λ_{max} (ϵ) (pH 11) 303 nm (15 100); ^{1}H NMR (Me_2SO-d_6) δ 15.84 (broad singlet, 1, 3-NH), 10.54 (s, 1, 5-NH), 8.44 (d, 1, H-7, $J_{6,7}$ = 9.6 Hz), 8.00 (d, 1, H-6, $J_{6,7}$ = 9.6 Hz), 4.22 (q, 2, CH_2CH_3), 1.31 (t, 3, CH_2CH_3). Anal. Calcd for $C_8H_9N_5O_2$: C, 46.37; H, 4.38; N, 33.80. Found: C, 46.22; H, 4.42; N, 33.67.

Registry No.—**1**, 38359-73-8; **2**, 22860-91-9; **3**, 62805-39-4; **4**, 67505-63-9; **5**, 62805-40-7; **6**, 67505-64-0; **7**, 67505-65-1; **8**, 67505-66-2; **9**, 67505-67-3; **10**, 67505-68-4; **11**, 67505-69-5; **12**, 62805-41-8; **13**, 67505-70-8; **14**, 62805-42-9; **15** 2 HCl, 53995-24-7; **16**, 62805-37-2; **17**, 60282-60-2; **18**, 67505-71-9; **19**, 67505-72-0; **20**, 67505-73-1; **21**, 60282-66-8; **22**, 67505-74-2.

References and Notes

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(25) Subsequent to our communication on the synthesis[2,18] of **17**, another synthetic route[23] for the preparation of **17** was described using 2,3,6-triaminopyridin-4-one (2 HCl, 0.2 C_2H_6O) as starting material. Ring closure of this material afforded a 47% yield of **17**.

Synthesis and Carbon-13 Nuclear Magnetic Resonance Spectra of *all-trans*-Geranylgeraniol and Its Nor Analogues

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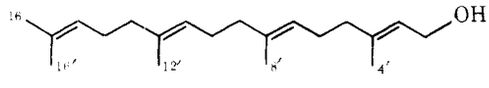
Syntheses of the five possible nor analogues of *all-trans*-geranylgeraniol are described. The 4′-nor isomer (**10**) is prepared from *trans,trans*-farnesol by means of two-carbon chain extension and phosphonate olefination reactions (Scheme I). The 16′- and 16-nor analogues (**26** and **27**) are obtained through Biellmann isoprenoid coupling reactions of 3-methyl-2,6(*E,Z*)-octadien-1-yl phenyl sulfide (8′-norgeranyl phenyl sulfide, **22**) and its 6,7(*E*) isomer (**23**) with benzyl 8-chloro-3,7-dimethyl-2,6(*E,E*)-octadien-1-yl ether (**15**, Scheme II). The Wittig–Schlosser reaction for stereoselective trans olefination is the key reaction in the synthetic routes (Scheme IV) to 8′-nor- and 12′-norgeranylgeraniol (**34** and **43**). Proton-decoupled carbon-13 NMR spectral data are reported for *all-trans*-geranylgeraniol and the series of nor analogues and the distinctive shifts associated with the disubstituted double bonds and nearby carbons are noted.

Structural analogues of *trans,trans*-farnesyl pyrophosphate and 2,3-dihydrosqualene 2,3-oxide lacking one or more of the methyl groups have proven useful in investigations on the mechanism and substrate specificity of squalene synthetase[2] and various triterpene cyclases.[3] Since *all-trans*-geranylgeranyl pyrophosphate (1-OPP) serves similarly as the



1-OH

biosynthetic precursor of the diterpene and carotene families of natural products, it would clearly be desirable to have synthetic access to its nor analogues. In this paper we report syntheses of the five possible nor analogues of *all-trans*-geranylgeraniol as well as carbon-13 NMR spectral data for the parent diterpene alcohol and the series of nor analogues.

all-trans-Geranylgeraniol (1-OH) was synthesized by two different methods previously described in the literature, one originating from *trans,trans*-farnesol[4] and the other from geraniol.[5] In the former approach (Scheme I) *trans,trans*-farnesylacetone (**3**) was prepared by alkylation of ethyl sodioacetoacetate with farnesyl bromide (**2**-Br) followed by hydrolysis and decarboxylation of the resulting β-keto ester.[4b,c] Condensation of farnesylacetone with the sodium salt of trimethyl phosphonoacetate[4d] afforded methyl *all-trans*-geranylgeranate (**4**) which, after purification by column chromatography to remove a small amount of the 2,3-cis isomer, was reduced to geranylgeraniol (1-OH) with lithium aluminum monoethoxyhydride.[6]

The preceding reaction sequence was modified in order to synthesize 4′-norgeranylgeraniol (**10**). The reaction of farnesyl

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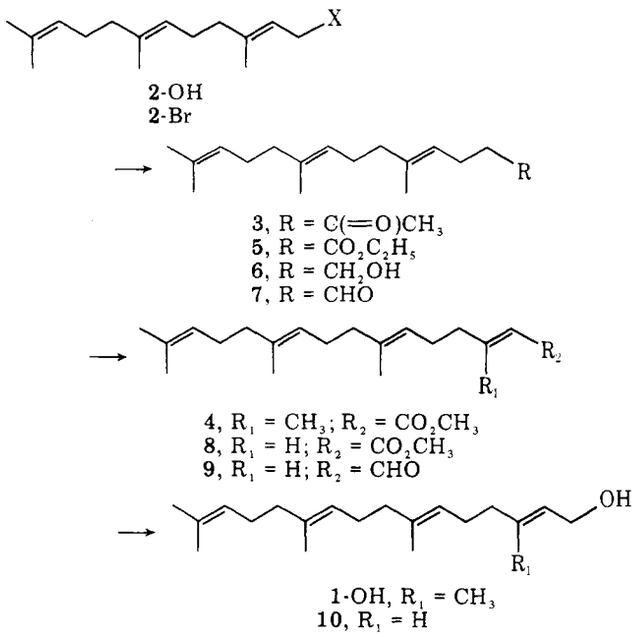
Scheme I



bromide with the copper–lithium enolate of ethyl acetate[7] afforded ester **5**, which was converted to the corresponding aldehyde (**7**) by reduction with lithium aluminum hydride and oxidation with chromium trioxide–dipyridine complex in dichloromethane. The 4′-nor ester **8** was obtained as before by condensation with trimethylsodiophosphonoacetate. However, the reduction of **8** with lithium aluminum monoethoxyhydride was complicated by competitive formation of the conjugate reduction product (2,3-dihydro-**10**). Although 4′-norgeranylgeraniol (**10**) was isolated in pure form by chromatography on silver nitrate impregnated silica gel, the low yield (20%) led us to examine an alternative reaction sequence. Condensation of **7** with diethyl 2-(cyclohexylamino)-vinylphosphonate in the presence of sodium hydride[8] gave rise to the trans α,β-unsaturated aldehyde **9** following hydrolysis with aqueous oxalic acid. Sodium borohydride reduction of **9** furnished 4′-norgeranylgeraniol in 36% overall yield. The 15-Hz coupling constant between the vinyl protons on C-2 and C-3 in the α,β-unsaturated ester **8** and aldehyde **9** affirms the trans stereochemistry at this position.

The second synthetic route to *all-trans*-geranylgeraniol follows that reported by Altman, Ash, and Marson,[5a] but with modifications which facilitate operations on larger scale (Scheme II). Regioselective ozonolysis of benzyl geranyl ether in dichloromethane containing 1 equiv of pyridine[9] gave rise to aldehyde **12** in 43% yield after purification by bisulfite extraction. Ester **13** was obtained from a Wittig reaction between ethyl 2-(triphenylphosphoranylidene)propionate and **12** and was subsequently reduced to the previously reported hydroxy ether **14**[5a] with aluminum hydride.[10] The corresponding chloride (**15**) was prepared and utilized to alkylate 1-phenylthiogeranyllithium as described. Simultaneous reductive cleavage of the phenylthio and benzyl groups from the alkylated sulfide was conveniently accomplished by exposure to lithium in liquid ammonia with tetrahydrofuran as cosolvent at −78 °C. Although gram quantities of geranylgeraniol are readily prepared by this reaction sequence, GLC analysis of the trimethylsilyl derivative of the product shows the presence of three byproducts totaling approximately 20% of the mixture. The purity of the geranylgeraniol may be further enhanced by chromatography on silver nitrate impregnated silica gel.

