Formation of Vinyl Halides from Vinyl Cations Generated by Acetylenic Participation in Biomimetic Polyene Cyclizations[1-3]

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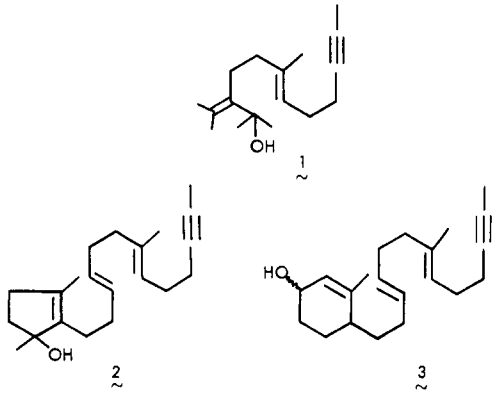
Abstract: The object of this study was to examine the fate of vinyl cations of type **4** (resulting from biomimetic polyene cyclizations) in the presence of various halides as sources of nucleophiles. Treatment of the dienynol **1** with trifluoroacetic acid in methylene chloride for 45 min at −78 °C resulted in the isolation of the rearranged bicyclic vinyl chloride **6** in 56% yield. Confirmation of the structure and isomeric purity of **6** was obtained by exhaustive ozonization to give diketo ester **9** followed by Wolff-Kischner reduction and then esterification to yield ester **10**, the structure of which was confirmed by hydrogen–deuterium exchange of the protons α to the carbomethoxy group. The configuration of the ring fusion in **6** was shown to be trans in the following manner. Selective ozonization gave chloro ketone **11**, which was converted into chloro olefin **12** by Wolff-Kischner reduction. Further ozonization afforded keto ester **13**, which was converted into diacid **15** by sodium hypobromite oxidation. Esterification afforded diester **16**, which was identical with the material obtained via Wolff-Kischner reduction of the known keto diester **17**. More careful examination of the products from the aforementioned cyclization also showed the presence of 8% ketone **8** (after hydrolytic workup). Identical cyclization conditions of **1**, except at 0 °C, gave 55% vinyl chloride **6** and 45% ketone **8** while use of a 7.5:1 pentane–1,2-dichloroethane mixture at 0 °C led to 11% vinyl chloride **6** and 89% ketone **8**. Cyclization of dienynol **1** with stannic chloride in 1,1-dichloroethylene at −35 °C for 45 min gave a 53% yield of three isomeric vinyl chlorides, **7b**, **7a**, and **6**, in a ratio of 8:75:12. The successful cyclization of dienynol **1** led to more extensive cyclization studies of substrates such as **2**, **3**, and **35**, which provided tetracyclic products. The most thoroughly studied case was that of trienynol **3**, which, on treatment with stannic chloride in 1,1-dichloroethylene at ca. −30 °C for 50 min, gave a 64% yield of three tetracyclic products A, B, and C in a ratio of 15:73:12 by VPC. Product A was shown to be chloro diene **22** by hydrogenation of the Δ^1-olefinic bond followed by ozonization to give 5β,13α-androstan-17-one (**29**), which was compared with an authentic sample prepared by irradiation of 5β-androstan-17-one (**25**). Products B and C were shown to be chloro dienes **18** and **20** by conversion of the mixture into 5β-androstan-17-one (**25**) and keto ester **27**. A systematic variation of reaction conditions as well as the use of mixed-halide sources led to evidence for a possible mechanism for the formation of all three products from an intermediary tricyclic cation **43**.

Recently we described[4] the stereoselective cyclization of alcohols **1**–**3** to provide bicyclic (from **1**) and tetracyclic (from **2** and **3**)



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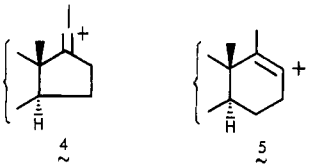
products. The products can all be rationalized as arising from an intermediate or a transition state having vinyl cationic character (see formula **4**). Such vinyl cations are produced efficiently under extremely mild conditions[2] starting from relatively stable ditertiary allylic cations (from **1** and **2**) or a secondary–tertiary allylic cation (from **3**), the energy being provided by the conversion of sp^2 to sp^3 bonds (affording ca. 40 kcal/mol per bond) and an sp^1 to an sp^2 bond (>40 kcal/mol) in the cyclization process. The vinyl cation **4** proved to be a very potent electrophile which reacts



4 5

efficiently with a variety of nucleophiles (e.g., formic acid, acetonitrile, ethylene carbonate, olefins, aromatic hydrocarbons, and nitroalkanes).[2]

The present study addresses the question of the fate of the vinyl cation **4** in the presence of various halides as sources of nucleophiles.[3]

Cyclization of Dienynol 1 and Identification of Products. When a solution of dienynol **1** in dry methylene chloride was stirred with a large excess of trifluoroacetic acid for 45 min at −78 °C and then neutralized with potassium carbonate in methanol–water at room temperature, an oily product, which was >98% one peak on VPC, was isolated in 56% yield by chromatography on Florisil. The analytical and spectral data (see Experimental Section) for this material were consistent with the product of a cyclization in which chloride ion acted as the nucleophile to terminate the process, giving the chloro diene **6** which is derived from the vinyl cation **5**, formed, presumably, by rearrangement of **4** (see below). By GC–MS the crude product appeared to contain 82% of the vinyl chloride **6** and 8% of ketone **8**. The structure and configuration of chloro diene **6** were proved in the following manner. Exhaustive ozonization in 1:3 methanol–ethyl acetate at −78 °C followed by treatment with dimethyl sulfide gave a 40% yield of the diketo ester **9**. There was no evidence by TLC or VPC for

(1) For a recent paper in this series on biomimetic polyene cyclizations, see: Hughes, L. R.; Schmid, R.; Johnson, W. S. *Bioorg. Chem.* **1979**, *8*, 513–8.

(2) For a recent review of biomimetic polyene cyclizations, see: Johnson, W. S. *Bioorg. Chem.* **1976**, *5*, 51–98.

(3) A preliminary account of part of the present work has appeared: Johnson, W. S.; Gravestock, M. B.; Parry, R. J.; Okorie, D. A. *J. Am. Chem. Soc.* **1972**, *94*, 8604–5.

(4) (a) Gravestock, M. B.; Johnson, W. S.; McCarry, B. E.; Parry, R. J.; Ratcliffe, B. E. *J. Am. Chem. Soc.* **1978**, *100*, 4274–82. (b) Johnson, W. S.; McCarry, B. E.; Markezich, R. L.; Boots, S. G. *Ibid.* **1980**, *102*, 352–9.

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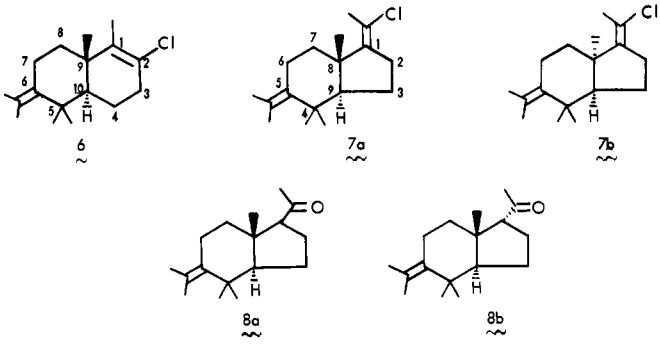


6 7a 7b 8a 8b

the presence of *trans*-4,4,8-trimethylhydrindan-1,5-dione,[5] which would have been produced from the chloro diene **7a** arising from cation **4**. Wolff–Kishner reduction of the diketo ester **9** followed by esterification with diazomethane afforded the ester **10** in 31% yield.

If the presumed skeletal rearrangement during the cyclization occurred in the opposite manner to give the isomer of **6** in which the groups at C-1 and C-2 are interchanged, the substance resulting from the aforementioned transformations would be an isomer of ester **10** in which the carbomethoxy group and the ethyl (at C-6) are interchanged. This isomer has no hydrogens α to the carbomethoxy group. The presence of two such α hydrogens in the substance at hand was confirmed by a hydrogen–deuterium exchange experiment in which ester **10** was treated with sodium dissolved in methanol-*d* for 10 h at 25 °C. The resulting acid was esterified with diazomethane to give an ester, the ^{1}H NMR spectrum of which showed significant diminution of the intensity of the signal at δ 2.23–2.53, attributable to protons α to the carbomethoxy residue. Also, the mass spectrum showed three molecular ion peaks of about equal intensity, corresponding to the incorporation of two, one, and zero deuteriums, respectively.

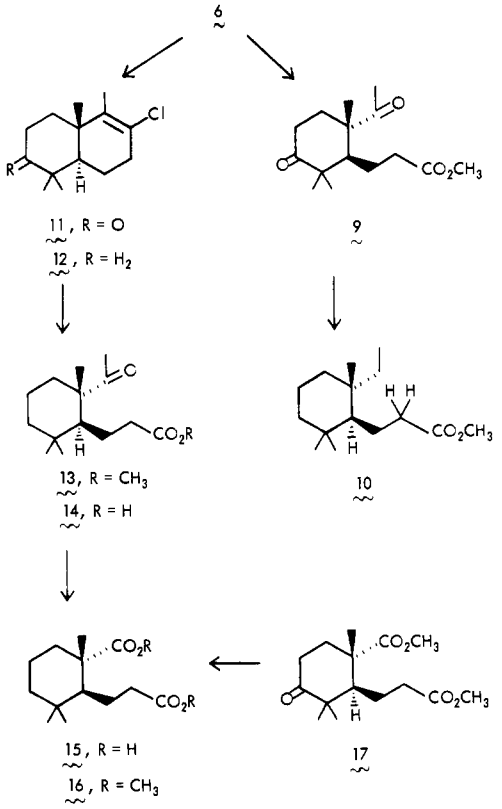
The configuration of the ring fusion of the chloro diene **6** was proved to be trans in the following manner. Selective ozonization in methylene chloride at −78 °C, using a Rubin ozonizer,[6] followed by treatment with dimethyl sulfide afforded a 72% yield of ketone **11**. Wolff–Kischner reduction of ketone **11** gave a 57% yield of the chloro olefin **12**, which was treated with excess ozone in 2:1 ethyl acetate–methanol at −78 °C and then with dimethyl sulfide to afford keto ester **13** in 80% yield. The ester **13** was saponified with aqueous methanolic sodium hydroxide and the resulting crude keto acid **14** was oxidized with sodium hypobromite in aqueous sodium hydroxide solution to give diacid **15**, which was esterified directly with diazomethane to afford diester **16** in 43% yield. This product was identical (by IR, ^{1}H NMR, and VPC coinjection) with an authentic specimen of **16** prepared as described below. Saponification of the diester specimen derived from the vinyl chloride **6** with methanolic sodium hydroxide afforded diacid **15**, mp 106–109 °C, undepressed on admixture with authentic diacid **15**, mp 107–110 °C, prepared as described below. The IR spectra of the two specimens were identical.

An authentic specimen of diester **16** was obtained by Wolff–Kischner reduction of the known[5] keto diester **17**, followed by esterification with diazomethane. Saponification of **16** with methanolic sodium hydroxide provided an authentic specimen of diacid **15**, mp 107–110 °C.

When the aforementioned cyclization of dienynol **1** with trifluoroacetic acid in methylene chloride was carried out in an identical manner except that the temperature was maintained at 0 °C instead of −78 °C, three products were formed in a ratio of 55:37:8, as shown by VPC. Coinjection experiments in addition to GC–MS showed these to be chloro diene **6**, ketone **8a**, and ketone **8b**, respectively.

Furthermore, cyclization of substrate **1** under conditions similar to those employed in the cyclization of **2** which led to tetracyclic material containing the $\Delta^{17,20}$-enol trifluoroacetate five-membered D ring as the only isolable material,[4a] i.e., with trifluoroacetic acid in 7.5:1 pentane–1,2-dichloroethane at 0 °C, followed by treatment with potassium carbonate in methanol–water gave a mixture of **6**, **8a**, and **8b** in a ratio of 11:76:14, identified as above by GC–MS and VPC coinjection.

