superimposable to that of **3a** prepared in this study. The yield of **3a** was 20% by GLC.

DCB-Photosensitized (*E*)/(*Z*) Isomerization of 11b. A solution of **3b** (25 mg, 0.22 mmol) and DCA (12 mg, 0.05 mmol) in acetonitrile (10 mL) was irradiated until 80% of **3b** was consumed. The photolyzed mixture was worked up as described above, and **11b** produced was isolated by preparative GLC (column D, 100 °C). The ^{1}H NMR spectrum of **11b** thus obtained indicated that the ratio of **12a**:**12b** in it was 71:29.

An acetonitrile solution (2 mL) containing **11b** (7 mg, 0.06 mmol) obtained above and DCB (2 mg, 0.016 mmol) was irradiated until ca. 20% of **11b** was consumed. The photolysate was subjected to preparative GLC to recover the unreacted **11b**. The ratio of **12a**:**12b** in the recovered **11b** had decreased to 55:45.

DCB-Sensitized Photolysis of 14e. A solution of **14e** (9 mg, 0.036 mmol) and DCB (12 mg, 0.094 mmol) in acetonitrile (1 mL) was irradiated to examine the possible formation of **15b** via secondary photolysis of **14e**. The diene **14e** was consumed under the photolysis conditions, but no volatile product was detected by GLC (column A, 170 °C).

Acknowledgment. We thank Professors K. Yagi and F. Morita for the use of their instrument for the measurement of fluorescence spectra.

The Fluorine Atom as a Cation-Stabilizing Auxiliary in Biomimetic Polyene Cyclizations. 1. Background and Exploratory Experiments[1]

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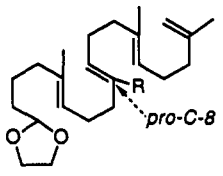
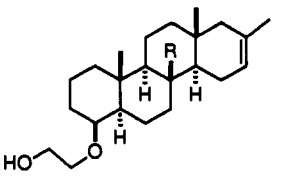
Abstract: With the aim of testing the fluorine atom as a potential cation-stabilizing (C-S) auxiliary for enhancing polyene cyclizations, new methodology has been developed for the stereoselective synthesis of polyenic cyclization substrates in which the vinyl H of an *E*-trisubstituted olefinic bond is replaced by F. Thus the substrate **5** was produced, as suggested by formulas **13**–**24**, the Claisen rearrangements **15** → **17** and **18** → **19** being the key steps for producing the vinyl fluoride moiety. $SnCl_4$-catalyzed cyclization of substrate **5** gave a relatively high yield of a complex mixture of tetracyclic materials indicating that, in principle, the fluorine atom can serve effectively as a C-S auxiliary. The major product of the cyclization was proved by X-ray crystallography to be **25**, resulting from dehydrofluorination of compound **6**. A fluorine-containing substance was isolated in low yield, and it most likely was the compound **6**, because when treated with the Ohsawa–Oishi reagent (Na/K, crown ether, toluene) it was converted into a product which appeared to be identical with compound **2**. That this reduction is synthetically useful and does, indeed, proceed stereoselectively with retention of configuration has been confirmed unequivocally in another example described in the next paper of this series.

For more than 20 years, efforts to simulate the biological conversion of squalene to tetracyclic triterpenoids such as lanosterol have been abortive. At best, poor yields of tetracyclic products were obtained in model systems. Thus, the aim to effect such transformations efficiently, without the agency of the enzyme, was generally regarded as futile. Recently a new concept for improving such cyclizations was disclosed.[1a] This principle employs a polyene substrate with a cation-stabilizing (C-S) substituent appended to the carbon that is likely to become positively charged in the transition state, e.g., at the bicyclic stage, thus lowering the activation energy of the process. In the seminal work, the cyclization of the tetraenic acetal substrate **1**[2] was compared with that of the modified form **3**, in which the hydrogen atom at



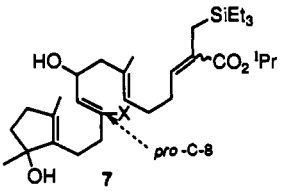


1 R = H
3 R = -CH=CMe$_2$
5 R = F

2 R = H
4 R = -CH=CMe$_2$
6 R = F

pro-C-8 (steroid numbering) was replaced by the cation-stabilizing isobutenyl group. The yields of tetracyclic products, consisting mainly of substances **2** and **4**, respectively, along with some isomers also having the all-trans configuration of the ring fusions, were 30% for the cyclization of **1**[2] and 77% for the cyclization of **3**.[1a] Thus, the effect of the C-S auxiliary at *pro*-C-8 was to more than double the yield of the tetracyclic product.

