



# An Improved and Plant Viable Synthesis of Vitamin K1

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## **Authors' contributions**

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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## **ABSTRACT**

An improved and simplified process of vitamin K1 preparation. The article confers the new reagent BF3. Acetic acid complex as a condensation reagent for phytol with compound III in vitamin K1 synthesis, which eludes the use of ethereal reagent and make the process hazard free. Further innovation presents base catalyzed synthesis of vitamin K1 which is an oxidative product of compound IV. Sodium methoxide base is used in synthesis which eliminates use of metal oxidant, costly and hazardous reagent. The new approach ensures the non-generation of epoxide impurity (V) which tends to form during Ag<sub>2</sub>O catalyzed synthesis. Finally, article also focused on formation and conformation of 7R and 11R diastereomeric centers and ensure the formation of vitamin k1 with desired stereochemistry also article submit proof of concept and supporting literature survey for desired stereochemistry.

**Keywords:** Acetyl chloride and zinc dust; BF3 acetic acid; Sodium methoxide; silica gel; desired diastereomer C7 and C11; "Z" isomer content; diastereomeric centers (7R and 11R).

## 1. INTRODUCTION

Vitamin K plays a vital role in coagulation, bone development, and cardiovascular health. The Vitamin K deficiency leads to the osteoporosis, and increased risk of cardiovascular disease and can be the cause of excessive blood loss and poor bone development. The deficiency syndrome is traditionally known as haemorrhagic disease. Vitamin K is a fat soluble compounds and had a common nucleus 2-methyl-1, 4-naphthoquinone. The series of vitamin k is differs by differing the side chain at 3- position.

The article discloses the improved synthesis of vitamin K1, which consist with nucleus 2-methyl-1, 4-naphthoquinone and phytyl side chain at 3 position.

Vitamin K1 of formula (I), chemically known as 1, 4-Naphthalenedione, 2-methyl-3-(3, 7, 11, 15-tetramethyl-2-hexadecenyl)-[R-[R\*, R\*-(E)]]-and also known as phyloquinone, phytomenadione, or phytonadione is used as an Antihemorrhagic agent for nausea associated with gastrointestinal disturbances, motion sickness, or nausea induced by the administration of other therapeutics agents.

Vitamin K1 (I), is synthesized by plants, and is found in highest amounts in green leafy vegetables and some plant oils [1] because it is directly involved in photosynthesis. It may be

thought of as the "plant" form of vitamin K. It is active as a vitamin in animals and performs the classic functions of vitamin K, including its activity in the production of blood-clotting proteins.

Vitamin K is the generic name for 2-methyl-1, 4-naphthoquinone derivatives having activity on blood-coagulation and electron transport systems. Vitamin K was first identified in 1929 by Danish scientist Henrik Dam during his investigations regarding the role of cholesterol in metabolism of chicken. The identified substances were found to be essential for synthesizing prothrombin in the liver, which is a precursor of the enzyme thrombin causing blood coagulation reaction and were also known to prevent release of calcium from the bones.

Amongst these derivatives, Vitamin K1, also known as phyloquinone, phytonadione or phytomenadione is known to be the active ingredient which exhibits the aforementioned activity. Vitamin K1, chemically identified as 2-Methyl-3-[(2E,7R,11R)-3,7,11,15-tetramethyl-2-hexadecenyl]-1,4-naphthalenedione has two geometrical isomers (cis / trans or Z / E isomers) as well as two asymmetric centres at C7 and C11, each generating a pair of two enantiomers. Thus, there are total eight diastereomers for the molecule, out of which, 2'trans-7R, 11R stereoisomer is the only active and hence, desired diastereomer.

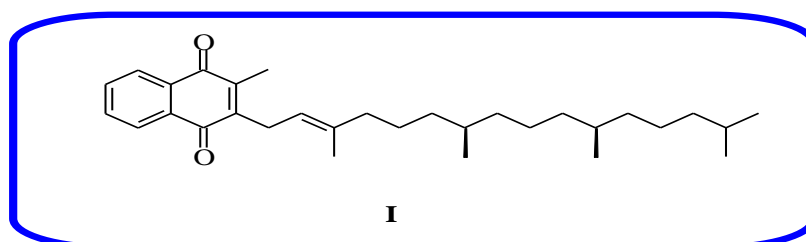


Fig. 1.

