Biomimetic Polyene Cyclizations.[1] Synthesis and Cyclization of 1,3-Dimethyl-2-(3-methyl-*trans*-3,7-octadienyl)cyclohex-2-en-1-ol

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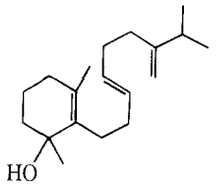
The aim of this study was to determine if the trienol **5**, having a trisubstituted internal olefinic bond, would undergo biomimetic polyene cyclization to give products of "natural" configuration derived from the hypothetical cation **6**, having two angular methyl groups in a 1,3-diaxial relationship. Alkylation of Hagemann's ester **7** with the bromodiene **8** gave the keto ester **9**. Saponification followed by decarboxylation (to give **10**) and treatment with methyllithium afforded the trienol **5**. On shaking with anhydrous formic acid in pentane, the trienol **5** underwent cyclization to give the tricyclic products **17**, **19**, and **20** isolated in yields of 9, 3.6, and 56%, respectively. These substances were shown to belong to the same stereochemical series by interconversion experiments and by reductive degradation to the hydrocarbon **22**, which was independently synthesized from substance **23** via a stereorational route.

As part of a study in our laboratory of allylic cation promoted biomimetic polyene cyclizations,[3] it was previously shown that the trienol **1**, on treatment with anhydrous formic acid at room temperature, was converted in 94% yield into a mixture of the hydrocarbons **2** and the carbinol **3**. The cyclization proved to be stereospecific since these products were separated and shown to belong to the same stereochemical series having the "natural" anti,trans configuration, by interconversion experiments and by their reductive transformation into the natural product, fichtelite **4**.[4]



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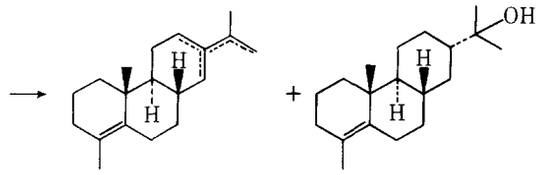

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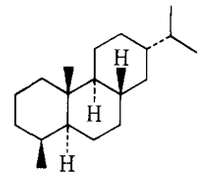

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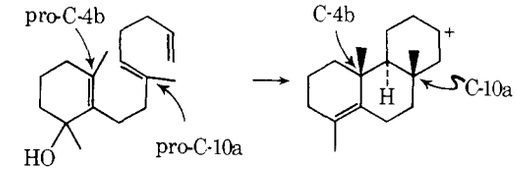
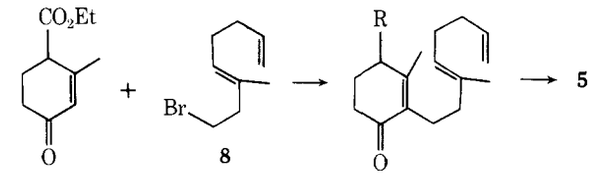
The present study was undertaken in order to ascertain if the trienol **5**, which differs from **1** by having a tri- instead of a disubstituted internal olefinic bond, would undergo cyclization in an analogous manner. In this event, the expected products would be those derived from the hypothetical cation **6**, having two β-oriented angular methyl groups (at C-4b and C-10a, phenanthrene numbering) in a 1,3-diaxial relationship—a structural feature found in most of the polycyclic triterpenoids formed by the biocyclization of squalene. It was considered important to determine if the aforementioned 1,3-diaxial interaction of the angular methyl groups might be "felt" in the transition state of the cyclization to such an extent that the normal reaction would be inhibited. The study described in the present paper shows that this is not the case, and that the cyclization of the trienol **5** does indeed proceed stereospecifically to give products derived from cation **6**, thereby providing a model for the production of an important structural feature in many polycyclic isoprenoids.



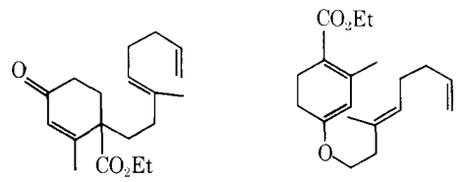
5 **6**

Synthesis of the Trienol 5. The synthetic scheme was analogous to that employed in the preparation of trienol **1**,[4] involving alkylation of Hagemann's ester **7** with the appropriate bromodiene **8**, followed by hydrolysis and decarboxylation of the resulting keto ester **9**, and finally by reaction with methyllithium.



7 **8** **9**, R = CO_2Et; **10**, R = H

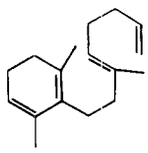
Alkylation of the enolate anion of **7** with the known bromodiene **8**[5] under a variety of conditions always afforded the desired α-alkylated product **9** contaminated with the isomeric products **11** and **12** resulting from γ- and O-alkylation. When the reaction was conducted in *N*,*N*-dimethylformamide at 52 °C, a 41% yield of C-alkylated products was obtained along with 23% of the enol ether **12**. The structure of this product **12** was determined by ir and NMR spectroscopy (see Experimental Section), and by its facile degradation by acid-catalyzed hydrolysis which afforded a convenient means of eliminating it from the reaction mixtures. The extent of O-alkylation could be markedly reduced by conducting the reaction at room temperature in either dimethyl sulfoxide or *tert*-butyl alcohol.[6] Thus alkylation of **7** in *tert*-butyl alcohol at 23 °C



11 **12**

in the presence of potassium iodide followed by treatment with dilute hydrochloric acid afforded a 67% yield of C-alkylated product consisting of 93% of the desired keto ester **9** contaminated with 7% of the γ-alkylated material **11**, as determined by vapor phase chromatographic (VPC) analysis. The desired enone **10** was obtained in 84% yield and in >99% purity by submitting the above C-alkylated mixture to selective saponification under conditions (see Experimental Section) which were too mild to attack the more hindered ester group of substance **11**.[4,7]

Two consecutive treatments of the trienone **10** with methyllithium gave in 83% yield the trienol **5**, the structure and configuration of which were confirmed by ir and NMR spectroscopy. As in the case of the related trienol **1**, the cyclization substrate **5** was exceedingly prone to dehydration. Heating with a trace of acid or dissolution in acetic acid converted **5** into a 56:44 mixture of tetraenes **13** and **14**.



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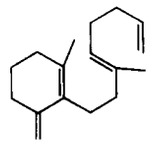

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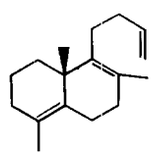
Cyclization Studies. A mixture of trienol **5**, anhydrous formic acid, and pentane was shaken for 5 min at room temperature. The crude product was treated with lithium aluminum hydride to cleave formate esters, and then was separated by column chromatography into a hydrocarbon ($C_{17}H_{26}$) and alcoholic ($C_{17}H_{28}O$) fraction, isolated in yields of 29 and 65%, respectively.

