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Efficient Syntheses of Vitamin K Chain-Shortened Acid Metabolites

Aaron M. Teitelbaum*, Michele Scian, Wendel L. Nelson, and Allan E. Rettie

Department of Medicinal Chemistry, School of Pharmacy, University of Washington, Seattle, WA 98195

Abstract

Vitamin K sequentially undergoes ω -oxidation followed by successive rounds of β -oxidation to ultimately produce two chain-shortened carboxylic acid metabolites, vitamin K acid 1 and vitamin K acid 2. Two facile syntheses of these acid metabolites are described, each starting from commercially available menadione-cyclopentadiene adduct **3**. Vitamin K acid 1 was synthesized in five steps *via* alkylation with a geranyl halide followed by subsequent oxidation reactions, while fully retaining the *trans* configuration of the side chain 2',3'-double bond. Vitamin K acid 2 was synthesized in 5 steps from **3** *via* alkylation with dimethylallyl chloride and subsequent oxidation reactions.

Vitamin K is an umbrella term describing a family of molecules containing the 2-methyl-1,4,-naphthoquinone core. The most widely studied are phyloquinone (Vitamin K₁) and a form of Vitamin K₂, menaquinone-4 (MK-4), that differ in the degree of unsaturation along the C20-phytyl chain (Scheme 1). Whereas Vitamin K₁ primarily functions as a regulator of hemostasis, MK-4 appears important for bone health;¹ it is also implicated in vascular calcification² and it regulates ATP production in mitochondria.³ While the physiological roles of Vitamin K continue to be evaluated, little information regarding metabolism and excretion of Vitamin K metabolites is available. In humans, Vitamin K₁ and MK-4 are metabolized to two glucuronide conjugates of chain-shortened carboxylic acid metabolites, referred to as vitamin K acid 1 (**1**) and vitamin K acid 2 (**2**) (Figure 1).^{4–6} In order to quantify Vitamin K acid metabolites in biological matrices to understand Vitamin K metabolism, authentic analytical standards are required.

Reported syntheses of vitamin K acid 1 (**1**) are incompletely described and required several laborious steps, some of which result in the partial isomerization of the side chain 2',3'-double bond.^{7–10} The menadione-cyclopentadiene adduct **3** previously alkylated with C20-phytyl allylic halides¹¹ to obtain Vitamin K₁ was used as starting material for **1** in our synthesis (Scheme 2). Alkylation with geranyl bromide gave *trans*-geranyl adduct **4** in 79% yield. The cyclopentadiene protecting group was removed by heating **4** in AcOH with catalytic dodecyl-trimethylammonium bromide to produce **5** in 97% yield. The previously

Tel: 206-543-2224; Fax: 206-685-3252; atbaum@uw.edu.

Supporting Information

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reported regioselective epoxidation of geraniol derivatives, followed by oxidative cleavage with periodic acid to yield corresponding aldehydes¹² was utilized to obtain aldehyde **7**. Epoxidation (*m*CPBA) of alkene **5** afforded **6** (67% yield), and subsequent periodic acid oxidation gave aldehyde **7** (65% yield). Aldehyde **7** was oxidized with potassium peroxymonosulfate¹³ yielding *trans*-vitamin K acid 1 (**1**) (70% yield). The *trans* configuration of (**1**) was confirmed by a 2D-NOESY experiment (supplemental), which did not show a strong NOE cross-peak between the vinyl proton at C2' and the vinyl methyl group at C3'.