An even more dramatic effect of the C-S auxiliary was observed in the following case. The rate of TFA-catalyzed cyclization of the substrate **7** (X = H) is strongly attenuated by the OH at *pro*-C-11; therefore, side reactions become a significant factor,



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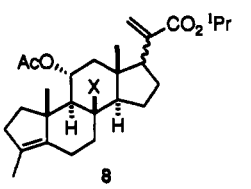

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and the optimized yield of product **8** (X = H) was only 20% after a reaction time of 24 h. In striking contrast, the cyclization of the substrate **7** (X = CH=CMe$_2$), having the isobutenyl C-S auxiliary at *pro*-C-8, was complete in about 1 min, and the product **8** (X = CH=CMe$_2$) was isolated in 80–83% yield.[1b]

† 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. 4 on cation-stabilizing auxiliaries in polyene cyclizations. For the first three 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.

(2) Johnson, W. S.; Wiedhaup, K.; Brady, S. F.; Olson, G. L. *J. Am. Chem. Soc.* **1968**, *90*, 5277–5279. Johnson, W. S.; Wiedhaup, K.; Brady, S. F.; Olson, G. L. *J. Am. Chem. Soc.* **1974**, *96*, 3979–3984.

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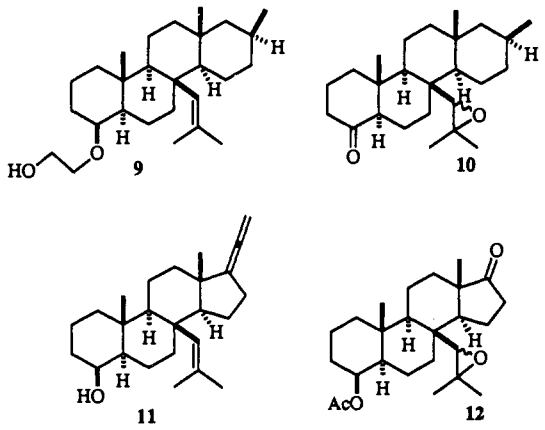
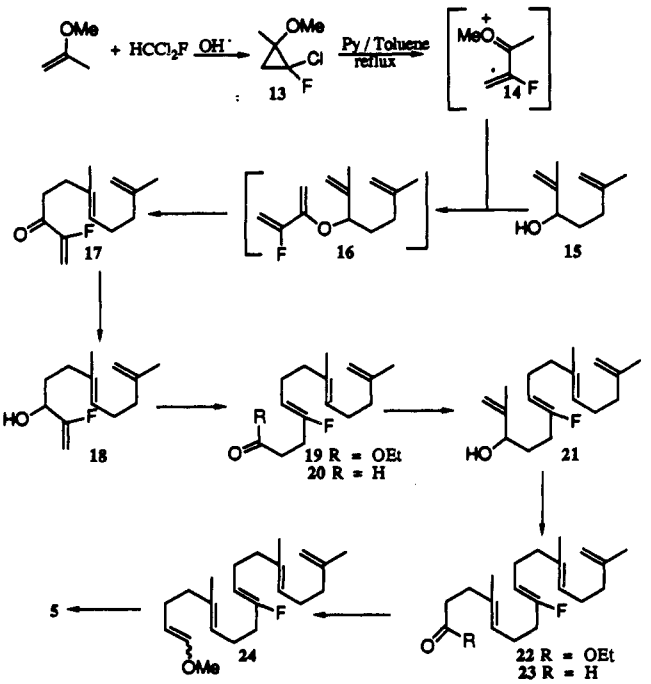
In order for the C-S auxiliary concept to be useful as a practical tool in synthesis, three requirements must be satisfied: (1) the cyclization substrate containing the C-S auxiliary should be easy to synthesize, (2) the auxiliary must perform its function satisfactorily as a C-S stabilizer, and (3) it should be possible to remove the auxiliary readily. Up to the present, the isobutenyl group appears to have met all but the third requirement. The failure of attempts to degrade the isobutenyl group are clearly associated with the steric 1,3-diaxial crowding of its olefinic bond by the angular methyl group at C-10 and C-13, as shown in the X-ray crystallographic plot of the benzoate of **4**.[1a] Thus, on catalytic hydrogenation of compound **4**, only the olefinic bond in ring D was reduced to give a single isomer, almost certainly having the configuration shown in formula **9**.[3] In an attempt to effect oxidative cleavage of the olefinic bond with the aim of producing the 8-aldehydo compound which could then be decarbonylated, compound **9** was converted to the benzoate and treated with excess ozone. The major product isolated was shown by NMR and mass



spectroscopy to be the keto epoxide **10**. Precedents are available for the reaction of ozone with hindered olefins to give epoxides[4] and with ethers of secondary alcohols to give ketones.[5] It is noteworthy that the acetate of **9** failed to react with peracid or ruthenium tetraoxide and periodate. In a related study, the tetracyclic allenic compound **11**,[1c] upon acetylation followed by treatment with ozone, gave a 1:1 mixture of diastereomeric epoxides **12** in 55% yield.[6] This epoxide mixture was inert to strong bases; on the other hand, treatment with boron trifluoride etherate or trifluoromethanesulfonic acid yielded products which appeared to result from cationic rearrangements to give a seven-membered ring C. So far, all attempts to degrade the isobutenyl group in a useful manner have been unsuccessful.

