Naphtho[*b,e*]dicyclobutene (7). To a solution of 0.18 g (0.5 mmol) of **13** in 5 ml of dry dimethyl sulfoxide and 0.197 g (2.5 mmol) of dry pyridine was added 0.48 g (1.08 mmol) of lead tetraacetate in small portions. An exothermic reaction was observed with copious gas evolution. Monitoring of this gas evolution with a water manometer showed that approximately 4 equiv of gas was given off. An ice bath was used to maintain reaction temperature at 35 °C. After stirring for 1 h, the reaction mixture was poured into 50 mL of saturated sodium chloride solution and extracted five times with ether. The combined ether extracts were dried over magnesium sulfate. Filtration and evaporation of ether gave a solid material which was taken up in hexane and washed with water to remove lead(II) acetate. The hexane solution was dried over sodium sulfate and evaporated to give 36 mg of a white solid. This material was purified by passing through a short silica gel column eluted with petroleum ether, providing 10.4 mg of material which appeared by NMR to be a 1:2:1 mixture of **14:15:7** (see discussion). To the NMR sample (0.5 mL of CCl_4) was added 0.10 g of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and the tube allowed to stand overnight at room temperature, thereby accomplishing complete oxidation to **7**: NMR (CCl_4) δ 7.28 (s, 4 H, ArH) and 3.30 ppm (s, 8 H, ArCH_2). Filtration through silica gel to remove hydroquinone and unreacted DDQ gave a crystalline solid, mp 220–222 °C, from which several high-quality crystals could be grown by slow evaporation of an ether solution: mass spectrum (70 eV) *m/e* (rel intensity) 180 (100, parent), 179 (22), 178 (23), 165 (16), 152 (17), and 28 (33). Anal. Calcd for $C_{14}H_{12}$: *m/e* 180.0939. Found: 180.0946.

1,2,3,4,7,8,9,10-Octahydronaphthacene (17) was prepared according to the method of Skvarchenko et al.,[22] mp 173–175 °C (lit.[22] mp 174 °C).

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Studies in Terpene Biosynthesis. Synthesis and Resolution of Presqualene and Prephytoene Alcohols

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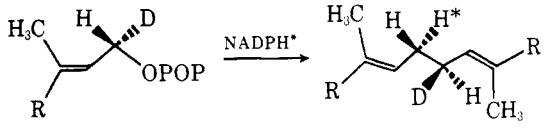
Abstract: Presqualene alcohol and prephytoene alcohols have been synthesized and resolved through their etienate esters. Only (1*R*,2*R*,3*R*)-presqualene alcohol (as its tritiated pyrophosphate) is efficiently converted to squalene by a yeast microsomal fraction. Similarly, only (1*R*,2*R*,3*R*)-prephytoene alcohol (as its tritiated pyrophosphate) is efficiently converted to carotenoids. Thus, the stereochemical course of carotene biosynthesis parallels that of sterol biosynthesis.

In the late 1960's one remaining unresolved transformation in the biosynthesis of sterols from acetate was the elucidation of the biochemical transformations involved in the head-to-head dimerization of two farnesyl pyrophosphate molecules to yield squalene. The elegant work of Cornforth and Popjak[2] had established the overall stereochemistry of the transformation (Scheme I). Numerous proposals[3-5] were set forth to accommodate the observed stereochemistry of this transformation. In 1966,[6] Rilling isolated a free intermediate, now called presqualene pyrophosphate, from a TPNH-starved microsomal yeast fraction to which he assigned structure **3**. Corey and Ortiz de Montellano[7] showed that the original structure assignment was incorrect by synthesizing a mixture

Scheme I. Stereochemistry of Squalene Formation



5 **7**

R = $C_{11}H_{19}$

of all possible stereoisomers of **3** and demonstrating that none of the components of the mixture had the properties of the isolated intermediate. On the basis of further work and more material Rilling and Epstein,[8] in 1969, revised the proposed

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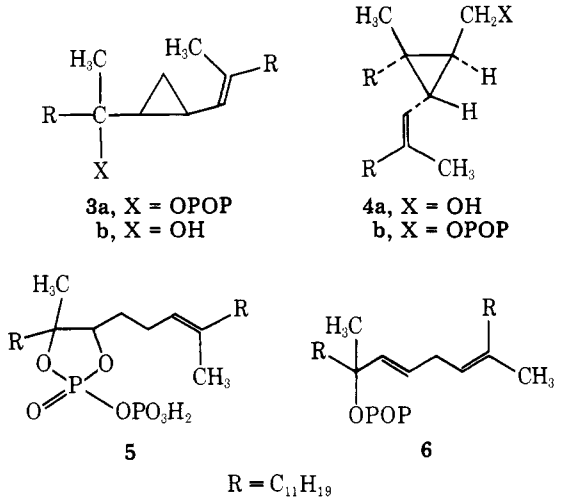


3a, X = OPOP
b, X = OH

4a, X = OH
b, X = OPOP

5

6

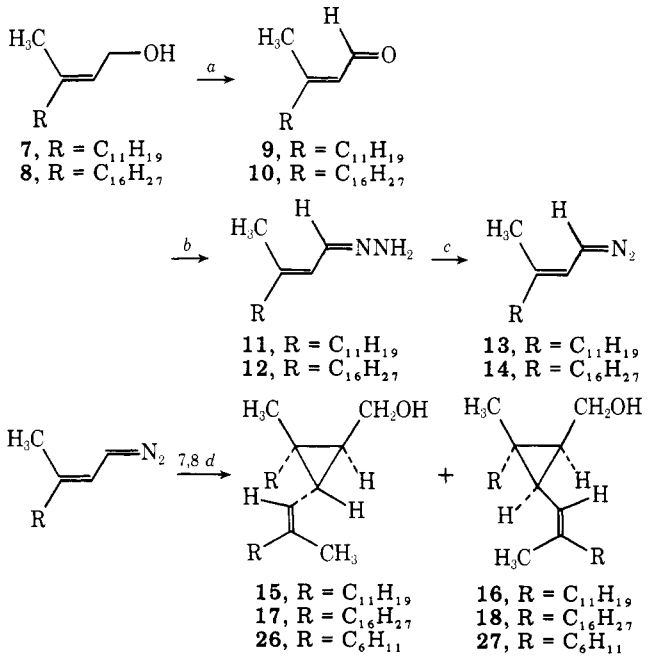
$R = C_{11}H_{19}$

structure of the intermediate to **4**. Working independently, Popjak,[9] in 1969, isolated apparently the same intermediate from a TPNH-starved microsomal yeast fraction and proposed the structure of the intermediate as **5**. Later, in 1970, Lynen[10] isolated an intermediate to which he proposed structure **6**.

Although there has been some question as to whether presqualene pyrophosphate is a "normal" intermediate in squalene synthesis,[11] a series of elegant freeze-clamp experiments by Rilling[12] as well as in vitro competition studies by Corey[13] has established the necessary intermediacy of presqualene pyrophosphate in in vivo squalene biosynthesis.

It appeared to us that one satisfactory method of establishing the structure of the intermediate was by an unambiguous synthesis and, in 1971, we published[14] the preliminary communication describing a synthesis of the racemic modification of presqualene alcohol (Scheme II). We were able to unambiguously determine the structure of **15** and to demonstrate the identity of the biosynthetic intermediate as one of the enantiomers of this racemic modification corresponding to **4**. We were further able to demonstrate the efficient transformation of **4** to squalene by a yeast microsomal fraction. Concurrently, in 1971,[15,16] two other groups published syntheses of materials

Scheme II. General Synthesis of Cyclopropylcarbinols



7, R = $C_{11}H_{19}$
8, R = $C_{16}H_{27}$

9, R = $C_{11}H_{19}$
10, R = $C_{16}H_{27}$

11, R = $C_{11}H_{19}$
12, R = $C_{16}H_{27}$

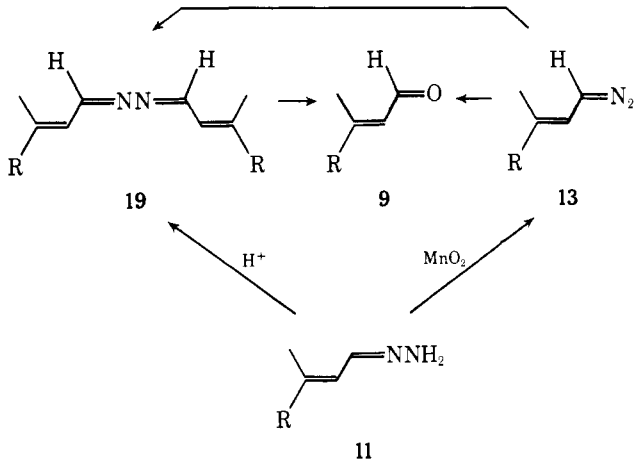
13, R = $C_{11}H_{19}$
14, R = $C_{16}H_{27}$

15, R = $C_{11}H_{19}$
17, R = $C_{16}H_{27}$
26, R = C_6H_{11}

16, R = $C_{11}H_{19}$
18, R = $C_{16}H_{27}$
27, R = C_6H_{11}

[a] Manganese dioxide, 10 equiv; petroleum ether, 0 °C. [b] Triethylamine and hydrazine, 6 equiv each; ethanol, 25 °C. [c] Manganese dioxide, 10 equiv; sodium carbonate, 8 equiv; ether, 0 °C. [d] Zinc iodide, 0.3–1.5 equiv based on complexed farnesol; ether, 0 °C.