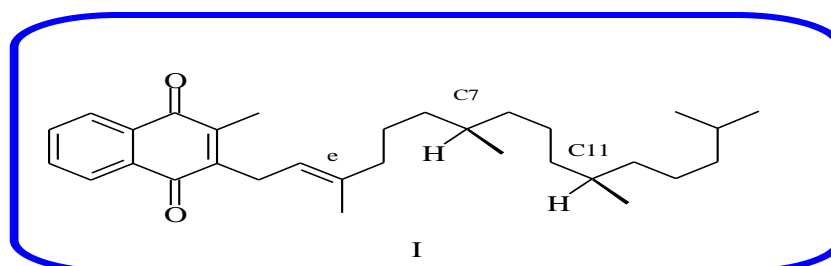


Fig. 2.

Various researchers have attempted to synthesize vitamin K1 formula (I). For example, Otto Isler, Karl Doebel and et.al. [2] discloses a method for preparing vitamin K1 comprising reaction of 2-methyl-1, 4-naphthohydroquinone and phytol acetate (prepared by boiling Phytol with acetic anhydride) by using boron trifluoride etherate as a catalyst acetyl glycol monomethyl ether is as a solvent. The process further comprises stirring the condensation product in petroleum ether using hydrogen in presence of palladium catalyst, followed by oxidation of resulting hydroquinone using silver oxide to give vitamin K1. Finally the patent comprises the isolation and purification of Vitamin K1 by column chromatography. Otto Isler, Karl Doebel and et.al. [3] discloses a process wherein acetyl phytol is condensed with 2-methyl-1,4-naphthohydroquinone in presence of zinc chloride to give monoacetyl  $\beta$ -phytyl 1,4-naphthohydroquinone, which after hydrolysis and oxidation yields vitamin K1. Louis F. Fieser, Belmont and et.al. [4] discloses the reaction of 2-methyl-1, 4-naphthohydroquinone with phytol or phytadiene in the temperature range of 70-180°C wherein oxalic acid and trichloroacetic acid are used as condensation agents and the reaction takes about twenty four hours for completion. These described processes of vitamin K1 (I) preparation poses serious drawbacks especially for a commercial scale application. The processes consist of the reagents like acetic anhydride for acylation, boron trifluoride [3,4], trichloroacetic acid [3], oxalic acid [5,6] for phytol condensation, silver oxide [3,4] oxidation. The process consist of expensive, extremely hazardous, highly flammable, high-boiling and ozone depletion solvents like dioxane<sup>5,6</sup>, acetyl glycol monomethyl ether, ether. Use of these reagents and solvents make process extremely hazardous, particularly the solvents and not applicable on plant scale. Finally the processes describes the tedious methods for the isolation and purification of vitamin K1 (I) which leads to give the lower yields and less assay of vitamin K1 (I). Thus, there still exists a need for an industrially viable and simplified process for synthesis of vitamin K1 (I) which avoids the use of hazardous reagent and solvents.

## 2. EXPERIMENTAL SECTION

All materials were purchased from commercial suppliers. Unless specified otherwise, all reagents and solvents were used as supplied by manufacturers. Varian <sup>1</sup>H NMR spectra (400 MHz) and <sup>13</sup>C NMR spectra (100 MHz)

were recorded in CDCl<sub>3</sub>, and mass spectra were determined on API-2000LCMS mass spectrometer, Applied Biosciences. IR spectrum was taken in potassium bromide and recorded on Shimadzu 8400S FTIR instrument. The UV spectrum was recorded in the range 200 nm to 400 nm on UV-VIS spectrophotometer

**Example 1: Preparation of 1, 2 diacetoxy 2-methylnaphthalene (II):** Charge 2-methyl 1, 4-naphthoquinone (10 g, 0.058 mol) in round bottom flask and add zinc dust (15.19 g, 0.232 mol) and 50 ml ethyl acetate at 25 to 30°C. Heat reaction at 60 to 65°C and add acetyl chloride (16 g, 0.203 mol) slowly at 60 to 65°C. After stirring at 60 to 65°C for 3 hours, monitor progress of reaction by TLC and add 50 ml of water cool at 25 to 30°C and filter zinc dust. After layer separation organic layer distilled out under vacuum and residue purified from 50 ml cyclohexane gives diacetoxy product Compound II (weight 11.0 g, 86.6%).