The fluorine atom was considered to be a promising candidate as a C-S auxiliary because the vinyl fluoride function has been shown to participate as a very good terminator of polyene cyclizations.[7] The Boswell–Ripka[8] precedent is seminal to this type of cation stabilization. It was decided to test the concept first by preparing the fluoro substrate **5** which, on cyclization, would offer a direct comparison with the known cyclizations **1** → **2** and **3** → **4** (see above). The present paper consists of a report on the synthesis and cyclization of the substrate **5**.

Attention is now turned to the problem of synthesizing the fluoro substrate **5**. There are no known general methods for the stereoselective synthesis of trisubstituted vinyl fluorides of the sort found in the polyene **5**. One of our plans was to try to apply a version of the olefinic ketal Claisen reaction.[9] In this case, the fluoro olefinic ketal, such as $CH_2{=}CFC(OMe)_2CH_3$ or the corresponding dienol ether, was required. Such compounds have been described by Schlosser et al.,[10] who obtained them via the fragmentation of the cyclopropane derivative **13** by heating **13** with pyridine in toluene to give the protonated form **14** of a dienol ether, the methoxy group of which can readily be exchanged by an alkoxy group simply by introducing the corresponding alcohol into the reaction mixture. When the dienol **15**[11] was used for



the exchange reaction, the enol ether **16** thus produced in situ proved to be the substance required for the Claisen rearrangement, which, as it turned out, proceeded smoothly under the reaction conditions for fragmentation of compound **13**, giving the fluoro enone **17**. This one-pot process proceeded in 71% yield.[12] The fluoro allylic alcohol **18**, obtained in 93% yield by reduction of the enone **17** with DIBAH, was submitted to the orthoacetate Claisen reaction,[13] giving the trienic ester **19** in 76% yield. The corresponding aldehyde **20**, formed in 94% yield by DIBAH reduction of the ester **19**, was treated with a large excess of the Grignard reagent from 2-bromopropene, and the resulting allylic alcohol **21** (isolated in 78% yield) was submitted to the orthoacetate Claisen reaction.[13] The resulting tetraenic ester **22**, isolated in 75% yield, was reduced with DIBAH, giving aldehyde **23** in 82% yield. This aldehyde, on reaction with the Wittig reagent from (methoxymethyl)triphenylphosphonium chloride and *sec*-butyllithium, yielded the enol ether **24**, which, without purification, was treated with ethylene glycol and a catalytic amount of *p*-toluenesulfonic acid to give the tetraenic acetal **5** in 71% yield.

For comparative purposes, the cyclization of acetal **5** was carried out under essentially the same conditions, i.e., with $SnCl_4$ in pentane at 0 °C, that were used previously for the cyclization of acetals **1** and **3**. Under these conditions, the reaction was rapid and the acetal **5** disappeared completely in less than 1 min. Flash

(3) The preparation of compound **9** and its further reactions were performed by Soan Cheng, unpublished observations at Stanford University.
(4) Bailey, P. S. *Ozonation in Organic Chemistry*; Academic Press: New York, 1982; Vol. II, Chapter IX.
(5) Bailey, P. S.; Hwang, H. H.; Chiang, C.-Y. *J. Org. Chem.* **1985**, *50*, 231–234.
(6) This work and the further reactions of epoxide **12** were performed by Daniel Guay, unpublished observations at Stanford University.
(7) (a) Johnson, W. S.; Daub, G. W.; Lyle, T. A.; Niwa, M. *J. Am. Chem. Soc.* **1980**, *102*, 7800–7802. (b) Johnson, W. S.; Lyle, T. A.; Daub, G. W. *J. Org. Chem.* **1982**, *47*, 161–163.
(8) See footnote 7 of ref 7a.
(9) Johnson, W. S.; Brocksom, T. J.; Loew, P.; Rich, D. H.; Werthemann, L.; Arnold, R. A.; Li, T.-t.; Faulkner, D. J. *J. Am. Chem. Soc.* **1970**, *92*, 4463–4464.
(10) Bessière, Y.; Savary, D. N.-H.; Schlosser, M. *Helv. Chim. Acta* **1977**, *173*, 1739–1746.
(11) The dienol **15** was readily prepared by the olefinic ketal Claisen reaction (see ref 9) of the ketal $H_2C{=}CCH_3C(OMe)_2CH_3$ with methallyl alcohol, followed by sodium borohydride reduction of the α,β-unsaturated ketone.
(12) An improvement in the yield by a modified two-step procedure is described in the next paper of this series (ref 17).
(13) 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.

