Table II. Bond Angles (deg) for 25

C(2)-C(1)-C(10)	113.5 (3)	C(1)-C(2)-C(3)	111.7 (3)
C(2)-C(3)-C(4)	111.9 (3)	C(3)-C(4)-C(5)	111.2 (3)
C(3)-C(4)-O(4A)	110.4 (3)	C(5)-C(4)-O(4A)	109.2 (3)
C(4)-C(5)-C(6)	112.3 (3)	C(4)-C(5)-C(10)	116.4 (3)
C(6)-C(5)-C(10)	110.8 (3)	C(5)-C(6)-C(7)	112.0 (3)
C(6)-C(7)-C(8)	125.0 (3)	C(7)-C(8)-C(9)	120.4 (3)
C(7)-C(8)-C(14)	122.4 (3)	C(9)-C(8)-C(14)	116.8 (3)
C(8)-C(9)-C(10)	114.4 (3)	C(8)-C(9)-C(11)	112.8 (3)
C(10)-C(9)-C(11)	113.0 (3)	C(1)-C(10)-C(5)	109.1 (2)
C(1)-C(10)-C(9)	109.9 (2)	C(5)-C(10)-C(9)	107.8 (2)
C(1)-C(10)-C(19)	109.5 (2)	C(5)-C(10)-C(19)	110.3 (2)
C(9)-C(10)-C(19)	110.2 (2)	C(9)-C(11)-C(12)	113.2 (3)
C(11)-C(12)-C(13)	112.9 (3)	C(12)-C(13)-C(14)	107.8 (2)
C(12)-C(13)-C(17A)	109.0 (3)	C(14)-C(13)-C(17A)	108.1 (3)
C(12)-C(13)-C(18)	110.6 (2)	C(14)-C(13)-C(18)	111.0 (2)
C(17A)-C(13)-C(18)	110.4 (2)	C(8)-C(14)-C(13)	114.1 (3)
C(8)-C(14)-C(15)	114.4 (3)	C(13)-C(14)-C(15)	109.5 (3)
C(14)-C(15)-C(16)	112.3 (3)	C(15)-C(16)-C(17)	124.8 (3)
C(16)-C(17)-C(17A)	121.0 (3)	C(16)-C(17)-C(17B)	123.1 (3)
C(17A)-C(17)-C(17B)	115.9 (3)	C(13)-C(17A)-C(17)	115.2 (3)
C(4)-O(4A)-C(4A)	116.0 (3)	O(4A)-C(4A)-C(4B)	107.9 (3)
C(4A)-C(4B)-O(4B)	115.0 (4)		

14.73; HRMS calcd for $C_{23}H_{36}O_2$, 344.27153, found, 344.27152.

Crystallization (as above) of fraction 2 yielded about 1 mg of what is probably the fluoro compound **6** in about 90% purity as indicated by GC. (Fraction 2 contained about 13% of this material as indicated by GC.) **6**: ^{1}H NMR (400 MHz) δ 5.35 (br s, 1 H), 3.2-3.7 (m, 6 H), 0.7-2.3 (m, 21 H), 1.61 (s, 3 H), 1.04 (d, 3 H, J = 2.4 Hz), 0.93 (d, 3 H, J = 2.4 Hz); MS m/e (rel. intensity) 364 (26), 349 (2), 344 (5), 282 (53), 145 (60), 91 (100); HRMS calcd for $C_{23}H_{37}FO_2$, 364.2777, found, 364.2771.

A small specimen (<1 mg) of the above fluoro compound **6** was added to a dark blue solution of 5 mg of sodium-potassium alloy (Aldrich 78% K, 22% Na) and 5 mg of dicyclohexyl-crown-6 in 3 mL of toluene at 23 °C. The mixture was stirred for 2.5 h, and then the reaction was quenched by the addition of isopropyl alcohol. Ether and water were added, and then the ether layer was dried over magnesium sulfate. The solvents were evaporated at reduced pressure, and the residue was passed through a column of Florisil. The total product appeared to consist mainly of one compound as indicated by GC, which showed identical GC behavior on coinjection with the authentic tetracyclic material **2**.[2]

Crystallographic Data. The bond lengths and bond angles for compound **25** (see ball and stick printout, Figure 1) are given in Tables I and II, respectively.

The interpretation of the solvent of crystallization is uncertain due to the limitation that the quality of the crystal imposed on the accuracy of the measured intensities. These uncertainties do not cast any doubt on the conclusions about the structure of the main molecule.

Acknowledgment. We are indebted to the National Institutes of Health (NIH DK 03787) and the National Science Foundation for support of this research. We also thank the Mass Spectrometry Resource, School of Pharmacy, University of California, San Francisco, for high-resolution mass spectral analyses.

Supplementary Material Available: Additional X-ray crystallographic structure determination information in tables of crystal data, data collection method, and solution and refinement data; Table 3, atomic coordinates including equivalent isotropic displacement coefficients; Table 4, anisotropic displacement coefficients; and Table 5, H-atom coordinates including isotropic displacement coefficients (6 pages). Ordering information is given on any current masthead page.

The Fluorine Atom as a Cation-Stabilizing Auxiliary in Biomimetic Polyene Cyclizations. 2. Asymmetric Synthesis of a Steroid[1]

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Received June 2, 1992

Abstract: The use of the fluorine atom as a cation-stabilizing (C-S) auxiliary for enhancing polyene cyclizations has been improved in synthetic effectiveness by the demonstration that the *dl* acetal **5** can be converted to the racemic fluorocycle **6**, bearing the natural backbone configuration of the steroids. Cyclization of enantiopure *S,S* acetal **5a** afforded the fluorocycle **6a** in 38% yield with 93% ee. Retention of the fluorine atom in the tetracycle allowed for the smooth reduction of **6a**, using the Ohsawa-Oishi reagent, to compound **22a**, in which the fluorine atom is replaced stereoselectively by hydrogen, with retention of configuration, as shown by the conversion of **22a** to the known steroid 4β-hydroxyandrostan-17-one (**27a**). Five compounds make up the relatively high-yielding (69-83%) tetracyclic portion of the cyclization product mixture, affording the possibility that further structural modifications of the cyclization substrate bearing the *pro*-C-8 fluoro group as a C-S auxiliary will lead to practical synthetic routes to fluorosteroids and triterpenoids. In the next two papers in this series, this potential is demonstrated further by the synthesis of β-amyrin.

A recent concept[1] is opening up a new vista for achieving polyenic tetracyclizations, which have previously been generally low-yielding processes. The guiding principle for realizing efficient stereoselective tetracyclizations in the absence of enzymatic control involves the use of substrates modified so as to effect stabilization of one or more of the positive sites that develop in the cyclization transition state. To this end, we have been studying the effect of appending cation-stabilizing (C-S) auxiliaries to the appropriate carbons in the cyclization substrate. In the previous paper in this series,[1d] it was disclosed that the yield of tetracyclic compounds from cyclization of an acyclic tetraenic acetal could be enhanced

† The X-ray crystallographic analyses reported herein were performed by F.S.T. and R.K.K. at the Department of Chemistry, Rensselaer Polytechnic Institute, Troy, NY 12180.

(1) This represents paper no. 5 on cation-stabilizing auxiliaries in polyene cyclizations. For the first four papers in the series, see: (a) Johnson, W. S.; Telfer, S. J.; Cheng, S.; Schubert, U. *J. Am. Chem. Soc.* **1987**, *109*, 2517-2518. (b) Johnson, W. S.; Lindell, S. D.; Steele, J. *J. Am. Chem. Soc.* **1987**, *109*, 5852-5853. (c) Guay, D.; Johnson, W. S.; Schubert, U. *J. Org. Chem.* **1989**, *54*, 4731-4732. (d) Johnson, W. S.; Chenera, B.; Tham, F. S.; Kullnig, R. K. *J. Am. Chem. Soc.*, preceding paper in this issue.

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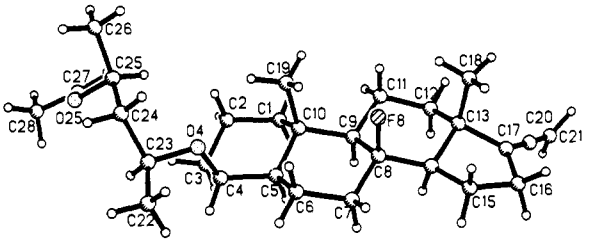
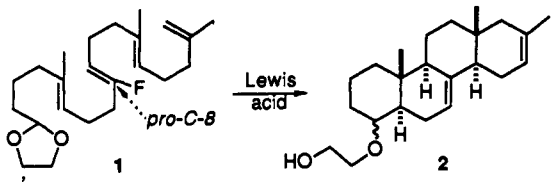


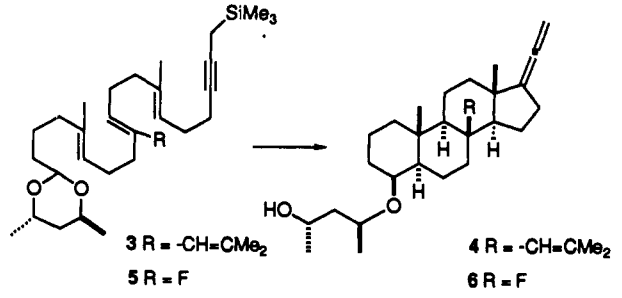
Figure 1. Diagram of the 140° compound, the acetate of **6**.

by the presence of a fluorine atom at *pro*-C-8 (steroid numbering) acting as a C-S group. Thus, acetal **1** was converted with $SnCl_4$ in pentane at 0 °C into a mixture of dehydrofluorinated tetracyclic compounds consisting mainly of the epimeric dienols **2**, formed by loss of HF following cyclization. The enhanced yield of



tetracyclic products brought about by the fluorine atom as a C-S auxiliary was highly encouraging; however, the complexity of the product mixture[2] precluded using substrate **1** as a practical synthetic precursor of the tetracyclic products. It is synthetically advantageous for the fluorine atom to be retained in the cyclized product in order to afford greater control over subsequent synthetic manipulations en route to steroids (see below).

