109. Total Synthesis of All Eight Stereoisomers of α-Tocopheryl Acetate. Determination of Their Diastereoisomeric and Enantiomeric Purity by Gas Chromatography

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Dedicated to Professor *G. Büchi* on the occasion of his 60th birthday

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Summary

All eight stereoisomers of α-tocopheryl acetate have been synthesized in a state of high chemical and stereoisomeric purity. Key chiral side-chain intermediates were prepared from (+)-(*S*)-3-hydroxy-2-methylpropanoic acid. New routes to (2*R*,4′*RS*,8′*RS*)-α-tocopheryl acetate, a mixture of four diastereoisomers, were also developed. A sensitive gas chromatographic method was developed to determine the diastereoisomeric and enantiomeric purity of α-tocopherol samples as the methyl ethers. It was established for the first time that naturally occurring α-tocopherol is essentially a single enantiomer (2*R*,4′*R*,8′*R*), synthetic all-rac-α-tocopherol an equimolar mixture of four racemates, and that natural (*E*)-(7*R*,11*R*)-phytol is diastereoisomerically and enantiomerically homogeneous.

Introduction. – Of the eight possible stereoisomers of α-tocopherol, only two, the naturally occurring (2*R*,4′*R*,8′*R*)-isomer **3a** and its (2*S*)-epimer **4b** *(Scheme 1)* have been isolated or synthesized in chemically and apparently enantiomerically pure form [1–3]. Although the remaining six isomers are present in the all-rac-α-tocopherol manufactured commercially by total synthesis (mixture of four racemates), little is known of their individual biopotencies owing to the unavailability of the pure compounds. Thus the development of synthetic methods to prepare the pure stereoisomers and enantiomers appeared to be an undertaking of considerable interest within the context of current biological and biochemical research in the vitamin-E area.

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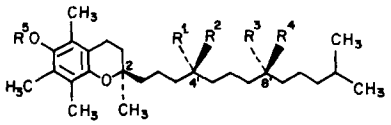
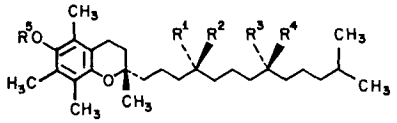
Scheme 1



1a–d, $R^5 = COCH_3$; **3a–d**, $R^5 = H$; **5a–d**, $R^5 = CH_2C_6H_5$; **7a–d**, $R^5 = CH_3$

	R^1	R^2	R^3	R^4	Configuration
a	CH_3	H	CH_3	H	2*R*,4′*R*,8′*R*
b	H	CH_3	H	CH_3	2*R*,4′*S*,8′*S*
c	CH_3	H	H	CH_3	2*R*,4′*R*,8′*S*
d	H	CH_3	CH_3	H	2*R*,4′*S*,8′*R*



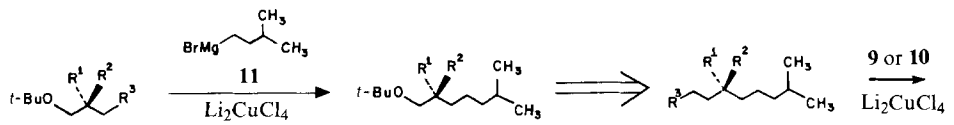
2a–d, $R^5 = COCH_3$; **4a–d**, $R^5 = H$; **6a–d**, $R^5 = CH_2C_6H_5$; **8a–d**, $R^5 = CH_3$

	R^1	R^2	R^3	R^4	Configuration
a	H	CH_3	H	CH_3	2*S*,4′*S*,8′*S*
b	CH_3	H	CH_3	H	2*S*,4′*R*,8′*R*
c	H	CH_3	CH_3	H	2*S*,4′*S*,8′*R*
d	CH_3	H	H	CH_3	2*S*,4′*R*,8′*S*

We have developed an approach to the total synthesis of **3a** (natural isomer) and its acetate **1a** having the potential for application to the preparation of *all* of the α-tocopherol stereoisomers [4]. This strategy was based on the utilization of optically pure C_4-units such as **9** and **10** *(Scheme 2)* for constructing the side chain. These key synthons, available in both enantiomeric forms [4], are derived from (+)-(*S*)-3-hydroxy-2-methylpropanoic acid, itself a convenient chiral starting material produced by bacterial oxidation of isobutyric acid [5]. Thus access to C_{14}-side chain intermediates (**15–18**) having the four possible stereochemical combinations was assured. Given the ready availability of the enantiomeric chroman components **19a, b** [4] [6], all the synthetic fragments required for synthesis of the α-tocopherol stereoisomers were in hand, in high enantiomeric purity.

Synthesis. – The sequences and procedures adapted for assembling the α-tocopheryl acetates **1b–d** and **2a–d** were identical with those originally employed for synthesis of **1a** [4] with the obvious exception that different combinations of stereoisomers were coupled. The elegant method of *Fouquet & Schlosser* [7] was again extensively utilized for linking the various chiral components and the results (yields 60–90%) are summarized in *Table 1*, together with physical and microanalytical data for the coupling products. Data for the C_{14}-intermediates **16** and **17** are given in *Table 2*, and those for the α-tocopheryl acetate stereoisomers in *Table 3*. The latter materials were all shown to be of greater than 99% chemical purity by gas chromatography (GC.).

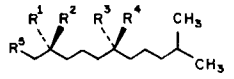
Scheme 2



9, R^3 = MgBr; **10**, R^3 = OTs
a, $R^1 = CH_3$, R^2 = H
b, R^1 = H, $R^2 = CH_3$

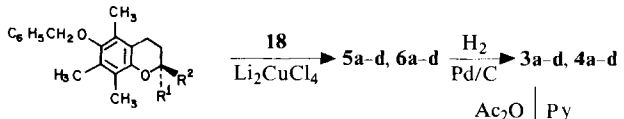
12a, $R^1 = CH_3$, R^2 = H (*R*)
b, R^1 = H, $R^2 = CH_3$ (*S*)

13, R^3 = MgBr, **14**, R^3 = OTs
a, $R^1 = CH_3$, R^2 = H (*R*)
b, R^1 = H, $R^2 = CH_3$ (*S*)



15, R^5 = O*t*-Bu; **16**, R^5 = OH;
17, R^5 = Br; **18**, R^5 = MgBr

	R^1	R^2	R^3	R^4	Configuration
a	CH_3	H	CH_3	H	2*R*,6*R*
b	H	CH_3	H	CH_3	2*S*,6*S*
c	CH_3	H	H	CH_3	2*R*,6*S*
d	H	CH_3	CH_3	H	2*S*,6*R*



19a, $R^1 = CH_3$, $R^2 = (CH_2)_2OTs$ (*S*)
b, $R^1 = (CH_2)_2OTs$, $R^2 = CH_3$ (*R*)

For convenience, natural products were employed in certain cases for preparing isomers having the (8′*R*)-configuration. Thus in the synthesis of **1a**, **1d** and **2c**, the (*R*)-C_{10}-*Grignard* reagent **13a** was derived from abundant natural (*R*)-pulegone [4] [8]. Since this natural product exhibits an enantiomeric purity of 96–98% [9], a small amount (2–4%) of (8′*S*)-epimer is present in the samples of *α*-tocopheryl acetates **1a**, **1d** and **2c** (see below). In the case of the (2*S*,4′*R*,8′*R*)-isomer **2b** [1], the chromanyl tosylate **19b** was coupled with the (2*R*,6*R*)-*Grignard* reagent **18a**, the latter synthon being derived from natural (7*R*,11*R*)-phytol [6].

