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Studies on Allenes as Participants in Cationic π-Cyclizations[1,2]

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Cationic π-cyclization of two allenyl alcohols **12a** and **12b** and two allenyl ketones **11a** and **11b** provided evidence that the mode of ring closure of γ-allenyl cation systems is strongly dependent upon the substitution pattern of the allene functionality. The monosubstituted systems **11a** and **12a** gave only decalin-type products resulting from reaction at the terminal carbon of the allene. The disubstituted allene systems **11b** and **12b** gave only hydrindane-type products resulting from reaction only at the central carbon of the allene. A general rationale for the cyclization results observed with γ-allenyl cation systems is developed based upon considerations of orbital overlap, as determined from molecular models, and of the effect of alkyl substituents on electrophilic addition to allenes.

INTRODUCTION

Cationic π-cyclization has become one of the well-established methods for generation of carbocyclic ring systems (*2*). The utility of this methodology has been increasing through continued study of several aspects of such reactions. Areas of continuing interest include the examination of functionalities suitable for initiating such cyclizations (*3*) and for participating as the π-moiety in such cyclizations [e.g., acetylenic bonds (*2a*, *4*), allenes (*5*), and silyl enol ethers (*6*)].

Our interest in new methods for utilizing π-cyclization to generate five-membered rings with functionality in the five-membered ring led us to consider the γ-allenyl cation system (**1**). Examination of molecular models suggested that the allene π-system should interact readily with the cationic center and could lead to the allyl cation **2**.[4] Cyclization studies with the homologous δ-allenyl cation system (**3**) by Hall and Johnson (*5a*) and by Sekera *et al.* (*5b*) showed that reaction did occur at the central carbon of the allene, giving products resulting from allyl cation **4**. However, one previous study (*5c*) with γ-allenyl cation systems reported the formation of both five-membered and six-membered ring products in low yield (**5** → **6** and **7**).[5]

We decided to investigate further the γ-allenyl cation system using cyclization substrates which would be expected to give higher yields of cyclic products than simple

[1] This paper is dedicated to W. S. Johnson on the occasion of his 65th birthday and in recognition of his pioneering efforts in the development of synthetic utility of biogenetic-like cationic cyclizations.

[2] A portion of this work has been reported in preliminary form (*1*).

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[4] It has been pointed out that, although attack of an electrophile on the central carbon of an allene gives an allyl cation, little of this potential stabilization can be realized in the transition state (*5a, b, 7*).

[5] The comparatively high nucleophilicity of the solvent used may be one reason for the low yield of cyclization with **6**. Sekera *et al.* (*5b*) showed that a non-nucleophilic solvent such as trifluoroethanol was necessary for good yields in his studies.

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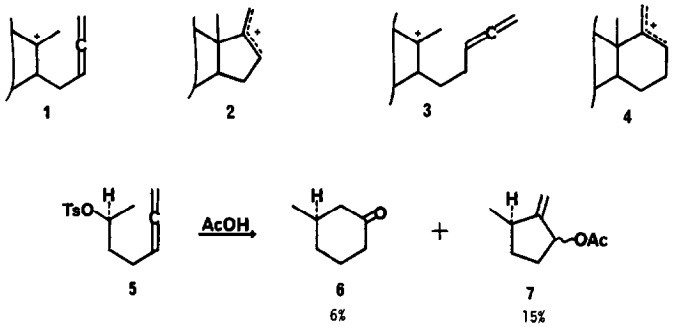
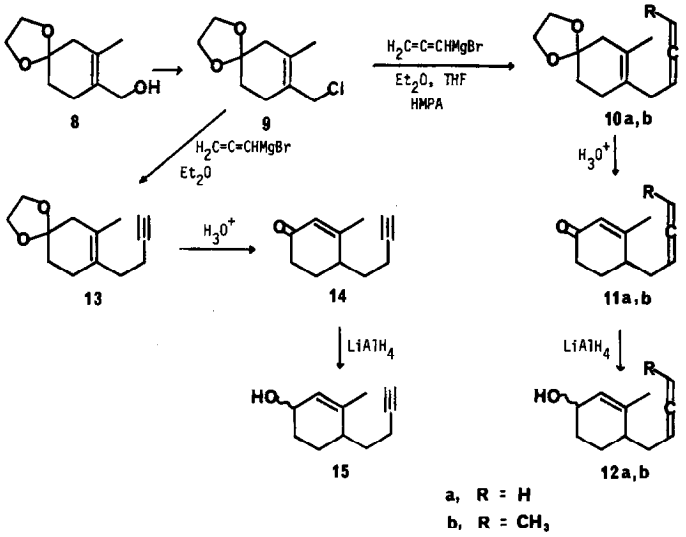


solvolysis reactions [cf. Ref (*2a*)]. For this purpose we have studied the cyclization reactions of the allenic allylic alcohols **12a** and **12b** and the corresponding allenic enones **11a** and **11b**. These compounds and related acetylenes **14** and **15** were prepared as outlined in Scheme I.

The allylic alcohol **8** is converted to chloride **9** by treatment with hexamethylphosphorous triamide and carbon tetrachloride (*8*). Reaction of the crude chloride with allenylmagnesium bromide (*9*) in ether gave acetylene **13**.[6] However, when the coupling reaction was carried out in the presence of tetrahydrofuran (THF) and hexamethyl phosphoric triamide HMPA, the product contained ~80% allene **10a** and only ~20% acetylene **13**.[7] Hydrolysis of the mixture and removal of acetylenic material by precipitation with silver nitrate in methanol gave the allenyl ketone **11a**. Reduction with lithium aluminum hydride gave alcohol **12a** in excellent yield. In a similar manner reaction of the Grignard reagent prepared from 3-bromo-1-butyne (*9*) with



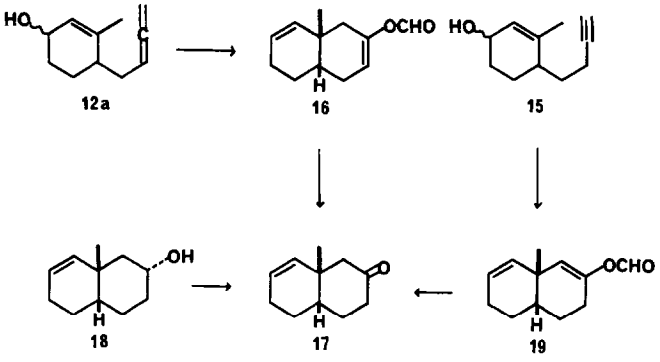
SCHEME I

[6] Only a trace of allenic material was detected in the product, although a previous preparation (*8b*) of **11** reported the formation of significant amounts of allene.