From studies of tetracyclizations of substrates having the isobutenyl C-S auxiliary at *pro*-C-8, it has been found that use of the pentanediol acetal initiator in conjunction with the propargylsilane terminator results in improved stereoselectivity, presumably because relatively mild reaction conditions could be used. In the hope that the undesired dehydrofluorination process would be minimized under such mild conditions, we elected to examine the cyclization of the substrate **5**, which is the major concern of the present paper.



In this paper, we describe the synthesis of a cyclization substrate, both in the racemic (**5**) and the optically active (**5a**) acetal forms, which upon low-temperature cyclization give tetracyclic compounds in over 70% yield with high enantiomeric excess containing as the major component fluorotetracycle **6**. The Ohsawa–Oishi[3] reagent was found to effect replacement of the quaternary fluorine atom at *pro*-C-8 by hydrogen stereoselectively with retention of configuration, allowing **6** to be converted in high yield to the known 4β-hydroxyandrostan-17-one (**27**). An improved route to (*Z*)-fluoro trisubstituted olefins is also reported.

Synthesis of the Cyclization Substrate. The synthesis of acetals **5** and **5a** was accomplished by a linear sequence, starting with the known[4] allylic alcohol **7**,[5] in which the trisubstituted olefinic

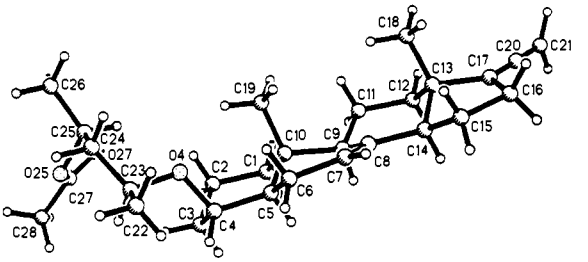


Figure 2. Diagram of the 121° compound, the acetate of **19**.

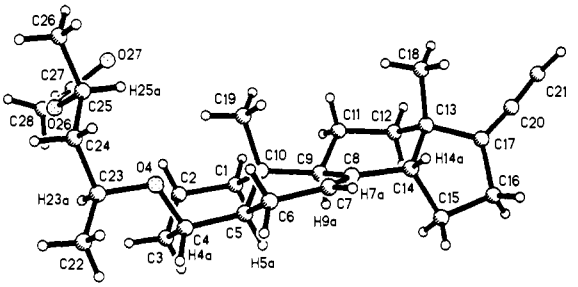


Figure 3. Diagram of the 117° compound, the acetate of **20**.

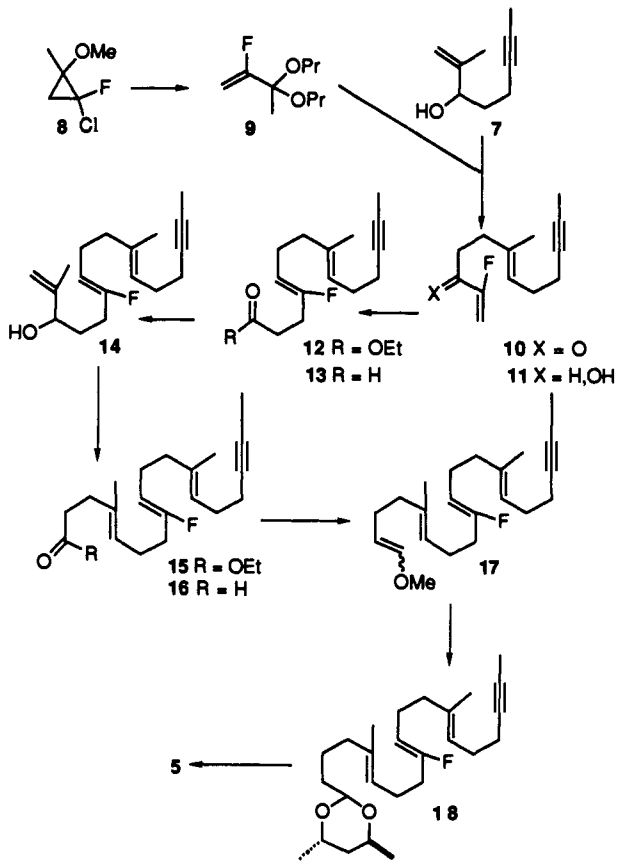
bonds were established in the correct stereochemistry by a series of Claisen rearrangements, as outlined in Scheme I. Fluoro enone **10** could be prepared in reasonable yield by the in situ Claisen rearrangement[1d] of alcohol **7** with the fluorocyclopropane **8**.[6] However, a higher yield (79%) of the product was achieved when the fluorocyclopropane **8** was converted first, by solvolysis with propanol, into the fluoro acetal **9**[6] and then combined in equimolar amounts with alcohol **7**, dissolved in toluene, and heated. The unstable fluoro enone **10**, contaminated with less than 1% of its *Z*-isomer, was immediately reduced with diisobutylaluminum hydride to yield the alcohol **11** (85%), which smoothly underwent the orthoester Claisen rearrangement,[7] giving, in 88% yield, the dienynic ester **12** and its *E*-isomer in a ratio of 30:1. This two-step sequence, using the readily available fluoro acetal **9**, is high yielding and produces the (*Z*)-fluoroolefin with excellent stereoselectivity.

Diisobutylaluminum hydride reduction of ester **12** yielded the aldehyde **13**, which upon treatment with 2-propenylmagnesium bromide followed by orthoester Claisen rearrangement[7] gave the

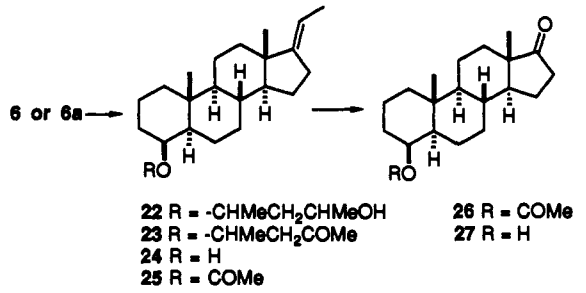
(2) See ref 1d, footnote 15.
(3) Ohsawa, T.; Takagaki, T.; Haneda, A.; Oishi, T. *Tetrahedron Lett.* **1981**, 2583–2586.
(4) Johnson, W. S.; Gravestock, M. B.; McCarry, B. E. *J. Am. Chem. Soc.* **1971**, *93*, 4332–4334.

(5) In the present study, alcohol **7** was prepared by a procedure developed by P. Nederlof and R. G. Andrew, Stanford University, as follows: Propyne (15 g, 0.374 mol) was condensed at −78 °C, followed by the slow addition of 450 mL of dry dimethoxyethane and 50 g of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone to the cooled flask. Butyllithium (100 mL, 2.5 M) was added dropwise, and the temperature was allowed to rise to 0 °C. After 1 h, 36.2 g (0.200 mol) of 2-(2-bromoethyl)-1,3-dioxolane in 50 mL of dry dimethoxyethane was added, the mixture was stirred at room temperature for 66 h, washed with brine, and dried over magnesium sulfate, and solvent was removed by distillation through a Vigreux column at reduced pressure. The residue was dissolved in ether, washed with water and brine, and dried over magnesium sulfate. Removal of solvent at reduced pressure followed by distillation of the residue gave 16.7 g (65% yield) of 2-(3-pentynyl)-1,3-dioxolane as a colorless oil, 98% pure by GC, bp 92 °C (13 mmHg). A 16.6-g sample of this acetal in 150 mL of THF was added to 400 mL of cold 2.4 M hydrochloric acid. After 2 h at 25 °C, ether (300 mL) was added, and then the organic layer was separated, washed with saturated $NaHCO_3$ and brine, combined with a back-extraction with ether, and dried over magnesium sulfate. The solvent was removed through a Vigreux column until the volume of the residue was 75 mL. This solution of aldehyde was added dropwise over 1.5 h to a cold (0 °C) solution of propenylmagnesium bromide that had been prepared by the addition of 21.2 g (0.175 mol) of 2-bromopropene in 225 mL of dry tetrahydrofuran dropwise to 4.2 g (0.175 mol) of magnesium turnings. After an additional 30 min at 0 °C, the reaction was quenched with saturated ammonium chloride. The organic layer was separated, washed with brine, combined with an ethereal back-extraction, and dried over magnesium sulfate. The solution was concentrated and distilled through a Vigreux column, giving 11.9 g (75% yield) of alcohol **7** (bp 106–109 °C/14 mmHg, 98% pure by GC).
(6) Bessiere, Y.; Savary, D. N.-H.; Schlosser, M. *Helv. Chim. Acta* **1977**, *60*, 1739–1746.
(7) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.-T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741–743.

Scheme I

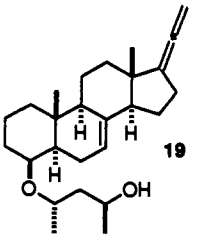


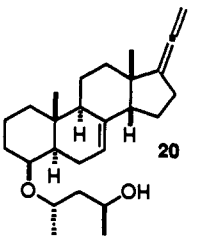
Scheme II

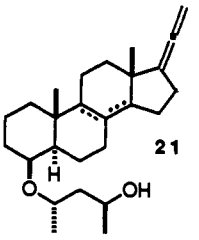


trienynic ester **15** in 75% overall yield. The corresponding aldehyde **16**, formed in 100% yield by diisobutylaluminum hydride reduction of ester **15**, on reaction with the ylide prepared from (methoxymethyl)triphenylphosphonium chloride and *sec*-butyllithium yielded the enol ether **17** in 93% yield. Conversion to the acetal **18** by reaction with *dl*-2,4-pentanediol in benzene followed by treatment[8] with *tert*-butyllithium and trimethylsilyl chloride in tetrahydrofuran at −78 °C gave the cyclization substrate **5** in 60% yield. Enantiopure acetal **5a** was prepared from an enol ether, corresponding to **17**, already containing the trimethylsilyl group. Due to the simplicity of the sequence and the ease of preparation, the substrates could be obtained readily by this route in 31% overall yield from alcohol **7**.

