The Synthesis of Coenzyme Q

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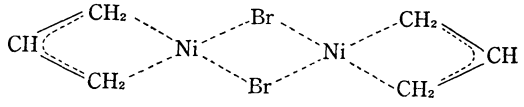
A new, efficient synthesis of coenzyme Q is described. The bromination of 2,3-dimethoxy-5-methyl-*p*-benzoquinone gives 6-bromo-2,3-dimethoxy-5-methyl-*p*-benzoquinone, which is then converted to the corresponding hydroquinone diacetate by the action of zinc dust in acetic anhydride. 6-Bromo-2,3-dimethoxy-5-methylhydroquinone diacetate is reacted with 1,1-dimethyl-π-allylnickel bromide in hexamethylphosphoramide at 60 °C to afford a 70% yield of 2,3-dimethoxy-5-methyl-6-prenylhydroquinone diacetate, which is hydrogenolyzed with lithium aluminum hydride in ether and then oxidized with aqueous ferric chloride to give coenzyme Q_1 in a 76% yield. Similarly, coenzyme Q_2, Q_9, and Q_{10}, and 6′, 10′, 14′-hexahydrocoenzyme Q_4 are synthesized by the reaction of the aryl bromide with π-geranyl-, π-solanesyl-, π-decaprenyl-, and π-phytylnickel bromide respectively and by subsequent treatment with $LiAlH_4$ and $FeCl_3$. The stereochemistry of the products is also described.

A new synthetic method which involves a selective carbon-carbon bond formation between π-allylnickel halide complexes (**1**) and organic halides has recently been reported by Corey and Semmelhack,[1] and the intrinsic value of this coupling reaction for the synthetic chemistry has been shown in the syntheses of various



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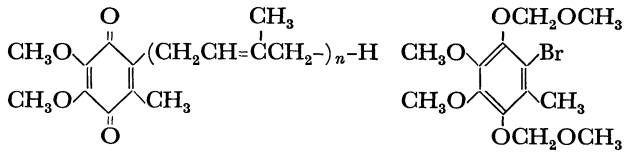
natural substances, α-santalene,[1] epi-β-santalene,[1] ethyl geranate,[2] geranyl acetate,[2,3] coenzyme Q_1,[4,5] and vitamin K.[6]

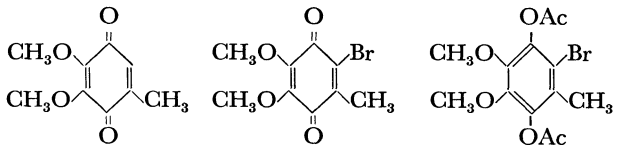
We wish to report here a new synthesis of coenzyme Q (**2**) employing the promising allylation reaction of π-allylnickel bromides.

In a previous work, we utilized 6-bromo-2,3-dimethoxy-5-methylhydroquinone bis(methoxymethyl) ether (**3**) for the construction of the aromatic moiety of coenzyme Q_1.[4] It was found that the regeneration of the hydroquinone in the later stage of synthetic sequences could be achieved conveniently by the acid-catalized solvolysis of the bis(methoxymethyl) ether in methanol. However, **3** is not crystalline and is rather unstable, so it must be purified carefully by column chromatography. Therefore, we investigated another synthetic equivalent of **3**.



2 **3**

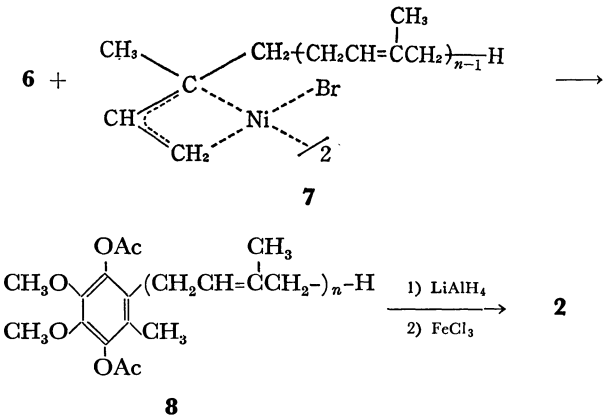
The bromination of 2,3-dimethoxy-5-methyl-*p*-benzoquinone (**4**)[7] afforded 6-bromo-2,3-dimethoxy-5-methyl benzoquinone (**5**),[4] which was then converted to the



