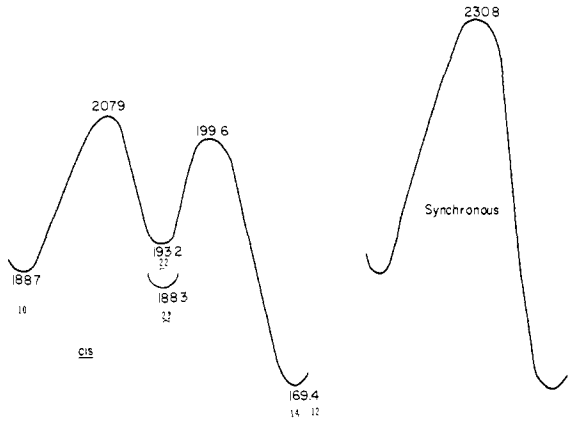

Figure 7. MINDO/3 reaction profile for the conversion of **10** to **14** (**12**).

As a final check on our calculated mechanisms, we examined possible concerted paths for the double cyclizations of **10** and **11**. While no true transition state could be located for either process, an indication of their feasibility was obtained by a calculation in which the lengths of the forming CC bonds were constrained to be equal. The activation energies for these paths were very large, greater than those for the two-step mechanisms by 23 kcal/mol in the case of **10** → **12** and 24 kcal/mol in the case of **11** → **13**.

Summary and Conclusions

The calculations reported here provide very strong support for a stepwise mechanism for biomimetic polyene cyclizations, each step involving the formation of a cyclic π-complex by electrophilic addition to a C=C bond. The reactions consequently take place stereospecifically by trans addition, as has been observed. There seems to be no question that concerted mechanisms are not involved in processes of this kind. The intermediate π-complexes are not, however, symmetrical, being distorted by angle strain. Distortion of an olefin π-complex by displacement of the apical group in a plane parallel to the basal atoms should be very facile, but it should not alter the essential stereochemical integrity of the π-complex because the basal atoms still remain linked by a strong π bond. The role of such distorted π-complexes has been underestimated in the past because of the misleading terminology and symbolism commonly used by organic chemists to describe "nonclassical carbocations". As we have repeatedly pointed out, the majority of such ions can be represented as olefin π-complexes and this description represents their properties far more effectively than the alternative dotted-line notation, which in fact was introduced several years later and for reasons unconnected with chemistry. The relationship between the two parallels that between the localized bond and MO descriptions of classical conjugated systems. The latter obscures the main characteristics of such molecules, i.e., the fact that they contain localized[7,8] single and double bonds.

Acknowledgment. This work was supported by the Air Force Office of Scientific Research (Grant F49620-83-C-0024), the Robert A. Welch Foundation (Grant F-126), and the National Science Foundation (Grant CHE82-17948).

Registry No. 10, 88657-48-1; **11**, 88657-49-2; **12**, 88657-50-5; **13**, 88657-51-6; **16**, 88657-52-7; **17**, 88657-53-8; **18**, 88657-54-9; **19**, 88657-55-0; **21**, 88669-40-3; **22**, 88728-83-0.

Supplementary Material Available: Summaries of MINDO/3 calculations (9 pages). Ordering information is given on any current masthead page.

Base-Catalyzed Fragmentation of 2,3-Dioxabicyclo[2.2.1]heptane, the Bicyclic Peroxide Nucleus of Prostaglandin Endoperoxides: Large Secondary Deuterium Kinetic Isotope Effects[1]

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Abstract: The influence of deuterium substitution on the rates of base-catalyzed rearrangements of 2,3-dioxabicyclo[2.2.1]heptane (**1**) is examined. The kinetic isotope effect observed previously with 1,4,5,6,7,7-hexadeuterio-**1** (k_H/k_D = 7–8) is much larger than that observed with 1-deuterio-**1** (k_H/k_D = 3–4) during fragmentation to levulinaldehyde. This reveals a large cumulative secondary deuterium isotope effect which accompanies rate-determining cleavage of the bridgehead C–H bond. Presumably cleavage of the C4–C7 bond also occurs during the rate-determining step and deuterium substitution on these carbons produces large secondary kinetic isotope effects.

Fragmentation of the prostaglandin (PG) endoperoxide PGH_2 produces the levulinaldehyde derivatives LGE_2 and LGD_2.[1] This process competes with disproportionation of PGH_2, which affords prostaglandins PGE_2 and PGD_2, important natural mediators of cellular activities.[2] As a basis for understanding how in vivo biosynthesis might be channeled to disproportionation or fragmentation, we are carefully studying the mechanisms of these rearrangements for 2,3-dioxabicyclo[2.2.1]heptane (**1**), the strained

(1) Prostaglandin Endoperoxides. 13. For previous papers in this series see: Zagorski, M. G.; Salomon, R. G. *J. Am. Chem. Soc.* **1982**, *104*, 3498–3505 and references cited therein.

(2) For a recent review see: Wolfe, L. J. *J. Neurochem.* **1982**, *38*, 1. Also see van dorp, D. A. In "Chemistry, Biochemistry and Pharmacological Activity of Prostanoids"; Roberts, S. M., Scheinmann, F., Eds.; Pergamon: New York, 1979; pp 233–242 and references cited therein.

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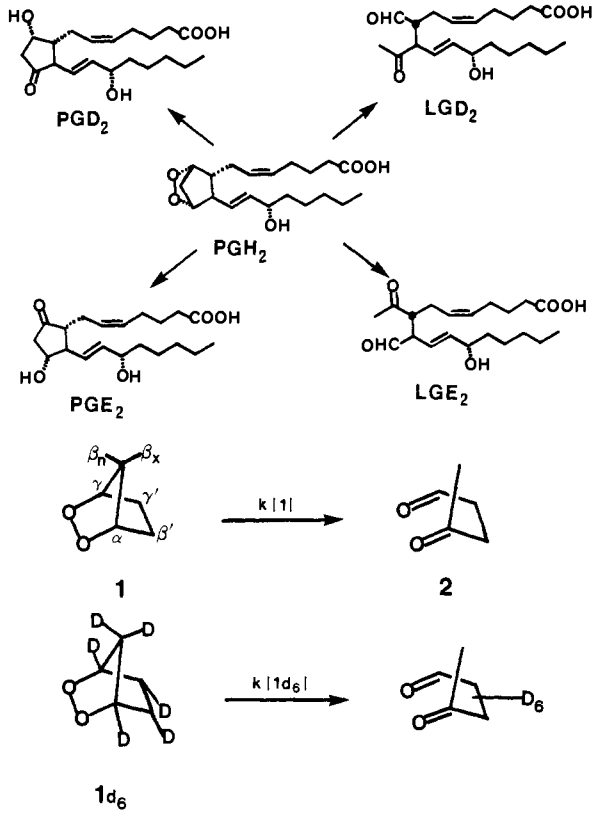


bicyclic peroxide nucleus of PGH_2.[3] It was especially important to test the hypothesis[1] that fragmentation and disproportionation of **1** involve a common β-keto alkoxide intermediate which affords disproportionation product by protonation and fragmentation product by retro-aldol cleavage.

Previously we showed that fragmentation of the hexadeuterated analogue **1**-d_6 is 7–8 times slower than fragmentation of **1** to generate **2** in amine-[3] and acetate-[1]catalyzed reactions. It occurred to us that this large net kinetic isotope effect, KIE_6, might be the cumulative result of a primary KIE_α, owing to deuterium substitution at C_α, and secondary effects, $KIE_{\beta x}$, $KIE_{\beta n}$, $KIE_{\beta'}$, KIE_γ, and $KIE_{\gamma'}$, owing to the exo and endo deuterons at C_β and deuterium at $C_{\beta'}$, C_γ, and $C_{\gamma'}$.[4] To discern the operation of secondary

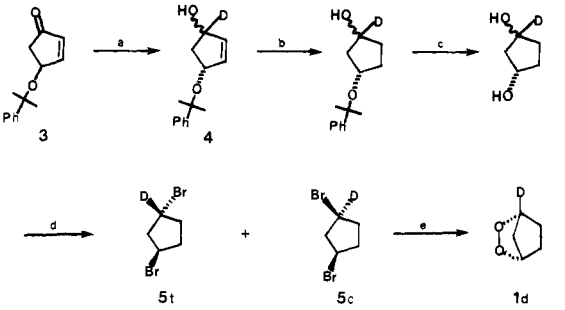
$$KIE_6 = KIE_\alpha \times KIE_{\beta x} \times KIE_{\beta n} \times KIE_{\beta'} \times KIE_\gamma \times KIE_{\gamma'} = k(\mathbf{1})/k(\mathbf{1}\text{-}d_6) \quad (1)$$

isotope effects, the intramolecular competition for bridgehead C–H and C–D bond rupture in 1-deuterio-2,3-dioxabicyclo[2.2.1]-heptane (**1d**) was examined for base-induced fragmentation and disproportionation. We now report that base-catalyzed fragmentation of **1** is subject to large secondary deuterium kinetic isotope effects. This is not consistent with a stepwise process involving the β-keto alkoxide which is an intermediate in the accompanying disproportionation. Rather, the fragmentation apparently occurs by a novel concerted rate-determining cleavage of three bonds.

Results

Synthesis of 1-Deuterio-2,3-dioxabicyclo[2.2.1]heptane (1d). The bridgehead monodeuterated peroxide **1d** was prepared from 4-(cumyloxy)cyclopent-2-en-1-one[5] as outlined in Scheme I. Borodeuteride reduction of the α,β-unsaturated ketone **3** was performed in the presence of $CeCl_3$ to avoid 1,4-addition of deuteride.[6] Hydrogenation of the resulting olefin **4** and hydrogenolysis of the cumyl ether were performed in two steps to avoid

Scheme I



a) $NaBD_4/CeCl_3$(95%); b) H_2/Pt(50%); c) $H_2/Pd/C$(100%); d) Et_4NBr/2-chloro-3-ethyl benzoxolium tetrafluoroborate/$CaCO_3$(75%); e) AgOTFA/H_2O_2(20%)

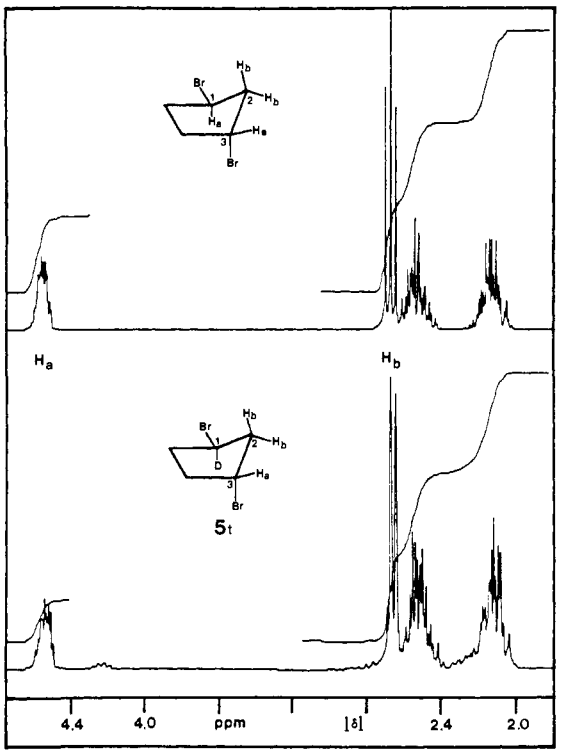


Figure 1. 200-MHz ^1H NMR spectra of *trans*-1,3-dibromocyclopentane and *trans*-1,3-dibromocyclopentane-*1-d* (**5t**) in $CDCl_3$.

