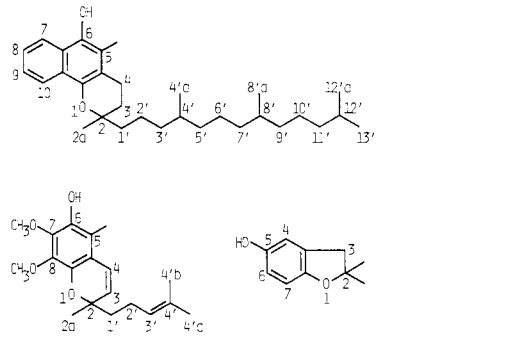
^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.30 (s, 9 H, 7-t-Bu), 1.44 (s, 6 H, 2-CH_3), 2.07 (s, 3 H, 4-CH_3), 2.85 (s, 2 H, 3-CH_2), 4.13 (s, 1 H, 5-OH), 6.46 (s, 1 H, 6-H); UV spectrum λ_{max} = 299 nm (log ε = 3.66 in ethanol). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.95; H, 9.63.

2,3-Dihydro-5-hydroxy-2,2-dimethyl-4,6-diisopropylbenzofuran (Tocopherol 6). Tocopherol 6 was prepared by the reaction of 2,6-diisopropylhydroquinone with 2-methyl-2-propen-1-ol in anhydrous formic acid in the presence of H_2SO_4, according to the method of Nilsson et al.:[18] mp 96.5–97.0 °C; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.20 (d, 6 H, J = 6.5 Hz, 4- or 6-CH-(CH_3)$_2$), 1.25 (d, 6 H, J = 6.5 Hz, 4- or 6-CH(CH_3)$_2$), 1.43 (s, 6 H, 2-CH_3), 2.98 (s, 2 H, 3-CH_2), 3.05 (sep, 2 H, J = 6.5 Hz, 4- and 6-CH(CH_3)$_2$), 4.17 (s, 1 H, 5-OH), 6.34 (s, 1 H, 7-H); UV spectrum λ_{max} = 298 nm (log ε = 3.69 in ethanol). Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.49; H, 9.73.

Acknowledgment. We wish to express our gratitude to Dr. Shinji Terao of Takeda Chemical Industries Ltd. for the generous gift of Coenzyme Q_1 and Q_2. We are grateful to Professor Kashiro Kuroda and Professor Yoichi Kitamura for the use of the stopped-flow spectrophotometer and to Professor Kazuhiko Ishizu for his helpful discussions. We are also very grateful to Kazuyuki Fukuda for his kind help in the preparation of tocopherol compounds.



Registry No. 1, 4208-84-8; 2, 19274-66-9; 3, 3626-85-5; 4, 3625-63-6; 5, 118111-99-2; 6, 118112-00-8; 7, 118112-01-9; 8, 6956-76-9; 9, 84574-05-0; PhO•, 6257-34-7; α-tocopherol, 59-02-9; vitamin K_1, 84-80-0; coenzyme Q_2, 606-06-4; 2-*tert*-butyl-5-methylhydroquinone, 2349-76-0; 2-methyl-2-propen-2-ol, 513-42-8; 2,6-diisopropylhydroquinone, 1988-10-9.

Chiral Effects on the ^{13}C Resonances of α-Tocopherol and Related Compounds. A Novel Illustration of Newman's "Rule of Six"[1]

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The 100-MHz ^{13}C NMR spectrum of (2*R*,4′*R*,8′*R*)-α-tocopherol (natural vitamin E) has been completely assigned with the aid of a number of selectively deuteriated (2*R*,4′*R*,8′*R*)-α-tocopherols. The ^{13}C NMR spectrum of (2*RS*,4′*RS*,8′*RS*)-α-tocopherol (all-racemic, synthetic vitamin E) has also been measured. Many of the individual carbons in this all-racemic mixture of eight α-tocopherol stereoisomers give more than one resonance with eight of the carbons (2-CH_3, 2′, 3′, 4′, 4′-CH_3, 5′, 8′, and 9′) giving the maximum number of four resonances from each of the four enantiomeric pairs; these resonances have also been assigned. The structurally related 5′-hydroxy-2-(4′,8′,12′-trimethyltridecyl)-2,4,6,7-tetramethyl-2,3-dihydrobenzofuran (HTDBF) has been synthesized for the first time in the 2*R*,4′*R*,8′*R* and 2*S*,4′*R*,8′*R* configurations and their ^{13}C resonances have been assigned. In its all-racemic form this compound also shows up to four resonances from a single carbon. Related observations have been made with phytol and isophytol. A careful examination of these chirally induced chemical shift differences for the individual carbon atoms, Δ, reveals a bond-alternation effect with maxima at a separation of one, three, and five bonds from the closest chiral center and with the maximum at a five-bond separation being greater than that at a three-bond separation. For example, the total Δ, $\sum\Delta$, averaged over the number of carbon aroms, n, which are separated from the nearest chiral center by the same number of bonds has been conservatively calculated for α-tocopherol to be 54, 106, 43, 66, 40, and 75 ppb at separations from the closest chiral center of zero, one, two, three, four, and five bonds, respectively. For HTDBF the corresponding $\sum\Delta/n$ values are 45, 67, 12, 0, 0, and 20 ppb. We attribute these remarkable long-range (five-bond) effects to differences in 1,6 nonbonded repulsions for different enantiomeric pairs and consider that it provides direct evidence for the operation of Newman's classic "rule of six".

Nuclear magnetic resonance spectrscopy provides a unique and sensitive tool for studying the propagation down a hydrocarbon chain of the effect of a change in the chirality of an asymmetric center. This is a subject of considerable scientific interest and of practical utility. Thus, we required a simple and unequivocal method for identifying the chirality of α-tocopherol (vitamin E) for our in vivo studies on the uptake, transport, and elimination of the various stereoisomers of (specifically deuteriated) α-tocopherol in animals[2,3] and in man.[4,5] Principally, we needed a means to distinguish between the natural, 2*R*,4′*R*,8′*R* (*RRR*) stereoisomer and the synthetic, all-racemic compound (see Scheme I). We also needed to be able to distinguish between natural, *trans*-(7*R*,11*R*)-phytol and synthetic, *all-rac*-phytol (see Scheme I) since this compound is frequently employed in the synthesis of α-tocopherol. Literature data suggested that ^{13}C NMR would prove suitable for both tasks. Thus, Bremser and

(1) Issued as NRCC No. 29823.
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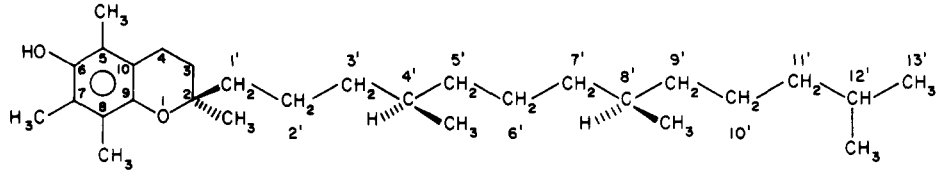
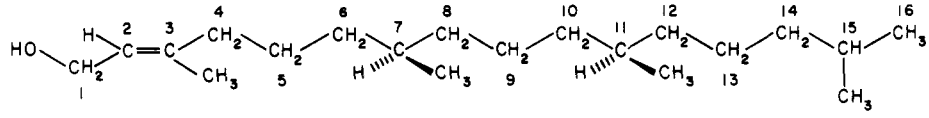
Scheme I

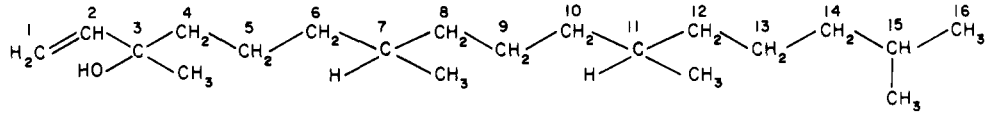
Natural,2R,4'R,8'R-α-Tocopherol (RRR-α-Tocopherol)



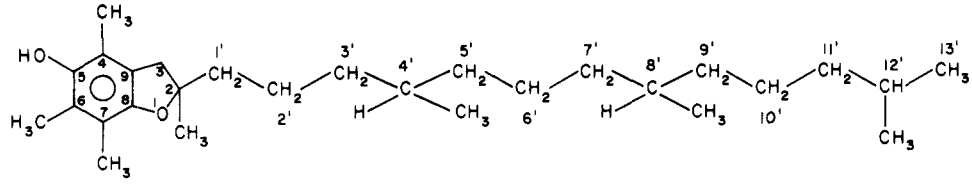
Natural,7R,11R-Phytol (Trans-RR-Phytol)



Isophytol



HTDBF



Vogel,[6] building on earlier work,[7-9] reported that the carbon atoms at position 2', 3', 5', 6', 7', and 8' in the trimethyltridecyl hydrocarbon "tail" of *all-rac*-α-tocopherol each gave four separate lines at 100 MHz, one line arising from each of the four possible enantiomeric pairs. Some of these lines were even assigned to particular enantiomeric pairs.[6] A similar phenomenon has not been reported for *all-rac*-phytol. However, most of the ^{13}C resonance signals in natural phytol have been assigned.[10]

Since differences in chemical shift between enantiomeric pairs are often very small they may be obscured by effects due to minor changes in temperature or concentration. For this reason, the present study was conducted upon carefully chosen mixtures of pure stereoisomers as well as upon some of the individual stereoisomers.

