The First Examples of Nonenzymic, Biomimetic Polyene Pentacyclizations. Total Synthesis of the Pentacyclic Triterpenoid Sophoradiol[1]

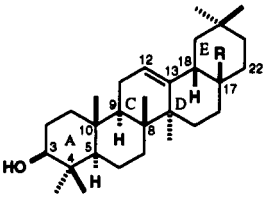
Paul V. Fish and William S. Johnson*

Department of Chemistry, Stanford University, Stanford, California 94305

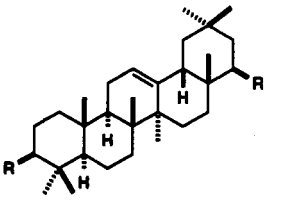
Received January 20, 1994•

The first examples of nonenzymic, biomimetic, polyene *pentacyclizations* are reported. A series of closely related (*E,E,Z,Z*)-polyenes **10–13** with the same tetraene carbon backbone but with differing initiator groups were synthesized and cyclized. The polyenes **10–12** were all synthesized from the known bromo triene **14** using established protocol. Polyene **13** was prepared from aldehyde **16** by reaction of **16** with (1-methyl-1-cyclopropyl)magnesium bromide to give cyclopropylcarbinol **21**. Rearrangement of **21** with $MgBr_2$ to bromide **22** and then alkylation of the lithium enolate of ethyl 3,3-dimethylacrylate with **22** furnished **23**. Isomerization of the double bond into conjugation with the ester and dimethylation of enoate **24** gave **13**. Polyene acetal **10** was cyclized with $SnCl_4$ to pentacycles **26** (4β:4α, 5.5:1) in 51% isolated yield accompanied by regiospecific *in situ* dehydrofluorination. Polyene **11**, with the aldehyde initiator, was cyclized with $SnCl_4$ to yield alcohols **27** (4β:4α, 5.4:1) in 49% yield, again with loss of HF. Cyclization of the epoxide **12** using the preferred conditions of (*i*-PrO)$TiCl_3$ as the Lewis acid gave pentacycle **28** as a major product (GC yield, 21%; 10% isolated) along with the bicyclic ether **29** (13%) and backbone-rearranged bicyclic triene **30** (24%). The protic acid-catalyzed cyclization of tetramethylallyl alcohol **13** furnished fluoropentacycle **33** as the major product in 31% yield. In contrast, the Lewis acid-catalyzed cyclization of **13** gave the dehydrofluorinated pentacycle **32** in 50% yield. Fluoropentacycle **33** was converted to sophoradiol (**3**), a biologically active pentacyclic triterpenoid of the oleanane series, by oxidative cleavage of the C3 isopropylidene and C22 vinylidene groups, regiospecific dehydrofluorination to introduce the C12–13 alkene, and finally stereoselective reduction of diketone **35**. The conversion of **13** → **33** → **3** has demonstrated that the tetramethylallylic alchol group is an effective substitute for the epoxide (cf. **12** → **28**) as an initiator of biomimetic polyene cyclizations.

The pentacyclic triterpenoids of the oleanane series,[2] e.g. β-amyrin (**1**), oleanolic acid (**2**), sophoradiol (**3**),[3] and olean-12-ene (**4**), are derived in Nature by the enzymatic cyclization of oxidosqualene (**5**)[2,4] (Scheme 1). In contrast, the acid-catalyzed cyclization of **5** leads neither to the steroid nor triterpenoid ring structures that are produced by the enzymatic processes but instead to the tricyclic products **6** and **7**.[5] The premature termination of the acid-catalyzed cyclization of **5** can be rationalized by comparison of the relative stabilities of the C-ring cationic intermediates **II** and **III**. Cyclization of **5** initially furnishes the tertiary bicyclic cation **I**, which under enzyme control yields secondary tricyclic cation **II** with the six-membered C ring in an anti-Markovnikov sense. In the absence of enzyme control, cation **I** is converted to the more stable tertiary tricyclic cation **III**, resulting in formation of the five-membered C ring. Cationic intermediate **III** then undergoes α-proton elimination to furnish **6** or cationic rearrangement to **7**. The completion of the enzymatic synthesis of the oleananes involves the cyclization of **II** to dammarane-type cation **IV**, which subsequently undergoes a series of cation-initiated rearrangements and cyzlization to form the six-six DE ring system with the oleanane methyl substitution.



1: R = Me
2: R = CO_2H



3: R = OH
4: R = H

This intrinsic tendency of **5** to follow a Markovnikov cyclization pathway in the absence of enzyme control has probably been the major reason that strategies for the synthesis of the oleananes have not employed the cyclization of acyclic polyene substrates. Syntheses of the oleananes have involved conversion of other triterpenoids,[6] cation–olefin cyclization of a tetracyclic intermediate to form the central C ring,[7] stepwise annelation reactions constructing a single ring at a time,[8] or cyclization of polyene substrates with preformed DE rings.[9]

• Abstract published in *Advance ACS Abstracts,* April 1, 1994.

(1) Preliminary communications: (a) Fish, P. V.; Sudhakar, A. R.; Johnson, W. S. *Tetrahedron Lett.* **1993**, *34*, 7849–7852. (b) Fish, P. V.; Johnson, W. S. *Tetrahedron Lett.* **1994**, *35*, 1469–1472.

(2) (a) Dev, S.; Gupta, A. S.; Patwardhan, S. A. Triterpenoids. In *CRC Handbook of Terpenoids*; Dev, S., Ed.; CRC Press, Inc.: Boca Raton, FL, 1989; Vol. II, pp 7–61, 326–489. (b) Connolly, J. D.; Hill, R. A. *Nat. Prod. Rep.* **1989**, *6*, 475–501.

(3) (a) Mak, T. C. W.; Chiang, T.-C.; Chang, H.-M. *J. Chem. Soc., Chem. Commun.* **1982**, 785–786. (b) Kinjo, J.; Matsumoto, K.; Inoue, M.; Takeshita, T.; Nohara, T. *Chem. Pharm. Bull.* **1991**, *39*, 116–119, and references therein.

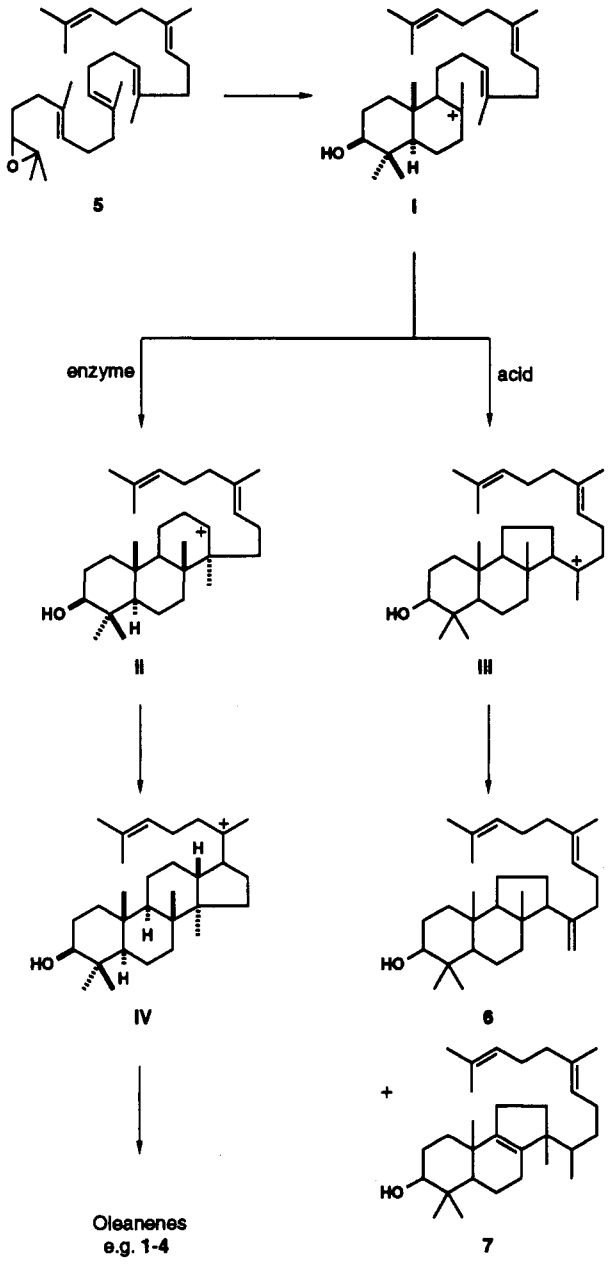
(4) For *in vitro* enzymatic syntheses of β-amyrin (**1**), see: (a) Corey, E. J.; Ortiz de Montellano, P. R. *J. Am. Chem. Soc.* **1967**, *89*, 3362–3363. (b) Suga, T.; Shishibori, T.; Kimoto, S. *Chem. Lett.* **1972**, 129–130.

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

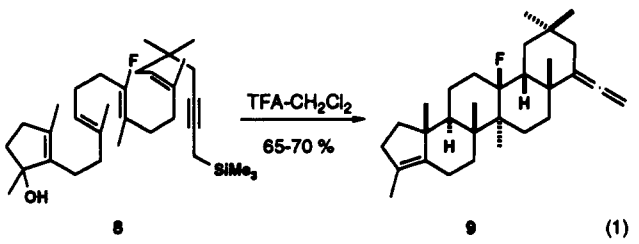
(6) β-Amyrin: (a) Barton, D. H. R.; Lier, E. F.; McGhie, J. F. *J. Chem. Soc. C* **1968**, 1031–1040. Oleanolic acid: (b) Boar, R. B.; Knight, D. C.; McGhie, J. F.; Barton, D. H. R. *J. Chem. Soc. C* **1970**, 678–682. 18α-Oleanane: (c) Corbett, R. E.; Ding, H. L. *J. Chem. Soc. C* **1971**, 1884–1885.

0022-3263/94/1959-2324$04.50/0

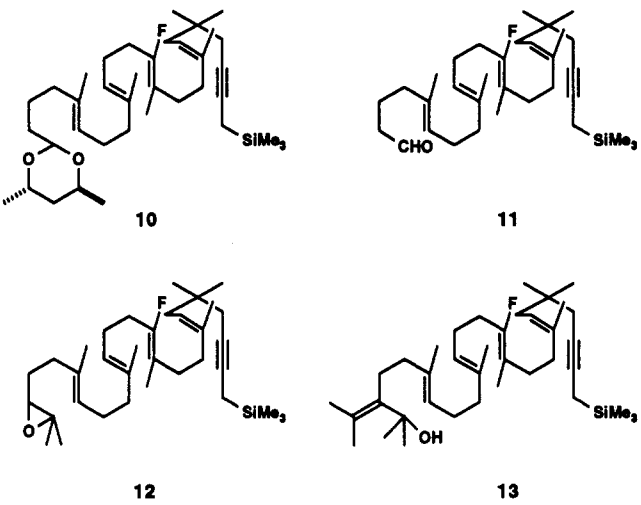
Scheme 1. Comparison of Enzymatic and Acid-Catalyzed Cyclization of Oxidosqualene (5)



Recently, the development of the fluorine atom as a cation-stabilizing (C-S) auxiliary[10] allowed for a total synthesis of β-amyrin (1) which involved the tetracyclization of polyene 8 to pentacycle 9 in 65–70% yield (eq 1).[10d] The fluorine atom appended at *pro*-C13 (oleanane numbering) not only enhanced the cyclization but also controlled the regiochemistry so as to give exclusively the six-membered C ring (by stabilization of the *pro*-C13 cationic intermediate, cf. **II**). Pentacycle **9** was then converted to **1** by the process of (1) degradation of the C22 allene to the corresponding methylene, (2) regiospecific dehydrofluorination to create the C12–13 alkene, and (3) A-ring expansion and functionalization. As an extension of this study, we wished to investigate the nonenzymic cyclization of suitably functionalized acyclic polyene substrates that would potentially yield pentacyclic products in a single step.



We selected a series of related polyenes, **10–13**, as candidate substrates for cyclization. The polyenes share a common carbon framework which upon pentacyclization should yield the oleanane ring system. The polyenes differed in their initiator groups, which allowed for direct comparison of their ability to promote cyclization and also some flexibility of the A-ring functionality of the cyclization products. Preliminary studies involved the polyene substrate **10** with the acetal initiator group at *pro*-C4 as



these types of cyclizations have been achieved in high yield with the cyclization products well characterized.[11] The pentanediol acetal was selected as it has proven to be a preferred acetal initiator group because of the relatively mild cyclization conditions that can be employed and the potential for asymmetric induction during cyclization if the homochiral diol is used.[10b,12] The corresponding

(7) Oleana-11,13(18)-diene: (a) Corey, E. J.; Hess, H.-J.; Proskow, S. *J. Am. Chem. Soc.* **1959**, *81*, 5258–5259; **1963**, *85*, 3979–3983. 18α(H)-Olean-12-ene and olean-13(18)-ene: (b) Barltrop, J. A.; Littlehailes, J. D.; Rushton, J. D.; Rogers, N. A. J. *Tetrahedron Lett.* **1962**, 429–432. (c) Ghera, E.; Sondheimer, F. *Tetrahedron Lett.* **1964**, 3887–3891.

(8) Germanicol: Ireland, R. E.; Baldwin, S. W.; Dawson, D. J.; Dawson, M. I.; Dolfini, J. E.; Newbould, J.; Johnson, W. S.; Brown, M.; Crawford, R. J.; Hudrlik, P. F.; Rasmussen, G. H.; Schmiegel, K. K. *J. Am. Chem. Soc.* **1970**, *92*, 5743–5746.

(9) δ-Amyrin: (a) van Tamelen, E. E.; Seiler, M. P.; Wierenga, W. *J. Am. Chem. Soc.* **1972**, *94*, 8229–8231. (+)-β-Amyrin, (+)-erythrodiol, (+)-oleanolic acid, (−)-δ-amyrin: (b) Corcy, E. J.; Lee, J. *J. Am. Chem. Soc.* **1993**, *115*, 8873–8874.

(10) (a) Johnson, W. S.; Chenera, B.; Tham, F. S.; Kullnig, R. K. *J. Am. Chem. Soc.* **1993**, *115*, 493–497. (b) Johnson, W. S.; Fletcher, V. R.; Chenera, B.; Bartlett, W. R.; Tham, F. S.; Kullnig, R. K. *J. Am. Chem. Soc.* **1993**, *115*, 497–504. (c) Johnson, W. S.; Buchanan, R. A.; Bartlett, W. R.; Tham, F. S.; Kullnig, R. K. *J. Am. Chem. Soc.* **1993**, *115*, 504–515. (d) Johnson, W. S.; Plummer, M. S.; Reddy, S. P.; Bartlett, W. R. *J. Am. Chem. Soc.* **1993**, *115*, 515–521.

(11) For reviews, see: (a) Johnson, W. S. *Tetrahedron* **1991**, *47(41)*, xi–1. (b) Bartlett, P. A. Olefin Cyclization Processes That Form Carbon-Carbon Bonds. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp 341–409. (c) Sutherland, J. K. *Chem. Soc. Rev.* **1980**, *9*, 265–280. (d) Johnson, W. S. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 9–17. (e) Johnson, W. S. *Bioorg. Chem.* **1976**, *5*, 51–98. (f) Johnson, W. S. *Acc. Chem. Res.* **1968**, *1*, 1–8.

