SYNTHESIS OF 2R,4'R,8'R-α-TOCOPHEROLS SELECTIVELY LABELLED WITH DEUTERIUM*

K.U. Ingold, L. Hughes, M. Slaby and G.W. Burton

Division of Chemistry, National Research Council of Canada

Ottawa, Ontario, Canada K1A 0R6

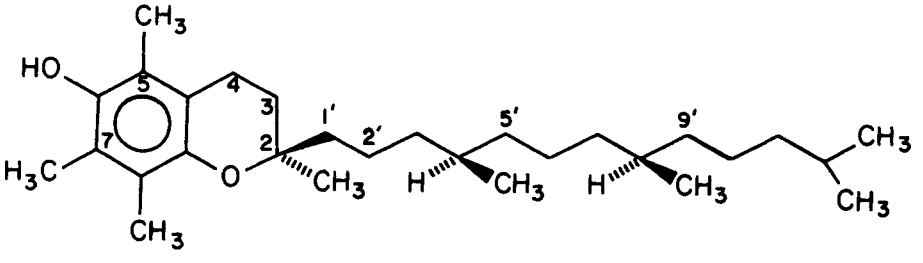
SUMMARY

Nine deuterium-labelled α-tocopherols having the natural, 2R,4'R,8'R, stereochemistry have been synthesized for study by ^2H NMR of the orientation and dynamics of natural α-tocopherol in a phospholipid bilayer.

Keywords: Deuterated α-tocopherols

INTRODUCTION

Vitamin E plays a vital role in protecting biological membranes from peroxidative damage (1). The major component of vitamin E and the component with the most bioactivity is α-tocopherol (1). There are eight possible stereoisomers of α-tocopherol but the natural compound, which has the 2R,4'R,8'R structure, 1, is the most active *in vivo* (2). We have



1

shown that vitamin E is the major (and possibly only) peroxyl-radical trapping, chain-breaking antioxidant present in the lipid extractable fractions of human plasma and erythrocyte ghost membranes (3) and of various animal

---

*Issued as NRCC No. 26593

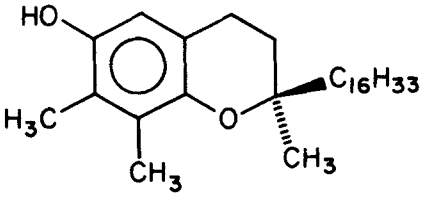
0362-4803/87/070817–15$07.50
© 1987 by John Wiley & Sons, Ltd.
Received November 18, 1986

tissues (4). We have also shown that in phospholipid bilayers natural α-tocopherol is located with the chromanol head group (which contains the phenolic OH group) fairly close to the surface of the bilayer (5). The hydrophobic phytyl "tail" is presumably buried deep within the hydrocarbon region of the bilayer. In order to obtain more information regarding the overall orientation and dynamics of natural α-tocopherol in a phospholipid bilayer and, by extension, in a biological membrane we required 2R,4'R,8'R-α-tocopherol specifically labelled with deuterium in a number of positions. These compounds were then incorporated into egg lecithin phosphatidyl choline unilamellar vesicles for study by deuterium NMR (6). In this paper, we describe the synthesis of nine 2R,4'R,8'R-α-tocopherols that have been specifically labelled with deuterium at the numbered positions, or the methyl groups attached to these positions, indicated in structure 1.

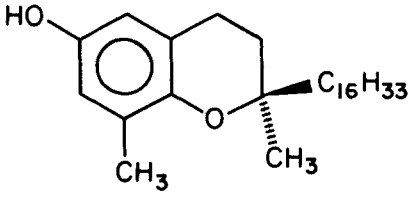
DISCUSSION

The deuterium labelled 2R,4'R,8'R-α-tocopherols (α-T) that have been prepared are: 2, (5-CD_3-α-T); 3, (5,7-$(CD_3)_2$-α-T); 4, (3,4-D_2-α-T); 5, (3-D_1-α-T); 6, (1',1'-D_2, 2-CD_3, 3,3-D_2-α-T); 7, (1',1'-D_2-α-T); 8, (2',2'-D_2-α-T); 9, (5',5'-D_2-α-T); and 10, (9',9'-D_2-α-T). Incorporation of deuterium was verified by ^1H, ^2H and ^{13}C NMR spectroscopy and by GC/MS (see Table I).

Compounds 2, (5-CD_3-α-T) and 3, (5,7-$(CD_3)_2$-α-T) were prepared by the $SnCl_2$-catalyzed deuteromethylation with perdeutero-paraformaldehyde (7) of (natural) 2R,4'R,8'R-γ-tocopherol, 11, and (natural) 2R,4'R,8'R-δ-tocopherol, 12, respectively.