In the case of α-tocopherol, selective deuteriation was utilized to aid in the assignment of chemical shifts with the following compounds being employed: (2*R*,4'*R*,8'*R*)-α-(5-C^2H_3)tocopherol, (2*R*,4'*R*,8'*R*)-α-(5,7-$(C^2H_3)_2$)tocopherol, (2*R*,4'*R*,8'*R*)-α-(1',1'-$^2H_2$)tocopherol, (2*R*,4'*R*,8'*R*)-α-(2-C^2H_3;3,3,1',1'-$^2H_4$)tocopherol, (2*R*,4'*R*,8'*R*)-α-(2',2'-$^2H_2$)tocopherol, (2*RS*,4'*RS*,8'*RS*)-α-(2',2',3'-$^2H_{3;4}$)tocopherol, (2*R*,4'*R*,8'*R*)-α-(5',5'-$^2H_2$)tocopherol, (2*R*,4'*R*,8'*R*)-α-(9',9'-$^2H_2$)tocopherol. All but one of these compounds had been synthesized earlier[11] for other purposes.[12]

In addition to the ^{13}C NMR measurements on α-tocopherol and phytol, we have also carried out similar, but less detailed, measurements on two other compounds. One is an α-tocopherol analogue, 5-hydroxy-2-(4',8',12'-trimethyltridecyl)-2,4,6,7-tetramethyl-2,3-dihydrobenzofuran (HTDBF, see Scheme I), which differs from α-tocopherol in having a fused five-membered, rather than a fused six-membered, heterocyclic ring. This reduction in ring size produces a better overlap between the p-type lone pair on the 1-oxygen and the π orbital containing the unpaired electron in the corresponding aryloxyl radical derived from HTDBF than in that derived from α-tocopherol.[13] For this stereoelectronic reason, HTDBF is a better peroxyl radical trapping antioxidant than α-tocopherol by ca. 47%.[14] We have also shown that *all-rac*-HTDBF has ca. 76% more vitamin E activity in vivo than *all-rac*-α-tocopherol.[14] The other compound examined was isophytol (see Scheme I), an all-racemic synthetic material which is currently employed in the commercial synthesis of *all-rac*-α-tocopherol.

An almost unequivocal assignment of all the ^{13}C resonances could be made for *all-rac*-α-tocopherol and we discovered that the averaged chemical shift differences between enantiomeric pairs exhibited an alternating effect with maxima at a distance of one, three, and five bonds from the nearest asymmetric center, with the maximum at five bonds being greater than that at three bonds! We attribute this totally unexpected, long-range effect to 1,6-steric interactions of the type documented by Newman and described by his classic "rule of six".[15] The operation of this rule is also apparent in HTDBF, which has a sig-

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Table I. Stereochemical Assignments of All ^{13}C Resonances of α-Tocopherol[a]

	enantiomeric pairs			
postn	*RRR/SSS*	*SRR/RSS*	*RSR/SRS*	*RRS/SSR*
C10	146.295	146.196	146.196	146.295
C9	145.949	145.975	145.975	145.949
C7	122.930	122.854	122.854	122.930
C8	122.421	122.421	122.421	122.421
C6	120.503	120.412	120.412	120.503
C5	117.764	117.764	117.764	117.764
C2	74.857	74.846	74.846	74.857
C1′	40.336[b]	40.421	40.421	40.336
C11′	40.089	40.089	40.089	40.089
C3′	38.230[b]	38.276[b]	38.358[b]	38.316[b]
C9′	38.126[b]	38.145	38.077	38.087
C5′	38.011[b]	38.052	38.069	38.077
C7′	37.984	37.990	37.951	37.990
C8′	33.486	33.494	33.463	33.456
C4′	33.383	33.426	33.355	33.391
C3	32.501[b]	32.440	32.440	32.501
C12′	28.656	28.656	28.656	28.656
C10′	25.484	25.484	25.494	25.500
C6′	25.086	25.086	25.075	25.058
C2-CH_3	24.173[b]	24.168	24.155	24.162
C12′-CH_3	22.981	22.981	22.981	22.981
C13′	22.896	22.896	22.896	22.896
C2′	21.651[b]	21.676[b]	21.722[b]	21.703[b]
C4	21.363	21.363	21.363	21.363
C8′-CH_3	20.095	20.103	20.038	20.038
C4′-CH_3	20.052	20.095	19.995	20.038
C7-CH_3	12.723[b]	12.711	12.711	12.723
C8-CH_3	12.022	12.018	12.018	12.022
C5-CH_3	11.772[b]	11.762	11.762	11.772

[a] Data obtained with *all-rac*-α-tocopherol in deuterioacetone at room temperature. Chemical shifts are given in ppm relative to TMS. The resonances for the *RRR/SSS* and *SRR/RSS* enantiomeric pairs were identified by studying the pure *RRR* and *SRR* stereoisomers, respectively, by "spiking" *ambo*-α-tocopherol with the pure *RRR* and *SRR* stereoisomers, and by studying selectively deuteriated *RRR*-α-tocopherol (see text). [b] This assignment was confirmed by selective deuterium substitution at this carbon. Resonances due to adjacent carbons were also generally broadened.

nificant chirally induced chemical shift difference between enantiomeric pairs at a distance of five bonds from the closest asymmetric center but has no chemical shift differences at distances of three and four bonds. All compounds studied showed maxima in their averaged chemical shift differences between enantiomeric pairs at a distance of one bond from the nearest asymmetric carbon atom. Phytol and isophytol, however, showed no differences at distances of three bonds or more.

Results

α-Tocopherol. The ^{13}C resonances of interest in α-tocopherol have been listed and assigned in Table I. Some of these resonances have not previously been assigned to a specific carbon while others appear to have been misassigned on certain occasions. For example, for the signals in the 38.0–38.15 ppm range the group with the larger chemical shift (38.145–38.077 ppm, Table I) were previously assigned[6] to C5′ and the group (or rather some members of the group) with the smaller chemical shift (38.077–38.010 ppm, Table I) were assigned to C9′. A study of (2*R*,4′*R*,8′*R*)-α-(5′,5′-$^2H_2$)tocopherol revealed that these two assignments must be reversed. That is, it is well-known that the effect of the replacement of hydrogen by deuterium on the proton noise-decoupled ^{13}C NMR spectrum is to reduce the intensity of the signal due to the carbon bearing the deuterium by removal of the nuclear Overhauser effect and division of the remaining intensity among several lines arising from ^{13}C–^2H spin-coupling. For dilute solutions, the net result is the disappearance of the ^{13}C signal from those carbon atoms directly bonded to deuterium and the broadening of signals from carbon atoms with long-range spin-coupling to the deuterium. The ^{13}C spectrum of (*RRR*)-α-(5′,5′-$^2H_2$)tocopherol showed no resonance at 38.01 ppm (C5′), but the resonance at 38.12 ppm (C9′) was unchanged, proving that the earlier assignment[6] of these two resonances must be reversed. The lines due to C5′ for the *RRR/SSS* and *SRR/RSS* enantiomeric pairs were also misassigned to C7′.[6]

Another misassignment involves the signals at ca. 33.4 ppm, which were initially[7,8] assigned to C4′ and C8′ but were subsequently[6] reassigned to C6′ and C8′. We concur with the earlier assignment since appropriately gated proton decoupling showed that the signals with the smaller chemical shift (33.35–33.43 ppm in Table I) arose from a carbon atom that is directly bonded to only one hydrogen, which rules out C6′ but is consistent with C4′. Furthermore, the ^{13}C resonance spectrum of 2′,3′-dideuterio-*all-rac*-α-tocopherol does not show signals at ca. 21.7 ppm (C2′) nor at ca. 38.3 ppm (C3′) and has signals at ca. 33.4 ppm that are substantially broadened (C4′).

Additional confirmation of the ^{13}C resonance assignments was obtained by two-dimensional carbon–proton correlation spectroscopy.[16] Long-range connectivity patterns, together with the definitive assignments of the ^{13}C resonances for each of the aromatic methyl groups (via (*RRR*)-α-(5-C^2H_3)tocopherol and (*RRR*)-α-(5,7-$(C^2H_3)_2$)-tocopherol, allowed the aromatic ring carbons to be unequivocally assigned.

All the appropriate resonances listed in Table I for the *RRR/SSS* enantiomeric pair were shown by gated proton decoupling and relayed coherence transfer (using (*RRR*)-α-tocopherol) to belong to carbon atoms directly bonded to the appropriate number (1, 2, or 3) of hydrogen atoms. There are only two resonances in the trimethyltridecyl "tail" of α-tocopherol for which the assignments are not absolutely unequivocal as a result of our own deuterium labeling. These are for C7′ and C11′, but there can be little doubt that these have also been correctly assigned.[6-8,17]

For those carbon atoms for which changes in the configuration at one of the asymmetric centres (C2, C4′, and C8′) produces observable changes in chemical shift, it should be possible to correlate these changes with the distance of these carbons from the asymmetric center. Since some of these small changes would be of similar magnitude to changes induced by minor variations in sample concentration or temperature, it seemed desirable to attempt spectral assignments using samples with carefully chosen compositions. Figure 1 shows portions of the spectrum of α-tocopherol in those regions where the chemical shift is affected by stereoisomerism. This figure shows spectra obtained for the 2*R*,4′*R*,8′*R* stereoisomer (natural α-tocopherol), an equimolar mixture of the 2*R*,4′*R*,8′*R*, and 2*S*,4′*R*,8′*R* stereoisomers (*ambo*-α-tocopherol), and the four enantiomeric pairs (2*RS*,4′*RS*,8′*RS*) that are present in roughly equal amounts in *all-rac*-α-tocopherol.

