the finding that the basicity of $RCOO^-$ and the presence of proton sources (excess RCOOH) can dramatically affect the course of the reaction nicely complements the present study. The zero-order dependence, in [$R'COO^-$] was interpreted in terms of a "salt effect"; however, ion pair aggregate formation seems equally probable.

Any equilibria between **16** and phosphoranes **17** or **5** might be expected to slow down the formation of ion pair aggregates (and possibly the rate of reaction). However, the presence of the dialkoxyphosphorane **5** (Scheme I, preceding paper) means that there must be an excess of carboxylate ion in solution (in the form of **8**). Aggregation of **8** with **6** (to form a complex analogous to **19** for example) might also result in ester formation, i.e. **8** may act as a catalyst for Mitsunobu esterification. There is some evidence for this. Thus, Walker has shown[2] that in the trifluoroacetylation of sterols, addition of triphenylphosphine last gives rise to an alkoxyphosphonium trifluoroacetate, which slowly converts to the steroid trifluoroacetate. However, when the acid is added last (resulting in the formation of equimolar amounts of the alkoxyphosphonium trifluoroacetate, the trifluoroacetate analogue of **8**, and the sterol) significant amounts of the steroid trifluoroacetate are formed immediately. Generation of the alkoxyphosphonium trifluoroacetate in the absence of the trifluoroacetate analogue of **8** resulted in only small amounts of the steroid trifluoroacetate. We suggest, therefore, that dialkoxytriphenylphosphoranes do play a role (albeit an indirect role) in normal Mitsunobu esterification reactions, whereas (acyloxy)alkoxytriphenylphosphoranes are probably only present as "spectator" phosphoranes in most cases. The effect of both types of phosphorane can be minimized by employing an excess of acid (R'COOH) or a more polar solvent.

Experimental Section

The procedures used to obtain the ^{31}P NMR data (Tables I–III) are as described in the preceding paper (Part 1). Tetrabutylammonium benzoate was prepared from tetrabutylammonium hydroxide and benzoic acid and dried by azeotropic removal of water with benzene. Tributyltin benzoate was prepared from bis(tributyltin) oxide and benzoic acid in benzene by azeotropic removal of water. Diphenyl-2-pyridylphosphine was prepared by using the literature procedure.[25]

Acknowledgment. We acknowledge the support of the ARGS and the award of a CPRA (to D.C.). We thank Dr. Keith Walker for useful discussions. The ^{31}P NMR spectra were recorded at the Brisbance NMR Centre, Griffith University, and we thank David Tucker for his assistance in obtaining some of the spectra.

Registry No. **1**, 75-84-3; **2**, 582-52-5; **4**, 86825-70-9; **4'**, 120711-43-5; **5**, 105785-75-9; **5'**, 120711-44-6; **6**, 120609-90-7; **6'**, 120711-46-8; **7**, 120609-91-8; **7'**, 120711-47-9; **8**, 120418-13-5; **10**, 120609-92-9; **11**, 120609-93-0; **12**, 120711-41-3; **13**, 120711-42-4; **14**, 37943-90-1; **14** oxide, 64741-30-6; TFA, 76-05-1; pNBA, 62-23-7; TPP, 603-35-0; DIAD, 2446-83-5; PhCOOH, 65-85-0; CH_3COOH, 64-19-7; glycolic acid, 79-14-1; triphenylphosphine oxide, 791-28-6; 3-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, 13964-22-2; benzoic anhydride, 93-97-0.

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Mechanism of the Transannular Cyclization of 5-Cyclodecynone

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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 (**8**) as the only product. In earlier reports the reaction was formulated as involving triple-bond participation with a polarized carbonyl group to give a vinyl cation, followed by external attack by a nucleophile. Studies of the rearrangement using Lewis acids in aprotic solvents, taking care to exclude water and moist air during workup, have shown that the oxygen atom in the starting acetylenic ketone **1** is the same as that in the bicyclic product **8**. When the reaction was carried out with HCl in a solvent of methanol–$H_2{}^{18}O$, oxygen-18 incorporation in the final product was not significantly above exchange levels observed when the bicyclic ketone itself was treated with methanol–$H_2{}^{18}O$ under similar conditions. A mechanism that will account for these observations is presented.

