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Efficient Syntheses of Vitamin K Chain-Shortened Acid Metabolites

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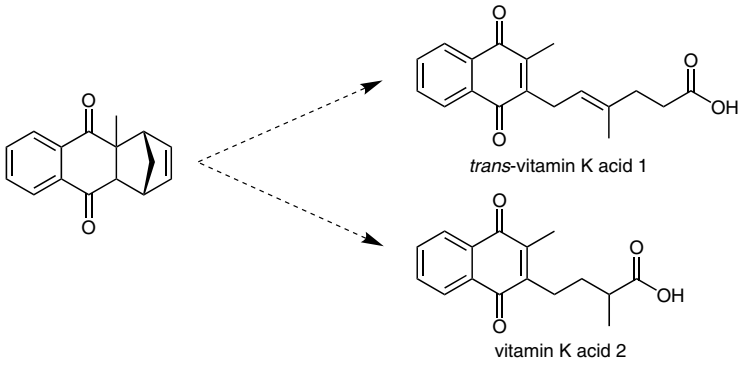

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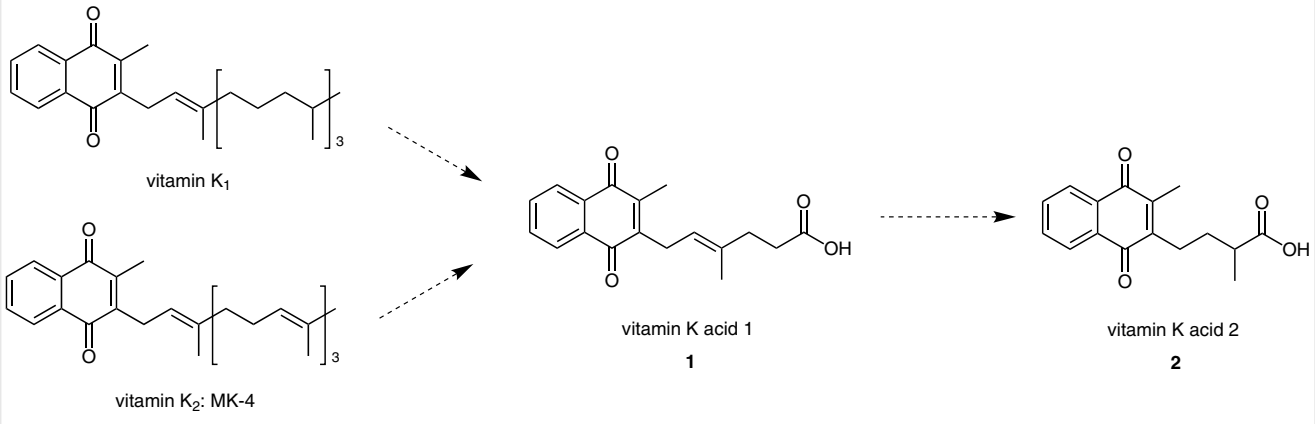
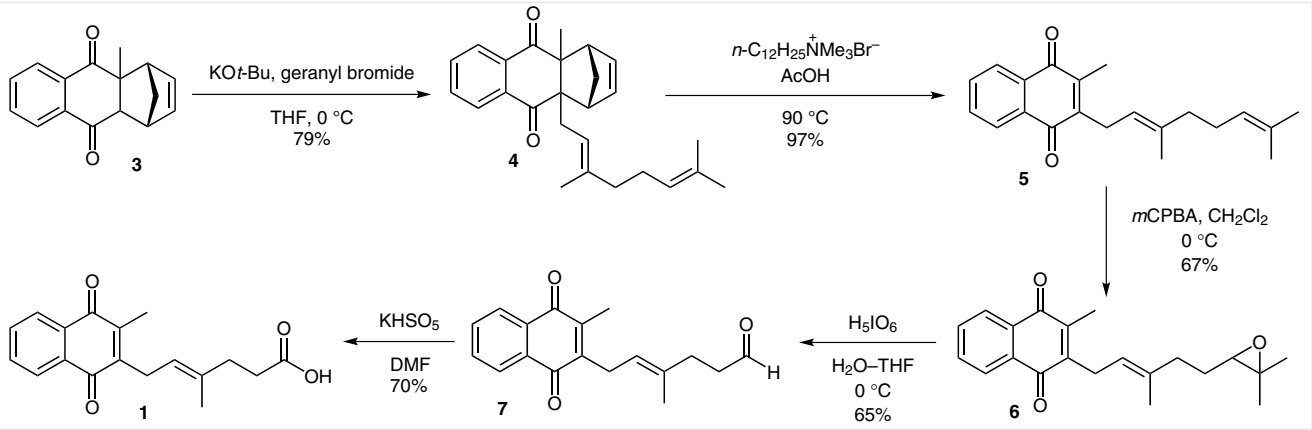
Abstract Vitamin K sequentially undergoes ω-oxidation followed by successive rounds of β-oxidation to ultimately produce two chain-shortened carboxylic acid metabolites, vitamin K acid 1 and vitamin K acid 2. Two facile syntheses of these acid metabolites are described, each starting from the same commercially available menadione-cyclopentadiene adduct. Vitamin K acid 1 was synthesized in five steps via alkylation with geranyl bromide 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 five steps via alkylation with dimethylallyl chloride and subsequent oxidation reactions.

