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Recent Advances in the Synthesis of K-Vitamins**

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Dedicated to Professor George Büchi on the occasion of his 65th birthday

The term «Vitamin K» is a collective name and embraces a whole series of 2-methyl-1,4-naphthoquinone derivatives which play a decisive part in the control of blood clotting. The most important representative, vitamin K_1 (phylloquinone), has a phytyl group as substituent in the 3-position. On the other hand, K_2-vitamins (menaquinones) possess polyunsaturated, isoprenoid side-chains of varying length in this position. – The first technical syntheses of vitamin K_1 were accomplished by Isler (F. Hoffmann-La Roche & Co. Ltd.) and Hirschmann (Merck & Co. INC., Research Laboratories) more than thirty years ago. In analogy to Fieser's early work, a protected menadiol is reacted with isophytol or phytol in a Friedel-Crafts type alkylation and vitamin K_1 is obtained as a mixture of E- and Z-isomers. – However, biological investigations on vitamin K deficient chicks have clearly indicated that the Z-isomer has virtually no vitamin K activity. In addition, the large number of reaction steps make these syntheses rather unattractive in terms of economy. Therefore, the design of a highly stereoselective and economical synthesis of (E)-vitamin K_1 has received increasing attention during the last decade; in particular, methodology had to be developed for an efficient coupling of the (E)-phytyl side-chain with the naphthoquinone ring with full retention of the trans double bond.

1. Introduction

1.1. History [1]

In 1929, Professor *Henrik Dam* [2] in Copenhagen observed in connection with studies of cholesterol metabolism that chicks kept on diets that had been extracted with unpolar solvents, exhibited hemorrhages under the skin, in muscles and in other tissues, and delayed blood coagulation (Fig. 1).

Studies in a number of laboratories [3] soon demonstrated that this disease could not be cured by the administration of any of the known vitamins or other known physiologically active lipids including cholesterol. In 1935, *Dam* [4] proposed that this antihemorrhagic factor was a new fat-soluble vitamin, which he called vitamin K. The letter K was suggested as an abbreviation of the word «Koagulation» in the German and Scandinavian spelling.

1.2. First Isolation and Elucidation of Structures

The discovery of a new, still unknown vitamin was followed by a report [5] describing the success obtained in curing the hemorrhagic disease with ether extracts of alfalfa. Subsequently, *Dam*, *Karrer* and coworkers [6] and *Doisy* et al. [7] succeeded in isolating from the same source this deficiency factor, called vitamin K_1 (phylloquinone) in pure form as a yellow oil. Further studies soon established the constitution of this vitamin [8].

From knowledge of the structural formula, five different groups working with *Doisy* [8], *Almquist* [9], and *Fieser* [10] in America and *Karrer* [11] and *Isler* [12] in Switzerland succeeded in synthesizing this vitamin. The stereochemistry was not elucidated until much later by *Mayer*, *von Planta* and *Jackman* et al. [13] (Fig. 2).

Phytol, the isoprenoid constituent of vitamin K_1, was first prepared in pure form in 1907 by *Willstätter* et al. [14] by the saponification of chlorophyll. The absolute configuration was elucidated by *Weedon* [15] and *Djerassi* [16].

In 1939, *Doisy* and his group [17] isolated from putrefied fish meal a crystalline compound with a melting point of 54 °C and similar biological properties to vitamin K_1. Subsequent chemical studies by *Isler* and co-workers [18] demonstrated that this crystalline K-vitamin contained an unsaturated side chain at the 3-position of the naphthoquinone ring, consisting of seven isoprene units. It was subsequently named vitamin $K_{2(35)}$ or menaquinone-7 (35 relates to the number carbon atoms, 7 to the number of isoprene units in the side chain [19]).

1.3. Occurrence

Vitamin K_1 occurs mainly in the photosynthetic tissues of higher plants and in many green, brown, red, and blue-green algae [20]. Few data are available on the distribution of phylloquinone and the methods used for the assay have not always been very reliable. In addition, phylloquinone is apparently difficult to extract and the amounts present are relatively small. In general, green or leafy vegetables are the best source of the vitamin, the content varying from about 10 to 100 µg/100 g fresh food [21].

K_2-vitamins (menaquinones) possessing side chains varying in length from C_5 to C_{65}

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Fig 1. Vitamin K-deficiency symptoms in chicks (photograph by Dr. Marcel Huber).

aided by calcium ions. Prothrombin binds Ca^{II} ions, an affinity that drops drastically if vitamin K_1 is absent. This intriguing observation began to be explained when it was discovered that the first 40 N-terminal residues of prothrombin include 9 γ-carboxy glutamate residues which serve as bidentate ligands for Ca^{II} ions.

The reduced 1,4-dihydro form of vitamin K_1 is required for carboxylation of the glutamic acid residues of preprothrombin to prothrombin, a reaction that also requires molecular oxygen.

In 1970, a metabolite of vitamin K_1 was discovered in the rat liver by *Matschiner* et al.[25]: the 2,3-epoxide of vitamin K_1 which is normally present to an extent of about 10%. They postulated that the formation of the epoxide is an obligatory step in the action of the vitamin in promoting prothrombin synthesis[26]. The relationship between this epoxidase and the vitamin K_1-dependent carboxylase has now been studied in more detail[27] (Fig. 3).

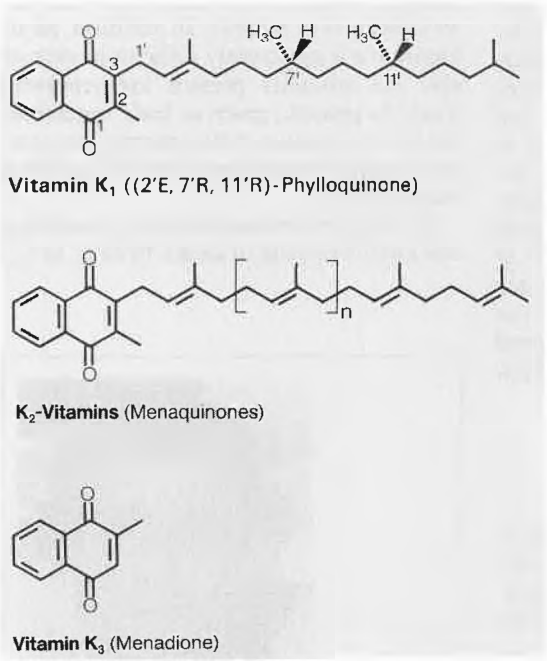


Fig. 2. Structure of vitamins K_1, K_2, and K_3.

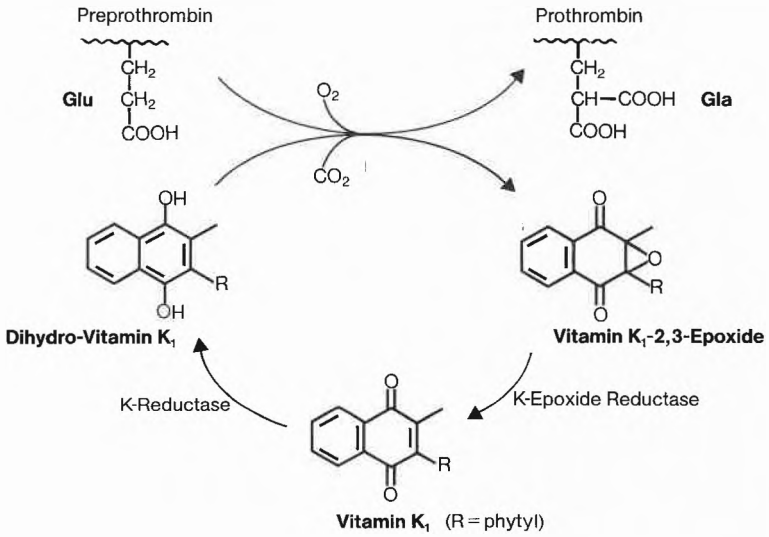


Fig. 3. Vitamin K epoxide cycle[23]. Abbreviations: Glu = glutamic acid residue, Gla = γ-carboxy glutamic acid residue, R = phytyl residue.

have been isolated from various bacteria[22]. The most common representatives are vitamin $K_{2(35)}$, $K_{2(40)}$, and $K_{2(45)}$. The concentration of these vitamins in bacteria is small, being in the range 0.3–4 μmol/g dry weight[22].

Vitamin K_3 (menadione) is not naturally occurring.

2. Biology

2.1. Vitamin K and Blood Coagulation

The relationship between vitamin K-deficiency, decreased blood clotting ability, and plasma hypoprothrombinaemia was first observed by *Dam*[1,2] in the 1930's. This association with the blood clotting cascade is the only certain, but highly significant function of vitamin K_1[23]. Whether this vitamin has other functions in the human body is still uncertain. Involvement of vitamin K_1 in oxidative phosphorylation processes of cellular respiration was proposed by *Martius*[24] in the 1950's.

Several proteins of the blood clotting cascade are known to be affected by vitamin K_1: Factor II (prothrombin), Factor VII, Factor IX (Christmas factor), and Factor X (Stuart factor). In clot formation, prothrombin molecules form aggregates with phospholipids, a process

The metabolism of vitamin K_1 thus includes cyclic conversion to the hydroquinone, oxidation to the epoxide, and its reduction back to vitamin K_1.

Recently, it has been demonstrated that the vitamin K action is not restricted to the coagulation system, but that the vitamin plays a role in the synthesis of numerous proteins in man as well as in other organisms[28]. Furthermore, vitamin K-dependent proteins are involved in the transport of calcium from the egg shell to chicken embryos[29] and in the deposition of calcium in the bone of the human foetus[30].

Vitamin K_1 and related compounds (including (*Z*)-isomers) may also act as antibiotics, antiinflammatories or analge-

sics[31]. The mechanism of these activities has not yet been elucidated, but it appears to be different from that involving γ-carboxyglutamic acid.

2.2. Metabolism

Vitamin K_1 is absorbed from the intestine into the lymphatic system[32]. The absorption of nonpolar lipids such as vitamin K_1 requires the presence of bile and pancreatic juice. *Wiss* and *Gloor*[33] could show that phylloquinone administered to rats was specifically concentrated and retained in the liver.

Animals cannot synthesize the naphthoquinone ring, and this portion of the vitamin must be furnished in the diet. It appears that bacterial synthesis of K_2-vitamins usually does not involve free menadione as aromatic intermediate, but rather 1,4-dihydroxy-2-naphtoic acid, which is prenylated, decarboxylated, and methylated to form menaquinones (cf. section 2.5). The transformation of ingested menadione (vitamin K_3) to vitamin $K_{2(20)}$ in animals was first observed by *Martius* and *Esser*[34], and *Martius*[35] subsequently presented evidence that administered phylloquinone or other prenylated forms of menadione could be converted by a dealkylation/realkylation sequence to menaquinone-4.

Early studies[36] of the metabolism of phylloquinone and the menaquinones demonstrated that the major excretion route of intravenously administered radioactive vitamin K_1 was the faeces. In 1966, *Wiss* and *Gloor*[33, 37] observed that the side chain of phylloquinone and menaquinone-4 were oxidatively degraded by the rat to seven carbon atoms, yielding a carboxylic acid group at the end that cyclized to form a γ-lactone. This lactone was excreted in the urine, presumably as a glucuronic acid conjugate[38].

2.3. Biological Activity

2.3.1. Methods

The classic method for the biological testing of K-active substances consists in measuring the change in the blood clotting time after administration to chicks with a vitamin K deficiency.

In this curative method[39, 40], which was introduced by *Dam*[41], the concentration of the test preparations for administration is varied until the blood clotting time is consistent with that obtained for the standard quantity of vitamin K_1. The activity factor can then be calculated. The chicks used in this test are fed with a mixed feed devoid of vitamin K until the blood clotting time, which is normally approximately 50–60 s, has increased to more than 180 s; this generally takes a few weeks. When this has been done, the preparation to be tested is dissolved in arachis oil and administered orally. After approximately 20 h, the clotting time is measured and compared with the standard.

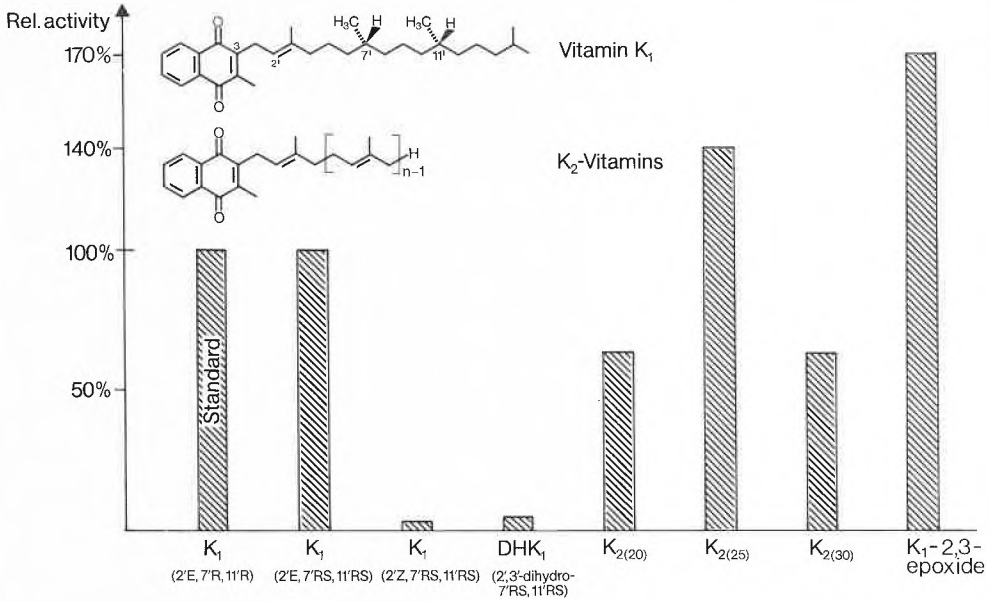


Fig. 4. Comparison of the action of various K-vitamins and analogs as determined in curative prothrombin time tests in vitamin K-deficient chicks.

