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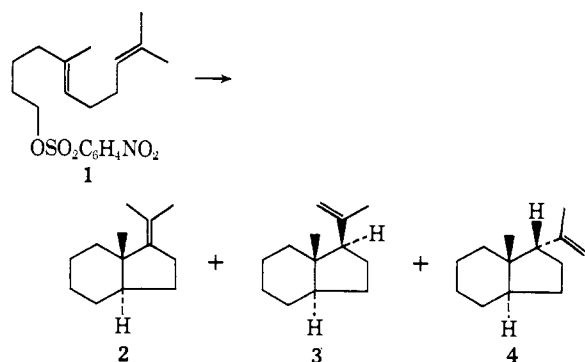
The Synthesis and Cyclization of 4-(*trans,trans*-7,12-Dimethyl-3,7,11-tridecatrienyl)-3-methyl-2-cyclohexen-1-ol and of Its Allylic Isomer¹

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Abstract: The aim of this study was to synthesize the tetraenols **5** and **6** in the hope that they could be induced to undergo acid-catalyzed cyclization to produce products derived from the tetracyclic carbonium ion **7**. Substrate **5** was synthesized by the sequence outlined in Scheme II, the key step being the coupling of the lithium acetylide of **14** with the bromodiene **13** (prepared according to Scheme I). Substrate **6** was produced by the convergent synthesis shown in Scheme V, involving the Biellmann coupling of the allylic chloride **28** (Scheme III) with the lithium anion of the allylic sulfide **32** (Scheme IV). Substance **6**, on treatment in methylene chloride at -78° with either stannic chloride or trifluoroacetic acid, underwent cyclization. A major product was the tetracyclic hydrocarbon **37** evidently produced from the carbonium ion **7** by a $17\alpha \rightarrow 20$ hydride shift, followed by a $13\beta \rightarrow 17\beta$ methyl migration and finally loss of the 14α proton. Cyclization of the isomer **5** gave similar results. So far it has not been possible to trap the cation **7** before it undergoes rearrangement.

The successful stereospecific generation of tetracyclic products with D-homosteroid ring systems from monocyclic polyenols^{1,2} raised the question of similarly producing the naturally occurring steroid system with a five-membered D ring. Preliminary studies have been made on functionalized 1,5-dienes designed to give hydrindan systems.³ For example, the cyclization of *trans*-5,10-dimethyl-5,9-undecadienyl *p*-nitrobenzenesulfonate (**1**) in anhydrous acetic acid buffered with sodium acetate afforded a 7.6% yield of a mixture of bicyclic hydrocarbons **2**, **3**, and **4**, produced *via* the



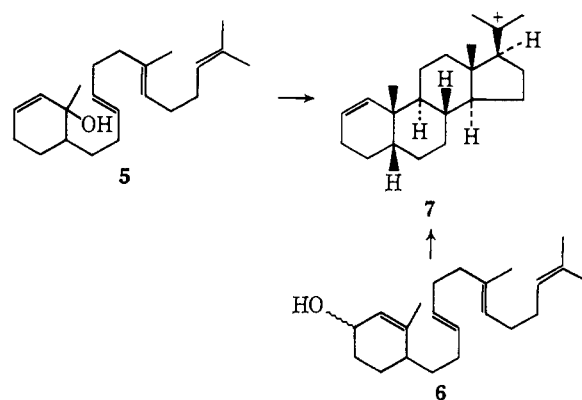
more stable of the two possible bicyclic carbonium ions. Even though the major products were monocyclic, these results were encouraging in that all of the bicyclic material detected contained the *trans* hydrindan ring system. Accordingly, we were prompted

(1) This represents part of a general study of Non-Enzymic Biogenetic-Like Cyclizations. For the previous paper in this series, see R. L. Carney and W. S. Johnson, *J. Amer. Chem. Soc.*, **96**, 2549 (1974).

(2) K. E. Harding, E. J. Leopold, A. M. Hudrlík, and W. S. Johnson, *J. Amer. Chem. Soc.*, **96**, 2540 (1974).

(3) Unpublished observations of S. F. Brady and W. S. Johnson. See S. F. Brady, Ph.D. Thesis, Stanford University, 1967.

to see if, under the mild conditions shown to be effective for the cyclization of allylic alcohols to tetracyclic products,^{1,2} the tetraenol **5** and its allylic isomer **6** would afford *cis,anti,trans,anti,trans* systems derived from the carbonium ion **7**.



The approach to the synthesis of cyclization substrate **5** (Scheme II) was based on previous work in these laboratories.^{1,2} The required homoallylic bromide **13** was obtained (Scheme I) according to a procedure⁴ for the synthesis of *trans*-1-bromo-3,7-octadiene.

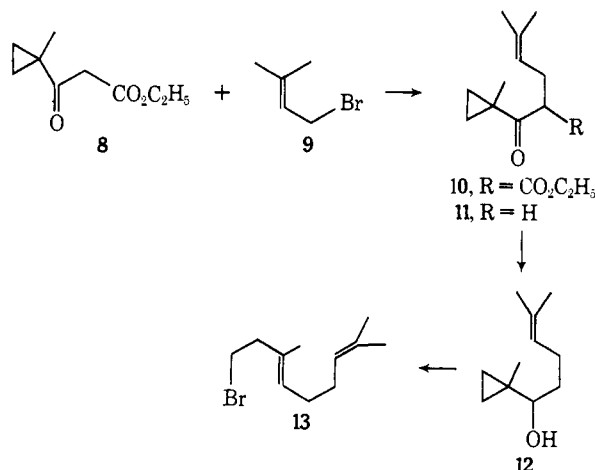
The sodium enolate of 1-methylcyclopropyl carbethoxymethyl ketone (**8**)^{4,5} in tetrahydrofuran was treated with 1-bromo-3-methyl-2-butene (**9**)⁶ to afford keto ester **10** in 80% yield. Treatment of this substance with barium hydroxide in aqueous ethanol followed by acidification effected decarbonylation to give ketone **11** in 58% yield, reduction of which with lithium

(4) S. F. Brady, M. A. Ilton, and W. S. Johnson, *J. Amer. Chem. Soc.*, **90**, 2882 (1968).

(5) M. Julia, S. Julia, and Y. Noel, *Bull. Soc. Chim. Fr.*, 1708 (1960).

(6) M. Andrac, *Ann. Chim. (Paris)*, [13] **9**, 287 (1964).

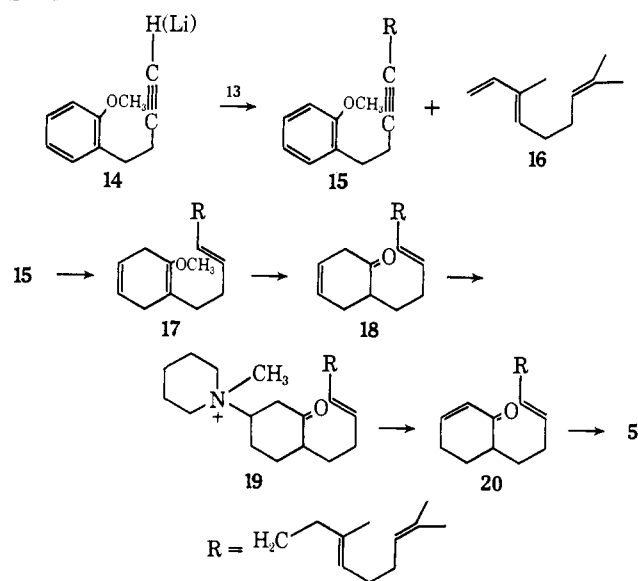
Scheme I



aluminum hydride proceeded in 67% yield to afford carbinol **12**. Treatment of alcohol **12** with phosphorus tribromide in the presence of collidine, lithium bromide, and anhydrous ether afforded a crude bromide mixture, which, when treated with zinc bromide in ether,⁴ gave a 66% yield of a colorless oil, the nmr spectrum of which was consistent with trans bromodiene structure **13**.

The lithium acetylide of 2-(3-butynyl)anisole¹ (**14**) was formed by the addition of methyl lithium to the neat acetylene. Treatment of this acetylide with the aforementioned bromodiene **13** in THF (room temperature, 6 days) gave the desired alkylation product **15** (Scheme II) in 23% yield. Attempts to improve the yield by use

Scheme II



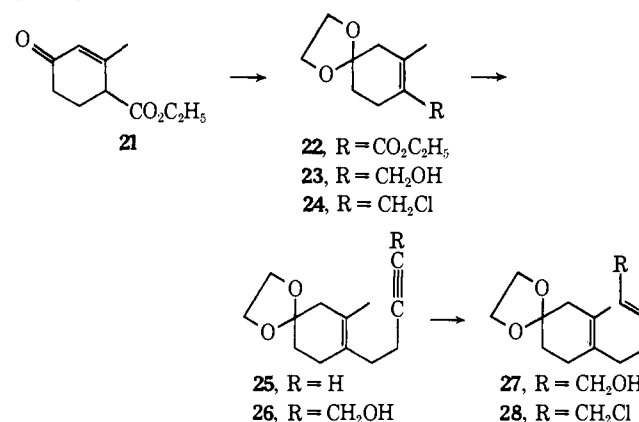
of the tosylate corresponding to bromide **13** or by use of HMPA as the solvent gave lower yields. A major reason for the low yields in this step is that the homoallylic bromide **13** readily eliminates hydrogen bromide in the presence of base to give the triene **16**, which was easily separated by chromatography and identified by nmr spectroscopy.

