Natural and Unnatural Terpenoid Precursors of Insect Juvenile Hormone

Stephanie E. Sen* and Gregory J. Ewing

Department of Chemistry, Indiana University−Purdue University at Indianapolis (IUPUI), 402 North Blackford Street, Indianapolis Indiana 46202

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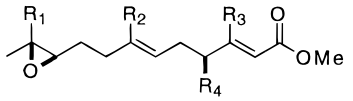
The biosynthesis of insect juvenile hormone (JH) is due, in part, to the precise head-to-tail coupling of allylic and homoallylic diphosphate substrates, as catalyzed by one or more prenyltransferases. To better understand this enzyme's role in JH production, homodimethylallyl diphosphate and both the natural and unnatural homologs of geranyl diphosphate have been prepared as potential substrates for insect prenyltransferase. These latter materials were constructed in a convergent manner by olefination of the corresponding trisnoraldehydes obtained from either terminal oxidative cleavage of geraniol or higher-order cuprate conjugate addition to acrolein. To aid in characterizing the nature of the terpenoid skeletons formed from our *in vitro* studies, homologous derivatives of farnesol were also prepared by anion coupling of the geranyl derivatives to either C_5 or C_6 allylic bromides. The preparation of these materials and the results of incubations with larval corpora allata homogenates of the lepidopteran *Manduca sexta* are described.

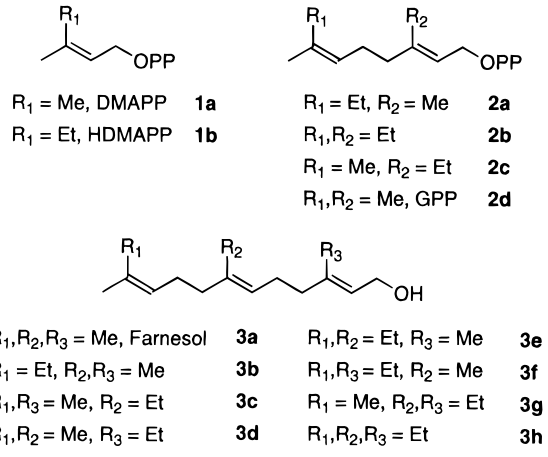
Introduction

We are currently studying the activity of insect prenyltransferase, a key enzyme in the biosynthesis of insect juvenile hormone (JH).[1] JH III, the most commonly-occurring JH structure, is derived from farnesyl diphosphate which is obtained from the coupling of two molecules of isopentenyl diphosphate (IPP) with dimethylallyl diphosphate (DMAPP).[2] Interestingly, lepidopteran insects produce a complex mixture of JH structures; for example, in the tobacco hornworm, *Manduca sexta*, JH has been identified as five different epoxy-farnesoate homologs (JH 0−JH III, and methyl JH I, Figure 1).[3] Despite considerable research in the area of JH biosynthesis,[4] the factors which control JH homolog formation have yet to be fully elucidated. Because of the potential utility of agents which disrupt JH biosynthesis as insecticides and because of the pivotal role that prenyltransferase plays in the construction of the JH carbon skeletons, we felt that a systematic study of the substrate specificity of lepidopteran prenyltransferase would be useful in determining whether this enzyme could serve as a new target for anti-juvenoid development.[5] To perform these experiments, we required homodimethylallyl diphosphate (HDMAPP, **1b**) and all possible homologs of the intermediate geranyl diphosphate (GPP, compounds **2a**−**d**, Figure 2). Herein, we report on the preparation of these compounds, as well as the synthesis



R_1,R_2,R_3 = Et, R_4 = H	JH 0
R_1,R_2 = Et, R_3 = Me, R_4 = H	JH I
R_1 = Et, R_2,R_3 = Me, R_4 = H	JH II
R_1,R_2,R_3 = Me, R_4 = H	JH III
R_1,R_2 = Et, R_3 = Me, R_4 = Me	Me-JH I

Figure 1. Lepidopteran juvenile hormone (JH) structures.



R_1 = Me, DMAPP	**1a**	R_1 = Et, R_2 = Me	**2a**
R_1 = Et, HDMAPP	**1b**	R_1,R_2 = Et	**2b**
		R_1 = Me, R_2 = Et	**2c**
		R_1,R_2 = Me, GPP	**2d**

R_1,R_2,R_3 = Me, Farnesol	**3a**	R_1,R_2 = Et, R_3 = Me	**3e**
R_1 = Et, R_2,R_3 = Me	**3b**	R_1,R_3 = Et, R_2 = Me	**3f**
R_1,R_3 = Me, R_2 = Et	**3c**	R_1 = Me, R_2,R_3 = Et	**3g**
R_1,R_2 = Me, R_3 = Et	**3d**	R_1,R_2,R_3 = Et	**3h**

Figure 2. Allylic diphosphate precursors to natural and unnatural insect JH and corresponding farnesol derivatives.

of the corresponding farnesol homologs which serve as authentic analytical samples for our *in vitro* assays (**3a**−**h**, Figure 2). Although many natural and unnatural JH carbon skeletons have been constructed by others,[6] we were interested in developing a shorter, higher-yielding, convergent synthetic scheme which would allow the preparation of a variety of homologous terpenoid structures for future structure−activity relationship and inhibitor studies.

Results and Discussion

Synthesis of GPP Homologs and HDMAPP. A retrosynthetic analysis of the geraniol homologs sug-

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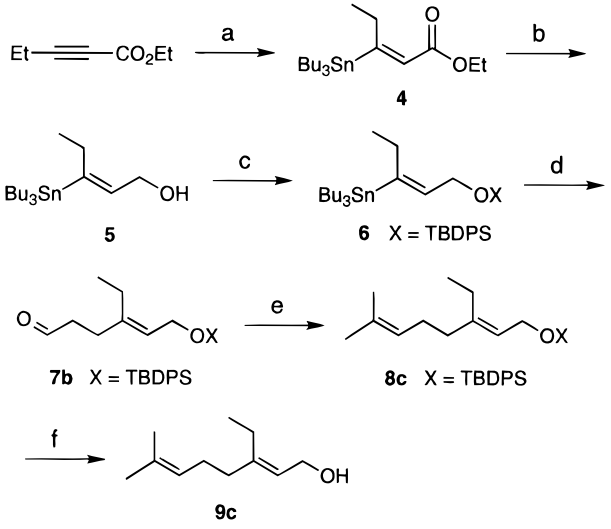
Scheme 1. Synthesis of Unnatural Geraniol Homolog 9c[a]

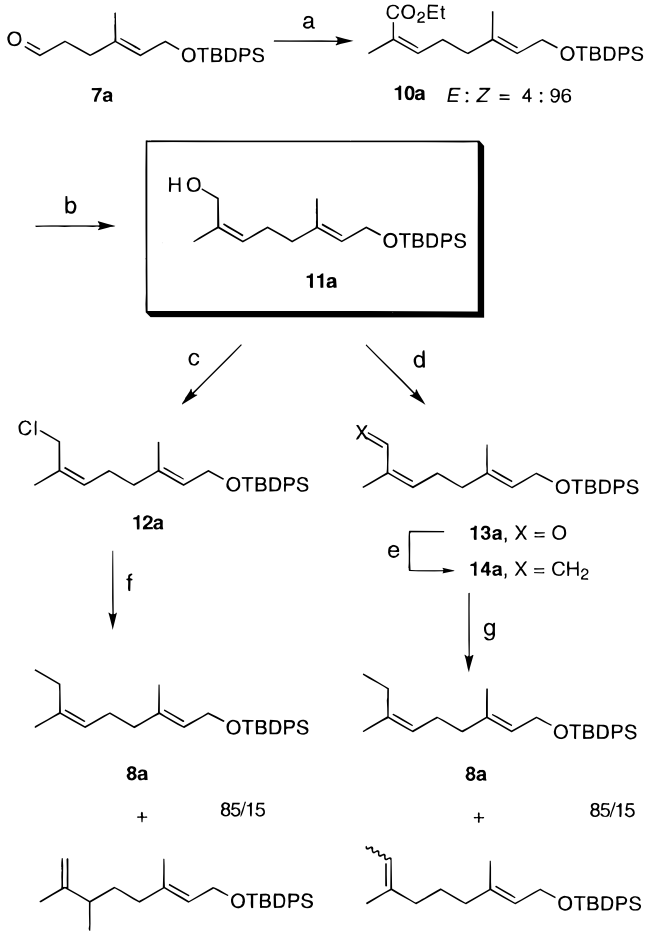


[a] (a) $(Bu_3Sn)_2CuLi$, THF, −78 °C (80%); (b) DIBALH, THF, −40 to 0 °C (82%); (c) *t*-$BuPh_2SiCl$, DMAP, Et_3N, CH_2Cl_2 (91%); (d) (1) *n*-BuLi, THF, −40 °C; (2) 2-ThCu(CN)Li, −25 °C; (3) acrolein, TMSCl, −78 °C (63%); (e) *i*-$PrPPh_3Br$, *n*-BuLi, THF, 0 °C (92%); (f) TBAF, THF, 0 °C (quant).

gested that the Δ-6,7 olefin could be constructed from the corresponding trisnoraldehyde derivatives by either Wittig or Horner−Emmons−Wadsworth olefination. The homologous 4-ethyl aldehyde precursor (**7b**, Scheme 1) could be formed from conjugate addition to acrolein of the corresponding higher-order vinyl cuprate, generated by vinylstannane transmetalation,[7] while the truncated derivative of geraniol (**7a**, Scheme 2) would be prepared by known methodology involving the selective oxidative cleavage of TBDPS-protected geraniol.[8]

Following the procedure developed by Piers and coworkers,[9] regioselective conjugate addition of bis(tri-*n*-butylstannyl)lithium cuprate to ethyl 2-pentynoate produced *trans*-stannene **4** as the sole product (Scheme 1). DIBALH reduction of the α,β-unsaturated ester of **4** yielded the corresponding alcohol (**5**) which was protected as the TBDPS ether. Vinylstannane **6** was converted into the higher-order mixed cuprate by transmetalation (*n*-BuLi, then reaction with lithium 2-thienylcyanocuprate)[10] and reacted with acrolein in the presence of TMSCl.[11] Wittig olefination of the conjugate addition product, aldehyde **7b**, using isopropyltriphenylphosphorane and subsequent alcohol deprotection with TBAF proceeded as expected to provide **9c** (six steps, 32% overall yield).

