Acid-catalysed Intramolecular Cyclization of Geranyl Hydroquinone Derivatives from *Cordia alliodora*. *X*-Ray Crystal and Molecular Structure of 1,2,3,3a,4,9,10,10a-Octahydro-5,8-dimethoxy-3,10-dimethyl-3a,9-epoxybenz[*f*]azulene

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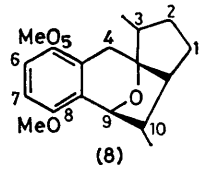
The aqueous acid-catalysed intramolecular cyclization of dimethylated alliodorin (2) obtained from the heartwood of *Cordia alliodora* has been characterized by *X*-ray analysis as the unusual tetracyclic di-*O*-methyl hydroquinone title compound (8). A new synthesis of di-*O*-methylalliodorin (2) from a terminal methylallylic sulphide derivative of 2-geranyl-1,4-dimethoxybenzene is described.

Crystals of the title compound (8) are monoclinic, space group $P2_1/c$, unit cell dimensions a = 14.984(7), b = 5.206(4), c = 20.131(9) Å, β = 99.77(1)°, Z = 4. The structure was solved by direct methods and refined by least-squares calculations to an R value of 0.078 for 1 832 independent reflections measured on a diffractometer using Cu-K_α radiation.

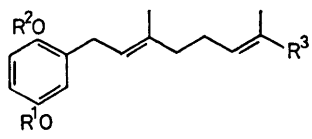
THE characterization of cordiachromes [1] from the wood of several *Cordia* species (Boraginacae) and the subsequent identification of several geranyl hydroquinone derivatives [2] from the marine borer-resistant heartwood of *Cordia alliodora* Ruiz and Pav. led to a proposal [2] that the biogenesis of these compounds may involve an acid-catalysed intramolecular cyclization of geranyl carbinol intermediates. The relatively high concentration of alliodoron (1) in *C. alliodora* suggests its biogenetic prominence in this tree and its possible role as a precursor to *Cordia* geranyl hydroquinone derivatives and related compounds which may co-occur, but are as yet undetected, in *Cordia* spp. The availability of alliodorin, and the desire to eliminate the complications of hydroquinone oxidation as an experimental factor, dictated the selection of di-*O*-methylalliodorin (2) for an initial investigation of the effect of aqueous acid on geranyl hydroquinone derivatives in relation to the biogenesis of these compounds in *Cordia* spp.

We now report the isolation and characterization of an unusual tetracyclic di-*O*-methyl hydroquinone compound (8) obtained from the aqueous acid-catalysed intramolecular cyclization of di-*O*-methylalliodorin (2). We also report an alternative synthesis of di-*O*-methylalliodorin.

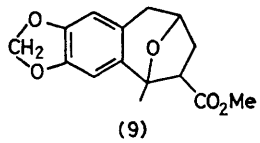
Di-*O*-methylalliodorin (2), obtained from the methylation of naturally occurring alliodorin, was suspended in aqueous formic acid–ascorbic acid under nitrogen. The dark oil obtained was chromatographed on silica and one of the chromatographic fractions crystallized upon concentration. Recrystallization yielded compound (8) ($C_{18}H_{24}O_3$) as needles (m.p. 112—113 °C). Its ^{1}H n.m.r. spectrum showed two alkyl methyl groups as doublets (J 6 Hz) at δ 1.00 and 1.10, seven alkyl protons in two multiplets at δ 1.3—1.8 (3 H) and 2.2—2.5 (4 H), two geminally coupled benzylic protons as doublets (J 14 Hz) at δ 2.48 and 2.92, a single benzylic ether or alcohol proton as a singlet at δ 4.96, two equivalent *ortho*-coupled protons as a singlet at δ 6.57, and two aromatic methoxy-protons as a singlet at δ 3.75. Its ^{13}C n.m.r. spectrum showed the presence of oxygen-substituted quaternary and tertiary carbons atoms at δ 94.1 and 80.0 p.p.m., respectively. Other significant signals in the aliphatic region include those of three methylene



(8)



(1) $R^1 = R^2 = H$, $R^3 = CHO$
(2) $R^1 = R^2 = Me$, $R^3 = CHO$
(3) $R^1 = R^2 = COMe$, $R^3 = CHO$
(4) $R^1 = R^2 = Me$, $R^3 = CH_2OH$
(5) $R^1 = R^2 = COMe$, $R^3 = CH_2OH$
(6) $R^1 = R^3 = Me$, $R^2 = H$
(7) $R^1 = R^2 = R^3 = Me$



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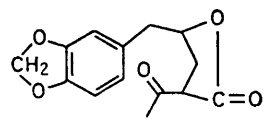

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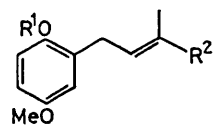
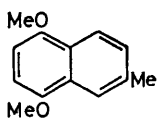


(11) $R^1 = H$, $R^2 = Me$
(12) $R^1 = R^2 = Me$
(13) $R^1 = Me$, $R^2 = CHO$



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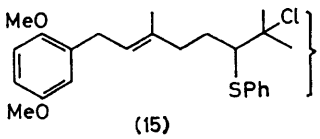

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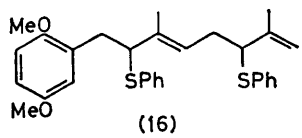

