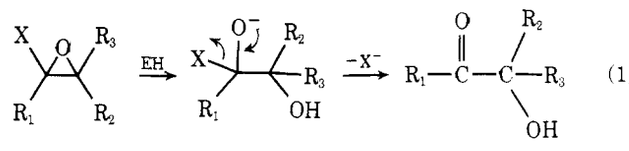
The synthesis of styrene oxides bearing potential leaving groups as α substituents was attempted via peracid epoxidation of the corresponding olefins. Such epoxides were sought as potential photometric substrates for epoxide hydrase. Peracid epoxidations of α-chloro-, α-trimethylsilyloxy-, α-ethoxy-, or α-bromostyrene, as well as α-bromo- or α-(*tert*-butyl)dimethylsilyloxy-*p*-nitrostyrene, lead only to oxidized rearranged products; their epoxides could not be detected among the reaction products. Peracid epoxidation of α-acetoxystyrene and α-methoxy-*p*-nitrostyrene did lead to mixtures containing the desired epoxides, as judged by their NMR spectra, but attempts to isolate these epoxides were unsuccessful due to their great reactivity in the presence of acids or protic solvents. However, using similar methods we were able to synthesize, purify, and characterize the epoxides of α-acetoxy-, α-trifluoroethoxy-, and α-fluoro-*p*-nitrostyrene (**4d, 4h,** and **4i,** respectively). The half-lives of these oxides (0.25 mM) in 0.1 M phosphate buffer (pH 8.00) were 35, 0.4, and 0.4 min, respectively, and each was cleanly hydrated to α-hydroxy-*p*-nitroacetophenone. The hydration of **4d** (which could be monitored conveniently at 310 nm) was accelerated 11-fold by solubilized liver microsomal epoxide hydrase; this compound was not significantly affected by microsomal esterases. The effects of α substituents on the reactivity of styrene oxides and the mechanisms of their rearrangements are discussed. A mechanism involving a halonium ion–enol π complex is proposed to account for the fact that chloro- and bromooxiranes readily undergo proton-catalyzed halogen migrations, whereas fluorooxirane **4i** was much less reactive and reacted only with loss of fluoride ion.

The recognition of epoxides as cytotoxic, carcinogenic, and mutagenic metabolites of arenes and olefins has over the past few years stimulated considerable interest in both the enzymatic and nonenzymatic reactivity of this class of compounds.[1-3] The enzyme epoxide hydrase is thought to play a protective role in vivo by converting chemically reactive epoxides to relatively nontoxic diols. The relatively broad substrate specificity of epoxide hydrase has led to the development of numerous chromatographic and radiometric assays for this enzyme.[4] Unfortunately these assays do not lend themselves readily to mechanistic studies of the enzyme, because they are rather tedious and often tend to be less precise than one would like. A photometric assay for epoxide hydrase which could provide continuous data rather than data points would be greatly preferred. Since the oxirane ring itself is not a chromophore which can be observed spectrally in the presence of protein, it thus becomes necessary to consider substrates whose enzymatic hydration can be chemically coupled to the unmasking of a suitable chromophore. In contemplating this problem we came upon the idea that a styrene oxide with a suitable leaving group at the α position should, upon enzymatic hydration, generate an aromatic ketone chromophore as shown below (eq 1). Our reasoning was based on the fact that 1,1-disubstituted epoxides are relatively good substrates for epoxide hydrase[5] and that their enzymatic hydration involves exclusive ($\geq$97%) cleavage of the O–CH_2 bond by a nucleophilic mechanism.[6]

Epoxides bearing good leaving groups directly on the oxirane ring are known to be very unstable and highly prone to rearrangement or hydrolysis.[7] Thus it was apparent from the outset that synthesis of epoxides suitable for enzymatic use according to eq 1 would require a delicate compromise between the electronic (and possibly steric) properties of the aryl group R_1 and the leaving group X. In this paper we report the synthesis and characterization of three such epoxides, one of which is suitable for photometric assay of epoxide hydrase. We also report the attempted syntheses of several related epoxides and discuss the effects of the substituents on the relative reactivity of epoxides of this type.



(1)

Results and Discussion

In designing a photometric substrate for a particular enzyme a number of factors must be taken into consideration. For example, the enzyme catalyzed reaction must generate, at a wavelength not subject to interference by other chromophores in the system, a large enough difference in absorption to give the desired sensitivity. If chromophore generation is to depend on the occurrence of nonenzymatic steps subsequent to the initial enzymatic event, then the former must be considerably faster than the latter. In addition, the substrate should be chemically stable under the assay conditions, so that nonenzymatic background rates are negligible. Finally, the compound should be a good substrate, conforming to the

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