Mechanism of the Intramolecular Cyclization of Acetylenic Ketones

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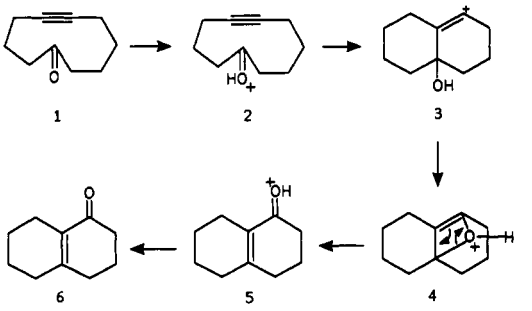
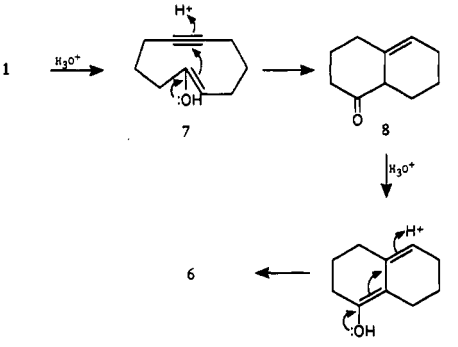
Acid-catalyzed intramolecular cyclization of 5-cyclodecynone (1) under a variety of conditions gives bicyclo-[4.4.0]-1(6)-decen-2-one (6) as the only product. In a recent report, evidence for a reaction mechanism involving transannular triple-bond participation with a polarized carbonyl group followed by attack of the original carbonyl oxygen on the developing vinyl cation to give an unstable oxete intermediate (4) was presented. Subsequently, several workers have suggested a mechanism involving acid-catalyzed enolization of 1, followed by the transannular attack of the enol double bond at the acetylenic function, as the first two steps in an alternate process for explaining this rearrangement. When 6-octyn-2-one (9) was treated with either mineral or Lewis acids, a mixture of 1-acetyl-2-methyl-1-cyclopentene (12) and 2,3-dimethyl-2-cyclohexen-1-one (14) were produced. Experiments have shown that the oxygen atoms in the starting acetylenic ketone 9 are the same ones found in the cyclic products 12 and 14. A mechanism involving cyclization of enol intermediates cannot account for the formation of 14. On the other hand, formation and rearrangement of oxete intermediates demonstrates how both 12 and 14 are produced. The results from acid-catalyzed cyclization of 6-octyn-2-one (9) are also compared to those reported for the solvolysis of the tosylate of 6-octyn-2-ol (18).

It has been clearly established that 5-cyclodecynone (1) undergoes transannular cyclization to give only bicyclo-[4.4.0]-1(6)-decen-2-one (6) when treated with HCl in aqueous methanol or with boron trifluoride etherate in aprotic solvents.[1-3] Like 5-cyclodecen-1-yl derivatives[4,5] and 5-cyclodecyn-1-yl derivatives,[1-3,6] 1 appears to prefer reaction via a transition state involving only six-membered rings. Similarly, the acid-catalyzed cyclization of 5-cyclononynone gives bicyclo[4.3.0]-1(6)-nonen-2-one as the only product.[7] In a recent report,[8] the mechanism outlined in Scheme I was suggested to explain additional observations that were made in connection with the rearrangement of 1. One important experiment involved the rearrangement in the presence of $H_2{}^{18}O$. When 1 was rearranged in 1.5 M methanolic HCl that contained $H_2{}^{18}O$, incorporation of oxygen-18 in the final product was not much above that observed when the bicyclic ketone itself was treated with methanol-$H_2{}^{18}O$ under similar conditions. Rearrangement through an oxete derivative[9] 4 requires that the oxygen atom in the starting acetylenic ketone 1 be the same as that in the bicyclic product 6. Several correspondents have suggested that the mechanism outlined in Scheme II will also account for these results. In this process, the acetylenic ketone 1 undergoes an acid-catalyzed enolization to give 7. The other possible enol cannot react via a six-membered ring transition state and is not included in the scheme. Regeneration of the carbonyl group is accompanied by transannular attack of the enol at the acetylenic function forming the β,γ-unsaturated ketone 8. It has been reported that the acid-catalyzed conversion of 6-ketocyclodecyl *p*-toluenesulfonate to give a bicyclodecanone derivative apparently involves enolization followed by a unimolecular cyclization of the enol, i.e., transannular participation by the enol double bond.[10] Ketone 8 would readily isomerize under acid conditions to the conjugated α,β-unsaturated system in 6. Here again,