The allylic crossed-coupling reaction was also employed for the synthesis of 16- and 16′-norgeranylgeraniol. The norgeraniol isomers required for this purpose were secured through stereoselective Wittig reactions of tetrahydropyranyloxyaldehyde **19**, which was available from partial ozonolysis of geranyl tetrahydropyranyl ether (Scheme III).[11] Thus, the reaction of ethylidenetriphenylphosphorane with **19** under the "salt-free" conditions[12] afforded 8-norgeraniol (**20**) after methanolysis of the tetrahydropyranyl protecting group. The trans isomer was formed from the same components by the Schlosser–Wittig method[13] as modified by Johnson and coworkers.[14] The *cis*- and *trans*-norgeranyl phenyl sulfides (**22** and **23**), prepared from the corresponding bromides by reaction with sodium thiophenoxide, were carried through the same three-step reaction sequence (Scheme II) to connect the 8,9 bond and produce the 16- and 16′-norgeranylgeraniol isomers **26** and **27**.

Scheme II

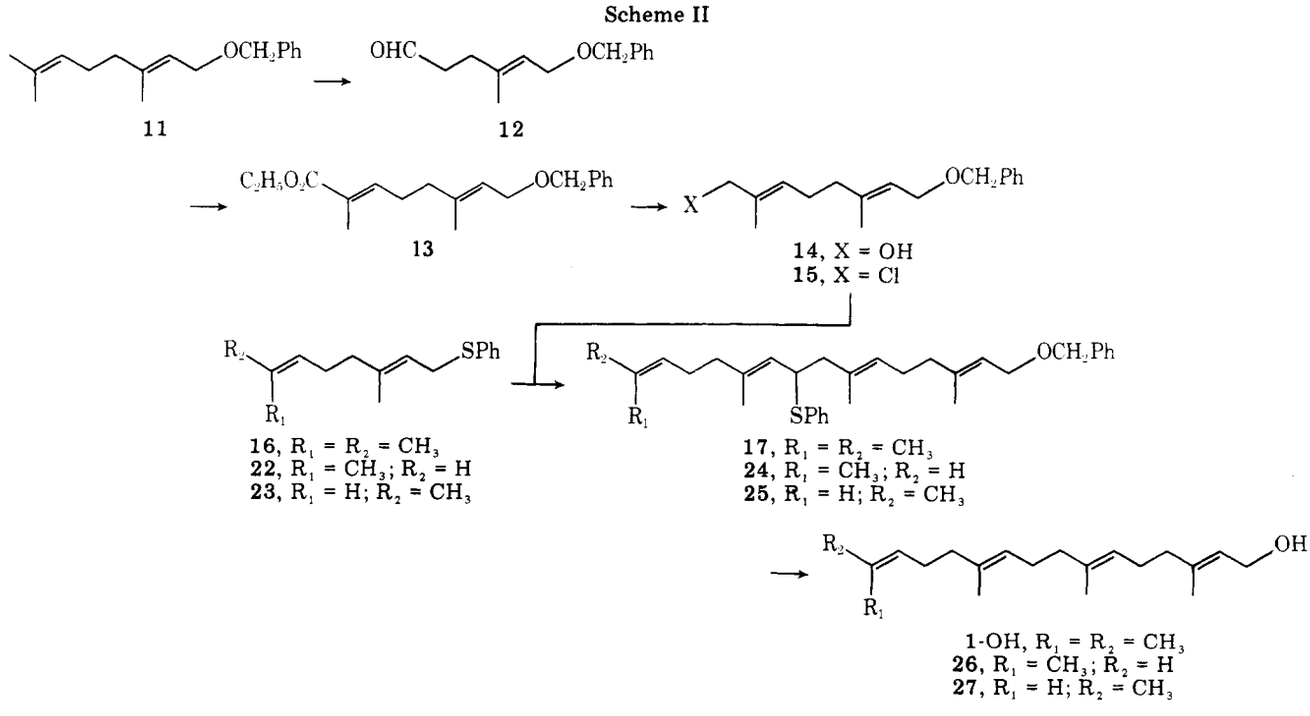
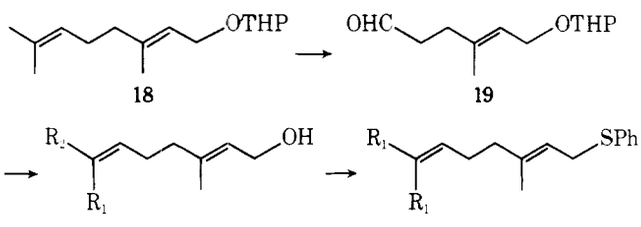


Table I. Carbon-13 NMR Chemical Shifts and Positional Assignments for *all-trans*-Geranylgeraniol (1-OH) and its Nor Analogues [e]

position	1-OH	4′-nor (10)	8′-nor (34)	12′-nor (43)	16′-nor (27)	16-nor (26)
1	59.4	63.8[d]	59.3	59.4	59.4	59.4
2	123.5	129.2	123.7	123.5	123.5	123.5
3	139.7	135.1[b]	139.4	139.7	139.8	139.7
4	39.6[b]	32.5	39.6	39.6[b]	39.6	39.6[b]
4′	16.3		16.3	16.3	16.3	16.3
5	26.8[c]	27.7	30.9[d]	26.3	26.4[b]	26.4[c]
6	123.9	123.8	129.8	124.0	123.8	123.9
7	135.5	135.6	130.5	135.2	135.4	135.4
8	39.8[b]	39.8	32.8	39.8[b]	39.6	39.7[b]
8′	16.0	16.0		16.0	16.0	16.0
9	26.7[c]	26.8[c]	28.1	31.1[d]	26.7[b]	26.7[c]
10	124.3	124.3	124.1	130.1	124.4	123.9
11	135.0	135.0[b]	135.3	130.1	134.8	134.7
12	39.8[b]	39.8	39.6	32.9	39.6	39.7[b]
12′	16.0	16.0	16.0		16.0	16.0
13	26.4[c]	26.7[c]	26.8	28.3	31.3[d]	26.6[d]
14	124.5	124.5	124.5	124.3	131.3	130.4
15	131.3	131.4	131.3	131.5	124.7	124.5
16	25.7	25.7	25.7	25.7	17.9	
16′	17.7	17.7	17.7	17.7		12.7

[a] Chemical shifts are relative to tetramethylsilane as internal standard. The solvent was chloroform-*d*. [b] These assignments may be interchanged. [c] These assignments may be interchanged. [d] The resonances within the block are from the disubstituted olefinic carbons and those carbons nearby which are perturbed appreciably by the disubstituted double bond. [e] Registry no.: 1-OH, 24034-73-9; **10**, 67858-73-5; **34**, 67858-74-6; **43**, 67858-75-7; **27**, 67858-76-8; **26**, 67919-58-8.

Scheme III



20, $R_1 = CH_3$; $R_2 = H$ **22**, $R_1 = CH_3$; $R_2 = H$
21, $R_1 = H$; $R_2 = CH_3$ **23**, $R_1 = H$; $R_2 = CH_3$

The 8′- and 12′-nor analogues (**34** and **43**) were assembled as shown in Scheme IV, the key step being Schlosser–Wittig reactions to generate the internal trans disubstituted double bonds. Alkylation of the copper–lithium enolate anion of ethyl acetate with geranyl and dimethylallyl bromides provided the chain-extended esters **29** and **36**, which were converted to the requisite phosphonium salts **32** and **39** by standard procedures. The Schlosser–Wittig reaction between phosphorane **33** and aldehyde **19** gave rise to 8′-norgeranylgeraniol (**34**) after removal of the protecting group. Ozonolysis of farnesyl tetrahydropyranyl ether furnished a chromatographically separable mixture of aldehydes **19** and **42** from attack at the two double bonds remote from the ether function. Reaction of the latter with phosphorane **40** according to the modified Wittig–Schlosser procedure afforded 12′-norgeranylgeraniol (**43**).

The cis or trans configuration assigned to the disubstituted double bonds in the five nor analogues is supported by their infrared spectra, which show the expected C–H bending peaks at 970 cm^{-1} for the four trans isomers and 700 cm^{-1} for the one cis isomer. The purity of the compounds was estimated to be ≥~85% by GLC and/or TLC on silver nitrate impregnated silica gel. However, the uncertainties inherent in these methods prompted us to obtain the carbon-13 NMR spectra of the compounds for more definitive characterization.

