126. Synthesis of All Four Stereoisomers of (*E*)-Vitamin K_1 (Phylloquinone), Analysis of Their Diastereoisomeric and Enantiomeric Purities and Determination of Their Biopotencies[1])

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Dedicated to Dr. *Otto Isler* on the occasion of his 80th birthday

(18.V.90)

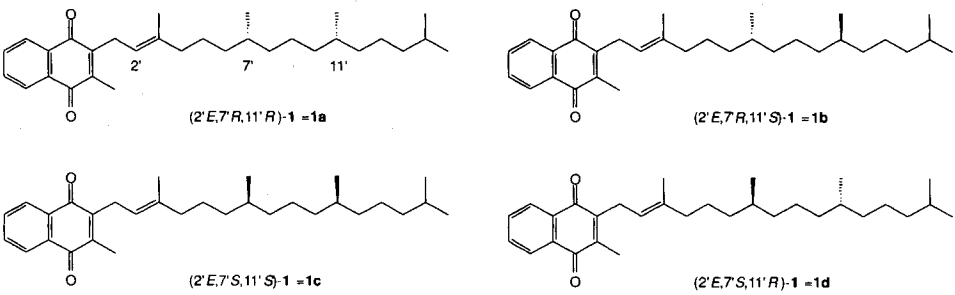
All four stereoisomers of (*E*)-vitamin K_1, *i.e.* (2′*E*,7′*R*,11′*R*)-**1** (= **1a**), (2′*E*,7′*R*,11′*S*)-**1** (= **1b**), (2′*E*,7′*S*,11′S)-**1** (= **1c**), and (2′*E*,7′*S*,11′*R*)-**1** (= **1d**), have been synthesized in a state of high chemical and stereoisomeric purity. The synthesis of stereoisomers **1b–d** relied on the use of the optically active C_5^*- and C_{10}^*-building blocks (*R*)- or (*S*)-4-(benzyloxy)-3-methylbutanal ((*R*)- or (*S*)-**2**) and (*R*)- or (*S*)-citronellal ((*R*)- or (*S*)-**3**) which had been secured by the Rh^I-catalyzed allylamine-to-enamine isomerization technology. For the synthesis of the natural (*E*)-vitamin-K_1 stereoisomer **1a**, a new route starting from natural phytol was developed, based on an *O*-alkylation/rearrangement procedure. A HPLC method was developed which separates with remarkable efficiency all four stereoisomers of (*E*)- as well as three out of the four stereoisomers of (*Z*)-vitamin K_1 on optically active poly(trityl methacrylate) as the chiral stationary phase supported on *Nucleosil*. By this method, the stereoisomeric content of the stereoisomers **1b–d** synthesized was shown to be in the range of 96–98%, while the natural isomer **1a** was configurationally uniform. The biological activity of the four (*E*)-vitamin-K_1 stereoisomers was determined by means of the curative prothrombin time test with vitamin-K-depleted chicks. A high precision of the results was obtained with the recently introduced up-and-down organization of the test and the statistical evaluation according to an estimation procedure. With the natural (*E*)-vitamin-K_1 stereoisomer **1a** as standard (set at 1.0), activities of 0.93, 1.19, and 0.99 were found for stereoisomers **1b**, **1c**, and **1d**, respectively. Within the confidence limits, these activity ratios can be regarded as identical. A very similar efficacy was obtained by comparison of (*E*, all-*rac*)-vitamin K_1 ((2′*E*,7′*RS*,11′*RS*)-**1**; equimolar mixture of the four stereoisomers **1a–d**) with the natural (*E*)-vitamin-K_1 stereoisomer **1a**). A synergistic effect was not detectable, as was the case with the eight α-tocopheryl-acetate stereoisomers.

Introduction. – Vitamin K_1 (phylloquinone) of natural origin (or synthesized from natural phytol) has been shown by *Isler*, *Mayer* and coworkers [1] to have (*E*)-configuration at the C(2′)=C(3′) bond and to occur as the (7′*R*,11′*R*)-stereoisomer, *i.e.* (2′*E*,7′*R*,11′*R*)-**1** (= **1a**). (*E*, all-*rac*)-vitamin K_1 ((2′*E*,7′*RS*,11′*RS*)-**1**), manufactured by total synthesis from synthetic phytol or isophytol (*cf.* review [2] and lit. cit. therein), consists of an equimolar mixture of two racemates or, in other words, of an equimolar

[1]) Presented in part at the '6th International Symposium on Homogeneous Catalysis', Vancouver, Canada, August 21–26, 1988.

[2]) Deceased on November 4, 1989.

mixture of the four stereoisomers **1a–d**[3])[4]). In terms of biopotencies, the naturally occurring (*E*)-vitamin K_1 (**1a**) and the totally synthetic (*E*, all-*rac*)-vitamin K_1 ((2′*E*,7′*RS*,11′*RS*)-**1**) have about the same activity in the curative blood-clotting test in chicken (*Weiser et al.* [4]; *cf.* also [2])[5]), and the synthetic material, therefore, is a viable substitute for the natural isomer. However, nothing was known so far about the individual biopotencies of the three remaining stereoisomers **1b–d**. In the light of the observation of significant synergystic effects of mixtures of stereoisomers in the α-tocopherol series (*Weiser* and *Vecchi* [6]), the study of the individual biopotencies of the four (*E*)-vitamin-K_1 stereoisomers and of potential synergystic effects of mixtures of (*E*)-vitamin-K_1 stereoisomers became of interest as well. Therefore, the development of synthetic methods to prepare the stereoisomers of (*E*)-vitamin K_1 was undertaken.



This report describes, in the first part, the total synthesis of the three stereoisomers **1b–d** of (*E*)-vitamin K_1. These syntheses rely on the utilization of enantiomerically highly pure building blocks. Moreover, a novel synthetic route to the natural stereoisomer **1a** by an *O*-alkylation/rearrangement procedure is described using natural phytol as starting material. Chiroptical properties of the four stereoisomers and a remarkably efficient analysis of all four stereoisomers on an optically active HPLC stationary phase will be disclosed.

In the second part, the results of the determination of the biopotencies of the four stereoisomers are presented.

Synthesis of the Four (*E*)-Vitamin-K_1 Stereoisomers. – *Total Synthesis of the Stereoisomers* **1b–d**. A common synthetic strategy was used to synthesize the stereoisomers **1b–d**. This strategy is based firstly on the utilization of the optically active C_5^*- and C_{10}^*-building blocks **2** and **3** for constructing the C_{15}^{**}-side-chain alcohols **12** and bromides **13** (see below, *Scheme 1*) and, secondly, on the subsequent coupling of the *Grignard* reagents derived from **13** with the prenyl-substituted naphthalene moiety **20** to complete

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[3]) It has been shown by GC diastereoisomer analysis that (*E*, all-*rac*)-vitamin K_1 (as its dihydro-dimethyl-ether derivative), prepared from synthetic isophytol, consists of a 1:1 mixture of 2 diastereoisomeric pairs of enantiomers (*Vecchi* and coworkers [3a]). Moreover, the 1:1 ratio of the 2 diastereoisomeric pairs of (*E*, all-*rac*)-phytol has also been established by ^{13}C-NMR spectroscopy (*Mayer, Englert,* and *Arnold* [3b]; *cf.* also the diasteroisomer analysis of (all-*rac*)-α-tocopherol by ^{13}C-NMR spectroscopy [3c]).

[4]) Throughout this work, the term 'stereoisomer' will be used only for the four possible stereoisomers originating from the two chiral C-atoms C(7′) and C(11′), while the term 'geometrical isomer' will be used for the (*E*/*Z*)-double-bond isomers.

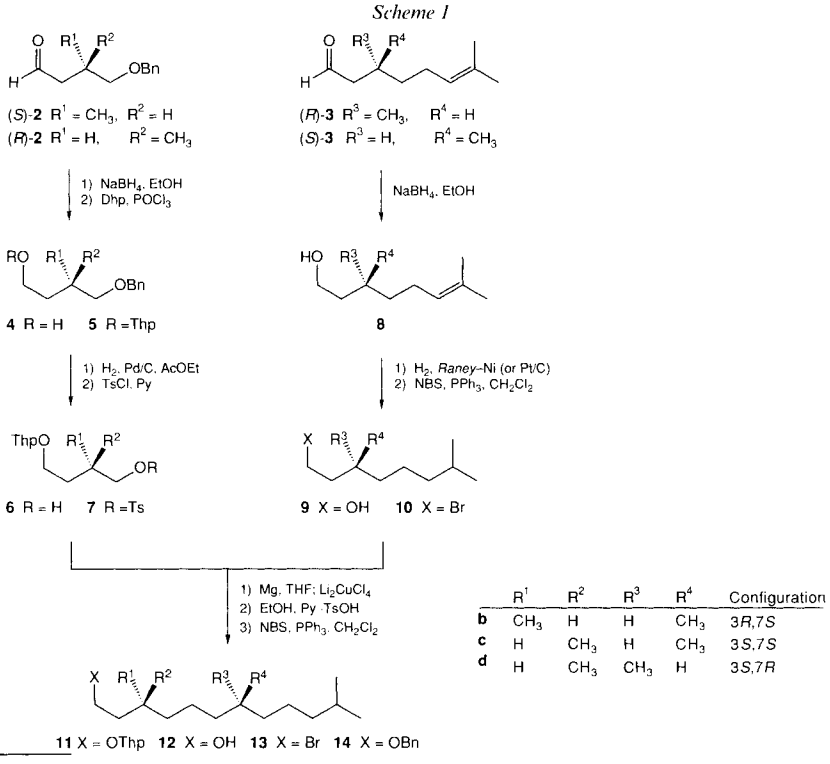
[5]) The corresonding (*Z*, all-*rac*)-vitamin K_1 ((2′*Z*,7′*RS*,11′*RS*)-**1**) is, in contrast, practically devoid of vitamin-K activity [5].

the assembly of the C-framework of vitamin K_1 (see below, *Scheme 3*). The latter coupling approach, previously developed in the racemic series (*Rüttimann* [2]), was considered more attractive than an approach which would involve chain lengthening of each C_{15}^{**}-side-chain intermediate to phytol and a subsequent *Friedel-Crafts* alkylation of a menadiol derivative (*cf.* [2]), because the coupling proceeds with high *trans*-stereoselectivity and, moreover, because this approach is also shorter with regard to the total number of steps in the three stereoisomeric series.

The key C_5^*- and C_{10}^*-units **2** and **3** required for the construction of the C_{15}^{**}-side chain are available by the Rh^I-catalyzed asymmetric allylamine-to-enamine isomerization methodology. This methodology had been pioneered by *Otsuka*, *Tani*, *Noyori*, and coworkers [7] for the preparation of the optically active citronellals **3** and was applied by us later on to the bifunctional C_5^*-series[6]). Given the ready accessibility of these chiral units in both configurations and in high enantiomeric purities (98–99% ee), all the elements for establishing the chirality in the 3 stereoisomeric series were in hand.

Starting from the optically active building blocks **2** and **3**, the assembly of the C_{15}^{**}-side-chain intermediates (**12** and **13**) was carried out as depicted in *Scheme 1*. The method of *Fouquet* and *Schlosser* [9] was used for the linking of the two chiral units. The required protection of the tail end and the activation of the head end of the bifunctional isoprenoid building blocks **2** ((*R*)-**2** (99.2% ee) and (*S*)-**2** (99.3% ee)) was achieved by

Scheme 1



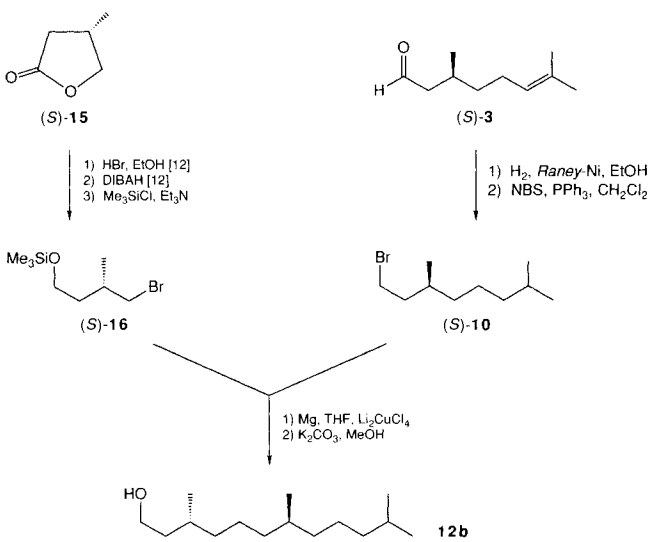
	R^1	R^2	R^3	R^4	Configuration
b	CH_3	H	H	CH_3	3*R*,7*S*
c	H	CH_3	H	CH_3	3*S*,7*S*
d	H	CH_3	CH_3	H	3*S*,7*R*

[6]) See the preceding paper in this issue [8].

reduction of the aldehyde function ($NaBH_4$, EtOH, 0°; 96–97% of **4**; *cf.* [10]), protection of the resulting OH function as tetrahydro-2*H*-pyranyl (Thp) ether (3,4-dihydro-2*H*-pyron (Dhp), cat. $POCl_3$; 76–85% of **5**), hydrogenolytic debenzylation (H_2, Pd/C, AcOEt; 94–96% of **6**), and tosylation (TsCl, Py, 0° to r.t.; 86–91% of **7**) to provide the bifunctional tosylates **7**. Overall yields of these transformations amounted to 69% in the (*R*)- and 66% in the (*S*)-series. Attempts to prepare the corresponding bromides (**7**, Br instead of TsO) by bromination of **6** (*N*-bromosuccinimide (NBS), PPh_3) failed due to the sensitivity of the Thp ether protecting group. Citronellals (*R*)-**3** (98.8% ee) and (*S*)-**3** (98.4% ee) were converted to saturated C_{10}^*-bromides (*R*)- and (*S*)-**10** by hydride reduction of the aldehyde function ($NaBH_4$, EtOH, 0°; 87–93% of **8**), catalytic hydrogenation of the olefinic double bond (81–100% of **9**), and bromination (NBS, PPh_3, CH_2Cl_2; 88–90% of **10**; overall yields, 76% of (*R*)-**10**, 70% of (*S*)-**10**). The catalytic-hydrogenation step was initially carried out with a Pt/C catalyst. This, however, was replaced with the *Raney*-Ni catalyst, when it became evident later on in the synthesis that the Pt catalyst apparently had caused some racemization of the Me-substituted chiral C-atom (*vide infra*). Coupling of tosylates **7** with the *Grignard* reagents derived from bromides **10** (1.5 mol-equiv.) in the presence of 2 mol-% of Li_2CuCl_4 according to *Fouquet* and *Schlosser* [9] afforded Thp ethers **11** (77–89% with respect to **7** or 52–60% with respect to **10**) which were converted to C_{15}^{**}-alcohols **12** (EtOH, pyridinium *p*-toluenesulfonate (Py·TsOH), 60°; 82–91%). Bromination then finally provided C_{15}^{**}-bromides **13** (NBS, PPh_3, CH_2Cl_2; 70–92%).

