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Nonenzymic, Biogenetic-Like Cyclization of a Trienic Acetal

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The stereoselective synthesis of the *trans,trans* trienic acetal **9** is described. Alkylation of the lithio derivative of 2-methyl-1-hexene-5-yne (**10**) with ethylene oxide gave the acetylenic alcohol **11**, which on reduction with sodium in liquid ammonia afforded the *trans* diene **12**. Alkylation of the sodium enolate of acetylacetone with **13**, the mesylate derived from **12**, gave the dione **14**; chlorination of **14** and deacylation of the resulting chloro dione **15** provided the α-chloro ketone **16**. Conversion of **16** to the *trans,trans* acetal **9** was accomplished by means of a Cornforth olefin synthesis. Thus, stereoselective attack by the Grignard reagent derived from 1-ethylenedioxy-4-chlorobutane afforded from **16** the chlorohydrin **17**, which on treatment with methanolic base was converted to the *trans* epoxide **18**. Deoxygenation of **18** to give the *trans,trans* acetal **9** was accomplished *via* the intermediacy of the iodohydrin **19**.

Cyclization of the acetal **9** with stannic chloride in benzene gave as the sole isolable tricyclic products the 4b-methyldodecahydrophenanthrene mixtures **20** and **21**, with the "natural" *trans,anti,trans* ring fusion, in yields of 45 and 17.5%, respectively. In contrast, cyclization of **9** with stannic chloride in nitromethane at −25°C gave rise to the rearranged system **37** in 44% yield as the major tricyclic product. The structures of **20** and **21** were determined by degradation of each to the same ketone mixture **24**, conversion of **24** to the hydrocarbons **25a** and **25b**, and comparison of **25a** and **25b** with authentic materials prepared from the known ketone **26**. The structures of the rearranged tricyclic system **37** and its degradation products, inferred on spectroscopic grounds, were confirmed by X-ray crystallographic analysis of the *p*-bromobenzoate **48** derived from **37**.

For several years our laboratories have been engaged in testing the validity of the hypothesis that the stereospecificity of squalene biocyclization is a consequence more of intrinsic stereoelectronic factors than of enzymic conformational control (*1*). During the course of these studies, the acetal moiety has been found to be an efficient initiating group for the nonenzymic biogenetic-like cyclization of polyolefins. Thus, for example, treatment of the *trans* dienic acetal **1** (R = H) with stannic chloride in benzene or nitromethane effected rapid stereospecific cyclization of the diene in high yield to the *trans* bicyclic material **2** ($R = HOCH_2CH_2$) (*2*, *3*). In contrast, treatment of the *cis* acetal **3** with stannic chloride–benzene gave as the sole bicyclic material the *cis*-fused ring system **4** in approximately 88% yield (*2*). The enzymatic cyclization of squalene proceeds with total asymmetric induction to produce only one enantiomeric form of the polycyclic products. Of particular significance, therefore, was the observation that stannic chloride catalyzed cyclization of **1** ($R = CH_3$), the diene acetal derived from *l*-2,3-butanediol, gave *trans*-fused bicyclic products **2** ($R = HOCH(CH_3)CH(CH_3)$) that are 92% optically pure with respect to one enantiomer (*3*). This extraordinarily high degree of asymmetric induction approaches that of enzymic processes.

[1] NATO science postdoctoral fellow, 1969–70.

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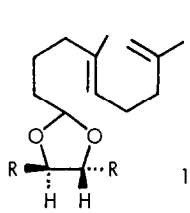

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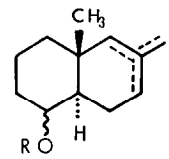

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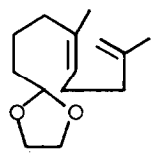

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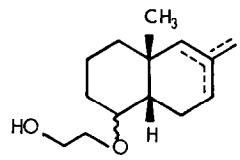

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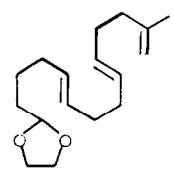
The rapidity and stereospecificity with which the dienic acetals **1** and **3** are converted to bicyclic products suggested that acetals with three or more suitably disposed olefinic bonds might be induced to cyclize to carbocyclic systems containing three or more rings, and that the configurations at the ring junctions of the cyclic products might be controlled by the stereochemistry about the double bonds in the polyene precursors. The trienic acetal **5** (*4*) and the tetraenic acetal **7** (*5*) were therefore prepared, and their behavior under cyclization conditions in hydrocarbon solvents studied (*4*, *5*). The results obtained with the tetraene **7** were particularly gratifying: treatment of **7** with stannic chloride in pentane gave in about 30% yield the two tetracyclic products **8**, epimeric about C-4 (steroid numbering system), with the rings fused exclusively in the



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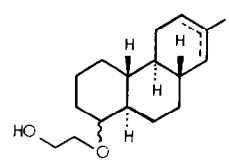

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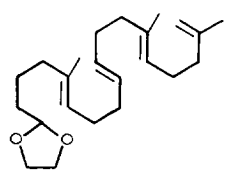

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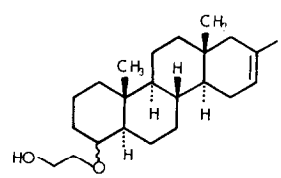


8

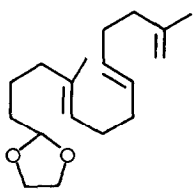
natural *trans,anti,trans,anti,trans* configuration. Significantly, no tetracyclic products with ring-fusion stereochemistry other than that indicated in structure **8** were detected in the cyclization mixture.

Treatment of the triene acetal **5** with stannic chloride in benzene was found to give the *trans,anti,trans* carbocyclic systems **6** in about 50% yield as the only tricyclic products formed, however the rate of conversion of **5** to **6** was much slower than those observed for the cyclizations of **1** and **3**. The marked decrease in rate and yield on

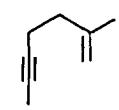
tricyclization as compared with bicyclization was ascribed to the lower nucleophilicity of the 5,6-disubstituted olefinic bond of **5** compared with that of the analogous trisubstituted olefinic functions in the diene acetals **1** and **3**. In order to test the validity of this hypothesis, the synthesis of the 5-methyl trienic acetal **9** was undertaken. The preparation of **9**, and the remarkable influence of solvent on the nature of the cyclization products obtained from this acetal, form the basis of the present paper.

Synthesis

The enyne **10** was converted to its lithio derivative by means of lithium amide, then treated with excess ethylene oxide in ether–liquid ammonia to give the alcohol **11** in 91% yield. Reduction of **11** with a sixfold excess of sodium in ether–liquid ammonia (*6*) afforded in 97% yield the *trans* dienol **12**, homogeneous by both vpc and tlc. The *trans* stereochemistry about the 3,4 double bond formed by the sodium–ammonia reduction was confirmed by the band at 10.35 μ (*trans* —CH=CH—) in the ir spectrum of **12**. The crude oily mesylate **13**, obtained in nearly quantitative yield on treatment of **12**

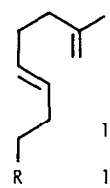


9



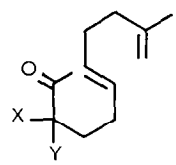
10 R = H

11 R = CH_2CH_2OH



12 R = OH

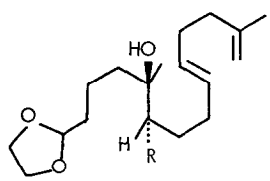
13 R = OSO_2CH_3



14 X = H, Y = $COCH_3$

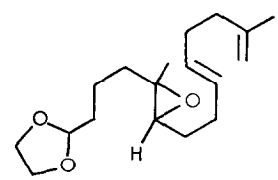
15 X = Cl, Y = $COCH_3$

16 X = Cl, Y = H



17 R = Cl

19 R = I



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with methanesulfonyl chloride in pyridine, was used without further purification to alkylate the sodium enolate of acetylacetone in a dimethylformamide–benzene solvent mixture containing potassium iodide. The resulting dione **14** was obtained as an oil, contaminated with 10% of an impurity presumed to be dialkylated material. Although a sample of the dione after purification by preparative tlc and short-path distillation appeared to be homogeneous by both tlc and vpc, a satisfactory combustion analysis could not be obtained. The assignment of the structure **14** to the dione rests on the ir and nmr spectra of the substance (see Experimental Section), and on the subsequent transformations of the material to more completely characterized products (see below).

The yield of the dione **14** after correction for the presence of the impurity was 69%.

Chlorination of **14** with lithium chloride and cupric chloride in dimethylformamide according to the procedure of Kosower (*7*) gave the chloro dione **15**, which was deacylated with barium hydroxide in ethanol at 0°C to yield the chloro ketone **16** in 80% overall yield from **14**. Transformation of **16** to the trienic acetal **9** was effected by means of a Cornforth stereoselective olefin synthesis (*8*).

Reaction in tetrahydrofuran at −78°C of the chloro ketone **16** with the Grignard reagent (*9*) derived from 1-ethylenedioxy-4-chlorobutane (*10*) gave the chlorohydrin **17** which was converted, without prior purification, to the *trans* epoxide **18** in 93% overall yield from **16** by treatment with methanolic potassium hydroxide at 0°C. Epoxide of sufficient purity (90%) for deoxygenation to the triene **9** was readily obtained by bulb-to-bulb distillation of volatile impurities from the crude reaction mixture.

Treatment of epoxide **18** at −20°C with sodium iodide and sodium acetate in a mixture of propionic and acetic acids effected conversion to the unstable iodohydrin **19** in quantitative yield. According to the original Cornforth procedure (*8*), iodohydrins such as **19** are efficiently converted to *trans*-trisubstituted olefins by removal of the elements of hypoiodous acid on treatment over 2–3 hr with a 25% solution of stannous chloride in pyridine in the presence of phosphorus oxychloride. In the present case, however, yields of only 15–30% of **9** were realized by reaction of **19** under these conditions. This difficulty was overcome by using a more dilute solution of stannous chloride and a longer reaction time. Thus, when the iodohydrin was treated with a 10% solution of stannous chloride in pyridine for 10–12 hr, the *trans,trans* trienic acetal **9** was obtained in yields of 50–75%.

The vapor-phase chromatogram of the acetal **9** displayed two peaks comprising 99% of the total area in the ratio 7:93, with the major peak having the longer retention time. A study in our laboratories of the chromatographic behavior of ten other *cis-trans*-trisubstituted double-bond isomer mixtures has revealed that the *trans* isomer usually has the longer retention time, and accordingly the *trans,trans* configuration could tentatively be assigned to the major isomer of the mixture obtained from the Cornforth sequence. More convincing evidence for the *trans* configuration about the trisubstituted double bond in **9** was provided by the nmr spectrum, which showed the signal for the C-5 vinyl methyl protons at δ 1.60 (*11*).