Cyclization Studies. The cyclization of acetal **5** was studied under a variety of temperature and solvent conditions using $SnCl_4$ as catalyst. The most favorable conditions proved to be reaction with 3 equiv of $SnCl_4$ in methylene chloride at −90 °C, producing five tetracyclic compounds in 69% yield. The major component, isolated from the mixture in 32% yield, was shown to be the fluorotetracycle **6**, which gave a nicely crystalline acetate, mp 148–149 °C. In addition, the dehydrofluorination product **19** (acetate, mp 120–121 °C) was present in a small amount (4%)







along with 19% of the cis C/D ring-fused alkene **20** (acetate, mp 115–117 °C). The structures and relative configurations of the acetates of **6**, **19**, and **20** were determined by X-ray crystallographic analysis. Plots of the structures of the 149°, 121°, and 117° compounds are shown in Figures 1, 2, and 3, respectively. The other two tetracycles, isolated in 7% yield each, possessed neither fluorine nor vinyl hydrogens and are presumed to be the $\Delta^{8,9}$ or $\Delta^{8,14}$ alkenes **21**.

It is noteworthy that when the cyclization reaction was conducted at a higher temperature (−40 °C), the product distribution changed, with dehydrofluorination products greatly predominating. The fluorotetracycle **6** now comprised only 8% of the product mixture, while alkene **19** comprised 32%, and the balance consisted of the cis C/D alkene **20** (25%) and the two tetrasubstituted alkenes **21**, each obtained in 9% yield.

To investigate the synthetic potential of the fluorotetracycle **6**, this compound was converted to the known steroid 4β-hydroxyandrostan-17-one (**27**), as shown in Scheme II. Thus, when **6** was reduced with the Ohsawa–Oishi reagent[3] (Na/K alloy and crown ether in toluene), an inseparable mixture (79:2:7 by GC) was produced in 91% yield, the major component of which evidently (see below) was either compound **22** or its geometrical ethylidene isomer. (One of the minor components probably was the equally useful alternative geometric isomer.) The conversion of this mixture to the racemic steroid **27** was performed without purification of any of the intermediates. Thus, oxidation to the ketone **23** with pyridinium chlorochromate followed by β-elimination with potassium hydroxide in refluxing methanol led to alcohol **24**, which was first acetylated to give **25** and then ozonolyzed in methanol with pyridine, yielding **26**. Hydrolysis of the ozonolysis product afforded racemic 4β-hydroxyandrostan-17-one (**27**) in 38% overall yield from alcohol **22**. This compound, mp 171–174 °C, was compared with an authentic sample of *d*-**27**,[9] mp 161–165 °C. The NMR, IR, and high-resolution mass spectra (including a complex fragmentation pattern) of the synthetic product were identical in every detail with the corresponding spectra of the authentic (naturally derived) sample. Also, the two samples exhibited identical behavior on GC coinjection experiments.

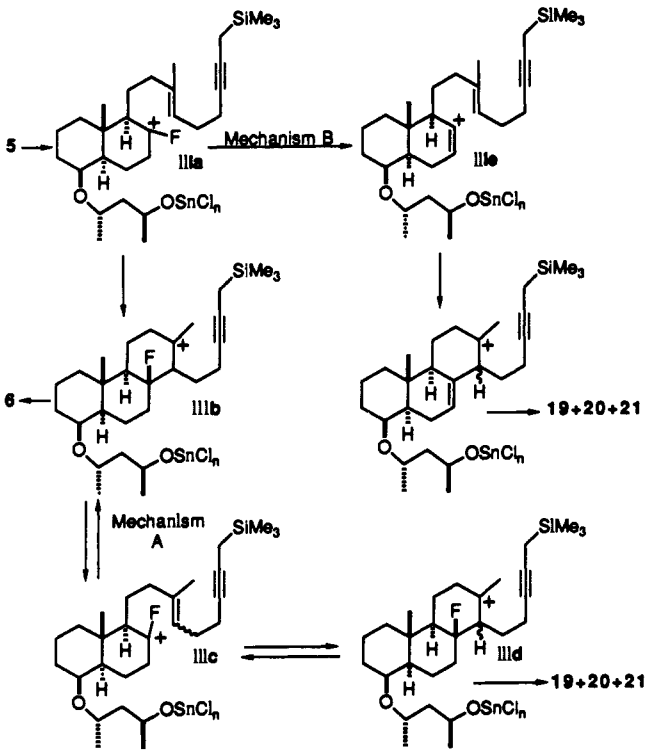
Another objective of this study was to determine the degree of asymmetric induction that could be produced with the fluorine atom as a C-S auxiliary, using the chiral acetal methodology.[10]

(8) Rajagopalan. S.; Zweifel, G. *Synthesis* **1984**, 111.

(9) Klimstra, P. D.; Zigman, R.; Counsell, R. E. *J. Med. Chem.* **1966**, *9*, 924–929.

(10) Johnson, W. S.; Elliott, J. D.; Hanson, G. *J. Am. Chem. Soc.* **1984**, *106*, 1138–1139. For the seminal work on asymmetric bicyclizations, see: Johnson, W. S.; Harbert, C. A.; Stipanovic, R. D. *J. Am. Chem. Soc.* **1968**, *90*, 5279–5280. Johnson, W. S.; Harbert, C. A.; Ratcliffe, B. E.; Stipanovic, R. D. *J. Am. Chem. Soc.* **1976**, *98*, 6188–6193. See also ref 1c.

Scheme III



To this end, the cyclization of the *S,S* acetal **5a**[14] was investigated. For this cyclization, the chiral substrate was dissolved in methylene chloride and hexamethyldisiloxane and cooled to −78 °C, and $SnCl_4$ was added. Purification of the product of a 10-min reaction, quenched with triethylamine/methanol, yielded a mixture of tetracycles (79%), of which fluorotetracycle **6a** was the major component (38%). Conversion of this compound, as described above (Scheme II), to optically active *d*-4β-hydroxyandrostan-17-one (**27a**) was accomplished in 21% overall yield, producing a crystalline substance, mp 153–161 °C. The optical rotation of this material ($[\alpha]_D$ +85.7°) was somewhat lower than that ($[\alpha]_D$ +93°) for the authentic material.[9] Except for the possibility of some enantioenrichment by, e.g., crystallization, it may be concluded that the cyclization to give the fluorotetracycle **6a** had proceeded with ca. 93% ee, which is consistent with previous results.[1c] The presence of about 7% of the racemic form of **27** in the synthetic sample is surely responsible for its depressed melting point.

Theoretical Considerations. The efficacy of the fluoro C-S auxiliary has been demonstrated by the high yield (69–83%) of tetracyclic compounds produced upon cyclization of acyclic acetal **5** with $SnCl_4$. It is noteworthy that this cyclization can be carried out at a temperature as low as −90 °C, conditions under which the C-8 fluorine atom is not as labile in the presence of $SnCl_4$, thereby permitting the isolation of significant amounts of the fluorotetracycle **6**. The hitherto unknown C-8 fluorosteroids are now accessible using this methodology.

Of interest mechanistically in this study are the observations that (a) the production of dehydrofluorination products is highly temperature dependent and (b) an unexpected 13β,14β-C/D cis-fused tetracycle is formed in significant amounts. The production of 13α,14α-C/D cis-fused tetracycles had been observed previously and was thought to occur via axial rather than equatorial closure of ring D.[11] To account for the formation of the 13β,14β cis C/D product, it has been suggested[12] that the intermediate cation IIIb may be in equilibrium under Lewis acid conditions with ions IIIc and IIId, as depicted in Scheme III (Mechanism A). Thus, the unusual stability of the fluoro carbocation may be the source of this loss of stereospecificity in the cyclization, allowing reversible carbocation formation. Alternatively, the Lewis acid may be inducing elimination of hydrogen fluoride at the bicyclic stage IIIa (Mechanism B), thus forming the vinyl cation IIIe, a type known from prior work to produce cis C/D ring fusion products.[13]

In situations in which the rate of closure of the terminal ring is probably relatively high (as in the cases described in the following two papers), an isomer corresponding to **20** is not produced in any detectable amounts. Therefore, the formation of this abnormal isomer seems to be dependent on the bicyclic fluoro cation IIIa having a relatively long life in the overall cyclization process.

Conclusion

The stereoselective synthesis of (*Z*)-fluoroolefins was improved by a high-yielding two-step Claisen rearrangement route. Cyclization of acetal **5** gave a satisfactory yield of fluorotetracycle **6**, which could be stereoselectively reduced with the Ohsawa–Oishi reagent to give **22**, which was converted into the known steroid 4β-hydroxyandrostan-17-one (**27**). These results, together with the demonstration of high asymmetric induction in the cyclization of the *S,S* acetal **5a**, suggest the effectiveness of the C-8 fluoro atom as a C-S auxiliary. Additional realization of this potential is disclosed in the next two papers in this series, in which the methodology is applied to the synthesis of β-amyrin.

Experimental Section

General Considerations. The prefix *dl* has been omitted from the names of the racemic compounds described in this section. Unless otherwise specified, all reaction procedures were carried out under an atmosphere of nitrogen or argon. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium benzophenone ketyl, and dichloromethane was distilled from CaH_2. Analytical thin-layer chromatography (TLC) was performed on kieselgel 60 F_{254} plastic-backed plates using ether–hexane or ethyl acetate–hexane solvent mixtures and iodine impregnated on silica gel or anisaldehyde visualization. Flash chromatography was performed using E. Merck silica gel 60 (230–400 mesh). For gas chromatography (GC), a Hewlett-Packard (HP5710A) instrument was used with a 15-m SE-54 capillary column and hydrogen carrier gas within the temperature ranges of 50–290 °C. Most reactions were followed by TLC or GC and stopped upon disappearance of starting material. NMR spectra were obtained on a Varian XL-400 instrument with deuteriochloroform used as the solvent. HPLC was performed on a Dupont 870 instrument using a Zorbax silica (normal phase) or Zorbax ODS (reverse phase) column (21.2 mm × 25 cm) and UV detection. IR spectra were obtained on a Perkin-Elmer 1310 or Beckman Acculab-3 spectrophotometer. Analytical samples for combustion analysis were purified by column chromatography, followed by distillation in a glass tube under vacuum, using a Kugelrohr oven. The samples were sealed directly in the tube under vacuum without exposure to air and sent to Desert Analytical in Tucson, AZ. Melting points were taken with a Kofler hot-stage microscope calibrated against totally immersed Anschutz thermometers and are not corrected. An Autopol III polarimeter with a 1-dm cell was used for determining optical rotations.