11



12

Compound 4, (3,4-D_2-α-T) was synthesized by a Bouveault-Blanc reduction of [3,4-dehydro]-2R,4'R,8'R-α-tocopherol, 13, with Na in C_2H_5OD (8) (see Scheme 1). The ^1H, ^2H and ^{13}C NMR, as well as GC/MS indicated a 1:1 addition of deuterium across the double bond. Hydroboration of 13

TABLE I. Principal Ions in the Mass Spectra of Selectively Deuterium Labelled 2R,4'R,8'R-α-Tocopherols

Compound (No.)	Mol. Wt.	No. of D atoms	m/e (relative intensity)[a]
D_0-α-T (1)	430	0	428(1.5),430(100),431(35.5),432(5.4), 433(0.7)
(5-CD_3)-α-T (2)	433	3	430(1.5),432(15.8),433(100),434(41.4)
(5,7-(CD_3)$_2$)-α-T (3)	436	6	430(<0.1),435(24.9),436(100),437(44.6)
(3,4-D_2)-α-T (4)	432	2	430(25.5),432(100),433(44.9)
(3-D_1)-α-T (5)	503[b]	1	502(<0.1),503(88.2),504(100),505(42.1)
(1',1'-D_2,2-CD_3, 3,3-D_2)-α-T (6)	437	7	430(0.4),433(10.0),434(20.6),435(44.9), 436(88.5),437(100),438(33.2)
(1',1'-D_2)-α-T (7)	432	2	430(4.5),431(15.0),432(100),433(398)
(2',2'-D_2)-α-T (8)	432	2	430(6.2),432(100),433(36.5)
(5',5'-D_2)-α-T (9)	432	2	430(9.3),432(100),433(37.3)
(9',9'-D_2)-α-T (10)	432	2	430(6.4),432(100),433(35.1)

[a]Normalized to base peak

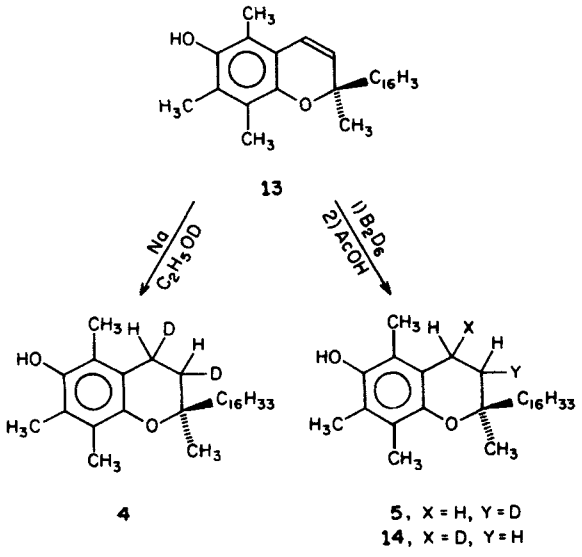
[b]$(CH_3)_3Si$ ether derivatives of a mixture of 58% 5 and 42% 4.

with deuterodiborane and subsequent protonolysis with glacial acetic acid gave 5 (3-D_1-α-T) (see Scheme 1) and 4 (3,4-D_2-α-T). We were surprised to find the di-deuterated compound but the mass spectrum of the product mixture leaves no doubt as to its presence. The combined MS and ^2H NMR data also lead to the surprising conclusion that the other anticipated monodeuterated compound, 14 (4-D_1-α-T) was not present in detectable quantities. The actual mixture contained 58% 5 and 42% 4.

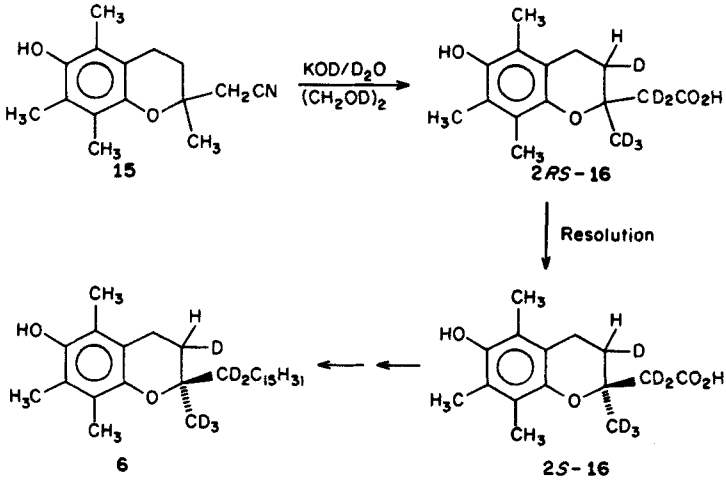
Compound 6 (1,1'-D_2,2-CD_3,3,3-D_2-α-T) (see Scheme 2) was synthesized by a KOD/D_2O saponification of the nitrile (9), 15, in ethylene glycol-$(OD)_2$ to give the acid 2RS-16. This acid was resolved with (S)-(-)-α-

methylbenzylamine to obtain 2S-16 and a complete synthesis of 6 was achieved by the procedure of Cohen et al (10).

