A MICROBIAL LIPASE BASED STEREOSELECTIVE SYNTHESIS OF (*d*)-α-TOCOPHEROL FROM (*R*)-CITRONELLAL AND (*S*)-(6-HYDROXY-2,5,7,8-TETRAMETHYLCHROMAN-2-YL)ACETIC ACID

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Abstract – A new synthesis of natural vitamin E (2*R*,4'*R*,8'*R*)-α-tocopherol) based on (*R*)-citronellal and (*S*)-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)acetic acid is described. The citronellal is elaborated into an optically pure C_{13} allylic carbonate using a lipase catalyzed kinetic resolution to control the new chiral center. Palladium catalyzed coupling of this C_{13} carbonate with either a β-ketoester or β-ketosulphone derived from the chromanylacetic acid completes the assembly of the α-tocopherol skeleton. Appropriate functional group modifications are used to complete the synthesis.

Vitamin E comprises a group of substances present in various grain and vegetable oils, and which was recognized in 1922 as an essential dietary component for the maintenance of fertility in rats.[1a] This association with mammalian reproduction (Gr. τοκο φερω) gave rise to the name tocopherols, by which these substances are individually known. Subsequent work established that the vitamin E of some oils contained a sub-group, now known as the tocotrienols. The most biopotent member of the vitamin E family is the side-chain saturated and fully methylated homolog, α-tocopherol, now recognized as the primary fat-soluble antioxidant and free radical chain terminator in most tissues.[1b] Exciting results of clinical studies carried out recently suggest that α-tocopherol will play an increasingly important role in the prevention of serious health problems including cancer and cardiovascular disease.[1c-i]

Respectfully dedicated to our friend and former director, Dr. Arnold Brossi, on the occasion of his 70th birthday.

An analytical trace, e.g. hplc, of a typical vitamin E sample from a natural source will display four peaks (Figure 1), a feature shared with gc traces from manufactured vitamin E (Figure 2). In the natural source material, these four peaks arise from the number and disposition of methyl groups on the aromatic ring. Commercial "natural" (*d*)-α-tocopherol (3) is produced by exhaustive methylation of this ring. The four peaks in a gc trace of the methyl ether of manufactured vitamin E reflect the stereorandom nature of the current manufacturing methods; each peak arising from one of the four racemates contained in synthetic α-tocopherol.

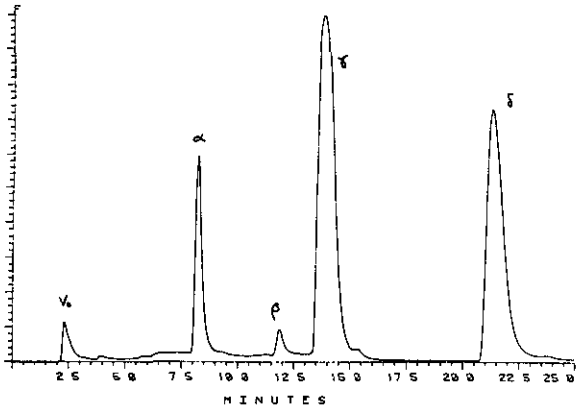


Figure 1

Hplc trace of a natural vitamin E sample containing the four tocopherols (3% EtOAc in hexane)

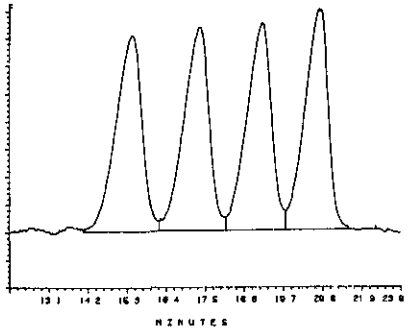
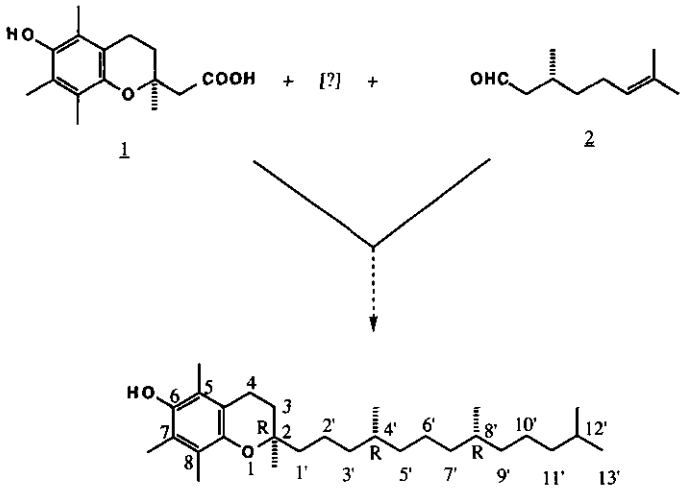


Figure 2

Gc trace of the methyl ether derivative of a synthetic vitamin E sample containing four racemates. SP2340 (100M x 0.25MM I.D.) glass capillary column at 190° C (isothermal) using H_2 carrier gas at 14 cm/sec.

The conception and execution of stereoselective schemes for the synthesis of the (*R,R,R*)-isomer of α-tocopherol is an ongoing scientific activity that spans the last twenty-five years[2] and, in some respects, serves as a litmus test for evolving methods in asymmetric synthesis. The ultimate goal of replacing current manufacturing methods with a cost-effective process for "nature identical" (*d*)-α-tocopherol may be attained eventually and we report here another step in this direction based on the technique of catalytic kinetic resolution with enzymes.

The problem was framed in terms of two raw materials which are made available with a high degree of optical purity using processes developed by other workers.

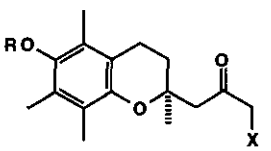


3 (*d*)-α-tocopherol

(S)-(6-Hydroxy-2,5,7,8-tetramethylchroman-2-yl)acetic acid (1) is produced from trimethylhydroquinone, methyl vinyl ketone and acetonitrile in a process that includes an efficient resolution with *S*-(-)-methylbenzylamine.[3] Facile racemization of esters of the *R*-enantiomer via reversible base-catalyzed β-elimination enhances the overall efficiency of the route to 1.

High optical purity (*R*)-citronellal (2) has become available through the pioneering work of Noyori, Otsuka, and coworkers in asymmetric catalysis using BINAP ligated rhodium and ruthenium complexes.[4] The preparation of *N,N*-diethylnerylamine from isoprene and diethylamine[5] followed by enantiospecific isomerization to the enamine of 2 using a rhodium complex of *R*-(+)-BINAP provides ready access to multi-kilo quantities of 2 with e.e. of 95% or greater.

Thus with 1 and 2 as raw materials, it remains only to devise a linking strategy that provides four additional carbon atoms and assures the (*R*)-configuration at the 4'-position. Elaboration of 1 and 2 into 4 and 5 respectively, suitable partners for the palladium-catalyzed coupling chemistry introduced to organic synthesis by Tsuji[6] and Trost,[7] proved to be an effective plan for achieving this goal.



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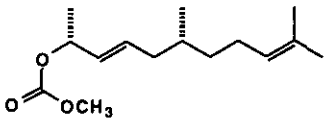

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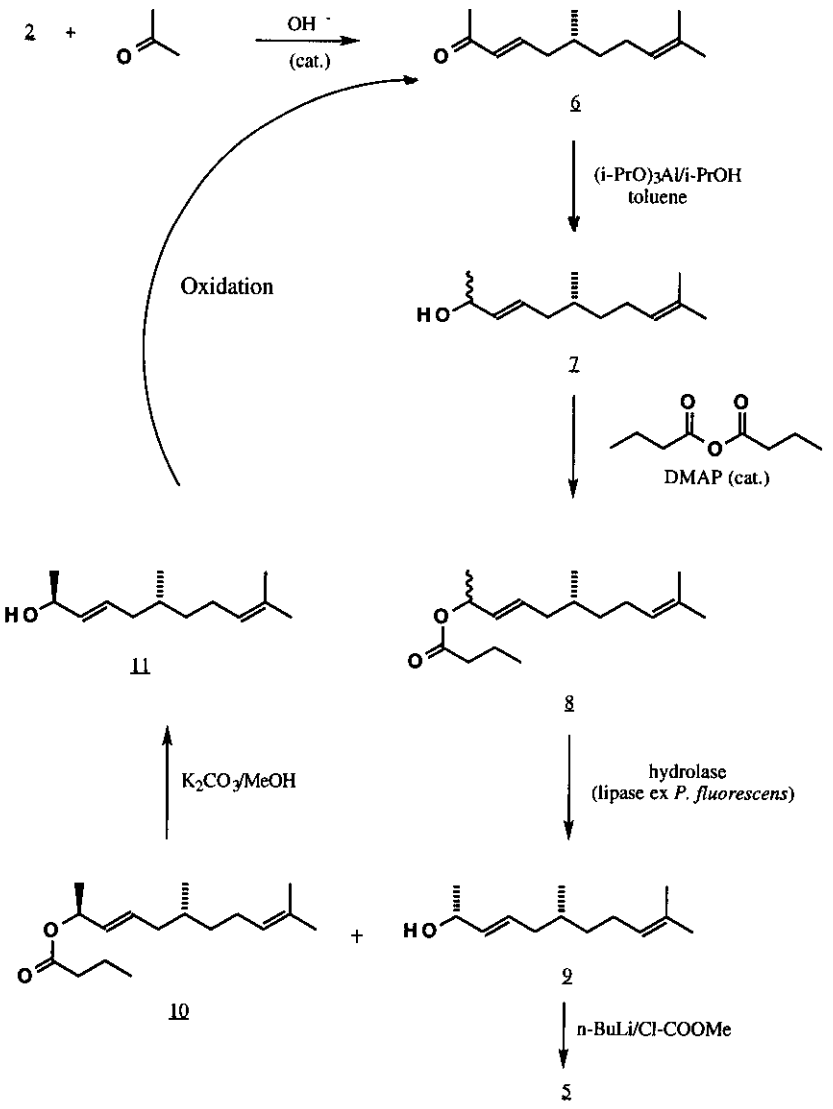
Although this plan was potentially compromised by obvious stereochemical and regiochemical ambiguities, compound (5) proved, in the event, to exhibit a remarkably high degree of fidelity in both these respects.

