involves little or no vertical stabilization [18]. (See [19] for a striking example of th kind).

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REFERENCES

[1] *H. R. Pfändler, H. Tanida & E. Haselbach*, Helv. *57*, 383 (1974).
[2] *E. Heilbronner & H. Martin*, Helv. *55*, 1490 (1972); *P. Bischof, J. A. Hashmall, E. Heilbronne & V. Hornung*, Helv. *52*, 1745 (1969).
[3] *E. Heilbronner*, private communication.
[4] *C. Batich, P. Bischof & E. Heilbronner*, J. Electron Spectrosc. *1*, 1 (1972/73).
[5] *R. W. Hoffmann, R. Schüttler, W. Schäfer & A. Schweig*, Angew. Chem. *84*, 533 (1972).
[6] *F. Brogli, E. Giovannini, E. Heilbronner & R. Schurter*, Chem. Ber. *106*, 961 (1973).
[7] *R. Sustmann*, Pure appl. Chemistry *1976*, in press.
[8] *K. N. Houk, J. Sims, C. R. Watts & L. J. Luskus*, J. Amer. chem. Soc. *95*, 7301 (1973) *J. Bastide & O. Henri-Rousseau*, Bull. Soc. chim. France *1973*, 2294 and references there cited.
[9] *K. Müller*, Helv. *53*, 1112 (1970).
[10] *L. Salem*, J. Amer. chem. Soc. *90*, 543, 553 (1968).
[11] *P. Diehl & E. E. Burnell*, Canad. J. Chemistry *50*, 3566 (1972).
[12] a) *M. J. S. Dewar & E. Haselbach*, J. Amer. chem. Soc. *92*, 590 (1970); b) *N. Bodor, M. J. S. Dewar, A. Harget & E. Haselbach*, ibid. *92*, 3854 (1970); c) *J. N. Murrell & A. Harget*, 'Semi-empirical SCF-MO Theory of Molecules', *Wiley*, New York 1972.
[13] *H. D. Martin, C. Heller, E. Haselbach & Z. Lanyiova*, Helv. *57*, 465 (1974); *E. Haselbach & H. D. Martin*, Helv. *57*, 472 (1974).
[14] *V. Rautenstrauch*, Chem. Commun. *1969*, 1122.
[15] *G. W. Gribble, N. R. Easton, Jr. & J. T. Eaton*, Tetrahedron Letters *1970*, 1075.
[16] *G. R. Underwood & H. S. Friedmann*, J. Amer. chem. Soc. *96*, 4989 (1974).
[17] *J. Ipaktschi, M. N. Iqbal & D. Lenoir*, Chem. Ber. *107*, 1126 (1974).
[18] *D. F. Eaton & T. G. Traylor*, J. Amer. chem. Soc. *96*, 1226 (1974) and references there cited.
[19] *A. F. Diaz, J. Fulcher, M. Sakai & S. Winstein*, J. Amer. chem. Soc. *96*, 1264 (1974).

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34. Syntheses of (2*R*,4′*R*,8′*R*)-α-Tocopherol and (2*R*,3′*E*,7′*E*)-α-Tocotrienol

by **John W. Scott, Fred T. Bizzarro, David R. Parrish** and **Gabriel Saucy**
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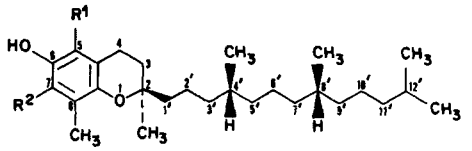
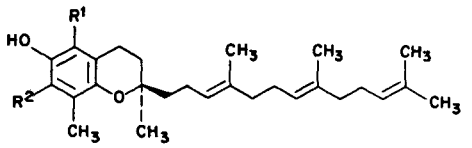
(24. X. 75)

Summary. Reaction of trimethyl-hydroquinone with methyl vinyl ketone in acidic methanol gave *rac.*-2-methoxy-2,5,7,8-tetramethyl-chroman-6-ol (**8**). This acetal was converted in four steps to *rac.*-(6-hydroxy-2,5,7,8-tetramethyl-chroman-2-yl)acetic acid (**13**). Acid **13** was readily resolved with α-methyl-benzylamine to give the (*S*)-enantiomer **14**. Treatment of the unwanted (2*R*)-isomer with acid regenerated **13**, thus leading to an efficient use of this compound. Employing a side chain derived from phytol, **14** was converted to (2*R*, 4′*R*, 8′*R*)-α-tocopherol (**1d**, 'natural' vitamin E). A reaction sequence from **14** involving two highly stereoselective *Claisen* rearrangements has provided the first total synthesis of (2*R*,′*E*, 7′*E*)-α-tocotrienol (**2d**).

Introduction. – Since the isolation by *Evans*[1]) in 1927 of a substance (vitamin E) required by animals for normal reproduction, a total of eight compounds having this 'vitamin E-activity' have been reported[2]). These compounds fall into two distinct groups, the tocopherols (**1**) and the tocotrienols (**2**)[3]). Of these compounds, the biologically most active [5] and the only one having commercial significance is α-tocopherol (**1d**). The illustrated (2*R*,4′*R*,8′*R*) absolute configuration of α-tocopherol was shown by *Mayer, Isler et al.* [6]. This same group has demonstrated [7] that α-tocotrienol also has the (2*R*)-configuration and that the 3′ and 7′ double bonds have



1a	$R^1=R^2=H$	δ-tocopherol
1b	$R^1=H$ $R^2=CH_3$	γ-tocopherol
1c	$R^1=CH_3$ $R^2=H$	β-tocopherol
1d	$R^1=R^2=CH_3$	α-tocopherol



2a	$R^1=R^2=H$	δ-tocotrienol
2b	$R^1=H$ $R^2=CH_3$	γ-tocotrienol
2c	$R^1=CH_3$ $R^2=H$	β-tocotrienol
2d	$R^1=R^2=CH_3$	α-tocotrienol

the (*E*)-stereochemistry. It is now assumed[4]) that all the tocopherols and tocotrienols have the configurations shown.

Despite the commercial significance of (2*R*,4′*R*,8′*R*)-α-tocopherol (**1d**), this compound has been the subject of very few synthetic investigations [2]. The only total synthesis is due to *Mayer, Isler et al.* [8]. In this work, an optically active (chroman-2-yl)carbaldehyde prepared by total synthesis was coupled with a C_{15} phosphonium salt derived from phytol to give a 1′,2′-dehydro-α-tocopherol. Subsequent hydrogenation gave the desired (2*R*,4′*R*,8′*R*)-α-tocopherol.

We now wish to report a conceptually similar synthesis involving however, as the penultimate step, *Wittig* formation of the (2′,3′), rather than the (1′,2′) bond. A facile synthesis of the chroman portion of the molecule has been achieved. Two highly stereoselective *Claisen* rearrangements have allowed the use of this chroman unit also for the synthesis of (2*R*,3′*E*,7′*E*)-α-tocotrienol (**2d**), the probable biogenetic precursor [9] of (2*R*,4′*R*,8′*R*)-α-tocopherol.

Results and Discussion. – *Asymmetric Chromans.* A classical approach [2] to the synthesis of chromans involves the acid-catalyzed reaction of a phenol [*e.g.*, trimethyl-hydroquinone (**3**, TMHQ)] with an allylic alcohol **4**. It occurred to us that protonated methyl vinyl ketone might react with TMHQ in a manner similar to that of an allylic alcohol. When such an experiment was carried out (*Scheme 1*), the results were extremely discouraging in that none of the desired hemiacetal **7** was

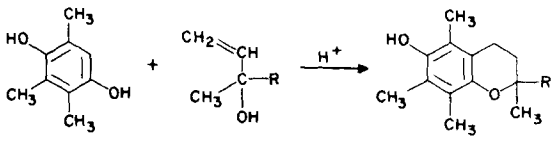
1) For a review of the early history of vitamin E, see [1].

2) For excellent reviews of the chemistry and synthesis of the tocopherols and tocotrienols, see [2] and [3].

3) The recommended *IUPAC-IUB* nomenclature for tocopherols and related compounds is given in [4].

4) For a review of pertinent references, see [3].

obtained. We soon learned, however, that carrying out the reaction in methanol [10] in the presence of a dehydrating agent gave a virtually quantitative yield of the acetal **8**[5]). In addition to effecting the desired condensation, this reaction gave a product in which the two phenolic groups of the starting hydroquinone were chemically

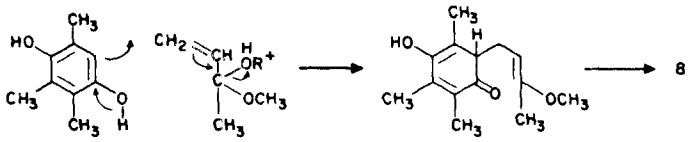


3 4 5

ly differentiated. We made use of this differentiation by acetylation (→ **9**) followed by acidic deacetalization. The resultant ketone **10**, obtained in 90% yield from TMHQ (**3**), exists almost exclusively in the hemiacetal form **10a**. A rapid equilibrium between the two forms apparently occurs, since *Horner*-type reaction of **10** with 2.25 equivalents of the anion from trimethyl phosphonoacetate gave (presumably *via* **11**) the diester **12**. Saponification of the crude **12** gave the racemic acid **13** in 80% yield (from **10**)[6]). Resolution of **13** proved to be no problem and was readily effected with (*S*)-α-methyl-benzylamine. The desired (*S*)-acid **14**[7]) was obtained in 34% yield. Since the acid **13** was formed by a process involving addition of a phenolic hydroxyl group to an α,β-unsaturated ester, it seemed possible that we might be able to use the reverse of this process as a means of racemizing the unwanted (*R*)-enantiomer **15**. This turned out to be the case, since heating the acid (enriched in **15**) recovered from the mother liquors of the resolution with 12N sulfuric acid at reflux gave a 52% yield of racemic acid **13**. Based on a conversion of 48%, the effective yield of (*S*)-acid **14** was thus 71%.

(2R,4′R,8′R)-α-*Tocopherol*. With the asymmetric (chroman-2-yl)acetic acid unit in hand, we turned our attention to the preparation of the C_{14} isoprenoid segment

[5]) A number of observations have led us to the conclusion that hemiacetal **7** is not an intermediate in this reaction. Rather, we believe that the reaction proceeds *via* *i* and *ii* as shown below.

