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]

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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.

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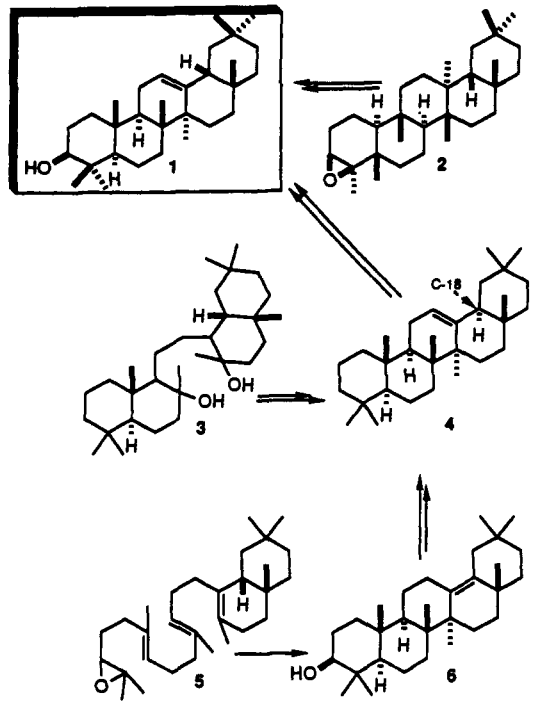
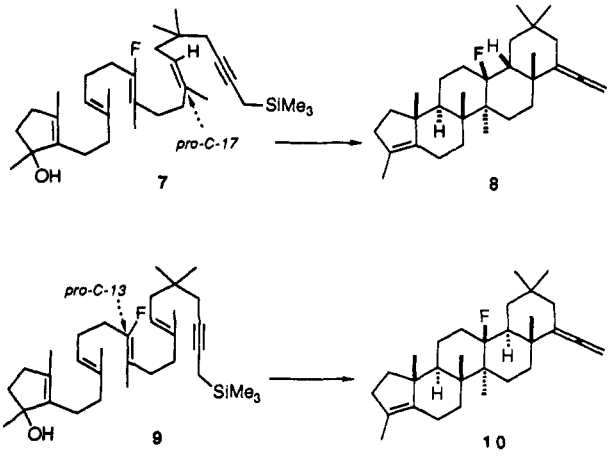


Figure 1. Previous synthetic studies directed toward β-amyrin (1).

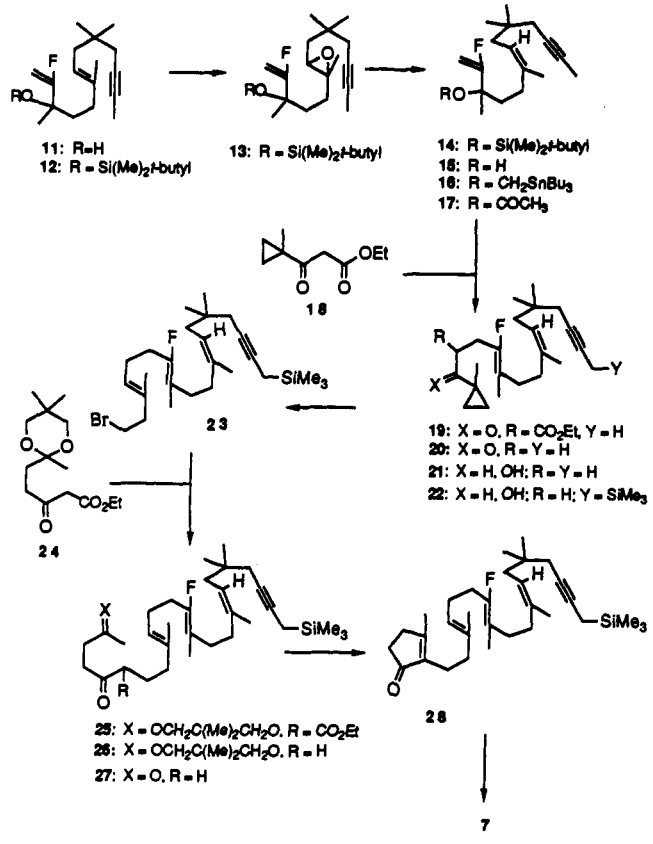
β-Amyrin has also been produced[7] by backbone rearrangement of the triterpenes taraxerol and multiflorenol, neither of which has been synthesized.

In the present paper, we disclose a total synthesis of racemic β-amyrin (1) in ca. 0.2% overall yield, based on a biomimetic polyene cyclization that generates in one step (7 → 8) and 65–70% yield six of the eight chiral centers of the pentacyclic triterpene. The success of this route relied upon our earlier studies,[1d,e] in which it was found that the fluorine atom, suitably positioned on the polyolefin, could effectively stabilize incipient cationic centers during acid-catalyzed cyclization, leading to greatly enhanced yields of tetracyclic and pentacyclic compounds. Of particular importance to this study was the additional discovery[1f] that the fluorine atom acting as a cation-stabilizing (C-S) auxiliary at the *pro*-C-13 position in substrate 9 controlled the regiochemistry of the cyclization so as to produce exclusively the 6-membered ring C in pentacycle 10.



In order to apply these findings to the synthesis of β-amyrin, it was necessary to modify the substrate 9[1f] such that the olefinic bond at *pro*-C-17 possessed the cis configuration for production of the cis D/E ring fusion found in 1. The synthesis and cyclization of 7, employing a novel stereoselective approach to the tetra-substituted trans fluoroalkene bond,[8] and the conversion of pentacycle 8 to β-amyrin (1) are described below.

Scheme I



Synthesis of the Cyclization Substrate. The synthesis of cyclopentenol 7 was linear in design, incorporating the fluoro dienynol 11, prepared as described previously.[1f] Transposition of the 11-trans alkene to the cis configuration and stereoselective formation of the 7-trans fluoroalkene by the palladium-catalyzed alkylation of allylic acetate 17 constituted the major new departures from prior art.

Thus, fluoro dienynol 11 was prepared[1f] in 20% overall yield (nine steps) from mesityl oxide. Transposition of the trans trisubstituted alkene to the cis isomer was accomplished by the epoxidation/phosphine elimination route of Vedejs and Fuchs.[9] Prior protection of the alcohol[10] to prevent cyclic ether formation gave the *tert*-butyl(dimethylsilyl) ether 12, which upon treatment with *m*-chloroperoxybenzoic acid yielded the epoxide 13 (Scheme I). Treatment of 13 with lithium diphenylphosphide followed by iodomethane yielded the cis trisubstituted alkene 14 in 81% overall yield from 11 (99:1, cis:trans). Removal of the alcohol protective group with tetra-*n*-butylammonium fluoride gave the alcohol 15, which provided the acetate 17 in 83% yield upon acetylation.

The approach taken to the synthesis of the required trans fluoro tetrasubstituted alkene was predicated on our earlier studies,[1f] in which it was discovered that Claisen-type rearrangements of tertiary alcohol 11 produced mixtures predominating in the undesired cis fluoro tetrasubstituted alkenes. Thus, thermal rearrangement of alcohol 11 with *N*,*N*-dimethylacetamide dimethyl acetal using Eschenmoser–Claisen conditions had given a 1:1 mixture of the cis and trans amides, while the acetate derivative of 11, upon rearrangement under Ireland enolate Claisen con-

(7) Nakanishi, K.; Goto, T.; Ito, S.; Natori, S.; Nozoe, S. *Natural Products Chemistry*; Academic Press, Inc.: New York, 1974; Vol. 1.

(8) Because of the fluorine atom, the tetrasubstituted olefinic bonds, as in formulas 7 and 9, have the *Z*-configuration; however, for the sake of clarity in the discussion section, we prefer to refer to this configuration as trans, while the stereoisomers having the *E*-configuration will be referred to as cis.

(9) Vedejs, E.; Fuchs, P. L. *J. Am. Chem. Soc.* **1973**, *95*, 822–825.

(10) Corey, E. J.; Cho, H.; Rucker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, 3455–3458.

