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Synthetic Studies on Isoprenoidquinones. II.[1] Syntheses of Ubiquinone-10, Phylloquinone, and Menaquinone-4 by a Chain-Extending Method Utilizing Terminally Functionalized Isoprenoidhydroquinones

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Physiologically active polyisoprenoidquinones, ubiquinone-10 (coenzyme Q_{10}), phylloquinone (vitamin K_1), and menaquinone-4 (vitamin $K_{2(20)}$) were synthesized by a chain-extending method utilizing protected hydroquinones with the omega-hydroxyprenyl or omega-hydroxygeranyl side chain. Conditions for reductive desulfurization subsequent to allylic homologation were investigated.

Keywords——polyisoprenoidquinone synthesis; ubiquinone-10; phylloquinone; menaquinone-4; chain-extending method; sulfone coupling; reductive desulfurization

Among the various devices for regio- and stereocontrolled synthesis of polyisoprenoidquinones and -hydroquinones reported,[2] a new strategy involving a tandem process composed of terminal functionalization of simple prenylhydroquinones and subsequent chain elongation has been recently introduced.[3a] Easy availability of protected hydroquinones with the prenyl or geranyl side chain makes the method attractive for practical use.

Carbon–carbon bond formation utilizing α-sulfonyl or α-sulfenyl carbanions is well known to be one of general and versatile methods for homologation of carbon chains of allylic compounds with retention of olefinic geometry.[4] The versatility of the method has been demonstrated in polyisoprenoid[5] and also in polyisoprenoidquinone synthesis.[3,6] Various methods for reductive desulfurization have been also studied in order to remove undesirable side reactions, particularly regio- and stereochemical isomerization of neighboring olefinic bonds.[5b,7] Investigation of the efficiency of methods for reductive desulfurization in polyisoprenoidhydroquinone derivatives seems to be of particular interest in order to establish a chain-extending method as a general tool for the synthesis of polyisoprenoidquinones.

Along this context, in the preceding paper we developed a regio- and stereoselective synthetic version for terminally functionalized isoprenoidhydroquinones (**2**).[1] Here we report syntheses of physiologically important quinones,[8] ubiquinone-10 (**1a**), phylloquinone (**1b**), and menaquinone-4 (**1c**), by the chain-extending method utilizing **2** illustrated in Chart 1, and discuss some aspects of the reductive desulfurization of the sulfur-containing intermediary polyisoprenoidhydroquinones. We chose as the synthons A and B for these assemblies the allylic bromides (**3**) and the allylic sulfone (**4**), alkyl sulfone (**5**), or allylic sulfide (**6**). The bromides (**3**) were prepared from **2** by treatment with PBr_3 in Et_2O in the usual manner. The sulfur-containing isoprenoids (**4**) and (**6**) were obtained by routine procedures from geraniol, farnesol,[9] and solanesol[9] *via* bromination and sulfonylation, and the alkyl sulfone (**5**)[10] was obtained from commercially available farnesol *via* hydrogenation, bromination, and sulfonylation.

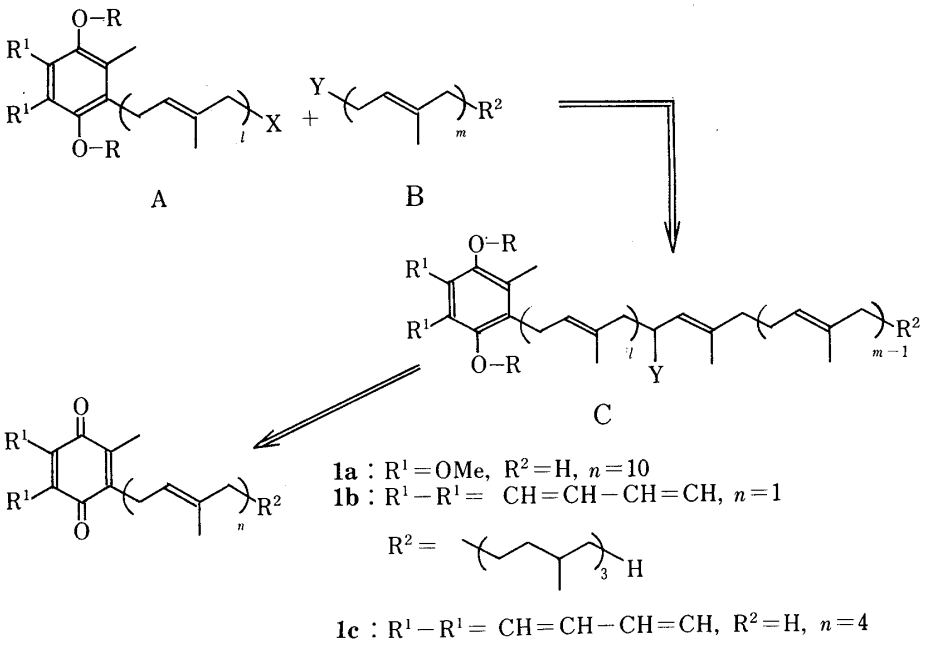

Chart 1

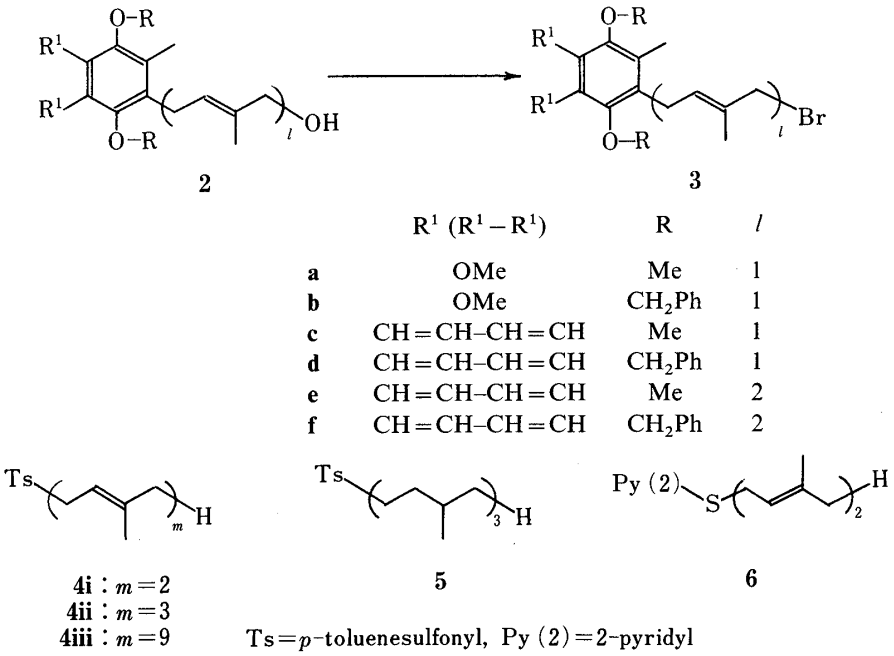

Chart 2

Synthesis of Ubiquinone-10 (1a) (Chart 3)