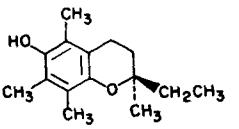


3 i ii 8

R=H or CH_3

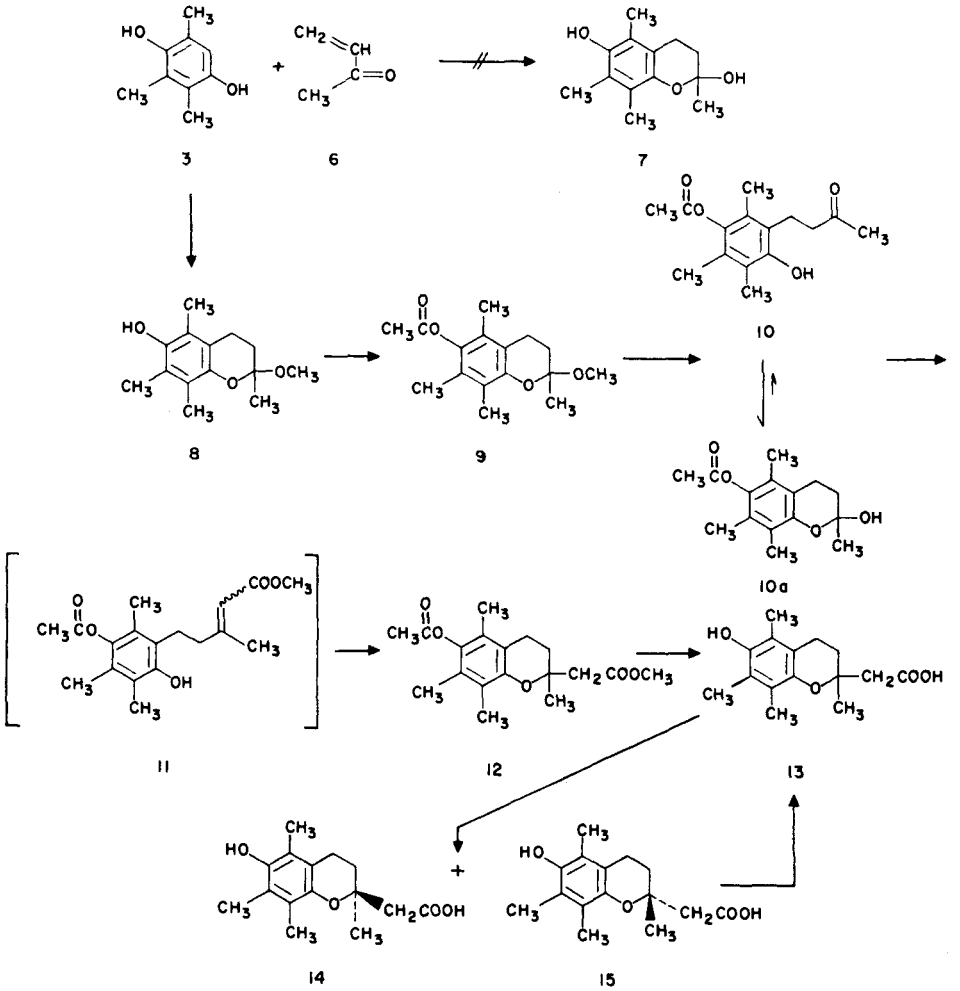
[6]) A brief account of this initial phase of our work has appeared [11] in another context.

[7]) The absolute configuration of this material was established by its conversion to (2*R*, 4′*R*, 8′*R*)-α-tocopherol (*vide infra*) and by the following transformations which gave the known [6] phenol *iii*: a) NaH, $C_6H_5CH_2Br$; b) $NaAlH_2(OCH_2CH_2OCH_3)_2$; c) *p*-$CH_3C_6H_4SO_2Cl$, C_5H_5N; d) $NaBH_4$, DMSO [12]; e) H_2, Pd/C, C_2H_5OH.



iii

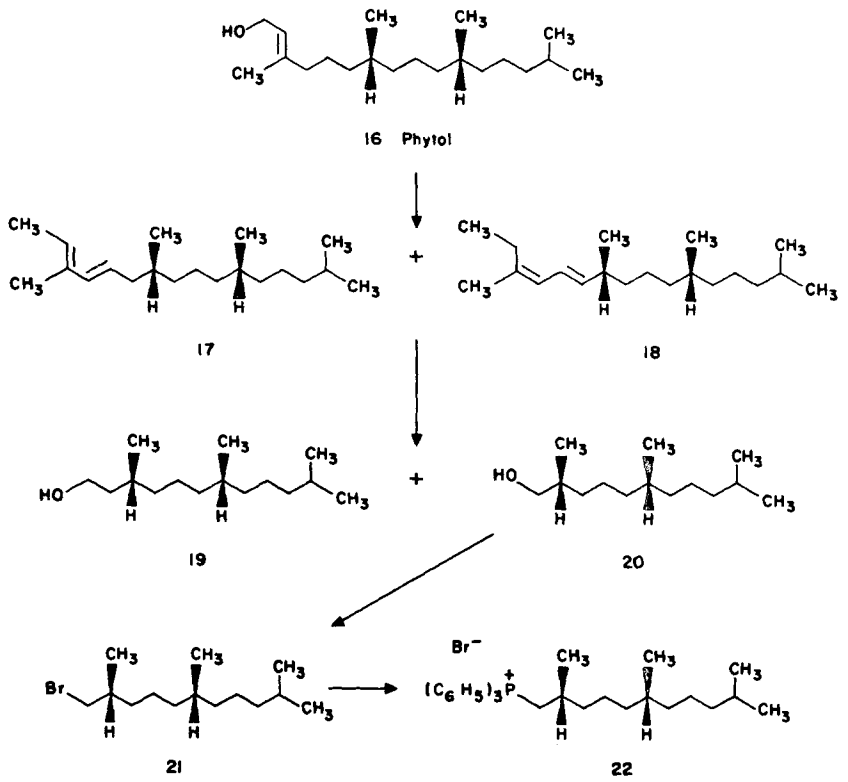
Scheme 1



with which this compound was to be coupled. The desired material was obtained (*Scheme 2*) by modification of the known [8] [13] degradation of (7*R*,11*R*)-phytol (**16**)[8]). The mixture of phytadienes (**17**, **18** and double bond isomers) obtained by the dehydration of phytol was ozonized at −50 to −70° in pentane. The crude ozonide solution was then reduced with $NaAlH_2(OCH_2CH_2OCH_3)_2$. The resultant 1:3 mixture of alcohols **19** and **20** proved to be readily separable by spinning band or, preferably, *Goodloe* column distillation. Treatment of the desired C_{14} alcohol **20** with HBr at 140° [8] gave the bromide **21**. A neat mixture of this bromide and triphenylphosphine was heated at 200° for 6 hours to give the phosphonium salt **22**. This compound was a hygroscopic gum and was used without purification.

[8]) The total synthesis of (7*R*, 11*R*)-phytol has been reported [13]. In this work material of natural origin supplied by the *Aldrich Chemical Co.* was used.

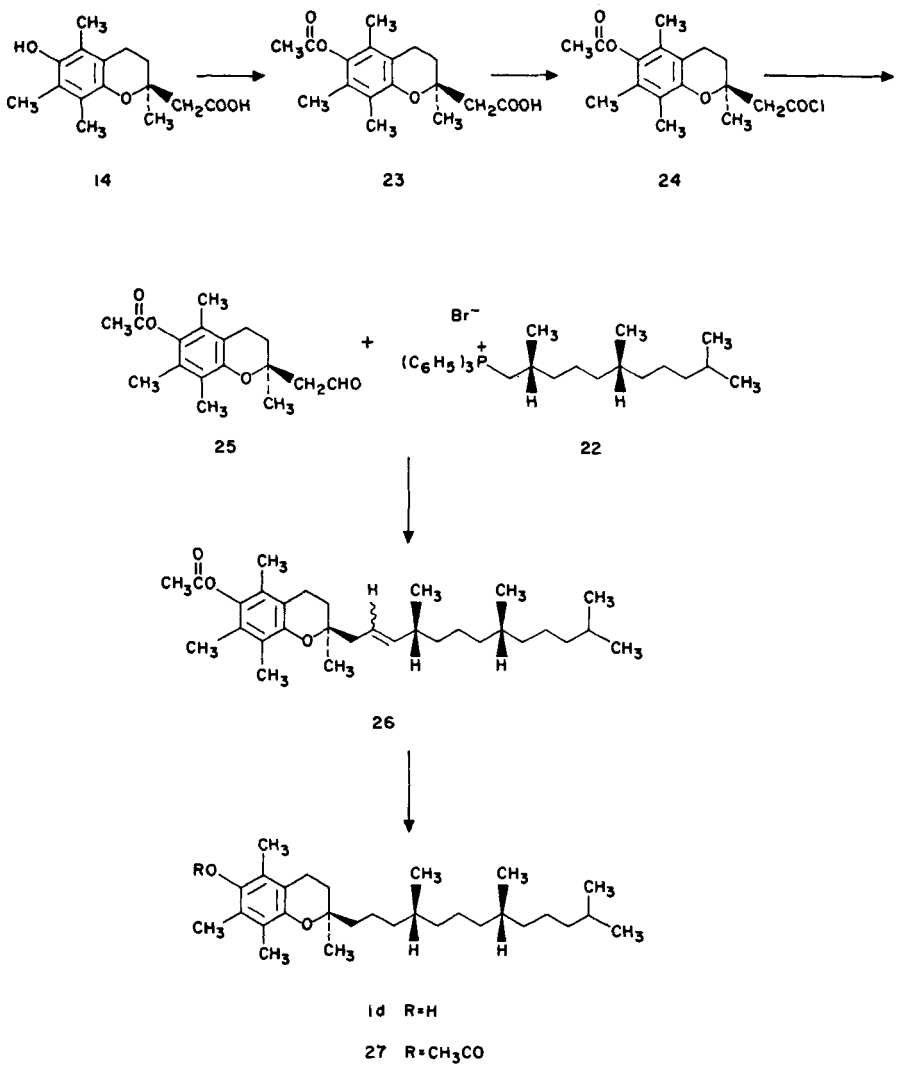
Scheme 2



In order to effect the coupling of the chroman and chain units, it was necessary to modify the functionality of the former. To this end, the acid **14** was acetylated to give the phenol-protected compound **23** (*Scheme 3*). Treatment of this material with oxalyl chloride in benzene gave the unstable acid chloride **24** which was immediately subjected to a modified *Rosenmund* reduction [14]. The aldehyde **25** was thus obtained in 35% yield (from **14**). The *Wittig* coupling of **25** with the phosphonium salt **22** was carried out as described by *Mayer* [8]. Reacetylation of the partially deacylated product mixture gave (2*R*,4′*R*,8′*R*)-2′,3′-dehydro-α-tocopheryl acetate (**26**) as a mixture of double bond isomers. Hydrogenation of this mixture over pre-reduced platinum oxide gave (2*R*,4′*R*,8′*R*)-α-tocopheryl acetate (**27**, 83% yield from **25**) which was identical in all respects with an authentic sample[9]). Reductive saponification of the acetate **27** with $NaAlH_2(OCH_2CH_2OCH_3)_2$ gave a quantitative yield of (2*R*,4′*R*,8′*R*)-α-tocopherol (**1d**). Again, this material was identical with an authentic sample[9]). In addition, the *p*-phenylazobenzoates [15] of synthetic and reference materials were identical, as were the optical rotations of the products of potassium hexacyanoferrate(III) oxidation [16].

