Pergamon

Tetrahedron, Vol. 52, No. 1, pp. 119-130, 1996
Copyright © 1995 Elsevier Science Ltd
Printed in Great Britain. All rights reserved
0040-4020/96 $15.00 + 0.00

0040-4020(95)00909-4

Synthesis of Analogs of Farnesyl Diphosphate

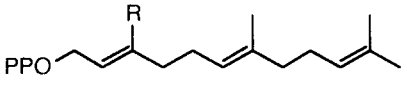
Julia M. Dolence and C. Dale Poulter*

Department of Chemistry, University of Utah, Salt Lake City, UT 84112

Abstract: Syntheses of analogs of farnesyl diphosphate (FPP) bearing substitutions at C3 are described. The mono-, di-, and trifluoromethylFPP derivatives were prepared by alkylation of appropriately substituted acetoacetates with geranyl bromide, followed by decarboxylation to obtain fluorinated ketones and a Wittig condensation to give the farnesyl skeleton. A similar sequence was used to synthesize 13-desmethylFPP.

Protein farnesyl transferase (PFTase) catalyzes the posttranslational modification of a variety of proteins, including Ras, by attachment of a farnesyl group to a cysteine residue to form a thioether bond. Ras proteins are major components in the signal transduction pathway leading to cell division. Both normal and mutant Ras must associate with the inner surface of the outer membrane to participate in signal transduction,[1,2] and farnesylation is required for Ras proteins to associate with plasma membranes.[1] The discovery that farnesylation is required for oncogenic forms of Ras to promote unregulated cell division has prompted widespread interest in protein prenylation.[1] While several studies have focused on substrate specificity and inhibition of PFTase, little has been reported about the chemical mechanism of the farnesyl transfer reaction.

Substitution of hydrogen atoms by fluorine in an organic molecule can produce prounounced biological effects. The electron-withdrawing effect of fluorine[3] has been exploited in earlier mechanistic studies of enzymes in the isoprene biosynthetic pathway through the development of potent reversible[4] and irreversible[5] inhibitors. We recently reported evidence for an electrophilic alkylation of cysteine by yeast PFTase using analogs of FPP (figure 1, R = CH_3) where the methyl at C3 was replaced by a variety of substituents.[6]



FPP R = CH_3 **3** R = CF_3
1 R = CH_2F **4** R = H
2 R = CHF_2

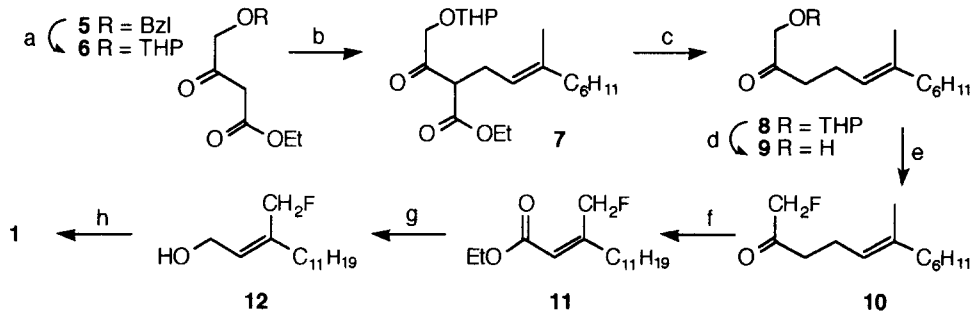
Figure 1

Although several syntheses of fluorinated terpenes have been reported for studies of enzyme mechanisms[4a,7] and as analogs of juvenile hormones,[8] we wished to devise a general route that allowed us to construct analogs of different chain lengths with a variety of substituents for the C3 methyl group in isoprenoid diphosphates. We now report a synthesis of FPP analogs containing fluoromethyl (**1**), difluoromethyl (**2**),

trifluoromethyl (**3**) and hydrogen (**4**) substituents at C3 that should be applicable for a variety of isoprenoids of different chain lengths.

Results and Discussion

A synthesis of 13-fluorofarnesyl diphosphate (**1**) based on a Horner-Emmons Wittig condensation with a derivative of geranylacetone to generate the farnesyl skeleton is described in Scheme 1. Although ethyl fluoroacetoacetate has been prepared,[9] poor yields and reports of its toxicity[9] led us to defer incorporation of the fluorine atom until later in the reaction sequence.



Reagents: a) 1. H_2/Pd-C, EtOH; 2. DHP, PPTS, CH_2Cl_2. b) NaH, geranyl bromide. c) KOH, EtOH. d) PPTS, EtOH, 50 °C. e) 1. Tf_2O, 2,6-lutidine, CH_2Cl_2; 2. TBAF, THF. f) triethyl phosphonoacetate, NaH, PhH. g) DIBAL, CH_2Cl_2, -78 °C to -50 °C. h) 1. CBr_4, PPh_3, CH_2Cl_2; 2. $(Bu_4N)_3HP_2O_7$, CH_3CN.

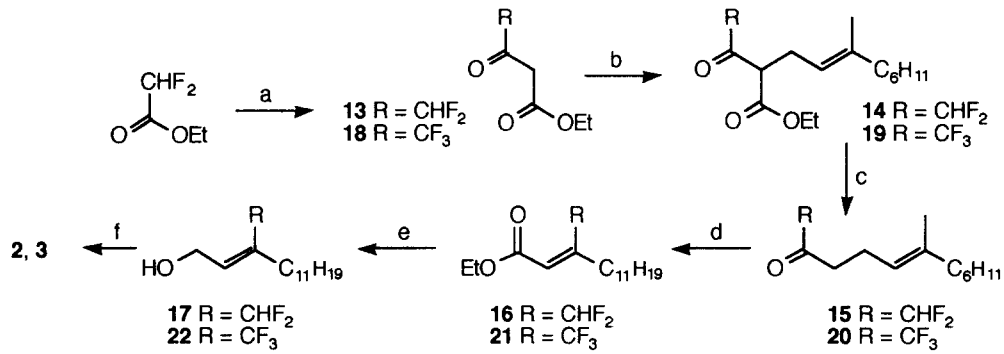
Scheme 1

Ethyl 4-hydroxy acetoacetate was prepared from ethyl *O*-benzyloxyacetoacetate (**5**) as described by Muel and coworkers,[10] and the hydroxyl group was protected as a THP ether (**6**).[11] Attempts to purify **6** by chromatography and distillation were not successful, and the material (~80% pure by proton and ^{13}C NMR spectroscopy) was used in the next step. Acetoacetate **6** was treated with sodium hydride and geranyl bromide to give compound **7** as a mixture of diastereomers. The mixture was decarboxylated with KOH in ethanol to give ketone **8** in 77% yield. The THP protecting group of **8** was readily removed with PPTS in ethanol in quantitative yield to produce **9**, which was used in the next step without purification. Several other hydroxyl protecting groups, including 2-trimethylsilylethyoxy, *t*-butyldiphenylsilyl, and *p*-methoxybenzyl, were investigated and discarded because of problems associated with their removal, including long reaction times, incomplete reaction, or formation of nonvolitile by-products.

The hydroxyl group of **9** was replaced by fluorine in two steps by treatment of the alcohol with triflic anhydride followed by TBAF[12] to give fluoroketone **10** in 46% yield. A Horner-Emmons condensation gave ester **11** as a mixture of *Z* and *E* isomers in a ratio of 66:34, respectively. The stereochemistry of the double bond was assigned by comparison of ^1H chemical shifts to those seen for the corresponding fluorinated geranate esters.[7b] The isomers were separated by multiple elution thin layer chromatography, and the *Z* isomer was isolated in 62% yield. Ester **11** was reduced using diisobutyl aluminum hydride (DIBAL) to afford fluoro alcohol **12**. Alternatively, the *E* and *Z* mixture of esters could be reduced first, and the resulting alcohols separated by normal phase HPLC (2% 2-propanol in hexane).

