New Synthesis of Vitamin K

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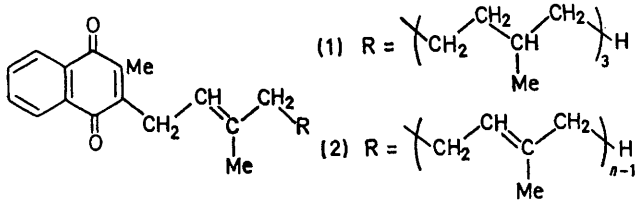
Summary A new and effective synthesis of vitamin K_1 (**1**) and $K_{2(5)}$, (**2**; $n = 1$), is described, using a π-allylic nickel(I) complex; solvent effects and the *trans*-stereoselectivity have been investigated.

VITAMIN K_1, (**1**) and $K_{2(5n)}$, (**2**), are quinones involved in the normal clotting of the blood, each containing an isoprenoid side chain. All the double bonds in the side chain have the *trans* configuration in the naturally occurring compounds.

The usual methods for introducing the side chain into the 3-position of menadione consist of acid-catalysed condensation of phytol or polyprenyl alcohols with 2-methyl-1,4-naphthohydroquinone or the 1-mono-ester derivatives in dioxan followed by oxidation with silver oxide.[1,2] These methods, however, yield many by-products which are difficult to remove.



We report here a new and effective synthesis of vitamin K_1 and $K_{2(5)}$ using π-allylic nickel(I) bromide (**5** or **6**) and derivatives of 3-bromo-2-methyl-1,4-naphthoquinone. Vitamin $K_{2(5)}$, considered as the most fundamental structure of both vitamin K_1 and $K_{2(5n)}$, was synthesized successfully in the following manner.

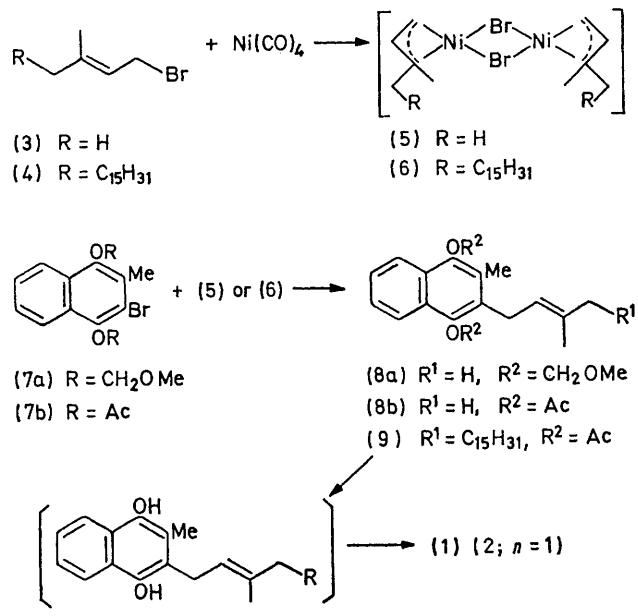
Treatment of (**3**) with excess of nickel carbonyl in benzene at 50 °C under nitrogen for 3 h gave the 1,1-dimethyl-π-allylnickel(I) bromide (**5**). After the removal of benzene under reduced pressure, the crude nickel complex (**5**) was dissolved in dimethylformamide and treated with (**7a**) or (**7b**) at 50—70 °C for several hours.

Dihydrovitamin $K_{2(5)}$ bis-methoxymethyl ether (**8a**) or the diacetate (**8b**) was obtained in good yield (*ca.* 75%).

Hydrolysis of (**8a**) and (**8b**) with acid or alkali, respectively, followed by ferric chloride oxidation gave vitamin $K_{2(5)}$ in quantitative yield.

We extended this reaction to the synthesis of vitamin K_1. Treatment of (**4**) with nickel carbonyl at 52 °C for 3 h in benzene under nitrogen gave the π-complex (**6**). After changing the solvent to hexamethylphosphoramide, (**7b**) was added and reacted for 5 h at 50 °C. The reaction mixture was chromatographed on silica gel to give (**9**) (85%).

Hydrolysis of (**9**) was carried out with alkali and ferric chloride oxidation afforded vitamin K_1 (**1**) in 93% yield after purification by silica gel chromatography.



The n.m.r. spectrum of (**1**) showed two singlet peaks at δ 1·72 and 1·62, assignable to the *trans* and *cis* olefinic methyl groups, respectively, attached to the double bond in the side chain. The ratio of *trans* to *cis* isomers was determined quantitatively by calculation of the area of these two peaks.

To obtain a higher yield and higher *trans* stereoselectivity, solvent effects and temperature dependence of this reaction were investigated. It was found that a strongly co-ordinating solvent gives the product in excellent yield, but with poor stereoselectivity, *i.e.*, in hexamethylphosphoramide at 50 °C, yield 85%, *trans*:*cis* = 51:49. On the other hand, a less co-ordinating solvent shows good stereoselectivity, *i.e.*, in *N*-methylpyrrolidone at 30 °C, yield = 44% *trans*:*cis* = 80:20.

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[1] L. F. Fieser, *J. Amer. Chem. Soc.*, 1939, **61**, 3467.
[2] R. Hirschmann, R. Miller, and N. L. Wendler, *J. Amer. Chem. Soc.*, 1954, **76**, 4592.