In an alternative scheme, C_{15}^{**}-alcohol **12b** ((3*R*,7*S*)-series) was synthesized starting from the microbiologically produced C_5^*-lactone (*S*)-**15** [11] (of 97.2% ee; *Scheme 2*). Lactone (*S*)-**15** was converted into bromide (*S*)-**16** by treatment with HBr/EtOH [12], ester reduction with DIBAH [12], and subsequent silylation. Bromide (*S*)-**16** was linked with the *Grignard* reagent derived from (*S*)-**10** according to *Tamura* and *Kochi* [13] in the

Scheme 2

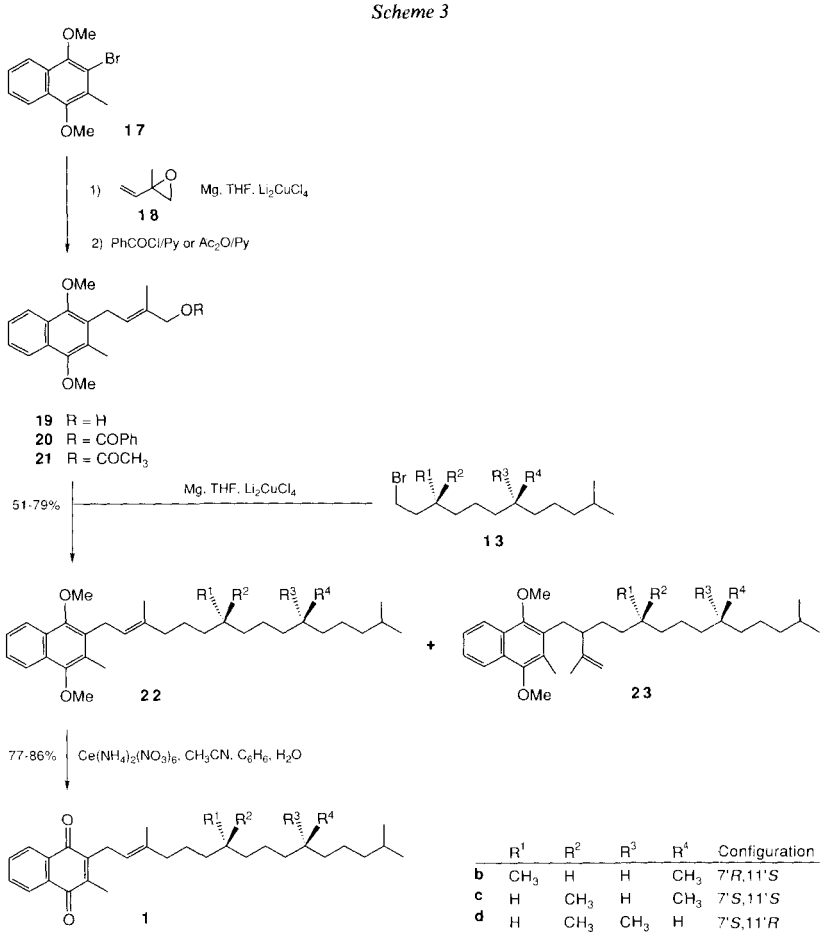


presence of Li_2CuCl_4 to afford, after desilylation, C_{15}^{**}-alcohol **12b**. The C_{10}^{*}-bromide (*S*)-**10** had been secured in this case by a direct catalytic reduction of (*S*)-**3** to (*S*)-**9** using *Raney*-Ni as catalyst (96% of (*S*)-**9**) and a subsequent bromination (NBS, PPh_3, CH_2Cl_2; 74% of (*S*)-**10**)[7]).

All C_{15}^{**}-alcohols **12** and bromides **13** were of > 98% chemical purity according to GC analysis. Specific rotations of these compounds, together with those of the corresponding compounds in the natural series, are listed in *Table 1*. The stereoisomeric purities of alcohols **12b–d** were determined by GC diastereoisomer analysis of the corresponding benzyl-ether derivatives **14b–d**; contents of 95–99% of the major diastereoisomers were found in all cases (*cf. Table 2*).

As mentioned above, the formation of the vitamin-K_1 C-framework was then completed by a *Schlosser*-type coupling of the allylic benzoate **20** (or acetate **21**) with the *Grignard* reagents derived from bromides **13** (*Scheme 3*). The allylic substrates **20** and **21**

Scheme 3



	R^1	R^2	R^3	R^4	Configuration
b	CH_3	H	H	CH_3	7'*R*,11'*S*
c	H	CH_3	H	CH_3	7'*S*,11'*S*
d	H	CH_3	CH_3	H	7'*S*,11'*R*

[7]) We thank Dr. *Bryant E. Rossiter* for carrying out these 2 steps.

Table 1. *Specific Optical Rotation Data* $[\alpha]_D^{20}$ *of (*E*)-Vitamin-*K_1 *Stereoisomers and of Synthetic Intermediates*[a])

Config. series[b])	C_{15}^{**}-Alcohols **12**	C_{15}^{**}-Bromides **13**	Dihydro-Dimethyl Ethers **22**	*trans*-Vitamin K_1 (**1**)
a (*R,R*)	+3.7 (*c* = 1.0, octane)[c])	−3.6 (*c* = 1.0, octane)[c])	−0.53 (*c* = 7.8, dioxane)	−0.28 (*c* = 12.95, dioxane)[d])
b (*R,S*)	+3.8 (*c* = 0.8, $CHCl_3$)	−3.3 (*c* = 3.6, $CHCl_3$)	+0.10 (*c* = 8.2, dioxane)	+0.42 (*c* = 19.3, dioxane)
c (*S,S*)	−3.9 (*c* = 0.85, octane)	+4.3 (*c* = 1.0, $CHCl_3$)	+0.54 (*c* = 3.14, dioxane)	+0.25 (*c* = 13.7, dioxane)
d (*S,R*)	−4.1 (*c* = 1.0, $CHCl_3$)	+2.2 (*c* = 1.0, $CHCl_3$)	−0.11 (*c* = 10.4, dioxane)	−0.38 (*c* = 16.6, dioxane)

[a]) All compounds **12**, **13** and **22** exhibited chemical purities of > 98% by GC. All vitamin-K_1 samples **1** showed purities > 97% by HPLC.
[b]) The configurational assignment is referring to C(3) and C(7) for **12** and **13** and to C(7′) and C(11′) for **22** and **1**, respectively; *cf. Schemes 1* and *3*.
[c]) Data from [12].
[d]) Data from [1a].

Table 2. *GC Diasteroisomer Analysis of* C_{15}^{**}*-Benzyl-Ether Derivatives* **14b–d** *and HPLC Analysis of (*E*)-Vitamin-*K_1 *Stereoisomers* **1b-d**

Entry	Config. series[a])	% ee of substrates[b])		% Diastereoisomer composition of **14**[c])		% Stereoisomer composition of **1**[d])		% (*Z*)-**1**
				(*RS*/*SR*) to (*RR*/*SS*) ratio		(*RR*)/(*SR*)/(*SS*)/(*RS*)	(*RR*)/(*SR*)/(*SS*)/(*RS*)	
		C_5^*-unit	C_{10}^*-unit	calc.	obs.	calc.	obs.	
1	**b** (*R,S*)	99.2	98.4	*98.8*: 1.2	*98.1*: 1.9	0.8: 0 : 0.4:*98.8*	n.d.	
2	**b** (*R*/*S*)[e])	97.2	98.4	*97.8*: 2.2	*98.7*: 1.3	0.8: 0 : 1.4:*97.8*	1.8: 0 : 0.3: *97.9*	1.1
3	**c** (*S,S*)[f])	99.3	98.4	1.2: *98.8*	4.7: *95.3*	0: 0.8: *98.8*: 0.4	0 : 3.2: *96.2*: 0.5	0.6
4	**c** (*S,S*)	99.3	98.4	1.2: *98.8*	3.1: *96.9*	0: 0.8: *98.8*: 0.4	n.d.	
5	**d** (*S*/*R*)	99.3	98.8	*99.0*: *1.0*	*98.8*: 1.2[g])	0.3: 99.0: 0.6: 0	0.4: 98.3: 1.3: 0	0.45

[a]) The configurational assignment is referring to C(3) and C(7) in the case of **14** and to C(7′) and C(11′) in the case of **1**; cf. *Schemes 1* and *3*.
[b]) All enantiomeric purities of the C_5^*- and C_{10}^*-building blocks are based on GC and/or HPLC diastereoisomer analyses of the amide derivatives of the corresponding acids with (*R*)-α-methyl-4-nitrobenzylamine; *cf.* [26] [8].
[c]) By GC diastereoisomer analysis of **14**. The (*RS*/*SR*)-pair of stereoisomers is eluted before the (*RR*/*SS*) pair.
[d]) By HPLC analysis on optically active poly(trityl methacrylate) (see text).
[e]) Synthesized *ex* C_5^*-lactone (*S*)-**15** (97.2% ee) according to *Scheme 2*.
[f]) In this case, the hydrogenation of the C_{10}^*-derivative **8** was performed over Pt/C; in all the other cases, *Raney*-Ni was used as catalyst.
[g]) A double determination was carried out in this case, and a ratio of 97.3:2.7 was found in the second determination.

Table 3. *Results of the Coupling Reactions of C_{15}^{**}-Bromides* **13** *with Allylic Benzoate* **20** *or Acetate* **21**

Entry	Coupling reaction	Molar ratio **13**/**20** or **21**	Catalyst (mol-%)[a]	Yield [%][b]	GC composition[c]			NMR composition[d]		
					(*E*)-**22**	(*Z*)-**22**	**23**	(*E*)-**22**	(*Z*)-**22**	**23**
1	**13b**[e]) +**20**→**22b**	1.45:1	Li_2CuCl_4 (3)	73	98[g])		1.5			
2	**13b**[f]) +**21**→**22b**	1 :1.2	CuI (5)	65	83	2	12	89	1	9
3	**13c** +**20**→**22c**	1 :1	Li_2CuCl_4 (2.3)	55	96.5	0.5	2.5	97	1	2
4	**13c** +**20**→**22c**	1 :1.2	Li_2CuCl_4 (2.5)	51	91.5	1	7.5			
5	**13d** +**20**→**22d**	1 :1	Li_2CuCl_4 (2.5)	79	91[g])		0.2	99	1	–

[a]) Amount of catalyst (mol-%) based on bromide **13**.

[b]) Isolated yield of (*E*)-**22**/(*Z*)-**22**/**23** after non-discriminative chromatography on SiO_2, based on the component used in lower mol amount.

[c]) In % based on total of all peaks (= 100%).

[d]) In % based on relative intensities of the ^{1}H-NMR (250 MHz, $CDCl_3$) absorptions of the olefinic Me group ((*E*)-**22**: 1.81 ppm; (*Z*)-**22**: 1.70 ppm; **23**: 1.74 ppm).

[e]) Material *ex* aldehyde (*S*)-**2** *(Scheme 1)*.

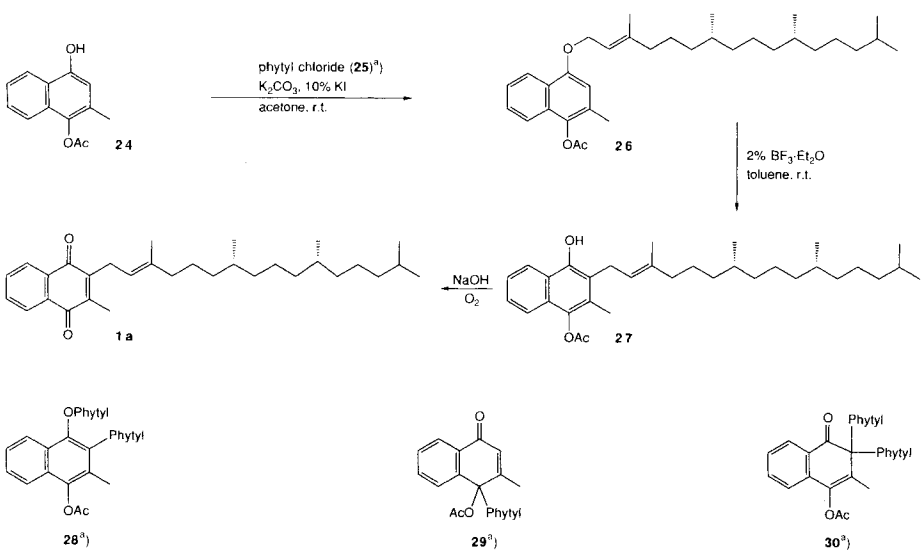
[f]) Material *ex* lactone (*S*)-**15** *(Scheme 2)*.

