Nonenzymic, Biogenetic-Like Cyclization of a Tetraenic Acetal to Produce the *D*-Homosteroid Nucleus[1,2]

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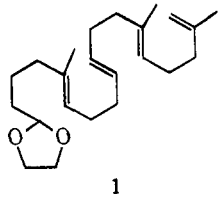
Abstract: The tetraenic acetal **1** was synthesized as outlined in the flow sheet. Treatment of substrate **1** with stannic chloride in pentane effected cyclization giving tetracyclic material as a mixture of C-4 epimers **2a** and **2b** in about 30% yield. Degradation of the side chain of pure **2a** yielded the 4β-hydroxy compound **3a** which on oxidation afforded the ketone **4**. This same ketone was produced from the epimer **2b** *via* the 4α-hydroxy compound **3b**. Wolff–Kishner reduction of ketone **4** afforded the *dl* form of the hydrocarbon **5** which was identified by comparison with authentic, enantiomeric **5** produced from a natural steroid **16** *via* the sequence **17** → **18** → **19** → **20** → **21** → **22** → **23** → **24** → **25** → **5**.

In the course of an extensive study to test the hypothesis that the stereospecificity of certain biocyclizations of acyclic polyterpenes, *e.g.*, squalene, may be controlled more by stereoelectronic factors than by enzymic influence on conformation,[3] we have demonstrated that appropriately constructed dienic and trienic acetals undergo stereospecific acid-catalyzed cyclization to give bi-[4] and tricyclic[5] substances having "natural" configuration. The present paper constitutes a detailed report of the synthesis and cyclization of the tetraenic acetal **1**. Thus a nonenzymic cyclization has been developed whereby no less than six asymmetric centers are produced in a single step stereospecifically from an acyclic tetraenic system having no asymmetric centers. Moreover the product has the *D*-homosteroid nucleus, *i.e.*, it has the natural (trans,anti,trans,anti,trans) configuration.



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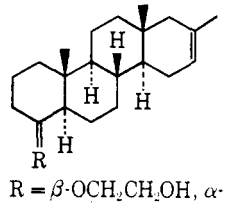


2a, R = β-OCH_2CH_2OH, α-H
b, R = α-OCH_2CH_2OH, β-H
3a, R = β-OH, α-H
b, R = α-OH, β-H
4, R = O=
5, R = H_2

Synthesis of the Tetraenic Acetal 1. The known *trans*-dienol **7**,[6] which is obtained essentially stereochemically pure from **6** *via* the cyclopropylcarbinyl–homoallylic rearrangement, was converted to *p*-toluenesulfonate **8**. Reaction of this substance **8** with the lithium salt of 1-benzyloxy-3-butyne in tetrahydrofuran (THF) gave the dienyne ether **9** in yields of 41–57%.

Treatment of substance **9** with sodium in liquid ammonia effected hydrogenolysis of the benzyl ether as well as stereospecific reduction of the acetylenic bond to give the *trans,trans*-trienol **10** in 67% yield. The development of the remaining acetal portion of the molecule **1** was carried out by a sequence analogous to that already described for producing a trienic acetal from a dienol,[5b] the additional trans-trisubstituted olefinic bond being introduced by an application of the Cornforth stereoselective olefinic synthesis.[7]

Thus the substance **10** was converted to the methanesulfonate **11** which was used to alkylate the sodium enolate of 2,4-pentanedione in dimethylformamide. The crude product **12** (obtained in about 60% yield) was chlorinated with cupric chloride and lithium chloride in dimethylformamide according to the method of Kosower,[8] giving the chloro dione **13**, which was deacylated with barium hydroxide in ethanol at 0° to afford the chloro ketone **14** in 60% yield.

Reaction in THF at −95° of the chloro ketone **14** with the Grignard reagent[4,9] produced from 1-ethylenedioxy-4-chlorobutane[10] gave the chlorohydrin **15** (X = Cl) which, without purification, was converted into the epoxide by treatment with methanolic potassium hydroxide at 0°. The crude epoxide, thus obtained in 90% overall yield from **14**, was treated at −20° with sodium iodide and sodium acetate in a mixture of propionic and acetic acid giving the unstable iodohydrin **15** (X = I) which was then treated with stannous chloride and phosphorus oxychloride in pyridine to give the tetraenic acetal **1**. Short-path distillation gave (42% overall yield from **14**) material which, by vapor-phase chromatography (vpc), appeared to contain 91% of the all-trans product and about 4% of the trans,trans,Δ^5-cis isomer. This material was used for the cyclization studies described below. After preparative thin layer chromatography and redistillation, vpc indicated the composition to be

(1) For a recent publication in this series, see K. A. Parker and W. S. Johnson, *J. Amer. Chem. Soc.*, **96**, 2556 (1974).

(2) A preliminary announcement of the present work has appeared: W. S. Johnson, K. Wiedhaup, S. F. Brady, and G. L. Olson, *J. Amer. Chem. Soc.*, **90**, 5277 (1968).

(3) G. Stork and A. W. Burgstahler, *J. Amer. Chem. Soc.*, 77, 5068 (1955); A. Eschenmoser, L. Ruzicka, O. Jeger, and D. Arigoni, *Helv. Chim. Acta*, **38**, 1890 (1955); for a review, see W. S. Johnson, *Accounts Chem. Res.*, **1**, 1 (1968).

(4) A. van der Gen, K. Wiedhaup, J. J. Swoboda, H. C. Dunathan, and W. S. Johnson, *J. Amer. Chem. Soc.*, **95**, 2656 (1973).

(5) (a) W. S. Johnson and R. B. Kinnel, *J. Amer. Chem. Soc.*, **88**, 3861 (1966); (b) G. D. Abrams, W. R. Bartlett, V. A. Fung, and W. S. Johnson, *Biorg. Chem.*, **1**, 243 (1971).