Scheme I



Scheme II



the original oxygen in the acetylenic ketone is retained in the final product. The two mechanisms differ in the fact that the process involving an oxete derivative leads to a product with the oxygen on a different carbon than the starting material, whereas the mechanism involving the enol produces a product with the oxygen on the same carbon. Either process will explain the isomerization of both 5-cyclodecynone and 5-cyclononynone in aqueous acid. Several different experiments could be conducted to distinguish between the two mechanisms in these systems. For example, 4-methyl-5-cyclodecynone would be expected to produce 3-methylbicyclo[4.4.0]-1(6)-decen-2-one through the "oxete mechanism" but 5-methylbicyclo-[4.4.0]-1(6)-decen-2-one through the "enol mechanism". However, there are additional systems that may be used to distinguish between the two processes.

For some time, we had been interested to see if acylic acetylenic ketones such as 6-octyn-2-one (9) would undergo intramolecular cyclization to give α,β-unsaturated ketones where the original oxygen is retained. If so, we reasoned

(1) Harding, C. E.; Hanack, M. *Tetrahedron Lett.* **1971**, 1253.
(2) Hanack, M.; Harding, C. E.; Derocque, J. *Chem. Ber.* **1972**, 105, 421.
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(4) Cope, A. C.; Martin, M. M.; McKervey, M. A. *Q. Rev.* **1966**, *20*, 119.
(5) Goering, H. L.; Closson, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 3511.
(6) Rao, B.; Weiler, L. *Tetrahedron Lett.* **1971**, 927.
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(8) Harding, C. E.; Stanford, G. R. *J. Org. Chem.* **1989**, *54*, 3054.
(9) Buchi, G.; Kofron, J. T.; Koller, E.; Rosenthal, D. *J. Am. Chem. Soc.* **1956**, *78*, 876.
(10) Goering, H. L.; Olson, A. C.; Espy, H. H. *J. Am. Chem. Soc.* **1956**, *78*, 5371.

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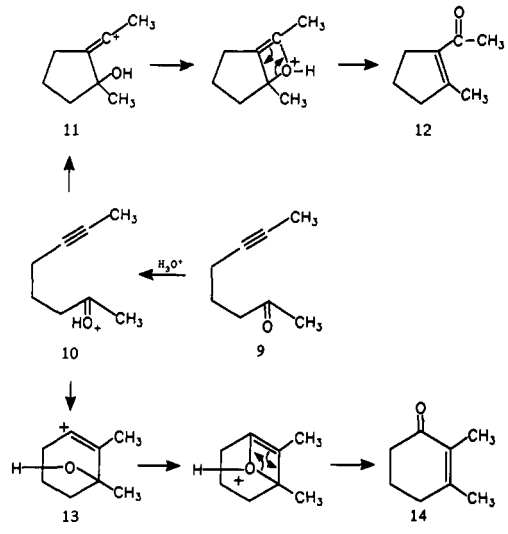
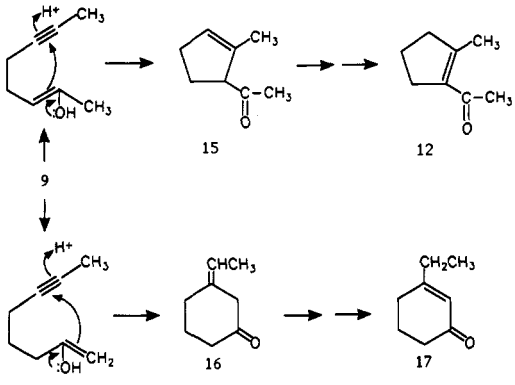
Scheme III

