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Improved Synthesis of Vitamin K_1

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ABSTRACT

With (*E*/*Z*)-isomeric phytyl halides as side-chain materials, vitamin K_1 is synthesized via a Diels–Alder reaction to activate the free bridgehead hydrogen of **3** for the alkylation and a *retro*-Diels–Alder reaction to eliminate cyclopentadiene from **2** in a high yield, in which the configuration of the double bond in the phytyl side-chain is retained.

Vitamin K_1 (**1**) is the blood-clotting vitamin and it is important as an obligatory cofactor for the enzyme which carboxylates selected glutamate

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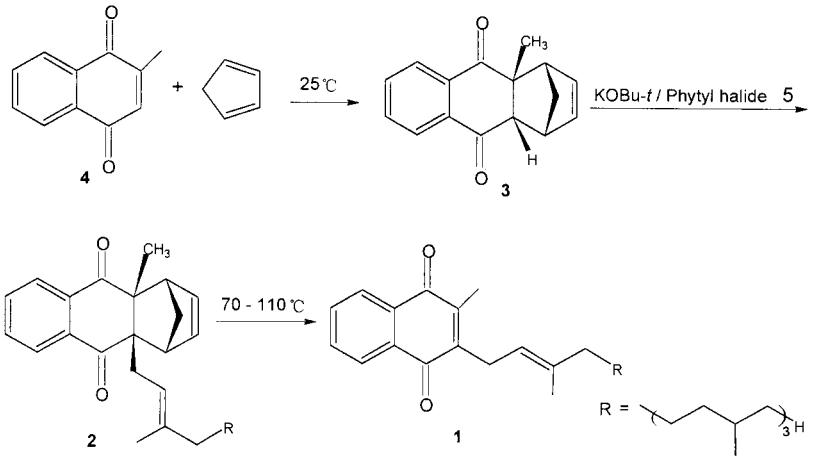
residues in the proteins of the blood coagulation cascade. The detailed review on **1** has already been given by Ruttimann for its history, biological activity, and synthetic advances.[1] The mechanism of action of **1** has been investigated by Dowd et al.[2] Though the synthesis of all four stereoisomers of (*E*)-vitamin K_1, i.e., (2′*E*, 7′*R*, 11′*R*)-**1**, (2′*E*, 7′*R*, 11′*S*)-**1**, (2′*E*, 7′*S*, 11′*S*)-**1**, and (2′*E*, 7′*S*, 11′*R*)-**1** and the determination of their biopotencies have been achieved,[3] a geometrical stereoselective synthesis of (*E*)-vitamin K_1 received increasing attention during the last decade for the practical inactivity of (*Z*)-vitamin K_1.[4–7]

In search for alternative procedures, we devoted our attention to the strategy that in the vitamin K series a Diels–Alder approach for the alkylation had successfully been employed where the non-acidic olefinic hydrogen is activated for enolization by intermediate formation of a cyclopentadiene–menadione cycloadduct (**3**).[1] After alkylation of **3**, the cyclopentadiene adduct (**2**) is readily decomposed to release cyclopentadiene in a *retro*-Diels–Alder reaction (Sch. 1). In terms of this principle, the stereochemistry in the side-chain can be retained from phytyl halide (**5**) to **1** by virtue of the basic conditions of alkylation. In particular, this methodology can meet the prerequisites for economical geometrical stereoselective synthesis of **1**,[1] and may be extended to other stereoselective syntheses of vitamin K derivatives and coenzyme Q derivatives.[1,4,5,8] Therefore, it is very necessary for this method to be improved to satisfy efficient and practical manufacture of **1** for the future. In the present report, we describe certain syntheses of **1** for exploring to