Diphosphate **1** was synthesized by the procedure of Davisson *et al.*[13] Alcohol **12** was converted to the corresponding bromide using PPh_3 and CBr_4. PBr_3 was less satisfactory because of the presence of a small amount of an unidentified contaminant that was difficult to remove. Diphosphate **1** was obtained in 59% yield after purification by reversed phase HPLC.[14]

The syntheses of 13-difluorofarnesyl diphosphate (**2**) and 13-trifluorofarnesyl diphosphate (**3**) followed the same general procedure (Scheme 2). In contrast to **1**, fluorine was introduced into the acetoacetates before alkylation with geranyl bromide. Ethyl 4,4-difluoroacetoacetate (**13**) was synthesized from ethyl difluoroacetate as shown in Scheme 2. Attempts to prepare **13** by mixed Claisen condensations according to literature methods[15] were unsuccessful. However, acetoacetate **13** was obtained by a Reformatsky reaction[16] between ethyl difluoroacetate and ethyl bromoacetate. The ^1H and ^{19}F NMR spectra of the reaction mixture showed three new difluoromethyl-containing species due to the keto and enol forms of **13** and the ketone hydrate. The relative proportion of hydrate varied from run to run but was separated from the tautomeric forms of **13** by chromatography on silica gel. When the crude reaction mixture was distilled, only **13** was obtained, presumably because the hydrate lost water when heated. Ethyl 4,4,4-trifluoroacetoacetate was commercially available.



Reagents: a) ethyl bromoacetate, Zn, Et_2O. b) 1. NaH, Et_2O; 2. geranyl bromide, KI, acetone, reflux. c)LiCl, H_2O, DMF, reflux. d) triethyl phosphonoacetate, NaH, PhH. e) DIBAL, CH_2Cl_2, -78 °C to -50 °C. f) 1. CBr_4, PPh_3, CH_2Cl_2 or TsCl, DMAP, CH_2Cl_2; 2. $(Bu_4N)_3HP_2O_7$, CH_3CN.

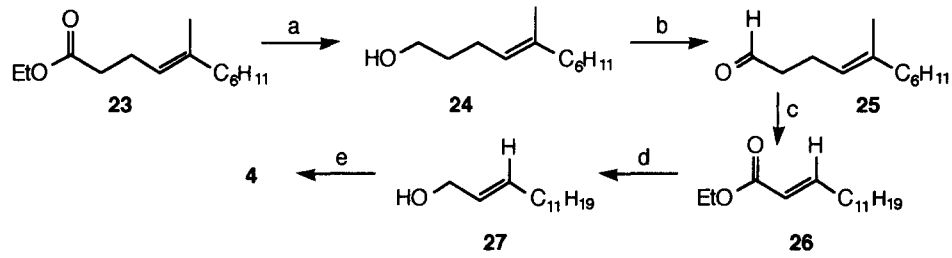
Scheme 2

Alkylation of the fluorinated acetoacetates was accomplished following the method of Begue *et al.*[17] Ethyl 4,4-difluoroacetoacetate (**13**) was treated with sodium hydride in anhydrous ether to form the sodium enolate. The enolate was then heated at reflux with geranyl bromide and potassium iodide in dry acetone to provide ester **14** in 73% yield. The alkylation was slow presumably because of the poor nucleophilicity of the difluoroacetoacetate anion.[17] Initial attempts with ethyl difluoroacetoacetate, sodium hydride and geranyl bromide at room temperature were unsuccessful. Compound **19** was decarboxylated with lithium chloride in aqueous DMF[18] under reflux to give difluoroketone **15** in 50% yield. The ketone was converted to ester **16** by a Horner-Emmons Wittig reaction using triethyl phosphonoacetate in anhydrous benzene. Analysis of the proton NMR spectrum of the crude reaction mixture indicated a 65:35 mixture of *Z*:*E* products was obtained. The *Z* isomer was isolated by preparative thin layer silica gel chromatography in 47% yield. Ester **16** was reduced with DIBAL to give difluoroalcohol **17** in 73% yield.

Ethyl 4,4,4-trifluoroacetoacetate **18** was condensed with geranyl bromide to provide **19** in the same manner as **14**. The presence of an additional fluorine atom required a longer reaction time (96 h). Decarboxylation of **19** to **20** was also slower to give a 50% yield of **20**. The Horner-Emmons condensation produced a 28:72 *Z*:*E* mixture of isomers. Attempts to improve production of the *Z* isomer by changing temperature or solvent were unsuccessful. Camps[8] reported a similar *Z*:*E* ratio in the synthesis of trifluorinated analogs of juvenile hormones using a Horner-Emmons approach.

Diphosphates **2** and **3** were obtained as described for **1**. Diphosphate **2** was synthesized from alcohol **17** in 48% yield. A poor yield (7%) of trifluoromethyl diphosphate **3** was obtained from alcohol **22** using a similar sequence of reactions. However, tosylate proved to be a much better leaving group for the phosphorylation, and the overall yield of **3** from **22** improved to 71% for the two steps.

The synthesis of 13-desmethylfarnesyl diphosphate (**4**) followed the procedure of Kuwajima[19] for the condensation of the cupric anion of ethyl acetate with geranyl bromide to provide ester **23** (Scheme 3). The ester was reduced to alcohol **24** in 91% yield using lithium aluminum hydride (LAH), and the alcohol was oxidized to aldehyde **25** with tetrapropylammonium perruthenate (TPAP) and 4-methylmorpholine *N*-oxide (NMO).[20]



Reagents: a) LAH, Et_2O, -78 °C. b) TPAP, NMO, CH_2Cl_2. c) triethyl phosphonoacetate, NaH, THF. d) DIBAL, CH_2Cl_2, -78 °C to -50 °C. e) 1. CBr_4, PPh_3, CH_2Cl_2; 2. $(Bu_4N)_3HP_2O_7$, CH_3CN.

Scheme 3

The aldehyde was sensitive to silica gel chromatography and was carried on to the next step without purification. Treatment of **25** with triethyl phosphonoacetate and sodium hydride gave ester **26** as a single isomer in 49% overall yield. Reduction of the conjugated ester with DIBAL provided alcohol **27** in 91% yield. Diphosphate **4** was produced from desmethyl alcohol **27** in the same manner described for compounds **1** and **2** in 76% yield.

Experimental.

General Methods. All nonaqueous reactions were performed under a dry N_2 atmosphere with dry solvents and reaction vessels. "Dried and concentrated" refers to the removal of residual water with anhydrous $MgSO_4$, filtration, and evaporation of solvent on a rotary evaporator. Silica gel grade 60, 230-400 mesh was used for chromatography with the solvent system indicated. Preparative thin layer chromatography was performed on silica gel 60 F254 (1000 μ). Analytical thin layer chromatography was done on silica gel 60 F254. The plates were visualized with UV light and developed with phosphomolybdic acid. ^1H, ^{19}F and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 MHz, 282 MHz and 75 MHz, respectively, unless otherwise stated. For ^1H NMR

TMS at 0 ppm, for ^{19}F NMR C_6F_6 at 0 ppm, and for ^{13}C NMR $CDCl_3$ the 77.00 ppm center line served as internal standards unless otherwise stated. ^{31}P NMR spectra were recorded in D_2O at 121 MHz with H_3PO_4 in D_2O (0 ppm) as an external standard. Mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded using electron impact (EI) at 70 eV unless otherwise stated. All solvents and volatile reagents were distilled prior to use. Tetrahydrofuran, diethyl ether, and benzene were distilled from sodium/benzophenone; CH_2Cl_2 and CH_3CN were distilled from CaH_2.