Scheme I



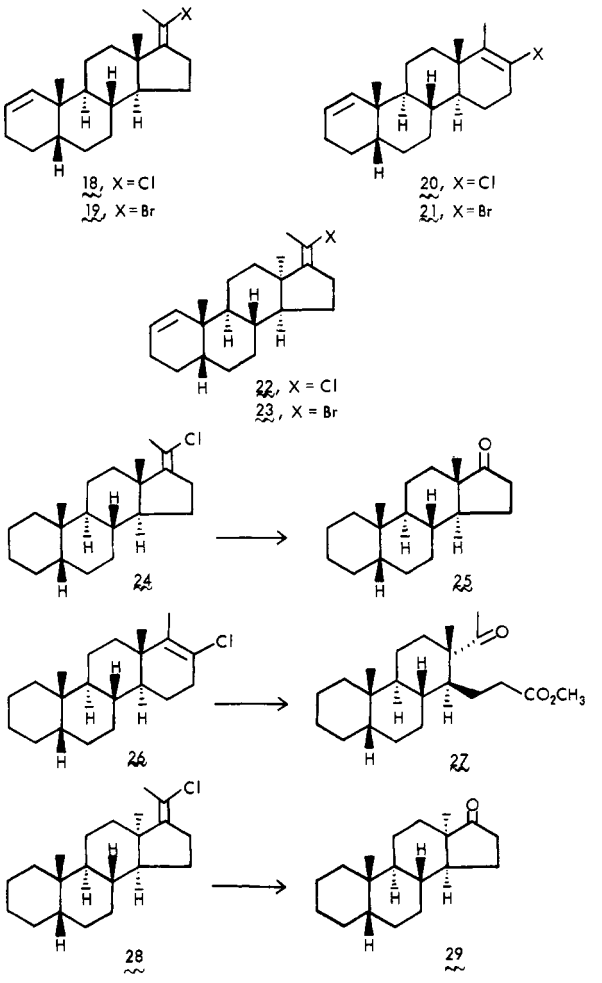
Lewis acid promoted cyclization gave quite different results. For example, in a preliminary study, cyclization of dienynol **1** was effected by treatment with stannic chloride in 1,1-dichloroethylene at −35 °C for 45 min. Filtration of the crude product through silica gel gave a 53% yield of a colorless oil which showed one spot on TLC and was 95% three peaks (A, B, and C) in a ratio of 8:75:12 on VPC. GC–MS showed A, B, and C to be isomeric chlorides with very similar mass spectra. C was identified by VPC coinjection and GC–MS as chloro diene **6**. Ozonolysis of the total cyclization product mixture gave ketonic material which was identified by VPC coinjection as *trans*-4,4,8-trimethylhydrindan-1,5-dione. Therefore, cyclization of dienynol **1** with stannic chloride occurred mainly by trapping of vinyl cation **4** to give chloro diene **7a** (product B). Product A is probably the cis-fused hydrindan **7b** (see below for a discussion of the formation of the cis-fused five-membered D-ring tetracycle from the substrate **3**).

With the structure of the rearranged chloride **6** reasonably secure and a preliminary indication that cyclization of dienynol **1** with stannic chloride in 1,1-dichloroethylene provided predominantly the normal 6/5 fused-ring vinyl chloride **7a**, our attention was turned to an investigation of the cyclization of trienynol **3** in the presence of halo compounds.

Cyclization of the Trienynol 3 and Identification of Products. When a solution of trienynol **3** in 1,1-dichloroethylene was treated with stannic chloride at ca. −30 °C for 50 min, a colorless oil, which showed three peaks on VPC (A, B, and C, in increasing order of retention time), was formed in 64% yield. A appeared as a single peak amounting to 15% of the total peak area, while B and C appeared as two overlapping peaks, in a ratio of 86:14, and accounted for 85% of the total peak area. Crystallization of the aforementioned oil from absolute ethanol gave colorless plates, mp 106–109 °C, which were shown by VPC to contain only B and C in an 88:12 ratio. The analytical and spectral data (see Experimental Section) for the crystalline material were consistent with the chloro diene structures **18** and **20** for com-

(5) Johnson, W. S.; Gravestock, M. B.; Parry, R. J.; Myers, R. F.; Bryson, T. A.; Miles, D. H. *J. Am. Chem. Soc.* **1971**, *93*, 4330–2.
(6) Rubin, M. B. *J. Chem. Educ.* **1964**, *41*, 388.

Scheme II



pounds B and C, respectively. Confirmation of these assignments was obtained in the following manner. Catalytic hydrogenation over palladium-on-carbon effected reduction of the Δ^1-olefinic bond, as evidenced by the spectral data, and afforded a mixture of chloro olefins **24** and **26**, in a ratio of 88:12 by VPC. Ozonization of this mixture in ethyl acetate–methanol, followed by treatment with dimethyl sulfide, gave a crude product which was purified by chromatography on Florisil. Elution with 3:1 hexane–ether afforded ketone **25**, 92% one peak on VPC, in 50% yield, which was identical (by IR, ^{1}H NMR, and VPC coinjection) with an authentic specimen[7] of 5β-androstan-17-one (**25**). Elution with ether gave keto ester **27**, 95% one peak on VPC, in a yield of 70%. The IR and ^{1}H NMR spectra were similar to those of the aforementioned bicyclic keto ester **13** and were identical with those of a specimen of keto ester **27**, obtained from the degradation of the mixture of **36**, **37**, and **38** produced on cyclization of substrate **35** (see below). In addition, VPC coinjection experiments showed the two specimens to behave identically.

With the structures of **18** and **20** presumably established, attention was directed to the identification of component A of the original cyclization mixture. The mother liquors obtained from the crystallization of **18** and **20** were subjected to preparative VPC, to afford a sample of A which exhibited one peak on VPC. The IR and ^{1}H NMR spectra were similar to those of the mixture of chloro dienes **18** and **20** and the mass spectrum exhibited a molecular ion at m/e 318, confirming that this material was indeed isomeric with substances **18** and **20**. Hydrogenation over palladium-on-carbon effected reduction of the Δ^1-olefinic bond, and subsequent ozonolysis yielded a sample which appeared to contain ketone **29**, as shown by VPC coinjection with an authentic mixture of ketones **25** and **29** described below. Additional studies were performed on a mixture of **18**, **20**, and **22** (15% **22** by VPC) obtained from other cyclization experiments. Catalytic hydrogenation, followed by ozonolysis of the mixture of **24**, **26**, and **28**, as described above, yielded a crude product which was purified by preparative TLC to afford a mixture which appeared by VPC coinjection experiments to contain 60% of the C/D cis ketone **29**, 30% 5β-androstan-17-one (**25**), and 10% unidentified material. An authentic specimen of 5β,13α-androstan-17-one (**29**) was prepared by irradiation[8] of 5β-androstan-17-one (**25**) in a Rayonet "reactor" at 2537 Å for 3 h. VPC examination of the crude product showed a mixture of 70% 13α-ketone **29** and 30% 13β-ketone **25**, which was purified by preparative TLC to give pure 5β,13α-androstan-17-one (**29**), mp 150–151 °C. The IR, ^{1}H NMR, and mass spectra were consistent with the assigned structure. Similarly, irradiation of a mixture of **25** and **29**, in a ratio of 62:38 by VPC, derived from a cyclization product (see above), afforded material which consisted of 72% of the 13α-ketone **29**, 13% of the 13β-ketone **25**, and 15% of an unidentified peak by VPC. The IR spectrum showed all the peaks present in authentic 5β,13α-androstan-17-one (**29**), described above. In addition, the ^{1}H NMR spectrum showed a diminution of the signals at δ 0.83 and 0.93, attributable to the C-18 and C-19 methyl groups in the 13β-ketone **25**.

The following evidence indicated that the chloro diene **20** was not formed by the stannic chloride induced isomerization of chloro diene **18**. Treatment of a solution of chloro dienes **18** and **20**, mp 100–106 °C (in a ratio of 61:39 by VPC), with stannic chloride at ca. −5 °C for 20 min did not alter the ratio of chloro diene isomers.

Effect of Varying Reaction Conditions on the Product Composition of Cyclization of Trienynol 3. In an effort to determine which, if any, experimental parameters affected the relative proportions of **18**, **20**, and **22** formed in the cyclization of trienynol **3**, a study of the effect of varying reaction conditions was carried out. Cyclizations were performed with 0.1 M stannic chloride in a variety of solvents, i.e., *n*-butyl chloride, methylene chloride, chloroform, carbon tetrachloride, 1,1-dichloroethylene, and tetrachloroethylene at ca. 22 °C for 15 min.[9] The relative amount of C/D cis chloro diene **22** remained essentially constant (ca. 14–19%), while the ratio of C/D trans five-membered D-ring chloro diene **18** to the C/D trans six-membered D-ring chloro diene **20** varied considerably from a ratio of 46:34 in *n*-butyl chloride to a ratio of 75:10 in 1,1-dichloroethylene. No readily apparent correlation could be made between solvent properties and product ratios.

The cyclization temperature was varied from −30 to +40 °C with stannic chloride in methylene chloride, from −78 to +22 °C with stannic chloride in 1,1-dichloroethylene, and from −110 to +22 °C with titanium tetrachloride in 1,1-dichloroethylene. The relative amount of C/D cis chloro diene **22** remained relatively constant throughout (ca. 12–16%) while the ratio of **18** to **20** increased from 51:37 to 73:10 with stannic chloride in methylene chloride and from 64:21 to 75:10 with stannic chloride in 1,1-dichloroethylene as the temperature was increased. In contrast no significant difference in product ratios was found when the temperature was changed in the titanium tetrachloride cyclizations.

Varying the reaction time did not seem to affect the proportions of the three cyclization products. Cyclization of trienynol **3** with stannic chloride in methylene chloride at −30 °C afforded the same ratio of products whether the reaction was allowed to proceed for 15 or 60 min. At −78 °C, cyclizations with stannic chloride in 1,1-dichloroethylene required at least 30 min for completion, while those catalyzed by titanium tetrachloride were complete in 15 min.

No significant effect on the proportions of chloro dienes formed was observed when the concentration of stannic chloride was varied from a 0.1 to a 2 M solution in methylene chloride or from a 0.1 to a 1 M solution in 1,1-dichloroethylene.[9] In one cyclization a 0.01 M solution of trienynol **3** was added to a 0.05 M solution

(7) Tökés, L.; LaLonde, R. T.; Djerassi, C. *J. Org. Chem.* **1967**, *32*, 1012–9.

(8) Wehrli, H.; Schaffner, K. *Helv. Chim. Acta* **1962**, *45*, 385–9.

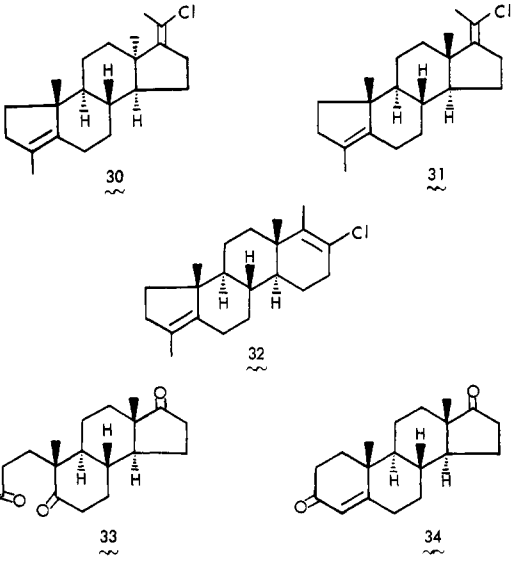
(9) The substrate concentration was ca. 0.03 M in all runs.

of stannic chloride in methylene chloride (inverse addition) at −30 °C for 90 min. The ratio of chloro dienes **18**, **20**, and **22** formed was essentially the same as that for cyclizations carried out by the addition of a 0.1 M solution of stannic chloride to a 0.03 M solution of trienynol **3** at −30 °C for 60 min.

The addition of a 0.2 M solution of tetra-*n*-butylammonium chloride to the cyclization mixture containing stannic chloride in methylene chloride or a 0.3 M solution of tetra-*n*-butylammonium chloride to the cyclization mixture containing titanium tetrachloride in 1,1-dichloroethylene, both at 22 °C for 15 min, produced no significant effect upon the product ratios. Cyclizations in the presence of higher salt concentrations (i.e., 0.65 M) gave rise to a number of unidentified products in addition to the usual chloro dienes **18**, **20**, and **22**. Cyclization of trienynol **3** with stannic chloride in methylene chloride at 22 °C for 15 min in the presence of dry hydrogen chloride afforded the same ratio of products as did the comparable cyclization without added hydrogen chloride. In addition, attempted cyclization of **3** with dry hydrogen chloride alone in methylene chloride afforded only recovered starting material after 15 min at 22 °C.

