The Fluorine Atom as a Cation-Stabilizing Auxiliary in Biomimetic Polyene Cyclizations: Total Synthesis of dl-Dammarenediol1

ARTICLE *in* THE JOURNAL OF ORGANIC CHEMISTRY · NOVEMBER 1999

Impact Factor: 4.72 · DOI: 10.1021/jo991196s

9 AUTHORS, INCLUDING:

Arnaud Gautier
Université Blaise Pascal - Clermont-Ferrand II
94 PUBLICATIONS **1,592** CITATIONS

The Fluorine Atom as a Cation-Stabilizing Auxiliary in Biomimetic Polyene Cyclizations: Total Synthesis of *dl*-Dammarenediol[1]

William S. Johnson,† William R. Bartlett,* Boris A. Czeskis, Arnaud Gautier, Cheol H. Lee, Rémy Lemoine, Eric J. Leopold, Gregory R. Luedtke, and Katherine J. Bancroft

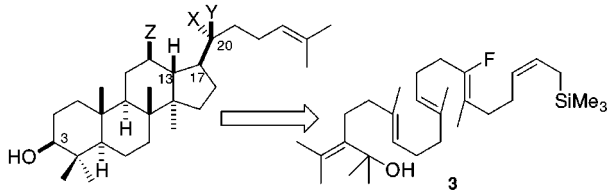
Department of Chemistry, Stanford University, Stanford, California 94305

Received July 27, 1999

Dammarenediols I (**1a**) and II (**1b**) were prepared by an efficient nonenzymatic biomimetic polyene tetracyclization route. The cyclization substrate, pentaenol **3**, contains a tetramethylallylic alcohol initiator, an allyltrimethylsilane terminating group, and a fluorine atom at *pro*-C-13 to serve as a cation-stabilizing (C-S) auxiliary controlling the regiochemistry of the C/D ring juncture. The synthesis of **3** employed lithium−halogen exchange to create alcohols **10** and **19**. The *Z*-fluoroalkene in **3** was introduced stereoselectively via the Trost palladium-catalyzed alkylation of allylic acetate **11** (*Z*/*E*: 4.6/1). The cyclization of **3** was most efficient (62% isolated yield) when it was added as a dilute solution in dichloromethane to trifluoroacetic acid at −45 °C to afford tetracyclic fluoro diene **24** possessing the trans−anti−trans−anti−trans ring stereochemistry of the dammaranes. Replacement of the fluorine atom of **24** with hydrogen with complete retention of configuration was accomplished using the Ohsawa−Oishi reagent (Na/K alloy and crown ether). Wacker oxidation of the resulting hydrocarbon provided ketone **28**, which after ketalization was ozonolyzed with a reductive workup to give the 3*β*-alcohol **30**. Ketal hydrolysis followed by Grignard reaction with isopentenylmagnesium bromide afforded the dammarenediols (1/3, **1a**/**1b**).

Introduction

Dammarenediol II (**1b**), the primary biosynthetic product of the tetracyclization of (*S*)-2,3-oxidosqualene in



1a: X=OH, Y=Me, Z=H
1b: X=Me, Y=OH, Z=H
2: X=Me, Y=OH, Z=OH

plants, possesses modest in vitro antiviral activity against herpes simplex.[2,3] Other important members of the widespread dammarane class of triterpenoids include the ginsenosides[4] (glycosides of protopanaxadiol (**2**)), which are believed to possess the medicinal properties of ginseng. The dammarenediols were first isolated (in 0.05% yield) by Mills in 1956 from dammar resin produced by various *Dipterocarpus* species.[2] Dammarenediols have since been found esterified with fatty acids in the seed oil of *Cacalia atriplicifola L.* and as components of extracts of *Cowania mexicana* (Rosaceae) and other plants.[5] The conversion of dammarane-3α,20(*S*)-diol to protopanaxadiol (**2**) by remote oxidation has also been reported.[6]

The dammarenediols had been synthesized only from other triterpenes[8,9] until a recent report by Corey and

* Address correspondence to W.R.B., Department of Chemistry, Fort Lewis College, Durango, CO 81301. Fax: 970 247 7567. E-mail: bartlett_t@fortlewis.edu.

† Deceased August 19, 1995.

(1) The fluorine atom as a cation-stabilizing auxiliary: (a) Johnson, W. S.; Chenera, B.; Tham, F. S.; Kullnig, R. K. *J. Am. Chem. Soc.* **1993**, *115*, 5, 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. (e) Fish, P. V.; Johnson, W. S. *J. Org. Chem.* **1994**, *59*, 2324−2335. (f) Fish, P. V.; Johnson, W. S.; Jones, G. S.; Tham, F. S.; Kullnig, R. K. *J. Org. Chem.* **1994**, *59*, 6150−6152.

(2) (a) Mills, J. S.; Werner, A. E. A. *J. Chem. Soc.* **1955**, 3132−3140. (b) Mills, J. S. *J. Chem. Soc.* **1956**, 2196−2202. (c) Lehn, J.-M.; Ourisson, G. *Bull. Soc. Chim. Fr.* **1962**, 1137. (d) Biellmann, J.-F. *Bull. Soc. Chim. Fr.* **1967**, 3459.

(3) Poehland, B. L.; Carte, B. K.; Francis, T. A.; Hyland, L. J.; Allaudeen, H. S.; Troupe, N. *J. Nat. Prod.* **1987**, *50*, 706−713.

(4) Tanaka, O.; Kasai, R. Saponins of Ginseng and Related Plants. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Tamm, Ch., Eds.; Springer-Verlag: New York, 1984; Vol. 46, pp 1−76.

(5) (a) Spencer, G. F. *J. Nat. Prod.* **1981**, *44*, 166−168. (b) Biftu, T.; Stevenson, R. *J. Chem. Soc., Perkin Trans. 1* **1978**, 360−363. (c) Caputo, R.; Mangoni, L.; Monaco, P.; Palumbo, G.; Aynehchi, Y.; Bagheri, M. *Phytochemistry* **1978**, *17*, 815−817. (d) Baker, P. M., Barreiro, E. J. L.; Gilbert, B. *Phytochemistry* **1976**, *15*, 785−787. (e) Fattorusso, E.; Santacroce, C.; Xaasan, C. F. *Phytochemistry* **1985**, *24*, 1035−1036. (f) Bianchini, J.-P.; Gaydou, E. M.; Rafaralahitsimba, G.; Waegell, B.; Zahra, J.-P. *Phytochemistry* **1988**, *27*, 2301−2304. (g) Barnes, C. S.; Galbraith, M. N.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1965**, *18*, 1411−1422.

(6) (a) Kasai, R.; Shinzo, K.; Tanaka, O.; Kawai, K. *Chem. Pharm. Bull. (Jpn.)* **1974**, *22*, 1213−1216. (b) Kasai, R.; Shinzo, K.; Tanaka, O. *Chem. Pharm. Bull. (Jpn.)* **1976**, *24*, 400−406.

(7) For reviews, see: (a) Johnson, W. S. Fifty Years of Research: A Tribute To My Coworkers. *Tetrahedron* **1991**, *47* (41), xi−1. (b) Sutherland, J. K. Polyene Cyclizations. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, U.K., 1991; Vol. 3, pp 341−377. (c) 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. (d) Sutherland, J. K. *Chem. Soc. Rev.* **1980**, *9*, 265−280. (e) Johnson, W. S. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 9−17. (f) Johnson, W. S. *Bioorg. Chem.* **1976**, *5*, 51−98. (g) Johnson. W. S. *Acc. Chem. Res.* **1968**, *1*, 1−8.

(8) The synthesis of dammarenediol II from hydroxyhopanone: Fujimoto, H.; Tanaka, O. *Chem. Pharm. Bull. (Jpn.)* **1970**, *18*, 1440−1445.

10.1021/jo991196s CCC: $18.00
Published on Web 11/25/1999

Lin[10] in which they demonstrated that a chiral epoxide prepared from the sesquiterpene farnesol could be cyclized in an enantioselective fashion to produce a tricyclic compound which was transformed to the dammarenediols (**1a**,**b**). Biomimetic nonenzymatic polyene cyclizations have been employed in the syntheses of a wide variety of steroids and terpenes.[7] The discovery[1] that a suitable cation-stabilizing (C-S) auxiliary, such as the fluorine atom, when appended at appropriate sites on the polyene substrate serves the dual purposes of enhancing the yield of the cyclization (particularly important for tetra- and pentacyclizations) while controlling the regiochemistry of the annulation process has greatly expanded the range of natural products that can be constructed efficiently with this synthetic methodology. Furthermore, the fluorine atom can either be eliminated to provide an alkene, as illustrated by the syntheses of the pentacyclic triterpenes β-amyrin[1d] and sophorodiol,[1e] or it can be stereospecifically replaced by a hydrogen atom,[1a] as in this synthesis of the dammarenediols **1a**,**b**.

The principal synthetic challenges in the design of a biomimetic route to the dammaranes are the need to control the stereochemistry at seven incipient chiral centers during the tetracyclization process, while directing the regiochemistry of the C/D ring formation. The lanostane-type A ring of the dammaranes presents a strategic synthetic challenge as well. For the present synthesis of dammarenediols **1a**,**b**, we chose to employ the tetramethylallyl (TMA) initiator,[11] which upon cyclization produces A-ring functionality that can be readily converted to the dammaranes in one efficient operation. Retrosynthetic analysis of the cyclization substrate, pentaenol **3**, suggested the use of the Trost palladium-catalyzed alkylation[12] to produce the *Z*-fluoroalkene functionality, the Johnson−Brady−Julia cyclopropylcarbinol rearrangement[13] to construct the two *E*-trisubstituted alkenes, and a nickel-catalyzed cross-coupling reaction[14] to prepare the *Z*-allylsilane terminating group.[15] We report herein an efficient stereoselective synthesis of the acyclic pentaenol **3** which under acid-catalyzed cyclization conditions affords fluoro diene **24** *bearing the tetracyclic ring system of the dammaranes* with the correct relative stereochemistry at seven chiral centers in 55−62% isolated yields. Compound **24** was converted in six steps to dammarenediols **1a**,**b**.

Results

Synthesis of the Cyclization Substrate 3. The synthesis of pentaenol **3** is summarized in Scheme 1. The stereoselective nickel-catalyzed reaction of ((trimethylsilyl)methyl)magnesium chloride and 2,3-dihydrofuran (**4**), employing the methods of Wenkert[14a] and Kocienski,[14b] afforded alcohol **5**[14c] in 78% yield (>98% *Z*-stereoisomer). Alcohol **5** was smoothly converted to bromide **6** using bromine and triphenylphosphine[16] (95% yield). Standard Grignard conditions using magnesium turnings gave erratic results and disappointingly low yields (8−25% at best) of alcohol **10** from the Grignard reagent **6a** and fluoro enone **9**.

Recourse was therefore taken to the well-studied[17] halogen−lithium exchange procedure. Thus, when a solution of bromide **6** in THF was reacted with *tert*-butyllithium at −78 °C, to form the alkyllithium compound **6b**, followed immediately by the addition of fluoro enone **9** (prepared separately by hydrolysis of ketal **8**), alcohol **10** was formed in 49−52% distilled yield on a scale as large as 200 mmol. Alcohol **10** was then converted by standard methods (88% yield) to the acetate **11** required for the Trost reaction.