### 2.1 Characterization Data

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  2.32 (s, 3H, CH<sub>3</sub>), 2.45-2.48 (2s, 6H, 2CH<sub>3</sub>), 7.15 (s, 1H, CH), 7.45-7.54 (m, 2H, 2CH), 7.45-7.83 (m, 2H, 2CH), Infrared spectroscopy:- 3069 -C-H aromatic stretch, 1757 -C=O stretch, 1603 -C=C- ring stretch, 1209 -C-O- stretch; Mass M/Z (M+NH<sub>4</sub>): - 276.1

### Example 2: Preparation of 1-acetoxy-4-hydroxy 2-methylnaphthalene (III)

The reaction of 10 g of 1,2 diacetoxy 2-methylnaphthalene (II) with 20 % 6.5 ml Methanolic ammonia at 15 to 20°C for 6 hours followed by isolation with 50 ml mixture of ethyl acetate and cyclohexane (1:19) gives 1-acetoxy-4-hydroxy 2-methyl, 3-[(2E)-3,7,11,15-tetramethyl hexadec-2-en-1-yl) naphthalene (weight 7.5 g 89.6%).

**Characterization data:** <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  2.20 (s, 3H, CH<sub>3</sub>), 2.48 (s, 3H, CH<sub>3</sub>), 5.53 (s, 1H, OH), 6.44 (s, 1H, CH), 7.38-7.50 (m, 2H, 2CH), 7.65 (J=8.4Hz) (d, 1H, CH) 8.00 (J=8.36) (d, 1H, CH),;

Infrared spectroscopy: 3350 -OH stretch, 3069 -C-H aromatic stretch, 1721 -C=O stretch, 1638 and 1580 -C=C- ring stretch, 1244 and 1209 -C-O- stretch; Mass M/Z: (M-H)<sup>+</sup> 215.2.

### Example 3: Preparation of 1-acetoxy-4-hydroxy 2-methyl, 3-[(2E)-3, 7, 11, 15

**tetramethyl hexadec-2-en-1-yl) naphthalene (IV):** 3, 7, 11, 15 tetramethyl hexadecane-2-en-1-ol (Phytol) (16.46 g, 0.055 mol) was gradually added to the mixture of 1- acetoxy-4-hydroxy 2-methylnaphthalene (compound III) (10 g, 0.046 mol) in 90 ml dichloromethane, and the resulting mixture was stirred at 25-35°C. A mixture of boron trifluoride-acetic acid complex (2.0 g, 0.010 mol) in 10ml dichloromethane was gradually added to the reaction mass and stirring was continued at 25-35°C. After completion of the reaction as monitored by TLC, water was added to the reaction mass and the organic layer was separated and concentrated to give compound (IV). Compound IV was isolated for characterization in first batch using procedure mentioned below. In all other batches the crude product was directly subjected to the next step.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 0.82-0.87 (m, 12H, 4CH<sub>3</sub>), 1.0-1.54 (m, 19H, 8CH<sub>2</sub>, 3 CH), 1.86 (s, 3H, CH<sub>3</sub>), 2.01-2.05 (m, 2H, CH<sub>2</sub>), 2.26 (s, 3H, CH<sub>3</sub>), 2.47 (s, 3H, CH<sub>3</sub>); Infrared spectroscopy:3466 –OH stretch,2953-2866 –C-H aliphatic stretch, 1742 –C=O stretch, 1661 and 1580 –C=C- stretch, 1229 and 1207 –C-O- stretch; Mass M/Z: (M-H): 493.4.

**Example 4: Preparation of vitamin K1 (I):** 320 ml Toluene was added to compound IV (22.8 g, 0.050 mol), followed by lot-wise addition of sodium methoxide (2.5 g, 0.046 mol) and the reaction mixture was stirred at 25-35°C for 12 hours. After completion of the reaction as monitored by TLC, dilute 10 ml hydrochloric acid with 10 ml water was gradually added to the reaction mixture. The mass was stirred; 140 ml water was added to it, followed by layer separation and concentration of the organic layer. 120 ml n-Heptane was then added to the residue and Silica gel (60-120 mesh size) 60 g was added to it. The mixture was stirred at 25-30°C and silica gel was filtered. The filtered silica gel stirred with 100 ml toluene and filtered. The filtrate was concentrated under vacuum to give crude vitaminK1. Further crude Phytonadione purified by flash chromatography by using n-Heptane and acetone solvent which gives pure vitamin K1 (Weight 12.0 g yield 54.5%).