Carbon-13 NMR spectral data for *all-trans*-geranylgeraniol and its nor analogues are compiled in Table I and summarized in Table II and on the partial structures shown below. The

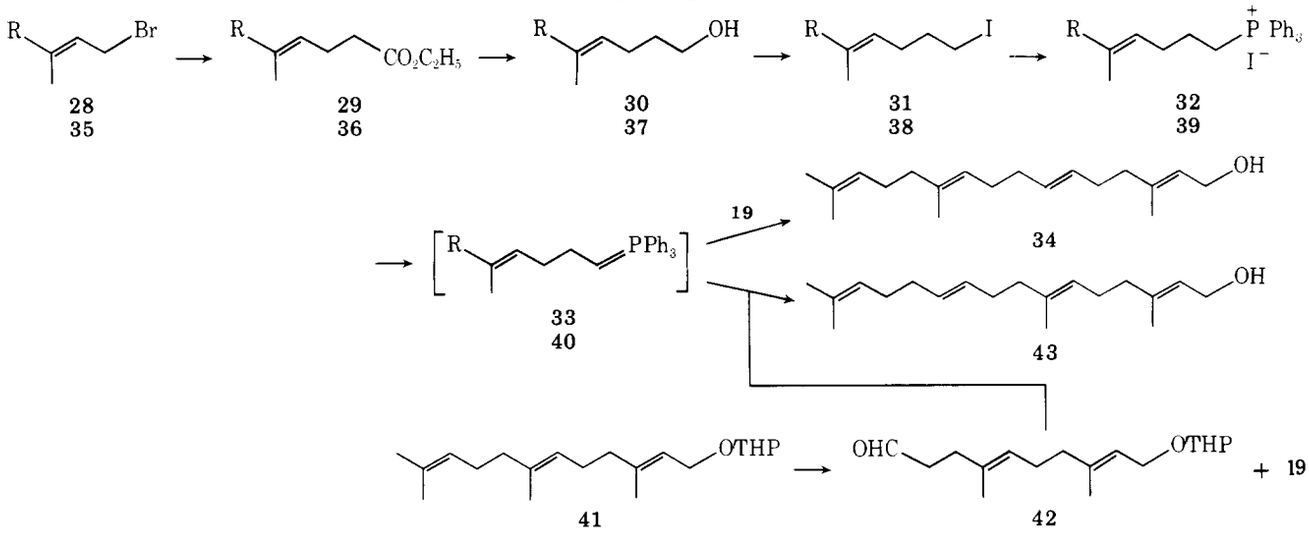
Table II. Average and Range of Carbon-13 Chemical Shifts for Carbon Atoms in *all-trans*-Geranylgeraniol (1-OH) and its Nor Analogues Having Similar Structural Environments[a]

part structure	positions (s)	no. of resonances	av δ_C	range δ_C
$-CH_2OH$	1	5	59.4	0.1
>C=**C**H–	2, 6, 10, 14	19	124.0	1.0
>**C**=CH–	3	5	139.7	0.4
>**C**=CH–	7, 11	10	135.2	0.9
>**C**=CH–	15	4	131.4	0.2
$-CH_2-$	4, 8, 12	15	39.7	0.2
$-CH_2-$	5, 9, 13	11	26.6	0.5
CH_3	4′	5	16.3	0
CH_3	8′, 12′	10	16.0	0
CH_3 (cis)	16′	4	17.7	0
CH_3 (trans)	16	4	25.7	0

[a] Excluding the carbon atoms in the immediate vicinity of the disubstituted double bonds in the nor analogues (i.e., the data in the blocked regions of Table I).

resonances were assigned by comparison with available data for related isoprenoid and olefinic compounds.[15,16] The fact that the peaks for the carbon atoms in the vicinity of the disubstituted double bond in the nor analogues are shifted away from the otherwise similar carbons in the same region served as another guide in making the assignments. The sp^2 carbons of the trisubstituted double bonds at positions 3, 7, 11, and 15 were assigned assuming a regular progression to higher field as reported for the corresponding carbon atoms of farnesol and related compounds.[16a] A progression in the reverse direction was assumed for the sp^2 carbons at positions 2, 6, 10, and 14. However, the relatively small differences in chemical shift render the individual assignments within this group uncertain. The resonances for the internal methylene groups attached to the trisubstituted double bonds separate cleanly into two groups, one at lower field for the methylene carbons cis to hydrogen (C-4, C-8, and C-12) and the other at higher field for the methylene carbons cis to methyl (C-5, C-9, and C-13).

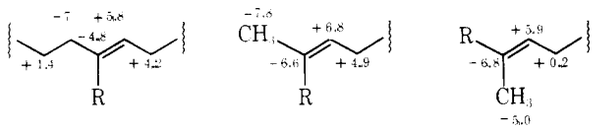
Scheme IV[a]



[a] **28–33**, R = 4-methyl-3-pentenyl; **35–40**, R = CH_3.

Once again the assignments within these groups are arbitrary.

The average chemical-shift increments for the carbon atoms in the immediate vicinity of the disubstituted double bonds in the nor analogues as compared to the corresponding carbon of geranylgeraniol are marked on the partial structures below. The resonances for the internal olefinic carbon atoms at which the substitution change ($CH_3 \rightarrow H$) occurs and the attached methylene carbons are shifted upfield while those for the other internal olefinic carbon and its adjacent methylene carbon move downfield. Similar shifts are seen for the two terminal nor analogues (**26** and **27**) with the exception that the signal



$\Delta\delta_C$ for R = $CH_3 \rightarrow$ H

for the C-13 methylene group in the cis isomer is essentially unchanged. Since the C-13 methylene group is two bonds removed from and trans to the site of substitution, the small shift at this position is to be expected.

Experimental Section

General. Spectra were determined with the following instruments: Varian Associates Model A 56/60, A 60A, HA-100, HR-220 proton NMR spectrometers, and an XL-100 carbon-13 NMR spectrometer; Perkin-Elmer Model 137 and Beckman IR-12 infrared spectrometers; Varian MAT Bremen CH-5, 311, and 731 mass spectrometers. Chemical shifts are reported as δ values with tetramethylsilane as an internal standard. Melting points were measured on a Thomas-Hoover capillary melting point or Reichert hot stage apparatus and are uncorrected. Combustion analyses were performed in the University of Illinois Microanalytical Laboratory.

Gas–liquid chromatographic (GLC) analyses were performed with Varian Aerographs Model 600-D, A90-P3, or 1700 instruments using the following columns: A, 1.5 m × 3.2 mm, 5% Apiezon L on 60/80 mesh Chromosorb W; B, 3.3 m × 6.4 mm, 20% SE-30 on 60/80 mesh Chromosorb W; C, 1.8 m × 3.2 mm, glass column, 3% OV-17 on 100/120 mesh Gas Chrom Q. The allylic alcohols were analyzed as their trimethylsilyl ethers, which were prepared by addition of 10 μL of *N,O*-bis(trimethylsilyl)acetamide to a solution of 5 mg of alcohol in 10 μL of hexane. The solution was allowed to stand for at least 15 min before injection onto the column.

1,2-Dimethoxyethane and tetrahydrofuran (THF) were dried by distillation from the sodium ketyl of benzophenone. Pyridine was dried over potassium hydroxide pellets and decanted before use. Acetonitrile and dichloromethane were dried over 4 Å molecular sieves and decanted before use.

Column chromatographies were performed with silica gel from Brinkmann Instruments having particle diameters in the range of 0.05–0.2 mm. The height-to-diameter ratios were normally between 8:1 and 12:1. Fractions (6 to 20 mL) were taken on a fraction collector and analyzed by thin layer chromatography (TLC) or GLC to determine which contained the product(s). Silver nitrate impregnated silica gel for column chromatography was prepared by addition of a solution of silver nitrate in acetonitrile to the silica gel and then removal of the solvent on a rotary evaporator. TLC plates impregnated with 10% silver nitrate were prepared in the following manner: 5 cm × 20 cm × 0.25 mm GF-254 analytical TLC plates (E. Merck AG) were submerged in a solution of 10% silver nitrate in acetonitrile until completely saturated. The plates were then removed and the solvent was allowed to evaporate.

The standard extraction procedure for product isolation consisted of extracting the aqueous phase three times with the solvent indicated and washing the combined organic phases with 5 or 10% sodium bicarbonate and saturated sodium chloride solutions. The organic phase was then dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure on a rotary evaporator.

