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The Biomimetic Cyclization of 1,3-Dimethyl-2-(*trans-trans*-7,11-dimethyl-3,7,11-dodecatrienyl)-2-cyclohexenol to Give the D-Homosteroid Nucleus (*1*)

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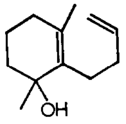
The cyclization of tetraenols **3** and **4** has been studied. The tetraenols were prepared as follows: alkylation of the lithium salt of 1-benzyloxy-3-butyne with the previously known *trans*-tosylates **19** and **20** gave the dienynes **21** and **22**. Reduction with sodium in ammonia gave the *trans,trans*-trienols **25** and **26**, which were used to alkylate, via the tosylates **27** and **28**, the sodio salt of Hagemann's ester **7**. Decarbethoxylation gave the tetraenones **29** and **30** which were converted with methyllithium to **3** and **4**. Treatment of tetraenol **3** with trifluoroacetic acid in pentane at −78°C to −10°C gave tetracyclic diene **5** stereoselectively in 45% yield, along with 5% tricyclic triene **32** and a mixture of esters. The esters were reduced and eliminated, giving a mixture (25% yield based on **3**) of 66% diene **5** and 34% triene **32**. Tetraenol **3** was cyclized with stannic chloride in nitromethane at 22°C giving a 77% yield of a 4:1 mixture of **5** and **32**. Treatment of tetraenol **4** with anhydrous formic acid followed by cleavage of the formate esters gave tetracyclic alcohol **6** (isolated in 9% yield) and a mixture of tricyclic trienes **36** and alcohols **37**. Cyclization of **4** in trifluoroacetic acid led to larger amounts of tetracyclic diene **40**. The structure and configuration (*anti,trans,anti,trans*) of the cyclization products, **5** and **6**, were established by conversion of **6** into the *dl* ketone **38** and comparison with authentic *d*-**38**. Also *d*-**38** was converted into authentic *d*-**5** which was compared with the synthetic *dl*-**5**. The comparison substances were prepared as follows. Testosterone benzoate (**41**) was methylated at C-4, and the C-3 carbonyl group was removed by conversion to the acetate **44**, followed by reductive cleavage of the allylic acetate with lithium in ethylamine. Oxidation of the C-17 alcohol gave the ketone **46**, which was converted to the carbinolamine **49** by epoxidation with dimethylsulfonium methylide, followed by conversion to the hydroxyazide and reduction with lithium aluminum hydride. Nitrous acid deamination led to the D-homoketone *d*-**38**. Treatment of *d*-**38** with methyllithium followed by dehydration led to a mixture of dienes from which *d*-**5** was isolated.

It has been demonstrated that the dienol **1** (*2*) and trienol **2** (*3*) can be transformed by acid-catalyzed cyclization stereospecifically and in high yield into bicyclic and tricyclic products, respectively. It became of particular interest then to see if the monocyclic tetraenols **3** and **4** could be cyclized to form the tetracyclic compounds **5** and **6**, having the *anti,trans,anti,trans* stereochemistry commonly found in the steroid and terpenoid classes of natural products (*4*). The present paper describes the synthesis and cyclization of the tetraenol **3** to give the tetracyclic diene **5**. The cyclization of the lower homolog



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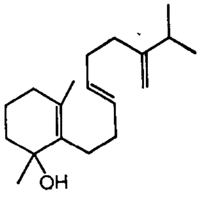

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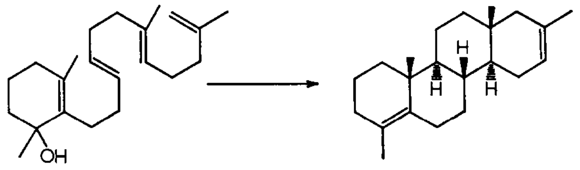
4 is also described, and this study provides a comparison of the effect of the terminal isopropenyl and vinyl groups upon such cyclizations.



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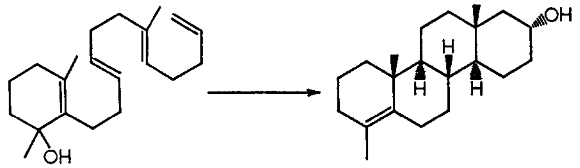

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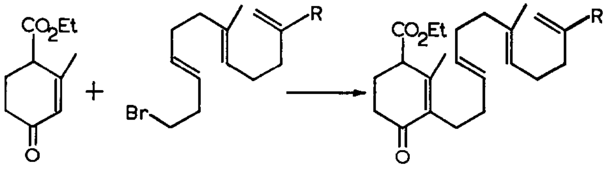
Synthesis of Tetraenols **3** *and* **4**

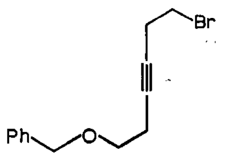
As in the preparation of dienol **1** (*2*) and trienol **2** (*3*), we envisioned using the alkylation of Hagemann's ester **7** with the bromotrienes **8** and **9** to give keto esters **10** and **11**, which could be converted to the tetraenols **3** and **4** by decarbethoxylation and treatment with methyllithium.



7   8: R = H   10: R = H

9: $R = CH_3$ 11: $R = CH_3$

The synthesis of the bromides **8** and **9** required, as a key element, a method of stereoselectively producing the *trans*-trisubstituted double bond. At the time this work began, the Cornforth olefin synthesis (*5*) was the method of choice. However, when the Cornforth sequence was tried in this case, it was found that the Grignard reagents prepared from both the bromide **12** and bromide **13** abstracted a proton (apparently from the solvent, tetrahydrofuran) rather than adding to the chloroketone **14**, as expected.



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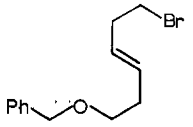

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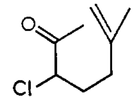

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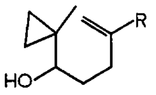
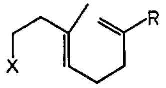
Attention was then turned to utilizing the bromides **17** and **18**, which are produced stereoselectively and in high yield by the rearrangement of the cyclopropyl carbinols **15** and **16**, respectively, with phosphorus tribromide and zinc bromide (*6*). The tosylates **19** and **20**, obtained from the corresponding bromides, were used to synthesize the dienynes **21** and **22** by the alkylation of benzyloxy-3-butyne. Thus, the addition of a solution of the lithium salt of benzyloxy-3-butyne in tetrahydrofuran over a 60-hr period to a solution of the tosylate **19** or **20** in refluxing tetrahydrofuran gave the dienynes **21** and **22** in 41–57% yield. The discovery of varying amounts of benzyl ether **23** or **24** among the reaction products from the alkylations suggested that a major side reaction is the elimination of the benzyloxide anion from the acetylide. When the bromides **17** or **18** were submitted to the same alkylation conditions used for the tosylates, yields of only 8–10% of the dienynes were realized.



15: R = H

16: R = CH_3



17: R = H, X = Br

18: R = CH_3, X = Br

19: R = H, X = OTs

20: R = CH_3, X = OTs

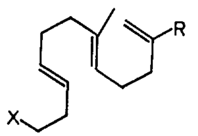
21: R = H, X = $C{\equiv}C(CH_2)_2OC_6H_5$

22: R = CH_3, X = $C{\equiv}C(CH_2)_2OC_6H_5$

23: R = H, X = $OCH_2C_6H_5$

24: R = CH_3, X = $OCH_2C_6H_5$

Treatment of the aforementioned dienynes **21** and **22** with sodium in liquid ammonia effected stereoselective reduction of the acetylenic bond with concomitant cleavage of the benzyl ether, giving the *trans,trans*-trienols **25** and **26** in 85 and 67% yields, respectively. The trienols were then converted to the tosylates **27** and **28** which were used to alkylate Hagemann's ester **7** by a modification of the previously described procedure (*3*). The immediate alkylation products, keto esters **10** and **11**, were not isolated, but were converted directly to the ketones **29** and **30** by saponification and decarboxylation. After chromatography and distillation, the pure ketones **29** and **30** were obtained in 30 and 35% yields, respectively. The structures of ketones **29** and **30** were confirmed by

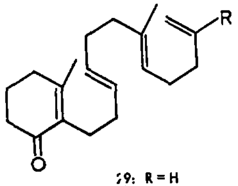


25: R = H, X = OH

26: R = CH$_3$, X = OH

27: R = H, X = OTs

28: R = CH$_3$, X = OTs



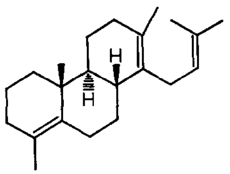
29: R = H

30: R = CH$_3$

ir, uv, and nmr spectroscopy. The ketones were then converted to the cyclization substrates, tetraenols **3** and **4**, in quantitative yield using methyllithium in ether.

