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Synthesis of 6-(Poly)prenyl-substituted Polyprenols and Their Phosphates

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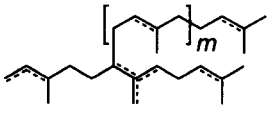
Abstract: The 6-(poly)prenyl-substituted polyprenols **7**, **9**, **11**, and **13** were synthesized: (1) **7** from 2-geranyl-farnesal and methyl 4-bromo-3-methyl-2-butenoate, (2) **9** from 2-prenyl-geranyl bromide and ethyl acetoacetate, *via* ketone **29**, (3) **11** from ethyl acetoacetate, geranyl bromide, and (*E*)-1-*t*-butyldiphenylsiloxy-5-iodo-3-methyl-2-pentene, *via* β-keto ester **35**, and (4) **13** from geraniol by acid catalyzed condensation. These highly branched polyprenols **7**, **9**, **11**, and **13** were transformed into the corresponding disodium phosphates **8**, **10**, **12**, and **14**, respectively.

Highly branched isoprenoid alkanes and alkenes **1** (C_{20}, C_{25}, C_{30}, and C_{35}), which are distributed widely and abundantly in sediments,[1] have been postulated by Ourisson and Nakatani to be derived from the corresponding polyprenylated polyprenyl amphiphiles present in biomembranes in primitive organisms.[2, 3] Recent isolation of these branched isoprenoid hydrocarbons from diatomaceous algae indicates that such primitive branched membrane constituents may still exist on Earth,[4, 5] although these have been isolated neither from sediments nor from present-day microbial sources. The availability of synthetic samples of these highly branched polyprenols **2** would greatly facilitate the search for such primitive microorganisms and the testing of this interesting speculation by evaluating the physicochemical properties of phosphates or diphosphates **3** in water.[3] Furthermore, dehydration and reduction of the polyprenols **2** will provide authentic samples for the search of highly branched isoprenoid hydrocarbons from diatomaceous algae and sediments.



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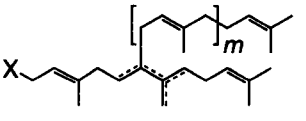
$m = 0, 1, 2, 3$



2 X = OH
3 X = $OPO_3^{2-}Na^+_2$ or $OP_2O_6^{3-}Na^+_3$

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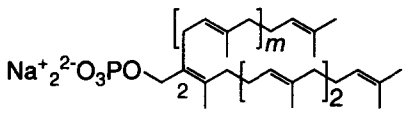
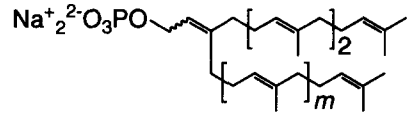
PII: S0040-4020(99)00057-5

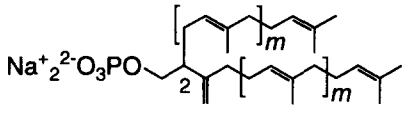
We have recently reported the synthesis of 2-geranyl- and 2-farnesyl-substituted geranylgeranyl phosphates and their isomers **4a**—**6a** and **4b**—**6b**.[6, 7] We now report the synthesis of 6-geranyl- and 6-prenyl-substituted polyprenols **7**, **9**, **11**, and **13**, and their phosphates **8**, **10**, **12**, and **14** possessing a hydrophobic portion of about 20 Å in length, a half of the thickness of all known biomembranes, or shorter.



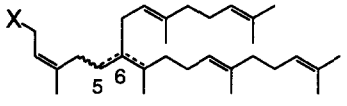
4a $m = 1$
4b $m = 2$



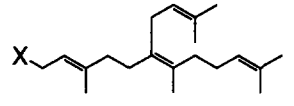
5a $m = 1$
5b $m = 2$



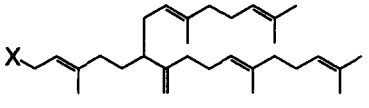
6a $m = 1$
6b $m = 2$



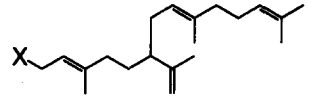
7 X = OH, Δ^6 and Δ^5
8 X = $OPO_3^{2-}Na^+_2$, Δ^6 and Δ^5



9 X = OH
10 X = $OPO_3^{2-}Na^+_2$

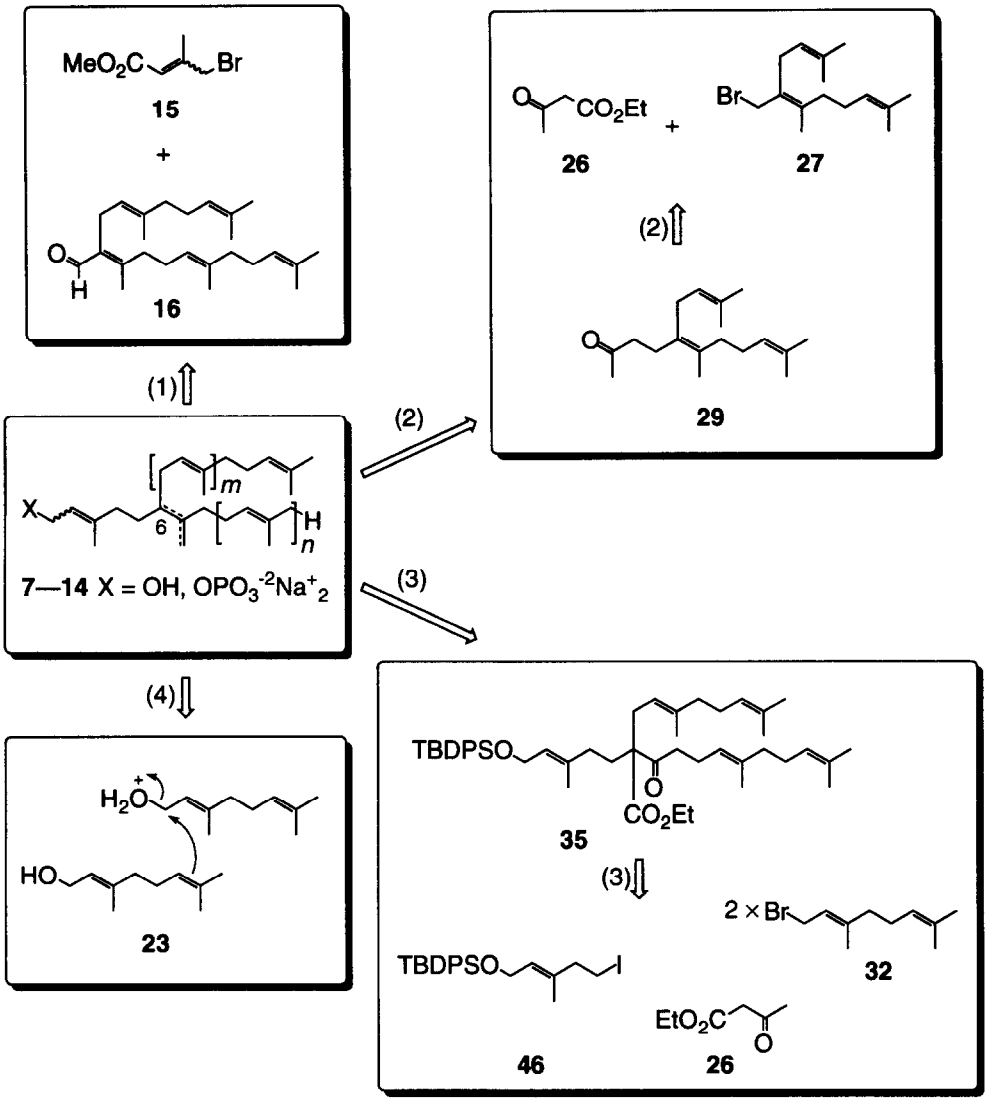


11 X = OH
12 X = $OPO_3^{2-}Na^+_2$



13 X = OH
14 X = $OPO_3^{2-}Na^+_2$

Retrosynthetic pathways (1)—(4) for the synthesis of 6-geranyl-substituted polyprenols and their phosphates **7**—**14** are shown in Scheme 1. The pathways involve (1) the elongation of a C_5 unit, methyl 4-bromo-3-methyl-2-butenoate **15**,[8] to 2-geranyl-farnesal **16**,[6a] (2) the alkylation of ethyl acetoacetate **26** with 2-prenyl-geranyl bromide **27**, (3) the successive substitution of ethyl acetoacetate **26** with geranyl bromide **32**, iodide **46**, and then geranyl bromide **32**, and (4) the acid-catalyzed condensation of two molecules of (*E*)-geraniol **23**.

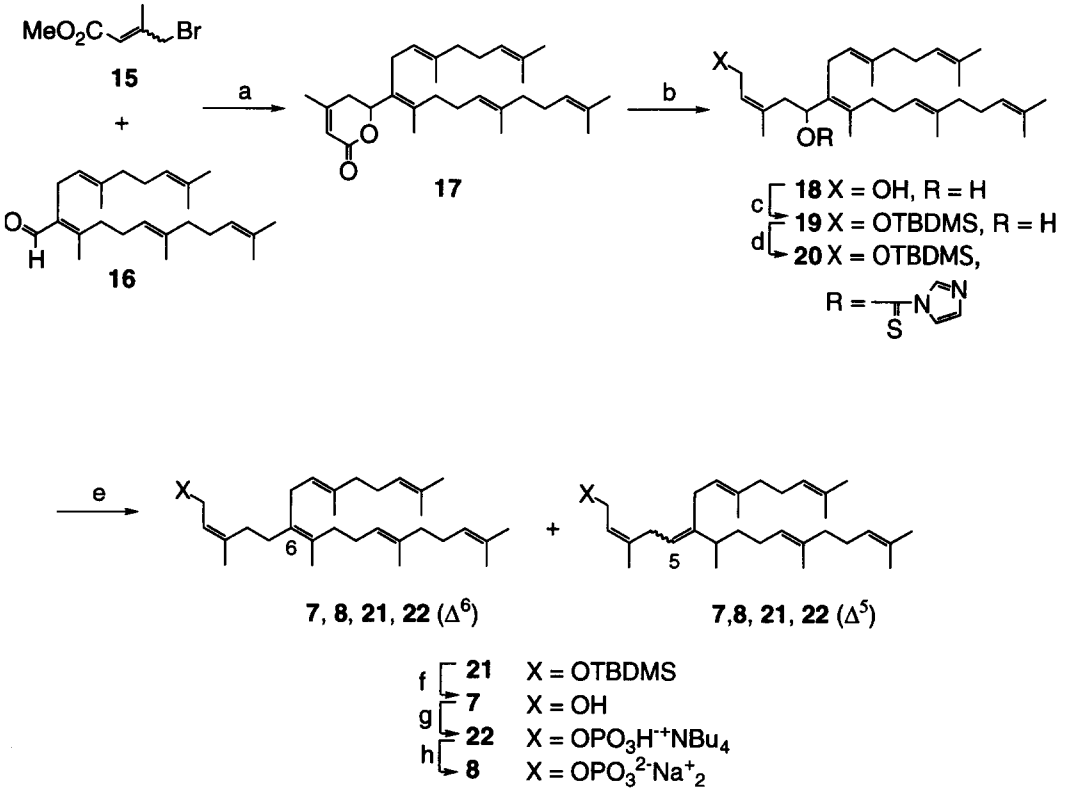


Scheme 1. Retrosynthetic pathways (1)—(4) for the synthesis of **7**—**14**.

