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Convenient Syntheses of Vitamin K and Coenzyme Q by the Coupling of Grignard Reagents with Allylic Phosphate

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Convenient syntheses of vitamin K and coenzyme Q are described. Grignard coupling of polyprenyl diethyl phosphates with 1,4-dimethoxy-3-methyl-2-naphthylmagnesium bromide gave high yields of the polyprenylated hydroquinone dimethyl ethers regioselectively with the preservation of the stereochemistry. The precursors of coenzyme Q were similarly obtained by the coupling of 2,3,4,5-tetramethoxy-6-methylphenylmagnesium bromide and the polyprenyl phosphates. The synthesized (polyprenyl)hydroquinone dimethyl ethers are known to be oxidized to the biologically active quinones.

Regio- and stereoselective carbon–carbon bond formation at either the α- or γ-position of an allylic system is a fundamental subject in synthetic organic chemistry. A number of methods with satisfactory selectivity have been developed, some of which involve the coupling of allylic species and organometallics.[1] Recently we have reported that phosphate esters of primary allylic alcohols such as geraniol and nerol allylate a variety of Grignard reagents at the α-position with the preservation of the stereochemistry of the allylic double bond.[2] As an application of this coupling reaction, the syntheses of the biologically active quinones, vitamin K and coenzyme Q, are described in the present paper.

Vitamin K and coenzyme Q are composed of a polyprenyl chain and a naphthoquinone or a benzoquinone nucleus.[3] The synthetic methods of these quinones hitherto reported can be classified into four groups in regard to the fashion of the coupling between the nucleus and the side chain: (a) Friedel-Crafts type coupling,[4] (b) reaction of π-allylnickel complex with halohydroquinone,[5] (c) Lewis acid catalyzed coupling of (polyprenyl)stannane with quinone,[6] and (d) reaction of aryl Grignard reagent or arylcuprate(I) with polyprenyl halide.[7] The method reported in this paper is a modification of the last group, which involves the reaction of polyprenyl phosphates with the Grignard reagents of hydroquinone dimethyl ethers. The coupling proceeded regioselectively in excellent yields without loss of the stereochemistry.

Results and Discussion

To a stirred solution of 1,4-dimethoxy-3-methyl-2-naphthylmagnesium bromide (**1**) in tetrahydrofuran (THF) was added prenyl diethyl phosphate (**2a**) and the mixture was stirred overnight at room temperature. After hydrolysis and vacuum distillation, the coupling product, 1,4-dimethoxy-3-methyl-2-prenylnaphthalene (**3a**), was isolated in high yield (93%) (Table 1). As expected,[2] the coupling occurred exclusively at the α-position of the prenyl phosphate (**2a**), and the formation of the γ-attack product [1,4-dimethoxy-3-methyl-2-(1,1-dimethyl-2-propenyl)naphthalene] was not observed by glc and ^{1}H NMR analyses. In a similar way, geranyl (**2b**) and neryl diethyl phosphates (**2c**) gave the respective coupling products (**3b** and **3c**) in 80 and 86% yields, respectively. Glc showed that no *E*-*Z* isomerization occurred during the coupling. Snyder reported[7a] that the reaction of the Grignard reagent (**1**) and geranyl and neryl bromides gave **3b** and **3c**, however the yield of the *Z*-isomer (**3c**) was relatively lower (62%) than that of the *E*-isomer (**3b**) (92%). The present coupling using allylic phosphates did not show such suppression of the yield even in the reaction of the neryl phosphate (**2c**). (2*E*)- and (2*Z*)-Farnesyl derivatives were also obtained regioselectively with the preservation of the stereochemistry of the farnesyl group (confirmed by HPLC). The precursor (**3f**) of vitamin K_1 was similarly prepared from phytyl diethyl phosphate (**2f**) in 87% yield. The synthesized (polyprenyl)hydroquinone dimethyl ethers (**3a—f**) are known[7a,7c] to be demethylatively oxidized by silver(II) oxide or cerium(IV) diammonium nitrate to the respective vitamin K_2 (**4a—e**) and vitamin K_1 (**4f**).