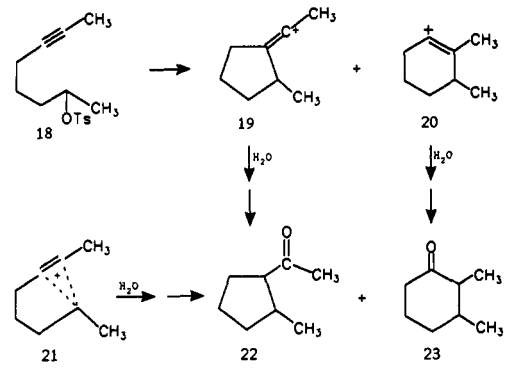


Scheme IV



that it would also be possible to utilize this compound to distinguish between the two mechanisms mentioned earlier. Scheme III provides a sketch of the results predicted for the acid-catalyzed rearrangement of **9** by a mechanism involving oxete intermediates. Two different α,β-unsaturated ketones, 1-acetyl-2-methyl-1-cyclopentene (**12**) and 2,3-dimethyl-2-cyclohexen-1-one (**14**) might be produced. The oxete intermediate leading to **14** contains a strained "anti-Bredt" structure that would be expected to be of relatively high energy. Lesko and Turner[11] have described the strain energy of a bridgehead olefin as a composite of the extra strain associated with the double bond along with the strain associated with the carbon skeleton. Martella, Jones, Schleyer, and Maier[12] proposed that this extra strain associated with the double bond, abbreviated as OS (olefinic strain) energy, could be used as an index of bridgehead olefin stability and reactivity. In a later paper[13] they reported calculated OS values for some 80 different anti-Bredt olefins. By comparison with their data, we have estimated the OS value for the anti-Bredt structure in Scheme III to be on the order of 35 kcal/mol. This value compares to the calculated value of 34.9 kcal/mol for bicyclo[2.2.1]hept-1-ene which has been shown to be an intermediate in the dehydrohalogenation of 1-bromonorbornane.[14] Intermediates of similar energies have been

Scheme V



shown to be involved in intramolecular Wittig reactions that generate anti-Bredt bicycloalkenones.[15]

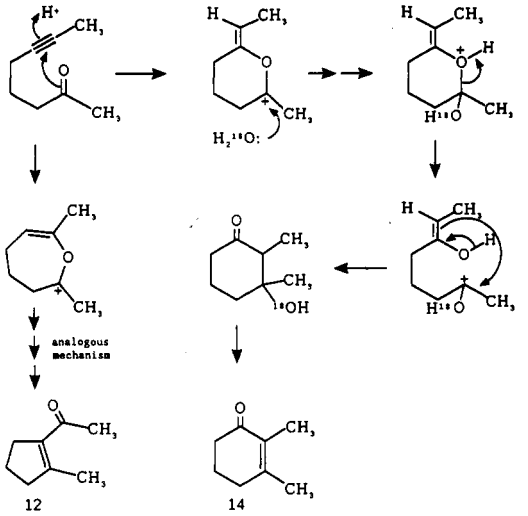
On the other hand, a mechanism involving enol intermediates should lead to different results as outlined in Scheme IV. In this scheme, the first-formed β,γ-unsaturated ketones **15** and **16** would isomerize to the α,β-unsaturated compounds **12** and **17** in a manner analogous to that described in Scheme II. To summarize, both mechanisms can produce **12** but the "enol mechanism" *cannot* produce **14** nor can the "oxete mechanism" produce **17**. If it can be established that **9** undergoes acid-catalyzed cyclization to produce products containing the original oxygen, then this difference can be used in choosing between the two mechanisms.

We have synthesized 6-octyn-2-one and have examined its Lewis and mineral acid-catalyzed rearrangement in detail. Boron trifluoride etherate in absolute ether and dilute aqueous ethanolic HCl will both rearrange the ketone but the isomerization is much slower than in 5-cyclodecynone. Complete rearrangement of **9** with BF_3 etherate required 10 d as compared to a few minutes in the cyclodecyl system. The reaction and workup were carried out under anhydrous conditions to ensure that the process is entirely intramolecular. The reaction product proved to be a mixture of 55% **12** and 45% **14** (by GC), and the ratio of **12** to **14** did not change when one reaction mixture was allowed to stand an additional 10 d in BF_3 etherate. Compounds **12** and **14** from the reaction mixture were identified by comparing their GC retention times and their NMR, IR, and mass spectra with those of authentic samples.

