# Synthesis of Chlorobiumquinone[1]

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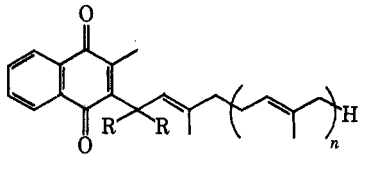
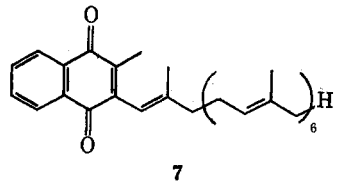
The synthesis of chlorobiumquinone, *all-trans*-1′-oxomenaquinone-7, is reported. A key intermediate in this synthesis is the naphthalenic fragment, 2-lithio-3-methyl-1,4-dimethoxynaphthalene, which when condensed with an $\alpha,\beta$-unsaturated aldehyde side-chain component yields the dimethyl ether of 1′-oxymenaquinol. This allylic alcohol can either be oxidatively demethylated with acidic argentic oxide (AgO), leading to a 1′-oxymenaquinone, or oxidized first at the 1′ position with manganese dioxide and then demethylated to give a 1′-oxomenaquinone. In order to construct the all-trans $C_{35}$ $\alpha,\beta$-unsaturated aldehyde required for chlorobiumquinone synthesis, *all-trans*-farnesylfarnesylacetone ($C_{33}$) was assembled from geranylacetone ($C_{13}$) and the masked-functional ylide of triphenyl (4-methyl-8,8-ethylenedioxy-4-*trans*-nonenyl)phosphonium iodide as the $C_{10}$ repeating unit. The first condensation gave geranylgeranylacetone ($C_{23}$) after hydrolysis of the ethylene ketal, and repetition of reaction with the masked-functional $C_{10}$ ylide and hydrolysis gave farnesylfarnesylacetone ($C_{33}$). $\Delta^9$-Cis,trans separation was effected by thiourea inclusion after each condensation. The other double bonds in the $C_{33}$ unit are trans by virtue of their origin in geraniol. The masked-functional $\Delta^9$-trans $C_{10}$ phosphonium salt was prepared most efficiently by removing three carbons from the ethylene ketal of geranylacetone *via* terminal epoxidation, $\Delta^9$-oxidative cleavage, and terminal modification to the required iodide. Condensation of triethyl phosphonoacetate with the all-trans $C_{33}$ ketone followed by aluminum hydride reduction and manganese dioxide oxidation then effected a two-carbon extension to yield the necessary $C_{35}$ side-chain aldehyde.

The quinones of the anaerobic photosynthetic bacterium, *Chlorobium thiosulfatophilum*, are unique in that the usual phytobacterial quinones, plastoquinone and ubiquinone, are supplanted by a family of menaquinones: menaquinone-7 (**1**), 1′-oxymenaquinone-7 (**3**), and 1′-oxomenaquinone-7 (**5**).[3] The last quinone, which is apparently specifically associated with sulfide metabolism,[3b] was named chlorobiumquinone upon its initial isolation. At that time, the $C_{45}H_{62}O_2$ structure **7**, lacking the first methylene of the normal isoprenoid side chain, was assigned.[4] Subsequently a mass spectrum of chlorobiumquinone was obtained in which a molecular ion at *m/e* 662 revealed the necessity of insertion of a CO unit into the proposed structure **7**. Similar observations by other investigators led to suggestion of the 1′-oxomenaquinone-7 structure (**5**) for chlorobiumquinone.[3a] The vinyl quinone structure was conclusively eliminated by synthesis of **7** which, although deceptively similar to chlorobiumquinone in uv, ir, and nmr spectra, was obviously dissimilar when compared chromatographically or by mass spectrometry.[5] To confirm the 1′-oxomenaquinone-7 structure for chlorobiumquinone its synthesis was therefore undertaken and is now reported in detail. A preliminary communication of this work has appeared.[5]



**1**, $n = 6$; R, R = H, H
**2**, $n = 1$; R, R = H, H
**3**, $n = 6$; R, R = H, OH
**4**, $n = 1$; R, R = H, OH
**5**, $n = 6$; R, R = =O
**6**, $n = 1$; R, R = =O



**7**

Of the various approaches to the synthesis of chlorobiumquinone which one can envisage, several of the more promising were tested in model studies using $C_5$ or $C_{10}$ side chains to simplify the analysis. In theory, the most direct approach to a 1′-oxomenaquinone would be selective oxidation at C-1′ of the corresponding menaquinone, since many menaquinones are naturally available. The biosynthetic analogy in this approach is obvious and somewhat justified in view of the augmented yields of chlorobiumquinone obtained from an oxidative (acetone–aqueous potassium ferricyanide) extraction of the bacteria[4] and the observation of 1′-oxomenaquinone formation from 1′-oxymenaquinone *in vitro*.[3b]

Menaquinone-7 itself, however, proved stable to mild oxidants such as potassium ferricyanide. Since alkyl groups on quinones are resistant to oxidation, the quinone nucleus usually suffering oxidation first, more drastic oxidation can only proceed on a suitably protected hydroquinone; however, such a procedure raises the question of subsequent removal of the protecting groups. Complete aromatization of the nucleus would also have the effect of activating the 1′ position to oxidative attack, since it would become both benzylic and allylic, although considerable activation is necessary for favorable competition with the other less hindered benzylic position (2-methyl) as well as the allylic methyls and methylenes of the side chain.

A recently investigated oxidant, AgO, was particularly attractive in that under mildly acidic conditions various substituted toluenes can be oxidized to the corresponding aldehydes with improvement in yield if an activating group is ortho or para to the site of oxidation.[6] When this oxidant was applied to the dimethyl ether of menaquinol-1 (**8**), a relevant model for our studies, the anticipated mode of oxidation was not

(1) This research was supported in part by Grants AI-04888 and AM-13688 from the National Institutes of Health, U. S. Public Health Service.

(2) National Institutes of Health Predoctoral Fellow.

(3) (a) R. Powls, E. Redfearn, and S. Trippett, *Biochem. Biophys. Res. Commun.*, **33**, 408 (1968); (b) R. Powls and E. R. Redfearn, *Biochim. Biophys. Acta*, **172**, 429 (1969).

(4) B. Frydman and H. Rapoport, *J. Amer. Chem. Soc.*, **85**, 823 (1963).

(5) W. E. Bondinell, C. D. Snyder, and H. Rapoport, *ibid.*, **91**, 6889 (1969).

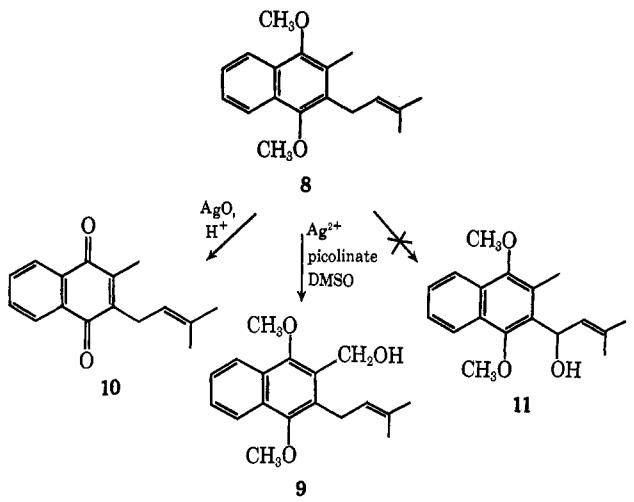
(6) L. Syper, *Tetrahedron Lett.*, 4193 (1967).

observed and, somewhat surprisingly, menaquinone-1 was the only product obtained. This previously unobserved oxidative demethylation reaction, which we will consider in detail in a future publication, has considerable import for quinone chemistry in that it allows protection as the hydroquinone methyl ethers. These groups are particularly stable to strongly anionic conditions and can then be removed by mild, selective oxidation. In fact, the further studies reported herein will make exclusive use of this protection–deprotection scheme.

Since acidic $Ag^{2+}$ effected only demethylation, a nonacidic species, $Ag^{2+}$ picolinate in DMSO, was then applied to **8** and an alcohol was obtained in 25% yield. Unfortunately, as confirmed by nmr and mass spectral analyses, oxidation occurred exclusively at the 2-methyl group, yielding benzyl alcohol **9**. Thus, at least chemically, selective oxidation is not a feasible method for 1′-oxomenaquinone synthesis (Scheme I).

SCHEME I

OXIDATION OF 8 WITH $Ag^{2+}$ SPECIES



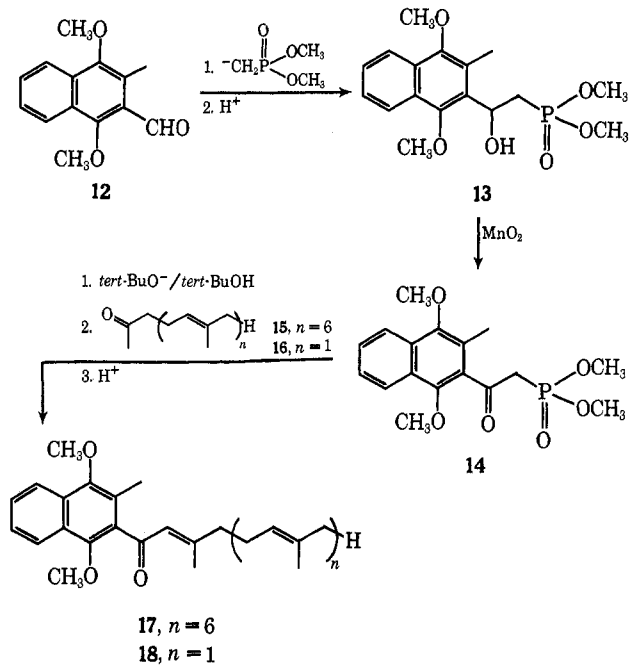

Chlorobiumquinone synthesis by bond formation at the $\Delta^{2'}$ position appears attractive especially if one considers reaction between β-ketophosphonate **14** and farnesylfarnesylacetone (**15**) in which the advantage is that the two carbon atoms necessary for completion of a $C_{35}$ side chain are added to the naphthalenic nucleus rather than to the more valuable $C_{33}$ side-chain component (Scheme II).

The required β-ketophosphonate **14** was derived in 75% yield from manganese dioxide oxidation of the corresponding β-hydroxyphosphonate **13**, which in turn was obtained (85% yield) by attack of the anion of methylphosphonic acid dimethyl ester[7] upon 2-methyl-3-formyl-1,4-dimethoxynaphthalene (**12**). Generation of **14** directly in the correct oxidation state by reaction with 2-methoxycarbonyl-3-methyl-1,4-dimethoxynaphthalene proved impossible because of hindrance about the ester. Formation of the anion of **14**, required for a Horner-type reaction, was then accomplished with potassium *tert*-butoxide in *tert*-butyl alcohol. However, reaction in the presence of 1 equiv of the $C_8$ ketone **16** for 1 week at 110° (conditions required for complete consumption of ketone) resulted in

(7) E. J. Corey and G. I. Kwiatkowski, *J. Amer. Chem. Soc.*, **88**, 5656 (1966), and references cited therein.