Scheme 2. Attempted Synthetic Route for the Construction of Geraniol Homologs 9a,b[a]



[a] (a) $MeCH(CO_2Et)P(O)(OEt)_2$, KHMDS, 18-C-6, THF, −78 °C, (80%); (b) DIBALH, THF, −40 to 0 °C (95%); (c) NCS, DMS, CH_2Cl_2, −40 to 0 °C (95%); (d) MnO_2, hexane, 0 °C (80%); (e) $CH_2{=}PPh_3$, THF, 0 °C (95%); (f) Me(2-Th)Cu(CN)Li_2, THF, −78 °C; (g) Ph_3RhCl, H_2, PhH, 1 atm or $Cp_2Zr(H)Cl$, THF, 0 °C to rt.

Attempts to prepare the C-7 ethyl and C-3,7 diethyl geraniol homologs (**9a** and **9b**, respectively) from aldehydes **7a** and **7b** by Horner−Emmons olefination are summarized in Schemes 2 and 3. The (2*Z*)-α,β-unsaturated ester **10a** was first prepared by condensation of **7a** with the potassium anion of triethyl 2-phosphonopropionate in the presence of 18-crown-6;[12] however, subsequent approaches to convert the ester functionality into the required ethyl group were not successful (Scheme 2). Attempts to displace the halide of **12a** with several methyl cuprates led to both S_N2 and S_N2' products; the best results were achieved with Me(2-Th)Cu(CN)Li_2 which yielded an 85/15 ratio of C-8 to C-6 addition products.[13] An alternative method involving methylidenation of aldehyde **13a** to produce triene **14a**, followed by selective reduction of the terminal olefin, was also attempted. However, both homogenous hydrogenation

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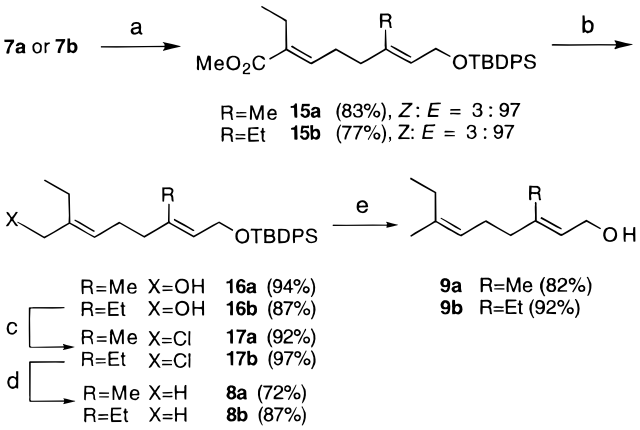
Scheme 3. Synthesis of Geraniol Homologs 9a and 9b[a]



[a] (a) $Et(CO_2Me)C{=}PPh_3$, THF, rt; (b) DIBALH, THF, −40 °C to 0 °C; (c) (1) MsCl, Et_3N, CH_2Cl_2, −40 °C; (2) LiCl, THF, 0 °C; (d) $LiEt_3BH$, THF, 0 °C; (e) TBAF, THF, 0 °C.

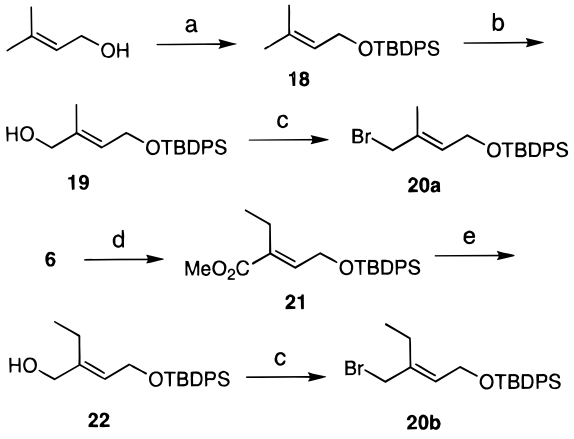
(Wilkinson's catalyst) and reduction with $Cp_2Zr(H)Cl$ yielded approximately 15% of the corresponding Δ-7,8 rearranged olefin in addition to the desired product.[14,15]

Because of the unsatisfactory results obtained from transformations involving the Δ-6,7 *cis* olefin, a modified synthesis was developed (Scheme 3). Wittig olefination of either **7a** or **7b** with (1-carbomethoxypropylidene)-triphenylphosphorane generated the Δ-2,3 *trans* olefin as the predominant product (80% yield, 97% isomeric purity).[16] Esters **15a** and **15b** were then reduced with DIBALH and converted into the allylic chlorides **17** by *in situ* displacement of the corresponding mesylates with LiCl.[17] Reduction with Super-Hydride[18] provided **8a** and **8b** in 72 and 87% yields, respectively. In contrast to the trisubstituted *cis*-allylic chloride **12a**, reduction of both **17a** and **17b** occurred regioselectively to provide alcohols **9a** and **9b** after silyl deprotection.

The alcohol of HDMAPP was synthesized by known methodology.[6k,19] Initially, methylation of the anion of vinylstannene **6** was attempted; however, this approach led to a significant amount of protonated byproduct which could not be easily separated from the desired material.[9] Once prepared, geraniol homologs **9a**−**9c** and homodimethylallyl alcohol were converted into diphosphates by displacement of the corresponding allylic chlorides with tris(tetra-*n*-butylammonium) diphosphate.[20]

Synthesis of Farnesyl Homologs. A retrosynthetic analysis of farnesol homologs **3b**−**h** suggested that these materials could be obtained from the corresponding geraniol homologs by coupling of the homogeranylbarium anions to either C_5 or C_6 allylic bromide derivatives (**20a** or **20b**, Scheme 4). Bromide **20a** was synthesized from TBDPS-protected dimethylallyl alcohol by SeO_2 allylic oxidation and subsequent bromination of the resulting hydroxyl moiety.[21] Compound **20b** was synthesized by the reaction of the vinyl anion of **6** with methyl chloroformate, followed by DIBALH reduction and allylic bromination.[22]

Scheme 4. Synthesis of 20a,b[a]



[a] (a) *t*-$BuPh_2SiCl$, DMAP, Et_3N, CH_2Cl_2 (82%); (b) catalytic SeO_2, *t*-BuOOH, salicylic acid, CH_2Cl_2 (58%); (c) (1) MsCl, Et_3N, CH_2Cl_2, −40 °C; (2) LiBr, THF, 0 °C (86%); (d) (1) *n*-BuLi, THF, −40 °C; (2) $CH_3OC(O)Cl$, −78 °C (74%); (e) DIBALH, THF, −40 to 0 °C.

Using the procedure first developed by Yamamoto and co-workers,[22,23] the coupling of the geranyl derivatives **23a**−**d** (obtained from alcohols **9a**−**d**, by conversion to the mesylate followed by *in situ* treatment with LiCl) to allylic bromides **20a** and **20b** was performed (Scheme 5). Unfortunately, the reaction suffered from significant Wurtz and γ-addition coupling. To minimize the amount of dimerization, the allylic anion was generated at a low concentration (20 mM) by dropwise (>10 min) addition of an allylic chloride solution to a rapidly stirring Rieke barium metal suspension at −78 °C. Similar alterations have been successfully applied to the generation of Grignard reagents[24] and, in the case of allylic barium anion formation, reduced the amount of Wurtz coupling to less than 10%. Despite these modifications, the reaction produced a mixture of heterocoupling products, including the desired one (i.e., **24a**−**h**, 70−75% by GC) and the γ-addition isomer (**25a**−**h**, 20−25%).

Because of the inconvenience in obtaining isomerically pure farnesol homologs by the above synthetic method, attempts were made to find a different approach to the barium coupling reaction. Since allylic transposition with barium anions is greatly diminished when aldehydes are used as the electrophile,[23a] we attempted to utilize aldehyde **26** in place of allylic bromides **20a**,**b** (Scheme 6). As expected, the desired α-coupling occurred in >95%; however, subsequent removal of the secondary allylic alcohol functionality from **27** proved difficult. Several