Cyclization of Tetraenol 3

When a heterogeneous mixture of tetraenol **3** in anhydrous formic acid was shaken at room temperature, a complex mixture of hydrocarbons and formate esters was produced. The composition of the mixture was estimated by vapor phase chromatography (vpc), ir, and nmr spectroscopy to consist of approximately equal amounts of tricyclic and tetracyclic products (see Experimental). Analysis of the hydrocarbon fraction, which was separated by chromatography indicated that the tricyclic portion of the mixture was chiefly the triene **31** which had undergone isomerization of the terminal methylene double bond. To the extent that the acid-sensitive isopropenyl group in tetraenol **3** isomerized at a rate competitive with cyclization, the formation of tetracyclic products was precluded.



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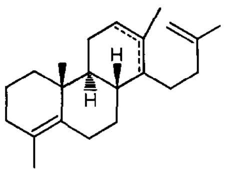

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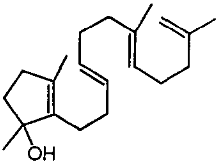
When the cyclization conditions were moderated by the addition of pentane (pentane/formic acid, 1/9), nmr analysis of the isolated hydrocarbon products revealed that isomerization of the isopropenyl group no longer occurred. However, the relative proportions of the tricyclic trienes **32** and the tetracyclic products appeared essentially unchanged, indicating that the isomerization noted above occurred after the tricyclic product was formed.

In an attempt to decrease the basicity and nucleophilicity of the external medium so as to enhance the ability of the terminal methylene double bond to compete for the developing cationic center at the tricyclic stage of the cyclization, a dilute solution of the stronger acid, trifluoroacetic acid, in pentane was employed as the cyclization solvent. Cyclization of tetraenol **3** in 0.4 *M* trifluoroacetic acid in pentane led to a product mixture in which the ratio of tetracyclic to tricyclic compounds had increased from 1/1 (in formic acid) to ca. 2.5/1.

An even greater increase in the proportion of tetracyclic products resulted when the trifluoroacetic acid solution was cooled to −78°C before addition of the tetraenol **3**. The cyclization mixture was allowed to warm slowly to −10°C, and the acid which had crystallized out of solution gradually dissolved. After 1 hr, the reaction mixture was quenched with water and the isolated products were treated with lithium aluminum hydride to cleave the trifluoroacetate esters. Column chromatography afforded a crystalline hydrocarbon fraction (50% yield), and an alcohol fraction (50% yield). The hydrocarbon fraction was shown by vpc analysis to consist of 90% of a tetracyclic compound and only 5% tricyclic products (tetracyclic/tricyclic, 18/1). A pure sample of the tetracyclic hydrocarbon was obtained by recrystallization. The tetracyclic compound was shown to have the structure **5** from its spectral properties and comparison with the authentic compound prepared as described below.

The alcohol fraction from the cyclization was dehydrated and chromatographed, giving a mixture of tetracyclic and tricyclic compounds (2/1 ratio). Thus, the tetraenol **3** was converted to tetracyclic diene **5**, in over 60% yield.

In a further study of the cyclization of tetraenol **3**, the Lewis acid stannic chloride was used as the catalyst in nitromethane at −22°C. These conditions are similar to those that were found to be highly effective in converting tetraenol **33** stereospecifically to the tetracyclic diene **34**, which in turn could be transformed into *dl*-16,17-dehydroprogesterone (**35**) (*7*). In the present case, the cyclization proceeded to give a 77% yield of a mixture of hydrocarbons consisting of 80% of the tetracyclic diene **5**.



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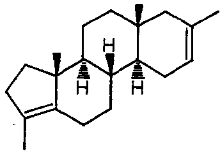

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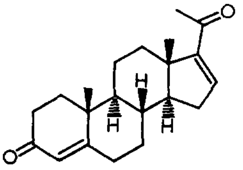

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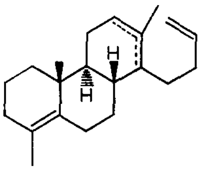
Cyclization of Tetraenol 4

Treatment of tetraenol **4** with anhydrous formic acid at room temperature for 1 min, followed by cleavage of the formate esters with lithium aluminium hydride, gave a complex mixture of products. Column chromatography yielded a hydrocarbon fraction (61% yield) that was shown by ir and nmr spectroscopy to consist chiefly of the tricyclic triene **36** and three alcohol fractions: A (18%), B (4%), and C (17%). Alcohol A was assigned the structure of the tricyclic dienol **37**, and alcohol C was assigned the structure of the tetracyclic alcohol **6** (see Experimental). Oxidation of alcohol

C with Collins reagent gave the crystalline ketone **38**, the structure and stereochemistry of which were confirmed by comparison with authentic material prepared as described below.



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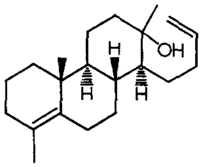

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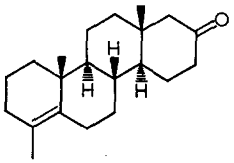

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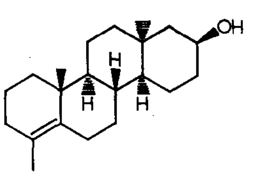
Exploratory studies of the cyclization of tetraenol **4** revealed that longer cyclization times (22 min) in formic acid led to increased amounts of a new tetracyclic alcohol (comparable in R_f value on tlc to the aforementioned alcohol fraction B). Likewise, resubmission of the tricyclic hydrocarbon fraction to formic acid treatment for 23 min yielded a mixture containing a large proportion of this isomeric tetracyclic alcohol. The new alcohol was assigned the structure **39**, having the *anti,trans,anti,cis* ring juncture stereochemistry in analogy to the results of the cyclization of a structurally related tetraenol having a terminal vinyl group (*8*). The *cis* C/D ring juncture appears to arise from the tricyclic triene **36** by a *trans* addition of a proton and the terminal vinyl group to the double bond in ring C (*8*, *9*). Under cyclization conditions which preclude the intermediacy of olefins such as triene **36**, the cyclization products of *trans* polyolefins have consistently possessed the *anti,trans* relative configuration as proposed by Stork (*10*) and Eschenmoser et al. (*11*).

Further exploratory cyclizations revealed that when tetraenol **4** was submitted to the low temperature trifluoroacetic acid conditions (see above), a larger proportion of a tetracyclic hydrocarbon, presumably **40**, was formed than in the formic acid cyclization.



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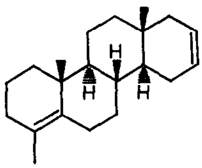

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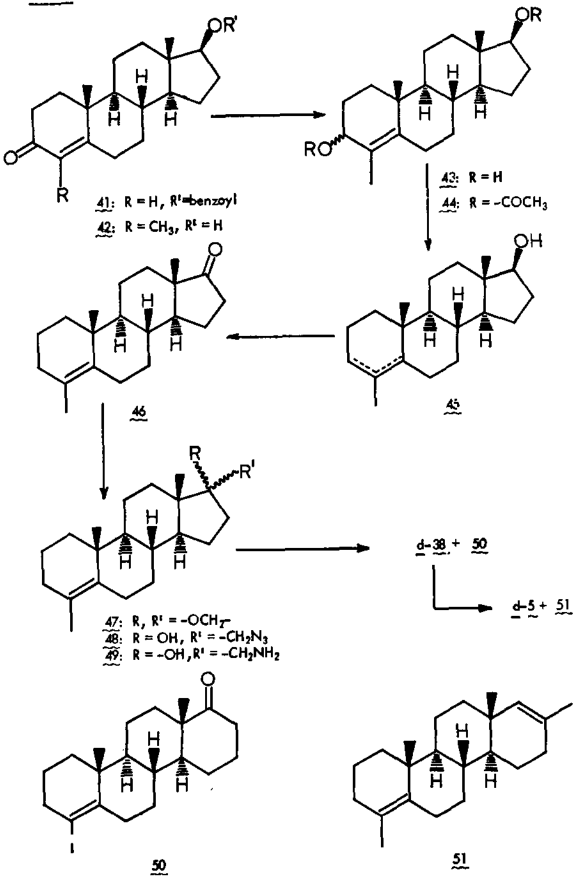
Synthesis of Comparison Compounds

Authentic *d*-D-homo-4-methylandrost-4-en-17-one (*d*-**38**) was prepared from a compound of known stereochemistry, testosterone benzoate (**41**), as follows (Chart 1).

Chart I



Methylation of testosterone benzoate with methyl iodide and potassium *tert*-butoxide, according to the procedure of Atwater (*12*), followed by methanolysis of the derived esters, gave a mixture of testosterone and mono- and di-methylated products from which the crystalline 4-methyl-testosterone (**42**) could be obtained, after chromatography and recrystallization, in 31 % yield.