A second method involves the antidotal effect of vitamin K on anticoagulants in rats, and the first quantitative results were published in 1958[42].

2.3.2. Activity of Different K-Vitamins

Early in the history of the discovery of this vitamin, it became apparent that vitamin K_1 was not the only biologically active form. *Doisy* and co-workers[17] isolated in 1939 a crystalline K_2-vitamin, which showed similar biological properties. Equal activities of vitamin K_1 and menadione (vitamin K_3) on a molar basis was reported in 1953[43] using the curative assay.

However, menadione and its water-soluble analogs (see section 2.7) are much less active than vitamin K_1 in normalizing the prolonged blood clotting times caused by anticoagulants[39].

In an extensive study, *Isler* et al.[44] examined a great number of vitamin K_1 and K_2 derivatives for their antidotal action on different anticoagulants. It was clearly established that a side chain of minimum length is necessary for this activity.

A number of isoprenologs in the vitamin K_1 and K_2 series were tested in vitamin K-deficient chicks[39, 40, 45, 46]. Phylloquinone analogs having unbranched or less branched side chains than vitamin K_1 proved to be less active. The natural (2'*E*,7'*R*,11'*R*)-vitamin K_1 served as a standard, accepted as having a relative activity of 100% (Fig. 4). The optically inactive (2'*E*,7'*RS*,11'*RS*)-vitamin K_1, which is obtained by total synthesis, also has about the same activity. A very surprising fact is that the corresponding (2'*Z*,7'*RS*,11'*RS*)-vitamin K_1 is practically inactive[31, 47]. In addition, the activity disappears almost completely when the trisubstituted double bond is hydrogenated[40].

As regards the K_2-vitamins, there is a marked dependence on the length of the side-chain. A special case here is vitamin $K_{2(25)}$, which, on a weight basis, achieves an activity 1.4 times greater than that of the standard[46]. All other K_2 compounds investigated are less active and the activity drops slightly with increasing side-chain length.

As already found in 1940[48], phylloquinone-2,3-epoxide, which is a metabolite of vitamin K_1, has a high vitamin K-activity. Recently, *Weiser* and *Kormann*[40] demonstrated very clearly that the 2,3-epoxide of phylloquinone is 1.7 times more active than vitamin K_1, using the curative prothrombin time assay.

2.4. Antagonists

At the beginning of this century, a hemorrhagic disease in cattle was observed in the U.S.A., which was found to be caused by feeding the animals with spoiled sweet clover hay[49]. Subsequently, the toxic principle was isolated by *Campbell* and *Link*[50, 51] and was shown to be 3,3'-methylenebis(4-hydroxycoumarin), commonly called dicoumarol (Fig. 5). Since then, many anticoagulants based on the 4-hydroxycoumarin structure have been developed, and the relation between their structures and activity has been studied[52]. The most successful of these, which are clinically used for long-term lowering of the vitamin K-dependent clotting factors, are Warfarin and Marcoumar.

In the course of a series of investigations into the structural requirements of vitamin K-activity, it was furthermore found[53] that replacement of the 2-methyl group of phylloquinone by a chlorine atom resulted in a compound that was a potent antagonist of vitamin K_1.

Although various theories about the active site of the physiological action of the

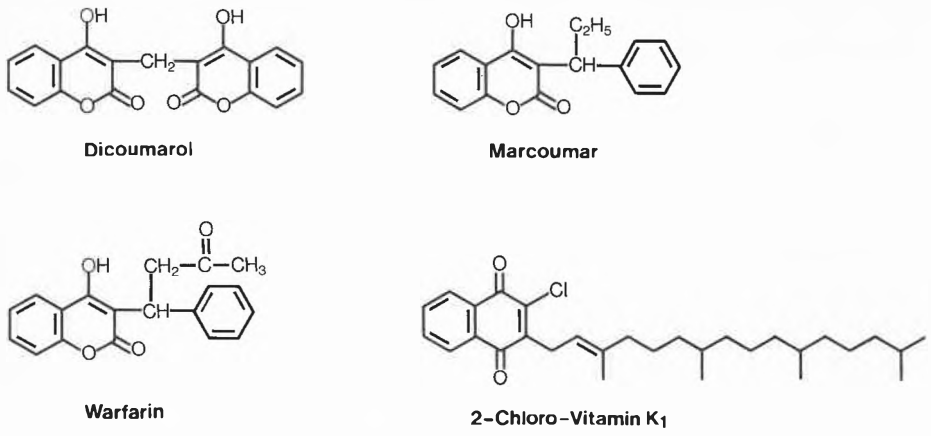


Fig. 5. Antagonists of vitamin K-activity.

4-hydroxycoumarins have been proposed[54], it is now believed that the epoxide reductase in the vitamin K epoxide cycle (see section 2.1; Fig. 3) is inhibited by these anticoagulants[55].

2.5 Biosynthesis

The discovery by *Cox, Gibson* and *Goodwin* et al. in the mid sixties, that labeled [^{14}C]shikimic acid was incorporated by *E. coli* into menaquinones[56] and by maize shoots into phylloquinone[57], prompted a long discussion about the biogenetic pathway of these vitamins. In recent years, a good deal of information has been obtained using isotopically labeled precursors and it has been shown that the K-vitamins are formed by the shikimate pathway[58] (Fig. 6).

As in other biogenetic routes to aromatic compounds, chorismic acid functions as the branch point[59] and is converted with α-ketoglutaric acid in the presence of thiamine pyrophosphate (TPP) as cofactor to the aromatic intermediate *o*-succinylbenzoic acid (OSB). A succinic semialdehyde-TPP anion is presumably formed as an intermediate[60]. The formation of 1,4-dihydroxy-2-naphthoic acid (DHNA) from *o*-succinylbenzoic acid (OSB) is CoA- and ATP-dependent and requires two enzyme systems: The OSB-CoA synthetase and DHNA synthase[61]. In a subsequent prenylation reaction followed by decarboxylation, desmethyl menaquinones are formed. Recently, it was shown that there exists an enzyme in spinach chloroplasts, which reduces geranylgeranyl pyrophosphate to phytyl pyrophosphate[62], which is reacted afterwards with 1,4-dihydroxy-2-naphthoic acid[63]. These enzymes are involved in the biosynthesis of vitamin K_1. In the last step, the missing methyl group at the aromatic ring system is introduced by (*S*)-adenosyl-L-methionin (SAM) to yield, after oxidation, menaquinones and phylloquinone, respectively[64].

2.6. Nutritional Requirements

Knowledge about man's dietary sources and requirements of K-vitamins is both meagre and imprecise. Undoubtly, a major reason for this is the additional synthesis of menaquinones by the gastrointestinal microflora of humans and of most animals, supplementing the food and feed supply, respectively.

The low requirement and the fact that vitamin K_1 is found in most diets make a simple dietary deficiency in man unlikely. The daily need for vitamin K (K_1 and K_2) is considerably less than 1 mg and, on the basis of present evidence, it is probably 20–100 μg per day in adults and less than 10 μg in infants[1a].

Detailed discussions of the vitamin K requirements of various species are available in articles by *Scott*[65] and *Almquist*[66]. The data indicate that the requirement for most animals falls in the range of 2–200 μg vitamin K per kilogram body weight per day.

2.7. Commercial Forms and Applications

The major use of vitamin K in the animal industry is in poultry farming. Since chicks are very sensitive to vitamin K

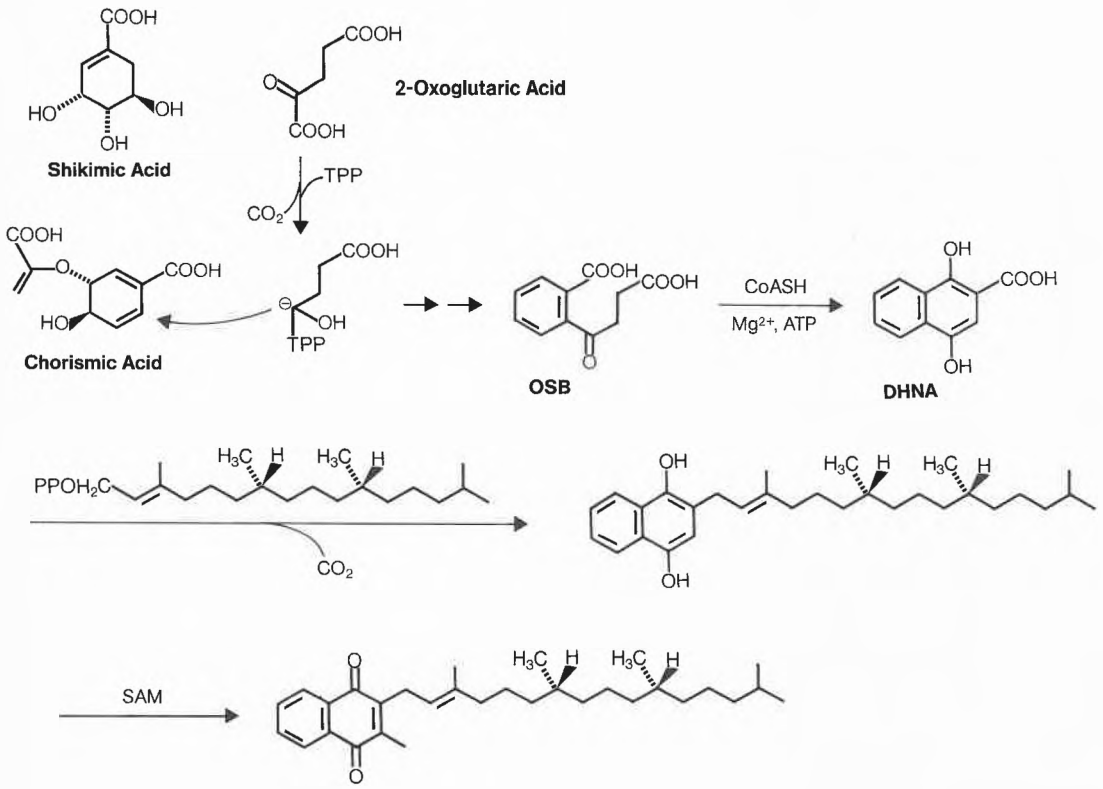


Fig. 6. Biosynthesis of K-vitamins (vitamin K_1). TPP: thiamine pyrophosphate, OSB: o-succinylbenzoic acid, DHNA: 1,4-dihydroxy-2-naphthoic acid, SAM: (S)-adenosyl-L-methionin.

restriction and since the site of the intestinal vitamin K synthesis is too close to the distal end of the tract to permit full absorption, supplementation is required to ensure an adequate supply of this vitamin.

Different forms of menadione (vitamin K_3) have been used for this purpose[67] (Fig. 7).

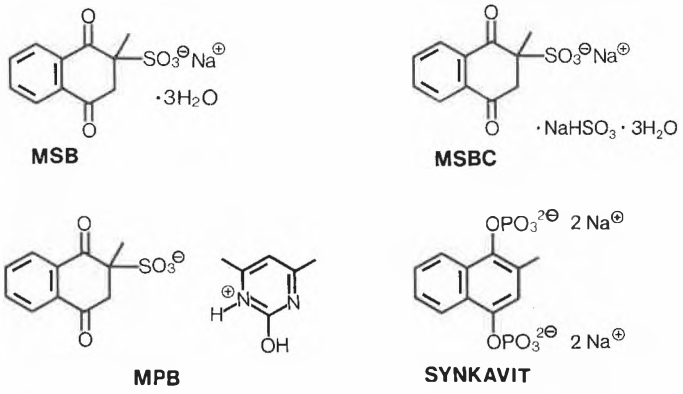


Fig. 7. Some water-soluble commercial forms of menadione (vitamin K_3)

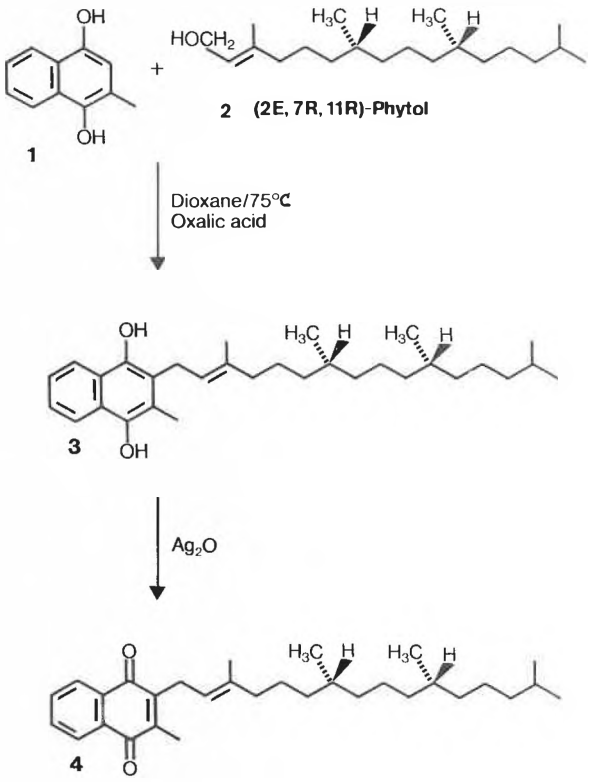


Fig. 8. Fieser's synthesis of vitamin K_1.