[7] The predominant formation of allenes in the coupling of propargyl magnesium bromide with allyl bromide in THF has been previously noted (*11*).

chloride **9** gave the allene **10b** from which allene **11b** was obtained after hydrolysis, treatment with silver nitrate, and column chromatography. Reduction of **11b** gave **12b** in high yield. The acetylenic substrates **14** and **15** were obtained from acetylene **13** by hydrolysis and reduction.

Our initial cyclization studies were conducted with the unsubstituted allenes **11a** and **12a** (Scheme II) (*1*). Treatment of alcohol **12a** with anhydrous formic acid for 30 min gave a cyclized product (angular methyl by nmr) in 75% yield. Hydrolysis of the formate ester present gave a single product in 67% yield from alcohol **12a**. The product was shown to be *cis*-9-methyl-Δ^7-2-octalone (**17**) by comparison with an authentic sample prepared by oxidation of octalol **18** (*8*, *11*). No evidence for any five-membered ring product was observed. Ketone **17** was also obtained in 67% yield from cyclization of acetylenic alcohol **15** followed by hydrolysis of formate.[8]



SCHEME II

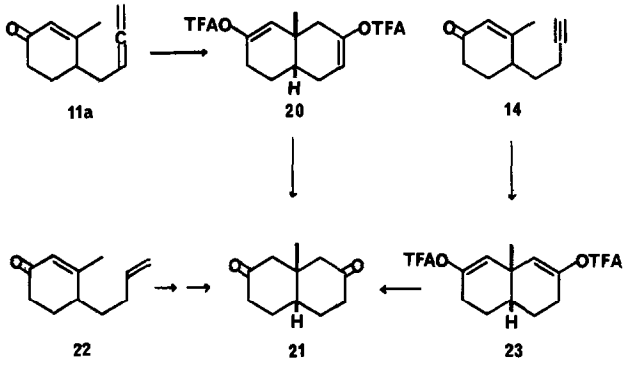
The formation of only six-membered ring products was also observed in the cyclization of enone **11a** (Scheme III). Cyclization was effected readily with acetic anhydride in acetic acid with perchloric acid catalysis (*3a*), but cyclization with trifluoracetic anhydride (TFAA) in trifluoroacetic acid (TFA) gave a higher yield. After hydrolysis of the trifluoroacetate esters the crystalline *cis*-diketone **21** was obtained in 86% yield. This material was identical with material prepared by cyclization of 4-(3-butenyl)-3-methyl-2-cyclohexenone (**22**) (*8*, *11*) with TFAA/TFA, followed by hydrolysis and oxidation. Diketone **21** was also obtained in a 92% yield by TFAA/TFA cyclization of acetylenic ketone **14**.

Analysis of the results obtained with **11a** and **12a**, compared with previous work by Ragonnet *et al.* (*5c*) with tosylate **5** and the work with δ-allenyl systems by Hall (*5a*) and Sekera *et al.* (*5b*), led us to expect [See Discussion section below and Ref. (*1*)] that the additional methyl group in substrates **11b** and **12b** would lead to preferential formation of five-membered ring products. This has now been shown to be the case.

Treatment of allylic alcohol **12b** with anhydrous formic acid for 30 min gave cyclic formate product in high yield (Scheme IV). Hydrolysis gave an alcoholic product in 74% yield. The ir spectrum showed no more than a trace of carbonyl absorption[9]

[8] The enol formates **16** and **19** from cyclizations of alcohols **12a** and **15** were isomeric as expected on mechanistic considerations. These cyclizations could thus be useful as a means for regiospecific generation of enolates.

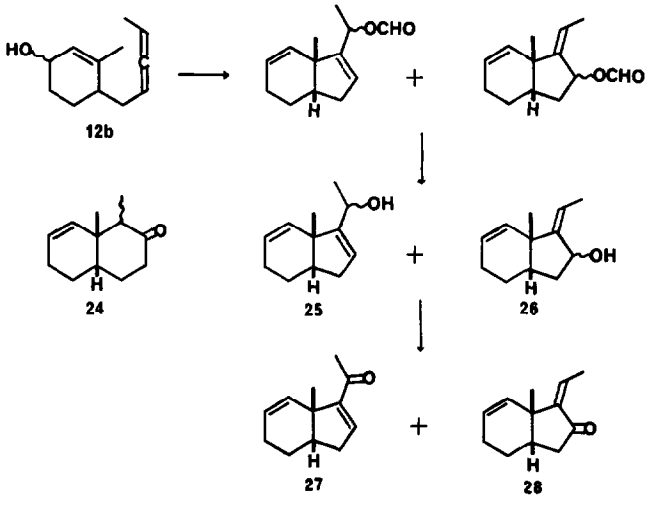
[9] The enone **11b** used to prepare **12b** contained 2–3% acetylenic material (VPC analysis).



