Acid-Catalyzed Rearrangement of Two Cyclohexadienone Monoepoxides

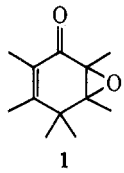
Harold Hart,* Irene Huang, and Paul Lavrik

Department of Chemistry, Michigan State University, East Lansing, Michigan 48824

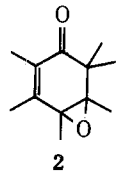
Received September 6, 1973

Rearrangement of 2,3-epoxy-2,3,4,4,5,6-hexamethyl-5-cyclohexenone (**1**) in trifluoroacetic acid (TFA) at room temperature gave 5-acetyl-2,3,4,4,5-pentamethyl-2-cyclopentenone (**3**, 50%), 2-acetyl-2,3,4,5,5-pentamethyl-3-cyclopentenone (**4**, 35%), and 6-hydroxy-4-methylene-2,3,5,5,6-pentamethyl-2-cyclohexenone (**5**, 10%). Independent treatment of **5** with TFA gave **4**, but at a much slower rate than the formation of **4** from **1**. Deuterium-labeling experiments support the mechanisms in Schemes I and II for the rearrangement of **1**, all products arising from opening the epoxy ketone to a cation (B) in which the positive charge is not adjacent to the carbonyl group. 4,5-Epoxy-2,3,4,5,6,6-hexamethyl-2-cyclohexenone (**2**), prepared from the corresponding dienone and *m*-chloroperbenzoic acid, rearranged quantitatively in aqueous acid to 5-hydroxy-4-methylene-2,3,5,6,6-pentamethyl-2-cyclohexenone (**12**). In neat TFA, **12** rearranged to 5-isopropenyl-4-methylene-2,3,5-trimethyl-2-cyclopentenone (**15**) which, on longer treatment with TFA, was dealkylated to 4-methylene-2,3,5-trimethyl-2-cyclopentenone (**16**) and acetone. When **2** was treated directly with neat TFA, there was formed, in addition to **15** and **16**, a small yield of **4** and a larger amount of 4-acetyl-2,3,4,5,5-pentamethyl-2-cyclopentenone (**14**). Deuterium-labeling experiments support the mechanism in Scheme IV for the formation of **12** from **2**, and the mechanisms in Schemes VI and VII for the rearrangement of **2** in neat TFA. The formation of **4** from **1** and from **2** is unexpected, and that mechanism, in each case, is of more than usual interest.

The acid-catalyzed rearrangement of epoxy ketones can take several paths which may be synthetically useful, provided that one can predict in any particular case what the major products will be.[1] Little is known regarding the acid-catalyzed rearrangement of cyclohexadienone monoepoxides. As examples of cross- and fully conjugated cyclohexadienone epoxides, we prepared the hexamethyl derivatives **1** and **2**, and describe here their rearrangement in trifluoracetic acid (TFA). Each epoxide was prepared in good yield by oxidizing the corresponding dienone with *m*-chloroperbenzoic acid (*m*-CPBA).



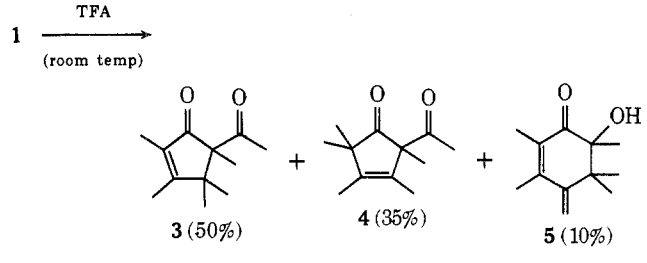
1



2

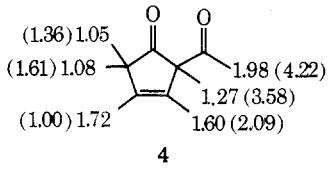
Results

Rearrangement of 1. Treatment of **1** with TFA at room temperature for 3 hr afforded a high yield of three isomers, two diketones and a hydroxy ketone, to which we assign the structures **3**–**5**.



Compound **3** was identical with the sole photoisomer of **1**; evidence for its structure has already been presented.[2]

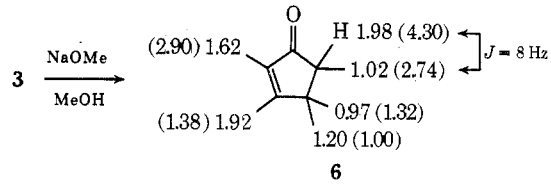
The structure of **4** is based on its spectra and cleavage with base. The compound showed two carbonyl absorp-



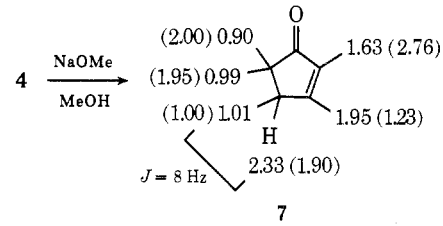
4

tions,[3] at 1740 and 1710 cm^{-1}, and only weak uv absorption, indicating that neither carbonyl group was conjugated with the double bond. The nmr spectrum with europium shift data[4] is consistent with the structure.[5]

Cleavage of **3** and **4** with sodium methoxide in methanol afforded two different conjugated cyclopentenones ($\nu_{C=O}$ 1700 cm^{-1}, $\nu_{C=C}$ 1650 cm^{-1}), assigned structures **6** and **7**, respectively.



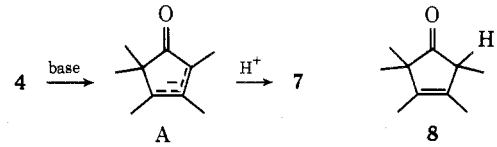
6



7

Structure **6** is the only plausible one which can be obtained from **3**, and the nmr data support the assignment. The two allylic methyls were distinguished on the basis of chemical and europium shifts, and the *gem*-dimethyl was located as remote from the carbonyl group by comparing the europium shifts of **6** and **7**.

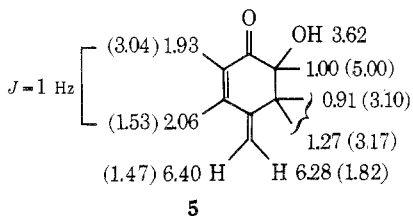
Cleavage of **4** should give the allylic anion A, which is protonated in the γ position to give **7**. Structure **8**, which could be formed by α protonation, is eliminated by the ir and uv data. Consistent with these structural assignments is the observation that **4**, which gives an allylic enolate anion, was cleaved by base much more rapidly than was **3**.