Menadione itself launches high biological activity in a deficient chick, but it has been recognized to be unstable as well as irritating to the skin. It has been replaced almost completely by less toxic water-soluble derivatives, e.g. menadione sodium bisulfite (MSB), menadione sodium bisulfite complex (MSBC), or menadione pyrimidinol bisulfite (MPB), which are believed to be alkylated in the liver to yield menaquinone-4 (see section 2.2).

The clinical use of vitamin K is largely limited to two forms, a water-soluble form of menadione, menadione tetrasodium bisphosphate (SYNKAVIT) and vitamin K_1. But the margin of safety is certainly greatest with vitamin K_1 and this form is considered the compound of choice. Vitamin K_1 is mainly applied as aqueous emulsions. It can be given orally, if bile is present in the intestine to promote absorption, or parenterally.

The primary therapeutic use of vitamin K_1 is the restoration of the clotting mechanism after interference by anticoagulants (see section 2.4).

Vitamin K_1 prophylaxis is often undertaken for the newborn. At birth, the gastrointestinal tract is practically sterile, lacking a bacterial flora which could synthesize menaquinones. In addition, liver stores appear to be poor because the passage of vitamin K_1 across the placenta from mother to foetus is limited. Moreover, human milk contains only little vitamin K.

Vitamin K_1 is also used in human medicine during operations in which bleeding is expected to be a problem, for example gallblader surgery.

3. Early Syntheses

3.1. *Vitamin K_1*

The first syntheses of vitamin K_1 in 1939 started from 2-methyl-1,4-naphthoquinone or its hydroquinone as the ring component and from natural phytol or a corresponding derivative[8–12] (Fig. 8).

Fieser et al.[10], whose synthesis long remained the preferred method, condensed menadiol (**1**) with less than the equimolar quantity of natural phytol (**2**) in dioxane at 75°C, using anhydrous oxalic acid as a catalyst. The excess menadiol (**1**) was subsequently extracted with dilute alkali and the remaining phytyl-substituted hydroquinone **3** was precipitated with petroleum ether. Oxidation of this waxy residue with silver oxide gave vitamin K_1 (**4**) in ca. 30 % yield (based on **2**).

This synthesis can be described in a very simple and elegant way. It is in no way without its problems, however, as is suggested by the low yield. The great problem, which has not been completely solved so far, is the Friedel-Crafts alkylation, which takes place non-selectively in respect of position 2 and 3 and with partial isomerization at the *E* double bond in the phytol. In addition to the desired (*E*)-alkylation product **3**, an approximately equal proportion of the isomeric product **5** is formed (Fig. 9). Moreover, the acid alkylation conditions, in combination with the elevated temperature, cause a ca. 5–10% isomerization of the trisubstituted double bond in the side-chain. The (*Z*)-vitamin K_1-hydroquinone **6** formed in this process gives (*Z*)-vitamin K_1 after oxidation, which exhibits practically no vitamin K action, i.e. it is a wasted substance, and cannot easily be separated from the (*E*)-vitamin K_1. Also formed under these conditions are phyllochromanol **7,** which is a cyclization product, and phytadienes of type **8,** which are derived from phytol (**2**) by the elimination of water.

A breakthrough in terms of a practicable industrial synthesis came in the early fifties (Fig. 10). Almost simultaneously, *Isler* et al.[68] at Hoffmann-La Roche and *Hirschmann* et al.[69] at Merck & Co. found that monoacylated menadiols, for example the monobenzoate **11,** can advantageously be used in the alkylation step **11** → **13.** This suppresses the undesired alkylation in the 2-position of the menadiol. It was furthermore found that boron trifluoride etherate is a much better catalyst than oxalic acid and that the natural, optically active (2*E*,7*R*,11*R*)-phytol (**2**) can be replaced with the optically inactive (3*RS*,7*RS*,11*RS*)-isophytol (**12**), which is readily obtainable by synthesis. Later biological investigations showed that the biological activity of the final product is not reduced by this loss of optical activity (see section 2.3; Fig. 4).

The monobenzoate **11** can be prepared in three reaction steps starting from menadione (**9**): catalytic reduction of **9,** fol-

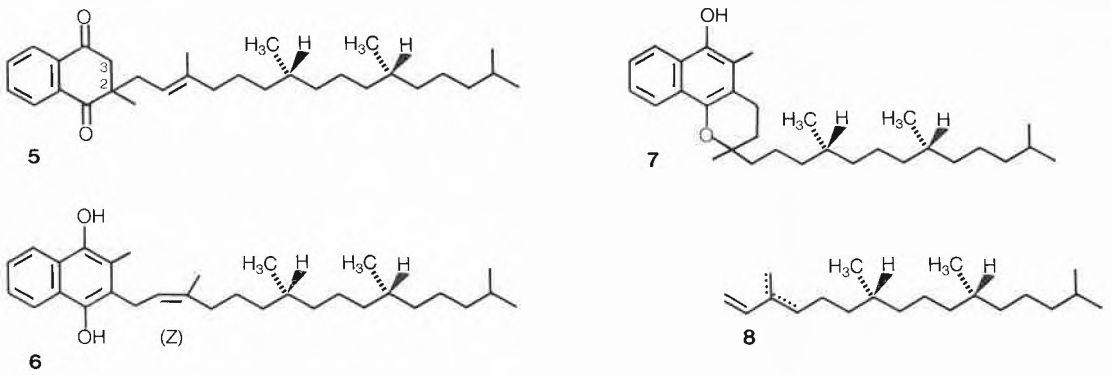


*Fig. 9. Some by-products of the alkylation of menadiol (**1**) with natural phytol (**2**).*

lowed by esterification with benzoyl chloride, gives the dibenzoate **10,** which is converted to the crystalline monobenzoate **11** by partial saponification. According to *Isler* and *Lindlar* [68], **11** is then condensed with less than the stoichiometric quantity of isophytol (**12**) with a $BF_3 \cdot OEt_2$ catalyst to give dihydrovitamin K_1 monobenzoate **13.** The unreacted menadiol monobenzoate **11** is precipitated with petroleum ether. The condensation product **13** is crystallized from a methanol/ethanol mixture, saponified with KOH, and oxidized with air to the corresponding quinone. This method produces vitamin K_1 (**14**) in ca. 60–70% yield (based on **12**).

Since the tertiary alcohol **12** is used as the alkylating agent in this synthesis in place of the natural phytol **2** of the (*E*)-configuration, the alkylation product **13** and hence also the final product **14** are obtained as (*E*/*Z*)-mixtures, although this was not discovered until the early sixties with the advent of the first NMR spectra [13].

As the product **13** is crystalline, the (*E*)-form can be obtained virtually pure by repeated recrystallization.

Synthetic vitamin K_1 was introduced in 1953 by Roche under the brand name Konakion; it is marketed as drops or as aqueous emulsions in ampoules or as chewable tablets.

The starting material used for the synthesis of isophytol (**12**) is 3-methylbuten-3-ol (**15**), which can be obtained from acetylene and acetone (Fig. 11). Firstly, the length of the molecule is increased by three carbon atoms, which can be carried out by

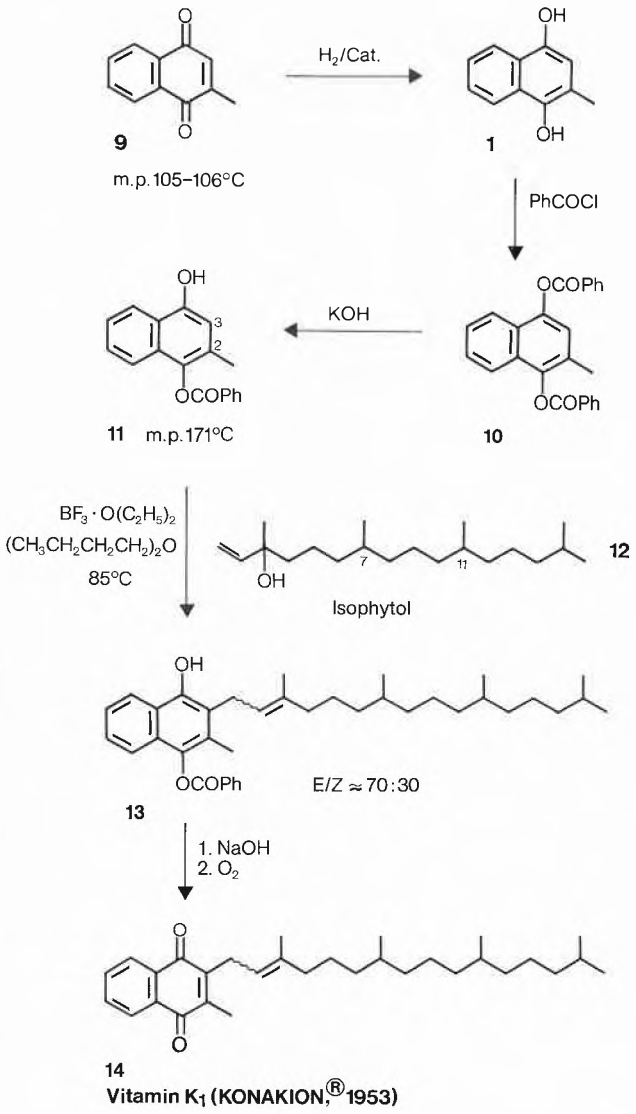


Fig. 10. First industrial synthesis of vitamin K_1.

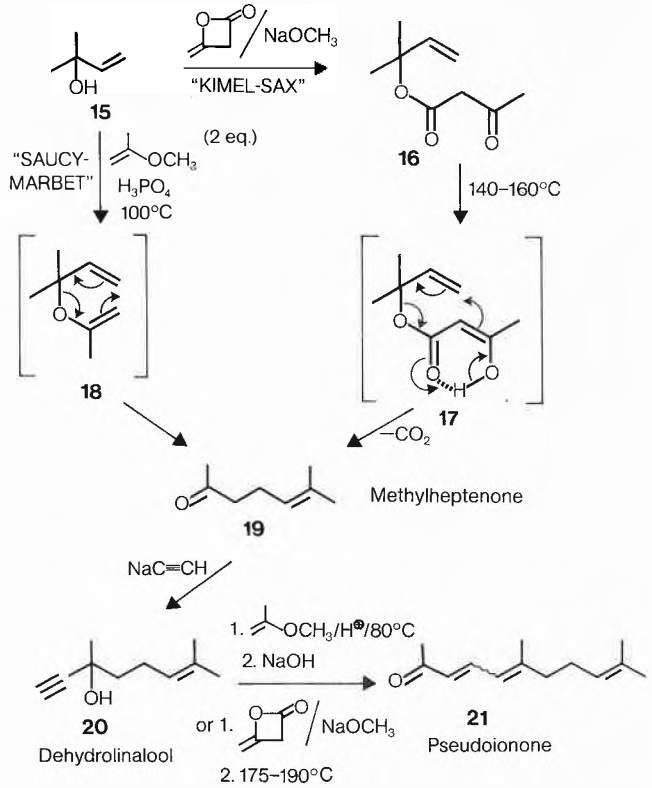


*Fig. 11. Synthesis of pseudoionone (**21**).*

a variety of methods[70]. The method of *Kimel* and *Sax* [71] is based on work done by *Cope* [72]. Here, **15** is reacted with diketen in the presence of catalytic quantities of sodium methanolate to give the acetoacetate **16,** which, after a Claisen-Cope rearrangement and decarboxylation, gives methylheptenone **19**.

A second variant, which is preparatively even simpler and higher yielding, was developed by *Saucy* and *Marbet* [73] in the sixties: the reaction of **15** with 2 equivalents of isopropenyl methyl ether in the presence of phosphoric acid at 100 °C in a pressure vessel gives methylheptenone **19** in more than 90% yield. Subsequent lengthening of the molecule with monosodium acetylide in liquid ammonia gives dehydrolinalool (**20**). In the same way as the vinyl alcohol **15,** this propargyl alcohol **20** can be lengthened with isopropenyl methyl ether or diketen to give pseudoionone (**21**), which is also an important structural unit for vitamin A and ß-carotene.