SCHEME III

indicating that ketone **24** was not present. The absence of ketone **24** was proven conclusively by comparison [vapor-phase chromatography (VPC) on 0V-101 at 135°C] of this product with authentic ketone **24**.[10] Analysis of the nmr spectrum showed clearly that the product was a mixture of alcohol **25** (equal amounts of two diastereomers) and alcohol **26** (one epimer predominating) in a ratio of ~2:1. This alcohol mixture was oxidized with Collins reagent to give a mixture of ketones **27** and **28**.[11]

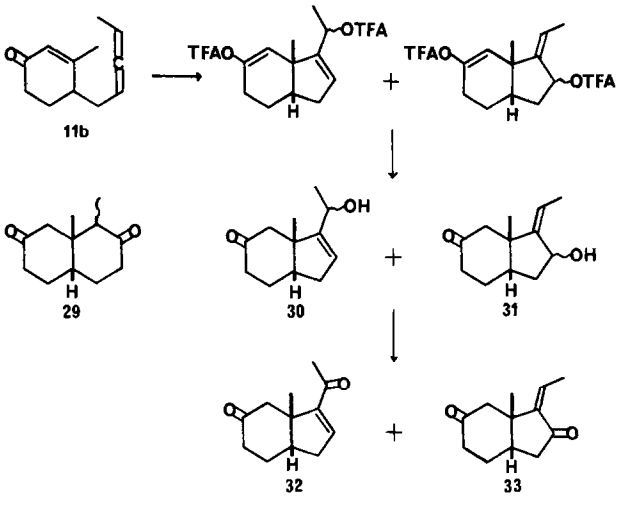
The enone **11b** was treated with TFAA/TFA to give a mixture of cyclic trifluoroacetates (Scheme V) which, upon hydrolysis, gave ketoalcohol **30** (1:1 mixture of diastereomers) and ketoalcohol **31** in 80% yield. In this case the ratio of **30**:**31** was ~4:1. The absence of diketone **29** in this cyclization was proved by comparison (VPC on 0V-101 at 130°C) of the product with authentic diketone **29**.[10] Oxidation of the alcohol mixture gave unsaturated diketones **32** and **33**.



SCHEME IV

[10] Prepared by Jones oxidation of the corresponding alcohol. The synthesis and characterization of these materials will be reported at a later date.

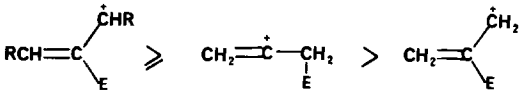
[11] The *cis* stereochemistry for both the decalin and hydrindane derivatives formed from these cyclizations is a result of the cyclohexenyl cation system used to initiate cyclization [see Ref. (*11a*)].



SCHEME V

DISCUSSION

The cyclizations reported in this paper offer an interesting divergence of results both between the two γ-allenyl systems studied here and previous results with δ-allenyl systems (*5a, 5b*) and acyclic γ-allenyl systems (*5c*). A rationale for this variety of results can be developed from consideration of orbtial overlap as determined from examination of molecular models and of the effect of alkyl substituents upon electrophilic addition to allenes (*7*). Electrophilic attack on an unsubstituted allene takes place exclusively at the terminal carbon, but substitution of alkyl groups on the allene leads to increased attack on the central carbon. Thus, it has been considered (*7*) that the relative stabilities of the *initial* cations generated by attack of an electrophile, E^+, on an allene could be as shown below.[12]

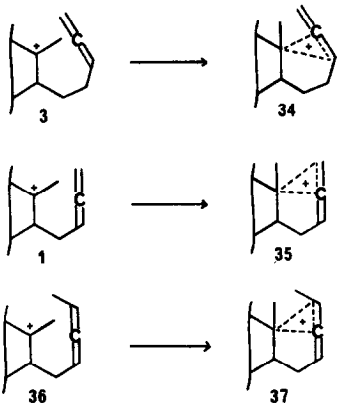


Examination of a molecular model of the δ-allenyl cation system **3** shows that the *p* orbital of a cationic carbon readily interacts with the C-2,C-3 π-orbital of the allene bond (**3** → **34**). The orbital overlap in **34** is exactly analogous to that found in simple cationic olefin cyclizations. The cation resulting from bond formation at the central carbon of **34** would be a vinyl-substituted 2° cation (Type A) whereas formation of a bond at C-3 would give a less stable vinyl cation (Type B). Thus reaction, as observed by Hall (*5a*) and Sekera *et al.* (*5c*), is predicted.[13] However, with the γ-allenyl cation system **1**, the

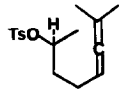
[12] It should be noted that A and C do not represent allyl cations, but are vinyl-substituted 2° and 1° cations in which the π-bond is orthogonal to the cationic *p* orbital.

[13] Although protonation of monosubstituted allenes appears to involve attack on the unsubstituted terminal allene carbon (*7*), this type of reaction is not observed with **3** because the constraints of intramolecular attack lead to interaction with the C-2,C-3 π-bond rather than the C-1,C-2 π-bond.

best orbital overlap is not with the C-2,C-3 bond but with the orthogonal C-1,C-2 π-bond (**1** → **38**).[14] Bond formation at the central allene carbon in **35** would lead to a vinyl-substituted 1° cation (Type C), but reaction at the terminal carbon gives a vinyl cation (Type B). This leads to the prediction that six-membered ring formation should be preferred, and this was observed with **11a** and **12a**. In the cases of **11b** and **12b** with an additional methyl group at the terminus of the allene, the analysis differs markedly (**36** → **37**). Now reaction at the central carbon gives a Type A ion and would be favored over reaction at the terminal carbon to give a Type B vinyl cation. Thus these considerations predict the reversal of behaviour observed between **11a** and **11b** (and **12a** and **12b**). There remains the necessity to rationalize the formation of both types of products in the solvolysis reaction of tosylate **5** (*5c*). In this case, reaction presumably



requires anchimeric assistance of the π-moiety during solvolysis (reaction without assistance leads to simple acyclic substitution products). Molecular models show that the additional degree of freedom (rotation about the C–C bond adjacent to the tosylate) available in this acyclic system allows more favorable overlap with the C-2,C-3 bond than is possible when the cationic carbon is part of a ring.[15] It is also possible that the nucleophilicity of the π-bond is more important in this case than in reactions involving cationic intermediates and that the C-2,C-3 π-bond is more nucleophilic as a result of the additional alkyl substituent. The high yield (83%) of only five-membered ring products formed upon acetolysis of tosylate **38** (*5c*) is consistent with the above rationale.[16]



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[14] This preference is larger when the cationic carbon is part of a ring system, as is the case for the substrates **10** and **11**, than in totally acyclic systems.

[15] Since the ions generated from **11** and **12** are cyclohexenyl cations, the exact geometries will differ from those that would result from a saturated cyclohexyl cation. However, models suggest that reactions involving cyclohexyl cations would be expected to closely resemble the reactions of **11** and **12**.