Scheme III. Acid and Manganese Dioxide Catalyzed Interconversions



19 **9** **13**

11

which corresponded to presqualene alcohol. In 1973, Popjak[17] reported experiments demonstrating that presqualene alcohol has the 1*R*,2*R*,3*R* absolute configuration.

The biosynthesis of carotenoids[18a] involves an analogous head-to-head dimerization of an allylic pyrophosphate. However, in this case the dimerization product of geranylgeranyl pyrophosphate is phytoene.[18b] It appeared reasonable that the dimerization proceeds through a cyclopropylcarbinyl intermediate and, in 1972,[19] we published a synthesis of prephytoene alcohol and demonstrated that the pyrophosphate was efficiently converted into carotenoids. Subsequently, Crombie et al.[20] have published a synthesis of prephytoene alcohol. Due to the lack of natural prephytoene alcohol, its absolute configuration remained a mystery. Recently,[21] we were able to resolve synthetic presqualene and prephytoene alcohols and demonstrated that the biologically active (+)-prephytoene alcohol has the 1*R*,2*R*,3*R* absolute configuration. We now report the full details of our synthetic work.

Results

The synthesis of cyclopropylcarbinyl alcohols proceeded as outlined in Scheme II.

Reaction a, oxidation of *trans,trans*-farnesol **7** to *trans,trans*-farnesal **9**, was accomplished in 95–100% yield with minimal isomerization with either activated manganese dioxide[22] or Collins reagent.[23] Sarett reagent[24] or Jones oxidation[25] caused extensive isomerization.

Reaction b, hydrazone formation, was accomplished by addition *in order* of 6 equiv each of triethylamine and hydrazine (either anhydrous or aqueous solution) to an ethanolic solution of the aldehyde. In a control experiment without triethylamine base, the solution deeply yellowed within 20 s, indicating formation of the intractable azine dimer **19**.[26] With added base, the solution remained colorless or at most very light yellow. The aldehyde was depleted after 40 min.

Reaction c, oxidation of the allyl hydrazone **11** with manganese dioxide, proved at first quite capricious, yielding a variety of unwanted products (Scheme III). Infrared analysis showed four distinct components: starting hydrazone **11** (ν max 3450 cm^{-1}), the desired diazo product **13** (ν max 2055 cm^{-1}), azine dimer **19** (ν max 1640 cm^{-1}),[27] and farnesal **9** (ν max 1675 cm^{-1}). Indeed, carbonyl compounds are smoothly formed from either azines or hydrazones treated with manganese dioxide.[28]

Protonation of a resonance-stabilized diazo compound **13** is necessary for azine formation by a nonpyrolytic, nonphotolytic pathway.[29] The major proton source in the oxidation was found to be the manganese dioxide itself, which contains about 4% bound water.[30] Distilled water, pH 6.2 (carbon dioxide saturated), typically showed pH 5.2–5.6 after washing of freshly made oxidant. The yield of the diazo compound was

Table I. Variation of J_{bc} with L/S

alcohol	J_{bc} (±0.1 Hz)	L/S
15	5.2	0.62
15	5.1	0.70
15	5.0	0.80
16	8.8	0.41
16	8.7	0.49
21	4.9	0.71
22	7.9	0.45
17	5.0	0.41
17	5.1	0.42
26	5.0	0.30
26	5.2	0.40
26	5.1	0.52
26	5.0	0.63
27	7.9	0.56
27	8.2	0.65
27	8.2	0.80

then maximized by addition of inorganic bases to the diazo-forming reaction. Optimum conditions called for mechanical stirring of a mixture containing 7.9 equiv of Na_2CO_3, 10 equiv of MnO_2, allylic hydrazone, and ether for a period of 60 min at 0 °C. Workup of the reaction mixture was effected by simple filtration of the reaction mixture followed by evaporation of solvent.

Reaction d, the zinc iodide catalyzed cyclopropanation,[31] was more effective in anhydrous diethyl ether than anhydrous tetrahydrofuran. The yield of partially purified product was typically 20–25%, based on starting farnesol. Nitrogen evolved by diazo decomposition was typically 70–85% of the theoretical, again based on starting farnesol.

Two 30-carbon cyclopropane containing products, **15** and **16**, were isolated by preparative layer chromatography. Nuclear magnetic resonance showed in each two protons α to oxygen at δ 3.6, and a cyclopropylmethyl at δ 1.1. The protons on carbon-1 of farnesol resonate at δ 4.15 and would be undisturbed in the event of remote cyclopropanation. No products containing both a cyclopropylmethyl resonance and a two-proton doublet at δ 4.15 were found. The reaction was therefore regiospecific for the olefin nearest the hydroxyl.

The major (70% of 30-carbon alcohols), more polar isomer was shown by Eu(DPM)$_3$-shifted decoupling experiments to have a vicinal cyclopropyl proton coupling constant of 5.1 Hz, whereas the less polar, minor isomer had an analogous coupling constant of 8.8 Hz.

Stereochemical assignments based upon the determination of unshifted coupling constants from lanthanide-shifted spectra would be invalid unless it could be demonstrated that either the coupling constants are invarient upon complexation or, at the very least, that the magnitude of the variation of coupling constants is much smaller than the differences in coupling constants between epimeric pairs of compounds.[32] If the complexed molecule were to have different coupling constants, the observed coupling constants would be found to be a function of the lanthanide/substrate (L/S) ratio in the region of 0–1 (assuming a 1:1 complex).[33] Table I shows, however, that for all epimeric pairs (**15** and **16**; **21** and **22**; **26** and **27**, the epimeric pair of C_{20} cyclopropylcarbinyl alcohols derived from the addition of diazogeranial to geraniol), J_{bc} cis is significantly greater than J_{bc} trans for the L/S ratios studied. The stereochemical assignments are secure on this point.

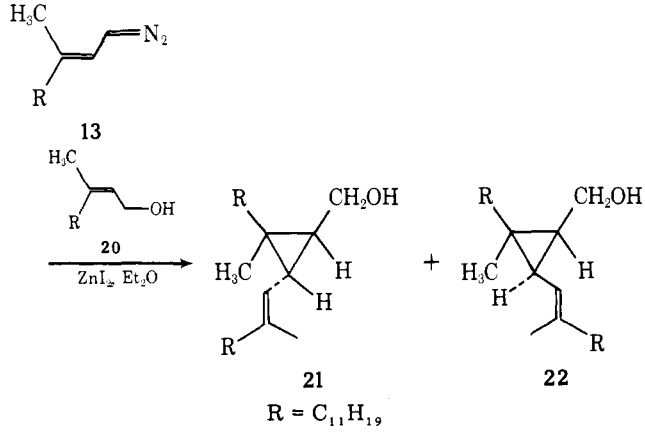
Therefore, the ring geometry of the more polar isomer should be represented as **15** and the less polar isomer as **16**.[34] The stereoselectivity (70% anti, 30% syn with respect to the hydroxyl) is typical for organozinc carbenoid additions to hydroxylic olefins.[35]

Cis stereospecificity in the cyclopropanation has been assumed, based on the reported cis stereospecificity of other organozinc carbenoid additions[35-39] and the isolation of two cyclopropylcarbinols. (Isolation of only two products is a necessary but not sufficient criterion to assign cis stereospecificity.) The diazo compound from *trans,trans*-farnesol **13** was then added to pure *cis,trans*-farnesol **20** to test the stereospecificity assumption and to determine the specificity of squalene synthetase for ring geometry in the substrate (Scheme IV).

Table II. Chromatographic Comparison of 30 Carbon Alcohols from Addition of *trans*-Diazo Compound to *cis*- and *trans*-Farnesol

	R_f			
Compd	ether–carbon tetrachloride (20:80)	benzene (3.0 h)	ethyl acetate–petroleum ether (5:95, 4.16 h)	6-ft rel retentions, 3% OV-225, 36 mL of N_2/min, 225 °C
15	0.28	0.29	0.32	1.06
16	0.37	0.39	0.48	1.35
21	0.36	0.35	0.37	1.35
22	0.38	0.39	0.46	1.00

Scheme IV. *trans*-Diazo Addition to *cis*-Farnesol



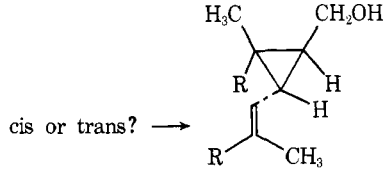
21 22

R = $C_{11}H_{19}$

Double-elution TLC indicated the presence of only one cyclopropylcarbinol product in about 20% yield, but continuous-elution TLC differentiated this single spot into two, which were preparatively separated by high-pressure liquid chromatography. The major (76%), more polar epimer was shown by Eu(DPM)$_3$-shifted NMR experiments to have a vicinal cyclopropyl proton decoupling constant of 4.9 Hz and, hence, the geometry shown by **21**. The minor, less polar epimer was shown to have a cyclopropyl coupling constant of 7.9 Hz and is best represented by **22**.