Scheme 2 shows the synthetic pathway to the highly branched polyprenols **7** starting from methyl 4-bromo-3-methyl-2-butenoate **15** and 2-geranyl-farnesal **16**.[6a, 9] The Reformatsky reaction of **15** with **16** in THF under reflux gave lactone **17**,[10] which was then reduced with diisobutylaluminium hydride (DIBAL-H) to give diol **18** in 48% yield. The primary hydroxyl group of **18** was selectively protected with *t*-butyldimethylsilyl chloride (TBDMSCl) to give alcohol **19** in 90% yield. The alcohol **19** was transformed into thiocarbonylimidazolate **20** in 74% yield. Reduction of **20** with *n*-Bu3SnH gave an inseparable mixture of Δ^6-**21** and its isomer Δ^5-**21** (a mixture of 5*E* and 5*Z*) in 97% yield and in a ratio of 2 : 1. Hutchinson has

reported that the double bond migration in the reduction of thiocarbonylimidazolate of 7-oxobrefeldin A with *n*-Bu3SnH was suppressed when the reaction was performed in the presence of $Pd(PPh_3)_4$[11]. However, in our case the addition of $PdCl_2(PPh_3)_2$ or $Pd(PPh_3)_4$ gave a complex mixture. Neither the silyl ethers **21** nor the corresponding acetates (X = AcO) were not separated on silica gel TLC plate impregnated with silver nitrate. Finally, the silyl protecting group of **21** was removed using tetrabutylammonium fluoride to give a mixture of alcohols **7** (Δ^6 and Δ^5) in 84% yield

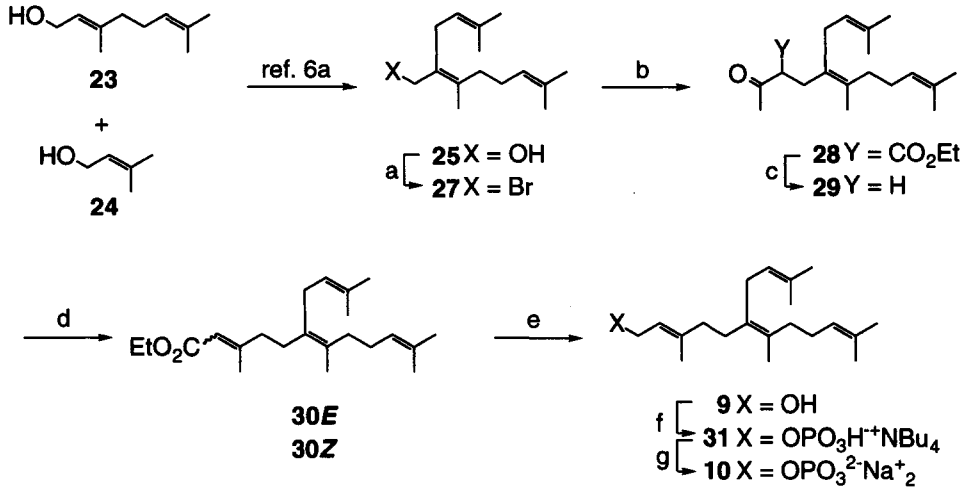
The alcohols **7** were then transformed into the corresponding disodium phosphates **8** via tetrabutylammonium hydrogenphosphates **22** in 48% yield.[6]



Scheme 2. (a) Zn, THF, reflux; (b) DIBAL-H, CH_2Cl_2, r.t.; (c) TBDMSCl, imidazole, DMF, 0 °C; (d) 1,1'-thiocarbonyldiimidazole, CH_2Cl_2, r.t.; (e) *n*-Bu3SnH, AIBN, toluene, 100 °C; (f) *n*-Bu4NF; (g) Cl_3CCN, (*n*-Bu4N)H2PO4, $CHCl_3$, r. t., then Sephadex LH-20 (eluent: MeOH); (h) CM-Sepharose FF(Na^+) (eluent: MeOH-$CHCl_3$, 2 : 1).

The second synthetic route, from geraniol **23** and prenol **24** into the phosphate **10**, is shown in Scheme 3. (*E*)-2-Prenyl-geraniol **25**[7, 12] was prepared from geraniol **23** and prenol **24** following the procedures reported for the synthesis of **4**,[6a] except for the isomerization of (*Z*)-2-prenyl-geranial to (*E*)-2-prenyl-geranial, the precursor of **25**. Trifluoroacetic acid catalyzed isomerization of the aldehydes was superior to the previously

reported photoisomerization in yield. The acetoacetic ester synthesis using ethyl acetoacetate **26** and 2-prenylgeranyl bromide **27**, prepared from the alcohol **25**, gave α-substituted β-keto ester **28** in 69% yield. The keto ester **28** was successively hydrolyzed and decarboxylated to give the methyl ketone **29** in 92% yield. The Horner-Emmons reaction of **29** with $(EtO)_2POCH_2CO_2Et$ gave α,β-unsaturated esters **30*E*** and **30*Z*** in 85% and 11% yields, respectively. The ester **30*E*** was then reduced with DIBAL-H to give the allylic alcohol **9** in 95% yield. The alcohol was transformed into the disodium phosphate **10** via tetrabutylammonium hydrogenphosphate **31** in 67% yield.

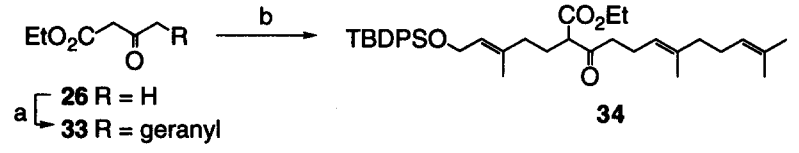


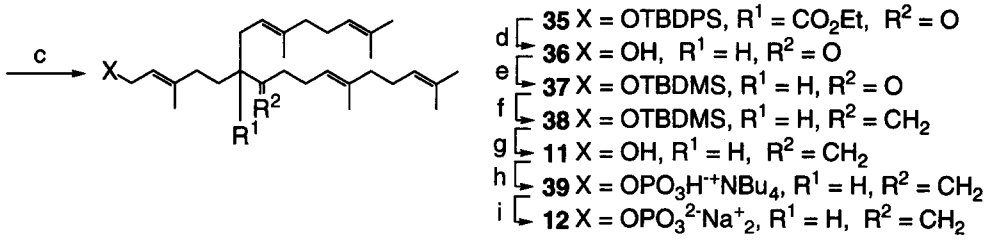
Scheme 3. (a) Ph_3P, CBr_4; (b) ethyl acetoacetate **26**, NaH, then bromide **27**; (c) NaOH, then AcOH; (d) $(EtO)_2POCH_2CO_2Et$, NaH, DME; (e) DIBAL-H; (f) Cl_3CCN, $(n\text{-}Bu_4N)H_2PO_4$, $CHCl_3$, r. t., then Sephadex LH-20 (eluent: MeOH); (g) CM-Sepharose FF(Na^+) (eluent: MeOH-$CHCl_3$, 2 : 1).

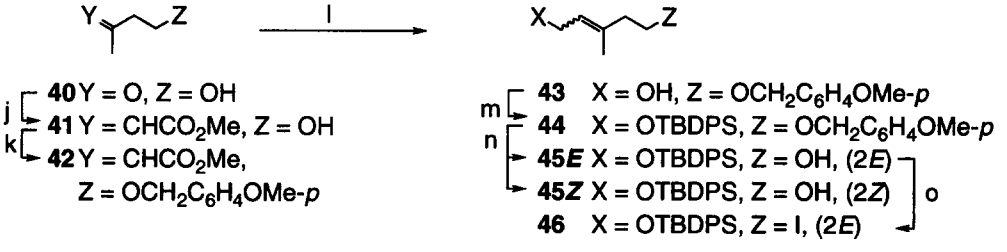
The third synthetic route, from ethyl acetoacetate **26**, geranyl bromide **32**, and iodide **46** (a C_6 unit; *vide infra*) to the phosphate **12**, is shown in Scheme 4. Allylation of the dianion derived from ethyl acetoacetate **26** with geranyl bromide **32** gave γ-geranyl-substituted β-keto ester **33** in 76% yield. The anion of β-keto ester **33** was then alkylated with iodide **46** to give α,γ-disubstituted β-keto ester **34** in 49% yield. Subsequent allylation of **34** with geranyl bromide **32** gave the α,α,γ-trisubstituted β-keto ester **35** in 88% yield. Hydrolysis and subsequent decarboxylation of the β-keto ester **35** gave hydroxy ketone **36**, which was then silylated with TBDMSCl to give ketone **37** in 66% yield. The methylenation of **37** using the Zn-CH_2Br_2-$TiCl_4$ system modified by Lombardo[13] gave **38** in 71% yield. The TBDMS ether was cleaved with tetrabutylammonium fluoride to give the alcohol **11** in 92% yield.

The iodide **46** (*vide supra*) was prepared from 4-hydroxy-2-butanone **40** as follows. The hydroxy ketone **40** was treated with stabilized ylide $Ph_3P{=}CHCO_2Me$ in boiling benzene to give hydroxy ester **41** as an inseparable mixture of *E*- and *Z*-isomers (*E* : *Z* = 2 : 1) in 57% yield.[14] Protection of the hydroxyl group in **41** with *p*-methoxybenzyl chloride, followed by reduction with DIBAL-H, gave allylic alcohol **43** in 74% yield.

After protection of the hydroxyl group in **43** with *t*-butyldiphenylsilyl chloride (TBDPSCl), the *p*-methoxybenzyl group was selectively deprotected with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to give alcohols **45*Z*** and **45*E*** in 47% yield. The diastereomers were easily separated using flash column chromatography on silica gel to give **45*Z*** (less polar) and **45*E*** in 4% and 35% yields, respectively.[15] The alcohol **45*E*** was transformed into the iodide **46** using I_2, hexamethylphosphorous triamide (HMPA), and triphenylphosphine in 97% yield.







