Stereoselective Synthesis of Moenocinol and Assignment of Its Carbon-13 Nuclear Magnetic Resonance Spectrum

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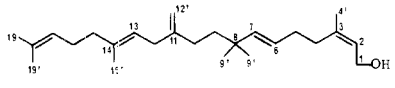
A stereoselective synthesis of moenocinol (1), the sesterterpene alcohol liberated by hydrolysis of the antibiotic moenomycin, is described. Alkylation of isobutyric acid dianion with 5-bromo-1-pentene followed by reduction with lithium aluminum hydride and benzylation provided 1-(benzyloxy)-2,2-dimethyl-6-heptene (**4**). Hydrolysis and cleavage of the epoxide of **4** with periodic acid gave 6-(benzyloxy)-5,5-dimethylhexanal (**6**). 2-(Phenylthio)-6-(benzyloxy)-5,5-dimethylhexanoic acid (**8a**) was prepared from **6** by chromic acid oxidation and α-phenylsulfenylation. Reaction of the dianion of **8a** with geranyl bromide followed by esterification and hydride reduction afforded phenylthio alcohol **10a**. Simultaneous reductive elimination and debenzylation of the corresponding acetate (**10b**) with lithium in ammonia gave (*E*)-2,2,8,12-tetramethyl-5-methylene-7,11-tridecadien-1-ol (**11**). (*Z*)-1-(Benzyloxy)-6-bromo-3-methyl-4-hexene (**17b**) was prepared from the benzyl ether of nerol by the following four steps: regioselective ozonolysis, borohydride reduction, formation of the tosylate, and displacement with bromide ion. The reaction of the Grignard reagent from **17b** with the aldehyde (**12**) secured by oxidation of 11 afforded an alcohol which was oxidized to (2*Z*,13*E*)-1-(benzyloxy)-3,8,8,14,18-pentamethyl-11-methylene-2,13,17-nonadecatrien-7-one (**33**). The 6,7-trans (*Z*) enol phosphate **34**, formed by phosphorylation of the enolate anion of **33**, underwent reduction with lithium in ammonia to (2*Z*,6*E*,13*E*)-3,8,8,14,18-pentamethyl-11-methylene-2,6,13,17-nonadecatetraen-1-ol (**1**) which was identical with moenocinol obtained from moenomycin. The 6,7-cis isomer (**32b**) of moenocinol was also prepared by a Witting reaction between aldehyde **12** and phosphorane **18** and subsequent reductive debenzylation. Carbon-13 NMR spectral data for synthetic and natural moenocinol compared favorably; a consistent set of assignments for the ^{13}C NMR absorptions is deduced from comparisons with model compounds.

Moenomycin[2] and prasinomycin[3] are two members of an unusual group of phosphorus-containing antibiotics produced by various *Streptomyces* strains.[4] These compounds are distinguished by novel biological properties including long-lasting activity against gram-negative bacteria, remarkable stability to a variety of hydrolytic enzymes, inhibition of bacterial cell-wall biosynthesis, and effective growth-promoting activity in animals. Hydrolysis of moenomycin[5] and prasinomycin[6] in aqueous acid at elevated temperatures liberates a C_{25} lipid alcohol, moenocinol (1), which undergoes partial rearrangement to its



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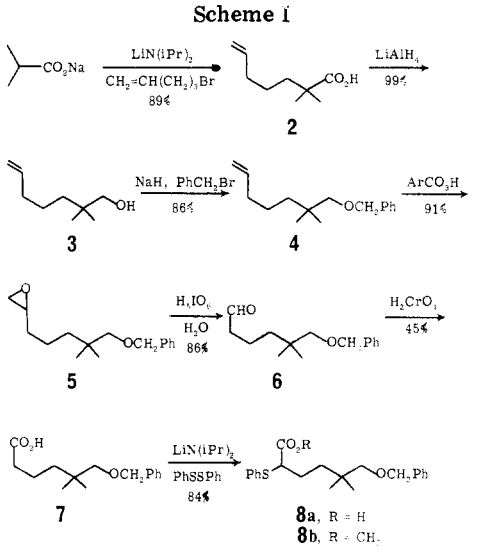
allylic isomer, isomoenocinol, and dehydration to moenocene under the rather severe hydrolytic conditions. Moenocinol is linked to the antibiotic via an ether bridge to the 2-position of D-3-phosphoglyceric acid which is in turn connected to a pentasaccharide.[7,8]

The structure of moenocinol (1) was elucidated independently by Tschesche, Brock, and Duphorn[5] and by Slusarchyk and Weisenborn[6] from IR, NMR, and mass spectra of moenocinol, isomoenocinol, moenocene, and products derived from them by oxidative cleavage of the double bonds. The configuration of the 2,3 double bond, originally assigned as trans,[5] has since been revised to cis,[9] in line with the stereochemistry of diumycinol,[10] the structurally related lipid component of diumycin.[11] Although the presence of 25 carbons and obvious terpenoid groups in moenocinol suggests that the compound is a sesterterpene, the central C_{10} (C-5 through C-11) is nonisoprenoid and not readily derivable by standard biogenetic pathways. In order to confirm the unprecedented structure of moenocinol, we have carried out an unambiguous, ste-

Scheme I



(1) This paper is based in part upon the Ph.D. thesis of M.W.J., University of Illinois, 1978.

(2) (a) Lidner, F.; Wallhäusser, K. H. *Arch. Mikrobiol.* **1955**, *22*, 219–34; (b) Wallhäusser, K. H.; Nesemann, G.; Präve, P.; Steigler, A. *Antimicrob. Agents Chemother.* **1966**, 734–6 and the immediately following papers.

(3) Weisenborn, F. L.; Bouchard, J. L.; Smith, D.; Pansy, F.; Maestrone, G.; Miraglia, G.; Meyers, E. *Nature (London)* **1967**, *213*, 1092–94.

(4) For a brief review, see: Slusarchyk, W. A. *Biotechnol. Bioeng.* **1971**, *13*, 399–407.

(5) (a) Tschesche, R.; Brock, F.-X.; Duphorn, I. *Tetrahedron Lett.* **1968**, 2905–9; (b) *Justus Liebigs Ann. Chem.* **1968**, *720*, 58–70.

(6) Slusarchyk, W. A.; Weisenborn, F. L. *Tetrahedron Lett.* **1969**, 659–62.

(7) Welzel, P.; Witteler, F.-J.; Müller, D. *Tetrahedron Lett.* **1976**, 1665–8.

(8) Witteler, F.-J.; Welzel, P.; Duddeck, H.; Höfle, G.; Riemer, W. *Tetrahedron Lett.* **1979**, 3493–6.

(9) Tschesche, R.; Reden, J. *Justus Liebigs Ann. Chem.* **1974**, 853–63.

(10) Slusarchyk, W. A.; Osband, J. A.; Weisenborn, F. L. *J. Am. Chem. Soc.* **1970**, *92*, 4486–8; *Tetrahedron* **1973**, *29*, 1465–72.

(11) Meyers, E.; Slusarchyk, D. S.; Bouchard, J. L.; Weisenborn, F. L. *J. Antibiot.* **1969**, *22*, 490–3.

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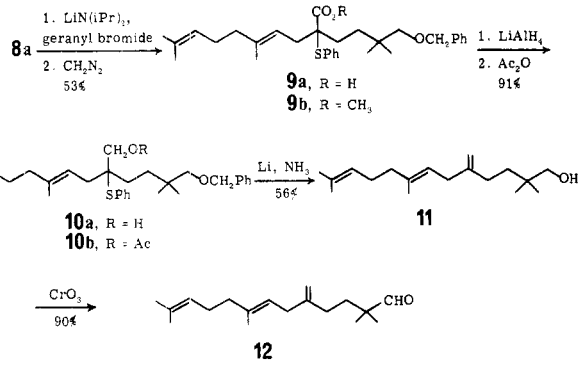
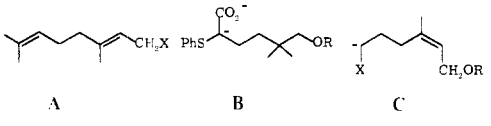
Scheme II



reoselective synthesis of the compound.[12] The identity of synthetic moenocinol with "natural product" from moenomycin was established by direct spectral comparisons, including previously unreported carbon-13 NMR spectral data.

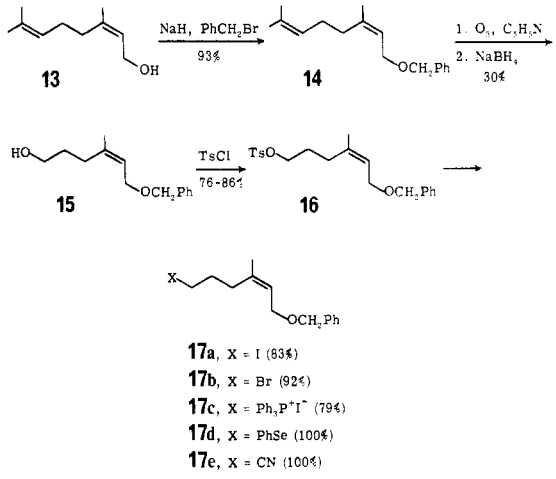
The plan of the synthesis involved the preparation of three main components (A, B, and C). Components A and



B were to be joined first by alkylation of a phenylthio-stabilized anion, thus ensuring the preservation of the trans (*E*) configuration at the 13,14 double bond and setting the stage for introduction of the off-chain methylene group at C-11 by regiospecific reductive elimination.[14] In the original plan component C (X = Ph_3P^+) was to be linked to the A–B unit by means of a modified Wittig reaction. However, it proved necessary to develop an alternative approach in order to generate the requisite trans double bond at the 6,7 position.

The sequence of reactions used to prepare component B is shown in Scheme I. Alkylation of the dianion of isobutyric acid with 5-bromo-1-pentene was accomplished by Creger's procedure.[15] The resulting unsaturated acid **2** was reduced to the alcohol **3** with lithium aluminum hydride and the latter converted to benzyl ether **4**. Ozonolysis of **4** followed by oxidation with chromic acid[16] afforded mixtures of the benzyl ether acid **7** and a benzoyloxy acid (**7**, PhCO in place of $PhCH_2$). The byproduct evidently arises from competitive attack of ozone on the benzyl protecting group.[17] Oxidation of **4** with sodium periodate and ruthenium tetraoxide in a heterogeneous mixture of water and chloroform[18] gave **7** in variable, and usually low, yields (average ca. 20%). Since these direct procedures were not fruitful, an indirect route involving epoxidation, hydrolysis to the diol, in situ cleavage with

Scheme III



periodic acid,[19] and finally chromic acid oxidation[20] of the aldehyde **6** was adopted.

The phenylthio group was then introduced by inverse addition of the dianion of acid **7** to 2 equiv of diphenyl disulfide according to the procedure of Trost and coworkers.[21] When diphenyl disulfide was added to the dianion, a mixture of **7** and bis(α-phenylthio) acid was obtained. α-Phenylthio acid **8a** was esterified with diazomethane, the resulting ester (**8b**) was purified by column chromatography, and the acid was regenerated by saponification.

The union of components A and B and the formation of the off-chain methylene group was accomplished as shown in Scheme II. The phenylthio-stabilized carboxylate dianion was generated from **8a** with lithium diisopropylamide in tetrahydrofuran–hexamethylphosphoramide and alkylated with geranyl bromide (component A)[22] over a temperature range of −25 °C to room temperature. α-Phenylthio ester **9b** was obtained in 53% yield after esterification with diazomethane and column chromatography. Reduction of **9b** with lithium aluminum hydride and acetylation afforded phenylthio acetate **10b**. Reductive elimination[14] and simultaneous cleavage of the benzyl ether protecting group were effected with lithium in liquid ammonia. The resulting alcohol (**11**) was oxidized to the triene aldehyde **12** with the chromium trioxide–dipyridine complex.[23]

Component C (**17**) was prepared from nerol in 5 or 6 steps (Scheme III). Ozonolysis of neryl benzyl ether (**14**) in dichloromethane containing 1 equiv of pyridine[24] followed by bisulfite extraction and sodium borohydride reduction gave benzyloxy alcohol **15**. The corresponding tosylate was converted to iodide **17a** (NaI, acetone, 25 °C), bromide **17b** (LiBr, acetone, reflux), phenyl selenide **17d** (NaSePh, ethanol, 26 °C), and nitrile **17e** (NaCN, DMF,

(12) During the course of this work two independent syntheses of moenocinol were published.[9,13] We elected to continue and complete the synthesis described here in order to exemplify the use of reductive elimination for regiospecific introduction of double bonds[14] and to contribute further evidence in support of the unusual structure proposed for this presumed sesterterpene.

(13) Grieco, P. A.; Musaki, Y.; Boxler, D. *J. Am. Chem. Soc.* **1975**, *97*, 1597–9.

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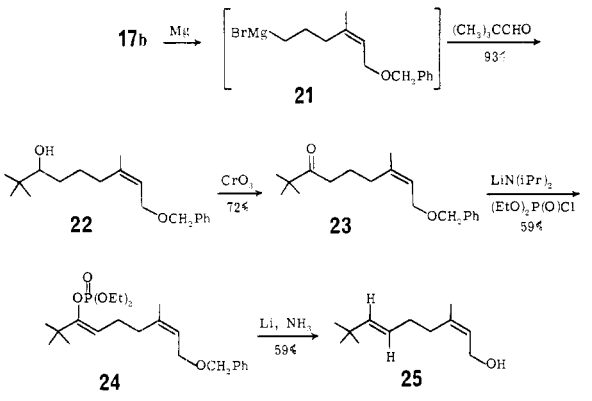
(21) Trost, B.; Salzman, J. *J. Am. Chem. Soc.* **1973**, *95*, 6840–2; Trost, B.; Salzman, T.; Hiroi, K. *Ibid.* **1976**, *98*, 4887–902.

(22) Ruzicka, L.; Firmenich, G. *Helv. Chim. Acta* **1939**, *22*, 392–6. Nadeau, R. G. Ph.D. Thesis, Stanford University, 1968.

(23) Ratcliffe, R.; Rodehurst, R. *J. Org. Chem.* **1970**, *35*, 4000–2. Collins, J. C.; Hess, W. W.; Frank, F. J. *Tetrahedron Lett.* **1968**, 3363–6.

(24) (a) Slomp, G., Jr.; Johnson, J. L. *J. Am. Chem. Soc.* **1958**, *80*, 915–21. (b) Coates, R. M.; Ley, D. A.; Cavender, P. L. *J. Org. Chem.* **1978**, *43*, 4915–22.

Scheme IV



98 °C). The triphenylphosphonium iodide, **17c**, was obtained by reaction of **17a** and triphenylphosphine in benzene at reflux for 4.5 days.

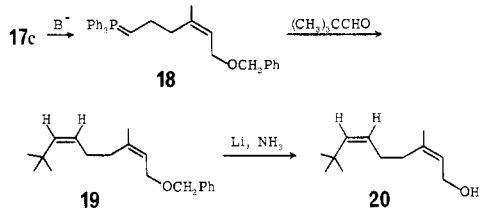
In the original plan the A–B and C components were to be joined in a Schlosser–Wittig reaction (**12** + **18**)[24b,25-27] thus forming the C_{25} skeleton and the trans 6,7 double bond simultaneously. While this approach has the virtue of directness, there was reason for concern over the stereochemical course of the reaction. In general, Wittig reactions with sterically hindered aldehydes such as pivaldehyde tend to give cis olefins almost exclusively.[28] Furthermore, the elimination of triphenylphosphine oxide from the oxaphosphetane intermediate formed in the reaction of pivaldehyde with triphenylphosphonium ethylide occurs relatively rapidly even at −70 °C.[28a] The success of the Schlosser–Wittig procedure for the synthesis of trans olefins depends critically upon the epimerization of the cis oxaphosphetane (or betaine) intermediate to the trans isomer prior to elimination.