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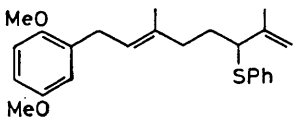
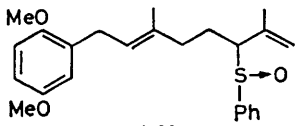


(17)



(18)

groups (24.4, 31.6, and 35.0 p.p.m.), three methine groups (41.6, 46.2, and 48.6 p.p.m.), and two alkyl methyl groups (14.7 and 16.0 p.p.m.). The spectrum also shows two aromatic methoxy-groups (55.5 and 55.8 p.p.m.), two aromatic CH resonances (107.5 and 107.8 p.p.m.), and four substituted aromatic carbon atoms (122.9, 130.9, 148.8, and 157.5 p.p.m.). Its i.r. spectrum showed no hydroxy-band and attempted catalytic hydrogenation and derivative-formation were unsuccessful.

These data provide evidence that the compound is a 2,3-substituted, tetracyclic derivative of di-*O*-methylalliodorin having no unsaturation with the exception of the aromatic system; thus an epoxy-bridge is indicated. The structure of compound (8) was established by single-crystal *X*-ray analysis.

The molecular conformation, the thermal motion of the atoms, and the numbering system used in the *X*-ray investigation are illustrated in Figure 1, which shows the

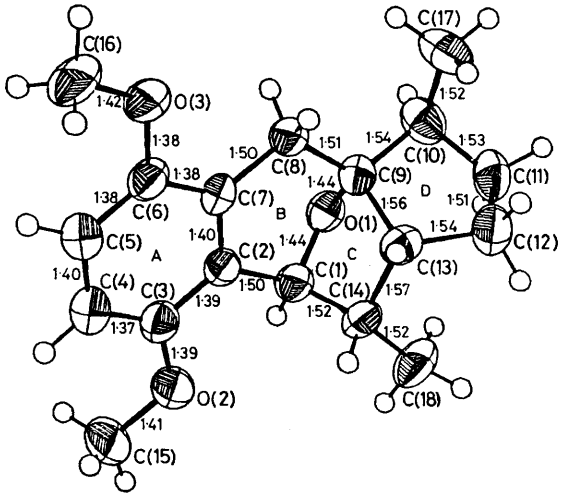


FIGURE 1

aromatic ring (A) to be coplanar with the C(8), C(9), and C(1) carbon atoms of the adjacent B ring.[3] The bridged oxygen is oriented below the A/B plane and is nearly coplanar with the carbon atoms of ring C. The angle of the B/C ring junction approaches 90° (Table 1). The

TABLE 1

Dihedral angle (°) between planes [a]

Plane	Angle	Plane	Angle
A–B	6.4	B–C	−88.9
A–C	86.1	B–D	68.5
A–D	62.5	C–D	60.3

[a] Definition of planes (see Figure 1): A, C(2)—C(7); B, O(1), C(1), C(2), C(7)—C(9); C, O(1), C(1), C(13), C(14), C(9); D, C(9)—C(13).

furan and cyclopentane rings are nearly planar, maximum deviations from a least-squares plane being ±0.3 Å. The hydrogen atoms on C(1) and C(10) are *cis* to the bridged oxygen and *trans* to the hydrogen atoms on C(13) and C(14). The observed interatomic bond distances (Figure 1) and angles between non-hydrogen atoms (Figure 2) are in good agreement with the expected values. Intermolecular bonding is absent in the crystal which indicates that the molecules are bound solely by van der Waals interactions.

The epoxide-bridged ring system of (8) has previously been reported in an isochroman intermediate (9) isolated

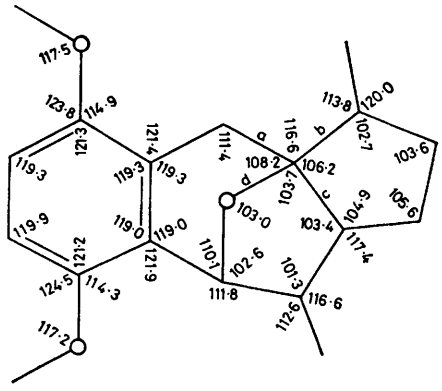
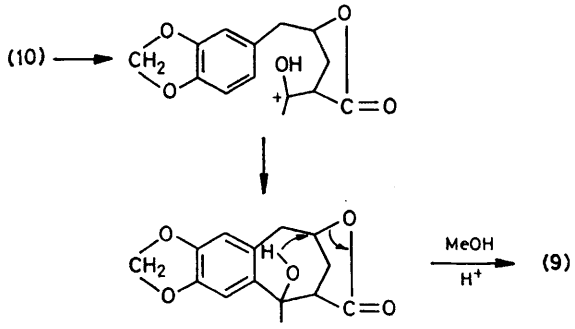


FIGURE 2

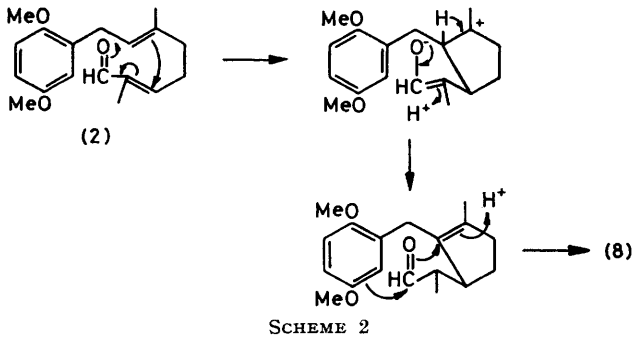
in the synthesis of arylnaphthalene lignans.[4] It was proposed that the isochroman originated from the acid-catalysed cyclization of the lactone (10) by the route in Scheme 1. A similar acid-catalysed mechanism (Scheme



SCHEME 1

2) can be proposed for the formation of (8) from di-*O*-methylalliodorin (2).

