calcium hydride) was heated at reflux for 2 hr. Water was added and the product, which was isolated by ether extraction,[18] was crystallized from pentane to give colorless crystals, mp 122–142°. This material showed two major spots on tlc (R_f 0.21, 0.25, 4:1 cyclohexane–ethyl acetate) but no spot corresponding to the ketone (R_f 0.4).

B. By Reduction with Aluminum Isopropoxide. A solution of 202 mg of purified (dissolved in hot benzene, filtered, and concentrated) aluminum isopropoxide, 15 mg of ketone **35**, and 2 ml of isopropyl alcohol (distilled from calcium hydride) was heated at reflux under nitrogen for 3 hr. An additional 2 ml of alcohol was added, and 2 ml of solvent was distilled. The solution was heated at reflux for another 30 min and cooled. Dilute hydrochloric acid was added and the product was isolated by ether extraction.[18] Repeated recrystallization of the residue from pentane afforded colorless crystals, mp 184–186°, which showed two spots on tlc corresponding to the two major spots produced by the product from the sodium borohydride reaction.

The two mixtures of alcohols were combined and chromatographed on Florisil yielding 24.3 mg of colorless crystals which produced two major spots on tlc. A portion of the material was submitted to preparative thin layer chromatography (10% ethyl acetate in cyclohexane, continuous elution for 2.5 hr). The faster moving band yielded 5.3 mg of colorless crystals: mp 188–189°; $\lambda_{max}^{CHCl_3}$ 2.95 μ (OH); nmr ($CDCl_3$) 0.88 (s, CH_3C), 1.18 (s, CH_3C), and 4.15 ppm (m, $W_{h/2}$ = 10 Hz, equatorial proton on carbon bearing oxygen); mass spectrum, *m/e* 290 (calcd $C_{20}H_{34}O$, 290).

The slower moving band yielded 4.9 mg of alcohol *d*-**22** as colorless crystals, mp 148–150°, which appeared to be homogeneous by tlc. Recrystallization from pentane produced pure material: mp 149.5–150°; $\lambda_{max}^{CHCl_3}$ 2.95 μ (OH); nmr [HA-100, $CDCl_3$) 0.89 (s, CH_3C), 0.97 (s, CH_3C), and 3.9 ppm (m, $W_{h/2}$ = 20 Hz, axial hydrogen on carbon bearing oygen); mass spectrum, *m/e* 290 (calcd for $C_{20}H_{34}O$, 290).

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Cyclization of 1-Methyl-6-(*trans,trans*-7,11-dimethyl-3,7,11-dodecatrienyl)-2-cyclohexen-1-ol[1]

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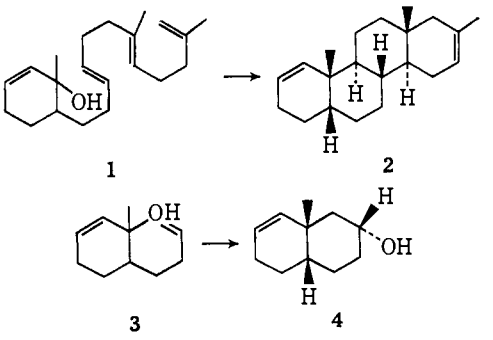
Contribution from the Department of Chemistry, Stanford University, Stanford, California 94305. *Received October 8, 1973*

Abstract: The tetraenol **1** has been synthesized by addition of methyllithium to the α,β-unsaturated ketone **14**, derived in turn from the β,γ-isomer **13**, which has been produced by two different convergent pathways. Scheme I involved alkylation of *tert*-butyl acetoacetate with 4-iodo-1-butyne to give **7** which, on Michael addition of acrolein, was converted into **8**. This substance, on treatment with acetic and hydrochloric acid, underwent ester cleavage, decarboxylation, and cyclization affording the acetylenic ketone **9**, which was ketalized (to give **10**) and then, as its lithium salt, alkylated with the previously known bromodiene **6**. The product **11**, on reduction with lithium in ammonia (to give **12**), followed by acid hydrolysis, afforded the tetraenone **13**. Alternatively, the butynylanisole **17**, prepared by coupling of *o*-methoxybenzyl bromide with propargylmagnesium bromide, was alkylated with the bromodiene **6** to give **18**. Birch reduction of **18**, followed by hydrolysis with oxalic acid, also afforded the tetraenone **13**. Treatment of the tetraenol **1** with stannic chloride in nitroethane at −78° proceeded stereoselectively to give the tetracyclic diene **2** in 60% yield. The structure and configuration (cis,anti,trans,anti,trans) of this product were proved by hydrogenation to give two crystalline epimeric saturated hydrocarbons *dl*-**20a** and *dl*-**20b** which were separated and compared with authentic *d*-**20a** and *d*-**20b** prepared as follows. Methyllithium was added to the previously known 5β-*D*-homoandrostan-17-one, and the resulting carbinol dehydrated, then hydrogenated to give the mixture of *d*-**20a** and *d*-**20b** which was separated into its components. Cyclization of **1** with trifluoroacetic acid in dichloromethane also gave **2** in 20% yield. When deuteriotrifluoroacetic acid was used as the catalyst, no deuterium was incorporated in the product **1**, thus showing that the mechanism of this cyclization does not involve deprotonation and reprotonation of carbonium ion intermediates.

As part of a continuing program to investigate stereospecific, nonenzymic cyclizations of polyolefins,[2] we wish to report the synthesis of monocyclic tetraenol **1** and its efficient transformation into the tetracyclic diene **2** under mild, acidic conditions.

As a cyclization substrate the tetraenol **1** incorporates two structural features of particular significance: the tertiary allylic cyclohexenol system which promised to be more readily available than the previously used isomeric system,[3,4] and the terminal isopropenyl group.



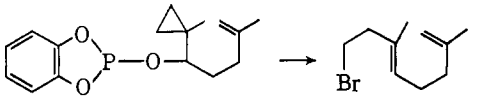
In comparison with the less nucleophilic vinyl group employed in several previous studies,[1] the terminal isopropenyl group was expected to enhance formation of the final ring without deprotonation or nucleophilic

(1) This represents part of a general study of nonenzymic, biogenetic like olefinic cyclizations. For the previous paper of this series, see K. E. Harding, E. J. Leopold, A. M. Hudrlik, and W. S. Johnson, *J. Amer. Chem. Soc.*, **96**, 2540 (1974).
(2) W. S. Johnson, *Accounts Chem. Res.*, **1**, 1 (1968).
(3) W. S. Johnson, P. J. Neustaedter, and K. K. Schmiegel, *J. Amer. Chem. Soc.*, **87**, 5148 (1965).
(4) W. S. Johnson and K. E. Harding, *J. Org. Chem.*, **32**, 478 (1967).

interception of the tricyclic carbonium ion intermediate.

The suitability of the tertiary allylic alcohol system as a function for initiating olefin cyclization under mild conditions was first established in a model series. Thus the dienol **3** was readily prepared by addition of methyllithium to 6-(3-butenyl)-2-cyclohexen-1-one.[5] The resulting mixture of diastereomeric alcohols was treated with anhydrous formic acid, and after formate ester cleavage, the known *trans,syn*-octalol **4**[3,4] was obtained in nearly quantitative yield.

Synthesis of the tetraenol **1** was accomplished by two routes, which differed primarily in the method employed for elaborating the cyclohexenol moiety. Both routes involved, at the stage of convergency, the alkylation of a substituted acetylene (**10** or **17**) with the known homoallylic bromide **6** which was produced by the previously described cyclopropylcarbinol route,[6] employing modifications developed in this laboratory by B. Staskun. Thus the phosphite ester **5**, obtained from the corresponding alcohol[6] by reaction with *o*-phenylene phosphorochloridite,[7] underwent rearrangement with zinc bromide in ether to give the trans-bromodiene **6**, contaminated with 4% of the cis isomer. Migration of the terminal double bond which sometimes occurs in the synthesis of the bromodiene from the corresponding cyclopropylcarbinyl bromide[6] could not be detected in this product.