SCHEME II

PHOSPHONATE APPROACH TO SYNTHESIS OF 5



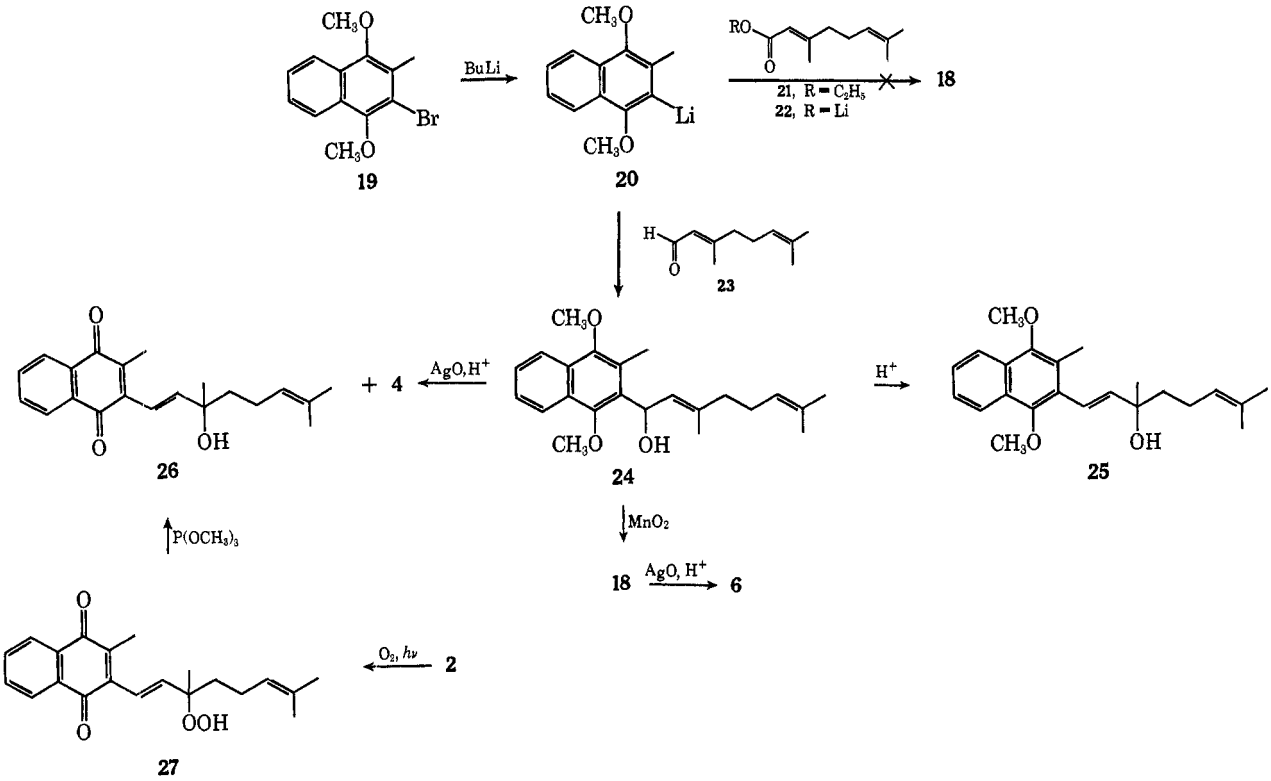

only a 7% yield of 1′-oxomenaquinol-2 dimethyl ether (**18**). Steric factors are obviously contributing to the low yield, and since the reaction with several other base–solvent systems gave even lower yields, the method was rejected as a resonable approach to chlorobiumquinone synthesis. This failure is interesting in that it demonstrates a limiting condition under which a β-ketophosphonate–ketone condensation can be considered useful.

The remaining approaches to 1′-oxomenaquinone synthesis involve addition of the side chain as a $C_{35}$ unit. Acid-catalyzed electrophilic substitution of an α,β-unsaturated acyl chloride or an α,β-unsaturated aldehyde into the aromatic nucleus cannot reasonably be considered because of the inevitable simultaneous acid-catalyzed cyclizations of the polyunsaturated side chain. On the other hand, the anionic stability of the hydroquinone dimethyl ether suggested an alternative approach in which the organometallic nucleus, 2-lithio-3-methyl-1,4-dimethoxynaphthalene (**20**), could be condensed with a side-chain fragment leading directly or indirectly to the desired product. Reaction leading to product in the correct oxidation state, *i.e.*, by condensation with an α,β-unsaturated carboxylic acid derivative, is obviously preferable in that a step is saved, but condensation with an aldehyde fragment also is feasible since the resulting 1′-oxymenaquinol derivative should be easily oxidizable.

Formation of the desired lithio derivative **20** was first attempted by direct exchange of 2-methyl-1,4-dimethoxynaphthalene and butyllithium, but this was unsuccessful since quenching with $D_2O$ gave no isotope incorporation. The alternative approach of transmetalation with 2-bromo-3-methyl-1,4-dimethoxynaphthalene (**19**) and butyllithium was employed. In order to test the reactivity of **20** with variously functionalized side-chain fragments, the ten-carbon α,β-unsaturated ester **21** was first conveniently synthesized by condensation of triethyl phosphonoacetate with 6-

SCHEME III

MODEL STUDIES LEADING TO 1′-OXOMENAQUINONE SYNTHESIS *via* 2-LITHIO-3-METHYL-1,4-DIMETHOXYNAPHTHALENE (20)




methyl-5-hepten-2-one (**16**). Reaction of the lithio reagent **20** with ester **21** yielded only a trace of condensation product; mostly recovered starting ester and 2-methyl-1,4-dimethoxynaphthalene were isolated. Extension of the reaction time did not lead to any improvement in yield, so that one can only assume that most of the lithio reagent **20** had been consumed by enolizable proton abstraction from the ester. Ester **21** was next hydrolyzed and the lithium salt of the corresponding acid **22** was obtained; again attack of **20** upon this salt did not occur. The next logical step would have been to utilize the acid chloride derived from **22** in which reactivity should have been sufficient. In anticipation of difficulties involved in preparing the long-chain, acid-sensitive fragment necessary for chlorobiumquinone, this approach was avoided and the similarly reactive $\alpha,\beta$-unsaturated aldehyde **23** was tested instead.

As expected, citral (**23**) and 2-lithio-3-methyl-1,4-dimethoxynaphthalene (**20**) reacted immediately at room temperature to give allylic alcohol **24**, which was subjected to manganese dioxide oxidation to obtain the dimethyl ether of 1′-oxomenaquinol-2 (**18**) in 60% yield from citral (Scheme III). The resulting $\Delta^{2'}$ cis–trans mixture (cis:trans = 3:7) was easily separable by column chromatography on kieselgel, the cis isomer being eluted first. Vinyl methyl absorption in the trans isomer, located at $\delta$ 2.30 (d, $J$ = 1 Hz), is distinctly separated from the corresponding methyl signal in the cis isomer, upfield at $\delta$ 1.92 (d, $J$ = 1 Hz), as expected from the deshielding effect exerted by a carbonyl on a cisoid methyl group.

Conversion of hydroquinone dimethyl ether **18** to 1′-oxomenaquinone-2 (**6**) with acidic AgO led in about 50% yield to products which for the most part retained the stereochemistry about the $\Delta^{2'}$ position. Again the vinyl methyl signals were diagnostic: vinyl methyl absorption in the trans isomer at $\delta$ 2.24 (d, $J$ = 1 Hz) and in the cis isomer at $\delta$ 1.93 (d, $J$ = 1 Hz). As estimated by integration the trans isomer was contaminated with about 5% of the cis form whereas the cis isomer contained 15% trans. Cis–trans isomerization in this quinone series could be expected under mild conditions, especially in view of the lability of the $\Delta^{2'}$ position of menaquinone to isomerization even where conjugation to the chromophore is not involved.[8] As expected the uv spectra of the two quinones are almost superimposable [cis, $\lambda_{max}$ 251 nm ($\epsilon$ 29,200), 265 sh (22,500), 325 (3600), and trans, $\lambda_{max}$ 250 nm ($\epsilon$ 33,200), 265 sh (23,000), 325 (3800)].

If prior to $MnO_2$ oxidation the dimethyl ether of 1′-oxymenaquinol-2 (**24**) is subjected to AgO oxidative demethylation a mixture of two quinone alcohols is obtained without concomitant oxidation at C-1′. Isolated from the reaction in 26% yield, 1′-oxymenaquinone-2 (**4**) was resolved into its $\Delta^{2'}$ cis–trans components (cis:trans = 3:7) by tlc on kieselgel. These isomers were also distinguishable in their nmr spectra, with the vinyl methyl absorption of the cis isomer at $\delta$ 2.04 falling slightly downfield from the trans absorption at $\delta$ 2.00.

The uv spectrum of 1′-oxymenaquinone-2 (**4**) is qualitatively and quantitatively identical with the rather unique spectrum reported for 1′-oxymenaquinone-7 (**3**)[3b] in which the characteristic four-fingered absorption pattern of menaquinone is distorted by diminution of the conjugated quinone bands at 258 and 265 nm. Intramolecular hydrogen bonding, which might cause

(8) S. J. DiMari and H. Rapoport, *Biochemistry*, **7**, 2650 (1968).

such an effect, cannot be deduced from an ir comparison of 1′-oxymenaquinone-2 (**4**) and menaquinone-2 (**2**) since the two quinone carbonyls absorb identically at 1610 $cm^{-1}$. Unfortunately, 1′-oxymenaquinone-7 as isolated from the Chlorobacteria was characterized only by its tlc and uv properties, but comparison with the simpler isoprenolog, 1′-oxymenaquinone-2 (**4**), shows complete coincidence of properties, thus providing strong confirmatory evidence for the structure assigned this polar quinone.

In addition to 1′-oxymenaquinone-2 (**4**), another deep yellow, more polar ($R_f$ 0.36) quinone was obtained from the above reaction in 34% yield. That this was the allylically rearranged trans quinone **26** was suggested by the uv similarity to other vinylnaphthoquinones [$\lambda_{max}$ 250, 280 (sh), and 330 nm] and a low field vinyl hydrogen ($\Delta^{1'}$) singlet at $\delta$ 6.53 which is characteristic of this series.[9] Spectrometric comparison with authentic material obtained *via* reduction of the corresponding photohydroperoxide **27** conclusively established its identity.