2-Fluoro-6-methyl-1,6(*E*)-dodecadien-10-yn-3-one (10). To a solution of 5.0 g (36.2 mmol) of allylic alcohol **7**[4,5] were added 6.9 g (36.5 mmol) of dipropyl ketal **9**,[6] a trace of hydroquinone, and a catalytic amount of pyridinium *p*-toluenesulfonate in 50 mL of toluene. The solution was heated in a simple distillation apparatus such that propanol–toluene slowly distilled from the mixture for 5 h. The mixture was then cooled, diluted with ether, washed with 5% $NaHCO_3$ and brine, dried over magnesium sulfate, and concentrated at reduced pressure. The residue was purified by flash chromatography using 5% ethyl acetate in hexane to give 5.9 g (79% yield) of the ketone **10** as a colorless oil, 97% pure by GC. The ketone polymerizes slowly at room temperature: IR (film) 3140, 1710, 1670, 1640 cm^{-1}; ^1H NMR δ 5.5 (dd, 1 H, J = 3, 45 Hz),

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(14) Acetal **5a** was prepared by a route analogous to Scheme I, except that the trimethylsilyl group was introduced at the outset. Thus, 2-(3-pentynyl)-1,3-dioxolane[4] was treated with *sec*-butyllithium and trimethylsilyl chloride, giving 2-(5-(trimethylsilyl)-3-pentynyl)-1,3-dioxolane, and this acetal was converted as described above[4,5] to 2-methyl-8-(trimethylsilyl)oct-1-en-6-yn-3-ol. This alcohol was converted to acetal **5a**, as shown in Scheme I.

5.2 (dd plus m, 2 H, J = 3, 12 Hz), 2.75 (dt, 2 H, J = 2, 15 Hz), 2.3 (t, 2 H, J = 8 Hz), 2.15 (m, 4 H), 1.76 (t, 3 H, J = 2 Hz), 1.62 (s, 3 H). Anal. Calcd for $C_{13}H_{17}FO$: C, 74.97; H, 8.23. Found: C, 73.96; H, 8.30. A (2,4-dinitrophenyl)hydrazone derivative was crystallized from ethanol, mp 115–116 °C. Anal. Calcd for $C_{19}H_{21}FN_4O_4$: C, 58.76; H, 5.45. Found: C, 58.67; H, 5.37.

2-Fluoro-6-methyl-1,6(*E*)-dodecadien-10-yn-3-ol (11). To a solution of 5.9 g (28.4 mmol) of ketone **10** in 100 mL of dry ether at −78 °C was added 34 mL of diisobutylaluminum hydride (1 M in cyclohexane) via syringe over a period of 10 min. Stirring was continued for 10 min, and then 6 mL of methanol was added in one portion. The solution was warmed to 23 °C, and then 250 mL of 1 N H_2SO_4 was added. After the solution was shaken for 10 min in a separatory funnel, additional ether was added. The organic layer was separated, washed with 5% $NaHCO_3$ and brine, and dried over magnesium sulfate, and the solution was concentrated at reduced pressure. The residue was purified by flash chromatography with 10–15% ethyl acetate in hexane to give 5.0 g (85% yield) of alcohol **11** as a colorless oil, 97% pure by GC: IR (film) 3400, 1670 cm^{-1}; ^{1}H NMR δ 5.23 (br m, 1 H), 4.6 (2 dd, 2 H, J = 3, 24, 56, 3 Hz), 4.1 (m, 1 H), 2.2 (m, 6 H), 2.0 (d, 1 H, J = 6 Hz), 1.8 (t, 3 H, J = 2 Hz), 1.7 (m, 2 H), 1.6 (s, 3 H). The analytical sample was distilled at an oven temperature of 85 °C (0.25 mmHg). Anal. Calcd for $C_{13}H_{19}FO$: C, 74.25; H, 9.11. Found: C, 73.97; H, 9.08.

Ethyl 4-Fluoro-8-methyltetradeca-4(*Z*),8(*E*)-dien-12-ynoate (12). A mixture of 5.0 g (17.8 mmol) of alcohol **11** in 50 mL of triethyl orthoacetate with 0.7 g of propionic acid was heated to 125 °C for 3 h in an oil bath and then was heated at 135 °C for an additional hour with continuous removal of the ethanol produced from the reaction by slow distillation.[7] The reaction mixture was cooled, added to 300 mL of cold 0.5 N H_2SO_4, and stirred for 15 min. Ether (150 mL) was added, the organic layer was washed with 5% $NaHCO_3$ and brine and dried over magnesium sulfate, and then the solvent was removed at reduced pressure. The residue was purified by flash chromatography (5% ethyl acetate in hexane) to give 5.8 g (88% yield) of ester **12** as a colorless oil, 95.4% pure by GC: IR (film) 1730, 1700 cm^{-1}; ^{1}H NMR δ 5.15 (br t, 1 H, J = 6 Hz), 4.5 (dt, 1 H, J = 7, 39 Hz), 4.15 (q, 2 H, J = 7 Hz), 2.46 (m, 4 H), 2.15 (m, 6 H), 2.0 (t, 2 H, J = 8 Hz), 1.78 (t, 3 H, J = 2 Hz), 1.6 (s, 3 H), 1.25 (t, 3 H, J = 7 Hz). Anal. Calcd for $C_{17}H_{25}FO_2$: C, 72.82; H, 8.99. Found: C, 72.91; H, 9.25.

4-Fluoro-8-methyltetradeca-4(*Z*),8(*E*)-dien-12-ynal (13). To a solution of 5.8 g (20.7 mmol) of ester **12** in 80 mL of dry ether at −78 °C was added 21.7 mL of a 1 M solution of diisobutylaluminum hydride in cyclohexane. The reaction mixture was stirred for an additional 15 min, the reaction was quenched with 5 mL of methanol, and then the mixture was stirred vigorously for 10 min with 100 mL of cold 1 N H_2SO_4. Ether (100 mL) was added, and the organic layer was washed with 5% $NaHCO_3$ and brine and dried over magnesium sulfate. The solvent was removed at reduced pressure to give 4.9 g (100% yield) of aldehyde **13** as a colorless oil, 96% pure by GC, used without purification: IR (film) 2720, 1725, 1700 cm^{-1}; ^{1}H NMR δ 9.8 (br s, 1 H), 5.15 (br t, 1 H, J = 5 Hz), 4.5 (dt, 1 H, J = 7, 38 Hz), 2.6 (t, 2 H, J = 7 Hz), 2.45 (m, 2 H), 2.15 (m, 6 H), 2.0 (t, 2 H, J = 7 Hz), 1.76 (t, 3 H, J = 2 Hz), 1.6 (s, 3 H). The analytical sample was distilled at an oven temperature of 100 °C (0.25 mmHg). Anal. Calcd for $C_{15}H_{21}FO$: C, 76.23; H, 8.96. Found: C, 75.94; H, 9.11.

6-Fluoro-2,10-dimethylhexadeca-1,6(*Z*),10(*E*)-trien-14-yn-3-ol (14). To a suspension of 720 mg (30 mmol) of magnesium chips in 40 mL of dry THF was added 3.6 g (30 mmol) of 2-bromopropene. After the magnesium disappeared, the solution was cooled to 0 °C, and 4.9 g (20.7 mmol) of aldehyde **13** in 15 mL of THF was added with stirring over 10 min. The reaction mixture was stirred at 0 °C for an additional 30 min, and then the reaction was quenched with saturated ammonium chloride solution. The mixture was extracted with ether, washed with water and brine, and dried over magnesium sulfate. The solvent was removed at reduced pressure to give 5.7 g (98% yield) of alcohol **14**, 98% pure by GC, which was used without purification: IR (film) 3400, 3060, 1695, 1680–1630 cm^{-1}; ^{1}H NMR δ 5.2 (br t, 1 H, J = 6 Hz), 4.92 and 4.82 (2 s, 2 H), 4.5 (dt, 1 H, J = 7, 38 Hz), 4.1 (br s, 1 H), 2.2 (m, 8 H), 2.0 (t, 2 H, J = 8 Hz), 1.76 (t, 3 H, J = 2 Hz), 1.7 (s, 3 H), 1.7 (t, 3 H, J = 2 Hz), 1.6 (s, 3 H). The analytical sample was distilled at an oven temperature of 130 °C (0.25 mmHg). Anal. Calcd for $C_{18}H_{27}FO$: C, 77.65; H, 9.78. Found: C, 77.59; H, 9.58.

Ethyl 8-Fluoro-4,12-dimethyloctadeca-4(*E*),8(*Z*),12(*E*)-trien-16-ynoate (15). A solution of 5.6 g (16.1 mmol) of allylic alcohol **14**, 50 mL of triethyl orthoacetate, and 0.5 g of propionic acid was heated at 125 °C for 2 h. This procedure and the workup were similar to those described above for the conversion of **11** to **12**. Flash chromatography (1:20 EtOAc:hexane) yielded 5.3 g (76%) of ester **15** as a colorless oil, 94% pure by GC: IR (film) 1730, 1700, 1680–1630 cm^{-1}; ^{1}H NMR δ 5.15 (m, 2 H), 4.45 (dt, 1 H, J = 7, 38 Hz), 4.1 (q, 2 H, J = 7 Hz), 2.4 (m, 2 H), 2.3 (m, 2 H), 2.15 (br m, 10 H), 2.0 (t, 2 H, J = 7 Hz), 1.77 (t, 3 H, J = 2 Hz), 1.6 (s, 6 H), 1.25 (t, 3 H, J = 7 Hz). Anal. Calcd for $C_{22}H_{33}FO_2$: C, 75.82; H, 9.54. Found: C, 75.69; H, 9.62.

8-Fluoro-4,12-dimethyloctadeca-4(*E*),8(*Z*),12(*E*)-trien-16-ynal (16). To a solution of 2.5 g (7.2 mmol) of ester **15** in 40 mL of dry ether at −78 °C was added 7.8 mL of a 1 M solution of diisobutylaluminum hydride in cyclohexane. The reaction mixture was stirred for an additional 10 min, the reaction was quenched with 6 mL of methanol, and then the mixture was worked up as described above for the conversion of **12** to **13**. The solution was concentrated at reduced pressure to give 2.2 g (100% yield) of aldehyde **16**, 95% pure by GC, which was used without purification: IR (film) 2700, 1720, 1700, 1680–1630 cm^{-1}; ^{1}H NMR δ 9.7 (t, 1 H, J = 2 Hz), 5.15 (m, 2 H), 4.45 (dt, 1 H, J = 7, 38 Hz), 2.5 (dt, 2 H, J = 2, 7 Hz), 2.3 (t, 2 H, J = 7 Hz), 2.1 (m, 10 H), 2.0 (t, 2 H, J = 7 Hz), 1.77 (t, 3 H, J = 2 Hz), 1.61 (s, 3 H), 1.60 (s, 3 H). The analytical sample was distilled at an oven temperature of 140 °C (0.25 mmHg). Anal. Calcd for $C_{20}H_{29}FO$: C, 78.90; H, 9.60. Found: C, 78.92; H, 9.86.

