SYNTHESIS OF METHOXYNOR POLYISOPRENOID ALCOHOLS BY ALKYLATION OF (3-METHOXYALLYL)LITHIUM REAGENTS

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Dedicated to the memory of Dr Václav Černý.

A series of six methyl enol ether analogs **8**–**13** of geraniol, (*E*,*E*)-farnesol, and (*E*,*E*,*E*)-geranylgeraniol was synthesized from a group of three allylic methyl ethers and three allylic chlorides. Lithiation of the 1-methyl-, or 1-alkenylvinyl ethers with *sec*-butyllithium at –78 °C followed by alkylations of the resulting (*Z*)-(3-methoxyallyl)lithium reagents afforded the six possible Z-configured(trans) methoxynor polyprenyl benzyl ethers bearing the methoxy substituent at the internal and terminal double bonds with high Z/E ratios (5 : 1–31 : 1) and 47–80% yields. Reductive cleavage of the benzyl groups with lithium in liquid ammonia gave the corresponding methoxynor polyprenols. 11-Methoxy-18-nor and 7-methoxy-19-nor geranylgeraniols (**13** and **12**) were converted to the corresponding diphosphates, **7** and **32**, by the Poulter displacement method. The stability of the enol ether in **7** in aqueous solution at pH 8 was verified by NMR analyses. The diphosphates of the methoxynor polyprenols may prove useful as substrate analogs for terpene synthases to capture transient intermediates in cyclization reactions catalyzed by these enzymes.

Keywords: Lithiations; Allyllithium reagents; Alkylations; Enol ethers; Terpenoids; Isoprenoids; Polyenes.

The cyclic structures commonly found in naturally occurring isoprenoid natural products are usually formed by the action of cyclase enzymes upon one member of a small set of acyclic precursors: geranyl diphosphate (GPP, **1**) for monoterpenes, (*E*,*E*)-farnesyl diphosphate (FPP, **2**) for sesquiterpenes, (*E*,*E*,*E*)-geranylgeranyl diphosphate (GGPP, **3**) for diterpenes, and either squalene or (*S*)-2,3-oxidosqualene for triterpenes[1]. The cyclization mechanisms are thought to proceed through complex, multi-step sequences in-

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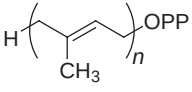
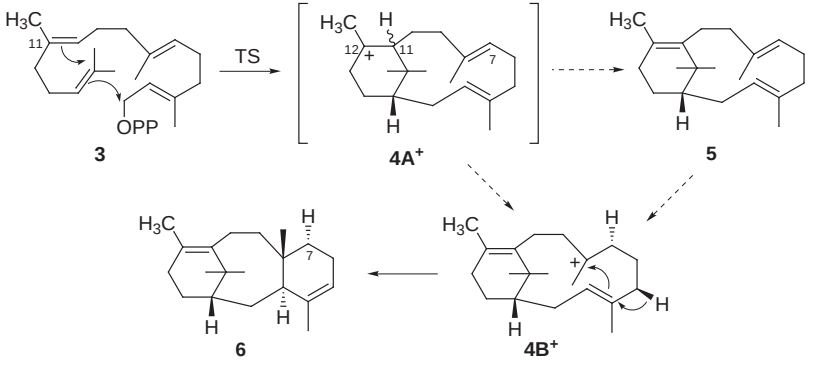
volving hypothetical carbocation intermediates, and in some cases, through neutral partially cyclized olefin or alcohol intermediates which may or may not escape from the active site of the cyclase. The transient existence of the carbocations along the reaction pathway and the inaccessibility of enzymatically enclosed terpenes or terpenol intermediates necessitate the use of indirect methods to gain evidence about the structure and stereochemistry of these intermediates. The indirect approaches used to elucidate the nature of these intermediates include (i) evaluation of inhibitors that mimic the proposed structures[2,3], (ii) disruption of the cyclization mechanism by use of substrate or intermediate analogs[4], and (iii) experiments with mutant forms of the cyclases lacking key residues necessary to convert the intermediate to the final product[2g,5].



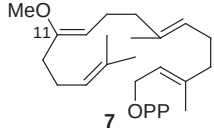
1, *n* = 2 (GPP)
2, *n* = 3 (FPP)
3, *n* = 4 (GGPP)

Some types of analogs utilized to derail the cyclization mechanisms are 2,3-methano- and 6,7-dihydro-GPP (refs[4a,4b]), 6,7-dihydro- and 13-methylidene-FPP (refs[4c,4d]), 8-oxo- and 8-hydroxy-17-norcopalyl diphosphate[4e], as well as oxa, dehydro, methylidene, and other modified forms of 2,3-oxidosqualene[1d,3]. A significant classic example is the enzymatic cyclization of 2,3-oxido-20-oxasqualene to a norprotosterol ketone product arising from hydrolysis of an oxo-carbenium ion intermediate[6]. The discovery that the norprotosterol possessed the unexpected 13α,17α stereochemistry contravened predictions based on the expected stereochemical preference for antarafacial hydride shifts during the subsequent backbone rearrangements.



SCHEME 1

Our interest in elucidating the C-11 stereochemistry of the verticillenyl carbocation intermediate (**4A**$^+$) formed in the first stage of the cyclization of **3** to taxadiene (**6**) catalyzed by taxadiene synthase[7] (Scheme 1) prompted consideration of a similar strategy. We proposed that enzyme-catalyzed cyclization of a GGPP analog bearing a methoxy substituent at C-11 (**7**) instead of the methyl group would lead to an exocyclic oxo-carbenium ion which likely would undergo hydrolysis to a bicyclic product rather than proton transfer and further cyclization. The C-11 configuration of the resulting norverticillone should reveal the unknown stereochemistry of **4A**$^+$ and provide further insight into the remarkable proton transfer that concludes the normal cyclization mechanism leading to taxadiene[7] (**4A**$^+$ → **4B**$^+$). Furthermore it seemed likely that other methoxynor analogs of **1**–**3** would be useful tools for mechanistic studies of other terpene cyclases. In this paper we report syntheses of the six possible Z-configured(trans) methoxynor polyprenols **8**–**13** at the remote double bonds of geraniol, (*E*,*E*)-farnesol, and (*E*,*E*,*E*)-geranylgeraniol by means of alkylations of (3-methoxyallyl)lithium reagents, and the conversion of 11-methoxy-18-nor and 7-methoxy-19-nor geranylgeraniols (**13** and **12**) to the corresponding diphosphates (**7** and **32**).



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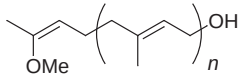
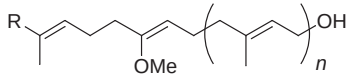


8, *n* = 1
9, *n* = 2
10, *n* =3



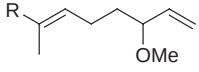
11, R = CH_3, *n* = 1
12, R = 4-methylpent-3-enyl, *n* = 1
13, R = CH_3, *n* = 2

Regio- and stereoselective synthesis of 1,2-disubstituted enol ethers has been accomplished by Horner–Wadsworth–Emmons condensations of α-ethoxy(phosphono)acetate with aldehydes[8a,8b], by base-catalyzed addition of methanol to alkynylmethyl sulfones[8c], by Tebbe olefination of esters[8d], by Wittig olefinations with methoxy substituted ylides[8e], by similar Horner–Wittig olefination with a dimethylallyloxy substituted ylide[6], and by base-catalyzed isomerization γ-methoxy-α,β-unsaturated sulfones[8f]. It is also known that (*Z*)-(3-alkoxyallyl)lithium reagents (homoenolate anions)

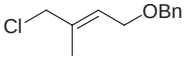
can be generated by lithiation of alkyl and allyl triethylsilyl ethers with *sec*-butyllithium at low temperatures[9]. Recently moderate to good yields of α-alkylations have been accomplished following transmetallations to the corresponding (3-alkoxyallyl)barium reagents[10]. We have found that 1-alkylallyl methyl ethers can be similarly metallated with *sec*-butyllithium and that the resulting (*Z*)-(3-methoxyallyl)lithium reagents so formed can be alkylated with allylic chlorides to form polyisoprenoid chains bearing remote methoxy groups on the terminal and internal double bonds.