A question remaining is at what stage in the AgO oxidation reaction did allylic rearrangement take place; *i.e.*, is the starting alcohol **24** rearranged with this equilibrium perpetrated upon oxidation, is the quinone product rearranged, or are both compounds liable to rearrangement? To test these possibilities the product quinones **4** and **26** were subjected separately to the oxidation conditions and after a 5-min exposure were recovered unchanged as assayed by tlc, establishing that within the time period of the reaction the quinones are completely stable to rearrangement. On the other hand, **24**, when subjected to the acidic solvent conditions minus AgO, was converted quantitatively into a new alcohol which by tlc was slightly more polar and more strongly uv absorbing than starting **24**. Nmr analysis confirmed that, as expected, the rearranged trans allylic alcohol **25** had been obtained. Evidence was a low-field vinyl AB quartet ($\delta$ 6.20 and 6.67, $J_{AB}$ = 16 Hz) as well as a shift of the 3′-methyl absorption upfield to $\delta$ 1.38 (s) consistent with double bond migration. The strong uv absorption at 250 nm ($\epsilon$ 42,800) is also expected for the vinylnaphthalene chromophore.

This rearrangement was quantitative in less than a minute and the product quinones are stable to rearrangement; therefore, the fact that both rearranged and unrearranged quinone alcohols are obtained from the oxidation reaction can only reflect a rate competition between oxidation and rearrangement. Fortunately, the rates are close enough to allow isolation of both quinones and, although not investigated, factors such as acidity could probably be varied to obtain a product ratio favoring either isomer.

Since the model studies reported herein and as summarized in Scheme III provided a procedure for chlorobiumquinone synthesis, construction of the side chain was next undertaken.

**Synthesis of the Side Chain.**—Most syntheses of head-to-tail polyprenyl compounds proceed by repetition of a series of reactions which add one prenyl unit at a time to the growing chain. Some require separation of cis and trans isomers after each double bond is introduced to obtain all-trans geometry in the final product,[10a-d] while others are highly stereoselective and yield products with >90% trans content.[10e-n] We wished to proceed in a manner whereby head-to-tail polyprenyl compounds could be rapidly assembled from a few appropriately functionalized multiprenyl units. The Wittig reaction between multiprenyl ketones, *e.g.*, geranylacetone (**29**) and the masked functional ylide **40**, seemed the most promising approach for rapid assembly of such long-chain polyprenyl compounds, specifically ketones.[10o] This approach had been previously applied but the reactants, themselves prepared *via* the Wittig reaction, were mixtures of cis and trans isomers leading to products which contained only very small amounts of all-trans isomers.[10c]

To overcome these drawbacks, we planned our synthesis around the trans double bond of geraniol, which would remain intact throughout the chain assembly. Since a $C_{33}$ ketone (**15**) was required initially, it was to be constituted from a $C_{13}$ ketone and a $C_{10}$ repeating unit, used twice. The $C_{13}$ ketone was geranylacetone (**29**), in which the double bond is trans because of its origin from geraniol. The $C_{10}$ repeating unit was to be derived from geranylacetone by masking the ketone, cleaving at the terminal double bond, and converting the new terminus to halide and then phosphonium salt. Thus the desired $C_{10}$ unit would be available for Wittig reaction at one end and subsequent unmasking of the ketone function at the other, with its double bond trans and unaffected by the transformations.

By this plan, three of the five double bonds with stereochemistry in the final $C_{33}$ ketone would be fixed as trans; the other two would be formed as cis–trans mixtures. Two separations would be necessary, and they should be easily effected by thiourea inclusion, since the $C_{23}$ and $C_{33}$ all-trans isomers have sufficient length to form stable complexes. On the other hand, complete rejection of the cis isomers should occur, since the cis double bond is situated well enough within the chain to result in a folded molecule.

Geranylacetone (**29**) was prepared as reported[11] from pure geraniol (**28**) (*ca.* 100% trans)[12] and was converted to the ethylene ketal **30** with ethylene glycol and *p*-toluenesulfonic acid in benzene. Ozonolysis of this ketal with 1 equiv of ozone either in methanol at −78° or in pentane (in the hope that monozonides

(9) (a) W. E. Bondinell, S. J. DiMari, B. Frydman, K. Matsumoto, and H. Rapoport, *J. Org. Chem.*, **33**, 4351 (1968); (b) C. D. Snyder and H. Rapoport, *J. Amer. Chem. Soc.*, **91**, 731 (1969).

(10) (a) A. Langemann and O. Isler, "Biochemistry of Quinones," R. A. Morton, Ed., Academic Press, New York, N. Y., Chapter 4; (b) J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, *J. Chem. Soc.*, 2539 (1959); (c) G. I. Samokhalov and E. A. Obol'nikova, *Usp. Khim.*, **36**, 413 (1967); (d) M. Julia, S. Julia, and R. Guegan, *Bull. Soc. Chim. Fr.*, 1072 (1960); (e) E. J. Corey, J. A. Katzenellenbogen, and G. H. Posner, *J. Amer. Chem. Soc.*, **89**, 4245 (1967); (f) R. Zurfluh, E. N. Wall, J. B. Siddall, and J. A. Edwards, *ibid.*, **90**, 6224 (1968); (g) S. F. Brady, M. A. Ilton, and W. S. Johnson, *ibid.*, **90**, 2882 (1968); (h) E. J. Corey and J. A. Katzenellenbogen, *ibid.*, **91**, 1851 (1969); (i) E. J. Corey, H. Yamamoto, D. K. Herron, and K. Achiwa, *ibid.*, **92**, 6635 (1970); (j) W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brockson, T. Li, D. J. Faulkner, and M. R. Peterson, *ibid.*, **92**, 741 (1970); (k) D. J. Faulkner and M. R. Peterson, *Tetrahedron Lett.*, 3243 (1969); (l) R. J. Anderson, C. A. Henrick, and J. B. Siddall, *J. Amer. Chem. Soc.*, **92**, 735 (1970); (m) E. E. van Tamelen and J. P. McCormick, *ibid.*, **92**, 737 (1970); (n) B. M. Trost, *Accounts Chem. Res.*, **3**, 120 (1970). (o) For examples of procedures joining multiprenyl units in a head-to-head fashion, see J. F. Biellman and J. B. Ducep, *Tetrahedron Lett.*, 3707 (1969); E. H. Axelrod, G. M. Milne, and E. E. van Tamelen, *J. Amer. Chem. Soc.*, **92**, 2139 (1970); L. Werthemann and W. S. Johnson, *Proc. Nat. Acad. Sci. U. S.*, **67**, 1465 (1970).

(11) O. Isler, R. Ruegg, L. Chopard-dit-Jean, H. Wagner, and K. Bernhard, *Helv. Chim. Acta*, **39**, 897 (1956).

(12) A generous gift of Givaudan Corp.

would precipitate),[13] followed by reductive isolation using sodium borohydride,[14] gave 9-hydroxy-6-methyl-5-*trans*-nonen-2-one ethylene ketal (**36**). The ozonolysis was not selective[15] and 1,4-dihydroxypentane, 2-hydroxy-6-methyl-5-heptene, and 5-hydroxy-2-pentanone ethylene ketal were also formed, decreasing the yield of desired ketal **36** to 20–33% in this one-step process.

Alternatively, **36** was obtained from geranylacetone (**30**) in seven steps and 45% overall yield, selective epoxidation[16] of the terminal double bond being achieved initially *via* reaction with *N*-bromosuccinimide to the bromohydrin **31** followed by alkali to form the terminal epoxide **32**. The terminal epoxide structure for **32** was established by its nmr absorption which showed two methyls on an epoxide ring at $\delta$ 1.20 and 1.23, one vinyl methyl on a trans double bond at $\delta$ 1.64, and one $\alpha$-epoxy proton at $\delta$ 2.62.[17,18]

In order to convert epoxide **32** to cleaved alcohol **36**, it was necessary to open the oxide ring to the glycol while leaving the ketal intact. For this reason, alkaline reagents.[19] were tried first, but glycol formation was slow and incomplete. Glacial acetic acid buffered with sodium acetate[20] hydrolyzed both epoxide and ketal; however, addition of acetic anhydride repressed ketal hydrolysis and the glycol monoacetate **33** was isolated in 77% yield. Its structure was established as the C-9 acetate by absorption at $\delta$ 1.18 for the gem-dimethyl and $\delta$ 4.8 for the acetoxy proton in the nmr. Treatment with methanolic potassium hydroxide gave the glycol **34** in which the C-9 proton absorption had shifted to $\delta$ 3.3. Oxidation with periodate than gave aldehyde **35**, and this was reduced with borohydride to alcohol–ketal **36**. the last three steps all proceeding in excellent yields.

To prepare the ketal phosphonium salt **39**, the alcohol was converted to iodide **38** *via* the tosylate **37**, and this was heated with triphenylphosphine to yield the semisolid phosphonium salt **39**. Attempts at crystallization from a number of solvents failed; acetone–benzene[10c] did yield crystalline material, but this had lost its ethylene ketal and was characterized as the ketophosphonium salt. Therefore the noncrystalline ketal-phosphonium salt **39**, which showed the requisite nmr absorption, was converted directly to the masked-functional ylide **40** in dimethyl sulfoxide using butyllithium.

Reaction of masked-functional ylide **40** with geranylacetone (**29**) followed by chromatography and molecular distillation gave some recovered **29** and an 88% yield of geranylgeranylacetone ethylene ketal (**41**) as a 3:2 cis–trans mixture at $\Delta^9$ as indicated by glpc. No attempt was made to alter the isomer distribution in the Wittig reaction, and the isomers were separated by thiourea inclusion of the all-trans ketal from saturated methanolic thiourea, since this isomer now just exceeds the minimum length required for formation of a stable inclusion complex.[21] Configurational assignments made on the basis of this method of separation were confirmed by comparison of the nmr absorptions due to methyl groups on cis and trans double bonds at $\delta$ 1.66 and 1.60.[22] Deketalization with aqueous phosphoric acid in refluxing acetone gave *all-trans*-geranylgeranylacetone (**42**).

Repetition of this process, now using the ylide **40** and *all-trans*-geranylgeranylacetone (**42**) gave a 70% yield of farnesylfarnesylacetone ethylene ketal (**43**), again as a 3:2 cis–trans mixture at $\Delta^9$. Separation of isomers and deketalization as previously led to *all-trans* farnesylfarnesylacetone (**15**), consistent with nmr, ir, and mass spectral data and homogeneous by tlc and glpc. This method for constructing long trans polyprenyl chains appears quite general and convenient; *e.g.*, a similar all-trans $C_{15}$ masked-functional ylide unit could be prepared from farnesylacetone.

*all-trans*-Farnesylfarnesylacetone (**15**) was next condensed with the anion derived from triethyl phosphonoacetate to yield almost quantitatively the $C_{35}$ ester **44**. Without further purification, this ester was subjected to lithium aluminum hydride reduction in the presence of aluminum chloride, giving $C_{35}$ allylic alcohol **45** in 90% yield, which was directly oxidized with manganese dioxide to the $C_{35}$ $\alpha,\beta$-unsaturated aldehyde **46**. Purification by chromatography at this stage was particularly convenient and effective, giving **46** in 50% overall yield from **15**. A cis:trans ratio of 1:3 about the $\Delta^2$ double bond was demonstrated in the nmr by separate aldehyde hydrogen absorptions at $\delta$ 9.85 (cis) and 9.90 (trans) (d, $J$ = 8 Hz), and the 3-methyl absorption of the trans isomer at 2.13. These reactions leading to the synthesis of **46** are given in Scheme IV.