[g]) Sum of (*E*)-**22** and (*Z*)-**22**, no base-line separation achieved in this case.

were secured according to the method developed by *Sato et al.* [14] by a Cu^{I}-catalyzed reaction of the *Grignard* reagent derived from bromide **17** [15] with isoprene epoxide (**18**) to yield allylic alcohol **19** [16] (90% of a 93:7 (*E*/*Z*)-mixture, 75% of ≥ 99:1 (*E*/*Z*)-mixture after recrystallization) and subsequent acylation. In the event, the coupling reactions of **20** (or **21**) with the *Grignard* reagents derived from bromides **13** in the presence of 2–3 mol-% of Li_2CuCl_4 afforded the dihydro-vitamin-K_1 dimethyl ethers **22** in yields of 51–79%. The results are compiled in *Table 3*. High retention of the (*E*)-double-bond geometry was observed (99–98% (*E*), 0.5–2% (*Z*)). As a side reaction, S_N2' attack at the allylic system did occur to some extent to produce varying amounts (1–12%) of products **23**; excess of the allylic benzoate or acetate appears to favour the formation of **23**, while the use of an excess of the *Grignard* reagent reduces its formation. Chromatography on silica gel impregnated with 10% of $AgNO_3$ allowed the separation of **22** from **23**. The pure dihydro-vitamin-K_1 dimethyl ethers **22** then were subjected to oxidative demethylation ($Ce(NH_4)_2(NO_3)_6$, CH_3CN, C_6H_6, H_2O) [17] to afford the (*E*)-vitamin-K_1 stereoisomers **1b–d** in 77–86% yield, after chromatographic purification. The stereoisomers **1b–d** were 97–99% chemically pure by HPLC, contained ≤ 0.3% of (*Z*)-isomer, and displayed contents of 98–101% of (*E*)-vitamin K_1 by HPLC when compared to a standard sample. At r.t., the stereoisomers **1b–d**, like the natural stereoisomer **1a** (see below), are clear, light-yellow oils. At −15°, the two enantiomeric stereoisomers **1b** and **1d** solidified to yellow solids.

Synthesis of the Natural Stereoisomer **1a**. Nature-identical (*E*)-vitamin K_1 (**1a**) has been synthesized in a number of ways which have mostly involved *Friedel-Crafts* alkylations of menadiol (= 2-methylnaphthalene-1,4-diol) or a suitable derivative thereof with natural phytol or derivatives thereof (*cf.* [2] and lit. cit. therein). Phytol itself has been

Scheme 4



[a]) Phytyl = (2*E*,7*R*,11*R*)-3,7,11,15-tetramethylhexadec-2-enyl

obtained also by total synthesis from smaller optically active building blocks [18]. We have elaborated a novel synthesis of **1a** *(Scheme 4)* which is based on the (O→C)-rearrangement method developed by *Yoshizawa et al.* [19] for polyprenyl aryl ethers, specifically within the context of the synthesis of ubiquinones. Alkylation of menadiol monoacetate (**24**) with 1.1 mol-equiv. of (*E*)-phytyl chloride (**25**; (*E*/*Z*) 99.7:0.3; prepared from natural phytol with PPh_3/CCl_4) under *O*-alkylation conditions (K_2CO_3, KI, acetone) afforded, after chromatography, 79–87% of phytyl ether **26** and 7–8% of the bis(phytyl) derivative **28**. The (*E*)-configuration of the phytyl double bond was completely retained in this alkylation (99.5% of (*E*) in **26** by ^{1}H-NMR). The *Lewis*-acid-catalyzed rearrangement of **26** with 2 mol-% of $BF_3 \cdot OEt_2$ (toluene, r.t., 18–24 h) occurred with high regio- and stereoselectivity to produce dihydro-vitamin-K_1 monoacetate **27** as a 97:3 (*E*/*Z*)-mixture (by ^{1}H-NMR) in 76–80% yield. As by-products, the ketones **29** (2–4%) and **30** (5–7%) were formed, together with some of the cleavage product **24**. Isolated yields of 61–63% of **27** based on **24** were achieved when the *O*-alkylation/rearrangement was carried out as through-process without purification at the ether stage. Conversion of **27** into (*E*)-vitamin K_1 (**1a**) was then carried out as described by *Isler*, *Mayer*, and coworkers [1b] by saponification and aerial oxidation to afford **1a** as a 97:3 (*E*/*Z*)-mixture before and as a 99:1 (*E*/*Z*)-mixture after chromatography.

This *O*-alkylation/rearrangement protocol may be looked upon at as an intramolecular version of a *Friedel-Crafts* alkylation. The advantages of this intramolecular version in comparison with the normal, intermolecular *Friedel-Crafts* alkylation are the milder reaction conditions, the requirement of low amounts of catalyst only, and the higher (*E*)-stereoselectivity. Thus, there was only *ca.* 3% loss of (*E*)-configuration of the double bond in the intramolecular version compared to *ca.* 8–10% in the BF_3-catalyzed *Friedel-Crafts* alkylation of menadiol monobenzoate with phytol [1b] or phytyl methyl ether [18d]. Even higher stereoselectivities, in fact virtually complete retention of the (*E*)-configuration, have been observed by *Yoshizawa et al.* [19] when performing rearrangements of polyprenyl aryl ethers at −15° in the presence of 1.5 mol-equiv. of the $BF_3 \cdot OEt_2$ catalyst.

*Chiroptical Properties of the (*E*)-Vitamin-K_1 Stereoisomers and of Synthetic Intermediates.* The optical rotation dispersion curves (ORD) of the four stereoisomers **1a–d** of (*E*)-vitamin K_1 in dioxane solutions (c = 12.9–19.3%) in the wavelength region of 490–700 nm are represented in *Fig. 1*. The data for the natural isomer **1a** are those reported earlier by *Isler*, *Mayer*, and coworkers [1a] for a sample isolated from natural sources. Mirror-image ORD curves are observed for the two pairs of enantiomers **1a**, **1c** and **1b**, **1d**. The curves for the pair **1a**, **1c** are plain, while those for **1b**, **1d** display an extremum at *ca.* 540 nm. Interestingly, the signs of rotation in the 500–700-nm region are the same for the stereoisomer pairs **1a**, **1d** and **1b**, **1c**, *i.e.* for pairs of epimers at the C(7′) chiral centres, but extrapolation to shorter wavelengths indicates that, below *ca.* 480 nm, pairs of epimers having the same configuration at C(7′) show the same direction of optical rotation.

The ORD curves of the four stereoisomers of *(E)*-dihydro-vitamin-K_1 dimethyl ether **22a–d** are displayed in *Fig. 2*. Data for the stereoisomers **22b–d** are from the samples obtained by total synthesis *(cf. Scheme 3)*, while the data for the isomer of natural configuration **22a** are from a sample which had been synthesized from **1a** *(Scheme 4)* by reductive methylation [3a]. Again, the mirror-image course of the curves for the two pairs of enantiomers **22a**, **22c** and **22b**, **22d** is clearly evident. Curves for the pair **22b**, **22d** are

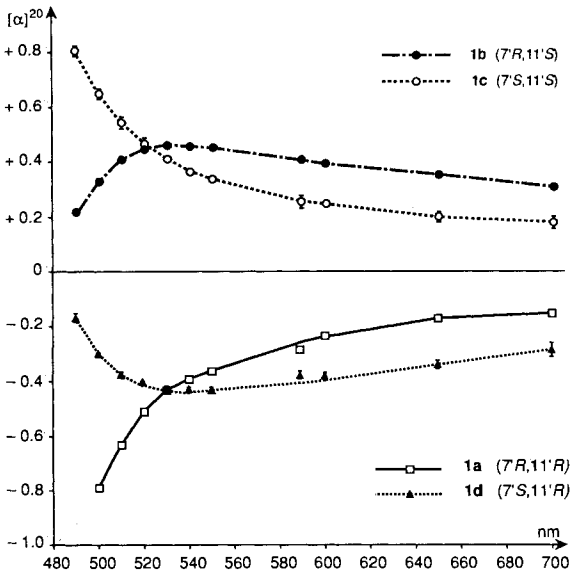


Fig. 1. *ORD spectra of (E)-vitamin-K_1 stereoisomers* **1a–d** (dioxane, c = 12.95–19.3%)

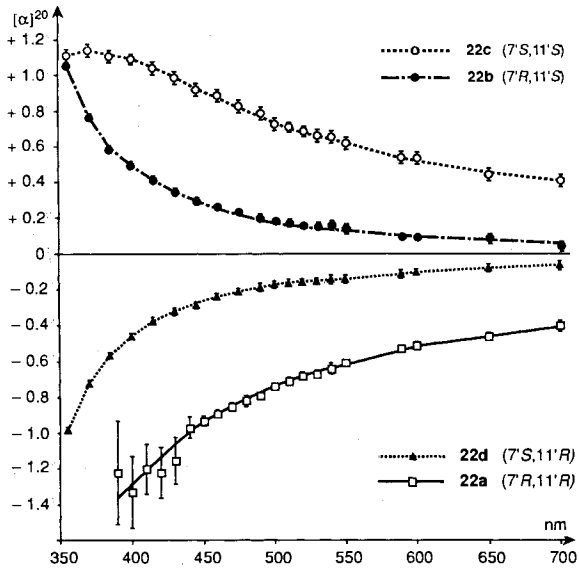


Fig. 2. *ORD spectra of (E)-dihydro-vitamin-K_1 dimethyl ethers* **22a–d** (dioxane, c = 5.1–10%)

plain, while those for the pair **22a**, **22c** probably go through an extremum at *ca.* 380 nm[8]). As observed already for the stereoisomers of **1**, the direction of the optical rotations is the same for pairs of epimers at C(7') (*i.e.* for **22a**, **22d** and **22b**, **22c**). *Table 2* compiles numerical data for the specific rotations at the Na D-line ($[\alpha]_D^{20}$) for the stereoisomers of

[8]) The course of the ORD of **22a** could not be exactly determined in the region below 430 nm due to the presence of an intensely absorbing impurity which required dilution of the sample and led to a decrease in measurement accuracy.

(*E*)-vitamin K_1 (**1**) and the corresponding dihydro-dimethyl ethers **22** as well as for the synthetic C_{15}^{**}-side chain intermediates **12** and **13**.

In principle, the optical-rotation data, particularly the ORD curves of vitamin K_1 or of the dihydro-dimethyl-ether derivatives, may be used for identifying samples of (*E*)-vitamin K_1 with natural configuration and for distinguishing them from totally synthetic (*E*, all-*rac*)-vitamin K_1 (*cf.* [1a]). It has to be taken into account, however, that the rotations are small, and that they apparently also depend on the geometric purity at the double bond. For example, we have found specific rotations of $[\alpha]_D^{20} = +0.52$ and $[\alpha]_{436}^{20} = +0.83$ ($c = 0.97$, $CHCl_3$) for stereoisomer **22c** of $\geqslant 99\%$ (*E*)-configuration, while values of $[\alpha]_D^{20} = -1.0$ and $[\alpha]_{436}^{20} = -2.2$ ($c = 1.0$, $CHCl_3$) have been reported for a 4:1 (*E*/*Z*)-mixture of the enantiomeric stereoisomer **22a** [3a].

Diastereoisomeric Purities. The GC diastereoisomer analysis of the dihydro-vitamin-K_1-dimethyl-ether derivatives **22** which had been previously described (*Vecchi et al.* [3a]), in principle, would constitute the most simple method to determine the stereoisomeric purities of vitamin-K_1 samples. Unfortunately, this analysis is not sufficiently sensitive to quantify small amounts of a minor diastereoisomer. In contrast, GC diastereoisomer analysis of C_{15}^{**}-alcohol intermediates **12**, specifically of their benzyl-ether derivatives **14**, allowed us to determine the diastereoisomeric composition at this stage with reasonable precision. In this analysis, the pair of enantiomers **14b**/**14d** (3*R*,7*S*/3*S*,7*R*) is eluted before the pair **14a**/**14c** (3*R*,7*R*/3*S*,7*S*). The observed diastereoisomer compositions of the synthetic stereoisomers of **14** are compiled in *Table 2*, together with the values calculated from the individual ee's of the C_5^*- and C_{10}^*-building blocks. All samples – with one exception – showed a content of 97–99% of the major diastereoisomer. Considering an estimated inaccuracy of *ca.* ±0.5 to 1.0% (*cf.* double determination for **14d**, *Entry 5*), the observed and calculated compositions are in good agreement. The diastereoisomer content of 95.3% for sample **14c** is lower by *ca.* 3.5% than calculated (*Entry 3*). We presume that, since in this case the hydrogenation (*S*)-**8**→(*S*)-**9** had been carried out over Pt/C (rather than over *Raney*-Ni as in all other cases), some racemization of the chiral Me-substituted C-atom had taken place. It is known that secondary Me-substituted C-atoms in allylic positions undergo partial racemization in hydrogenations over Pd and Pt catalysts [20][9]). Confirmation of this assumption was brought about by HPLC analysis of the derived vitamin-K_1 sample **1c** on a chiral stationary phase (*vide infra*).

The GC analysis utilizing an achiral liquid phase distinguishes two diastereoisomers but not the individual enantiomers of each diastereoisomer. However, since the stereoisomers have been synthesized from chiral synthons of high enantiomeric purities (98–99% ee), the observed diastereoisomeric purity of the major diastereoisomer directly corresponds to its enantiomeric purity; or in other words, the amount of racemate in the major diastereoisomer is negligibly small[10]). The diastereoisomeric purities determined at the C_{15}^{**}-stage reflect also the diastereoisomeric purities at the vitamin-K_1 stage as is shown below by HPLC analysis on a chiral support.

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[9]) The racemization most likely occurs *via* double-bond migration during hydrogenation [21]; *cf.* also [22].

[10]) *E.g.*, the calculated diastereoisomer ratio of 98.8:1.2 for **14b** (*Table 2*, Entry *1*) translates directly into a content of 98.8% (3*R*,7*S*)-stereoisomer (amount of (3*S*,7*R*)-isomer: 0.0032%). The 1.2% of the minor diastereoisomer is composed, however, of 0.4% of the (3*S*,7*R*)- and 0.8% of the (3*R*,7*R*)-stereoisomer. *Cf.* also the discussion of the corresponding situation in the case of the eight stereoisomers of α-tocopherol [23].