During the course of these studies, we required samples of (2*R*,4′*RS*,8′*RS*)-*α*-tocopheryl acetate (**24** = **1a** + **1b** + **1c** + **1d**) *(Scheme 3)* [1]. The original synthesis of this material involved a convergent *Wittig* coupling of racemic-(hexahydrofarnesyl)-triphenylphosphonium bromide with (+)-(*S*)-6-acetoxy-3,4-dihydro-2,5,7,8-tetramethylchroman-2-carbaldehyde followed by catalytic hydrogenation [1]. We developed three alternative approaches to the synthesis of **24**. In the first, similar to the synthesis of **1a** [4], chromanyl tosylate **19a** was coupled with racemic 2,6,10-trimethyl-1-undecylmagnesium bromide giving (2*R*,4′*RS*,8′*RS*)-*α*-tocopheryl benzyl ether which upon catalytic hydrogenolysis and acetylation produced **24**.

Table 1. *Coupling reactions and products*[a])

Product	Starting materials	Yield %[b])	b.p. °C/Torr	$[\alpha]_D^{25}$	Formula (M)	Microanalysis Calc./Found	
						C	H
12a[c])	**10a, 11**	83	94–96/20	+9.91°[d])	$C_{13}H_{28}O$ (200.37)	77.93 78.08	14.08 14.40
12b	**10b, 11**	75	77/7	−9.70°[d])	$C_{13}H_{28}O$ (200.37)	77.93 77.97	14.08 14.41
15a[c])	**9a, 14a**	69	75–80/0.05[e])	+1.29°[f])	$C_{18}H_{38}O$ (270.50)	79.93 80.14	14.16 14.32
15a[c])	**10a, 13a**	71	91–95/0.3	+0.94°[f])			
15b	**10b, 13b**	76	86–89/0.08	−1.10°[f])	$C_{18}H_{38}O$ (270.50)	79.93 79.95	14.16 14.38
15c	**9a, 14b**	81	92–95/0.1[e])	+1.85°[f])	$C_{18}H_{38}O$ (270.50)	79.93 79.99	14.16 13.88
15d	**10b, 13a**	79	83/0.05	−1.76°[f])	$C_{18}H_{38}O$ (270.50)	79.93 79.61	14.16 13.90
5a[c])	**19a, 18a**	93		+0.72°[d])	$C_{36}H_{56}O_2$ (520.81)	83.02 83.22	10.84 10.90
6a	**19b, 18b**	79		−0.69°[d])	$C_{36}H_{56}O_2$ (520.81)	83.02 82.77	10.84 10.60
5b	**19a, 18b**	78		N.D.[h])	$C_{36}H_{56}O_2$ (520.81)		
6b	**19b, 18a**[g])	89		−1.24°[d])	$C_{36}H_{56}O_2$ (520.81)	83.02 82.85	10.84 10.89
5c	**19a, 18c**	82		N.D.[h])	$C_{36}H_{56}O_2$ (520.81)		
6c	**19b, 18d**	64		N.D.[h])	$C_{36}H_{56}O_2$ (520.81)		
5d	**19a, 18d**	59		N.D.[h])	$C_{36}H_{56}O_2$ (520.81)		
6d	**19b, 18c**	85		N.D.[h])	$C_{36}H_{56}O_2$ (520.81)		

[a]) Li_2CuCl_4 catalysis – see [4] [7]. [b]) Yields refer to chromatographically pure products exhibiting compatible IR., ^{1}H-NMR., and mass spectra. [c]) See [4]. [d]) $c = 2$, C_6H_6. [e]) Evaporative distillation – bath temperature. [f]) $c = 2$, hexane. [g]) Derived from natural (7*R*,11*R*)-phytol – see [6]. [h]) Not determined.

The second route to **24** *(Scheme 3)* is a modification of the original approach utilizing a *Wittig* coupling [1]. Treatment of racemic-tetrahydronerolidol (**20**) with triphenylphosphonium bromide gave the salt **21** (*E,Z* mixture) which, although crystalline, was too hygroscopic to be purified. Therefore the crude salt was utilized in the *Wittig* condensation with (*S*)-aldehyde **22** [10] [11] (sodium methoxide/dichloromethane). This procedure afforded the desired α-tocodiene ether **23** as a mixture of geometric isomers and diastereoisomers. Hydrogenation over Pd/C followed by acetylation gave **24** (chemical purity *ca.* 99%, GC.).

Table 2. *Data for C_{14} intermediates*

Compound	B.p. °C/Torr	$[\alpha]_D^{25}$ [a])	Formula (M)	Microanalysis Calc./Found	
				C	H
16a[b])	96–99/0.4	+9.13°	$C_{14}H_{30}O$ (214.39)		
16b	70–76/0.025[c])	−9.27°	$C_{14}H_{30}O$	78.43 78.23	14.11 14.16
16c	95/0.1[c])	+9.24°	$C_{14}H_{30}O$	78.12	14.06
16d	95–97/0.05[c])	−9.21°	$C_{14}H_{30}O$	78.57	13.94
17a[b])	90–93/0.4	1.15°[d])	$C_{14}H_{29}Br$ (277.29)		
17b	80–85/0.1[c])	+1.05°	$C_{14}H_{29}Br$	60.64 60.87	10.54 10.67
17c	95–97/0.1[c])	+0.45°	$C_{14}H_{29}Br$	60.47	10.74
17d	100/0.25	+0.40°	$C_{14}H_{29}Br$	60.79	10.48

[a]) $c = 2$, hexane. [b]) See [4] [6]. [c]) Evaporative distillation – bath temperature. [d]) Neat.

An homologous *Wittig* route to **24** was also developed *(Scheme 4)*. Treatment of methacrolein with racemic 3,7-dimethyloctylmagnesium bromide (**25c**)[2]) gave the allylic alcohol **26** which underwent S_Ni' rearrangement [12] [13] upon exposure to thionyl chloride in hexane. The resulting allylic chloride was immediately heated with triphenylphosphine in acetonitrile giving the crystalline (*E*)-phosphonium salt **27** in 37% overall yield from **25a**.