**Characterization data:** <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 0.81-0.87 (m, 12H, 4CH<sub>3</sub>), 0.97-1.43 (m, 18H, 8CH<sub>2</sub>,2CH), 1.45-1.55 (m, 1H, CH), 1.78 (S, 3H, CH<sub>3</sub>), 1.92-1.96 (m, 2H, CH<sub>2</sub>), 2.19 (s, 3H, CH<sub>3</sub>), 3.37 (d, 2H, CH<sub>2</sub>), 4.99-5.02 (m,1H, CH),7.66-7.71 (m,2H, 2CH), 8.06-8.00

(m,2H,2CH); <sup>13</sup>C NMR:-12.61 (CH<sub>3</sub>), 16.25 (CH<sub>3</sub>), 19.67 and 19.74 (2 CH<sub>3</sub>), 22.53 and 22.63 (2 CH<sub>3</sub>), 24.40 (CH<sub>2</sub>), 24.74 (CH<sub>2</sub>), 25.23 (CH<sub>2</sub>), 25.95 (CH<sub>2</sub>), 27.92 (CH), 32.59 and 32.72 (2CH), 36.59 (CH<sub>2</sub>), 37.24 (CH<sub>2</sub>), 37.34 and 37.35 (2 CH<sub>2</sub>), 39.32 (CH<sub>2</sub>), 39.98 (CH<sub>2</sub>), 118.80 (CH), 126.11 and 126.23 (2 CH), 132.10 and 132.14 (2 C), 133.17 and 133.22 (2 CH), 137.86 ( C), 143.25 ( C ), 146.13 (C), 184.39 and 185.32 (2 C) ;

**Elemental analysis:** % C-82.77% (Theoretical value 82.61%), % of H:- 10.50% (Theoretical :- 10.29%)

**Infrared spectroscopy:**-2953-2866 –CH aliphatic stretch, 1663 –C=O stretch, 1618 and 1597 –C=C ring stretch; Mass M/Z: 473.2 (M+Na)<sup>+</sup>, 451.2 (M+H)<sup>+</sup> ; UV – λ max 332.00, SOR: Obtained value of Phytonadione is [α]<sub>D</sub> -0.280 (dioxane), reported value of Phytonadione is [α]<sub>D</sub> -0.310 (dioxane).

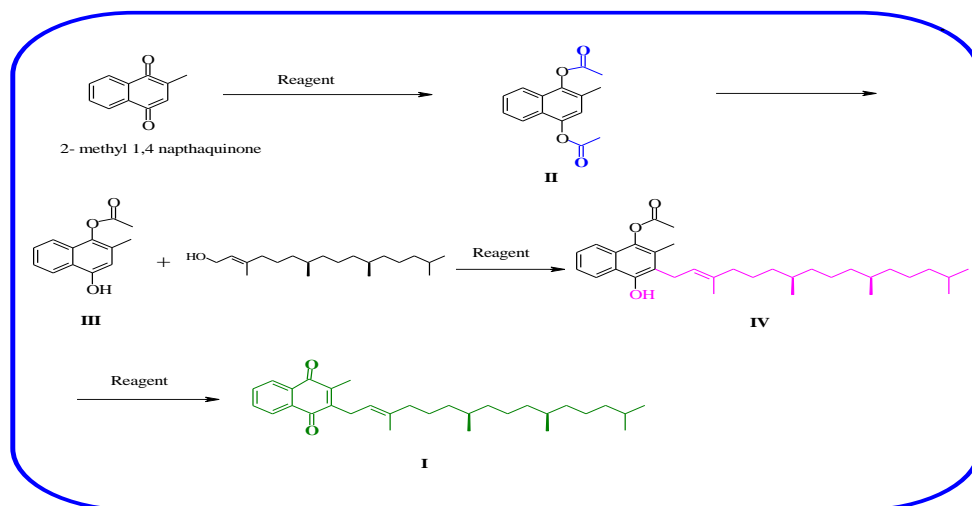
### 3. RESULTS AND DISCUSSION

An improved process for preparation of Vitamin K1, which is free from associated impurities and does not use hazardous and inflammable reagents and solvents. Also, involves the simplified isolation and purification methods yielding to give high pure Vitamin K1.