Enantiomeric Purity of the Vitamin-K_1 Stereoisomers by HPLC Analysis on a Chiral Stationary Phase. The development of an analytical method for distinguishing, identifying, and quantifying directly all four stereoisomers of (*E*)- and possibly also the four stereoisomers of (*Z*)-vitamin K_1 would be of course the ultimate goal in the area of vitamin-K_1 analysis. We have now found a highly efficient separation of vitamin-K_1 stereoisomers on optically active poly(trityl methacrylate) on a silica-gel stationary phase [24] which comes close to this goal. As shown in *Fig. 3* (top trace), HPLC analysis of synthetic (*E*/*Z*, all-*rac*)-vitamin K_1 ((*E*/*Z*) *ca.* 10:1) on an in-house-made column of (+)-poly(trityl methacrylate)[11]) on *Nucleosil 1000-5* with MeCN/H_2O 9:1 as eluent neatly separates three out of the four stereoisomers of the minor (*Z*)- and all four stereoisomers of the major (*E*)-geometrical isomer. This analysis allows the quantitation of these stereoisomers, although there is no complete base-line separation. Thus, the first three eluted peaks of the (*Z*)-isomer are present in a 1:2:1 ratio, while the four peaks of the

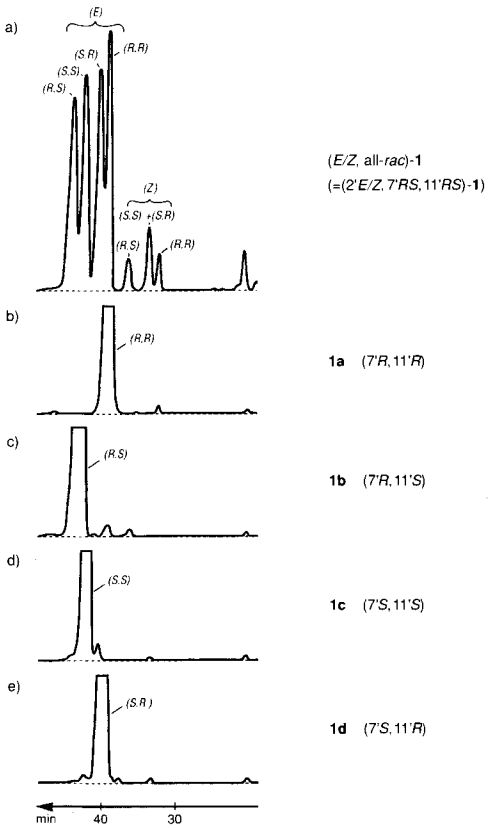

Fig. 3. *Vitamin-K_1-stereoisomer analysis by HPLC on (+)-poly(trityl methacrylate).* Conditions, see text.

[11]) Prepared according to *Okamoto* and coworkers [24b] using (+)-6-benzylsparteine/BuLi as catalyst. See [25] for experimental description. The commercially available columns (*Chiralpak OT*(+); *Daicel Chem. Ind., Ltd.*, Tokyo, Japan) showed less efficient separations.

(*E*)-isomer are present in essentially equal amounts. By coinjection with authentic samples of the synthetic (*E*)-vitamin-K_1 stereoisomers of known absolute configurations, the order of elution of the stereoisomers of the (*E*)-series was established as follows: peak 1, **1a** (7′*R*,11′*R*); peak 2, **1d** (7′*S*,11′*R*); peak 3, **1c** (7′*S*,11′*S*); peak 4, **1b** (7′*R*,11′*S*). The order of elution of the stereoisomers of the (*Z*)-series could be assigned on the basis of the presence of trace amounts (0.5–1%) of (*Z*)-isomers in the synthetic samples of the (*E*)-series: peak 1, (7′*R*,11′*R*); peak 2, (7′*S*,11′*R*) together with (7′*S*,11′*S*); peak 3, (7′*R*,11′*S*); *i.e.* the elution order in the (*Z*)-series is the same as in the (*E*)-series.

The vitamin-K_1 stereoisomer **1a** (synthesized from natural phytol as depicted in *Scheme 4*) consisted, according to this HPLC analysis, of a single peak for the (*E*)-(99.3%) and a single peak for the (*Z*)-geometrical isomer (0.7%) which, thus, again established that natural phytol is enantiomerically and diastereoisomerically homogeneous (*cf.* [23]). The analyzed samples of the totally synthetic stereoisomers **1b–d** exhibited stereoisomer contents of 97.9, 96.2, and 98.3% (*cf. Fig. 3c–e*; and *Table 2, Entries 2, 3*, and *5*). These values correspond well to the values for the diastereoisomeric composition at the C_{15}^{**}-stage (98.7, 95.3, 98.8%; *cf. Table 3*), thus indicating that there was no change of the diastereoisomer composition in the course of the synthetic elaboration of the C_{15}^{**}-side chains into the final vitamin-K_1 framework. The observed contents of the stereoisomeric impurities in the synthesized stereoisomers **1b–d** correspond only grossly with the values calculated from the individual ee's of the C_5^*- and C_{10}^*-building blocks. This may be due to an insufficient precision of the HPLC analysis (insufficient separation, presence of underlying impurities) or to an imprecision of the ee analyses of the building blocks or to a combination of both. Nonetheless, amounts of as little as 0.5% of the minor stereoisomer are clearly detectable. The presence of *ca.* 3.2% of the (7′*S*,11′*R*)-stereoisomer in the sample **1c** of the (7′*S*,11′*S*)-series (*cf. Fig. 3d*, and *Table 2, Entry 3*) also clearly demonstrates the validity of our assumption, that some racemization did take place in this case during the Pt-catalyzed hydrogenation at the C_{10}^*-stage (*vide supra*).

Also clearly detectable are amounts of *ca.* 0.5–1% of the (*Z*)-isomers of the individual major stereoisomers of the (*E*)-series. These amounts are slightly higher than originally observed by HPLC on achiral phases ($\leqslant 0.3\%$), probably due to some light-induced double-bond isomerization.

The results of these HPLC analyses on a chiral support demonstrate that our synthetic strategy, involving sequential coupling of chiral units, was highly effective in constructing the vitamin-K_1 stereoisomers.

Biopotencies of the Four (*E*)-Vitamin-K_1 Stereoisomers. – From the widely differing physiological functions of vitamin K_1, the participation in the formation of the four coagulation proteins is well known. In the liver, vitamin K_1 catalyzes the γ-carboxylation of certain glutamic-acid residues into the preprothrombin and their transformation into the coagulative prothrombin (factor II). Analogous carboxylations also take place with the precursor of coagulation factor VII (proconvertin), IX (plasma thromboplastin component), and *Stuart* factor X. The modifications result in negatively charged γ-carboxyglutamate (Gla) residues with strong calcium-binding capacities which, in turn, allow interactions with phospholipid surfaces and all subsequent steps of the coagulation cascade [27]. Other proteins and peptides are also similarly γ-carboxylated and play an important role in calcium metabolism, such as osteocalcin, the major non-collagenous bone protein.

The parameter to determine the activity of vitamin-K-active substances is, above all, their *anti-hemorrhagic properties*. Tests may be performed with prophylactic or curative procedures, and the experimental animals of choice are rats and chicks. The curative prothrombin (PT) time test was chosen for the comparative examination of (*E*)-vitamin-K_1 stereoisomers, and was carried out with chicks [28]. The curative test is always employed, when precise results are required. The test was not performed as usual with 2–3 dosages per preparation in order to carry out a statistical evaluation by means of the parallel line assay, but was laid out according to the up-and-down procedure we have described recently [4]. With small quantities or expensive compounds, this procedure offers the advantage that the steep and interesting part of the dosis-activity curve is reached quickly, so that a repetition of the test is very seldom necessary. A condition for the curative use of vitamin-K-active compounds is a delayed blood coagulation, which in our case corresponds with a prolonged PT time. The prolongation is achieved by means of a vitamin-K-free feed or the administration of anticoagulants or bactericidals.

The examination of the nutritive effect of vitamin K_1 requires an increase of the PT time of normally 30–40 s to > 180 s in our test system. The basic mash diet for chicks was formulated from fat-extracted compounds according to established poultry feeding standards [29]. As soon as all fat is extracted, one may assume that the compounds are vitamin-K-free. With proteins, which are difficult to extract, it is advantageous to add their amino-acid portion in the form of crystalline amino acids. The semi-synthetic diet contained 22.4% of digestible protein and 13.68 MJ/kg of metabolizable energy. It was supplemented with minerals, micronutrients, and vitamins as required for broiler chicks of up to 8 weeks of life. Female day-old chicks were kept in groups of 15 in heated batteries at an initial temperature of 32°, which was gradually lowered to room temperature of 26°. For six days, they were fed the starter diet containing 1 ppm of vitamin K_1 and given thereafter the vitamin-K-deficient diet. After three weeks, the chicks were transferred to individual wire cages. Strict hygienic conditions were necessary in order to achieve the required degree of vitamin-K deficiency. Two times per week and then daily, determinations of the PT time in whole blood were carried out. Chicks with PT times of 180–200 s were selected for examination, and test compounds were applied as single doses, dissolved in 0.5 ml of arachis oil, into the crop. The effect of the dose was determined 22–23 h after administration, by means of another PT time analysis. A reduction to 70 s was set arbitrarily as the expected effect of any dose. If the PT time exceeded 70 s, then the applied dose was designated negative. In the case of such a negative result, the next higher dose of the same compound was applied to another deficient animal. Correspondingly, a dose resulting in a positive effect was followed up by administration of the next lower dose. Succeeding doses differed by a factor of 1.15. This experimental set-up led consequently to an accumulation of highly useful data. The duration of an experiment could be shortened by working simultaneously with several lots of birds. The calculation of the mean effective dose (*ED*) was carried out by means of an estimation procedure [30] and an example of a complete evaluation included in another experiment [4a].

The results of the comparison of the vitamin-K activity of the stereoisomer **1c** (= (2′*E*,7′*S*,11′*S*)-**1**) with the stereoisomer of natural configuration **1a** (= (2′*E*,7′*R*,11′*R*)-**1**) are compiled in *Table 4*. In the dose range of 9.20–28.14 μg per animal, the frequencies of the positive (+) and negative (−) results achieved with each

Table 4. *Comparison of* **1c** (= (2′*E*,7′*S*,11′*S*)-**1**) *with* **1a** (= (2′*E*,7′*R*,11′*R*)-**1**) *in the Curative Prothrombin* (PT) *Time Test.* Vitamin-K-deficient diet without anticoagulants, individual dosing of chicks, organisation according to the up-and-down procedure, evaluation according to an estimation procedure [30].

Dose [μg] in 0.5 ml of arachis oil	Standard: **1a** (= (2′*E*,7′*R*,11′*R*)-**1**) PT time in whole blood, results at 70 s			Sample: **1c** (= (2′*E*,7′*S*,11′*S*)-**1**) PT time in whole blood, results at 70 s		
	Positive	Negative	Frequencies	Positive	Negative	Frequencies
8.00	–	–	–	–	1	1
9.20	–	3	3	1	4	5
10.58	3	6	9	4	17	21
12.16	6	12	18	16	22	38
13.99	11	15	26	22	17	39
16.09	15	16	31	17	7	24
18.50	14.5	14.5	29	8	1	9
21.28	12	4	16	2	–	2
24.47	4	1	5	–	–	–
28.14	1	–	–	–	–	–
Σ	66.5	71.5	138	70	69	139
Mean effective dose (*ED*)	15.73 μg (13.68–18.10 μg, *P* 0.05)			13.21 μg (12.15–14.26 μg, *P* 0.05)		
Relative activity and confidence limits (standard set at 1.0)				*1.19* (1.10–1.28, *P* 0.05)		

single dose were listed separately. Then, the frequencies of positive and negative values were totalized and the smaller figure (66.5 for the standard **1a** and 69 for the sample **1c**) was used for the calculation of the mean *ED*. A mean *ED* of 15.73 μg, within the confidence limits of 13.68–18.10 μg at *P* 0.05, was calculated for the standard preparation **1a**. For the sample **1c**, the mean *ED* was 13.21 μg (confidence limits 12.15–14.25 μg, *P* 0.05). The activity ratio for the standard and sample was obtained from the reciprocals as 1: *1.19* (confidence limits 1.10–1.28, *P* 0.05).

In a second experiment, stereoisomers **1b** (= (2′*E*,7′*R*,11′*S*)-**1**) and **1d** (= (2′*E*,7′*S*,11′*R*)-**1**) were compared to the standard preparation **1a** (= (2′*E*,7′*R*,11′*R*)-**1**; see *Table 5*). For the standard, the statistical evaluation resulted in a mean *ED* of 14.17 μg (confidence limits 12.70–15.82 μg, *P* 0.05). The mean *ED* of sample **1b** was 15.25 μg (confidence limits 12.28–18.96 μg, *P* 0.05) and of sample **1d** 14.32 μg (confidence limits 12.72–16.4 μg, *P* 0.05). Again from the reciprocals of the *ED*'s, the relative activities were calculated, and the standard preparation was set at 1.0. The activity of **1b** was found to be *0.93* (confidence limits 0.75–1.15, *P* 0.05) and of **1d** to be *0.99* (confidence limits 0.88–1.11, *P* 0.05).

By adding the vitamin-K activities of the four (*E*)-configurated stereoisomers determined experimentally, an activity of *1.03* was found for (*E*, all-*rac*)-vitamin K_1 ((2′*E*,7′*RS*,11′*RS*)-**1**), *i.e.* the sum of $0.25 \cdot 1.00 = 0.25$ (**1a**), $0.25 \cdot 0.93 = 0.23$ (**1b**), $0.25 \cdot 1.19 = 0.30$ (**1c**), and $0.25 \cdot 0.99 = 0.25$ (**1d**).

By means of a direct comparison of (*E*, all-*rac*)-vitamin K_1 ((2′*E*,7′*RS*,11′*RS*)-**1**) with the stereoisomer of natural configuration **1a** (= (2′*E*,7′*R*,11′*R*)-**1**) as standard, it should be tested whether the mixture containing equal portions of the four (*E*)-stereoisomers behaves synergistically. Again, PT times were determined by means of the up-and-down organization after application of the two compounds in the dose range of 8.00–28.14 μg per animal, and the frequencies were coordinated according to dosage, positive and

Table 5. *Comparison of* **1b** (= (2′*E*,7′*R*,11′*S*)-**1**) *and* **1d** (= (2′*E*,7′*S*,11′*R*)-**1**) *with* **1a** (= (2′*E*,7′*R*,11′*R*)-**1**) *in the Curative Prothrombin (*PT*) Time Test.* Vitamin-K-deficient diet without anticoagulants, individual dosing of chicks, organisation according to the up-and-down procedure, evaluation according to an estimation procedure.