The hydrocarbon fraction consisted of four major components, A, B, C, and D, in a ratio of 5:48:17:30, as estimated by their relative VPC peak areas. The components were separated by preparative VPC, evaporatively distilled, and characterized by their spectral properties. Hydrocarbon A evidently decomposed during its purification and was not further examined. The ir and NMR spectra of hydrocarbons B and C were very similar, both exhibiting ir absorptions at 6.05, 10.05, and 10.95 μ characteristic of a terminal vinyl group. The NMR spectra showed the presence of two vinyl methyl groups and one angular methyl group. Absorptions for three vinyl protons at δ 4.78–6.10 ppm appeared in the spectrum of B, whereas the spectrum of C showed four vinyl protons as overlapping multiplets at δ 4.75–6.20 ppm. These data are consistent with the bicyclic structures **15** and **16** for B and C,



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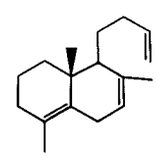

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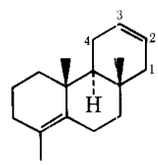
respectively. The NMR spectrum of hydrocarbon D showed absorptions for one vinyl methyl group, two angular methyl groups, and two vinyl protons. The signals for the vinyl protons were broad and complex, indicating extensive allylic coupling characteristic of a Δ^2 (see formula **17**) rather than a Δ^1 system.[8] Hydrogenation of D over platinum catalyst in ethanol gave a single crystalline product, dihydro-D ($C_{17}H_{28}$), mp 54–56 °C, the NMR spectrum of which was similar to that of D, except that there were no absorptions for vinyl protons. Presuming that hydrocarbon D arises by deprotonation of cation **6**, the above data for D and dihydro-D are consistent with the tricyclic structures represented by formulas **17** and **18**.



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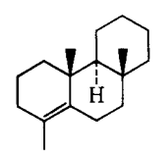

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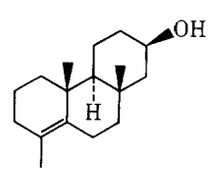
The alcohol fraction from the cyclization experiment appeared to consist of two components on thin layer chromatography (TLC). Separation by preparative TLC afforded two crystalline alcohols, A and B (in order of decreasing mobility), in yields of 3.6 and 56%, respectively. The NMR spectra of A and B were similar, exhibiting three-proton singlets for two angular methyl groups and one vinyl methyl group. The spectrum of alcohol A, mp 97–99 °C, displayed a one-proton multiplet of 13 Hz width centered at 4.03 ppm, characteristic of an equatorial proton on a carbon bearing an axial hydroxyl group. The corresponding absorption for alcohol B, mp 115–116 °C, was centered at 3.70 ppm with a width of 50 Hz, indicating an axial proton on a carbon bearing an equatorial hydroxyl group.[9] Oxidation of both alcohols with Jones reagent[10] gave the same crystalline ketone, mp 94.5–95.5 °C, thus providing firm evidence that A and B were epimeric at the carbon bearing the hydroxyl group. This conclusion was confirmed by reduction of the ketone with lithium aluminum hydride to give a mixture of alcohols A and B. Wolff–Kishner reduction of the ketone gave a crystalline hydrocarbon, mp 54–56 °C, in 82% yield, which was identical with hydrocarbon dihydro-D (see above), as shown by VPC behavior and ir and NMR spectroscopy, proving that alcohols A and B belonged to the same stereochemical series as tricyclic diene **17**. The evidence cited above, along with the presumption that alcohols A and B originate via formolysis of cation **6**, led to assignment of the structures **19**, **20**, and **21** to alcohols A and B and their



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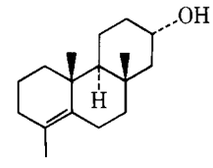

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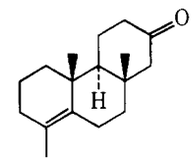

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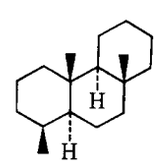
oxidation product, respectively. These assignments were further strengthened by the result of the reduction of ketone **21** with lithium tri-*tert*-butoxyaluminohydride, which gave alcohol **19** exclusively, in accord with the expected delivery of hydride to the less hindered α side of the carbonyl group.

Attempts to synthesize an authentic specimen of hydrocarbon **18** by an independent route from substance **23** of known stereochemistry were unsuccessful; however, the related perhydrophenanthrene **22** was produced in a stereorational manner as discussed below. This substance could be obtained from either the cyclization product **17** or the dihydro hydrocarbon **18**, by hydrogenation over platinum dioxide in acetic acid. The major component in both cases, isolated by preparative VPC, was a crystalline hydrocarbon, mp 45.0–46.5 °C, which was found to be identical with the synthetic perhydrophenanthrene **22**, described below.

Preparation of the Comparison Compound 22. The keto ketal **23** of known configuration[11] was reduced with lithium



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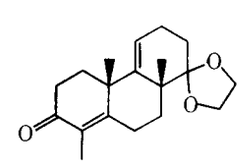
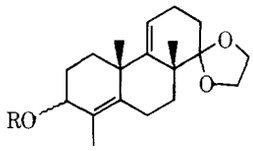
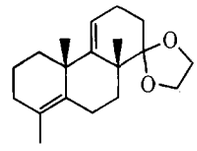


23

aluminum hydride to give a mixture of the epimeric α- and β-oriented allylic alcohols **24** in a ratio of 14:86 as evidenced by the C-4b angular methyl signals in the NMR spectrum of the crude product. Treatment of the corresponding acetates **25** with lithium in ethylamine[12] effected hydrogenolysis of the allylic acetoxy group to give the dienic ketal **26.** Hydrolysis



24, R = H
25, R = Ac



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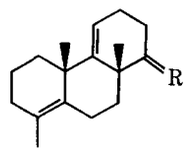
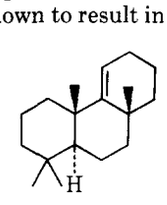
of ketal **26** gave the ketone **27** which was converted, by the Huang-Minlon modification[13] of the Wolff–Kishner reduction, into the diene **28** contaminated with 7% of other double



27, R = O
28, R = H_2

bond isomers. Purification by preparative VPC afforded the crystalline hydrocarbon **28,** mp 38–39 °C. All attempts to selectively reduce the trisubstituted double bond of diene **28** so as to give the compound **18** failed. Hydrogenation of diene **28** over platinum dioxide in acetic acid gave a mixture of four components in a ratio of 6:2:26:66 (in order of increasing retention time) as determined by VPC. The major component, isolated by preparative VPC, was identical (as shown by mixture melting point, VPC behavior, and NMR and ir spectroscopy) with hydrocarbon **22,** the predominant saturated hydrocarbon obtained by catalytic reduction of both **17** and **18.** Thus the tricyclic nature and gross structural features of the major cyclization products **17, 19,** and **20** have been firmly established.