Comparison of the spectrum obtained from natural (*RRR*)-α-tocopherol with the spectrum obtained from *ambo*-α-tocopherol (*RRR* + *SRR*) allows a unique assignment to be made for the lines from the *SRR/RSS* enantiomeric pair. Unfortunately, a similar procedure cannot be applied to identify lines from the *RSR/SRS* and *RRS/SSR* enantiomeric pairs. However, by making the reasonable assumption that changes in chemical shift will

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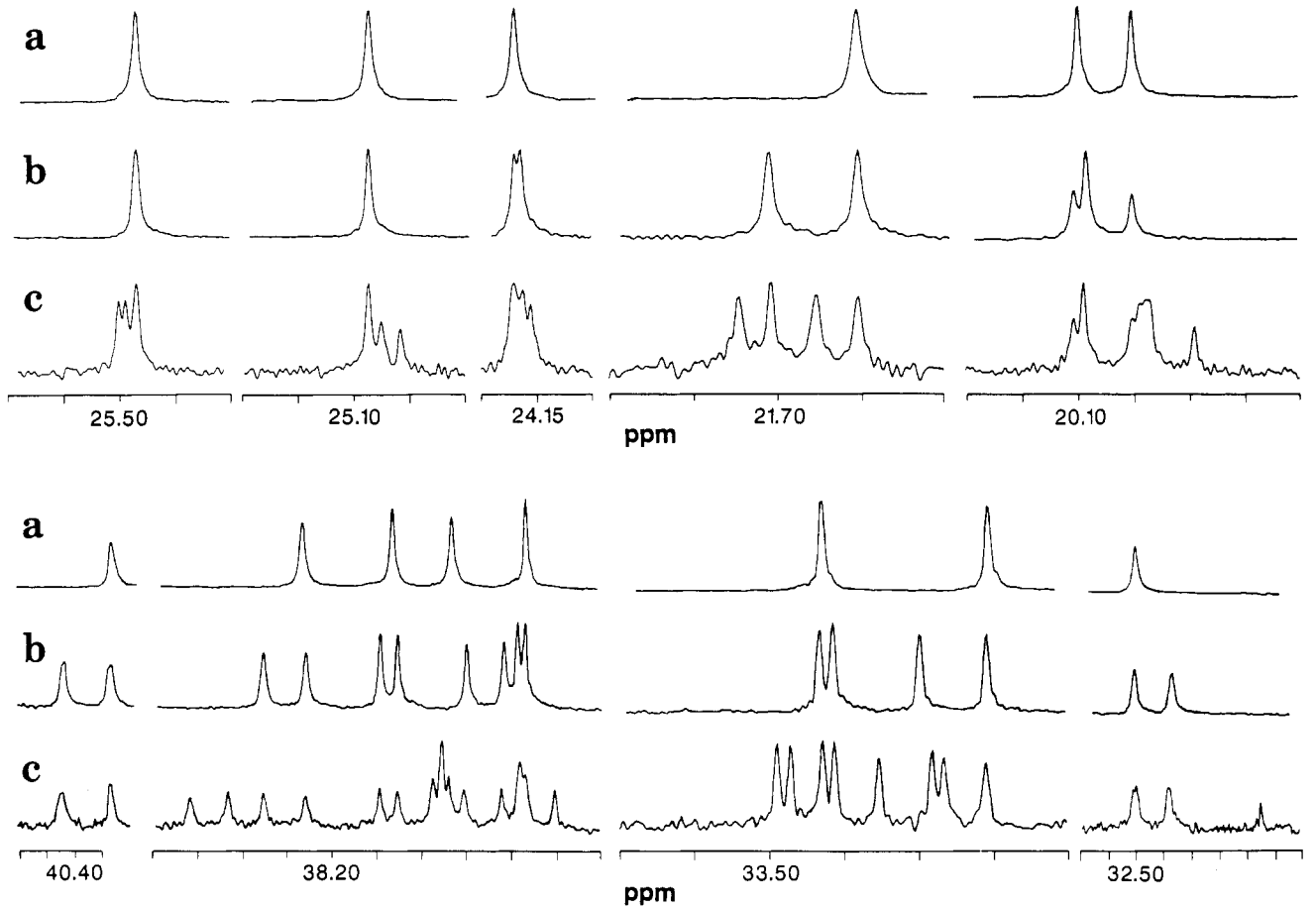

Figure 1. Portions of the 100-MHz ^{13}C NMR spectrum of α-tocopherol measured in deuterioacetone at ambient temperature. All scale markers have been placed at intervals of 0.05 ppm, the various spectral regions being defined at one scale marker only: (a) (2*R*,4′*R*,8′*R*)-α-tocopherol (natural); (b) (2*RS*,4′*R*,8′*R*)-α-tocopherol (*ambo*); (c) (2*RS*,4′*RS*,8′*RS*)-α-tocopherol (*all-rac*). Some of the (a) and (b) segments have been shifted very slightly relative to the corresponding (c) segment to align the appropriate resonances.

be attenuated with distance from an asymmetric center we obtain the stereochemical assignments of the ^{13}C signals from α-tocopherol that are given in Table I. The chemical shifts given in this table were actually those observed for a sample of *all-rac*-α-tocopherol in order to avoid any minor differences in temperature or in α-tocopherol concentration that could have produced small differences in chemical shifts between different samples.

Phytol. Natural phytol has the 7*R*,11*R* configuration and a trans arrangement of the hydrogen atom and methyl group about the 2,3 double bond (see Scheme I).[18] When isophytol is isomerized to phytol, it yields both the trans and cis isomers (81.5% and 18.5%, respectively, see Experimental Section), each as a racemic mixture containing two enantiomeric pairs (i.e., *RR*/*SS* and *RS*/*SR*).[18] Many of the carbon atoms of phytol show ^{13}C chemical shift differences between enantiomeric pairs (see Figure 2). The various ^{13}C signals were assigned in the same general manner as for α-tocopherol and are given in Table II. However, for this compound we had no selectively deuteriated materials and were therefore forced to rely heavily on our assignments for (*RRR*)-α-tocopherol (which were obtained in the same solvent and at the same temperature). Gated proton decoupling was employed to show that the number of hydrogen atoms (odd or even) directly attached to the carbon were appropriate for the assignment. Confirmatory evidence for these assignments was also obtained by relayed coherence transfer to get long-range carbon–carbon connectivities by proton–proton spin-coupling.[19] We are less confident of these assignments than of those given in Table I for α-tocopherol.

Our assignments of ^{13}C phytol resonances differ somewhat from the earlier assignment of Goodman et al.,[10] which were based on measurements in chloroform at 48 °C. These workers relied on Grant and Paul's[17] chemical shift parameters, comparison with pristane and with a phytol–pristane mixture, and on ^{13}C spin–lattice relaxation times. We see no reason to doubt any of their assignments but believe the following changes are warranted under our conditions so that the chemical shifts of the carbons more remote from the double bond of phytol will fall into the same order as "equivalent" carbons in α-tocopherol. The relevant group of carbons in α-tocopherol are, in order of decreasing chemical shift, those at positions 3′, 9′, 5′, and 7′, which correspond, respectively, to positions 6, 12, 8, and 10 in phytol. In order to fit the same pattern of chemical shifts to phytol we have therefore interchanged in Table II the earlier assignments[10] of C6 and C10 and of C8 and C12.

A comparison of phytol and α-tocopherol reveals a peculiar phenomenon: the carbons directly bonded to the functional group, viz., C4 and C1′, respectively, have chemical shifts that are virtually identical, viz., 40.54 ppm and 40.33 ppm, respectively, whereas the next carbons have distinctly different chemical shifts, viz., C5 at 26.0 ppm in phytol and C2′ at 21.65 ppm in α-tocopherol. Even if carbons 5, 13, and 9 in phytol have been incorrectly as-

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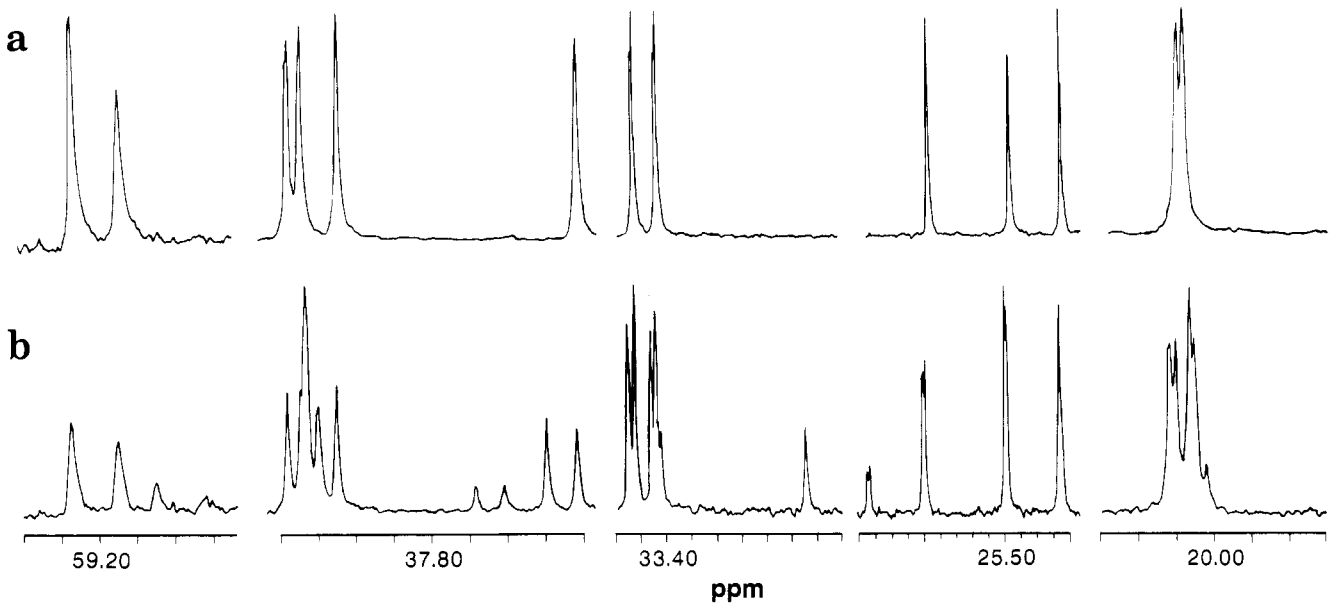


Figure 2. Portions of the 100-MHz ^{13}C NMR spectrum of phytol measured in deuterioacetone at ambient temperature. All scale markers have been placed at intervals of 0.10 ppm, the various spectral regions being defined at one scale marker only: (a) (7*R*,11*R*)-*trans*-phytol (natural); (b) 81.5% (7*RS*,11*RS*)-*trans*-phytol plus 18.5% (7*RS*,11*RS*)-*cis*-phytol.