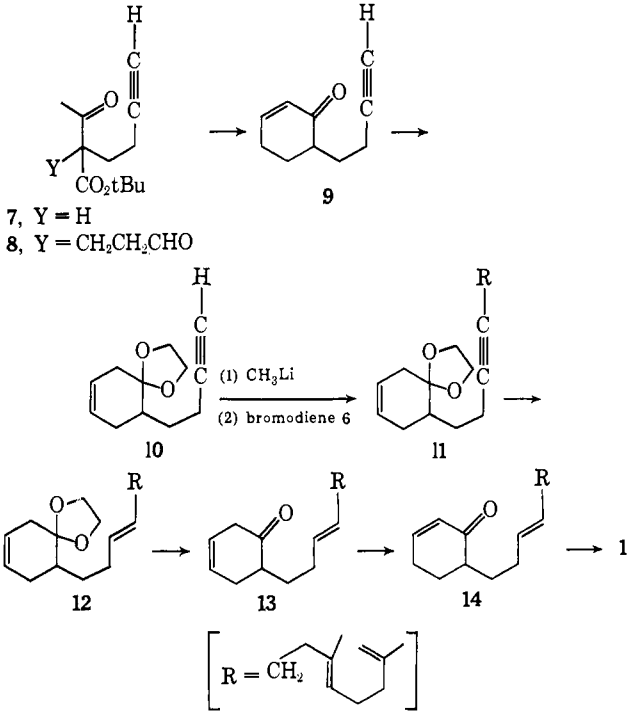
5 6

The preferred route to the tetraenol **1** is outlined in Scheme I.[8] Ketoester **7** was obtained by alkylation of the sodium salt of *tert*-butyl acetoacetate with 4-iodo-1-butyne in acetonitrile. Base-catalyzed condensation of the ketoester with acrolein at −40° furnished the Michael adduct **8** which was dissolved directly in a mixture of acetic and hydrochloric acids to effect aldol cyclization, ester cleavage, and decarboxylation in a single step. In this manner, 6-(3-butynyl)-2-cyclohexen-1-one (**9**) was obtained in 62% overall yield from ketoester **7**. Protection of the enone function by conventional ketalization with ethylene glycol afforded a mixture of the desired ketal **10** and the hydroxy ketal **15**. Distillation of the mixture from a trace of 2-naphthalenesulfonic acid effected elimination of the hydroxyethoxy side chain from **15**. A small amount of the Δ^2 isomer was removed by chromatography, affording the ketal **10** in 83% yield.

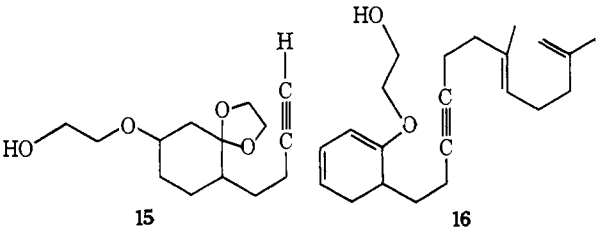
Alkylation of the ketal **10** as its lithium acetylide with the bromodiene **6** provided a 46% yield of trienyne **11**, accompanied by a small amount of what appeared to be the alcohol **16**. Reduction of the disubstituted acetylene **11** to the trans-olefin **12** by sodium in liquid ammonia was complicated by ring opening of **4** to give **16** followed by reduction of the 1,3-diene unit and hydrogenolysis of the resulting allylic ether. This undesired

(5) W. S. Johnson, W. H. Lunn, and K. Fitzi, *J. Amer. Chem. Soc.*, **86**, 1972 (1964).
(6) S. F. Brady, M. A. Ilton, and W. S. Johnson, *J. Amer. Chem. Soc.*, **90**, 2882 (1968).
(7) *Cf.* E. J. Corey and J. E. Anderson, *J. Org. Chem.*, **32**, 4160 (1967).
(8) This is basically an approach that was suggested independently by K. E. Harding.

Scheme I

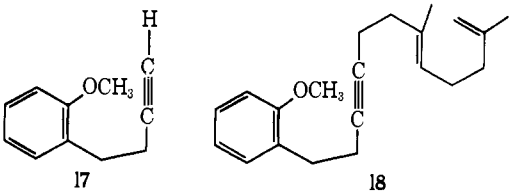


sequence of reactions was suppressed when the reduction was carried out with lithium and *tert*-butyl alcohol. In order to minimize reduction of the sensitive terminal isopropylidene group, the reaction was carried out at −78°. Mild, acid hydrolysis of the ethylene ketal **12** gave the β,γ-unsaturated ketone **13**, which was isomerized to the α,β-unsaturated isomer **14** by treatment with diazabicyclo[2.2.2]octane (DABCO) in methanol. Addition of ketone **14** to a solution of methyllithium in ether afforded the tetraenol **1**.



15 16

The alternative synthesis of the tetraenol **1** was accomplished as follows. Alkylation of propargylmagnesium bromide with 2-methoxybenzyl bromide afforded 2-(3-butynyl)anisole (**17**) contaminated by a small amount of the corresponding allene. The lithium acetylide of **17** was alkylated with the bromodiene **6** in hexamethylphosphoric triamide to give the dienyne **18**

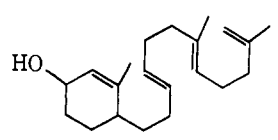


17 18

in 26% yield. Reduction of the dienyne by lithium and ethanol in ammonia at −78°, followed by hydrolysis of the resulting enol ether with oxalic acid, afforded the tetraenone **13**. Conversion to the α,β-unsaturated ketone **14** was accomplished through a sequence de-

vised by Stork and White,[9] involving formation of the β-piperidino adduct, methylation to give the easily purified quaternary ammonium salt, and finally elimination with pyridine. The overall yield of trienone **14** from dienyne **18** was 33%. The tetraenol **1** was obtained as described above by reaction of **14** with methyllithium.

Cyclization Studies. Reaction of the tetraenol **1** with stannic chloride or trifluoroacetic acid in a nonnucleophilic solvent gave a tetracyclic diene as the dominant hydrocarbon product. Thus a solution of stannic chloride in nitroethane[10] at −78° (2.5 hr) transformed the tetraenol to the diene in 60% yield. The remainder of the product consisted of an unresolvable mixture of unsaturated hydrocarbons (about 5%) and a complex mixture of more polar compounds. The minor hydrocarbon fraction, on hydrogenation and mass spectrometric analysis, appeared to contain material with a maximum of three olefinic linkages per molecule, presumably tricyclic material. The production of tricyclic trienes in the cyclization of a similar substrate has been observed.[1] Cyclization of the tetraenol **1** with trifluoroacetic acid in pentane at −75° to −16° over a period of 110 min (conditions not optimized for complete cyclization) produced a mixture of hydrocarbons and esters. After ester cleavage, the aforementioned tetracyclic diene was isolated by chromatography in 20% yield as a crystalline solid. Hydrocarbon impurities, apparently the same as those described above, accounted for 1.5% of the hydrocarbon fraction. The balance of the reaction product consisted of a mixture of polar compounds, of which the product of oxotropic rearrangement, tetraenol **19**, was the dominant component.