The characterization of (9) in the lignan synthesis offers evidence for the proposed acid-catalysed cyclization of aroylbutyrolactones. A similar acid-catalysed cyclization of allylic aldehydes, *e.g.*, di-*O*-methyl-

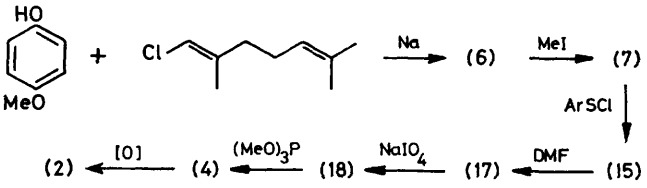


SCHEME 2

alliodorin, was observed (*vide infra*) in the action of aqueous acid on (13) obtained by selenium dioxide oxidation of (12) which was prepared from (11) *via* methylation. Treatment of (13) with aqueous formic–ascorbic acid yielded an oily product which, upon chromatography, yielded a major product ($C_{13}H_{14}O_2$) as fine needles (m.p. 55—57 °C). Its ^{1}H n.m.r. spectrum showed an aromatic methyl resonance at δ 2.45 (s), and other aromatic resonances including two isolated *ortho*-coupled doublets (*J* 10 Hz) at δ 6.48 and 6.58, and *ortho–meta* (δ 7.23, *J* 10 and 3 Hz), *meta–para* (δ 7.92, m), and *ortho–para* (δ 8.09, *J* 10, and 0.5 Hz) coupled resonances. It contains no hydroxy-groups (i.r.) and is not catalytically hydrogenated. These data are consistent with the compound being 1,4-dimethoxy-6-methylnaphthalene (14) which may be obtained from (13) through the intramolecular phenol–aldehyde condensation proposed for (8) followed by dehydration.

The prior characterization of (1) and the formation of (14) under conditions identical to those producing (8) from di-*O*-methylalliodorin offers evidence in support of the proposed mechanisms leading to (8) or (9). The synthesis and characterization of (8) and (14) strongly support the proposed biogenetic derivation of geranyl hydroquinone derivatives in *Cordia* spp.

Synthesis of Di-O-methylalliodorin (2).—The limited supply of natural geranyl hydroquinone derivatives for continuing and future studies established the need for a reliable synthetic source of terminally oxidized geranyl hydroquinone derivatives. Di-*O*-methylalliodorin has previously been synthesized by a multi-step procedure in 3.3% overall yield.[5] Selenium dioxide oxidation of geranyl hydroquinone diacetate has yielded alliodorin diacetate (3) and alliodorol diacetate (5) in 0.6 and 4.7%



SCHEME 3 DMF = dimethylformamide

overall yield respectively from geraniol and hydroquinone starting materials.[6,7]

Recent synthetic procedures producing high yields of *ortho*-geranyl phenols[8] and terminal allylic alcohol derivatives of geraniol[9] suggest an alternative synthesis of di-*O*-methylalliodorin (Scheme 3). This approach has now been applied to a synthesis producing di-*O*-methylalliodorin (2) in 11.2% overall yield.

Addition of geranyl chloride to an ether solution of *p*-methoxyphenol containing metallic sodium yielded 2-geranyl-4-methoxyphenol (6) as an oil (68.3%) upon distillation. Methylation of (6) yielded 2-geranyl-1,4-dimethoxybenzene (7) (97%). Treatment of (7) with benzenesulphenyl chloride in dry methylene dichloride (—50 °C) yielded an oily mixture of sulphide chloride adducts (15) which was treated, without further purification, with dimethylformamide (100 °C) to produce a mixture of the methylallylic sulphides (16) and (17). The mixture was separated on silica to yield the bis-methylallylic sulphide (16) (22%) and the desired methylallylic sulphide (17) (39.6%) as oils.

The dimethylallylic sulphide (16) ($C_{30}H_{34}O_2S_2$) was characterized by a ^{1}H n.m.r. spectrum showing two vinyl methyl singlets at δ 1.53 and 1.65, an isolated alkyl-methylene triplet (*J* 7 Hz) at δ 2.15, a benzylic methylene multiplet at δ 2.8—3.0, two sulphide proton triplets (*J* 7 Hz) at δ 3.29 and 4.00, two geminal vinylic methylene protons as broad singlets at δ 4.35 and 4.38, a single vinyl proton as a triplet (*J* 6.5 Hz) at δ 5.0, two aromatic methoxy-singlets (δ 3.63 and 3.66), and multiplets for three aromatic protons (δ 6.4—6.8), and ten phenylthio-protons (δ 6.9—7.5). Specific significant ^{1}H resonances observed for the sulphide (17) ($C_{24}H_{30}O_2S$) include a benzylic methylene doublet (*J* 8 Hz) at δ 3.29, a single sulphide proton triplet (*J* 7 Hz) at δ 3.59, two alkyl-methylene multiplets at δ 1.9—2.25, two vinyl methyl singlets at δ 1.67 and 1.73, a vinyl proton triplet (*J* 8 Hz) at δ 5.53, and two geminal vinylic methylene multiplets at δ 4.57 and 4.70.