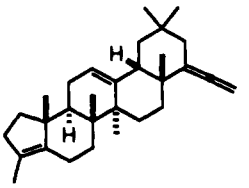
ditions, afforded a 4:1 (cis:trans) mixture of acids. As before, we attempted to utilize the Wittig rearrangement of the (tributylstannyl)methyl derivative **16**.[1f] However, unlike our experience with the rearrangement of the (tributylstannyl)methyl derivative of alcohol **11**, compound **16** resulted in a decreased trans/cis stereoselectivity (2:1).

In an effort to improve both the yield and the stereoselectivity, recourse was taken to Trost methodology,[11] utilizing the palladium-catalyzed alkylation of allylic acetate **17** with keto ester **18**. This synthetic strategy promised to effect introduction of the cyclopropyl group, required for the subsequent formation of the 3-trans alkene by the Brady–Julia rearrangement, while at the same time producing the trans fluoroalkene bond. Fortunately, when acetate **17** was allowed to react with the sodium enolate of keto ester **18** in the presence of palladium tetrakis(triphenylphosphine), there was produced an 88:12 mixture of the *pro*-C-13 trans keto ester **19** and its cis isomer, which was readily separated by a single flash chromatography, giving **19** in 73% yield. Decarbethoxylation of keto ester **19**, followed by reduction of the ketone, afforded cyclopropylcarbinol **21** in 95% yield, thereby improving the efficiency of the conversion **15** → **21**, which is now realized in four steps and 61% overall yield.

Conversion of the alcohol **21** to cyclopentenone **28** followed the earlier-established protocol.[1f] Thus, Zweifel methodology[12] was employed to incorporate the propargylsilane moiety by adding *tert*-butyllithium solution to alcohol **21**, followed by treatment with trimethylchlorosilane, affording alcohol **22** in 79% yield. The Brady–Julia rearrangement[13] of **22** entailed bromination with phosphorous tribromide, followed by zinc bromide-catalyzed rearrangement to give bromide **23** (82% yield, trans:cis >97:3). Alkylation of the keto ester **24** with bromide **23** produced keto ester **25**, which could be decarbethoxylated by heating with aqueous base to give ketone **26**.[14] Conversion to diketone **27** by treatment with pyridinium *p*-toluenesulfonate followed by cyclodehydration with aqueous base at ambient temperature afforded the cyclopentenone **28** in 61% overall yield from bromide **23** without isomerization of the base-sensitive propargylsilane moiety.

Completion of the synthesis of cyclopentenol **7** was accomplished by adding methyllithium to cyclopentenone **28** (97% yield). Thus cyclopentenol **7**, bearing the propargylsilane terminating group and having the 3-trans,7-trans,11-cis alkene stereochemistry, was synthesized in over 18% yield for the 15 steps from alcohol **11**.

Cyclization Studies. A variety of reaction conditions were explored in the course of optimizing the cyclization process, including testing different solvents, temperatures, Lewis and protic acid catalysts, varying the concentrations of both the catalyst and the substrate, and changing the order of addition of the reagents. As in earlier studies,[1f] cyclization with trifluoroacetic acid generally yielded some partially cyclized (tricyclic and tetracyclic) compounds, particularly in hydrocarbon solvents. Lewis acid catalysis was observed to cause increased elimination of HF in the cyclization product, producing variable amounts of the tetraene **29**. Tetraene **29**, it should be noted, cannot be used in the present synthetic scheme because the ring C alkene cannot be present prior to the oxidation of the olefinic bonds in ring A and at C-22 during the conversion to β-amyrin (see Scheme II). Optimum conditions for the cyclization were found to require addition of a solution



29

of cyclopentenol **7** in dichloromethane to trifluoroacetic acid in dichloromethane at −70 °C, giving pentacycle **8**, mp 136–138 °C, in 65–70% yield.

Preparation of β-Amyrin from Pentacycle 8. This straightforward series of transformations entailed (a) removal of the allene moiety from ring E, (b) elimination of the fluorine atom to produce the C-12 alkene, and (c) construction of the correctly functionalized six-membered ring A with the trans A/B ring fusion (Scheme II).

Pentacycle **8** was oxidized by the method of Sharpless,[15] using ruthenium trichloride and sodium metaperiodate, which provided the triketone **30**, mp 141–142 °C, in 75% yield. Treatment with aqueous base gave the enone **31**, which upon standing in a solution of tin tetrachloride in dichloromethane at −10 °C underwent regioselective elimination of hydrogen fluoride, affording alkene **32**, a highly crystalline material, mp >240 °C, in 70% overall yield from **30**.

Selective removal of the C-22 ketone required experimentation. Because the C-22 ketone is more sterically hindered, the C-3 ketone could be selectively protected as the ketal **33**. Reduction of the C-22 ketone was attempted, albeit unsuccessfully, by the Wolff–Kishner and *p*-toluenesulfonohydrazide/sodium cyanoborohydride methods. The ultimately successful scheme, based on Barton methodology,[16] involved lithium aluminum hydride reduction of **33** to the alcohols **34** (1:1 mixture) followed by formation of the methyl xanthate **35** by reaction with carbon disulfide and iodomethane (77% yield overall from **33**). Reduction of **35** with tributyltin hydride and azobis(isobutyronitrile) afforded the C-22 deoxygenated pentacycle **36**, mp 182–184 °C, which upon hydrolysis provided the ketone **37** in 87% overall yield from **35**.

With rings B, C, D, and E constructed, there remained only to modify the A ring by introduction of the 4,4-dimethyl groups and reduction of the C-3 ketone to the 3β-alcohol. The first objective was accomplished according to established methodology.[17] Thus, treatment of **37** with benzenethiol and formaldehyde in the presence of triethanolamine gave the 4-phenylthiomethylated enone **38** in 73% yield. This compound could then be converted to the 4,4-dimethyl ketone **39** by reductive methylation, employing lithium in ammonia, followed by quenching of the C-4 enolate with iodomethane. Sodium borohydride reduction of crude ketone **39**, followed by careful chromatographic purification, led to crystalline *dl*-β-amyrin (**1**), mp 195–196 °C, in 19% overall yield from **37**, which was identified by rigorous comparison with a sample of the natural product by GC coinjection, ^{1}H NMR, solution IR, and mass spectrometric analysis.

Discussion and Conclusions

The synthetic challenges presented by the preparation of the cyclization substrate cyclopentenol **7** centered chiefly on the design of stereoselective routes to the 3-trans, 7-trans, and 11-cis alkene bonds. As few selective methods exist for producing cis trisubstituted alkenes, the alternative of converting the 11-trans to the 11-cis alkene was employed and proved to be highly efficient in practice (84% yield, 99:1, cis:trans).

(11) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4730–4743.

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

(13) Brady, S. F.; Ilton, M. A.; Johnson, W. S. *J. Am. Chem. Soc.* **1968**, *90*, 2882–2889. This procedure, which has since been used quite extensively, has now been improved by increasing the reaction temperature of the first step and also by using 2,6-lutidine instead of the weaker base collidine. These changes (see Experimental Section) have resulted in consistently improved yields of over 80% for the total process **22** → **23**.

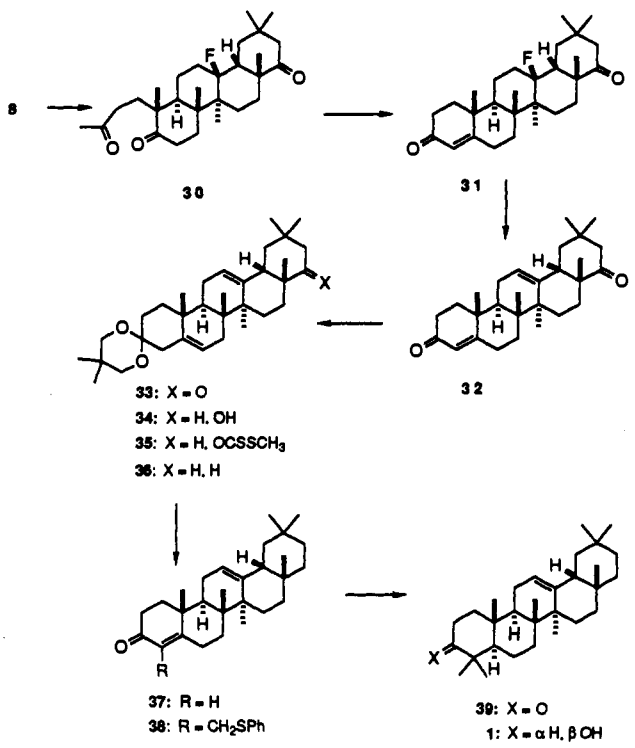
(14) The original methodology (Johnson, W. S.; Semmelhack, M. F.; Sultanbawa, M. U. S.; Dolak, L. A. *J. Am. Chem. Soc.* **1968**, *90*, 2994–2996) for this type of conversion involved the use of the ethylene glycol ketals corresponding to **24**, **25**, and **26**, which were very unstable, even toward flash chromatography. The six-membered ring ketals with the *gem*-dimethyl group, in contrast, were relatively stable, and their use resulted in significant improvement in the methodology as described in the Experimental Section on the conversion of **23** → **27**.