Compound **9** was completely isomerized by treatment with 6.0 M ethanolic HCl at 60 °C for 6 d. The ether soluble reaction product proved to be nearly pure **14** (only about 1% of **12** was present). When a run was interrupted after 3 d the ratio of **12** to **14** was shown by GC to be 10% to 90%, respectively. Clearly **12** is not stable to the reaction conditions. In fact, when a 2-g sample of **12** was heated in 6 M ethanolic HCl for 8 d, no significant amounts of ether soluble reaction products could be detected by GC. In comparison, more than 90% of a 2-g sample of **14** could be recovered after similar treatment. Rearrangement of a 4.00-g sample of **9** by treatment with ethanolic HCl produced 1.66 g (41.5% yield) of **14**. These results, taken together, are interpreted to mean that the ratio of **12** to **14** actually formed in aqueous acid solution is not much different than the 55% **12** to 45% **14** that is formed by treatment of **9** with BF_3 in ether solution. Finally, when **9** was rearranged with HCl in a solvent of ethanol–$H_2{}^{18}O$, oxygen-18 incorporation in the final product **14** was about the same as that observed when pure **14** itself was treated

(11) Lesko, P. M.; Turner, R. B. *J. Am. Chem. Soc.* **1968**, *90*, 688.
(12) Martella, D. J.; Jones, M., Jr.; Scheleyer, P. v. R.; Maier, W. F. *J. Am. Chem. Soc.* **1979**, *101*, 7634.
(13) Maier, W. F.; Scheleyer, P. v. R. *J. Am. Chem. Soc.* **1981**, *103*, 1891.
(14) Keese, R.; Krebs, E. P. *Angew. Chem.* **1971**, *83*, 254; *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 262.
(15) Bestmann, H. J.; Schade, G. *Tetrahedron Lett.* **1982**, *23*, 3543.

Scheme VI



with ethanol–$H_2{}^{18}O$ under the same conditions (less than 1%). Thus the rearrangement of **9**, even in the presence of water, is a completely intramolecular process and does not involve oxygen from the solvent.

In 1969, Petterson and Kamat[16] reported that the solvolysis of the tosylate of 6-octyn-2-ol (see Scheme V) produces 1-acetyl-2-methylcyclopentane (**22**) and 2,3-dimethylcyclohexane (**23**) in a ratio of 57% to 43%, respectively. Interestingly, the products **22** and **23** are formed in about the same ratio as the corresponding α,β-unsaturated ketones **12** and **14** in Scheme III. The major difference between the two reaction processes is that nucleophilic attack in ions **11** and **13** of Scheme III is intramolecular, while ions **19** and **20** (or bridged **21**) undergo nucleophilic attack by solvent molecules.

Finally, a reviewer has suggested that we consider the mechanism outlined in Scheme VI to explain our results. This mechanism, in effect, involves the acid-catalyzed addition of water to the triple bond of the acetylenic ketone, followed by intramolecular aldol condensation of the resulting diketones. As shown in Scheme VI, it is possible to produce **14** that contains no oxygen-18 from the cyclization of oxygen-18 containing 2,6-octanedione. However, cyclization of the oxygen-18 containing symmetrical diketone, 2,7-octanedione, that would lead to the formation of **12** requires the incorporation of 50% oxygen-18 into the compound. In a like manner, production of **6** from **1** in the presence of $H_2{}^{18}O$ by a mechanism similar to the one described in Scheme VI requires the incorporation of 50% oxygen-18. It has been shown experimentally that significant amounts of oxygen-18 are not incorporated into these compounds.