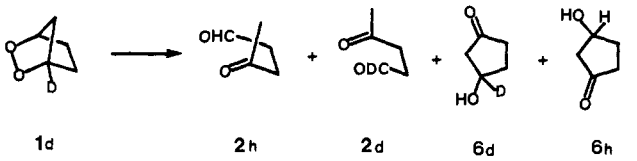
undesired hydrogenolysis of the allylic cumyloxy or hydroxy substituents in **4**. Fortunately, the reduction of **3** exhibits a significant favorable stereoselectivity for generating the cis isomer of **4** (cis/trans = 4:1) presumably owing to steric approach control

4t **4c**

by the bulky cumyloxy substituent. The isomers of 4-(cumyl oxy)cyclopent-2-en-1-ol-*1-d* (**4**) were characterized by the chemical shifts of the hydrogen at C-4 in their ^1H NMR spectra. The resonance appears at much lower field (δ 4.52) for the trans isomer **4t** than for the cis isomer **4c** (δ 4.12) owing to van der Waals deshielding by the C-1 hydroxyl group which is intimately juxtaposed to the C-4 hydrogen in **4t** but not in **4c**.[7]

(3) Zagorski, M. G.; Salomon, R. G. *J. Am. Chem. Soc.* **1980**, *102*, 2501–3.
(4) For an example of cumulative isotope effects see Shiner, Jr., V. J.; Stoffer, J. O. *J. Am. Chem. Soc.* **1970**, *92*, 3191–2.
(5) Stork, G.; Isobe, M. *J. Am. Chem. Soc.* **1975**, *97*, 6260–1.
(6) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226–7.
(7) Cooks, R. G.; Stout, G. H. "Organic Structural Analysis"; Macmillan: New York, 1976; p 33.

Table I. Catalyzed Rearrangement of 1d



1d 2h 2d 6d 6h

catalyst[a]	T, °C	product yields, %[b] 2d	2h	6d	6h	product ratios[c] 2d/2h	6d/6h
Dabco (0.016 M)	37	64	17	14	4	3.8	3.5
Dabco (0.018 M)	30	63	19	14	4	3.3	3.4
Me_4NOAc (0.012 M)	45	42	13	33	11	3.3	2.9
Me_4NOAc (0.017 M)	37	42	11	34	12	3.7	2.8
Me_4NOAc (0.017 M) + HOAc (3.0 equiv)	37	39	10	36	15	3.7	2.4
Me_4NOAc (0.017 M) + HOAc (11.6 equiv)	37	29	8	47	16	3.7	2.9

[a] Benzene solvent with Dabco catalyst, chloroform solvent with Me_4NOAc catalyst, concentration of 1d ~ 0.4 M. [b] Yields reported for 6d and 6h are the sums of the final yields of these products and their corresponding dehydration products (see text), determined from ratios since overall yields are quantitative. [c] The precision of these ratios is ±0.3.[11]

The isomeric monodeuterated dibromides (**5t** and **5c**) were prepared by the mild benzoxazolium method[8a] and separated by chromatography (see Experimental Section). For ^1H NMR comparison, the corresponding undeuterated dibromides were prepared stereospecifically[8] from the known isomeric diols.[9] The ^1H NMR spectra of **5t** and the undeuterated *trans*-1,3-dibromocyclopentane are presented in Figure 1. Because the undeuterated trans-dibromide is symmetrical, the methylene hydrogens at C-2 are equivalent. They give rise to a single resonance at δ 2.68 which appears as a triplet owing to accidentally equivalent coupling (J = 5.5 Hz) with the hydrogens at C-1 and C-3. For **5t** this resonance appears as a doublet (J = 5.5 Hz) of triplets (J = 0.7 Hz) owing to coupling with the C-3 hydrogen and C-1 deuterium, respectively. The ^1H NMR spectra of **5c** and the undeuterated *cis*-1,3-dibromocyclopentane are presented in Figure 2. The methylene hydrogens at C-2 are nonequivalent. The hydrogen H_c cis to the bromo groups appears at lower field (δ 2.92) than the hydrogen H_t trans to the bromo groups (δ 2.51) owing to van der Waals deshielding.[7] In the undeuterated dibromide these resonances are doublets of triplets owing to one geminal and two vicinal couplings while in the monodeuterated **5c** they appear as doublets of doublets since one vicinal coupling is absent.

The monodeuterated peroxide **1d** was obtained from the cis-dibromide **5c** by the well-precedented reaction with hydrogen peroxide in the presence of silver trifluoroacetate.[10] Purification of the peroxide **1d** is complicated by its appreciable volatility and chemical instability, especially in polar or protic solvents.[35d] Crystalline peroxide, pure by ^1H NMR analysis, was obtained in 20% yield by thin-layer chromatography on silica gel at 5 °C using CH_2Cl_2 as developing solvent. Methyl ethyl ether was an excellent solvent for elution of the peroxide since it is not only polar, but also sufficiently volatile (bp 11 °C) to facilitate complete removal from the purified peroxide. A different solvent, CCl_3F, was best for storage and ^1H NMR analysis since it is less polar and contains no protons. Furthermore, this solvent which boils at 24 °C is also easily removable from the volatile peroxide.

As shown in Figure 3, the ^1H NMR spectrum of the bridgehead monodeuterated peroxide **1d** is very similar to that of **1**. As expected, however, the resonance for the bridgehead hydrogen (δ 4.54) integrates for one atom of hydrogen per molecule of **1d** while the corresponding resonance for **1** integrates for two atoms of hydrogen. There is also a notable difference in the hyperfine

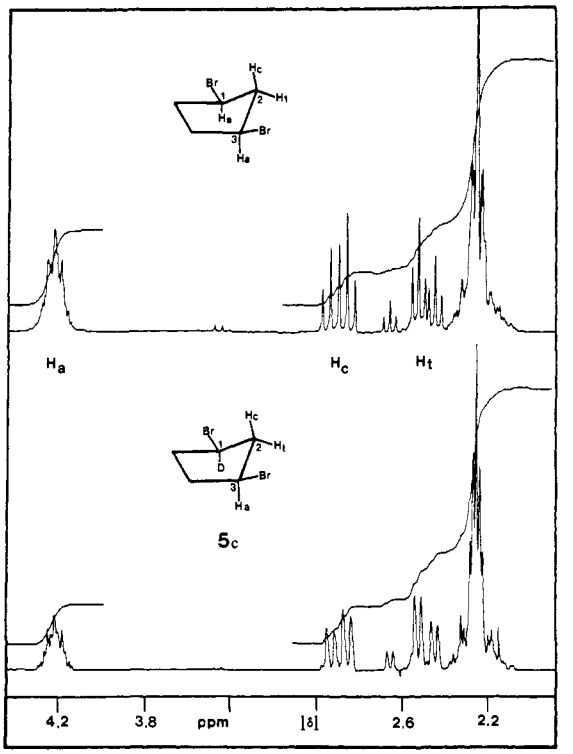
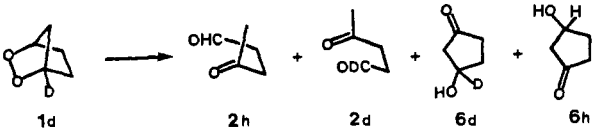


Figure 2. 200-MHz ^1H NMR spectra of *cis*-1,3-dibromocyclopentane and *cis*-1,3-dibromocyclopentane-*1-d* (**5c**) in $CDCl_3$.

coupling of the resonance at δ 2.14 corresponding to H_s. Thus, in the spectrum of **1** this resonance appears as a doublet of apparent quintets owing to geminal coupling with H_a (J = 10 Hz) and nearly equivalent coupling with two bridgehead and two endo hydrogens H_b and H_n, respectively. In contrast, in the spectrum of **1d** this resonance appears as a doublet of apparent quartets owing to geminal coupling with H_a (J = 10 Hz) and nearly equivalent coupling with two endo hydrogens, H_n, but only one bridgehead hydrogen, H_b.

Isotope Discrimination in the Base-Induced Rearrangement of 1d. The peroxide **1d** was dissolved in a solution of the appropriate catalyst and the mixture heated until decomposition was complete (1–5 days). Yields of the four products, **2d**, **2h**, **6d**, and **6h**, are



1d 2h 2d 6d 6h

presented in Table I for rearrangement of **1d** promoted by various

(8) (a) Mukaiyama, T.; Shoda, S.; Watanabe, Y. *Chem. Lett.* **1977**, 383. (b) *cis*- and *trans*-1,3-Dibromocyclopentane have been prepared by the following: Eisch, J. J.; Merkley, J. H.; Galle, J. E. *J. Org. Chem.* **1979**, *44*, 587. Porter, N. A.; Gilmore, D. W. *J. Am. Chem. Soc.* **1977**, *99*, 3503. They were not thoroughly characterized by NMR and MS.

(9) Salomon, M. F.; Salomon, R. G.; Gleim, R. D. *J. Org. Chem.* **1976**, *41*, 3983.

(10) Porter, N. A.; Byers, J. D.; Ali, A. E.; Eling, T. E. *J. Am. Chem. Soc.* **1980**, *102*, 1183 and references cited therein.

Table II. Distribution of Deuterium in Levulinaldehyde Products

catalyst[a]	T, °C	product yields, %[b] CDH_2	CDH	CDH_2 + CDH	CHO	CDO	total D
Dabco (0.016 M)	37	16	7	23	21	79	102
Dabco (0.018 M)	30	13	9	22	23	77	99
Me_4NOAc (0.012 M)	45	10	7	17	21	79	96
Me_4NOAc (0.017 M)	37	19	6	25	23	77	102
Me_4NOAc (0.017 M) + HOAc (3.0 equiv)	37	14	5	19	21	79	98
Me_4NOAc (0.017 M) + HOAc (11.6 equiv)	37	18	3	21	21	79	100

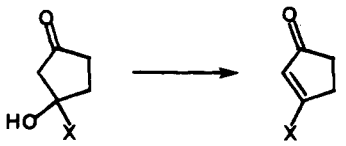
[a] Benzene solvent with Dabco catalyst, chloroform solvent with Me_4NOAc catalyst. [b] Yields reported for each type of deuterated group are percent of one atom of deuterium per molecule of levulinaldehyde product; e.g., $\%CDH_2 = 100[CDH_2]/([CHO] + [CDO])$.