Carbon–carbon bond formation between the bromides (**3a**) or (**3b**) and solanesyl *p*-tolylsulfone (**4iii**)[3b] was carried out with BuLi in the presence of hexamethylphosphoric triamide (HMPA) in tetrahydrofuran (THF) at −70—0 °C to lead to the decaprenylated hydroquinone (**7**) (86%) or (**8**) (85%), respectively. Compound **7** was desulfurized by means of modified Bouvault–Blanc reduction (8 eq of Na and 10 eq of EtOH in THF at −20 °C)[3b] to produce the sulfur-free product in 87% yield. Observation of a doublet at δ 0.95 (J=7.0 Hz) assignable to the secondary methyl group in the proton nuclear magnetic resonance (^{1}H-

NMR) spectrum indicated that the product contains not only the desired compound **9** but also a substantial amount of the Δ^5-double bond isomer **10**. The sulfur-free product was demethylated oxidatively with ceric ammonium nitrate (CAN)[11] in a CH_2Cl_2–CH_3CN–H_2O solvent system to afford a mixture of decaprenylquinones **1a** and **11** in 72% yield. The composition of the mixture was estimated as **1a**:**11**=69:31 by high performance liquid chromatography (HPLC) on 5% $AgNO_3$-impregnated silica gel with a hexane–dioxane solvent system. Separation of the mixture was achieved by column chromatography on 5% $AgNO_3$-impregnated silica gel to give pure ubiquinone-10 (**1a**) as a crystalline compound, which was identical with an authentic sample[3a] by spectral comparisons, and the Δ^5-double bond isomer (**11**), which was characterized by ^{1}H-NMR analysis. Thus, in our experiment reductive desulfurization under the modified Bouvault–Blanc conditions proved to be relatively inefficient in regard to positional retention of the neighboring olefinic bond.[12]

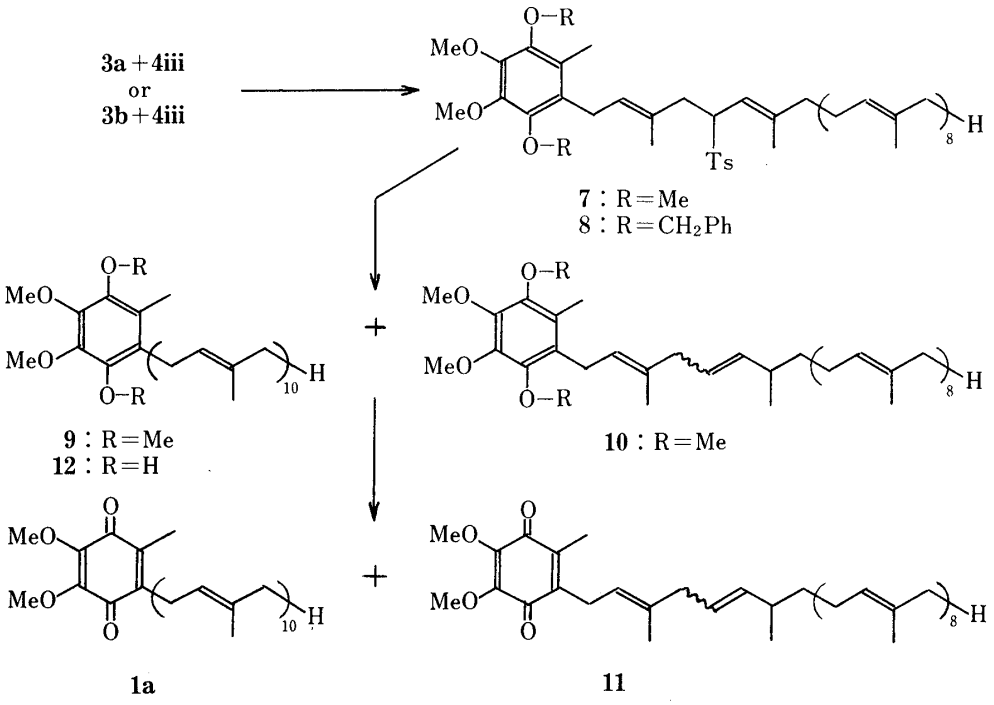

Chart 3

An alternative condition for desulfurization (wtih Li in $EtNH_2$ at $-70\,^\circ C$), which is claimed to be efficient and to occur without or with minimal isomerization of the olefinic bond,[3a,5] was applied to the conversion of **7** to **9**, but gave a complex mixture as a result of over-reduction of the aromatic portion.[3b] Subjection of the dibenzyl ether (**8**), in turn, to the condition yielded a satisfactory result, affording **1a** with little contamination by **11** *via* the aerobic oxidation[3a] of the intermediate decaprenylhydroquinone (**12**). The isomer ratio of **1a** and **11** was indicated to be 93:7 by HPLC analysis and pure **1a** was obtained by column chromatography on 5% $AgNO_3$-impregnated silica gel in 71% overall yield from **8**.

Synthesis of Phylloquinone (1b) (Chart 4)

In the synthesis of ubiquinone-10 (**1a**) mentioned above, the modified Bouvault–Blanc condition proved to be convenient for large-scale operations due to the simple experimental procedure, although of poor reliability concerning the retention of the olefinic bond in desulfurization of allylic sulfones. It seemed feasible that the method might work well in the synthesis of phylloquinone (**1b**) if the sulfone (**13**), which is a homo-allylic sulfone, is used as an intermediate.