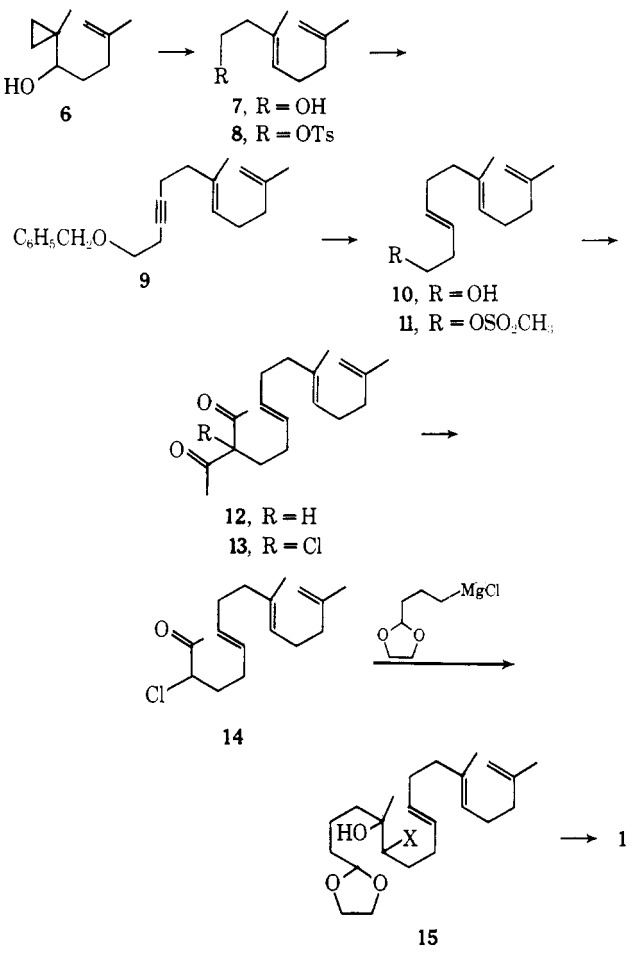
(6) S. F. Brady, M. A. Ilton, and W. S. Johnson, *J. Amer. Chem. Soc.*, **90**, 2882 (1968).

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

(8) E. M. Kosower, W. J. Cole, G.-S. Wu, D. E. Cardy, and G. Meisters, *J. Org. Chem.*, **28**, 630 (1963).

(9) *Cf.* C. Feugeas and H. Normant, *Bull. Soc. Chim. Fr.*, 1441 (1963).

(10) M. G. Pleshakov, A. E. Vasil'ev, I. K. Sarycheva, and N. A. Preabrazhenskii, *J. Gen. Chem. USSR*, **31**, 1443 (1961).



95–96% all-trans and 4–5% trans,trans,Δ^5-cis. Confirmation that the major component was the all-trans isomer was provided by the nmr signals for the methyls (at C-5 and -13) of the trisubstituted olefinic bonds which appeared at δ 1.59 ppm[11] and by the ir spectrum which showed a strong signal at 10.30 μ for the trans-disubstituted olefinic bond.

Cyclization Studies and Proof of Constitution of Products. Since stannic chloride had proved to be especially effective in promoting the cyclization of olefinic acetals,[4,5] we explored the use of this catalyst in several solvents, *i.e.*, nitromethane, benzene, methylene chloride, and cyclohexane. In none of these experiments was there more than 10% of tetracyclic material formed as roughly estimated by the presence of long retention time peaks in the vpc and by examination of the nmr spectrum (presence of high-field, angular methyl signals and diminution of vinyl proton absorption). When pentane was employed as the cyclization solvent, unlike the other systems an insoluble complex formed immediately on mixing the reactants (0.05 *M* solution of substrate and 0.2 *M* solution of stannic chloride) at 0°. After 15 min at 0°, then 5 min without cooling, the product was estimated (see above) to contain about 30% of tetracyclic material. Chromatography on alumina gave four fractions, a, b, c, and d (in order of elution), two of which (b and c) were semicrystalline. Fraction a consisted mainly of materials that exhibited short retention times on vpc, and the nmr spectrum showed only very weak high-field absorption for angular methyl groups; therefore, it contained little, if any, tetracyclic product. Fraction d appeared to be mainly polymeric material as evidenced by its failure to undergo short-path distillation without decomposition. Crystallization of fraction b (24% weight yield) from methanol gave material mp 161–163.5° which proved to be the tetracyclic substance **2a**. The nmr spectrum ($CDCl_3$) showed singlet absorption for three protons at δ 0.75 ppm (C-18 methyl), for three protons at 0.96 (C-19 methyl), and for three protons at 1.61 (vinyl methyl at C-17); in addition there was a broad one-proton multiplet at 5.33 (vinyl H at C-16). The β (axial) side chain at C-4 is responsible for the downfield shift of the signal for the C-19 methyl group, just as was found in the bicyclic series.[4] The nmr spectrum of the residue from the crystallization of fraction b showed absorption at 4.70 ppm (for the vinyl proton of the terminal isopropenyl group) of sufficient intensity to ensure that this was largely incompletely cyclized material. The crystalline material appeared to be homogeneous by tlc and vpc. Quantitative vpc analysis (see Experimental Section) indicated that crude fraction b contained about 60% of the pure material, corresponding to a 14% yield of **2a** in the cyclization.

Parallel results were obtained with fraction c (24% weight yield). Crystallization from methanol gave a product, mp 120–125°, that was homogeneous by tlc and vpc. The nmr spectrum was similar to that of **2a** except that the signal for both the C-18 and -19 methyls appeared as a six-proton singlet at 0.77 ppm. The high-field absorption for the C-19 methyl is consistent with the α (equatorial) configuration of the C-4 side chain and this substance was therefore the expected[4,5] epimeric tetracyclic substance **2b**. The nmr spectrum of the residue from the crystallization indicated (see above) that it consisted largely of incompletely cyclized product, and vpc analysis of crude fraction c indicated that the yield of **2b** in the cyclization was about 13%. In contrast to what would have been expected from the cyclization results in other series,[4,5] there was no evidence (*i.e.*, sharper, high-field vinyl H absorption in the nmr) for the presence of the $\Delta^{17(17a)}$ isomer in either of the tetracyclic epimers.

The side chain of the tetracyclic substances was degraded by the method employed in other series.[4,5] Thus fraction b was treated with *p*-toluenesulfonyl chloride in pyridine, and the resulting crude toluenesulfonate was heated in glyme with sodium iodide and zinc powder. Crystallization of the product from methanol gave the 4β-hydroxy isomer **3a**, mp 125–126°. The nmr spectrum showed singlet absorption for three protons at δ 0.77 ppm (C-18 methyl), for three protons at 1.02 (C-19 methyl, shifted downfield due to the 1,3-diaxial interaction with the C-4 axial hydroxyl group[4]), and for three protons at 1.61 (vinyl methyl at C-17). In addition there was a narrow one-proton multiplet at 3.81 (equatorial, 4α-H[4]) and a broad one-proton multiplet at 5.34 (vinyl H at C-16). The yield of **3a** from the amount of **2a** present in fraction b was estimated by vpc to be about 88%.