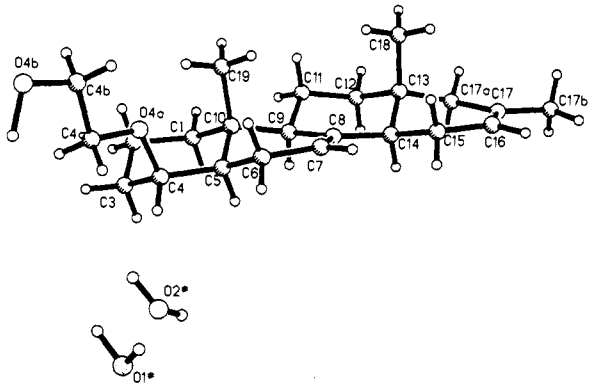
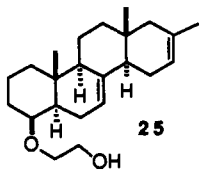


Figure 1. Diagram of the all-trans tetracyclic diene **25**.

chromatography of the crude product gave three fractions representing a total of 86% weight yield of material, which was estimated on the basis of its physical properties, particularly its GC behavior, to consist mainly of a complex mixture of tetracyclic products. A pure specimen, mp 131–133 °C, of the major component of the mixture was isolated by crystallization of the fastest-moving fraction (1) of the chromatogram. The structure and relative configuration of this compound was shown to be the all-trans tetracyclic diene **25** by X-ray crystallographic analysis.



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A plot of the structure is shown in Figure 1. The next most abundant product, mp 103–105 °C, was similarly isolated from fraction 3 of the chromatogram. This compound is most likely the 4α (equatorial) epimer of the tetracyclic diene **25**, as expected by precedent[1a,2] and indicated by its higher chromatographic retention times as well as by its ^{1}H NMR spectrum revealing, in particular, a characteristic signal for an axial proton at C-4.

Since it is known that a Lewis acid catalyzes facile dehydrofluorination of bridgehead fluorine-substituted fused ring systems,[14] it may be concluded that the tetracyclic dienes **25** and 4-*epi*-**25** are formed by dehydrofluorination of the expected primary cyclization product **6** and 4-*epi*-**6**, respectively. A compound, isolated in about 90% GC purity by crystallization of fraction 2 of the chromatogram, was shown by NMR, mass spectroscopy, and reaction behavior (see below) to be, without much doubt, the tetracyclic fluoro compound **6**. The proportion of this compound that could be detected by GC analysis varied from run to run, and usually it was found in only trace amounts, presumably because of its facile conversion into **25**.[15] Treatment of alkyl fluorides with Na–K alloy and crown ether in toluene has been shown to effect replacement of fluorine by hydrogen.[16] This procedure was employed in a pilot experiment with a small sample of what was presumed to be the tetracyclic fluoro compound **6**. The product was nearly homogeneous by GC, and coinjection experiments with authentic **2** indicated that the two materials were identical. This observation provides suggestive evidence that the substrate has the structure **6** and that the Ohsawa–Oishi reagent[16] effects replacement of a quaternary fluorine atom by hydrogen stereoselectively with retention of configuration, a conclusion which has been confirmed unequivocally by experiments in a related system, described in the next paper of this series.[17]

Although the complexity of the product mixture[15] from the cyclization of substrate **5** renders this case useless for practical synthesis, the study has served to indicate that the appropriate use of the fluorine atom as a C-S auxiliary has real promise for enhancing the formation of polycyclic products from which the C-S auxiliary can be removed. Indeed, the present study has inspired the work that is described in the following three papers of this series, in which it is shown that appropriate modification of the initiator and terminator functions of the cyclization substrates has made it possible to perform reactions under very mild conditions resulting in high-yield cyclizations that are regio- and diastereoselective and are therefore practical for the synthesis of complex polycyclic molecules, e.g., β-amyrin.

Experimental Section

General Considerations. The prefix *dl* has been omitted from the names of the racemic compounds mentioned in this section. Unless otherwise specified, all reaction procedures were carried out under an atmosphere of nitrogen or argon. Deuteriochloroform was used as the solvent for NMR samples. For gas chromatography (GC), a 50-m SE-54 capillary column with hydrogen carrier gas was used. Flash chromatography was performed using E. Merck silica gel 60 (230–400 mesh).

2-Fluoro-6,10-dimethylundeca-1,6(*E*),10-trien-3-one (17). To a solution of 8.6 g (61.4 mmol) of 2,6-dimethylhepta-1,6-dien-3-ol (**15**)[11] in 25 mL of toluene at 23 °C were added 11.0 g (79.7 mmol) of 1-chloro-1-fluoro-2-methyl-2-methoxycyclopropane (**13**)[10] and 5.0 g (63.3 mmol) of pyridine. This mixture was heated under reflux (bath temperature 115 °C) for 10 h and then cooled and diluted with hexane. The precipitated pyridinium hydrochloride was removed by filtration and washed with hexane, and the combined organic solutions were concentrated under reduced pressure. The pale yellow residue was submitted to flash chromatography using 200 g of adsorbant and eluting with 1:30 EtOAc:hexane to give 9.32 g (71% yield) of the product as a colorless oil: IR ($CHCl_3$) 1710, 1645, 900 cm^{-1}; ^{1}H NMR (400 MHz) δ 5.55 (dd, 1 H, J = 3.4, 45.3 Hz), 5.2 (dd, 1 H, J = 3.4, 14.3 Hz), 5.15 (t, 1 H, J = 3 Hz), 4.7 (br s, 1 H), 4.66 (br s, 1 H), 2.73 (dt, 2 H, J = 2, 7 Hz), 2.3 (t, 2 H, J = 7 Hz), 2.12 (q, 2 H, J = 7 Hz), 2.0 (t, 2 H, J = 7 Hz), 1.71 (s, 3 H), 1.62 (s, 3 H); ^{13}C NMR (100 MHz) δ 194.1 (d, J = 32 Hz), 159.8 (d, J = 267 Hz), 145.62, 133.29, 125.12, 109.93, 100.3 (d, J = 16.5 Hz), 37.63, 36.86, 33.08, 26.15, 22.46, 16.1. Anal. Calcd for $C_{13}H_{19}FO$: C, 74.28; H, 9.05. Found: C, 74.70; H, 8.69.