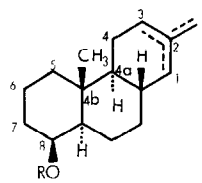
Cyclization in Benzene

Cyclization of the acetal **9** (92% *trans,trans* isomer) as a 0.05 *M* solution in benzene containing 1 mol-equiv of stannic chloride at room temperature was complete in 1 min. Analytical vapor-phase chromatography of the crude product showed nine peaks **A** (5% of total peak area) with retention times of 2–9 min, four broad partially resolved peaks **B** (19%) with retention times between 12.3 and 18.5 min, two partially resolved peaks **C** (54%) at 20.5 and 22.5 min, and two partially resolved peaks **D** (21%) at 24.5 and 26.0 min. Preparative column and thin-layer chromatography of the crude cyclization product resolved the mixture into four fractions. Fraction **I**, which comprised 5% of the weight of the original acetal **9** and corresponded to material **A**, showed no hydroxyl absorption in the ir spectrum. Fraction **II**, obtained in 21% yield, consisted mainly of material **B** contaminated with **C** and **D** to the extent of about 20%. On the basis of the nmr spectrum of fraction **II**, which showed signals for more than three vinylic protons at δ 4.70 and 5.3, and of the ir spectrum, which displayed bands at 10.35 μ (*trans* —CH=CH—) and at 6.07 and 11.25 μ (C=CH_2), this fraction was presumed to consist mainly of mono and bicyclic products. Fractions **III** and **IV**, obtained in yields of 45 and 17.5%, respectively, both displayed weak terminal vinyl

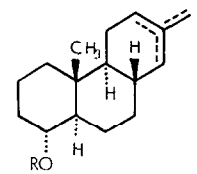
absorption in the ir at 6.07 and 11.25 μ, and signals for 1.1 vinyl hydrogens at δ 4.70, 5.05, and 5.35 in the ratio 1:4:8 in the nmr spectra. Fraction **III** corresponded to material **C**, and fraction **IV** to **D**. The nmr spectrum of **III** showed absorption for two angular methyl groups in the ratio 1:2 at δ 0.93 and 0.95, corresponding to a total of three protons; that of **IV** displayed only a single three-proton angular methyl singlet at δ 0.76. The spectra of **III** and **IV** also had bands attributable to the presence of β-hydroxyethoxy groups in each compound. Combustion analysis indicated the molecular formula $C_{18}H_{30}O_2$ for each of the two fractions.

On the basis of the above evidence, fractions **III** and **IV** (the substances giving rise to the vpc peak groups **C** and **D**) were tentatively assigned structures **20** and **21** respectively, each a mixture of double-bond isomers. These assignments involved the reasonable assumption of a *trans,anti,trans* stereochemistry at the ring junctions. According to this scheme, mixture **20** differed from mixture **21** only in the configuration at C-8. Removal of the β-hydroxyethyl side chains from fractions **III** and **IV** by formation of the tosylates followed by treatment of each with zinc and sodium iodide in glyme (*4*, *12*) gave dissimilar alcohol mixtures (**22** and **23**). On oxidation with Jones reagent (*13*) each of these mixtures was converted to the same mixture of ketones (**24**), thereby establishing the epimeric relationship.

Compilations of data (*14*) derived from the nmr spectra of substituted androstanes have allowed the generalization that the chemical shift of an angular methyl group involved in 1,3-diaxial interaction with an ether or hydroxyl function is shifted downfield by about 0.2 ppm relative to that of an angular methyl free of such interaction. 1,3-Diaxial interactions of the type described would be anticipated in mixture **20**, but not in **21**, where the substituents at C-8 have equatorial configurations. The appearance (see above) of the angular methyl signals in the spectrum of fraction **III**



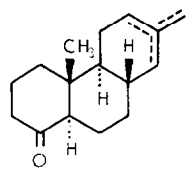
20 R = $HOCH_2CH_2$



21 R = $HOCH_2CH_2$

22 R = H

23 R = H



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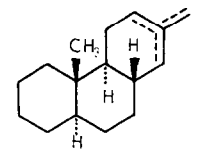

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at about 0.18 ppm lower field than the analogous resonance in the spectrum of fraction **IV** permitted the assignment of structure **20** (axial epimers) to the mixture of double-bond isomers comprising fraction **III**, and of **21** (equatorial epimers) to fraction **IV**. The observation that in the spectrum of the mixture **20** the 4b methyl groups give rise to two separate singlets at δ 0.93 and 0.95, whereas in that of the mixture **21** the 4b methyl groups give only a single signal at δ 0.76 may be a result of the buttressing effect of the C-8 axial side chain in **20** tending to push the angular methyl groups

closer to the regions of influence of the individual double bonds. In mixture **21** there is no such buttressing effect and the 4b methyl groups are influenced by very similar local fields in each of the double-bond isomers.

The characteristic nmr pattern for terminal methylene at δ 4.70 was assigned to the isomers of **20** and **21** having exocyclic double bonds, and the signals at δ 5.05 and 5.35 were associated with the vinyl protons of the endocyclic double bond isomers. In the Δ^1 isomers, the vinyl hydrogens are flanked by only one vicinal methine proton, whereas in the Δ^2 cases, the olefinic protons bear a vicinal relationship to two methylene hydrogens. Therefore, the spectra of the Δ^1 and Δ^2 isomers would be anticipated to display greater broadening (by coupling) of the vinyl hydrogen signal for the Δ^2 isomers than for the Δ^1 cases. Measurement of the width at half-height ($w^{1/2}$) of the signals at δ 5.05 and 5.35 in the spectra of fraction **III** gave values of 5 and 8 Hz, respectively; thus the resonance at δ 5.05 was associated with the Δ^1 olefin constituent of **20**, and that at 5.35 with the Δ^2 isomer. From the relative areas of the three vinyl hydrogen signals in the spectrum of fraction **III** (see above) the composition of the double-bond mixture was estimated to be external double-bond isomer:Δ^1 isomer:Δ^2 isomer = 1:8:16. Because both fractions **III** and **IV** led to the same mixture of ketones (**24**), under conditions not anticipated to isomerize isolated olefinic bonds, the distribution of double-bond isomers in both fractions **III** and **IV** must have been the same. The 1:2 ratio of areas of the two angular methyl signals in the spectrum of fraction **III** indicated that the higher field signal at δ 0.93 was associated with the Δ^1 isomer, and the resonance at 0.95 corresponded to the Δ^2 compound.

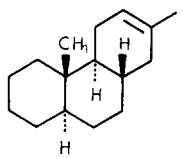
The foregoing structural assignments were based upon the assumption of a *trans, anti,trans* backbone for the cyclization products **20** and **21**. That this assumption was indeed correct was proved by reduction of the ketones **24** to the hydrocarbons **25** and comparison of the latter mixture with authentic materials prepared as described below.

It is known (*15*) that isomerization may occur during the Wolff–Kishner reduction of an epimerizable ketone; however, by forming the hydrazone under mild conditions before addition of the base the epimerization process can be minimized (*16*). Wolff–Kishner reduction of the ketone mixture **24** under these latter conditions gave a hydrocarbon mixture in 84% yield, vapor-phase chromatography of which showed two peaks in the ratio 2:1 constituting 95% of the total area. The other 5% was seen as a shoulder on the major peak, and was assumed to be due to an isomer resulting from cyclization of the *cis,trans* contaminant in the substrate. Preparative vpc effected separation of the mixture into two fractions corresponding to the major peaks evident on vpc analysis of the crude reduction product. The nmr spectrum of the more abundant material exhibited a signal for one vinyl proton at δ 5.35, $w^{1/2} = 8.5$ Hz; that of the second fraction displayed absorptions for one proton at δ 5.05, $w^{1/2} = 5$ Hz, and at 4.70, in the ratio of 4:1. On this basis the more abundant hydrocarbon was assigned the structure **25a**. The other hydrocarbon appeared to be a mixture (**25b**).

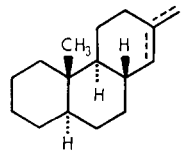
Treatment of the known ketone **26** (*17*),[2] with methyllithium gave in 98% yield a mixture of the epimeric alcohols **27** in the ratio 2:1. Dehydration with phosphorus oxychloride in pyridine afforded an olefinic mixture in 76% yield, the nmr spectrum of which exhibited signals for one vinylic proton at δ 4.70, 5.05, and 5.35 in the ratio 2:5:5. Preparative vpc resolved the mixture into two fractions. The first fraction exhibited a single vinyl hydrogen nmr signal at δ 5.35, $w^{1/2} = 8.5$ Hz, and proved to be identical with **25a** by ir, nmr, mass spectroscopy, tlc, and coinjection vpc. The second

[2] Grateful acknowledgment is made to Dr. R. L. Clarke of the Sterling-Winthrop Research Institute for a generous gift of this material.

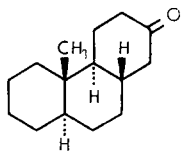
fraction displayed signals for one vinyl proton at δ 4.70 and at 5.05, $w^{1/2} = 5$ Hz; comparison of the material with **25b** showed the two mixtures to be essentially identical. Thus the tricyclic products **III** and **IV** obtained on cyclization of the trienic acetal **9** with stannic chloride in benzene solution have the *trans,anti,trans* structures **20** and **21**.



25a



25b



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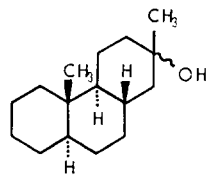

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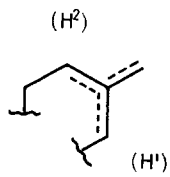
Cyclization in Nitromethane

Cyclization of the acetal **9** (91% *trans,trans* isomer) at –25°C as a 0.05 *M* solution in nitromethane containing 5 mol-equiv of stannic chloride was complete in 1 min. Chromatography over Florisil of the crude product enabled isolation in 44% yield of a white solid, $\bar{v}$, mp 57–61°C. Comparison of $\bar{v}$ with the tricyclic products obtained on cyclization of **9** in benzene showed that **V** was not identical with either **20** or **21**. Further treatment of **V** with stannic chloride in benzene or nitromethane did not give rise to formation of **20** or **21**, nor did similar treatment of **20** and **21** produce any of **V**.

The spectral properties of **V** implied that the cyclization product was tricyclic. In addition to nmr and ir absorptions consistent with the presence of a β-hydroxyethoxy function, **V** displayed in its nmr spectrum two sharp angular methyl singlets for three protons at δ 0.76 and 0.78 in the ratio 1:2, and absorption for one vinyl hydrogen at δ 4.70, 5.35, and 5.55 in the ratio 2:5:3. These latter signals suggested that **V** was a mixture of three double-bond isomers, and that, by analogy with the spectra of the tricyclic materials obtained on cyclization of **9** in benzene discussed above, the partial structure **28** could be written for the ring of **V** containing the double



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bond. The signal at δ 4.70 was, therefore, associated with the isomer containing the exocyclic double bond ("exo" isomer), and the resonances at δ 5.35 and 5.55 to the isomers with endocyclic olefin functions. On the basis of the widths at half-height of the signals at δ 5.35 and 5.55, shown in Table 1, the absorption at δ 5.35 was attributed

to H^2, the vinyl proton flanked by two methylene hydrogens in the Δ^2 isomer, and that at δ 5.55 to H^1, the vinyl proton adjacent to one (or fewer) hydrogens in the Δ^1 isomer.[3] Comparison of the areas under the vinyl hydrogen signals with those under

TABLE 1

SELECTED CHEMICAL SHIFT AND LINE-WIDTH DATA FOR Δ^1 AND Δ^2 ISOMERS[a]

Mixture or compound	Angular methyl, ppm Δ^1	Angular methyl, ppm Δ^2	Vinyl proton, ppm ($w^{1/2}$, Hz) Δ^1	Vinyl proton, ppm ($w^{1/2}$, Hz) Δ^2
V	0.76	0.78	5.55 (5.5)	5.35 (9.0)
VI	0.76	0.78	5.55 (5.0)	5.35 (9.0)
VII	0.82	0.84	5.20–5.40	
VIII	1.03	1.06	4.99 (2.5)	5.35 (6.5)
IX	0.91		5.55 (5.0)	
X		0.91		5.35 (9.0)

[a] Chemical shift values given in ppm downfield from internal tetramethylsilane = 0. Determined in deuterochloroform solution at 60 MHz.

the methyl singlets suggested that the resonance at δ 0.78 was due to the angular methyls of the exo and Δ^2 isomers, whereas the signal at δ 0.76 was associated with the analogous methyl group of the Δ^1 isomer.

Repeated recrystallization of **V** enriched the mixture somewhat in the Δ^2 isomer. Thus, five recrystallizations from pentane gave in 15% recovery a mixture, mp 67–67.5°C, with an isomeric ratio of 4:1 in favor of the Δ^2 over the Δ^1 isomer; further recrystallizations neither raised the melting point nor increased the isomeric ratio. Combustion analysis and mass spectroscopy indicated the molecular formula $C_{18}H_{30}O_2$ for the material mp 67–67.5°C. Attempts to resolve the mixture **V** into its isomeric components by vpc and tlc were uniformly unsuccessful, as were efforts to separate the acetoxy and trimethylsilyloxy derivatives of the cyclization product.