Table II. Stereochemical Assignments of Certain ^{13}C Resonances of Phytol and Isophytol[a]

	phytol				isophytol[b]	
postn	trans-*RR*/*SS*	trans-*RS*/*SR*	cis-*RR*/*SS*	cis-*RS*/*SR*		
C3	137.216	137.216	137.777	137.777	72.708 (1)	72.825 (3)
C2	125.864	125.864	126.763	126.763	147.018 (1)	147.037 (2)
					147.051 (1)	
C1	59.148	59.148	58.919	58.919	111.040 (4)	
C4	40.534	40.534	40.534	40.534	43.759 (2)	43.797 (2)
C14	40.149	40.149	40.149	40.149	40.142 (4)	
C6	38.180	38.132			38.413 (2)	38.489 (2)
C12	38.145	38.128		38.089[c]	38.186 (3)	38.208 (1)
C8	38.047	38.098			38.140 (3)	38.159 (1)
C10	37.415	37.493	37.608	37.683	38.043 (2)	38.126 (2)
C11	33.545	33.517	33.517	33.517	33.536 (2)	33.545 (2)
C7	33.452	33.432	33.432	33.413	33.514 (2)	33.521 (2)
C15	28.673	28.673	28.673	28.673	28.662 (4)	
C5	25.987	26.005	26.327	26.342	28.237 (1)	28.253 (1)
					28.286 (1)	28.304 (1)
C13	25.476	25.488	25.476	25.488	25.467 (2)	25.480 (2)
C9	25.159	25.152	25.142	25.132	25.142 (2)	25.154 (2)
C15-CH_3	22.959	22.959	22.959	22.959	22.958 (4)	
C16	22.882	22.882	22.882	22.882	22.881 (4)	
C11-CH_3	20.144	20.059	20.066	20.059	20.097 (1)	20.110 (3)
C7-CH_3	20.097	20.046	20.046	19.939	20.044 (1)	20.054 (3)
C3-CH_3	16.164	16.164	16.164	16.164	22.087 (1)	22.099 (2)
					22.109 (1)	

[a] Data for phytol obtained with the all-racemic, trans, and cis mixture formed by isomerization of isophytol (see text) in deuterioacetone at room temperature. The resonances of the trans-*RR*/trans-*SS* enantiomeric were identified by studying pure, natural *trans*-*RR*-phytol and the *all-rac*-, *trans*-, and *cis*-phytol mixture "spiked" with natural phytol. It was not possible to assign all the *cis*-phytol resonances because of accidental overlap by peaks from the higher concentration of *trans*-phytol. [b] Numbers in parentheses refer to the relative intensities of the resonances, e.g., for C3 the signal at 72.825 has three times the intensity of that at 72.708 ppm and for C2 the signal at 147.037 ppm is twice as intense as the other two signals. [c] Only signal assignable to *cis*-phytol observable in this region of the spectrum.

signed and C5 actually has the smallest chemical shift, it will still differ in chemical shift from the corresponding carbon in α-tocopherol by 3.5 ppm.

Isophytol. The ^{13}C resonance assignments for isophytol have been included in Table II for comparative purposes. The line positions and differences in chemical shifts between enantiomeric pairs are similar to those found for α-tocopherol and phytol. In view of the absence of a stereochemically pure reference compound, we have made no attempt to assign isophytol's resonances to specific pairs of enantiomers. However, it is interesting to note that for both phytol and isophytol only the carbon atoms at positions 14, 15, 15-CH_3, and 16 show no stereochemically induced splittings (see Table II) and that these carbon atoms correspond to the 11′, 12′, 12′-CH_3, and 13′ carbons, respectively, of α-tocopherol which are also the only carbons in this molecule (and in HTDBF, vide infra) that show no stereochemically induced splittings (see Table I).

HTDBF. In addition to the *all-rac*-HTDBF we have now synthesized the pure *RRR* and *SRR* stereoisomers of this compound (see Experimental Section). The driving force for carrying out the syntheses of these two stereoisomers was both the possibility that they would exhibit different vitamin E activity in vivo and the need to check for the long-range transmission of chiral effects (as measured by ^{13}C NMR) on a molecule other than α-tocopherol.

The assignments of many of the ^{13}C resonances for the four enantiomeric pairs that make up *all-rac*-HTDBF (see

Table III. Stereochemical Assignments of Certain ^{13}C Resonances of HTDBF[a]

	enantiomeric pairs			
postn	*RRR/SSS*	*SRR/RSS*	*RSR/SRS*	*RRS/SSR*
C2	87.600	87.600	87.600	87.600
C3′	42.421	42.421	42.421	42.421
C1′	42.022	42.022	42.022	42.022
C11′	40.157	40.157	40.157	40.157
C3	38.247	38.247	38.328	38.320
C9′	38.187	38.187	38.137	38.154
C5′	38.137	38.137	38.128	38.128
C7′	38.054	38.054	38.072	38.091
C8′	33.545	33.545	33.517	33.517
C4′	33.417	33.417	33.375	33.380
C12′	28.690	28.690	28.690	28.690
C10′	26.876	26.876	26.876	26.876
C6′	25.495	25.495	25.504	25.504
C2-CH_3	25.162	25.100	25.104	25.133
C12′-CH_3 / C13′	22.969 / 22.892	22.969 / 22.892	22.969 / 22.892	22.969 / 22.892
C2′	22.342	22.357	22.379	22.366
C8′-CH_3	20.115	20.115	20.074	20.061
C4′-CH_3	20.086	20.061	20.027	20.016
C6-CH_3	13.236	13.226	13.226	13.236
C7-CH_3	12.419	12.419	12.419	12.419
C4-CH_3	12.255	12.255	12.255	12.255

[a] Data obtained with *all-rac*-HTDBF in deuterioacetone at room temperature. Chemical shifts are given in ppm relative to TMS. The resonances for the *RRR/SSS* and *SRR/RSS* enantiomeric pairs were identified by studying the pure *RRR* and *SRR* stereoisomers, respectively, and by "spiking" *all-rac*-HTDBF with the pure *RRR* and *SRR* stereoisomers. The aromatic ring's carbon atoms were not influenced by chirality. These atoms and their chemical shifts were C9, 151.729; C8, 146.991; C6, 123.458; C7, 123.165; C5, 119.274; C4, 115.447. Note that the foregoing assignments are based on a comparison with the ^{13}C resonance of "comparable" carbon atoms in α-tocopherol and cannot, therefore, be considered to be unambiguous.

Table III) have been made on a similar basis to that used for the α-tocopherol assignments, although with more limitations since specifically deuteriated forms of HTDBF were not available. From carbon–proton correlation spectroscopy, it was possible to show that the orderings of the carbon and proton chemical shifts for the HTDBF aromatic ring methyl groups differ from the ordering found in α-tocopherol which (in ppm) are for ^{13}C: C7-CH_3 (12.723–12.711) > C8-CH_3 (12.022–12.018) > C5-CH_3 (11.772–11.762, see Table I), and for ^1H: C7-CH_3 (2.13) > C5-CH_3 (2.09) > C8-CH_3 (2.04). In order to identify "comparable" carbon atooms in HTDBF with those in α-tocopherol, we have assumed that the ordering of the ^{13}C chemical shifts for the aromatic methyl carbons and aromatic ring carbons will provide a better guide than the ordering of the aromatic methyl group ^1H chemical shifts. This assumption yields the ^{13}C resonance assignments listed in Table III and in the footnote to this table. For the aromatic methyl groups of HTDBF, the ordering of the carbon and proton chemical shifts (in ppm) are, therefore, for ^{13}C: C6-CH_3 (13.236–13.226) > C7-CH_3 (12.419) > C4-CH_3 (12.255, see Table III), and for ^1H: C7-CH_3 (2.09) > C6-CH_3 (2.07) > C4-CH_3 (2.02).