Comparison of chromatographic properties of the product alcohols indicates that the zinc iodide catalyzed cyclopropanation is indeed stereospecific (Table II). Alcohols **15** and **16** derived only from *trans*-diazo addition to *trans,trans*-farnesol are clearly differentiable from each other and from alcohols **21** and **22**, derived only from *trans*-diazo addition to *cis,trans*-farnesol. All four compounds are chromatographically unique, and we assign cis stereospecificity to the addition. (Trans stereospecificity in carbenoid additions is unknown.[39])

Having ascertained the stereospecificity of the cyclopropanation reaction, attention was focused upon the configuration of the olefin in conjugation with the ring.



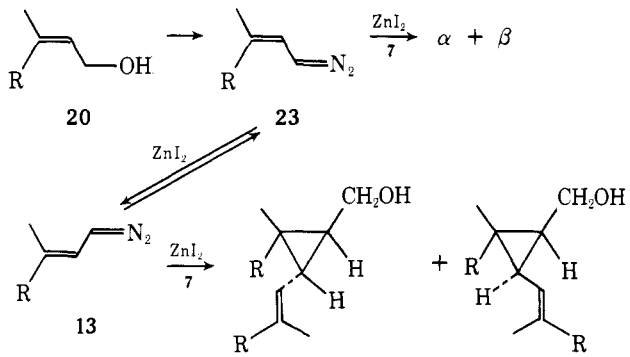
15

Table III. Silica Thin-Layer Chromatographic Comparisons of 30 Carbon Alcohols from Addition of *cis*- and *trans*-Diazo Compound to *trans*-Farnesol

alcohol	solvent system[a]						
	A	B	C	D	E	F	G
β	0.43	0.40	0.63	0.84	0.34	0.62	0.54
16	0.43	0.40	0.63	0.84	0.34	0.62	0.54
α[b]	0.35	0.26	0.43	0.60	0.26	0.61	0.46
15[b]	0.35	0.26	0.43	0.60	0.26	0.61	0.47

[a] A, ether–carbon tetrachloride (20:80); B, ethyl acetate–petroleum ether (8:92, 3.0 h); C, benzene (7.0 h); D, *i*-PrOH–benzene (1:99, 2.0 h); E, 10% Ag^+, ethyl acetate; F, 10% Ag^+, acetone; G, 10% Ag^+, *i*-PrOH–benzene (10:90, double elution). [b] Alcohols α and **15** also cochromatographed under the following VPC conditions: 32 in. × 2 mm 1% OV-225, 110 mL of He/min, 175 °C, 10.9 min; 6 ft × 2 mm 3% OV-225, 50 mL of He/min, 230 °C, 3.7 min; 4 ft × 3 mm 3.8% SE-30, 70 mL of He/min, 230 °C, 17.1 min; 6 ft × 2 mm 3% OV-1, 110 mL of He/min, 210 °C, 14.2 min.

Scheme V. *cis*-Diazo Addition to *trans*-Farnesol



Corey had noted that mercuric iodide was an excellent catalyst for cis,trans isomerization as well as decomposition of allylic diazo compounds.[40] The *cis,trans*-diazo compound **23** was then added to *trans,trans*-farnesol **7** and two cyclopropylcarbinol products, α and β, were obtained in 6% yield. Coinjection (GLC) of this reaction mixture with the reaction mixture derived from addition of *trans,trans*-diazofarnesol to **13** to *trans,trans*-farnesol **7** (containing alcohols **15** and **16**) gave only two peaks with retention times appropriate to 30-carbon alcohols. Alcohol α cochromatographed with alcohol **15**, and alcohol β cochromatographed with alcohol **16**.

Chromatographic comparison of isolated alcohols, α and β, with alcohols **15** and **16** are given in Table III. As the cis,-trans-isomeric alcohols **15** and **24**, prepared by an independent route, were shown to be separable by silver nitrate impregnated thin-layer chromatography,[16] and no difference between α and **15** and our β and **16** was observed, one must conclude that α is actually **15**, and β is actually **16** and that only the *trans*-diazo compound will react intermolecularly (Scheme V). The farnesal recovered from the *cis*-diazo was 33% trans by NMR integration of the aldehyde proton; this finding implies extensive cis,trans isomerization.

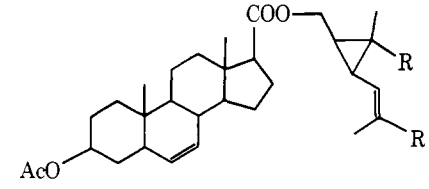
For biosynthetic studies, each cyclopropylcarbinyl alcohol (**15, 16, 21,** and **22**) was oxidized to the corresponding aldehyde, reduced with either lithium [^{3}H]borohydride or lithium aluminum [^{3}H]hydride, and then transformed to the ^{3}H-labeled pyrophosphate. Only **15** was transformed into squalene in significant quantities (37.5% yield). Thus, the stereochemistry of natural presqualene alcohol has been established as that of **15**.

Resolution of alcohol **15** was accomplished by separation of the diastereomeric etienate esters **25**. The separation was accomplished utilizing high-pressure liquid chromatography. The individual diastereomeric esters were then reduced with $LiAlH_4$ to yield (+)- and (−)-presqualene alcohol. The rotations of the individual enantiomers are reported in Table IV. The (−)-presqualene alcohol (as its pyrophosphate) was not

Table IV. Optical Rotatory Dispersion Data[a]

wavelength, λ, nm	(+)-prephytoene (c 0.0037), [α]	(−)-prephytoene (c 0.0035), [α]	(+)-presqualene (c 0.0010), [α]	(−)-presqualene (c 0.0011), [α]
365 (Hg)	149	−143	193	−206
436 (Hg)	90	−83	103	−110
546 (Hg)	45	−46	48	−52
578 (Hg)	39	−40	48	−48
589 (Na)	38	−37	47	−48

[a] Rotations were measured at 20.0 °C in $CHCl_3$ using a Perkin-Elmer Model 241 polarimeter; deviations no larger than 10% of the reported values were observed.



25

incorporated into squalene using a yeast subcellular enzyme preparation whereas (+)-presqualene alcohol (as its pyrophosphate) was converted to squalene in comparable yields to the natural, biosynthetically produced (+)-presqualene pyrophosphate.

In order to test whether carotenogenic systems utilized a 40-carbon intermediate analogous to that shown for the 30-carbon squalene biosynthesis, the 40-carbon analogue to presqualene alcohol was synthesized from *trans,trans,trans*-geranylgeraniol **8** (Scheme II).[46,47]