A series of Witting and Schlosser–Wittig reactions between ylide **18** and pivaldehyde were carried out to determine whether the trans olefination could be achieved. The four procedures tried were as follows: (A) generation of the ylide with butyllithium in tetrahydrofuran (THF) and reaction with pivaldehyde at −78 °C; (B) formation of the ylide with sodium amide in liquid ammonia and reaction with pivaldehyde in ether at room temperature (salt-free procedure);[25b,26,29] (C) generation of the ylide with phenyllithium in THF at −78 °C, reaction with pivaldehyde for 15 min at −78 °C, addition of a second equivalent of phenyllithium to form the ylide alkoxide, and addition of methanol as proton source at −25 °C;[24b,27] (D) formation of the ylide with butyllithium in THF–ether, reaction with pivaldehyde at −75 °C, introduction of a second equivalent of butyllithium followed by warming to −20 °C, addition of the 1:1 complex of potassium *tert*-butoxide and *tert*-butyl alcohol, and hydrolysis at −20 °C.[9] Each of these procedures afforded the same diene ether (the yields were 82, 50, 49, and 30%, respectively) which is assigned the cis,cis stereochemistry (**19**) on the basis of evidence to be presented later. Judging from the *tert*-butyl region of the NMR spectrum of the product, we estimate that no more than 3–4% of the desired trans isomer was present in the purified product. Cleavage of the benzyl ether with lithium in liquid ammonia liberated the cis,cis dienol **20**.

Table I. Carbon-13 NMR Chemical Shifts and Assignments for (2*Z*,6*Z*)- and (2*Z*,6*E*)-3,8,8-Trimethyl-2,6-nonadien-1-ols (20 and 25)[a]

carbon	20 (*Z*,*Z*)	25 (*Z*,*E*)
1	58.56	58.75
2	125.07	124.60[b]
3	138.09	138.76
4	32.48	32.33[c]
4′	23.41	23.46
5	27.00	31.26[c]
6	127.82	123.70[b]
7	140.08	142.03
8	33.13	32.75
9	31.20	29.76

[a] The spectra were recorded with a Varian XL-100 NMR spectrometer using tetramethylsilane as internal standard and chloroform-*d* as both solvent and deuterium lock signal. The concentration was 1.29 M, and 3000–3500 scans were accumulated over a 3000-Hz sweep width. [b] These assignments may be interchanged. [c] These assignments may be interchanged.



The exclusive formation of the cis double bond in these model Wittig reactions necessitated a search for alternative routes. An efficient, stereospecific route to the cis,trans dienol **25** was found in the reductive cleavage of enol phosphate **24** (Scheme IV).[30,31] Grignard reagent **21**, formed from bromide **17b** by entrainment with ethylene dibromide,[32] reacted with pivaldehyde to give hydroxy ether **22** (93%) which was oxidized to ketone **23**. The lithium enolate anion of **23** was generated and allowed to stand in THF solution for 40 min at room temperature and in the presence of hexamethylphosphoramide for 5 min at 0 °C to effect equilibration to the presumably more stable trans configuration.[33] Addition of diethyl chlorophosphate to the solution gave the trans (*Z*) enol phosphate **24** in 59% yield (75% based upon recovered **23**) evidently uncontaminated by the cis (*E*) isomer. Reduction of **24** with lithium in ammonia afforded cis,trans dienol **25**.[30,31]

The cis and trans configurations assigned to the 6,7 double bonds in dienols **20** and **25** are based upon both chemical and NMR spectral evidence. The predominant formation of cis alkenes in Wittig reactions carried out under salt-free conditions (procedure B) is models[34b,35] established[25b,26,29] and, as mentioned above, is accentuated in the case of *tert*-butyl-substituted alkenes from pivaldehyde.[28] The chemical shift of the *tert*-butyl group protons in the NMR spectrum of the cis isomer (δ 1.11) is found at somewhat lower field (Δδ = 0.13 ppm) than that

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(28) (a) Vedejs, E.; Snoble, K. A. J. *J. Am. Chem. Soc.* **1973**, *95*, 5778–80. (b) Corey, E. J.; Kwiatkowski, G. T. *Ibid.* **1966**, *88*, 5653–4.
(29) Anderson, R. J.; Henrick, C. A. *J. Am. Chem. Soc.* **1975**, *97*, 4327–34 and references cited therein.
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(31) Swenton, J. S.; Smyser, G. L. *J. Org. Chem.* **1978**, *43*, 165–7.
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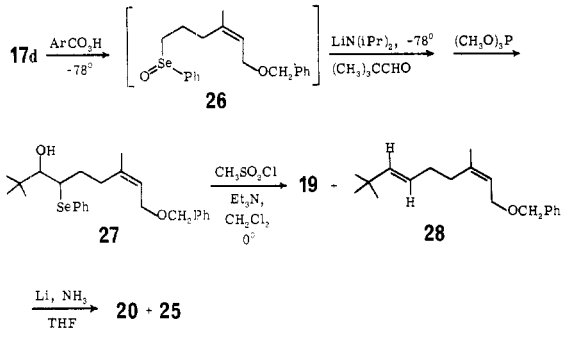
(33) House, H. O.; Auerbach, R. A.; Gall, M.; Peet, N. P. *J. Org. Chem.* **1973**, *38*, 514–22; House, H. O.; Trost, B. M. *Ibid.* **1965**, *30*, 1341–8.

of the trans (δ 0.98), as is that observed for the structurally similar cis and trans alkenes 4,4-dimethyl-2-pentene and 2,2-dimethyl-3-hexene.[34] The NMR coupling constants for the vinyl protons on the 6,7 double bond of **20** and **25** are 12 and 16 Hz, respectively, data which are in good agreement with J values for alkenes of this type.[34]

Carbon-13 NMR chemical shifts and assignments for the isomeric dienols **20** and **25** are presented in Table I. The assignments are based upon chemical shift trends and comparisons with data for the same two alkene models[34b,35] as well as nerol.[36] The allylic methylene group at C-5 is shifted upfield ($\Delta\delta$ = −4.26 ppm) in the cis isomer, presumably owing to steric compression with the *tert*-butyl group. The vinylic carbon at C-6 is shifted in the opposite sense ($\Delta\delta$ = 4.12 ppm). The chemical shift data are in good accord with the literature data[34b,35] and serve as further support for the configurational assignments.

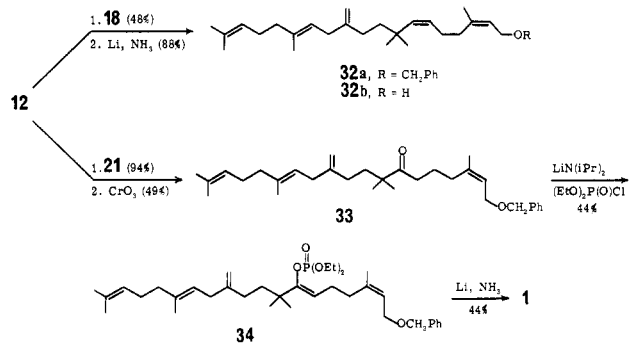
In addition to the Wittig reaction and the enol phosphate reduction, two other approaches to the model cis,-trans dienol **25** were studied briefly. Reich, Chow, and Shah have developed a regioselective olefin synthesis via reduction of vicinal β-hydroxy selenides[37] which seemed suited to our need. Selenoxide **26** was formed by oxidation



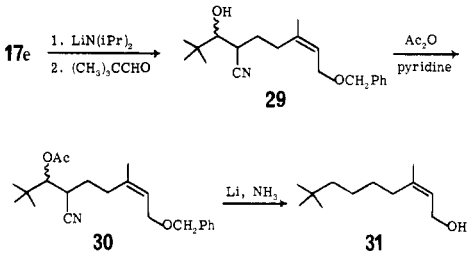
of selenide **17d** with *m*-chloroperoxybenzoic acid and metalated with lithium diisopropylamide at −78 °C. Reaction of the α-lithio selenoxide with pivaldehyde and subsequent reduction with trimethyl phosphite afforded the β-hydroxy selenide **27**. When subjected to reaction with methanesulfonyl chloride and triethylamine, the hydroxy selenide underwent elimination to a 60:40 mixture of cis,cis and cis,trans dienyl benzyl ethers, **19** and **28**, in 35% overall yield. The presence of both isomers was apparent from the proton NMR spectrum of the product which exhibits peaks at δ 1.09 and 0.97 for the cis and trans *tert*-butyl groups. The stereochemistry of the olefins produced in this reaction sequence is evidently determined by the ratio of diastereomeric hydroxy selenoxides formed initially from pivaldehyde and the α-lithio selenoxide. Removal of the benzyl ether protecting group provided a 57:43 mixture of dienols **20** and **25** according to GLC analysis.

The reductive elimination of the β-acetoxy nitrile **30** was also attempted as a route to **25**.[38] Metalation of nitrile

Scheme V



17e with lithium diisopropylamide followed by reaction with pivaldehyde furnished β-hydroxy nitrile **29** as a



mixture of diastereomers. However, reduction of the corresponding acetate **30** with lithium in liquid ammonia gave only the over-reduction product **31** in several experiments at −33 and −78 °C both with and without *tert*-butyl alcohol as proton donor. Since **20** and **25** are clearly stable to the lithium–ammonia conditions, these compounds cannot be intermediates in the formation of **31**, and the reductive elimination evidently did not take place. The most likely alternative pathway to **31** involves elimination of acetate to give an α,β-unsaturated nitrile followed by conjugate reduction and cleavage of the cyano group.

Syntheses of 6-*cis*-moenocinol (**32b**) and moenocinol itself from aldehyde **12** were completed by using the stereoselective procedures developed with pivaldehyde (Scheme V). The reactions generally proceeded in a similar fashion to those in the model studies, albeit with consistently lower yields. It proved necessary to employ a minimum amount (0.95–1.00 equiv) of lithium diisopropylamide to form the enolate anion from ketone **33**. When more than 1 equiv was used, changes in the appearance of the peaks in the vinyl region were seen in the NMR spectrum of the product, evidently from isomerization of the 1,4-diene moiety. The relatively low yield (44%) of enol phosphate **34** is attributed to either incomplete enolate formation or adventitious proton sources since the balance of the material (56%) was recovered as unreacted ketone.

The commercially available moenomycin complex (Flavomycin), a crude mixture of at least four components (moenomycins A, B_1, B_2, and C), was hydrolyzed with 2 N hydrochloric acid at about 90 °C for 15 min to liberate moenocinol.[5] A suitable comparison sample of the natural sesterterpene was isolated and purified by careful column chromatography on silica gel.

Chromatographic and spectral comparisons were carried out to establish the identity of the synthetic and naturally derived moenocinol and to determine the effect of the cis double bond in **32b** upon the spectral characteristics. The synthetic and natural samples of moenocinol were inseparable by TLC on silica with 40:1 benzene–methanol and 9:1 hexane–acetone as developing solvents. Although the IR spectra as thin films are essentially superimposable, the

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significance of this comparison is diminished by the absence of distinctive fine structure. However, the IR spectra of both synthetic and natural moenocinol exhibit a sharp peak at 973 cm^{-1} for the out-of-phase C–H deformation of the trans 6,7 double bond. The IR spectrum of **32b**, although generally quite similar to the spectra of moenocinol, does not show the band at 973 cm^{-1}. One of the two broad and poorly defined absorptions at 699 and 724 cm^{-1} presumably arises from the out-of-phase C–H deformation of the cis 6,7 double bond.

A more meaningful comparison between synthetic and natural moenocinol is based upon 220-MHz proton NMR spectra in carbon tetrachloride solutions. Both the gross features of the spectra in general and the intricate fine structure of the vinyl hydrogen and saturated methylene regions in particular match each other quite precisely. The *gem*-dimethyl group appears as a singlet at δ 0.96 in the spectra of moenocinol and at δ 1.10 in the spectrum of 6,7-*cis*-moenocinol. The proton NMR spectra of **1** and **32b** also differ in the appearance of the vinyl hydrogen region, δ 4.9–5.5. The spectra of moenocinol exhibit a two-proton multiplet at δ 4.9–5.2 for the protons at C-13 and C-17 and a separate three-proton multiplet at δ 5.2–5.4 for the protons at C-2, C-6, and C-7. In the spectrum of 6,7-*cis*-moenocinol, the absorptions for the vinyl hydrogens at C-6, C-7, C-13, and C-17 overlap to form a four-proton multiplet at δ 4.9–5.25, and the C-2 vinyl proton appears as a clean triplet at δ 5.38. The NMR spectrum of **32b** is also distinguished by a triplet at δ 2.24 for the C-5 methylene group allylic to the cis double bond.

As a final basis for comparison, the proton-decoupled carbon-13 NMR spectra of synthetic and natural moenocinol in benzene-d_6 were recorded. The peak numbers, assignments, chemical shifts, and chemical shift discrepancies are collected in Table II. Since two pairs of resonances (C-2 and C-6; C-3 and C-7) in the vinyl carbon region coincide, a total of 22 peaks are assigned.[39] The discrepancies in chemical shifts ($|\Delta\delta|$) range from 0.00 to 0.04 ppm and average 0.01 ppm. The excellent agreement between these spectral data is convincing proof for the identity of the two samples.

The ^{13}C NMR data for synthetic moenocinol are also shown in order of carbon positional numbers in Table III along with the corresponding data for the model dienol **25** and the intermediate trienol **11**. The assignments for C-7 through C-13′ of **11** follow from comparisons with ^{13}C NMR data for C-10 through C-16′ in *all trans* geranylgeraniol.[24c] The distinctive resonances for the vinylic carbons at C-5 and C-6′, the hydroxymethyl group (C-1), and the double-intensity *gem*-dimethyl groups (C-3′) are readily assigned. The assignment of the peak at 30.50 ppm to the quaternary carbon at C-2 in **11** is in reasonable accord with the chemical shifts for the quaternary carbons in **25** (C-8, δ 32.75) and neopentyl alcohol (C-2, 32.9).[40] The coincident peaks at 35.00 ppm and the single peak at 36.95 ppm are tentatively ascribed to the saturated methylene groups at C-6, C-4, and C-3, respectively.