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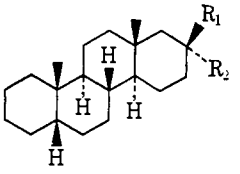

20a, $R_1 = CH_3$; $R_2 = H$
b, $R_1 = H$; $R_2 = CH_3$

Deprotonation and reprotonation of carbonium ion intermediates were shown *not* to intervene significantly in the formation of tetracyclic product in deuteriotrifluoroacetic acid–dichloromethane. No deuterium incorporation into the hydrocarbon was detected mass spectrometrically. This observation is similar to that made in another series.[1]

The structure of the tetracyclic hydrocarbon was shown to be **2** by its spectral properties and by comparison of its hydrogenation product with authentic material derived from natural sources by unambiguous synthesis (see below). The nmr spectrum exhibited sharp singlets at δ 0.77 and 0.98 ppm. The value of 0.77 is consistent with an angular methyl group (C-18) on a trans ring junction,[11] whereas the singlet at 0.98 corresponds to an angular methyl group (C-19) on a cis ring junction[11] shifted downfield by unsaturation at C-1. The magnitude of this shift is consistent with predictions based upon steroidal examples. The small diamagnetic shift of the C-18 methyl resonance relative to that of authentic 17α-methyl-5β-*D*-homoandrostane suggests that C-18 is well above the plane of the D-ring olefin. Models suggest that this situation exists for the Δ^{16} but not for the $\Delta^{17,17a}$ isomer. By analogy the introduction of Δ^2 unsaturation in the A ring of 5α steroids has no detectable effect upon the C-19 proton resonance, whereas Δ^1 unsaturation produces a paramagnetic shift of 0.05 ppm.[11]

Hydrogenation of the tetracyclic diene afforded two saturated hydrocarbons which were separated by preparative gas chromatography. The major product (68%), mp 64–65.5°, was *dl*-17β-methyl-5β-*D*-homoandrostane (*dl*-**20a**), and the minor product, mp 60–61.5°, (30%) was its C-17 epimer (*dl*-**20b**). The compounds were identical by chromatographic, nmr, and ir analyses with the two crystalline hydrocarbons, *d*-**20a** and *d*-**20b**, produced by hydrogenation of authentic Δ^{16} and Δ^{17}-17-methyl-5β-*D*-homoandrostene. This mixture of methylandrostenes was obtained by reaction of methyllithium with 5β-*D*-homoandrostan-17-one,[1] followed by dehydration with phosphoryl chloride in pyridine.

Experimental Section[12]

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-stage microscope.

Nmr spectra were determined under the supervision of Dr. L. J. Durham. Chemical shifts are reported as δ values in ppm relative to tetramethylsilane = 0. Mass spectra were determined on an A. E. I. MS-9 or CEC 21-103C spectrometer under the supervision of Dr. A. M. Duffield. Relative peak intensities were corrected for ^{13}C natural abundance.

Unless otherwise indicated, short-path (two-bulb) distillations were carried out at <150° (<0.02 mm) in a Kugelrohr apparatus.

Vapor phase chromatographic (vpc) analyses of unstable or high molecular weight compounds were performed on a Hewlett-Packard Model 402 instrument equipped with glass columns and using helium as the carrier gas. Preparative vpc separations were performed on the same instruments equipped with a 6 ft. × 8 mm glass column packed with 10% SE-30 on 60–80 mesh support. The effluent splitter and sample collection assemblies were entirely glass and Teflon. Dry-column chromatography was performed according to the procedure of Loev and Snader[13] using Woelm activity grade II neutral alumina containing 0.5% Woelm Fluorescent Indicator packed in a column of nylon tubing.

1-Methyl-6-(3-butenyl)-2-cyclohexen-1-ol (3). A solution of 0.186 g of 6-(3-butenyl)-2-cyclohexen-1-one[5] containing 29% of 6-butyl-2-cyclohexen-1-one in 2 ml of dry ether was treated with 2.3 mmol of methyllithium in 2 ml of ether. The solution was stirred for 5 min and discharged into a flask containing crushed ice. The product, which was isolated by ether extraction,[12] was distilled (short-path) at 50–60° (1 mm) to give 0.166 g of alcohol **3** as a colorless oil: λ_{max}^{film} 2.94 (OH), 6.06 (C=C), 10.05, and 10.93 μ (terminal vinyl); nmr (CDl_3) 1.14, 1.27 (diastereomeric methyl singlets), 1.5 (s, 1 H, OH), 4.8–5.2 (m, C=CH_2), and 5.7 ppm (m, vinyl CH= and cyclohexene –CH=CH–).

***cis*-9-Methyl-7-*syn*-2-octalol (4).** A 0.0436-g sample of alcohol **3**, redistilled at 50–80° (2.5 mm) immediately before use, was

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

(10) 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).

(11) R. F. Zürcher, *Helv. Chim. Acta*, **46**, 2054 (1963).

(12) 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.

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

stirred with 5 ml of anhydrous formic acid[14] at 23° for 11 min under an atmosphere of nitrogen. Then 2 ml of water was added and the resulting suspension was pipetted slowly into a cold solution of 5.4 g of sodium hydroxide in 20 ml of water. The mixture of formate esters, which was isolated by ether extraction,[12] was stirred with 75 mg of lithium aluminum hydride in 20 ml of refluxing ether for 1 hr. This solution was poured into 10% hydrochloric acid and the product isolated by ether extraction.[12] Quantitative vpc analysis of this material on a Carbowax 20M column at 200°, using 2-(3-butenyl)anisole as an internal standard and authentic *cis*-9-methyl-7-*syn*-2-octalol[15] for peak enhancement, indicated an absolute yield of octalol **4** amounting to 0.0333 g (76%, 100% corrected for impurity of the starting alcohol).

tert-**Butyl 2-Acetyl-5-hexynoate (7).** *tert*-Butyl acetoacetate was added to 1.15 equiv of sodium hydride in tetrahydrofuran (13 ml/g of ester). The resulting solution was filtered with rigorous exclusion of air and concentrated. The dry sodium enolate, a white powder, was relatively stable and could be weighed in air.

A solution of the enolate (113.5 g, 0.630 mol) in 1500 ml of acetonitrile (freshly distilled from calcium hydride and degassed) was heated to 70° under nitrogen, then 4-iodo-1-butyne[16] (100 g, 0.555 mol) was added slowly. The mixture was heated at reflux for 15 hr. The solvent was evaporated at reduced pressure; then the residue was diluted with water and made slightly acidic with dilute hydrochloric acid. The product was isolated by ether extraction using a base wash.[12] Three consecutive distillations of the residue through a 2-ft spinning band column gave 55.3 g (47.4%) of the acetylenic ketoester **7**, bp 62–63° (0.02 mm), homogeneous by vpc analysis: λ_{max}^{film} 3.03 (C≡CH), 4.50 (C≡C), 5.75 (ester C=O), and 5.85 μ (ketone C=O); nmr ($CDCl_3$) 1.45 (s, 9 H, *tert*-butyl), 2.18 (s, methyl ketone), and 3.50 ppm (t, J = 6 Hz, 1 H, C-2); mass spectrum (70 eV) *m/e* 210, M^+ (less than 1%), 154, M − 56 (isobutylene).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.3; H, 8.65.

tert-**Butyl 2-Acetyl-2-(3-oxopropyl)-5-hexynoate (8).** A degassed solution of the keto ester **7** (45.72 g, 0.218 mol) in 58 ml of methanol (freshly distilled from magnesium methoxide) was cooled to −40° under an atmosphere of nitrogen, and 5.6×10^{-4} mol of sodium methoxide in 5.4 ml of methanol was added. Acrolein (18.5 ml, 0.278 mol, freshly redistilled and containing about 1 mg of hydroquinone per ml) was added dropwise by motor-driven syringe at a rate of 1.68 ml/hr to the stirred, cold solution. After a total of 14 hr at −40 to −45°, the solution was warmed to 0° for 0.5 hr. The reaction was terminated by adding 7.2×10^{-4} mol of acetic acid in 6 ml of ether, then pouring the reaction mixture into water containing a little sodium bicarbonate and overlaid with ether. The ether phase was washed with brine, dried over magnesium sulfate, and evaporated at reduced pressure (0.3 mm) to give the crude aldehyde **8** as a viscous, colorless liquid which was used in the succeeding reaction without purification.

Material prepared in another run according to this procedure was purified by chromatography on Florisil followed by short-path distillation to give a colorless oil: $n^{20}D$ 1.4692; ir (film) 2.9 (w, OH), 3.02 (C≡CH), 3.65 (O=CH), 4.67 (C≡C), and 5.75 μ (C=O); nmr (CCl_4) 1.45 (s, *tert*-butyl), 2.10 (s, methyl ketone), 4.8–5.8 (m, 0.6 H, olefinic proton in a cyclic hemiketal or hemiacetal), and 9.7 ppm (m, 0.7 H, O=CH); mass spectrum, *m/e* 210, M − 56 (isobutylene).

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: 67.4; H, 8.3.

The spectra indicate that the sample contained about 70% of the aldehyde and 30% of a cyclic enol ether tautomer.