Although the configuration of the 46 °C hydrocarbon has not been unequivocally established, it is most surely the trans,anti,trans substance **22.** Hydrogenation of the trisubstituted double bond of diene **28** would be expected to occur from the less hindered α side, thereby generating the trans B/C ring fusion. Reduction of the related compound **29** has been shown to result in exclusive formation of **30**;[11,14] more-



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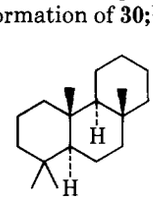

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over, the literature abounds in examples of the catalytic hydrogenation of the double bond of 9,11-dehydro steroids to give the trans B/C ring fusion.[15] The stereochemical course of the hydrogenation of the olefinic bond in ring A of **18** and **28** to give the trans A/B ring fusion is analogous to the established course of the hydrogenation of hydrocarbon **2** to give *dl*-fichtilite (**4**).[4] The configurational similarities of hydrocarbon **22** and fichtilite (**4**) are reflected by the nearly identical positions of the C-4b and C-8 methyl signals in the NMR spectra. Finally the shifts in the position of the angular C-10a methyl absorption resulting from alterations of ring C substituents correlates well with observed shifts for trans-fused ring systems. Thus the signal, which occurs at 61.5 Hz with no substituent in ring C (hydrocarbon **18**), shows a shift of +14.5 Hz (predicted +15.0[16]) for the 2β-OH substituent (compound **19**). The shift is −1.5 Hz (predicted −1.5[16]) for the 2-keto substituent (compound **21**), and −1.5 Hz (predicted 0,[16] −3.0[17]) for the 2,3-dehydro substance (**17**).

Thus it has been demonstrated that the substrate **5** does indeed undergo cyclization to give tricyclic products having "natural configuration". This process involves the development of a transition state or an intermediate having two angular methyl groups with 1,3-diaxial interactions, which may account for the lower yield (66%) as compared with that (93%) obtained for cyclization of the trienol **1** with a di- instead of a trisubstituted internal olefinic bond. It is noteworthy that when the bicyclic products **15** and **16** were subjected to the cyclization conditions, they were recovered unchanged, and therefore they cannot be intermediates in the formation of the tricyclic products.

Experimental Section[18]

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

Vapor phase chromatographic (VPC) analyses were performed on Aerograph Hi-Fi Models A-600B and A-600C instruments equipped with 7.5 ft × 0.125 in. columns packed with either 15% Carbowax or 5% SE-30 on Chromosorb W, 60/80 mesh. Preparative VPC separations were carried out on an Aerograph Model A-710 instrument equipped with 20 ft × 0.37 in. columns packed with either 20% Carbowax 20M or 20% SE-30 on Chromosorb W, 45/60 mesh.

Nuclear magnetic resonance (NMR) spectra were determined under the supervision of Dr. L. J. Durham on a Varian Associates A-60 or HA-100 NMR spectrometer. Unless otherwise stated, carbon tetrachloride was used as solvent for the samples; chemical shifts are reported as δ values in parts per million relative to tetramethylsilane (δ_{TMS} 0.0 ppm). Infrared (ir) spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer, and ultraviolet (uv) spectra were obtained on a Cary Model 14M recording spectrophotometer. Refractive indices were determined on Bausch-Lomb Models 8885 and Abbe-3L refractometers.

Silica gel G (E. Merck AG) was used as the absorbent for thin layer chromatography (TLC) experiments. The spots were detected either by use of iodine or by spraying the plate with a 2% solution of ceric sulfate in 2 N sulfuric acid followed by heating the plate at 150 °C for 10 min.

Alkylation of Hagemann's Ester with the Bromodiene 8. A. In Dimethyl Sulfoxide. Isolation of the *O*-Alkylate 12. The dimethylsulfinyl carbanion was generated by a reported procedure.[19] A mixture of 182 mg (4.14 mmol) of a 54.7% dispersion of sodium hydride in mineral oil and 10 ml of dry dimethyl sulfoxide was heated under nitrogen for 0.5 h at 82 °C. The resulting solution was cooled to room temperature and 780 mg (4.3 mmol) of Hagemann's ester[20] was added. The solution was stirred for 15 min, 382 mg (1.88 mmol) of bromodiene 8[5] (n^{20}D 1.490) was added, and stirring was continued for 16 h at 23 °C. The mixture was diluted with 20 ml of water and extracted with pentane and ether.[18] The crude product was chromatographed on 30 g of neutral alumina (4% water added) with 92:8 petroleum ether–methylene chloride to give, after evaporative distillation at 125–135 °C (7 μ), 255 mg (44% yield) of C-alkylated material as a colorless oil and 61 mg (11% yield) of O-alkylated material as a colorless liquid. The *O*-alkylate (**12**) exhibited the following spectral properties: ir λ_{max} (film) 5.92 (ester C=O), 6.40 (enol ether), and 6.09, 10.05, and 10.95 μ (C=C); NMR 1.26 (t, J = 7 Hz, 3 H, ester CH_3), 1.67 (s, 3 H, octadienyl vinyl CH_3), 2.14 (s, 3 H, C-3 vinyl CH_3), 3.82 (t, J = 7 Hz, 2 H, C=$COCH_2$–), 4.10 (q, J = 7 Hz, 2 H, ester CH_2), 4.87 (s, 1 H, C-2 vinyl proton), and 4.75–6.10 ppm (m, 4 H, vinyl protons).

Anal. ($C_{19}H_{28}O_3$) C, H.

An ethereal solution of the enol ether **12** was shaken for a few minutes at 23 °C with 10% aqueous hydrochloric acid. Extraction with ether using a base wash[18] afforded a residue which exhibited new carbonyl absorptions at 5.75 and 5.95 μ in the ir spectrum. The enol ether absorption at 6.40 μ was appreciably diminished.