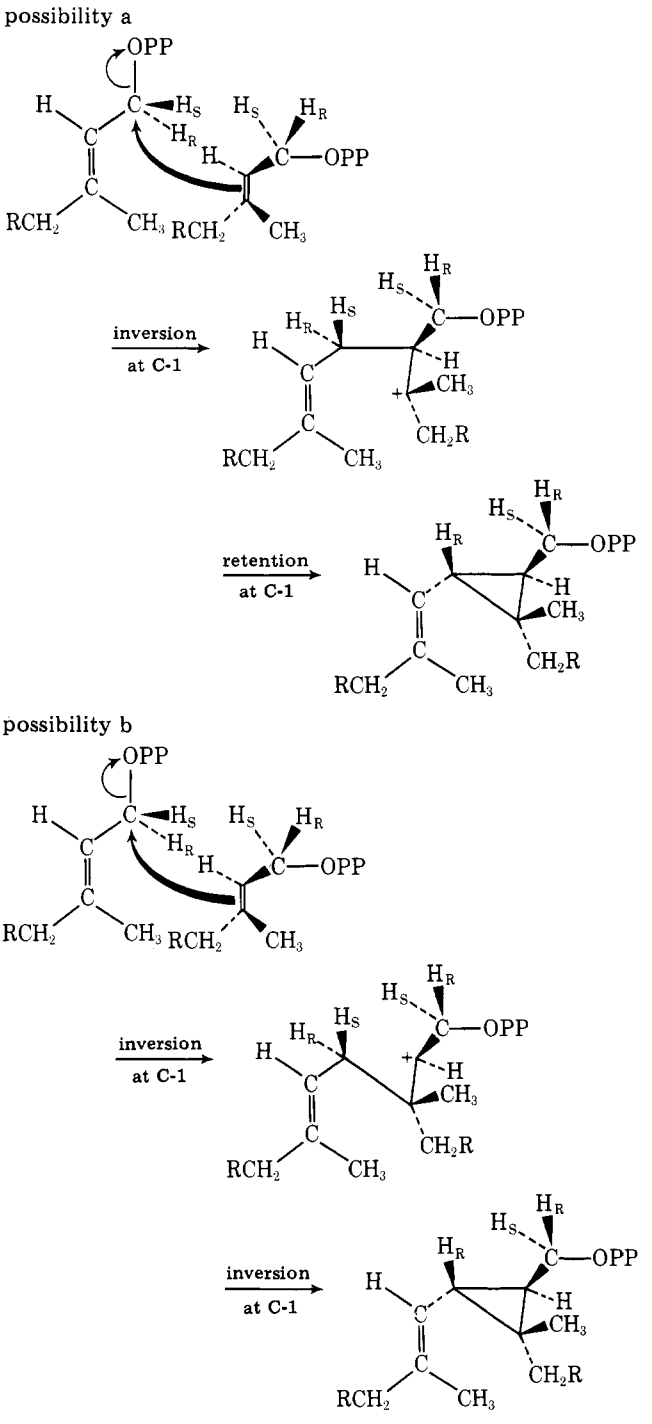
Two 40-carbon alcohols were obtained in 23% yield based on starting geranylgeraniol. The major (60%) isomer was shown by Eu(DPM)$_3$-shifted decoupling experiments to have a cyclopropyl proton coupling constant of 5.1 Hz and, therefore, the geometry shown as **17**. This isomer (as its tritiated pyrophosphate) was found to be incorporated into carotenoids in approximately 40% yield by a Mycobacterium.[19] Thus, the biosynthesis of carotenoids proceeds along pathways analogous to squalene biosynthesis.

Prephytoene alcohol was resolved through its etienate ester analogously to presqualene alcohol. Only the (+)-prephytoene alcohol (as its tritiated pyrophosphate) was incorporated into unspecified carotenoids. As the ORD curves for (+)-prephytoene alcohol and (+)-presqualene alcohol are almost identical, it is clear that the natural prephytoene alcohol must have the 1*R*,2*R*,3*R* absolute configuration.

Discussion

The synthetic studies described herein allow for an unambiguous assignment of both the relative and absolute stereo-

Scheme VI. Possible Stereochemical Consequences during the Biosynthesis of Presqualene Pyrophosphate



chemistry of presqualene and prephytoene alcohols. Thus, sterol biogenesis and carotenoid biogenesis follow similar stereochemical pathways.

Little attention has been given to the mechanistic implications of the stereochemical details in the biosynthesis of presqualene (and prephytoene) pyrophosphates from farnesyl pyrophosphate. The conversion of the cyclopropylcarbinyl pyrophosphates to squalene (and phytoene), on the other hand, has received much mechanistic attention.[48]

In the biosynthesis of presqualene pyrophosphate from farnesyl pyrophosphate, two carbon–carbon bonds from C-1 of one farnesyl moiety to C-2 and C-3 of the second farnesyl pyrophosphate are formed. A reasonable mechanistic postulate would involve Mg^{2+}-assisted solvolysis of the pyrophosphate from one farnesyl pyrophosphate with concomitant carbon–carbon bond formation to the other farnesyl pyrophosphate. This process most likely would involve inversion of stereochemistry about C-1 of the farnesyl pyrophosphate which is undergoing solvolytic loss of pyrophosphate. An ambiguity remains as to which carbon (C-2 or C-3) of the second farnesyl pyrophosphate the initial bond is made. If the initial bond is made to C-2 (Scheme VI, possibility a), the new carbon–carbon bond (between C-3 of the second farnesyl moiety of C-1 of the first farnesyl moiety) must be formed with complete retention of stereochemistry about C-1 (of the first farnesyl moiety). If, however, the initial bond is made to C-3 (Scheme VI, possibility b), then the new carbon–carbon bond must be formed with complete inversion of stereochemistry. The former pathway seems most likely to us and would seem reasonable if one postulated the intermediacy of an edge-protonated cyclopropane intermediate. Although no experiment in the presqualene pyrophosphate biosynthetic pathway is apparent to elaborate upon this point, an analogous cyclopropane intermediate is formed in cycloartenol biosynthesis, and recent experiments[49] have shown that the stereochemistry of cyclopropane formation in this case proceeds with retention of configuration.

Experimental Section

All solvents used in this study were of reagent grade. Ether refers to Mallinckrodt analytical reagent grade anhydrous diethyl ether. Petroleum ether refers to redistilled (bp 60–68 °C) petroleum ether.

The silica used for column chromatography was E. Merck 7734 (70–230 mesh ASTM). Analytical thin-layer chromatography was performed using 5 × 20 cm Analtech 1511 plates, the adsorbent being silica GF_{254} of 0.25-mm thickness. Preparative layer chromatography was usually done with plates of 1-mm thickness, using E. Merck 7734 silica HF_{254}, to which was added 0.05–0.1% by weight of Rhodamine 6G (K & K Laboratories) as a visualization aid. Preparative layer chromatography plates of 2.0-mm thickness were made from silica PF_{254} and Rhodamine 6G as above; Analtech commercial plates were used for small-scale preparative work. A visualization spray comprised of 85 mg of Rhodamine 6G, 90 mL of methanol, and 10 mL of water was used for all preparative work in which the Rhodamine 6G was not premixed in the slurry with the silica.

For simplicity, the thin-layer chromatographic solvent system ether–carbon tetrachloride, with proportions as noted in the text, will be referred to as system A. Likewise, the solvent system ethyl acetate–petroleum ether will be designated system B.

Vapor-phase chromatography was performed on either a Hewlett-Packard Model 402 Hi-efficiency gas chromatograph using helium as the carrier gas or a Varian Model 2100 gas chromatograph using nitrogen as the carrier gas. Both machines used Pyrex columns and flame ionization detectors.

The following gas chromatographic columns will be defined: column one, 6 ft × 2 mm 3% OV-225 on 100–120 mesh Gas Chrom Q; column two, 6 ft × 2 mm 3% OV-17 on 100–120 mesh Gas Chrom Q; column three, 1 ft × 2 mm 1% OV-225 on 100–120 mesh Gas Chrom Q. Precoated column packings one and two are available from Applied Science Laboratories as was the separate liquid phase and packing for column three.

Nuclear magnetic resonance spectra were taken on either Varian T-60, HA-100, CFT-20, or XL-100 spectrometers. Chemical shifts are given in parts per million downfield (δ) from internal tetramethylsilane standard. The $Eu(DPM)_3$ shift reagent was prepared by nuclear magnetic resonance laboratory personnel, according to the method of Eisentraut and Sievers,[50] and stored in a desiccator.

Infrared spectra were taken on a Perkin-Elmer 237B grating infrared spectrometer calibrated by external polystyrene. The ultraviolet spectrum was taken on a Cary 14M spectrometer. Mass spectra were obtained on an Atlas CH-4 spectrometer utilizing the direct inlet mode; mass spectra for alcohols **21** and **22** were obtained on a Varian MAT 711 spectrometer with direct inlet.

Combustion analyses were performed by the Stanford Microanalytical Laboratory or Galbraith Laboratory.

Preparation of Manganese Dioxide. Activated manganese dioxide was prepared by the method of Attenburrow.[22a] On one occasion, the water used was freshly distilled from potassium permanganate, resulting in slightly more active oxidant than when nonpermanganate

distilled water was used. (After 90 min, permanganate distilled water manganese dioxide had converted 95% of geraniol to geranial. Under identical conditions the conversion level for nonpermanganate distilled water manganese dioxide was 85%.) The reaction mixture was filtered on two layers of filter paper (Whatman 1), the residue being washed well with water. The wet filter cake was dried in a preequilibrated oven at 105 °C overnight, after which time the cake was removed, powdered, and then returned to the oven for an additional 12 h. At no time did the oven temperature exceed 105 °C. Higher drying temperatures reduce oxidant activity.

Preparation of Zinc Iodide. Ten grams of zinc powder (Baker Chemical, purified powder) was purified by the method of Tsuda.[51] The resulting ethereal slurry was transferred to a tared, dry round-bottom flask equipped with nitrogen sweep, reflux condenser, addition funnel, and magnetic stirrer. The flask was reweighed after nitrogen sweeping to determine the weight of zinc present. Iodine in ether was then added dropwise according to Brauer.[52] The resultant mixture was filtered through a glass frit into a foil-wrapped round-bottom flask. Ether was removed at reduced pressure until the solution was cloudy. Ether (20 mL) was added, giving a clear solution which was stored overnight at −20 °C. The cold supernatant was decanted in a glove bag (nitrogen atmosphere); the remaining solvent was removed from the white, solid product at aspirator pressure and then high vacuum. This first crop of zinc iodide (15 g) was then only handled in a glove bag.