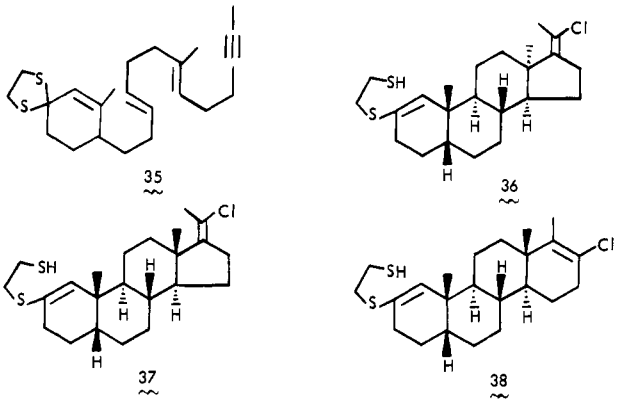
The origin of the halogen in chloro dienes **18**, **20**, and **22** remained an enigma, as both the catalyst and solvent were likely possibilities. The use of mixed-halogen sources shed some light on the problem. When the cyclization of trienynol **3** was carried out with stannic bromide in methylene bromide at 22 °C for 15 min, three products were formed in a ratio of 16:38:46 by VPC. Since the VPC retention times of these products were slightly longer than those of the corresponding chloro dienes **18**, **20**, and **22**, these new products were presumed to be the analogous bromo dienes **19**, **21**, and **23**. The following "mixed-halide" cyclizations were performed. Experiment a: Treatment of trienynol **3** with stannic bromide in methylene chloride at 22 °C for 15 min afforded five products in a ratio of 9:24:22:35:10, which were identified by VPC coinjection as the two chloro dienes **22** and **20** and the three bromo dienes **23**, **19**, and **21**. Experiment b: When trienynol **3** was treated with stannic chloride in methylene bromide at 22 °C for 15 min, four products were formed in a ratio of 12:68:11:9, which were similarly identified as the three chloro dienes **22**, **18**, and **20** and the bromo diene **21**. Apparently, all intermediate vinyl cations can react with halogen originating from the Lewis acid; however, the C/D trans five-membered-ring vinyl cation fails to abstract halogen from the solvent.[10]

Cyclization Experiments with Substrates 2 and 35. Some cyclizations of other substrates with stannic chloride have been examined, and because of the preliminary nature of the work some of the details have been omitted from the Experimental Section. Treatment of a solution of the known[4a] trienynol **2** in 1,2-dichloroethane with stannic chloride at 0 °C for 20 min yielded a product which, in analogy with the study described above, showed three peaks on VPC in a ratio of 12:68:14, presumed to be chloro dienes **30**, **31**, and **32**, respectively. Preparative TLC followed by recrystallization from pentane afforded a crystalline solid, mp 107–113 °C, which was shown by VPC to consist of a 5:1 mixture of presumed **31** and **32**. The analytical and spectral data (see Experimental Section) were consistent with the assigned structures. Evidence for the presence of chloro diene **31** was obtained by ruthenium tetraoxide[11] oxidation of the aforementioned mixture (to give **33**) followed by cyclodehydration to give a crude product, the major component of which appeared to be the androstenedione



34, as shown by VPC coinjection with authentic material.

Similarly, a solution of partially resolved trienyne thioketal **35**,[4b,12] in methylene chloride was treated with stannic chloride at 0 °C for 15 min to afford a crude product, which appeared to consist of 12% **36**, 55% **37**, and 32% **38** by VPC. That the



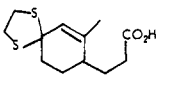
ethylene dithioketal ring had opened was evident from the ^{1}H NMR spectrum. The protons on the carbon atoms adjacent to the sulfur atoms appeared as two multiplets at δ 2.78 and 3.30. Likewise, the presence of a C-1 vinyl proton was indicated by absorption at δ 5.62. The mixture of vinyl sulfides **36**, **37**, and **38** was desulfurized with Raney nickel in ethyl acetate–acetone to afford chloro dienes **22**, **18**, and **20** in a ratio of 12:55:32, identical by VPC coinjection with the specimens obtained from the cyclization of trienynol **3** (see above). The ^{1}H NMR spectrum was essentially identical with the aforementioned spectrum of **18** and **20**, except that peak heights varied due to the different isomer ratio. Conversion of the mixture of **22**, **18**, and **20** to 5β-androstan-17-one (**25**) and keto ester **27** was effected as described above. Catalytic reduction of the Δ^1-olefinic bond followed by ozonolysis afforded, after preparative TLC, *l*-5β-androstan-17-one (**25**), $[\alpha]_D$ −48.5° (reported for naturally derived material,[7] $[\alpha]_D$ +94°), which was 93% one peak on VPC and was identical by IR, ^{1}H NMR, and VPC coinjection with an authentic specimen[7] of *d*-5β-androstan-17-one. It is noteworthy that this cyclization appears to proceed with a high degree of asymmetric induction.[4b]

(10) This generalization appears to apply as well to the bicyclic case (see above). Thus no five-membered-ring vinyl chloride **7a** was produced when substrate **1** was cyclized with trifluoroacetic acid in methylene chloride; however, it is a major product in the stannic chloride promoted cyclization. Seemingly the unidentified isomer (A) of this latter reaction is the cis-fused vinyl chloride **7b**, in analogy to the behavior found in the tetracyclic series.

It appears contradictory to find that the cis-fused five-membered-ring vinyl cation appears to abstract halogen from methylene chloride to form **22** (mixed-halide experiment a) but not from methylene bromide (no **23** found in experiment b). Since it seems improbable that there could be appreciable halogen exchange between the tin salt and solvent in experiment a but not in experiment b, we are inclined to dismiss as untenable any rationalization involving in situ formation of tin chlorides in experiment a.

(11) Nagata, H. *Tetrahedron* **1963**, *19*, 1959–63.

(12) This specimen was derived from acid i, $[\alpha]_D$ −10.1° (about 75% ee), described in ref 4b.



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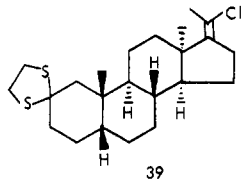
The analytical and spectral data of the keto ester were consistent with the structure **27**. This assignment is reasonable by analogy with the bicyclic keto ester **13** of established structure.

Interestingly, cyclization of trienyne thioketal **35** with titanium tetrachloride in 1,2-dichloroethane at ca. −30 °C for 10 min afforded a crude product in 79% yield which showed four peaks on VPC in a ratio of 15:3:70:12, which were different from those obtained in the stannic chloride catalyzed cyclization. Analytical and spectral data were consistent with tetracyclic vinyl chlorides in which the ethylene thioketal residue had remained intact. The ^{1}H NMR spectrum, in contrast to the aforementioned spectrum of the mixture of **36**, **37**, and **38**, showed absorption for the ethylene thioketal moiety as a broad singlet at δ 3.25; likewise, there was no absorption for vinyl protons. Therefore, the mixture appeared to consist of 15% of the C/D cis epimer **39**, 3% of an



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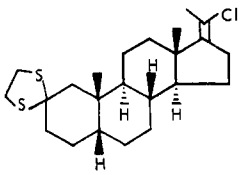

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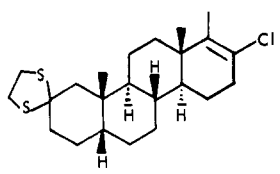


41

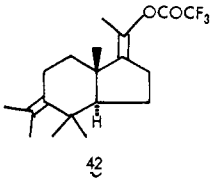
unidentified compound, 70% of **40**, and 12% of **41**, by analogy with **22**, **18**, and **20**. Recrystallization from hexane afforded a specimen, mp 139–142 °C, which was shown by VPC to consist of a mixture of **40** and **41**, in the same ratio found in the crude product. Desulfurization with Raney nickel followed by ozonolysis, as described above, afforded 5β-androstan-17-one (**25**), identified by VPC coinjection with an authentic specimen.[7]

Cyclization conditions were varied as follows. When trienyne thioketal **35** was treated with 0.2 M stannic chloride at 0 °C for 15 min, the relative amount of presumed C/D cis chloro diene **36** remained almost constant (ca. 12–15%), while the ratio of **37** to **38** was 55:32 with methylene chloride and 64:19 with 1,2-dichloroethane as solvent. With titanium tetrachloride in place of stannic chloride essentially no significant difference in the ratio of products formed was noted in the two aforementioned solvents.

The temperature of the cyclization reaction mixture was varied from 0 to −25 °C with stannic chloride in methylene chloride, from 0 to −35 °C with stannic chloride in 1,2-dichloroethane, from 0 to −78 °C with titanium tetrachloride in methylene chloride, and from 0 to −35 °C with titanium tetrachloride in 1,2-dichloroethane. The relative amount of presumed C/D cis chloro diene **36** remained relatively constant throughout (ca. 12–18%) while the ratio of **37** to **38** increased from 36:43 to 56:27 in methylene chloride and from 52:34 to 64:19 in 1,2-dichloroethane as the temperature was increased in the stannic chloride catalyzed cyclizations. The product ratios were essentially independent of temperature when titanium tetrachloride was used as the catalyst. The ratio of products formed was identical when the cyclization was effected with stannic chloride in methylene chloride at 0 °C for either 15 or 45 min.

Mechanistic Considerations. The methylacetylenic group participates in the cyclization of substrates like **1**, **2**, or **3** so as to form a five- or six-membered ring. Under most conditions (see above) the major product observed is the result of five-membered-ring formation, as if the vinyl cation **4** were produced and immediately trapped by a nucleophile. So far, six-membered-ring formation has been observed only in media of relatively low nucleophilicity containing sources of halide ion which act as the nucleophile.[2] The mechanism has not been established. Of the several possibilities, one of the simplest rationalizations is given below.

As described above the cyclization of substrate **1** with trifluoroacetic acid in methylene chloride at −78 °C gave, after hydrolytic workup, a 10:1 mixture of "abnormal" vinyl chloride **6** and "normal" ketone **8**. Identical cyclization conditions at 0 °C led to an ca. 1:1 mixture of **6** and **8** but when a less polar medium at 0 °C (7.5:1 pentane–1,2-dichloroethane) was used, a reversal was observed in the ratio of **6** and **8** formed (1:9). Seemingly, at least two factors are operative here. First, it appears that the cation **4** is the primary (kinetically favored) intermediate of such cyclizations but that under certain conditions (see above) it can undergo Wagner–Meerwein rearrangement to the cation **5**. Although the latter is a bent vinyl cation, its formation may be favored energetically, due to the relief of torsional strain in the conversion of a 6/5 (in **4**) to a 6/6 (in **5**) trans-fused ring system. This hypothesis finds support in the fact that no cis-fused six-membered-ring vinyl chloride has ever been observed in either the bicyclic or tetracyclic series. Secondly, as the polarity of the reaction media is decreased (compare the two runs at 0 °C), the ion pair becomes "tighter" and the linear vinyl cation **4** is more likely to trap the trifluoroacetate counterion to give enol trifluoroacetate **42** rather than to rearrange to **5** which extracts chloride from the solvent.[13]



42

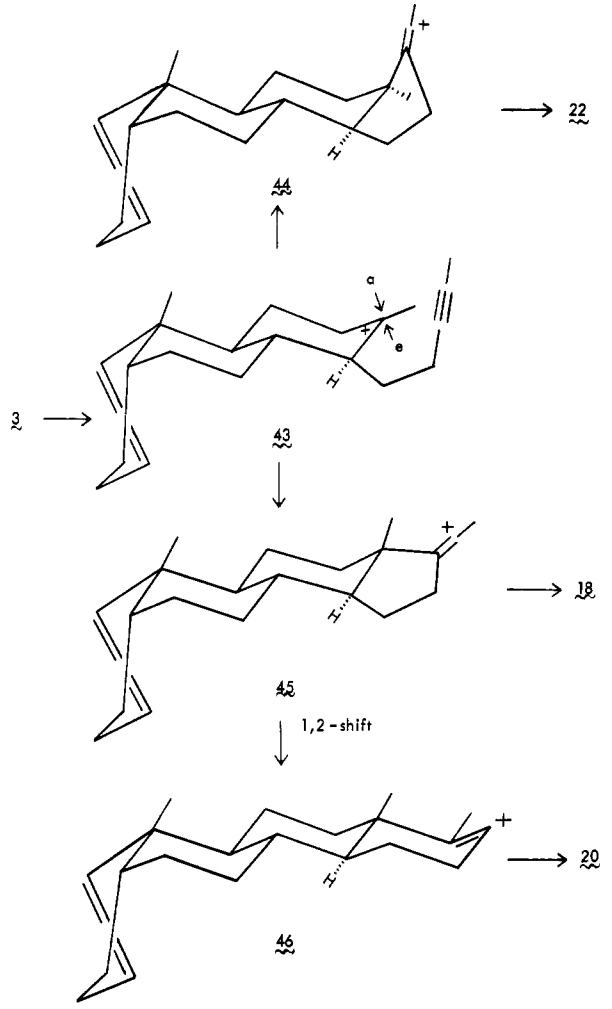
Attention is now turned to the stannic halide catalyzed cyclization of the substrate **3** and the matter of rationalizing the formation of the C/D cis product **22** as well as the results of employing competitive halide sources (see above). In another study[14] it has been suggested that the formation of C/D cis products in the cyclization of substrates like **3** with acetylenic terminators may be the result of axial attack by the acetylenic center on a tricyclic cation like **43**. This concept may be applied to the matter at hand as follows; however, it should be emphasized that other mechanisms have not been excluded, e.g., an approach involving equilibration via a ring-opening fragmentation of the primary vinyl cation.