2-(8-Fluoro-4,12-dimethyloctadeca-4(*E*),8(*Z*),12(*E*)-trien-16-ynyl)-4,6-dimethyl-1,3-dioxane (18). To a suspension of 4.0 g (11.8 mmol) of (methoxymethyl)triphenylphosphonium chloride in 40 mL of THF at −78 °C was added dropwise 8.6 mL (11.2 mmol) of *sec*-butyllithium (1.3 M in cyclohexane). The red solution was stirred at −78 °C for 30 min, allowed to warm to 0 °C for 30 min, and then cooled to −78 °C. To this phosphorane solution was added slowly a solution of 2.2 g (7.2 mmol) of aldehyde **16** in 10 mL of THF. The mixture was stirred at −78 °C for 45 min and slowly warmed to 0 °C for 45 min. Water was added, and the solution was extracted with ether. The organic layer was washed with brine and dried over magnesium sulfate. The solvent was evaporated at reduced pressure, and hexane was added to precipitate the phosphine oxide. Flash chromatography (50:1 hexane:EtOAc) gave 2.2 g (93% yield) of enol ether **17** as a colorless oil, a mixture of Z/E isomers (36:60) by GC.

To a solution of 2.2 g (6.6 mmol) of enol ether **17** in 50 mL of benzene were added 800 mg (8.0 mmol) of 2,4-pentanediol and 5 mg of *p*-toluenesulfonic acid. This solution was heated at 75 °C for 30 min, cooled, washed with 5% $NaHCO_3$, and dried over magnesium sulfate. Evaporation of the solvent at reduced pressure gave 2.6 g (100% yield) of acetal **18** as a colorless oil, 90% pure by GC, which was used without purification: IR (film) 1700, 1680–1620 cm^{-1}; ^{1}H NMR δ 5.18 (t, 2 H, J = 6 Hz), 5.1 (br s, 1 H), 4.8 (t, 1 H, J = 6 Hz), 4.45 (dt, 1 H, J = 7, 38 Hz), 4.3 (m, 1 H), 3.9 (m, 1 H), 2.15 and 2.0 (2 m, 14 H), 1.77 (t, 3 H, J = 2 Hz), 1.6 (s, 3 H), 1.58 (s, 3 H), 1.5 (m, 4 H), 1.34 (d, 3 H, J = 7 Hz), 1.2 (d, 3 H, J = 6 Hz). The analytical sample was distilled at 160 °C (0.01 mmHg). Anal. Calcd for $C_{26}H_{41}FO_2$: C, 77.18; H, 10.21. Found: C, 77.27; H, 10.46.

2-[8-Fluoro-4,12-dimethyl-18-(trimethylsilyl)octadeca-4(*E*),8(*Z*),12(*E*)-trien-16-ynyl]-4,6-dimethyl-1,3-dioxane (5). To a solution of 2.6 g (6.4 mmol) of acetal **18** and 750 mg (6.5 mmol) of tetramethylethylenediamine in 7 mL of THF at −78 °C was added dropwise 4.0 mL (6.8 mmol) of *tert*-butyllithium (1.7 M in pentane).[8] The mixture was allowed to warm to −20 °C over 70 min and then to 0 °C for 1 h. It was then cooled to −78 °C. Trimethylsilyl chloride (1.25 mL, 10 mmol, freshly distilled from CaH_2) was added dropwise. The reaction mixture was stirred at −78 °C for 5 min and then allowed to warm to 23 °C for 1 h. Ether was added, and the mixture was washed with water, 1 N H_2SO_4 and 5% $NaHCO_3$ and dried over magnesium sulfate. The solution was concentrated at reduced pressure to give 2.6 g of acetal **5** as a yellow oil, 74% pure by GC. Flash chromatography (1:25 EtOAc:hexane) followed by a second analysis by chromatography of fractions of less than 90% purity gave 1.8 g (60% yield) of acetal **5**, 93% pure by GC, as a colorless oil: IR (film) 1700, 1680–1600 cm^{-1}; ^{1}H NMR δ 5.22 (br s, 1 H), 5.12 (br s, 1 H), 4.88 (t, 1 H, J = 6 Hz), 4.5 (dt, 1 H, J = 7, 38 Hz), 4.3 (m, 1 H), 4.0 (m, 1 H), 2.2 and 2.0 (2 m, 14 H), 1.65 (s, 3 H), 1.63 (s, 3 H), 1.5 (m, 4 H), 1.45 (s, 2 H), 1.4 (d, 3 H, J = 7 Hz), 1.25 (d, 3 H, J = 6 Hz), 0.13 (s, 9 H). The analytical sample was distilled at an oven temperature of 185 °C (0.01 mmHg). Anal. Calcd for $C_{29}H_{49}FSiO_2$: C, 73.11; H, 10.29. Found: C, 73.16; H, 10.53.

Cyclization of Acetal 5. A. At −40 °C. To a solution of 200 mg (0.42 mmol) of acetal **5** in 40 mL of methylene chloride at −40 °C was added dropwise 1.26 mL of stannic chloride (1 M in CH_2Cl_2). The reaction mixture was stirred for 5 min at −40 °C, and then 40 mL of ice-cold 5% NaOH was added in one portion, followed by immediate shaking of the reaction flask until the ice melted. Ether was added, and the organic layer was washed with brine and dried over magnesium sulfate. The solvent was evaporated at reduced pressure. Flash chromatography (15% ethyl acetate in hexane) gave 90–105 mg (ca. 65% yield) of a mixture of tetracyclic alcohols as a viscous oil. This mixture was determined by GC analysis to consist of fluorotetracycle **6** (8%), alkene **19** (32%), alkene **20** (25%), and alkenes **21** (two peaks of 9% each).

B. At −90 °C. When the cyclization reaction was run with 200 mg of acetal **5** in the same manner but at a temperature of −90 °C, the product mixture consisted of 90–105 mg (65% yield) of a viscous oil, determined by GC to consist of fluorotetracycle **6** (32%), alkene **19** (4%), alkene **20** (19%), and alkenes **21** (two peaks of 7% each). When the cyclization reaction was conducted at −78 °C for 20 min followed by quenching with NEt_3–CH_3OH (1:1, cooled to −78 °C), similar results were obtained. This alternative quenching procedure may be more suitable for a large-scale cyclization reaction. The crude product mixture was purified by preparative HPLC using a Zorbax ODS reverse-phase column (acetonitrile:diethyl ether:methanol 88:10:2), and the separated fractions were recrystallized.

A sample of the purified major component (32%) from the cyclization reaction at −90 °C was recrystallized from acetonitrile, giving fluorotetracycle **6**, mp 117–120 °C: ^{1}H NMR δ 4.7 (m, 2 H), 4.15 (m, 1 H), 3.7 (m, 1 H), 3.5 (sm, 1 H), 3.1 (s, 1 H), 2.55 and 2.35 (2 m, 2 H), 1.17 (d, 3 H, J = 6 Hz), 1.13 (d, 3 H, J = 6 Hz), 1.03 (d, 3 H, J = 4 Hz), 1.02 (d, 3 H, J = 3 Hz).

A sample of the purified component which comprised 4% of the cyclization reaction mixture obtained at −90 °C was recrystallized from acetonitrile, giving alkene **19**, mp 114–116 °C: ^{1}H NMR δ 5.25 (m, 1 H), 4.7 (m, 2 H), 4.15 (m, 1 H), 3.7 (m, 1 H), 3.5 (br s, 1 H), 3.1 (br s, 1 H), 2.6 and 2.4 (2 m, 2 H), 2.3 (m, 1 H), 1.19 (d, 3 H, J = 6 Hz), 1.15 (d, 3 H, J = 6 Hz), 0.96 (s, 3 H), 0.71 (s, 3 H).

A sample of the purified component which comprised 19% of the cyclization reaction mixture at −90 °C was recrystallized from acetonitrile, giving alkene **20**, mp 93–96 °C: ^{1}H NMR δ 5.45 (m, 1 H), 4.7 (m, 2 H), 4.15 (m, 1 H), 3.7 (m, 1 H), 3.5 (br s, 1 H), 3.0 (d, 1 H, J = 3 Hz), 2.5 (m, 2 H), 2.2 (m, 2 H), 1.19 (d, 3 H, J = 6 Hz), 1.14 (d, 3 H, J = 6 Hz), 1.01 (s, 3 H), 0.89 (s, 3 H).

A sample of the purified component which comprised 7% of the cyclization reaction mixture at −90 °C was recrystallized from methanol, giving alkene **21a**, mp 128–131 °C: ^{1}H NMR δ 4.7 (m, 2 H), 4.15 (m, 1 H), 3.7 (m, 1 H), 3.5 (sm, 1 H), 3.3 (s, 1 H), 2.6–2.3 (3 m, 6 H), 1.17 (d, 3 H, J = 6 Hz), 1.14 (d, 3 H, J = 7 Hz), 1.03 (s, 3 H), 0.86 (s, 3 H). Anal. Calcd for $C_{26}H_{40}O_2$: C, 81.20; H, 10.48. Found: C, 81.05; H, 10.33.

A sample of the purified component which comprised the other 7% of the cyclization reaction mixture at −90 °C was recrystallized from acetonitrile, giving alkene **21b**, mp 114–117 °C: ^{1}H NMR δ 4.7 (m, 2 H), 4.15 (m, 1 H), 3.75 (m, 1 H), 3.5 (br s, 1 H), 3.3 (s, 1 H), 2.65–2.3 (m, 5 H), 1.17 (d, 3 H, J = 6 Hz), 1.14 (d, 3 H, J = 6 Hz), 1.05 (s, 3 H), 0.87 (s, 3 H). Anal. Calcd for $C_{26}H_{40}O_2$: C, 81.20; H, 10.48. Found: C, 80.94; H, 10.40.

