Synthesis of Ubiquinones. Elongation of the Heptaprenyl Side-chain in Ubiquinone-7

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Regio- and stereo-chemically selective transformation of the terminal *trans*-methyl group of the heptaprenyl side-chain in ubiquinone-7 (1a; $n = 6$) and its *O*-benzylated quinol (1b) into the *trans*-chloromethyl group and the coupling of the resulting compound (10b) with prenyl, geranyl, and farnesyl *p*-tolyl sulphones (14a, b, c), with subsequent reductive elimination of *p*-tolylsulphonyl and benzyl groups and oxidation of the corresponding quinols, have resulted in a novel synthesis of ubiquinone-8, -9, and -10 (1a; $n = 7$, 8, and 9). ^{1}H and ^{13}C n.m.r. spectra of ubiquinone-7 and its derivatives, and of several sulphones as reference compounds, are discussed.

UBIQUINONES are a family of 2,3-dimethoxy-5-methyl-6-polyprenyl-1,4-benzoquinones which function in the electron transport and oxidative phosphorylation processes in mitochondria. Ubiquinones having an all-*trans* polyprenyl side-chain and containing from one to twelve isoprenoid units have been found in nature. Ubiquinone-10 is the most common member in animals.[1-6] Classically,[7-9] ubiquinone-8, -9, and -10 (1a; $n = 7$, 8, and 9) have been synthesised by acid-catalysed condensation of 2,3-dimethoxy-5-methylhydroquinone with the corresponding polyprenyl alcohol or isopolyprenyl alcohol, followed by oxidation of the resulting ubiquinol to the quinone. Optimal yields for ubiquinones synthesised by this method rarely exceed 20%. Recently [10] the prenyl component has been activated as a nucleophile *via* the π-allylnickel complex and condensed with a protected 6-bromo-2,3-dimethoxy-5-methylhydroquinone with subsequent oxidation to the corresponding prenylated quinone. By this method ubiquinone-10 has been synthesised in 28% yield from decaprenyl bromide. These approaches remain fundamentally limited by the inherent instability of the allylic alcohol component under the acidic conditions employed and by the lack of complete retention of *trans*-stereochemistry at the Δ^2 position. The present method overcomes these difficulties in synthesis and provides a novel and versatile synthesis of quinones with a polyprenyl side-chain.

For this coupling reaction, one type of component that seemed possible was a ubiquinone derivative in which the terminal *trans*-methyl group † of the polyprenyl side-chain had been converted into a chloromethyl group. The synthesis of such compounds appeared possible based on the report by Johnson *et al.*[11] in which a *trans*-trisubstituted olefinic bond was generated stereospecifically by the S_Ni' reaction of thionyl chloride with an allylic alcohol. We further considered the modification of the terminal prenyl group of the side-chain of a ubiquinone possible by the same type of reaction employed by van Tamelen *et al.*[12] in the synthesis of 2,3-epoxysqualene. Ubiquinone-7 (1a; $n = 6$) was chosen by us as the starting material because of its availability from the fermentation of *Candida utilis*.

The second type of component for the coupling reaction which appeared attractive was a prenyl *p*-tolyl sulphone based on an analogous study by Grieco *et al.*[13]

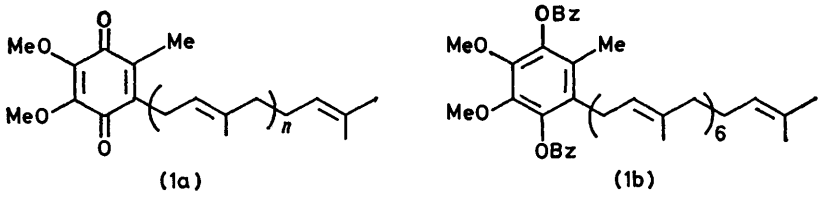
Below we described the preparation of these two types of components and the coupling reactions involving them. Because of the known sensitivity of the quinonoid moiety of ubiquinones to nucleophiles and to alkaline reaction conditions, we have carried out parallel series of reactions involving ubiquinone-7 (1a; $n = 6$) and its corresponding *O*-benzylated hydroquinone (1b).

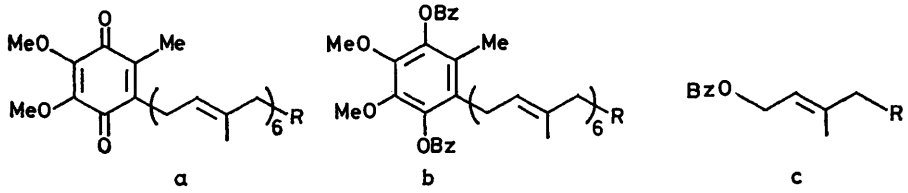
Bromohydrination of (1a; $n = 6$) and (1b) with *N*-bromosuccinimide (NBS) in 20% aqueous 1,2-dimethoxyethane at −5 °C gave the terminal monobromohydrins (2a, b) in good yields. During this reaction a small amount of presumably more than one dibromohydrin compound was obtained, but these were not further investigated. The ^{1}H n.m.r. spectra of (2a) and (2b) showed a new dimethylcarbinol group at δ 1.34 (singlet) and >CHBr at δ 3.97 (quartet) with the disappearance of the terminal *trans*-methyl (δ 1.68) of the starting materials. When monobromohydrins (2a, b) were treated with an equimolar amount of potassium

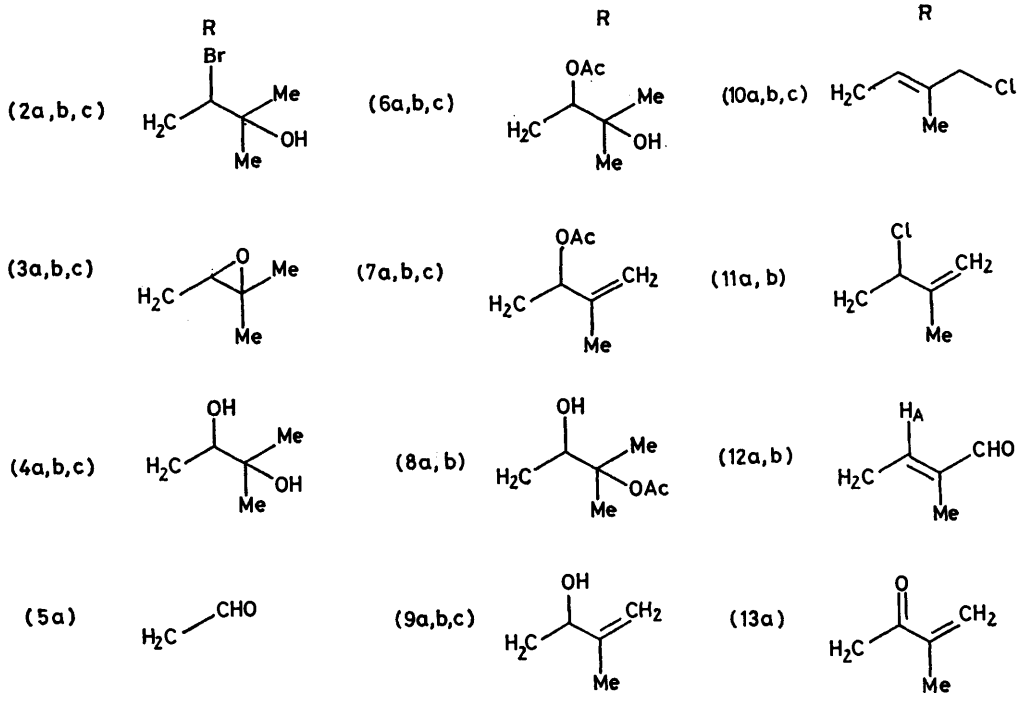
† Geometrical configurations of the two methyl groups of the terminal prenyl group in the side-chain of ubiquinones follow the IUPAC-IUB Tentative Rules for Nomenclature (*J. Biol. Chem.*, 1972, **247**, 2638).