2-Fluoro-6,10-dimethylundeca-1,6(*E*),10-trien-3-ol (18). To a solution of 6.5 g (31 mmol) of the fluoro enone **17** in 150 mL of methylene chloride at −78 °C was added 40 mL of diisobutylaluminum hydride (1 M in hexane) via syringe over a period of 15 min. The reaction mixture was stirred at −78 °C for 1 h, and the reaction was quenched by the careful addition of 2 mL of methanol. The reaction mixture was then warmed to 23 °C, and 100 mL of water followed by 40 mL of 1 M sulfuric acid was added. The aqueous layer was extracted with methylene chloride, and the combined organic layers were washed with brine and dried over magnesium sulfate. Removal of the solvents at reduced pressure followed by flash chromatography (1:10 EtOAc:hexane) gave 6.01 g (93% yield) of trienol **18** as a colorless oil, 96% pure by GC: IR ($CHCl_3$) 3600, 2950, 1680, 1650, 1450, 900, 870 cm^{-1}; ^{1}H NMR (400 MHz) δ 5.18 (t, 1 H, J = 7 Hz), 4.71 (br s, 1 H), 4.67 (dd, 1 H, J = 3, 17.5 Hz), 4.67 (br s, 1 H), 4.54 (dt, 1 H, J = 3, 50 Hz), 4.11 (m, 1 H), 1.6–2.2 (m, 9 H), 1.72 (s, 3 H), 1.60 (s, 3 H); ^{13}C NMR (100 MHz) δ 166.65 (d, J = 260 Hz), 145.74, 134.36, 125.16, 109.95, 90.19 (d, J = 18 Hz), 69.96 (d, J = 31.8 Hz), 37.71, 35.21, 31.98, 26.11, 22.43, 15.89; HRMS calcd for $C_{13}H_{21}FO$, 212.1576, found, 212.1570.

Ethyl 4-Fluoro-8,12-dimethyltrideca-4(*Z*),8(*E*),12-trienoate (19). A mixture of 2.51 g (11.85 mmol) of fluoro allylic alcohol **18**, 7.0 g (43.15 mmol) of triethyl orthoacetate, and 50 μL (0.67 mmol) of propionic acid was heated to 140 °C in an oil bath, with the continuous removal of ethanol produced from the reaction by slow distillation. After 4 h, the reaction mixture was cooled, diluted with 100 mL of ether, and stirred with 25 mL of 1 M sulfuric acid. The organic layer was then washed with water and brine and dried over magnesium sulfate. The solvent was removed at reduced pressure, and the residue was flash chromatographed

(14) Rozen, S.; Chava, G. *J. Org. Chem.* **1987**, *52*, 2769–2779, and references cited therein, particularly that of Barton, D. H. R., et al.

(15) The multitude of cyclization products detected by GC and presumed to be tetracyclic in nature may possibly include regioisomers of **25** and 4-*epi*-**25** resulting from dehydrofluorination of 6 and 4-*epi*-6 so as to form an 8,9- or an 8,14-olefinic bond (cf. ref 14). In addition, all of the aforementioned major and minor tetracyclic substances would be expected to be accompanied by relatively minor proportions of regioisomers resulting from termination of the cyclization by loss of a proton from the "12 o'clock" position of ring D to give the $\Delta^{17(17a)}$ olefinic bond of the D-homosteroidal system, analogous to the established byproducts described in ref 1a. A set of 14β epimers of the aforementioned compounds are also additional possibilities as minor components by analogy to the case described in ref 17.

(16) Ohsawa, T.; Takagaki, T.; Haneda, A.; Oishi, T. *Tetrahedron Lett.* **1981**, 2583–2586.