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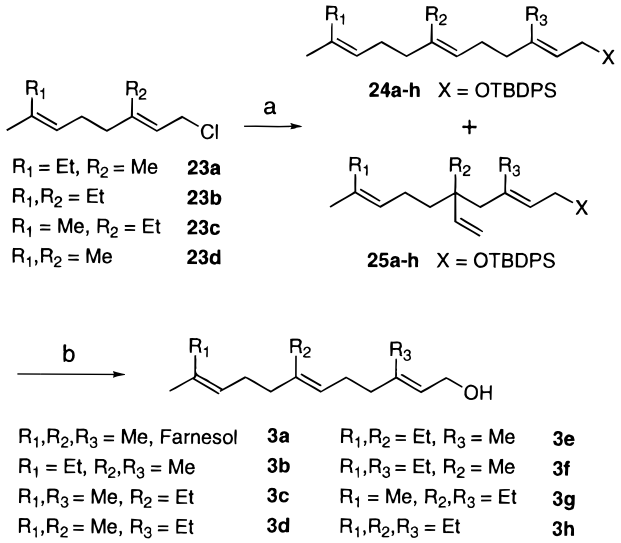
Table 1. Coupling Efficiency of Homologous Allylic Diphosphate Precursors for Prenyltransferase of Larval Lepidopteran Insect, *M. sexta*

	prenyltransferase activity larval *M. sexta* corpora allata[a]		relative prenyltransferase activity			
allylic substrate	% GPP or homologue formed	% FPP or homologue formed	prenyltransferase larval *M. sexta* corpora allata	FPP synthase pig liver[b]	FPP synthase I *Bombyx mori*[b]	FPP synthase II *B. mori*[b]
1a (DMAPP)	5	1.5	1	1	1	1
1b	9	3	2	0.4	0.04	0.07
2a		14.9	1.28	0.5	0.38	0.53
2b		11.4	0.98	0.76	0.38	0.57
2c		4.2	0.36	nd[c]	nd	nd
2d (GPP)		11.6	1	1	1	1

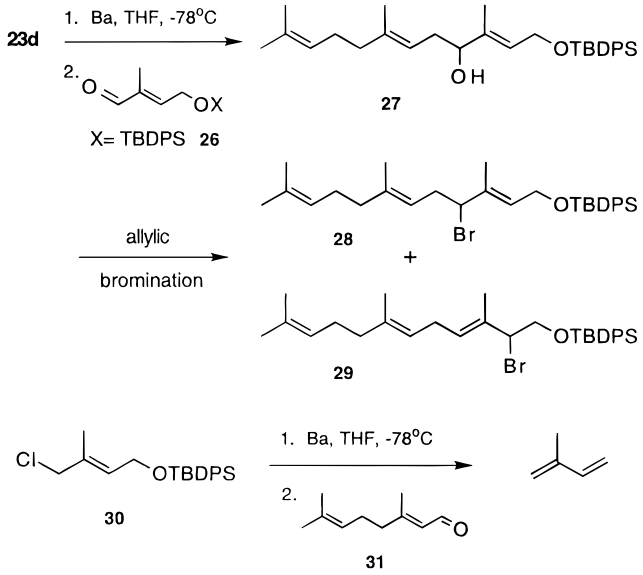
[a] Results from this study; see text for experimental details. [b] From ref 27b. [c] Not determined.

Scheme 5. Allyl Barium Coupling of Allylic Chlorides 23a−d with Bromides 20a and 20b[a]



[a] (a) 1) Ba, THF, −78 °C; (2) **20a** or **20b**, −78 °C; (b) (1) TBAF, THF, 0 °C; (2) HPLC purification.

Scheme 6. Attempted Synthesis of 3a−h Using Carbonyl Electrophiles



methods (PBr_3, Ph_3P/CBr_4, MsCl/LiBr, and NBS/DMS) utilized to convert **27** into the C-4 halide **28** were unsuccessful, producing an inseparable mixture of C-2- and C-4-halogenated products (30−40% undesired isomer).[25] Attempts to reduce the corresponding C-4 mesylate *in situ* with both Super-Hydride and N-Selectride were also problematic as both hydride reagents gave S_N2 and S_N2' addition products.[26] This latter result was surprising since it would seem that the TBDPS ether should provide enough steric hindrance to preclude attack at the C-2 position by the bulky hydride reagents. An umpolung approach to the barium coupling method (i.e., coupling of **30** with **31**, Scheme 6) was also attempted; however, this too failed because of competing elimination of the silyl ether of **30**. Thus, farnesol homologs **3b**−**h** were best prepared by the original allylic barium coupling method, and the desired isomer was purified by reversed phase HPLC separation of the deprotected terpenols to give typical isolated yields of 30−40%.

***In Vitro* Studies.** Using each of the prepared allylic diphosphates and the farnesol homolog standards, an examination of substrate specificity for larval prenyltransferase of *M. sexta* was performed (Table 1). Unlike purified FPP synthase from vertebrate or whole body insect sources,[27] the larval enzyme obtained from *M. sexta* corpora allata (the site of hormone production) shows a high tolerance for the homologous substrates, in accord with the insect's ability to prepare JH homolog structures. HDMAPP was a better substrate than DMAPP, and geranyl homologs **2a** and **2b** were converted into the corresponding farnesyl homolog skeletons with comparable efficiency to GPP. Interestingly, the unnatural geranyl homolog **2c** was a poorer substrate of the larval prenyltransferase, suggesting that this enzyme is at least in part the source of JH skeleton specificity in the lepidopteran insects. A more comprehensive study of the substrate selectivity of prenyltransferase in both lepidopteran and non-lepidopteran insects is currently under investigation in our laboratory.

Experimental Section

General Procedures. Synthetic Methods. Unless otherwise stated, chemicals obtained from commercial sources

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were used without further purification. THF was distilled from sodium benzophenone ketyl, C_6H_6, CH_2Cl_2, CH_3CN, and methyl chloroformate were distilled from CaH_2, and Et_3N was distilled from KOH. Acrolein was freshly distilled before use. NCS and Wittig salts were recrystallized (from H_2O and CH_2Cl_2/hexane, respectively) and dried *in vacuo* at 60 °C. Standard workup refers to a brine wash of the combined organic extracts, followed by drying over $MgSO_4$ and rotary evaporation. Unless otherwise indicated, chromatography refers to flash chromatography using silica gel 60 (EM Science). Ion-exchange chromatography was performed on Dowex 50WX8-200 (NH_4^+ or H^+ form) which was prepared by treating the resin with a 3−4 N solution of the desired ion (HCl for H^+ and NH_4OH for NH_4^+ forms) for 1 h at a flow rate of 1 mL/min. Cellulose chromatography was performed using Whatman CF11 fibrous cellulose powder which was prepared by consecutive washings with 1 N HCl and 1 N NaOH for 30 min, followed by extensive rinsing with H_2O. For monitoring diphosphate formation, TLC was performed with MN CEL 300 fibrous cellulose TLC plates (prewashed as described for the cellulose powder) using Hanes stain for visualization.[28] Gas−liquid chromatography (GC) was performed using a DB-5HT 30 m column with elution conditions as follows: flow rate 1.5 mL/min, initial temperature 50 °C for 1 min, increasing at 10 °C/min to a final temperature of 325 °C. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, using $CDCl_3$ as solvent, except for diphosphates **1b** and **2a**−**d** which were dissolved in D_2O with MeOH added as an internal standard. ^{31}P NMR spectra were obtained at 81 MHz, using D_2O as solvent and 30% H_3PO_4 as an external standard. Preparative HPLC was performed on an 10 × 250 mm Ultrasphere-ODS column, monitoring at 210 nm. **Biological Assays.** [4-^{14}C]Isopentenyl diphosphate was purchased from DuPont New England Nuclear. Corpora cardiaca−corpora allata complexes of day zero, 5th stadium larvae (V/0) were obtained using previously established microsurgical methods.[29]

Ethyl (*E*)-3-(Tributylstannyl)-2-penten-1-oate (4). To a cold (−20 °C) solution of hexabutylditin (16 g, 27.6 mmol) in THF (250 mL) was added *n*-BuLi (1.6 M in hexanes, 17.3 mL, 27.7 mmol). After being stirred for 20 min at −20 °C, a yellow solution was obtained. The reaction vessel was cooled to −50 °C, and CuBr·DMS (2.8 g, 13.6 mmol) was added in one portion. The reaction gradually became a dark brown suspension as it stirred at −50 °C for 30 min. Ethyl 2-pentynoate (1.9 g, 15 mmol) was then added at −78 °C, and the mixture was stirred for 4 h. The reaction was quenched by the addition of saturated NH_4Cl/NH_4OH (9/1, 100 mL) and Et_2O (50 mL). After being stirred for 30 min at rt, the solution was rinsed with NH_4Cl/NH_4OH (3 × 100 mL) and extracted with Et_2O (3 × 50 mL), and the combined organics were subjected to the standard workup. Chromatography using EtOAc/hexane (0/100 to 10/90 gradient) as the eluent provided **4** as a clear oil (4.6 g, 11 mmol, 80%): GC 20.8 min; IR (neat) cm^{-1} 2958, 2873, 1720, 1595, 1171, 863; ^{1}H NMR δ 0.87−0.98 (m, 15H), 1.04 (t, 3H, J = 7.5 Hz), 1.25−1.39 (m, 9H), 1.42−1.58 (m, 6H), 2.86 (q, 2H, J = 7.6 Hz, $^3J_{Sn-H}$ = 56.6 Hz), 4.15 (q, 2H, J= 7.1 Hz), 5.90 (s, 1H, $^3J_{Sn-H}$ = 65.8 Hz); ^{13}C NMR δ 10.0, 13.6, 14.1, 14.3, 27.3, 28.5, 29.0, 59.6, 127.3, 164.2, 175.5.

(*E*)-3-(Tributylstannyl)-2-penten-1-ol (5). To a solution of **4** (4.6 g, 11 mmol) in THF (300 mL) at −40 °C was added DIBALH (1.0 M in hexane, 26 mL, 26 mmol) over 15 min. The reaction was warmed to 0 °C over 2 h and was then quenched by pouring the mixture into 2:1 H_2O/Et_2O (300 mL). The aluminum oxides were dissipated by the slow addition of 1 N HCl to pH 4 (lower pH led to tin cleavage).[30] The aqueous layer was extracted with Et_2O (3 × 50 mL) and subjected to the standard workup. Chromatography using EtOAc/hexane (20/80) as eluent yielded **5** (3.4 g, 9 mmol, 82%): GC 19.4 min; IR (neat) cm^{-1} 3320, 2958, 2922, 2872, 2855, 1658, 875; ^{1}H NMR δ 0.85−0.91 (m, 15H), 0.94 (t, 3H, J = 7.6 Hz), 1.30 (sextet, 6H, J = 7.2 Hz), 1.42−1.52 (m, 6H), 2.27 (q, 2H, J = 8.0 Hz, $^3J_{Sn-H}$ = 57.1 Hz), 4.22 (d, 2H, J = 6.2 Hz, $^3J_{Sn-H}$ = 9.5 Hz), 5.69 (t, 1H, J = 6.2 Hz, $^3J_{Sn-H}$ = 68.3 Hz); ^{13}C NMR δ 9.7, 13.7, 15.1, 26.5, 27.4, 29.1, 58.8, 138.5, 149.9.