Scheme 4. (a) LiN*i*-Pr2 (2 equiv), THF, then geranyl bromide **32**; (b) NaH, THF, then iodide **46**; (c) NaH, THF, then geranyl bromide **32**; (d) NaOH, then AcOH; (e) TBDMSCl, imidazole, DMF, r.t.; (f) Zn-CH_2Br_2-$TiCl_4$; (g) *n*-Bu4NF; (h) Cl_3CCN, (*n*-Bu4N)H_2PO_4, $CHCl_3$, r.t., then Sephadex LH-20 (eluent: MeOH); (i) CM-Sepharose FF(Na^+) (eluent: MeOH-$CHCl_3$, 2 : 1); (j) Ph_3P=$CHCO_2Me$; (k) *p*-$MeOC_6H_4CH_2Cl$ (l) DIBAL-H, CH_2Cl_2, -60 °C; (m) TBDPSCl, imidazole, DMF, r.t.; (n) DDQ; (o) I_2, PPh_3, HMPA, Et_2O, r.t.

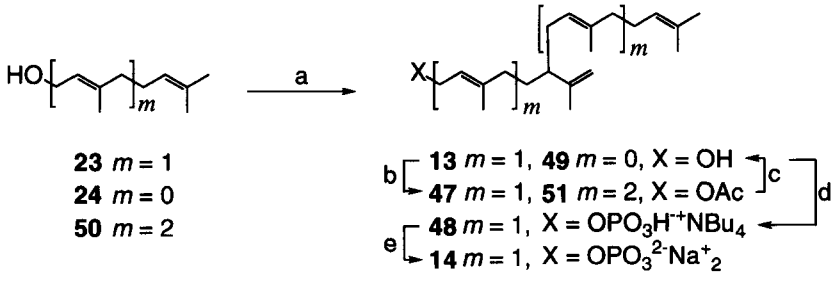
The alcohol **11** was then transformed into the disodium phosphates **12** via tetrabutylammonium hydrogenphosphates **39** in 75% yield.

The acetoacetic ester synthesis mentioned above, i.e. routes (2) and (3), will be applied to the synthesis of the prenyl- or farnesyl-substituted polyprenols and their phosphates.

Finally, the biomimetic direct condensation of (*E*)-geraniol **23** on montmorillonite K 10 was performed (Scheme 5). To our knowledge, little is known about biomimetic direct non-head-to-tail condensation of polyprenols.[16, 17] Treatment of (*E*)-geraniol **23** with montmorillonite K 10 (1 : 3 w/w ratio) under solvent-free conditions gave an inseparable mixture of alcohols along with linalool, digeranyl ether, and geranyl linaly ether. Acetylation of the alcohols, followed by chromatography on silica gel impregnated with 10% silver nitrate (hexane–ethyl acetate, 12 : 1), gave 6-geranyl-substituted geranyl acetate **47** in 3.5% yield. The structure of **47** was deduced from its IR and NMR spectra showing the presence of partial structures, H_2C=C(Me)-CH [IR 890 cm^{-1}; ^1H NMR δ 5.08 (1H, m), 4.75 (1H, m), 4.66 (1H, d, *J* = 1.8 Hz), and 1.61 (3H, s); ^{13}C NMR δ 147.39 (s), 111.41 (d), and 47.25 (d)] and $AcOCH_2CH$=CMe [^1H NMR δ 5.32 (1H, tq, *J* = 7.0 and 1.2 Hz), 4.58 (2H, d, *J* = 7.0 Hz), 2.05 (3H, s), and 1.68 (3H, s)]. The *E*-geometry of the Δ^8 double bond was assigned on the basis of the chemical shift of 9-Me (δ = 1.60 or 1.59). The stronger association of the sterically less encumbered methylene double bond with silver ion has enabled the isolation of acetate **47**, but the other acetates were not purified.

The alcohol **13** was then transformed into the disodium phosphate **14**[7] *via* tetrabutylammonium hydrogenphosphate **48** in 65% yield.

The similar treatment of prenol **24** on montmorillonite K 10 gave lavandulol **49** (5%)[18, 19] and diprenyl ether (13%). The condensation of (2*E*,6*E*)-farnesol **50** on montmorillonite K 10 followed by acetylation gave a mixture of acetates. After elimination of farnesyl acetate from the mixture under reduced pressure (115 °C, 2 mmHg), the residue was successively chromatographed on silica gel and on silica gel impregnated with 10% silver nitrate (hexane-ethyl acetate, 15 : 1 and then 9 : 1) to give 10-farnesyl-substituted farnesyl acetate **51** in 3% yield. Furthermore, 6-farnesyl-substituted farnesyl acetate [*m/z* 468, M^+; ^1H NMR δ 2.68 (t, *J* = 6.9 Hz, 9-H); ^{13}C NMR δ 48.84 (C-6)] was detected in the slightly less polar fractions (ca. 2 % yield), but its purification was not succeeded.



Scheme 5. (a) montmorillonite K10, r.t.; (b) Ac_2O, pyridine, then 10% $AgNO_3$-SiO_2 column chromatography (eluent: hexane-ethyl acetate, 12 : 1); (c) K_2CO_3, aq. EtOH, r.t.; (d) Cl_3CCN, (*n*-Bu_4N)H_2PO_4, $CHCl_3$, r. t., then Sephadex LH-20 (eluent: MeOH); (e) CM-Sepharose FF(Na^+) (eluent: MeOH-$CHCl_3$, 2 : 1).

The condensation of polyprenols on montmorillonite K 10 provided a simple and easy method for the synthesis of branched acyclic polyprenols, although the yields were low due to the polymerization reactions. The alcohol **13** will be prepared from ethyl acetoacetate **26**, iodide **46**, and geranyl bromide **32** following the third synthetic route described above.

EXPERIMENTAL

IR spectra were taken on a JASCO A-3 spectrometer for thin-layer films on sodium chloride plates. ^{1}H NMR spectra were recorded on a JEOL GSX-270 (270 MHz) or GSX-400 (400 MHz) spectrometer with $CDCl_3$ as the solvent and tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded on the instruments operating at 67.9 or 100.5 MHz with $CDCl_3$ as the solvent and internal standard (δ 77.05). ^{31}P NMR spectra with complete proton decoupling were recorded on the JEOL GSX-270 spectrometer operating at 109.4 MHz in $CDCl_3$ (external standard: phosphoric acid in D_2O). Mass spectra were obtained on a JEOL JMS-700 mass spectrometer. Precoated Merck Kieselgel 60 F_{254} and Wakogel C-300 were used for thin layer chromatography (TLC) and flash column chromatography, respectively. Sephadex LH-20 and CM-Sepharose FF were purchased from Pharmacia. Montmorillonite K 10 purchased from Aldrich was used without activation.

(2*Z*,6*E*,10*E*)-6-[(2*E*)-3,7-Dimethyl-2,6-octadienyl]-3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraene-1,5-diol (18)

To a mixture of **16** (294 mg, 0.83 mmol) and activated Zn powder (1.1 g, 17 mmol) in THF (2.0 cm^3) was added a solution of methyl 4-bromo-3-methyl-2-butenoate **15** (*E* : *Z* = 3 : 2; 3.2 g, 17 mmol) in THF (6.0 cm^3), and the mixture was heated under reflux for 1 h. The mixture cooled and acidified with 2% HCl was extracted with diethyl ether. The ethereal layer was washed successively with 5% HCl, water, saturated aqueous $NaHCO_3$, water, and brine, and then dried over anhydrous Na_2SO_4. Flash chromatography on silica gel (20 g; benzene) gave lactone **17** as an oil. To a solution of the lactone in CH_2Cl_2 (10 cm^3) was added a solution of DIBAL-H in hexane (0.95 mol dm^{-3}; 15 cm^3, 14 mmol) at 0 °C and the solution was stirred at room temperature for 20 h. An aqueous solution of NaOH (10%) and then diethyl ether were added. The organic layer was washed successively with 10% aqueous NaOH, water (until neutral), and brine, and dried over anhydrous Na_2SO_4. Chromatography on silica gel (20 g; hexane–AcOEt, 5 : 1) gave diol **18** (176 mg, 48% yield), an oil, IR 3327, 1045, 1025, and 997 cm^{-1}; ^{1}H NMR δ 5.75 (1H, dd, *J* = 8.4 and 6.8 Hz, 2-H), 5.22-4.95 (4H, m, 4 × CH=), 4.67 (1H, dd, *J* = 10.4 and 2.4 Hz, 5-H), 4.15 (1H, dd, *J* = 11.8 and 8.4 Hz, 1-H), 3.87 (1H, dd, *J* = 11.8 and 6.8 Hz, 1-H), 2.92 (1H, dd, *J* = 15.3 and 6.7 Hz, 1'-H), 2.82 (1H, dd, *J* = 15.3 and 6.7 Hz, 1'-H), 2.74 (1H, dd, *J* = 13.4 and 10.4 Hz, 4-H), 2.14–1.91 (12H, m, 6 × CH_2C=), 1.81 (3H, s, 3-Me), 1.74 (3H, s, Me), 1.69 (3H, s, Me), 1.68 (3H, s, Me), 1.65 (3H, s, Me), 1.61 (3H, s, Me), 1.60 (3H, s, Me), and 1.58 (3H, s, Me); ^{13}C NMR δ 138.32, 135.36, 135.03, 134.27, 131.85, 131.55, 131.40, 126.78, 124.88, 124.32, 124.26, 123.93, 68.84, 57.71, 39.74, 38.07, 35.01, 26.74, 26.66, 26.57, 25.97, 25.69, 23.72, 17.70, 17.66, 16.15, and 16.03; EI-MS *m/z* 442 (M^+, relative intensity 0.5%), 424 (M^+ - H_2O, 52), 406 (M^+ - 2H_2O, 17), 357 (100), 287 (45), 269 (35), 137 (55), 109 (51), 81 (61), and 69 (94). Found: *m/z* 424.3721 (M^+ - H_2O). Calcd for $C_{30}H_{48}O$: M - H_2O, 424.3705.