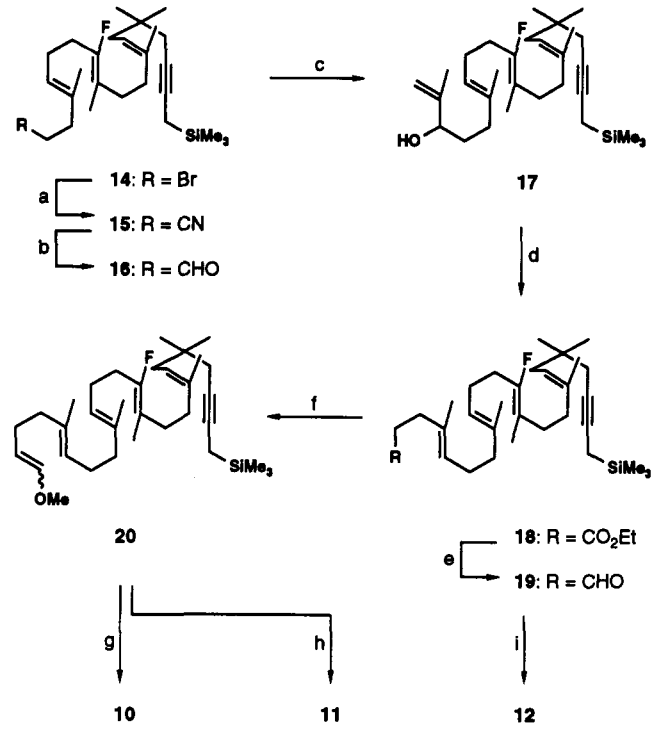
(12) (a) Guay, D.; Johnson, W. S.; Schubert, U. *J. Org. Chem.* **1989**, *54*, 4731–4732. (b) Johnson, W. S.; Elliot, J. D.; Hanson, G. J. *J. Am. Chem. Soc.* **1984**, *106*, 1138–1139.

aldehyde initiator **11** was also investigated.[13] The substrate **12** with the epoxide initiator was an obvious candidate because of its similarity to the enzymatic substrate, namely, oxidosqualene (**5**). In addition, cyclization of **12** would furnish pentacyclic products most closely resembling the oleananes. However, epoxide-initiated cyclizations have proven to be capricious in attempts to apply them to the creation of three or four carbocyclic rings in a single step, and isolated yields of fully cyclized products have been low.[14] Hence, an alternative to the epoxide initiator was required that would prove to be an effective polyene cyclization initiator and then be readily degraded to yield the necessary A-ring functionality. Therefore we decided to explore, as a surrogate initiator, the tetramethylallyl (TMA) cation that would be generated by acid treatment of the corresponding tetramethylallylic alcohol **13**.[15] The expected products of cyclization of **12** and **13** are suitably functionalized to allow for conversion to sophoradiol (**3**) (and subsequently to **4**, **1**, and **2**) and we hoped, by this expedience, to realize the first total synthesis of a pentacyclic triterpenoid by the cyclization of an acyclic substrate.

The polyenes **10**–**13** incorporate several key features which have been shown in a related series to promote and control the cyclization.[10c,d] The fluorine atom cation-stabilizing auxiliary at *pro*-C13 would be expected to control the regiochemistry to give the six-membered C ring.[10c] The olefinic bond *pro*-C17–18, involved in the formation of ring D, has the (*Z*) stereochemistry so that, according to the Stork–Eschenmoser principle,[16] the closure would give the required D/E syn-cis configuration in the cyclization products. The cyclization would be terminated by the highly nucleophilic propargylsilane group.[10b–d] A detailed account of the synthesis and cyclization of these four substrates and the elaboration of pentacycle **33** to sophoradiol (**3**) are described below.

Synthesis of Cyclization Substrates. The synthesis of the cyclization substrates acetal **10**, aldehyde **11**, epoxide **12**, and tetramethylallylic alcohol **13** was linear in design and involved the stereoselective construction of four olefinic bonds. The bromo trienyne **14**, incorporating the *trans*-alkene at *pro*-C8, the *trans*-fluoroalkene at *pro*-C13,[17] the *cis*-alkene at *pro*-C17, and the propargylsilane terminator, has been synthesized previously (21 steps)[10d] and was the starting point for all four substrates. The three substrates **10**–**12** initially shared a common synthetic pathway (Scheme 2) whereby the trisubstituted *trans*-alkene at *pro*-C5–10 was created by an orthoester Claisen rearrangement,[18] **17** → **18**. The construction of the *trans*-alkene at *pro*-C5–10 of **13** required an alternative approach

Scheme 2[a]



[a] (a) NaCN (70%); (b) DIBALH, then H_3O^+ (93%); (c) CH_2=C(Me)MgBr (42%); (d) $MeC(OEt)_3$, H^+ (82%); (e) DIBALH (90%); (f) $Ph_3P^+CH_2OMe\ Cl^-$, *t*-BuLi (55%); (g) (±)-2,4-pentanediol, H^+ (88%); (h) HCl (73%); (i) $(Ph_2S^+CHMe_2)\ BF_4^-$, *t*-BuLi (69%).

(Scheme 3), branching at aldehyde **16**, which involved the rearrangement of cyclopropylcarbinol **21** to homoallylic bromide **22**. The elaboration of **18** to **10**–**12** followed established protocols,[11] but the introduction of the tetramethylallylic alcohol initiator group of **13** by the alkylation of bromide **22** with the enolate of ethyl 3,3-dimethylacrylate, and then subsequent enoate isomerization and dimethylation, represented a departure from previously reported procedures.[15]

Thus, treatment of **14** with sodium cyanide gave nitrile **15** which was then reduced with diisobutylaluminum hydride to aldehyde **16** (Scheme 2). Reaction of **16** with 2-propenylmagnesium bromide gave allylic alcohol **17** which underwent orthoester Claisen rearrangement[18] to ester **18** with high *trans* stereoselectivity (96:4). Reduction of **18** with diisobutylaluminum hydride and treatment of the resulting aldehyde **19** with (methoxymethyl)triphenylphosphorane gave the homologated enol ethers **20** (50:50), which underwent smooth acid-catalyzed acetalization with (±)-2,4-pentanediol to yield the (*E*,*E*,*Z*,*Z*)-tetraene (±)-acetal **10**. Alternatively, careful acid hydrolysis of the enol ethers **20** with dilute hydrochloric acid in THF gave the aldehyde **11**. For an optimum yield of **11**, it proved more efficient to quench the reaction after about 50% conversion and then separate **11** from unreacted **20**. If complete hydrolysis of **20** is allowed, the isolable yield of **11** falls substantially. Epoxide **12** was synthesized by the alkylation of aldehyde **19** with the sulfur ylide derived from diphenyl(2-propyl)sulfonium tetrafluoroborate.[19,20]

(13) The first successful use of the aldehyde function as an initiator of polyene tetracyclizations was performed by Vidyasagar Vuligonda and W. S. Johnson, unpublished experiments.

(14) For reviews, see: (a) Taylor, S. K. *Org. Prep. Proc. Int.* **1992**, *24*, 247–284. (b) van Tamelen, E. E. *Pure Appl. Chem.* **1981**, *53*, 1259–1270. (c) van Tamelen, E. E. *Acc. Chem. Res.* **1975**, *8*, 152–158. (d) van Tamelen, E. E. *Acc. Chem. Res.* **1968**, *1*, 111–120.

(15) (a) Johnson, W. S.; Schaaf, T. K. *Chem. Commun.* **1969**, 611–612. (b) Johnson, W. S.; Gravestock, M. B.; Parry, R. J.; Myers, R. F.; Bryson, T. A.; Miles, D. H. *J. Am. Chem. Soc.* **1971**, *93*, 4330–4332. (c) Prestwich, G. D.; Labovitz, J. N. *J. Am. Chem. Soc.* **1974**, *96*, 7103–7105. (d) Johnson, W. S.; Bunes, L. A. *J. Am. Chem. Soc.* **1976**, *98*, 5597–5602. (e) Gravestock, M. B.; Johnson, W. S.; Myers, R. F.; Bryson, T. A.; Miles, D. H.; Ratcliffe, B. E. *J. Am. Chem. Soc.* **1978**, *100*, 4268–4273. (f) Gravestock, M. B.; Johnson, W. S.; McCarry, B. E.; Parry, R. J.; Ratcliffe, B. E. *J. Am. Chem. Soc.* **1978**, *100*, 4274–4282.

(16) (a) Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5068–5077. (b) Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* **1955**, *38*, 1890–1904.

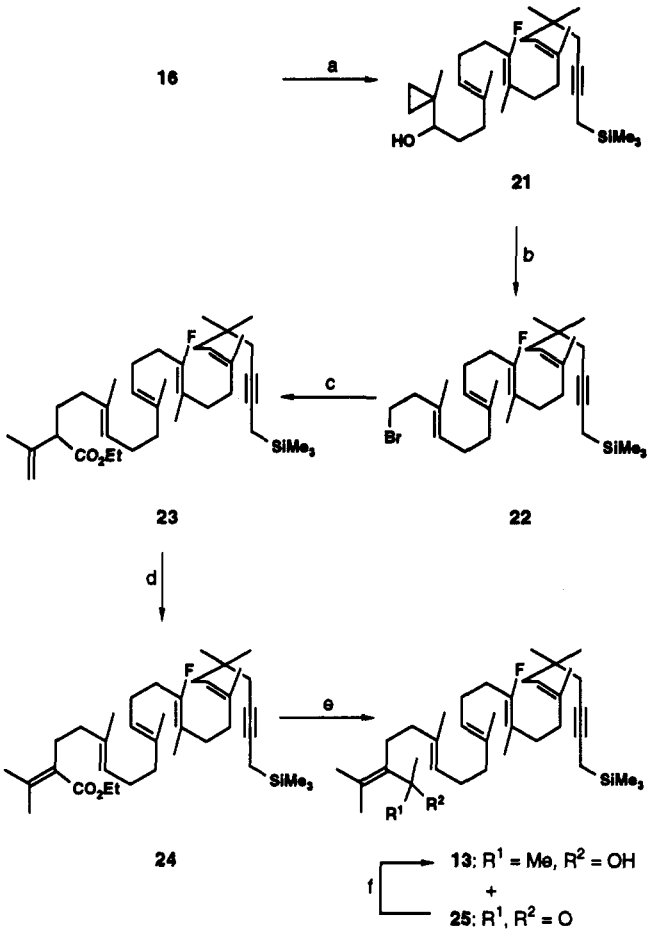
(17) Fish, P. V.; Reddy, P. S.; Lee, C. H.; Johnson, W. S. *Tetrahedron Lett.* **1992**, *33*, 8001–8004.

(18) 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.

(19) Corey, E. J.; Jautelat, M.; Oppolzer, W. *Tetrahedron Lett.* **1967**, 2325–2328.

(20) Badet, B.; Julia, M. *Tetrahedron Lett.* **1979**, 1101–1104.

Scheme 3[a]



[a] (a) (1-Methyl-1-cyclopropyl)magnesium bromide (55%); (b) $MgBr_2$ (69%); (c) $Me_2C{=}CHCO_2Et$, LDA (93%); (d) *t*-BuOK (74%); (e) MeLi, **13** (68%), **25** (21%); (f) MeLi (52%).

The synthesis of the cyclization substrate **13** was performed according to the procedure outlined in Scheme 3. Reaction of **16** with (1-methyl-1-cyclopropyl)magnesium bromide[21] gave cyclopropylcarbinol **21**[22] which underwent rearrangement with magnesium bromide to homoallylic bromide **22** with high *trans* stereoselectivity (99:1).[23] The one-step rearrangement of **21** to **22** was slightly more *trans*-selective than the corresponding two-step Brady–Julia conditions (98:2).[24] Alkylation of the lithium enolate of ethyl 3,3-dimethylacrylate[25] with **22** in the presence of HMPA gave the β,γ enoate **23** in excellent yield (93%) which was isomerized to the α,β-isomer **24** by treatment with potassium *tert*-butoxide (equilibrium ratio, **24**:**23**, 91:9). Methylation of **24** with excess methyllithium invariably gave a mixture of predominantly tertiary alcohol **13** along with ketone **25**, which were separated by chromatography. Retreatment of **25** with MeLi also furnished **13** along with a small quantity of recovered **25**.

(21) 1-Bromo-1-methylcyclopropane was prepared by application of the following procedures: (a) Meek, J. S.; Osuga, D. T. *Organic Synthesis*; Wiley: New York, 1973; Collect. Vol. 5, pp 126–130. (b) Roberts. J. D.; Chambers, V. C. *J. Am. Chem. Soc.* **1951**, *73*, 3176–3179.

(22) The attempted preparation of **21** by the addition of 1-formyl-1-methylcyclopropane and bromide **14** to lithium metal under modified Barbier-type conditions proved unsuccessful (see: ref 10c and references therein).

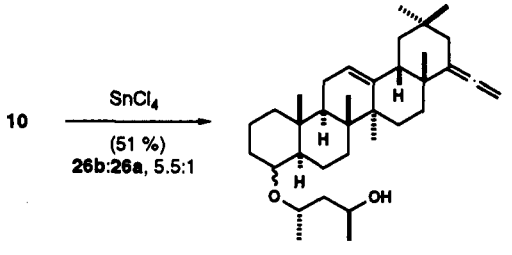
(23) For a closely related rearrangement, see: McCormick, J. P.; Barton, D. L. *J. Org. Chem.* **1980**, *45*, 2566–2570.

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

(25) Cf. Herrmann, J. L.; Kieczykowski, G. R.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 2433–2436.

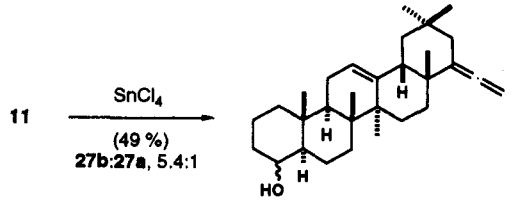
Cyclization Studies. Prior art suggested that cyclization of acetal **10** and aldehyde **11** would be most efficiently achieved with tin(IV) chloride in methylene chloride; however these conditions were also expected to enhance hydrogen fluoride elimination. The cyclization of epoxide **12** was expected to be more problematic, but recent studies have shown that (*i*-PrO)$TiCl_3$ is an effective reagent for promoting this type of polyene cyclization.[26,27] Cyclization of tetramethylallylic alcohol **13** with Lewis acid was expected to yield relatively few cyclization products but could enhance loss of HF. Cyclization of **13** with protic acid was expected to minimize dehydrofluorination but give increased amounts of partially cyclized products. In all cyclizations studied, the reaction product mixture was analyzed by both GC and high-field ^1H NMR in order to determine the product composition. In addition to the major isolated products listed below, a complex mixture of minor components resulting from only partial cyclization of the polyene substrates was also formed.

Thus, treatment of acetal **10** with tin(IV) chloride (3.0 equiv, CH_2Cl_2, −78 °C, 10 min) gave a facile cyclization to afford a separable mixture of C4 isomeric pentacycle alcohols **26** in 51% yield (4β:4α, 5.5:1) (eq 2). Note, no fluoropentacyclic products were isolated; indeed these evidently underwent regiospecific *in situ* dehydrofluorination to generate the C12–13 olefinic bond. The stereochemistry of the products **26b** and **26a** was predicted by previous precedent and was established from spectral data and by correlation with the data for the ABCD and BCDE rings of several closely related tetra- and pentacycles.[10,11]



26b: $4\beta_{ax}$
26a: $4\alpha_{eq}$ (2)

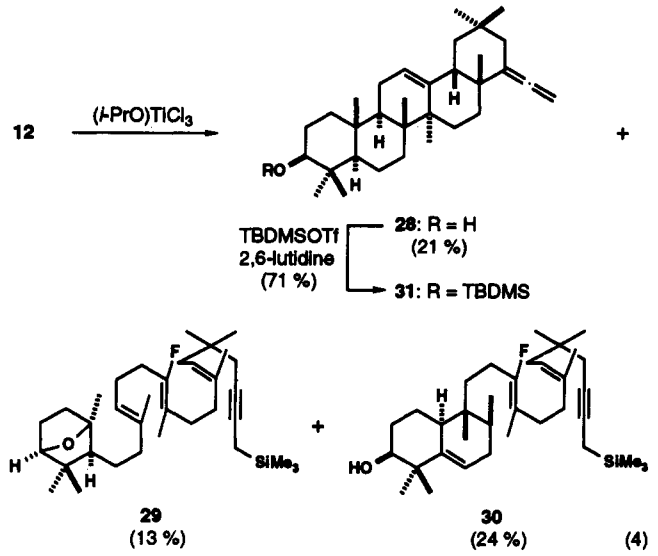
Cyclization of aldehyde **11** under identical conditions ($SnCl_4$ (3.0 equiv), CH_2Cl_2, −78 °C, 10 min) also furnished a mixture of alcohols **27** (4β:4α, 5.4:1), again with loss of HF, in 49% yield (eq 3). The stereochemistry of **27b** and **27a** was again established from spectral data and by correlation with related systems. In addition, **27b** was also unequivocally identified by comparison with a sample of **27b** prepared from **26b** by cleavage of the C4 pentyl auxiliary,[12b] which also confirmed that the substrates **10** and **11** had cyclized to yield the same triterpenoid carbon skeleton.