Compound 7 (1',1'-D_2-α-T) (see Scheme 3) was synthesized (9) via a sodium methoxide/CH_3OD ring-opening of the methyl ester, 17, to give the



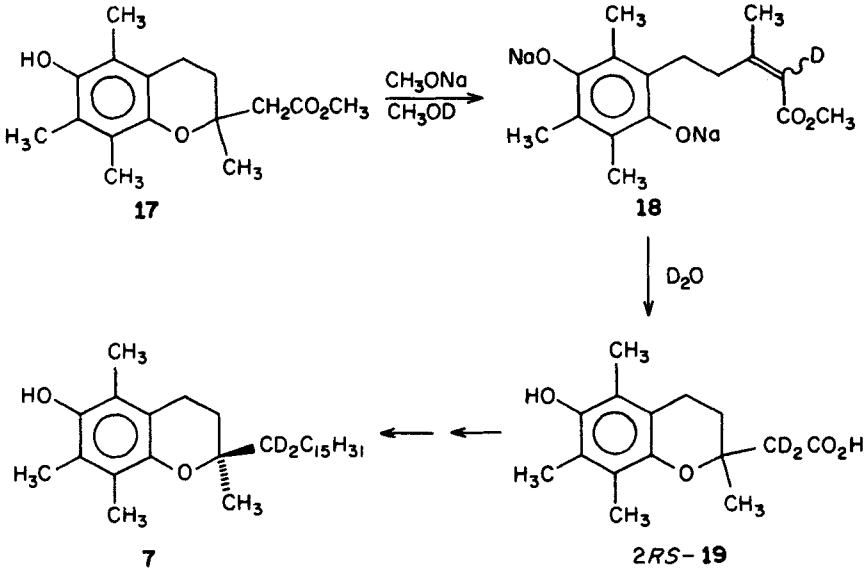
SCHEME 1



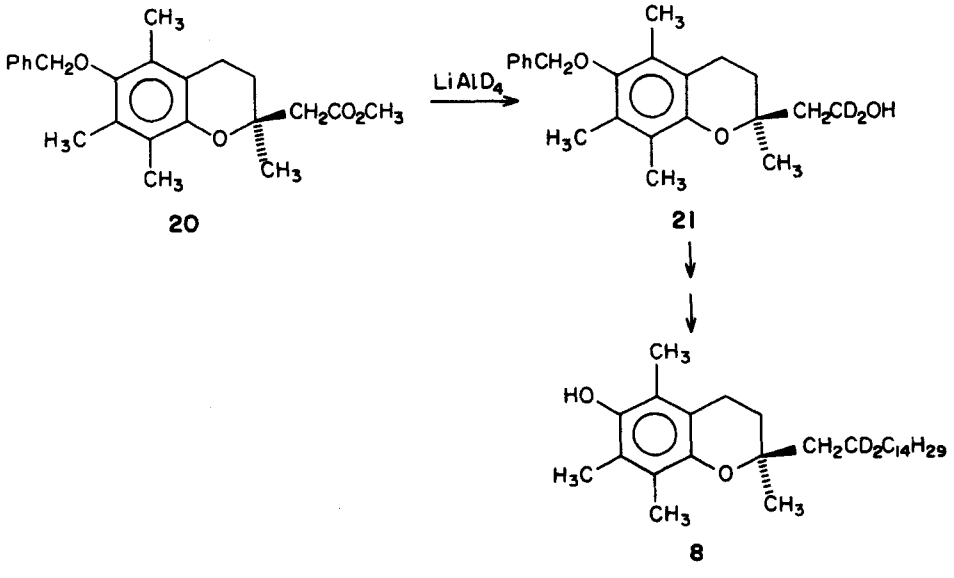
SCHEME 2

achiral ester, 18, treatment of which gave the acid, 2RS-19, which was resolved and chain extended as above for 2R,2S-16.

Compound 8 (2',2'D_2-α-T) (see Scheme 4) was synthesized by a $LiAlD_4$ reduction of the ester 20, (11), to give the alcohol, 21, from which 8 was obtained by the procedure of Cohen et al (10).

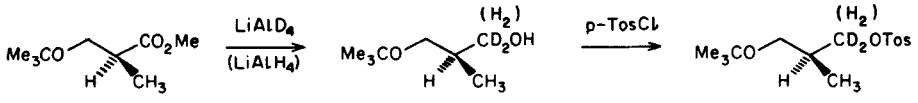


SCHEME 3



SCHEME 4

To prepare compounds 9 (5,5'-D_2-α-T) and 10 (9',9'-D_2-α-T) (see Schemes 6 and 7, respectively) we first synthesized the appropriate di-deuterated bromides 27 and 30, respectively, by homologation of the tosylate, 24-D_2 with appropriate alkyl group synthons (10). This tosylate was prepared from (S)-(+)-methyl-3-tert-butoxy-2-methylpropionate (10) (see Scheme 5). The di-deutero bromides were coupled with the 2-chromanethyl tosylate, 28, by the Fouquet-Schlosser procedure (12). Subsequent hydrogenation yielded 9 and 10.



22 23 24 - D_2 (24 - H_2)