Compound (5) was prepared from (*R*)-citronellal by the reaction sequence depicted in Scheme 1.

The cornerstone of Scheme 1 is the hydrolase catalyzed kinetic resolution of the diastereomeric ester mixture 8 into the single stereoisomers (9) and (10). However, as with any cost effective resolution process, efficient recycle of the wrong diastereomer (10) is another critical element of the scheme.

Scheme 1



A recycle loop was readily closed in this instance by taking advantage of the reversible nature of the Meerwein, Ponndorf, Verley reduction reaction. Prior equilibration of recovered alcohol (11) with each new batch of ketone (6) is a simple matter. Based on successful application in other areas, we believe this to be a broadly applicable tactic, particularly when allylic chiral alcohols are involved.

In screening hydrolases for the resolution step, fortuitous assistance to the analytical aspect was afforded by the second chiral center in 7. The TMS ethers of the two diastereomers of 7 separate well on capillary gc.

The results obtained with five hydrolases from various sources are shown in Table 1.

Table 1

Lipase (or source)	de of C_{13}-alcohol*
PPL	77%
Cholesterol Esterase (Porcine)	78%
Lipoprotein Lipase (Genzyme Corp.)	90%
Candida Cylindracea	28%
Pseudomonas Fluorescens (Amano)	96%

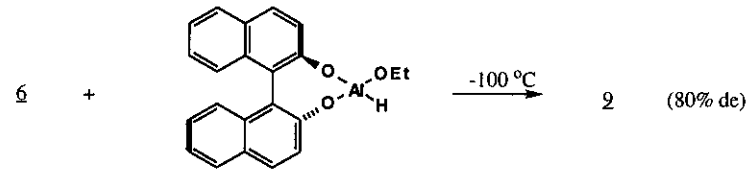
*By capillary gc analysis of TMS ethers

The best results were obtained with the lipase from Pseudomonas fluorescens, supplied by the Amano International Enzyme Co. of Troy, Virginia.

This is a relatively simple enzymatic process to carry out, particularly on a larger scale. The enzyme is an exocellular lipase, easily isolated from culture filtrate, and cheap enough to be discarded at the end of a run. Several enantioselective syntheses involving a prostaglandin, a prostacyclin, a leukotriene antagonist, and an ACE inhibitor, all based on enzyme-catalyzed kinetic resolutions with this *P. fluorescens* lipase, have been completed.[8]

The progress of the hydrolysis can be monitored both by NaOH uptake from the automatic titrator and by gc analysis. The product alcohol (9) is separated from the diastereomeric butyrate (10) by fractional distillation through a Goodloe column. Mixed fractions can be recycled to the next batch or separated on a silica gel column. Typical yields and de values are 46% yield of alcohol (9) in 95.8% de and 46.9% yield of butyrate (10) in 93.8% de. The de of any given lot of alcohol (9) can be enhanced by re-esterification and second pass enzymatic hydrolysis. Thus, for example, a sample of 9 with de of 91.8% was esterified and hydrolyzed with P. fluorescens lipase to 80.1% conversion giving 84.5% yield of 9 in 96.2% de and 13.7% yield of 10 in 77.8% de.

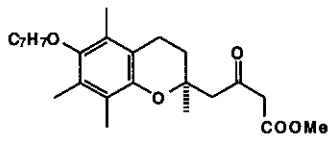
The question of whether the alcohol or ester had the correct relative configuration for the tocopherol side chain was answered by reducing a sample of ketone (6) with Noyori's (*R*)-BINAL reagent.



The product of this reduction, obtained with 80% de, is the same diastereomer as the alcohol produced by the *P. fluorescens* lipase and is predicted on the basis of Noyori's[9] results to be the (*R,R*)-isomer.

The acetate of allylic alcohol (9) can be coupled with a chroman moiety (4), however, some racemization at the 4'-position accompanied this coupling reaction. As reported in another instance by Tsuji and coworkers,[10] the problem can be minimized by using carbonates. Accordingly, the methyl carbonate (5) was prepared and used as the coupling partner for this application, with salutary effects on both yield and retention of 4' configuration.

Three possibilities for the carbanion-stabilizing group X in the chroman moiety (4) appeared to be consistent with the goal of the project.



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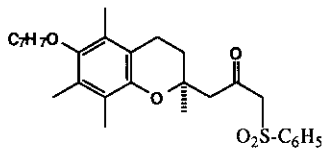

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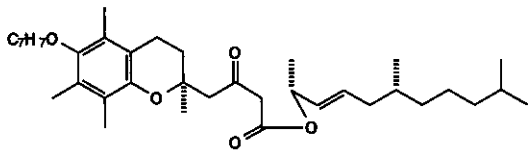

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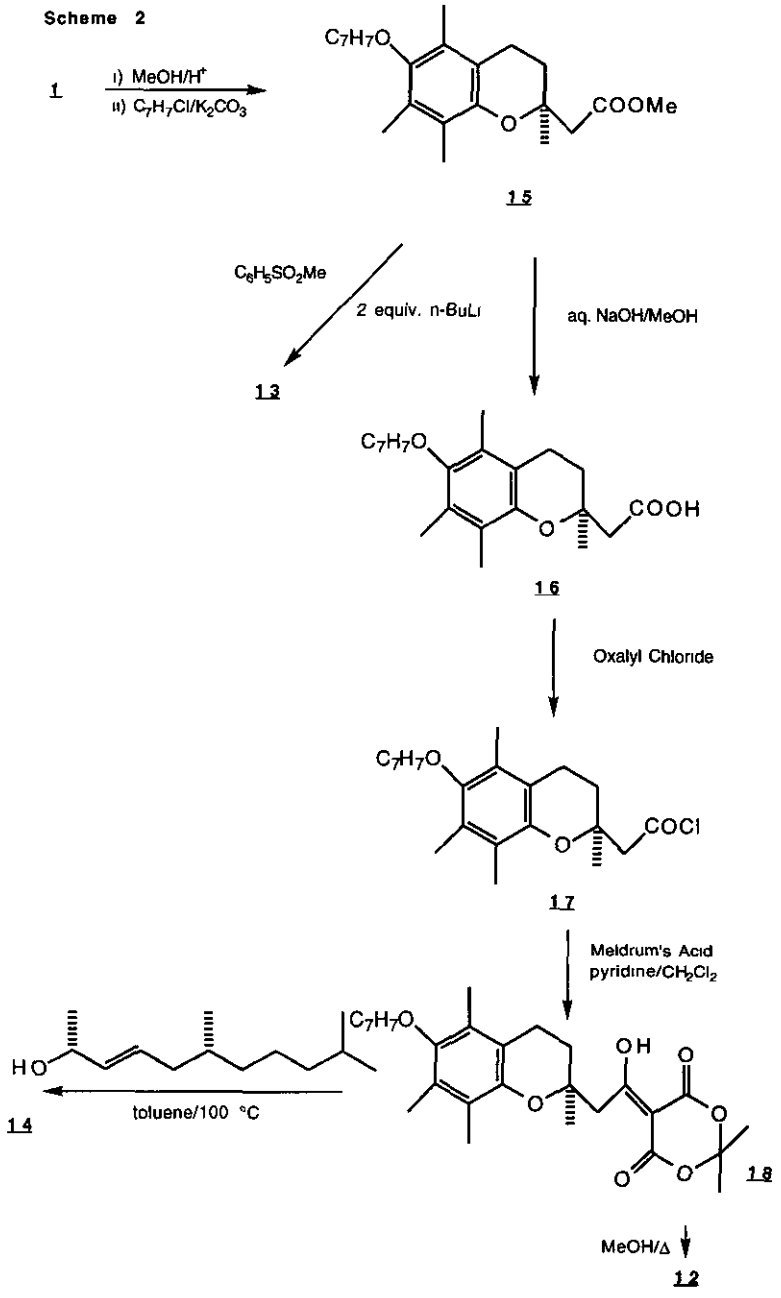
Ample precedent suggested that keto ester (12) and keto sulfone (13) should work well in the palladium-catalyzed coupling reactions and even more appealing, from the viewpoint of technical simplicity, was the intramolecular expression of this chemistry[11] embodied in compound (14).

Preparation of 12, 13, and 14 from chromanylacetic acid (1) was accomplished using the reaction sequences depicted in Scheme 2.

Scheme 2



The sequence of reactions used to convert the chromanylacetic acid (1) into the *O*-benzyl acid chloride (17) was based on methods reported by Cohen and coworkers.[12] The Meldrum's acid adduct of this acid chloride (18), prepared in a now standard fashion,[13] provided access to two of the proposed candidates for the palladium-catalyzed coupling chemistry.