A sample of **V**, mp 63–65°C and consisting of a mixture of the Δ^1 and Δ^2 isomers in the ratio 5:2, was dehydroxyethylated (see above) to give **VI**, an inseparable mixture of secondary alcohols. A significant feature of the nmr spectrum of **VI** was the appearance of the methine proton on the carbon bearing the hydroxyl group as a very broad multiplet extending from δ 3.20–3.95, which implied that the proton was axial, and, therefore, that the hydroxyl group was equatorial, to an assumed cyclohexane ring. Oxidation of the alcohol mixture **VI** with Jones reagent (*13*) afforded in 93% yield a mixture of ketones, **VII**. That the mixture was comprised of two double-bond isomers was indicated by the presence of two angular methyl singlets in the nmr spectrum at δ 0.82 and 0.84, however in this case the broad vinyl hydrogen absorption could not be resolved into signals ascribable to the individual Δ^1 and Δ^2 isomers (see Table 1). The material gave only a single spot on tlc, and showed two only partially resolved peaks on vpc, rendering separation of the mixture into its isomeric components unfeasible. Mixture **VII** displayed absorption in the ir at 5.82 μ, consistent with a carbonyl group in a six-membered ring.

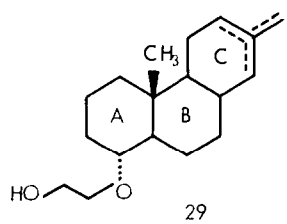
[3] The symbols Δ^1 and Δ^2, H^1, and H^2, arise by analogy with the tricyclic substances **20** and **21**, and are used throughout this discussion as convenient descriptors for the endocyclic double-bond isomers and their respective vinyl hydrogens. The superscripts are not intended as indicators of the locations of the double bonds and vinyl hydrogens under a systematic nomenclature.

As epimerization about a center adjacent to the carbonyl group in **VII** might give information about the geometry of the ring fusion, the ketone was heated with 1 *M* potassium hydroxide in methanol at reflux temperature for 1 hr. Under these conditions, **VII** was epimerized to the extent of approximately 85% to a new ketonic material, **VIII**, giving rise to the appearance of two new angular methyl singlets in the nmr spectrum at δ 1.03 and 1.06 in the ratio 1:2, in addition to vinyl hydrogen signals at δ 4.99 and 5.35 in the approximate ratio 3:5 that could be assigned on the basis of their relative widths (see Table 1) to the Δ^1 and Δ^2 isomers, respectively. It was, therefore, evident that the ketone mixture **VII** was susceptible to epimerization to a more stable ketone mixture **VIII**.

Striking features of the nmr spectra of the mixtures comprising the sequence **V–VIII** (see Table 1) were the changes in the chemical shift of the vinyl hydrogen H^1 associated with the Δ^1 isomer of each of the transformation products. Whereas H^1 appeared at δ 5.55 in the spectra of each of the alcohols **V** and **VI**, on oxidation of **VI** to **VII**, the H^1 signal was shifted to higher field, appearing within the envelope at δ 5.20–5.40 in the spectrum of the latter compound. Epimerization of **VII** to **VIII** caused a further diamagnetic shift, resulting in displacement of the H^1 resonance to δ 4.99 in the spectrum of **VIII**. These diamagnetic shifts could be explained by postulating that in the ketone **VII**, H^1 was within the shielding region of the carbonyl group (*18*), and that on epimerization of **VII** to **VIII** H^1 was brought to a region in the environment of the carbonyl bond effecting a greater shielding of the vinyl proton. Evidence supporting this mechanism for the observed deshielding effect was obtained in the manner outlined below.

Wolff–Kishner reduction of both ketone mixtures **VII** and **VIII** gave rise to the same mixture of Δ^1 and Δ^2 hydrocarbons, indicating that the former ketone had epimerized during the reaction. The hydrocarbon mixture was separable by preparative vpc, giving the Δ^1 olefin **IX** and the Δ^2 olefin **X** in the ratio 2:5. As indicated in Table 1, the signal for H^2 in the nmr spectrum of **X** appeared at δ 5.35, identical in position with the analogous absorption in the spectrum of the epimerized ketone **VIII**. The H^1 resonance in the spectrum of **IX**, however, occurred at δ 5.55, shifted downfield by 0.56 ppm relative to the comparable signal in the spectrum of **VIII**. Such a shift would be anticipated if the deshielding effect observed for the Δ^1 components of **VII** and **VIII** was the result of the anisotropy of the carbonyl groups in the latter ketones.

The assignment of an equatorial configuration to the hydroxyl functions of the dehydroxyethylated alcohols **VI** implied that the side chains of the cyclization products **V** were also equatorial. The cyclization of the acetal **9** in benzene to the *trans,anti,trans* materials **20** and **21** having been demonstrated, it seemed reasonable to postulate a dodecahydrophenanthrene skeleton for the tricyclic products **V** obtained from the cyclization in nitromethane. Thus the partial structure **29** was tentatively assigned to **V**.



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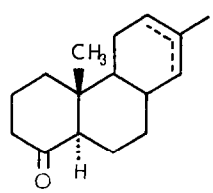

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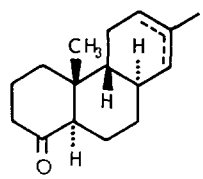
Consideration of the chemical shifts assigned to the angular methyl groups suggested (*14*) that the alcohols **V** and **VI** and the ketones **VII** had *trans*-fused A and B rings, and

that in the epimerized ketones **VIII** and the hydrocarbons **IX** and **X** these rings were fused in a *cis* manner. Thus the epimerization of **VII** to **VIII** was interpreted as a trans to *cis* isomerization, and the ketone mixture **VII** was tentatively assigned the partial structure **30**.

Of the four possible diastereoisomers incorporating the partial structure **30**, only the *trans,syn,trans* isomer **31** (with ring B in the energy-rich boat conformation) would be expected to undergo the aforementioned type of isomerization, i.e., to the *cis,syn,trans* form **32** (*19*). Consideration of molecular models of the Δ^1 isomers of **31** and **32**, however, revealed that in both compounds the vinyl hydrogen H^1 was not in the shielding region of the carbonyl group. Structures **31** and **32** were, therefore, not



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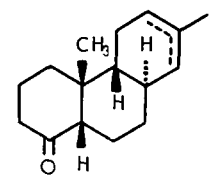

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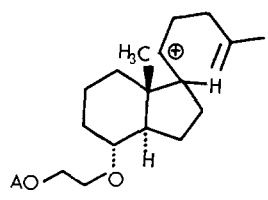
compatible with the observed diamagnetic effects of the carbonyl groups on the vinyl hydrogens of the Δ^1 isomers, and the postulate of a dodecahydrophenanthrene skeleton for **V** was untenable.

Mechanistic considerations suggested that a possible alternative route for the cationic cyclization of acetal **9** in nitromethane might involve the intermediacy of the ion **33**, containing a five-membered B ring. A 1,2-hydrogen shift to the secondary cationic center of **33** could then engender a tertiary carbonium ion, which after intramolecular attack by the terminal double bond followed by loss of a proton and hydrolysis of the Lewis acid complex would give rise to spiro systems such as **34**. That neither diastereo-



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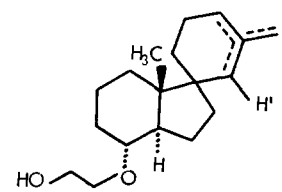

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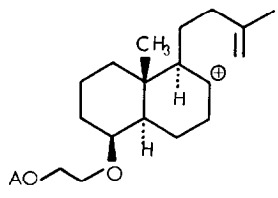
isomer of **34** was a satisfactory representation of the cyclization product **V** was indicated, however, on inspection of appropriate molecular models of the Δ^1 isomers of **34** and of the corresponding sequences of products anticipated to arise on dehydroxyethylation, oxidation, and epimerization. Neither series of Δ^1 compounds displayed geometries enabling a consistent explanation for the diamagnetic shifts of the H^1 vinyl proton signals observed (see above) in the nmr spectra of the sequence **VI** (secondary alcohols), **VII** (ketones), and **VIII** (epimeric ketones).

A more satisfactory structure for the cyclization product **V** was **37**, envisaged as arising from bicyclic cation **35** by a consecutive suprafacial 1,2-hydride and methyl shift to give the tertiary cation **36** followed by intramolecular attack of the terminal

olefinic bond, loss of a proton, and hydrolysis. In accordance with this assignment, **VI**, the product obtained on dehydroxyethylation of the Δ^1 and Δ^2 components of **V**, was given the structure **38**, and the epimerically related ketone mixtures **VII** and **VIII** were represented as **39** and **40**, respectively. The hydrocarbons **IX** and **X**, arising on



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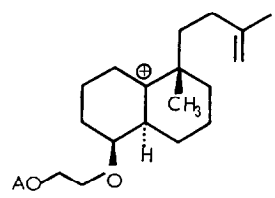

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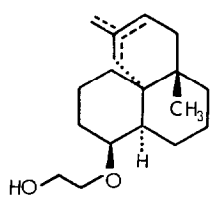

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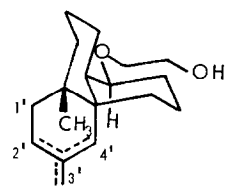

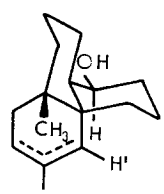

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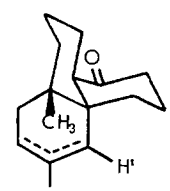

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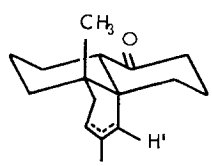

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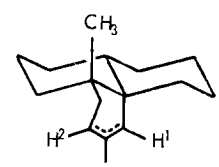


41 Δ^1 isomer[20]

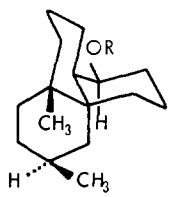
42 Δ^2 isomer[20]

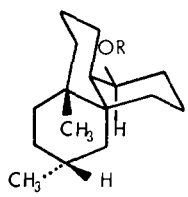
Wolff–Kishner reduction of either **VII** or **VIII**, were, therefore, formulated as **41** and **42**, respectively. Models of the postulated structures revealed that in the Δ^1 isomer of **39** the vinyl hydrogen H^1 was suitably disposed to be shielded by the anisotropy of the carbonyl group, and that in the case of the analogous isomer of **40**, H^1 was positioned still further into the shielding region of the carbonyl function, consistent with the increasing shifts of the H^1 signal to higher field observed in the nmr spectra of mixtures **VII** and **VIII** relative to the position of the H^1 absorption in the spectrum of **VI**.

Estimation of the theoretical relative stabilities of **39** and **40** indicated **40** to be preferred energically over **39**, consonant with the finding that **VII** was converted to a mixture rich in **VIII** on treatment with base.

The transformation of the bicyclic secondary cation **35** to the tertiary ion **36** was viewed as a truncated version of the rearrangement of closely related systems reported by van Tamelen (*20*) and by Stork (*21*). The hydroxyethyl side chain, axial in ions **35** and **36**, becomes equatorial in the cyclization product **37** as a result of the conformational inversion of the A ring that attends the intramolecular cyclization of **36**. Treatment of the acetal **1** (R = H) with stannic chloride in nitromethane has been found to yield the *trans*-fused bicyclic products **2** ($R = HOCH_2CH_2$) in which the isomers bearing axial hydroxyethyl side chains predominate. The stereochemistry of the initial cation **35**, with the ether function in the axial configuration, would therefore parallel that of the simpler case.