27b: $4\beta_{ax}$
27a: $4\alpha_{eq}$ (3)

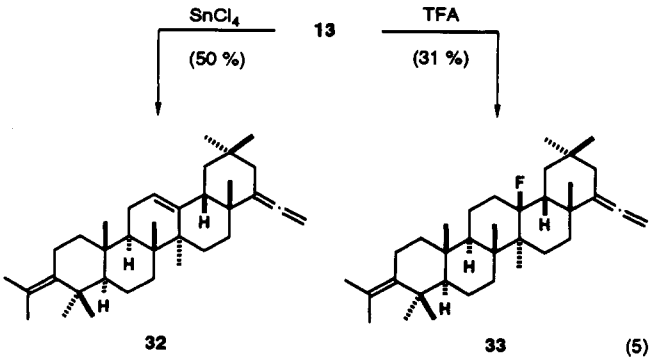
Cyclization of epoxide **12** was initially investigated on a semipreparative scale to determine the optimum condi-

tions for the formation of the pentacyclic products. The propensity of several Lewis acids ($SnCl_4$, $TiCl_4$, $(i\text{-PrO})_nTiCl_{4-n}$, $n = 1, 1.5, 2$, $MeAlCl_2$) to promote cyclization was investigated under standardized conditions. The most successful conditions for the cyclization of **12** employed $(i\text{-PrO})TiCl_3$, giving rise to three major products, **28–30** (eq 4), for a combined GC yield of 58–72% of the crude reaction mixture. (2-Propoxy)titanium trichloride gave



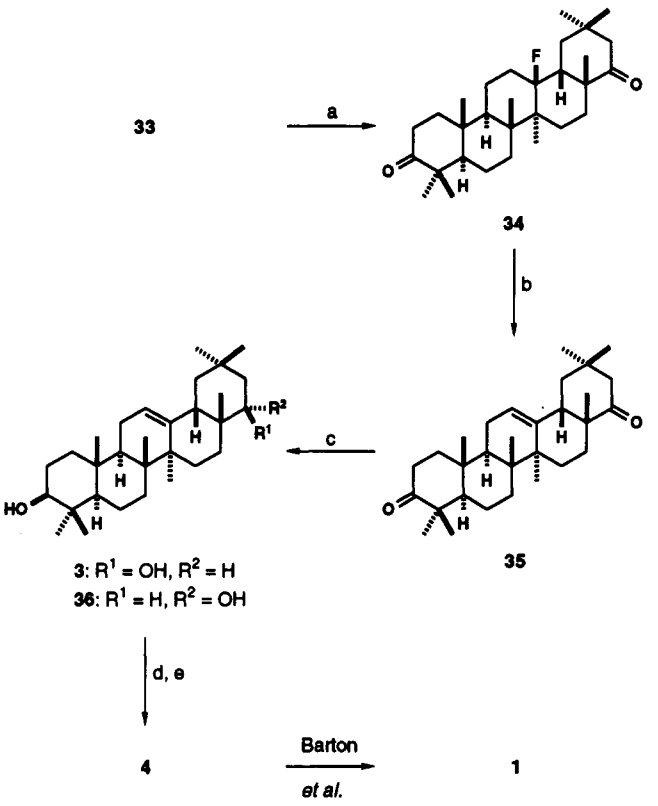
not only the highest yield of pentacycle **28** but also the highest yield of all major products, **28–30**. Treatment of epoxide **12** on a preparative scale with $(i\text{-PrO})TiCl_3$ (3.0 equiv) in CH_2Cl_2 at −78 °C for 10 min gave pentacycle **28** in 21% GC yield (10% isolated yield). The stereochemistry of **28** was established from spectral data, and that of the corresponding TBDMS ether **31** by correlation with the data of several closely related natural, and nonnatural, oleanenes including β-amyrin (**1**).[28] The fluoropentacycle (cf. *pro*-**28**, see discussion) was not isolated but evidently underwent *in situ* regioselective dehydrofluorination. The other major products of the cyclization were the bicyclic ether **29** (13%) and a rearranged bicyclic carbocycle **30** (24%), both resulting from only partial cyclization of the polyene.

Treatment of allylic alcohol **13** with tin(IV) chloride (3.0 equiv, CH_2Cl_2, −78 °C, 10 min) resulted in facile cyclization with loss of HF to afford pentacycle **32** in 50% isolated yield (eq 5). In comparison, cyclization of **13** under protic acid conditions with trifluoroacetic acid (1% TFA in CH_2Cl_2, −78 °C, 15 min) gave the fluoropentacycle **33** in 31% isolated yield and no dehydrofluorinated product **32** was observed.



Preparation of Sophoradiol from Pentacycle 33. The cyclization product **33** is suitably functionalized at

Scheme 4[a]



[a] (a) $RuCl_3$ (cat), $NaIO_4$ (88%); (b) $SnCl_4$ (92%); (c) DIBALH, **3**:**36**, 4:1, (87%); (d) *n*-BuLi, CS_2, MeI; (e) *n*-Bu_3SnH, AIBN (cat), (31% over two steps).

C3, C13, and C22 to allow conversion to **3** with a minimum of synthetic manipulations.[29] Simultaneous oxidative cleavage of the C3 isopropylidene and C22 vinylidene groups of **33** by the method of Sharpless,[30] with catalytic $RuCl_3$ and $NaIO_4$, furnished the diketone **34** (Scheme 4) which then underwent regiospecific dehydrofluorination (C12–13) to yield the enedione **35** when treated with $SnCl_4$. Stereoselective reduction of **35** with diisobutylaluminum hydride gave predominantly (±)-sophoradiol (**3**) along with olean-12-ene-3β,22α-diol (**36**)[31] (87%, ratio 4.1:1), which were separable by recrystallization. Synthetic (±)-sophoradiol (**3**), mp 234–236 °C, was unequivocally identified with an authentic sample of nature (+)-**3** by rigorous comparison of spectral and chromatographic properties. As a natural extension of this study, synthetic (±)-sophoradiol (**3**) was converted to (±)-olean-12-ene (**4**)[32] by conversion to the bis-methyl xanthate and then reduction with *n*-Bu_3SnH.

(26) Taton, M.; Benveniste, P.; Rahier, A.; Johnson, W. S.; Lui, H.-t.; Sudhakar, A. R. *Biochemistry* **1992**, *31*, 7892–7898.
(27) For an example of an epoxide-initiated polyene bicyclization employing $(i\text{-PrO})_3TiCl$ as the Lewis acid, see: Tanis, S. P.; Herrinton, P. M. *J. Org. Chem.* **1983**, *48*, 4572–4580.
(28) Ito, S. Sester-, Tri- and Higher Terpenoids. In *Natural Products Chemistry*; Nakanishi, K., Goto, T., Ito, S., Natori, S., Nozoe, S., Eds.; Academic Press, Inc.: New York, 1974; Vol. 1, pp 365–366.
(29) The presence of the C-ring alkene of pentacycles **28**, **31**, and **32** precluded the use of either of these olean-12-enes in conjunction with the experimental procedures required to unmask the C3 and C22 hydroxyl groups in order to complete a synthesis of **3**.
(30) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936–3938.
(31) Spectral data of (±)-**36** were identical with published values, see: Ito, S.; Kodama, M.; Sunagawa, M.; Oba, T.; Hikino, H. *Tetrahedron Lett.* **1969**, 2905–2908.
(32) Spectral data of (±)-**4** were identical with published values, see: Ageta, H.; Arai, Y. *Phytochem.* **1983**, *22*, 1801–1808.

Discussion and Conclusions

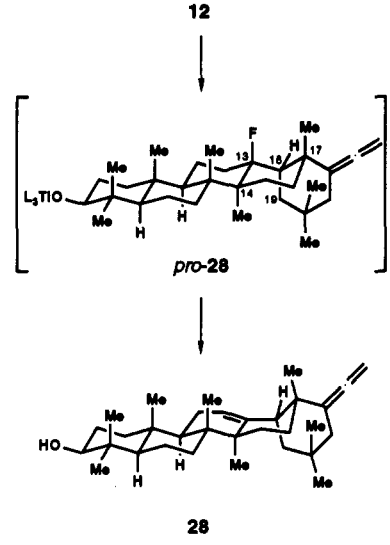
The synthetic challenges presented by the preparation of the cyclization substrates **10–13** largely involved the introduction of the tetramethylallylic alcohol initiator group. The stereoselective construction of polyenes **10–12** had been achieved in good yield and with high selectivity by the application of established protocol. The synthesis of **13** however involved several noteworthy transformations. Rearrangement of cyclopropylcarbinol **21** to homoallylic bromide **22** was most selectively accomplished using magnesium bromide,[23] and this reagent complements established procedures for effecting this type of reaction.[24] The alkylation of **22** with the enolate of ethyl 3,3-dimethylacrylate to give β,γ enoate **23** represented an improvement in yield, milder reaction conditions, and fewer synthetic steps when compared to previously reported procedures.[15] The conversion of **23** to **13** simply involved isomerization of the double bond into conjugation with the ester and then methylation of the enoate **24** to the corresponding tertiary alcohol **13**. Complete dimethylation of **24** was not achieved in a single treatment with methyllithium despite investigating reaction conditions involving a large excess of alkylating agent or prolonged reaction times or both. It proved more satisfactory to treat **24** with excess methyllithium and to separate alcohol **13** from ketone **25**. The incomplete methylation of **24** was due to partial enolization of the ketone intermediate **25** by MeLi.

Cyclization of acetal **10** gave two major products **26b** and **26a** in good yield, which were isomeric at C4. The ratio of 4β- (axial) **26b** to 4α-alcohols (equatorial) **26a** (5.5:1, by ^{1}H NMR) was in accord with previous results, suggesting that the Lewis acid induced preferential cleavage of the carbon–oxygen bond of the acetal which adopts a pseudoequatorial position in the cyclization transition state. No fluoropentacyclic products were isolated or observed even though the reaction was performed at low temperature, which should have minimized the dehydrofluorination process.[10b] Cyclization of aldehyde **11** also gave a mixture of C4 alcohols **27** and in a similar ratio as was observed for the products of the cyclization of **10**. The preferential formation of the axial alcohol **27b** indicated that the aldehyde initiator group had a strong preference for adoption of a pseudoaxial orientation during cyclization.

The epoxide-initiated cyclization of polyene **12** to pentacycle **28** was a significant result when compared to the acid-catalyzed cyclization of oxidosqualene (**5**) (Scheme 1) and other previous cyclization studies but was impractical with regard to an application to the synthesis of pentacyclic triterpenoids as the overall yield of isolable pentacyclic product **28** was low. Moreover, **28** was unsuitably functionalized as it was not possible to selectively cleave the C22 allene in the presence of the C-ring alkene. Cyclization of **12** yields not only the pentacycle **28** but also two products of incomplete cyclization of the polyene. The bicyclic ether **29** is formed by the trapping of the carbenium ion at *pro*-C10 by transannular attack of the *pro*-C3 metal alkoxide, a process that is commonly observed in epoxide-initiated cyclizations of this nature.[33] The rearranged bicycle **30** has interesting structural features (C5–6 alkene, C8 *sec*-methyl, C9 *tert*-methyl) and its formation can be rationalized as arising from a series of sequential 1,2-methyl and hydride shifts starting with a bicyclic carbenium ion analogous to **I** (Scheme 1). The constitution, including the stereochemistry, of the AB rings of **30** was determined by interpretation of spectroscopic data and by comparison with a similarly rearranged triterpenoid produced by the acid-catalyzed cyclization of oxidosqualene (**5**).[34]

Cyclization of tetramethylallylic alcohol **13** was achieved with either elimination or retention of the fluorine atom at C13, depending on the selection of acid used to initiate the cyclization. Tin(IV) chloride gave pentacycle **32** in good yield (50%) but with loss of HF, whereas trifluoroacetic acid gave fluoropentacycle **33** in lower yield (31%). These results are similar to those obtained with cyclopentenol **8** upon cyclization with both Lewis and protic acid.[10d]

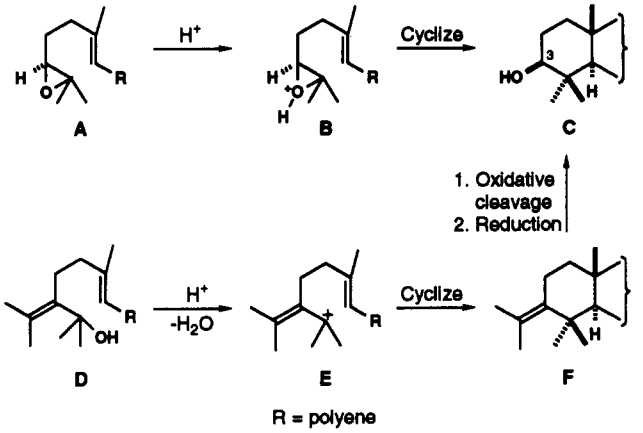
The complete *in situ* regiospecific dehydrofluorination observed upon cyclization of polyene substrates **10–13** with Lewis acid deserves further comment. This susceptibility to elimination would appear to arise from the strain within the structure of the fluoropentacyclic intermediates and the ability of the Lewis acid to induce dehydrofluorination so as to alleviate this strain. For example, cyclization of *trans,trans,trans,cis*-tetraene **12**, *via* a chair-chair-chair-chair transition state, produces fluoropentacycle *pro*-**28**, with a D/E syn-cis configuration creating steric congestion in this region of the molecule which results in strain. There



is a severe transannular 1,3-diaxial interaction between the C19 and C14-Me groups. This repulsion may be sufficient to distort the ring-D chair confirmation and so promote Pitzer strain between the C13-F, C18-H, and C17-Me groups and to promote an additional minor 1,3-diaxial repulsion between the C13-F and C17-Me. The Lewis acid used to initiate the cyclization is also able to facilitate dehydrofluorination and produce a planar sp^2 carbon at C13 which greatly alleviates this strain.[35] The regiospecific nature of the elimination to give exclusively the trisubstituted C12–13 olefin, **28**, arises from an anti-1,2-diaxial elimination of HF (C13–F$_{ax}$, C12–H$_{ax}$). The formation of the alternative double-bond position isomer (C13–18) would require the less favored proces of syn elimination (C13–F$_{ax}$, C18–H$_{eq}$). In addition, the acidic conditions required for the cyclization of **12** and the *in situ* dehydrofluorination of *pro*-**28** were sufficiently mild so as not to promote equilibriation of the product **28** to the tetrasubstituted C13–18 alkene isomer.[36]

The transformation of pentacycle **33** to sophoradiol (**3**) simply required the introduction of the C12–13 alkene and the two β-hydroxyl groups at C3 and C22. The oxidative cleavage of the C3 isopropylidene and C22

Scheme 5. Comparison of Epoxide and Allylic Cation Initiated Polyene Cyclizations



vinylidene groups of **33** and the regiospecific introduction of the C-ring alkene proceeded in high yield to furnish enedione **35**. The stereoselective reduction of diketone **35** required experimentation and was most selectively achieved using DIBALH, giving predominantly sophoradiol (**3**) along with the 3β,22α diol **36** (ratios, 4.1:1). The use of reducing agents such as sodium borohydride, lithium aluminum hydride, lithium tri-*tert*-butoxyaluminohydride gave less satisfactory results (ratio, 3.8:1, 1.5:1, 1.0:1, respectively). The synthesis of olean-12-ene (**4**) also constitutes a totally synthetic pathway to β-amyrin (**1**) and to oleanolic acid (**2**) since **4** was an intermediate in Barton's formal total synthesis of **1**,[6a] and **1** was subsequently converted to **2**.[6b]

The synthesis of **3** by the application of the protic acid cyclization of tetramethylallylic alcohol **13** to fluoropentacycle **33** has illustrated that the TMA cation is a beneficial substitute for the epoxide (cf. **12** → **28**) as an initiator for polyene cyclizations. The intimate relationship between these two initiators is outlined in Scheme 5. Tetramethylallylic alcohol **D** on treatment with acid generates the symmetric TMA cation **E**, which in turn undergoes cyclization **E** → **F**. Degradation of the resulting isopropylidene group in the cylization product **F** yielded the C3-β-OH. The overall conversion **D** → **F** → **C** is the equivalent of the epoxide-initiated process, **A** → **C**. Hence, the TMA cation initiator allows for a substantial increase in the the yield of pentacyclic products in the cyclization step, and since the conversion equivalent to **F** → **C** proved to be highly efficient, the surrogate approach was very successful.