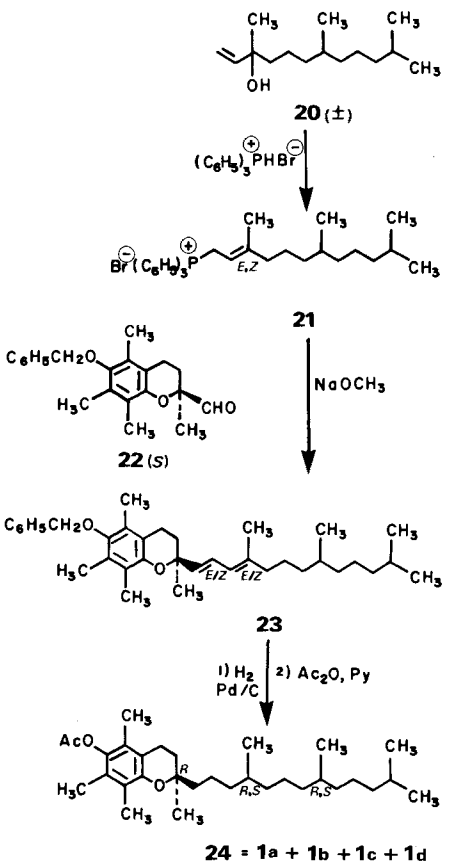
Table 3. *α-Tocopheryl acetate stereoisomers*

Compound	B.p.[a])	$[\alpha]_D^{25}$ [b])	Microanalysis[c]) Found	
			C	H
1a[d])	180–200/0.7	+3.03°[e])		
2a	200/4	−3.07°[e])	78.87	10.92
1b	165–170/2	+1.50°[f])	78.72	11.38
2b[g])	197/4	−2.95°[e])		
1c	180–192/0.8	+2.46°[f])	78.83	11.25
2c	N.D.[h])	−2.46°[f])	78.76	10.84
1d	195/3	+1.09°[f])	78.88	10.93
2d	190–195/1	−1.10°[f])	78.80	10.94

[a]) Evaporative distillation: bath temperature in °C, pressure in Torr × 10^{-3}. [b]) Pure *d*-α-tocopheryl acetate (2*R*,4′*R*,8′*R*) from *Eastman Kodak* exhibits $[\alpha]_D^{25} = +3.29°$ ($c = 5$, EtOH), +2.23° ($c = 5$, hexane). [c]) Calculated for $C_{31}H_{52}O_3$ (M = 472.76): C, 78.76; H, 11.09. [d]) See [4]. [e]) $c = 5$, EtOH. [f]) $c = 5$, hexane. [g]) See [1]; side chain precursor **18a** derived from natural (7*R*,11*R*)-phytol (see [6]). [h]) Compound not distilled.

[2]) Prepared from racemic dihydrocitronellol (**25a**) *via* the bromide **25b**. Alcohol **25a** was secured by catalytic hydrogenation of citral.

Scheme 3

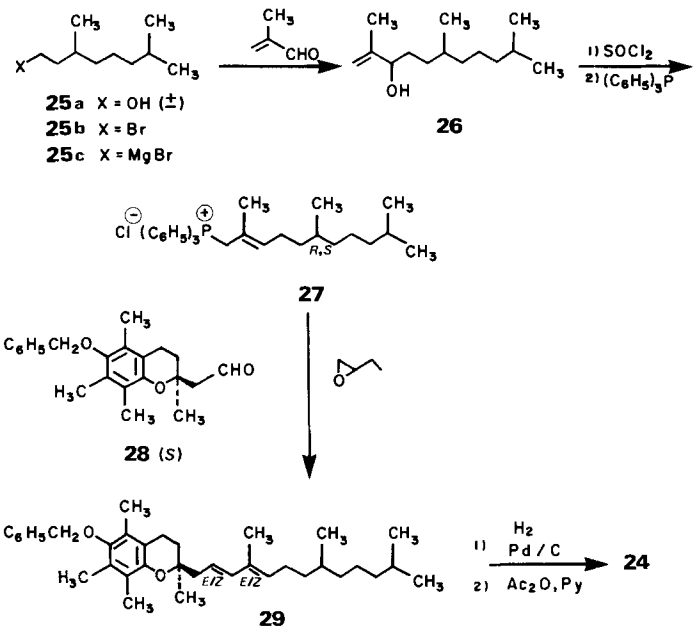


Our initial studies involving *Wittig* condensation of **27** with the (*S*)-chroman-2-acetaldehyde **28** [6] in the presence of sodium methoxide were unrewarding in that totally racemic (*i.e.*, 2 *RS*) α-tocopherol was obtained after hydrogenation of the intermediate diene ((2 *RS*)-**29**). Subsequently it was found that **28** was rapidly and quantitatively racemized in the presence of a catalytic amount of methoxide, at RT., presumably *via* a facile β-elimination[3]).

Therefore, an alternative procedure was employed [14–16]. Treatment of **28** with a molar equivalent of **27** in refluxing 1,2-epoxybutane produced α-tocodiene **29**, as an inseparable mixture of geometric isomers and diastereoisomers, in 80–85% yield, after chromatographic purification. Catalytic hydrogenation then afforded (2*R*,4′*RS*,8′*RS*)-α-tocopherol essentially homogeneous at C(2) (optical rotation of the derived potassium ferricyanide oxidation product: $[\alpha]_D^{25} = +30°$, isooctane) [17]). The acetate **24** obtained from this α-tocopherol was greater than 99% chemically pure (GC.).

[3]) Aldehydes such as **28** have been employed in *Wittig* reactions, *without racemization*, when the ylide was generated using phenyllithium [6].

Scheme 4



Diastereoisomeric and enantiomeric analysis by gas chromatography. – The availability of a reliable, facile analytical method for distinguishing and quantitating the diastereoisomeric forms of α-tocopherol has long been desirable in vitamin-E research. For example, the large-scale, commercial production of all-rac-α-tocopherol involves well-developed synthetic schemes which result in a mixture of four racemates [1–3] [17]. Since the synthetic sequences employed should, *a priori*, be nonstereoselective regarding introduction of the three chiral methyl centers, it has generally been assumed without verification that the four racemates are produced in equal amounts. Similarly, it has never been firmly demonstrated that natural *d*-α-tocopherol ($2R,4'R,8'R$) is, in fact, a single enantiomer, as was always assumed. Optical methods commonly employed to distinguish natural from synthetic α-tocopherol provide information only regarding the enantiomeric composition at C(2) [1] [17].

Very recently, two important breakthroughs regarding analytical methodology in the vitamin-E area were disclosed. In the first and most pertinent to our own work, *Slover & Thompson* developed a gas chromatographic method for determining the diastereoisomeric composition of α-tocopherol samples as the trimethylsilyl (TMS) ether, using a glass capillary column coated with a polar liquid phase [18][4]). In addition, after the completion of our studies, workers at *BASF* reported a method for determination of the enantiomeric purity of α-tocopherol samples by ^{13}C-NMR. spectroscopy [19].

[4]) We are extremely grateful to Mr. *H. Slover*, U.S. Dept. of Agriculture, Beltsville, Maryland, for providing us with much helpful information prior to disclosure of his results.

We have now refined the GC. method to the point that near base-line resolution of the diastereoisomers is observed. The important modification centered upon the particular α-tocopherol derivative analyzed. The methyl ether was superior to the TMS ether in terms of resolution. Methylation of α-tocopherol is a trivial procedure and can be performed on very small samples [20] (see experimental part).