The tetrasubstituted *Z*-fluoro alkene was prepared diastereoselectively by the Trost reaction.[12] Thus, the sodium enolate of ethyl 3-(1-methylcycloprop-1-yl)-3-oxopropanoate[13] was combined with allylic acetate **11** in the presence of a palladium(0) catalyst to yield keto ester **12** as an 83/17 (*Z*/*E*) mixture of stereoisomers (79% yield). The purified *Z*-isomer could be readily obtained in 53% isolated yield (>97% *Z*-isomer) by vacuum-flash chromatography.[18] Keto ester **12** was subsequently transformed into cyclopropylcarbinol **14** by alkaline decarboethoxylation followed by borohydride reduction of the intermediate ketone **13** (89% yield overall). Cyclopropylcarbinol **14** was then submitted to the Johnson−Brady−Julia rearrangement protocol[13] providing bromo alkene **15** (>96% *E*-isomer) in 83−87% yield for the two-step process. Occasionally the acid-labile allylsilane moiety was partially protodesilylated during this transformation, requiring extreme care to prevent formation of hydrogen bromide by hydrolysis of the brominating agents throughout the operations.

Cyclopropylcarbinol **19** was prepared by conversion of bromide **15** to the organolithium reagent (*t*-BuLi, THF, −78 °C),[17] followed by addition of 2.2 equiv of aldehyde **18**.[19] This aldehyde showed a marked tendency toward *gem*-diol (hydrate) formation; hence the yield of the reaction giving **19** was found to be critically dependent upon the use of pure **18**, free of its hydrate. Anhydrous **18** could be readily prepared by using the Dess−Martin reagent[20] for the oxidation of 1-methyl-1-cyclopropanemethanol followed by distillation of the crude reaction product from dicyclohexylcarbodiimide (80% yield). Alcohol **19** could be reproducibly secured in 50−55% yield from bromide **15** when aldehyde **18** was prepared in this manner. Hydrocarbon **17** was observed to be the major side product from the halogen−lithium exchange reaction

(9) (a) Ohta, S.; Tori, M.; Tsuyuki, T.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2187−2188. (b) Crabbe, P.; Ourisson, G.; Takahashi, T. *Tetrahedron* **1958**, *3*, 279−302.

(10) Corey, E. J.; Lin, S. *J. Am. Chem. Soc.* **1996**, *118*, 8765−8766.

(11) (a) Johnson, W. S.; Schaaf, T. K. *Chem. Commun.* **1969**, 611−612. (b) Fish, P. V.; Johnson, W. S. *Tetrahedron Lett.* **1994**, *35*, 1469−1472.

(12) (a) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4730−4743 et seq. (b) Fish, P. V.; Reddy, S. P.; Lee, C. H.; Johnson, W. S. *Tetrahedron Lett.* **1992**, *33*, 8001−8004.

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

(14) (a) Wenkert, E.; Michelotti, E. L.; Swindell, C. S.; Tingoli, M. *J. Org. Chem.* **1984**, *49*, 4894−4899. (b) Hayashi, T.; Katsuro, Y.; Kumada, M. *Tetrahedron Lett.* **1980**, *21*, 3915−3918. (c) Kocienski, P. J.; Pritchard, M.; Wadman, S. N.; Whitby, R. J.; Yeates, C. L. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3419−3429. (d) Hiemstra, H.; Sno, M. H. A. M.; Vijn, R. J.; Speckamp, W. N. *J. Org. Chem.* **1985**, *50*, 4014−4020.

(15) (a) Hughes, L. R.; Schmid, R.; Johnson, W. S. *Bioorg. Chem.* **1979**, *8*, 513−518. (b) Schmid, R.; Huesmann, P. L.; Johnson, W. S. *J. Am. Chem. Soc.* **1980**, *102*, 5122−5123.

(16) Wiley, G. A.; Hershkowitz, R. L.; Rein, B. M.; Chung, B. C. *J. Am. Chem. Soc.* **1964**, *86*, 964−965.

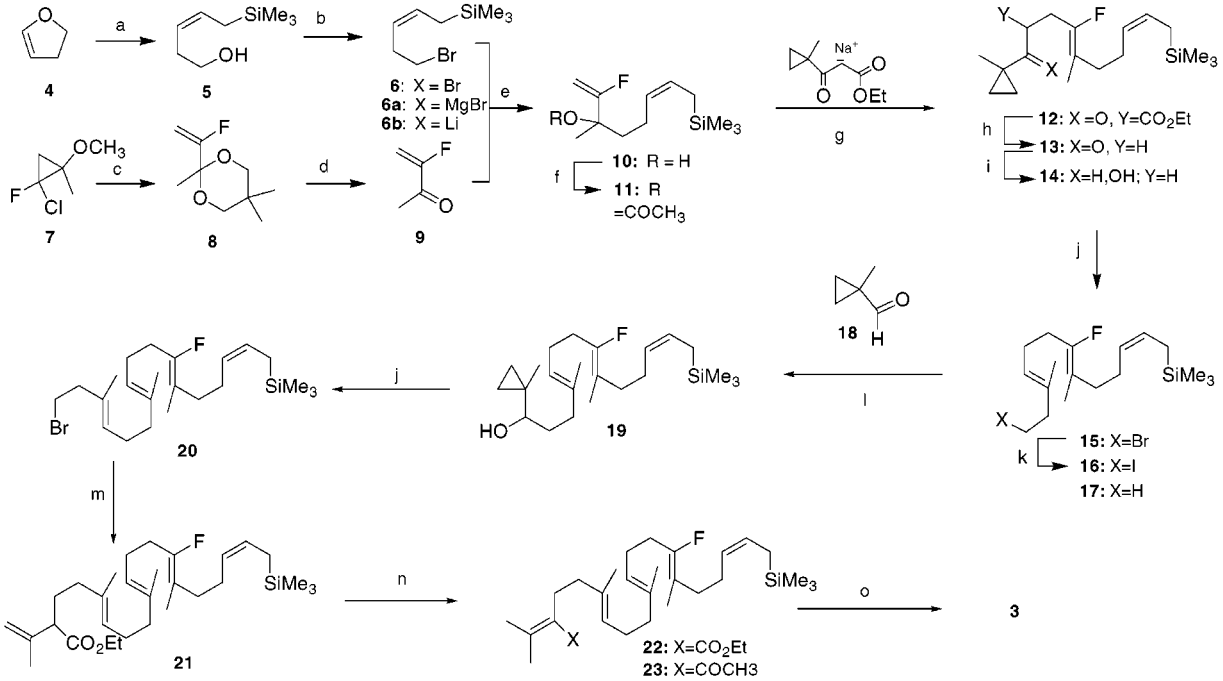
(17) (a) Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.* **1990**, *55*, 5404−5406. (b) Negishi, E.-i.; Swanson, D. R.; Rousset, C. J. *J. Org. Chem.*, **1990**, *55*, 5406−5409. (c) Ashby, E. C.; Pham, T. N. *J. Org. Chem.* **1987**, *52*, 1291−1300. (d) Lansbury, P. T.; Pattison, V. A.; Clement, W. A. Sidler, J. D. *J. Am. Chem. Soc.* **1964**, *86*, 2247−2251.

(18) Harwood: L. M. *Aldrichim. Acta* **1985**, *18*, 25.

(19) Moiseenkov, A. M.; Czeskis, B. A.; Kudryavtseva, G. A.; Nesmeyanova, O. A.; Semenovskii, A. V. *Bull. Acad. Sci. USSR* **1982**, *31*, 1396−1400.

(20) (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287. (b) Ireland, R. E.; Liu, L. B. *J. Org. Chem.* **1993**, *58*, 2899.

Scheme 1[a]



[a](a) $(Ph_3P)_2NiCl_2$, MeMgBr, then Me_3SiCH_2Cl, Mg, 78%; (b) Ph_3PBr_2, 95%; (c) $Me_2C(CH_2OH)_2$, 83%; (d) p-TsOH, H_2O, 73%; (e) *t*-BuLi, 52%; (f) Ac_2O, Py, 88%; (g) $Pd(PPh_3)_4$, 53%; (h) NaOH, 97%; (i) $NaBH_4$, 92%; (j) PBr_3, LiBr, then $ZnBr_2$, 83−87%; (k) NaI, 97%; (l) *t*-BuLi, 70%; (m) $Me_2C{=}CHCO_2Et$, $LiN(i\text{-}Pr)_2$, 85%; (n) *t*-BuOK, 98%; (o) MeLi, (72%).

using bromide **15**. This hydrocarbon appeared to be formed by hydrogen atom abtraction from the solvent in a single-electron transfer (SET) process.[17c] Ashby and Pham have shown that, in contrast to bromides, iodides apparently do not exchange with *tert*-butyllithium by a SET pathway at −78 °C in ether solvents. Accordingly, we investigated the exchange reaction using the iodide **16** in place of the bromide. Bromide **15** was easily converted to iodide **16** using Finkelstein conditions (97% yield). Using the same reaction conditions that had been employed with bromide **15**, alcohol **19** was reproducibly produced in 70% isolated yield from iodide **16**.

The remaining *E*-trisubstituted alkene in the cyclization substrate was constructed by submitting alcohol **19** to the Johnson−Brady−Julia rearrangement conditions,[13] giving bromo tetraene **20** in 85% yield (>97% *E*-isomer). Alkylation of bromide **20** with the lithium enolate of ethyl 3,3-dimethylacrylate afforded β,γ-unsaturated ester **21**, which upon treatment with potassium *tert*-butoxide (down to −78 °C) isomerized to give the α,β-unsaturated ester **22** in 83% overall yield (97/3, **22**/**21**).[11b,21] Finally, treatment of ester **22** with excess methyllithium in ether afforded the cyclization substrate, pentaenol **3**, in 72% yield (90% yield based on recovered ketone **23**, which could be converted to **3** by retreatment with methyllithium).

Cyclization Studies. A detailed study was performed to optimize the cyclization of pentaenol **3**. The effects of variations in solvent, the acid catalyst, concentrations of both the acid and the cyclization substrate, reaction time and temperature, and the order of addition were investigated. During these studies it was observed that cyclization with tin(IV) chloride in dichloromethane (DCM) produced dehydrofluorinated tetracyclic compounds, while no reaction was observed with trifluoroacetic acid (TFA) as the acid catalyst in pentane or tetrahydrofuran at −80 °C. However, TFA in DCM caused rapid cyclization to form a complex mixture of products at −80 °C. Variations in the temperature produced dramatic changes in the proportions of tetracycles (see Table 1).