Treatment of the alkynyl anisole **15** with lithium and ethanol in liquid ammonia gave material which contained the enol ether **17**. Hydrolysis with aqueous lactic acid gave ketonic product, $\lambda_{\text{max}}^{\text{film}}$ 5.80 μ , presumably mainly the β,γ -unsaturated ketone **18**, which was isomerized to the α,β tautomer **20** by the method of

Stork and White.⁷ Thus, the ketone mixture was treated with piperidine followed by methyl iodide to afford the quaternary ammonium salt **19**, which was washed with pentane to remove by-products, in particular, any saturated ketone resulting from overreduction of **15**. Decomposition of **19** with pyridine afforded a 17% yield of the crude α,β -unsaturated ketone **20**. This product was submitted to preparative tlc, from which ketone **20**, $\lambda_{\text{max}}^{\text{film}}$ 5.97 μ , was recovered in only 3% yield. Reaction of the chromatographed ketone with methyllithium afforded alcohol **5**, which was used directly for cyclization studies (see below).

In view of the extremely low yield of the synthetic sequence described above, further work aimed at producing **5** was abandoned and our attention was turned to a scheme for producing the allylic isomer **6** which promised to be equally useful. This approach envisaged, as the key reaction, the Biellmann coupling⁸ of the allylic chloride **28** with the anion of the thioether **32** as represented in Scheme V. The former substance was prepared as shown in Scheme III *via* the enyne ketal **25**.⁹

Scheme III



Treatment of commercially available 4-carbomethoxy-3-methyl-2-cyclohexen-1-one (Hagemann's ester, **21**) with ethylene glycol in the presence of ethyl orthoformate and *p*-toluenesulfonic acid afforded the ketal ester **22**, $\lambda_{\text{max}}^{\text{film}}$ 5.82 μ , in 85% yield. Reduction of ester **22** to allylic alcohol **23**, $\lambda_{\text{max}}^{\text{film}}$ 2.90 μ , was effected in 51% yield by the action of sodium bis(2-methoxyethoxy)aluminum hydride in benzene. Alcohol **23** was converted in 58% yield to the corresponding chloride by the action of hexamethylphosphorous triamide and carbon tetrachloride in ether.¹⁰ The nmr spectrum of the crude product was consistent with structure **24** but also contained a spurious, weak singlet at δ 3.93 ppm. Treatment of the crude chloride with a solution of propargylmagnesium bromide in ether¹¹ gave an oil, containing mainly the terminal acetylene **25**, in 35% yield from alcohol **23**.

The enyne ketal **25** was titrated with methyllithium to give the acetylide which, on treatment with paraformaldehyde in refluxing tetrahydrofuran, was con-

(7) G. Stork and W. N. White, *J. Amer. Chem. Soc.*, **78**, 4604 (1956).

(8) J. F. Biellmann and J. B. Ducep, *Tetrahedron Lett.*, 3707 (1969).

(9) For a preliminary discussion of this work, see K. E. Harding and K. A. Parker, *Tetrahedron Lett.*, 1633 (1971).

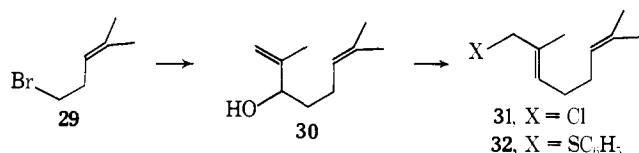
(10) I. M. Downie, J. B. Lee, and M. F. S. Matough, *Chem. Commun.*, 1350 (1968).

(11) Cf. R. E. Ireland, M. I. Dawson, and C. A. Lipinski, *Tetrahedron Lett.*, 2247 (1970). We express our thanks to Professor Ireland for providing us with procedural details.

verted into the propargylic alcohol **26**. Reduction of this substance to the trans allylic alcohol **27** was effected by lithium aluminum hydride in refluxing tetrahydrofuran.¹² Alcohol **27** was easily separated, by chromatography, from allenes generated in the Grignard coupling reaction¹¹ and in the lithium aluminum hydride reduction.¹² The nmr spectrum of distilled alcohol **27** (obtained in 13% overall yield from **23**) showed a broad two-proton singlet at δ 5.75 ppm (vinyl protons) and a sharp six-proton "singlet" at 3.85 (ethylene ketal and protons on carbon bearing hydroxyl). Alcohol **27** was converted to the corresponding chloride by the action of hexamethylphosphorous triamide and carbon tetrachloride in ether.¹⁰ The nmr spectrum of chloride **28**, obtained in quantitative yield, was consistent with the assigned structure and the infrared spectrum showed no absorption in the hydroxyl region. The crude chloride was used in the alkylation of thioether **32**, which was synthesized as described below.

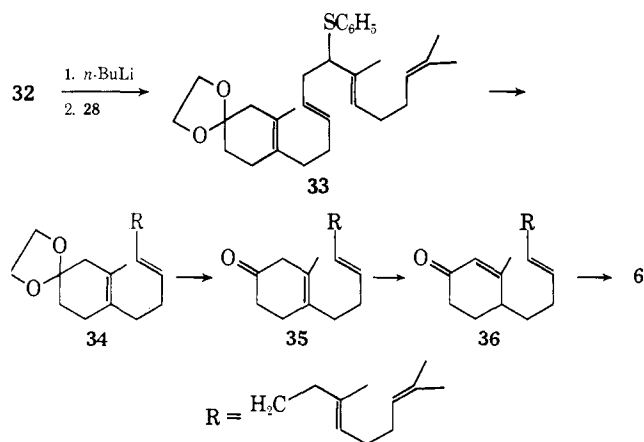
Addition of 1-bromo-4-methyl-3-pentene (**29**)¹³ to lithium in ether at -20° afforded the corresponding lithium derivative.¹⁴ Addition of freshly distilled methacrolein at -70° gave 2,7-dimethyl-1,6-octadien-3-ol (**30**) in 52% yield from bromide **29**. The S_{Ni} rearrangement¹⁵ involving addition of the allylic alcohol **30** to excess thionyl chloride in hexane gave the chlorodiene **31** in 78% yield. On stirring with lithium thiophenylate in HMPA, chloride **31** was converted to the corresponding phenyl thioether **32** in 95% yield (Scheme IV).

Scheme IV



Alkylation of the anion of thioether **32** with chloride **28** proceeded smoothly to afford the crude thioether **33**, which was reduced to ketal **34** by lithium in ethylamine at -78° (Scheme V). Ketal **34** was isolated in 59%

Scheme V



(12) Cf. R. A. Raphael, "Acetylenic Compounds in Organic Synthesis," Butterworths, London, 1955, p 29.

(13) M. Julia, S. Julia, and R. Guegan, *Bull. Soc. Chim. Fr.*, 1072 (1960).

(14) J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, *J. Chem. Soc.*, 2539 (1959).

(15) Cf. W. S. Johnson, T. Li, C. A. Harbert, W. R. Bartlett, T. R. Herrin, B. Staskun, and D. H. Rich, *J. Amer. Chem. Soc.*, **92**, 4461 (1970).

overall yield from alcohol **27**. The nmr spectrum of this product contained a spurious signal, representing 0.6 proton at δ 2.59 ppm. An attempt to remove the impurity responsible for this signal by preparative vpc was unsuccessful. Ketal **34** was hydrolyzed (H_2O , acetone, HCl) to ketone **35** which was isomerized (NaOC_2H_5 , $\text{C}_2\text{H}_5\text{OH}$) to the α,β -unsaturated ketone **36**, $\lambda_{\text{max}}^{\text{film}}$ 6.00 μ . The yield of ketone **36**, based on ketal **34**, was 66%. Ketone **36** was reduced by lithium aluminum hydride to the allylic alcohol **6** in 61% yield. This material was used for the studies described below.

Cyclization Studies. When a solution of tetraenol **6** in methylene chloride saturated with trifluoroacetic acid was allowed to stand at -78° for 4.5 hr, a mixture of hydrocarbon and trifluoroacetate was produced. The crude product was treated with lithium aluminum hydride in ether to afford a mixture of hydrocarbon and alcoholic components, which were separated by chromatography. The hydrocarbon fraction, obtained in 36% yield, appeared to be homogeneous by tlc and vpc and is designated "hydrocarbon A." The 100-MHz nmr spectrum exhibited a singlet at δ 5.55 ppm, a series of unresolved peaks from 2.0 to 1.2, two sharp singlets at 0.97 and 0.95, and two doublets ($J = 7$ Hz) at 0.84 and 0.73 ppm. The mass spectrum of hydrocarbon A was dominated by the $(M - \text{C}_3\text{H}_7)^+$ peak. The probable structure of hydrocarbon A is discussed below.