In conclusion, we have performed the first examples of biomimetic polyene *pentacyclizations* employing acetal, aldehyde, epoxide, and tetramethylallylic alcohol groups as initiators. These cyclizations proceed in high yield considering the degree of molecular complexity that is furnished in a single step. The cyclization of **13** to **33** occurs in respectable yield and the subsequent elaboration of **33** to sophoradiol (**3**) demonstrates that such cyclizations represent a viable strategy for the total synthesis of pentacyclic triterpenoids.

Experimental Section

General Considerations. The prefix (±) has been omitted from the names of the racemic compounds. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Infrared spectra were recorded on either a Perkin-Elmer 1310 infrared spectrophotometer or a Nicolet 205 FTIR spectrometer as thin films on sodium chloride windows or as diluted solutions in chloroform. All proton NMR spectra were obtained on a Varian XL-400 at 400 MHz as dilute solutions in deuteriochloroform and chemical shifts (δ) are reported relative to either internal tetramethylsilane or residual chloroform. Carbon-13 NMR spectra were recorded as dilute solutions in deuteriochloroform in the broad band decoupled mode on a Varian XL-400 at 100.6 MHz. HRMS were recorded in electron-impact mode by the Regional Mass Spectrometry Facility at the University of California, San Francisco. Analytical samples for elemental analysis were distilled in a glass tube under vacuum using a Kugelrohr oven and then sealed directly in the tube; the analyses were performed by Desert Analytics in Tucson, AZ. Gas chromatographic (GC) analyses were performed on a Hewlett-Packard HP 5890 instrument, with a HP 3396a integrator, employing a 50-m SE-54 capillary column and hydrogen carrier gas within temperature ranges of 30–300 °C. Analytical thin layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} precoated glass backed plates which were visualized with ultraviolet light and then stained with iodine impregnated silica gel, acidic *p*-anisaldehyde, or basic potassium permanganate solution. Column chromatography was carried out using Merck silica gel 60 (230–400 mesh) (sg). Medium pressure liquid chromatography (MPLC) was performed using a FMI RP-SY Lab pump. When necessary, reactions requiring dry conditions were conducted in an oven- or flame-dried apparatus under an inert argon (Ar) atmosphere. Organic extracts were dried over magnesium sulfate and concentrated under aspirator pressure on a Buchi rotary evaporatory. Organic solvents were distilled from the following drying agents: tetrahydrofuran (THF) (sodium–benzophenone ketyl), diethyl ether (ether) (sodium–benzophenone ketyl), hexane (sodium), dimethyl sulfoxide (calcium hydride under reduced pressure), dichloromethane (calcium hydride). (Methoxymethyl)triphenylphosphonium chloride was recrystallized from hot acetonitrile and dried under vacuum prior to use. (±)-2,4-Pentanediol was obtained by careful chromatographic separation, from the *meso* isomer, of the commericially available mixture [Aldrich]. Yields refer to chromatographically purified compounds and may be contamined with ca. 1–2% of isomeric impurities which can often be removed by further purification (e.g. recrystallization) at a late stage in the synthesis.

8-Fluoro-4,9,12,15,15-pentamethyl-19-(trimethylsilyl)-4(*E*),8(*Z*),12(*Z*)-nonadecatrien-17-ynenitrile (15). A solution of the bromide **14**[10d] (3.22 g, 6.66 mmol) in dry dimethyl sulfoxide (15 mL) was stirred with powdered sodium cyanide (0.682 g, 2.1 equiv) at 80 °C under Ar for 1.5 h. The cooled mixture was partitioned between ether (300 mL) and half-saturated brine (100 mL), and the aqueous phase was reextracted with ether (2 × 100 mL) and hexanes (100 mL). The combined extracts were washed with saturated brine (3 × 100 mL), dried, and then evaporated to leave an oil. [NB: Allow all phases to separate completely.] Purification on sg with mixtures of ether–hexanes as eluant (10–15%) gave, after a quantity of mixed fractions (0.288 g; GC: **15**, 76% pure), the nitrile **15** (2.004 g, 70%) (GC: 97% pure): oil; bp 98 °C (oven temperature) at 0.007 mmHg; R_f 0.39 (4:1 hexanes–ether); IR (film) ν 2910, 2880, 2220, 2200, 1685, 1430, 1365, 1230, 835 cm^{-1}; ^{1}H NMR δ 5.27 (t, J = 7.0 Hz, 1 H), 5.17 (td, J = 7.6, 1.1 Hz, 1 H), 2.42 (td, J = 7.4, 1.3 Hz, 2 H), 2.35–2.17 (m, 6 H), 2.14–2.04 (m, 4 H), 2.02 (t, J = 2.7 Hz, 2 H),

(33) For examples, see: (a) Goldsmith, D. J. *J. Am. Chem. Soc.* **1962**, *84*, 3913–3918. (b) van Tamelen, E. E.; Storni, A.; Hessler, E. J.; Schwartz, M. *J. Am. Chem. Soc.* **1963**, *85*, 3295–3296. (c) van Tamelen, E. E.; Schwartz, M. A.; Hessler, E. J.; Storni, A. *Chem. Commun.* **1966**, 409–411. (d) van Tamelen, E. E.; Coates, R. M. *Chem. Commun.* **1966**, 413–415. (e) van Tamelen, E. E.; Murphy. J. W. *J. Am. Chem. Soc.* **1970**, *92*, 7204–7206. (f) van Tamelen, E. E.; Leiden, T. M. *J. Am. Chem. Soc.* **1982**, *104*, 2061–2062.

(34) Sharpless, K. B.; van Tamelen, E. E. *J. Am. Chem. Soc.* **1969**, *91*, 1848–1849.

(35) It should be noted that cyclization of the acetal analogous to **10** but with the *trans*-alkene at *pro*-C17-18 yields the corresponding pentacyclic product with the anti-trans configuration at the D/E ring junction but with *retention* of the fluorine atom at C13 to yield 23,24-dinor-13β-fluoro-4β-(2′(*S**)-hydroxy-4′(*S**)-pentoxy)-22-vinylidene-18α-(H)-oleanane. This result is in accord with our theoretical considerations. Fish, P. V.; Johnson, W. S. Unpublished results. For a related cyclization, see ref 10c.

(36) For a discussion of the acid-catalyzed isomerization of oleanenes, see: Brownlie, G.; Fayez, M. B. E.; Spring, F. S.; Stevenson, R.; Strachan, W. S. *J. Chem. Soc.* **1956**, 1377–1381.

1.97 (d, J = 6.8 Hz, 2 H), 1.72 (d, J = 1.2 Hz, 3 H), 1.65 (s, 3 H), 1.58 (d, J = 2.6 Hz, 3 H), 1.44 (t, J = 2.7 Hz, 2 H), 0.92 (s, 6 H), 0.09 (s, 9 H); ^{13}C NMR δ 153.8 (d, J = 242.2 Hz), 136.6, 132.1, 126.1, 121.7, 119.3, 111.8 (d, J = 18.1 Hz), 78.8, 76.7, 39.1, 34.9, 34.4, 32.1, 30.0, 28.6, 28.2, 28.2 (d, J = 14.7 Hz), 26.6, 26.6, 25.1, 23.5, 16.2, 15.6 (d, J = 5.7 Hz), 7.0, -2.0, -2.0, -2.0; HRMS calcd for $C_{27}H_{44}FNSi$ 429.3227, found 429.3228. Anal. Calcd for $C_{27}H_{44}FNSi$: C, 75.46; H, 10.32; N, 3.26. Found: C, 75.29; H, 10.35; N, 3.20.

8-Fluoro-4,9,12,15,15-pentamethyl-19-(trimethylsilyl)-4(E),8(Z),12(Z)-nonadecatrien-17-ynal (16). A solution of diisobutylaluminum hydride (8.7 mL, 1.0 M in hexanes, 2.0 equiv) was added dropwise over 9 min to a stirred solution of the nitrile **15** (1.874 g, 4.359 mmol) in hexanes (55 mL) at -78 °C under Ar, and the mixture was stirred for 2 h. The mixture was quenched with ethyl acetate (50 mL) and then H_2O (5 mL). The mixture was warmed to 23 °C, diluted with hexanes (50 mL), and washed with dilute HCl (2 × 50 mL, 0.5 M), and the aqueous washings were reextracted with ether (50 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (25 mL), dried, filtered through a short pad of sg, and then evaporated to leave the aldehyde **16** (1.751 g, 93%) which was used without further purification (GC: 95% pure): oil; bp 93 °C (oven temperature) at 0.005 mmgHg; R_f 0.60 (4:1 hexanes–ether); IR (film) ν 2910, 2880, 2700, 2210, 1705, 1690, 1655, 1435, 1370, 1235, 1160, 830, 695 cm^{-1}; ^{1}H NMR δ 9.76 (t, J = 1.8 Hz, 1 H), 5.19–5.15 (m, 2 H), 2.51 (td, J = 7.0, 1.9 Hz, 2 H), 2.32 (t, J = 7.4 Hz, 2 H), 2.28–2.14 (m, 4 H), 2.14–2.04 (m, 4 H), 2.02 (t, J = 2.7 Hz, 2 H), 1.96 (d, J = 7.6 Hz, 2 H), 1.73 (d, J = 1.2 Hz, 3 H), 1.63 (s, 3 H), 1.57 (d, J = 2.5 Hz, 3 H), 1.44 (t, J = 2.7 hz, 2 H), 0.92 (s, 6 H), 0.09 (s, 9 H); LRMS m/z (rel intensity) 417 (0.3, M - Me), 331 (0.2), 327 (0.2), 307 (0.2), 269 (0.3), 235 (16), 183 (14), 161 (14), 109 (14), 73 (100). Anal. Calcd for $C_{27}H_{45}FOSi$: C, 74.94; H, 10.48. Found: C, 75.06; H, 10.60.

10-Fluoro-2,6,11,14,17,17-hexamethyl-3-hydroxy-21-(trimethylsilyl)-1,6(E),10(Z),14(Z)-heneicosatetraen-19-yne (17). A solution of 2-propenylmagnesium bromide (22.5 mL, 0.35 M in THF, 2.0 equiv) was added dropwise over 12 min to a stirred solution of the aldehyde **16** (1.704 g, 3.936 mmol) in THF (20 mL) at -78 °C under Ar, and the mixture was stirred for 15 min. The mixture was warmed to 23 °C and stirred for an additional 90 min, and then the reaction was quenched with saturated aqueous NH_4Cl (75 mL) and concentrated. The residue was diluted with ether–hexanes (250 mL, 1:1), washed with saturated aqueous NH_4Cl (50 mL), dried, and then evaporated to leave an oil. Purification on sg with mixtures of ether–hexanes as eluant (10–20%) gave the s-allylic alcohol **17** (0.793 g, 42%) (GC: 96% pure): oil; bp 104 °C (oven temperature) at 0.004 mmHg; R_f 0.22 (4:1, hexanes–ether); IR (film) ν 3600–3140, 3040, 2920, 2880, 2830, 2200, 1685, 1635, 1430, 1365, 1235, 1155, 890, 840, 690 cm^{-1}; ^{1}H NMR δ 5.17 (d, J = 6.7 Hz, 1 H), 5.17 (d, J = 6.7 Hz, 1 H), 4.94 (t, J = 1.8 Hz, 1 H), 4.84 (t, J = 1.5 Hz, 1 H), 4.05 (t, J = 6.4 Hz, 1 H), 2.28–2.14 (m, 4 H), 2.13–1.97 (m, 6 H), 2.02 (t, J = 2.7 Hz, 2 H), 1.96 (d, J = 7.6 Hz, 2 H), 1.73 (s, 3 H), 1.73 (s, 3 H), 1.68–1.54 (m, 3 H), 1.62 (s, 3 H), 1.57 (d, J = 2.5 Hz, 3 H), 1.44 (t, J = 2.7 Hz, 2 H), 0.92 (s, 6 H), 0.09 (s, 9 H); ^{13}C NMR δ 154.2 (d, J = 243.4 Hz), 147.4, 136.7 , 135.7, 123.4, 121.0, 111.5 (d, J = 17.1 Hz), 111.0, 78.8, 76.8, 75.6, 39.1, 35.6, 34.4, 33.1, 32.1, 30.0, 28.9, 28.6, 28.2 (d, J = 8.0 Hz), 26.6, 26.6, 25.2, 23.6, 17.6, 15.6 (d, J = 6.1 Hz), 7.0, -2.0, -2.0, -2.0; LRMS m/z (rel intensity) 459 (0.1, M - Me), 369 (0.4), 301 (0.4), 235 (24), 161 (23), 107 (13), 93 (15), 73 (100). Anal. Calcd for $C_{30}H_{51}FOSi$: C, 75.95; H, 10.83. Found: C, 76.02; H, 10.81.

Ethyl 12-Fluoro-4,8,13,16,19,19-hexamethyl-23-(trimethylsilyl)-4(E),8(E),12(Z),16(Z)-tricosatetraen-21-ynoate (18). A solution of the allylic alcohol **17** (724 mg, 1.52 mmol) in triethyl orthoacetate (10 mL) was heated at 125 °C with a catalytic amount of propionic acid (10 μL) under Ar for 2 h. The cooled mixture was diluted with ether (100 mL) and washed with dilute HCl (50 mL, 0.5 M). The aqueous washings were reextracted with ether (50 mL) and the combined ethereal solutions were then washed with saturated aqueous $NaHCO_3$ (25 mL), dried, and evaporated to leave an oil (GC: selectivity, 4(E):4(Z), 96:4). Purification on sg with mixtures of ether–hexanes as eluant (2.5–5%) gave initially a quantity of mixed isomer C4 esters (24 mg, 3%) (GC: 96% pure; 4(E):4(Z), 86:14) and then the ester **18** (653 mg, 79%) (GC: 97% pure; 4(E):4(Z), 97:3): oil; bp 111 °C (oven temperature) at 0.004 mmHg; R_f 0.49 (9:1 hexanes–ether); IR (film) ν 2910, 2880, 2200, 1710, 1685, 1430, 1365, 1230, 1145, 840, 695 cm^{-1}; ^{1}H NMR δ 5.17 (t, J = 6.9 Hz, 1 H), 5.17–5.10 (m, 2 H), 4.12 (q, J = 7.2 Hz, 2 H), 2.42–2.34 (m, 2 H), 2.32–2.21 (m, 4 H), 2.21–2.13 (m, 4 H), 2.12–2.03 (m, 6 H), 2.02 (t, J = 2.8 Hz, 2 H), 1.97 (d, J = 6.6 Hz, 2 H), 1.73 (s, 3 H), 1.61 (s, 6 H), 1.58 (d, J = 2.5 Hz, 3 H), 1.44 (t, J = 2.6 Hz, 2 H), 1.25 (t, J = 7.2 Hz, 3 H), 0.92 (s, 6 H), 0.09 (s, 9 H); HRMS calcd for $C_{34}H_{57}FO_2Si$ 544.4112, found 544.4083. Anal. Calcd for $C_{34}H_{57}FO_2Si$: C, 74.94; H, 10.55. Found: C, 75.05; H, 10.68.