[16] The case of β-allenyl cation systems (*12*) has not been considered here because of the relationship of this system to homoallyl systems and the complications of rearrangement of initially formed cations or products.

The varied results observed with γ-allenyl cations thus can be understood on the basis of simple mechanistic considerations. This understanding should allow the application of π-cyclizations involving γ-allenyl cation intermediates to the synthesis of complex molecules.

EXPERIMENTAL

General Procedures

Infrared spectra were recorded on a Perkin–Elmer Model 237B or Beckmann Instruments Model IR8 spectrophotometer. High-resolution mass spectra were obtained on a CEC Model 21-110 spectrometer under the supervision of Dr. R. Grigsby.

The ^{1}H-nmr spectra were obtained in CCl_4 or $CDCl_3$ solution on a Varian Associates HA-100 or T-60 spectrometer. The ^{13}C-nmr spectra were obtained in $CDCl_3$ solution in the Fourier transform mode on a JEOL PFT-100 spectrometer system operating at 25.034 MHz (proton resonance frequency: 99.539 MHz) and equipped with a Nicolet 1085 data system. All chemical shifts (^{1}H and ^{13}C) are reported on the δ scale as parts per million downfield from tetramethylsilane (TMS) as internal reference.

The vapor-phase chromatographic (VPC) analyses were performed on a Varian Instruments Model 940 chromatograph equipped with a flame ionization detector. Columns used for analyses were $\frac{1}{8}$ in. × 6 ft, 3% SE-30 on Chromasorb W column, a $\frac{1}{8}$ in. × 6 ft, 10% Carbowax on Chromasorb W column, and a $\frac{1}{8}$ in. × 6 ft, 0V-101 on Chromasorb G column. All percentage composition values are reported as relative peak areas without correction for relative detector response. Preparative VPC separations were performed on a Varian Instruments Model 920 instrument equipped with a thermal conductivity detector using a 0.25 in. × 6 ft, 10% SE-30 on Chromasorb A column.

The isolation procedure normally consisted of dilution of the product with water and extraction with the solvent indicated. The combined organic extracts were then washed with the stated solutions, dried, and concentrated by removal of solvent at about 30 mm using a rotary evaporator.

Evaporative distillation refers to bulb-to-bulb (Kugelrohr) short-path distillation. The temperatures cited for these distillations are the maximum temperatures of the oven during the distillation.

"Acid" refers to 10% hydrochloric acid. "Bicarbonate" refers to a saturated aqueous solution of sodium bicarbonate. "Brine" refers to a saturated aqueous solution of sodium chloride. Tetrahydrofuran was distilled from the sodium benzophenone dianion just before use. Anhydrous ether was stored over sodium. Hexamethylphosphoric triamide was distilled from lithium metal at 0.25 mm and stored over molecular sieves. Hexamethylphosphorous triamide was doubly distilled before use. Formic acid was distilled from boric anhydride and stored at +3°C (*13*).

Preparation of Cyclization Substrates

4-(2,3-Butadienyl)-3-methyl-2-cyclohexen-1-one (**11a**) *and 4-(3-butynyl)-3-methyl-2-cyclohexene-1-one* (**14**). These materials were prepared by the coupling of allenylmagnesium bromide (*9*) with chloride **9** in different solvents (*9*).[7]

Hexamethylphosphorous triamide (21.5 g, 0.13 mol) was added slowly to a solution of 20 g (0.11 mol) of 1-hydroxymethyl-2-methyl-4-ethylenedioxy-1-cyclohexane (**8**) (*8*) and 20.3 g (0.13 mol) of carbon tetrachloride in ~300 ml of anhydrous ether at 0°C. After the addition was complete, the reaction was stirred at 0°C for 1 hr, quenched with water, and extracted with ether. The combined extracts were washed (water, bicarbonate, and brine), dried (Na_2SO_4 and molecular sieves), and concentrated to give ~15 g of crude chloride **9** (*8a, b*). This material was used immediately without further purification.

The Grignard reagent from propargyl bromide was prepared according to Guademar (*9*). Magnesium (17.6 g, 0.726 mol; washed with 5% HCl, water, and acetone followed by drying in a vacuum oven), 200 ml of anhydrous ether, and a catalytic amount of mercuric chloride were added to a flame-dried 500-ml flask equipped with a condenser, addition funnel, nitrogen inlet, and magnetic stirrer. Several milliliters of propargyl bromide (Aldrich, distilled and stored over $CaCl_2$) was added to the solution, and the solution was stirred until it began to reflux. It was then cooled to 0°C and the remaining propargyl bromide (77 g, 0.66 mol total) was added slowly in ~30 ml of ether. After the addition the reaction mixture was stirred at room temperature for 1 hr. (This Grignard in ether is a two-phase liquid–liquid system.)

For the preparation of allene **11a**, one-half of the chloride **9** (~7.5 g) was dissolved under nitrogen in ~400 ml of 4:1 THF/HMPA, and then approximately one-half of the Grignard reagent was transferred into the solution. The solution was stirred for 12 hr at room temperature and quenched with several drops of saturated NH_4Cl (formation of solid salt cake). Magnesium sulfate was added and the salts were removed by filtration using an ether wash. VPC analysis (SE-30 at 150°C) of the solution indicated that the product contained allene **10a** and acetylene **13** in a ratio of 4:1. The yellow oil resulting from concentration was dissolved in methanol and treated with a small amount of 10% HCl under N_2 for 10 hr. Solid K_2CO_3 was added to neutralize the acid, and the solution was filtered and concentrated. The resulting oil was diluted with water and extracted with ether. The extracts were washed (water, bicarbonate, and brine), dried ($MgSO_4$), and concentrated. The oil was dissolved in methanol and then a 5% solution of methanolic silver nitrate was added to precipitate acetylene **14**. The acetylide salts were removed by filtration. After the solution had been concentrated, it was diluted with water, extracted with ether, washed (water, bicarbonate, and brine), dried ($MgSO_4$), concentrated, and evaporatively distilled at 0.05 mm/90°C to give 2.3 g (~26% yield from alcohol **8**) of allene **11a**: ir (film) 1950 (allene) and 1660 (enone) cm^{-1}; ^{1}H-nmr (CCl_4, 100 MHz) δ 1.98 (d, 3H, J = 1.4 Hz, vinyl methyl), 4.65 (m, 2H, C=C=CH_2), 5.1 (m, 1H, –CH=C=C), and 5.85 (bs, 1H, C-2 H); ^{13}C-nmr δ 209.2 (C-3′), 198.7 (C-1), 164.3 (C-3), 127.3 (C-2), 87.6 (C-2′), 75.2 (C-4′), 39.4 (C-4), 34.0 and 30.4 and 26.6 (C-5, C-6, and C-1′), and 22.8 (C-3 CH_3–).