3,7,11-Trimethyldodeca-2,6,10(*E,E*)-trien-1-ol (*trans,trans*-Farnesol, 2-OH). The trans,trans isomer was separated from either a commercially available mixture of all four farnesol isomers (Givaudan Corp.) by fractional distillation with a spinning band column,[17] or from a two-isomer mixture (Fluka AG) by fractional crystallization of the *N,N*-diphenylurethane derivative.[18]

Methyl 3,7,11,15-Tetramethylhexadeca-2,6,10,14(*E,E,E*)-tetraenoate (4). *trans,trans*-Farnesylacetone (**3**, 7.14 g, 2.27 mmol), prepared from farnesol as described by van Tamelen and Nadeau,[4b,c] was converted to a mixture of methyl *all-trans*-geranylgeranate (**4**) and its 2,3-cis isomer by reaction with 4.91 g (27 mmol) of trimethyl phosphonoacetate and 0.85 g (35 mmol) of sodium hydride in 50 mL of 1,2-dimethoxyethane according to the procedure of Upper and West.[4d] Purification and separation of the isomers from the crude product (7.6 g) was accomplished by chromatography on 700 g of silica gel eluting with benzene–hexane mixtures ranging from 15:85 to 40:60. The cis ester (0.74 g, 8%) was typically eluted with the 30:70 benzene–hexane; elution of the trans ester **4** (2.51 g, 29%) normally commenced with 35:65 benzene–hexane. Analysis by GLC (column A, 230 °C) showed one peak with a retention time of 6.3 min (the cis isomer has a retention time of 5.3 min under these conditions): ^{1}H NMR (CCl_4) δ 5.50 (s, 1, C=C**H**CO_2), 4.9–5.2 (br, 3, other vinyl H), 3.50 (s, 3, CO_2CH_3), 2.14 (d, 3, J = 1.5 Hz, (CH_3)C=CHCO$_2$), 2.1 (m, 2, CH_2C=CHCO$_2CH_3$), 1.96 (br s, 10, 5CH_2), 1.65 (sh, ~3, 1CH_3), 1.58 (br s, ~9, 3CH_3).

3,7,11,15-Tetramethylhexadeca-2,6,10,14(*E,E,E*)-tetraen-1-ol (Geranylgeraniol, 1-OH). Absolute ethanol (931 mg, 20.2 mmol) was added to a suspension of 765 mg (20.2 mmol) of lithium aluminum hydride in 36 mL of anhydrous ether. The resulting suspension was added in four equal portions at 1-h intervals to a stirred solution of 3.25 g (10.1 mmol) of ester **4** in 10 mL of anhydrous ether at room temperature.[6] After 1 h, water was added to destroy the excess hydride. The mixture was poured into water and the product was isolated by the standard extraction procedure with ether. Purification by chromatography on 50 g of silica gel impregnated with 5% silver nitrate with 25% ethyl acetate in hexane as eluent yielded 1.65 g (50%)

of geranylgeraniol (1-OH). GLC analysis of the trimethylsilyl derivative (column B, 255 °C) showed one peak with a retention time of 28 min. The IR and NMR spectral data are given below following an alternative synthesis of this compound.

Ethyl 5,9,13-Trimethyltetradeca-4,8,12(*E,E*)-trienoate (5). A solution of 74.6 mmol of lithium diisopropylamide in 30 mL of dry THF was slowly added to a stirred suspension of 6.56 g (74.6 mmol) of ethyl acetate and 28.3 g (149.2 mmol) of cuprous iodide in 135 mL of THF at −110 °C under nitrogen according to the procedure of Kawajima and Doi.[7] The suspension was warmed to −30 °C and 10.6 g (37.3 mmol) of farnesyl bromide (**2**-Br)[4b,c] in 30 mL of THF was added. After 1 h at −30 °C, the suspension was poured into 1 L of water and sufficient ammonium chloride was added to dissolve the copper salts. Isolation of the organic products by the standard extraction procedure with hexane afforded 10.6 g (97%) of the known ester (**5**):[19] ^{1}H NMR (CCl_4) δ 4.9–5.2 (br, 3, vinyl H), 4.10 (q, 2, J = 7 Hz, $CO_2CH_2CH_3$), 2.26 (unsymmetrical t, 2, J = 3 Hz, $CH_2CO_2CH_2CH_3$), 1.96 (br s, 10, $5CH_2$), 1.66 (sh, ~3, $1CH_3$), 1.58 (br s, ~9, $3CH_3$), 1.25 (t, 3, J = 7 Hz, $CO_2CH_2CH_3$).

5,9,13-Trimethyltetradeca-4,8,12(*E,E*)-trienal (7). A solution of 10.6 g (36 mmol) of ethyl farnesylacetate (**5**) in 20 mL of ether was slowly added to a stirred suspension of 2.77 g (72 mmol) of lithium aluminum hydride in 60 mL of ether at room temperature. After 2 h at room temperature, the mixture was heated at reflux for another 0.5 h. The excess lithium aluminum hydride was destroyed using the procedure of Micovic and Mihailovic[20] and the reaction mixture was poured into water. The product was isolated by the standard extraction procedure with ether affording 8.12 g (90%) of *trans,trans*-farnesylethanol (**6**). Analysis of the trimethylsilyl ether by GLC (column B, 220 °C) showed the presence of a small amount (<3%, retention time 19 min) of a double bond isomer[7] along with the desired alcohol **6** (retention time 22 min).

Alcohol **6** (6.58 g, 26 mmol) was added to a stirred solution of 15.6 g (26 mmol) of chromium trioxide and 24.6 g (312 mmol) of pyridine in 400 mL of dichloromethane.[21] After 30 min at room temperature, the supernatant solution was decanted and the remaining tar was washed with ether. Evaporation of the combined solutions and purification by chromatography on 100 g of silica gel with 15% ethyl acetate in hexane as eluent afforded 4.21 g (65%) of the aldehyde (**7**): IR (neat) 1730 cm^{-1} (C=O); ^{1}H NMR (CCl_4) δ 9.64 (t, 1, J = 1.5 Hz, CHO), 4.9–5.2 (br, 3, vinyl H), 2.35 (m, 2, CH_2CHO), 1.96 (br s, 10, $5CH_2$), 1.64 (sh, ~3, $1CH_3$), 1.58 (br s, ~9, $3CH_3$). The 2,4-dinitrophenylhydrazone was prepared by a standard procedure,[22] mp 89–93 °C. Anal. Calcd for $C_{23}H_{32}N_4O_4$: C, 64.47; H, 7.53; N, 13.07. Found: C, 64.47; H, 7.51; N, 12.75.

Methyl 7,11,15-Trimethylhexadeca-2,6,10,14(*E,E,E*)-tetraenoate (8). Aldehyde **7** (3.77 g, 15.2 mmol) was added to a stirred suspension of 4.63 g (25.4 mmol) of trimethyl phosphonoacetate and 1.39 g (33 mmol) of sodium hydride (57% dispersion in mineral oil) in 20 mL of dry 1,2-dimethoxyethane. After 15 h at room temperature, the reaction mixture was poured into water. Isolation of the organic product using the standard extraction procedure with ether gave 4.7 g of crude ester. Purification by chromatography on 350 g of silica gel with 25% ethyl acetate in hexane as eluent afforded 1.36 g (29%) of the trans ester (**8**): ^{1}H NMR (CCl_4) δ 6.80 (dt, 1, J = 15 and 6 Hz, $CH{=}CHCO_2$), 5.65 (dt, 1, J = 15 and 1.5 Hz, $CH{=}CHCO_2$), 4.9–5.2 (br, 3, other vinyl H), 3.61 (s, 3, CO_2CH_3), 2.17 (apparent t, 2, J = 3 Hz, $CH_2CH{=}CH$), 1.97 (br s, 10, $5CH_2$), 1.65 (sh, ~3, $1CH_3$), 1.56 (br s, 9, $3CH_3$). Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.90; H, 10.59. Found: C, 78.89; H, 10.41.

7,11,15-Trimethylhexadeca-2,6,10,14(*E,E,E*)-tetraen-1-ol (10). Procedure A. Aldehyde **9** (300 mg, 1.09 mmol) was added to a stirred solution of 12 mg (0.32 mmol) of sodium borohydride in 1 mL of methanol at 0 °C. After 2 h at room temperature, the mixture was poured in 2 mL of saturated sodium chloride and extracted with ether. Evaporation of the solvent and purification by chromatography on 15 g of silica gel with 25% ethyl acetate in hexane as eluant provided 170 mg (56%) of alcohol (**10**): ^{1}H NMR (CCl_4) δ 5.5–5.6 (m, 2, $CH{=}CHCH_2O$), 4.9–5.2 (m, 3, other vinyl H), 3.93 (2 d, J = 2 and 3 Hz, CH_2OH), 1.95–2.2 (m, 12, $3CH_2CH_2$), 1.67 (br s, 3, $1CH_3$), 1.60 (br s, 9, $3CH_3$).

Analysis of the trimethylsilyl derivative by GLC (column B, 250 °C) showed the presence of a small amount (<6%, retention time 21.4 min) of an impurity along with alcohol **10** (retention time 23.2 min). Anal. Calcd for $C_{19}H_{32}O$: C, 82.55; H, 11.67. Found: C, 82.38; H, 11.50.