Similarly, side-chain degradation of fraction c afforded the 4α-hydroxy isomer **3b**, mp 150–153°, after recrystallization. The nmr spectrum differed from that of the 4β epimer in that it showed singlet absorption for six protons at δ 0.78 ppm (C-18 and C-19 methyls)

(11) See footnote 11 of ref 5b.

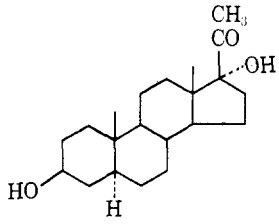
and a broad one-proton multiplet at 3.44 (axial, 4β-H[4]). When benzene was used instead of deuteriochloroform as the solvent, the C-18 and C-19 methyl absorptions in the nmr were resolved, appearing as singlets at 0.67 and 0.80 ppm, respectively. The yield of **3b** from the amount of **2b** present in fraction c was estimated by vpc to be about 90%.

Oxidation of the 4β-hydroxy compound **3a** with Jones reagent[12] gave, in 87% yield, the ketone **4**, mp 132.5–134.5°, after recrystallization. This same ketone was obtained in 93% by oxidation of the 4α epimer **3b**. The identity of the two ketone specimens (established by mixture melting point, vpc behavior, and ir and nmr spectroscopy) proved that the 126 and 153° hydroxy compounds were indeed epimeric at C-4.

The ketone **4** was converted, by the Huang–Minlon modification of the Wolff–Kishner reduction, into a mixture of hydrocarbons consisting of approximately 85% of substance **5** and 15% of what was almost surely the A/B cis (5β) epimer,[13] as shown by nmr spectroscopy (see Experimental Section). Crystallization of the mixture from methanol gave the pure A/B trans (5α) isomer **5**, mp 95–97°. The nmr spectrum showed singlet absorption for six protons at δ 0.76 ppm (C-18 and C-19 methyls), a singlet for three protons at 1.60 (vinyl methyl at C-17), and a broad "singlet" for one proton at 5.30 (vinyl proton at C-16). The tlc behavior as well as the nmr, solution ir, and mass spectra of the 97° hydrocarbon (racemic) was identical respectively with that of authentic 17-methyl-*D*-homo-5α-androst-16-ene, mp 108.5–110°, which was prepared as described below.

Synthesis of the Comparison Compound. The known[14] 3β,17α-dihydroxy-5α-pregnan-20-one (**16**) was converted, by treatment with boron trifluoride in acetic acid and acetic anhydride,[15] into the known *D*-homo keto diacetate **17**.[16] Saponification with methanolic potassium hydroxide (to give **18**)[15] followed by selective acetylation (pyridine–acetic anhydride) afforded the known[16] mono acetate **19**. Mesylation[17] (to give **20**) followed by heating with potassium acetate in acetone gave the known[17] unsaturated ketone **21** in 26% overall yield from **16**.

Reduction of the acetoxy ketone **21** with lithium aluminum hydride gave the diol **22** as a mixture of C-17a epimers. This diol was acetylated and the crude diacetate **23** was reduced with lithium in ethylamine[18] to effect hydrogenolysis of the allylic acetoxy group giving a mixture of the Δ^{16} and $\Delta^{17(17a)}$ enols **24** and **27** in a ratio of 3:2 as estimated by integration of the vinylic proton nmr absorption (see Experimental Section). By analogy to these absorptions in the bicyclic cases,[4] the broad multiplet observed at δ 5.30 ppm and the "singlet" at 5.10 were attributed to the vinyl proton of the Δ^{16} and $\Delta^{17(17a)}$ isomers, respectively. Oxidation of



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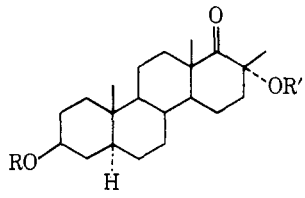
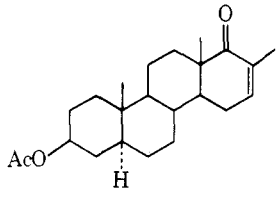


17, R = R' = Ac
18, R = R' = H
19, R = Ac; R' = H
20, R = Ac; R' = Ms



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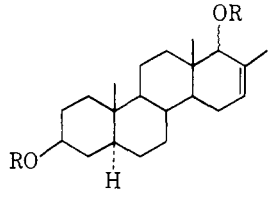
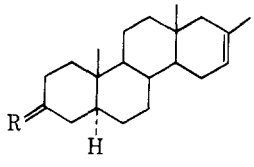
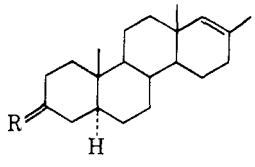


22, R = H
23, R = Ac



24, R = β-OH, α-H
25, R = O=
26, R = H_2



27, R = β-OH, α-H
28, R = O=
29, R = H_2

the mixture of enols **24** and **27** with Jones reagent[12] afforded the mixture of ketones **25** and **28** which was converted, by Huang–Minlon modification of the Wolff–Kishner reduction, into the mixture of Δ^{16} and $\Delta^{17(17a)}$ olefins **26** and **29** in 28% overall yield from **21**. This mixture of hydrocarbons was cleanly separated by extended elution preparative tlc on silica gel impregnated with silver nitrate. The desired Δ^{16} isomer **26**, with vinylic proton nmr absorption at δ 5.30 ppm, melted at 108.5–110° after recrystallization.

Experimental Section[19]

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

Vapor-phase chromatographic analyses were performed on Aerograph Model A-550 instruments or on Hewlett-Packard Model 402 instruments equipped with stainless steel or glass columns. Most of the analyses were carried out on a 5 or 7.5 ft × 0.125 in. column packed with 5% SE-30 on Chromosorb W 60–80 mesh, referred to below as the "SE-30" column.

Low-resolution mass spectra were determined under the supervision of Dr. A. M. Duffield on an Atlas CH-4 or a CEC Model 21-103C spectrometer. An AEI MS-9 spectrometer was employed for the high-resolution spectra.

Nuclear magnetic resonance spectra were determined under the supervision of Dr. L. J. Durham on Varian Associates Model T-60, A-60, or HA-100 spectrophotometers. Deuteriochloroform was

(12) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(13) For similar isomerizations during Wolff–Kishner reductions, see C. Djerassi, T. T. Grossnickle, and L. B. High, *J. Amer. Chem. Soc.*, **78**, 3166 (1956).