Analysis by VPC (SE-30 at 150°C) showed ~5% of alkyne **14** and a trace of lower retention time impurities. An analytical sample was obtained by preparative VPC.

Anal. Calcd for $C_{11}H_{14}O$: 162.104460. Found: 162.103922 (3.3 ppm) HRMS.

For the preparation of alkyne **14** the other half of the chloride **9** was dissolved in 250 ml of anhydrous ether under N_2 and the remaining Grignard reagent was added. After the mixture had been stirred for ~12 hr, it was quenched with a small amount of saturated NH_4Cl followed by solid $MgSO_4$. The solution obtained after removal of the

salts by filtration (ether wash) was washed (water, bicarbonate, and brine), dried ($MgSO_4$), and concentrated. Analysis by VPC (SE-30 at 150°C) showed that only a small amount of allene **10a** was present. The oil was dissolved in methanol and treated with 10% HCl at room temperature for 12 hr. The oil obtained after workup as described above for allene **11a** was chromatographed on silica gel (20% Et_2O/hexane) to remove low-R_f impurities and evaporatively distilled at 0.05 mm/90°C to give 3.5 g (~39% yield from alcohol **8**) of alkyne **14**: ir (film) 3300 and 2120 (alkyne) and 1660 (enone) cm^{-1} (no allene absorption observable); ^{1}H-nmr (CCl_4, 100 MHz) δ 1.95 (d, J = 1.5 Hz, 3H, $-CH_3$) and 5.70 (m, 1H, C-2 H); ^{13}C-nmr δ 198.2 (C-1), 164.8 (C-3), 126.8 (C-2), 83.2 (C-3′), 69.9 (C-4′), 38.1 (C-4), 33.6 and 29.3 and 25.6 (C-5, C-6, and C-1′), 22.7 (C-3 CH_3–), and 16.7 (C-2′).

The C-13 spectrum and VPC analysis showed a trace of allene **11a**. An analytical sample was prepared by preparative VPC.

Anal. Calcd for $C_{11}H_{14}O$: 162.104460. Found: 162.104078 (2.4 ppm) HRMS.

4-(2,3-Pentadienyl)-3-methyl-2-cyclohexen-1-one (**11b**). This material was prepared in the same manner as allene **11a**. A Grignard reagent was prepared (*9*) from 33.25 g (0.25 mol) of 2-bromo-3-butyne prepared as described by Gaudemar (*9*). This was added to the chloride **9** prepared from 9.15 g (0.05 mol) of alcohol **8**. After workup and purification as described for allene **11a**, 5.5 g (60% from alcohol **8**) of crude allene **11b** was obtained. Analysis by VPC showed ~16% acetylenic material. Chromatography of 3.0 g of the product on silica gel (20% Et_2O/hexane) gave, after evaporative distillation at 0.08 mm/88°C, 1.85 g of material containing ~3% acetylene and small amounts (<7%) of low retention time material. This was satisfactory for the cyclization studies, ir (film) 1950 (allene) and 1150 (enone) cm^{-1}; ^{1}H-nmr (CCl_4, 60 MHz) δ 1.6 (d, J = 10 Hz, 3H, $CH_3CH{=}C{=}C$), 1.68 (bs, 3H, $-CH_3$), 4.93–5.33 (m, 2H, allene H), and 5.8 (bs, 1H, $-OC-CH{=}C-$); ^{13}C-nmr[17] δ 205.4 and 205.6 (C-3′), 199.0 (C-1), 164.7 (C-3), 127.2 (C-2), 87.8 and 87.7 (C-2′), 86.2 and 86.1 (C-4′), 39.4 (C-4), 34.0 and 33.9, 31.1 and 30.8, and 26.5 (C-5, C-6, and C-1′), 22.9 (C-3 CH_3–), and 14.3 (C-5′). An analytical sample was prepared by preparative VPC.

Anal. Calcd for $C_{12}H_{16}O$: 176.120110. Found: 176.119449 (3.8 ppm) HRMS.

4-(2,3-Butadienyl)-3-methyl-2-cyclohexen-1-ol (**12a**). Enone **11a** (500 mg, 3.14 mmol) was added to a solution of lithium aluminum hydride (0.12 g, 3.14 mmol) in 40 ml of anhydrous ether at 0°C. The mixture was stirred for 1 hr at 0°C, then quenched with 0.1 ml of H_2O, 0.1 ml of 10% NaOH, and 0.3 ml of H_2O. Solid $MgSO_4$ was added, and, after 10 min, the salts were removed by filtration using an ether wash. Concentration and evaporative distillation at 0.05 mm/90°C gave 500 mg (100% yield) of alcohol **12a**:[18] ir (film) 3400 (OH) and 1950 (allene) cm^{-1}; ^{1}H-nmr ($CDCl_3$, 100 MHz) δ 1.70 (3H, $-CH_3$), 4.0 (m, 1H, C-1 H), 4.6 (m, 2H, $C{=}C{=}CH_2$), 5.0 (m, 1H, $-CH{=}C{=}CH_2$), and 5.5 (m, 1H, C-2 H); ^{13}C-nmr[17] δ 209.1 (C-3′), 140.4 and 139.9 (C-3), 126.7 and 126.4 (C-2), 88.2 and 87.9 (C-2′), 74.5 and 74.4 (C-4′), 66.2 and 65.9 (C-1), 38.6 (C-4), 31.4 and 31.2, 29.6 and 29.2, and 23.9 (C-5, C-6, and C-1′), and 21.8 (C-3 $-CH_3$).