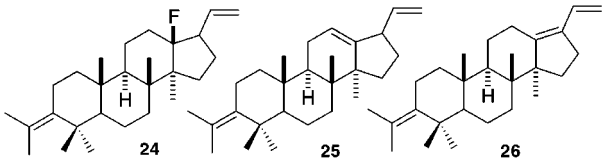


Table 1. Effect of Temperature and Catalyst Amount on the Cyclization of Pentaenol 3

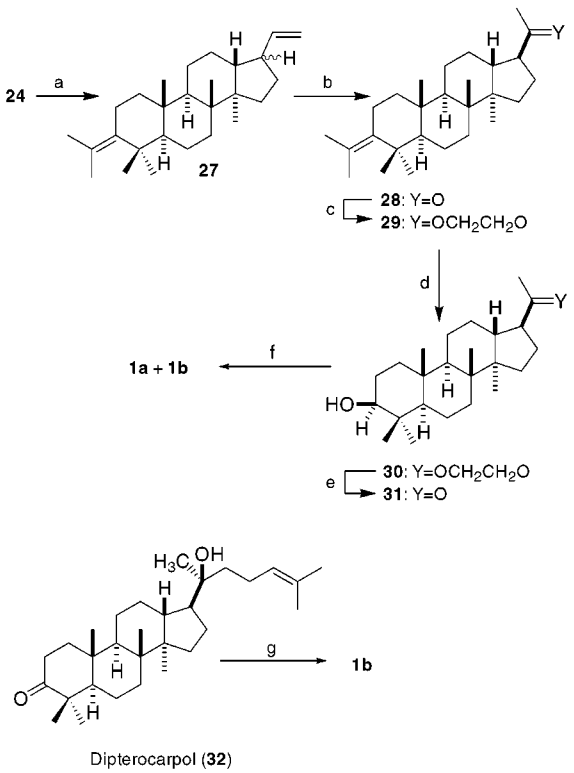
catalyst (in CDM)	temp (°C)	% yield 24	25	26
TFA (1 mol %)	−90	37	14	28
TFA (1 mol %)	−35	40	8	0
TFA (2.5 mol %)	−45	62	0	0
$SnCl_4$ (1 mol %)	−78	0	*a*	*a*

[a] % yield not determined.

Several critical observations were made during the search for optimal cyclization conditions to produce **24**: (1) Dehydrofluorination occurs rapidly in the NMR solvent $CDCl_3$, requiring prior elution of the solvent through neutral alumina to remove acid. (2) Dehydrofluorination occurs during silica gel chromatography requiring the use of neutral alumina adsorbent for purification of the cyclization products. (3) In order to minimize both dehydrofluorination and polymerization, pentaenol **3** must be added dropwise down the side of

(21) (a) Herrman, J. L.; Kieczykowski, G. R.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 2433−2436. (b) Gesson, J.-P.; Jacquesy, J.-C.; Mondon, M. *Tetrahedron Lett.* **1980**, 2509−2512. (c) Danishefsky, S. J.; Uang, B. J.; Quallich, G. *J. Am. Chem. Soc.* **1985**, *107*, 1285−1293. (d) Rathke, M. W.; Sullivan, D. *Tetrahedron Lett.* **1972**, 4249−4252.

Scheme 2[a]



[a] (a) Na/K alloy, 74%; (b) $CuCl_2$, $PdCl_2$, O_2, 85%; (c) $HOCH_2CH_2OH$, H^+, 98%; (d) O_3 then $NaBH_4$, 93%; (e) H^+, H_2O, 96%; (f) *iso*-hexenyl magnesium bromide, 62%; (g) $NaBH_4$, 93%.

the cold flask as a dilute solution (0.0021 M) to a vigorously stirred solution of TFA in DCM at −45 °C. When all of these precautions were taken, fluoro tetracycle **24** could be isolated in 55−62% yields, as an 87:13 (β:α) mixture at C-17.

Conversion of Fluoro Tetracycle 24 to the Dammarenediols. Completion of the synthesis of the dammarenediols required the stereoselective replacement of the fluorine atom in fluorotetracycle **24** by a hydrogen atom. The Ohsawa−Oishi reagent (sodium−potassium alloy and crown ether in toluene)[22] was utilized to convert fluoro tetracycle **24** to the tetracyclic diene **27** in 74% yield (Scheme 2). Diene **27** was then converted to ketone **28** in 85% yield by selective Wacker oxidation of the vinyl side chain,[23] followed by ethylene ketalization under standard conditions to protect the C-20 ketone during ozonolysis. It should be noted that the stereoisomeric mixture at C-17 in the fluoro tetracycle **24** was converted to a single (17-β) isomer during the purification of **28**, presumably by isomerization during silica gel chromatography. Ozonolysis of ketal **29**, followed by a reductive workup (alcoholic sodium borohydride), stereoselectively afforded alcohol **30** (3β-hydroxy) in 93% yield overall from ketone **28**. Subsequent hydrolysis of the ketal gave 3β-hydroxyhexanordammaran-20-one (**31**) in 96% yield which was rigorously identified by comparison of ^{1}H and ^{13}C NMR and mass spectra to reported literature values[24,25] and by GC co-injection of **31** with the authentic natural product.[26]

Incorporation of the side chain of the dammarenediols was readily accomplished using excess isohexenylmagnesium bromide which provided a mixture of *dl*-dammarenediols **1a**,**b** in a 1:3 ratio (62% yield, unoptimized). The structures of these compounds were proven conclusively by comparison of the ^{1}H and ^{13}C NMR and mass spectra with literature values,[3,5,27] as well as by IR, ^{1}H and ^{13}C NMR, mass spectral comparison, and GC co-injection with an authentic sample prepared by sodium borohydride reduction of the natural product dipterocarpol (**32**).[28]

Discussion

The cyclization substrate, pentaenol **3**, was prepared in 14 steps in ca. 6% overall yield from dihydrofuran **4**. Marked improvement to prior art in the synthesis of polyenes such as pentaenol **3** was achieved by utilizing the lithium−halogen exchange process in place of the standard Grignard reaction to prepare the alcohol intermediates **10** and **19**. Indeed, the severalfold improvement in reaction yields, from ca. 20% to 52% for alcohol **10** and up to 70% for alcohol **19**, demonstrates the valuable synthetic utility of the lithium−iodine exchange reaction when the Grignard reaction performs erratically. Presumably, the lithium−iodine exchange reaction is more effective because it can be performed at low temperature, diminishing some of the side reactions during the formation of the highly reactive homoallylic Grignard reagent **6a**, and also because the mechanism for the formation of the organometallic changes from SET to a nonradical process. Another discovery that greatly improved the efficiency of the synthesis was the use of vacuum-assisted flash chromatography[18] which allowed *large-scale* chromatographic purifications to be performed in a fraction of the time required for standard flash chromatography.

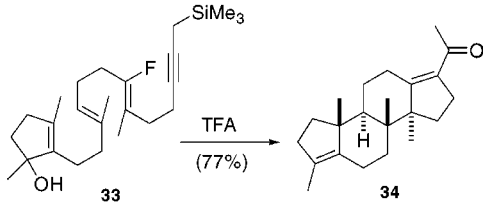
We were gratified by the efficacy of the fluorine atom as a C-S auxiliary. Indeed, the yield for *tetracyclization* (62%) was superior to the TMA initiated *tricyclization* yield (52%) reported earlier.[11] Although chiral induction in the cyclization process is not available with the TMA initiator, the facile conversion (95% yield) of the C-3 isopropylidene group to the 3β-hydroxyl group found in the A ring of the dammaranes makes the TMA initiator synthetically complementary to the epoxide initiator while superior in cyclization efficiency for tetra- and pentacyclizations.[10,29]

Conversion of the fluoro tetracycle **24** to the dammarenediols **1a**,**b** involved only six steps (36% yield overall) and took advantage of the stereospecific replacement of the fluorine atom with hydrogen using the Ohsawa−Oishi reagent, and the selective Wacker oxidation of the

(22) Ohsawa, T.; Takagaki, T.; Haneda, A.; Oishi, T. *Tetrahedron Lett.* **1981**, 2583−2586.
(23) Tsuji, J. *Synthesis* **1984**, (5), 369−384.
(24) Tanaka, R.; Matsuda, M.; Matsunaga, S. *Phytochem*istry **1987**, *26*, 3365−3366.
(25) (+)-3β-Hydroxyhexanordammarane-20-one (**31**) was recently isolated[24] from *Euphorbia supina* and has been also been reported as the product of degradation of the triterpenoids lupeol,[9a] dipterocarpol,[9b] dammaranediol,[2b] and carnaubadiol.[5g]
(26) A sample of natural (+)-**31** for comparison purposes has been kindly provided by Professor S. Matsunaga of the Osaka University of Pharmaceutical Sciences.
(27) (a) Nagai, M.; Tanaka, O.; Shibata, S. *Tetrahedron Lett.* **1966**, 4797−4801. (b) Asakawa, J.; Kasai, R.; Yamasaki, K.; Tanaka, O. *Tetrahedron* **1977**, *33*, 1935−1939. (c) Tori, M.; Matsuda, R.; Sono, M.; Asakawa, Y. *Magn. Reson. Chem.* **1988**, *26*, 581−590.
(28) Warnhoff, E. W.; Halls, C. M. M. *Can. J. Chem.* **1965**, *43*, 3311−3321.
(29) For a review of the epoxide-initiated polyene cyclization, see: Fish, P. V.; Sudhakar, A. R.; Johnson, W. S. *Tetrahedron Lett.* **1993**, *34*, 7849−7852.

vinylic side chain of **27** in the presence of the C-3 isopropylidene functionality.

Our initial studies[30] directed toward the synthesis of the dammarenediols involved the preparation of trienynol **33** possessing the dimethylcyclopentenol (DMC) initiator and the propargylsilane terminator, a functional group combination that was found highly effective in earlier steroid syntheses in these laboratories.[7] Indeed, the cyclization of trienynol **33** in TFA was efficient, producing



dienone **34** in over 77% isolated yield! Although this DMC-initiated tricyclization process affords a tetracycle in higher yield than the TMA-initiated tetracyclization reported herein, conversion of the A ring functionality of **34** to that required by the dammaranes currently involves more synthetic steps and proceeds in far lower overall yield. Furthermore, ancillary studies by C.H.L. in our laboratories found that the reduction of dienone **34** with lithium in ammonia and other reducing agents produced a disappointing 60:40 t:c ring fusion (C/D). Because we wished to improve the stereoselectivity of the dammarenediol synthesis, we shifted our attention to the TMA-initiated cyclization strategy reported herein.[30]

A fitting test of biomimetic polyene cyclization synthetic methodology has been demonstrated by the synthesis of a tetracyclic plant triterpene in synthetically useful yield bearing the dammarane ring structure from an *acyclic* precursor, thus mimicking the oxidosqualene biosynthesis of terpenoids. The success of this methodology owes its creative origins to the pioneering research on the biosynthesis of lanosterol and other triterpenes by Bloch and Woodward[31] together with the elegant insights into the mechanism of this remarkable process by Stork and Eschenmoser and their co-workers.[32,33] Exploratory studies in these laboratories directed toward the enantioselective biomimetic synthesis of the dammarenediols utilizing a chiral cyclization initiator in place of the TMA group in **3** will be reported.