It may be proposed that **3**, upon reaction with stannic chloride, cyclizes in the "normal" fashion[2] to yield the intermediary tricyclic cation **43**, which is tightly ion paired with a tin species formulated as $[SnCl_4OH]^-$. Equatorial attack on the ring-C cation by the acetylenic group (indicated by "e") leads to the C/D trans five-membered-ring vinyl cation **45**, which is still tightly ion paired. This species may then collapse to yield **18**, bearing only Lewis acid derived halogen, or undergo rearrangement to afford the solvent-separated ion pair **46**. The resulting six-membered D-ring bent vinyl cation **46** may then capture halogen from solvent or from the counterion to yield **20**. On the other hand, axial attack (indicated by "a") leads to the C/D cis five-membered D-ring linear vinyl cation **44**, which is tightly ion paired but subsequently collapses, like **45**, to give **22**, containing only Lewis acid derived halogen.[10] The observed 85:15 ratio of C/D trans to C/D cis products may be regarded as the result of equatorial vs. axial steric approach control in the transition state. The observation that no significant change in the amount of C/D cis product was found

(13) Chloride abstraction from chlorinated hydrocarbon solvents by carbonium ions has been noted previously: (a) Cohen and Lipowitz (Cohen, T.; Lipowitz, J. *Tetrahedron Lett.* **1964**, 3721–5) reported that the thermal decomposition of aryldiazonium fluoroborates led to benzene carbonium ions which gave rise to aryl chlorides. The yield of the major product (aryl fluorides) increased dramatically as the dielectric constant of the medium was decreased, indicating the importance of tight ion pairing when competitive processes are involved. (b) White et al. (White, E. H.; Tiwari, H. P.; Todd, M. J. *J. Am. Chem. Soc.* **1968**, *90*, 4734–6) also described the "trapping" of norbornyl cations. Again, less chloride ion abstraction from the solvent was observed when the polarity of the solvent was decreased.

(14) Johnson, W. S.; Hughes, L. R.; Carlson, J. L. *J. Am. Chem. Soc.* **1979**, *101*, 1281–2.

Scheme III



over a wide range in temperature suggests a process with a low activation energy and a negative entropy.

The exact nature of the metal complex counterion is uncertain, but it has been postulated as $[SnCl_4OH]^-$. Although this species has never been isolated, the hydrated form of its chloride-abstraction product, i.e., $[SnCl_3(OH)(H_2O)_2]$, is known.[15] Furthermore, the analogous pentacoordinate anion $[SnCl_5]^-$ has been isolated as its salt with triphenylmethyl cation.[16] Also, spectral data (IR and Raman) indicate the existence of $[SnCl_5]^-$ in solutions containing stannic chloride and tetra-*n*-butylammonium chloride.[17] Neutral five-coordinate tin complexes such as $(CH_3)_3NSnCl_4$ are also known.[18]

Several difficulties would have to be overcome before the biomimetic cyclization of substrates involving the trapping of vinyl cation **4** to give vinyl chlorides could be used in the synthesis of biologically important tetracycles. Recent reports by Matsumoto[19] afford a synthetically useful method for the conversion of vinyl chlorides to the corresponding ketones; however, the formation of the 13α isomer as well as the trans-fused six-membered D-ring vinyl chloride mars the elegance of terminating biomimetic cyclizations in this manner.

(15) Sneed, M. C.; Brasted, R. C. "Comprehensive Inorganic Chemistry"; Van Nostrand: Princeton, N.J., 1958; Vol. 7, p 223.
(16) Harmon, K. M.; Hesse, L.-L.; Klemann, L. P.; Kocher, C. W.; McKinley, S. V.; Young, A. E. *Inorg. Chem.* **1969**, *8*, 1054–60.
(17) Beattie, I. R.; Gilson, T.; Livingston, K.; Fawcett, V.; Ozin, G. A. *J. Chem. Soc. A* **1967**, 712–8.
(18) Rochow, E. G.; Abel, E. W. "The Chemistry of Germanium, Tin and Lead"; Pergamon Press: New York, 1973; p 88.
(19) Yoshioka, H.; Takasaki, K.; Kobayashi, M.; Matsumoto, T. *Tetrahedron Lett.* **1979**, 3489–92.

Experimental Section[20]

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 calibrated against totally immersed Anschutz thermometers. NMR spectra were recorded under the supervision of Dr. L. J. Durham on Varian Associates T-60 and XL-100 spectrometers. Deuteriochloroform was used as the solvent unless indicated otherwise and chemical shifts are reported as δ values in parts per million relative to tetramethylsilane ($\delta_{Me_4Si} = 0$). Mass spectra were determined on an Atlas CH-4 spectrometer under the supervision of Dr. A. M. Duffield. GC–MS were run on a Varian MAT-44 spectrometer. Infrared (IR) spectra were recorded on Perkin-Elmer Model 137 and 421 spectrometers or a Beckman Acculab 3 spectrometer. Optical rotations were determined on a Perkin-Elmer Model 141 polarimeter. Chloroform was used as the solvent and rotations were measured at 22 °C (*c* 0.003–0.08 M) in a 1-dm tube. Vapor-phase chromatographic (VPC) analyses were performed on either a Hewlett-Packard HP 402 chromatograph using $^1/_8$-in. glass columns (4 ft 5% SE-30, 6 ft 3% SE-30, 6 ft 3% OV-17, 6 ft 3% OV-225, and 6 ft 3% XE-60 on Gas Chrom Q; 3.8% SE-30 on Chromosorb WHP) or a Hewlett-Packard HP 5710A chromatograph using a 10-m WCOT OV-101 glass column. Helium was used as the carrier gas and disk-chart integrations are uncorrected for detector response. Analytical and preparative thin-layer chromatography (TLC) were performed with silica gel GF_{254}, HF_{254}, or PF_{254} (E. Merck AG) as the adsorbent at 0.25-mm and 1.0-mm thicknesses, respectively, unless otherwise indicated. Analytical plates were visualized by spraying with a solution of 2% ceric sulfate in 2 N sulfuric acid and then heating the plate at 180 °C for 5–10 min. "Evaporative distillation" refers to bulb-to-bulb short-path distillation in which the bulb was heated in a hot-air oven (Büchi Kugelrohrofen). The cited temperatures for these distillations refer to the maximum temperature attained by the oven during the distillation and are thus not true boiling points.

Cyclization of Dienynol 1 with Trifluoroacetic Acid in Methylene Chloride at −78 °C. *trans*-2-Chloro-6-isopropylidene-1,5,5,9-tetramethyl-1-octalin (6). A cold (−78 °C) solution of 30 mg (0.09 mmol) of the known[4a] alcohol **1** (contaminated with 24% of the homoallylic alcohol) in 6.5 mL of dry methylene chloride was stirred under argon while 0.065 mL (100 mg, 0.86 mmol) of trifluoroacetic acid was added slowly via syringe. The yellow solution containing fine white crystals was stirred at −78 °C for 45 min and then poured into saturated aqueous sodium bicarbonate solution. Ether extraction[20] afforded 44 mg of brown oil: IR (film) 5.59 μm (w, enol trifluoroacetate). The aforementioned crude product was stirred at room temperature under argon for 18 h with 0.2 mL of saturated aqueous potassium carbonate solution and 2 mL of methanol. Ether extraction[20] gave 48 mg of a pale yellow oil which was filtered through 10 g of Florisil (19:1 hexane–ether) to give 37 mg of colorless oil which showed five spots on TLC (R_f 0.69, 0.58, 0.49, 0.15, and 0.04, 9:1 hexane–ethyl acetate) and nine peaks on VPC (WCOT OV-101, 180 °C): IR (film) 5.85 μm (w, C=O). VPC coinjection and GC–MS (6 ft 3% OV-17, 174 °C) showed the presence of chloro diene **6** (62%), ketone **8a** (6%), and seven unidentified peaks (32%) by comparison of retention times and mass spectra with authentic specimens of **6** and **8a**.

A 60-mg sample from a comparable run was chromatographed on 11 g of Florisil (hexane) to give 26 mg (56% yield) of chloro diene **6** as a colorless oil which was >98% one peak on VPC (WCOT OV-101, 185 °C): IR (film) 13.2 μm; ^{1}H NMR 0.95 (s, 3, C-5 or C-9 CH_3), 1.12 (s, 3, C-5 or C-9 CH_3), 1.20 (s, 3, C-5 or C-9 CH_3), 1.4–1.8 (br m, methylene envelope), 1.66 and 1.80 (s, 3 each, isopropylidene CH_3's), 1.68 (s, 3, C-1 CH_3), 1.9–2.5 ppm (m, 4, allylic protons); GC–MS (6 ft 3% OV-17, 168 °C) *m/e* 266 (M^+), 251 (M − 15), 215 (M − 51), 209 (M − 57), 195 (M − 71), 187 (M − 79), 185 (M − 81), 184 (M − 82), 183 (M − 83).

An analytical specimen was prepared by preparative TLC (9:1 hexane–ethyl acetate) of a sample from a comparable run to give a colorless oil which showed one peak on VPC (5% SE-30, 160 °C).

Anal. Calcd for $C_{17}H_{27}Cl$: C, 76.50; H, 10.10; Cl, 13.30. Found: C, 76.79; H, 10.25; Cl, 13.13.

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

Methyl *trans*-3-(6-Acetyl-3-oxo-2,2,6-trimethylcyclohexyl)propionate (9). Ozone was bubbled through a solution of 88 mg (0.31 mmol) of chloro diene **6** (93% one peak on VPC) in 4 mL of 3:1 ethyl acetate–methanol at −78 °C until a permanent blue color developed. After 30 min at −78 °C, the blue color faded; then ozone was bubbled through until the blue color was restored, and the mixture was allowed to stand at −78 °C for 10 min. Excess ozone was flushed from the solution with oxygen; then 0.5 mL (423 mg, 6.8 mmol) of dimethyl sulfide was added and the solution was stirred at room temperature for 1 h. The solvent was removed at reduced pressure and the residue was extracted with ether[20] to give 70 mg of diketo ester **9** as a colorless oil. Preparative TLC (R_f 0.33, 1:1 hexane–ethyl acetate) gave 36 mg (40% yield) of **9** which was 92% one peak on VPC (3% SE-30, 160 °C).

An analytical specimen was prepared by evaporative distillation at 105 °C (0.07 mm): IR (film) 5.75 (ester C=O), 5.85 μm (C=O); ^{1}H NMR 1.13 (s, 6, C-2 CH_3's), 1.33 (s, 3, C-6 CH_3), 2.22 (s, 3, acetyl CH_3), 3.66 ppm (s, 3, CO_2CH_3).

Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.14; H, 9.01. Found: C, 67.14; H, 8.86.

Methyl *trans*-3-(6-Ethyl-2,2,6-trimethylcyclohexyl)propionate (10). A cold (0 °C) solution of 139 mg (0.48 mmol) of diketo ester **9** (92% one peak on VPC) in 18 mL of triethylene glycol was stirred under nitrogen while 2.8 mL (2.8 g, 0.085 mol) of 97% hydrazine was added. The mixture was stirred at 0 °C under nitrogen for 4 h and then at room temperature for 20 h, after which time 300 mg (4.6 mmol) of 85% potassium hydroxide pellets was added. The mixture was heated at ca. 105 °C for 1 h and then at ca. 200 °C for 3 h, during which time volatile material was slowly distilled from the mixture. The solution was cooled and then diluted with 75 mL of water. The distillate was added to the aforementioned solution, and then enough concentrated hydrochloric acid was added to adjust the pH to 2. Ether extraction[20] afforded 54 mg of a colorless oil, which was treated directly with diazomethane to give ester **10** as a colorless oil. Preparative TLC (R_f 0.50, 19:1 hexane–ethyl acetate) gave 36 mg (31% yield) of ester **10** as a colorless oil which was ca. 97% one peak on VPC (5% SE-30, 160 °C).

An analytical specimen was prepared by evaporative distillation at 65 °C (0.01 mm): IR (film) 5.74 μm (ester C=O); ^{1}H NMR 0.82 (3, s, C-6 CH_3), 0.87 (s, 3, C-2 CH_3), 0.88 (s, 3, C-2 CH_3), 2.23–2.53 (2, m, $CH_2CO_2CH_3$), 3.68 ppm (s, 3, CO_2CH_3); mass spectrum (70 eV), *m/e* 240 (M^+), 225 (M − 15), 211 (M − 29), 179 (M − 61), 143 (M − 97, base peak).

Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 75.18; H, 11.60.

Hydrogen–Deuterium Exchange in Methyl *trans*-3-(6-Ethyl-2,2,6-trimethylcyclohexyl)propionate (10). A solution of sodium methoxide in methanol-*d* was prepared from 95 mg (4.1 mmol) of sodium metal in 2.0 mL of Stohler "99% D" methanol-*d*. A 24-mg sample (0.1 mmol) of analytically pure ester **10** was added to the aforementioned solution, and the mixture was allowed to stand at room temperature for 10 h. Deuterium oxide and sulfuric acid-d_2 were added, followed by enough concentrated hydrochloric acid to adjust the pH to 2. Sodium carbonate was added to adjust the pH to 5; then the mixture was extracted with ether[20] to give 7 mg of free acid, which was converted directly to the deuterated methyl ester **10** with diazomethane. The ^{1}H NMR spectrum showed significant diminution of the intensity of the signal at δ 2.23-2.53. The mass spectrum (70 eV) showed three M^+ peaks of ca. equal intensity, corresponding to two, one, and zero deuteriums having been incorporated.

