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CONVERGENT SYNTHESIS OF MENAQUINONE-7 (MK-7)

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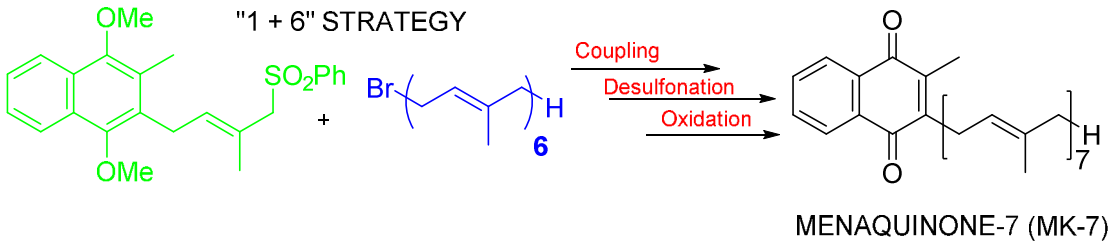
GRAPHICAL ABSTRACT



MENAQUINONE-7 (MK-7)

ABSTRACT:

A practical synthesis of menaquinone-7 (MK-7, vitamin K_2) in the all-*trans* form was designed. Stereoselective synthesis of MK-7 was achieved through a "1 + 6" convergent strategy by condensation of two building blocks, menadione monoprenyl derivative (fragment "1") with hexaprenyl bromide (fragment "6", 82%). Pd-catalyzed desulfonation with $LiEt_3BH$ (78%) was followed by oxidation of the hydroquinone moiety using ammonium cerium(IV) nitrate (72%). The major challenge in our methodology was the preparation of all-*trans* hexaprenyl bromide by coupling of two triprenyl units derived from *trans,trans*-farnesol. Manufacturing on a pilot scale was accomplished through our approach. The scalable method was designed especially for a large, kg-scale production from easily available intermediates. Furthermore, the proposed methodology avoids many chromatographic purifications and allows for a relatively cost-effective manufacturing. Moreover, our synthesis yielded high-purity (99.9%) final product MK-7, which can be used as a dietary supplement as well as an active pharmaceutical ingredient.

Keywords: vitamin K_2, menaquinone-7, prenylation, convergent synthesis, MK-7

INTRODUCTION

Vitamin K is the family of fat-soluble compounds that contain a 2-methyl-1,4-naphthoquinone moiety and differ in an alkenyl substituent at the 3-position.[1] There are two natural forms of vitamin K: vitamin K_1 (phylloquinone or phytonadione) bearing a long phytyl side chain and vitamin K_2 (menaquinones) with a polyprenyl side chain (Figure 1). Vitamin K_3 (menadione) is a synthetic form of vitamin K which acts as a provitamin. However, it is not recommended for humans as a dietary supplement. According to some reports, menadione might be toxic to the liver, and in addition may lead to hemolytic anemia and allergic reactions.[2–4]

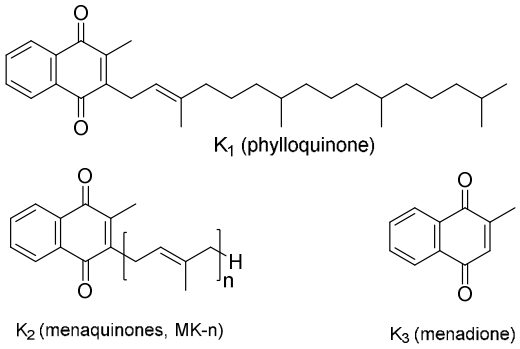
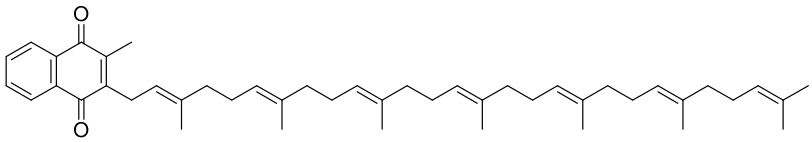


Figure 1. Chemical structure of vitamins K.

The major dietary source of vitamin K is phylloquinone, which is synthesized by plants and algae.[2] High concentration of vitamin K_1 is present in green leafy vegetables (e.g. broccoli, iceberg lettuce, spinach) and some plant oils (e.g. soybean oil, olive oil).[5] Vitamin K_2 is a group of related compounds described as MK-n, where n is the number of unsaturated isoprenoid units in the side chain (from 4 to 13)[6]. The chain length and number of double bonds have an influence on the activity and bioavailability. The main dietary source of vitamin K_2 are animal products e.g. eggs, meet and fermented foods such as natto, cheese, curd and sauerkraut.[2,7,8] High concentration of MK-7 (Figure 2) is present in traditional Japanese "natto" (900-1200

μg/100 g[9], when the content of vitamin K_1 in spinach is 380 μg/100 g[5]). Menaquinones are synthetized by bacteria, except for MK-4 (menatetrenone),[4] which can be formed in direct conversion of dietary phylloquinone or by alkenylation of menadione.[10] In humans, deficiency of vitamin K_2 may occur after prolonged treatment with sulfonamide antibacterials when bacterial flora may be partially or completely destroyed.



MK-7 (**1**)

Figure 2. Chemical structure of Menaquinone-7 (MK-7).

It is commonly known that vitamin K is required for proper blood clotting.[8] In the liver it catalyzes the synthesis of prothrombin, the inactive precursor of thrombin, which converts fibrinogen of blood plasma into fibrin. Vitamin K is an essential cofactor in the γ-glutamyl carboxylation pathway. γ-Glutamyl carboxylase is responsible for post-translational conversion of some glutamate residues to γ-carboxyglutamic acid residues in osteocalcin.[2,11]

Recent studies have shown that vitamin K play an important role in bone health,[4,9,12,13] reduction of vascular calcification and cardiovascular risk processes.[7,14] Some data suggest that vitamins D and K work synergistically on bone density.[9] Furthermore, vitamin K reveals antibacterial,[15,16] anti-inflammatory and anticancer activity.[2] For example, vitamin K_2 has been reported to induce apoptosis in hepatocellular carcinoma and leukemia.[17–19]

Currently, vitamin K_1 (synthetic and natural), MK-4 (synthetic), and MK-7 (from natto) are used in food supplementation. With regard to therapeutic aspects, menaquinone-4 (MK-4) and menaquinone-7 (MK-7) are the most important forms of vitamin K_2. Nowadays, there is a