4 **5** **6**

corresponding hydroquinone diacetate **6** by the action of zinc in acetic anhydride.

When **6** reacted to 1,1-dimethyl-π-allylnickel bromide (**7**, $n=1$)[8] in hexamethylphosphoramide (HMPA) at 60 °C for 7 hr, 2,3-dimethoxy-5-methyl-6-prenylhydroquinone diacetate (**8**, $n=1$) was obtained in a 70% yield. By this fact, the diacetate **6** was found to be as sufficiently reactive toward **7** ($n=1$) as the corresponding bis(methoxymethyl) ether **3**, which had afforded the coupling product with **7** ($n=1$) in HMPA at 60 °C in a 57% yield.[4] All earlier attempts at the alkaline hydrolysis or acid-catalyzed hydrolysis of **8** ($n=1$) to the corresponding hydroquinone had failed. Finally, the diacetate **8** ($n=1$) was treated with excess $LiAlH_4$ in ether at reflux for 24 hr and then oxidized with aqueous $FeCl_3$ to afford coenzyme Q_1(**2**, $n=1$) in a 76% yield. The IR and NMR spectra were satisfactory for the structure **2**($n=1$).



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8

Although the nature of π-allylnickel complexes, except for π-geranylnickel bromide,[1] possessing in their own molecule some olefin moieties which may act as stable π-ligands, has not yet been clarified, the above results distinctly suggest the possibility of synthesizing the higher homologues of coenzyme Q. Such an anticipation was successfully realized, as will be indicated below. The bromide **6** reacted to π-geranylnickel bromide (**7**, $n=2$)[8] in HMPA at 60 °C to afford 6-geranyl-2,3-dimethoxy-5-methylhydroquinone diacetate (**8**, $n=2$) (88% yield), which was then converted, by the removal of the acetate groups with $LiAlH_4$

and by subsequent oxidation by aqueous $FeCl_3$, to coenzyme Q_2 (**2**, $n=2$) in a 75% yield.

The procedure was also extended to the synthesis of the higher homologues of coenzyme Q. The bromide **6** reacted to π-solanesylnickel bromide (**7**, $n=9$)[8] in HMPA at 70 °C for 10 hr. After purification with a silica-gel column we obtained 6-solanesyl-2,3-dimethoxy-5-methylhydroquinone diacetate (**8**, $n=9$) (45 % yield), which was then converted to coenzyme Q_9 (**2**, $n=9$) by the above-described procedure (71% yield); this substance melted at 26—28 °C (lit,[10] mp 45 °C for naturally-occurring coenzyme Q_9). The synthesis of coenzyme Q_{10} (**2**, $n=10$) was similarly effected by the reaction of π-decaprenylnickel bromide (**7**, $n=10$)[8] with **6** in HMPA at 75 °C for 7 hr (40% yield), followed by the treatment of **8** ($n=10$) with $LiAlH_4$ and then aqueous $FeCl_3$ to give **2** ($n=10$) in a 69% yield; mp 20—22 °C (lit,[10,11] mp 49 °C for the natural coenzyme Q_{10}).

