

A New Efficient and Stereoselective Synthesis of Ubiquinone-10

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Synopsis. Coupling reaction of 6-cupro-2,3-dimethoxy-5-methylhydroquinone bis(2-methoxyethoxymethyl) ether with (2*E*)-1-(phenylsulfonyl)-2-methyl-4-chloro-2-butene afforded the sulfone-functionalized prenylhydroquinone (**6**) in 82% yield. Stereoselective synthesis of ubiquinone-10 was achieved by the condensation of **6** and solanesyl bromide (yield 92%), reductive elimination of the sulfone group by sodium-ethyl alcohol in THF (yield 80%), and followed by air oxidation of the hydroquinone.

Recently much attention has been paid to ubiquinone-10 (**1**) owing to its remarkable physiological and clinical activity.¹ Various synthetic routes to **1** have been developed and these involve alkylation of the appropriate quinone or hydroquinone precursor.^{2,3} However, the alkylating agent, decaprenyl bromide is obtained as a *Z/E* (=3/7) mixture *via* multi-step procedures from solanesol.⁴ Thus, its use presents an intrinsic disadvantage for obtaining all-*E* ubiquinone-10. Terao and co-workers have demonstrated an efficient route to **1** using a sulfone-functionalized prenylhydroquinone **6**.⁵ However, a simpler procedure for the synthesis of **6** starting with 2,3-dimethoxy-5-methylhydroquinone (**2**) still remains. Previously we have developed a new effective and simple method⁶ for the introduction of the sulfone-functionalized isoprene skeleton into aromatic moieties using (2*E*)-1-(phenylsulfonyl)-2-methyl-4-chloro-2-butene (**5**) as a building block which is easily obtainable by the reaction of isoprene and benzene-sulfonyl chloride in the presence of copper(I) chloride-triethylamine hydrochloride catalyst.⁷ Here we extend the investigation to a stereoselective synthesis of **1** applicable to large scale production.

Alkylation of **3**⁸ with 2-methoxyethoxymethyl [MEM] chloride⁹ according to the previously reported procedure⁸ afforded **4** in 91% yield, and the coupling reaction of **4** with **5** in the presence of copper(I) bromide afforded **6** in 82% yield.⁶

Condensation of **6** and solanesyl bromide in the

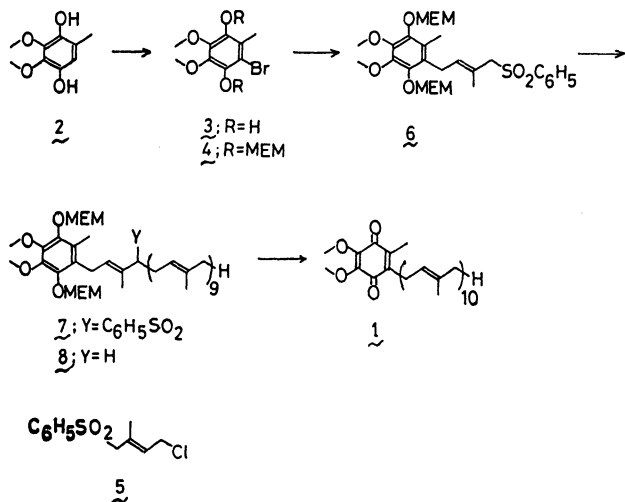
presence of potassium *t*-butoxide, gave **7** in 92% yield. The next problem is to find the method of selective and economical reduction of the sulfone group. The well established method for this purpose is use of lithium-ethylamine system,¹⁰ but it requires low reaction temperature (*ca.* -70 °C) and the product usually contains *ca.* 10—15% of $\Delta^{3,4}$ -isomer. Then the modified Bouveault-Blanc reduction recently reported by Tsuchihashi *et al.*¹¹ was very attractive as an alternative. The reaction could be carried out at room temperature by treating **7** with sodium (8 equiv.)-ethyl alcohol (12 equiv.) in THF. The product **8** obtained in 80% yield was found to contain a trace of $\Delta^{3,4}$ -isomer, although its amount could not be quantitatively determined because the retention time in high pressure chromatography (HPLC) is same as that of **8**. The mixture was treated with 48% hydrobromic acid catalyst in isopropyl alcohol at 50 °C to remove the protecting group. Neutralization of the reaction mixture with potassium hydroxide in methyl alcohol, followed by air oxidation at room temperature yielded a mixture consisting of 93% of **1** and 7% of $\Delta^{3,4}$ -isomer (HPLC). Pure (all *E*)-ubiquinone-10 (mp 50 °C) was obtained by recrystallization of the mixture from ethyl alcohol.

Experimental

Boiling points and melting points are uncorrected. IR spectra were determined on a Digilab FTS-20 C/D spectrometer. NMR spectra were taken with a Varian EM 390 (with hexamethyldisiloxane as an internal standard) and mass spectra with Finnigan 9500 or JEOL JMS-D 300 instruments. HPLC analyses were made with a Waters Associate.