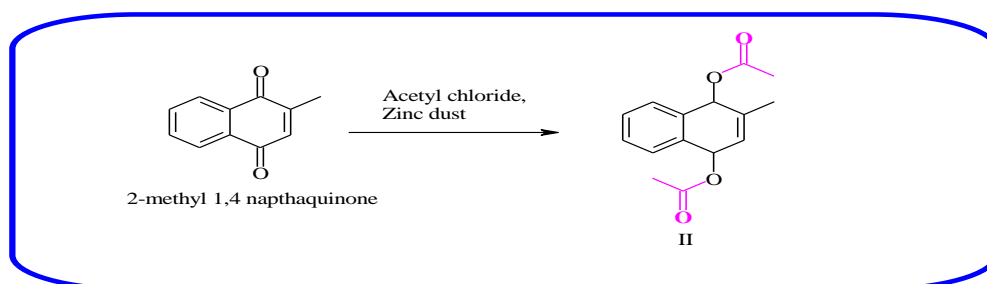
We started our work by following reported process [2,3] and we got required compound (I) and developed a commercially viable, sturdy process, which would be applicable to different analogues in the vitamin K family, especially keeping in view the most active compound, vitamin K1. The synthetic strategy would avoid use of hazardous reagents, inflammable solvents, like diethyl ether. Also elaborate synthetic processes free from oxidized impurities and extensive chromatographic purifications at intermediate stages.

#### 3.1 Synthesis of Compound (II)

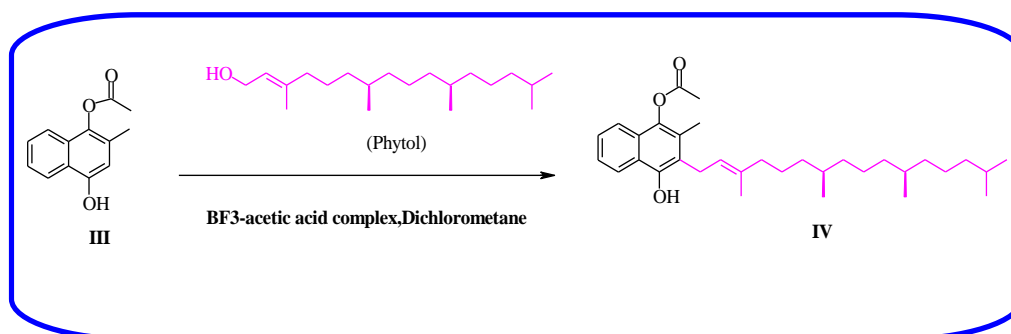
Compound (II) formation observed on the treatment Acetyl chloride with of 2-methyl, 1, 4 naphthaquinone in presence of Zinc and ethyl acetate solvent. The reaction progress was monitored by HPLC and compound (II) was isolated more than 98% HPLC purity. Which on further treatment with methanolic ammonia in methanol yielded the monoacetyl derivative, Compound (III).



**Scheme 1.**



**Scheme 2.**



**Scheme 3.**

Numerous methods are available for acylation of 2- methyl 1, 4 naphthaquinone. The Acetyl chloride was selected as reagent for acylation. It is commercially viable, easily available, does not comes under control substance.

### 3.2 Synthesis of Compound (IV)

During the screening of condensation reagent, we have encountered with several reagents. The

screening study of these reagents is done in R&D during optimization study .Table –I emphasize the optimization study.

These are the reagents which need a peculiar reaction conditions which consist with the higher temperature, longer hour reaction time, ethereal solvent and are discussed in introduction section. Among of all reagents,BF3 etherate and BF3-acetic acid complex [7] has hope for further

development. We choose BF<sub>3</sub>-acetic acid complex [8], over BF<sub>3</sub> etherate, as condensation reagent. BF<sub>3</sub> etherate [9] is not efficient catalyst on bulk scale production also explosive in nature.

Hence in order to avoid the consequences, we developed an improved process with BF<sub>3</sub>-acetic acid complex as a condensation reagent for compound (IV) synthesis. Reaction is carried out in dichloromethane solvent at the temperature range of 15-45°C and reaction mixture was monitored by HPLC. After completion of reaction, water was added to the reaction mass and the organic layer containing compound (IV) was separated and concentrated.