Catalytic hydrogenation of the double bonds of pseudoionone (**21**), followed by a repeated application of the previous reaction sequence once again, gives, via tetrahydronerolidol (**22**), the ketone **23** and then isophytol (**12**) (Fig. 12).

Pure (*E*)- and (*Z*)-vitamin K_1 (**24** and **25**) was first synthesized in the sixties using (*E*)- and (*Z*)-phytol (**30** and **31**), respectively, as alkylating agents[13b]. These two alcohols needed for these syntheses were synthesized from ketone **26**, a precursor of isophytol (**12**) (Fig. 13).

Condensation of **26** with triethyl phosphonoacetate (**27**) by *Horner*'s method[74] gave an (*E*/*Z*)-mixture of the ethyl esters **28/29** in a ratio of 63:37, which could be separated into the two pure components by preparative gas chromatography or by fractional distillation. Reduction with diisobutylaluminium hydride (DIBAH) gave both the (*E*)- and (*Z*)-phytols **30** and **31** in virtually pure form.

Menadiol monobenzoate **11** was then alkylated with these two allyl alcohols **30** and **31** under the usual conditions in the presence of a Lewis acid (Fig. 14). It was thus possible for the first time to show, by means of TLC and ^{1}H-NMR spectroscopy, that the trisubstituted double bond in the phytol partially isomerized under these Friedel-Crafts conditions. The isomerization was approximately 5–10% in the case of the (*E*)-phytol (**30**) and more than 30% in the case of the (*Z*)-phytol (**31**). However, the pure (*E*)- and (*Z*)-alkylation products **32b** and **33b** could be obtained pure by chromatography and recrystallization. Saponification of the benzoate protecting group and subsequent oxidation gave the compounds **24** and **25,** respectively, with a purity of more than 98%.

The first total synthesis of enantiomerically pure (2′*E*,7′*R*,11′*R*)-vitamin K_1 has been achieved[75] few years ago (Fig. 15).

Enantioselective reduction of the double bond in **34** by fermentation with compressed yeast, in which the acetal group is also reduced to the corresponding alcohol, probably via aldehyde, gave the optically pure (*S*)-β-methyl-butyrolactone **35** after working-up under acid conditions, and this was opened with HBr in ethanol to give the γ-bromoester **36.** Reduction of the ester group with DIBAH gave the corresponding bromoalcohol, which was protected with dihydropyran and then reacted with magnesium to give the Grignard compound **37.**

By means of a Schlosser coupling[76], the compound **37** was then lengthened by a C_5-unit with the tosylate **38** and gave the compound **39** after acid hydrolysis and reaction with tosyl chloride. Further lengthening of **39** with the C_5-Grignard reagent **37** gave the optically active (3*R*,7*R*)-hexahydrofarnesol (**40**). Bromination of **40** with NBS/triphenylphosphane (NBS = *N*-bromosuccinimide) and subsequent reaction with magnesium led to the Grignard compound **41,** which was coupled with the allylic (*E*)-configurated acetate **42** in the presence of a lithium tetrachlorocuprate catalyst to give the optically active (2*E*,7*R*,11*R*)-phytol (**2**)[77] (Fig. 16).

This substitution proceeds with complete retention of the *E*-geometry of the

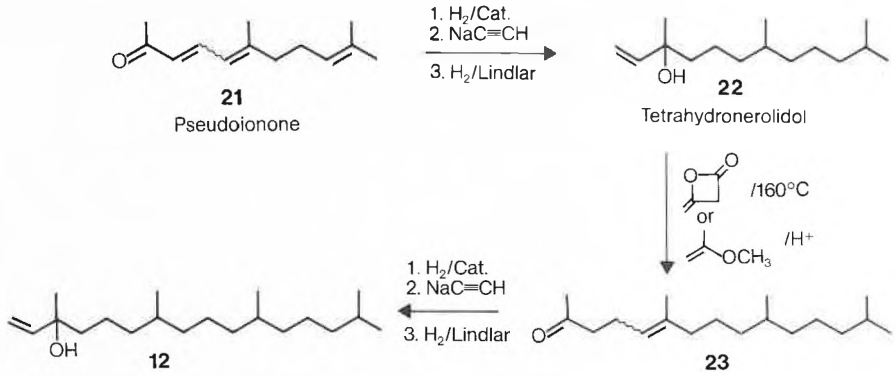


Fig. 12. Synthesis of isophytol (**12***).*

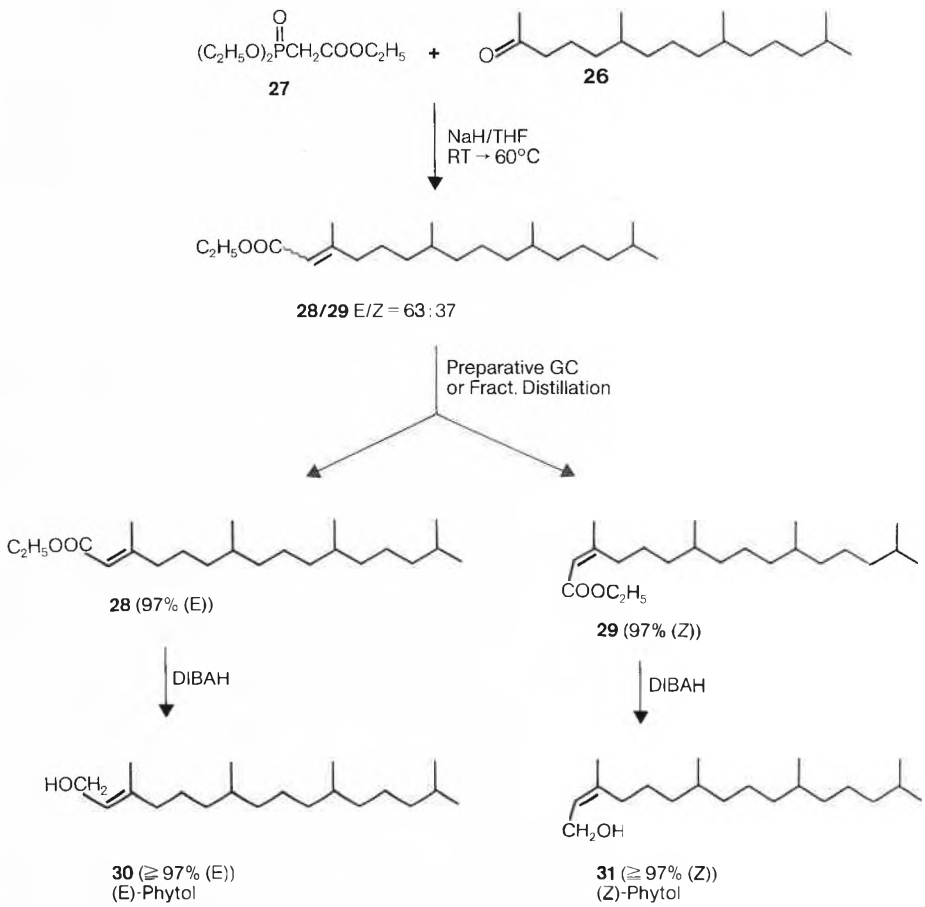


Fig. 13. Synthesis of (E)- and (Z)-phytol (**30** *and* **31***).*

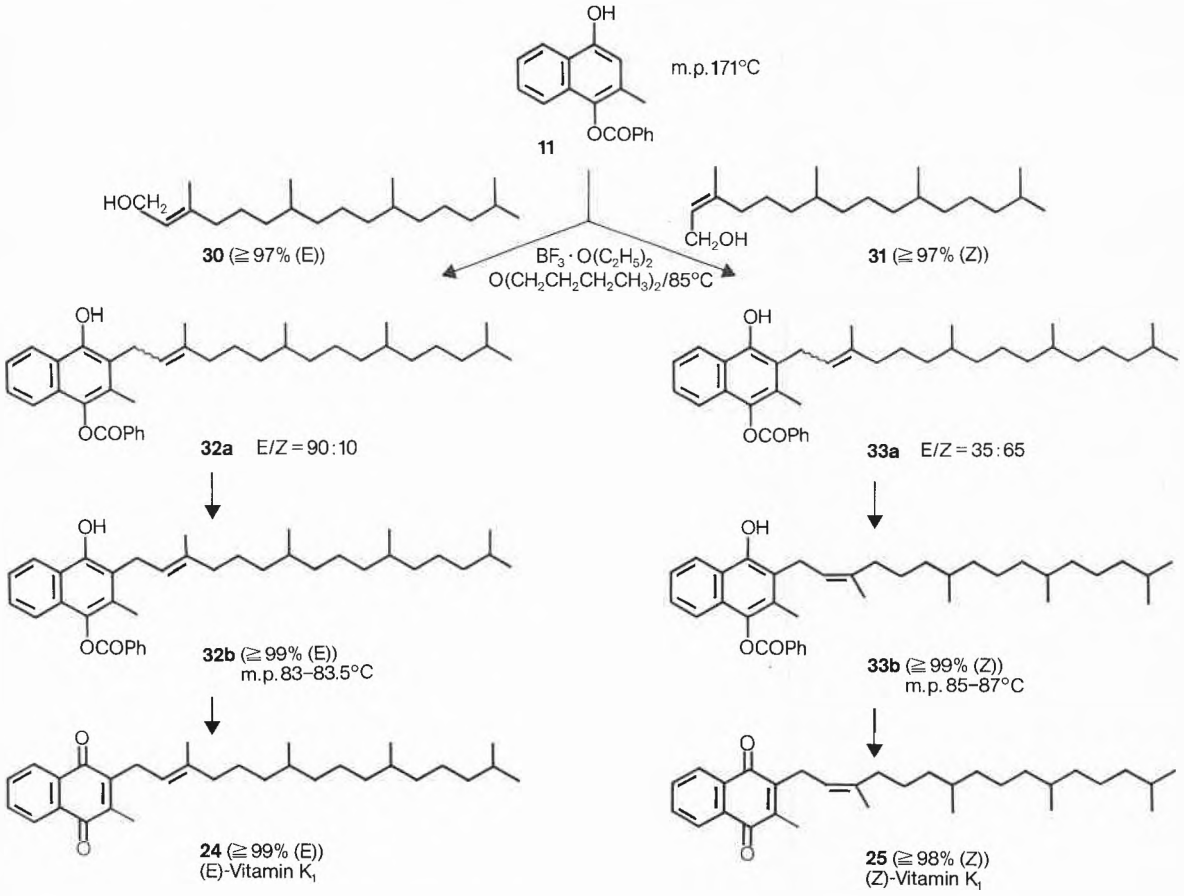


*Fig. 14. Synthesis of (E)- and (Z)-vitamin K_1 (**24** and **25**).*

double bond in the C_5 structural unit **42**.

The pure, optically active (*E*)-phytol (**2**) obtained was then reacted with the monobenzoate **11** in the usual manner and converted to (2′*E*,7′*R*,11′*R*)-phylloquinone (**4**).

3.2. K_2-Vitamins

Vitamins of the K_2 series, i.e. 2-methyl-1,4-naphthoquinones substituted in the 3-position by an unsaturated polyisoprenoid side-chain, were first synthesized by *Isler* et al. in 1958 [78] (Fig. 17b).

Analogously to the first syntheses of vitamin K_1, unprotected menadiol (**1**) was alkylated with a primary or tertiary allyl alcohol of the type **42** or **43** in the presence of a $BF_3/ZnCl_2$ catalyst, in dioxane at 50°C, to give **44**, which was then oxidized. For reasons already known, however, the yield of K_2-vitamins **45** was relatively low (formation of (*E*/*Z*)-isomers in the Friedel-Crafts reaction, undesired alkylation in the 2-position). In addition, another secondary reaction occurred here: cyclization of the unsaturated side-chains under the acid alkylation conditions. The isolation of these vitamins after the reaction did not present any difficulties, however, because the K_2-vitamins obtained – except for vitamin $K_{2(5)}$ – are crystalline compounds with melting points around 35–60 °C (Fig. 17a).

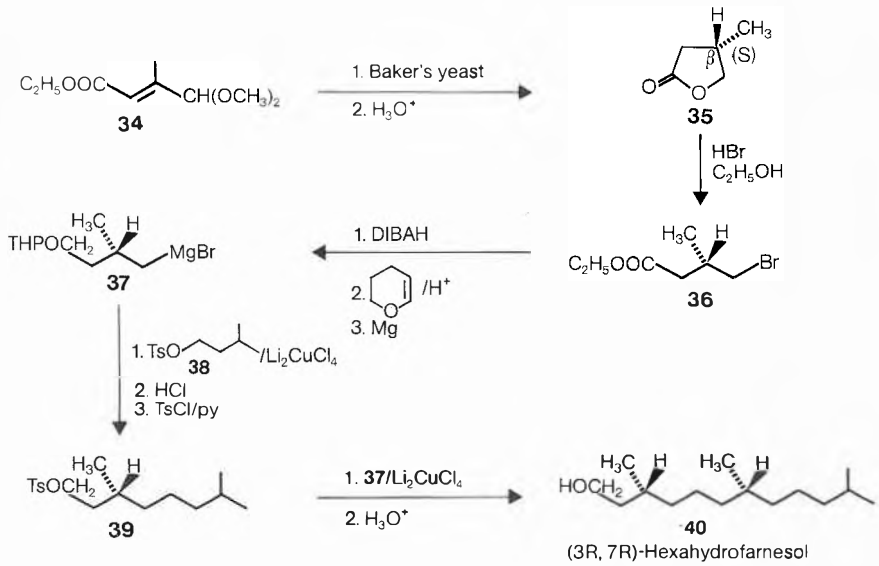


*Fig. 15. Synthesis of (3R, 7R)-hexahydrofarnesol (**40**).*

Fig. 17a. Photograph of vitamin $K_{2(25)}$ crystals (crystallized from ethanol, m.p. 43°C; photograph by Inge Pracht).