The carbonyl group at C-3 was removed by the procedure of Henbest and co-workers (*13*). Thus, the ketone **42** was reduced with lithium aluminum hydride to give the epimeric alcohol mixture **43** from which the acetates **44** (2:1 ratio, $3\beta:3\alpha$) were obtained, using acetic anhydride in pyridine. The mixture was submitted to allylic acetate hydrogenolysis conditions with lithium metal in ethylamine, giving a mixture of Δ^3 and Δ^4-olefinic alcohols, **45**, which were oxidized directly with Jones reagent to give the corresponding mixture of Δ^3 and Δ^4 olefinic ketones. Chromatography and recrystallization permitted the separation of pure crystalline ketone **46**, in 34 % overall yield from 4-methyltestosterone (**42**).

Modification of the D-ring proceeded as follows. Ketone **46** was converted, by treatment with dimethylsulfonium methylide in dimethyl sulfoxide (*14*), to the epimeric epoxides **47** in 84 % yield. The oxirane ring was opened with sodium azide and ammonium chloride in dimethyl sulfoxide, giving the hydroxyazides **48**, which were reduced with lithium aluminum hydride to give the crystalline carbinolamine **49** in 86% overall yield after recrystallization. Dem'janov rearrangement with nitrous acid (*8*, *15*) gave a mixture of *d*-D-homo-4-methylandrost-4-en-17-one (*d*-**38**) and *d*-D-homo-4-methylandrost-4-en-17a-one (**50**), which were separated by column chromatography and differentiated by nmr and ORD spectroscopy (see Experimental).

Treatment of a portion of ketone *d*-**38** with methyllithium in ether, followed by dehydration with phosphoryl chloride in pyridine, gave a mixture of *d*-D-homo-4,17-dimethylandrosta-4,16-diene (*d*-**5**) and *d*-D-homo-4,17-dimethylandrosta-4,17(17a)-diene (**51**). A pure crystalline sample of diene *d*-**5** was prepared by thin-layer chromatography on silver nitrate impregnated silica gel, followed by recrystallization. The dienes *d*-**5** and **51** were distinguished by comparison of the width at half-height of their respective vinyl protons in the nmr spectra. The Δ^{16} isomer *d*-**5** exhibits a broadened absorption at δ 5.25 ppm (W1/2 = 10 Hz), due to coupling with adjacent methylene protons not found in the $\Delta^{17(17a)}$ isomer **51**, which showed a vinyl proton absorption at δ 5.05 ppm (W1/2 = 5 Hz).

The authentic comparison compounds, ketone *d*-**38** and diene *d*-**5** were identical by chromatographic, nmr, solution ir, and mass spectral analyses with the corresponding compounds derived from cyclization, i.e., ketone *dl*-**38** and diene *dl*-**5**. This correlation verifies the assignment of *anti,trans,anti,trans* stereochemistry to the primary tetracyclic cyclization products of tetraenols **3** and **4**.

EXPERIMENTAL[1]

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 host-stage microscope.

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

Vapor phase chromatographic (vpc) analyses were performed on an Aerograph A-600-C instrument equipped with hydrogen flame ionization detector using a 6 ft × $\frac{1}{8}$-in. column packed with 5% SE-30 on 80/100 mesh Chromosorb W.

Infrared (ir) spectra were obtained using Perkin–Elmer spectrophotometers, Models 137B and 421. Band intensities are referred to as strong (s), medium (m), or weak (w). Mass spectra were obtained on an A.E.I. MS-9 spectrometer, using a direct inlet system. Ultraviolet (uv) spectral determinations were performed on a Cary recording spectrophotometer (Model 14M). The optical rotatory dispersion (ORD) spectrum was

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[1] In cases where products were isolated by solvent extraction, the procedure generally followed was to extract the aqueous layer with several portion of the indicated solvent, then the organic layers were combined and washed with water followed by the stated solutions. The organic layer was dried over anhydrous 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.

recorded on a Jasco Model ORD/UV-5 scanning spectrophotometer. Refractive indices were determined with a Bausch and Lomb refractometer.

Unless otherwise indicated, evaporative (two-bulb) distillations were carried out at >150°C (0.02 mm) in a Büchi Kugelrohr apparatus. Silica gel G and GF_{254} (E. Merck) were used for thin-layer chromatography (tlc). Column chromatography was performed on acid-washed alumina (Merck and Co., Inc.) unless otherwise noted. The order of solvents used for elution was pentane (or petroleum ether), pentane–ether mixtures, and finally, ether.

Trans-1-Benzyloxy-7-methyldodeca-7,11-dien-3-yne (**21**)

A solution of 19.5 g (0.122 mol) of 1-benzyloxy-3-butyne (*1*), bp 51–52°C/0.2 mm, in 150 ml of dry ether (distilled from lithium aluminum hydride), was cooled to 0°C, and 72.4 ml (0.117 mol) of a 1.62 *M* solution of methyllithium in ether was added slowly to the rapidly stirred solution; nitrogen atmosphere was maintained at all times. The heavy white suspension was stirred at room temperature for 3 hr, and then the ether was removed at reduced pressure, leaving a white paste. The residue was dissolved in 300 ml of dry tetrahydrofuran, forming a pale yellow solution of the lithium acetylide. A 200-ml portion (ca. 0.08 mol) of the lithium acetylide solution was added to a solution of 22.7 g (0.077 mol) of *trans*-3-methyl-3,7-octadienyl *p*-toluenesulfonate (*6*) (**19**) in 50 ml of dry tetrahydrofuran, and the mixture was stirred at reflux temperature for 94 hr, the remainder of the acetylide solution (ca. 0.02 mol each) being added in equal portions after 17 and 47 hr. The ir of aliquots removed at 63 and 89 hr indicated a steady decrease in absorption attributed to tosylate **19** remaining in the reaction mixture. The orange-colored mixture was poured into brine overlaid with ether and the product was isolated, using an ether extraction followed by an acid and a base wash (see footnote 1). The lower-boiling materials were removed from the resulting mixture by fractional distillation. Then the residue was dissolved in 300 ml of absolute ethanol, 100 ml of 5% silver nitrate solution was added, and the solution was vigorously shaken for about 10 min. Ether and water were added, and the product was isolated by ether extraction.[1] Chromatography on Merck acid-washed alumina followed by short-path distillation at 120°C/0.01 mm, gave 10.2 g (47% yield) of **21** as a colorless oil: $n^{25}D$ 1.5145, $\lambda_{\max}^{\text{film}}$ 6.10,10.95 ($RHC{=}CH_2$), 9.05, 13.5, 14.3 μ (s, benzyloxy-); nmr 1.61 (s, 3H, CH_3 at C-7), 3.48 (t, $J = 7$ Hz, 2H at C-1), 4.48 (s, 2H, benzyl methylene), 4.75–5.3 (m, 3H at C-8 and C-12), 5.3–6.0 (m, 1H at C-11), 7.22 (s, 5H, aromatic protons). This product gave a single peak on vpc analysis.

Anal. Calcd for $C_{20}H_{26}O$: C, 85.05; H, 9.28. Found: C, 84.75, H; 9.51.

Trans-7-Methyldodeca-3,7,11-trien-1-ol (**25**)

A solution of 0.97 g (3.4 mmol) of the dienyne **21** in 25 ml of dry ether was added to a solution of 0.396 g (0.017 mol) of sodium in 65 ml of anhydrous ammonia (distilled from sodium), and the reaction mixture was stirred for 5.5 hr at –33°C. Then, excess ammonium chloride was added and the ammonia was allowed to evaporate overnight. The residue taken up in ether and water, and the product, isolated by an ether extraction, was chromatographed on Merck acid-washed alumina. The trienol **25** was recovered from ether–pentane mixtures and evaportively distilled at 90°C/0.04 mm to give 0.569 g (85% yield) of a colorless oil: $n^{24}D$ 1.478, $\lambda_{\max}^{\text{film}}$ 3.0, 9.6 (s, –OH), 3.25, 6.1,11.0

(s, RHC=CH$_2$), 6.1, 10.35 μ (s, *trans* RHC=CHR); nmr 1.59 (s, 3H, methyl at C-7), 3.5 (t, $J = 7$ Hz, CH$_2$ at C-1), 4.7–6.2 (m, 6H, vinyl protons at C-3, C-4, C-8, C-11, C-12). The product exhibited only one peak on vpc analysis.

Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.2; H, 11.3.

In another similar experiment, 5 g of pure product **25** was obtained in 72% yield.