[9]) Purchased from *Eastman Kodak Company*.

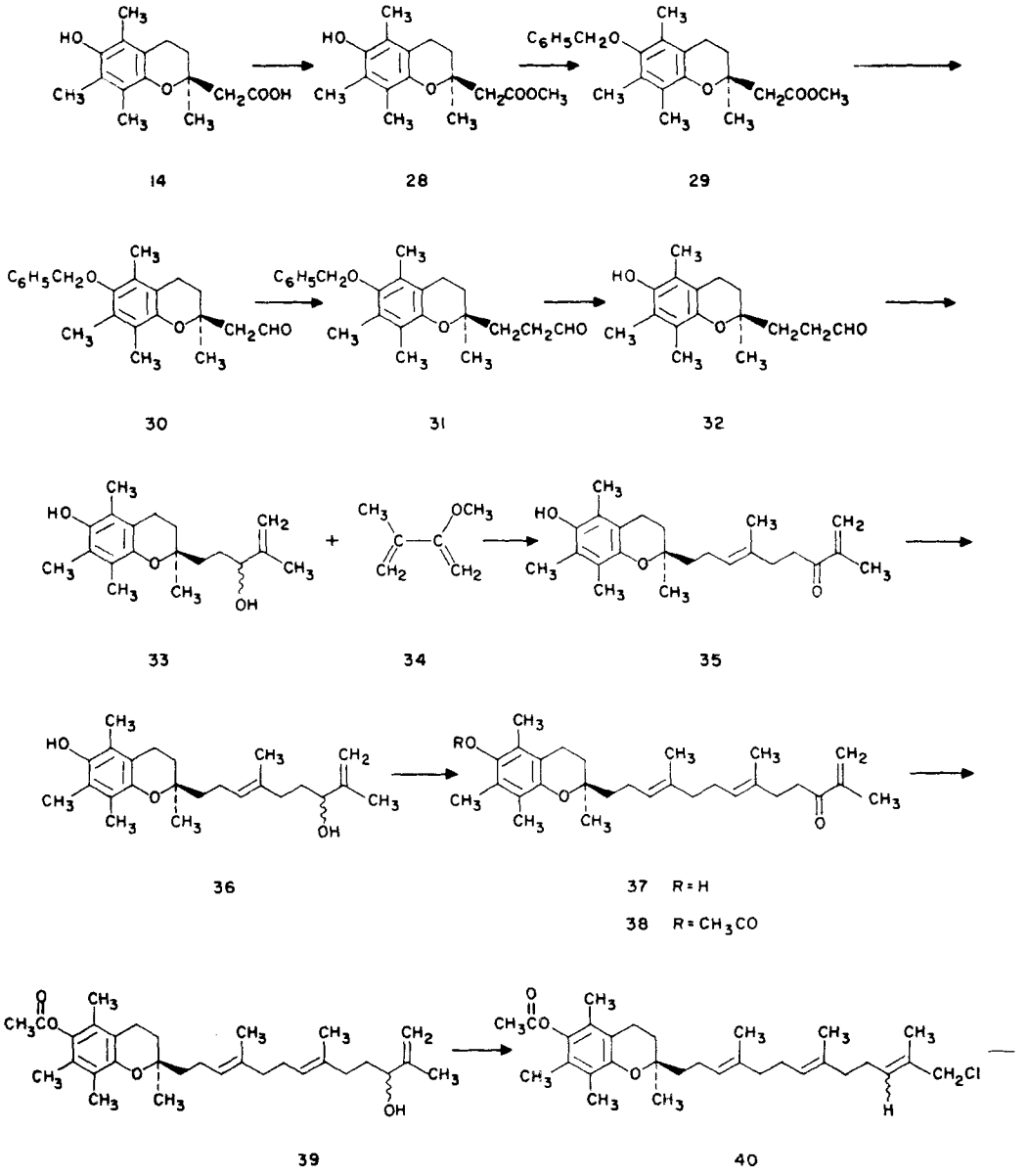
Scheme 3



(2R,3'E,7'E)-α-*Tocotrienol.* The ready availability of the asymmetric (chroman-2-yl)acetic acid **14** combined with recent developments in methodology for the stereoselective synthesis of trisubstituted olefinic bonds[10]) indicated to us that a synthesis of (2*R*,3'*E*,7'*E*)-α-tocotrienol (**2d**) should be attempted. Of the several possible olefin-forming reactions available to us[10]), we chose to concentrate on the highly stereoselective *Claisen* rearrangement employing 2-methoxy-3-methyl-butadiene. This reaction, developed by *Faulkner* [18], gives good yields of (*E*)-trisubstituted olefins contaminated with only traces of the unwanted (*Z*)-isomers and has

[10]) For a review, see [17].

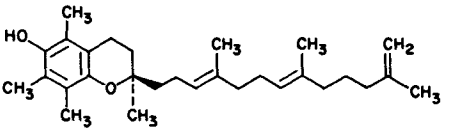
Scheme 4



been employed in an elegant synthesis of squalene. In order to determine if this reaction was suitable for our purposes it was first necessary to synthesize the allylic alcohol **33** (*Scheme 4*). To this end, the acid **14** was esterified with methyl iodide and sodium hydrogencarbonate in dimethylformamide. Etherification of **28** with benzyl chloride and potassium carbonate in dimethylformamide gave **29**. Reduction of the

ester function with diisobutylaluminium hydride [19] in pentane at $-70°$ gave an 80% yield (from **14**) of aldehyde **30**. One-carbon homologation with methoxymethylidenetriphenylphosphorane [20] gave, after acidic hydrolysis of the intermediate enol ether, aldehyde **31**. The benzyl ether protecting group was removed hydrogenolytically to give the phenolic aldehyde **32** (74% from **30**). Reaction of this material with isopropenylmagnesium bromide gave the desired allylic alcohol **33** as a noncrystalline, presumably diastereomeric mixture in 54% yield. Heating a mixture of alcohols **33**, 2-methoxy-3-methyl-butadiene (**34**) [18] and oxalic acid as catalyst at reflux in glyme (1,2-dimethoxyethane) gave an 80% yield of the vinyl ketone **35**. As we had hoped, the phenolic group of **33** was too sterically hindered to react with **34** and no evidence for a mixed acetal was seen. Although the vinyl ketone **35** was noncrystalline, NMR. indicated that the (3',4') double bond had largely, if not exclusively, the (*E*)-configuration. Encouraged by this result, we set forth to introduce the remaining five carbon atoms of the α-tocotrienol skeleton. Thus, reduction of **35** with $NaAlH_2(OCH_2CH_2OCH_3)_2$[11]) gave the diastereomeric alcohols **36**. Repetition of the homologation sequence gave the vinyl ketone **37**, which was acetylated to give **38** (37% yield from **32**). Although noncrystalline, this material was homogeneous on three GLC. columns. In addition, NMR. indicated, as expected, that the (3',4') and (7',8') double bonds had the required (*E*)-configuration.

With vinyl ketone **38** in hand, it was only necessary to modify the terminal functionality to obtain our synthetic goal. For this purpose we used the sequence employed by *Faulkner* [18] in his squalene synthesis. Thus, $NaBH_4$ reduction gave the diastereomeric alcohols **39** (contaminated with *ca.* 20% saturated alcohol[11]). This mixture was treated with thionyl chloride and the chloride **40** was reduced with $LiAlH_4$. Although the α-tocotrienol (**2b**) thus obtained was of greater than 98% purity under GLC. conditions known [21] to separate the (*Z*,*E*)-isomers, NMR. clearly showed the presence of *ca.* 20% of an impurity which we believe to be the isomer **41**. Extremely careful GLC. (6 h run) confirmed the presence of such an



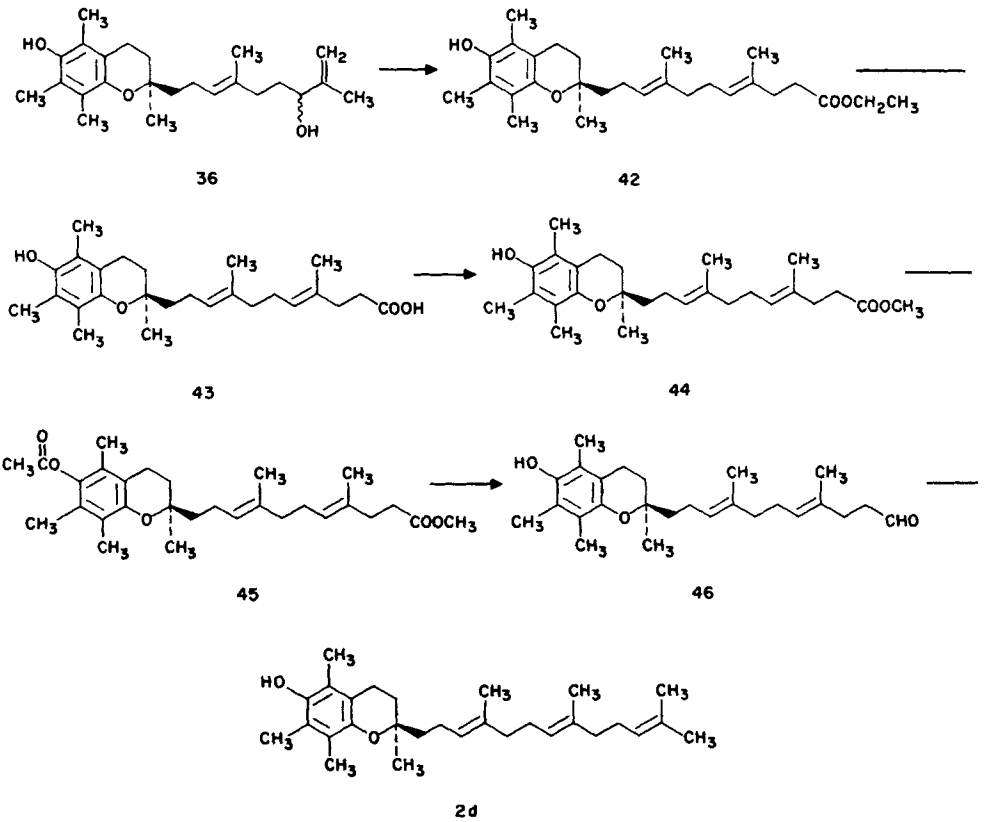
41

impurity. All attempts to separate compounds **41** and **2d** proved fruitless and, despite rigorous purification of reagents and control of the reaction conditions [22], we were never able to obtain mixtures containing less than 10% of isomer **41**.

In order to circumvent the isomer problems, another approach to the introduction of the final five carbon atoms was employed (*Scheme 5*). Treatment of the alcohols **36** with triethyl orthoacetate and a trace of propionic acid according to the method of *Johnson* [23] gave, after chromatography and distillation, a 78% yield of ester **42**. GLC. analysis indicated a 94% purity with at least six impurity peaks present.