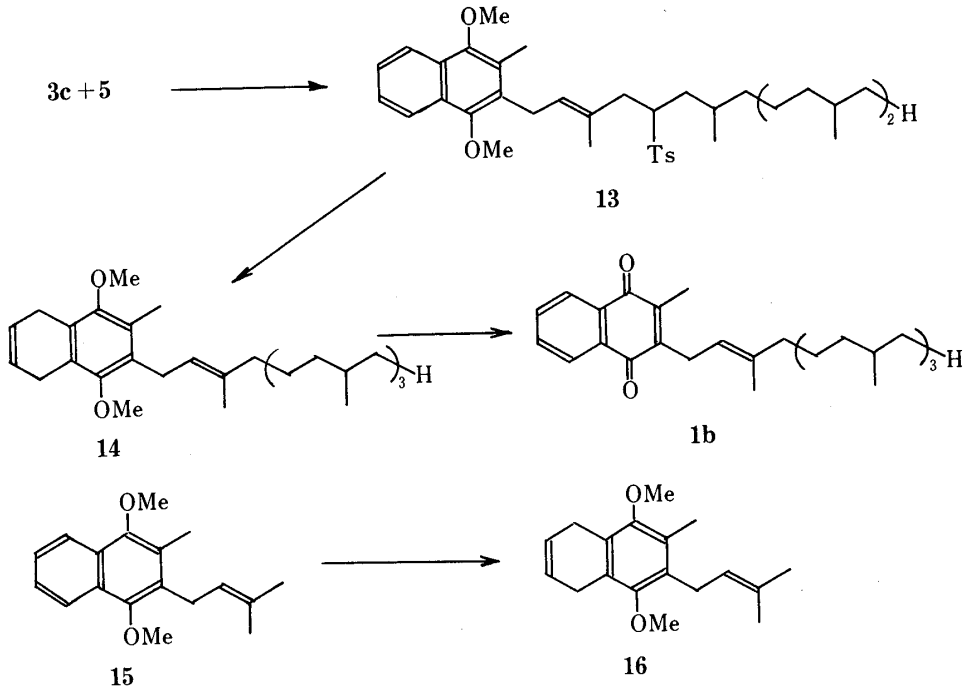

Chart 4

The bromide (**3c**) was treated with a carbanion generated from hexahydrofarnesyl *p*-tolylsulfone (**5**) in THF in the presence of HMPA at −70—0 °C to give the coupled sulfone (**13**) in 72% yield. The sulfone (**13**) was subjected to the modified Bouvault–Blanc condition to lead in 70% yield to a sulfur-free product which was characterized as not the expected compound but the 5,8-dihydronaphthalene derivative (**14**) on the basis of spectral analysis: the parent peak at *m/e* 480 was observed in the mass spectrum (MS), and six benzylic methylene protons at δ 3.20—3.40 (br), one olefinic proton at δ 5.02 (br t), two olefinic protons at δ 5.83 (br s), and no aromatic protons were detected in the ^{1}H-NMR spectrum. This unusual behavior of the protected naphthohydroquinone system under the Bouvault–Blanc condition turned out to be general; 2-prenyl-3-methyl-1,4-dimethoxynaphthalene (**15**) underwent analogous aromatic reduction under the same condition to furnish in high yield (92%) the 5,8-dihydronaphthohydroquinone derivative (**16**). Oxidative demethylation of **14** was carried out with an excess of CAN to produce in one step the final naphthoquinone (**1b**) as a diastereoisomeric mixture in 70% yield. Compound **1b** obtained was identified with the authentic compound[8b] by spectral comparison. In a preliminary experiment, we observed that analogous aromatization occurred in the oxidative demethylation of **16** with CAN, providing 2-prenyl-3-methyl-1,4-naphthoquinone.

Synthesis of Menaquinone-4 (1c) (Chart 5)

We chose combinations of a naphthohydroquinone derivative bearing the geranyl side chain with a geraniol derivative and of a naphthohydroquinone derivative bearing the prenyl side chain with a farnesol derivative for the synthesis of **1c**. First we applied the Mukaiyama's method[13] using the 2-pyridylsulfenyl group as the activating auxiliary for allylic homologation to the requisite chain length.

Coupling of the bromide (**3e**) with geranyl 2-pyridylsulfide (**6**) was achieved in the usual manner using BuLi to give the assembled product (**17**) in 75% yield. Treatment of **17** with the reagent system (a complex prepared from $LiAlH_4$, MeOLi, and $CuCl_2$) developed by Mukaiyama in THF under reflux gave the sulfur-free product in 65% yield. The product unfortunately appeared to contain a substantial amount of the rearranged olefinic isomer