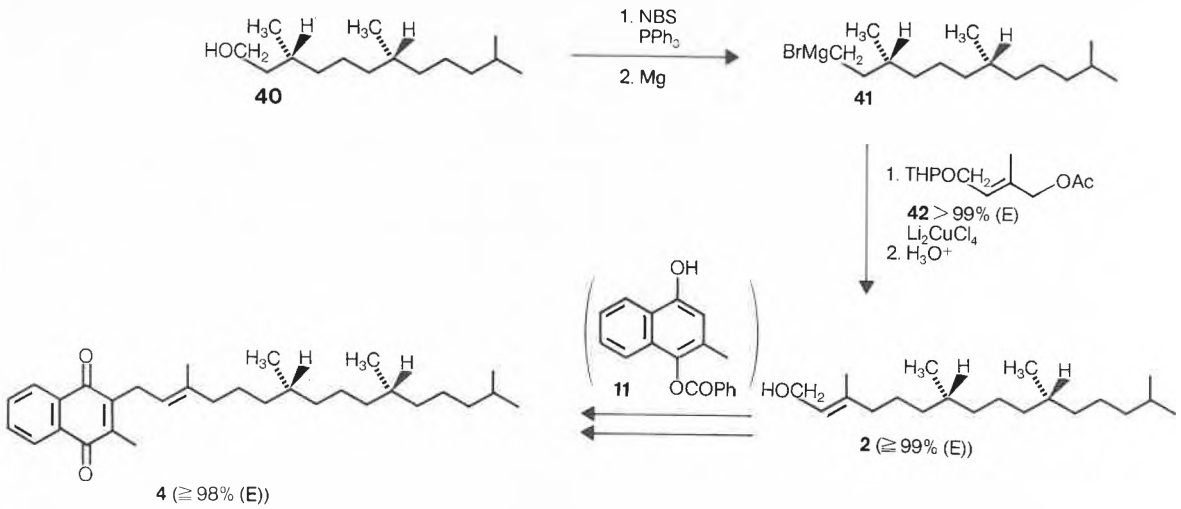
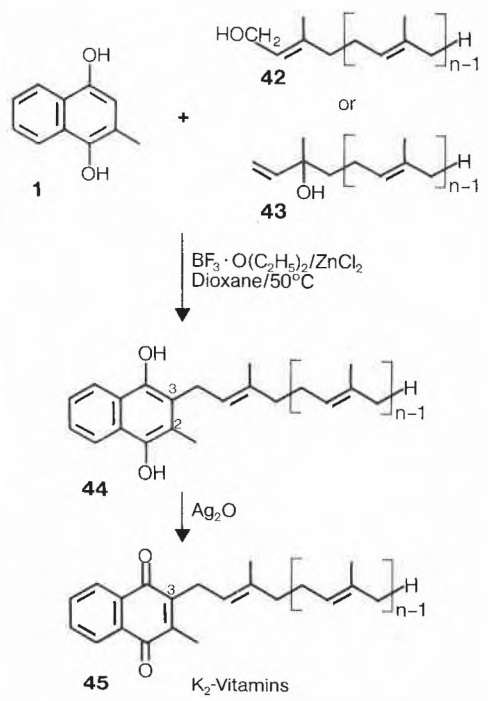


*Fig. 16. Total synthesis of (2'E, 7'R, 11'R)-vitamin K_1 (**4**).*

The side-chains required for the preparation of these vitamins were obtained analogously to the isophytol process[70] (Fig. 18).

Linalool (**46**), an intermediate in the synthesis of isophytol, was lengthened with diketen or isopropenyl methyl (IPM) ether to give a mixture of geranylacetone and nerylacetone (**47a/b**). The *E*/*Z*-ratio was approximately 60:40 in favour of the (*E*)-isomer, which was purified by fractional distillation. Reaction with sodium acetylide, followed by partial hydrogenation, gave (*E*)-nerolidol (**48**), which was lengthened as above with diketen or IPM ether to give a mixture of the two isomeric farnesylacetones **49a** and **49b** (ratio ≈ 60:40). Pure (all-*E*)-farnesyl-acetone (**49a**) could be obtained by crystallization of the corresponding semicarbazones or more simply by fractional distillation or crystallization at low temperature. Repetition of the above reactions led to (all-*E*)-geranyl-linalool **50**, which is the side-chain for vitamin $K_{2(20)}$.

Other polyprenyl alcohols of the type **50** of any desired length, and hence also the corresponding K_2-vitamins, were prepared using this reaction sequence.



n	1	2	3	4	5	6	7	8
Chain-length	C_5	C_{10}	C_{15}	C_{20}	C_{25}	C_{30}	C_{35}	C_{40}
m.p. (°C)	–	56	35	37	43	50	54	56

*Fig. 17b. Synthesis of K_2-vitamins (**45**).*

4. Recent Syntheses

The biological results discussed in section 2.3.2, especially the fact that the *E*-configurated double bond in vitamin K_1 is necessary for its K-activity, are the reason, why the problem of stereoselective synthesis of (*E*)-vitamin K_1 has received increasing attention, in particular in more recent times.

The prerequisites for economical syntheses of vitamin K_1 and K_2 are:

a) A high coupling yield of the aromatic part with the side-chain, without using an undue excess of the prenyl component.
b) Easy access to these reactants.
c) Maintenance of the *E*-stereochemistry in the side-chain.
d) Absence of side reactions such as chromanol formation and side-chain cyclizations.
e) Cheap reagents.

On paper, vitamin K_1 can be obtained by a variety of synthetic routes. Some of the many possibilities which have recently been investigated are outlined in Fig. 19 in a simplified retrosynthetic scheme:

① The method which is most obvious, and which was therefore discovered as early as 1939, consists in linking menadione (menadiol), the C_{11} fragment, with the C_{20} side-chain, for example via Friedel-Crafts alkylation of phytol.
② Another possibility, which has only recently been put into practice, is to link a suitable C_8 structural unit with a C_{23} chain, for example via a Diels-Alder reaction between suitable components.
③ Scission of the C1'–C2' bond affords a further variant, in which the side-chain of the *E*-configuration (for example a C_{19}-(*E*)-alkenyl cuprate) could be coupled with a suitably functionalized naphthoquinone.
④ Scission of the C3–C1' and C4'–C5' bonds represents another possible synthetic route, in which firstly the *E*-trisubstituted double bond could be synthesized stereoselectively by reacting a naphthoquinone derivative with a suitable C_5-synthone, and then the product could be lengthened with the missing C_{15}-alkyl residue.

Since the first syntheses of vitamin K_1 in 1939[8–12], many modifications to the direct Friedel-Crafts alkylation of menadiol (or a derivative of it) with allylic alcohols have been reported[68,69]. Here, however, the instability of the allylic moiety to *E*/*Z*-

isomerizations[79] largely restricts the application of this reaction to the synthesis of (*E*/*Z*)-mixtures of vitamin K_1.

In recent years, several multistep syntheses of K-vitamins using organometallic intermediates (e.g. Grignard reagents[80], zink reagents[81], arylcuprates[82], trialkylpolyprenylstannanes[83], π-allylnickel-[84], phthaloylcobalt-[85], and chromium carbene-complexes[86]) have been carried out. More recently, some other strategies have been developed: formation of hydroquinone-polyprenyl ethers followed by O-to-C rearrangement of the side-chain[87]; carbon-carbon bond formation utilizing terminally functionalized, protected isoprenoid hydroquinones and α-sulfonyl carbanions[88]. However, only part of the above mentioned prerequisites are satisfied by all these approaches.

In the process discovered by *Dötz*[86], the complex pentacarbonyl(methoxyphenylcarbene)chromium(0) (**51**)[89] is used as an important reactive intermediate (Fig. 20). This crystalline compound is readily obtainable from $Cr(CO)_6$ by reaction with phenyllithium and alkylation with trimethyloxonium tetrafluoroborate.

When this carbene complex is heated gently to ca. 50 °C in a donor solvent, for example dibutyl ether, it loses one molecule of CO, which is replaced with an acetylene, for example the alkyne **52a**, to form the intermediate **53.** As the reaction proceeds, the hydroquinone monomethyl ether complexed with $Cr(CO)_3$, **54,** is formed as a regioisomeric mixture, but the mechanism involved is purely a matter for speculation.

This complexed hydroquinone monomethyl ether **54** can be converted directly to the corresponding K-vitamin **56** with customary oxidizing agents, or the following, more economical method can be used: the naphthohydroquinone derivative **55** can be liberated under CO pressure and the $Cr(CO)_6$ recovered and recycled. Subsequent oxidation of **55** gives the K-vitamin **56** in 70–80% yield (based on the carbene-complex **51**).

In this synthesis, the *E*-configuration of the enyne **52** is retained quantitatively, since no allylic cation is formed as an unstable intermediate. If in this reaction sequence an acetylene of type **52b** is used instead of **52a,** menaquinones are obtained in high yield.

Attemps have also been made in our laboratory to couple (*E*)-phytol (or a derivative of it) with the naphthoquinone (Fig. 19) with full retention of the *E*-configurated double bond, and to synthesize this isoprenoid part stereoselectively as it will be demonstrated in the following.

Vitamin K_1 could formally be synthesized by means of a Diels-Alder reaction from the isobenzofurane **57** and the enyne **52a** followed by hydrolysis of the resulting acetal moiety (Fig. 21). The acetylene **52a** is a known compound[86, 90] and can be synthesized in a straightforward manner from propyne and phytol. The isobenzofurane

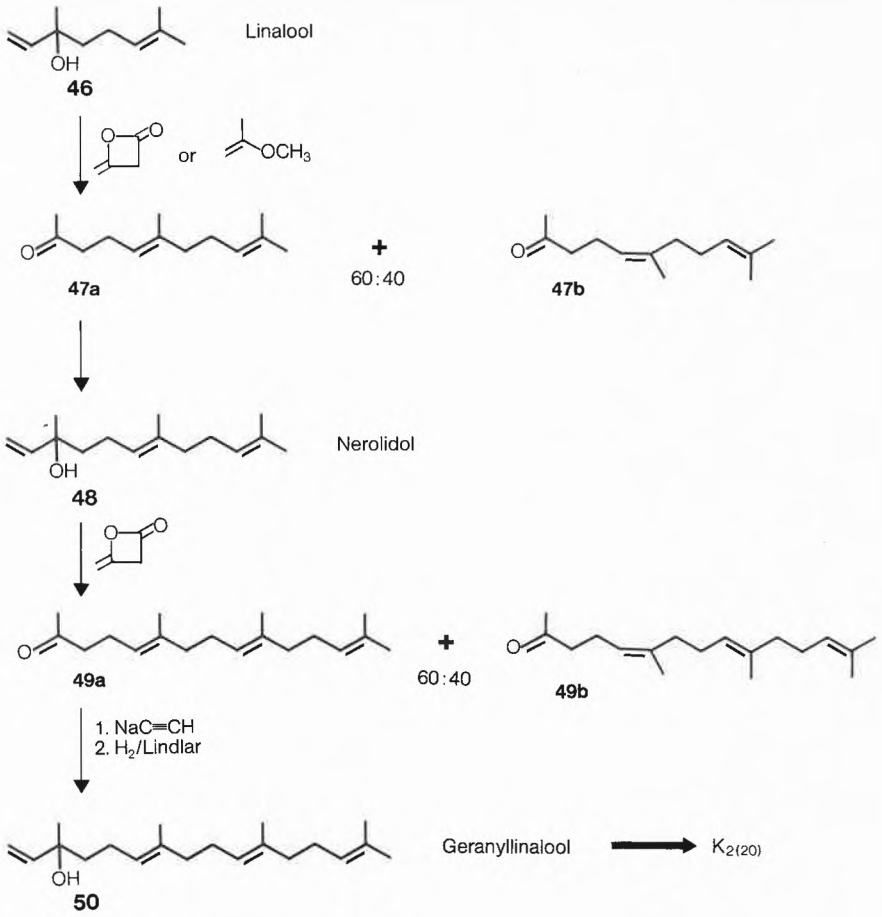


Fig. 18. Synthesis of (all-E)-polyprenols.

57 was first described recently by *Troll* et al.[91]. This compound can be prepared in situ from 1,2-dihydrophthalic anhydride with trimethylsilyl chloride/triethylamine/$ZnCl_2$ at −20 °C, but it is not very stable and already decomposes above this temperature. The authors tried to trap the isobenzofurane **57** at 0°C with dienophiles, like e.g. fumaric acid dimethylester. The corresponding cycloaddition products, which hydrolyzed to the naphthohydroquinones during work up, however, were isolated in only low yields (10%).