B. In *tert*-Butyl Alcohol. Isolation of 4-Carbethoxy-3-methyl-2-(3-methyl-*trans*-3,7-octadienyl)cyclohex-2-en-1-one (9). A solution of 39.0 g (0.214 mol) of Hagemann's ester 7[20] in 50 ml

of anhydrous *tert*-butyl alcohol was added over a period of 15 min to a stirred suspension prepared from 8.78 g (0.20 mol) of a 54.7% dispersion of sodium hydride in mineral oil and 300 ml of anhydrous *tert*-butyl alcohol under nitrogen. The resulting red-orange solution was stirred for 15 min; then a solution of 23.5 g (0.116 mol) of crude bromodiene **8**[5] (prepared by W. R. Bartlett) in 20 ml of *tert*-butyl alcohol was added over a period of 10 min followed by the addition of a 16.0-g portion (0.096 mol) of potassium iodide (dried at 120 °C and 14 mm for 8 h). The mixture was stirred for 24 h at 23 °C and then heated at reflux for 2 h. The mixture was cooled and poured into 150 ml of water overlaid with 200 ml of ether. The aqueous layer was acidified to pH 3 with 10% aqueous hydrochloric acid and extracted with ether.[18] The crude product was chromatographed on 1 kg of neutral alumina (2.5% water added) with petroleum ether, bp 68–70 °C, and divided into three fractions as follows: fraction a amounted to 6.4 g of a mixture of mineral oil and unreacted bromide **8**; fraction b amounted to 21.7 g (62% yield) of the desired ester **9** contaminated with 4% of the γ-alkylated product **11** as shown by VPC (SE-30, 182 °C); fraction c amounted to 2.9 g (5% yield) of a mixture of **9** and **11** in a ratio of 69:31, as shown also by VPC.

Fraction b was used directly in the decarboxylation step described below. A sample of comparable material was evaporatively distilled at 125–135 °C (3 μ) to afford ester **9** as a colorless liquid: n^{25}D 1.496; ir λ_{max} (film) 5.75 (ester C=O), 5.95 (α,β-unsaturated C=O), 6.10, 10.03, and 10.95 μ (C=C); uv λ_{max} (95% EtOH) 248 nm (ε 9750); NMR 1.27 (t, J = 7 Hz, 3 H, ester CH_3), 1.65 (s, 3 H, octadienyl vinyl CH_3), 1.94 (s, 3 H, C-3 vinyl CH_3), 3.18 (t, J = 4 Hz, 1 H, C-4 proton), 4.16 (q, J = 7 Hz, 2 H, ester CH_2), and 4.75–6.1 ppm (m, 4 H, vinyl protons).

Anal. ($C_{19}H_{28}O_3$) C, H.

3-Methyl-2-(3-methyl-*trans*-3,7-octadienyl)cyclohex-2-en-1-one (10). A modification of a published procedure[21] was employed. An ice-cold 28-ml portion of a 15% solution of potassium hydroxide in 95% ethanol was added to 13.8 g (45.4 mmol) of the above chromatographed ester **9**. The resulting solution was stirred for 8 h at 5–10 °C under nitrogen, diluted with 40 ml of water, and extracted with ether[18] to give 0.94 g (7% recovery) of ester **11**. The aqueous layer was acidified to pH 3 with 10% aqueous hydrochloric acid and extracted with ether and dichloromethane[18] to afford a pale yellow, oily acid: ir λ_{max} (film) 2.9–3.4 (CO_2H), 5.75 (acid C=O), 6.0 (α,β-unsaturated C=O), 10.03 and 10.95 μ (C=C). The crude acid was evaporatively distilled at 140–145 °C (3 μ) from a flask filled with glass wool to give 9.09 g (86% yield) of a mixture of α,β-unsaturated ketone **10** and its β,γ isomer in a ratio of 12:88 as shown by VPC (SE-30, 189 °C): ir λ_{max} (film) 5.83 and 6.0 μ (β,γ- and α,β-unsaturated C=O).

The above mixture of ketones was isomerized by stirring under nitrogen for 3 h with 39 ml of a 10% solution of potassium hydroxide in ethylene glycol.[22] The mixture was diluted with water and extracted with ether and dichloromethane.[18] The crude product was evaporatively distilled at 140–145 °C (3 μ) to afford 8.83 g (84% overall yield) of ketone **10** as a pale yellow liquid which appeared to be >99% pure by VPC (SE-30, 173 °C). A sample of comparable material was evaporatively distilled at 100 °C (3 μ) to give an analytical specimen of **10** as a pale yellow liquid: n^{24}D 1.505; ir λ_{max} (film) 6.0 (α,β-unsaturated C=O), 10.05, and 10.95 μ (C=C); uv λ_{max} (95% EtOH) 245 nm (ε 11 100); NMR 1.63 (s, 3 H, vinyl CH_3), 1.91 (s, 3 H, vinyl CH_3 on ring), and 4.8–6.1 ppm (m, 4 H, vinyl protons).

Anal. ($C_{16}H_{24}O$) C, H.

The **2,4-dinitrophenylhydrazone** was obtained as red-orange crystals, mp 89–90 °C, after two recrystallizations from 95% ethanol.

Anal. ($C_{22}H_{28}N_4O_4$) C, H, N.

1,3-Dimethyl-2-(3-methyl-*trans*-3,7-octadienyl)cyclohex-2-en-1-ol (5). A solution of 3.10 g (13.4 mmol) of the distilled ketone **10** in 80 ml of anhydrous ether was stirred under nitrogen while 72 ml of a 1.2 M solution of methyllithium in ether was added. Stirring was continued for 0.5 h; then the mixture was poured onto 300 g of ice–brine and extracted with ether.[18] The ir spectrum of the crude product exhibited a weak carbonyl absorption at 6.0 μ indicative of the presence of unreacted enone **10**. The above procedure was repeated using 72 ml of a 2.1 M solution of methyllithium to afford 2.76 g (83% yield) of the trienol **5** after evaporative distillation at 100 °C (3 μ): n^{23}D 1.500; ir λ_{max} (film) 2.95 (OH), 6.09, 10.02, and 10.95 μ (C=C); NMR 1.22 (s, 3 H, C-1 CH_3), 1.64 (s, 3 H, vinyl CH_3), 1.65 (s, 3 H, vinyl CH_3), and 4.80–6.10 ppm (m, 4 H, vinyl protons).

Anal. ($C_{17}H_{28}O$) C, H.

Examination of trienol **5** by VPC (Carbowax, 170 °C) showed two overlapping peaks with retention times of 15.5 (41%) and 17.5 min (59%), which were identified as the tetraenes **13** and **14** (see below) by coinjection.