(2*Z*,6*E*,10*E*)-1-*t*-Butyldimethylsiloxy-6-[(2*E*)-3,7-dimethyl-2,6-octadienyl]-3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraen-5-ol (19)

To a solution of **18** (91 mg, 0.21 mmol) in *N*,*N*-dimethylformamide (1 cm^3) were added *t*-butyldimethylsilyl chloride (150 mg, 0.99 mmol) and imidazole (167 mg, 2.5 mmol). The mixture was stirred at 0 °C for 45 min and then extracted with pentane. The extract was washed successively with water and brine, and then dried over anhydrous Na_2SO_4. The crude product was chromatographed on silica gel (10 g; hexane–ethyl acetate, 30 : 1) to give *t*-butyldimethylsilyl ether **19** (105 mg, 90% yield), an oil, ^{1}H NMR δ 5.57 (1H, t, *J* = 7.0 Hz, 2-H),

5.23-5.03 (4H, m, 4 × CH=), 4.65 (1H, td, J = 10.0 and 3.3 Hz, 5-H), 4.18 (1H, dd, J = 11.9 and 7.0 Hz, 1-H), 4.08 (1H, dd J = 11.9 and 6.7 Hz, 1-H), 2.94 (1H, dd J = 15.3 and 7.0 Hz, 1'-H), 2.78 (1H, dd J = 15.3 and 5.8 Hz, 1'-H), 2.59 (1H, dd, J = 13.4 and 10.0 Hz, 4-H), 2.48 (1H, d, J = 3.3 Hz, 4-H), 2.12–1.85 (12H, m, 6 × CH_2C=), 1.80 (3H, s, 3-Me), 1.72 (3H, s, Me), 1.68 (6H, d, J = 0.9 Hz, 2 × Me), 1.66 (3H, d, J = 0.6 Hz, Me), 1.60 (6H, s, 2 × Me), 1.59 (3H, s, Me), 0.90 (9H, s, t-Bu), and 0.08 (6H, s, $SiMe_2$).

Thiocarbonylimidazolate 20

To a solution of **19** (105 mg, 0.12 mmol) in CH_2Cl_2 (2 cm^3) was added 1,1'-thiocarbonyldiimidazole (694 mg, 3.9 mmol) and the solution was stirred at room temperature for 14.5 h. Chromatography on silica gel (20 g; hexane–ethyl acetate, 15 : 1) gave thiocarbonylimidazolate **20** (90 mg, 74% yield), an oil, IR 1698, 1220, 1100, 1062, 882, 838, and 775 cm^{-1}; ^1H NMR δ 8.11 (1H, s, NCH=N), 7.40 (1H, d, J = 1 Hz, =CHNC=S), 7.04 (1H, d, J = 1 Hz, =CHN=), 5.50 (1H t, J = 7.1 Hz, 2-H), 5.38 (1H, m, 5-H), 5.17-4.88 (4H, m, 4 × CH=), 4.20 (2H, d, J = 6.4 Hz, 1-H), 2.94 (2H, m, CH_2), 2.84 (2H, d, J = 7.1 Hz, CH_2), 2.14-1.81 (12H, m, 6 × CH_2C=), 1.80 (3H, s, 3-Me), 1.73 (3H, d, J = 1.0 Hz, Me), 1.68 (3H, s, Me), 1.66 (3H, s, Me), 1.64 (3H, s, Me), 1.60 (3H, s, Me), 1.59 (3H, s, Me), 1.56 (3H, s, Me), 0.90 (9H, s, t-Bu)], and 0.07 (6H, s, $SiMe_2$).

(2*Z*,6*Z*,10*E*)-1-*t*-Butyldimethylsiolxy-6-[(2*E*)-3,7-dimethyl-2,6-octadienyl]-3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraene (Δ^6-21) and (2*Z*,10*E*)-1-*t*-Butyldimethylsiolxy-6-[(2*E*)-3,7-dimethyl-2,6-octadienyl]-3,7,11,15-tetramethyl-2,5,10,14-hexadecatetraene (Δ^5-21)

To a solution of **20** (21 mg, 0.031 mmol) in toluene (0.25 cm^3) were added n-Bu_3SnH (0.15 cm^3, 0.56 mmol) and a catalytic amount of AIBN. The solution was stirred at 100 °C for 15 min, and then chromatographed on silica gel (20 g; hexane–ethyl acetate, 20 : 1 and then 4 : 1) to give a mixture of Δ^6-**21** and Δ^5-**21** in a ratio of 2 : 1 (16 mg, 97% yield) as an oil, ^1H NMR δ 5.31 (1H, t, J = 5.1 Hz, 2-H), 5.22-4.93 (4.3H m, CH=), 4.19 (2H, d, J = 5.6 Hz, 1-H), 2.88-2.60 (2.7H, m, 1'-H and 4-H for Δ^5-**21**), 2.18-1.80 (14.7H, m, CH_2C=), 1.73, 1.68, 1.66, 1.60, 1.57, 1.55, (23H, 6 × s, 7 × Me and 7-Me for Δ^6-**21**), 0.97 (0.9H, d, J = 6.8 Hz, 7-Me for Δ^5-**21**), 0.90 (9H, s, t-Bu), and [0.067 and 0.065 (6H, 2 × s, $SiMe_2$)]; ^{13}C NMR δ 144.84, 144.42, 137.75, 137.52, 137.29, 136.73, 135.03, 134.79, 134.73, 134.54, 132.20, 132,15, 131.35, 131.30, 129.30, 125.13, 125.01, 124.82, 124.78, 124.46, 124.36, 123.70, 123.64, 123.50, 121.69, 121.57, 60.43, 60.06, 40.55, 39.86, 39.79, 35.86, 35.78, 34.56, 34.45, 31.26, 31.13, 30.90, 30.77, 29.12, 27.89, 27.38, 27.15, 26.80, 26.74, 26.69, 26.08, 25.73, 23.75, 23.62, 23.56, 22.31, 20.31, 20.23, 18.49, 18.19, 19.10, 17.71, 16.62, 16.19, 16.16, 16.02, 15.04, 13.71, 9.38, and -5.01.

(2*Z*,6*Z*,10*E*)-6-[(2*E*)-3,7-Dimethyl-2,6-octadienyl]-3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraen-1-ol (Δ^6-7) and (2*Z*,10*E*)-6-[(2*E*)-3,7-Dimethyl-2,6-octadienyl]-3,7,11,15-tetramethyl-2,5,10,14-hexadecatetraen-1-ol (Δ^6-7)

To a solution of **21** (216 mg, 0.32 mmol) in THF (3 cm^3) was added tetrabutylammonium fluoride (318 mg, 1.0 mmol), and the mixture was stirred at room temperature for 1 h. A drop of water was added and then the solvent was evaporated. The residue was extracted with diethyl ether and the ethereal layer was washed successively with water and brine, and then dried over anhydrous Na_2SO_4. The crude product was chromatographed on silica gel (20 g; benzene) to give a mixture of alcohols Δ^5- and Δ^6-**7** (116 mg, 84%), an oil, IR 3333 and 1001 cm^{-1}; ^1H NMR δ 5.48-5.37 (1H, m, 2-H), 5.20-4.97 (4.3H m, 4 × CH= and 5-H for Δ^5-**7**), 4.14 (1.3H, d, J = 7.1 Hz, 1-H for Δ^6-**7**), 4.09 (0.7H, m, 1-H for Δ^5-**7**), 2.80 (0.7H, d, J = 7.3 Hz, 4-H for Δ^5-**7**), 2.74 (2H, m, 1'-H), 2.18-1.78 (14.7H, m, CH_2C=), [1.76, 1.73, 1.66, 1.60, and 1.58 (23H,

7 × Me and 7-Me for Δ^6-**7**), and [0.99, and 0.98 (1H, d, J = 6.8 Hz, 7-Me for Δ^5-**7**)]; ^{13}C NMR δ 145.15, 144.71, 140.42, 140.33, 139.99, 139.60, 135.03, 134.96, 134.90, 134.85, 134.80, 134.73, 134.57, 132.07, 131.33, 131.29, 131.25, 129.62, 129.58, 127.68, 124.73, 124.68, 124.41, 124.29, 124.25, 123.85, 123.56, 123.53, 123.36, 121.54, 121.24, 59.41, 59.14, 59.07, 40.58, 39.80, 39.74, 39.72, 37.71, 35.77, 35.70, 34.52, 31.19, 30.98, 30.89, 30.56, 27.81, 27.07, 26.74, 26.67, 26.61, 26.56, 26.04, 25.69, 23.62, 20.25, 20.18, 18.20, 17.67, 16.16, 16.13, 16.10, and 15.97; EI-MS *m/z* 426 (M^+, 28%), 408 (M^+ - H_2O, 23), 339 (34), 271 (36), 189 (35), 159 (36), 147 (41), 121 (52), 119 ((52), 109 (49), 107 (54), 105 (47), 95 (53), 93 (48), 81 (70), and 69 (100). Found: *m/z* 426.3882 (M^+). Calcd for $C_{30}H_{50}O$: M, 426.3862.

Tetrabutylammonium (2*Z*,6*Z*,10*E*)-6-[(2*E*)-3,7-Dimethyl-2,6-octadienyl]-3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraenyl Hydrogenphosphate (Δ^6-22) and Tetrabutylammonium (2*Z*,10*E*)-6-[(2*E*)-3,7-Dimethyl-2,6-octadienyl]-3,7,11,15-tetramethyl-2,5,10,14-hexadecatetraenyl Hydrogenphosphate (Δ^5-22)

Alcohols **7** (108 mg, 0.25 mmol) were transformed to Δ^6-**22** and Δ^5-**22** (107 mg, 56% yield) following the procedures described previously.[6a] Compounds Δ^6-**22** and Δ^5-**22**, a viscous oil, ^{1}H NMR δ 6.60 (1H, br s, P–OH), 5.40 (1H, t, J = 6.1 Hz, 2-H), 5.20–4.88 (4.3H, m, CH=), 4.54–4.37 (2H, m, 1-H), 3.39–3.18 (8H, m, 4 × CH_2), 2.82–2.60 (2.7H, 1'-H and 4-H for Δ^5-**22**), 2.16–1.77 (14.7H, m, CH_2C=), [1.67, 1.64, 1.62, 1.59, 1.57 (23H, 7 × Me and 7-Me for Δ^6-**22**)], 1.45 (8H, q, J = 7.1 Hz, 4 × CH_2), and 0.98 (13H, t, J = 7.3 Hz, 4 × Me and 7-Me for Δ^5-**22**): ^{13}C NMR δ 144.25, 143.99, 136.03, 135.88, 135.67, 134.79, 134.63, 134.54, 134.44, 132.37, 132.11, 131.19, 131.16, 129.22, 128.84, 124.78, 124.71, 124.59, 124.46, 124.42, 124.39, 124.35, 124.29, 123.67, 123.59, 122.10, 122.02, 61.27, 61.20, 58.55, 40.26, 39.73, 35.81, 30.59, 27.85, 26.74, 26.63, 26.05, 25.65, 24.05, 19.66, 17.63, 16.10, 15.93, and 13.74; ^{31}P NMR δ 1.84 (s); negative FAB-MS (glycerol), *m/z* 505 [M - (2 × *n*-Bu_4N^+)]. Found: *m/z* 505.3409 [M - (2 × Bu_4N^+)]. Calcd for $C_{30}H_{50}O_4P$: 505.3447.