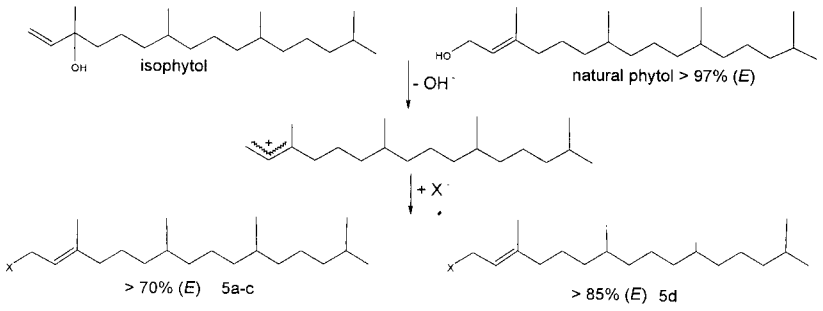


Scheme 1.

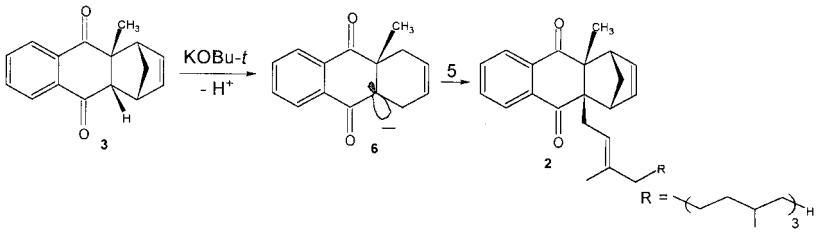
make the E/Z-ratio > 79.0:21.0 accord with the request of pharmacopoeia[9] utilizing isophytol or natural phytol as starting material via (E/Z)-isomeric **5** to prepare **1**. A milder and more efficient technique should be developed for a practical process.

In our investigations, with isophytol as the precursor, the E/Z-ratio = 80.5:19.5 phytyl chloride was prepared by hydrochloric acid as chlorinating agent but only the E/Z-ratio = 75.5:24.5 phytyl bromide was prepared using hydrobromic acid as brominating agent, and besides, the E/Z-ratio = 70.0:30.0 phytyl bromide was synthesized using phosphorus tribromide as brominating agent. On the other hand, with phytol as the precursor, the E/Z-ratio = 90:10–85:15 phytyl bromides can be produced using phosphorus tribromide as brominating agent. In these preparations of (E/Z)-isomeric **5**, we suggest that a mechanism concerning allylic cation rearrangement results in (E/Z)-**5** in favor of the (E)-isomer under the acidic conditions (Sch. 2). In contrast with that, the alkylation of **3** results in full retention of the stereochemistry of double bond in the side-chain under the basic conditions and it implies that the mechanism of nucleophilic substitution with carbon anion (**6**) as nucleophilic agent should be considered without a rearrangement of allylic cation resulting from **5** (Sch. 3). The spectroscopic data determined by 500 MHz NMR other than **5a** by 300 MHz NMR for the stereochemistry at phytyl chain are listed in Table 1.

The *endo*-configuration and the steric compression of the angular methyl group indicated for **3** were confirmed by a single-crystal X-ray analysis.[10] These analytic results can also expect that the steric compression of the *cis*-arrangement of the phytyl group with respect to the angular methyl group in **2** is the structural reason why the diketone **2** is extremely thermally unstable.[1] In order to understand and demonstrate their thermal instability and steric effect, detailed thermal studies have

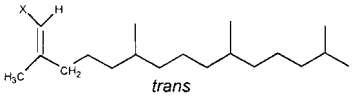


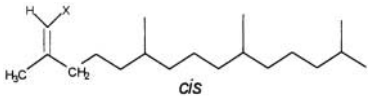
Scheme 2.

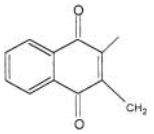


Scheme 3.

Table 1. Stereochemistry at phytyl chain.