***trans*-2-Chloro-6-oxo-1,5,5,9-tetramethyl-1-octalin (11).** A solution of 220 mg (ca. 0.8 mmol) of chloro diene **6** (ca. 90% one peak on VPC) in 8 mL of 2:1 ethyl acetate–methanol was stirred at −78 °C in a Rubin ozonizer[6] while 24 mL of methylene chloride saturated with ozone (ca. 0.87 mmol) at −78 °C was slowly added under a positive nitrogen pressure. The resulting mixture was stirred for 3 min at −78 °C; then 2 mL (1.69 g, 0.027 mmol) of dimethyl sulfide was added in a dropwise manner. The mixture was stirred for 1 h at room temperature; then the solvent was removed at reduced pressure. Extraction with hexane[20] afforded 210 mg of ketone **11** as a pale yellow oil which was 95% one peak on VPC (3% XE-60, 145 °C). Preparative TLC (R_f 0.3, 9:1 hexane–ethyl acetate) gave 144 mg (72% yield) of **11** as a colorless oil which crystallized on standing. VPC examination showed the product to be >97% one peak.

An analytical specimen, as a colorless solid, was prepared by evaporative distillation at 75 °C (0.02 mm): IR ($CHCl_3$) 5.88 μm (C=O); ^{1}H NMR 1.05 (s, 3, C-5 or C-9 CH_3), 1.11 (s, 6, C-5 or C-9 CH_3), 1.75 (t, J = 1 Hz, 3, C-1 CH_3), 2.32–2.66 ppm (m, 4, C=CCH_2 and $OCCH_2$).

Anal. Calcd for $C_{14}H_{21}ClO$: C, 69.84; H, 8.79; Cl, 14.72. Found: C, 70.08; H, 8.80; Cl, 14.74.

***trans*-2-Chloro-1,5,5,9-tetramethyl-1-octalin (12).** A cold (0 °C) solution of 150 mg (0.63 mmol) of ketone **11** (95% one peak on VPC) in 15 mL of triethylene glycol was stirred under nitrogen while 2.2 mL (2.2 g, 0.07 mol) of anhydrous hydrazine was added. The mixture was stirred at 0 °C under nitrogen for 3 h and then at room temperature overnight, after which time 250 mg (3.8 mmol) of 85% potassium hydroxide pellets was added. The mixture was heated at ca. 105 °C for 3 h and then at ca. 205 °C for 4 h, during which time volatile material was slowly distilled from the mixture. The solution was cooled and then diluted with 100 mL of water. The distillate was added to the aforementioned solution and enough concentrated hydrochloric acid was added to adjust the pH to 2. Ether extraction[20] gave an oil which was purified by preparative TLC (9:1 hexane–ethyl acetate) to afford 80 mg (57% yield) of chloro olefin **12** as a colorless oil which was 98% one peak on VPC (3% XE-60, 130 °C).

An analytical specimen was prepared by evaporative distillation at 78 °C (0.04 mm): IR (film) 6.90, 10.18 μm; ^{1}H NMR 0.71 (s, 3, C-5 or C-9 CH_3), 0.90 (s, 3, C-5 or C-9 CH_3), 1.00 (s, 3, C-5 or C-9 CH_3), 1.70 (t, J = 1 Hz, 3, C-1 CH_3), 2.20–2.56 ppm (m, 2, CH_2C=C); mass spectrum (70 eV), *m/e* 226 (M^+), 211 (M − 15), 191 (M − 35, base peak).

Anal. Calcd for $C_{14}H_{23}Cl$: C, 74.14; H, 10.22; Cl, 15.64. Found: C, 74.21; H, 10.09; Cl, 15.40.

Methyl *trans*-3-(6-Acetyl-2,2,6-trimethylcyclohexyl)propionate (13). Ozone was bubbled for 45 min through a cold (−78 °C) solution of 90 mg (0.4 mmol) of chloro olefin **12** (95% one peak on VPC) in 12 mL of 2:1 ethyl acetate–methanol. Excess ozone was flushed from the solution with oxygen; then 2 mL (1.69 g, 27 mmol) of dimethyl sulfide was added, and the solution was stirred overnight at room temperature. The solvent was removed at reduced pressure and the residue was extracted with ether[20] to give 90 mg of keto ester **13** as an oil. Preparative TLC (4:1 hexane–ethyl acetate) gave 80 mg (80% yield) of **13** as a colorless oil which was >98% one peak on VPC (3% XE-60, 150 °C).

An analytical sample was prepared by evaporative distillation at 105 °C (0.01 mm): IR (film) 5.76 (ester C=O), 5.87 μm (C=O); ^{1}H NMR 0.93 (s, 6, C-2 CH_3's), 1.20 (C-6 CH_3), 2.14 (s, 3, acetyl CH_3), 3.64 ppm (s, 3, CO_2CH_3); mass spectrum (70 eV), *m/e* 254 (M^+), 211 (M − 43), 179 (M − 75, base peak), 129 (M − 125), 69.

Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.95; H, 10.11.

***trans*-3-(6-Acetyl-2,2,6-trimethylcyclohexyl)propionic Acid (14).** A solution of 140 mg (0.55 mmol) of keto ester **13** (>99% one peak on VPC) in 3 mL of methanol and 10 mL of 5% sodium hydroxide in 1:1 methanol–water was stirred at room temperature for 66 h. The methanol was removed at reduced pressure and the residue poured into water. Concentrated hydrochloric acid was added to adjust the pH to 2; then the mixture was extracted with ether[20] to give 130 mg (quantitative yield) of keto acid **14** as a colorless oil which was >99% one peak on VPC (3% XE-60, 180 °C). The keto acid **14** was not purified further but was used directly below.

Methyl *trans*-3-[6-(Carbomethoxy)-2,2,6-trimethylcyclohexyl]-propionate (16). A modification of a published procedure[21] was used. A 1.3 M sodium hypobromite solution was prepared by the addition of 1.4 mL (4.38 g, 0.028 mol) of bromine to a cold (0 °C) solution of 4.4 g (0.11 mol) of sodium hydroxide in 18.2 mL of water. A 130-mg sample (0.6 mmol) of keto acid **14** (>99% one peak on VPC) was suspended in 1 mL of the aforementioned cold (0 °C) aqueous sodium hydroxide solution; then 5.85 mL (7.68 mmol) of the aforementioned cold (0 °C) sodium hypobromite solution was added with vigorous stirring. The mixture was stirred at 0 °C for 6.5 h, after which time excess hypobromite was destroyed by the addition of saturated aqueous sodium sulfite. The pH was adjusted to 5 with concentrated hydrochloric acid; then the mixture was extracted with ether[20] to give 130 mg of diacid **15** as an oil. Treatment of the crude diacid **15** directly with diazomethane afforded diester **16** as an oil which was 80% one peak on VPC (3% SE-30, 150 °C). Preparative TLC (9:1 hexane–ethyl acetate) gave 60 mg (43% yield) of diester **16**.

Evaporative distillation at 125 °C (0.01 mm) of a sample from a comparable run gave an analytical specimen as a colorless oil: IR (film) 5.77 μm (ester C=O); ^{1}H NMR 0.92 (s, 3, C-2 CH_3), 0.94 (s, 3, C-2 CH_3), 1.18 (s, 3, C-6 CH_3), 1.97–2.43 (m, 2, $CH_2CO_2CH_3$), 3.66 ppm (s, 6, 2 CO_2CH_3); mass spectrum (70 eV), *m/e* 270 (M^+), 238 (M − 32), 211 (M − 59), 197 (M − 73), 69 (M − 211, base peak). The IR and ^{1}H NMR spectra were identical with the spectra of authentic diester **16** described below, and VPC coinjection experiments (3% SE-30, 150 °C) also indicated that the two specimens were identical.

Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.64; H, 9.69. Found: C, 66.42; H, 9.50.

***trans*-3-(6-Carboxy-2,2,6-trimethylcyclohexyl)propionic Acid (15).** Sufficient methanol to cause complete solution was added to a mixture

(21) Levine, R.; Stephens, J. R. *J. Am. Chem. Soc.* **1950**, *72*, 1642–4.

of 57 mg (0.21 mmol) of diester **16** in 10 mL of 5% sodium hydroxide in 1:1 methanol–water. The resulting solution was heated at reflux for 28 h, after which time the methanol was removed at reduced pressure. The residue was diluted with water, and then concentrated hydrochloric acid was added to adjust the pH to 2. Ether extraction[20] gave 50 mg (97% yield) of diacid **15** as an oil which was crystallized from hexane, mp 103.5–104.5 °C. Recrystallization from ether–hexane gave colorless prisms, mp 106–109 °C, undepressed on admixture with an authentic specimen of **15**, mp 107–110 °C, described below. The sample exhibited the following properties: IR (KBr) 5.88, 5.96 μm (CO_2H); ^1H NMR 0.89 (s, 3, C-2 CH_3), 0.98 (s, 3, C-2 CH_3), 1.18 (s, 3, C-6 CH_3), 1.3–2.0 (methylene envelope), 2.36 (t, J = 3 Hz, 2, CH_2CO_2H), 11.27 ppm (s, 2, CO_2H); mass spectrum (70 eV), m/e 242 (M^+), 224 (M − 18), 206 (M − 36), 198 (M − 44), 160 (M − 82), 142 (M − 100), 69 (M − 173, base peak).

Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.27; H, 9.04.

Methyl *trans*-3-[6-(Carbomethoxy)-2,2,6-trimethylcyclohexyl]-propionate (16) from 17. A cold (0 °C) solution of 100 mg (0.3 mmol) of known[5] keto ester **17** (78% one peak on VPC) in 8 mL of triethylene glycol was stirred under nitrogen while 1.9 mL (1.9 g, 0.06 mol) of 97% hydrazine was added. The mixture was stirred at 0 °C under nitrogen for ca. 2 h and then at room temperature overnight, after which time 200 mg (3.1 mmol) of 85% potassium hydroxide pellets was added. The mixture was heated at ca. 105 °C for 1 h and then at ca. 200 °C for 3 h. The mixture was allowed to cool to room temperature and then poured into 50 mL of water, adjusted to pH 2 with concentrated hydrochloric acid, and concentrated at reduced pressure. Ether extraction[20] gave 175 mg of a yellow oil. Water was added and the mixture was extracted with chloroform[20] to give 70 mg of yellow gum which was treated directly with ethereal diazomethane. The yellow oil was shown to consist of 35% of triethylene glycol and 65% of the desired diester **16** by VPC coinjection experiments (3% SE-30, 160 °C). Preparative TLC (R_f 0.22, 9:1 hexane–ethyl acetate) gave 15 mg (19% yield) of diester **16** which was >98% one peak on VPC. The IR and ^1H NMR spectra were identical with the spectra of diester **16** described above.

***trans*-3-(6-Carboxy-2,2,6-trimethylcyclohexyl)propionic Acid (15) from 16.** Sufficient methanol to cause complete solution was added to a mixture of 15 mg (0.055 mmol) of diester **16** described directly above in 3 mL of 5% sodium hydroxide in 1:1 methanol–water. The resulting solution was heated at reflux for 20 h, after which time the methanol was removed at reduced pressure. Sufficient concentrated hydrochloric acid was added to the residue to adjust the pH to 2. Ether extraction[20] gave 13 mg (98% yield) of diacid **15** as an oil. Crystallization from ether–hexane afforded colorless prisms, mp 107–110 °C. The IR spectrum was identical with the spectrum of diacid **15** described above.

Cyclization of Dienynol 1 with Trifluoroacetic Acid in Methylene Chloride at 0 °C. A cold (0 °C) solution of 30 mg (0.09 mmol) of the known[4a] alcohol **1** (contaminated with 24% of the homoallylic alcohol) in 6.5 mL of dry methylene chloride was stirred under argon while 0.065 mL (100 mg, 0.86 mmol) of trifluoroacetic acid was added slowly via syringe. The gold-colored solution was stirred at 0 °C for 45 min and then poured into saturated aqueous sodium bicarbonate solution. Ether extraction[20] afforded 52 mg of brown oil: IR (film) 5.59 μm (m, enol trifluoroacetate). The aforementioned crude product was stirred at room temperature under argon for 18 h with 0.2 mL of saturated aqueous potassium carbonate solution and 2 mL of methanol. Ether extraction[20] gave 53 mg of a pale yellow oil, which was filtered through 10 g of Florisil (19:1 hexane–ether) to give 48 mg of colorless oil which showed five spots on TLC (R_f 0.69, 0.58, 0.49, 0.15, and 0.04, 9:1 hexane–ethyl acetate) and six peaks on VPC (WCOT OV-101, 180 °C): IR (film) 5.85 μm (m, C=O). VPC coinjection showed the presence of chloro diene **6** (41%), ketone **8a** (28%), ketone **8b** (6%), and three unidentified peaks (25%). (See below for assignment of ketone **8b**.) GC–MS (6 ft 3% OV-17, 173 °C) gave two major peaks whose mass spectra were identical with the mass spectra of authentic **6** and **8a**.