SCHEME 5

EXPERIMENTAL

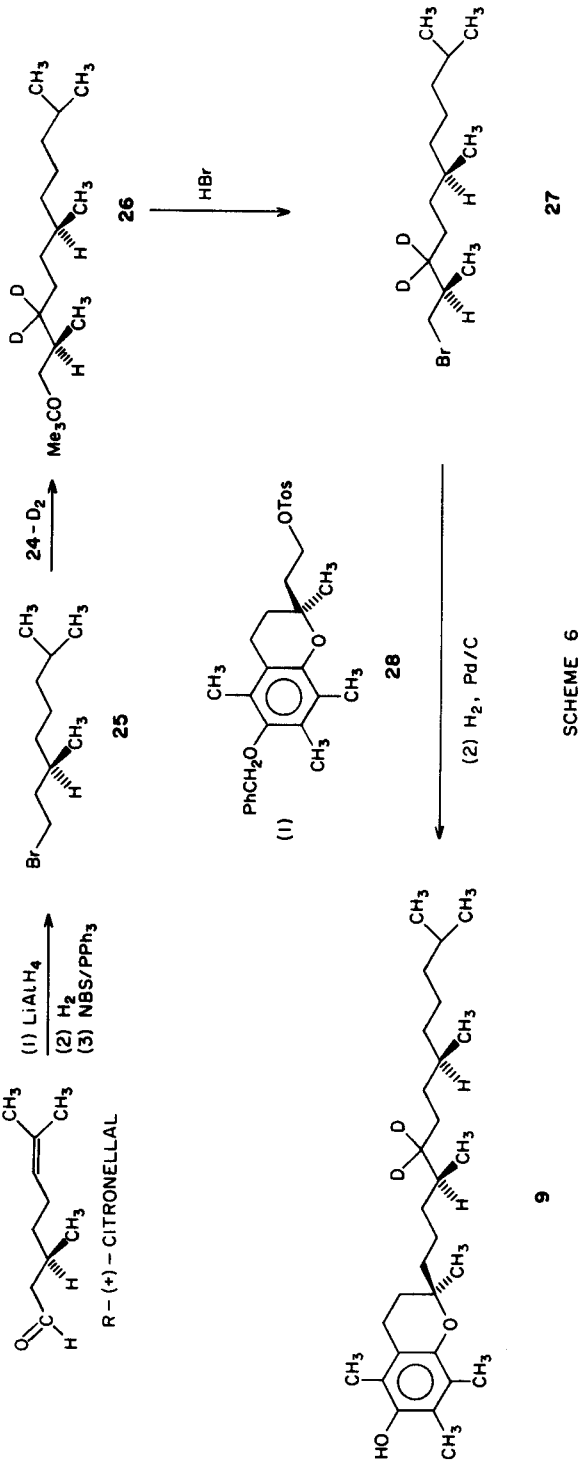
Materials

2R,4'R,8'R-γ-tocopherol, 11, and 2R,4'R,8'R-δ-tocopherol, 12, were obtained from soybean deodorizer distillate via saponification and flash chromatography (13). The soybean distillate was a gift from the Central Soya Corporation.

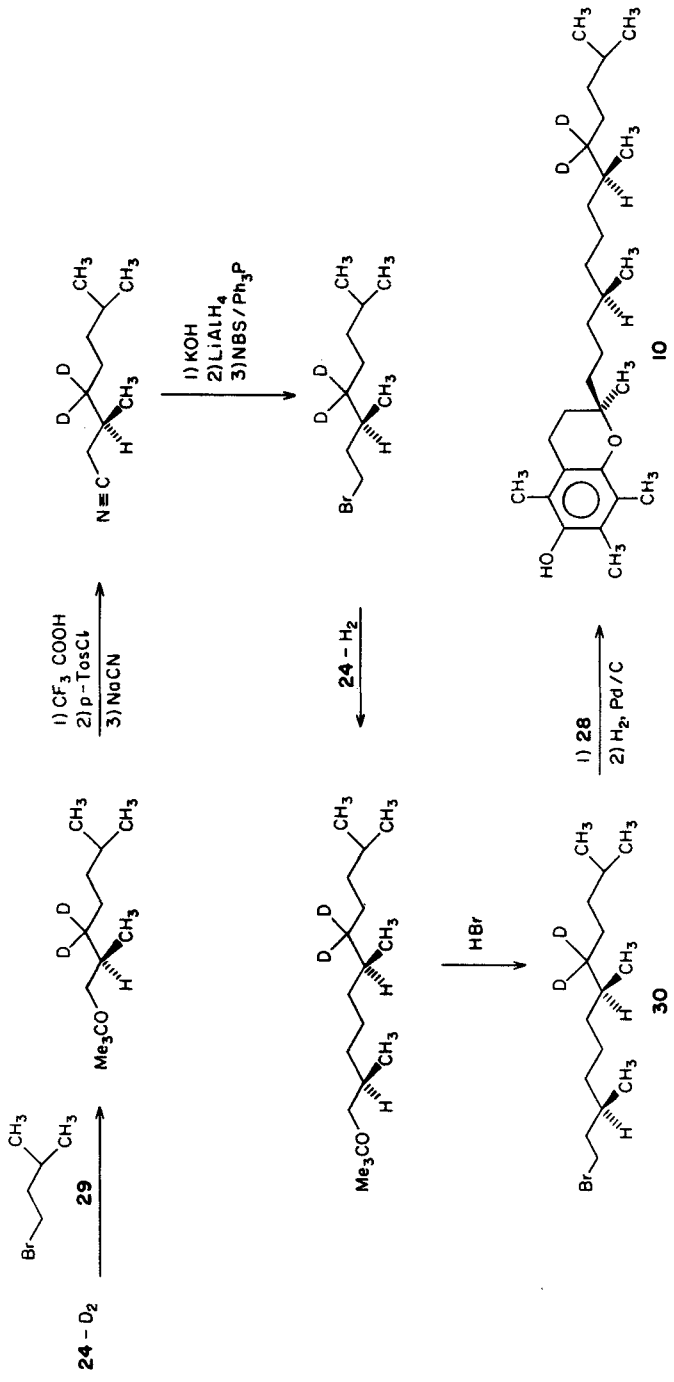
Commercial stannous chloride was made anhydrous by treatment with acetic anhydride, filtration, washing with ether and drying under high vacuum for 24 hrs. Perdeutero-formaldehyde, DCl (35% in D_2O) and KOD (40% in D_2O) were obtained from Merck, Sharp and Dohme. Lithium aluminum deuteride, (S)-(-)-α-methylbenzylamine, and (S)-(+)-methyl-3-hydroxy-2-methylpropionate were obtained from Aldrich. (R)-(+)-Citronellal, was obtained from Fluka Biochemicals and was purified by column chromatography. Tetrahydrofuran was fractionally distilled from calcium hydride under an atmosphere of nitrogen.