Dehydration of Trienol 5. A mixture of 156 mg (0.63 mmol) of trienol **5** (n^{23}D 1.500), 30 ml of acetic acid (distilled from chromium trioxide, bp 116–117 °C), and 6 drops of acetic anhydride was stirred under nitrogen for 20 min at room temperature, then poured into an ice-cold solution of 22 g of sodium hydroxide in 50 ml of water overlaid with 50 ml of ether. An additional 100 ml of water was added to dissolve the precipitated sodium acetate and the mixture was extracted with ether.[18] Chromatography of the crude product on 10 g of Woelm neutral alumina (4% added water; pentane) followed by evaporative distillation at 95–105 °C (3 μ) gave 112 mg (77% yield) of colorless oil which appeared to consist of tetraenes **13** and **14** in a ratio of 60:40 by VPC (Carbowax, 190 °C): ir λ_{max} (film) 6.10, 10.05, and 10.95 (C=C), and 6.14 μ (diene); λ_{max} (95% EtOH) 242 nm (ε 14 700) (trans diene of **14**) and 273 (345) (cis diene of **13**).

Anal. ($C_{17}H_{26}$) C, H.

The ratio of dienes **13** and **14** was estimated by integration of the NMR spectrum. Comparison of the total vinyl proton integral (5.5 protons) with that of the 5.30–6.15-ppm region (m, 1.6 H, vinyl proton on ring of **13** and chain C=CH) indicated a 59:41 ratio of dienes **13:14**. The ring methyl groups at 1.74 and 1.76 ppm integrated for 4.7 protons, which indicated a 56:44 ratio of **13:14**. The geminal protons for the exo methylene of diene **14** appeared as two signals at 4.62 and 4.80 ppm. The signal for the C-3 chain methyl group was at 1.63 ppm.

Cyclization of Trienol 5 with Formic Acid. A test tube containing 1.00 g (4.02 mmol) of the distilled trienol **5** was placed in a round-bottomed flask containing 17 ml of anhydrous pentane and 39 ml of formic acid [distilled from boric anhydride,[23] bp 19–21 °C (21 mm)]. After evacuation and flushing with nitrogen, the flask was inverted and shaken vigorously for 5 min. The contents of the flask were poured into 50 ml of water overlaid with 100 ml of pentane, and the flask and test tube were rinsed with water and pentane. The aqueous phase was saturated with sodium chloride and extracted with pentane using a base wash[18] to give 1.13 g of cloudy, pale yellow oil: ir λ_{max} (film) 5.80 (ester C=O), 6.10, 10.05, and 10.95 μ (C=C).

A solution of the above crude cyclization product in 5 ml of anhydrous ether was added to a suspension of 0.304 g (8.0 mmol) of lithium aluminum hydride in 10 ml of anhydrous ether. The mixture was stirred under nitrogen for 1 h at 23 °C; then it was cooled to 0 °C and 0.3 ml of water, 0.3 ml of 15% aqueous sodium hydroxide solution, and 0.9 ml of water were added in succession. The mixture was stirred until a white, granular suspension formed; then anhydrous magnesium sulfate was added and stirring was continued for 8 h. The mixture was filtered and the filtrate evaporated at reduced pressure to afford 0.94 g of cloudy, viscous oil which exhibited three spots by TLC (7:3 pentane–ether), R_f 0.17, 0.28, and 0.92.

The above 0.94-g sample of material was chromatographed on 30 g of Merck acid-washed alumina and separated into five fractions as follows: fraction a, eluted with petroleum ether, 68–70 °C, amounted to 270 mg (29% yield) of colorless oil which appeared to consist of a mixture of four hydrocarbons, A, B, C, and D, with VPC (Carbowax, 181 °C) retention times of 3.8 (5%), 5.5 (46%), 6.8 (16%), and 9.5 min (28%), respectively; fraction b, eluted with 9:1 petroleum ether–ether, amounted to 22 mg of material which appeared to be a complex mixture by TLC; fraction c, eluted with 4:1 petroleum ether–ether, amounted to 26 mg (2.6% yield) of alcohol A (R_f 0.28); fraction d, eluted with 4:1 petroleum ether–ether, amounted to 147 mg (14.7% yield) of a mixture of alcohol A and alcohol B (R_f 0.17); fraction e, eluted with 7:3 petroleum ether–ether, amounted to 477 mg (47.7% yield) of alcohol B.

A portion of fraction a was evaporatively distilled at 70–80 °C (3 μ) to afford a 98% recovery of colorless oil: ir λ_{max} (film) 6.10, 10.05, and 10.95 μ (C=C).

Anal. ($C_{17}H_{26}$) C, H.

The hydrocarbons A, B, C, and D were separated by preparative VPC (Carbowax, 205 °C) from the undistilled portion of fraction a and the collected fractions were evaporatively distilled at 70–80 °C (3 μ).

Examination of hydrocarbon A by VPC (Carbowax, 190 °C) revealed the presence of two new components in addition to hydrocarbon A. Apparently hydrocarbon A decomposed during the isolation procedure and was not further characterized.

Hydrocarbon B was assigned the bicyclic structure (**15**) on the basis of its spectral properties: ir λ_{max} (film) 6.09, 10.05, and 10.95 μ (C=C); NMR 1.11 (s, 3 H, angular CH_3), 1.60 (s, 6 H, vinyl methyls), and 4.78–6.30 ppm (m, 3 H, vinyl protons).

Anal. ($C_{17}H_{26}$) C, H.

Hydrocarbon C was assigned the bicyclic structure (**16**) on the basis of its spectral properties: ir λ_{max} (film) 6.09, 10.05, and 10.95 μ (C=C); NMR 0.88 (s, 3 H, angular CH_3), 1.56 (s, 3 H, vinyl CH_3), 1.70 (s, 3 H, vinyl CH_3), and 4.78–6.30 ppm (m, 4 H, vinyl protons).

Hydrocarbon D was identified as **4bβ,8,10aβ-trimethyl-Δ²,Δ⁸-4aα-decahydrophenanthrene (17):** NMR 1.00 (s, 3 H, angular CH_3), 1.58 (s, 3 H, vinyl CH_3), and 5.48 ppm (broad m, 2 H, vinyl protons).

Anal. ($C_{17}H_{26}$) C, H.

The components of fraction d were separated by preparative TLC (7:3 pentane–ether) to give 10 mg of alcohol A and 102 mg of alcohol B. These separated components were combined with fractions c and e, respectively.

Alcohol A (fraction c) was evaporatively distilled at 100–110 °C (7 μ) to afford 36 mg (3.6% yield) of **4bβ,8,10aβ-trimethyl-2β-hydroxy-Δ⁸-4aα-dodecahydrophenanthrene (19)** as colorless crystals, mp 97–99 °C: ir λ_{max} ($CHCl_3$) 2.70 and 2.85 μ (OH); NMR 0.95 (s, 3 H, angular CH_3), 1.23 (s, 3 H, angular CH_3), 1.60 (s, 3 H, vinyl CH_3), and 4.03 ppm (m, W = 13 Hz, 1 H, C-2 equatorial proton).