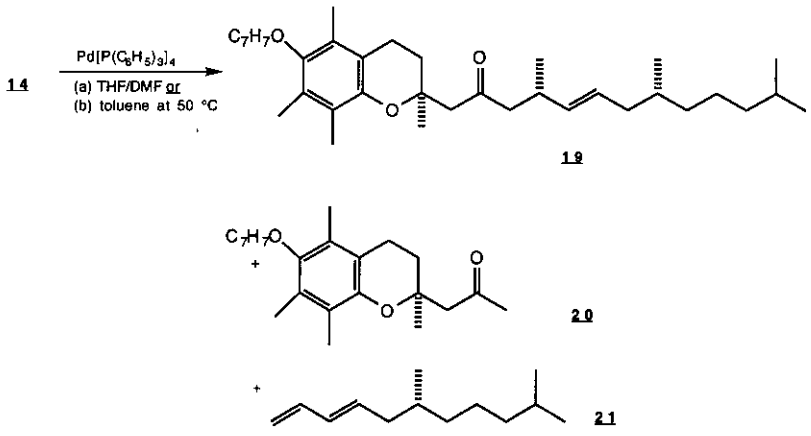
Exposure of crude adduct (18) to methanol at reflux afforded methyl keto ester (12) in 66% yield based on acid (16). This material, purified on a Separations Technology 2000 preparative hplc and recrystallized from aqueous methanol, was typically of $\geq$ 97.5% optical purity based on optical rotation and europium shift reagent nmr analysis at 400 MHz.

In a similar manner, the adduct (18) was combined with an equimolar quantity of allylic alcohol (9) in hot toluene solution to give keto ester (14).

In terms of its ease of preparation, the keto sulfone (13) has definite advantages over the keto esters. This highly crystalline intermediate is obtained in a single step from chromanylacetate (15) in nearly quantitative yield by treatment with the dianion of methyl phenyl sulfone.[14]

With compounds (12, 13, and 14) in hand, an evaluation of the various options for palladium-catalyzed coupling reactions could proceed.

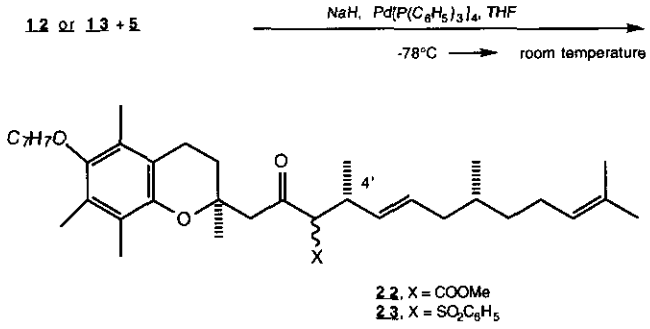
First, the Tsuji intramolecular variant involving extrusion of CO_2 from 14 can be dispensed with summarily because of by-products and stereochemical problems.



The cleavage pathway leading to methyl ketone (20) and diene (21) was signficant in the polar solvent (a) (28% yield of 20) and predominant in the non-polar solvent (b) (60% yield of 20). Nmr and hplc analyses of the ketone (19) and gc analysis of the α-tocopheryl methyl ether derived therefrom all indicated a minimum of 18% epimerization at the 4'-position. For these reasons, this approach was not further developed.

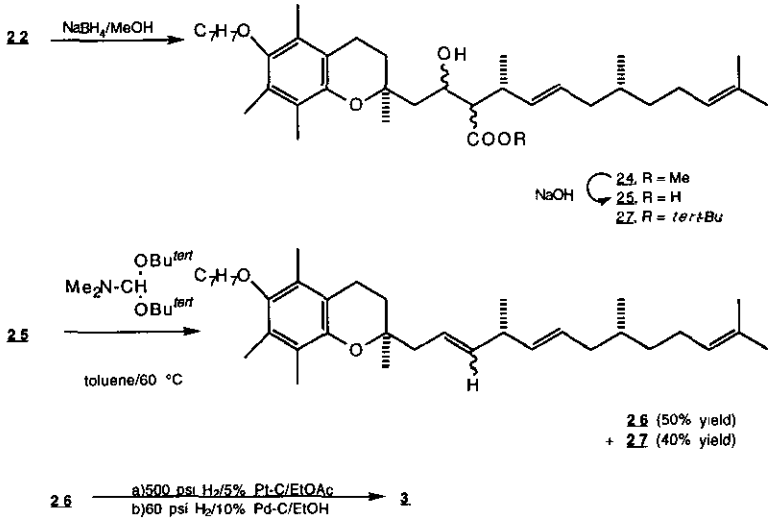
Chroman derivatives (12) and (13) both gave excellent results in coupling reactions with allylic carbonate (5) and both led to successful synthesis of α-tocopherol. With respect to the potential for coupling in the wrong regiochemical sense and for racemization at the 4'-position, both compounds gave equivalent results.

As anticipated on the basis of Keinan's[15] study, only the coupling product corresponding to displacement of the carbonate group from 5 without allylic rearrangement was obtained, in essentially quantitative yields in both cases.



In typical runs, between 1 and 3 mol percent of palladium catalyst was employed and the reactions were started at -78 °C with gradual warming to room temperature overnight. A full equivalent of sodium hydride was used, the intent being to minimize the lifetime of the π-allyl palladium complex and, therefore, its opportunity to epimerize.[16] Under these conditions, epimerization at the 4'-position proceeded to the extent of 3-4%. Samples of α-tocopherol prepared from 12 and 13 contained 5.7% and 6.5% respectively of the 4'*S* epimer. Of this, 2.5% is introduced by using allylic carbonate 5 of 95% ee.

The endgame sequences required for conversion of the coupling products (22) and (23) to α-tocopherol were fairly similar, both converging on the benzyl ether of a tocotrienol (26).



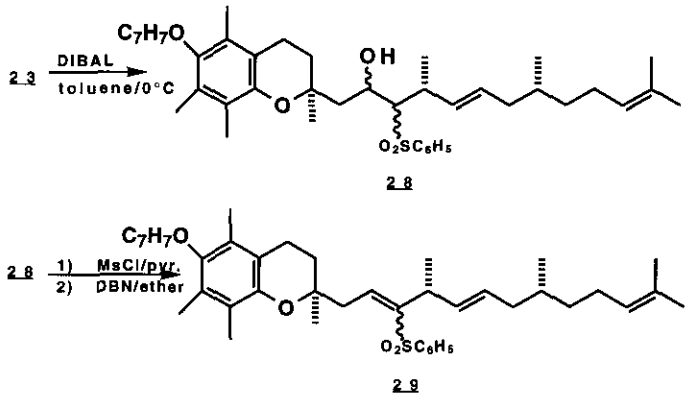
The borohydride reduction of keto ester (22) to hydroxy ester (24) proved to be a flawed step in the overall route via ketoester intermediates. This reduction proceeds very slowly and during the 2-3 day period required, up to 10% of the batch suffers epimerization at the 2-position. This is understood to be a consequence of base-induced reversible β-elimination of the chroman oxygen of unreacted ketone. The epimizered material appears as the (2*S*)-epimer of α-tocopherol in the final product.

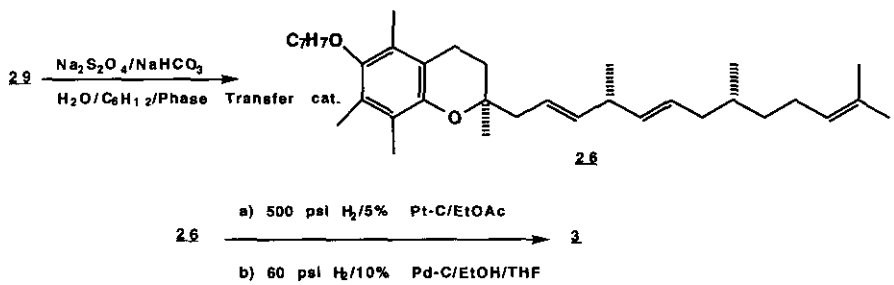
Hydrolysis of 24 affords the β-hydroxy acid (25) which is then subjected to Eschenmoser's[17] DMF acetal-induced fragmentation reaction. Both the dineopentyl acetal recommended by the inventors of this reaction and the di-t-butyl acetal can be used. The latter, being more readily prepared[18] and more economical, would be preferable on a larger scale but, unfortunately, produces the *t*-butyl ester (27) as a significant by-product.

Catalytic reduction and debenzylation of 26 required delicate handling as the configuration at the 4'-position is particularly vulnerable to epimerization in this intermediate. The overall transformation proceeded satisfactorily using the two step method depicted in Scheme 3.

In the case of the keto sulfone (23), the removal of redundant functionality and protecting group was accomplished in the five steps delineated in Scheme 4.

Scheme 4





A notable improvement in control of the stereocenter on the chroman ring was realized with the change from the β-ketoester series to the β-ketosulfone series, the (*S,R,R*)- diastereomer content of the final product having dropped from 9.97% to 2.66%. This is attributed to replacing the sluggish borohydride reduction of the ketone in 22 with the rapid, low temperature DIBAL reduction of the ketone in 23.

The resulting alcohol (28) is converted to the corresponding mesylate which, on base-induced elimination with DBN, afforded the vinyl sulfone (29). Application of the Julia procedure[19] for reductive cleavage of a vinyl sulfone group brought the sequence to the tocotrienol intermediate (26), the point of convergence with the sequence used in the β-ketoester series.

The two-stage hydrogenation of 26 (83.5% yield) provided a sample of vitamin E containing 90.02% of the natural (*R,R,R*)-stereoisomer, (*d*)-α-tocopherol. This was determined by capillary gc analysis of the methyl ether prepared from this material.[20] The results of this analysis on samples from both routes is presented in Table 2:

Table 2

α-tocopherol	*2R,4'R,8'R*	*2S,4'R,8'R*	*2R,4'S,8'R*	*2R,4'R,8'S*
ex keto ester (22)	82.85%	9.97%	5.71%	1.46%
ex keto sulfone (23)	90.02%	2.66%	6.46%	0.86%

While further refinements would be needed to bring the (*R,R,R*) content of vitamin E made this way into the desirable ≥98% range, the overall stereochemical outcome, chemical yields, and practical nature of the reactions employed, all meet with our original expectations. The marriage of enzyme-catalyzed kinetic resolution and palladium-catalyzed coupling chemistry provides the key to an effective vitamin E process based on the chromanylacetic acid (1) and (*R*)-citronellal (2).