Methods

Thin layer chromatography was performed on silica gel (60F-254) BDH plates and developed with ethyl acetate/hexane (usually 12% ethyl acetate


R-(+)-CITRONELLAL
(1) LiAlH4
(2) H2
(3) NBS/PPh3
25
24-D2
26
HBr
27
(1)
28
(2) H2, Pd/C
9

SCHEME 6


24 - D2
29
Me3CO
1) CF3 COOH
2) p-TosCl
3) NaCN
N≡C
1) KOH
2) LiAlH4
3) NBS / Ph3P
Br
24 - H2
Me3CO
HBr
30
1) 28
2) H2, Pd/C
HO
10

SCHEME 7

in hexane). Spots were visualized using a phosphomolybdic acid spray (3.5% in ethanol) followed by heating at 80°C. Column chromatographic purifications followed the "flash" method (13) using Merck grade 60 silica gel (230-400 mesh, 60Å) from Aldrich.

Unless otherwise noted, reactions were carried out under a nitrogen atmosphere. The "usual" work-up involved 3 extractions into the solvent specified. The organic extracts were combined, washed with water, $NaHCO_3$ solution or dilute HCl as required, saturated brine, dried over Na_2SO_4, filtered, and concentrated at 30°C on a rotary evaporator. The residue was further dried to constant weight under high vacuum. All yields given refer to isolated yields obtained after a final purification by column chromatography using ethyl acetate in hexane as the eluting agent.

Mass spectra were measured on a Hewlett-Packard 5970A Mass Selective Detector using an HP-Ultra I fused silica capillary gas chromatographic column (10m × 0.2 mm i.d., OV-101 type, cross-linked bonded phase).

^2H NMR spectra were recorded on a Bruker 300 MHz instrument. ^1H and ^{13}C spectra were recorded on a 500 MHz Bruker instrument unless otherwise noted. Published (14,15) ^{13}C NMR spectral data for α-tocopherol were used as an aid in determining the extent of deuteration at specific positions. All the deuterated α-tocopherols exhibited either broadening or complete absence of the ^{13}C NMR peaks at the expected (14,15) (i.e., deuterated) positions. In addition, all deuterated tocopherols had ^1H NMR spectra identical to that of undeuterated 1 except for the absence of peaks at the appropriate position(s). ^2H NMR further confirmed the precise nature of the deuterated tocopherols.

Compounds 2-10 were homogeneous on T.L.C. (12% ethyl acetate/hexane) with a reference sample of 1, R_f = 0.59.

Syntheses

(5-CD_3)-2R,4'R-8'R-α-Tocopherol, 2: The synthesis followed that of Urano et al (7). Minor modifications improved the yield from 44% (7) to 67%. γ-Tocopherol, 11, 4 g (9.6 mmol) was dissolved in 400 ml anhydrous isopropyl ether. To this solution were added 17 g (89.9 mmol) $SnCl_2$

(anhydrous), 57 ml DCl (35%) and 0.7 g $(CD_2O)_n$. The solution was refluxed 3.5 hrs, after which time no 11 could be detected by T.L.C. (12% ethyl-acetate/hexane). The reaction mixture was poured onto ice and the organic phase was washed with water until the aqueous phase was neutral to litmus, then dried over Na_2SO_4, filtered, evaporated to dryness and purified by column chromatography (3% ethyl acetate in hexane). Yield 6.7 g (67%). ^{1}HNMR (60 MHz, $CDCl_3$, Me_4Si (int)) δ 2.1 (s, 3H, 7-Ar-CH_3), 2.2 (s, 3H, 8-Ar-CH_3), 2.6 (t, 2H, Ar-CH_2-CH_2, J = 9 Hz).

(5,7-$(CD_3)_2$)-2R,4'R,8'R-α-Tocopherol, 3: δ-Tocopherol, 12, 0.3 g (0.72 mmol) was dissolved in 30 ml anhydrous isopropyl ether and reacted with 2.57 g (13.5 mmol) $SnCl_2$ (anhydrous), 8.5 ml DCl (35%), and 0.256 g $(CD_2O)_n$. The mixture was refluxed for 24 hrs, "Usual" work-up gave 3; yield = 1.8 g (60%). ^{1}H NMR (60 MHz, $CDCl_3$, Me_4Si (int)) δ 2.2 (s, 3H, 8-Ar-CH_3), 2.6 (t, 2H, Ar-CH_2-CH_2, J = 9 Hz).