While designing the synthetic strategy and carrying out the requisite experimentation, we found that with the use of BF<sub>3</sub>-acetic acid complex, the reaction was very convenient, relatively clean and free from the impurities. The used condensation reagent i.e BF<sub>3</sub>-acetic acid is a cost-effective, commercially available could be easily handled and gave the desired condensation product with satisfactory results. BF<sub>3</sub>-acetic acid complex mostly has an

application in desilylation and Destannylation Reactions, now this invention introduces BF<sub>3</sub>-acetic acid complex as a condensation reagent.

### 3.3 Synthesis of Vitamin K1 (I)

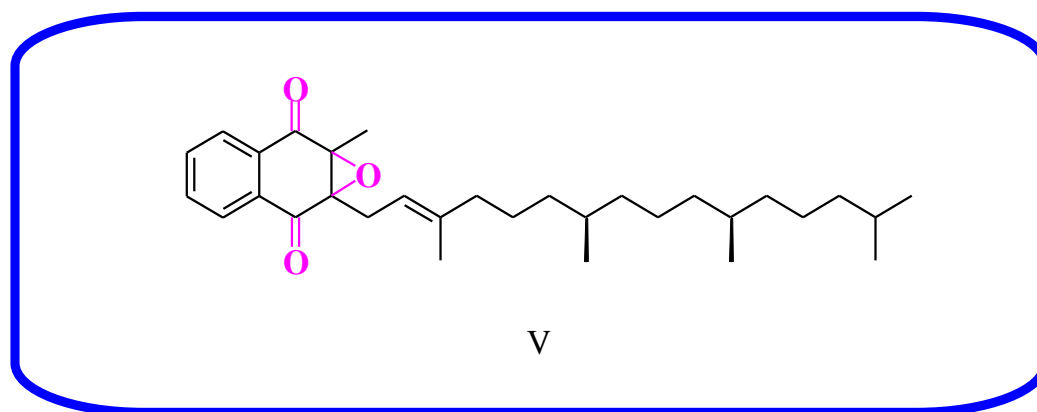
The mechanistic pathway and the synthetic approach for the conversion of compound IV to vitamin K1 (I) is an oxidation process. Various literature are available for conversion by using reagents like Ag<sub>2</sub>O [2,3], Ceric ammonium nitrate [1], Lithium Aluminum hydride and Ferric chloride [10] Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub> [11]. The outcome of the literature study, the conversion is require oxidizing agent, preferably Ag<sub>2</sub>O [12] which may leads the formation of epoxide impurity.

It was challenging task to avoid the use of metal oxidant from the synthesis of Vitamin K1 (I). Our optimization experimentation was started with various reported conditions, and we found that there is no need of metal oxidant for conversion and conversion can take place under the basic condition.

**Table 1. Compound synthesis and reagents**

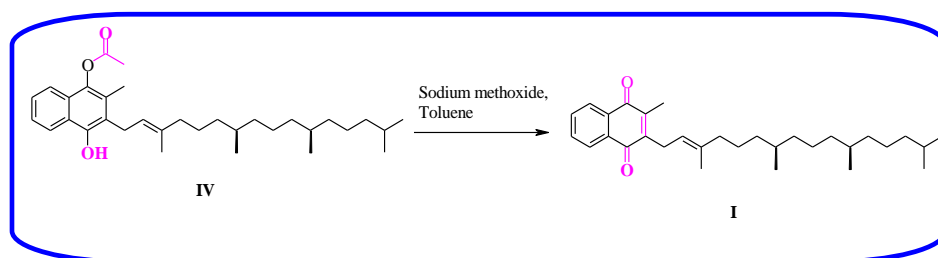
Entry	Reagent	Results <sup>b</sup>	Reference
01.	BF <sub>3</sub> -etherate	Product with Impurity formation observed	2,3
02.	Oxalic acid and trichloroacetic acid	No reaction, impurities formation observed	5,6
03.	ZnCl <sub>2</sub>	No product reaction	7
04.	AlCl <sub>3</sub>	Incomplete reaction with numerous impurity formation	8
05	BF <sub>3</sub> -acetic acid complex	Product formation observed	9

<sup>a</sup>All the reactions were carried out at 15 to 45°C with MDC as a solvent. <sup>b</sup> Reaction progress checked as on TLC.