**Synthesis of Chlorobiumquinone.**—The next steps in chlorobiumquinone synthesis were performed exactly as in the model studies. Condensation of the side-chain aldehyde **46** with 2-lithio-3-methyl-1,4-dimethoxynaphthalene (**20**) proceeded quantitatively and the resulting allylic alcohol was immediately oxidized with manganese dioxide to give the dimethyl ether of 1′-oxomenaquinol-7 (**17**) in 60% yield from **46**. Separation of $\Delta^2$ cis–trans isomers by chromatography was facile, the vinyl methyl (C-3′) absorption of the trans isomer being a diagnostic doublet ($J$ = 1 Hz) at $\delta$ 2.20 while the corresponding signal of the cis isomer was

(13) J. A. Sousa and A. L. Bluhm, *J. Org. Chem.*, **25**, 108 (1960).

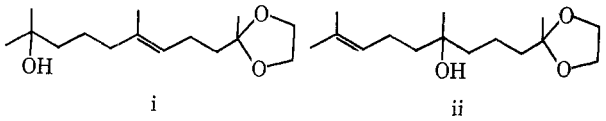
(14) C. G. Overberger and H. Kaye, *J. Amer. Chem. Soc.*, **89**, 5640 (1967).

(15) Compare the selective ozonolysis of geranyl acetate reported by (a) G. Stork, M. Gregson and P. A. Grieco, *Tetrahedron Lett.*, 1391 (1969), and (b) E. J. Corey, K. Achiwa and J. A. Katzenellenbogen, *J. Amer. Chem. Soc.*, **91**, 4318 (1969).

(16) E. E. van Tamelen and T. J. Curphey, *Tetrahedron Lett.*, 121 (1962); E. E. van Tamelen and K. B. Sharpless, *ibid.*, 2655 (1967). The conditions reported to selectively epoxidize the terminal double bond of geranyl acetate [M. Mousseron-Canet, M. Mousseron, and C. Levallois, *Bull. Soc. Chim. Fr.*, 297 (1964)] were not selective when applied to geranylacetone ethylene ketal.

(17) K. H. Dahm, B. M. Trost, and H. Roller, *J. Amer. Chem. Soc.*, **89**, 5292 (1967).

(18) The homogeneity of **32** was confirmed by reduction to i with lithium aluminum hydride in tetrahydrofuran [H. C. Brown, P. M. Weissman, and N. M. Yoon, *J. Amer. Chem. Soc.*, **88**, 1458 (1966)] and glpc of the trimethylsilyl ether. Comparison mixtures of i and ii were prepared by reduction of the monoepoxides obtained by *m*-chloroperbenzoic and peracetic acid oxidation (3:2) and by oxymercuration (9:1) of **30** followed by sodium borohydride reduction [H. C. Brown and P. Geoghegan, Jr., *ibid.*, **89**, 1522 (1967)]: $R_T$ (as the trimethylsilyl ethers) for i, 18 min, and for ii, 20 min, column a (see ref 23); mass spectra (70 eV) *m/e* 328 ($M^+$).




i ii

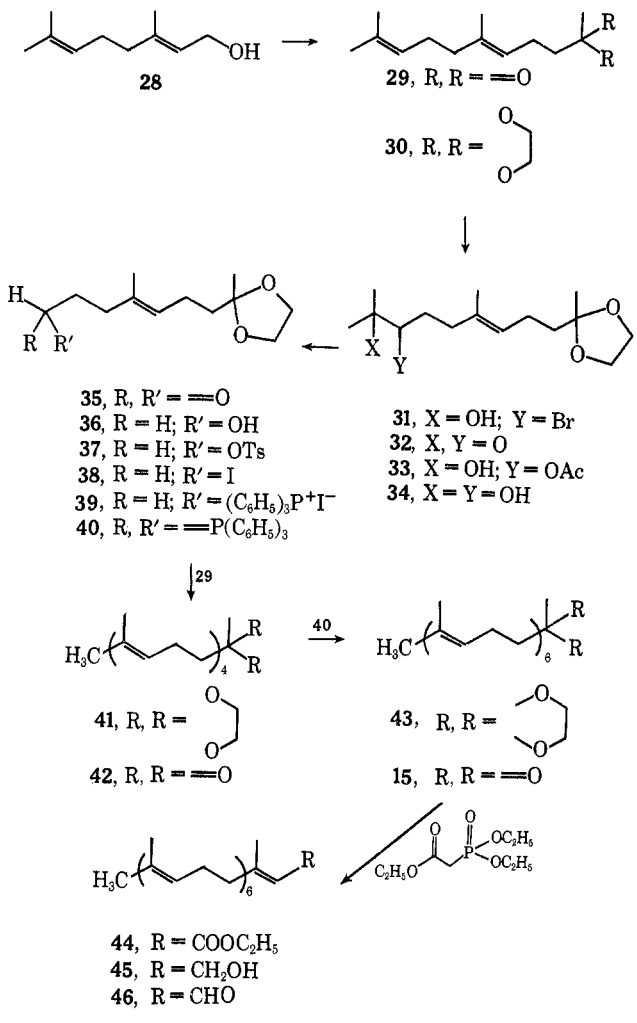
(19) G. Berti, B. Macchia, and F. Macchia, *Tetrahedron*, **24**, 1755 (1968).

(20) E. E. Royals and J. C. Leffingwell, *J Org. Chem.*, **31**, 1937 (1966).

(21) R. W. Schliessler and D. Flitter, *J. Amer. Chem. Soc.*, **74**, 1720 (1952); D. L. Dare, I. D. Entwistle, and R. A. W. Johnstone, *J. Chem. Soc. C*, 977 (1968).

(22) J. W. K. Burrell, R. F. Garwood, L. M. Jackman, E. Oskay, and B. C. L. Weedon, *ibid.*, *C*, 2144 (1966).

SCHEME IV
SYNTHESIS OF $C_{35}$-MULTIPRENYL SIDE CHAIN




merged with methylene absorptions at 1.95. Separate oxidation of *cis*- and *trans*-**17** yielded *cis*- and *trans*-1′-oxomenaquinone-7 (**5**) in 55% yield. As judged by tlc using a chloroform–benzene (1:1) solvent system which resolves chlorobiumquinone into $\Delta^{2'}$-*cis*-(chlorobiumquinone-1) and -*trans*-(chlorobiumquinone-2)[3b] isomers, *trans*-**5** was prepared completely free of the cis isomer. On the other hand, *cis*-**5** was contaminated with *ca.* 10% of *trans*-**5**; however, by repeated preparative, tlc a pure sample of *cis*-**5** was obtained. After recrystallization from petroleum ether (bp 30–60°), *cis*-**5** and *trans*-**5** exhibited melting points of 42 and 50°, respectively, identical with those reported for the natural products.[3b]

The nmr spectra of *cis*- and *trans*-**5** shown in Table I are completely consistent with that originally reported for chlorobiumquinone[4] but somewhat at variance with a more recently presented spectrum.[3b] Apparently the quinone methyl signal has been incorrectly assigned[3b] to the methylene absorption region, thus confusing the quinone methyl with the vinyl methyl (C-3′) signal at $\delta$ 2.28. As anticipated from the model studies, the corresponding vinyl methyl absorption of *cis*-**5** is buried in methylene absorptions at $\delta$ 1.95.

The ultraviolet absorption spectra of synthetic *cis*- and *trans*-chlorobiumquinone (**5**) are almost superimposable and also identical with a redetermined spectrum of chlorobiumquinone, the extinctions reported[4] originally being in error: natural chlorobiumquinone, $\lambda_{max}$ 250 nm ($\epsilon$ 31,000), 245 sh (30,200), 255 sh (30,100), 265 sh (21,800), 325 (3000); *trans*-**5**, 250 (32,000), 245 sh (31,000), 255 sh (31,000), 265 sh (22,000), and 325 (3000). Similarly the infrared and mass spectra were coincident with the natural material, thus confirming the structure of chlorobiumquinone as *all-trans*-1′-oxomenaquinone-7 by total synthesis.

## Experimental Section[23]

**2-Methyl-3-(3-methyl-2-butenyl)-1,4-dimethoxynaphthalene (8).**—Menaquinone-1 (**10**)[24] (1.00 g, 4.17 mmol) was reduced in ethereal solution by shaking with aqueous hydrosulfite, and to the hydroquinone obtained after removal of solvent was added under nitrogen a KOH solution (4 g in 6 ml) and then dimethyl sulfate at room temperature. An oil formed after shaking with cooling for 10 min and the mixture was allowed to stand overnight. The product obtained by ether extraction of the dark brown mixture was chromatographed on kieselgel (eluent: 6% ether in petroleum ether) to yield starting quinone (111 mg) and menaquinol-1 dimethyl ether (**8**) as a colorless oil (700 mg, 70%): nmr $\delta$ 1.70, 1.83 [s, $=C(CH_3)_2$], 2.35 (s, $ArCH_3$), 3.53 (d, $J$ = 6 Hz, $-CH_2-$), 3.85, 3.87 (s, $OCH_3$), 5.1 (t, $J$ = 6 Hz, $-CH=$), 7.7 (m, ArH).

*Anal.* Calcd for $C_{18}H_{22}O_2$: C, 80.0; H, 8.2. Found: C, 79.7; H, 8.0.

**Oxidation of Menaquinol-1 Dimethyl Ether (8) with $Ag^{2+}$ Species. With AgO.**—Menaquinol-1 dimethyl ether (**8**) (68 mg, 0.25 mmol), AgO[25] (496 mg, 4.00 mmol), dioxane (10 ml), and 85% $H_3PO_4$ (1 ml) were mixed and sonicated for 15 min. The product was isolated by partitioning between petroleum ether and water, and the crude product so obtained was chromatographed on kieselgel to yield menaquinone-1 (**10**) as a mobile yellow oil (41 mg, 69%), identical with authentic material.[24]

**With Silver(II) Picolinate.**—Menaquinol-1 dimethyl ether (**8**) (67 mg, 0.25 mmol), $Ag^{2+}$ picolinate[26] (350 mg, 1.00 mmol), and DMSO (10 ml) were mixed and heated for 30 min at 80°, after which time the disappearance of the red color indicated consumption of the silver salt. Tlc (eluent: 90% ether in petroleum ether) showed some conversion to product in the polarity range ($R_f$ 0.5) expected for an alcohol. The mixture was diluted with water and extracted with ether, and the combined ether extracts were washed with water and dried. The product mixture was chromatographed on kieselgel to yield starting material (20 mg) and a product (12 mg, 25% conversion) which by its nmr and mass spectrum was identified as 2-hydroxymethyl-3-(3-methyl-2-butenyl)-1,4-dimethoxynaphthalene (**9**): nmr $\delta$ 1.52, 1.72 [s, $=C(CH_3)_2$], 3.72 [d, $J$ = 6 Hz, $-CH_2-$), 3.84, 3.92 (s, $OCH_3$), 5.05 (t, $J$ = 6 Hz, $-CH=$), 5.60 (s, $-CH_2O$), 7.4, 8.0 (m, ArH); mass spectrum $m/e$ 286 ($M^+$, 100), 272 (30), 269 (30).