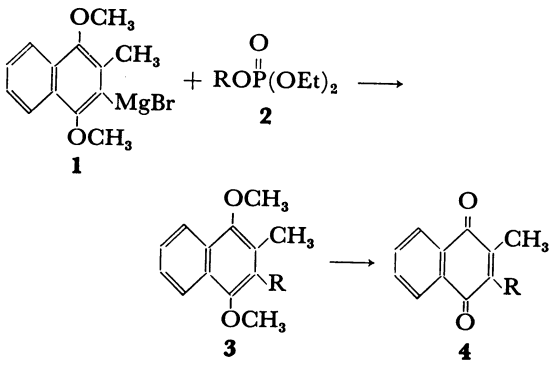
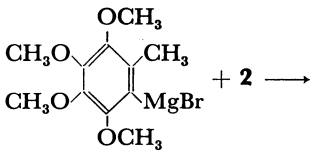


TABLE 1. YIELDS AND STEREOCHEMISTRY OF 1,4-DIMETHOXY-2-METHYL-3-POLYPRENYLNAPHTHALENES (**3a—f**)

R	Yield/%	Stereochemistry at Δ^2 (*E*/*Z*)
Prenyl (**3a**)	93	—
Geranyl (**3b**)	80	10/0[a]
Neryl (**3c**)	86	0/10[a]
(2*E*)-Farnesyl (**3d**)	76	10/0[b]
(2*Z*)-Farnesyl (**3e**)	87	2/8[b,c]
Phytyl (**3f**)	87	10/0[d]

a) Determined by glc. b) Determined by HPLC. c) Due to (2*E*)-farnesol mixed in the (2*Z*)-farnesol used (*E*/*Z*=2/8). d) Determined by ^{1}H NMR (200 MHz).

The precursors (**6a—e**) of coenzyme Q were analogously prepared from 2,3,4,5-tetramethoxy-6-methylphenylmagnesium bromide (**5**) and polyprenyl diethyl phosphates (**2a—e**). The yields are listed in Table 2. Again, no detectable amounts of γ-coupling nor *E-Z* isomerization were observed. The dimethyl ethers (**6a—e**) can be demethylatively oxidized to coenzyme Q (**7a—e**).[7a,7c]



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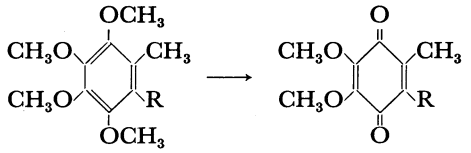

6 **7**

In summary, several examples of vitamin K and coenzyme Q precursors bearing a polyprenyl chain of different length and stereochemistry were synthesized. The advantages of the present method are (1) regioselectivity is very high and the isomerization of the allylic double bond is negligible, (2) the yields are excellent, (3) reaction conditions are mild, and (4) experimental operations are simple. Therefore, this method provides a convenient route for the syntheses of vitamin K and coenzyme Q.

Experimental

General. Infrared spectra were recorded on a JASCO IRA-1 spectrophotometer. ^{1}H NMR spectra were determined with a Hitachi R-24A (60 MHz) spectrometer, or with a Varian XL-200 (200 MHz) spectrometer in CCl_4 or $CDCl_3$. Chemical shifts (δ) are recorded in ppm downfield from Me_4Si. Mass spectra were measured on a Hitachi M-52 mass spectrometer, operating with an ionization energy of 20 eV. HPLC analysis was performed by using a JASCO TRI ROTAR-II with a silica-gel column (Fine Sil 20, 4.6 mm× 25 cm) eluting with hexane–chloroform (100:1). Glc analysis was done on a Yanaco G1800 gas chromatograph, equipped with a column packed with Apiezon Grease L on Uniport B. Elemental analysis was performed at the Elemental Analysis Center of Kyoto University. Polyprenyl diethyl phosphates (**2a—f**) were prepared from polyprenyl alcohols and diethyl phosphorochloridate according to the method for the corresponding diphenyl phosphates.[8] (2*Z*)-Farnesol (2*Z*/2*E*=8/2) was prepared by the diisobutylaluminum hydride reduction of ethyl (2*Z*)-farnesoate (2*Z*/2*E*=8/2) which was obtained by the fractional distillation of a mixture of the (2*Z*)- and (2*E*)-isomers (2*Z*/2*E*=2/8) synthesized by the Wittig-Horner reaction of geranylacetone.[9]

Grignard Coupling of 1,4-Dimethoxy-3-methyl-2-naphthylmagnesium Bromide (1) with Polyprenyl Diethyl Phosphates (2a—f). The following preparation of **3a** is a representative. The Grignard reagent, 1,4-dimethoxy-3-methyl-2-naphthylmagnesium bromide (**1**), was prepared in a conventional manner using tetrahydrofuran (THF) as a solvent. To a stirred solution of **1** (2.28 mmol) in 3 ml of THF was added a solution of prenyl diethyl phosphate (**2a**) (297 mg, 1.34 mmol) in 3 ml of THF at 0 °C. The reaction mixture was stirred overnight at room temperature and then quenched by the addition of water. The product was extracted with ether and the extracts were dried over anhydrous sodium sulfate and then concentrated. The residue was distilled (Kugelrohr) to give 1,4-dimethoxy-2-methylnaphthalene [bp 130 °C/5 Torr (1 Torr≈133.322 Pa), 177 mg] and **3a** (bp 150 °C/5 Torr, 335 mg, 93%). Higher analogs of the polyprenylated compounds (**3b—f**) were similarly prepared and purified by column chromatography on silica-gel (benzene–ether gradient).