***trans,trans*-Farnesal [3,7,11-Trimethyl-2,6,10-(2*E*,6*E*)-dodecatrienal] (9).** Powdered manganese dioxide (18.7 g, 215 mmol, 15 equiv) was added to a mechanically stirred solution of 3.18 g of *trans,trans*-farnesol **7** (14.3 mmol) in 150 mL of petroleum ether under nitrogen at 0 °C. The reaction was followed by TLC (methylene chloride), which showed no alcohol after about 1.5 h. The mixture was filtered, the residue being washed well with ether. The solvent was removed under reduced pressure, giving a recovery of 3.00 g of aldehyde **9** (95%): NMR ($CDCl_3$, 60 MHz) δ 10.00 (1 H, d, J =8 Hz, aldehydic proton) [lit.[41b] δ 10.00 (1 H, d, J = 8 Hz, aldehydic proton)] [other resonances were δ 5.86 (1 H, d, J = 8 Hz, vinyl proton split by aldehydic proton), 5.07 (2 H, br, vinylic protons), 2.25, 2.16, 2.15, 2.04, 1.98 (11 H, s, methylene protons and conjugated allylic methyl), 1.67, 1.58 (s, 9 H, unconjugated allylic methyls)]; IR (film) 2970, 2920, 2850, 2770, *1675*, 1630, 1610, 1440, 1385, 1190, 1120, 925, 730 cm^{-1}.

The 2,4-dinitrophenylhydrazone gave mp 101.5–102.0 °C (lit.[41b] 92–94 °C). This sample was a 2:1 *trans,trans-cis,trans* mixture.

***trans,trans*-Farnesal Hydrazone [3,7,11-Trimethyl-2,6,10-(2*E*,6*E*)-dodecatrienal Hydrazone] (11).** *In order,* 5.8 mL of triethylamine (40.8 mmol, 6 equiv) and 1.27 mL of anhydrous hydrazine (40.8 mmol, 6 equiv) were added to a stirred solution of 1.51 g of *trans,trans*-farnesal **9** (6.8 mmol) in 100 mL of anhydrous ethanol under nitrogen. The reaction was followed by TLC (methylene chloride) which showed no aldehyde remaining after 0.75 h. Volatile material was removed at 1 mmHg pressure and bath temperature less than 40 °C. The residue was extracted twice with ether (10 mL), the organic layer was washed twice with ice-cold brine (15 mL), and the brine was back extracted with ether (5 mL). The organic layers were combined, dried over sodium carbonate, and used immediately: IR (film) *3340, 3175*, 2960, 2910, 2840, 2725, 1635, 1575, 1450, 1380, 1375 cm^{-1}.

***trans,trans*-Diazofarnesal [Diazo-3,7,11-trimethyl-2,6,10-(2*E*,6*E*)-dodecatriene] (13).** The *trans,trans*-farnesal hydrazone **11** (6.8 mmol) in 25 mL of ether was added to a mechanically stirred suspension of 5.65 g of granular sodium carbonate (53.3 mmol) in 130 mL of ether under nitrogen at 0 °C. Powdered manganese dioxide (5.65 g, 65 mmol, 9.6 equiv) was added and the suspension rapidly stirred for 1 h. The mixture was filtered through a glass frit containing anhydrous sodium sulfate, the residue being washed well with ether. The receiver for the red-orange filtrate was a 500-mL round-bottom flask containing a magnetic stirring bar. The solvent was removed at 1 mmHg pressure and 0 °C bath temperature to a final volume about 10 mL. The blood red solution was used immediately: IR (film) 2960, 2910, 2840, *2055*, 1645, 1440, 1385 cm^{-1}.

(±)-Presqualene Alcohol [2-[4,8-Dimethyl-3,7-(3*E*)-nonadienyl]-2-methyl-3-[2,6,10-trimethyl-1,5,9-(1*E*,5*E*)-undecatrienyl]-*trans*-1,2-*trans*-1,3-cyclopropanemethanol] (15) and (±)-[2-[4,8-Dimethyl-3,7-(3*E*)-nonadienyl]-2-methyl-3-[2,6,10-trimethyl-1,5,9-(1*E*,5*E*)-undecatrienyl]-*trans*-1,2-*cis*-1,3-cyclopropanemethanol] (16). The chilled ethereal solution (13 mL) containing *trans,trans*-diazofarnesal **13** was added dropwise to a magnetically stirred suspension of 1.53 g of zinc iodide (4.8 mmol) and 1.02 g of *trans,trans*-farnesol **7** (4.02 mmol) in 15 mL of ether under nitrogen at 0 °C. Gas evolution was immediate, as was loss of the red-orange diazo color. The mixture was stirred 0.25 h at 0 °C, allowed to warm to room temperature, and extracted with three portions of brine (15 mL each). The ether was then removed under reduced pressure in the presence of fresh brine (50 mL), and this brine was then extracted with three portions of petroleum ether (25 mL each). The combined organic layer was then dried over sodium sulfate and the solvent removed under reduced pressure, yielding 2.27 g of yellow-orange oil.

Purification of 15. Two grams of the above mixture was separated by preparative TLC (system A, 25:75) to give 232 (R_f 0.57) and 153 mg (R_f 0.45), the second and third yellow bands, respectively.

The more polar band showed leading and trailing impurities, as well as chromatographically nonmobile material. Twice repeated preparative TLC (system A, 20:80) gave 86 mg of **15** (R_f 0.32). This material proved homogeneous in the following VPC systems: column one, 215 °C, 38 mL of N_2/min, 9.50 min; column two, 220 °C, 32 mL of N_2/min, 16.5 min. NMR ($CDCl_3$, 100 MHz) δ 5.2 (4 H, br, vinylic protons), 4.93 (d, J = 8 Hz, 1 H, vinyl proton coupled with cyclopropyl proton), 3.60 (2 H, AB of an ABX pattern, J_{ab} = 11.5, J_{ax} = 6.7, J_{bx} = 8.8 Hz, $\Delta\nu_{ab}$ = 0.25 ppm, CH_2OH), 2.00 (16 H, br, allylic methylenes), 1.68 and 1.60 (21 H, s, allylic methyls), 1.15 (s, cyclopropylmethyl) [there were also additional unresolved resonances between δ 1.5 and 0.8 (cyclopropyl protons)]; IR (film) 3400, 2970, 2925, 2855, 1665, 1450, 1380, 1375, 1110, 1045, 835 cm^{-1}; mass spectrum (70 eV, direct inlet) 426 (M^+), 408, 395, 357, 339, 289, 271, 257, 215, 203 (base) 147, 137, 69. Anal. Calcd for $C_{30}H_{50}O$: C, 84.44; H, 11.81. Found: C, 84.35, 84.29; H, 11.69, 11.71.

Purification of 16. The second band from the initial separation was twice thin-layer chromatographed (system A, 25:75) to yield 40 mg (R_f 0.57). Minor impurities were observed by analytical TLC, but the sample was pure to preparative layer chromatography (1-mm plate) in the following systems: system A (25:75), R_f 0.57; system A (20:80), R_f 0.45; methylene chloride, R_f 0.39; system B (30:70), R_f 0.56. VPC data: column one, 215 °C, 38 mL of N_2/min, 12.6 min; column two, 220 °C, 32 mL of N_2/min, 21.5 min. This compound slowly decomposed upon storage in solvent at −20 °C; NMR ($CDCl_3$, 100 MHz) δ 5.04 (5 H, br, vinylic protons), 3.60 (2 H, d, J = 7.5 Hz, CH_2OH), 2.00 (16 H, br, allylic methylenes), 1.65 and 1.57 (21 H, s, allylic methyls), 1.02 (s, cyclopropylmethyl) [there were additional unresolved resonances between δ 1.5 and 0.8 (cyclopropyl protons)]; IR (film) 3400, 2970, 2950, 2875, 1450, 1380, 1375, 1110, 1020, 835 cm^{-1}; mass spectrum (70 eV, direct inlet) 426 (M^+), 408, 395, 357, 339, 289, 271, 257, 215, 203 (base), 147, 137, 69. Anal. Calcd for $C_{30}H_{50}O$: C, 84.44; H, 11.81. Found: C, 84.40; H, 12.00.