EXPERIMENTAL SECTION

General.

Routine nmr spectra were recorded on a Varian T-60 or a Varian XL-200 spectrometer. Infrared spectra were recorded on a Perkin-Elmer Model 7108 spectrophotometer. Optical rotations were measured on a Perkin-Elmer Model 241 polarimeter. Gc quantifications were made using a Hewlett-Packard HP-5890 gas chromatograph equipped with a flame ionization detector, and integrated using Nelson Analytical chromatography software on an HP 200 series workstation. Column conditions: 5% phenylmethylsilicone, 25m capillary, initial temperature 125 °C, program rate 5 °C/min., final temperature 225 °C.

Preparative chromatography was carried out at the bench using Merck silica gel Si-60 (230-400 mesh). Large scale preparative hplc was performed on a Separations Technology Lab-2000 hplc unit. Hexane used for these runs was flashed distilled prior to use. Ethyl acetate was from Burdick & Jackson. The solvents were mixed in 55 gal drums in a cold room, and thoroughly stirred using an air driven stirrer. Fractions were collected in 20 l carboys.

Reagents unless otherwise noted were obtained in the highest practical grade from Aldrich or Fluka. (*R*)-citronellal and (*S*)-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)acetic acid were produced using previously described methods. Solvents were from J.T. Baker. Dry THF was distilled from sodium/benzophenone ketyl under an atmosphere of argon.

Spectroscopic data consistent with assigned structures were obtained for all compounds described. Nmr data for selected key intermediates is included.

(6R,3E)-6,10-Dimethyl-3,9-undecadien-2-one (6)

1.071 kg (6.94 mol) of (*R*)-(+)-citronellal and 2.67 l of acetone were added to 8.0 l of 1% aqueous potassium hydroxide. The resulting mixture was stirred at reflux for 6 h, at which time gc analysis showed that all of the starting material had been consumed. The reaction was cooled to room temperature and was poured into 1.75 l of ethyl acetate. The mixture was stirred for 5 min, the phases were allowed to settle and were then separated. The aqueous phase was extracted two more times with two portions of 1.5 l of ethyl acetate. The combined organics were washed with two portions of saturated aqueous sodium chloride solution, dried over anhydrous Na_2SO_4, filtered, and concentrated at 50°C on the rotary evaporator . The product was then vacuum distilled through a 12-inch Goodloe column. The material was collected as two major fractions: 806 g, (bp 81-87 °C, 0.5 torr. 87% gc purity), 147 g, (bp 87-90 °C, 0.5 torr. 86.8% gc purity). The total yield was 953 g. Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.55; H, 11.29. $[\alpha]^{25}_D$ -3.39° (c=2.0, $CHCl_3$). ^1H Nmr ($CDCl_3$) 0.92 (d, 3H, J=7 Hz, CH_3), 1.10-1.47 (m, 2H, CH_2), 1.57-1.76 (m, 1H, CH), 1.61 (d, 3H, J~1.5 Hz, CH_3), 1.70 (d, 3H, J~2 Hz, CH_3), 1.90-2.34 (m, 4H, 2 CH_2), 2.27 (s, 3H, CH_3), 5.09 (tm, 1H, J_{vic} = 7 Hz, CH), 6.08 (dt, 1H, J_{trans} = 16 Hz, $J_{allylic}$ = 2 Hz, =CH-), 6.80 (dt, 1H, J_{trans} = 16 Hz, J_{vic} = 7 Hz, =CH-).

(3E,2RS,6R,)-6,10-Dimethyl-2-hydroxy-3,9-undecadiene (7)

A flame-dried, 22 l, 3-necked flask equipped with mechanical stirrer, thermometer, Vigreux column, distilling head, and nitrogen inlet was charged with 12.6 l of 2-propanol, 1.015 kg of aluminum isopropoxide and 934 g (4.85 mol) of the enone (6). The mixture was stirred at gentle reflux and acetone was removed through the

distilling head. Gc analysis showed that the starting material was completely consumed after 5.5 h. The reaction mixture was then cooled to room temperature, house vacuum (approx. 27 mm) was applied and 2-propanol was distilled out. The residue was cooled to 0°C and carefully acidified with 3.0 l of 2N HCl. After stirring for 0.5 h, 1.0 l of water was added and the mixture was extracted with three 2.0 l portions of ether. The combined organics were washed with two 1.0 l portions of saturated $NaHCO_3$, followed by one 1.0 l portion of saturated NaCl. The ether solution was dried with $MgSO_4$, filtered, and the solvent removed on the rotary evaporator . The residual oil obtained weighed 942 g (99% yield) and had a gc purity of 87%. This material was used as is in the following step. An analytical sample was distilled at 72-8°C/0.06-0.08 mm. Anal. Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found C, 79.78; H, 12.20. $[\alpha]^{25}_D$ 0.0° (c=1.99, $CHCl_3$).

(*3E,2RS,6R*)-6,10-Dimethyl-3,9-undecadien-2-yl Butanoate (8)

A 12 l, 3-necked flask equipped with mechanical stirrer, thermometer, dropping funnel and nitrogen inlet was charged with 642 g (3.27 mol) of alcohol (8), and 173 g of pyridine. The solution was cooled to +5°C and a solution of 594 g (0 mmol)of butyric anhydride and 7.5 g of *N,N*-dimethylaminopyridine (DMAP) in 173 g of pyridine was added over 1 h. The batch temperature was maintained at 5-10°C. When the addition was complete, the reaction was allowed to warm to room temperature while stirring for 3 h. Subsequent gc analysis showed that all of the alcohol had been consumed.

The reaction was quenched by slow addition of the mixture to a 3.5 l stirring solution of saturated $NaHCO_3$. The mixture was stirred for an additional h. An additional 100 g of $NaHCO_3$ was added over 10 min and then stirred for 0.5 h. 2.0 l of water was added to the mixture, which was then extracted with two 2.0 l portions of ether. The ether layers were combined and washed with 2.0 l of 2N HCl, followed by 2.0 l of saturated aqueous NaCl, dried with $MgSO_4$, filtered, and condensed on the rotary evaporator at 50 °C, to give 822 g (94.1%) of crude butyrate (80% gc purity). This material was then fractionally distilled through a 16" Goodloe column. The main fractions taken were at 95-100 °C, 0.5 torr, 137 g (95.6% gc purity), and 100-104 °C, 0.5 torr, 337 g (94.7% gc purity). The total yield was 514 g (59%). ^{1}H Nmr ($CDCl_3$) 0.86 (d, 3H, J=7 Hz, CH_3), 0.95 (t, 3H, J=7 Hz, CH_3), 1.02-1.38 (m, 2H, CH_2), 1.30 (d, 3H, J=6 Hz, CH_3), 1.48 (m, 1H, CH), 1.61 (d, 3H, J~1.5 Hz, CH_3), 1.56-1.74 (m, 2H, CH_2), 1.69 (d, 3H, J~2 Hz, CH_3), 1.77-2.14 (m, 4H, $2CH_2$), 2.27 (t, 2H, J=7 Hz, CH_2), 5.09 (tm, 1H, J_{vic} = 7 Hz, =CH-), 5.34 (m, 1H, CH), 5.46 (dd, 1H, J_{trans} = 16 Hz, J_{vic} = 7 Hz, =CH-), 5.66 (dt, 1H, J_{trans} = 16 Hz, J_{vic} = 7 Hz, =CH). Anal. Calcd for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35. Found C, 76.84; H, 11.54. $[\alpha]^{25}_D$ -2.0° (c=5.0, $CHCl_3$).

(*3E,2R,6R,*)-6,10-Dimethyl-2-hydroxy-3,9-undecadiene (9)

A 3 l three-necked flask was fitted with a mechanical stirrer and a pH electrode which automatically delivered 4N aqueous NaOH solution from a reservoir. The flask was charged with 1170 ml of pH 8 buffer solution (0.05 M monobasic potassium phosphate/NaOH), 280.5 g (0.958 mol) of (*2RS,3E,6R*)-6,10-dimethyl-3,9-undecadien-2-yl butyrate (91.0% gc purity). Stirring was started and the pH of the mixture was adjusted to 7.5 by dropwise addition of sufficient 85% phosphoric acid. Then 7.6 g of Triton X-100 was added, followed by 12.1 g of lipase from a Pseudomonas sp. (Lipase P Amano).

The pH of the reaction mixture was maintained between 7.4 and 7.6 by automatic addition of the 4N NaOH solution. Based on the rate of addition, the enzyme activity at t=15 min was calculated to be 67.2 units/gram of enzyme.

At 46% conversion, based on consumption of 111.6 ml of 4N NaOH solution, the reaction was quenched by addition of 1300 ml of 2B ethanol. The mixture was allowed to stir over the weekend.