Discussion

Calculation of Averaged Chemical Shift Differences ($\sum\Delta/n$). Since we have observed and assigned to specific enantiomeric pairs of α-tocopherol a complete set of ^{13}C resonances, we have attempted to correlate chemical shift differences with distance from the asymmetric carbon atoms. There are various ways in which the stereochemically induced chemical shift differences might be computed or assigned. We have taken a very conservative approach that minimizes rather than enhances long-range effects. Specifically, we have assumed that chemical shift differences induced by changes in chirality will be attenuated with distance and must therefore be assigned to the closest chiral center. This means that when a chiral effect is transmitted from two chiral centers toward one another, it is assumed not to proceed beyond the central carbon atom, i.e., for α-tocopherol the chiral transmission from C2 "down" the hydrocarbon "tail" goes only as far as C2′ at which atom it meets the chiral transmission from C4′ traveling "up" the "tail"; similarly, the chiral effects due to C4′ and C8′ meet and do not transmit beyond C6′. For the chroman ring, we again count only the shortest through-bond pathway to a particular carbon atom. The total of these restrictions ensures that the chemical shift differences (if any) found for each carbon atom in α-tocopherol are counted no more than once. Rather than attempting to assign chemical shift differences to a specific $R \rightarrow S$ configurational change (e.g., *RRR/SSS* → *SRR/RSS*), *although this can indeed be done*, we have further simplified the procedure by summing the total effect of changes in chirality on the chemical shift differences for the carbon atom in question. That is, if the ^{13}C resonances for the four enantiomeric pairs have chemical shifts in the order $a > b > c > d$, we have calculated a total difference in chemical shift $\Delta = (a - d) + (b - c)$. The results of this procedure are summarized in Table IV. Unfortunately, one ambiguity remains. This concerns the C12′-CH_3 and C13′ carbon atoms that are separated by five bonds from the C8′ asymmetric center and show separate resonances at 22.981 and 22.896 ppm for each enantiomeric pair. A change in chirality (e.g., *RRR/SSS* → *RRS/SSR*) might produce a "switch" in the chemical shifts of the two individual carbon atoms, i.e., 22.981 → 22.896 and 22.896 → 22.981 ppm, but in order not to be accused of overemphasizing five-bond long-range effects, we have eliminated these two carbons from consideration in Table IV.

The total chemical shift differences, $\sum\Delta$, averaged over the number of carbon atoms, n, which are separated from the nearest chiral center by the same number of bonds are given as $\sum\Delta/n$ for α-tocopherol in Table IV. There is clearly a bond-alternation effect with maxima in average chemical shift differences at a separation of one, three, and five bonds and minima at a separation of zero, two, and four (and six) bonds from the chiral center. The maximum at the five-bond separation (which may even have been underestimated, vide supra) is greater than the maximum at the three-bond separation.

The chemical shift differences for the HTDBF enantiomeric pairs (Table III) turned out to be a little disappointing since they were less striking than for α-tocopherol, particularly with regard to C2 chirality. Thus, there are no chirally induced chemical shift differences for any of the aromatic carbons nor for two of the aromatic methyl groups. However, the aromatic methyl at a five-bond separation from C2, i.e., C6-CH_3, does have a significant chirally induced chemical shift difference. We attribute the less pronounced effect of chirality on chemical shift differences in HTDBF to the more planar geometry of the five-membered heterocyclic ring present in this compound compared with the six-membered heterocyclic ring present in α-tocopherol. Treatment of the data in Table III in the same conservative fashion as for α-tocopherol leads to $\sum\Delta/n$ values of 45, 67, 12, 0, 0, and 20 ppb at separations from the nearest chiral center of zero, one, two, three, four, and five bonds, respectively.

Like α-tocopherol and HTDBF, isophytol has three chiral centers and hence each carbon atom can, in principle, have as many as four distinct ^{13}C resonances.

Table IV. Stereochemically Induced Differences in ^{13}C Chemical Shifts as a Function of Bond Separation in α-Tocopherol As Calculated from the Data Given in Table I[a]

	asymmetric carbon[c,d]								
connectivity no.[b]	C2(Δ)		C4′(Δ)		C8′(Δ)		$\sum\Delta^d$	$n^{d,e}$	$\sum\Delta/n^d$
0	C2	(22)	C4′	(80)	C8′	(60)	162	3	54
1	C2-CH_3	(24)	C4′-CH_3	(113)	C8′-CH_3	(121)	956	9	106
	C1′	(171)	C5′	(83)	C9′	(108)			
	C3	(122)	C3′	(169)	C7′	(45)			
2		C2′ (98)		C6′ (39)			215	5	43
	C4	(0)			C10′	(26)			
	C9	(52)							
3	C8	(0)			C11′	(0)	197	3	66
	C10	(197)							
4	C8-CH_3	(10)			C12′	(0)	161	4	40
	C5	(0)							
	C7	(151)							
5	C5-CH_3	(20)					226	3	75
	C7-CH_3	(24)			*f*				
	C6	(182)							

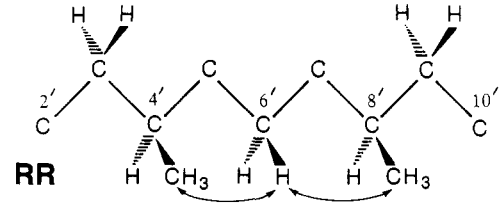
[a] No stereochemically induced difference in chemical shift is counted twice and each difference is assumed to be due to the closest chiral center. [b] Number of bonds between the asymmetric center and the carbon indicated. [c] For each carbon Δ represents the sum of the largest and smallest differences in chemical shifts for that carbon, i.e., if the chemical shifts decrease in the order $a > b > c > d$, then $\Delta = (a - d) + (b - c)$. [d] Values of Δ, $\sum\Delta$, and $\sum\Delta/n$ are in ppb. [e] Numbers of carbons with the specified connectivity. [f] Data for the C12′-CH_3 and C13′ carbon atoms have not been included.

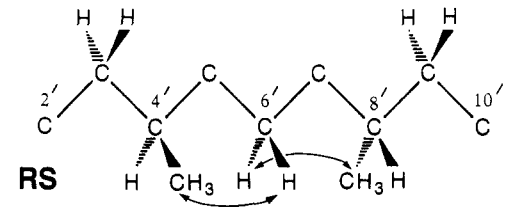
However, only C5, which is midway between the C3 and C7 asymmetric centers, is this "rich" in resonances. Three of the four possible lines are shown by C2 and C3-CH_3 with one line having twice the intensity of the other two lines for each of these carbon atoms. The carbon atoms at positions 14, 15, and 16 show a single line while those at all other positions show two resonances with relative intensities of 2:2 or 1:3 (see Table II). Treatment of the isophytol data in the same (conservative) fashion as for α-tocopherol and HTDBF gives $\sum\Delta/n$ = 50, 57, 37, 0, 0, and 0 ppb at distances from the closest chiral carbon atom of zero, one, two, three, four, and five bonds, respectively.

Phytol, in contrast to the other compounds examined, has only two asymmetric centers and therefore both *trans*- and *cis*-phytol can give no more than two ^{13}C resonances for any particular carbon atom. The usual treatment of the data for *trans*-phytol (and of the more limited data for *cis*-phytol) yields $\sum\Delta/n$ values of 25 (9), 55 (63), 13 (12), 0 (0), 0 (0), and 0 (0) ppb at separations of zero, one, two, three, four, and five bonds, respectively.

Our results with isophytol and with *trans*-(and *cis*-)phytol are disappointing from the viewpoint of potential long-range chirally induced chemical shift differences since such differences are not detectable at distances of three bonds or more from the nearest chiral center. Nevertheless, these compounds do serve to confirm that averaged chemical shift differences are greater at a distance of one bond than at a distance of zero or two bonds.

Variation in Averaged Chemical Shift Differences with Bond Separation. Differences in ^{13}C chemical shifts at or near an asymmetric carbon atom can be produced only if the molecule contains at least one other asymmetric center. For all the molecules studied in this work, the asymmetric centers are separated by four bonds and rotation about each of these bonds must be relatively unrestricted. The distribution of conformer populations that will most strongly influence a carbon atom's chemical shift will depend primarily on the chirality of the two nearest asymmetric centers since these will interact with one another more strongly than would a more remote asymmetric center. In some of the higher energy, "curled-up" conformers the two chiral centers may interact more or less directly with each other. However, in the statistically more important, lower energy, chain-extended conformers the interaction between the two nearest asymmetric carbon atoms is likely to occur by a "relay" type of mechanism. For example, for α-tocopherol in its fully extended conformation the interaction between the 4′ and 8′ carbon atoms in the 4′*R*,8′*R* configuration, *RR*, and in the 4′*R*,8′*S* configuration, *RS*, is likely to involve primarily the methyl groups attached to the 4′ and 8′ carbon atoms in a process which is "relayed" by way of the hydrogen atoms on the 6′ carbon atoms.





The interaction between two asymmetric carbon atoms separated by four bonds will therefore involve a pair of nonbonded repulsions (arrows) between hydrogen atoms in a 1,6 arrangement, i.e., between hydrogen atoms separated by five bonds. Steric effects arising from 1,6 interactions are well-documented in the literature and have been formalized by Newman in his classic "rule of six".[15] This rule states that "the greater the number of atoms in the six position the greater will be the steric effect", i.e., the importance of 1,6 steric interactions increases as the number of atoms connected by five bonds (the "six number") increases. The "six number" of the 6′ hydrogen atoms is 12 (10 hydrogen: 4′C-CH_3, 8′C-CH_3, 3′CH_2, and 9′CH_2; plus two carbons: C2′ and C10′) which is relatively high. Conformations of somewhat higher energy will involve other 1,6 repulsive interactions, e.g., between the 6′ hydrogens and the 3′ and 9′ hydrogens. It is therefore easy to rationalize our observation that the averaged, chirally induced ^{13}C chemical shift differences are greatest at a

distance of one bond from the asymmetric center for all of the compounds examined in this work.