(*E*)-3-(Tributylstannyl)-1-((*tert*-butyldiphenylsilyl)oxy)-2-pentene (6). To a solution of **5** (3.4 g, 9 mmol) in CH_2Cl_2 (75 mL) were added Et_3N (1.45 mL, 10.4 mmol), *tert*-butylchlorodiphenylsilane (2.6 g, 9.5 mmol), and a catalytic amount of DMAP (50 mg, 0.4 mmol). After the solution was stirred for 2 h at rt, H_2O (50 mL) was added, and the reaction mixture was extracted with Et_2O (3 × 50 mL). The combined organics were subjected to the standard workup and chromatographed using EtOAc/hexane (5/95) as eluent to provide **6** (5.0 g, 8.2 mmol, 91%): GC 30.3 min; IR (neat) cm^{-1} 3072, 3051, 2958, 2929, 2871, 2857, 1584, 1112, 823; ^{1}H NMR δ 0.82−0.95 (m, 18H), 1.08 (s, 9H), 1.35 (sextet, 6H, J = 6.5 Hz), 1.47−1.56 (m, 6H), 2.09 (q, 2H, J = 7.4 Hz, $^3J_{Sn-H}$ = 57.9 Hz), 4.36 (d, 2H, J = 5.5 Hz, $^3J_{Sn-H}$ = 16.5 Hz), 5.73 (t, 1H, J = 5.5 Hz, $^3J_{Sn-H}$ = 70.8 Hz), 7.41 (m, 6H), 7.71 (m, 4H); ^{13}C NMR δ 9.7, 13.8, 14.9, 19.2, 26.6, 26.9, 27.5, 29.2, 60.7, 127.6, 129.6, 134.1, 135.7, 139.4, 147.1.

(*E*)-6-((*tert*-Butyldiphenylsilyl)oxy)-4-ethyl-4-hexen-1-al (7b). To a solution of **6** (5.0 g, 8.2 mmol) in THF (200 mL) at −40 °C was added *n*-BuLi (1.6 M in hexanes, 6.1 mL, 9.8 mmol) over 5 min. After the solution was stirred for 1 h at −40 °C, lithium 2-thienylcyanocuprate (0.25 M in THF, 40 mL, 10 mmol) was added dropwise, and the reaction was warmed to −25 °C over 45 min to yield a clear honey-colored solution of the higher-order mixed cuprate. The reaction was cooled to −78 °C, and a solution of acrolein (1.7 mL, 25 mmol) and TMSCl (6.2 mL, 49 mmol) in THF (12 mL) was added over 20 min in the dark. The mixture was stirred at −78 °C for 3 h and then quenched by the addition of 1 N HCl (200 mL). The solution was extracted with Et_2O (3 × 75 mL) and subjected to the standard workup. Chromatography of the resulting oil using EtOAc/hexane (5/95) as the eluent yielded **7b** (2.0 g, 5.2 mmol, 63%): GC 26.0 min; IR (neat) cm^{-1} 3071, 2962, 2719, 1726, 1680, 1602, 1112; ^{1}H NMR δ 0.89 (t, 3H, J = 7.5 Hz), 1.09 (s, 9H), 1.90 (q, 2H, J = 7.5 Hz), 2.35 (t, 2H, J = 7.4 Hz), 2.53 (t, 2H, J = 7.3 Hz), 4.29 (d, 2H, J = 6.1 Hz), 5.38 (t, 1H, J = 6.1 Hz), 7.40−7.45 (m, 6H), 7.72−7.75 (m, 4H), 9.78 (br s, 1H); ^{13}C NMR δ 13.2, 19.2, 23.8, 26.9, 28.3, 42.0, 60.6, 124.5, 127.7, 129.7, 133.9, 135.7, 140.9, 202.2.

(2*E*)-1-((*tert*-Butyldiphenylsilyl)oxy)-3-ethyl-7-methyl-2,6-octadiene (8c). *n*-BuLi (1.6 M in hexanes, 1.85 mL, 3.0 mmol) was added dropwise to a suspension of isopropyltriphenylphosphonium iodide (1.3 g, 3.0 mmol) in THF (70 mL) at −78 °C. After 5 min the reaction was warmed to 0 °C and stirred for 1 h. A solution of **7b** (450 mg, 1.2 mmol) in THF (5 mL) was added dropwise to the resulting red ylide. After the solution was stirred at 4 °C for 2 h, the reaction was quenched with H_2O (50 mL) and subjected to the standard workup. Chromatography using EtOAc/hexane (5/95) as eluent yielded **8c** (440 mg, 1.1 mmol, 92%): GC 26.4 min; IR (neat) cm^{-1} 3071, 2931, 1665, 1586, 1112; ^{1}H NMR δ 0.86 (t, 3H, J = 7.6 Hz), 1.06 (s, 9H), 1.63 (s, 3H), 1.71 (s, 3H), 1.88 (q, 2H, J = 7.5 Hz), 2.02−2.09 (br m, 4H), 4.26 (d, 2H, J = 6.1 Hz), 5.14 (t, 1H, J = 6.3 Hz), 5.37 (t, 1H, J = 6.1 Hz), 7.35−7.45 (m, 6H), 7.70−7.73 (m, 4H); ^{13}C NMR δ 13.2, 17.7, 19.2, 23.5, 25.7, 26.6, 26.8, 36.2, 60.8, 123.6, 124.3, 127.6, 129.5, 131.4, 134.1, 135.6, 142.9.

(2*E*)-3-Ethyl-7-methyl-2,6-octadien-1-ol (9c). To **8c** (440 mg, 1.1 mmol) in THF (40 mL) at 0 °C was added TBAF (1.0 M in THF, 2.5 mL, 2.5 mmol). After 1 h at 0 °C, the solution was warmed to rt and stirred for 3 h. The reaction was quenched by the addition 0.5 N HCl (30 mL) and extracted with Et_2O (3 × 40 mL). Following the standard workup, chromatography using EtOAc/hexane (20/80) as eluent yielded **9c** (190 mg, 1.1 mmol, quant): GC 12.3 min; IR (neat) cm^{-1} 3335, 2985, 1657, 1112; ^{1}H NMR δ 0.87 (t, 3H, J = 6.6 Hz), 1.59 (s, 3H), 1.67 (s, 3H), 2.04−2.11 (br m, 6H), 4.14 (d, 2H, J = 7.0 Hz), 5.10 (t, 1H, J = 6.5 Hz), 5.36 (t, 1H, J = 6.9 Hz); ^{13}C NMR δ 13.7, 17.7, 23.5, 25.7, 26.6, 36.4, 59.1, 122.9, 124.0, 131.7, 145.6.

Methyl (2*E*,6*E*)-8-((*tert*-Butyldiphenylsilyl)oxy)-2-ethyl-6-methyl-2,6-octadien-1-oate (15a). To a suspension of *n*-propyltriphenylphosphonium bromide (6.6 g, 17.1 mmol) in benzene (25 mL) at 4 °C was added KHMDS (0.5 M in toluene,

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34 mL, 17 mmol). The solution was stirred for 30 min and then warmed to rt over 30 min at which time methyl chloroformate (650 μL, 8.4 mmol) was added. The resulting yellow suspension was filtered and the eluent concentrated to yield the crude ylide (4.0 g, yellow oil). The oil was dissolved in THF (25 mL), and aldehyde **7a** (1.3 g, 3.5 mmol, prepared as previously described)[8] in THF (5 mL) was added dropwise. The reaction was stirred at rt for 7 days and then quenched by the addition of saturated aqueous NH_4Cl (50 mL). The solution was extracted with Et_2O (3 × 50 mL), and the combined organic extracts were subjected to the standard workup. Chromatography using EtOAc/hexane (5/95) as eluent yielded **15a** (1.3 g, 2.9 mmol, 83%, >98% isomeric purity): GC 28.9 min, (2*Z*,6*E*) isomer 28.5 min; IR (neat) cm^{-1} 3071, 2932, 2857, 1712, 1585, 1111; ^1H NMR δ 0.98−1.04 (m, 12H), 1.45 (s, 3H,), 2.08 (t, 2H, *J* = 7.6 Hz), 2.23−2.35 (m, 4H), 3.72 (s, 3H), 4.22 (d, 2H, *J* = 6.2 Hz), 5.40 (t, 1H, *J* = 5.9 Hz), 6.69 (t, 1H, *J* = 7.3 Hz), 7.34−7.45 (m, 6H), 7.67−7.70 (m, 4H); ^{13}C NMR δ 13.9, 16.3, 19.1, 20.1, 26.6, 26.8, 38.3, 51.5, 61.0, 124.8, 127.5, 129.5, 131.3, 133.9, 135.6, 135.9, 141.5, 171.2.

