**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.

**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 and Drs. John S. Baran and Tony B. Martinez of G. D. Searle & Co. for arranging for us to receive an authentic sample of *d*-4β-hydroxyandrostan-17-one.

**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]

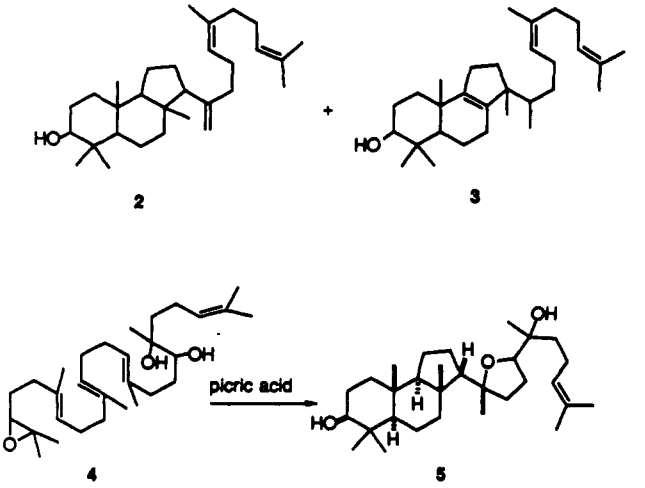
**William S. Johnson,* Robert A. Buchanan, William R. Bartlett, Fook S. Tham,† and Rudolph K. Kullnig†**

*Contribution from the Department of Chemistry, Stanford University, Stanford, California 94305.*
*Received June 2, 1992*

**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.

0002-7863/93/1515-504$04.00/0 

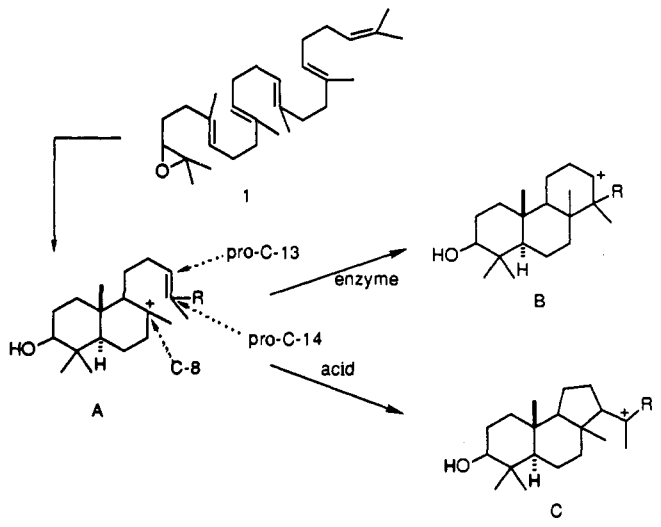
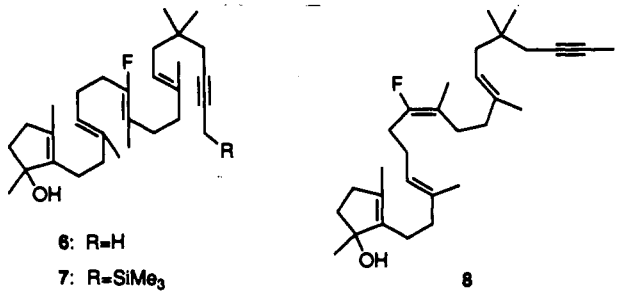



**Figure 1.** Cationic cyclization of oxidosqualene. The enzymatic vs nonenzymatic closure of ring C.

**1** to follow a Markovnikov cyclization pathway in the absence of enzyme control was later exploited by Sharpless, who reported[5] that the acid-catalyzed cyclization of the squalene 2,3-oxide derivative **4** gave in 7% yield the tricyclic triterpene malabaricanediol **5**, a member of a rare type of tricyclic triterpenes.

It has been suggested[1a,b] that the abnormal regiochemical consequence of the closure of ring C in the aforementioned enzymatic process is promoted by a negative point charge delivered by the enzyme so as to form an ion pair with, and thus effect stabilization of, the positive charge at *pro*-C-13 in cation **B**. Cation-stabilizing (C-S) functions appended to *pro*-C-8 have produced significant enhancements of the yields and rates of nonenzymatic cyclizations;[1] therefore, we felt that the desired regiocontrol of the nonenzymatic process might be realized by attachment of a C-S auxiliary at *pro*-C-13 of a cyclization substrate. The fluorine atom appeared to be a good candidate as a C-S auxiliary in this case, because when located at *pro*-C-8 it not only has been effective in enhancing tetracyclizations but also has led to products from which the fluorine atom could be removed in a synthetically useful stereoselective manner.[1d,e] Therefore, we chose the tetraenynes **6** and **7** as candidate substrates which not only promised to test our proposed solution to the regiochemical problem but also afforded the potential of providing a synthetic entry into the oleanene type of pentacyclic triterpene structure.




As we could not envisage a stereoselective pathway for the generation of the tetrasubstituted olefinic bond, we anticipated that tetraenyne **8**, the geometric isomer of **6**, would also be available for cyclization studies. A detailed account of the synthesis and cyclization of these three substrates follows.

**Synthesis of the Cyclization Substrates.** The synthesis of the cyclopentenols **6**, **7**, and **8** proceeded by a linear route, starting from the known ketone **9** (Scheme I). The three substrates shared a common initial synthetic pathway, branching first at alcohol **19**, establishing the stereochemistry of the tetrasubstituted fluoro alkene bonds. Alcohol **34** (Scheme II) served as the second branch point in the synthesis, leading either to substrate **6** or, after conversion into the trimethylsilyl derivative **41**, to substrate **7**.

Enone **11** could be prepared on a 70-g scale by condensation of the keto ester **10** with mesityl oxide (**9**) in 56% yield.[6] Epoxidation of this enone with basic hydrogen peroxide gave epoxy ketone **12**, which underwent Eschenmoser fragmentation[7] during tosylhydrazone formation, affording ketone **13** in 65% overall yield. Conversion to the alcohol **17** was accomplished by a four-step procedure in which the methyl ketone **13** underwent the haloform reaction to give acid **14**, which on treatment with $LiAlH_4$ was reduced to the alcohol **15**. Oxidation to aldehyde **16** by the Swern method, followed by the addition of 2-propenylmagnesium bromide, led to the required alcohol **17** in 56% overall yield from **13**. The Claisen rearrangement[1d,e] of the intermediate derived from alcohol **17** and 1-chloro-1-fluoro-2-methoxy-2-methylcyclopropane[1d,8] afforded the fluoro enone **18**, which upon treatment with methylmagnesium bromide was converted to the tertiary alcohol **19** in 60% overall yield.

At this branch point in the synthesis, attention was directed to developing the tetrasubstituted fluoroolefinic bond in order to produce stereoselectively both the trans and the cis stereoisomers.[9] The orthoester Claisen rearrangement[10] was attempted at the outset as a reference reaction but failed due to the unreactivity of the tertiary allylic alcohol **19** with triethyl orthoacetate. The use of the more reactive *N,N*-dimethylacetamide dimethyl acetal in the Eschenmoser Claisen rearrangement[11] was successful but required high temperature and a large excess of reagent to produce a nearly 1:1 mixture of the trans and cis isomers **22** and **23** in only 56% yield. Because of the difficulty with the Claisen rearrangements, attributed to a combination of steric hindrance and the electronic effect of a $\beta$-fluorine atom, the Ireland enolate Claisen[12] and the Wittig rearrangement[13] were investigated. As it turned out, when the Ireland procedure was applied to the acetate **20** there resulted a 4:1 mixture (cis:trans) of acids **25** and **24** in 69% yield, from which the cis isomer, acid **25**, could be separated readily by chromatography.

In the hope of realizing selectivity that favors formation of the trans isomer, the Wittig rearrangement was also studied. It was first necessary to convert the tertiary alcohol **19** to the (tributylstannyl)methyl ether **21** by alkylation of the potassium salt of alcohol **19** with (iodomethyl)tri-*n*-butylstannane in glyme.[13] Treatment of **21** with *n*-butyllithium produced the carbanion, which rearranged at −78 °C to produce alcohols **26** and **27** as a 7:3 mixture (trans:cis) in 85% yield. As before, the trans fluo-

(1) This represents paper no. 6 on cation-stabilizing auxiliaries in polyene cyclizations. For the first five 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. and (e) Johnson, W. S.; Fletcher, R.; Chenera, B.; Bartlett, W. R.; Tham, F. S.; Kullnig, R. K. *J. Am. Chem. Soc.*, preceding two papers in this issue.

(2) Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp 341–409.

(3) Simply for the sake of argument, the cyclization processes discussed here are regarded as stepwise processes, even though they may have concerted features.

(4) van Tamelen, E. E.; Willet, J.; Schwartz, M.; Nadeau, R. *J. Am. Chem. Soc.* **1966**, *88*, 5937–5938.

(5) Sharpless, K. B. *J. Am. Chem. Soc.* **1966**, *88*, 6999–7001.

(6) Stork, G.; Ponaras, A. A. *J. Org. Chem.* **1976**, *41*, 2937–2939.

(7) (a) Schreiber, J.; Felix, D.; Eschenmoser, A.; Winter, M.; Gautschi, F.; Schulte-Elte, K. H.; Sundt, E.; Ohloff, G.; Kalvoda, J.; Kaufmann, H.; Wieland, P.; Anner, G. *Helv. Chim. Acta* **1967**, *50*, 2101–2108. (b) Tanabe, M.; Crowe, D. F.; Dehn, R. L. *Tetrahedron Lett.* **1967**, 3943–3946.

(8) For an improved procedural modification, see ref 1e.

(9) Because of the fluorine atom, the tetrasubstituted olefinic bonds as in formulas 6 and 8 are *Z* and *E*, respectively; however, for the sake of clarity in the Discussion section, we prefer to refer to these configurations as trans and cis, respectively.

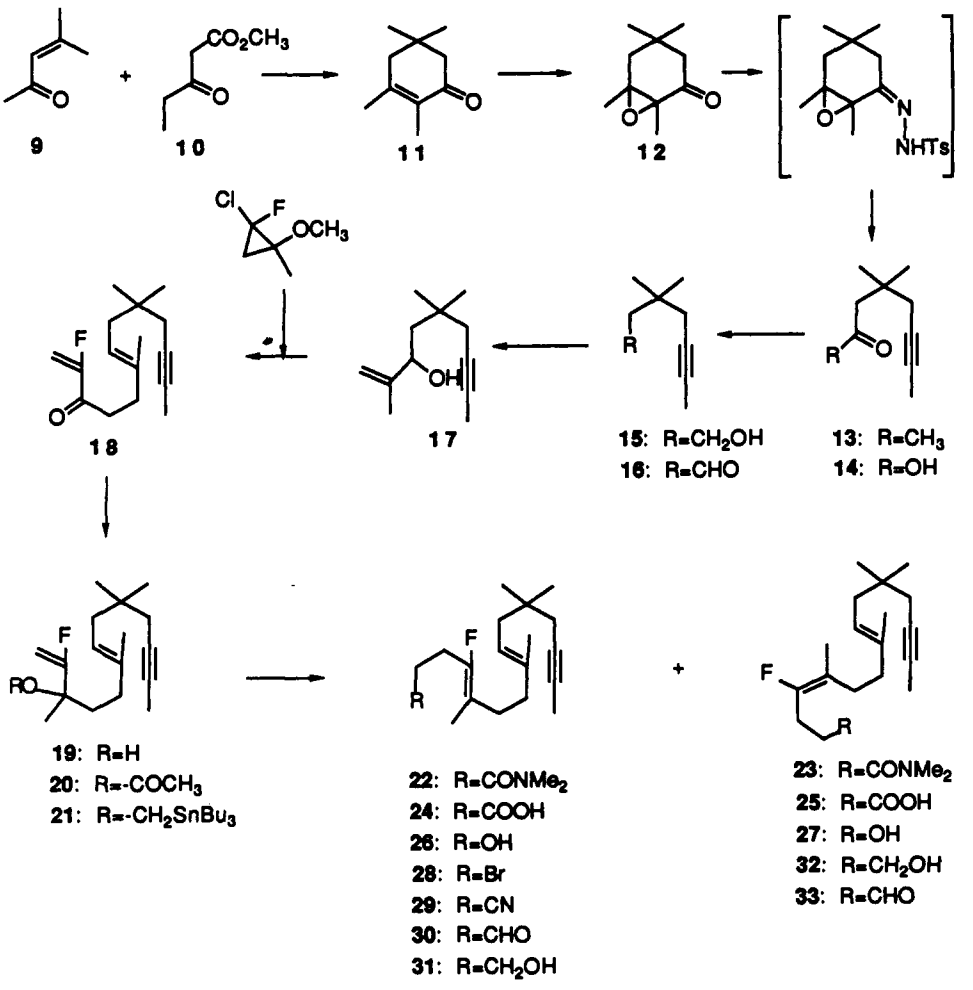
(10) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.-T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741–743.

(11) Wick, A. E.; Felix, D.; Steen, K.; Eschenmoser, A. *Helv. Chim. Acta* **1964**, *47*, 2425–2429.

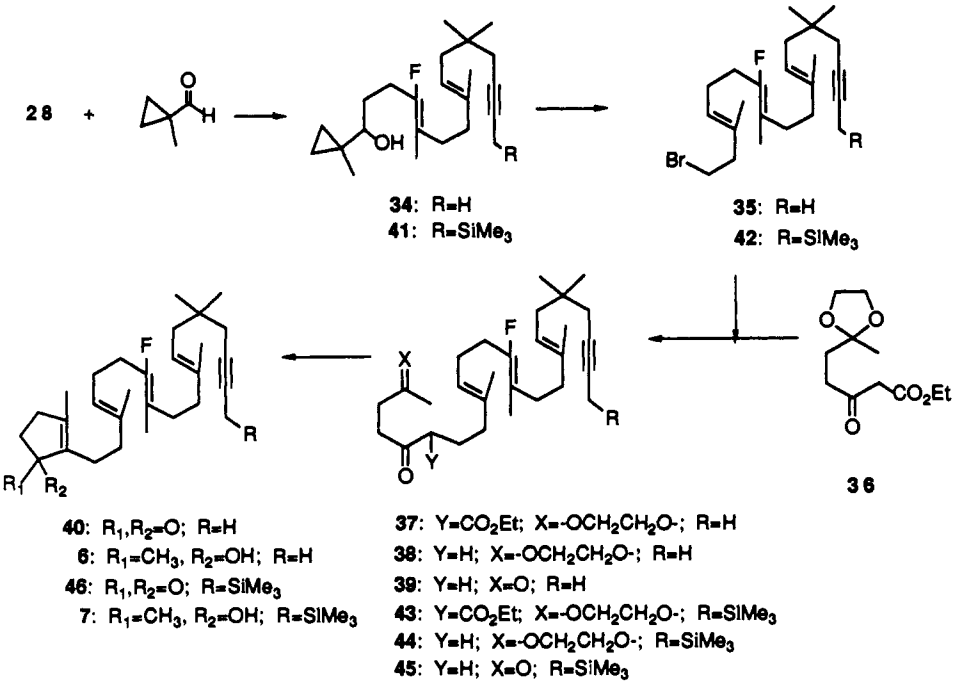
(12) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897–5898.

(13) (a) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481–1487. (b) Still, W. C.; Mitra, A. *J. Am. Chem. Soc.* **1978**, *100*, 1927–1928.