Trans-7-Methyldodeca-3,7,11-trienyl p-toluenesulfonate (**27**)

A solution of 7.62 g (0.040 mol) of *p*-toluenesulfonyl chloride in 50 ml of dry pyridine was cooled to 0°C and added to a cold solution of 4.89 g (0.025 mol) of trienol **25** in 70 ml of pyridine. The mixture was stored under a nitrogen atmosphere at 0°C for 29 hr; then water was added dropwise at 0°C, and the mixture was poured onto ice. The product, isolated by an ether extraction with a lactic acid and a base wash,[1] amounted to 8.84 g of a pale yellow oil: $\lambda_{\text{max}}^{\text{film}}$ 6.10, 10.3, 10.90 (RHC=CH$_2$ and *trans* RCH=CHR), 6.25, 7.35, 8.4, 8.5 μ (s, tosylate). The product was used in the next step without further purification.

3-Methyl-2-(trans,trans-7-methyl-3,7,11-dodecatrienyl)-2-cyclohexenone (**29**)

The previously described alkylation method (*3*) was modified. To a sample of 0.262 g (6.10 mmol) of sodium hydride (54% mineral oil dispersion) was added 14 ml of dry tert-butyl alcohol (distilled from calcium hydride). The white suspension was stirred for 15 min after gas evolution had ceased, and a solution of 1.18 g (6.50 mmol) of Hagemann's ester **7** (*16*) in 3 ml of tert-butyl alcohol was added. The clear yellow reaction mixture was degassed and stirred under nitrogen at room temperature for 20 min, and then a solution of 0.897 g (2.58 mmol) of tosylate **27** in 3 ml of tert-butyl alcohol was added, followed by 0.430 g (2.58 mmol) of dry potassium iodide. The mixture was stirred at room temperature for 24 hr, and then at reflux temperature for 5 hr. Then the mixture was cooled and 15 ml of an ethanol–water mixture (7:3 to give 15% water) was added, followed by 0.560 g (10 mmol) of 85% potassium hydroxide. The mixture was stirred at reflux temperature for 19 hr in a nitrogen atmosphere and then poured into brine, and the product was isolated with an ether extraction followed by an acid wash and a base wash.[1] Chromatography on Merck acid-washed alumina gave an impure middle fraction (vpc analysis) which was chromatographed again on Merck alumina, giving a fraction, 0.045 g (6% yield), shown by vpc to be 95% pure and another fraction, 0.176 g (24% yield), which was one peak on vpc. The latter fraction was evaporatively distilled at 110–120°C/0.001 mm giving 0.175 g of tetraenone **29** as a colorless oil: $n^{24}D$ 1.5068, $\lambda_{\text{max}}^{\text{film}}$ 6.02, 6.15, (s, C=C–C=O), 3.25, 6.10, 10.35, 11.0μ (*trans* RHC=CHR, RHC=CH$_2$); nmr 1.60 (s, 3H, methyl of trisubstituted olefin), 1.90 (s, 3H, vinyl methyl on ring), 4.75–6.2 (m, 6H, vinyl protons).

Anal. Calcd for $C_{20}H_{30}O$: C, 83.86; H, 10.56. Found: C, 84.0, H, 10.5.

A similar preparation gave a product which exhibited an ultraviolet absorption band at $\lambda_{\text{max}}^{95\%\ \text{EtOH}}$ 245 nm ($\varepsilon = 11\,400$).

1,3-Dimethyl-2-(trans,trans-7-methyl-3,7,11-dodecatrienyl)-2-cyclohexenol (**4**)

To a solution of 0.160 g (0.560 mmol) of the pure tetraenone **29** in 5 ml of dry ether was added 1.87 ml (3.0 mmol) of a 1.6 *M* solution of methyllithium in ether. The mixture was stirred (nitrogen atmosphere) at room temperature for 20 min, poured onto ice, and the product was isolated by ether extraction.[1] The product exhibited a small carbonyl absorption in the ir spectrum, so it was retreated with methyllithium as described above, giving 0.17 g (quantitative yield) of tetraenol **4** as a colorless oil: $\lambda_{\max}^{\text{film}}$ 2.9 (s, -OH), 6.10, 10.35, 10.90 μ (*trans* RHC=CHR and RCH=CH_2); nmr 1.20 (s, 3H, $O{-}\overset{|}{\underset{|}{C}}{-}CH_3$), 1.7 broad s, 6H, vinyl methyls), 4.7–6.1 (m, 6H, vinyl protons). This material showed two peaks on vpc analysis in a 9:1 ratio. The low retention time suggests that the pentaenes derived from elimination of the allylic alcohol on the vpc column were observed.

Another preparation gave a product which underwent dehydration upon evaporative distillation, giving a mixture of pentaenes as a colorless oil: $\lambda_{\max}^{\text{film}}$ 6.25 (C=C–C=C), 6.1, 10.3, 11.0 μ (C=C).

Anal. Calcd for $C_{21}H_{32}$: C, 88.64; H, 11.36. Found: C, 88.7; H, 11.3.

Trans-1-Benzyloxy-7,11-dimethyldodeca-7,11-dien-3-yne (**22**)

The procedure described above for the preparation of dienyne **21** was used. The lithium acetylide was prepared from 13.6 g (0.850 mol) of 1-benzyloxy-3-butyne, and 49.3 ml (0.790 mol) of a 1.6 *M* solution of methyllithium in 100 ml of dry ether. After formation of the acetylide, the ether was replaced by 250 ml of dry tetrahydrofuran. A 150-ml portion (ca. 0.5 mol) of the lithium acetylide solution was added to a solution of 13.6 g (0.044 mol) of *trans*-3,7-dimethyl-3,7-octadienyl *p*-toluenesulfonate (*6*) (**20**) in 50 ml of dry tetrahydrofuran. The mixture was stirred at reflux temperature (nitrogen atmosphere) for 112 hr, the remainder of the lithium acetylide solution being added in equal portions (50 ml, ca. 0.16 mol each) after 24 and 44 hr. The reaction mixture was worked up as described above, giving 5.3 g (41 % yield) of pure dienyne **22**, after evaporative distillation at 140°C/0.03 mm, as a nearly colorless oil: $n^{24}D$ 1.5142, $\lambda_{\max}^{\text{film}}$ 3.26, 6.08, 11.3 ($RCH_3C{=}CH_2$), 3.31, 6.7, 9.1, 13.6, 14.4 μ (benzyl ether). This product was 97% pure by vpc analysis. Following essentially identical reaction conditions, S. Brady was able to obtain pure **22** in 57% yield (*6*).

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

Trans,trans-7,11-Dimethyldodeca-3,7,11-trien-1-ol (**26**)

The procedure described above for the preparation of trienol **25** was followed. To a solution of 1.98 g (0.086 mol) of sodium metal in 200 ml of ammonia was added a solution of 5.3 g (0.0179 mol) of dienyne **22**, in 50 ml of dry ether. The solution was stirred at −33°C for 7 hr and the product isolated as described above giving, after evaporative distillation at 110°C/0.05 mm, 2.48 g (67 % yield) of trienol **26** as a colorless oil: $n^{24}D$ 1.4800, $\lambda_{\max}^{\text{film}}$ 3.0, 9.55 (s, -OH), 3.25, 6.08, 10.35, 11.3 μ (s, *trans* RHC=CHR and $RCH_3C{=}CH_2$); nmr 1.60 (s, 3H, methyl at C-7), 1.70 (broad s, 3H, methyl at C-11), 2.50 (s, 1H, -OH), 3.52 (t, $J = 7$ Hz, 2H, CH_2 at C-1), 4.68 (broad s, 2H, C=CH_2), 4.9–5.3 (m, 1H, vinyl proton at C-8), 5.3–5.6 (m, 2H at C-3 and C-4). This material was 95% one peak by vpc analysis.

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

Trans,trans-7,11-Dimethyldodeca-3,7,11-trienyl p-toluenesulfonate (**28**)

A solution of 2.45 g (0.0118 mol) of trienol **26** in 45 ml of dry pyridine was cooled to 0°C, and a cooled solution of 3.62 g (0.019 mol) of *p*-toluenesulfonyl chloride in 45 ml of dry pyridine was added. The mixture was stored at 0°C for 29 hr, and the product was isolated as described for **27**, giving 4.35 g of **28** as a rose-colored oil: λ_{max}^{film} 6.05, 10.3, 11.2 (s, *trans* RHC=CHR and RCH$_3$C=CH$_2$), 6.25, 7.3, 8.4, 8.5, 10.3, 10.9, 12.2, 13.0 μ (s, tosylate). The crude product was used in the next step without further purification.