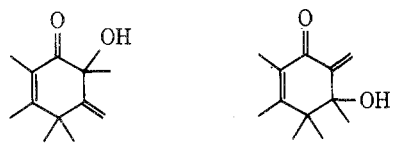
A **8**

The structure of the minor product **5** is based on its spectra. The $\nu_{C=O}$ at 1660 cm^{-1} was consistent with a conjugated carbonyl in a six-membered ring; the presence of a hydroxyl group was clear from the ν_{OH} at 3600 cm^{-1} and from the presence of a broad one-proton peak in the

nmr at δ 3.62 which was removed on D_2O exchange. The nmr spectrum showed two vinyl protons (δ 6.28, 6.40). The ir spectrum indicated that these were on a terminal methylene group (935 cm^{-1}) and the uv maximum at 281 nm (ε 7500) suggested that both double bonds were conjugated with the carbonyl group. The remainder of the nmr spectrum was consistent with the structure, with two mutually coupled vinyl methyl groups and three sharp aliphatic methyl singlets. Alternate structures for the hydroxy ketone, such as **9** or **10**, which can be envisioned as arising from **1**, do not fit the spectral data as well as **5**, and were eliminated conclusively by deuterium-labeling experiments to be described below.



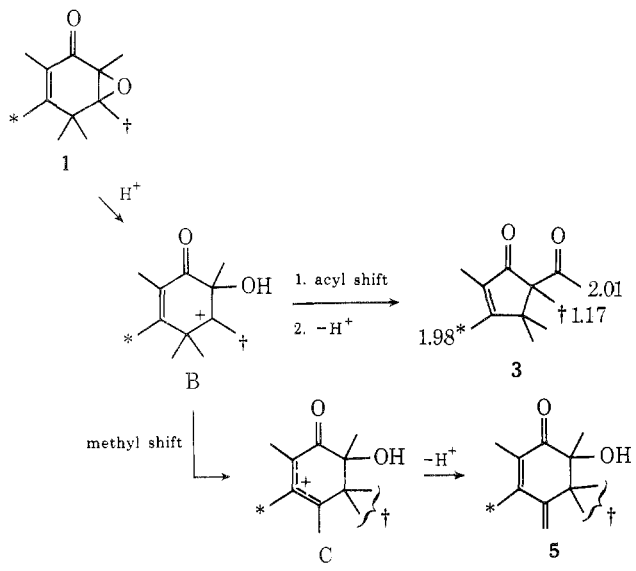
5



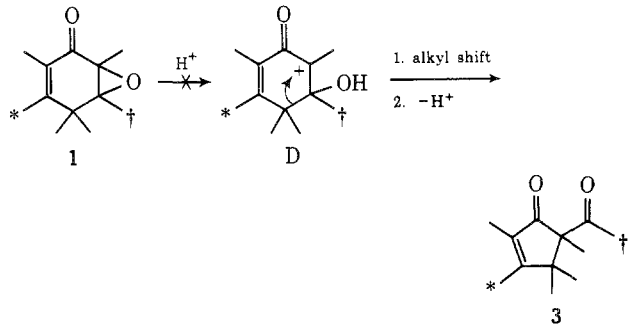
9 **10**

Mechanisms. The mechanisms leading from **1** to **3** and **5** are quite obvious, as shown in Scheme I. The epoxide ring opens to give B, in which the positive charge is remote from the carbonyl group. An acyl shift or a methyl shift, followed by proton loss, leads to **3** and **5**, respectively.

Scheme I



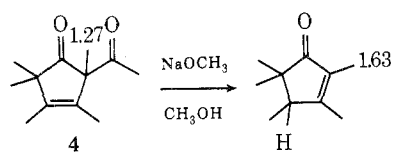
A less likely route to **3** might involve opening the epoxide ring in the opposite sense, to give D, followed by an alkyl shift and proton loss. To distinguish between these alternatives, **1** labeled with CD_3 groups in the positions marked * and † (called **1***,†) was rearranged. The nmr spectrum of the resulting **3** lacked the methyl singlet at δ 1.17 and the allylic signal at δ 1.98, but contained the sharp acetyl methyl singlet at δ 2.01. When **1** labeled with a CD_3 group only at the position marked * (called **1***) was rearranged, the resulting **3** lacked only the signal at δ 1.98. These results show that **3** is formed by the acyl shift mechanism shown in Scheme I (and not *via* D).



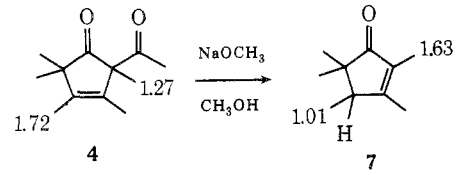
The minor product **5**, which was isolated from these labeling experiments when **1*** was the reactant, lacked the signal at δ 2.06 (and that at δ 1.93 became a sharp singlet). Starting with **1***,†, the resulting **5** lacked the δ 2.06 signal and the singlets at δ 1.27 and 0.91 integrated for only 1.5 instead of 3 protons each. This result shows that the methyl shift (B → C) is not stereospecific.[6]

The mechanistic route from **1** to **4** is less obvious. Treatment of **3** with TFA at room temperature for several hours showed that it is stable and does not rearrange to **4**. Treatment of **5** with TFA under similar conditions did give **4**, but much more slowly than the rate at which it is formed from **1**, requiring the existence of a more direct route from **1** to **4**.[7] The labeling results which must be accommodated by such a mechanism are as follows. Starting with **1***, the resulting **4** lacked the allylic methyl signal at δ 1.60 (and the other allylic signal at δ 1.72 sharpened to a singlet). Starting with **1***,†, the product **4** lacked no signals except that at δ 1.60, but the combined areas of the methyl singlets at δ 1.05 and 1.08 was reduced to only three protons.

In order to ascribe meaning to these results it was necessary to establish unequivocally the nmr assignments of **4**. Although the europium shift data support the assignment shown in the structure, they are open to some uncertainty because the molecule contains two functional groups with which coordination of the europium can occur. Consequently, an absolute, though somewhat indirect, route was used. Compound **4** labeled with a CD_3 group at δ 1.27 was obtained from CD_3-labeled **2** (*vide infra*). When this material was cleaved with base, the resulting **7** lacked the allylic methyl signal at δ 1.63 (whose location is unambiguous from both chemical and europium-shift data). Consequently, the methyl in **4** corresponding to the signal at δ 1.27 must be the methyl between the two carbonyl groups. The signals at δ 1.05 and 1.08 in **4** must therefore correspond to the *gem*-dimethyl group.

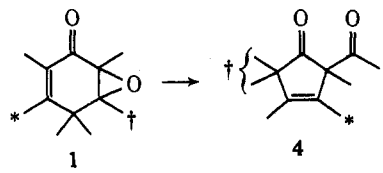


The assignment of the allylic methyl signals was made from yet a differently labeled **4**. Treatment of a particular **2**-d_6 with acid (*vide infra*) gave a sample of **4** lacking the methyl signals at δ 1.27 and 1.72. Cleavage of this labeled **4** with base gave **7** lacking the allylic methyl signal at δ



1.63 and the doublet (J = 8 Hz) at δ 1.01. This result establishes unequivocally that the allylic methyl furthest from the acetyl group is at 1.72, and that all the other assignments for **4** are correct as shown in the first structure.