Previously reported syntheses of vitamin K acid 2 (**2**) required several steps with poor yields of intermediates.^{7,10} New methodology was utilized to synthesize vitamin K acid 2 (**2**) more efficiently (Scheme 3). Menadione-cyclopentadiene adduct **3** was alkylated with dimethylallyl chloride to afford compound **8** in 82% yield. Following deprotection, **9** was subjected to allylic oxidation¹⁴ with SeO₂ to give allylic alcohol **10** (57% yield). Subsequent reduction of the allylic alcohol by ruthenium-catalyzed transfer hydrogenation¹⁵ afforded saturated alcohol **11** in 17% yield. Multiple attempts at improving the percent conversion and yield of **11** were made by experimenting with several ruthenium catalysts. Initially, transfer hydrogenation was attempted with [{RuCl(μ -Cl)(η^6 -C₆Me₆)}₂] and Cs₂CO₃, but the double bond remained intact as evidenced by the corresponding ¹H NMR triplet signal at C3'. Subsequently, saturation of **10** with [Ru(cod)Cl₂]_n and potassium hydroxide¹⁶ resulted in a 1:1 mixture of **10** and **11** (34% yield). Lastly, we tried [{RuCl(μ -Cl)(η^6 -para-cymene)}₂] with Cs₂CO₃ and the ¹H NMR showed 70% conversion. After increasing the catalyst:base ratio to 25:50 mol%, respectively, pure **11** was isolated in 17% yield. Naphthoquinone containing molecules such as Vitamin K and menadione are notoriously unstable when exposed to heat, light, alkali, and reducing conditions. In each of the transfer hydrogenation reactions attempted, greater than 60% of the starting material was not recovered, which we attribute to probable degradation of the naphthoquinone. To complete the synthesis, **11** was oxidized to the carboxylic acid with periodic acid and pyridinium chlorochromate¹⁷ to afford vitamin K acid 2 (**2**) (84% yield).

The syntheses described herein provide facile routes to vitamin K acid 1 and 2 utilizing established reaction procedures and inexpensive starting materials. Overall yields for vitamin K acid 1 and 2 were 23% and 5%, respectively. The limiting step in the vitamin K acid 2 synthesis is the saturation of **11**, which is mainly the result of naphthoquinone instability under the experimental conditions described. During the synthesis of vitamin K acid 1, the *trans* configuration of the 2',3'-double bond was retained resulting in the production all *trans*-vitamin K acid 1 without the need for geometric isomer recrystallization as previously described⁷. Overall, the synthesized metabolites will serve as authentic standards for our future investigations of vitamin K metabolism.

Experimental Procedures

All chemicals and solvents were of reagent grade and purchased from Sigma Aldrich (St. Louis, MO) unless otherwise indicated. All reactions were performed under nitrogen and were monitored by TLC analysis utilizing SiO₂ 60 F₂₅₄ plates (EMD Chemicals, Inc, Gibbstown, NJ). Flash column chromatography was performed with a CombiFlash® R_f

purification system (Teledyne Isco, Lincoln, NE) with a mixture of hexane and ethyl acetate as the elution solvent system. Melting points were acquired with a MEL-TEMP capillary melting apparatus equipped with a Fluke 51 II thermometer (Thermo Scientific). ^1H and ^{13}C NMR spectra were obtained on an Agilent DD2 500 MHz spectrometer at 25 °C. Proton chemical shifts (δ) are reported in ppm and referenced to the chloroform signals (^1H δ = 7.27 ppm; ^{13}C δ = 77.23 ppm). Coupling constants (J) are reported in Hz and multiplicities are: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, and ovlp = overlapping. Full proton and carbon assignments for vitamin K acid 1 (**1**) and vitamin K acid 2 (**2**) were completed by 2D ^1H - ^{13}C HSQC and HMBC experiments at natural abundance. High-resolution mass spectrometry (HRMS) was acquired on a Thermo Fisher LTQ Orbitrap equipped with an ESI probe.

Protected menadione geranyl adduct 4

Protected menadione adduct **3** (Toronto Research Chemicals, Toronto, Ontario) (100 mg, 0.42 mmol) was dissolved in 2.2 mL of a 1.0 M solution of potassium *tert*-butoxide in THF. After the resulting blood-red solution was cooled to 4 °C and stirred for 30 min, geranyl bromide (104 mg, 0.48 mmol) was added dropwise, and the solution was warmed to room temperature. After 2 hours, 1.0 N HCl was added until the pH became acidic. The yellow solution was then evaporated and the residue was re-dissolved in EtOAc (20 mL), which was subsequently washed with water (5 mL) and brine (5 mL). After drying (MgSO_4) and evaporation, the crude product was purified by flash column chromatography (10% EtOAc/hexanes) to afford the title compound **4** as a yellow oil; yield: (124 mg, 79%); 1:1 ratio of diastereomers.