Preparation of the Acetates of Alcohols 6, 19, and 20 for X-ray Analysis. To the alcohols dissolved in pyridine were added acetic anhydride and a catalytic amount of 4-(dimethylamino)pyridine. After being allowed to stand at 25 °C for 12 h, the mixtures were added to ether, washed with saturated $CuSO_4$ solution, 1 N H_2SO_4, 5% $NaHCO_3$, and brine, and dried over magnesium sulfate. The solvents were evaporated at reduced pressure, giving white solids.

The acetate of alcohol **6** was recrystallized from acetonitrile, giving colorless prisms, mp 148–149 °C: ^{1}H NMR δ 5.05 (1 H, m), 4.7 (2 H, m), 3.4 (2 H, m), 2.55 and 2.35 (2 H, 2 m), 2.0 (3 H, s), 1.22 (3 H, d, J = 6 Hz), 1.04 (3 H, d, J = 6 Hz), 1.03 (3 H, d, J = 3 Hz), 1.02 (3 H, d, J = 3 Hz).

The acetate of alcohol **19** was recrystallized from acetonitrile, giving colorless prisms, mp 120–121 °C: ^{1}H NMR δ 5.25 (2 H, m), 5.05 (1 H, m), 4.7 (2 H, m), 3.4 (2 H, m), 2.55 and 2.45 (2 H, 2 m), 2.3 (1 H, m), 2.0 (3 H, s), 1.2 (3 H, d, J = 6 Hz), 1.0 (3 H, d, J = 6 Hz), 0.97 (3 H, s), 0.71 (3 H, s).

The acetate of alcohol **20** was recrystallized from ethanol/water, giving colorless prisms, mp 115–117 °C: ^{1}H NMR δ 5.45 (1 H, m), 5.04 (1 H, m), 4.7 (2 H, m), 3.4 (2 H, m), 2.5 (2 H, m), 2.2 (2 H, m), 2.0 (3 H, s), 1.2 (3 H, d, J = 6 Hz), 1.05 (3 H, d, J = 6 Hz), 1.0 (3 H, s), 0.90 (3 H, s).

4β-Hydroxyandrostan-17-one (27). A sample of 32 mg (0.0791 mmol) of fluorotetracycle **6** was added to a dark blue solution of 70 mg of sodium–potassium alloy (Aldrich 78% K, 22% Na) and 120 mg of dicyclohexyl-18-crown-6 in 3 mL of toluene at 23 °C. The mixture was stirred for 2.5 h, and then the reaction was quenched with 1 mL of isopropyl alcohol. Ether and water were added, the organic layer was dried over magnesium sulfate, and the solvents were evaporated at reduced pressure. The residue was purified by flash chromatography (1:8 EtOAc:hexane) to give 28 mg (91% yield) of the defluorinated alkene **22** as a white solid, one spot by TLC, a mixture by GC (79.2:14.0:6.8).

To a solution of 28 mg (0.072 mmol) of alkene **22** in 3 mL of methylene chloride was added 100 mg of Celite, 50 mg of sodium acetate, and 50 mg (0.248 mmol) of pyridinium chlorochromate. The mixture was stirred at 23 °C for 2.5 h, ether was added, and the solution was filtered through a column of Celite. The colorless eluate was washed with 1 N H_2SO_4 and 5% $NaHCO_3$ and dried over magnesium sulfate. Removal of the solvent at reduced pressure gave 23 mg (83% yield) of crude ketone **23** as a white solid, one spot by TLC.

A solution of 23 mg (0.0594 mmol) of crude ketone **23** in 1 mL of methanol, 2 mL of THF, and 0.5 mL of aqueous potassium hydroxide (7.5 N) was heated at 65 °C for 6 h. The solution was cooled, ether was added, and the organic layer was washed with water and brine and dried over magnesium sulfate. Removal of the solvent at reduced pressure gave 16 mg (89% yield) of crude alcohol **24** as a yellow solid.

To a solution of 16 mg (0.0528 mmol) of crude alcohol **24** in 0.5 mL of pyridine were added 6 drops of acetic anhydride and a catalytic amount of 4-(dimethylamino)pyridine. The mixture was stirred at 23 °C for 12 h, and ether was added. The organic layer was washed with saturated copper sulfate solution, 1 N H_2SO_4, and 5% $NaHCO_3$ and dried over magnesium sulfate. Removal of the solvent at reduced pressure gave 18 mg (99% yield) of crude acetate **25** as a light orange solid.

Ozone was passed into a solution of 18 mg (0.0522 mmol) of the crude acetate **25** in 20 mL of methylene chloride, 4 mL of methanol, and 0.2 mL of pyridine at −78 °C until a blue color indicative of excess ozone persisted. Dimethyl sulfide (0.5 mL) was added dropwise, followed by stirring for 1 h as the cold solution warmed to 23 °C. The mixture was washed with 1 N H_2SO_4 and 5% $NaHCO_3$ and dried over magnesium sulfate. Evaporation of the solvent at reduced pressure gave 16 mg of a semisolid colorless residue, 76% pure by GC. Flash chromatography (1:8 EtOAc:hexane) gave 11 mg (63% yield) of acetate **26** as a white crystalline solid, a single spot on TLC, 97.6% pure by GC.

To a solution of 11 mg (0.033 mmol) of acetate **26** in 1 mL of methanol was added 0.1 mL of aqueous potassium hydroxide solution (7.5 N). The solution was stirred at 23 °C for 35 h, and ether was added.

Table I. Bond Lengths (Å) and Bond Angles (deg) for the 149° Compound (Acetate of **6**)

Bond Lengths			
C(1)–C(2)	1.532 (3)	C(1)–C(10)	1.547 (3)
C(2)–C(3)	1.508 (3)	C(3)–C(4)	1.529 (3)
C(4)–C(5)	1.534 (3)	C(4)–O(4)	1.443 (3)
C(5)–C(6)	1.533 (3)	C(5)–C(10)	1.555 (3)
C(6)–C(7)	1.519 (3)	C(7)–C(8)	1.520 (3)
C(8)–C(9)	1.555 (3)	C(8)–C(14)	1.524 (3)
C(8)–F(8)	1.414 (2)	C(9)–C(10)	1.564 (3)
C(9)–C(11)	1.540 (3)	C(10)–C(19)	1.544 (3)
C(11)–C(12)	1.533 (3)	C(12)–C(13)	1.513 (3)
C(13)–C(14)	1.547 (3)	C(13)–C(17)	1.528 (3)
C(13)–C(18)	1.532 (3)	C(14)–C(15)	1.537 (3)
C(15)–C(16)	1.545 (3)	C(16)–C(17)	1.516 (3)
C(17)–C(20)	1.295 (3)	C(20)–C(21)	1.293 (3)
O(4)–C(23)	1.424 (2)	C(22)–C(23)	1.501 (4)
C(23)–C(24)	1.519 (4)	C(24)–C(25)	1.491 (3)
C(25)–C(26)	1.508 (4)	C(25)–O(25)	1.450 (3)
O(25)–C(27)	1.341 (3)	C(27)–O(27)	1.187 (3)
C(27)–C(28)	1.479 (3)		
Bond Angles			
C(2)–C(1)–C(10)	112.6 (2)	C(1)–C(2)–C(3)	112.1 (2)
C(2)–C(3)–C(4)	112.9 (2)	C(3)–C(4)–C(5)	111.9 (2)
C(3)–C(4)–O(4)	111.2 (2)	C(5)–C(4)–O(4)	109.0 (2)
C(4)–C(5)–C(6)	113.6 (2)	C(4)–C(5)–C(10)	114.7 (2)
C(6)–C(5)–C(10)	112.1 (2)	C(5)–C(6)–C(7)	110.9 (2)
C(6)–C(7)–C(8)	112.9 (2)	C(7)–C(8)–C(9)	112.2 (2)
C(7)–C(8)–C(14)	112.8 (2)	C(9)–C(8)–C(14)	108.2 (1)
C(7)–C(8)–F(8)	106.5 (2)	C(9)–C(8)–F(8)	108.9 (2)
C(14)–C(8)–F(8)	108.1 (2)	C(8)–C(9)–C(10)	114.6 (1)
C(8)–C(9)–C(11)	111.8 (2)	C(10)–C(9)–C(11)	114.6 (2)
C(1)–C(10)–C(5)	107.8 (2)	C(1)–C(10)–C(9)	109.0 (1)
C(5)–C(10)–C(9)	106.2 (2)	C(1)–C(10)–C(19)	108.7 (2)
C(5)–C(10)–C(19)	113.4 (2)	C(9)–C(10)–C(19)	111.8 (2)
C(9)–C(11)–C(12)	112.5 (2)	C(11)–C(12)–C(13)	111.2 (2)
C(12)–C(13)–C(14)	108.3 (2)	C(12)–C(13)–C(17)	116.4 (2)
C(14)–C(13)–C(17)	98.6 (2)	C(12)–C(13)–C(18)	110.3 (2)
C(14)–C(13)–C(18)	115.8 (2)	C(17)–C(13)–C(18)	107.3 (2)
C(8)–C(14)–C(13)	115.2 (2)	C(8)–C(14)–C(15)	120.8 (2)
C(13)–C(14)–C(15)	103.6 (2)	C(14)–C(15)–C(16)	102.7 (2)
C(15)–C(16)–C(17)	105.6 (2)	C(13)–C(17)–C(16)	108.0 (2)
C(13)–C(17)–C(20)	124.7 (2)	C(16)–C(17)–C(20)	127.2 (2)
C(17)–C(20)–C(21)	177.0 (3)	C(4)–O(4)–C(23)	114.8 (2)
O(4)–C(23)–C(22)	110.6 (2)	O(4)–C(23)–C(24)	106.0 (2)
C(22)–C(23)–C(24)	113.4 (2)	C(23)–C(24)–C(25)	114.3 (2)
C(24)–C(25)–C(26)	114.8 (2)	C(24)–C(25)–O(25)	106.6 (2)
C(26)–C(25)–O(25)	107.3 (2)	C(25)–O(25)–C(27)	118.4 (2)
O(25)–C(27)–O(27)	122.1 (2)	O(25)–C(27)–C(28)	112.1 (2)
O(27)–C(27)–C(28)	125.8 (2)		