Table III. Deuterium Incorporation Studies

substrates[a]	solvent	catalyst[b]	T, °C	time, days	product yields, % CDH_2	CDH	product ratio CDH_2/CDH
levulinaldehyde + Me_2CHOD	C_6H_6	Dabco	30	2.3	1.9	18	0.11
levulinaldehyde + Me_2CHOD	CCl_4	Dabco	30	2.3	1.3	14	0.09
levulinaldehyde + Me_2CHOD	$CHCl_3$	Me_4NOAc	37	2.7	10	65	0.15
levulinaldehyde + CH_3COOD (0.16 M)	$CHCl_3$	Me_4NOAc	37	2.7	0.4	3.8	0.11
levulinaldehyde + CH_3COOD (3 M)	C_6H_6	Dabco	30	4	3.0	16	0.19
levulinaldehyde + CH_3COOD (3 M)	CCl_4	Dabco	30	4	3.1	25	0.12
2,3-dioxabicyclo[2.2.1]heptane + CH_3COOD (0.33 M)	$CHCl_3$	Me_4NOAc	45	4	16	≤ 1	≥ 16

[a] Levulinaldehyde (0.6 M), 2,3-dioxabicyclo[2.2.1]heptane (1.0 M), Me_2CHOD (0.5 M). [b] Dabco (0.018 M), Me_4NOAc (0.012 M). [c] Yields reported for each type of deuterated group are percent of one atom of deuterium per molecule of levulinaldehyde product; e.g., $\%CDH_2 = 100[CDH_2]/([CHO] + [CDO])$.

catalysts. These yields were determined by a combination of ^1H and ^2H NMR spectroscopy (see Experimental Section). Since some of **6d** and **6h** produced initially underwent dehydration to



6d, X=D **7d**, X=D

6h, X=H **7h**, X=H

the corresponding enones **7d** and **7h**, the actual yields of the hydroxy ketones **6d** and **6h** reported in Table I were calculated as the sum of the final yields of **6d** + **7d** and **6h** + **7h**. Previously we demonstrated that **2h** and **6h** are *not* interconverted by aldol reaction under any of the reaction conditions listed in Table I.[1,3]

Deuterium Distribution in Levulinaldehyde Product. The deuterium which is removed from the bridgehead position of **1d** is found in the 2, 3, and 4 positions of the keto aldehyde products. The ^1H decoupled ^2H NMR spectrum of the reaction product mixture shows a singlet owing to deuterium on the methyl group (CDH_2) and a singlet owing to deuterium on the methylene (CDH) groups. The distribution of deuterium in the levulinaldehyde products is reported in Table II as the percent of one atom of deuterium per molecule of levulinaldehyde product. The percent of levulinaldehyde product which has hydrogen on the aldehyde carbon is also presented for comparison with the sum of the yields of methyl- and methylene-deuterated levulinaldehyde.

Since deuterium incorporation in the methylene and methyl groups of levulinaldehyde might conceivably occur by an intermolecular pathway, AcOD (produced by deuteron abstraction by acetate) or O-deuterated 3-hydroxycyclopentanone might serve as a source of deuterium for exchange with protium of the methylene or methyl groups of levulinaldehyde; Table III presents the results of several experiments designed to detect deuterium incorporation from O-deuterated acetic acid and isopropanol (as a model for O-deuterated 3-hydroxycyclopentanone).

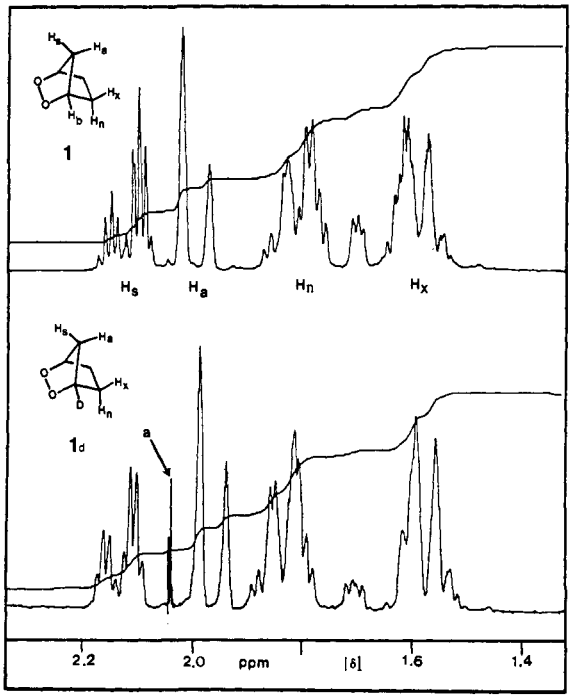


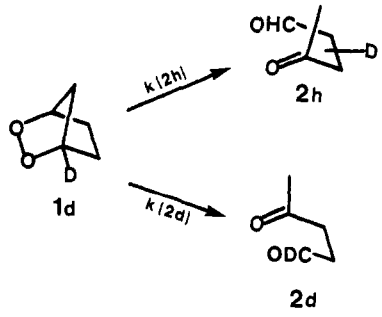
Figure 3. Upfield region of the 200-MHz ^1H NMR spectra of 2,3-dioxabicyclo[2.2.1]heptane (**1**) and 1-deuterio-2,3-dioxabicyclo[2.2.1]-heptane (**1d**) in freon 11 (CCl_3F) at 0 °C. a corresponds to resonance for acetone-d_6 used as an internal deuterium lock.

Discussion

Kinetic Deuterium Isotope Effects. The large difference between KIE_6 observed with **1**-d_6 (7.9 with Dabco as catalyst[3] at 30 °C and 7.6 with Me_4NOAc as catalyst[1] at 45 °C) and the product ratio **2d**/**2h** (see Table I) determined with **1d** in the present study dramatically reveals the susceptibility of the **1** → **2** fragmentation reaction to secondary deuterium kinetic isotope effects. The ratio of the rate constant k(**2h**) for fragmentation of **1d** with C–D bond

(11) Repeated measurements of the concentration of a standard sample by ^1H and ^2H NMR within five days gave confidence limits which were ±8.5% of the mean concentration at a 95% probability level. Thus, we believe that the product ratios in Table I are precise ±8.5%. The confidence limits were calculated by the method described in Fritz, J. S.; Schenk, G. H. "Quantitative Analytical Chemistry"; Allyn and Bacon: Boston, 1974; p 35.

rupture (**1d** → **2h**) and the rate constant k(**2d**) for fragmentation



of **1d** with C–H bond rupture (**1d** → **2d**) equals the ratio of the primary $KIE_\alpha = k(\mathbf{1})/k(\mathbf{2h})$ and the secondary $KIE_\gamma = k(\mathbf{1})/k(\mathbf{2d})$. This ratio also corresponds to the experimentally observed product ratio **2d**/**2h** presented in Table I. Combining eq 1 and 2 provides an expression for secondary KIEs alone (eq 3).

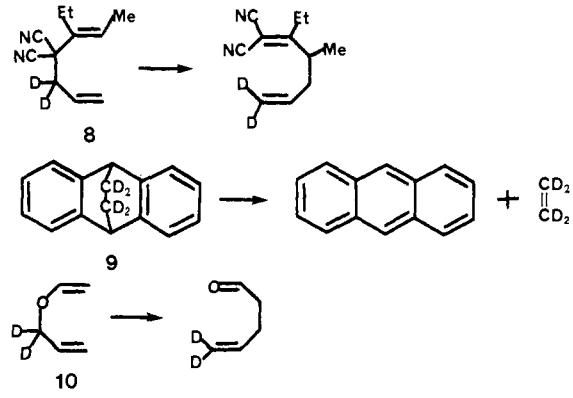
$$\mathbf{2d}/\mathbf{2h} = k(\mathbf{2d})/k(\mathbf{2h}) = KIE_\alpha/KIE_\gamma \quad (2)$$

$$KIE_6/(\mathbf{2d}/\mathbf{2h}) = KIE_{\beta x} \times KIE_{\beta n} \times KIE_{\beta'} \times KIE_{\gamma'} \times (KIE_\gamma)^2 \quad (3)$$

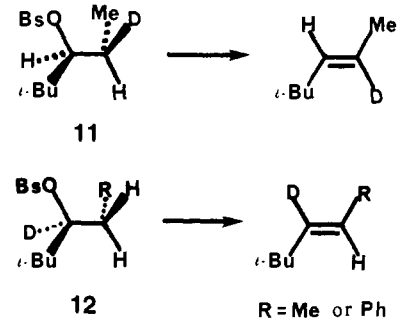
$KIE_6/(\mathbf{2d}/\mathbf{2h})$ equals 2.4 with Dabco as catalyst at 30 °C and 2.3 with Me_4NOAc as catalyst.

Mechanistic interpretation of this large cumulative secondary KIE is crucially dependent on whether it is ascribed to α or remote effects. For C–H bonds not ruptured during a reaction, substitution of deuterium for hydrogen can cause rate changes if progress toward the transition state causes changes in vibrations of the C–H bond.[12] For reactions involving rate-determining bond cleavage(s), two categories of secondary KIEs must be considered. α effects arise from cleavage of another bond to the same carbon, and remote effects arise from cleavage of a more remote bond in the molecule.

Normal α effects ($k_H/k_D > 1$) may arise, for example, if cleavage of another bond to the same carbon is accompanied by rehybridization of the C–H bond from sp^3-s toward sp^2-s and therefore a change in the C–H bond force constant during generation of the transition state.[13] α effects of 1.15–1.20 per deuterium are usually observed in solvolytic reactions.[13,14] Radical-forming decomposition of azobis(α-phenylethane)-α,α'-d_2 as well as β-scission of the cumyloxy radical exhibit α effects of 1.10–1.15 per deuterium.[15] An α effect of 1.06 per deuterium is found for thermal decomposition of *tert*-butyl phenylperacetate-α,α-d_2 presumably owing to rate-determining homolysis of the benzyl to carboxyl C–C bond.[16] Normal α effects are also known for various reactions involving formation of a C=C bond to the carbon atom to which a hydrogen isotope is bound. α effects of 1.08 per deuterium are found for the Cope rearrangement of **8**[17] or the reverse Diels–Alder reaction of **9**,[18] while Cope rearrangement of **10** shows $k_H/k_D = 1.045$ per deuterium.[19] E2



elimination in the presence of a variety of bases exhibits α effects of 1.11 ± 0.01 and 1.14 ± 0.06 for *p*-bromobenzenesulfonates **11** and **12**, respectively.[19] For **11** the C–H bond α to deuterium is



cleaved during elimination while for **12** the C–OBs bond α to deuterium is cleaved.[20]

Substitution of deuterium for hydrogen of C–H bonds not ruptured during a reaction can cause rate changes even if another bond to the same carbon is not cleaved in the reaction. Thus, electronic (hyperconjugative or inductive) or steric intramolecular interactions between the C–H bond and a remote reaction center may cause a change in the C–H force constant during generation of the transition state.[12b] For example, hyperconjugative interaction of a developing vicinal carbocation is considered to account for isotope effects in S_N1 reactions of β-deuterated substrates.[22] These remote effects exhibit a strong conformational dependence being negligible for an X–C–C–H dihedral angle of 90° and rising, for example, to $k_H/k_D = 1.31$ for a dihedral angle of 180°.[23] Hyperconjugation with a developing vicinal carbon free radical results in remote isotope effects of less than 2%.[16,24] Nevertheless, cumulative effects of multiple vicinal deuteration can be substantial. Thus, thermal decomposition of **13**, generating *tert*-butyl

13, X = H
13-d$_9$, X = D

radicals by homolysis of the acyl to carbon bond, is 1.13 times faster than for **13**-d_9.[16] Anionic hyperconjugation[22a,25] was adduced

(12) (a) Collins, C. J., Bowman, N. S., Eds. "Isotope Effects in Chemical Reactions"; Van Nostrand-Reinhold: New York, 1970. (b) Shiner, V. J., Jr. In "Isotopes and Chemical Principles"; Rock, P. A., Ed.; American Chemical Society: Washington, DC, 1975; ACS Symposium Series, No. 11.