The aforementioned alcohol fraction, isolated in 56% yield, was shown by tlc to consist of three minor components and a more polar, major component. The alcohols were separated by further chromatography and the major component was identified as tetraenol **6**.

Cyclization of **6** with 0.6 equivalent of stannic chloride in methylene chloride at -78° for 5 min afforded a mixture of hydrocarbon and alcoholic components. The hydrocarbon fraction, obtained by chromatography in 46% yield, was shown by tlc to be approximately 80% one component. The nmr spectrum of this hydrocarbon mixture was identical with that of hydrocarbon A, obtained from the trifluoroacetic acid cyclization, except that it contained an additional large broad singlet at δ 1.25 ppm. (In another similar experiment, a sample of hydrocarbon A which showed only one spot on tlc was isolated in 34% yield.) On tlc, the alcoholic fraction exhibited six to eight spots, corresponding to components present in approximately equal amounts. The stannic chloride catalyzed cyclization was repeated in nitromethane at -23° to afford a product mixture which appeared to be essentially identical with that obtained in methylene chloride.

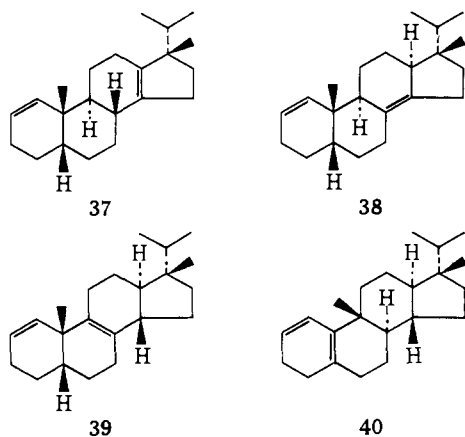
Cyclization of crude tetraenol **5** with stannic chloride in methylene chloride at -78° afforded a 33% yield of a hydrocarbon fraction, the nmr spectrum of which was essentially identical with that of hydrocarbon A. In addition a 25% yield of a complex mixture of alcohols was isolated. The cyclization of tetraenol **5** was not pursued further.

The only tetracyclic material isolated in the above experiments was hydrocarbon A, apparently the product of the facile rearrangement of carbonium ion **7** prior to deprotonation. Hydrocarbon A has been tentatively assigned the structure **37** on the basis of the following considerations. Mass spectral evidence suggested that hydrocarbon A was tetracyclic and possessed an isopropyl group. In addition, the nmr spec-

trum of A indicated the presence of only two olefinic protons, accounted for by the olefinic bond in ring A. On hydrogenation over platinum in ethanol, hydrocarbon A absorbed 1.08 mol equiv of hydrogen, affording dihydro A, probably the substance **42** (see below). On further hydrogenation over platinum in acetic acid, conditions known to effect the hydrogenation of tetrasubstituted olefinic bonds,¹⁶ dihydro A absorbed 0.82 equivalent of hydrogen to give tetrahydro A.

Seemingly the most likely means of generating the isopropyl group of hydrocarbon A from **7** is by migration of the C-17 (α) hydrogen. The developing cationic center at C-17 would then be expected to promote the 1,2 shift of the C-18 methyl group (the K \ddot{a} gi-Miescher rearrangement). With no nearby functionality to influence the direction of deprotonation, the developing C-13 cation is deprotonated to give the 13,14-tetrasubstituted bond,¹⁷ affording substance **37**. This sequence of a hydride followed by a methyl shift and then deprotonation¹⁸ may be a concerted process.

It should be noted that carbonium ion **7**, in keeping with previous results,^{1,2} should possess the cis,anti-trans,anti,trans carbon skeleton which is stereochemically composed to undergo a succession of trans antiplanar hydrogen and methyl shifts culminating with the trans elimination of a proton. Thus carbonium ion **7** could conceivably also give compound **38**, **39**, or **40**.



Structure **40**, which would result from nonconcerted loss of the β C-5 proton, was ruled out since no absorption for conjugated diene was observed in the ir spectrum of hydrocarbon A. Mass spectral evidence suggested that structures **38** and **39** were unlikely. The expected retro-Diels-Alder fragmentation of the C ring of compound **38** would result in an $(M - C_2H_4)^+$ peak which was not observed. Structure **39** cannot be ruled out, although loss of the C-19 methyl group to form a doubly allylic ion radical would be expected to be the predominant fragmentation here and this was not observed. Since the mass spectra of both A and dihydro A were dominated by the loss of isopropyl from the molecular ion and subsequent fragmentations of the $(M - C_3H_7)^+$ species, and since the loss of isopropyl from the molecular ion corresponding to structure **37**

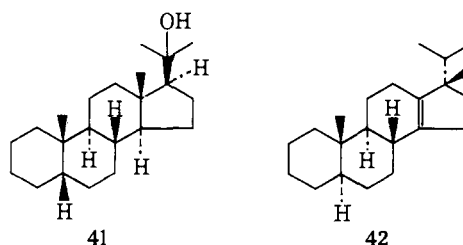
(16) Cf. W. S. Johnson, N. P. Jensen, and J. Hooz, *J. Amer. Chem. Soc.*, **88**, 3859 (1966).

(17) P. de Mayo, "Molecular Rearrangements," Part 2, Interscience, New York, N. Y., 1964, pp 1020-1027.

(18) This sequence of transformations has been observed in other systems; see, e.g., E. E. van Tamelen, J. Willett, M. Schwartz, and R. Nadeau, *J. Amer. Chem. Soc.*, **88**, 5937 (1966); G. Stork and M. Marx, *ibid.*, **91**, 2371 (1969).

would be favored by the formation of an allylic ion, it is likely that this is the observed fragmentation. The loss of isopropyl was relatively unimportant in the mass spectrum of tetrahydro A, a fact which supports the argument that the tetrasubstituted olefinic bond enhances this fragmentation. In view of this evidence, the 13,14 position seems the most probable location for the tetrasubstituted double bond.

One additional experiment is pertinent to consideration of the pathway by which hydrocarbon A is formed. If a carbonium ion like **7** were to be generated unequivocally from some steroidal precursor, and if it afforded a rearranged product like A, then the intermediacy of **7** in the cyclization of alcohol **6** would be confirmed. The carbinol **41**, prepared by reaction of methylmagnesium bromide with 5 β -pregnan-20-one,¹⁹ was treated with stannic chloride in methylene chloride at -78 to -30° . The product, formed in 97% yield, appeared to be >98% pure by vpc, and its nmr and mass spectral properties were identical with those of dihydro A.



In an unsuccessful effort to trap the carbonium ion **7** prior to rearrangement, the trifluoroacetic acid catalyzed cyclization of substrate **6** was repeated with the addition of propanethiol. However, the mixture of propyl thioethers which was isolated appeared to correspond to uncyclized substrate (see Experimental Section).

Experimental Section²⁰

The prefix "dl" has been omitted from the names of most of the racemic compounds described in this section. Microanalyses and microhydrogenations were performed by E. H. Meier and J. Consul, Department of Chemistry, Stanford University. Melting points were determined on a Kofler hot-state microscope.

Vapor phase chromatography (vpc) analyses were performed on Aerograph Model 600 and 600-C instruments equipped with glass-lined injector blocks, or on Hewlett-Packard Model 402 instruments equipped with glass columns. The latter instrument was also used for the preparative separations.

Mass spectra were determined under the supervision of Dr. A. M. Duffield on an Atlas CH-4 spectrophotometer using a direct inlet system or on a CEC Model 21-103C using a heated inlet system.

Nuclear magnetic resonance (nmr) spectra were determined under the supervision of Dr. L. J. Durham on Varian Associates Model A-60 or HA-100 spectrometers. Carbon tetrachloride was used as solvent unless otherwise stated and tetramethylsilane (TMS) was employed as the internal reference. Chemical shifts are reported as δ values in ppm relative to TMS (δ_{TMS} 0.0 ppm).

(19) L. Gyermek, J. Imiarte, and P. Crabbe, *J. Med. Chem.*, **11**, 117 (1968).

(20) In cases where products were isolated by solvent extraction, the procedure generally followed was to extract the aqueous layer with several portions of the indicated solvent; then the organic layers were combined and washed with water followed by saturated brine. The organic layer was dried over anhydrous sodium sulfate or magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure (water aspirator) using a rotary evaporator. The use of the term "base wash" or "acid wash" indicates washing the combined organic layers with saturated aqueous sodium bicarbonate solution or with dilute aqueous hydrochloric acid, respectively, prior to the aforementioned washing with water.