Disodium (2*Z*,6*Z*,10*E*)-6-[(2*E*)-3,7-Dimethyl-2,6-octadienyl]-3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraenyl Phosphate (Δ^6-8) and Disodium (2*Z*,10*E*)-6-[(2*E*)-3,7-Dimethyl-2,6-octadienyl]-3,7,11,15-tetramethyl-2,5,10,14-hexadecatetraenyl Phosphate (Δ^5-8)

Ion-exchange of phosphates **22** (101 mg, 0.14 mmol) using CM-Sepharose FF(Na^+) (eluent: MeOH–$CHCl_3$, 2 : 1) gave disodium phosphates Δ^6-**8** and Δ^5-**8** (68 mg, 86% yield), a viscous oil, ^{1}H NMR δ 5.39 (1H, m, 2-H), 5.20–4.87 (4.3H, m, CH=), 4.42 (2H, br s, 1-H), 2.88–2.58 (2.7H, m, 1'-H and 4-H for Δ^5-**8**), 2.13–1.77 (14.7H, m, CH_2C=), 1.70, 1.66, 1.64, 1.58, 1.57, 1.55 (23H, 7 × Me and 7-Me for Δ^6-**8**), and 0.94 (1H, d, J = 6.4 Hz, 7-Me for Δ^5-**8**); ^{13}C NMR δ 144.81, 139.83, 139.21, 134.77, 134.63, 134.56, 132.17, 131.84, 131.12, 129.52, 124.77, 124.49, 124.41, 123.50, 123.41, 121.45, 121.31, 62.32, 39.82, 35.93, 30.96, 30.57, 28.01, 26.81, 26.69, 26.15, 25.69, 23.59, 23.24, 20.16, 18.26, 18.18, 17.67, 16.13, and 15.97; ^{31}P NMR δ 3.38 (s); negative FAB-MS (glycerol), *m/z* 505 [M - (2 × Na^+) + H^+].

(2*E*)-3,7-Dimethyl-2-(3-methyl-2-butenyl)-2,6-octadien-1-ol (25)

To a solution of (*Z*)-2-prenyl-geranial (550 mg, 2.5 mmol), prepared from (*E*)-geranial and prenyl chloride following the reported procedures,[6a] in THF (19 cm^3) cooled to 0 °C was added a mixture of trifluoroacetic acid and THF (1 : 1 v/v; 38 cm^3). The solution was stirred at 35 °C for 3.5 h under nitrogen, and then saturated aqueous $NaHCO_3$ was added. After evaporation of the organic solvent the residue was extracted with ethyl acetate. The extract was washed successively with water and brine, and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated to give a mixture of (*E*)- and (*Z*)-2-prenyl-geranials (630 mg). Flash chromatography on silica gel (50 g; hexane-ether, 60 : 1) gave (*E*)-2-prenyl-geranial (154 mg, 28% yield) and

(*Z*)-2-prenyl-geranial (232 mg, 42% yield). (*E*)-2-Prenyl-geranial was reduced with DIBAL-H to give **25** in 87% yield. Compound **25**: an oil, ^{1}H NMR δ 5.15-5.03 (2H, m, 2 × CH=), 4.10 (2H, s, 1-H), 2.86 (2H, d, *J* = 6.9 Hz, 1'-H), 2.08 (4H, m, 2 × CH_2C=), 1.76 (3H, s, Me), 1.69 (9H, s, 3 × Me), and 1.61 (3H, s, Me); ^{13}C NMR δ 133.82, 132.06, 131.77, 131.60, 124.04, 122.99, 62.49, 34.74, 29.54, 26.93, 25.87, 25.77, 18.12, 17.89, and 17.70; EI-MS *m/z* 222 (M^+, 26) and 69 (100). Found: *m/z* 222.1972 (M^+). Calcd for $C_{15}H_{26}O$: M, 222.1984.

(5*E*)-5-Bromomethyl-2,6,10-trimethyl-2,5,9-undecatriene (27)

A mixture of alcohol **25** (398 mg, 1.79 mmol), CBr_4 (1.07 g, 3.2 mmol), and Ph_3P (798 mg, 3.05 mmol) in CH_2Cl_2 (8 cm^3) was stirred at 0 °C for 5 h. An aqueous $NaHCO_3$ and CH_2Cl_2 were added. The organic layer was washed successively with water and brine. Extraction of the crude product with hexane gave a mixture of **27** (*m/z* 286, M^+) and bis (2-prenyl-geranyl) ether (537 mg) in a ratio of 4 : 1.

Ethyl (4*E*)-2-Acetyl-5,9-dimethyl-4-(3-methyl-2-butenyl)-4,8-decadienoate (28)

Following the procedures reported for the synthesis of **6**,[6b] the β-keto ester **28** was prepared from ethyl acetoacetate **26** and bromide **27** in 69% yield. Compound **28**: an oil, IR 1719 cm^{-1}; ^{1}H NMR δ 5.09 (1H, m, CH=), 4.97 (1H, t, *J* = 6.8 Hz, CH=), 4.15 (2H, q, *J* = 7.3 Hz, CH_2), 3.58 (1H, t, *J* = 7.6 Hz, 2-H), 2.71 (2H, d, *J* = 6.8 Hz, 1'-H), 2.59 (2H, m, 3-H), 2.21 (3H, s, Ac), 2.02 (4H, m, 2 × CH_2C=), 1.68 (6H, s, 2 × Me), 1.67 (3H, s, Me), 1.65 (3H, s, Me), 1.60 (3H, s, Me), and 1.25 (3H, t, *J* = 7.3 Hz, Me); ^{13}C NMR δ 203.11, 169.72, 132.41, 131.74, 131.43, 128.04, 124.12, 123.08, 61.25, 58.23, 34.75, 30.75, 30.29, 29.36, 27.02, 25.84, 25.78, 18.58, 17.92, 17.69, and 14.18.

(5*Z*)-6,10-Dimethyl-5-(3-methyl-2-butenyl)-5,9-undecadien-2-one (29)

To a solution of keto ester **28** (373 mg, 1.12 mmol) in ethanol (8 cm^3) was added an aqueous solution of sodium hydroxide (1.2 mol dm^{-3}; 48 cm^3). The mixture was stirred at 50 °C for 3 h, and then acidified with acetic acid. After evaporation of the organic solvent, the residue was extracted with diethyl ether. The crude product was chromatographed on silica gel (30 g; hexane-ethyl acetate, 40 : 1) to give methyl ketone **29** (270 mg, 92% yield), an oil, IR 1717, 1161, and 829 cm^{-1};^{1}H NMR δ 5.10 (1H, m, CH=), 5.00 (1H, t, *J* = 6.9 Hz, CH=), 2.70 (2H, d, *J* = 6.9 Hz, 1'-H), 2.47-2.41 (2H, m, CH_2), 2.27-2.21 (2H, m, CH_2), 2.13 (3H, s, Ac), 2.02 (4H, m, 2 × CH_2C=), 1.68 (6H, s, 2 × Me), 1.65 (6H, s, 2 × Me), and 1.60 (3H, s, Me); ^{13}C NMR δ 208.85, 131.35, 131.27, 130.64, 129.85, 124.25, 123.25, 42.59, 34.54, 30.80, 29.89, 27.12, 26.74, 25.82, 25.76, 18.17, 17.86, and 17.66; EI-MS *m/z* 262 (M^+, 31%), 219 (11), 204 (20), 175 (26), 161 (18), 149 (21), 135 (100), 119 (25), 107 (28), 105 (24), 93 (27), and 69 (32). Found: *m/z* 262.2295 (M^+). Calcd for $C_{18}H_{30}O$: M, 262.2297.

Ethyl (2*E*,6*Z*)-3,7,11-Trimethyl-6-(3-methyl-2-butenyl)-2,6,10-dodecatrienoate (30*E*)

To a suspension of NaH (60% in mineral oil, 412 mg, 10.3 mmol) in 1,2-dimethoxyethane (21 cm^3) was added dropwise triethyl phosphonoacetate (2.05 cm^3, 10.3 mmol) at room temperature. The mixture was stirred at this temperature for 1h. A solution of ketone **29** (270 mg, 1.03 mmol) in DMF (20 cm^3) was added and the mixture was stirred at 50 °C for 3 h. Water was added and the aqueous solution was extracted with diethyl ether. The crude product was chromatographed on silica gel (50 g; hexane-benzene, 4 : 1) to give **30*E*** (291 mg, 85% yield) and its diastereomer **30*Z*** (39 mg, 11% yield). Compound **30*E***: an oil, IR 1718, 1648, 1222, 1145, 1051, and 863 cm^{-1}; ^{1}H NMR δ 5.66 (1H, s, 2-H), 5.11 (1H, m, CH=), 5.00 (1H, br t, *J* = 6.9 Hz, CH=), 4.14 (2H, q, *J* = 6.9 Hz, CH_2O), 2.71 (2H, d, *J* = 6.9 Hz, 1'-H), 2.17 (3H, d, *J* = 1 Hz, 3-Me), 2.13 (4H, m, 2 × CH_2C=), 2.04 (4H, m, 2 × CH_2C=), 1.69 (6H, s, 2 × Me), 1.65 (6H, s, 2 × Me), 1.61 (3H, s, Me), and 1.28 (3H, t, *J* = 6.9 Hz, Me); ^{13}C NMR δ 166.75, 160.15, 131.29, 131.06, 129.78, 124.30, 123.32,

115.29, 59.46, 39.87, 34.59, 30.89, 30.82, 27.18, 25.86, 25.78, 18.99, 18.20, 17.90, 17.70, and 14.43; EI-MS *m/z* 332 (M^+, 100%), 205 (88), 189 (83), 175 (70), 149 (65), 135 (75), 121 (59), 109 843), 107 (55), and 69 (60). Found: *m/z* 332.2681 (M^+). Calcd for $C_{22}H_{36}O_2$: M, 332.2715. Compound **30*Z***: an oil, ^{1}H NMR δ 5.63 (1H, s, 2-H), 5.12 (1H, m, CH=), 5.03 (1H, br t, *J* = 7.1 Hz, CH=), 4.13 (2H, q, *J* = 7.1 Hz, CH_2O), 2.76 (2H, d, *J* = 6.9 Hz, 1'-H), 2.63 (2H, m, CH_2C=), 2.14-2.08 (2H, m, CH_2C=), 2.04 (4H, m, 2 × CH_2C=), 1.89 (3H, d, *J* = 1 Hz, Me), 1.72 (3H, s, Me), 1.68 (6H, s, 2 × Me), 1.67 (3H, s, Me), 1.61 (3H, s, Me), and 1.26 (3H, t, *J* = 7.1 Hz, Me).