It has been clearly established that 5-cyclodecynone (**1**) undergoes transannular cyclization to bicyclo[4.4.0]-1-(6)-decen-2-one (**8**) when treated with HCl in aqueous methanol or with boron trifluoride etherate in aprotic solvents.[1-3] Although bicyclo[5.3.0]decanone (**5**) was shown to be stable to the reaction conditions, its presence could not be detected in any of the reaction products. Similar to 5-cyclodecen-1-yl derivatives[4,5] and to 5-cyclodecyn-1-yl derivatives,[1-3,6] the acetylenic ketone **1** appears to prefer reaction via a six-membered-ring transition state. In earlier reports[1,2] the mechanism outlined in Scheme I was suggested to account for the isomerization of **1** to **8** when treated with HCl in aqueous methanolic solution. This same mechanism has been presumed by others[7] to explain the acid-catalyzed cyclization of 5-cyclononynone to give bicyclo[4.3.0]-1(6)-nonen-2-one as the only product. Such a mechanism is analogous to that postulated by Arens et al.[8] for the reactions of aldehydes and ketones with 1-alkynyl ethers in aqueous solution to give β-hydroxy esters.

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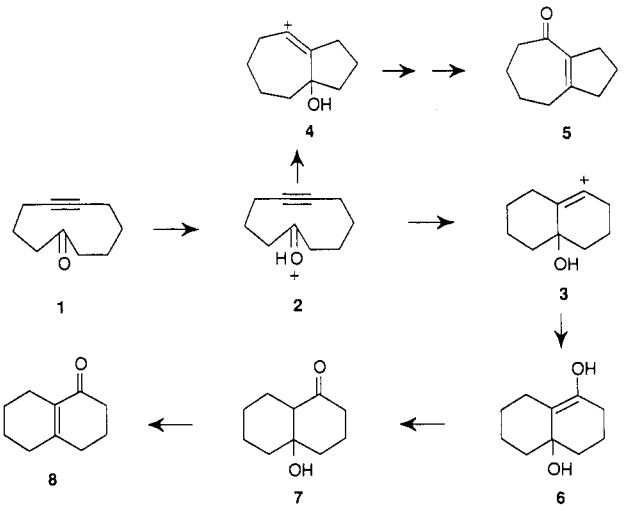
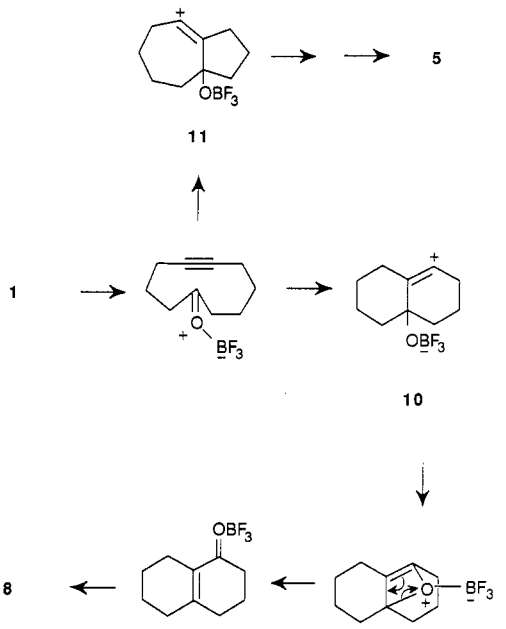
Scheme I

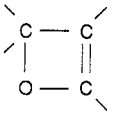


Scheme II



We have again synthesized 5-cyclodecynone and have examined its Lewis and mineral acid catalyzed rearrangement in more detail. Neutral alumina, anhydrous HCl in dry benzene, anhydrous HCl in absolute ether, anhydrous HCl in absolute methanol, BF_3 etherate in absolute ether, BF_3 etherate in methylene chloride, $AlCl_3$ in absolute ether, and dilute aqueous methanolic or ethanolic HCl will all rearrange 1 to 8. The isomerization was found to be slower in nonpolar solvents. In all cases only 8 and never any trace of 5 could be detected in the reaction mixtures although 5 was shown to be stable to reactions conditions. The ketones 5 and 8 could be clearly separated by GC (5 has the shorter retention time), and they have several differences in their IR spectra. Workup of the reactions that were carried out under anhydrous conditions was performed so as to prevent the products from coming into contact with moisture. Still, the rearrangement of 1 to 8 occurred. Clearly a mechanism similar to that outlined earlier[1,2] and described here in Scheme I cannot account for the rearrangement when carried out as reported above.

Lewis acid (usually BF_3) catalyzed additions of aldehydes, ketones, esters, and amides to 1-alkynyl ethers to form α,β-unsaturated esters are well documented.[9] The acid catalyst can sometimes be omitted with highly electrophilic carbonyl compounds such as benzoquinone[10] or hexafluoroacetone.[11] Also alkynes such as phenylacetylene react with aromatic aldehydes in the presence of boron trifluoride etherate to form 1,3-diarylpropenones.[12] In all these cases[9-12] the reactions were postulated as proceeding through an unstable oxete derivative (9) as an intermediate. Such an intermediate was first suggested by Büchi[13]



9

for the photochemical addition of aromatic carbonyl compounds to disubstituted acetylenes. A mechanism involving 9 (see Scheme II) allows us to account for the rearrangement of 1 to 8 under the anhydrous conditions described.