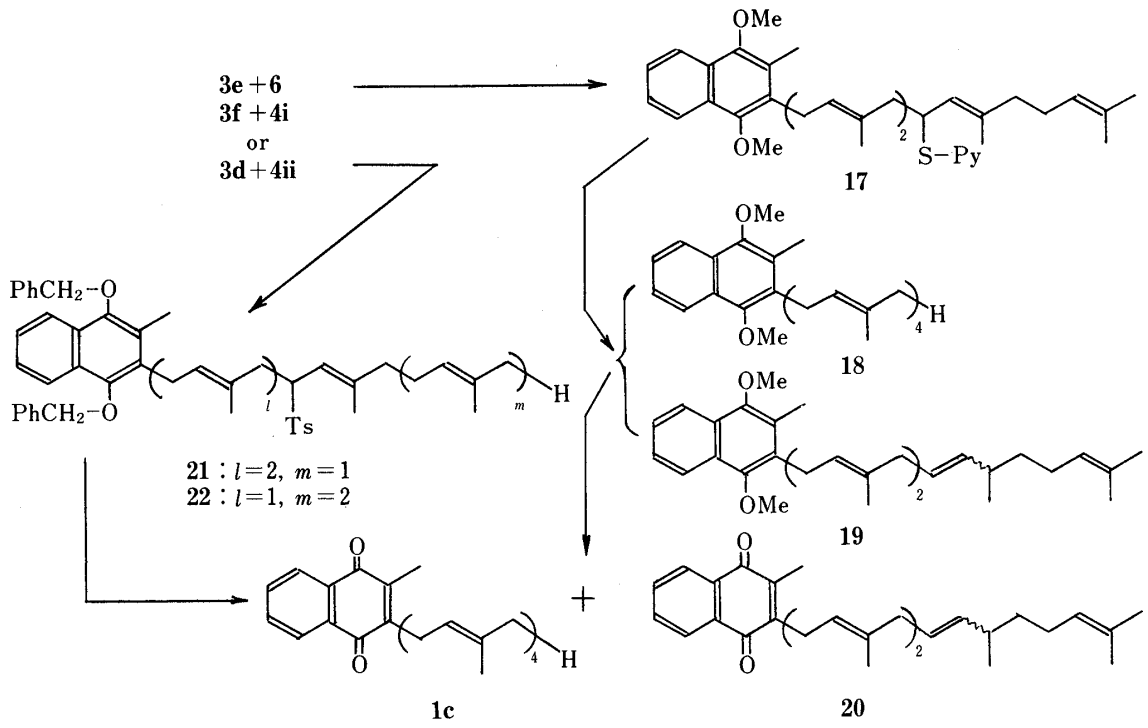

Chart 5

(**19**) as well as the desired compound (**18**) on the basis of ^{1}H-NMR analysis: a secondary methyl signal was observed at δ 0.92 as a doublet. The product mixture of (**18**) and (**19**) was demethylated oxidatively with CAN to provide in 70% yield the final naphthoquinones (**1c**) and (**20**) in a ratio of 59 : 41 as determined by HPLC.

Considering the above results from the viewpoint of efficiency of C–C bond formation and minimal over-reduction of the naphthalene nucleus and double bond isomerization in the desulfurization step, coupling of geranyl (**4i**) or farnesyl sulfone (**4ii**) with the appropriate naphthohydroquinone (**3f**) or (**3d**) in which the hydroquinone functionality is protected in the form of the benzyl ether, and desulfurization of the coupled sulfone with Li in $EtNH_2$ seemed to be the method of choice for the synthesis of **1c**. Thus, the chain assembly was performed between **4i** and **3f** or **4ii** and **3d** in the usual manner using BuLi to provide the coupled sulfones (**21**) and (**22**) respectively in 86 and 87% yields. Each sulfone (**21**) or (**22**) was successively treated with Li in $EtNH_2$ and then air was bubbled through the mixture to give the final product, the HPLC analysis of which showed minor contamination by impurities (5—7%) resulting from double bond isomerization. Purification of the product by chromatography on 5% $AgNO_3$-impregnated silica gel afforded pure crystalline menaquinone-4 (**1c**), which was identified with the authentic sample[8b] by HPLC, and ^{1}H-NMR and infrared (IR) spectral comparisons.

In conclusion, we offer a general method for the stereocontrolled synthesis of polyisoprenoid-quinones and -hydroquinones using a chain elongation technique, and have demonstrated the versatility of omega-hydroxyprenyl- and -hydroxygeranyl-hydroquinones as building blocks for the synthesis of such compounds. The importance of selection of suitable reaction conditions for desulfurization in relation to the functionalities of the hydroquinone components is emphasized.

Experimental

The IR spectra were determined on a JASCO IRA-1 spectrometer in $CHCl_3$ solution and characteristic bands

(ν_{max}) are reported in cm^{-1}. Mass spectra were taken on a JMS-D300 instrument by direct insertion at 70 eV and peaks are represented in *m/e*. The ^{1}H-NMR spectra were taken on a Hitachi R-20B spectrometer (60 MHz) in CCl_4 solution; chemical shifts are reported in δ units (ppm) relative to tetramethylsilane (TMS) as an internal standard, and coupling constants (*J*) are reported in hertz (Hz). All reactions were carried out in general under an atmosphere of nitrogen, or argon particularly for C–C bond formation. Usual work-up of the reaction mixture was as follows: products were extracted with Et_2O, washed with water, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* at below room temperature. HPLC was carried out by using a column (4.0 mm × 25 cm) packed with 5% $AgNO_3$-impregnated silica gel, which was prepared by drying a slurry of LiChrosorb Si 60 (Merck) (10 g) and $AgNO_3$ (0.5 g) in water (40 ml) at 100—110 °C for 20 h, and by elution with a hexane–dioxane (30 : 1—5 : 1) solvent system. Thin layer chromatography (TLC) was performed on Wakogel B-5F silica gel or 5% $AgNO_3$-impregnated silica gel (dried mixture of Wakogel B-5F 20 g, $AgNO_3$ 1.0 g, and water 40 ml) by developing with a hexane–Et_2O solvent system. Column chromatography was performed on Wakogel C-200 (100—200 mesh), 5% $AgNO_3$-impregnated silica gel (dried mixture of Wakogel C-200, $AgNO_3$, and water in a ratio 20 g/1.0 g/40 ml), or activated alumina (Wako), with hexane–Et_2O or hexane–AcOEt as the elution system.

General Procedure for Preparation of Terminal *trans*-Allylic Bromides (3) from Terminal *trans*-Allylic Alcohols (2)——PBr_3 (0.35 mmol) was added dropwise to a solution of an alcohol[1] (1.0 mmol) in Et_2O (10 ml) with a syringe under stirring at 0 °C and the mixture was stirred for 1.5 h at 0 °C then kept in refrigerator for 15 h. The mixture was extracted with Et_2O, washed successively with 5% $NaHCO_3$ and water, dried, and concentrated to leave the crude bromide (**3**) in 70—90% yield. All the bromides (**3**) exhibited a sharp singlet in the region of δ 8.50—8.90 assignable to the allylic methylene bearing Br in the ^{1}H-NMR spectrum. They were used, without further purification, for the coupling reactions.

Synthesis of the Sulfur-Containing Isoprenoids——Geranyl *p*-Tolylsulfone (**4i**) and Farnesyl *p*-Tolylsulfone (**4ii**): Compounds **4i** and **4ii** were obtained by the reported method.[5a,6]

Solanesyl *p*-Tolylsulfone (**4iii**): Sodium *p*-toluenesulfinate dihydrate (*p*-TsNa·$2H_2O$) (430 mg, 2.0 mmol) was added in portions to a solution of solanesyl bromide (690 mg, 1.0 mmol) [freshly prepared from solanesol[9] and PBr_3] at room temperature and the mixture was worked up in the usual manner. The crude product was purified by column chromatography on silica gel to give pure **4iii** (545 mg, 71%). NMR: 1.40 (3H, s, $=CCH_3$), 1.57 (24H, s, $8\times=CCH_3$), 1.65 (3H, s, $=CCH_3$), 2.44 (3H, s, Ar–CH_3), 1.90—2.20 (32H, br, $8\times=CH_2CH_2=$), 3.63 (2H, d, J=8.0, $=CHC\underline{H}_2Ts$), 4.90—5.20 (9H, br, $9\times=CH$), 7.20—7.82 (4H, A_2B_2q, J=8.5, arom-H).