Experimental Section

General Methods. The prefix (±)- has been omitted from the names of the racemic compounds. All reaction procedures were carried out under an atmosphere of nitrogen or argon. Tetrahydrofuran (THF), diethyl ether (ether), hexanes, and pentanes were distilled from sodium−benzophenone ketyl. Dichloromethane (DCM), triethylamine, and 2,6-lutidine were distilled from calcium hydride. Hexamethyl phosphoric triamide (HMPT) was distilled under reduced pressure from sodium metal.

Analysis. Analytical thin-layer chromatography (TLC) was performed on kieselgel 60 F_{254} precoated glass-backed plates using ethyl acetate−hexane solvent mixtures. Spots were visualized with ultraviolet light and then stained with phosphomolybdic acid or *p*-anisaldehyde. Chromatography was performed either by the method of Still[34] using E. Merck silica gel 60 (230−400 mesh) or by vacuum-assisted flash chromatography.[18] For gas chromatography (GC), analyses were with a 50 m SE-54 capillary column and hydrogen carrier gas within temperature ranges of 30−300 °C. Infrared spectra were as thin films on NaCl windows or as KBr pellets. Proton NMR spectra were obtained at 400 MHz as dilute solutions in deuteriochloroform. Carbon-13 NMR were recorded as dilute solutions in deuteriochloroform in the broad band decoupled at 100.6 MHz. Chemical shifts (δ) are reported relative to internal residual chloroform. HRMS were recorded in electron-impact mode by the Regional Mass Spectrometry Facility at the University of California, San Francisco, CA. Combustion analyses were performed by Desert Analytics in Tucson, AZ. Melting points were taken with a Kofler hot-stage microscope. Yields refer to chromatographically purified compounds which may be contaminated with ca. 1−3% of stereoisomeric impurities which are often removed by further purification at a later stage in the synthesis.

5-(Trimethylsilyl)pent-3(*Z*)-en-1-ol (5). The procedure was adapted from the method of Wenkert.[14] A solution of (chloromethyl)trimethylsilane (51.6 g, 420 mmol) in ether (50 mL) was added to Mg turnings (11.4 g, 470 mmol) in ether (250 mL) at a rate which maintained a gentle reflux. The reaction mixture was stirred for 45 min at 24 °C while the nickel catalyst was being prepared. In a separate flask, a dark green solution of bis(triphenylphosphine)nickel dichloride (25.0 g, 38.0 mmol) in dry benzene (300 mL) was prepared. An ethereal solution of methylmagnesium bromide (3 M, 24.0 mL, 72 mmol) was added dropwise to the rapidly stirred suspension at 25 °C, causing it to turn black. After 30 min, the gray suspension of ((trimethylsilyl)methyl)magnesium chloride, prepared earlier, was added via cannula to the black nickel suspension and then the ether was removed under reduced pressure leaving a viscous black residue. Benzene (500 mL) was added, followed by dropwise addition of a solution of 2,3-dihydrofuran (**4**) (28.6 g, 409 mmol) in benzene (50 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 15 h and then slowly poured into a well-stirred solution of saturated NH_4Cl (750 mL). The blue aqueous layer was saturated with sodium chloride and extracted with ether. The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered, and fractionally distilled through a bubble column. Short-path distillation of the residue gave the known alcohol **5**[17b,c] (64.6 g, 78% yield) as a colorless oil: bp 85−92 °C (8 mmHg); 99% pure by GC; ^{1}H NMR δ 5.59 (m, 1H), 5.32−5.22 (m, 1H), 3.64 (t, J = 7.0 Hz, 2H), 2.29 (q, J = 7.0 Hz, 2H), 1.52 (d, J = 8.7 Hz, 2H), 0.00 (s, 9H). Anal. Calcd for $C_8H_{18}OSi$: C, 60.70; H, 11.46. Found: C, 60.71; H, 11.64.

1-Bromo-5-(trimethylsilyl)pent-3(*Z*)-ene (6). To a solution of triphenylphosphine (62.1 g, 237 mmol) in DCM (300 mL) at −10 °C was added bromine (12.2 mL, 237 mmol) dropwise. After 5 min a solution of alcohol **5** (28.8 g, 182 mmol) and pyridine (22.5 mL, 278 mmol) in DCM (30 mL) was added to the white suspension of triphenylphosphine dibromide complex over 10 min. The reaction mixture was stirred for 2 h at 5 °C, diluted with ether in hexane (1:1, 300 mL), and filtered. The filtrate was treated to the following sequence twice: concentration under reduced pressure, dilution with hexane to produce a precipitate, and filtration. A final filtration through silica gel with hexane eluant, followed by concentration and short-path distillation, gave bromide **6** (38.2 g, 95% yield) as a colorless oil: bp 63−65 °C (1.0 mmHg); 97% pure by GC; IR (film) 3012, 1644, 1248, 854 cm^{-1}; ^{1}H NMR δ 5.57

(30) Alternative synthesis routes to the dammarenediol nucleus were explored by C.H.L. and D. Rajapaksa.

(31) Woodward, R. B.; Bloch, K. *J. Am. Chem. Soc.* **1953**, *75*, 2023−2024 et seq. (Bloch).

(32) (a) Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5068−5077. (b) Stadler, P. A.; Eschenmoser, A.; Schinz, H.; Stork, G. *Helv. Chim. Acta* **1957**, *40*, 2191−2198. (c) Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* **1955**, *38*, 1890−1904.

(33) Johnson, William S. *A Fifty-Year Love Affair with Organic Chemistry*; In PROFILES, PATHWAYS, AND DREAMS: Autobiographies of Eminent Chemists; Seeman, J. I., Series Editor; American Chemical Society: Washington, DC, 1998.

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

(dt, J = 10.0, 8.0 Hz, 1H), 5.30−5.22 (m, 1H), 3.36 (t, J = 7.3 Hz, 2H), 2.57 (q, J = 8.6 Hz, 2H), 1.49 (d, J = 8.0 Hz, 2 H), 0.01 (s, 9H); ^{13}C NMR δ 128.8, 123.4, 32.6, 30.7, 18.9, −1.8. Anal. Calcd for $C_8H_{17}BrSi$: C, 43.44; H, 7.75. Found: C, 43.78; H, 7.62.

3-Fluoro-2,2-((2′,2′-dimethylpropane-1′,3′-diyl)dioxy)-3-butene (8). The method of Bessiere was adapted.[35] A solution of the known fluorocyclopropane **7**[35] (50.0 g, 361 mmol) and 2,2-dimethyl-1,3-propanediol (52.5 g, 505 mmol) with 0.1 g of hydroquinone in pyridine (120 mL) was heated to 125 °C and stirred vigorously for 5 h. The reaction mixture was cooled to 0 °C, filtered, diluted with pentane (100 mL), washed with brine, dried ($MgSO_4$), filtered, and concentrated to give an oil. Fractional distillation (Vigreaux) gave ketal **8** (52 g, 83% yield) as a colorless oil: bp 47−52 °C (10 mmHg); 100% pure by GC; IR (film) 1680, 1090, 1050, 1020, 940, 890 cm^{-1}; ^{1}H NMR δ 4.93 (dd, J = 16, 3.0 Hz, 1H), 4.75 (dd, J = 49, 3.0 Hz, 1H), 3.60 (d, J = 11 Hz, 2H), 3.39 (d, J = 11 Hz, 2H), 1.52 (s, 3H), 1.19 (s, 3H), 0.73 (s, 3H); ^{13}C δ 162.8, 160.1, 96.5, 96.2, 93.4, 93.3, 72.0, 29.5, 27.3, 22.7, 21.9. Anal. Calcd for $C_9H_{15}O_2F$: C, 62.05; H, 8.68. Found: C, 61.74; H, 8.97.

2-Fluoro-3-methyl-8-(trimethylsilyl)octa-1,6(*Z*)-dien-3-ol (10). A mixture of fluoro ketal **8** (24.3 g, 122 mmol), *p*-toluenesulfonic acid (1.0 g), hydroquinone (0.02 g), and water (2.2 g) was heated to 95 °C with a stream of nitrogen carrying the distillate through a short-path distilling apparatus into a cooled receiver (−78 °C) containing hydroquinone (0.02 g). Whenever distillation ceased, additional water (9 mL) was added in portions. The distillate, a white solid consisting of ketone **9** and water, was warmed to 5 °C and then recooled to −78 °C; the lower organic layer, containing **9**, was removed by syringe (9.0 g, 73% yield) and then dried by adding ether (5 mL) and $MgSO_4$. The ethereal solution of **9** was stored at −78 °C until needed.

To a cold (−78 °C) solution of 2,2′-dipyridyl (0.005 g) and anhydrous magnesium bromide etherate (1.0 g) in anhydrous THF (600 mL) was added *tert*-butyllithium (80 mL, 1.7 M in hexane, 136 mmol) at a rate which maintained the temperature below −70 °C. To the resulting deep red solution was added bromide **6** (21.2 g, 95.5 mmol) over a 17 min period, while keeping the reaction temperature below −70 °C. The solution was stirred at −75 °C for 8 min, and then the ethereal solution of fluoro enone **9** (see above) was added over a 12 min period at −70 °C, forming a pale yellow solution which was stirred at −78 °C for 8 min before adding saturated aqueous NH_4Cl (60 mL) and allowing the reaction mixture to warm to 25 °C. Ether (100 mL) was added, and the aqueous layer was removed and reextracted with ether. The combined organic layer was concentrated to give a suspension which was extracted with ether, washed with saturated brine, dried ($MgSO_4$), filtered, and concentrated to give a pale yellow oil (20.8 g). Short-path distillation gave alcohol **10** (11.4 g, 52% yield) as a colorless oil: bp 85−90 °C (1.0 mmHg); 90% pure by GC; IR (film) 3450, 3007, 1673, 1249, 1151, 1107, 855 cm^{-1}; ^{1}H NMR δ 5.44 (m, 1H), 5.32−5.23 (m, 1H), 4.69 (m, 1H), 4.60 (dd, J = 29.1, 3.1 Hz, 1H), 2.08 (m, 2H), 1.80−1.60 (m, 2H), 1.48 (m, 2H), 1.39 (d, J = 1.1 Hz, 3H), 0.00 (s, 9H); ^{13}C NMR δ 170.6, 168.0, 166.5, 126.7, 126.5, 88.9, 88.7, 73.2, 72.9, 39.1, 26.0, 21.7, 18.5, −1.8. Anal. Calcd for $C_{12}H_{23}FOSi$: C, 62.56; H, 10.06. Found: C, 62.38; H, 10.22.