(14) T. H. Kritchevsky and T. F. Gallagher, *J. Amer. Chem. Soc.*, **73**, 184 (1951).

(15) R. B. Turner, *J. Amer. Chem. Soc.*, **75**, 3484 (1953).

(16) D. K. Fukushima, S. Dobriner, M. S. Heffler, T. H. Kritchevsky, F. Herling, and G. Roberts, *J. Amer. Chem. Soc.*, **77**, 6585 (1955).

(17) D. K. Fukushima, S. Dobriner, and R. S. Rosenfeld, *J. Org. Chem.*, **26**, 5025 (1961).

(18) A. S. Hallsworth, H. B. Henbest, and T. I. Wrigley, *J. Chem. Soc.*, 1969 (1957).

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

used as solvent unless otherwise stated and tetramethylsilane was employed as the internal reference. Chemical shifts are reported as δ values in parts per million relative to TMS (δ_{TMS} 0.0 ppm).

Silica gel G or GF_{254} (E. Merck A. G.) was used as the absorbent for thin layer chromatography.

1-Benzyloxy-3-butyne. This experiment was carried out by E. K. W. Wat. A solution of 56.0 g of 3-butyn-1-ol (Farchan Research Laboratories) in 50 ml of THF was added over a period of 1 hr to an ice-cooled, stirred suspension of 33.6 g of 53.5% sodium hydride–mineral oil dispersion in 1 l. of THF. The mixture was stirred for 3 hr at room temperture then cooled (ice-bath) while 134 g of benzyl bromide in 50 ml of THF was added over a period of 1 hr. This mixture was stirred under a nitrogen atmosphere at room temperature for 19 hr. Then the minimum amount of water was added in order to dissolve the precipitated salts with the formation of two layers. The organic layer was dried over anhydrous sodium sulfate and fractionally distilled through a 2-ft spinning band column to give 105 g (87% yield) of a colorless liquid: bp 78–79° (2 mm); $n^{25}D$ 1.5137; λ_{max}^{film} 3.0 (C≡CH), 4.7 (C≡C), 9.1 (COC), 13.5 and 14.3 μ (C_6H_5). This product was homogeneous by vpc.

Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.3; H, 7.5.

***trans*-1-Benzyloxy-7,11-dimethyldodeca-7,11-dien-3-yne (9).** This experiment was performed by W. R. Bartlett. A solution of 7.2 g of *trans*-3,7-dimethylocta-3,7-dien-1-ol[6] (**7**) in 85 ml of dry pyridine was mixed with a solution of 14.3 g of *p*-toluenesulfonyl chloride in 85 ml of dry pyridine. The mixture was stored under nitrogen at 0° for 31 hr then poured into ice–water overlaid with ether. Ether extraction using a 20% lactic acid followed by a base wash[19] gave 13.6 g (95% yield) of crude *p*-toluenesulfonate **8** as a pale yellow oil: λ_{max}^{film} 6.05, 11.2 (C=CH_2), 6.25, 7.4, 8.4, 8.5, 10.3, 11.0, 12.2, 12.9 μ. This material was used directly in the alkylation of 1-benzyloxy-3-butyne as described below.

A solution of 13.6 g of 1-benzyloxy-3-butyne in 100 ml of dry ether was cooled to 0°; then 49.3 ml of a 1.6 *M* solution of methyllithium in ether was added slowly under nitrogen with stirring. The resulting heavy white suspension was stirred at room temperature; then the ether was evaporated at reduced pressure and the residue was dissolved in 250 ml of dry THF. A 150-ml portion of this solution was added to a solution of the aforementioned 13.6-g sample of crude *p*-toluenesulfonate **8** in 50 ml of dry THF. The mixture was stirred at reflux temperature (nitrogen atmosphere) for 112 hr, the remainder of the acetylide solution being added in two equal portions after 24- and 44-hr intervals. The orange-colored mixture was poured into brine overlaid with ether, and the product was isolated by ether extraction using an acid followed by a base wash.[19] The lower boiling materials were removed from the resulting mixture by fractional distillation. The residue was dissolved in about 200 ml of absolute ethanol, 66 ml of 5% silver nitrate solution was added, and this mixture was shaken for 10 min. Ether and water were added, and the product was isolated by ether extraction.[19] Chromatography on Merck acid-washed alumina, followed by short-path distillation at 140° (0.03 mm), gave 5.3 g (41% yield) of **9** as a nearly colorless oil: $n^{24}D$ 1.5142; λ_{max}^{film} 3.26, 6.08, 11.3 (C=CH_2), 3.31, 6.7, 9.1, 13.6, 14.4 μ. This product gave a single peak on vpc analysis.

Anal. Calcd for $C_{21}H_{28}O$: C, 85.08; H, 9.52. Found: C, 85.0; H, 9.6.

In another similar experiment the pure product **9** was obtained in 57% yield.

***trans,trans*-7,11-Dimethyldodeca-3,7,11-trien-1-ol (10).** This experiment was performed by W. R. Bartlett. A solution of 5.3 g of the benzyl ether **9** in 50 ml of dry ether was added to a solution of 1.98 g of sodium in 200 ml of ammonia (redistilled from sodium), and the mixture was stirred at −33° for 7 hr. The ammonia was allowed to evaporate at room temperature and then ether and water were added. The product, isolated by ether extraction,[19] was chromatographed on 200 g of Merck acid-washed alumina. The fraction eluted with 20% ether in pentane was distilled (short-path) at 110° (0.05 mm) to give 2.48 g (67% yield) of colorless oil: $n^{24}D$ 1.4800; λ_{max}^{film} 3.0, 9.55 (OH), 3.25, 6.08, 10.55, 11.3 μ (*trans*-RCH=CHR′ and C=CH_2); nmr 1.60 (s, 3 H, CH_3 at C-7), 1.70 (t, 3 H, CH_3 at C-11), 2.50 (s, 1 H, OH), 3.52 (t, J = 7 Hz, 2 H at C-1), 4.68 (broad s, 2 H at C-12), 4.9–5.3 (m, 1 H at C-8), 5.3–5.6 ppm (multiplet, 2 H at C-3 and C-4). This product appeared to be 98% pure by vpc.

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.3; H, 11.6.