Hexahydrofarnesyl *p*-Tolylsulfone (**5**):[10] Commercially available farnesol (2.2 g, 10 mmol) was hydrogenated in the presence of PtO_2 (150 mg, 0.65 mmol) under atmospheric pressure of H_2 in AcOEt (50 ml) to give hexahydrofarnesol (1.82 g, 80%). NMR: 0.87 (12H, d, J=5.5, $4\times CHC\underline{H}_3$), 1.00—1.80 (17H, br, $7\times CH_2$ and $3\times C\underline{H}CH_3$), 2.86 (1H, s, OH), 3.57 (2H, t, J=6.5, $C\underline{H}_2OH$). The alcohol was mixed with PPh_3 (2.36 g, 9.0 mmol) in CH_2Cl_2 (15 ml) and *N*-bromosuccinimide (NBS) (2.14 g, 12 mmol) was added in portions at room temperature. Stirring was continued for 1.5 h then the mixture was concentrated *in vacuo* at 5—10 °C. The residue was directly chromatographed on silica gel with hexane to give hexahydrofarnesyl bromide (1.95 g, 84%). NMR: 0.87 (12H, d, J=5.5, $4\times CHC\underline{H}_3$), 1.05—2.00 (17H, br, $7\times CH_2$ and $3\times C\underline{H}CH_3$), 3.37 (2H, t, J=6.5, CH_2Br). The bromide obtained was treated with *p*-TsNa·$2H_2O$ (2.5 g, 11.7 mmol) in *N*,*N*-dimethylformamide (DMF) (20 ml) at 60 °C for 24 h. Usual work-up of the mixture and product isolation by column chromatography gave the sulfone (**5**) (1.79 g, 73%). NMR: 0.87 (12H, d, J=5.5, $4\times CHC\underline{H}_3$), 1.00—1.80 (17H, br, $7\times CH_2$ and $3\times C\underline{H}CH_3$), 2.45 (3H, s, Ar–$CH_3$), 2.90 (2H, t, J=8.0, CH_2Ts), 7.23—7.80 (4H, A_2B_2q, J=8.5, arom-H).

Geranyl 2-Pyridyl Sulfide (**6**): To a mixture of NaH (500 mg of NaH-oil dispersion was washed with anhydrous hexane) and 2-mercaptopyridine (1.11 g, 10 mmol) in DMF (8.0 ml) was added dropwise a solution of geranyl bromide (2.17 g, 10 mmol) in DMF (2.0 ml) at room temperature, and the mixture was stirred for 16 h at the same temperature. Usual work-up and product isolation by column chromatography on silica gel gave the sulfide (**6**) (2.08 g, 85%). NMR: 1.58, 1.60, 1.73 (each 3H, s, $3\times=CCH_3$), 1.90—2.20 (4H, br, CH_2CH_2), 3.80 (2H, d, J=8.0, $=CHC\underline{H}_2SPy$), 4.85—5.15 (1H, br, $=CH$), 5.32 (1H, br t, J=8.0, $=C\underline{H}CH_2SPy$), 6.70—7.53 (3H, m, arom-H), 8.23—8.42 (1H, br d, J=6.0, arom-H).

Synthesis of Ubiquinone-10 (1a)——1-(5′-*p*-Tosyl-all-*trans*-decaprenyl)-2-methyl-3,4,5,6-tetramethoxybenzene (**7**): To a solution of solanesyl sulfone (**4iii**) (350 mg, 0.45 mmol) and HMPA (1.0 ml) in THF (5.0 ml) was added dropwise a 1.6 M hexane-solution of BuLi (0.35 ml, 0.55 mmol) at −70 °C, and the mixture was stirred for 30 min at −70——40 °C then cooled again to −70 °C. Next, a solution of the freshly prepared bromide (**3a**) (161 mg, 0.45 mmol) in THF (0.6 ml) was added and the mixture was stirred for 2 h with gradual warming up to 0 °C. The reaction mixture was taken up in Et_2O and worked up in the usual manner to give the crude product, which was purified by column chromatography on silica gel to provide the pure oily sulfone (**7**) (405 mg, 86%). IR: 1650, 1590, 1465, 1405, 1380, 1345, 1310. NMR: 1.23 (3H, s, $=CCH_3$), 1.58. (24H, s, $8\times=CCH_3$), 1.66 (6H, br s, $2\times=CCH_3$), 1.80—2.20 (35H, br, $8\times=CCH_2CH_2C=$ and Ar–CH_3), 2.42 (3H, s, Ar–CH_3(Ts)), 2.20—2.80 (2H, m, $=CC\underline{H}_2CH$(Ts)), 3.19 (2H, d, J=7.0, Ar–CH_2), 3.20—3.50 (1H, m, CH(Ts)), 3.69, 3.78 (each 6H, s, $4\times OCH_3$), 4.76 (1H, br d, J=9.0, $=C\underline{H}CH$(Ts)), 4.85—5.25 (9H, br, $9\times=CH$), 7.10—7.73 (4H, A_2B_2q, J=9.0, arom-H). *Anal.* Calcd for $C_{68}H_{102}O_6S$: C, 77.96; H, 9.81. Found: C, 77.73; H, 10.04.