4-(3-Butynyl)-3-methyl-2-cyclohexen-1-ol (**15**). Reduction of 0.85 g (5.35 mmol) of

[17] This material is a mixture of diastereomers. Some carbons have observably different chemical shifts for each of the isomers.

[18] This alcohol was not stable to VPC and was used directly in the cyclization studies.

enone **14** was effected with 0.20 g (5.35 mmol) of lithium aluminum hydride using the same procedure as described for alcohol **12a**. After evaporative distillation (0.05 mm/90°C) there was obtained 0.85 g (100% yield) of alcohol **15**:[18] ir (film) 3300, 2120 (alkyne), and 3400 (—OH) cm^{-1}; ^{1}H-nmr ($CDCl_3$, 100 MHz) δ 1.7 (3H, $-CH_3$), 1.92 (t, $J = 3$ Hz, 1H, $-C\equiv C-H$), 4.1 (m, H, C-1 H), and 5.5 (b, 1H, C-2 H).

4-(2,3-Pentadienyl)-3-methyl-2-cyclohexen-1-ol (**12b**). Reduction of 750 mg (4.3 mmol) of enone **11b** was effected with 160 mg (4.3 mmol) of lithium aluminum hydride using the same procedure as described for alcohol **12a**. After evaporative distillation (0.1 mm/85°C) there was obtained 680 mg (91% yield) of alcohol **12b**.[18] ^{1}H-nmr ($CDCl_3$, 100 MHz) δ 1.61 (d, $J = 7$ Hz, 3H, C-5′ H), 1.7 (3H, C-3 CH_3—), 4.14 (b, 1H, C-1 H), 5.02 (m, 2H, allene protons), and 5.54 (bs, 1H, C-2 H); ^{13}C-nmr[17] δ 205.4 (C-3′), 140.5 and 140.0 (C-3), 126.6 and 126.3 (C-2), 88.5 and 88.0 (C-2′), 85.4 and 85.2 (C-4′), 66.2 and 65.9 (C-1), 38.6 (C-4), 32.0, 31.8 and 31.7, 29.6 and 29.3, and 23.9 (C-5, C-6, and C-1′), 21.8 (C-3 CH_3—), and 14.4 (C-5′).

Cyclization Studies

Cyclization of allenyl alcohol **12a**. A mixture of 30 ml of anhydrous formic acid and 400 mg (2.44 mmol) of alcohol **12a** was stirred under N_2 at room temperature for 30 min, then poured into methylene chloride and water. The aqueous layer was extracted with methylene chloride, and the combined extracts were washed (water, bicarbonate, and brine), dried (sodium sulfate), concentrated, and distilled to give 319 mg of enol formate **16** (partially hydrolyzed as shown by ir). This material was dissolved in methanol containing 2 equiv of KOH. The solution was stirred for 3 hr, neutralized with 10% HCl followed by bicarbonate, and concentrated to remove methanol. The residue was extracted with ether, and the combined extracts were washed (water, bicarbonate, and brine), dried ($MgSO_4$), concentrated, and evaporatively distilled (0.05 mm/90°C) to give 270 mg (67% yield from **12a**) of ketone **17**. ir (film) no OH, 1715 (C=O) cm^{-1}; ^{1}H-nmr (CCl_4, 60 MHz) δ 1.1 (s, angular methyl) and 5.2–5.9 (m, vinyl H).

Analysis by VPC (SE-30 at 130°C) showed one peak with only a trace of impurities observable. The retention time was identical with authentic ketone **17** (see below). The spectral data (ir and ^{1}H-nmr) for the cyclization product was essentially identical with the analogous data obtained from authentic ketone **17** and from the product from cyclization of alkyne **15**.

Cyclization of alkynyl alcohol **15**. A mixture of 300 mg (1.83 mmol) of alcohol **15** and 40 ml of anhydrous formic acid was stirred under N_2 for 1 hr. Workup and hydrolysis in the manner described for alcohol **12a** gave, after evaporative distillation (0.05 mm/90°C), 200 mg (67% from alcohol **15**) of *cis*-9-methyl-Δ^7-2-octalone (**17**). ^{13}C-nmr δ 211.2 (C-2), 135.2 (C-8), 125.4 (C-7), 52.0, 40.0 (C-9), 38.7, 38.6, 28.7, 28.4, 24.0, and 23.9. The ir, ^{1}H-nmr, and ^{13}C-nmr data for this product were essentially identical with those for authentic ketone **17** (see below).

Anal. Calcd for $C_{11}H_{16}O$: 164.119697. Found: 164.120110 (2.5 ppm) HRMS.

cis-9-Methyl-Δ^7-2-octalone (**17**) *from cis-9-methyl-Δ^7-2-octalol* (**18**). A solution of 120 mg (0.72 mmol) of alcohol **18** (*8a*, *11*) in 20 ml of acetone was stirred under N_2 at 0°C, and Jones reagent was added dropwise until an excess was present. Isopropyl alcohol was added to destroy excess reagent. The mixture was diluted with water and extracted with ether. The extracts were washed (water, 10% NaOH, bicarbonate, and brine),

dried ($MgSO_4$), concentrated, and evaporatively distilled (0.05 mm/90°C) to give pure ketone **17**. This material was identical in all respects with the ketonic materials obtained from cyclization of alcohols **12a** and **15**.

Cyclization of allenyl ketone **11a**. A mixture of 7 ml of trifluoroacetic acid and 3 ml of trifluoroacetic anhydride was added to 155 mg (0.95 mmol) of enone **11a**. The reaction was stirred under N_2 at room temperature for 1.5 hr. The mixture was concentrated and evaporatively distilled (0.2 mm/100°C) to give 313 mg (88% yield) of bisenol ester **20**: ir (film) 1775 (CF_3CO_2–) and 1690 (C=C–O) cm^{-1}; ^{1}H-nmr (CCl_4, 60 MHz) δ 1.2 (angular methyl) and 5.53 (bs, vinyl H).