Ethyl 4-*O*-tetrahydropyran acetoacetate (6). Ethyl 4-benzyloxyacetoacetate **5** (8.50 g, 36.3 mmol) was dissolved in 75 mL of anhydrous ethanol. Pd-C (10%, 1.70 g, 20% w/w) was added, and the solution was agitated in a Parr shaker under a H_2 atmosphere at 40 psi for 12 h. The solution was filtered through Celite to remove the catalyst, and the filtrate was concentrated under reduced pressure to give 4.70 g (94%) of ethyl 4-hydroxyacetoacetate.[10] The oil was dissolved in 100 mL of anhydrous CH_2Cl_2 under nitrogen. Dihydropyran (6.6 mL, 72.3 mmol) and pyridinium *p*-toluenesulfonate (PPTS) (0.913 g, 3.6 mmol) were added, and the solution was stirred overnight. The solvent was removed under reduced pressure, and the resulting oil was diluted with ethyl acetate and water. The organic layer was washed with water and brine, dried, and concentrated to afford 7.25 g of an amber oil. The oil was partially purified by silica gel chromatography, eluting with 1:3 EtOAc:hexanes to afford 5.36 g (60%) of a colorless oil which was contaminated with ~20% of polymerized tetrahydropyran as determined by ^1H and ^{13}C NMR analysis: ^1H NMR δ 1.28 (t, J = 7 Hz, 3H), 1.50-1.90 (m, 4H), 3.45-3.60 (m, 1H), 3.56 (dd, J = 16 and 6 Hz, 2H), 3.75-3.85 (m, 1H), 4.10-4.30 (m, 2H), 4.19 (q, J = 7 Hz, 2H), 4.24 (dd, J = 17 and 30 Hz, 2H), 4.62-4.64 (m, 1H); ^{13}C NMR δ 13.9, 19.0, 25.1, 30.1, 46.1, 61.2, 62.3, 71.9, 98.9, 166.9, 201.8.

Ethyl 2-(3,7-dimethylocta-2,6-diene)-4-*O*-tetrahydropyran-acetoacetate (7). To a suspension of NaH (0.96 g, 21.1 mmol) in 60 mL of THF at 0 °C was added ethyl 4-*O*-tetrahydropyran acetoacetate **6** (4.85 g, 1.05 mmol) in 20 mL of THF. The solution was warmed to room temperature and stirred for 1 h. Geranyl bromide (4.0 mL, 20.1 mmol) was added, and the solution was stirred overnight. THF was removed under reduced pressure. The residue was diluted with EtOAc, washed with water and brine, dried, and concentrated to give 8.20 g of a yellow oil. The oil was purified by silica gel chromatography eluting with 1:8 EtOAc:hexane to afford 2.91 g (40%) of **7** as an inseparable mixture of diastereomers: IR (neat) 2939, 2874, 2854, 1730, 1725 cm^{-1}; ^1H NMR δ 1.25 (t, J = 7 Hz, 3H), 1.50-1.75 (m, 4H), 1.78-1.90 (m, 2H), 1.92-2.10 (m, 4H), 2.50-2.68 (m, 2H), 3.46-3.56 (m, 1H), 3.60-3.72 (m, 1H), 3.74-3.86 (m, 1H), 4.10-4.38 (m, 4H), 4.60-4.68 (m, 1H), 5.00-5.14 (m, 2H); ^{13}C NMR δ 14.0, 15.9, 17.5, 18.7, 18.9, 25.1, 25.5, 26.2, 26.3, 26.4, 29.9, 30.0, 39.5, 55.0, 55.1, 61.0, 61.7, 62.1, 71.4, 71.7, 98.2, 98.7, 119.6, 123.8, 131.2, 137.9, 138.0, 169.0, 203.1, 203.3; HRMS calc'd for $C_{21}H_{34}O_5$ 366.2406, found: 366.2399.

1-*O*-Tetrahydropyran-6,10-dimethylundeca-5,10-diene-2-one (8). Ester **7** (1.01 g, 2.76 mmol) was dissolved in 75 mL of ethanol and 15 mL of water. KOH (1.161 g, 20.7 mmol) was added, and the solution was stirred for 24 h. The solvent was removed under reduced pressure. The residue was diluted with EtOAc, washed with water and brine, dried, and concentrated to give 0.66 g of a yellow oil. The oil was purified by silica gel chromatography, eluting with 1:8 EtOAc:hexane to afford 0.609 g (77%) of a colorless oil: IR (neat) 2939, 2850, 1720, 1442, 1383 cm^{-1}; ^1H NMR δ 1.60 (s, 3H), 1.61 (s, 3H), 1.67 (s, 3H), 1.50-1.90 (m, 6H), 1.95-2.20 (m, 4H), 2.25-2.34 (m, 2H), 2.46-2.55 (m, 2H), 3.45-3.55 (m, 1H), 3.80-3.90 (m, 1H), 4.20 (dd, J = 17 and 26 Hz, 2H), 4.64 (t, J = 4 Hz, 1H), 5.05-5.15 (m, 2H); ^{13}C NMR δ 15.7, 17.4, 18.9,

21.7, 25.1, 25.4, 26.4, 30.0, 38.9, 39.4, 61.9, 71.8, 98.4, 122.2, 123.9, 130.9, 136.0, 208.0; HRMS calc'd for $C_{18}H_{30}O_3$: 294.2194, found: 294.2182.

1-Hydroxy-6,10-dimethylundeca-5,10-diene-2-one (9). Compound **8** (2.07 g, 7.05 mmol) was dissolved in 60 mL of ethanol under nitrogen. PPTS (0.177 g, 0.71 mmol) was added, and the solution was stirred at room temperature overnight, then at 50 °C for 1 h. The solvent was removed under reduced pressure. The residue was diluted with ethyl acetate, washed with brine, dried, and concentrated to give 1.62 g of an oil. The oil was chromatographed on silica gel, eluting with 1:4 EtOAc:hexane to afford 0.910 g (61% yield) of a colorless oil: IR (neat) 3400, 2968, 2918, 2858, 1722, 1442 cm^{-1}; ^1H NMR δ 1.59 (s, 3H), 1.61 (s, 3H), 1.67 (s, 3H), 1.96-2.05 (m, 4H), 2.32-2.50 (m, 4H), 3.17 (s, 1H), 4.23 (s, 2H), 5.06 (t, J = 7 Hz, 2H); ^{13}C NMR δ 15.9, 17.6, 22.3, 25.6, 26.5, 38.4, 39.5, 68.2, 121.7, 123.9, 131.4, 137.0, 209.4; HRMS calc'd for $C_{13}H_{22}O_2$: 210.1620, found: 210.1620.