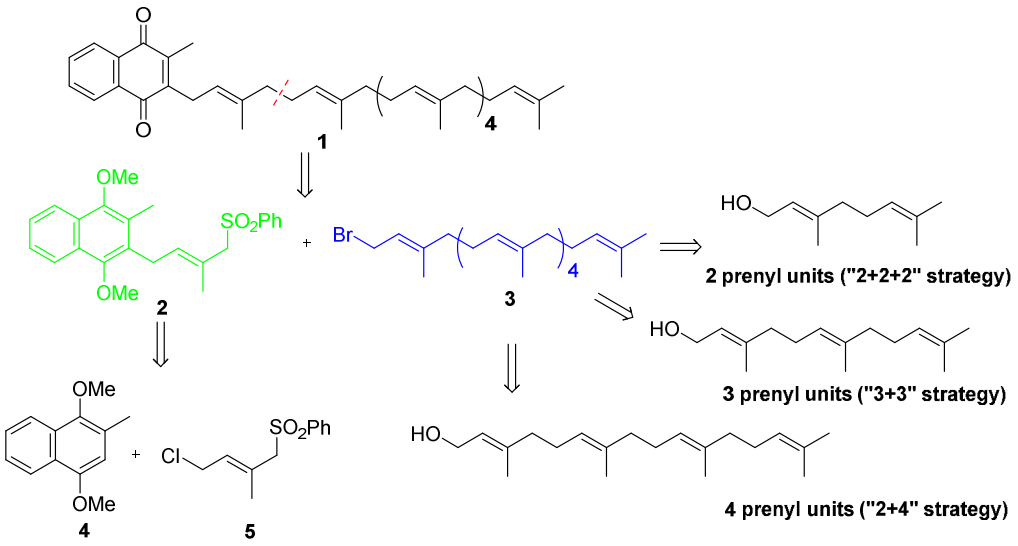
growing interest in MK-7 supplementation. Vitamin K_1 is the primary dietary form of vitamin K but is poorly absorbed by the human body (5-15%). Vitamin MK-4 has a poor bioavailability at nutrition level dose (420 μg/day), requires high doses (15-45 mg/day) and frequent administration. On the contrary, vitamin MK-7 is more lipophilic, has better bioavailability in small intestine and longer half-life (about 3 days) compared to vitamin MK-4 (1 h) and phylloquinone (several hours). Moreover, MK-7 is highly effective in the carboxylation of osteocalcin (OC) at nutritional dose (45-90 μg/day), where larger amount of MK-4 (1500 μg/day) is required to activate OC. [4,20–22]

All natural menaquinones have all-*trans* configurations for the appropriate side chain double bonds. In view of this was planned to design an efficient and stereoselective method for preparing high purity all-*trans* vitamin MK-7 which would meet the quality requirements approved for the dietary supplements.

RESULTS AND DISCUSSION

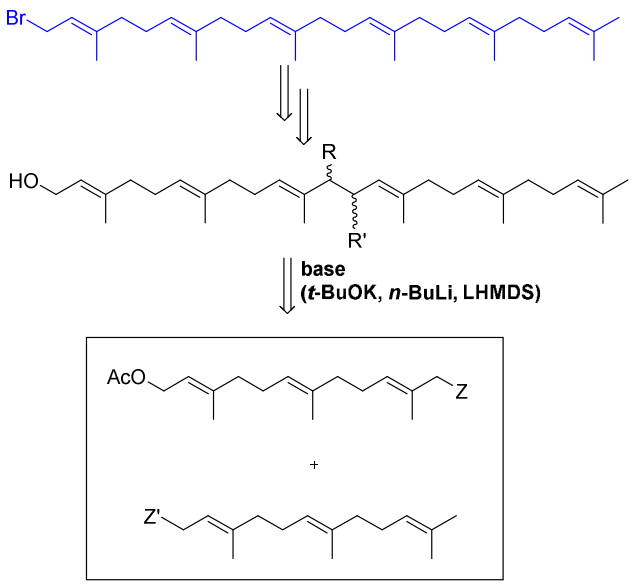
Vitamin MK-7 (**1**) has seven all-*trans* double bonds in the side chain. Based on retrosynthetic analysis vitamin MK-7 can be obtained by coupling "1 + 6" (Scheme 1). Key to this strategy is a reaction of α-phenylsulfonyl carbanion generated in situ from protected menadiol derivative **2** with all-*trans*-hexaprenyl bromide (**3**). The methodology based on formation of a phenylsulfonyl derivative followed by its reaction with an electrophile, such as halide, in the presence of base (e.g. potassium *tert*-butoxide) is widely used in syntheses of many important natural products such as solanesol[23] or ubiquinone (coenzyme Q_{10})[24–26].

Compound **2** is a convenient substrate due to the presence of a monoprenyl chain, which can be extended by further prenyl units. Additionally, the presence of sulfonyl group may facilitate purification of this product by crystallization.



Scheme 1. Retrosynthetic analysis of Menaquinone-7 (MK-7).

The required hexaprenyl fragment **3** can be prepared from commercially available terpenes, e.g. geraniol, farnesol or geranylgeraniol according to one of the three strategies: "2+2+2", "2+4" or "3+3" (Scheme 1). Preliminary experiments allowed to choose "3+3" strategy and inexpensive (*E*,*E*)-farnesol as a convenient substrate. In this case, it was planned to synthesize hexaprenyl moiety *via* coupling of two building blocks containing three prenyl units using sulfonyl methodology. This strategy can be performed in two variants, depending on the structure of the substrate as depicted in Scheme 2. Allyl halide can be reacted with polyprenyl sulfone to form sulfonated polyprenol derivative. Sulfonyl coupling group was chosen due to its easy preparation and removal by selective reduction.[27]