Methyl (2*E*,6*E*)-8-((*tert*-Butyldiphenylsilyl)oxy)-2,6-diethyl-2,6-octadien-1-oate (15b). Aldehyde **7b** (1.8 g, 4.7 mmol) was olefinated using the procedure described for the preparation of **15a**. Ester **15b** was obtained (1.7 g, 3.6 mmol, 77%, >98% isomeric purity): GC 29.1 min, (2*Z*,6*E*) isomer 28.7 min; IR (neat) cm^{-1} 3037, 2953, 2852, 1705, 1652, 1105; ^1H NMR δ 0.86 (t, 3H, *J* = 7.5 Hz), 1.00−1.05 (m, 12H), 1.86 (q, 2H, *J* = 7.6 Hz), 2.11 (t, 2H, *J* = 7.6 Hz), 2.24−2.37 (m, 4H), 3.73 (s, 3H), 4.25 (d, 2H, *J* = 6.2 Hz), 5.37 (t, 1H, *J* = 6.1 Hz), 6.72 (t, 1H, *J* = 7.2 Hz), 7.35−7.43 (m, 6H), 7.69−7.71 (m, 4H); ^{13}C NMR δ 13.1, 13.9, 19.1, 20.1, 23.5, 26.8, 35.1, 51.5, 60.6, 124.3, 127.6, 129.5, 133.9, 134.0, 135.6, 141.6, 141.7, 168.2.

(2*E*,6*E*)-8-((*tert*-Butyldiphenylsilyl)oxy)-2-ethyl-6-methyl-2,6-octadien-1-ol (16a). Ester **15a** (1.3 g, 2.9 mmol) was reacted with DIBALH using the procedure described for the preparation of **5**. Alcohol **16a** was obtained (1.15 g, 2.7 mmol, 94%): GC 28.7 min; IR (neat) cm^{-1} 3384, 2999, 2932, 1669, 1589, 1059; ^1H NMR δ 1.02 (t, 3H, *J* = 7.65 Hz), 1.06 (s, 9H), 1.46 (s, 3H), 2.00−2.19 (m, 6H), 4.05 (s, 2H), 4.24 (d, 2H, *J* = 6.1 Hz), 5.35−5.42 (m, 2H), 7.36−7.46 (m, 6H), 7.69−7.73 (m, 4H); ^{13}C NMR δ 13.3, 16.3, 19.2, 21.1, 25.6, 26.9, 39.4, 61.1, 66.8, 124.3, 125.7, 127.6, 129.5, 134.0, 135.6, 136.6, 140.9.

(2*E*,6*E*)-8-((*tert*-Butyldiphenylsilyl)oxy)-2,6-diethyl-2,6-octadien-1-ol (16b). Ester **15b** (1.65 g, 3.6 mmol) was reacted with DIBALH using the procedure described for the preparation of **5**. Alcohol **16b** was obtained (1.35 g, 3.1 mmol, 87%): GC 29.0 min; IR (neat) cm^{-1} 3328, 3071, 2931, 1658, 1587, 1112; ^1H NMR δ 0.85 (t, 3H, *J* = 7.6 Hz), 0.96−1.05 (m, 12H), 1.87 (q, 2H, *J* = 7.6 Hz), 2.02−2.16 (m, 6H), 4.04 (br s, 2H), 4.24 (d, 2H, *J* = 6.2 Hz), 5.33−5.40 (m, 2H), 7.26−7.45 (m, 6H), 7.69−7.71 (m, 4H); ^{13}C NMR δ 13.2, 13.3, 19.1, 21.1, 23.5, 25.8, 26.8, 36.1, 60.7, 66.8, 123.8, 125.9, 127.5, 129.5, 134.0, 135.6, 140.8, 142.5.

(2*E*,6*E*)-1-((*tert*-Butyldiphenylsilyl)oxy)-7-(chloromethyl)-3-methyl-2,6-nonadiene (17a). To a solution of **16a** (1.15 g, 2.7 mmol) in CH_2Cl_2 (30 mL) at −40 °C were added Et_3N (520 μL, 3.7 mmol) and MsCl (240 μL, 3.1 mmol). After the solution had stirred at −40 °C for 1 h, THF (20 mL) and LiCl (290 mg, 6.8 mmol) were added and the reaction mixture was stirred at 0 °C for 2 h. The reaction was poured into pentane (60 mL), washed with H_2O (8 × 15 mL), and subjected to the standard workup. Chloride **17a** was obtained (1.1 g, 2.5 mmol, 92%): ^1H NMR δ 1.00−1.05 (m, 12H), 1.45 (s, 3H), 2.00−2.25 (m, 6H), 4.05 (s, 2H), 4.23 (d, 2H, *J* = 6.2 Hz), 5.39 (t, 1H, *J* = 6.0 Hz), 5.48 (t, 1H, *J* = 7.0 Hz), 7.26−7.46 (m, 6H), 7.69−7.72 (m, 4H); ^{13}C NMR δ 12.9, 16.3, 19.2, 21.0, 26.0, 26.9, 39.0, 50.1, 61.1, 124.6, 127.6, 129.6, 130.4, 134.0, 135.6, 136.3, 137.6.

(2*E*,6*E*)-1-((*tert*-Butyldiphenylsilyl)oxy)-7-(chloromethyl)-3-ethyl-2,6-nonadiene (17b). Alcohol **16b** (1.35 g, 3.1 mmol) was converted to the allylic chloride using the procedure described for the preparation of **17a**. Chloride **17b** was obtained (1.35 g, 3.0 mmol, 97%): ^1H NMR δ 0.86 (t, 3H, *J* = 7.6 Hz), 0.93−1.06 (m, 12H), 1.87 (q, 2H, *J* = 7.5 Hz), 2.03−2.26 (m, 6H), 4.07 (br s, 2H), 4.25 (d, 2H, *J* = 6.2 Hz), 5.36 (t, 1H, *J* = 6.1 Hz), 5.51 (t, 1H, *J* = 6.8 Hz), 7.37−7.46 (m, 6H), 7.69−7.72 (m, 4H); ^{13}C NMR δ 12.9, 13.2, 19.2, 21.1, 23.5, 26.2, 26.9, 35.7, 50.1, 60.7, 124.1, 127.6, 129.6, 130.5, 134.1, 135.6, 137.6, 142.2.

(2*E*,6*Z*)-1-((*tert*-Butyldiphenylsilyl)oxy)-3,7-dimethyl-2,6-nonadiene (8a). To **17a** (1.1 g, 2.5 mmol) in THF (75 mL) at −78 °C was added $LiEt_3BH$ (1.0 M in THF, 4 mL, 4.0 mmol) dropwise over 10 min. After the solution was warmed to 0 °C, the reaction was stirred for 2 h and then quenched with H_2O (40 mL), followed by saturated aqueous NH_4Cl (10 mL). The mixture was extracted with Et_2O (2 × 20 mL), and the combined organic extracts were subjected to the standard workup. Chromatography using EtOAc/hexane (2/98) as eluent yielded **8a** (740 mg, 1.8 mmol, 72%): GC 26.5 min; IR (neat) cm^{-1} 3071, 2930, 1729, 1663, 1112; ^1H NMR δ 0.98 (t, 3H, *J* = 7.6 Hz), 1.06 (s, 9H), 1.45 (s, 3H), 1.69 (s, 3H), 1.97−2.12 (br m, 6H), 4.24 (d, 2H, *J* = 6.2 Hz), 5.09 (t, 1H, *J* = 6.5 Hz), 5.40 (t, 1H, *J* = 5.9 Hz), 7.37−7.46 (m, 6H), 7.70−7.72 (m, 4H); ^{13}C NMR δ 12.6, 16.2, 19.1, 22.6, 24.7, 26.0, 26.8, 39.7, 61.1, 123.7, 124.2, 127.4, 129.3, 134.3, 135.6, 137.0, 137.1.

(2*E*,6*Z*)-1-((*tert*-Butyldiphenylsilyl)oxy)-3-ethyl-7-methyl-2,6-nonadiene (8b). Chloride **17b** (1.35 g, 3.0 mmol) was reacted with $LiEt_3BH$ using the procedure described for the preparation of **8a**. Compound **8b** was obtained (1.1 g, 2.6 mmol, 87%): GC 26.7 min; IR (neat) cm^{-1} 3070, 2964, 1676; ^1H NMR δ 0.85 (t, 3H, *J* = 7.4 Hz), 0.98 (t, 3H, *J* = 7.4 Hz), 1.06 (s, 9H), 1.69 (s, 3H), 1.87 (q, 2H, *J* = 7.4 Hz), 1.98−2.08 (m, 6H), 4.25 (d, 2H, *J* = 5.9 Hz), 5.10 (t, 1H, *J* = 5.9 Hz), 5.36 (t, 1H, *J* = 5.9 Hz), 7.35−7.43 (m, 6H), 7.69−7.72 (m, 4H); ^{13}C NMR δ 12.9, 13.1, 19.2, 22.8, 23.6, 24.8, 26.1, 26.9, 36.6, 60.8, 123.6, 123.9, 127.7, 129.5, 134.5, 135.7, 137.3, 142.9.

(2*E*,6*Z*)-3,7-Dimethyl-2,6-nonadien-1-ol (9a). Ether **8a** (700 mg, 1.7 mmol) was deprotected with TBAF using the procedure described for the preparation of **9c**. Alcohol **9a** was obtained (240 mg, 1.4 mmol, 82%): GC 12.5 min; IR (neat) cm^{-1} 3332, 2961, 1665; ^1H NMR δ 0.95 (t, 3H), 1.66 (s, 6H), 1.99−2.10 (m, 6H), 4.13 (d, 2H, *J* = 6.9 Hz), 5.05 (t, 1H, *J* = 6.5 Hz), 5.40 (t, 1H, *J* = 6.9 Hz); ^{13}C NMR δ 12.7, 16.2, 22.8, 24.7, 26.0, 39.8, 59.3, 123.3, 123.4, 137.5, 139.6.

