3,[6] mp 96–97 °C. Recrystallization from 95% gave a colorless polymorphic form, mp 94–5 °C. Both samples had identical IR and TLC patterns. From the next ten fractions of eluate was isolated 125 mg (14%) of **1**, mp and mmp 135–137 °C (lit,[16] mp 140.2–140.8 °C, corr) and TLC identity.

7-Fluoro-12-methylbenz[*a*]anthracene* (9). As described above for the synthesis of **3** from **6**, 200 mg of **12a** and/or **12b** yielded 100 mg (53%) of **9**, mp 80–82.5 °C, as pale yellow crystals from aqueous alcohol. In addition 20 mg (11%) of **10**, mp 136.0–137.5 °C (lit.[17] mp 138.6–139.6 °C), was obtained.

Pyrolysis of 12-Methyl-7,12-peroxy-7,12-dihydrobenz[*a*]anthracene (11). On pyrolysis of **11** at 105 °C for 1 min in a melting point tube TLC showed that **10** was the main product produced.

Registry No.—**1**, 2541-69-7; **3**, 23683-71-8; **4**, 2498-66-0; **5**, 17513-43-8; **6a**, 68781-42-0; **6b**, 68781-43-1; **7**, 55125-19-4; **8**, 68781-44-2; **9**, 68781-45-3; **10**, 2422-79-9; **11**, 68781-46-4; **12a**, 68781-47-5; **12b**, 68781-48-6; **13**, 17513-39-2.

References and Notes

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(2) Postdoctoral Research Associate.
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(14) All temperatures are uncorrected and are in °C. All new compounds are marked with an asterisk and gave analyses within ±0.3% of the theoretical by the Galbraith Microanalytical Laboratories. The term "conventional or usual workup" means that the organic layer containing the product was washed with water and/or alkali and acid and saturated NaCl and filtered through anhydrous $MgSO_4$. The solvent was then removed on a rotary evaporator. All compounds gave IR, mass, and NMR spectra consistent with the structure assigned.
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Synthesis of Ubiquinones. 2.[1] An Efficient Preparation of Ubiquinone-10

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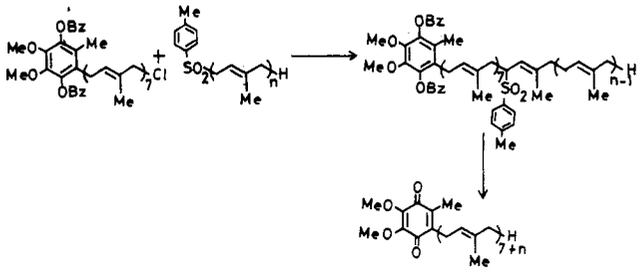
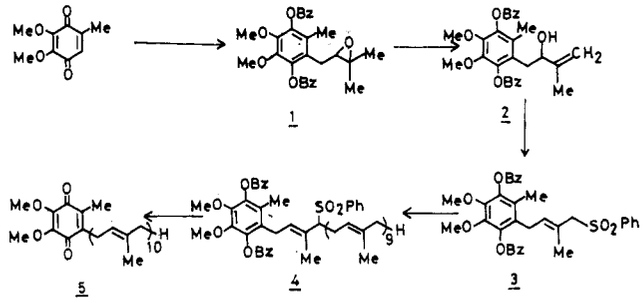
Since ubiquinone-10 (**5**) has a biological activity such as an electron carrier[2] in mitochondria, clinical effect in human congestive heart failure,[3] and implications in essential hypertension,[4] host defense,[5] and prevention of cardiotoxicity of adriamycin,[6] there is an increasing need for an efficient and stereospecific method of synthesis which is feasible for a large scale production.

Scheme I



Scheme II



Recently,[1] we have developed a new synthetic route for the ubiquinones by (i) the coupling between a sulfonyl component and a halide and (ii) and Benkerser's reductive elimination of the sulfone group followed by the oxidation of the resulting hydroquinone (Scheme I).