1-Fluoro-6,10-dimethylundeca-5,10-diene-2-one (10). Hydroxyketone **9** (0.95 g, 4.56 mmol) was dissolved in 20 mL of anhydrous CH_2Cl_2 under nitrogen. 2,6-Lutidine (1.3 mL, 10.85 mmol) was added, and the solution was cooled to 0 °C. Triflic anhydride (0.92 mL, 5.47 mmol) was added, and the solution was stirred at 0 °C for 45 min. The solvent was removed under reduced pressure. The residue was diluted with ethyl acetate; washed with 10% $CuSO_4$, $KHCO_3$, and brine; dried; and concentrated to give a red oil. The oil was immediately dissolved in anhydrous THF under nitrogen. TBAF (9.0 mL, 9.0 mmol) was added, and the solution was stirred for 1.5 h. The solution was concentrated, and the residue chromatographed on silica gel eluting with 1:15 EtOAc:hexane to give 0.583 g of a brown oil. The oil was further purified by silica gel chromatography, eluting with 1:20 EtOAc:hexane to give 445 mg (46%) of a light yellow oil: IR (neat) 2968, 2922, 2858, 1728, 1437 cm^{-1}; ^1H NMR δ 1.59 (s, 3H), 1.62 (s, 3H), 1.67 (s, 3H), 1.95-2.10 (m, 4H), 2.25-2.35 (m, 2H), 2.55 (dt, J = 3 and 7 Hz, 2H), 4.78 (d, J = 48 Hz, 2H), 5.00-5.10 (m, 2H); ^{13}C NMR δ 15.9, 17.6, 21.4, 25.6, 26.5, 38.3, 39.6, 84.9 (d, J_{CF} = 184 Hz), 121.9, 124.0, 131.3, 136.8, 206.5 (d, J_{CF} = 20 Hz); ^{19}F NMR δ 111.6 (t, J = 47 Hz); HRMS calc'd for $C_{13}H_{21}FO$: 212.1576, found: 212.1573.

Ethyl (Z)-3-fluoromethyl-7,11-dimethyldodeca-2,6,9-trienoate (11). NaH (0.124 g, 2.58 mmol) was suspended in 5 mL of anhydrous benzene under N_2. Triethyl phosphonoacetate (0.51 mL, 2.57 mmol) was added dropwise, and the solution was stirred for 1 h. Ketone **10** was added in 8 mL of anhydrous benzene, and the solution was stirred overnight. The solution was concentrated, and the residue was diluted with EtOAc and 1 *M* HCl. The organic layer was washed with water and brine, dried, and concentrated to give 0.65 g of a yellow oil. The mixture was chromatographed on silica gel, eluting with 1:40 EtOAc:hexane to provide 0.465 g of the ester as a mixture of *E*/*Z* isomers. The *Z* isomer was isolated by preparative thin layer chromatography, eluting three times with 1:80 EtOAc:hexane to afford 0.36 g (62%) of ester **11**: IR (neat) 2978, 2930, 2860, 1712, 1645, 1446, 1383 cm^{-1}; ^1H NMR δ 1.26 (t, J = 8 Hz, 3H), 1.60 (s, 6H), 1.67 (s, 3H), 1.98-2.12 (m, 4H), 2.14-2.30 (m, 2H), 2.32-2.40 (m, 2H), 4.13 (q, J = 7 Hz, 2H), 5.05-5.20 (m, 2H), 5.54 (d, J = 48 Hz, 2H), 5.70 (s, 1H); ^{13}C NMR δ 14.2, 16.0, 17.6, 25.6, 26.3, 26.6, 33.6 (d, J_{CF} = 8 Hz), 39.6, 60.0, 82.0 (d, J_{CF} = 162 Hz), 115.9 (d, J_{CF} = 6 Hz), 122.6, 124.1, 131.3, 136.3, 158.6 (d, J_{CF} = 18 Hz), 165.7; ^{19}F NMR δ 113.8 (t, J = 49 Hz); HRMS calc'd for $C_{17}H_{27}FO_2$: 282.1995, found: 282.1988.

E isomer: IR (neat) 2962, 2924, 1718, 1660, 1446 cm^{-1}; ^1H NMR δ 1.29 (t, J = 7 Hz, 3H), 1.60 (s, 6H), 1.68 (s, 3H), 1.95-2.12 (m, 4H), 2.16-2.26 (m, 2H), 2.53-2.60 (m, 2H), 4.18 (q, J = 7 Hz, 2H), 4.86 (dd, J = 47 and 2 Hz, 2H), 5.04-5.18 (m, 2H), 5.92 (d, J = 1 Hz, 1H); ^{13}C NMR δ 14.5, 16.0, 17.6, 25.6, 26.6, 27.0, 29.0 (d, J_{CF} = 97 Hz), 39.7, 60.0, 84.1 (d, J_{CF} = 177 Hz), 115.1 (d, J_{CF} = 13 Hz), 123.0, 124.5, 131.4,

136.5, 155.8 (d, J_{CF} = 12 Hz), 165.9 (d, J_{CF} = 1 Hz); ^{19}F NMR 120.3 (t, J = 49 Hz); HRMS calc'd for $C_{17}H_{27}FO_2$: 282.1995, found: 282.2017.

(Z)-3-Fluoromethyl-7,11-dimethyl-2,6,9-trien-1-ol (12). Ester **11** (0.099 g, 0.35 mmol) was dissolved in 4 mL of anhydrous CH_2Cl_2 under N_2 and cooled to -78 °C. DIBAL (0.74 mL, 0.74 mmol) was added dropwise, and the solution was stirred at -78 °C for 1 h. The solution was slowly warmed to -60 °C, stirred for 30 min, cooled to -78 °C, and quenched with 5 mL of methanol. The solution was warmed to room temperature, and stirred with 10 mL of a saturated solution of NaK tartrate for 2 h. The organic layer was separated, and the aqueous layer was extracted twice with CH_2Cl_2. The organic layers were combined, dried, and concentrated to give 80 mg of a yellow oil. The oil was chromatographed on silica gel, eluting with 1:5 EtOAc:hexane to afford 0.061 g (73%) of a colorless oil: IR (neat) 3364 (br), 2966, 2858, 1670, 1448, 1381 cm^{-1}; ^{1}H NMR δ 1.60 (s, 6H), 1.68 (s, 3H), 1.95-2.14 (m, 4H), 2.15-2.18 (m, 4H), 4.21 (dd, J = 2 and 7 Hz, 1H), 4.93 (d, J = 47 Hz, 2H), 5.07-5.12 (m, 2H), 5.66 (dt, J = 2 and 7 Hz, 1H); ^{13}C NMR δ 16.0, 17.7, 25.7, 26.4, 26.7, 34.6, 39.7, 58.5, 80.3 (d, J_{CF} = 161 Hz), 123.2, 124.2, 129.1 (d, J_{CF} = 8 Hz), 131.3, 135.8, 137.8 (d, J_{CF} = 14 Hz); ^{19}F NMR δ 124.8 (t, J = 48 Hz); HRMS calc'd for $C_{15}H_{25}FO$: 240.1189, found: 240.1189.