[11]) We found reduction with $NaBH_4$, as recommended by *Faulkner* [18], to be inferior since significant amounts of saturated alcohol were obtained.

Scheme 5



It appeared that most of the impurities were of chemical nature rather than being geometrical isomers since they generally had significantly different GLC. retention times from that of **42**. The MS. of **42** showed minor peaks at $M^+ - 28$, $M^+ - 14$ and $M^+ + 14$. The largest impurity peak (2.6%) was shown by GLC./MS. to have a molecular weight of 428 (mol.-wt. of **42** = 442).

Saponification of the ester **42** gave acid **43**. After 2 crystallizations from acetonitrile, acid of m.p. 100.5–102° was obtained in 74% yield. This material was determined to be of >99% purity by GLC., thus indicating that we had succeeded in removing not only chemical impurities, but also whatever isomeric impurities were present.

The completion of the synthesis was then straightforward. Esterification ($NaHCO_3$, methyl iodide, dimethylformamide, 80% yield) gave **44** which was acetylated (85% yield) to give the diester **45**. Treatment of this material with diisobutylaluminum hydride at −70° [19] caused reduction of both ester groups. Treatment of the aldehyde **46** with isopropylidenetriphenylphosphorane gave, after chromatography and distillation, an 80% yield (from **45**) of (2*R*,3′*E*,7′*E*)-α-tocotrienol (**2d**) which was homogeneous by GLC. [21]. Subsequent crystallization from methanol at −70° gave

material of m.p. 31.5–32°, $[\alpha]_D^{25} = -5.71°$ ($c = 1.02$, $CHCl_3$)[12]. The IR. and NMR. of this material agreed completely with those[13]) of (2*R*,3'*E*,7'*E*)-α-tocotrienol [21] isolated from natural sources. These, and other spectral data, confirmed the structure of the product and its homogeneity.

The overall yield of (2*R*,3'*E*,7'*E*)-α-tocotrienol from THMQ was 3.44%, an average of 84.5% for each of the 20 steps.

The authors wish to thank the members of our Physical Chemistry Department for their help during this work. In addition we acknowledge the encouragement given us by Dr. *A. Brossi*, helpful discussions with Drs. *H. Mayer* and *R. Rüegg* and, in particular, Dr. *O. Isler* who pointed out the desirability of attempting a synthesis of (2*R*, 3'*E*, 7'*E*)-α-tocotrienol.

Experimental

General. M.p. were determined on a *Thomas Hoover* capillary melting point apparatus and are not corrected. Spectral and gas chromatographic measurements were performed by members of the Physical Chemistry Department of *Hoffmann-La Roche Inc.* using the following instruments: NMR., *Varian* A-60 or HA-100 spectrometer with tetramethylsilane as internal standard and, unless otherwise specified, deuteriochloroform as solvent (chemical shifts in δ (ppm) and coupling constants in Hz); IR., *Beckmann* IR 9 spectrometer with chloroform as solvent unless otherwise noted (absorptions in cm^{-1}); UV., *Cary* Model 14 spectrometer with ethanol as solvent (λ_{max} in nm, ε in parentheses); MS., *Joelco* OISG or CEC 21-110 spectrometers with a direct inlet system (70 eV); GLC., *Hewlett-Packard* HP5710A gas chromatograph. The phrase 'worked-up as usual' indicates extraction or dilution with the indicated solvent, washing, where appropriate, with H_2O, 2N HCl, saturated $NaHCO_3$, and/or saturated brine, drying (Na_2SO_4), and solvent removal in a rotary evaporator at 30–50°. Chromatography was carried out on *E. Merck* Silica Gel 60 (0.063–0.200 mm). Thin layer chromatograms (TLC.) were run on *E. Merck* pre-coated Silica Gel 60 F-254 plates in tanks saturated with the indicated solvent mixtures. The spots were detected by: a) observation under a 254 nm source, b) spraying with a 5% solution of phosphomolybdic acid in ethanol, and c) heating with a hot air gun. Phenolic compounds are particularly sensitive to the latter reagent and, in many cases, develop blue spots with little or no heating. Abreviations: THF = Tetrahydrofuran, RT. = room temperature.

rac.-*6-Acetoxy-2,5,7,8-tetramethyl-chroman-2-ol* (**10a**). To a degassed solution of 304.4 g (2.0 mol) of trimethyl-hydroquinone in 1.2 l of methanol and 0.3 l of trimethyl orthoformate under N_2, and cooled in an ice bath to 3°, 5.0 ml of concentrated sulfuric acid were added followed, dropwise over 3 h, by 340 ml (*ca.* 4.0 mol) of methyl vinyl ketone. The suspension was stirred without cooling for 44 h (completion of the reaction checked by TLC. (benzene/ethyl acetate 4:1)). The mixture was worked-up as usual with ether to give, after drying at 50°/0.1 Torr, 490 g of crude acetal **8** as a light tan solid. A sample prepared in a similar manner from recrystallized trimethyl-hydroquinone and redistilled methyl vinyl ketone was crystallized from methanol to give analytically pure rac.-*2-methoxy-2,5,7,8-tetramethyl-chroman-6-ol* (**8**) as white crystals: m.p. 125–126°. – IR.: 3625 (phenolic OH). – UV.: 220 (10,500) 288 (2860). – NMR.: 1.52 (*s*, 3 H, H_3C–C(2); and 2.14 (2 *s*, 3 H and 6 H, 3 H_3C–Ar); 3.18 (*s*, 3 H, OCH_3); 4.33 (*s*, 1 H, OH)). – MS. (*m/e*): 236 (M^+), 165 (100%).

$C_{14}H_{20}O_3$ (236.30) Calc. C 71.16 H 8.53% Found C 71.32 H 8.56%

To a solution of the crude acetal **8** in 600 ml of pyridine were added 900 ml of acetic anhydride. The orange solution was degassed and stirred under N_2 at 23° for 18 h. It was then poured into 8 l of ice/H_2O to give a suspension which was stirred at 23° for 3 h. After *ca.* 1 h, seeding with acetate **9** caused the suspended oil to crystallize. The solid was removed by filtration, washed with H_2O, and worked up in the usual manner with methylene chloride to give 570 g of red-brown oil which slowly crystallized upon standing. A similarly prepared sample was distilled at 175–180°/0.015 Torr to give analytically pure rac.-*2-methoxy-2,5,7,8-tetramethyl-chroman-6-yl-acetate* (**9**) as

[12]) To our knowledge, there is no reported melting point or rotation for (2*R*, 3'*E*, 7'*E*)-α-tocotrienol.

[13]) Kindly supplied by Dr. *H. Mayer*.

a colorless oil which soon crystallized: m.p. 71–72.5°. – IR.: 1755 (acetate). – UV.: 223 (9670), 273 (1410), 279.5 (1530), 282.5 (1530). – NMR.: 1.52 (*s*, 3 H, H_3C–C(2)); 1.99, 2.04 and 2.15 (3 *s*, 9 H, 3 H_3C–Ar); 2.29 (*s*, 3 H, H_3C–COO); 3.20 (*s*, 3 H, CH_3–O).

$C_{16}H_{22}O_4$ (278.34) Calc. C 69.04 H 7.97% Found C 69.35 H 8.00%

To a solution of the crude acetate **9** in 2.5 l of acetone were added 2 l of H_2O followed by 16.6 ml of concentrated hydrochloric acid. Solvent was distilled from the stirred mixture until the head temperature reached 90°. The suspension was cooled to 50°: at 70°, 2 l of acetone were added, and the clear solution was seeded occasionally until crystallization began. After 3.5 h, 1.5 l of H_2O were added and the suspension was cooled in an ice bath. The solid was removed by filtration, washed with H_2O and dried at 50°/0.1 Torr to give acetoxy hemiacetal **10a** as 475.4 g (90%) of granular yellow-tan solid, sintering from 114°, m.p. 127–132° TLC. (benzene/ethyl acetate 4:1) showed traces of two impurities (Rf = 0.65 and 0.51) in addition to the spot for acetoxy hemiacetal **10a** (Rf = 0.33). A similarly prepared sample was crystallized twice from acetone/H_2O to give analytically pure **10a** as white prisms: m.p. 124–126°. – IR.: 3600 (OH), 1753 (acetate). – UV.: 223 (sh, 10,000), 275.5 (1500), 282.5 (1740). – NMR.: 1.63 (*s*, 3 H, H_3C–C(2)); 2.00, 2.07 and 2.15 (3*s*, 9 H, 3 H_3C–Ar), 2.35 (*s*, 3 H, H_3C–COO); 2.90 (*s*, 1 H, OH). – MS. (*m/e*): 264 (M^+), 221 (100%), 164.

$C_{15}H_{20}O_4$ (264.31) Calc. C 68.16 H 7.63% Found C 68.45 H 7.59%

rac.-(*6-Hydroxy-2,5,7,8-tetramethyl-chroman-2-yl)acetic Acid* (**13**). To a stirred suspension of 47.2 g (1.10 mol) of 56% NaH in mineral oil in 1 l of dry THF and under N_2, 209.4 g (1.15 mol) of trimethyl phosphonoacetate (*Aldrich*) were added over 2.25 h. The white paste was stirred for 1/4 h and then a solution of 132.2 g (0.50 mol) of acetoxy hemiacetal **10a** in 1 l of THF was added over 1/2 h. The pale yellow suspension was stirred at 23° for 18 h and then heated at reflux for 4 h. The cooled solutions from two such reactions were stripped of solvent and worked-up with ether in the usual manner to give 366 g of the diester **12** as a cloudy red-brown oil. To a solution of this material in 2 l of ethanol were added 2 l of H_2O and 240 g (6.0 mol) of NaOH. The solution was stirred at 23° for 4 h, washed with petroleum ether (30–60°), diluted with 6 l of ice/H_2O and acidified by the dropwise addition over 1/2 h of 600 ml of concentrated hydrochloric acid. The thus formed solid was removed by filtration, washed with H_2O and crystallized from ethanol/H_2O to give acid **13** as 211.4 g (80%) of light tan powder, m.p. 168–171°. A similarly prepared sample was crystallized again (charcoal) from ethanol/H_2O to give the analytical sample as a white powder: m.p. 172–174°. – IR. (KBr): 3500 (phenol OH), 3400–2300 (carboxylic acid), 1670 (acid C=O). – UV.: 225 (11,200), 291.5 (3150). – NMR. (CD_3OD): 1.40 (*s*, 3 H, H_3C–C(2)); 2.05, 2.08 and 2.11 (3*s*, 9 H, 3 H_3C–Ar); 2.55 (*s*, 2 H, –CH_2COOH). – MS. (*m/e*): 264 (M^+, 100%), 165.