[1] 'Ciba Foundation Symposium on Quinones in Electron Transport', ed. G. E. W. Wolstenholme and C. M. O'Connor, J. & E. Churchill, London, 1961.
[2] A. F. Wagner and K. Folkers, 'Vitamins and Coenzymes', Interscience, New York, 1964, p. 435.
[3] 'Biochemistry of Quinones', ed. R. A. Morton, Academic Press, New York, 1965.
[4] 'Vitamins and Hormones', Vol. 24, ed. R. S. Harris, I. G. Wool, and J. A. Loraine, Academic Press, New York, 1966, pp. 427, 465, and 551.
[5] 'Methods in Enzymology', ed. D. B. McCormick and L. D. Wright, Academic Press, New York and London, 1971, Vol. 18, Part C, p. 135.
[6] H. Morimoto and I. Imada, 'Methodicum Chimicum', ed. F. Korte, Georg Thieme Verlag, Stuttgart, 1977, vol. 11, part 2, p. 117.
[7] C. H. Shunk, R. E. Erickson, E. L. Wong, and K. Folkers, *J. Amer. Chem. Soc.*, 1959, **81**, 5000.
[8] R. Rüegg, U. Gloor, R. N. Goel, G. Ryser, O. Wiss, and O. Isler, *Helv. Chim. Acta*, 1959, **42**, 2616.
[9] R. Rüegg, U. Gloor, A. Langemann, M. Kofler, C. von Planta, G. Ryser, and O. Isler, *Helv. Chim. Acta*, 1960, **43**, 1745.
[10] K. Sato, S. Inoue, and R. Yamaguchi, *J. Org. Chem.*, 1972, **37**, 1889.
[11] W. S. Johnson, T.-t. Li, C. A. Harbert, W. R. Bartlett, T. R. Herrin, B. Staskun, and D. H. Rich, *J. Amer. Chem. Soc.*, 1970, **92**, 4461.
[12] E. E. van Tamelen and T. J. Curphey, *Tetrahedron Letters*, 1962, 121.
[13] P. A. Grieco and Y. Masaki, *J. Org. Chem.*, 1974, **39**, 2135.

carbonate in methanol, the terminal epoxides (3a, b) were obtained in good yields. The epoxide (3b) could also be prepared by treatment of (3a) with sodium borohydride in ethanol to give the hydroquinone epoxide, which was then benzylated with benzyl bromide in the presence of sodium hydride. The epoxides (3a, b) were treated in aqueous 1,2-dimethoxyethane in the presence of perchloric acid to give the glycols (4a, b) in good yields. When oxidised with metaperiodic acid, the glycol (4a) produced acetone and the aldehyde (5a). This confirms that the double bond of the terminal prenyl unit of (1a; $n = 6$) was modified regiospecifically. Acetylation of the glycols (4a, b) with acetic anhydride and pyridine gave the monoacetates (6a, b) in good yields. The monoacetate (6a) was also prepared by treatment of (3a) with a hot mixture of acetic acid and sodium acetate. The two terminal methyl groups showed different chemical shifts at δ 1.26 and 1.30 in (3a, b) and at δ 1.16 and 1.20 in (4a, b) while appearing as a single signal at δ 1.34 in (2a, b), at δ 1.20 in (6a), and at δ 1.17 in (6b). Dehydration of (6a) and (6b) in n-hexane with thionyl chloride and pyridine at 0 °C gave the allyl acetates (7a, b), respectively, together with a small amount of the isomeric monoacetates (8a, b).







The structures of (2a), (3a), (4a), (6a), and (7a) are also supported by the ^{13}C n.m.r. spectra shown in the Table. The carbon assignments * were based on chemical shifts, multiplicities in the off-resonance spectra, comparison with polyisoprenoid compounds, ubiquinones, and theoretical considerations. It is believed that assignments for the quinone ring carbons (1—6), isoprenoid carbons (1′—4′ and 24′—28′), and carbons of vinyl methyl groups are reasonably certain, although assign-

* Chemical shifts of the carbons in ubiquinones and the related polyprenylated compounds will be published elsewhere.

ments for carbons (5′—23′) in the heptaprenyl side-chains are somewhat doubtful.

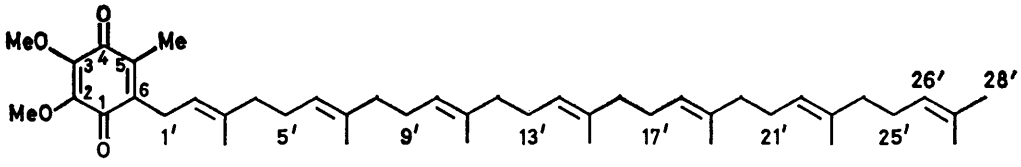
Hydrolysis of the allyl acetates (7a, b) with sodium hydroxide gave the desired allyl alcohols (9a, b) in good yields. The allyl alcohol (9b) could also be prepared by the direct isomerisation [14] of the epoxide (3b) with an excess of lithium di-isopropylamide in absolute tetrahydrofuran. This reaction was also convenient for the preparation of the allylic alcohol (9b). By reaction with 1.5 molar equivalents of thionyl chloride in n-hexane the allyl alcohols (9a, b) were converted into the desired *trans*-chloromethyl compounds (10a, b) *via* an S_Ni' reaction; a small amount (<5%) of the secondary chloride (11a, b) arose from direct S_Ni substitution. CHCl (δ 4.80). To clarify the relationship between the chloromethyl group and the vinyl proton (H_A), (10a) and (10b) were converted into the corresponding formyl compounds (12a, b) by the silver-assisted dimethyl sulphoxide oxidation of Ganem *et al.*[15] From the n.m.r. spectra of the formyl compounds (12a, b), the relationship between the vinyl proton (H_A, δ 6.46) and the formyl group (δ 9.37) can be assigned as *cis*, by comparison with values in the literature.[16,17] Therefore, it is clear that CH_2Cl and H_A in the chloromethyl compounds (10a, b) must be in a *cis*-relationship. Similar oxidation of (11a) led to the αβ-unsaturated ketone (13a).

Grieco *et al.*[13] have succeeded in activating the methylene group adjacent to the hydroxy-group in

^{13}C N.m.r. chemical shifts [a] of ubiquinone-7 and its derivatives

Carbon [b] No.	(1a) n = 6	(2a)	(3a)	(4a)	(6a)	(7a)	Carbon [b] No.	(1a) n = 6	(2a)	(3a)	(4a)	(6a)	(7a)
1	184.4	184.0	184.0	184.3	184.3	184.3	15′	134.6	134.4	134.4	134.6	134.6	134.7
2	144.0	144.1	144.1	144.2	144.2	144.1	16′	39.7	39.5	39.4	39.6	39.6	39.6
3	144.2	144.2	144.2	144.3	144.4	144.2	17′	26.6	26.5	26.5	26.7	26.5	26.7
4	183.6	183.3	183.2	183.5	183.5	183.5	18′	124.0	124.2	124.1	124.1	124.1	124.2
5	141.5	141.3	141.3	141.5	141.5	141.5	19′	134.6	134.2	134.2	134.6	134.6	135.0
6	138.6	138.7	138.3	138.6	138.6	138.6	20′	39.7	39.5	39.4	39.6	39.6	39.6
2-OCH_3	61.0	60.6	60.6	60.8	60.8	60.9	21′	26.4	26.3	26.3	26.7	26.5	26.7
3-OCH_3	61.0	60.6	60.6	60.8	60.8	60.9	22′	124.2	125.6	124.6	124.3	124.8	124.7
5-CH_3	11.9	11.6	11.6	11.8	11.7	11.8	23′	135.0	132.7	133.5	134.5	133.7	133.6
1′	25.2	25.1	25.1	25.2	25.2	25.2	24′	39.7	38.0	36.1	36.7	36.1	35.2
2′	118.7	118.7	118.7	118.8	118.9	118.8	3′-CH_3	16.3	16.1	15.8	16.2	16.2	16.2
3′	137.4	137.0	137.0	137.3	137.3	137.3	7′-CH_3	16.0	15.8	15.8	15.9	15.9	15.9
4′	39.7	39.5	39.4	39.6	39.4	39.6	11′-CH_3	16.0	15.8	15.8	15.9	15.9	15.9
5′	26.6	26.5	26.5	26.5	26.5	26.7	15′-CH_3	16.0	15.8	15.8	15.9	15.9	15.9
6′	123.6	123.6	123.6	123.7	123.7	123.7	19′-CH_3	16.0	15.8	15.8	15.9	15.9	15.9
7′	134.6	134.7	134.7	134.9	134.7	134.6	23′-CH_3	16.0	15.8	15.8	15.9	15.9	15.9
8′	39.7	39.5	39.4	39.6	39.6	39.6	25′	25.6	32.0	27.3	29.8	28.0	31.1
9′	26.6	26.5	26.5	26.5	26.5	26.7	26′	123.6	70.0	63.7	78.2	79.7	76.9
10′	124.0	124.0	123.9	124.0	124.1	124.1	27′	130.9	72.1	57.7	72.7	72.3	143.0
11′	134.6	134.4	134.4	134.6	134.6	134.7	28′	25.4	26.1	24.6	23.4	24.9	112.4
12′	39.7	39.5	39.4	39.6	39.6	39.6	27′-CH_3	17.5	22.7	18.5	25.2	26.7	18.0
13′	26.6	26.5	26.5	26.7	26.5	26.7	CH_3COO					20.8	20.9
14′	124.0	124.0	124.0	124.1	124.1	124.1	CH_3COO					170.7	169.7

[a] In parts per million downfield from $SiMe_4$. [b] The numbering system of ubiquinone-7 and its derivatives follows the IUPAC–IUB nomenclature (see *Biochim. Biophys. Acta*, 1965, **107**, 5).