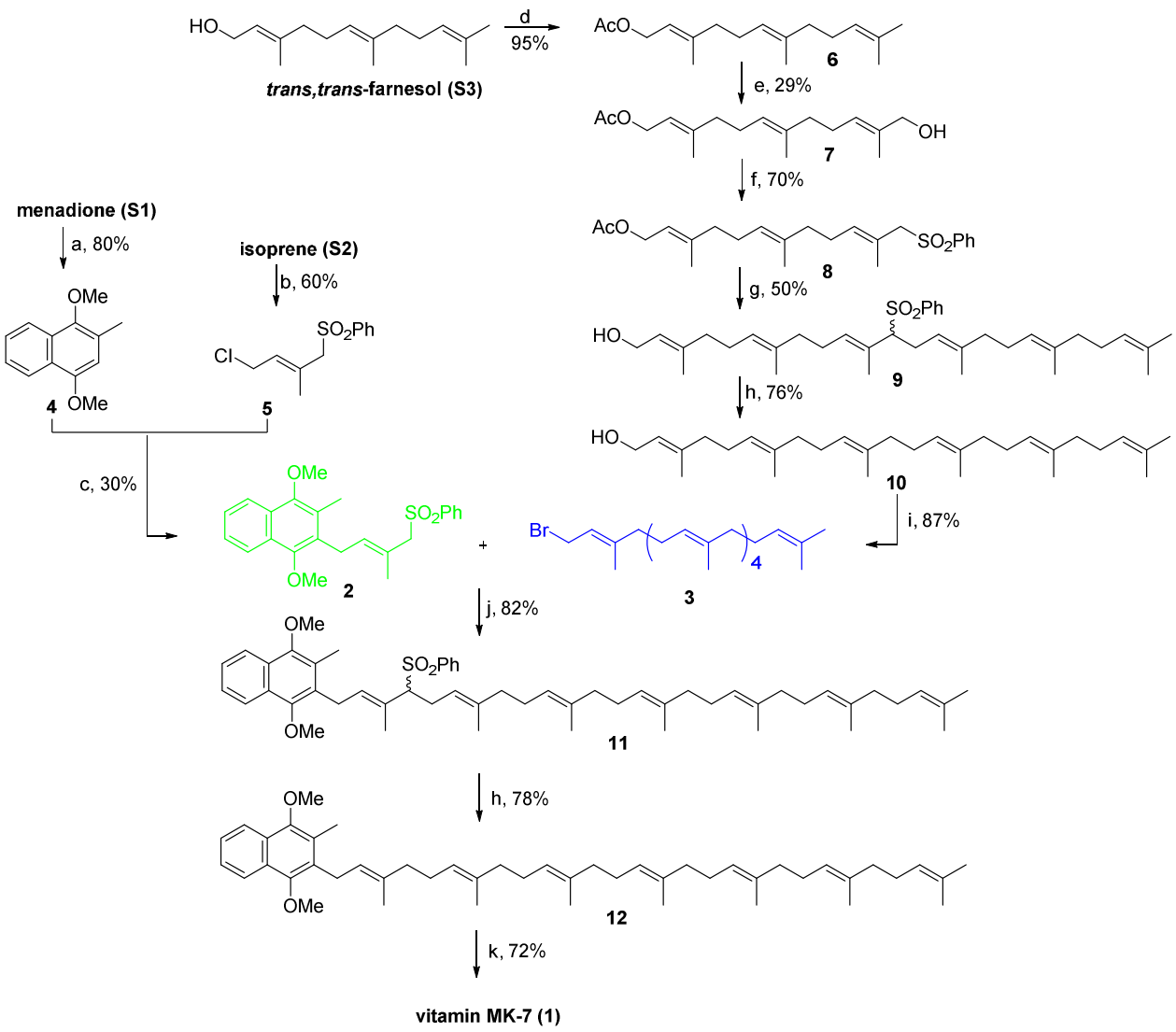


I variant: R = SO_2Ph, R' = H, where Z = SO_2Ph and Z' = Br
II variant: R = H, R' = SO_2Ph, where Z = Br and Z' = SO_2Ph

Scheme 2. Synthetic route to bromide 3.

Vitamin MK-7 (**1**) was prepared from the readily available and inexpensive starting materials as shown in Scheme 3. Compound **2** was obtained in moderate yield (24% from menadione) in a simple and efficient way according to slightly modified procedures.[26,28–31] The formation of intermediate **4** involved two-step protocol including reduction of menadione (**S1**) with sodium dithionate ($Na_2S_2O_4$) followed by methylation (Me_2SO_4). In the parallel experiment, the reaction of isoprene (**S2**) with benzenesulfonyl chloride in the presence of copper chloride and triethylamine hydrochloride as catalysts afforded a mixture of *E/Z*-isomers. The desired compound **5** (*E*-isomer) was isolated by crystallization of the crude product from 2-propanol. Finally, Friedel-Crafts alkenylation of **4** by chlorosulfone **5** provided the desired product **2**. After purification by DFC, followed by crystallization from methanol the HPLC purity of sulfone **2** (*E*-isomer, exclusively) achieved 99.6%.

Scheme 3. Synthesis of Menaquinone-7 (MK-7).[a]



[a]**Reagents and conditions:** a) 1. $Na_2S_2O_4$, AcOEt/water, RT; 2. Me_2SO_4, K_2CO_3, acetone, reflux; b) $PhSO_2Cl$, CuCl, $Et_3N{\cdot}HCl$, acetonitrile, 60 °C; c) $SnCl_4$, 1,2-dichloroethane, 80 °C; d) Ac_2O, Py, RT; e) 1. SeO_2, *t*-BuO_2H, salicylic acid, CH_2Cl_2, RT; 2. $NaBH_4$, THF/MeOH, -10 °C; f) 1. PBr_3, THF, 0 °C; 2. $PhSO_2Na$, DMF, RT; g) 1. *t*-BuOK, THF/DMF, -78 °C; 2. *trans, trans*-farnesyl bromide; 3. NaOH, MeOH, RT; h) $LiEt_3BH$, $Pd(dppe)Cl_2$, THF, 0 °C to RT; i) PBr_3, THF, 0 °C; j) *t*-BuOK, THF/DMF, -20 °C; k) CAN, CH_2Cl_2/acetonitrile /water, 0 °C.

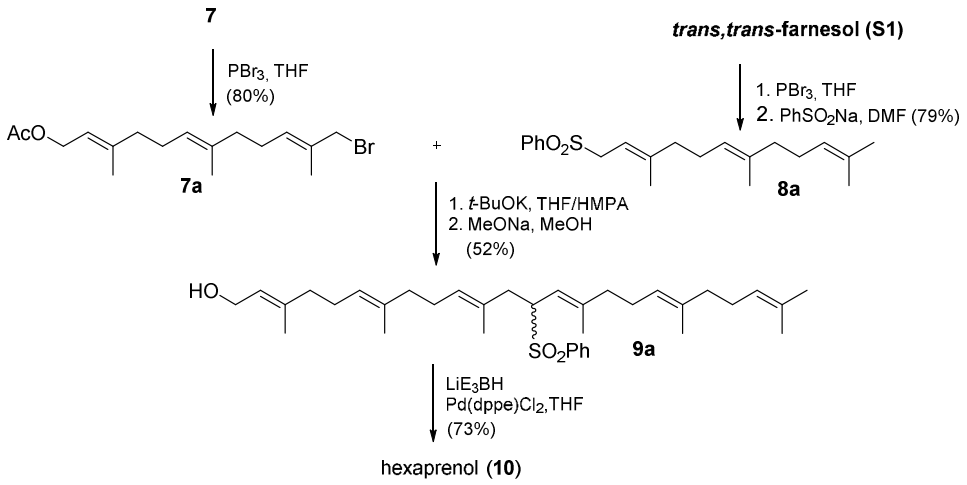
The current method requires functionalization at the head of the isoprenoid skeleton. For this purpose (*E,E)*-farnesol (**S3**) was acetylated and then subjected to stereoselective allylic

oxidation[32,33] at the terminal methyl group. The oxidation using 10 mol% of SeO_2 and 3.6 equiv. of *t*-BuO_2H in the presence of 10 mol% of salicylic acid followed by reduction with $NaBH_4$ gave allylic alcohol **7** in 29% yield. In the next step, hydroxyl in **7** was replaced by bromine with PBr_3 and the freshly prepared bromide, without purification, was converted to the sulfone **8**. The reaction of sulfur-stabilized allylic carbanion, generated from **8** by *n*-BuLi in THF/DMF, with (*E*,*E*)-farnesyl bromide followed by deacetylation afforded compound **9**. Desulfonation of **9** was carried out using lithium triethylborohydride (Super-hydride, $LiEt_3BH$) and $Pd(dppe)Cl_2$ (dppe = 1,2-bis(diphenylphosphino)ethane) as a catalyst in anhydrous THF (76% yield). The resulting hexaprenol (**10**) was characterized by ^1H and ^{13}C NMR. The carbon chemical shift for one of the geminal vinylic methyl groups amounts 25.6 ppm, while for other methyl groups appear in the range of 15-18 ppm. These data confirm that all the double bonds are of *trans* geometry. The purity of all-*trans* hexaprenol **10** was determined by HPLC (91%).