(15) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936–3938.

(16) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574–1585.

(17) (a) Smith, A. B., III; Mewshaw, R. *J. Org. Chem.* **1984**, *49*, 3685–3689. (b) Kirk, D. N.; Petrow, V. *J. Chem. Soc.* **1962**, 1091–1096. (c) Stork, G.; Rosen, P.; Goldman, N.; Coombs, R. V.; Tsuji, J. *J. Am. Chem. Soc.* **1965**, *87*, 275–286. (d) Bartlett, W. R.; Johnson, W. S.; Plummer, M. S.; Small, V. R., Jr. *J. Org. Chem.* **1990**, *55*, 2215–2224.

Scheme II



Synthesis of the 7-trans tetrasubstituted fluoroalkene moiety challenged our earlier methodology,[1f] which had employed the Wittig rearrangement of the (tributylstannyl)methyl derivative of alcohol **11**. It was not anticipated that the presence of the cis alkene in place of the trans alkene at C-6 would affect the stereoselectivity and yield of this rearrangement. It should be noted, however, that a change in rearrangement stereoselectivity (from 4:1 to 1:1 cis:trans) had been observed earlier when the proximate trans alkene was replaced by a saturated alkane chain in our related studies of the Ireland enolate Claisen rearrangement.[1f] To account for the enolate Claisen stereoselectivity, it may be conjectured that a π-stacking interaction of the nearby trans alkene with the electron-rich π-bonds participating in the rearrangement transition state is enhanced in the conformation in which the extended chain is axial to the chairlike transition-state ring, thus favoring production of the cis fluoroalkene.

In an effort to improve the 7-trans alkene selectivity, we elected a synthetic strategy which did not involve a rearrangement through a cyclic transition state: the Trost palladium-catalyzed enolate alkylation of an allylic acetate. The high trans fluoroalkene stereoselectivity (88:12 trans:cis) observed in the palladium-catalyzed alkylation of keto ester **18** may possibly be attributed to decreased steric interactions in the conformation leading to the trans alkene, i.e., the bulky cyclopropyl keto ester enolate preferentially binds *away* from the extended chain bearing the proximate cis alkene when both moieties are bound to the palladium atom in the transition state. The high yield (83%) of this alkylation, together with the favorable stereoselectivity, promises to make it a favored approach to the synthesis of trans fluoroalkenes. The Brady–Julia rearrangement of cyclopropylcarbinol **22** proceeded highly stereoselectively in improved[13] (83%) yield (>97:3 trans:cis), thus completing the synthesis of the requisite alkene functions in the substrate.

The regioselectivity of the cyclization of cyclopentenol **7**, in which the 6-membered ring C was produced in pentacycle **8**, provides further evidence of the effectiveness of the C-13 fluorine atom as a C-S auxiliary in stabilizing cationic charge. The high degree of stereoselectivity observed in the production of **8** in over 65% yield, possessing the A/B/C/D/E anti-trans-anti-trans-syn-cis backbone configuration with seven chiral centers, is particularly noteworthy. The propargylsilane terminating group, with its greater nucleophilicity compared to that of the methylacetylene terminator, ensured that the mildest cyclization conditions could be employed, affording a high yield of pentacycle **8** with retention of the fluorine atom, even under acidic conditions that favor elimination of HF.

The transformation of fluoropentacycle **8** to β-amyrin required modification of rings A and E along with introduction of the remaining chiral centers at C-3 and C-5. Removal of the allene moiety in ring E and cleavage of the ring A alkene without affecting the fluorine atom at C-13 was accomplished effectively by the Sharpless oxidation methodology.[15] Subsequent mild Lewis acid treatment of the fluoro ketone **31** (using $SnCl_4$) caused rapid regioselective dehydrofluorination, producing the C-12 alkene exclusively in 80% yield. In contrast, protic acid treatment of **31**, using trifluoroacetic acid, resulted in the formation of a mixture of olefinic bond isomers.

Advantage was taken of the superior efficiency[14] of preparation and cleavage of ketals of 2,2-dimethylpropane-1,3-diol (87% overall yield) in the selective protection of the C-3 ketone in ring A prior to reduction of the ring E ketone. The three-step xanthate reduction sequence effectively overcame the problem of extreme steric hindrance at the C-22 ketone position, enabling the production of the reduced ketal **36** in an acceptable 73% yield from ketone **33**.

Completion of the A-ring transformations on a small scale was quite problematical. After considerable effort, modification of the phenylthiomethylation step gave respectable yields; however, numerous attempts to perform the reductive methylation step on a 0.05-mmol (or less) scale, using either **38** or closely modeled compounds, gave capricious results and generally poor yields. (The main impurity was the monomethylated product.) In spite of these operational difficulties, the eventual formation of a compound that was rigorously shown to be *dl*-β-amyrin provides unequivocal proof of the stereochemical course of the cyclization of **7**.

In conclusion, this report of the complete total synthesis of *dl*-β-amyrin (**1**) by a polyolefinic cyclization enlarges the scope of practical biomimetic synthesis to include naturally occurring (as well as unnatural) pentacyclic triterpenes. The overall yield of **1** was approximately 0.2%, although it should be noted that the overall yield of ketone **37** was nearly 1%. The cornerstone of the synthesis is the incorporation of the fluorine atom as a C-S auxiliary at the *pro*-C-13 position in substrate **7**, which effects regiocontrol over the formation of the 6-membered ring C in pentacycle **8** and greatly enhances the yield of pentacyclic product.

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[18] 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 a 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. The complex envelopes of signals elicited by the methylene protons in the ^1H NMR spectra of the polycyclic compounds are not recorded in this paper. 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. The

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

yields given for the synthetic intermediates are for material that is used in the next step of the synthetic sequence. These materials are generally contaminated with ca. 1–2% of an isomeric substance, which can often be eliminated by further purification (e.g., crystallization) at a late stage in the synthesis.

3-((*tert*-Butyldimethylsilyl)oxy)-2-fluoro-3,6,9,9-tetramethyl-1,6(*E*)-tridecadien-11-yne (12). To a solution of 6.67 g (25.1 mmol) of alcohol **11**[1f] and 5.86 mL (50.1 mmol) of 2,6-lutidine in 30 mL of dichloromethane was added 8.6 mL (37.6 mmol) of *tert*-butyldimethylsilyl triflate dropwise. The mixture was stirred at 20 °C for 1 h and then cooled to 0 °C, and the reaction was quenched by the addition of saturated aqueous sodium bicarbonate. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane) to give 9.14 g (96% yield) of the ether **12** as a colorless oil, 98% pure by GC: IR (film) 1665 cm^{-1}; ^1H NMR δ 5.15 (dt, J = 7.71, 1.2 Hz, 1 H), 4.57 (dd, J = 50.67, 2.62 Hz, 1 H), 4.56 (dd, J = 18.34, 2.54 Hz, 1 H), 2.12–1.88 (m, 6 H), 1.78 (t, J = 2.56 Hz, 3 H), 1.80–1.67 (m, 1 H), 1.57 (s, 3 H) 1.60–1.52 (m, 1 H), 1.38 (d, J = 1.12 Hz, 3 H), 0.89 (br s, 15 H), 0.10 (s, 3 H), 0.09 (s, 3 H). Anal. Calcd for $C_{23}H_{41}FOSi$: C, 72.57; H, 10.86. Found: C, 72.72; H, 11.12.