Silica gel GF₂₅₄ was used for thin-layer chromatography (tlc). The alumina used for column chromatography was either Woelm neutral aluminum oxide (activity I) mixed with the requisite amount of water to lower the activity or Merck acid-washed aluminum oxide (reagent grade). Dry column chromatography was performed according to Loev and Snader²¹ using Woelm activity grade II neutral alumina containing 0.5% Woelm Fluorescent Indicator packed in a column of nylon tubing.

1-Methylcyclopropyl 1-Carboxy-4-methyl-3-pentenyl Ketone (10). A procedure for the synthesis of 1-methylcyclopropyl 1-carboxy-3-butenyl ketone⁴ was used. Thus 5.48 g (36.8 mmol) of 1-bromo-3-methyl-2-butene⁶ (**9**) was converted to 8.23 g of crude alkylated keto ester **10**. This product was distilled through a 30-in. platinum spinning band column. The fraction distilling at 110–115° (2 mm) amounted to 6.92 g (80% yield) of a colorless oil, $\lambda_{\text{max}}^{\text{film}}$ 5.72 (ester C=O), 5.90 (ketone C=O), 8.34, 8.64, 9.21, and 9.70 μ .

Anal. Calcd for C₁₄H₂₂O₂: C, 70.55; H, 9.31. Found: C, 70.4; H, 9.2.

1-Methylcyclopropyl 4-Methyl-3-pentenyl Ketone (11). The procedure of Brady, Ilton, and Johnson⁴ was applied to 6.75 g (28.4 mmol) of keto ester **10**, affording 3.93 g of a colorless oil. Distillation of this material through a 30-in. platinum spinning band column at 108° (15 mm) afforded 2.76 g (58% yield) of pure ketone: n_D^{20} 1.4714; $\lambda_{\text{max}}^{\text{film}}$ 5.90 (ketone C=O), 9.22, and 10.52 μ ; nmr 0.62 and 1.13 (m, 2 H and m, 2 H, cyclopropyl), 1.33 (s, 3 H, CH₃C), 1.66 (m, 6 H, (CH₂)₂C=C), 2.28 (m, 4 H, CH₂ α and β to C=O), and 5.05 ppm (t, 1 H, vinylic).

Anal. Calcd for C₁₁H₁₈O: C, 79.46; H, 10.92. Found: C, 79.4; H, 10.9.

1-Methylcyclopropyl-4-methyl-3-pentenylcarbinol (12). To a suspension of 0.54 g (14 mmol) of lithium aluminum hydride in 75 ml of ether at 0°, was added 2.54 g (15.3 mmol) of ketone **11** in 35 ml of ether. The mixture was stirred at 0° for 1 hr and then 0.6 ml of water, 0.6 ml of 15% sodium hydroxide solution, and 1.8 ml of water were added. The mixture was stirred for 15 min at room temperature, filtered, and concentrated. The residue distilled at 100–110° (15 mm) to give 1.73 g (67% yield) of a colorless oil: $\lambda_{\text{max}}^{\text{film}}$ 2.90 (OH), 6.00 (C=C), 9.40, 9.82, and 10.64 μ ; nmr 0.25 and 0.32 (s, 2 H and s, 2 H, cyclopropyl), 0.98 (s, 3 H, CH₃C), 1.6 (m, 8 H, (CH₂)₂C=C and -CH₂CHOH-), 2.05 (m, 3 H, OH and CH₃C=C), 2.83 (t, 1 H, RR'CHOH), and 5.12 ppm (t, 1 H, vinylic). Vapor phase chromatography of this material showed one peak.

Anal. Calcd for C₁₁H₂₀O: C, 78.51; H, 11.98. Found: C, 78.3; H, 11.8.

trans-1-Bromo-3,8-dimethyl-3,7-nonadiene (13). The procedure of Brady, Ilton, and Johnson⁴ was modified. To a solution of 36.3 g (0.216 mol) of alcohol **12** and 19.5 ml (17.9 g, 0.148 mol) of collidine in 500 ml of ether was added 38 g (0.44 mol) of anhydrous lithium bromide. The resulting suspension was placed under an atmosphere of nitrogen and cooled to -30°. Then 12.2 ml (34.8 g, 0.128 mol) of phosphorus tribromide was added over 10 min. After the addition was complete, the mixture was allowed to warm to 0° and to stir for 1.5 hr. Then 18 ml (16.5 g, 0.138 mol) of collidine was added, followed by 12 ml of water. The reaction mixture was poured into water overlaid with pentane. The aqueous phase was washed twice with pentane, and the combined organic layers were washed with water, 2% sulfuric acid, water, sodium bicarbonate, and brine. The pentane solution was dried over sodium sulfate and concentrated to give 45.8 g of a colorless oil.

A 25.0-g portion of this crude oil was added to a suspension of 6.63 g (0.118 mol) of calcium oxide and 29.6 g (0.131 mol) of anhydrous zinc bromide (dried at 135° (0.2 mm)) in 250 ml of ether at 0°, under nitrogen. The reaction mixture was stirred for 3 hr, allowed to warm to room temperature, and poured into pentane. The resulting suspension was washed with water, 2% sulfuric acid, water, sodium bicarbonate, and brine, and dried over sodium sulfate. The pentane solution was filtered and concentrated to give 17.9 g (66% yield from alcohol **12**) of *trans*-1-bromo-3,8-dimethyl-3,7-nonadiene (**13**) which was used in the next step without purification.

A comparable sample of crude product was purified by preparative tlc and distilled (short-path) at 75° (0.05 mm): $\lambda_{\text{max}}^{\text{film}}$ 6.00 (C=C), 7.63, 7.89, 8.25, and 12.00 μ ; nmr 1.65 (s, 9 H, CH₃C=C), 2.00 (m, 4 H at C-5 and C-6), 2.46 (t, 2 H at C-2), 3.35 (t, 2 H at C-1), 4.80 (m, 0.2 H, impurity), 5.08 and 5.21 ppm (overlapping singlets, 2 H at C-4 and C-7). Vpc of this material showed a major

peak accounting for 90% of the total area and a lower retention time peak accounting for the remainder.

Anal. Calcd for C₁₁H₁₉Br: C, 57.15; H, 8.28; Br, 34.56. Found: C, 57.6; H, 8.3; Br, 34.4.

trans-2,7-Dimethyl-13-(2-methoxyphenyl)-2,6-trideca-10-yne (14). A 1.72-g sample (10.7 mmol) of purified 2-(3-butynyl)anisole (**14**), prepared by R. Carney,¹ was treated at 0° with 5.8 ml of 1.4 M methylolithium solution (8.1 mmol). After methane evolution had ceased, 5.0 ml of hexamethylphosphoric triamide (HMPA, freshly distilled from calcium hydride and flushed with nitrogen) was slowly added. The acetylide solution was stirred at 50° under a stream of nitrogen for 1 hr to remove ether; then it was cooled and 1.10 g (4.76 mmol) of crude *trans*-1-bromo-3,8-dimethyl-3,7-nonadiene (**13**) was added. The mixture was stirred at room temperature for 5 days and then poured into water overlaid with pentane. The aqueous phase was extracted with two portions of pentane and the combined pentane solutions were washed twice with brine and dried over magnesium sulfate. The pentane solution was washed with 16 2-ml portions of a 1.6 M solution of dimethyl sulfoxide sodium salt in dimethyl sulfoxide,²² once with water, and twice with brine. Drying over magnesium sulfate and concentrating afforded 1.12 g of a pale yellow oil, the infrared spectrum of which showed no absorption of 3.0 μ .

The alkylation product was subjected to dry column chromatography on 125 g of Woelm neutral alumina, activity grade II. Elution with pentane afforded a major fraction which was purified further by preparative extended elution tlc with pentane. A short-path distillation at 114° (4 × 10⁻⁴ mm) afforded 231 mg (16% yield from bromide **13**) of disubstituted acetylene **15** as a colorless oil: n_D^{20} 1.5255, $\lambda_{\text{max}}^{\text{film}}$ 6.00 (C=C), 6.70 (Ar), 8.07 (C-O-Ar), 9.00, 9.68, and 13.30 μ (Ar); nmr 1.58 and 1.66 (s, 3 H and s, 6 H, CH₃-C=C), 1.8–2.9 (m, 12 H at C-4, -5, -8, -9, -12, -13), 3.74 (s, 3 H, CH₃O), 5.08 (sharp m, 2 H, HC=C), and 6.92 ppm (m, 4 H, aromatic). This material appeared to be homogeneous by vpc.

Anal. Calcd for C₂₂H₃₀O: C, 85.11; H, 9.74. Found: C, 84.9; H, 9.9.

6-(trans,trans-7,12-Dimethyl-3,7,11-tridecatrienyl)-2-cyclohexen-1-one (20). To a solution of 3.25 g (0.46 mol) of lithium in 225 ml of ammonia (distilled from lithium wire) at -78°, was added 2.09 g (6.74 mmol) of the substituted anisole **15**, and the reaction mixture was allowed to stir at -78° for 15 min. Then 60 ml of absolute ethanol was added in 5-ml portions over a 1-hr period. The mixture was stirred until the blue color disappeared (about 5 min), the ammonia was allowed to evaporate, then the residue was poured into water overlaid with pentane.