Key words vitamin K acids, C-3 alkylation, 2-methyl-1,4,-naphthoquinone adduct, 5C-aglycones, 7C-aglycones, vitamin K, metabolism

Vitamin K is an umbrella term describing a family of molecules containing the 2-methyl-1,4,-naphthoquinone core. The most widely studied are phylloquinone (vitamin K_1) and a form of vitamin K_2, menaquinone-4 (MK-4), that differ in the degree of unsaturation along the C20-phytyl chain (Scheme 1). Whereas vitamin K_1 primarily functions as a regulator of hemostasis, MK-4 appears important for bone health;[1] it is also implicated in vascular calcification[2] 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 K_1 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**) (Scheme 1).[4–6] In order to quantify vitamin K acid metabolites in biological matrices to understand vitamin K metabolism, authentic analytical standards are required.



Scheme 1 Terminal oxidation products of vitamin K metabolism

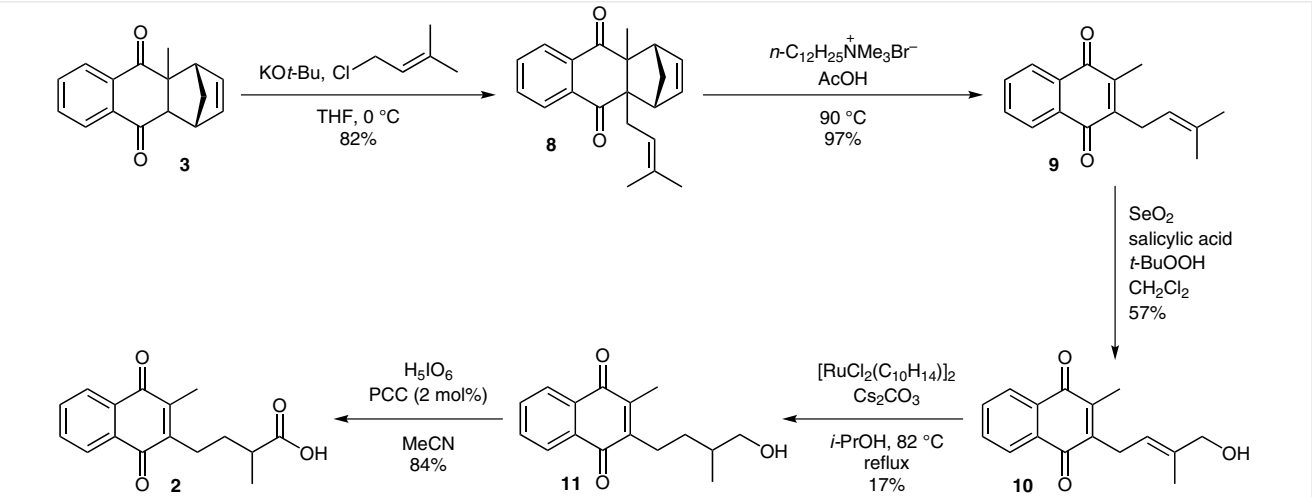


Scheme 2 Improved synthesis of vitamin K acid 1 (**1**)

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 halides[11] to obtain vitamin K_1 was used as the 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 acetic acid with catalytic dodecyltrimethylammonium bromide to produce **5** in 97% yield. The previously reported regioselective epoxidation of geraniol derivatives, followed by oxidative cleavage with periodic acid to yield corresponding aldehydes[12] was utilized to obtain aldehyde **7**. Thus, 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 peroxymonosulfate[13] yielding *trans*-vitamin K acid 1 (**1**) (70% yield). The *trans*-configuration of **1** was confirmed by a 2D-NOESY experiment (see Supporting Information), 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] A new method 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 oxidation[14] with SeO_2 to give allylic alcohol **10** (57% yield). Subsequent reduction of the allylic alcohol by ruthenium-catalyzed transfer hydrogenation[15] 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 $[RuCl(\mu\text{-}Cl)(\eta^6\text{-}C_6Me_6)]_2$ and cesium carbonate, but the double bond remained intact as evidenced by the corresponding ^{1}H NMR triplet signal at C3′. Subsequently, saturation of



Scheme 3 Improved synthesis of vitamin K acid 2 (**2**)

10 with $[Ru(cod)Cl_2]_n$ and potassium hydroxide[16] resulted in a 1:1 mixture of **10** and **11** (34% yield). Lastly, we tried $[RuCl(\eta\text{-}Cl)(\eta^6\text{-}p\text{-cymene})]_2$ with cesium carbonate and the ^1H NMR spectrum showed 70% conversion. After increasing the catalyst-to-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 chlorochromate[17] to afford vitamin K acid 2 (**2**) in 84% yield.