Dose [μg] in 0.5 ml of arachis oil	Standard: **1a** (= (2′*E*,7′*R*,11′*R*)-**1**) PT time in whole blood, results at 70 s			Sample: **1b** (= (2′*E*,7′*R*,11′*S*)-**1**) PT time in whole blood, results at 70 s			Sample: **1d** (= (2′*E*,7′*S*,11′*R*)-**1**) PT time in whole blood, results at 70 s		
	Positive	Negative	Frequencies	Positive	Negative	Frequencies	Positive	Negative	Frequencies
8.00	–	1	1	–	–	–	–	1	1
9.20	1.5	4.5	6	–	5	5	1	4	5
10.58	4	11	15	5	10	15	4	8	12
12.16	9	20	29	9.5	15.5	25	8	19	27
13.99	17	20	37	15.5	14.5	30	16.5	16.5	33
16.09	18	14	32	12	13	25	15	16	31
18.50	13	8	21	12	12	24	14	9	23
21.28	6	–	6	11	4	15	5	3	8
24.47	–	–	–	4	3	7	1	–	1
28.14	–	–	–	3	–	3	–	–	–
Σ	68.5	80.5	149	72	77	149	68.5	80.5	149
Mean effective dose (*ED*)	14.17 μg (12.70–15.82 μg, *P* 0.05)			15.25 μg (12.25–18.96 μg, *P* 0.05)			14.32 μg (12.72–16.14 μg, *P* 0.05)		
Relative activity and confidence limits (standard set at 1.0)				*0.93* (0.75–1.15, *P* 0.05)			*0.99* (0.88–1.11, *P* 0.05)		

Table 6. *Comparison of (*E, *all*-rac)-*Vitamin* K_1 ((2′*E*,7′*RS*,11′*RS*)-**1**) *with* **1a** (= (2′*E*,7′*R*,11′*R*)-**1**) *in the Curative Prothrombin* (PT) *time test.* Vitamin-K-deficient diet without anticoagulants, individual dosing of chicks, organisation according to the up-and-down procedure, evaluation according to an estimation procedure.

Dose [μg] in 0.5 ml of arachis oil	Standard: **1a** (= (2′*E*,7′*R*,11′*R*)-**1**) PT time in whole blood, results at 70 s			Sample: (2′*E*,7′*RS*,11′*RS*)-**1** PT time in whole blood, results at 70 s		
	Positive	Negative	Frequencies	Positive	Negative	Frequencies
8.00	–	–	–	–	2	2
9.20	–	3	3	3	11	14
10.58	5	13	18	12	16	28
12.16	14.5	10.5	25	18	12	30
13.99	13	14	27	14	9	23
16.09	15	11	26	11	3	14
18.50	12	4	16	4	3	7
21.28	5	3	8	4	1	5
24.47	3	1	4	1	1	2
28.14	1	–	1	1	–	1
Σ	68.5	59.5	138	68	58	126
Mean effective dose (*ED*)	15.66 μg (14.22–17.23 μg, *P* 0.05)			14.15 μg (12.32–16.24 μg, *P* 0.05)		
Relative activity and confidence limits (standard set at 1.0)				*1.11* (1.00–1.22, *P* 0.05)		

negative results separately (*Table 6*). The statistical evaluation resulted in mean *ED*'s of 15.66 μg (confidence limits 14.22–17.23 μg, *P* 0.05) for the standard, and 14.15 μg (confidence limits 12.31–16.14 μg, *P* 0.05) for the (all-*rac*)-sample. The stereoisomer mixture was found to have an acitivity of *1.11* (confidence limits 1.00–1.22, *P* 0.05), and was within these limits identical with the standard. With a single application and registration of the very rapid setting in of the normalization of the blood coagulation after only a few hours, the three (*E*)-stereoisomers **1b–1d** examined were biologically highly active. The repetition of the comparison of stereoisomer **1a** and (2′*E*,7′*RS*,11′*RS*)-**1**, carried out several times, resulted in activity ratios within the range of 1:1.10 to 1.30.

To enable us to gain more detailed information on the different activities of the four (*E*)-stereoisomers, the biodiscrimination after a prolonged application of (*E*,all-*rac*)-vitamin K_1 ((2′*E*,7′*RS*,11′*RS*)-**1**) will be investigated. Similar experiments were already carried out with (2*RS*,4′*RS*,8′*RS*)-α-tocopheryl acetate to determine the biodiscrimination of the eight stereoisomers above all in plasma, liver, fatty tissue, and brain [31].

Conclusion. – The synthetic work described above has provided, for the first time, chemically and configurationally highly pure samples of the three (*E*)-vitamin-K_1 stereoisomers **1b–d**. The extensive exploitation of the optically active C_5^*- and C_{10}^*-building blocks **2** and **3** demonstrates the versatility and synthetic utility of the asymmetric isomerization technology [7] [8] for the total synthesis of terpenoid products. In addition, the development of a HPLC method for distinguishing all four stereoisomers of (*E*)-vitamin K_1 (and three of the four stereoisomers of (*Z*)-vitamin K_1) represents a milestone in the analysis of chiral compounds containing chiral $CH(CH_3)$ centres and affords now a valuable analytical tool for vitamin-K_1 research. In this context, we refer also to our recent improvements of the analysis of α-tocopherol stereoisomers [25].

The determination of the bioactivities of the four (*E*)-vitamin-K_1 stereoisomers was carried out by means of the curative prothrombin time test with chicks. The delayed blood coagulation was achieved by a vitamin-K-free diet. A high precision of the results was obtained with the established up-and-down procedure. For the first time, the effectiveness of the synthesized stereoisomers **1b–d** was determined in comparison to natural stereoisomer **1a** (= (2′*E*,7′*R*,11′*R*)-**1**) as the standard. The activity ratios were found to be 1:0.93, 1.19, and 0.99 for **1b** (= (2′*E*,7′*R*,11′*S*)-**1**), **1c** (= (2′*E*,7′*S*,11′*S*)-**1**), and **1d** (= (2′*E*,7′*S*,11′*R*)-**1**), respectively. Within the confidence limits, these ratios can be regarded as identical. A synergistic effect of the (*E*)-vitamin-K_1 stereoisomers could not be detected, because identical activities resulted from the evaluation of natural stereoisomer **1a** and (*E*, all-*rac*)-vitamin K_1 ((2′*E*,7′*RS*,11′*RS*)-**1**).

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Experimental Part

We thank Mr. *Alfred Grieder* for his excellent experimental assistance

General: Cf. [32]. HPLC system for vitamin K_1 and derivatives: *Lichrosorb SI60* (5 µm, column 3 × 300 mm), 0.5% of $(i\text{-Pr})_2O$ and 0.1% of octan-1-ol in hexane; benzyl benzoate as internal standard; see [25] for HPLC system for the separation of vitamin-K_1 stereoisomers on (+)-poly(trityl methacrylate). Specific rotations $[\alpha]_D^{20}$: at 589, 546, 436, 405, and 365 nm at 20°; *Perkin-Elmer-241* polarimeter. Optical rotation dispersion (ORD): in-house-built, self-balancing spectral polarimeter; indication of [α] (nm). IR spectra: neat, unless otherwise noted. ^{1}H-NMR spectra: in $CDCl_3$ at 250 MHz (*Bruker AC 250*), unless otherwise noted.

1. C_5^*-Intermediates. – 1.1. *C_5^*-Tosylate (*R*)-**7**. (R)-4-(Benzyloxy)-3-methylbutan-1-ol* ((*R*)-**4**) [10]. To a mixture of 1.1 g (29 mmol) of $NaBH_4$ in 100 ml of EtOH were added, at 0°, 11.0 g (57.6 mmol) of *(R)-4-(benzyloxy)-3-methylbutanal* ((*R*)-**2**; 99.3% ee [8]). The mixture was stirred at 0° to r.t. for 1 h, then quenched with 50 ml of 1N H_2SO_4, evaporated to about half of its volume, and worked up with Et_2O as usual. Bulb-to-bulb distillation at 150°/0.03 mbar afforded 10.8 g (96.5%) of (*R*)-**4**. Colourless liquid. GC: purity 99.3%. $[\alpha]_D^{20} = -2.4$ (*c* = 1.1, EtOH), −6.26 (*c* = 5.5, $CHCl_3$); [10]: $[\alpha]_D^{20} = -2.8$ (*c* = 1.1, EtOH). IR: 3370 (br., OH); 1095, 1070 (C–O–C, alcohol II); 737, 697 (monosubst. benzene). ^{1}H-NMR: 7.4–7.3 (*m*, 5 arom. H); 4.52 (*s*, $PhCH_2$); 3.65, 3.35 (2 *m*, CH_2(1), CH_2(4)); 2.29 (*s*, OH); 1.94 (*m*, H–C(3)); 1.75–1.5 (*m*, CH_2(2)); 0.94 (*d*, *J* = 7, CH_3–C(3)). MS: 194 (0.5, M^+), 176 (1, $[M^+ - H_2O]^+$), 107 (36), 91 (100). Anal. calc. for $C_{12}H_{18}O_2$ (194.27): C 74.19, H 9.34; found: C 74.00, H 9.32.

(2R)-1-(Benzyloxy)-2-methyl-4-[(tetrahydro-2H-pyran-2-yl)oxy]butane ((*R*)-**5**). To a soln. of 1.0 g (51.5 mmol) of (*R*)-**4** in 8.0 g of 3,4-dihydro-2*H*-pyran were added, at 0°, 0.15 ml of $POCl_3$, and the mixture was stirred for 1 h at 0° and for 2 h at r.t. Then the mixture was diluted with 30 ml of hexane, washed with sat. NH_4Cl soln. and worked up as usual. Chromatography on 300 g of silica gel (hexane/AcOEt 97:3) afforded 10.9 g (76%) of (*R*)-**5**. Colourless oil. In an analogous experiment, a yield of 80.5% of (*R*)-**5** was achieved. $[\alpha]_D^{20} = -3.6$ (*c* = 1.0, EtOH). IR: 1116, 1099 (C–O–C); 736, 697 (monosubst. benzene). ^{1}H-NMR: 7.35–7.25 (*m*, 5 arom. H); 4.57 (*s*, OCHO); 4.50 (*s*, $PhCH_2$); 3.87–3.72 (*m*, CH_2O); 3.55–3.25 (*m*, 2 CH_2O); 2.0–1.35 (*m*, 4 CH_2, H–C(2)); 0.97 (*d*, *J* = 6.5, CH_3–C(2)). MS: 193 (6, $[M - C_5H_9O]^+$), 91 (100), 85 (100, $C_5H_9O^+$).

(2R)-2-Methyl-4-[(tetrahydro-2H-pyran-2-yl)oxy]butan-1-ol ((*R*)-**6**). To a suspension of 1.0 g of 5% Pd/C in 150 ml of AcOEt, prehydrogenated for 30 min at 1 atm, were added *via* syringe 10.0 g (35.9 mmol) of (*R*)-**5**. The

mixture was stirred for 2 h under H_2 at 1 atm., then filtered and the filtrate evaporated. Chromatography on silica gel (250 g, hexane/AcOEt 10→25%) afforded 6.6 g (97.5%) of (*R*)-**6**. Colourless oil. GC: purity 96%. $[\alpha]_D^{20} = +8.2$ ($c = 0.6$, EtOH). IR: 3410 (br., OH); 1121, 1076, 1026 (C–O–C, alcohol II). ^{1}H-NMR: 4.61 (*m*, OCHO); 3.9–3.35 (*m*, 3 CH_2O); 2.28 (br. *s*, OH); 1.95–1.45 (*m*, 4 CH_2, H–C(2)); 0.952, 0.947 (2 *d*, $J = 6.7$, CH_3–C(2) of 2 diastereoisomers, ratio *ca.* 1:1). MS: 87 (58, $[M - C_5H_9O_2]^+$), 85 (100, $C_5H_9O^+$). Anal. calc. for $C_{10}H_{20}O_3$ (188.27): C 63.80, H 10.71; found: C 63.85, H 10.82.

(R)-2-Methyl-4-[(tetrahydro-2H-pyran-2-yl)oxy]butyl p-Toluenesulfonate ((*R*)-**7**). To a soln. of 5.0 g (26.5 mmol) of (*R*)-**6** in 17 ml of pyridine were added, at 0°, 5.6 g (29.4 mmol) of TsCl. The mixture was stirred for 6 h at 0° to r.t. Pyridinium hydrochloride separated as white precipitate. Addition of Et_2O and H_2O followed by usual workup and chromatography on silica gel (250 g, hexane/AcOEt 0→10%) afforded 8.3 g (91.5%) of (*R*)-**7**. Colourless oil. $[\alpha]_D^{20} = -7.1$ ($c = 0.8$, EtOH). IR: 1360, 1177 (SO_2); 814 (*p*-disubst. benzene). ^{1}H-NMR: 7.78, 7.36 (2 *d*, $J = 8$, 4 arom. H); 4.50 (*m*, OCHO); 4.0–3.6 (*m*, 2 CH_2O); 3.55–3.25 (*m*, 1 CH_2O); 2.45 (*s*, arom. CH_3); 2.08–1.88 (*m*, H–C(2)); 1.85–1.2 (*m*, 4 CH_2); 0.94 (*d*, $J = 6.5$, CH_3–C(2)). MS: 241 (5, $[M - C_5H_9O_2]^+$), 155 (42, $CH_3C_6H_4SO_2$), 91 (58), 85 (100, $C_5H_9O^+$).

1.2. *C_5^*-Tosylate (S)-***7***.* Synthesis exactly as described for (*R*)-**7** in *1.1*, starting from (*S*)-**2** (99.2% ee) [8], *via* the following intermediates:

(*S*)-**4** (*cf.* [10]); 96% yield, after chromatography on silica gel (hexane/AcOEt 4:1). $[\alpha]_D^{20} = +2.3$ ($c = 1.03$, EtOH).

(*S*)-**5**: 85% yield. $[\alpha]_D^{20} = +5.1$ ($c = 1.0$, EtOH). IR, ^{1}H-NMR, MS: identical with corresponding spectra of (*R*)-**5**. Anal. calc. for $C_{17}H_{26}O_3$ (278.39): C 73.35, H 9.41; found: C 73.42, H 9.69.