Anal. ($C_{17}H_{28}O$) C, H.

Alcohol B (fraction e) was evaporatively distilled at 100–110 °C (7 μ) to afford 560 mg (56% yield) of crystalline **4bβ,8,10aβ-trimethyl-2α-hydroxy-Δ⁸-4aα-dodecahydrophenanthrene (20),** mp 113–114 °C. Recrystallization from pentane gave an analytical sample as colorless prisms: mp 115–116 °C; ir λ_{max} ($CHCl_3$) 2.72 and 2.90 μ (OH); NMR 0.90 (s, 3 H, angular CH_3), 1.05 (s, 3 H, angular CH_3), 1.61 (s, 3 H, vinyl CH_3), and 3.70 ppm (m, W = 50 Hz, 1 H, C-2 axial proton).

Anal. ($C_{17}H_{28}O$) C, H.

Hydrogenation of Hydrocarbon D in Ethanol. A mixture of 15 mg (0.065 mmol) of hydrocarbon D, 18 mg of platinum dioxide, and 5.5 ml of 95% ethanol was stirred under hydrogen for 14 h at room temperature. The resulting mixture was filtered and the solvent was removed at reduced pressure to give, after evaporative distillation at 80 °C (3 μ), 10 mg (66% yield) of dihydro-D (**18**) as a colorless oil which appeared to be 97% of one component by VPC (Carbowax, 192 °C). The NMR spectrum and VPC behavior of this material were identical with those of hydrocarbon **18,** obtained via Wolff–Kishner reduction of ketone **21.** The ir spectra of the two hydrocarbons were also nearly identical.

4bβ,8,10aβ-Trimethyl-2-keto-Δ⁸-4aα-dodecahydrophenanthrene (21). A. By Oxidation of Alcohol A. A 0.2-ml portion of Jones reagent[10] was added to a cold (0 °C) solution of 16 mg (0.06 mmol) of alcohol A (**19**), mp 97–98 °C, in 5 ml of acetone. The mixture was stirred at 0 °C for 10 min and then poured into 50 ml of water. Ether extraction[18] followed by chromatography on 1 g of Merck acid-washed alumina (9:1 pentane–ether) afforded 10 mg (63% yield) of crystalline ketone **21,** mp 85–87 °C. Three recrystallizations from pentane gave **21** as colorless prisms, mp 94.5–95.5 °C.

B. By Oxidation of Alcohol B. Similar oxidation of 198 mg of alcohol B (**20**), mp 113–114 °C, afforded after chromatography on 10 g of Merck acid-washed alumina followed by evaporative distillation at 100–110 °C (9 μ), 169 mg (86% yield) of ketone **21,** mp 78–79 °C. An analytical sample was obtained after three recrystallizations from pentane as colorless prisms, mp 93.0–94.5 °C: ir λ_{max} (CCl_4) 5.85 μ (C=O); NMR 0.99 (s, 3 H, angular CH_3), 1.00 (s, 3 H, angular CH_3), and 1.63 ppm (s, 3 H, vinyl CH_3).

Anal. ($C_{17}H_{26}O$) C, H.

The **2,4-dinitrophenylhydrazone** was obtained as yellow-orange plates, mp 218–219 °C, after two recrystallizations from 95% ethanol.

Anal. ($C_{23}H_{30}N_4O_4$) C, H, N.

The mixture melting point of the recrystallized ketones obtained from alcohols A (**19**) and B (**20**) was 92–95 °C. The ir spectra of the two ketones were identical.

Wolff–Kishner Reduction of Ketone 21. The Huang-Minlon modification[13] of the Wolff–Kishner reduction was employed. A mixture of 97.3 mg (0.40 mmol) of ketone **21,** mp 78–79 °C, 224 mg of powdered potassium hydroxide, 2.9 ml of triethylene glycol, and 0.42 ml of anhydrous hydrazine was heated under nitrogen for 2.5 h at 90–104 °C in a flask fitted with a short-path condenser. The bath temperature was raised to 190–230 °C and heating was continued for an additional 3 h. After cooling to room temperature, the contents of the pot and the receiver were poured into 10 ml of water and the condenser was rinsed with ether. Ether extraction[18] followed by chromatography on 4 g of Merck acid-washed alumina (pentane) afforded 76 mg (82% yield) of **4bβ,8,10aβ-trimethyl-Δ⁸-4aα-dodecahydrophenanthrene (18)** as colorless crystals, mp 54–55 °C. An analytical sample was obtained by evaporative distillation at 80 °C (3 μ) as colorless prisms, mp 54–56 °C: NMR 0.89 (s, 3 H, angular CH_3), 1.03 (s, 3 H, angular CH_3), and 1.59 ppm (s, 3 H, vinyl CH_3).

Anal. ($C_{17}H_{28}$) C, H.

Reduction of Ketone 21 with Lithium Tri-*tert*-butoxyaluminohydride. A mixture of 17.8 mg (0.072 mmol) of ketone **21,** mp 78–79 °C, and 182 mg (0.72 mmol) of lithium tri-*tert*-butoxyaluminohydride[24] in 4 ml of dry THF was stirred at room temperature under nitrogen for 24 h; then 0.1 ml of water and 0.1 ml of 10% sodium hydroxide solution were added. The resulting mixture was stirred for 3 h, poured into 10 ml of water, and extracted with ether.[18] Chromatography of the crude product on 2 g of Merck acid-washed alumina (7:3 pentane–ether) followed by evaporative distillation at 100–110 °C (3 μ) afforded 10.9 mg (61% yield) of alcohol **19,** mp 96–98 °C, which appeared as one spot (R_f 0.28) on TLC (7:3 pentane–ether): ir λ_{max} ($CHCl_3$) 2.70 and 2.85 μ (OH).

Anal. ($C_{17}H_{28}O$) C, H.

Recrystallization from pentane did not raise the melting point of the alcohol which existed in dimorphic forms. Some crystals melted at 96–98 °C; then needles formed at 107–111 °C, which remelted at 127–129 °C. The ir spectra of this alcohol and alcohol A (**19**) obtained via cyclization were identical.