**2-Formyl-3-methyl-1,4-dimethoxynaphthalene (12).**—2-Chloromethyl-1,4-dimethoxy-3-methylnaphthalene[27] (12.8 g, 51 mmol) was added to a solution of potassium *tert*-butoxide in *tert*-butyl alcohol (8.3 g, 212 mg-atoms of potassium in 800 ml) and then freshly distilled 2-nitropropane was added (21.7 g, 244 mmol). A white suspension of the salt formed and the reaction

(23) All melting points are uncorrected; microanalyses were performed by the Analytical Laboratory, University of California, Berkeley; uv absorptions were measured in isooctane; and nmr spectra were obtained on an A-60 Varian Associates instrument in deuteriochloroform unless otherwise stated with internal TMS ($\delta$ 0). All evaporations were *in vacuo* using a Berkeley rotary evaporator and all reactions were carried out in a nitrogen atmosphere. Chromatography was performed on Merck silica gel (60–80 mesh) or Camag kieselgel (>250 mesh) as specified. Glpc analyses were performed on (a) 30% QF-1 on acid-washed, DMCS-treated, 60–80 Chromosorb P, 10 ft × 0.25 in.; (b) 20% Carbowax 20M on 60–80 Firebrick, 10 ft × 0.25 in.; (c) Apiezon J on 60–80 Chromosorb P, 5 ft × 0.25 in.; (d) Apiezon L, capillary column, 100 ft × 0.1 mm.

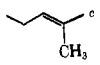
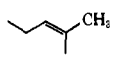
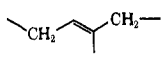
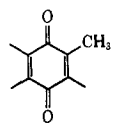
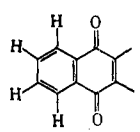
(24) O. Isler, R. Ruegg, A. Studer, and R. Jurgens, *Z. Physiol. Chem.*, **295**, 290 (1953).

(25) R. N. Hammer and J. Kleinberg, *Inorg. Syn.*, **4**, 12 (1953).

(26) E. G. Cox, W. Wardlaw, and K. C. Webster, *J. Chem. Soc.*, 775 (1936).

(27) L. I. Smith, S. Wawzonek, and H. C. Miller, *J. Org. Chem.*, **6**, 229 (1941).

TABLE I
NMR SPECTRAL COMPARISON OF CHLOROBIUMQUINONE AND SYNTHETIC 1′-OXOMENAQUINONE-7 (5) IN $CDCl_3$

| Structure element | Chlorobiumquinone assignments, δ | | Synthetic 1′-oxomenaquinone-7 assignments (60 MHz), δ | |
|---|---|---|---|---|
| | 60 MHz[a] | 220 MHz[b] | *all-trans*-5 | $\Delta^{2'}$-Mono-*cis*-5 |
|  | 1.6 (br) | 1.58 (s) | 1.58 (s) | 1.57 (s) |
|  | 1.7 (s)[d] | 1.66 (s) | 1.64 (s) | 1.65 (s) |
|  | 2.0 (br) | 1.99–2.08 (m) | 1.95 (br) | 1.95 (br) |
|  | 2.1 (s) | 2.28 (s) | 2.08 (s) | 2.02 (s) |
|  | 2.3 (d) | 2.22 (br) | 2.28 (d, $J$ = 2 Hz) | |
|  | 5.1 (br) | 5.08 (br) | 5.05 (br) | 5.05 (br) |
|  | 6.2 (br) | 6.15 (s) | 6.15 (b, s) | 6.02 (br, s) |
|  | 7.9 (m) | 7.73, 8.06 (br) | 7.7, 8.0 (m) | 7.6, 7.9 (m) |

[a] Reference 4. [b] Reference 3b. [c] In chain and terminal cisoid methyls. [d] Incorrectly reported[4] as a doublet.

was stirred at room temperature for 36 hr. The solvent was then removed *in vacuo* and the product was distributed between ether and water to remove acetone oxime and the last traces of solvent. Crude product obtained from the ethereal extract was then sublimed at 75° (10 μ) to give the aldehyde (10.8 g, 92%) as a white, crystalline product: mp 88°; glpc (column a) at 175° gave one peak, $R_T$ 2.5 min; nmr 2.57 (s, $ArCH_3$), 3.80, 4.01 (s, $OCH_3$), 7.5, 8.1 (m, ArH), 10.58 (s, CHO).[9a]

**Dimethyl 2-(1,4-Dimethoxy-2-methyl-3-naphthyl)-2-oxyethylphosphonate (13).**—Dry THF (15 ml) was placed in one side of a double erlenmeyer flask along with dimethyl methylphosphonate[28] (645 mg, 5.2 mmol) while butyllithium (2.95 ml, 4.8 mmol) was placed in the other side. The solutions were cooled in Dry Ice–acetone and then mixed; aldehyde **12** (1.00 g, 4.35 mmol) was dissolved in dry THF (10 ml) and added to the now empty side. After cooling, the two solutions were mixed. After 15 min at −78°, the flask was allowed to warm to room temperature and the product solution was added to 2 $N$ $H_2SO_4$, which was then extracted with chloroform. The chloroform extracts were washed with water, dried, and evaporated. Crude product was chromatographed on kieselgel (eluent: 15% methanol in benzene) to yield white, crystalline phosphonate **13** (1.33 g, 87%): mp 117°; nmr δ 2.56 (s, $ArCH_3$), 3.60 (q, $J_{H-H}$ = 5 Hz, $J_{P-H}$ = 22 Hz, $-CH_2P$), 3.83 (d, $J$ = 11 Hz, $POCH_3$), 3.76, 3.92 (s, $ArOCH_3$), 4.70 (m, −CHOH−), 7.4, 8.0 (m, ArH).

*Anal.* Calcd for $C_{17}H_{23}O_6P$: C, 57.6; H, 6.5. Found: C, 57.7; H, 6.6.

**Dimethyl 2-(1,4-Dimethoxy-2-methyl-3-naphthyl)-2-oxoethylphosphonate (14).**—The hydroxy phosphonate **13** (650 mg, 1.84 mmol) was dissolved in chloroform (25 ml) and refluxed for 4 hr with active manganese dioxide. The $MnO_2$ was removed and the solvent was evaporated *in vacuo* to yield crude product (478 mg) which was chromatographed on kieselgel to yield pure keto phosphonate **14** (450 mg, 75%) as a viscous, light yellow oil: nmr δ 2.37 (s, $ArCH_3$), 3.62 (d, $J_{P-H}$ = 11 Hz, $POCH_3$), 3.74 (d, $J_{P-H}$ = 22 Hz, $-CH_2P$), 3.76, 3.79 (s, $ArOCH_3$), 7.4, 8.0 (m, ArH).

**2-Methyl-3-(1-oxo-3,7-dimethyl-2,6-octadienyl)-1,4-dimethoxynaphthalene (18).**—Keto phosphonate **14** (306 mg, 0.87 mmol), 6-methyl-5-hepten-2-one (127 mg, 1.00 mmol), potassium *tert*-butoxide in *tert*-butyl alcohol (0.83 mmol in 0.83 ml), and *tert*-butyl alcohol (4 ml) were mixed and heated at 110° for 1 week in a sealed tube. The reaction mixture was then partitioned between ether and water and the crude product (330 mg) obtained from the ether layer was chromatographed on kieselgel (eluent: benzene) to yield two bands which were *cis*- (3.3 mg) and *trans*- (3.5 mg) **18**: mass spectrum *m/e* (rel intensity) 352 ($M^+$, 20), 253 (20), 229 (100), 171 (15), 112 (20), 70 (75), 55 (50), identical for *cis*- and *trans*-**18**.

**3,7-Dimethyl-2,6-octadienoic Acid (22).**—Ethyl 3,7-dimethyl-2,6-octadienoate (**21**)[29] (1.82 g, 9.3 mmol) was suspended in 1 $N$ NaOH solution (50 ml), and methanol (5 ml) was added. The solution was refluxed for 3 hr and after cooling was extracted with benzene to yield some recovered starting material (200 mg). The aqueous solution was acidified and then extracted again with benzene. The benzene extracts were distilled to remove residual water and then evaporated to yield pure acid **22** as a viscous, colorless oil: yield 1.25 g (90%); nmr δ 1.62, 1.68 [s, $=C(CH_3)_2$], 2.17 [d, $J$ = 2 Hz, $=C(CH_3)-$], 5.07 (t, −CH=), 5.66 (b, COCH=).

*Anal.* Calcd for $C_{10}H_{16}O_2$: C, 71.4; H, 9.6. Found: C, 71.1; H, 9.4.

**Reactions with 2-Lithio-3-methyl-1,4-dimethoxynaphthalene (20). A. Preparation of 20.**—2-Bromo-3-methyl-1,4-dimethoxynaphthalene (**19**)[30] (281 mg, 1.00 mmol) was dissolved in ether (2 ml), and addition of butyllithium in hexane (0.62 ml, 1.00 mmol) led to a white precipitate. Water was added and the products in the ether layer were examined by nmr. Complete conversion to 2-methyl-1,4-dimethoxynaphthalene (δ 6.40, ArH) indicated that the organolithium compound **20** had been formed quantitatively.

**B. Reaction of 20 with Ester 21.**—To **20**, prepared as above, was added ester **21** (198 mg, 1.00 mmol). After 0.5 hr the reaction mixture was partitioned between ether and 2 $N$ $H_2SO_4$ and evaporation of the ether followed by tlc indicated only starting ester, 2-methyl-1,4-dimethoxynaphthalene, and a trace of product

(28) A. H. Ford-Moore and J. H. Williams, *J. Chem. Soc.*, 1465 (1947).

(29) H. Machleidt, V. Hartmann, and H. Bunger, *Justus Liebigs Ann. Chem.*, **667**, 35 (1963).

(30) R. Adams, T. A. Geissman, B. R. Baker, and H. M. Teeter, *J. Amer. Chem. Soc.*, **63**, 528 (1941).

18. Extending the reaction time to overnight gave the same result.

**C. Reaction of 20 with the Lithium Salt of Acid 22.**—**20** was prepared as above and to it was added acid **22** (168 mg, 1.00 mmol) dissolved in THF (2 ml) to which butyllithium (0.62 ml, 1.00 mmol) in hexane had been added. After 2 hr the reaction was examined as above and no product **18** could be detected by tlc.