The ^{13}C NMR assignments for moenocinol are based upon comparisons with the data for **11** and **25**. The rather good agreement ($|\Delta\delta|$ = 0.05–0.68 ppm) between the chemical shifts for C-10 through C-19′ in moenocinol and C-4 through C-13′ in trienol **11** lends credence to these assignments although some uncertainties remain for some narrowly separated peaks (C-10 and C-12; C-17, C-2, and C-6). The rather poor agreement between the shifts for C-2 and C-3 in moenocinol and dienol **25** ($\Delta\delta$ = 1.13 and 1.79 ppm) is attributed to solvent effects accentuated by the nearby hydroxyl group. The spectrum of moenocinol was obtained in benzene-d_6 while the spectra of **11** and **25** were determined in chloroform-*d*. The chemical shift differences shown for C-6 through C-8 ($|\Delta\delta|$ = 2.03, 1.48 and 2.66 ppm) and C-9′ ($\Delta\delta$ = 2.28 ppm) probably arise from small steric interactions with the longer chain in moenocinol. The downfield shifts of C-9 ($\Delta\delta$ = 4.89 ppm) and C-9′ ($\Delta\delta$ = 3.72 ppm) in moenocinol as compared to C-3 and C-3′ in **11** are evidently shift increments for the replacement of the CH_2OH group in the latter with a trans $CH{=}CHCH_2R$ substituent. Thus, the methyl signal (δ 29.76) of the *tert*-butyl group in **11** is shifted downfield by 3.16 ppm compared to that of neopentyl alcohol (δ^{CDCl_3} 26.6).[40]

Table II. Carbon-13 NMR Chemical Shifts, Positional Assignments, and Chemical Shift Discrepancies for Synthetic and Natural Moenocinol (1)[a]

peak	carbon	chemical shifts, δ[b] synthetic	natural	$\lvert\Delta\delta\rvert$
1	15′	16.01	16.03	0.02
2	19′	17.68	17.69	0.01
3	4′	23.38	23.34	0.04
4	19	25.79	25.80	0.01
5	16	27.08	27.08	0.00
6	9′	27.48	27.48	0.00
7	8	30.09	30.11	0.02
8	5	31.75	31.75	0.00
9	4	32.41	32.42	0.01
10	10[c]	35.42	35.40	0.02
11	12[c]	35.68	35.69	0.01
12	15	40.12	40.12	0.00
13	9	41.84	41.82	0.02
14	1	58.95	58.95	0.00
15	12′	108.92	108.91	0.01
16	13	122.49	122.48	0.01
17	17[d]	124.65	124.63	0.02
18	2 + 6[d]	125.73	125.76	0.03
19	18	131.00	130.99	0.01
20	14	136.28	136.27	0.01
21	3 + 7	140.55	140.54	0.01
22	11	149.61	149.61	0.00

[a] The spectra were determined with a Varian XL-100 NMR spectrometer in the Fourier transform mode using tetramethylsilane as internal standard and benzene-d_6 as solvent and internal lock. The spectra were run one after the other over a 6024-Hz sweep width with ca. 25 mg (0.44 M) of synthetic moenocinol and ca. 17 mg (0.37 M) of natural moenocinol. A total of ca. 50 000 scans was accumulated for each spectrum. [b] Chemical shifts are expressed in parts per million downfield from tetramethylsilane. [c] These assignments may be interchanged. [d] These assignments may be interchanged.

Experimental Section

All boiling points are uncorrected. Spectra were determined with the following instruments: Varian Associates Models A56/60, A-60A, HA100, EM390, and HR 220 proton NMR spectrometers; Varian Associates Model XL-100 and JEOL FX-60 carbon-13 NMR spectrometers; Perkin-Elmer Models 137 and 237B infrared spectrophotometers; Varian MAT Bremen CH-5 and 731 mass spectrometers.[41] Chemical shifts are reported as δ values with tetramethylsilane as an internal standard. Combustion analyses

(39) In addition to solvent resonances, computer artifacts, and negative peaks, the ^{13}C NMR spectra also showed a few extraneous signals which are presumed to arise from impurities. The extraneous peaks in the spectrum of synthetic moenocinol are as follows: two small peaks at δ 23.07 and 29.82, a peak at δ 31.60 which overlaps the assigned peak at δ 31.75, and an almost full-sized peak at δ 137.88. The extraneous peaks in the spectrum of natural moenocinol included two small peaks at δ 29.60 and 124.97 as well as a shoulder at δ 31.60 on the assigned peak at δ 31.75.

(40) Stothers, J. B. "Carbon-13 NMR Spectroscopy"; Academic Press: New York, 1972; p 141.

(41) The cost of the high-resolution mass spectra was funded in part by a grant from the National Cancer Institute (CA 11,388).

Table III. Carbon-13 NMR Chemical Shifts (δ), Positional Assignments, and Chemical Shift Differences for Synthetic Moenocinol (1), (2Z,6E)-3,8,8-Trimethyl-2,6-nonadien-1-ol (25), and (E)-2,2,8,12-Tetramethyl-5-methylene-7,11-tridecadien-1-ol (11)

moenocinol (1)[a]			dienol 25[b]			trienol 11[c]		
carbon	peak	δ	carbon	δ	|Δδ|	carbon	δ	|Δδ|
1	14	58.95	1	58.75	0.20			
2	18	125.73[d,e]	2	124.60	1.13			
3	21	140.55[f]	3	138.76	1.79			
4	9	32.41	4	32.33	0.08			
4′	3	23.38	4′	23.46	0.08			
5	8	31.75	5	31.26	0.49			
6	18	125.73[d,e]	6	123.70	2.03			
7	21	140.55[f]	7	142.03	1.48	1	71.83	
8	7	30.09	8	32.75	2.66	2	30.50	0.41
9	13	41.84				3	36.95	4.89
9′	6	27.48	9	29.76	2.28	3′	23.76	3.72
10	10	35.42[g]				4	35.00	0.42
11	22	149.61				5	149.80	0.19
12	11	35.68[g]				6	35.00	0.68
12′	15	108.92				6′	108.71	0.21
13	16	122.49				7	121.99	0.50
14	20	136.28				8	136.48	0.20
15	12	40.12				9	39.80	0.32
15′	1	16.01				9′	15.96	0.05
16	5	27.08				10	26.72	0.36
17	17	124.65[e]				11	124.34	0.31
18	19	131.00				12	131.32	0.32
19	4	25.79				13	25.66	0.13
19′	2	17.68				13′	17.66	0.02

[a] The solvent was benzene-d_6. The other conditions are given in footnote *a*, Table II. [b] The spectrum was determined in chloroform-*d* with a JEOL FX-60 NMR spectrometer. [c] A Varian XL-100 NMR spectrum was used. The solvent was chloroform-*d*. [d] The signals for C-2 and C-6 are superimposed. [e] These assignments may be interchanged. [f] The peaks for C-3 and C-7 are superimposed. [g] These assignments may be interchanged.

were performed in the University of Illinois Microanalytical Laboratory.

1,2-Dimethoxyethane and tetrahydrofuran were dried by distillation from a purple solution of sodium benzophenone ketyl. Pyridine was dried over potassium hydroxide pellets and/or Linde 4-Å molecular sieves and decanted before use. Dichloromethane was dried over 4-Å molecular sieves and decanted before use. Hexamethylphosphoramide was dried by distillation from metallic sodium or calcium hydride.

Silica gel chromatographic purifications were performed with Brinkmann silica gel having a particle size of 0.02–0.05 mm. Height to diameter ratios were normally between 8 and 12 to 1. Fractions (1–25 mL) were taken on a fraction collector and analyzed by TLC. Liquid samples were purified for combustion analysis by distillation or preparative high-pressure LC. High-pressure LC purifications were performed by using a Water Associates Model 6000A pump, a 0.6 × 30 cm μ-Porasil column, and a Schoeffel Instrument Corp. variable-wavelength UV detector (Model 770). Flow rates were usually 2–3 mL/min with pressures ranging from 1000 to 3500 psi. The solvents used were varying percentages of ether in either hexane or 2,2,4-trimethylpentane. After preparative high-pressure LC traces of solvent were removed on a high-vacuum line at 0.05 mm for 24–48 h.

2,2-Dimethyl-6-heptenoic acid (2) was prepared according to the procedure of Creger.[15] Isobutyric acid (118.2 g, 1.34 mol) was added to a stirred suspension of 64.32 g (1.34 mol) of a 50% mineral oil dispersion of sodium hydride in a solution of 135.6 g (1.34 mol) of diisopropylamine in 1.3 L of tetrahydrofuran under nitrogen over a 10–15-min period. The internal temperature was kept between 50 and 60 °C by adjusting the rate of addition. Hydrogen evolution was completed by heating the mixture at reflux for 15 min. After the mixture was cooled to 0 °C, 593 mL of a 2.26 M solution (1.34 mol) of *n*-butyllithium in hexane was added at a rate such that the temperature of the mixture remained below 10 °C. The mixture was kept at 0 °C for 15 min and then heated to 30–35 °C for 30 min to complete the metalation. The resultant green-brown solution was cooled to 0 °C, and 100 g (0.67 mol) of 5-bromo-1-pentene was added over a 30-min period. Sodium bromide began to precipitate almost immediately. The mixture was maintained at 0 °C for 30 min and then heated at 30–35 °C for 1 h.

After addition of 150 mL of water and separation of the aqueous layer, the organic layer and reaction flask were washed with a 3:2 mixture of ether and water. The aqueous layers were combined, extracted with ether, and acidified to a Congo red endpoint (~pH 3) with hydrochloric acid (ca. 6 M). The mixture was extracted with two 200-mL portions of ether, and the ether solution was washed with saturated brine and dried ($MgSO_4$). The ether was removed, and the product was distilled under reduced pressure to yield 93.15 g (89%) of acid **2**: bp 87–88 °C (0.1 mm); IR (neat) 2980 (OH), 1700 (C=O), 1645 (C=C) cm^{-1}; ^1H NMR (CCl_4) δ 1.18 (s, 6 H, $C(CH_3)_2$), 1.48 (m, 4 H, CH_2CH_2), 2.03 (m, 2 H, CH_2=$CHCH_2$), 4.92 (m, 2 H, CH_2=CH), 5.71 (br m, 1 H, CH_2=CH), 11.68 (s, 1 H, CO_2H).

Anal. Calcd for $C_{19}H_{15}O_2$: C, 69.19; H, 10.32. Found: C, 69.44; H, 10.37.

2,2-Dimethyl-6-hepten-1-ol (3). A solution of 92.74 g (0.59 mol) of acid **2** in 400 mL of tetrahydrofuran was added dropwise at 0 °C over a 30–45-min period to a suspension of 25.00 g (0.66 mol) of lithium aluminum hydride in 900 mL of tetrahydrofuran. The mixture was stirred at room temperature under nitrogen for 3 h and heated at reflux for 45 min.

After the mixture was cooled to below 0 °C with an ice–salt bath, 10% sulfuric acid was added dropwise until the aluminum salts dissolved.[42] The organic layer was diluted with ether, washed twice with 15% sodium hydroxide, and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the product was distilled under reduced pressure to give 83.78 g (100%) of alcohol **3**: bp 84–86 °C (20 mm); IR (neat) 3350 (OH), 1640 (C=C), 1040 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (s, 6 H, $C(CH_3)_2$), 1.27 (m, 4 H, CH_2CH_2), 1.98 br s, 2 H, CH_2=$CHCH_2$), 3.22 (s, 2 H, CH_2OH), 3.38 (s, 1 H, D_2O exchangeable, OH), 4.93 (m, 2 H, CH_2=CH), 5.69 (br m, 1 H, CH_2=CH).

Anal. Calcd for $C_9H_{18}O_2$: C, 76.00; H, 12.76. Found: C, 75.51; H, 12.66.

1-(Benzyloxy)-2,2-dimethyl-6-heptene (4). Sodium hydride (32.72 g of a 50% mineral oil dispersion, 0.68 mol) was washed three times with *n*-pentane to remove the mineral oil and suspended in 1 L of 1,2-dimethoxyethane. The mixture was stirred

(42) Reference 19a, p 581.

and heated at 60–65 °C under nitrogen while a solution of 83.78 g (0.59 mol) of alcohol **3** in 300 mL in 1,2-dimethoxethane was added slowly. After the addition was complete (1.5 h), the mixture was maintained at 65–70 °C until hydrogen evolution had ceased (2 h). The mixture was cooled slowly to room temperature, and 116.31 g (0.68 mol) of benzyl bromide was added dropwise over a 1-h period. The mixture was heated at reflux for 1 h, allowed to cool slowly to room temperature, and stirred at room temperature overnight.

The reaction was diluted with 200 mL of water, and the solution was extracted twice with *n*-pentane. The combined organic extracts were washed twice with dilute aqueous ammonia (~1 M), once with water, and once with saturated sodium chloride. The pentane solution was dried ($MgSO_4$), the solvent was removed under reduced pressure, and the residue was distilled to yield 121.83 g (86%) of benzyl ether **4**: bp 95 °C (0.1 mm); IR (neat) 1640 (C=C), 1205 (CO), 1095 (CO), 732 and 695 (C_6H_5) cm^{-1}; ^1H NMR (CCl_4) δ 0.88 (s, 6 H, $C(CH_3)_2$), 1.27 (m, 4 H, CH_2CH_2), 1.96 (br s, 2 H, CH_2=$CHCH_2$), 3.02 (s, 2 H, CH_2OCH_2Ph), 4.35 (s, 2 H, $PhCH_2O$), 4.88 (m, 2 H, CH_2=CH), 5.71 (br m, 1 H, CH_2=CH), 7.13 (s, 5 H, Ar H).

Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.47; H, 10.54.

2-[5-(Benzoyloxy)-4,4-dimethylpentyl]oxirane (5). A solution of 121.8 g (0.52 mol) of benzyl ether **4** and 161.05 g (0.78 mol) of 85% *m*-chloroperoxybenzoic acid in 2.5 L of chloroform was allowed to stand at room temperature for 4.5 h under nitrogen. The chloroform was removed under reduced pressure, and the residue was taken up in ether. The ether solution was washed once with 10% sodium sulfite, three times with 10% sodium hydroxide, and once with water. After the solution was dried ($MgSO_4$), the solvent was removed under reduced pressure to yield 121.12 g (94%) of the epoxide **5**: IR (neat) 1275 (epoxide CO), 1110 (ether CO), 835 and 715 (epoxide) cm^{-1}; ^1H NMR (CCl_4 δ 0.89 (s, 6 H, $C(CH_3)_2$), 1.33 (br s, 6 H, $(CH_2)_3$), 2.49 (br m, 3 H, H_2C–CH–O), 3.06 (s, 2 H, CH_2OCH_2Ph), 4.39 (s, 2 H, OCH_2Ph), 7.19 (s, 5 H, Ar H).

Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.47; H, 9.94.

6-(Benzyloxy)-5,5-dimethylhexanal (6). A solution of 86.15 g (0.35 mol) of epoxide **5** in 1 L of dioxane was added to a solution of 221.12 g (0.97 mol) of periodic acid in 1 L of water, and the resulting mixture was allowed to stand for 3 h at room temperature.[19] The internal temperature of the mixture rose slightly as the reaction proceeded but cooled back to room temperature when the reaction was finished. The progress of the reaction was monitored by the disappearance of the IR band due to the epoxide at 1275 cm^{-1}. The mixture was diluted with water and extracted three times with *n*-pentane. The pentane solution was washed several times with water, dried ($MgSO_4$), and evaporated. The crude product (76.14 g) was purified by chromatography on 800 g of silica gel with 20% ethyl acetate in hexane as eluent to give 75.7 g (92.4%) of aldehyde **6**: IR (neat) 1730 (C=O), 1110 (CO) cm^{-1}; ^1H NMR (CCl_4) δ 0.89 (s, 6 H, $C(CH_3)_2$), 1.46 (m, 4 H, CH_2CH_2), 2.26 (m, 2 H, CH_2CHO), 3.08 (s, 2 H, CH_2OCH_2Ph), 4.42 (s, 2 H, $PhCH_2$), 7.23 (s, 5 H, Ar H), 9.60 (t, 1 H, J = 2 Hz, CHO).

Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.85; H, 9.59.