The mixture was then filtered through a pad of Celite and the solid washed with 3 x 500 ml of 1:1 ether/hexane mixture. The filtrate and washing mixture was divided into two portions and each, separately was treated with 200 ml of brine and extracted with 3 x 1 l of 1:1: ether/hexane mixture. The combined organic layers were dried over Na_2SO_4 and stripped of solvent under reduced pressure, yielding 254.8 g of cloudy yellow liquid. This liquid contained (*2R,6R,3E*)-6,10-dimethyl-2-hydroxy-3,9-undecadiene and (*2S,6R,3E*)-6,10-dimethyl-3,9-undecadien-2-yl butyrate. This crude alcohol/butyrate mixture was vacuum distilled through a 30 cm Goodloe column to give (*2R,6R,3E*)-6,10-dimethyl-2-hydroxy-3,9-undecadiene in the following fractions:

Fraction#	Temp(°C)	press (mmHg)	Wt.(g)	Gc purity & alcohol/butyrate ratio	Color
1	77-9	0.05	1.8	58.6/0.0	colorless
2	73-5	0.075	4.4	68.3/0.0	colorless
3	76	0.05	45.3	92.2/0.0	colorless
4	77	0.075	42.9	92.3/0.0	colorless
5	78-91	0.1	47.7	8.7/83.5	light yellow
6	94-6	0.05	31.8	0.0/92.6	light yellow
7	91-4	0.1	15.7	0.0/94.1	light yellow
8 (pot)	--	--	~52.4	--	yellow

After the distillation, some material rinsed out of the column with hexane was combined with the pot residue as recyclable butyrate.

The (*2R,6R,3E*)-6,10-dimethyl-2-hydroxy-3,9-undecadiene contained in fraction 5 was isolated by chromatography on silica gel (543 g of 70-230 mesh) initially using 2% ethyl acetate in hexane as eluent. In this manner, 40.8 g of the butyrate (90.0% purity) was recovered from distillation fraction 5. By eluting with 25% ethyl acetate in hexane, 5.0 g of 100% pure (Kugelrohr distilled) alcohol was recovered from distillation fraction 5.

The total isolated yields of the alcohol and the butyrate were 46.0% and 46.9% respectively, based on gc chemical purity of the various fractions.

The diastereomeric excess of the alcohol obtained was 95.8%. The diastereomeric excess of the butyrate obtained was 93.8%.

Methyl (*2R,6R,3E*)-6,10-Dimethyl-3,9-undecadien-2-yl Carbonate

A flame dried, argon filled, 5 l three-necked Morton flask was set up with a mechanical stirrer and dry ice/acetone cooling bath. The flask was charged with 279.2 g (1.33 mol) of (*2R,6R,3E*)-6,10-dimethyl-2-hydroxy-3,9-

undecadiene having a chemical purity of 93.8% and a diastereomeric excess of ~95%. To this was added 500 ml of dry THF *via* syringe. An addition funnel mounted on the flask was charged via cannula with 860 ml (1.33 mol) of n-butyl lithium (1.55 M in hexane solution). After chilling the flask contents in the dry ice/acetone bath for 10 min, dropwise addition of the n-butyllithium was started, and completed during 80 min. The addition funnel was rinsed into the flask with 1 x 50 ml and 1 x 30 ml of dry THF. The funnel was then charged with 114.4 ml (139.9 g, 1.48 mol) of distilled methyl chloroformate (97%). Thirty min after the n-butyllithium addition was completed, dropwise addition of the methyl chloroformate was started. After this addition was complete, the cooling bath was removed, and the mixture was stirred overnight under argon and at room temperature. By tlc analysis, the reaction was complete.

The reaction mixture was poured in four portions into a separatory funnel containing 1400 ml of saturated NH_4Cl solution, with shaking between addition. The reaction flask was rinsed into the funnel with 500 ml of water and 600 ml of ether. After thoroughly shaking the mixture, the organic layer was removed, and combined with 2 x 600 ml ether extracts of the aqueous layer. The combined organic material was washed with 1 l of water, dried over 550 g of Na_2SO_4, filtered and stripped of solvent on the rotary evaporator. Finally, after pumping under a vacuum (<1 mm Hg) the yield of the crude carbonate was 381 g.

This material was chromatographed in two portions on a total of 8 kg of silica gel, first using 2% (v/v) ethyl acetate/hexane and then 4% (v/v) ethyl acetate/hexane. The columns were run at a flow rate of 150-200 ml/min, collecting 450 ml fractions. The elution of product was monitored by tlc. The fractions containing pure carbonate were stripped of solvent with the rotary evaporator , and then put under high vacuum to yield 342.1 g (101%) of methyl (*2R, 6R, 3E*)-6,10-dimethyl-3,9-undecadien-2-yl carbonate as a colorless liquid. An analytical sample was Kugelrohr distilled at *ca.* 115-140°C/0.2 mm. $[\alpha]^{25}_D$ 41.63° (c=1.2%, $CHCl_3$). Anal. Calcd for $C_{15}H_{28}O_3$: C, 70.27; H, 11.01. Found: C, 70.09; H, 10.38.

Methyl (*S*)-(6-Benzyloxy-2,5,7,8-tetramethylchroman-2-yl)acetate (15)

The methyl ester of (*S*)-2,5,7,8,-tetramethylchromanyl-2-yl)acetic acid was made by the method described previously.[3] A 200 g lot (0.76 mol) of (*S*)-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)acetic acid was dissolved in 3.5 l methanol in a magnetically stirred 5 l flask. Then 20 g of toluene sulfonic acid monohydrate was added, and the solution was brought to reflux, under argon atmosphere for 18 h. The reaction was determined to be complete by tlc (2:1 petroleum ether:ether). The methanol was removed under reduced pressure, and the resulting tacky oil was taken up in 0.5 l ethyl acetate. This solution was washed with two 0.5 l portions of saturated aqueous $NaHCO_3$. After separating the organic layer, the aqueous layer was extracted with three 100 ml portions of ethyl acetate. The combined organics were then dried with 40 g $MgSO_4$, filtered, and the solvent was removed in vacuo giving 214.2 g of material which solidified.

200 g (0.72 mol) of this methyl (*S*)-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)acetate was dissolved in 1.0 l of dimethylformamide (DMF) (which was stored over molecular sieves), in a 3.0 l three-neck flask equipped with a magnetic stirrer. Benzyl chloride was passed through a 100 g plug of neutral alumina, to remove color and any water. A 216 ml (1.88 mol) portion was treated this way just prior to adding it to the DMF solution. To the resulting solution 252.2 g (1.83 mol) of anhydrous K_2CO_3 which had been finely powdered in small batches with a mortar and pestle was added. The reaction was stirred 4 days at ambient temperature. Tlc (2:1, petroleum

ether:ether) showed that the reaction was still not complete. A second charge of K_2CO_3, 100 g (0.72 mol was added and the reaction was stirred an additional day. The reaction was quenched by adding 1 l of water to the K_2CO_3 slurry. Three layers formed; two organic and one aqueous. The organic layers merged on addition of the four 200 ml portions of ethyl acetate used to extract the aqueous layer. The combined organics were dried with 100 g $MgSO_4$, filtered, and the solvent removed under vacuum. This solvent removal was first done with house vacuum at 40 °C to remove the ethyl acetate, and then at approximately 1 mm pump vacuum at 60 °C to remove the DMF and benzyl chloride. This resulted in 250 g of crude material (94.3% yield) which was chromatographed on 1000 g of silica with 10% EtOAc/hexane. 239.3 g (90.4%) of the pure material was obtained.

(*S*)-(6-Benzyloxy-2,5,7,8-tetramethylchroman-2-yl)acetic Acid (16)

210.9 g (0.57 mol) of methyl (*S*)-(6-benzyloxy-2,5,7,8-tetramethyl-chroman-2-yl)acetate was dissolved in 6.0 l of methanol in a 12 l three-neck flask, which was mechanically stirred. 572 ml of freshly prepared 2N NaOH solution was added and the solution was stirred for three days (With less methanol the starting material crystallizes out). After the three days the reaction was not complete and two additional 100 ml portions of 2N NaOH were added at 24- h intervals. On the fifth day tlc indicated that the starting material was consumed and at this point the methanol was removed by rotary evaporation to yield a white salt. 872 ml of 2N HCl was used to acidify the salt, and this aqueous solution was then extracted with four 500 ml portions of 1:1 ether/hexane. (After the first extraction, 40 g NaCl was added for better partition of the layers). The combined organics were dried with 100 g $MgSO_4$, filtered, and the solvent removed by rotary evaporation, yielding 197.0 g (97%) of white residue which crystallized on standing. Recrystallization from ether/hexane afforded colorless crystals with mp 94-96° and $[\alpha]^{25}_D$ -10.63° (c=1.52, EtOH). Based on reported[3] rotation of -11.15°, this material has an optical purity of 93-5%.

(*S*)-(6-Benzyloxy-2,5,7,8-tetramethylchroman-2-yl)acetic Acid Chloride

201.0 g (0.57 mol) of (*S*)-(6-benzyloxy-2,5,7,8-tetramethylchroman-2-yl) acetic acid was dissolved in 1.0 l of toluene and transferred to a 3.0 l three necked flask equipped with a Dean-Stark trap, condenser, magnetic stirrer, and a thermometer connected to a heating mantle. The solution was refluxed for 1 h with no appreciable amount of water collecting in the Dean-Stark trap. This was removed, and the solution was cooled to 50 °C. Then a pressure equalizing addition funnel was placed on top and 58.5 ml (0.68 mol, 1.2 equiv.) of oxalyl chloride was added, dropwise, at a rate of about one drop per second. The color became orange, the temperature increased to about 60 °C as gas evolution began smoothly. The rate of addition was monitored so that gas evolution was not to vigorous. The gas evolved was bubbled through two aqueous sodium hydroxide traps. The slow addition was continued over about 1 h and then heating was applied using the temperature controller to keep the temperature at 60 °C. The solution was then concentrated by rotary evaporation, and after pumping off any residual solvent for 2 h, 215.2 g (~100%) of the acid chloride was obtained.