(±)-[2-[4,8-Dimethyl-3,7-(3*E*)-nonadienyl]-2-methyl-3-[2,6,10-trimethyl-1,5,9-(1*E*,5*E*)-undecatrienyl]-*cis*-1,2-*trans*-1,3-cyclopropanemethanol] (21) and (±)-[2-(4,8-Dimethyl-3,7-(3*E*)-nonadienyl]-2-methyl-3-[2,6,10-trimethyl-1,5,9-(1*E*,5*E*)-undecatrienyl]-*cis*-1,2-*cis*-1,3-cyclopropanemethanol] (22). A chilled ethereal solution (15 mL) of *trans,trans*-diazofarnesal **13,** derived from 2.62 g of *trans,trans*-farnesal (11.9 mmol), was added dropwise to a magnetically stirred suspension of 1.12 g of zinc iodide (3.5 mmol) and 1.11 g of *cis,trans*-farnesol **20** (5.0 mmol) in 15 mL of ether under nitrogen at 0 °C. Gas evolution was immediate, as was loss of the red-orange diazo color. The mixture was stirred 0.5 h at 0 °C, allowed to warm to room temperature, and extracted with three portions of brine (25 mL each). The ether was then removed under reduced pressure in the presence of fresh brine (50 mL), and this brine was extracted with three portions of petroleum ether (35 mL each). The combined organic layer was dried over sodium sulfate and the solvent removed under reduced pressure yielding 3.12 g of yellow-brown oil.

The mixture was chromatographed on 425 g of silica on a 37 × 765 mm column at a flow of 10 mL/min. Elution with 1000 mL of petroleum ether and then 1000 mL each of 1, 2, 5, and 10% ether-petroleum ether yielded 310 mg of nonpolar impurities. The flow was lowered to 3 mL/min and elution continued using an additional 3000 mL of 10% and 3000 mL of 20% ether-petroleum ether, taking 21-mL fractions. The desired products were predominantly in fractions 110–130 (150 mg), 131–155 (220 mg), and 156–195 (420 mg). The total material eluted was 2.23 g.

Purification of 21. Fraction 156–195 (420 mg) was separated by preparative TLC (system A, 20:80) to give 299 mg of yellow oil (R_f 0.36) which was further purified as follows.

(a) An 83-mg sample was separated by continuous elution preparative TLC (toluene, 3.0 h) to give major fractions of 38 (R_f 0.45)

and 21 mg (R_f 0.25). Although homogeneous to double-elution TLC (system A, 15:85; R_f 0.47), the NMR spectrum showed each fraction to be impure. This mixture was separated by high-pressure liquid chromatography (Waters Associates ALC 201, 6 ft × 1/8 in. Corasil II, 37-75 μ) using 1% ethyl acetate (distilled from phosphorus pentoxide) in hexane (acid washed and distilled from calcium hydride). At an indicated flow of 2.3 mL/min, the major product **21** had a retention time of 31 min (33 mg, 40%) and was homogeneous in the following TLC systems: system A (20:80), R_f 0.36; system B (5:95, 4.16 h), R_f 0.37. VPC data: column one, 225 °C, 38 mL of N_2/min, 8.50 min; column one, 205 °C, 38 mL of N_2/min, 23.2 min; column two, 220 °C, 32 mL of N_2/min, 13.1 min.

(b) A 215-mg portion was separated by continuous-elution preparative TLC (system B, 5:95; 3.0 h) to yield 98 mg (R_f 0.52), which was then rechromatographed in the same system for 4.0 h. There appeared a single heavy band (R_f 0.40), the middle three-eights of which yielded pure **21** (81 mg, 38%), homogeneous as in part a.

The total yield of pure **21** was 114 mg. In addition, there was isolated another 40 mg containing less than 5% of epimer **22** as the only impurity: NMR ($CDCl_3$, 100 MHz) δ 5.16 (4 H, br, vinylic protons), 4.90 (1 H, d, J = 8 Hz, vinyl proton split by cyclopropyl proton), 3.71 (2 H, AB of an ABX pattern, J_{ab} = 11.5, J_{ax} = 7.1, J_{bx} = 7.9 Hz, $\Delta\nu_{ab}$ = 0.08 ppm, CH_2OH), 2.03 (16 H, br, allylic methylenes), 1.69 and 1.61 (21 H, s, allylic methyls), 1.13 (s, cyclopropylmethyl) [there were additional unresolved resonances between Δ 1.6 and 0.8 (cyclopropyl protons)]; IR (film) 3325, 2970, 2925, 2850, 1665, 1450, 1380, 1375, 1100, 1045, 835 cm^{-1}; mass spectrum (Varian MAT 711, 70 eV, direct inlet) 426 (M^+), 408, 395, 357, 339, 289, 271, 257, 215, 203, 147, 137, 69 (base). *Anal.* Calcd for $C_{30}H_{50}O$: C, 84.44; H, 11.81. Found: C, 84.18; H, 11.78.

Purification of 22. Column fraction 111-130 (150 mg) was separated by preparative TLC (system A, 15:85) to yield, as major bands, 97 (band A, R_f 0.50) and 35 mg (band B, R_f 0.40). Bands A and B were then purified separately by continuous-elution TLC (system B, 5:95; 3.33 h) to yield a total of 25 mg (R_f 0.33) of impure **22.**

Column fraction 131-155 (262 mg) was twice continuously eluted as above for 4.25 h to yield 24 mg of **22** (R_f 0.47).

A total of 49 mg of **22,** contaminated with **21** in approximately 1:1 ratio, was purified by high-pressure liquid chromatography (6 ft × 1/8 in. Corasil II, 37-75 μ, ethyl acetate-petroleum ether, 1:99) to yield 0.33) of impure **22.**

Column fraction 131-155 (262 mg) was twice continuously eluted as above for 4.25 h to yield 24 mg of **22** (R_F]/47(/

A total of 49 mg of **22,** contaminated with **21** in approximately 1:1 ratio, was purified by high-pressure liquid chromatography (6 ft × 1/8 in. Corasil II, 37-75 μ, ethyl acetate-petroleum ether, 1:99) to yield 23 mg of **22,** retention time 20.0 min.

In addition, other chromatographic fractions gave a total of 92 mg of a 40:60 mixture of **21** and **22.**

The final material was homogeneous in the following TLC systems: system A (20:80), R_f 0.38; system B (5:95; 4.16 h), R_f 0.46. The following VPC systems showed less than 3% of epimer **21** as the only impurity: column one, 225 °C; 38 mL of N_2/min, 6.35 min; column two, 220 °C, 32 mL of N_2/min, 10.0 min. NMR ($CDCl_3$, 100 MHz) δ 5.09 (5 H, br, vinylic protons), 3.70 (2 H, AB of an ABX pattern, J_{ab} = 11.5, J_{ax} = 7.1, J_{ab} = 8.4, $\Delta\nu_{ab}$ = 0.16 ppm, CH_2OH), 2.06 and 2.01 (16 H, s, allylic methylenes), 1.69 and 161 (21 H, s, allylic methyls), 1.12 (s, cyclopropylmethyl) [there were additional unresolved resonances between δ 1.6 and 1.0 (cyclopropyl protons)]; IR (film) 3400, 2970, 2925, 2850, 1665, 1450, 1380, 1375, 1100, 1045, 835 cm^{-1}; mass spectrum (Varian MAT 711, 70 eV, direct inlet) 426 (M^+), 408, 395, 357, 339, 289, 271, 257, 203, 147, 137, 69 (base). Anal. Calcd for $C_{30}H_{50}O$: C, 84.44; H, 11.81. Found: C, 84.32; H, 11.68.

***cis,trans*-Farnesal [3,7,11-Trimethyl-2,6,10-(2*Z*,6*E*)-dodecatrienal].** Powdered manganese dioxide (4.55 g, 523 mmol, 16 equiv) was added to a mechanically stirred solution of 0.71 g of *cis,trans*-farnesol **20** (3.25 mmol) in 40 mL of petroleum ether under nitrogen at 0 °C. The reaction was followed by TLC (methylene chloride), which indicated no alcohol remaining after 0.9 h. The mixture was filtered, the residue being washed well with ether. The solvent was removed under reduced pressure, leaving 0.70 g of *cis,trans*-farnesal (99%): NMR ($CDCl_3$, 60 MHz) δ 9.90 (1 H, d, J = 8 Hz, aldehydic proton) [lit.[41b] δ 9.90 (1 H, d, J = 8 Hz, aldehydic proton)]. Other resonances were δ 5.86 (1 H, d, J = 8 Hz, vinyl proton split by aldehydic proton), 5.12 (2 H, br, vinylic protons), 2.60, 2.50, 2.40, 2.30, 2.18, 2.05, 1.98, 1.95 (s, 11 H, methylene protons and conjugated allylic methyls), 1.67, 1.58 (s, 9 H, unconjugated allylic methyls). Integration of the aldehydic proton showed the presence of 6% of *trans,trans*-farnesal isomerization product: IR (film) 2970, 2920, 2850, 2770, *1675,* 1630, 1610, 1440, 1385, 1190, 1150, 1120, 835 cm^{-1}.