(2*E*,6*Z*)-3-Ethyl-7-methyl-2,6-nonadien-1-ol (9b). Ether **8b** (1.1 g, 2.6 mmol) was deprotected with TBAF using the procedure described for the preparation of **9c**. Alcohol **9b** was obtained (430 mg, 2.4 mmol, 92%): GC 13.1 min; IR (neat) cm^{-1} 3316, 2966, 1658; ^1H NMR δ 0.97 (2 overlapping t, 6H, *J* = 6.9 Hz), 1.67 (s, 3H), 1.98−2.12 (m, 8H), 4.16 (d, 2H, *J* = 7.3 Hz), 5.08 (t, 1H, *J* = 5.9 Hz), 5.37 (t, 1H, *J* = 7.0 Hz); ^{13}C NMR δ 14.4, 15.2, 24.4, 25.1, 26.4, 27.8, 38.3, 60.7, 124.5, 125.2, 139.1, 147.3.

Ethyl (*Z*)-3-Methyl-2-penten-1-oate. To a suspension of CuBr·DMS (900 mg, 4.4 mmol) in THF (25 mL) at −40 °C was added MeLi (1.4 M in Et_2O, 6.2 mL, 8.7 mmol). After being stirred for 40 min at −40 °C, the clear yellow solution was cooled to −78 °C, and ethyl 2-pentyn-1-oate (500 mg, 4.0 mmol) was added over 15 min. The reaction was stirred for 90 min at −78 °C and then quenched by the slow addition of MeOH (1.5 mL), followed by NH_4Cl/NH_4OH (9/1, 5 mL). The solution was warmed to rt and the organic layer separated and rinsed with NH_4Cl/NH_4OH (2 × 5 mL). Standard workup yielded ethyl (*Z*)-3-methyl-2-penten-1-oate (550 mg, 3.9 mmol 98%): GC 8.8 min; IR (neat) cm^{-1} 2961, 2925, 2856, 1717, 1652, 1212, 1149; ^1H NMR δ 1.04 (t, 3H, *J* = 7.5 Hz), 1.23 (t, 3H, *J* = 7.3 Hz), 1.85 (s, 3H), 2.59 (q, 2H, *J* = 7.5 Hz), 4.10 (q, 2H, *J* = 7.1 Hz), 5.59 (s, 1H); ^{13}C NMR δ 12.49, 14.27, 24.57, 26.48, 59.36, 115.46, 161.96, 166.30.

(*Z*)-3-Methyl-2-penten-1-ol. Ethyl (*Z*)-3-methyl-2-penten-1-oate (550 mg, 3.9 mmol) was reacted with DIBALH using the procedure described for the preparation of **5**. Alcohol was obtained (230 mg, 2.3 mmol, 59%): GC 5.9 min; IR (neat) cm^{-1} 3333, 2936, 1678; ^1H NMR δ 0.97 (t, 3H, *J* = 7.6 Hz), 1.72 (s, 3H), 2.66 (q, 2H, *J* = 7.6 Hz), 4.11 (d, 2H, *J* = 7.0 Hz), 5.35 (t, 1H, *J* = 6.9 Hz); ^{13}C NMR δ 13.17, 22.93, 24.93, 58.92, 123.23, 142.04.

1-((*tert*-Butyldiphenylsilyl)oxy)-3-methyl-2-butene (18). 3-Methyl-2-buten-1-ol (1.5 g, 17.4 mmol) was protected as the TBDPS ether using the procedure described for the preparation of **6**. Ether **18** was obtained (4.6 g, 14.2 mmol, 82%): GC 22.2 min; IR (neat) cm^{-1} 3071, 2931, 2857, 1590, 1112; ^1H NMR

δ 1.07 (s, 9H), 1.48 (s, 3H), 1.72 (s, 3H), 4.22 (d, 2H, J = 6.3 Hz), 5.41 (t, 1H, J = 6.1 Hz), 7.38−7.47 (m, 6H), 7.71−7.74 (m, 4H); ^{13}C NMR δ 17.9, 19.2, 25.7, 26.8, 61.1, 124.2, 127.6, 129.5, 133.8, 134.1, 135.6.

(*E*)-4-((*tert*-Butyldiphenylsilyl)oxy)-2-methyl-2-buten-1-ol (19). To a mixture of SeO_2 (480 mg, 4.3 mmol), salicylic acid (400 mg, 2.9 mmol), H_2O (1.9 mL, 11 mmol), and *t*-BuOOH (5.0−6.0 M in nonane, 8.5 mL, approximately 42 mmol) in CH_2Cl_2 (90 mL) which had stirred in the dark at rt for 30 min was added **18** (4.6 g, 14.2 mmol) in CH_2Cl_2 (5 mL). The reaction was stirred for 20 h at rt and poured into saturated aqueous $NaHCO_3$ (30 mL). The organic layer was then treated to the standard workup, and the resulting oil was chromatographed using EtOAc/hexane (10/90) as eluent to yield **19** (1.8 g, 5.3 mmol, 37%), 0.7 g of the corresponding aldehyde, and 0.5 g of recovered **18**: GC 24.8 min; IR (neat) cm^{-1} 3365, 3072, 2931, 2858, 1694, 1651, 1428, 1112; ^{1}H NMR δ 1.06 (s, 9H), 1.49 (s, 3H), 3.97 (s, 2H), 4.29 (d, 2H, J = 6.1 Hz), 5.63 (t, 1H, J = 5.6 Hz), 7.37-7.47 (m, 6H), 7.69−7.72 (m, 4H); ^{13}C NMR δ 13.8, 19.2, 26.9, 60.8, 68.3, 124.9, 127.7, 129.6, 133.9, 135.6, 136.2.

(*E*)-1-((*tert*-Butyldiphenylsilyl)oxy)-4-bromo-3-methyl-2-butene (20a). Alcohol **19** (1.0 g, 2.9 mmol) was brominated using the procedure described for the preparation of **17a**, where LiBr was used in place of LiCl. Bromide **20a** was obtained (1.0 g, 2.5 mmol, 86%): ^{1}H NMR δ 1.06 (s, 9H), 1.59 (s, 3H), 4.00 (s, 2H), 4.25 (d, 2H, J = 6.0 Hz), 5.81 (t, 1H, J = 6.1 Hz), 7.36−7.48 (m, 6H), 7.66−7.71 (m, 4H); ^{13}C NMR δ 16.6, 20.8, 28.4, 42.3, 62.7, 129.3, 131.3, 131.9, 134.5, 135.2, 137.2.

Methyl (*E*)-4-((*tert*-Butyldiphenylsilyl)oxy)-2-ethyl-2-buten-1-oate (21). To a solution of **6** (3.0 g, 4.9 mmol) in THF (70 mL) at −40 °C was added *n*-BuLi (1.6 M in hexanes, 3.5 mL, 5.6 mmol) over 5 min, and after being stirred for 1 h at −40 °C, a clear yellow solution was obtained. The reaction was cooled to −78 °C and transferred by cannula over 10 min into a solution of methyl chloroformate (2 mL, 25.9 mmol) in THF (10 mL) at −78 °C. After the solution was stirred for 1 h at −78 °C, the reaction was quenched by the addition of H_2O (40 mL) and the solution was extracted with Et_2O (3 × 20 mL). The combined organic extracts were then subjected to the standard workup. Chromatography using EtOAc/hexane (2/98) as eluent yielded **21** (1.4 g, 3.6 mmol, 74%): GC 24.2 min; IR (neat) cm^{-1} 3071, 2932, 2858, 1718, 1651, 1586, 1115; ^{1}H NMR δ 0.87 (t, 3H, J = 7.4 Hz), 1.02 (s, 9H), 2.12 (q, 2H, J = 7.4 Hz), 3.76 (s, 3H), 4.38 (d, 2H, J = 5.9 Hz), 6.85 (t, 1H, J = 5.9 Hz), 7.38−7.45 (m, 6H), 7.67−7.70 (m, 4H); ^{13}C NMR δ 15.2, 20.8, 22.1, 28.3, 53.4, 62.5, 129.4, 131.5, 134.9, 135.1, 137.2, 142.4, 169.5.

(*E*)-4-((*tert*-Butyldiphenylsilyl)oxy)-2-ethyl-2-buten-1-ol (22). Ester **21** (1.4 g, 3.6 mmol) was reduced with DIBALH using the procedure described for the preparation of **5**. Alcohol **22** was obtained (1.0 g, 2.7 mmol, 75%): GC 24.0 min; IR (neat) cm^{-1} 3334, 3071, 2942, 1669, 1586, 1110; ^{1}H NMR δ 0.89 (t, 3H, J = 7.4 Hz), 1.06 (s, 9H), 1.94 (q, 2H, J = 7.4 Hz), 4.04 (s, 2H), 4.30 (d, 2H, J = 6.6 Hz), 5.61 (t, 1H, J = 5.9 Hz), 7.37−7.44 (m, 6H), 7.69−7.72 (m, 4H); ^{13}C NMR δ 13.3, 19.1, 21.2, 26.8, 60.4, 66.1, 124.8, 127.6, 129.6, 133.8, 135.6, 142.0.

(*E*)-1-((*tert*-Butyldiphenylsilyl)oxy)-3-(bromomethyl)-2-pentene (20b). Alcohol **22** (1.0 g, 2.7 mmol) was brominated using the procedure described for the preparation of **20a**. Bromide **20b** was obtained (950 mg, 2.3 mmol, 85%): ^{1}H NMR δ 0.92 (t, 3H, J = 7.7 Hz), 1.06 (s, 9H), 2.04 (q, 2H, J = 7.6 Hz), 4.00 (s, 2H), 4.26 (d, 2H, J = 6.6 Hz), 5.79 (t, 1H, J = 5.9 Hz), 7.37−7.45 (m, 6H), 7.68−7.71 (m, 4H); ^{13}C NMR δ 14.3, 20.8, 23.3, 28.4, 39.7, 62.2, 129.3, 131.3, 131.9, 135.2, 137.2, 140.1.