**Scheme I**



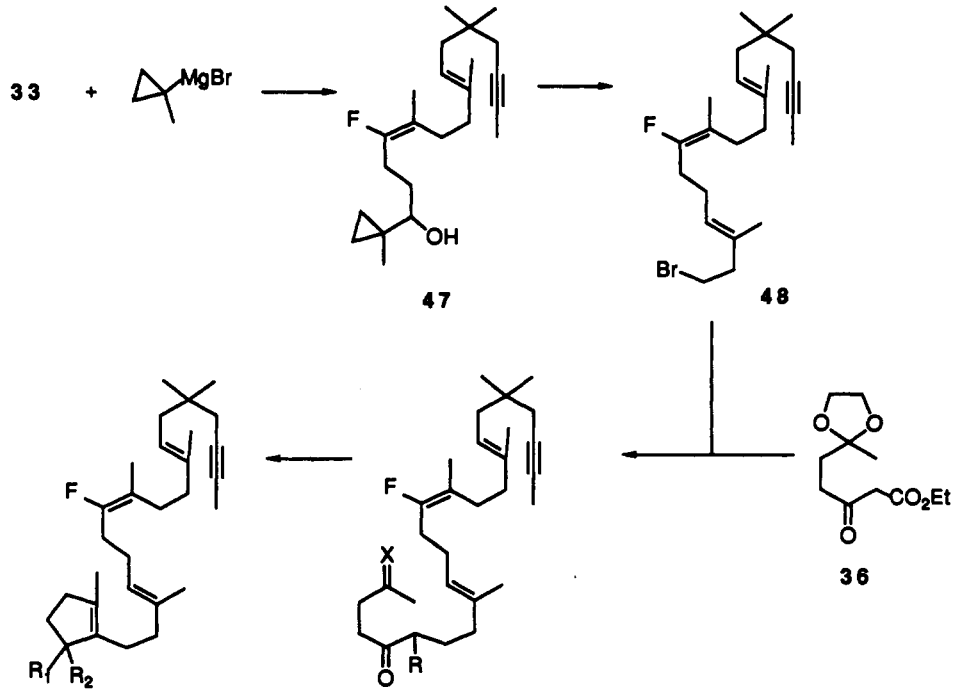

**Scheme II**




roolefin **26** was easily separated by chromatography.

Due to the difficulty in assigning definitive structures to the fluoroolefin stereoisomers, this study relied on the general observation[14] that a methyl group positioned cis to the fluorine atom

**Scheme III**




on an olefinic bond has a larger coupling constant with the fluorine atom (ca. 3.3 Hz) than a methyl group positioned trans to the fluorine atom (ca. 2.6 Hz). Proof that the two rearrangement products, cis acid **25** and trans alcohol **26**, indeed differed in stereochemistry at the fluoroolefinic bond was obtained in the following manner. Alcohol **26** was homologated by a four-step sequence: conversion to the bromide **28** with carbon tetrabromide and triphenylphosphine,[15] followed by cyanide substitution, diisobutylaluminum hydride reduction of **29** to the aldehyde **30**, and reduction to alcohol **31** with sodium borohydride. The comparison of alcohol **31** with the alcohol produced by $LiAlH_4$ reduction of acid **24** (the minor stereoisomer produced in the enolate Claisen rearrangement) verified that the two rearrangement reactions had proceeded in the opposite stereoselective sense.

To complete the synthesis of substrate **6** possessing the trans fluoroolefin stereochemistry, it was first necessary to convert bromide **28**, prepared as described above, to the cyclopropylcarbinol **34** (Scheme II). Addition of 1-formyl-1-methylcyclopropane[17] and bromide **28** to lithium metal under modified Barbier-type[16] conditions gave alcohol **34** in 72% yield. The Brady–Julia rearrangement[18] was effected in 76% yield by the two-step process involving bromination with phosphorus tribromide followed by treatment with zinc bromide, giving the rearranged bromide **35** with the *E*-olefinic configuration predominating at C-3 (>33:1), Bromide **35** was then used to alkylate the enolate of the known keto ester **36**,[19] producing keto ester **37** which could be decarbethoxylated by heating with aqueous base and then converted to diketone **39** with aqueous acid in 54% overall yield from bromide **35**. Diketone **39** was cyclized in aqueous base, giving cyclopentenone **40** (71% yield), which upon treatment with methyllithium afforded the substrate alcohol **6**, which was used without purification for cyclizations.

Cyclopentenol **7** was also prepared from cyclopropylcarbinol **34**, which was first treated with excess *tert*-butyllithium,[20] followed by trimethylchlorosilane, to give the propargylsilane **41** in 76% yield (Scheme II). This compound was then converted to cyclopentenol **7** according to the protocol described above for the synthesis of substrate **6**. Thus bromination followed by zinc bromide rearrangement afforded the bromide **42** in 82% yield, which was used to alkylate keto ester **36**, giving keto ester **43**. Decarbethoxylation of **43** followed by acid hydrolysis yielded diketone **45**, which on cyclodehydration with aqueous base gave cyclopentenone **46** in 25% overall yield from bromide **42**. Finally, treatment with methyllithium produced cyclopentenol **7**, which was used without purification for cyclizations.

Cyclopentenol **8**, possessing the fluorine-substituted double bond with cis geometry, was prepared in the same manner as **6**. Thus acid **25** was reduced to the alcohol **32** with $LiAlH_4$, followed by oxidation to the aldehyde **33** (Scheme I). Subsequent conversion to the cyclopropylcarbinol **47** with 1-(methylcyclopropyl)magnesium bromide[21] was accomplished in 62% overall yield (Scheme III). Bromination of alcohol **47** followed by zinc bromide-catalyzed rearrangement gave bromide **48**. As described above, bromide **48** obtained in 77% yield via the Brady–Julia rearrangement, was used to alkylate keto ester **36**, and then the product **49** was decarbethoxylated (to give **50**), the ketal group was removed in aqueous acid, and the diketone **51** was converted to the enone **52** in 44% overall yield from bromide **48**. Treatment of enone **52** with methyllithium afforded cyclopentenol **8**.

**Cyclization Studies.** The general procedure used in the cyclization studies was to test each substrate with protic and Lewis acid catalysts in a variety of solvents while monitoring the reaction products by gas chromatographic analysis using an internal

(14) (a) Emsley, J. W.; Phillips, L.; Wray, V. *Fluorine Coupling Constants*; Pergamon Press Ltd.: Elmsford, NY, 1977. (b) Reilly, C. A. *J. Chem. Phys.* **1962**, *37*, 456–457. (c) Saika, A.; Gutowsky, H. S. *J. Am. Chem. Soc.* **1956**, *78*, 4818–4819.

(15) Verheyden, J.; Moffatt, J. G. *J. Org. Chem.* **1972**, *37*, 2289–2299.

(16) (a) Luche, J.; Damiano, J. *J. Am. Chem. Soc.* **1980**, *102*, 7927–7928. (b) Pearce, P. J.; Richards, D. H.; Scilly, N. F. *J. Chem. Soc., Perkin Trans.* **1972**, 1655–1660.

(17) Moiseenkov, A. M.; Cheskis, B. A.; Kudryavatseva, G. A.; Nesmeyanova, O. A.; Semenovskii, A. B. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1982**, *No. 7*, 1572–1576.

(18) Brady, S. F.; Ilton, M. A.; Johnson, W. S. *J. Am. Chem. Soc.* **1968**, *90*, 2882–2889.

(19) Johnson, W. S.; Semmelhack, M. F.; Sultanbawa, M. U. S.; Dolak, L. A. *J. Am. Chem. Soc.* **1968**, *90*, 2994–2996.

(20) Rajagopalan, S.; Zweifel, G. *Synthesis* **1984**, 111–112.

(21) Roberts, J. D.; Chambers, V. *J. Am. Chem. Soc.* **1951**, *73*, 3176–3179.

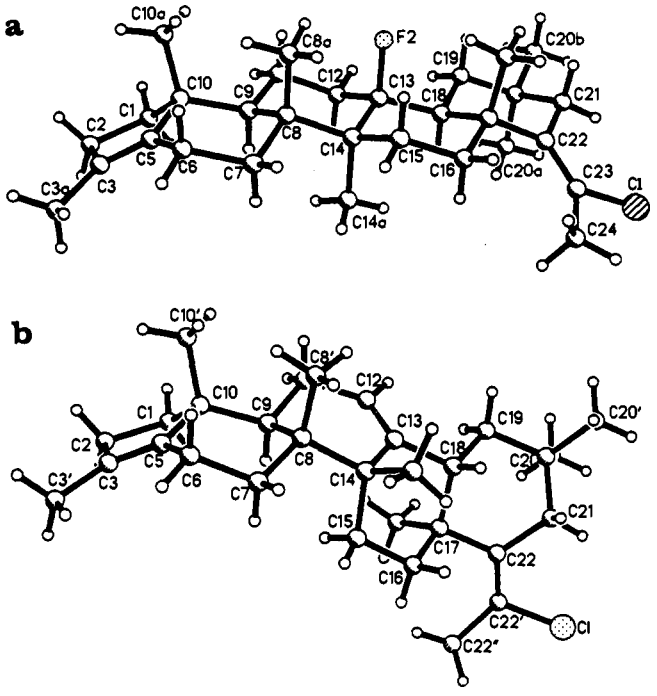
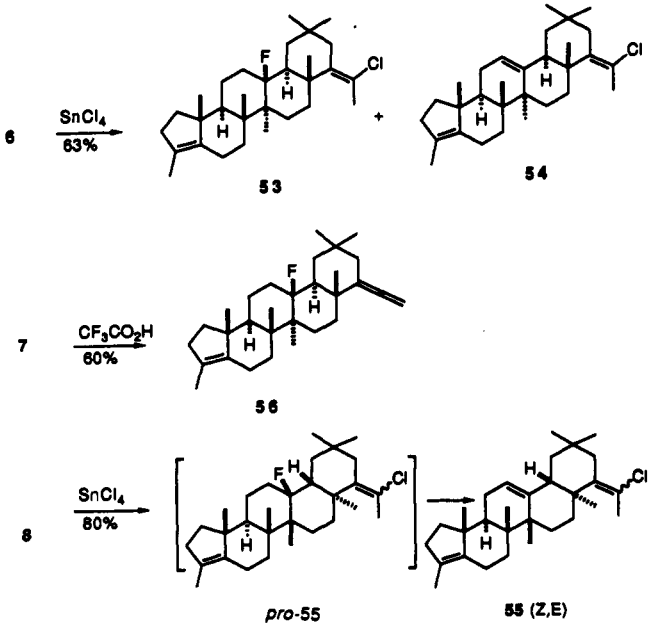



Figure 2. (a) Diagram of the 172° compound, pentacycle **53**. (b) Diagram of the 188° compound, pentacycle **55** (*E*-isomer).

standard. Prior art suggested that the Lewis acid $SnCl_4$ would yield clean cyclizations but could also enhance hydrogen fluoride elimination. Protic acids such as trifluoroacetic acid would be expected to minimize hydrogen fluoride elimination but also tended to give increased amounts of partially cyclized materials. Optimum conditions were found which minimized the formation of cyclization byproducts for each of the cyclopentenol substrates.

Thus cyclopentenol **6**, possessing the trans fluoroolefinic bond and the methylacetylenic terminating group, was added to a solution of $SnCl_4$ in dichloromethane at −78 °C, affording a mixture of two compounds (6:1) in 63% yield. Purification of this mixture gave the major compound as colorless crystals, mp 171–172 °C, shown by X-ray crystallographic analysis to possess the pentacyclic structure **53** (Figure 2a). The minor component of the mixture, mp 189–191 °C, was deduced from spectral and analytical data to have undergone elimination of hydrogen fluoride, giving triene **54**. As had been observed in related studies,[1e] pentacycle **54** became the exclusive product when the cyclization was carried out at a higher temperature (−43 °C).



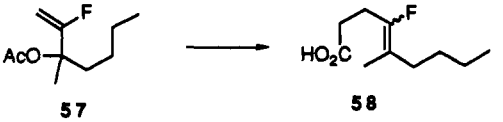

Cyclopentenol **7**, the trans fluoroolefinic substrate possessing the propargylsilane terminating group, was found to form pentacyclic material cleanly upon addition to a solution of either $SnCl_4$ or trifluoroacetic acid in dichloromethane at −78 °C (79% and 72% yields, respectively, by GC analysis). A preparative scale reaction using trifluoroacetic acid catalyst resulted in the isolation of colorless crystals, mp 178.5–180 °C, in 60% yield. Although crystals suitable for X-ray analysis were not obtained for this compound, NMR comparison with pentacycle **53** and analytical evidence showed that the fluorine atom had been retained and suggested a pentacyclic structure consistent with that of fluoro triene **56**.

Cyclopentenol **8**, the substrate bearing the cis fluoroolefinic bond, upon addition to a solution of $SnCl_4$ in dichloromethane at −78 °C was observed to form a mixture of two pentacycles (11:1) in 80% yield. The major product, obtained as colorless crystals, mp 185–188 °C, was pentacycle **55** (*E*-isomer), which had eliminated hydrogen fluoride as shown by NMR spectroscopy and confirmed by X-ray crystallographic analysis (see Figure 2b). The minor product was the stereoisomeric vinyl chloride **55** (*Z*-isomer).

## Discussion

The initial step in the synthesis of substrates **6**, **7**, and **8** involved the problem of constructing the methylacetylenic group in aldehyde **16** and was approached by using the known fragmentation of cyclic epoxy hydrazones[7] to establish the requisite functionality. The preparation of fluoroalkene **19** was thus accomplished readily in 17% overall yield from the mesityl oxide. The highly stereoselective fluoroolefinic ketal Claisen[1d] and cyclopropylcarbinol[18] rearrangements were used to establish the required trans trisubstituted alkene bonds at *pro*-C-8 and *pro*-C-17, respectively.

The synthesis of substrates **6**, **7**, and **8** required the development of stereoselective routes to both cis and trans tetrasubstituted fluoroolefins at *pro*-C-13. The fortuitous reversal in stereoselectivity in the preparation of the tetrasubstituted fluoroalkene bonds by the Ireland enolate Claisen[12] and the Wittig[13] rearrangements allowed for the preparation of both the cis and the trans fluoroolefin stereoisomers in satisfactory yields. Thus, the Wittig rearrangement of stannyl ether **21** afforded predominately the trans stereoisomer, alcohol **26** (7:3, 85% yield), while the Ireland enolate Claisen rearrangement of acetate **20** produced mainly the cis stereoisomer, acid **25** (4:1, 69% yield). In preliminary studies (to be reported at a later date) aimed at determining whether the selectivity of the enolate Claisen rearrangement is induced by the nearby trans trisubstituted olefinic bond present in acetate **20**, the saturated acetate **57** was prepared and subjected to the enolate Claisen rearrangement. The result was




57 58

a 1:1 mixture of cis and trans olefins **58** rather than the 4:1 mixture observed from acetate **20**. This result, produced perhaps by a $\pi$-stacking type of stabilization of the rearrangement transition state, together with the absence of selectivity demonstrated in the elevated temperature Eschenmoser–Claisen rearrangement (**19** → **22** + **23**), shows the sensitivity of these reactions to minor differences in steric and electronic interactions, an effect that may indeed be enhanced by the fluorine atom. The ease of chromatographic separation of the fluoroolefinic isomers facilitated the preparation of pure cis and trans fluoroalkenes **25** and **26**.

By studying the cyclization of substrates **6**, **7**, and **8**, it was possible to test the effectiveness of the fluorine atom at *pro*-C-13 as a C-S auxiliary in directing the regioselectivity as well as the stereoselectivity of the C/D ring fusion. That the fluorine atom proved effective as a C-S auxiliary was demonstrated by the production of pentacycles bearing 6-membered C and D rings in high yield in all three cyclizations. Of particular note is the formation of a single diastereoisomeric pentacycle (**55**) in a record high yield (80%) from the monocyclic substrate **8**. The efficient

stereoselective cyclization of substrates **6** and **7** to give pentacycles **53** and **56** retaining the fluorine atom at C-13 and possessing a total of seven chiral centers with A/B/C/D/E anti-trans-anti-trans-anti-trans backbone stereochemistry was also a gratifying result. It should be emphasized that all of the cyclizations described in this paper proceed according to the stereochemical predictions evolving from the Stork–Eschenmoser postulate.[2]

Regarding the cyclization of substrate **8**, it seems likely that it proceeds via the fluoropentacycle *pro*-**55**, having the A/B/C/D/E anti-trans-syn-cis-syn-trans backbone configuration as predicted by theory. The relief of considerable strain would account for the facile loss of HF in going from *pro*-**55** to **55**. The alternative mechanism involving loss of HF at the tricyclic state seems unlikely, because the resulting tricyclic vinyl cation would be expected,[1c] on further cyclization, to yield a mixture of pentacyclic diastereomers including the D/E cis isomer, which was not found in the product. In the cyclization of substrates **6** and **7**, the trans fluoroolefin stereoselectivity led to the anti-trans-anti-trans-anti-trans backbone observed in pentacycles **53** and **56**. The lack of strain in this ring system and the mildness of the reaction conditions may account for the observed retention of the fluorine atom in these pentacycles. Substrate **7**, having the more nucleophilic propargylsilane terminating group, underwent extremely facile cyclization (5 min at −78 °C) in the presence of either $SnCl_4$ or trifluoroacetic acid.