2-Fluoro-3-methyl-8-(trimethylsilyl)octa-1,6(*Z*)-dien-3-yl Acetate (11). To a solution of alcohol **10** (16.1 g, 69.9 mmol) in THF (130 mL) was added pyridine (31.6 g, 400 mmol), acetic anhydride (15.3 g, 150 mmol), and DMAP (1.83 g, 15 mmol), and the solution was stirred at 60 °C for 53 h. To the dark orange mixture was added methanol (2.4 g, 75 mmol) at 0 °C, and after the exothermic reaction ceased, the mixture was concentrated, diluted with ether in pentane (200 mL, 1:1), washed with saturated brine, 10% aqueous sodium bisulfate, 10% HCl, and saturated $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated to give a yellow oil. Short-path distillation gave acetate **11** (16.6 g, 88% yield) as a colorless oil: bp 68−72 °C (0.1 mmHg); 96% pure by GC; IR (film) 3010, 1748, 1673, 1248, 935, 856 cm^{-1}; ^{1}H NMR δ 5.41 (dt, J = 10.6, 9.0 Hz, 1H), 5.27−5.18 (m, 1H), 4.73 (dd, J = 18.7, 3.5 Hz, 1H), 4.55 (dd, J = 49.9, 3.5 Hz, 1H), 2.04 (s, 3H), 1.99 (m, 2H), 1.93−1.87 (m, 2H), 1.62 (d, J = 1.2 Hz, 3H), 1.45 (d, J = 8.6 Hz, 2H), 0.00 (s, 9H); ^{13}C NMR δ 169.3, 166.5, 163.9, 126.4, 125.9, 90.4, 90.2, 80.5, 80.2, 37.4, 22.1, 21.9, 18.5, 1.7. Anal. Calcd for $C_{14}H_{25}FO_2Si$: C, 61.72; H, 9.25. Found: C, 61.94; H, 9.36.

1-(1-Methylcylopropyl)-2-(ethoxycarbonyl)-4-fluoro-5-methyl-10-(trimethylsilyl)deca-4(*Z*),8(*Z*)-dien-1-one (12). A solution of allylic acetate **11** (16.6 g, 61.0 mmol), triphenylphosphine (7.9 g, 30 mmol), and tetrakis(triphenylphosphine)palladium(0) (7.1 g, 6.1 mmol) in THF (100 mL) was stirred at 25 °C. In a separate flask the known ethyl 3-(1-methylcycloprop-1-yl)-3-oxopropanoate (20.7 g, 122 mmol)[13] was added to a suspension of sodium hydride (5.0 g, 60% dispersion in mineral oil, 125 mmol, washed with pentane) in THF (100 mL) at 0 °C. The resulting mixture was stirred for 40 min at 25 °C giving a clear solution of the sodio derivative which was then transferred by cannula to the allylic acetate mixture described above. The reaction mixture was stirred for 44 h at 70 °C with an additional portion of the palladium catalyst (3.2 g, 2.8 mmol) added after 16 h. The mixture was then cooled to 25 °C, quenched with saturated NH_4Cl (75 mL), and concentrated to give a dark oil. The oil was diluted with ether (150 mL), washed with saturated brine (50 mL), dried, and concentrated to give 43.3 g of an orange oil. Short-path distillation yielded 11.3 g of unreacted keto ester and 33 g of a viscous gum. The gum was dissolved in pentane (600 mL) and stirred vigorously with a solution of 3% hydrogen peroxide (300 mL) and 0.2 g potassium iodide for 2 h, producing a white precipitate of triphenylphosphine oxide. The mixture was filtered, and the organic layer was washed with 5% aqueous sodium thiosulfate, dried ($MgSO_4$), vacuum filtered through a column of silica gel (80 g), and concentrated to give a pale yellow oil (18.5 g, 79% yield) which consisted of a mixture of keto ester **12** diastereomers (80/20, *Z*/*E*). Vacuum flash chromatography[18] of the oil (0−10% ether in hexane) on silica gel gave purified (*Z*)-keto ester **12** (12.5 g, 53% yield) as a colorless oil: 97% pure by GC; IR (film) 1747, 1694, 1249, 856 cm^{-1}; ^{1}H NMR δ 5.39 (dt, J = 10.6, 8.8 Hz, 1H), 5.24−5.13 (m, 1H), 4.15 (q, J = 7.1 Hz, 2H), 3.82 (dd, J = 8.3, 6.3, 8.8 Hz, 2H), 1.40 (m, 1H), 1.36 (s, 3H), 1.32 (m, 1H), 1.21 (t, J = 7.1 Hz, 3H), 0.80 (m, 2H), 0.00 (s, 9H); ^{13}C NMR δ 205.8, 168.8, 151.9, 149.5, 126.5, 125.8, 114.4, 114.2, 61.4, 48.5, 29.7, 29.6, 28.6, 28.3, 27.4, 25.0, 19.5, 18.4, 17.7, 17.6, 15.5, 15.4, 14.0, −1.8. Anal. Calcd for $C_{21}H_{35}FO_3Si$: C, 65.93; H 9.22. Found: C, 66.21; H, 9.41.

1-(1-Methylcylopropyl)-4-fluoro-5-methyl-10-(trimethylsilyl)deca-4(*Z*),8(*Z*)-dien-1-one (13). A suspension of keto ester **12** (12.3 g, 32.2 mmol), methanol (300 mL), THF (300 mL), and 5% NaOH (90 mL) was thoroughly degassed and stirred at 60 °C under an argon atmosphere for 50 min. Saturated NH_4Cl was added (90 mL), and the mixture was concentrated to give an oil which was extracted with ether. The combined ether layers were washed with saturated brine, dried ($MgSO_4$), filtered, and concentrated to give ketone **13** (9.7 g, 97% yield) as a colorless oil: 98% pure by GC; IR (film) 3001, 1692, 1248, 855 cm^{-1}; ^{1}H NMR δ 5.40 (dt, J = 10.6, 8.8 Hz, 1H), 5.23−5.18 (m, 1H), 2.57−2.40 (m, 4H), 2.04 (m, 4H), 1.59 (d, J = 2.6 Hz, 3H), 1.46 (d, = 9.0 Hz, 2H), 1.35 (s, 3H), 1.23 (dt, J = 6.8, 4.0 Hz, 2H), 0.72 (dt, J = 6.8, 4.0 Hz, 2H), 0.00 (s, 9H); ^{13}C NMR δ 210.6, 154.5, 152.1, 126.8, 125.7, 112.0, 111.8, 34.6, 29.6, 29.5, 26.6, 25.1, 23.4, 23.1, 18.5, 18.0, 15.5, 15.4, −1.8. Anal. Calcd for $C_{18}H_{31}FOSi$: C, 69.62; H, 10.06. Found: C, 69.51; H, 10.08.

1-(1-Methylcylopropyl)-4-fluoro-5-methyl-10-(trimethylsilyl)deca-4(*Z*),8(*Z*)-dien-1-ol (14). To a solution of ketone **13** (9.7 g, 30.9 mmol) in methanol (125 mL) was slowly added sodium borohydride (3.04 g, 80 mmol) at 0 °C. The reaction was stirred for 15 min, and then saturated NH_4Cl (25 mL) was added, followed by saturated brine (25 mL). The mixture was extracted with ether, and the combined organic layer was dried ($MgSO_4$), filtered, and concentrating giving a colorless oil.

(35) Bessiere, Y.; Savary, D. N.-H.; Schlosser, M. *Helv. Chim. Acta* **1977**, *60*, 1739−1746.

Vacuum flash chromatography[18] on silica gel (80 g, 0−10% ethyl acetate in hexane) gave alcohol **14** (8.84 g, 92% yield) as a colorless oil: 99% pure by GC; IR (film) 3395, 3073, 1708, 1248, 1047, 855 cm^{-1}; ^1H NMR δ 5.36 (dt, J = 10.0, 8.6 Hz, 1H), 5.28−5.18 (m, 1H), 2.83−2.78 (m, 1H), 2.42−2.13 (m, 2H), 2.08−2.00 (m, 4H), 1.74−1.66 (m, 2H), 1.56 (d, J = 2.7 Hz, 3H), 1.43 (d, J = 8.5 Hz, 2H), 1.01 (s, 3H), 0.42−0.27 (m, 4H), 0.00 (s, 9H); ^{13}C NMR δ 155.4, 153.0, 126.8, 125.7, 111.5, 111.4, 78.0, 30.9, 29.6, 29.5, 25.6, 25.3, 25.2, 22.5, 18.5, 17.2, 15.5, 15.5, 12.1, 11.1, −1.8. Anal. Calcd for $C_{18}H_{31}FOSi$: C, 69.17; H, 10.64. Found: C, 69.34; H, 10.84.

1-Bromo-3,8-dimethyl-7-fluoro-13-(trimethylsilyl)trideca-3(*E*),7(*Z*),11(*Z*)-triene (15). The following procedure was adapted from the method of Brady, Ilton, and Johnson.[13] Note that the presence of the acid-labile allyltrimethylsilyl group in alcohol **14** requires several modifications. The reaction afforded 80−90% yields reproducibly on a 1−2 g scale but became capricious on a larger scale, with partial loss of the TMS group occurring during the workup procedure at times. A typical procedure is described below.

To a white suspension of alcohol **14** (1.0 g, 3.2 mmol), lithium bromide (0.95 g, 16 mmol, dried at 150 °C under vacuum), and anhydrous 2,6-lutidine (0.56 mL, 4.8 mmol) in anhydrous ether (70 mL) at −78 °C was added phosphorus tribromide (0.27 mL, 3.74 mmol) dropwise. The reaction mixture was allowed to warm slowly to 25 °C and stirred for 10 h before cooling to −10 °C. Lutidine (1.6 g, 15 mmol) was added dropwise followed by water (0.22 mL, 12 mmol), and the reaction mixture was stirred for 10 min before the addition of pentane (60 mL) and saturated $NaHCO_3$ (10 mL). The organic layer was extracted with 5% HCl, saturated $NaHCO_3$, and saturated brine, dried ($MgSO_4$), filtered through silica gel (25 g, pentane eluant), and concentrated to give a colorless oil.

The oil was added to a solution of anhydrous zinc bromide (2.16 g, 9.6 mmol, finely ground and dried at 150 °C under vacuum for 3 h) in anhydrous ether (40 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h and then was allowed to warm to 0 °C and stored at that temperature for 14 h. Water (0.06 g) was added, the mixture was stirred for 45 min, and then pyridine (1.5 g, 19 mmol) was added. The solution was stirred vigorously for 15 min, and then hexane (50 mL) and saturated $NaHCO_3$ (10 mL) were added. The organic layer was extracted with 5% HCl, brine, saturated $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and concentrated to give bromo triene **15** (1.04 g, 87% yield from alcohol **14**) as a colorless oil: unstable on GC (89% one peak); IR (film) 1707, 1248, 1152, 855 cm^{-1}; ^1H NMR δ 5.40 (dt, J = 10.0, 8.6 Hz, 1H), 5.28−5.20 (m, 2H), 3.40 (t, J = 7.4 Hz, 2H), 2.51 (t, J = 7.4 Hz, 2H), 2.32−2.14 (m, 4H), 2.06 (m, 4H), 1.61 (s, 3H), 1.55 (d, J = 2.7 Hz, 3H), 1.45 (d, J = 8.5 Hz, 2H), 0.00 (s, 9H); ^{13}C NMR δ 155.2, 152.8, 132.9, 126.8, 126.3, 125.7, 111.6, 111.4, 42.9, 31.4, 29.6, 29.5, 28.6, 28.3, 25.2, 18.5, 15.6, −1.8. Anal. Calcd for $C_{18}H_{32}BrFSi$: C, 57.58; H, 8.59. Found: C, 57.62; H, 8.80.