The identity of the cyclization product **V** with the tricyclic rearranged structure **37**, and therefore the identities of substances **VI–X** with structures **38–42** respectively, was demonstrated unequivocally in the manner outlined below. A sample of **V** (structure **37**), containing the Δ^1, Δ^2, and exocyclic double-bond isomers in the ratio 1.5:5:1.5, was partially hydrogenated over platinum (*22*) to give a mixture containing **43**, **44** and the unreduced Δ^1 isomer of **37**. Oxidation of the mixture with *m*-chloroperbenzoic acid in methylene chloride converted the olefinic material to an epoxide, separable from the saturated materials **43** and **44** by preparative tlc. Preparative vpc resolved





43 R = $HOCH_2CH_2$ 44 R = $HOCH_2CH_2$

45 R = H 46 R = H

47 R = p-BrC_6H_4CO 48 R = p-BrC_6H_4CO

the mixture of saturated ethers to give **43**, mp 55–56°C, and **44**; the latter was obtained as an oil contaminated with 5% of **43**. Compound **43** displayed absorption for the tertiary and equatorial methyl groups in the nmr spectrum at δ 0.80 and 0.83 ($J = 5$ Hz), respectively, and **44** showed resonances for the tertiary methyl hydrogens at δ 0.80 and for the axial secondary methyl group at 1.12 ($J = 6$ Hz). Dehydroxyethylation of the ethers **43** and **44** by the procedure described above afforded the crystalline epimeric secondary alcohols **45** (mp 114–115°C) and **46** (mp 107–109°C), which in turn were converted to the solid *p*-bromobenzoates **47** (mp 132–133°C) and **48** (mp 114–115°C), respectively. The assignment of structure **48** to the lower melting bromo ester was confirmed by single-crystal X-ray analysis.[4]

The formation of **37** on cyclization of the acetal **9** with stannic chloride in nitromethane stands in sharp contrast with the course of cyclization of **9** in benzene. Analy-

[4] We are indebted to Dr. Luther Smithson for performing the X-ray crystallographic analysis at Syntex Analytical Instruments.

tical vpc studies have indicated that whereas in benzene the *trans,anti,trans* structures **20** and **21** are the only tricyclic materials formed, in nitromethane both the *trans, anti,trans* and the rearranged ring systems are generated, the relative proportions of the two being dependent on the cyclization conditions. Thus, when a 0.05 *M* solution of **9** in nitromethane was treated with 5 mol-equiv of stannic chloride at −20°C, **37** comprised 50% and **20** and **21** 5% of the volatile reaction products. In contrast, cyclization at 24°C resulted in formation of 32% of **37** and 13% of **20** + **21**. Decreasing the relative amount of stannic chloride further increased the proportion of the normal products **20** and **21**: cyclization at 24°C of a 0.05 *M* solution of **9** in nitromethane containing 0.1 mol-equiv of stannic chloride gave rise to 25% **20** + **21** and 30% **37**. In each case, 20–30% of relatively nonvolatile (presumably polymeric) material was formed during the reactions in nitromethane.

EXPERIMENTAL SECTION

All asymmetric compounds described are racemic; the prefix *dl* is omitted. Melting points were determined on a Kofler hot-stage microscope, and are uncorrected. Thin-layer chromatography was performed according to Stahl (E. Stahl, Ed., "Dünnschicht-Chromatographie; ein Laboratoriumshandbuch," Springer-Verlag, Berlin, 1962), with silica gel G (E. Merck AG) as adsorbent. Spots were visualized by means of iodine vapor, or by spraying the plate with a 2% solution of ceric sulfate in 2 *N* sulfuric acid, then heating for 10 min at 150°C. Preparative thin-layer chromatography bands were located by hot-wire charring. Analytical vapor-phase chromatography was performed on Wilkins Aerograph Hy-Fi vapor-phase chromatographs (models A-600 and A-600C) and a Hewlett–Packard 402 Gas Chromatograph, all equipped with hydrogen-flame ionization detectors. Relative peak areas were determined with disk chart integrators; analyses based on relative peak areas are uncorrected for differing molar response factors. The Aerograph machines used nitrogen as carrier gas at a flow rate of approximately 25 ml/min, and were equipped with a metal 7.5-ft × 0.125-in. 15% Carbowax 20-M on 60/80 mesh Chromosorb W column (column A), and a metal 7.5-ft × 0.125-in. 5% SE-30 on 60/80 mesh Chromosorb W column (column B). A glass 4-ft × 0.236-in. 3.5% SE-30 on 60/80 mesh Chromosorb W column (column C) was used for analytical separations with the Hewlett–Packard instrument; helium was employed as carrier gas at a flow rate of approximately 30 ml/min. Preparative vapor-phase chromatography was performed with the Hewlett–Packard machine described above, equipped with a glass 6-ft × 0.314-in. 10% SE-30 on 60/80 mesh Chromosorb W column (column D). Also used was an Aerograph A-700 preparative gas chromatograph employing helium at approximately 200 ml/min as carrier gas and a metal 20-ft × 0.375-in. 15% Carbowax 20-M on 45/60 mesh Chromosorb W (column E) or a 20-ft × 0.375-in. 20% SE-30 on 60/80 mesh Chromosorb W (column F) column. Nuclear magnetic resonance spectra were determined under the supervision of Dr. Lois J. Durham, Department of Chemistry, Stanford University, on Varian Associates T-60, A-60, or HA-100 spectrometers. Unless otherwise stated, deuterochloroform was employed as solvent, and tetramethylsilane as the internal reference. Chemical shifts are reported as δ values in parts per million 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. Spectra were measured at 70 eV nominal beam energy. Microanalyses were performed by Messrs. E. H. Meier and J. Consul, Department of Chemistry, Stanford University.

2-Methyl-1-hexen-5-yne (**10**). A modification of a procedure developed by K. E. Harding was used. To a stirred boiling mixture of magnesium turnings (120 g) and tetrahydrofuran (600 ml) was added over 3 hr 175 ml of a solution of methallyl chloride (110 g) in tetrahydrofuran. After the first 10 ml of the chloride had been added, a few crystals of iodine were introduced to the mixture to initiate the reaction. On completion of the methallyl chloride addition, the reaction mixture was heated at reflux for 1 hr, then cooled and siphoned under nitrogen into a clean dry flask equipped with a stirrer. The solution of the Grignard reagent was cooled to −20°C, and 100 ml of a solution of propargyl bromide (64.4 g, 0.54 mol) was added over 2.25 hr, the temperature not being allowed to exceed −15°C. The reaction mixture was then stirred at ambient temperature overnight.

The stirred mixture was cooled to 0°C, and a saturated solution (80 ml) of ammonium chloride in water was added, followed by solid magnesium sulfate. Stirring was continued for 1 hr, after which the mixture was filtered, and the solid residue washed well with ether. The combined filtrate and washings were dried over magnesium sulfate. Distillation through a 2-ft spinning band column gave 27.3 g of **10** (54%), bp 96–100°C, n^{24}D 1.4290, ir (film) 3.03, 4.75 (—C≡CH), 6.07, 11.25 μ (C=CH_2); nmr δ 1.73 (3 H, d, $J = 1$ Hz), 2.00 (1 H, m), 2.32 (4 H, broad m) and 4.70 (2 H, narrow m).

In a comparable run, distillation through a spinning band of the product gave a fraction bp 96–97°C, $n^{22.5}$D 1.4295.

Anal. Calcd for C_7H_{10}: C, 89.29; H, 10.71. Found: C, 89.1; H, 10.5.

7-Methyl-7-octen-3-yn-1-ol (**11**). To a stirred suspension of lithium amide, prepared by gradual addition of lithium (3.83 g, 0.55 mol) to liquid ammonia (1.5 liter) containing a few crystals of ferric nitrate, was added over 15 min a solution of the alkyne **10** (42.0 g, 0.45 mol) in anhydrous ether (100 ml). The mixture was stirred for 45 min, and then ethylene oxide (200 ml) was added and stirring at −32°C continued for 9 hr. Concentrated ammonium hydroxide (6 ml) was added to destroy excess lithium amide, following which the ammonia was allowed to evaporate overnight. The residue was dissolved in water and extracted with ether. The combined ether extracts were washed with water and brine, and dried over magnesium sulfate. Removal of the solvent under reduced pressure gave 61.2 g of a red oil, which was distilled through a 6-in. Vigreux column to afford 55.9 g (91%) of **11** as a colorless oil, bp 70–71°C (1.0 mm); n^{25}D 1.4740; ir (film) 3.00 (OH), 3.25, 6.07, 11.25 (C=CH_2), and 9.55 μ (—CH_2—O); nmr δ 1.73 (3 H, d, $J = 1$ Hz), 2.08–2.18 (7 H, m), 3.67 (2 H, t, $J = 5$ Hz, R—CH_2—O), and 4.75 (2 H, narrow m).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 77.9; H, 10.2.

trans-*7-Methyl-3,7-octadien-1-ol* (**12**). To a stirred solution of sodium (55 g) in liquid ammonia (2 liters) was added over 30 min a solution of **11** (55.3 g) in anhydrous ether (250 ml). The blue reaction mixture was stirred for 11 hr at −32°C, and then solid ammonium chloride was added to discharge the color. The ammonia was allowed to evaporate overnight, and the residue taken up in water and extracted three times with ether. The combined ether extracts were washed with saturated aqueous sodium bicarbonate, water, and brine, and dried over magnesium sulfate. Removal of the solvent at reduced pressure gave 60.5 g of a light-yellow oil which was distilled through a 6-in. Vigreux column to afford 54.1 g (97%) of **12** as a colorless liquid, bp 90–91°C (4.0 mm); n^{25}D 1.4618; ir (film) 2.95 (OH), 3.25, 6.07, 11.25 (C=CH_2), 9.55 (RCH_2—O), and 10.35 μ (*trans* —CH=CH—); nmr δ 1.70 (3 H, d, $J = 1$ Hz), 2.03–2.53 (7 H, m), 3.62 (2 H, t, $J = 6$ Hz, —CH_2—O), 4.70 (2 H, narrow m), and 5.46 (2 H, m, —CH=CH—). The material was homogeneous as determined by vpc (column A at 135°C) and tlc (20% ethyl acetate–benzene).

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.0; H, 11.5.

trans-*7-Methyl-3,7-octadienyl mesylate* (**13**). To an ice-cold solution of **12** (53.1 g, 0.379 mol) in dry pyridine (500 ml) was added redistilled methanesulfonyl chloride (bp 82–83°C (50 mm), 47.0 g, 0.410 mol), and the mixture maintained at 0°C for 15 min, then at −20°C for 16 hr. The mixture was poured into crushed ice (1.5 kg) mixed with concentrated hydrochloric acid (500 ml), and the aqueous mixture extracted with ether. The combined ether extracts were washed with saturated sodium bicarbonate, water and brine, and dried over magnesium sulfate. Removal of the solvent under reduced pressure at room temperature afforded 84.9 g of **13** as a yellow oil; $n^{25}D$ 1.4643; ir (film) 6.07, 11.25 (C=CH_2), 7.40, and 8.50 μ (—OSO_2CH_3). This material was used without further purification.

trans-*3-Acetyl-10-methyl-6,10-undecadien-2-one* (**14**). A solution of acetylacetone (24.1 g, 0.241 mol) in dry dimethylformamide (10 ml) was added slowly to a vigorously stirred ice-cold suspension of sodium hydride (10.0 g of a 47% dispersion in mineral oil, 0.196 mol) in dimethylformamide (1 liter) and benzene (40 ml). The mixture was warmed to room temperature, and 38.2 g (0.230 mol) of potassium iodide, previously dried at 120°C (0.5 mm) for 4 hr, was added, followed by a solution of the mesylate **13** (51.8 g, 0.238 mol) in dimethylformamide (20 ml). The pale orange solution was stirred at 50–55°C for 21 hr, cooled to room temperature, and poured into 1 liter of water overlaid with 300 ml of pentane. The aqueous phase was separated and extracted with three 250-ml portions of pentane. The combined pentane extracts were washed with cold 2% hydrochloric acid, water, saturated sodium bicarbonate, and brine, and dried over magnesium sulfate. Removal of the solvent under reduced pressure left 57.8 g of a yellow oil, which was distilled through a 6-in. Vigreux column to give, after a forerun of 1.91 g of colorless oil, bp 65–68°C (0.001 mm), the dione **14** as 33.4 g of a colorless liquid, bp 78–80°C (0.001 mm). Vapor-phase chromatographic analysis of the major fraction (column B at 150°C) showed two peaks with retention times of 7 (90%) and 12 min (10%); the latter peak was presumed to be due to dialkylated material. The yield of **14** after correction for the purity of the distilled product was 69%. The material was used without further purification for the next step.