Hydrogenation of Hydrocarbon D (17) in Ethanol and Acetic Acid. A mixture of 23 mg (0.1 mmol) of hydrocarbon D (**17**), 25 mg of platinum dioxide, 10 ml of ethanol, and a few drops of acetic acid was stirred under hydrogen for 18 h at room temperature. The mixture was filtered and the solvent was evaporated at reduced pressure. The crude product was filtered through 1 g of Merck acid-washed alumina (pentane) to afford a colorless oil consisting of three major components with VPC retention times (Carbowax, 184 °C) of 10.5 (6%), 13 (11%), and 15 min (77%). The major component was isolated by preparative VPC (Carbowax, 200 °C), then evaporatively distilled at 70–80 °C (2 μ) to yield 9 mg (39% yield) of colorless needles, mp 45.0–47.5 °C. The VPC behavior, ir, and NMR spectra of this material were identical with those of hydrocarbon **22.** The mixture melting point of the two hydrocarbons was 44–47 °C.

Hydrogenation of Hydrocarbon 18 in Acetic Acid. A mixture of 22 mg (0.095 mmol) of hydrocarbon **18,** mp 54–55 °C, 20 mg of platinum dioxide, and 6.0 ml of acetic acid (distilled from chromium trioxide) was stirred under hydrogen for 24 h at room temperature. The mixture was filtered and the acetic acid was removed at reduced pressure (14 mm). The cloudy residue was washed through 1 g of Merck acid-washed alumina with pentane to yield 20.5 mg of material consisting of a mixture of five hydrocarbons with VPC retention times (Carbowax, 203 °C) of 7.0 (7%), 7.5 (5%), 8.3 (11%), 9.3 (74.5%), and 10.0 min (3%). The major component was isolated by preparative VPC (SE-30, 201 °C), then evaporatively distilled at 70–80 °C (3–5 μ) to afford 13 mg (59% yield) of hydrocarbon **22** as colorless needles, mp 45.0–46.5 °C.

Anal. ($C_{17}H_{30}$) C, H.

4bβ,8,10aβ-Trimethyl-1-ethylenedioxy-7-hydroxy-Δ⁴,⁸-decahydrophenanthrene (24). A suspension of 0.546 g (14.4 mmol) of lithium aluminum hydride in 12 ml of anhydrous ether was stirred under nitrogen while 3.00 g (9.94 mmol) of the keto ketal **23,**[11] mp 73.0–74.5 °C (prepared by K. Schmiegel), in 24 ml of anhydrous ether was added over a period of 10 min. The addition funnel was rinsed with 3 ml of ether and the mixture was stirred at room temperature for 4 h. The mixture was cooled to 0 °C and the excess hydride was decomposed with 2 ml of 10% sodium hydroxide solution, then an additional 35 ml of the base was added to dissolve the aluminum salts. The crude product was isolated by extraction with 1:1 benzene–ether (3 × 50 ml) and benzene (100 ml),[18] and then recrystallized from pentane to give 2.81 g (93% yield) of alcohol **24** as colorless prisms, mp 130–140 °C: ir λ_{max} (CCl_4) 2.9 μ (OH); NMR 14:86 peak ratio of two singlets at 1.24 and 1.32 (3 H, angular CH_3), 1.44 (s, 3 H, angular CH_3), two singlets at 1.73 and 1.78 (3 H, vinyl CH_3), 3.99 (s 4 H, ketal methylenes), and 5.49 ppm (m, 1 H, vinyl proton). A comparable sample, mp 130–139 °C, from another run was recrystallized several times from pentane to give colorless prisms, mp 138–139 °C.

Anal. ($C_{19}H_{28}O_3$) C, H.

4bβ,8,10aβ-Trimethyl-1-ethylenedioxy-7-acetoxy-Δ⁴,⁸-decahydrophenanthrene (25). A mixture of 2.77 g (9.10 mmol) of the hydroxy ketal **24,** mp 130–140 °C, 36 ml of anhydrous pyridine, and 27 ml of acetic anhydride was stirred at room temperature under nitrogen for 24 h. The solvent was removed at reduced pressure (0.05 mm) to give a yellow-orange oil which, upon crystallization from pentane–ether, afforded 1.82 g (58% yield) of ketal acetate **25** as colorless prisms, mp 109–110 °C: ir λ_{max} (CCl_4) 5.75 μ (ester C=O); NMR ($CDCl_3$) 1.33 (s, 3 H, angular CH_3), 1.42 (s, 3 H, angular CH_3), 1.57 (s, 3 H, vinyl CH_3), 2.06 (s, 3 H, acetate CH_3), 3.96 (s, 4 H, ketal methylenes), 5.25 (m, 1 H, C-7 proton), and 5.48 ppm (m, 1 H, vinyl proton).

Anal. ($C_{21}H_{30}O_4$) C, H.

The mother liquors from the above crystallization afforded a further 0.57 g (76% total yield) of crystalline acetate **25,** mp 108–110 °C.

4bβ,8,10aβ-Trimethyl-1-ethylenedioxy-Δ^{4,8}-decahydrophenanthrene (26). A modification of a published procedure[12] was employed. A solution of 1.705 g (4.92 mmol) of the allylic acetate **25,** mp 109–110 °C, in 125 ml of anhydrous ethylamine was cooled in a dry ice–isopropyl alcohol bath while 0.377 g (54.7 mmol) of lithium wire was added with vigorous stirring. The cooling bath was removed and stirring was continued until a dark blue color persisted. The mixture was recooled and poured into 200 ml of 1:1 benzene–ether; then the excess lithium was destroyed by the addition of ammonium chloride. The resultant mixture was diluted with 20 ml of water and extracted with benzene[18] to afford a white semisolid which appeared to be a mixture of the desired ketal **26** (R_f 0.60) and the allylic alcohol **24** (R_f 0.09) by TLC (7:3 pentane–ether). Chromatography on 40 g of neutral alumina (9:1 petroleum ether–ether) followed by recrystallization from pentane yielded 0.898 g (63% yield) of ketal **26** as colorless crystals, mp 86.5–89.0 °C. A second crop of 0.271 g (82% total yield) of **26,** mp 70–85 °C, was obtained from the mother liquors. An analytical sample was prepared from 8 mg of comparable material, mp 86.5–89.0 °C, by recrystallization from pentane to give 6 mg of colorless crystals, mp 89–90 °C: NMR 1.22 (s, 3 H, angular CH_3), 1.35 (s, 3 H, angular CH_3), 1.60 (s, 3 H, vinyl CH_3), 3.86 (s, 4 H, ketal methylenes), and 5.37 ppm (m, 1 H, vinyl proton).

Anal. ($C_{19}H_{28}O_2$) C, H.