Cyclization of Dienynol 1 with Trifluoroacetic Acid in Pentane–1,2-Dichloroethane at 0 °C. A cold (0 °C) solution of 133 mg (0.38 mmol) of the known[4a] alcohol **1** (contaminated with 30% of the homoallylic alcohol) in 15 mL of dry pentane and 2 mL of dry 1,2-dichloroethane was stirred under argon while 0.76 mL (1.17 g, 10.3 mmol) of trifluoroacetic acid was added slowly via syringe. The pale yellow-green solution was stirred at 0 °C for 1 h and then poured into saturated aqueous sodium bicarbonate solution. Ether extraction[20] afforded 156 mg of orange oil: IR (film) 5.89 μm (m, enol trifluoroacetate). The aforementioned crude product was stirred at room temperature under argon for 18 h with 0.6 mL of saturated aqueous potassium carbonate solution and 6 mL of methanol. Ether extraction[20] gave 106 mg of a yellow oil which was filtered through 10 g of Florisil (19:1 hexane–ether) to give 84 mg of colorless oil which showed nine peaks on VPC (WCOT OV-101, 175 °C): IR (film) 5.85 μm (m, C=O). VPC coinjection showed the presence of chloro diene **6** (7%), ketone **8a** (50%), ketone **8b** (9%), and six unidentified peaks (37%). GC–MS (6 ft 3% OV-17, 175 °C) gave mass spectra for **6** and **8a** which were identical with authentic specimens.

***trans*-1-(α-Chloroethylidene)-5-isopropylidene-4,4,8-trimethylhydrindane (7a).** A cold (ca. −35 °C) solution of 142 mg (0.4 mmol) of the known[4a] alcohol **1** (contaminated with 30% of the homoallylic alcohol) in 5 mL of 1,1-dichloroethylene was stirred under nitrogen while a solution of 0.06 mL (130 mg, 0.5 mmol) of stannic chloride in 6 mL of 1,1-dichloroethylene was added slowly via syringe. The mixture was stirred at ca. −35 °C for 45 min; then 20 mL of ether followed by 0.15 mL of pyridine and an additional 20 mL of ether were added. The mixture was filtered and the solid washed with ether. Ether extraction[20] gave 90 mg of a viscous yellow oil, which was filtered through silica gel with petroleum ether (bp 60–68 °C) to give 56 mg (53% yield) of a colorless oil which showed one spot on TLC (R_f 0.59, 9:1 hexane–ethyl acetate) and was 95% three peaks (A, B, and C) on VPC (WCOT OV-101, 175 °C) in a ratio of 8:75:12: IR (film) 6.00 (C=C), 7.24, 9.35, 9.62 μm; ^1H NMR 0.94 (s, 3, C-8 CH_3), 1.12 (s, 3, C-4 CH_3), 1.27 (s, 3, C-4 CH_3), 1.69 (d, J = 1 Hz, 6, isopropylidene CH_3's), 1.80 ppm (s, 3, ethylidene CH_3). GC–MS (9 ft 3% OV-17, 158 °C) for A: (R_t 8.3 min) 266 (M^+), 251 (M − 15), 215 (M − 51), 209 (M − 57), 195 (M − 71), 183 (M − 83); B: (R_t 9.1 min) 266 (M^+), 251 (M − 15), 215 (M − 51), 209 (M − 57), 195 (M − 71), 187 (M − 79), 185 (M − 81), 184 (M − 82), 183 (M − 83); C: (R_t 10.2 min) 266 (M^+), 251 (M − 15), 215 (M − 51), 209 (M − 57), 195 (M − 71), 187 (M − 79), 185 (M − 81), 184 (M − 82), 183 (M − 83). Compound C was shown to be vinyl chloride **6** by VPC coinjection (WCOT OV-101, 175 °C) with authentic **6** described above and comparison of the mass spectra.

Oxidative Degradation of Vinyl Chloride 7a. Ozone was bubbled through a solution of 8 mg (0.03 mmol) of chloro diene **7a** (88% one peak on VPC) in 3 mL of 1:1 ethyl acetate–methanol at −78 °C until a permanent blue color developed. After 8 min at −78 °C, excess ozone was flushed from the solution with oxygen; then 1 mL (846 mg, 14 mmol) of dimethyl sulfide was added and the solution was stirred at room temperature for 2 h. The solvent was removed at reduced pressure and the residue was extracted with ether[20] to give 4 mg (41% yield) of a colorless oil which showed one peak on VPC (3% XE-60, 160 °C; 3.8% SE-30, 160 °C; 3.8% SE-30, 130 °C) and one peak when coinjected with authentic[22] *trans*-4,4,8-trimethylhydrindan-1,5-dione.

1-Acetyl-5-isopropylidene-4,4,8β-trimethyl-9α-hydrindan (8a). A modification of a published procedure[4a] was used. A cold (0 °C) solution of 50 mg (0.17 mmol) of the known[4a] alcohol **1** (contaminated with 24% of the isomeric homoallylic alcohol) in 30 mL of dry *n*-pentane was stirred vigorously while 0.43 mL (525 mg, 11.4 mmol) of anhydrous formic acid was added. The mixture was stirred under argon at room temperature for 4 h; then excess aqueous sodium bicarbonate was added. Extraction with ether[20] gave 64 mg of a colorless oil: IR (film) 5.74 μm (C=O).

The aforementioned crude enol formate was stirred at room temperature under argon for 19 h with 4 mL of methanol and 0.2 mL of saturated aqueous potassium carbonate solution. Ether extraction[20] gave 60 mg of colorless oil which showed three spots on TLC (R_f 0.13, 0.29, and 0.58, 9:1 hexane–ethyl acetate): IR (film) 5.87 μm (C=O). Chromatography on 10 g of Florisil afforded 24 mg of colorless oil (eluted with hexane) which was 65% two peaks (ca. 1:1 mixture) on VPC (WCOT OV-101, 175 °C). Elution with 49:1 hexane–ether gave 30 mg of colorless oil which was 73% two peaks in a 14:1 ratio on VPC (WCOT OV-101, 175 °C). Further chromatography of the second fraction on 10 g of silica gel (49:1 hexane–ether) gave 14% mg of colorless oil which showed one spot on TLC (R_f 0.23, 9:1 hexane–ethyl acetate) and was 95% two peaks in an 18:1 ratio on VPC (WCOT OV-101, 175 °C). The IR, ^1H NMR, and mass spectrum were identical with the spectra of authentic methyl ketone **8a**.[4a]

A similar 3-mg sample of **8** (19:1, **8a**:**8b**) in 2 mL of a 1 M solution of potassium hydroxide in 1:1 methanol–water was heated under argon at 70 °C for 3 h. Ether extraction[20] gave 3 mg of colorless oil which was 89% **8a**:**8b** in a 9:2 ratio on VPC (WCOT OV-101, 175 °C).

Cyclization of Trienynol 3 with Stannic Chloride in 1,1-Dichloroethylene. $\Delta^{1,17}$-5β,13α,20-Chloropregnadiene (22), $\Delta^{1,17}$-5β,20-Chloropregnadiene (18), and $\Delta^{1,17(17a)}$-5β,17-Chloro-*D*-homopregnadiene (20). A cold (ca. −30 °C) solution of 361 mg (1.2 mmol) of the known[4b] allylic alcohol **3** in 36 mL of dry 1,1-dichloroethylene was stirred while 0.35 mL (780 mg, 3 mmol) of stannic chloride was added slowly via syringe. The mixture was stirred at ca. −30 °C for 50 min, after which time 16 mL

(22) Gravestock, M. B.; Johnson, W. S.; Myers, R. F.; Bryson, T. A.; Miles, D. H.; Ratcliffe, B. E. *J. Am. Chem. Soc.* **1978**, *100*, 4268–73.

of ether followed by 0.25 mL of pyridine was added. The mixture was centrifuged, and then the white solid was washed with methylene chloride. Ether extraction, using an acid wash followed by a base wash,[20] gave a cloudy yellow oil which was purified by chromatography on Florisil (hexane) to give 246 mg (64% yield) of colorless oil which was shown by VPC (3% OV-17, 205 °C) to consist of three peaks (a single peak and two overlapping peaks). The first peak integrated for 15% of the total peak area and was assigned structure **22** based on data described below. The two overlapping peaks, found in an 86:14 ratio, integrated for 85% of the total peak area and were assigned structures **18** and **20** based on data described below.

An analytical specimen of the mixture of isomeric vinyl chlorides **18** and **20** was prepared by crystallization of the aforementioned oil from absolute ethanol, followed by recrystallization from the same solvent, to give 92% mg of white plates, mp 106–109 °C, which was shown by VPC to contain only **18** and **20** in an 88:12 ratio: IR ($CHCl_3$) 6.00 (C=C), 9.18, 9.97, 10.43, 11.97 μm; ^1H NMR 0.87 (s, C-18 CH_3 in **18**), 0.93 (s, C-18 CH_3 in **20**), 1.00 (s, C-19 CH_3), 1.72 (t, J = 1.5 Hz, C-21 CH_3), 2.13 (m, C-16 protons), 5.52 ppm (s, C-1 and C-2 protons); TLC R_f 0.63 (4:1 hexane–ethyl acetate).

Anal. Calcd for $C_{21}H_{31}Cl$: C, 79.09; H, 9.80. Found: C, 79.24; H, 9.56.

Δ^{17}-5β,20-Chloropregnene (24) and $\Delta^{17(17a)}$-5β,17-Chloro-*D*-homopregnene (26). A mixture of 57 mg (0.18 mmol) of the aforementioned chloro dienes **18** and **20** (mp 106–109 °C, in an 88:12 ratio), 2 mL of ethyl acetate, 2 mL of 95% ethanol, and a spatula tip of Raney nickel was stirred at room temperature for 30 min. The mixture was filtered through Celite, and the solvent was removed at reduced pressure to give 57 mg of white solid which was hydrogenated over 2 mg of 10% palladium-on-carbon in 4 mL of 1:1 ethyl acetate–ether at room temperature and atmospheric pressure for 50 min. The mixture was filtered through Celite, and the solvent was removed at reduced pressure to give 56 mg (99% yield) of chloro enes **24** and **26** as a colorless oil in a ratio of 88:12 by VPC (3% OV-17, 200 °C). IR ($CHCl_3$) 6.00 (C=C), 8.49, 9.16, 9.72, 9.95, 11.00, 12.00 μm; ^1H NMR 0.86 (s, 3, C-18 CH_3), 0.90 (s, 3, C-19 CH_3), 2.14 ppm (m, 2, allylic protons).

5β-Androstan-17-one (26) and Methyl *cis,anti,trans,anti,trans*-3-(2-Acetyl-2,4b-dimethyl-1,2,3,4,4a,4b,5,6,7,8,8a,9,10,10a-tetradecahydro-1-phenanthryl)propionate (27). Ozone was bubbled through a solution of 64 mg (0.2 mmol) of chloro olefins **24** and **26** (89% one peak in a 62:38 ratio by VPC) in 4 mL of ethyl acetate and 1.2 mL of methanol at −78 °C until a permanent blue color developed. Excess ozone was flushed from the solution with nitrogen; then 0.4 mL (338 mg, 5.5 mmol) of dimethyl sulfide was added. The solution was stirred at room temperature for 30 min and then extracted with ether, using a base wash,[20] to give a yellow oil which was purified by chromatography on Florisil. Elution with 19:1 hexane–ether afforded 5.5 mg of nonpolar components. Elution with 3:1 hexane–ether gave 15 mg (50% yield) of ketone **25** as a colorless oil which was 92% one peak on VPC (3% XE-60, 190 °C; 3% OV-225, 205 °C): IR ($CHCl_3$) 5.78 (C=O), 7.13, 9.15, 9.51, 9.95, 12.05 μm; ^1H NMR 0.85 (s, 3, C-18 CH_3), 0.93 ppm (s, 3, C-19 CH_3); TLC R_f 0.49 (4:1 hexane–ethyl acetate). Ketone **25** was identical (by IR, ^1H NMR, and VPC coinjection) with an authentic specimen[7] of 5β-androstan-17-one.

Elution with ether afforded 16 mg (70% yield) of keto ester **27** as a colorless oil which was 95% one peak on VPC (3% XE-60, 210 °C): TLC R_f 0.31 (4:1 hexane–ethyl acetate). The IR and ^1H NMR spectra were identical with the spectra of keto ester **27**, obtained from the degradation of cyclization mixture **36**, **37**, and **38** described below. VPC coinjection experiments (3% XE-60) showed a single peak.

A specimen of **27**, obtained from the degradation of a mixture of **36**, **37**, and **38**, was purified by preparative TLC followed by evaporative distillation at 150 °C (0.02 mm) to give analytically pure keto ester **27** as a colorless oil: IR (film) 5.74 (ester C=O), 5.88 μm (C=O); ^1H NMR 0.89 (s, 3, CH_3), 1.10 (s, 3, CH_3), 2.11 (s, 3, acetyl CH_3), 3.62 ppm (s, 3, CO_2CH_3); mass spectrum (70 eV), m/e 348 (M^+), 305 (M − 43), 149 (M − 199), 109 (M − 139), 95 (M − 253), 55 (M − 293), 43 (M − 305, base peak).

Anal. Calcd for $C_{22}H_{36}O_3$: C, 75.82; H, 10.41. Found: C, 75.54; H, 10.05.