Hexaprenol **10** was reacted with PBr_3 and the resulting bromide was used directly for alkenylation. Coupling of menadione derivative **2** with hexaprenyl bromide **3** produced the required carbon skeleton of menaquinone MK-7 in 82% yield. Finally, desulfonation ($LiEt_3BH$, $Pd(dppe)Cl_2$) followed by oxidation (cerium(IV) ammonium nitrate, CAN) gave the target product **1** as a yellow oil. After purification by DFC, followed by crystallization from ethanol and ethyl acetate vitamin MK-7 (**1**) was obtained as a yellow powder (99.9% purity by HPLC).

A different approach to the synthesis of all-*trans*-hexaprenol (**10**) was also examined (Scheme 4). Alcohol **7** was transformed into bromide **7a**, which reacted in the same manner as in the first approach, with phenylsulfone **8a** obtained from *trans,trans*-farnesol. Deacetylation of crude coupling product afforded alcohol **9a**. No isomeric products of the coupling at the γ position was observed. Reductive removal of the sulfonyl group afforded hexaprenol **10** in high yield (73%).

The NMR spectra were identical with those disclosed earlier and thus confirmed the molecular structure of the product.



Scheme 4. Alternative approach to the synthesis of all-*trans* hexaprenol (10).

CONCLUSIONS

In conclusion, we have developed an efficient synthetic pathway for preparation of vitamin K_2 in MK-7 form starting from easily available substrates. Our "1 + 6" convergent strategy is based on condensation of monoprenyl derivative of menadione (**2**; fragment "1") with hexaprenyl bromide (**3**; fragment "6"). Compound **2** was prepared in a moderate yield (24% from menadione) in a simple and efficient way using crystallization as a method for the isolation of highly pure desired *E*-isomer. In turn, bromide **3** was obtained from readily available (*E,E)*-farnesol in six steps in 7% overall yield. The main advantage of the reported method is high purity of both substrates. The final product was obtained from **2** and **3** in three steps in 46% overall yield. The proposed method allows to isolate menaquinone-7 in the all-*trans* configuration with high purity (99.9%) in moderate overall yield (11% starting from menadione). This procedure can be used on industrial scale. Furthermore, very high purity of the

final product (MK-7) allows to use it as a dietary supplement. The described methodology in a large production scale has been patented.[34]

EXPERIMENTAL SECTION

General. Starting materials and reagents were obtained from commercial sources and used without further purification. Solvents were dried by distillation over appropriate drying agents under argon atmosphere. All moisture and air-sensitive reactions were carried out under argon using oven-dried glassware. Thin layer chromatography (TLC) was performed using Merck silica gel plates (0.25 mm, 60F-254), visualized by spraying with H_2SO_4/MeOH solution (1:9, v/v) followed by heating. Flash chromatography (FC) and dry-column flash chromatography (DFC) were performed on J. T. Baker silica gel (230-400 mesh). Melting points were determined by capillary method using MP70 Melting Point System (Mettler Toledo). ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a Bruker Avance II 400 MHz spectrometer. The chemical shifts (δ) are given in parts per million (ppm) relative to tetramethylsilane (TMS). IR spectra were recorded on a Nicolet series II Magna-IR 550 FT-IR spectrometer. ESI-MS spectra were obtained using time-of-flight detector on a MicroMass LCT mass spectrometer. HRMS data were acquired on an Agilent Technologies 6530 Accurate-Mass Q-TOF LC/MS. HPLC was performed with LabAlliance apparatus consisted of pumps (III Pump series), UV-VIS detector (525 Dualwavelength) and injection valve (Rheodyne Model 7725i). Analytical HPLC was carried out with a SUPELCOSIL LC-NH_2-NP HPLC column (5 μm), 0.46x25 cm.

2-Methyl-1,4-naphthohydroquinone; Menadiol (4a). To a solution of menadione (**S1**, 10 g, 58 mmol) in EtOAc (70 mL) was added solution of $Na_2S_2O_4$ (20 g, 115 mmol) in water (70 mL) under argon atmosphere[28]. The reaction mixture was stirred vigorously at room temperature for

20 min. The organic layer was separated, washed with water (2 x 40 mL), brine (1 x 40 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was removed under reduced pressure to give **4a** as a bright purple powder (9.6 g, yield 95%) which was used directly in the next step. **Mp** 179-181 °C (181 °C[35], 166 °C[30]). **^{1}H NMR** (400 MHz, DMSO-d_6, ppm): δ 9.32 (s, 1H), 8.22 (s, 1H), 8.06 (d, J = 8.2 Hz, 1H), 8.00 (d, J = 8.2 Hz, 1H), 7.42-7.31 (m, 2H), 6.63 (s, 1H), 2.27 (s, 3H). **^{13}C NMR** (100 MHz): δ 145.8, 141.7, 126.5, 124.9, 123.8, 123.5, 121.8, 121.7, 118.7, 111.1, 16.6. **IR** (KBr): ν 3270, 1603, 1205 cm^{-1}.

2-Methyl-1,4-dimethoxynaphthalene (4). To a solution of menadiol (**4a**, 9.54 g, 0.055 mol) in anhydrous acetone (250 mL) were added K_2CO_3 (76 g, 0.55 mol) and Me_2SO_4 (27 mL, 0.28 mol) and the reaction mixture[29] was stirred under reflux for 6 h. After cooling to room temperature, the inorganic material was filtered off and the filtrate was concentrated under reduced pressure. To the residue dissolved in Et_2O (300 ml) 20% aqueous KOH solution (150 mL) was added and the mixture was stirred vigorously for 2 h. The organic layer was separated, washed with water (1 x 100 mL), brine (1 x 100 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo and the crude product was purified using DFC (hexane) to obtain **4** as a yellow oil (9.35 g, yield 80%, after 2 steps). $\mathbf{R_f}$ = 0.54 (hexane/EtOAc, 9:1). **^{1}H** NMR (400 MHz, $CDCl_3$, ppm): δ 8.21 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.55-7.51 (m, 1H), 7.46-7.42 (m, 1H), 6.62 (s, 1H), 3.98 (s, 3H), 3.88 (s, 3H), 2.47 (s, 3H).**^{13}C** NMR (100 MHz): δ 151.5, 147.0, 128.6, 126.4, 125.6, 125.2, 124.5, 122.2, 121.4, 106.8, 61.2, 55.6, 16.3 ppm. **IR** ($CHCl_3$): ν 3011, 2938, 1598, 1508, 1462, 1266, 1121 cm^{-1}.