Preparation of Allylic Chlorides 23a−c and (*Z*)-1-Chloro-3-methyl-2-pentene. Alcohols **9a−c** and (*Z*)-3-methyl-2-penten-1-ol were converted to the corresponding allylic chlorides using the procedure described for the preparation of **17a**.

(2*E*,6*Z*)-1-Chloro-3,7-dimethyl-2,6-nonadiene (23a). From **9a** (76 mg, 0.45 mmol), **23a** was obtained (73 mg, 0.39 mmol, 87%): ^{1}H NMR δ 0.96 (t, 3H, J = 7.7 Hz), 1.68 (s, 3H), 1.73 (s, 3H), 1.98−2.12 (m, 6H), 4.10 (d, 2H, J = 8.8 Hz), 5.05 (t, 1H, J = 6.2 Hz), 5.49 (t, 1H, J = 8.1 Hz); ^{13}C NMR δ 14.4, 17.7, 24.4, 26.4, 27.4, 41.4, 42.8, 121.9, 124.8, 139.3, 144.4.

(2*E*,6*Z*)-1-Chloro-3-ethyl-7-methyl-2,6-nonadiene (23b). From **9b** (82 mg, 0.45 mmol), **23b** was obtained (75 mg, 0.37 mmol, 82%): ^{1}H NMR δ 0.96 (t, 3H, J = 7.4 Hz), 1.02 (t, 3H, J = 7.4 Hz), 1.68 (s, 3H), 1.98−2.17 (m, 8H), 4.11 (d, 2H, J = 8.1 Hz), 5.07 (t, 1H, J = 6.6 Hz), 5.41 (t, 1H, J = 8.1 Hz); ^{13}C NMR δ 12.8, 13.3, 22.8, 23.3, 24.8, 26.0, 37.1, 41.2, 120.2, 123.7, 138.1, 148.8.

(2*E*)-1-Chloro-3-ethyl-7-methyl-2,6-octadiene (23c). From **9c** (54 mg, 0.32 mmol), **23c** was obtained (50 mg, 0.27 mmol, 84%): ^{1}H NMR δ 1.03 (t, 3H, J = 7.7 Hz), 1.61 (s, 3H), 1.69 (s, 3H), 2.08−2.17 (m, 6H), 4.11 (d, 2H, J = 8.1 Hz), 5.10 (t, 1H, J = 6.6 Hz), 5.40 (t, 1H, J = 8.1 Hz); ^{13}C NMR δ 13.2, 17.6, 23.2, 25.6, 26.3, 36.3, 40.7, 119.7, 123.6, 131.8, 148.3.

(*Z*)-1-Chloro-3-methyl-2-pentene. From (*Z*)-3-methyl-2-penten-1-ol (40 mg, 0.40 mmol), (*Z*)-1-chloro-3-methyl-2-pentene was obtained (38 mg, 0.32 mmol, 80%): ^{1}H NMR δ 1.03 (t, 3H, J = 7.6 Hz), 1.77 (s, 3H), 2.13 (q, 2H, J = 7.6 Hz), 4.09 (d, 2H, J = 8.1 Hz), 5.41 (t, 1H, J = 8.0 Hz).

General Procedure for the Preparation of Allylic Diphosphates 2a−d and 1b: (2*E*)-3,7-Dimethyl-2,6-octadien-1-yl Diphosphate (Geranyl Diphosphate, 2d). To a solution of geranyl chloride (80 mg, 0.46 mmol) in CH_3CN (5 mL) was added *tris*(tetra-*n*-butyl)ammonium hydrogen diphosphate (830 mg, 0.9 mmol). After the solution was stirred at rt for 3 h, the solvent was stripped at rt by rotary evaporation at high vacuum to give approximately 900 mg of a white taffy solid. This material was dissolved in 25 mM NH_4HCO_3/2-propanol (49:1, 2 mL) and applied to a 20 × 1.5 cm Dowex 50WX8-200 (NH_4^+ form) column. Cation exchange was conducted at a flow rate of 1 mL/min, and the eluent was collected in 2.5 mL fractions with the product eluting between 10 and 20 mL. The diphosphate-containing fractions were diluted with 2-propanol (4 mL), concentrated *in vacuo*, and the resulting solid was purified by cellulose chromatography using 5:2.5:2.5 (v/v/v) 2-propanol/CH_3CN/0.1 M NH_4HCO_3 as eluent to give pure GPP as a white solid (80 mg, 0.22 mmol, 48%, ^{1}H and ^{13}C NMR are consistent with those of authentic geranyl diphosphate): ^{31}P NMR δ −10.23, −6.97. The allylic diphosphate was dissolved in 1:1 0.25 mM NH_4HCO_3/2-propanol and stored in this form at −20 °C for several months.

(2*E*,6*Z*)-3,7-Dimethyl-2,6-nonadien-1-yl Diphosphate (2a). From chloride **9a** (55 mg, 0.29 mmol), **2a** was obtained (40 mg, 0.10 mmol, 34%): ^{1}H NMR δ 0.98 (t, 3H, J = 6.4 Hz), 1.71 (s, 3H), 1.74 (s, 3H), 1.79−2.21 (m, 6H), 4.50 (dd, 2H, J = 6.6, 6.6 Hz), 5.21 (t, 1H, J = 6.0 Hz), 5.48 (t, 1H, J = 6.6 Hz); ^{13}C NMR δ 12.3, 15.7, 22.1, 24.5, 25.3, 39.2, 62.6, 120.0 (d, 7.3 Hz), 123.8, 139.9, 142.8; ^{31}P NMR δ −10.16, −7.91.

(2*E*,6*Z*)-3-Ethyl-7-methyl-2,6-nonadien-1-yl Diphosphate (2b). From chloride **9b** (20 mg, 0.10 mmol), **2b** was obtained (9 mg, 0.02 mmol, 23%): ^{1}H NMR δ 0.98 (t, 3H, J = 7.6 Hz), 1.00 (t, 3H, J = 7.0 Hz), 1.71 (s, 3H), 2.03−2.22 (m, 8H), 4.51 (dd, 2H, J = 6.4, 6.4 Hz), 5.23 (t, 1H, J = 6.3 Hz), 5.45 (t, 1H, J = 7.2 Hz); ^{13}C NMR δ 12.3, 13.0, 22.2, 23.1, 24.5, 25.6, 36.2, 62.5, 119.6 (d, J = 8.5 Hz), 124.0, 139.8, 148.7; ^{31}P NMR δ −9.65, −6.85.

(2*E*)-3-Ethyl-7-methyl-2,6-octadien-1-yl Diphosphate (2c). From chloride **9c** (25 mg, 0.13 mmol), **2c** was obtained (25 mg, 0.08 mmol, 61%): ^{1}H NMR δ 1.01 (t, 3H, J = 7.7 Hz), 1.66 (s, 3H), 1.72 (s, 3H), 2.11−2.22 (m, 6H), 4.52 (dd, 2H, J = 6.4, 6.4 Hz), 5.20−5.28 (m, 1H), 5.45 (t, 1H, J = 7.2 Hz); ^{13}C NMR δ 13.1, 17.1, 23.2, 25.0, 25.9, 35.9, 62.4, 119.6 (d, J = 7.3 Hz), 124.4, 133.7, 148.7; ^{31}P NMR δ −9.89, −8.01.

(2*Z*)-3-Methyl-2-penten-1-yl Diphosphate (1b). From (*Z*)-1-chloro-3-methyl-2-pentene (70 mg, 0.60 mmol), **1b** was obtained (52 mg, 0.17 mmol, 34%): ^{1}H NMR δ 0.99 (t, 3H, J = 7.5 Hz), 1.77 (s, 3H), 2.17 (q, 2H, J = 7.4 Hz), 4.49 (dd, 2H, J = 6.2, 6.2 Hz), 5.46 (t, 1H, J = 6.0 Hz); ^{13}C NMR δ 12.6, 22.3, 24.7, 62.5 (d, J = 4.9 Hz), 119.2 (d, J = 7.3 Hz), 146.0; ^{31}P NMR δ −9.85, −7.93.

General Procedure for the Preparation of 3a−h. $BaI_2 \cdot 2H_2O$ (141 mg, 0.33 mmol) was placed in an amber vial and dried *in vacuo* for 2 h at 210 °C. Upon cooling to rt, the solid was immediately transferred to an Ar-filled flask equipped with a stir bar and suspended in THF (10 mL), and a solution

of biphenyl radical anion (prepared by adding excess Li wire (20 mg, 2.9 mmol) to a solution of biphenyl (105 mg, 0.68 mmol) in THF (2.7 mL)) was added dropwise. After the solution was stirred at rt for 1 h, the dark brown suspension was cooled to −78 °C and chloride **23** (0.27 mmol) in THF (2 mL) was added over 10 min. The resulting red solution was stirred at −78 °C for 15 min. Bromide **20** (0.31 mmol) in THF (2 mL) was then added dropwise over 5 min, during which time the color began to fade to a faint yellow. The reaction was stirred at −78 °C for1 h and then quenched by the addition of saturated aqueous NH_4Cl (2 mL). The solution was diluted with H_2O (20 mL) and extracted with Et_2O (3 × 10 mL), and the combined organics were subjected to standard workup. Chromatography using EtOAc/hexane (1/99) as eluent yielded isomerically impure **24** which was deprotected with TBAF using the procedure described for the preparation of **9c**. Chromatography using EtOAc/hexane (15/85) as eluent followed by reverse phase semipreparative HPLC (20/80 H_2O/CH_3CN) provided pure **3a**−**h**.