IR (neat): 2989, 2934, 1683, 1597, 1457, 1378, 1279, 983, 717, 653 cm^{-1}

^1H NMR (500 MHz, CDCl_3) δ (s, 6 H) 1.49 (d, J = 9.3 Hz, 2 H) 1.57 (s, 12 H), 1.59 (s, 6 H) 1.75 – 1.87 (m, 8 H) 1.91 (d, J = 9.3 Hz, 2 H) 2.49 (dd, J = 15.2, 6.9 Hz, 2 H) 2.87 (dd, J = 15.2, 6.9 Hz, 2 H) 3.14 (br. s, 2 H) 3.22 (br s, 2 H) 4.89 (br s, 4 H), 6.05 (dd, J = 8.1, 1.7 Hz, 4 H), 7.62 – 7.71 (m, 4 H) 7.86 – 7.92 (m, 2 H) 7.93 – 7.99 (m, 2 H).

^{13}C NMR (125 MHz, CDCl_3) δ 16.2, 17.5, 23.6, 25.6, 26.2, 36.5, 39.6, 43.7, 54.2, 55.5, 57.2, 60.5, 119.9, 123.9, 126.2, 126.9, 131.3, 133.5, 133.8, 134.9, 136.8, 137.4, 137.5, 138.3, 201.7, 202.3.

HRMS (ESI calcd for $\text{C}_{26}\text{H}_{31}\text{O}_2$ $[\text{M} + \text{H}]^+$ 375.2319, found: 375.2330 (error 3.0 ppm).

trans-2-methyl-3-(3',7'-dimethylocta-2',6'-dienyl)-1,4-naphthoquinone (**5**)

Compound **4** (30.3 mg, 0.081 mmol) was dissolved in acetic acid (1.0 mL) followed by the addition of 1.7 mg of dodecyltrimethylammonium bromide. The solution was heated to 90 °C for 60 min. After cooling to room temperature, the solvent was evaporated, and the crude product was purified by flash column chromatography (5% EtOAc/hexanes) to afford the product **5** as yellow oil; yield: 23.8 mg (96%).

^1H NMR (500 MHz, CDCl_3) δ 1.56 (s, 3 H) 1.62 (s, 3 H) 1.79 (s, 3 H) 1.93 – 2.01 (m, 2 H) 2.02 – 2.10 (m, 2 H) 2.19 (s, 3 H) 3.37 (d, J = 6.8 Hz, 2 H) 4.94 – 5.10 (m, 2 H) 7.64 – 7.74 (m, 2 H) 8.04 – 8.12 (m, 2 H).

^{13}C NMR (125 MHz, CDCl_3) δ 12.6, 16.3, 17.6, 25.6, 25.9, 26.5, 39.6, 109.8, 119.1, 123.9, 126.1, 126.2, 131.4, 132.1, 133.5 (ovlp 2C), 137.4, 143.3, 146.1, 184.4, 185.4.

HRMS (ESI calcd for $\text{C}_{21}\text{H}_{25}\text{O}_2$ $[\text{M} + \text{H}]^+$ 309.1849, found: 309.1855 (error 1.8 ppm).

***trans*-2-methyl-3-(6',7'-epoxy-3',7'-dimethylocta-2'-enyl)-1,4-naphthoquinone (6)**

A solution of 70% *m*CPBA (42.5 mg, 0.246 mmol) in CH_2Cl_2 (2.5 mL) was added dropwise to a solution of olefin **5** (53.9 mg, 0.175 mmol) in CH_2Cl_2 (2.5 mL) at 4 °C. The reaction mixture was warmed to room temperature and was stirred overnight. After evaporation, the residue was dissolved in EtOAc (20 mL) and washed successively with aqueous 5% NaHCO_3 (5 mL), water (5 mL), and brine (5 mL). The organic layer was dried (MgSO_4), evaporated, and the product was purified by flash column chromatography (5% EtOAc/hexanes) to give epoxide **6** as a yellow oil; yield: 37 mg (67%).