The low melting points of our products are attributable to the coexistence of the *cis* isomer[12] in regard to the first double bond in the side chain originating in the π-allyl moiety of **7**. This was supported by the 100 MHz NMR spectroscopy measurement; the calculation of the peak areas of olefinic methyl protons revealed that the *trans*-to-*cis* ratio of the product was 55 : 45. For the synthetic utility and isolation of all-*trans*-coenzyme Q, a higher *trans* stereoselectivity is needed. For the investigation of the stereoselectivity of this coupling reaction, the geranyl side chain was not a suitable model, because the NMR spectrum of **2** ($n=2$) showed complicated olefinic methyl signals at δ 1.5—1.7, so the determination of the *trans*-to-*cis* ratio was very difficult.[13] For this purpose, the phytyl side chain or a much higher (*i.e.* solanesyl or decaprenyl) side chain was suitable. We have already found[6] that the conduction of the coupling reaction in lesser coordinative polar solvents, such as *N*,*N*-dimethylacetamide (DMAc) or *N*-methyl-2-pyrrolidone (MPD), and at lower temperature leads to higher *trans*-to-*cis* ratios of the coupling products in the synthesis of vitamin K. A similar solvent effect was also observed in the present work. The reaction of **6** with π-phytylnickel bromide in DMAc or MPD gave the *trans* isomer of the coupling product (6′,10′,14′-hexahydrocoenzyme Q_4) above a 70% stereoselectivity. In the synthesis of coenzyme Q_9 with **6** and **7** ($n=9$) in DMAc at 60 °C, the products **8**($n=9$) (48% yield) and, therefore, **2** ($n=9$) were both 74 : 26 mixtures fo *trans* and *cis* forms.

The isolation of the all-*trans*-coenzyme Q_9 was effected by silica-gel column chromatography, eluting with *n*-hexane–diisopropyl ether (90 : 10). The first several fractions eluted contained only the *cis*-isomer, while the all-*trans* compound (mp 42—4 °C) was eluted in the rather late fractions in a high *trans* recovery.

The efficacy of the synthesis of **2** by the π-allylnickel complex allylation process depends on the unreactivity of σ- or π-allylnickel complexes toward the ester function and the facile reactivity thereof toward the trigonal carbon halides. This procedure avoids the disadvantages of several kinds of side reactions, which render the product isolation much difficult. The sole by-product of the present method, hydrocarbons arising from the thermal decomposition of **7**, can easily be separated, and the unchanged diacetate **6** is recovered quantitatively. This method seems to be highly effective for the synthesis of naturally-occurring isoprenoid quinones and related substances, including coenzyme Q, vitamin K, and tocophenols,[14] for which there exists only a very limited synthetic methodology.

Investigations are continuing from the mechanistic point of view and concerning reaction conditions which would realize a much higher stereoselectivity.

Experimental

The melting points were taken on a hot-stage apparatus and are uncorrected. The spectral measurements were determined with the following instruments; IR, a Hitachi Model 215 spectrophotometer; NMR, a JEOL Model C-60 or PS-100 spectrometer in a carbon tetrachloride or deuteriochloroform solution, with tetramethylsilane as the internal reference; UV, a Hitachi Model EPS-3T spectrophotometer.

6-Bromo-2,3-dimethoxy-5-methyl-*p*-benzoquinone (**5**),[4] geranyl bromide, phytyl bromide, solanesyl bromide,[9] and decaprenyl bromide[9] were obtained by the methods described in the literature, their physical properties agreed with those previously reported. Reactions involving π-allylnickel complexes were carried out under nitrogen or argon.

*6-Bromo-2,3-dimethoxy-5-methylhydroquinone Diacetate (**6**).* A solution of 5.0 g of **5** in 20 ml of acetic anhydride containing a few drops of pyridine was warmed to 60—65 °C, and then 7.5 g of zinc dust was added to this solution. The mixture was stirred well until the red color faded and was then kept at 60 °C for a further 30 min. The mixture was filtered, and the residue was washed with acetone. The combined