(17) Johnson, W. S.; Fletcher, V. R.; Chenera, B.; Bartlett, W. R.; Tham, F. S.; Kullnig, R. K. *J. Am. Chem. Soc.*, following paper in this issue.

over 200 g of silica gel (1:15, EtOAc:hexane), giving 2.55 g (76%) of ester **19** as a colorless oil, GC purity 98%: IR ($CHCl_3$) 2950, 1720, 1450, 1375, 900 cm^{-1}; ^1H NMR (400 MHz) δ 5.11 (br t, 1 H, J = 7 Hz), 4.70 (br s, 1 H), 4.67 (br s, 1 H), 4.51 (dt, 1 H, J = 7, 38.0 Hz), 4.13 (q, 2 H, J = 7 Hz), 1.8–2.6 (m, 12 H), 1.72 (s, 3 H), 1.59 (s, 3 H), 1.25 (t, 3 H, J = 7 Hz); ^{13}C NMR (100 MHz) δ 172.35, 157.6 (d, J = 251 Hz), 145.75, 134.35, 124.54, 109.74, 105.4 (d, J = 15 Hz), 60.46, 39.14, 37.73, 31.34, 27.5 (d, J = 30 Hz), 26.10, 22.41, 21.92, 15.7, 14.15. Anal. Calcd for $C_{17}H_{27}FO_2$: C, 72.34; H, 9.57; F, 6.74. Found: C, 72.07; H, 9.78; F, 6.83.

4-Fluoro-8,12-dimethyltrideca-4(*Z*),8(*E*),12-trienal (20). To a solution of 2.55 g (9.05 mmol) of trienic ester **19** in 100 mL of diethyl ether at −78 °C was added 10 mL (10 mmol) of a 1 M solution of diisobutylaluminum hydride in hexane. The reaction mixture was stirred at −78 °C for 20 min, the reaction was quenched with 2 mL of methanol, and the mixture was slowly warmed to 0 °C. It was then diluted with 200 mL of ether, washed with 20 mL of 1 M H_2SO_4 and brine, and dried over magnesium sulfate. Removal of solvents at reduced pressure followed by flash chromatography (1:10 EtOAc:hexane) yielded 2.03 g (94%) of aldehyde **20** as a colorless oil: IR ($CHCl_3$) 2860, 2750, 1730, 1650, 900 cm^{-1}; ^1H NMR (400 MHz) δ 9.78 (s, 1 H), 5.11 (t, 1 H, J = 7 Hz), 4.70 (s, 1 H), 4.65 (s, 1 H), 4.5 (dt, 1 H, J = 7, 38.0 Hz), 2.63 (t, 2 H, J = 7 Hz), 2.48 (dt, 2 H, J = 7.17 Hz), 1.9–2.2 (m, 8 H), 1.72 (s, 3 H), 1.59 (s, 3 H); ^{13}C NMR (100 MHz) δ 200.69, 157.39 (d, J = 252 Hz), 145.73, 134.26, 124.61, 109.77, 105.75 (d, J = 16 Hz), 40.46, 39.09, 37.73, 26.08, 24.74 (d, J = 30 Hz), 22.41, 21.89, 15.67. Anal. Calcd for $C_{15}H_{23}FO$: C, 75.63; H, 9.66; F, 7.98. Found: C, 75.48; H, 9.88; F, 7.77.

6-Fluoro-3-hydroxy-2,10,14-trimethylpentadeca-1,6(*Z*),10(*E*),14-tetraen-3-ol (21). To a suspension of 400 mg (16.7 m equiv) of magnesium chips (Aldrich, gold label) in 30 mL of THF was added at 23 °C 2.4 g (20 mmol) of 2-bromopropene (Aldrich, 99%) over a period of 10 min. As the mixture was stirred, it refluxed gently without external heating. After the magnesium disappeared, the solution was cooled to 0 °C and 2.03 g (7.6 mmol) of aldehyde **20** in 10 mL of THF was added with stirring over a period of 10 min. The reaction mixture was stirred at 0 °C for an additional 1 h, and the reaction was quenched with saturated ammonium chloride solution. This mixture was extracted with ether and washed with water and brine. The solution was dried over magnesium sulfate and evaporated at reduced pressure. Flash chromatography (1:10 EtOAc:hexane) gave 1.83 g (78% yield) of allylic alcohol **21** as a colorless oil, 98% pure by GC: IR ($CHCl_3$) 3580, 3400, 2900, 1690, 1640, 1440, 900 cm^{-1}; ^1H NMR (400 MHz) δ 5.12 (t, 1 H, J = 6.5 Hz), 4.95 (s, 1 H), 4.86 (br s, 1 H), 4.7 (br s, 1 H), 4.67 (br s, 1 H), 4.48 (dt, 1 H, J = 7, 38.0 Hz), 4.4 (m, 1 H), 1.5–2.5 (m, 13 H), 1.73 (s, 3 H), 1.72 (s, 3 H), 1.60 (s, 3 H); HRMS calcd for $C_{18}H_{29}FO$, 280.2202, found, 280.2243.

Ethyl 8-Fluoro-4,12,16-trimethylheptadeca-4(*E*),8(*Z*),12(*E*),16-tetraenoate (22). A stirred solution of 298 mg (1.11 mmol) of allylic alcohol **21**, 2 mL of triethyl orthoacetate, and 15 μL of propionic acid was heated at 120 °C for 3 h. This procedure and the workup were similar to those described above for the conversion **18** → **19**. Flash chromatography (1:10 EtOAc:hexane) yielded 280 mg (75%) of **22** as a colorless oil, 96% pure by GC: IR ($CHCl_3$) 2950, 1720, 1690, 1635, 880 cm^{-1}; ^1H NMR (400 MHz) δ 5.1 (m, 2 H), 4.7 (s, 1 H), 4.67 (s, 1 H), 4.44 (dt, 1 H, J = 7, 38.0 Hz), 4.11 (q, 2 H, J = 7 Hz), 2.0–2.5 (m, 16 H), 1.72 (s, 3 H), 1.60 (s, 3 H), 1.25 (t, 3 H, J = 7.0 Hz). Anal. Calcd for $C_{22}H_{35}FO_2$: C, 75.43; H, 10.0; F, 5.43. Found: C, 75.55; H, 10.32; F, 5.68.