IR (neat): 2932, 2898, 1741, 1663, 1650, 1462, 1381, 1298, 716 cm^{-1}

^1H NMR (500 MHz, CDCl_3) δ 1.24 (s, 3 H) 1.26 (s, 3 H) 1.57 – 1.66 (m, 2 H) 1.82 (s, 3 H) 2.07 – 2.17 (m, 2 H) 2.19 (s, 3 H) 2.67 (t, J = 6.1 Hz, 1 H) 3.32 – 3.46 (m, 2 H) 5.08 (t, J = 6.60 Hz, 1 H) 7.69 (dd, J = 5.62, 3.18 Hz, 2 H) 8.00 (d, J = 7.8 Hz, 2 H).

^{13}C NMR (125 MHz, CDCl_3) δ 12.7, 16.3, 18.7, 24.7, 26.0, 27.3, 36.3, 60.3, 64.0, 119.7, 126.2, 126.3, 132.1 (ovlp 2C), 133.3, 133.4, 136.7, 143.4, 145.9, 184.5, 185.4.

HRMS (ESI calcd for $\text{C}_{21}\text{H}_{25}\text{O}_3$ $[\text{M} + \text{H}]^+$ 325.1798, found 325.1801 (error 0.78 ppm).

***trans*-2-methyl-3-(5'-formyl-3'-methyl-2'-pentenyl)-1,4-naphthoquinone (7)**

Periodic acid (38.7 mg, 0.170 mmol) dissolved in water (2.0 mL) was added dropwise to a solution of epoxide **6** (37.0 mg, 0.114 mmol) in THF (2.0 mL) at room temperature. After stirring for 60 minutes, the reaction mixture was diluted with Et_2O (20 mL) and washed successively with aqueous 5% NaHCO_3 (5 mL), water (5 mL), and brine (5 mL). The organic layer was collected, dried (MgSO_4), evaporated, and the product was purified by flash column chromatography to yield aldehyde **7** as a yellow oil; yield: 20.7 mg (65%).

IR (neat): 2935, 2893, 1729, 1662, 1598, 1462, 1298, 718 cm^{-1}

^1H NMR (500 MHz, CDCl_3) δ 1.82 (s, 3 H) 2.18 (s, 3 H) 2.29 – 2.37 (m, 2 H) 2.49 – 2.55 (m, 2 H) 3.37 (d, J = 6.8 Hz, 2 H) 5.07 (t, J = 6.6 Hz, 1 H) 7.70 (m, 2 H) 8.05 – 8.13 (m, 2 H) 9.73 (s, 1 H).

^{13}C NMR (125 MHz, CDCl_3) δ 12.7, 16.4, 26.0, 31.7, 42.0, 120.3, 126.2, 126.3, 132.1 (ovlp 2C), 133.3 (ovlp 2C), 135.5, 143.5, 145.6, 184.4, 185.3, 202.0.

HRMS (ESI calcd for $\text{C}_{18}\text{H}_{19}\text{O}_3$ $[\text{M} + \text{H}]^+$ 283.1329, found: 283.1332 (error 1.3 ppm).