X	δ_{trans}-CH_3	δ_{cis}-CH_3	δ_{trans}-CH_2	δ_{cis}-CH_2
CH_2OH[a]	1.66	1.74	—	—
CH_2Cl	1.78	1.86	—	—
CH_2Br	1.72	1.77	2.01	2.10
	1.78	1.68	—	—

[a]In natural phytol *E*-isomer > 97% determined by 500 MHz NMR.

been carried out. The thermogravimetry-differential scanning calorimetry (TG-DSC) analyses for **2** and **3** revealed that the decomposition of **2**, even at room temperature, is easier than that of **3**.[10]

The steric effect similarly exists in Diels–Alder reactions of 1,4-naphthoquinones with cyclopentadiene. For example, at room temperature in the presence of conventional catalyst like Lewis acid, 1,4-naphthoquinone reacts with cyclopentadiene for only 2 h to result in their adduct in 94% isolated yield,[4] but it takes more than 48 h for the reaction of 2-methyl-1,4-naphthoquinones with cyclopentadiene to achieve their cycloadditions in ca. 90% isolated yields.[5,11] Singh et al. reported that the micelle catalyzed Diels–Alder reaction of cyclic dienes with various quinone in aqueous media were remarkably faster and gave

better yields of the adducts compared with the conventional reaction.[12] We performed herein a cycloaddition of menadione with cyclopentadiene in acetic acid catalyzed by dodecyltrimethylammonium bromide to give **3** in 93.2% isolated yield only requiring 3–5 h at room temperature, confirming again the unusual ability of micelles to enhance the rate of Diels–Alder reaction.

We found that the remarkable excess of potassium *tert*-butanolate (ca. 5.0–6.0 equiv.) was necessary for accomplishing a highly yield of alkylation of **3** to produce **2**. If appropriate excess of potassium *tert*-butanolate (ca. 1.0–2.0 equiv.) was introduced, the alkylation of **3** would possibly lead to a failing result. Desimoni et al. indicated that the nature of the solvent effect was the same in both Diels–Alder and *retro*-Diels–Alder reaction, and that the rate constant of the *retro*-Diels–Alder reaction of **3** was the largest in acetic acid by contrast with in different solvents thereof.[13] Furthermore, we reported that the cycloreversion of **2** in acetic acid, which reacted at 90°C catalyzed by dodecyltrimethylammonium bromide to give **1** and cyclopentadiene quantitatively, was easier than that of **2** in toluene.[4,5,11] Apparently, the low temperature and the short time of the cycloreversion of **2** are favorable for the quality and refining of **1**. As such, these works to improve the preparation of **1** will intensify the understanding on its mechanism and technique for practical application.

EXPERIMENTAL

All reactions were monitored by TLC and the spots were visualized with iodine vapor. Column chromatography was performed on domestic silica gel (particle size 120–200 mesh). Melting points were determined by capillary method without correction. Elemental analyses were performed on a PE240-C element analysis instrument. Ultraviolet spectra were recorded on a Shimadzu UV-240 spectrometer. Infrared spectra were measured on a Nicolet Magna FTIR-560 spectrometer as neat films. Proton NMR spectra were recorded on a Bruker AVANCE DRX-500 spectrometer using $CDCl_3$ as solvent and the solvent peak (7.260 ppm) was used as reference, unless otherwise noted. Chemical shifts were expressed in parts per million (δ, ppm). Mass spectra were recorded on a VG-12-250 low-resolution quadrupole spectrometer and m/z values were given with relative intensities in parentheses. With a flow of 1 mL/min (*n*-hexane/*n*-amyl alcohol 2000:1.5), HPLC was performed on

a HP 1050 chromatograph using an Alltech HPLC column (hypersil silica 5 μm, 250 mm × 4.6 mm) and a UV monitor by 254 nm.[9]