6-(Benzoyloxy)-5,5-dimethylhexanoic Acid (7). A solution of 8 N chromic acid solution was prepared according to the procedure of Bowers, Halsall, Jones, and Lemin[20] and slowly added to a solution of 75.67 g (0.32 mol) of aldehyde **6** in 150 mL of acetone at 0 °C until the solution maintained a persistent orange color (about 40 mL was required). After addition of a small amount of sodium sulfite to destroy any excess chromic acid, the mixture was diluted with water and extracted with hexane. The hexane solution was extracted three times with 15% sodium hydroxide. The aqueous layers were acidified with 6 M hydrochloric acid and extracted with ether. The ether solution was washed with saturated sodium chloride and dried ($MgSO_4$). The solvent was removed, and the residue was distilled under reduced pressure to yield 35.96 g (45%) of acid **7**: bp 165–167 °C (0.1 mm); IR (neat) 2950 (OH), 1720 (C=O), 1285 and 1211 (CO from acid), 1100 (CO from ether) cm^{-1}; ^1H NMR (CCl_4) δ 0.90 (s, 6 H, $C(CH_3)_2$), 1.42 (br m, 4 H, CH_2CH_2), 2.25 (m, 2 H, CH_2COOH), 3.06 (s, 2 H, CH_2OCH_2Ph), 4.40 (s, 2 H, $PhCH_2$), 7.19 (s, 5 H, Ar H), 11.52 (s, 1 H, COOH).

For an elemental analysis, acid **7** was treated with an excess of diazomethane in ether to give the methyl ester in 84% yield after distillation, bp 122–123 °C (0.2 mm).

Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.82; H, 9.49.

Methyl 2-(Phenylthio)-6-(benzyloxy)-5,5-dimethylhexanoate (8b). A 124-mL aliquot of a 2.26 M solution (0.28 mol) of *n*-butyllithium in hexane was added to a solution of 28.28 g (0.28 mol) of diisopropylamine in 560 mL of tetrahydrofuran at −30 °C under nitrogen,[21] and the resulting solution of lithium diisopropylamide was allowed to stand at −30 °C for 30 min. A solution of 35.96 g (0.14 mol) of acid **7** in 140 mL of tetrahydrofuran was added over a 10-min period at −30 to −40 °C. The solution was stirred for 5 min, and 25.2 mL (0.14 mol) of hexamethylphosphoramide was added. The resulting dianion was added to a solution of 61.04 g (0.28 mol) of diphenyl disulfide in 224 mL of tetrahydrofuran at room temperature. The solution was stirred for 2.5 h at room temperature and added to 500 mL of aqueous 10% hydrochloric acid. The mixture was extracted with ether, the ether solution was extracted twice with sodium hydroxide, the combined alkaline extracts were acidified with 5% hydrochloric acid, and the liberated acid was extracted with ether.

After the ether solution was dried ($MgSO_4$), the solvent was removed under reduced pressure, and the crude acid (**8a**) was treated with an excess of diazomethane (0.7 mol).[43] Excess diphenyl disulfide was removed from the crude mixture by sublimation (80 °C at 0.3–0.4 mm, 28.58 g of sublimate collected) and by chromatography on 2.5 kg of silica gel with 2% methanol in hexane as eluent. The eluent was changed to 40% ethyl acetate in hexane to elute 47.09 g (90%) of α-phenylthio ester **8b**: IR (neat) 1740 (C=O), 1265 and 1210 (ester CO), 1100 (ether CO) cm^{-1}; ^1H NMR (CCl_4) δ 0.86 (s, 6 H, $C(CH_3)_2$), 1.50 (br m, 4 H, CH_2CH_2), 3.04 (s, 2 H, CH_2OCH_2Ph), 3.44 (t, 1 H, J = 8 Hz, $CHCO_2CH_3$), 3.52 (s, 3 H, CO_2CH_3), 4.38 (s, 2 H, $PhCH_2$), 7.18 (s, 5 H, $CH_2C_6H_5$), 7.23 (m, 5 H, SC_6H_5).

Anal. Calcd for $C_{22}H_{28}O_3S$: C, 70.93; H, 7.58; S, 8.61. Found: C, 70.60; H, 7.55; S, 8.50.

2-(Phenylthio)-6-(benzyloxy)-5,5-dimethylhexanoic Acid (8a). A suspension of 46.9 g (0.13 mol) of α-phenylthio ester **8b** in 390 mL of aqueous 25% sodium hydroxide was heated at reflux for 4 h. The mixture was then acidified with 6 M hydrochloric acid and extracted with ether. The ether solution was dried ($MgSO_4$) and the solvent removed under reduced pressure to yield 43.0 g (92%) of acid **8a**: IR (neat) 2950 (OH), 1700 (C=O), 1285 and 1210 (CO), 1100 (CO) cm^{-1}; ^1H NMR (CCl_4) δ 0.88 (s, 6 H, $C(CH_3)_2$), 1.50 (m, 4 H, CH_2CH_2), 3.10 (s, 2 H, CH_2OCH_2Ph), 3.48 (t, 1 H, J = 7 Hz, $CHCO_2H$), 4.45 (s, 2 H, $PhCH_2$), 7.33 (br s 10 H, Ar H), 10.50 (s, 1 H, CO_2H).

(*E*)-1-Bromo-3,7-dimethyl-2,6-octadiene (Geranyl Bromide).[22] Phosphorus tribromide (7.54 g, 28 mmol) was added to a solution of 8.48 g (55 mmol) of geraniol in 30 mL of hexane at 0 °C under nitrogen over a 15–20-min period. After addition of 2 mL of methanol, the solution was washed with water, saturated sodium bicarbonate solution, and water again. The pentane solution was dried ($MgSO_4$) and evaporated under reduced pressure to yield 10.86 g (90%) of geranyl bromide (one spot by TLC analysis, 10% ether in hexane) which was used without further purification.

Methyl (*E*)-6-(Benzyloxy)-5,5-dimethyl-2-(3,7-dimethyl-2,6-octadien-1-yl)-2-(phenylthio)hexanoate (9b). A 22-mL aliquot from a 2.2 M solution (0.048 mol) of *n*-butyllithium in hexane was added to a solution of 5.06 g (0.05 mol) of diisopropylamine in 44 mL of tetrahydrofuran under nitrogen at 0 °C. After 30 min, a solution of 7.65 g of acid **8a** (0.021 mol) in 25 mL of tetrahydrofuran was added over a 5-min period. The mixture was allowed to warm to room temperature and stirred for 1 h. Hexamethylphosphoramide (7.56 mL, 0.042 mol) was added, and the mixture was stirred for 10 min. The mixture was cooled to −25 °C, and a solution of 10.86 g (0.05 mol) of freshly prepared

(43) Arndt, F. "Organic Syntheses"; Wiley: New York, 1943; Collect. Vol. 2, pp 195–7, 461–2.

geranyl bromide in 15 mL of tetrahydrofuran was added over a 5–10-min period. The reaction mixture was allowed to warm slowly to room temperature overnight, diluted with 200 mL of 10% hydrochloric acid, and extracted with ether. The ether solution was washed with saturated sodium chloride, dried ($MgSO_4$), and evaporated. The crude residue was treated with an excess of diazomethane (0.05 mol) in 50 mL of ether, and the unreacted diazomethane was allowed to evaporate overnight. After the mixture was dried ($MgSO_4$) and the solvent evaporated, the crude ester (14.85 g) was purified by chromatography on 800 g of silica gel with 10% ether in hexane as eluent to give 5.64 g (53%) of α-phenylthio ester **9b**: IR (neat) 1730 (C=O), 1600 (C=C), 1100 (CO) cm^{-1}; ^1H NMR (CCl_4) δ 0.84 (s, 6 H, $C(CH_3)_2$), 1.22 (m, 4 H, CH_2CH_2), 1.56 (s, 6 H, CH_3 at C-3′ and C-7′), 1.65 (s, 3 H, $C{=}CCH_3$), 1.97 (br s, 4 H, $CH_2C{=}C$), 2.39 (t, 2 H, J = 7 Hz, CH_2 at C-3), 3.00 (s, 2 H, CH_2OCH_2Ph), 3.50 (s, 3 H, CO_2CH_3), 4.37 (s, 2 H, $PhCH_2$), 5.03 (m, 2 H, C=H), 7.15 (br s, 10 H, Ar H).

Anal. Calcd for $C_{32}H_{44}SO_3$: C, 75.55; H, 8.72; S, 6.30. Found: C, 75.65; H, 8.84; S, 6.14.

(*E*)-6-(Benzyloxy)-5,5-dimethyl-2-(3,7-dimethyl-2,6-octadienyl)-2-(phenylthio)-1-hexanol (10a). A solution of 5.64 g (11.1 mmol) of ester **9** in 15 mL of tetrahydrofuran was added dropwise to a suspension of 0.422 g (11.1 mmol) of lithium aluminum hydride in 10 mL of tetrahydrofuran. The mixture was heated at reflux for 4.5 h and stirred at room temperature for 2 h. The mixture was cooled to 0 °C, and aqueous 10% hydrochloric acid was added dropwise until the aluminum salts dissolved. The organic layer was diluted with ether, washed with saturated sodium chloride, and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the crude product (5.79 g) was purified by chromatography on 300 g of silica gel with 10% acetone in hexane as eluent to give 5.00 g (94%) of alcohol **10a**: IR (neat) 3450 (OH) cm^{-1}; ^1H NMR (CCl_4) δ 0.85 (s, 6 H, $C(CH_3)_2$), 1.25 (m, 4 H, CH_2), 1.55 (s, 6 H, CH_3 at C-3′ and C-7′), 1.64 (s, 3 H, $CH_3C{=}C$), 1.99 (br s, 4 H, $CH_2C{=}C$), 2.39 (m, 2 H, CH_2 at C-6), 3.04 (s, 2 H, CH_2OCH_2Ph), 3.51 (s, 2 H, CH_2OH), 3.89 (s, 1 H, OH), 4.40 (s, 2 H, OCH_2Ph), 5.15 (m, 2 H, C=CH), 7.23 (m, 10 H, Ar H).

Anal. Calcd for $C_{31}H_{44}SO_2$: C, 77.45; H, 9.23; S, 6.67. Found: C, 77.04; H, 9.13; S, 6.59.

(*E*)-6-(Benzyloxy)-5,5-dimethyl-2-(3,7-dimethyl-2,6-octadienyl)-2-(phenylthio)-1-hexanyl Acetate (10b). A solution of 6.14 g (12.8 mmol) of alcohol **10a** in 12 mL of pyridine and 10.25 mL of acetic anhydride was allowed to stand at room temperature under nitrogen for 16 h. The reaction mixture was diluted with water and extracted with ether. The ether solution was washed three times with aqueous 10% hydrochloric acid, three times with saturated sodium bicarbonate, and once with saturated sodium chloride. After the ether solution was dried ($MgSO_4$), the solvent was evaporated, giving 6.45 g (97%) of acetate **10b** which was chromatographically pure (TLC, 10% acetone in hexane): IR (neat) 1740 (C=O), 1600 (C=C), 1240 (acetate CO), 1120 (ether CO), 1030 (acetate) cm^{-1}; ^1H NMR (CCl_4), δ 0.88 (s, 6 H, $C(CH_3)_2$), 1.42 (br s, 4 H, CH_2CH_2), 1.63 (m, 9 H, $C{=}CCH_3$), 1.92 (s, 3 H, $OCOCH_3$), 2.02 (br s, 6 H, $CH_2C{=}C$), 3.06 (s, 2 H, CH_2OCH_2Ph), 3.88 (s, 2 H, CH_2OAc), 4.43 (s, 2 H, $PhCH_2O$), 5.27 (m, 2 H, C=CH), 7.34 (m, 10 H, Ar H).

Anal. Calcd for $C_{33}H_{46}SO_3$: C, 75.82; H, 8.87; S, 6.13. Found: C, 75.91; H, 8.63; S, 5.71.

(*E*)-2,2,8,12-Tetramethyl-5-methylene-7,11-tridecadien-1-ol (11). Lithium wire (0.32 g, 4.5 mmol) was added slowly in approximately 2.5-mm portions to 15 mL of liquid ammonia at −78 °C. The resulting blue solution was warmed to −33 °C and allowed to reflux for 30 min under nitrogen.[14] A solution of 6.45 g (12.3 mmol) of acetate **10b** in 25 mL of dry ether was added to the refluxing solution over a 5–10-min period. The mixture was allowed to remain at reflux (−33 °C) for an additional 25 min. The solution was cooled to −78 °C, the blue color was discharged by addition of solid ammonium chloride, and 100 mL of *n*-pentane was added. The ammonia was allowed to evaporate, saturated ammonium hydroxide was added, and the mixture was extracted three times with pentane. The combined pentane extracts were extracted twice with 5% aqueous sodium hydroxide, twice with water, and once with saturated sodium chloride. The solution was dried ($MgSO_4$) and evaporated to give 2.65 g of crude products. Purification by chromatography on 300 g of silica gel with 10% acetone in hexane as eluent afforded 1.81 g (56%) of alcohol **11**: IR (neat) 3350 (OH), 1645 (C=C), 1050 (CO), 890 ($C{=}CH_2$) cm^{-1}; ^1H NMR (CCl_4) δ 0.85 (s, 6 H, $R_2C(CH_3)_2$), 1.27 (m, 3 H, CH_2 and OH), 1.59 (s, 6 H, CH_3 at C-8 and C-12), 1.65 (s, 3 H, CH_3 at C-12), 1.97 (m, 6 H, $CH_2C{=}C$), 2.66 (d, 2 H, J = 7 Hz, CH_2 at C-6), 3.24 (s, 2 H, CH_2OH), 4.64 (br s, 2 H, $C{=}CH_2$), 5.08 (m, 2 H, $CH_3C{=}CH$). Carbon-13 NMR data and assignments are given in Table III.

Anal. Calcd for $C_{18}H_{32}O$: C, 81.75; H, 12.20. Found: C, 81.47; H, 12.13.

(*E*)-2,2,8,12-Tetramethyl-5-methylene-7,11-tridecadienal (12). Chromium trioxide (2.22 g, 22.2 mmol) was added to a solution of 3.51 g (44.4 mmol) of dry pyridine in 60 mL of dry dichloromethane, and the solution was allowed to stand for 20 min at room temperature under nitrogen.[23] A solution of 0.989 g (3.7 mmol) of alcohol **11** in 4 mL of dichloromethane was added slowly to the solution of the chromium trioxide–pyridine complex, and the mixture was stirred at room temperature for 1.5 h. The reaction mixture was then decanted into a separatory funnel, and the remaining tar was washed several times with ether. The combined ether solutions (ether–dichloromethane, >10:1) were washed twice with aqueous 0.1 N potassium hydroxide. The combined potassium hydroxide washes were extracted once with ether. The combined ether solutions were washed once with water, twice with 10% hydrochloric acid, and once with water. The ethereal solution was dried ($MgSO_4$) and evaporated, and the residue (0.948 g) was purified by chromatography on 100 g of silica gel with 10% acetone in hexane as eluent. The yield of aldehyde **12** was 0.872 g (90%): IR (neat) 1730 (C=O), 1640 (C=C), 885 ($R_2C{=}CH_2$), 825 (C=C) cm^{-1}; ^1H NMR (CCl_4) δ 0.97 (s, 6 H, $C(CH_3)_2$), 1.52 (s, 6 H, CH_3 at C-8 and C-12), 1.60 (s, 3 H, CH_3 at C-12), 1.81 (m, 2 H, CH_2), 1.94 (br s, 6 H, $C{=}CCH_2$), 2.60 (d, 2 H, J = 7 Hz, $C{=}CCH_2C{=}C$), 4.60 (br s, 2 H, $C{=}CH_2$), 5.00 (m, 2 H, C=CH), 9.30 (s, 1 H, CHO).