A typical chromatogram of all-rac-α-tocopheryl methyl ether is shown in *Figure 1.* As expected, the four well-resolved peaks (representing four racemates)

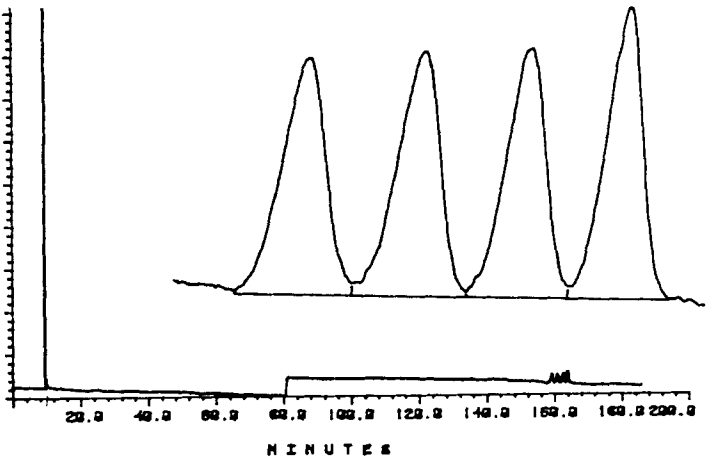


Figure 1. *GC. of all-rac-α-tocopheryl methyl ether at 190°*

are essentially equivalent in magnitude (see *Table 4*). The compositions of several samples of commercially produced all-rac-α-tocopherol were consistent within the limits of the analytical method ($\pm$ 1%). Similarly, the four diastereoisomers in (2*R*,4′*RS*,8′*RS*)-α-tocopherol (synthesized as described above) are present in essentially equivalent amounts[5]). By co-injection with authentic samples of the synthetic diastereoisomers of known absolute configuration, we established the elution order as follows: peak 1, *R, R, S* and *S, S, R;* peak 2, *R, R, R* and *S, S, S;* peak 3, *R, S, R* and *S, R, S;* peak 4, *R, S, S* and *S, R, R.*

The methyl ether of natural α-tocopherol isolated directly from soybean 'deodorizer distillate'[6]) produced essentially a single peak corresponding to peak 2 of the totally synthetic mixture *(Fig. 2).* When (2*RS*,4′*R*,8′*R*)-α-tocopherol (2-*ambo*) [1][7]) was analyzed in this manner, two peaks, of equal magnitude,

[5]) It appears, therefore, that hydrogenation of the double bonds in **23** and **29** occurs without asymmetric induction at C(4′). Thus the chiral center at C(2) has no apparent effect on the course of the hydrogenation.

[6]) This is the major commercial source of 'natural' *d*-α-tocopherol and also contains substantial amounts of β-, γ-, and δ-tocopherol as well as sterols, fatty acids, and triglycerides. In practice, the entire tocopherol fraction is subjected to a methylation procedure (*e.g.* chloromethylation followed by catalytic or chemical reduction) in order to transform all of the lower tocopherol homologs to α-tocopherol [17].

[7]) Prepared by condensation of trimethylhydroquinone with natural (7*R*,11*R*)-phytol in trifluoroacetic acid [21].

Table 4. *Gas chromatographic anylsis of α-tocopheryl methyl ethers*

Compound	% Composition[a])			
	Peak 1 *R,R,S* *S,S,R*	Peak 2 *R,R,R* *S,S,S*	Peak 3 *R,S,R* *S,R,S*	Peak 4 *R,S,S* *S,R,R*
7a[b])		⩾99.5		trace
7a[c])	1.3	94.4	3.3	1.0
8a		97.3	1.6	1.1
7b	2.0	1.7	trace	95.5
8b[d])		trace		99.6
7c	96.5	2.0	1.5	
8c	93.3	3.8	1.9	1.0
7d			96.7	3.3
8d	1.9		98.1	
(2*RS*,4′*R*,8′*R*)-α-Tocopheryl methyl ether[e])		49.9		50.1
(2*R*,4′*RS*,8′*RS*)-α-Tocopheryl methyl ether[f])	24.9	24.9	25.2	24.9
(2*RS*,4′*RS*,8′*RS*)-α-Tocopheryl methyl ether[g])	24.9	25.1	24.8	25.0

[a]) Variability of ±1%. [b]) From *d*-α-tocopherol isolated directly from soybean deodorizer distillate by liquid chromatography. [c]) From totally synthetic *d*-α-tocopherol; see [4]. [d]) Side chain derived from natural (7*R*,11*R*)-phytol [6]. [e]) Mixture of 2 epimers (**7a**,**8b**)-tocopherol obtained by condensation of trimethylhydroquinone with natural (7*R*,11*R*)-phytol; see [1] [21]. [f]) Mixture of 4 diastereomers (**7a–d**). [g]) Mixture of 4 racemates (**7a–d**, **8a–d**)-tocopherol obtained from Chemical Production Department, *Hoffmann-La Roche Inc.*, Nutley, N.J., USA.

corresponding to **7a** and **8b** (epimers) were observed. Since this modification of α-tocopherol is synthesized from natural (7*R*,11*R*)-phytol, the GC. result proves for the first time that natural phytol is enantiomerically and diastereoisomerically homogeneous [22]. If it were not, other α-tocopherol diastereoisomers would have been detected in the chromatogram[8]).

Before discussing the stereochemical purities observed for the synthetic isomers **7a–d** and **8a–d**, some comments regarding interpretation of the GC. analytical results presented in *Table 4* are required. As described above, our approach to the synthesis of these compounds involved the sequential coupling of three chiral units (*i.e.*, (**13** or **14**)+(**9** or **10**)+**19**), each of high enantiomeric purity [4] [6] [9]. Thus our goal was to produce individual stereoisomers of α-tocopherol having high enantiomeric as well as diastereoisomeric purities. The GC. separation method utilizing an achiral liquid phase, however, is capable of distinguishing only the four diastereoisomers and not eight enantiomers. On the other hand, the fact that these isomers are prepared from chiral synthons of approximately 96–100% enantiomeric purity [4] [6] [9] dictates that the gas chromatographic diastereoisomeric purities observed are, for all practical purposes, also the enantiomeric purities. For example, let us examine a hypothetical synthesis of (2*R*,4′*R*,8′*R*)-α-tocopherol from the three appropriate chiral units, each having an enantiomeric purity of 98%. The statistical composition of the α-tocopherol should be as follows: 94.120% *R,R,R*, 0.001% *S,S,S*, 0.039% *R,S,S*, 1.920% *S,R,R*, 1.920% *R,S,R*, 0.039% *S,R,S*, 1.920% *R,R,S*, and 0.039% *S,S,R*. Thus the quantities of four of

[8]) The same conclusion regarding the enantiomeric purity of natural phytol is reached based on the GC. analysis of **8b** (99.6%) whose side chain was derived from natural phytol.

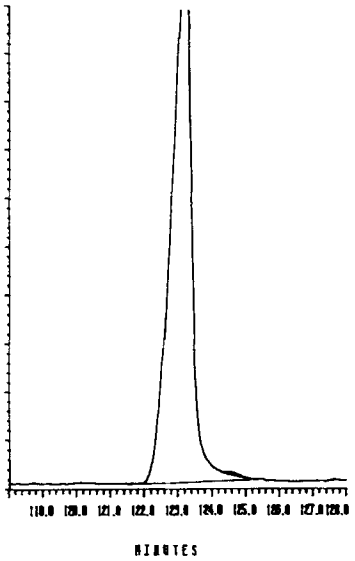


Figure 2. *GC. of* d-*α-tocopheryl methyl ether* (**7a**) *(from soybean deodorizer distillate)*

these isomers are insignificant relative to the amounts of their respective mirror images. The amount of racemate present in each peak is, therefore, negligible, especially in the case of the major isomer. In this discussion, we have assumed that there is no kinetic stereoselection inherent in the coupling reactions involving the various combinations of stereoisomers. Given the generally high yields observed in these reactions, the distances separating the asymmetric centers (three C-atoms),