3-Methyl-2-(trans,trans,7,11-dimethyl-3,7,11-dodecatrienyl)-2-cyclohexenone (**30**)

The procedure described above for the preparation of trienone **29** was followed. Thus, the sodium enolate of Hagemann's ester was prepared from 0.155 g (3.54 mmol) of Hagemann's ester in 7 ml of dry tert-butyl alcohol. A solution of 0.444 g (1.22 mmol) of crude tosylate **28** in 3 ml of tert-butyl alcohol and 0.212 g (1.41 mmol) of sodium iodide was added and the mixture was stirred at room temperature (nitrogen atmosphere) for 26 hr and at reflux temperature for 4 hr. Then 6 ml of absolute ethanol, 2 ml of water, and 0.840 g (0.015 mol) of 85% potassium hydroxide were added, and the reaction mixture was stirred under reflux for 22 hr. Chromatography on Merck acid-washed alumina, followed by evaporative distillation at 100–130°C/0.004 mm gave 0.128 g (35% yield) of tetraenone **30** as a colorless oil: λ_{max}^{film} 6.02, 6.14 (s, C=C-C=O),3.25, 6.14, 10.38, 11.35 μ (*trans*-RHC=CHR and $>$C=CH$_2$); nmr 1.61 (s, 3H, methyl on *trans*-trisubstituted olefin), 1.71 (s, 3H, isopropenyl methyl), 1.92 (s, 3H, ring vinyl methyl), 4.68 (broad s, 2H, C=CH$_2$), 5.12 (m, 1H, trisubstituted olefin proton), 5.38 (t, $J = 3$ Hz, 2H on *trans*-disubstituted olefin). This material was 98% pure by vpc analysis.

From a similar preparation, tetraenone **30**, purified by chromatography and evaporative distillation, exhibited the following data: n^{24}D 1.5075, $\lambda_{max}^{95\%\ EtOH}$ 245 nm ($\varepsilon = 11\,000$).

Anal. Calcd for $C_{21}H_{32}O$: C, 83.95; H, 10.73. Found: C, 83.9; H, 10.75.

1,3-Dimethyl-2-(trans,trans-7,11-dimethyl-3,7,11-dodecatrienyl)-2-cyclohexenol (**3**)

The procedure described above for the preparation of tetraenol **4** was employed. Thus, a solution of 0.053 g (0.176 mmol) of tetraenone **30** in 4 ml of anhydrous ether was treated with 1.1 ml (1.76 mmol) of methyllithium solution (1.6 *M* in ether). The isolated product was retreated with methyllithium solution, giving 0.051 g (92% yield) of a colorless oil: λ_{max}^{film} 2.95 (s, -OH), 6.08, 10.31, 11.25 μ (s, *trans*-RHC=CHR and $>$C=CH$_2$). This material also showed two peaks, presumably the pantaenes, on vpc analysis.

Anal. Calcd for $C_{22}H_{36}O$: C, 83.48, H, 11.47. Found: C, 83.8; H, 11.4.

Cyclization of Tetraenol **3**

With formic acid. To 21.0 mg of tetraenol **3** was added 3 ml of anhydrous formic acid. The light pink mixture was shaken for 23 min at room temperature and then was poured into brine overlaid with ether. The product was isolated by an ether extraction followed by a base wash[1] giving a colorless oil.

The crude product was dissolved in 5 ml of ether, then a solution of 0.100 g of lithium aluminum hydride in 5 ml of ether was added. After 30 min at room temperature 0.1 g of water was added, followed by 0.1 g of 15% potassium hydroxide solution, then another 0.3 g of water. The mixture was stirred for 15 min, then treated with anhydrous magnesium sulfate. The salts were filtered and washed with ether and the solvent was removed at reduced pressure, leaving a colorless oil: $\lambda_{\max}^{\text{film}}$ 2.95 (w, -OH), 11.25 μ (w, $\rangle C{=}CH_2$). Chromatography on Merck acid-washed alumina gave a hydrocarbon fraction (9.9 mg, 50% yield, pentane eluant), and an alcohol fraction (4.6 mg, 25% yield, 3:2 ether/pentane eluant). The hydrocarbon fraction was a colorless oil which showed two broad peaks on vpc analysis (SE-30, 208°C) with retention times of ca. 15 min (51%, tricyclic) and 18 min (49%, tetracyclic), and was shown by nmr analysis to be a mixture comprised chiefly of tricyclic triene **31** and tetracyclic diene **5**: nmr 0.78 (s, ca. 1.5 H, diene **5**, C-18 methyl), 0.94 and 0.98 (overlapping s, ca. 2 H, C-19 methyls of triene **31** and diene **5**), 1.60 (broad s, ca. 9H, diene **5** and triene **31** vinyl methyls), 5.0–5.5 (m, ca. 1.3H, diene **5** and triene **31** vinyl protons). There was no evidence of a terminal methylene ($\rangle C{=}CH_2$) absorption.

With formic acid and pentane. A sample of 51.0 mg of tetraenol **3** was dissolved in 0.9 ml of dry pentane, and 7 ml of anhydrous formic acid was added. The light orange biphasic mixture was shaken for 8 min at room temperature (nitrogen atmosphere), and then it was poured into brine overlaid with pentane. The product was isolated by a pentane extraction followed by a base wash,[1] giving 50.0 mg (quantitative yield) of a colorless oil: $\lambda_{\max}^{\text{film}}$ 5.8, 8.5 (m, formate), 6.05, 11.25 (m, $\rangle C{=}CH_2$), 10.3 μ (w, *trans* RHC=CHR).

The crude mixture of formates and hydrocarbons was treated with lithium aluminum hydride as described above to give 44.1 mg (89% yield) of a colorless oil which was submitted to preparative thin-layer chromatography on silica gel (pentane eluant). Three fractions were separated: alcohol fraction A (11.5 mg, 23% yield, R_f ca. 0.05), hydrocarbon fraction B (7.9 mg, 17% yield, R_f ca. 0.65), and hydrocarbon fraction C (18.3 mg, 39% yield, R_f ca. 0.8). Hydrocarbon fraction B showed three peaks on vpc analysis (SE-30, 213°C) with retention times of 11 min (13%, triene **31**?), 13 min (78%, tricyclic) and 15 min (10%, tetracyclic), and was shown by nmr analysis to consist mainly of tricyclic triene **32**: nmr 0.95 (s, 3H, C-19 methyl), 1.60 (broad s, ca. 7H, ring and trisubstituted olefin methyls and triene **31** vinyl methyls), 1.72 (s, 3H, isopropenyl methyl), 4.68 (m, ca. 1.8H, terminal methylene vinyl protons), 5.2–5.6 (m, ca. 0.2H, triene **31** vinyl proton?). Hydrocarbon fraction C showed two peaks on vpc with retention times of 13 min (34%, tricyclic) and 16 min (66%, tetracyclic), and was shown by nmr to be chiefly tetracyclic diene **5**: nmr 0.79 (s, ca. 2H, C-18 methyl), 0.99 (s, 3H, C-19 methyl), 1.60 (broad s, ca. 9H, vinyl methyls, 5.0–5.5 (m, 1H, vinyl proton).

The aforementioned alcohol fraction A was dissolved in 0.7 ml of dry pyridine, and 0.05 ml of phosphoryl chloride was added at 0°C. The mixture was allowed to warm to room temperature and then was stirred for 20 hr and poured into water overlaid with ether. The product was isolated by ether extraction followed by lactic acid wash and base wash,[1] giving a hazy oil which was purified by chromatography yielding 4.5 mg (42% yield) of a colorless oil. Vpc analysis revealed the product to consist of 30% tricyclic and 70% tetracyclic material.

Isolation of dl-D-*Homo-4,17-dimethylandrosta-4,16-diene* (**5**). A sample of 20.95 mg of the undistilled tetraenol **3** was dissolved in 19.4 ml of dry pentane and the solution was cooled to −78°C (Dry Ice–propanol bath). Then a sample of 0.6 ml (0.94 g, 8.2 mmol, to make ca. 0.4 *M* solution) of trifluoroacetic acid (distilled from phosphorus pentoxide, bp 72°C) was added rapidly. The acid solidified at once as the mixture was swirled at −78°C. Then the temperature of the bath was allowed to rise slowly (5°C/5min) over a 1.25 hr period as the mixture was swirled gently. When the temperature reached −10°C, the solution was poured into brine overlaid with pentane, and the product was isolated by a pentane extraction followed by a base wash.[1] The product was dissolved in 10 ml of dry ether, treated with 120 mg of lithium aluminum hydride for 30 min, and then worked up as in the formic acid cyclization. Chromatography on Merck acid-washed alumina gave a hydrocarbon fraction (9.55 mg, 50% yield, pentane eluant), and an alcohol fraction (10.6 mg, 50% yield, ether–pentane eluant). The hydrocarbon fraction was evaporatively distilled at 115–130°C/0.003 mm to give 9.35 mg of a white solid, mp 50–75°C, which was shown by vpc analysis (SE-30, 195°C) to consist of one main peak (retention time 17 min, 90%, tetracyclic) and two minor peaks (13 min, 5%, tricyclic and 20 min, 5%). Two recrystallizations from absolute ethanol gave colorless plates, mp 80–82°C, homogeneous on tlc (R_f 0.73, pentane) and vpc; nmr 0.77 (s, 3H, C-18 methyl), 0.97 (s, 3H, C-19 methyl), 1.56 (s, 6H, vinyl methyls at C-4 and C-17), 5.25 (broad s, 1H, vinyl proton at C-16).