Oxidation of (17) with sodium metaperiodate in aqueous ethanol yielded a mixture of two racemic sulphoxide diastereoisomers (18) ($C_{24}H_{30}O_2S$), (78%, i.r. 1 050 cm^{-1}). The mixture could not be resolved chromatographically and specific interpretation of ^{1}H n.m.r. data was limited; however, the expected downfield shift of the *E*-terminal methylene proton from δ 4.70 in (17) to δ 4.98 in (18) was apparent.

Treatment of the sulphoxide mixture (18) with trimethyl phosphite in methanol yielded the terminal allylic alcohol (4) (81%; 93% *E*, 7% *Z*), following chromatography. The alcohol (4) ($C_{18}H_{26}O_3$) displayed a strong i.r. hydroxy-band (3 400 cm^{-1}) and a characteristic carbinol methylene resonance in the ^{1}H n.m.r. spectrum (δ 3.92).

Oxidation of the alcohol mixture (4) with pyridinium chlorochromate in methylene dichloride yielded, after chromatography, the terminal allylic aldehyde (2) ($C_{18}H_{24}O_3$) as an oil (76%; 96% *E*, 4% *Z*). The chromatographic and spectral properties of the product were in agreement with those observed for di-*O*-methylalliodorin obtained from naturally occurring alliodorin. The overall yield of (2) was 11.2%.

The ultimate yield of (2) by the described procedure is severely limited by the formation of (16) in the reaction of (7) with benzenesulphenyl chloride. Similar reactions with geraniol have produced high yields of monomethylallyic sulphides;[9] however, reactions of farnesol derivatives[10] with benzenesulphenyl chloride are reported to yield the unwanted bis-methylallylic sulphides. Control of the disubstitution of (7) with benzenesulphenyl chloride will be necessary to optimize the yield (2) by the described procedure.

EXPERIMENTAL

N.m.r. spectra (90 MHz) were measured on a Varian EM 390 spectrometer, i.r. spectra on a Perkin-Elmer 727 B spectrometer, and mass spectra on a VG-micromass 70/70 instrument. Preparative silica chromatography was done on a Waters Prep 500 HPLC chromatograph.

Di-O-methylalliodorin [8-(2,5-*Dimethoxyphenyl*)-2,6-*dimethylocta*-2,6-*dienal*] (2). (*Natural Source*).—Alliodorin (1) (5 g, 2 mmol) was dissolved in acetone (80 ml) containing powdered anhydrous potassium carbonate (20 g). Methyl iodide (3 ml) was added and the stirred mixture refluxed (efficient condenser) for 6 h. Additional methyl iodide (2 ml) was added and the stirred mixture refluxed overnight. The mixture was then filtered hot, concentrated, and refiltered hot. Water (100 ml) was added and the mixture extracted with ether (2 × 200 ml). The extract was washed with water (200 ml), dried ($MgSO_4$), and concentrated. Preparative silica chromatography (hexane–ethyl acetate, 10 : 1) yielded *the aldehyde* (2) as a light yellow oil (5.3 g) (Found: C, 75.0; H, 8.4. $C_{18}H_{24}O_3$ requires C, 75.0; H, 8.4%); ^{1}H n.m.r. ($CDCl_3$) δ 1.70br. (6 H, s), 2.03—2.63 (4 H, m), 3.29 (2 H, d, *J* 7 Hz), 3.70 (3 H, s), 3.73 (3 H, s), 5.33 (1 H, t, *J* 7 Hz), 6.43 (1 H, t, *J* 7 Hz), 6.58—6.75 (3 H, m), and 9.33 (1 H, s); i.r. (neat) $\nu_{max.}$ 2 950, 1 690, 1 500, 1 220, 1 050, 860, 800, and 700 cm^{-1}.