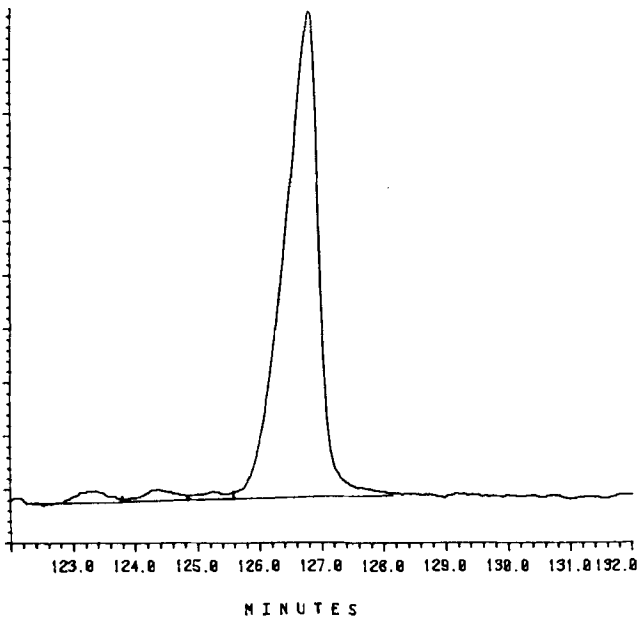


Figure 3. *GC. of totally synthetic (2*R,*4'*S,*8'*S*)-α-tocopheryl methyl ether* (**7b**)

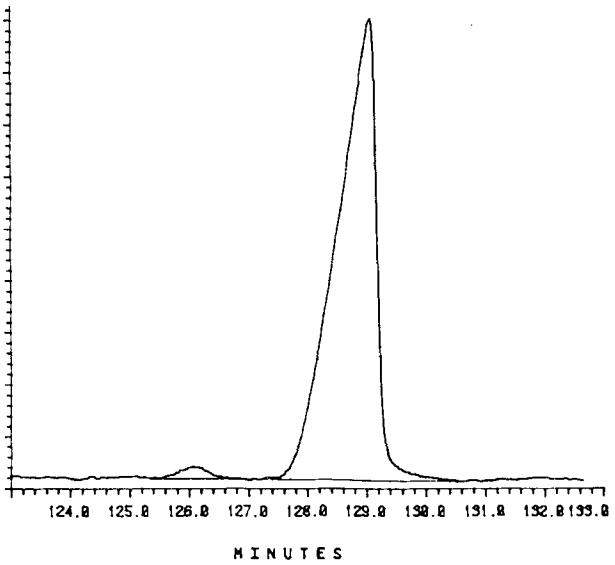


Figure 4. *GC. of totally synthetic (2S, 4'R, 8'S)-α-tocopheryl methyl ether* (**8d**)

and the non-rigid, acyclic nature of most of the intermediates, we feel that this is a reasonable assumption.

All of our totally synthetic samples of the α-tocopheryl acetate stereoisomers exhibited high stereochemical purities (93–99%) when subjected to the methyl ether GC. analysis. These results demonstrate that our synthetic strategy, involving sequential coupling of chiral units, was highly effective. Two representative chromatograms are shown in *Figure 3* (**7b**) and *Figure 4* (**8d**). As noted above, we had expected the stereochemical purities of **7a** (synthetic), **7d**, and **8c** to be less than 100% since the C(8') center in these compounds had been derived from natural (*R*)-pulegone having an optical purity of only 96–98%. The resultant diastereoisomeric impurities in these methyl ethers, although minor, are clearly detectable using this GC. method. The small amounts of isomeric impurities in the remaining samples apparently arise from enantiomeric impurities in the chiral components which escaped detection by the optical ($[\alpha]_D$) and spectral (^{1}H-NMR. optically-active-shift reagents) methods used for their analysis.

Conclusion. – The synthetic work described above has provided, for the first time, highly pure samples of all eight stereoisomers of α-tocopheryl acetate. The availability of these substances will now allow a determination of their relative biopotencies and thus answer a long standing question involving the relationship of α-tocopherol stereochemistry to vitamin-E activity[9]). The extensive exploitation in this work of chiral C_4-intermediates derived from (+)-(*S*)-3-hydroxy-2-methylpropanoic acid provides further demonstration of the versatility of this readily

[9]) The synthetic α-tocopheryl acetate diastereoisomers are currently undergoing biological evaluation in the laboratory of Dr. *H. Weiser*, Central Research Department, *Hoffmann-La Roche & Co. AG*, CH-4002 Basel. The results will be published in due course.

available, optically pure hydroxy acid in the total synthesis of natural products. In addition, our refinement of the GC. method for distinguishing the α-tocopherol diastereoisomers now affords a valuable analytical tool having broad potential applications in vitamin-E research.

We are grateful to the personnel of the Fermentation Pilot Plant and the Kilo Laboratory, both part of the Chemical Research Department, *Hoffmann-La Roche Inc.*, Nutley, N.J. for providing large quantities of (+)-(*S*)-3-hydroxy-2-methylpropanoic acid. Most of the spectral, microanalytical, and polarimetric determinations required in this work were carried out by the personnel of the Physical Chemistry Department, Chemical Research Department, *Hoffmann La Roche Inc.*, Nutley, N.J. to whom we are also indebted.

Experimental Part

General Remarks. Unless otherwise noted, reactions were carried out under argon. Melting points (m.p.) were obtained using a *Thomas-Hoover* capillary apparatus and are uncorrected. The 'usual work-up' involves 3 extractions with the specified solvent. The organic extracts were combined, washed with water and saturated brine then dried ($MgSO_4$), filtered and concentrated at 40–50° on a rotatory evaporator. The residue was further dried to constant weight under high vacuum (HV.). Column chromatography was peformed using *EM* silica gel 60, 0.063–0.2 mm. Thin layer chromatographic analysis was carried out using pre-coated *EM* silica gel 60 F-254 plates developed with 1:1 hexane/ether, unless otherwise noted. Spots were detected with UV. light and/or by spraying with methanolic phosphomolybdic acid followed by heating. UV. spectra were measured in 95% alcohol, IR. spectra in $CHCl_3$, ^{1}H-NMR. spectra in $CDCl_3$ (chemical shifts (δ) are reported relative to Me_4Si as an internal standard). Benzyl chloride was distilled from and stored over anhydrous K_2CO_3. *Aldrich* 1,2-epoxybutane was redistilled. *Englehard* 5% Pd/C was used for the catalytic hydrogenations. Tetrahydrofuran (THF) and pyridine were dried by slurrying over *Woelm* grade I, neutral alumina just prior to use. Optical rotations were measured on a *Perkin-Elmer* model 141 polarimeter. Natural, (7*R*,11*R*)-(*E*)-phytol was purchased from *Bioclinical Laboratories*, Phillipsburg, N.J. and from *Takasago Perfumery* in Japan. Soybean 'deodorizer distillate' was obtained from *Central Soya Corp.*, Decatur, Indiana. Tetrahydronerolidol and samples of all-rac-α-tocopherol and all-rac-α-tocopheryl acetate were obtained from the Chemical Production Department, *Hoffmann-La Roche Inc.*, Nutley, N.J.

(*S*)-C_{10}-Intermediates 13b and 14b. – These synthons were prepared, exactly as described for the (*R*)-antipodes [4], starting from **12b**, *via* the following intermediates: (–)-*(S)-2,6-dimethylheptan-1-ol*, b.p. 100–105°/7 Torr; $[\alpha]_D^{25} = -10.97°$ ($c = 2$, C_6H_6).