$C_{15}H_{20}O_4$ (264.31) Calc. C 68.16 H 7.63% Found C 68.00 H 7.78%

(S)-(*6-Hydroxy-2,5,7,8-tetramethyl-chroman-2-yl)acetic Acid* (**14**). To a solution of 26.43 g (0.10 mol) of *rac.*-acid **13** in 500 ml of tetrahydrofuran were added 15 ml (ca. 115 mmol) of (*S*)-α-methyl-benzylamine (*Aldrich*). The mixture was stirred at 25° under N_2 for 1 h, filtered and stripped of solvent to give a brownish resin. Two crystallizations from methanol/ether gave 13.65 g of α-methyl-benzylamine salt as shiny, cream-white prisms, sintering at 162°, m.p. 164–166°, $[\alpha]_D^{25} = -15.20°$ (*c* = 1.04, C_2H_5OH). A similarly prepared sample was crystallized again to give analytically pure (*S*)-(6-hydroxy-2,5,7,8-tetramethyl-chroman-2-yl)acetic acid (*S*)-α-methyl-benzylamine salt as colorless prisms: m.p. 164–166.5°, $[\alpha]_D^{25} = -15.66°$ (*c* = 1.0088, C_2H_5OH). – IR. (KBr): 3600–2000 (OH, acid salt). – UV.: 225 (9400), 291.5 (3350).

$C_{23}H_{31}N_1O_4$ (385.49) Calc. C 71.66 H 8.11 N 3.63% Found C 71.80 H 8.34 N 3.54%

A suspension of the α-methyl-benzylamine salt in 200 ml of ether and 200 ml of 2 N HCl was stirred at 23° for 1 h and worked-up as usual to give a cream-white solid. Crystallization from ethanol/H_2O gave 9.20 g (35%) of acid **14** as a white granular solid, m.p. 145.5–148.5°, $[\alpha]_D^{25} = -14.8°$ (*c* = 0.915, C_2H_5OH). A similarly prepared sample was recrystallized to give analytically pure material as fine, white prisms: m.p. 124–127°[14]; $[\alpha]_D^{25} = -15.39°$ (*c* = 0.9878, C_2H_5OH). – IR., UV., NMR. and MS. identical with those of racemic acid **13**.

$C_{15}H_{20}O_4$ (264.31) Calc. C 68.16 H 7.63% Found C 68.33 H 7.62%

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[14]) Apparently polymorphic forms of this compound exist. Our first samples had this lower m.p., (124–127°) while later preparations had the higher m.p. (146–149°).

(S)-(6-Hydroxy-2,5,7,8-tetramethylchroman-2-yl)acetic Acid (**14**) *with racemization of the* (R)-*enantiomer* **15**. A suspension of 13.22 g (50 mmol) of *rac.*-acid **13** in 30 ml of methanol and 170 ml of ether was stirred at 20° as 7.5 ml (*ca.* 62.5 mmol) of (*S*)-α-methyl-benzylamine (*Aldrich*) were added. The solution was immediately seeded with the (*S*)-acid (*S*)-salt. Stirring and cooling, finally to – 20°, gave 7.80 g of white powder. Crystallization from 25 ml of methanol and 175 ml of ether gave 6.78 g of (*S*)-acid (*S*)-salt as a white powder, m.p. 162.5–165°, $[\alpha]_D^{25} = -13.68°$ ($c = 0.9942$, C_2H_5OH). Conversion of this salt to the free acid **14** and crystallization as above gave 4.50 g (34%) of white powder: m.p. 146–149°[14], $[\alpha]_D^{25} = -16.89°$ ($c = 1.2147$, C_2H_5OH). The mother liquors from the preparation and crystallization of the (*S*)-acid (*S*)-salt were stripped of solvent to give 19.3 g of orange-brown resin which was converted as above to free acid, giving 8.70 g of tan solid. This acid, enriched in the (*R*)-enantiomer **15**, was suspended in 480 ml of 12N H_2SO_4, degassed, placed under N_2, and heated at reflux for 30 h. Work-up of the red-orange suspension with ethyl acetate in the usual manner gave 8.40 g of brown solid. This material was triturated with 60 ml of hot ether, cooled to – 20°, and filtered. The resulting 7.1 g of tan powder were crystallized from 25 ml each of ethanol and H_2O to give 6.88 g (52%) of *rac.*-acid **13** as a light tan powder: m.p. 173.5–175°, mixed m.p. with authentic acid undepressed, $[\alpha]_D^{25} = \pm 0°$ ($c = 0.9463$, C_2H_5OH). The effective yield of (*S*)-acid **14** was thus 71%, based on a conversion of 48%. – NMR., IR., UV., and MS. identical with those of authentic *rac.*-acid.

(S)-(6-Acetoxy-2,5,7,8-tetramethyl-chroman-2-yl)acetic Acid (**23**). A mixture of 62.5 g (0.237 mol) of (*S*)-acid **14**, 250 ml of pyridine and 150 ml of acetic anhydride was degassed, placed under N_2, and stirred for 20 h. The solution was poured into ice/H_2O, stirred 2 h, and worked-up with ether in the usual manner. The yellow resin obtained upon solvent removal was crystallized from acetone/hexane to give 55.3 g (72%) of acetate **23** as a white powder: sintering at 121°, m.p. 123–125.5°, $[\alpha]_D^{25} = -14.62°$ ($c = 0.9900$, C_2H_5OH). A similarly prepared sample, after drying at 60°/0.005 Torr, had m.p. 125–126.5°, $[\alpha]_D^{25} = -15.56°$ ($c = 0.9770$, C_2H_5OH). – IR.: 3500–2800 (carboxylic acid), 1758 (acetate C=O), 1720 (acid C=O). – UV.: 223 (*sh*, 10,600), 276 (1670), 282.5 (1860). – NMR.: 1.45 (*s*, 3 H, H_3C–C(2)); 1.98, 2.02 and 2.08 (3*s*, 9 H, 3 H_3C—Ar); 2.32 (*s*, 3 H, H_3C—COO); 2.67 (*s*, 2 H, –CH_2COOH); 11.00 (*s*, 1 H, COOH). – MS. (*m/e*): 306 (M^+), 264 (100%), 164.

$C_{17}H_{22}O_5$ (306.35) Calc. C 66.65 H 7.24% Found C 66.74 H 7.27%

(S)-(6-Acetoxy-2,5,7,8-tetramethyl-chroman-2-yl)acetaldehyde (**25**). A solution of 27.30 g (89 mmol) of acetoxy acid **23** in 200 ml of benzene was heated in a 50° oil bath as 40 ml of oxalyl chloride were added over 30 min (gas evolution). The orange solution was heated 15 min, cooled and stripped of solvent. The residue was twice diluted with dry toluene and stripped to remove residual oxalyl chloride. A mixture of the resultant acid chloride **24**, 25 g of sodium acetate (dried 18 h at 105°/0.05 Torr), 2.5 g of Pd/C (10%) (dried 18 h at 105°/0.05 Torr), 0.50 ml of quinoline and 250 ml of dry toluene was hydrogenated on a *Parr* apparatus at 30–60 psi. After 22 h, the uptake of hydrogen had ceased. The catalyst was removed by filtration and washed with benzene. The combined filtrates were stripped of solvent and worked-up with ether in the usual manner. The crude product was chromatographed (elution with benzene/ethyl acetate 95:5) and crystallized twice from acetone/hexane to give the aldehyde **25** as 12.72 g (49%) of shiny needles: m.p. 86–87.5°, $[\alpha]_D^{25} = +7.13°$ ($c = 1.0796$, C_6H_6). The analytical sample, similarly prepared, was obtained as small, colorless rods: m.p. 87.5–90°, $[\alpha]_D^{25} = +7.51°$ ($c = 1.0119$, C_6H_6). – IR.: 2760 (aldehyde C–H), 1755 (acetate C=O), 1730 (aldehyde C=O). – UV.: 225 (9500), 277.5 (1740), 284 (1950). – NMR.: 1.40 (*s*, 3 H, H_3C–C(2)); 1.98, 2.02 and 2.09 (3*s*, 9 H, 3 H_3C—Ar); 2.32 (*s*, 3 H, H_3C—COO); 8.25 (*t*, $J = 2.5$, 1 H, CHO). – MS.: (*m/e*): 290 (M^+). 248 (100%), 164.

$C_{17}H_{22}O_4$ (290.36) Calc. C 70.32 H 7.64% Found C 70.55 H 7.74%

(2R,6R)-2,6,10-Trimethyl-undecan-1-ol (**20**). Phytol (**16**, *Aldrich*) was dehydrated to mixed $\Delta^{2,4}$- and $\Delta^{3,5}$-phytadienes (**17**, **18**) by the published procedure [8]. A solution of 21.25 g (76.5 mmol) of this material, b.p. 131–140°/0.5 Torr, in 150 ml of pentane was cooled to – 50°. Ozone (0.80–0.88 mmol/min) was bubbled through the solution at – 50° to – 70° for 3.5 h (total O_3 = *ca.* 175 mmol). Nitrogen was then introduced for 20 min. The ozonide solution was transferred to a cooled (– 7°) dropping funnel and added, dropwise over 1.5 h, to 107 ml of 70% $NaAlH_2(OCH_2CH_2OCH_3)_2$ solution (*Aldrich* Red-Al®) cooled in an ice/salt bath (internal temp. during addition 5–8°). The solution was allowed to come to 20°, stirred at 20° for 1 h, and poured onto ice and

80 ml of 10N NaOH. Work-up in the usual manner with ether gave a pale yellow oil. The product from four such reactions (95.4 g) was distilled through a *Vigreux* column (20 cm) to give a mixture of (2*R*,6*R*)-2,6,10-trimethyl-undecan-1-ol (**20**) and (3*R*,7*R*)-3,7,11-trimethyl-dodecan-1-ol (**19**) in a ratio of *ca.* 3:1 by GLC. (10% SE-30, 160°). The desired C_{14} alcohol **20** was separated from this mixture by distillation through a spinning band or 30 cm *Goodloe* column and obtained as a colorless liquid: b.p. 76–78°/0.05 Torr, $[\alpha]_D^{25} = +9.36°$ ($c = 2.02$, C_6H_{14}). – IR.: 3640 (OH). – NMR.: 1.99 (*s*, 1 H, OH); 3.47 (br. *d*, $J = 5$, 2 H, CH_2OH). – MS. (*m/e*): 196 ($M^+ - H_2O$).

$C_{14}H_{30}O$ (214.38) Calc. C 78.43 H 14.11% Found C 78.68 H 14.25%

(2R,6R)-*1-Bromo-2,6,10-trimethylundecane* (**21**). 21.4 g (0.10 mol) of alcohol **20** were stirred and heated at 140° as HBr gas was bubbled in. After 4 h, the two-phase mixture was cooled and worked-up with petroleum ether (30–60°) as usual. The crude material was filtered through *Woelm* neutral Alumina III with petroleum ether (30–60°) and distilled to give 25.1 g (91%) of bromide **21** as a colorless oil, b.p. 94–95°/0.25 Torr. The analytical sample was similarly prepared: b.p. 80–82°/0.05 Torr, $[\alpha]_D^{25} = -0.73$ ($c = 1.9204$, C_6H_{14}). – IR.: no bands for functional groups. – NMR.: 3.35 (*d*, $J = 5.5$, 2 H, CH_2Br). – MS. (*m/e*): 276 (M^+), 113, 71 (100%).