1,2,3,3a,4,9,10,10a-*Octahydro*-5,8-*dimethoxy*-3,10-*dimethyl*-3a,9-*epoxybenz*[f]*azulene* (8).—Di-*O*-methylalliodorin (2) (4 g) in 80% formic acid containing 5% of ascorbic acid was heated (60—75 °C) for 1 h, under nitrogen. Water (100 ml) was added and the mixture extracted with ether (200 ml). The ether extract was treated with saturated aqueous sodium hydrogen carbonate (100 ml), washed with water (2 × 100 ml) and concentrated to a dark oil (3.8 g). The oil was boiled with hexane (3 × 200 ml) and the hot hexane-soluble portions were combined and concentrated to a yellow oil (1.1 g) which was subjected to preparative chromatography on silica (hexane–ethyl acetate, 30 : 1), 300 ml fractions being collected. Concentration of the third fraction yielded an oil (0.15 g) which crystallized when set aside. Recrystallization (acetone–methanol) yielded the *epoxide* (8) (0.11 g), m.p. 112—113 °C (Found: C, 79.4; H, 8.8%; M^+ 288.1733. $C_{18}H_{24}O_3$ requires C, 79.4; H, 8.9%; M^+ 288.1725); ^{1}H n.m.r. ($CDCl_3$) δ 1.00 (3 H, d, *J* 6 Hz), 1.10 (3 H, d, *J* 6 Hz), 1.3—1.8 (3 H, m), 2.2—2.5 (4 H, m), 2.48 (1 H, d, *J* 14 Hz), 2.92 (1 H, d, *J* 14 Hz), 3.75 (6 H, s), 4.96 (1 H, s), and 6.57 (2 H, s); ^{13}C n.m.r. ($CDCl_3$) δ 14.75, 16.0, 24.4, 31.6, 35.0, 41.6, 46.2, 48.6, 55.5, 55.8, 80.8, 94.1, 107.5, 107.8, 122.9, 130.9, 148.8, and 157.5 p.p.m.; i.r. (Nujol) $\nu_{max.}$ 2 940, 2 860, 1 460, 1 379, 1 255, 1 110, and 780 cm^{-1}; *m/e* (%) 288 (100), 255 (34), 191 (29), 190 (30), 180 (30), and 109 (34).

X-*Ray Crystal Structure Determination of Compound* (8).—A crystal of dimensions 0.24 × 0.26 × 0.07 mm parallel to *a*, *b*, and *c*, respectively, obtained from acetone–methanol, was used for the intensity measurements. Integrated intensities were obtained on a four-circle automatic diffractometer at room temperature using Ni-filtered Cu-K_α radiation. One quarter of the reflections in the reciprocal sphere were recorded in the range $0° \leqslant 2\theta \leqslant 120°$ by means of the θ—2θ scan technique, with a scan rate of 1° min^{-1}. A total of 2 398 reflections were measured of which 2 293 were unique; of these, 461 had $I < \sigma(I)$, and were not used in the refinement. Intensity data were corrected for Lorentz and polarization effects but not for absorption.

Crystal Data. $C_{18}H_{24}O_3$, M = 288. Monoclinic, a = 14.984(7), b = 5.206(4), c = 20.131(9) Å, β = 99.77(1)°, Z = 4, space group $P2_1/c$, $F(000)$ = 624, D_c = 1.24 g cm^{-3}, λ(Cu-K_α) = 1.5418 Å, μ(Cu-K_α) = 6.62 cm^{-1}.

The structure was solved by direct methods using MULTAN.[11] The positional and thermal parameters were refined by a full-matrix least-squares method. The positions of all hydrogen atoms were located from a difference Fourier synthesis. A secondary extinction correction was applied during the final stages of refinement to minimize the discrepancy between the observed and calculated structure factors of the most intense reflections. The final discrepancy index R is 0.078 for 1 832 [$I > \sigma(I)$] reflections. The positional parameters for non-hydrogen atoms are listed in Table 2. Thermal parameters for the non-hydrogen atoms, fractional co-ordinates and isotropic thermal parameters for hydrogen atoms, bond lengths involving hydrogen atoms, and observed and calculated structure factors are in Supplementary Publication No. SUP 23034 (14 pp.).*

TABLE 2

Fractional co-ordinates for non-hydrogen atoms in (8) with e.s.d.s in parentheses

Atom	*x*	*y*	*z*
O(1)	0.276 3(2)	0.880 0(5)	−0.115 5(1)
O(2)	0.095 1(2)	0.749 7(6)	0.011 8(1)
O(3)	0.485 8(2)	0.170 1(6)	0.025 2(1)
C(1)	0.197 4(3)	0.797 8(9)	−0.089 2(2)
C(2)	0.224 6(2)	0.622 5(8)	−0.030 0(2)
C(3)	0.172 4(3)	0.596 3(9)	0.020 5(2)
C(4)	0.196 9(3)	0.431(1)	0.073 1(2)
C(5)	0.275 2(3)	0.283(1)	0.076 5(2)
C(6)	0.326 6(2)	0.305 3(8)	0.026 1(2)
C(7)	0.302 4(2)	0.471 2(7)	−0.027 4(2)
C(8)	0.357 2(3)	0.491 5(9)	−0.083 1(2)
C(9)	0.308 1(2)	0.645 5(7)	−0.141 7(2)
C(10)	0.362 6(3)	0.719 1(9)	−0.196 8(2)
C(11)	0.288 6(4)	0.765(1)	−0.258 1(2)
C(12)	0.221 9(4)	0.550(1)	−0.254 0(2)
C(13)	0.219 5(3)	0.514 9(8)	−0.178 6(2)
C(14)	0.142 7(3)	0.657 2(9)	−0.148 9(2)
C(15)	0.045 2(4)	0.757(2)	0.065 4(3)
C(16)	0.428 3(4)	−0.026(1)	0.073 9(3)
C(17)	0.429 3(4)	0.514(1)	−0.210 5(3)
C(18)	0.082 2(4)	0.837(1)	−0.196 5(3)