A sample of the distilled material was purified by preparative tlc (20% ethyl acetate–benzene) followed by bulb-to-bulb distillation at 70°C (0.001 mm), giving 0.18 g of **14** as a colorless oil; ir (film), 5.80, 5.85 (C=O), 6.30 (enol C=C), 3.25, 6.07, 11.30 (C=CH_2), and 10.30 μ (*trans* —CH=CH—); nmr δ 1.70 (3 H, "singlet," vinyl CH_3), 1.80–2.14 (8 H, m, —CH_2—), 2.16 (6 H, s, —$COCH_3$), 3.1–5.0 (1 H, m, —COCH-RCO—), 4.70 (2 H, narrow m, C=CH_2), and 5.50 (2 H, m, *trans* —CH=CH—). Although the material was homogeneous as determined by vpc (column B at 130°C) and tlc (20% ethyl acetate–benzene), a satisfactory elemental analysis could not be obtained.

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 74.6; H, 10.1.

trans-*3-Acetyl-3-chloro-10-methyl-6,10-undecadien-2-one* (**15**). A procedure based on that of Kosower (*7*) was used. A solution of the dione **14** (90% pure, 32.8 g, 0.133 mol) in dimethylformamide (20 ml) was added slowly to a stirred solution of lithium chloride (17.0 g, 0.402 mol) and cupric chloride dihydrate (90.5 g, 0.531 mol) in dimethylformamide (1 liter). The green solution was stirred at room temperature for 2 hr and at 55°C for 3 hr, and was then poured into water (1.2 liter) overlaid with 300 ml of pentane. The aqueous phase was extracted with five 200-ml portions of pentane. The combined pentane extracts were washed with water, saturated sodium bicarbonate, and brine, and dried over magnesium sulfate. Removal of the solvent under reduced pressure left 35.8 g (94% after correction for impurities) of **15** as a green oil of 90%

purity as determined by vpc (column B at 150°C). The material was used for the next step without further purification.

A small sample (0.25 g) was purified by preparative tlc (20% ethyl acetate–benzene) followed by bulb-to-bulb distillation at 120°C (0.005 mm), affording 0.19 g of a colorless oil; ir (film) 5.80 (C=O), 6.07, 11.25 (C=CH_2), 10.35 μ (*trans* —CH=CH—); nmr δ 1.70 (3 H, d, J = 1 Hz), 2.05–2.23 (8 H, complex m, —CH_2—), 2.30 (6 H, s, —$COCH_3$), 4.70 (2 H, narrow m, C=CH_2), and 5.45 (2 H, m, *trans* —CH=CH—).

Anal. Calcd for $C_{14}H_{21}O_2Cl$: C, 65.46; H, 8.24; Cl, 13.85. Found: C, 65.5; H, 8.35; Cl, 14.0.

trans-*3-Chloro-10-methyl-6,10-undecadien-2-one* (**16**). To an ice-cold solution of the chloro dione **15** (90% pure, 35.5 g, 0.125 mol) in 95% ethanol (500 ml) was added barium hydroxide octahydrate (22.2 g, 0.0703 mol), and the mixture stirred for 1 hr at 0°C, then poured into water (1.2 liter) overlaid with 350 ml of pentane. The aqueous layer was extracted with four 200-ml portions of pentane. The combined pentane extracts were washed with cold 1% hydrochloric acid, water, saturated sodium bicarbonate, and brine, and were dried over magnesium sulfate. Removal of the solvent under reduced pressure left 26.4 g of a yellow oil which on distillation through a 6-in. Vigreux column afforded 22.8 g (80% overall yield from dione **14**) of **16** as a colorless oil, bp 88–90°C (0.50 mm); n^{25}D 1.4689; ir (film) 5.80 (C=O), 6.07, 11.25 (C=CH_2), 10.35 μ (*trans* —CH=CH—); nmr δ 1.70 (3 H, d, J = 0.5 Hz), 1.80–2.20 (8 H, complex m, —CH_2—), 2.30 (3 H, s, —$COCH_3$), 4.18 (1 H, t, RCHClCO—), 4.65 (2 H, narrow m, C=CH_2), and 5.45 (2 H, m, *trans* —CH=CH—). The material was homogeneous as determined by vpc (column B at 150°C) and tlc (20% ethyl acetate–benzene).

Anal. Calcd for $C_{12}H_{19}OCl$: C, 67.07; H, 8.85; Cl, 16.50. Found: C, 67.4; H, 8.6; Cl, 16.4.

trans-*1-Ethylenedioxy-5,6-epoxy-5,13-dimethyl-9,13-tetradecadiene* (**18**). The following is an application of the general procedure of Cornforth (*8*). To a stirred mixture of oven-dried magnesium turnings (3.6 g, 0.15 g-atoms), tetrahydrofuran (40 ml), and 1,2-dibromoethane (0.5 ml) was added 1 ml of a solution prepared from 1-ethylenedioxy-4-chlorobutane (*10*) (7.4 g, 0.049 mol, bp 93–94°C (17 mm), n^{23}D 1.4515) and tetrahydrofuran (5 ml), and the mixture maintained at 45°C until the reaction was initiated (5–30 min). The remainder of the chloride solution was then added at a rate sufficient to maintain vigorous reflux. The mixture was heated at reflux for 30 min after completion of the addition, and was then cooled gradually to −78°C. A solution of **16** (3.0 g, 0.014 mol) in tetrahydrofuran (5 ml) was added over 30 min, and the mixture stirred at −78°C for 5.5 hr. The reaction mixture was warmed to 0°C, treated with 5 ml of saturated ammonium chloride followed by magnesium sulfate, and filtered. The solid residue was washed with ether, and the combined filtrate and washings were washed with saturated sodium bicarbonate, water and brine, and were dried over magnesium sulfate. Removal of the solvent under reduced pressure left the chlorohydrin **17** as 8.6 g of a yellow oil; ir (film) 2.90 μ (OH).

To the crude chlorohydrin **17** in methanol (60 ml) at 0°C was added with stirring over 30 min a cold solution prepared from 85% potassium hydroxide (3.6 g, 0.054 mol) and methanol (50 ml). The mixture was stirred at 0°C for 2 hr and poured into 300 ml of water containing 50 ml of brine and overlaid with 100 ml of ether. The aqueous phase was extracted with three 100-ml portions of ether. The combined ether extracts were washed with water and brine and dried over magnesium sulfate; removal of the solvent under reduced pressure afforded 5.8 g of a yellow oil. Removal of volatile impurities by distillation at 0.005 mm through a 3-in. Vigreux column (bath temperature 80°C) left epoxide **18** as a residue (4.2 g) of yellow oil of 90% purity as determined by vpc (column

B at 190°C). The crude epoxide (93% yield from chloro ketone **16** after correction for impurities) was used for the preparation of **9** without further purification. A small sample was purified by preparative tlc (20% ethyl acetate–benzene) followed by bulb-to-bulb distillation at 130°C (0.005 mm) to give a colorless oil; ir (film) 6.07, 11.25 (C=CH_2), 10.35 (*trans* —CH=CH—), and 8.80 μ (acetal); nmr δ 1.25 (3 H, broadened singlet, CH_3 on epoxide ring), 2.72 (1 H, t, $J = 6$ Hz, H on epoxide ring), 4.70 (2 H, narrow m, C=CH_2), 4.88 (1 H, unresolved m, O—CHR—O), and 5.49 (2 H, m, *trans* —CH=CH—). The material showed a single spot, R_f 0.35, on tlc (20% ethyl acetate–benzene); vpc (column B at 190°C) indicated one peak, retention time 16 min, with a small shoulder at lower retention time assumed due to the *cis* epoxide.

Anal. Calcd for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.2; H, 10.3.

trans,trans-*1-Ethylenedioxy-5,13-dimethyl-5,9,13-tetradecatriene* (**9**). A modification (see text) of the general procedure devised by Cornforth (*8*) was employed. To a stirred solution at −25°C prepared from sodium iodide (dried at 130°C (0.5 mm) for 12 hr; 20.4 g, 0.14 mol), fused sodium acetate (6.8 g, 0.083 mol), propionic acid (distilled from chromium trioxide; 85 ml), and acetic acid (distilled from chromium trioxide; 25 ml) was added epoxide **18** (90% pure; 3.9 g, 0.13 mol). The orange mixture was stirred at −20°C for 2 hr, at 0–10°C for 1.5 hr, and then added over a period of 30 min to 2.5 liters of saturated sodium bicarbonate overlaid with 1 liter of ether. The aqueous phase was extracted with four 200-ml portions of ether. The combined ether extracts were washed with 5% sodium bisulfite, saturated sodium bicarbonate, water and brine, and dried over magnesium sulfate. Removal of the solvent at 30°C under reduced pressure left the iodohydrin **19** as 6.1 g (quantitative yield) of a red oil that darkened on standing; ir (film) 2.95, 6.07, 8.80, 10.35, and 11.25 μ. The iodohydrin was used immediately for the next step.

The crude iodohydrin **19** (6.1 g) in dry pyridine (10 ml) was added to a solution of anhydrous stannous chloride (9.2 g, 0.48 mol) in pyridine (92 ml). The mixture was cooled to 10°C, and redistilled phosphorus oxychloride (2.4 ml) added over 5 min. The resulting orange-red sludge was stirred at room temperature for 12 hr, diluted with ether (250 ml), and poured into 750 ml of pentane. The mixture was filtered, and the solid residue washed with pentane. The combined filtrate and washings were washed with a dilute solution of iodine in aqueous potassium iodide until the organic phase was saturated with iodine, then with 5% sodium bisulfite, saturated sodium bicarbonate, water and brine. The organic solution was dried over magnesium sulfate, and the solvent removed under reduced pressure to give 3.5 g of a yellow oil which after chromatography over 90 g of Florisil (10% ether–pentane) afforded 3.1 g of a colorless oil. Bulb-to-bulb distillation at 50°C (0.005 mm) gave a minor fraction (0.2 g) containing ca. 15% of the acetal **9** as determined by vpc (see below). Distillation of the residue at 120°C (0.005 mm) afforded 2.7 g (74% yield from epoxide **18**) of **9** as a colorless oil; ir (film) 6.07, 11.25 (C=CH_2), 8.80 (acetal), 10.35 μ (*trans* —CH=CH—); nmr δ 1.60 (3 H, s, CH_3 at C-5), 1.70 (3 H, s, CH_3 at C-13), 4.70 (2 H, narrow m, C=CH_2), 4.88 (1 H, t, $J = 3.5$ Hz, O—CHR—O), 5.15 (1 H, m, vinyl H at C-6), and 5.48 (2 H, m, *trans* —CH=CH—). Vapor-phase chromatography (column B at 190°C) indicated two components in the ratio 7:93, comprising 99% of the total peak area, at retention times of 10.5 and 11.0 min, respectively.

Anal. Calcd for $C_{18}H_{30}O_2$: C, 77.65; H, 10.85. Found: C, 77.7, H, 10.9.