(2*E*,6*Z*)-3,7,11-Trimethyl-6-(3-methyl-2-butenyl)-2,6,10-dodecatrien-1-ol (9)

Following the procedures described for the preparation of **18**, α,β-unsaturated ester **30*E*** was reduced with DIBAL-H to yield **9** in 95% yield. Compound **9**, an oil, IR 3327 and 1003 cm^{-1}; ^{1}H NMR δ 5.41 (1H, t, *J* = 6.6 Hz, 2-H), 5.11 (1H, m, CH=), 5.01 (1H, t, *J* = 6.9 Hz, CH=), 4.15 (2H, t, *J* = 6.6 Hz, 1-H), 2.72 (2H, d, *J* = 6.9 Hz, 1'-H), 2.03 (8H, m, 4 × CH_2C=), 1.69 (6H, s, 2 × Me), 1.66 (6H, s, 2 × Me), and 1.61 (3H, s, Me); ^{13}C NMR δ 140.19, 131.81, 131.22, 131.01, 129.08, 124.37, 123.52, 122.93, 59.30, 38.22, 34.39, 30.98, 30.73, 27.04, 25.67, 25.60, 17.95, 17.69, 17.49, and 16.20; EI-MS *m/z* 290 (M^+, 56%), 205 (51), 149 (50), 135 (89), 109 (59), 107 (61), 95 857), 93 (71), 81 (42), and 69 (100). Found: *m/z* 290.2583(M^+). Calcd for $C_{20}H_{34}O$: M, 290.2609.

Tetrabutylammonium (2*E*,6*Z*)-3,7,11-Trimethyl-6-(3-methyl-2-butenyl)-2,6,10-dodecatrienyl Hydrogenphosphate (31)

Alcohol **9** (103 mg, 0.36 mmol) was transformed into **31** (165 mg, 76% yield) following the procedures described previously.[6a] Compound **31**: a viscous oil, ^{1}H NMR δ 5.38 (1H, t, *J* = 5.9 Hz, 2-H), 5.11 (1H, m, CH=), 5.00 (1H, br t, *J* = 7.0 Hz, CH=), 4.44 (2H, t, *J* = 5.9 Hz, 1-H), 3.33 (8H, m, 4 × CH_2N), 2.70 (2H, d, *J* = 6.9 Hz, 1'-H), 2.02 (8H, m, 4 × CH_2C=), 1.68 (6H, s, 2 × Me), 1.63 (9H, s, 3 × Me), 1.60 (3H, s, Me), 1.70-1.60 (8H, m, 4 × CH_2), 1.51-1.39 (8H, sext. *J* = 7.3 Hz, 4 × CH_2), and 0.99 (12H, t, *J* = 7.3 Hz, 4 × Me); ^{13}C NMR δ 136.73, 132.19, 131.18, 130.90, 128.67, 124.43, 123.54, 123.10, 61.46, 58.44, 38.32, 34.38, 31.20, 30.73, 27.03, 25.65, 23.90, 19.54, 17.89, 17.72, 17.51, 16.34, and 13.64; ^{31}P NMR δ 1.53 (s).

Disodium (2*E*,6*E*)-3,7,11-Trimethyl-6-(3-methyl-2-butenyl)-2,6,10-dodecatrienyl Phosphate (10)

Ion-exchange of the phosphate **31** (117 mg, 0.19 mmol) using CM-Sepharose FF(Na^+) (eluent: MeOH–$CHCl_3$, 2 : 1) gave disodium phosphates **10** (70 mg, 88% yield) as a viscous oil, ^{1}H NMR δ 5.37 (1H, m, 2-H), 5.09 (1H, m, CH=), 4.97 (1H, m, 2'-H), 4.38 (2H, m, 1-H), 2.67 (2H, m, 1'-H), 1.98 (8H, m, 3-H), 2.27-2.21 (2H, m, 4-H), 2.13 (3H, s, Ac), 2.02 (4H, m, 2 × CH_2CH=), 1.74 (3H, s, Me), 1.71 (3H, m, 4 × CH_2), 1.66 (3H, s, Me), 1.64 (6H, s, 2 × Me), 1,61 (6H, s, 2 × Me), and 1.58 (3H, s, Me); ^{13}C NMR δ 140.87, 131.93, 131.14, 130.79, 129.01, 124.60, 123.67, 120.47, 62.38, 38.51, 34.63, 31.44, 30.89, 27.17, 25.75, 25.69, 18.00, 17.78, 17.56, and 16.23; ^{31}P NMR δ 4.96 (br s); negative FAB-MS (glycerol): *m/z* 369 [M - (2 × Na^+) + H^+; 100]. Found: *m/z* 369.2224 [M - (2 × Na^+) + H^+]. Calcd for $C_{20}H_{34}O_4P$: 369.2194.

Ethyl (6*E*)-7,11-Dimethyl-3-oxo-6,10-dodecadienoate (33)

To a solution of Li*N*-*i*-Pr2, prepared from diisopropylamine (2.5 cm^3) and *n*-BuLi (1.6 mol dm^{-3} in hexane; 11.0 cm^3, 17.6 mmol) in anhydrous THF (11 cm^3) was added a solution of ethyl acetoacetate **26** (0.9 cm^3, 7.06 mmol) in anhydrous THF (1 cm^3), and the mixture was stirred at -75 °C for 30 min under nitrogen. A solution of geranyl bromide **32** (1.25 g, 5.76 mmol) in anhydrous THF (5 cm^3) was added, and the resulting

solution was stirred at 0 °C for 1 h. Usual workup and flash chromatography on silica gel (87 g; hexane-ethyl acetate, 60 : 1) gave **33** (1.16 g, 76% yield), an oil, IR 1749, 1719, 1235, and 1038 cm^{-1}; ^1H NMR δ 5.07 (2H, m, CH=), 4.20 (2H, q, J = 7.2 Hz, OCH_2), 3.43 (2H, s, 2-H), 2.57 (2H, t, J = 7.4 Hz, CH_2), 2.30 (2H, m, CH_2), 2.10-1.93 (4H, m, 2 × CH_2CH=), 1.68 (3H, s, Me), 1.61 (3H, s, Me), 1.60 (3H, s, Me), and 1.28 (3H, t, J = 7.2 Hz); ^{13}C NMR δ 202.6, 167.2, 136.8, 131.5, 124.1, 122.1, 61.3, 49.4, 43.0, 39.6, 26.6, 25.7, 22.1, 17.7, 16.0, and 14.1.

Ethyl (6*E*)-2-[(3*E*)-5-*t*-Butyldiphenylsiloxy-3-methyl-3-pentenyl]-7,11-dimethyl-3-oxo-6,10-dodecadienoate (34)

To a suspension of NaH (60% in mineral oil; 98 mg, 2.5 mmol) in anhydrous THF (2.2 m^3) cooled to 0 °C was added a solution of **33** (543 mg, 2.0 mmol) in anhydrous THF (7.3 cm^3) under nitrogen. The mixture was stirred at room temperature for 30 min, and then a solution of iodide **46** (1.1 g, 2.4 mmol) in anhydrous THF (7.5 cm^3) was added. The mixture was heated under reflux for 23 h. After evaporation of the solvent under reduced pressure, the residue was extracted with diethyl ether. Usual workup and flash chromatography on silica gel (62 g; hexane-ethyl acetate, 80 : 1 and then 110g; benzene) gave **34** (598 mg, 49% yield), an oil, IR 3072, 1745, 1716, 1112, 824, 740, and 702 cm^{-1}; ^1H NMR δ 7.67 (4H, m, Ph), 7.40 (6H, m, Ph), 5.38 (1H, m, CH=), 5.08 (2H, m, 2 × CH=), 4.19 (4H, m, 2 × CH_2O), 3.40 (1H, m, CH), 2.55 (1H, m), 2.27 (1H, m), 2.15-1.80 (8H, m), 1.67 (3H, s, Me), 1.61 (3H, s, Me), 1.59 (3H, s, Me), 1.42 (3H, s, Me), 1.26 (3H, t, J = 7.1 Hz, Me), and 1.04 (9H, s, *t*-Bu); EI-MS *m/z* 602 (M^+, 3%), 545 (48), 515 (36), 499 (50), 329 (52), 255 (52), 199 (100), 81 (42), and 69 (57). Found: *m/z* 602.3788 (M^+). Calcd for $C_{38}H_{54}O_4Si$: M, 602.3791.

Ethyl (6*E*)-2-[(3*E*)-5-*t*-Butyldiphenylsiloxy-3-methyl-3-pentenyl]-2-[(2*E*)-3,7-dimethyl-2,6-octadienyl)]-7,11-dimethyl-3-oxo-6,10-dodecadienoate (35)

To a suspension of NaH (60% in mineral oil; 31 mg, 0.78 mmol) in anhydrous THF (0.7 cm^3) cooled to 0 °C was added a solution of **34** (423 mg, 0.70 mmol) in anhydrous THF (2.5 cm^3). The mixture was stirred at room temperature for 30 min, and then a solution of geranyl bromide **32** (229 mg, 1.05 mmol) in anhydrous THF (2.5 cm^3) was added. The solution was heated under reflux for 1 h. After evaporation of the solvent under reduced pressure, the residue was extracted with diethyl ether. Usual workup and flash chromatography on silica gel (32 g; hexane-benzene, 1 : 1) gave **35** (457 mg, 88% yield), an oil, IR 1741, 1713, 112, 824, 740, and 703 cm^{-1}; ^1H NMR δ 7.69 (4H, m, Ph), 7.39 (6H, m, Ph), 5.35 (1H, m, CH=), 5.05 (3H, m, 3 × CH=), 4.88(1H, m, CH=), 4.18 (4H, m, 2 × CH_2O), 2.59 (2H, d, J = 7.1 Hz, CH_2), 2.40 (2H, m, CH_2), 2.27 (2H, m, CH_2), 2.10-1.85 (10H, m), 1.67 (6H, s, 2 × Me), 1.62 (3H, s, Me), 1.60 (3H, s, Me), 1.59 (3H, s, Me), 1.57 (3H, s, Me), 1.40 (3H, s, Me), 1.25 (3H, t, J = 7.1 Hz, Me), and 1.03 (9H, s, *t*-Bu); ^{13}C NMR δ 206.88, 172.41, 138.86, 136.40, 136.29, 135.64, 134.01, 131.56, 131.46, 129.55, 128.38, 127.63, 124.64, 124.23, 124.05, 122.62, 117.71, 63.10, 61.20, 61.08, 39.97, 39.73, 39.15, 33.83, 29.82, 26.87, 26.70, 26.61, 25.72, 22.50, 19.18, 17.73, 16.38, 16.29, 16.00, and 14.17; EI-MS *m/z* 739 (M^+, 5%), 681 (36), 199 (100), 81 (35), and 69 (70). Found: *m/z* 738.5008 (M^+). Calcd for $C_{48}H_{70}O_4Si$: M, 738.5043.