The product obtained by pentane extraction²⁰ was stirred under nitrogen with 23 ml of dimethoxyethane, 9 ml of methanol, and 7.6 ml of 6.7% aqueous lactic acid for 72 hr; then the mixture was poured into water overlaid with pentane. The residue obtained by pentane extraction using a base wash²⁰ was treated according to the procedure of Stork and White⁷ for the formation and isolation of α , β -unsaturated ketones. Thus, to the crude product was added 5.0 ml of piperidine (freshly distilled from calcium hydride) and the mixture was stirred for 10 hr under nitrogen. Excess piperidine was removed at reduced pressure. The residue was cooled to 0° and 20 ml of pentane was added followed by 10 ml of methyl iodide. The reaction mixture was stored overnight at 5° and then stirred at room temperature for 6 hr. The tan solid which formed was washed with two portions of pentane and then, at 0°, treated with 5 ml of pyridine under nitrogen. The resulting dark red solution was stirred at 80° for 5 hr, then diluted with water. The crude product, isolated by pentane extraction using a 10% lactic acid followed by a base wash,²⁰ amounted to 341 mg of a pale yellow oil. Preparative tlc gave 65 mg (3% yield from substance **15**) of α , β -unsaturated ketone **20**, $\lambda_{\text{max}}^{\text{film}}$ 5.97 μ .

Another sample was prepared by a similar sequence except that the isomerization of the α , β -unsaturated ketone was carried out with potassium hydroxide in ethylene glycol. Preparative tlc (benzene) of the crude product gave two ketonic fractions. The one with lower *R_f* showed only one carbonyl absorption at 5.97 μ in the infrared. Short-path distillation at 125° (10 μ) afforded ketone **20**: $\lambda_{\text{max}}^{\text{film}}$ 5.97 (C=CC=O), 8.21, and 10.33 μ ; nmr 1.58 and 1.66 (s, 3 H, and s, 6 H, CH₃C=C), 2.2 (unresolved, 17 H), 5.07 (s, 2 H at C-8 and C-11), 5.34 (s, 2 H at C-3 and C-4), 5.85 (d, 1 H, vinyl H α to C=O), 6.75 ppm (narrow m, 1 H, vinyl H β to C=O). This product appeared to be homogeneous by vpc.

(21) B. Loev and K. M. Snader, *Chem. Ind. (London)*, 15 (1965).

(22) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).

Anal. Calcd for $C_{21}H_{32}O$: C, 83.94; H, 10.73. Found: C, 83.7; H, 10.95.

6-(trans,trans-7,12-Dimethyl-3,7,11-tridecatrienyl)-1-methyl-2-cyclohexen-1-ol (5). To a solution of 12.1 mg (0.0403 mmol) of ketone **20** (purified by way of the piperidine adduct, chromatographed, and distilled) in 0.56 ml of anhydrous ether was added 1.15 ml of 1.59 M methylolithium solution (1.81 mmol). The reaction mixture was stirred under nitrogen at room temperature for 30 min and poured into brine. The product, isolated by ether extraction,²⁰ amounted to 14.0 mg (quantitative yield) of alcohol **5**, $\lambda_{\text{max}}^{\text{film}}$ 2.90 μ , a colorless oil. This material was used directly for cyclization (see below).

1-Carbethoxy-2-methyl-4-ethylenedioxy-1-cyclohexene (22).²³ A mixture of 42.0 g (0.231 mol) of Hagemann's ester (**21**), 126 ml of ethylene glycol, 126 ml of ethyl orthoformate, and 0.445 g of *p*-toluenesulfonic acid was stirred at room temperature for 48 hr. Then 0.5 ml of pyridine was added, followed by a 5% aqueous solution of potassium dihydrogen phosphate. The reaction mixture was allowed to stir for 15 min and then was extracted with three portions of ether. The combined ether solution was washed with 5% potassium dihydrogen phosphate solution, sodium bicarbonate, and brine, dried over magnesium sulfate, and concentrated. Distillation of the crude product through a 12-in. Vigreux column afforded 44.7 g (86%) of a colorless oil, bp 92–97° (0.06 mm), which appeared to be 99% one component by vpc.

A sample of comparable material was purified by preparative tlc (50% ether–pentane) and short-path distillation at 75° (20 μ) to give a colorless oil: n_D^{25} 1.4884; $\lambda_{\text{max}}^{\text{film}}$ 5.82 (ester C=CC=O), 8.00, 8.26, and 9.30 (ketal), 9.76, and 10.55 μ .²⁴

1-Hydroxymethyl-2-methyl-4-ethylenedioxy-1-cyclohexene (23).²³ To 105 g (0.464 mol) of ketal ester **22** was slowly added 250 ml of a 70% solution of sodium bis(2-methoxyethoxy)aluminum hydride in benzene (0.87 mol of reagent). Considerable foaming occurred during this addition. The reaction mixture, a viscous, pale yellow solution, was allowed to stir for 24 hr and was then poured into water. The product, isolated by ether extraction,²⁰ was fractionally distilled through a 4-in. Vigreux column. The material which distilled at 142° (0.17 mm) consisted of 43.5 g (51% yield) of a colorless oil: $\lambda_{\text{max}}^{\text{film}}$ 2.90 (OH), 5.95 (C=C), 7.96, 8.68, 9.18 and 9.30 (ketal), 9.98, and 11.91 μ .²³

1-Chloromethyl-2-methyl-4-ethylenedioxy-1-cyclohexene (24). To a solution of 5.70 g (31.0 mmol) of alcohol **23**, 1.5 ml of pyridine, and 6.0 ml of carbon tetrachloride in 21 ml of ether at 0°, was slowly added a solution of 5.41 g (33.1 mmol) of hexamethylphosphorous triamide in 18 ml of ether.¹⁰ The mixture, which became cloudy, was stirred for 45 min at 0° and overnight at room temperature. Then it was poured into water overlaid with pentane. The crude product, isolated by pentane extraction,²⁰ amounted to 3.67 g (58% yield) of a pale yellow oil, which was washed through a 10 \times 0.5 in. silica gel column with 800 ml of pentane. The chloride **24** is very sensitive to air and was used immediately or stored under vacuum. Spectra were obtained from a sample comparable to that described above: $\lambda_{\text{max}}^{\text{film}}$ 5.98 (C=C), 7.95, and 8.93 and 9.38 μ (ketal); nmr 3.82 (s, 4 H, -OCH₂CH₂O-), 3.93 (s, 0.4 H, impurity) and 4.00 ppm (s, 2 H, CH₂Cl).

1-(5-Hydroxy-3-pentynyl)-2-methyl-4-ethylenedioxy-1-cyclohexene (26). To 2.03 g (86 mmol) of magnesium turnings, a trace of iodine, and a trace of mercuric chloride in ether at 0°, a solution of 5.0 ml (7.9 g, 66 mmol) of propargyl bromide in 500 ml of ether was added over 5 hr. The solution was allowed to stir at 0° for 2 hr and then was filtered through a plug of glass wool. To this solution was added 3.67 g (18.1 mmol) of crude chloride **24** in 50 ml of ether and the mixture was allowed to stir at 0° for 3 hr and at room temperature for 9 hr. Water was then slowly added and the product isolated by ether extraction.²⁰ The crude residue was filtered through a 12 \times 0.5 in. Florisil column with 200 ml of pentane to give 1.85 g of a yellow oil. The ir of this substance showed the presence of terminal allene, $\lambda_{\text{max}}^{\text{film}}$ 5.10 μ , as well as of terminal acetylene, $\lambda_{\text{max}}^{\text{film}}$ 3.00 and 4.70 μ .

This mixture was dissolved in 200 ml of tetrahydrofuran and cooled to 0°. A trace of 1,10-phenanthroline²⁵ was added and the acetylene was titrated with methylolithium solution to the rust-

(23) Subsequent to our preparation of this compound (see ref 9), its preparation in essentially the same manner was reported by E. Baggiolini, H. P. Hamlow, and K. Schaffner, *J. Amer. Chem. Soc.*, **92**, 4906 (1970).

(24) The combustion analysis of comparable material was obtained by K. E. Harding, Texas A & M University (see ref 9).

(25) S. C. Watson and J. F. Eastham, *J. Organometal. Chem.*, **9**, 165 (1967).

colored endpoint indicative of the alkylolithium complex. Then a 7% excess of methylolithium was added, followed by 1.99 g (66 mmol of free formaldehyde) of paraformaldehyde (dried at 125° (0.05 mm)). The mixture was stirred at reflux for 10 hr, cooled, and poured into water. The product, isolated by ether extraction,²⁰ amounted to 2.13 g of a crude orange oil which was used in the next step of the synthesis (see below)

A sample of comparable material was purified by chromatography on Florisil. Elution with 50% ether–pentane afforded a fraction which distilled (short-path) at 125° (40 μ): $\lambda_{\text{max}}^{\text{film}}$ 2.90 (OH), 4.37 and 4.49 (C \equiv CCH₂OH), 6.00 (C=C), 8.80, 9.16 and 9.35 (ketal), 9.80, and 11.90 μ ; nmr 3.02 (broad s, 1 H, OH), 3.87 (s, 4 H, -OCH₂CH₂O-), and 4.03 ppm (s, 2 H on carbon holding hydroxyl). This material appeared to be homogeneous by vpc.