Cyclization of acetal **9** *in benzene.* trans,anti,trans-*2,4b-Dimethyl-8β-(2-hydroxyethoxy)-dodecahydrophenanthrenes* **20** (*Fraction* **III**) *and* trans,anti-trans-*2,4b-dimethyl-8α-(2-hydroxyethoxy)-dodecahydrophenanthrenes* **21** (*Fraction* **IV**). To a stirred solution

of acetal **9** (92% *trans,trans* isomer; 1.0 g, 3.6 mmol) in dry benzene (72 ml) at room temperature was added 0.42 ml (3.6 mmol) of stannic chloride. The mixture immediately turned yellow, and a white solid precipitated after 15 sec. After 1 min, the reaction mixture was poured into 500 ml of cold 2 *N* hydrochloric acid overlaid with 100 ml of ether. The aqueous layer was extracted with three 100-ml portions of ether, and the combined ether extracts were washed with water, saturated sodium bicarbonate, water, and brine, and were dried over magnesium sulfate. Evaporation of the solvent left 0.98 g of viscous yellow oil. Vapor-phase chromatography (column B, 210°) showed nine peaks (5%) with retention times of 1–9 min, four broad partially resolved peaks (19%) at 12.3, 14, 17, and 18.5 min, two partially resolved peaks (54.3%) at 20.5 and 22.5 min, and two partially resolved peaks (21%) at 24.5 and 26.0 min. Chromatography over Florisil (5% ethyl acetate–benzene) and preparative tlc (10% ethyl acetate–benzene) resolved the mixture into four fractions. Fraction **I** consisted of 55 mg of a pale yellow oil having no hydroxyl absorption in the ir, and displaying nine peaks with retention times of 1–9 min (column B, 210°C) on vpc analysis. Fraction **II** (210 mg), a colorless oil, ir (film), 2.90, 6.07, 10.35, and 11.25 μ, displayed absorptions for ca. 3.5 vinyl hydrogens in the nmr spectrum at δ 4.70 and 5.35, and was presumed to consist predominantly of mono- and bicyclic products. Vapor-phase chromatography indicated the presence of ca. 20% of **20** and **21**. Tricyclic alcohol **20** was obtained as fraction **III**, and weighed 0.45 g (45% by weight from starting acetal) after bulb-to-bulb distillation at 130°C (0.005 mm). The colorless oil, ir (film) 2.90, 9.05 and 9.55 ($HOCH_2CH_2OC$), 6.07 (w) and 11.25 (w) μ ($C{=}CH_2$), displayed two partially resolved peaks (98% of total peak area) on vpc (column B, 210°C) at 20.5 and 22.5 min, and a single spot, R_f 0.35 on tlc (10% ethyl acetate–benzene). The nmr spectrum exhibited absorptions for ca. 1.1 vinyl protons at δ 4.70 (exo isomer), 5.05 ($w^{1/2} = 5$ Hz; Δ^1 isomer), and 5.35 ($w^{1/2} = 8$ Hz; Δ^2 isomer) in the ratio 1:4:8; for 5 hydrogens as a multiplet at δ 3.40–3.80 ($CH{-}O{-}CH_2CH_2{-}O$); and for 3 protons as two singlets in the ratio 1:2 at δ 0.93 and 0.95.

Anal. Calcd for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86. Found: C, 77.4; H, 10.8.

Fraction **IV** was obtained as 175 mg (17.5% by weight from starting acetal) of colorless oil after bulb-to-bulb distillation at 130°C (0.005 mm); ir (film) 2.90, 9.05 and 9.50 μ ($HOCH_2CH_2OC$); 6.07 (w) and 11.25 (w) μ ($C{=}CH_2$). Vapor-phase chromatography (column B, 210°C) indicated **IV** to consist of 10% **20** (peaks at 20.5 and 22 min) and 90% **21** (peaks at 24.5 and 26.0 min); tlc (10% ethyl acetate–benzene) showed a major spot with R_f 0.20 (**21**), and a trace with R_f 0.35 (**20**). The nmr spectrum showed absorptions for 1.1 vinylic hydrogens at δ 4.70 (exo isomer), 5.05 ($w^{1/2} = 5$ Hz; Δ^1 isomer), and 5.35 ($w^{1/2} = 8$ Hz; Δ^2 isomer) in the ratio 1:4:8; and for 5 protons as a multiplet at δ 0.78 (angular methyls). A pure specimen of the equatorial isomers **21** was obtained from 60 mg of fraction **IV** by preparative vpc (column D at 220°C) followed by bulb-to-bulb distillation at 130°C (0.005 mm), affording 40 mg of **21** as a colorless oil.

Anal. Calcd for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86. Found: C, 77.7; H, 10.7.

trans,anti,trans-*2,4b-Dimethyl-8β-hydroxydodecahydrophenanthrenes* **22**. To a solution of **20** (300 mg 1.1 mmol) in dry pyridine (1.5 ml) at 0°C was added an ice-cold solution of *p*-toluenesulfonyl chloride (230 mg, 1.2 mmol) in pyridine (1.5 ml), and the mixture maintained at 0°C for 15 min and at −22°C for 21 hr. Eighty-five percent lactic acid (0.2 ml) was added, and the mixture swirled and poured into 10 ml of 10% lactic acid in water overlaid with 10 ml of ether. The aqueous layer was extracted with three 10-ml portions of ether, and the combined ether extracts washed with cold 2 *N* hydrochloric acid, saturated sodium bicarbonate, water, and brine, and dried over

magnesium sulfate. Removal of the solvent under reduced pressure gave the *p*-toluenesulfonate ester of **20** as 400 mg of pale yellow oil; ir (film) 8.45, 8.55 μ.

The crude tosylate was dissolved in dry glyme (30 ml); zinc dust (500 mg, 7.7 mg-atom) and anhydrous sodium iodide (500 mg, 3.3 mmol) were added, and the mixture heated at reflux for 3.5 hr. The mixture was cooled, filtered, and the solid residue washed with ether. The combined filtrate and washings were washed with 5% sodium bisulfite, water, saturated sodium bicarbonate, and brine, and dried over magnesium sulfate. Removal of the solvent left 234 mg of yellow oil, which after bulb-to-bulb distillation at 130°C (0.005 mm) afforded 201 mg (80% from **20**) of **22** as a colorless oil, ir (film) 2.90, 9.51 μ. Vapor-phase chromatography (column B at 195°C) showed two partially resolved peaks with retention times of 10.8 and 11.4 min; tlc (25% ether–pentane) showed one spot, R_f 0.25. The nmr spectrum exhibited absorptions for 1.1 vinyl hydrogens at δ 4.70 (exo isomer), 5.05 ($w^{1/2} = 5$ Hz; Δ^1 isomer), and 5.35 ($w^{1/2} = 8.2$ Hz; Δ^2 isomer); for 1 proton as a broad signal at δ 3.85 (H—C—O); and for 3 hydrogens as two singlets at δ 0.95 and 0.98 (angular methyls).

Anal. Calcd for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 81.9; H, 11.1.

trans,anti,trans-*2,4b-Dimethyl-8α-hydroxydodecahydrophenanthrenes* **23**. The procedure described above for the formation of **22** from **20** was used. Thus, treatment of **21** (36 mg, 0.13 mmol) with *p*-toluenesulfonyl chloride (36 mg, 0.19 mmol) in dry pyridine (0.6 ml) gave the tosylate of **21** as 54 mg of a yellow oil, ir (film) 8.45, 8.50, and 9.05 μ. Reaction of the crude tosylate with zinc dust (500 mg) and anhydrous sodium iodide (500 mg) in dry glyme (18 ml) gave 29 mg of a yellow oil which afforded 24 mg (79% from **21**) of **23** as a colorless oil on bulb-to-bulb distillation at 130°C (0.005 mm); ir (film) 2.90, 9.51 μ. Vapor-phase chromatography (column B at 195°C) showed two partially resolved peaks with retention times of 10.8 and 11.4 min; tlc (25% ether–pentane) showed one spot, R_f 0.18. The nmr spectrum exhibited absorptions for 3 protons as a singlet at δ 0.76 (angular methyls), for 1 proton as a very broad signal at δ 3.20–3.85 (H—C—O), and for 1.1 vinyl hydrogens as multiplets at δ 4.70, 5.05, and 5.35. The mass spectrum showed a molecular ion peak at *m/e* 234, however a satisfactory combustion analysis could not be obtained.

Anal. Calcd for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 81.2; H, 11.2.

trans,anti,trans-*2,4b-Dimethyl-8-ketododecahydrophenanthrenes* **24**: (a) *From the axial alcohols* **22**. Jones reagent (*13*) was added to a solution of **22** (100 mg, 0.42 mmol) in acetone (10 ml) at 0°C until an orange color persisted for 5 min. Isopropyl alcohol was added to discharge the orange color, and the resulting mixture was diluted with water and extracted with three 15-ml portions of ether. The combined ether extracts were washed with saturated sodium bicarbonate, water, and brine, and dried over magnesium sulfate. Removal of the solvent under reduced pressure gave 98 mg of a yellow oil, which on bulb-to-bulb distillation at 130°C (0.005 mm) afforded **24** as 95 mg (96%) of a colorless oil; ir (film) 5.81 μ. Vapor-phase chromatography (column B at 195°C) showed two partially resolved peaks with retention times of 10.5 and 11.2 min; tlc (25% ether–pentane) revealed a single spot, R_f 0.40. The nmr spectrum showed absorption for 3 hydrogens as a sharp singlet at δ 0.70 (angular methyls), and for 1 vinyl proton as signals at δ 4.70 (exo isomer) and 5.35 ($w^{1/2} = 5$ Hz).

Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.4; H, 10.4.

(b) *From the equatorial alcohols* **23**. Oxidation of **23** (18 mg, 0.07 mmol) by the procedure described above for the conversion of **22** to **24** gave after evaporation of the solvent 16 mg of a yellow oil, which was distilled (bulb-to-bulb) at 130°C (0.005 mm) to yield 14 mg (76%) of a colorless oil. This material was essentially identical (ir, nmr, mass spectroscopy) with the ketone mixture **24** obtained on oxidation of **22**.

trans,anti,trans-*2,4b-Dimethyl-Δ²-dodecahydrophenanthrene* (**25a**) *and* trans,anti,trans-*2,4b-dimethyldodecahydrophenanthrenes* **25b**. To a solution of **24** (95 mg, 0.41 mmol) in triethylene glycol (6 ml) was added 1 ml of 97% hydrazine, and the solution kept at 0°C for 16 hr. Eighty-five percent potassium hydroxide (150 mg, 2.3 mmol) was added, and the mixture heated at 135°C for 1 hr and at 195°C for 3 hr, then cooled to room temperature and diluted with water. The aqueous mixture was extracted with pentane, and the combined pentane extracts were washed with water and brine and dried over magnesium sulfate. Removal of the solvent left 85 mg of a yellow oil, which on bulb-to-bulb distillation at 120°C (0.005 mm) afforded 75 mg (84%) of hydrocarbon mixture **25** as a colorless oil. Analytical vpc (column B at 160°C) showed two peaks (95% of total peak area) with retention times of 8.7 and 9.5 min, and a third peak (5%) with a retention time of 8.4 min. The nmr spectrum displayed absorptions for 1 proton at δ 4.70 (exo isomer), 5.05 ($w^{1/2} = 5$ Hz; Δ^1 isomer), and 5.35 ($w^{1/2} = 8.5$ Hz; Δ^2 isomer), and for 3 hydrogens as a singlet at δ 0.73 (angular methyls). Preparative vpc (column E at 180°C) afforded two fractions. The first fraction was distilled (bulb-to-bulb) at 120°C (0.005 mm) to give **25a** as 25 mg of a colorless oil; nmr δ 0.73 (3 H, s, angular CH_3) and 5.35 (1 H, m, vinyl H). Analytical vpc (column B, 160°C) showed the substance to be >99% pure, retention time 8.7 min. This material was essentially identical (ir, nmr, mass spectroscopy, vpc, and tlc) with authentic *trans,anti,trans*-2,4b-dimethyl-Δ^2-dodecahydrophenanthrene prepared as described below.