Anal. Calcd for $C_{18}H_{30}O$: C, 82.38; H, 11.52. Found: C, 82.63; H, 11.64.

(*Z*)-1-(Benzyloxy)-3,7-dimethyl-2,6-octadiene (14). Sodium hydride (17.76 g of a 50% mineral oil dispersion, 0.37 mol) was washed three times with *n*-pentane to remove the mineral oil and suspended in 525 mL of dry 1,2-dimethoxyethane. The mixture was stirred and heated at 70 °C while a solution of 50 g (0.32 mol) of nerol (**13**) in 175 mL of 1,2-dimethoxyethane was added over a 45-min period, and the temperature was maintained at 80–85 °C for 1.5 h. The mixture was cooled slowly to 40 °C, and 63.28 g (0.37 mol) of benzyl bromide was added dropwise over 30 min. The reaction was heated at reflux for 1 h, allowed to cool slowly to room temperature, and stirred for 16 h. The reaction was diluted with 200 mL of water and extracted three times with *n*-pentane. The combined pentane extracts were washed with aqueous 1 M ammonia, water, and saturated sodium chloride. The solution was dried ($MgSO_4$), the solvent was evaporated, and the residue was distilled under reduced pressure to yield 72.9 g (93%) of benzyl ether **14**: bp 98–108 °C (0.05 mm); IR (neat) 1670 (C=C), 1610 (C=C), 1090 (CO) cm^{-1}; ^1H NMR (CCl_4) δ 1.57 (br s, 3 H, CH_3 at C-7), 1.66 (br s, 3 H, CH_3 at C-7), 1.74 (d, 3 H, J = 1.5 Hz, CH_3 at C-3), 2.02 (br d, 4 H, J = 3 Hz, $C{=}CCH_2$), 3.92 (d, 2 H, J = 6 Hz, CH_2OCH_2Ph), 4.42 (s, 2 H, OCH_2Ph), 5.20 (br m, 2 H, C=CH), 7.24 (s, 5 H, Ar H).

Anal. Calcd for $C_{17}H_{24}O$: C, 83.55; H, 9.90. Found: C, 83.42; H, 9.90.

(*Z*)-6-(Benzyloxy)-4-methyl-4-hexenal. Ozone (101.26 mmol; 69.83 min at 1.45 mmol of O_3/min) was bubbled through a solution of 14.9 g (61 mmol) of benzyl ether **14** and 5.23 mL (61 mmol) of dry pyridine in 150 mL of dry dichloromethane at −78 °C.[24] Excess dimethyl sulfide (15 mL) was added, and the mixture was allowed to warm to room temperature and stir overnight. The solvent and excess dimethyl sulfide were removed under reduced pressure, and the residue was diluted with water and extracted three times with dichloromethane. The dichloromethane solution was extracted with 5% aqueous hydrochloric acid and water and dried ($MgSO_4$). Darco activated carbon was added to remove most of the highly colored materials.

Removal of solvent under reduced pressure gave a crude residue (12.96 g) which was shaken with 100 mL of freshly prepared saturated sodium bisulfite. After 10 min the slurry was filtered, and the precipitate was washed thoroughly with dichloromethane. The dichloromethane was removed under reduced pressure, and

the shaking procedure was repeated two or three times until TLC analysis (10% ethyl acetate in hexane) showed no aldehyde present in the dichloromethane layer. The bisulfite adduct was dissolved in 10% sodium carbonate, and the mixture was extracted three times with ether. The ether solution was washed with water and saturated sodium chloride, dried, and evaporated to give 4.6 g (35%) of the aldehyde which was chromatographically pure by TLC (10% ethyl acetate in hexane): IR (neat) 2700 (aldehydic CH), 1725 (C=O), 1670 (C=C) cm^{-1}; ^1H NMR (CCl_4) δ 1.67 (br s, 3 H, C=CCH$_3$), 2.27 (br s, 4 H, C**H$_2$**C**H$_2$**), 3.92 (d, 2 H, J = 7 Hz, C**H$_2$**OCH$_2$Ph), 4.38 (s, 2 H, OCH$_2$Ph), 5.38 (t, 1 H, J = 7 Hz, C=CH), 7.22 (s, 5 H, Ar H), 9.52 (br s, 1 H, CHO).

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.91; H, 8.19.

(*Z*)-6-(Benzyloxy)-4-methyl-4-hexen-1-ol (15). A solution of 5.19 g (24 mmol) of (*Z*)-6-(benzyloxy)-4-methyl-4-hexenal and 0.912 g (24 mmol) of sodium borohydride in 85 mL of absolute ethanol was allowed to stand under nitrogen at room temperature for 3.5 h, after which the reaction was complete by TLC analysis (10% acetone in benzene). The solution was acidified carefully with 10% aqueous sulfuric acid, diluted with water, and extracted with hexane. The hexane solution was washed twice with saturated sodium chloride and dried ($MgSO_4$). The solvent was removed, and the residue was distilled under reduced pressure to give 4.58 g (87%) of alcohol **15**: bp 113–144 °C (0.05 mm); IR (neat) 3400 (OH), 1660 (C=C), 1060 (CO) cm^{-1}; ^1H NMR (CCl_4) δ 1.45 (m, 2 H, CH$_2$), 1.68 (br s, 3 H, C=CCH$_3$), 2.08 (m, 2 H, C=CCH$_2$), 3.40 (m, 3 H, C**H$_2$**OH), 3.92 (d, 2 H, J = 7 Hz, C**H$_2$**OCH$_2$Ph), 4.38 (s, 2 H, OCH$_2$Ph), 5.38 (t, 1 H, J = 7 Hz, C=CH), 7.22 (s, 5 H, Ar H).

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.10; H, 9.16.

(*Z*)-4-Methyl-6-(benzyloxy)-4-hexen-1-yl Tosylate (16). A solution of 8.44 g (38 mmol) of alcohol **15** and 19.11 g (100 mmol) of *p*-toluenesulfonyl chloride in 200 mL of dry pyridine was allowed to stand at 0 °C for 96 h. The solution was diluted with water and extracted three times with pentane. The pentane solution was washed three times with 10% cupric sulfate, once with water, and once with saturated sodium chloride. Drying ($MgSO_4$) and evaporation afforded 10.58 g (76%) of the crude tosylate **16** which was kept at −20 °C and used without further purification.[44] In two other runs the reaction times were 24 and 48 h, and the yields of the crude tosylate were 93 and 86%. The IR spectrum of the tosylate (neat) has the following absorptions: 1675 (C=C), 1600 (C=C), 1170 (SO_2-O), 1090 (CO), 1065 (CO) cm^{-1}.

(*Z*)-1-(Benzyloxy)-6-iodo-3-methyl-2-hexene (17a). A solution of 7.28 g of the unpurified tosylate **16** [prepared from 4.58 g (0.021 mol) of alcohol **15**] and 25.7 g (0.17 mol) of sodium iodide in 380 mL of acetone was allowed to stand at room temperature under nitrogen for 35 h.[45,46] The mixture was diluted with water containing 2.8 g of sodium thiosulfate and extracted three times with hexane. The hexane solution was dried (Na_2SO_4) and evaporated, and the residue was distilled under reduced pressure to give 5.35 g (77% based on **15**, ~83% based on **16**) of iodide **17a**: bp 118–120 °C (0.1 mm); IR (neat) 1670 (C=C), 1075 (CO) cm^{-1}; ^1H NMR (CCl_4) δ 1.68 (br s, 3 H, CH$_3$), 2.01 (m, 4 H, C**H$_2$**C**H$_2$**), 2.99 (t, 2 H, J = 6.5 Hz, CH$_2$I), 3.93 (d, 2 H, J = 6 Hz, C**H$_2$**OCH$_2$Ph), 4.41 (s, 2 H, PhCH$_2$O), 5.41 (t, 1 H, J = 7 Hz, C=CH), 7.22 (s, 5 H, Ar H).

(*Z*)-1-(Benzyloxy)-6-bromo-3-methyl-2-hexene (17b). A solution of 10.47 g (28 mmol) of the crude tosylate **16** and 9.68 g (112 mmol) of anhydrous lithium bromide in 280 mL of dry acetone (freshly distilled from calcium chloride after having been stored over calcium chloride for 24 h) was heated at reflux for 21.5 h under nitrogen and cooled to room temperature.[47] The solvent was evaporated, the residue was taken up in a mixture of 250 mL of water and 50 mL of ether, and the aqueous layer was extracted three times with hexane. The combined organic extracts were washed with water and saturated sodium chloride and dried ($MgSO_4$). After filtration through a short pad of Celite, the solvent was removed under reduced pressure, and the residue distilled under reduced pressure to give 7.33 g (92%) of bromide **17b**: bp 108–112 °C (0.0002 mm); IR (neat) 1718 and 1667 (C=C), 1073 (CO) cm^{-1}; ^1H NMR (CCl_4) δ 1.73 (s, 3 H, CH$_3$), 1.93 (t, 2 H, J = 6 Hz, C=CCH$_2$), 2.13 (m, 2 H, CH$_2$), 3.22 (t, 2 H, J = 6 Hz, CH$_2$Br), 3.36 (t, ~0.4 H, J = 6 Hz, CH$_2$Cl), 3.92 (d, 2 H, J = 7.5 Hz, CH$_2$O), 4.40 (s, 2 H, PhCH$_2$O), 5.40 (t, 1 H, J = 6 Hz, C=CH), 7.23 (s, 5 H, Ar H). The product was contaminated by a substantial amount of the corresponding chloride as can be seen in the following microanalytical data.[44]

Anal. Calcd for $C_{14}H_{19}OBr$: C, 59.37; H, 6.76; Br, 28.21. Found: C, 59.45; H, 6.70; Br, 22.04; Cl, 3.18 (converting Cl percentage to Br gives total Br as 28.06).

(*Z*)-[6-(Benzyloxy)-4-methyl-4-hexen-1-yl]triphenylphosphonium Iodide (17c). A solution of 6.61 g (20 mmol) of iodide **17a** and 13.11 g (50 mmol) of triphenylphosphine in 45 mL of dry benzene was heated at reflux under nitrogen in the dark for 107 h. The mixture was cooled to room temperature and poured into 450 mL of ether with rapid stirring. The resulting white precipitate was filtered after 10 min and washed thoroughly with ether. The yield of phosphonium salt **17c** amounted to 9.35 g (79%): mp 134.5–135.5 °C; ^1H NMR ($CDCl_3$) δ 1.60 (br s, 3 H, CH$_3$), 1.90 (m, 2 H, CH$_2$C=C), 2.49 (t, 2 H, J = 7 Hz, CH$_2$), 3.58 (m, 2 H, CH$_2$P), 4.07 (d, 2 H, J = 7 Hz, CH$_2$O), 4.53 (s, 2 H, PhCH$_2$O), 5.53 (t, 1 H, J = 7 Hz, C=CH), 7.25 (s, 5 H, CH$_2$C$_6$**H$_5$**), 7.76 (m, 15 H, P(C$_6$H$_5$)$_3$).

Anal. Calcd for $C_{32}H_{34}IOP$: C, 64.87; H, 5.78. Found: C, 64.61; H, 6.03.

(*Z*)-6-(Benzyloxy)-4-methyl-1-(phenylseleno)-4-hexene (17d). Sodium borohydride (0.3 g, 7.9 mmol) was added in portions to a solution of 0.156 g (0.5 mmol) of diphenyl diselenide in 5 mL of absolute ethanol under nitrogen until the solution was colorless. A solution of 0.374 g (1 mmol) of tosylate **16** in 1 mL of absolute ethanol was added, and the mixture was stirred for 2 h at room temperature.[37b] The reaction mixture was diluted with 150 mL of water and extracted three times with a 1:1 ether–pentane solution. The combined ether–pentane extracts were washed twice with 10% hydrochloric acid, once with saturated sodium bicarbonate, and once with saturated sodium chloride. After the extracts were dried ($MgSO_4$), the solvent was removed to give 0.359 g (100%) of phenyl selenide **17d**: IR (neat) 1680 (C=C), 1075 (CO) cm^{-1}; ^1H NMR (CCl_4) δ 1.66 (s, 3 H, C=CCH$_3$), 1.69 (m, 2 H, C=CCH$_2$), 2.1 (m, 2 H, CH$_2$), 2.76 (m, 2 H, CH$_2$SePh), 3.88 (d, 2 H, J = 6 Hz, C**H$_2$**OCH$_2$Ph), 4.36 (s, 2 H, PhCH$_2$), 5.32 (t, 1 H, J = 6.5 Hz, C=CH), 7.19 (s, 5 H, CH$_2$C$_6$**H$_5$**), 7.23 (m, 5 H, SeC$_6$H$_5$).

Anal. Calcd for $C_{20}H_{24}OSe$: C, 66.84; H, 6.73; Se, 21.97. Found: C, 66.84; H, 6.92; Se, 22.02.

(*Z*)-7-(Benzoyloxy)-5-methyl-5-heptenenitrile (17e). Sodium cyanide (0.735 g, 15 mmol) was added to a solution of 3.74 g (10 mmol) of tosylate **16** in 30 mL of *N*,*N*-dimethylformamide, and the mixture was heated at 98 °C for 24 h. The progress of the reaction was followed by the disappearance of the IR band due to the tosylate at 1170 cm^{-1}. The mixture was poured into 250 mL of water containing 3 g of ammonium chloride and extracted three times with pentane. The pentane solution was washed several times with water and dried ($MgSO_4$). After removal of solvent the crude residue was distilled at reduced pressure to give 2.29 g (100%) of nitrile **17e**: bp 108–110 °C (0.1 mm); IR (neat) 2240 (CN), 1730 and 1670 (C=C), 1080 (CO) cm^{-1}; ^1H NMR (CCl_4) δ 1.57 (br s, 2 H, C**H$_2$**C**H$_2$**CN), 1.68 (s, 3 H, C=CCH$_3$), 2.08 (t, 4 H, J = 7 Hz, CH$_2$CN and C=CCH$_2$), 3.87 (d, 2 H, J = 7 Hz, C**H$_2$**OCH$_2$Ph), 4.38 (s, 2 H, PhCH$_2$O), 5.40 (t, 1 H, J = 7 Hz, C=CH), 7.2 (s, 5 H, Ar H).

Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.42; H, 8.09; N, 6.00.

(2*Z*,6*Z*)-1-(Benzyloxy)-3,8,8-trimethyl-2,6-nonadiene (19). Procedure A. A 0.437-mL aliquot of a 2.2 M solution (1 mmol)

(44) Bromide **17b** prepared from the crude tosylate was contaminated by a substantial amount of the corresponding chloride. It is not clear whether the chloride was present as a contaminant of the crude tosylate or whether it arises from chloride ion liberated from tosyl chloride during the preparation of **17b**.

(45) Brown, H. C.; Wheeler, O. H. *J. Am. Chem. Soc.* **1956**, *78*, 2199–202.

(46) (a) Coates, R. M.; Robinson, W. H. *J. Am. Chem. Soc.* **1971**, *93*, 1785–6. (b) Robinson, W. H. Ph.D. Thesis, University of Illinois, Urbana, IL, 1972.