(13) Streitwiser, A., Jr. "Solvolytic Displacement Reactions"; McGraw Hill: New York, 1962; p 172.

(14) (a) Streitwiser, A., Jr.; Jagow, R. H.; Fahey, R. C.; Suzuki, S. *M. Am. Chem. Soc.* **1958**, *80*, 2326. (b) Streitwiser, A., Jr.; Wilkens, C. L.; Kiehlmann *Ibid.* **1968**, *90*, 1598.

(15) (a) Seltzer, S.; Dunne, F. T. *J. Am. Chem. Soc.* **1965**, *87*, 2628. (b) Seltzer, S.; Zavitsas, A. *Ibid.* **1964**, *86*, 1265.

(16) (a) Koenig, T.; Wolf, R. *J. Am. Chem. Soc.* **1969**, *91*, 2574. (b) Koenig, T. W.; Brewer, W. D. *Tetrahedron Lett.* **1965**, 2773–8.

(17) Humski, K.; Malojcic, R.; Borcic, S.; Sunko, D. E. *J. Am. Chem. Soc.* **1970**, *92*, 6531.

(18) (a) Taagepera, M.; Thornton, E. R. *J. Am. Chem. Soc.* **1972**, *94*, 1165. (b) These results are typical for reverse Diels–Alder reactions: Brown, P.; Cookson, H. C. *Tetrahedron* **1965**, *21*, 1993. Seltzer, S. *Tetrahedron Lett.* **1962**, 457. Seltzer, S. *J. Am. Chem. Soc.* **1963**, *85*, 1360. Seltzer, S. *Ibid.* **1965**, *87*, 1534.

(19) Basinger, B. B. "Secondary Deuterium Isotope Effects in Biomolecular Elimination Reactions", Thesis, Indiana University, Bloomington, IN, 1981.

(20) Similar α effects were detected in a previous albeit more complicated, study of various deuterated cyclohexyl tosylates.[21]

(21) Cook, D.; Hutchinson, R. E. J.; Parker, A. J. *J. Org. Chem.* **1974**, *39*, 3029.

(22) (a) DeFrees, D. J.; Taagepera, M.; Levi, B. A.; Pollock, S. K.; Summerhays, K. D.; Taft, R. W.; Wolfsberg, M.; Hehre, W. J. *J. Am. Chem. Soc.* **1979**, *101*, 5532. (b) Shiner, V. J., Jr. In ref 12a, pp 137–150. (c) Sunko, D. E.; Borcic, S. In ref 12a, pp 167–171.

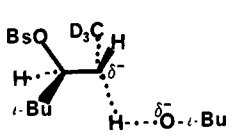
(23) (a) Shiner, V. J., Jr.; Humphrey, J. S., Jr. *J. Am. Chem. Soc.* **1963**, *85*, 2416. (b) Shiner, V. J., Jr.; Murr, B. L.; Heinemann, G. *Ibid.* **1963**, *85*, 2413.

(24) (a) Seltzer, S.; Hamilton, E. *J. Am. Chem. Soc.* **1966**, *88*, 3775. (b) Rummel, S.; Huebner, H.; Krumbiegel, A. *Z. Chem.* **1967**, *7*, 351.

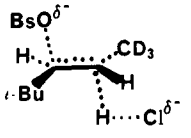
to explain the small normal isotope effect (k_{CH_3}/k_{CD_3} = 1.05) observed for *tert*-butoxide-promoted elimination from **14** vs. **14**-d_3.[19] Thus, elimination is presumed to involve a buildup of

14, X = H
14-d^3, X = D

negative charge as, for example, in **15**. Anionic hyperconjugation



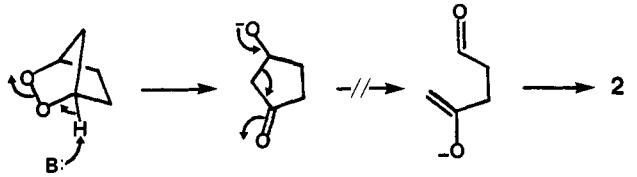
15



16

with the vicinal CH(D) bonds causes weakening of these bonds and therefore a normal isotope effect. For elimination from **14** vs. **14**-d_3 promoted by the weaker bases acetate or chloride, remote isotope effects are all within experimental error of 1.00.[19] For these bases a transition state **16** with appreciable C=C double bond character was presumed, and hyperconjugative interaction of this double bond with the vicinal methyl CH(D) bonds does not produce detectable isotope effects.[19]

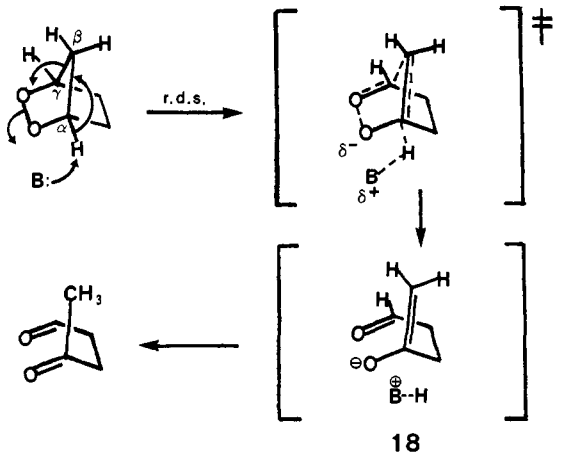
According to our earlier hypothesis,[1] fragmentation and disproportionation of **1** could involve a common β-keto alkoxide intermediate **17** which affords disproportionation product by



1 **17** **18**

protonation and fragmentation product **2** by retro-aldol cleavage to the enolate **18**. But if the **1** → **17** conversion is the rate-determining step in **1** → **2** fragmentation, then the large cumulative secondary deuterium isotope effects observed for this reaction must be entirely of the remote variety. However, if hyperconjugative effects of an incipient C=C bond can be taken as a model, hyperconjugation of deuteriums at the β_x, β_n, and β' positions with an incipient C=O bond should result in very small rate effects. Anionic hyperconjugative interaction of deuterium of the γ position with the incipient alkoxide might produce a small normal isotope effect. Nevertheless, a cumulative KIE k_H/k_D = 2.3 seems far too great to ascribe exclusively to remote secondary isotope effects.

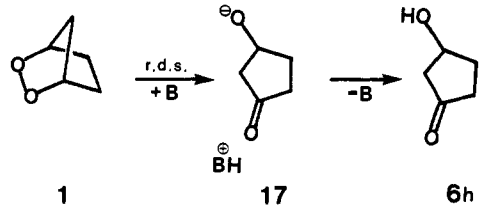
Rather, observation of large primary and secondary KIEs suggests a *novel rate determining concerted cleavage of three bonds*, C_α–H, C_β–C_γ, and O–O. This process generates the enolate **18** of levulinaldehyde directly from the endoperoxide **1**. Rehybridization of the C_β–H and C_γ–H bonds from sp^3–s toward sp^2–s would accompany generation of the transition state. Therefore,



18

deuterium substitution at C_β and C_γ could produce α secondary deuterium KIEs. Even if remote secondary KIEs owing to deuterium at the β' and γ' positions (the ethano bridge) were negligible, the average α effect per deuterium ($KIE_{\beta x}$, $KIE_{\beta n}$, KIE_γ) would be 1.24.[29] Alpha secondary deuterium isotope effects of this magnitude are well precedented.

If we assume that KIE_γ = 1.24, then since **2d**/**2h** = KIE_α/KIE_γ, we calculate that KIE_α = 4.5. This primary kinetic deuterium isotope effect in the fragmentation of the prostaglandin endoperoxide nucleus **1** → **2** is significantly different from that observed in the **1** → **6h** disproportionation. This isotope effect, revealed



1 **17** **6h**

by the ratio **6d**/**6h** = k_H/k_D = 3.0 ± 0.5 (see Table I) supports the presumption of different rate-determining steps in the fragmentation and disproportionation reactions. Interestingly, isotope effects of similar magnitude were noted previously during biosynthesis of PGE_2 and PGD_2 from 5,6,8,9,11,12,14,15-octadeuterioarachidonic acid.[30] With Dabco and Me_4NOAc as basic catalysts the involvement of a β-keto alkoxide intermediate **17** in the disproportionation **1** → **6h** is probable. However, with acetic acid as cocatalyst, a different mechanism not involving **17** seems important (vide infra). Thus, if **17** is produced, it does not undergo retro-aldol cleavage to **18** although it can be an intermediate in the formation of 3-hydroxycyclopentan-1-one (**6h**).

Fate of the Migrating Deuterium Atom. Two important facts are evident from the data presented in Table II. Deuterium incorporation in the methyl group (CDH_2) is favored over deuterium incorporation in the methylene group (CDH) of the levulinaldehyde product from monodeuterated peroxide **1d**. Also, the total deuterium content of the levulinaldehyde product is 100 ± 4% of one deuterium atom even when the acetate-catalyzed rearrangement of **1d** is conducted in the presence of 0.2 M HOAc, or about 0.5 equiv relative to **1d**. Bridgehead deuteron abstraction from **1d** by acetate would generate a molecule of *O*-deuterioacetic acid in intimate juxtaposition with the enolate **18**, a contact ion–molecule pair **19**. In **19** a hydrogen bonding interaction between a molecule of DOAc and the enolate **18** of levulinaldehyde is presumed.[31] Transfer of deuterium from DOAc to the enolate generates **20**, levulinaldehyde which is monodeuterated at the

(25) DeFrees, D. J.; Bartmess, J. E.; Kim, J. K.; McIver, R. T., Jr.; Hehre, W. J. *J. Am. Chem. Soc.* **1977**, *99*, 6451.