On the other hand, the dihydroisobenzofurane **58** of greater thermal stability did not undergo a Diels-Alder reaction with the unactivated acetylene **52a**, even at elevated temperatures (up to 180–190 °C). It was therefore necessary to activate the acetylenic function by means of a methoxycarbonyl group.

These two modified components **58** and **59** were then subjected to a Diels-Alder reaction at 80 °C overnight, without solvent or catalyst (Fig. 22). The adduct **60** obtained as an intermediate in this reaction

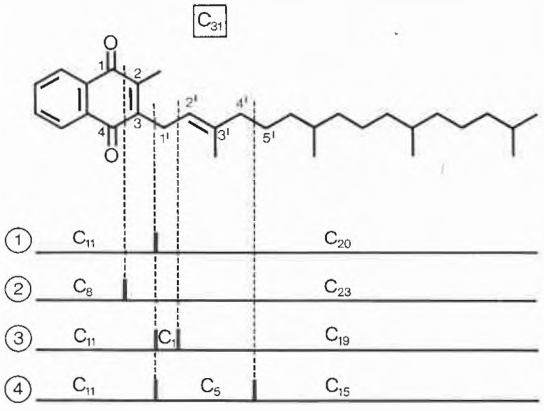


Fig. 19. Possible synthetic routes to vitamin K_1.

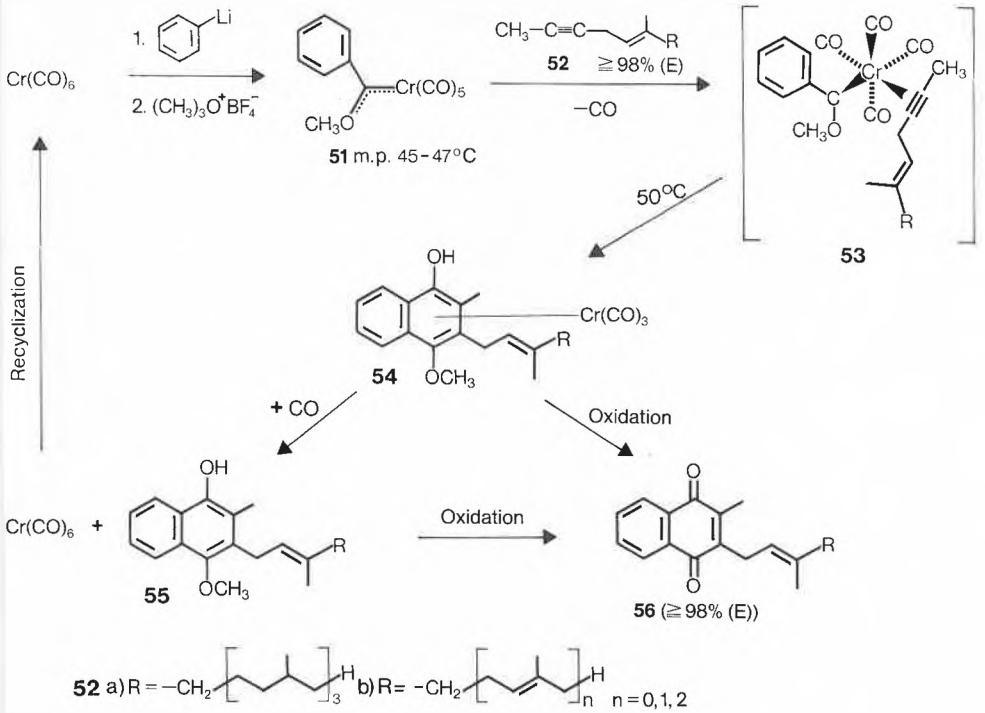


Fig. 20. Dötz's synthesis of vitamins K_1 and K_2.

was desilylated with methanol, without purification, and the methoxycarbonyl group was reduced to the methyl group with sodium bis(2-methoxyethoxy)aluminium hydride in toluene under reflux.

The reduction of a carboxy or methoxycarbonyl group to the methyl group with this reducing agent only works in special cases[93], i.e. when this function is located on an aromatic ring system; in addition, the aromatic compound must be activated in the *ortho*- or *para*-position by an electron donor, for example a methyl ether or a hydroxy function.

Subsequent acidification with 1% aqueous sulfuric acid at 0 °C in air gave Vitamin K_1 directly in a yield of ca. 50% (based on the propargyl ester **59**).

The disiloxyfurane **58** is very readily obtainable in virtually quantitative yield from the inexpensive *cis*-1,2,3,6-tetrahydrophthalic anhydride by reaction with $NEt_3/(CH_3)_3SiCl/ZnCl_2$ and was described by *Chan* et al.[94] in 1980.

The starting material used for the second component was (*E*)-phytyl bromide (**61**), which was reacted with bromomagnesium acetylide to give the terminal alkyne **62** (Fig. 23). Deprotonation of the acetylenic hydrogen with ethylmagnesium bromide and carboxylation with CO_2 gave the unsaturated acid **63**. Mild esterification with $(CH_3)_2SO_4/NaHCO_3/CH_3OH$ at room temperature led to the desired methyl (*E*)-phytyl-propargylate (**59**) with an *E*/*Z*-ratio of 96:4 and a total yield of ca. 60%.

A synthesis of vitamin K_1, in which the (*E*)-trisubstituted double bond of the sidechain is synthesized stereoselectively by means of an organometallic reaction, is illustrated in Fig. 24.

The starting material used was the trimethylpentadecanone **26**, an intermediate in the synthesis of isophytol. This was converted with PCl_5 at room temperature to the geminal dichloride **64**, which was dehydrochlorinated with NaH in 1,3-diaminopropane[95], without purification, to give the terminal alkyne **65**. The acetylene **65**, obtained in approximately 70% yield, is very pure because, under these strongly basic conditions, allenes or non-terminal alkynes formed as intermediates are isomerized to **65**.

The Reaction of **65** with a $CH_3Cu \cdot S(CH_3)_2 \cdot MgBr_2$ complex[96], formed in situ from CH_3MgBr and $Cu^IBr \cdot S(CH_3)_2$, gave the intense dark green (*E*)-alkenylcopper compound **66**. As can be seen from the purity of the end product, this addition reaction proceeds with exceptional stereoselectivity.

Coupling of this copper compound with the bromomethylnaphthoquinone **67**, which can be obtained in a single step by the bromomethylation of menadione **9**[97], gave vitamin K_1 with a purity of > 99% (*E*) in 38% yield (based on **67**).

(*Z*)-Vitamin K_1 (**25**) can also be prepared by the same technique (Fig. 25).

Starting from hexahydropseudoionone **68**, the chloride **69** was prepared by reduction with $NaBH_4$ and reaction with triphenylphosphane/CCl_4. Reaction with magnesium and subsequent lengthening by three C-atoms with trimethylene oxide[98] led to the saturated alcohol **70** with a total yield of 58%, and this was converted with NBS/triphenylphosphane[99] to the corresponding bromide **71**. Subsequent reaction with magnesium, followed by $Cu^IBr \cdot S(CH_3)_2$ and propyne at −23°C, then gave the (*Z*)-alkenylcopper compound **72**, which was coupled with the bromomethylquinone **67** at −30 °C. (*Z*)-Vitamin K_1 (**25**) was thereby obtained with a very high purity (> 99% *Z*) in 31% yield (based on the quinone **67**).

A synthesis, in which firstly the (*E*)-trisubstituted double bond is constructed stereoselectively using isoprene epoxide **74** as a suitable C_5-synthon, is shown in Fig. 26. The starting material used was the bromodimethoxynaphthalene **73**[101], which is readily obtainable from menadione **9**. The corresponding Grignard compound prepared with magnesium was reacted with isoprene epoxide **74** in the presence of catalytic quantities of Cu^IBr at − 20°C[102]. The crystalline allyl alcohol **75**[88] obtained in 91% yield after chromatography already contained 94% of the (*E*)-isomer. The *E*/*Z*-ratio of this alcohol mixture was increased to more than 99:1 by a single crystallization. Subsequent reaction with benzoyl chloride in pyridine gave the crystalline activated benzoate **76**.

A Schlosser coupling[76] of the allylic benzoate **76** with the C_{15}-Grignard compound **77**[88b], which is very easily obtainable from hexahydropseudoionone (**68**), gave (*E*)-dihydrovitamin K_1 dimethyl ether **78** in 69% yield (*E*/*Z* = 98.5:1.5), which could very easily be oxidized with

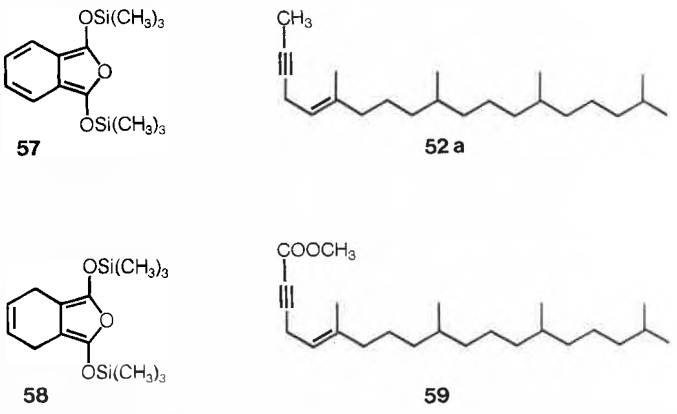


Fig. 21. «Diels-Alder» components for the synthesis of vitamin K_1.

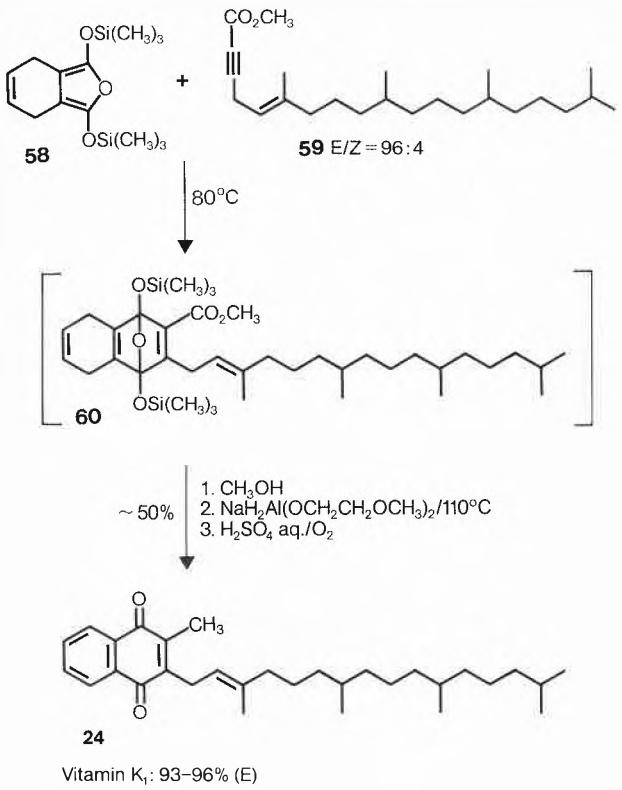


Fig. 22. Synthesis of vitamin K_1: «Diels-Alder method» [92].

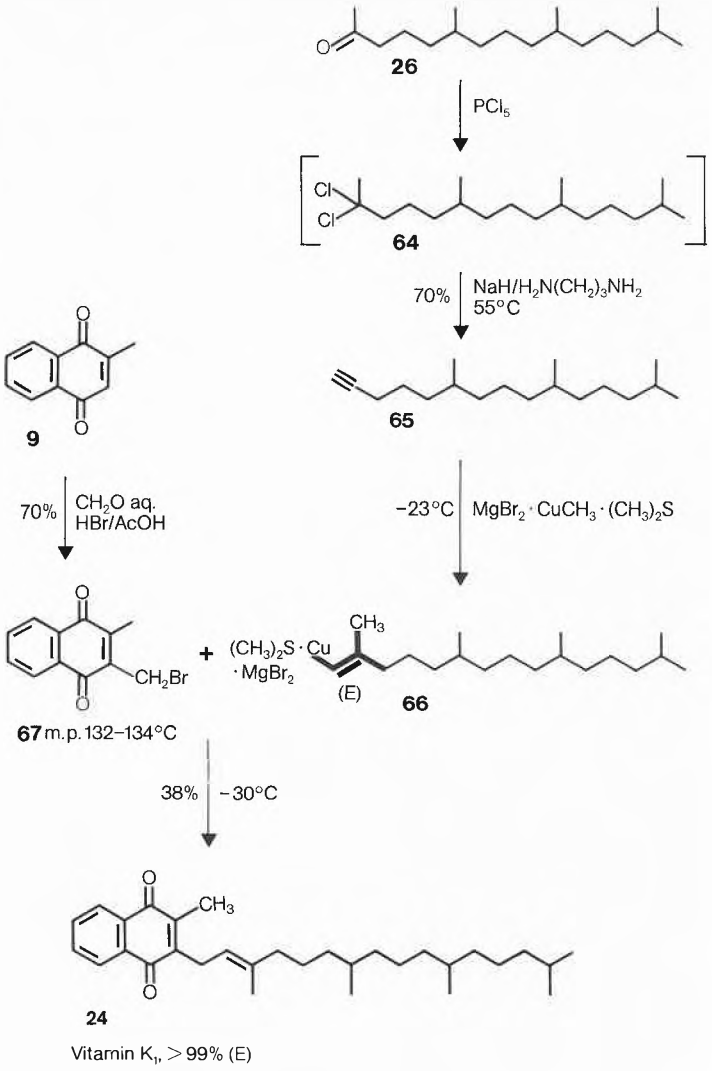


Fig. 24. Synthesis of vitamin K_1: «Organocopper method» [92].