Anal. Calcd for $C_{16}H_{26}$: C, 88.00; H, 12.00. Found: C, 88.1; H, 11.95.

The second fraction from the preparative vpc separation was distilled (bulb-to-bulb) at 100°C (0.005 mm) to afford mixture **25b** as 11 mg of a colorless oil. Analytical vpc (column B, 160°C) showed a single peak with retention time 9.5 min. The nmr spectrum of the oil showed absorptions for 1 vinyl hydrogen at δ 4.70 (exo isomer) and 5.05 (Δ^1 isomer) in the ratio 1:4. This material was essentially identical (ir, nmr, mass spectroscopy, vpc, and tlc) except for the relative amounts of the two components to an authentic mixture of *trans,anti,trans*-2,4b-dimethyl-Δ^1-dodecahydrophenanthrene and *trans,anti,trans*-4b-methyl-2-methylideneperhydrophenanthrene prepared as described below.

Anal. Calcd for $C_{16}H_{26}$: C, 88.00; H, 12.00. Found: C, 88.0; H, 12.1.

Authentic comparison compounds: trans,anti,trans-*2,4b-Dimethyl-Δ²-dodecahydrophenanthrene* (**25a**) *and* trans,anti,trans-*2,4b-dimethyldodecahydrophenanthrenes* **25b**. To a stirred solution of ketone **26** (*17*),[2] (100 mg, 0.46 mmol) in ether (5 ml) at 0°C was added 5 ml (8.5 mmol) of ethereal 1.7 *M* methyllithium (Foote Mineral Company) over 5 min. Stirring was continued at 0°C after completion of the addition for 20 min. The reaction mixture was diluted with water, and extracted with three 20-ml portions of ether. The combined ether extracts were washed with water and brine and dried over magnesium sulfate. Evaporation of the solvent gave 105 mg (98%) of the epimeric mixture **27** as a colorless viscous oil; ir (film) 2.90 μ. Vapor-phase chromatography (column B at 160°C) showed two peaks in the ratio 2:1 with retention times of 17.4 and 19.2 min, respectively.

To a stirred solution of **27** (60 mg, 0.25 mmol) in pyridine (0.8 ml) at 0°C was added 0.18 ml of phosphorus oxychloride. The solution was stirred at 0°C for 30 min, then at room temperature for 18 hr, and poured into cold 2 *N* hydrochloric acid. The aqueous mixture was extracted with ether, and the combined ether extracts were washed with saturated sodium bicarbonate, water, and brine, and dried over magnesium sulfate. Evaporation of the solvent left 50 mg of a yellow oil which afforded 42 mg (76%) of an olefinic mixture of hydrocarbons as a colorless oil on bulb-to-bulb distillation at 120°C (0.005 mm). Vapor-phase chromatography (column B at 160°C)

showed two peaks at 8.7 and 9.5 min in the ratio 48:52, respectively; tlc (20% ethyl acetate–benzene) revealed a single spot, R_f 0.72. The nmr spectrum showed absorption for 1 vinyl hydrogen at δ 4.70 (exo isomer), 5.05 ($w^{1/2} = 5$ Hz; Δ^1 isomer), and 5.35 ($w^{1/2} = 8.4$ Hz, Δ^2 isomer), and for 3 protons as a singlet at δ 0.72 (angular methyls). Preparative vpc (column E at 180°C) followed by bulb-to-bulb distillation at 100°C (0.005 mm) gave two fractions as colorless oils. The first (13 mg) was the Δ^2 isomer **25a**; nmr δ 0.72 (3 H, s, angular CH_3) and 5.35 (1 H, $w^{1/2} = 8.4$ Hz, vinyl H). Vapor-phase chromatography (column B at 160°C) indicated one peak, retention time, 8.7 min. The second fraction (15 mg) was mixture **25b**. Vapor-phase chromatography (column B, 160°C) indicated a single peak, retention time, 9.5 min. The nmr spectrum showed absorption for 1 vinyl hydrogen at δ 4.70 (exo isomer) and 5.05 ($w^{1/2} = 5$ Hz, Δ^1 isomer) in the ratio 1:2, and a signal for 3 angular methyl protons at δ 0.72.

Cyclization of acetal **9** *in nitromethane. Tricyclic alcohols* **37**. To a stirred solution of acetal **9** (91% *trans,trans* isomer; 2.0 g, 7.2 mmol) in nitromethane (146 ml) at −25°C was added 4.2 ml (36 mmol) of stannic chloride over 10 sec. The reaction mixture immediately turned pale orange, and a precipitate developed within 10 sec of completion of the addition. The mixture was stirred for 1 min, and poured into 1 liter of cold 2 *N* hydrochloric acid overlaid with 300 ml of ether. The aqueous layer was extracted with three 200-ml portions of ether, and the combined ether extracts were washed with cold 2 *N* hydrochloric acid, water, saturated sodium bicarbonate, and brine, and dried over magnesium sulfate. Removal of the solvent under reduced pressure left 1.91 g of a viscous yellow oil. Vapor-phase chromatography (column B at 210°C) showed a major peak (75% of total peak area; **37**) with a retention time of 17.5 min, in addition to at least six peaks (5%) at 2–9 min, four peaks (17%) between 11 and 16 min, and two partially resolved peaks (3%; *trans,anti,trans* alcohols **20**) at 20.2 and 22.4 min.

Column chromatography over 100 g of Florisil (4:1 pentane–ether) afforded three main fractions. The first (95 mg) consisted of a colorless oil having no hydroxyl absorption in the ir and displaying at least nine peaks between 2 and 9 min on vpc. The second fraction (940 mg) was a colorless oil containing 65% of **37** as indicated by the area of the peak at 17.5 min on vpc. The oil was distilled (bulb-to-bulb) at 135°C (0.005 mm), and the distillate dissolved in pentane and seeded with a crystal of **37** (see below). Crystallization at −20°C afforded 455 mg of **37**, mp 41–45°C. The third fraction (796 mg) was distilled (bulb-to-bulb) at 130°C (0.005 mm) to give 732 mg of an oil containing 85% **37** as estimated by vpc. A solution of the oil in pentane at −20°C after seeding afforded 520 mg of **37**, mp 47–51°C. The two crops were combined and recrystallized twice from pentane at −20°C to give 875 mg (44% by weight from acetal **9**) of **37**, mp 57–61°C. The nmr spectrum indicated an isomer ratio of 3:5:1 for the Δ^1, Δ^2, and exo isomers, respectively. Four more recrystallizations from pentane afforded a sample of **37** (350 mg) with mp 63–65°C, consisting of the Δ^1 and Δ^2 isomers in the ratio 2:5 as estimated by nmr. This material was used for degradation to the secondary alcohols **38** (see below).

In a smaller scale run, 1 ml (9 mmol) of stannic chloride was added all at once to 0.5 g (1.8 mmol) of acetal **9** in 36 ml of nitromethane at −25°C. The mixture was stirred for 1 min and worked up as described above to give 0.45 g of a red oil. Chromatography over 50 g of Florisil (1:1 ether–pentane) fortuitously afforded an oily fraction (50 mg) rich in **37** which partially solidified on storage at −20°C; ir (film) 2.90, 6.07 (vw), 9.05, 9.35, 11.25 (w) μ. The nmr spectrum exhibited absorptions for 1.1 vinyl protons at δ 4.70 (exo isomer), 5.35 ($w^{1/2} = 9$ Hz; Δ^2 isomer[3]) and 5.55 ($w^{1/2} = 5.5$ Hz; Δ^1 isomer[3]), in the ratio 1:3:6, respectively. Four recrystallizations from pentane afforded 11 mg of a mixture of **37**, mp 67–67.5°C, consisting of the Δ^1 and Δ^2 isomers in the ratio

1:4. This material was used to provide seed crystals for use in the isolation of **37** from the larger scale cyclization described above. Further recrystallization did not alter the melting point or the isomeric ratio of the sample.

Anal. Calcd for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86. Found: C, 77.5; H, 10.9.

Dehydroxyethylation of **37**. *Secondary alcohols* **38**. The procedure described for the preparation of **22** from **20** was used. Thus, treatment of **37** (mp 57–61°C; 290 mg, 1.04 mmol) with *p*-toluenesulfonyl chloride (222 mg, 1.2 mmol) in dry pyridine (2.8 ml) afforded the tosylate of **37** (445 mg) as a pale-yellow oil; ir (film) 8.45, 8.55 μ. Reaction of the crude tosylate with zinc dust (1.0 g) and anhydrous sodium iodide (1.0 g) in dry glyme (25 ml) gave 252 mg of a colorless oil. Column chromatography over Florisil (1:1 pentane–ether) afforded in two fractions 216 mg (88%) of **38** as a colorless oil; ir (film) 2.98 μ. A small portion was distilled (bulb-to-bulb) at 150°C (0.005 mm) to provide a sample for elemental analysis; the remainder afforded 177 mg after distillation under the same conditions.

Anal. Calcd for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 81.8; H, 11.0.

The nmr spectrum of a sample of **38** obtained from a comparable experiment exhibited absorptions for 1 vinyl proton at δ 5.35 ($w^{1/2} = 9$ Hz; Δ^2 isomer[3]) and 5.55 ($w^{1/2} = 5$ Hz; Δ^1 isomer), for 1 proton as a broad signal at δ 3.25–3.95 (H—C—O), and for 3 protons as two singlets at δ 0.76 and 0.78 in the ratio 1:2 (angular methyls). Vapor-phase chromatography and tlc failed to separate the isomeric mixture.

Oxidation of **38** *to ketone mixture* **39**. A solution of **38** (167 mg, 0.72 mmol) in acetone (5 ml) was oxidized with Jones reagent (*13*) by the procedure described above for the preparation of **24** to give 165 mg of a yellow oil, which on bulb-to-bulb distillation at 130°C (0.005 mm) afforded **39** as 157 mg (93%) of a colorless oil; ir (film) 5.82 μ. Vapor-phase chromatography (column B at 160°C) showed two partially resolved peaks. The nmr spectrum displayed absorptions for 1 proton as a broad signal at δ 5.20–5.40 (vinyl H), and for 3 protons as two singlets at δ 0.82 and 0.84 in the ratio 1:2. The mass spectrum showed a molecular ion peak at *m/e* 232, however a satisfactory combustion analysis could not be obtained.

Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.1, H, 10.4.

Epimerization of **39**. The ketone mixture **39** (20 mg) in 1 ml of 1 *M* potassium hydroxide was heated at reflux for 1 hr, then cooled and poured into 10 ml of cold 1 *N* hydrochloric acid overlaid with 10 ml of ether. The aqueous layer was extracted with three 5-ml portions of ether, and the combined ether extracts were washed with saturated sodium bicarbonate, water, and brine, and dried over magnesium sulfate. Removal of the solvent under reduced pressure left 20 mg of a yellow oil, which was distilled (bulb-to-bulb) at 130°C (0.005 mm) to give a ca. 86:14 mixture of **39** and **40**; ir (film) 5.82 μ. Vapor-phase chromatography (column B at 160°C) showed two partially resolved peaks. The nmr spectrum exhibited absorptions for 1 proton at δ 4.99 ($w^{1/2} = 2.5$ Hz; Δ^1 isomer[3] of **40**) and 5.35 ($w^{1/2} = 6.5$ Hz; Δ^2 isomer[3] of **40**) in the ratio 2:5, for 2.6 protons as two singlets at δ 1.03 and 1.06 (angular methyls of **40**) in the ratio 1:2, and for 0.4 protons as two singlets at δ 0.82 and 0.84.

Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.5; H, 10.6.