Synthesis of Phytyl Chloride 5a

A mixture of 300 mL of 37% aqueous hydrochloric acid (excess) and 2 g of dodecyltrimethylammonium bromide were placed in a 3-necked round-bottomed flash equipped with a mechanical stirrer, and the solution was cooled to −20°C. To this 100.0 g (0.338 mol) of isophytol were added and the resultant mixture was stirred vigorously for more than 20 h at −20°C. The oil layer was separated and the acid layer was extracted with benzene twice (150 mL × 2). The benzene extract was added to the solid oil layer, the combined liquids were washed with water twice (150 mL × 2), and the washed organic layer was dried over anhydrous calcium chloride. The organic layer was filtered and the solvent was removed by rotary evaporation. Thus, 84.3 g (79.3%) of **5a** was obtained as a colorless oil (80.5%-*trans* by NMR). ^{1}H NMR (300 MHz, TMS as the internal standard in $CDCl_3$): $\delta = 0.94$ (d, 12H, $J = 7$ Hz, 4CH_3), 1.31 (m, 19H, CH and CH_2), 1.78 (d, 3H, $J = 1$ Hz, *trans*-CH_3), 1.86 (d, 3H, $J = 1$ Hz, *cis*-CH_3), 2.05 (t, 2H, $J = 8$ Hz, CH_2 at C4), 4.05 (d, 2H, $J = 8.5$ Hz, CH_2 at C1), 5.46 (t, 1H, $J = 2$ Hz, =CH at C2).

Synthesis of Phytyl Bromide 5b

Following above procedure, isophytol (100.0 g, 0.338 mol) was treated with 300 mL of 48% aqueous hydrobromic acid (excess) to give 93.0 g (76.7%) of **5b** as a light yellow oil (75.5%-*trans* by NMR). ^{1}H NMR: $\delta = 0.85$ (s, 6H, 2CH_3), 0.87 (s, 6H, 2CH_3), 1.01–1.42 (br. m, 17H, CH and CH_2), 1.52 (m, 2H, CH_2 at C5), 1.72 (s, 3H, $J = 1$ Hz, *trans*-CH_3), 1.77 (s, 3H, $J = 1$ Hz, *cis*-CH_3), 2.01 (t, 2H, $J = 8$ Hz, *trans*-CH_2 at C4), 2.10 (t, 2H, $J = 8$ Hz, *cis*-CH_2 at C4), 4.02 (d, 2H, $J = 8.5$ Hz, CH_2 at C1), 5.53 (t, 1H, $J = 2$ Hz, =CH at C2).

Synthesis of Phytyl Bromide 5c

Following the procedure of Isler et al.,[14] 9.0 g (0.030 mol) of isophytol was treated with 9.0 g (0.033 mol) of phosphorus tribromide at 0–5°C for 6 h to yield 8.2 g (75.2%) of **5c** as a light yellow oil (70.0%-*trans* by NMR). ^{1}H NMR spectra are in accordance with **5b**.

Synthesis of Phytyl Bromide 5d

Following the procedure of Davisson et al.,[15] 9.0 g (0.030 mol) of natural phytol was treated with 9.0 g (0.033 mol) of phosphorus tribromide at 0–5°C for 6 h to yield 8.0 g (73.6%) of **5d** as a light yellow oil (86.6%-*trans* by NMR). ^{1}H NMR spectra are in accordance with **5b**.