***cis,trans*-Farnesal Hydrazone [3,7,11-Trimethyl-2,6,10-(2*Z*,6*E*)-dodecatrienal Hydrazone].** *In order,* 2.7 mL of triethylamine (18.8 mmol) and 0.58 mL of anhydrous hydrazine (18.8 mmol) were added to a stirred solution of 690 mg of *cis,trans*-farnesal (3.14 mmol) in 50 mL of anhydrous ethanol under nitrogen. The reaction was monitored and worked up following the procedure for *trans,trans*-farnesyl hydrazone **11**: IR (film) *3395, 3220,* 2970, 2925, 2850, 2725, 1640, 1575, 1450, 1380, 1375 cm^{-1}.

***cis,trans*-Diazofarnesal [Diazo-3,7,11-trimethyl-2,6,10-(2*Z*,6*E*)-dodecatriene] (23).** The *cis,trans*-farnesal hydrazone (3.1 mmol) in 20 mL of ether was added to a mechanically stirred suspension of 2.35 g of sodium carbonate (22 mmol) in 30 mL of ether under nitrogen at 0 °C. Powdered manganese dioxide (2.35 g, 27 mmol) was added and the suspension rapidly stirred for 1.0 h. This reaction was worked up following the procedure for *trans,trans*-diazofarnesal **13**: IR (film) 2965, 2925, 2845, *2055,* 1640, 1450, 1380, 1375, 1190, 1155, 850 cm^{-1} [lit.[41a] 2050 cm^{-1} (diazo function)].

Presumed Alcohols α and β Reaction Mixture. The chilled ethereal solution (10 mL) containing *cis,trans*-diazofarnesal was added dropwise to a magnetically stirred suspension of 0.33 g of zinc iodide (1.03 mmol) and 0.60 g of *trans,trans*-farnesol **7** (2.70 mmol) in 10 mL of ether under nitrogen at 0 °C. The usual procedure gave 1.23 g of yellow oil.

Analysis of the crude reaction mixture by VPC (column one, 215 °C, 38 mL of N_2/min) showed two peaks at 9.8 and 12.6 min in approximately 75.25 ratio. Coinjection of this reaction mixture with the crude reaction mixture derived from addition of *trans*-diazo to *trans,trans*-farnesol **7** (containing known alcohols **15** and **16**) gave only two polar peaks with alcohol α coinjecting with alcohol **15** and alcohol β coinjecting with alcohol **16.**

The above mixture from *cis*-diazo addition was separated (system A, 20:80) into 338 mg of I (R_f 0.85), 138 mg of II (R_f 0.72), 93 mg of III (R_f 0.54), and 531 mg of IV (R_f 0.35).

Band I, homogeneous to TLC, contained only sesquicarene, the NMR and IR spectra in accordance with the literature.[41] No 30-carbon triene **26** was detectable by NMR in this fraction.

Band IV was homogeneous, consisting of *trans,trans*-farnesol.

Band II was heterogeneous. Further purification in TLC solvent system A (20:80) gave two bands, IIa (63 mg, R_f 0.60) and IIb (31 mg, R_f 0.45).

Band IIa was the bright yellow azine dimer **19,** an isomer mixture, as two barely resolved spots were noted by analytical TLC: NMR (CCl_4, 60 MHz) δ 8.35 (2 H, d, J = 10 Hz, proton on carbon attached to nitrogen), 6.10 (2 H, d, J = 10 Hz, conjugated vinyl proton), 5.12 (4 H, br, vinylic protons), 2.14, 2.07, 1.93, (s, 22 H, allylic methylenes and conjugated allylic methyl), 1.65, 1.58 (s, 18 H, unconjugated allylic methyls); IR (film) 2970, 2920, 2850, 2730, *1640,* 1585, 1440, 1385, 1110, 1030, 855, 785 cm^{-1}.

By NMR, band IIb was a mixture of *cis*- and *trans*-farnesal (67:33) and alcohol β in a 1:1 ratio.

Band III was also heterogeneous. Double-elution TLC (system A, 20:—)(GAVE TWO MAJOR BANDS= IIc (22 mg, R_f 0.60) and IIId (48 mg, R_f 0.50). Band IIIc was by NMR and TLC a mixture of alcohol β and alcohol α in 3:1 ratio.

Pure samples of alcohols α (14 mg, R_f 0.51) and δ (6 mg, R_f 0.75) were obtained by TLC of band IIId (system B, 8:92; 4.0 h). An intermediate band (22 mg, R_f 0.66) was a mixture of α and β. The NMR spectrum of pure α was indistinguishable from that of alcohol **15.** The NMR spectrum of alcohol β was indistinguishable from that of alcohol **16.** Further chromatographic comparisons of these alcohols are given in Table III and indicate that alcohols α and β are identical with alcohols **15** and **16.**

***trans,trans,trans*-Geranylgeranial [3,7,11,15-Tetramethyl-2,6,10,14-(2*E*,6*E*,10*E*)-hexadecatetraenal].** Powdered manganese dioxide (2.03 g, 23.3 mmol, 15 equiv) was added to a mechanically stirred solution (98% by VPC) of 450 mg of *trans,trans,trans*-geranylgeraniol **8** (1.55 mmol) in 65 mL of petroleum ether under nitrogen at 0 °C. The reaction was followed by TLC (methylene chloride), which showed no alcohol after 1.1 h. The mixture was filtered, the residue being washed well with ether. The solvent was removed under reduced pressure, giving a recovery of 433 mg of geranylgeranial

(97%): NMR (CCl_4, 60 MHz) δ 9.93 (1 H, d, J = 8 Hz, aldehydic proton), 5.75 (1 H, d, J = 8 Hz, vinyl proton split by aldehydic proton), 5.05 (3 H, br, vinylic protons), 2.21, 2.14, 1.99 (15 H, s, 4 allylic methylenes nearest carbonyl, allylic methyl nearest carbonyl, remaining allylic methylenes), 1.58, sh 1.65 (12 H, br s, allylic methyls); IR (film) 2970, 2915, 2850, 2765, 2725, *1670,* 1630, 1610, 1440, 1385, 1190, 1120 cm^{-1}.

***trans,trans,trans*-Geranylgeranial Hydrazone [3,7,11,15-Tetramethyl-2,6,10,14-(2*E*,6*E*,10*E*)-hexadecatetraenal Hydrazone].** *In order,* 0.64 mL of triethylamine (9.1 mmol, 6 equiv) and 0.32 mL of 85% hydrazine solution (9.1 mmol, 6 equiv) were added to a stirred solution of 433 mg of *trans,trans,trans*-geranylgeranial (1.50 mmol) in 60 mL of anhydrous ethanol under nitrogen. The reaction was followed by TLC (methylene chloride), which showed no aldehyde after 0.75 h. Volatile material was removed at 1 mmHg pressure and bath temperature less than 40 °C. The residue was extracted twice with ether (10 mL each); the organic layer was washed twice with ice-cold brine (15 mL each), and the brine was back extracted with ether (5 mL). The combined organic layers were dried over sodium carbonate and used immediately: IR (film) *3390, 3220,* 2970, 2925, 2850, 2725, 1640, 1580, 1450, 1380, 1375, 1030 cm^{-1}.

***trans,trans,trans*-Diazogeranylgeranial [Diazo-3,7,11,15-tetramethyl-2,6,10,14-(2*E*,6*E*,10*E*)-hexadecatetraene] (14).** The *trans,trans,trans*-geranylgeranial hydrazone (1.5 mmol) in 25 mL of ether was added to a mechanically stirred suspension of 910 mg of granular sodium carbonate (—/6 MMOL(IN [] ML of ether under nitrogen at 0 °C. Powdered manganese dioxide (910 mg, 10.5 mmol, 7 equiv) was added and the suspension was rapidly stirred for 1.0 h. The mixture was filtered through a glass frit containing sodium sulfate, the residue being washed well with ether. The receiver for the deep red-orange filtrate was a 250-mL round-bottom flask with a magnetic stirring bar; the solvent was removed at 1 mmHg pressure and 0 °C bath temperature to a final volume about 3 mL; the blood red solution was used immediately: IR (film) 2965, 2925, 2850, *2055,* 1645, 1450, 1385 cm^{-1}.

(±)-Prephytoene Alcohol [2-[4,8,12-Trimethyl-3,7,11-(3*E*,7*E*)-tridecatrienyl]-2-methyl-3-[2,6,10,14-tetramethyl-1,5,9,13-(1*E*,5*E*,9*E*)-pentadecatetraenyl]-*trans*-1,2-*trans*-1,3-cyclopropanemethanol] (17). The chilled ethereal solution (10 mL) containing diazogeranylgeranial **14** was added dropwise to a magnetically stirred suspension of 420 mg of zinc iodide (1.3 mmol) and 420 mg of *trans,trans,trans*-geranylgeraniol **8** (1.45 mmol) in 8 mL of ether under nitrogen at 0 °C. Gas evolution was immediate, as was loss of the red-orange diazo color. Evolved nitrogen (28.2 mL, theory = 34.7 mL, 81%) was measured with a gas buret. The mixture was stirred 0.25 h at 0 °C, allowed to warm to room temperature, and extracted with three portions of brine (10 mL each). The ether was removed under reduced pressure in the presence of fresh brine (20 mL), and this brine was then extracted with three portions of petroleum ether (10 mL each); the combined organic layers were dried over sodium sulfate and, after removal of solvent, yielded 685 mg of yellow oil.