The reaction of (9a) with thionyl chloride and pyridine in methylene chloride gave the secondary chloride (11a) in good yield.

Compounds (10a) and (10b) were characterised and their chloromethyl groups were shown to have a *trans*-configuration, as described below. The ^1H n.m.r. spectra of (10a) and (10b) showed characteristic methylene protons of the chloromethyl group at δ 3.99 (singlet) with disappearance of the terminal methylene protons (δ 4.85 and 4.94) observed in the allyl alcohols (9a, b). The compounds (10a, b) can be clearly distinguished from the secondary chloride (11a) by the comparison of their ^1H n.m.r. spectra. The latter (11a) shows absorption characteristic of the terminal methylene protons (δ 4.95 and 5.00) and the methine proton of farnesol by introducing a sulphonyl group and in using this intermediate in synthesising squalene in a highly stereospecific manner. By this method the prenyl derivatives (14a, b, c and 15a, b) were prepared from the reaction of sodium toluene-*p*-sulphinate with 1-bromo-3-methylbut-2-ene, geranyl chloride, *trans,trans*-farnesyl bromide, neryl chloride, and *cis,trans*-farnesyl bromide, respectively. As expected the more mobile *cis*-isomer was readily separated from the *trans*-isomer by chromatography on silica gel. In the ^1H n.m.r. spectra, the γ-methyl to the sulphone group in the *trans*-isomers (14a, b, c) appears at a considerably higher field (δ *ca.* 1.37) compared with the other methyl groups,

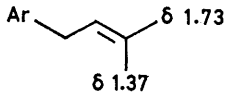
[14] *cf.* J. F. Crandall and L.-Ho Chang, *J. Org. Chem.*, 1967, **32**, 435.

[15] B. Ganem and R. K. Boeckman, jun., *Tetrahedron Letters*, 1974, 917.

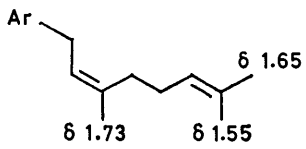
[16] A. F. Thomas, *Chem. Comm.*, 1968, 1657.

[17] D. J. Faulkner, *Synthesis*, 1971, 175.

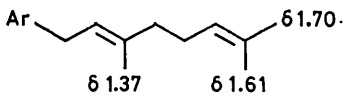
while the γ-methyl in the *cis*-isomers (15a, b) appears at a much lower field (δ *ca.* 1.72). It was difficult to this could be done by a combination of ^{1}H n.m.r. and ^{13}C n.m.r. spectroscopy for the specific decoupling of



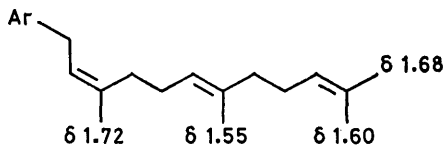
(14a)



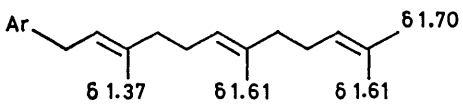
(15a)



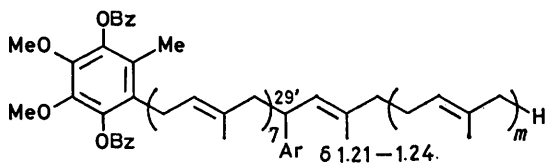
(14b)



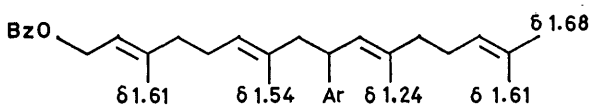
(15b)



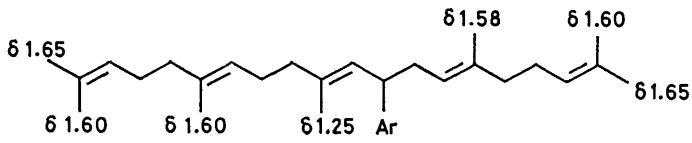
(14c)



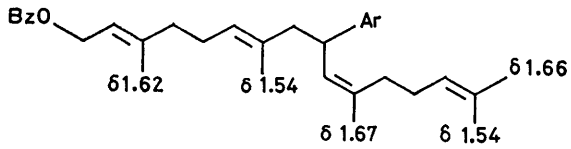
(16) a; m = 0
b; m = 1
c; m = 2



(17)



(18)



(19)

Ar = *p*-$MeC_6H_4SO_2$

assign each chemical shift of the vinyl methyl groups in the *cis*-isomers (15a, b) by comparing their ^{1}H n.m.r. with those of *trans*-isomers (14a, b, c). However, each vinyl methyl group of (15a). Our results [see (15a)] are inconsistent with the data (δ 1.50, 1.60, and 1.65 for methyls at positions 3 and 7, and for 8-methyl,

respectively) which were reported by Campbell *et al.*[18] This characteristic difference of the γ-methyls between *cis*- and *trans*-isomers is helpful for the judgement of *cis*- and *trans*-configuration in the products of the coupling reactions described below.

When 1 mol equivalent of (10b) was added at −70 °C to each of orange coloured carbanionic solutions, produced from the sulphonyl compounds (14a, b, c) with n-butyl-lithium in absolute tetrahydrofuran–hexamethylphosphoramide at −20 °C, the orange colour faded as the reaction proceeded. After gradual warming of the reaction mixtures to 0 °C, the coupled compounds (16a, b, c) were obtained by purification on silica gel. In the ^{1}H n.m.r. spectra of (16a, b, c) the γ-methyl group [−(β)C=(γ)C−CH_3] to the sulphonyl group appeared at a much higher field (δ *ca.* 1.24) as a split doublet. This characteristic methyl group indicates that it is *cis* to the bulky $CHSO_2Ph$–CH_3 group. Some coupled compounds, (17), (19), and (18), were synthesised, as reference compounds in order to compare their ^{1}H n.m.r. spectra with those of (16a, b, c) by using the same coupling reaction of the chloride (10c) which was prepared from geranyl benzyl ether according to the same transformation employed above, with (14b) and (15a), and of geranyl chloride with (14c), respectively. Our result in the coupling reaction is consistent with the finding of Grieco *et al.*[13] that no isomerisation of the double bonds is observed during the synthesis of squalene.

Reductive elimination of the sulphonyl and benzyl groups of the coupled compounds (16a, b, c) was conveniently carried out at −30 °C with lithium in ethylamine. The resulting hydroquinones were oxidised with ferric chloride to give the crude quinones, which were purified by silica gel chromatography. The synthesised ubiquinone-8 (1a; $n = 7$), ubiquinone-9 (1a; $n = 8$), and ubiquinone-10 (1a; $n = 9$) were identified by ^{1}H n.m.r. and mass spectroscopy and by mixed melting points with authentic samples.[19]

Clearly applicable to the synthesis of other quinone derivatives, this modification of the terminal *trans*-methyl group, followed by a coupling reaction with a reactive carbanion of an appropriate prenyl compound, could well provide a general synthesis of menaquinones, plastoquinones, and other natural products bearing a prenylated aromatic nucleus. The regio- and stereoselectivity, as demonstrated here, makes this method ideal for such syntheses.

EXPERIMENTAL

M.p.s are uncorrected. ^{1}H and ^{13}C n.m.r. spectra were recorded for $CDCl_3$ solutions with a Varian XL-100 spectrometer using internal Me_4Si (δ = 0) as a standard. I.r. spectra were obtained on a Hitachi EPI-510 spectrometer. Mass spectra were determined on a JEOL JMS-01SC spectrometer. U.v. spectra were recorded with a Hitachi EPS-3T spectrometer in ethanol. High-pressure liquid chromatographic analyses (h.p.l.c.) were performed on a Yanagimoto L-1030 liquid chromatograph using a silica gel column. The latter were conducted by Mr. M. Hattori of our Chemical Laboratories. Liquid column chromatography was carried out on Merck silica gel (less than 0.08 mm) for thin-layer chromatography under a pressure of 10—20 kg/cm^2. Tetrahydrofuran (THF), hexamethylphosphoramide (HMPA), dimethyl sulphoxide (DMSO), and isopropyl ether (IPE) were dried by distillation from calcium hydride.

In the ^{1}H n.m.r. spectra of the compounds, derived from ubiquinone-7 (1a; $n = 6$) and its hydroquinone dibenzyl ether (1b), the only signals described are for the protons at positions which were chemically changed, since the others appear at essentially the same positions as those in the spectra of (1a; $n = 6$) and (1b).

Ubiquinone-7 (1a; n = 6).—Ubiquinone-7 [20,21] was isolated from *Candida utilis*. It had m.p. 31—32 °C, δ 1.61 (18 H, broad s, six methyl groups), 1.68 (3 H, s, Me at position 28′), 1.74 (3 H, s, Me at position 3′), 2.02 (24 H, twelve methylene groups), 3.14 and 3.22 (2 H, AB d, CH_2 at position 1′), 3.97 and 3.99 (6 H, two s, OMe), *ca.* 5.10 (7 H, m, vinyl protons).