Lithiations and Alkylations

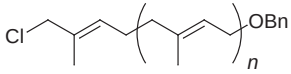
14



15, R = CH_3
16, R = 4-methyl-3-pentenyl



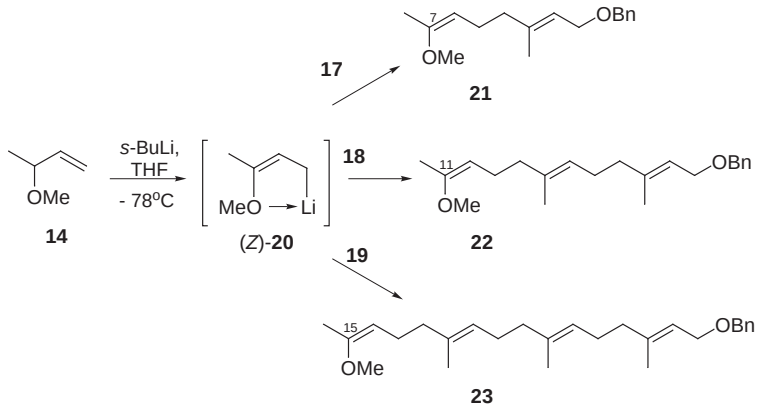
17



18, *n* = 1
19, *n* = 2

Allyl methyl ethers **14**–**16**, and allylic chlorides **17**–**19** were used as starting materials for synthesis of the six methoxynor polyenyl benzyl ethers. The known ether **14** was prepared as described[11a], and the unknown ethers **15** and **16** were obtained by *O*-methylation[11b,12] (NaH, CH_3I, ether) of the corresponding allylic alcohols resulting from vinyl Grignard additions to the precursor aldehydes[13]. The allylic chlorides **17**–**19**, all three of which are known[14–16], were prepared by E-selective Wittig olefinations to form the α,β-enoate esters[17], AlH_3 reductions to the allylic alcohols[15,16], and conversion to the halides by Meyers' method[18] (MsCl, LiCl, collidine, DMF).

Allylic ethers **14** and **15** were lithiated with limiting amounts of *sec*-BuLi (0.75–0.80 equiv.) in THF (refs[9b,9c]), and the deprotonations were found to be complete after 30 min at –78 °C upon quenching and analysis by ^1H NMR spectroscopy (Schemes 2 and 3). The allylic chlorides (0.33–0.67 equiv. with respect to *sec*-BuLi) were added as neat oils at –78 °C. The yields based on the chlorides ranged from 47 (**26**) to 80% (**23**), and Z/E ratios varied from 5 : 1 (**21**) to 31 : 1 (**28**) (see Table I). It was found that the proportion of the chloride used in the alkylation affected both the yield and the stereoselectivity. For example, during the preparation of geranyl analog **21**, use of 0.68 equivalent of the chloride resulted in 35% yield and 3.5 : 1 Z/E



SCHEME 2

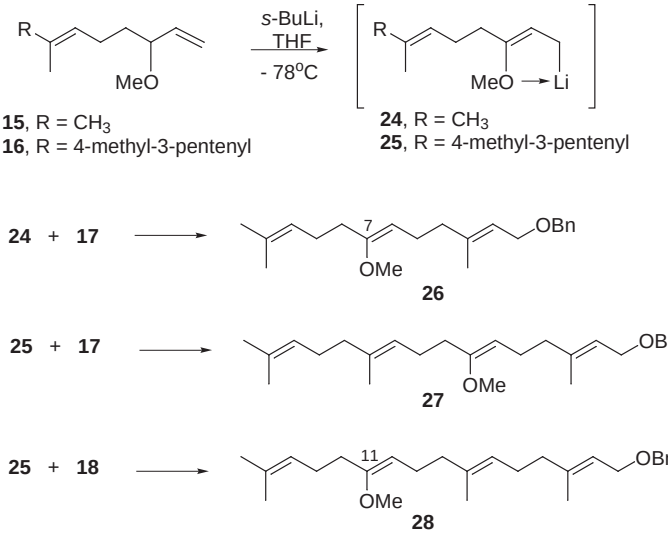
selectivity. When 0.41 equivalent of chloride was used, the yield increased to 71% and the selectivity improved to 5 : 1. Although the longer chain ether **16** could not be lithiated under the same conditions, upon addition of TMEDA (1 equiv. with respect to *sec*-BuLi)[19] the metallation proceeded smoothly at –78 °C within 1 h, and alkylation with **17** afforded 7-methoxy-19-nor geranylgeranyl ether (**27**) with a typical 6 : 1 Z/E ratio in 51% yield.

TABLE I

Yields and Z/E isomer ratios of methoxynor polyenyl benzyl ethers from lithiation/alkylations (Schemes 2 and 3), and yields of methoxynor polyene alcohols from benzyl ether cleavages

Starting materials		Methoxynor benzyl ether[a]			Methoxynor alcohol[b]	
allylic ether	allylic chloride	No.	Yield, %	Z/E ratio[c]	No.	Yield, %[d]
14	**17**	**21**	71	5 : 1	**8**	82
14	**18**	**22**	73	7 : 1	**9**	78
14	**19**	**23**	80	7 : 1	**10**	41
15	**17**	**26**	47	15 : 1	**11**	56
16	**17**	**27**	51	6 : 1[e]	**12**	61
15	**18**	**28**	78	31 : 1	**13**	66

[a] Lithiation of allylic ethers (*s*-BuLi, THF, –78 °C) followed by alkylations with allylic chlorides at –78 °C. [b] Benzyl groups cleaved with Li in 3 : 2 NH_3–THF (–78 °C). [c] Determined by NMR integration after purification. [d] Includes 7–18% of E isomer present. [e] TMEDA additive was used.



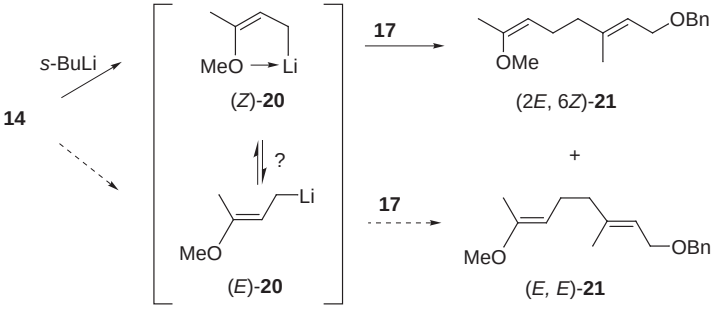
SCHEME 3

Purifications were carried out by silica gel chromatography with 2% Et_3N in the eluents to remove the large excess of methyl ether starting material and other impurities[6]. In the absence of the Et_3N additive, the enol ethers were found to decompose during the purifications. In some cases unreacted allylic chloride starting material was also present, and its separation from the enol ether product was difficult. This problem was solved by allowing the chloride to react with an amine base (Et_2NH, 5 equiv. relative to the allylic chloride, DMF, room temperature, 12 h). The diethylamine and amine alkylation product were removed by fast extraction with chilled, dilute 0.1 M HCl, after which purification by chromatography gave the pure enol ethers free from the chloride contaminants.

The Z/E isomer ratios were determined after chromatographic purifications by ^1H NMR integration of either the vinyl or methoxy protons of the enol ether groups. The spectra were acquired in benzene-d_6 instead of the usual $CDCl_3$ to avoid the risk of isomer alteration or decomposition from traces of HCl often present in the latter solvent. Unfortunately, the spectra of the crude products were too complicated for reliable measurement of the small amounts of E isomers owing to the presence of large quantities of the allylic ether starting materials, minor unidentified products, and in some instances unreacted chloride. Although the isomers exhibited very similar chromatographic mobilities, the possibility of small changes in the ratios by inadvertent fractionation during purification cannot be excluded. Some perturbations of the Z/E ratios by traces of HCl re-

leased from unreacted allylic chlorides might also have occurred during the reactions or isolation procedures which would increase the proportion of the presumably more stable E isomer somewhat. Despite these concerns, repeated experiments with the same compounds gave reasonably reproducible yields (±10%) and selectivities.

The ^{1}H NMR spectra of the major alkylation products all show one-proton triplets (J = 7.0 Hz) at δ 4.3–4.5 ppm for the vinyl proton on the enol ether double bond, upfield (Δδ = –0.8 to –1.0 ppm) from the vinyl proton peaks at δ 5.1–5.3 ppm for the other trisubstituted double bonds in the polyene chains. The vinyl protons of the E isomers resonate somewhat further upfield at around δ 4.3 ppm as a triplet (J = 7.1 Hz). The Z/E isomer ratios were usually determined by integration of these two enol ether vinyl proton peaks; however, in some cases more accurate estimates were obtained from the methoxy peak ratios. The peaks for the CH_2 protons across the double bond from the methoxy group consistently appeared as quartets at δ 2.4 ppm (J = 7.4 Hz), downfield from other CH_2 protons at δ 2.0–2.2 ppm.