(*E*)-4-Chloro-2-methyl-1-phenylsulfonyl-2-butene (5). A mixture of $PhSO_2Cl$ (13 mL, 0.1 mol), isoprene (**S2**, 10 mL, 0.1 mol), CuCl (0.201 g, 2 mmol) and $Et_3N{\cdot}HCl$ (0.419 g, 3 mmol) in dry acetonitrile (6 mL) was stirred under reflux. After 3 h the reaction mixture was cooled to

room temperature and an additional portion of isoprene (6 mL, 60 mmol) was added. The reaction mixture was refluxed for 6 h, further stirred for 14 h at room temperature, and finally for 3 h again under reflux. After evaporation, the residue was dissolved in chloroform (20 mL) and 1% aqueous HCl solution (100 mL) was added. The organic phase was separated and water layer was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was treated with 2-propanol and the crystals were collected by filtration, washed with 2-propanol and dried under reduced pressure to give **5** as a white crystalline powder (14.68 g, 60%, purity by HPLC 99%). $\mathbf{R_f}$ = 0.24 (hexane/EtOAc, 7:2); **Mp** 72-73 °C. $^{\mathbf{1}}$**H** NMR (400 MHz, $CDCl_3$, ppm): δ 7.87 (d, *J* = 7.4 Hz, 2H), 7.68-7.65 (m, 1H), 7.58-7.54 (m, 2H), 5.31 (tm, 1H), 3.97 (d, *J* = 7.8 Hz, 2H), 3.77 (s, 2H), 1.88 (s, 3H).$^{\mathbf{13}}$**C** NMR (100 MHz): δ 138.1, 133.8, 130.5, 129.8, 129.1, 128.5, 65.5, 39.3, 16.9 ppm[26]. **IR** ($CHCl_3$): ν 3028, 1661, 1587, 1448, 1319, 1309, 1136 cm^{-1}.

(2'*E*)-2-(3'-Methyl-4'-phenylsulfonylbut-2'-enyl)-1,4-dimethoxy-3-methylnaphthalene (2). To a solution of **4** (9.0 g, 44 mmol) and **5** (13.0 g, 53 mmol) in anhydrous 1,2-dichloroethane (80 mL) $SnCl_4$ (6.2 mL, 53 mmol) was slowly added at room temperature.[31] The reaction mixture was stirred for 5 h at 80 °C and cooled to room temperature. Then, water (20 mL) and CH_2Cl_2 (40 mL) were added. The organic phase was separated, washed with 10% aqueous NH_4Cl solution, dried over anhydrous Na_2SO_4, the drying agent was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified using DFC (hexane/EtOAc, 7:2) to obtain an oily product (9.128 g). Further crystallization from methanol afforded compound **2** as a white crystalline powder (5.480 g, 30%, purity by HPLC 99.6%). $\mathbf{R_f}$ = 0.21 (hexane/EtOAc, 7:2); **Mp** (from methanol) 155.1-157.2 °C, 156-157 °C[36]; $^{\mathbf{1}}$**H** NMR (400 MHz, $CDCl_3$, ppm): δ 8.08-8.00 (m, 2H), 7.76-7.74 (m, 2H), 7.50-7.47 (m, 2H), 7.39-7.35 (m,

1H), 7.31-7.27 (m, 2H), 5.03 (t, *J* = 6.6 Hz, 1H), 3.86 (s, 3H), 3.80 (s, 3H), 3.74 (s, 3H), 3.49 (d, *J* = 6.6 Hz, 2H), 2.22 (s, 3H), 2.02 (s, 3H) ppm; **^{13}C** NMR (100 MHz): δ 150.1, 149.9, 138.2, 134.3, 133.3, 128.77, 128.75, 128.2, 127.6, 127.1, 126.2, 125.7, 125.4, 123.9, 122.2, 122.1, 66.0, 62.1, 61.3, 26.7, 17.1, 12.4 ppm[36]; **IR** ($CHCl_3$): ν 3028, 1592, 1448, 1353, 1308, 1133 cm^{-1}.

(2*E*,6*E*)-3,7,11-Trimethyldodeca-2,6,10-trien-1-yl acetate; (*E,E)*-farnesyl acetate (6). To a solution of *E,E*-farnesol (**S3**, 15 g, 67 mmol) in anhydrous pyridine (50 mL) acetic anhydride (30 mL) was added at 0 °C under argon atmosphere. The reaction mixture was stirred at room temperature overnight. Upon completion (TLC control) the reaction mixture was poured into ice water and extracted with EtOAc (3 x 60 mL). The organic layers were collected, washed with 10% HCl solution, 10% $NaHCO_3$ solution and brine, dried over Na_2SO_4 and, after removal of the drying agent, evaporated in vacuo. The crude product was purified using DFC (hexane) to give **6** as a light yellow oil (16.94 g, 95%). $\mathbf{R_f}$ = 0.70 (hexane/EtOAc, 7:2).**^{1}H NMR** (400 MHz, $CDCl_3$, ppm): δ 5.36–5.32 (m, 1H), 5.11–5.07 (m, 2H), 4.59 (d, *J* = 7.1 Hz, 2H), 2.13-1.96 (m, 8H), 2.05 (s, 3H) 1.71 and 1.68 (2s, 6H), 1.60 (s, 6H). **^{13}C NMR** (100 MHz): δ 171.0, 142.2, 135.4, 131.2, 124.3, 123.6, 118.3, 61.3, 39.6, 39.5, 26.7, 26.1, 25.6, 21.0, 17.6, 16.4, 15.9.[33] **IR** ($CHCl_3$): ν 2968, 1737, 1228 cm^{-1}.