Procedure B. Lithium aluminum monoethoxyhydride was prepared from 408 mg (8.88 mmol) of ethanol and 335 mg (8.88 mmol) of lithium aluminum hydride in 20 mL of dry ether and added to a solution of 1.35 g (4.44 mmol) of methyl ester **8** in 15 mL of ether as described above for the reduction of **4**. TLC and NMR analysis of the product revealed the presence of a large proportion of the 2,3-dihydro byproduct. Purification by chromatography on 50 g of silica gel impregnated with 5% silver nitrate using a step gradient of ethyl acetate in hexane yielded 275 mg (20%) of the 4′-nor alcohol (**10**).

7,11,15-Trimethylhexadeca-2,6,10,14(*E,E,E*)-tetraenal (9). A solution of 1.80 g (7.26 mmol) of **7** in 4 mL of dry THF was slowly added to a stirred suspension of 20.6 g (7.91 mmol) of diethyl 2-(cyclohexylamino)vinylphosphonate[8] and 0.38 g (7.91 mmol) of sodium hydride (50% dispersion in oil) in 7 mL of THF at 0 °C under nitrogen. After 1.5 h, the product was isolated in the described manner[8] and the residue was dissolved in 18 mL of benzene. Oxalic acid (4.32 g, 9.5 mmol) in 54 mL of water was added and the mixture was heated at reflux temperature for 2 h under nitrogen. Isolation of the organic products by the standard extraction procedure with ether gave 1.5 g of crude aldehyde. Purification by chromatography on 150 g of silica gel with 25% ethyl acetate in hexane as eluent afforded 0.66 g (33%) of aldehyde **9**: ^{1}H NMR (CCl_4) δ 9.38 (d, 1, J = 7 Hz, CHO), 6.70 (dt, 1, J = 15 and 6 Hz, $CH{=}CHCHO$), 6.00 (2d, 1, J = 15 and 7 Hz, $=CHCHO$), 4.9–5.2 (br, 3, other vinyl H), 2.25 (br m, 2, $CH_2CH{=}CH$), 2.0 (br s, 10, $5CH_2$), 1.67 (sh, ~3, $1CH_3$), 1.58 (br s, ~9, $3CH_3$). The oily 2,4-dinitrophenylhydrazone, prepared according to a standard procedure,[22] could not be induced to crystallize. Anal. Calcd for $C_{25}H_{34}N_4O_4$: C, 66.06; H, 7.54; N, 12.33. Found: C, 65.98; H, 7.35; N, 12.09.

3,7-Dimethyl-2,6(*E*)-octadienyl Benzyl Ether (11). One half (26 mL, 0.15 mol) of the geraniol to be used was added to a mechanically stirred suspension of 18.2 g (0.35 mol) of sodium hydride (50% oil suspension washed with pentane) in 400 mL of 1,2-dimethoxyethane.[9,23] Hydrogen evolution began immediately and the remaining 26 mL (0.15 mol) of alcohol was added dropwise over a 1-h period. The suspension was maintained at 70 °C for 2 h, after which time hydrogen evolution had ceased. Benzyl chloride (42 mL, 0.36 mol) was added dropwise to the warm solution over a 20-min period. After 2 h at 70 °C (or overnight at room temperature), TLC analysis showed that no starting material remained. The reaction was allowed to cool, diluted with water, and extracted three times with pentane. The combined extracts were washed with water, dilute aqueous ammonia, water, and brine. The solution was dried and evaporated and the residue was distilled to give 47.27 g (65%) of the ether as a colorless liquid: bp 113 °C (0.3 mm); IR (film) 1070 cm^{-1} (CO); ^{1}H NMR (CCl_4) δ 7.16 (br s, 5, aryl H), 5.28 (br t, 1, $=CHCH_2O$–), 5.02 (m, 1, $=CHCH_2CH_2$), 4.36 (s, 2, $-OCH_2C_6H_5$), 3.89 (d, 2, $=CHCH_2O$–), 2.00 (m, 4, CH_2CH_2–), 1.58 (s, 9, $3CH_3$).

6-(Benzyloxy)-4-methyl-4(*E*)-hexenal (12). A stream of ozone in oxygen (flow rate, 2.25 mmol/min; total, 0.52 mol) generated with a Welsbach Ozonator was bubbled through a solution containing 85.15 g (0.35 mol) of ether **11** and 30 mL (0.35 mol) of pyridine in 850 mL of dry dichloromethane for approximately 4 h at −78 °C.[9,24] Dimethyl sulfide (60 mL) was added and the solution was allowed to warm to room temperature. After 5 h, the volatiles were carefully removed under reduced pressure. The residue was diluted with water and extracted four times with hexane. The combined extracts were washed with 5% hydrochloric acid and saturated aqueous sodium chloride, dried with magnesium sulfate, and evaporated to give 61 g of a mixture of starting ether **11** and desired aldehyde **12**.

The mixture was shaken with 260 mL of saturated sodium bisulfite solution.[25] The precipitated bisulfite adduct was filtered, washed with ethanol and ether, and decomposed by dissolution in 400 mL of 10% sodium carbonate solution. The solution was extracted three times with ether and the combined extracts were washed with 5% sodium bicarbonate and water. After drying and evaporation of the solvent, 33 g of crude aldehyde **12** was obtained. Distillation of 18.42 g furnished 15.15 g (35%): bp 130 °C (0.2 mm) [lit.[9c] 122–125 °C (0.1 mm)]; IR (film) 2725 (CH), 1725 cm^{-1} (C=O); ^{1}H NMR (CCl_4) δ 9.54 (s, CHO), 7.16 (s, 5, aryl H), 5.28 (t, 1, J = 7 Hz, $=CHCH_2O$–), 4.36 (s, 2, $-OCH_2C_6H_5$), 3.89 (d, 2, J = 7 Hz, $=CHCH_2O$–), 4.36 (s, 2, $-OCH_2C_6H_5$), 3.89 (d, 2, J = 7 Hz, $=CHCH_2O$), 2.30 (br s, CH_2CH_2), 1.57 (s, 9, $3CH_3$).

8-(Benzyloxy)-2,6-dimethyl-2,6(*E,E*)-octadien-1-ol (14). Aldehyde **12** (11.5 g, 52.6 mmol) was added dropwise over a 15-min period to a refluxing solution containing 24.0 g (66.4 mmol) of ethyl 2-(triphenylphosphoranylidene)propionate in 50 mL of dichloromethane.[26] TLC analysis with 20% ethyl acetate in hexane as developing solvent indicated that the reaction was complete after 3.5 h at reflux. The solvent was evaporated and the residue was dissolved in petroleum ether and filtered through silica gel to separate starting phosphorane and triphenylphosphine oxide. Evaporation of the solvent gave 15.64 g (98%) of the unsaturated ester **13** as a pale yellow oil: IR (film) 1710 (C=O), 1650 (C=C), 1260 cm^{-1} (CO); ^{1}H NMR

(CCl_4) δ 7.20 (s, 5, aryl H), 6.66 (br t, 1, J = 7 Hz, C(6) vinyl H), 5.34 (br t, 1, J = 7 Hz, =C**H**CH_2O); 4.36 (s, 2, $OCH_2C_6H_5$), 4.04 (q, 2, J = 7 Hz, $COOCH_2CH_3$), 3.91 (d, 2, J = 7 Hz, =CHCH_2O), 2.12 (br m, 2, CH_2CH_2), 1.78 (s, 3, C(2) CH_3), 1.57 (s, 3, C(6) CH_3), 1.16 (t, 3, J = 7 Hz, $COOCH_2CH_3$). The appearance of a peak in the NMR spectrum at δ 5.80 indicated the presence of about 4% of the 2,3(Z) isomer.

Aluminum chloride (28.9 g, 0.22 mol) was added to a suspension of 25.0 g (0.66 mol) of lithium aluminum hydride in 2.5 L of dry ether at −5 °C.[27] After 30 min, a solution of 43.8 g (0.145 mol) of ester **13** in 300 mL of ether was added dropwise over 2.5 h. TLC analysis with 40% ethyl acetate–hexane as developing solvent indicated that the reaction was complete after 10 min. Water was added slowly until the solids were completely precipitated. The solids were removed by filtration and the ether solution was washed with brine. Drying and evaporation of the solvent yielded 36.39 g (97%) of alcohol **14**, which was used without further purification. The spectral data for this compound are in agreement with literature values.[5a]

Geranyl Phenyl Sulfide (16). Phosphorus tribromide (23.7 mL, 0.25 mol) was added dropwise over a 20-min period to a solution of 86.8 mL (0.50 mol) of geraniol in 250 mL of hexane at 0 °C. Immediately after the addition was complete, 14 mL of methanol was added. The hexane solution was washed with water, 10% sodium bicarbonate, and brine. Evaporation of the dried solution afforded 101.4 g (93%) of geranyl bromide.