6-(3-Butynyl)-2-cyclohexen-1-one (9). A solution of 66.2 g of the crude aldehyde **8** in 500 ml of glacial acetic acid, 5 ml of water, and 50 ml of concentrated hydrochloric acid was degassed under vacuum and stirred under nitrogen at room temperature for 7 hr. The solvent was evaporated at reduced pressure over a period of 2 hr, the temperature of the mixture not being allowed to exceed 35°. The residual brown oil was dissolved in ether, extracted twice with saturated brine, dried over anhydrous magnesium sulfate, and concentrated. Distillation through a short Vigreux column gave 6-(3-butynyl)-2-cyclohexen-1-one, 20.1 g (62% yield based on the keto ester **7**), bp 68–71° (0.2 mm). Analysis by vpc showed a major component as a peak with retention time 4 min and a contaminant amounting to about 3% of the mixture at 3 min.

Comparable material from another experiment had the following properties: λ_{max}^{film} 3.05 (C≡CH), 3.30 (C=CH), 4.72 (C≡C), and 5.99 μ (conjugted C=O); nmr (CCl_4) 5.86 (d, J = 10 Hz, of triplets, J = 2 Hz, 1 H, cyclohexenone C-2), 6.6–7.1 ppm (m, 1 H, cyclohexenone C-3); mass spectrum (70 eV) *m/e* 148, M^+.

Anal. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 80.8; H, 8.25.

1-Ethylenedioxy-6-(3-butynyl)-3-cyclohexene (10). A mixture of 2.90 g (19.6 mmol) of ketone **9**, 3 ml of ethylene glycol (54 mmol), and 30 mg of *p*-toluenesulfonic acid monohydrate in benzene was stirred at reflux for 20 hr under nitrogen with azeotropic removal of water through a Dean-Stark trap. The mixture was poured into saturated brine overlaid with ether, and the product was isolated by ether extraction.[12] A trace (about 0.5 mg) of 2-naphthalenesulfonic acid dissolved in a small volume of ether was added and the residue was distilled at 4 to 3.5 mm, 130 to 145°, to give a two-phased distillate. This material was poured into saturated sodium bicarbonate solution overlaid with pentane. The product, which was isolated by pentane extraction,[12] was chromatographed on 80 g of Florisil. Elution with 5% ether in pentane afforded a total of 3.13 g (83% yield) of the β,γ-unsaturated ketal contaminated by a trace of the α,β-unsaturated ketal. Further elution gave 0.26 g of a mixture of the two ketals which was not used in subsequent reactions. The first 1.54 g of ketal eluted from the column was distilled (short-path) at 75° (0.04 mm), $n^{26}D$ 1.4993: λ_{max}^{film} 3.05 (C≡CH), 3.30 (C=CH), 4.76 (C≡C), and 6.02 μ (C=C); nmr (CCl_4) 3.90 (s, 4 H, ethylenedioxy), and 5.50 ppm (m, 2 H, CH=CH); mass spectrum (70 eV) *m/e* 192 (1%, M^+), 138 (27%, retro Diels–Alder elimination of butadiene), 99 (100%, loss of $\cdot CH_2C{\equiv}CH$ from *m/e* 138, metastable signal at *m/e* 71).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.1; H, 8.35.

trans-**8-Bromo-2,6-dimethyl-1,5-octadiene (6).** A solution of 1-methylcyclopropyl-3-methyl-3-butenylcarbinol[6] (4.0 g, 26 mmol) in 20 ml of dry ether was added rapidly with stirring to a solution of *o*-phenylene phosphorochloridite[17] (5.0 g, 29 mmol) and pyridine (5.0 ml) in 80 ml of dry ether at 0°. The resulting suspension was stirred for 2 hr at room temperature. Then it was extracted with water, 5% aqueous lactic acid until the washings were acidic, 5% sodium bicarbonate solution, and brine. The ether solution was dried over magnesium sulfate and concentrated to give the crude phosphite ester **5** as an unstable, colorless oil (7.83 g): λ_{max}^{film} 3.23 (aromatic CH), 6.06 (C=C), 8.13 (CO), 10.42, 12.05, and 13.51 μ; nmr (CCl_4) 0.317 (m, 4 H, cyclopropane), 0.97 (s, 3 H, cyclopropyl methyl), 1.67 (m, 3 H, CH_3C=C), 3.14 (m, 1 H, CHOP), 4.65 (m, 2 H, C=CH_2), and 6.90 ppm (m, 4 H, aromatic).

Anhydrous zinc bromide (12.1 g, 53.8 mmol) was dissolved in 100 ml of dry ether by stirring for 1 hr at room temperature. (Calcium oxide (100 mg) was added to this homogeneous solution as an acid scavenger. Use of calcium oxide subsequently was found to be unnecessary, though not detrimental.) The crude freshly prepared phosphite ester **5** (7.83 g, 26.8 mmol) in 25 ml of ether was added rapidly to this vigorously stirring solution. The mixture was stirred at room temperature for 32 hr and then was poured into 150 ml of water overlaid with 150 ml of pentane. The pentane phase was washed with water, with three portions of ethylenedinitrilotetraacetic acid solution (prepared by mixing 5 g of the acid with 50 ml of water, adding sodium hydroxide to give a pH of about 8.5, and diluting the solution with 300 ml of water), water, and brine. The solution was dried over sodium sulfate and concentrated to give 5.5 g of crude bromodiene, which exhibited low-frequency ir bands corresponding to the phosphite residue. Rapid filtration of this material through 20 g of Woelm neutral alumina, activity grade I, with 40 ml of pentane, gave 4.21 g (75% yield from the cyclopropylcarbinol) of material with spectrometric properties very similar to those previously reported.[6] Analysis by vpc (glass SE-30 column) indicated the presence of about 4% of the cis bromodiene.[6] No material arising from migration of the terminal double bond[6] was evident.

1-Ethylenedioxy-6-(*trans*-7,11-dimethyl-7,11-dodecadien-3-ynyl)-3-cyclohexene (11). A 1.55 *M* solution of methyllithium (prepared from lithium and methyl bromide) in ether (7.0 ml, 10.8 mmol) was added slowly to 2.00 g (10.4 mmol) of the acetylenic ketal **10** under

(14) Purified by distillation from boric anhydride according to H. I. Schlesinger and A. W. Martin, *J. Amer. Chem. Soc.*, **36**, 1589 (1914), and stored frozen in the refrigerator.

(15) Prepared by formic acid cyclization of 4-(3-butenyl)-3-methyl-2-cyclohexenol: see ref 3.

(16) G. Eglinton and M. C. Whiting, *J. Chem. Soc.*, 3650 (1950).

(17) P. C. Crofts, J. H. H. Markes, and H. N. Rydon, *J. Chem. Soc., London*, 4250 (1958).

argon in a stirred, water-cooled flask. Much of the ether was removed from the resulting solution by briefly evacuating the flask to water-aspirator pressure. Tetrahydrofuran (5 ml, freshly distilled from lithium aluminum hydride under nitrogen) and the bromodiene **6** (2.26 g, 10.4 mmol) were added and the solution was heated to 60–65° under a positive pressure of argon for 95 hr. Then it was cooled in an ice bath and 1.8 ml of methyllithium (2.8 mmol) was added, followed by 0.514 g of additional bromodiene (2.37 mmol). The solution was heated once again to 60–65° for 24 hr; then it was poured into water overlaid with pentane. The pentane phase was washed with saturated brine, dried over sodium sulfate, and concentrated to give 4.52 g of a pale yellow liquid. This crude product was dissolved in 6 ml of methanol and added to a solution of 1.5 g of silver acetate in 2 ml of concentrated aqueous ammonia and 2 ml of methanol. This mixture was extracted three times with pentane, then diluted with an equal volume of water and extracted twice more with pentane. The combined pentane solutions were washed with water and brine, dried over sodium sulfate, and concentrated to give 3.16 g of liquid, essentially free of terminal acetylenic material. Chromatography on 80 g of Florisil gave, in the pentane eluate, 1.38 g of a mixture of the bromodiene **6** and its dehydrobromination product. Elution with 5% ether in pentane afforded 1.56 g of disubstituted acetylene **11** (46% yield from **10**). Further elution with ether gave 0.113 g of the alcohol **16** (see below).