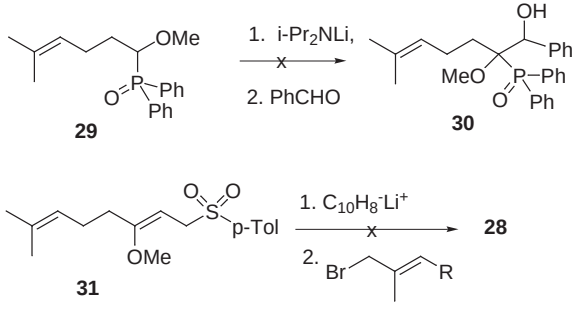


SCHEME 4

The reasons for the substantial variations in the isomer ratios and yields are unclear at this time. It seems likely that the (*Z*)-(3-methoxyallyl)lithium intermediates are thermodynamically more stable than their E isomers, owing to strong chelation in the former. However, the rates of the reactions with the allylic chlorides may be quite different for the two isomers, and the presumably less stable E form may undergo faster alkylation. One possible mechanism and explanation for the formation of Z/E mixtures is that (*Z*)- and (*E*)-(3-methoxyallyl)lithiums are formed irreversibly in kinetically controlled reactions with *sec*-butyllithium (Scheme 4). In this scenario the Z/E ratios of the products would reflect the ratios of the isomeric lithium reagents present. However, it is also plausible that the (*Z*)- and (*E*)-(3-methoxyallyl)lithium isomers undergo partial or complete equilibration at

–78 °C, and a low proportion of the (*E*)-(3-methoxyallyl)lithium is increased in the product by a faster alkylation. Thus it seems plausible that the somewhat higher ratios (7 : 1) of the longer chain terminal methoxynor isomers **22** and **23** compared to **21** (5 : 1) might be attributed to somewhat faster alkylations of (*Z*)-**20** with chlorides **18** and **19**, since the reactivity of **17** might be depressed by the inductive influence of the proximal allylic benzyloxy group. However, the presumably less reactive **17** gave an enhanced Z/E ratio (15 : 1) in the alkylation of (*Z*)-**24** (R = CH_3) to form **26**. In this case the longer chain substituent on the (methoxyallyl)lithium reagent (**20**, R = methyl *vs* **24**, R = homoprenyl) may affect the outcome.

Attempts to synthesize **28** by Horner–Wittig olefination[6,8e] and by tandem reduction-alkylations of a 3-methoxyallyl sulfone were unsuccessful, despite numerous trial experiments (Scheme 5). Lithiation of α-methoxyphosphine oxide **29** (i-Pr_2NLi, THF, –78 °C) followed by reactions with benzaldehyde afforded complex product mixtures rather than the expected β-hydroxy phosphine oxide diastereomers **30** (refs[6,8e]). Another attractive approach involved reductive cleavage of 3-methoxyallyl *p*-tolyl sulfone[8f] (**31**) with lithium naphthalenide which seemed likely to produce (3-methoxyallyl)lithium **24**. However, attempts to obtain **28** from reductions of **31** ($C_{10}H_8$-Li, THF, –78 °C) followed by addition of the allylic bromide corresponding to **18** (Br in place of Cl) were fruitless. Furthermore, the likelihood of radical intermediates in the reductive lithiation was indicated by the lack of deuterium incorporation into the reduction product after addition of D_2O.

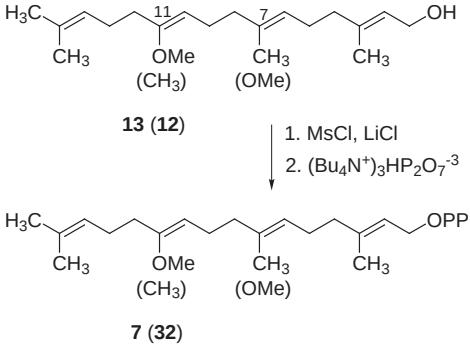


SCHEME 5

Methoxynor Polyprenyl Alcohols and Diphosphates

Li/NH_3 reductions to remove the benzyl protecting groups of **21**–**23** and **26**–**28** were carried out at –78 °C with a large excess of the metal in a 3 : 2 mixture of NH_3 and THF as solvent[20] (Table I). The alcohol products **8**–**13**

were purified by flash chromatography with 2% Et_3N in the eluent. The amount of E isomer present (7–18%) was estimated as above by integration of the respective enol ether vinyl protons in the ^1H NMR spectra, and the E/Z ratios were essentially the same as those of the benzyl ethers from which they were derived. The yields for the reductive cleavages varied widely from 41% of the terminal methoxynor diterpene analog **10** to 82% of the monoterpene derivative **8** (see Table I). 7- and 11-Methoxynor geranylgeraniol (**12** and **13**) were converted to the diphosphates **32** and **7** by formation of the corresponding allylic chlorides[18] and displacement with inorganic pyrophosphate[21] (Scheme 6). The ^1H NMR spectra showed a vinyl proton peak at δ 4.5 ppm (t, J = 7.1 Hz), indicating that the enol ether was not hydrolyzed during the two-step procedures. ^{31}P NMR spectra showed two doublets at δ –8.55 and –8.01 ppm (J = 19.5 Hz) diagnostic for monoalkyl diphosphates.



SCHEME 6

The stability of diphosphate **7** was evaluated at pH 8 in D_2O solution with phosphate buffer as a prelude to incubations with taxadiene synthase. The solution was analyzed intermittently by ^1H (400 MHz) and ^{31}P NMR (162 MHz) spectroscopy. After 24 h at room temperature, the triplet from the C-10 vinyl proton at δ_H 4.46 ppm and the two doublets from the diphosphate at δ_P –5.4 and –9.6 ppm indicated that the sensitive enol ether was intact. A preliminary incubation of **7**-OPP with recombinant taxadiene synthase resulted in slow conversion to a major product (*ca* 50%) having GC retention time and apparent molecular weight (GC/MS, *m/z* 274) appropriate for a nor diterpene ketone ($C_{19}H_{32}O$) and demonstrably different than hydrolysis products arising from acid hydrolysis of **7** followed by dehydration[22,23].

Conclusion

All trans polyene isoprenoid alcohols bearing methoxy groups in place of methyl substituents on the remote double bonds are now available by sequential lithiation of allyl methyl ethers **14**–**16**, coupling with allylic chlorides **17**–**19**, and benzyl ether cleavage. The stability of the enol ether to conditions required for conversion of the corresponding diphosphates and to aqueous buffer at pH 8 indicates the potential utility of these methoxynor analogs of **1**–**3** as mechanistic probes in terpene synthase reactions.

EXPERIMENTAL[2f,18b]

Compounds were named in accordance with the IUPAC conventions[24]. Solvents were distilled from the indicated drying agents prior to use: THF, diethyl ether, benzene (Na/benzophenone); CH_2Cl_2 (CaH_2); hexane, ethyl acetate (none). CH_3CN, DMSO and DMF were distilled from P_2O_5, and stored over 3 Å molecular sieves. Et_3N and pyridine were distilled from CaH_2, and stored over KOH. CuI was purified as described by Kauffman and Teter[25]. Methanesulfonyl chloride was obtained from Aldrich Chemical Company, and distilled from P_2O_5. Dihydrogen disodium pyrophosphate was obtained from Sigma Chemical Company, and was converted to the tetrabutylammonium salt according to a procedure reported by Poulter[21]. Most other reagents were purchased from Aldrich Chemical Co., and were used without further purifications. *sec*-BuLi (1.3 M solution in cyclohexane) was obtained from Aldrich, and titrated before use[26].

The progress of all reactions was monitored by TLC unless stated otherwise. TLC analyses were performed on plastic-backed Merck Kieselgel 60 F254 plate with visualization by UV fluorescence at 254 nm, I_2 staining, or phosphomolybdic acid spray followed by development on a hot plate at 120 °C.

GC analyses were performed on a Shimadzu GC-14A with a 30-m Restek Rtx-5 column. GC/MS analyses were conducted with a Hewlett–Packard 5890A instrument GC/5970 with a mass selective detector (EI). Dowex AG 50W-X8 ion exchange resin (H^+ form) obtained from BioRad was converted to the ammonium form before each chromatography according to a published procedure[21]. Cellulose TLC plates (American Scientific Products) were developed with cellulose chromatography buffer. Cellulose chromatography was performed on Whatman CF-11 fibrous cellulose[21].

Flash chromatography was performed according to the procedure of Still[27] using Merck 0.040–0.063 mm silica gel. Chromatographic purifications of the enol ether products were carried out with eluents containing 2% v/v Et_3N. The enol ether products were stored at –20 °C in hexane containing 1% Et_3N. Samples for elemental analyses were prepared by flash chromatography followed by evacuation under reduced pressure. Elemental analyses were performed by the Microanalytical Laboratory at the University of Illinois. The purity of all products was estimated to be at least 90–95% by inspection and integration of NMR spectra and/or GC analyses.

^1H NMR spectra were acquired on Unity 400 or Unity 500 spectrometers at 400 or 500 MHz in $CDCl_3$ or C_6D_6 with the solvent as the internal reference ($\delta(CHCl_3)$ 7.26 or $\delta(C_6D_5H)$ 7.15 ppm). Coupling patterns were analyzed as if first-order, and the coupling constants reported (*J*, Hz) are the corresponding line spacings. Multiplets and coupling con-

stants designated "apparent" (app) may in fact be second-order in which case the data should be regarded as descriptive. ^{13}C NMR spectra were recorded with the Unity 400 or 500 spectrometer at 101 or 126 MHz in $CDCl_3$ with $CDCl_3$ as the reference ($\delta(CDCl_3)$ 77.0 ppm). ^{31}P NMR spectra were obtained with the Unity 400 at 162 MHz in CD_3OD or D_2O with 85% H_3PO_4 as the external reference ($\delta(H_3PO_4)$ 0.00 ppm). IR spectra (wavenumbers in cm^{-1}) were recorded on a Mattson Galaxy Series 5000 FT-IR spectrometer as neat liquids on NaCl plates.