In this report, an application of this method in the synthesis of ubiquinone-10 from readily available components is presented (Scheme II).

Epoxide **1** is readily prepared in high yield by acid-catalyzed condensation of 2,3-dimethoxy-5-methyl-1,4-hydroquinone with 2-hydroxy-2-methylbut-3-ene followed by benzylation of the resulting prenylated hydroquinone and by epoxidation of the prenyl double bond with peracetic acid. When epoxide **1** is treated with aluminum isopropoxide in refluxing toluene, allylic alcohol **2** is obtained in good yield. The catalytic reagent has been used for the conversion[7] of cyclic monoterpenoid epoxides into the corresponding allylic alcohols. We found that this conversion could be widely used for the preparation of allylic alcohols from epoxides of (poly)prenylated compounds.[8]

Reaction of allylic alcohol **2** with phenylsulfenyl chloride in the presence of triethylamine and subsequent oxidation of the resulting sulfoxide with peracetic acid leads to the formation of the sulfonyl compound **3** as a single product whose double bond was confirmed to be exclusively trans by TLC and ^1H NMR analyses. The transformation of this type has been reported by Evans and Anderson.[9]

Coupling reaction of sulfonyl compound **3** with solanesyl bromide in the presence of potassium *tert*-butoxide gives coupled compound **4** in 91.3% yield after purification on silica gel. Removal of the benzyl and phenylsulfonyl groups in **4** was efficiently carried out by applying the Benkerser reduction.[10] The resulting hydroquinone is smoothly oxidized with air to give ubiquinone-10 (**5**) in 77.3% after recrystallization from ether–ethanol. The synthesized ubiquinone-10 was confirmed by TLC, LC, ^1H NMR, IR, and MS analyses and identified by the mixed melting point with an authentic sample.[11]

Experimental Section

Melting points were determined on a Yanagimoto Micro Melting Point apparatus and are uncorrected. High-resolution MS spectra

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were determined on a JEOL JMS-01SC spectrometer. The ^1H NMR spectra were determined on a Varian XL-100 instrument. The spectra were determined in $CDCl_3$, and chemical shifts are reported downfield from the Me_4Si internal standard. IR spectra were obtained on a Hitachi EPI-510 spectrometer. Microanalyses were carried out by Mr. M. Kan and his co-workers. High-pressure liquid chromatographic analysis (LC) was 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.

6-(2′,3′-Epoxy-3′-methylbutyl)-2,3-dimethoxy-5-methylhydroquinone *O,O′*-Dibenzyl Ether (1). 2,3-Dimethoxy-5-methyl-1,4-benzoquinone[12] (9.1 g, 50 mmol) was dissolved in a mixture of hexane (200 mL) and isopropyl ether (100 mL) and hydrogenated using 5% Pd/C (500 mg) as a catalyst until the absorption of hydrogen stopped at approximately 1 mol. The hydrogen was replaced with argon and boron trifluoride etherate (1 mL) was added to the reaction mixture which was then warmed to 45 °C. 2-Hydroxy-2-methylbut-3-ene (11 g, 128 mmol) was added over a period of 30 min with stirring which was continued for two additional hours. The reaction mixture was then cooled and the catalyst was removed by filtration. The organic solution was washed with water, dried over sodium sulfate, and evaporated in vacuo to dryness. The residue was dissolved in DMF (150 mL) and benzylated with benzyl bromide (20 g, 117 mmol) in the presence of sodium hydride (50% in mineral oil, 6.0 g) and sodium borohydride (0.1 g) under nitrogen. After 3 h, the reaction mixture was poured into water, extracted with isopropyl ether, washed with water, and dried over sodium sulfate. The solvent was removed by evaporation in vacuo to yield the crude product which was chromatographed on silica gel using hexane–isopropyl ether (4:1) as a solvent to yield 6-(3′-methylbut-2′-enyl)-2,3-dimethoxy-5-methylhydroquinone *O,O′*-dibenzyl ether (19.8 g, 91.6%) as an oil. The benzyl ether (14.4 g, 33.3 mmol) was dissolved in methylene chloride (50 mL) and epoxidized with 40% peracetic acid (7.0 g, 36.6 mmol) in the presence of sodium acetate (5 g) at 0 °C. The completed reaction was extracted with methylene chloride, treated with sodium carbonate, water washed, dried over sodium sulfate, and evaporated in vacuo. The residue was purified by silica gel chromatography using isopropyl ether to yield the epoxide **1** (14.8 g, 99.3%) as an oil: ^1H NMR ($CDCl_3$) δ 1.26 (3 H), 1.32 (3 H), 2.19 (3 H), 2.76 (2 H), 2.77 (1 H), 3.96 (6 H), 4.97 (2 H), 5.05 (2 H), 7.25–7.60 (10 H). Anal. Calcd for $C_{28}H_{32}O_5$: C, 74.97; H, 7.19. Found: C, 74.66; H, 7.18.