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 70.9; H, 8.3.

trans-1-(5-Hydroxy-3-pentenyl)-2-methyl-4-ethylenedioxy-1-cyclohexene (27). To a suspension of 536 mg (14.1 mmol) of lithium aluminum hydride in 45 ml of tetrahydrofuran at room temperature was slowly added a solution of 2.13 g of crude propargylic alcohol **26** in 8 ml of tetrahydrofuran. The reaction mixture was stirred at reflux for 3 hr, cooled to room temperature, and quenched with water. The product, isolated by ether extraction,²⁰ amounted to 1.95 g of a pale yellow oil, which was chromatographed on a 12 \times 0.5 in. Florisil column. After elution of nonpolar material with pentane, 1.31 g (18% yield from alcohol **23**) of the trans allylic alcohol¹² **27** was eluted with ether–pentane mixtures.

A 2.00-g sample of comparable material was distilled (short-path) at 114° (11 μ) to give 1.47 g (74% recovery from the distillation) of a colorless oil: $\lambda_{\text{max}}^{\text{film}}$ 2.88 (OH), 5.98 (C=C), 7.91, 8.80, 9.10, and 9.36 (ketal), 10.25, 10.50, and 11.85 μ .

Anal. Calcd for $C_{14}H_{20}O_3$: C, 70.55; H, 9.31. Found: C, 70.4; H, 9.2.

trans-1-(5-Chloro-3-pentenyl)-2-methyl-4-ethylenedioxy-1-cyclohexene (28). To a solution of 1.47 g (6.18 mmol) of distilled allylic alcohol **27**, 0.35 ml of pyridine, and 2.0 ml of carbon tetrachloride in 20 ml of ether at 0° was slowly added a solution of 2.175 g (13.3 mmol) of hexamethylphosphorous triamide¹⁰ in 10 ml of ether. The mixture was allowed to warm to room temperature and stirred for 3.5 hr. Then it was cooled to 0° and 0.6 ml of methanol was added. This mixture was stirred for 10 min at room temperature and then 0.4 ml of methanol and 62 ml of ether were added. After stirring for another 10 min, the reaction mixture was poured into water overlaid with pentane. Isolation by pentane extraction²⁰ gave 1.65 g (quantitative yield) of crude chloride **28** as a pale yellow oil. This product was used immediately in the synthesis of ketal **34**.

A sample of comparable material was submitted to preparative tlc (25% ether–pentane) and distilled (short-path) at 105° (20 μ): n_D^{25} 1.5196; $\lambda_{\text{max}}^{\text{film}}$ 6.00 (C=C), 7.30, 7.98, 8.85, 9.12, 9.40 (ketal), 10.30, and 11.90 μ .

Anal. Calcd for $C_{14}H_{21}O_2Cl$: C, 65.48; H, 8.25; Cl, 13.81. Found: C, 65.2; H, 8.15; Cl, 13.9.

2,7-Dimethyl-1,6-octadien-3-ol (30). Lithium wire (2.5 g) containing 1% sodium was added to 100 ml of ether under argon. The resulting suspension was cooled to -20°, then a solution of 24.1 g (0.148 mol) of 1-bromo-4-methyl-3-pentene (**29**, prepared by S. Brady by treatment of dimethylcyclopropylcarbinol with 48% hydrobromic acid)¹³ in 100 ml of ether was added over a 2-hr period. An additional 100 ml of ether was added and the reaction mixture was stirred at -20° for 2 hr more. After cooling to -70°, 31 ml (26 g, 0.37 mol) of methacrolein, which had been dried over magnesium sulfate and then over calcium hydride and distilled, was added over a 10-min period. The reaction mixture was allowed to come slowly to room temperature and to stir overnight. Then 15 ml of glacial acetic acid in 30 ml of ether was added at -70° and 60 ml of water was added at room temperature. Isolation by ether extraction using a base wash,²⁰ followed by distillation through a 1.5-in. Vigreux column, gave 11.9 g (52% yield) of a colorless oil, bp 90–105° (0.1 mm), which appeared to be 94% one component by vpc.

A comparable sample was purified by chromatography on 36 g of silica gel. Dienol **30** was eluted by 20% ether–pentane and distilled at 84° (0.4 mm); n_D^{25} 1.4655; $\lambda_{\text{max}}^{\text{film}}$ 2.98 (OH), 6.08 (C=C), 9.50, and 11.12 μ (RR'C=CH₂); nmr 3.87 (t, 1 H at C-3), 4.68 and 4.81 (s, 1 H and s, 1 H, C=CH₂), and 5.02 ppm (t, 1 H at C-6).

Anal. Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C,

77.6; H, 11.7.

trans-1-Chloro-2,7-dimethyl-2,6-octadiene (31). A previously reported procedure¹⁵ was modified. A solution of 7.34 g (47.7 mmol) of dienol **30** (distilled but not chromatographed) in 2 l. of

hexane was cooled to 0°. To this was slowly added 7.8 ml (12.9 g, 108 mmol) of thionyl chloride (distilled from triphenyl phosphite). The resulting colorless solution was allowed to stir overnight at room temperature; then excess sodium bicarbonate solution was carefully added. The crude product, isolated by pentane extraction using a base wash,²⁰ was chromatographed on a 10 × 0.5 in. Florisil column. Three fractions were eluted with 100-ml portions of pentane. Fractions 2 and 3 were rechromatographed and the first fraction from this chromatography was combined with fraction 1 from the first chromatography. The combined material was distilled (short-path) at 115–120° (20 mm) giving 6.54 g (78% yield) of a colorless oil: n_D^{20} 1.4822; $\lambda_{\text{max}}^{\text{flim}}$ 5.99 (C=C), 6.92, 7.22, 7.89, and 14.65 μ (C-Cl); nmr 1.58 and 1.68 (s and s, 9 H, CH₃-C=C), 2.03 (m, 4 H, CH₂C=C), 3.94 (s, 2 H, CH₂Cl), 5.04 and 5.47 ppm (t, 1 H and t, 1 H at C-3 and C-6). This material appeared to be 97% one component by vpc.

Anal. Calcd for C₁₀H₇Cl: C, 69.55; H, 9.92; Cl, 20.53. Found: C, 69.6; H, 9.9; Cl, 20.35.

trans-2,7-Dimethyl-2,6-octadienyl Phenyl Thioether (32). A solution of 5.63 g (32.9 mmol) of chlorodiene **31** in 70 ml of HMPA (distilled from calcium hydride and stored over molecular sieves) was placed under an atmosphere of nitrogen; then 4.31 g (37.1 mmol) of lithium thiophenylate was added and the mixture was stirred at room temperature for 3 hr. After dilution with water, the product was isolated by pentane extraction using a base wash.²⁰ The crude product was chromatographed on a 10 × 0.5 in. Florisil column with pentane. Short-path distillation of the appropriate fraction at 120° (0.6 mm) afforded 7.70 g (95% yield) of a colorless liquid, n_D^{20} 1.5470; $\lambda_{\text{max}}^{\text{flim}}$ 6.01 (C=C), 6.30 (phenyl), 9.72, and 13.55 μ . This material appeared to be 94% one component by vpc.

Anal. Calcd for C₁₆H₂₂S: C, 77.99; H, 9.00; S, 13.01. Found: C, 77.9; H, 9.05; S, 13.2.

1-(trans,trans-7,12-Dimethyl-3,7,11-tridecatrienyl)-2-methyl-4-ethylenedioxy-1-cyclohexene (34). The coupling procedure of Biellman and Ducep⁸ was followed. To a solution of 3.65 g (14.8 mmol) of thioether **32** in 150 ml of tetrahydrofuran at -78° was slowly added 7.5 ml of 1.6 M butyllithium solution (12.0 mmol). The mixture was stirred for 1.5 hr; then 1.65 g (6.43 mmol) of crude chloride **31** in 30 ml of tetrahydrofuran was added. This mixture was allowed to stir at -78° for 0.5 hr and at room temperature overnight; then it was poured into brine overlaid with ether. The product, isolated by ether extraction,²⁰ was chromatographed on a 12 × 0.5 in. Florisil column. Starting thioether **32** was recovered from the pentane eluent. The alkylated thioether **33**, 2.24 g of a colorless, odorless oil, was eluted by 2% ethyl acetate-pentane.