The syntheses described herein provide facile routes to vitamin K acids 1 and 2 utilizing established reaction procedures and inexpensive starting materials. Overall yields for vitamin K acids 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 recrystallization of the geometric isomer as previously described.[7] Overall, the synthesized metabolites will serve as authentic standards for our future investigations of vitamin K metabolism.

Protected menadione adduct **3** was obtained from Toronto Research Chemicals, Toronto, Ontario, Canada and $[RuCl(\mu\text{-}Cl)(\mu^6\text{-}p\text{-cymene})]_2$ from Strem Chemicals, Newburyport, MA, USA. Other chemicals and solvents were of reagent grade and purchased from Sigma Aldrich (St. Louis, MO, USA). All reactions were performed under N_2 and were monitored by TLC analysis utilizing SiO_2 60 F_{254} plates (EMD Chemicals, Inc., Gibbstown, NJ, USA). Flash column chromatography was performed with a CombiFlash® R_f purification system (Teledyne Isco, Lincoln, NE, USA) with a mixture of hexane and EtOAc 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 recorded on an Agilent DD2 500 MHz spectrometer at 25 °C. Proton chemical shifts (δ) are reported in ppm and referenced to the residual $CHCl_3$ signals (δ_H = 7.27, δ_C = 77.23). Coupling constants (*J*) are reported in Hz and standard abbreviations were used to denote the spin multiplicities; 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 spectra (HRMS) were acquired on a Thermo Fisher LTQ Orbitrap equipped with an ESI probe.

Protected Menadione Geranyl Adduct 4

Protected menadione adduct **3** (100 mg, 0.42 mmol) was dissolved in a 1.0 M solution of KO*t*-Bu in THF (2.2 mL). 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 r.t. After 2 h, aq 1.0 M HCl was added until the pH became acidic. The yellow solution was then evaporated and the residue was redissolved in EtOAc (20 mL), which was subsequently washed with H_2O (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 = 1.47 (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): *m*/*z* calcd for $C_{26}H_{31}O_2$ $[M + H]^+$: 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 AcOH (1.0 mL) followed by the addition of dodecyltrimethylammonium bromide (1.7 mg). The solution was heated to 90 °C for 60 min. After cooling to r.t., the solvent was evaporated, and the crude product was purified by flash column chromatography (5% EtOAc–hexanes) to afford the product **5** as a 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 2 C), 137.4, 143.3, 146.1, 184.4, 185.4.

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{25}O_2$ $[M + H]^+$: 309.1849; found: 309.1855 (error 1.8 ppm).

trans-2-Methyl-3-(6′,7′-epoxy-3′,7′-dimethyloct-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 r.t. and stirred overnight. After evaporation, the residue was dissolved in EtOAc (20 mL) and washed successively with aq 5% $NaHCO_3$ (5 mL), H_2O (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 2 C), 133.3, 133.4,136.7, 143.4, 145.9, 184.5, 185.4.

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{25}O_3$ $[M + H]^+$: 325.1798; found: 325.1801 (error 0.78 ppm).

trans-2-Methyl-3-(5′-formyl-3′-methylpent-2′-enyl)-1,4-naphthoquinone (7)

A solution of periodic acid (38.7 mg, 0.170 mmol) in H_2O (2.0 mL) was added dropwise to a solution of epoxide **6** (37.0 mg, 0.114 mmol) in THF (2.0 mL) at r.t. After stirring for 60 min, the reaction mixture was diluted with Et_2O (20 mL) and the organic layer was washed successively with aq 5% $NaHCO_3$ (5 mL), H_2O (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, 1 Hz), 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 2 C), 133.3 (ovlp 2 C), 135.5, 143.5, 145.6, 184.4, 185.3, 202.0.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{19}O_3$ $[M + H]^+$: 283.1329; found: 283.1332 (error 1.3 ppm).

trans-2-Methyl-3-(5′-carboxy-3′-methylpent-2′-enyl)-1,4-naphthoquinone (1)