4-Methoxy-2-(3-*methylbut*-2-*enyl*)*phenol* (11).—*p*-Methoxyphenol (50 g, 0.4 mol) was heated at 80 °C in 5% aqueous citric acid (400 ml). 2-Methylbut-3-en-2-ol (40 g, 0.46 mol) was added dropwise during 1 h and the reaction was continued overnight (17 h). The cooled mixture was extracted with ether (200 ml). The ether extract was washed with 10% aqueous sodium hydroxide (250 ml) and water (2 × 200 ml), dried ($MgSO_4$), and concentrated to a light yellow oil (43 g) which was distilled to yield the *phenol* (11) as an oil, b.p. 105—107 °C at 0.001 mmHg (Found: C, 74.9; H, 8.4. $C_{12}H_{16}O_2$ requires C, 75.0; H, 8.4%); ^{1}H n.m.r. ($CDCl_3$) δ 1.68 (3 H, s), 3.25 (2 H, d, *J* 6.5 Hz), 3.78 (3 H, s), 5.26 (1 H, t, *J* 6.5 Hz), and 6.4—6.8 (3 H, m).

1,4-*Dimethoxy*-2-(3-*methylbut*-2-*enyl*)*benzene* (12).—The prenyl phenol (11) (20 g) was methylated according to the procedure for (2) to yield a light yellow oil (11 g). Preparative chromatography of the oil on silica (hexane–ethyl acetate, 10 : 1) yielded the *dimethoxy-compound* (12)

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as a slightly yellow oil (18.6 g) (Found: C, 75.5; H, 8.8. $C_{13}H_{18}O_2$ requires C, 75.7; H, 8.8%); ^{1}H n.m.r. ($CDCl_3$) δ 1.71br. (6 H, s), 3.25 (2 H, d, *J* 7 Hz), 3.70 (3 H, s), 3.73 (3 H, s), 5.28 (1 H, t, *J* 7 Hz), and 6.55—6.85 (3 H, m).

4-(2,5-Dimethoxyphenyl)-2-methylbut-2-enal (13).—Compound (12) (15.5 g, 75 mmol) was dissolved in ethyl alcohol (100 ml). Freshly sublimed selenium dioxide [12] (17.0 g, 0.15 mol) was added and the mixture was refluxed (3 h). The mixture was then cooled, concentrated to dryness, and rinsed with water (100 ml). The water rinse was decanted off and the rinsing repeated with ether (100 ml). The combined ether and water rinses were shaken together. The resulting ether extract was washed with saturated aqueous sodium hydrogen carbonate (100 ml) and water (2 × 150 ml), dried ($MgSO_4$), and concentrated to a dark oil (8.3 g). Preparative chromatography of the oil on silica (hexane–ethyl acetate, 6 : 1) yielded the *aldehyde* (13) as a yellow oil (5.7 g) (Found: C, 70.9; H, 7.3. $C_{13}H_{16}O_3$ requires C, 70.9; H, 7.3%); ^{1}H n.m.r. ($CDCl_3$) δ 2.83 (3 H, s), 3.60 (2 H, d, *J* 7 Hz), 3.72 (3 H, s), 3.75 (3 H, s), 6.55 (1 H, t, *J* 7 Hz), 6.6—6.8 (3 H, m), and 9.88 (1 H, s).

1,4-Dimethoxy-6-methylnaphthalene (14).—The aldehyde (13) (2.2 g, 0.1 mol) was dissolved in 80% aqueous formic acid containing 5% of ascorbic acid (20 ml) and heated (100 °C) for 4 h. The mixture was then cooled, diluted with water (100 ml), and extracted with ether (2 × 75 ml). The combined ether extracts were washed with saturated aqueous sodium hydrogen carbonate (2 × 200 ml), washed with water (200 × 100 ml), dried (Na_2SO_4), and concentrated to yield a dark oil (2.1 g). Preparative chromatography on silica (hexane–ethyl acetate, 50 : 1) yielded an oil which crystallized when set aside. Recrystallization (MeOH) yielded the *dimethoxynaphthalene* (14) (0.7 g) as colourless needles, m.p. 55—57 °C (Found: C, 77.2; H, 7.0. $C_{13}H_{14}O_2$ requires C, 77.2; H, 7.0%); ^{1}H n.m.r. ($CDCl_3$) δ 2.55 (3 H, s), 3.83 (6 H, s), 6.43 (1 H, d, *J* 10 Hz), 6.53 (1 H, d, *J* 10 Hz), 7.25 (1 H, dd, *J* 10 and 3 Hz), 7.91br. (1 H, s), and 8.05 (1 H, d, *J* 10 Hz).

2-(3,7-Dimethylocta-2,6-dienyl)-4-methoxyphenol (6).—To a stirred solution of *p*-methoxyphenol (49.6 g, 0.4 mol) in anhydrous ether (1 l) were added small pieces of sodium [8] (27.6 g, 1.2 mol). The mixture was stirred (3 h), geranyl chloride [13] (68.8 g, 0.4 mol) added dropwise, and the resulting mixture refluxed overnight. The cooled mixture was decanted from the residual sodium, which was rinsed with ether, and the ether suspensions were combined and extracted with water (2 × 500 ml), 10% aqueous hydrochloric acid (300 ml), and water (300 ml). The ether layer was dried ($MgSO_4$), concentrated to an oil (76 g), and distilled *in vacuo* to yield the *geranyl-phenol* (6) (70.9 g) as a pale yellow oil, b.p. 148 °C at 0.05 mmHg (Found: C, 78.3; H, 9.3. $C_{17}H_{24}O_2$ requires C, 78.4; H, 9.3%); ^{1}H n.m.r. ($CDCl_3$) δ 1.55 (3 H, s), 1.64 (3 H, s), 1.70 (3 H, s), 1.95—2.15 (4 H, m), 3.28 (2 H, d, *J* 8 Hz) 3.68 (3 H, s), 5.05 (1 H, m), 5.09 (1 H, m) 5.28 (1 H, t, *J* 8 Hz), and 6.5—6.8 (3 H, m).