**D. Reaction of 20 with Citral (23).**—**20** was prepared as above. After 10 min citral (152 mg, 1.00 mmol) was added and after another 10 min the reaction mixture was partitioned between ether and 2 *N* $H_2SO_4$. The crude product from the ether solution (350 mg) was examined by tlc (eluent: benzene), which indicated only a trace of starting materials and mostly product in the polarity range ($R_f$ 0.1) expected for 2-methyl-3-(1-oxy-3,7-dimethyl-2,6-octadienyl)-1,4-dimethoxynaphthalene (**24**). Pure **24** (304 mg, 86%) was obtained as a viscous, colorless oil from column chromatography: nmr $\delta$ 1.53, 1.62 [s, $=C(CH_3)_2$], 1.72 (s, $-CH_2CH_2-$), 2.00 (trans), 2.15 (cis) [br s, $=C(CH_3)-$], 2.45, 2.47 (s, $ArCH_3$), 3.77, 3.86 (s, $ArOCH_3$), 5.0 (br t, $-CH=$), 5.63, 5.87 (q, $J_{AB}$ = 7 Hz, $-CHOHCH=$), 7.3, 7.9 (m, ArH); mass spectrum *m/e* (rel intensity) 354 ($M^+$, 40), 336 (100), 235 (30), 229 (25), 69 (40), 41 (40).

*Anal.* Calcd for $C_{23}H_{30}O_3$: C, 77.9; H, 8.5. Found: C, 78.0; H, 8.6.

**Oxidation of 1′-Oxymenaquinol-2 Dimethyl Ether (24) with Manganese Dioxide.**—**24** (300 mg, 0.85 mmol) was oxidized with $MnO_2$ (1.5 g) by refluxing for 0.5 hr in chloroform. The $MnO_2$ was removed and crude product was chromatographed on kieselgel (eluent: 10% ether in petroleum ether) to yield cis ketone **18** (35 mg, 12%) and trans ketone **18** (128 mg, 43%), as colorless oils: nmr, cis, $\delta$ 1.67 [s, $=C(CH_3)_2$], 1.92 (d, $J$ = 1 Hz, $=CCH_3-$), 2.25 (s, $ArCH_3$), 3.80 (s, $ArOCH_3$), 5.17 (t, $J$ = 6 Hz, $-CH=$), 6.28 (br, $COCH=$), 7.4, 8.0 (m, ArH); trans, 1.60, 1.67 [s, $=C(CH_3)_2$], 2.20 (d, $J$ = 1 Hz, $=CCH_3-$), 2.30 (s, $ArCH_3$), 3.83, 3.86 (s, $ArOCH_3$), 5.07 (t, $J$ = 6 Hz, $-CH=$), 6.37 (br, $COCH=$), and 7.5, 8.1 (m, ArH); uv $\lambda_{max}$, cis, 222 nm ($\epsilon$ 40,200), 232 sh (37,000), 330 (1900); trans, 223 (42,400), 232 sh (39,400), 330 (2100); mass spectrum, see **18** above prepared from $\beta$-ketophosphonate **14** and 6-methyl-5-hepten-2-one.

*Anal.* Calcd for $C_{23}H_{28}O_3$: C, 78.4; H, 8.0. Found: cis, C, 78.3; H, 7.8; trans, C, 78.4; H, 7.9.

**2-Methyl-3-(1-oxo-3,7-dimethyl-2,6-octadienyl)-1,4-naphthoquinone (6).**—*cis*-1′-Oxomenaquinol-2 dimethyl ether (**18**) (30 mg, 0.085 mmol), AgO (42 mg, 0.34 mmol), 85% $H_3PO_4$ (0.1 ml), and dioxane (1 ml) were mixed and sonicated for 15 min. The product was distributed between petroleum ether and water and the residue from the evaporation of the petroleum ether phase was chromatographed to obtain *cis*-1′-oxomenaquinone **6** as a yellow oil (10 ml, 36%), although some decomposition occurred on chromatography. *trans*-**18** (30 mg) was similarly treated to obtain *trans*-**6** (11 mg, 40%). Nmr, cis, $\delta$ 1.68 [s, $=C(CH_3)_2$], 1.93 (d, $J$ = 1 Hz, $=CCH_3-$), 2.03 (s, $ArCH_3$), 5.15 (t, $J$ = 6 Hz, $-CH=$), 6.07 (br, $COCH=$), 7.7, 8.0 (m, ArH); trans, 1.60, 1.67 [s, $=C(CH_3)_2$], 2.08 (s, $ArCH_3$), 2.28 (d, $J$ = 2 Hz, $=CCH_3-$), 5.07 (t, $J$ = 6 Hz, $-CH=$), 6.15 (br, $COCH=$), 7.7, 8.0 (m, ArH); uv $\lambda_{max}$, cis, 251 nm ($\epsilon$ 29,200), 265 sh (22,500), 325 (3600); trans, 250 (33,200), 265 sh (23,000), 325 (3800).

*Anal.* Calcd for $C_{21}H_{22}O_3$: C, 78.2; H, 6.9. Found for cis: C, 77.9; H, 6.8. Found for trans: C, 78.0; H, 6.8.

**Oxidation of 1′-Oxymenaquinol-2 Dimethyl Ether (24) with AgO.**—Crude **24** (0.3 mmol), AgO (150 mg, 1.2 mmol), and dioxane were mixed and then 6 *N* $HNO_3$ (0.3 ml) was added. After stirring for several minutes, the crude product (98 mg), obtained by partitioning between benzene and water, was chromatographed (eluent: 40% ether in petroleum ether) to obtain first 1-oxymenaquinone-2 (**4**) and then 2-methyl-3-(3-oxy-3,7-dimethyl-1,6-octadienyl)-1,4-naphthoquinone (**26**) both as yellow oils.

**4**: nmr $\delta$ 1.62 [s, $=C(CH_3)_2$], 1.6–1.8 (m, $-CH_2CH_2-$), 2.00 (trans), 2.04 (cis) [s, $=C(CH_3)$], 2.20 (s, $ArCH_3$), 5.0 (br, $-CH=$), 5.43 (br s, $-CHOHCH=$), 7.6, 7.9 (m, ArH); uv $\lambda_{max}$ 244 nm ($\epsilon$ 19,250), 249 (19,400), 258 (14,00), 265 sh (13,300), 326 (3300); mass spectrum *m/e* (rel intensity) 324 ($M^+$, 8), 306 (10), 241 (40), 225 (70), 199 (100), 171 (50).

*Anal.* Calcd for $C_{21}H_{24}O_3$: C, 77.9; H, 7.5. Found: C, 78.1; H, 7.7.

**26**: nmr $\delta$ 1.38 [s, $-C(OH)CH_3-$), 1.62, 1.66 [s, $=C(CH_3)_2$], 2.22 (s, $ArCH_3$), 5.1 (t, $J$ = 7 Hz, $-CH=$), 6.55 (s, $-CH=CH-$), 7.6, 8.0 (m, ArH); uv $\lambda_{max}$ 250 nm ($\epsilon$ 22,800), 280 sh (8330), 330 3700); mass spectrum *m/e* (rel intensity) 324 ($M^+$, 5), 306 (20), 291 (20), 281 (25), 266 (50), 225 (50), 198 (100).

*Anal.* Calcd for $C_{21}H_{24}O_3$: C, 77.9; H, 7.5. Found: C, 77.8; H, 7.8.

**2-Methyl-3-(3-oxy-3,7-dimethyl-1,6-octadienyl)-1,4-naphthoquinone (26)** also was obtained from 2-methyl-3-(3-hydroperoxy-3,7-dimethyl-1,6-octadienyl)-1,4-naphthoquinone (**27**)[9b] (30 mg, 0.088 mmol) upon reduction in methylene chloride solution with 1 equiv of trimethyl phosphite; pure **26** (22 mg, 75%) was obtained by chromatography.

**Acid-Catalyzed Rearrangement of 1′-Oxymenaquinol-2 Dimethyl Ether (24).**—Crude **24** (0.2 mmol) was dissolved in dioxane (2 ml) and 6 *N* $HNO_3$ (0.2 ml) was added. An aliquot taken after 1 min indicated (tlc) complete conversion to a slightly less polar alcohol. The reaction mixture was distributed between water and petroleum ether and the crude product so obtained was chromatographed (eluent: 30% ether in petroleum ether) to yield a colorless oil, 2-methyl-3-(3-oxy-3,7-dimethyl-1,6-octadienyl)-1,4-dimethoxynaphthalene (**25**) (50 mg, 65%): nmr $\delta$ 1.36 [s, $-C(OH)CH_3-$], 1.63, 1.67 [s, $=C(CH_3)_2$], 2.35 (s, $ArCH_3$), 3.72, 3.77 (s, $ArOCH_3$), 5.1 (t, $J$ = 7 Hz, $-CH=$), 6.20 6.6, (q, $J$ = 16 Hz, $-CH=CH-$), 7.3, 7.9 (m, ArH); uv $\lambda_{max}$ 251 nm ($\epsilon$ 42,800), 298 (6080); mass spectrum *m/e* (rel intensity) 354 ($M^+$, 100), 336 (40), 305 (10), 271 (90), 69 (80).

*Anal.* Calcd for $C_{23}H_{30}O_3$: C, 77.9; H, 8.5. Found: C, 77.8; H, 8.9.

Similar treatment of vinylhydroxyquinones **4** and **26** gave no change.

**Geranylacetone (29).**—Pure geraniol (**28**)[12] was converted to geranyl bromide with phosphorus tribromide and pyridine in petroleum ether at −10°. The bromide was treated with ethyl acetoacetate and ethanolic sodium ethoxide at −10° and then with aqueous sodium hydroxide at 80° to yield pure geranylacetone: glpc (column b) $R_T$ 19 min (nerylacetone, $R_T$ 17 min).

*Anal.* Calcd for $C_{13}H_{22}O$: C, 80.4; H, 11.4. Found: C, 80.2; H, 11.4.

When phosphorus tribromide in ether[31] at −78° and then at room temperature was used to effect bromide formation the geranylacetone contained 5% of methylene isomers as determined by the nmr spectrum (methylene protons at $\delta$ 4.8). These isomers probably arise by dehydrohalogenation of tertiary bromides formed by addition of hydrogen bromide to the double bond.

**Geranylacetone Ethylene Ketal (30).**—Geranylacetone (**29**), 90 g, was dissolved in 400 ml of dry benzene, 40 g of ethylene glycol and 300 mg of *p*-toluenesulfonic acid were added, and the mixture was stirred and heated under reflux for 9 hr with removal of water. Aqueous sodium carbonate was added to the cooled reaction mixture, the benzene layer was separated, and the aqueous phase was washed with petroleum ether. The combined organic phases were washed, dried, and evaporated to give the ketal which was chromatographed on silica gel, eluting with benzene, yield 105 g (95%) of geranylacetone ethylene ketal (**30**), <99% pure by glpc (column b).

*Anal.* Calcd for $C_{15}H_{26}O_2$: C, 75.6; H, 11.0. Found: C, 75.5; H, 10.6.