Ubiquinol-7 *Dibenzyl Ether* (1b).—Ubiquinone-7 (1a; $n = 6$) (1.32 g, 2 mmol) was reduced to the corresponding hydroquinone in ethanol with sodium borohydride (500 mg). The ethanolic solution was concentrated *in vacuo* to dryness. The residue was dissolved in dimethylformamide (DMF) (20 ml). To the solution was added benzyl bromide (513 mg, 6 mmol) and 50% sodium hydride (300 mg, dispersed in oil, 6 mmol) under nitrogen at room temperature. This was stirred for 3 h. The crude product, obtained by addition of water and extraction of the aqueous mixture with n-hexane, was chromatographed on silica gel (60 g) using n-hexane–IPE (3 : 1) for elution to give the *benzyl ether* (1b) (1.56 g); δ 1.60 (18 H, broad s, six vinyl methyls), 1.68 (6 H, s, two vinyl methyls at 3′ and 28′), 2.01 (methylenes), 2.11 (3 H, s, arom-Me), 3.30 and 3.36 (2 H, AB d, CH_2 at 1′), 3.93 and 3.94 (6 H, two s, OMe), 4.96 (4 H, s, CH_2Ph), *ca.* 5.10 (7 H, m, vinyl protons), and 7.3—7.60 (10 H, m, arom-H) (Found: C, 82.9; H, 9.3. $C_{58}H_{80}O_4$ requires C, 82.81; H, 9.59%).

6-(26′-*Bromo*-27′-*hydroxy*-3′,7′,11′,15′,19′,23′,27′-*heptamethyloctacosa*-2′,6′,10′,14′,18′,22′-*hexenyl*)-2,3-*dimethoxy*-5-*methyl*-1,4-*benzoquinone* (2a).—To a solution of ubiquinone-7 (1a; $n = 6$) (1.977 g, 3 mmol) in 20% aqueous 1,2-dimethoxyethane (100 ml), cooled to −5 °C and well stirred, was added NBS (590 mg, 3.6 mmol) portionwise over a period of 1 h. The reaction mixture was stirred for a further 2 h and then diluted with ethyl acetate. The organic layer was washed with water, dried (Na_2SO_4), and evaporated *in vacuo* to yield an orange oil (2.29 g) which was chromatographed on silica gel (100 g) using 2 : 1 n-hexane–IPE for elution to give the starting material (238 mg). Elution with IPE gave the *bromohydrin* (2a) (1.542 g, 68%) as an orange oil; $\nu_{max.}$ (neat) 3 500 (OH), 1 650 and 1 614 (quinone and double bond), and 1 265 cm^{-1}; δ 1.34 (6 H, s, Me_2COH) and 3.97 (1 H, q, J = 6 and 13 Hz, =CHBr) (Found: C, 69.6; H, 8.9. $C_{44}H_{67}BrO_5$ requires C, 69.91; H, 8.93%).

Further elution with 9 : 1 IPE–ethyl acetate gave the *dibromohydrin* (78 mg) which was not further investigated.

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6-(26′-*Bromo*-27′-*hydroxy*-3′,7′,11′,15′,19′,23′,27′-*heptamethyloctacosa*-2′,6′,10′,14′,18′,22′-*hexenyl*)-2,3-*dimethoxy*-5-*methylhydroquinone* OO′-*Dibenzyl Ether* (2b).—Ubiquinol-7 dibenzyl ether (1b) (1.682 g, 2 mmol) in 20% aqueous 1,2-dimethoxyethane (100 ml) was bromohydrinated with NBS (427 mg, 2.4 mmol) as described above. The usual work-up gave a colourless oil which was chromatographed on silica gel (100 g) using 95 : 5 IPE–ethyl acetate for elution to yield the *bromohydrin* (2b) (1.21 g, 72%); δ 1.34 (6 H, s, Me_2C–OH), 3.97 (1 H, q, J = 6 and 13 Hz) (Found: C, 74.1; H, 8.5. $C_{58}H_{81}BrO_5$ requires C, 74.25; H, 8.70%).

Further elution with 9 : 1 IPE–ethyl acetate gave the *dibromohydrin* (287 mg) which was not further investigated.

6-(26′,27′-*Epoxy*-3′,7′,11′,15′,19′,23′,27′-*heptamethyloctacosa*-2′,6′,10′,14′,18′,22′-*hexenyl*)-2,3-*dimethoxy*-5-*methyl*-1,4-*benzoquinone* (3a).—To a stirred solution of the bromohydrin (2a) (756 mg, 1 mmol) in methanol (10 ml) was added potassium carbonate (140 mg) at room temperature. After the reaction was completed, the mixture was concentrated *in vacuo*. The residue was dissolved in n-hexane and the solution was washed with water and dried; the solvent was evaporated off to yield the *epoxide* (3a) (672 mg, 99.7%). This was used without purification in the following reaction, $\nu_{max.}$ (neat) 1 650 and 1 612 (quinone and double bond) and 1 265 cm^{-1}; *m/e* 81, 197, 235, 250, 678 (M^+), and 676 ($M^+ + 2$); δ 1.26 and 1.30 (6 H, two s, $=CMe_2$) and 2.68 (1 H, t, J = 6 Hz, =CH–O) (Found: C, 78.5; H, 9.6. $C_{44}H_{66}O_5$ requires C, 78.29; H, 9.86%).

6-(26′,27′-*Epoxy*-3′,7′,11′,15′,19′,23′,27′-*heptamethyloctacosa*-2′,6′,10′,14′,18′,22′-*hexenyl*)-2,3-*dimethoxy*-5-*methylhydroquinone* (3b).—(*a*) Treatment of the bromohydrin (2b) (983 mg, 1 mmol) with potassium carbonate (140 mg) in methanol (10 ml) as described above gave the *epoxide* (3b) (896 mg, 99.3%) as a colourless oil; δ 1.26 and 1.30 (6 H, two s, $=CMe_2$) and 2.68 (1 H, t, J = 6 Hz, =CH–O) (Found: C, 81.3; H, 11.6. $C_{58}H_{80}O_5$ requires C, 81.26; H, 9.41%).

(*b*) Reduction of the epoxide (3a) (675 mg, 1 mmol) in 95% ethanol (10 ml) was performed with sodium borohydride (100 mg), and the resulting hydroquinone compound, after removal of the ethanol, was dissolved in DMF (30 ml) and then benzylated with benzyl bromide (350 mg) in the presence of 50% sodium hydride (200 mg, dispersed in oil) at room temperature for 1 h. The reaction mixture was worked up as usual and then chromatographed on silica gel (30 g) using 3 : 2 n-hexane–IPE for elution to yield the *epoxide* (3b) (791 mg, 92.3%).

6-(26′,27′-*Dihydroxy*-3′,7′,11′,15′,19′,23′,27′-*heptamethyloctacosa*-2′,6′,10′,14′,18′,22′-*hexenyl*)-2,3-*dimethoxy*-5-*methyl*-1,4-*benzoquinone* (4a).—To a solution of the epoxide (3a) (1.348 g, 2 mmol) in aqueous 1,2-dimethoxyethane (50 ml) was added 70% perchloric acid (0.1 ml) at room temperature. The solution was then set overnight. The product was extracted with ethyl acetate and the organic layer was washed, dried, and evaporated. The residue was chromatographed on silica gel (100 g) using 96 : 4 n-hexane–ethyl acetate for elution to give the *glycol* (4a) (1.312 g, 94.7%) as an orange oil; $\nu_{max.}$ (neat) 3 400 (OH), 1 650 and 1 612 (quinone and double bond), and 1 265 cm^{-1}; δ 1.16 and 1.20 (6 H, two s, Me_2COH) and 3.34 (1 H, q, J = 3 and 9 Hz, =CH–O) (Found: C, 76.0; H, 10.1. $C_{44}H_{68}O_6$ requires C, 76.26; H, 9.89%).

6-(26′,27′-*Dihydroxy*-3′,7′,11′,14′,19′,23′,27′-*octamethyloctacosa*-2′,6′,10′,14′,18′,22′-*hexenyl*)-2,3-*dimethoxy*-5-*methylhydroquinone* OO′-*Dibenzyl Ether* (4b).—Treatment of the epoxide (3b) (857 mg, 1 mmol) with 70% perchloric acid (0.1 ml) in 10% aqueous 1,2-dimethoxyethane (30 ml) as described above gave the *glycol* (4b) (865 mg, 98.8%) as a colourless oil; δ 1.16 and 1.20 (6 H, two s, $=CMe_2$) and 3.34 (1 H, q, J = 3 and 9 Hz, =CH–O) (Found: C, 79.4; H, 9.6. $C_{58}H_{82}O_6$ requires C, 79.59; H, 9.44%).