To a solution of aldehyde **7** (19.7 mg, 0.070 mmol) in DMF (2 mL) was added $KHSO_5$ (94.4 mg, 0.307 mmol) and the reaction mixture was stirred at r.t. for 2.5 h. Et_2O (20 mL) was added to the mixture and the Et_2O layer was subsequently washed with H_2O (5 mL) and brine (5 mL). The organic layer was dried ($MgSO_4$), 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, $CDCl_3$): δ = 1.82 (s, 3 H, CH_3 at C3′), 2.18 (s, 3 H, CH_3 at C2), 2.28–2.36 (m, 2 H, CH_2 at C4′), 2.38–2.48 (m, 2 H, CH_2 at C5′), 3.38 (d, *J* = 6.9 Hz, 2 H, CH_2 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).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.6 (CH_3 at C2), 16.2 (CH_3 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): *m*/*z* calcd for $C_{18}H_{19}O_4$ $[M + H]^+$: 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 a 1.0 M solution of KO*t*-Bu in THF (2.2 mL, 2.24 mmol) under N_2 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 r.t. After 3 h, the pH of the solution was adjusted to 2–3 by the addition of aq 1 M HCl, and Et_2O (20 mL) was added. The organic layer was washed with H_2O (5 mL) and brine (5 mL), dried ($MgSO_4$), 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, $CDCl_3$): 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).

^{13}C NMR (125 MHz, $CDCl_3$): 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): *m*/*z* calcd for $C_{21}H_{23}O_2$ $[M + H]^+$: 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 h and then cooled to r.t. Et_2O (30 mL) was added followed by successive washes of the organic phase with distilled H_2O (10 mL) and brine (10 mL). The organic layer was collected, dried ($MgSO_4$), concentrated, and purified by flash column chromatography (5% EtOAc–hexanes) to afford **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, $CDCl_3$): 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).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.6, 17.9, 25.7, 26.1, 119.1, 126.1, 126.2, 132.0, 133.2, 133.2 (ovlp 2 C), 133.9, 143.2, 146.0, 184.4, 185.3.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{17}O_2$ $[M + H]^+$: 241.1223; found: 241.1227 (error 1.6 ppm).

trans-2-Methyl-3-(4′-hydroxy-3′-methylbut-2′-enyl)-1,4-naphthoquinone (10)

SeO_2 (2.73 mg, 0.025 mmol) and salicylic acid (3.41 mg, 0.025 mmol) were suspended in CH_2Cl_2 (1.25 mL) followed by the addition of aq 70% *tert*-butyl hydroperoxide (65.1 mg, 0.723 mmol). The mixture was stirred for 10 min at r.t. and then cooled to 0 °C. A solution of compound **9** (59.2 mg, 0.246 mmol) in CH_2Cl_2 (1.25 mL) was added dropwise and the mixture was allowed to warm to r.t. and stirred for 48 h. After dilution with Et_2O (20 mL), the organic layer was washed with aq 5% $NaHCO_3$ (5 mL), sat. aq $CuSO_4$ (5 mL), sat. aq Na_2SO_3 (5 mL), H_2O (5 mL), and brine (5 mL). The organic layer was collected, dried ($MgSO_4$), and the solvent was evaporated. The crude product was purified by flash column chromatography (10–50% EtOAc–hexanes) to afford 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, $CDCl_3$): 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).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.7, 13.9, 25.7, 68.4, 120.4, 126.2, 126.3, 132.1 (ovlp 2 C), 133.4 (ovlp 2 C), 137.0, 143.6, 145.4, 184.4, 185.3.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{17}O_3$ $[M + H]^+$: 257.1172; found: 257.1176 (error 1.5 ppm).

2-Methyl-3-(4′-hydroxy-3′-methylbutyl)-1,4-naphthoquinone (11)

Cs_2CO_3 (49.2 mg, 0.152 mmol) and ruthenium catalyst [RuCl(μ-Cl)(μ^6-*p*-cymene)]$_2$ (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 Et_2O (20 mL), and the organic layer was washed with H_2O (5 mL) and brine (5

mL). The organic layer was dried ($MgSO_4$), filtered, concentrated and the product was purified by flash column chromatography (0–50% EtOAc–hexanes) to give **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, 2 H), 3.58 (d, *J* = 6.4 Hz, 2 H), 7.64–7.76 (m, 2 H), 8.01–8.16 (m, 2 H).

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

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{19}O_3$ $[M + H]^+$: 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 MeCN (0.25 mL) and the solution was stirred at r.t. for 15 min. The mixture was cooled to 0 °C and compound **11** (13.3 mg, 0.051 mmol) in MeCN (0.75 mL) was added followed by pyridinium chlorochromate (0.219 mg, 0.001 mmol). The reaction mixture was warmed to r.t. and stirred for 2 h 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 = 1.30 (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): *m*/*z* calcd for $C_{16}H_{17}O_4$ $[M + H]^+$: 273.1121; found: 273.1127 (error 2.1 ppm).

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380002.

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