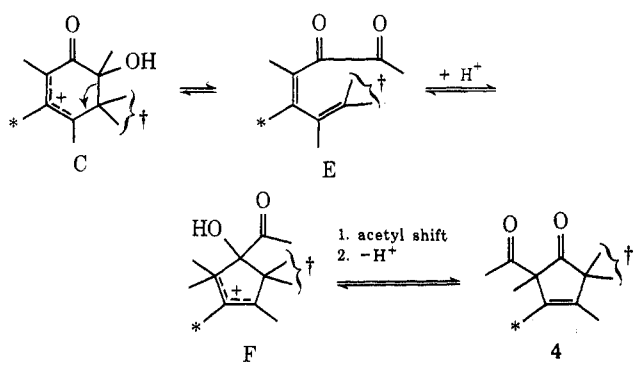
The label result which must be accommodated, in the conversion of **1** → **4**, is therefore as shown. One possible



1 **4**

mechanism is shown in Scheme II.[8] Intermediate C (from Scheme I) may either lose a proton to give **5** or may suffer carbon–carbon bond cleavage and proton loss to give the intermediate diketone E. This cleavage of a bond between a tertiary alcohol function and a quaternary carbon might be expected to be facile. Reprotonation of E at the unsaturated carbonyl group should be favored, and recyclization can afford the allylic cation F. Acetyl migration and proton loss completes the reaction.

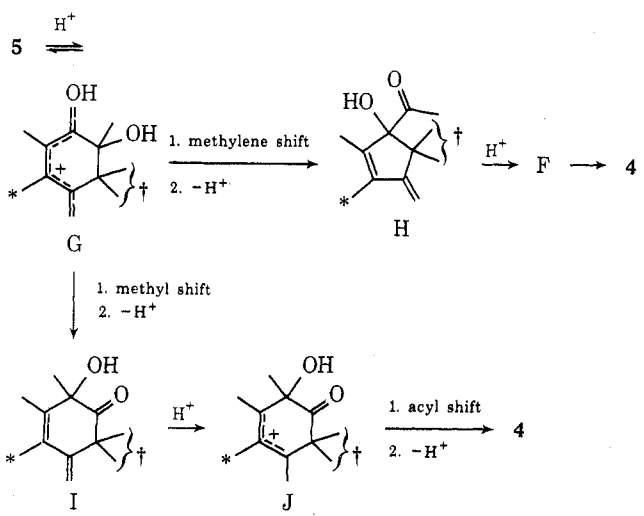
Scheme II



C E F **4**

To rationalize the much slower formation of **4** from **5**, we suggest (Scheme III) that **5** is protonated preferentially on oxygen to give G, which may rearrange to **4** by either of two routes, the first of which (*via* H) seems the more probable.

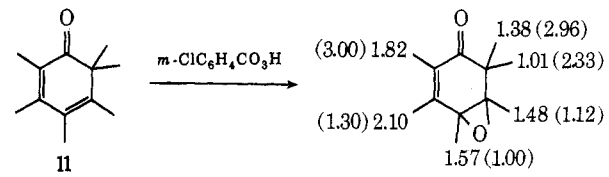
Scheme III



G H I J

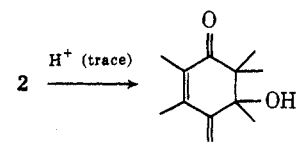
In summary, all three products from the acid-catalyzed isomerization of **1** arise from epoxide ring opening in the direction which places the positive charge remote from the carbonyl group (intermediate ion B). B may rearrange *via* either an acyl shift to give **3** or a methyl shift to give ion C, which in turn may either lose a proton to give **5** or suffer carbon–carbon bond cleavage leading to **4**.

Rearrangement of 2. The epoxy enone **2** has not been previously described. It was obtained as colorless crystals, mp 48–49.5°, in high yield from the corresponding dienone **11**. Its infrared and ultraviolet spectra showed that the carbonyl group was still conjugated with a double bond [$\nu_{C=O}$ 1680 cm^{-1}, λ_{max} (cyclohexane) 253 nm (ϵ 7230), 324 (240)], and the nmr spectrum was also consistent with epoxidation having occurred solely at the γ,δ double bond.



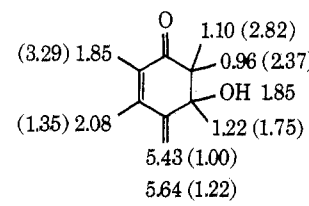
11 **2**

The epoxy enone **2** could be purified by chromatography over Florisil or neutral alumina, but it was sensitive to small amounts of acid. Chromatography on silica gel, or treatment with a little aqueous acid, resulted in nearly quantitative rearrangement to a hydroxy ketone assigned structure **12**, based on its spectral properties and further



12

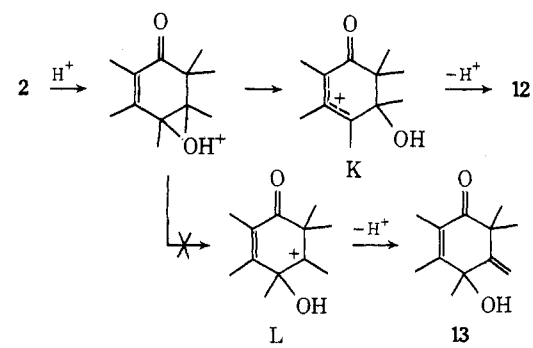
rearrangements in stronger acid (*vide infra*). The ir ($\nu_{C=O}$ 1670 cm^{-1}) and uv [λ_{max} 282 nm (ϵ 11,700), 273 (15,200), 266 (14,500)] spectra support conjugation of the carbonyl group with both double bonds. The ir spectrum also showed a terminal methylene group (960, 930 cm^{-1}) and a hydroxyl group [3620 (sharp, free OH), 3590 (sharp, intramolecular π H bond), 3500 cm^{-1} (broad, intermolecular H bond)]. The nmr spectrum was consistent with the structure.



12

12 is undoubtedly formed from **2** by proton loss from the intermediate cation K (Scheme IV). The alternative ring-

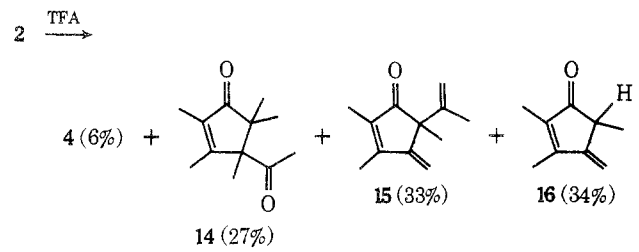
Scheme IV



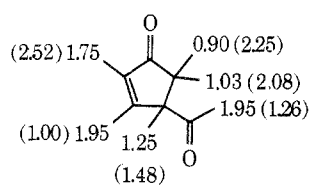
opening mode to give L would lead to structure **13**, which is also reasonably consistent with the observed nmr spectrum, but which is less consistent with the uv and ir data and is conclusively eliminated by labeling results. Prepa-

ration of **2** from **11** containing CD_3 groups at C-3 and C-5[9] gave **2**-d_6 lacking methyl signals at δ 1.48 and 2.10. This in turn, with acid, gave **12**-d_6 lacking methyl signals at δ 1.22 and 2.08. Had the hydroxy ketone been **13**, the product would have contained only five deuteriums and would have lacked the vinyl proton signals.