(*S*)-**6**: 94% yield. GC: purity 98.6%. $[\alpha]_D^{20} = -7.30$ ($c = 0.9$, EtOH). IR, ^{1}H-NMR, MS: identical with corresponding spectra of (*R*)-**6**. Anal. calc. for $C_{10}H_{20}O_3$ (188.27): C 63.80, H 10.17; found: C 63.81, H 10.61.

(*S*)-**7**: 86% yield. $[\alpha]_D^{20} = +7.1$ ($c = 0.8$, EtOH). IR, ^{1}H-NMR, MS: identical with corresponding spectra of (*R*)-**7**. Anal. calc. for $C_{17}H_{26}O_5S$ (342.45): C 59.63, H 7.65, S 9.36; found: C 59.32, H 7.56, S 9.19.

1.3. *C_5^*-Bromide (S)-***16***.* *(S)-4-Bromo-3-methylbutan-1-ol* [12] was prepared exactly as described in [12] starting from (*S*)-**15** of 97.2% ee. Overall yield 89%.

1-Bromo-2-methyl-4-[(trimethylsilyl)oxy]butane ((*S*)-**16**). To a soln. of 14.97 g (0.109 mol) of *(S)-4-bromo-3-methylbutan-1-ol* and 30.0 g (0.3 mol) of Et_3N in 200 ml of Et_2O were added, at *ca.* 10°, within 20 min, 21.7 g (0.20 mol) of Me_3SiCl. The mixture was stirred for 2 h at r.t., then poured onto ice and worked up as usual with petroleum ether. The obtained brown oil (19.3 g) was purified by filtration through silica gel (230 g, petroleum ether) and subsequent bulb-to-bulb distillation at *ca.* 50–60°/0.01 mbar to afford 8.40 g (35%) of (*S*)-**16**. Colourless liquid. $[\alpha]_D^{20} = -3.1$ ($c = 4.7$, $CHCl_3$). IR: 1251, 1098, 841, 747 (Me_3SiO). ^{1}H-NMR (60 MHz): 3.68 (*t*, $J = 6$, $CH_2(4)$); 3.45 (*d*, $J = 5$, $CH_2(1)$); 2.3–1.25 (*m*, H–C(2), $CH_2(3)$); 1.05 (*d*, $J = 6$, CH_3–C(2)); 0.1 (*s*, Me_3Si). MS: 223 (1, $[M - CH_3]^+$), 147 (55), 69 (100). Anal. calc. for $C_8H_{19}BrOSi$ (239.23): C 40.17, H 8.01, Br 33.40; found: C 40.61, H 7.93, Br 32.28.

2. C_{10}^*-Intermediates. – 2.1. *C_{10}^*-Bromide* (*R*)-**10**. *(R)-3,7-Dimethyloct-6-enal* ((*R*)-**3**) was synthesized *via* Rh-catalyzed asymmetric isomerization of *N,N*-diethylnerylamine (*cf.* [7] [32]); 98.8% ee by GC diastereoisomer analysis of amide derivative of corresponding acid with (*R*)-α-methyl-4-nitrobenzylamine (*cf.* [26] [32]).

(R)-3,7-Dimethyloctan-1-ol ((*R*)-**9**). To a mixture of 3.0 g (79 mmol) $NaBH_4$ in 200 ml of EtOH were added, at 0–10°, 25 g (162 mmol) of (*R*)-**3**. The mixture was stirred for 30 min at 0°, then quenched by dropwise addition of 150 ml of 1N H_2SO_4, evaporated to about half of its volume, and worked up as usual with Et_2O. Chromatography on silica gel (hexane/AcOEt 9:1) afforded 22.4 g (87%) of *(R)-3,7-dimethyloct-6-en-1-ol* ((*R*)-**8**). Colourless liquid. GC: purity 97.4%. This material was dissolved in 100 ml of EtOH and hydrogenated over 15 g of *Raney*-Ni at 6 bar H_2 pressure and at 50° for 2 h. After removal of the catalyst by filtration, the filtrate was evaporated and the residue dried *in vacuo* to afford 22.7 g of *(R)-3,7-dimethyloctan-1-ol* ((*R*)-**9**) [12] [20]. Colourless liquid. GC: purity 98%.

(R)-1-Bromo-3,7-dimethyloctane ((*R*)-**10**) [12] [33]. To a soln. of 22.7 g (143 mmol) of (*R*)-**9** and 47.3 g (183.5 mmol) of Ph_3P in 200 ml of CH_2Cl_2 were added, at 0°, 30.3 g (173 mmol) of *N*-bromosuccinimide (NBS) in portions. After stirring at 0° for 2 h, the solvent was evaporated. The residue was treated with hexane and filtered, the solids were washed thoroughly with hexane and the combined hexane extracts evaporated. The residue was dissolved again in hexane and the soln. kept overnight at 0°. After removal of some precipitate by filtration, the filtrate was evaporated and the residue chromatographed (900 g of silica gel, hexane): 28.1 g (88%) of (*R*)-**10**. Colourless liquid. GC: purity 98%. $[\alpha]_D^{20} = -6.0$ ($c = 7.0$, $CHCl_3$); [12]: $[\alpha]_D = -5.0$ ($c = 0.82$, $CHCl_3$).

2.2. *C_{10}^*-Bromide (S)-***10***.* *Aldeyhde* (*S*)-**3** was synthesized *via* Rh-catalyzed asymmetric isomerization of *N,N*-diethylnerylamine (*cf.* [7] [32]); 98.4% ee by GC diastereoisomer analysis of amide derivative of corresponding acid with (*R*)-α-methyl-4-nitrobenzylamine (*cf.* [26] [32]).

Alcohol (S)-**9**. a) Via (*S*)-**8**: $NaBH_4$ reduction of (*S*)-**3** as described above for (*R*)-**3** afforded 93% of (*S*)-**8**. Colourless oil. GC: purity 95%. Hydrogenation of (*S*)-**9** over *Raney*-Ni as described above for (*R*)-**8** afforded, after chromatography on silica gel, (*S*)-**9** in 91% yield. Alternatively, hydrogenation of (*S*)-**8** over 5% Pt/C in EtOH at 1 atm H_2 (r.t., 6 h) afforded (*S*)-**9** in 92% yield.

b) By direct hydrogenation of (*S*)-**3**: A soln. of 15.5 g (100 mmol) of (*S*)-**3** in 200 ml of EtOH was hydrogenated over 6 g of *Raney*-Ni at 10 bar of H_2 pressure (r.t., 7.5 h). Since hydrogenation under these conditions was incomplete, it was repeated using 6 g of fresh catalyst. Filtration, evaporation, and drying *in vacuo* afforded 15.1 g (96%) of (*S*)-**9**. Colourless liquid. GC: purity 98%.

Bromide (S)-**10** [23] was synthesized from (*S*)-**9** as described above for (*R*)-**10**: 93% yield. GC: purity 98.5%. $[\alpha]_D^{20} = +5.8$ (*c* = 5.1, $CHCl_3$); [23]: $[\alpha]_D = +4.98$ (*c* = 2.0, hexane).

3. C_{15}^*-Intermediates. – 3.1. *(3R,7S)-Series* (= **b**-*Series*). 3.1.1. *Coupling of C_5^*-Tosylate (S)*-**7** *with C_{10}^*-Bromide (S)*-**10**. *(3R,7S)-3,7,11-Trimethyldodecan-1-ol* (**12b**). To a suspension of 1.50 g (61.7 mmol) of Mg turnings in 10 ml of anh. THF were added 0.15 ml of 1,2-dibromoethane. After stirring at r.t. for 15 min, the soln. was removed *via* syringe, and the Mg turnings were washed twice with 10 ml of THF. Then, 5 ml of THF were added, and a soln. of 9.56 g (43.2 mmol) of (*S*)-**10** in 50 ml of THF was added dropwise, with occasional ice-bath cooling, keeping the temp. at 25–30°. After the addition, the mixture was stirred at r.t. for additional 2 h. The *Grignard* soln. obtained was transferred *via* cannula to a cold (−78°) soln. of 10.0 g (29.2 mmol) of (*S*)-**7** in 40 ml of THF, and 9 ml of 0.1M Li_2CuCl_4 in THF (0.9 mmol, 2 mol-%) were added *via* syringe. The cooling bath was removed and the mixture allowed to attain r.t. and stirred at r.t. for additional 2 h. Treatment with 100 ml of sat. NH_4Cl soln. followed by usual workup with Et_2O and chromatography on 500 g of silica gel (hexane/AcOEt 1→15%) afforded 8.1 g of **11b** (89% based on (*S*)-**7**, 60% based on (*S*)-**10**). To a soln. of this material in 60 ml of EtOH was added 1.0 g (4 mmol) of pyridinium *p*-tolenesulfonate (Py·TsOH), and the mixture was stirred at 50–60° for 2 h. The residue obtained after evaporation was partitioned between Et_2O and H_2O and the org. phase worked up as usual. Chromatography (350 g of silica gel, hexane/AcOEt 95:5) afforded 5.1 g (86%) of **12b**. Colourless liquid. GC: purity 98%. $[\alpha]_D^{20} = +3.8$ (*c* = 0.8, $CHCl_3$).

(3R,7S)-1-Bromo-3,7,11-trimethyldodecane (**13b**). Treatment of 4.0 g (17.5 mmol) of **12b** with 3.49 g (19.6 mmol) of NBS and 5.49 g (10.9 mmol) of PPh_3 in 80 ml of CH_2Cl_2 according to the procedure described in *2.1* afforded, after chromatography (silica gel, hexane), 4.9 g (96%) of **13b**. Colourless liquid. GC: purity 98.8%. $[\alpha]_D^{20} = -3.0$ (*c* = 0.8, $CHCl_3$).

3.1.2. *Coupling of C_5^*-Bromide (S)*-**16** *with C_{10}^*-Bromide (S)*-**10**. *Alcohol* **12b**. To a *Grignard* soln. derived from 4.81 g (17.5 mmol) (*S*)-**16** in 80 ml of THF (prepared as described above using 2.1 g (87.5 mmol) of Mg powder, then filtered from the excess of Mg *via* cannula) were added, at −78°, 4.6 g (21 mmol) of (*S*)-**10** and 1.3 ml of 0.1M Li_2CuCl_4 in THF. The mixture was stirred overnight while allowing to attain r.t. Usual workup with sat. NH_4Cl soln. and petroleum ether afforded 8.1 g of yellow oil which, for desilylation, was dissolved in 30 ml of MeOH and 0.65 ml of sat. K_2CO_3 soln. in MeOH. After stirring at r.t. for 3 h, the mixture was evaporated and the residue worked up as usual with petroleum ether. Chromatography (Al_2O_3, neutral, act. III; hexane/Et_2O 10→30%) afforded 2.5 g of **12b** as colourless liquid (50% based on (*S*)-**16**, 41% based on (*S*)-**10**). A sample for analysis was obtained by bulb-to-bulb distillation at *ca.* 140°/0.01 mbar. $[\alpha]_D^{20} = +3.6$ (*c* = 2.3, $CHCl_3$). IR: 3326 (br., OH); 1057 (alcohol II). ^{1}H-NMR: 3.68 (*m*, CH_2(1)); 1.7–1.0 (*m*, 18 H); 0.86 (*m*, 4 CH_3). MS: 210 (1, $[M - H_2O]^+$), 182 (3), 69 (80), 57 (100). Anal. calc. for $C_{15}H_{32}O$ (228.42): C 78.87, H 14.12; found: C 78.94, H 14.51.

Bromide **13b**. Treatment of 2.5 g of **12b** with NBS/PPh_3 as described in *2.1* followed by chromatography (Al_2O_3, neutral, act. III; hexane) and bulb-to-bulb distillation at *ca.* 100°/0.01 mbar afforded 2.95 g (92%) of **13b**. Colourless liquid. GC: purity 98.7. $[\alpha]_D^{20} = -3.3$ (*c* = 3.6, $CHCl_3$). IR: 1379, 1365 (Me); 1261 (CH_2Br). ^{1}H-NMR: 3.45 (*m*, CH_2(1)); 1.95–1.8 (*m*, 1 H); 1.75–1.0 (*m*, 16 H); 0.86 (*m*, 4 CH_3). MS: 207, 205 (each 5, $[M - C_6H_{13}]^+$); 179, 177 (each 3); 165, 163 (each 3); 151, 149 (each 6); 113 (27); 71 (73); 57 (100). Anal. calc. for $C_{15}H_{31}Br$ (291.32): C 61.85, H 10.73; found: C 62.18, H 11.05.

3.2. *(3S,7S)-Series* (= **c**-*Series*). *Alcohol* **12c**. Coupling of 6.0 g (17.5 mmol) of (*R*)-**7** with the *Grignard* reagent derived from 5.74 g (25.95 mmol) of (*S*)-**10** (prepared from (*S*)-**8** by catalytic hydrogenation over Pt/C and subsequent bromination) as described in *3.1.1* afforded 4.30 g of **11c** (79% based on (*R*)-**7**, 53% based on (*S*)-**10**) and, subsequently, 2.7 g (88%) of **12c** as colourless oil. GC: purity 98.4%. $[\alpha]_D^{20} = -4.2$ (*c* = 0.8, EtOH). IR, NMR, MS: identical with corresponding spectra of **12b**. In an analogous coupling experiment of (*R*)-**7** with (*S*)-**10** (prepared from (*S*)-**8** by catalytic hydrogenation over *Raney*-Ni and subsequent bromination), yields of 77% of **11c** and of 82% of **12c** were obtained. GC: purity 98.4%. $[\alpha]_D^{20} = -2.9$ (*c* = 1.0, $CHCl_3$), −4.9 (*c* = 1.0, EtOH), −3.9 (*c* = 0.85, octane); [12]: $[\alpha]_D = +3.7$ (*c* = 1.0, octane) for antipode **12a**.

Bromide **13c** was synthesized by NBS/PPh_3 treatment of the two batches of **12c** as described in *2.1*, yield 92 and 70%, resp. GC: purity 99%. $[\alpha]_D^{20} = +2.7$ ($c = 0.8$, EtOH), +4.3 ($c = 1.0$, $CHCl_3$), +3.9 ($c = 0.96$, octane; [12]: $[\alpha]_D = -3.6$ ($c = 1.0$, octane) for antipode **13a**). IR, ^{1}H-NMR, MS: identical with the corresponding spectra of **13b**.