1-(5′-Tosyl-all-*trans*-decaprenyl)-2-methyl-3,6-dibenzyloxy-4,5-dimethoxybenzene (**8**): Compound **8** was obtained from the bromide (**3b**) and **4iii** in 85% yield by the same procedure as described for **7**, IR: 1650, 1590, 1450, 1420, 1370. NMR: 1.18 (3H, s, $=CCH_3$), 1.59 (24H, s, $8\times=CCH_3$), 1.67 (6H, s, $2\times=CCH_3$), 1.80—2.20 (35H, br, $8\times=CCH_2CH_2C=$ and Ar–CH_3), 2.41 (3H, s, Ar–CH_3 (Ts)), 2.20—3.00 (2H, m, $=CCH_2CH$(Ts)), 3.19 (2H, br d, $J=7.0$, Ar–CH_2), 3.40—3.85 (1H, m, CH(Ts)), 3.85 (6H, s, $2\times OCH_3$), 4.88 (4H, s, $2\times OCH_2Ph$), 4.74 (1H, br d, $J=9.0$, $=CHCH$(Ts)), 4.85—5.25 (9H, br, $9\times=CH$), 7.30 (10H, br s, $2\times OCH_2C_6H_5$), 7.10—7.73 (4H, A_2B_2q, $J=9.0$, arom-H (Ts)). *Anal.* Calcd for $C_{80}H_{110}O_6S$: C, 80.09; H, 9.24. Found: C, 80.07; H; 9.49.

Ubiquinone-10 (1a)——Method A (Reductive Desulfurization of **7** under the Modified Bouvault–Blanc Condition):[3b] To a mixture of the sulfone (**7**) (150 mg, 0.15 mmol) and EtOH (100 μl, 1.5 mmol) in THF (1.0 ml) was added a piece of Na (28 mg, 1.2 mg atom) at −20 °C, and the mixture was stirred for 2 h at −20—0 °C. The reaction mixture was extracted with Et_2O and worked up as usual. The crude product was purified by column chromatography on alumina to give the sulfur-free product (275 mg, 87%) as a low-melting crystalline mass (mp 35—36 °C). ^{1}H-NMR indicated the product to be composed of the desired 1-(all-*trans*-decaprenyl)-2-methyl-3,4,5,6-tetramethoxybenzene (**9**) as the major product and the double bond isomer (**10**) as a minor one. NMR: 0.95 (d, $J=7.0$, secondary methyl group of **10**), 1.58 (27H, s, $9\times=CCH_3$), 1.65, 1.75 (each 3H, s, $2\times=CCH_3$), 1.90—2.15 (36H, br, $9\times=CCH_2CH_2C=$), 2.07 (3H, s, Ar–CH_3), 3.22 (2H, br d, $J=7.0$, Ar–CH_2), 3.72, 3.81 (each 6H, s, $4\times OCH_3$), 4.90—5.25 (10H, br, $10\times=CH$). *Anal.* Calcd for $C_{61}H_{96}O_4$: C, 82.00; H, 10.83. Found: C, 82.00; H, 11.09. The product (120 mg, 0.13 mmol) obtained was dissolved in a mixture of CH_3CN (0.5 ml) and CH_2Cl_2 (0.5 ml) and kept at 0 °C. A solution of CAN (220 mg, 0.4 mmol) in 50% aq. CH_3CN (1.0 ml) was added dropwise to the above solution over a period of 5 min and stirring was continued for an additional 5 min, then the reaction was quenched by addition of water (10 ml). The product was extracted with Et_2O, washed successively with 5% $NaHCO_3$ and water, dried, and concentrated to leave an oily substance (116 mg). Purification was achieved by column chromatography on ordinary silica gel with hexane–Et_2O (20 : 1—10 : 1) as the elution system to give a fraction (85 mg, 72%) which appeared homogeneous on the usual TLC, but was proved to contain two compounds in a ratio of 69 : 31 by HPLC analysis on 5% $AgNO_3$-impregnated silica gel. The major component was identified as ubiquinone-10 (**1a**) by co-injection in HPLC. The mixture was separated by column chromatography on the 5% $AgNO_3$-impregnated silica gel using an elution system of hexane–AcOEt (6 : 1) to give the pure compound (**1a**) and the isomerized compound (**11**). The crystalline product (**1a**) (mp 48—49 °C (Et_2O–hexane)) was identical with an authentic sample.[3a] IR: 1650, 1605, 1445, 1375. NMR ($CDCl_3$): 1.59 (27H, s, $9\times=CCH_3$), 1.68, 1.73 (each 3H, s, $2\times=CCH_3$), 1.90—2.20 (39H, br, $18\times=CCH_2$ and quinone-CH_3), 3.19 (2H, d, $J=7.0$, quinone-CH_2), 3.99 (6H, s, $2\times OCH_3$), 4.95—5.35 (10H, br, $10\times=CH$). The data for the minor product (**11**) were as follows: IR: 1640, 1605, 1450, 1370; NMR: 0.96 (3H, d, $J=7.0$, $CHCH_3$), 1.20—1.40 (2H, br, CH_2), 1.61 (24H, s, $8\times=CCH_3$), 1.70 (6H, br s, $2\times=CCH_3$), 1.90—2.40 (31H, br, $15\times=CCH_2$ and $=CHCH$(Me)), 2.00 (3H, s, Ar–CH_3), 2.55—2.75 (2H, m, $=CCH_2CH=$), 3.19 (2H, br d, $J=7.0$, $=CHCH_2$-quinone), 3.98 (6H, s, $2\times OCH_3$), 4.90—5.30 (11H, br, $11\times=CH$).

Method B (Reductive Desulfurization of **8** with Li in $EtNH_2$): To a stirred blue solution of Li (30 mg, 4.3 mg atom) in $EtNH_2$ (5.0 ml) was added dropwise a solution of **8** (140 mg, 0.12 mmol) in THF (0.5 ml) at −70 °C. Stirring was continued for 30 min at the same temperature and the excess metal was destroyed by the successive introductions of gaseous butadiene, MeOH (0.3 ml), and saturated aq. NH_4Cl (2.0 ml). After dilution of the mixture with Et_2O, the whole was bubbled through with oxygen for 15 min. The resulting mixture was shaken with Et_2O and worked up as usual to leave a crude mass, which was purified by column chromatography on ordinary silica gel to give a solid (85 mg). The HPLC analysis indicated the product to be accompanied by a small amount of the isomerized compound (**11**) (7%). Purification of the product by column chromatography on 5% $AgNO_3$-impregnated silica gel gave ubiquinone-10 (**1a**) (73 mg, 71% overall yield from **8**) as orange crystals (mp 48—49 °C (Et_2O–hexane)).