We were intrigued by the possibility that the rearrangement might proceed, even in aqueous solution, by a mechanism which would exclude incorporation of oxygen from the solvent into 8. When 1 was rearranged in 1.5 M methanolic HCl which 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 (25% as compared to 20%). Since the mechanism in Scheme I requires 100% incorporation of oxygen-18, it seems to be ruled out in favor of one similar to that in Scheme II with H^+ replacing BF_3.

A reaction involving acid-catalyzed hydration of the triple bond to form a mixture of 1,5- and 1,6-cyclodecanediones followed by intramolecular aldol condensation can be ruled out by several observations. First, the diketones cannot be detected in the reaction mixture at intermediate stages during the progress of the reaction. Second, 1,6-cyclodecanedione can give only 5 upon intramolecular aldol condensation and no trace of this compound can be detected. Finally, if for some reason only 1,5-cyclodecanedione is formed by hydration (in $H_2{}^{18}O$) of the triple bond, subsequent condensation and elimination requires that the unsaturated ketone 8 contain 50% oxygen-18, considerably more than that observed.

The ketone 1 is generally depicted as containing a linear four-atom acetylenic group, and examination of molecular models suggest that the carbonyl oxygen points in toward the center of the ring. A similar situation has been observed for 5-cyclononynone.[7] In these models the sp-hybridized carbons are very nearly equidistant from the carbonyl carbon, causing one to expect a mixture of 5 and 8 when 1 undergoes cyclization. Indeed, if the reaction proceeds via a free cation then a preference for 11 might be expected since the intermediate vinyl cation should be more readily accommodated in a seven-membered ring.[14] Conformational analyses of the C_8–C_{10} cycloalkynes, however, have indicated that the sp–sp^3 linkages are relatively easy to distort, thus relieving ring strain.[15] The bending

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force constants for these bonds are much less (about one-third) than those for the sp^3–sp^3 bonds.[16] The extreme ease of rearrangement of 1 and the preference for transannular cyclization to proceed exclusively via a six-membered-ring transition state seems to indicate that C-6 is ideally situated for electrophilic attack by the polarized carbonyl group. Models indicate that the transition state leading to the bicyclo[4.4.0]decane skeleton has less steric interference and less torsional strain than the transition state leading to the bicyclo[5.3.0]decane skeleton.

In conclusion, we have outlined in this report several new sets of conditions under which 1 undergoes transannular cyclization. Several observations, along with the results of oxygen-18 studies, have ruled out the previously suggested mechanism[1,2] for the reaction. A mechanism that accounts for the new observations has been proposed.

Experimental Section

Purchased organic starting materials were used without purification. $H_2{}^{18}O$ (99% O-18) was purchased from Stohler Isotope Chemicals. 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 mass spectra on a Varian EM-600 operating at 70 eV. Gas chromatography (GC) analyses were carried out on a Bendix 2600 instrument with an FID detector using a 5 ft × $^1/_{16}$ in. column of 20% Carbowax 20M on Chromosorb W, 60–80 mesh.

Preparation of Bicyclo[5.3.0]-1(7)-decen-2-one (5). The bicyclic ketone was prepared by a procedure previously described[17] and exhibited the reported physical and spectral properties.

Preparation of Bicyclo[4.4.0]-1(6)-decen-2-one (8). The ketone 8 was prepared in three steps from *trans*-1-decalone,[18] which was in turn readily available through the chromic acid oxidation of α-decalol.[19] The α-decalol was prepared by the hydrogenation of α-tetralone over rhodium (5%) on alumina. In a typical run 26.0 g (0.178 mol) of α-tetralone in 200 mL of absolute ethanol was added to a 500-mL hydrogenation bottle that contained 5.0 g of catalyst. Hydrogenation at 25–50 psi was carried out until uptake of hydrogen ceased. Removal of the catalyst and evaporation of the solvent afforded the alcohol in greater than 95% yield. With this particular catalyst, hydrogenolysis is not a problem.[20]

Preparation of 5-Cyclodecynone (1). A solution of 38.4 g (0.256 mol) of 8 in 160 mL of methanol was treated with 26 mL of 6 M sodium hydroxide. The reaction mixture was stirred and cooled in a water bath at 15 °C while 65 mL of 30% hydrogen peroxide were added dropwise over a period of 2 h. After being stirred at room temperature for 20 h, the mixture was again cooled to 15 °C and an additional 26 mL of 30% hydrogen peroxide was added. The solution was then allowed to stir for 15 h, after which the methanol was removed by means of a rotary evaporator. Water was added (300 mL), and the mixture was extracted three times with 75-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 under reduced pressure. Distillation gave 28.0 g (70%) of 1,6-oxidobicyclo[5.3.0]decan-2-one as a colorless liquid, which was 95% pure by GC analysis: bp 78–81 °C (0.5 mm). A 25.0-g (0.151-mol) sample of the epoxy ketone was treated with tosylhydrazine by a previously described procedure[21] to give 18.1 g (80%) of 5-cyclodecynone (1): bp 67–69 °C (1.0 mm).