Ketal **11** was distilled (short-path) giving an oil: λ_{max}^{film} 6.06 (C=C), 10.53, 11.23 (terminal methylene), and 11.83 μ; nmr (CCl_4) 1.61 (s, methyl of trans trisubstituted olefin), 1.70 (m, 3 H, methyl of terminal olefin), 3.88 (s, 4 H, ethylenedioxy), 4.67 (m, 2 H, $C{=}CH_2$), 5.14 (m, 1 H, vinyl H of trisubstituted olefin), and 5.52 ppm (m, 2 H, cyclohexene olefinic protons); mass spectrum (70 eV) *m/e* 328 (1%, M^+), 99 (100%, retro Diels–Alder loss of butadiene, followed by side-chain cleavage between C-1 and C-2).

Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.83. Found: C, 80.65; H, 10.0.

The structure of alcohol **16** was tentatively assigned on the basis of spectra data: λ_{max}^{film} 2.94 (OH), 6.10 (C=C), 6.33 (conjugated olefin), 8.26 (CO), and 11.23 μ (terminal methylene); nmr (CCl_4) 3.75–3.90 (m, 4 H, hydroxyethoxy side chain), and 4.7–6.0 ppm (m, 4 H, trisubstituted olefin, 1,3-cyclohexadiene). The remainder of the nmr signals were similar to those found for the ketal **11**.

1-Ethylenedioxy-6-(*trans,trans*-7,11-dimethyl-3,7,11-dodecatrienyl)-3-cyclohexene (12). To a solution of 50 ml of liquid ammonia and 40 ml of tetrahydrofuran (freshly distilled from lithium aluminum hydride) under argon was added 0.250 g (36 mmol) of clean lithium wire. The resulting solution was cooled to −78° and 2 ml of *tert*-butyl alcohol was added, followed by a solution of 8 ml of *tert*-butyl alcohol, 10 ml of tetrahydrofuran, and 1.64 g (4.99 mmol) of the trienyne ketal **11**. Sufficient liquid ammonia was added to give a permanent dark blue color. This solution was maintained under a positive pressure of argon at −78° with vigorous stirring for 2 hr. Excess lithium was then destroyed by careful addition of 3 g of solid ammonium chloride. The mixture was kept at low temperature until the blue color had disappeared (about 10 min). Most of the ammonia was allowed to evaporate and water and ether were added. The product, which was isolated by ether extraction,[12] was chromatographed on 80 g of Florisil to afford 1.35 g (82% yield) of material suitable for the next step. Analysis by vpc indicated the presence of 5% impurity.

A sample of comparable material was distilled (short-path) giving an oil: λ_{max}^{film} 3.26, 3.31 (olefinic CH), 6.06 (C=C), 10.42 (*trans*-CH=CH), 11.36 (terminal methylene), and 11.76 μ; nmr (CCl_4) 1.58 (s, methyl of trisubstituted olefin), 1.70 (m, methyl of terminal olefin), 3.87 (s, 4 H, ethylenedioxy), 4.63 (m, 2 H, $=CH_2$), 5.10 (m, 1 H, vinyl H of trisubstituted olefin), 5.35 (m, *trans*-CH=CH), and 5.50 ppm (m, cyclohexene) (4 H total for 5.34 and 5.50 signals); mass spectrum (70 eV) *m/e* (0.7%, M^+), 99 (100%, retro Diels–Alder loss of butadiene, followed by side-chain cleavage between C-1 and C-2).

Anal. Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 80.0; H, 10.4.

6-(*trans,trans*-7,11-Dimethyl-3,7,11-dodecatrienyl)-3-cyclohexen-1-one (13). To a solution of the tetraene ketal **12** (1.29 g, 3.90 mmol) in 80 ml of methanol was added 10 ml of 1% hydrochloric acid. The homogeneous solution was degassed and stirred under nitrogen at room temperature for 12 hr. Aqueous sodium bicarbonate (5%, 6 ml) was added and most of the methanol was removed at reduced pressure. The residual suspension was diluted with water and the product isolated by extraction with pentane[12] to give 1.1 g of crude ketone.

A comparable sample of crude product was chromatographed on Florisil with 5% ether in pentane, then distilled (short-path) giving an oil; λ_{max}^{film} 3.26, 3.30 (olefinic CH), 5.81 (C=O), 6.6 (C=C), 10.36 (*trans*-CH=CH), and 11.36 μ ($C{=}CH_2$); nmr (CCl_4) 1.58 (s, methyl of trisubstituted olefin), 1.70 (m, methyl of terminal olefin), 2.78 (m, 2 H, $=CCH_2C{=}O$), 4.66 (m, 2 H, $=CH_2$), 5.09 (m, vinyl H of trisubstituted olefin), 5.35 (m, *trans* -CH=CH), and 5.74 ppm (m, 2 H, cyclohexene); mass spectrum (70 eV) *m/e* 286 (3.4%, M^+), 96 (100%).

Anal. Calcd for $C_{20}H_{30}O$: C, 83.86; H, 10.56. Found: C, 83.85; H, 10.6.

6-(*trans,trans*-7,11-Dimethyl-3,7,11-dodecatrienyl)-2-cyclohexen-1-one (14). The crude β,γ-unsaturated ketone **13** (1.1 g) was dissolved in 40 ml of methanol (freshly distilled from magnesium methoxide under nitrogen), 2.0 g of DABCO was added, and the solution was degassed twice and heated at 40° under nitrogen in the dark for 25 hr. At the end of that time, 50 ml of 1% hydrochloric acid was added and the solution was poured into water overlaid with pentane. The pentane phase was washed with water and saturated brine, dried over sodium sulfate, and evaporated to give 1.15 g of crude α,β-unsaturated conjugated ketone **14**. Chromatography on 80 g of Florisil gave, on elution with 5% ether in pentane and with 25% ether in pentane, 0.568 g of the pure ketone (51% yield based on the ketal **12**). This material corresponded closely by vpc, ir, and nmr with material prepared by the alternative route, described below. An additional 0.100 g of somewhat less pure material, which was not used in subsequent reactions, was obtained from later chromatographed fractions. Exhaustive elution of the column with 25% ether in pentane gave 0.231 g of what appeared to be the product of conjugate addition of methanol to the α,β-unsaturated ketone: λ_{max}^{film} 5.85 μ (C=O); nmr (CCl_4) 3.28 ppm (methoxy).

2-(3-Butynyl)anisole (17). Propargylmagnesium bromide was prepared[18] from propargyl bromide (83.5 g, 0.702 mol) in 88% yield, as determined by acidifying an aliquot and titrating to the phenolphthalein end point. To the 0.966 *M* solution of this reagent (0.615 mol, total), 86.0 g (0.428 mol) of 2-methoxybenzyl bromide[19] in a small volume of ether was added dropwise over a period of 1 hr. The solution was stirred at room temperature for 20 hr and at reflux for 3 hr. Excess Grignard reagent was destroyed by dropwise addition of water. The resulting mixture was extracted with aqueous ammonia–ammonium chloride solution, 5% aqueous ammonium chloride, water, and brine and then dried over magnesium sulfate and concentrated. Distillation through a spinning band column afforded 2-(3-butynyl)anisole (42.5 g) as a colorless liquid, bp 70–75° (1 mm). The infrared spectrum of this substance exhibited a weak band at 5.07 μ indicating contamination by the terminal allene isomer. The allene was removed by the following procedure.

Sodium amide was prepared from 8.0 g of sodium metal (0.35 g-atom) and a trace of hydrated ferric nitrate in 800 ml of liquid ammonia. To this was added 42.2 g of the aforementioned butynylanisole (0.263 mol) in 30 ml of ether over a period of 30 min. The mixture was stirred for 8 hr, and then 300 ml of ammonia was distilled into the mixture. This was followed by cautious addition of 30 g of solid ammonium chloride. After this slurry had been vigorously stirred and shaken, 200 ml of ether was added and the ammonia was allowed to evaporate. The residue was diluted with water and the product isolated by ether extraction.[12] Distillation through a spinning band column gave pure 2-(3-butynyl)anisole (33.17 g, 36% yield), bp 70° (0.8 mm), which was homogeneous by vpc analysis: λ_{max}^{film} 2.94 (C≡CH), 4.70 (C≡C), 8.00 (CO), and 13.33 μ (1,2-disubstituted benzene); nmr ($CDCl_3$) 1.78 (t, J = 2 Hz, 1 H, C≡CH), 2.4 (m, 2 H, propargylic CH_2), 2.8 (m, 2 H, benzylic CH_2), 3.74 (s, 3 H, methoxy), and 7.0 ppm (m, 4 H, aromatic).

Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.6; H, 7.6.

***trans*-2,6-Dimethyl-12-(2-methoxyphenyl)-1,5-dodecadien-9-yne (18).** Methyllithium (36 ml of a 0.79 *M* solution in ether) was added slowly with stirring at 0° under nitrogen to 2-(3-butynyl)-anisole (5.6 g, 35 mmol). After the methane evolution had ceased, 13 ml of hexamethylphosphoric triamide (freshly distilled from calcium hydride at 85° (2.5 mm) and kept under nitrogen) was

(18) *Cf.* M. Gaudemar, *Ann. Chim.* (*Paris*), (13) 1, 161 (1956).

(19) Prepared by reaction of *N*-bromosuccinimide with 2-methylanisole in carbon tetrachloride. Since distillation of the crude bromide involves an explosion hazard, an alternative synthesis by A. Lapworth and J. B. Shoesmith, *J. Chem. Soc.*, *London*, 1391 (1922), is recommended.

added gradually to the colorless solution. Some heat was evolved and the solution turned slightly green. Addition of bromodiene **6** (4.08 g, 18.8 mmol) caused a rapid color change to pale yellow. The solution was allowed to stir for 32 hr at 50 to 55° under a small positive pressure of nitrogen and then was cooled, poured into water, and extracted with pentane. The pentane phase was washed with saturated brine, dried over sodium sulfate, then extracted with six 4-ml portions of a 2 *M* solution of dimethyl sulfoxide sodium salt in dimethyl sulfoxide.[20] The combined pentane phases were washed with water and brine, dried over sodium sulfate, and concentrated to give 3.27 g of a liquid which showed no terminal acetylenic bands in the ir spectrum.

Dry-column chromatography of this material on 75 g of Woelm neutral alumina, activity grade II, gave, on elution with pentane, 0.464 g of the triene arising from dehydrobromination of bromodiene **6** and 2.465 g of disubstituted acetylene. This fraction was rechromatographed on 200 g of alumina to give 1.49 g of material showing no bands for triene or terminal acetylene in the ir spectrum. Short-path distillation at 100–120° (0.017 mm) gave 1.44 g (26% yield from the bromodiene) of product: λ_{max}^{film} 3.26 (aromatic CH), 6.06 (C=C), 6.25, 6.33 (aromatic C=C), 7.75 (CO), 11.36 (terminal methylene), and 13.33 μ (1,2-disubstituted benzene); nmr (CCl_4) 1.60 (s, methyl of trisubstituted olefin), 1.69 (m, methyl of terminal olefin), 3.74 (s, 3 H, methoxy), 4.67 (m, 2 H, $=CH_2$), 5.14 (m, 1 H, vinyl H of trisubstituted olefin), and 6.6–7.3 ppm (m, 4 H, aromatic); mass spectrum (70 eV) *m/e* 296 (M^+). A comparable sample of compound **18**, obtained by analogous alkylation of acetylene **17** with the *p*-toluenesulfonate ester corresponding to bromide **6**, was used for combustion analysis.

Anal. Calcd for $C_{21}H_{28}O$: C, 85.08; H, 9.52. Found: C, 85.0; H, 9.35.

Birch Reduction of Dienyne 18. Liquid ammonia (150 ml) was distilled directly from lithium metal into a 250-ml three-necked flask fitted with an addition funnel, a glass paddle stirrer, and a reflux condenser cooled with Dry Ice–acetone. The distillation and subsequent reduction were performed under dry nitrogen at slightly greater than atmospheric pressure. Clean lithium wire (2.25 g, 0.324 g-atom) was added to the 150 ml of liquid ammonia, followed by a solution of substrate **18** (1.40 g, 4.73 mmol) in 20 ml of dry tetrahydrofuran. The blue solution was allowed to stir at reflux for 5 min and then was cooled to −78°. Anhydrous ethanol (50 ml) was added dropwise over a period of 20 min. The reaction mixture was allowed to stir at −78° until the blue color disappeared (about 30 min total reaction time). Evaporation of the ammonia over a period of 4 hr gave a cloudy solution which was diluted with water. The product, which was isolated by extraction with pentane,[12] was obtained as a colorless oil (1.37 g): λ_{max}^{film} 5.88 (ketone impurity), 6.06 (C=C), 8.20 (CO), 10.31 (*trans* -CH=CH), 11.23 (terminal methylene), and 13.33 μ (trace of aromatic impurity); nmr (CCl_4) 1.58 (s, methyl of trisubstituted olefin), 1.69 (m, methyl of terminal olefin), 2.70 (m, 4 H, bisallylic methylenes), 3.46 (singlet with upfield shoulder, methoxy), 4.65 (m, 2 H, terminal methylene), 5.08 (m, 1 H, vinyl H of trisubstituted olefin), 5.37 (m, 2 H, *trans*-CH=CH), and 5.59 ppm (m, 2 H, cyclohexene). The nmr spectrum also showed the presence of about 12% of unreduced material containing the anisole nucleus. Integration of the bis allylic methylene signal against the methoxy signal indicated that tetrahydroaromatic (over reduced) material was present to an extent of about 20%. No contamination by the terminal isopropyl compound could be detected. This mixture was not amenable to vpc analysis.

Transformation of the Birch Reduction Product to the Tetraenone 14. A solution of 1.37 g of the reduction mixture from the preceding experiment in 10 ml of dimethoxyethane (freshly distilled from lithium aluminum hydride) was stirred vigorously with 10 ml of 6.7% aqueous oxalic acid under nitrogen at room temperature for 87 hr. The heterogeneous solution was diluted with water and the product was isolated by extraction with pentane, using a base wash,[12] giving the crude β,γ-unsaturated ketone **13** as a colorless oil containing no detectable enol ether by nmr. The spectra of this material were similar to those of the product produced, as described above, from the ketal **12**.

Isomerization of this product to the α,β-unsaturated ketone **14** and purification of the latter compound were accomplished by a modification of the Stork and White procedure.[9] A deoxygenated solution of the crude ketone **13** (1.29 g) in 8 ml of piperidine (freshly distilled from calcium hydride under nitrogen) was stirred at 100° under nitrogen for 5.5 hr. The flask containing this mixture was then cooled to −10° and evacuated to a pressure of 1.3 mm. Evaporation of the piperidine at this pressure and ambient temperature left a dark brown oil containing some suspended solid. This crude β-piperidino ketone (unstable in air) was kept under nitrogen and used directly. Excess methyl iodide (3.55 ml) was added and the mixture allowed to stand at 5° for 10 hr, then at room temperature for 11 hr. The partially crystalline product was triturated with pentane, centrifuged, and washed again with pentane. This tan, soap-like methiodide was used directly without further purification or characterization. Thus, it was dissolved in 1.5 ml of pyridine (distilled from calcium hydride, stored over barium oxide, and deoxygenated just prior to use) and the solution was warmed to 80° for 5 hr under nitrogen, then diluted with water. The product was isolated by extraction with pentane using a 5% aqueous lactic acid wash.[12] The crude α,β-unsaturated ketone **14** amounted to 0.550 g. An additional 0.025 g of comparable material was obtained by retreating the pentane soluble material from the methiodide purification with piperidine, methyl iodide, and pyridine, as described above.