In conclusion, we have demonstrated that the acyclic ketone **9** will undergo acid-catalyzed cyclization to give the α,β-unsaturated ketones **12** and **14** containing the same oxygen that was originally present in the starting material. The same mechanism appears to be in operation whether the reaction occurs in ethanolic HCl solution or in BF_3 etherate solution. Careful analysis of the reaction products have ruled out a possible mechanism involving cyclization of enol intermediates. A process involving an oxete intermediate seems to be best suited in explaining the results. Ratios of five-membered to six-membered cyclized products coming from the treatment of **9** with acid are very similar to those obtained during the solvolysis of the tosylate of 6-octyn-2-ol **18**. We have concluded that the mechanisms of the two processes are similar except for the sources of the attacking nucleophiles upon the vinyl cations formed during cyclization.

(16) Peterton, P. E.; Kamat, R. J. *J. Am. Chem. Soc.* **1969**, *91*, 4521.

Experimental Section

Purchased organic starting materials were used without purification. $H_2{}^{18}O$ (97–98% ^{18}O) was purchased from Cambridge Isotope Laboratories. Neutral aluminum oxide, 90 active, from Brinkmann Instruments was used for column chromatography. Anhydrous solvents were prepared by standard methods. Infrared spectra were recorded on a Perkin-Elmer Model 599B infrared spectrophotometer and NMR spectra on a Varian T-60 NMR instrument. Gas chromatography–mass spectrometry analyses were carried out using a Hewlett-Packard 5890A GC interfaced to a Hewlett-Packard 5970 mass selective detector. All separations were conducted using a 12 m × 0.2 mm, narrow-bore GC column with a 0.3-μm film of cross-linked methyl silicone (HP 19091-60312).

Preparation of 2,3-Dimethyl-2-cyclohexen-1-one (14). The ketone **14** was prepared in two steps by a method similar to that described by Buchta and Satzinger.[17] Two mL of a sodium ethoxide solution (prepared by reacting 0.25 g of Na with 4.0 mL of absolute ethanol) were added to 70.0 g (0.486 mol) of ethyl propionylacetate. The temperature was maintained at 30–35 °C while 34.0 g (0.486 mol) of methyl vinyl ketone was added dropwise and with stirring. The reaction mixture was then allowed to stir at room temperature for an additional 36 h, after which it was taken up in 250 mL of ether and washed two times with water, once with ice-cold dilute HCl and then an additional two times with water. The ether solution was dried over anhydrous magnesium sulfate and filtered, and the solvent was removed under reduced pressure. Distillation gave 77.5 g (74.5%) of the ethyl ester of 5-oxo-2-propionylhexanoic acid as a colorless liquid: bp 103–104 °C (0.03 mm). The ester had the expected NMR and IR spectra and could be chromatographed using injection port and column temperatures of 175 °C or somewhat lower. At higher temperatures, the compound decomposes on the injection port.

A 66.0-g sample (0.308 mol) of the ethyl 5-oxo-2-propionylhexanoate was mixed with a solution of sodium ethoxide (7.2 g of Na in 150 mL of absolute ethanol) under a dry nitrogen atmosphere. The reaction mixture was heated for 4 h at 100–120 °C during which time it became very thick. The pasty mixture was cooled, and the ethanol was removed with a rotary evaporator. The solid residue was acidified with 150 mL of 3.5 M HCl whereby evolution of CO_2 started to occur. After being stirred for 2.5 h at room temperature, the reaction mixture was extracted three times with 75-mL portions of ether. The combined ether extracts were washed twice with water, twice with cold 5% sodium hydroxide solution, and again with water. The ether solution was dried over anhydrous magnesium sulfate and filtered, and the solvent was removed under reduced pressure. Distillation gave 32.0 g (83.8%) of 2,3-dimethyl-2-cyclohexen-1-one (**14**): bp 115–117 °C (46 mm); ^{1}H NMR δ 1.7 (s, 3 H, CH_3), 1.9 (s, 3 H, CH_3), 1.9–2.2 (m, 2 H, methylene H, C-5), 2.2–2.6 (m, 4 H, methylene H, C-4, C-6); IR (cm^{-1}) 1640 (C=C) 1670 (C=O); MS *m/e* 124 (67%, M^+), 109 (4, $M^+ - CH_3$), 96 (100, $M^+ - CO$), 67 (53, 96 – C_2H_5).