## Conclusions and Theoretical Considerations

The present study demonstrates that the fluorine atom located at *pro*-C-13 in a squalene-like substrate (a) controls the regiochemistry to give exclusively a product with a 6-membered ring C, (b) enhances the tetracyclization process, which proceeds in good to excellent yield, and (c) yields a product from which the fluorine atom promises to be eliminated in a synthetically useful manner. Finally, the effect of the C-S auxiliary in controlling closure of ring C in the manner observed in the enzymatic process may be regarded as further inferential documentation of the recently proposed mechanism for oxidosqualene cyclases.[1a,b]

In regard to the mechanism of the action of oxidosqualene cyclases, there have been various reports[22] suggesting or implying that an important part of the process involves the pairing of counterions in the enzyme and carbocationic centers developing in the cyclizing substrate. Our own views on the matter[1a,b] are that negative point charges on the enzyme, which are available for the aforementioned ion pairing, play a far-reaching role in the enzymic process: (a) they serve to stabilize the cyclization transition states and thus facilitate polycyclizations which proceed very poorly nonenzymatically; (b) the direction ($\beta$ or $\alpha$) of delivery of the negative point charge at *pro*-C-8 determines whether the A/B/C ring closure occurs in the all-trans manner or the trans-syn-trans configuration, respectively; (c) delivery of a point charge at *pro*-C-10 assists the cyclization initiation step; and (d) availability of a negative point charge at *pro*-C-13 promotes the anti-Markovnikov closure of ring C.

In the case of the anti-Markovnikov closure of ring C, Cornforth[23] invokes conformational control by the enzyme so that the carbon at *pro*-C-14 in the side chain of cation **A** (Figure 1) is held in position to form a bond with the cationic center at C-8. In contrast, we prefer to avoid any conformational control by assuming that cation **A** first forms a $\pi$-complex with the olefinic bond, as suggested in the classical concept of Eschenmoser et al.[24] and also favored by Dewar on the basis of ab initio calculations.[25] This complex has some positive character at *pro*-C-13 which can interact with the negative center provided by the enzyme; thus, collapse of the $\pi$-complex to the charge-stabilized form of cation **B** is a reasonable event.[26]

Application of the results of these studies to the synthesis of the pentacyclic triterpenoid $\beta$-amyrin is the subject of the next paper in this series.[27]

## Experimental Section

**General Considerations.** The prefix *dl* has been omitted from most of the names of the racemic intermediates 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; dichloromethane, benzene, triethylamine, and 2,6-lutidine were distilled from $CaH_2$. Analytical thin-layer chromatography (TLC) was performed on kieselgel 60 $F_{254}$ plastic-backed plates using ethyl acetate–hexane solvent mixtures and iodine impregnated on silica gel, phosphomolybdic acid, potassium permanganate, or *p*-anisaldehyde visualization. All chromatography was performed according to the method of C. Still[28] using E. Merck silica gel 60 (230–400 mesh). Medium-pressure liquid chromatography (MPLC) was performed using either a 300-mm or a 600-mm Michel-Miller chromatographic column with a FMI RP G-150 pumping system. For gas chromatography (GC), either a Hewlett-Packard HP5710A or HP 5890 instrument was used with 50-m or 15-m SE-54 capillary columns and hydrogen carrier gas within the temperature ranges of 50–290 °C. Nuclear magnetic resonance (NMR) spectra were obtained on a Varian XL-400 instrument with deuteriochloroform as solvent. Infrared (IR) spectra were obtained on a Beckman Acculab-3 spectrophotometer. Mass spectra were recorded in electron-impact mode by the Regional Mass Spectrometric Service at the University of California, San Francisco. Combustion analyses were performed by Desert Analytics in Tucson, AZ. Melting points were taken with a Kofler hot-stage microscope calibrated against totally immersed Anschutz thermometers.

**2,3,5,5-Tetramethylcyclohex-2-en-1-one**[6] **(11).** To a solution of sodium ethoxide, prepared by reacting 19.5 g of sodium (0.848 mol) with 400 mL of ethanol, was added over 1 h 99 mL (0.87 mol) of mesityl oxide (**9**) combined with 110 mL (0.88 mol) of methyl 3-oxopentanoate (**10**) in 500 mL of ethanol. The mixture was heated at 80 °C for 48 h and then poured into cold 25% aqueous HCl, extracted with 50% ether in hexane, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was distilled, giving 72.2 g (56% yield) of enone **11** as a clear oil, bp 71–74 °C (1.0 mmHg), 97% pure by GC: IR (film) 1668, 1640 $cm^{-1}$; $^1H$ NMR $\delta$ 2.23 (s, 2 H), 2.21 (s, 2 H), 1.89 (s, 3 H), 1.76 (s, 3 H), 0.99 (s, 6 H).

**2,3-Epoxy-2,3,5,5-tetramethylcyclohexanone (12).** To a solution of 72.2 g (0.475 mol) of enone **11** in 450 mL of methanol at 50 °C were added 60 mL of 30% hydrogen peroxide (0.523 mol) and 9.0 mL (0.054 mol) of 6 N NaOH. Hydrogen peroxide and 6 N NaOH were added at intervals (35 and 8 mL, respectively, at 5 h, and 30 and 2 mL, respectively, at 17 h) while the mixture was stirred at 50 °C for 23 h. The reaction was cooled and extracted with 50% ether–hexane, dried over magnesium sulfate, and concentrated under reduced pressure. Distillation gave 68.6 g (86% yield) of epoxy ketone **12** as a clear oil, bp 48 °C (0.5 mmHg), 97% pure by GC: IR (film) 1704, 1254, 805 $cm^{-1}$; $^1H$ NMR $\delta$ 2.73 (d, $J$ = 13.2 Hz, 1 H), 2.09 (d, $J$ = 15.0 Hz, 1 H), 1.83 (dd, $J$ = 13.2, 2.2 Hz, 1 H), 1.67 (dd, $J$ = 15.0, 2.4 Hz, 1 H), 1.40 (s, 3 H), 1.39 (s, 3 H), 0.98 (s, 3 H), 0.85 (s, 3 H). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.38; H, 9.59. Found: C, 71.66; H, 9.75.

**4,4-Dimethyl-2-oxooct-6-yne**[7] **(13).** To a solution of 52.2 g (0.311 mol) of epoxy ketone **12** in 150 mL of methanol at 0 °C was added 66.0 g (0.354 mol) of *p*-toluenesulfonylhydrazide over 1 h. The solution was stirred at 24 °C for 72 h and then diluted with ether, washed with 10% NaOH, dried over magnesium sulfate, and concentrated under reduced pressure. The orange residue was distilled to give 35.2 g (74.6% yield) of ketone **13** as a nearly colorless oil, bp 53–62 °C (0.8 mmHg), 97% pure by GC: IR (film) 1708 $cm^{-1}$; $^1H$ NMR $\delta$ 2.44 (s, 3 H), 2.15 (q, $J$ = 2.5 Hz, 2 H), 2.14 (s, 2 H), 1.79 (t, $J$ = 2.5 Hz, 3 H), 1.04 (s, 6 H). Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.60. Found: C, 78.96; H, 10.73.

**3,3-Dimethylhept-5-ynoic Acid (14).** To a solution of sodium hypobromite, prepared by adding 42 mL (0.439 mol) of bromine to 135 g (3.4 mol) of sodium hydroxide in 600 mL of water at 5 °C, was added 36.4 g (0.239 mol) of ketone **13** in 400 mL of 1,4-dioxane. The solution was

(22) (a) Cornforth, J. W. In *Ciba Foundation Symposium on the Biosynthesis of Terpenes and Sterols*; Wolstenholme, G. E. W., O'Connon, M., Eds.; Little, Brown & Co.: Boston, 1958; pp 299–300. (b) Ourisson, G.; Rohmen, M.; Poralla, K. *Ann. Rev. Microbiol.* **1987**, *41*, 301–333. (c) Benveniste, P. *Ann. Rev. Plant Physiol.* **1986**, *37*, 275–308 et sequel.

(23) Cornforth, J. W. *Angew. Chem.* **1968** *7(12)*, 903–910.

(24) Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* **1955**, *38*, 1890–1904.

(25) Dewar, M. J. S.; Reynolds, C. H. *J. Am. Chem. Soc.* **1984**, *106*, 1744–1750.

(26) This argument has been briefly outlined elsewhere: Johnson, W. S. *Tetrahedron* **1991**, *47(41)*, xi–1.

(27) Johnson, W. S.; Plummer, M. S.; Reddy, S. P.; Bartlett, W. R. *J. Am. Chem. Soc.*, following paper in this issue.

(28) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

stirred vigorously for 7 h, and then 30 g of sodium metabisulfite was added, followed by 125 mL of hydrochloric acid. The mixture was extracted with ether and concentrated under reduced pressure to give 36.3 g of an oil. This oil was further purified by being dissolved in 20% ether in hexane followed by extraction into 5% NaOH. Acidification with 6 N HCl was followed by extraction into 20% ether–hexane to give 32.4 g (88% yield) of acid **14** as a clear oil, 99% pure by GC: IR (film) 3600–2350, 1700 $cm^{-1}$; $^1H$ NMR $\delta$ 2.37 (s, 2 H), 2.20 (q, $J$ = 2.6 Hz, 2 H), 1.80 (t, $J$ = 2.6 Hz, 3 H), 1.09 (s, 6 H). This material appeared to be hygroscopic, making it difficult to obtain satisfactory elemental analyses. Anal. Calcd for $C_9H_{14}O_2$: C, 70.08; H, 9.16. Found: C, 69.41; H, 9.01.

**3,3-Dimethylhept-5-yn-1-ol (15).** To a solution of 6.50 g (0.169 mol) of $LiAlH_4$ in 80 mL of ethyl ether was added 20.0 g (0.130 mol) of acid **14** in 200 mL of ether at 0 °C over 40 min. The solution was heated at 35 °C for 4 h and then cooled to 5 °C. The reaction was quenched by the dropwise addition of 6.5 mL of water, 6.5 mL of 15% NaOH, and 22.4 mL of water. Filtration, followed by drying over magnesium sulfate and solvent removal under reduced pressure, gave 15.1 g (83% yield) of alcohol **15** as a cloudy yellow oil, 99% pure by GC, which was used without further purification: IR (film) 3340 $cm^{-1}$; $^1H$ NMR $\delta$ 3.68 (t, $J$ = 7.4 Hz, 2 H), 2.04–2.00 (m, 2 H), 1.78 (t, $J$ = 2.4 Hz, 3 H), 1.61 (t, $J$ = 7.4 Hz, 2 H), 1.50–1.40 (s, 1 H), 0.96 (s, 6 H). Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.97; H, 11.35.

**3,3-Dimethylhept-5-yn-1-al (16).** To a solution of 22.5 mL (0.236 mol) of oxalyl chloride in 300 mL of dichloromethane at −78 °C was added 38 mL (0.536 mol) of DMSO. The solution was warmed to −43 °C, and 15.0 g (0.107 mol) of alcohol **15** in 90 mL of dichloromethane was added. The white solution was stirred for 10 min, and then 59 mL (0.43 mol) of triethylamine was added. The mixture was stirred for 10 min and then allowed to warm to 23 °C over 1 h. After dilution with dichloromethane, the mixture was washed with 5% sulfuric acid and water, dried over magnesium sulfate, and concentrated under reduced pressure, giving 15.9 g (100% yield) of aldehyde **16** as a colorless oil, 93% pure by GC. The oil was used without further purification in the next reaction. A portion was purified by chromatography (5% ether in hexane): IR (film) 2825, 2730, 1715 $cm^{-1}$; $^1H$ NMR $\delta$ 9.85 (t, $J$ = 2.9 Hz, 1 H), 2.38 (d, $J$ = 2.9 Hz, 2 H), 2.15 (q, $J$ = 2.5 Hz, 1 H), 1.80 (t, $J$ = 2.5 Hz, 3 H), 1.10 (s, 6 H).

**2,5,5-Trimethyl-1-nonen-7-yn-3-ol (17).** To a solution of 2-propenylmagnesium bromide at 0 °C, prepared from 19 mL (0.214 mol) of 2-bromopropene and 7.7 g (0.321 mol) of magnesium turnings in 150 mL of THF, was added 14.8 g (0.107 mol) of aldehyde **16** in 30 mL of THF. After being stirred for 10 min at 0 °C, the mixture was warmed to 22 °C for 30 min and then poured into a 5% sulfuric acid solution. The solution was diluted with 40% ether in hexane and then washed with 10% sulfuric acid, water, and saturated aqueous potassium carbonate, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by chromatography (5–30% ether in hexane) to give 14.7 g (76% yield) of alcohol **17** as a colorless oil, 100% pure by GC: IR (film) 3410, 1642, 895 $cm^{-1}$; $^1H$ NMR $\delta$ 4.96 (dd, $J$ = 1.8, 0.9 Hz, 1 H), 4.78 (dd, $J$ = 1.8, 1.4 Hz, 1 H), 4.19 (ddd, $J$ = 7.6, 4.2, 3.9 Hz, 1 H), 2.19–2.07 (m, 2 H), 1.80 (t, $J$ = 2.6 Hz, 3 H), 1.74 (d, $J$ = 0.9 Hz, 3 H), 1.62 (d, $J$ = 3.9 Hz, 1 H), 1.57–1.49 (m, 2 H), 1.03 (s, 3 H), 1.02 (s, 3 H). Anal. Calcd for $C_{12}H_{20}O$: C, 79.93; H, 11.19. Found: C, 79.68; H, 11.42.

**2-Fluoro-3-oxo-6,9,9-trimethyl-1,6(*E*)-tridecadien-11-yne (18).** To a solution of 3.85 g (0.0214 mol) of alcohol **17** in 10 mL of toluene and 4.3 mL (0.054 mol) of pyridine was added 11.80 g (0.0856 mol) of 1-chloro-1-fluoro-2-methoxy-2-methylcyclopropane.[8] The mixture was stirred at 120 °C for 22 h and then filtered through silica gel (50% ether in hexane). The solvent was removed by distillation, and the residue was purified by chromatography (1–10% ether in hexane) to give 4.5 g (72% yield) of fluoro enone **18**, 90% pure by GC. This enone was stable at −20 °C but decomposed at room temperature: IR (film) 1709, 1640, 1075, 897 $cm^{-1}$; $^1H$ NMR $\delta$ 5.56 (dd, $J$ = 45.3, 3.3 Hz, 1 H), 5.23–5.18 (m, 1 H), 5.20 (dd, $J$ = 14.3, 3.3 Hz, 1 H), 2.77–2.72 (m, 2 H), 2.34 (t, $J$ = 7.6 Hz, 2 H), 1.99–1.94 (m, 4 H), 1.79 (t, $J$ = 2.5 Hz, 3 H), 1.63 (s, 3 H), 0.90 (s, 6 H).

**2-Fluoro-3-hydroxy-3,6,9,9-tetramethyl-1,6(*E*)-tridecadien-11-yne (19).** To a solution of 12.3 g (0.0492 mol) of fluoro enone **18** in 400 mL of ether at −78 °C was added dropwise 24 mL (0.072 mol) of methylmagnesium bromide solution (Aldrich, 3 M in ether). The solution was stirred at −78 °C for 20 min and then allowed to warm to 23 °C. After being stirred for 2 h, the reaction was poured into a solution of saturated ammonium chloride overlaid with 33% ether in hexane. The organic layer was washed with water, dried over magnesium sulfate, and concentrated under reduced pressure to give 12.1 g (92% yield) of alcohol **19** as a colorless oil, 91% pure by GC, which was used in the next reaction without further purification: IR (film) 3620–3100, 1668, 850 $cm^{-1}$; $^1H$ NMR $\delta$ 5.25 (ddd, $J$ = 6.6, 6.6, 1.1 Hz, 1 H), 4.68 (dd, $J$ = 3.6, 3.1 Hz, 1 H), 4.59 (dd, $J$ = 29.5, 3.1 Hz, 1 H), 2.16–1.97 (m, 2 H), 2.04–1.94 (m, 5 H), 1.81–1.66 (m, 2 H), 1.79 (t, $J$ = 2.5 Hz, 3 H), 1.62 (s, 3 H), 1.38 (s, 3 H), 0.91 (s, 6 H). Anal. Calcd for $C_{17}H_{27}FO$: C, 76.63; H, 10.22; F, 7.14. Found: C, 76.24; H, 10.33; F, 7.07.