(47) Bonjouklian, R.; Ruden, R. A. *J. Org. Chem.* **1977**, *42*, 4095–103.

of *n*-butyllithium in hexane was added to a stirred suspension of 0.4738 g (0.8 mmol) of phosphonium salt **17c** in 15 mL of tetrahydrofuran under nitrogen at room temperature. The deep red ylide solution was stirred for 5 min and then cooled to −78 °C after which a solution of 0.086 g (1.0 mmol) of pivaldehyde in 3 mL of tetrahydrofuran was added over 5 min. The reaction mixture was allowed to warm slowly to room temperature overnight and then quenched with 20 mL of methanol. The mixture was diluted with 300 mL of water and extracted three times with ether. The ether solution was washed with saturated sodium chloride and dried ($MgSO_4$). After removal of solvent, the crude residue (0.49 g) was purified by chromatography on 50 g of silica gel with 10% ether in hexane as eluent to give 0.179 g (82%) of benzyl ether **19**: IR (neat) 1670 (C=C), 1070 (C=O), 696 (cis C=C) cm^{-1}; 220-MHz ^1H NMR (CCl_4) δ 1.02 (s, 9 H, $C(CH_3)_3$), 1.70 (s, 3 H, $C{=}CCH_3$), 1.99 (t, 2 H, J = 7.5 Hz, CH_2 at C-4), 2.18 (q, 2 H, J = 7.5 Hz, CH_2 at C-5), 3.84 (d, 2 H, J = 7 Hz, CH_2OCH_2Ph), 4.33 (s, 2 H, $PhCH_2O$), 4.97 (dt, 1 H, J = 7 and 12 Hz, $(CH_3)_3CCH{=}CH$), 5.18 (dt, 1 H, J = 1.5 and 12 Hz, $(CH_3)_3CCH{=}CH$), 5.29 (t, 1 H, J = 7 Hz, C=CH at C-2), 7.14 (s, 5 H, Ar H).

Anal. Calcd for $C_{19}H_{28}O$: C, 83.77; H, 10.36. Found: C, 84.07; H, 10.57.

Procedure B (Salt-Free).[25b,26,29] To a suspension of 0.045 g (1.2 mmol) of sodium amide in 50 mL of anhydrous ammonia under nitrogen was added 0.592 g (1 mmol) of phosphonium salt **17c**. The mixture was allowed to reflux (−33 °C) for about 30 min, after which the color changed from orange to yellow. The ammonia was allowed to evaporate, 15 mL of ether was added, and the mixture was stirred for 2 h at room temperature. A solution of 0.086 g (1 mmol) of pivaldehyde in 3 mL of ether was added, and the mixture was stirred for 1 h at room temperature. After addition of 20 mL of methanol, the mixture was diluted with water and extracted three times with ether. The ether solution was washed with 10% citric acid, 5% sodium bicarbonate, and saturated sodium chloride and dried ($MgSO_4$). After solvent removal and purification by chromatography on 45 g of silica gel with 10% ether in hexane as eluent, 0.137 g (50%) of benzyl ether **19** was obtained. See procedure A for the spectral data.

Procedure C (Schlosser-Wittig). In an oven-dried, 250-mL three-necked flask fitted with two serum caps and an argon inlet was placed 0.296 g (0.5 mmol) of phosphonium salt **17c**.[24b,27] The flask was evacuated at 0.1 mm for 90 min, argon was introduced, and 10 mL of freshly dried and distilled tetrahydrofuran was added. An amount (2 or 3 drops) of 0.144 M phenyllithium in tetrahydrofuran (for preparation of phenyllithium, see below) sufficient to produce a lasting ylide color was added to the stirred suspension and was followed by an additional 3.47 mL (0.5 mmol) of the phenyllithium solution. The resulting orange-red solution was stirred at room temperature for 5 min, cooled to −78 °C, and stirred an additional 10 min. A solution of 0.0431 g (0.5 mmol) of pivaldehyde in 1.5 mL of tetrahydrofuran was then added dropwise, via syringe, down the wall of the flask. The wall of the flask was rinsed with an additional 0.5 mL of tetrahydrofuran, and the solution was stirred for 15 min. An additional 4.96 mL of the 0.144 M phenyllithium solution (0.71 mmol) was added dropwise down the wall of the flask over a 20-min period. After 5 min the solution was diluted with sufficient dry ether (21 mL) to make the solvent 50% ether. This dilution was accomplished in the same fashion as the aldehyde addition. The cooling-bath temperature was raised to −25 °C, and stirring was continued for 30 min, at which time the reaction was quenched by addition of 10 mL of methanol. The cooling bath was removed, and stirring was continued overnight. The reaction mixture was diluted with water and extracted three times with ether. The ether solution was washed with saturated sodium chloride and dried ($MgSO_4$). After evaporation of the solvent the resulting oil (0.288 g) was purified by chromatography on 30 g of silica gel with 3% ether in hexane as eluent; mixed fractions were rechromatographed on 15 g of silica gel with a linear gradient of hexane–dichloromethane as eluent. The yield of benzyl ether **19** was 67 mg (49%). The NMR spectrum was identical with that of the benzyl ether obtained from procedures A and B above.

Procedure D.[9] A 0.908-mL aliquot of 2.2 M *n*-butyllithium (2 mmol) in hexane was added to a slurry of 1.18 g (2 mmol) of phosphonium salt **17c** in 4 mL of tetrahydrofuran and 2 mL of ether. The deep red solution was stirred for 20 min at room temperature and then cooled to −75 °C, after which a solution of 0.172 g (2 mmol) of pivaldehyde in 1.5 mL of ether was added. When the red color was discharged, another 0.908-mL aliquot of 2.2 M *n*-butyllithium (2 mmol) in hexane was added. The mixture was allowed to warm to −20 °C, and 0.466 g (2.5 mmol) of a 1:1 complex of potassium *tert*-butoxide–*tert*-butyl alcohol was added. After 1 h at −20 °C, the mixture was diluted with water and extracted three times with 1:1 ether–hexane. The ether–hexane solution was washed with saturated sodium chloride, dried ($MgSO_4$), and evaporated. Purification of the residue (0.372 g) by chromatography on 39 g of silica gel with 10% ether in hexane as eluent gave 0.164 g (30%) of benzyl ether **19**. The NMR spectrum was identical with that of the benzyl ether from procedures A and B above.

Preparation of Phenyllithium in Tetrahydrofuran.[48] Bromobenzene was dried by passage over a 100-g column of silica gel and stored over molecular sieves (Linde 4 Å) until used. Lithium wire (1 g, 0.144 mol; 23.64 cm) was cut into approximately 2-mm pieces and placed in a flask containing 34 mL of ether. A solution of 10.56 g (0.68 mol) of bromobenzene in 16 mL of ether was placed in the attached dropping funnel. Approximately 5 mL of the bromobenzene solution was added to the slurry of lithium pieces which began to turn cloudy and reflux almost immediately. Addition of bromobenzene was continued at a rate that maintained a gentle reflux for 1 h. The solution was allowed to cool to room temperature and filtered through a loose glass wool plug. The solvent was then removed under high vacuum, and the flask was filled with an argon atmosphere. The flask was cooled to 0 °C, 140 mL of tetrahydrofuran was added, and the resulting solution was stored at −25 °C. The phenyllithium solution was standardized before use by diluting a 2.5-mL aliquot with 10 mL of benzene and titrating with a 1 M solution of 2-butanol in xylene according to the procedure of Watson and Eastham[49] with 1,10-phenanthroline as indicator.

(2*Z*,6*Z*)-3,8,8-Trimethyl-2,6-nonadien-1-ol (20). Lithium wire (0.025 g, 3.6 mmol; 0.6 cm) was added in 2-mm pieces to 20 mL of ammonia, and the mixture was allowed to reflux (−33 °C) for 30 min. A solution of 0.179 g (0.6 mmol) of benzyl ether **19** in 2 mL of tetrahydrofuran was added to the blue solution. The solution was allowed to reflux for 20 min, after which the blue color was discharged by the addition of solid ammonium chloride. *n*-Pentane (25 mL) was added, and the ammonia was allowed to evaporate. A 150-mL portion of saturated ammonium chloride was added, and the mixture was extracted three times with pentane. The pentane solution was washed with saturated sodium bicarbonate and saturated sodium chloride and dried ($MgSO_4$). After evaporation of the solvent, the crude residue (0.14 g) was purified by chromatography on 15 g of silica gel with 10% acetone in hexane as eluent to yield 0.070 g (64%) of alcohol **20**: IR (neat) 3260 (OH), 1660 (C=C), 1005 (CO), 723 and 698 (cis CH=CH and $R_2C{=}CH$) cm^{-1}; 220-MHz ^1H NMR (CCl_4) δ 1.11 (s, 9 H, $C(CH_3)_3$), 1.74 (s, 3 H, $C{=}CCH_3$), 2.08 (t, 2 H, J = 7 Hz, CH_2 at C-4), 2.24 (q, 3 H, J = 7 Hz, CH_2 at C-5 and OH), 3.99 (d, 2 H, CH_2O), 5.06 (dt, 1 H, J = 7.1 and 12 Hz, $(CH_3)_3CCH{=}CH$), 5.28 (dt, 1 H, J = 1.5 and 12 Hz, $(CH_3)_3CCH{=}CH$), 5.36 (t, 1 H, J = 7 Hz, $C{=}CHCH_2OH$); ^{13}C NMR spectral data and assignments are given in Table I; mass spectrum, m/e 182.1671 (M^+) (calcd for $C_{12}H_{22}O$, 182.1871).

(*Z*)-9-(Benzyloxy)-2,2,7-trimethyl-7-nonen-3-ol (22). Magnesium turnings (0.51 g, 21 mmol) were placed in an oven-dried flask which was then flamed dry while being flushed with argon. After the flask had cooled, 3 mL of dry ether was introduced, and 0.5 mL (5.8 mmol) of 1,2-dibromoethane was added to the stirred suspension.[31] When the reaction mixture had cooled to room temperature, the ether was removed by suction through an 18-gauge needle, and 4 mL of fresh ether was added. Freshly distilled bromide **17b** (0.283 g, 1 mmol) was then added over a 5-min period, and the syringe was rinsed with 0.5 mL of ether. Another 0.5 mL (5.8 mmol) of 1,2-dibromoethane was added, and the reaction mixture was heated at reflux for 1 h. The mixture was cooled to room temperature, and a solution of 0.0431 g (0.5

(48) Jones, R. G.; Gilman, H. *Org. React.* **1951**, *6*, 339–66.
(49) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165–8.

mmol) of pivaldehyde in 0.5 mL of ether was added over 5 min. The reaction mixture was heated at reflux for 1 h and stirred for 18.5 h at room temperature. The reaction mixture was added to 150-mL of saturated ammonium chloride, and the product was extracted into ether. The ether solution was washed with saturated sodium bicarbonate and saturated sodium chloride, dried ($MgSO_4$), and evaporated. Purification of the residue (0.287 g) by chromatography on 30 g of silica gel with 25% ether in hexane as eluent provided 0.136 g (93%) of alcohol **22**: IR (neat) 3400 (OH), 1670 (C=C), 1080 (CO) cm^{-1}; ^1H NMR (CCl_4) δ 0.85 (s, 9 H, $C(CH_3)_3$), 1.33 (m, 5 H, $CH(OH)CH_2CH_2$), 1.73 (s, 3 H, $C=CCH_3$), 2.02 (m, 2 H, $C=CCH_2$), 3.03 (m, 1 H, R_2CHOH), 3.92 (d, 2 H, J = 7.5 Hz, CH_2O), 4.40 (s, 2 H, $PhCH_2O$), 5.35 (t, 1 H, J = 6 Hz, C=CH), 7.23 (s, 5 H, Ar H).

Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.28; H, 10.53.

(*Z*)-9-(Benzyloxy)-2,2,7-trimethyl-7-nonen-3-one (23). A. A solution of 1.42 g (4.9 mmol) of alcohol **22** in 12 mL of dry dichloromethane was oxidized with Collins reagent[23] by following the procedure for alcohol 11 except that 3.43 g (34.4 mmol) of anhydrous chromium trioxide and 5.45 g (68.6 mmol) of dry pyridine in 95 mL of dry dichloromethane were used and the mixture was stirred for 8 h. The crude product (1.41 g) was purified by chromatography on 150 g of silica gel with 10% acetone in hexane as eluent to afford 1.02 g (72%) of ketone **23**: IR (neat) 1700 (C=O), 1070 (CO) cm^{-1}; ^1H NMR (CCl_4) δ 1.10 (s, 9 H, $C(CH_3)_3$), 1.60 (m, 2 H, CH_2), 1.77 (br s, 3 H, $C=CCH_3$), 2.03 (t, 2 H, J = 7.5 Hz, $C=CCH_2$), 2.40 (t, 2 H, J = 6 Hz, $CH_2C=O$), 4.01 (d, 2 H, J = 7.5 Hz, CH_2O), 4.53 (s, 2 H, $PhCH_2O$), 5.52 (t, 1 H, J = 7.5 Hz, C=CH), 7.43 (s, 5 H, Ar H).

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 78.81; H, 9.58.

B. A solution of 0.0225 g (0.08 mmol) of alcohol **22** in 0.5 mL of dry dichloromethane was added to a stirred suspension of 0.120 g (0.56 mmol) of pyridinium chlorochromate[50] and 0.0102 g (0.12 mmol) of sodium acetate in 0.5 mL of dry dichloromethane. After 5.5 h at room temperature under nitrogen, the mixture was diluted with 50 mL of ether, and the precipitate was washed four times with ether until it became granular. The ether solutions were combined and filtered through a short pad of Fluorisil, and the solvent was evaporated. Purification by chromatography on 3 g of silica gel with 10% acetone in hexane as eluent furnished 0.0164 g (71%) of ketone **23**. See part A for the spectral data.