(26) It was noted[19] that these results do not support the earlier analysis of secondary deuterium isotope effects on elimination reactions of variously substituted cyclohexyl bromides and tosylates. Thus, "secondary hyperconjugative effects" k_H/k_D = 1.11–1.22 owing to hyperconjugation of an allylic CH(D) bond with a developing C=C double bond were suggested.[21,27] But the maximum possible effect per deuterium for hyperconjugation with an incipient double bond is estimated to be 1.03 from the calculated fractionation factor[28] for the isotopic exchange reaction between $CH_3CH_2CH_2D$ and CH_2=$CHCH_2D$.[19]

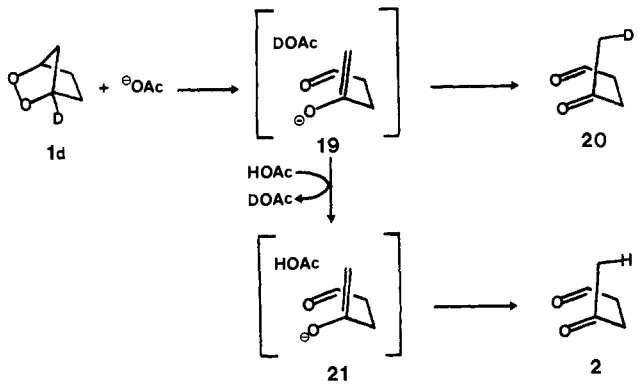
(27) Cook, D. *J. Org. Chem.* **1976**, *41*, 2173.

(28) (a) Shiner, V. J., Jr.; Buddenbaum, W. E. In "Isotope Effects on Enzyme-Catalyzed Reactions"; Cleland, W. W., O'Leary, M. H., Northrop, D. B., Eds.; University Park Press: Baltimore, 1977. (b) Hartshorn, S. R.; Shiner, V. J., Jr. *J. Am. Chem. Soc.* **1972**, *94*, 9002.

(29) Our data do not allow a more definite evaluation of the individual secondary KIE's. However, if some values are less than 1.24, then others must be even larger.

(30) Wlodawer, P.; Samuelson, B. *J. Biol. Chem.* **1973**, *248*, 5673.

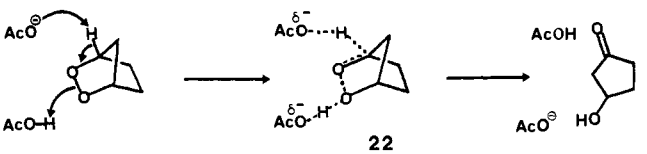
(31) Similar intermediates are presumed for alkoxide-catalyzed intramolecular hydrogen transfer in allylic rearrangement: Cram, D. J.; Uyeda, R. T. *J. Am. Chem. Soc.* **1962**, *84*, 4358; *Ibid.* **1964**, *86*, 5466 and references cited therein.



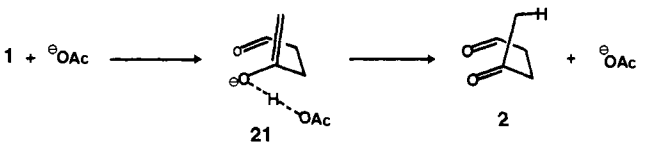
methyl carbon, the product of an apparent intramolecular deuterium transfer. This deuteron transfer is somewhat faster than exchange of deuterated acetic acid with unlabeled acetic acid to give **21** which would produce deuterium-free levulinaldehyde **2**. The data in Table II show that such deuterium loss is not a frequent event. Within the experimental uncertainty of the measurements, which we estimate to be ±8%, one atom of deuterium is incorporated per molecule of levulinaldehyde formed from **1d**. The possibility that deuterated levulinaldehyde might be generated by hydrogen–deuterium exchange between **2** and DOAc or O-deuterated alcohol products was examined in the presence of Dabco or Me_4NOAc as catalyst. The data presented in Table II show that only a small amount of deuterium incorporation occurs under conditions which resemble those encountered in the catalyzed decomposition of the peroxide **1d** except with Me_2CHOD as the source of exchangeable deuterium and Me_4NOAc as basic catalyst. Most importantly, in all cases the deuterium which is incorporated into **2** is found mainly in the methylene rather than methyl groups of levulinaldehyde in stark contrast with the deuterium distribution encountered in the product from rearrangement of **1d**. The preference observed is in qualitative agreement with that observed in acetate-catalyzed hydrogen–deuterium exchange for 2-butanone in D_2O.[32]

A small intermolecular component is detected in the rearrangement of undeuterated peroxide **1** promoted by Me_4NOAc (0.012 M) in the presence of DOAc (0.33 M) which produces a 16% yield of deuterated levulinaldehyde (Table III). Deuteration is confined to the methyl group of the levulinaldehyde product.

Mechanism of Proton Donor Induced Preference for Endoperoxide Disproportionation. Previously we showed that rearrangement of the prostaglandin endoperoxide nucleus **1** catalyzed by acetate is channeled by the presence of added acetic acid to favor disproportionation to 3-hydroxycyclopentanone (**6h**) over fragmentation to levulinaldehyde (**2**).[1] Our present observation of appreciable secondary deuterium isotope effects is not consistent with the intermediacy of a β-keto alkoxide **17** in the **1** → **2** rearrangement. Therefore, the influence of added acetic acid which favors production of **6h** over **2** cannot be explained by interception of **17** before it has a chance to undergo retro-aldol fragmentation. Rather the added acid probably provides an additional route to 3-hydroxycyclopentanone (**6h**) involving simultaneous bridgehead proton abstraction by acetate and protonation of the remote peroxidic oxygen by acetic acid as in **22**.



This pathway avoids generation of an alkoxide with negative charge concentrated on a single oxygen atom. The negative charge can be delocalized in **22** during its transfer from one carboxylate to another because the acetic acid cocatalyst hydrogen bonds with the incipient alkoxide. The fragmentation **1** → **2** cannot derive a similar benefit from the acetic acid cocatalyst since the nascent acetic acid, created upon bridgehead proton abstraction by acetate anion, already serves this role in the contact ion–molecule pair generated in the rate-determining step. Production of **2** from **21** then presumably involves a conducted-tour prototropic shift.[31]



Experimental Section

General Procedures. All proton nuclear magnetic resonance (NMR) spectra were recorded on Varian A-60-A, Varian EM-360-A, Varian XL-100, or Varian XL-200 spectrometers. Deuterium NMR spectra were recorded on a Varian XL-100 spectrometer at 15.36 MHz in the FT mode with an external ^{19}F lock. ^1H NMR spectral data are reported in ppm on the δ scale relative to tetramethylsilane (δ 0.00), and ^2H NMR spectral data are reported in ppm on the δ scale relative to chloroform-d_1 (δ 7.27). High resolution mass spectra were recorded on a AEI Kratos Model MS-30 instrument equipped with a Nier-Johnson double-focusing mass analyzer. Preparative thin-layer chromatography was performed by using precoated silica gel plates (20 × 20 cm, Merck).

Materials. Chloroform and methylene chloride were boiled under reflux over P_2O_5 for 4 h followed by distillation. Diethyl ether was boiled under reflux over $LiAlH_4$ for 4 h followed by distillation. Pentane was stirred over concentrated H_2SO_4 for 2 days, washed with water, saturated $NaHCO_3$, and water, dried over anhydrous magnesium sulfate, and distilled from P_2O_5. Freon 11 (CCl_3F) was carefully fractionally distilled (25 °C, 760 mm) through a fractionating column cooled to 20 °C and into a receiver kept at 0 °C. Methyl ethyl ether was prepared[33] and purified by distillation from sodium into a receiver cooled to −78 °C. Benzene was purified by distillation from potassium benzophenone ketyl. Acetic acid was stirred over Na_2EDTA for 2 days and then distilled. Tetraethylammonium bromide was dried in a vacuum dessicator over P_2O_5 (0.05 mm) for 2 days. 1,4-Diazabicyclo[2.2.2]octane (Dabco) was sublimed at 40 °C (0.05 mm) onto a cold finger under an atmosphere of dry N_2. Tetramethylammonium acetate from Matheson Coleman and Bell was recrystallized in dry methylene chloride and dried at 100 °C (760 mm) for 3 days. 2-Propanol-*d* (Aldrich, 98+ atom % D), acetic acid-*d* (Wilmad, 99+ atom % D) were used without further purification. Levulinaldehyde (**12**) was prepared[34a] and purified[34b] according to known procedures. Phenol-d_6 was purchased from KOR Isotopes, Inc., Cambridge, MA. 2,3-Dioxabicyclo[2.2.1]heptane (**1**)[35a–c] and *exo,exo*-5,6-diprotio-2,3-dioxabicyclo[2.2.1]heptane-d_6 (**1**-d_6)[1] were prepared and purified[35d] according to methods established in our laboratories.

(A) Syntheses. (a) Synthesis of 2,3-Dioxabicyclo[2.2.1]heptane-*1*-*d* (1d). 4-(Cumyloxy)cyclopent-2-en-1-one (3). The method of Stork and Isobe[5] was used for preparation of **3**. The enone **3** was purified by distillation [130 °C (0.15 mm)]: ^1H NMR ($CDCl_3$, 60 MHz) δ 7.68–7.17 (m, 6 H), 6.12 (dd, 1 H, J = 6.0, 1.8 Hz), 4.62–4.33 (m, 1 H, C*H*OC$(CH_3)_2$Ph), 2.41 (d, 1 H, J = 8 Hz), 2.40 (s, 1 H), 1.60 (s, 6 H, −C$(CH_3)_2$Ph).

4-(Cumyloxy)cyclopent-2-en-1-ol-*1*-*d* (4). The procedure of Luche[6] was modified. To a stirred solution of hydrated cerous chloride ($CeCl_3 \cdot 7H_2O$, 373 mg, 1.0 mmol) and 4-(cumyloxy)cyclopent-2-en-1-one (**3**) (160 mg, 0.74 mmol) in absolute ethanol (6.0 mL) under N_2 was added sodium borodeuteride (Aldrich, 98 atom % D, 33 mg, 0.80 mmol). The progress of the reduction was monitored by TLC (silica gel, chloroform (containing 0.75% ethanol) and 10% diethyl ether); the R_f's of **3** and **4** are 0.33 and 0.13, respectively. Once **3** was no longer detectable by TLC (ca. 4 h), the reaction mixture was poured into a separatory funnel containing ice chips (15 g) and aqueous HCl (6%, 15 mL). The ethanolic aqueous layer was saturated with NaCl and extracted with ether (4 × 30 mL). The combined ether extracts were washed with saturated NaCl (30 mL) and dried over anhydrous magnesium sulfate. After removal of the ether by rotary evaporation, a yellow liquid consisting of the cis isomer **4c** (80%) and trans isomer **4t** (20%) of the allylic alcohol **4** was obtained (154 mg, 95% yield).

(32) Warkentin, J.; Tee, O. S. *J. Chem. Soc., Chem. Commun.* **1966**, 190.

(33) Maercker, A.; Demuth, W. *Liebigs Ann. Chem.* **1977**, *11*, 1909.

(34) (a) Mondon, V. A. *Angew. Chem.* **1952**, *64*, 224. (b) Purified by gas–liquid phase chromatography at 120 °C through a 3 ft × 0.25 in. column packed with 10% Dow Corning 710 silicone oil on 60/80 Chromosorb W.

(35) (a) Coughlin, D. J.; Salomon, R. G. *J. Am. Chem. Soc.* **1977**, *99*, 655. (b) Coughlin, D. J.; Brown, R. S.; Salomon, R. G. *Ibid.* **1979**, *101*, 1533–9. (c) Adam, W.; Eggelte, H. J. *J. Org. Chem.* **1977**, *42*, 3987. (d) Coughlin, D. J., Thesis, Case Western Reserve University, 1979, p 139.