3-Methoxybut-1-ene (**14**)

The literature procedure[11a] (but-3-en-2-ol, NaH, Me_2SO_4, *o*-xylene, 140 °C, 23 h) afforded 6.4 g (48%), b.p. 49–56 °C. The ^1H NMR data matched the published values[28]. ^1H NMR ($CDCl_3$, 500 MHz): 1.23 d, 3 H, J = 6.4 (CH_3); 3.27 s, 3 H (OCH_3); 3.70 quintet, 1 H, J = 6.6 (C**H**OCH_3); 5.14 app ddd, 1 H, J_{app} = 10.2, 1.6, 0.7 (H-1); 5.18 app ddd, 1 H, J_{app} = 17.2, 1.6, 1.1 (H-1); 5.70 ddd, 1 H, J = 17.4, 10.2, 7.3 (H-2).

5-Methylhex-4-enal

A solution of 2-methylbut-3-en-2-ol (10.9 g, 0.13 mol), ethyl vinyl ether (20.0 g, 0.28 mol), and H_3PO_4 (85% in H_2O, 6 drops) was heated for 4 h at 150 °C in a sealed tube[29]. The solution was allowed to cool to room temperature, and Et_3N (1 ml) was added. Distillation at 96–126 °C (40 torr) afforded 14.0 g of a yellow oil that was a 1 : 1.77 mixture of the aldehyde and its diethyl acetal according to NMR analysis. The oil (7.0 g) was dissolved in acetone (150 ml) and H_2O (2.2 g, 0.12 mol), and Amberlyst-15 sulfonic acid resin (1.5 g) was added. The suspension was stirred at room temperature for 2 h and filtered. Concentration of the filtrate and distillation at reduced pressure gave the known aldehyde[29] as a colorless oil: yield 3.21 g (52%), b.p. 78–79 °C (35 torr) [ref.[29] b.p. 90 °C (100 torr)]. The following ^1H NMR data are consistent with the reported values[30]. ^1H NMR ($CDCl_3$, 400 MHz): 1.60 s, 3 H (CH_3); 1.61 s, 3 H (CH_3); 2.30 q, 2 H, J = 7.2 (CH_2); 2.45 t, 2 H, J = 7.2 (CH_2); 5.09 t of quintets, J = 7.6, 1.3 (vinyl H); 9.75 t, 1 H, J = 1.7 (CHO).

7-Methylocta-1,6-dien-3-ol

The procedure by Gadwood for a different compound was followed[13] to prepare the known alcohol[31]. A solution of vinylmagnesium bromide (1.0 M in THF, 100 ml) in THF (60 ml) was stirred and cooled at 0 °C as the aldehyde (7.1 g, 40 mmol) in THF (40 ml) was added over 1 h. After an additional 2 h, saturated NH_4Cl (10 ml) was added, and the solvent was removed by simple distillation. Saturated NH_4Cl (100 ml) and H_2O (100 ml) were added, and the product was extracted with Et_2O (3 × 100 ml). The combined ethereal extracts were washed with saturated $NaHCO_3$ (1 × 60 ml) and saturated NaCl (1 × 60 ml). Drying (anhydrous Na_2SO_4), evaporation under reduced pressure, and purification by flash chromatography (30% EtOAc in hexane) gave the title alcohol as a yellow oil (3.6 g, 69%). The following ^1H NMR data are consistent with the reported values[32]. ^1H NMR ($CDCl_3$, 400 MHz): 1.54 m, 2 H (CH_2); 1.59 s, 3 H (CH_3); 1.67 d, 3 H, J = 0.7 (CH_3); 1.80 s, 1 H (OH); 2.06 q, 2 H, J = 7.4 (CH_2); 4.08 q, 1 H, J = 6.4 (C**H**OH); 5.08 app d of quintets, 1 H, J_{app} = 10.4, 1.4 (H-1); 5.12 app d of quintets, 1 H, J_{app} = 7.3, 1.3 (H-6); 5.20 dt, 1 H, J = 17.2, 1.4 (H-1); 5.85 ddd, 1 H, J = 17.0, 10.4, 6.0 (H-2). ^{13}C NMR ($CDCl_3$, 126 MHz): 17.7, 24.0, 25.7, 37.0, 72.8, 114.5, 123.9, 132.2, 141.2.

3-Methoxy-7-methylocta-1,6-diene (**15**)[11b]

The reaction was carried out according to a literature procedure for a different compound[12]. MeI (1.82 g, 12.8 mmol) was added to a suspension of NaH (616 mg, 12.8 mmol) in a solution of the preceding alcohol (900 mg, 6.42 mmol) in Et_2O (25 ml). The suspension was stirred for 18 h at room temperature, water (30 ml) was added, and the product was extracted with Et_2O (3 × 30 ml). The combined ethereal extracts were washed with saturated NaCl (1 × 20 ml), dried (anhydrous Na_2SO_4), and concentrated under reduced pressure to give a dark green oil (1.61 g). Purification by flash chromatography (3% Et_2O in pentane) afforded ether **15** as a light yellow oil: yield 72 mg (76%). IR (neat): 2 931, 1 449, 1 107. ^{1}H NMR ($CDCl_3$, 400 MHz): 1.37 dddd, 1 H, J = 13.4, 8.3, 7.3, 6.1 (CH_2); 1.53–1.57 m, 1 H (CH_2); 1.50 s, 3 H (CH_3); 1.59 d, 3 H, J = 1.0 (CH_3); 1.93 sextet, 2 H, J = 8.0 (CH_2); 3.16 s, 3 H (OCH_3); 3.39 q, 1 H, J = 6.9 (C**H**OMe); 5.00 app t of quintets, 1 H, J_{app} = 7.3, 1.3 (H-1); 5.07 app ddd, 1 H, J_{app} = 9.3, 2.0, 0.7 (H-1); 5.10 m, 1 H (H-6); 5.55 ddd, 1 H, J = 16.8, 10.7, 7.6 (H-2). ^{13}C NMR ($CDCl_3$, 101 MHz): 17.5, 23.6, 25.5, 35.3, 55.9, 82.2, 116.8, 123.9, 131.6, 138.7. MS (*m/z*, rel.%): low resolution EI: 154 (<0.4) [M^+], 104.1 (37), 89 (10), 73.1 (100), 59.0 (55); low resolution CI: (CH_4) 131.1 (19), 105.1 (15), 73.0 (6.0), 59.0 (100).

(*E*)-5,9-Dimethyldeca-4,8-dienal

The reduction was carried out according to the procedure of Szantay *et al.* for a different compound[33]. To a solution of ethyl (*E*)-5,9-dimethyldeca-4,8-dienoate[34] (1.0 g, 4.5 mmol) in hexane (35 ml) at –78 °C was added diisobutylaluminum hydride (1.0 M in hexane, 5.8 ml). After 2 h at –78 °C, MeOH (2 ml) was added, and the solution was allowed to warm to room temperature. Saturated aqueous potassium, sodium tartrate solution (35 ml) was added, and the aqueous layer was extracted with hexane (1 × 35 ml). The hexane layer washed with saturated. NaCl (1 × 25 ml), dried (anhydrous Na_2SO_4), and concentrated. Purification by flash chromatography (5% EtOAc in hexane) gave 0.68 g (84%) of the known dienal as a colorless oil. The following ^{1}H NMR data agree with the values reported by Poulter[35]. ^{1}H NMR ($CDCl_3$, 400 MHz): 1.59 s, 3 H (CH_3); 1.61 s, 3 H (CH_3); 1.67 s, 3 H (CH_3); 1.93–2.09 m, 4 H (CH_2); 2.32 q, 2 H, J = 7.0 (CH_2); 2.46 td, 2 H, J = 6.8, 1.0 (CH_2); 5.08 m, 2 H (vinyl H); 9.76 t, 1 H, J = 1.7 (CHO).

(*E*)-7,11-Dimethyldodeca-1,6,10-trien-3-ol

Reaction of the preceding dienal (0.67 g, 3.7 mmol) and vinylmagnesium bromide according to the procedure described above with 5-methylhex-4-enal gave 583 mg (69%) of the known alcohol[36] prepared by a photochemical method. The ^{1}H NMR data corresponded well with the literature values[36]. ^{1}H NMR ($CDCl_3$, 400 MHz): 1.56 m, 2 H (CH_2); 1.59 s, 3 H (CH_3); 1.60 s, 3 H (CH_3); 1.67 s, 3 H (CH_3); 1.95–2.11 m, 6 H (CH_2); 4.10 q, 1 H, J = 6.3 (C**H**OH); 5.08 m, 1 H (vinyl H); 5.10 app d of quintets, 1 H, J_{app} = 10.5, 1.3 (vinyl H); 5.13 app t of sextets, 1 H, J_{app} = 7.1, 1.2 (vinyl H); 5.21 dt, 1 H, J = 17.1, 1.5 (vinyl H); 5.86 ddd, 1 H, J = 17.1, 10.5, 6.1 (vinyl H). ^{13}C NMR ($CDCl_3$, 101 MHz): 15.9, 17.6, 23.7, 25.6, 26.5, 36.8, 39.6, 72.7, 114.4, 123.6, 124.1, 131.3, 135.6, 141.0.