6-(25′-*Formyl*-3′,7′,11′,15′,19′,23′-*hexamethylpentacosa*-2′,6′,10′,14′,18′,22′-*hexenyl*)-2,3-*dimethoxy*-5-*methyl*-1,4-*benzoquinone* (5a).—To a solution of the glycol (4a) (207 mg, 0.3 mmol) in 5% aqueous 1,2-dimethoxyethane (10 ml) was added a solution of sodium metaperiodate (77 mg, 0.36 mmol) and concentrated sulphuric acid (26 mg, 0.36 mmol) in a minimum amount of water. The mixture was stirred at room temperature until the reaction was completed. Water (25 ml) and n-hexane (30 ml) were added to the mixture and shaken. Then the organic layer was separated, washed, dried, and evaporated. The residue was chromatographed on silica gel (10 g) using IPE for elution to yield the *aldehyde* (5a) (153 mg, 81.8%); $\nu_{max.}$ (neat) 2 720 and 1 720 (CHO), 1 650 and 1 610 (quinone and double bond), and 1 270 cm^{-1}; δ 2.40 (2 H, m, CH_2CHO), 9.73 (1 H, t, J = 1.7 Hz, CHO) (Found: C, 77.6; H, 9.6. $C_{41}H_{60}O_5$ requires C, 77.80; H, 9.56%).

6-(26′-*Acetoxy*-27′-*hydroxy*-3′,7′,11′,15′,19′,23′,27′-*heptamethyloctacosa*-2′,6′,10′,14′,18′,22′-*hexenyl*)-2,3-*dimethoxy*-5-*methyl*-1,4-*benzoquinone* (6a).—(*a*) A mixture of the epoxide (3a) (674 mg, 1 mmol) and sodium acetate (400 mg) in acetic acid (4 ml) was warmed at 65 °C under nitrogen for 3 h, then cooled, and diluted with water (20 ml) and IPE (40 ml). The organic layer was separated, washed, dried, and evaporated. The residue was chromatographed on silica gel (50 g) using IPE for elution to give the *monoacetate* (6a) (525 mg, 78%) as an orange oil; $\nu_{max.}$ (neat) 3 450 (OH), 1 735 (OAc), 1 650 and 1 612 (quinone and double bond), and 1 265 cm^{-1}; δ 1.20 (6 H, s, $=CMe_2$), 2.10 (3 H, s, OAc), 4.84 (1 H, q, J = 3 and 9 Hz, =CHOAc) (Found: C, 75.2; H, 9.7. $C_{46}H_{70}O_7$ requires C, 75.16; H, 9.60%).

(*b*) To a solution of the glycol (4a) (693 mg, 1 mmol) in methylene chloride (20 ml) was added pyridine (0.3 ml) and acetic anhydride (0.2 ml) at room temperature. The mixture was set aside overnight and then worked up as usual to give an orange oil. This material was chromatographed on silica gel (50 g) using IPE for elution to yield the *monoacetate* (699 mg, 95.2%).

6-(26′-*Acetoxy*-27′-*hydroxy*-3′,7′,11′,15′,19′,23′,27′-*heptamethyloctacosa*-2′,6′,10′,14′,18′,22′-*hexenyl*)-2,3-*dimethoxy*-5-*methylhydroquinone* OO′-*Dibenzyl Ether* (6b).—Acetylation of the glycol (4b) (438 mg, 0.5 mmol) in methylene chloride (5 ml) containing pyridine (0.1 ml) and acetic anhydride (0.1 ml) was carried out at room temperature overnight. The reaction mixture was diluted with IPE (30 ml) and worked up as usual to give an oil which was chromatographed on silica gel (20 g) using IPE for elution to yield the *monoacetate* (6b) (450 mg, 98.3%) as a colourless oil; δ 1.17 (6 H, s, Me_2COH), 2.07 (3 H, s, OAc), 4.84 (1 H, q, J = 3 and 9 Hz, =CHOAc) (Found: C, 78.4; H, 9.3. $C_{60}H_{84}O_7$ requires C, 78.56; H, 9.23%).

6-(26′-*Acetoxy*-27′-*methylene*-3′,7′,11′,15′,19′,23′-*hexamethyloctacosa*-2′,6′,10′,14′,18′,22′-*hexenyl*)-2,3-*dimethoxy*-5-*methyl*-1,4-*benzoquinone* (7a).—To a solution of the monoacetate (6a) (735 mg, 1 mmol) in n-hexane (20 ml), cooled to 0 °C, was added thionyl chloride (178 mg, 1.5 mmol) in n-hexane (5 ml). After the mixture had been stirred for

10 min, an n-hexane solution (5 ml) containing pyridine (0.25 ml) was added to the mixture. The reaction was further stirred for 20 min after which it was washed with water, dried, and concentrated. The residue was chromatographed on silica gel (50 g) using 2 : 3 n-hexane–IPE to give the *allyl acetate* (7a) (687 mg, 95.8%) as an oil; $\nu_{max.}$ (neat) 1 735 (AcO), 1 650 and 1 613 (quinone and double bond), 1 265, and 1 235 cm^{-1}; δ 1.74 (6 H, broad s, two vinyl methyl groups at 3′ and 27′ positions), 2.05 (3 H, s, OAc), and 4.89 and 4.95 (3 H, m, =CHOAc and $=CH_2$) (Found: C, 76.9; H, 9.4. $C_{46}H_{68}O_6$ requires C, 77.05; H, 9.56%).

Further elution with IPE containing 3% ethyl acetate gave the *isomeric acetate* (8a) (21 mg) as an orange oil. When heated at 65 °C for 2 h in a mixture of sodium acetate (20 mg) and acetic acid (0.5 ml), this material was converted into (6a).

6-(26′-*Acetoxy*-27′-*methylene*-3′,7′,11′,15′,19′,23′-*hexamethyloctacosa*-2′,6′,10′,14′,18′,22′-*hexenyl*)-2,3-*dimethoxy*-5-*methylhydroquinone* OO′-*Dibenzyl Ether* (7b).—Dehydration of the monoacetate (6b) (458 mg, 0.5 mmol) with thionyl chloride (120 mg, 1 mmol) and pyridine (0.2 ml) in n-hexane (10 ml) as described above gave the *allyl acetate* (7b) (437 mg, 97.3%), after purification through a short column of silica gel; δ 1.74 (3 H, broad s, vinyl methyl at 27′ position), 2.10 (3 H, s, OAc), and 4.89 and 4.95 (3 H, m, =CH–O and $C=CH_2$) (Found: C, 79.9; H, 9.1. $C_{60}H_{82}O_6$ requires C, 80.13; H, 9.19%).

Further elution with IPE containing 3% ethyl acetate gave the *isomeric acetate* (8b) (18 mg) as an oil. When heated at 65 °C for 2 h in a mixture of sodium acetate (20 mg) and acetic acid (0.5 ml), this material was converted into (6b).

6-(26′-*Hydroxy*-27′-*methylene*-3′,7′,11′,15′,19′,23′-*hexamethyloctacosa*-2′,6′,10′,14′,18′,22′-*hexenyl*)-2,3-*dimethoxy*-5-*methyl*-1,4-*benzoquinone* (9a).—A stirred solution of the allyl acetate (7a) (717 mg, 1 mmol) in 95% ethanol (20 ml) was treated with sodium borohydride (1 g) under nitrogen at room temperature until the orange colour had disappeared and then the mixture was treated with 10% aqueous sodium hydroxide (5 ml). After the hydrolysis was completed, 4% aqueous hydrochloric acid (25 ml) and IPE (40 ml) were added to the mixture. The usual work-up gave an oil which was dissolved in 10% aqueous 1,2-dimethoxyethane (20 ml) and oxidised with ferric chloride dihydrate (600 mg) with stirring at room temperature for 2 h. The reaction mixture was worked up as usual and the crude product was chromatographed on silica gel (30 g) using IPE for elution to yield the *allyl alcohol* (9a) (635 mg, 96.9%) as an orange oil; $\nu_{max.}$ (neat) 3 400 (OH), 1 650 and 1 612 (quinone and double bond), and 1 265 cm^{-1}; δ 1.74 (6 H, broad s, two vinyl methyls at 3′ and 27′ positions), 4.03 (1 H, t, J = 6 Hz, =CHOH), and 4.85 and 4.94 (2 H, m, $C=CH_2$) (Found: C, 78.3; H, 9.7. $C_{44}H_{66}O_5$ requires C, 78.29; H, 9.86%).