$C_9H_{20}O$ (144.26) Calc. C 74.94 H 13.98% Found C 74.40 H 13.94%

(–)-*(S)-3,7-Dimethyloctanoic acid*, b.p. 93–95° (bath temperature)/0.25 Torr; $[\alpha]_D^{25} = -7.33°$ ($c = 5$, $CHCl_3$). Analysis by high performance liquid chromatography of the amide derived from (+)-(*R*)-α-methyl-*p*-nitrobenzylamine [9] showed an enantiomeric purity of at least 99.7%.

(–)-*(S)-3,7-Dimethyl-1-octanol*, b.p. 100–105° (bath temperature)/17 Torr; $[\alpha]_D^{25} = -4.25°$ ($c = 5.03$, $CHCl_3$).

$C_{10}H_{20}O$ (158.29) Calc. C 75.88 H 14.01% Found C 75.77 H 14.20%

(+)-*(S)-1-Bromo-3,7-dimethyloctane*, b.p. 86°/8 Torr; $[\alpha]_D^{25} = +4.98°$ ($c = 2$, hexane).

$C_{10}H_{21}Br$ (221.19) Calc. C 54.30 H 9.57% Found C 54.62 H 9.89%

(*R*)-6-Benzyloxy-2,5,7,8-tetramethylchroman-2-ethanol-*p*-toluenesulfonate (19b). – This compound was prepared, exactly as described for the (*S*)-antipode **19a** [4], starting from (+)-(*R*)-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)acetic acid [6], *via* the following intermediates: (+)-*(R)-methyl(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)acetate*, viscous oil, b.p. 160–165° (bath temperature)/0.001 Torr; $[\alpha]_D^{25} = +18.01°$ ($c = 1.18$, C_6H_6).

$C_{16}H_{22}O_4$ (278.34) Calc. C 69.04 H 7.97% Found C 69.10 H 7.93%

(+)-(R)-*Methyl(6-benzyloxy-2,5,7,8-tetramethylchroman-2-yl)acetate*, colorless solid, m.p. 37.5–38.5° (from pentane); $[\alpha]_D^{25} = +3.30°$ ($c = 1$, C_2H_5OH), +16.67° ($c = 1$, C_6H_6).

$C_{23}H_{28}O_4$ (368.47) Calc. C 74.97 H 7.66% Found C 75.16 H 7.66%

(+)-(R)-*6-Benzyloxy-2,5,7,8-tetramethylchroman-2-ethanol*, colorless solid, m.p. 51–56°; $[\alpha]_D^{25} = +15.68°$ ($c = 2$, $CHCl_3$).

$C_{22}H_{28}O_3$ (340.47) Calc. C 77.61 H 8.29% Found C 77.39 H 8.40%

(+)-(*S*)-6-Benzyloxy-2,5,7,8-tetramethylchroman-2-carbaldehyde (22). – A solution of 10 g (40 mmol) of (−)-(*S*)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid [23] ($[\alpha]_D^{25} = -63.45°$ ($c = 1.8$, EtOH)) in 200 ml of methanol was stirred and refluxed for 4 h. After cooling, the solution was poured into 500 ml of water containing 50 ml of saturated aqueous $NaHCO_3$-solution. The resulting slurry was chilled in an ice bath then filtered with suction. The solid was washed with water and dried, first under aspirator pressure, then under HV. at 40–50° to constant weight. There was obtained 10.0 g (95%) of *methyl(−)-(S)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylate* [10] as a colorless solid which was used without further purification.

To a solution of 2 g (7.58 mmol) of this ester in 7.5 ml of *N,N*-dimethylformamide (DMF) was added 2.6 g (18.8 mmol) of anhydrous, granular K_2CO_3 followed by 2.3 ml (20 mmol) of benzyl chloride. The resulting slurry was stirred at RT. for 41 h then poured into 50 ml of water and worked up with ether in the usual way. The product was freed of excess benzyl chloride at 50° under high vacuum. There was obtained 2.69 g (100%) of pure (TLC.) *(−)-(S)-6-benzyloxy-2,5,7,8-tetramethylchroman-2-carboxylic acid methyl ester* as a yellow solid, m.p. 102–106°; $[\alpha]_D^{25} = -43.21°$ ($c = 5$, $CHCl_3$). An analytical specimen of this compound was first prepared by Dr *K.-K. Chan* of our laboratories as a colorless solid, m.p. 108–109° (from ether/methanol); $[\alpha]_D^{25} = -44.02°$ ($c = 5$, $CHCl_3$)

$C_{22}H_{26}O_4$ (354.43) Calc. C 79.55 H 7.39% Found C 79.80 H 7.54%

A solution of 3.54 g (10 mmol) of the above ether ester, in 20 ml of toluene and 10 ml of CH_2Cl_2 was stirred with cooling from a dry ice/acetone bath while 12 ml (18 mmol) of 25% diisobutylaluminum hydride in toluene *(Texas Alkyls)* was added dropwise, over 10 min. After stirring at *ca.* −70° for 30 min, the reaction mixture was cautiously decomposed (−70°) with 10 ml of MeOH. Following the addition of 50 ml of water and 50 ml of 1N aqueous H_2SO_4-solution, the mixture was warmed to RT. and worked up with ether in the usual way giving 3.2 g (100%) of crude aldehyde **22** [10] as a viscous oil which was used without further purification. TLC. and IR. analysis revealed the presence of a small amount of primary alcohol resulting from over-reduction.

(−)-(2*S*,8′*RS*)-6-Benzyloxy-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltrideca-1,3-dien-1-yl)chroman (mixture of geometric isomers) (**23**). – A solution of 2.5 g (11 mmol) of racemic tetrahydronerolidol (**20**) in 11 ml of CH_2Cl_2 was stirred at RT. while 3.8 g (11 mmol) of triphenylphosphonium bromide was added in one portion. The mixture was stirred at RT. for 25 h then the resulting solution was dried (Na_2SO_4), filtered and concentrated i.V. The residue was dried under HV. giving 6.1 g of crude salt **21** as a colorless, gummy solid. To a solution of this salt in 10 ml of CH_2Cl_2, cooled to 0–5°, was added 4.7 ml of 2.34M methanolic sodium methoxide, dropwise, over 12 min, with stirring. The mixture was stirred at 0–5° for 0.5 h then treated with a solution of 3.24 g (10 mmol) of crude aldehyde **22** in 8 ml of CH_2Cl_2. The resulting mixture was stirred at reflux for 4 h then at RT. for 17.5 h. The solvent was removed i.V. and the oily residue was treated with 20 ml of hexane. The insoluble material was removed by filtration and washed with hexane. The filtrate and washes were combined, concentrated i.V. then the oily residue was redissolved in hexane and washed with 1M aqueous cupric chloride (2×25 ml). Processing in the usual manner gave 5.47 g of an oil which was chromatographed on 250 g of silica gel. Elution with 49:1 hexane/ether afforded 3.88 g of **23** which still contained a trace of triphenylphosphine. This material was redissolved in hexane and the cupric chloride wash was repeated. This yielded 3.46 g (67%) of pure (TLC.) α-tocodiene ether **23** as a pale-yellow oil, $[\alpha]_D^{25} = -12.50°$ ($c = 1.98$, benzene). – UV.: 242 (29,200), 283 (2100), 289 (2275). – ^{1}H-NMR.: compatible with the presence of 4 geometric isomers. – MS.: 516 (M^+).