(3,4-D_2)-2R,4'R,8'R-α-Tocopherol, 4: Compound 13 (which was obtained by reduction of its acetate prepared according to ref. 8) 0.5 g (1.16 mmol) was dissolved in 30 ml C_2H_5OD and 4.3 g Na (0.186 g-atom) was added in small portions. The mixture was refluxed 1.5 hrs and was then left for 24 hrs at room temperature. After this time a further 20 ml C_2H_5OD was added and this was followed by 30 ml of brine. "Usual" work-up in ether (followed by column chromatography with 5% ethyl acetate in hexane) gave 4; yield 3.5 g (70%). ^{2}H NMR ($CHCl_3$, $CDCl_3$ (int)) δ 1.78 (s, 1D, Ar-CHD-CHD), 2.59 (s, 1D, Ar-CHD-CHD). ^{1}H NMR ($CDCl_3$, Me_4Si (int)) δ 1.71 and 1.77 (2d, 1H, Ar-CHD-CHD, $J_{1.71}$ = 6.5 Hz, $J_{1.77}$ = 7.3 Hz), 2.1 (s, 6H, 5- and 7-Ar-CH_3), 2.2 (s, 3H, 8-Ar-CH_3), 2.6 (d, 1H, Ar-CHD-CHD, J = 5.7 Hz). ^{13}C NMR ($CDCl_3$, Me_4Si (int)) δ 20.5 (t, Ar-CHD-CHD, J = 28.3 Hz), 31.15 (t, Ar-CHD-CHD, J = 28.3 Hz), broadened signals at δ 23.75 (CH_3-C-CH_2) and 40.5 (CH_3-C-CH_2).

(3-D)-2R,4'R,8'R-α-Tocopherol, 5: 3,4-Dehydro-2R,4'R,8'R-α-tocopherol acetate (8), 0.5 g (1.16 mmol) was dissolved in 6 ml anhydrous ether, cooled to 0°C and treated with B_2D_6. The B_2D_6 was generated in a separate flask as follows: A slurry of 0.297 g (7.07 mmol) $LiAlD_4$ in 10 ml anhy-

drous ether was added dropwise during 1 hr to a cooled (0°C) solution of 1.16 ml (8.9 mmol) $BF_3 \cdot O(Et)_2$. The gaseous B_2D_6 produced was continuously bubbled via a double-tipped needle into the ethereal solution of the dehydro-α-tocopherol, the entire system being kept under a slight positive nitrogen pressure. Both the B_2D_6 generating flask and the ether solution were allowed to come to room temperature and were left at this temperature for 24 hrs, after which time a T.L.C. analysis (12% ethyl acetate in hexane) showed that none of the dehydro-α-tocopherol acetate remained. The reaction mixture was treated with 10 ml glacial acetic acid and stirring was continued for 40 hrs at room temperature. Addition of brine, the "usual" work-up with ether and a final purification by column chromatography (5% ethyl acetate in hexane) gave a yellow resin; yield 0.15 g (30%). From the MS, ^1H NMR and ^2H NMR the deuterium content of this mixture can be represented by:

$$Ar\text{-}CH_{ca.1.58}\text{—}D_{ca.0.42}\text{—}CH_{ca.1.0}\text{—}D_{ca.1.0}\ .$$

^2H NMR ($CHCl_3$, $CDCl_3$ (int)) δ 1.78 (s, Ar-C-C<u>D</u>), 2.59 (s, Ar-C<u>D</u>-C). ^1H NMR ($CDCl_3$ Me_4Si (int)), δ 1.73 and 1.78 (2t, Ar-C-C<u>H</u>, $J_{1.73}$ = 7.1 Hz, $J_{1.78}$ = 6.8 Hz), 2.1 (s, 6H, 5- and 7-Ar-C<u>H</u>$_3$), 2.2 (s, 3H, 8-Ar-C<u>H</u>$_3$), 2.6 (t, Ar-C<u>H</u>-C, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$, Me_4Si (int)) broadened signals at δ 20.5 (Ar-<u>C</u>D-C), 23.7 (<u>C</u>H$_3$-C-CH$_2$), 31.15 (Ar-C-<u>C</u>D) and 40.5 (CH$_3$-C-<u>C</u>H$_2$). We conclude on the basis of the NMR and mass spectral data that this material contains 58% <u>5</u>, and 42% <u>4</u>.

(1',1'-D_2,2CD_3,3,3,-D_2)-2<u>R</u>,4'<u>R</u>,8'<u>R</u>-α-Tocopherol, <u>6</u>: The starting material was <u>15</u> prepared according to Cohen et al's procedure (9). Pure <u>15</u>, 11.2 g (45.7 mmol), was treated with 25 ml ethylene glycol-$(OD)_2$ and 50 g (35.0 mmol) KOD (40% w/w in D_2O) and refluxed for 17 hrs at 145°C using an oil bath. After this time the solution was cooled in ice, 170 ml D_2O was added and the pH was adjusted to 8.8 by the dropwise addition of 32 ml conc. (35% w/w) DCl. After removal of neutral products by filtration and ether extraction (x2), the aqueous phase was further acidified to a pH of 1.1 with conc. DCl. A tan precipitate was formed and crystallization was completed by stirring the slurry at 0°C for 2 hrs. The material,