To 2.18 g of the chromatographed alkylated thioether in 250 ml of ethylamine (freshly distilled from lithium wire) at -78° was added 0.59 g (84 mmol) of lithium wire. The reaction mixture became deep blue after 15 min and then was allowed to stir for an additional 15 min. Solid ammonium chloride was then added until the reaction mixture became colorless. Excess lithium was removed. An equal volume of pentane was added to the mixture, which was then allowed to warm to room temperature and stirred for 45 min. Brine was added and the product isolated by pentane extraction using a base wash.²⁰ Chromatography on a 12 × 0.5 in. Florisil column afforded on elution with 5% ethyl acetate-pentane, 1.28 g of the ketal **34** (59% yield from alcohol **27**): $\lambda_{\text{max}}^{\text{flim}}$ 6.00 (C=C), 8.00, 8.85, 9.15, and 9.40 (ketal), 10.35, 10.58, and 11.93 μ ; nmr 1.60 and 1.68 (two s, 14 H, CH₃C=C), 2.03 (s, 16 H, CH₂C=C), 2.59 (broad s, 0.6 H, impurity), 3.85 (s, 4 H, -OCH₂CH₂O-), 5.05 (t, 2 H, RCH=CR'R''), and 5.35 ppm (s, 2 H, RCH=CHR'). Vpc analysis gave a single peak. A small sample was distilled (short-path) at 130° (8–9 mm).

Anal. Calcd for C₂₄H₂₈O₂: C, 80.39; H, 10.68. Found: C, 80.1; H, 10.6.

4-(trans,trans-7,12-Dimethyl-3,7,11-tridecatrienyl)-3-methyl-2-cyclohexen-1-one (36). To 241 mg (0.673 mmol) of ketal **34** were added 50 ml of acetone containing 5 drops of concentrated hydrochloric acid and 20 ml of water. The mixture was then stirred under nitrogen at reflux for 70 min. After cooling, the reaction mixture was poured into sodium bicarbonate solution, and the product, $\lambda_{\text{max}}^{\text{flim}}$ 5.82 μ , was isolated by ether extraction using a base wash.²⁰

Isomerization of this crude β,γ -unsaturated ketone **35** to the α,β -unsaturated ketone **36** was accomplished by stirring at 55° for 10 min with 5 ml of sodium ethoxide in ethanol (prepared from 82 mg of sodium and 50 ml of ethanol). The mixture was poured into water overlaid with ether and neutralized with glacial acetic acid. The product, isolated by ether extraction using a base wash,²⁰

amounted to 204 mg. Chromatography on 25 g of Woelm neutral alumina, activity grade II (25% ether-pentane), gave 139 mg (66% yield) of α,β -unsaturated ketone **36**: $\lambda_{\text{max}}^{\text{flim}}$ 6.00 (α,β -unsaturated C=O), 6.19, 8.05, 8.40, and 10.34 μ ; nmr 5.05 (t, 2 H, RCH=CR'R''), 5.35 (s, 2 H, RCH=CHR'), and 5.69 ppm (s, 1 H, vinyl H α to C=O). This material appeared to be 96% one component by vpc.

Anal. Calcd for C₂₂H₃₄O: C, 84.01; H, 10.90. Found: C, 83.75; H, 10.9.

4-(trans,trans-7,12-Dimethyl-3,7,11-tridecatrienyl)-3-methyl-2-cyclohexen-1-ol (6). A solution of 79.6 mg (0.253 mmol) of ketone **36** in 5 ml of ether was added to a suspension of 79 mg (2.1 mmol) of lithium aluminum hydride in 20 ml of ether at 0°. The mixture was stirred for 15 min, then poured into brine, and extracted with ether.²⁰ Short-path distillation of the product at 150° (0.02 mm) afforded 48.7 mg (61% yield) of alcohol **6**, $\lambda_{\text{max}}^{\text{flim}}$ 3.02 (OH), 5.83 and 6.01 (C=C), 9.63, and 10.30 μ .

Anal. Calcd for C₂₂H₃₆O: C, 83.48; H, 11.47. Found: C, 83.6; H, 11.5.

Cyclization of Tetraenol 6. (a) With Trifluoroacetic Acid in Methylene Chloride at -78° (Isolation of Hydrocarbon A). To a solution of 27 mg (0.085 mmol) of crude alcohol **6** in 27 ml of dry methylene chloride at -78° was added 0.27 ml (410 mg, 3.6 mmol) of anhydrous trifluoroacetic acid. This was stirred for 4.5 hr, poured into a stirred solution of saturated sodium bicarbonate, and extracted with ether.²⁰

The product was added to a suspension of 286 mg (7.5 mmol) of lithium aluminum hydride in 10 ml of ether, and the mixture was stirred at room temperature for 10 min and at reflux for 1 hr. Then it was cooled and poured into brine, overlaid with ether. The product, isolated by ether extraction,²⁰ was chromatographed on 10 g of Florisil. Elution with 25 ml of pentane gave a hydrocarbon fraction which on tlc (pentane) showed a major component, R_f 0.8, and a minor component, R_f 0.9. Further elution of the column with ether afforded a mixture of hydrocarbon and alcohol components. Preparative tlc (25% ether-pentane) afforded a hydrocarbon corresponding to the R_f 0.8 component of the pentane eluent. This material was 95% one component as indicated by vpc. The nmr spectrum exhibited a singlet at δ 5.55 ppm, a series of unresolved peaks from 2.0 to 1.2, of which a singlet at 1.25 was prominent, a sharp singlet at 0.95, and a distorted but sharp triplet, centered at 0.85 ($J = 7$ Hz). This product was designated hydrocarbon A.

(b) With Stannic Chloride in Methylene Chloride at -78°. To a solution of 8.9 mg (0.028 mmol) of distilled alcohol **6** in 7 ml of dry methylene chloride at -78° was added 4.8 mg (0.019 mmol) of stannic chloride in 0.22 ml of methylene chloride. The mixture was stirred at -78° for 5 min and then 0.1 ml (0.098 g, 1.2 mmol) of pyridine was added. The mixture was poured into 0.1 N hydrochloric acid, which was extracted with two portions of ether. The ether solutions were combined, extracted with 0.1 N hydrochloric acid and two portions of sodium bicarbonate, dried over magnesium sulfate, and concentrated, leaving 9.3 mg of a pale, yellow oil. This material was chromatographed on a 5 × 0.25 in. Florisil column. Elution with 50 ml of pentane afforded 3.8 mg (46%) of a hydrocarbon fraction, which on tlc (pentane) appeared to be 80% one component. The nmr spectrum of this material was identical with that of hydrocarbon A (see above). Further elution of the column with 50 ml of ether afforded 2 mg (20%) of an alcoholic fraction. Tlc of this product (50% ether-pentane) showed it to be a mixture of 6–8 components in approximately equal amounts; hence it was not investigated further.

(c) With Stannic Chloride in Nitromethane at -23°. To a solution of 6.0 mg (0.019 mmol) of crude alcohol **6** in 5 ml of nitromethane at -23° was added 7.8 mg (0.030 mmol) of stannic chloride in 0.35 ml of nitromethane. After 5 min, 0.1 ml (0.098 g, 1.2 mmol) of pyridine was added. Isolation and chromatography of the product were performed exactly as described above under part (b). The behavior of this product mixture on tlc and its nmr spectrum were similar to those of the product mixture obtained with stannic chloride in methylene chloride at -78°.

(d) With Trifluoroacetic Acid and Propanethiol in Methylene Chloride. To a solution of 10 mg (0.031 mmol) of distilled tetraenol **6** and 0.17 ml (140 mg, 1.86 mmol) of propanethiol in 7.8 ml of methylene chloride at -78° was added 0.08 ml (120 mg, 1.1 mmol) of trifluoroacetic acid. The mixture was stirred at -78° for 1.5 hr and at -30° for 0.5 hr. Then 0.5 ml of pyridine was added, and the product isolated as described under part (b). Short-path distillation at 150° (0.03 mm) gave material, the vpc of which indicated two long retention time components in approximately equal

amounts. The nmr spectrum of this material suggested that it was a mixture of two epimeric thioethers (formula **6** with $\text{CH}_2\text{CH}_2\text{-CH}_2\text{S}$ in place of HO): nmr 0.98 (t, 3 H, CH_3 of propyl), 2.44 (t, 2 H, $-\text{CH}_2\text{S}-$), and 3.20 ppm (multiplet, 1 H, $\text{SCHC}=\text{C}$).