Anal. Calcd for $C_{22}H_{34}$: C, 88.51; H, 11.49. Found: C, 88.2; H, 11.4.

The infrared spectrum (CCl_4), nmr spectrum, and mass spectrum (MS-9, parent ion at *m/e* 298, calcd for $C_{22}H_{34}$: 298.27) of the above material were identical with the corresponding spectra of authentic *d*-D-homo-4,17-dimethylandrosta-4,16-diene (*d*-**5**), prepared as described below.

The alcohol fraction from chromatography exhibited ir spectral bands at 2.9 (m, –OH) and 11.2 μ (m, $RCH_3C{=}CH_2$) and was shown by tlc to consist of at least three components (R_f 0.30, 0.50, 0.54, ether–pentane). The sample was dehydrated with phosphoryl chloride as described in the aforementioned formic acid cyclization, giving, after chromatography and evaporative distillation at 120°C/0.003 mm, 4.49 mg (48% yield) of a colorless oil which crystallized on standing. Vpc analysis showed three peaks with retention times of 13 min (30%, tricyclic), 16 min (66%, tetracyclic) and 19 min (4%). The tetracyclic hydrocarbons could be separated from the tricyclics by preparative tlc on 10% silver nitrate silica gel.

With stannic chloride. A sample of 43.2 mg of a mixture containing ca. 20% of the tetraenol **3** and 80% of the pentaene from dehydration (determined by nmr) was dissolved in 9 ml of dry nitromethane, and the solution was cooled to −22°C (Dry Ice–CCl_4 bath). To the stirred solution was added a solution of 0.178 g of stannic chloride (redistilled) in 0.7 ml of dry nitromethane. The mixture was stirred (nitrogen atmosphere) at −22°C for 3 hr, and then 0.4 ml of pyridine was added. The white suspension was poured into cold 1 *N* hydrochloric acid overlaid with ether, and the product was isolated by an ether extraction followed by a base wash.[1] Chromatography on Florisil gave 32.3 mg (77% yield) of a colorless oil (pentane eluant) which showed peaks on vpc analysis (SE-30, 190°C) with retention times of 12–16 min (20%, tricyclic) and 19 min (80%, tetracyclic).

Cyclization of Tetraenol **4** *with Formic Acid. Isolation of dl-*D*-Homo-4-methylandrost-4-en-17α-ol* (**6**)

A sample of 114.3 mg of tetraenol **4** was shaken with 10 ml of anhydrous formic acid for 1 min at room temperature, and then the mixture was poured into water and the product isolated by ether extraction followed by a base wash[1] giving a colorless viscous oil: $\lambda_{\max}^{\text{film}}$ 5.80, 8.4 (s, formate), 6.1, 11.0 μ (m, RHC=CH$_2$).

The crude product was treated with lithium aluminum hydride as described in the aforementioned formic acid cyclization of tetraenol **3** to give 115 mg of an oil which was chromatographed on Merck alumina. Elution gave a hydrocarbon fraction (64 mg, 61 % yield), $\lambda_{\max}^{\text{film}}$ 6.1, 11.0 μ (terminal vinyl), and three alcohol fractions: alcohol fraction A (20.4 mg, 18 % yield), $\lambda_{\max}^{\text{film}}$ 2.9, 9.0 (m, –OH), 6.1, 11.0 μ (terminal vinyl), alcohol fraction B (3.1 mg, 4 % yield); alcohol fraction C (19.2 mg, 17 % yield). Alcohol fraction C was purified by thin layer chromatography and recrystallization from ether, giving 9.8 mg (9 % yield) of **6** as colorless needles, mp 106–115°C: nmr 0.84 (s, 3H, C-18 methyl), 0.98 (s, 3H, C-19 methyl), 1.60 (s, 3H, vinyl methyl at C-4), 3.8 (broad multiplet (W 1/2 = 20 Hz), 1H, $\mathrm{H{-}\underset{|}{\overset{|}{C}}{-}O{-}}$, axial hydrogen).

Conversion of Alcohol **6** *to dl-*D*-Homo-4-methylandrost-4-en-17-one* (**38**)

A sample of 9.8 mg (0.0326 mmol) of alcohol **6** was dissolved in 1.5 ml of dry methylene chloride; then a solution of 100 mg (0.388 mmol) of dipyridine chromium trioxide[17] in 0.8 ml of methylene chloride was added dropwise, and the mixture was stirred at room temperature (nitrogen atmosphere) for 30 min. Chromatography of the mixture directly on Merck acid-washed alumina (methylene chloride eluant) gave 9.3 mg of a white solid, which was recrystallized from pentane to give 6.1 mg of ketone **38** as colorless needles, mp 130–132°C, $\lambda_{\max}^{\text{CCl}_4}$ 5.80 μ (s, C=O); nmr 0.79 (s, 3H, C-18 methyl), 0.98 (s, 3H, C-19 methyl), 1.59 (s, 3H, C-4 vinyl methyl), 1.97 (s, 2H, C-17a methylene).

The infrared spectrum (CCl$_4$), nmr spectrum, and mass spectrum (MS-9, parent ion at *m/e* 300, calcd for $C_{21}H_{32}O$: 300.47) of the above material were essentially identical in all respects with the corresponding spectra of authentic D-homo-4-methylandrost-4-en-17-one (*d*-**38**) prepared as described below.

Evidence for the Formation of the Isomeric Tetracyclic Alcohol **39**

A sample of 16.3 mg of tetraenol **4** was treated with 5 ml of anhydrous formic acid for 11 min, and the product was isolated as described above. The formate esters were cleaved with lithium aluminium hydride, and the product was chromatographed. The alcohol fraction showed three spots on tlc, tentatively assigned as follows (*8*): R_f 0.21 (alcohol **6**), R_f 0.26 (alcohol **39**), and R_f 0.39 (alcohol **37**). The nmr spectrum of the alcohol mixture provided the following information, the assignments being made in analogy to previous work (*8*): nmr 0.82 (s, ca. 1H, C-18 methyl), 0.93 (s, ca. 2H, C-18 methyl of C/D *cis* isomer **39**), 0.96 (s, 3H, C-19 methyl), 1.25 (s, ca. 2H, $\mathrm{O{-}\underset{|}{\overset{|}{C}}{-}CH_3}$, tricyclic alcohol **37**), 1.60 (s, 3H, C-4 vinyl methyl).

When the alcohol fraction from a similar cyclization experiment was oxidized with Jones reagent (acetone, 0°C, 15 min, ether extraction with base wash (see footnote 1)), the ketones showed two peaks on vpc analysis (SE-30, 233°C) with retention times of 13 min (10%, C/D *cis* isomer) (*8*) and 14 min (90%, ketone **38**).

When the 7.6 mg hydrocarbon fraction ($\lambda_{\max}^{\text{film}}$ 6.1, 10.95 μ, terminal vinyl) from a formic acid cyclization of tetraenol **4** was shaken with formic acid for 23 min at room temperature and then worked up as described above, including lithium aluminum hydride treatment, 8.1 mg of a semicrystalline oil was recovered: $\lambda_{\max}^{\text{film}}$ 2.95 (m,–OH), 6.1, 10.95 μ (w, terminal vinyl). Thin layer chromatography showed four spots tentatively assigned as follows: R_f 0.21, tetracyclic alcohol **6**; R_f 0.26, isomeric tetracyclic alcohol **39**; R_f 0.39, tricyclic alcohol **37**; and R_f 0.88, hydrocarbons.

Cyclization of Tetraenol 4 *with Trifluoroacetic Acid*

A sample of 4.53 mg of tetraenol **4** was treated with 0.4 *M* trifluoroacetic acid in pentane following the procedure used with the aforementioned tetraenol **3**. The crude product was reduced with lithium aluminum hydride, followed by oxidation with Jones reagent. Analysis by vpc (SE-30, 233°C) showed five peaks tentatively assigned as follows: 4 min (7%, tricyclic triene **36**), 6–8 min (43%, tetracyclic dienes **40**), 10 min (15%, tricyclic alcohol **37**), and 12–14 min (35%, ketone **38**). These results can be compared with the following vpc analysis of a similar cyclization product from a run using 2.1 mg tetraenol **4** and 2 ml formic acid for 1 min. The assignments were as follows 5 min (20%, tricyclic triene **36**), 7 min (20%, tetracyclic diene **40**), 10 min (15%, tricyclic alcohol **37**), 12.5 min (5%, C/D *cis* ketone), and 14 min (42%, C/D *trans* ketone **38**).