***trans,trans*-3-Acetyl-10,14-dimethylpentadeca-6,10,14-trien-2-one (12).** The methanesulfonate **11** was prepared as follows. The mixture resulting from the addition of 2.87 g of methanesulfonyl chloride to a cold (−20°) solution of 4.00 g of the trienol **10** in 23 ml of dry pyridine was allowed to stand under nitrogen at −20° for 22 hr and then poured into a mixture of ice and excess hydrochloric acid. The product, isolated by ether extraction using a base wash,[19] amounted to 5.45 g, λ_{max}^{film} 7.40 and 8.51 μ (methanesulfonate). This material was used directly in the alkylation step described below.

To a cooled (0°) suspension of 0.98 g of sodium hydride (54.7% dispersion in mineral oil, washed with four portions of pentane) in 35 ml of dry dimethylformamide and 3.5 ml of dry benzene under nitrogen was added slowly with stirring 2.40 g of 2,4-pentanedione over a period of 15 min. The mixture was warmed to 25° and stirred for 20 min, and then 3.05 g of potassium iodide followed by a solution of the aforementioned 5.45-g sample of crude methanesulfonate **11** in 7 ml of dimethylformamide was added. The resulting mixture was stirred at 25° for 1 hr and at 45–55° for 19 hr, diluted with a small amount of water, and then poured into ice-cold water. The product, isolated by pentane extraction,[19] was dried by evaporating a solution of it in absolute ethanol. Short-path fractional distillation of the residue at 110–150° (0.002 mm) gave 3.22 g (58% yield) of a colorless oil which appeared to be 97% pure by vpc and was used in the next step of the synthesis (see below). Redistillation of a sample at 140–150° (0.003 mm) followed by preparative tlc gave material appearing to be 99% pure by vpc (SE-30 column, 185°): λ_{max}^{film} 5.78, 5.85 (C=O) 3.25, 6.05, 11.25 (C=CH_2), 10.25 μ (*trans*-CH=CH); nmr 1.60 (s, 3 H, CH_3 at C-10), 1.71 (s, 3 H, CH_3 at C-14), 2.17 (s, 6 H, acetyl CH_3), 4.71 (s, 2 H at C-15), and 5.42 ppm (sharp m, 2 H at C-6 and C-7). This material appeared to be sensitive to oxygen as suggested by the consistently low carbon analyses.

Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 76.8; H, 10.2; and, after long standing in air, C, 71.2; H, 9.4.

***trans,trans,trans*-1-Ethylenedioxy-5,13,17-octadecatetraene (1).** The trienic chloro ketone **14** was prepared as follows. According to the procedure of Kosower,[8] a solution of 2.66 g of the aforementioned dione **12** in 4 ml of dimethylformamide was added to a stirred solution of 4.9 g of cupric chloride dihydrate and 0.95 g of lithium chloride in 15 ml of dimethylformamide under nitrogen. The mixture was stirred at 25° for 12 hr and at 50° for 2 hr; then it was diluted with water. Extraction with pentane[19] gave 2.58 g (87% yield) of crude chloro dione **13** as a greenish-yellow oil: λ_{max}^{film} 5.78, 5.82 (C=O), 3.25, 6.05, 11.22 (C=CH_2), 10.26 μ (*trans*-CH=CH). To a cooled (0°) solution of this crude chloro dione in 20 ml of 95% ethanol under nitrogen was added with stirring 1.40 g of solid barium hydroxide octahydrate. The mixture was stirred at 0° for 75 min and then diluted with water. The product, isolated by pentane extraction using an acid, followed by a base wash[19] amounted to 2.28 g of crude yellow oily chloro trienone **14**, which appeared to be 77% pure by vpc. Repeated fractional short-path distillation at 95–130° (0.01 mm) afforded 1.58 g (60% yield from dione **12**) of oil which appeared to be 91% pure by vpc (SE-30 column, 180°): λ_{max}^{film} 5.80 (C=O), 3.25, 6.05, 11.22 (C=CH_2), and 10.28 μ (*trans*-CH=CH). This material, which gave a single spot on tlc, was used directly in the Cornforth olefin synthesis sequence described below.

The Grignard reagent was formed as previously described[4] from 3.67 g of 1-ethylenedioxy-4-chlorobutane in THF. The total volume of the solution was then increased to about 20 ml by the addition of THF, the mixture was cooled to −95°, and a solution of 1.57 g of the aforementioned chloro trienone **14** (91% pure) in 5 ml of THF was added slowly over a 15-min period. The resulting mixture was stirred at −95° for 7.75 hr and warmed to −75°, and a mixture of 25 ml of saturated ammonium chloride solution and 6 drops of concentrated ammonium hydroxide was slowly added over a 10-min period. The resulting mixture was allowed to warm to 10° and stirred with magnesium sulfate for 10 min, and then the crude chlorohydrin **15** (X = Cl) was isolated as described for a similar case.[5b] The resulting 2.87 g of a crude yellow oil (λ_{max}^{film} 2.82 (OH), 3.25, 6.05, 11.22 (C=CH_2), 8.78 μ (acetal)) was dissolved in 10 ml of anhydrous methanol, placed under nitrogen, and cooled to 0°. A solution of 18 ml of a 1 *N* solution of potassium hydroxide in anhydrous methanol was then added under nitrogen over a 30-min period; the resulting mixture was stirred at 0° for 2 hr and poured into brine. The residue, isolated by ether extraction,[19] was partially purified by removing by short-path distillation the fraction boiling at 30–90° (0.01 mm) leaving 1.81 g (90% yield from the chloro ketone **14**) of crude epoxide (λ_{max}^{film} 3.25, 6.07, 11.25 (C=CH_2), and 8.75 μ (acetal)) which was used in the next step.

To a cold (−25°) solution of 2.98 g of anhydrous sodium iodide and 0.34 g of anhydrous sodium acetate in 9.0 ml of dry propionic acid and 3.4 ml of dry acetic acid, under nitrogen, was added the aforementioned 1.81-g sample of crude epoxide, the transfer being assisted by an additional 1.5 ml of propionic acid. The resulting mixture was stirred at −20° for 1 hr and at −10° for 1 hr; then it was cooled to −30° and poured into a vigorously stirred ice-cold mixture of 90 ml of ether and a solution of 20 g of sodium bicarbonate and 3.5 g of sodium bisulfite in 140 ml of water. Ether extraction with a base wash[19] gave 2.15 g of the crude yellow oily iodohydrin **15** (X = I) (λ_{max}^{film} 2.85 (OH), 3.22, 6.05, 11.22 (C=CH_2), and 8.75 μ) which was used immediately in the next step.