The stereoisomeric alcohols **4c** and **4t** were separable by the preparative TLC (silica gel, chloroform (containing 0.75% ethanol) and 2% methanol); the R_f's of isomers **4t** and **4c** are 0.17–0.14 and 0.14–0.05, respectively. However, slight decomposition of the sensitive allylic alcohols occurred on the TLC plates. Therefore, the isomeric alcohols **4c** and **4t** were not separated at this stage of the synthesis.

cis-4-(Cumyloxy)cyclopent-2-en-1-ol-*1-d* (**4c**) showed ^{1}H NMR ($CDCl_3$, 60 MHz) δ 7.60–7.15 (m, 5 H), 5.87 (s, 2 H), 4.12 (dd, 1 H, J = 4.5, 7.0 Hz, C*H*OC$(CH_3)_2$Ph), 2.56 (dd, 1 H, J = 14, 7.0 Hz), 2,30 (s, 1 H, OH), 1.58 (dd, 1 H, J = 14, 4.5 Hz), 1.56 (s, 6 H, –C$(CH_3)_2$Ph).

trans-4-(Cumyloxy)cyclopent-2-en-1-ol-*1-d* (**4t**) showed ^{1}H NMR ($CDCl_3$, 60 MHz) δ 7.60–7.15 (m, 5 H), 5.87 (s, 2 H), 4.52 (dd, 1 H, J = 4.0, 7.0 Hz, C*H*OC$(CH_3)_2$Ph), 1.90 (dd, 1 H, J = 14, 4.0 Hz), 1.83 (dd, 1 H, J = 14, 7.0 Hz), 1.75 (s, 1 H, OH), 1.52 (s, 6 H, C$(CH_3)_2$Ph).

3-(Cumyloxy)cyclopentan-1-ol-*1-d* (23). The procedure of Milas and Maloney[36] was modified. An isomeric mixture of alcohols **4t** and **4c** (219 mg, 1.0 mmol) in absolute ethanol (10 mL) containing platinum oxide (9.0 mg) was hydrogenated at room temperature until the starting materials **4t** and **4c** were no longer detectable by TLC analysis (silica gel, chloroform (containing 0.75% ethanol), 1% methanol, and 2% ethanol); **4** and **23** have R_f's of 0.29 and 0.36, respectively. Longer reaction times led to considerable quantities of 2-phenyl-2-propanol (R_f = 0.53). The reaction mixture was filtered through a Celite pad and the ethanol removed by rotary evaporation. The alcohols **23c** and **23t** were purified by preparative TLC (silica gel, chloroform (containing 0.75% ethanol) and 10% ether); R_f = 0.20–0.07 to give 111 mg (50% yield).

Spectral data for **23c**: ^{1}H NMR ($CDCl_3$, 60 MHz) δ 7.60–7.13 (m, 5 H), 3.95–3.52 (m, 1 H), 2.22 (s, 1 H, OH), 1.85–1.67 (m, 6 H), 1.53 (s, 6 H).

23t: ^{1}H NMR ($CDCl_3$, 60 MHz) δ 7.60–7.13 (m, 5 H), 4.44–3.96 (m, 1 H), 2.22 (s, 1 H, OH), 1.96–1.67 (m, 6 H), 1.58 (s, 6 H).

Cyclopentan-1,3-diol-*1-d* (24). A mixture of alcohols **23c** and **23t** (221 mg, 1.0 mmol) in methanol (15 mL) was combined with a methanolic suspension of freshly prepared PdH_2[37] (100 mg of 5% on carbon in 3 mL of methanol) and left stirring overnight under an atmosphere of H_2. The reaction mixture was filtered through a Celite pad, and the methanol and 2-phenylpropane were removed by rotary evaporation and high vacuum (0.05 mm for ca. 4 h) leaving, quantitatively, 100 mg of the isomeric diols **24c** and **24t**.

Spectral data for **24c**: ^{1}H NMR ($CDCl_3$, 60 MHz) δ 4.49–4.25 (br, 1 H), 3.15 (s, 1 H, OH), 2.00–1.75 (m, 6 H).

24t: ^{1}H NMR ($CDCl_3$, 60 MHz) δ 4.63–4.45 (br, 1 H), 3.15 (s, 1 H, OH), 2.00–1.75 (m, 6 H).

1,3-Dibromocyclopentane-*1-d* (5c and 5t). The procedure of Mukaiyama, Shoda, and Watanabe[8a] was modified.[38] To a stirred suspension of freshly prepared, dry 2-chloro-3-ethylbenzoxazolium tetrafluoroborate (792 mg, 2.94 mmol), dry tetraethylammonium bromide (1.29 g, 6.17 mmol), and calcium carbonate (437 mg, 4.37 mmol) in dry, ethanol-free chloroform (25 mL) under N_2 at 0 °C was added, dropwise, a solution (5.0 mL) of the diols **24c** and **24t** (103 mg, 1.0 mmol) in dry, ethanol-free chloroform. The reaction mixture was allowed to slowly warm to room temperature (3–4 h) and stirred 2 days at room temperature under N_2.

The reaction mixture was diluted to 100 mL with olefin-free, dry pentane and then filtered. After removal of the solvents from the filtrate, the isomeric dibromides **5c** and **5t** were separated from 2-oxo-3-ethylbenzoxazolamide by preparative TLC (silica gel, chloroform (containing 0.75% ethanol) and hexane (1:1)), **5c** and **5t** have an R_f of 0.55–0.39, in 75% yield. Attempted vacuum transfer (45–52 °C, 0.04 mm) of the dibromides to a receiver cooled to –15 °C led to partial isomerization (15–20%) of the desired cis isomer to the undesired trans isomer. However, the isomeric dibromides **5c** and **5t** were separable by preparative TLC (silica gel, hexane and 5% ethyl acetate); the R_f's of **5c** and **5t** were 0.36–0.24 and 0.49–0.39, respectively.

Spectral data for **5c**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.41–4.09 (m, 1 H), 2.92 (br, dd, 1 H, J = 15, 7.5 Hz), 2.51 (dd, 1 H, J = 15, 6.0 Hz), 2.35–2.20 (m, 4 H); high-resolution mass spectrum (70 eV), measured mass (% intensity of base) 230.9117 (0.7), 228.9151 (1.6), 226.9190 (0.7), 150.9883 (0.5), 149.9825 (8.0), 148.9772 (7.3), 147.9852 (8.6), 146.9814 (6.7), 145.9738 (0.6), 81.9279 (1.5), 80.9213 (1.9), 79.9303 (1.5), 78.9208 (1.8), 69.0670 (7.5), 68.0623 (100.0), 67.0554 (20.0), 66.0440 (3.6), 65.0373 (1.6), 42.0549 (10.1), 41.0483 (8.7).

For **5t**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.72–4.45 (m, 1 H), 2.67 (dt, 2 H, J v 5.6, 0.7 Hz), 2.64–2.44 (m, 2 H), 2.26–2.05 (m, 2 H); high-resolution mass spectrum (70 eV), measured mass (% intensity of base) 230.9092 (0.1), 228.9117 (0.3), 226.9132 (0.1), 150.9951 (1.1), 149.9916 (12.9), 148.9885 (4.0), 147.9966 (13.6), 146.9913 (3.0), 81.9369 (1.3), 80.9322 (1.3), 79.9413 (1.4), 78.9328 (1.1), 69.0758 (9.2), 68.0709 (100.0), 67.0646 (21.8), 66.0540 (3.8).

***cis*- and *trans*-1,3-Dibromocyclopentane (25c and 25t).** The procedure for preparation of **25c** and **25t** was identical with that for the preparation of **5**, except that unlabeled *cis*- and *trans*-1,3-cyclopentanediol[9] were used instead of 1,3-cyclopentanediol-*1-d*.

Spectral data for **25c**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.49–4.13 (m, 2 H), 2.92 (dt, 1 H, J = 15, 7.4 Hz), 2.51 (dt, 1 H, J = 15, 6.0 Hz), 2.35–2.20 (m, 4 H); high-resolution mass spectrum (70 eV), measured mass (% intensity of base) 229.8925 (0.3), 227.8956 (0.7), 225.9012 (0.4), 149.9821 (0.2), 148.9801 (5.9), 147.9735 (5.5), 146.9823 (6.3), 145.9762 (5.4), 81.9304 (1.3), 80.9223 (1.7), 79.9314 (1.3), 78.9242 (1.5), 68.0748 (5.7), 67.0714 (100.0), 66.0625 (3.9), 65.0549 (4.6), 41.0464 (23.0), 39.0302 (20.1).

For **25t**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.77–4.37 (m, 2 H), 2.68 (t, 2 H, J = 5.5 Hz), 2.62–2.44 (m, 2 H), 2.24–2.05 (m, 2 H); high-resolution mass spectrum (70 eV), measured mass (% intensity of base) 229.8996 (0.1), 227.9033 (0.3), 225.9066 (0.2), 149.9980 (0.5), 148.9957 (10.5), 147.9903 (2.1), 146.9980 (11.0), 81.9312 (1.4), 80.9229 (1.1), 79.9323 (1.4), 68.0737 (5.6), 67.0705 (100.0), 66.0610 (3.6), 65.0529 (4.3), 41.0488 (12.5).

2,3-Dioxabicyclo[2.2.1]heptane-*1-d* (1d).[39] The procedure of Porter et al.[10] for synthesizing PGH_2 was modified. Two solutions of *cis*-1,3-dibromocyclopentane-*1-d* (**5c**) (150 mg, 0.655 mmol) and 90% H_2O_2 (10 mL, 1.25 g, 658 mmol) in dry ether (25 mL) were prepared in two round bottomed flasks (50 mL) equipped with magnetic stirring bars. Silver trifluoroacetate[40] (4.92 g, 22.3 mmol) was added to each flask while stirring at 0 °C, and the resulting solutions were stirred at 0 °C for 10 min. Cold water (10 mL) was added to each solution and the resulting mixture was stirred for ca. 1–2 min at 0 °C. The solutions were combined in a separatory funnel at 5 °C, rinsing each flask with ether (45 mL) and adding the rinsings to the separatory funnel. Cold water (10 mL) was added to the separatory funnel, and the combined water layers removed. The combined ether layers were washed with cold saturated $NaHCO_3$ (1 × 25 mL) and then cold water (1 × 30 mL) while at 5 °C, dried by stirring over anhydrous magnesium sulfate under dry N_2 at 5 °C for 2 h, and filtered under dry N_2.