Table II. Bond Lengths (Å) and Bond Angles (deg) for the 117° Compound (Acetate of **20**)

Bond Lengths			
C(1)–C(2)	1.522 (8)	C(1)–C(10)	1.537 (10)
C(2)–C(3)	1.506 (19)	C(3)–C(4)	1.576 (15)
C(4)–C(5)	1.533 (9)	C(4)–O(4)	1.422 (9)
C(5)–C(6)	1.451 (12)	C(5)–C(10)	1.537 (9)
C(6)–C(7)	1.493 (10)	C(7)–C(8)	1.318 (9)
C(8)–C(9)	1.494 (8)	C(8)–C(14)	1.505 (7)
C(9)–C(10)	1.563 (6)	C(9)–C(11)	1.537 (9)
C(10)–C(19)	1.515 (7)	C(11)–C(12)	1.523 (7)
C(12)–C(13)	1.519 (8)	C(13)–C(14)	1.530 (7)
C(13)–C(17)	1.526 (6)	C(13)–C(18)	1.546 (8)
C(14)–C(15)	1.534 (10)	C(15)–C(16)	1.546 (10)
C(16)–C(17)	1.521 (9)	C(17)–C(20)	1.285 (8)
C(20)–C(21)	1.308 (9)	O(4)–C(23)	1.441 (7)
C(22)–C(23)	1.527 (12)	C(23)–C(24)	1.494 (10)
C(24)–C(25)	1.531 (9)	C(25)–C(26)	1.506 (9)
C(25)–O(25)	1.428 (8)	O(25)–C(27)	1.317 (16)
C(27)–O(27)	1.209 (17)	C(27)–C(28)	1.510 (13)
Bond Angles			
C(2)–C(1)–C(10)	113.6 (7)	C(1)–C(2)–C(3)	108.9 (8)
C(2)–C(3)–C(4)	111.8 (7)	C(3)–C(4)–C(5)	110.8 (7)
C(3)–C(4)–O(4)	112.1 (6)	C(5)–C(4)–O(4)	109.6 (7)
C(4)–C(5)–C(6)	114.5 (7)	C(4)–C(5)–C(10)	114.9 (6)
C(6)–C(5)–C(10)	112.3 (6)	C(5)–C(6)–C(7)	115.0 (8)
C(6)–C(7)–C(8)	122.7 (7)	C(7)–C(8)–C(9)	122.0 (5)
C(7)–C(8)–C(14)	122.9 (6)	C(9)–C(8)–C(14)	114.7 (5)
C(8)–C(9)–C(10)	113.5 (5)	C(8)–C(9)–C(11)	114.4 (4)
C(10)–C(9)–C(11)	112.4 (4)	C(1)–C(10)–C(5)	110.1 (6)
C(1)–C(10)–C(9)	109.4 (5)	C(5)–C(10)–C(9)	107.4 (4)
C(1)–C(10)–C(19)	108.9 (5)	C(5)–C(10)–C(19)	110.5 (5)
C(9)–C(10)–C(19)	110.5 (4)	C(9)–C(11)–C(12)	115.3 (5)
C(11)–C(12)–C(13)	109.6 (5)	C(12)–C(13)–C(14)	108.4 (4)
C(12)–C(13)–C(17)	116.1 (4)	C(14)–C(13)–C(17)	101.1 (4)
C(12)–C(13)–C(18)	111.1 (4)	C(14)–C(13)–C(18)	112.2 (5)
C(17)–C(13)–C(18)	107.7 (4)	C(8)–C(14)–C(13)	112.7 (4)
C(8)–C(14)–C(15)	122.4 (6)	C(13)–C(14)–C(15)	103.5 (5)
C(14)–C(15)–C(16)	103.3 (6)	C(15)–C(16)–C(17)	105.2 (5)
C(13)–C(17)–C(16)	108.2 (4)	C(13)–C(17)–C(20)	124.8 (5)
C(16)–C(17)–C(20)	127.0 (5)	C(17)–C(20)–C(21)	177.6 (6)
C(4)–O(4)–C(23)	116.2 (5)	O(4)–C(23)–C(22)	109.7 (6)
O(4)–C(23)–C(24)	107.4 (5)	C(22)–C(23)–C(24)	111.0 (8)
C(23)–C(24)–C(25)	114.7 (7)	C(24)–C(25)–C(26)	111.0 (6)
C(24)–C(25)–O(25)	107.5 (5)	C(26)–C(25)–O(25)	108.8 (5)
C(25)–O(25)–C(27)	116.8 (7)	O(25)–C(27)–O(27)	123.7 (8)
O(25)–C(27)–C(28)	114.2 (11)	O(27)–C(27)–C(28)	122.0 (12)

Table III. Bond Lengths (Å) and Bond Angles (deg) for the 121° Compound (Acetate of **19**)

Bond Lengths			
C(1)–C(2)	1.523 (5)	C(1)–C(10)	1.546 (4)
C(2)–C(3)	1.511 (6)	C(3)–C(4)	1.512 (5)
C(4)–C(5)	1.531 (4)	C(4)–O(4)	1.441 (3)
C(5)–C(6)	1.521 (4)	C(5)–C(10)	1.542 (4)
C(6)–C(7)	1.492 (4)	C(7)–C(8)	1.333 (4)
C(8)–C(9)	1.525 (3)	C(8)–C(14)	1.510 (3)
C(9)–C(10)	1.552 (3)	C(9)–C(11)	1.545 (4)
C(10)–C(19)	1.535 (4)	C(11)–C(12)	1.513 (4)
C(12)–C(13)	1.538 (4)	C(13)–C(14)	1.542 (4)
C(13)–C(17)	1.526 (3)	C(13)–C(18)	1.517 (4)
C(14)–C(15)	1.553 (4)	C(15)–C(16)	1.526 (4)
C(16)–C(17)	1.516 (4)	C(17)–C(20)	1.306 (5)
C(20)–C(21)	1.295 (7)	O(4)–C(23)	1.434 (3)
C(22)–C(23)	1.500 (5)	C(23)–C(24)	1.529 (4)
C(24)–C(25)	1.498 (4)	C(25)–C(26)	1.505 (5)
C(25)–O(26)	1.462 (3)	O(26)–C(27)	1.342 (4)
C(27)–O(27)	1.200 (5)	C(27)–C(28)	1.484 (7)
Bond Angles			
C(2)–C(1)–C(10)	113.5 (3)	C(1)–C(2)–C(3)	110.9 (3)
C(2)–C(3)–C(4)	111.4 (3)	C(3)–C(4)–C(5)	111.4 (3)
C(3)–C(4)–O(4)	112.4 (2)	C(5)–C(4)–O(4)	108.5 (3)
C(4)–C(5)–C(6)	112.7 (2)	C(4)–C(5)–C(10)	116.5 (2)
C(6)–C(5)–C(10)	110.8 (2)	C(5)–C(6)–C(7)	111.5 (2)
C(6)–C(7)–C(8)	125.0 (2)	C(7)–C(8)–C(9)	121.2 (2)
C(7)–C(8)–C(14)	120.5 (2)	C(9)–C(8)–C(14)	118.2 (2)
C(8)–C(9)–C(10)	113.1 (2)	C(8)–C(9)–C(11)	111.0 (2)
C(10)–C(9)–C(11)	113.0 (2)	C(1)–C(10)–C(5)	108.2 (2)
C(1)–C(10)–C(9)	109.0 (2)	C(5)–C(10)–C(9)	107.7 (2)
C(1)–C(10)–C(19)	109.7 (2)	C(5)–C(10)–C(19)	111.3 (2)
C(9)–C(10)–C(19)	110.8 (2)	C(9)–C(11)–C(12)	112.0 (2)
C(11)–C(12)–C(13)	112.8 (2)	C(12)–C(13)–C(14)	109.1 (2)
C(12)–C(13)–C(17)	108.3 (2)	C(14)–C(13)–C(17)	102.8 (2)
C(12)–C(13)–C(18)	111.8 (2)	C(14)–C(13)–C(18)	111.9 (2)
C(17)–C(13)–C(18)	112.5 (2)	C(8)–C(14)–C(13)	115.0 (2)
C(8)–C(14)–C(15)	115.5 (2)	C(13)–C(14)–C(15)	103.3 (2)
C(14)–C(15)–C(16)	104.1 (2)	C(15)–C(16)–C(17)	104.8 (2)
C(13)–C(17)–C(16)	109.8 (2)	C(13)–C(17)–C(20)	122.8 (2)
C(16)–C(17)–C(20)	127.3 (2)	C(17)–C(20)–C(21)	175.5 (3)
C(4)–O(4)–C(23)	116.7 (2)	O(4)–C(23)–C(22)	113.3 (2)
O(4)–C(23)–C(24)	105.1 (2)	C(22)–C(23)–C(24)	112.1 (3)
C(23)–C(24)–C(25)	116.4 (3)	C(24)–C(25)–C(26)	113.3 (3)
C(24)–C(25)–O(26)	105.6 (2)	C(26)–C(25)–O(26)	109.1 (2)
C(25)–O(26)–C(27)	117.4 (3)	O(26)–C(27)–O(27)	123.8 (4)
O(26)–C(27)–C(28)	110.4 (4)	O(27)–C(27)–C(28)	125.7 (4)

The organic layer was washed with water and dried over magnesium sulfate. Evaporation of the solvent at reduced pressure gave 8 mg (83% yield) of the hydroxy ketone **27** as a white solid, mp 171–174 °C (with phase transitions at 150 and 160 °C), 97.6% pure by GC, and one spot by TLC. The compound was identical on TLC, GC (by coinjection), NMR, IR, and HRMS with an authentic sample[9] of 4β-hydroxyandrostan-17-one and with a sample of compound **27a**, discussed below.