The ester mixture was hydrolyzed by treatment with 500 mg of K_2CO_3 in 25 ml of methanol. Concentration and normal workup gave, after evaporative distillation at 0.2 mm/110°C, 147 mg (86% yield from enone **11a**) of crystalline diketone **21**: ir (film) 1710 (C=O) cm^{-1}; ^{1}H-nmr (CCl_4, 100 MHz) δ 1.05 (s, angular methyl); ^{13}C-nmr δ 209.6 (C=O), 51.1 (C-1 and C-8), 42.6 (C-9 quaternary C), 39.4 (C-10), 38.7 (C-3 and C-6), 28.5 ($-CH_3$), and 27.2 (C-4 and C-5). Recrystallization from hexane gave material with mp 115–116°C.

Anal. Calcd for $C_{11}H_{16}O_2$: 180.115020. Found: 180.114345 (3.7 ppm) HRMS.

Cyclization of alkynyl ketone **14**. A mixture of 10 ml of trifluoroacetic acid and 8 ml of trifluoroacetic anhydride was added to 265 mg (1.64 mmol) of enone **14**. The mixture was stirred under N_2 at room temperature for 2 hr, concentrated, and evaporatively distilled (0.25 mm/110°C) to give 580 mg (95% yield) of bisenol ester **23**: ir (film) 1780 (CF_3CO_2–) and 1680 (C=C–O) cm^{-1}; ^{1}H-nmr (CCl_4, 60 MHz) δ 1.26 (s, 3H, angular methyl) and 5.37 (bs, 2H, vinyl H).

The ester mixture was hydrolyzed by treatment with 500 mg of K_2CO_3 in 10 ml of 95% ethanol at room temperature for 5 min. The solvent was removed by rotary evaporation; the residue was diluted with water and extracted with ether; and the combined extracts were washed with brine, dried (Na_2SO_4), and concentrated. Evaporative distillation (0.3 mm/110°C) gave 271 mg (92% from enone **14**) of diketone **21**. Crystallization from hexane gave material with mp 114–116°C. This product gave ir and ^{1}H-nmr spectra essentially identical with data from diketone **21** prepared from alkenyl enone **22** and from the product from cyclization of allene **11a**.

Cyclization of Alkenyl Ketone **22**. A mixture of 5 ml of trifluoroacetic acid, 2 ml of trifluoroacetic anhydride, and 230 mg (1.40 mmol) of enone **22** was stirred under N_2 at room temperature for 1 hr. Concentration and evaporative distillation (0.25 mm/90°C) gave 480 mg (92%) of trifluoroacetate product. This material was treated with 1 g of K_2CO_3 in 25 ml of methanol at room temperature for 30 min. The mixture was concentrated, diluted with water, and extracted with ether. The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated to give a mixture of ketoalcohol and ketoolefin (*3a*). Chromatography on silica gel (10% ether/hexane) gave 25 mg of ketoolefin and 204 mg of ketoalcohol. Evaporative distillation of the ketoalcohol fraction gave 197 mg (77% yield from enone **22**) of pure *cis*-9-methyl-hydroxy-2-decalone: ir (film) 3400 (OH) and 1715 (C=O) cm^{-1}; ^{1}H-nmr (CCl_4, 100 MHz) δ 1.02 (angular methyl) and 3.7–4.1 (m, carbinyl H); ^{13}C-nmr δ 212.1 (C-2), 67.1 (C-7), 53.9 (C-1), 42.1 (C-9), 39.9, 39.6, 30.7, 28.4, 28.1, and 24.2. Analysis by VPC (SE-30 at 210°C) showed one peak with a trace of low retention time impurities. An analytical sample was obtained by preparative VPC.

Anal. Calcd for $C_{11}H_{18}O_2$: 182.130670. Found: 182.131201 (2.9 ppm) HRMS.

A similar sample was prepared in lower yield from cyclization of enone **22** with perchloric acid and acetic anhydride in acetic acid (*3a*).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49 H, 9.95. Found: C, 72.53 H, 9.59.

A sample (45 mg, 0.25 mmol) of the ketoalcohol was dissolved in 15 ml of acetone at 0°C and treated with an excess of Jones reagent followed by isopropyl alcohol to destroy the excess. The mixture was diluted with ether, washed (5% NaOH, acid, bicarbonate, and brine), dried (Na_2SO_4), concentrated, and evaporatively distilled (0.2 mm, 110°C) to give 42 mg (94%) of diketone **21**. Crystallization from hexane gave material with mp 115–116°C. This material was identical by ir and ^{1}H-nmr to the ketone products obtained from cyclization of **11a** and **14**.

Cyclization of allenyl alcohol **12b**. A mixture of 380 mg (2.13 mmol) of alcohol **12b** and 40 ml of anhydrous formic acid was stirred under N_2 for 30 min. The mixture was then poured into methylene chloride and water, and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were washed (H_2O, bicarbonate, and brine), dried (Na_2SO_4), concentrated, and evaporatively distilled (0.1 mm/80°C) to give a mixture of cyclic formates: ir (film) 1720 (formate carbonyl) and 1175 (C=C) cm^{-1}; ^{1}H-nmr (CCl_4, 100 MHz) δ 1.08 and 1.10 (major, angular methyls), 1.06 and 1.16 (minor, angular methyls), 1.34 (d, J = 7 Hz, CH_3–$\underset{|}{C}$H–O–), 1.36 (d, J = 7 Hz, CH_3–$\underset{|}{C}$H–O–), and 1.63 (d, J = 7 Hz, CH_3–CH=C).

The formate mixture was treated with 53 mg (1.39 mmol) of lithium aluminum hydride in ether at 0°C for 30 min. The reaction was quenched by adding 50 μl of water, 50 μl of 10% NaOH, and 150 μl of water. Solid $MgSO_4$ was added and the mixture was filtered using ether to wash the salts. The filtrate was concentrated and evaporatively distilled (0.1 mm/90°C) to give 280 mg (74% from alcohol **12b**) of alcohols **25** and **26**: ir (film) 3400 (OH) cm^{-1}.