(6*E*,13*E*)-9-[(3*E*)-5-Hydroxy-3-methyl-3-pentenyl]-2,6,14,18-tetramethyl-2,6,13,17-nonadecatetraen-10-one (36)

To a solution of **35** (199 mg, 0.27 mmol) in ethanol (13 cm^3) cooled to 0 °C was added a solution of sodium hydroxide (2.2 g, 56 mmol) in aqueous ethanol [water (10 cm^3)/ethanol (26 cm^3)]. The mixture was stirred at 55 °C for 7 h and then at room temperature for 17 h. After acidification with acetic acid, the solvent was evaporated under reduced pressure to give a residue, which was extracted with diethyl ether. The extract was washed successively with water and saturated brine, and dried over anhydrous Na_2SO_4. The crude product was chromatographed on silica gel (30 g; hexane-ethyl acetate, 8 : 1) to give keto alcohol **36** (80 mg, 69% yield), an

oil, IR 3399, 1701, 999, and 835 cm^{-1}; ^1H NMR δ 5.38 (1H, t, J = 6.9 Hz, CH=), 5.07 (4H, m, 4 × CH=), 4.13 (2H, d, J = 6.8 Hz, OCH_2), 2.47-2.40 (3H, m), 2.27-2.17 (3H, m), 2.17-1.90 (11H, m), 1.68 (6H, s, 2 × Me), 1.65 (3H, s, Me), 1.61 (3H, s, Me), and 1.59 (9H, s, 3 × Me); ^{13}C NMR δ 213.94, 139.29, 137.35, 136.24, 131.53, 124.26, 124.16, 123.87, 122.87, 121.22, 59.37, 51.88, 42.90, 39.79, 39.73, 37.37, 30.44, 29.00, 26.73, 26.66, 25.72, 22.12, 17.71, 16.15, 16.11, and 16.04; Found: *m/z* 428.3659 (M^+). Calcd for $C_{29}H_{48}O_2$: M, 428.3654.

(6*E*,13*E*)-9-[(3*E*)-5-*t*-Butyldimethylsiloxy-3-methyl-3-pentenyl]-2,6,14,18-tetramethyl-2,6,13,17-nonadecatetraen-10-one (37)

To a solution of **36** (148 mg, 0.35 mmol) in *N*,*N*-dimethylformamide (1.4 cm^3) were added imidazole (147 mg, 2.2 mmol) and *t*-butyldimethylsilyl chloride (115 mg, 0.76 mmol). The mixture was stirred at room temperature for 1.8 h, and then extracted with hexane. The extract was washed successively with water and saturated brine, and then dried over anhydrous Na_2SO_4 . The crude product was chromatographed on silica gel (11 g; hexane-ethyl acetate, 10 : 1) to give **37** (184 mg, 98%), an oil, IR 1714, 1256, 1069, 836, and 776 cm^{-1}; ^1H NMR δ 5.28 (1H, m, CH=), 5.06 (4H, m, 4 × CH=), 4.16 (2H, d, J = 6.3 Hz, OCH_2), 2.43 (3H, m), 2.24 (3H, m), 2.15-1.85(11H, m), 1.67 (6H, s, 2 × Me), 1.61 (3H, s, Me), 1.59 (12H, s, 4 × Me), 7 × Me], 0.90 (9H, s, *t*-Bu), and 0.06 (6H, s, $SiMe_2$); ^{13}C NMR δ 214.05, 137.25, 136.43, 136.15, 131.51, 131.42, 125.00, 124.29, 124.18, 122.89, 121.31, 65.91, 60.23, 51.77, 43.00, 39.80, 39.73, 37.33, 30.41, 29.02, 26.73, 26.66, 26.05, 25.73, 22.12, 18.45, 17.71, 16.16, 16.04, 15.32, and -5.04.

(6*E*,13*E*)-9-[(3*E*)-5-*t*-Butyldimethylsiloxy-3-methyl-3-pentenyl]-2,6,14,18-tetramethyl-10-methylene-2,6,13,17-nonadecatetraene (38)

To a mixture of activated zinc dust (3.4 g, 53.0 mmol) and CH_2Br_2 (1.2 cm^3, 17.2 mmol) in THF (30 cm^3) cooled to -45 °C was added dropwise $TiCl_4$ (1.4 cm^3, 12.7 mmol). The mixture was allowed to warm to 4 °C, and stirred at this temperature for 3 days to give a thick gray slurry. To a solution of **37** (166 mg, 0.31 mmol) in CH_2Cl_2 (10 cm^3) cooled to 0 °C was added portionwise the ice-cold slurry, and the resulting mixture was stirred at room temperature for 4 h. The mixture was poured into a slurry of $NaHCO_3/H_2O$/ether. The resulting mixture was shaken until a clear organic solution was obtained. Chromatography on silica gel (105 g; hexane-benzene, 6: 1) gave **38** (117 mg, 71% yield), an oil, IR 1070, 836, and 775 cm^{-1}; ^1H NMR δ 5.28 (1H, t, J = 6.4 Hz, CH=), 5.17-5.05 (4H, m, 4 × CH=), 4.79 (1H, s, =C*H*H), 4.75 (1H, s, =CH*H*), 4.17 (2H, d, J = 6.4 Hz, OCH_2), 2.20-1.80 (17H, m), 1.68 (9H, s, 3 × Me), 1.60 (12H, s, 4 × Me), 0.90 (9H, s, *t*-Bu), and 0.06 (6H, s, $SiMe_2$). Found: *m/z* 540.4733 (M^+). Calcd for $C_{36}H_{64}OSi$: M, 540.4727.

(2*E*,10*E*)-6-[(2*E*)-3,7-Dimethyl-2,6-octadienyl]-3,11,15-trimethyl-7-methylene-2,10,14-hexadecatrien-1-ol (11)

To a solution of **38** (103 mg, 0.20 mmol) in THF (1.4 cm^3) was added a solution of TBAF (256 mg, 0.98 mmol) in THF (1.9 cm^3), and the mixture was stirred at 25 °C for 3 h. Workup as described above and flash chromatography on silica gel (5.4 g; hexane-ethyl acetate, 10 : 1) gave **11** (75 mg, 92% yield), an oil, IR 3340, 1108, 1018, and 889 cm^{-1}; ^1H NMR δ 5.39 (1H, t, J = 6.9 Hz, 2-H), 5.25-5.0 (4H, m, 4 × CH=), 4.80 (1H, s, =C*H*H), 4.75 (1H, s, =CH*H*), 4.14 (2H, t, J = 6.9 Hz, OCH_2), 2.4-1.9 (19H, m), 1.68 (6H, s, 2 × Me), 1.66 (3H, s, Me), and 1.60 (12H, s, 4 × Me); ^{13}C NMR δ 151.72, 140.37, 135.55, 135.15, 131.36, 131.29, 124.41, 124.35, 123.10, 109.27, 59.48, 46.57, 39.85, 39.74, 37.40, 33.34, 32.76, 31.22, 26.77, 26.34, 25.73, 17.73, 16.35, 16.23, and 16.09; EI-MS *m/z* 426 (M^+, 6%), 408 (M^+ - H_2O, 14), 339 (15), 271 (18), 81 (42), and 69 (100). Found: *m/z* 426.3829 (M^+). Calcd for $C_{30}H_{50}O$: M, 426.3862.

Disodium (2*E*,10*E*)-6-[(2*E*)-3,7-Dimethyl-2,6-octadienyl]-3,11,15-trimethyl-7-methylene-2,10,14-hexadecatrienyl Phosphate (12)

^{1}H NMR δ 5.32 (1H, t, *J* = 5.7 Hz, 2-H), 5.15-5.00 (4H, m, 4 × CH=), 4.77 (1H, s, =C*H*H), 4.71 (1H, s, =CH*H*), 4.34 (2H, br s, 1-H), 2.15-1.80 (17H, m), 1.66 (6H, s, 2 × Me), 1.61 (3H, s, Me), and 1.59 (12H, s, 4 × Me); ^{31}P NMR δ 2.91 (s); negative FAB-MS (glycerol) *m/z* 505 [M - (2 × Na^+) + H^+; 100]. Found: *m/z* 505.3422 [M - (2 × Na^+) + H^+]. Calcd for $C_{30}H_{50}O_4P$: 505.3446.

Methyl 5-Hydroxy-3-methyl-2-pentenoates (41)

A solution of Ph_3P=$CHCO_2Me$ (7.4 g, 22 mmol) and 4-hydroxy-2-butanone **40** (6.4 g, 72 mmol) in benzene (36 cm^3) was heated under reflux for 11 h, and then stirred at room temperature for 11 h. The solvent was evaporated, and the residue was chromatographed on silica gel (150g; hexane-ethyl acetate, 3 : 1) to give a mixture of **41*E*** and **41*Z*** in a ratio of 2 : 1 (1.8 g, 57% yield) as an oil. **41*E***: ^{1}H NMR δ 5.75 (1H, d, *J* = 1.2 Hz, CH=), 3.80 (2H, m, OCH_2), 3.69 (3H, s, Me), 2.41 (2H, t, *J* = 6.3 Hz, CH_2), and 2.20 (3H, d, *J* = 1.2 Hz, Me). **41*Z***: ^{1}H NMR δ 5.85 (1H, s, CH=), 3.80 (2H, m, OCH_2), 3.70 (3H, s, Me), 2.85 (t, *J* = 6.3 Hz, CH_2), and 1.96 (3H, d, *J* = 1.2 Hz, Me).

5-*p*-Methoxybenzyloxy-3-methyl-2-penten-1-ols (43)

To a solution of **41** (*E* : *Z* = 2 : 1; 1.8 g, 12.7 mmol) in $CHCl_3$ (70 cm^3) cooled to 0 °C were added Ag_2O (9.96 g) and 4-methoxybenzyl chloride (12.2 cm^3, 89.6 mmol). The mixture was stirred at room temperature for 21 h, and then filtered. The crude product was chromatographed on silica gel (160g; hexane-ethyl acetate, 25: 1) to give **42** containing 4-methoxybenzyl alcohol. To a solution of the crude ester **42** (9.1 g) in CH_2Cl_2 (50 cm^3) cooled to 0 °C was added DIBAL-H (0.94 mol dm^{-3} in hexane; 28.3 cm^3, 26.6 mmol). The mixture was stirred at 0 °C for 2.8 h. Workup as described above and chromatography on silica gel (70 g; hexane-ethyl acetate, 6 : 1) gave a mixture of (2*E*)- and (2*Z*)-**43** (2.2 g, 74% yield from **41**) as an oil. (2*E*)-**43** was partly isolated by chromatography on silica gel: ^{1}H NMR δ 7.25 (2H, d, *J* = 8.5 Hz, ArH), 6.88 (2H, d, *J* = 8.5 Hz, ArH), 5.46 (1H, tt, *J* = 7.0 and 1.2 Hz, 2-H), 4.44 (2H, s, O-CH_2), 4.15 (2H, d, *J* = 7.0 Hz, 1-H), 3.80 (3H, s, OMe), 3.54 (2H, t, *J* = 6.8 Hz, CH_2), 2.33 (2H, t, *J* = 6.8 Hz, CH_2), and 1.69 (3H, s, Me).