Table 1. Summary of the yields and stereoselectivity of the coupling reaction

π-Complex	Solvent	Temp.	Time	Product	Yield[a]	*trans* : *cis*[b]
Phytyl	DMAc	50 °C	6 hr	H. H. Q_4[c]	30%	71 : 29
phytyl	MPD	50	20	H. H. Q_4	42	73 : 27
solanesyl	HMPA	70	10	Q_9[d]	45	55 : 45
solanesyl	DMAc	70	5	Q_9	35	67 : 33
solanesyl	DMAc	60	20	Q_9	48	74 : 26
solanesyl	DMAc	50	20	Q_9	41	70 : 30
solanesyl	MPD	50	20	Q_9	25	70 : 30

a) Isolated yield of the cross-coupling product and based on the diacetate **6**. b) These ratios were determined by 100 MHz NMR spectroscopy. c) H. H. Q_4 indicates 6′,10′,14′-hexahydrocoenzyme Q_4 hydroquinone diacetate. d) Q_9 indicates coenzyme Q_9 hydroquinone diacetate **8** ($n=9$).

filtrate was poured into water, after which the separated oily product slowly crystallized. The collected precipitates were recrystallized from petroleum ether to give 5.9 g (83%) of **6** as colorless needles; mp 68—69 °C; IR (KBr) 2940, 1750, 1470, 1420, 1365, 1200, 1080, and 1020 cm^{-1}; NMR ($CDCl_3$) δ 3.75 (6H, s, $2CH_3O$), 2.31, 2.28 (each 3H, 2s, 2AcO), 2.16 (3H, s, $ArCH_3$).

Found: C, 44.93; H, 4.34%. Calcd for $C_{13}H_{15}O_6Br$: C, 44.98; H, 4.36%.

General Preparative Method of π-Allylnickel Bromide (7). To a stirred solution of a 15% benzene solution of nickel carbonyl (*ca.* 1.5-fold excess), a 15% benzene solution of the allylic bromide was added drop by drop over 1—1.5-hr period at 50 °C; the mixture was then stirred for a further 2—3 hr. The resulting solution was cooled to below 10 °C, and the benzene and excess nickel carbonyl were removed under reduced pressure. The red residue was the corresponding π-complex and was used directly in the next reaction.

Coenzyme Q_1 (2, n=1). 1,1-Dimethyl-π-allylnickel bromide (**7**, $n=1$) was prepared from 4.5 g of 1-bromo-3-methyl-2-butene and 8.7 g of nickel carbonyl by means of the above-described procedure. After the removal of the benzene, 36 ml of HMPA and 5.2 g of **6** in 36 ml of HMPA were added to the dark residue at 10 °C. The mixture was heated to 60 °C for 7 hr, and then poured into water and extracted with petroleum ether. The extract was washed with water, dried ($MgSO_4$), and freed of the solvent. The crude product (5.1 g) was found by NMR assay to consist of 70% of **8** ($n=1$) and 30% of **6**, but **8** could not be isolated by silica gel column chromatography.[15] This mixture (1.3 g) was dissolved in 30 ml of dry ether and reduced by the use of 0.8 g of $LiAlH_4$ at reflux for 24 hr. The excess $LiAlH_4$ was decomposed by the addition of a small portion of ethanol and ethyl acetate, neutralized by an aqueous saturated ammonium chloride solution, and extracted with ether. The extract was concentrated to a small volume, oxidized by aqueous $FeCl_3$ at room temperature for 3 hr, and extracted with ether. The extract was washed with water, dried ($MgSO_4$), and evaporated. The crude product was chromatographed on silica gel, using *n*-hexane–diisopropyl ether (80 : 20) for elution, to give 0.5 g of coenzyme Q_1 (**2**, $n=1$). All the spectral data were identical with those previously obtained in our laboratory.[4]