(*E*)-3-Methoxy-7,11-dimethyldodeca-1,6,10-triene (**16**)

The methylation of the preceding alcohol (491 mg, 2.36 mmol) was carried out as described for **15** to give allylic ether **16** as a light yellow oil: yield 562 mg (100%). ^{1}H NMR ($CDCl_3$, 400 MHz): 1.47 dddd, 1 H, *J* = 13.4, 11.1, 6.8, 4.9 (CH_2); 1.63 m, 1 H (CH_2); 1.59 s, 3 H (CH_3); 1.60 s, 3 H (CH_3); 1.68 s, 3 H (CH_3); 1.95–2.10 m, 6 H (CH_2); 3.26 s, 3 H (OCH_3); 3.49 q, 1 H, *J* = 7.0 (C**H**OCH_3); 5.06–5.13 m, 2 H (vinyl H); 5.17 ddd, 1 H, *J* = 12.2, 1.7, 0.7 (vinyl H); 5.20 br d, 1 H, *J* = 3.9 (vinyl H); 5.65 ddd, 1 H, *J* = 17.1, 10.5, 7.6 (vinyl H). ^{13}C NMR ($CDCl_3$, 101 MHz): 15.8, 17.6, 23.5, 25.6, 26.5, 35.2, 39.6, 56.0, 82.2, 116.9, 123.8, 124.2, 131.2, 135.3, 138.7. MS (*m/z*, rel.%): low resolution EI: 222.2 (0.4) [M^+], 207.2 (2.5), 147.1 (18), 121.1 (34), 105.1 (16), 93.1 (75), 79.1 (52), 69.1 (100), 55.1 (32); high resolution EI: calculated for $C_{15}H_{26}O$ 222.198366, found 222.199191.

(*E*)-4-(Benzyloxy)-1-chloro-2-methylbut-2-ene (**17**)

The conversion to chloride was carried out according to Meyers' procedure[18] (see also procedure for preparation of **32** below). The ^{1}H NMR data agree with the values reported by Hayashi[14]. A solution of (*E*)-4-(benzyloxy)-2-methylbut-2-en-1-ol[37] (400 mg, 2.08 mmol), LiCl (441 mg, 10.4 mmol), and collidine (2.0 g, 16.6 mmol) in DMF (40 ml) was stirred and cooled at 0 °C as CH_3SO_2Cl (715 mg, 6.24 mmol) was added. After 1.5 h at 0 °C, ice-water (35 ml) was added, and the product was isolated by extraction with cold pentane (3 × 35 ml). The combined organic extracts were washed with saturated $Cu(NO_3)_2$ (1 × 100 ml and 3 × 25 ml), saturated NaCl (1 × 25 ml), saturated $NaHCO_3$ (1 × 25 ml), and saturated NaCl (1 × 25 ml). Drying (anhydrous Na_2SO_4), and evaporation gave **17** as a yellow oil: yield 338 mg (77%). ^{1}H NMR (C_6D_6, 400 MHz): 1.40 d, 3 H, *J* = 1.0 (CH_3); 3.54 s, 3 H (CH_2); 3.73 dd, 2 H, *J* = 6.3, 0.7 (CH_2); 4.22 s, 2 H (CH_2); 5.50 app t of sextet, 1 H, J_{app} = 6.1, 1.2 (vinyl H); 7.03–7.26 m, 5 H (aryl H). ^{13}C NMR ($CDCl_3$, 101 MHz): 13.8, 50.8, 65.9, 71.8, 126.9, 127.2, 127.3, 128.1, 134.2, 138.5.

(*E,E*)-8-Benzyloxy-1-chloro-2,6-dimethylocta-2,6-diene (**18**)

The preceding procedure for **17** using (*E,E*)-8-benzyloxy-2,6-dimethylocta-2,6-dien-1-ol[15] (240 mg, 0.92 mmol) gave 267 mg (quantitative) of the known chloride[15] **18** as a yellow oil. The ^{1}H NMR data agree with the values reported[15]. ^{1}H NMR (C_6D_6, 400 MHz): 1.38 s, 3 H (CH_3); 1.49 d, 3 H, *J* = 0.7 (CH_3); 1.79–1.92 m, 4 H (CH_2); 3.63 s, 2 H (CH_2); 3.92 dd, 2 H, *J* = 6.3, 0.5 (CH_2); 4.34 s, 2 H (CH_2); 5.17 td, 1 H, *J* = 6.3, 0.7 (vinyl H); 5.42 app t of sextet, 1 H, J_{app} = 6.6, 1.2 (vinyl H); 7.03–7.31 m, 5 H (aryl H). ^{13}C NMR ($CDCl_3$, 101 MHz): 13.5, 15.9, 25.9, 38.4, 51.7, 66.3, 71.5, 122.0, 127.1, 127.3, 128.0, 129.6, 131.6, 138.0, 139.0.

(*E,E,E*)-12-Benzyloxy-1-chloro-2,6,10-trimethyldodeca-2,6,10-triene (**19**)

Reaction of (*E,E,E*)-12-benzyloxy-2,6,10-trimethyldodeca-2,6,10-trien-1-ol[16] (400 mg, 1.22 mmol) as described for **17** and **18** gave the known[16] **19** (400 mg, 95%) as a light yellow oil. The following ^{1}H NMR data match the literature values[16]. ^{1}H NMR (C_6D_6, 500 MHz): 1.45 s, 3 H (CH_3); 1.47 s, 3 H (CH_3); 1.53 s, 3 H (CH_3); 1.85–2.02 m, 6 H (CH_2); 2.08 q, 2 H, *J* = 7.2 (CH_2); 3.68 s, 2 H (CH_2); 3.96 d, 2 H, *J* = 6.4 (CH_2); 4.36 s, 2 H (CH_2); 5.11 td, 1 H, *J* = 6.8, 1.1 (vinyl H); 5.24 t, 1 H, *J* = 6.6 (vinyl H); 5.53 td, 1 H, *J* = 6.6, 1.3 (vinyl H); 7.04–7.32 m, 5 H (aryl H).

Representative Procedure for Lithiation/Alkylation of 1-Alkylallyl Methyl Ethers

(2E,6E,10Z)-1-Benzyloxy-11-methoxy-3,7,15-trimethylhexadeca-2,6,10,14-tetraene (**28**). The lithiation step was carried out according to the procedure by Still and McDonald for different compounds[9b,9c]. A solution of ether **15** (144 mg, 0.93 mmol) in THF (1 ml) was stirred and cooled at –78 °C as *sec*-BuLi (1.3 M in cyclohexane, 0.54 ml, 0.70 mmol) was added. After 20 min, chloride **18** (130 mg, 0.47 mmol) was added dropwise to the orange solution, and the light yellow solution was stirred at –78 °C for 40 min. MeOH (4 drops) was added, and the solution was allowed to warm to room temperature. After addition of H_2O (20 ml), the product was extracted with Et_2O (3 × 20 ml). The combined ethereal extracts were washed with saturated NaCl (1 × 20 ml), dried (anhydrous Na_2SO_4), and concentrated under reduced pressure to give a colorless oil (275 mg). Purification by flash chromatography (2% Et_3N in hexane) gave enol ether **28** (145 mg, 78%) as a colorless oil. The E/Z ratio (31 : 1) was estimated from the integral ratio of the enol ether vinyl proton triplet (δ 4.56) and a weak peak at δ 4.22 attributed to the E isomer. The product was stored in hexane containing 1% Et_3N, and storage of the neat oil was avoided. TLC R_F 0.37 (10% EtOAc in hexane). IR (neat): 2 923, 1 675, 1 454, 1 070. ^{1}H NMR (C_6D_6, 500 MHz): 1.46 s, 3 H (CH_3); 1.51 s, 3 H (CH_3); 1.56 s, 3 H (CH_3); 1.62 d, 3 H, J = 1.1 (CH_3); 2.01 q, 2 H, J = 7.5 (CH_2); 2.05–2.14 m, 6 H (CH_2); 2.17 q, 2 H, J = 7.5 (CH_2); 2.38 q, 2 H, J = 7.4 (CH_2); 3.25 s, 3 H (OCH_3); 3.96 dd, 2 H, J = 6.6, 0.5 (OCH_2); 4.36 s, 2 H (CH_2Ph); 4.56 t, 1 H, J = 7.0 (vinyl H); 5.18 app t of quintet, 1 H, J_{app} = 7.0, 1.4 (vinyl H); 5.23 tq, 1 H, J = 7.0, 1.3 (vinyl H); 5.53 tq, 1 H, J = 6.6, 1.3 (vinyl H); 7.04–7.16 m, 3 H (aryl H); 7.30–7.33 m, 2 H (aryl H). ^{13}C NMR (C_6D_6, 126 MHz): 15.7, 16.1, 17.4, 23.6, 25.5, 26.1, 26.4, 31.5, 39.6, 40.2, 55.6, 66.5, 71.5, 109.1, 121.8, 124.03, 124.05, 127.2, 128.2, 131.3, 135.1, 139.0, 139.3, 154.9. MS: low resolution EI: *m/z* 396.5 [M^+]; high resolution EI: calculated for $C_{27}H_{40}O_2$ 396.302831, found 396.302424.