2-(3,7-Dimethylocta-2,6-dienyl)-1,4-dimethoxybenzene (7).—The geranyl-phenol (6) (30 g) was methylated by the procedure for (2) and (12) to yield a yellow oil (30.6 g). Distillation (*in vacuo*) yielded the *dimethoxy-compound* (7) as an oil (27.8 g), b.p. 140 °C at 0.002 mmHg (Found: C, 79.2; H, 9.5. $C_{18}H_{26}O_2$ requires C, 78.8; H, 9.55%); ^{1}H n.m.r. ($CDCl_3$) δ 1.57 (3 H, s), 1.66 (6 H, s), 1.95—2.2 (4 H, m), 3.29 (2 H, d, *J* 8 Hz), 3.71 (3 H, s), 3.73 (3 H, s), 5.10 (1 H, m), 5.30 (1 H, d, *J* 8 Hz), and 6.5—6.85 (3 H, m).

1,4-Dimethoxy-2-(3,7-dimethyl-2,6-bisphenylthio-octa-3,7-dienyl)benzene (16) *and* *1,4-Dimethoxy-2-(3,7-dimethyl-6-phenylthio-octa-3,7-dienyl)benzene* (17).—To a stirred solution of (14) (28 g, 0.102 mol), and anhydrous sodium carbonate (20 g, 0.19 mol) in dry methylene dichloride (300 ml) at −50 °C was added benzenesulphenyl chloride [14] (14.4 g, 0.1 mol) during 10 min. The mixture was allowed to reach room temperature and was then refluxed with stirring overnight. The mixture was filtered and concentrated to dryness *in vacuo* and water (200 ml) and chloroform (200 ml) were added. The chloroform extract was washed with water (2 × 200 ml), dried ($MgSO_4$), and concentrated to a yellow oil (39.2 g). Dry dimethylformamide (50 ml) was added, and the solution was heated on a steam-bath (90 min) under a stream of nitrogen. Saturated aqueous sodium hydrogen carbonate (100 ml) was added and the solution was extracted with chloroform (250 ml). The chloroform extract was washed with water (200 ml), dried ($MgSO_4$), and concentrated to give dark yellow oil (31.6 g). Chromatography of the oil on silica (hexane–ethyl acetate, 70 : 1) yielded two major constituents in addition to starting material. Following the elution of starting material the bisphenylthio-compound (17) was eluted and obtained as an oil (15.1 g) (Found: C, 73.0; H, 7.7; S, 8.4. $C_{24}H_{30}O_2S$ requires C, 75.35; H, 7.9; S, 8.4%); ^{1}H n.m.r. ($CDCl_3$) δ 1.67 (3 H, s), 1.73 (3 H, s), 1.9—2.25 (4 H, m), 3.29 (2 H, d, *J* 8 Hz), 3.59 (1 H, t, *J* 7 Hz), 3.70 (3 H, s), 3.73 (3 H, s), 4.52br. (1 H, s), 4.70 (1 H, m), 5.33 (1 H, t, *J* 8 Hz), 6.55—6.85 (3 H, m), and 7.10—7.50 (5 H, m); i.r. (neat) $\nu_{max.}$ 2 950, 1 700, 1 225, and 750 cm^{-1}.

The phenylthio-compound (16) was eluted next and obtained as an oil (10.8 g) (Found: C, 74.0; H, 7.4; S, 12.85. $C_{30}H_{34}O_2S_2$ requires: C, 73.4; H, 7.0; S, 13.0%); ^{1}H n.m.r. δ 1.53 (3 H, s), 1.65 (3 H, s), 2.15 (2 H, t, *J* 7 Hz), 2.8—3.0 (2 H, m), 3.29 (1 H, t, *J* 7 Hz), 4.00 (1 H, t, *J* 7 Hz), 3.63 (3 H, s), 3.66 (3 H, s), 4.35br. (1 H, s), 4.38br. (1 H, s), 5.00 (1 H, t, *J* 6.5 Hz), 6.4—6.8 (3 H, m), and 6.9—7.5 (5 H, m).