**3-Acetoxy-2-fluoro-3,6,9,9-tetramethyl-1,6(*E*)-tridecadien-11-yne (20).** To a solution of 3.35 g (12.6 mmol) of alcohol **19** and 0.30 g (2.5 mmol) of 4-(dimethylamino)pyridine in 20 mL of pyridine was added 2.9 mL (31.5 mmol) of acetic anhydride. The solution was stirred at 72 °C for 44 h and then diluted with ether, washed with 10% sulfuric acid and saturated aqueous sodium bicarbonate, and dried over magnesium sulfate, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (1–10% ether in hexane) to give 3.1 g (81% yield) of acetate **20** as a colorless oil, 96% pure by GC: IR (film) 1738, 1668, 1245, 854 $cm^{-1}$; $^1H$ NMR $\delta$ 5.20 (ddd, $J$ = 7.8, 7.7, 1.2 Hz, 1 H), 4.73 (dd, $J$ = 18.8, 3.5 Hz, 1 H), 4.60 (dd, $J$ = 49.9, 3.5 Hz, 1 H), 2.05–1.91 (m, 8 H), 2.04 (s, 3 H), 1.80 (t, $J$ = 2.5 Hz, 3 H), 1.62 (d, $J$ = 1.2 Hz, 3 H), 1.61 (s, 3 H), 0.91 (s, 6 H). Anal. Calcd for $C_{19}H_{29}FO_2$: C, 73.97; H, 9.48; F, 6.16. Found: C, 73.79; H, 9.65; F, 5.93.

**2-Fluoro-3-(((tri-*n*-butylstannyl)methylen)oxy)-3,6,9,9-tetramethyl-1,6(*E*)-tridecadien-11-yne (21).** To a suspension of 0.505 g (35% in oil, 4.34 in mmol) of potassium hydride (washed with ether) in 4 mL of glyme at 23 °C was added dropwise a solution of 0.962 g (3.617 mmol) of alcohol **19** in 15 mL of glyme. After 15 min, a solution of 1.87 g (4.34 mmol) of (iodomethyl)tri-*n*-butylstannane[13] in 2 mL of glyme was added, and the mixture was stirred for 22 h at 23 °C. Ethanol was added, and the mixture was diluted with 5% ether–hexane and poured into 10% sulfuric acid. The organic layer was washed with water, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by MPLC (0–5% ether in hexane solvent gradient) to give 2.1 g (80% yield) of stannane **21**, 97% pure by GC, as a colorless oil: IR (film) 1660, 1465 $cm^{-1}$; $^1H$ NMR $\delta$ 5.19 (t, $J$ = 7.2 Hz, 1 H), 4.71 (dd, $J$ = 18.8, 2.8 Hz, 1 H), 4.47 (dd, $J$ = 50.8, 2.8 Hz, 1 H), 3.58–3.42 (m, 2 H), 2.05–1.91 (m, 6 H), 1.80 (t, $J$ = 2.5 Hz, 3 H), 1.72–1.62 (m, 2 H), 1.61 (s, 3 H), 1.51 (s, 3 H), 1.60–1.40 (m, 4 H), 1.38–1.25 (m, 8 H), 1.26 (s, 3 H), 0.99–0.82 (m, 12 H), 0.91 (s, 6H). Anal. Calcd for $C_{30}H_{55}FOSn$: C, 63.16; H, 9.89; F, 3.33. Found: C, 62.15; H, 9.72, F, 3.70).

**4-Fluoro-5,8,11,11-tetramethyl-4(*Z*),8(*E*)-pentadecadien-13-ynoic Acid *N*,*N*-Dimethylamide (22) and 4-Fluoro-5,8,11,11-tetramethyl-4(*E*),8(*E*)-pentadecadien-13-ynoic Acid *N*,*N*-Dimethylamide (23).** To a solution of 0.208 g (0.78 mmol) of alcohol **19** in 1.0 mL of distilled *N*,*N*-dimethylacetamide dimethyl acetal was added 0.24 g of powdered 4-Å molecular sieves. The tube was sealed under argon, heated to 175 °C for 1.75 h, and then cooled to 23 °C. The mixture was diluted with ether, filtered, and concentrated under reduced pressure to give 0.170 g (65% yield) of an oil, consisting of three major peaks on GC: alcohol **19** (8%), amide **23** (41%), and amide **22** (50%). The assignment of configurations is based on the presumption that the cis isomer is the faster moving isomer on column chromatography and has the shorter retention time on GC, as proved in a number of related cases. The crude product was purified by MPLC (30% ethyl acetate in hexane) to give 0.047 g of amide **23** and 0.073 g of amide **22** as colorless oils.

Amide **23**: IR (film) 2920, 1670 $cm^{-1}$; $^1H$ NMR $\delta$ 5.15 (t, $J$ = 7.0 Hz, 1 H), 2.97 (s, 3 H), 2.92 (s, 3 H), 2.68–2.40 (m, 4 H), 2.08–2.00 (m, 4 H), 1.98–1.88 (m, 4 H), 1.80–1.72 (m, 3 H), 1.65–1.55 (m, 6 H), 0.89 (s, 6 H); HRMS calcd for $C_{21}H_{34}FNO$, 335.2613, found, 335.2607.

Amide **22**: IR (film) 2910, 1650 $cm^{-1}$; $^1H$ NMR $\delta$ 5.14 (t, $J$ = 7.0 Hz, 1 H), 2.98 (s, 3 H), 2.92 (s, 3 H), 2.60–2.42 (m, 4 H), 2.18–2.00 (m, 4 H), 1.97–1.90 (m, 4 H), 1.76 (t, $J$ = 3.0 Hz, 3 H), 1.58 (s, 3 H), 1.55 (d, $J$ = 2.5 Hz, 3 H), 0.88 (s, 6 H); HRMS calcd for $C_{21}H_{34}FNO$, 335.2613, found, 335.2632.

**4-Fluoro-5,8,11,11-tetramethyl-4(*Z*),8(*E*)-pentadecadien-13-ynoic Acid (24) and 4-Fluoro-5,8,11,11-tetramethyl-4(*E*),8(*E*)-pentadecadien-13-ynoic Acid (25).** To a solution of 3.11 g (10.2 mmol) of acetate **20** in 15 mL of THF at −78 °C was added 8.6 mL (1.35 M in THF, 11.6 mmol) of lithium diisopropylamide. The solution was stirred for 40 min, and 4 mL of HMPA was added. After the solution was stirred for 20 min, 1.84 g (12.2 mmol) of *tert*-butyldimethylsilyl chloride in 2 mL of THF was added, and the solution was warmed to 40 °C for 17 h. The mixture was diluted with ether, washed with 10% sulfuric acid and water, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in 30 mL of acetonitrile and treated with 1.5 mL of 48% HF for 15 min at 23 °C. The solution was then diluted with ether and washed with water, dried over magnesium sulfate, and concentrated under reduced pressure to give an oil. Purification by flash chromatography (40% ether in hexane) gave 1.12 g (38% yield) of acid **25** with 4(*E*) stereochemistry, as a colorless oil, 99% pure by GC: IR (film) 3660–2250, 1706 $cm^{-1}$; $^1H$ NMR $\delta$ 5.16 (t, $J$ = 6.7 Hz, 1 H),

2.63–2.51 (m, 4 H), 2.10–2.01 (m, 4 H), 2.00–1.93 (m, 4 H), 1.80 (t, $J$ = 2.5 Hz, 3 H), 1.62 (d, $J$ = 3.4 Hz, 3 H), 1.61 (s, 3 H), 0.91 (s, 6 H). Anal. Calcd for $C_{19}H_{29}FO_2$: C, 73.97; H, 9.48; F, 6.16. Found: C, 73.98; H, 9.73; F, 5.99.

A second fraction consisted of 0.240 g (8% yield) of the 4($Z$)-acid **24** as an oil, 100% pure by GC: IR (film) 3600–2250, 1721, 1709 cm$^{-1}$; $^1$H NMR $\delta$ 5.16 (dd, $J$ = 7.6, 6.9 Hz, 1 H), 2.63–2.51 (m, 4 H), 2.21–2.14 (m, 2 H), 2.12–2.03 (m, 2 H), 2.02–1.93 (m, 4 H), 1.80 (t, $J$ = 2.4 Hz, 3 H), 1.61–1.58 (s, 1 H), 1.61 (s, 3 H), 1.58 (m, 3 H), 0.91 (s, 6 H). Anal. Calcd for $C_{19}H_{29}FO_2$: C, 73.97; H, 9.48; F, 6.16. Found: C, 73.76; H, 9.70; F, 6.07.

An additional fraction consisted of 0.71 g (23% yield) of a 3:1 mixture of acids **25** and **24**.

**3-Fluoro-1-hydroxy-4,7,10,10-tetramethyl-3($Z$),7($E$)-tetradecadien-12-yne (26) and 3-Fluoro-1-hydroxy-4,7,10,10-tetramethyl-3($E$),7($E$)-tetradecadien-12-yne (27).** To a solution of 8.1 g (14.2 mmol) of stannane **21** in 450 mL of THF at −78 °C was added 8.5 mL (2.5 M in hexane, 21.3 mmol) of $n$-butyllithium. The mixture was stirred at −78 °C for 75 min, and then 1 mL of ethanol was added. The mixture was diluted with 300 mL of 10% ether in hexane, washed with 10% sulfuric acid, water, and saturated sodium carbonate solution, dried over magnesium sulfate, and concentrated under reduced pressure. Purification by MPLC (20–30% ether in hexane solvent gradient) gave 2.39 g (60% yield) of alcohol **26** (with 3($Z$) stereochemistry) as a colorless oil, 98% pure by GC: IR (film) 3340, 1710 cm$^{-1}$; $^1$H NMR $\delta$ 5.17 (dd, $J$ = 7.7, 6.9 Hz, 1 H), 3.74 (t, $J$ = 6.3 Hz, 2 H), 2.50 (dt, $J$ = 23.1, 6.3 Hz, 2 H), 2.24–2.20 (m, 2 H), 2.12–2.08 (m, 2 H), 1.99–1.93 (m, 6 H), 1.80 (t, $J$ = 2.5 Hz, 3 H), 1.62 (s, 3 H), 1.60 (d, $J$ = 2.5 Hz, 3 H), 1.54 (s, 1 H), 0.91 (s, 6 H). Anal. Calcd for $C_{18}H_{29}FO$: C, 77.10; H, 10.42. Found: C, 76.88; H, 10.48.

Another fraction consisted of 0.97 g (25% yield) of the 3($E$)-alcohol **27** as a colorless oil, 95% pure by GC: IR (film) 3350, 1710 cm$^{-1}$; $^1$H NMR $\delta$ 5.18 (dd, $J$ = 7.6, 6.7 Hz, 1 H), 3.76 (t, $J$ = 6.3 Hz, 2 H), 2.51 (dt, $J$ = 22.3, 6.3 Hz, 2 H), 2.12–2.02 (m, 4 H), 2.02–1.93 (m, 4 H), 1.80 (t, $J$ = 2.6 Hz, 3 H), 1.66 (d, $J$ = 3.4 Hz, 3 H), 1.61 (s, 3 H), 1.53 (s, 1 H), 0.91 (s, 6 H). Anal. Calcd for $C_{18}H_{29}FO$: C, 77.10; H, 10.42. Found: C, 77.30; H, 10.63.

**1-Bromo-3-fluoro-4,7,10,10-tetramethyl-3($Z$),7($E$)-tetradecadien-12-yne (28).** To a solution of 2.36 g (8.44 mmol) of alcohol **26** and 2.43 g (9.28 mmol) of triphenylphosphine in 60 mL of dichloromethane at 0 °C was added 3.08 g (9.28 mmol) of carbon tetrabromide in 12 mL of dichloromethane. The reaction mixture was stirred for 15 min and then warmed to 24 °C for 2 h, diluted with 5% ether in hexane, and filtered through silica gel. Purification by MPLC (5% ether in hexane) gave 2.9 g (100% yield) of bromide **28** as a colorless oil, 97% pure by GC: IR (film) 1710 cm$^{-1}$; $^1$H NMR $\delta$ 5.17 (dd, $J$ = 8.3, 7.2 Hz, 1 H), 3.46 (t, $J$ = 7.3 Hz, 2 H), 2.77 (dt, $J$ = 22.2, 7.3 Hz, 2 H), 2.27–2.16 (m, 2 H), 2.17–2.05 (m, 2 H), 2.08–1.87 (m, 4 H), 1.80 (t, $J$ = 2.4 Hz, 3 H), 1.61 (s, 3 H), 1.60 (d, $J$ = 2.8 Hz, 3 H), 0.91 (s, 6 H). Anal. Calcd for $C_{18}H_{28}BrF$: C, 62.97; H, 8.22. Found: C, 62.94; H, 8.31.

**4-Fluoro-1-hydroxy-5,8,11,11-tetramethyl-4($E$),8($E$)-pentadecadien-13-yne (32).** To a solution of 1.12 g (3.66 mmol) of acid **25** in 40 mL of THF was added 7.0 mL (1 M in THF, 7.0 mmol) of $LiAlH_4$ at 0 °C. The mixture was stirred at 50 °C for 1 h and then cooled to 0 °C, and 0.28 mL water, 0.28 mL 15% NaOH, and 0.82 mL of water were added. The mixture was dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give 0.96 g (90% yield) of an oil, 88% pure by GC. Further purification by chromatography gave alcohol **32** as a colorless oil, 99% pure by GC: $^1$H NMR $\delta$ 5.18 (t, $J$ = 7.7 Hz, 1 H), 3.67 (t, $J$ = 6.4 Hz, 2 H), 2.35 (dd, $J$ = 7.3, 7.3 Hz, 1 H), 2.29 (dd, $J$ = 7.3, 7.3 Hz, 1 H), 2.10–1.93 (m, 8 H), 1.80 (t, $J$ = 2.5 Hz, 3 H), 1.78–1.71 (m, 2 H), 1.62 (d, $J$ = 3.3 Hz, 3 H), 1.61 (s, 3 H), 1.45–1.32 (br s, 1 H), 0.91 (s, 6 H). Anal. Calcd for $C_{19}H_{31}FO$: C, 77.49; H, 10.62; F, 6.46. Found: C, 77.27; H, 10.81; F, 6.67.

**4-Fluoro-5,8,11,11-tetramethyl-4($E$),8($E$)-pentadecadien-13-ynal (33).** To a solution of 1.24 mL (13.0 mmol) of oxalyl chloride in 100 mL of dichloromethane at −78 °C was added 2.5 mL (34.6 mmol) of DMSO. The solution was stirred at −78 °C, and 2.5 g (8.66 mmol) of alcohol **32** in 20 mL of dichloromethane was added. The white solution was stirred for 20 min, and then 6.0 mL (43.3 mmol) of triethylamine was added. The mixture was stirred for 10 min and then allowed to warm to 23 °C over 1 h. After dilution with dichloromethane, the mixture was washed with 5% sulfuric acid and water, dried over magnesium sulfate, filtered through Florisil (25% ether in hexane), and concentrated under reduced pressure to give 0.95 g (90% yield) of aldehyde **33** as a colorless oil, 95% pure by GC: IR (film) 2865, 2735, 1738 cm$^{-1}$; $^1$H NMR $\delta$ 9.80 (s, 1 H), 5.17 (t, $J$ = 7.8 Hz, 1 H), 2.62–2.48 (m, 4 H), 2.12–1.96 (m, 8 H), 1.80 (t, $J$ = 2.4 Hz, 3 H), 1.62 (d, $J$ = 3.1 Hz, 3 H), 1.61 (s, 3 H), 0.91 (s, 6 H); HRMS calcd for $C_{19}H_{29}FO$, 292.2202, found, 292.2207.