4-Methylandrost-4-en-17β-ol-3-one (42)

The method of Atwater was employed (*12*). Thus, a mixture of potassium tert-butoxide (prepared from 3.74 g (95.6 mmol) of potassium metal and 220 ml of dry tert-butyl alcohol) and 25.0 g (63.7 mmol) of testosterone benzoate (**41**), mp 188–192°C, in 300 ml of tert-butyl alcohol, was stirred at reflux temperature for 15 min, and then a solution of 11.3 g (79.6 mmol) of methyl iodide in 1000 ml of tert-butyl alcohol was added dropwise over a 5-hr period. The mixture was stirred at reflux temperature for an additional 0.5 hr and was then cooled, acidified with concentrated hydrochloric acid, and the solvent was removed at reduced pressure leaving a gum which was extracted with ether.[1] The product mixture showed six spots on tlc corresponding to unmethylated, mono- and di-methylated testosterone and the corresponding benzoates. The crude product was dissolved in methanol, potassium carbonate was added, and the mixture was stirred at reflux temperature for 2 hr (nitrogen atmosphere) and then cooled. The solvent was removed at reduced pressure leaving a white solid (three spots on tlc). Chromatography on Merck acid-washed alumina (ethyl acetate-benzene mixtures) gave 6.2 g of a solid, which was recrystallized from acetone, giving 4.92 g (25.4% yield) of **42** as a colorless solid, mp 168.5–170.5°C, $\lambda_{\max}^{\text{KBr}}$ 2.89 (OH), 6.05, 6.21 μ (O=C–C=C); $\lambda_{\max}^{95\%\ \text{EtOH}}$ 250 nm ($\varepsilon = 15\,000$); $[\alpha]_{\text{D}}^{\text{HCCl}_3} + 132°$; nmr 0.80 (s, 3H, C-18 methyl), 1.19 (s, 3H, C-19 methyl), 1.79 (s, 3H, C-4 methyl), 3.68 (t, $J = 8$ Hz, 1H at C-17); (reported: (*12*) mp 168.5–170.5°C, $\lambda_{\max}^{95\%\ \text{EtOH}}$ 250.5 nm ($\varepsilon = 14\,800$); $[\alpha]_{\text{D}}^{\text{HCCl}_3} = +137°$, 44% yield). A second crop (1.1 g 6% yield, mp 163–168.5°C) was also recovered.

4-Methylandrost-4-ene-3,17β-diol (**43**)

A sample of 2.94 g (9.73 mmol) of ketone **42**, mp 168.5–170.5°C, was dissolved in 30 ml of dry tetrahydrofuran and added dropwise to a stirred mixture of 0.84 g (24.3 mmol) of lithium aluminum hydride in 100 ml of tetrahydrofuran and 20 ml of dry ether. The mixture was stirred at room temperature for 5 hr (nitrogen atmosphere), and then 0.9 ml of water was added dropwise, followed by 0.9 ml of 15% potassium hydroxide solution and 3.0 ml of water. Stirring was continued overnight, excess anhydrous magnesium sulfate was added, and the mixture was stirred an additional 15 min and filtered. The salts were washed with hot ethyl acetate, and the solvent was removed at reduced pressure, leaving 2.9 g of colorless crystals of the mixture of epimers at C-3, mp 201–211°C, $\lambda_{\max}^{\mathrm{KBr}}$ 2.9, 9.5 μ (s, –OH); (reported (*12*) for pure 3β alcohol obtained in 39% yield by repeated recrystallizations: mp 138.5–140.5°C).

Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59. Found: C, 78.9; H, 10.7.

4-Methylandrost-4-ene-3,17β-diol 3,17-diacetate (**44**)

To a solution of 0.541 g (1.77 mmol) of the epimeric alcohol mixture **43**, mp 179–210°C, prepared as described above, in 12 ml of dry pyridine at 0°C was added 7 ml of acetic anhydride. The solution was stirred at room temperature (nitrogen atmosphere) for 20 hr; then the volatile materials were removed at 50°C/0.5 mm, leaving a light yellow solid which was chromatographed on Florisil, giving 0.579 g (84% yield) of the epimeric mixture as a colorless crystalline solid, mp 88–122°C, $\lambda_{\max}^{\mathrm{KBr}}$ 5.75, 8.0 μ (s, acetate); nmr 0.81 (s, 3H, C-18 methyl), 1.06 (s, 3H, C-19 methyl), 1.58 (s, 3H, C-4 methyl), 2.03 (s, 3H, acetate), 2.06 (s, 3H, acetate), 4.60 (t, $J = 8$ Hz, 1H, C-17), 5.0–5.7 (broad multiplet, 1H, C-3 proton epimers). The material was homogeneous on tlc (ether–pentane, R_f 0.7) and showed two peaks on vpc analysis with retention times of 7.9 min (37%) and9 .2 min (63%).

Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.0; H, 9.3.

4-Methylandrost-3-and-4-en-17β-ol (**45**)

The procedure of Henbest (*13*) was modified. A vigorously stirred solution of 3.76 g (9.73 mmol) of crude acetates **44**, prepared as described above, in 260 ml of anhydrous ethylamine (redistilled from lithium metal) was cooled to –75°C (Dry Ice–isopropyl alcohol bath), while 0.700 g (100 mmol) of lithium wire was added in small pieces. The stirring was continued for 1 hr at –78°C until a dark blue color developed. Ammonium chloride was added to destroy excess lithium, and the solvent was removed under reduced pressure. The product was isolated by ether extraction with an acid and a base wash[1] giving 2.65 g (95% yield) of the mixture of double bond isomers **45** as a colorless solid, mp 100–200°C: $\lambda_{\max}^{\mathrm{KBr}}$ 2.95 μ (s, –OH). The product gave a single spot on tlc (R_f 0.5, ether–pentane). It evidently absorbs oxygen; the best combustion analysis on carefully chromatographed material out of four attempts was the following.

Anal. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found: C, 82.5; H, 11.2.

Another preparation of alcohol **45** gave a product which was chromatographed giving 0.028 g of a colorless crystalline solid, mp 130–135°C: nmr 0.72 (s, 3H, C-18 methyl

0.99 (s, 3H, C-19 methyl), 1.58 (s, 3H, C-4 methyl), 3.63 ($J = 7$ Hz, C-17 proton). This material showed two peaks on vpc analysis with retention times of 8 min (15%, Δ^3 isomer) and 9.8 min (85%, Δ^4 isomer). The crude product was used in the next step without further purification.

4-Methylandrost-4-en-17-one (**46**)

A solution of 1.01 g (3.29 mmol) of the crude mixture of alcohols **45** in 200 ml of acetone (distilled from potassium permanganate) was cooled to 0°C and a slight excess of Jones reagent was added dropwise. The mixture was stirred at 0°C for 0.5 hr, and then excess isopropyl alcohol was added and the mixture was poured into water overlaid with ether. The product was isolated by ether extraction with a base wash (see footnote 1) giving a colorless solid, mp 92–102°C. Preparative tlc on silica gel (30% ether–pentane eluant) gave a colorless solid, mp 102.5–105°C, which was recrystallized from pentane, giving 0.314 g (34% overall yield from ketone **42**) of ketone **46**, mp 104–105.5°C: $\lambda_{\max}^{\mathrm{KBr}}$ 5.77 μ (s, C=O); nmr 0.837 (s, 3H, C-18 methyl), 1.007 (s, 3H, C-19 methyl), 1.585 (s, 3H, C-14 methyl). The product was homogeneous on tlc, and vpc analysis showed one peak.

Anal. Calcd for $C_{20}H_{30}O$: C, 83.86; H, 10.56. Found: C, 83.8, H; 10.6.

Another preparation gave crystalline **46**, mp 104–106.5°C, $[\alpha]_{\mathrm{D}}^{\mathrm{HCCl_3}} + 199°$.

17-Oxidomethylene-4-methylandrost-4-ene (**47**)

The procedure of Corey (*14*) was employed. A sample of 0.348 g (14.5 mmol) of sodium hydride (55% mineral oil dispersion) was freed of oil (pentane wash, nitrogen atmosphere) and then 75 ml of dry dimethylsulfoxide was added and the mixture was stirred at 50°C for 0.5 hr, and at room temperature for 2 hr. Dry tetrahydrofuran (65 ml) was added, the solution was cooled to –2°C, and 3.06 g (15 mmol) of trimethylsulfonium iodide was added. After stirring at –2°C for 2 min, a solution of 0.952 g (3.33 mmol) of ketone **46**, mp 101–105°C, in a mixture of 6 ml of dry tetrahydrofuran and 4 ml of dimethylsulfoxide was added dropwise over a 5 min period. The mixture was stirred at 0°C for 20 min, and at room temperature for 1.5 hr and was poured into ether. The product was isolated by ether extraction,[1] giving a solid which upon recrystallization from pentane gave 0.836 g (84% yield) of the C-17 epimeric mixture of epoxides **47** as colorless crystals, mp 113–127°C: nmr 0.85 (s, 3H, C-18 methyl), 0.99 (s, 3H, C-19 methyl), 1.58 (s, 3H, C-4 methyl), 2.41 (d, $J = 5$Hz, 1H, epoxide methylene proton), 2.72 (d, $J = 5$ Hz, 1H, epoxide methylene proton.)