Synthesis of Phylloquinone (1b)——2-(5′-*p*-Tosyl-phytyl)-3-methyl-1,4-dimethoxynaphthalene (**13**): To a solution of hexahydrofarnesyl *p*-tolylsulfone (**5**) (400 mg, 1.1 mmol) and HMPA (0.5 ml) in THF (5.0 ml) was added dropwise a 1.6 M hexane-solution of BuLi (0.8 ml, 1.3 mmol) at −70 °C. After stirring of the mixture for 30 min at the same temperature, a solution of the bromide (**3c**) (350 mg, 1.0 mmol) in THF (1.0 ml) was added and the whole was stirred for 2 h with gradual warming to 0 °C. The reaction mixture was worked up in the usual manner. The crude product (735 mg) was purified by column chromatography on silica gel to give **13** (456 mg, 72%) as an oil. IR: 1590, 1450, 1370, 1345. NMR: 0.72 (3H, d, $J=6.0$, $CHCH_3$), 0.85 (9H, d, $J=6.0$, $3\times CHCH_3$), 1.00—2.00 (17H, m, $6\times CH_2$, $3\times$CH(Me), and $=CCH_2$), 1.73 (3H, s, $=CCH_3$), 2.28 (3H, s, Ar–CH_3), 2.35 (3H, s, Ar–CH_3 (Ts)), 2.60—3.20 (1H, m, CH(Ts)), 3.45 (2H, br d, $J=6.0$, Ar–CH_2), 3.78 (6H, s, $2\times OCH_3$), 5.13 (1H, br t, $J=6.0$, $=CH$), 7.05—7.75 (4H, A_2B_2q, $J=8.0$, arom-H (Ts)), 7.20—7.50, 7.80—8.10 (each 2H, m, arom-H). *Anal.* Calcd for $C_{40}H_{58}O_4S$: C, 75.66; H, 9.21. Found: C, 75.73; H, 9.41.

2-Phytyl-3-methyl-5,8-dihydro-1,4-dimethoxynaphthalene (**14**): Compound **13** was desulfurized by method A as described for **1a** to afford the 5,8-dihydronaphthalene (**14**) in 70% yield. MS: 480 (M^+, 100%), 465 (37%), 449 (33%). NMR: 0.83 (3H, d, $J=6.0$, $CHCH_3$), 0.86 (9H, d, $J=6.0$, $3\times CHCH_3$), 1.00—2.00 (17H, br, $6\times CH_2$, $3\times$CH(Me), and $=CCH_2$), 1.75 (3H, s, $=CCH_3$), 2.12 (3H, s, Ar–CH_3), 3.20—3.40 (6H, br, $3\times$Ar–CH_2), 3.61 (6H, s, $2\times OCH_3$), 5.02 (1H, br t, $J=6.0$, $=CH$), 5.83 (2H, br s, $2\times=CH$).

Phylloquinone (**1b**): To a solution of **14** (240 mg, 0.5 mmol) in CH_3CN (2.0 ml)–CH_2Cl_2 (2.0 ml) was added

dropwise over 10 min a solution of CAN (1.10 g, 2.0 mmol) in water (1.5 ml)–CH_3CN (1.5 ml) at 0 °C, and the mixture was stirred for 30 min at 0—20 °C. Then water (30 ml) was added and the whole was taken up with Et_2O and worked up as usual. Purification of the crude product by column chromatography on silica gel gave pure **1b** (157 mg, 70%) as an oil, which was shown to be identical with the authentic compound[8b] by spectral comparison. MS: 450 (M^+, 100%), 224 (25%), 197 (23%), 185 (20%). IR: 1655, 1615, 1595, 1460, 1370, 1325. NMR: 0.85 (12H, d, J=6.0, 4×CHC$\underline{H}_3$), 1.00—1.50 (19H, br, 8×CH_2 and 3×C$\underline{H}$CH$_3$), 1.78 (3H, s, =CC$\underline{H}_3$), 1.98 (2H, br t, J=6.0, =CC$\underline{H}_2$), 2.16 (3H, s, quinone-CH_3), 3.31 (2H, d, J=7.0, quinone-CH_2), 5.00 (1H, br t, J=7.0, =CH), 7.52—7.80, 7.87—8.18 (each 2H, m, arom-H).

2-Prenyl-3-methyl-5,8-dihydro-1,4-dimethoxynaphthalene (16)——2-Prenyl-3-methyl-1,4-dimethoxynaphthalene (**15**) was treated under the conditions of method A as described for **1a** to give the 5,8-dihydronaphthalene (**16**) as an oil in 92% yield. MS: 272 (M^+, 100%), 257 (43%), 241 (39%). NMR: 1.68, 1.76 (each 3H, br s, =C(CH_3)$_2$), 2.10 (3H, s, Ar–CH_3), 3.13—3.40 (6H, br, 3×Ar–CH_2), 3.60 (6H, s, 2×OCH_3), 5.00 (1H, br t, J=6.0, =CH), 5.82 (2H, br s, 2×=CH).

Synthesis of Menaquinone-4 (1c)——2-[9′-(2-Pyridylthio)-tetraprenyl]-3-methyl-1,4-dimethoxynaphthalene (**17**): To a solution of geranyl 2-pyridyl sulfide (**6**) (300 mg, 1.2 mmol) and HMPA (0.5 ml) in THF (7.5 ml) was added dropwise over a period of 5 min a 1.6 M hexane-solution of BuLi (0.8 ml, 1.3 mmol) at −70 °C, and the mixture was stirred for 20 min at the same temperature. Then, a solution of the bromide **3e** (420 mg, 1.0 mmol) in THF (2.0 ml) was added at −70 °C over a period of 5 min. The mixture was gradually warmed up to 0 °C with stirring. The reaction mixture was worked up as usual to give the crude product (550 mg). Purification of the product by column chromatography on silica gel afforded the coupled sulfide (**17**) (438 mg, 75%) as an oil. IR: 1650, 1585, 1570, 1450, 1410, 1370, 1345. NMR: 1.53, 1.68, 1.81 (each 3H, br s, 3×=CCH_3), 1.61 (6H, br s, 2×=CCH_3), 1.90—2.25 (10H, br, 5×=CH_2), 2.32 (3H, s, Ar–CH_3), 3.50 (2H, br d, J=7.0, Ar–CH_2), 3.80 (6H, s, 2×OCH_3), 4.45—4.75 (1H, m, CH(S–Py)), 4.80—5.30 (4H, m, 4×=CH), 6.70—8.40 (8H, m, arom-H). *Anal.* Calcd for $C_{38}H_{49}NO_2S$: C, 78.17; H, 8.46; N, 2.40. Found: C, 77.91; H, 8.68; N, 2.45.