**1-Methyl-1-(4-fluoro-1-hydroxy-5,8,11,11-tetramethyl-4($Z$),8($E$)-pentadecadien-13-yn-1-yl)cyclopropane (34).** To 0.350 g (50.6 mmol) of lithium metal in 45 mL of THF at 0 °C was added one-third of the volume of a solution of 2.90 g (8.44 mmol) of bromide **28** and 2.13 g (25.3 mmol) of 1-formyl-1-methylcyclopropane[17] in 10 mL of THF. The remainder of this solution was added over 20 min, and the mixture was stirred for 90 min at 0 °C. The mixture was diluted with hexane, washed with saturated ammonium chloride and saturated sodium carbonate, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by MPLC (ether:dichloromethane:hexane 1:2:3) to give 2.11 g (72% yield) of alcohol **34** as a colorless oil, 95% pure by GC: IR (film) 3410, 1708 cm$^{-1}$; $^1$H NMR $\delta$ 5.16 (t, $J$ = 6.9 Hz, 1 H), 2.82 (br s, 1 H), 2.43–2.18 (m, 2 H), 2.21–2.09 (m, 2 H), 2.11–2.00 (m, 2 H), 2.02–1.91 (m, 4 H), 1.85–1.55 (m, 2 H), 1.79 (t, $J$ = 2.3 Hz, 3 H), 1.61 (s, 3 H), 1.57 (s, 3 H), 1.44 (s, 1 H), 1.03 (s, 3 H), 0.91 (s, 6 H), 0.46–0.26 (m, 4 H); HRMS calcd for $C_{23}H_{37}FO$, 348.2828, found, 348.2831. Anal. Calcd for $C_{23}H_{37}FO$: C, 79.25; H, 10.71; F, 5.45. Found: C, 79.35; H, 10.84; F, 5.83.

**1-Bromo-7-fluoro-3,8,11,14,14-pentamethyl-3($E$),7($Z$),11($E$)-octadecatrien-16-yne (35).** To a suspension of 0.949 g (2.743 mmol) of alcohol **34**, 0.85 g (9.7 mmol) of anhydrous lithium bromide, and 0.48 mL (4.1 mmol) of 2,6-lutidine in 50 mL of ether at −78 °C was added 0.30 mL (3.15 mmol) of phosphorous tribromide. After being stirred for 20 min, the mixture was warmed to 24 °C, stirred for 2 h and then poured into 50% NaCl solution. The mixture was diluted with 50% ether in pentane, washed with 10% sulfuric acid and saturated sodium carbonate solution, dried over magnesium sulfate, and concentrated under reduced pressure to give an oil. The oil was added to a suspension of 1.85 g (8.2 mmol) of anhydrous zinc bromide in 50 mL of ether at −78 °C. The mixture was stirred at 24 °C for 17 h, diluted with 50% ether in pentane, washed with 10% sulfuric acid and water, dried over magnesium sulfate, and concentrated under reduced pressure to give 0.854 g (76% yield) of bromide **35** as a colorless oil, 91% pure by GC, containing 2.9% of the 3($Z$)-isomer: IR (film) 1704, 1265 cm$^{-1}$; $^1$H NMR $\delta$ 5.22 (t, $J$ = 6.5 Hz, 1 H), 5.17 (t, $J$ = 7.4 Hz, 1 H), 3.41 (t, $J$ = 7.5 Hz, 2 H), 2.52 (t, $J$ = 7.5 Hz, 2 H), 2.29–2.21 (m, 1 H), 2.22–2.11 (m, 5 H), 2.10–2.02 (m, 2 H), 2.02–1.89 (m, 4 H), 1.80 (t, $J$ = 2.1 Hz, 3 H), 1.63 (s, 3 H), 1.61 (s, 3 H), 1.55 (d, $J$ = 2.5 Hz, 3 H), 0.91 (s, 6 H); HRMS calcd for $C_{23}H_{36}BrF$, 412.1984, found, 412.1942.

**6-Carbethoxy-2,2-(ethylenedioxy)-13-fluoro-5-oxo-9,14,17,20,20-pentamethyl-9($E$),13($Z$),17($E$)-tetracosatrien-22-yne (37).** To a suspension of 0.395 g (9.8 mmol, 60% in oil, washed with THF) of sodium hydride in 6 mL of THF was added 2.27 g (9.79 mmol) of ethyl 6,6-(ethylenedioxy)-3-oxoheptanoate (**36**).[19] After being stirred for 10 min, the solution was added to 0.834 g (2.04 mmol) of bromide **35**, and the solvent was removed under reduced pressure and replaced with a solution of 0.020 g of sodium iodide in 6 mL of acetonitrile. The mixture was stirred at 70 °C for 72 h, diluted with 50% ether in hexane, washed with 10% sulfuric acid, water, and saturated sodium bicarbonate, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by MPLC (30% ether in hexane) to give 0.72 g (63% yield) of keto ester **37** as a colorless oil, one spot on TLC ($R_f$ = 0.34, ether:hexane 1:1), which decomposes on GC: IR (film) 1743, 1710 cm$^{-1}$; $^1$H NMR $\delta$ 5.16 (t, $J$ = 7.8 Hz, 1 H), 5.12 (t, $J$ = 5.7 Hz, 1 H), 4.2–4.12 (q, $J$ = 7.1 Hz, 2 H), 3.96–3.85 (m, 4 H), 3.46–3.38 (m, 1 H), 2.60 (ddd, $J$ = 17.7, 7.7, 7.0 Hz, 2 H), 2.26–2.21 (m, 1 H), 2.20–2.11 (m, 5 H), 2.09–2.05 (m, 2 H), 2.05–1.88 (m, 8 H), 1.79 (t, $J$ = 2.5 Hz, 3 H), 1.61 (s, 3 H), 1.59 (s, 3 H), 1.55 (d, $J$ = 2.4 Hz, 3 H), 1.34–1.21 (m, 2 H), 1.30 (s, 3 H), 1.26 (t, $J$ = 7.1 Hz, 3 H), 0.91 (s, 6 H). Anal. Calcd for $C_{34}H_{53}FO_5$: C, 72.81; H, 9.53; F, 3.39. Found: C, 72.55; H, 9.50; F, 3.27.

**2,2-(Ethylenedioxy)-13-fluoro-5-oxo-9,14,17,20,20-pentamethyl-9($E$),13($Z$),17($E$)-tetracosatrien-22-yne (38).** A suspension of 0.706 g (1.26 mmol) of keto ester **37** and 5 mL of 5% sodium hydroxide solution in 50 mL of degassed THF and methanol (1:1) was stirred at 65 °C for 3 h. The mixture was then diluted with 50% ether in hexane, washed with 10% sulfuric acid, saturated sodium bicarbonate and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by MPLC (20% ether in hexane) to give 0.525 g (85% yield) of ketal **38** as a colorless oil, 94% pure by GC: IR (film) 1714, 1710 cm$^{-1}$; $^1$H NMR $\delta$ 5.17 (t, $J$ = 7.5 Hz, 1 H), 5.13 (t, $J$ = 6.4 Hz, 1 H), 3.98–3.86 (m, 4 H), 2.47 (t, $J$ = 7.3 Hz, 2 H), 2.37 (t, $J$ = 7.5 Hz, 2 H), 2.23–2.18 (m, 1 H), 2.21–2.10 (m, 5 H), 2.10–2.01 (m, 2 H), 2.02–1.90 (m, 8 H), 1.79 (t, $J$ = 2.2 Hz, 3 H), 1.71–1.58 (m, 2 H), 1.61 (s, 3 H), 1.58 (s, 3 H), 1.55 (d, $J$ = 2.4 Hz, 3 H), 1.31 (s, 3 H), 0.91 (s, 6 H); HRMS calcd for $C_{31}H_{49}FO_3$, 488.3666, found, 488.3655.

**2,5-Dioxo-13-fluoro-9,14,17,20,20-pentamethyl-9(*E*),13(*Z*),17(*E*)-tetracosatrien-22-yne (39).** To a solution of 0.510 g (1.50 mmol) of ketal **38** in 15 mL of methanol was added 2 mL of 5% hydrochloric acid. The solution was stirred at 22 °C for 17 h, diluted with 50% ether in hexane, washed with water and saturated sodium bicarbonate, dried over magnesium sulfate, and concentrated under reduced pressure to give 0.470 g (100% yield) of diketone **39** as a nearly colorless oil, 92% pure by GC: IR (film) 1725, 1715 $cm^{-1}$; $^1H$ NMR $\delta$ 5.17 (t, $J$ = 7.4 Hz, 1 H), 5.11 (t, $J$ = 6.2 Hz, 1 H), 2.73–2.58 (m, 4 H), 2.41 (t, $J$ = 7.3 Hz, 2 H), 2.18 (s, 3 H), 2.27–2.18 (m, 2 H), 2.21–2.08 (m, 6 H), 2.09–2.01 (m, 2 H), 2.02–1.84 (m, 4 H), 1.79 (t, $J$ = 2.4 Hz, 3 H), 1.73–1.60 (m, 2 H), 1.60 (s, 3 H), 1.58 (s, 3 H), 1.54 (d, $J$ = 2.5 Hz, 3 H), 0.90 (s, 6 H); HRMS calcd for $C_{29}H_{45}FO_2$, 444.3403, found, 444.3415.

**2-(7-Fluoro-3,8,11,14,14-pentamethyl-3(*E*),7(*Z*),11(*E*)-octadecatrien-16-yn-1-yl)-3-methylcyclopent-2-en-1-one (40).** A suspension of 0.449 g (1.01 mmol) of diketone **39** in 30 mL of THF and methanol (2:1) and 10 mL of 5% sodium hydroxide was rigorously degassed and stirred at 65 °C for 7 h. The mixture was diluted with 50% ether in hexane, washed with saturated sodium carbonate, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by MPLC (1:1:11 dichloromethane:ether:hexane) to give 0.291 g (71% yield) of enone **40** as a colorless oil, 97% pure by GC: IR (film) 1695, 1648 $cm^{-1}$; $^1H$ NMR $\delta$ 5.16 (t, $J$ = 7.8 Hz, 1 H), 5.08 (t, $J$ = 6.0 Hz, 1 H), 2.47 (br d, $J$ = 3.7 Hz, 2 H), 2.34 (dd, $J$ = 8.6, 4.3 Hz, 2 H), 2.30–2.20 (m, 2 H), 2.21–2.10 (m, 5 H), 2.09–1.91 (m, 9 H), 2.00 (s, 3 H), 1.79 (t, $J$ = 2.4 Hz, 3 H), 1.63 (s, 3 H), 1.61 (s, 3 H), 1.55 (d, $J$ = 2.4 Hz, 3 H), 0.90 (s, 6 H); $^{19}F$ NMR $\delta$ −113.4 (t, $J$ = 22.1 Hz). Anal. Calcd for $C_{29}H_{43}FO$: C, 81.63; H, 10.17; F, 4.46. Found: C, 82.02; H, 10.19; F, 4.47.

**2-(7-Fluoro-3,8,11,14,14-pentamethyl-3(*E*),7(*Z*),11(*E*)-octadecatrien-16-yn-1-yl)-1,3-dimethylcyclopent-2-en-1-ol (6).** To a solution of 0.124 g (0.291 mmol) of enone **40** in 30 mL of ether at −78 °C was added 1.2 mL (1.2 M in ether, 1.45 mmol) of methyllithium. The reaction was allowed to warm to 24 °C and stirred for 30 min, and then 1 mL of methanol was added. The mixture was diluted with hexane, washed with 5% sodium carbonate solution, dried over sodium sulfate, and concentrated under reduced pressure to give 0.129 g (100% yield) of cyclopentenol **6** as a colorless oil, unstable on GC. The unstable alcohol was stored in a base-washed vial at 0 °C: IR (film) 3480, 1702 $cm^{-1}$; $^1H$ NMR $\delta$ 5.17 (t, $J$ = 7.8 Hz, 1 H), 5.15 (t, $J$ = 5.5 Hz, 1 H), 2.38–2.02 (m, 12 H), 2.01–1.91 (m, 6 H), 1.79 (t, $J$ = 2.5 Hz, 3 H), 1.89–1.78 (m, 2 H), 1.65 (s, 3 H), 1.65 (s, 3 H), 1.61 (s, 3 H), 1.55 (d, $J$ = 2.6 Hz, 3 H), 1.41 (s, 1 H), 1.31 (s, 3 H), 0.91 (s, 6 H). Cyclopentenols did not give satisfactory analysis.

**Cyclization of Cyclopentenol 6.** A solution of 0.0642 g (0.145 mmol) of cyclopentenol **6** in 4 mL of dichloromethane was added slowly (18 min) to a solution of 0.43 mL (1 M in dichloromethane, 0.435 mmol) of tin tetrachloride in 80 mL of dichloromethane at −78 °C. The yellow mixture was stirred for 10 min, and then 1 mL of triethylamine and ethanol (1:1) was added. The mixture was allowed to warm to 24 °C and was purified by chromatography (5% ether in hexane). Further purification by MPLC (hexane) gave 0.0354 g (53% yield) of fluoropentacycle **53** as a white solid, 96% pure by GC, and 0.0061 g (10% yield) of pentacycle **54** as a white solid.

**Preparation of Pentacycle 53 for X-ray Analysis.** Fluoropentacycle **53** was recrystallized (acetonitrile:dichloromethane 2:1), giving rectangular prisms, mp 171–172 °C, suitable for X-ray analysis: IR 1460, 1260 $cm^{-1}$; $^1H$ NMR $\delta$ 2.69 (d, $J$ = 13.7 Hz, 1 H), 2.40 (d, $J$ = 1.2 Hz, 3 H), 2.24 (ddd, $J$ = 14.6, 4.5, 2.7 Hz, 1 H), 2.12 (br d, $J$ = 13.8 Hz, 1 H), 1.93 (dd, $J$ = 12.6, 3.7 Hz, 1 H), 2.42–1.91 (m, 4 H), 1.88–1.81 (m, 2 H), 1.78–1.57 (m, 2 H), 1.59 (s, 3 H), 1.49–1.32 (m, 4 H), 1.34–1.22 (m, 4 H), 1.24 (d, $J$ = 4.5 Hz, 3 H), 1.22–1.14 (m, 2 H), 1.15 (d, $J$ = 5.2 Hz, 3 H), 1.05 (s, 3 H), 0.98 (s, 3 H), 0.90 (s, 3 H), 0.85 (s, 3 H); $^{19}F$ NMR $\delta$ −163.2 (br t, $J$ = 40 Hz).

Pentacycle **54**, 79% pure by GC (containing 8% of the vinylchloride stereoisomer), was recrystallized from acetonitrile, giving rectangular prisms, mp 189–191 °C: IR 1510, 1380 $cm^{-1}$; $^1H$ NMR $\delta$ 5.28 (d, $J$ = 2.1 Hz, 1 H), 2.52 (d, $J$ = 14.0 Hz, 1 H), 2.42 (dt, $J$ = 12.8, 2.3 Hz, 1 H), 2.35–2.16 (m, 2 H), 2.25 (d, $J$ = 1.7 Hz, 3 H), 2.13–1.94 (m, 2 H), 1.94–1.65 (m, 4 H), 1.65–1.50 (m, 3 H), 1.60 (s, 3 H), 1.51–1.34 (m, 1 H), 1.47 (dt, $J$ = 16.0, 3.9 Hz, 1 H), 1.41 (dd, $J$ = 7.7, 4.4 Hz, 1 H), 1.33–1.22 (m, 2 H), 1.22–0.81 (m, 2 H), 1.09 (s, 3 H), 1.01 (s, 3 H), 0.97 (s, 3 H), 0.96 (s, 3 H), 0.93 (s, 3 H), 0.88 (s, 3 H); HRMS calcd for $C_{30}H_{45}Cl$, 440.3210, found, 440.3231.