Treatment of **2** with neat trifluoroacetic acid gave four products, only two of which were isomers (mass spectrum) of the starting epoxy enone. One of these was **4**, already identified as a rearrangement product of **1** (*vide supra*). The other products are assigned structures **14**–**16**. The product ratios depend on time, and those shown are for 20 hr at room temperature. Monitoring the products showed that **16** was formed at the expense of **15**, and independent treatment of **15** with TFA showed that it was converted cleanly to **16** and acetone.

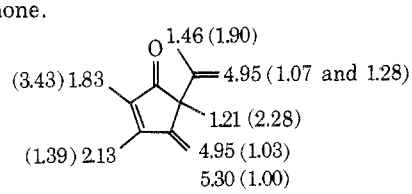


The product structures were established primarily by their spectral properties. The diketone **14** had ir and uv spectra similar to those of **3** but was isomeric with it. The nmr data fit the assigned structure; shift-reagent appears to coordinate primarily at the cyclopentenone carbonyl group. The base peak in the mass spectrum was M − 42 (loss of CH_2=C=O) and the next most intense peak (rel intensity 60) was at M − 57 (loss of CH_2=C=O) and CH_3).



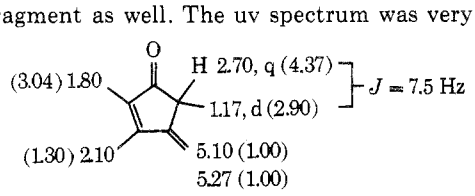
14

The product assigned structure **15** corresponded in analysis to loss of water from the epoxy enone **2**. The nmr spectrum showed four vinyl protons and three allylic methyl groups, as well as one sharp aliphatic methyl singlet. The ir spectrum was consistent with a cyclopentenone carbonyl (1710 cm^{-1}), showing strong carbon–carbon double bond absorptions (1645, 1620 cm^{-1}) and a strong terminal methylene band (915 cm^{-1}). The uv maxima [340 nm (ϵ 63), 270 (13,700)] were consistent with a conjugated dienone.



15

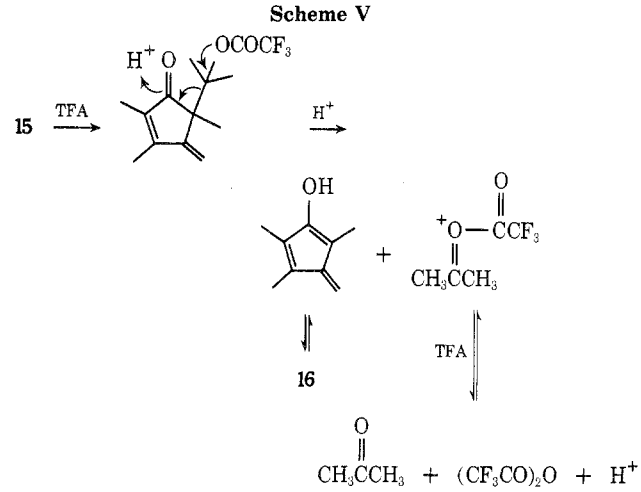
The product assigned structure **16** corresponded in analysis not only to loss of water from the epoxy enone, but a C_3H_4 fragment as well. The uv spectrum was very similar to that of **15** [267 nm (ϵ 15,200)], as was the ir spectrum ($\nu_{C=O}$ 1710, $\nu_{=CH_2}$ 905 cm^{-1}). The nmr spectrum showed two vinyl protons, two allylic methyls, and a >$CHCH_3$ moiety. The proton at δ 2.70 was readily exchanged at room temperature in $NaOCH_3$–CH_3OD, causing collapse of the doublet at δ 1.17 to a singlet.



16

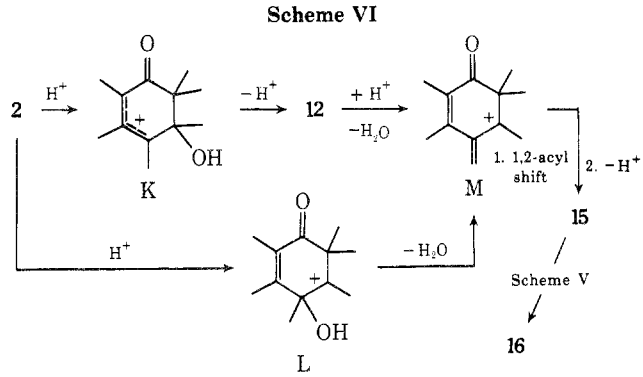
Mechanisms. Scheme V gives a plausible mechanism for the formation of **16** from **15**. When the reaction was carried out in an nmr tube, the appearance of the sharp singlet due to the acetone was observed.

Scheme V



Independent treatment of the hydroxy ketone **12** with TFA at room temperature gave only **15** and **16**, in ratios which depended on the reaction time. After 2 hr the product was 94% **15** and 6% **16**, whereas after 46 hr it was 3% **15** and 97% **16**. These products can be rationalized as in Scheme VI, either with **12** as a discrete intermediate on the route **2** → **12** → **15** → **16** or by-passing **12** *via* intermediate L. If the reaction proceeds *via* L, dehydration may precede the 1,2-acyl shift as shown in Scheme VI, or the order of these steps may be reversed. Unfortunately, no simple experiment can distinguish between these alternatives. It is clear, however, that the remaining two rearrangement products **4** and **14** are not produced from **12**.

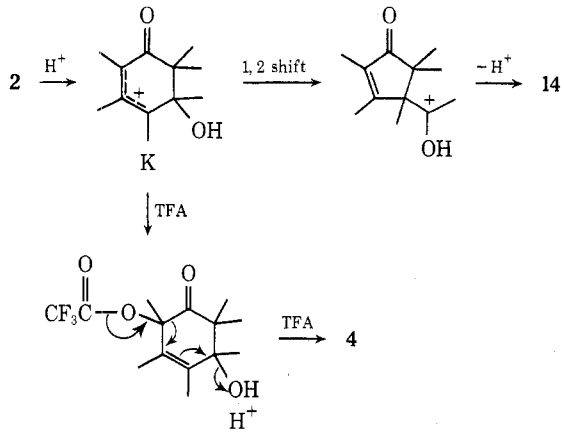
Scheme VI



Possible routes to **4** and **14** are shown in Scheme VII. The first-formed intermediate is once again K; ring contraction and proton loss lead to **14**, whereas attack of a nucleophile at the carbon α to the carbonyl group followed by an acyl shift (again, a ring contraction) and loss of hydroxyl lead to **4**.[10]

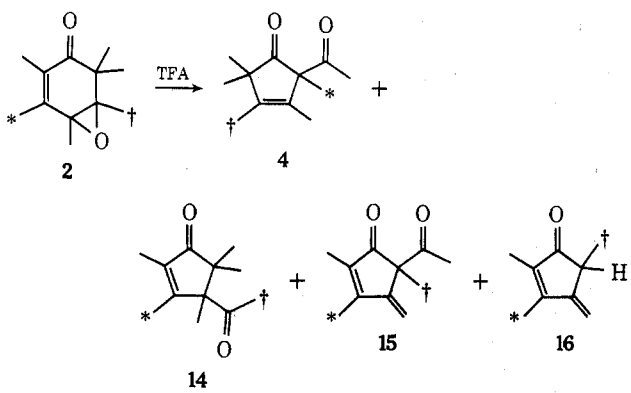
Several labeling experiments were done to test the plausibility of the mechanisms in Schemes VI and VII. The results are shown in Scheme VIII. Experiments were done with trideuterio- (2*) and hexadeuterio- (2*,†) epoxy ketone.[11] The mechanisms leading from **2** to **14**–**16** are fairly obvious, and the labeling results fully support the proposals in Schemes VI and VII. The route from **2** to **4** is