6-(26′-*Hydroxy*-27′-*methylene*-3′,7′,11′,15′,19′,23′-*hexamethyloctacosa*-2′,6′,10′,14′,18′,22′-*hexenyl*-2,3-*dimethoxy*-5-*methylhydroquinone* OO′-*Dibenzyl Ether* (9b).—(*a*) The allyl acetate (7b) (450 mg, 0.5 mmol) in 10% aqueous 1,2-dimethoxyethane (10 ml) was hydrolysed with 10% aqueous sodium hydroxide (0.4 ml) at room temperature for 6 h. The mixture was then concentrated *in vacuo*. The residue was dissolved in IPE (30 ml) and the solution was washed and dried. The solvent was evaporated to give the *allyl alcohol* (9b) (405 mg, 94.5%) as a colourless oil, after purification through a short column of silica gel; δ 1.74 (3 H, broad s, vinyl methyl at 27′ position), 4.03 (1 H, t, J = 6 Hz, =CHOH), and 4.85 and 4.94 (2 H, m, $C=CH_2$) (Found: C, 81.2; H, 9.3. $C_{58}H_{80}O_5$ requires C, 81.26; H, 9.41%).

(*b*) A solution of the epoxide (3b) (875 mg, 1 mmol) in absolute THF (5 ml) was added to a THF solution (25 ml) containing lithium di-isopropylamide (500 mg). The mixture was set aside at 5 °C for 10 h and then neutralised with 2% aqueous hydrochloric acid (50 ml). The product was extracted with IPE and worked up as usual to yield an oil. This material was chromatographed on silica gel (30 g) using IPE for elution to give the *allyl alcohol* (9b) (756 mg, 86.4%).

6-(28′-*Chloro*-3′,7′,11′,15′,19′,23′,27′-*heptamethyloctacosa*-2′,6′,10′,14′,18′,22′,26′-*heptenyl*)-2,3-*dimethoxy*-5-*methyl*-1,4-*benzoquinone* (10a).—A stirred mixture of the allyl alcohol (9a) (693 mg, 1 mmol) and thionyl chloride (144 mg, 1.2 mmol) in n-hexane (10 ml) was set aside at room temperature. After the reaction was completed, the solution was washed with 3% aqueous sodium hydrogencarbonate and water, dried, and evaporated. The residue was chromatographed on silica gel (50 g) using 1 : 1 n-hexane–IPE for elution to yield the *chloromethyl compound* (10a) (587 mg, 84.7%) as an orange oil; $\nu_{max.}$ (neat) 1 650 and 1 613 (quinone and double bond) and 1 265 cm^{-1}; δ 1.74 (6 H, broad s, two vinyl methyls at 3′ and 27′ positions), 3.99 (2 H, s, CH_2Cl), 5.52 (1 H, t, vinyl proton at 26′ position) (Found: C, 76.0; H, 9.3. $C_{44}H_{65}ClO_4$ requires C, 76.21; H, 9.45%).

The h.p.l.c. analysis of the chloromethyl compound indicated the presence of the *secondary chloride* (11a) less than 5%.

6-(28′-*Chloro*-3′,7′,11′,15′,19′,23′,27′-*heptamethyloctacosa*-2′,6′,10′,14′,18′,22′,26′-*heptenyl*)-2,3-*dimethoxy*-5-*methylhydroquinone* OO′-*Dibenzyl Ether* (10b).—Chlorination of the allyl alcohol (429 mg, 0.05 mmol) with thionyl chloride (120 mg, 1 mmol) in n-hexane (10 ml) as described above yielded the *chloride* (10b) (430 mg, 98.3%); δ 1.72 (3 H, s, vinyl methyl at 27′ position), 3.98 (2 H, s, CH_2Cl) ,and 5.50 (1 H, t, vinyl proton at 26′ position) (Found: C, 79.2; H, 8.9. $C_{58}H_{79}ClO_4$ requires C, 79.55; H, 9.09%).

The h.p.l.c. analysis of the chloromethyl compound indicated the presence of the *secondary chloride* (11b) less than 5%.

6-(26′-*Chloro*-27′-*methylene*-3′,7′,11′,15′,19′,23′-*hexamethyloctacosa*-2′,6′,10′,14′,18′,22′-*hexenyl*)-2,3-*dimethoxy*-5-*methyl*-1,4-*benzoquinone* (11a).—To a stirred solution containing the allyl alcohol (9a) (135 mg, 0.2 mmol) and pyridine (1 ml) in methylene chloride (10 ml) at −20 °C was added slowly a methylene chloride solution (3 ml) containing thionyl chloride (29 mg, 0.24 mmol). The temperature was raised to room temperature and stirred for 1 h. The mixture was diluted with 3% aqueous hydrochloric acid (25 ml) and methylene chloride (20 ml). The organic layer was separated, washed with water and aqueous sodium hydrogencarbonate, dried, and evaporated. The residue was chromatographed on silica gel (10 g) using IPE for elution to give the *allyl chloride* (11a) (127 mg, 91.6%) as an orange oil; $\nu_{max.}$ (neat) 1 650 and 1 612 (quinone and double bond), 1 265, and 1 205 cm^{-1}; δ 1.74 (6 H, s, two vinyl methyls at 3′ and 27′ positions), 4.80 (1 H, q, J = 6 and 14 Hz, =CHCl), and 4.95 and 5.00 (2 H, m, $C=CH_2$) (Found: C, 76.1; H, 9.2. $C_{44}H_{65}ClO_4$ requires C, 76.21; H, 9.45%).

Oxidation of the Chloromethyl and the Secondary Chloro-compounds.—(a) 6-(27′-*Formyl*-3′,7′,11′,15′,19′,23′-*hexamethyloctacosa*-2′,6′,10′,14′,18′,22′,26′-*heptenyl*)-2,3-*dimethoxy*-5-*methyl*-1,4-*benzoquinone* (12a). To a solution of the chloromethyl compound (10a) (166 mg, 0.239 mmol) in absolute Me_2SO (5 ml) was added silver tetrafluoroborate (50 mg, *ca.* 90% with n-pentane) under nitrogen. The mixture was stirred at room temperature. A fine white precipitate developed as the reaction proceeded. After 2 h, triethylamine (0.6 ml) was added and the mixture was further stirred for 20 min. It turned black, water (10 ml) was added to the reaction mixture, and the product was extracted with IPE. The organic layer was separated, washed, dried, and evaporated. The residue was chromatographed on silica gel (10 g) using 1 : 2 n-hexane–IPE for elution to afford the *formyl compound* (12a) (137 mg, 85.1%) as an orange oil; $\lambda_{max.}$ 227 (ε 19 700, shoulder), 253 (ε 9 100, trough), and 275 nm (ε 14 800); $\nu_{max.}$ (neat) 2 700, 1 690 and 1 660 (α,β-unsaturated aldehyde), and 1 650 and 1 610 cm^{-1} (quinone and double bond); δ 1.74 (6 H, s, two vinyl methyls at 3′ and 27′ positions), 6.46 (1 H, t, J = 7 Hz, vinyl proton at 26′ position), and 9.37 (1 H, s, CHO) (Found: C, 78.3; H, 9.4. $C_{44}H_{64}O_5$ requires C, 78.53; H, 9.59%).

(b) 6-(27′-*Formyl*-3′,7′,11′,15′,19′,23′-*hexamethyloctacosa*-2′,6′,10′,14′,18′,22′,26′-*heptenyl*)-2,3-*dimethoxy*-5-*methylhydroquinone* OO′-*Dibenzyl Ether* (12b).—Similar oxidation of the chloromethyl compound (10b) (220 mg, 0.25 mmol) with silver tetrafluoroborate (70 mg) in absolute Me_2SO (5 ml) as described above gave the *aldehyde* (12b) (185 mg, 86.5%) as a colourless oil; δ 1.72 (3 H, s, vinyl methyl at 27′ position), 6.44 (1 H, t, J = 7 Hz, vinyl proton at 26′ position), and 9.37 (1 H, s, CHO) (Found: C, 81.2; H, 9.3. $C_{58}H_{78}O_5$ requires C, 81.45; H, 9.19%).

(c) 6-(27′-*Methylene*-3′,7′,11′,15′,19′,23′-*hexamethyl*-26′-*oxo-octacosa*-2′,6′,10′,14′,18′,22′-*hexenyl*)-2,3-*dimethoxy*-5-*methyl*-1,4-*benzoquinone* (13a). Similar oxidation of the secondary chloride (11a) (100 mg, 0.144 mmol) with silver tetrafluoroborate (30 mg) in absolute Me_2SO (3 ml) as described above gave the αβ-*unsaturated ketone* (13a) (58 mg, 65%) as an orange oil; $\nu_{max.}$ (neat) 1 680, 1 660, 1 650, and 1 610 cm^{-1} (α,β-unsaturated ketone, quinone and double bond); δ 1.87 (3 H, s, vinyl methyl at 27′ position), 5.84 and 5.93 (2 H, m, C=CH_2) (Found: C, 78.4; H, 9.4. $C_{44}H_{64}O_5$ requires C, 78.53; H, 9.59%).