3-((*tert*-Butyldimethylsilyl)oxy)-6,7(*E*)-epoxy-2-fluoro-3,6,9,9-tetramethyl-1-tridecen-11-yne (13). To a solution of 4.69 g (12.34 mmol) of silyl ether **12** in 75 mL of dichloromethane at 0 °C was added 5.54 g (16.04 mmol) of *m*-chloroperoxybenzoic acid. The solution was stirred for 30 min, and then it was washed with 10% aqueous sodium bisulfite and saturated sodium bicarbonate, dried over magnesium sulfate, and concentrated under reduced pressure to give 4.81 g (98.5% yield) of the epoxide **13** as a colorless oil, unstable on GC. The analytical sample was purified by flash chromatography (2% ethyl acetate in hexane): IR (film) 1670, 1250, 840 cm^{-1}; ^1H NMR δ 4.56 (dt, J = 50.90, 3.20 Hz, 1 H), 4.55 (dd, J = 18.31, 2.44 Hz, 1 H), 2.74 (t, J = 6.07 Hz, 1 H), 2.06 (m, 2 H), 1.77 (t, J = 2.48 Hz, 3 H), 1.80–1.33 (m, 6 H), 1.38 (s, 3 H), 1.21 (d, J = 1.76 Hz, 3 H), 1.01 (s, 3 H), 1.00 (s, 3 H), 0.87 (s, 9 H), 0.10 (s, 3 H), 0.09 (s, 3 H). Anal. Calcd for $C_{23}H_{41}FO_2Si$: C, 69.45; H, 10.42. Found: C, 69.48; H, 10.52.

3-((*tert*-Butyldimethylsilyl)oxy)-2-fluoro-3,6,9,9-tetramethyl-1,6(*Z*)-tridecadien-11-yne (14). To a solution of 25 mL (1.0 M, 25 mmol) of lithium diphenylphosphide in THF was added dropwise a solution of 4.81 g (12.1 mmol) of epoxide **13** in 35 mL of THF. The mixture was stirred at 20 °C for 15 h and then cooled to 0 °C, and 2.5 mL of iodomethane was added. The resulting mixture was stirred at 20 °C for 40 min, diluted with water, and concentrated under reduced pressure until the THF was removed. The residue was extracted with hexane and filtered, and the organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The crude residue was purified by flash chromatography (hexane) to give 3.94 g (85% yield) of the silyl ether **14** as a colorless oil, containing ca. 1% of the trans isomer by GC: IR (film) 1670 cm^{-1}; ^1H NMR δ 5.13 (t, J = 7.33 Hz, 1 H), 4.58 (dd, J = 17.43, 2.61 Hz, 1 H), 4.58 (dd, J = 18.34, 2.61 Hz, 1 H), 2.12–1.90 (m, 6 H), 1.77 (t, J = 2.56 Hz, 3 H), 1.70–1.47 (m, 2 H), 1.67 (d, J = 1.12 Hz, 3 H), 1.38 (d, J = 1.12 Hz, 3 H), 0.89 (br s, 15 H), 0.11 (s, 3 H), 0.10 (s, 3 H). Anal. Calcd for $C_{23}H_{41}FOSi$: C, 72.57; H, 10.86. Found: C, 72.71; H, 11.13.

2-Fluoro-3-hydroxy-3,6,9,9-tetramethyl-1,6(*Z*)-tridecadien-11-yne (15). To a solution of 4.16 g (10.94 mmol) of silyl ether **14** in 50 mL of THF was added **22** mL (1.0 M, 22 mmol) of tetrabutylammonium fluoride in THF, and the solution was stirred at 21 °C for 6 h. Water was then added, the THF was removed at reduced pressure, and the residue was extracted with ether, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by flash chromatography (7% ethyl acetate in hexane) to give 2.85 g (97% yield) of the alcohol **15** as a colorless oil, containing ca. 1% of the trans isomer by GC: IR (film) 3460, 1670, 860 cm^{-1}; ^1H NMR δ 5.16 (t, J = 7.63 Hz, 1 H), 4.64 (dd, J = 19.46, 3.12 Hz, 1 H), 4.60 (dd, J = 49.61, 3.12 Hz, 1 H), 2.15–1.90 (m, 6 H), 1.84 (s, 1 H), 1.78 (t, J = 2.58 Hz, 3 H), 1.77–1.59 (m, 2 H), 1.70 (d, J = 1.19 Hz, 3 H), 1.37 (d, J = 1.09 Hz, 3 H), 0.89 (s, 6 H). Anal. Calcd for $C_{17}H_{27}FO$: C, 76.65; H, 10.22. Found: C, 76.39; H, 10.35.

3-Acetoxy-2-fluoro-3,6,9,9-tetramethyl-1,6(*Z*)-tridecadien-11-yne (17). A solution of 2.8 g (10.6 mmol) of alcohol **15**, 0.27 g (2.21 mmol) of 4-(dimethylamino)pyridine, and 2.5 mL (26.5 mmol) of acetic anhydride in 17 mL of pyridine was stirred at 65 °C for 26 h. The solution was diluted with ether, washed with water, 3% sulfuric acid, water, saturated aqueous sodium bicarbonate, and brine, dried over magnesium sulfate, and concentrated under reduced pressure to give an oil. The residue was purified by flash chromatography (2.5–8% ethyl acetate in hexane) to give 0.135 g (4.8% yield) of the unreacted alcohol **15** and 2.72 g (83% yield) of acetate **17** as a colorless oil, containing ca. 1% of the trans isomer by GC: IR (film) 1740, 1670, 1240 cm^{-1}; ^1H NMR δ 5.16 (t, J = 7.72, 1 H), 4.72 (dd, J = 18.72, 3.47, 1 H), 4.55 (dd, J = 49.86, 3.54 Hz, 1 H), 2.03 (s, 3 H), 2.02–1.85 (m, 8 H), 1.77 (t, J = 2.56 Hz, 3 H), 1.68 (d, J = 1.15 Hz, 3 H), 1.61 (d, J = 1.15 Hz, 3 H), 0.89 (s, 6 H). Anal. Calcd for $C_{19}H_{29}FO_2$: C, 73.99; H, 9.48. Found: C, 73.93; H, 9.34.

1-Methyl-1-(2-carbethoxy-4-fluoro-1-oxo-5,8,11,11-tetramethyl-4(*Z*),8(*Z*)-pentadecadien-13-ynyl)cyclopropane (19). A solution of 1.95 g (11.45 mmol) of keto ester **18**[13] in 12 mL of THF was added dropwise to a suspension of 0.435 g (60% in mineral oil, 10.90 mmol) of sodium hydride in 12 mL of THF. After being stirred for 30 min at 20 °C, the clear solution was added to a solution of 1.67 g (5.42 mmol) of acetate **17**, 0.3 g (0.26 mmol) of tetrakis(triphenylphosphine)palladium(0), and 0.64 g (2.45 mmol) of triphenylphosphine in 12 mL of THF. The mixture was stirred at 65 °C for 38 h as three additional 0.26-g (0.23 mmol) portions of the palladium catalyst were added at 9-h intervals. The mixture was cooled to 0 °C and added to saturated aqueous ammonium chloride overlaid with ether and filtered, and the organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography (2–5% ethyl acetate in hexane) to give 0.06 g (3% yield) of unreacted acetate **17**, 0.24 g (10% yield) of the cis keto ester, and 1.66 g (73% yield) of the trans keto ester **19** as a colorless oil: IR (film) 1750, 1690 cm^{-1}; ^1H NMR δ 5.16 (t, J = 7.48 Hz, 1 H), 4.13 (q, J = 7.22 Hz, 2 H), 3.84 (dd, J = 8.24, 6.35 Hz, 1 H), 2.86–2.64 (m, 2 H), 2.12–1.90 (m, 8 H), 1.77 (t, J = 2.53 Hz, 3 H), 1.69 (d, J = 1.05 Hz, 3 H), 1.57 (d, J = 2.51 Hz, 3 H), 1.43–1.22 (m, 2 H), 1.33 (s, 3 H), 1.22 (t, J = 7.14 Hz, 3 H), 0.89 (s, 6 H), 0.81–0.72 (m, 2 H). Anal. Calcd for $C_{26}H_{39}FO_3$: C, 74.60; H, 9.39. Found: C, 74.64; H, 9.48.