(2*E*,6*E*,10*E*)-12-Hydroxy-3,7,11-trimethyldodeca-2,6,10-trien-1-yl acetate; (*E,E,E*)-12-hydroxyfarnesyl acetate (7). *Tert*-butyl hydroperoxide (31 mL, 70 wt.% in H_2O) was added to a stirred suspension of SeO_2 (710 mg, 6.4 mmol) and salicylic acid (884 mg, 6.4 mmol) in CH_2Cl_2 (120 mL). The stirring was continued for 30 min at room temperature, then cooled to 0 °C and the solution of **6** (16.94 g, 76 mmol) in CH_2Cl_2 (12 mL) was added dropwise. The reaction was carried out for 24 h at room temperature and concentrated under vacuo. The residue dissolved in Et_2O (120 mL) was washed with 5% aqueous KOH solution and brine, dried over

anhydrous Na_2SO_4. The drying agent was filtered off and the clear solution was evaporated under reduced pressure. The oily residue was dissolved in a mixture of MeOH (6 mL) and THF (114 mL) and $NaBH_4$ (4.9 g, 130 mmol) was added portionwise at -10°C. After stirring for 30 min the reaction mixture was poured into saturated aqueous NH_4Cl solution (120 mL) and extracted with EtOAc (3x100 mL). Combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and, after removal the drying agent, evaporated to dryness. The residue was purified by FC (hexane/EtOAc, 88:12), to yield **7** as a colorless oil (5.2 g, yield 29%). $\mathbf{R_f}$ = 0.27 (hexane/EtOAc, 7:2); ^{1}**H** NMR (400 MHz, $CDCl_3$, ppm): δ 5.41-5.33 (m, 2H), 5.12-5.09 (m, 1H), 4.59 (d, *J* = 7.1 Hz, 2H), 3.99 (s, 2H), 2.16-2.00 (m, 8H), 2.05 (s, 3H), 1.71 (s, 3H), 1.67 (s, 3H), 1.61 (s, 3H). ^{13}**C** NMR (100 MHz): δ 171.1, 142.2, 135.1, 134.7, 125.9, 123.9, 118.3, 68.9, 61.4, 39.4, 39.2, 26.13, 26.10, 21.0, 16.4, 16.0, 13.6 ppm; **IR** ($CHCl_3$): ν 3604, 3467, 2927, 1728, 1610, 1239 cm^{-1}.

(2*E*,6*E*,10*E*)-3,7,11-Trimethyl-12-(phenylsulfonyl)dodeca-2,6,10-trien-1-yl acetate (8). To a stirred solution of **7** (5.2 g, 18.5 mmol) in dry THF (5 mL) PBr_3 (0.8 mL, 8.5 mmol) was added at 0 °C under argon atmosphere. After 3 h the reaction mixture was quenched by pouring to ice water and extracted with Et_2O (3 x 50 mL). Combined organic extracts were washed with 5% aqueous $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, filtered through a filter paper and evaporated under vacuum to yield crude bromide **7a** as a colorless oil (5.08 g, yield 80%) which was used directly in the next step without further purification.

To a solution of **7a** (5.08 g, 14.8 mmol) in anhydrous DMF (50 mL) sodium benzenesulfinate ($PhSO_2Na$) (3.15 g, 19.2 mmol) was added and the resulting suspension was stirred at room temperature in the dark. After 18 h the reaction mixture was poured into water (100 mL) and extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed with saturated

aqueous NH_4Cl solution and brine, dried over anhydrous Na_2SO_4 and filtered. Solvent was removed under vacuum at 40 °C and the crude product was purified by DFC (hexane/EtOAc, 7:2) to give **8** as a colorless oil (5.25 g, yield 70% after two steps). $\mathbf{R_f}$ = 0.41 (hexane/EtOAc = 7:2). **^{1}H** NMR (400 MHz, $CDCl_3$, ppm): δ 7.86-7.84 (m, 2H), 7.66-7.62 (m, 1H), 7.56-7.52 (m, 2H), 5.35-5.31 (m, 1H), 5.07-4.99 (m, 2H), 4.58 (d, *J* = 7.1 Hz, 2H), 3.72 (s, 2H), 2.05 (s, 3H), 2.09-2.01 (m, 8H), 1.76 (s, 3H), 1.70 (s, 3H), 1.54 (s, 3H) ppm; **^{13}C** NMR (100 MHz): δ 171.1, 142.0, 138.5, 136.0, 134.6, 133.4, 128.8, 128.5, 124.1, 123.2, 118.3, 66.2, 61.3, 39.4, 38.5, 26.9, 26.1, 21.0, 16.7, 16.4, 15.9 ppm; **IR** ($CHCl_3$): ν 2930, 1728, 1667, 1145 cm^{-1}.

(2*E*,6*E*,10*E*,14*E*,18*E*)-3,7,11,15,19,23-Hexamethyl-12-(phenylsulfonyl)tetracosa-2,6,10,14,18,22-hexaen-1-ol (9). To a stirred solution of **8** (5.21 g, 12.9 mmol) in dry THF (40 mL) and DMF (10 mL) a suspension of *t*-BuOK (1.594 g, 14.2 mmol) in anhydrous THF was added at -78 °C. The stirring was continued at -78°C for 2.5 h and a solution of *trans,trans*-farnesyl bromide (4.051 g, 14.2 mmol, purity: 95%) in THF (10 mL) was added dropwise. The reaction was carried out at -78 °C for 2 h and at room temperature overnight. Then the reaction mixture was poured to saturated aqueous NH_4Cl solution (100 mL) and extracted with Et_2O (3 x 50 mL). Combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered through a filter paper and evaporated under reduced pressure. To the residue dissolved in MeOH (20 mL) was added 1M NaOH solution to pH 12 and stirred at room temperature for 1 h. After removal of MeOH under vacuum water was added and the reaction mixture was extracted with Et_2O (3 x 100 mL). Combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The crude product was purified by DFC (hexane/EtOAc, 7:2) to afford **9** as a light yellow oil (3.61 g, yield 50%). $\mathbf{R_f}$ = 0.23 (hexane/EtOAc, 7:2). **^{1}H** NMR (400 MHz, $CDCl_3$, ppm): δ 7.82-7.51 (3m, 5H), 5.42-5.38 (m,

1H), 5.08-4.99 (m, 4H), 4.90-4.86 (m, 1H), 4.15 (d, *J* = 6.9 Hz, 2H), 3.47 (dd, *J* = 11.6, 3.9 Hz, 1H), 2.82-2.78 (m, 1H), 2.62-2.60 (m, 1H), 2.08-1.92 (m, 16H), 1.67 (s, 6H), 1.64 (2s, 6H), 1.58 (s, 3H), 1.56 (s, 3H), 1.52 (s, 3H) ppm; **^{13}C** NMR (100 MHz): δ 139.6, 138.4, 138.2, 135.6, 135.2, 134.7, 133.2, 131.3, 128.79, 128.75, 126.6, 124.3, 124.1, 123.8, 123.4, 118.8, 74.1, 59.4, 39.7, 39.6, 39.4, 38.6, 26.8, 26.5, 26.3, 25.7, 24.1, 17.7, 16.3, 16.0, 15.9, 13.8 ppm; **IR** ($CHCl_3$): ν 3607, 3532, 2926, 1667, 1586, 1144 cm^{-1}. **ESI-MS** (m/z): 589.1 $[MNa]^+$. **HRMS** (ESI) calcd for $C_{36}H_{55}O_3S$ $[MH]^+$ 567.3866, found 567.3877 (1.9 ppm error).