The crude α,β-unsaturated ketone was chromatographed on 15 g of Florisil. Elution with benzene, 6:1 benzene–ethyl acetate, and 3:1 benzene–ethyl acetate afforded 0.475 g of a colorless oil, which was distilled (short-path) at 100–120° (0.02 mm), to give 0.447 g (33% yield from **18**): $n^{26}D$ 1.5020; $\lambda_{max}^{95\% EtOH}$ 224 mμ (ϵ 1.15 × 10^4), shoulder at 285 mμ (ϵ 650); λ_{max}^{film} 6.01 (conjugated C=O), 10.42 (*trans*-CH=CH), and 11.36 μ (terminal methylene); nmr (CCl_4) 1.59 (s, methyl of trisubstituted olefin), 1.69 (m, methyl of terminal olefin), 4.65 (m, 2 H, $=CH_2$), 5.08 (m, 1 H, vinyl H of trisubstituted olefin), 5.85 (doublet, J = 10 Hz, of triplets, J = 2 Hz, 1 H, C-2 of cyclohexenone), and 6.80 ppm (m, 1 H, C-3 of cyclohexenone); mass spectrum (12 and 70 eV) *m/e* 286 (M^+). Analysis by vpc showed one component, with a small leading shoulder.

Anal. Calcd for $C_{20}H_{30}O$: C, 83.86; H, 10.56. Found: C, 83.9; H, 10.7.

1-Methyl-6-(*trans*,*trans*-7,11-dimethyl-3,7,11-dodecatrienyl)-2-cyclohexen-1-ol (1). A solution of 118 mg of the tetraenone **14** in 1 ml of ether was added to 1 ml of 1.51 *M* methyllithium (prepared from lithium and methyl bromide) in ether with vigorous stirring under nitrogen. After 15 min at room temperature, water was added and the product was isolated by extraction with pentane,[12] to afford 121 mg (97% yield) of alcohol **1** as a colorless liquid: λ_{max}^{film} 2.97 (OH), 6.06 (C=C), 9.09 (C—O), 10.36 (*trans*-CH=CH), 10.87, and 11.30 μ (terminal methylene); nmr (CCl_4) 1.07, 1.20 (pair of singlets for the methyl attached to the carbinol carbon, two diastereoisomers), 1.59 (s, methyl of trisubstituted olefin), 1.70 (m, methyl of terminal olefin), 4.67 (m, 2 H, $=CH_2$), 5.10 (m, 1 H, vinyl H of trisubstituted olefin), 5.39 (m, 2 H, *trans*-CH=CH), and 5.53–5.61 ppm (m, 2 H, cyclohexene); mass spectrum (12 and 70 eV) *m/e* 284 (M − 18), no molecular ion. This product, which was very susceptible to dehydration and was not amenable to vpc analysis, was used for cyclization without purification. Combustion analysis gave a value 1% low in carbon.

Cyclization. A. With Trifluoroacetic Acid in Pentane. Pentane was purified by extraction with concentrated sulfuric acid, distillation from potassium carbonate, and prolonged drying over clean sodium wire. A degassed solution of 22.77 mg of the tetraenol **1** in 20 ml of pentane was cooled to −78° under nitrogen and 0.6 ml of trifluoroacetic acid (distilled from phosphorus pentoxide) was added with stirring. The mixture was allowed to warm gradually from −75 to −16° over a period of 110 min, then it was cooled to −78°, 2 ml of water was added, and the cold mixture was poured into saturated brine overlaid with pentane. The pentane phase was washed with water, 5% potassium bicarbonate, and brine, dried over sodium sulfate, and evaporated. The residue was dissolved in 10 ml of ether, 110 mg of lithium aluminum hydride was added, and the solution was allowed to stir at room temperature for 45 min. Water, followed by dilute hydrochloric acid, was added, and the product was isolated by ether extraction using a base wash.[12] Chromatography on 8 g of Woelm neutral alumina, activity grade I, gave 4.29 mg of hydrocarbon fraction (eluted with 30 ml of pentane) and 17.4 mg of polar material (eluted with ether).

On vpc analysis, the hydrocarbon material showed one component which accounted for 98.5% of the mixture. The nmr and mass spectra of this material were identical with those respectively of the analytical specimen of *dl*-**17-methyl-5β-*D*-homoandrosta-1,16-diene (2)** described below (part C). On standing for several days at −20°, this substance slowly crystallized. Washing the solid with cold methanol gave colorless plates, mp 52–53°.

The polar fraction was shown on the basis of the following data

(20) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **84**, 866 (1962).

to consist primarily of alcohol **19**: $\lambda_{max}^{CHCl_3}$ 2.70 (OH), 6.06 (C=C), 10.31 (*trans*-CH=CH), and 11.23 μ (terminal methylene); nmr (CCl_4) 1.60 (s, methyl of trans-trisubstituted olefin), 1.69 (m, methyl of terminal olefin), 4.0 (broad m, 1 H, H attached to carbinol carbon), 4.65 (m, 2 H, $=CH_2$), 5.1 (m, 1 H, vinyl H of trisubstituted olefin), and 5.4 ppm (m, 3 H, *trans*-CH=CH and vinyl H of allylic alcohol). These spectra closely resembled those found for 3-methyl-4-(*trans*,*trans*-7-methyl-3,7,11-dodecatrienyl)-2-cyclohexen-1-ol.[1]

B. With Deuteriotrifluoroacetic Acid in Dichloromethane. A mixture of 0.75 ml of deuteriotrifluoroacetic acid[21] and 0.75 ml of dichloromethane (distilled from phosphorus pentoxide) was added in one portion with stirring to a solution of the tetraenol **1** (43.0 mg) in 40 ml of dichloromethane at −78° under an atmosphere of nitrogen. After 8 hr at −78°, 1 ml of dry pyridine was added and the reaction mixture was poured into water overlaid with ether. The ether phase was washed with 5% lactic acid, water, 5% sodium bicarbonate, and brine, dried over sodium sulfate, and concentrated. The oily residue was dissolved in 10 ml of ether and stirred with 100 mg of lithium aluminum hydride for 30 min. Isolation and chromatography (on Florisil) as described in the preceding experiment gave 9.5 mg of hydrocarbon fraction and 28.3 mg of polar material.

Analysis by vpc of the hydrocarbon fraction showed a sharp peak corresponding to the tetracyclic diene integrating for about 80% of the mixture. This mixture was subjected to short-path distillation at 100° (0.02 mm) and analyzed mass spectrometrically. There was no enhancement of the M + 1 peak relative to the molecular ion (*m/e* 284) by comparison with the spectrum of the analytical specimen of diene **2**.

C. With Stannic Chloride in Nitroethane. A solution of 38.9 mg of the tetraenol **1** in 8 ml of nitroethane (distilled through a 2-ft spinning band column from 2 Å Molecular Sieves, degassed at reduced pressure and stored under nitrogen) was cooled to −68° under a positive pressure of nitrogen. A solution of 156 mg of stannic chloride in 1 ml of nitroethane was added. The reaction mixture which immediately turned pale yellow was allowed to stir at −78° for 2.5 hr and then was neutralized at that temperature by adding 0.1 ml of dry pyridine. The cold mixture was poured into 7 ml of 1 *N* hydrochloric acid overlaid with ether. The product, which was isolated by ether extraction using a base wash,[12] was chromatographed on 4 g of Florisil. Elution with 20 ml of pentane gave 30 mg of hydrocarbon shown by vpc analysis to contain 92% of the tetracyclic diene **2** (see above). A polar fraction amounting to 17.4 mg was eluted with 20 ml of ether and shown by vpc and tlc analysis to be a complex mixture which was not investigated further.

The hydrocarbon fraction obtained from a comparable cyclization on a somewhat larger scale was purified by preparative vpc on a glass SE-30 column at 210°, followed by short-path distillation at 100° (0.02 mm): nmr (CCl_4) 0.77 (s, 3 H, C-18 methyl), 0.98 (s, 3 H, C-19 methyl), 1.58 (partially obscured, vinyl methyl), 5.30 (m, 1 H, C=CH), and 5.51 ppm (s, 2 H, -CH=CH-); mass spectrum (70 eV) *m/e* 284 (M^+)

Anal. Calcd for $C_{21}H_{32}$: C, 88.66; H, 11.34. Found: C, 88.8; H, 11.1.