12-Fluoro-4,8,13,16,19,19-hexamethyl-23-(trimethylsilyl)-4(E),8(E),12(Z),16(Z)-tricosatetraen-21-ynal (19). A solution of diisobutylaluminum hydride (0.91 mL, 1.0 M in hexanes, 1.15 equiv) was added dropwise over 4 min to a stirred solution of the ester **18** (431 mg, 0.791 mmol) in ether (8.0 mL) at -78 °C under Ar, and the mixture was stirred for 35 min. The mixture was quenched with ethyl acetate (100 μL) and then MeOH (250 μL) and warmed to 23 °C. The mixture was diluted with hexanes–ether (40 mL, 1:1) and washed with dilute HCl (10 mL, 0.5 M). The aqueous washings were reextracted with hexanes–ether (10 mL, 1:1) and then the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (5 mL), dried, filtered through a plug of sg, and evaporated to leave the aldehyde **19** (357 mg, 90%), which was used without further purification (GC: 91% pure): oil; bp 108 °C (oven temperature) at 0.005 mmHg; R_f 0.41 (9:1 hexanes–ether); IR (film) ν 2920, 2890, 2840, 2700, 2210, 1710, 1690, 1655, 1435, 1370, 1235, 840, 760, 695, 670 cm^{-1}; ^{1}H NMR δ 9.75 (t, J = 1.9 Hz, 1 H), 5.17 (t, J = 7.6 Hz, 1 H), 5.17–5.11 (m, 2 H), 2.51 (td, J = 7.4, 1.8 Hz, 2 H), 2.31 (t, J = 7.3 Hz, 2 H), 2.28–2.22 (m, 1 H), 2.21–2.14 (m, 3 H), 2.12–2.01 (m, 6 H), 2.02 (t, J = 2.7 Hz, 2 H), 2.00–1.94 (m, 4 H), 1.72 (d, J = 1.1 Hz, 3 H), 1.61 (s, 3 H), 1.60 (s, 3 H), 1.58 (d, J = 2.7 Hz, 3 H), 1.44 (t, J = 2.7 Hz, 2 H), 0.92 (s, 6 H), 0.09 (s, 9 H); HRMS calcd for $C_{32}H_{53}FOSi$ 500.3850, found 500.3820. Anal. Calcd for $C_{32}H_{53}FOSi$: C, 76.74; H, 10.67. Found: C, 76.79; H, 10.82.

13-Fluoro-5,9,14,17,20,20-hexamethyl-1-methoxy-24-(trimethylsilyl)-1(E/Z),5(E),9(E),13(Z),17(Z)-tetracosapentaen-22-yne (20). A solution of *tert*-butyllithium (405 μL, 1.7 M in pentane, 2.0 equiv) was added dropwise over 5 min to a stirred suspension of dry, powdered (methoxymethyl)triphenylphosphonium chloride (322 mg, 2.7 equiv) in anhydrous THF (5.0 mL) at -78 °C under Ar, and the orange-red mixture was stirred for 80 min while being warmed slowly to -20 °C. After an additional 60 min at -20 °C, the red solution of the ylide was cooled to -78 °C and a solution of the aldehyde **19** (172 mg, 0.344 mmol) in THF (2.4 mL) was added dropwise over 10 min, and after a further 20 min at -78 °C, the mixture was allowed to warm to -10 °C over 60 min. The mixture was quenched with saturated aqueous NH_4Cl (10 mL), the solvents were evaporated, and the residue was extracted with hexanes (3 × 20 mL). The combined organic extracts were washed with saturated brine (5 mL) and then the combined aqueous washings were diluted with water (12 mL) and extracted further with hexanes (4 × 65 mL) and hexanes–ether (3 × 60 mL, 1:1). The combined organic extracts were dried, filtered through a plug of Celite on sg, and then evaporated to leave an oil. Purification by MPLC on sg with ether–hexanes as eluent (0–2%) gave the alkenes **20** (101 mg, 55%) (GC: 97% pure; 1(E):1(Z), 50:50): oil; R_f 0.27 (49:1 hexanes–ether); IR (film) ν 3010, 2910, 2880, 2200, 1685, 1635, 1430, 1365, 1235, 1195, 1100, 920, 835, 690 cm^{-1}; ^{1}H NMR δ 6.29 (d, J = 12.5 Hz, 1 (E)), 5.86 (dt, J = 6.2, 1.4 Hz, 1(Z)), 5.17 (t, J = 6.7 Hz, 1 H), 5.17–5.10 (m, 2 H), 4.75–4.67 (m, 2(Z)), 4.31 (dd, J = 13.4, 7.0 Hz, 2(E)), 3.57 (s, OMe(Z)), 3.49 (s, OMe(E)), 2.28–1.95 (m, 18 H), 2.02 (t, J = 2.7 Hz, 2 H), 1.73 (d, J = 1.1 Hz, 3 H), 1.61 (s, 3 H), 1.58 (d, J = 2.7 Hz, 3 H), 1.58 (s, C5-Me(E or Z)), 1.55 (s, C5-Me(E or Z)), 1.44 (t, J = 2.7 Hz, 2 H), 0.92 (s, 6 H), 0.09 (s, 9 H); HRMS calcd for $C_{34}H_{57}FOSi$ 528.4163, found 528.4166.

4(S*),6(S*)-Dimethyl-2-[12-fluoro-4,8,13,16,19,19-hexamethyl-23-(trimethylsilyl)-4(E),8(E),12(Z),16(Z)-tricosatetraen-21-yn-1-yl]-1,3-dioxane (10). A mixture of the enol ethers **20** (120 mg, 0.227 mmol), (±)-2,4-pentanediol (75 mg, 3.2 equiv), and catalytic p-toluenesulfonic acid monohydrate (5 mg) in benzene (15 mL) was heated at reflux, under a Dean–Stark condensor with the side arm packed with molecular sieves (4A), under Ar for 1.5 h. The cooled mixture was diluted with hexanes–ether (25 mL, 1:1), washed with saturated aqueous $NaHCO_3$ (4.5

mL), dried, and evaporated to leave an oil. Purification by MPLC on 10% silver nitrate impregnated sg with ether–hexanes as eluant (2–16%) gave, initially, a quantity of material of lower purity (12.8 mg, 10%) (GC: 85% pure) and then the acetal **10** (107.0 mg, 78%) (GC: 94.5% pure; two impurities: 4.2 and 1.2%): oil; bp 123 °C (oven temperature) at 0.006 mmHg; R_f 0.36 (9:1 hexanes-ether); IR (film) ν 2920, 2890, 2830, 2200, 1685, 1645, 1435, 1365, 1235, 1150, 985, 840, 695 cm^{-1}; ^{1}H NMR δ 5.17 (td, J = 7.7, 1.1 Hz, 1 H), 5.14–5.08 (m, 2 H), 4.83 (t, J = 4.8 Hz, 1 H), 4.29 (dq, J = 6.7, 6.7 Hz, 1 H), 3.93 (dqd, J = 11.6, 5.7, 2.2 Hz, 1 H), 2.27–2.21 (m, 1 H), 2.21–2.13 (m, 3 H), 2.10–2.01 (m, 6 H), 2.02 (t, J = 2.6 Hz, 2 H), 2.00–1.93 (m, 6 H), 1.87–1.78 (m, 2 H), 1.73 (d, J = 1.1 Hz, 3 H), 1.60 (s, 3 H), 1.58 (d, J = 2.7 Hz, 3 H), 1.58 (s, 3 H), 1.55–1.45 (m, 4 H), 1.44 (t, J = 2.7 Hz, 2 H), 1.34 (d, J = 7.0 Hz, 3 H), 1.20 (d, J = 6.1 Hz, 3 H), 0.92 (s, 6 H), 0.09 (s, 9 H); ^{13}C NMR δ 154.1 (d, J = 243.1 Hz), 136.7, 136.0, 134.8, 124.4, 122.9, 121.6, 111.3 (d, J = 18.3 Hz), 94.2, 78.8, 76.7, 67.8, 67.3, 39.7, 39.4, 39.0, 36.8, 34.9, 34.4, 32.1, 30.0, 29.0, 28.7, 28.2, 28.2 (d, J = 7.8 Hz), 26.6, 26.6, 25.2, 23.6, 22.5, 21.8, 17.2, 15.9, 15.7 (d, J = 12.3 Hz), 7.0, -2.0, -2.0, -2.0; HRMS calcd for $C_{38}H_{65}FO_2Si$ 600.4738, found 600.4729. Anal. Calcd for $C_{38}H_{65}FO_2Si$: C, 75.94; H, 10.90. Found: C, 76.20; H, 10.59.

Cyclization of Acetal 10. 23,24-Dinor-4β-(2′(*S)-hydroxy-4′(*S**)-pentoxy)-22-vinylideneolean-12-ene (26b) and 23,24-Dinor-4α-(2′(*S**)-hydroxy-4′(*S**)-pentoxy)-22-vinylideneolean-12-ene (26a).** A solution of tin(IV) chloride (501 μL, 1.0 M in dichloromethane, 3.00 equiv) was added dropwise over 4 min to a stirred solution of the acetal **10** (100.2 mg, 0.167 mmol) in dichloromethane (52.7 mL) at −78 °C under Ar, and after 30 min (TLC indicated no starting material after 10 min) the yellow solution was quenched with NEt_3 (400 μL) followed by MeOH (400 μL). After an additional 10 min, the mixture was warmed to 23 °C, diluted with CH_2Cl_2 (10 mL), washed with saturated aqueous $NaHCO_3$ (8 mL), dried, filtered through a pad of sg, and then evaporated to leave a smear (ca. 79.4 mg) (C4 selectivity: **26b**:**26a**, 5.5:1 by ^{1}H NMR). Purification by MPLC on sg with ether–hexanes as eluant (4–10%) gave the C4-axial ether **26b** (38.3 mg, 45%) (GC: dec), then predominantly the C4-equatorial ether **26a** (5.1 mg, 6%) (GC: dec), a quantity of mixed fractions (16.2 mg) which included small amounts of **26b** and **26a**, and the remainder was products of partial cyclization. Pentacycle **26b** was recrystallized from acetonitrile to >98% purity, whereas **26a** failed to crystallize under a variety of conditions.

For **26b**: colorless clusters; mp 142–144 °C; R_f 0.37 (2:1 hexanes–ether); IR ($CHCl_3$) ν 3540–3290, 2890, 2830, 1930, 1690, 1440, 1365, 1110, 1060 cm^{-1}; ^{1}H NMR δ 5.22 (t, J = 3.4 Hz, 1 H), 4.63 (dd, J = 9.1, 3.7 Hz, 1 H), 4.54 (dd, J = 9.1, 4.2 Hz, 1 H), 4.21–4.14 (m, 1 H), 3.78–3.72 (m, 1 H), 3.53 (d, J = 1.8 Hz, 1 H), 3.49 (d, J = 2.5 Hz, 1 H), 2.12 (dt, J = 13.2, 4.3 Hz, 1 H), 2.04 (td, J = 14.0, 4.5 Hz, 1 H), 1.97–0.80 (m, 23 H), 1.18 (d, J = 6.3 Hz, 3 H), 1.16 (d, J = 6.3 Hz, 3 H), 1.16 (s, 3 H), 1.02 (s, 3 H), 1.01 (s, 3 H), 0.99 (s, 3 H), 0.92 (s, 3 H), 0.86 (s, 3 H); LRMS m/z (rel intensity) 508 (1, M$^+$, $C_{35}H_{56}O_2$), 493 (1), 421 (1), 407 (1), 389 (4), 295 (3), 281 (2), 267 (3), 242 (18), 227 (100), 162 (54), 81 (20), 69 (23); HRMS calcd for $C_{35}H_{56}O_2$ 508.4280, found 508.4266. Anal. Calcd for $C_{35}H_{56}O_2$: C, 82.62; H, 11.09. Found: C, 82.80; H, 11.02.

For **26a**: glassy solid; R_f 0.32 (2:1 hexanes–ether); ^{1}H NMR δ 5.22 (t, J = 3.4 Hz, 1 H), 4.62 (dd, J = 9.0, 3.7 Hz, 1 H), 4.54 (dd, J = 9.2, 4.3 Hz, 1 H), 4.16–4.06 (br m, 1 H), 3.89–3.85 (m, 1 H), 3.29 (d, J = 3.7 Hz, 1 H), 3.16 (dd, J = 10.7, 4.3 Hz, 1 H), 2.25–0.80 (m, 25 H), 1.19 (d, J = 6.3 Hz, 3 H), 1.15 (s, 3 H), 1.14 (d, J = 6.0 Hz, 3 H), 1.01 (s, 3 H), 0.99 (s, 3 H), 0.92 (s, 3 H), 0.88 (s, 3 H), 0.86 (s, 3 H); LRMS m/z (rel intensity) 508 (0.2, M$^+$, $C_{35}H_{56}O_2$), 490 (2), 475 (3), 389 (15), 242 (23), 227 (100), 213 (24), 175 (28), 161 (68), 147 (33), 73 (87); HRMS calcd for $C_{35}H_{56}O_2$ 508.4280, found 508.4275.

Cleavage of the Hydroxy Ether Auxiliary of 26b. 23,24-Dinor-4β-hydroxy-22-vinylideneolean-12-ene (27b). Pyridinium chlorochromate (13 mg, 3.5 equiv) was added to a stirred solution of the hydroxy ether **26b** (8.8 mg, 0.0173 mmol) in dichloromethane (1.5 mL) containing sodium acetate (19 mg) and activated, powdered molecular sieves (4A) (41 mg) at 23 °C under Ar, and the mixture was stirred for 3 h. The mixture was diluted with hexanes–ether (12 mL, 2:1), filtered through a pad of sg with ether (4 mL) rinsing, and then evaporated to leave 23,24-dinor-4β-(2′-oxo-4′(*S**)-pentoxy)-22-vinylideneolean-12-ene as a colorless solid which was used without further purification (GC: 90%): R_f 0.44 (4:1 hexane–ether); ^{1}H NMR δ 5.22 (t, J = 3.5 Hz, 1 H), 4.62 (dd, J = 9.2, 4.0 Hz, 1 H), 4.54 (dd, J = 9.1, 4.2 Hz, 1 H), 3.89–3.80 (m, 1 H), 3.41 (d, J = 2.5 Hz, 1 H), 2.67 (dd, J = 14.9, 8.5 Hz, 1 H), 2.35 (dd, J = 14.7, 4.5 Hz, 1 H), 2.19 (s, 3 H), 2.13 (dt, J = 13.4, 4.0 Hz, 1 H), 2.09–2.01 (m, 2 H), 1.90–1.68 (m, 7 H), 1.63–1.50 (m, 3 H), 1.35–0.75 (m, 10 H), 1.16 (s, 3 H), 1.08 (d, J = 6.0 Hz, 3 H), 1.02 (s, 3 H), 0.99 (s, 3 H), 0.98 (s, 3 H), 0.92 (s, 3 H), 0.86 (s, 3 H); LRMS m/z (rel intensity) 506 (1.6, M$^+$, $C_{35}H_{54}O_2$), 475 (2), 404 (1), 389 (4), 340 (1), 295 (1), 242 (26), 227 (100), 213 (15), 186 (14), 162 (58), 147 (11), 107 (12); HRMS calcd for $C_{35}H_{54}O_2$ 506.4124, found 506.4119.

A solution of potassium hydroxide (0.25 mL, 7.5 M in water) was added to a stirred solution of the foregoing keto ether (ca. 0.017 mmol) in THF–methanol (3.0 mL, 2:1) at 23 °C under Ar, and the mixture was warmed to 65 °C. After 5.5 h, the mixture was diluted with saturated aqueous NH_4Cl (1 mL) and then concentrated in vacuo. The residue was extracted with ether (3 × 5 mL), and the combined organic extracts were dried, filtered through a plug of sg, and evaporated. Purification on 10% silver nitrate impregnated sg with ether–hexanes as eluant (5–10%) gave alcohol **27b** (5.2 mg, 71% over two steps) (GC: 97% pure) as colorless needles when crystallized with acetonitrile. This sample was identical (by 400-MHz ^{1}H NMR, GC coinjection) to the sample of **27b** prepared by the cyclization of aldehyde **11**.