Sodium thiophenoxide (prepared by the reaction of sodium and thiophenol in xylene at 100 °C) (73 g, 0.55 mol) was added in portions to a stirred solution of freshly prepared geranyl bromide in 650 mL of ether at 0 °C.[28] After 15 min, the suspension was filtered to remove sodium bromide. The filtrate was washed with water and 5% sodium hydroxide and dried. Evaporation of the solvent gave 106.3 g (94%) of sulfide **16**. Column chromatography on silica gel (25 g/g of sulfide) with dichloromethane as eluent prior to use gave 70–75% yield of pure sulfide. The spectral data are in agreement with literature values.[5a]

3,7,11,15-Tetramethyl-9-phenylthio-2,6,10,14(*E,E,E*)-hexadecatetraenyl Benzyl Ether (17). Chloride **15** was prepared by the method of Stork, Grieco, and Gregson[5a,29] from 15.4 g of allylic alcohol **14** and purified by rapid chromatography on 700 g of silica gel with dichloromethane as eluant: yield, 13.2 g (79%). The reaction of 16.55 g (60 mmol) of the chloride with the lithio derivative prepared from 19.5 g (79 mmol) of sulfide **16** was carried out as reported by Altman, Ash, and Marson.[5] Chromatography on silica gel (50 g/g of product) with 10% hexane in dichloromethane as eluent provided the purified sulfide **17** in 43% yield.

3,7,11,15-Tetramethylhexadeca-2,6,10,14(*E,E,E*)-tetraen-1-ol (Geranylgeraniol, 1-OH). A solution of 7.6 g (17.3 mmol) of sulfide **17** in 90 mL of THF was added slowly to a solution of 3.79 g (546 mmol) of lithium (1% sodium) in 330 mL of ammonia at −78 °C. After 15 min, the excess lithium was destroyed with 3-hexyne and methanol as described.[5a] The ammonia was allowed to evaporate and the product was isolated by extraction with ether according to the standard procedure to give 6.6 g of crude alcohol. Chromatography on a column of silica gel with a height-to-diameter ratio of 20:1 and with 40% ether in hexane as eluent afforded 4.24 g (84%) of geranylgeraniol (1-OH): IR (film) 3300 (OH), 1670 (C=C), 1000 (CO), 787 cm^{-1} (trisubstituted olefin); ^1H NMR ($CDCl_3$) δ 5.43 (br t, 1, J = 7 Hz, C(2) vinyl H), 5.13 (br m, 3, vinyl H), 4.14 (d, 2, J = 7 Hz, CH_2OH), 1.9–2.2 (m, 12, $6CH_2$), 1.68 (s, 6, $2CH_3$), 1.61 (s, 9, $3CH_3$). GLC analysis of the trimethylsilyl ether (column C, 210 °C) showed a major peak with a retention time of 32 min which was presumed to be *all-trans*-geranylgeraniol. Three peaks from minor contaminants had retention times of 24 (4% relative area), 27, and 29 min (16% combined relative areas). The purity of the geranylgeraniol may be increased to about 90% by chromatography on silica gel impregnated with 15% silver nitrate and with hexane and 20–40% ethyl acetate in hexane as eluent.[5a,30]

In some runs the geranylgeraniol was contaminated with variable amounts of geraniol. The presence of geraniol is indicated by an increased integral for the hydroxymethyl protons (δ 4.14) in the NMR spectrum and by GLC and TLC analyses. The majority of the geraniol may be separated by Kugelrohr distillation [oven temperature 135–140 °C (0.1 mm)] and/or careful chromatography on silica gel with hexane, 5% ethyl acetate in hexane, and 10% ethyl acetate in hexane as eluent. Geraniol is somewhat more polar than geranylgeraniol.

Evidently the geraniol arises from lithium–ammonia reduction of chloride **15**, which was present as a contaminant of sulfide **17** in some runs. It was found subsequently that unreacted chloride could be removed from the sulfide by slower and more careful chromatography, the chloride undergoing decomposition on the column. The amount of unreacted chloride in the product may also be suppressed by using a 1.6:1.6:1.0 ratio of geranyl phenyl sulfide, n-butyllithium, and chloride **15** in the alkylation reaction.

6-(2′-Tetrahydropyranyloxy)-4-methyl-4(*E*)-hexenal (19). A stream of ozone (flow rate, 2.25 mmol/min; 155 mmol) was passed through a solution of 23 g (96.8 mmol) of geranyl tetrahydropyranyl ether (**18**) in 150 mL of dichloromethane at −78 °C.[11] The cooling bath was removed, 60 mL of dimethyl sulfide was added, and the solution was allowed to warm to room temperature overnight with stirring. The solvent was evaporated and the crude product was purified by chromatography on 400 g of silica gel with 30% ether in hexane as eluent: yield, 9.67 g (41%). The NMR spectral data for aldehyde **19** are in agreement with those reported.[11]

3-Methyl-2,6(*E,Z*)-octadien-1-ol (20). Ethyltriphenylphosphonium bromide (26 g, 70 mmol) was added to a stirred suspension of 2.73 g (70 mmol) of sodium amide in 275 mL of liquid ammonia at −33 °C. After 1 h at −33 °C, the ammonia was allowed to evaporate and 275 mL of dry benzene was added. The resulting deep red suspension was heated at reflux temperature for 1 h, cooled, filtered to remove sodium bromide, and transferred to a cold (0 °C), vigorously stirred solution of 7.42 g (35 mmol) of aldehyde **19** in 68 mL of 1:1 benzene–pentane. After 1 h at 0 °C, the cooling bath was removed and the solvent was removed on a rotary evaporator. The residue was suspended in hexane and filtered through silica gel to remove triphenylphosphine oxide. The resulting tetrahydropyranyl ether (7.1 g, 32 mmol) was subjected to methanolysis with 200 mg of p-toluenesulfonic acid in 200 mL of methanol. The product was isolated by a standard extraction procedure with hexane and purified by chromatography on 180 g of silica gel with 25% ethyl acetate in hexane as eluent, affording 2.62 g (53%) of the cis alcohol (**20**): IR (neat) 700 cm^{-1} (C=C cis); ^1H NMR ($CDCl_3$) δ 5.3–5.6 (br, 3, vinyl H), 4.15 (d, 2, J = 7 Hz, CH_2OH), 2.12 (m, 4, $-CH_2CH_2-$), 1.70 (br s, ~4.5, $1.5CH_3$), 1.56 (br s, ~1.5, $0.5CH_3$). A TLC analysis on silica gel impregnated with 10% silver nitrate using 50% ethyl acetate in hexane as developing solvent showed the presence of a small amount of the trans isomer (R_f 0.13) along with the cis alcohol (R_f 0.07). Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.66; H, 11.42.

3-Methyl-2,6(*E,E*)-octadien-1-ol (21). The trans alcohol was prepared by the Schlosser method as described in detail below for the synthesis of **34**. A solution of 15 g (70 mmol) of aldehyde **19** in 50 mL of dry THF was allowed to react with the phosphorane prepared from 27.5 g (74.3 mmol) of ethyltriphenylphosphonium bromide in 10 mL of THF and two successive 95-mL portions (71.3 mmol) of an 0.75 M solution of phenyllithium in THF. The resulting crude ether (15.8 g, 70.5 mmol) was subjected to methanolysis with 400 mg of p-toluenesulfonic acid in 400 mL of methanol. The product was isolated by the standard extraction procedure with hexane and purified by chromatography on 450 g of silica gel with 25% ethyl acetate in hexane as eluent. The resulting yellow oil was distilled to afford 4.21 g (42%) of the trans alcohol (**21**): bp 71–73 °C (0.8 mm); IR (neat) 970 cm^{-1} (C=C trans); ^1H NMR ($CDCl_3$) δ 5.3–5.6 (br, 3, vinyl H), 4.15 (d, 2, J = 7 Hz, CH_2OH), 2.06 (br s, 4, $-CH_2CH_2-$), 1.65 (br, s, ~4.5, $1.5CH_3$), 1.58 (sh, ~1.5, $0.5CH_3$). A TLC analysis of the alcohol on silica gel impregnated with 10% silver nitrate using 50% ethyl acetate in hexane as developing solvent showed the presence of a small amount of the cis isomer (R_f 0.07) along with the trans (R_f 0.13). Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.14; H, 11.59.

3,7,11-Trimethylhexadeca-2,4,10,14(*E,E,E,E*)-tetraen-1-ol (27). A solution of 4.16 g (29.7 mmol) of alcohol **21** in 16 mL of pentane was allowed to react with 4.0 g (14.8 mmol) of phosphorous tribromide for 1 h at 0 °C following the procedure of Nadeau for the preparation of farnesyl bromide.[4c] After addition of 1 mL of methanol, the solution was washed twice with water, twice with 10% sodium bicarbonate, and again with water. The solution was dried (Na_2SO_4) and evaporated to give 5.56 g (92%) of the allylic bromide, which was converted to the phenyl sulfide by reaction with 3.79 g (28.7 mmol) of sodium thiophenoxide as described above for geranyl phenyl sulfide. The yield of sulfide **23** was 3.5 g (51% from alcohol **21**) after purification by chromatography on 65 g of silica gel with 10% ether in hexane as eluent.