(*S*)-3-Oxo-4-[3,4-dihydro-2,5,7,8-tetramethyl-6-benzyloxychroman-2-yl]butanoic Acid Methyl Ester (12)

211.4 g (0.57 mol of (*S*)-(6-benzyloxy-2,5,7,8-tetramethylchroman-2-yl)acetic acid chloride was dissolved in 250 ml of dichloromethane and placed in a 1000 ml pressure equalizing addition funnel. 89.9 g (0.62 mol, 1.1 equiv.) of recrystallized Meldrum's acid was dissolved in 200 ml of dichloromethane. Because of some insoluble material present, the solution was passed through a fritted funnel and 0.1 equiv. (8 g) of additional Meldrum's acid was dissolved in 100 ml of dichloromethane (1.2 equiv. total Meldrum's acid added) and also filtered. This solution was transferred to a 3.0 l round bottom flask and cooled in an ice water bath. 114 ml (1.42 mol, 2.5 equiv.) of pyridine was added quickly to the magnetically stirred solution. The acid chloride solution was added dropwise at about two drops per second. The solution became characteristically crimson and was stirred overnight, coming to room temperature during that time.

The reaction was then poured into a 4.0 l separatory funnel containing 500 ml of crushed ice and 300 ml of 6N HCl. After vigorous shaking, the layers were allowed to separate, and after removing the organic layer the aqueous phase was extracted with three portions of 100 ml dichloromethane. The organic phase was washed with 300 ml saturated aqueous sodium chloride. The aqueous wash was then extracted with three 100 ml portions of dicloromethane. The combined organics were dried with 100 g Na_2SO_4 and 30 g $MgSO_4$, filtered, and the solvent was removed on the rotary evaporator. This resulted in 288.1 g of material (272.5 g theoretical, which was taken up in 2000 ml of methanol. This solution was brought to reflux, with magnetic stirring under argon atmosphere, and thus reacted for 4 h. The methanol was then removed on the rotary evaporator to obtain 234.5 g of dark red crude material.

This crude material was dissolved in 100 ml of 15% ethyl acetate/hexanes, and the minimum amount of ethyl acetate required to dissolve all of the material. This solution was then applied to a 500 g plug of silica gel, eluted with 15% ethyl acetate/hexanes and five 500 ml fractions were taken. Then five 500 ml fractions with 25% ethyl acetate/hexanes, and finally five 500 ml fractions with ethyl acetate. Those fractions containing the product were condensed on the rotary evaporator. This amounted to 232 g of yellow oil which was taken up in 1000 ml of hot 5% ethyl acetate/hexanes. On cooling some material precipitated and thus 40 ml (4%) of ethyl acetate was added to redissolve the solids. The solution was loaded onto a Separations Technologies Lab 2000 preparative hplc instrument and eluted with 6% ethyl acetate (3 gal. ethyl acetate per 55 gal. drum of hexane). The refractive index detector was of little help, and 5 gal. fractions were taken. The fractions containing the desired product were condensed with a Buchi 10 l rotary evaporator, to give 174.9 g (75%). The ketoester obtained was recrystallized by dissolution in 2000 ml methanol and then water was added to the cloud point, followed by warming. The solution was cooled with mechanical stirring overnight. 153.6 g (66%) of crystals thus formed were filtered and dried under vacuum.

The rotation of the recrystallized material was $[\alpha]^{25}_D$ +15.29° (c=2.54, $CHCl_3$) i.e. 97.45% ee (reference sample $[\alpha]^{25}_D$ +15.69° (c=2.54, $CHCl_3$). It was determined to be one enantiomer by nmr and shift reagents at 400 MHz. The mp was 86-87 °C. Anal. Calcd for $C_{25}H_{30}O_5$: C, 73.15; H, 7.37. Found: C, 73.23; H, 7.49. Material recrystallized from ether/hexane has mp 68-69°C.

(2*S*,4'*R*,8'*R*)-6-Benzyloxy-2-(3'-carbomethoxy-2'-oxo-4',8',12'-trimethyl-5',11'-tridecadienyl)-2,5,7,8-tetramethylchroman (22)

18.00 g (0.37 mol) of 50 % NaH was weighed into a 3000 ml three-neck flask equipped with magnetic stirrer, septum, and two vacuum take-offs; one take-off connected to a mineral oil bubbler, and the other connected to the vacuum/argon manifold. The flask was purged three times, evacuating and then flushing with argon. The NaH was washed with three portions of 50 ml of hexanes which were added by syringe, stirred, allowed to settle, and then removed by syringe. The flask was then evacuated and the argon atmosphere was added. Following this, 100 ml of anhydrous THF (distilled from sodium/benzophenone ketyl) was added by syringe.

153.6 g (0.37 mol) of (*S*)-3-oxo-4[3,4-dihydro-2,5,7,8-tetramethyl-6-(benzyloxy)chroman-2-yl]-butanoic acid methyl ester was weighed into a 500 ml Schlenk tube, equipped with magnetic stirrer and septum. The flask was purged three times (evacuating at high vacuum and replacing the atmosphere with argon) and then 300 ml of anhydrous THF was transferred from the THF still to this flask by cannula. (The cannula was first blown through with argon from the THF still, and then connected to the Schlenk tube. A slight vacuum was applied to the Schlenk tube to facilitate the THF transfer. The starting material was fully dissolved within 10 min of stirring. During this time a positive pressure of argon was maintained.

The ketoester solution was then transferred to the NaH slurry by cannula. Here again positive pressure in the Schlenk tube, and a slight vacuum in the reaction flask facilitated the transfer. The rate of addition was monitored to keep the gas evolution from being too vigorous. Several times the gas was bled off with the vacuum to sustain the flow.

During the addition, the flask did become warm, but no cooling was used. Finally, 50 ml of anhydrous THF was added by syringe to the Schlenk tube (as a wash) and this wash was also flushed through the cannula. Once pressure was equalized, the bubbler was again opened and positive pressure maintained while the subsequent solutions were prepared.

95.9 g (0.37 mol) of methyl (*2R,6R,3E*)-6,10-dimethyl-3,9-undecadien-2-yl carbonate (**15**) was weighed into a 250 ml Schlenk tube equipped with stirbar and septum. This system was purged three times with argon and then 50 ml of anhydrous THF was added by syringe.

5.0 g (0.0043 mol, 1.1%) of $Pd(PPh_3)_4$ (Aldrich) was quickly transferred from the ampule it was shipped in to a 500 ml Schlenk tube equipped with stirbar and septum. The system was purged three times with argon. Then, 200 ml of anhydrous THF was transferred to the flask by syringe, and the catalyst dissolved with stirring to give a lime green solution.

The NaH/ketoester solution in the main reaction vessel was now cooled to about -78 °C with a dry ice/acetone bath. While maintaining positive argon pressure, the cannula was disconnected at the ketoester Schlenk tube and connected to the C_{13}-carbonate Schlenk tube. The main vessel bubbler was closed, and by applying a slight vacuum the carbonate solution was transferred to the main reaction flask. 50 ml of anhydrous THF was added (as a wash) to the Schlenk tube, by syringe and this wash was passed through the cannula to the reaction.

Under positive argon pressure, the cannula was disconnected at the carbonate Schlenk tube and quickly connected to the catalyst Schlenk tube. In the same manner a partial vacuum applied to the reaction vessel aided the transfer of the catalyst to the reaction flask. The Schlenk tube was washed with 50 ml of anhydrous THF, which was added by syringe and passed through the cannula to the reaction.

The reaction was stirred overnight, allowing it to come to room temperature during this time. A small aliquot was removed from the reaction by syringe, and worked up with 1.0 ml of 3N HCl and extracted with 2.0 ml of hexane. The solution was analyzed by tlc with 10% ethyl acetate/hexane against samples of the C_{13}-carbonate and the ketoester. The reaction was determined to be complete, having consumed the carbonate, and leaving some ketoester.

The reaction was diluted with 500 ml of hexane and quenched with a solution of 150 ml of 3N HCl added to 500 ml of crushed ice, all of which was poured into the reaction mixture. Gas was evolved as the acid solution was added. After vigorous mixing in a 4.0 l separatory funnel the layers were separated and the organic layer was washed with 500 ml of saturated aqueous sodium chloride. The aqueous layer was extracted with three 500 ml portions of hexane, then 100 ml of dichloromethane which dissolved the last traces of solids believed to be organic. The combined organics were dried with 200 g $MgSO_4$, filtered, and condensed on the rotary evaporator. After pumping, the crude mass weighed 243.2 g (220.32 g theoretical). A parallel reaction yielded 158.3 g (147.21 g theoretical). These two samples were combined, dissolved in 100 ml of 25% ethyl acetate/hexanes, and eluted through a 1000 g plug of silica gel with 25% ethyl acetate/hexanes, collecting 1000 ml fractions. The fractions containing product were concentrated, made up to 1000 ml and loaded onto the Separations Technologies Lab 2000 Prep hplc. The product was eluted with 5% ethyl acetate/hexane. 352.5 g (96%) of crystal clear golden oil was obtained. Anal. Calcd for $C_{38}H_{52}O_5$: C, 77.51; H, 8.90. Found: C, 77.48; H, 9.07%, $[\alpha]^{25}_D$ +15.85° (c = 0.9648, $CHCl_3$).