8-Fluoro-4,12,16-trimethylheptadeca-4(*E*),8(*Z*),12(*E*),16-tetraenal (23). Similarly to the reduction **19** → **20**, 0.9 mL of a 1 M solution of diisobutylaluminum hydride in hexane was added with stirring over a 3-min period to a solution of 280 mg (0.9 mmol) of ester **22** in 3 mL of diethyl ether at −78 °C. After an additional 30 min, the reaction was quenched with 0.4 mL of methanol and worked up as described above. Flash chromatography (1:10 EtOAc:hexane) gave 195 mg (82% yield) of aldehyde **23** as a colorless oil, 99% pure by GC: IR ($CHCl_3$) 2750, 1720, 1690, 1640, 890 cm^{-1}; ^1H NMR (400 MHz) δ 9.74 (t, 1 H, J = 2 Hz), 5.1 (m, 2 H), 4.7 (br s, 1 H), 4.67 (br s, 1 H), 4.43 (dt, 1 H, J = 7, 38.0 Hz), 1.5–2.5 (m, 16 H), 1.71 (s, 3 H), 1.61 (s, 3 H), 1.596 (s, 3 H); ^{13}C NMR (100 MHz) δ 202.48, 158.9 (d, J = 252 Hz), 145.84, 134.58, 134.11, 124.48, 123.99, 109.81, 104.89 (d, J = 16 Hz), 42.13, 39.34, 37.83, 32.02 (d, J = 28.0 Hz), 31.80, 26.20, 24.87, 22.49, 22.08, 16.08, 15.80. This material appeared to be oxygen-sensitive, the combustion analysis giving very low carbon values.

1,1-(Ethylenedioxy)-9-fluoro-5,13,17-trimethyloctadeca-5(*E*),9(*Z*),13(*E*),17-tetraene (5). To a suspension of 1.0 g (2.9 mmol) of anhydrous (methoxymethyl)triphenylphosphonium chloride in 10 mL of THF at −78 °C was added dropwise 2.1 mL of *sec*-butyllithium (1.3 M in cyclohexane). The deep red solution was stirred at −78 °C for 30 min and slowly warmed to 0 °C over a period of 1 h. To this phosphorane solution was added a solution of 140 mg (0.46 mmol) of aldehyde **23** in 2 mL of THF. This mixture was stirred at 0 °C for 30 min and slowly warmed to 23 °C. Saturated ammonium chloride was then added, and the aqueous layer was extracted with ether. The combined organic layers were washed with water and brine and dried over magnesium sulfate. Evaporation of the solvents at reduced pressure gave the crude enol ether **24**, containing triphenylphosphine oxide.

To a solution of the crude enol ether in 10 mL of benzene was added 5 mL of ethylene glycol and 10 mg of *p*-toluenesulfonic acid. This mixture was heated at 80 °C for 2 h, cooled, diluted with water, and extracted with ether. The combined extracts were washed with saturated sodium bicarbonate and brine and dried over magnesium sulfate. Evaporation at reduced pressure followed by flash chromatography (1:20 EtOAc:hexane) gave 117 mg (71% yield) of acetal **5** as a colorless oil, 96% pure by GC: IR ($CHCl_3$) 1700, 1640, 1140, 890 cm^{-1}; ^1H NMR (400 MHz) δ 5.2 (m, 2 H), 4.84 (t, 1 H, J = 5 Hz), 4.69 (br s, 1 H), 4.67 (br s, 1 H), 4.44 (dt, 1 H, J = 7, 38.0 Hz), 3.8–4.0 (m, 4 H), 1.5–2.2 (m, 18 H), 1.72 (s, 3 H), 1.60 (s, 3 H), 1.59 (s, 3 H); ^{13}C NMR (100 MHz) δ 159.1 (d, J = 249.9 Hz), 145.64, 135.63, 134.51, 124.37, 123.19, 109.77, 104.56 (d, J = 15.2 Hz), 104.52, 64.77, 39.33, 37.76, 33.30, 32.10 (d, J = 27.6 Hz), 26.11, 24.8, 22.38, 22.16, 22.0, 21.95, 15.68 (two overlapping methyls); HRMS calcd for $C_{23}H_{37}FO_2$, 364.2777, found, 364.2783. Anal. Calcd for $C_{23}H_{37}FO_2$: C, 75.82; H, 10.16; F, 5.22. Found: C, 75.82; H, 10.14; F, 5.07.