$\Delta^{1,17}$-5β,13α,20-Chloropregnadiene (22). The mother liquors obtained from crystallization of chloro dienes **18** and **20**, from a comparable cyclization of **3** with stannic chloride in 1,1-dichloroethylene, were subjected to preparative VPC (3% OV-17, 230 °C). The peak of lowest retention time (3.6 min) was collected to give 3 mg of **22** as a colorless oil: IR (film) 6.06 (C=C), 6.95, 7.30, 8.93, 13.5, 14.2 μm; ^1H NMR 0.90 (s, 3, C-18 CH_3), 1.03 (s, 3, C-19 CH_3), 1.10–1.87 (m, 16, methylene envelope), 2.07 (m, 2, C-3 protons), 2.13 (br s, 3, C-21 CH_3), 2.27–2.67 (m, 2, C-16 protons), 5.52 ppm (s, 2, C-1 and C-2 protons); mass spectrum (70 eV), m/e 318 (M^+), 283 (M − 35, base peak).

Degradation of $\Delta^{1,17}$-5β,13α,20-Chloropregnadiene (22). A mixture of 3 mg (0.009 mmol) of the aforementioned chloro diene **22** (>99% one peak on VPC), 4 mL of ether, and a spatula tip of deactivated Raney nickel was stirred at room temperature for 30 min. The mixture was filtered through Celite, and the filtrate was concentrated at reduced pressure. The resulting oil was hydrogenated over 3 mg of 10% palladium-on-carbon in 2.5 mL of 1:1 ether–ethyl acetate for 3 h at room temperature. The mixture was filtered through Celite, and the filtrate was concentrated at reduced pressure to give 3 mg (quantitative yield) of chloro ene **28** as a colorless oil which was >99% one peak on VPC (3% OV-17, 220 °C).

Ozone was bubbled through a solution of 3 mg (0.009 mmol) of the aforementioned chloro ene **28** in 1 mL of 4:1 ethyl acetate–methanol at −78 °C until a permanent blue color developed. Excess ozone was flushed from the solution with nitrogen; then 0.14 mL (18 mg, 1.9 mmol) of dimethyl sulfide was added and the solution was stirred at room temperature for 30 min. Ether extraction[20] afforded 2 mg of cloudy oil which consisted of 74% starting material **28** and 26% ketone **29**, identified by VPC coinjection (3% XE-60, 200 °C) with a mixture of authentic ketones **25** and **29** described below.

Degradation of a Mixture of 18, 20, and 22. A mixture of 146 mg (0.46 mmol) of desulfurized chloro dienes **18**, **20**, and **22** (15% 22 by VPC, 3% XE-60, 190 °C), 15 mL of 1:1 ether–ethyl acetate, and 10 mg of 10% palladium-on-carbon was hydrogenated at room temperature and atmospheric pressure for ca. 4 h. The mixture was filtered through Celite, and the filtrate was concentrated at reduced pressure to afford 145 mg of colorless oil which contained 14% of the desired chloro ene **28** by VPC analysis (3% XE-60, 190 °C).

Ozone was bubbled through a solution of 145 mg of the aforementioned mixture of chloro enes **24**, **26**, and **28** in 15 mL of 4:1 ethyl acetate–methanol at −78 °C until a permanent blue color developed. After the mixture was stirred for 5 min at −78 °C, excess ozone was flushed from the solution with nitrogen; then 0.5 mL (423 mg, 6.8 mmol) of dimethyl sulfide was added. The mixture was stirred at room temperature for 30 min and then extracted with ether[20] to give 131 mg of clear oil which was purified by preparative TLC (7:3 hexane–ether). Three major bands were evident: R_f 0.76 (starting material), R_f 0.31–0.41 (mixture of ketones **25** and **29**), and R_f 0.17 (keto ester **27**). The band R_f ca. 0.41 was shown by VPC coinjection (3% XE-60, 200 °C) to consist of 58% ketone **29**, 22% ketone **25**, and 20% unidentified material. Additional preparative TLC (7:3 hexane–ether) gave ca. 1 mg of colorless oil which consisted of 60% ketone **29**, 30% ketone **25**, and 10% unidentified material by VPC (3% XE-60, 200 °C). The ^1H NMR spectrum was identical with the spectrum of authentic 5β,13α-androstan-17-one (**29**) described below, except for absorption at δ 0.82, possibly attributable to the C-18 methyl in 5β-androstan-17-one (**25**), and unidentified absorption at δ 1.48.

5β,13α-Androstan-17-one (29). An adaptation of a published procedure[8] was utilized. A solution of 18 mg (0.06 mmol) of authentic[7] 5β-androstan-17-one (**25**) in 8 mL of peroxide-free dioxane, freshly filtered through basic alumina, in a quartz tube was deoxygenated with nitrogen for 30 min and then irradiated in a Rayonet "reactor", Model RPR-100, at 2537 Å for 3 h. VPC examination (3% OV-17, 220 °C) showed a mixture of **29** and **25** in a 70:30 ratio. The mixture was concentrated at reduced pressure and then purified by preparative TLC (7:3 hexane–ether) to afford 12 mg (67% yield) of 5β,13α-androstan-17-one (**29**) as a colorless solid which showed one peak on VPC. Recrystallization from methanol–water gave colorless prisms, mp 150–151 °C: IR (CCl_4) 5.75 (C=O), 6.83, 6.90, 7.09, 7.27, 7.63, 8.13, 8.62, 8.93, 9.13, 9.71 μm; ^1H NMR 0.72 (s, 3, C-18 CH_3), 0.92 (s, 3, C-19 CH_3), 1.03-1.97 (methylene envelope), 1.97–2.40 ppm (m, 2, CH_2CO); mass spectrum (70 eV), m/e 274 (M^+), 259 (M − 15), 241 (M − 23), 230 (M − 44), 217 (M − 57).

Irradiation of a Mixture of 5β-Androstan-17-one (25) and 5β,13α-Androstan-17-one (29). A published procedure[8] was used. A solution of ca. 3 mg of a mixture of ketones **25** and **29** (in a 62:38 ratio by VPC) which was prepared by ozonolysis of a mixture of **24** and **28**, similar to that described above, in 2 mL of peroxide-free dioxane was irradiated as described above for 3.5 h. VPC examination (3% XE-60, 180 °C) showed the resulting mixture to consist of 72% of the C/D cis ketone **29**, 13% of the C/D trans ketone **25**, and 15% of an unidentified peak. The IR spectrum (CCl_4) showed all the peaks present in authentic C/D cis ketone **29** described above. The ^1H NMR spectrum showed diminution of the signals at δ 0.83 and 0.93, attributable to the C-18 and C-19 methyl groups in the C/D trans ketone **26**.

Attempted Equilibration of Chloro Dienes 18 and 20 with Stannic Chloride. A solution of ca. 1 mg of a mixture of chloro dienes **18** and **20**, mp 100–106 °C (in a ratio of 61:39 by VPC) in 0.3 mL of 1,1-dichloroethylene and 2 drops of stannic chloride was stirred at ca. −5 °C for 20 min. Ether was added, followed by excess pyridine, and the

mixture was filtered through Celite. The solvent was removed at reduced pressure to give a yellow oil which was shown by VPC (3% OV-17, 215 °C) to contain chloro dienes **18** and **20** in a ratio of 61:39.

Cyclization of Trienynol 3. Solvent, Temperature, Time, and Concentration Studies. Variations were made in the solvent, temperature, time, and concentration of stannic chloride and substrate used in the cyclization of trienynol **3**. The product ratios reported were determined by VPC (3% OV-17, ca. 220 °C) and are reproducible within ±3%.

Cyclizations of a 0.03 M solution of trienynol **3** were carried out with 0.1 M stannic chloride in various solvents at 22 °C for 15 min. The relative amounts of the three chloro dienes **22**, **18**, and **20** formed in the different solvents were as follows: *n*-butyl chloride, 19:46:34; methylene chloride, 14:67:16; chloroform, 14:69:17, carbon tetrachloride, 19:52:29; 1,1-dichloroethylene, 15:75:10; tetrachloroethylene, 16:60:24.

Temperature studies were carried out with 0.1 M solutions of stannic chloride in methylene chloride, stannic chloride in 1,1-dichloroethylene, and titanium tetrachloride in 1,1-dichloroethylene.[9] The relative amounts of **22**, **18**, and **20** formed were as follows: stannic chloride in methylene chloride, −30 °C, 12:51:37; 22 °C, 14:67:16; 40 °C, 17:73:10; stannic chloride in 1,1-dichloroethylene, −78 °C, 15:64:21;[23] −30 °C, 15:73:12; 22 °C, 15:75:10; titanium tetrachloride in 1,1-dichloroethylene, −110 °C, 13:79:8; −90 °C, 16:71:13; −78 °C, 16:69:15; 22 °C, 15:69:16.

Cyclization of a 0.03 M solution of trienynol **3** was carried out with a 0.1 M solution of stannic chloride in methylene chloride at −30 °C for 15 and 60 min. The product ratios of **22**, **18**, and **20** were as follows: 15 min, 12:51:37; 60 min, 11:55:34. Cyclization of a 0.03 M solution of trienynol **3** was effected with either a 0.1 M solution of stannic chloride in 1,1-dichloroethylene at −78 °C for 15 min to give a product ratio of 15:64:21[23] or with a 0.1 M solution of titanium tetrachloride in 1,1-dichloroethylene at −78 °C for 15 min to give a product ratio of 16:69:15.

The concentration of stannic chloride in both methylene chloride and 1,1-dichloroethylene at 22 °C for 15 min was varied to give the following product ratios:[9] methylene chloride, 0.1 M, 14:67:16; methylene chloride, 2 M, 13:68:18; 1,1-dichloroethylene, 0.1 M, 15:75:10; 1,1-dichloroethylene, 1 M, 17:74:9. In one cyclization a 0.01 M solution of trienynol **3** was added to a 0.05 M solution of stannic chloride in methylene chloride at −30 °C for 90 min. The ratio of **22**, **18**, and **20** formed was 15:52:33.

Cyclization of Trienynol 3 with Titanium Tetrachloride in 1,1-Dichloroethylene. A cold (−78 °C) solution of 200 mg (0.67 mmol) of allylic alcohol **3** in 50 mL of dry 1,1-dichloroethylene was stirred under nitrogen while 0.69 g (3.6 mmol) of titanium tetrachloride was added rapidly via syringe. The resulting orange mixture was stirred at −78 °C for 15 min, after which time 1.5 mL of pyridine was added, and the resulting precipitate was removed by filtration through Celite. Ether extraction, using an acid wash followed by a base wash,[20] gave a light yellow oil, which was purified by chromatography on Florisil. Elution with hexane afforded 136 mg (64% yield) of a mixture of **22**, **18**, and **20** as a colorless oil which crystallized on standing. VPC coinjection (3% OV-17, 220 °C) showed the presence of **22**, **18**, and **20** in a ratio of 16:69:15.

Cyclization of Trienynol 3 with Stannic Chloride in Methylene Chloride with Added Tetra-*n*-butylammonium Chloride. A solution of 10 mg (0.03 mmol) of allylic alcohol **3** in 1 mL of methylene chloride was stirred under nitrogen while 0.5 mL of 0.65 M tetra-*n*-butylammonium chloride in methylene chloride and 0.01 mL (22.3 mg, 0.086 mmol) of stannic chloride were added via syringe. The mixture was stirred at room temperature for 15 min, 0.14 mL of pyridine and 1 mL of ether were added, and the resulting precipitate was removed by filtration through Celite. Ether extraction, using an acid wash followed by a base wash,[20] afforded a colorless oil which was shown by VPC coinjection (3% OV-17, 220 °C) to consist of **22**, **18**, and **20** in a ratio of 14:72:14.

Cyclization of Trienynol 3 with Stannic Chloride in Methylene Chloride with Added Hydrogen Chloride. A 1-mL sample of a solution prepared from 5 mL of methylene chloride saturated with dry hydrogen chloride at 0 °C and 0.22 g (0.84 mmol) of stannic chloride was added via syringe to 3 mg (0.01 mmol) of allylic alcohol **3**. The resulting orange solution was stirred under nitrogen at room temperature for 15 min, after which time 0.14 mL of pyridine and 1 mL of ether were added, and the resulting precipitate was removed by filtration through Celite. Ether extraction, using an acid wash followed by a base wash,[20] gave a colorless oil which consisted of **22**, **18**, and **20** in a ratio of 17:67:16, as shown by VPC coinjection (3% OV-17, 220 °C).

Cyclization of Trienynol 3 with Stannic Bromide in Methylene Bromide. A solution of 5 mg (0.017 mmol) of allylic alcohol **3** in 1 mL of dry methylene bromide was stirred under nitrogen while 0.15 mL (65.7 mg, 0.15 mmol) of 1 M stannic bromide in methylene bromide was added via syringe. The pale orange solution was stirred at room temperature for 15 min, after which time 0.14 mL of pyridine and 1 mL of ether were added, and the resulting precipitate was removed by filtration through Celite. Ether extraction, using an acid wash followed by a base wash,[20] gave a colorless oil which showed three peaks in a ratio of 16:38:46 on VPC (3% OV-17, 220 °C).