Wolff–Kishner reduction of ketone mixture **39**. *1α,9α-(3′-Methyl-$\Delta^{3',4'}$-buteno)-1β-methyl-10β-decalin* (**41**) *and 1α,9α-(3′-methyl-$\Delta^{2',3'}$-buteno)-1β-methyl-10β-decalin* (**42**). The procedure described for the analogous reduction of **24** was employed. Thus, 1 ml of 97% hydrazine was added to a solution of **39** (54 mg, 0.23 mmol) in 5 ml of triethylene glycol, and the yellow solution kept at 0°C for 12 hr. Potassium hydroxide (85%, 150 mg, 2.3 mmol) was added, and the mixture heated at 115° for 1 hr, and at 195°C for 3 hr. The product amounted to 45 mg of yellow oil, which afforded 33 mg (65%)

of a mixture of **41** and **42** on bulb-to-bulb distillation at 120°C (0.005 mm). Vapor-phase chromatography (column C at 130°C) indicated two major peaks with retention times of 7.1 and 8.2 min, with a minor peak (5%) appearing as a shoulder at longer retention time on the peak at 8.2 min. The nmr spectrum exhibited absorptions for 1 proton at δ 5.35 ($w^{1/2} = 9$ Hz; vinyl H of Δ^2 isomer[3] **42**) and 5.55 ($w^{1/2} = 5$ Hz; vinyl H of Δ^1 isomer[3] **41**) in the ratio 5:2, and for 3 protons as a singlet at δ 0.91 (angular methyls). Preparative vpc (column F) afforded two fractions. The first fraction, after bulb-to-bulb distillation at 100°C (0.005 mm), gave **42** (10 mg); nmr δ 0.91 (3 H, s, angular CH_3) and 5.35 (1 H, $w^{1/2} = 9$ Hz, vinyl H); M^+ peak at *m/e* 218. Vapor-phase chromatography (column C at 130°C) indicated a single peak with retention time 7.2 min.

Anal. Calcd for $C_{16}H_{26}$: C, 88.00; H, 12.00. Found: C, 88.2; H, 12.1.

The second fraction was distilled (bulb-to-bulb) at 120°C (0.005 mm) to give **41** (6 mg); nmr δ 0.91 (3 H, s, angular CH_3) and 5.55 (1 H, $w^{1/2} = 5$ Hz, vinyl H); M^+ peak at *m/e* 218. Vapor-phase chromatography (column C at 130°C) showed a single peak, retention time 8.2 min.

Anal. Calcd for $C_{16}H_{26}$: C, 88.00; H, 12.00. Found: C, 88.2; H, 11.9.

Wolff–Kishner reduction of epimeric ketone mixture **39** + **40**. A portion (11 mg, 0.05 mmol) of the ketone mixture **39** + **40** obtained on epimerization of **39** as described above was treated with 97% hydrazine (0.2 ml) in ethylene glycol (1 ml), and then with 85% potassium hydroxide (30 mg, 0.46 mmol) under the conditions described in the case of the reduction of **39**. Bulb-to-bulb distillation at 120°C (0.005 mm) afforded 8 mg (78%) of a mixture of **41** and **42** identical (ir, nmr, tlc, and vpc) with the mixture obtained on Wolff–Kishner reduction of **39**.

Partial hydrogenation of **37**. *1α,9α-(3′β-Methyltetramethylene)-1β-methyl-5β-(2-hydroxyethoxy)-10α-decalin* (**43**) *and 1α,9α-(3′α-methyltetramethylene)-1β-methyl-5β-(2-hydroxyethoxy)-10α-decalin* (**44**). The sample of **37** employed, mp 57–62°C, was 90% tricyclic material as estimated by vpc, and contained the Δ^1, Δ^2, and exocyclic isomers[3] of **37** in the ratio 1.5:5:1.5.

To a stirred mixture of platinum oxide (23 mg) in absolute ethanol (5 ml), prereduced with hydrogen at atmospheric pressure, was added a solution of **37** (230 mg, 0.81 mmol) in absolute ethanol (5 ml). After an uptake at atmospheric pressure of 14 ml of hydrogen, absorption practically ceased. The mixture was filtered through a pad of Celite which was then rinsed with ether. Removal of the solvent from the combined filtrate and washings left 220 mg of an oil which on bulb-to-bulb distillation at 130°C (0.005 mm) afforded 210 mg (91% by weight) of a mixture consisting predominantly of **43**, **44**, and the Δ^1 isomer[3] of **37**; nmr δ 5.55 (ca. 0.2 H, $w^{1/2} = 5$ Hz, Δ^1 isomer[3] of **37**).

The reduction mixture, 85% *m*-chloroperbenzoic acid, (81 mg, 0.40 mmol), and dichloromethane (5 ml) were stirred for 12 hr. Aqueous 10% sodium bisulfite (1 ml) and water (5 ml) were added, and the aqueous layer was extracted with ether. The combined ether extracts were washed with saturated sodium bicarbonate, water, and brine, and dried over magnesium sulfate. Removal of the solvent, followed by bulb-to-bulb distillation of the residue, gave 170 mg of a colorless oil. Preparative tlc (30% ether–pentane) gave a mixture of **43** and **44** (120 mg). Bulb-to-bulb distillation at 130°C (0.005 mm) followed by preparative vpc (column D at 220°C) afforded two main fractions. The first fraction was distilled (bulb-to-bulb) at 130°C (0.005 mm) to give 44 mg of **43** as a colorless oil that crystallized on standing; mp 55–56°C; ir (film) 2.90, 9.05, 9.50 μ. The nmr spectrum exhibited absorptions for 6 protons as a singlet at δ 0.80 (angular CH_3) superimposed on a doublet at δ 0.83, $J = 5$ Hz (CH_3 at C-3′).

Anal. Calcd for $C_{18}H_{32}O_2$: C, 77.09; H, 11.50. Found: C, 77.2; H, 11.4.

Bulb-to-bulb distillation of the second fraction at 130°C (0.005 mm) gave 23 mg of **44** as a colorless oil; ir (film) 2.90, 9.05, 9.50 μ; nmr δ 0.80 (3 H, s, angular CH_3) and 1.12 (3 H, d, $J = 6$ Hz, CH_3 at C-3′). Vapor-phase chromatography (column C at 180°C) indicated that this material was contaminated with ca. 5% of **43**. All attempts to induce crystallization were unsuccessful.

Anal. Calcd for $C_{18}H_{30}O_2$: C, 77.09; H, 11.50. Found: 77.4; H, 11.7.

1α,9α-(3′β-Methyltetramethylene)-1β-methyl-5β-hydroxy-10α-decalin (**45**). The procedure described for the preparation of **22** from **20** was used. Treatment of **43** (44 mg, 0.16 mmol) with *p*-toluenesulfonyl chloride (38 mg, 0.2 mmol) in dry pyridine (0.2 ml) gave the tosylate of **43** as 70 mg of a colorless oil; ir (film) 6.25, 8.45–8.55 μ. Reaction of the crude tosylate with zinc dust (0.5 g, 7.7 mmol) and sodium iodide (0.5 g, 3.3 mmol) in glyme (10 ml) afforded 35 mg of a yellow solid. Bulb-to-bulb distillation at 130°C (0.005 mm) gave **45** as 33 mg (89%) of a colorless solid, mp 112–114°C; ir (CCl_4) 2.70, 2.80, 8.95, 9.50 μ. The nmr spectrum exhibited absorptions for 6 protons as a singlet at δ 0.80 (angular CH_3) superimposed on a doublet, $J = 5$ Hz, at δ 0.90 (secondary CH_3 at C-3′), and for 1 proton as a multiplet centered at δ 3.98 (H—C—O). One recrystallization from petroleum ether (30–60°C) afforded material mp 114–115°C.

Anal. Calcd for $C_{16}H_{28}O$: C, 81.29; H, 11.94. Found: C, 81.3; H, 11.8.

1α,9α-(3′α-Methyltetramethylene)-1β-methyl-5β-hydroxy-10α-decalin (**46**). The procedure described for the preparation of **22** from **20** was employed. Reaction of **44** (22 mg, 0.079 mmol) with *p*-toluenesulfonyl chloride (19 mg, 0.1 mmol) in pyridine (0.2 ml) gave the tosylate of **44** (38 mg) as a colorless oil; ir (film) 6.25, 8.45–8.55 μ. Treatment of the crude tosylate with zinc dust (0.3 g, 4.6 mmol) and sodium iodide (0.3 g, 2.0 mmol) in glyme (6 ml), followed by bulb-to-bulb distillation of the crude product at 130°C (0.005 mm) afforded 18 mg of a solid, mp 107–109°C. Two recrystallizations from petroleum ether (30–60°C) gave **46** as 9 mg of a white solid, mp 118–119.5°C; ir (CCl_4) 2.74, 2.90, 8.95, 9.55 μ. The material was homogeneous as determined by vpc (column C at 150°C) and by tlc (25% ether–pentane).

1α,9α-(3β′-Methyltetramethylene)-1β-methyl-5β-hydroxy-10α-decalin p-*bromobenzoate* (**47**). Prior to its use in the preparation of **47** and **48**, *p*-bromobenzoyl chloride (Aldrich Chemical Co., Inc.) was heated with thionyl chloride at reflux for 3 hr. The thionyl chloride was removed by distillation.

A solution of *p*-bromobenzoyl chloride (50 mg, 0.23 mmol) in dry pyridine (0.3 ml) was added to a solution of **45** (33 mg, 0.14 mmol) in pyridine (0.7 ml), and the mixture stirred for 12 hr. Lactic acid (85%, 0.1 ml) was added, and the mixture was stirred for 5 min, then poured into 15 ml of cold 10% lactic acid overlaid with 5 ml of ether. The aqueous layer was extracted with ether, and the combined ether extracts were washed with water, four 5-ml portions of 5% sodium carbonate, water and brine, and dried over magnesium sulfate. Removal of the solvent left 60 mg of a colorless oil, which on crystallization from petroleum ether (30–60°C) afforded **47** as 55 mg of solid, mp 128–131°C. Three further recrystallizations gave 21 mg of material, mp 132–133°C; ir (CCl_4) 5.81, 6.25 μ. The nmr spectrum exhibited absorptions for 6 protons as a singlet at δ 0.80 (angular CH_3) superimposed on a doublet, $J = 5$ Hz, at δ 0.91 (secondary CH_3 at C-3′), and for 1 proton as a multiplet at δ 5.18 (H—C—O). Vapor-phase chromatography (column C at 220°C) indicated a single peak with retention time 12.2 min.

1α,9α-(3′-Methyltetramethylene)-1β-methyl-5β-hydroxy-10α-decalin p-*bromobenzoate* (**48**). The procedure described for the preparation of **47** was used. Thus, treatment of **46** (9 mg) with *p*-bromobenzoyl chloride (11 mg) in pyridine (0.4 ml) gave 18 mg of a solid, which after two recrystallizations from petroleum ether (30–60°C) afforded

5 mg of **48**, mp 114–115°C; ir (CCl_4) 5.84, 6.25 μ; nmr δ 0.92 (3 H, s, angular CH_3), 1.20 (3 H, d, $J = 6$ Hz, CH_3 at C-3′), and 5.45 (1 H, m, H—C—O). Vapor-phase chromatography (column C at 220°C) indicated a single peak, retention time 14.5 min.

Cyclization product distribution studies. Acetal **9** (30–50 mg) was dissolved in an appropriate volume of benzene or nitromethane at the required temperature, and the desired amount of stannic chloride was added. When cyclization was complete the reaction mixture was poured into 2 *N* hydrochloric acid overlaid with ether. The ether layer was washed with water, aqueous sodium bicarbonate, and brine, and dried over magnesium sulfate. The residue remaining after evaporation of the solvent was weighed and distilled (bulb-to-bulb) at 130°C (0.005 mm). The distillate was weighed and analyzed by vpc (column B). The proportions of the tricyclic materials **20**, **21** and **37** were determined as percentages of the total peak area; the assumption was made that the detector responses were the same for all cyclization products. An estimate of the yield of each of the tricyclic cyclization products was obtained using the relationship

$$\text{yield (\%)} = \frac{\text{wt distillate}}{\text{wt crude product}} \times 100 \times \text{tricyclic product in distillate (\%)}.$$

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