Preparation of Prenyl Sulphone Derivatives.—(a) 3-*Methyl*-1-(p-*tolylsulphonyl*)*but*-2-*ene* (14a).—A stirred solution of 1-bromo-3-methylbut-2-ene (1.49 g, 10 mmol) in DMF (20 ml) was allowed to react with sodium toluene-*p*-sulphinate dihydrate (2.5 g, 11.6 mmol) at room temperature for 3 h. The usual work-up gave the *sulphone* (14a) (2.1 g, 96.4%), m.p. 71—72 °C, after recrystallisation from n-hexane; δ 1.37 (3 H), 1.73 (3 H), 2.46 (3 H), 3.77 (2 H), 5.20 (1 H), 7.34, and 7.76 (4 H) (Found: C, 64.1; H, 7.0. $C_{12}H_{16}O_2S$ requires C, 64.25; H, 7.19%).

(b) trans-3,7-*Dimethyl*-1-(p-*tolylsulphonyl*)*octa*-2,6-*diene* (14b). Reaction of geranyl chloride (1.8 g, 10 mmol) with sodium toluene-*p*-sulphinate dihydrate (2.5 g, 11.6 mmol) in DMF (20 ml) as described above gave the trans-*sulphone* (14b) (2.82 g, 96.6%) as needles, m.p. 44 °C, after recrystallisation from n-hexane; δ 1.37 (3 H), 1.61 (3 H), 1.70 (3 H), 2.00 and 2.04 (4 H), 2.46 (3 H), 3.78 (2 H), 5.06 (1 H), 5.18 (1 H), 7.34, and 7.76 (4 H) (Found: C, 69.6; H, 8.4. $C_{17}H_{24}O_2S$ requires C, 69.82; H, 8.27%).

(c) cis-3,7-*Dimethyl*-1-(p-*tolylsulphonyl*)*octa*-2,6-*diene* (15a). Reaction of neryl chloride (1.8 g, 10 mmol) with sodium toluene-*p*-sulphinate dihydrate (2.5 g, 11.6 mmol) in DMF (20 ml) as described above gave the cis-*sulphone* (15a) (2.54 g, 87%), m.p. 15—16 °C, from n-hexane; δ 1.55 (3 H), 1.65 (3 H), 1.73 (3 H), 1.8—2.0 (4 H), 2.46 (3 H), 3.77 (2 H), 4.96 (1 H), 5.20 (1 H), 7.34, and 7.76 (4 H) (Found: C, 69.7; H, 8.1. $C_{17}H_{24}O_2S$ requires C, 69.82; H, 8.27%).

(d) cis,trans-3,7,11-*Trimethyl*-1-(p-*tolylsulphonyl*)*dodeca*-2,6,10-*triene* (15b) *and* trans,trans-3,7,11-*trimethyl*-1-(p-*tolylsulphonyl*)*dodeca*-2,6,10-*triene* (14c). Reaction of the bromide (2.85 g, 10 mmol), prepared by the reaction of neloridol with phosphorus tribromide, with sodium toluene-*p*-sulphinate in DMF (20 ml) as described above gave a mixture of (14c) and (15b) which was chromatographed on silica gel (200 g). Elution with 2 : 1 n-hexane–IPE gave the cis,trans-*compound* (15b) (980 mg, 27%) as an oil; δ 1.55 (3 H), 1.60 (3 H), 1.68 (3 H), 1.72 (2 H), 1.83 (4 H), 1.98 (4 H), 2.44 (3 H), 3.77 (2 H), 4.86—5.18 (2 H), 5.20 (1 H), 7.31, and 7.74 (4 H) (Found: C, 73.3; H, 8.7. $C_{22}H_{32}O_2S$ requires C, 73.28; H, 8.94%).

Further elution with the same solvent gave the trans,trans *compound* (14c) (2.43 g, 68%) as an oil; δ 1.37 (3 H), 1.61 (6 H), 1.70 (3 H), 2.0—2.07 (8 H), 2.46 (3 H), 3.77 (2 H), 4.86—5.18 (2 H), 5.20 (1 H), 7.31 and 7.74 (4 H) (Found: C, 73.2; H, 8.7. $C_{22}H_{32}O_2S$ requires C, 73.28; H, 8.94%).

6-(3′,7′,11′,15′,19′,23′,27′,31′-*Octamethyl*-29′-*p-tolylsulphonyldotriaconta*-2′,6′,10′,14′,18′,22′,26′,30′-*octenyl*)-2,3-*dimethoxy*-5-*methylhydroquinone* OO′-*Dibenzyl Ether* (16a).—To a stirred solution of the sulphone (14a) (134 mg, 0.6 mmol) in absolute THF–HMPA (4 ml, 3 : 1) was added 10% (w/v) solution (0.39 ml) of n-butyl-lithium in n-hexane at −20 °C under nitrogen to generate an orange carbanion. After 10 min, the mixture was cooled to −70 °C. A solution of the chloromethyl compound (10b) (440 mg, 0.5 mmol) in absolute THF (3 ml) was slowly added to the mixture with stirring for 1 h. The orange colour faded as the reaction proceeded. The product was isolated by allowing the mixture to warm to room temperature, adding acetic acid (0.5 ml) and water (50 ml), extracting with IPE, and evaporating the latter. The crude product was chromatographed on silica gel (30 g) using 3 : 1 n-hexane–IPE for elution to give the coupled *compound* (16a) (448 mg, 84.2%) as a colourless oil; δ 1.21 (3 H, d, J = 1.2 Hz, vinyl methyl at 31′ position), 1.52 (3 H, s, vinyl methyl at 27′ position), 1.59 (15 H, broad s, five vinyl methyls), 1.66 (6 H, broad s, two vinyl methyls at 3′ and 32′ positions), 2.01 (methylene protons), 2.12 (3 H, s, methyl at 5 position), 2.43 (3 H, s, arom-CH_3), 3.31 and 3.37 (2 H, AB d, CH_2 at 1′ position), 3.86 (1 H, sextet, J = 3 and 11 Hz, methine proton at 29′ position), 3.95 (6 H, s, OCH_3), 4.95 (4 H, s, CH_2Ph), *ca.* 5.10 (8 H, m, vinyl protons), 7.29 and 7.71 (4 H, AB q, arom-H), and 7.3—7.6 (10 H, m, arom-H) (Found: C, 79.2; H, 8.8. $C_{70}H_{94}O_6S$ requires C, 79.05; H, 8.91%).

6-(3′,7′,11′,15′,19′,23′,27′,31′,35′-*Nonamethyl*-29′-p-*tolylsulphonylhexatriaconta*-2′,6′,10′,14′,18′,22′,26′,30′,34′-*nonenyl*)-2,3-*dimethoxy*-5-*methylhydroquinone* OO′-*Dibenzyl Ether* (16b).—The lithium carbanion of the sulphone (14b) (175 mg, 0.6 mmol) was generated with 10% (w/v) n-butyl-lithium in n-hexane (0.4 ml) as described above. The carbanion was then coupled with the chloromethyl compound (10b) (440 mg, 0.5 mmol) according to the above procedure. The reaction mixture was worked up as usual to give an oil which was chromatographed on silica gel (30 g) using 3 : 1 n-hexane–IPE for elution to yield the

coupled compound (16b) (452 mg, 79.8%); δ 1.24 (3 H, d, J = 1.2 Hz, vinyl methyl at 31′ position), 1.51 (3 H, s, vinyl methyl at 27′ position), 1.59 and 1.60 (18 H, six vinyl methyls), 1.68 (6 H, s, two vinyl methyls at 3′ and 36′ positions), 2.01 (methylenes), 2.12 (3 H, s, methyl at 5 position), 2.42 (3 H, s, arom-CH_3), 3.30 and 3.36 (2 H, AB d, CH_2 at 1′ position), 3.84 (1 H, sextet, J = 3 and 11 Hz, =CH–SO_2), 3.93 and 3.94 (6 H, two s, OCH_3), 4.97 (4 H, s, CH_2Ph), *ca.* 5.10 (9 H, m, vinyl protons), 7.28 and 7.72 (4 H, AB q, arom-H), and 7.3—7.6 (10 H, arom-H) (Found: C, 79.5; H, 8.8. $C_{75}H_{102}O_6S$ requires C, 79.60; H, 9.08%).