(*2S,2'RS,4'R,8'R*)-6-Benzyloxy-2-(3'-carboxy-2'-hydroxy-4',8',12'-trimethyl-5',11'-tridecadienyl)-2,5,7,8-tetramethylchroman (25)

350.0 g (0.59 mol) of the coupled keto ester (22) was dissolved in 4000 ml of methanol, with 100 ml of ether added as a cosolvent to facilitate dissolution, in a 12 l flask equipped with a mechanical stirrer. 9.25 g (0.59 mol) of $NaBH_4$ was added, to the stirring solution. After 1 h the reaction was analyzed by tlc (24% ethyl acetate/hexane) against starting material. Not being complete, another 9.25 g portion of $NaBH_4$ was added. After another h, by tlc, the reaction was still incomplete. Five subsequent portions of $NaBH_4$ were added. The reaction was then stirred for two days unattended. tlc after that time showed a little starting material still present. The solution was concentrated to a volume less than 1000 ml and a final portion of $NaBH_4$ was added (8 mol equiv. total).

After stirring for 2 h there was still a trace of starting material, but the reaction was essentially complete.

The reaction was quenched by slow addition of 500 ml of 3N HCl to the stirring solution. The mixture was extracted with five portions of 1:1 petroleum ether:ether. The combined organics were dried with 200 g $MgSO_4$, filtered, and the solvent removed on the rotary evaporator. After pumping off the residual solvent 350.9 g (99.9%) of a viscous white oil was obtained. Anal. Calcd for $C_{38}H_{54}O_5$: C, 77.25; H, 9.21. Found: C, 76.61; H, 9.22. $[\alpha]^{25}_D$ -31.66° (c=1.0106, $CHCl_3$).

350.6 g (0.59 mol) of this hydroxy ester was dissolved in 1000 ml of methanol, adding 50 ml ether to get the material into solution. Then, 47.5 g (1.19 mol, 2 equiv.) of sodium hydroxide was dissolved in 1000 ml of methanol, and 18 ml of water. These solutions were combined in a 5 l flask. After stirring at reflux for 3 h, little reaction had occurred and a second 47.5 g portion of sodium hydroxide was added in 36 ml of water. 500 ml

THF (distilled) and 500 ml water were also added and the solution was brought to reflux for 3 h. The solution was milky white. Refluxing clarified the solution, and as it did, at 1 h intervals three 100 ml portions of water were added to the solution causing the cloudiness to reappear.

At the end of this time the reaction was still not complete, by tlc (25% ethyl acetate/hexane). Then a third 47.5 g portion of sodium hydroxide was added and the reaction was refluxed overnight (6 equiv./NaOH total, 850 ml water total, 500 ml THF, 2000 ml MeOH). The cooled solution was concentrated as much as possible on the rotary evaporator, using house vacuum. Then 500 ml of 6N HCl (cold) was slowly added to the cold stirring solution. The hydroxy acid was then extracted with three 500 ml portions of dichloromethane. The combined extracts were dried with 200 g $MgSO_4$, filtered, and concentrated on the rotary evaporator. After pumping off residual solvents, 350.6 g (>100% yield) was obtained which later solidified. Anal. Calcd for $C_{37}H_{52}O_5$: C, 77.04; H, 9.09 Found: C, 76.60; H, 9.16. $[\alpha]^{25}_D$ +5.79° (c=1.123, $CHCl_3$).

(2*S*,4'*R*,8'*R*)-2',5',11'-α-Tocotrienol Benzyl Ether (26)

The hydroxy acid (**25**) thus prepared was dissolved in 1000 ml of toluene in a 3.0 l three-neck flask equipped with a thermometer, magnetic stirrer, and topped with a Dean-Stark trap and condenser. The solution was brought to reflux, and the first 20 ml of distillate was removed. Cloudy as it was, no water separated. Then the solution was cooled to 60 °C and the Dean-Stark trap was replaced with a 1000 ml pressure equalizing addition funnel. 120.65 g of di-*tert*-butyldimethylformamide acetal was added to the addition funnel. This reagent was added dropwise to the stirring solution, which vigorously evolved gas and foamed. After complete addition the reaction was stirred overnight, allowing the reaction to cool. tlc (25% ethyl acetate/hexane) showed that the reaction was not complete.

The reaction was warmed again to 60 °C and checked after 2 h. At this point a second 120.65 g (0.59 mol, 1.0 equiv.) of the di-*tert*-butyldimethylformamide acetal was added, by slow dropwise addition. Again there was vigorous gas evolution and foaming. After stirring for 3 h at 60 °C the reaction was determined to be complete by tlc. There were two major high Rf products and at least four minor low Rf products. The solvent was removed on the rotary evaporator at 60 °C with house vacuum. This resulted in 340 g of crude yellow oil. This was taken up in 100 ml of 5% ethyl acetate/hexane and passed through a 1000 g plug of silica gel with 10% ethyl acetate/hexane. 500 ml fractions were taken, and all the non-polar material was collected and concentrated. This material was diluted to 1000 ml in 5% ethyl acetate/hexane and loaded onto the Separations Technologies Lab 2000 Prep hplc. It was eluted with 5% ethyl acetate/hexane. The refractive index detector was only marginally useful in deciding where to cut the fractions. Basically, 20 l fractions were taken. After concentrating the appropriate fractions on the Buchi 5 l rotary evaporator , 140.2 g (45.9% yield) of pure triene (highest Rf material) was obtained. Anal. Calcd for $C_{36}H_{50}O_2$: C, 83.99; H, 9.79. Found: C, 82.93; H, 9.81. $[\alpha]^{25}_D$ +37.01° (c=1.1105, $CHCl_3$). 13.8 g (4.5% yield, 50.4% total yield) of material contaminated with the lower Rf material, and 137.8 g (36.7% yield) of lower Rf material were also obtained. The lower Rf material was determined to be the *tert*-butyl ester (27). Anal. Calcd for $C_{41}H_{60}O_5$: C, 77.80; H, 9.56. Found: C, 77.53; H, 9.38. Some more polar materials were also eluted from the column, but were not characterized.

nmr analysis of the triene (26) prepared in this manner showed it to be a cis/trans mixture at the newly formed (2') double bond.

Vitamin E, (*d*)-α-Tocopherol (3)

126.0 g (0.24 mol) of the triene (26) was dissolved in 1000 ml of ethyl acetate. This was hydrogenated at 500 psi with 6.3 g of 5% platinum on carbon at 25 °C. After 4 h the uptake of hydrogen was complete. Filtration and solvent removal under vacuum resulted in 126.5 g (99.2%) of the saturated product.

126.0 g of this material was dissolved in 600 ml of 100% ethanol, and 50 ml of dry THF was added to get all of the material into solution. 10 g of 10% palladium on carbon was added as catalyst and the solution was hydrogenated at 60 psi for 4 h, at which time the hydrogen uptake was complete.

Tlc of the reaction was cleanly one spot, and the solution was colorless. While filtering in air and concentrating the material at 40 °C on the rotary evaporator using aspirator vacuum, the product picked up cloudiness and became brown in color. This amounted to 110.1 g (>100% crude yield). This material was dissolved in 100 ml of 5% ethyl acetate/hexane which was saturated with argon. This solution was applied to a 500 g plug of silica gel and flash eluted with 5% ethyl acetate/hexane (argon saturated) using argon as the pressurizing gas. The 500 ml fractions taken were covered, and quickly sealed after removal from the collection point. At the time of chromatography several minor impurities were seen in some of the fractions. the major amount 89.3 g (86% yield) of pure (one spot) material was obtained by concentrating the appropriate fractions and then pumping at 10^{-5}mm for 4 days. The other fractions were condensed, and pumped down and amounted to 8.6551 g (8.3%) (94% total yield).

The essential identify of this material with natural (*d*)-α-tocopherol was established by spectroscopic comparison, particularly nmr.

Diastereomer analysis (results in text) was carried out using capillary gas chromatography of the derived methyl ether, using the published method of preparation and analysis.[20]

(*S*)-1-[3,4-Dihydro-2,5,7,8-tetramethyl-6-benzyloxychroman-2-yl]-3'-phenylsulfonyl-2-propanone (13)

25.8 g (0.070 mol) of methyl (*S*)-(6-benzyloxy-2,5,7,8-tetramethyl-chroman-2-yl)-acetate (15) was added to a 500 ml three-neck flask equipped with a magnetic stirring bar and argon inlet and outlet adaptors. The flask was evacuated and refilled with argon. 50 ml of dry THF was added by syringe to dissolve the compound.

Methyl phenyl sulfone (10.94 g, 0.070 mol) was weighed into a 300 ml Schlenk tube equipped with a stirring bar and septum. The Schlenk tube was evacuated, refilled with argon, and charged with 150 ml of dry THF, using a syringe. The Schlenk tube and contents were chilled to 0 °C. A solution of 2.6 M butyllithium in hexane (2 x 27 ml = 0.144 mol) was added from a syringe in two portions. The second addition produced a creamy orange slurry of the dianion. After stirring for 15 min, this mixture was transferred *via* cannula to the three-neck flask containing the methyl ester in THF. A 50 ml portion of dry THF was then used to complete the transfer by washing the walls of the Schlenk tube. After stirring the resulting mixture for two h, the reaction had warmed to room temperature, and was quenched with 40 ml of 2N HCL. The mixture was transferred to a 1 l separatory funnel. Hexane (100 ml) and brine (50 ml) were added and, after shaking, the layers were separated. The aqueous layer was extracted with 3 x 30 ml of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ an evaporated to a solid residue (43.7 g). This material was recrystallized from 500 ml of ethanol giving 31.3 g

(90.8% yield) of product as a pale yellow solid. A second crop of 4.0 g of less pure material was also obtained, but kept separate.