A solution of 3.55 g (12.1 mmol) of chloride **15** in 15 mL of dry THF was added slowly to the lithio derivative of sulfide **23** which had been generated from 3.46 g (14.9 mmol) of the sulfide and 6.03 mL (13.4 mmol) of a 2.2 M solution of n-butyllithium in 90 mL of THF following the procedure of Altman, Ash, and Marson.[5a] The product was isolated as described and purified by chromatography on 630 g of silica gel with dichloromethane as eluent affording 4.97 g (86%) of alkylated sulfide **25**. The reduction of 4.92 g (10.3 mmol) of **25** with 2.1 g (300 mmol) of lithium in 150 mL of liquid ammonia at −78 °C was carried out in the same manner as described above for the reduction of sulfide **17**. The crude alcohol (3.6 g) was purified by chromatography on 300 g of silica gel with 40% ether in hexane as eluent to give 1.6 g (56%) of

the 16′-nor alcohol (**27**): IR (neat) 970 cm^{-1} (*trans*-CH=CH); ^1H NMR ($CDCl_3$) δ 5.0–5.6 (br, 5, vinyl H), 4.18 (d, 2, J = 7 Hz, CH_2OH), 2.06 (br s, 12, 3-CH_2CH_2–), 1.68 (br s, ~4.5, ~1.5CH_3), 1.60 (br s, ~7.5, ~2.5CH_3). A TLC analysis on silica gel impregnated with 5% silver nitrate using 50% ethyl acetate in hexane as developing solvent showed the presence of a small amount (estimated to be 5% or less) of the cis isomer (R_f 0.13) along with **27** (R_f 0.2). Anal. Calcd for $C_{19}H_{32}O$: C, 82.55; H, 11.67. Found: C, 82.48; H, 11.67.

3,7,11-Trimethylhexadeca-2,6,10,14(*E,E,E,Z*)-tetraen-1-ol (26). This compound was prepared in exactly the same manner as described above for its trans isomer. Phenyl sulfide **22** (2.15 g), prepared in 54% yield from 2.46 g of dienol **20**, was lithiated and coupled to chloride **15** to give 3.42 g (86%) of sulfide **24** after chromatographic purification. Reductive cleavage of the phenylthio and benzyl groups with lithium in liquid ammonia gave rise to 1.12 g (56%) of the 16-nor alcohol **26** following purification by column chromatography: IR (neat) 700 cm^{-1} (*cis*-CH=CH); ^1H NMR ($CDCl_3$) δ 5.3–5.6 (br, 5, vinyl H), 4.15 (d, 2, J = 7 Hz, CH_2OH), 2.08 (br s, 12, 3 CH_2CH_2), 1.68 (br s, ~4.5, ~1.5CH_3), 1.60 (br s, ~7.5, ~2.5CH_3); high resolution MS, calcd for $C_{19}H_{32}O$ 276.2453, found 276.2455. A TLC analysis on silica gel impregnated with 5% silver nitrate as above revealed the presence of a small amount of the cis isomer.

5,9-Dimethyl-4,8(*E*)-decadien-1-ol (30) was prepared as described above for the synthesis of **6.** Geranyl bromide (22.1 g, 0.1 mol) was added at −30 °C to a suspension of the copper–lithium enolate of ethyl acetate, prepared from 0.2 mol of lithium diisopropylamide, 17.6 g (0.2 mol) of ethyl acetate, and 76 g (0.4 mol) of cuprous iodide in 425 mL of dry THF.[7] The resulting ester (26.4 g, 0.1 mol) without purification was slowly added to a suspension of 3.78 g (0.1 mol) of lithium aluminum hydride in 50 mL of dry ether. The reaction was heated at reflux for 2 h and the product was isolated as described above. Purification by chromatography on 290 g of silica gel with 40% ethyl acetate in hexane as eluent afforded 11.7 g (64% from geraniol) of geranylethanol (**30**).[31]

5,9-Dimethyl-4,8(*E*)-decadienyl Iodide (31). A solution of 4.96 g (27.3 mmol) of alcohol **30** and 6.23 g (32.8 mmol) of *p*-toluenesulfonyl chloride in 20 mL of pyridine was allowed to stand at −20 °C for 24 h and the product was isolated by extraction.[11] Analysis by TLC with 25% ethyl acetate in hexane as developing solvent showed the presence of a less polar impurity (R_f 0.75) along with the tosylate (R_f 0.6). Inspection of the NMR spectrum indicated the impurity to be the corresponding chloride, which was removed by chromatography on 500 g of silica gel with 25% ethyl acetate in hexane as eluent. The NMR spectral data of the purified tosylate (4.38 g, 48%) were identical with those reported.[11]

The tosylate (4.38 g, 13 mmol) was added to a suspension of 4.32 g (28.8 mmol) of sodium iodide in 40 mL of refluxing acetone.[31,32] After 45 min at reflux temperature, the mixture was diluted with water and extracted with pentane. Isolation of the product by the standard extraction procedure with ether followed by chromatography on 225 g of silica gel with pentane as eluent afforded 1.56 g (41%) of iodide (**31**). The NMR spectral data were identical with those reported.[31]

[5,9-Dimethyl-4,8(*E*)-decadienyl]triphenylphosphonium Iodide (32). A solution of 1.55 g (5.3 mmol) of **31** and 1.7 g (6.5 mmol) of triphenylphosphine in 1.2 mL of benzene was shielded from light and allowed to stand for 4 days at room temperature.[31] The solution was added to 100 mL of ether with rapid stirring. After 15 min, the precipitate was filtered and washed thoroughly with ether to give 1.29 g (44%) of phosphonium salt **32:** mp 97–98 °C (lit.[31] 97–98 °C).

3,11,15-Trimethylhexadeca-2,6,10,14(*E,E,E*)-tetraen-1-ol (34). 8′-Norgeranylgeraniol (**34**) was prepared by the Schlosser method[13] as modified by Johnson and co-workers.[14] Phenyllithium was prepared in ether solution,[33] the ether was evaporated, and THF was added. The use of commercial phenyllithium (Ventron Corp.) resulted in the formation of detectable amounts of the cis isomer. Phosphonium salt **32** (4.54 g, 8.2 mmol) was placed in a three-neck flask equipped with a mechanical stirrer, an addition funnel, and a gas inlet. The flask was evacuated for 1 h at 0.5 mm and filled with an argon atmosphere, and 8 mL of dry THF was added. A 6.8-mL aliquot (8.0 mmol) of a 1.17 M solution of phenyllithium in THF was added to the well-stirred suspension and the resulting deep red solution was stirred for 10 min at room temperature. The solution was then cooled to −78 °C and 1.65 g (7.8 mmol) of aldehyde **19** in 8 mL of dry THF was added over 15 min by slowly dripping the solution down the side of the cold reaction flask. After 15 min, an additional 6.8 mL (8.0 mmol) of phenyllithium solution in THF was added in the same manner. The resulting deep red solution was then diluted with an amount (30 mL) of anhydrous ether sufficient to bring the THF–ether ratio to 1:1. The reaction mixture was allowed to warm to −25 °C, stirred for 30 min, and quenched by addition of 16 mL of methanol. The cooling bath was removed and the stirring was continued overnight. The solution was poured into water and the organic products were isolated by the standard extraction procedure with ether. After purification by chromatography on 200 g of silica gel with 15% ether in hexane as eluent, the tetrahydropyranyl ether (975 mg) was dissolved in 30 mL of methanol containing 30 mg of *p*-toluenesulfonic acid and the solution was allowed to stand overnight at room temperature. Water was added and the organic products were isolated by the standard extraction procedure with ether. Purification by chromatography on 100 g of silica gel with 25% ethyl acetate in hexane as eluent gave 620 mg (29% overall) of 8′-nor alcohol (**34**): IR (neat) 970 cm^{-1} (*trans*-CH=CH); ^1H NMR ($CDCl_3$) δ 5.3–5.5 (br, 2, C**H**=C**H**), 4.9–5.2 (br, 3, other vinyl H), 4.13 (d, 2, J = 7 Hz, CH_2OH), 2.07, 1.98 (2 br s, 12, 3-CH_2CH_2–), 1.66 (br s, 6, 2CH_3), 1.58 (br s, 6, 2CH_3).