6-(2′-Hydroxy-3′-methylbut-3′-enyl)-2,3-dimethoxy-5-methylhydroquinone *O,O′*-Dibenzyl Ether (2). The epoxide **1** (14.0 g, 30 mmol) was reduced with aluminum isopropoxide in toluene (100 mL) by refluxing for 7 h. The cooled reaction mixture was acidified with 2 N HCl (300 mL) and the product was extracted with isopropyl ether. The organic layer was washed, dried over sodium sulfate, and evaporated in vacuo. The residue was purified by silica gel chromatography using hexane–isopropyl ether (1:1) to yield the allylic alcohol **2** (12.6 g, 91%) as an oil: IR (neat liq) 3500, 2950, 2850, 1650, 1603, and 1594 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.72 (3 H), 2.17 (3 H), 2.6–3.0 (2 H), 3.96 (6 H), 4.78 (1 H), 4.94 (1 H), 4.96 (2 H), 5.05 (2 H), 7.26–7.60 (10 H). Anal. Calcd for $C_{28}H_{32}O_5$: C, 74.97; H, 7.19. Found: C, 74.82; H, 7.04.

6-(3′-Methyl-4′-phenylsulfonylbut-2′-enyl)-2,3-dimethoxy-5-methylhydroquinone *O,O′*-Dibenzyl Ether (3). The allylic alcohol **2** (12.0 g, 26.7 mmol) and triethylamine (3.3 g, 32 mmol) were dissolved in absolute methylene chloride (100 mL) and the solution was stirred and cooled to −10 °C under nitrogen. To this was slowly added phenylsulfenyl chloride (4.26 g, 29.4 mmol) in methylene chloride (20 mL). After stirring for 20 min, the reaction mixture was poured into ice–water and the organic layer was separated, washed with additional water, dried over sodium sulfate, and evaporated in vacuo. The residue was dissolved in methylene chloride and oxidized with 40% peracetic acid (6.3 g, 33 mmol) in the presence of sodium bicarbonate (1 g) at 20–25 °C. After the oxidation was completed, the reaction mixture was treated with sodium carbonate and was extracted with methylene chloride. The organic layer was washed with water, dried over sodium sulfate, and evaporated to afford a solid, which was recrystallized from isopropyl ether to give the sulfonyl compound **3** (12.84 g, 84%): mp 84–85 °C; IR (KBr) 2900, 1443, 1360, and 1238 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.79 (3 H), 1.93 (3 H), 3.18 (2 H), 3.61 (2 H), 3.87 (3 H), 3.91 (3 H), 4.82 (1 H), 4.85 (2 H), 4.90 (2 H), 7.34 (13 H), 7.70 (2 H). Anal. Calcd for $C_{34}H_{36}O_6S$: C, 71.30; H, 6.34. Found: C, 71.14; H, 6.25.