5-*t*-Butyldiphenylsiloxy-3-methyl-3-penten-1-ols (45)

To a solution of **43** (*E* : *Z* = 2 : 1; 2.2 g, 9.4 mmol) in *N*,*N*-dimethylformamide (16 cm^3) were added imidazole (2.0 g, 29 mmol) and *t*-butyldiphenylsilyl chloride (2.5 cm^3, 9.9 mmol). The mixture was stirred at room temperature for 3.5 h. Workup as described above gave **44** as an oil. To a mixture of **44** (*E* : *Z* = 2 : 1; 2.4 g, 5.1 mmol) in CH_2Cl_2 (31 cm^3) and water (2.8 cm^3) cooled to 0 °C was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (1.36 g, 6.0 mmol) in CH_2Cl_2 (20 cm^3). The mixture was stirred at room temperature for 40 min. To the solution cooled to 0 °C was added saturated aqueous $NaHCO_3$ and the resulting precipitate was removed by decantation. The organic layer was washed successively with aqueous $NaHCO_3$ and brine, and then dried over anhydrous Na_2SO_4 . The crude product was chromatographed on silica gel (150 g; hexane-ethyl acetate, 8 : 1) to give a mixture of **45*E*** and **45*Z*** (849 mg, 47% yield from **43**). The mixture was carefully chromatographed on silica gel to give **45*E*** (an oil; 631 mg, 35% yield) and **45*Z*** (an oil; 73 mg, 4% yield). Compound **45*E***: IR 3352, 1113, 1067, 823, 739, and 702 cm^{-1}; ^{1}H NMR δ 7.71-7.67 (4H, m, Ph), 7.46-7.35 (6H, m, Ph), 5.46 (1H, td, *J* = 6.1 and 1.2 Hz, 4-H), 4.24 (2H, dd, *J* = 6.1 and 0.7 Hz, 5-H), 3.64 (2H, q, *J* = 6.1 Hz, 1-H), 2.23 (2H, t, *J* = 6.1 Hz, CH_2), 1.46 (3H, d, *J* = 0.5 Hz, Me), 1.33 (1H, m, OH), and 1.04 (9H, s, *t*-Bu); ^{13}C NMR δ 135.54, 133.80, 133.40, 129.57, 127.60, 127.11, 60.86, 59.92, 42.34, 26.80, 19.09, and 16.05. Compound **45*Z***: IR 3374, 1113, 1063, 824, 739, and 702 cm^{-1}; ^{1}H NMR δ 7.72-7.67 (4H, m, Ph), 7.46-7.35 (6H, m, Ph), 5.59 (1H, td, *J* = 7.1 and 0.7 Hz, 4-H), 4.15 (2H, dd, *J* = 7.1 and 0.7 Hz, 5-H), 3.61 (2H, q, *J* = 6.0 Hz, 1-H), 2.25 (2H, t, *J* = 6.0 Hz, CH_2), 2.06 (1H, t, *J* = 6.0 Hz, OH),

1.76 (3H, d, J = 1.2 Hz, Me), and 1.04 (9H, s, t-Bu); ^{13}C NMR δ 136.24, 135.60, 133.53, 129.64, 127.65, 126.70, 60.04, 59.75, 35.14, 26.72, 23.45, and 19.06.

(2*E*)-1-*t*-Butyldiphenylsiloxy-5-iodo-3-methyl-2-pentene (46)

To a solution of triphenylphosphine (554 mg, 2.11 mmol) and HMPA (0.7 cm^3) in diethyl ether (3.7 cm^3) was added iodine (543 mg, 2.1 mmol). The mixture was stirred at room temperature for 20 min. A solution of alcohol **45*E*** (228 mg, 0.64 mmol) in diethyl ether (1.9 cm^3) was then added, and the mixture was stirred for 3 h. After dilution with diethyl ether, the ethereal solution was washed successively with 10% Na_2SO_3, dilute H_2SO_4, aqueous $NaHCO_3$, water, and brine. The crude product was chromatographed on silica gel (31 g; hexane) to give iodide **46** (290 mg, 97% yield), an oil, IR 1609, 1112, 899, 824, 739, and 701 cm^{-1}, ^{1}H NMR δ 7.69 (4H, m, Ph), 7.40 (6H, m, Ph), 5.43 (1H, t, J = 6.1 Hz, CH=), 4.21 (2H, d, J = 6.1 Hz, CH_2O), 3.18 (2H, t, J = 7.6 Hz, CH_2), 2.52 (2H, t, J = 7.6 Hz, CH_2), 1.44 (3H, s, Me), and 1.04 (9H, s, t-Bu).

(2*E*,8*E*)-6-Isopropenyl-3,9,13-trimethyl-2,8,12-tetradecatrienyl Acetate (47)

A mixture of geraniol **23** (1.0 g) and montmorillonite K 10 (3.0 g) was allowed to stand at room temperature for 2 h. The product was extracted with ethyl acetate. Volatile components (419 mg) containing geraniol and linalool were eliminated by bulb-to-bulb distillation (110 °C, 4 mmHg). The residue (485 mg) was chromatographed on silica gel (hexane-ethyl acetate, 10 : 1) to give fractions containing ethers (64 mg), and fractions containing alcohols (91 mg). From the former mixture, geranyl linalyl ether (12 mg, 1%) and digeranyl ether (45 mg, 4%) were isolated. The alcohols were treated with acetic anhydride (1.0 cm^3) and pyridine (1.0 cm^3). The mixture of acetates was chromatographed on silica gel impregnated with silver nitrate (10%; 6 g) to give **47** (37 mg, 3.5%), an oil, IR 3080, 1745, 1670, 1645, 1230, 1025, and 890 cm^{-1}; ^{1}H NMR δ 5.32 (1H, tq, J = 7.0 and 1.2 Hz, 2-H), 5.08 (2H, m, 2 × CH=), 4.75 (1H, m, =C*H*H), 4.66 (1H, d, J = 1.8 Hz, =CH*H*), 4.58 (2H, d, J = 7.0 Hz, OCH_2), 2.10-1.87 (9H, m, 4 × CH_2 and CH), 2.05 (3H, s, Ac), 1.68 (3H, s, Me), 1.67 (3H, s, Me), 1.61 (3H, s, Me), 1.60 (3H, s, Me), 1.59 (3H, s, Me), and 1.55-1.37 (2H, m, CH_2); ^{13}C NMR δ 171.10, 147.39, 142.63, 135.48, 131.21, 124.35, 122.95, 118.02, 111.41, 61.41, 47.25, 39.76, 37.33, 32.20, 30.55, 26.66, 25.66, 21.03, 18.59, 17.66, 16.46, and 16.13; EI-MS m/z 332 (M^+, 6%), 272 (24), 204 (51), 161 (23), 135 (54), 121 (47), 107 (56), 95 (50), 93 (86), 81 (93), and 69 (100). Found: m/z 332.2725 (M^+). Calcd for $C_{22}H_{36}O_2$: M, 332.2715.

(2*E*,8*E*)-6-Isopropenyl-3,9,13-trimethyl-2,8,12-tetradecatrien-1-ol (13)

^{1}H NMR δ 5.43 (1H, tq, J = 6.8 and 1.2 Hz, 2-H), 5.08 (2H, m, 8-H and 12-H), 4.76 (1H, m, =C*H*H), 4.68 (1H, m, =CH*H*), 4.14 (2H, d, J = 6.8 Hz, OCH_2), 2.05-1.89 (9H, m, 4 × CH_2 and CH), 1.68 (3H, s, Me), 1.67 (3H, s, Me), 1.62 (3H, s, Me), 1.60 (6H, s, 2 × Me), and 1.53-1.39 (2H, m, CH_2).

Disodium (2*E*,8*E*)-6-Isopropenyl-3,9,13-trimethyl-2,8,12-tetradecatrienyl Phosphate (14)

^{1}H NMR δ 5.33 (1H, m, 2-H), 5.07 (2H, m, 8-H and 12-H), 4.72 (1H, m, =C*H*H), 4.64 (1H, m, =CH*H*), 4.34 (2H, m, OCH_2), 2.00-1.85 (9H, m, 8 × CH_2 and CH), 1.66 (3H, s, Me), 1.61 (3H, s, Me), 1.57 (9H, s, 3 × Me), and 1.43 (2H, m, CH_2); ^{31}P NMR δ -2.31 (s); negative FAB-MS (glycerol): m/z 369 [M - (2 × Na^+) + H^+; 100]. Found: m/z 369.2216 [M - (2 × Na^+) + H^+]. Calcd for $C_{20}H_{34}O_4P$: 369.2194.

(2*E*,6*E*,12*E*,16*E*)-10-Isopropenyl-3,7,13,17,21-pentamethyl-2,6,12,16,20-docosapentaenyl Acetate (51)

IR 3080, 1745, 1670, 1645, 1230, 1025, and 890 cm^{-1}; ^{1}H NMR δ 5.34 (1H, tq, J = 7.0 and 1.2 Hz, 2-H), 5.15-5.05 (4H, m, 4 × CH=), 4.73 (1H, m, =C*H*H), 4.65 (1H, d, J = 1.7 Hz, =CH*H*), 4.59 (2H, d, J = 7.0 Hz, OCH_2), 2.15-1.80 (17H, m, 8 × CH_2 and CH), 2.05 (3H, s, Ac), 1.70 (3H, s, Me), 1.68 (3H, s, Me),

1.61 (3H, s, Me), 1.59 (9H, s, Me), 1.58 (3H, s, Me), and 1.51-1.32 (2H, m, CH_2); ^{13}C NMR δ 171.10, 147.71, 142.29, 135.78, 135.39, 134.88, 131.24, 124.42, 124.27, 123.44, 123.10, 118.25, 111.20, 61.41, 47.20, 39.81, 39.73, 39.57, 37.44, 32.20, 31.09, 26.80, 26.69, 26.22, 25.69, 21.04, 18.65, 17.67, 16.48, 16.19, and 16.00; EI-MS *m/z* 468 (M^+, 6%), 408 (12), 339 (20), 272 (33), 203 (28), 161 (29), 149 (43), 137 (64), 135 (57), 123 (60), 121 (91), 109 (42), 107 (57), 95 (60), 93 (67), 81 (67), and 69 (100). Found: *m/z* 468.3955 (M^+). Calcd for $C_{32}H_{52}O_2$: M, 468.3967.

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