(e) **On a Preparative Scale, with Trifluoroacetic Acid in Methylene Chloride (Preparation and Structure Determination of Hydrocarbon A).** To a solution of 38.2 mg (0.121 mmol) of distilled alcohol **6** in 30 ml of methylene chloride at -78° was slowly added 0.30 ml (460 mg, 4.0 mmol) of trifluoroacetic acid. The mixture was stirred at -78° for 4 hr and then poured into a stirred solution of sodium bicarbonate and extracted with ether using a base wash.²⁰ The ir of the product, $\lambda_{\text{max}}^{\text{film}}$ 5.63 (trifluoroacetate $\text{C}=\text{O}$), 8.22, and 8.62 μ (COC), indicated that no starting alcohol remained. The residue was dissolved in 6 ml of ether and added to a suspension of 297 mg (7.8 mmol) of lithium aluminum hydride in 10 ml of anhydrous ether. This mixture was stirred at room temperature for 10 min and at reflux for 1 hr. Then it was cooled and poured slowly into brine; then extracted with ether²⁰ to give 38.7 mg of a colorless oil. Chromatography on 25 g of Woelm neutral alumina, activity grade I, afforded, on elution with 200 ml of pentane, 12.9 mg (36% yield) of hydrocarbon A (see below). Elution with 500 ml of ether afforded 4.0 mg of what appeared by tlc to be a mixture of hydrocarbon and alcohol. This material was not investigated further. Finally, elution with 250 ml of 20% methanol-methylene chloride gave 21.4 mg (56% yield) of alcoholic material. On tlc (50% ether-pentane), this material showed three spots corresponding to minor components and a lower R_f spot corresponding to a major component. Chromatography of the alcoholic mixture on a 3×0.5 in. column of Merck acid-washed alumina afforded material, eluted by ether, corresponding to the low R_f , major component of the mixture. The ir and nmr spectra of this compound were identical with those of the starting alcohol **6**.

Short-path distillation of hydrocarbon A at 120° (0.02 mm) afforded material which appeared homogeneous by vpc, $\lambda_{\text{max}}^{\text{film}}$ 5.95 and 6.10 (very weak, $\text{C}=\text{C}$) and 9.85 μ (weak). The 60-MHz nmr spectrum of this sample showed a two-proton singlet at δ 5.55, a series of unresolved peaks from 2.0 to 1.2, a sharp singlet at 0.96, and an apparent triplet centered at 0.78 ppm ($J = 7$ Hz). The 100-MHz nmr spectrum showed this "triplet" to be two overlapping doublets, centered at δ 0.84 and 0.73 ppm ($J = 7$ Hz). In addition, the singlet at δ 0.96 ppm was seen to be overlapping singlets at 0.97 and 0.95. The mass spectrum of this material showed a molecular ion at m/e 298 (3%), a base peak at 255, and one other major peak at 147 (46%). A metastable peak at m/e 85 indicated that the 147 peak is derived from the 255 peak (calcd, 84.7).

A quantitative hydrogenation of hydrocarbon A was performed by Mr. E. Meier, using a microhydrogenation apparatus. A 6.380-mg sample (0.0214 mmol) of hydrocarbon A, hydrogenated over reduced platinum oxide in ethanol at room temperature and atmospheric pressure, absorbed 1.08 mol equiv of hydrogen (corrected to STP) to afford 4.6 mg of material which appeared to be homogeneous by vpc. The 100-MHz nmr spectrum of this product showed a series of unresolved peaks from δ 2.0 to 1.2 ppm, sharp singlets at 0.95 and 0.88, and two doublets centered at 0.84 ($J = 7$ Hz) and 0.73 ppm ($J = 7$ Hz). The mass spectrum showed a molecular ion peak at m/e 300 (2%), a base peak at 257, and peaks at 285 (1%), 258 (21%), 161 (15%), 149 (4%), and 147 (16%). Metastable peaks at 101 and 84 indicated that the peaks at 161 and 147 were derived from the 257 peak (calcd, 100.9 and 84.1).

Quantitative microhydrogenation of a comparable sample of the dihydro product (obtained from cyclization of tetraenol **6** with stannic chloride at -78° as described under part (f) followed by hydrogenation as above) over reduced platinum oxide in acetic acid was performed by Mr. E. Meier. Thus a 3.608-mg sample (0.012 mmol) of dihydro A, hydrogenated at room temperature and atmospheric pressure, took up 0.222 ml (0.826 mol equiv) of hydrogen (corrected to STP). The mixture was poured into sodium bicarbonate solution, and the product was isolated by ether extraction using a base wash.²⁰ The mass spectrum showed a molecular ion at m/e 302, a base peak at 84, and sizable peaks at 259 (47%), 258 (32%), 257 (42%), 163 (35%), 149 (60%), 109 (77%), and 95 (85%).

(f) **On a Preparative Scale with Stannic Chloride in Methylene**

Chloride. To a solution of 73.1 mg (0.231 mmol) of distilled alcohol **6** in 65 ml of methylene chloride at -78° was added 38 mg (0.15 mmol) of stannic chloride in 0.7 ml of methylene chloride. The mixture was stirred at -78° for 1 hr, then poured into a stirred solution of sodium bicarbonate, and the product was isolated by ether extraction.²⁰ Chromatography on 25 g of Woelm neutral alumina, activity grade I, afforded, on elution with 35 ml of pentane, a hydrocarbon fraction, which on tlc (pentane) showed one spot, R_f 0.9. Further elution with two 35-ml portions of pentane afforded a fraction which showed two spots, R_f 0.8 and 0.9, and a later fraction which showed only the spot with R_f 0.8. Chromatography of the former fraction on 37 g of Woelm neutral alumina, activity grade I, efficiently separated the two components. When like fractions were combined, 6.2 mg (8% yield) of the less polar compound and 23.2 mg (34% yield) of the component with R_f 0.8 were obtained. The nmr spectrum of the former showed signals at δ 1.25 and 0.88 ppm. This material was not investigated further. The more polar hydrocarbon had nmr and mass spectra identical with those of hydrocarbon A.

Cyclization of Tetraenol 5 with Stannic Chloride in Methylene Chloride. A 14.0-mg sample (0.44 mmol) of crude alcohol **5** was dissolved in 10 ml of dry methylene chloride and the solution was placed under nitrogen and cooled to -78° . A solution of 42 mg (0.16 mmol) of stannic chloride in 0.56 ml of dry methylene chloride was then added. After stirring at -78° for 1 hr, 0.1 ml (0.098 g, 1.1 mmol) of pyridine was added, then the mixture was poured into 6 ml of 1 *N*-hydrochloric acid and extracted with methylene chloride using a base wash.²⁰ The residue was chromatographed on 0.76 g of Florisil. Elution with 10 ml of pentane afforded 4.5 mg (33% yield) of a colorless oil, which, on tlc (pentane), showed a major component, R_f 0.6, and a minor component, R_f 0.75. The ir spectrum of this material showed no absorption in the hydroxyl region, and the 60-MHz nmr spectrum was similar to that of hydrocarbon A. Further elution of the Florisil column with 10 ml of ether afforded 3.9 mg of a colorless oil, which, on tlc (15% ether-pentane), showed a multitude of components. This material was not investigated further.

20-Methyl-5 β -pregnan-20-ol (41). This experiment was performed by Douglas R. Morton. A 0.45-ml sample of a 3.0 *M* solution of methylmagnesium bromide in ether was added to a solution of 0.2025 g of 5 β -pregnan-20-one,¹⁹ mp 114-115 $^\circ$, in 18 ml of ether (argon atmosphere). The mixture was stirred at room temperature for 15 min; then excess aqueous ammonium chloride was added slowly, followed by water. The product, isolated by ether extraction,²⁰ amounted to 0.213 g of colorless crystalline carbinol. Two recrystallizations from pentane-ether (at -17°) gave colorless needles: mp 83-84 $^\circ$; nmr 0.80 (s, 3 H, C-18 methyl), 0.90 (s, 3 H, C-19 methyl), 1.17 (s, 3 H, CH_3CO), and 1.27 ppm (s, 3 H, CH_3CO). Anal. Calcd for $\text{C}_{22}\text{H}_{38}\text{O}$: C, 82.95; H, 12.02. Found: C, 82.9; H, 12.3.

17 β -Methyl-17 α -isopropyl-18-nor-5 β -androst-13-ene (42).²⁶ This experiment was performed by Douglas R. Morton. To a stirred solution of 0.033 g of the carbinol **41**, mp 83-84 $^\circ$, in 15 ml of methylene chloride (nitrogen atmosphere) was slowly added 0.18 ml of stannic chloride; then the mixture was allowed to warm to -30° over a period of 30 min. After an additional 15 min at -30° the mixture was treated with 5 ml of saturated aqueous sodium bicarbonate. Dilute hydrochloric acid was added and the mixture extracted with ether.²⁰ The colorless oily product amounted to 0.030 g (97% yield) which appeared to be >98% one component by vpc. Short-path distillation at 150° (0.05 mm) afforded an analytical sample: nmr 0.75 (d, 3 H, $J = 6$ Hz, isopropyl CH_3), 0.85 (d, 3 H, $J = 6$ Hz, isopropyl CH_3), 0.89 (s, 3 H, C-19 methyl), and 0.94 ppm (s, 3 H, 17 β methyl).

Anal. Calcd for $\text{C}_{22}\text{H}_{36}$: H, 87.93; H, 12.07. Found: C, 88.1; H, 11.8.

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(26) Tentative structure.