Cyclization of Trienynol 3 with Stannic Bromide in Methylene Chloride. A solution of 1 mg (0.003 mmol) of allylic alcohol **3** in 0.2 mL of dry methylene chloride was stirred under nitrogen while 0.03 mL (13.2 mg, 0.03 mmol) of 1 M stannic bromide in methylene chloride was added via syringe. The pale orange solution was stirred at room temperature for 15 min, after which time 0.14 mL of pyridine and 1 mL of ether were added, and the resulting precipitate was removed by filtration through Celite. Ether extraction, using an acid wash followed by a base wash,[20] gave a colorless oil which showed five peaks in a ratio of 8:22:24:39:7 on VPC (3% OV-17, 220 °C). VPC coinjection with product mixtures from the aforementioned stannic chloride–methylene chloride and stannic bromide–methylene bromide cyclizations of **3** showed enhancement of the peaks identified as **19**, **20**, **21**, **22**, and **23**.

Cyclization of Trienynol 3 with Stannic Chloride in Methylene Bromide. A solution of 5 mg (0.017 mmol) of allylic alcohol **3** in 1 mL of dry methylene bromide was stirred under nitrogen while 22.3 mg (0.09 mmol) of stannic chloride was added. The pale orange solution was stirred at room temperature for 15 min, after which time 0.14 mL of pyridine and 1 mL of ether were added, and the resulting precipitate was removed by filtration through Celite. Ether extraction, using an acid wash followed by a base wash,[20] gave a colorless oil which showed four peaks in a ratio of 12:68:11:9 on VPC (3% OV-17, 220 °C). VPC coinjection with product mixtures from the aforementioned stannic chloride–methylene chloride and stannic bromide–methylene bromide cyclizations of **3** showed enhancement of the peaks identified as **18**, **20**, **21**, and **22**.

Cyclization of Trienynol 2 with Stannic Chloride in 1,2-Dichloroethane. A cold (0 °C) solution of 95 mg (30 mmol) of the known[4a] allylic alcohol **2** (containing 5% of the homoallylic alcohol) in 8 mL of 1,2-dichloroethane was stirred while 0.84 mL (1.88 g, 7.2 mmol) of stannic chloride was added via syringe. The brown mixture was stirred at 0 °C for 20 min, poured into water, and then extracted with ether, using a wash with 5% aqueous sodium hydroxide,[20] to give 90 mg of orange oil which showed three peaks in a ratio of 12:68:14 on VPC (3% XE-60, 180 °C). Preparative TLC (R_f 0.60, pentane) afforded 58 mg (63% yield) of a crystalline solid which was shown to be a 5:1 mixture of **31** and **32** on VPC.

An analytical specimen as colorless plates, mp 107–113 °C, was prepared by recrystallization from pentane. VPC examination showed this specimen to be a 5:1 mixture: IR (film) 13.16, 13.51 μm; ^{1}H NMR 0.88 (s, C-18 CH_3 in **31**), 0.93 (s, C-18 CH_3 in **32**), 1.25 (s, C-19 CH_3), 1.56 (s, C-4 CH_3), 1.66 (s, C-21 CH_3 in **32**), 2.13 ppm (s, C-21 CH_3 in **31**); mass spectrum (70 eV), *m/e* 318 (M^+), 303 (M − 15, base peak), 283 (M − 35), 282 (M − 36).

Anal. Calcd for $C_{21}H_{31}Cl$: C, 79.09; H, 9.80; Cl, 11.12. Found: C, 78.83; H, 9.67; Cl, 10.77.

Oxidative Degradation of Chloro Dienes 31 and 32. *dl*-Δ^4-Androstene-3,17-dione (34). To a solution of 41 mg (0.13 mmol) of the aforementioned 5:1 mixture of **31** and **32** (purified by preparative TLC) in 5 mL of carbon tetrachloride (spectroquality) was added 10 mL of a solution of ruthenium tetraoxide in carbon tetrachloride (prepared according to a published procedure[11]), resulting in an instantaneous precipitation of black ruthenium dioxide. The mixture was stirred for 20 min and the excess oxidant was destroyed by titration with isopropyl alcohol; then the mixture was diluted with chloroform and washed with 5% aqueous sodium hydroxide[20] to give 24 mg of crude yellow oil which was used directly in the aldol condensation described below.

A solution of 24 mg of the aforementioned crude yellow oil in 5 mL of methanol and 7 mL of 5% methanolic potassium hydroxide was stirred under nitrogen at room temperature for 20 h. The mixture was neutralized with acetic acid and the solvent was removed at reduced pressure. The residue was poured into water and then extracted with ether[20] to give 17 mg of pale yellow oil which consisted of 80% androstenedione **34** as shown by VPC coinjection (3% XE-60, 240 °C) with authentic *dl*-Δ^4-androstene-3,17-dione (**34**).[24] The positions of the carbonyl bands in the infrared spectra of the two specimens were also identical.

Cyclization of Trienyne Thioketal 35 with Stannic Chloride in Methylene Chloride. A cold (0 °C) solution of 247 mg (0.66 mmol) of the (−)-thioketal **35**[4b,12] in 20 mL of dry methylene chloride was stirred while 0.5 mL (1.12 g, 4.37 mmol) of stannic chloride was added slowly via syringe. The resulting orange solution was stirred for 15 min at 0 °C, poured into 10% aqueous hydrochloric acid, and extracted with ether,

(23) The presence of starting material was also indicated by VPC.

(24) Johnson, W. S.; Vredenburgh, W. A.; Pike, J. E. *J. Am. Chem. Soc.* **1960**, *82*, 3409–15.

using a base wash,[20] to give 243 mg (90% yield) of a white semisolid which showed three peaks in a ratio of 12:55:32 on VPC (3% XE-60, 190 °C): ^{1}H NMR 0.87 (C-18 CH_3 in **37**), 0.93 (C-18 CH_3 in **38**), 1.03 (C-19 CH_3), 2.78, 3.30 (2 m, $HSCH_2CH_2S$), 5.62 ppm (C-1 vinyl proton). No attempt was made to purify this mixture which was used directly for the following experiment.

Conversion of Vinyl Chlorides 36, 37, and 38 into 5β-Androstan-17-one (26) and Keto Ester 27. A mixture of the aforementioned crude vinyl sulfide mixture of **36**, **37**, and **38**, in an ethyl acetate–acetone mixture, and Raney nickel sludge was stirred at room temperature for 45 min and then at reflux until the ^{1}H NMR spectrum indicated the absence of the absorption at 2.78 and 3.30 ppm attributable to the $RSCH_2CH_2SH$ moiety (ca. 2.5 h). The resulting colorless oil showed three peaks (A, B, and C) in a ratio of 12:55:32 on VPC (3% XE-60, 188 °C). VPC coinjection with the aforementioned sample of **18** and **20** showed enhancement of peaks B and C. The ^{1}H NMR spectrum was essentially identical with the aforementioned spectrum of **18** and **20** except that peak heights varied due to a different ratio of isomers in the mixture.

A mixture of the aforementioned chloro dienes in ethyl acetate was hydrogenated at room temperature and atmospheric pressure over 10% palladium-on-carbon until the ^{1}H NMR spectrum indicated the absence of vinyl proton absorption (ca. 6 h). The ^{1}H NMR spectrum of the resulting colorless oil was essentially identical with that of **24** and **25** described above, except that peak heights varied due to a different ratio of isomers.

Ozone was bubbled through a solution of 118 mg (0.37 mmol) of the aforementioned chloro ene mixture in 2 mL of ethyl acetate and 1 mL of methanol at −78 °C until a permanent blue color developed. The solution was allowed to stand for 5 min, the excess ozone was flushed from the solution with oxygen, and 0.5 mL (423 mg, 6.8 mmol) of dimethyl sulfide was added. The solution was stirred at room temperature for 30 min, and the solvent was removed at reduced pressure to give 134 mg of yellow oil which showed three peaks in a ratio of 13:55:26 on VPC (3% XE-60, 225 °C). Preparative TLC (4:1 hexane–ethyl acetate) afforded 24 mg (17% yield from thioketal **35**) of 5β-androstan-17-one (**26**) as a colorless oil, $[\alpha]_D$ −48.5° (reported[7] $[\alpha]_D$ +94°), which was 93% one peak on VPC (3% XE-60, 180 °C). This sample was identical by IR, ^{1}H NMR, and VPC coinjection with an authentic specimen[7] of *d*-5β-androstan-17-one (**26**).

In addition, 15 mg (8% yield from thioketal **35**) of keto ester **27**, which showed one peak on VPC (3% XE-60, 225 °C), was obtained by preparative TLC (4:1 hexane–ethyl acetate). An analytical specimen of **27** as a colorless oil was prepared by preparative TLC followed by evaporative distillation at 150 °C (0.02 mm): IR (film) 5.74 (ester C=O), 5.88 μm (C=O); ^{1}H NMR 0.89 (s, 3, CH_3), 1.10 (s, 3, CH_3), 2.11 (s, 3, acetyl CH_3), 3.62 ppm (s, 3, CO_2CH_3); mass spectrum (70 eV), *m/e* 348 (M^+), 305 (M − 43), 149 (M − 199), 109 (M − 139), 95 (M − 253), 55 (M − 293), 43 (M − 305, base peak).

Anal. Calcd for $C_{22}H_{36}O_3$: C, 75.82; H, 10.41. Found: C, 75.54; H, 10.05.

Cyclization of Trienyne Thioketal 35 with Titanium Tetrachloride in 1,2-Dichloroethane. A cold (−30 °C) solution of 278 mg (0.74 mmol) of thioketal **35** in 20 mL of dry 1,2-dichloroethane was stirred while 0.5 mL (850 mg, 4.5 mmol) of titanium tetrachloride was added slowly via syringe. The resulting dark purple solution was stirred at ca. −30 °C for 10 min and then poured into 75 mL of 10% aqueous hydrochloric acid. Ether extraction, using a base wash,[20] afforded 295 mg of a pale yellow oil which was purified by preparative TLC (4:1 hexane–ethyl acetate) to give 242 mg (79% yield) of a clear oil which crystallized on standing. VPC examination (3% XE-60, 240 °C) showed three major peaks in a ratio of 15:70:12. Recrystallization from hexane afforded 67 mg of colorless needles, mp 139–142 °C, which showed two peaks on VPC in a 6:1 ratio (**40**:**41**): ^{1}H NMR 0.86 (s, C-18 CH_3), 0.96 (s, C-19 CH_3), 3.25 ppm (br s, SCH_2CH_2S); mass spectrum (70 eV), *m/e* 410 (M^+), 375 (M − 35), 374 (M − 36) (M − 256), 57 (M − 353), 43 (M − 367).

Anal. Calcd for $C_{23}H_{35}ClS_2$: C, 67.22; H, 8.58; S, 15.57. Found: C, 67.84; H, 8.55; S, 15.55.

Degradation of the Product Mixture from the Titanium Tetrachloride Cyclization. 5β-Androstan-17-one (26). The procedure employed was similar to that described above for the degradation of vinyl sulfides **36**, **37**, and **38**. Thus 175 mg (0.43 mmol) of the aforementioned crude thioketal mixture was treated with Raney nickel at room temperature for 4 h to afford 109 mg of a colorless oil. Ozonolysis afforded 140 mg of a yellow oil which was purified by preparative TLC (R_f 0.5, 4:1 benzene–ethyl acetate) to give 21 mg (24% yield) of 5β-androstan-17-one (**26**), identified by VPC coinjection (3% XE-60, 220 °C) with an authentic specimen.[7]

Cyclization of Trienyne Thioketal 35. Solvent, Temperature, and Time Studies. Variations were made in the solvent, temperature, and time used in the cyclization of trienyne thioketal **35**. The yields reported were determined by VPC (3% XE-60, 240 °C). The substrate concentration was ca. 0.04 M when titanium tetrachloride was used as the catalyst and ca. 0.03 M when stannic chloride was used as the catalyst. The catalyst concentration was maintained at ca. 0.2 M.

Cyclizations were effected with stannic chloride in either methylene chloride or 1,2-dichloroethane at 0 °C for 15 min. The ratio of products formed (presumably **36**, an unidentified compound, **37**, and **38**) was 12:2:55:32 in methylene chloride and 15:2:64:19 in 1,2-dichloroethane. The product ratios remained essentially unchanged with titanium tetrachloride in either methylene chloride or 1,2-dichloroethane under the same conditions.

The relative amounts of the four products formed with stannic chloride at different temperatures were as follows: −25 °C in methylene chloride, 18:3:36:43; 0 °C in methylene chloride, 15:2:56:27; −35 °C in 1,2-dichloroethane, 12:2:52:34; 0 °C in 1,2-dichloroethane, 15:2:64:19. The ratio of products formed (presumably **39**, an unidentified compound, **40**, and **41**) with titanium tetrachloride at different temperatures in either methylene chloride (−78, 0 °C) or 1,2-dichloroethane (−35, −30, −25, 0 °C) remained essentially unchanged.

Cyclizations with stannic chloride in methylene chloride were carried out for 15 and 45 min, giving product ratios of 12:2:55:32 and 15:3:55:27, respectively.

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