Except for α-tocopherol and HTDBF, the chirally induced ^{13}C chemical shift differences "die away" at distances of three bonds or more from the nearest asymmetric center. This is easy to understand for a flexible hydrocarbon chain and, indeed, α-tocopherol and HTDBF show longer range effects only in their more-or-less rigid[20] phenolic head groups not in their flexible tails (see Table IV). These long-range effects are again most readily explained in terms of differences in 1,6 nonbonded repulsions for different enantiomeric pairs. For example, in α-tocopherol at a three-bond separation from C2 the large chirally induced (C2, C4′) ^{13}C chemical shift difference at C10 might be attributed to relatively strong 1,6 interactions with C10 of the hydrogen atoms on the C2 methyl group relayed from C4′ via the hydrogen atoms on C2′. The observation of very significant chemical shift differences even at distance of five bonds from C2 both in α-tocopherol (see Table IV) and in HTDBF (viz. 20 ppb for C6-CH_3) provides the most direct evidence for the operation of Newman's "rule of six" in ^{13}C NMR spectroscopy.

Experimental Section

NMR Spectroscopy. ^{13}C resonance spectra were obtained on a Bruker AM400 spectrometer at 100.6 MHz using power gated decoupling to minimize radio frequency heating of the sample.[21] A spectral width of only 8 kHz was employed in order to maximize the digital resolution and the transmitter frequency was adjusted to observe the high-field 80-ppm region in such a way that lower field signals folded back only into empty regions of the spectrum. Free induction decays of 32 K were collected and subsequently expanded to 128 K by zero-filling. This gave a final digitization of 0.123 Hz/data point. Discrimination between carbon atoms directly bonded to even or odd numbers of hydrogen atoms was achieved by an appropriately gated proton decoupling sequence.[22] Samples contained ca. 20 mg of the material under study in approximately 0.5 mL of deuterioacetone with 1% tetramethylsilane (TMS). Chemical shifts are referred to TMS as zero. There was no apodization of the free induction decay.

Materials and Synthetic Methods. Isophytol; synthetic, *all-rac*-(2*RS*,4′*RS*,8′*RS*)-α-tocopherol; and (2*R*,6*R*)-1-bromo-2,6,10-trimethyldodecane (derived from natural phytol)[18,23] were generously supplied by Hoffmann-La Roche, Nutley, NJ. Natural (2*R*,4′*R*,8′*R*)-α-tocopherol was purchased from Eastman Kodak Chemicals, Rochester, NY. Natural phytol was generously supplied by Tama Biochemicals, Tokyo, Japan. *all-rac*-2,6,10-Trimethylundecan-1-ol was purchased from Givaudan Research, Clifton, NJ. *all-rac*-3,7,11-Trimethyldodecan-1-al was obtained from Wiley Organics, Columbus, OH. Quinine was purchased from Aldrich Chemicals, Milwaukee, WI. Dimethoxyethane was fractionally distilled under nitrogen from calcium hydride. Methylene chloride was similarly distilled from anhydrous calcium sulfate.

The α-tocopherol and HTDBF were analyzed to identify the enantiomeric pairs present in the various samples using GC according to a published procedure.[24] The enantiomeric purities of (*R*)-(+)- and (*S*)-(−)-2,4,6,7-tetramethyl-5-hydroxy-2,3-dihydrobenzofuran-2-carboxylic acid (3 in Scheme II) were verified as their methyl esters on a Bakerbond chiral phase HPLC column (RP-7103-0, (*R*)-(3,5-dinitrobenzoyl)phenylglycine stationary phase, 25 cm × 4.6 mm i.d., eluted with 5% 2-propanol in *n*-hexane). The configurations of (*R*)-(+)-3 and (*S*)-(−)-3 at carbon 2 were assigned on the basis of the sign of their optical rotations relative to (*R*)-(+)- and (*S*)-(−)-2,5,7,8-tetramethyl-6-hydroxychroman-2-carboxylic acid[25] and by comparison of the relative retention times of their methyl esters on the chiral HPLC column. (The *S*-(−) methyl ester of the chroman-2-carboxylic acid eluted before the *R*-(+) ester.)

Column chromatographic purification followed the "flash" method[27] using Merck grade 60 silica gel (230–400 mesh, 60 Å) from Aldrich. Unless otherwise noted, reactions were carried out under a nitrogen atmosphere. The "usual" workup involved three extractions into the solvent specified. The organic extracts were combined, washed with water, $NaHCO_3$ or dilute HCl as required, and saturated brine, dried over Na_2SO_4, filtered, and concentrated at 30 °C on a rotary evaporator. The residue was further dried to constant weight at high vacuum. All yields given refer to isolated yields obtained after a final purification by column chromatography using ethyl acetate in hexane as eluent.

Mass spectra were measured on a Hewlett-Packard 5970A mass selective detector using an HP-Ultra I fused silica capillary gas chromatographic column (10 m × 0.2 mm i.d., OV-101 type, cross-linked bonded phase). ^1H NMR spectra that were needed in connection with the syntheses were recorded on a 500-MHz Bruker instrument unless otherwise noted. Thin layer chromatography was performed on silica gel (60F-254) BDH plates and developed with ethyl acetate/hexane (usually 12% ethyl acetate in hexane). Spots were visualized by using phosphomolybdic acid spray (3.5% in ethanol) followed by heating at 80 °C. All compounds were homogeneous on TLC after final chromatographic purification.

Synthesis of α-Tocopherol Stereoisomers and a Deuteriated α-Tocopherol. (2*RS*,4′*R*,8′*R*)-α-Tocopherol (*ambo*-α-Tocopherol). Trimethylhydroquinone (3.0 g, 19.7 mmol) in *n*-heptane (12 mL) was reacted with $BF_3{\cdot}OEt_2$ (0.4 mL, 2.8 mmol) at 90 °C for 5 min. Natural phytol (6.0 g, 20.2 mmol) was subsequently added, dropwise, over 1 h. The mixture was refluxed 18 h, cooled, filtered, and evaporated in vacuo. Column chromatography (12% ethyl acetate/hexane) gave pure *ambo*-α-tocopherol as a yellow oil. GC analysis[24] confirmed an *RS*,*R*,*R*, mixture of stereoisomers.

(2*S*,4′*R*,8′*R*)-α-Tocopherol. This compound was obtained via Wittig coupling of (*R*)-(−)-2,5,7,8-tetramethyl-6-(benzyloxy)-3,4-dihydro-2*H*-1-benzopyran-2-carboxaldehyde[28] (starting from (*R*)-(+)-2,5,7,8-tetramethyl-6-hydroxychroman-2-carboxylic acid[26] and (2*R*,6*R*)-1-bromo-2,6,10-trimethyldodecane phosphonium salt[23]). Subsequent hydrogenation and purification by column chromatography gave (2*S*,4′*R*,8′*R*)-α-tocopherol (GC analysis[24] indicated an enantiomeric purity of 83.6%).

(2*RS*,4′*RS*,8′*RS*)-α-(2′,2′,3′-$^2H_{3,4}$)Tocopherol. This compound was prepared by Fouquet–Schlosser[29] coupling of the tosylate of *all-rac*-2,5,7,8-tetramethyl-6-(benzyloxy)chroman-(2′,2′-$^2H_2$)ethanol (which was prepared by $LiAlD_4$ reduction of *all-rac*-methyl [2,5,7,8-tetramethyl-6-(benzyloxy)chroman-2-yl]-acetate)[30] and *all-rac*-2,6,10-trimethyl(1-$^2H_{1,2}$)undecyl bromide. The bromide was synthesized from *all-rac*-2,6,10-trimethyl(1-$^2H_{1,2}$)undecanol, which was itself obtained by hydrogenation and $LiAlD_4$ reduction of *all-rac*-2,6,10-trimethyl-9-undecanal. GC analysis[24] indicated an all-racemic mixture of the four possible pairs of diastereomers.

***all-rac*-Phytol (Cis and Trans).** Isophytol was isomerized with acetic anhydride according to the method of Burrell et al.[18] to give *cis*- and *trans*-phytyl acetates. Subsequent reduction with

(20) Note, however, that the heterocyclic ring in α-tocopherol undergoes half-chair to half-chair interconversion at a rate which is rapid on the NMR time scale.[12]

(21) Levy, G. C.; Peat, I. R.; Rosanske, R.; Parks, S. *J. Magn. Reson.* **1975**, *18*, 205–208.

(22) LeCocq, E.; Lallemand, J. Y. *J. Chem. Soc., Chem. Commun.* **1981**, 150–152.

(23) Mayer, H.; Schudel, P.; Rüegg, R.; Isler, O. *Helv. Chim. Acta* **1963**, *46*, 650–671.

(24) Cohen, N.; Scott, C. G.; Neukom, C.; Lopresti, R. J.; Weber, G.; Saucy, G. *Helv. Chim. Acta* **1981**, *64*, 1158–1173.

(25) The (*S*)-(−)-hydroxychroman-2-carboxylic acid has been used as a precursor in the synthesis of (2*R*,4′*R*,8′*R*)-α-tocopherol, see ref 24. The synthesis and resolution of the hydroxychroman-2-carboxylic acid have been described.[26]

(26) Scott, J. W.; Cort, W. M.; Harley, H.; Parrish, D. R.; Saucy, G. *J. Am. Oil Chem. Soc.* **1974**, *51*, 200–203.