2RS-16, was homogeneous on T.L.C. (25% ethyl acetate in hexane) with an undeuterated, authentic reference sample; yield 7.5 g (66.9%). ^{2}H NMR (CH_3OH, CD_3OH (int)) δ 1.41 (s, 3D, CD_3-C-CD_2), 1.89 (s, 1D, Ar-CH_2-CDD), 2.03 (s, 1D, Ar-CH_2-CDD), 2.54 (s, 2D, CD_2-CO_2H). ^{1}H NMR (Me_2SO, Me_4Si (int)) δ 1.95 (s, 3H, Ar-CH_3), 2.01 (s, 3H, Ar-CH_3), 2.04 (s, 3H, Ar-CH_3), 2.61 (d, 2H, Ar-CH_2-CHD, J = 8 Hz). ^{13}C NMR ($CDCl_3$, Me_4Si (int)) δ 11.1 (5-Ar-CH_3), 11.7 (8-Ar-CH_3), 12.1 (7-Ar-CH_3), 21.5 (Ar-CH_2-CD_2), signals absent at: 32.5 (Ar-CH_2-CD_2), 32.7 (CD_3-C-CD_2CO_2H), 41.5 (CD_3-C-CD_2-CO_2H).

The racemic acid was resolved with (S)-(-)-α-methylbenzylamine (9) to obtain 2S-16 and the synthesis was continued exactly as described by Cohen et al (10). Final yield of 6 1.2 g (23.5% based on starting 2S-16). ^{2}H NMR ($CHCl_3$, $CDCl_3$ (int)) δ 1.17 (s, 3D, CD_3-C-CD_2), 1.47 (s, 2D, CD_3-C-CD_2), 1.72 (s, 2D, Ar-CH_2-CD_2). ^{1}H NMR ($CDCl_3$, Me_4Si (int)), 2.1 (s, 6H, 5- and 7-Ar-CH_3), 2.2 (s, 3H, 8-Ar-CH_3), 2.6 (s, 2H, Ar-CH_2-CD_2). ^{13}C NMR ($CDCl_3$, Me_4Si (int)) signals absent at δ 23.7 (CD_3-C-CD_2), 31.5 (Ar-CH_2-CD_2), 39.8 (CD_3-C-CD_2) and 74.1 (CD_3-C-CD_2).

(1,1'-D_2)-2R,4'R,8'R-α-Tocopherol, 7: The starting material was the methyl ester of rac-3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-acetic acid, 17, which was prepared according to the procedure of Cohen et al (9). Following their procedure further, a solution of 3.1 g Na (0.134 g-atoms) in 34 ml CH_3OD was prepared by careful addition of the sodium with stirring but without cooling. To this was added dropwise 13 g (49.2 mmol) 17 which had been previously dissolved in 92 ml CH_3OD. After refluxing for 48 hrs, 23 ml D_2O were added and refluxing was resumed for 30 m. The solution was cooled to 0°C and 175 ml of conc. DCl were added dropwise. The turbid solution was stirred at 0°C for 30 m and the white precipitate was filtered and dried under high vacuum. The product, 2RS-19, was homogeneous on T.L.C. (25% ethyl acetate in hexane) with an undeuterated reference sample of the acid. The synthesis of 7 was continued as with 2RS-16 according to the procedure of Cohen et al (10). Final yield of 7 0.21 g (12.3% based on starting 17). ^{1}H NMR ($CDCl_3$, Me_4Si (int)) δ 1.55 (m, 2H, 2'CH_2), the normally overlapping multiplet from the 1'CH_2 protons

was absent. ^{13}C NMR ($CDCl_3$ Me_4Si (int)) signals absent at δ 39.9 (1'-$\underline{C}D_2$) and of reduced intensity at δ 74.1 (CH_3-$\underline{C}$-CD_2).

(2,2'-D_2)-2R,4'R,8'R-α-Tocopherol, 8: The starting material was methyl-(S)-(-)-6-benzyloxy-2,5,7,8-tetramethylchroman-2-yl acetate, 20 (11). This compound, 1,1 g (2.9 mmol) was dissolved in 10 ml anhydrous ether and the solution was added dropwise to 0.126 g (3.0 mmol) $LiAlD_4$ so as to maintain a gentle reflux. The reaction mixture was stirred 30 m without cooling, after which time T.L.C. analysis (12% ethyl acetate in hexane) indicated that none of the starting ester 20 remained. Cooling to 0°C followed by cautious, dropwise treatment with 12 ml moist ether, 6 ml water and 4.6 ml 1N H_2SO_4 gave, after the "usual" work-up with ether, the dideuterio-alcohol 21 as a white powder, homogeneous by T.L.C. (18% ethyl acetate in hexane) with an authentic, undeuterated sample: yield 0.99 g (100%). The synthesis was continued in the normal way (10) to obtain 8 in a final yield of 0.03 g (2.3% based on starting 20). ^1H NMR ($CDCl_3$, Me_4Si (int)) δ 1.55 (m, 2H, 1'-$C\underline{H}_2$), the normally overlapping multiplet from the 2'-$C\underline{H}_2$ protons was absent. ^{13}C NMR ($CDCl_3$, Me_4Si (int)) signal absent at δ 21.0 (2'-$\underline{C}D_2$).