Scheme VII



less obvious, but the label results support the mechanism shown in Scheme VIII.[12]

Scheme VIII



In summary, the dienone epoxide **2** rearranges quantitatively in dilute acid to the hydroxy ketone **12** *via* the allylic cation K (Scheme IV). In less basic solvents (such as neat TFA) the same intermediate may rearrange by a 1,2-alkyl shift to give **14** or may, following nucleophilic attack α to the carbonyl group, undergo a ring contraction similar to a benzilic acid rearrangement, leading to **4** (Scheme VII). Product **15** may arise from protonation of **12** or may be formed by the alternate method of epoxide ring opening (*via* L, Scheme VI); product **16** is formed by dealkylation of **15** (Scheme V).

The manner in which the various methyl groups in **1** and **2**, or other substituents, may determine the mode of the acid-catalyzed rearrangements of cyclohexadienone epoxides remains to be further explored, but it is clear from these studies that such reactions can be useful for the synthesis, for example, of cyclopentenones.

Experimental Section[13]

Acid-Catalyzed Rearrangement of 2,3-Epoxy-2,3,4,4,5,6-hexamethyl-5-cyclohexenone (1). A solution containing 200 mg of **1**[2] and 2 ml of trifluoroacetic acid, prepared at 0°, was allowed to stir for 3 hr. The mixture was then poured into cold Na_2CO_3 solution and extracted several times with ether. The combined ether extracts were washed successively with Na_2CO_3 solution and saturated NaCl solution, and dried ($MgSO_4$). After solvent removal, the residue was subjected to analytical gas chromatography (vpc, 5 ft × 0.125 in. 20% FFAP on Chromosorb W, 150°) and showed three main products: **3**[2] (50%, retention time 7.1 min), **4** (35%, 2.5 min) and **5** (10%, 4.8 min). The products were separated by preparative vpc on a similar column. The mixture of **4** and **5** could also be separated from **3** by column chromatography on silica gel using hexane–ether (10:1), the last fractions being pure **3**. The mass spectrum of each product had a parent peak at *m/e* 194, establishing that they were all isomers of **1**.

2-Acetyl-2,3,4,5,5-pentamethyl-3-cyclopentenone (**4**) had ir (neat) 1740 (s), 1710 (s), 1455 (w, br), 1370 (w), 1270 (w), 1210 (w), 1140 (w), 1100 (w), 1035 cm^{-1} (w); uv (95% ethanol) 282 nm (ϵ 81), 203 (3560); nmr (CCl_4) see structure; the peaks at δ 1.60 and 1.72 were mutually coupled quartets, J = 1.5 Hz; mass spectrum (70 eV) *m/e* (rel intensity) 194 (<1), 152 (94), 137 (100), 123 (22), 109 (12), 91 (12), 81 (27), 67 (14), 43 (55).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 73.94; H, 9.41.

6-Hydroxy-4-methylene-2,3,5,5,6-pentamethyl-2-cyclohexenone (**5**) had ir (neat) 3500 (m, br), 1660 (s), 1470 (w), 1440 (m), 1380 (m), 1340 (m), 1215 (w), 1160 (w), 1125 (w), 1105 (w), 1085 (w), 1040 (m), 935 cm^{-1} (m); uv (95% ethanol) 281 nm (ϵ 7500); nmr (CCl_4) see structure; the peaks at δ 1.93 and 2.06 were mutually coupled quartets, J = 1.0 Hz.

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 73.75; H, 9.37.

Preparation and Rearrangement of 2,3-Epoxy-5-trideuteriomethyl-2,3,4,4,6-pentamethyl-5-cyclohexenone (1*). To a solution of 1.0 g of unlabeled **1**[2] in 5 ml of dimethyl sulfoxide-d_6, N_2 atmosphere, was added slowly with stirring 0.8 g of potassium *tert*-butoxide. The mixture was stirred at room temperature for 1 hr, quenched in ice–water, and extracted with ether. The organic layer was dried ($MgSO_4$) and solvent was evaporated to give a nearly quantitative yield of **1***. Its nmr spectrum was identical with that of **1**[2] except for the absence of the peak at δ 1.81 (C-5 methyl) and a sharpening to a singlet of the peak at δ 1.74 (C-6 methyl).

Treatment of **1*** with TFA as described for unlabeled **1** afforded **3*** (lacked the C-3 signal at δ 1.98, and the C-2 signal at δ 1.70 sharpened to a singlet), **4*** (lacked the C-3 signal at δ 1.60, and the C-4 signal at δ 1.72 sharpened to a singlet), and **5*** (lacked the C-3 signal at δ 2.06, and the C-2 signal at δ 1.93 sharpened to a singlet).

Rearrangement of 2,3-Epoxy-3,5-trideuteriomethyl-2,4,4,6-tetramethyl-5-cyclohexenone (1*,†). Labeled epoxy ketone, treated with TFA as described for unlabeled **1**, gave **3*,†** (sharp singlets, equal in area, at δ 1.02, 1.10, 1.70, and 2.01), **4*,†** [sharp singlets at δ 1.05 and 1.08 (total area 3 H), and at δ 1.27, 1.72, and 1.98 (3 H each)], and **5*,†** [singlets at δ 0.91 (1.5 H), 1.00 (3 H), 1.27 (1.5 H), 1.93 (3 H), 3.62 (1 H, br), 6.28 (1 H), and 6.40 (1 H)].

Cleavage of 3 with Base. A solution of **3** (100 mg) and sodium methoxide (20 mg) in 3 ml of methanol was stirred at room temperature for 8 hr. The mixture was poured into ice–water and extracted with ether. The combined ether layers were washed with water and saturated sodium chloride solution and dried ($MgSO_4$). After evaporation of the solvent, the residue was analyzed by vpc (5 ft × 0.125 in., 20% FFAP, 120°) and consisted of 80% recovered recovered **3** (retention time 21 min) and 20% of 2,3,4,4,5-pentamethyl-2-cyclopentenone (**6**), retention time 1.7 min. This product was collected by preparative vpc: ir (neat) 1700 (s), 1650 (s), 1460 (m, br), 1400 (m), 1335 (m), 1235 (w), 1100 cm^{-1} (w, br); nmr (CCl_4) see structure; the peaks at δ 1.02 (3 H) and 1.98 (1 H) were a mutually coupled doublet and quartet, respectively, J = 8.0 Hz, and the peaks at δ 1.62 and 1.92 were mutually coupled quartets, J = 1.0 Hz.

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.75; H, 10.73.