1-Iodo-3,8-dimethyl-7-fluoro-13-(trimethylsilyl)trideca-3(*E*),7(*Z*),11(*Z*)-triene (16). To a solution of anhydrous sodium iodide (2.25 g, 15.0 mmol) in acetone (30 mL) was added bromide **15** (1.1 g, 2.92 mmol) at 25 °C. The reaction mixture was thoroughly degassed and stirred at 55 °C for 4 h. The reaction mixture was then cooled to 24 °C, and hexane (80 mL) was added creating a yellow precipitate. The mixture was filtered, extracted with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give an oil. Vacuum filtration through silica gel (25 g, hexane) followed by concentration gave iodo triene **16** (1.22 g, 97% yield) as a colorless oil: 97% pure on GC; IR (film) 1700, 1243, 1150, 850 cm^{-1}; ^1H NMR δ 5.40 (dt, J = 9.2, 8.8 Hz, 1H), 5.26−5.16 (m, 2H), 3.18 (t, J = 7.4 Hz, 2H), 2.51 (t, J = 7.4 Hz, 2H), 2.30−2.14 (m, 4H), 2.06 (m, 4 H), 1.60 (s, 3H), 1.55 (d, J = 2.7 Hz, 3H), 1.45 (d, J = 8.9 Hz, 2H), −0.02 (s, 9H); HRMS calcd for $C_{18}H_{32}FISi$ 422.1302, found 422.1307. Anal. Calcd for $C_{18}H_{32}FISi$: C, 51.18; H, 7.63. Found: C, 51.87; H, 7.65.

1-(1-Methylcylopropyl)-4,9-dimethyl-8-fluoro-14-(trimethylsilyl)tetradeca-4(*E*),8(*Z*),12(*Z*)-trien-1-ol (19). A solution of 2,2′-dipyridyl (0.005 g) in anhydrous THF (50 mL) was cooled to −78 °C, and *tert*-butyllithium (4.3 mL, 1.7 M in hexane, 7.3 mmol) was added at a rate to maintain the temperature below −70 °C. To the resulting deep red solution was added iodide **16** (1.40 g, 3.32 mmol) in 6 mL of THF over an 8 min period, while keeping the reaction temperature below −70 °C. The solution was stirred at −75 °C for 80 min while the exchange reaction was being monitored by quenching aliquots with water and detecting the presence of unreacted iodide **16** by GC analysis. Then a solution of 1-methylcylopropanecarboxaldehyde[19] (0.36 g, 4.4 mmol, prepared by oxidation of the alcohol with Dess−Martin reagent in ether followed by distillation from excess DCC to remove water of hydration, 80% yield, bp 56−58 °C, 125 mmHg) in 4 mL of THF was added dropwise slowly at −70 °C. The pale yellow reaction mixture was stirred at −78 °C for 15 min, then NH_4Cl (2 mL) was added, and the mixture was allowed to warm to 25 °C and concentrated to give an oily suspension. An ether and hexane solution (100 mL, 1:1) was added, and the organic layer was separated and extracted with 5% sodium thiosulfate and saturated brine, dried ($MgSO_4$), filtered, and concentrated to give a pale yellow oil. Vacuum flash chromatography of the residue on silica gel (0−10% ether in hexane) gave alcohol **19** (0.93 g, 70% yield) as a colorless oil: 97% pure by GC; IR (film) 3350, 1665, 1215, 1120, 820 cm^{-1}; ^1H NMR δ 5.40 (dt, J = 10.0, 8.6 Hz, 1H), 5.28−5.20 (m, 1H), 5.18 (br, t, J = 6.5 Hz, 1H), 2.80 (t, J = 6.1 Hz, 1H), 2.30−1.98 (m, 10H), 1.64 (m, 2H), 1.62 (s, 3H), 1.57 (d, J = 2.5 Hz, 3H), 1.47 (d, J = 8.6 Hz, 2H), 1.03 (s, 3H), 0.40−0.28 (m, 4H), 0.00 (s, 9H); ^{13}C NMR δ 155.5, 153.1, 136.1, 126.9, 125.7, 123.3, 111.4, 111.3, 78.8, 36.4, 32.4, 29.7, 29.6, 29.0, 28.7, 25.3, 20.6, 18.5, 17.2, 16.0, 11.9, 11.3, −1.8. Anal. Calcd for $C_{23}H_{41}FOSi$: C, 72.57; H, 10.86. Found: C, 72.79; H, 10.68.

1-Bromo-11-fluoro-3,7,12-trimethyl-17-(trimethylsilyl)-heptadeca-3(*E*),7(*E*),11(*Z*),15(*Z*)-tetraene (20). To a suspension of alcohol **19** (0.458 g, 1.46 mmol), lithium bromide (0.60 g, 0.69 mmol), and 2,6-lutidine (0.28 mL, 2.40 mmol) in ether (30 mL) at −78 °C was added phosphorus tribromide (0.14 mL, 1.93 mmol) dropwise. The reaction mixture was allowed to reach 25 °C, stirred for 16 h, and then cooled to −10 °C. 2,6-Lutidine (1 mL) was added dropwise followed by water (0.13 g), and the mixture was stirred for 15 min. Hexane (60 mL) was added, followed by saturated $NaHCO_3$ (15 mL), and the organic layer was separated, washed with brine, dried ($MgSO_4$), filtered through silica gel, and concentrated at reduced pressure to give a colorless oil (0.53 g, 96% yield).

A solution of the oil in ether (2.0 mL) was added dropwise to a suspension of anhydrous zinc bromide (1.56 g, 6.93 mmol) in ether (35 mL) at −78 °C. The reaction mixture was allowed to warm to 0 °C, stirred for 16 h, and then cooled to −10 °C, and pyridine (1.0 mL) was added. The solution was stirred vigorously for 15 min, and then hexane (50 mL) and saturated $NaHCO_3$ (10 mL) were added to the vigorously stirred mixture. The organic layer was extracted with 5% HCl, brine, saturated $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give bromo tetraene **20** as a colorless oil (0.455 g, 83% yield from alcohol **19**): unstable on GC (83% one peak); IR (film) 1240, 1150, 850 cm^{-1}; ^1H NMR δ 5.40 (dt, J = 10.0, 8.6 Hz, 1H), 5.28−5.20 (m, 1H), 5.21 (t, J = 6.8 Hz, 1H), 5.14 (t, J = 6.5 Hz, 1H), 3.42 (t, J = 7.5 Hz, 2H), 2.52 (t, J = 7.5 Hz, 2H), 2.30−2.13 (m, 4H), 2.13−1.96 (m, 8H), 1.62 (s, 3H), 1.61 (s, 3H), 1.57 (d, J = 2.5 Hz, 3H), 1.47 (d, J = 8.5 Hz, 2H), 0.00 (s, 9H); ^{13}C NMR δ 155.9, 153.1, 135.7, 131.9, 127.6, 126.9, 125.7, 123.3, 111.3, 111.2, 43.0, 39.4, 31.8, 29.7, 29.6, 29.0, 28.7, 26.6, 25.3, 18.5, 15.7, −1.8. Anal. Calcd for $C_{23}H_{40}BrFSi$: C, 62.28; H, 9.09. Found: C, 62.49; H, 9.26.

Ethyl 13-Fluoro-2-isopropenyl-5,9,14-trimethyl-19-(trimethylsilyl)nonadeca-5(*E*),9(*E*),13(*Z*),17(*Z*)-tetraenoate (21). To a solution of diisopropylamine (0.75 g, 7.42 mmol) in THF (10 mL) was added *n*-butyllithium (4.5 mL, 1.6 M in hexane, 7.2 mmol) dropwise at −40 °C. After 15 min, the resulting solution of lithium diisopropylamide was cooled to −78 °C and HMPT (1.9 mL, 10.92 mmol) was added dropwise. The coral colored mixture was stirred for 30 min at −78 °C, and then ethyl 3,3-dimethylacrylate (0.93 g, 7.26 mmol) was

added dropwise. The solution was stirred for 35 min, and then a solution of bromide **20** (1.2 g, 2.7 mmol) in THF (4 mL) was added to the reaction mixture which was stirred for 20 min at −78 °C and then warmed over 1 h to 0 °C. The mixture was stirred at 0 °C for an additional 1.5 h, treated with saturated NH_4Cl, and extracted with hexane. The extract was washed with brine (diluted with water, 1:1) and saturated brine, dried ($MgSO_4$), and concentrated. Flash chromatography of the residue on silica gel (5−15% ether in hexane) gave β,γ-ester **21** (1.13 g, 85% yield) as a colorless oil: 90% pure by GC; IR (film) 1715, 1630, 1235, 1140, 840 cm^{-1}; ^1H NMR δ 5.40 (dt, J = 10.8, 8.6 Hz, 1H), 5.28−5.20 (m, 1H), 5.12 (t, J = 6.5 Hz, 1H), 5.11 (t, J = 6.5 Hz, 1H), 4.88 (br, s, 1H), 4.87 (s, 1H), 4.14 (q, J = 7.1 Hz, 2H), 2.98 (t, J = 7.0 Hz, 1H), 2.28−2.13 (m, 4H), 2.13−2.02 (m, 6H), 2.02−1.85 (m, 6H), 1.74 (s, 3H), 1.61 (s, 3H), 1.59 (s, 3H), 1.57 (d, J = 2.0 Hz, 3H), 1.47 (d, J = 8.6 Hz, 2H), 1.25 (t, J = 7.1 Hz, 3H), 0.00 (s, 9H); ^{13}C NMR δ 173.7, 155.9, 153.1, 142.6, 136.0, 134.1, 126.9, 125.7, 125.0, 123.0, 113.7, 111.3, 111.2, 60.4, 52.5, 39.7, 37.3, 29.7, 29.6, 29.0, 28.7, 28.3, 26.6, 25.2, 20.2, 18.5, 16.0, 15.9, 15.6, 14.2, −1.8; MS m/z (rel intensity) 490 (25), 213 (37), 135 (89), 81 (100), 73 (97); HRMS calcd for $C_{30}H_{51}FO_2Si$ 490.3644, found 490.3660. Anal. Calcd for $C_{30}H_{51}FO_2Si$: C, 73.41; H, 10.47. Found: C, 73.76; H, 10.32.