The ^{1}H-nmr spectrum ($CDCl_3$, 100 MHz) showed singlet absorptions at 1.08 and 1.13 for the angular methyls of the two diastereomers of **25**, singlet absorption at 1.04 and 1.15 for the two angular methyls of **26**, a pair of doublets (J = 7 Hz) at 1.29 and 1.31 for the side-chain methyls in **25**, a doublet (J = 7 Hz) at 1.75 for the vinyl methyl of the major isomer of **26**, a broadened quartet centered at 4.31 for the carbinyl proton of **25**, and a broad signal at 4.72 for the carbinyl proton of **26**. The olefinic region from 5.2 to 5.8 was complex. Integration of the areas of the carbinyl protons indicated that the ratio of **25**:**26** was approximately 2:1.

In another experiment the formate mixture was hydrolyzed using methanolic KOH. Analysis of the product by ir showed no more than a trace of ketonic product. Comparison of this material with authentic ketone **24**[10] by VPC (OV-101 at 135°C) showed conclusively that **24** was not present in the cyclization product.

The mixture of alcohols **25** and **26** was oxidized using the procedure of Ratcliffe and Rodehorst (*14*). Chromic anhydride (942 mg, 9.42 mmol) was added to a mixture of 1.49 g (18.84 mmol) of pyridine in 40 ml of CH_2Cl_2. The mixture was stirred under N_2 for 15 min and 280 mg (1.57 mmol) of alcohols **25** and **26** was added. The mixture was stirred at room temperature for 30 min and filtered using ether to wash the salts. The combined organics were washed (10% NaOH, acid, bicarbonate, and brine), dried ($MgSO_4$), concentrated, and evaporatively distilled to give 210 mg (75% yield) of

ketones **27** and **28**. Analysis by VPC showed two major peaks with three small high retention time peaks. ^{1}H-nmr (CCl_4, 100 MHz) showed absorption for the major product **27** at δ 1.20 (s, angular methyl), 2.51 (s, CH_3CO-), and 6.53 (t, J = 3 Hz, $-CH{=}C-O-$). A sample of the major component was obtained by preparative VPC.

Anal. Calcd for $C_{12}H_{16}O$: 176.120110. Found: 176.119449 (3.8 ppm) HRMS.

Cyclization of allenyl ketone **11b**. A mixture of 220 mg (1.25 mmol) of ketone **11b** in 5 ml of trifluoroacetic acid and 3 ml of trifluoroacetic anhydride was stirred under N_2 at room temperature for 65 min. The TFA and TFAA were removed by concentration on a rotary evaporator and the residue was evaporatively distilled (0.1 mm/110°C) to give 380 mg of a mixture of trifluoroacetates: ir (film) 1780 (CF_3CO_2), 1720 (C=C−O), and 1680 (C=C) cm^{-1}; ^{1}H-nmr (CCl_4, 100 MHz) δ 1.21 and 1.20 (s, angular methyls of major product), 1.13 and 1.31 (s, angular methyls of minor products), and 1.51 and 1.53 (pair of doublets, J = 7 Hz, CH_3—CHO— diastereomers).

The ester mixture was treated with 1 g of K_2CO_3 dissolved in 25 ml of methanol at room temperature for 1 hr. The methanol was removed by concentration, ether and water were added, and the aqueous layer was extracted with ether. The combined extracts were washed with brine, dried over Na_2SO_4, concentrated, and evaporatively distilled (0.2 mm/130°C) to give 195 mg (80% yield from enone **11b**) of a mixture of ketoalcohols **30** and **31**: ir (film) 3400 (OH), 1715 (C=O), and 1650 (C=C) cm^{-1}.

The ^{1}H-nmr spectrum showed absorption for ketoalcohol **30** (equal mixture of two diastereomers) at 1.13 and 1.22 (s, angular methyl), 1.31 and 1.33 (pair of doublets, J = 7 Hz, side-chain methyl), 4.1–4.4 (broadened quartet, carbinyl proton), and 5.7 (broad singlet, vinyl proton) and for ketoalcohol **31** (unequal mixture of diastereomers) at 1.02 and 1.16 (s, angular methyl), 1.67 (d, J = 7 Hz, CH_3—CH= of major diastereomer), 4.78–4.95 (broadened triplet, carbinyl proton), and 5.2–5.6 (m, vinyl proton). Integration of the peak areas for the two carbinyl protons indicated that the ratio of **30**:**31** was ~4:1.

Analysis of this material by VPC (OV-101 at 135°C) showed no peak with the retention time of authentic ketone **29**.[10]

The mixture of alcohols **30** and **31** was oxidized to the corresponding ketones using Collins reagent according to the procedure of Ratcliffe and Rodehorst (*14*). A mixture of chromic anhydride (260 mg, 2.6 mmol), 1 ml of dried pyridine, and 20 ml of dried methylene chloride was stirred at room temperature for 15 min. Then a 100-mg (0.515 mmol) sample of the alcohol mixture was added in 1 ml of CH_2Cl_2. The mixture was stirred at room temperature for 1 hr. The methylene chloride was decanted, and the residue was washed with ether. The combined organics were washed (acid, 5% NaOH, bicarbonate, and brine), dried (Na_2SO_4), concentrated, and evaporatively distilled (0.2 mm/110°C) to give 89 mg (90% yield) of a mixture of diketones **32** and **33**: ir (film) 1710 (C=O), 1660 and 1615 (C=C−C=O) cm^{-1}; ^{1}H-nmr (CCl_4, 100 MHz) 1.21 (s, angular methyl of **32**), 1.18 (s, angular methyl of **33**), 2.20 (CH_3—CO−), 5.91 (q, J = 7 Hz, vinyl H of **33**), and 6.62 (t, J = 2.5 Hz, vinyl H of **32**); ^{13}C-nmr (easily assigned peaks for major isomer only) δ 212.9 (cyclohexyl C=O), 195.8 (acetyl C=O), 149.8 (α-vinyl C), and 143.5 (β-vinyl C). A sample of the major isomer was obtained by preparative VPC.

Anal. Calcd for $C_{12}H_{16}O_2$: 192.115020. Found: 192.114487 (2.8 ppm) HRMS.

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