$C_{14}H_{29}Br$ (277.28) Calc. C 60.61 H 10.54 Br 28.82%
Found ,, 60.54 ,, 10.56 ,, 28.62%

(2R,4'R,8'R)-α-*Tocopheryl Acetate* (**27**). The procedure of *Mayer* [8] was used with only slight variation. A mixture of 6.66 g (24 mmol) of the bromide **21** and 6.56 g (25 mmol) of triphenylphosphine was degassed, and heated at 200° under N_2 for 6 h. Cooling gave the phosphonium salt **22** as a clear glass which was dissolved in 100 ml of glyme (distilled from CaH_2). This solution was treated at 20°, *via* syringe, with a 2.4M solution of phenyllithium in benzene/ether 70:30 (*Ventron*) until the red color of the ylide appeared. An additional 9.16 ml (20 mmol) of phenyllithium solution were then added. The resultant dark red solution was stirred for 15 min and a solution of 2.90 g (10 mmol) of aldehyde **25** in 25 ml of glyme was added over 5 min. The resulting red-orange solution was heated at 60° for 3 h, poured into ice and 100 ml of 1N H_2SO_4, and worked-up with ether as usual. The crude mixture was reacetylated with 50 ml of acetic anhydride/pyridine 1:1 at 20° under N_2 overnight, poured into ice/H_2O, stirred 30 min, and worked-up as usual with ether. Chromatography with benzene gave (2R,4'R,8'R)-*2',3'-dehydro-α-tocopheryl acetate* (**26**) as a yellow resin. A similarly prepared sample was distilled to give a viscous, slightly yellow resin: b.p. 200°/0.005 Torr, $[\alpha]_D^{25} = +13.56°$ ($c = 0.8260$, C_2H_5OH). – IR.: 1745 (acetate C=O). – UV.: 227 (sh, 10,385), 278 (1795), 284.5 (2030). – NMR.: 1.99, 1.03 and 2.11 (3*s*, 9 H, 3 H_3C–Ar); 2.29 (*s*, 3 H, H_3C–COO); 5.35 (*m*, 2 H, *cis* and *trans* –CH=CH–). – MS. (*m/e*): 484 (M^+), 247 (100%). $C_{31}H_{50}O_3$ (470.71) Calc. C 79.10 H 10.71% Found C 78.92 H 10.49%

A solution of the chromatographed unsaturated acetate **26** in 25 ml of ethyl acetate was added to a suspension of 500 mg of prereduced platinum oxide in ethyl acetate and the mixture was hydrogenated at atmospheric pressure and RT. After 18 h, the uptake of hydrogen was complete, and the catalyst was removed by filtration and washed with ethyl acetate. Solvent removal, followed by distillation, gave 3.90 g (83%) of (2*R*.4'*R*,8'*R*)-α-tocopheryl acetate (**27**) as a slightly yellow, viscous oil: b.p. 200°/0.004 Torr, $[\alpha]_D^{25} = +3.42°$ ($c = 0.9945$, C_2H_5OH). The authentic sample had $[\alpha]_D^{25} = +3.34°$ ($c = 1.0175$, C_2H_5OH) (Lit. [3] $[\alpha]_D^{25} = +3.2°$ (C_2H_5OH)). The IR., UV., NMR. and MS. of the synthetic material were the same as those of an authentic material (*Eastman Kodak*, highest purity). – The material was 97.4% pure by GLC. (10° OV-101, 250°; retention time 69.5 min; coinjection with authentic material gave one peak).

(2R,4'R,8'R)-α-*Tocopherol* (**1d**). To a stirred solution of 2.8 ml (10 mmol) of $NaAlH_2(OCH_2CH_2OCH_3)_2$ (*Aldrich* Red-Al®) in 25 ml of anhydrous ether was added over 15 min a solution of 2.36 g (5.0 mmol) of the acetate **27** in 10 ml of ether. The solution was stirred 1 h, poured onto ice and 6N H_2SO_4, and worked-up in the usual manner with ether. Distillation gave **1d** as a pale yellowish resin: b.p. 200°/0.005 Torr, $[\alpha]_D^{25} = -3.58°$ ($c = 1.0895$, C_6H_6) [Lit. [24] $[\alpha]_D^{25} = -3.0°$ (C_6H_6)]. – IR., UV., MS., and NMR. identical with those of an authentic sample (*Eastman Kodak Co.*, from vegetable oil). – GLC.: 97.7% purity (10% OV 101, 250°; retention time 61.9 min).

The material was subjected to $K_3Fe(CN)_6$ oxidation in the usual manner [16] and the crude product was chromatographed with petroleum ether (30–60°)/ether 98:2. TLC. (petroleum ether (30–60°)/ether 9:1) showed the material thus obtained to be contaminated with a small amount

of a faster running material. The yellow resins from the synthetic and authentic α-tocopherols had $[\alpha]_D^{25} = +36.1°$ ($c = 1.60$, hexane) and $[\alpha]_D^{25} = +36.4°$ ($c = 1.61$, hexane), respectively (Lit. [15] $[\alpha]_D^{25} = +24$ to $+28°$ (isooctane) for unchromatographed samples). Both samples of α-tocopherol gave a 3,5-dinitrobenzoate sintering at 84°, m.p. 88–90°, mobile at 93° (Lit. [25] m.p. 86–87°), from ethanol. The *p*-phenylazobenzoate of the synthetic α-tocopherol had m.p. 61–63.5°, $[\alpha]_{600}^{25} = +7.26°$ ($c = 0.639$, $CHCl_3$) (Lit. [3] m.p. 62–65; Lit. [15] $[\alpha]_{600}^{25} = +7.07°$ ($CHCl_3$)).

(S)-(*6-Benzyloxy-2,5,7,8-tetramethyl-chroman-2-yl*)-*acetaldehyde* (**30**). To a solution of 6.608 g (25 mmol) of (*S*)-(6-hydroxy-2,5,7,8-tetramethyl-chroman-2-yl)acetic acid (**14**) in 25 ml of dimethylformamide were added 10.50 g (125 mmol) of $NaHCO_3$ and 7.8 ml (17.7 g = 125 mmol) of methyl iodide. The mixture was degassed and stirred under N_2, at RT. TLC. (benzene/ethyl acetate/acetic acid 90:10:2) showed the reaction to be complete after 30 h. The mixture was poured into H_2O and worked-up with ether as usual to give crude methyl (*S*)-(6-hydroxy-2,5,7,8-tetramethyl-chroman-2-yl)acetate (**28**) as an orange oil. A similarly prepared sample was chromatographed (elution with benzene/ethyl acetate 97.5:2.5) and distilled at 160°/0.04 Torr to give a very slightly yellow resin: $[\alpha]_D^{25} = -19.33°$ ($c = 1.0397$, C_6H_6). – IR.: 3640 (OH), 1735 (ester C=O). – UV.: 223 (sh, 10,000), 290 (3150). – NMR.: 1.42 (*s*, 3 H, H_3C—C(2)); 2.10 and 2.14 (2*s*, 6 H and 3 H, 3 H_3C—Ar); 2.61 (*s*, 2 H, —CH_2COO—); 3.68 (*s*, 3 H, $COOCH_3$); 4.58 ppm (*s*, 1 H, OH). – MS. (*m/e*): 278 (M^+, 100%), 165, 164.

$C_{16}H_{22}O_4$ (278.34) Calc. C 69.04 H 7.97% Found C 68.75 H 7.97%

To a solution of the crude ester **28** in 25 ml of dimethylformamide were added 8.65 g (62.5 mmol) of K_2CO_3 and 7.20 ml (7.91 g = 62.5 mmol) of benzyl chloride (distilled from and into K_2CO_3). The mixture was degassed, and stirred under N_2 at RT. TLC. (benzene/ethyl acetate/acetic acid 90:10:2) showed that reaction was complete after 42 h. The mixture was worked-up with ether as above and stripped of solvent, finally in a rotary evaporator at 70°/0.1 Torr (to remove excess benzyl chloride), to give crude methyl (*S*)-(6-benzyloxy-2,5,7,8-tetramethyl-chroman-2-yl)acetate (**29**) as a yellow-orange resin. The analytical sample was prepared by crystallization from hexane/petroleum ether (30–60°): m.p. 51–52°, $[\alpha]_D^{25} = -3.44°$ ($c = 0.9303$, C_2H_5OH). – IR.: 1735 (ester C=O). – UV.: 227 (sh, 12,000), 258 (870), 280 (1920), 287 (2140). – NMR.: 1.42 (*s*, 3 H, H_3C—C(2)); 2.09, 2.14 and 2.18 (3*s*, 9 H, 3 H_3C—Ar); 2.59 (*s*, 2 H, —CH_2COO—); 3.62 (*s*, 3 H, $COOCH_3$); 4.62 (*s*, 2 H, —CH_2O—); 7.30 (*m*, 5 H, C_6H_5). – MS. (*m/e*): 368 (M^+), 277 (100%). $C_{23}H_{28}O_4$ (368.47) Calc. C 74.97 H 7.66% Found C 74.98 H 7.77%

A solution of the crude ester **29** in 625 ml of pentane was cooled under N_2 in a dry ice/ethanol bath to –70°. To the resulting suspension were added, dropwise over 6 min, 21.80 ml (37.5 mmol) of a 25% solution of diisobutylaluminum hydride in hexane (*Texas Alkyls*). TLC. (petroleum ether/methanol (30–60°) 9:1) at 8 min showed that some ester remained. It is important that all ester be reduced, since its separation from the desired aldehyde is very difficult. Thus, an additional 4.4 ml (7.5 mmol) of diisobutylaluminum hydride solution were added at 17 min over a period of 1 min. TLC. at 19 min indicated that all of the ester had been reduced. The reaction was quenched at –70° with methanol and water and worked-up as usual with ether. The crude product was chromatographed (benzene/ethyl acetate 9:1) and triturated with petroleum ether (30–60°) to give aldehyde **30** as 6.80 g (80%) of white solid: sintering at 86°, m.p. 88.5–90°, $[\alpha]_D^{25} = +16.20°$ ($c = 1.0435$, $CHCl_3$). The analytical sample was similarly prepared: sintering at 85.5°, m.p. 87.5–90°, $[\alpha]_D^{25} = +15.16°$ ($c = 1.78$, $CHCl_3$). – IR.: 2750 (aldehyde C—H), 1715 (aldehyde C=O). – UV.: 227 (sh, 11,400), 357 (sh, 1060), 364 (sh, 1070), 368 (sh, 1200), 380.5 (sh, 2125), 387.5 (2375). – NMR.: 1.40 (*s*, 3 H, H_3C—C(2)); 2.07, 2.14 and 2.18 (3*s*, 9 H, 3 H_3C—Ar); 4.62 (*s*, 2 H, —CH_2O—); 7.30 (*m*, 5 H, C_6H_5); 9.77 ppm (*t*, $J = 2.5$, 1 H, CHO). – MS. (*m/e*): 338 (M^+), 247 (100%).