Preparation of 6-Octyn-2-one (9). A sample of 2,3-dimethyl-2-cyclohexen-1-one was converted to the corresponding epoxide by a method similar to that used in the preparation of isophorone oxide from isophorone.[18] A solution of 20.0 g (0.161 mol) of **14** and 50 mL of 30% H_2O_2 in 160 mL of methanol was stirred and maintained at 20–25 °C while 135 mL of 6 M NaOH was added dropwise over a period of 1 h. After being stirred at room temperature for an additional 4 h, the reaction mixture was poured into 200 mL of water and extracted with three 100-mL portions of ether. The combined ether extracts were washed three times with water, dried over anhydrous magnesium sulfate, and filtered, and the solvent was removed by distillation through a short column at atmospheric pressure. Distillation of the residue gave 14.6 g (64.8%) of 2,3-epoxy-2,3-dimethylcyclohexanone: bp

(17) Buchta, C.; Satzinger, G. *Chem. Ber.* **1959**, *92*, 468.
(18) Wasson, R. L.; House, H. O. *Organic Syntheses*; Wiley: New York, 1963; *Collect.* Vol. 4, p 552.

95–97 (30 mm). The compound exhibited the expected NMR, IR, and mass spectra. A 14.0-g (0.100-mol) sample of the epoxy ketone was treated with tosylhydrazine by a previously described procedure[19] to give 9.70 g (78.2%) of 6-octyn-2-one (9): bp 98–101 °C (40 mm); ^{1}H NMR δ 1.5–1.8 (m, 5 H, methylene H, C-4; methyl H, C-8), 2.1 (s 3 H, CH_3), 1.9–2.3 (m, 2 H, methylene H, C-5), 2.5 (t, 2 H, CH_2); IR (cm^{-1}) 2220 (C≡C, weak), 1715 (C=O); MS m/e 124 (3%, M^+), 109 (11, $M^+ - CH_3$), 81 (16, $M^+ - C_2H_3O$), 43 (100, $C_2H_3O^+$).

Analytical Data for 1-Acetyl-2-methyl-1-cyclopentene (12). Compound 12 was obtained from Aldrich Chemical Co. and exhibited the following analytical data: ^{1}H NMR δ 1.7–2.2 (m, 2 H, methylene H, C-4), 2.1 (s, broad, 3 H, CH_3C=C), 2.2 (s, 3 H, CH_3), 2.4–2.7 (m, 4 H, methylene H, C-3, C-5); IR (cm^{-1}) 1620 (C=C), 1660, 1685 (C=O); MS m/e 124 (53%, M^+), 109 (100, $M^+ - CH_3$), 81 (39, $M^+ - C_2H_3O$), 43 (38, $C_2H_3O^+$).

Boron Trifluoride Catalyzed Cyclization of 9. A stirred solution of 502 mg (4.05 mmol) of 9 in 10 mL of absolute ether was treated with 1.0 mL of boron trifluoride etherate. After being stirred for 10 d in a closed container, the solution was chromatographed through a short column of aluminum oxide to remove BF_3. Care was taken to prevent water or moist air from coming into contact with the sample. A small portion of the ether solution was diluted and analyzed by GC/MS. The gas chromatograph (in this and in subsequent experiments described in the Experimental Section) was run in the "split/splitless" mode with a "splitless on time" of 0.75 min. An initial oven temperature of 50 °C for 3.0 min was followed by a ramp at 7.5 °C/min to 150 °C and held there for 4.0 min. Only two compounds were found to be present in the reaction mixture. The first had the same retention time (7.8 min) and mass spectrum as an authentic sample of 12. The second peak eluted at 9.1 min and was tentively identified as 14 by comparison of its retention time and mass spectrum with those from an authentic sample. The relative amounts of the two compounds was established to be 55% for the first peak and 45% for the second by using calibration standards prepared from authentic samples of 12 and 14. This ratio did not change when a 250-mg sample of 9 was treated with BF_3 etherate for a period of 20 d.