The ether was carefully removed (110 mm, 5 °C, under a dry N_2 bleed) until ca. 5 mL remained. Freon II (10 mL) and anhydrous magnesium sulfate (0.5 g) were added to the ether–freon 11 solution, and the suspension was stirred at 5 °C under dry N_2 for ca. 30 min, then filtered, and concentrated (110 mm, 5 °C, under a dry N_2 bleed) to a volume of about 2 mL. Anhydrous magnesium sulfate (ca. 100 mg) was again added to the solution, and the suspension was rapidly streaked via syringe onto three preparative TLC plates (silica gel, 0.5-mm thickness) and immediately developed (dry CH_2Cl_2, one development) at 5 °C. The peroxide (R_f = 0.58–0.27) gave a positive test for peroxide with ferrous thiocyanate[41] and was extracted from the silica gel at 5 °C with dry methyl ethyl ether. After careful removal of the methyl ethyl ether (110 mm, 5 °C, under a dry N_2 bleed),[42] 26 mg of pure crystalline peroxide was obtained (19% yield):[43] ^{1}H NMR (freon 11, 0 °C, 200 MHz) δ 4.54 (br s, 1 H), 2.14 (dt, br d, J = 10, 2.3 Hz), 1.98 (d, 1 H, J = 9.7 Hz), 1.90–1.70 (m, 2 H), 1.70–1.50 (m, 2 H).

4-Deuterio-1-methoxybenzene (26). An oven-dried 100-mL three-necked flask equipped with reflux condenser, N_2 inlet, and magnetic stirring bar was charged with magnesium chips (1.20 g, 48.1 mmol) and dry ether (10 mL). A solution (50 mL) of 4-bromoanisole (4.02 mL, 6.01 g, 32.1 mmol) in dry ether was added dropwise to the magnesium in the three-necked flask at a rate to maintain a gentle reflux. Once the addition was complete, the solution was allowed to stir overnight under N_2.

The solution was cooled to 0 °C with an external ice bath while stirring under N_2, and 8 mL of D_2O (99+ atom % D) was added dropwise via a dry syringe. After the addition was complete, the solution was allowed to warm to room temperature and then stirred for 2 h. The solution was poured into a separatory funnel and extracted with pentane (3 × 70 mL). The combined pentane extracts were washed with satu-

(36) Milas, N. A.; Maloney, L. S. *J. Am. Chem. Soc.* **1940**, *62*, 1841.
(37) Mozingo, R. "Organic Syntheses"; Wiley: New York, 1955; Collect. Vol 3, p 685.
(38) The modifications for this reaction were performed by D. B. Miller, graduate student, Case Western Reserve University, Cleveland, OH.
(39) This reaction was performed in a cold room kept at 5 °C.
(40) Janseen, D. E.; Wilson, C. J. "Organic Syntheses"; Wiley: New York, 1963, Collect. Vol 4, p 547.
(41) Johnson, R. A.; Nidy, E. G. *J. Org. Chem.* **1975**, *40*, 1681.
(42) Silica gel is partially soluble in methyl ethyl ether. Therefore, after removal of nearly all the methyl ethyl ether, the residue was taken up in freon 11 at 5 °C and filtered.
(43) In some instances, the peroxide **1d** was slightly (10–15%) contaminated with some nonvolatile alkyl impurity. However, the peroxide could be quantitatively separated from this impurity by methods previously established in our laboratories.[20d]

rated NaCl (50 mL) and dried over anhydrous magnesium sulfate. After removal of the solvents by rotary evaporation, the crude product was distilled, collecting the largest fraction (3.12 g) at 65–70 °C (20 mm) in 89% yield: ^{1}H NMR (CCl_4, 60 MHz) δ 7.18 (br d, 2 H, J = 8.5 Hz), 6.79 (dd, 2 H, J = 8.5, 1.5 Hz), 3.74 (s, 3 H); ^{1}H decoupled ^{2}H NMR (15.36 MHz) (C_6H_6, $CHCl_3$, CCl_4, CH_3COOH, Me_2SO) δ 7.80, 7.02, 6.96, 6.67, 5.95, respectively for each solvent (s, 1 ^{2}H).

2,3,4,5,6-Pentadeuterio-1-methoxybenzene (27). The procedure of Vogel[44] was followed except that phenol-d_6 (98+ atom % D) was used instead of phenol. The crude product (80% yield) was purified by gas–liquid phase chromatography at 105 °C through a 3 ft × 0.25 in. column packed with 10% Dow Corning 710 silicone oil on 60/80 Chromosorb W: ^{1}H NMR (CCl_4, 60 MHz) δ 3.74 (s, 3 H); ^{1}H NMR (CCl_4, 200 MHz) δ 7.60–6.80 (m, 5 H, integral height was 14 arbitrary units), 3.74 (s, 3 H, integral height was 234 arbitrary units). Thus, when the latter set of ^{1}H NMR data were used, **18** was calculated to be 2.8/80.8 (100) = 3.5 atom % H = 96.5 atom % D. ^{1}H decoupled ^{2}H NMR (15.36 MHz) (CCl_4) δ 7.27 (s, 2 ^{2}H), 6.90 (s, 3 ^{2}H).

(B) Rearrangements of 2,3-Dioxabicyclo[2.2.1]heptane-*1*-*d* (1d). (a) Preparation of Catalyst Solutions. (i) Dabco. A solution (5.0 mL) was prepared volumetrically from freshly sublimed Dabco (10.0 g, 0.089 mmol) and dry benzene.

(ii) Me_4NOAc and Me_4NOAc Plus Acetic Acid. A solution (10 mL) was prepared containing dry $CHCl_3$ saturated with dry Me_4NOAc. Another solution (1.0 mL) was prepared volumetrically containing phenyltrimethylsilane (3.4 μL, 3.0 mg, 0.020 mmol) and dry $CHCl_3$ saturated with dry Me_4NOAc. The concentration of Me_4NOAc relative to the internal standard phenyltrimethylsilane was determined by ^{1}H NMR using ratios of integrated areas of the signals at δ 0.01 (s, 9 H) and δ 3.12 (s, 16 H) for the standard and catalyst, respectively.

Two solutions (2.0 mL) were prepared volumetrically containing purified acetic acid[45] (16 μL, 16 mg, 0.28 mmol and 4.1 μL, 4.3 mg, 0.072 mmol) and the above Me_4NOAc in $CHCl_3$ solution. The concentration of acetic acid relative to Me_4NOAc was determined by ^{1}H NMR spectroscopy using ratios of integrated areas of the signals at δ 3.12 (s, 12 H) and 1.72–1.50 (s, 3 H)[46] which correspond to resonances for the N-methyl substituents or the acetate methyl groups of Me_4NOAc and acetic acid, respectively. When the resonance at δ 3.12 was used, the portion of integral area of the δ 1.72–1.50 resonance corresponding to the catalyst, Me_4NOAc, was calculated, and the remaining area was used to calculate the amount of acetic acid present relative to Me_4NOAc. The calculated equivalents of acetic acid relative to Me_4NOAc are reported in Tables I and II.

(b) Decomposition of 1d. For all studies, the peroxide **1d** (12–14 mg, 0.12–0.14 mmol) stored in freon 11 in a 5-mm NMR tube was concentrated to dryness under reduced pressure (110 mm, 5 °C, under a dry N_2 bleed) by placing the NMR tube containing the peroxide and freon 11 inside a vacuum dessicator at 5 °C[33] and capping the tube with a serum cap equipped with a syringe needle piercing the cap. When only crystalline peroxide remained in the NMR tube, 0.3 mL of each catalyst solution or solvent (vide infra) was added to the NMR tube. The solution was immediately mixed thoroughly by shaking and then heated in a thermostated oil bath at 30.0, 37.0, or 45.0 °C. For the rearrangements catalyzed by Dabco and Me_4NOAc, the solutions were heated for one day, whereas for the rearrangements catalyzed by Me_4NOAc in the presence of acetic acid, the solutions were heated for 5 days.[47]

(c) Analysis of Products from Decomposition of 1d. A solution (10.0 mL) was prepared volumetrically containing 2,3,4,5,6-pentadeuterio-1-methoxybenzene (**27**) (11 μL, 11 mg, 0.099 mmol) in CCl_4. The solvents, which were C_6H_6 for Dabco and $CHCl_3$ for Me_4NOAc or Me_4NOAc plus acetic acid studies, respectively, were removed directly from the 5-mm NMR tubes containing the products from decomposition of **1d**. The NMR tubes were capped with serum caps equipped with syringe needles piercing the caps and the NMR tubes were placed within a vacuum dessicator. The solvents were removed under reduced pressure (20 mm, 25 °C) and the residue remaining within the NMR tube was dissolved in 0.3 mL of 0.010 M 2,3,4,5,6-pentadeuterio-1-methoxybenzene (**27**) in CCl_4 solution. The tubes were fitted with coaxial inner cells containing acetone-d_6 which was used as an internal ^{2}H lock for homogeneity optimization of the Varian XL-200 NMR spectrometer.

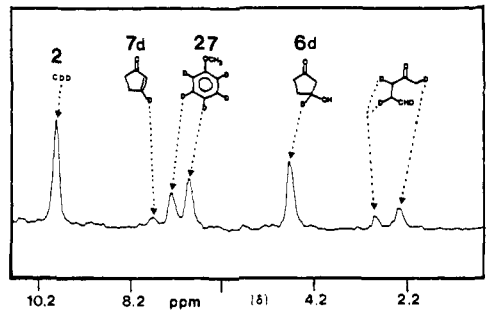


Figure 4. 15.36-MHz ^{2}H NMR spectrum of reaction product mixture from Me_4NOAc catalyzed decomposition of 1-deuterio-2,3-dioxabicyclo[2.2.1]heptane (**1d**) in CCl_4 containing 2,3,4,5,6-pentadeuterio-1-methoxybenzene (**27**).

Since the aldehydic ^{1}H NMR resonance of levulinaldehyde (**2h**) is easily saturated,[48] the spin lattice relaxation time (T_1) for this resonance (δ 9.72 (s, 1 H)) in CCl_4 at 200 MHz was determined and found to 5.5 s. Thus, to ensure quantitative integral measurements of the concentration of **2h**, a 40-s delay between each 90° pulse (6.5 μs) for each transient was used. For determination of the concentrations of the deuterated products **2d** and **6d** by ^{2}H NMR (15.36 MHz), 10-s delays between each 90° pulse (50 μs) were used, and T_1 was not measured since T_1's of deuterated compounds are relatively short due to a quadrupolar relaxation mechanism.[49]

The concentrations of three products, levulinaldehyde (**2h**), 3-hydroxycyclopentanone (**6h**), and cyclopent-2-en-1-one (**7h**), from decomposition of **1d** were determined relative to the internal standard **18** by ^{1}H NMR (200 MHz) spectroscopy using ratios of integrated areas of the peaks at δ 9.72 (s, 1 H), 4.52 (m, 1 H), 7.61 (dd, 1 H), and 3.74 (s, 3 H) for the three products (**2h**, **6h**, and **7h**) and **18** (0.010 M), respectively. Next, the acetone-d_6 was removed from the coaxial inner cell and the concentrations of the deuterated products **2d**, **6d**, and **7d** were determined relative to internal standard **27** by ^{2}H NMR spectroscopy (Figure 4). The ratios of the integrated areas of the ^{1}H-decoupled ^{2}H NMR signals at δ 9.82 (s, 1 ^{2}H), 7.66 (s, 1 ^{2}H), 4.59 (s, 1 ^{2}H), 2.72 (s, 1 ^{2}H), 2.18 (s, 1 ^{2}H), and 7.27 (s, 2 ^{2}H) and 6.90 (s, 3 ^{2}H) which correspond to the aldehydic absorption of **2d**, β enone signal of **7d**, α to OH resonance of **6d**, methylene resonance of levulinaldehyde, methyl resonance of levulinaldehyde, and **23** were used to calculate the amount of deuterium incorporation in **2** (Table II) and the concentrations of **2d**, **6d**, and **7d** (Table I).