6-(2,5-Dimethoxyphenyl)-1-isopropenyl-4-methylhex-4-enyl Phenyl Sulphoxide (18).—A solution of (17) (9.0 g, 23 mmol) in ethyl alcohol (200 ml) was added to a stirred aqueous solution of sodium metaperiodate [15] (0.5M; 23 mmol) in an ice-bath. The mixture was stirred for 4 h at 0 °C and overnight at room temperature. The mixture was then concentrated *in vacuo*, water (100 ml) added, and the mixture extracted with ether (2 × 100 ml). The combined ether extracts were dried ($MgSO_4$) and concentrated to a pale yellow oil (10.4 g). Chromatography on silica (hexane–ethyl acetate, 4 : 1) yielded a mixture of the diastereoisomeric sulphoxides (17) as a pale yellow oil (7.3 g) (Found: C, 72.6; H, 7.85; S, 7.45%; M^+, 398.1932. $C_{24}H_{30}O_3S$ requires C, 72.3; H, 7.6; S, 8.04%; M^+, 398.1916); ^{1}H n.m.r. ($CDCl_3$) (integration values relative to vinyl resonance at δ 4.98; resonances suspected as being due to the minor diastereoisomer in italics) δ *1.50* (1—2 H, s), 1.59 (3 H, s), 1.8—2.3 (3—4 H, m), 2.8—3.2 (1—2 H, m), 3.27 (2+ H. d, *J* 6.5 Hz), 3.75br. (7 H, s), *4.60*br. (0.4 H, s), 4.72br. (0.6 H, s), 4.98 (1 H, m), 5.26 (1+ H, t, *J* 6.5 Hz), 6.5—6.8br. (3+ H, s), and 7.2—7.7 (5+ H, m).

8-(2,5-Dimethoxyphenyl)-2,6-dimethylocta-2,6-dienol (4).—Freshly distilled trimethyl phosphite (1.3 g, 11 mmol) was added to a stirred solution of (18) (4 g, 10 mmol) in methanol (20 ml; room temp.) and the reaction continued overnight. The mixture was poured into saturated aqueous sodium hydrogen carbonate (100 ml) and extracted with chloroform

(200 ml). The chloroform extract was washed with water (3 × 100 ml), dried ($MgSO_4$), and concentrated to an oil (2.6 g). Preparative silica chromatography (hexane–ethyl acetate 3 : 1) yielded the *alcohol* (4) (2.7 g) as an oil (Found: C, 73.2; H, 9.4%. $C_{18}H_{26}O_3$ requires: C, 73.3; H, 9.4%); ^{1}H n.m.r. ($CDCl_3$) δ 1.60 (3 H, s), 1.65 (3 H, s), 2.0—2.3 (4 H, m), 3.28 (2 H, d, *J* 7 Hz), 3.70 (3 H, s), 3.73 (3 H, s), 3.92br. (3 H, s), 4.13br. (1 H, s), 5.30 (1 H, t, *J* 7 Hz), and 6.5—6.8 (3 H, m); i.r. (neat) $\nu_{max.}$ 3 400, 2 900, 1 500, 1 220, 1 010, 850, 800, and 700 cm^{-1}.

Di-O-methylalliodorin (2) (*Synthetic Material*).—A solution of (4) (1.5 g, 5 mmol) in dry methylene dichloride (5 ml) was added to a stirred suspension (10 °C) of pyridinium chlorochromate [16] (1.6 g, 7.5 mmol) and sodium acetate (0.1 g) in dry methylene dichloride (20 ml). After 2 h, ether (50 ml) was added and the supernatant liquid was decanted from the black gummy residue. The ether washing was repeated and the combined ether portions were concentrated; preparative chromatography on silica (hexane–ethyl acetate, 3 : 1) yielded synthetic (2) as an oil (1.1 g) (Found: C, 74.8; H, 8.4. Calc. for $C_{18}H_{29}O_3$: C, 75.0; H, 8.4%). The spectral data for the synthetic (2) were in close agreement with data for (2) obtained from the natural source.

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REFERENCES

[1] M. Moir and R. H. Thomson, *J. Chem. Soc., Perkin Trans. 1*, 1973, 1352.
[2] G. D. Manners and L. Jurd, *J. Chem. Soc., Perkin Trans. 1*, 1977, 405.
[3] C. K. Johnson, Ortep: Report ORNL–3794, Oak Ridge National Laboratory, Oak Ridge, Tennesse, 1965.
[4] D. C. Ayres and J. W. Mundy, *J. Chem. Soc. C*, 1969, 637.
[5] O. P. Vig, S. D. Sharma, N. K. Verma, and V. K. Handa, *Indian J. Chem., Sect. B*, 1977, **15**, 988.
[6] H. Inouye, K. Tokura, and S. Tobita, *Chem. Ber.*, 1968, **101**, 4057.
[7] H. Inouye, S. Ueda, K. Inoue, and H. Matsumura, *Phytochemistry*, 1979, **18**, 1301.
[8] S. Yamada, F. Ono, T. Katagiri, and J. Tanaka, *Synth. Commun.*, 1978, **8**, 241.
[9] Y. Masaki, K. Hashimoto, and K. Kaji, *Tetrahedron Lett.*, 1978, 4539.
[10] Y. Masaki, K. Hasimoto, and K. Kaji, *Tetrahedron Lett.*, 1978, 5123.
[11] G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. A*, 1971, **27**, 368.
[12] U. T. Bhalerao and H. Rapoport, *J. Am. Chem. Soc.*, 1971, **93**, 4835.
[13] E. W. Collington and A. I. Meyers, *J. Org. Chem.*, 1971, **36**, 3044.
[14] W. H. Mueller and P. E. Butler, *J. Am. Chem. Soc.*, 1968, **90**, 2075.
[15] N. J. Leonard and C. R. Johnson, *J. Org. Chem.*, 1962, **27**, 282.
[16] E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 1975, 2647.