Table 2. Yields and stereochemistry of 1,2,3,4-tetramethoxy-5-methyl-6-polyprenylbenzenes (**6a—e**)

R	Yield/%	Stereochemistry at Δ^2 (*E*/*Z*)
Prenyl (**6a**)	85	—
Geranyl (**6b**)	82	10/0[a]
Neryl (**6c**)	84	0/10[a]
(2*E*)-Farnesyl (**6d**)	70	10/0[b]
(2*Z*)-Farnesyl (**6e**)	75	2/8[b,c]

a) Determined by glc. b) Determined by ^{1}H NMR (200 MHz). c) Due to (2*E*)-farnesol mixed in the (2*Z*)-farnesol used (*E*/*Z*=2/8).

1,4-Dimethoxy-2-methyl-3-prenylnaphthalene (3a):[7c] IR (neat) 2950, 1594, 1452, 1355, 1266, 1195, 1065, 1018, 975, 775, and 712 cm^{-1}: ^{1}H NMR (CCl_4) 7.16—8.01 (m, 4H, aromatic), 5.07 (t, *J*=6 Hz, 1H, olefin), 3.81 (s, 3H, OCH_3), 3.78 (s, 3H, CH_3), 3.47 (d, *J*=6 Hz, 2H, CH_2), 2.33 (s, 3H, CH_3), 1.81 (s, 3H, CH_3), 1.70 (s, 3H, CH_3); Mass *m*/*z* 270 (M^+).

1,4-Dimethoxy-2-methyl-3-geranylnaphthalene (3b):[7a] IR (neat) 2950, 1590, 1450, 1355, 1265, 1190, 1060, 830, and 770 cm^{-1}; ^{1}H NMR (CCl_4) 7.16—8.05 (m, 4H, aromatic), 4.81—5.24 (m, 2H, olefin), 3.75 (s, 3H, OCH_3), 3.44 (d, *J*=6 Hz, 2H, CH_2), 2.26 (s, 3H, CH_3), 1.94 (m, 4H, CH_2×2), 1.75 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 1.50 (s, 3H, CH_3); Mass *m*/*z* 338 (M^+).

1,4-Dimethoxy-2-methyl-3-nerylnaphthalene (3c):[7a] IR (neat) 2950, 1600, 1460, 1360, 1270, 1200, 1070, 830, and 780 cm^{-1}; ^{1}H NMR (CCl_4) 7.12—8.04 (m, 4H, aromatic), 4.86—5.22 (m, 2H, olefin), 3.73 (s×2, 6H, OCH_3), 3.43 (d, *J*=7 Hz, 2H, CH_2), 2.26 (s, 3H, CH_3), 2.17 (m, 4H, CH_2×2), 1.58—1.71 (m, 9H, CH_3×3); Mass *m*/*z* 338 (M^+).

1,4-Dimethoxy-2-methyl-3-[(2E)-farnesyl]naphthalene (3d): IR (neat) 2945, 1592, 1456, 1355, 1268, 1066, and 770 cm^{-1}; ^{1}H NMR ($CDCl_3$) 8.10 (m, 2H, aromatic), 7.50 (m, 2H, aromatic), 5.11 (m, 3H, olefin), 3.89 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.59 (d, *J*=6 Hz, 2H, CH_2), 2.39 (s, 3H, CH_3), 2.06 (m, 8H, CH_2×4), 1.84 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 1.60 (s, 6H, CH_3×2); Mass *m*/*z* 406 (M^+). Found: C, 82.44; H, 9.17%. Calcd for $C_{28}H_{38}O_2$: C, 82.71; H, 9.42%.

1,4-Dimethoxy-2-methyl-3-[(2Z)-farnesyl]naphthalene (3e): IR (neat) 2950, 1596, 1456, 1356, 1269, 1068, and 774 cm^{-1}; ^{1}H NMR ($CDCl_3$) 8.10 (m, 2H, aromatic), 7.50 (m, 2H, aromatic), 5.27 (m, 1H, olefin), 5.16 (m, 2H, olefin), 3.88 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.59 (d, *J*=6 Hz, 2H, CH_2), 2.40 (s, 3H, CH_3), 2.35—1.90 (m, 8H, CH_2×4), 1.73 (m, 3H, CH_3), 1.70 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), 1.63 (s, 3H, CH_3); Mass *m*/*z* 406 (M^+). Found: C, 82.63; H, 9.52%. Calcd for $C_{28}H_{38}O_2$:

C, 82.71; H, 9.42%.