***trans*-2-methyl-3-(5'-carboxy-3'-methyl-2'-pentenyl)-1,4-naphthoquinone (1)**

To a solution of aldehyde **7** (19.7 mg, 0.070 mmol) in DMF (2 mL), was added KHSO₅ (94.4 mg, 0.307 mmol) and the reaction mixture stirred at room temperature for 2.5 hrs. Et₂O (20 mL) was added to the reaction mixture and the ether was subsequently washed with water (5 mL) and brine (5 mL). The organic layer was collected, dried (MgSO₄), evaporated, and the product was purified by flash column chromatography (40% EtOAc/hexanes) to yield vitamin K acid **1** (**1**) as a yellow solid; yield: 14.3 mg (70%); mp 118 – 120 °C

IR (KBr): 2935, 2899, 1702, 1661, 1645, 1437, 1300, 1226, 866, 787, 717 cm⁻¹

¹H NMR (500 MHz, CDCl₃) δ 1.82 (s, 3 H, CH₃ at C3') 2.18 (s, 3 H, CH₃ at C2) 2.28 – 2.36 (m, 2 H, CH₂ at C4') 2.38 – 2.48 (m, 2 H, CH₂ at C5') 3.38 (d, *J* = 6.9 Hz, 2 H, CH₂ at C1') 5.09 (t, *J* = 6.4 Hz, 1 H, CH at C2') 7.65 – 7.77 (m, 2 H, CH at C6, CH at C7) 8.03 – 8.15 (m, 2 H, CH at C5, CH at C8).

¹³C NMR (125 MHz, CDCl₃) δ 12.6 (CH₃ at C2), 16.2 (CH₃ at C3'), 25.9 (C1'), 32.5 (C5'), 34.2 (C4'), 120.3 (C2)', 126.2 (C5) 126.3 (C8), 132.1 (ovlp C9, C10), 133.3 (C6), 133.4 (C7), 135.4 (C3'), 143.6 (C2), 145.6 (C3), 178.5 (C6'), 184.4 (C4), 185.3 (C1).

HRMS (ESI calcd for C₁₈H₁₉O₄ [M + H]⁺ 299.1278, found: 299.1284 (error 2.2 ppm).

Protected menadione dimethylallyl adduct (8)

Protected menadione adduct **3** (102.4 mg, 0.430 mmol) was dissolved in 2.2 mL (2.24 mmol) of a 1.0 M solution of potassium *tert*-butoxide solution in THF under nitrogen at 0 °C. The blood-red solution stirred for 30 min and dimethylallyl chloride (89.9 mmol, 1.72 mmol) was added dropwise and the stirred reaction mixture was warmed to room temperature. After 3 hrs, the solution was adjusted to pH 2–3 by the addition of aqueous 1M HCl and Et₂O (20 mL) was added. The organic layer was washed with water (5 mL), brine (5 mL), dried (MgSO₄), and concentrated. The crude product was purified by flash column chromatography (10% EtOAc/hexanes) to afford compound **8** as a dark yellow oil; yield: 108 mg (82%); 1:1 pair of diastereomers

IR (neat): 2989, 2935, 2365, 1662, 1596, 1297, 715, 668 cm⁻¹

¹H NMR (500 MHz, CDCl₃) δ 1.51 (s, 6 H) 1.53 – 1.57 (m, 12 H) 1.67 (s, 1 H) 1.78 (s, 1 H) 1.88 (d, *J* = 9.3 Hz, 2 H) 2.45 (dd, *J* = 14.7, 6.9 Hz, 2 H) 2.82 (dd, *J* = 14.9, 7.1 Hz, 2 H) 3.12 (br s, 2 H) 3.20 (br. s., 2 H) 4.89 (t, *J* = 6.9 Hz, 2 H) 6.00 – 6.05 (m, 4 H) 7.61 7.67 (m, 4 H) 7.83 – 7.90 (m, 2 H) 7.91 – 7.96 (m, 2 H).

¹³C NMR (125 MHz, CDCl₃) δ 17.8, 23.5, 25.7, 36.2, 43.6, 53.8, 55.3, 57.2, 68.9, 119.9, 126.1, 126.8, 133.4, 133.8, 133.9, 134.9, 136.8, 137.4, 138.2, 201.4, 202.2.

HRMS (ESI calcd for C₂₁H₂₃O₂ [M + H]⁺ 307.1693, found: 307.1698 (error 1.7 ppm).