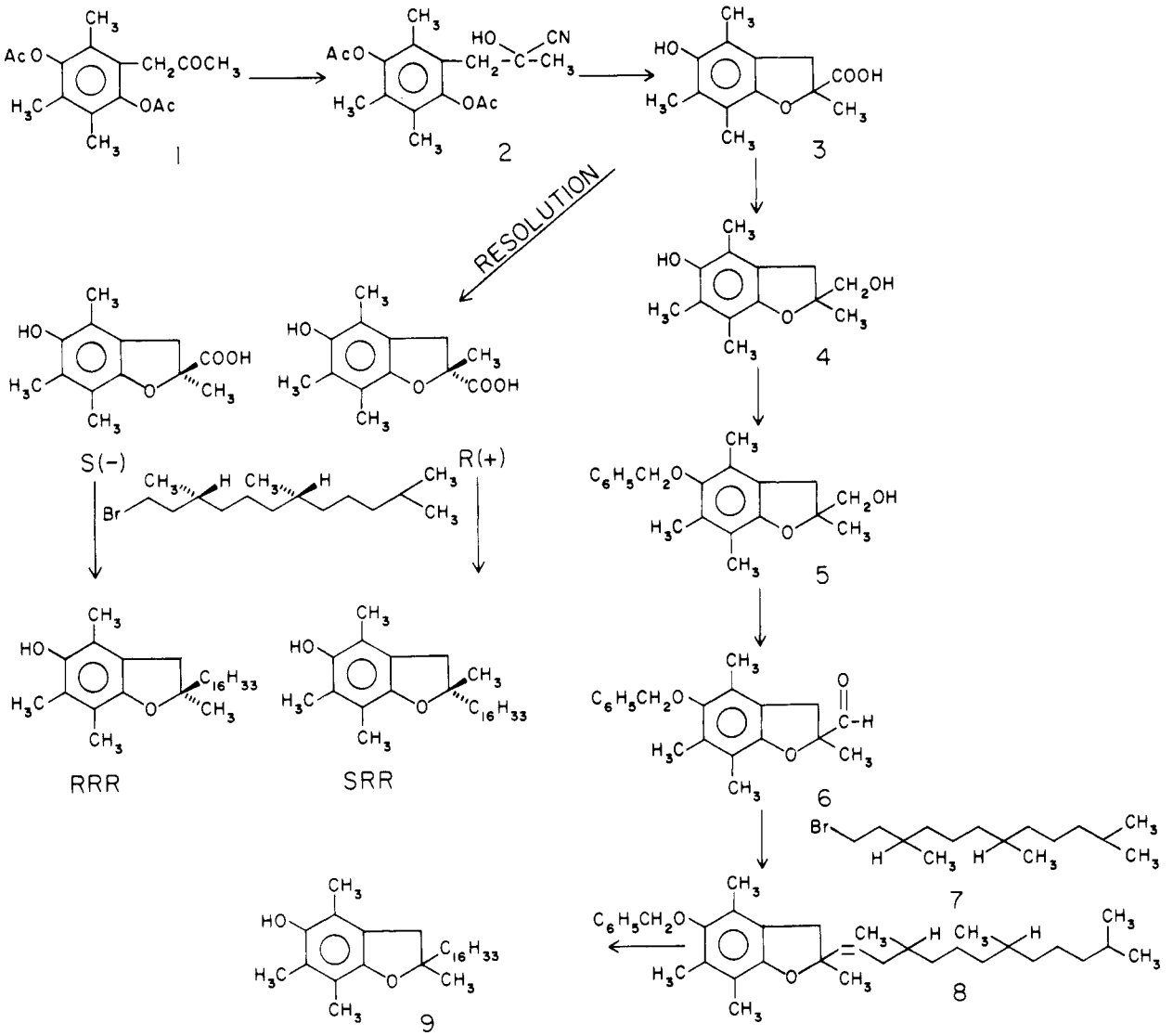
(27) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

(28) Cohen, N.; Lopresti, R. J.; Saucy, G. *J. Am. Chem. Soc.* **1979**, *101*, 6710–6716.

(29) Fouquet, G.; Schlosser, M. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 82–83.

(30) Scott, J. W.; Bizarro, F. T.; Parrish, D. R.; Saucy, G. *Helv. Chim. Acta* **1976**, *59*, 290–306.

Scheme II



$LiAlH_4$ and column chromatography gave pure *all-rac*-phytol. GC analysis indicated 18.5% *cis*- and 81.5% *trans*-phytol.

Synthesis of HTDBF. *all-rac*-5-Hydroxy-2,4,6,7-tetramethyl-2,3-dihydrobenzofuran-2-carboxylic Acid (3). (3,6-Diacetoxy-2,4,5-trimethylphenyl)acetone[31] (1) (30 g (102 mmol)) was dissolved in 264 mL of DMSO, cooled to 4 °C, and 7.5 g (115 mmol) of KCN dissolved in 23 mL of water was added dropwise. This was followed by the addition during a period of 1 h of 17.4 mL of 6 N H_2SO_4 diluted with 50 mL of water. The internal temperature of the reaction was carefully maintained between 3 and 5 °C. The resultant yellow, gummy mixture was stirred at this temperature for 1 h after the addition of acid was completed. After this time 400 mL of water was added and the intermediate cyanohydrin, **2**, was taken up into CH_2Cl_2 (3 × 300 mL). The usual workup gave the crude cyanohydrin as a brown oil. Hydrolysis to product **3** was effected by heating crude **2** at 70 °C in 200 mL of concentrated HCl for 18 h. The mixture was then cooled, poured onto 1 L of ice, stirred 30 min, and washed with ether (3 × 200 mL). The combined ether extracts were washed with saturated $NaHCO_3$ and the aqueous layer was also treated with saturated $NaHCO_3$ (400 mL). The $NaHCO_3$ aqueous extracts were combined, cooled to 0 °C, stirred, treated dropwise with 320 mL of 3 N HCl, stirred at 0 °C for 30 min, filtered, and dried under high vacuum to give 5.2 g (21.4%) of the acid, **3**, as white crystals: mp 161.3–162.8 °C. Anal. Calcd: C, 66.08; H, 6.82. Found: C, 66.05; H, 6.91. ^1H NMR δ ($CDCl_3$, $(CD_3)_2SO$, TMS_{int}): 1.65 (s, 3 H, 2-CH_3), 2.09 (s, 3 H, Ar-CH_3), 2.12 (s, 3 H, Ar-CH_3), 2.16 (s, 3 H, Ar-CH_3), 3.05 (d, 1 H, J = 15 Hz, CH), 3.52 (d, 1 H, J = 15 Hz, CH).

Resolution of 3. *all-rac*-**3** (22.9 g, 97 mmol) was suspended in 458 mL of ethyl acetate, heated to reflux, cooled slightly, and treated with a warm (~50 °C) solution of 36.6 g (112 mmol) of quinine in 917 mL of ethyl acetate. The solution was allowed to cool to 25 °C and was then further cooled to 2 °C for 40 h. After this time, the *R*-(+) quinine salt of **3** (28.0 g, 96.9%) was obtained by filtration, washing with cold ethyl acetate, and drying under high vacuum. The (*S*)-(−) quinine salt of **3** was obtained from the mother liquors following evaporation of the ethyl acetate. Recrystallization of the latter from methanol/water gave, after filtration and drying at high vacuum, 28.0 g (98.6%) of *S*-(−) salt as a white powder.

Liberation of (*R*)-(+)-3 and (*S*)-(−)-3. A total of 28.0 g (50 mmol) of the *R*-(+) quinine salt of **3** was treated with 2 L of ethyl acetate and, to the resultant suspension, 200 mL of 1 N HCl was added. Stirring for 10 min gave a heterogeneous solution. The aqueous phase was separated and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated to give 10.13 g (88.5%) of (*R*)-(+)-**3**: $[\alpha]^{25}_D$ = +9.60° (c = 1.6 in ethanol). (*S*)-(−)-**3** was obtained in the same manner, $[\alpha]^{25}_D$ = −9.09° (c = 1.6 in ethanol). HPLC analyses (chiral column) indicated that (*R*)-(+)-**3** and (*S*)-(−)-**3** had enantiomeric purities of 92.0% and 89.9%, respectively.

Further Use of 3. *all-rac*-**3**, (*S*)-(−)-**3**, and (*R*)-(+)-**3** were converted to *all-rac*-HTDBF, (2*R*,4′*R*′,8′*R*)-HTDBF, and (2*S*,4′*R*,8′*R*)-HTDBF, respectively, according to Scheme II. We

(31) Smith, L. I.; Kaiser, E. W. *J. Am. Chem. Soc.* **1940**, *62*, 133–138.

describe below the conversion of the all-racemic acid, **3**, to *all-rac*-HTDBF as a representative example.

***all-rac*-5-Hydroxy-2,4,6,7-tetramethyl-2,3-dihydrobenzofuran-2-methanol (4).** *all-rac*-**3** (4.9 g, 20.7 mmol) was dissolved in 450 mL of ether and added dropwise to a suspension of 2.7 g (67.5 mmol) of $LiAlH_4$ in 100 mL of ether so as to maintain a gentle reflux. The suspension was subsequently stirred at 25 °C for 1 h, poured onto 300 mL of ice (containing 5–6 mL of concentrated H_2SO_4), and extracted into ether. Usual workup gave 3.5 g (70%) of **4** as beige crystals: mp 133.9–136.6 °C. ^1H NMR (60 MHz) δ ($CDCl_3$, $(CD_3)_2SO$, TMS_{int}): 1.4 (s, 1 H, 2-CH_3), 2.1 (s, 9 H, 3(Ar-CH_3)), 2.8–3.1 (m, 2 H, CH_2), 3.6 (s, 2 H, CH_2OH).

***all-rac*-5-(Benzyloxy)-2,4,6,7-tetramethyl-2,3-dihydrobenzofuran-2-methanol (5).** To a stirred solution of 3.5 g (14.8 mmol) of **4** in 30 mL of DMF were added 5.4 g (39.1 mmol) of anhydrous K_2CO_3 and 4.7 mL (41.0 mmol) of distilled benzyl chloride. The reaction mixture was stirred at 25 °C for 24 h, poured onto ice, and extracted into ether. Usual workup and drying under high vacuum at 70 °C for 1.5 h gave 3.3 g (74.7%) of **5** as a yellow oil. ^1H NMR (60 MHz) δ ($CDCl_3$, TMS_{int}): 1.4 (s, 3 H, 2-CH_3), 2.1 (s, 3 H, (Ar-CH_3)), 2.15 (s, 6 H, 2(Ar-CH_3)), 2.7–3.0 (m, 2 H, CH_2), 3.5 (s, 2 H, CH_2OH), 4.6 (s, 2 H, C$H_2C_6H_5$), 7.2 (m, 5 H, C_6H_5).