Cleavage of 4 with Base. The reaction conditions were identical with the conditions given for the cleavage of **3**. Vpc analysis (5 ft × 0.125 in., 20% FFAP, 120°) showed that all of **4** was consumed, the sole product being 2,3,4,5,5-pentamethyl-2-cyclopentenone (**7**), retention time 1.4 min. Pure **7** was collected by preparative vpc: ir (neat) 1700 (s), 1650 (s), 1460 (m, br), 1400 (m), 1335 (m), 1040 cm^{-1} (m, br); uv (95% ethanol) 235 nm (ϵ 6000); nmr (CCl_4) see structure; the peaks at δ 1.01 (3 H) and 2.33 (1 H) were a mutually coupled doublet and quartet, respectively, J = 8.0 Hz, and the peaks at δ 1.63 and 1.95 were mutually coupled quartets, J = 1.0 Hz. Treatment of **7** with sodium methoxide in excess methanol-*d* for several hours at room temperature, followed by work-up, gave **7**-d_4 whose nmr spectrum lacked the quartets at δ 1.95 (3 H), and 2.33 (1 H), the three-proton peaks at δ 1.01 and 1.63 now becoming sharp singlets.

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.75; H, 10.71.

Cleavage of **4**-d_3 lacking the singlet at δ 1.27 (*vide infra*) gave **7**-d_3 lacking the signal at δ 1.63 and with the peak at δ 1.95 a sharp singlet. Cleavage of **4**-d_6 lacking the methyl signals at δ 1.27 and 1.72 (*vide infra*) gave **7**-d_6 lacking the quartet at δ 1.63 and the doublet at δ 1.01, and having the signal at δ 1.95 a sharp singlet and that at δ 2.33 a broadened one-proton singlet.

Treatment of 3 with TFA. To 8 mg of vpc-collected **3** cooled in an ice bath was added dropwise 1 ml of TFA. The solution was stirred at 0° for 4 hr, then quenched with ice-cold $NaHCO_3$ solution and extracted with ether. The ether layer was washed successively with cold $NaHCO_3$ solution and saturated NaCl solution, then dried and analyzed by vpc as in the rearrangement of **1**. The only product was recovered **3**.

Treatment of 5 with TFA. To 10 mg of vpc-collected **5** cooled in an ice bath was added dropwise 1 ml of TFA. The solution was stirred at 0°. After 0.5 hr an aliquot was withdrawn, quenched, worked up, and analyzed as above. It consisted of 7% **4** and 93% recovered **5**. After 4 hr, the product consisted of 10% **4** and 90% recovered **5**.

4,5-Epoxy-2,3,4,5,6,6-hexamethyl-2-cyclohexenone (2). To a solution of 0.600 g (3.37 mmol) of 2,3,4,5,6,6-hexamethyl-2,4-cyclohexadienone (**11**)[9] in 10 ml of methylene chloride was added, at 0°, a solution of 0.620 g (3.60 mmol) of *m*-chloroperbenzoic acid in 10 ml of methylene chloride. The mixture was stirred for 2 hr at 0°, during which time *m*-chlorobenzoic acid precipitated from solution. The solvent was evaporated, petroleum ether (bp 30–60°) was added to the residue, and the *m*-chlorobenzoic acid was removed by filtration. Evaporation of the solvent from the filtrate left 0.648 g of a light yellow oil; an nmr spectrum of the crude material showed it to be >90% **2**. The crude product was chromatographed on Florisil using ether–hexane (1:10) as eluent, to give 0.523 g (2.70 mmol, 80%) of epoxide **2**: mp 48–49.5°; ir (KBr) 2970 (m), 2920 (m), 2860 (w), 1680 (s), 1465 (m), 1380 (m), 1310 (m), 1070 (m), 840 cm^{-1} (s); uv (cyclohexane) λ_{max} 253 nm (ϵ 7230); nmr ($CDCl_3$) see structure; all peaks had equal areas; all were sharp singlets except those at δ 1.82 and 2.10, which were mutually coupled quartets, J = 1.0 Hz; mass spectrum (70 eV) *m/e* (rel intensity) 194 (14), 179 (14), 178 (19), 163 (18), 152 (46), 151 (70), 147 (21), 137 (29), 135 (25), 126 (29), 124 (29), 123 (27), 109 (31), 91 (16), 81 (30), 43 (100).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.06, H, 9.32.

Similar oxidation of **11** with a CD_3 group at C-3[9] gave **2*** whose nmr spectrum lacked the quartet at δ 2.10, and with the quartet at δ 1.82 sharpened to a singlet. Oxidation of **11** with CD_3 groups at C-3 and C-5[9] gave **2***† whose nmr spectrum, in addition to the changes just cited, lacked the singlet at δ 1.48.

4-Methylene-5-hydroxy-2,3,5,6,6-pentamethyl-2-cyclohexenone (12). To a solution of **2** (0.250 g, 1.29 mmol) in ether (15 ml) at 0° was added a solution of trifluoroacetic acid (0.5 ml) in water (5 ml). After the mixture was stirred for 0.5 hr, the layers were separated, and the ether layer was washed successively with saturated $NaHCO_3$ solution, water, and saturated NaCl solution, and dried ($MgSO_4$). Evaporation of the ether left 0.238 g (95%) of the hydroxy ketone **12** as a colorless liquid which was not further purified: ir (CCl_4) 3620 (w, sharp), 3590 (w, sharp), 3500 (m, br), 2980 (s), 2930 (m), 2870 (w), 1670 (s), 1590 (w), 1460 (w), 1380 (s), several w bands from 1350–1170, 1150 (m), 1130 (w), 1070 (m), 1040 (m), 1010 (w), 960 (m), 930 cm^{-1} (m). The bands at 3620 and 3590 cm^{-1} did not change in relative intensity as a function of the concentration of **12** in CCl_4, whereas the intensity of the band at 3500 cm^{-1} decreased drastically with a decrease in concentration of **12**: uv (cyclohexane) 282 nm (ϵ 11,700, sh), 273 (15,200), 266 (14,500, sh); nmr (CCl_4) see structure; the peaks at δ 1.85 and 2.08 were broadened, all other peaks being sharp singlets; mass spectrum (70 eV) *m/e* (rel intensity) 194 (29), 179 (31), 176 (8), 161 (16), 151 (100), 137 (30), 133 (44), 123 (15), 121 (15), 109 (26), 105 (15), 91 (23), 83 (16), 79 (23), 78 (25), 67 (13), 65 (15), 56 (18), 54 (26), 51 (15), 43 (80), 39 (42).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.05; H, 9.36.

Treatment of **2***† with aqueous TFA as above gave **12**-d_6 with the following nmr spectrum: δ 0.96 (s, 3 H), 1.10 (s, 3 H), 1.85 (s, 3 H), 5.43 (s, 1 H), 5.64 (s, 1 H).