$C_{36}H_{52}O_3$ (516.8) Calc. C 83.67 H 10.14% Found C 83.57 H 10.29%

rac-(*E*)-(2,6,10-Trimethyl-2-undecen-1-yl)triphenylphosphonium chloride (27). – A mixture of 100 g (0.63 mol) of rac-dihydrocitronellol (**25a**) and 1500 ml of 48% aqueous HBr-solution was stirred

and refluxed for 21 h. After cooling, the reaction mixture was worked up in the usual manner with hexane (the combined hexane extracts were additionally washed with saturated aqueous $NaHCO_3$). Distillation of the product afforded 127.9 g (92%) of *bromide* **25b** as a colorless liquid b.p. 103–105°/14 Torr.

To a stirred mixture of 13.86 g (0.58 g-atom) of magnesium turnings and 50 ml of anhydrous ether, containing a few crystals of I_2 were added several ml of a solution of the above bromide **25b** (0.58 mol) in 645 ml of anhydrous ether. After slight warming, the reaction began and the remainder of the bromide solution was added over 3 h, maintaining gentle reflux. After the addition was complete, stirring and refluxing were continued for 1 h whereupon the mixture containing the *Grignard* reagent **25c** was cooled to 4° and a solution of 40.4 g (0.58 mol) of freshly distilled methacrolein in 275 ml of dry ether was added dropwise, keeping the temperature at 4–6°. Stirring was continued at 0–5° for 1 h then at RT. for 17.5 h. The reaction was usually complete at this point; however, for convenience, this reaction mixture was kept at RT. over the week-end before being cautiously poured into 1200 ml of saturated aqueous NH_4Cl-solution. Work-up with ether in the usual manner gave an orange oily product which was carefully fractionated using a 12 in. *Goodloe* column. The main fraction was a colorless liquid, b.p. 100°/0.4 Torr (86.4 g, 70.3%). This material contained 95.5% alcohol **26** (GC., *Carbowax*, 20–200°). In a separate run (7.7 mmol scale), the crude product (1.5 g) was chromatographed on 50 g of silica gel. Elution with 9:1, 4:1, and 2:1 hexane/ether gave pure **26** which was evaporatively distilled providing the analytical specimen (0.87 g) of *rac-2,6,10-trimethylundec-1-en-3-ol* (**26**) as a colorless oil, b.p. 92–95° (bath temp.)/0.45 Torr. – IR.: 3610 (OH), 1647 (C=C), 903 (C=CH_2). – ^{1}H-NMR.: 4.92, 4.82 (2 br. *s*, 2, C=CH_2); 4.02 (*t*, *J* = 5 Hz, 1, C*H*OH); 1.80 (*s*, 1, OH); 1.71 (br. *s*, 3, CH_3C=); 0.85 (*d*, *J* = 6 Hz, 9, 3 CH_3CH–). – MS. (*m/z*): 194 ($M - H_2O$), 169, 140, 43.

$C_{14}H_{28}O$ (212.38) Calc. C 79.18 H 13.29% Found C 79.10 H 13.13%

To a stirred solution of **26** (86.4 g, 0.407 mol) in 500 ml of hexane, at 5° (ice-bath cooling) was added, dropwise, 31.8 ml (52.2 g, 0.44 mol) of thionyl chloride. Vigorous gas evolution was noted. After complete addition, the solution was stirred for 1 h at 0–5° and then for 4.5 h at RT. before being concentrated i.V. After drying under HV., 94 g of a pale-yellow oil was obtained which was dissolved in 820 ml of acetonitrile. Triphenylphosphine (106.6 g, 0.407 mol) was added and the solution was stirred and refluxed for 16.5 h then cooled and concentrated i.V. to give a colorless solid residue. This material was triturated with 350 ml of hot ethyl acetate and the solids were filtered off with suction from the hot mixture. The solid was suspended in 300 ml of fresh ethyl acetate and vigorously stirred under reflux, for 3 h. The hot mixture was filtered to give 115.6 g (57.6%, 37.2% overall yield from **25a**) of phosphonium salt **27**, as a colorless solid, m.p. 158–162°, after drying under HV. The analytical sample was obtained from a separate experiment by washing the crude salt with ether, colorless solid, m.p. 168–170°. – ^{1}H-NMR.: 7.75 (*m*, 15, $(C_6H_5)_3$); 5.29 (*m*, 1, –CH=); 4.66 (*d*, *J* = 16 Hz, 2, $-CH_2\overset{\oplus}{P}(Ph)_3$); 1.97 (*m*, 2, $-CH_2$CH=); 1.47 (*d*, CH_3C=); 0.84 (*d*, *J* = 6 Hz, 6, $(CH_3)_2$CH); 0.76 (*d*, *J* = 6 Hz, 3, CH_3CH).

$C_{32}H_{42}ClP$ (493.12) Calc. C 77.94 H 8.58% Found C 78.05 H 8.54%

(2*S*,8'*RS*)-6-Benzyloxy-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltrideca-2,4-dien-1-yl)chroman (mixture of geometric isomers) (**29**). – A solution of 10 g (37.8 mmol) of (–)-(*S*)-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)acetic acid [6] (m.p. 144–146°; $[\alpha]_D^{25} = -14.24°$ (*c* = 1, EtOH)) and 1 g of *p*-toluenesulfonic acid monohydrate in 200 ml of methanol was stirred and refluxed for 18 h then cooled and concentrated i.V. The oily residue was dissolved in ether and the solution was washed twice with saturated aqueous $NaHCO_3$-solution then processed in the usual manner giving 10.8 g of *(–)-(S)-methyl(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)acetate* [6] as a solid, m.p. 68–71°.

To a solution of this ester in 41 ml of DMF was added 13.2 g (95.8 mmol) of anhydrous K_2CO_3 followed by 12.4 g (98.3 mmol) of benzyl chloride. The resulting slurry was stirred at RT. for 67 h then poured into 300 ml of water. Work-up with ether in the usual manner gave 14.8 g of *(–)-(S)-methyl(6-benzyloxy-2,5,7,8-tetramethylchroman-2-yl)acetate* [6] as a yellow oil.

To a stirred solution of this ether ester in 950 ml of hexane, at –72° (dry-ice/acetone bath), was added 41 ml (61 mmol) of a 25% solution of diisobutylaluminum hydride in toluene, dropwise. After stirring at –72° for 40 min, the reaction mixture was cautiously decomposed by the dropwise addition of 43 ml of methanol (–72°). Water (43 ml) was then added and the mixture was warmed to 0°, diluted with 300 ml of ether and treated with 75 ml of 6N aqueous HCl. Work-up with ether in the

usual manner (the organic extracts were additionally washed with 6N aqueous HCl) gave 12.47 g (97.6% overall) of *aldehyde* **28** [6] as a pale-yellow solid. This material was used without further purification.