Coenzyme Q_2 (2, n=2). π-Geranylnickel bromide (**7**, $n=2$) was prepared from 8.7 g of geranyl bromide and 10.3 g of nickel carbonyl by means of the above-described method. After changing the solvent to 40 ml of HMPA, 5.3 g of **6** in 35 ml of HMPA were added at 10 °C, and the mixture was treated at 60 °C for 7 hr. When the reaction mixture was worked up in the usual manner, 7.2 g of a crude product was obtained. This was found by NMR assay to be a mixture of **8** ($n=2$) (88%) and **6** (12%), but the removal of the **6** by the use of the silicagel column was very difficult.[16] This mixture (1.5 g) was reduced by the use of 0.7 g (of $LiAlH_4$ in dry ether at reflux for 24 hr, and then worked up in the usual manner. The ether extract was concentrated to a small volume and then oxidized by aqueous $FeCl_3$ at room temperature for 3 hr. The organic layer was washed with water, dried ($MgSO_4$), and freed of the solvent. The crude product was chromatographed on silica gel; subsequent elution with *n*-hexane–diisopropyl ether (80 : 20) gvae 0.7 g of coenzyme Q_2 (**2**, $n=2$). The estimated yield of **2** ($n=2$) from **8** ($n=2$) was 75%. IR (neat) 2930, 1650, 1610, 1450, 1270, 1210, 1160, 1100, 1010, 950, and 740 cm^{-1}; NMR ($CDCl_3$) δ 4.96 (2H, t, 2-CH=), 3.97 (6H, s, $2CH_3O$), 3.16 (2H, d, $ArCH_2$), 1.99 (4H, bs, methylene chain), 1.97 (3H, s, $ArCH_3$), 1.72, 1.67 (3H, 2s, *trans* and *cis* olefinic CH_3), 1.63 1.56 (each 3H, 2s, terminal olefinic CH_3);[13] UV λ_{max} (*n*-hexane) 270 nm (15600).

Found: C, 71.87; H, 8.35%. Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23%.

6′,10′,14′-Hexahydrocoenzyme Q_4. π-Phytylnickel bromide was prepared from 1.9 g of phytyl bromide and 1.3 g of nickel carbonyl; after the solvent had been changed to 30 ml of DMAc, 1.3 g of **6** was added, and the mixture was treated under the conditions shown in Table 1. The reaction mixture was then worked-up in the usual manner, and silica-gel-column chromatography afforded the corresponding diacetate: IR (neat) 2930, 1770, 1485, 1475, 1370, and 1195 cm^{-1}; NMR ($CDCl_3$) δ 5.00 (1H, t, -CH=), 3.86 (6H, s, $2CH_3O$), 3.25 (2H, d, $ArCH_2$), 2.26, 2.24 (each 3H, 2s, 2AcO), 2.08 (3H, s, $ArCH_3$), 1.72 (3H, bs, olefinic CH_3), 1.20 (21H, bs, methylene chain), 0.88 (12H, d, side-chain CH_3).

Found: C, 72.77; H, 10.16%. Calcd for $C_{33}H_{54}O_6$: C, 72.49; H, 9.95%.

To a suspension of 0.7 g of $LiAlH_4$ in 40 ml of dry ether, 1.00 g of the hydroquinone diacetate in 20 ml of ether was added, and the mixture was treated at reflux for 7 hr. After extraction, the extract was concentrated to a small volume and oxidized by aqueous $FeCl_3$ at room temperature for 3 hr. The crude product, obtained by the usual work-up, was chromatographed on silica gel; subsequent elution with *n*-hexane–diisopropyl ether (70 : 30) gave 0.61 g of 6′,10′,14′-hexahydrocoenzyme Q_4 (72%); IR (neat) 2920, 1645, 1602, 1457, 1375, 1285, 1260, and 1202 cm^{-1}; NMR ($CDCl_3$) δ 4.94 (1H, t, -CH=), 3.97 (6H, s, $2CH_3O$), 3.19 (2H, d, $ArCH_2$), 2.00 (3H, s, $ArCH_3$), 1.78, 1.72 (3H, 2s, *trans* and *cis* olefinic CH_3), 1.20 (21H, bs, methylene chain), 0.88 (12H, d, side-chain CH_3).