**1-Methyl-1-(4-fluoro-1-hydroxy-5,8,11,11-tetramethyl-15-(trimethylsilyl)-4(*Z*),8(*E*)-pentadecadien-13-yn-1-yl)-cyclopropane (41).** To a solution of 9.7 mL (1.5 M in pentane, 14.55 mmol) of *tert*-butyllithium and 2.6 mL (17.4 mmol) of tetramethylethylenediamine in 40 mL of ether at −78 °C was added 2.00 g (5.79 mmol) of alcohol **34** in 5 mL of ether.[20] The mixture was allowed to warm to −22 °C for 15 min and then to −10 °C for 1 h. The deep yellow mixture was then cooled to −78 °C and treated with 2.91 mL (17.4 mmol) of chlorotrimethylsilane. The mixture was warmed to 24 °C for 30 min and was then diluted with hexane, washed with saturated ammonium chloride and saturated sodium carbonate, and dried over magnesium sulfate. The solvent was removed to give an oil. Treatment with 35 mL of methanol and 3 g of potassium carbonate for 1.5 h at 24 °C, followed by dilution with hexane, extraction with water, drying with magnesium sulfate, and removal of solvent at reduced pressure, gave an oil. The oil was purified by MPLC (15% ether in hexane) to give 1.84 g (76% yield) of alcohol **41**, 95% pure by GC, as a clear oil: IR (film) 3500, 1708, 1252 $cm^{-1}$; $^1H$ NMR $\delta$ 5.17 (t, $J$ = 7.6 Hz, 1 H), 2.81 (dd, $J$ = 8.9, 4.3 Hz, 1 H), 2.33 (ddd, $J$ = 22.6, 7.6, 7.2 Hz, 2 H), 2.21–2.14 (m, 2 H), 2.12–2.03 (m, 2 H), 2.01 (t, $J$ = 2.6 Hz, 2 H), 1.96 (d, $J$ = 7.6 Hz, 2 H), 1.81–1.63 (m, 2 H), 1.61 (s, 3 H), 1.58 (d, $J$ = 2.4 Hz, 3 H), 1.51 (s, 1 H), 1.44 (t, $J$ = 2.6 Hz, 2 H), 1.03 (s, 3 H), 0.91 (s, 6 H), 0.28–0.42 (m, 4 H), 0.09 (s, 9 H). Anal. Calcd for $C_{26}H_{45}FOSi$: C, 74.23; H, 10.78; F, 4.52. Found: C, 74.39; H, 10.51; F, 5.02.

**1-Bromo-7-fluoro-3,8,11,14,14-pentamethyl-18-(trimethylsilyl)-3(*E*),7(*Z*),11(*E*)-octadecatrien-16-yne (42).** To a suspension of 2.03 g (4.85 mmol) of alcohol **41**, 1.1 g (12.64 mmol) of anhydrous lithium bromide, and 0.64 mL (5.34 mmol) of 2,6-lutidine in 50 mL of ether at −78 °C was added 0.45 mL (4.85 mmol) of phosphorous tribromide. After 10 min, the mixture was warmed to 24 °C for 1.6 h, diluted with 50% ether in pentane, washed with saturated brine and saturated sodium bicarbonate, dried over magnesium sulfate, and concentrated under reduced pressure to give an oil. This oil was added to a suspension of 2.8 g (12.6 mmol) of anhydrous zinc bromide in 50 mL of ether at −78 °C. The mixture was stirred at 25 °C for 12 h, diluted with hexane, washed with water, dried over magnesium sulfate, and concentrated under reduced pressure to give 1.92 g (82% yield) of bromide **42**, 90% pure by GC, as a colorless oil: IR (film) 1705, 1255 $cm^{-1}$; $^1H$ NMR $\delta$ 5.22 (t, $J$ = 6.7 Hz, 1 H), 5.18 (t, $J$ = 7.6 Hz, 1 H), 3.42 (t, $J$ = 7.5 Hz, 2 H), 2.53 (t, $J$ = 7.5 Hz, 2 H), 2.29–2.11 (m, 6 H), 2.10–2.02 (m, 2 H), 2.01 (t, $J$ = 2.6 Hz, 2 H), 1.99 (d, $J$ = 7.6 Hz, 2 H), 1.62 (s, 3 H), 1.61 (s, 3 H), 1.55 (d, $J$ = 2.5 Hz, 3 H), 1.44 (d, $J$ = 2.6 Hz, 2 H), 0.91 (s, 6 H), 0.09 (s, 9 H). Anal. Calcd for $C_{26}H_{44}BrFSi$: C, 64.57; H, 9.17; F, 3.93. Found: C, 64.03; H, 9.28; F, 4.28.

**6-Carbethoxy-2,2-(ethylenedioxy)-13-fluoro-5-oxo-9,14,17,20,20-pentamethyl-24-(trimethylsilyl)-9(*E*),13(*Z*),17(*E*)-tetracosatrien-22-yne (43).** To a suspension of 0.415 g (12.6 mmol, 60% in oil, washed with THF) of sodium hydride in 6 mL of THF was added 3.2 g (13.9 mmol) of ethyl 6,6-(ethylenedioxy)-3-oxoheptanoate (**36**).[19] After being stirred for 10 min, the solution was added to 1.60 g (3.31 mmol) of bromide **42**, and the solvent was removed under reduced pressure and replaced with a solution of 0.020 g of sodium iodide in 6 mL of acetonitrile. The mixture was stirred at 65 °C for 72 h, diluted with ether, washed with 10% sulfuric acid, water, and saturated sodium bicarbonate, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by MPLC (25% ether in hexane) to give 1.80 g (86% yield) of keto ester **43** as a nearly colorless oil, one spot on TLC ($R_f$ = 0.24, ether:hexane, 2:3), which decomposed on GC analysis: IR (film) 1750, 1728 $cm^{-1}$; $^1H$ NMR $\delta$ 5.17 (t, $J$ = 7.7 Hz, 1 H), 5.12 (t, $J$ = 6.4 Hz, 1 H), 4.17 (q, $J$ = 7.1 Hz, 2 H), 3.98–3.86 (m, 4 H), 3.42 (dd, $J$ = 8.0, 5.6 Hz, 1 H), 2.56 (dddd, $J$ = 25.3, 17.8, 7.3, 7.3 Hz, 2 H), 2.69–2.51 (m, 2 H), 2.27–2.10 (m, 6 H), 2.09–2.02 (m, 2 H), 2.00 (t, $J$ = 2.6 Hz, 2 H), 2.00–1.90 (m, 6 H), 1.61 (s, 3 H), 1.58 (s, 3 H), 1.55 (d, $J$ = 2.5 Hz, 3 H), 1.44 (t, $J$ = 2.6 Hz, 2 H), 1.31 (s, 3 H), 1.26 (t, $J$ = 7.1 Hz, 2 H), 0.90 (s, 6 H), 0.09 (s, 9 H). Anal. Calcd for $C_{37}H_{61}FO_5Si$: C, 70.21; H, 9.71. Found: C, 70.39; H, 9.97.

**2,2-(Ethylenedioxy)-13-fluoro-5-oxo-9,14,17,20,20-pentamethyl-24-(trimethylsilyl)-9(*E*),13(*Z*),17(*E*)-tetracosatrien-22-yne (44).** A suspension of 1.77 g (2.79 mmol) of keto ester **43** and 10 mL of 5% sodium hydroxide solution in 80 mL of degassed THF and methanol (1:1) was stirred at 65 °C for 3 h. The mixture was then diluted with ether, washed with 10% sulfuric acid, saturated sodium bicarbonate, and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by MPLC (25% ether in hexane) to give 1.19 g (76% yield) of ketal **44** as a colorless oil, one spot by TLC ($R_f$ = 0.23, 25% ether in hexane): IR (film) 1713, 1705 $cm^{-1}$; $^1H$ NMR $\delta$ 5.17 (t, $J$ = 7.3 Hz, 1 H), 5.11 (t, $J$ = 6.4 Hz, 1 H), 3.99–3.87 (m, 4 H), 2.48 (t, $J$ = 7.4 Hz, 2 H), 2.37 (t, $J$ = 7.6 Hz, 2 H), 2.21–2.10 (m, 6 H), 2.01–1.90 (m, 8 H), 2.00 (t, $J$ = 2.7 Hz, 2 H), 1.72–1.60 (m, 2 H), 1.60 (s, 3 H), 1.58 (s, 3 H), 1.54 (d, $J$ = 2.6 Hz, 3 H), 1.44 (t, $J$ = 2.7 Hz, 2 H), 1.31 (s, 3 H), 0.91 (s, 6 H), 0.09 (s, 9 H). Anal. Calcd for $C_{34}H_{57}FO_3Si$: C, 72.81; H, 10.24. Found: C, 73.08; H, 10.11.

**2,5-Dioxo-13-fluoro-9,14,17,20,20-pentamethyl-24-(trimethylsilyl)-9(*E*),13(*Z*),17(*E*)-tetracosatrien-22-yne (45).** To a solution of 0.709 g (1.26 mmol) of ketal **44** in 50 mL of 5% water in acetone was added 0.32 g of pyridinium *p*-toluenesulfonate. The solution was stirred at 60

°C for 8 h, diluted with ethyl acetate, washed with water and saturated sodium bicarbonate, dried over magnesium sulfate, and concetrated under reduced pressure to give an oil. The oil was purified by MPLC (30% ether in hexane) to give 0.585 g (90% yield) of diketone **45** as a nearly colorless oil, 94% pure by GC: IR (film) 1720 $cm^{-1}$; $^1H$ NMR $\delta$ 5.17 (t, $J$ = 7.5 Hz, 1 H), 5.11 (t, $J$ = 5.8 Hz, 1 H), 2.76–2.62 (m, 4 H), 2.41 (t, $J$ = 7.3 Hz, 2 H), 2.26–2.11 (m, 6 H), 2.19 (s, 3 H), 2.09–1.92 (m, 8 H), 2.05 (t, $J$ = 2.6 Hz, 2 H), 1.71–1.58 (m, 2 H), 1.60 (s, 3 H), 1.58 (s, 3 H), 1.55 (d, $J$ = 2.5 Hz, 3 H), 1.44 (t, $J$ = 2.6 Hz, 2 H), 1.35–1.20 (m, 2 H), 0.90 (s, 6 H), 0.09 (s, 9 H). Anal. Calcd for $C_{32}H_{53}FO_2Si$: C, 74.36; H, 10.34. Found: C, 74.60; H, 10.62.

**2-(7-Fluoro-3,8,11,14,14-pentamethyl-18-(trimethylsilyl)-3(*E*),-7(*Z*),11(*E*)-octadecatrien-16-yn-1-yl)-3-methylcyclopent-2-en-1-one (46).** A suspension of 0.922 g (1.78 mmol) of diketone **45** in 42 mL of THF and methanol (2:1) and 15 mL of 5% sodium hydroxide was rigorously degassed and stirred at 65 °C for 7 h. The mixture was diluted with ethyl acetate, washed with saturated ammonium chloride, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by MPLC (1:1:11 dichloromethane:ether:hexane) to give 0.45 g (51% yield) of enone **46** as a colorless oil, 94% pure by GC: IR (film) 1695, 1640 $cm^{-1}$; $^1H$ NMR $\delta$ 5.17 (t, $J$ = 7.6 Hz, 1 H), 5.08 (t, $J$ = 6.0 Hz, 1 H), 2.50–2.46 (m, 2 H), 2.38–2.33 (m, 2 H), 2.26 (dd, $J$ = 8.4, 7.3 Hz, 2 H), 2.23–2.12 (m, 6 H), 2.08–1.96 (m, 4 H), 2.03 (s, 3 H), 2.00 (t, $J$ = 2.6 Hz, 2 H), 1.95 (d, $J$ = 7.6 Hz, 2 H), 1.63 (s, 3 H), 1.61 (s, 3 H), 1.55 (d, $J$ = 2.6 Hz, 3 H), 1.44 (d, $J$ = 2.6 Hz, 2 H), 0.90 (s, 6 H), 0.09 (s, 9 H). Anal. Calcd for $C_{32}H_{51}FOSi$: C, 77.05; H, 10.30. Found: C, 76.82; H, 10.40.

**2-(7-Fluoro-3,8,11,14,14-pentamethyl-18-(trimethylsilyl)-3(*E*),-7(*Z*),11(*E*)-octadecatrien-16-yn-1-yl)-1,3-dimethylcyclopent-2-en-1-ol (7).** To a solution of 0.080 g (0.160 mmol) of enone **46** in 25 mL of ether at −78 °C was added 1.3 mL (1.2 M in ether, 1.76 mmol) of methyllithium. The reaction was allowed to warm to 24 °C and was stirred for 40 min, and then 1 mL of methanol was added. The mixture was diluted with hexane, washed with saturated sodium carbonate solution, dried over sodium sulfate, and concentrated under reduced pressure to give 0.080 g (97% yield) of cyclopentenol **7** as a colorless oil, unstable on GC. The unstable alcohol was stored in a base-washed vial at 0 °C: IR (film) 3500, 1706 $cm^{-1}$; $^1H$ NMR $\delta$ 5.17 (dd, $J$ = 8.8, 7.7 Hz, 1 H), 5.15 (t, $J$ = 6.2 Hz, 1 H), 2.39–1.80 (m, 16 H), 2.00 (t, $J$ = 2.4 Hz, 2 H), 1.78–1.52 (m, 2 H), 1.65 (s, 3 H), 1.61 (s, 3 H), 1.55 (d, $J$ = 2.2 Hz, 3 H), 1.44 (t, $J$ = 2.4 Hz, 2 H), 1.40 (s, 1 H), 1.31 (s, 3 H), 0.90 (s, 6 H), 0.09 (s, 9 H). Cyclopentenyl carbinols did not give satisfactory analysis.

**Cyclization of Cyclopentenol 7.** A solution of 0.0389 g (0.0757 mmol) of cyclopentenol **7** in 6 mL of dichloromethane was added slowly (60 min) to a solution of 0.50 mL of trifluoroacetic acid in 100 mL of dichloromethane at −78 °C. The mixture was stirred for 10 min and then was poured into 5% sodium carbonate solution and purified by chromatography (hexane). Further purification by MPLC (hexane) gave 0.0192 g (60% yield) of fluoropentacycle **56** as a white solid, 100% pure by GC. Recrystallization from acetonitrile gave needles, mp 178.5–180 °C, unsuitable for X-ray analysis: IR 1946, 1605 $cm^{-1}$; $^1H$ NMR $\delta$ 4.65 (dd, $J$ = 8.9, 4.2 Hz, 1 H), 4.60 (dd, $J$ = 8.9, 4.2 Hz, 1 H), 2.39–2.10 (m, 4 H), 2.11–1.81 (m, 4 H), 1.80–1.59 (m, 6 H), 1.59 (s, 3 H), 1.45–1.30 (m, 8 H), 1.17 (d, $J$ = 5.2 Hz, 3 H), 1.15 (d, $J$ = 4.3 Hz, 3 H), 1.04 (s, 3 H), 1.00 (s, 3 H), 0.90 (s, 3 H), 0.85 (s, 3 H). $^{19}F$ NMR $\delta$ −163.2 (dd, $J$ = 41, 39 Hz); HRMS calcd for $C_{30}H_{45}F$, 424.3505, found, 424.3500. Anal. Calcd for $C_{30}H_{45}F$: C, 84.85; H, 10.68; F, 4.47. Found: C, 85.25; H, 10.29; F, 4.78.

**1-Methyl-1-(4-fluoro-1-hydroxy-5,8,11,11-tetramethyl-4(*E*),8(*E*)-pentadecadien-13-yn-1-yl)cyclopropane (47).** A solution of 1-(bromomagnesio)-1-methylcyclopropane was prepared from 3.26 g (24.0 mmol) of 1-bromo-1-methylcyclopropane[21] and 0.58 g (24.7 mmol) of magnesium dust in 25 mL of THF stirred at 65 °C for 1 h. The solution was diluted with 40 mL of THF and cooled to −25 °C, and 2.34 g (7.98 mmol) of aldehyde **33** in 12 mL of THF was added. The mixture was stirred at 25 °C for 1 h, diluted with 50% ether in hexane, washed with 50% ammonium chloride solution and saturated sodium bicarbonate, dried over magnesium sulfate, and concentrated under reduced pressure to give an oil. This material was purified by MPLC (10% ether in hexane) to give 2.14 g (77% yield) of alcohol **47** as a colorless oil, 97% pure by GC: IR (film) 3450, 1710 $cm^{-1}$; $^1H$ NMR $\delta$ 5.18 (t, $J$ = 7.6 Hz, 1 H), 2.82 (dd, $J$ = 8.7, 4.5 Hz, 1 H), 2.41–2.20 (m, 2 H), 2.12–1.93 (m, 5 H), 1.80 (t, $J$ = 2.6 Hz, 3 H), 1.78–1.56 (m, 6 H), 1.62 (d, $J$ = 3.3 Hz, 3 H), 1.61 (s, 3 H), 1.03 (s, 3 H), 0.91 (s, 6 H), 0.45–0.28 (m, 4 H). Anal. Calcd for $C_{23}H_{37}FO$: C, 79.25; H, 10.71; F, 5.45. Found: C, 79.45; H, 10.84; F, 5.53.