Representative Procedure for Removal of Allylic Chloride by Reaction with Diethylamine

If NMR and/or TLC analyses showed that allylic chloride was present in the crude alkylation product mixture, it was removed by reaction with diethylamine. For example, the crude oil (120 mg) was dissolved in 1 ml of DMF containing 0.10 ml of diethylamine. The solution was stirred for 15 h at room temperature, and diluted with cold hexane (30 ml). After washes with cold 0.1 M HCl (3 × 10 ml) and saturated $NaHCO_3$ (1 × 10 ml), the organic layer was dried (anhydrous Na_2SO_4) and concentrated to give a yellow oil (93 mg).

The starting materials, yields, and product data for the following enol ethers prepared by the representative procedure above are presented in an abbreviated format below. The Z/E isomer ratios were determined as described in the text and collected in Table I.

(2E,6Z)-1-Benzyloxy-7-methoxy-3-methylocta-2,6-diene (**21**). Allyl ether **14** (90 mg, 1.04 mmol), 1.3 M *sec*-BuLi (0.60 ml, 0.78 mmol), and chloride **17** (67 mg, 0.32 mmol); yield 59 mg (71%) of **21**, Z/E 5 : 1, TLC R_F 0.23 (10% EtOAc in hexane). For $C_{17}H_{24}O_2$ (260.3) calculated: 78.42% C, 9.29% H; found: 78.37% C, 9.37% H. IR (neat): 2 931, 1 677, 1 452, 1 070. ^{1}H NMR (C_6D_6, 400 MHz): 1.50 s, 3 H (CH_3); 1.53 d, 3 H, J = 1.2 (CH_3); 2.06 t, 2 H, J = 7.6 (CH_2); 2.36 qd, 2 H, J = 7.4, 1.0 (CH_2); 3.14 s, 3 H (OCH_3); 3.96 dd, 2 H, J = 6.6, 0.5 (OCH_2); 4.35 s, 2 H (CH_2Ph); 4.36 td, 1 H, J = 6.8, 1.0 (vinyl H); 5.57 tq, 1 H, J = 6.6, 1.2 (vinyl H); 7.03–7.16 m, 3 H (aryl H); 7.29–7.33 m, 2 H (aryl H). ^{13}C NMR (C_6D_6, 126 MHz): 16.0, 17.0, 23.1, 39.8, 54.7, 66.5, 71.4, 107.2, 121.7, 127.1, 128.1, 139.24, 139.32, 151.0. MS: low resolution EI: *m/z* 260.3 [M^+]; high resolution EI: calculated for $C_{17}H_{24}O_2$ 260.177630, found 260.178248.

(2E,6E,10Z)-1-Benzyloxy-11-methoxy-3,7-dimethyldodeca-2,6,10-triene (**22**). Allyl ether **14** (74 mg, 0.86 mmol), 1.3 M *sec*-BuLi (0.50 ml, 0.65 mmol), and chloride **18** (120 mg, 0.43 mmol); yield 103 mg (73%) of **22**, TLC R_F 0.32 (10% EtOAc in hexane). IR (neat): 2 931, 1 680, 1 452, 1 069, 734, 696. ^{1}H NMR (C_6D_6, 400 MHz): 1.45 s, 3 H (CH_3); 1.56 s, 3 H (CH_3); 1.57 s, 3 H (CH_3); 2.00 q, 2 H, J = 8.1 (CH_2); 2.07–2.14 m, 4 H (CH_2); 2.40 q, 2 H, J = 7.6 (CH_2); 3.16 s, 3 H (OCH_3); 3.96 d, 2 H, J = 6.6 (OCH_2); 4.36 s, 2 H (CH_2Ph); 4.43 td, 1 H, J = 7.1, 1.0 (vinyl H); 5.23 td, 1 H, J = 6.8, 1.2 (vinyl H); 5.52 tq, 1 H, J = 6.6, 0.8 (vinyl H); 7.03–7.17 m, 3 H (aryl H); 7.29–7.33 m, 2 H (aryl H). ^{13}C NMR (C_6D_6, 101 MHz): 15.7, 16.1, 17.0, 23.5, 26.3, 39.6, 40.1, 54.7, 66.5, 71.5, 107.6, 121.8, 123.9, 127.2, 127.5, 128.2, 135.2, 139.0, 139.3, 150.7. MS: low resolution EI: *m/z* 328.4 [M^+]; high resolution EI: calculated for $C_{22}H_{32}O_2$ 328.240231, found 328.240138.

(2E,6E,10E,14Z)-1-Benzyloxy-15-methoxy-3,7,11-trimethylhexadeca-2,6,10,14-tetraene (**23**). Allyl ether **14** (80 mg, 0.93 mmol), 1.2 M *sec*-BuLi (0.58 ml, 0.70 mmol), and chloride **19** (80 mg, 0.23 mmol); yield 74 mg (80%) of **23**, TLC R_F 0.35 (10% EtOAc in hexane). For $C_{27}H_{40}O_2$ (399.6) calculated: 81.77% C, 10.17% H; found: 81.68% C, 10.11% H. IR (neat): 2 932, 1 679, 1 452, 1 382, 1 070. ^{1}H NMR (C_6D_6, 500 MHz): 1.47 s, 3 H (CH_3); 1.53 s, 3 H (CH_3); 1.57 d, 3 H, J = 1.1 (CH_3); 1.60 s, 3 H (CH_3); 1.97–2.18 m, 10 H (CH_2); 2.41 qd, 2 H, J = 7.4, 1.1 (CH_2); 3.17 s, 3 H (OCH_3); 3.97 d, 2 H, J = 6.2 (CH_2O); 4.36 s, 2 H (CH_2Ph); 4.44 td, 1 H, J = 7.0, 0.9 (vinyl H); 5.19 td, 1 H, J = 7.0, 1.3 (vinyl H); 5.28 td, 1 H, J = 7.1, 1.1 (vinyl H); 5.53 td, 1 H, J = 6.6, 1.3 (vinyl H); 7.04–7.16 m, 3 H (aryl H); 7.29–7.33 m, 2 H (aryl H). ^{13}C NMR (C_6D_6, 126 MHz): 15.70, 15.75, 16.1, 17.0, 23.5, 26.3, 26.7, 39.6, 39.8, 40.1, 46.2, 54.7, 66.5, 71.5, 107.7, 121.8, 124.0, 124.3, 127.2, 128.2, 134.9, 135.0, 139.0, 139.2, 150.7.

(2E,6Z)-1-Benzyloxy-7-methoxy-3,11-dimethyldodeca-2,6,10-triene (**26**). Allyl ether **15** (130 mg, 0.84 mmol), 1.3 M *sec*-BuLi (0.49 ml, 0.63 mmol), and chloride **17** (71 mg, 0.34 mmol); yield 52 mg (47%) of **26**, TLC R_F 0.38 (10% EtOAc in hexane). For $C_{22}H_{32}O_2$ (328.5) calculated: 80.44% C, 9.82% H; found: 80.30% C, 9.85% H. IR (neat): 2 919, 1 675, 1 452, 1 071, 737, 696. ^{1}H NMR (C_6D_6, 400 MHz): 1.50 s, 3 H (CH_3); 1.62 d, 3 H, J = 0.5 (CH_3); 2.02–2.08 m, 4 H (CH_2); 2.16 q, 2 H, J = 7.2 (CH_2); 2.35 q, 2 H, J = 7.4 (CH_2); 3.22 s, 3 H (OCH_3); 3.97 d, 2 H, J = 6.6 (OCH_2); 4.36 s, 2 H (CH_2Ph); 4.51 t, 1 H, J = 7.1 (vinyl H); 5.16 t of quintet, 1 H, J_{app} = 6.8, 1.4 (vinyl H); 5.56 tq, 1 H, J = 6.6, 1.2 (vinyl H); 7.03–7.17 m, 3 H (aryl H); 7.28–7.32 m, 2 H (aryl H). ^{13}C NMR (C_6D_6, 101 MHz): 15.9, 17.2, 23.1, 25.3, 25.9, 31.3, 39.8, 55.4, 66.4, 71.4, 108.5, 121.7, 123.8, 127.0, 127.3, 128.0, 131.2, 138.9, 139.1, 154.9.