***all-rac*-5-(Benzyloxy)-2,4,6,7-tetramethyl-2,3-dihydrobenzofuran-2-carbaldehyde (6).** To a stirred mixture of Collin's[32] reagent (6.1 mL of dry CH_2Cl_2, 0.48 mL of dry pyridine, and 0.25 g of anhydrous CrO_3) was added in one portion a solution of 0.1 g (0.33 mmol) of **5** in 0.85 mL of CH_2Cl_2. The dark mixture was stirred for 40 min at 25 °C. The organic solution was decanted from the dark residue and washed with CH_2Cl_2 (5 mL) and ether (30 mL). The organic extracts were combined and washed with 1 N NaOH. Usual workup and column chromatography (12% ethyl acetate/hexane) gave pure **6**, (0.033 g, 33%) as a yellow oil. ^1H NMR δ ($CDCl_3$, TMS_{int}): 1.57 (s, 3 H, 2-CH_3), 2.14 (s, 6 H, 2(Ar-CH_3)), 2.20 (s, 3 H, Ar-CH_3), 2.92 (d, 1 H, J = 15.0 Hz, CH), 3.40 (d, 1 H, J = 15.0 Hz, CH), 4.68 (s, 2 H, C$H_2C_6H_5$), 7.30–7.50 (m, 5 H, C_6H_5), 9.50 (s, 1 H, O=CH). Anal. Calcd: C, 77.39; H, 7.14. Found: C, 77.22; H, 7.28.

***all-rac*-5-(Benzyloxy)-2-(4′,8′,12′-trimethyltridecenyl)-2,4,6,7-tetramethyl-2,3-dihydrobenzofuran (8).** The procedure of Mayer[23] was followed with minor modifications. The all-racemic bromide **7** (4.5 g, 15.6 mmol) and 4.2 g (16.0 mmol) of triphenylphosphine were heated 5 h at 200 °C to give the phosphonium salt of **7** as a clear glass. Dry dimethoxyethane (DME) (58 mL) was added and on heating to 50 °C gave a clear solution. After cooling to 15 °C, 5.8 mL (14.5 mmol) of *n*-butyllithium (2.5 M solution in hexanes) was added dropwise. The resultant red solution was stirred 1 h at 25 °C after which time 2.0 g (6.5 mmol) of the aldehyde, **6**, in 20 mL of DME was added. The solution was heated to 80 °C for 2 h and then kept for 3 days at 25 °C. The brown-red solution was cooled in an ice bath and poured onto a mixture of ice (200 mL) and concentrated H_2SO_4 (4.2 mL). Usual workup gave crude **8** (5.93 g) as a brown oil. Column chromatography (hexane followed by 1% ethyl acetate/hexane) gave 1.2 g (37.5%) of pure **8** as a yellow oil. ^1H NMR δ ($CDCl_3$, TMS_{int}): 0.78–1.41 (m, 29 H, 4(CH_3), 7(CH_2), 3(CH), phytyl tail), 1.50 (s, 3 H, 2-CH_3), 2.09 (s, 3 H, Ar-CH_3), 2.12 (s, 3 H, Ar-CH_3), 2.17 (s, 3 H, Ar-CH_3), 3.01 (d, 1 H, J = 13.9 Hz, CH), 3.15 (d, 1 H, J = 13.9 Hz, CH), 4.70 (s, 2 H, C$H_2C_6H_5$), 5.41 (m, 1 H, CH=CH), 5.70 (d, 1 H, J = 10.3 Hz, CH=CH), 7.22–7.50 (m, 5 H, C_6H_5). Anal. Calcd: C, 82.62; H, 10.30. Found: C, 82.87; H, 10.44.

***all-rac*-5-Hydroxy-2-(4′,8′,12′-trimethyltridecyl)-2,4,6,7-tetramethyl-2,3-dihydrobenzofuran (HTDBF).** **8** (1.2 g, 2.3 mmol) dissolved in 50 mL of ethyl acetate was hydrogenated at 1 atm over 5% Pd on activated carbon (0.6 g) for 24 h or until H_2 uptake ceased. Filtration through Celite 545 and evaporation gave 0.95 g (100%) of pure HTDBF as a yellow oil. ^1H NMR δ ($CDCl_3$, TMS_{int}): 0.79–1.73 (m, 33 H, 4(CH_3), 9(CH_2), 3(CH), phytyl tail), 1.50 (s, 3 H, 2-CH_3), 2.09 (s, 3 H, Ar-CH_3), 2.10 (s, 3 H, Ar-CH_3), 2.13 (s, 3 H, Ar-CH_3), 2.80 (d, 1 H, J = 15.0 Hz, CH), 2.95 (d, 1 H, J = 15.0 Hz, CH). GC/MS, m/e (rel intensity): 416 (M^+, 100), 191 (41), 165 (50). Anal. Calcd: C, 80.71; H, 11.61. Found: C, 80.88; H, 11.77.

***all-rac*-3,7,11-Trimethyldodecyl Bromide (7).** To a solution of 1 g (4.3 mmol) of 3,7,11-trimethyldodecan-1-ol in 4 mL of CH_2Cl_2 was added 1.65 g (6.2 mmol) of triphenylphosphine. The clear solution was cooled in an ice bath and 1.06 g (5.9 mmol) of *N*-bromosuccinimide was added in portions, keeping the temperature less than 30 °C. The mixture was subsequently stirred 1 h at 25 °C, evaporated in vacuo, and treated with 4 × 15 mL of hexane. Filtration and evaporation gave crude **7**. Column chromatography (hexane) gave 1.2 g (95%) of pure **7**. ^1H NMR (60 MHz) δ ($CDCl_3$, TMS_{int}): 0.7–1.9 (m, 31 H, 4(CH_3), 8(CH_2), 3(CH)), 3.2–3.5 (t, 2 H, J = 9 Hz, CH_2Br). Anal. Calcd: C, 61.84; H, 10.73. Found: C, 62.02; H, 10.55.

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Registry No. **1**, 93645-32-0; (±)-**2**, 118017-22-4; (±)-**3**, 118017-23-5; (*R*)-(+)-**3**, 118100-80-4; (*S*)-(−)-**3**, 118100-79-1; (*R*)-**3** (methyl ester), 118017-29-1; (*S*)-**3** (methyl ester), 118017-28-0; (*R*-**3**·quinine, 118100-86-0; (*S*)-**3**·quinine, 118100-87-1; (±)-**4**, 118017-24-6; (±)-**5**, 118017-25-7; (±)-**6**, 118017-26-8; **7**, 17081-92-4; (*R*,*R*)-**7**, 65528-01-0; **7** (alcohol), 6750-34-1; **7**·PPh_3, 105375-24-4; (*R*,*R*)-**7**·PPh_3, 60919-78-0; **8**, 118017-27-9; (*RRR*/*SSS*)-**9**, 118100-77-9; (*SRR*/*RSS*)-**9**, 118100-78-0; (*RSR*/*SRS*)-**9**, 118100-91-7; (*RRS*/*SSR*)-**9**, 118100-90-6; (*RRR*)-**9**, 118100-88-2; (*SRR*)-**9**, 118100-89-3; $OHCCH(CH_3)(CH_2)_3CH(CH_3)(CH_2)_3CH(CH_3)_2$, 105-88-4; $OHCCH(CH_3)(CH_2)_3CH(CH_3)(CH_2)CH{=}C(CH_3)_2$, 141-13-9; (*RRR*)-$\alpha$-tocopherol, 59-02-9; (*SRR*)-α-tocopherol, 18920-63-3; *trans*-(*RR*)-phytol, 150-86-7; *trans*-(*RR*/*SS*)-phytol, 118100-85-9; *trans*-(*RS*/*SR*)-phytol, 118138-58-2; *cis*-(*RR*/*SS*)-phytol, 118100-92-8; *cis*-(*RS*/*SR*)-phytol, 118100-93-9; *trans*-(*RR*/*SS*)-phytyl acetate, 118100-84-8; *trans*-(*RS*/*SR*)-phytyl acetate, 118138-59-3; *cis*-(*RR*/*SS*)-phytyl acetate, 118100-83-7; *cis*-(*RS*/*SR*)-phytyl acetate, 118100-94-0; isophytol, 505-32-8; trimethylhydroquinone, 700-13-0; (*R*)-(−)-2,5,7,8-tetramethyl-6-(benzyloxy)-3,4-dihydro-2*H*-1-benzopyran-2-carboxaldehyde, 118100-81-5; (*R*)-(+)-2,5,7,8-tetramethyl-6-hydroxychroman-2-carboxylic acid, 53101-49-8; (*RRR*)-1′,2′-didehydro-*O*-benzyl-α-tocopherol, 69427-84-5; (±)-2,5,7,8-tetramethyl-6-(benzyloxy)-chroman-2-(2′,2′-$^2H_2$)ethanol, 118100-82-6; (±)-2-[2,5,7,8-tetramethyl-6-(benzyloxy)chroman-2-yl]ethyl-(1,1-$^2H_2$) tosylate, 118017-30-4; methyl (±)-[2,5,7,8-tetramethyl-6-(benzyloxy)chroman-2-yl]acetate, 53713-37-4.

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