To a cold (0°) solution of 2.36 g of freshly prepared anhydrous[20] stannous chloride in 10 ml of dry pyridine, under nitrogen, was added with stirring a solution of the aforementioned 2.15-g sample of iodohydrin **15** (X = I) in 3 ml of pyridine, followed by 0.60 ml of phosphorus oxychloride in 2.3 ml of pyridine. The resulting mixture was stirred at 0° for 30 min and at 25° for 6 hr; then the yellowish green, pasty mixture was diluted with 50 ml of ether and allowed to stand overnight at 25°. The mixture was filtered and the precipitated salts were thoroughly washed with ether. The combined filtrate and washings were washed successively with a dilute solution of sodium iodide–iodine, 5% sodium bisulfite, 5% oxalic acid, 5% sodium bicarbonate, and saturated brine. The residue obtained after drying over magnesium sulfate and evaporation of the solvent at reduced pressure amounted to 1.30 g of an orange oil. Repeated fractional short-path distillation at 125–165° (0.005 mm) gave 0.800 g (42% overall yield from the chlorotrienone **14**) of colorless tetraenic acetal **1** which was used for the cyclization experiment described below. The vpc (5-ft SE-30 column, 215°) showed one sharp peak (retention time 19 min, representing 91% of the total area) due to the all-trans isomer with a leading shoulder (4%) probably corresponding to the Δ^5-cis isomer. The remaining 5% represented peaks with shorter retention times.

A specimen obtained by further purification involving tlc followed by short-path distillation at 125–145° (0.005 mm) appeared by vpc to contain only the all-trans (95–96%) and Δ^5-cis isomer (4–5%): λ_{max}^{film} 3.20, 6.05, 11.24 (C=CH_2), 8.75 (acetal), and 10.30 μ (*trans*-CH=CH); nmr 1.59 (s, 6 H, CH_3 at C-5 and C-13 superimposed on m, 4 H at C-2 and C-3), 1.71 (s, 3 H, CH_3 at C-17), 2.02 (sharp m, 14 H at C-4, -7, -8, -11, -12, -15, -16), 3.73 (d, 4 H, $-OCH_2-CH_2O-$), 4.68 (s, 2 H at C-18), 4.75 (broad m, 1 H at C-1), 5.12 (broad m, 2 H at C-6 and C-14), and 5.38 ppm (sharp m, 2 H at C-9 and C-10).

Anal. Calcd for $C_{23}H_{38}O_2$: C, 79.71; H, 11.05. Found: C, 79.5; H, 10.8.

Cyclization of the Tetraenic Acetal 1. To a cold (0°) solution of 0.173 g of the aforementioned tetraenic acetal **1** (91% pure by vpc) in 5.0 ml of dry pentane, under nitrogen, was added with stirring a solution of 0.24 ml of freshly distilled stannic chloride in 5.0 ml of pentane over a 20-sec period. A pale yellow semisolid precipitate formed almost immediately and the resulting suspension was stirred at 0° for 15 min and then, after removal of the cooling bath, for an additional 5 min. The precipitate was dissolved by stirring with 5 ml each of 1 *N* hydrochloric acid and ether. The product, isolated by ether extraction using a 1 *N* hydrochloric acid followed by a base wash,[19] amounted to 0.178 g of a pale yellow oil.

Short-path distillation at 150–190° (0.003 mm) of a comparable cyclization mixture gave in about 70% recovery a product, vpc analysis of which (5-ft SE-30 column, 230°) showed two peaks (25–30% of total area) at retention times of 19 and 22 min (tetracyclic material), at least nine peaks at 6–15 min, and seven peaks at 2–6 min. The nmr spectrum showed the high-field angular methyl singlets for tetracyclic material (see below) as well as vinyl and terminal methylene proton absorption indicative of incompletely cyclized products.

The 0.178-g sample of crude cyclization product was chromatographed on 20 g of Merck acid washed alumina and separated into four fractions as follows: fraction a (eluted with 60–68° petroleum ether) amounted to 0.027 g and consisted of material which gave only short retention time responses on vpc; fraction b (eluted with 20% ether in 60–68° petroleum ether) amounted to 0.043 g of semicrystalline material which contained about 60% of one component with a long retention time response on vpc; fraction c (eluted with 50% ether in 60–68° petroleum ether) amounted to 0.044 g of semicrystalline material which contained about 50% of one component with long retention time response on vpc; fraction d (eluted with 10% methanol in ether) amounted to 0.058 g of viscous oil which could not be distilled (short-path) without decomposition and appeared to consist mainly of polymeric products.

Recrystallization of fraction b from methanol yielded 4β-(2′-hydroxyethoxy)-17-methyl-*D*-homo-5α-androst-16-ene (**2a**): mp 161–163.5°; λ_{max}^{KBr} 2.85 (OH) and 9.15 μ (COC); nmr 0.75 (s, 3 H, C-18 methyl), 0.96 (s, 3 H, C-19 methyl), 1.61 (s, 3 H, CH_3 at C-17), and 5.33 ppm (m, 1 H at C-16). This material gave one spot on tlc and one peak on vpc (5-ft SE-30 column, 240°, retention time 12.3 min).

Anal. Calcd for $C_{23}H_{38}O_2$: mol wt 346.2872; M^+(obsd), 346.2876.

The nmr spectrum of the mother liquor fraction showed significant absorption at 4.70 ppm (C=CH_2) indicative of incompletely cyclized material.

Recrystallization of fraction c from methanol gave 4α-(2′-hydroxyethoxy)-17-methyl-*D*-homo-5α-androst-16-ene (**2b**): mp 120–125°; λ_{max}^{KBr} 2.90 (OH) and 9.10 μ (COC); nmr 0.77 (s, 6 H, C-18 and C-19 methyls), 1.61 (s, 3 H, CH_3 at C-17), and 5.35 ppm (m, 1 H at C-16). This product gave a single spot on tlc and essentially one peak on vpc (as above, retention time 14.4 min).

Anal. Calcd for $C_{23}H_{38}O_2$: mol wt 346.2872; M^+(obsd), 346.2891.

Absorption at 4.70 ppm (C=CH_2) in the nmr spectrum of the mother liquor fraction indicated the presence of incompletely cyclized material.