Ethyl 4,4-difluoroacetoacetate (13). In an oven-dried flask equipped with an addition funnel and a reflux condenser, Zn (8.80 g, 135.0 mmol) was suspended in 30 mL of anhydrous Et_2O. Dibromoethane (0.5 mL) was added; the mixture was heated to reflux and then cooled to room temperature. Ethyl difluoroacetate (5.4 mL, 54.0 mmol) was added. Ethyl bromoacetate (15.0 mL, 135 mmol) in 70 mL of Et_2O was added dropwise. The addition was controlled so that a gentle reflux was maintained. After addition was complete (1 h), the solution was heated at reflux for an additional hour, at which time almost all the Zn was consumed. The light green solution was cooled in an ice bath and quenched with 1 *M* HCl with stirring. The Et_2O layer was separated, washed with 1 *M* HCl, water, dried, and concentrated to afford 7.8 g (88%) of a yellow oil. A portion of the oil was distilled for characterization [bp = 153-154 °C (lit[15b] 162 °C)]: Mixture of keto and enol tautomers (35:65) ^{1}H NMR δ 1.29 (t, J = 7 Hz, 3H, keto), 1.32 (t, J = 7 Hz, 3H, enol), 3.70 (t, J = 1 Hz, 2H, keto), 4.23 (q, J = 7 Hz, 2H, keto), 4.26 (q, J = 7 Hz, 2H, enol), 5.49 (s, 1H, enol), 5.91 (t, J = 54 Hz, 1H, keto), 6.03 (t, J = 54 Hz, 1H, enol), 11.80 (s, 1H, enol); ^{19}F NMR δ 34.0 (d, J = 55 Hz, keto), 35.3 (d, J = 55 Hz, enol); MS *m/z* (rel int) 166 (M, 7.3), 121 (86.3), 115 (100), 87 (53.0), 73 (20.0), 69 (56.9), and 51 (28.5). Chromatography of a portion (0.75 g) of the crude reaction mixture with 1:4 Et_2O:hexane gave two fractions. The first fraction (0.168 g, 22%) was identified as the hydrate of **13**: ^{1}H NMR δ 1.28 (t, J = 7 Hz, 3H), 2.76 (s, 2H), 4.18 (q, J = 7 Hz, 2H), 5.00 (s, 1H), 6.04 (t J = 56 Hz, 1H); ^{13}C NMR δ 14.0, 37.5, 61.2, 72.0 (t, J_{CF} = 22 Hz), 115.7 (t, J_{CF} = 248 Hz), 170.7; ^{19}F NMR δ 29.6 (d, J = 56 Hz). The second fraction (0.34 g, 45%) was a mixture of the keto and enol tautomers of **13** and the hydrate.

Ethyl 2-(3,7-dimethylocta-2,6-diene)-4,4-difluoroacetoacetate (14). NaH (0.36 g, 7.53 mmol) was suspended in 15.0 mL of anhydrous ether under nitrogen and cooled to 0 °C. Ethyl 4,4-difluoroacetoacetate (2.50 g, 15.0 mmol) was added dropwise, and the solution was warmed to room temperature and stirred for 1 h. Ether was removed under reduced pressure, and the resulting yellow solid was suspended in anhydrous acetone (30 mL) under nitrogen. KI (0.125 g, 0.75 mmol) was added followed by geranyl bromide (1.6 mL, 8.28 mmol), and the solution was heated at reflux for 48 h. The mixture was concentrated at reduced pressure, diluted with ether, washed with water, 1 *M* HCl, and brine, dried, and concentrated to give 3.51 g of a brown oil. The oil was purified by silica gel chromatography, eluting with 1:15 EtOAc:hexanes to give 1.16 g (73%) of

a yellow oil: IR (neat) 2987, 2931, 1758, 1733, 1463, 1378 cm^{-1}; ^1H NMR (data given for keto form only) δ 1.29 (t, J = 7 Hz, 3H), 1.61, (s, 3H), 1.66 (s, 3H), 1.70 (s, 3H), 1.95-2.10 (m, 4H), 2.60-2.74 (m, 2H), 3.85 (dd, J = 7 and 8 Hz, 1H), 4.19 (m, 2H), 5.00-5.10 (m, 2H), 5.86 (t, J = 54 Hz, 1H); ^{13}C NMR (data given for keto form only) δ 14.0, 16.0, 17.6, 25.6, 26.1, 26.4, 39.6, 53.1, 61.8, 109.4 (t, J = 251 Hz), 118.8, 123.8, 131.6, 139.1, 167.9, 194.6 (t, J = 26 Hz); ^{19}F NMR δ 34.0 (d, J = 55 Hz, keto), 39.0 (d, J = 63 Hz, enol); HRMS calc'd for $C_{16}H_{24}F_2O_3$: 302.1693, found: 302.1702.

1-Difluoromethyl-6,10-dimethylundeca-5,10-diene-2-one (15). Ester **14** (1.19 g, 3.94 mmol) was dissolved in 15 mL of DMF. LiCl (0.334 g, 7.88 mmol), and water (70 μL) were added, and the mixture was heated at reflux for 4 h. The DMF was removed under reduced pressure. The residue was diluted with EtOAc and water. The organic layer was washed with water and brine, dried, and concentrated to afford a dark brown oil. The oil was purified by silica gel chromatography, eluting with 1:10:250 MeOH:EtOAc:hexane to afford 488 mg (50%) of a yellow oil: IR (neat) 2977, 2931, 2856, 1748, 1448, 1382, 1340 cm^{-1}; ^1H NMR δ 1.60 (s, 3H), 1.63 (s, 3H), 1.68 (s, 3H), 1.92-2.12 (m, 4H), 2.33 (dd, J = 8 and 7 Hz, 2H), 2.70 (t, J = 7 Hz, 2H), 5.03-5.12 (m, 2H), 5.67 (t, J = 54 Hz, 1H); ^{13}C NMR δ 16.0, 17.6, 21.0, 25.6, 26.5, 36.3, 39.6, 109.8 (t, J_{CF} = 252 Hz), 121.5, 124.0, 131.5, 137.2, 199.5 (t, J_{CF} = 26 Hz); ^{19}F NMR δ 34.6 (d, J = 55 Hz); HRMS calc'd for $C_{13}H_{20}F_2O$: 230.1482, found: 230.1462.

Ethyl (*Z*)-3-difluoromethyl-7,11-dimethyldodeca-2,6,9-trienoate (16). Using a procedure similar to that described for **11**, ketone **15** (53 mg, 0.23 mmol) was converted to ester **16** with triethyl phosphonoacetate (0.11 mL, 0.57 mmol). The *Z* isomer was isolated by preparative thin layer chromatography, eluting 4 times with 1:80 ethyl acetate: hexanes to afford **16** in 47% yield: IR (neat) 2968, 2930, 2874, 1722, 1446 cm^{-1}; ^1H NMR δ 1.29 (t, J = 7 Hz, 3H), 1.61 (s, 6H), 1.68 (s, 3H), 1.97-2.10 (m, 4H), 2.18-2.36 (m, 4H), 4.19 (q, J = 7 Hz, 2H), 5.05-5.15 (m, 2H), 5.92 (s, 1H), 7.38 (t, J = 55 Hz, 1H); ^{13}C NMR δ 14.1, 16.0, 17.6, 25.6, 26.1, 26.6, 29.6, 39.6, 60.8, 64.6, 110.6, (t, J_{CF} = 234 Hz), 122.3, 122.6 (t, J_{CF} = 8 Hz), 124.1, 131.4, 136.8, 151.0 (t, J_{CF} = 23 Hz); ^{19}F NMR δ 41.6 (d, J = 56 Hz); HRMS calc'd for $C_{17}H_{26}F_2O_2$: 300.1901, found: 300.1901.

E isomer: IR 2978, 2967, 2931, 1725, 1665, 1367 cm^{-1}; ^1H NMR δ 1.31 (t, J = 7 Hz, 3H), 1.60 (s, 3H), 1.61 (s, 3H), 1.68 (s, 3H), 1.95-2.10 (m, 4H), 2.20-2.30 (m, 2H), 2.61-2.70 (m, 2H), 4.21 (q, J = 7 Hz, 2H), 5.08 (t, J = 7 Hz, 1H), 5.17 (t, J = 7 Hz, 1H), 6.03 (t, J = 56 Hz, 1H), 6.06 (s, 1H); ^{13}C NMR δ 14.1, 15.9, 17.6, 25.6, 26.7, 27.3, 39.7, 60.5, 115.3 (t, J_{CF} = 240 Hz), 121.3 (t, J_{CF} = 15 Hz), 122.9, 124.3, 131.4, 136.5, 150.6 (t, J_{CF} = 22 Hz), 165.1; ^{19}F NMR δ 43.6 (d, J = 55 Hz); HRMS calc'd for $C_{17}H_{26}F_2O_2$: 300.1901, found: 300.1891.