1-Methyl-1-(4-fluoro-1-oxo-5,8,11,11-tetramethyl-4(*Z*),8(*Z*)-pentadecadien-13-ynyl)cyclopropane (20). A suspension of 2.38 g (5.69 mmol) of keto ester **19**, 24 mL of 5% aqueous sodium hydroxide in 80 mL of THF, and 80 mL of methanol was stirred at 70 °C for 40 min. Water was then added, the organic solvents were removed at reduced pressure, and the aqueous residue was neutralized with 5% sulfuric acid and extracted with ether. The organic layer was washed with water, saturated aqueous sodium bicarbonate, and brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by flash chromatography (3% ethyl acetate in hexane) to give 1.92 g (97% yield) of ketone **20** as a colorless oil, 99% pure by GC: IR (film) 1685 cm^{-1}; ^1H NMR δ 5.15 (t, J = 7.69 Hz, 1 H), 2.58–2.40 (m, 4 H), 2.06 (br s, 4 H), 1.99–1.91 (m, 4 H), 1.77 (t, J = 2.56 Hz, 3 H), 1.70 (d, J = 1.08 Hz, 3 H), 1.59 (d, J = 2.68 Hz, 3 H), 1.33 (s, 3 H), 1.25–1.18 (m, 2 H), 0.90 (s, 6 H), 0.73–0.67 (m, 2 H). Anal. Calcd for $C_{23}H_{35}FO$: C, 79.71; H, 10.18; F, 5.48. Found: C, 79.93; H, 10.18; F, 5.33.

1-Methyl-1-(4-fluoro-1-hydroxy-5,8,11,11-tetramethyl-4(*Z*),8(*Z*)-pentadecadien-13-ynyl)cyclopropane (21). To a solution of 1.65 g (4.75 mmol) of ketone **20** in 35 mL of ether at 0 °C was added 5.3 mL (1.0 M, 5.3 mmol) of lithium aluminum hydride solution in THF. The mixture was stirred for 10 min, warmed to 22 °C for 3 h, and then cooled to 0 °C, followed by the successive additions of 0.3 mL of water, 0.3 mL of 15% aqueous sodium hydroxide, and 0.9 mL of water. The solution was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (6% ethyl acetate in hexane) to give 1.63 g (98% yield) of alcohol **21** as a colorless oil, 99% pure by GC: IR (film) 3400 cm^{-1}; ^1H NMR δ 5.14 (t, J = 7.25 Hz, 1 H), 2.81 (dd, J = 8.73, 4.21 Hz, 1 H), 2.42–2.20 (m, 2 H), 2.16–2.00 (m, 4 H), 1.98–1.91 (m, 4 H), 1.77 (t, J = 2.48 Hz, 3 H), 1.80–1.60 (m, 2 H), 1.70 (s, 3 H), 1.59 (d, J = 2.51 Hz, 3 H), 1.41 (s, 1 H), 1.01 (s, 3 H), 0.90 (s, 6 H), 0.40–0.25 (m, 4 H). Anal. Calcd for $C_{23}H_{37}FO$: C, 79.25; H, 10.70. Found: C, 79.44; H, 10.61.

1-Methyl-1-(4-fluoro-1-hydroxy-5,8,11,11-tetramethyl-15-(trimethylsilyl)-4(*Z*),8(*Z*)-pentadecadien-13-ynyl)cyclopropane (22). To a solution of 9.4 mL (1.7 M in pentane, 15.95 mmol) of *tert*-butyllithium and 2.89 mL (19.15 mmol) of tetramethylethylenediamine in 15 mL of ether at −78 °C was added 1.85 g (5.32 mmol) of alcohol **21** in 15 mL of ether. The mixture was allowed to warm to 0 °C while being stirred for 1.3 h, and then it was cooled to −78 °C and treated with 3.37 mL (26.6 mmol) of chlorotrimethylsilane. The mixture was warmed to 23 °C for 30 min, treated with 5 mL of water, diluted with hexane, washed with saturated aqueous ammonium chloride and saturated sodium carbonate, dried over anhydrous potassium carbonate, and concentrated under reduced pressure. The oily residue was stirred with 35 mL of methanol and 4.0 g of potassium carbonate for 2 h at 23 °C, concentrated under reduced pressure, extracted with ether, washed with water, dried with magnesium sulfate, and concentrated under reduced pressure to give an oil. The oil was purified by flash chromatography (5.5–7% ethyl acetate in hexane) to give 2.01 g (79% yield) of alcohol **22**, 97% pure by GC, as a colorless oil: IR (film) 3420, 1710, 1260 cm^{-1}; ^1H NMR δ 5.15 (t, J = 7.14 Hz, 1 H), 2.80 (dd, J = 8.24, 4.12 Hz, 1 H), 2.41–2.20 (m, 2 H), 2.12–2.01 (m, 4 H), 2.00 (t, J = 2.75 Hz, 2 H), 1.94 (d, J = 7.8 Hz, 2 H),

1.78–1.62 (m, 2 H), 1.70 (s, 3 H), 1.58 (d, J = 2.44 Hz, 3 H), 1.43 (s, 1 H), 1.42 (t, J = 2.71 Hz, 2 H), 1.02 (s, 3 H), 0.90 (s, 6 H), 0.38–0.24 (m, 4 H), 0.07 (s, 9 H). Anal. Calcd for $C_{26}H_{45}FOSi$: C, 74.21; H, 10.79. Found: C, 73.96; H, 10.67.

1-Bromo-7-fluoro-3,8,11,14,14-pentamethyl-18-(trimethylsilyl)-3(*E*),7(*Z*),11(*Z*)-octadecatrien-16-yne[13] **(23).** To a mixture of 1.26 g (3.00 mmol) of alcohol **22**, 0.68 g (7.8 mmol) of anhydrous lithium bromide, and 0.46 mL (3.97 mmol) of 2,6-lutidine in 30 mL of ether at −78 °C was added 0.29 mL (3.00 mmol) of phosphorous tribromide. After 10 min, the mixture was warmed to 22 °C for 2 h and then cooled to −10 °C, and 0.60 mL of 2,6-lutidine was added, followed by 0.5 g of water. The mixture was diluted with ether in pentane (1:1), washed with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate, and concentrated under reduced pressure. A solution of the above crude product in 10 mL of ether was added to a suspension of 1.75 g (7.80 mmol) of anhydrous zinc bromide in 25 mL of ether at −78 °C. The resulting mixture was stirred at 22 °C for 5 h, diluted with hexane, washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by flash chromatography (1–2% ethyl acetate in hexane) to give 1.18 g (82% yield) of bromide **23** as a colorless oil, containing ca. 3% of the cis isomer by GC: IR (film) 1720, 1270 cm^{-1}; ^{1}H NMR δ 5.21 (t, J = 6.80 Hz, 1 H), 5.17 (t, J = 7.25 Hz, 1 H), 3.40 (t, J = 7.55 Hz, 2 H), 2.51 (t, J = 7.32 Hz, 2 H), 2.28–2.13 (m, 4 H), 2.10–2.02 (m, 4 H), 2.00 (t, J = 2.67 Hz, 2 H), 1.95 (d, J = 7.63 Hz, 2 H), 1.71 (d, J = 1.16 Hz, 3 H), 1.60 (s, 3 H), 1.56 (d, J = 2.68 Hz, 3 H), 1.42 (t, J = 2.61 Hz, 2 H), 0.90 (s, 6 H), 0.08 (s, 9 H). Anal. Calcd for $C_{26}H_{44}BrFSi$: C, 64.68; H, 9.19. Found: C, 64.57; H, 9.10.