The yields of tetracyclic materials were estimated by vpc analysis of fractions b and c. The internal standard technique was not employed because the vpc peaks for these products showed considerable tailing which interfered with the signal from any reasonable standard. The analysis was therefore performed by alternately injecting the same volumes of ether solutions of purified tetracyclic alcohol and the fractions containing the same isomer and estimating yields from comparison of peak areas. Thus the amount of alcohol **2a** in fraction b (derived from cyclization of 31.0 mg of tetraenic acetal) was estimated to be 4.5 mg, corresponding to a yield of 14%. Similarly, the amount of **2b** in fraction c of the same cyclization experiment was measured to be 3.9 mg, corresponding to a yield of 13%. The accuracy of these gas chromatographic determinations was estimated to be within 1.5%.

17-Methyl-*D*-homo-5α-androst-16-en-4β-ol (3a). The procedure for side-chain degradation in the bicyclic series[4] was employed. Thus a 0.050-g sample of fraction b (see above), containing approximately 60% of alcohol **2a**, was converted into 0.060 g of pale yellow oily *p*-toluenesulfonate: λ_{max}^{film} 3.25, 6.25, 7.35, and 8.50 μ.

A 0.085-g specimen of crude *p*-toluenesulfonate (a combination of the aforementioned product and 0.025 g of a comparable sample from another run), on treatment with 0.165 g of zinc and 0.165 g of sodium iodide in 1.7 ml of glyme,[4] afforded 0.055 g of colorless, semicrystalline product. Analysis by vpc (5-ft SE-30 column, 230°) showed one major peak (area about 60% of total) at a retention time of 9.1 min, the remaining peaks appearing at shorter retention times. Recrystallization from methanol yielded colorless crystals: mp 125–126°; λ_{max}^{KBr} 2.95 μ (OH); nmr 0.77 (s, 3 H, C-18 methyl), 1.02 (s, 3 H, C-19 methyl), 1.61 (s, 3 H, CH_3 at C-17), 3.81 (sharp m, 1 H at C-4α), and 5.34 ppm (m, 1 H at C-16). Analysis by vpc (as above, but at 240°) showed a single peak with a retention time of 8.4 min.

17-Methyl-*D*-homo-5α-androst-16-en-4α-ol (3b). In a similar manner 0.070 g of fraction c material (see above) yielded 0.074 g of crude oily *p*-toluenesulfonate: λ_{max}^{film} 3.25, 6.27, 7.35, and 8.50 μ. The side-chain degradation of this product yielded, in turn, 0.050 g of a colorless oil. Analysis by vpc as for the C-4 epimer (230°) showed one major peak (area about 60% of total) at a retention time of 9.5 min, the remaining peaks appearing at shorter retention times. Preparative tlc followed by crystallization from methanol gave colorless crystals: mp 150–153°; λ_{max}^{KBr} 2.98 μ (OH); nmr 0.78 (s, 6 H, C-18 and C-19 methyls), 1.62 (s, 3 H, CH_3 at C-17), 3.44 (broad m, 1 H at C-4β), and 5.34 ppm (m, 1 H at C-16). The nmr of a benzene solution showed singlet absorption at 0.67 and 0.80 ppm for the C-18 and C-19 methyls, respectively. Analysis by vpc (as for pure **3a**) showed a single peak with a retention time of 8.7 min.

Anal. Calcd for $C_{21}H_{34}O$: mol wt 302.2610; M^+(obsd), 302.2624.

17-Methyl-*D*-homo-5α-androst-16-en-4-one (4). (a) From the 4β (Axial) Alcohol 3a. To a cold (0°) solution of 0.0125 g of alcohol **3a**, mp 125–126°, in 0.75 ml of acetone was added with stirring 0.03 ml of Jones reagent[12] over a period of 30 sec. After stirring at 0°

(20) *Cf.* A. I. Vogel, "Practical Organic Chemistry," 3rd ed, Longmans, Green and Co., London, 1957, p 197.

for 10 min, the mixture was treated with 0.07 ml of isopropyl alcohol and the product was isolated as described for the bicyclic case,[4] giving 0.0108 g (87% yield) of crude crystalline ketone: λ_{max}^{KBr} 5.88 μ. Recrystallization from methanol gave colorless needles: mp 132.5–134.5°; nmr 0.72 (s, 3 H) and 0.77 (s, 3 H) for the two angular methyl groups, 1.60 (s, 3 H, CH_3 at C-17), 5.30 ppm (m, 1 H at C-16). This material showed one peak on vpc (5-ft SE-30 column, 210°, retention time 11.9 min).

Anal. Calcd for $C_{21}H_{32}O$: C, 83.94; H, 10.73. Found: C, 84.0; H, 10.5.

(b) From the 4α (Equatorial) Alcohol 3b. Similar oxidation of a 0.0081-g specimen of alcohol **3b**, mp 150–153°, afforded 0.0075 g (93% yield) of crude crystalline ketone. Recrystallization from methanol gave colorless needles, mp 133.5–135°, undepressed on admixture with the 132.5–134.5° specimen obtained from oxidation of the epimer **3a** (see above). The ir and nmr spectra were identical with the corresponding spectra of the 132.5–134.5° specimen, and the vpc responses of the two samples were also identical.

***dl*-17-Methyl-*D*-homo-5α-androst-16-ene (5).** A mixture of 0.007 g of ketone **4**, mp 132–134°, 0.7 ml of triethylene glycol, and 0.11 ml of hydrazine hydrate was stirred at 25° for 1 hr; then 0.015 g of powdered potassium hydroxide (purity 85%) was added and the mixture was stirred at 100–120° for 1.5 hr and then at 200–220° for 3 hr. After cooling and diluting with water, the mixture was extracted with ether[19] giving 0.0055 g (82% yield) of an almost colorless crystalline product. Analysis by vpc (5-ft SE-30 column, 185°) showed a peak (*ca.* 15% of total area) at a retention time of 14.0 min and a second peak (*ca.* 85%) at 14.9 min corresponding to the 5β and 5α epimers, respectively (see below). The nmr spectrum of a benzene solution of this mixture showed sharp singlets at 0.74 (C-19 methyl of the 5α isomer), 0.82 (C-18 methyl of both the 5α and 5β isomers), and 0.89 ppm (C-19 methyl of the 5β isomer). The relative areas under these signals corresponded to a 1:4 ratio of the 5β and 5α isomers, respectively.

Recrystallization of this mixture from methanol gave the pure 5α epimer **5**, mp 95–97°, which showed a single peak on vpc; nmr 0.76 (s, 6 H, C-18 and C-19 methyls), 1.60 (s, 3 H, CH_3 at C-17), and 5.30 ppm (m, 1 H at C-16). When benzene was used as solvent, the angular methyl peaks appeared at 0.74 (C-19) and 0.82 ppm (C-18). Major peaks in the mass spectrum appeared at *m/e* 286 (M^+, parent), 271, 218, 175, and 148. A metastable peak at *m/e* 256.8 is consistent with the fragmentation $286^+ \rightarrow 271^+ + 15$ (calcd 256.8).