$C_{22}H_{26}O_3$ (338.43) Calc. C 78.08 H 7.74% Found C 78.04 H 7.73%

(S)-(*6-Hydroxy-2,5,7,8-tetramethyl-chroman-2-yl*)*propionaldehyde* (**32**). A suspension of 70.65 g (0.206 mol) of methoxymethyltriphenylphosphonium chloride (*Aldrich*) in 625 ml of glyme (freshly filtered through *Woelm* neutral Alumina I) under N_2 was cooled in an ice bath. Phenyllithium (1.8 M in benzene/ether 70:30; *Ventron*) was added *via* syringe until the red ylide color appeared. An additional 95 ml (0.171 mol) of phenyllithium solution were then added over the next 10 min. The red-brown suspension was stirred 10 min, and then a solution of 21.15 g (62.5 mmol) of aldehyde **30** in 150 ml of glyme was added over 5 min. The mixture was stirred without cooling

for 2 h and then at a gentle reflux for 1 h, cooled to 3°, treated with 625 ml of 6N HCl, stirred for 2 h without cooling and worked-up with ether as usual. Chromatography of the crude product (benzene/ethyl acetate 97.5:2.5) gave the aldehyde **31** as 23.91 g of yellow-orange resin. To a solution of this material in 250 ml of ethanol were added 2.5 g of Pd/C (10%) and the mixture was hydrogenated at atmospheric pressure and RT. After 5 h, the uptake of H_2 (1.75 l) had ceased. The catalyst was removed by filtration and washed with ethanol. The combined filtrates were stripped of solvent to give a pale yellow oil. To a solution of this material in 250 ml of tetrahydrofuran were added 250 ml of 1N HCl. The mixture was stirred 1 h[15]) and worked-up with ether as usual. Chromatography (benzene/ethyl acetate 95:5 and 9:1) and crystallization from ether/petroleum ether (30–60°) gave aldehyde **32** as 12.14 g (74%) of granular white powder: m.p. 86–89°. The analytical sample was recrystallized from ether/petroleum ether (30–60°) to give a white powder: m.p. 90.5–92.5°, $[\alpha]_D^{25} = -17.02°$ ($c = 0.9398$, C_6H_6). – IR.: 3580 (OH), 2760 (aldehyde CH), 1720 (aldehyde C=O). – UV.: 225 (sh, 9400), 291 (3260). – NMR.: 1.17 (*s*, 3 H, H_3C–C(2)); 2.05 and 2.13 (2*s*, 6 H and 3 H, 3 H_3C–Ar); 4.46 (*s*, 1 H, OH); 9.64 (*s*, 1 H, CHO). – MS. (*m/e*): 262 (M^+), 165 (100%).

$C_{16}H_{22}O_3$ (262.34) Calc. C 73.25 H 8.45% Found C 73.14 H 8.56%

Ethyl (R)-*11-(6-Hydroxy-2,5,7,8-tetramethyl-chroman-2-yl)-4,8-dimethyl-(4*E*,8*E*)-4,8-undecadienoate* (**42**). Isopropenylmagnesium bromide was prepared under N_2 by the addition, over 1.5 h, of a solution of 87.12 g (0.72 mol) of 2-bromopropene (*Aldrich*) in 200 ml of tetrahydrofuran (distilled from CaH_2) to a suspension of 21.9 g (0.90 mol) of magnesium in 300 ml of THF in an oil bath at 46–48°. The brown solution was stirred 30 min and then a solution of 38.0 g (0.145 mol) of the aldehyde **32** in 100 ml of THF was added over 15 min. The suspension was heated at a gentle reflux for 2.5 h, cooled, poured onto ice and 1.5 l of saturated NH_4Cl solution, and worked-up with ether as usual. Chromatography (benzene/ethyl acetate 9:1 and 8:2) gave the allylic alcohol **33** as 23.8 g (53.9%) of orange resin. – NMR.: 1.24 (*s*, 3 H, CH_3); 1.74 (*s*, 3 H, CH_3); 2.11 and 2.15 (2*s*, 6 H and 3 H, 3 H_3C–Ar); 2.52 (*t*, 2 H, H_2C–Ar); 4.06 (*t*, 1 H, CHOH); 4.45 (*s*, 1 H, OH); 4.91 (*d*, 2 H, C=CH_2). – MS. (*m/e*): 304. 2086 (M^+); calc. for $C_{19}H_{28}O_3$: 304. 2040.

A mixture of the allylic alcohol **33**, 38.0 g (0.387 mol) of 2-methoxy-3-methyl-butadiene (**34**) [18], 0.30 g of oxalic acid dihydrate, 0.30 g of hydroquinone and 300 ml of glyme (freshly filtered through *Woelm* neutral alumina I) was degassed and heated at reflux under N_2 for 18 h. Work-up with ether in the usual manner followed by chromatography (benzene/ethyl acetate 97.5:2.5 and 95:5) gave the unsaturated ketone **35** as 21.0 g of light orange resin. – NMR.: 1.22 (*s*, 3 H, CH_3), 1.59 (*s*, 3 H, vinylic CH_3), 1.84 (*s*, 3 H, CH_3), 2.08 and 2.11 (2*s*, 6 H and 3 H, 3 H_3C–Ar), 4.35 (*s*, 1 H, OH), 5.14 (*t*, 1 H, C=CH–), 5.82 (*d*, 2 H, C=CH_2). – MS. (*m/e*): 370.2513 (M^+); calc. for $C_{24}H_{34}O_3$ 370.2510.

A solution of 75 ml of $NaAlH_2(OCH_2CH_2OCH_3)_2$ (*Aldrich* Red-Al®) in 75 ml of THF under N_2 was cooled in an ice bath as a solution of the ketone **35** in 75 ml of THF was added over 30 min. The solution was stirred without cooling for 1 h, poured onto ice and 300 ml of 6N HCl, and worked-up with ether as usual. Chromatography (benzene/ethyl acetate 9:1 and 8:2) gave the allylic alcohol **36** as 19.0 g of light orange resin. – NMR.: 1.25 (*s*, 3 H, CH_3); 1.62 (*s*, 3 H, vinylic CH_3); 1.73 (*s*, 3 H, CH_3); 2.11 and 2.16 (2*s*, 6 H and 3 H, 3 H_3C–Ar); 2.62 (*t*, 2 H, H_2C–Ar); 4.04 (*m*, 1 H, CHOH); 4.21 (*s*, 1 H, OH); 4.89 (*d*, 2 H, C=CH_2); 5.20 (*t*, 1 H, C=CH–). – MS. (*m/e*): 372.2740 (M^+); calc. for $C_{24}H_{36}O_3$: 372.2734.

A mixture of the allylic alcohol **36**, 90 ml of triethyl orthoacetate and 0.75 ml of propionic acid in a flask topped by a short-path distilling head was degassed and heated under N_2 in an oil bath at 135°. During the first 1/2 h 6.5 ml of distillate, b.p. 70–80°, were collected. After a total of 3 h heating, the solution was cooled, stripped of excess triethyl orthoacetate and worked-up with ether as usual. Chromatography (benzene/ethyl acetate 97.5:2.5 and 95:5) followed by distillation at 190°/0.008 Torr gave the desired ester **42** as 18.11 g (52.3% from **33**) of pale yellow resin. The analytical sample was similarly prepared: b.p. 205–210°/0.015 Torr, $[\alpha]_D^{25} = -5.99°$ ($c = 1.0354$, $CHCl_3$). – IR.: 3620 (OH), 1728 (ester C=O). – UV.: 225 (sh, 9790), 292 (3240). – NMR.: 1.20 (*s* and *t*, 6 H, CH_3 and $COOCH_2CH_3$); 1.55 (*s*, 6 H, 2 vinylic CH_3); 2.08 (*s*, 9 H,

[15]) The purpose of this step was to hydrolyze the diethylacetal of **32** which formed to some extent during the hydrogenation.

3 H_3C—Ar); 4.12 (*q*, 2 H, $COOCH_2$—); 4.35 (*s*, 1 H, OH); 5.12 (*t*, 2 H, 2 C=CH—). – MS. (*m/e*): 442 (M^+), 165 (100%). – GLC.: purity 94.1% (OV101, 10%, 260°, retention time 66 min).

$C_{28}H_{42}O_4$ (442.62) Calc. C 75.97 H 9.56% Found C 76.05 H 9.18%

(R)-*11-(6-Hydroxy-2,5,7,8-tetramethyl-chroman-2-yl)-4,8-dimethyl-(4*E,*8*E)*-4,8-undecadienoic Acid* (**43**). To a degassed solution of 18.00 g of ester **42** in 100 ml of ethanol under N_2 100 ml of 2N NaOH solution were added over 10 min and the mixture was stirred overnight and worked-up as usual with ether to give 14.23 g of peach-colored solid. Two crystallizations from acetonitrile at –20° gave the acid **43** as 12.44 g (73.8%) of granular, offwhite solid: m.p. 100.5–102°. The analytical sample was similarly prepared: m.p. 97–101°, $[\alpha]_D^{25} = -5.67°$ (*c* = 1.0232, $CHCl_3$). – IR.: 3630 (OH), 3200 and 2780–2600 (acid OH), 1748, 1740 and 1715 (acid C=O). – UV.: 235 (sh, 10.750), 291 (3120). – NMR.: 1.23 (*s*, 3 H, CH_3); 1.57 (*s*, 6 H, 2 vinylic CH_3); 2.08 (*s*, 9 H, 3 H_3C—Ar); 5.11 (*m*, 2 H, 2 C=CH—). – MS. (*m/e*): 414 (M^+), 165 (100%). – GLC.: purity > 99% (OV-101, 10%, programmed at 2.5°/min from 100 to 270°; retention time 113 min, as the bis(trimethylsilyl) derivative).