Rearrangement of 2 in Neat Trifluoroacetic Acid. A solution of 0.100 g (0.515 mmol) of **2** in 2 ml of ice-cold trifluoroacetic acid was stirred at 0° for 1 hr, then at room temperature for 20 hr. The reaction was monitored by nmr after the spectrum of each product had been determined. The reaction was quenched by pouring the mixture into ice and saturated $NaHCO_3$ solution. The products were extracted with ether, and the combined ether layers were washed successively with saturated $NaHCO_3$ solution, water, and saturated NaCl solution and dried ($MgSO_4$). Evaporation of the solvent left 0.092 g of a light yellow liquid which was analyzed by vpc (5 ft × 0.125 in., 10% FFAP on Chromosorb W, AW-DMCS 80/100, 160°, 30 ml/min). Four products (retention time in minutes, %) were observed: **4** (1.5, 6), **14** (4.4, 27), **15** (1.8, 33), **16** (1.2, 34). At 150° the retention times were respectively 3.5, 10.9, 4.0, and 2.5 min. After only 30 min reaction time, the yields follow: **4** (7%), **14** (32%), **15** (53%), **16** (8%). After 20 hr, the respective yields were 6, 27, 33, and 34%. The ratio of **4**:**14**:(**15** + **16**) was time independent, but the yield of **16** increased with reaction time at the expense of **15**.

The products from this and larger scale experiments were separated by preparative vpc (10 ft × 0.25 in., 20% FFAP on Chromosorb W P/G 30/60, 160°). The spectral data for 2-acetyl-2,3,4,5,5-pentamethyl-3-cyclopentenone (**4**) have been presented (*vide supra*).

4-Acetyl-2,3,4,5,5-pentamethyl-2-cyclopentenone (**14**) had ir (CCl_4) 2970 (s), 2940 (m), 2920 (m), 2860 (w), 1710 (s), 1660 (s), several medium-intensity bands at 1475–1400, 1380 (m), 1350 (m), 1320 (m), 1215 (m), 1150 (m), 1075 (m), 1025 (m), 960 cm^{-1} (w); uv (cyclohexane) 237 nm (ϵ 7720), 209 (6000); nmr (CCl_4) see structure; the bands at δ 1.75 and 1.95 were mutually coupled, J = 1.0 Hz; mass spectrum (70 eV) *m/e* (rel intensity) 194 (1.5), 179 (1.0), 166 (1.0), 152 (100), 137 (60), 123 (53), 109 (9), 95 (8), 93 (9), 91 (12), 81 (35), 67 (12), 55 (12), 53 (12).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.25; H, 9.29.

5-Isopropenyl-4-methylene-2,3,5-trimethyl-2-cyclopentenone (**15**) had ir (CCl_4) 3080 (w), 2965 (s), 2910 (s), 2865 (m), 1710 (s), 1645 (s), 1620 (s), 1455 (s), 1400 (s), 1370 (m), 1340 (w), 1290 (m), 1175 (w), 1160 (w), 1120 (w), 1030 (m), 1010 (w), 915 cm^{-1} (s); uv (cyclohexane) 278 nm (ϵ 10,030, sh), 270 (13,700) 262 (11,070, sh); nmr (CCl_4) see structure; the band at δ 1.46 was a doublet, J = 1.7 Hz, those at δ 1.83 and 2.13 were broadened by mutual coupling, that at δ 4.95 was a multiplet (three vinyl protons), and that at δ 5.30 was a broadened singlet. The peak at δ 1.21 was a sharp singlet: mass spectrum (70 eV) *m/e* (rel intensity) 176 (13), 161 (34), 148 (24), 133 (100), 105 (31), 91 (35), 79 (19), 77 (26), 65 (16), 53 (14), 51 (19), 41 (37), 39 (41).

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.72; H, 9.11.

4-Methylene-2,3,5-trimethyl-2-cyclopentenone (**16**) had ir (CCl_4) 3080 (w), 2960 (m), 2925 (m), 2860 (w), 1710 (s), 1640 (s), 1620 (s), several medium-intensity bands at 1460–1375, 1340 (w), 1310 (m), 1265 (m), 1145 (w), 1120 (m), 1050 (m), 990 (m), 905 cm^{-1} (s); uv (cyclohexane) 275 nm (ϵ 10,020, sh), 267 (15,200), 258 (13,450, sh); nmr (CCl_4) see structure; the peaks at δ 1.80 and 2.10 were broadened by mutual coupling, and the singlets at δ 5.10 and 5.27 were also broad; mass spectrum (70 eV) *m/e* (rel intensity) 136 (35), 121 (13), 93 (100), 91 (37), 79 (19), 77 (36), 67 (16), 65 (13), 55 (11), 54 (23), 53 (25), 52 (12), 51 (23), 50 (10), 41 (18), 39 (44).

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found C, 79.15; H, 9.04.

A solution of **16** (50 mg, 0.368 mmol) in 4 ml of CH_3OD containing 54 mg (1.0 mmol) of sodium methoxide was stirred for 1 hr at room temperature, then quenched with 15 ml of D_2O and extracted three times with pentane (10 ml). Combined organic layers were washed with water (twice) and saturated NaCl solution and dried ($MgSO_4$). Evaporation of the solvent left 45 mg of **16**-d_1 with the following nmr (CCl_4): δ 1.17 (s, 3 H), 1.80 (br s, 3 H), 2.10 (br s, 3 H), 5.10 (br s, 1 H), 5.27 (br s, 1 H).

Treatment of 5-Isopropenyl-4-methylene-2,3,5-trimethyl-2-cyclopentenone (15) with TFA. A solution of **15** (0.060 g, 0.34 mmol) in 1 ml of trifluoroacetic acid was allowed to stand at room temperature for 20 hr, the reaction being monitored by nmr. During the reaction, a sharp singlet appeared at δ 2.33, shown to correspond to acetone in TFA. The reaction was quenched by pouring it into ice and saturated $NaHCO_3$ solution. The mixture was extracted with ether, and the ether extract was worked up and analyzed as in the rearrangement of **2**. The sole components (determined by vpc) after 20 hr were **15** (55%) and **16** (45%). When the reaction was carried out at higher temperatures, conversion to **16** was quantitative.

Rearrangement of 5-Hydroxy-4-methylene-2,3,5,6,6-pentamethyl-2-cyclohexenone (12) in TFA. A solution of **12** (0.100 g, 0.515 mmol) in 1.5 ml of trifluoroacetic acid was stirred at room temperature. Aliquots were withdrawn at various time intervals, quenched and worked up as usual, and analyzed by vpc (5 ft × 0.125 in., 10% FFAP on Chromosorb W, AW-DMCS 80/100, 150°, N_2 flow rate 30 ml/min). Only two components were present, **15** (4.0 min) and **16** (2.5 min), identified by nmr and ir. The relative amounts at various time intervals follow: 2 hr, 94% **15**, 6% **16**; 26 hr, 32% **15**, 68% **16**; 46 hr, 3% **15**, 97% **16**.

Rearrangement of Labeled 2 in TFA. A solution of **2*** (lacking the signal at δ 2.10; 500 mg, 2.58 mmol) in 5 ml of TFA was

stirred at room temperature for 21 hr, then quenched and worked up as described for unlabeled **2**. The products had the following nmr spectra (CCl_4): **4**, δ 1.05 (s, 3 H), 1.08 (s, 3 H), 1.60 (m, 3 H), 1.72 (m, 3 H), 1.98 (s, 3 H); **14**, δ 0.90, 1.03, 1.25, 1.75, and 1.95, all s, 3 H; **15**, δ 1.21 (s, 3 H), 1.46 (d, 3 H, J = 1.7 Hz), 1.83 (s, 3 H), 4.95 (m, 3 H), 5.30 (br s, 1 H); **16**, δ 1.17 (d, 3 H, J = 7.5 Hz), 1.80 (s, 3 H), 2.70 (q, 1 H, J = 7.5 Hz), 5.10 (br s, 1 H), 5.27 (br s, 1 H).