17-Methyl-*D*-homo-5α-androst-16-en-3β-ol-17a-one Acetate (21). The elimination of methanesulfonic acid from the ester **20** was accomplished by a modification of the published procedure.[17] A mixture of 0.980 g of the crude methanesulfonate **20**, mp 77–85° (prepared from Reichsteins substance "L," **16**, according to the various procedures cited in the discussion part), and 1.8 g of anhydrous powdered potassium acetate in 125 ml of acetone was heated at reflux (under nitrogen) for 20 hr. The solvent was evaporated, water was added, and the product was isolated by ether extraction.[19] Crystallization from ethyl acetate gave 0.223 g (29% yield) of colorless needles (first crop): mp 204.5–206.5° (lit.[17] 206.5–210°); nmr 0.82 (s, 3 H, C-19 methyl), 0.97 (s, 3 H, C-18 methyl), 2.01 (s, 3 H, acetate methyl), and 6.61 ppm (s, 1 H at C-16).

17-Methyl-*D*-homo-5α-androst-16-ene (26). Lithium aluminum hydride (0.124 g) was added to a stirred solution of 0.118 g of the acetoxy ketone **21**, mp 204.5–206.5°, in 20 ml of dry ether. The mixture was stirred at 25° for 3.5 hr and then a saturated solution of magnesium sulfate was added to destroy the excess hydride. The resulting slurry was dissolved in 1 *N* hydrochloric acid and extracted with ether using a base wash.[19] The product, a mixture of the 17α and β epimeric diols **22**, amounted to 0.096 g of a colorless solid, mp 200–207°. A 0.130-g specimen of comparable material from another experiment was treated with 3 ml of acetic anhydride in 20 ml of pyridine for 16 hr at 25°. The excess anhydride was decomposed by adding 10 ml of water and stirring the mixture for 1.5 hr. The solution was acidified (to pH 1) with 3 *N* hydrochloric acid, and this mixture was extracted with ether using an acid followed by a base wash.[19] The product, a mixture of the 17α and β epimeric diacetates **23**, amounted to 0.150 g of pale yellow solid, mp 135–145°, showing a single spot on tlc.

According to the published procedure,[18] 0.035 g of lithium was added at −78° to a solution of 0.139 g of the aforementioned mixture of diacetates **23** in 25 ml of dry ethylamine. The mixture was stirred for 4 hr at −78° and then for 45 min at reflux temperature. Solid ammonium chloride was added, then the ethylamine was evaporated, water was added, and the mixture was extracted with ether using an acid followed by a base wash.[19] The product, on tlc, showed two spots corresponding to the diol mixture **22** and a monohydric alcohol fraction. Preparative tlc (using 20% acetone in pentane) gave 0.048 g of a solid mixture of olefinic alcohols **24** and **27**: 100-MHz nmr 0.76, 0.78, 0.79, 0.81 (4s, total 12 H, angular methyls), 1.61 (broad s, 3 H, CH_3 at C-17), 5.10 (s, 0.37 H at C-17a of **27**), and 5.30 ppm (broad s, 0.63 H at C-16 of **24**).

Jones reagent[12] was added with stirring to a cold (0°) solution of 0.030 g of the aforementioned mixture of alcohols **24** and **27** until the brown color of excess reagent persisted. The mixture was stirred for 30 min at 0°; then it was diluted with water, solid sodium bisulfite was added until the solution turned green, and the mixture was extracted with ether using a base wash.[19] The product, consisting of a mixture of the olefinic ketones 25 and 28, amounted to 0.021 g of colorless solid which gave a single spot on tlc: 100-MHz nmr 0.78, 0.84, 0.98, 1.00 (4 s, total 12 H, angular methyls), 1.60 (broad s, 3 H, CH_3 at C-17), 5.10 (s, 0.4 H at C-17a of **28**), and 5.30 ppm (broad s, 0.6 H at C-16 of **25**).

A 0.022-g specimen of the aforementioned mixture of ketones **25** and **28** was reduced by the Wolff–Kishner procedure described above for the conversion of ketone **4** to hydrocarbon **5** to give a total of 0.022 g of crude mixture of olefins **26** and **29**. These hydrocarbons were separated by tlc as described below.

Silver nitrate impregnated tlc plates were prepared as follows. Silica gel G (50 g) was shaken for 90 sec with a solution of 5 g of silver nitrate in 100 ml of water. This slurry was spread (750 μ thickness) on three 20 × 20-cm glass plates which were then dried in a dark drying oven overnight. All of the following operations were carried out in a dimly lighted room. A plate was removed from the drying oven and allowed to cool for 10 min in a tank which was flushed with nitrogen. An ether solution of 0.071 g of the crude mixture of olefins **26** and **29** was applied to the plate which was replaced in the developing tank. Argon was admitted to the tank; then pentane, which had been deoxygenated by alternately evacuating and filling a flask of the solvent with nitrogen, was introduced under a positive pressure of nitrogen. A very slow stream of argon was admitted to the tank during the development period (2.3 hr). The plate was then dried for 15 min in a box through which a stream of nitrogen was passing. The two bands, detected by the hot-wire technique, were scraped off and extracted with ether. Evaporation of the solvent gave 0.021 g of the Δ^{16} isomer **26** and 0.027 g of the $\Delta^{17(17a)}$ isomer **29** as shown by spectroscopy (see below). A second 0.013-g sample of the crude mixture of olefins was chromatographed as described above to give 0.005 g of the Δ^{16} isomer making the total amount 0.027 g (34% yield). Recrystallization of this material from methanol–ethyl acetate gave colorless plates, mp 108.5–110°. The nmr and mass spectra of this substance were identical in every respect with the respective spectra of the racemic substance **5**, described above. In addition the solution ir spectra, which had numerous bands in the long-wave region, of the two specimens were identical.

The nmr spectrum of the $\Delta^{17(17a)}$ isomer **29** showed bands at 0.78 (s, 3 H, C-19 methyl), 0.82 (s, 3 H, C-18 methyl), 1.59 (broad s, 3 H, CH_3 at C-17), and 5.10 ppm (s, 1 H at C-17a). This last signal was significantly sharper than that at 5.30 ppm for the proton at C-16 of the isomer **26**.

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