$C_{26}H_{38}O_4$ (414.56) Calc. C 75.32 H 9.24% Found C 75.59 H 9.07%

Methyl (R)-*11-(6-Hydroxy-2,5,7,8-tetramethyl-chroman-2-yl)-4,8-dimethyl-(4*E,*8*E)*-4,8-undecadienoate* (**44**). A mixture of 12.32 g (29.7 mmol) of acid **43**, 7.8 ml (17.7 g = 125 mmol) of methyl iodide, 10.50 g (125 mmol) of $NaHCO_3$ and 25 ml of dimethylformamide was degassed and stirred under N_2 for 46 h. Work-up with ether in the usual manner, followed by chromatography (benzene/ethyl acetate 97.5:2.5 and 95:5) and crystallization from ether/petroleum ether (30–60°) gave the ester **44** as 10.20 g (80.1%) of colorless prisms: m.p. 64–66°. The analytical sample was similarly prepared: m.p. 63–65°, $[\alpha]_D^{25} = -6.79°$ (*c* = 1.0313, $CHCl_3$). – IR.: 3620 (OH), 1735 (ester C=O). – UV.: 215 (sh, 10,400), 291 (3240). – NMR.: 1.23 (*s*, 3 H, CH_3); 1.56 (*s*, 6 H, 2 vinylic CH_3); 2.11 and 2.14 (2*s*, 6 H and 3 H, 3 H_3C—Ar); 3.62 (*s*, 3 H, $COOCH_3$); 4.45 (*s*, 1 H, OH), 5.11 (*m*, 2 H, 2 C=CH—). – MS. (*m/e*): 428 (M^+), 165 (100%), 164. – GLC.: purity > 99% (OV-101, 10%, 245°, retention time 70.5 min).

$C_{27}H_{40}O_4$ (428.59) Calc. C 75.66 H 9.41% Found C 75.59 H 9.35%

Methyl (R)-*11-(6-Acetoxy-2,5,7,8-tetramethyl-chroman-2-yl)-4,8-dimethyl-(4*E,*8*E)*-4,8-undecadienoate* (**45**). 10.10 g (23.6 mmol) of ester **44** suspended in 35 ml of acetic anhydride were degassed, placed under N_2, and cooled in an ice bath. Pyridine (7 ml) was added over 5 min and the mixture (solution after 10 min) was stirred overnight as the ice bath was allowed to melt. The solution was diluted with ice/H_2O, stirred 30 min and worked-up with ether as usual. Crystallization from petroleum ether (30–60°) gave diester **45** as 9.44 g (85.1%) of white powder: m.p. 43.5–45°. The analytical sample was similarly prepared: m.p. 44–46°, $[\alpha]_D^{25} = -1.27°$ (*c* = 1.0175, $CHCl_3$). – IR.: 1735 (ester C=O). – UV.: 227 (sh, 10,000), 278 (1760), 284,5 (1980). – NMR.: 1.25 (*s*, 3 H, CH_3); 1.60 (*s*, 6 H, 2 vinylic CH_3); 1.98, 2.02 and 2.09 (3*s*, 9 H, 3 H_3C—Ar); 2.31 (*s*, 3 H, H_3C—COO); 3.64 (*s*, 3 H, $COOCH_3$); 5.14 (*m*, 2 H, 2 C=CH—). – MS. (*m/e*): 470 (M^+), 428, 165 (100%). – GLC.: purity > 99% (OV-101, 10%, programmed at 4°/min from 80 to 270°, retention time 68 min). $C_{29}H_{42}O_5$ (470.63) Calc. C 74.01 H 9.00% Found C 74.23 H 9.21%

(2R,*3'*E,*7'*E)-α-*Tocotrienol* (**2d**). A solution of 1.18 g (2.5 mmol) of diester **45** in 62.5 ml of dry pentane was cooled under N_2 in a dry ice-ethanol bath to –70°. A 25% diisobutylaluminum hydride solution in hexane (4.4 ml = *ca.* 7.5 mmol, *Texas Alkyls*) was added *via* syringe over 4 min. TLC. (benzene/ethyl acetate 9:1) at 6 min indicated that the reaction was not complete. Two additional 2.2 ml portions of the diisobutylaluminum hydride solution were required before all the diester **45** was consumed. The reaction was quenched at –70° with methanol and H_2O and worked-up with ether as usual to give crude aldehyde **46** as a light yellow resin. A similarly prepared sample was chromatographed on *Woelm* neutral alumina III with benzene/ethyl acetate 95:5 and 9:1 and crystallized from ether/petroleum ether (30–60°) to give a white powder: sintering at 57.5°, m.p. 61–64°, $[\alpha]_D^{25} = -5.03°$ (*c* = 0.9934, $CHCl_3$). – IR.: 3620 (OH), 2730 (aldehyde C—H), 1725 (aldehyde C=O). – UV.: 225 (sh, 11,100), 292.5 (3270). – NMR.: 1.25 (*s*, 3 H, CH_3); 1.59 (*s*, 6 H, 2 vinylic CH_3); 2.07 and 2.12 (2*s*, 6 H and 3 H, 3 H_3C—Ar); 4.30 (*s*, 1 H, OH); 5.13 (*m*, 2 H, 2 C=CH—); 9.70 (*t*, *J* = 1, 1 H, CHO). – MS. (*m/e*): 398 (M^+), 165 (100%). $C_{26}H_{38}O_3$ (398.56) Calc. C 78.35 H 9.61% Found C 78.60 H 9.67%

A suspension of 9.65 g (25 mmol) of isopropyltriphenylphosphonium bromide [26], m.p 239–242°, in 50 ml of THF (distilled from CaH_2) was stirred under N_2 as 11.6 ml (20 mmol) of a 1.76M phenyllithium solution in benzene/ether 70:30 (*Ventron*) were added *via* syringe over 3 min. The dark red mixture was stirred for 1 h and then a solution of the crude aldehyde **46** in 10 ml of THF was added over 3 min. The mixture was stirred 1 h and worked-up with ether as usual. In order to facilitate the isolation of the α-tocotrienol the crude material in 10 ml of THF was added to a cold (3°) solution of 5 ml of $NaAlH_2(OCH_2CH_2OCH_3)_2$ (*Aldrich* Red Al®) in 10 ml of THF. The dark solution was stirred without cooling 1 h, poured onto ice and 50 ml of 6N HCl and worked-up with ether as usual. Chromatography (benzene and benzene/ethyl acetate 97.5:2.5) followed by distillation at 220°/0.03 Torr gave (2*R*,3'E,7'E)-α-tocotrienol (**2d**) as 851 mg (80.2%) of clear, virtually colorless resin. Crystallization from 5 ml of methanol with cooling, finally to −70°, gave 763 mg of flaky white solid: m.p. 31.5–32° (Lit. [27] m.p. 30.5–31°), $[\alpha]_D^{25} = -5.71°$ (c = 1.0155, $CHCl_3$). – IR.: 3620 (OH). – UV.: 225 (sh, 10,200), 291 (3200). – NMR.: 1.24 (*s*, 3 H, H_3C—C(2)); 1.59 (*s*, 9 H, 3 vinylic CH_3 in *cis*); 1.67 (*s*, 3 H, vinylic CH_3 in *trans*); 2.00, 2.10 and 2.19 (3*s*, 9 H, 3 H_3C—Ar); 2.60 (*t*, J = 6, H_2C—Ar); 4.14 (*s*, 1 H, OH); 5.1 (*m*, 3 H, 3 C=CH—). – MS. (*m/e*): 424 (M^+), 165 (100%). – GLC.: homogeneous product (OV-101, 10%, 260°, retention time 34 min). – The IR. and NMR. were identical with those[13]) of material isolated from natural sources.

$C_{29}H_{44}O_2$ (422.63) Calc. C 82.02 H 10.44% Found C 82.17 H 10.45%

REFERENCES

[1] *H. M. Evans*, Vitamins and Hormones *20*, 379 (1962).
[2] *H. Mayer & O. Isler*, in 'Methods in Enzymology', ed. S. P. Colowick & N.O. Kaplan, Academic Press, New York 1971, Vol. XVIIIC, p. 241–348.
[3] *P. Schudel, H. Mayer & O. Isler*, in 'The Vitamins', ed. W. H. Sebrell, jr. & R. S. Harris, Academic Press, New York 1972, Vol. V, p. 168–218.
[4] Eur. J. Biochemistry *46*, 217 (1974).
[5] *S. R. Ames*, Lipids *6*, 281 (1971).
[6] *H. Mayer, P. Schudel, R. Rüegg & O. Isler*, Helv. *46*, 963 (1963).
[7] *O. Isler, H. Mayer, J. Metzger, R. Rüegg & P. Schudel*, Angew. Chem. *75*, 1030 (1963).
[8] *H. Mayer, P. Schudel, R. Rüegg & O. Isler*, Helv. *46*, 650 (1963).
[9] *H. H. Draper*, in 'Fat Soluble Vitamins', Vol. 9 of 'International Encyclopaedia of Food and Nutrition', ed. R. A. Morton, Pergamon Press, Oxford 1970, p. 336–338.
[10] *H. Arai & N. Murata*, Kogyo Kagaku Zasshi *61*, 563 (1958); Chem. Abstr. *55*, 10371b (1961).
[11] *J. W. Scott, W. M. Cort, H. Harley, D. R. Parrish & G. Saucy*, J. Amer. Oil chem. Soc. *51*, 200 (1974).
[12] *H. M. Bell, C. W. Vanderslice & A. Spehar*, J. org. Chemistry *34*, 3923 (1969).
[13] *J. W. K. Burrell, L. M. Jackman & B. C. L. Weedon*, Proc. chem. Soc. *1959*, 263.
[14] *D. P. Wagner, H. Gurien & A. I. Rachlin*, Ann. N. Y. Acad. Sci. *172*, 186 (1970).
[15] *P. Schudel, H. Mayer, J. Metzger, R. Rüegg & O. Isler*, Helv. *46*, 333 (1963).
[16] *P. Schudel, H. Mayer, J. Metzger, R. Rüegg & O. Isler*, Helv. *46*, 636 (1963).
[17] *D. J. Faulkner*, Synthesis *1971*, 175.
[18] *D. J. Faulkner & M. R. Peterson*, J. Amer. chem. Soc. *95*, 553 (1973).
[19] *L. I. Zakharkin & I. M. Khorlina*, Tetrahedron Letters *1962*, 619.
[20] *G. Wittig, W. Böll & K.-H. Krück*, Chem. Ber. *95*, 2514 (1962).
[21] *P. Schudel, H. Mayer, J. Metzger, R. Rüegg & O. Isler*, Helv. *46*, 2517 (1963).
[22] *W. G. Young, F. F. Caserio, Jr. & D. D. Brandon, jr.*, J. Amer. chem. Soc. *82*, 6163 (1960).
[23] *W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T. Li, D. J. Faulkner & M. R. Peterson*, J. Amer. chem. Soc. *92*, 741 (1970).
[24] 'The *Merck* Index', 8th Ed., Merck and Company, Inc., Rahway, N. J., p. 1114 (1968).
[25] *P. Karrer, H. Fritzsche, B. H. Ringier & H. Salomon*, Helv. *21*, 520 (1938); see correction in *P. Karrer, R. Escher, H. Fritzsche, H. Keller, B. H. Ringier & H. Salomon*, ibid. *21*, 939 (1938).
[26] *U. H. M. Fagerlund & D. R. Idler*, J. Amer. chem. Soc. *79*, 6473 (1957).
[27] *H. Mayer*, personal communication.