Boron Trifluoride Catalyzed Cyclization of 1. A stirred solution of 500 mg (3.33 mmol) of 1 in 10 mL of absolute ether was treated with 0.5 mL of boron trifluoride etherate. After 15 min the ether and boron trifluoride etherate were removed under reduced pressure. Care was taken to prevent water or moist air from coming into contact with the sample. A small portion of the yellowish-green crude sample was dissolved in hexane and reserved for GC analysis. The remainder of the crude product was purified by column chromatography, with hexane–diethyl ether (80:20 to 50:50) as eluant, to give 455 mg (91%) of 8. The starting ketone 1, along with 5 and 8, were separated by GC, and no trace of 1 or 5 could be detected in either the crude or the purified reaction product. The purified product was compared by IR to an authentic sample of 8 prepared by the method of House and Thompson.[18] Similar results were obtained when the crude product from a run utilizing a 5.0-g sample of 1 was purified by distillation under reduced pressure.

A 500-mg (3.33-mmol) sample of 1 was treated with 0.5 mL of boron trifluroide etherate in methylene chloride solution. After 15 min the sample was worked up and analyzed as described above. No trace of 5 could be detected. Column chromatography of the crude product gave 360 mg (72%) of 8, which was compared by IR spectroscopy to an authentic sample.

Anhydrous Hydrogen Chloride Catalyzed Cyclization of 1. Anhydrous HCl was bubbled into absolute methanol until the solution reached a molarity of approximately 1.5 (1.38 g of HCl in 25 mL of alcohol). A 500-mg (3.33-mmol) sample of 1 was added to the HCl solution all at one time. Care was exercised to avoid exposing the solution to moisture. After 8 min the methanol and HCl were removed under reduced pressure to give 461 mg (92%) of a pale yellow oil, which was shown by IR and GC analyses to be 8.

The ketone 1 also rearranges in benzene and in ether solutions containing HCl, although at much slower rates. A solution of 500 mg of 1 in 15 mL of benzene, which was saturated with HCl, was analyzed after 24 h. Only 30% rearrangement (GC, IR) was observed. Compounds other than starting ketone 1 and the bicyclic ketone 8 could not be detected in the reaction mixture.

Acid-Catalyzed Rearrangement of 1 in Methanol–$H_2{}^{18}O$. Hydrogen chloride was bubbled into 1.0 g of $H_2{}^{18}O$ (99% oxygen-18) until the total weight of the sample reached 1.25 g. The molarity of the solution was adjusted to 1.5 by diluting the $H_2{}^{18}O$/HCl solution to a volume of 4.5 mL with methanol. The methanolic HCl solution was divided into two portions. To one was added 125 mg of 1 and to the other was added 125 mg of 8. After 5 h at room temperature[22] the methanol and acid were removed from each sample under reduced pressure. The residues were taken up in ether and washed quickly with sodium bicarbonate solution and with water. Aftr drying over anhydrous magnesium sulfate, the solvent was removed. Oxygen-18 incorporation was measured by comparing the signal intensity of the molecular ion at a m/e of 150 with that of oxygen-18-containing molecular ion at a m/e of 152. Compound 8, when produced from 1 via rearrangement, contained 25% oxygen-18. In the parallel experiment, unlabeled 8 incorporated 20% oxygen-18 by exchange.

Rearrangement with Neutral Alumina. A 1.88-g sample of 1 was placed on a 20 cm × 1 cm column of aluminum oxide, neutral, 90 active (Brinkmann Instruments), and eluted with hexane–ether (80:20). Evaporation of the solvent afforded 1.6 g (85%) of pure 8.

Several other sets of conditions that are effective in the isomerization of 1 to 8 have been reported previously.[1-3]

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Registry No. 1, 17522-30-4; 5, 13031-01-1; 8, 18631-96-4; 8-^{18}O, 120609-30-5; O_2, 7782-44-7; *trans*-1-decalone, 21370-71-8; α-decalol, 529-32-8; α-tetralone, 529-34-0; 1,6-oxidobicyclo[5.3.0]decan-2-one, 120609-29-2.

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