(2E,6Z,10E)-1-Benzyloxy-7-methoxy-3,11,15-trimethylhexadeca-2,6,10,14-tetraene (**27**). A literature procedure[19] for lithiation in the presence of TMEDA was followed. A solution of TMEDA (84 mg, 0.72 mmol) in THF (1 ml) was stirred and cooled at –78 °C as 1.3 M *sec*-BuLi (0.55 ml, 0.72 mmol) was added. After 5 min, allyl ether **16** (200 mg, 0.90 mmol) in THF (1 ml) was added dropwise. After 1 h at –78 °C, chloride **17** (95 mg, 0.45 mmol) was added, the solution was stirred at –78 °C for 1 h, and methanol (4 drops) was added. Isolation of the product as described above for **28** including an additional extraction with cold 0.1 M HCl to remove TMEDA and chromatographic purification gave 91 mg (51%) of **27**, TLC R_F 0.40 (10% EtOAc in hexane). IR (neat): 2 926, 1 675, 1 454, 1 068, 734, 696. ^{1}H NMR (C_6D_6, 500 MHz): 1.51 s, 3 H (CH_3); 1.52 s, 3 H (CH_3); 1.54 s, 3 H (CH_3); 1.64 s, 3 H (CH_3); 2.02–2.22 m, 10 H (CH_2); 2.36 q, 2 H, J = 7.4 (CH_2); 3.23 s, 3 H (OCH_3); 3.97 d, 2 H, J = 4.3 (OCH_2); 4.36 s, 2 H (CH_2Ph); 4.52 t, 1 H, J = 7.1 (vinyl H); 5.21 m, 2 H (vinyl H); 5.57 tq, 1 H, J = 6.5, 1.0 (vinyl H); 7.03–7.17 m, 3 H (aryl H); 7.29–7.32 m, 2 H (aryl H). ^{13}C NMR

(C_6D_6, 126 MHz): 15.7, 16.0, 17.4, 23.3, 25.5, 26.0, 26.8, 31.4, 39.8, 39.9, 55.5, 66.6, 71.5, 108.7, 121.8, 123.9, 124.6, 127.2, 128.0, 128.2, 130.8, 135.2, 139.1, 139.3, 155.1. MS: low resolution EI: *m/z* 396.5 [M^+]; high resolution EI: calculated for $C_{27}H_{40}O_2$ 396.302831, found 396.303311.

Representative Procedure for Cleavage of Benzyl Ethers with Li/NH_3

(2E,6Z)-7-Methoxy-3-methylocta-2,6-dien-1-ol (**8**) A literature procedure[20] for analogs of geranylgeranyl benzyl ether was followed. A solution of benzyl ether **21** (89 mg, 0.34 mmol) in THF (6 ml) and NH_3 (9 ml) was stirred and cooled at –78 °C as Li pieces (47 mg, 6.84 mmol) were added. After 30 min at –78 °C, hex-3-yne (1 ml) followed by MeOH (2 ml) were added, and the white suspension was allowed to warm to room temperature. Saturated $NaHCO_3$ (5 ml) was added, and the THF solvent was evaporated under reduced pressure. Saturated $NaHCO_3$ (15 ml) was added to the residue, and the product was extracted with Et_2O (3 × 20 ml). The combined ethereal extracts were washed with saturated NaCl (3 × 20 ml), dried (anhydrous Na_2SO_4) and evaporated. Purification of the remaining yellow oil (62 mg) by flash chromatography (2% Et_3N and 20% EtOAc in hexane) gave 48 mg (82%) of **8**, Z/E 4.3 : 1, TLC R_F 0.22 (30% EtOAc in hexane). For $C_{10}H_{18}O_2$ (170.3) calculated: 70.55% C, 10.66% H; found: 70.22% C, 10.71% H. IR (neat) 3 376, 2 938, 1 675, 1 452, 1 380. ^{1}H NMR (C_6D_6, 400 MHz): 1.17 br s, 1 H (OH); 1.48 s, 3 H (CH_3); 1.54 d, 3 H, *J* = 1.0 (CH_3); 2.01 t, 2 H, *J* = 7.6 (CH_2); 2.32 qd, 2 H, *J* = 7.5, 1.2 (CH_2); 3.15 s, 3 H (OCH_3); 3.97 dd, 2 H, *J* = 6.6, 0.5 (C**H**$_2$OH); 4.36 td, 1 H, *J* = 7.1, 1.0 (vinyl H); 5.41 app t of sextet, 1 H, J_{app} = 6.7, 1.2 (vinyl H). ^{13}C NMR (C_6D_6, 101 MHz): 15.6, 16.8, 23.0, 39.6, 54.5, 58.8, 107.1, 124.3, 137.8, 150.8.

The following benzyl ether cleavages were carried out according to the representative procedure described above. The identity and amounts of benzyl ether starting materials and product data are presented in abbreviated format.

(2E,6E,10Z)-11-Methoxy-3,7-dimethyldodeca-2,6,10-trien-1-ol (**9**). Ether **22** (79 mg, 0.24 mmol); yield 45 mg (78%), Z/E 6 : 1, TLC R_F 0.33 (30% EtOAc in hexane). For $C_{15}H_{26}O_2$ (238.4) calculated: 75.58% C, 10.99% H; found: 75.73% C, 10.86% H. IR (neat): 3 345, 2 921, 1 677, 1 451. ^{1}H NMR (C_6D_6, 400 MHz): 1.06 br s, 1 H (OH); 1.43 s, 3 H (CH_3); 1.57 s, 6 H (CH_3); 1.92–1.97 m, 2 H (CH_2); 2.04–2.12 m, 4 H (CH_2); 2.38 q, 2 H, *J* = 7.4 (CH_2); 3.17 s, 3 H (OCH_3); 3.97 d, 2 H, *J* = 6.6 (C**H**$_2$OH); 4.42 td, 1 H, *J* = 7.0, 1.0 (vinyl H); 5.21 app t of sextet, 1 H, J_{app} = 7.1, 1.2 (vinyl H); 5.37 app t of sextet, 1 H, J_{app} = 6.6, 1.2 (vinyl H). ^{13}C NMR (C_6D_6, 101 MHz): 15.6, 15.7, 16.9, 23.4, 26.2, 39.4, 39.9, 54.6, 58.8, 107.5, 123.8, 124.4, 135.0, 137.6, 150.6.

(2E,6E,10E,14Z)-15-Methoxy-3,7,11-trimethylhexadeca-2,6,10,14-tetraen-1-ol (**10**). Ether **23** (44 mg, 0. 11 mmol); yield 14 mg (41%), Z/E 7 : 1, TLC R_F 0.27 (30% EtOAc in hexane). For $C_{20}H_{34}O_2$ (306.5) calculated: 78.38% C, 11.18% H; found: 78.26% C, 11.09% H. IR (neat): 3 327, 2 931, 1 678, 1 449, 1 380. ^{1}H NMR (C_6D_6, 400 MHz): 0.55–0.70 br s, 1 H (OH); 1.43 s, 3 H (CH_3); 1.53 s, 3 H (CH_3); 1.57 d, 3 H, *J* = 1.2 (CH_3); 1.60 s, 3 H (CH_3); 1.93–1.99 m, 2 H (CH_2); 2.02–2.19 m, 8 H (CH_2); 2.41 q, 2 H, *J* = 7.4 (CH_2); 3.17 s, 3 H (OCH_3); 3.94 d, 2 H, *J* = 6.6 (C**H**$_2$OH); 4.44 td, 1 H, *J* = 7.1, 1.0 (vinyl H); 5.18 td, 1 H, *J* = 7.0, 1.2 (vinyl H); 5.28 td, 1 H, *J* = 6.8, 1.2 (vinyl H); 5.36 td, 1 H, *J* = 6.7, 1.2 (vinyl H). ^{13}C NMR (C_6D_6, 101 MHz): 15.6, 15.7, 16.9, 23.4, 26.2, 26.6, 39.4, 39.7, 40.0, 54.6, 58.9, 107.5, 123.9, 124.1, 124.4, 134.8, 137.6, 150.6.

(2E,6Z)-7-Methoxy-3,11-dimethyldodeca-2,6,10-trien-1-ol (**11**). Ether **26** (52 mg, 0.16 mmol); yield 21 mg (56%), Z/E 12 : 1, TLC R_F 0.33 (30% EtOAc in hexane). For $C_{15}H_{26}O_2$ (238.4) calculated: 75.58% C, 10.99% H; found: 75.54% C, 10.92% H. IR (neat): 3 356, 2 931, 1 672, 1 448, 1 376. ^{1}H NMR (C_6D_6, 400 MHz): 0.73 br s, 1 H (OH); 1.47 s, 3 H (CH_3); 1.51 s, 3 H (CH_3); 1.63 d, 3 H, J = 1.0 (CH_3); 1.98–2.07 m, 4 H (CH_2); 2.16 q, 2 H, J = 7.6 (CH_2); 2.31 q, 2 H, J = 7.5 (CH_2); 3.23 s, 3 H (OCH_3); 3.95 d, 2 H, J = 6.6 (C**H**$_2$OH); 4.50 t, 1 H, J = 7.1 (vinyl H); 5.17 t of quin, 1 H, J = 7.0, 1.3 (vinyl H); 5.40 t of sextet, 1 H, J = 6.7, 1.2 (vinyl H). ^{13}C NMR (C_6D_6, 101 MHz): 15.6, 17.2, 23.2, 25.3, 25.9, 31.3, 39.7, 55.4, 58.8, 108.6, 123.8, 124.4, 131.2, 137.8, 154.9.