Cyclization of Acetal 5. To a solution of 125 mg (0.34 mmol) of acetal **5** in 30 mL of pentane (gold label, Aldrich) was added 36 μL (0.16 mmol) of 2,6-di-*tert*-butylpyridine. The mixture was stirred at 0 °C while 1.7 mL of a 1 M solution of stannic chloride in methylene chloride was added. The reaction mixture was stirred at 0 °C for 5 min, and the reaction was quenched with 1 mL of a 4:1 solution of methanol and triethylamine. This mixture was stirred for 15 min, diluted with ether, washed with water and brine, and dried over magnesium sulfate. Filtration through Florisil followed by evaporation of solvents at reduced pressure gave 120 mg of a colorless oil. This material was flash chromatographed using 1:9 EtOAc:hexane for elution. The faster-moving eluates containing tetracyclic material with a β (axial) side chain at C-4 were combined in fraction 1 (54 mg). Intermediate eluates composed fraction 2 (32 mg), and the slowest moving eluates containing material with an α (equatorial) side chain at C-4 constituted fraction 3 (22 mg).

A sample of the major component, representing 37% of fraction 1 and 13% of fraction 2 by GC analysis, was isolated by crystallization of fraction 1 from pentane containing a trace amount of dichloromethane. Recrystallizations gave colorless crystals, mp 131–133 °C, which were satisfactory for X-ray crystallographic analysis (see below) showing that this material is **4β-(2′-hydroxyethoxy)-17-methyl-D-homo-5α-androsta-7,16-diene (25)**: IR (Nujol) 3300–3500, 1640, 1210 cm^{-1}; ^1H NMR (400 MHz) δ 5.36 (m, 2 H, olefins), 3.70 (t, 2 H, J = 4 Hz), 3.64 (dt, 1 H, J = 4, 9.6 Hz), 3.43 (d-like, 1 H, J = 2.8 Hz), 3.3 (dt, 1 H, J = 4.8, 9.6 Hz), 0.9–2.4 (m, 20 H), 1.63 (s, 3 H), 0.95 (s, 3 H), 0.63 (s, 3 H); ^{13}C NMR (100 MHz) δ 138.82, 131.76, 119.79, 118.27, 78.76, 70.42, 62.29, 51.94, 46.56, 44.9, 43.98, 40.93, 39.01, 35.09, 33.24, 29.29, 26.44, 26.08, 23.64, 20.34, 17.25, 16.91, 15.58. Anal. Calcd for $C_{23}H_{36}O_2$: C, 80.23; H, 10.47. Found: C, 80.03; H, 10.68.

Crystallization of fraction 3 (as above) yielded a specimen of what is presumed to be (see discussion section) **4α-(2′-hydroxyethoxy)-17-methyl-D-homo-5α-androsta-7,16-diene (4-*epi*-25)**. This material represented about 41% of fraction 3 by GC. Recrystallization gave colorless crystals, mp 103–105 °C: IR ($CHCl_3$) 3600, 1450, 1260, 1100 cm^{-1}; ^1H NMR (400 MHz) δ 5.38 (m, 1 H), 5.32 (d, 1 H, J = 6 Hz), 3.69 (m, 3 H), 3.42 (m, 1 H), 3.17 (dt, 1 H, J = 4.4, 8.8 Hz), 0.8–2.4 (m, 20 H), 1.63 (s, 3 H), 0.77 (s, 3 H), 0.64 (s, 3 H); ^{13}C NMR (100 MHz) δ 138.85, 131.71, 119.82, 117.54, 79.76, 69.50, 62.28, 50.87, 46.83, 46.56, 43.89, 40.92, 38.10, 33.23, 31.72, 26.01, 25.78, 23.62, 20.74, 20.19, 17.28,

Table I. Bond Lengths (Å) for **25**

C(1)–C(2)	1.525 (6)	C(1)–C(10)	1.529 (4)
C(2)–C(3)	1.511 (6)	C(3)–C(4)	1.533 (6)
C(4)–C(5)	1.527 (5)	C(4)–O(4A)	1.427 (5)
C(5)–C(6)	1.522 (5)	C(5)–C(10)	1.545 (4)
C(6)–C(7)	1.488 (5)	C(7)–C(8)	1.333 (5)
C(8)–C(9)	1.517 (5)	C(8)–C(14)	1.511 (5)
C(9)–C(10)	1.537 (4)	C(9)–C(11)	1.526 (5)
C(10)–C(19)	1.544 (4)	C(11)–C(12)	1.508 (5)
C(12)–C(13)	1.541 (4)	C(13)–C(14)	1.550 (4)
C(13)–C(17A)	1.524 (5)	C(13)–C(18)	1.528 (4)
C(14)–C(15)	1.539 (5)	C(15)–C(16)	1.496 (5)
C(16)–C(17)	1.315 (5)	C(17)–C(17A)	1.487 (5)
C(17)–C(17B)	1.506 (4)	O(4A)–C(4A)	1.403 (5)
C(4A)–C(4B)	1.468 (7)	C(4B)–O(4B)	1.416 (5)

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.

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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 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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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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