6-Carbethoxy-2,2-((2′,2′-dimethylpropane-1′,3′-diyl)dioxy)-13-fluoro-5-oxo-9,14,17,20,20-pentamethyl-24-(trimethylsilyl)-9(*E*),13(*Z*),17(*Z*)-tetracosatrien-22-yne[14] **(25).** To a suspension of 0.50 g (12.44 mmol, 60% in oil, washed with THF) of sodium hydride in 2.0 mL of THF was added a solution of 3.51 g (12.91 2 mmol) of the known[19] keto ester **24** in 5 mL of THF. The mixture was stirred for 15 min, and then a solution of 1.55 g (3.11 mmol) of bromide **23** in 5 mL of THF was added. Most of the solvent was removed under reduced pressure and replaced with a solution of 0.20 g of sodium iodide in 10 mL of acetonitrile. The mixture was stirred at 60 °C for 16 h, diluted with ether, washed with 5% sulfuric acid, water, saturated aqueous sodium bicarbonate, and brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by flash chromatography (8% ethyl acetate in hexane) to give 1.73 g (83% yield) of keto ester **25** as a colorless oil, unstable on GC; IR (film) 1730, 1705 cm^{-1}; ^{1}H NMR δ 5.16 (t, J = 7.10 Hz, 1 H), 5.12 (t, J = 8.70 Hz, 1 H), 4.17 (q, J = 7.19 Hz, 2 H), 3.55 (d, J = 11.36 Hz, 2 H), 3.47–3.42 (m, 1 H), 3.38 (d, J = 11.36 Hz, 2 H), 2.80–2.62 (m, 2 H), 2.26–1.90 (m, 18 H), 1.72 (s, 3 H), 1.59 (s, 3 H), 1.57 (d, J = 2.21 Hz, 3 H), 1.43 (t, J = 2.20 Hz, 2 H), 1.36 (s, 3 H), 1.26 (t, J = 7.14 Hz, 3 H), 1.04 (s, 3 H), 0.92 (s, 6 H), 0.85 (s, 3 H), 0.09 (s, 9 H). Anal. Calcd for $C_{40}H_{67}FO_5Si$: C, 71.16; H, 10.01. Found: C, 71.16; H, 10.04.

2,2-((2′,2′-Dimethylpropane-1′,3′-diyl)dioxy)-13-fluoro-5-oxo-9,14,17,20,20-pentamethyl-24-(trimethylsilyl)-9(*E*),13(*Z*),17(*Z*)-tetracosatrien-22-yne (26). A mixture of 1.63 g (2.42 mmol) of keto ester **25** and 9.6 mL of 5% aqueous sodium hydroxide in 40 mL of THF and 40 mL of methanol was stirred at 65 °C for 30 min. The mixture was then cooled and diluted with water, and the organic solvents were removed at reduced pressure. The solution was neutralized with 5% sulfuric acid and extracted with ether. The organic layer was washed with water, saturated aqueous sodium bicarbonate, and brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by flash chromatography (8% ethyl acetate in hexane) to give 1.34 g (92% yield) of ketal **26** as a colorless oil, unstable on GC: IR (film) 1700, 850 cm^{-1}; ^{1}H NMR δ 5.17 (t, J = 7.14 Hz, 1 H), 5.13 (t, J = 6.10 Hz, 1 H), 3.55 (d, J = 11.43 Hz, 2 H), 3.40 (d, J = 11.59 Hz, 2 H), 2.58 (t, J = 7.75 Hz, 2 H), 2.39 (t, J = 7.44 Hz, 2 H), 2.27–1.92 (m, 14 H), 2.02 (t, J = 2.4 Hz, 2 H), 1.72 (s, 3 H), 1.70–1.62 (m, 2 H), 1.60–1.55 (m, 6 H), 1.44 (t, J = 2.4 Hz, 2 H), 1.36 (s, 3 H), 1.04 (s, 3 H), 0.92 (s, 6 H), 0.86 (s, 3 H), 0.09 (s, 9 H). Anal. Calcd for $C_{37}H_{63}FO_3Si$: C, 73.69; H, 10.54. Found: C, 73.90; H, 10.73.

13-Fluoro-9,14,17,20,20-pentamethyl-24-(trimethylsilyl)-9(*E*),13(*Z*),17(*Z*)-tetracosatrien-22-yne-2,5-dione (27). To a solution of 1.34 g (2.23 mmol) of ketal **26** in 100 mL of acetone and 10 mL of water was added 0.60 g (2.39 mmol) of pyridinium *p*-toluenesulfonate. The solution was stirred at 60 °C for 2 h, and then most of the acetone was removed at reduced pressure. The residue was diluted with ether, washed with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by flash chromatography (15% ethyl acetate in hexane) to give 1.12 g (97% yield) of diketone **27** as a nearly colorless oil, unstable on GC: IR (film) 1715 cm^{-1}; ^{1}H NMR δ 5.15 (t, J = 7.09 Hz, 1 H), 5.12 (t, J = 5.61 Hz, 1 H), 2.72–2.61 (m, 4 H), 2.39 (t, J = 7.48 Hz, 2 H), 2.27–1.90 (m, 12 H), 2.06 (s, 3 H), 2.00 (t, J = 2.44 Hz, 2 H), 1.72–1.60 (m, 2 H), 1.70 (d, J = 1.19 Hz, 3 H), 1.60–1.52 (m, 6 H), 1.42 (t, J = 2.45 Hz, 2 H), 0.90 (s, 6 H), 0.07 (s, 9 H). Anal. Calcd for $C_{32}H_{53}FO_2Si$: C, 74.35; H, 10.34. Found: C, 74.63; H, 10.52.

2-(7-Fluoro-3,8,11,14,14-pentamethyl-18-(trimethylsilyl)-3(*E*),7(*Z*),11(*Z*)-octadecatrien-16-ynyl)-3-methylcyclopent-2-en-1-one (28). A mixture of 0.488 g (0.94 mmol) of diketone **27**, 13.5 mL of 10% aqueous sodium hydroxide, 14 mL of THF, and 22 mL of methanol was stirred at 22 °C for 96 h. The mixture was then diluted with water, most of the organic solvent was removed under reduced pressure, and the residue was extracted with ether. The aqueous layer was acidified with 5% sulfuric acid and extracted with ether, and the combined ethereal layers were washed with water, saturated aqueous sodium bicarbonate, and brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by flash chromatography (8% ethyl acetate in hexane) to give 0.404 g (86% yield) of enone **28** as a colorless oil, 96% pure by GC: IR (film) 1705, 1650 cm^{-1}; ^{1}H NMR δ 5.15 (t, J = 7.29 Hz, 1 H), 5.07 (t, J = 6.41 Hz, 1 H), 2.49–2.42 (m, 2 H), 2.37–2.30 (m, 2 H), 2.28–1.91 (m, 19 H), 1.70 (s, 3 H), 1.62 (s, 3 H), 1.56 (t, J = 5.53 Hz, 3 H), 1.42 (t, J = 2.54 Hz, 2 H), 0.89 (s, 6 H), 0.07 (s, 9 H). Anal. Calcd for $C_{32}H_{51}OFSi$: C, 77.03; H, 10.31; F, 3.81. Found: C, 76.91; H, 10.15; F, 3.75.

2-(7-Fluoro-3,8,11,14,14-pentamethyl-18-(trimethylsilyl)-3(*E*),7(*Z*),11(*Z*)-octadecatrien-16-ynyl)-1,3-dimethylcyclopent-2-en-1-ol (7). To a solution of 0.107 g (0.215 mmol) of enone **28** in 7 mL of ether at −13 °C was added 1.4 mL (1.5 M in ether, 2.15 mmol) of methyllithium complexed with lithium bromide. The resulting mixture was stirred at −13 °C for 1.5 h, and then 0.5 g of methanol was added. The mixture was diluted with ether, washed with brine, dried over potassium carbonate, filtered through a plug of basic alumina, and concentrated under reduced pressure to give 0.107 g (97% yield) of cyclopentenol **7** as a colorless oil, unstable on GC: IR (film) 3340, 1440, 1370, 1240 cm^{-1}; ^{1}H NMR δ 5.15 (m, 2 H), 2.35–1.74 (m, 18 H), 1.99 (t, J = 2.75 Hz, 2 H), 1.72 (s, 3 H), 1.65 (s, 6 H), 1.58 (d, J = 2.51 Hz, 3 H), 1.43 (t, J = 2.75 Hz, 2 H), 1.31 (s, 3 H), 1.23 (s, 1 H), 0.92 (s, 6 H), 0.09 (s, 9 H). Because of susceptibility to dehydration, these types of cyclopentenylcarbinols do not give satisfactory combustion analyses.