Purification of 17. The reaction mixture (685 mg) was separated by preparative TLC (system A, 15:85) to give 115 mg of impure **17** (R_f 0.45). Fifty-six milligrams of this was rechromatographed in the same system to yield 36 mg (R_f 0.40); its NMR spectrum showed no extraneous resonances. This material was then chromatographed on a 5.0-g Florisil column, eluting in ether–petroleum ether (3:97) to give 33 mg of **17** homogeneous to analytical TLC [(system A, 15:85) R_f 0.36] and VPC (column three, 240 °C, 100 mL of He/min, 2.5 min): NMR (CCl_4, 100 MHz) δ 5.03 (6 H, br, vinylic protons), 4.87 (1 H, d, H = 8 Hz, vinyl proton split by cyclopropyl proton), 3.56 (2 H, AB of an ABX pattern, J_{ab} = 11.5, J_{ax} = 6.5, J_{bx} = 9.0, $\Delta\nu_{ab}$ = 0.26 ppm, CH_2OH), 2.01 (24 H, s, allylic methylenes), 1.65 and 1.56 (27 H, s, allylic methyls), 1.12 (s, cyclopropylmethyl) [there were additional unresolved resonances between δ 1.4 and 0.8 (cyclopropyl protons)]; IR (film) 3350, 2970, 2925, 2850, 1665, 1450, 1380, 1375, 1115, 1045, 835 cm^{-1}; mass spectrum (70 eV, direct inlet) 562 (M^+), 544, 531, 493, 475, 425, 407, 357, 339, 271, 257, 176, 149, 137 (base), 81, 69. Anal. Calcd for $C_{40}H_{66}O$: C, 85.34; H, 11.82. Found: C, 85.06; H, 11.56.

Resolution of Presqualene Alcohol 15. Presqualene alcohol (200 mg) in pyridine (0.5 mL) was added to freshly prepared 3β-acetoxy-17β-chloroformylandrost-5-ene (184 mg) in dry pyridine (3 mL). After stirring for 24 h at room temperature, the mixture was poured into ice-cold diluted HCl (20%) and extracted with methylene chloride. The combined methylene chloride extracts were washed with more cold diluted HCl and then water, dried over $MgSO_4$, and evaporated to give a residue. This was purified by preparative layer chromatography (15% Et_2O–CCl_4) to yield the mixed diastereomeric esters (132 mg, 60%) and unreacted presqualene alcohol (80 mg): $[\alpha]_D$ −14.5° (c 0.029, $CHCl_3$); NMR ($CDCl_3$) δ 5.2 (4 H, br, vinylic protons), 5.3 (1 H, br, d, J = 4 Hz, ring β vinyl proton), 4.93 (d, J = 8 Hz, 1 H, vinyl proton), 4.55 (1 H, br, CHOAc), 3.6 (2 H, multiplet of 12 lines for two diastereomers), 2.01 (sharp $OCOCH_3$), 2.0 (br, allylic and ring methylenes), unresolved resonances between 1.5 and 0.8 (cyclopropyl protons), 1.01 (C-18 Me), and 0.70 (C-19 Me). Anal. Calcd for $C_{52}H_{80}O_4$: C, 81.20; H, 10.28. Found: C, 81.41; H, 10.68.

The diastereomers were separated by high-pressure liquid chromatography on μ-Porasil (Water Associates, 3.9 mm i.d. × 30 cm; eluent dichloromethane; 1 mL/min). The less polar ester had $[\alpha]^{20}_D$ −8.0° (c 0.0025, $CHCl_3$).

The less polar ester (5.0 mg) in anhydrous ether (2 mL) was refluxed for 30 min with lithium aluminum hydride (18 mg, 0.5 mmol). Workup in the usual fashion and chromatographing on a short Florisil column then afforded (+)-presqualene alcohol (2.5 mg): 90% yield; $[\alpha]^{20}_D$ 47.0° (c 0.0010, $CHCl_3$). The more polar isomeric ester similarly gave (−)-presqualene alcohol, $[\alpha]^{20}_D$ −48.0° (c 0.0011, $CHCl_3$).

Resolution of Prephytoene Alcohol 17. This was performed exactly as described above for presqualene alcohol. The mixed diastereomeric esters were obtained in 75% yield: $[\alpha]^{20}_D$ (c 0.0078, $CHCl_3$). The diastereomers were separated by high-pressure liquid chromatography on μ-Porasil (Waters Associates, 3.9 mm i.d. × 30 cm; eluent dichloromethane; 1 mL/min): NMR ($CDCl_3$) δ 5.2 (6 H, br, vinyl protons), 5.3 (1 H, br d, J = 4 Hz), 4.93 (d, J = 8 Hz, 1 H, vinyl proton), 4.5 (1 H, br, C*H*OAc), 3.6 (2 H, multiplet of 12 lines for cyclopropyl carbinyl diastereotopic protons), 2.61 (sharp, -O-$COCH_3$), 2.0 (br allylic and ring methylenes), 1.68 and 1.66 (27 H, s, allylic methyls), 1.14 (s, cyclopropylmethyl), unresolved resonances between δ 1.5 and 0.8 for cyclopropyl protons, 1.01 (C-18 Me), and 0.70 (C-19 Me). Anal. Calcd for $C_{62}H_{96}O_4$: C, 82.24; H, 10.69. Found: C, 82.45; H, 10.81.

The less polar ester had $[\alpha]^{20}_D$ 5.5° (c 0.0054, $CHCl_3$) and the more polar ester had $[\alpha]^{20}_D$ −20.0° (c 0.0050, $CHCl_3$).

The less polar ester (6.8 mg) in anhydrous ether (2 mL) was refluxed for 30 min with lithium aluminum hydride (18 mg, 0.5 mmol). Workup in the usual fashion and chromatographing on a short Florisil column then afforded (+)-prephytoene alcohol (3.8 mg): 90% yield; $[\alpha]^{20}_D$ 38.0° (c 0.0037, $CHCl_3$). The more polar isomeric ester similarly gave (−)-prephytoene alcohol, $[\alpha]^{20}_D$ −37.0° (c 0.0035, $CHCl_3$).

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Model Studies for Anthracyclinone Synthesis. The Chemistry of 1-Lithio-3,3,6,6-tetramethoxycyclohexa-1,4-diene, an Umpolung† for Quinone‡[1]

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Abstract: Anodic oxidation of 2-bromo-1,4-dimethoxybenzene (**6b**) in 1–2% methanolic potassium hydroxide affords 1-bromo-3,3,6,6-tetramethoxycyclohexa-1,4-diene (**8**) in 70–80% yield. This bromo bisketal undergoes metal–halogen exchange with alkyllithiums at −70 °C to afford solutions of the corresponding lithio derivative, **9**. The resulting organolithium reagent reacts with cyclohexanone (81%), cycloheptanone (40%), benzaldehyde (68%), benzophenone (72%), benzil (60%), methyl benzoate (78%), benzoylpiperidine (68%), benzoyl chloride (67%), and dimethyl phthalate (70%) to form adducts in the indicated yields. This comprises a method for preparation of functionalized protected quinones. However, **9** yields adducts in poor yields with alkyl, allyl, and benzyl halides and easily enolized substrates. The regioselectivity of the reaction of **9** and dimethyl 3-methoxyphthalate involves attack at the more reactive and the less hindered 1-carbonyl group. A brief comparison is made of the reactions of **9** and 2-lithio-1,4-dimethoxybenzene.

Introduction

While the quinone moiety is widely represented in naturally occurring compounds, few methods are available for direct carbon–carbon bond formation on the quinone nucleus.[4] C-Alkylation has been accomplished via a radical addition–oxidation sequence[5] while C-arylation is generally performed in high yield by reaction of benzoquinones with diazonium salts.[6] Hegedus has extensively explored the utility of the coupling of quinones to allylic fragments via π-allyl nickel halide complexes.[7] Recent routes to the isoprenylation of naphthoquinones have involved the use of trimethylsilyl cyanide protected quinones[8] and quinone bisketal copper–lithium reagents.[9] Aside from the novel approach of Moore[10a] to 2,5-disubstituted 1,4-benzoquinones, conventional methodology for preparing substituted quinones has involved either additions to quinones to afford reduced derivatives followed by oxidation in a sub-

† A reagent which reverses the normal type of reactivity, in this case causing the quinone to be a nucleophile rather than an electrophile.
‡ Dedicated to Professor Melvin S. Newman on his 70th birthday.

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