13-Fluoro-5,9,14,17,20,20-hexamethyl-24-(trimethylsilyl)-5(*E*),9(*E*),13(*Z*),17(*Z*)-tetracosatetraen-22-ynal (11). A solution of the enol ethers **20** (69.3 mg, 0.131 mmol) in THF (1.5 mL) was stirred with dilute hydrochloric acid (340 μL, 10%) at 23 °C for 40 min. The reaction was quenched by the addition of ice-cold, saturated aqueous $NaHCO_3$ (2 mL) and the mixture then extracted with ether (3 × 15 mL). The combined organic extracts were then washed with saturated brine (4 mL), dried, filtered through a plug of sg, and evaporated to leave an oil. Purification by MPLC on sg with ether–hexanes as eluant (2–4%) gave unreacted **20** (19.5 mg) (GC: 96.5% pure) and then the aldehyde **11** (35.5 mg, 53%; 73% based on recovered starting material) (GC: 90% pure; two impurities: 2 and 5%): oil; R_f 0.33 (9:1 hexanes–ether); IR (film) ν 2920, 2880, 2690, 2200, 1720, 1695 cm^{-1}; ^{1}H NMR δ 9.77 (t, J = 1.7 Hz, 1 H), 5.17 (t, J = 6.5 Hz, 1 H), 5.15–5.09 (m, 2 H), 2.39 (td, J = 7.3, 1.7 Hz, 2 H), 2.28–2.22 (m, 1 H), 2.21–2.14 (m, 3 H), 2.11–2.04 (m, 6 H), 2.02 (t, J = 2.7 Hz, 2 H), 2.02–1.96 (m, 6 H), 1.76–1.70 (m, 2 H), 1.73 (d, J = 1.1 Hz, 3 H), 1.61 (s, 3 H), 1.58 (d, J = 2.7 Hz, 3 H), 1.58 (s, 3 H), 1.44 (t, J = 2.7 Hz, 2 H), 0.92 (s, 6 H), 0.09 (s, 9 H); HRMS calcd for $C_{33}H_{55}FOSi$ 514.4006, found 514.4006.

Cyclization of Aldehyde 11. 23,24-Dinor-4β-hydroxy-22-vinylideneolean-12-ene (27b) and 23,24-Dinor-4α-hydroxy-22-vinylideneolean-12-ene (27a). A solution of tin(IV) chloride (158 μL, 1.0 M in dichloromethane, 3.00 equiv) was added dropwise over 2 min to a stirred solution of the aldehyde **11** (27.1 mg, 0.053 mmol) in dichloromethane (16.3 mL) at −78 °C under Ar, and after 20 min (TLC indicated no starting material after 10 min) the yellow solution was quenched with NEt_3 (200 μL) followed by MeOH (200 μL). After an additional 10 min, the mixture was warmed to 23 °C, diluted with CH_2Cl_2 (10 mL), washed with saturated aqueous $NaHCO_3$ (4 mL), dried, filtered through a pad of sg, and then evaporated to leave a smear (19.4 mg) (C4 selectivity: **27b**:**27a**, 5.4:1 by ^{1}H NMR). Purification by MPLC on sg with ether–hexanes as eluant (4–8%) gave axial alcohol **27b** (8.1 mg, 36%) (GC: 78%) and then equatorial alcohol **27a** (2.7 mg, 13%) (GC: 77%). Alcohol **27b** was recrystallized from acetonitrile to >98% purity, and **27a** was recrystallized from aqueous acetonitrile (MeCN:H_2O, 10:1) to >98.5% purity.

For **27b**: colorless needles; mp 162–163.5 °C; R_f 0.34 (2:1 hexanes–ether); IR ($CHCl_3$) ν 3580, 3540–3100, 2900, 2840, 1935, 1445, 1370, 1240, 985, 840 cm^{-1}; ^{1}H NMR δ 5.23 (t, J = 3.5 Hz, 1 H), 4.63 (dd, J = 9.2, 3.7 Hz, 1 H), 4.54 (dd, J = 9.2, 4.3 Hz, 1 H), 3.86 (d, J = 2.4 Hz, 1 H), 2.18–2.01 (m, 3 H), 1.96–0.80 (m, 21 H), 1.17 (s, 3 H), 1.11 (s, 3 H), 1.04 (s, 3 H), 1.00 (s, 3 H), 0.92 (s, 3 H), 0.87 (s, 3 H); LRMS m/z (rel intensity) 422 (2, M$^+$, $C_{30}H_{46}O$), 407 (5), 389 (3), 227 (100), 213 (16), 187 (15), 162 (20), 133 (15), 119 (16), 105 (16); HRMS calcd for $C_{30}H_{46}O$ 422.3549; found 422.3554. Anal. Calcd for $C_{30}H_{46}O$: C, 85.24; H, 10.97. Found: C, 85.53; H, 10.80.

For **27a**: colorless prisms; mp 152–155 °C; R_f 0.21 (2:1 hexanes–ether); ^{1}H NMR δ 5.23 (t, J = 3.7 Hz, 1 H), 4.63 (dd, J = 9.2, 3.7 Hz, 1 H), 4.54 (dd, J = 9.0, 4.1 Hz, 1 H), 3.51–3.42 (m, 1 H), 2.16–0.80 (m, 24 H), 1.17 (s, 3 H), 1.03 (s, 3 H), 1.00 (s, 3 H), 0.92 (s, 3 H), 0.88 (s, 3 H), 0.87 (s, 3 H); LRMS m/z (rel intensity) 422 (4, M^+, $C_{30}H_{46}O$), 407 (8), 389 (2), 242 (17), 228 (21), 227 (100), 213 (17), 187 (15), 173 (16), 161 (23), 159 (15), 133 (19), 119 (20); HRMS calcd for $C_{30}H_{46}O$ 422.3549, found 422.3546.

2,3-Epoxy-14-fluoro-2,6,10,15,18,21,21-heptamethyl-25-(trimethylsilyl)-6(*E*),10(*E*),14(*Z*),18(*Z*)-pentacosatetraen-23-yne (12). A solution of *tert*-butyllithium (0.66 mL, 1.7 M in pentane, 3.0 equiv) was added dropwise over 5 min to a stirred suspension of dry diphenyl(2-propyl)sulfonium tetrafluoroborate[20] (350 mg, 3.0 equiv) in anhydrous THF (5.0 mL) at −78 °C under Ar, and the orange-yellow solution was stirred for 60 min. A solution of the aldehyde **19** (186 mg, 0.37 mmol) in THF (3.5 mL) was then added dropwise over 7 min, and the mixture was stirred at −78 °C for 2.5 h. The mixture was then quenched with water (8 mL), warmed to 23 °C, and extracted with hexanes (2 × 30 mL) and ether–hexanes (30 mL, 1:1). The combined organic extracts were then washed with saturated brine (25 mL), dried, and evaporated to leave an oil. Purification by MPLC on sg with ether–hexanes as eluant (2–8%) gave epoxide **12** (138.5 mg, 69%) (GC: dec) (purity ca. 95% by ^{1}H NMR): oil; bp 117 °C (oven temperature) at 0.005 mmHg; R_f 0.37 (9:1 hexanes–ether); IR (film) ν 2920, 2890, 2840, 2210, 1690, 1655, 1435, 1365, 1235, 840, 690 cm^{-1}; ^{1}H NMR δ 5.17 (t, J = 6.5 Hz, 1 H), 5.17–5.11 (m, 2 H), 2.70 (t, J = 6.3 Hz, 1 H), 2.28–1.95 (m, 14 H), 2.02 (t, J = 2.7 Hz, 2 H), 1.97 (d, J = 7.8 Hz, 2 H), 1.72 (d, J = 1.1 Hz, 3 H), 1.71–1.58 (m, 2 H), 1.61 (s, 3 H), 1.61 (s, 3 H), 1.58 (d, J = 2.5 Hz, 3 H), 1.44 (t, J = 2.6 Hz, 2 H), 1.30 (s, 3 H), 1.26 (s, 3 H), 0.92 (s, 6 H), 0.09 (s, 9 H); HRMS calcd for $C_{35}H_{59}FOSi$ 542.4319, found 542.4330. Anal. Calcd for $C_{35}H_{59}FOSi$: C, 77.43; H, 10.95. Found: C, 77.59; H, 10.84.

Cyclization of Epoxide 12. 3β-Hydroxy-22-vinylideneolean-12-ene (28). A solution of (2-propoxy)titanium trichloride (792 μL, 0.5 M in dichloromethane, 3.00 equiv) [prepared from titanium(IV) chloride (3.0 mL, 1.0 M in dichloromethane, 3.0 mmol) and titanium(IV) isopropoxide (0.30 mL, 1.0 mmol) in dichloromethane (4.7 mL)] was added dropwise over 3 min to a stirred solution of the epoxide **12** (71.6 mg, 0.132 mmol) in dichloromethane (41.7 mL) at −78 °C under Ar, and after 16 min (TLC indicated no starting material after 10 min) the yellow solution was quenched with NEt_3 (250 μL) followed by MeOH (400 μL). After an additional 10 min, the mixture was warmed to 23 °C, dried, filtered through a pad of sg, and then evaporated to leave a smear (64.3 mg) (GC: **28**:**29**:**30**, 21:13:24%, all others <5%). Purification by MPLC on sg with ether–hexanes as eluant (1–12%) gave, in order of elution: (1) the 7-oxabicyclo[2.2.1]heptane **29** (6.4 mg) (GC: 96% pure), (2) predominantly the bicyclic triene **30** (10.2 mg) (GC: 71% pure), (3) a mixture containing the pentacycle **28** as the major component (11.2 mg) (GC: 51% pure), and (4) a quantity of mixed fractions (18.5 mg) which included small amounts of **28** and **30**. Fraction 3 was purified further by recrystallization from acetonitrile to yield pentacycle **28** (5.6 mg, 10% isolated) (GC: 98% pure). Fraction 2 was triturated with acetonitrile and evaporation of the mother liquors gave **30** (8.1 mg) (GC: 82% pure) which failed to crystallize under a variety of conditions.

For **28**: clusters of colorless microneedles; mp 184–186 °C; R_f 0.15 (4:1 hexanes–ether); IR ($CHCl_3$) ν 2920, 2900, 2840, 1940, 1445, 1370 cm^{-1}; ^{1}H NMR δ 5.21 (t, J = 3.6 Hz, 1 H), 4.62 (dd, J = 9.0, 3.9 Hz, 1 H), 4.54 (dd, J = 9.2, 4.3 Hz, 1 H), 3.26–3.18 (m, 1 H), 2.16–2.01 (m, 3 H), 1.92–1.73 (m, 5 H), 1.66–0.70 (m, 14 H), 1.16 (s, 3 H), 1.00 (s, 3 H), 0.99 (s, 3 H), 0.97 (s, 3 H), 0.94 (s, 3 H), 0.92 (s, 3 H), 0.86 (s, 3 H), 0.79 (s, 3 H); LRMS m/z (rel intensity) 450 (4, M^+, $C_{32}H_{50}O$), 435 (6), 281 (3), 242 (20), 227 (100), 213 (15), 207 (11), 187 (13), 173 (13), 133 (11), 119 (12), 69 (18); HRMS calcd for $C_{32}H_{50}O$ 450.3862, found 450.3848. Anal. Calcd for $C_{32}H_{50}O$: C, 85.27; H, 11.18. Found: C, 85.12; H, 11.01.

For **29**: oil; bp 123 °C (oven temperature) at 0.009 mmHg; R_f 0.64 (4:1 hexanes–ether); IR (film) ν 2935, 2900, 2840, 1690, 1585, 1445, 1370, 1235, 840 cm^{-1}; ^{1}H NMR δ 5.17 (t, J = 7.8 Hz, 1 H), 5.12 (t, J = 6.5 Hz, 1 H), 3.71 (d, J = 5.2 Hz, 1 H), 2.28–2.21 (m, 1 H), 2.21–2.14 (m, 3 H), 2.11–2.05 (m, 4 H), 2.02 (t, J = 2.7 Hz, 2 H), 1.97 (d, J = 6.8 Hz, 2 H), 1.96–1.85 (m, 3 H), 1.72 (d, J = 0.8 Hz, 3 H), 1.72–1.62 (m, 1 H), 1.60 (s, 3 H), 1.58 (d, J = 2.7 Hz, 3 H), 1.50–1.33 (m, 4 H), 1.44 (t, J = 2.7 Hz, 2 H), 1.32 (s, 3 H), 1.17 (dd, J = 8.4, 5.6 Hz, 1 H), 1.04 (s, 3 H), 1.01 (s, 3 H), 0.92 (s, 6 H), 0.09 (s, 9 H); LRMS m/z (rel intensity) 524 (0.4, M − H_2O, $C_{35}H_{57}FSi$), 235 (23), 161 (23), 135 (15), 121 (20), 107 (14), 81 (15), 73 (100); HRMS calcd for $C_{35}H_{57}FSi$ (M − H_2O) 524.4214, found 524.4229.

For **30**: colorless smear; R_f 0.20 (4:1 hexanes–ether); ^{1}H NMR selected data δ 5.46 (t, J = 3.2 Hz, 1 H), 5.17 (t, J = 7.5 Hz, 1 H), 3.44 (d, J = 8.2 Hz, 1 H), 2.08 (m, 3 H), 2.02 (t, J = 2.7 Hz, 2 H), 1.96 (d, J = 7.6 Hz, 2 H), 1.72 (s, 3 H), 1.57 (d, J = 2.4 Hz, 3 H), 1.44 (t, J = 2.7 Hz, 2 H), 1.10 (s, 6 H), 0.92 (s, 6 H), 0.87 (s, 3 H), 0.82 (d, J = 6.7 Hz, 3 H), 0.10 (s, 9 H); LRMS m/z (rel intensity) 542 (0.6, M^+, $C_{35}H_{59}FOSi$), 524 (0.3, M − H_2O), 450 (0.7), 435 (0.6), 390 (0.4), 235 (36), 189 (16), 161 (25), 109 (14), 73 (100); HRMS calcd for $C_{35}H_{59}FOSi$ 542.4319, found 542.4322.

3β-(*tert*-Butyldimethylsiloxy)-22-vinylideneolean-12-ene (31). *tert*-Butyldimethylsilyl trifluoromethanesulfonate (6.0 μL, 2.2 equiv) was added dropwise to a stirred solution of the alcohol **28** (5.6 mg, 0.012 mmol) and 2,6-lutidine (7.0 μL, 5.0 equiv) in dichloromethane (1.5 mL) at 23 °C under Ar. After 60 min, the mixture was diluted with hexanes (10 mL) and then washed with saturated aqueous $NaHCO_3$ (2 mL), dried, filtered through a pad of sg, and evaporated to leave the silyl ether **31** (4.8 mg, 71%) (GC: 95%): colorless crystals; R_f 0.85 (19:1 hexanes–ether); ^{1}H NMR δ 5.21 (t, J = 3.5 Hz, 1 H), 4.62 (dd, J = 9.1, 3.9 Hz, 1 H), 4.54 (dd, J = 9.1, 4.2 Hz, 1 H), 3.18 (dd, J = 11.0, 4.5 Hz, 1 H), 2.16–2.01 (m, 3 H), 1.92–1.72 (m, 5 H), 1.64–0.68 (m, 13 H), 1.15 (s, 3 H), 0.99 (s, 3 H), 0.97 (s, 3 H), 0.93 (s, 3 H), 0.93 (s, 3 H), 0.91 (s, 3 H), 0.89 (s, 9 H), 0.86 (s, 3 H), 0.75 (s, 3 H), 0.03 (s, 6 H).