(2E,6Z,10E)-7-Methoxy-3,11,15-trimethyl-2,6,10,14-hexadecatetraen-1-ol (**12**). Ether **27** (81 mg, 0.20 mmol); yield 38 mg (61%), Z/E ≈13 : 1, TLC R_F 0.32 (30% EtOAc in hexane). For $C_{20}H_{34}O_2$ (306.5) calculated: 78.38% C, 11.18% H; found: 78.30% C, 11.19% H. IR (neat): 3 385, 2 924, 1 675, 1 444. ^{1}H NMR (C_6D_6, 400 MHz): 0.61 s, 1 H (OH); 1.47 s, 3 H (CH_3); 1.52 s, 3 H (CH_3); 1.55 s, 3 H (CH_3); 1.64 d, 3 H, J = 0.7 (CH_3); 1.98–2.22 m, 10 H (CH_2); 2.32 q, 2 H, J = 7.4 (CH_2); 3.23 s, 3 H (OCH_3); 3.95 d, 2 H, J = 6.8 (C**H**$_2$OH); 4.51 t, 1 H, J = 7.2 (vinyl H); 5.21 m, 2 H (vinyl H); 5.40 t of sextet, 1 H, J = 6.6, 1.3 (vinyl H). ^{13}C NMR (C_6D_6, 101 MHz): 15.61, 15.63, 17.2, 23.2, 25.4, 25.8, 26.7, 31.3, 39.7, 55.4, 58.8, 108.6, 123.6, 124.4, 130.7, 135.1, 137.8, 154.9.

(2E,6E,10Z)-11-Methoxy-3,7,15-trimethylhexadeca-2,6,10,14-tetraen-1-ol (**13**). Ether **28** (69 mg, 0.17 mmol); yield 35 mg (66%), Z/E 10 : 1, TLC R_F 0.35 (30% EtOAc in hexane). For $C_{20}H_{34}O_2$ (306.5) calculated: 78.38% C, 11.18% H; found: 77.99% C, 11.21% H. IR (neat): 3 333, 2 931, 1 672, 1 444, 1 382. ^{1}H NMR (C_6D_6, 500 MHz): 0.76 s, 1 H (OH); 1.43 s, 3 H (CH_3); 1.51 s, 3 H (CH_3); 1.57 s, 3 H (CH_3); 1.62 s, 3 H (CH_3); 1.95 quin, 2 H, J = 7.6 (CH_2); 2.04–2.11 m, 4 H (CH_2); 2.16 quin, 2 H, J = 7.4 (CH_2); 2.37 q, 2 H, J = 7.4 (CH_2); 3.26 s, 3 H (OCH_3); 3.95 d, 2 H, J = 6.5 (C**H**$_2$OH); 4.56 t, 1 H, J = 7.0 (vinyl H); 5.15–5.24 m, 2 H (vinyl H); 5.36 tq, 1 H, J = 6.6, 1.3 (vinyl H). ^{13}C NMR (C_6D_6, 126, MHz): 15.7, 15.8, 17.4, 23.7, 25.5, 26.1, 26.3, 31.5, 39.5, 40.1, 55.6, 59.0, 109.2, 124.0, 124.6, 131.3, 135.0, 137.8, 154.9.

Triammonium (2*E*,6*Z*,10*E*)-7-Methoxy-3,11,15-trimethylhexadeca-2,6,10,14-tetraen-1-yl Diphosphate (**32**)

Conversion to the chloride and diphosphate formation were carried out according to the procedures of Meyers[18a] and Poulter[21] (see also ref.[18b]). A solution of alcohol **12** (13 mg, 0.0424 mmol), LiCl (18 mg, 0.42 mmol), and collidine (51 mg, 0.42 mmol) in DMF (1 ml) was stirred and cooled at 0 °C as methanesulfonyl chloride (15 mg, 0.13 mmol) was added. After 1 h at 0 °C, ice-water (10 ml) was added, and the aqueous layer was extracted with cold pentane (3 × 10 ml). The combined organic extracts were washed with saturated $Cu(NO_3)_2$ (1 × 15 ml, then 3 × 5 ml), saturated NaCl (1 × 10 ml), and saturated $NaHCO_3$ (1 × 10 ml). Drying (anhydrous Na_2SO_4), and evaporation gave the corresponding chloride as a light yellow oil (12 mg, 100%). A solution of the chloride in CH_3CN (0.5 ml) containing 3 Å molecular sieve powder (100 mg) and tetrabutylammonium pyrophosphate (83 mg, 0.0923 mmol) was stirred at room temperature for 16 h. The solids were filtered off and washed with CH_3CN (20 ml). The filtrate was washed with pentane (3 × 10 ml), and the CH_3CN layer was evaporated under reduced pressure to give the diphosphate (105 mg). Ion exchange chromatography (20 ml resin, 20 ml ion exchange buffer) and lyophilization of the eluate gave a white solid (42 mg) which was purified by cellulose chromatography (40 ml of cellulose, cellulose chromatography buffer) to give 11 mg (52%) of **32** as a white

solid, TLC R_F 0.67 (cellulose TLC, cellulose buffer). ^{1}H NMR (D_2O + EDTA, 400 MHz): 1.41 s, 6 H (CH_3); 1.48 s, 3 H (CH_3); 1.51 s, 3 H (CH_3); 1.78–2.02 m, 10 H (CH_2); 2.37 m, 2 H (CH_2); 3.35 s, 3 H (OCH_3); 4.27 t, 2 H, J = 6.5 (CH_2O); 4.46 t, 1 H, J = 7.1 (vinyl H); 4.97 m, 2 H (vinyl H); 5.25 t, 1 H, J = 6.8 (vinyl H). ^{31}P NMR (D_2O, 162 MHz): –9.67 d, J = 22.0; –5.75 d, J = 22.0.

Tris(tetrabutylammonium) (2*E*,6*E*,10*Z*)-11-Methoxy-3,7,15-trimethylhexadeca-2,6,10,14-tetraen-1-yl Diphosphate (**7**)

The same procedure described above for conversion of **12** to the corresponding chloride with **13** (14 mg, $4.57 \cdot 10^{-5}$ mol), LiCl (19 mg, $4.57 \cdot 10^{-4}$ mol), collidine (55 mg, $4.57 \cdot 10^{-5}$ mol), and CH_3SO_2Cl (16 mg, $1.37 \cdot 10^{-4}$ mol) gave 15 mg (100%) of (2*E*,6*E*,10*Z*)-1-chloro-11-methoxy-3,7,15-trimethylhexadeca-2,6,10,14-tetraene as a yellow oil. The chloride was dissolved in CH_3CN (0.5 ml), and tetrabutylammonium pyrophosphate (89 mg, 0.0914 mmol) and 3 Å molecular sieve powder (100 mg) were added. After 15 h at room temperature, the suspension was filtered and washed with CH_3CN (20 ml). The filtrate was washed with pentane (3 × 10 ml), and the CH_3CN layer was evaporated to give 148 mg of diphosphate product as tetrabutylammonium salts. ^{31}P NMR analysis showed that it was a 0.94 : 1.00 mixture of **7** and inorganic pyrophosphate. ^{1}H NMR (CD_3OD, 400 MHz): 1.02 t, 36 H, J = 7.3 (CH_3); 1.42 sextet, 24 H, J = 7.4 (CH_2); 1.66 m, 24 H (CH_2); 3.23 m, 24 H, (CH_2); 4.48 t, 1 H, J = 7.1 (vinyl H); 4.57 t, 2 H, J = 6.2 (CH_2); 5.12 m, 1 H (vinyl H); 5.44 m, 1 H (vinyl H). ^{31}P NMR (CD_3OD, 162 MHz): –8.55 d, J = 19.5; –8.01 d, J = 19.5; –6.04 s (PPi).

The stability of diphosphate **7** was evaluated at pH 8 in aqueous solution with phosphate buffer as a prelude for incubations with taxadiene synthase. Stock solutions of 0.1 M NaOH and 0.1 M KH_2PO_4 solutions were prepared by dissolving 0.4 g of NaOH in 100 ml of D_2O and 1.36 g of KH_2PO_4 in 100 ml of D_2O. The pH 8 buffer was prepared by mixing 0.1 M NaOH (4.7 ml) and 0.1 M KH_2PO_4 (5.0 ml) and adding 0.3 ml of D_2O (ref.[38]). A solution of 10 mg of **7** in the buffer (0.6 ml) was analyzed by ^{1}H and ^{31}P NMR (400 and 162 MHz) spectroscopy. After 24 h at room temperature, the triplet (J = 7.2 Hz, vinyl H) at δ_H 4.46 ppm (^{1}H NMR) and the two doublets at δ_P –5.4 and –9.6 ppm (J = 22.0 Hz) indicated that the enol ether was not hydrolyzed. The sensitivity of **7** to hydrolysis was revealed in another stability test. The diphosphate (10 mg) was dissolved in 10 ml of pH 8 buffer in H_2O (10 ml) prepared in the same way as the D_2O buffer. After 20 h at room temperature, the water was removed by rotary evaporation, and the remaining oil (116 mg) was dissolved in CD_3OD and analyzed by ^{1}H and ^{31}P NMR spectroscopy. The absence of the expected triplet for the enol ether vinyl H (δ_H 4.4–4.6 ppm) and the disappearance of the two doublets at δ_P –4.2 and –7.4 ppm (J = 18.3 Hz) indicated complete hydrolysis of the enol ether. It seems likely that the pH dropped below 8 during and/or after the evaporation.

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