A solution of 8 g (23.7 mmol) of this aldehyde and 11.6 g (23.5 mmol) of phosphonium salt **27** (m.p. 168–170°), in 240 ml of 1,2-epoxybutane was stirred and refluxed for 23 h then cooled and concentrated under reduced pressure (50°/170 Torr then 15 Torr; the excess epoxybutane was recovered). The residue was treated with 250 ml of hexane and the resulting mixture was stirred for 1 h at RT. then filtered with suction. The insoluble material was washed with hexane. Concentration of the combined filtrate and washes left a yellow oil which was redissolved in 200 ml of ethyl acetate. The solution was treated with some *Raney* nickel slurry and stirred for 5 min then dried ($MgSO_4$), filtered and concentrated i.V. The residue (12.1 g) was chromatographed on 500 g of silica gel. Elution with 19:1 hexane/ether afforded 9.9 g (82%) of pure (TLC.) α-tocodiene **29** as a colorless, viscous oil. The analytical sample of **29** was obtained from another experiment as a viscous, colorless oil, $[\alpha]_D^{25} = -0.18°$ ($c = 1$, C_6H_6). – UV.: 228 (22,200), 281 (1680), 287 (1870), infl. 240 (18,000). – ^{1}H-NMR. presence of geometric isomers. – MS.: *m/z* 516 (M^+), 425 ($M^+ - C_7H_7$), 295, 205 (base), 91 (C_7H_7).

$C_{36}H_{52}O_2$ (516.8) Calc. C 83.67 H 10.14% Found C 83.86 H 10.24%

(2*R*,4′*RS*,8′*RS*)-α-Tocopheryl acetate (24). – A. *From tosylate* **19a**. Coupling of (2*RS*,6*RS*)-2,6,10-trimethyl-1-undecylmagnesium bromide [24] with tosylate **19a**, in the presence of Li_2CuCl_4, [4], gave (2*R*,4′*RS*,8′*RS*)-α-tocopheryl benzyl ether in 66% yield. When this ether was hydrogenolyzed over Pd/C and acetylated as described previously for the preparation of **1a** [4], **24** [1] was obtained as a colorless oil, b.p. 196° (bath temperature)/0.004 Torr; $[\alpha]_D^{25} = +2.57°$ ($c = 5$, EtOH).

B. *From α-tocodiene ether* **23**. A 2.62 g (5.08 mmol) sample of α-tocodiene ether **23** was hydrogenated over 1 g of 5% Pd/C in 50 ml of ethyl acetate, at RT. and 1 atm. Hydrogen uptake was rapid at first then slowed drastically. After 19 h, gas uptake had ceased at 415 ml (381 ml theory). The catalyst was filtered off and the filtrate was concentrated i.V. giving 2.15 g of (2*R*,4′*RS*,8′*RS*)-α-tocopherol as a yellow oil. This material was immediately treated with 5 ml of acetic anhydride and 10 ml of pyridine and the resulting solution was kept at RT. for 20.5 h then concentrated under HV. The residue was taken up in hexane and processed in the usual manner (the hexane extracts were additionally washed with saturated aqueous $NaHCO_3$-solution) affording 2.31 g of an almost colorless, viscous oil. This material was chromatographed on 100 g of silica gel. Elution with 19:1 hexane/ether gave acetate **24** in 2 fractions, both of which were evaporatively distilled at 175° (bath temp.)/0.15 mm: 0.828 g, $[\alpha]_D^{25} = +2.43°$ ($c = 5.1$, EtOH), purity 99.8% (GC., 1 m × 4 mm ID. column of 10% *OV-101* on *GCQ* 100/120, 80°–270° program); 1.372 g, $[\alpha]_D^{25} = +2.46°$ ($c = 5.03$ EtOH), pure (GC.). Total yield 2.20 g (92%).

C. *From α-tocodiene ether* **29**. A mixture of 5.2 g (10 mmol) of α-tocodiene ether **29**, 3.4 g of 5% Pd/C and 750 ml of ethyl acetate was stirred under H_2 for 22 h at which point H_2-uptake ceased (880 ml H_2 taken up; 750 ml theory). The catalyst was filtered off on a *Celite* pad and the filtrate was concentrated i.V. giving 4.02 g (93.5%) of (2*R*,4′*RS*,8′*RS*)-α-tocopherol as an oil. The $K_3Fe(CN)_6$ oxidation product (purified by prep. TLC., 19:1 hexane/ether) derived from a sample of this material exhibited $[\alpha]_D^{25} = +30.93°$ ($c = 4$, isooctane) [17].

A solution of 3.79 g (8.8 mmol) of this α-tocopherol in 23 ml of pyridine and 18.8 ml of acetic anhydride was stirred for 3 days at RT. then concentrated under HV. The residue was dissolved in ether and the ether solution was processed in the usual manner (the ether solution was additionally washed with saturated aqueous $NaHCO_3$) giving 4.1 g of an oil. This material was chromatographed on 250 g of silica gel. Elution with 9:1 hexane/ether afforded 3.97 g (96%) of acetate **24** as a viscous colorless oil, $[\alpha]_D^{25} = +2.23°$ ($c = 5$, EtOH), purity 99.3% (GC.).

General procedure for conversion of α-tocopheryl acetate to the methyl ether. – To a stirred suspension of 10 mg of lithium aluminum hydride in 1.5 ml of anhydrous ether was added, dropwise, at RT., a solution of 26 mg of the α-tocopheryl acetate in 1.5 ml of anhydrous ether. The resulting mixture was stirred for 30–45 min, decomposed with moist ether, treated with 1N aqueous H_2SO_4, and extracted with ether. The ether extracts were combined, washed twice with water, dried ($MgSO_4$), filtered, and concentrated i.V. to give 22 mg of α-tocopherol as a colorless oil. This material was dissolved in 0.5 ml of acetone. To the stirred solution was added dropwise, simultaneously, using 2 different syringes, 0.04 ml of dimethyl sulfate and 0.06 ml of 50% aqueous NaOH-solution. The

mixture was stirred for 30 min at RT. then 1 ml of 10% aqueous NH_4OH-solution was added. After stirring for an additional 30 min, the mixture was extracted with petroleum ether (30–60°) and the organic solution was washed with 10% aqueous NH_4OH-solution, 50% aqueous ethanol, 50% aqueous ethanol containing 1% HCl, and twice again with 50% aqueous ethanol. The petroleum ether phase was dried ($MgSO_4$) and concentrated i.V. to give 23 mg of α-tocopheryl methyl ether as an oil ranging in appearance from colorless to light brown. Upon TLC. analysis using 1:1 petroleum ether/ether as the mobil phase, the following Rf values were observed: α-tocopheryl acetate, 0.73; α-tocopherol, 0.63; α-tocopherol methyl ether, 0.79. Spots were detected with 10% methanolic phosphomolybdic acid spray followed by heating.

Gas chromatographic analysis of α-tocopheryl methyl ether diastereoisomers

Gas chromatograph	*Hewlett-Packard* Model 5700
Column and liquid phase	100 m × 0.25 mm (ID.) glass capillary supplied ready coated with cyano silicone oil *Silar* 10 C by *Quadrex Corp.*, Woodbridge, CT, USA.
Temperatures	Column 200°. Injector 250°. Detector (FID) 300°.
Hydrogen carrier gas	Linear velocity 17 cm/s. Approx. split ratio 200:1
Detector gases	N_2 make-up 29 ml/min. H_2 make-up 30 ml/min. Air make-up 300 ml/min.
Sample	Sol. in CH_2Cl_2 1 mg/ml. Vol. injected 2 µl. Approx. mass to column 10 ng
Detector output	To *Computer Inquiry Systems* CALS laboratory data system

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