Synthesis of the Cyclopentadiene–Menadione Adduct 3

A mixture of 17.2 g (0.10 mol) of menadione and 1 g of dodecyltrimethylammonium bromide in 100 mL of acetic acid were placed in a flask. To this 23.0 mL (0.28 mol) of freshly cracked cyclopentadiene were then added and the resultant mixture was stirred at room temperature for 5 h. The solvent and the diene excess were evaporated with a rotary evaporator at 50°C. The residue was recrystallized from methanol. The crystals were filtered off and dried at 40°C for 5 h in vacuum to give 22.2 g (93.2%) of **3** as a white solid, m.p. 97–98°C (Lit. 98°C).[12] UV (methanol): $\lambda_{max} = 224$, 257 nm; IR (KBr): $\nu = 2950$, 1670, 1590 cm^{-1}; ^{1}H NMR: $\delta = 1.54$ (s, 3H, CH_3), 1.73 (ABq, $J = 9.5$ Hz, 2H, bridge CH_2), 3.04 (d, $J = 4.1$ Hz, ring junction CH), 3.20 (s, 1H, CH), 3.55 (m, 1H, CH), 5.89 (dd, $J_1 = 2.9$ Hz, $J_2 = 2.7$ Hz, 1H, olefinic =CH), 6.08 (dd, $J_1 = 2.9$ Hz, $J_2 = 2.7$ Hz, 1H, olefinic =CH), 7.68 (m, 2H, aromatic H), 8.02 (m, 2H, aromatic H). Anal. for $C_{16}H_{14}O_2$, calcd. (%) C 80.00, H 5.83; found C 79.81, H 5.92.

Synthesis of Vitamin K_1 1

A mixture of 12.3 g (0.110 mol) of freshly prepared potassium *tert*-butanolate and 100 mL of tetrahydrofuran were placed under argon in a flask equipped with a magnetic stirrer, a reflux condenser, and argon gasification. After cooling the mixture to −3°C, 5.0 g (0.021 mol) of **3** were added. The red solution obtained was stirred at −3 to 0°C for 30 min to dissolve **3**. A solution of ca. 0.24 mol (1.15 equiv.) of phytyl halide **5a–d** in 25 mL of tetrahydrofuran was then added dropwise during ca 30 min, respectively, followed by stirring at 0°C for additional 1 h. Thereupon, 1 N HCl was added until acidity, then the resultant yellow solution was concentrated with a rotary evaporator and extracted with toluene twice (100 mL × 2). The organic extracts were washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure.

Table 2. Synthesis and stereochemistry of vitamin K_1.

Starting material	Ratio of *trans*/*cis*[a] for **5**	Yield (%)[b] of vitamin K_1	Ratio of *trans*/*cis*[a] for vitamin K_1	Purity (%)[c] of vitamin K_1
5a	80.5/19.5	81.4	80.8/19.2 (82.3/17.7)[c]	99.9
5b	75.5/24.5	87.4	75.8/24.2 (76.6/23.3)[c]	100.0
5c	70.0/30.0	91.3	70.5/29.5 (72.2/27.8)[c]	99.7
5d	86.6/13.4	85.7	86.9/13.1 (88.9/11.1)[c]	100.0

[a]Determined by 500 MHz NMR other than **5a** by 300 MHz NMR.
[b]Isolated yield based on **3**.
[c]Determined by HPLC.

The above-obtained yellow oil **2** was dissolved in acetic acid (ca. 30 mL) in the presence of dodecyltrimethylammonium bromide (ca. 0.2 g) and heated at 90°C under argon in the dark for 15 min. The mixture was then cooled and concentrated with a rotary evaporator. This residue was purified by column chromatography on silica gel with *n*-hexane/diethyl ether (20:1) as eluent, thereby obtaining (*E*/*Z*)-isomeric **1** as a yellow oil in 80–91% yields (Table 2). UV (hexane): $\lambda_{max} = 243$, 249, 261, 270, 327 nm; IR (film): $\nu = 2940$, 2920, 2850, 1660, 1620, 1598, 718 cm^{-1}; ^1H NMR: $\delta = 0.81$ (d, 3H, $J = 6.5$ Hz, $CHCH_3$), 0.82 (d, 3H, $J = 6.5$ Hz, $CHCH_3$), 0.86 (d, 6H, $J = 6.5$ Hz, $CHCH_3$), 0.97–1.45 (m, 17H, C*H* and CH_2), 1.52 (m, 2H, CH_2 at C5′), 1.68 (s, 3H, *cis*-CH_3 at C3′), 1.78 (s, 3H, *trans*-CH_3 at C3′), 1.94 (t, 2H, $J = 9$ Hz, CH_2 at C4′), 2.19 (s, 3H, ring CH_3), 3.37 (d, 2H, $J = 7$ Hz, CH_2 at C1′), 5.00 (t, 1H, $J = 7$ Hz, =C*H* at C2′), 7.69 (m, 2H, aromatic *H*), 8.08 (m, 2H, aromatic *H*); EIMS $m/z = 450$ (M^+, 100), 435 (6), 224 (26), 197 (18), 185 (20%). Anal. for $C_{31}H_{46}O_2$, calcd. (%) C 82.61, H 10.29; found C 82.44, H 10.37.