((2*E*,6*E*)-3,7,11-Trimethyldodeca-2,6,10-trien-1-yl)benzenesulfonate (8a). Compound **8a** was prepared analogously to the procedure described above for **8** using *trans,trans*-farnesol (1 g, 4.5 mmol), PBr_3 (0.2 mL, 2.1 mmol), dry THF (5 mL) followed by using $PhSO_2Na$ (0.755 g, 4.6 mmol) and dry DMF (10 mL). The crude product was purified by FC (hexane/EtOAc, 95:5) to give **8a** as a colorless oil (1.23 g, 79%). $\mathbf{R_f}$ = 0.53 (hexane/EtOAc = 7:2).**^{1}H** NMR (400 MHz, $CDCl_3$, ppm): δ 7.89-7.86 (m, 2H), 7.66-7.62 (m, 1H), 7.56-7.52 (m, 2H), 5.20 (t, *J* = 8.0 Hz, 1H), 5.10-4.04 (m, 2H), 3.81 (d, *J* = 8.0 Hz, 2H), 2.07-2.1.96 (m, 8H), 1.68 (s, 6H), 1.60 (s, 3H), 1.59 (s, 3H), 1.32 (s, 3H) ppm; **^{13}C** NMR (100 MHz): δ 146.4, 138.7, 135.7, 133.5, 131.4, 128.9, 128.5, 124.20, 123.3, 110.3, 56.1, 39.67, 39.66, 26.7, 26.2, 25.7, 17.7, 16.2, 16.0 ppm; **IR** ($CHCl_3$): ν 2928, 1448, 1307, 1150, 1085 cm^{-1}.

(2*E*,6*E*,10*E*,14*E*,18*E*)-3,7,11,15,19,23-hexamethyl-13-(phenylsulfonyl)tetracosa-2,6,10,14,18,22-hexaen-1-ol (9a). Bromide **7a** was freshly prepared from alcohol **7** (1 g, 3.57 mmol) as described previously. To a stirred solution of **8a** (1.09 g, 3.14 mmol) in dry THF (12 mL) and HMPA (3 mL) *n*-BuLi (2.0 mL, 3.2 mmol, 1.6 M) was added at -78 °C. The stirring was continued at -78°C for 1.5 h and a solution of **7a** (0.98 g, 2.85 mmol) in dry THF was added. After 5 h the reaction mixture was allowed to warm up to 0 °C, poured to saturated

NH_4Cl solution (10 mL) and extracted with Et_2O (3 x 10 mL). Combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, the drying agent was filtered off and solvent was evaporated under reduced pressure. To the residue dissolved in MeOH (10 mL) catalytic amount of MeONa was added and the reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated under vacuum and the residue was purified by FC (hexane/EtOAc, 75:25) to give **9a** as a light yellow oil (0.84 g, 52%). **^{1}H** NMR (400 MHz, $CDCl_3$, ppm): δ 7.86-7.84 (m, 2H), 7.64-7.60 (m, 1H), 7.59-7.50 (m, 2H), 5.42 (t, *J* = 6.9 Hz, 1H), 5.15 (t, *J* = 6.8 Hz, 1H), 5.10-5.05 (m, 3H), 4.93 (d, *J* = 10.4 Hz, 2H), 4.16 (d, *J* = 6.8 Hz, 2H), 3.89 (dt, *J* = 10.9 and 3.0 Hz, 1H), 2.89 (d, *J* = 12.6 Hz, 1H), 2.29 (dd, *J* = 13.3 and 11.5 Hz, 1H), 2.05-1.94 (m, 16H), 1.69 (s, 6H), 1.61 (s, 3H), 1.59 (s, 3H), 1.57 (s, 3H), 1.53 (s, 3H), 1.18 (s, 3H) ppm; **^{13}C** NMR (100 MHz): δ 145.0, 139.6, 138.0, 135.6, 135.0, 133.3, 131.4, 129.8, 129.2, 128.7, 128.2, 124.2, 124.0, 123.5, 123.4, 117.3, 63.6, 59.4, 39.72, 39.70, 39.5, 39.3, 37.3, 26.7, 26.6, 26.4, 26.2, 25.7, 17.7, 16.33, 16.27, 15.9 ppm; **IR** ($CHCl_3$): ν 3606, 3515, 2927, 1666, 1447, 1145, 1084 cm^{-1}. **ESI-MS** (m/z): 589.1 $[MNa]^+$; **HRMS** (ESI) calcd for $C_{36}H_{55}O_3S$ $[MH]^+$ 567.3866, found 567.3875 (1.6 ppm error).

(2*E*,6*E*,10*E*,14*E*,18*E*)-3,7,11,15,19,23-Hexamethyltetracosa-2,6,10,14,18,22-hexaen-1-ol; all-*trans*-hexaprenol (10). To a solution of **9** (3.5 g, 6.2 mmol) in dry THF (20 mL) $Pd(dppe)Cl_2$ (345 mg, 0.6 mmol) and $LiEt_3BH$ (19 mL, 19 mmol, 1M solution in THF) were added at 0 °C under argon atmosphere. The reaction mixture was stirred at room temperature until completion as monitored by TLC (usually up to 2 h). The mixture was poured into 20% NH_4Cl (40 mL) and thoroughly extracted with EtOAc (3 x 30 mL). Combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by DFC (hexane/EtOAc, 70:5 to 70:20) to give **10** as a colorless oil (2.0 g,

yield 76%, HPLC purity: 91%). $\mathbf{R_f}$ = 0.47 (hexane/EtOAc, 7:2); **^{1}H** NMR (400 MHz, $CDCl_3$, ppm): δ 5.44-5.41 (m, 1H), 5.14-5.09 (m, 5H), 4.15 (d, *J* = 7.0 Hz, 2H), 2.10-1.98 (m, 20H), 1.69 and 1.61 (2s, 21H); **^{13}C** NMR (100 MHz): δ 139.7, 135.3, 134.94, 134.86, 134.8, 131.2, 124.4, 124.23, 124.15, 123.7, 123.4, 59.3, 39.7, 39.5, 26.7, 26.65, 26.63, 26.3, 25.6, 17.6, 16.2, 15.97, 15.95; **IR** ($CHCl_3$): ν 3611, 3452, 2918, 1667, 1449, 1383 cm^{-1}; **ESI-MS** (m/z): 449 $[MNa]^+$; **HRMS** (ESI) calcd for $C_{30}H_{51}O$ $[MH]^+$ 427.3934, found 427.3943 (2.1 ppm error).