6-(3′,7′,11′,15′,19′,23′,27′,31′,35′,39′-*Decamethyl*-29′-p-*tolylsulphonyltetraconta*-2′,6′,10′,14′,18′,22′,26′,30′,34′,38′-*decenyl*)-2,3-*dimethoxy*-5-*methylhydroquinone* OO′-*Dibenzyl Ether* (16c).—The lithium carbanion of the sulphone (14c) (216 mg, 0.6 mmol) was generated with 10% (w/v) n-butyl-lithium in n-hexane (0.4 ml) as described above. The carbanion was then coupled with the chloromethyl compound (10b) (440 mg, 0.5 mmol) according to the above procedure. The reaction mixture was worked up as usual to give an oil which was chromatographed on silica gel (30 g) 3 : 1 n-hexane–IPE for elution to yield the *coupled compound* (16c) (442 mg, 73.6%); δ 1.24 (3 H, d, J = 1.2 Hz, vinyl methyl at 31′ position), 1.51 (3 H, s, vinyl methyl at 27′ position), 1.60 (21 H, seven vinyl methyls), 1.68 (6 H, s, two vinyl methyls at 3′ and 40′ positions), 2.00 (methylenes), 2.12 (3 H, s, methyl at 5 position), 2.42 (3 H, s, arom-CH_3), 3.30 and 3.36 (2 H, AB d, CH_2 at 1′ position), 3.84 (1 H, sextet, J = 3 and 11 Hz, =CH–SO_2), 3.93 and 3.94 (6 H, s, OCH_3), *ca.* 5.10 (10 H, vinyl protons), 7.28 and 7.72 (4 H, AB q, arom-H), and 7.3—7.6 (10 H, arom-H) (Found: C, 80.3; H, 9.3. $C_{80}H_{110}O_6S$ requires C, 80.09; H, 9.24%).

All-trans-1-*benzyloxy*-3,7,11,15-*tetramethyl*-9-(p-*tolylsulphonyl*)*hexadeca*-2,6,10,14-*tetraene* (17).—(a) *Preparation of* trans,trans-1-*benzyloxy*-8-*chloro*-3,7-*dimethylocta*-2,6-*diene* (10c). Geranyl benzyl ether (10 g, 41.0 mmol) in 20% aqueous 1,2-dimethoxyethane (150 ml) was bromohydrinated with NBS (7.67 g, 43.0 mmol) to give the bromohydrin (2c) (13.9 g) which was followed by treatment with 2M-aqueous sodium hydroxide solution (25 ml) to give the epoxide (3c) (10.1 g, 94.6%). The epoxide (6 g, 23.1 mmol) in 15% aqueous 1,2-dimethoxyethane (120 ml) was hydrolysed in the presence of perchloric acid (0.1 ml) at 5 °C overnight to give the glycol (4c) (6.4 g) which was acetylated in methylene chloride (60 ml) containing acetic anhydride (8.8 ml) and pyridine (7.1 ml) at room temperature overnight to give the monoacetate (6c) (6.83 g, 92.4%). Dehydration of the monoacetate (5.0 g) with thionyl chloride (1.87 g) and pyridine (2.5 g) in IPE (50 ml) at 0 °C gave the allyl acetate (7c) (3.93 g, 82.9%); δ 1.66 (3 H), 1.73 (3 H), 2.04 (OAc), 4.06 (2 H), 4.52 (2 H), 4.97 (2 H), 5.20 (1 H), 5.45 (1 H), 7.36 (5 H). Hydrolysis of the allyl acetate (3.93 g), obtained above, with potassium hydroxide (1.29 g) in methanol (50 ml) gave the allyl alcohol (9c) (3.22 g, 95.3%) as an oil. Chlorination of the allyl alcohol (2.45 g, 9.0 mmol) in IPE–n-hexane (1 : 1, 100 ml) was effected at 0 °C with thionyl chloride (2.23 g) to give an oil. This material was purified by passage through a short column of silica gel to yield the chloro-compound (10c) (2.5 g, 95.5%) as an oil; δ 1.65 (3 H), 1.74 (3 H), 4.00 (2 H), 4.04 (2 H), 4.50 (2 H), 5.45 (1 H), 5.54 (1 H), and 7.34 (5 H).

(b) *Coupling reaction of the sulphone* (14b) *with the chloro-compound* (10c). The lithium carbanion of the sulphone (14b) (292 mg, 1 mmol) was generated with 10% (w/v) n-butyl-lithium (0.8 ml) in n-hexane as described above. The carbanion was then coupled with the chloro-compound (10c) (300 mg, 1.1 mmol) in THF (5 ml). The reaction mixture was worked up as usual to give an oil which was chromatographed on silica gel (30 g) using IPE for elution to yield the *coupled compound* (17) (473 mg, 88.1%); δ 1.24 (3 H), 1.54 (3 H), 1.61 (6 H), 1.68 (3 H), 2.44 (3 H), 2.16 and 2.87 (2 H), 3.86 (1 H, =$CHSO_2$), 4.01 (2 H), 4.49 (2 H), 4.89 (1 H), 5.0—5.2 (2 H), 5.37 (1 H), 7.28 and 7.71 (4 H), and 7.33 (5 H) (Found: C, 76.0; H, 8.8. $C_{34}H_{46}O_3S$ requires C, 76.36; H, 8.67%).

All-trans-2,6,11,15,19-*pentamethyl*-9-(p-*tolylsulphonyl*)-*eicosa*-2,6,10,14,18-*pentaene* (18).—The lithium carbanion of the sulphone (14c) (360 mg, 1 mmol) was generated with 10% (w/v) n-butyl-lithium in n-hexane (0.8 ml) as described above. The carbanion was then coupled with geranyl chloride (180 mg) in THF (5 ml). The reaction mixture was worked up as usual to give an oil which was chromatographed on silica gel (20 g) using IPE for elution to yield the *coupled compound* (18) (348 mg, 81.3%); δ 1.25 (3 H), 1.58 (3 H), 1.60 and 1.65 (15 H), 1.95 and 2.00 (CH_2), 2.42 (3 H), 3.74 (1 H, =$CHSO_2$), *ca.* 5.10 (5 H), and 7.30 and 7.75 (4 H) (Found: C, 77.1; H, 9.6. $C_{32}H_{48}O_2S$ requires C, 77.37; H, 9.74%).

trans,trans,cis-1-*Benzyloxy*-3,7,11,15-*tetramethyl*-9-(p-*tolylsulphonyl*)*hexadeca*-2,6,10,14-*tetraene* (19).—The lithium carbanion of the sulphone (15a) (292 mg, 1 mmol) in THF (5 ml) was generated with 10% (w/v) n-butyl-lithium in n-hexane (0.4 ml) as described above. The carbanion was coupled with the chloride (10c) (300 mg, 1.1 mmol) in THF (5 ml). The reaction mixture was worked up as usual to give an oil which was chromatographed on silica gel (20 g) using IPE for elution to yield the *coupled compound* (19) (460 mg, 86.1%); δ 1.54 (6 H), 1.62 (3 H), 1.66 (3 H), 1.67 (3 H), 2.0—2.4 (8 H), 2.43 (3 H), 2.16 and 2.81 (2 H), 3.87 (1 H, =$CHSO_2$), 4.01 (2 H), 4.49 (2 H), 4.8—5.3 (3 H), 5.40 (1 H), 7.29 and 7.74 (4 H), and 7.34 (5 H) (Found: C, 76.4; H, 8.5. $C_{34}H_{46}O_3S$ requires C, 76.36; H, 8.67%).

Formation of Ubiquinone-8, *Ubiquinone*-9, *and Ubiquinone*-10.—(a) *Ubiquinone*-10 (1a; n = 9). To a solution of the coupled compound (16c) (120 mg, 0.1 mmol) in ethylamine (5 ml) under nitrogen at −30 °C was added lithium (20 mg). The mixture was stirred and the temperature gradually raised to −20 °C. After the reaction mixture had turned blue, the reaction was further stirred for 10 min under the same conditions. Isoprene (1 ml) was added to the mixture to quench the excess of lithium and the ethylamine was evaporated. To the residue was added a tetrahydrofuran solution (30 ml) containing acetic acid (0.6 ml) and 10% aqueous ferric chloride solution (1 ml). The mixture was stirred for 2 h at room temperature and then the solvent was evaporated. The residue was dissolved in IPE (30 ml) and the organic layer was separated, washed with water, dried, and evaporated. The crude material was chromatographed on silica gel (30 g) using 3 : 1 n-hexane–IPE for elution to afford ubiquinone-10 (62 mg, 72%), m.p. 48—49 °C, as orange crystals.

(b) *Ubiquinone*-9 (1a; n = 8). Following the above procedure, the benzyl and *p*-tolylsulphonyl groups of the coupled compound (16b) (113 mg, 0.1 mmol) were eliminated and then oxidation of the resulting hydroquinone gave

ubiquinone-9 (64 mg, 79%), m.p. 43—44 °C, as orange crystals.

(c) *Ubiquinone*-8 (1a; n = 7). Following the above procedure, the benzyl and *p*-tolylsulphonyl groups of the coupled compound (16a) (106 mg, 0.1 mmol) were eliminated and then oxidation of the resulting hydroquinone gave ubiquinone-8 (54 mg, 74%), m.p. 36—37 °C, as orange crystals.

These ubiquinones were judged to be homogeneous by their t.l.c. and h.p.l.c. analyses on silica gel. The ^1H n.m.r. and mass spectra of the synthesised ubiquinone-8, ubiquinone-9, and ubiquinone-10 were identical with those of naturally occurring ubiquinone-8 (from *Escherichia coli*),[19] ubiquinone-9 (from *Penicillium chrysogenum*),[19] and ubiquinone-10 (from ox heart muscle),[19] respectively.

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