2-methyl-3-(3'-methylbut-2'-enyl)-1,4-naphthoquinone (9)

Intermediate **8** (583 mg, 1.90 mmol) and dodecyltrimethylammonium bromide (34 mg) were dissolved in AcOH (5 mL) and stirred at 90 °C for 1 hour and then cooled to room temperature. Et₂O (30 mL) was added followed by successive washes of the organic phases with distilled water (10 mL) and brine (10 mL). The organic layer was collected, dried (MgSO₄), concentrated, and purified by flash column chromatography (5% EtOAc/hexanes) to yield **9** as a yellow oil; yield: 357 mg (78%).

IR (neat): 2935, 1663, 1598, 1460, 1379, 1332, 1298, 715 cm⁻¹

¹H NMR (500 MHz, CDCl₃) δ 1.69 (s, 3 H) 1.79 (s, 3 H) 2.19 (s, 3 H) 3.35 (d, *J* = 6.9 Hz, 2 H) 5.01 (t, *J* = 6.4 Hz, 1 H) 7.63 – 7.70 (m, 2 H) 8.01 – 8.10 (m, 2 H).

¹³C NMR (125 MHz, CDCl₃) δ 12.6, 17.9, 25.7, 26.1, 119.1, 126.1, 126.2, 132.0, 133.2, 133.2 (ovlp, 2C), 133.9, 143.2, 146.0, 184.4, 185.3.

HRMS (ESI calcd for C₁₆H₁₇O₂ [M + H]⁺ 241.1223, found 241.1227 (error 1.6 ppm).

***trans*-2-methyl-3-(4'-hydroxy-3'-methylbut-2'-enyl)-1,4-naphthoquinone (10)**

Selenium dioxide (2.73 mg, 0.025 mmol) and salicylic acid (3.41 mg, 0.025 mmol) were suspended in CH₂Cl₂ (1.25 mL) followed by the addition of aqueous 70% *tert*-butyl hydroperoxide solution (65.1 mg, 0.723 mmol). The mixture was stirred for 10 minutes at room temperature and then cooled to 0 °C. A solution of compound **9** (59.2 mg, 0.246 mmol) in CH₂Cl₂ (1.25 mL) was added dropwise and the mixture was allowed to warm to room temperature and stirred for 48 hrs. After dilution with Et₂O (20 mL), the mixture was washed with aqueous 5% NaHCO₃ (5 mL), saturated aqueous CuSO₄ (5 mL), saturated aqueous Na₂SO₃ (5 mL), water (5 mL), and brine (5 mL). The organic layer was collected, dried (MgSO₄), and the solvent was evaporated. The crude product was purified by flash column chromatography (10–50% EtOAc/hexanes) to yield allylic alcohol **10** as a yellow oil; yield: 36.4 mg (57%).

IR (neat): 2929, 2858, 1662, 1598, 1298, 718 cm⁻¹

¹H NMR (500 MHz, CDCl₃) δ 1.86 (s, 3 H) 2.21 (s, 3 H) 3.43 (d, *J* = 7.3 Hz, 2 H) 4.02 (s, 2 H) 5.34 (t, *J* = 6.6 Hz, 1 H) 7.67 – 7.73 (m, 2 H) 8.06 – 8.11 (m, 2 H).

¹³C NMR (125 MHz, CDCl₃) δ 12.7, 13.9, 25.7, 68.4, 120.4, 126.2, 126.3, 132.1 (ovlp 2C), 133.4 (ovlp, 2C), 137.0, 143.6, 145.4, 184.4, 185.3.

HRMS (ESI calcd for C₁₆H₁₇O₃ [M + H]⁺ 257.1172, found: 257.1176 (error 1.5 ppm).

2-methyl-3-(4'-hydroxy-3'-methylbutyl)-1,4-naphthoquinone (11)

Cs₂CO₃ (49.2 mg, 0.152 mmol) and ruthenium catalyst [{Ru-Cl(μ-Cl)η⁶-*para*-cymene}]₂ (Strem Chemicals, Newburyport, MA) (46.3 mg, 0.076 mmol) was added to a solution of allylic alcohol (**10**) (77.8 mg, 0.304 mmol) in *i*PrOH (3 mL). The mixture was refluxed overnight at 80 °C and subsequently diluted with Et₂O (20 mL), and washed with water (5 mL) and brine (5 mL). The organic layer was dried (MgSO₄), filtered, concentrated and the

product was purified by flash column chromatography (0 – 50% EtOAc/hexanes) to yield (**11**) as a yellow oil; yield: 13.3 mg (17).