**Ozonolysis of Geranylacetone Ethylene Ketal (30).**—A solution of 24 of geranylacetone ethylene ketal (**30**) in 150 ml of methanol was cooled to −78°, and ozone (0.16 mmol/min) was passed through the solution until 1 equiv had been consumed (613 min). The reaction mixture was added immediately to a stirred solution of 7.6 g of sodium borohydride and 6.4 g of sodium hydroxide in 20 ml of water and 50 ml of methanol maintained at 5°. The resulting solution was stirred overnight and then refluxed for 10 min, cooled, diluted with water, and extracted with methylene chloride. Washing and evaporating the methylene chloride extract gave 14 g of oil. Glpc (column a) and comparison with authentic samples showed the oil to consist of 2-hydroxy-6-methyl-5-heptene, $R_T$ 1 min; 5-hydroxy-2-pentanone ethylene ketal, 1 min 30 sec; geranylacetone ethylene ketal (**30**), 15 min; and 9-hydroxy-6-methyl-5-*trans*-nonen-2-one ethylene ketal (**36**), 18 min. This oil was chromatographed on silica gel, eluting with ethyl acetate–benzene (1:9, then 1:4) to give recovered **30**, and **36** in 20–33% yields: nmr $\delta$ 1.62 (br s, 3, $=CCH_3$), 3.5 (t, $J$ = 6 Hz, $-CH_2OH$).

*Anal.* Calcd for $C_{12}H_{22}O_3$: C, 67.2; H, 10.3. Found: C, 67.1; H, 10.3.

(31) R. B. Bates and J. H. Schauble, *Tetrahedron Lett.*, 1683 (1963).

**Geranylacetone Ethylene Ketal 9,10-Oxide (32).**—A solution of 4.76 g of geranylacetone ethylene ketal (**30**) in 200 ml of 70% aqueous glyme was placed in a water bath at 18–20° and a solution of 3.56 g of *N*-bromosuccinimide in 50 ml of 70% aqueous glyme was added over 40 min. The glyme was distilled from lithium aluminum hydride before use and the NBS was crystallized from hot water. The internal temperature rose to 24° during the addition and the homogeneous solution was stirred for 30 min, diluted with water, and extracted with methylene chloride. Evaporation of the methylene chloride gave 6.8 g of an oil which was dissolved in 100 ml of methanol, stirred for 1 hr with 2.24 g of potassium hydroxide dissolved in 10 ml of methanol, diluted with water, and extracted with methylene chloride. Washing and evaporating the combined methylene chloride extracts gave 5.6 g of an oil which was chromatographed on silica gel, eluting with ethyl acetate–benzene (1:9) to give 1.54 g (31%) of recovered **30**, and 2.75 g (79% yield) of geranylacetone ethylene ketal 9,10-oxide (**32**).

*Anal.* Calcd for $C_{15}H_{26}O_3$: C, 70.8; H, 10.3. Found: C, 70.8; H, 10.0.

**Geranylacetone Ethylene Ketal 9,10-Diol (34).**—Geranylacetone ethylene ketal 9,10-oxide (**32**), 4.85 g, was dissolved in a mixture of 45 ml of glacial acetic acid, 5 ml of acetic anhydride, and 5 g of anhydrous sodium acetate. The resulting solution was stirred for 48 hr at room temperature and then was added slowly to a stirred solution of 50 g of sodium carbonate dissolved in 1 l. of water. This alkaline solution was further diluted with water and extracted with methylene chloride, which was evaporated, and the residue was chromatographed on silica gel, eluting with ethyl acetate–benzene (1:4) to give 4.6 g (77%) of the 9-acetate ester **33** of diol **34**: nmr $\delta$ 1.18 [$C(CH_3)_2$], 2.08 (s, $O_2CCH_3$), 4.8 (br, AcOCH).

The 9-acetate ester **33** was dissolved in 150 ml of methanol containing 0.25 g of potassium hydroxide and the solution was refluxed for 1 hr. Dilution with water, extraction with methylene chloride, evaporation, and chromatography on silica gel, eluting with ethyl acetate–benzene (3:7), gave 3.44 g (87%) of geranylacetone ethylene ketal 9,10-diol (**34**): nmr $\delta$ 1.15 [$C(CH_3)_2$], 3.3 (br, HOCH).

*Anal.* Calcd for $C_{15}H_{28}O_4$: C, 66.1; H, 10.4. Found: C, 66.2; H, 10.2.

**9-Oxo-6-methyl-5-*trans*-nonen-2-one Ethylene Ketal (35).**—Geranylacetone ethylene ketal 9,10-diol (**34**), 3.4 g, was stirred with 6.7 g of sodium metaperiodate in 100 ml of 30% aqueous dioxane for 30 min in the dark followed by dilution with water, extraction with methylene chloride, evaporation, and chromatography on silica gel, eluting with ethyl acetate–benzene (1:9), to give 2.4 g (90%) of 9-oxo-6-methyl-5-*trans*-nonen-2-one ethylene ketal (**35**), nmr $\delta$ 10.45 (t, –CHO).

*Anal.* Calcd for $C_{12}H_{20}O_3$: C, 67.9; H, 9.5. Found: C, 68.1; H, 9.6.

**9-Hydroxy-6-methyl-5-*trans*-nonen-2-one Ethylene Ketal (36).**—A solution of 2.1 g of 9-oxo-6-methyl-5-*trans*-nonen-2-one ethylene ketal (**35**) in 30 ml of absolute ethanol was added to 0.4 g of sodium borohydride in 20 ml of absolute ethanol and the solution was stirred for 1 hr at room temperature and then heated to reflux for 10 min. Dilution with water, extraction with methylene chloride, and evaporation gave 2.0 g (97%) of 9-hydroxy-6-methyl-5-*trans*-nonen-2-one ethylene ketal (**36**), identical with **36** obtained *via* ozonolysis of **6**.

**9-Iodo-6-methyl-5-*trans*-nonen-2-one Ethylene Ketal (38).**—To a solution of 10.6 g of 9-hydroxy-6-methyl-5-*trans*-nonen-2-one ethylene ketal (**36**) in 50 ml of dry pyridine, stirred and cooled to 5°, was added 15 g of *p*-toluenesulfonyl chloride. The reaction mixture was stirred for 3 hr, after which several milliliters of ice water was added while the internal temperature was kept below 10°. Water, 100 ml, was then added followed by extraction with methylene chloride, which was washed and evaporated leaving the tosylate **37**, nmr $\delta$ 3.9 (t, $J$ = 6 Hz, $-CH_2OTs$).

The tosylate, dissolved in 100 ml of dry acetone containing 15 g of sodium iodide, was left for 24 hr at room temperature. Dilution with water, extraction with methylene chloride, evaporation, and chromatography on silica gel, eluting with ethyl acetate–benzene (1:9), yielded 14 g (86%) of 9-iodo-6-methyl-5-*trans*-nonen-2-one ethylene ketal (**38**), nmr $\delta$ 3.08 (t, $J$ = 7 Hz, $-CH_2I$).

*Anal.* Calcd for $C_{12}H_{21}IO_2$: C, 44.5; H, 6.5; I, 39.2. Found: C, 44.4; H, 6.6; I, 39.2.

**Triphenylphosphonium Salt of 9-Iodo-6-methyl-5-*trans*-nonen-2-one.**—Triphenylphosphonium salt of 9-iodo-6-methyl-5-*trans*-nonen-2-one was obtained when the noncrystalline phosphonium salt **39** (below) was crystallized from hot acetone–benzene and then from hot acetone, mp 138–139.5°.

*Anal.* Calcd for $C_{28}H_{32}IOP$: C, 62.0; H, 6.0; I, 23.4. Found: C, 62.0; H, 6.0; I, 23.2.

***all-trans*-Geranylgeranylacetone Ethylene Ketal (41).**—A mixture of 20 g of sublimed triphenylphosphine and 20 g of 9-iodo-6-methyl-5-*trans*-nonen-2-one ethylene ketal (**38**) was stirred and warmed to 80°; after 14 hr a hard, glasslike solid gradually dissolved and stirring was resumed. After a total of 24 hr, tlc and glpc (column a) showed that iodide **38** had been consumed and to the mixture of phosphonium salt **39** and triphenylphosphine cooled to room temperature was added 175 ml of dimethyl sulfoxide and 1 equiv of butyllithium in hexane (37 ml, 1.7 *N*) to generate the ylide **40**. The solution was stirred for 1 hr, 12.2 g of geranylacetone (**29**) was added, and the resulting solution was stirred for 48 hr at room temperature and then diluted with water. Extraction with hexane, evaporation, and chromatography on silica gel, eluting with hexane–benzene (1:1) to separate triphenylphosphine followed by ethyl acetate–benzene (2:98) gave a mixture of recovered **29** and product. Short-path distillation at 70° (3 mm) removed 2.1 g (17% recovery) of **20** from the mixture. Further distillation at 110° (20 $\mu$) gave 17 g (88%) of geranylgeranylacetone ethylene ketal (**41**). Glpc (column c) showed that the $\Delta^9$ cis and trans isomers were present in the ratio of 3:2: $R_T$ cis 60 min, trans 67 min.

Separation of the $\Delta^9$ cis and trans isomers was effected by thiourea inclusion of the all-trans ketal from saturated methanolic thiourea by solution at room temperature and then cooling to 4°. The inclusion compound crystallized during the cooling and was filtered off and washed with saturated methanolic thiourea at 4°. The all-trans ketal was liberated by destruction of the inclusion compound with warm water and extracted into petroleum ether. Thus 16 g of the mixture was separated into 4.2 g of *all-trans*-geranylgeranylacetone ethylene ketal (**41**), 7 g of the $\Delta^9$-mono-cis isomer, and 4.0 g of unresolved ketal.

***all-trans*-Geranylgeranylacetone (42).**—*all-trans*-Geranylgeranylacetone ethylene ketal (**41**), 4.2 g, was dissolved in 50 ml of acetone, and 4 ml of 50% aqueous phosphoric acid was added. The resulting solution was refluxed for 3 hr, diluted with water, and extracted with methylene chloride, which was washed and evaporated to yield the ketone. Chromatography on silica gel, eluting with ethyl acetate–benzene (2:98), gave 3.65 g (98% yield) of *all-trans*-geranylgeranylacetone (**42**), glpc (column c), $R_T$ 31 min, identical with an authentic sample.[12]

***all-trans*-Farnesylfarnesylacetone Ethylene Ketal (43).**—A twofold excess of phosphonium salt **39** was dissolved in dimethyl sulfoxide and converted to ylide **40** as previously described. *all-trans*-Geranylgeranylacetone (**42**), 3.65 g, was added to the ylide solution and stirred for 48 hr at room temperature. Dilution with water, extraction with methylene chloride, and evaporation left a residue which was chromatographed on silica gel to give 4.1 (73% yield) of farnesylfarnesylacetone ethylene ketal (**43**). Glpc (column d) showed that the $\Delta^9$ cis and trans isomers were present in the ratio of 3:2: $R_T$ cis 215 min, trans 225 min.

The ketal was dissolved in 25 ml of saturated methanolic thiourea and the solution was cooled to 4° over several hours, leading to crystallization of the inclusion compound which was filtered, washed with cold, saturated methanolic thiourea, and decomposed with warm water. Extraction with hexane gave 1.6 g (39%) of *all-trans*-farnesylfarnesylacetone ethylene ketal (**43**). The filtrate from the crystallization yielded 2.4 g of pure $\Delta^9$-mono-cis isomer.