$(NH_4)_2$ $[Ce^{IV}(NO_3)_6]$ to vitamin K_1 (**24**) in 95% yield. As expected, the coupling reaction of **76** with **77** proceeded with virtually full retention of the configuration at the trisubstituted double bond.

A very short and simple method of synthesizing K_1- and K_2-vitamins was recently discovered (Fig. 27)[103].

In this synthesis, which comprises only three reaction steps, cyclopentadiene is used as an auxiliary reagent.

The starting material used was menadione (**9**), which, with cyclopentadiene at room temperature, gave the crystalline colourless *endo*-Diels-Alder adduct **79** (*m.p.* 96–97 °C) in 93% yield. In this reaction, the non-acidic olefinic hydrogen in the α-position to the quinone carbonyl group is converted to a hydrogen in the α-position to a ketone group, which can be deprotonated by a base; the C-4a in the diketone **79** is thus rendered susceptible to monoalkylation.

Deprotonation with a strong base, for example potassium amide, sodium amide or potassium *tert*-butanolate, and alkylation with (*E*)-phytyl bromide (**61**) ($\geqq$ 98% *E*)[104] gave the alkylated diketone **80** in ca. 90% yield. The corresponding *O*-alkylation product is also formed in low yield, but this is cleaved with aqueous HCl before the working-up process and can subsequently be separated from the desired product **80** without difficulty.

The particular aspect of this reaction, which we initially found very surprising, was the ease with which this tertiary neopentyl centre can be alkylated – even at 0°C.

The end point of this alkylation can also be seen very easily, as the blood-red colour of the reaction mixture is fading out towards the end of the reaction.

The stereochemical arrangement of the phytyl group with respect to the angular methyl group in **80** was determined by NOE measurements in the ^{1}H-NMR spectrum. Also using the Dreiding model, it immediately becomes clear that a *trans*-arrangement of these two substituents is absolutely impossible for steric reasons.

The diketone **80** is thermally unstable and already decomposes slowly at room temperature, and quickly and virtually

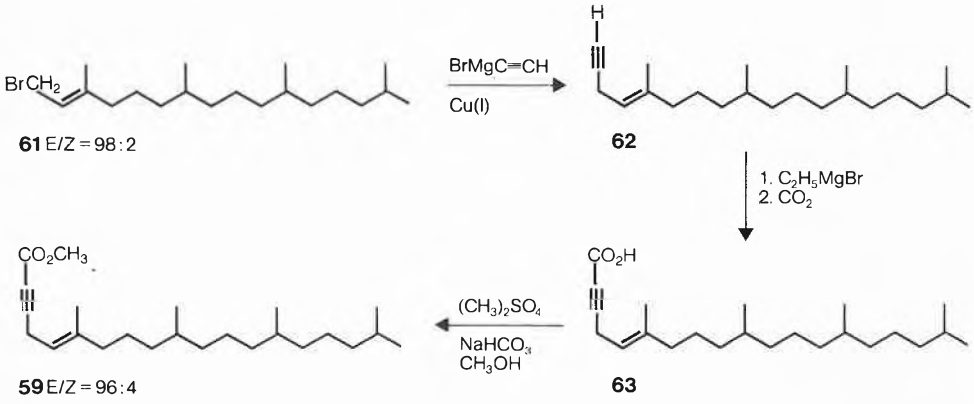


Fig. 23. Synthesis of the acetylenic dienophile **59** [92].

quantitatively on heating to 70–120 °C, into vitamin K_1 (**24**) (≧ 98% *E*).

According to this principle, by virtue of the basic alkylation conditions which leave the polyunsaturated side-chains untouched, it is now also possible to prepare K_2-vitamins in high yields: e.g. vitamin $K_{2(25)}$, as illustrated in Fig. 28.

Under the same conditions as for vitamin K_1, the diketone **79** was alkylated with (all-*E*)-geranylfarnesyl bromide **81** (≧ 97% all-*E*)[105] and gave the product **82** in 87% yield. A subsequent retro-Diels-Alder reaction gave an almost quantitative yield of crystalline vitamin $K_{2(25)}$ (**83**) with a melting point of 43°C and a content of 97.8% according to HPLC.

Other K_2-compounds were prepared under the same conditions and these are tabulated in Fig. 29. The alkylation yields **79** → **84** are summarized in the second column. With the requisite alkylating agent[105] (dimethylallyl, geranyl, (all-*E*)-farnesyl, (all-*E*)-geranylgeranyl, and (all-*E*)-farnesylgeranyl bromide), the corresponding alkylation products **84** were obtained in yields of around 80% to about 90%. The corresponding (all-*E*)-K_2-vitamins **85**, some of which are crystalline, could be obtained by a retro-Diels-Alder reaction (**84** → **85**) in a very high and sometimes almost quantitative yield and with high purity.

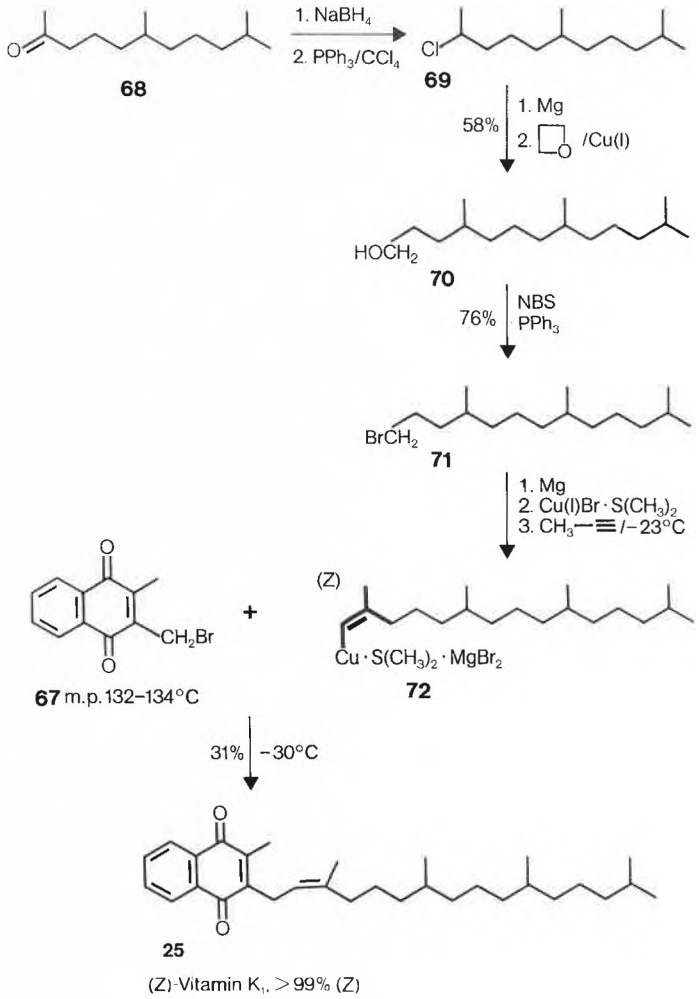


Fig. 25. Synthesis of (Z)-vitamin K_1: «Organocopper method» [92].

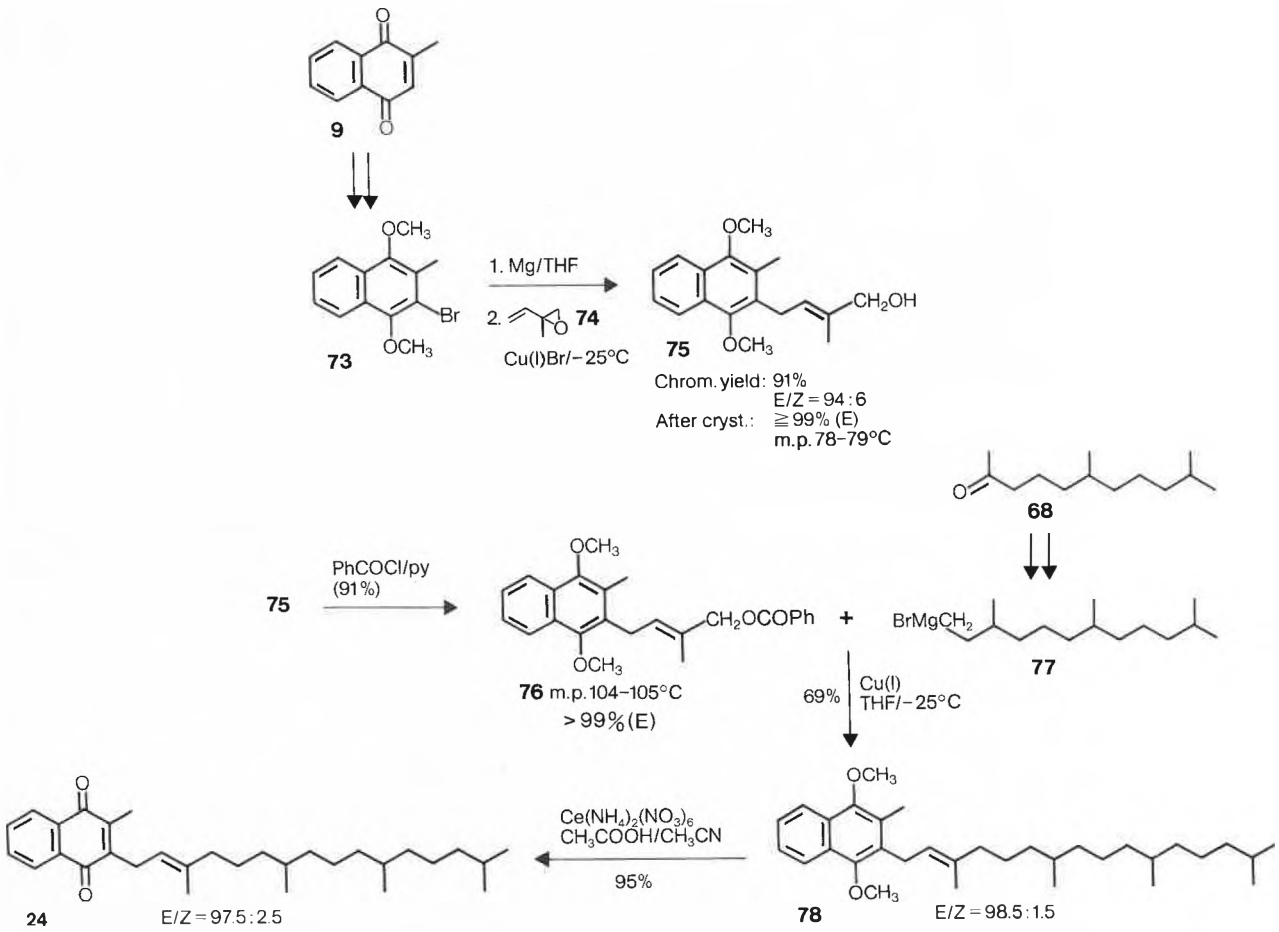


Fig. 26. Synthesis of vitamin K_1: «Epoxide method» [100].