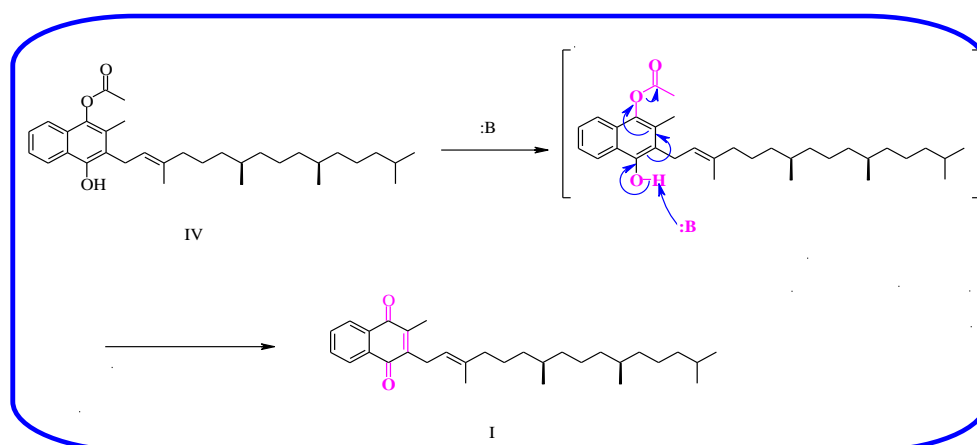
**Fig. 3.**

## Synthesis of vitamin K1



**Scheme 4.**

## The plausible mechanism for the conversion



**Fig. 4.**

The only use of base for the conversion ensure the formation of vitamin K1 (I) which was free from epoxide impurity (compound V) which may have generated during  $\text{Ag}_2\text{O}$  [13] process. Use of Sodium methoxide base in toluene solvent gives vitamin K1 (I) free from epoxide impurity. The conversion is carried out by dissolving the concentrated mass of insitu generated compound (III) in toluene and sodium methoxide was added to the reaction mixture and the stirring was continued at 15-40°C. The reaction progress was monitored by TLC and reaction mixture was treated with the dilute Hydrochloric acid. The layers were separated and concentrated the organic layer which was dissolved in toluene and treated with silica gel to form a slurry. Separated out the Silica gel by filtration and concentrated toluene filtrate to monitor the assay by HPLC, which was more than 80%.

The Optimum quantity of silica gel was found 6.0 times in which assay and yield were found satisfactory, and purifications such as column

chromatography, repeated crystallization, and extractions were not required to attain the desired quality. Further crude Phytionadione purified by flash chromatography by using n-Heptane and acetone solvent which gives pure vitamin K1 with the satisfactory yield and purity of minimum 99.8% and the "Z" isomer content less than 0.1%.

The two diastereomeric centers were present in the vitamin K1 and the configuration is 7R and 11R. In order to prove the formation of desired diastereomer i.e 7-R, 11-R in vitamin K1 large no of literature study experimentation was carried out.

These diastereomeric centers were generated from phytol. Phytol is synthesized from Chlorophyll which is a naturally occurring natural product [14,15,] with well-defined structure and stereochemistry. There is numerous literature reference [14,15] to prove that 7R and 11R stereo-chemical centers of phytol when obtained from natural chlorophyll. Interestingly the two

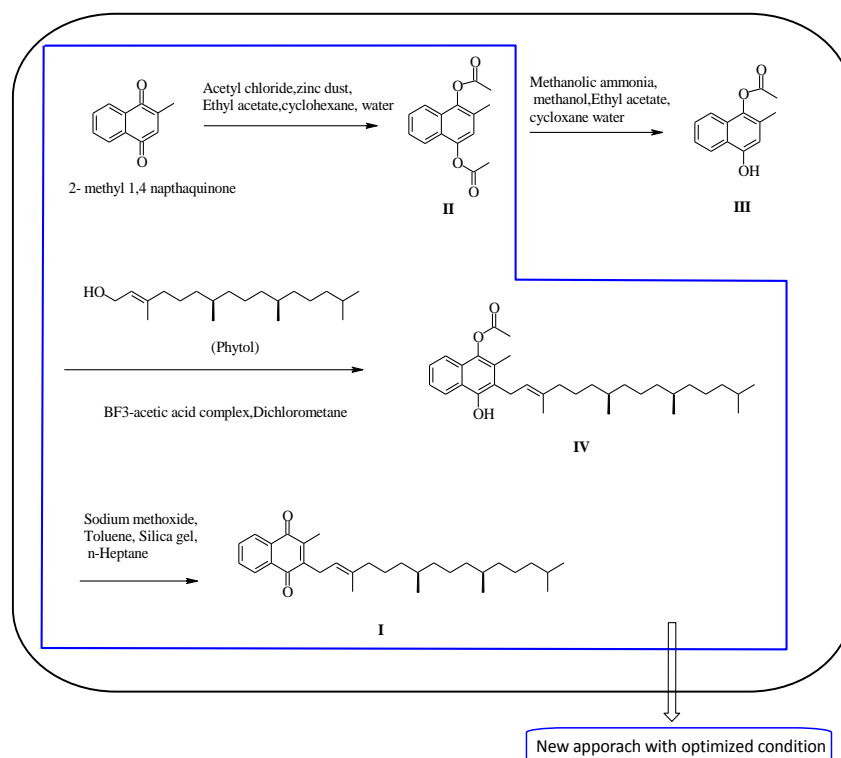
chiral centers at C-7 and C-11 are unique and deprived of any functional group adjacent to them. Therefore, under mild condition of degradation of chlorophyll to isolate natural phytol the possibility of racemization of phytol is remote. Many references in literature prove this point with scientific justification [16]. The current study on Phytonadione, the natural phytol obtained from chlorophyll has been used.