(3*Z*,7*Z*)-9-(Benzyloxy)-2,2,7-trimethyl-3,7-nonadien-3-yl Diethyl Phosphate (24). A 1.31-mL aliquot of 2.29 M *n*-butyllithium (3 mmol) in hexane was added slowly to a solution of 0.3 g (3 mmol) of diisopropylamine in 15 mL of tetrahydrofuran at 0 °C under nitrogen.[30,31] After 20 min at room temperature under nitrogen, the solution was cooled to 0 °C, and a solution of 0.846 g (3 mmol) of ketone **23** in 5 mL of tetrahydrofuran was added over 5 min. The resulting solution was allowed to stand for 40 min at room temperature, and, after being cooled to 0 °C, 5.25 mL of hexamethylphosphoramide was added. After another 5 min, 0.516 g (3 mmol) of diethyl chlorophosphate was added. The solution was allowed to warm to room temperature and stand for 19 h. The reaction mixture was diluted with 300 mL of saturated sodium bicarbonate and extracted three times with ether. The combined ethereal extracts were washed with saturated ammonium chloride, water, and saturated sodium chloride. The solution was dried ($MgSO_4$), the solvent was evaporated, and the residue (1.30 g) was applied to a column of 130 g of silica gel. Recovered ketone (0.170 g, 20%) was eluted with 25% ether in hexane, and enol phosphate **24** (0.748 g, 59%; 75% based upon recovered ketone) was eluted with ether: IR (neat) 1725, 1690 (C=C, C=C—O), 1250 (phosphate P=O), 1015 (CO), 950 and 798 (PO) cm^{-1}; ^1H NMR (CCl_4) δ 1.09 (s, 9 H, $C(CH_3)_3$), 1.29 (t, 6 H, J = 7 Hz, $2\ OCH_2CH_3$), 1.74 (s, 3 H, $C=CCH_3$), 2.12 (br s, 4 H, $2\ C=CCH_2$), 3.94 (d, 2 H, J = 6 Hz, CH_2OCH_2Ph), 4.08 (q, 4 H, J = 8 Hz, $2\ OCH_2CH_3$), 4.41 (s, 2 H, $PhCH_2O$), 4.80 (m, 1 H, P(O)C=CH), 5.36 (t, 1 H, J = 6 Hz, C=CH), 7.23 (s, 5 H, Ar H); ^{13}C NMR ($CDCl_3$) 16.14 (d, $J^{31}P-^{13}C$ = 7.3 Hz, $2\ OCH_2CH_3$), 23.28 (s, $C=CCH_3$ or $C=CCH_2$), 24.25 (s, $C=CCH_2$ or $C=CCH_3$), 28.35 (s, $C(CH_3)_3$), 31.69 (s, $C(CH_3)_3$), 36.38 (d, $J^{31}P-^{13}C$ = 1.6 Hz, $P(O)C=CCH_2$), 63.97 (d, $J^{31}P-^{13}C$ = 6.5 Hz, $2\ OCH_2CH_3$), 66.55 (s, CH_2O), 72.21 (s, $PhCH_2O$), 111.07 (d, $J^{31}P-^{13}C$ = 4.8 Hz, P(O)C=C), 122.60 (s, $C=CCH_2O$), 127.66 (s, *p*-Ar), 127.99 (s, *m*-Ar or *o*-Ar), 128.52 (s, *o*-Ar or *m*-Ar), 138.87 (s, $C=CCH_2O$), 140.11 (s, C-1 of Ar), 156.22 (d, $J^{31}P-^{13}C$ = 11.3 Hz, P(O)C=C).

(2*Z*,6*E*)-3,8,8-Trimethyl-2,6-nonadien-1-ol (25). Lithium wire (0.098 g, 14 mmol; 2.32 cm) was added in approximately 2.5-mm pieces to 90 mL of ammonia, and the mixture was allowed to reflux for 30 min under nitrogen.[30,31] A solution of 0.748 g (1.7 mmol) of enol phosphate **24** and 0.282 g (3.8 mmol) of *tert*-butyl alcohol in 15 mL of dry tetrahydrofuran was added to the blue solution, and the mixture was allowed to reflux for 1 h. *n*-Pentane (90 mL) was added, and the blue color was discharged by addition of solid ammonium chloride. The ammonia was allowed to evaporate, 250 mL of saturated aqueous ammonium chloride was added, and the mixture was extracted three times with pentane. The pentane solution was washed with saturated sodium bicarbonate and saturated sodium chloride. After the solution was dried ($MgSO_4$) and the solvent removed, the crude residue (1.01 g) was purified by chromatography on 125 g of silica gel with 10% acetone in hexane as eluent to give 0.183 g (59%) of alcohol **25**: IR (neat) 3300 (OH), 1740 and 1670 (C=C), 1010 (CO), 975 (trans CH=CH), 700 ($R_2C=CH$) cm^{-1}; 220-MHz ^1H NMR (CCl_4) δ 0.98 (s, 9 H, $C(CH_3)_3$), 1.27 (br s, 1 H, OH), 1.73 (s, 3 H, $C=CCH_3$), 2.09 (br s, 4 H, $2\ C=CCH_2$), 3.98 (d, 2 H, J = 7 Hz, CH_2OH), 5.23 (dt, J = 6 and 16 Hz, $(CH_3)_3CCH=CH$), 5.38 (t, 1 H, J = 7 Hz, $C=CHCH_2OH$), 5.42 (d, 1 H, J = 16 Hz, $(CH_3)_3CCH=CH$). ^{13}C NMR spectral data and assignments are give in Table I.

(*Z*)-9-(Benzoyloxy)-4-(phenylseleno)-2,2,7-trimethyl-7-nonen-3-ol (27). A solution of 0.334 g (1.67 mmol) of 85% *m*-chloroperoxybenzoic acid in 1.5 mL of tetrahydrofuran was added to a solution of 0.60 g (1.67 mmol) of phenyl selenide **17d** in 3.5 mL of tetrahydrofuran at −78 °C under nitrogen, and the solution was allowed to stand at −78 °C for 40 min.[37] A 4.63-mL aliquot of 0.792 M lithium diisopropylamide (3.67 mmol) in tetrahydrofuran was added. After 5 min, 0.181 g (2.1 mmol) of pivaldehyde was added, and the mixture was stirred at −78 °C for 75 min. A solution of 0.8 mL of glacial acetic acid in 3.2 mL of tetrahydrofuran was added, and the selenoxide was reduced by the addition of 0.2 mL (1.67 mmol) of trimethyl phosphite. The mixture was allowed to warm to room temperature overnight, diluted with aqueous 5% sodium carbonate, and extracted three times with ether. The combined ethereal extracts were washed with 10% hydrochloric acid, saturated sodium bicarbonate, and saturated sodium chloride. The solution was dried ($MgSO_4$) and evaporated, giving 0.767 of the crude, unstable hydroxy selenide **27** which was used without purification.

(2*Z*,6*Z*)- and (2*Z*,6*E*)-1-(Benzyloxy)-3,8,8-trimethyl-2,6-nonadienes (19 and 28). A solution of 0.767 g (~1.67 mmol) of hydroxy selenide **27** and 0.338 g (3.34 mmol) of triethylamine in 8 mL of dichloromethane was cooled to 0 °C, and 0.21 g (1.84 mmol) of methanesulfonyl chloride was added over 5 min.[37] After 1 h at 0 °C the solution was transferred to a separatory funnel with the aid of more dichloromethane. The organic layer was washed with water, 10% hydrochloric acid, saturated sodium bicarbonate, and saturated sodium chloride. The solution was dried ($MgSO_4$), the solvent was evaporated, and the residue (0.728 g) was chromatographed on 85 g of silica gel. Elution with 5% ether in hexane gave 0.160 g (35% from **17d**) of a 60:40 mixture of the isomeric benzyl ethers **19** and **28**: IR (neat) 1725 (C=C), 1670 (C=C), 1070 (CO), 972 (trans C=C), 693 (cis C=C) cm^{-1}; ^1H NMR (CCl_4) δ 0.97 (s, ~3.6 H, $C(CH_3)_3$, trans isomer), 1.09 (s, ~5.4 H, $C(CH_3)_3$, cis isomer), 1.72 (br s, 3 H, $C=CCH_3$), 2.06 (m, 4 H, $C=CCH_2$), 3.88 (d, 2 H, J = 7 Hz, CH_2OCH_2Ph), 4.36 (s, 2 H, $PhCH_2O$), 5.11 (m, 3 H, C=CH), 7.16 (s, 5 H, Ar H).

(2*Z*,6*Z*)- and (2*Z*,6*E*)-3,8,8-Trimethyl-2,6-nonadien-1-ols (20 and 25). Lithium wire (0.023 g, 3.3 mmol; 0.6 cm) was added in approximately 2-mm pieces to 15 mL of ammonia, and the solution was allowed to reflux (−33 °C) for 20 min. After the solution was cooled to −78 °C, 0.099 g (0.4 mmol) of the preceding mixture of benzyl ethers (**19** and **28**) in 1 mL of tetrahydrofuran was added. The reaction was kept at −78 °C for 5 min and was allowed to warm to −33 °C. After 5 min at reflux the blue color was discharged by addition of solid ammonium chloride. Ether (15 mL) was added and the ammonia was allowed to evaporate.

(50) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647–50.

Water was added, and the mixture was extracted three times with ether. The combined extracts were washed with 10% hydrochloric acid, saturated sodium bicarbonate, and saturated sodium chloride. The solution was dried ($MgSO_4$), the solvent was evaporated, and the remaining 0.11 g of residue was applied to a column of 11 g of silica gel. Elution with 10% acetone in hexane gave 0.042 g (58%) of a 57:43 mixture of alcohols **20** and **25**. The isomer ratio was determined by GLC analysis on a 1.8 m × 0.3 cm column packed with 2% OV-17 on 80/100-mesh Chromosorb W-HP. With a temperature program running from 90 to 120 °C at 2 °C/min, the retention times of **20** and **25** were 13.5 and 15.3 min, respectively. The spectral properties of the mixture are as follows: IR (neat) 3300 (OH), 1720 and 1660 (C=C), 1000 (C=O), 972 (trans C=C), 723 and 698 (cis C=C) cm^{-1}; ^1H NMR (CCl_4) δ 0.97 (s, trans $C(CH_3)_3$), 1.09 (s, cis $C(CH_3)_3$), 1.27 (br s, 1 H, OH), 1.70 (br s, 3 H, $C=CCH_3$), 2.10 (m, 4 H, $C=CCH_2$), 3.94 (d, 2 H, J = 7 Hz, CH_2OH), 5.19 (m, 3 H, C=CH).

(*Z*)-2-[5-(Benzyloxy)-3-methyl-3-penten-1-yl]-3-hydroxy-4,4-dimethylpentanenitrile (29). A 3.51-mL aliquot of 1.14 M *n*-butyllithium (4.0 mmol) in hexane was added dropwise to a solution of 0.41 g (4.05 mmol) of diisopropylamine in 4 mL of tetrahydrofuran. The solution was allowed to stand for 30 min at room temperature under nitrogen and was then cooled to −78 °C. A solution of 0.458 g (2 mmol) of nitrile **17e** and 0.222 g (2.6 mmol) of pivaldehyde in 2 mL of tetrahydrofuran was added over 10 min.[51] The reaction mixture was stirred at −78 °C under nitrogen for 4.5 h, hydrolyzed by the addition of 3 mL of saturated ammonium chloride, and allowed to warm to room temperature. Water was added, and the product was extracted with three portions of ether. The ether solution was washed three times with 10% hydrochloric acid, three times with water, and once with saturated sodium chloride. After the ether solution was dried ($MgSO_4$) and the solvent removed, the residue (0.85 g) was purified by chromatography on 90 g of silica gel. Elution with 10% acetone in hexane afforded 0.482 g (76%) of cyanohydrin **29**: IR (neat) 3490 (OH), 2260 (CN), 1675 (C=C), 1070, 1060 (CO) cm^{-1}; ^1H NMR (CCl_4) δ 0.89 (s, 9 H, $C(CH_3)_3$), 1.61 (br s, 2 H, $CH(CN)CH_2$), 1.72 (s, 3 H, $C=CCH_3$), 2.18 (m, 2 H, $C=CCH_2$), 2.57 (m, 1 H, CHCN), 2.92 (m, 2 H, **CHOH**), 3.90 (d, 2 H, J = 7 Hz, CH_2OCH_2Ph), 4.38 (s, 2 H, $PhCH_2O$), 5.38 (t, 1 H, J = 7 Hz, C=CH), 7.12 (s, 5 H, Ar H).

Anal. Calcd for $C_{20}H_{29}NO_2$: C, 76.15; H, 9.27; N, 4.44. Found: C, 75.81; H, 9.33; H, 4.55.

(*Z*)-2-[5-(Benzyloxy)-3-methyl-3-penten-1-yl]-3-acetoxy-4,4-dimethylpentanenitrile (30). A solution of 2.10 g (6.6 mmol) of cyanohydrin **29** and 7 mL of acetic anhydride in 14 mL of dry pyridine was allowed to stand at room temperature under nitrogen for 48 h. After addition of 300 mL of water, the mixture was extracted three times with ether. The combined extracts were washed with saturated sodium bicarbonate, 10% hydrochloric acid, water, and saturated sodium chloride. The ethereal solution was dried ($MgSO_4$) and evaporated to yield 2.36 g (100%) of a 3:1 diastereomeric mixture of cyano acetates **30** which was chromatographically pure by TLC (10% acetone in benzene): IR (neat) 2230 (CN), 1730 (C=O), 1070 (ether CO), 1025 (acetate CO) cm^{-1}; ^1H NMR (CCl_4, major isomer) δ 0.9 (s, 9 H, $C(CH_3)_3$), 1.57 (br s, 2 H, $CH(CN)CH_2$), 1.69 (s, 3 H, $C=CCH_3$), 2.04 (s, 3 H, CH_3CO), 2.14 (m, 2 H, $C=CCH_2$), 2.70 (m, 1 H, CHCN), 3.89 (d, 2 H, J = 7 Hz, CH_2OCH_2Ph), 4.40 (s, 2 H, $PhCH_2O$), 4.51 (s, 1 H, CH_3CO_2CH), 5.42 (t, 1 H, J = 7 Hz, C=CH), 7.12 (s, 5 H, Ar H); ^1H NMR (CCl_4, minor isomer) δ 0.93 (s, 9 H, $C(CH_3)_3$), 4.36 (s, 2 H, $PhCH_2O$).

Anal. Calcd for $C_{22}H_{31}NO_3$: C, 73.92; H, 8.74; N, 3.92. Found: C, 73.73; H, 8.77; N, 4.08.

(*Z*)-3,8,8-Trimethyl-2-nonen-1-ol (31). Lithium wire (0.042 g, 6 mmol; 0.99 cm) was added in approximately 2-mm pieces to 25 mL of ammonia, and the solution was allowed to reflux for 1 h under nitrogen. A solution of 0.323 g (0.9 mmol) of cyano acetate **30** in 3 mL of ether was added over a 5-min period during which the blue color was discharged. An additional 0.042 g (6 mmol) of lithium wire was added, and the resulting blue solution was allowed to reflux for 20 min. *n*-Pentane (30 mL) and solid ammonium chloride were added. The ammonia was allowed to evaporate, water was added, and the mixture was extracted three times with pentane. The pentane solution was washed with 2 N sodium hydroxide, water, and saturated sodium chloride. After the solution was dried ($MgSO_4$), the solvent was removed under reduced pressure to give 0.147 g (88%) of alcohol **31** which was chromatographically pure by TLC (10% acetone in benzene): IR (neat) 3250 (OH), 1660 (C=C), 1000 (CO) cm^{-1}; ^1H NMR (CCl_4) δ 0.86 (s, 9 H, $C(CH_3)_3$), 1.21 (br s, 6 H, 3 CH_2), 1.68 (s, 3 H, $C=CCH_3$), 2.0 (m, 2 H, $C=CCH_2$), 2.46 (s, 1 H, OH), 3.94 (d, 2 H, J = 7 Hz, CH_2OH), 5.25 (t, 1 H, J = 6 Hz, C=CH); mass spectrum, m/e 184.1827 (M^+) (calcd for $C_{12}H_{24}O$, 184.1830).