**1-Bromo-7-fluoro-3,8,11,14,14-pentamethyl-3(*E*),7(*E*),11(*E*)-octadecatrien-16-yne (48).** To a suspension of 2.10 g (6.07 mmol) of alcohol **47**, 1.50 g (17.0 mmol) of anhydrous lithium bromide, and 0.92 mL (7.9 mmol) of 2,6-lutidine in 50 mL of ether at −78 °C was added 0.66 mL (6.98 mmol) of phosphorous tribromide. After being stirred for 20 min, the mixture was warmed to 24 °C, stirred for 2 h, and then poured into saturated sodium chloride solution. The mixture was diluted with 50% ether in pentane, washed with saturated sodium bicarbonate solution, dried over magnesium sulfate, and concentrated under reduced pressure to give an oil. The oil was added to a suspension of 4.10 g (18.2 mmol) of anhydrous zinc bromide in 40 mL of ether at −78 °C. The mixture was stirred at 24 °C for 5 h, diluted with 50% ether in pentane, washed with 10% sulfuric acid and water, dried over magnesium sulfate, and concentrated under reduced pressure to give 2.09 g (84% yield) of bromide **48** as a colorless oil, 91% pure by GC, containing 2.7% of the 3(*Z*)-isomer: IR (film) 1705 $cm^{-1}$; $^1H$ NMR $\delta$ 5.23 (t, $J$ = 6.7 Hz, 1 H), 5.17 (t, $J$ = 7.6 Hz, 1 H), 3.42 (t, $J$ = 7.4 Hz, 2 H), 2.53 (t, $J$ = 7.6 Hz, 2 H), 2.23–2.12 (m, 4 H), 2.12–1.87 (m, 8 H), 1.80 (t, $J$ = 2.6 Hz, 3 H), 1.63 (s, 3 H), 1.61 (s, 3 H), 1.61 (s, 3 H), 0.91 (s, 6 H). Anal. Calcd for $C_{23}H_{36}BrF$: C, 67.12; H, 8.82; F, 4.62; Br, 19.43. Found: C, 67.12; H, 8.93; F, 4.82; Br, 19.26.

**6-Carbethoxy-2,2-(ethylenedioxy)-13-fluoro-5-oxo-9,14,17,20,20-pentamethyl-9(*E*),13(*E*),17(*E*)-tetracosatrien-22-yne (49).** To a suspension of 0.620 g (12.8 mmol, 60% in oil, washed with THF) of sodium hydride in 8 mL of THF was added 3.50 g (12.3 mmol) of ethyl 6,6-(ethylenedioxy)-3-oxoheptanoate (**36**).[19] After being stirred for 10 min, the solution was added to 2.02 g (4.93 mmol) of bromide **48**, and the solvent was removed under reduced pressure and replaced with a solution of 0.20 g of sodium iodide in 8 mL of acetonitrile. The mixture was stirred at 64 °C for 96 h, diluted with ether, washed with 10% sulfuric acid, water, and saturated sodium carbonate, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by chromatography (25% ether in hexane) to give 2.10 g (76% yield) of keto ester **49** as a colorless oil, one spot on TLC ($R_f$ = 0.34, ether:hexane 1:1), which decomposes on GC analysis: IR (film) 1734, 1710 $cm^{-1}$; $^1H$ NMR $\delta$ 5.19 (t, $J$ = 7.6 Hz, 1 H), 5.13 (t, $J$ = 5.7 Hz, 1 H), 4.17 (q, $J$ = 7.1 Hz, 3 H), 4.05–3.85 (m, 4 H), 3.43 (dd, $J$ = 6.7, 1.8 Hz, 1 H), 2.69–2.48 (m, 2 H), 2.19–2.11 (m, 4 H), 2.10–1.95 (m, 12 H), 1.80 (t, $J$ = 2.5 Hz, 3 H), 1.66–1.56 (m, 8 H), 1.30 (s, 3 H), 1.26 (t, $J$ = 7.1 Hz, 2 H), 0.91 (s, 6 H). Anal. Calcd for $C_{34}H_{53}FO_5$: C, 72.81; H, 9.53; F, 3.39. Found: C, 73.03; H, 9.84; F, 3.74.

**2,2-(Ethylenedioxy)-13-fluoro-5-oxo-9,14,17,20,20-pentamethyl-9(*E*),13(*E*),17(*E*)-tetracosatrien-22-yne (50).** A suspension of 2.10 g (3.74 mmol) of keto ester **49** and 20 mL of 5% sodium hydroxide solution in 150 mL of degassed THF and methanol (1:1) was stirred at 65 °C for 3 h. The mixture was then diluted with ether, washed with 1% hydrochloric acid, saturated sodium bicarbonate, and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by MPLC (30% ether in hexane) to give 1.585 g (87% yield) of ketal **50** as a colorless oil, 95% pure by GC: IR (film) 1715, 1710 $cm^{-1}$; $^1H$ NMR $\delta$ 5.17 (t, $J$ = 7.4 Hz, 1 H), 5.12 (t, $J$ = 6.1 Hz, 1 H), 4.02–3.86 (m, 4 H), 2.47 (t, $J$ = 7.4 Hz, 2 H), 2.37 (t, $J$ = 7.4 Hz, 2 H), 2.28–2.11 (m, 4 H), 2.10–1.91 (m, 12 H), 1.80 (t, $J$ = 2.2 Hz, 3 H), 1.62 (d, $J$ = 4.5 Hz, 3 H), 1.61 (s, 3 H), 1.58 (s, 3 H), 1.31 (s, 3 H), 0.91 (s, 6 H); HRMS calcd for $C_{31}H_{49}FO_3$, 488.3666, found, 488.3684.

**2,5-Dioxo-13-fluoro-9,14,17,20,20-pentamethyl-9(*E*),13(*E*),17(*E*)-tetracosatrien-22-yne (51).** To a solution of 1.58 g (3.23 mmol) of ketal **50** in 30 mL of methanol was added 1 mL of 5% hydrochloric acid. The solution was stirred at 22 °C for 23 h, diluted with ether, washed with water and 5% sodium bicarbonate, dried over magnesium sulfate, and concentrated under reduced pressure to give 1.43 g (100% yield) of diketone **51** as a nearly colorless oil, 95% pure by GC: IR (film) 1715, 1710 $cm^{-1}$; $^1H$ NMR $\delta$ 5.17 (t, $J$ = 7.8 Hz, 1 H), 5.14 (t, $J$ = 7.3 Hz, 1 H), 2.73–2.63 (m, 4 H), 2.41 (t, $J$ = 7.3 Hz, 2 H), 2.19 (s, 3 H), 2.80–2.12 (m, 2 H), 2.45–1.93 (m, 12 H), 1.80 (t, $J$ = 2.5 Hz, 3 H), 1.71–1.61 (m, 2 H), 1.61 (d, $J$ = 4.6 Hz, 3 H), 1.61 (s, 3 H), 1.58 (s, 3 H), 0.91 (s, 6 H); HRMS calcd for $C_{29}H_{45}FO_2$, 444.3403, found, 444.3412.

**2-(7-Fluoro-3,8,11,14,14-pentamethyl-3(*E*),7(*E*),11(*E*)-octadecatrien-16-yn-1-yl)-3-methylcyclopent-2-en-1-one (52).** A suspension of 1.42 g (9.20 mmol) of diketone **51** in 85 mL of THF and methanol (2:1) and 30 mL of 5% sodium hydroxide was rigorously degassed and stirred at 65 °C for 20 h. The mixture was diluted with ether, washed with 10% sulfuric acid and saturated sodium carbonate, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by MPLC (2:1:30 dichloromethane:ether:hexane) to give 1.06 g (78% yield) of enone **52** as a colorless oil, 94% pure by GC. Further purification by MPLC on a column containing 11% silver nitrate on silica gel (20% ethyl acetate in hexane) gave enone **52** as a colorless oil, 97% pure by GC: IR (film) 1692, 1642 $cm^{-1}$; $^1H$ NMR $\delta$ 5.17 (t, $J$ = 7.3 Hz, 1 H), 5.15–5.05 (br s, 1 H), 2.50–2.44 (m, 2 H), 2.38–2.32 (m, 2 H), 2.32–2.20 (m, 3 H), 2.21–2.09 (m, 3 H), 2.02 (s, 3 H), 2.09–1.93 (m,

Table I. Bond Lengths (Å) and Bond Angles (deg) for the 172° Compound 53

| Bond Lengths | | | |
|---|---|---|---|
| C(1)–C(2) | 1.530 (5) | C(1)–C(10) | 1.547 (4) |
| C(2)–C(3) | 1.499 (6) | C(3)–C(5) | 1.344 (4) |
| C(3)–C(3A) | 1.494 (7) | C(5)–C(6) | 1.486 (5) |
| C(5)–C(10) | 1.526 (6) | C(6)–C(7) | 1.542 (4) |
| C(7)–C(8) | 1.555 (6) | C(8)–C(9) | 1.549 (4) |
| C(8)–C(14) | 1.602 (3) | C(8)–C(8A) | 1.550 (5) |
| C(9)–C(10) | 1.561 (3) | C(9)–C(11) | 1.519 (6) |
| C(10)–C(10A) | 1.538 (5) | C(11)–C(12) | 1.524 (3) |
| C(12)–C(13) | 1.528 (4) | C(13)–C(14) | 1.557 (5) |
| C(13)–C(18) | 1.550 (3) | C(13)–F(2) | 1.425 (4) |
| C(14)–C(15) | 1.545 (4) | C(14)–C(14A) | 1.549 (5) |
| C(15)–C(16) | 1.530 (4) | C(16)–C(17) | 1.533 (6) |
| C(17)–C(18) | 1.581 (4) | C(17)–C(22) | 1.555 (4) |
| C(17)–C(17A) | 1.548 (5) | C(18)–C(19) | 1.529 (6) |
| C(19)–C(20) | 1.539 (4) | C(20)–C(21) | 1.549 (5) |
| C(20)–C(20A) | 1.525 (5) | C(20)–C(20B) | 1.528 (7) |
| C(21)–C(22) | 1.506 (6) | C(22)–C(23) | 1.326 (6) |
| C(23)–C(24) | 1.518 (6) | C(23)–Cl | 1.784 (3) |
| **Bond Angles** | | | |
| C(2)–C(1)–C(10) | 105.7 (2) | C(1)–C(2)–C(3) | 103.5 (2) |
| C(2)–C(3)–C(5) | 111.0 (4) | C(2)–C(3)–C(3A) | 120.9 (3) |
| C(5)–C(3)–C(3A) | 128.1 (3) | C(3)–C(5)–C(6) | 128.9 (4) |
| C(3)–C(5)–C(10) | 112.0 (3) | C(6)–C(5)–C(10) | 119.0 (3) |
| C(5)–C(6)–C(7) | 110.4 (2) | C(6)–C(7)–C(8) | 113.2 (3) |
| C(7)–C(8)–C(9) | 107.6 (2) | C(7)–C(8)–C(14) | 110.0 (3) |
| C(9)–C(8)–C(14) | 108.3 (2) | C(7)–C(8)–C(8A) | 107.4 (2) |
| C(9)–C(8)–C(8A) | 112.6 (3) | C(14)–C(8)–C(8A) | 111.0 (2) |
| C(8)–C(9)–C(10) | 116.3 (2) | C(8)–C(9)–C(11) | 112.4 (2) |
| C(10)–C(9)–C(11) | 113.5 (3) | C(1)–C(10)–C(5) | 101.4 (2) |
| C(1)–C(10)–C(9) | 111.2 (2) | C(5)–C(10)–C(9) | 109.5 (3) |
| C(1)–C(10)–C(10A) | 108.1 (3) | C(5)–C(10)–C(10A) | 110.9 (2) |
| C(9)–C(10)–C(10A) | 114.9 (3) | C(9)–C(11)–C(12) | 111.9 (3) |
| C(11)–C(12)–C(13) | 111.8 (2) | C(12)–C(13)–C(14) | 110.4 (2) |
| C(12)–C(13)–C(18) | 113.6 (2) | C(14)–C(13)–C(18) | 114.2 (3) |
| C(12)–C(13)–F(2) | 105.0 (3) | C(14)–C(13)–F(2) | 108.0 (2) |
| C(18)–C(13)–F(2) | 104.9 (2) | C(8)–C(14)–C(13) | 112.1 (3) |
| C(8)–C(14)–C(15) | 112.0 (2) | C(13)–C(14)–C(15) | 107.3 (2) |
| C(8)–C(14)–C(14A) | 109.6 (2) | C(13)–C(14)–C(14A) | 108.4 (2) |
| C(15)–C(14)–C(14A) | 107.3 (3) | C(14)–C(15)–C(16) | 113.2 (2) |
| C(15)–C(16)–C(17) | 113.6 (3) | C(16)–C(17)–C(18) | 108.0 (2) |
| C(16)–C(17)–C(22) | 115.5 (3) | C(18)–C(17)–C(22) | 105.9 (2) |
| C(16)–C(17)–C(17A) | 107.2 (2) | C(18)–C(17)–C(17A) | 113.2 (3) |
| C(22)–C(17)–C(17A) | 107.2 (2) | C(13)–C(18)–C(17) | 114.1 (2) |
| C(13)–C(18)–C(19) | 112.0 (3) | C(17)–C(18)–C(19) | 111.6 (2) |
| C(18)–C(19)–C(20) | 113.3 (3) | C(19)–C(20)–C(21) | 108.7 (3) |
| C(19)–C(20)–C(20A) | 110.8 (3) | C(21)–C(20)–C(20A) | 109.5 (3) |
| C(19)–C(20)–C(20B) | 109.2 (4) | C(21)–C(20)–C(20B) | 108.5 (3) |
| C(20A)–C(20)–C(20B) | 110.0 (3) | C(20)–C(21)–C(22) | 113.9 (3) |
| C(17)–C(22)–C(21) | 112.1 (3) | C(17)–C(22)–C(23) | 126.7 (4) |
| C(21)–C(22)–C(23) | 121.2 (3) | C(22)–C(23)–C(24) | 134.5 (3) |
| C(22)–C(23)–Cl | 119.3 (3) | C(24)–C(23)–Cl | 106.2 (3) |

7 H), 1.80 (t, $J$ = 2.5 Hz, 3 H), 1.63 (s, 3 H), 1.61 (d, $J$ = 4.6 Hz, 3 H), 1.60 (s, 3 H), 1.60 (s, 3 H), 0.91 (s, 6 H). Anal. Calcd for $C_{29}H_{43}FO$: C, 81.63; H, 10.17; F, 4.46. Found: C, 81.67; H, 10.31; F, 4.67.

**2-(7-Fluoro-3,8,11,14,14-pentamethyl-3(*E*),7(*E*),11(*E*)-octadecatrien-16-yn-1-yl)-1,3-dimethylcyclopent-2-en-1-ol (8).** To a solution of 0.070 g (0.165 mmol) of enone **52** in 30 mL of ether at −78 °C was added 1.5 mL (1.2 M in ether, 1.82 mmol) of MeLi–LiBr. The reaction was allowed to warm to 24 °C and stirred for 40 min, and then 1 mL of methanol was added. The mixture was diluted with hexane, washed with 5% sodium carbonate solution, dried over sodium sulfate, and concentrated under reduced pressure to give 0.071 g (98% yield) of cyclopentenol **8** as a colorless oil, unstable on GC. The unstable alcohol was stored in a base-washed vial at 0 °C: IR (film) 3500, 1703 cm$^{-1}$; $^1$H NMR $\delta$ 5.17 (t, $J$ = 7.6 Hz, 1 H), 5.16 (t, $J$ = 6.7 Hz, 1 H), 2.39–1.90 (m, 15 H), 1.90–1.75 (m, 3 H), 1.80 (t, $J$ = 2.5 Hz, 3 H), 1.65 (s, 3 H), 1.62 (d, $J$ = 3.3 Hz, 3 H), 1.61 (s, 3 H), 1.59 (s, 1 H), 1.45–1.20 (m, 2 H), 1.31 (s, 3 H), 0.91 (s, 6 H). The cyclopentenyl carbinols did not give satisfactory analysis.