The major constrain in specific optical rotation (SOR) of phytol is its low  $[\alpha]_D$  value (+ 0.570 in octane) [16]. The SOR study on phytol (supplier: Zhejiang Haining Fengming Chlorophyll Co. Ltd) was performed by using the method reported in literature "Die absolute Konfiguration des natuerlichen Phyllochinons"<sup>12</sup>. We have recorded SOR of available batch of phytol obtained from the vendor in octane solvent and found to be +1.240 ( $c=1$ , octane). The fact that the dextrorotatory rotation was recorded, it suggests that the stereo-chemical assignment of our natural phytol is 7R, 11R which is in conformity with literature. Literature studies [17] also reported that phytol can be converted in phytone by oxidation whose literature reported SOR is  $[\alpha]_D$

+0.660 (octane) [14,15,16]. Phytol used in the manufacturing of Phytonadione, was likewise converted into phytone by reaction with  $\text{KMnO}_4$  as described in literature [17]. We isolated phytone whose structure was supported by NMR and mass spectroscopic analysis. The SOR of phytone, obtained above, was found to  $[\alpha]_D$  +0.640 (octane). This study confirms that the stereo-chemical assignment of our phytol is 7R, 11R. Finally, we also compared the SOR of our Phytonadione values with reported value [18]. SOR of the prepared Phytonadione was found to be  $[\alpha]_D$  -0.280 (dioxane) while the reported value of Phytonadione is  $[\alpha]_D$  -0.310 (dioxane). Undoubtedly the above information clearly indicated that the phytol which we have used has 7R, 11R stereo chemical configuration. In addition, Phytonadione manufactured from phytol also has 7R, 11R configuration.

The following examples are meant to be illustrative of the present invention. These examples exemplify the invention and are not to be construed as limiting the scope of the invention.

### The optimized scheme



**Scheme 5.**



#### 4. CONCLUSION

The invention describes the improved synthesis of vitamin K1, which introduce new approach for the acylation reaction and avoids the usage of controlled substance like acetic anhydride. Also the synthesis eliminates the hazardous and ethereal reagents from the process which are particularly used during the phytol coupling reaction and identified a new reagent BF3. Acetic acid complex which is safer to handle and does not require high temperature for the conversion.

In addition to this invention contributes a usage of cheap reagent sodium methoxide and avoids the use of costlier oxidizing agent silver oxide and the hazardous reagents like lithium aluminum hydride, etc reagents which is not feasible and cost effective on bulk scale production. The new approach of conversion is eliminating the crucial epoxide impurity formation and makes the process superior.

The invention describes the new isolation technique of vitamin k1 and removes column chromatography from the process to give pure Vitamin K1. The process describes adsorption of vitamin K1 on silica gel and leaching in n-heptane solvent for impurity removal. Finally, silica gel obtained after n- heptane slurry is enriched with vitamin k1 and impurity free further Vitamin k1 is isolated by in toluene leaching to silica gel . This method avoids the use on gallons of solvent require for the column chromatography and makes the process viable on plant scale.

The objectives of the present invention will become more apparent from the following detailed description.

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The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

#### CONSENT

It is not applicable.

#### ETHICAL APPROVALS

It is not applicable.

#### COMPETING INTERESTS

Authors have declared that no competing interests exist.

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