(*Z*)-3-Difluoromethyl-7,11-dimethyl-2,6,9-trien-1-ol (17). Using a procedure similar to that described for **12**, ester **16** (0.126 g, 0.42 mmol) was reduced with DIBAL (0.92 mL, 0.92 mmol) to afford **17** as a light yellow oil in 64% yield: IR (neat) 3370, 2964, 2926, 2856, 1450 cm^{-1}; ^1H NMR δ 1.60 (s, 6H), 1.68 (s, 3H), 1.96-2.10 (m, 4H), 2.15-2.20 (m, 2H), 4.25-4.32 (m, 2H), 5.10-5.14 (m, 2H), 5.79 (t, J = 7 Hz, 1H), 6.48 (t, J = 55 Hz, 1H); ^{13}C NMR δ 16.0, 17.7, 25.7, 26.6, 26.7, 29.9, 39.6, 58.1, 112.7 (t, J_{CF} = 235 Hz), 123.0, 124.2, 132.5 (t, J_{CF} = 9 Hz), 131.4, 135.4 (t, J_{CF} = 21 Hz), 136.1; ^{19}F NMR δ 46.1 (d, J = 55 Hz); HRMS calc'd for $C_{15}H_{24}F_2O$: 258.1795, found: 258.1805.

Ethyl 2-(3,7-dimethylocta-2,6-diene)-4-trifluoroacetoacetate (19). Using a procedure similar to that described for **14**, ethyl 4,4,4-trifluoroacetoacetate (1.0 mL, 6.8 mmol) was alkylated with geranyl bromide (1.6 g, 7.5 mmol) upon heating at reflux for 72 h. The resulting brown oil was purified by silica gel

chromatography, eluting with 1:15 EtOAc:hexanes to give 1.486 g (68%) of **19** as a yellow oil: IR (neat) 2984, 2930, 1770, 1743, 1446 cm^{-1}; ^1H NMR δ 1.26 (t, J = 7 Hz, 3H); 1.59 (s, 3H), 1.63 (s, 3H), 1.66 (s, 3H), 1.92-2.10 (m, 4H), 2.65-2.75 (m, 2H), 3.86 (t, J = 7 Hz, 1H), 4.20 (q, J = 7 Hz, 2H), 5.00-5.10 (m, 2H); ^{13}C NMR δ 13.8, 16.0, 17.5, 25.5, 26.4, 26.6, 39.6, 53.3, 62.1, 115.2 (q, J_{CF} = 290 Hz), 118.2, 123.7, 131.5, 139.7, 166.8, 186.7 (q, J_{CF} = 36 Hz); ^{19}F NMR δ 84.0 (s); HRMS calc'd for $C_{16}H_{23}F_3O_3$: 320.1599, found: 320.1583.

1-Trifluoromethyl-6,10-dimethylundeca-5,10-diene-2-one (20). Using a procedure similar to that described for **15**, compound **19** (0.200 g, 0.62 mmol) was decarboxylated with LiCl (53 mg, 1.2 mmol). The resulting brown oil was purified by silica gel chromatography, eluting with 1:10 EtOAc:hexane to afford 0.104 g (68%) of a light yellow oil: IR (neat) 2970, 2920, 1765, 1450 cm^{-1}; ^1H NMR δ 1.59 (s, 3H), 1.63 (s, 3H), 1.67 (s, 3H), 1.90-2.15 (m, 4H), 2.30-2.41 (m, 2H), 2.74 (t, J = 7 Hz, 2H), 5.00-5.20 (m, 2H); ^{13}C NMR δ 16.0, 17.6, 21.1, 25.6, 26.5, 36.6, 39.6, 115.5 (q, J_{CF} = 290 Hz), 120.9, 123.9, 131.5, 137.7, 191.0 (q, J_{CF} = 35 Hz); ^{19}F NMR δ 82.6 (s); HRMS calc'd for $C_{13}H_{19}F_3O$: 248.1388, found: 248.1387.

Ethyl (*Z*)-3-(trifluoromethyl)-7,11-dimethyldodeca-2,6,9-trienoate (21). Using a procedure similar to that described for **11**, ketone **20** (0.80 g, 3.2 mmol) was converted to ester **21** with triethyl phosphonoacetate (0.80 mL, 4.0 mmol). The oil was purified by silica gel chromatography, eluting with 1:50 EtOAc:hexane. The oil was further purified by preparative thin layer chromatography, eluting with 1:50 EtOAc:hexane to give 0.206 g (26%) of the *Z* isomer: IR (neat) 2970, 2928, 1740, 1448 cm^{-1}; ^1H NMR δ 1.30 (t, J = 7 Hz, 3H), 1.60 (s, 3H), 1.61 (s, 3H), 1.68 (s, 3H), 1.95-2.10 (m, 4H), 2.20- 2.37 (m, 4H), 4.23 (q, J = 7 Hz, 2H), 5.00-5.15 (m, 2H), 6.03 (s, 1H); ^{13}C NMR δ 13.9, 16.0, 17.6, 25.6, 25.9, 26.6, 31.4, 39.6, 61.3, 121.6, 122.5 (q, J_{CF} = 274 Hz), 124.0, 124.9, 131.4, 137.2, 138.1 (q, J_{CF} = 30 Hz), 164.6; ^{19}F NMR δ 98.8 (s); HRMS calc'd for $C_{17}H_{25}F_3O_2$: 318.1806, found: 318.1789.

E isomer: IR (neat) 2980, 2930, 2860, 1730, 1450 cm^{-1}; ^1H NMR δ 1.30 (t, J = 7 Hz, 3H), 1.59 (s, 3H), 1.62 (s, 3H), 1.68 (s, 3H), 1.94-2.10 (m, 4H), 2.20-2.30 (m, 2H), 2.65-2.72 (m, 2H), 4.22 (q, J = 7 Hz, 2H), 5.05-5.10 (m, 1H), 5.12-5.20 (m, 1H), 6.30 (m, 1H); ^{13}C NMR δ 14.1, 15.8, 17.6, 25.6, 26.6, 26.8, 27.4, 39.7, 60.8, 122.17 (q, J_{CF} = 7 Hz), 123.5 (q, J_{CF} = 274 Hz), 122.4, 124.2, 131.3, 136.7, 145.6 (q, J_{CF} = 112 Hz), 164.5; ^{19}F NMR δ 93.1 (s); HRMS calc'd for $C_{17}H_{25}F_3O_2$: 318.1806, found: 318.1812.

(*Z*)-3-Trifluoromethyl-7,11-dimethyl-2,6,9-trien-1-ol (22). Using a procedure similar to that described for **12**, ester **21** (0.234 g, 0.74 mmol) was reduced with DIBAL (1.7 mL, 1.6 mmol). The resulting yellow oil was purified by silica gel chromatography eluting with 1:8 EtOAc:hexane to give 148 mg (74%) of a light yellow oil: IR (neat) 3330, 2968, 2928, 1450, 1377 cm^{-1}; ^1H NMR δ 1.60 (s, 6H), 1.68 (s, 3H), 1.96-2.15 (m, 4H), 2.16-2.22 (m, 4H), 4.39 (s, 2H), 5.05-5.10 (m, 2H), 5.86 (t, J = 6 Hz, 1H); ^{13}C NMR δ 16.0, 17.7, 25.7, 26.7, 26.8, 31.7, 36.7, 59.1, 122.3, 124.1 (q, J_{CF} = 270 Hz), 124.2, 129.8 (q, J_{CF} = 29 Hz), 131.4, 136.1, 136.6; ^{19}F NMR δ 101.2 (s); HRMS calc'd for $C_{15}H_{23}F_3O$: 276.1701, found 276.1703.