Found: C, 75.60; H, 10.60%. Calcd for $C_{29}H_{48}O_4$: C, 75.61; H, 10.50%.

Coenzyme Q_9 (2, n=9). π-Solanesylnickel bromide (**7**, $n=9$) was prepared from 6.0 g of solanesyl bromide and 1.6 g of nickel carbonyl. After the solvent had been changed to 40 ml of DMAc, a 1.6-g portion of **6** was added and the mixture was treated under the conditions shown in Table 1. After a usual work-up, followed by silica gel column chromatography, pure coenzyme Q_9 hydroquinone diacetate **8** ($n=9$) was obtained; IR (neat) 2920, 1770, 1660, 1480, 1450, 1370, 1260, 1200, 1190, and 1100 cm^{-1}; NMR ($CDCl_3$) δ 5.14 (9H, m, 9-CH=), 3.85 (6H, s, $2CH_3O$), 3.22 (2H, d, $ArCH_2$), 2.35, 2.31 (each 3H, 2s, 2AcO), 2.02 (35H, bs, methylene chain and $ArCH_3$), 1.62 (30H, bs, side chain CH_3).

Found: C, 79.29; H, 10.29%. Calcd for $C_{58}H_{88}O_6$: C, 79.09; H, 10.06%.

To a suspension of 0.8 g of $LiAlH_4$ in 20 ml of dry ether, we added 1.4 g of **8** ($n=9$) in 25 ml of ether, after which the mixture was refluxed for 7 hr. The reaction mixture was then worked-up into ether and oxidized by aqueous $FeCl_3$ at room temperature for 3 hr. The crude product, obtained by the usual work-up, was chromatographed on silica gel; subsequent elution with *n*-hexane–diisopropyl ether (75 : 25) gave 0.9 g of coenzyme Q_9(**2**, $n=9$) (71%); mp 26—28 °C; IR (neat) 2920, 1650, 1605, 1450, 1380, 1285, 1265, 1205, 1150, and 1100 cm^{-1}; NMR ($CDCl_3$) δ 5.15 (8H, m, 8-CH=), 4.96 (1H, t, -CH=), 4.00 (6H, s, $2CH_3O$), 3.19(2H, d, $ArCH_2$), 2.00 (35H, bs, methylene chain and $ArCH_3$), 1.72 (s, *trans* olefinic CH_3 on C-3′), 1.68 (s, *cis* olefinic CH_3 on C-3′ and terminal *cis* CH_3), 1.60 (24H, olefinic CH_3); UV λ_{max} (*n*-hexane) 272 nm (ε 4200).

Found: C, 81.59; H, 10.64%. Calcd for $C_{54}H_{82}O_4$: C, 81.54; H, 10.39%.

Isolation of all-trans-Coenzyme Q_9. Silica gel (72 g) was used to fill up a column (20 mm × 450 mm) with *n*-hexane. After the adsorption of 700 mg of the coenzyme Q_9 (mp 31 °C, *trans* : *cis* = 71 : 29), it was eluted with *n*-hexane–diisopropyl ether (90 : 10). The eluted solution was divided into 13 fractions, each 30 ml. The first 3 fractions contained only the *cis* isomer (119 mg), while the 7—13 fractions (total, 369 mg) had a mp of 42—44 °C, showing no melting-point depression upon mixing with the natural coenzyme Q_9. The NMR spectrum also supported the all-*trans* structure. The *trans* recovery amounted to 76%.