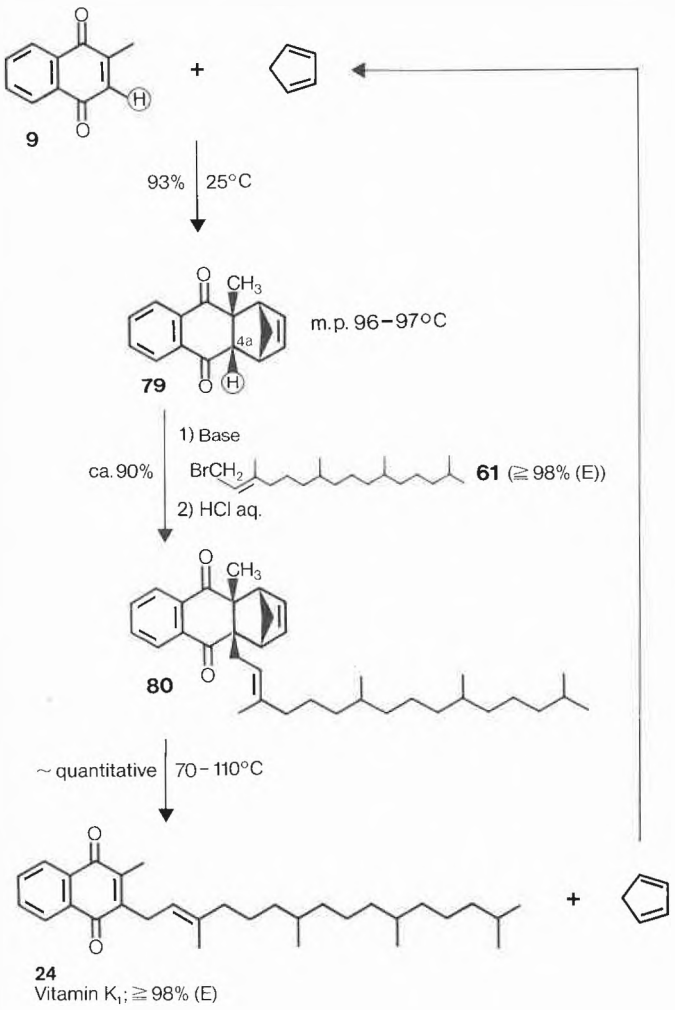


Fig. 27. Synthesis of vitamin K_1 via menadione-cyclopentadiene adduct [103]

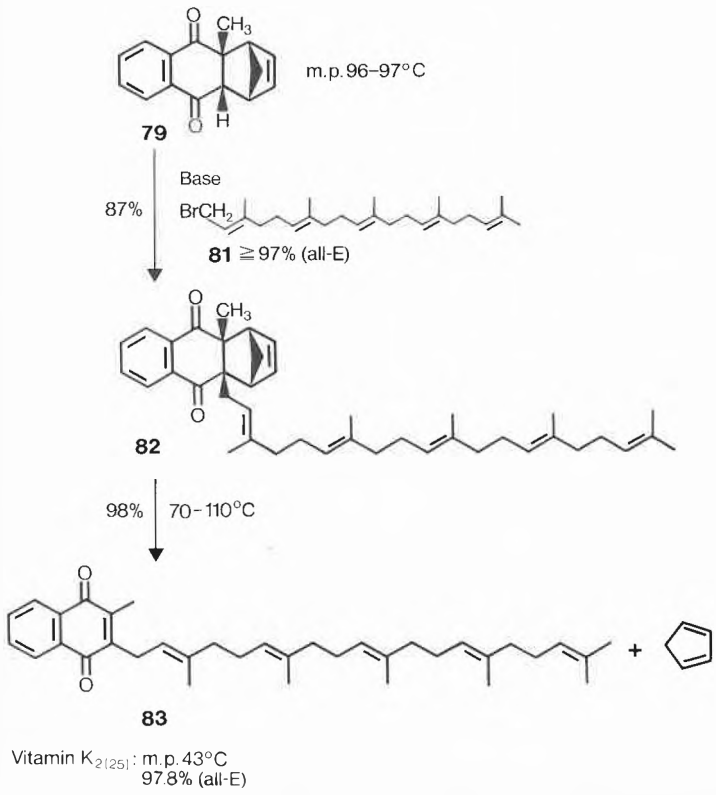


Fig. 28. Synthesis of vitamin $K_{2(25)}$ via menadione-cyclopentadiene adduct.

Crystalline K_2-vitamins, for example vitamin $K_{2(25)}$, can very easily be prepared directly from the crude product by a through-process **79** → **85** and subsequent crystallization. The overall yield of 73–76% is again remarkably high here.

The question arises whether it is also possible to use other dienes in place of the cyclopentadiene in this synthesis. The answer is provided in Fig. 30 and Fig. 31.

The first alternative diene to be investigated was cyclohexadiene, which underwent a Diels-Alder reaction with menadione **9.** This reaction only took place at elevated temperature, however, and the yield of 54% of crystalline adduct **86** is much lower than in the case of cyclopentadiene.

The diketone **86** was reacted under the standard conditions with e.g. dimethylallyl bromide (**87**) to give a 1:3 mixture of the two crystalline *C*- and *O*-alkylation products **88** and **89.** The stereochemistry of **88** was again determined by means of NOE measurements.

The elimination of the cyclohexadiene from **88** proceeded very slowly at 200°C, and it took 12 hours before no more educt could be seen on the TLC plate. 35% of pure quinone **90** was isolated from the dark-coloured reaction product obtained.

We next investigated acylic 1,3-dienes, e.g. 1,3-butadiene (Fig. 31).

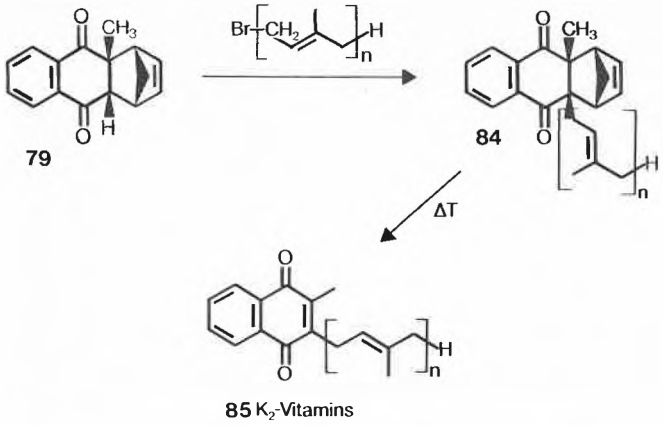
The Diels-Alder reaction of menadione **9** with butadiene gave a 62% yield of the crystalline *cis*-adduct **91** with a melting point of 81–82°C. When treated with potassium *tert*-butanolate, this compound isomerizes to the *trans*-product **93,** which is obviously thermodynamically more stable. The stereochemistry of both these compounds was determined unambigously by NOE measurements between the angular methyl group and the **H**-atom in the α-position to the carbonyl group.

Methylation of **91** with methyl iodide showed that the electrophilic attack occurred from «underneath» and gave the crystalline *trans*-alkylation product **94** in 66% yield. The *trans*-stereochemistry of these two methyl groups could be deduced unambiguously in the epoxidized product **95** from the ^{1}H-NMR spectrum.

Reaction of **91** with dimethylallyl bromide (**87**) and potassium *tert*-butanolate as the base gave the *trans*-linked product **92.** However, this was very stable under the action of heat and unchanged starting material was recovered after pyrolysis at 200°C.

5. Discussion and Outlook

A particular feature of our first approach to vitamin K_1 shown in Fig. 22 (Diels-Alder method) is the fact that it is one of the few syntheses not based on menadione (**9**) as the starting material. The aromatic precursor employed, the 1,3-di-



n	YIELD 79 → 84	m.p. 84	YIELD 84 → 85	m.p. 85	PURITY (85) (HPLC)
1	75%	106	85%	–	99.2%
2	78%	70	92%	56	99.2%
3	81%	–	96%	–	97.9%
4	88%	–	95%	36.5	96.3%
5	87%	–	98%	43	97.8%
5	79 → 85: 73–76%			43.5	99.5%

Fig. 29. Synthesis of K_2-vitamins (menaquinones); melting points (m.p.) in °C.

siloxyfuran derivative **58**, is very readily obtainable from the corresponding anhydride, which is again easily accessible from butadiene and maleic anhydride by a Diels-Alder reaction. The configuration of the (*E*)-trisubstituted double bond in the phytyl-propargylic ester **59** is practically 100% retained during the reaction sequence. The disadvantage of this very short sequence is the moderate yield of about 50% overall and the fact that a relatively expensive reagent, sodium bis(2-methoxyethoxy)aluminium hydride, has to be used to regenerate the methyl group at the 2-position at the end of the sequence.

The great advantage of the «organocopper approach», shown in Fig. 24, of yielding (*E*)-vitamin K_1 with exceptionally high purity is made up with the low yield of the coupling reaction. In addition, the transition metals used in this and in other syntheses[81–86] in stoichiometric amounts are problematic.

The key step in the «epoxide approach», shown in Fig. 26, is an efficient copper(I)-catalyzed coupling reaction of a Grignard reagent with isoprene epoxide, a cheap C_5-building block, to yield the *E*-configurated allylic alcohol **75**. This very easy access of the geometrically pure *E* double bond, however, is made up with the length of the route and the low overall yield of vitamin K_1 (based on menadione **9**).

In our opinion, most of the prerequisites for an economical route to vitamin K_1 specified at the beginning of this chapter are satisfied by the synthesis using cyclopentadiene as an auxiliary reagent (Fig. 27). It is very easy to appreciate the many advantages exhibited by this synthesis:

- three simple steps;
- the high yields;
- no exotic reagents and no transition metals are used;
- since this alkylation is performed under *basic* conditions, the configuration of the double bond in the phytyl bromide **61** is 100% retained;
- another advantage is the fact that no reduction/oxidation has to be carried out in the whole of this sequence, the oxidation state of the menadione (**9**) is retained in these reactions up to the final product;
- moreover, the auxiliary reagent cyclopentadiene can be regenerated very easily by distillation during the retro-Diels-Alder reaction.

In recent years, many attempts towards more economical syntheses of vitamin K_1 have been published. Mostly, these are based on the use of transition metals in stoichiometric amounts. However, these have to be recovered and recycled quantitatively for ecological and economical reasons. This makes their industrial application rather inefficient.

In contrast, the idea of using cheap cyclopentadiene as an auxiliary reagent for the connection of the (*E*)-phytyl side-chain with the naphthoquinone ring has led to a very short, efficient, and highly stereocontrolled synthesis of vitamin K_1. The successful realization of this concept clearly underlines that even today superior solutions can still be found by the skilled exploitation of traditional organic chemistry. Once more, this demonstrated the still competitive potential of classical methodology.

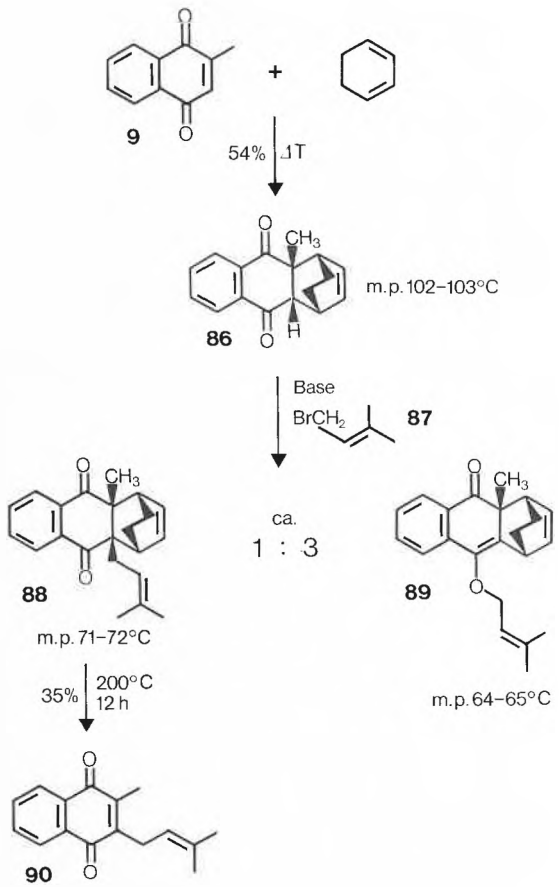


Fig. 30. Variation with cyclohexadiene.

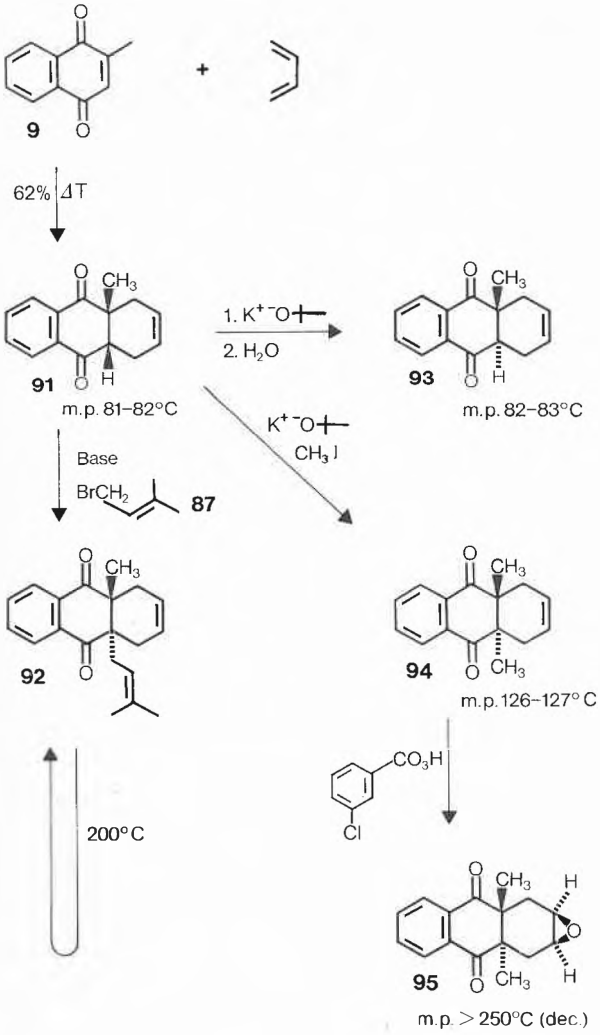


Fig. 31. Variation with 1,3-butadiene.

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