Cyclization of Cyclopentenol 7. A solution of 0.107 g (0.209 mmol) of cyclopentenol **7** in 10 mL of dichloromethane was added dropwise over 20 min to a solution of 2.7 mL of trifluoroacetic acid in 130 mL of dichloromethane at −70 °C. The mixture was stirred at −70 °C for 30 min and at −65 °C for 30 min, and then 5.2 mL of triethylamine was added. The mixture was allowed to warm to 23 °C, washed with saturated aqueous sodium bicarbonate, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane) to give 0.064 g (70% yield) of *A*,23-dinor-13-fluoro-22-vinylidene-olean-4-ene (**8**),[20] which was recrystallized from acetonitrile to give fine needles, mp 136–138 °C: IR (film) 1950, 1465 cm^{-1}; ^{1}H NMR δ 4.68–4.60 (m, 2 H), 1.57 (s, 3 H), 1.30 (d, J = 2.1 Hz, 3 H), 1.16 (d, J = 6.1 Hz, 3 H), 0.95 (s, 3 H), 0.92 (s, 3 H), 0.90 (s, 6 H); HRMS calcd for $C_{30}H_{45}F$, 424.3505, found, 424.3553. Anal. Calcd for $C_{30}H_{45}F$: C, 84.85; H, 10.67. Found: C, 84.71; H, 10.56.

13-Fluoro-23,24-dinoroleana-4-ene-3,22-dione (31). To a mixture of 0.039 g (0.092 mmol) of fluoroalkene **8** and 0.24 g (1.12 mmol) of sodium metaperiodate in 2 mL of acetonitrile, 2 mL of carbon tetrachloride, and 3 mL of water was added 5 mg of ruthenium trichloride. The mixture was rapidly stirred at 23 °C for 7 h, diluted with water, and extracted with dichloromethane. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography (30% ethyl acetate–hexane) to give 31 mg (75% yield) of triketone **30** as a solid which could be recrystallized from ethanol–water to give prisms, mp 141–142 °C: IR (film) 1715, 1465, 1390, 1370 cm^{-1}; ^{1}H NMR δ 2.52–2.26 (m, 5 H), 2.13 (s, 3 H), 1.32 (d, J = 2.14, 3 H), 1.10 (d, J = 3.67 Hz, 3 H), 1.06 (s, 3 H), 1.04 (s, 3 H), 1.03 (s, 3 H), 0.99 (s, 3 H); HRMS calcd for $C_{28}H_{43}FO_3$, 446.3196, found, 446.3128.

A suspension of 0.038 g (0.085 mmol) of trione **30** and 1.8 mL of 5% aqueous sodium hydroxide in 7 mL of THF and 7 mL of methanol was stirred at 70 °C for 40 min. Water was added, the organic solvents were removed at reduced pressure, and the aqueous residue was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by flash chromatography (25% ethyl acetate–hex-

(19) Eder, U.; Cleve, G.; Haffer, G.; Neef, G.; Sauer, G.; Wiechert, R.; Fuerst, A.; Meier, W. *Chem. Ber.* **1980**, *113*(6), 2249–2254.

(20) The GC of the tertiary alkylfluoro compounds was complicated by partial dehydrofluorination, probably in the injection port.

ane) to give 0.034 g (93% yield) of dione **31** as a colorless solid, mp 217 °C (with phase changes at 205 °C):[19] IR (evaporation onto salt plates) 1715, 1680, 1625 cm^{-1}; ^1H NMR δ 5.74 (s, 1 H), 2.65 (dt, J = 15.0, 5.0 Hz, 1 H), 2.50–2.30 (m, 2 H), 2.39 (d, J = 13.2 Hz, 1 H), 2.20–2.00 (m, 4 H), 1.98 (d, J = 13.2 Hz, 1 H), 1.31 (d, J = 2.1 Hz, 3 H), 1.28 (d, J = 6.0 Hz, 3 H), 1.18 (s, 3 H), 1.00 (s, 3 H), 0.97 (s, 3 H), 0.95 (s, 3 H); HRMS calcd for $C_{28}H_{41}FO_2$, 428.3090, found, 428.3107. Anal. Calcd for $C_{28}H_{41}FO_2$: C, 78.47; H, 9.63. Found: C, 78.07; H, 9.53.

23,24-Dinoroleano-4,12-diene-3,22-dione (32). To a solution of 0.073 g (0.17 mmol) of dione **31** in 8 mL of dichloromethane at −12 °C was added 0.2 mL of a solution of tin tetrachloride in dichloromethane (1.0 M, 0.2 mmol). The resulting solution was stirred at −12 °C for 40 min, and the reaction was then quenched by the addition of aqueous sodium bicarbonate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by flash chromatography (20% ethyl acetate–hexane) to give 0.056 g (80% yield) of dione **32** as a colorless solid. Recrystallization from hexane–ethyl acetate gave needles, mp >240 °C: IR (evaporation onto salt plates) 1700, 1675, 1619 cm^{-1}; ^1H NMR δ 5.76 (s, 1 H), 5.38 (t, J = 3.55 Hz, 1 H), 2.57–2.28 (m, 5 H), 2.18 (dt, J = 14.10, 3.39 Hz, 1 H), 2.13–1.92 (m, 6 H), 1.88–1.61 (m, 5 H), 1.54 (dt, J = 14.0, 3.40 Hz, 1 H), 1.38–1.32 (m, 1 H), 1.26 (s, 3 H), 1.19 (s, 3 H), 1.17 (s, 3 H), 1.01 (s, 3 H), 0.99 (s, 3 H), 0.85 (s, 3 H); HRMS calcd for $C_{28}H_{40}O_2$, 408.3028, found, 408.3009. Anal. Calcd for $C_{28}H_{40}O_2$: C, 82.30; H, 9.87. Found: C, 82.16; H, 9.59.

23,24-Dinor-3,3-((2′,2′-dimethylpropane-1′,3′-diyl)dioxy)oleana-5,12-dien-22-one (33). A mixture of 0.038 g (0.093 mmol) of dione **32**, 0.30 g (2.88 mmol) of 2,2-dimethylpropane-1,3-diol, and 0.05 g (0.20 mmol) of pyridinium *p*-toluenesulfonate in 10 mL of benzene was stirred at 100 °C for 3 h, with a Dean–Stark apparatus used to remove water. The solution was then washed with aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by flash chromatography (20% ethyl acetate–hexane) to give 0.035 g (76% yield) of ketal **33** and 0.007 g of dione **32** (96% yield based on recovered **32**), mp 191–193 °C: IR (KBr) 1690, 1450, 1380, 1100 cm^{-1}; ^1H NMR δ 5.37 (t, J = 2.29 Hz, 1 H), 5.32 (t, J = 3.51 Hz, 1 H), 3.58–3.40 (m, 4 H), 2.62 (dd, J = 14.66, 3.55 Hz, 1 H), 2.45 (d, J = 14.60 Hz, 1 H), 2.42–1.90 (m, 9 H), 1.85–1.75 (m, 1 H), 1.66–1.53 (m, 4 H), 1.38–1.32 (m, 1 H), 1.20 (s, 3 H), 1.13 (s, 3 H), 1.00 (s, 3 H), 0.99 (s, 3 H), 0.98 (s, 3 H), 0.93 (s, 3 H) 0.86 (s, 3 H); HRMS calcd, 494.3747, found, 494.3760. Anal. Calcd for $C_{33}H_{50}O_3$: C, 80.10; H, 10.19. Found: C, 80.18; H, 10.08.

23,24-Dinor-3,3-((2′,2′-dimethylpropane-1′,3′-diyl)dioxy)oleana-5,12-diene (36). To a solution of 0.052 g (0.105 mmol) of ketone **33** in 8 mL of ether at 0 °C was added 0.15 mL (1.0 M, 0.15 mmol) of a solution of lithium aluminum hydride in ether. The mixture was allowed to warm to 21 °C and was stirred for 4 h before it was cooled to 0 °C. The reaction was quenched by the successive addition of water (2 drops), 10% aqueous sodium hydroxide (2 drops), and water (3 drops). The suspension was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 0.052 g of a mixture of epimeric alcohols **34**.