IR (neat): 2929, 2857, 2367, 1662, 1598, 1299, 715, 668 cm^{-1}

^1H NMR (500 MHz, CDCl_3) δ 1.04 (d, J = 6.9 Hz, 3 H) 1.35 (tt, J = 12.0, 6.3 Hz, 1 H), 1.52 – 1.62 (m, 1 H) 1.70 (br. s, 1 H) 1.77 (dt, J = 12.7, 6.4 Hz, 1 H) 2.20 (s, 3 H) 2.56 – 2.76 (m, 2H) 3.58 (d, J = 6.4 Hz, 2 H) 7.64 – 7.76 (m, 2 H) 8.01 – 8.16 (m, 2H).

^{13}C NMR (125 MHz, CDCl_3) δ 12.5, 16.5, 24.3, 31.7, 35.8, 67.6, 126.5 (ovlp 2C), 132.2 (ovlp 2C), 133.4 (ovlp 2C), 143.2, 147.4, 185.8, 185.3.

HRMS (ESI calcd for $\text{C}_{16}\text{H}_{19}\text{O}_3$ $[\text{M} + \text{H}]^+$ 256.1329, found: 259.1334 (error 1.9 ppm).

2-methyl-3-(3'-3'-carboxymethylpropyl)-1,4-naphthoquinone (**2**)

Periodic acid (25.8 mg, 0.113 mmol) was added to acetonitrile (0.25 mL) and the solution was stirred at room temperature for 15 minutes. The mixture was cooled to 0 °C and compound **11** (13.3 mg, 0.051 mmol) in acetonitrile (0.75 mL) was added followed by pyridinium chlorochromate (0.219 mg, 0.001 mmol). The reaction mixture was warmed to room temperature and stirred for 2 hours and subsequently diluted with Et_2O (10 mL) and concentrated. The residue was purified by flash column chromatography (0 – 25% EtOH/hexanes containing 1% formic acid) to afford vitamin K acid **2** (**2**) as a yellow oil; yield: 11.6 mg (84%).

IR (neat): 2940, 2366, 1709, 1663, 1598, 1466, 1381, 1300, 718, 668 cm^{-1}

^1H NMR (500 MHz, CDCl_3) δ (d, J = 7.3 Hz, 3 H, CH_3 at C3') 1.57 – 1.72 (m, 1 H, CH at C2') 1.79 – 1.94 (m, 1 H, CH at C2') 2.22 (s, 3 H, CH_3 at C2) 2.55 – 2.81 (m, 3 H, CH at C3', CH_2 at C1') 7.65 – 7.75 (m, 2 H, CH at C6, CH at C7) 8.01 – 8.15 (m, 2 H, CH at C5, CH at C8).

^{13}C NMR (125 MHz, CDCl_3) δ 12.5 (CH_3 at C2), 17.0, (CH_3 at C3') 24.8 (C1'), 31.9 (C2'), 39.3 (C3'), 126.3 (ovlp C5, C8), 132.1 (ovlp C9, C10), 133.4 (ovlp C6, C7), 143.8 (C2), 146.3 (C3), 181.2 (C4'), 184.6 (C4), 185.2 (C1).

HRMS (ESI calcd for $\text{C}_{16}\text{H}_{17}\text{O}_4$ $[\text{M} + \text{H}]^+$ 273.1121, found: 273.1127 (error 2.1 ppm).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.
Terminal oxidation products of vitamin K metabolism

Scheme 2.
Improved Synthesis of vitamin K acid 1 (1)

Scheme 3.
Improved Synthesis of vitamin K acid 2 (2)