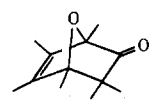
A solution of **2***,† (lacking the signals at δ 2.10 and 1.48) in TFA was allowed to rearrange in the amounts and manner described for **2***. The products had the following nmr spectra (CCl_4): **4**, δ 1.05, 1.08, 1.60, and 1.98 (all s, 3 H); **14**, δ 0.90, 1.03, 1.25, and 1.75 (all s, 3 H); **15**, δ 1.46 (d, 3 H, J = 1.7 Hz), 1.83 (s 3 H), 4.95 (m, 3 H), 5.30 (br s, 1 H); **16**, δ 1.80 (s, 3 H), 2.70 (br s, 1 H), 5.10 (br s, 1 H), 5.27 (br s, 1 H).

Acknowledgment. We are indebted to the National Institutes of Health and the National Science Foundation for their support of this research.

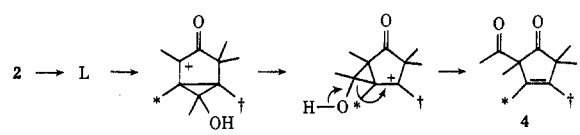
Registry No.—**1**, 40940-60-1; **1**-d_3, 50506-40-6; **1**-d_6, 50506-41-7; **2**, 50506-42-8; **2**-d_3, 50506-43-9; **2**-d_6, 50506-44-0; **3**, 40940-46-3; **3**-d_3, 50506-46-2; **3**-d_6, 50506-47-3; **4**, 50506-48-4; **4**-d_3, 50506-49-5; **4**-d_6, 50506-50-8; **5**, 50506-51-9; **5**-d_3, 50506-52-0; **5**-d_6, 50506-53-1; **6**, 50506-54-2; **7**, 50506-55-3; **11**, 3854-96-4; **12**, 50506-57-5; **12**-d_6, 50506-58-6; **14**, 50506-59-7; **15**, 50506-60-0; **16**, 29765-85-3.

References and Notes

(1) R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959); M. S. Malinovskii, "Epoxides and Their Derivatives," Daniel Davey, New York, N. Y., 1965; H. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, p 320.
(2) H. Hart, M. Verma, and I. Wang, *J. Org. Chem.*, **38**, 3418 (1973).
(3) Corresponding respectively to the cyclopentenone and acetyl moieties: K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, San Francisco, Calif., 1962, p 42.
(4) Shown in δ units, with the relative downfield shifts in the presence of Eu(fod)$_3$ given in parentheses; see D. R. Kelsey, *J. Amer. Chem. Soc.*, **94**, 1764 (1972).
(5) All peaks were sharp three-proton singlets except for those at δ 1.60 and 1.72, which were homoallylically coupled (J = 1.5 Hz). The acetyl methyl (δ 1.98), allylic methyls (δ 1.60, 1.72), and aliphatic methyls are readily assigned using chemical shifts. Specific assignments within the last two categories are based on labeling experiments to be described below.
(6) This result also argues against structures **9** and **10** for the hydroxy ketone. The most plausible route to **9** would involve proton loss from B; in this event, product from **1***,† should lack the vinyl protons. The most plausible route to **10** would involve proton loss from D; in this event, product from **1***,† should lack two methyl signals. The label results fit neither of these predictions.
(7) The kinetic experiments require that, when starting from **1**, less than 3% of **4** is produced from **5**; over 97% must be obtained directly from **1**.
(8) One can envision several other plausible mechanisms for the conversion of **1** to **4**. The most attractive of these involved cyclopropylcarbinyl cations derived from participation of the double bond in B. However, none of these fit the observed labeling results.
(9) H. Hart, P. M. Collins, and A. J. Waring, *J. Amer. Chem. Soc.*, **88**, 1005 (1966). (See particularly footnote 16.)
(10) The nucleophile shown is TFA, but may also be water or may even be the hydroxyl group, *via* an intermediate such as



(11) It was from these experiments that **4**, lacking only the singlet at δ 1.27, or lacking both signals at δ 1.27 and 1.72 referred to earlier, was obtained.
(12) Plausible alternative routes from **2** to **4** can be envisioned but can be eliminated as a consequence of the labeling experiments. One example, involving cyclopropylcarbinyl rearrangements, is



(13) Melting points are uncorrected. Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Ir spectra were calibrated against a polystyrene film; nmr spectra are referenced against tetramethylsilane.

Notes

Acid-Catalyzed Rearrangement of an Epoxy Ketone by Competitive Protonation at Each Oxygen

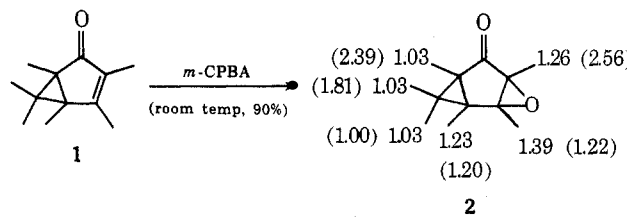
Harold Hart* and Irene Huang

Department of Chemistry, Michigan State University, East Lansing, Michigan 48824

Received September 6, 1973

In general, the acid-catalyzed rearrangement of epoxy ketones is initiated by protonation of the epoxide oxygen atom.[1] We describe here the rearrangement of an epoxy ketone to two principal products, one of which appears to arise from protonation of the carbonyl oxygen.

3,4-Epoxy-1,3,4,5,6,6-hexamethylbicyclo[3.1.0]hexan-2-one (**2**) was prepared in good yield from the corresponding unsaturated ketone **1**[2] and *m*-chloroperbenzoic acid. The structure is based on the method of synthesis and spectral properties. The $\nu_{C=O}$ in **2** was at 1715 cm^{-1} (1690 cm^{-1} in **1**). The nmr spectrum[3] showed that all methyl signals were aliphatic ($\delta \leq 1.39$), and europium shift reagent removed the accidental degeneracy of three methyls at δ 1.03 and gave a spectrum with six sharp, equal singlets. Vpc and nmr analysis showed that only a single stereoisomer of **2** was produced; the equal chemical shifts of the two methyl groups at C-6 suggest that the epoxide ring is trans to the cyclopropane ring. Epoxide prepared from **1** with a CD_3 group at C-4 lacked the singlet at δ 1.39 (**2***); epoxide prepared from **1** with CD_3 groups at C-1 and C-4 lacked the singlet at δ 1.39, and that at δ 1.03 was reduced in area to six protons (**2***,†). The labeling and Eu-shift data support the nmr assignments shown in the structure.



1 **2**

Treatment of **2** with trifluoroacetic acid (TFA) at 0° for 10 min resulted in complete rearrangement to **3** and **4**. Also formed was a small amount of **5** which is known to arise from the dealkylation of **3**.[4] The properties and structure proof of **3**-**5** are described elsewhere.[4]