(5,5'-D_2)-2R,4'R,8'R-α-Tocopherol, 9: The starting material, 22, was prepared by tert-butylation of (S)-(+)-methyl-3-hydroxy-2-methylpropionate (10). This compound, 6.7 g (38.9 mmol) was dissolved in 122 ml anhydrous ether and was then added dropwise to a slurry of 3.23 g (76.9 mmol) of $LiAlD_4$ and 122 ml anhydrous ether at 0°C. The mixture was stirred at room temperature for 3 hrs, after which time T.L.C. analysis (5% ethyl acetate in hexane) indicated that none of the starting ester, 22, remained. The mixture was then cooled to 0°C and the excess $LiAlD_4$ was cautiously destroyed by addition of 6 ml H_2O and 4.7 ml 10% aqueous NaOH. After stirring 18 hrs at room temperature, the mixture was filtered and washed with ether. Evaporation of the filtrate and washings in vacuo gave as a colorless liquid, (R)-(+)-3-tert-butoxy-2-methyl-(1,1-D_2)-propanol, 23: yield 6.7 g (100%). This product was homogeneous on T.L.C. (12% ethyl acetate in hexane) with an undeuterated reference sample. ^1H NMR (60 MHz,

$CDCl_3$, Me_4Si (int)) δ 0.86 (d, 3H, $C\underline{H}_3$-CH, J = 7 Hz), 1.2 (s, 9H, $(C\underline{H}_3)_3CO$), 1.95 (m, 1H, CH_3-C$\underline{H}$), 3.4 (m, 2H, $OC\underline{H}_2$), 4.65 (s, 1H, O$\underline{H}$).

Following the procedure of Cohen et al (10) the alcohol 23 was converted to its tosylate, 24-D_2, by reaction with para-toluenesulfonyl chloride (p-TSCl) and the tosylate was reacted with (R)-(+)-2,6-dimethyl-1-bromooctane, 25 (itself prepared from citronellal) by the Fouquet-Schlosser method (12) to form the tert-butyl ether, 26. Conversion to the bromide, 27, and reaction with the tosylate 28 eventually led to 9 in an overall yield of 0.3 g (1.8% based on starting 22). ^{13}C NMR ($CDCl_3$, Me_4Si (int)) signal of greatly reduced intensity at δ 37.55 (5'-$C\underline{D}_2$).

(9,9'-D_2)-2R,4'R,8'R-α-Tocopherol, 10: The tosylate 24-D_2 was coupled by the Fouquet-Schlosser method (12) with 1-bromo-3-methylbutane, 29. The remainder of the synthesis followed the procedure of Cohen et al (10) to give 10 in a final overall yield of 0.14 g (2.8% based on starting 22). ^{13}C NMR ($CDCl_3$, Me_4Si (int)) signal absent at δ 37.34 (9'-$C\underline{D}_2$).

ACKNOWLEDGEMENT

We are extremely grateful to Dr. N. Cohen for his advice and encouragement and for providing a number of the compounds used as starting or reference materials in this work. We thank the National Foundation of Cancer Research and the Association for International Cancer Research for their support of this work. We thank Dr. J.R. Brisson for recording the ^2H and high field ^1H and ^{13}C NMR spectra, Mr. D.A. Lindsay for the mass spectra and Dr. I. Ekiel for helpful discussions. We also thank the Central Soya Corporation, Decatur, Indiana for their extremely generous gift of soybean deodorizer distillate.

REFERENCES

1. Machlin, L.J., ed. - Vitamin E: A Comprehensive Treatise, Dekker, New York, 1980
2. Weiser, H. and Vecchi, M. - Internat. J. Vit. Nutr. Res. 52: 351 (1982)

3. Burton, G.W., Joyce, A. and Ingold, K.U. - Arch. Biochem. Biophys. 221: 281 (1983)

4. Cheeseman, K.H., Collins, M., Proudfoot, K., Slater, T.F., Burton, G.W., Webb, A.C. and Ingold, K.U. - Biochem. J. 235: 507 (1986)

5. Perly, B., Smith, I.C.P., Hughes, L., Burton, G.W. and Ingold, K.U. - Biochim. Biophys. Acta 819: 131 (1985)

6. Ekiel, I.H., Jovall, P.A., Smith, I.C.P., Burton, G.W., Hughes, L. and Ingold, K.U. - Manuscript in preparation.

7. Urano, S., Hattori, Y., Yamanoi, S. and Matsuo, M. - Chem. Pharm. Bull. 28: 1992 (1980)

8. Mayer, H. and Isler, O. - Methods in Enzymology XVIII: pp. 323 and 328 (1971)

9. Cohen, N., Banner, B.L. and Neukom, C. - Syn. Comm. 12: 57 (1982)

10. Cohen, N., Eichel, W.F., Lopresti, R.J., Neukom, C. and Saucy, G. - J. Org. Chem. 41: 3505 (1976)

11. Scott, J.W., Bizarro, F.T., Parrish, D.R. and Saucy, G. - Helv. Chim. Acta 59: 290 (1976)

12. Fouquet, G. and Schlosser, M. - Angew. Chem. Int. Ed. Engl. 13: 82 (1974)

13. Still, W.C., Kahn, M. and Mitra, A. - J. Org. Chem. 43: 2923 (1978)

14. Johnson, L.F. and Jankowski, W.C. - Carbon-13 NMR Spectra: Wiley Interscience, New York (1972): Spectrum No. 496

15. Matsuo, M. and Urano, S. - Tetrahedron 32: 229 (1976)