Ethyl 13-Fluoro-2-isopropyliden-5,9,14-trimethyl-19-(trimethylsilyl)nonadeca-5(*E*),9(*E*),13(*Z*),17(*Z*)-tetraenoate (22). To a solution of potassium *tert*-butoxide (0.22 g, 1.8 mmol) in THF (15 mL), from which oxygen had been rigorously excluded and replaced with argon at 0 °C, was added a solution of β,γ-ester **21** (1.0 g, 2.04 mmol) in THF (5 mL). The reaction mixture was stirred for 40 min at 0 °C, cooled to −78 °C, and stirred for 15 min before the reaction was quenched with saturated NH_4Cl (3 mL), and then warmed to 24 °C, diluted with hexane (30 mL), washed with saturated NH_4Cl and brine, dried ($MgSO_4$), filtered through silica gel, and concentrated to give ester **22** (0.98 g, 98% yield) as a colorless oil (97/3, **22**/**21**, by GC): IR (film) 1695, 1630, 1235, 845 cm^{-1}; ^1H NMR δ 5.40 (dt, J = 10.0, 8.6 Hz, 1H), 5.28−5.20 (m, 1H), 5.12 (br, t, J = 6.5 Hz, 2H), 4.19 (q, J = 7.1 Hz, 2H), 2.36 (m, 2H), 2.30−2.12 (m, 4H), 2.12−1.95 (m, 10H), 1.97 (s, 3H), 1.80 (s, 3H), 1.62 (s, 3H), 1.61 (s, 3H), 1.57 (d, J = 2.5 Hz, 3H), 1.46 (d, J = 8.6 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H), 0.00 (s, 9H); ^{13}C NMR δ 169.7, 155.5, 153.1, 142.0, 136.0, 134.7, 127.8, 126.9, 125.7, 124.5, 123.0, 111.3, 111.2, 59.9, 39.6, 38.9, 29.6, 29.0, 28.7, 26.7, 25.2, 22.9, 21.7, 18.5, 16.0, 15.5, 14.3, −1.8; MS m/z (rel intensity) 490 (11), 135 (30), 95 (32), 73 (100); HRMS calcd for $C_{30}H_{51}FO_2Si$ 490.3644, found 490.3642. Anal. Calcd for $C_{30}H_{51}FO_2Si$: C, 73.41; H, 10.47. Found: C, 73.09; H, 10.61.

14-Fluoro-3-isopropyliden-2,6,10,15-tetramethyl-20-(trimethylsilyl)eicosa-6(*E*),10(*E*),14(*Z*),18(*Z*)-tetraen-2-ol (3). To a solution of ester **22** (0.94 g, 1.92 mmol) in ether (20 mL) was added methyllithium (6.9 mL, 1.4 M in ether, 9.66 mmol) dropwise at −20 °C. The reaction mixture was allowed to reach 10 °C, stirred at this temperature for 1 h, and then cooled to −10 °C, diluted with ether (30 mL), and quenched with saturated NH_4Cl (5 mL). The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography of the residue on silica gel (4−10% ether in hexane) gave ketone **23** (0.18 g, 20% yield) and alcohol **3** (0.66 g, 72% yield) as colorless oils. Data for ketone **23**: ^1H NMR δ 5.39 (dt, J = 10.0, 8.6 Hz, 1H), 5.28−5.20 (m, 1H), 5.13 (br, t, J = 6.5 Hz, 2H), 2.34 (m, 2 H), 2.25 (s, 3H), 2.22−2.12 (m, 4H), 2.10−1.95 (m, 10H), 1.82 (s, 3H), 1.76 (s, 3H), 1.61 (s, 3H), 1.56 (d, J = 2.5 Hz, 3H), 1.46 (d, J = 8.6 Hz, 2H), 0.00 (s, 9H). Data for alcohol **3** (unstable on GC): IR (film) 3400, 1235, 1140, 840 cm^{-1}; ^1H NMR δ 5.39 (dt, J = 10.0, 8.6 Hz, 1 H), 5.28−5.20 (m, 1 H), 5.13 (br, t, J = 6.5 Hz, 2H), 2.28−2.12 (m, 6 H), 2.12−2.02 (m, 6 H), 2.02−1.95 (m, 4 H), 1.92 (s, 3 H), 1.70 (s, 3H), 1.63 (s, 3 H), 1.61 (s, 3 H), 1.57 (d, J = 2.5 Hz, 3 H), 1.47 (d, J = 7.7 Hz, 2 H), 1.42 (s, 6 H), 0.00 (s, 9 H); ^{13}C NMR δ 155.6, 153.2, 138.6, 136.0, 135.6, 128.1, 126.9, 125.7, 124.1, 123.0, 111.3, 111.2, 74.2, 40.1, 39.7, 30.9, 30.1, 29.7, 29.6, 29.0, 28.7, 26.6, 25.3, 22.8, 18.5, 16.0, 15.6, −1.8; MS m/z (rel intensity) 458 (54), 136 (68), 109 (73), 73 (100); HRMS calcd for $C_{30}H_{51}FSi$ ($M^+ - H_2O$) 458.3744, found 458.3756. Anal. Calcd for $C_{30}H_{53}FOSi$: C, 75.57; H, 11.20. Found: C, 75.68; H, 11.42.

13-Fluoro-3-isopropyliden-22,23,24,25,26,27-hexanordammar-20-ene (24). To a solution of TFA (1.05 mL, 13.7 mmol, 93.0 equiv) in DCM (70 mL) that had been degassed with argon and cooled to −45 °C was added alcohol **3** (70 mg, 0.147 mmol, 1.0 equiv) dropwise over a 30 min period with vigorous stirring. (Note: Each drop was cooled by contact with the cold wall of the reaction flask before mixing with the reaction mixture.) After the addition, the mixture turned a pale pink and was stirred an additional 10 min at −45 °C. The reaction was quenched slowly at −45 °C by the addition of a solution of triethylamine (1.05 mL) in ethanol (3 mL), then allowed to warm to 24 °C, extracted with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated to give a white gum (85 mg). Flash chromatography (hexane) gave tetracyclic fluoro diene **24** (31 mg, 55% yield) as a white semisolid. In other experiments, yields of 60−62% were achieved. An analytical sample of **24** was recrystallized from acetonitrile to give colorless crystals: mp 135−137 °C; IR (film) 1625, 900 cm^{-1}; ^1H NMR δ 5.80 (quint, J = 8.8 Hz, 1 H), 5.04 (d, J = 10.3 Hz, 1 H), 4.99 (d, J = 17.4 Hz, 1 H), 2.56 (dq, J = 34.8, 8.9, 1 H), 2.33 (ddd, J = 14.7, 6.8, 3.4 Hz, 1 H), 2.13−1.92 (m, 3 H), 1.78 (s, 3 H), 1.66 (s, 3 H), 1.8−1.2 (m, 14 H), 1.20 (s, 3 H), 1.10 (s, 3 H), 1.09 (d, J = 6.4 Hz, 3 H), 0.99 (s, 3 H), 0.83 (s, 3 H); ^{13}C NMR δ 138.6, 138.4, 138.3, 121.5, 116.0, 110.3, 108.6, 54.0, 53.0, 52.9, 51.1, 49.7, 49.5, 41.2, 39.3, 36.7, 35.0, 29.0, 28.6, 28.4, 28.1, 27.2, 24.7, 24.2, 23.9, 23.2, 21.3, 21.2, 19.6, 19.5, 18.3, 17.3, 17.1; MS m/z (rel intensity) 386 (9), 290 (42), 121 (100), 95 (92); HRMS calcd for $C_{27}H_{43}F$ 386.3351, found 386.3359. Anal. Calcd for $C_{27}H_{43}F$: C, 83.88; H, 11.21. Found: C, 83.49; H, 11.32.

A mixture of compounds **25** (C-17 epimers) from chromatographic separation gave the following data: ^1H NMR δ 5.90 (quint, J = 7.1 Hz, 1 H), 5.38 (br s, 1H), 4.96 (d, J = 6.1 Hz, 1 H), 4.89 (d, J = 17. Hz, 1 H), 2.94 (dd, J = 8, 18 Hz, 0.5 H), 2.41 (dt, J = 17, 6 Hz, 1 H), 2.3−2.0 (m, 3 H), 1.81 (s, 3 H), 1.68 (s, 3 H), 1.9−1.0 (m, 14 H), 1.56 (s, 3 H), 1.21 (s, 3 H), 1.15 (s, 3 H), 1.08 (s, 1.5 H), 0.98 (s, 1.5 H), 0.95 (s, 1.5 H), 0.90 (s, 1.5 H), 0.89 (s, 1.5 H).

3-Isopropylidene-22,23,24,25,26,27-hexanordammar-20-ene (27). To a suspension of sodium−potassium alloy (200 mg, 22%-78%) in toluene (6 mL) was added dicyclohexano-18-crown-6 (800 mg, 2.15 mmol). The resultant blue-black mixture was stirred for 10 min at 25 °C, and a solution of fluoro tetracycle **24** (83 mg, 0.215 mmol) in toluene (1 mL) was added dropwise. After 1.5 h the reaction mixture was diluted with hexane, quenched with 2-propanol, washed with water and brine, dried (Na_2SO_4), filtered, and concentrated. Flash chromatography of the residue on silica gel (hexane) gave diene **27** (59 mg, 74% yield) as a solid, 90% pure by GC. An analytical sample of **27** was recrystallized from acetonitrile to give colorless crystals: mp 126−128 °C; IR (KBr) 1625, 900 cm^{-1}; ^1H NMR δ 5.64 (quint., J = 8.6 Hz, 1H), 4.91 (d, J = 16.8 Hz, 1H), 4.88 (d, J = 9.7 Hz, 1H), 2.32 (ddd, J = 14.7, 6.8, 3.4 Hz, 1H), 2.20−1.85 (m, 5H), 1.79 (s, 3 H), 1.66 (s, 3H), 1.6−1.2 (m, 14H), 1.20 (s, 3H), 1.10 (s, 3H), 0.95 (s, 3H), 0.86 (s, 3H), 0.80 (s, 3H); ^{13}C NMR δ 144.0, 138.9, 121.4, 112.9, 54.1, 51.0, 49.4, 48.1, 45.8, 41.3, 40.4, 39.3, 36.7, 35.0, 31.2, 28.9, 28.6, 24.8, 24.6, 24.3, 23.9, 23.2, 22.4, 20.1, 19.8, 15.8, 15.1; MS m/z (rel intensity) 368 (18), 272 (100), 95 (93); HRMS calcd for $C_{27}H_{44}$ 368.3445, found 368.3443. Anal. Calcd for $C_{27}H_{44}$: C, 87.97; H, 12.03. Found: C, 88.33; H, 11.85.

3-Isopropyliden-22,23,24,25,26,27-hexasnordammar-20-one (28). A mixture of palladium chloride (5 mg, 0.028 mmol) and copper chloride (10 mg, 0.075 mmol) in DMF (2 mL) and water (0.2 mL) was stirred for 1 h under an oxygen atmosphere at 25 °C. Then a solution of diene **27** (45 mg, 0.122 mmol) in ether (1 mL) was added, and the reaction mixture was heated at 60 °C for 3 h and then diluted with water and extracted with hexanes−ether (1:1). The organic layer was extracted with brine, dried (Na_2SO_4), and concentrated. Flash chromatography of the residue on silica gel (0−5% ether in hexane) gave ketone **28** (40 mg, 85% yield) as a solid, 92% pure by GC. An analytical sample of **28** was crystallized from acetonitrile to give colorless needles: mp 141−142 °C; IR (film)

1695, 1170 cm^{-1}; ^1H NMR δ 2.59 (td, J = 11.0, 6.1 Hz, 1H), 2.31 (ddd, J = 14.7, 6.7, 3.3 Hz, 1H), 2.13 (s, 3H), 2.08−1.86 1.79 (m, 4H), 1.78 (s, 3H), 1.65 (s, 3H), 1.7−1.2 (m, 14H), 1.19 (s, 3H), 1.09 (s, 3H), 0.98 (s, 3H), 0.87 (s, 3H), 0.80 (s, 3H); ^{13}C NMR δ 212.6, 138.7, 121.5, 54.1, 54.0, 50.7, 49.9, 45.6, 41.2, 40.5, 39.2, 36.7, 35.0, 31.4, 30.0, 28.6, 25.9 (two carbons), 24.6, 24.2, 23.9, 23.2, 22.2, 20.1, 19.8, 15.7, 15.0; MS *m*/*z* (rel intensity) 384 (8), 288 (81), 95 (100), 81 (52), 69 (44); HRMS calcd for $C_{27}H_{44}O$ 384.3394, found 384.3397. Anal. Calcd for $C_{27}H_{44}O$: C, 84.31; H, 11.53. Found: C, 84.71; H, 11.48.