5,9-Dimethyldeca-4,8-diene-1-ol (24). In an oven-dried flask equipped with a reflux condenser and an addition funnel, LAH (0.388 g, 10.22 mmol) was suspended in 10 mL of anhydrous ether under N_2. Ethyl 5,9-dimethyldeca-4,8-dieneoate (**23**)[20] (1.907 g, 8.52 mmol) in 10 mL of anhydrous ether was added dropwise. The mixture was stirred for 45 min. Excess LAH was quenched with dropwise addition of 33 μL of H_2O, 33 μL of 15% NaOH, and 99 μL of H_2O. The resulting granular solid was removed by filtration. The filtrate was dried, and concentrated to afford 1.45 g of an oil which was purified by silica gel chromatography with 1:4 EtOAc:hexanes to give 1.41 g (91%) of a colorless oil: IR (neat) 3310, 2960, 2920, 2850, 1435, 1370 cm^{-1}; ^1H

NMR δ 1.61 (s, 6H), 1.68 (s, 3H), 1.96-2.10 (m, 8H), 2.18 (s, 1H), 3.62 (t, J = 7 Hz, 2H), 5.05-5.18 (m, 2H); ^{13}C NMR δ 15.6, 17.3, 23.9, 25.3, 26.3, 32.3, 39.3, 62.1, 123.3, 123.8, 130.9, 135.2; HRMS calc'd for $C_{12}H_{22}O$: 182.1669, found: 182.1671.

5,9-Dimethyl deca-4,8-diene-1-al (25). Alcohol **24** (0.887 g, 4.872 mmol) was dissolved in 20 mL of anhydrous CH_2Cl_2 under N_2. Powdered 4Å sieves (2.436 g) and NMO (0.856 g, 7.31 mmol) were added. The solution was cooled to 0 °C and TPAP (0.086 g, 0.24 mmol) was added. The solution was stirred for 30 min., warmed to room temperature, and stirred overnight. The reaction mixture was passed through a 2x4 cm column of silica gel, eluting with CH_2Cl_2. The solution was concentrated to give 800 mg (91% crude yield) of a yellow oil. A small sample was purified by silica gel chromatography for analysis: IR (neat) 2960, 2910, 2850, 2710, 1725, 1440, 1375 cm^{-1}; ^{1}H NMR δ 1.59 (s, 3H), 1.63 (s, 3H) 1.68 (s, 3H), 1.94-2.12 (m, 4H), 2.28-2.38 (m, 2H), 2.43-2.50 (m, 2H), 5.04-5.20 (m, 2H), 9.76 (t, J = 2 Hz, 1H); ^{13}C NMR δ 16.0, 17.6, 20.8, 25.6, 26.5, 39.5, 43.9, 122.0, 124.0, 131.4, 136.8, 202.6.

Ethyl 7,11-dimethyl dodeca-2,6,10-trieneoate (26). Using a procedure similar to that described for **11**, ester **26** was obtained from ketone **25** (0.887 g, 4.87 mmol) and triethyl phosphonoacetate (0.97 mL, 4.89 mmol) using toluene as the solvent. The product was purified by silica gel chromatography, eluting with 1:40 MeO*t*-Bu:hexane to give 0.551 g (49% from **24**) of a colorless oil: IR (neat) 2970, 2910, 2850, 1720, 1650, 1440 cm^{-1}; ^{1}H NMR δ 1.28 (t, J = 7 Hz, 3H), 1.60 (s, 6H), 1.68 (s, 3H), 1.96-2.30 (m, 8H), 4.17 (q, J = 7, 2H), 5.04-5.16 (m, 2H), 5.82 (dt, J = 1 and 16 Hz, 1H), 6.97 (dt, J = 7 and 16 Hz, 1H); ^{13}C NMR δ 14.1, 15.9, 17.5, 25.5, 26.4, 26.5, 32.3, 39.5, 59.9, 121.3, 122.7, 124.1, 131.2, 136.2, 148.7, 166.5; HRMS calc'd for $C_{16}H_{26}O_2$: 250.1932, found: 250.1924.

7,11-Dimethyl dodec-2,6,10-triene-1-ol (27). Using a procedure similar to that described for **12**, ester **26** (0.108 g, 0.43 mmol) was reduced with DIBAL (1.05 mL, 1.05 mmol). Alcohol **27** was isolated by silica gel chromatography, eluting with 1:9 EtOAc:hexane to afford 0.355 g (93%) of a colorless oil: IR (neat) 3300, 2960, 2910, 2840, 1435, 1370 cm^{-1}; ^{1}H NMR δ 1.60 (s, 6H), 1.68 (s, 3H), 1.95-2.13 (m, 8H), 4.07 (d, J = 5 Hz, 2H), 5.04-5.16 (m, 1H), 5.62-5.70 (m, 2H); ^{13}C NMR δ 16.0, 17.7, 25.7, 26.7, 27.6, 32.4, 39.7, 63.6, 123.3, 124.2, 129.0, 131.2, 132.8, 135.5; HRMS calc'd for $C_{14}H_{24}O$: 208.1827, found: 208.1832.

General Procedure for synthesis of diphosphates 1-4.

The alcohol (0.09-0.11 mmol, 1.0 eq) was dissolved in 0.5 mL of CH_2Cl_2 under N_2. CBr_4 (1.2 eq.) and PPh_3 (1.05 eq) were added, and the solution was stirred at room temperature for 2-4 h. Hexane was added, and the resulting white solid was removed by filtration. The filtrate was concentrated under reduced pressure to afford the allylic bromide in quantitative yield. For **4**, the tosylate was made according to the procedure of Davisson.[13] The bromide or tosylate (1.0 eq.) was dissolved in acetonitrile (0.5 mL) under nitrogen and tris(tetrabutylammonium) hydrogen diphosphate[13] (2.0 eq.) was added as a solid. The cloudy solution was stirred for 2 h and then concentrated under reduced pressure. The residue was applied to a 1.5 x 12 cm column of Dowex (NH_4^+ form) and eluted with 20-25 mL of 25 m*M* NH_4HCO_3/2% *i*-PrOH. The eluant was frozen and lyophilized. The diphosphates (**1-4**) were purified by preparative reversed phase HPLC on a C_{18} column [Shodex (Asahipak)], eluting with a linear gradient of 10% CH_3CN in 25 m*M* NH_4HCO_3 to 100% CH_3CN over 45 min.

13-Fluorofarnesyl diphosphate (1) was isolated in 59% yield as a white solid: ^{1}H NMR (D_2O) δ 1.57 (s, 6H), 1.62 (s, 3H), 1.94-2.10 (m, 4H), 2.15-2.15 (m, 4H), 4.47-4.56 (m, 2H), 5.01 (d, J = 47 Hz, 2H), 5.10-5.20 (m, 2H), 5.65-5.75 (m, 1H); ^{13}C NMR [D_2O, 3-(trimethylsilyl)propionic acid, sodium salt as internal

standard] δ 17.9, 19.7, 27.5, 28.4, 28.6, 36.5, 41.5, 64.1, 83.7 (d, J_{CF} = 154 Hz), 126.5, 127.0, 129.3 (d, J_{CF} = 8 Hz), 136.1, 139.5, 141.4 (d, J_{CF} = 13 Hz); ^{19}F NMR (D_2O, referenced to external TFA) δ 40.0 (t, J = 49 Hz); ^{31}P NMR δ -6.13 (d, J = 22 Hz), -10.42 (d, J = 22 Hz); MS (Negative ion FAB, glycerol/H_2O) 399 (M - 1).