1-(8-Fluoro-1-hydroxy-4,9,12,15,15-pentamethyl-19-(trimethylsilyl)-4(*E*),8(*Z*),12(*Z*)-nonadecatrien-17-yn-1-yl)-1-methylcyclopropane (21). A solution of (1-methyl-1-cyclopropyl)magnesium bromide (6.3 mL, 0.35 M in THF, 3.0 equiv) [prepared from 1-bromo-1-methylcyclopropane[21] (345 μL) and magnesium turnings (65 mg) in THF (7.5 mL)] was added dropwise over 10 min to a stirred solution of the aldehyde **16** (311 mg, 0.718 mmol) in THF (7.5 mL) at −78 °C under Ar, and the mixture was stirred for 10 min. The mixture was warmed to 23 °C and stirred for an additional 1.6 h, and then the reaction was quenched with saturated aqueous NH_4Cl (5 mL). The mixture was extracted with ether–hexanes (25 mL, 1:1) and ether (10 mL). The combined organic extracts were then washed with saturated brine (5 mL), dried, and evaporated to leave an oil. Purification by MPLC on 10% silver nitrate impregnated sg with mixtures of ether–hexanes as eluant (5–30%) gave the cyclopropylcarbinol **21** (193 mg, 55%) (GC: dec) (purity ca. >95% by ^{13}C NMR): oil; bp 108 °C (oven temperature) at 0.006 mmHg; R_f 0.25 (4:1 hexanes–ether); IR (film) ν 3570, 3500–3280, 3050, 2920, 2890, 2830, 2205, 1685, 1460, 1365, 1235, 1160, 1055, 1000, 830, 750, 690 cm^{-1}; ^{1}H NMR δ 5.17 (t, J = 6.7 Hz, 1 H), 5.17 (t, J = 6.7 Hz, 1 H), 2.80 (t, J = 6.7 Hz, 1 H), 2.28–2.22 (m, 1 H), 2.21–2.15 (m, 3 H), 2.16–2.10 (m, 1 H), 2.11–2.06 (m, 4 H), 2.08–2.00 (m, 1 H), 2.02 (t, J = 2.7 Hz, 2 H), 1.97 (d, J = 7.6 Hz, 2 H), 1.72 (d, J = 1.1 Hz, 3 H), 1.68–1.63 (m, 2 H), 1.62 (s, 3 H), 1.58 (d, J = 2.7 Hz, 3 H), 1.48 (br s, 1 H), 1.44 (t, J = 2.6 Hz, 2 H), 1.03 (s, 3 H), 0.92 (s, 6 H), 0.40–0.35 (m, 2 H), 0.37–0.27 (m, 2 H), 0.09 (s, 9 H); ^{13}C NMR δ 154.2 (d, J = 242.3 Hz), 136.6, 136.0, 123.2, 121.6, 111.5 (d, J = 16.7 Hz), 78.8, 78.6, 76.8, 39.1, 36.3, 34.4, 32.4, 32.0, 30.0, 28.9, 28.6, 28.2 (d, J = 7.5 Hz), 26.6, 26.6, 25.2, 23.6, 20.6, 17.2, 15.7 (d, J = 6.2 Hz), 11.9, 11.2, 7.0, −2.0, −2.0, −2.0; HRMS calcd for $C_{31}H_{51}FSi$ (M − H_2O) 470.3744, found 470.3741. Anal. Calcd for $C_{31}H_{53}FOSi$: C, 76.16; H, 10.93. Found: C, 76.15; H, 10.82.

1-Bromo-11-fluoro-3,7,12,15,18,18-hexamethyl-22-(trimethylsilyl)-3(*E*),7(*E*),11(*Z*),15(*Z*)-docosatetraen-20-yne (22). A mixture of the alcohol **21** (151 mg, 0.309 mmol) and magnesium bromide etherate (400 mg, 5.0 equiv) in ether (8.2 mL) was heated at reflux, under Ar, for 70 h. The cooled mixture was then diluted with ether–hexanes (10 mL, 1:1), washed with water (2.5 mL), dried, filtered through a plug of sg, and then evaporated to leave an oil (selectivity: 3(*E*):3(*Z*), 99:1, by ^{1}H NMR). Purification by MPLC on sg with mixtures of ether–hexanes as eluant (0–1%) gave the homoallylic bromide **22** (117 mg, 69%) (GC: dec) (purity ca. 95%; 3(*E*):3(*Z*), 99:1, by ^{1}H NMR): oil; bp 110 °C (oven temperature) at 0.003 mmHg; R_f 0.93 (4:1 hexanes–ether); IR

(film) ν 2920, 2880, 2830, 2200, 1685, 1645, 1430, 1365, 1345, 1230, 830, 750, 685, 645 cm^{-1}; ^{1}H NMR δ 5.21 (t, J = 6.8 Hz, 1 H), 5.21–5.10 (m, 2 H), 3.42 (t, J = 7.5 Hz, 2 H), 2.52 (t, J = 7.6 Hz, 2 H), 2.28–1.94 (m, 12 H), 2.02 (t, J = 2.7 Hz, 2 H), 1.97 (d, J = 7.7 Hz, 2 H), 1.73 (s, 3 H), 1.62 (s, 3 H), 1.61 (s, 3 H), 1.58 (d, J = 2.4 Hz, 3 H), 1.44 (t, J = 2.7 Hz, 2 H), 0.92 (s, 6 H), 0.09 (s, 9 H); HRMS calcd for $C_{31}H_{52}{}^{79}BrFSi$ 550.3006, found 550.3029. Anal. Calcd for $C_{31}H_{52}BrFSi$: C, 67.48; H, 9.50. Found: C, 67.78; H, 9.54.

Ethyl 13-Fluoro-5,9,14,17,20,20-hexamethyl-2-(1-propen-2-yl)-24-(trimethylsilyl)-5(*E*),9(*E*),13(*Z*),17(*Z*)-tetracosatetraen-22-ynoate (23). *n*-Butyllithium (0.75 mL, 1.6 M in hexanes, 2.6 equiv) was added dropwise to a stirred solution of diisopropylamine (160 μL, 2.5 equiv) in THF (4 mL) under Ar at −40 °C, and the mixture was stirred for 15 min. The resulting solution of lithium diisopropylamide (2.5 equiv) was cooled to −78 °C, hexamethylphosphoramide (330 μL, 4.1 equiv) was added, and the mixture was stirred for 30 min. Ethyl 3,3-dimethylacrylate (170 μL, 2.65 equiv) was added dropwise, the mixture was stirred for 35 min, and then a solution of the bromide **22** (255 mg, 0.462 mmol) in THF (3.0 mL) was added dropwise via a cannular needle. The mixture was stirred at −78 °C for 20 min and then warmed slowly to 0 °C over 60 min, at which it was maintained for an additional 4 h. The reaction was quenched with saturated aqueous NH_4Cl (5 mL), warmed to 23 °C, diluted with water (1 mL), and then extracted with hexanes (3 × 10 mL). The combined extracts were dried, filtered through a plug of sg, and evaporated to leave an oil. Purification by MPLC on sg with ether–hexanes as eluant (2%) gave the β,γ enoate **23** (257.3 mg, 93%) (GC: dec) (purity ca. 95% by ^{1}H NMR): oil; bp 118 °C (oven temperature) at 0.008 mmHg; R_f 0.56 (9:1 hexanes–ether); IR (film) ν 3050, 2920, 2880, 2830, 2200, 1710, 1685, 1620, 1430, 1365, 1350, 1230, 1135, 880, 835, 690 cm^{-1}; ^{1}H NMR δ 5.17 (t, J = 7.2 Hz, 1 H), 5.15–5.08 (m, 2 H), 4.89 (t, J = 1.5 Hz, 1 H), 4.86 (s, 1 H), 4.13 (q, J = 7.1 Hz, 2 H), 2.97 (t, J = 7.0 Hz, 1 H), 2.28–2.21 (m, 1 H), 2.21–2.13 (m, 3 H), 2.13–2.06 (m, 5 H), 2.06–1.85 (m, 7 H), 2.02 (t, J = 2.5 Hz, 2 H), 1.74 (s, 3 H), 1.72 (s, 3 H), 1.69–1.56 (m, 2 H), 1.60 (s, 3 H), 1.59 (s, 3 H), 1.57 (d, J = 2.7 Hz, 3 H), 1.43 (t, J = 2.5 Hz, 2 H), 1.24 (t, J = 7.1 Hz, 3 H), 0.91 (s, 6 H), 0.09 (s, 9 H); ^{13}C NMR δ 173.7, 154.3 (d, J = 242.4 Hz), 142.5, 136.7, 136.0, 134.1, 125.0, 123.0, 121.6, 113.7, 111.4 (d, J = 16.7 Hz), 78.8, 76.8, 60.4, 52.4, 39.6, 39.1, 37.3, 34.4, 32.1, 30.0, 29.0, 28.7, 28.3, 28.2 (d, J = 7.5 Hz), 26.6, 26.6, 25.2, 23.6, 20.2, 15.9, 15.8, 15.7 (d, J = 6.3 Hz), 14.2, 7.0, −2.0, −2.0, −2.0; HRMS calcd for $C_{38}H_{63}FO_2Si$ 598.4581, found 598.4554. Anal. Calcd for $C_{38}H_{63}FO_2Si$: C, 76.19; H, 10.60. Found: C, 76.29; H, 10.40.

Ethyl 13-Fluoro-5,9,14,17,20,20-hexamethyl-2-(2-propylidene)-24-(trimethylsilyl)-5(*E*),9(*E*),13(*Z*),17(*Z*)-tetracosatetraen-22-ynoate (24). A solution of the β,γ enoate **23** (255 mg, 0.426 mmol) in THF (7.5 mL) was stirred with potassium *tert*-butoxide (50 mg, 1.05 equiv) under Ar at 0 °C for 30 min. The reaction was quenched with saturated aqueous NH_4Cl (5 mL), warmed to 23 °C, diluted with water (1 mL), and then extracted with hexanes (3 × 10 mL). The combined extracts were dried, filtered through a plug of sg, and evaporated to leave an oil (equilibrium ratio: **24**:**23**, 91:9, by ^{1}H NMR). Purification by MPLC on sg with ether–hexanes as eluant (2%) gave predominantly the α,β enoate **24** (189.8 mg, 74%) (GC: dec) (**24**:**23**, 92:8, by ^{1}H NMR) which was inseparable, at this stage, from the β,γ isomer **23**. For **24**: oil; R_f 0.56 (9:1 hexanes–ether); IR (film) ν 2920, 2890, 2210, 1685, 1615, 1430, 1365, 1230, 1155, 1085, 840, 690 cm^{-1}; ^{1}H NMR δ 5.17 (t, J = 7.6 Hz, 1 H), 5.16–5.09 (m, 2 H), 4.19 (q, J = 7.0 Hz, 2 H), 2.39–2.33 (m, 2 H), 2.28–2.21 (m, 1 H), 2.21–2.14 (m, 3 H), 2.11–2.06 (m, 5 H), 2.06–1.94 (m, 7 H), 2.02 (t, J = 2.8 Hz, 2 H), 1.96 (s, 3 H), 1.80 (s, 3 H), 1.72 (s, 3 H), 1.62 (s, 3 H), 1.61 (s, 3 H), 1.58 (d, J = 2.4 Hz, 3 H), 1.44 (t, J = 2.5 Hz, 2 H), 1.30 (t, J = 7.1 Hz, 3 H), 0.92 (s, 6 H), 0.09 (s, 9 H); HRMS calcd for $C_{38}H_{63}FO_2Si$ 598.4581, found 598.4560.

14-Fluoro-2,6,10,15,18,21,21-heptamethyl-2-hydroxy-3-(2-propylidene)-25-(trimethylsilyl)-6(*E*),10(*E*),14(*Z*),18(*Z*)-pentacosatetraen-23-yne (13). A solution of methyllithium (1.1 mL, 1.4 M in ether, 5.0 equiv) was added to a stirred solution of α,β enoate **24** (187 mg, 0.312 mmol) in ether (5.0 mL) under Ar at −10 °C. After 5 min, the mixture was warmed to 23 °C and stirred for an additional 30 min. The mixture was quenched with saturated aqueous NH_4Cl (5.0 mL) and extracted with hexanes (10 mL), hexanes–ether (10 mL, 1:1), and ether (10 mL). The combined extracts were dried, filtered through a plug of sg, and evaporated to leave an oil. Purification by MPLC on sg with ether–hexanes as eluant (4–8%) gave, in order of elution, the α,β enone **25** (37.7 mg, 21%) (GC: 95%) and then the tertiary alcohol **13** (124.6 mg, 68%) (GC: dec) (purity ca. >90% by ^{1}H NMR). Methylation of α,β enone **25** (54 mg, 0.095 mmol) with methyllithium (3.0 equiv, Et_2O, 23 °C, 30 min) also gave the tertiary alcohol **13** (24.4 mg, 44%; 52% based on recovered **25** (8.3 mg)).

For **13**: oil; bp 122 °C (oven temperature) at 0.010 mmHg; R_f 0.23 (9:1 hexanes–ether); IR (film) ν 3580, 3550–3300, 2920, 2880, 2210, 1685, 1650, 1430, 1365, 1345, 1230, 835, 690 cm^{-1}; ^{1}H NMR δ 5.17 (t, J = 7.6 Hz, 1 H), 5.16–5.10 (m, 2 H), 2.28–2.21 (m, 1 H), 2.21–2.11 (m, 6 H), 2.11–2.07 (m, 5 H), 2.07–1.94 (m, 6 H), 2.02 (t, J = 2.7 Hz, 2 H), 1.92 (s, 3 H), 1.72 (d, J = 1.2 Hz, 3 H), 1.70 (s, 3 H), 1.66 (s, 1 H), 1.63 (s, 3 H), 1.61 (s, 3 H), 1.58 (d, J = 2.5 Hz, 3 H), 1.44 (t, J = 2.7 Hz, 2 H), 1.42 (s, 6 H), 0.92 (s, 6 H), 0.09 (s, 9 H); ^{13}C NMR δ 154.3 (d, J = 242.6 Hz), 138.6, 136.9, 136.0, 135.0, 128.1, 124.0, 123.0, 121.6, 111.4 (d, J = 17.1 Hz), 78.8, 76.8, 74.2, 40.1, 39.7, 39.1, 34.4, 32.1, 30.9, 30.9, 30.0, 29.9, 29.0, 28.7, 28.2 (d, J = 7.5 Hz), 26.6, 26.6, 25.2, 23.6, 22.8, 22.7, 16.0, 15.9, 15.7 (d, J = 5.1 Hz), 7.0, −2.0, −2.0, −2.0; HRMS calcd for $C_{38}H_{63}FSi$ (M − H_2O) 566.4683, found 566.4647. Anal. Calcd for $C_{38}H_{65}FOSi$: C, 78.02; H, 11.20. Found: C, 78.47; H, 10.99.

For **25**: oil; bp 123 °C (oven temperature) at 0.006 mmHg; R_f 0.31 (9:1 hexanes–ether); IR (film) ν 2920, 2880, 2840, 2210, 1660, 1430, 1365, 1340, 1230, 1150, 835, 690 cm^{-1}; ^{1}H NMR δ 5.17 (td, J = 7.6, 1.2 Hz, 1 H), 5.16–5.11 (m, 2 H), 2.37–2.31 (m, 2 H), 2.28–2.22 (m, 1 H), 2.25 (s, 3 H), 2.22–2.14 (m, 3 H), 2.12–2.06 (m, 5 H), 2.06–1.96 (m, 7 H), 2.02 (t, J = 2.7 Hz, 2 H), 1.82 (s, 3 H), 1.76 (s, 3 H), 1.72 (d, J = 1.2 Hz, 3 H), 1.61 (s, 6 H), 1.58 (d, J = 2.5 Hz, 3 H), 1.44 (t, J = 2.7 Hz, 2 H), 0.92 (s, 6 H), 0.09 (s, 9 H); HRMS calcd for $C_{37}H_{61}FOSi$ 568.4476, found 568.4451. Anal. Calcd for $C_{37}H_{61}FOSi$: C, 78.10; H, 10.81. Found: C, 78.37; H, 10.74.