3-Isopropyliden-20,20-(ethylenedioxy)-22,23,24,25,26,27-hexanordammarane (29). A mixture of ketone **28** (33 mg, 0.086 mmol), ethylene glycol (0.8 mL, 4.3 mmol), and *p*-toluenesulfonic acid monohydrate (3 mg, 0.016 mmol) in benzene (8 mL) was refluxed with a Dean−Stark separator containing 4 Å molecular sieves for 4 h. The reaction mixture was diluted with hexane, extracted with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated. Flash chromatography of the residue on silica gel (5% ether in hexane) gave ketal **29** (36 mg, 98% yield) as a solid, 93% pure by GC. An analytical sample of **29** was recrystallized from acetonitrile to give colorless crystals: mp 120−121 °C; IR (KBr) 1116 cm^{-1}; ^1H NMR δ 3.98−3.89 (m, 4H), 2.31 (ddd, J = 14.7, 6.7, 3.3 Hz, 1H), 2.04 (m, 1 H), 1.95−1.65 (m, 4H), 1.78 (s, 3H), 1.65 (s, 3H), 1.6−1.2 (m, 14H), 1.27 (s, 3H), 1.19 (s, 3H), 1.09 (s, 3H), 0.96 (s, 3H), 0.85 (s, 3H), 0.80 (s, 3H); ^{13}C NMR δ 138.9, 121.3, 113.0, 64.7, 64.3, 54.1, 50.8, 49.8, 48.2, 22.6, 22.3, 20.1, 19.8, 15.9, 15.0; MS *m*/*z* (rel intensity) 428 (17), 413 (28), 87 (100); HRMS calcd for $C_{29}H_{48}O_2$ 428.3656, found 428.3654. Anal. Calcd for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29. Found: C, 81.21; H, 11.17.

3β-Hydroxy-20,20-(ethylenedioxy)-22,23,24,25,26,27-hexanordammarane (30). A stream of ozone was bubbled through a solution of alkene **29** (30 mg, 0.070 mmol) in a mixture of DCM (3 mL) and methanol (3 mL) at −78 °C for 1 min. Excess ozone was swept from the apparatus with argon, and 0.5 M ethanolic sodium borohydride (1.5 mL) was added at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and 1 h at 25 °C, diluted with ether, and extracted with water and saturated brine, dried (Na_2SO_4), and concentrated. Flash chromatography of the residue on silica gel (5%−25% ether in hexane) gave alcohol **30** (27 mg, 95% yield) as a solid, 95% pure by GC. An analytical sample of **30** was recrystallized from acetonitrile to give colorless crystals: mp 201−202 °C; IR (film) 3420, 1140, 1045 cm^{-1}; ^1H NMR δ 3.98−3.89 (m, 4H), 3.19 (dd, J = 10.9, 4.8 Hz, 1H), 1.92−1.39 (m, 15H), 1.35−1.18 (s, 6H), 1.26 (s, 3H), 0.97 (s, 3H), 0.96 (s, 3H) 0.85 (s, 3H), 0.84 (s, 3H), 0.76 (s, 3H); ^{13}C NMR δ 113.0, 78.9, 64.7, 64.3, 55.8, 50.8, 50.0, 48.4, 42.6, 40.3, 39.1, 38.9, 37.1, 35.3, 31.1, 28.0, 27.4, 26.7, 25.2, 22.3, 21.6, 18.3, 16.2, 16.1, 15.5, 15.4; MS *m*/*z* (rel intensity) 404 (40), 87 (100); HRMS calcd for $C_{29}H_{48}O_3$ 404.3292, found 404.3289. Anal. Calcd for $C_{29}H_{48}O_3$: C, 77.18; H, 10.96. Found: C, 77.39; H, 10.78.

3β-Hydroxy-22,23,24,25,26,27-hexanordammarane-20-one (31). A solution of ketal **30** (21 mg, 0.052 mmol) and *p*-toluenesulfonic acid monohydrate (1 mg, 0.0053 mmol) in acetone (3 mL) was stirred for 5 h at 25 °C, and then diluted with 1:1 hexanes−ether, washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated. Flash chromatography of the residue on silica gel (10%−25% ether in hexane) gave hydroxyketone **31** (18 mg, 96% yield) as a solid, 96% pure by GC. An analytical sample of **31** was recrystallized from acetonitrile to give colorless crystals: mp 188−189 °C (lit.[24] mp 195−197 °C, MeOH/$CHCl_3$); IR (film) 3407, 1707, 1690 cm^{-1}; ^1H NMR δ 3.19 (dd, J = 11.3, 4.9 Hz, 1H), 2.58 (td, J = 11.0, 6.2 Hz, 1H), 2.12 (s, 3H), 1.96−1.87 (m, 2H), 1.73−1.38 (m, 12H), 1.35−1.13 (m, 6H), 0.97 (s, 3H), 0.96 (s, 3H), 0.86 (s, 3H), 0.84 (s, 3H), 0.77 (s, 3H); ^{13}C NMR δ 212.5, 78.9, 55.8, 54.3, 50.6, 50.0, 45.1, 40.4, 39.1, 38.9, 37.1, 35.5, 31.5, 30.0, 28, 27.3, 25.9, 25.6, 21.2, 18.2, 16.2, 15.8, 15.5, 15.3; MS *m*/*z* (rel intensity) 360 (7), 299 (63), 69 (100); HRMS calcd for $C_{24}H_{40}O_2$ 360.3028, found 360.3030. Anal. Calcd for $C_{24}H_{40}O_2$: C,79.94; H, 11.18. Found: C, 79.73; H, 11.06.

***dl*-Dammarenediols I (1a) and II (1b).** To a solution of the Grignard reagent prepared from 1-bromo-4-methyl-3-pentene (100 mg, 0.61 mmol) and magnesium powder (16 mg, 0.65 mg-atom) in THF (2 mL) was added a solution of hydroxy ketone **31** (15 mg, 0.0416 mmol) in THF (0.5 mL). The reaction mixture was stirred for 1 h at 25 °C and for 4 h at 60 °C and then cooled to 0 °C, diluted with ether, and quenched with saturated NH_4Cl. The organic layer was extracted with brine, dried (Na_2SO_4), and concentrated. The residue, still containing about 40% of the starting material (by GC), was diluted with THF (0.5 mL) and treated a second time with the Grignard reagent under the same conditions. Flash chromatography of the residue on silica gel (10%−25% ether in hexane) gave the dammarenediols I (**1a**) and II (**1b**) (11.5 mg, 62% yield, 1:3 by NMR) as a solid with mp 110−115 °C. Recrystallization from hexane gave dammarenediol I (**1a**) as colorless crystals: mp 154−159 °C (lit.[5] mp 152−154 °C, hexane); IR (film) 3430, 1115, 1090, 1045, 1035, 980 cm^{-1}. Data for **1a**: ^1H NMR δ 5.12 (t, J = 7.0 Hz, 1 H), 3.20 (dd, J = 11.0, 4.9 Hz, 1 H), 2.04 (m, 2 H), 1.69 (s, 3 H), 1.62 (s, 3 H), 1.84−1.40 (m, 16 H), 1.36−1.20 (m, 8 H), 1.12 (s, 3 H), 0.97 (s, 3 H), 0.96 (s, 3 H), 0.87 (s, 3 H), 0.84 (s, 3 H), 0.77 (s, 3 H); ^{13}C NMR δ 131.6, 124.7, 78.9, 75.8, 55.8, 50.6, 50.0, 49.5, 42.1, 41.8, 40.3, 39.0, 38.9, 37.1, 35.2, 31.0, 28.0, 27.5, 27.4, 25.7, 25.3, 23.6, 22.3, 21.4, 18.2, 17.7, 16.3, 16.2, 15.5, 15.3. MS *m*/*z* (rel intensity) 426 (17), 109 (100), 69 (85). Data for **Ib**: ^1H NMR δ 5.12 (t, J = 7.0 Hz, 1 H), 3.20 (dd, J = 11.0, 4.9 Hz, 1 H), 2.04 (m, 2 H), 1.69 (s, 3 H), 1.62 (s, 3 H), 1.84−1.40 (m, 16 H), 1.36−1.20 (m, 8 H), 1.14 (s, 3 H), 0.97 (s, 3 H), 0.95 (s, 3 H), 0.87 (s, 3 H), 0.84 (s, 3 H), 0.77 (s, 3 H); ^{13}C NMR δ 131.6, 124.7, 78.9, 75.4, 55.8, 50.6, 50.3, 49.8, 42.2, 40.4, 40.3, 39.0, 38.9, 37.1, 35.2, 31.2, 28.0, 27.5, 27.4, 25.7, 25.4, 24.8, 22.5, 21.5, 18.2, 17.7, 16.4, 16.2, 15.5, 15.3; HRMS calcd for $C_{30}H_{50}O$ ($M^+ - H_2O$) 426.3862, found 426.3858.

Synthesis of Dammarenediol II (1b) from Dipterocarpol (32). To a solution of dipterocarpol (**32**) (30 mg, 0.068 mmol) in ethanol/DCM (3:1, 2 mL) was added $NaBH_4$ (0.019 g, 0.5 mmol) in EtOH (0.5 mL). The mixture was stirred for 2 h at 25 °C, diluted with ether and hexane (1:1, 20 mL), extracted with water and brine, dried (Na_2SO_4), filtered, and concentrated. Flash chromatography on silica gel (20%−30% ether in hexane) gave 28 mg (93% yield) of dammarenediol II (**1b**).

Acknowledgment. This paper is dedicated to the memory of Professor William S. Johnson.[35] We are grateful to the National Science Foundation and the National Institutes of Health for their financial support. We thank Professor Shunyo Matsunaga of the Osaka University of Pharmaceutical Sciences for his generous sample of (+)-3β-hydroxy-22,23,24,25,26,27-hexanordammaran-20-one and Dr. Ray Conrow of Alcon Laboratories, Inc., for valuable contributions to the manuscript. We also thank the Council on Undergraduate Research and Pfizer, Inc., for an AIURP Fellowship and the Stanford University Summer Research Program in Biomedical Sciences for additional support (K.J.B.).

JO991196S