13-Difluorofarnesyl diphosphate (**2**) was isolated in 48% yield as a white solid: ^{1}H NMR (D_2O) δ 1.43 (s, 3H), 1.45 (s, 3H), 1.51 (s, 3H), 1.78-1.95 (m. 4H), 2.03 (br s, 4H), 4.40-4.50 (br s, 2H), 4.90-5.05 (m, 2H), 5.74 (s, 1H), 6.59 (t, J = 55 Hz, 1H); ^{13}C NMR [D_2O, 3-(trimethylsilyl)propionic acid, sodium salt as internal standard] δ 17.6, 19.3, 27.2, 28.7, 28.9, 31.6, 41.5, 63.1, 115.53 (t, J_{CF} = 234 Hz), 105.8, 126.7, 132,7 (m), 134.2, 138.2 (t, J_{CF} = 22 Hz), 138.7; ^{19}F NMR (D_2O, referenced to TFA) δ -185.8 (d, J = 55 Hz); ^{31}P NMR δ -6.30 (d, J = 22 Hz), -10.62 (d, J = 22 Hz); MS (Negative ion FAB, glycerol/H_2O) 417 (M - 1).

13-Trifluorofarnesyl diphosphate (**3**) was obtained in 71% yield as a white solid: ^{1}H NMR (D_2O) δ 1.53 (s, 3H), 1.54 (s, 3H), 1.60 (s, 3H), 1.88-2.08 (m, 4H), 2.10-2.20 (m, 4H), 4.63 (br s, 2H), 5.06-5.16 (m, 2H), 5.98 (t, J = 5 Hz, 1H); ^{13}C NMR [D_2O, 3-(trimethylsilyl)propionic acid, sodium salt as internal standard] δ 18.1, 19.8, 27.8, 28.9, 29.3, 34.1, 41.8, 64.7, 126.9 (q, J_{CF} = 273 Hz), 125.6, 127.1, 132.6 (q, J_{CF} = 28 Hz), 135.0, 136.7 (br), 139.6; ^{19}F NMR (D_2O, referenced to external TFA) δ 15.4 (s); ^{31}P NMR δ -6.13 (d, J = 21 Hz), -10.34 (d, J = 22 Hz); MS (Negative ion FAB, glycerol/H_2O) 435 (M - 1).

13-Desmethylfarnesyl diphosphate (**4**) was isolated in 76% yield as a white solid: ^{1}H NMR (D_2O) δ 1.57 (s, 6H), 1.63 (s, 3H), 1.94-2.10 (m, 8H), 4.34 (t, J = 6 Hz, 2H), 5.10-5.22 (m, 2H), 5.59-5.70 (m, 1H), 5.76-5.88 (m, 1H); ^{13}C NMR [D_2O, 3-(trimethylsilyl)propionic acid, sodium salt as internal standard] δ 18.1, 19.8, 27.7, 28.8, 29.7, 34.7, 41.8, 69.3 (d, J_{CP} = 4 Hz), 126.8, 127.1, 128.5 (d, J_{CP} = 7 Hz), 135.3, 137.9, 139.0; ^{31}P NMR δ -6.25 (d, J = 22 Hz), -10.43 (d, J = 22 Hz); MS (Negative ion FAB, glycerol/H_2O) 367 (M - 1).

Acknowledgements

This work was supported by National Institutes of Health Grant GM 21328.

REFERENCES

1. Clarke, S. *Ann. Rev. Biochem.* **1992**, *61*, 355-386.
2. Schafer, W. R.; Kim, R.; Stern, R.; Thorner, J.; Kim, S.-H.; Rine, J. *Science* **1989**, *245*, 379-385.
3. Pauling, L. "The Nature of the Chemical Bond", 3rd ed.; Cornell University Press; Ithica, New York, 1960, p. 93.
4. (a) Gebler, J. C.; Woodside, A. B.; Poulter, C. D. *J. Am. Chem. Soc.* **1992**, *114*, 7354-7360. (b) Poulter, C. D.; Wiggins, P. L.; Le, A. T. *J. Am. Chem. Soc.* **1981**, *103*, 3926.
5. Meulbacher, M.; Poulter, C. D. *Biochemistry* **1988**, *27*, 7315-7328.
6. Dolence, J. M.; Poulter, C. D. *Proc. Natl. Acad. Sci.* USA, in press.
7. (a) Poulter, C. D.; Satterwhite, D. M. *Biochemistry* **1977**, *16*, 5470. (b) Poulter, C. D.; Wiggins, P. L.; Plummer, T. L. *J. Org. Chem.* **1981**, *46*, 1532-1538. (c) Ortiz de Montellano, P. R.; Vinson, W. A. *J. Am. Chem. Soc.* **1979**, *101*, 2222-2224.
8. Camps, F.; Canela, R.; Coll, J.; Messeguer, A.; Roca, A. *Tetrahedron* **1978**, *34*, 2179-2182.
9. (a) Fraser, R. R.; Millington, J. E.; Pattison, F. L. M. *J. Am. Chem. Soc.* **1957**, *79*, 1959-1961. (b) Taylor, E. C.; Turchi, I. *J. Org. Prep. Proc. Int.* **1978**, *10*, 221.

10. Meul, T.; Miller, R.; Tenud, L. *Chimia* **1987**, *41*, 73-76.
11. Miyashita, N.; Yoshikoshi, A.; Grieco, P.A.; *J. Org. Chem.* **1977**, *42*, 3772-3774.
12. Bishop, J. E.; Mathis, C. A.; Gerdes, J. M.; Whitney, J. M.; Eaton, A. M.; Mailman, R. B. *J. Med. Chem.* **1991**, *34*, 1612-1624.
13. (a) Davisson, V. J.; Woodside, A B.; Neal, T. R.; Stremler, K. E.; Meuhlbacher, M.; Poulter, C. D. *J. Org. Chem.* **1986**, *51*, 4768-4779. (b) Davisson, V. J.; Neal, T. R.; Poulter, C. D. *J. Am. Chem. Soc.* **1993**, *115*, 1235-1245.
14. Zhang, D.; Poulter, C. D. *Anal. Biochem.* **1993**, *213*, 356-361.
15. (a) Henne, A. L.; Newman, M. S.; Quill, L. L.; Staniforth, R. A. *J. Am. Chem. Soc.* **1947**, *69*, 1819. (b) McBee, E. T.; Pierce, O. R.; Kilbourne, H. W.; Wilson, E. R. *J. Am. Chem. Soc.* **1953**, *75*, 3152-3153.
16. Furstner, A. *Synthesis* **1989**, 571-590.
17. (a) Begue, J.-P.; Charpentier-Morize, M.; Nee, G. *J. Chem. Soc. Chem. Commun.* **1989**, 83. (b) Aubert, C.; Begue, J.-P.; Charpentier-Morize, M.; Langlois, B. *J. Fluorine Chem.* **1989**, *44*, 361-376.
18. Aubert, C.; Begue, J.-P.; Charpentier-Morize, M.; Nee, G.; Langlois, B. *J. Fluorine Chem.* **1989**, *44*, 377-394.
19. Kuwajima, I.; Doi, Y. *Tetrahedron Lett.* **1972**, *12*, 1163-1166.
20. (a) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc. Chem. Commun.* **1987**, 1625-1627. (b) Ley, S. V.; Norman, J.; Griffith, W. P.; Mersden, S. P. *Synthesis* **1994**, 639.

(*Received* 4 *July* 1995)