Coenzyme Q_{10} (**2**, $n=10$). π-Decaparenylnickel bromide (**7**, $n=10$) was prepared from 10.0 g of decaprenyl bromide and 4.5 g of nickel carbonyl. After the solvent had been changed to 30 ml of HMPA, 2.0 g of **6** in 20 ml of HMPA was added at room temperature and the mixture was treated at 75 °C for 7 hr. After a usual work-up and silica gel column chromatography, eluting with *n*-hexane–diisopropyl ether (75 : 25), 2.2 g (40%) of **8** ($n=10$) were obtained; IR (neat) 2910, 1765, 1440, 1370, 1190, 1100, and 1020 cm^{-1}; NMR (CCl_4) δ 4.92 (10H, m, 10–CH=), 3.70 (6H, s, $2CH_3O$), 3.10 (2H, d, $ArCH_2$), 2.20 2.18 (each 3H, 2s, 2AcO), 1.95 (39H, bs, methylene chain and $ArCH_3$), 1.55 (33H, bs, side-chain CH_3).

Found: C, 79.54; H, 10.50%. Calcd for $C_{63}H_{96}O_6$: C, 79.70; H, 10.19%.

To a suspension of 0.5 g of $LiAlH_4$ in 20 ml of dry ether, we added 0.8 g of **8** ($n=10$) in 15 ml of ether; the mixture was then refluxed for 24 hr. After the decomposition of the excess $LiAlH_4$, the mixture was neutralized and extracted with ether. The extract was concentrated to a small volume and then oxidized by aqueous $FeCl_3$ at room temperature for 3 hr. The crude product, obtained by the usual work-up, was chromatographed on silica gel to give 0.5 g (69%) of coenzyme Q_{10} (**2**, $n=10$): mp 20—22 °C; IR (neat) 2900, 1650,1610, 1450, 1390, 1270, 1210, 1155, 1105, and 750 cm^{-1}; NMR (CCl_4) δ 4.92 (10H, m, 10–CH=), 3.84 (6H, s, $2CH_3O$), 3.05 (2H, d, $ArCH_2$), 1.92 (39H, bs, methylene chain and $ArCH_3$), 1.55 (33H, bs, side-chain CH_3); UV λ_{max} (*n*-hexane) 272 nm (ε 12300).

Found: C, 82.31; H, 10.69%. Calcd for $C_{59}H_{90}O_4$: C, 82.08; H, 10.51%.

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8) 1,1-Dimethyl-π-allynickel bromide (**7**, $n=1$) was generated by the reaction of 3,3-dimethyl-allyl bromide with excess nickel carbonyl. Other π-allylnickel bromides **7** were similarly prepared from geranyl bromide, phytyl bromide, solanesyl bromide[9] and decaprenyl bromide,[9] and used without further purification. See experimental section.

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12) Although naturally occurring coenzyme Q has all-*trans* configuration, the biochemical activity (restoration of succinoxidase activity of the 2′-*cis* isomer is as high as is *trans*-coenzyme Q. G. Lenaz, L. Szarkowska, K. Folkers, and Moore, *Biochim. Biophys. Res. Commun.*, **23**, 386 (1966).

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14) Regiospecific synthesis of three isomeric monomethyltocols was performed in high yields in these laboratories. Details will appear elsewhere.

15) As a result of comparison with the NMR spectrum of **6**, chemical shifts of protons in **8** ($n=1$) are as follows; (CCl_4) δ 4.83 (1H, t, –CH=), 3.68 (6H, s, $2CH_3O$), 3.08 (2H, d, CH_2), 2.21 (6H, s, 2AcO), 1.95 (3H, s, $ArCH_3$), 1.68, 1.65 (each 3H, 2s, side-chain methyls).

16) As a result of comparison with the NMR spectrum of **6**, chemical shifts of protons in **8** ($n=2$) are as follows; (CCl_4) δ 4.80 (2H, br.t, 2–CH=), 3.67 (6H, s, $2CH_3O$), 3.08 (2H, d, $ArCH_2$), 2.18, 2.16 (each 3H, 2s, 2AcO), 2.01—1.90 (7H, m, methylene chain and $ArCH_3$), 1.66—1.53 (9H, m, side-chain methyls).