3.3. *(3S,7R)-Series (= d-Series). Alcohol* **12d**. Coupling of 15.0 g (43.8 mmol) of (*R*)-**7** with the *Grignard* reagent derived from 14.35 g (64.9 mmol) of (*R*)-**10** as described in *3.1.1* afforded 11.9 g of **11d** (87% based on (*R*)-**7**, 59% based on (*R*)-**10**) and, subsequently, 7.9 g (91%) of **12d**. Colourless oil. GC: purity 99%. $[\alpha]_D^{20} = -4.1$ ($c = 0.8$, $CHCl_3$). ^{1}H-NMR: identical with spectrum of **12b**.

Bromide **13d** was synthesized by NBS/PPh_3 treatment of **12d** as described in *2.1*, yield 84%. GC: purity 98.5%. $[\alpha]_D^{20} = +2.2$ ($c = 1.0$, $CHCl_3$). ^{1}H-NMR: identical with spectrum of **13b**.

3.4. *Benzyl-Ether Derivatives* **14** *and GC Diastereoisomer Analysis. General Procedure.* A soln. of 20 mg (0.087 mmol) of **12** in 0.7 ml of DMSO was treated with 14 mg (0.26 mmol) of powdered KOH and 37 mg (34 ml, 0.30 mmol) of benzyl chloride and stirred at r.t. for 5 h. After addition of 1 ml of H_2O, the mixture was worked up as usual with hexane. The crude **14** (usually containing some dibenzyl ether as by-product) was analyzed by GC on a *Silar 10C* capillary column. The (*RS*/*SR*) pair of stereoisomers was eluted before the (*RR*/*SS*) pair of stereoisomers. The following ratios of diastereoisomers were observed: **14b**: 98.1:1.9 for the material *ex 3.1.1*, 98.7:1.3 for the material *ex 3.1.2*. **14c**: 4.7:95.3 and 3.1:96.9, resp., for the materials synthesized *via* hydrogenation of (*S*)-**8** over Pt/C or over *Raney*-Ni, resp. **14d**: 98.9:1.2 and 97.3:2.7 (double analysis).

4. Prenyl-naphthalenes 19–21. – *(E)-4-(1,4-Dimethoxy-3-methylnaphth-2-yl)-2-methylbut-2-en-1-ol* (**19**; *cf.* [16]) was prepared according to [14]: To a stirred suspension of 2.50 g (103 mol) of Mg turnings in 15 ml of THF was added a soln. of 20.0 g (71 mmol) of **17** [15] in 25 ml of THF at a rate which allowed the temp. to be kept < 30°. After the addition was complete, the mixture was stirred at r.t. for additional 45 min. The resulting *Grignard* soln. was added slowly, *via* cannula, to a cold (−78°), stirred soln. of 6.0 g (71 mmol) of isoprene epoxide (**18**) in 120 ml of THF and 10 ml of 0.1M Li_2CuCl_4 in THF. The cooling bath was removed and the mixture allowed to attain r.t. within 3 h. The mixture was hydrolyzed at 0° by addition of 100 ml of 2N H_2SO_4. Usual workup with Et_2O followed by chromatography on silica gel (hexane/AcOEt 10→25%) afforded 15.3 g of **19** as a 92:8 (*E*/*Z*)-mixture and 3.0 g of **19** as pure (*E*)-isomer (> 99.5% (*E*)). Crystallization of the (*E*/*Z*)-mixture from 500 ml of hexane afforded 12.3 g of **19** as a 99:1 (*E*/*Z*)-mixture. M.p. 75–76° ([16a]: 84°). Combined yield 15.3 g (75%).

(E)-4-(1,4-Dimethoxy-3-methylnaphth-2-yl)-2-methylbut-2-enyl Benzoate (**20**). To a soln. of 13.0 g (45.5 mmol) of **19** in 17 ml of pyridine was added at −10° a soln. of 6.4 g (45.5 mmol) of benzoyl chloride in 20 ml of $CHCl_2$. After the addition, the suspension was stirred at r.t. for 1 h, then quenched by addition of 100 ml of ice/H_2O and worked up as usual with Et_2O. The residue obtained was crystallized from hexane/AcOEt: 13.0 g (73%) of **20**, white powder, m.p. 101–103°. An anal. sample was obtained by recrystallization from AcOEt. GC: purity 100%. M.p. 104–105°. IR (KBr): 1713 (C=O); 1670 (C=C); 1270 (C–O). ^{1}H-NMR: 8.05 (*m*, 4 arom. H); 7.6–7.35 (*m*, 5 arom. H); 5.56 (*t*, $J = 6.5$, H–C(3′)); 4.72 (*s*, CH_2(1′)); 3.89, 3.86 (2*s*, 2 CH_3O); 3.66 (*d*, $J = 6.5$, CH_2(4′)); 2.39 (*s*, arom. CH_3); 1.97 (*s*, CH_3–C(2′)). MS: 390 (56, M^+), 268 (14, $[M - C_6H_5COOH]^+$), 253 (37), 237 (74), 105 (100, $C_6H_5CO^+$). Anal. calc. for $C_{25}H_{26}O_4$ (390.48): C 76.90, H 6.71; found: C 77.23, H 6.84.

(E)-4-(1,4-Dimethoxy-3-methylnaphth-2-yl)2-methylbut-2-enyl Acetate (**21**). To a soln. of 6.5 g (22.7 mmol) of **19** in 100 ml of CH_2Cl_2 and 20 ml of pyridine were added, at 5°, 10 ml of Ac_2O, and the mixture was stirred at r.t. for 24 h. The residue obtained after evaporation was poured onto ice/H_2O and the mixture extracted with Et_2O. The Et_2O extracts were washed 3 times with a 10% aq. $CuSO_4$ soln. and then further processed as usual. Chromatography (200 g of silica gel, hexane/AcOEt 1:1) afforded 5.34 g (72%) of **21**. White powder. GC: purity 99%. M.p. 46°. ^{1}H-NMR (60 MHz): 8.15–7.85 (*m*, 2 arom. H); 7.6–7.3 (*m*, 2 arom. H); 5.45 (*t*, $J = 6.5$, H–C(3′)); 4.45 (*s*, CH_2(1′)); 3.85 (*s*, 2 CH_3O); 3.6 (*d*, $J = 6.5$, CH_2(4′)); 2.3 (*s*, arom. CH_3); 2.0 (*s*, Ac); 1.85 (*s*, CH_3–C(2′)). Anal. calc. for $C_{20}H_{24}O_4$ (328.41): C 73.15, H 7.37; found: C 72.85, H 7.15.

5. (*E*)-Vitamin-K_1 Stereoisomers 1b–d. – 5.1. *(7′R,11′S)-Series (= b-Series). 1,4-Dimetoxy-2-methyl-3-[(2E,7R,11S)-3,7,11,15-tetramethylhexadec-2-enyl]naphthalene* (**22b**). To a soln. of 3.45 g (8.84 mmol) of **20** in 20 ml of THF was added, at −78°, *via* cannula, a soln. of the *Grignard* reagent derived from 3.8 g (13.0 mmol) of **13b** (*cf. 3.1.1* for the preparation of the *Grignard* reagent). After addition of 4 ml of 0.1M Li_2CuCl_4 in THF (0.4 mmol, 3 mol-% based on **13b**), the cooling bath was removed and the mixture allowed to warm to 0° and stirred at 0° for 12 h and at r.t. for 3 h. Usual workup with sat. NH_4Cl soln. and Et_2O followed by chromatography (250 g of silica gel, hexane/Et_2O 99:1) afforded **22b** in 3 fractions: 1.0 g (GC: 4.3% of **23b**, 95% of **22b**), 0.3 g (GC: 1.1% of **23b**, 98% of **22b**), and 1.8 g (GC: 0% **23b**, 96% **22b**). Combined yield, 3.1 g (73% based on **20**, 50% based on **13b**). ORD ($c = 8.2$, dioxane): +0.04 (700), +0.09 (650), +0.10 (600), +0.10 (589), +0.14 (550), +0.16 (540), +0.16 (530), +0.16 (520), +0.18 (510), +0.19 (500), +0.21 (490), +0.24 (475), +0.27 (460), +0.30 (445), +0.35 (430), +0.42 (415), +0.50 (400), +0.59 (385), +0.77 (370), +1.05 (335). IR: 3069 (arom. C–H); 1592, 1498 (Ar); 1065 (aryl ether); 770

(*o*-disubst. benzene). ^{1}H-NMR: 8.1–7.95 (*m* 2 arom. H); 7.5–7.4 (*m*, 2 arom. H); 7.5–7.4 (*m*, 2 arom. H); 5.1 (*t*, J = 6, H–C(2′)); 3.89, 3.87 (2*s*, 2 CH_3O); 3.55 (*d*, J = 6, CH_2(1′)); 2.38 (*s*, arom. CH_3); 1.95 (*t*, J = 7, CH_2(4′)); 1.81 (*s*, olef. CH_3); 1.65–0.9 (*m*, 19 H); 0.9–0.8 (*m*, 4 CH_3). MS: 480 (100, $M^{+\cdot}$), 465 (3), 215 (20). Anal. calc. for $C_{33}H_{52}O_2$ (480.77): C 82.44, H 10.90; found: C 82.18, H 10.99.

In a similar experiment, reaction of 1.56 (5.36 mmol) of **13b** (*ex (S)-***15**, *cf. 3.1.2*) and 2.11 g (6.43 mmol) of **21** in the presence of 51 mg (0.27 mmol, 5 mol-%) of CuI afforded 1.66 g (64.5%) of a colourless oil. GC: 12.4% of **23b**, 2.1% of (*Z*)-**22b**, 82.7% of (*E*)-**22b**. ^{1}H-NMR: in addition to signals of (*E*)-**22b**: 4.67, 4.57 (2*s*, with fine struct., C=CH_2 of **23b**); 2.40 (*s*, arom. CH_3 of **23b**); 1.74 (*s*, olef. CH_3 of **23b**); 1.70 (*s*, olef. CH_3 of (*Z*)-**22b**). Chromatography of 460 mg of this mixture on silica gel/10% $AgNO_3$ (hexane/Et_2O 0→1%) afforded 370 mg of **22b** ((*E*/*Z*) 99.7:0.3) and 20 mg of **22b** ((*E*/*Z*) 99:1). Yield of **22b**, 55% based on **13b**, 46% based on **21**.

*3-Methyl-2-[(2*E*,7*R*,11*S*)-3,7,11,15-tetramethylhexadec-2-enyl]naphthalene-1,4-dione* (**1b**). To a soln. of 1.80 g (3.7 mmol) of **22b** in 10 ml of benzene and 90 ml of MeCN was added, at 0°, a soln. of 4.10 g (7.22 mmol) of diammonium cerium(IV) hexanitrate in 25 ml of H_2O. The mixture was stirred at 0° for 30 min, then poured onto 500 ml of H_2O and worked up as usual with hexane. Chromatography (silica gel, hexane/Bu_2O 99:1) afforded 1.30 g (77%) of **1b** as light yellow oil in 3 fractions; HPLC contents 95.3–100.9% of (*E*)-vitamin K_1. On standing at −15°, the oils solidified. An analogous experiment afforded 81% of **1b**; HPLC: 0.1% of (*Z*)-**1b**, 99.6% of (*E*)-**1b**; HPLC content 96.9% of (*E*)-vitamin K_1. ORD (*c* = 19.2, dioxane): +0.31 (700), +0.35 (650), +0.40 (600), +0.425 (589), +0.45 (550), +0.46 (540), +0.46 (530), +0.45 (520), +0.41 (510), +0.33 (500), +0.22 (490). IR: 1661 (C=O); 1617 (C=C, conj.); 1597 (Ar); 1377 (CH_3); 714 (*o*-disubst. benzene). ^{1}H-NMR: 8.05 (*m*, 2 arom. H); 7.69 (*m*, 2 arom. H); 5.00 (*t*, J = 7, H–C(2′)); 3.37 (*d*, J = 7, CH_2(1′)); 2.19 (*s*, 1 arom. CH_3); 1.94 (*t*, J = 7, CH_2(4′)); 1.78 (*s*, CH_3–C(3′)); 1.6–0.9 (*m*, 19 H); 0.86 (*d*, J = 6.5, 2 CH_3); 0.82 (*d*, J = 6.5, 1 CH_3); 0.81 (*d*, J = 6.5, 1 CH_3). Anal. calc. for $C_{31}H_{46}O_2$ (450.71): C 82.61, H 10.29; found: C 82.00, H 10.22, H_2O 0.16.

5.2. *(7′S,11′S)-Series* (= **c**-*Series*). *Naphthalene* **22c**. Reaction of 3.0 g (10.3 mmol) of **13c** with 4.0 g (10.2 mmol) of **20** as described above afforded 2.70 g (55%) of **22c**. Colourless oil. GC: 2.6% of **23c**. HPLC: 2.1% of **23c**. An analogous coupling of 1.40 g (4.8 mmol) of **13c** and 2.25 g (5.76 mmol) of **20** afforded 1.17 g (51%) of **22c**. Colourless oil. GC: 7.5% of **23c**, 0.8% of (*Z*)-**22c**, 91.7% of (*E*)-**22c**. Chromatography of 0.95 g of this material on silica gel/10% $AgNO_3$ (hexane/Et_2O 1%) yielded 0.31 g of pure **22c** (GC 99.8%). ORD (*c* = 5.14, dioxane): +0.41 (700), +0.45 (650), +0.54 (600), +0.54 (589), +0.62 (550), +0.66 (540), +0.67 (530), +0.69 (520), +0.72 (510), +0.73 (500), +0.79 (490), +0.83 (475), +0.89 (460), +0.92 (445), +0.99 (430), +1.04 (415), +1.09 (400), +1.11 (385), +1.14 (370), +1.11 (355). IR, ^{1}H-NMR, MS: identical with corresponding spectra of **22c**. Anal. calc. for $C_{33}H_{52}O_2$ (480.77): C 82.44, H 10.90; found: C 82.73, H 11.14.