6-(4-Phenylsulfonyl-3-methyl-2-butenyl)-2,3-dimethoxy-5-methylhydroquinone Bis(2-methoxyethoxymethyl) Ether (**6**). This compound was synthesized in 82% yield according to the procedure reported previously⁶ by the reaction of **5** (0.5 mol) and copper derivative of **4** prepared by treating the Grignard reagent of **4** with copper (I) bromide (0.5 mol). NMR δ (in CDCl₃) 1.87 (s, 3H, CH₃), 1.97 (s, 3H, CH₃), *ca.* 3.03—4.00 (m, 24H, 6 × CH₂ + 4 × CH₃O), 5.00, 5.07 (s, 4H, 2 × CH₂), *ca.* 4.90—5.20 (m, 1H, -CH) and *ca.* 7.23—7.80 (m, 5H, arom).

6-(4-Phenylsulfonyl-3,7,11,15,19,23,27,31,35,39-decamethyltetraconta-2,6,10,14,18,22,26,30,34-decaenyl)-2,3-dimethoxy-5-methylhydroquinone Bis(2-methoxyethoxymethyl) Ether (**7**). Into a solution of **6** (20.5 g; 36 mmol) and solanesyl bromide (purity 95%; 17.5 g; 24 mmol) in THF-DMF (9 : 1; 150 ml) was added potassium *t*-butoxide (22.5 g; 29 mmol) at -20 °C under nitrogen atmosphere. Stirring was continued for 1 h at -20 °C, and further for 1 h at 20 °C. The reaction mixture was poured into saturated ammonium chloride solution and extracted with diisopropyl ether. Evaporation of the solvent and purification of the residue with silica-gel column chromatography (dioxane-hexane = 3 : 7) afforded **7** (26.0 g) in 92% yield. IR (neat) 1660, 1450, 1300, 1250, 975, and 875 cm⁻¹. NMR δ (in CDCl₃) 1.53, 1.63 (s, 30H, 10 × CH₃), 1.75 (s, 3H,



CH₃), *ca.* 1.95 (s, 35H, 16×CH₂+CH₃), *ca.* 2.68 (m, 2H, CH₂), *ca.* 3.00–4.00 (m, 23H, 4×CH₃O+5×CH₂+CH), 4.97, 5.05 (s, 4H, 2×CH₂), 5.07 (broad s, 10H, 10×CH) and 7.20–7.80 (m, 5H, arom). Found: C, 73.95; H, 9.34%. Calcd for C₇₃H₁₁₂O₁₀S: C, 74.19; H, 9.55%.

Ubiquinone-10 (1). Into a solution of **7** (118 g; 0.1 mol) in ethyl alcohol (70 ml) and dry THF (350 ml) was added a small piece of sodium (18.4 g; 0.8 atom) at 10–15 °C under nitrogen stream. After stirring was continued for 12 h, additional 100 ml of ethyl alcohol was dropped to consume the excess sodium, the reaction mixture was poured into saturated ammonium chloride solution and extracted with diisopropyl ether, washed with water, and dried over magnesium sulfate. Evaporation of the solvent, and purification with silica gel column chromatography (dioxane: hexane = 15 : 85) afforded **8** (83.6 g) in 80.4% yield. IR (neat) 2950, 1670, 1390, 1110 and 980 cm⁻¹. NMR δ (in CDCl₃) 1.57, 1.61, 1.69 (s, 33H, 11×CH₃), 1.97, 2.10 (s, 39H, 18×CH₂+CH₃), 3.32 (s, 6H, 2×CH₃O), 3.98 (s, 6H, 2×CH₃O), *ca.* 3.30–3.95 (m, 10H, 5×CH₂), *ca.* 5.05 (broad s, 10H, 10×CH) and 5.17 (s, 4H, 2×CH₂). Found: C, 77.02; H, 10.18%. Calcd for C₆₇H₁₀₈O₈: C, 77.26; H, 10.45%.

The NMR spectra agreed very closely with that of authentic sample obtained by reacting the Grignard reagent of **4** and (all *E*)decaprenyl bromide except for the signal of δ *ca.* 2.50 (m) which was supposed to originate from $\Delta^{3,4}$ -isomer. Quantitative analyses by HPLC resulted in failure because the retention time was same as that of **8**. Deprotection of **8** was carried out with 48% hydrobromic acid (5 ml) in isopropyl alcohol (1500 ml) at 50 °C for 3 h under nitrogen atmosphere. After neutralization with 10% KOH–MeOH, air was bubbled into the reaction system at 25 °C for 3 h. After evaporation of the solvent, the mixture was poured into water, extracted with hexane, and dried over magnesium sulfate. Reaction product was purified with silica gel column chromatography (diisopropyl ether: hexane = 2 : 8) to obtain **1** (67.9 g) quantitatively. HPLC analyses

[Lichrosorb SI 60-5; butyl acetate: hexane = 6 : 94] showed that the product consisted of 93% of **1** (5.8 min) and 7% of $\Delta^{3,4}$ -isomer (5.5 min). Pure all *E*-**1** (58.4 g; yield 77%) was obtained by recrystallization of the mixture from ethyl alcohol (2.5 l) at 5 °C. Mp 50 °C [lit,^{5a} mp 48–49 °C].

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