**Cyclization of Cyclopentenol 8.** A solution of 0.0713 g (0.161 mmol) of cyclopentenol **8** in 5 mL of dichloromethane was added slowly (40 min) to a solution of 0.50 mL of $SnCl_4$ (1 M in dichloromethane, 0.483 mmol) in 80 mL of dichloromethane at −78 °C. The yellow mixture was stirred for 10 min, and then 1 mL of triethylamine in ethanol (1:1) was added. The mixture was allowed to warm to 24 °C, worked up as described above, and purified by chromatography (5% ether in hexane). The residue was purified further by MPLC (hexane) to give 0.0579 g (80% yield) of a mixture of fluoropentacycles **55** (*E*-isomer) and **55** (*Z*-isomer), 84:8 by GC, as a white solid.

**Preparation of Fluoropentacycle 55 (*E*-isomer) for X-ray Analysis.** Recrystallization from dichloromethane–acetonitrile (1:1 to 1:2) gave fluoropentacycle **55** (*E*-isomer), mp 185–188 °C, suitable for X-ray analysis: IR 1624 cm$^{-1}$; $^1$H NMR $\delta$ 5.22 (d, $J$ = 6.3 Hz, 1 H), 2.52 (br d, $J$ = 13.2 Hz, 1 H), 2.41 (br d, $J$ = 14.5 Hz, 1 H), 2.38–2.09 (m, 2 H), 2.35 (d, $J$ = 14.5 Hz, 1 H), 2.27 (s, 3 H), 2.13–1.97 (m, 2 H), 1.96–1.69 (m, 1 H), 1.84 (dd, $J$ = 13.1, 4.2 Hz, 1 H), 1.82 (ddd, $J$ = 13.7, 5.1, 2.6 Hz, 1 H), 1.76 (ddd, $J$ = 15.2, 6.8, 4.2 Hz, 1 H), 1.60–1.36 (m, 3 H), 1.59 (s, 3 H), 1.42 (dd, $J$ = 12.2, 4.2 Hz, 1 H), 1.34–1.18 (m, 3 H), 1.13–0.92 (m, 2 H), 0.97 (s, 3 H), 0.96 (s, 3 H), 0.94 (s, 3 H), 0.93 (s, 3 H), 0.92 (s, 3 H).

Table II. Bond Lengths (Å) and Bond Angles (deg) for the 188° Compound 55 (*E*-isomer)

| Bond Lengths | | | |
|---|---|---|---|
| C(1)–C(2) | 1.525 (3) | C(1)–C(10) | 1.547 (2) |
| C(2)–C(3) | 1.527 (2) | C(3)–C(3′) | 1.486 (2) |
| C(3)–C(5) | 1.315 (2) | C(5)–C(6) | 1.495 (2) |
| C(5)–C(10) | 1.530 (2) | C(6)–C(7) | 1.532 (2) |
| C(7)–C(8) | 1.548 (2) | C(8)–C(8′) | 1.539 (2) |
| C(8)–C(9) | 1.561 (2) | C(8)–C(14) | 1.586 (2) |
| C(9)–C(10) | 1.552 (2) | C(9)–C(11) | 1.528 (2) |
| C(10)–C(10′) | 1.546 (2) | C(11)–C(12) | 1.485 (2) |
| C(12)–C(13) | 1.327 (2) | C(13)–C(14) | 1.540 (2) |
| C(13)–C(18) | 1.517 (2) | C(14)–C(14′) | 1.543 (2) |
| C(14)–C(15) | 1.551 (2) | C(15)–C(16) | 1.535 (2) |
| C(16)–C(17) | 1.545 (2) | C(17)–C(17′) | 1.545 (2) |
| C(17)–C(18) | 1.572 (2) | C(17)–C(22) | 1.549 (2) |
| C(18)–C(19) | 1.530 (2) | C(19)–C(20) | 1.554 (2) |
| C(20)–C(20′) | 1.530 (3) | C(20)–C(20″) | 1.531 (2) |
| C(20)–C(21) | 1.538 (2) | C(21)–C(22) | 1.504 (3) |
| C(22)–C(22′) | 1.323 (2) | C(22′)–C(22″) | 1.520 (2) |
| C(22′)–Cl | 1.764 (2) | | |
| **Bond Angles** | | | |
| C(2)–C(1)–C(10) | 106.2 (1) | C(1)–C(2)–C(3) | 103.1 (1) |
| C(2)–C(3)–C(3′) | 120.7 (1) | C(2)–C(3)–C(5) | 110.3 (1) |
| C(3′)–C(3)–C(5) | 129.0 (1) | C(3)–C(5)–C(6) | 129.4 (1) |
| C(3)–C(5)–C(10) | 113.6 (1) | C(6)–C(5)–C(10) | 117.0 (1) |
| C(5)–C(6)–C(7) | 109.5 (1) | C(6)–C(7)–C(8) | 113.8 (1) |
| C(7)–C(8)–C(8′) | 109.6 (1) | C(7)–C(8)–C(9) | 108.6 (1) |
| C(8′)–C(8)–C(9) | 110.0 (1) | C(7)–C(8)–C(14) | 110.6 (1) |
| C(8′)–C(8)–C(14) | 109.1 (1) | C(9)–C(8)–C(14) | 108.8 (1) |
| C(8)–C(9)–C(10) | 117.3 (1) | C(8)–C(9)–C(11) | 110.1 (1) |
| C(10)–C(9)–C(11) | 112.4 (1) | C(1)–C(10)–C(5) | 100.5 (1) |
| C(1)–C(10)–C(9) | 112.2 (1) | C(5)–C(10)–C(9) | 111.6 (1) |
| C(1)–C(10)–C(10′) | 108.0 (1) | C(5)–C(10)–C(10′) | 107.9 (1) |
| C(9)–C(10)–C(10′) | 115.6 (1) | C(9)–C(11)–C(12) | 111.4 (1) |
| C(11)–C(12)–C(13) | 125.1 (1) | C(12)–C(13)–C(14) | 123.1 (1) |
| C(12)–C(13)–C(18) | 112.3 (1) | C(14)–C(13)–C(18) | 114.0 (1) |
| C(8)–C(14)–C(13) | 111.1 (1) | C(8)–C(14)–C(14′) | 109.4 (1) |
| C(13)–C(14)–C(14′) | 110.0 (1) | C(8)–C(14)–C(15) | 113.3 (1) |
| C(13)–C(14)–C(15) | 105.3 (1) | C(14′)–C(14)–C(15) | 107.7 (1) |
| C(14)–C(15)–C(16) | 114.7 (1) | C(15)–C(16)–C(17) | 115.0 (1) |
| C(16)–C(17)–C(17′) | 111.3 (1) | C(16)–C(17)–C(18) | 105.2 (1) |
| C(17′)–C(17)–C(18) | 110.2 (1) | C(16)–C(17)–C(22) | 111.3 (1) |
| C(17′)–C(17)–C(22) | 110.4 (1) | C(18)–C(17)–C(22) | 108.3 (1) |
| C(13)–C(18)–C(17) | 108.3 (1) | C(13)–C(18)–C(19) | 115.7 (1) |
| C(17)–C(18)–C(19) | 110.9 (1) | C(18)–C(19)–C(20) | 111.5 (1) |
| C(19)–C(20)–C(20′) | 109.4 (1) | C(19)–C(20)–C(20″) | 108.9 (1) |
| C(20′)–C(20)–C(20″) | 109.2 (2) | C(19)–C(20)–C(21) | 110.5 (1) |
| C(20′)–C(20)–C(21) | 108.0 (1) | C(20″)–C(20)–C(21) | 110.7 (1) |
| C(20)–C(21)–C(22) | 114.8 (1) | C(17)–C(22)–C(21) | 114.7 (1) |
| C(17)–C(22)–C(22′) | 122.5 (2) | C(21)–C(22)–C(22′) | 122.8 (2) |
| C(22)–C(22′)–C(22″) | 131.0 (1) | C(22)–C(22′)–Cl | 120.5 (1) |
| C(22″)–C(22′)–Cl | 108.6 (1) | | |

**Crystallographic Data.** The bond lengths and angles obtained in the X-ray crystallographic determinations are given in Tables I and II. Table I refers to the 172° compound **53**, Figure 2a; Table II to the 188° compound **55** (*E*-isomer), Figure 2b.

**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.

**Registry No.** (±)-**6**, 144374-88-9; (±)-**7**, 144374-96-9; (±)-**8**, 144375-05-3; **9**, 141-79-7; **10**, 30414-53-0; **11**, 60417-86-9; (±)-**12**, 144374-63-0; **13**, 144374-64-1; **14**, 144374-65-2; **15**, 144374-66-3; **16**, 144374-67-4; (±)-**17**, 144374-68-5; **18**, 144374-69-6; (±)-**19**, 144374-70-9; (±)-**20**, 144374-71-0; (±)-**21**, 144374-72-1; **22**, 144374-74-3; **23**, 144374-73-2; **24**, 144374-76-5; **25**, 144374-75-4; **26**, 144374-77-6; **27**,

144374-78-7; **28**, 144374-79-8; **32**, 144374-80-1; **33**, 144374-81-2; (±)-**34**, 144374-82-3; **35**, 144374-83-4; **36**, 33579-86-1; (±)-**37**, 144374-84-5; **38**, 144374-85-6; **39**, 144374-86-7; **40**, 144374-87-8; (±)-**41**, 144374-91-4; **42**, 144374-92-5; (±)-**43**, 144384-94-1; **44**, 144374-93-6; **45**, 144374-94-7; **46**, 144374-95-8; (±)-**47**, 144374-99-2; **48**, 144375-00-8; (±)-**49**, 144375-01-9; **50**, 144375-02-0; **51**, 144375-03-1; **52**, 144375-04-2; (±)-**53**, 144374-89-0; (±)-**54**, 144374-90-3; (±)-**55Z**, 144409-53-0; (±)-**55E**, 144409-52-9; (±)-**56**, 144374-97-0; $CH_2$=$C(CH_3)MgBr$, 13291-18-4; $ICH_2SnBu_3$, 66222-29-5; $Me_2NC(OMe)_2Me$, 18871-66-4; 1-chloro-1-fluoro-2-methoxy-2-methylcyclopropane, 144346-53-2; 1-formyl-1-methylcyclopropane, 4515-89-3; 1-(bromomagnesio)-1-methylcyclopropane, 144374-98-1.

**Supplementary Material Available**: Additional X-ray crystallographic structure determination information in tables of crystal data, data collection method, and solution and refinement data; Table 4, atomic coordinates including equivalent isotropic displacement coefficient; Table 5, anisotropic displacement coefficients; and Table 6, H-atom coordinates including isotropic displacement coefficients (14 pages). Ordering information is given on any current masthead page.

# The Fluorine Atom as a Cation-Stabilizing Auxiliary in Biomimetic Polyene Cyclizations. 4. Total Synthesis of *dl*-β-Amyrin[1]

**William S. Johnson,* Mark S. Plummer, S. Pulla Reddy, and William R. Bartlett**

*Contribution from the Department of Chemistry, Stanford University, Stanford, California 94305.*
*Received June 2, 1992*

**Abstract:** A total synthesis of *dl*-β-amyrin (**1**) is reported, utilizing as the key step a cyclization of a polyolefin having a fluorine atom as the cation-stabilizing (C-S) auxiliary. Thus polyene substrate **7**, upon acid-catalyzed cyclization, gave fluoropentacycle **8**, a compound having five fused rings and bearing six of the eight chiral centers found in the natural product β-amyrin (**1**). The preparation of polyene **7** required the development of stereoselective methods for introducing the three alkene bonds of the cyclopentenol side chain. The trisubstituted 11-cis alkene was formed by stereoselective inversion of the corresponding trans alkene, utilizing an epoxidation/elimination sequence (84% yield, cis:trans 99:1). A new method of producing the tetrasubstituted 7-trans fluoroalkene bond was developed utilizing the Trost palladium-catalyzed alkylation of keto ester **18** with allylic acetate **17** (83% yield, trans:cis 88:12). The trisubstituted 3-trans alkene was constructed by the Brady–Julia rearrangement of cyclopropylcarbinol **22**, giving bromide **23** (82% yield, trans:cis 97:3). Optimum conditions for cyclization of cyclopentenol **7** afforded **8** in 65–70% yield. The fluorine atom acting as a C-S auxiliary at *pro*-C-13 in **7** exerted regiocontrol over the cyclization process, creating a 6-membered ring C and enhancing the yield of pentacyclic product. Conversion of **8** to *dl*-β-amyrin (**1**) entailed oxidative removal of the C-22 allene group, regioselective elimination of the C-13 fluorine atom to produce the C-12 alkene, enlargement and functionalization of ring A, and establishment of the trans A/B ring fusion. The identity of synthetic *dl*-β-amyrin was unequivocally established by comparison of its chromatographic and spectral properties with those of the natural product. This study, together with the earlier papers in this series, enlarges the scope of practical biomimetic synthesis of polycyclic natural (and unnatural) triterpenes to include pentacyclic compounds.

β-Amyrin (**1**), isolated from the latex of rubber trees and from *Erythroxylum coca*, is the parent compound of the oleanane family of pentacyclic triterpenoids. The challenge of assembling this compound, possessing five fused rings and eight chiral centers, has attracted synthetic chemists for several decades, resulting in a number of reports on the conversion of other triterpenes to β-amyrin as well as two formal total syntheses.

Barton and co-workers[2] reported the first formal total synthesis of **1** in 1968 by demonstrating that the natural product 18α-olean-12-ene (**4**) could be converted to β-amyrin in 19 steps (ca. 0.001% yield). Their strategy involved a clever utilization of the olefinic bond of substance **4** to produce modified functionality, which allowed for epimerization at C-18. The olefinic bond of the resulting 18-*epi*-**4** was then employed for delivering functionality in sequence to C-11, C-1, and finally C-2, allowing for introduction of the hydroxy group at C-3. Compound **4** had been synthesized earlier by Ghera and Sondheimer[3] (in unspecified yield) by a route which employed the strategy of joining two decalone derivatives together and, following a series of functional group manipulations, forming the C ring of the oleanene skeleton by cyclization of the tetracyclic diol **3** (Figure 1).

In 1972, van Tamelen and co-workers[4a] reported a synthesis of δ-amyrin (**6**), in which the D and E rings were preformed in the epoxy triene **5**. Acid-catalyzed cyclization (**5** → **6**), afforded δ-amyrin (ca. 4% yield), a compound which had earlier been converted by Brownlie and co-workers[4b] to **4**. Since Barton had converted **4** to **1**, van Tamelen's route also constituted a formal total synthesis of β-amyrin.

Tori and co-workers[5] reported the acid-catalyzed backbone rearrangement of the triterpene derivative 3β,4β-epoxyfriedelane (**2**) to a mixture containing β-amyrin (**1**) and other compounds. Ireland and Walba[6a] in 1976 and later Kametani and co-workers[6b] reported total syntheses of friedelin, from which **2** is derived.

(1) This represents paper no. 7 on cation-stabilizing auxiliaries in polyene cyclizations. For the first six 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.; (e) Johnson, W. S.; Fletcher, V. R.; Chenera, B.; Bartlett, W. R.; Tham, F. S.; Kullnig, R. K.; (f) Johnson, W. S.; Buchanan, R. A.; Bartlett, W. R.; Tham, F. S.; Kullnig, R. K. *J. Am. Chem. Soc.*, previous three papers in this issue.

(2) Barton, D. H. R.; Lier, E. F.; McGhie, J. F. *J. Chem. Soc. C* **1968**, 1031–1040.

(3) Ghera, E.; Sondheimer, F. *Tetrahedron Lett.* **1964**, 3887–3891.

(4) (a) van Tamelen, E. E.; Seiler, M. P.; Wierenga, W. *J. Am. Chem. Soc.* **1972**, *94*, 8229–8231. (b) Brownlie, G.; Fayez, M. B. E.; Spring, F. S.; Stevenson, R.; Strachen, W. S. *J. Chem. Soc.* **1956**, 1377.

(5) Tori, M.; Tsuyuki, T.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 3381–3383.

(6) (a) Ireland, R. E.; Walba, D. M. *Tetrahedron Lett.* **1976**, 1071–1074. (b) Kametani, T.; Hirai, Y.; Shiratori, Y.; Fukumoto, K.; Satoh, S. *J. Am. Chem. Soc.* **1978**, *100*, 554–560.

0002-7863/93/1515-515$04.00/0 