6-(4′-Phenylsulfonyl-3′,7′,11′,15′,19′,23′,27′,31′,35′,39′-decamethyltetraconta-2′,6′,10′,14′,18′,22′,26′,30′,34′,38′-decaenyl)-2,3-dimethoxy-5-methylhydroquinone *O,O′*-Dibenzyl Ether (4). The sulfonyl compound **3** (11.45 g, 20 mmol) and solanesyl bromide prepared from natural solanesol (more than 98% purity, 15.2 g, 24 mmol) and phosphorous tribromide (3.3 g, 12 mmol) essentially as described by R. Rüegg et al.[13] were dissolved in a mixture of THF–DMF (9:1, 150 mL) and the mixture was stirred and cooled to −20 °C. To this mixture was added potassium *tert*-butoxide (3.23 g, 28.8 mmol) at once. After stirring for 30 min under the same conditions, the reaction mixture was acidified with 5% aqueous phosphoric acid (50 mL) and was extracted twice with isopropyl ether. The extracts were combined, washed with water, dried over sodium sulfate, and evaporated to dryness. The residue was chromatographed on silica gel using hexane–isopropyl ether (9:1 to 3:1) to yield the coupled compound **4** (21.66 g, 91.3%) as a viscous oil: ^1H NMR δ 1.52 (3 H), 1.68 (24 H), 1.66 (3 H), 1.73 (3 H), 1.98 (32 H), 2.70 (2 H), 3.20 (2 H), 3.40 (1 H), 3.87 (3 H), 3.91 (3 H), 4.83 (2 H), 4.89 (2 H), 5.07 (10 H), 7.36 (13 H), and 7.70 (2 H). Anal. Calcd for $C_{79}H_{108}O_6S$: C, 80.01; H, 9.18. Found: C, 80.32; H, 9.26.

Ubiquinone-10 (5). To the stirred blue solution consisting of lithium (2.0 g, 0.29 g atom) in a mixture of methylamine (50 mL) and dimethylamine (150 mL), compound **4** (17.8 g, 15 mmol) in absolute THF was added at −70 to −75 °C. After the addition was completed, the reaction mixture was stirred for an additional 20 min under the same conditions.

The excess metal was destroyed by the subsequent additions of isoprene (5 mL), absolute methanol (22 mL), and ammonium chloride (17 g). The reaction mixture was poured over a mixture of ice (500 g) and isopropyl ether (200 mL) and the resulting mixture was stirred and exposed to air for 10 min to oxidize the resulting hydroquinone. The orange product was extracted twice with isopropyl ether and the extracts were combined, washed with dilute hydrochloric acid and water, dried over sodium sulfate, and evaporated in vacuo. The residue was chromatographed on silica gel using hexane–isopropyl ether (3:1) to yield an orange solid, which was recrystallized from ether–ethanol to give ubiquinone-10 (**5**) (10.02 g, 77.3%), mp 48–49 °C, as orange crystals: ^1H NMR ($CDCl_3$) δ 1.62 (24 H), 1.68 (3 H), 1.74 (3 H), 2.02 (39 H), 3.18 (2 H), 3.98 (3 H), 3.99 (3 H), 4.9–5.2 (10 H).

The synthesized crystalline ubiquinone-10 was judged to be homogeneous by its TLC and LC analyses on silica gel and also identified by comparing its ^1H NMR and MS spectra with those of naturally occurring ubiquinone-10 (from ox heart muscle).[11]

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Registry No.—**1**, 68708-11-2; **2**, 68708-12-3; **3**, 68708-13-4; **4**, 68708-14-5; **5**, 303-98-0; 2,3-dimethoxy-5-methyl-1,4-benzoquinone, 605-94-7; 2-hydroxy-2-methylbut-3-ene, 115-18-4; 6-(3′-methylbut-2′-enyl)-2,3-dimethoxy-5-methylhydroquinone *O,O′*-dibenzyl ether, 66958-67-6; solanesyl bromide, 52610-77-2.

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