(2*E*,6*E*)-3,7,11-Trimethyl-2,6,10-dodecatrien-1-ol (3a). Farnesol (**3a)** was obtained (22 mg, 0.10 mmol, 37%): GC 18.2 min; IR, ^{1}H and ^{13}C NMR are consistent with those of authentic farnesol.

(2*E*,6*E*,10*Z*)-3,7,11-Trimethyl-2,6,10-tridecatrien-1-ol (3b). Alcohol **3b** was obtained (18 mg, 0.08 mmol, 30%): GC 19.0 min; IR (neat) cm^{-1} 3348, 2919, 1665; ^{1}H NMR δ 0.96 (t, 3H, J = 7.7 Hz), 1.60 (s, 3H), 1.68 (s, 6H), 1.99−2.16 (m, 10H), 4.15 (d, 2H, J = 6.6 Hz), 5.04−5.09 (m, 2H), 5.42 (t, 1H, J = 6.6 Hz); ^{13}C NMR δ 14.8, 17.9, 19.3, 24.8, 27.3, 27.6, 28.5, 38.1, 41.5, 61.0, 124.9, 125.0, 126.1, 132.9, 141.5, 142.9.

(2*E*,6*E*)-3,11-Dimethyl-7-ethyl-2,6,10-dodecatrien-1-ol (3c). Alcohol **3c** was obtained (20 mg, 0.08 mmol, 31%): GC 19.1 min; IR (neat) cm^{-1} 3316, 2913, 1669; ^{1}H NMR δ 0.96 (t, 3H, J = 7.7 Hz), 1.59 (s, 3H), 1.67 (s, 3H), 1.68 (s, 3H), 1.95−2.13 (m, 10H), 4.15 (d, 2H, J = 7.4 Hz), 5.06 (t, 1H, J = 6.6 Hz), 5.11 (t, 1H, J = 5.9 Hz), 5.42 (t, 1H, J = 7.0 Hz); ^{13}C NMR δ 14.4, 17.6, 17.9, 24.5, 26.4, 27.9, 41.2, 41.6, 61.0, 124.9, 125.4, 125.5, 137.0, 138.7, 141.5.

(2*E*,6*E*)-7,11-Dimethyl-3-ethyl-2,6,10-dodecatrien-1-ol (3d). Alcohol **3d** was obtained (19 mg, 0.08 mmol, 30%): GC 19.1 min; IR (neat) cm^{-1} 3310, 2919, 1669; ^{1}H NMR δ 0.99 (t, 3H, J = 7.7 Hz), 1.60 (s, 6H), 1.68 (s, 3H), 1.98−2.13 (m, 10H), 4.16 (d, 2H, J = 6.6 Hz), 5.07−5.12 (m, 2H), 5.38 (t, 1H, J = 7.0 Hz); ^{13}C NMR δ 15.3, 17.6, 19.3, 25.1, 27.3, 28.1, 28.3, 38.0, 41.3, 60.7, 124.4, 125.5, 125.9, 133.0, 137.0, 147.4.

(2*E*,6*E*,10*Z*)-7-Ethyl-3,11-dimethyl-2,6,10-tridecatrien-1-ol (3e). Alcohol **3e** was obtained (24 mg, 0.1 mmol, 37%): GC 19.9 min; IR (neat) cm^{-1} 3331, 2921, 1668; ^{1}H NMR δ 0.95 (t, 6H, J = 7.3 Hz), 1.68 (s, 6H), 1.98−2.14 (m, 12H), 4.15 (d, 2H, J = 7.4 Hz), 5.07 (t, 2H, J = 6.3 Hz), 5.42 (t, 1H, J = 7.0 Hz); ^{13}C NMR δ 14.4, 14.8, 17.9, 24.5, 24.8, 26.4, 27.6, 28.2, 38.4, 41.5, 61.0, 124.9, 125.7, 138.7, 141.5, 142.9.

(2*E*,6*E*,10*Z*)-3-Ethyl-7,11-dimethyl-2,6,10-tridecatrien-1-ol (3f). Alcohol **3f** was obtained (25 mg, 0.1 mmol, 37%): GC 20.0 min; IR (neat) cm^{-1} 3320, 2917, 1671; ^{1}H NMR δ 0.96 (t, 3H, J = 7.4 Hz), 0.99 (t, 3H, J = 7.4 Hz), 1.60 (s, 3H), 1.67 (s, 3H), 1.95−2.13 (m, 12H), 4.16 (d, 2H, J = 6.6 Hz), 5.09 (t, 1H, J = 7.4 Hz), 5.10 (t, 1H, J = 6.6 Hz), 5.38 (t, 1H, J = 7.0 Hz); ^{13}C NMR δ 14.4, 15.3, 17.7, 24.5, 25.1, 26.4, 27.9, 28.1, 38.0, 41.6, 60.7, 124.4, 125.5, 136.9, 138.7, 147.4. Anal. Calcd for $C_{17}H_{30}O$: C, 81.54; H 12.13. Found: C, 81.14; H, 12.21.

(2*E*,6*E*)-3,7-Diethyl-11-methyl-2,6,10-dodecatrien-1-ol (3g). Alcohol **3g** was obtained (22 mg, 0.09 mmol, 33%): GC 19.8 min; IR (neat) cm^{-1} 3342, 2918, 1669; ^{1}H NMR δ 0.96 (t, 3H, J = 7.4 Hz), 0.99 (t, 3H, J = 7.4 Hz), 1.60 (s, 3H), 1.68 (s, 3H), 1.99−2.13 (m, 12H), 4.16 (d, 2H, J = 7.3 Hz), 5.06−5.11 (m, 2H), 5.38 (t, 1H, J = 6.6 Hz); ^{13}C NMR δ 14.8, 15.3, 19.3, 24.8, 25.1, 27.3, 27.8, 28.5, 38.1, 38.3, 60.7, 124.4, 125.0, 126.1, 132.9, 142.9, 147.4.

(2*E*,6*E*,10*Z*)-3,7-Diethyl-11-methyl-2,6,10-tridecatrien-1-ol (3h). Alcohol **3h** was obtained (27 mg, 0.1 mmol, 38%): GC 20.6 min; IR (neat) cm^{-1} 3373, 2917, 1669; ^{1}H NMR δ 0.96 (t, 3H, J = 7.4 Hz), 0.99 (t, 6H, J = 7.4 Hz), 1.68 (s, 3H), 1.99−2.13 (m, 14H), 4.16 (d, 2H, J = 7.3 Hz), 5.08 (t, 2H, J = 5.9 Hz), 5.38 (t, 1H, J = 7.0 Hz); ^{13}C NMR δ 14.4, 14.8, 15.3, 24.5, 24.8, 25.2, 26.4, 27.8, 28.2, 38.3, 38.4, 60.7, 124.4, 125.0, 125.7, 138.7, 142.9, 147.4. Anal. Calcd for $C_{18}H_{32}O$: C, 81.75; H 12.19. Found: C, 81.85; H, 12.14.

***In Vitro* Studies.** Assays were performed using previously published assay procedures.[1] Corpora cardiaca−corpora allata complexes were removed from fifth instar *M. sexta* larvae and immediately placed in a cold solution of 20 mM Tris−HCl buffer (pH 7), containing 25% glycerol, 0.15% BSA, 2% Triton X-100 (all w/v), 2.5 mM $MgCl_2$, 10 mM KF, and 0.5 mM mercaptoethanol. The glands were homogenized on ice and after removal of cellular debris by centrifugation at 16000*g* for 10 min, 50 μL aliquots of supernatant (containing approximately two gland pair equivalents) were placed into siliconized 500 μL plastic microcentrifuge tubes. Prenyltransferase activity was determined by incubating the partially purified homogenate in the presence of 100 μM allylic diphosphate (**1a**,**b** or **2a**−**d**) and 6 μM [4-^{14}C]IPP at 35 °C for 2 h. The reaction was terminated by heating the solution to 100 °C for 1 min, and the diphosphates were hydrolyzed to the corresponding terpenols by reaction with alkaline phosphatase (8 units in 30 μL of 100 mM Tris−HCl, 30 mM $MgCl_2$, pH 9.5, overnight at room temperature or 4 h at 37 °C).

Product Analysis. Terpenol formation was determined by radio-HPLC. After phosphatase treatment, the reaction mixture was diluted with a stock solution of acetonitrile (80 μL) containing appropriate terpenol standards. A portion of the aqueous acetonitrile solution from each assay tube (approximately 80 μL) was injected onto a C-18 reversed phase column (2.5 × 15 cm) and eluted with a two-step CH_3CN/H_2O gradient (1 mL/min, 60 to 70% CH_3CN over 10 min, 70 to 80% CH_3CN over 20 min, then isocratic at 80% CH_3CN for 15 min). Under these conditions, the following retention times for each of the terpenols were obtained: dimethylallyl alcohol, 3.3 min; homodimethylallyl alcohol, 4.3 min; geraniol, 5.5 min; **9a**, **9c**, 7.4 min; **9b**, 11.1 min; farnesol (**3a**), 13.0 min; **3b**, **3c**, **3d**, 18.5 min; **3e**, **3f**, **3g**, 22.3 min; **3h**, 25.2 min. The eluents were collected directly into scintillation vials (1 mL fractions) and then analyzed by liquid scintillation counting. Relative activity was determined by normalizing each of the conversions against those obtained with GPP (for **2a**−**d**) or DMAPP (for **1a**,**b**). Results were the average of three separate experiments performed in duplicate.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of all new compounds (as well ^{31}P spectra of compounds **1b** and **2a**−**c**) in the Experimental Section (68 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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