4bβ,8,10aβ-Trimethyl-1-keto-Δ^{4,8}-decahydrophenanthrene (27). A mixture of 0.890 g (3.1 mmol) of the ketal **26,** mp 86.5–89.0 °C, 47 ml of acetone, and 10 ml of 10% hydrochloric acid solution was heated at reflux under nitrogen for 2 h. The mixture was diluted with 35 ml of water and extracted with ether.[18] The crude product was chromatographed on 30 g of Merck acid-washed alumina (9:1 petroleum ether–ether) to yield 0.679 g (90% yield) of ketone **27** as colorless crystals, mp 37–39 °C. A portion of comparable material from another experiment was evaporatively distilled at 100 °C (3 μ) to afford a >99% recovery of crystalline material, mp 37–39 °C, which appeared to be a mixture of the desired ketone and two impurities with retention times of 7.5 (94%), 6.5 (4%), and 8.5 min (2%) by VPC (SE-30, 200 °C). Recrystallization from methanol afforded an analytical sample of ketone **27** as colorless plates, mp 43–44 °C, which appeared uncontaminated on VPC: ir λ_{max} (CCl_4) 5.85 μ (C=O); NMR 1.30 (s, 3 H, angular CH_3), 1.35 (s, 3 H, angular CH_3), 1.57 (s, 3 H, vinyl CH_3), and 5.86 ppm (m, 1 H, vinyl proton).

Anal. ($C_{17}H_{24}O$) C, H.

The **2,4-dinitrophenylhydrazone** was obtained as yellow-orange plates, mp 141.5–142.5 °C, after one recrystallization from 95% ethanol–ethyl acetate.

Anal ($C_{23}H_{28}N_4O_4$) C, H, N.

4bβ,8,10aβ-Trimethyl-Δ^{4,8}-decahydrophenanthrene (28). A modification of a reported procedure[13] was employed. A mixture of 621 mg (2.54 mmol) of ketone **27,** mp 37–39 °C, 738 mg of powdered potassium hydroxide (85% minimal purity), 9.5 ml of triethylene glycol, and 1.4 ml of anhydrous hydrazine was heated at 105–115 °C under nitrogen for 2 h in a flask fitted with a short-path condenser. The pot temperature was raised to 190–210 °C and maintained at this temperature for 4 h. The mixture was cooled to room temperature and the combined contents of the pot and receiver were diluted with 30 ml of water. Extraction with ether[18] followed by chromatography on 25 g of Merck acid-washed alumina (pentane) afforded 563 mg of colorless oil which exhibited three peaks with retention times of 7.3 (3%), 8.5 (93%), and 9.5 min (4%) on VPC (SE-30, 175 °C). Isolation of the major component by preparative VPC (SE-30, 225 °C) followed by evaporative distillation at 100 °C (5 μ) gave 352 mg (60% yield) of diene **28** as fine colorless needles, mp 38–39 °C. A sample of comparable material, mp 38–39 °C, from another run was submitted for combustion analysis: NMR 1.20 (s, 3 H, angular CH_3), 1.36 (s, 3 H, angular CH_3), 1.60 (s, 3 H, vinyl CH_3), and 5.45 ppm (t, J = 4.5 Hz, 1 H, vinyl proton).

Anal. ($C_{17}H_{26}$) C, H.

The low retention time component of the crude product was also isolated and evaporatively distilled. The NMR spectrum exhibited absorptions for two vinyl protons as two overlapping multiplets from 5.23 to 5.50 ppm, indicating it to be the Δ^7-double bond isomer of **28.** The vinyl methyl absorption appeared at 1.63 ppm, and the two angular methyl signals appeared at 1.12 and 1.20 ppm.

4bβ,8β,10aβ-Trimethyl-4aα,8aα-perhydrophenanthrene (22). A mixture of 260 mg (1.13 mmol) of the diene **28,** mp 38–39 °C, 100 mg of platinum dioxide, and 20 ml of acetic acid (distilled from chromium trioxide) was stirred under hydrogen at room temperature for 17 h. The mixture was filtered and the acetic acid was removed at reduced pressure (14 mm) to afford 246 mg of colorless oil which appeared to be a mixture of four components with retention times of 7.0 (5.5%), 7.6 (2.4%), 9.0 (25.6%), and 10.0 min (66.5%) on VPC (SE-30, 180 °C). The major component was isolated by preparative VPC (SE-30, 220 °C), then evaporatively distilled at 100 °C (7 μ) to give 158 mg (60% yield) of the hydrocarbon **22** as colorless needles, mp 44–47 °C, which appeared to be 94% pure on VPC (Carbowax, 203 °C): NMR 0.77 (s, 3 H, angular CH_3), 0.88 (d, J = 7.5 Hz, 3 H, C-8 CH_3), and 0.92 ppm (s, 3 H, angular CH_3).

Anal. ($C_{17}H_{30}$) C, H.

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Registry No.—**5,** 60562-27-8; **7,** 59323-55-6; **8,** 19788-88-6; **9,** 60525-77-1; **10,** 60525-78-2; **10** β,γ isomer, 60525-79-3; **10** 2,4-DNPH, 60525-80-6; **11,** 60525-81-7; **11** free acid, 60525-82-8; **12,** 60525-83-9; **13,** 60525-84-0; **14,** 60525-85-1; **15,** 60525-86-2; **16,** 60746-45-4; **17,** 60525-88-4; **18,** 60525-89-5; **19,** 60525-90-8; **20,** 60525-91-9; **21,** 60525-92-0; **21** 2,4-DNPH, 60525-93-1; **22,** 60525-94-2; **23,** 60525-95-3; **24,** 60525-96-4; **25,** 60525-97-5; **26,** 60525-98-6; **27,** 60525-99-7; **27** 2,4-DNPH, 60526-00-3; **28,** 60526-01-4; acetic acid, 64-19-7; formic acid, 64-18-6.

References and Notes

(1) For a recent paper in this series, see W. S. Johnson, S. Escher, and B. W. Metcalf, *J. Am. Chem. Soc.*, **98,** 1039 (1976).
(2) This paper represents work described in the Ph.D. Thesis of Marcia Ilton, Stanford University, 1967.
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(8) For example, the NMR signals for the vinyl protons of *trans*-9-methyl-1-octalin appear as slightly broadened singlets, whereas the vinyl protons of *trans*-9-methyl-2-octalin appear as a broader multiplet: W. S. Johnson, M. I. Dawson, and F. E. Brot, unpublished observations.
(9) Axial proton resonances are generally more widely split and appear further upfield than those of their equatorial counterparts. See N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry. Illustrations from the Steroid Field", Holden-Day, San Francisco, Calif., 1964, pp 77–85.
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(18) 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 "wash" indicates washing the combined organic layers with saturated aqueous sodium bicarbonate solution ("base wash"), with dilute aqueous hydrochloric acid ("acid wash"), or with the indicated solution prior to the aforementioned washing with water.
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