An analytical sample was recrystallized from ethanol to give colorless crystals with mp 130-138 °C, and $[\alpha]^{25}_D$ +14.09° (c=0.9225, $CHCl_3$). Anal. Calcd for $C_{29}H_{32}O_5S$: C, 70.70; H, 6.54; S, 6.50. Found: C, 70.40; H, 6.71, S, 6.59. ^1H Nmr ($CDCl_3$) 1.30 (s, 3H, CH_3), 1.84 (m, 2H, CH_2), 2.08 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 2.57 (m, 2H, CH_2), 2.86, 2.99 (AB, 2H, J=14 Hz, CH_2), 4.32 (s, 2H, CH_2), 4.70 (s, 2H, CH_2), 7.26-7.87 (m, 10H, 2 phenyl).

[*2S-(4R,5E,8R*]-1-[2,5,7,8-Tetramethyl-6-benzyloxychroman-2-yl]-4,8,12-trimethyl-3-phenylsulfonyltrideca-5,11-dien-2-one (23)

A 300 ml Schlenk tube containing a stirring bar was charged with 16.0 g (0.0325 mol) of the ketosulfone (13) and closed with a septum. The tube was evacuated and refilled with argon. A 50 ml portion of dry THF was added by syringe; giving a clear solution.

A 1 l three-neck flask was set up with a stirring bar, argon inlet and exit adaptors, and a septum to seal the center neck. This flask was charged with 1.559 g (0.0325 mol of NaH, 50% in oil. Two 10 ml portions of hexane were used to wash out the oil, a syringe being used to remove the hexane after the NaH had settled. The flask was evacuated, filled with argon, and charged with 100 ml of dry THF. The ketosulfone solution in the Schlenk tube was transferred in, *via* cannula, using 50 ml of dry THF to complete the transfer. A solution of 8.327 g (0.0325 mol) of allylic carbonate (5) in 10 ml of dry THF was prepared in a 100 ml Schlenk tube under argon. The main reaction flask was then chilled in a dry ice/acetone bath and the allylic carbonate solution was then transferred in via cannula. Some dry THF was also used here to complete the transfer. A solution of the catalyst $Pd(PPh_3)_4$, 1.126 g (0.000974 mol, 3 mol percent) in 100 ml of dry THF was prepared under argon, in a 100 ml Schlenk tube. This solution was also transferred to the main reaction flask *via* cannula.

The reaction mixture was allowed to stir overnight, during which time it warmed to room temperature. By tlc analysis of a 0.2 ml aliquot (partitioned between ether and 1N HCl), the reaction was judged to be complete.

The reaction was quenched by addition of 40 ml of 2N HCl and 100 ml of brine, followed by 100 ml of hexane. The mixture was transferred to a separatory funnel and shaken. The organic layer was separated and the aqueous layer was extracted with 3 x 25 ml of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated on the rotary evaporator. The 26.8 g of crude product thus obtained was taken up in 5% ethyl acetate/hexane, and applied to a 100 g plug of Florisil. The product was eluted with 5% ethyl acetate /hexane and collected in 50 ml fractions. The first six contained a less polar product which was discarded. Fractions 7-10 afforded 17.6 g of product containing a slight impurity at higher Rf. Fractions 11-30 afforded 3.7 g of analytically pure product. Both were viscous, colorless oils, total yield, 21.3 g (97.7%). Anal. Calcd for $C_{42}H_{54}O_5S$: C, 75.18; H, 8.11; S, 4.77. Found: C, 75.47; H, 8.11; S, 4.67.

The ^1H nmr spectrum of this product indicated a ca. 1:1 mixture of 3' epimers.

[2S-(4R,5E,8R)]-1-[2,5,7,8-Tetramethyl-6-benzyloxychroman-2-yl]-2-hydroxy-4,8,12-trimethyl-3-(phenylsulfonyl)trideca-5,11-diene (28)

A solution of β-keto sulfone (23) (3.7 g) in 80 ml of toluene was cooled to 0 °C and treated, while stirring, dropwise during 2 min, with 6.7 ml of a 25% solution of diisobutylaluminum hydride (DIBAL) in toluene. After 1 h of stirring at 0 °C, the reaction was quenched by adding 20 ml of 3N HCl. Stirring was continued for 30 min. After transfer to a separatory funnel, the organic layer was separated, washed with water, dried over Na_2SO_4 and evaporated. Crude β-hydroxy sulfone was obtained as a colorless oil, 3.8 g. The crude product showed two major spots by Tlc (diastereomers), and was used as is, after further characterization by ^1H nmr.

[2S-(4R,5E,8R)]-1-[2,5,7,8-tetramethyl-6-benzyloxychroman-2-yl]-4,8,12-trimethyl-3-phenylsulfonyltrideca-2,5,11-triene (29)

The crude β-hydroxysulfone (28) from the previous step (3.6 g) was taken up in 50 ml of pyridine, treated with 3 ml of methanesulfonyl chloride, and stirred at room temperature for 20 h. The pyridine was evaporated on the rotary evaporator at reduced pressure. The residue was stirred with 200 ml of hexane and the hexane then evaporated. An additional 200 ml of hexane was added and the insoluble material was filtered off and washed with ether. The filtrate and washing were combined and evaporated, finally under high vacuum, to leave 3.9 g of crude mesylate as a yellow gum. The product showed three main spots on tlc and was used as is, after further characterization by ^1H nmr.

The crude β-methanesulfonyloxysulfone from the previous step (3.9 g) was taken up in 75 ml of ether and treated with 2.5 ml of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and stirred at room temperature for 20 h. An additional 0.5 ml of DBN was added and stirring was continued overnight. tlc at this point showed the elimination to be complete. The reaction mixture was washed successively with 1N HCl and aqueous $NaHCO_3$, then dried over Na_2SO_4 and evaporated. The residue, 3.4 g of pale yellow oil, showed one major and several minor spots by tlc analysis. The material was used as is without further characterization by ^1H nmr.

(2S,4'R,8'R)-2',5',11'-α-Tocotrienol Benzyl Ether (26) (Ex Vinyl Sulfone 29)

The crude vinylsulfone (29) from the previous step (3.4 g) was taken up in 100 ml of cyclohexane. To this solution 100 ml of water, 1.0 g of "Aliquot 336" phase transfer reagent, 3.5 g of $NaHCO_3$, and 3.0 g of sodium dithionite ($Na_2S_2O_4$) were added. The stirring mixture was heated at reflux for 1.5 h. Then, an additional 1.0 g of $Na_2S_2O_4$ was added, followed by an additional h at reflux. A final addition of 0.5 g of $Na_2S_2O_4$ was followed by thirty min of reflux, and then stirring at room temperature overnight. The mixture was transferred to a separatory funnel and the organic layer was removed. The aqueous layer was extracted with hexane and the combined organic layers were washed with water, dried over Na_2SO_4 and stripped of solvent under reduced pressure. The residue was chromatographed on silica gel using 5% ethyl acetate/hexane. The fractions containing the triene were combined and evaporated leaving 730 mg (27.3%) of colorless oil. This actually represents an overall yield on four steps from ketosulfone (23). ^1H Nmr ($CDCl_3$) 0.84, 0.86 (d, 3H, J=6.5 Hz, CH_3), 0.90-1.50 (m, 3H, $CHCH_2$), 1.04, 1.07 (d, 3H, J=6.5 Hz, CH_3), 1.23, 1.24 (s, 3H, CH_3), 1.60 (brs, 3H, CH_3), 1.68 (brs, 3H, CH_3), 1.72-2.08 (m, 6H, $3CH_2$), 2.12 (brs, 3H, CH_3), 2.17 (s 3H, CH_3), 2.23 (s, 3H, CH_3), 2.29, 2.38 (m, d, 2H, J_{vic}=6 Hz, CH_2), 2.61 (t, 2H, J=7 Hz, CH_2), 2.85, 3.15 (br, 1H, CH), 4.71

(s, 2H, CH_2), 5.09 (brt, 1H, J=7 Hz, =CH-), 5.24-5.55 (m, 4H, 2CH=CH-), 7.24-7.55 (m, 5H, phenyl). This material appears to be a single (2'-trans) isomer.

Vitamin E, (*d*)-α-Tocopherol (3) (Ex Sulfone Route)

As in the previous route, the side-chain reductions and debenzylation were effected in two steps. (a) The triene (26) (730 mg) was dissolved in 15 ml of ethyl acetate, mixed with 60 mg of 10% platinum on carbon, and hydrogenated at 8°C overnight under 500 psi of hydrogen. The catalyst was filtered off and washed and the filtrate evaporated to leave 630 mg of (d)-α-tocopherol benzyl ether. ^{1}H Nmr ($CDCl_3$) 0.80-2.00 (9 side chain Hs), 2.10 (s, 3H), 2.18 (s, 3H), 2.23 (s, 3H), 2.60 (t, J=7 Hz, 2H), 4.72 (s, 2H), 7.40 (m, 5H).

(b) The benzyl ether of (*d*)-α-tocopherol (630 mg) was debenzylated by hydrogenation in ethanol/THF (10 ml of a 9:1 mixture) over 80 mg of 10% palladium on carbon at 8°C for 3 h under 60 psi of hydrogen. The catalyst was filtered off and washed and the clear, colorless filtrate was evaporated, transfers being conducted under argon to avoid exposure to air. The residue weighed 510 mg (83.5% from 26) and acquired a pale brownish color on storage. ^{1}H Nmr ($CDCl_3$) 0.85 (overlapping doublets, 12H side chain methyls), 1.00-1.90 (m with s at 1.23, side-chain Hs and ring methyl), 2.15 (s, 6H), 2.19 (s, 3H), 2.62 (t, J=7 Hz, 2H).

Diastereomer analysis (results in text) was carried out using capillary gas chromatography of the derived methyl ether, using the published method of preparation and analysis.[20]

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