Hydrogenation of Tetracyclic Diene 2. A 6.676-mg sample of the aforementioned analytical specimen of the tetracyclic diene product in ethanol over reduced platinum oxide at 0° (1 atm) consumed 1.150 ml of hydrogen (2.18 equiv). This hydrogenation was repeated on a larger scale using 42 mg of the diene **2**, prepared by stannic chloride–nitroethane cyclization and shown to be 94% pure by vpc. The product mixture which contained two components was subjected to preparative vpc on a glass SE-30 column at 210°. The major components were separated and collected, as well as a trace of material of somewhat shorter retention time. The trace constituent, amounting to less than 1 mg, gave three apparent mass spectrometric molecular ions: *m/e* 286, 288, and 290, in relative intensities of 1.0, 2.4, and 1.8, respectively.

The major component of shorter retention time (5.8 mg) was recrystallized from methanol to provide a sample of *dl*-**17α-methyl-5β-*D*-homoandrostane (20b)** as colorless crystals: mp 64–65.5°; mass spectrum (70 eV) *m/e* 288 (M^+). The nmr and solution ir spectra were identical with those, respectively, of authentic 17α-methyl-5β-*D*-homoandrostane (see below).

Anal. Calcd for $C_{21}H_{36}$: C, 87.42; H, 12.58. Found: C, 87.16; H, 12.32.

Purification of the major component of longer retention time (13.2 mg) by recrystallization from methanol furnished colorless crystals of *dl*-**20a**: mp 60–61.5°; mass spectrum (70 eV) *m/e* 288 (100%, molecular ion). The nmr and solution ir spectra were identical with those respectively of authentic 17β-methyl-5β-*D*-homoandrostane (see below).

17α-Methyl-5β-*D*-homoandrostan-17β-ol. To a solution of 63.5 mg of 5β-*D*-homoandrostan-17-one[1] (mp 146–147°) in 1 ml of ether was added 0.25 ml of 1.25 *M* methyllithium–lithium bromide in ether. The solution was stirred for 15 min at room temperature, treated with 9 μl of water, then with an additional 0.8 ml of methyllithium. Water was added and the product isolated by ether extraction.[12] Analysis by vpc on a glass SE-30 column at 200° showed one major peak with a shoulder which corresponded to the starting ketone. Addition of 1 ml of methyllithium to a solution of this mixture in ether, followed by isolation as described above, gave a crystalline solid which was recrystallized from pentane at −20°, from methanol at −20°, then once again from pentane at −20°. The resulting crystals underwent a solid phase change at 75° and melted at 103–106°. Short-path distillation at 120° (0.015 mm) gave colorless crystals: mp 109–111°; mass spectrum (70 eV) *m/e* 304 (M^+).

Anal. Calcd for $C_{21}H_{36}O$: C, 82.83; H, 11.92. Found: C, 83.1; H, 11.9.

The material recovered from the recrystallization mother liquors was treated again with methyllithium to provide an additional 52 mg of material melting at 103–106°, after undergoing a phase change at 75°. This substance was employed directly in subsequent reactions: λ_{max}^{film} 2.74, 2.86 (free and H-bonded OH), 8.47, 9.17, 9.61, 10.64, and 11.23 μ; nmr (CCl_4) 0.90 (s, C-18 methyl, shifted downfield by a 1,3-diaxial hydroxyl interaction), 0.98 (C-19 methyl), and 1.12 ppm (s, methyl on C-17).

Δ16- and Δ17-17-Methyl-5β-*D*-homoandrostene. To a degassed solution of 44.4 mg of the above alcohol in 2 ml of dry pyridine was added 0.10 ml of phosphoryl chloride. The solution was stirred under nitrogen for 5 hr at room temperature and then cooled in an ice bath as water was added dropwise. The reaction mixture was diluted with water and the product was isolated by extraction with pentane using an acid and a base wash.[12] Chromatography on 8 g of Florisil gave on elution with 25 ml of pentane 38 mg (91%) of a liquid which showed a single, symmetrical peak on vpc.

Nmr analysis (CCl_4) established that this was actually a mixture of two compounds. The spectrum showed a pair of singlets, the weaker one at 0.74 and the stronger at 0.79 ppm, corresponding to the C-18 methyls of the Δ^{16} and Δ^{17} compounds, respectively. Another pair of singlets appeared at 0.89 (weaker) and 0.91 ppm (stronger) corresponding to the C-19 methyls of the Δ^{16} and Δ^{17} compounds, respectively. The following signals also appeared: 1.57 (broadened singlet, C-17 vinyl methyl), 5.08 (m, =CH-, Δ^{17}), and 5.29 ppm (m, =CH-, Δ^{16}). Integration of the two vinyl proton signals indicated that the Δ^{16} isomer comprised about 40% of the mixture and the Δ^{17} isomer about 60%.

17α- and 17β-Methyl-5β-*D*-homoandrostane. In a quantitative microhydrogenation of 9.680 mg of the aforementioned olefinic mixture in ethanol over reduced platinum oxide at 0° and 1 atm, a total of 0.728 ml (0.96 equiv) of hydrogen was consumed after a 90 min reaction time. Filtration and evaporation of the solution gave 9 mg of crystalline solid, shown by vpc analysis to consist of 31% of a shorter retention time component and 69% of a second component. The vpc behavior of this material was shown by coinjection to be identical with that of the hydrocarbon mixture obtained by hydrogenation of the racemic diene **2** described above.

This hydrogenation reaction was repeated using 26 mg of the olefin mixture. A total of 20 hr was required for complete hydrogenation, as shown by monitoring the disappearance of the vpc peak for the olefin. Preparative vpc gave 5.9 mg of the shorter retention time component and 8.2 mg of the second component. Recrystallization of the former product from methanol gave colorless crystals, mp 67–69°, identified as the 17α-methyl compound *d*-**20b**: nmr (CCl_4) 0.785 (s, C-18 methyl), 0.81 (d, J = 5.8 Hz, methyl on C-17), and 0.893 ppm (s, C-19 methyl). Recrystallization of the major product from methanol gave an analytical specimen, mp 67–67.5°, shown to be the 17β-methyl isomer *d*-**20a**: nmr (CCl_4) 0.868 (s, C-18 methyl shifted downfield by a 1,3-diaxial methyl interaction), 0.894 (s, C-19 methyl), and 1.02 ppm (d, J = 7.4 Hz, methyl on C-17, shifted downfield by a 1,3-diaxial methyl interaction); mass spectrum (70 eV) *m/e* 288 (M^+).

Anal. Calcd for $C_{21}H_{36}$: C, 87.42; H, 12.58. Found: C, 87.6; H, 12.5.

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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 Isomer[1]

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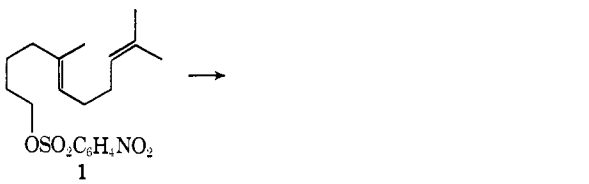
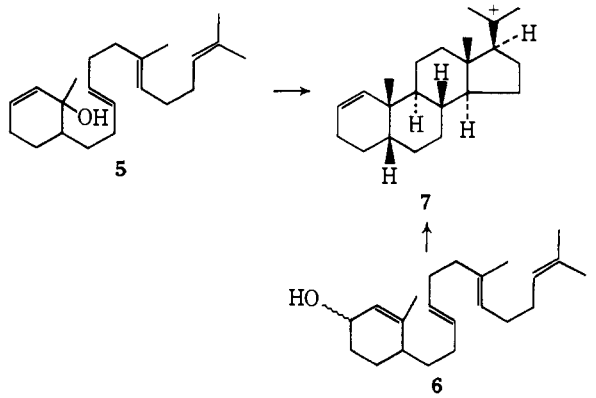
Abstract: The aim of this study was to synthesize the tetraenols **5** and **6** in the hope that they could be induced to undergo acid-catalyzed cyclization to produce products derived from the tetracyclic carbonium ion **7**. Substrate **5** was synthesized by the sequence outlined in Scheme II, the 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 17α → 20 hydride shift, followed by a 13β → 17β 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



1 2 3 4

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 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**.



5 7 6

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 procedure[4] 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 decarbethoxylation to give ketone **11** in 58% yield, reduction of which with lithium

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