Anal. Calcd for $C_{21}H_{32}O$: C, 83.94; H, 10.73. Found: C, 84.2; H, 10.8.

17-Azidomethylene-4-methylandrost-4-en-17-ol (**48**)

A mixture of 7.80 g (12.0 mmol) of sodium azide and 6.40 g (12.0 mmol) of ammonium chloride in 100 ml of dimethylsulfoxide was stirred at room temperature for 4 hr, and then 0.825 g (2.75 mmol) of the epimeric epoxide mixture **47**, mp 113–127°C, was added and the mixture was stirred under nitrogen at 70°C for 20 hr. Then the mixture was poured into ether and the product was isolated by ether extraction with an acid wash and a base wash[1]. Chromatography on acid-washed alumina gave 1.04 g of a solid, which was recrystallized from pentane to give 0.93 g (98 % yield) of the C-17 epimeric mixture **48** as a colorless solid, mp 67–76°C, $\lambda_{\max}^{\mathrm{KBr}}$ 2.80 (m, –OH), 4.70 μ (s, azide); nmr 0.90 (s, 3H, C-18 methyl), 1.00 (s, 3H, C-19 methyl), 1.58 (s, 3H, C-4 methyl), 1.90 (s, 1H, -OH), 3.18 (d, $J = 12$ Hz, 1H, azide methylene proton), 3.55 (d, $J = 12$ Hz, 1H, azide methylene proton).

Purification of a sample by preparative tlc followed by recrystallization from pentane evidently effected separation of one epimer, mp 74–76°C, $[\alpha]_{\mathrm{D}}^{\mathrm{HCCl_3}} + 73°$.

Anal. Calcd for $C_{21}H_{33}N_3O$: C, 73.42; H, 9.68; N, 12.23. Found: C, 73.6; H, 10.0; N, 12.6.

17-Aminomethylene-4-methylandrost-4-en-17-ol (**49**)

To a mixture of 0.587 g (15.4 mmol) of lithium aluminum hydride in 300 ml of anhydrous ether was added 0.936 g (2.73 mmol) of the epimeric mixture of hydroxyazides **48**, mp 67–76°C, in 15 ml of ether. The mixture was stirred at room temperature (nitrogen atmosphere) for 21 hr and was worked up as described for the aforementioned alcohols **43**, giving 0.759 g (88 % yield) of a colorless crystalline solid, mp 194–203°C.

Purification of a sample by recrystallization from methanol–ethyl acetate (1:1) evidently effected separation of one epimer of **49** as colorless plates, mp 202.5–203.5°C, $\lambda_{\max}^{\mathrm{KBr}}$ 2.9, 3.0 (m, –OH, –NH$_2$), 6.2 μ (–NH$_2$); $[\alpha]_{\mathrm{D}}^{\mathrm{HCCl_3}} + 88°$; nmr (deuteroacetic acid solvent) 0.95 (s, 3H, C-18 methyl), 1.03 (s, 3H, C-19 methyl), 1.59 (s, 3H, C-4 methyl), 2.68 (mult, 2H, amino methylene).

Anal. Calcd for $C_{21}H_{35}NO$: C, 79.44; H, 11.11; N, 4.41. Found: C, 79.2; H, 11.2; N, 4.15.

D-Homo-4-methylandrost-4-en-17-one (*d*-**38**)

A mixture of 0.696 g (2.19 mmol) of the hydroxyamine **49**, mp 194–203°C, in 65 ml of water and 6.5 ml of glacial acetic acid was cooled to 0°C and a solution of 0.304 g (4.40 mmol) of sodium nitrite in 5 ml of water was added dropwise. The milky mixture was stirred (nitrogen atmosphere) at 0°C for 3 hr and at room temperature for 12 h, and was poured into water. The product was isolated by ether extraction with a base wash[1] giving 0.769 g of a pale yellow solid. Column chromatography on acid-washed alumina gave two pure fractions: A (R_f 0.6 on tlc) and B (R_f 0.5).

Fraction A was recrystallized from pentane, giving 0.044 g of a colorless crystalline solid, assigned the structure of the C-17a ketone **50**: mp 110.5–111.5°C; $\lambda_{\max}^{\mathrm{KBr}}$ 5.88 μ (s, C=O); nmr 0.978 (s, 3H, C-19 methyl), 1.061 (s, 3H, C-18 methyl), 1.569 (s, 3H, C-4 methyl), 2.16 (broad mult, 2H, C-17 methylene).

Fraction B was recrystallized from pentane, giving 0.055 g (8 % yield) of the C-17 ketone *d*-**38** as colorless crystals: mp 104.5–106°C, $\lambda_{\max}^{\mathrm{KBr}}$ 5.80 μ (s, C=O); nmr 0.795 (s, 3H, C-18 methyl), 0.981 (s, 3H, 3-19 methyl), 1.588 (s, 3H, C-4 methyl), 1.98 (s, 2H, C-17a methylene protons).

The mass spectrum (MS-9)of ketone *d*-**38** (Fraction B) showed a molecular ion peak at *m/e* 300 and an ORD curve exhibiting a negative Cotton effect: (c, 0.142, dioxane) $[\Phi]_{589} + 133°$, $[\Phi]_{320} - 2602°$, $[\Phi]_{313} - 1726°$, $[\Phi]_{310} - 1780°$, $[\Phi]_{274} + 5681°$.

Anal. Calcd for $C_{21}H_{32}O$: C, 83.94; H, 10.73. Found: C, 84.0; H, 11.0.

D-Homo-4,17-dimethylandrosta-4,16-diene (*d*-**5**)

A solution of 37 mg (0.134 mmol) of ketone *d*-**38**, mp 104.5–106°C, in 15 ml of dry ether was treated with 0.96 ml (1.34 mmol) of methyllithium solution (1.4 *M* in ether) and stirred at room temperature for 1 hr (nitrogen atmosphere). The mixture was poured into ether and water, and the product was isolated by ether extraction.[1] Chromatography and recrystallization from pentane gave 29 mg of colorless prisms: mp 131–132.5°C, $\lambda_{\max}^{\mathrm{KBr}}$ 2.75 μ (m, -OH), nmr 0.99 (s, 3H, C-19 methyl), 1.04 (s, 3H, C-18 methyl), 1.12 (s, 3H, C-17 methyl), 1.575 (s, 3H, C-4 methyl).

A sample of 14 mg of the aforementioned alcohol, mp 131–132.5°C, was dissolved in 3 ml of dry pyridine and cooled to −5°C. Then 0.17 g (1.11 mmol) of phosphoryl chloride was added, and the mixture was stirred at 0°C for 17 hr (nitrogen atmosphere) and was poured into ether. The product was isolated by ether extraction with an acid and a base wash,[1] leaving a colorless solid which was recrystallized from ethanol three times: first, mp 96–110°C, second, mp 110–114°C, third, mp 111–113.5°C; nmr 0.813 (s, 3H, C-18 methyl), 0.978 (s, 3H, C-19 methyl), 1.557 (s, 6H, C-4 and C-16 methyls), 5.05 (s, W 1/2 = 5 Hz, 1H, C-17a proton on $\Delta^{17,17a}$ olefin **51**).

The mother liquors from the above crystallization were combined and a crop of crystals recovered, mp 84–108°C, which showed two spots on tlc using silver nitrate-impregnated silica gel (R_f 0.45 and 0.55, 1% ether–pentane). Preparative tlc on 10% silver nitrate-impregnated silica gel gave a fraction of colorless crystals, mp 82–86°C, which was recrystallized from ethanol, giving diene *d*-**5** as colorless plates, mp about 76°C, new crystals being formed at 79–81°C, mp 83.5–86.5°C; nmr 0.768 (s, 3H, C-18 methyl), 0.969 (s, 3H, C-19 methyl), 1.570 (s, 6H, C-4 and C-16 methyls), 5.25 (broad s, W 1/2 = 10 Hz, 1H, C-16 proton on Δ^{16} olefin of *d*-**5**). The ir spectrum (CCl_4) exhibited no diagnostic bands other than the C-H absorption bands, but showed considerable detail in the fingerprint region. The mass spectrum (MS-9) showed a molecular ion peak at *m/e* 298.

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