A TLC analysis on silica gel impregnated with 10% silver nitrate using 33% ethyl acetate in hexane as developing solvent showed one spot (R_f 0.33). A GLC analysis of the trimethylsilyl derivative (column B, 258 °C) showed the presence of a small amount (<3%, retention time, 22.4 min) of an impurity along with alcohol **34** (retention time, 24.6 min). Anal. for $C_{19}H_{32}O$: C, 82.55; H, 11.67. Found: C, 82.78; H, 11.55.

5-Methyl-4-hexen-1-ol (37) was prepared from 3-methyl-2-buten-1-ol in the same manner as described above for the syntheses of alcohols **6** and **30.** Thus, 8.6 g of 3-methyl-2-buten-1-ol was converted to the bromide (**35**; 14.8 g) with phosphorous tribromide and the latter was used to alkylate the copper–lithium enolate anion of ethyl acetate.[7] The resulting unpurified ester (15 g) was reduced with 3.8 g of lithium aluminum hydride in 50 mL of ether. The yield of 5-methyl-4-hexen-1-ol (**37**) was 7.9 g (69% overall) after purification by chromatography on 300 g of silica gel with 40% ethyl acetate in hexane as eluent. The NMR spectral data for this compound agreed with those in the literature.[11]

6-Iodo-2-methyl-2-hexene (38). Methanesulfonyl chloride (4.93 g, 43 mmol) was added over 5 min to a stirred solution of 4.48 g (39.3 mmol) of **37** and 6.06 g (60 mmol) of triethylamine in 50 mL of dichloromethane at 0 °C.[34] After 15 min at 0 °C, the solution was extracted with 50 mL of ice-cold water and the aqueous phase was extracted with dichloromethane. The combined dichloromethane layers were extracted twice with cold 10% hydrochloric acid, three times with 10% sodium bicarbonate, and once with saturated sodium chloride. Drying ($MgSO_4$) and evaporation provided 6.74 g (89%) of the methanesulfonate, which was converted to the iodide by reaction with 9.9 g (66 mmol) of sodium iodide in 100 mL of acetone for 21 h at room temperature.[11] The reaction mixture was diluted with pentane and filtered through Celite 545 to give 6.9 g of crude iodide after evaporation. Further purification by chromatography on 90 g of silica gel with pentane as eluent afforded 5.44 g (69%) of iodide **38,** the spectral properties of which agreed with data reported in the literature.[11]

(5-Methyl-4-hexenyl)triphenylphosphonium Iodide (39). Iodide **38** (5.44 g, 24.2 mmol) was allowed to react with 7.92 g (30 mmol) of triphenylphosphine in 9 mL of benzene for 7 days as described above for **32.** Precipitation of the salt from ether furnished 6.4 g (54%) of phosphonium iodide **39:** mp 142–143 °C (lit.[11] 134–135 °C). The difference in melting points may have been caused by the use of different solvents for crystallization.

3,7,15-Trimethylhexadeca-2,6,10,14(*E,E,E*)-tetraen-1-ol (43). A solution of 8.8 g (39 mmol) of *trans,trans*-farnesol, 4.9 g (59 mmol) of dihydropyran, and 40 mg of *p*-toluenesulfonic acid monohydrate in 25 mL of dry ether was allowed to stand overnight at 4 °C.[35] Evaporation of the solvent and excess dihydropyran afforded 10.8 g (91%) of the tetrahydropyranyl ether **41,** which was dissolved in 50 mL of dichloromethane and subjected to ozonolysis (flow rate, 2.25 mmol/min; 56 mmol) as described above for the preparation of aldehyde **19.** The crude product was purified by chromatography on 250 g of silica gel with 30% ether in hexane as eluent affording 2.2 g (29%) of **19,** as well as 2.2 g (22%) of the desired aldehyde (**42**).

A solution of 2.2 g (7.8 mmol) of aldehyde **42** in 8 mL of dry THF was allowed to react with the phosphorane generated from 4.0 g (8.2 mmol) of phosphonium salt **32** and two successive 20-mL (8.0 mmol) portions of a 0.4 M solution of phenyllithium in THF in the manner described above for the preparation of **34.** Isolation of the product followed by chromatographic purification on 200 g of silica gel with 15% ether in hexane as eluent afforded 1.48 g (53%) of tetrahydropyranyl ether **43.** Methanolysis of 1.48 g (4.12 mmol) of the ether with 50 mg of *p*-toluenesulfonic acid in 50 mL of methanol gave 1.23 g of crude alcohol. Purification by chromatography on 100 g of silica gel with 25% ethyl acetate in hexane as eluent provided 740 mg (34% overall from **42**) of the 12′-nor alcohol (**43**): IR (neat) 970 cm^{-1} (*trans*-CH=CH); ^1H NMR ($CDCl_3$) δ 5.3–5.5 (br, 2, C**H**=C**H**), 4.9–5.2 (br, 3, other vinyl H), 4.13 (d, 2, J = 7 Hz, CH_2OH), 2.05 (br s, 12, 3-CH_2CH_2–), 1.68 (br s, 6, 2CH_3), 1.60 (br s, 6, 2CH_3); high-

resolution MS, calcd for $C_{19}H_{32}O$ 276.2453, found 276.2452. A TLC analysis on silica gel impregnated with 10% silver nitrate using 33% ethyl acetate as developing solvent showed one spot (R_f 0.33). Analysis of the trimethylsilyl derivative by GLC (column B, 258 °C) showed the presence of a small amount (<3%, retention time 22.7 min) of an impurity along with alcohol **43** (retention time 25.3 min). Anal. Calcd for $C_{19}H_{32}O$: C, 82.55; H, 11.67. Found: C, 82.16; H, 11.61.

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Registry No.—**2**-OH, 106-28-5; **2**-Br, 28290-41-7; **3**, 1117-52-8; **4**, 42207-88-5; **5**, 59822-16-1; **6**, 67858-77-9; **7**, 67858-78-0; **7** 2,4-DNP, 67858-79-1; **8**, 67858-80-4; **9**, 67858-81-5; **9** 2,4-DNP, 67858-82-6; **11**, 52188-73-5; **12**, 32989-52-9; **13**, 67858-83-7; **14**, 52188-74-6; **15**, 52220-07-2; **16**, 35162-74-4; **17**, 52188-75-7; **18**, 59632-99-4; **19**, 64218-01-5; **20**, 67858-84-8; **21**, 67858-85-9; **22**, 67858-86-0; **23**, 67891-05-8; **24**, 67858-87-1; **25**, 67919-59-9; **28**, 6138-90-5; **29**, 19894-83-8; **30**, 67858-88-2; **31**, 67858-89-3; **32**, 32205-44-0; **33**, 67858-90-6; **35**, 870-63-3; **36**, 42272-93-5; **37**, 42272-94-6; **38**, 63588-94-3; **39**, 67858-91-7; **40**, 67858-92-8; **41**, 67858-93-9; **42**, 67858-94-0; 3,7,15-trimethylhexadeca-2,6,10,14(*E,E,E,E*)-tetraen-1-ol tetrahydropyranyl ether, 67858-95-1; methyl 3,7,11,15-tetramethylhexadeca-2,6,10,14(*Z,E,E,E*)-tetraenoate, 51906-19-5; 8-(benzyloxy)-2,6-dimethyl-2,6(*Z,E*)-octadien-1-ol, 67858-96-2; 3-methyl-2,6(*E,Z*)-octadien-1-ol tetrahydropyranyl ether, 67858-97-3; 3-methyl-2,6(*E,E*)-octadien-1-ol tetrahydropyranyl ether, 67858-98-4; 3-methyl-2,6(*E,E*)-octadien-1-yl bromide, 67858-99-5; 5,9-dimethyl-4,8-(*E,E*)-decadien-1-ol tosylate, 67859-00-1; 5-methyl-4-hexen-1-ol methanesulfonate 67859-01-2; trimethyl phosphonoacetate, 311-46-6; diethyl 2-(cyclohexylamino)vinylphosphonate, 20061-84-1; geraniol, 106-24-1; benzyl chloride, 100-44-7; ethyl 2-(triphenylphosphoranylidene)propionate, 54356-04-6; phosphorus tribromide, 7789-60-8; sodium thiophenoxide, 930-69-8; 1-(phenylthiol)geranyllithium, 67859-02-3; ethyltriphenylphosphonium bromide, 1530-32-1; ethylidenetriphenylphosphorane, 1754-88-7; 1-(phenylthio)-3-methyl-2,6(*E,E*)-octadienyllithium, 67859-03-4; triphenylphosphine, 603-35-0; 3-methyl-2-buten-1-ol, 556-82-1; sodium iodide, 7681-82-5.

References and Notes

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