2-[8-Fluoro-4,12-dimethyl-18-(trimethylsilyl)octadeca-4(*E*),8(*Z*),12(*E*)-trien-16-ynyl]-4(*S*),6(*S*)-dimethyl-1,3-dioxane (5a). To a suspension of 2.6 g (7.6 mmol) of (methoxymethyl)triphenylphosphonium chloride in 25 mL of THF at −78 °C was added dropwise 5.0 mL (3.99 mmol) of *sec*-butyllithium (1.3 M in cyclohexane). The red solution was stirred at −78 °C for 15 min, allowed to warm to −20 °C for 1 h, and then cooled to −78 °C. To this phosphorane solution was added slowly a solution of 1.5 g (3.99 mmol) of an aldehyde corresponding to **16**,[14] but containing the C-18 trimethylsilyl group, in 10 mL of THF. The mixture was stirred at −78 °C for 30 min and slowly warmed to 0 °C for 3 h, and then the reaction was quenched with saturated ammonium chloride solution. Ether was added, and the organic layer was washed with water and brine and dried over magnesium sulfate. The solvent was evaporated at reduced pressure, and hexane was added to precipitate the phosphine oxide. Filtration through a column of silica gel gave 1.53 g of crude enol ether as a colorless oil.

To a solution of 1.53 g of the enol ether in 15 mL of benzene were added 1.0 g (9.62 mmol) of (*S*,*S*)-2,4-pentanediol and 50 mg of *p*-toluenesulfonic acid. This solution was heated at 75 °C for 30 min, cooled, washed with 5% $NaHCO_3$, and dried over magnesium sulfate. Evaporation of the solvent at reduced pressure followed by flash chromatography (1:30 EtOAc:hexane) gave 1.38 g (73% yield) of acetal **5a** as a colorless oil, 99% pure by GC: IR ($CHCl_3$) 1700, 1140, 850 cm^{-1}; ^1H NMR δ 5.2 (br s, 1 H), 5.1 (br s, 1 H), 4.83 (t, 1 H, *J* = 5 Hz), 4.44 (dt, 1 H, *J* = 7, 38 Hz), 4.28 (q, 1 H, *J* = 7 Hz), 3.93 (m, 1 H), 2.2–1.4 (m, 22 H), 1.60 (s, 3 H), 1.58 (s, 3 H), 1.34 (d, 3 H, *J* = 7 Hz), 1.19 (d, 3 H, *J* = 7 Hz), 0.08 (s, 9 H); HRMS calcd for $C_{29}H_{49}FSiO_2$, 476.3473, found, 476.3568. Anal. Calcd for $C_{29}H_{49}FSiO_2$: C, 73.11; H, 10.29. Found: C, 71.26; H, 9.96.

Cyclization of Acetal 5a. To a solution of 168 mg (0.35 mmol) of acetal **5a** was added 10 mL of hexamethyldisiloxane (freshly distilled). The mixture was cooled to −78 °C, and 1 mL of stannic chloride (1 M in methylene chloride) in 5 mL of methylene chloride was added dropwise. The mixture was stirred for 10 min at −78 °C, and then the reaction was quenched with 2 mL of a solution of triethylamine in methanol (1:4). The resulting mixture was slowly warmed to 23 °C, ether was added, and the organic layer was washed with water and brine and dried over magnesium sulfate. Filtration through a column of Florisil followed by flash chromatography (1:10 EtOAc:hexane) gave 109 mg (79% yield) of a mixture. GC analysis indicated that the mixture consisted of fluorotetracycle **6a** (38%) and a mixture of alkenes **19a**, **20a**, and **21a** (32%). Recrystallization gave pure **6a** as a colorless solid, mp 93–95 °C, 100% pure by GC: IR ($CHCl_3$) 3400, 1950, 1450, 1120 cm^{-1}; ^1H NMR δ 4.65 (m, 2 H), 4.15 (m, 1 H), 3.7 (m, 1 H), 3.5 (m, 1 H), 3.1 (br s, 1 H), 2.6–0.8 (m, 23 H), 1.17 (d, 3 H, *J* = 6 Hz), 1.14 (d, 3 H, *J* = 6 Hz), 1.04 (d, 3 H, *J* = 4 Hz), 1.03 (d, 3 H, *J* = 2.8 Hz); HRMS calcd for $C_{26}H_{41}FO_2$, 404.3090, found, 404.3096.

4β-Hydroxyandrostan-17-one (27a). A sample of 32 mg (0.0791 mmol) of fluorotetracycle **6a** was submitted to the series of reactions described above for the conversion of **6** to **27** giving 4.9 mg (21% overall yield from **6a**) of hydroxy ketone **27a** as a white solid, mp 153–161 °C (with phase transitions at 140 °C), GC (210 °C, 8.78 min, 98%), $[\alpha]^{26}_D$ +85.7° (*c* = 0.49, $CHCl_3$). The compound was identical by TLC, GC, NMR, and HRMS with an authentic sample[9] of 4β-hydroxyandrostan-17-one, mp 161–165 °C (with phase transitions at 140 °C), GC (210 °C, 8.78 min, 100%), $[\alpha]^{25}_D$ +93° (*c* = 0.49, $CHCl_3$): ^1H NMR δ 3.8 (br s, 1 H), 2.45 (dd, 1 H), 2.06 (dd, 1 H), 1.06 (s, 3 H), 0.86 (s, 3 H). Coinjection of a sample of **27a** mixed with the authentic sample gave one peak by GC (210 °C, 8.83 min, 99%).

Crystallographic Data. The bond lengths and angles obtained in the X-ray crystallographic determinations are given in Tables I, II, and III. Table I refers to the 149° compound (acetate of **6**), Figure 1; Table II to the 117° compound (acetate of **20**), Figure 3; and Table III to the 121° compound (acetate of **19**), Figure 2.

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Supplementary Material Available: Additional X-ray crystallographic structure determination information in tables of crystal data, data collection method, and solution and refinement data; Table IV, atomic coordinates including equivalent isotropic displacement coefficients; Table V, anisotropic displacement coefficients; and Table VI, H-atom coordinates including isotropic displacement coefficients (18 pages). Ordering information is given on any current masthead page.

The Fluorine Atom as a Cation-Stabilizing Auxiliary in Biomimetic Polyene Cyclizations. 3. Use To Effect Regiospecific Control[1]

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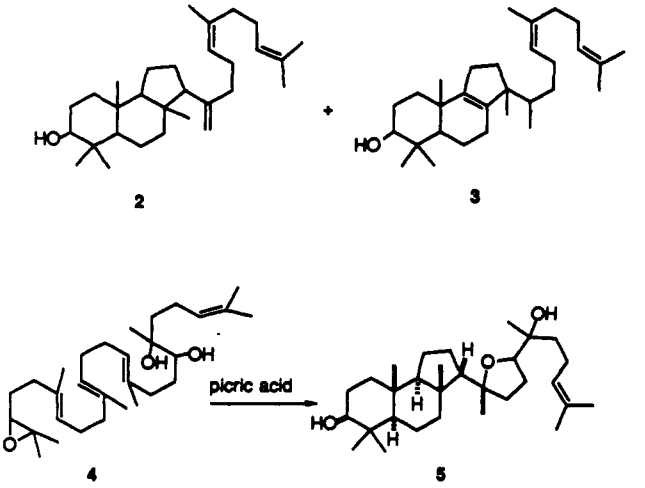
Abstract: The fluorine atom substituted at the *pro*-C-13 position (steroid numbering) has been shown to be an effective cation-stabilizing (C-S) auxiliary in the acid-catalyzed cyclization of the polyene substrates **6**, **7**, and **8**. The preparation of **6**, **7**, and **8** employed the known fragmentation of cyclic epoxy hydrazones to construct the methylacetylenic and *gem*-dimethyl groups. The fluoroolefinic ketal Claisen and cyclopropylcarbinol rearrangements established the 3(*E*) and 11(*E*) trisubstituted alkenes. Stereoselective routes were developed for the 7(*Z*) (found in substrates **6** and **7**) and 7(*E*) tetrasubstituted fluoroolefinic bond in **8**. The Wittig rearrangement of stannyl ether **21** provided the *Z*-stereoisomer **26** predominately (7:3, 85% yield), while the Ireland enolate Claisen rearrangement of acetate **20** produced predominately the *E*-stereoisomer **25** (4:1, 69% yield). Cyclopentenols **6** and **8** possessed the methylacetylene terminator group, while in **7** this group was converted to the propargylsilane terminator. Cyclization with stannic chloride or trifluoroacetic acid gave high yields of pentacyclic compounds. In all cases, the fluorine atom controlled the regiochemistry of the cyclization, giving exclusively products with a 6-membered ring C. Thus, cyclopentenol **8** afforded pentacycle **55** in 80% yield, while cyclopentenol **6** gave pentacycle **53** in 56% yield, retaining the fluorine atom at C-13 and possessing the anti-trans-anti-trans-anti-trans backbone, with a total of seven chiral centers, as shown by X-ray crystallographic analysis. The cyclopentenol **7**, similarly, was cyclized to give what is almost certainly the tetracycle **56**. The regiocontrol over the ring C closure effected by the fluorine atom acting as a C-S auxiliary may be regarded as inferential documentation of the proposed point-charge stabilization mechanism of the enzymatic process by which squalene oxide similarly undergoes an anti-Markovnikov closure of ring C. Application of this methodology to the synthesis of the pentacyclic triterpenoid β-amyrin is described in the next paper in this series.

The enzymatic cyclizations of 2,3-oxidosqualene (**1**), leading eventually to such ubiquitous products as lanosterol (the precursor of steroids and ergosterol), cycloartenol, tetracyclic triterpenoids, and pentacyclic triterpenoids, evidently proceed via cationic processes which follow established principles of cationic behavior,[2] with one notable exception being the closure of ring C, which proceeds in an anti-Markovnikov sense.

Thus, in the aforementioned enzyme-catalyzed cases, as shown in Figure 1, the ring closures of the tertiary bicyclic cation A proceed[3] so as to give the tricyclic secondary cation B with the generation of a six-membered ring and the A/B/C ring configuration either trans-syn-trans or trans-anti-trans. According to Markovnikov's rule, it would be expected, however, that cation A would be converted to the more stable tertiary cation C, resulting in formation of a five-membered ring. Indeed, this latter process occurs in the nonenzymatic cyclization of oxidosqualene. Thus, van Tamelen and co-workers[4] found that the nonenzymatic cyclization of **1** gave only the tricyclic compounds **2** and **3** rather than the steroid or triterpenoid ring structures that are produced in the enzyme-catalyzed reactions. This intrinsic tendency of



† The X-ray crystallographic analyses reported herein were performed by F.S.T. and R.K.K. at the Department of Chemistry, Rensselaer Polytechnic Institute, Troy, NY 12180.

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