*3-Methyl-2-[(2*E*,7*S*,11*S*)-3,7,11,15-tetramethylhexadec-2-enyl]naphthalene-1,4-dione* (**1c**). Oxidation of 0.50 g (1.04 mmol) of **22c** as described above yielded 405 mg (86%) of **1c** as light yellow oil; HLPC purity 100%; HPLC content 99.4% of (*E*)-vitamin K_1. ORD (*c* = 13.7, dioxane): +0.18 (700), +0.20 (650), +0.25 (600), +0.35 (550), +0.36 (540), +0.41 (530), +0.47 (520), +0.54 (510), +0.65 (500), +0.81 (490). IR, ^{1}H-NMR, MS: identical with corresponding spectra of **1b**. Anal. calc. for $C_{31}H_{46}O_2$ (450.71): C 82.61, H 10.29; found: C 82.70, H 10.52.

5.3. *(7′S,11′R)-Series* (= **d**-*Series*). *Naphthalene* (**22d**). Reaction of 5.50 g (18.9 mmol) of **13d** and 5.0 g (12.8 mmol) of **20** as described above afforded, after chromatography, 1.30 g of **22d**. (GC: purity 98.6%; 0.5% of **23d**) and 3.57 g of **22d** (GC: purity 98%; no **23d**). Yield 79% based on **20**, 54% based on **13d**. ORD (*c* = 10.4, dioxane): −0.07 (700), −0.08 (650), −0.105 (600), −0.11 (589), −0.14 (550), −0.15 (540), −0.155 (530), −0.16 (520), −0.16 (510), −0.17 (500), −0.19 (490), −0.21 (475), −0.24 (460), −0.29 (445), −0.32 (430), −0.37 (415), −0.46 (400). IR, ^{1}H-NMR, MS: identical with corresponding spectra of **22b**. Anal. calc. for $C_{33}H_{52}O_2$ (480.77): C 82.44, H 10.90; found: C 82.70, H 11.08.

*3-Methyl-2-[(2*E*,7*S*,11*R*)-3,7,11,15-tetramethylhexadec-2-enyl]naphthalene-1,4-dione* (**1d**). Oxidation of 1.08 g (2.08 mmol) of **22d** as described above afforded, after chromatography, 780 mg (83%) of **1d** as light yellow oil in 3 fractions; HLPC purities 97–99%; HPLC contents 96–101%. On standing at −15°, the oils solidified. ORD (*c* = 16.6, dioxane): −0.28 (700), −0.34 (650), −0.38 (600), −0.38 (589), −0.43 (550), −0.42 (540), −0.43 (530), −0.39 (520), −0.38 (510), −0.30 (500), −0.17 (490). IR, ^{1}H-NMR, MS: identical with corresponding spectra of **1b**. Anal. calc. for $C_{31}H_{46}O_2$ (450.71): C 82.61, H 10.29; found: C 82.53, H 10.22.

6. Natural Stereoisomer 1a of (*E*)-Vitamin K_1. – 6.1. *O-Alkylation.* A mixture of 1.08 g (5.0 mmol) of *4-hydroxy-2-methylnaphth-1-yl acetate* (= menadiol monoacetate, **24**), 1.73 g (5.25 mmol) of phytyl chloride (**25**, prepared from natural phytol by treatment with PPh_3/CCl_4; GC: purity 95%, (*E*/*Z*) 99.7:0.3), 0.83 g (6.0 mmol) of K_2CO_3, and 83 mg (0.5 mmol) of KI in 15 ml of dry acetone was stirred at r.t. for 15 h. The mixture was treated with 200 ml of H_2O and 100 ml of hexane and the org. phase separated, washed with H_2O, dried (Na_2SO_4), filtered, and evaporated: 2.65 g of slightly yellow oil. Chromatography (silica gel, hexane/Et_2O 5→20%) afforded 0.30 g (7.5%)

of **28** and 1.95 g (79%) of **26** as colourless oils. In an analogous experiment, yields of 8.5 and 87% for **28** and **26**, resp., were obtained.

2-Methyl-4-{[(2E,7R,11R)-3,7,11,15-tetramethylhexadec-2-enyl]oxy}naphth-1-yl Acetate (**26**): $[\alpha]_D^{20} = -0.56$ ($c = 7.2$, $CHCl_3$). IR: 1760, 1200 (aryl ester), 1268, 1160, 1085 (aryl ether); 765 (*o*-disubst. benzene). ^{1}H-NMR: 8.24 (*d*, $J = 7.5$, 1 arom. H); 7.56 (*d*, $J = 7.5$, 1 arom. H); 7.5–7.4 (*m*, 2 arom. H); 6.65 (*s*, H–C(3)); 5.57 (*t*, $J = 6.5$, H–C(2′)); 4.69 (*d*, $J = 6.5$, CH_2(1′)); 2.46, 2.30 (2*s*, Ac, CH_3–C(2)); 2.07 (*t*, $J = 7$, CH_2(4′)); 1.76 (*s*, CH_3–C(3′)); 1.55–0.9 (*m*, 19 H); 0.87–0.83 (*m*, 4 CH_3). MS: 452 (1.5, $[M - COCH_2]^+$), 216 (19), 174 (100). Anal. calc. for $C_{33}H_{50}O_3$ (494.76): C 80.11, H 10.19; found: C 80.15, H 10.31.

2-Methyl-3-[(2E,7R,11R)-3,7,11,15-tetramethylhexadec-2-enyl]-4-{[(2E,7R,11R)-3,7,11,15-tetramethylhexadec-2-enyl]oxy}naphth-1-yl Acetate (**28**): $[\alpha]_D^{20} = -0.53$ ($c = 6.0$, $CHCl_3$). IR: 1768, 1205 (aryl ester); 1180, 1160 (aryl ether); 765 (*o*-disubst. benzene). ^{1}H-NMR: 8.05 (*m*, 1 arom. H); 7.7 (*m*, 1 arom. H); 7.44 (*m*, 2 arom. H); 5.7 (*t*, $J = 7$, H–C(2′) of *O*-phytyl); 5.6 (*t*, $J = 6.5$, H–C(2′) of *C*-phytyl); 4.48 (*d*, $J = 7$, CH_2O); 3.6 (*d*, $J = 6.5$, CH_2(1′) of *C*-phytyl); 2.48 (*s*, Ac); 2.23 (*s*, CH_3–C(2)); 2.07, 1.95 (2*t*, $J = 7$, CH_2(4′) of *O*- and *C*-phytyl); 1.79, 1.68 (2*s*, CH_3–C(3′) of *O*- and *C*-phytyl); 1.55–0.9 (*m*, 38 H); 0.9–0.8 (*m*, 8 CH_3). MS: 772 (0.5, $M^{+\cdot}$), 714 (15), 494 (17, $[M - C_{20}H_{38}]^+$), 452 (100), 186 (66). Anal. calc. for $C_{53}H_{88}O_3$ (773.28): C 82.32, H 11.47; found: C 82.37, H 11.54.

6.2 *Rearrangement.* To a soln. of 4.94 g (10.0 mmol) of **26** in 10 ml of dry toluene were added *via* syringe 12.5 µl (1 mol-%) of $BF_3 \cdot Et_2O$, and the soln. was stirred for 17 h. Then, an additional 12.5 µl (1 mol-%) of $BF_3 \cdot Et_2O$ were added, and the soln. was stirred for further 5 h. The mixture was treated with 10 ml of sat. $NaHCO_3$ soln., then poured onto H_2O, and extracted with hexane. The extracts were washed (H_2O, sat. NaCl soln.), dried (Na_2SO_4), filtered, and evaporated: 5.15 g of yellow oil. Chromatography (silica gel, hexane/Et_2O 3→30%) afforded, in the order of their elution, 410 mg (5.5% based on phytyl groups) of **30**, 3.79 g (77%) of **27**, and 205 mg (4%) of **29** as yellow oils. Yields in through reactions (without purification of crude **26**) amounted to 4–7% of **30**, 61–63% of **27**, and 3.5–4.5% of **29** based on **24**.

4-Hydroxy-2-methyl-3-[(2E,7R,11R)-3,7,11,15-tetramethylhexadec-2-enyl]naphth-1-yl Acetate (**27**): $[\alpha]_D^{20} = -0.54$ ($c = 6.8$, $CHCl_3$). IR: 1765, 1745, 1230 (aryl ester); 1662 (C=C); 1600, 1505 (Ar); 765 (*o*-disubst. benzene). ^{1}H-NMR: 8.1 (*m*, 1 arom. H); 7.6 (*m*, 1 arom. H); 7.45 (*m*, 2 arom. H); 5.75 (*s*, OH); 5.25 (*t*, $J = 7$, H–C(2′)); 3.51 (*d*, $J = 7$, CH_2(1′)); 2.48 (*s*, Ac); 2.26 (*s*, CH_3–C(2)); 2.02 (*t*, $J = 7$, CH_2(4′)); 1.86 (*s*, CH_3–C(3′)); 1.75 (*s*, CH_3–C(3′) of *ca.* 3% (*Z*)-isomer); 1.6–0.9 (*m*, 19 H); 0.88–0.81 (*m*, 4 CH_3). MS: 494 (9, $M^{+\cdot}$), 452 (100, $[M - C_2H_2O]^+$), 186 (85). Anal. calc. for $C_{33}H_{50}O_3$ (494.76): C 80.11, H 10.19; found: C 79.59, H 10.43.

1,4-Dihydro-2-methyl-4-oxo-1-[(2E,7R,11R)-3,7,11,15-tetramethylhexadec-2-enyl]naphth-1-yl Acetate (**29**): $[\alpha]_D^{20} = -0.05$ ($c = 6.0$, $CHCl_3$). IR: 1750, 1230 (ester); 1665 (C=O, conj.); 1635 (C=C); 765 (*o*-disubst. benzene). ^{1}H-NMR: 8.05 (*d*, $J = 7$, 1 arom. H); 7.55–7.3 (*m*, 3 arom. H); 6.31 (*m*, H–C(3)); 4.52 (*t*, $J = 7$, H–C(2′)); 2.65 (*m*, CH_2(1′)); 2.14 (*s*, Ac); 2.02 (br. *s*, CH_3–C(2)); 1.75 (*m*, 2 H); 1.6–0.9 (*m*, 22 H); 0.88–0.78 (*m*, 4 CH_3). MS: 436 (6, $[M - CO - CH_2O]^+$), 216 (31, $[M - C_{20}H_{38}]^+$), 174 (100). Anal. calc. for $C_{33}H_{50}O_3$ (494.76): C 80.11, H 10.19; found: C 79.86, H 10.43.

3,4-Dihydro-2-methyl-4-oxo-3,3-bis[(2E,7R,11R)-3,7,11,15-tetramethylhexadec-2-enyl]naphth-1-yl Acetate (**30**): $[\alpha]_D^{20} = +1.08$ ($c = 5.0$, $CHCl_3$). IR: 1768, 1205 (ester); 1680 (C=O, conj.); 1660 (C=C); 765 (*o*-disubst. benzene). ^{1}H-NMR: 7.95 (*d*, $J = 7$, 1 arom. H); 7.50 (*m*, 1 arom. H); 7.28 (*m*, 1 arom. H); 7.18 (*d*, $J = 7$, 1 arom. H); 4.85 (br. *m*, H–C(2′), H–C(2″)); 2.85, 2.30 (2*m*, CH_2(1′), CH_2(1″)); 2.38 (*s*, Ac); 1.81 (*s*, CH_3–C(2)); 1.70 (*m*, 4 H); 1.6–0.75 (*m*, totally 62 H, with 1.52 (*s*, CH_3–C(3′), CH_3–C(3″)) and 0.88–0.82 (*m*, 6 CH_3)); 0.69 (*d*, $J = 6.5$, 2 CH_3). MS: 772 (0.5, $M^{+\cdot}$), 730 (1, $[M - C_2H_2O]^+$), 714 (5, $[M - CO - CH_2O]^+$), 496 (28, $[M - C_{20}H_{38}]^+$), 452 (100), 186 (41). Anal. calc. for $C_{53}H_{88}O_3$ (773.28): C 82.32, H 11.47; found: C 82.55, H 11.87.

6.3. *3-Methyl-2-[(2E,7R,11R)-3,7,11,15-tetramethylhexadec-2-enyl]naphthalene-1,4-dione* (**1a**). Acetate **27**, obtained from 12.29 g (56.8 mmol) of **24** and 19.68 g of **25** (GC: purity 94%; 59.0 mmol) as described above, was saponified with NaOH/MeOH and oxidized with air as reported in [1b] [18d] to afford 16.9 g of **1a** as yellow oil; 96.5% pure by HPLC, (*E*/*Z*) 97:3 by HPLC; overall yield 63.5% based on **24**, 61.5% based on **25**. The anal. sample was obtained by chromatography (silica gel, hexane/Bu_2O 95:5): 99.2% pure by HPLC, (*E*/*Z*) 99.2:0.8 by HPLC. ORD ($c = 10.1$, dioxane): −0.41 (546), −0.48 (530), −0.55 (520), −0.64 (510), −0.78 (500), −1.01 (490), −1.52 (480), −1.76 (470); [1a]: −0.39 (540), −0.43 (530), −0.51 (520), −0.63 (510), −0.79 (500), −1.10 (490), −1.55 (480).

6.4. *1,4-Dimethoxy-2-methyl-3-[(2E,7R,11R)-3,7,11,15-tetramethylhexadec-2-enyl]naphthalene* (**22a**). The reductive methylation of **1a** ((*E*/*Z*) 99.2:0.8 by HPLC) was carried out as described in [3a]. Yield, 20% of **22a** (*cf.* [3a] [34]). Pale yellow oil. GC: purity 98%, (*E*/*Z*) 99.4:0.6. ORD ($c = 7.86$, dioxane): −0.40 (700), −0.46 (650), −0.51 (600), −0.53 (589), −0.61 (550), −0.64 (540), −0.67 (530), −0.68 (520), −0.71 (510), −0.74 (500), −0.79 (490), −0.82 (480), −0.85 (470), −0.89 (460), −0.93 (450), −0.97 (440), −1.15 (430), −1.22 (420), −1.20 (410), −1.33 (400), −1.22 (390).

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