To a solution of the above alcohols **34** in 6 mL of THF at 0 °C was added dropwise 0.08 mL (1.6 M, 0.126 mmol) of a solution of *n*-butyllithium in hexane. The mixture was stirred for 45 min at 0 °C, followed by the addition of 0.1 mL of carbon disulfide. The mixture was stirred at 21 °C for 4 h. The mixture was cooled to 0 °C, and then 0.2 mL of iodomethane was added. The solution was allowed to warm to 23 °C and stirred for 18 h. The mixture was then diluted with ether, washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (2–5% ethyl acetate in hexane) to give 0.047 g (77% overall yield from ketone **33**) of epimeric xanthates **35**.

To a solution of 0.047 g (0.08 mmol) of the xanthates **35** in 18 mL of toluene were added 0.04 mL (0.016 mmol) of 0.4 M tributyltin hydride and 5 mg of azobis(isobutyronitrile). The mixture was heated to 120 °C for 30 min, cooled, and then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (2–4% ethyl acetate in hexane) to give 0.0365 g (95% yield) of ketal **36** as colorless plates, mp 184–186 °C: IR (KBr) 1450, 1400, 1100 cm^{-1}; ^1H NMR δ 5.37 (t, J = 2.32 Hz, 1 H), 5.21 (t, J = 3.51 Hz, 1 H), 3.60–3.40 (m, 4 H), 2.60 (dd, J = 16.00, 5.60 Hz, 1 H), 2.40 (m, 1 H), 2.30–2.12 (m, 3 H), 2.06–1.88 (m, 4 H), 1.80 (dt, J = 13.4, 5.7 Hz, 1 H), 1.12 (s, 3 H), 1.11 (s, 3 H), 0.99 (s, 6 H), 0.93 (s, 3 H), 0.88 (s, 3 H) 0.87 (s, 3 H), 0.84 (s, 3 H); HRMS calcd for $C_{33}H_{52}O_2$, 480.3954, found, 480.3967.

23,24-Dinoroleana-4,12-dien-3-one (37). To a solution of 0.030 g (0.0625 mmol) of ketal **36** in 8 mL of acetone was added 0.030 g (0.158 mmol) of *p*-toluenesulfonic acid, and the solution was stirred at 22 °C for 20 h. The solution was then neutralized with aqueous sodium bicarbonate and concentrated under reduced pressure. The residue was extracted with ether, and the organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (8–10% ethyl acetate in hexane) to give 0.0225 g (91% yield) of enone **37** as colorless crystals, mp 182–184 °C: IR (KBr) 1660, 1600, 1380 cm^{-1}; ^1H NMR δ 5.77 (s, 1 H), 5.27 (t, J = 2.51 Hz, 1 H), 2.57–2.40 (m, 2 H), 2.35–2.27 (m, 1 H), 2.19 (dt, J = 12, 3.6 Hz, 1 H), 2.10–1.90 (m, 6 H), 1.26 (s, 3 H), 1.18 (s, 6 H), 1.11 (s, 3 H), 0.87 (s, 3 H), 0.85 (s, 3 H). Anal. Calcd for $C_{28}H_{42}O$: C, 85.21; H, 10.73. Found: C, 85.29; H, 10.66.

23,24-Dinor-4-((phenylthio)methyl)oleana-4,12-dien-3-one (38). A solution of 12.5 mg (0.032 mmol) of the enone **37**, 0.43 g (excess) of triethanolamine, 0.31 g (excess) of benzenethiol, and 0.34 g (excess) of 37% aqueous formaldehyde solution was heated at 120–125 °C for 8 h. Another 0.43 g of triethanolamine, 0.31 g of thiophenol, and 0.34 g of 37% aqueous formaldehyde solution were then added, and heating was continued for a further 8 h. The mixture was then diluted with ether, washed with 5% aqueous KOH (3 × 12 mL), water, and brine, dried over anhydrous magnesium sulfate, and concentrated. The residue was chromatographed (7–8% ethyl acetate–hexane) to give 12 mg of the product **38** (73% yield): IR (film) 2980, 1675, 1610, 1590 cm^{-1}; ^1H NMR δ 7.40 (d, J = 7.16 Hz, 2 H), 7.33–7.17 (m, 3 H), 5.26 (t, J = 3.36 Hz, 1 H), 3.90 (AB q, J = 16.76, 11.57 Hz, 2 H), 2.61 (dt, J = 14.35, 3.48 Hz, 1 H), 2.50–2.32 (m, 2 H), 2.18 (dt, J = 13.80, 4.65 Hz, 1 H), 1.23 (s, 3 H), 1.16 (s, 3 H), 1.08 (s, 3 H), 0.87 (s, 6 H), 0.85 (s, 3 H); HRMS calcd for $C_{35}H_{48}OS$, 516.3435, found, 516.3444.

***dl*-β-Amyrin (1).** A solution of 11 mg (0.021 mmol) of enone **38** and 1.6 mg (0.042 mmol) of *tert*-butyl alcohol in 2.0 mL of tetrahydrofuran was added dropwise to a solution of 12 mg of lithium wire (excess) in 5.0 mL of liquid ammonia (distilled twice from sodium) at −33 °C, and the blue mixture was stirred at −33 °C for 30 min. The reaction mixture was then cooled to −78 °C, and a cold solution of 0.6 mL of iodomethane (excess) in 2.0 mL of THF was added dropwise. The cooling bath was removed and the mixture was stirred at −33 °C for 40 min. The reaction was then quenched by the addition of excess solid ammonium chloride, and the ammonia was allowed to evaporate. The residue was diluted with water and extracted with ether. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 11 mg of the crude product **39**. Sodium borohydride (10 mg excess) was added to a solution of the above crude product in 1.5 mL of methanol and 1.5 mL of THF at 21 °C. After 15 min, the excess hydride was quenched with acetic acid, and the mixture was extracted with ether. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure, and the residue was purified by flash chromatography (12% ethyl acetate in hexane) to give 2.4 mg of *dl*-β-amyrin (26% overall yield from **38**) which was 100% pure by GC. Recrystallization from petroleum ether gave clusters of fine needles, mp 195–196 °C. This substance was compared with authentic material as follows. The 400-MHz ^1H NMR (including the very complex methylene envelope), solution IR, and HRMS (with a highly detailed fragmentation pattern) of this material were superimposably identical in every detail with the corresponding spectra of natural β-amyrin. Also, the two specimens behaved identically on GC coinjection experiments at various temperatures. For the product **1**: ^1H NMR δ 5.18 (t, J = 3.2 Hz, 1 H), 3.27–3.18 (m, 1 H), 1.13 (s, 3 H), 1.00 (s, 3 H), 0.96 (s, 3 H), 0.93 (s, 3 H), 0.86 (s, 3 H), 0.83 (s, 3 H), 0.79 (s, 3 H).

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Registry No. (±)-**1**, 144666-16-0; (±)-**7**, 144610-24-2; (±)-**8**, 144666-17-1; (±)-**11**, 144374-70-9; (±)-**12**, 144610-25-3; **13**, 144610-26-4; (±)-**14**, 144610-27-5; (±)-**15**, 144610-28-6; (±)-**16**, 144610-29-7; (±)-**17**, 144610-30-0; **18**, 32249-37-9; (±)-**19**, 144610-31-1; **20**, 144610-32-2; (±)-**21**, 144610-33-3; (±)-**22**, 144610-34-4; **23**, 144610-35-5; **24**, 144610-36-6; (±)-**25**, 144610-37-7; (±)-**26**, 144610-38-8; **27**, 144610-39-9; **28**, 144610-40-2; (±)-**29**, 144610-41-3; (±)-**30**, 144633-49-8; (±)-**31**, 144610-42-4; (±)-**32**, 144610-43-5; (±)-**33**, 144610-44-6; (±)-22α-**34**, 144610-45-7; (±)-22β-**34**, 144610-46-8; (±)-22α-**35**, 144610-47-9; (±)-22β-**35**, 144610-48-0; (±)-**36**, 144610-49-1; (±)-**37**, 144610-50-4; (±)-**38**, 144610-51-5; (±)-**39**, 144666-18-2.