*1,4-Dimethoxy-2-methyl-3-phytylnaphthalene (**3f**)*: IR (neat) 2940, 1592, 1455, 1355, 1265, 1192, 1098, 1065, 1014, 970, and 770 cm^{-1}; ^1H NMR (CCl_4) 7.03—8.01 (m, 4H, aromatic), 5.03 (t, J=6 Hz, 1H, olefin), 3.81 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.41 (d, J=6 Hz, 2H, CH_2), 2.25 (s, 3H, CH_3), 2.20—1.50 (m, 5H, CH_2 and CHX3), 1.73 (s, 3H, CH_3), 1.12 (br, 16H, CH_2X8), 0.81 (d, J=7 Hz, 12H, CH_3X4); Mass m/z 480 (M^+). Found: C, 82.30; H, 11.17%. Calcd for $C_{33}H_{52}O_2$: C, 82.44; H, 10.90%.

Precursors (**6a—e**) of coenzyme Q were analogously obtained by the Grignard reactions of 2,3,4,5-tetramethoxy-6-methylphenylmagnesium bromide and the polyprenyl phosphates (**2a—e**), and characterized by IR, ^1H NMR, and Mass spectra.

*1,2,3,4-Tetramethoxy-5-methyl-6-prenylbenzene (**6a**)*: IR (neat) 2950, 1468, 1408, 1355, 1260, 1196, 1100, 1070, 1042, and 980 cm^{-1}; ^1H NMR (CCl_4) 4.96 (t, J=6 Hz, 1H, olefin), 3.82 (s, 6H, OCH_3X2), 3.73 (s, 6H, OCH_3X2), 3.22 (d, J=6 Hz, 2H, CH_2), 2.09 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 1.67 (s, 3H, CH_3); Mass m/z 280 (M^+). Found: C, 68.05; H, 8.78%. Cacld for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63%.

*1,2,3,4-Tetramethoxy-5-methyl-6-geranylbenzene (**6b**)*:[7c] IR (neat) 2950, 1470, 1410, 1350, 1260, 1200, 1100, 1040, and 980 cm^{-1}; ^1H NMR (CCl_4) 4.79—5.09 (m, 2H, olefin), 3.76 (s, 6H, OCH_3X2), 3.67 (s, 6H, OCH_3X2), 3.21 (d, J=7 Hz, 2H, CH_2), 2.11 (s, 3H, CH_3), 1.92 (m, 4H, CH_2X2), 1.68 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 1.51 (s, 3H, CH_3); Mass m/z 338 (M^+).

*1,2,3,4-Tetramethoxy-5-methyl-6-nerylbenzene (**6c**)*: IR (neat) 2950, 1470, 1410, 1350, 1260, 1200, 1100, 1040, and 980 cm^{-1}; ^1H NMR (CCl_4) 4.78—5.16 (m, 2H, olefin), 3.76 (s, 6H, OCH_3X2), 3.67 (s, 6H, OCH_3X2), 3.17 (d, J=7 Hz, 2H, CH_2), 2.10 (m, 4H, CH_2X2), 2.02 (s, 3H, CH_2), 1.62 (m, 9H, CH_3X3); Mass m/z 338 (M^+). Found: C, 72.09; H, 9.26%. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26%.

*1,2,3,4-Tetramethoxy-5-methyl-6-[(2E)-farnesyl]benzene (**6d**)*: IR (neat) 2950, 1465, 1408, 1355, 1108, 1042, and 980 cm^{-1}; ^1H NMR ($CDCl_3$) 5.08 (m, 3H, olefin), 3.92 (s, 6H, OCH_3X2), 3.80 (s, 6H, OCH_3X2), 3.33 (d, J=7 Hz, 2H, CH_2), 2.17 (s, 3H, CH_3), 2.04 (m, 8H, CH_2X4), 1.78 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 1.59 (s, 3H, CH_3); Mass m/z 406 (M^+). Found: C, 74.87; H, 9.72%. Calcd for $C_{26}H_{40}O_4$: C, 74.96; H, 9.68%.

*1,2,3,4-Tetramethoxy-5-methyl-6-[(2Z)-farnesyl]benzene (**6e**)*: IR (neat) 2930, 1465, 1406, 1352, 1103, 1041, and 978 cm^{-1}: ^1H NMR ($CDCl_3$) 5.24 (m, 1H, olefin), 5.07 (m, 2H, olefin), 3.92 (s, 6H, OCH_3X2), 3.80 (s, 6H, OCH_3), 3.36 (d, J=7 Hz, 2H, CH_2), 2.40—1.90 (m, 4H, CH_2X2), 2.16 (s, 3H, CH_3), 1.70 (s, 6H, CH_3X2), 1.66 (s, 3H, CH_3), 1.63 (s, 3H, CH_3); Mass m/z 406 (M^+). Found: C, 75.14; H, 9.74%. Calcd for $C_{26}H_{40}O_4$: C, 74.96; H, 9.68%.

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