(C) Control Experiments. (a) Deuterium Incorporation during Fragmentation of 1. A solution (1.0 mL) was prepared volumetrically containing 4-deuterio-1-methoxybenzene (**26**) (33 μL, 32 mg, 0.30 mmol), acetic acid-*d* (14 μL, 15 mg, 0.24 mmol),[45] and a 0.012 M Me_4NOAc in dry $CHCl_3$ solution. The concentration of acetic acid-*d* relative to Me_4NOAc was determined by ^{1}H NMR spectroscopy. The procedure for preparing the 0.012 M Me_4NOAc in $CHCl_3$ solution and the method for calculating the concentration of acetic acid-*d* relative to Me_4NOAc is described above under "Catalyst Solutions". An aliquot (0.4 mL) of the above solution was added to a 5-mm NMR tube containing 40 mg (0.40 mmol) of **1**, and the resulting catalyst–endoperoxide solution was immediately mixed thoroughly by shaking and then heated for 3 days at 45 °C in a thermostated oil bath.

The concentrations of the three products, levulinaldehyde (**2**), 3-hydroxycyclopentanone (**6h**), and cyclopent-2-en-1-one (**7h**), from decomposition of **1** were determined relative to the internal standard **26** by ^{1}H NMR (60 MHz) spectroscopy using ratios of integrated peaks at δ 9.77 (s, 1 H), 4.31 (m, 1 H), 5.95 (dd, 1 H), and 3.53 (s, 3 H) for the three products (**2**, **6h**, and **7h**) and **26** (0.30 M), respectively. Next, the concentration of deuterated levulinaldehyde (**2**) was determined relative to the internal standard **26** by ^{2}H NMR (15.36 MHz) spectroscopy. The ratios of the integrated areas of the ^{1}H-decoupled ^{2}H NMR signals[50] at 2.79 (s, 1 ^{2}H), 2.21 (s, 1 ^{2}H), and 7.02 (s, 1 ^{2}H), which correspond to the methylene resonance of deuterated **2**, methyl resonance of deuterated **2**, and **26**, were used to calculate the amount of deuterium incorporation in **2**. The concentration of deuterium found in the methyl and methylene positions of deuterated **2** were divided by the total concentration of **2** (which was determined from aldehydic proton resonance of **2**) and

(44) Vogel, A. I. "A Textbook of Practical Organic Chemistry"; Wiley: New York, 1957; p 669.

(45) All measurements of acetic acid were done using a special, nonmetal syringe to avoid possible contamination by trace metal ions. Syringes used were purchased from Oxford Laboratories, Inc., and were called "Adjustable Samplers".

(46) The chemical shift of the methyl signal of acetic acid varied about 0.15 ppm depending upon its concentration.

(47) The rate of fragmentation of **1** to **2** with Dabco or Me_4NOAc as catalyst is considerably depressed with added acetic acid.[1]

(48) Becker, E. D. "High Resolution NMR"; Academic Press: New York, 1969; p 202.

(49) Harris, R. K. "NMR and the Periodic Table"; Academic Press: New York, 1978; p 107.

(50) (a) No ^{2}H NMR signals corresponding to the aldehydic resonance of **2** or (b) products **6** and **7** were found.

multiplied by 100 to give the percent deuterium incorporation for each position.

(b) Hydrogen–Deuterium Exchange of Levulinaldehyde (2). (i) Dabco plus Acetic Acid-*d* and Dabco plus 2-Propanol-*d*. Two solutions (1.0 mL) were prepared volumetrically from freshly sublimed Dabco (2.0 mg, 0.018 mmol), 4-deuterio-1-methoxybenzene (**26**) (100 μL, 99.5 mg, 0.92 mmol), and pure[34b] levulinaldehyde (**2**) (59 mg, 0.59 mmol) in CCl_4 and in dry C_6H_6. Two aliquots (0.4 mL) of each solution were placed into four 5-mm NMR tubes. Acetic acid-*d* (70 μL, 73 mg, 1.2 mmol) was added to two of the aliquots, one in CCl_4 and the other in C_6H_6, and 2-propanol-*d* (16 μL, 13 mg, 0.20 mmol) was added to the two remaining aliquots.

The concentration of levulinaldehyde (**2**) relative to the internal standard **26** was determined by ^1H NMR (60 MHz) spectroscopy using the ratios of integrated areas of the peaks at δ 9.72 (s, 1 H) (CCl_4) and 9.38 (s, 1 H) (C_6H_6) and 3.74 (s, 3 H) (CCl_4) and 3.46 (s, 3 H) (C_6H_6) for **2** and **26** (0.92 M), respectively. Next, the amount of deuterium incorporation in **2** was determined relative to the internal standard **26** by ^2H NMR (15.36 MHz) spectroscopy. The ratios of the integrated areas of the ^1H-decoupled ^2H NMR signals at δ 2.72 (s, 1 ^2H) (CCl_4) and 3.18 (s, 1 ^2H) (C_6H_6) and 2.18 (s, 1 ^2H) (CCl_4) and 2.68 (s, 1 ^2H) (C_6H_6), which corresponded to signals for the methylene resonances of deuterated **2**, and δ 6.96 (s, 1 ^2H) (CCl_4) and 7.80 (s, 1 ^2H) (C_6H_6), which corresponded signals for the internal standard **26**, were used to calculate the amount of deuterium incorporated in **2**.[51]

The four NMR tubes were allowed to stand at room temperature for 60 h.[52] ^1H NMR (60 MHz) and ^2H NMR (15.36 MHz) were recorded periodically and the amount of deuterium incorporated in the methylene and methyl positions of **2** was determined and these values were divided by the concentration of **2** (which was determined from the aldehydic protium resonance) and multiplied by 100 to give the percent deuterium incorporation in each position.

(ii) Me_4NOAc plus Acetic Acid-*d* and Me_4NOAc plus 2-Propanol-*d*. A solution (0.42 mL) was prepared volumetrically in a 5-mm NMR tube containing 4-deuterio-1-methoxybenzene (**26**) (15 μL, 15 mg, 0.14 mmol, 0.33 M), acetic acid-*d* (2.8 μL, 2.9 mg, 0.048 mmol), and a 0.012 M Me_4NOAc in dry $CHCl_3$ solution. The concentration of acetic acid-*d* relative to Me_4NOAc was determined by ^1H NMR spectroscopy. The procedure for preparing the 0.012 M Me_4NOAc in $CHCl_3$ solution and the method for calculating the concentration of acetic acid-d_1 relative to Me_4NOAc is described above under "Preparation of Catalyst Solutions". A second solution (0.42 mL) was prepared volumetrically in a 5-mm NMR tube containing 4-deuterio-1-methoxybenzene (**26**) (15 μL, 15 mg, 0.14 mmol, 0.33 M), 2-propanol-*d* (19 μL, 15 mg, 0.25 mmol, 0.59 M), and a 0.012 M Me_4NOAc in dry $CHCl_3$. Both solutions were combined with levulinaldehyde (**2**) (25 mg, 0.25 mmol, 0.59 M) and mixed thoroughly by shaking. The concentration of levulinaldehyde (**2**) relative to the internal standard **26** was determined by ^1H NMR (60 MHz) spectroscopy using the ratios of integrated areas of the peaks at δ 9.77 (s, 1 H) and 3.53 (s, 3 H) for **2** and **26** (0.33 M), respectively. Next the amount of deuterium incorporation in **2** was determined relative to the internal standard **26** by ^2H NMR (15.36 MHz) spectroscopy. The ratios of the integrated areas of the ^1H decoupled ^2H NMR signals at δ 2.79 (s, 1 ^2H) and 2.21 (s, 1 ^2H), which correspond to signals for the methylene and methyl resonances of deuterated **2** and δ 7.02 (s, 1 ^2H) for **26** were used to calculate the amount of deuterium incorporated in **2**.

The two solutions were heated at 37 °C in a thermostated oil bath at 37 °C for 60 h.[51] ^1H NMR (60 MHz) and ^2H NMR (15.36 MHz) were recorded periodically, the concentrations of deuterium incorporated in the methylene and methyl positions of **2** were determined, and these values were divided by the concentration of **2** (which was determined from the aldehydic protium resonance) and multiplied by 100 to give the percent deuterium incorporation in each position.

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(51) As the amount of deuterium increased in methylene positions of **2** as measured by ^2H NMR, a corresponding decrease in the integral height of the methylene ^1H NMR resonance at δ 2.26 (C_6H_6) or 2.54 (CCl_4) occurred.

(52) Control experiments have shown that levulinaldehyde is stable to Dabco or Me_4NOAc plus acetic acid and neat acetic acid, even after prolonged heating at 45 °C.[1] In contrast, 3-hydroxycyclopentanone (**6**) is slowly and quantitatively converted to cyclopent-2-en-1-one (**7**) under these conditions.

Ring Expansion and Cleavage of Succinoin Derivatives. Geminal Acylation, Reductive Succinoylation, and Stereoselective Spiro Annelation Methods

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Abstract: The Lewis acid catalyzed aldol-type reaction of 1,2-bis(trimethylsiloxy)cyclobutene and a ketal or an acetal gives a succinoin derivative. This cyclobutanone undergoes several types of acid-catalyzed transformations either as it is or after alkylidenation or reduction of the carbonyl group. The reactions provide useful synthetic entries to various compounds such as 1,3-cyclopentanediones, 4-keto acids and esters, 3-alkylidenecyclopentan-1-ones, and 2- and 3-cyclopenten-1-ones. The stereochemistry of the initial aldol reaction and some of these acid catalyzed reactions have been examined to find a new and reliable approach to the stereoselective construction of (spiro) quaternary centers. Formal syntheses of two sesquiterpenes, *dl*-cuparene and *dl*-lanceol, are also described.

The use of chlorotrimethylsilane in acyloin condensation has immensely multiplied the value of this long-known reaction.[1] The effect of the added chlorosilane is particularly dramatic in the reductive cyclization of dialkyl succinates (eq 1), with which the conventional conditions failed to give the cyclized products.[2]

In relation to our interests in the reaction of enol silyl ethers and carbonyl compounds, we became intrigued by the aldol chemistry of **1** as well as the synthetic potential of the resultant aldol adduct **2a** as a precursor of cyclopentanones, inter, alia,

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(1) (a) Reviews: Ruhlmann, K. *Synthesis*, **1971**, 236. (b) Bloomfield, J. J.; Owsley, D. C.; Nelke, J. M. *Org. React. (N.Y.)* **1976**, *23*, 259.
(2) Bloomfield, J. J.; Nelke, J. M. *Org. Synth.* **1977**, *58*, 1.

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