***all-trans*-Farnesylfarnesylacetone (15).**—*all-trans*-Farnesylfarnesylacetone ethylene ketal (**43**), 1.6 g, was deketalized and purified by chromatography to yield 1.43 g (97%) of *all-trans*-farnesylfarnesylacetone (**15**): homogeneous by glpc (column d); mass spectrum (70 eV) $m/e$ 466 ($M^+$).

*Anal.* Calcd for $C_{33}H_{54}O$: C, 84.9; H, 11.7. Found: C, 84.9; H, 11.8.

**Ethyl 3,7,11,15,19,23,27-Heptamethyl-2,6,10,14,18,22,26-octacosaheptenoate (44).**—A 1-ml centrifuge tube was filled with NaH (33 mg, 50% oil dispersion) and dry THF (0.5 ml). Triethyl phosphonoacetate (150 mg, 0.67 mmol) was added at −80° and the tube was allowed to slowly warm to room temperature, adding more THF (0.5 ml) to achieve partial solubilization. The reagent was then added to another 1-ml centrifuge tube containing *all-trans*-farnesylfarnesylacetone (**15**) (150 mg, 0.34 mmol) and the mixture was heated to 68° for 5 hr. Partitioning between petroleum ether (2 ml) and 1 *N* NaOH (0.5 ml) gave crude ester **44**: yield 170 mg; nmr $\delta$ 1.23 (t, $J$ = 7 Hz, $CH_3$-

$CH_2$–), 1.57 (s, =$CCH_3$–), 1.93 (br, –$CH_2CH_2$–), 2.10 (d, $J$ = 1 Hz, COC=$CCH_3$–), 4.03 (q, $J$ = 7 Hz, $CH_3CH_2$), 5.03 (br, –CH=), 5.52 (br, COCH=).

**3,7,11,15,19,23,27-Heptamethyl-2,6,10,14,18,22,26-octacosaheptenol (45).**—$LiAlH_4$ (21 mg, 0.56 mmol) and $AlCl_3$ (12.3 mg, 0.092 mmol) were weighed into a 1-ml centrifuge tube and the above crude $C_{35}$ ester (**44**) dissolved in ether (0.5 ml) was added at −70°. After 1 hr at −10°, the reaction mixture was decomposed with wet ether and then partitioned between saturated $NH_4Cl$ solution and petroleum ether. The crude yield of alcohol **45** was 136 mg: nmr $\delta$ 1.58 (s, =$CCH_3$–), 1.95 (br, –$CH_2$-$CH_2$–), 4.00 (d, $J$ = 6 Hz, $OCH_2$–), 5.04 (br, –CH=), 5.34 (t, $J$ = 6 Hz, $OCH_2CH$=).

**3,7,11,15,19,23,27-Heptamethyl-2,6,10,14,18,22,26-octacosaheptenal (46).**—The $C_{35}$ alcohol **45** (above) was dissolved in chloroform (2 ml), $MnO_2$ (0.5 g) was added, the solution was sonicated for 15 min, and another portion of $MnO_2$ and chloroform was added and the sonication repeated. The $MnO_2$ was extracted exhaustively with chloroform to yield crude aldehyde (122 mg, 90%), which was chromatographed on silica gel yielding pure $\alpha,\beta$-unsaturated aldehyde **46** as a viscous oil (83 mg, 50% overall yield from **15**): nmr $\delta$ 1.58 (br, =$CCH_3$–), 1.96 (br, –$CH_2CH_2$–), 2.13 (d, $J$ = 2 Hz, trans COC=$CCH_3$–), 5.03 (br, –CH=), 5.75 (d, $J$ = 8 Hz, COCH=), 9.85 (cis), 9.90 (trans) (d, $J$ = 8 Hz, –CHO).

**Dimethyl Ether of 1′-Oxomenaquinol-7 (17).**—A suspension of **20** was prepared from 2-bromo-3-methyl-1,4-dimethoxynaphthalene (53 mg, 0.19 mmol), butyllithium (0.116 ml, 0.19 mol), and ether (0.5 ml). The $C_{35}$ aldehyde **46** (above) (83 mg, 0.17 mmol) was dissolved in ether (0.5 ml) and added to the lithium reagent. After 10 min at room temperature, the mixture was partitioned between 2 $N$ $H_2SO_4$ (0.2 ml) and petroleum ether. The crude product (120 mg) was oxidized with $MnO_2$ (1 g) in chloroform (5 ml) without further purification by sonicating for 15 min and then refluxing for 1 hr. Extraction of the $MnO_2$ with ether gave crude hydroquinone (108 mg) which was chromatographed to yield *cis*-**15** (20 mg) and *trans*-**15** (49 mg): overall yield from **46** was 60%; nmr, *trans*-**15**, $\delta$ 1.58 (s, =$CCH_3$), 1.95 (br, –$CH_2CH_2$–), 2.20 (d, $J$ = 1 Hz, COC=$CCH_3$–), 2.23 (s, $ArCH_3$), 3.80 (s, $ArOCH_3$), 5.03 (br, –CH=), 6.27 (br, CO-CH=), 7.4, 8.0 (m, ArH); uv, *trans*-**15**, $\lambda_{max}$ 220 sh (44,000), 232 sh (40,400), 325 (2500).

*Anal.* Calcd for $C_{46}H_{68}O_3$: C, 83.2; H, 9.9. Found: C, 83.1; H, 9.9.

**1′-Oxomenaquinone-7 (15).**—*trans*-**15** (52 mg, 0.06 mmol) was dissolved in dioxane (1 ml), 85% $H_3PO_4$ (0.1 ml) and AgO (42 mg, 0.34 mmol) were added, and the mixture was sonicated for 15 min. Extraction with ether gave crude product (42 mg) which was chromatographed on kieselgel to obtain pure *all-trans*-**5** (22 mg, 55%), mp 50° after crystallization from petroleum ether. *cis*-**15** (20 mg) was similarly treated to obtain $\Delta^{2'}$-mono-*cis*-**5**, mp 42°. Nmr is in Table I; uv, *all-trans*-**5**, $\lambda_{max}$ 250 nm ($\epsilon$ 32,000), 245 sh (31,000), 255 sh (31,000), 265 sh (22,000), 325 (3000); $\Delta^{2'}$-mono-*cis*-**5**, 250 (30,800), 245 sh (29,700), 255 sh (29,700), 265 (21,400), 325 (2900); ir (neat), *all-trans*-**5**, 2960, 2940, 2910, 2850, 1660, 1610, 1595 $cm^{-1}$ (C=O); mass spectrum $m/e$ (rel intensity) 664 ($M^+$ +2, 7), 662 ($M^+$, 2), 241 (44), 201 (57), 200 (65), 81 (44), 69 (100), identical for $\Delta^{2'}$-mono-cis and all-trans.

*Anal.* Calcd for $C_{46}H_{62}O_3$: C, 83.3; H, 9.4. Found ($\Delta^{2'}$-mono-cis and all-trans): C, 83.1; H, 9.3.

**Registry No.**—*cis*-**4**, 32247-28-2; *trans*-**4**, 32304-12-4; *all-trans*-**5**, 32247-29-3; 2-mono-*cis*-**5**, 32247-30-6; *cis*-**6**, 32247-31-7; *trans*-**6**, 32247-32-8; **8**, 32247-33-9; **9**, 32247-34-0; **12**, 47827-40-6; **13**, 32247-36-2; **14**, 32247-37-3; **15**, 32304-17-9; 2-mono-*cis*-**17**, 32304-13-5; *all-trans*-**17**, 32247-38-4; *cis*-**18**, 32247-39-5; *trans*-**18**, 32247-40-8; **22**, 459-80-3; *cis*-**24**, 32247-42-0; *trans*-**24**, 32247-43-1; **25**, 32247-44-2; **26**, 32247-45-3; **29**, 3796-70-1; **30**, 3796-62-1; **32**, 32247-48-6; **33**, 32247-49-7; **34**, 32367-44-5; **35**, 24183-02-6; **36**, 32247-51-1; **38**, 3790-61-2; **39**, 32247-53-3; **43**, 32304-14-6; 2-mono-*cis*-**44**, 32304-15-7; *all-trans*-**44**, 32247-54-4; 2-mono-*cis*-**45**, 32247-55-5; *all-trans*-**45**, 32304-16-8; 2-mono-*cis*-**46**, 32247-56-6; *all-trans*-**46**, 32247-57-7.

# Synthesis and Properties of α-Cyanoamino Acids. α-Cyanoglycine, L-β-Cyano-β-alanine, and L-γ-Cyano-γ-aminobutyric Acid[1a]

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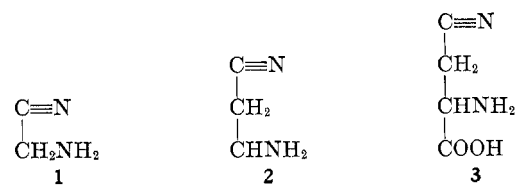
Syntheses of α-cyanoamino acids in the free state are reported for the first time. Enzymic deacylation of acetamidocyanoacetic acid gave α-cyanoglycine. *p*-Methoxybenzyloxycarbonyl-L-isoasparagine was dehydrated to *p*-methoxybenzyloxycarbonyl-L-β-cyano-β-alanine and treated with trifluoroacetic acid to give L-β-cyano-β-alanine. *p*-Methoxybenzyloxycarbonyl-L-isoglutamine was first converted to the methyl ester that was dehydrated and deprotected to give L-γ-cyano-γ-aminobutyric acid. Overall yields were 43–63%. Also synthesized were *p*-methoxybenzyloxycarbonyl-L-β-cyanoalanine, and, from it, L-β-cyanoalanine, and benzyloxycarbonyl-L-β-cyano-β-alanine and benzyloxycarbonyl-L-γ-cyano-γ-aminobutyric acid and their methyl esters. Characteristic physical properties and reactions of α-cyanoamino acids are given including hydration to amino acid amides and reductive cleavage of the cyano group as well as the kinetics of decomposition in aqueous solution.

Osteolathyrogens produce skeletal defects in experimental animals by inhibiting the maturation of collagen.[2] By contrast, the lathyrogens more recently isolated from legumes act as convulsants.[2] As part of an attempt to elucidate structure–activity relationships in the lathyrogens, it was desired to synthesize compounds that would incorporate structural features of both types. Such compounds would thus contain the α- or β-aminonitrile moiety of the osteolathyrogens, *viz.*, α-aminoacetonitrile (**1**) or β-aminopropionitrile (**2**), and the carboxyl group characterizing the neurolathyrogens, *viz.*, β-cyanoalanine (**3**). All these structural features



**1** **2** **3**

would be present in α-cyanoamino acids such as α-cyanoglycine (**4**), L-β-cyano-β-alanine (**5**), and L-γ-cyano-γ-aminobutyric acid (**6**), a class of compounds

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(2) For reviews see K. A. Piez, *Annu. Rev. Biochem.*, **37**, 563 (1968); C. Ressler, *Fed. Proc.*, **23**, 1350 (1964).