Following the previous procedure for **9**, the reaction of **9a** (0.83 g, 1.5 mmol) and $LiEt_3BH$ (5 mL, 5.0 mmol, 1M solution in THF) under $Pd(dppe)Cl_2$ (92 mg, 0.16 mmol) catalysis in THF (7 mL) at 0 °C afforded **10** as a colorless oil (0.456 g, 73%). The NMR spectra were identical with those disclosed above.

Hexaprenyl bromide (3). To a stirred solution of **10** (2.0 g, 4.69 mmol) in anhydrous THF (25 mL) PBr_3 (0.2 mL, 2.13 mmol) was added at 0 °C under argon atmosphere. After 3 h the reaction mixture was poured into ice water (50 mL) and extracted with Et_2O (3 x 50 mL). Combined organic extracts were washed with 5% $NaHCO_3$, brine and water, dried over anhydrous Na_2SO_4, and, after removal of inorganic material, evaporated under vacuum. The crude bromide **3** (2.27 g, 87%, colorless oil) was used in the next step without further purification.

2-((2*E*,6*E*,10*E*,14*E*,18E,22E)-3,7,11,15,19,23,27-Heptamethyl-4-(phenylsulfonyl)octacosa-2,6,10,14,18,22,26-heptaen-1-yl)-1,4-dimethoxy-3-methylnaphthalene (11). *t*-BuOK (493 mg, 4.4 mmol) was added to a stirred solution of **2** (1.52 g, 3.7 mmol) and **3** (2.27 g, 4.1 mmol) in THF (18 mL) and DMF (2 mL) at -20 ºC. The stirring was continued at -20 ºC until completion of the reaction (TLC control). After 1 h the reaction mixture was allowed to warm up to room temperature and poured to saturated NH_4Cl solution (40 mL). Crude product was extracted with

EtOAc (3 x 20 mL). The combined organic extracts were washed with water, dried over anhydrous Na_2SO_4 and, after removal of the drying agent, evaporated to dryness under reduced pressure. The residue was purified by FC (hexane/EtOAc, 7:2) to obtain compound **11** as a bright yellow oil (2.475 g, 82%). $\mathbf{R_f}$ = 0.32 (hexane/EtOAc, 7:2); **^{1}H** NMR (400 MHz, $CDCl_3$, ppm): δ 8.06-7.99 (m, 2H), 7.75 (d, *J* = 7.0 Hz, 2H), 7.49-7.31 (3m, 5H), 5.14-5.03 (m, 6H), 4.89 (t, *J* = 6.9 Hz, 1H), 3.84 (s, 3H), 3.74 (s, 3H), 3.52-3.38 (m, 3H), 2.85-2.62 (2m, 2H), 2.16 (s, 3H), 2.07-1.96 (m, 20H), 1.91 (s, 3H), 1.69 (s, 3H), 1.61 (s, 12H), 1.60 (s, 3H), 1.57 (s, 3H) ppm; **^{13}C** NMR (100 MHz): δ 150.1, 149.8, 138.7, 137.9, 135.3, 135.0, 134.9, 134.3, 133.1, 131.2, 129.0, 128.6, 127.6, 127.4, 127.2, 126.3, 125.6, 125.4, 124.4, 124.2, 124.1, 123.7, 122.2, 122.1, 118.5, 73.9, 62.0, 61.3, 39.7, 30.3, 29.7, 26.8, 26.7, 26.73, 26.71, 26.67, 26.64, 26.54, 26.49, 25.7, 23.9, 17.7, 16.3, 16.1, 16.02, 15.99, 13.9, 12.4; **IR** ($CHCl_3$): ν 2930, 2855, 1592, 1353, 1145 cm^{-1}; **ESI-MS** (m/z): 841.3 $[MNa]^+$; **HRMS** (ESI) calcd for $C_{54}H_{75}O_4S$ $[MH]^+$ 819.5381, found 819.5392 (1.3 ppm error).

Preparation of vitamin MK-7 (1).

Desulfonation. Following the previous procedure for **10**, the reaction of **11** (1.7 g, 2.1 mmol), $LiEt_3BH$ (4.6 mL, 4.6 mmol, 1M in THF) and $Pd(dppe)Cl_2$ (121 mg, 0.21 mmol) catalyst in dry THF (5 mL) at 0 ºC for 4 h afforded **12** as a colorless oil (1.094 g, 78%), which was used immediately in the next step without further purification.

Oxidation. A solution of ammonium cerium(IV) nitrate (CAN) (2.19 g, 4 mmol) in CH_3CN (12 mL) and H_2O (2 mL) was slowly added to a stirred solution of **12** (1.094 g, 1.6 mmol) in a mixture of CH_3CN (6 mL) and CH_2Cl_2 (6 mL) at 0°C. After 45 min (TLC control) the reaction mixture was poured into ice cold water (100 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The

combined organic layers were washed with brine and water, dried over anhydrous Na_2SO_4, filtrated and evaporated under reduced pressure at 40 °C. Crude product was purified by DFC (hexane/CH_2Cl_2, 5:1) to obtain **1** as a yellow oil (0.753 g, yield 72%, HPLC purity: 99.4%). Further crystallization from ethyl acetate and ethanol afforded vitamin MK-7 (**1)** as a yellow powder (0.64 g, purity by HPLC: 99.9%). $\mathbf{R_f}$ = 0.40 (hexane/EtOAc 7:2); **Mp** 51.5-53.5 ˚C (54.68 °C[34]); **^{1}H** NMR ($CDCl_3$): δ 8.12-8.07 (m, 2H), 7.72-7.67 (m, 2H), 5.14-5.01 (m, 7H), 3.38 (d, *J* = 6.9 Hz, 2H), 2.20 (s, 3H), 2.08-1.96 (m, 24H), 1.80 (s, 3H), 1.69 (s, 3H), 1.60 (s, 12H), 1.57 (2s, 6H) ppm; **^{13}C** NMR ($CDCl_3$): δ 185.45, 184.51, 146.18, 143.35, 137.57, 135.23, 134.94, 134.91, 134.88, 133.31, 133.25, 132.22, 132.18, 131.23, 126.31, 126.19, 124.42, 124.28, 124.16, 123.85, 119.09, 39.72, 39.69, 26.78, 26.71, 26.68, 26.52, 26.01, 25.68, 17.67, 16.43, 16.01, 16.00, 12.66; **IR** (KBr): ν 2963, 1660, 1618, 1594, 1295 cm^{-1}; **ESI-MS** (m/z): 671.9 $[MNa]^+$; **HRMS** (ESI) calcd for $C_{46}H_{65}O_2$ $[MH]^+$ 649.4979, found 236.1283 (1.5 ppm error).

ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{13}C NMR spectra for all intermediates and the final product (vitamin MK-7). IR, MS for compound **1** and HPLC chromatograms for compounds **2**, **3** and **1**.

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Notes

The authors declare no competing financial interest.

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