Cyclization of 13 with Tin(IV) Chloride. 3-(2-Propylidene)-22-vinylideneolean-12-ene (32). A solution of tin(IV) chloride (71 μL, 1.0 M in dichloromethane, 3.00 equiv) was added dropwise over 1 min to a stirred solution of the alcohol **13** (13.8 mg, 0.0236 mmol) in dichloromethane (10.0 mL) under Ar at −78 °C, and after 20 min (TLC indicated no starting material after 10 min) the yellow solution was quenched with NEt_3 (25 μL) followed by MeOH (25 μL). After an additional 10 min, the mixture was warmed to 23 °C, diluted with hexanes (10 mL), filtered through a pad of sg, and then evaporated to leave a smear. Purification on 10% silver nitrate impregnated sg with hexanes as eluant gave pentacycle **32** (5.6 mg, 50%) (GC: 92.5%) which was recrystallized with acetonitrile to >98% purity: colorless needles; mp 144.5–146 °C; R_f 0.80 (99:1 hexanes–ether); IR ($CHCl_3$) ν 2930, 2900, 2840, 1935, 1445, 1370, 1350, 835 cm^{-1}; ^{1}H NMR δ 5.26 (t, J = 3.6 Hz, 1 H), 4.63 (dd, J = 9.2, 3.6 Hz, 1 H), 4.54 (dd, J = 8.9, 4.0 Hz, 1 H), 2.28 (dt, J = 14.5, 5.7 Hz, 1 H), 2.14 (t, J = 3.6 Hz, 1 H), 2.11 (t, J = 4.3 Hz, 1 H), 2.07 (d, J = 4.2 Hz, 1 H), 2.03 (d, J = 4.6 Hz, 1 H), 1.98–0.78 (m, 16 H), 1.80 (s, 3 H), 1.66 (s, 3 H), 1.19 (s, 3 H), 1.17 (s, 3 H), 1.14 (s, 3 H), 1.00 (s, 3 H), 0.99 (s, 3 H), 0.93 (s, 3 H), 0.90 (s, 3 H), 0.87 (s, 3 H); LRMS m/z (rel intensity) 474 (26, M^+, $C_{35}H_{54}$), 459 (22), 378 (43), 271 (65), 232 (31), 227 (100), 173 (39), 161 (41), 149 (51), 135 (84), 121 (65), 95 (79); HRMS calcd for $C_{35}H_{54}$ 474.4226, found 474.4217.

Cyclization of 13 with Trifluoroacetic Acid. 13β-Fluoro-3-(2-propylidene)-22-vinylideneoleanane (33). Trifluoroacetic acid (150 μL) was added in one portion to a stirred solution of the alcohol **13** (28.8 mg, 0.0492 mmol) in dichloromethane (15.0 mL) under Ar at −78 °C. After 15 min, the mixture was poured onto ice-cold saturated aqueous $NaHCO_3$ (5 mL), diluted with hexanes (10 mL), and warmed to 23 °C. The aqueous phase was extracted with hexanes (10 mL), and the combined organic extracts were then washed with saturated aqueous $NaHCO_3$ (5 mL), dried, and evaporated to leave a smear. Purification on 10% silver nitrate impregnated sg with ether–hexanes as eluant (0–1%) gave fluoropentacycle **33** (7.5 mg, 31%) (GC: >97%) which was recrystallized with acetonitrile to >99% purity: colorless needles; mp 161–162 °C; R_f 0.58 (99:1 hexanes–ether); IR ($CHCl_3$) ν 2920, 2890, 2840, 1935, 1440, 1375, 1350 cm^{-1}; ^{1}H NMR δ 4.66 (dd, J = 8.9, 2.4 Hz, 1 H), 4.62 (dd, J = 9.1, 2.9 Hz,

1 H), 2.33 (ddd, J = 14.6, 7.1, 3.4 Hz, 1 H), 2.12–2.00 (m, 2 H), 1.93 (dt, J = 13.3, 3.0 Hz, 1 H), 1.81–0.78 (m, 19 H), 1.78 (d, J = 1.0 Hz, 3 H), 1.66 (s, 3 H), 1.30 (d, J = 2.3 Hz, 3 H), 1.20 (s, 3 H), 1.10 (d, J = 6.2 Hz, 3 H), 1.10 (s, 3 H), 1.00 (s, 3 H), 0.92 (s, 3 H), 0.91 (s, 3 H), 0.83 (s, 3 H); LRMS m/z (rel intensity) 494 (2.5, M^+, $C_{35}H_{55}F$), 474 (53), 459 (23), 378 (43), 375 (32), 232 (32), 229 (41), 227 (100), 213 (34), 161 (32), 149 (31), 135 (65), 121 (51), 95 (64); HRMS calcd for $C_{35}H_{55}F$ 494.4289, found 494.4274. Anal. Calcd for $C_{35}H_{55}F$: C, 84.96; H, 11.20. Found: C, 85.12; H, 11.17.

13β-Fluoro-3,22-oleananedione (34). A heterogeneous mixture of the allene **33** (24.2 mg, 0.0489 mmol) in acetonitrile (2.0 mL), tetrachloromethane (2.0 mL), and water (3.0 mL) was vigorously stirred with sodium periodate (108 mg, 10 equiv) and a catalytic amount of ruthenium trichloride hydrate (ca. 1.0 mg) at 23 °C for 15 h. The mixture was diluted with ether–hexanes (10 mL, 1:1), and the organic extracts were dried, filtered through a pad of sg, and then evaporated to leave an off-white solid. Purification on sg with ether–hexanes as eluant (50%) gave the dione **34** (19.8 mg, 88%) (GC: >97%) as colorless crystals: mp 188–190 °C; R_f 0.35 (3:2 hexanes–ether); IR ($CHCl_3$) ν 2910, 2830, 1665, 1435, 1360, 1345, 1095 cm^{-1}; ^1H NMR δ 2.52 (ddd, J = 15.7, 9.7, 7.6 Hz, 1 H), 2.42 (ddd, J = 11.8, 7.5, 4.4 Hz, 1 H), 2.39 (d, J = 13.1 Hz, 1 H), 2.13–1.93 (m, 2 H), 2.00 (d, J = 13.3 Hz, 1 H), 1.85 (td, J = 13.0, 4.5 Hz, 1 H), 1.79–1.64 (m, 3 H), 1.64–0.80 (m, 13 H), 1.31 (d, J = 2.2 Hz, 3 H), 1.13 (d, J = 7.3 Hz, 3 H), 1.07 (s, 3 H), 1.04 (s, 3 H), 1.01 (s, 3 H), 1.00 (s, 3 H), 0.98 (s, 3 H), 0.97 (s, 3 H); LRMS m/z (rel intensity) 458 (5, M^+, $C_{30}H_{47}FO_2$), 438 (11), 423 (7), 232 (100), 219 (62), 206 (44), 205 (53), 161 (27), 121 (26), 119 (27), 81 (30), 73 (59); HRMS calcd for $C_{30}H_{47}FO_2$ 458.3560, found 458.3564.

Olean-12-ene-3,22-dione (35). A solution of tin(IV) chloride (83 μL, 1.0 M in dichloromethane, 2.0 equiv) was added dropwise over 1 min to a stirred solution of the fluoropentacycle **34** (19.1 mg, 0.0416 mmol) in dichloromethane (5.0 mL) under Ar at −15 °C, and the mixture was stirred for 60 min. The mixture was quenched with saturated aqueous $NaHCO_3$ (1.0 mL), warmed to 23 °C, and then extracted with ether–hexanes (10 mL, 1:1), and ether (5 mL). The combined extracts were dried, filtered through a pad of sg, and then evaporated to leave alkene **35** (16.8 mg, 92%) (GC: 94%) which was crystallized with ether to 99% purity: colorless plates; mp 185–186 °C; R_f 0.44 (3:2 hexanes–ether); IR ($CHCl_3$) ν 2910, 2880, 2830, 1665, 1435, 1360, 1345, 1095, 955 cm^{-1}; ^1H NMR δ 5.32 (t, J = 3.4 Hz, 1 H), 2.55 (ddd, J = 16.3, 9.4, 5.7 Hz, 1 H), 2.44 (d, J = 14.0 Hz, 1 H), 2.40 (dd, J = 6.5, 3.2 Hz, 1 H), 2.38–2.30 (m, 1 H), 2.13 (d, J = 13.5 Hz, 1 H), 2.09–1.87 (m, 4 H), 1.78 (td, J = 13.8, 4.0 Hz, 1 H), 1.66 (dd, J = 11.2, 6.4 Hz, 1 H), 1.60–0.75 (m, 10 H), 1.24 (s, 3 H), 1.10 (s, 3 H), 1.08 (s, 3 H), 1.06 (s, 3 H), 1.02 (s, 3 H), 1.01 (s, 3 H), 1.00 (s, 3 H), 0.86 (s, 3 H); ^{13}C NMR δ 217.6, 216.9, 141.6, 123.5, 55.3, 50.8, 47.7, 47.6, 47.2, 46.8, 46.6, 42.0, 39.6, 39.3, 36.7, 34.1, 34.0, 32.2, 32.0, 29.7, 27.2, 26.4, 25.3, 25.1, 23.6, 21.5, 20.6, 19.6, 16.7, 15.2; LRMS m/z (rel intensity) 438 (6, M^+, $C_{30}H_{46}O_2$), 232 (100), 217 (27), 189 (14), 174 (14), 147 (18), 133 (17), 121 (14), 119 (17), 81 (14), 73 (18); HRMS calcd for $C_{30}H_{46}O_2$ 438.3498, found 438.3488.

Sophoradiol (Olean-12-ene-3β,22β-diol) (3). A solution of diisobutylaluminum hydride (167 μL, 1.0 M in hexanes, 5.0 equiv) was added to a stirred solution of the dione **35** (14.7 mg, 0.0335 mmol) in ether (4.0 mL) at 23 °C under Ar, and the mixture was then stirred for 1.5 h. The mixture was diluted with ether (10 mL), washed with saturated aqueous NH_4Cl (1.0 mL), dried, filtered through a pad of sg, and then evaporated to leave predominantly sophoradiol (**3**) along with olean-12-ene-3β,22α-diol (**36**) (12.9 mg, 87%; **3**:**36**, 4.1:1). Purification by recrystallization with acetonitrile separated (±)-sophoradiol (**3**) (6.9 mg) (GC: >98%) which was unequivocally identified with an authenic sample of natural (+)-**3** by rigorous comparison of spectral and chromatographic properties [^1H NMR (400 MHz) (including the complex methylene envelope); HRMS (highly detailed fragmentation pattern); GC coinjection experiments; TLC experiments].

For **3**: colorless microprisms; mp 234–236 °C; R_f 0.25 (3:2 hexanes–ether); FTIR (film) ν 3560–3250, 2965, 2940, 2870, 1480, 1400, 1375, 1175, 1060, 1020 cm^{-1}; ^1H NMR δ 5.25 (t, J = 3.5 Hz, 1 H), 3.44 (br s, 1 H), 3.24–3.20 (m, 1 H), 2.10 (d, J = 13.0 Hz, 1 H), 1.90–1.85 (m, 1 H), 1.84–0.72 (m, 20 H), 1.45 (d, J = 5.0 Hz, 1 H), 1.12 (s, 3 H), 1.04 (s, 3 H), 1.00 (s, 3 H), 0.98 (s, 3 H). 0.95 (s, 3 H). 0.91 (s, 3 H), 0.88 (s, 3 H), 0.79 (s, 3 H); LRMS m/z (rel intensity) 442 (5, M^+, $C_{30}H_{50}O_2$), 424 (3), 406 (2), 234 (100), 219 (32), 216 (34), 190 (20), 176 (22), 161 (24), 135 (23), 132 (30), 109 (31), 95 (32), 83 (34), 73 (64), 69 (43); HRMS calcd for $C_{30}H_{50}O_2$ 442.3811, found 442.3800.

Acetylation of (±)-**3** (Ac_2O–Py (1:1), 23 °C, 48 h) gave sophoradiol diacetate: partial ^1H NMR δ 5.26 (t, J = 3.5 Hz, 1 H), 4.64 (t, J = 3.5 Hz, 1 H), 4.50 (dd, J = 7.9, 4.0 Hz, 1 H), 2.05 (s, 3 H), 2.03 (s, 3 H), 1.14 (s, 3 H), 1.00 (s, 3 H), 0.97 (s, 3 H), 0.97 (s, 3 H), 0.89 (s, 3 H), 0.87 (s, 3 H), 0.86 (s, 3 H), 0.81 (s, 3 H).

For **36**: partial ^1H NMR δ 5.21 (t, J = 3.4 Hz, 1 H), 3.67–3.62 (m, 1 H), 3.58–3.52 (m, 1 H), 1.16 (s, 3 H), 1.00 (s, 3 H). 0.99 (s, 3 H), 0.98 (s, 3 H), 0.94 (s, 3 H), 0.93 (s, 3 H), 0.92 (s, 3 H), 0.79 (s, 3 H).

Olean-12-ene (4). A solution of n-butyllithium (42 μL, 1.6 M in hexanes, 5.0 equiv) was added to a stirred solution of a mixture of **3** and **36** (1:1) (6.0 mg, 0.0135 mmol) in THF (0.6 mL) at 0 °C under Ar, and the mixture was then stirred for 45 min. Carbon disulfide (8.0 μL, 10 equiv) was added, and the mixture was stirred for an additional 4 h at 23 °C. The mixture was cooled to 0 °C, iodomethane (8.5 μL, 10 equiv) was added, and the mixture was stirred at 23 °C for 18 h. The mixture was diluted with hexanes–ether (10 mL, 1:1), washed with saturated aqueous NH_4Cl (1.0 mL), dried, filtered through a pad of sg, and then evaporated to leave the epimeric xanthates.

The foregoing xanthates were dissolved in toluene (2.0 mL) and heated at reflux with tri-n-butyltin hydride (10 μL, 2.75 equiv) and AIBN (ca. 0.5 mg) under Ar for 60 min. The cooled mixture was diluted with hexanes (10 mL), washed with dilute HCl (1.0 mL, 1 M) and saturated aqueous $NaHCO_3$ (1.0 mL), dried, filtered through a pad of sg, and then evaporated. Purification on 10% silver nitrate impregnated sg with hexanes as eluant gave olean-12-ene (**4**) (1.7 mg, 31% over 2 steps) (GC: >98%) which was crystallized with acetonitrile–ether (1:1): colorless crystals; mp 150–153 °C; R_f 0.85 (99:1 hexanes–ether); FTIR (film) ν 2948, 2923, 2869, 2854, 1627, 1463, 1381, 1363 cm^{-1}; ^1H NMR δ 5.19 (t, J = 3.5 Hz, 1 H), 2.01 (dd, J = 13.7, 4.5 Hz, 1 H), 1.94 (dd, J = 12.1, 4.0 Hz, 1 H), 1.89–1.84 (m, 2 H), 1.75 (td, J = 13.9, 4.4 Hz, 1 H), 1.67 (t, J = 13.5 Hz, 1 H), 1.62–0.69 (m, 19 H), 1.14 (s, 3 H), 0.96 (s, 3 H), 0.93 (s, 3 H), 0.87 (s, 9 H), 0.83 (s, 3 H), 0.82 (s, 3 H); LRMS m/z (rel intensity) 410 (6, M^+, $C_{30}H_{50}$), 395 (3), 218 (100), 203 (37), 191 (17), 189 (12), 123 (11), 108 (14), 95 (18), 82 (11), 69 (21); HRMS calcd for $C_{30}H_{50}$ 410.3913, found 410.3916.

Acknowledgments. We thank the National Institutes of Health (DK 03787) and the National Science Foundation for their support of this work. High resolution mass spectra were recorded by the Regional Mass Spectrometric Service at the University of California, San Francisco. The conversion **22** → **23** was initially modeled by Dr. Boris Czeskis in related studies. We are grateful also to Dr. Junei Kinjo for providing an authentic sample of natural sophoradiol.