To assure the correct identification of the reaction products, a 2.0-g sample of 9 was cyclized by treatment with BF_3 etherate. The ether was removed by distillation through a short column, and the two compounds were separated on a 30 × 1 cm column of aluminum oxide by elution with pentane–ether (80:20). Final identification was made by comparing the NMR and IR spectra of these two compounds with those of authentic samples of 12 and 14.

Cyclization of 9 in Ethanolic HCl. A 252-mg (2.03-mmol) sample of 9 was sealed in a Pyrex container with 1.0 mL of ethanol and 1.0 mL of 12 M HCl and was heated at 60 °C for 6 d. After this period, the reaction mixture was diluted with water and extracted with three 25-mL portions of ether. The combined ether extracts were washed with water and sodium bicarbonate and dried over anhydrous magnesium sulfate. Analysis by GC/MS showed a ratio of 12 to 14 of about 1–99%. When a similar run under the same conditions was interrupted after 3 d the ratio was 10% 12 to 90% 14, indicating that 12 is formed in more substantial quantities but is not stable to the reaction conditions.

A 4.00-g (0.0323-mol) sample of 9 was treated with 6.0 M ethanolic HCl at 60 °C for 6 d and worked up as described above. Most of the ether was removed by distillation through a short column. The last traces of ether were removed under reduced pressure to leave 1.66 g (41.5% yield) of fairly pure 14. The IR, NMR, and mass spectra of the compound obtained in this way compared favorably to those from an authentic sample of 14.

Treatment of 12 and 14 with Ethanolic HCl. A 2.00-g sample of 12 was sealed in a Pyrex container with 15 mL of 6 M ethanolic HCl and heated at 60 °C for 8 d. The reaction mixture, which contained black solids, was then diluted with 50 mL of water and extracted with three 25-mL portions of ether. The combined ether extracts were washed and dried and the solution subjected to GC analysis. Compound 12 is apparently completely destroyed under these conditions, and no significant amounts of any compounds could be detected by GC. Clearly 12 is not converted to 14 under these conditions. In a similar experiment 1.82 g (91%) of a 2.00-g sample of 14 was recovered after treatment with ethanolic HCl as described above.

Acid-Catalyzed Rearrangement of 9 in Ethanol–$H_2{}^{18}O$. Hydrogen chloride was bubbled into a solution of 1.0 g of $H_2{}^{18}O$ (97–98% ^{18}O) in a small amount of absolute ethanol until the total weight of the sample increased by 1.17 g. The total volume was adjusted to 5.0 mL by adding absolute ethanol. The resulting solution, which was approximately 6.4 M in HCl, was divided into two equal portions. To one was added 354 mg of 9 and to the other was added 352 mg of 14. After being heated for 5 d at 60 °C in sealed containers, each sample was poured into 25 mL of water and extracted with three 25-mL portions of ether. The combined extracts from each sample were washed with water, were dried, and were subjected to analysis by GC/MS. The mass selective detector was run in the "SIM" mode with a dwell time of 50 μs at low mass resolution. The molecular ion at a m/e of 124 and the oxygen-18-containing molecular ion at a m/e of 126 were monitored. Oxygen-18 incorporation was measured by comparing the signal intensities of these two ions. Compound 14, when produced from 9 via rearrangement, contained approximately 0.8% oxygen-18. In the parallel experiment, unlabeled 14 incorporated about this same amount of oxygen-18 by exchange.

Acknowledgment. We thank Dr. William Solomons for several helpful suggestions and discussions related to this work. We also would like to acknowledge the support of the NSF-ILI program (Grant No. USE-8551275) for funds used in the purchase of the GC/MS system and the UT Martin Faculty Research Office for its support of this work.

Registry No. 9, 24395-06-0; 12, 3168-90-9; 14, 1122-20-9; ethyl propionylacetate, 4949-44-4; vinyl ketone, 78-94-4; ethyl 5-oxo-2-propionylhexanoate, 55262-18-5; 2,3-epoxy-2,3-dimethylcyclohexanone, 35502-46-6.

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