Method C (Reductive Desulfurization of **17**, with a Complex ($LiAlH_4$+MeOLi+$CuCl_2$)):[13] To a mixture of $LiAlH_4$ (81 mg, 2.1 mmol) and MeOLi (81 mg, 2.2 mmol) in THF (2.0 ml) was added dropwise a suspension of $CuCl_2$ (150 mg, 1.1 mmol) in THF (8.0 ml) at 0 °C over a period of 10 min, and the mixture was stirred for 1 h at room temperature. To the refluxed reagent mixture, a solution of the sulfide (**17**) (155 mg, 0.26 mmol) in THF (1.0 ml) was added dropwise and refluxing was continued for an additional 1 h. After cooling, the mixture was diluted with Et_2O, filtered to remove insoluble materials, washed with water, dried, and concentrated to leave the crude product, which was purified by column chromatography on silica gel to provide an oily substance (82 mg, 65%). The ^{1}H-NMR spectrum of the product showed a doublet at δ 0.92 of substantial intensity which indicated the product to contain the rearranged double bond isomer (**19**) as a by-product as well as the desired 2-tetraprenyl-3-methyl-1,4-dimethoxynaphthalene (**18**). NMR: 0.92 (d, secondary methyl group of **19**), 1.10—1.41 (br, isolated methylene of **19**), 1.54 (9H, s, 3×=CCH_3), 1.63, 1.81 (each 3H, s, 2×=CCH_3), 1.85—2.20 (12H, br, 3×=CCH_2CH_2C=), 2.30 (3H, s, Ar–CH_3), 2.47—2.75 (2H, m, =CC$\underline{H}_2$CH=), 3.51 (2H, d, J=7.0, Ar–CH_2), 3.79, 3.80 (each 3H, s, 2×OCH_3), 4.85—5.40 (4H, br, 4×=CH), 7.22—7.50, 7.85—8.05 (each 2H, m, arom-H). The product mixture was demethylated oxidatively with CAN by the method described for **1a** to give the crude quinone, which was purified by column chromatography on ordinary silica gel to give an oily fraction (54 mg, 70%). The fraction was shown by HPLC to consist of the desired **1c** and the double bond isomer (**20**) in a ratio of 59 : 41.

2-(9′-*p*-Tosyl-tetraprenyl)-3-methyl-1,4-dibenzyloxynaphthalene (**21**): Compound **21** was obtained as an oil in 86% yield in the same manner as described for **17** from the bromide (**3f**) and geranyl *p*-tolylsulfone (**4i**). IR: 1650, 1590, 1490, 1450, 1380, 1340. NMR: 1.18, 1.60, 1.66 (each 3H, s, 3×=CCH_3), 1.50 (6H, s, 2×=CCH_3), 1.80—2.20 (8H, br, 4×=CHC$\underline{H}_2$), 2.32 (6H, s, 2×Ar–CH_3), 2.20—3.00 (2H, m, =CC$\underline{H}_2$CH(Ts)), 3.50 (2H, d, J=7.0, Ar–CH_2), 3.50—3.90 (1H, m, =CHC$\underline{H}$(Ts)), 4.90 (4H, s, 2×OCH_2Ph), 4.73 (1H, br d, J=7.0, =C$\underline{H}$CH(Ts)), 4.80—5.25 (3H, br, 3×=CH), 7.00—8.13 (18H, m, arom-H).

2-(5′-*p*-Tosyl-tetraprenyl)-3-methyl-1,4-dibenzyloxynaphthalene (**22**): Compound **22** was also obtained as an oil in 87% yield in the same manner as described for **17** from the bromide (**3d**) and farnesyl *p*-tolylsulfone (**4ii**). IR: 1650, 1590, 1490, 1450, 1380, 1340. NMR: 1.12, 1.47, 1.57 (each 3H, s, 3×=CCH_3), 1.65 (6H, s, 2×=CCH_3), 1.70—2.10 (8H, m, 4×=CHC$\underline{H}_2$), 2.23 (3H, s, Ar–CH_3), 2.33 (3H, s, Ar–CH_3 (Ts)), 2.20—3.05 (2H, m, =CC$\underline{H}_2$CH(Ts)), 3.48 (2H, br d, J=7.0, Ar–CH_2), 3.50—4.00 (1H, m, =CCH_2C$\underline{H}$(Ts)), 4.88 (4H, s, 2×OCH_2Ph), 4.72 (1H, br d, J=7.0, =C$\underline{H}$CH(Ts)), 4.75—5.25 (3H, br, 3×=CH), 7.00—8.10 (18H, m, arom-H). *Anal.* Calcd for $C_{52}H_{60}O_4S$: C, 79.96; H, 7.74. Found: C, 79.71; H, 7.92.

Menaquinone-4 (**1c**): Compound **1c** was obtained in 68—73% overall yield from **21** or **22** by method B described for **1a**. HPLC analysis indicated the product to be accompanied by a small amount of the double bond isomer (less than 7%). Column chromatography on 5%$AgNO_3$-impregnated silica gel using a hexane–AcOEt (10 : 1) solvent system gave pure crystalline **1c** (mp 35—38 °C (Et_2O–hexane)). Compound **1c** obtained and an authentic sample[8b] exhibited identical IR and ^{1}H-NMR spectra and showed identical TLC and HPLC behavior. IR: 1650, 1615, 1600, 1440, 1370, 1330. NMR: 1.55 (9H, s, 3×=CCH_3), 1.65, 1.79 (each 3H, s, 2×=CCH_3), 1.87—2.14 (12H, br, 4×=CCH_2), 2.16 (3H, s, quinone-CH_3), 3.32 (2H, d, J=7.0, quinone-CH_2), 4.85—5.20 (4H, br, 4×=CH),

7.53—7.78, 7.90—8.15 (each 2H, m, arom-H).

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