(2*Z*,6*Z*,13*E*)-1-(Benzyloxy)-3,8,8,14,18-pentamethyl-11-methylene-2,6,13,17-nonadecatetraene (32a). A 0.227-mL aliquot of 2.2 M *n*-butyllithium (0.5 mmol) in hexane was added to a stirred slurry of 0.296 g (0.5 mmol) of phosphonium salt **17c** in 1.5 mL of tetrahydrofuran at room temperature under nitrogen. After 15 min, the mixture was cooled to −78 °C, and a solution of 0.0665 g (0.25 mmol) of aldehyde **12** in 0.5 mL tetrahydrofuran was added. The mixture was allowed to warm slowly to room temperature over a 6-h period. The reaction mixture was quenched with 3 mL of methanol, diluted with water, and extracted three times with hexane. The hexane solution was washed with saturated sodium chloride, dried ($MgSO_4$), and evaporated. The crude product (0.247 g) was purified by chromatography on 25 g of silica gel with 10% ether in hexane as eluent, affording 0.054 g (48%) of benzyl ether **32a**: IR (neat) 1670, 1640 (C=C), 1070 (C=O), 696 (cis C=C) cm^{-1}; ^1H NMR (CCl_4) δ 1.07 (s, 6 H, $C(CH_3)_2$), 1.56 (s, 6 H, $C=CCH_3$ at C-14 and C-18), 1.62 (s, 3 H, $C=CCH_3$ at C-18), 1.70 (s, 3 H, $C=CCH_3$ at C-3), 1.98 (m, 10 H, $C=CCH_2$), 2.59 (d, 2 H, J = 7 Hz, $C=CCH_2C=C$), 3.85 (d, 2 H, J = 6.5 Hz, CH_2O), 4.33 (s, 2 H, $PhCH_2O$), 4.57 (br s, 2 H, $C=CH_2$), 5.17 (m, 5 H, C=CH), 7.14 (s, 5 H, Ar H).

Anal. Calcd for $C_{32}H_{48}O$: C, 85.65; H, 10.78. Found: C, 85.41; H, 10.74.

(2*Z*,6*Z*,13*E*)-3,8,8,14,18-Pentamethyl-11-methylene-2,6,13,17-nonadecatetraen-1-ol (32b). Lithium wire (0.005 g, 0.74 mmol; 0.11 cm) was added in two pieces to 10 mL of liquid ammonia, and the mixture was allowed to reflux for 30 min under nitrogen. A solution of 0.05 g (0.11 mmol) of benzyl ether **32a** in 1 mL of dry tetrahydrofuran was added to the blue solution, and the solution was allowed to reflux for 20 min. Excess lithium was quenched by the addition of solid ammonium chloride, 14 mL of pentane was added, and the ammonia was allowed to evaporate. The residue was hydrolyzed with saturated ammonium chloride, and the aqueous mixture was extracted three times with pentane. The pentane solution was washed with saturated sodium bicarbonate and saturated sodium chloride, dried ($MgSO_4$), and evaporated. Purification of the remaining crude product (0.045 g) by chromatography on 4 g of silica gel with 10% acetone in hexane as eluent afforded 0.035 g (88%) of alcohol **32b**: IR (neat) 3279 (OH), 1748, 1678, 1653 (C=C), 1018 (CO), 888 ($C=CH_2$), 724 and 699 (cis C=C) cm^{-1}; 220-MHz ^1H NMR (CCl_4) δ 1.10 (s, 6 H, $C(CH_3)_2$), 1.48 (m, 2 H, CH_2 at C-9), 1.59 (s, 6 H, $C=CCH_3$ at C-14 and C-18), 1.66 (s, 3 H, $C=CCH_3$ at C-18), 1.73 (s, 3 H, $C=CCH_3$ at C-3), 2.01 (m, 9 H, $C=CCH_2$ and OH), 2.24 (t, 2 H, J = 6.6 Hz, $C=CCH_2$ at C-10), 2.65 (d, 2 H, J = 7.06 Hz, $C=CCH_2C=C$), 3.98 (d, 2 H, J = 6.93, CH_2OH), 4.63 (s, 2 H, $C=CH_2$), 5.14 (m, 4 H, C=CH), 5.38 (t, 1 H, J = 6.81 Hz, C=CH at C-2). The sensitivity and small amount of this substance precluded further purification to secure a more satisfactory elemental analysis.

Anal. Calcd for $C_{25}H_{42}O$: C, 83.73; H, 11.80. Found: C, 82.51; H, 11.67; and C, 83.80; H, 9.43.

(2*Z*,13*E*)-1-(Benzyloxy)-3,8,8,14,18-pentamethyl-11-methylene-2,13,17-nonadecatrien-7-ol. The preparation of Grignard reagent **21** from 2.76 g (115 mmol) of magnesium turnings, two 0.5-mL (5.8 mmol) aliquots of 1,2-dibromoethane, and 3.11 g (11 mmol) of bromide **17b** and its reaction with 0.872 g (3.3 mmol) of aldehyde **12** were carried out as described above for alcohol **22**. The product was isolated and purified in the same manner, affording 1.45 g (94%) of the alcohol named in the heading: IR (neat) 3450 (OH), 1680 and 1650 (C=C), 1060 (CO) cm^{-1}; ^1H NMR (CCl_4) δ 0.83 (s, 6 H, $C(CH_3)_2$), 1.30 (m, 7 H, three CH_2 and OH), 1.60 (s, 6 H, CH_3 at C-14 and C-18), 1.67 (s, 3 H, CH_3 at C-18), 1.74 (s, 3 H, CH_3 at C-3), 1.96 (m, 4 H, cis $C=CCH_2$ and $CH_2C=CH_2$), 2.03 (br s, 4 H, 2 $C=CCH_2$), 2.68 (d, 2 H, J

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= 7 Hz, C=CCH_2C=CH_2), 3.14 (m, 1 H, R_2C**H**OH), 3.91 (d, 2 H, J = 7 Hz, CH_2OCH_2Ph), 4.42 (s, 2 H, PhCH_2O), 4.66 (br s, 2 H, C=CH_2), 5.12 (m, 2 H, C=CH), 5.36 (t, 1 H, J = 7 Hz, C=C**H**CH_2O) 7.24 (s, 5 H, Ar H).

Anal. Calcd for $C_{32}H_{50}O_2$: C, 82.35; H, 10.80. Found: C, 82.15; H, 10.85.

(2*Z*,13*E*)-1-(Benzyloxy)-3,8,8,14,18-pentamethyl-11-methylene-2,13,17-nonadecatrien-7-one (33). A solution of 1.16 g (2.5 mmol) of the alcohol obtained from the preceding reaction in 3 mL of dichloromethane was oxidized with Collins reagent[23] by following the procedure given for alcohol 11 except that 2.99 g (29.9 mmol) of anhydrous chromium trioxide and 4.75 g (60 mmol) of dry pyridine in 80 mL of dry dichloromethane were used and the reaction was stirred for 8 h. The crude product (1.004 g) was purified by chromatography on 125 g of silica gel with 10% acetone in hexane as eluent to afford 0.565 g (49%) of ketone **33**: IR (neat) 1700 (C=O), 1640 (C=C), 1070 (CO) cm^{-1}; ^{1}H NMR (CCl_4) δ 1.06 (s, 6 H, C(CH_3)$_2$), 1.39 (m, 4 H, CH_2), 1.58 (s, 6 H, CH_3 at C-14 and C-18), 1.65 (s, 3 H, CH_3 at C-18), 1.73 (s, 3 H, CH_3 at C-3), 1.91 (m, 4 H, cis C=CCH_2 and C**H**$_2$C=CH_2), 2.00 (br s, 4 H, C=CCH_2), 2.30 (t, 2 H, J = 6 Hz, CH_2C=O), 2.64 (d, 2 H, J = 7 Hz, C=CCH_2C=C), 3.89 (d, 2 H, J = 6 Hz, CH_2O), 4.40 (s, 2 H, PhCH_2O), 4.63 (br s, 2 H, C=CH_2), 5.02 (m, 2 H, C=CH), 5.36 (t, 1 H, J = 7 Hz, C=C**H**CH_2O), 7.21 (s, 5 H, Ar H).

Anal. Calcd for $C_{32}H_{48}O_2$: C, 82.70; H, 10.41. Found: C, 82.29; H, 10.34.

(2*Z*,6*Z*,13*E*)-1-(Benzyloxy)-3,8,8,14,18-pentamethyl-11-methylene-2,6,13,17-nonadecatetraen-7-yl Diethyl Phosphate (34). A 0.42-mL aliquot of 1.07 M lithium diisopropylamide (0.45 mmol) in tetrahydrofuran, which had been freshly titrated against 0.0958 g (0.45 mmol) of diphenylacetic acid, was added to a solution of 0.1864 g (0.4 mmol) of ketone **33** in 5 mL of tetrahydrofuran at 0 °C under nitrogen. The solution was allowed to stand for 45 min at 0 °C, and 1.9 mL of hexamethylphosphoramide was added. After an additional 5 min, 0.078 g (0.45 mmol) of diethyl chlorophosphate was added, and the mixture was allowed to warm to room temperature and stirred for 4 h. The mixture was then diluted with 150 mL of saturated sodium bicarbonate solution and extracted three times with ether. The ether solution was washed with saturated ammonium chloride, water, and saturated sodium chloride. After the ether solution was dried ($MgSO_4$), the solvent was removed, and the crude product (0.223 g) was placed on a column of 25 g of silica gel. Elution with 25% ether in hexane gave 0.109 g (59%) of recovered ketone, and elution with ether gave 0.099 g (41%; 100% based on recovered **33**) of enol phosphate **34**: IR (neat) 1725, 1700, 1670, 1640 (C=C, C=CCO), 1265 (P=O), 1035 (CO), 980 (trans C=C), 890 (R_2C=CH_2), 698 (R_2C=CH), cm^{-1}; ^{1}H NMR (CCl_4) δ 1.06 (s, 6 H, C(CH_3)$_2$), 1.30 (m, 8 H, CH_2 and 2 OCH_2C**H**$_3$), 1.59 (s, 6 H, CH_3 at C-14 and C-18), 1.63 (s, 3 H, CH_3 at C-18), 1.73 (s, 3 H, CH_3 at C-3), 1.98 (br s, 4 H, C=CCH_2), 2.05 (m, 6 H, CH_2 at C-4, C-5, and C-10), 2.63 (d, 2 H, J = 7.2 Hz, C=CC**H**$_2$C=CH_2), 3.93 (d, 2 H, J = 6 Hz, CH_2O), 4.09 (q, 4 H, J = 7 Hz, 2 OC**H**$_2$CH_3), 4.40 (s, 2 H, PhCH_2O), 4.62 (br s, 2 H, C=CH_2), 4.78 (m, 1 H, P(O)C=CH), 5.06 (m, 2 H, vinyl H at C-13 and C-16), 5.33 (t, 1 H, J = 7 Hz, vinyl H at C-2), 7.20 (s, 5 H, Ar H).

(2*Z*,6*E*,13*E*)-3,8,8,14,18-Pentamethyl-11-methylene-2,6,13,17-nonadecatetraen-1-ol (Moenocinol, 1). A. By Reduction of Enol Phosphate 34. Lithium wire (0.012 g, 1.76 mmol; 0.288 cm) was added in two pieces to 30 mL of ammonia, and the mixture was allowed to reflux for 30 min. A solution containing 0.099 g (0.16 mmol) of enol phosphate **34** and 0.0352 g (0.48 mmol) of *tert*-butyl alcohol in 1 mL of tetrahydrofuran was added, and the blue color was discharged immediately. An additional 0.0128 g (1.76 mmol) of lithium wire was added to regenerate the blue color, and the solution was allowed to reflux for 40 min. The solution was cooled to −78 °C, the blue color was discharged by the addition of ammonium chloride, 30 mL of a 1:1 ether–hexane solution was added, and the ammonia was allowed to evaporate. A 300-mL portion of saturated ammonium chloride was added, and the product was extracted with three portions of 1:1 ether–hexane. The combined organic layers were washed with saturated sodium bicarbonate and saturated sodium chloride and dried ($MgSO_4$). After evaporation of solvent, the residue (0.0757 g) was purified by chromatography on 7.6 g of silica gel with 10% acetone in hexane as eluent to give 0.0253 g (44%) of synthetic moencinol (**1**): IR (neat) 3333 (OH), 1739–1639 (C=C), 1019 (CO), 973, 889, 801, 667 (C=CH) cm^{-1}; 220-MHz ^{1}H NMR (CCl_4) δ 0.96 (s, 6 H, C(CH_3)$_2$), 1.3 (m, 2 H, CH_2), 1.59 (s, 3 H, CH_3 at C-14 and C-18), 1.65 (s, 3 H, CH_3 at C-18), 1.72 (s, 3 H, CH_3 at C-3), 1.84 (t, ~1 H, J = 8.8 Hz, OH), 2.02 (m, 10 H, C=CCH_2), 2.64 (d, 2 H, J = 7.6 Hz, C=CCH_2C=C), 3.98 (d, 2 H, J = 6.9 Hz, C**H**$_2$OH), 4.61 (br s, 2 H, C=CH_2), 4.86–5.42 (br m, 5 H, C=CH); see Tables II and III for carbon-13 NMR data.

B. By Hydrolysis of Moenomycin. A suspension of 1 g of moenomycin[52] in 10 mL of 2 N hydrochloric acid was heated in an oil bath at 100–105 °C for 15 min (maximum internal temperature was 91 °C).[5] The mixture was diluted with 100 mL of water, extracted two times with ether, and dried (Na_2SO_4 plus $NaHCO_3$). The solvent was removed under reduced pressure, and the remaining brown lipid fraction (0.27 g) was preadsorbed on 2 g of silica gel. The resulting brown powder was placed on a column of 30 g of silica gel and eluted with benzene-methanol (40:1), collecting 10-mL fractions. Fractions containing a mixture of moenocinol and isomoenocinol were combined and rechromatographed on 10 g of silica gel with 10% acetone in hexane as eluent to give 0.0166 g of moenocinol (**1**). The IR and (^{1}H and ^{13}C) NMR spectra are identical with those of synthetic moenocinol as discussed in detail in the text. The TLC mobilities of synthetic and natural moenocinol on silica gel were coincident with both 9:1 hexane–acetone, R_f 0.28, and 40:1 benzene–methanol, R_f 0.09, as developing solvents.

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Registry No. **1**, 19953-93-6; **2**, 50592-83-1; **3**, 73454-31-6; **4**, 73454-32-7; **5**, 73454-33-8; **6**, 73454-34-9; **7**, 73454-35-0; **7** methyl ester, 73454-36-1; **8a**, 73454-37-2; **8b**, 73466-67-8; **9b**, 73454-38-3; **10a**, 73454-39-4; **10b**, 73454-40-7; **11**, 73454-41-8; **12**, 73454-42-9; **13**, 106-25-2; **14**, 55802-98-7; **15**, 73454-43-0; **16**, 73454-44-1; **17a**, 73454-45-2; **17b**, 73454-46-3; **17c**, 73454-47-4; **17d**, 73454-48-5; **17e**, 73454-49-6; **18**, 73454-50-9; **19**, 73454-51-0; **20**, 73454-52-1; **22**, 73454-53-2; **23**, 73454-54-3; **24**, 73454-55-4; **25**, 73454-56-5; **26**, 73454-57-6; **27**, 73454-58-7; **28**, 73454-59-8; **29**, isomer 1, 73454-60-1; **29**, isomer 2, 73454-61-2; **30**, isomer 1, 73454-62-3; **30**, isomer 2, 73454-63-4; **31**, 73454-64-5; **32a**, 73454-65-6; **32b**, 73454-66-7; **33**, 73454-67-8; **34**, 73454-68-9; diphenyl disulfide, 882-33-7; geranyl bromide, 6138-90-5; geraniol, 106-24-1; (*Z*)-6-(benzyloxy)-4-methyl-4-hexenal, 55802-99-8; diphenyl diselenide, 1666-13-3; pivaldehyde, 630-19-3; phenyllithium, 591-51-5; diethyl chlorophosphate, 814-49-3; (2*Z*,13*E*)-1-(benzyloxy)-3,8,8,14,18-pentamethyl-11-methylene-2,13,17-nonadecatrien-7-ol, 73454-69-0; moenomycin, 11015-37-5.

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