REFERENCES

1. Rüttimann, A. Recent advances in the synthesis of K-vitamins. Chimia **1986**, *40* (9), 290–306 and references cited therein.
2. Dowd, P.; Ham, S.W.; Geib, S.J. Mechanism of action of vitamins K. J. Am. Chem. Soc. **1991**, *113*, 7734–7743.
3. Schmid, R.; Antoulas, S.; Rüttimann, A.; Schmid, M.; Vecchi, M.; Weiser, H. Synthesis of all four stereoisomers of (*E*)-vitamins K_1 (phylloquinone), analysis of their diastereoisomeric and enantiomeric purities and determination of their biopotencies. Helvetica Chimica Acta **1990**, *73*, 1276–1299.
4. Kimio, H.; Tetsuo, I.; Chiaki, S.; Masayuki, K. Preparation process of quinone derivative and intermediate for the preparation thereof. EP Appl. 613, 877, Sept. 7, 1994.
5. Kimio, H.; Chiaki, S.; Masayuki, K. Preparation process of naphthoquinone derivatives and intermediates for the preparation thereof. EP Appl. 636, 598, Feb. 1, 1995.
6. Tso, H.-H.; Chen, Y.-J. A convenient one-flask synthesis of vitamins K. J. Chem. Research (*S*) **1995**, 104–105.
7. Lipshutz, B.H.; Kim, S.-K.; Mollard, P.; Stevens, K.L. An expeditious route to CoQ_n, vitamins K_1 and K_2, and related allylated *para*-quinones utilizing Ni (0) catalysis. Tetrahedron **1998**, *54*, 1241–1253.
8. Merz, A.; Ràuschel, M. Synthesis of crown ethers related to ubiquinones. Synthesis **1993**, 797–802.

9. The United States Pharmacopeial Convention, Inc. Phytonadione. *United States Pharmacopoeia*, 24th Ed.; the Board of Trustees: Rockville, Maryland, 2000; Vol. 2, p. 1330.
10. Ji, Y.-F. *Deep Processing and Utilization of Methylnaphthalene—The Stereoselective Synthesis of Vitamin K_1*. Doctoral Dissertation, China University of Mining and Technology: Xuzhou, 2001.
11. Ruttimann, A.; Büchi, G.H. Process for the Manufacture of Quinone Derivatives. US Patent 4,603,223, July 29, 1986.
12. Singh, V.K.; Raju, B.N.S.; Deota, P.T. Micellar catalysis $\pi^{4s} + \pi^{2s}$ cycloaddition in aqueous media. Synth. Commun. **1988**, *18* (6), 567–574.
13. Desimoni, G.; Faita, G.; Pasini, D.; Righetti, P.P. Solvent effect as the result of frontier molecular orbital interaction VII. The retro-Diels–Alder reaction. Tetrahedron **1992**, *48* (9), 1667–1674.
14. Isler, O.; Rüegg, R.; Chopard-dit-Jean, L.; Wagner, H.; Bernhard, K. Synthese von squalen aus natürlichem and synthetischem nerolidol. Helv. Chim. Acta **1956**, *39*, 897–904.
15. Davisson, V.J.; Woodside, A.B.; Neal, T.R.; Stremler, K.E.; Muehlbacher, M.; Poulter, C.D. Phosphorylation of isoprenoid alcohols. J. Org. Chem. **1986**, *51*, 4768–4779.

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