[Chem. Pharm. Bull.
36(2) 515—520 (1988)]

Synthesis of Fluorine Analogues of Vitamin E[1]

ITSUMARO KUMADAKI,* MIHOKO TAMURA, AKIRA ANDO,
TAKABUMI NAGAI, MAYUMI KOYAMA,
and TAKUICHI MIKI

*Faculty of Pharmaceutical Sciences, Setsunan University,
45–1, Nagaotoge-cho, Hirakata, Osaka 573–01, Japan*

(Received June 13, 1987)

As part of a search for biologically active analogues of vitamin E, fluorine derivatives of tocotrienol and related compounds were synthesized by the ring-closure of trifluoroprenols with trimethylhydroquinone. For this purpose, the trifluoroprenols were synthesized by the Wittig–Horner reaction of trifluoroacetone or its prenyl homologues with triethylphosphonoacetate followed by reduction of the trifluoromethylated acrylic ester derivatives. Although 4,4,4-trifluoroprenol itself did not react with the hydroquinone, 7,7,7-trifluorodiprenol and higher prenols gave 6-chromanols with a trifluoromethylated side-chain.

Keywords——vitamin E; tocotrienol; prenyl; trifluoromethyl ketone; prenol; trifluoro; cyclic condensation; trimethylhydroquinone; 6-chromanol

Vitamin E was reported as an anti-infertility factor by Evans and Bishop in 1922.[2] Since then, many reports have been published concerning its biological activities, isolation from natural products, determination of the structures of its analogues, and their synthesis. The biological activity is believed to be related to the anti-oxidative property of the 6-chromanol structure. On the other hand, vitamin E comprises a number of isomers, with differences in the number of methyl substituents on the benzene ring and the structure of the side chain at the 2-position (see Fig. 1). The activity of the vitamin E analogues is strongly affected by their side-chain structure. Thus, *d*-α-tocopherol is the most active analogue of vitamin E compounds. Vitamin E compounds are believed to combine with the cell membrane and suppress the oxidation of unsaturated fatty acids on the membrane. If this is correct, the differences of activity of vitamin E compounds must be attributed to differences in their affinity for the membrane. Namely, the lipophilicity and the steric factor must be important for the biological activity.

On the other hand, introduction of a perfluoroalkyl group into a compound was reported to enhance the lipophilicity remarkably.[3] Thus, introduction of a trifluoromethyl group in the place of a methyl group in the side-chain of a vitamin E analogue was expected to enhance its affinity for the lipophilic part of the membrane and consequently to improve its biological activity. Therefore, we attempted the synthesis of fluorinated analogues of vitamin E to examine the changes of biological activity. We would like to report here our synthesis of 6-chromanol derivatives with a trifluoroprenyl side-chain at the 2-position.

The simplest vitamin E analogues so far reported are 2,2,5,7,8-pentamethylchromanol derivatives[4] (see Fig. 2). First, we attempted the synthesis of a compound in which one of the 2-methyl groups of this compound is replaced by a trifluoromethyl group. Thus, 4,4,4-trifluoro-3-methyl-2-buten-1-ol (**2**), which was prepared from trifluoroacetone by means of the Wittig–Horner reaction followed by reduction with lithium aluminum hydride,[5,6] was treated with 2,3,5-trimethylhydroquinone in the presence of zinc chloride in acetic acid, but cyclization to the 6-chromanol compound was not observed and the starting materials were

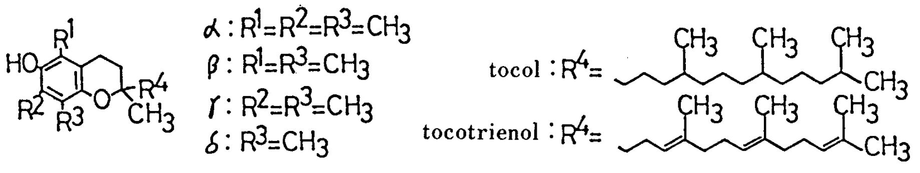

Fig. 1

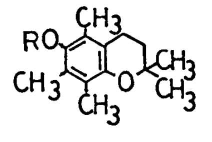

Fig. 2

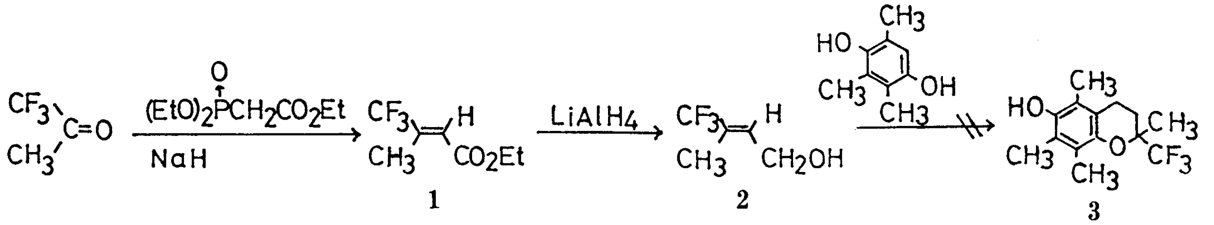

Chart 1

route 1

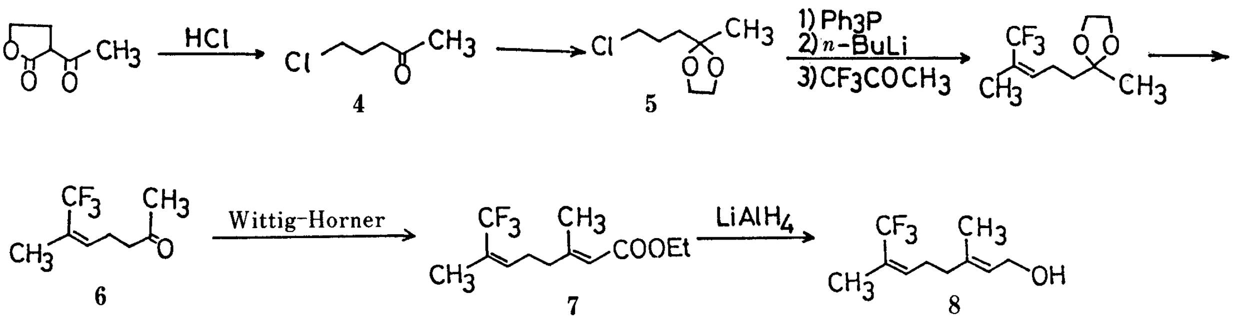

Chart 2

recovered. This cyclization was reexamined in the presence of stronger Lewis acids, such as aluminum chloride, but the chromanol compound was not formed. This may be explained by the strong electronegativity of the trifluoromethyl group, which prevented the alcohol from ionizing to form an allyl cation.(see Chart 1).

Next, the synthesis of a 2-prenyl analogue of vitamin E with fluorine substituent (**11**) was examined. For this purpose, 8,8,8-trifluoro-3,7-dimethyl-2,6-octadien-1-ol (**8**) was synthesized first. Thus, 3-acetyl-γ-butyrolactone was treated with hydrochloric acid to give 5-chloro-2-pentanone (**4**), which was converted to a ketal (**5**). Treatment of **5** with triphenylphosphine, butyllithium and trifluoroacetone in that order gave 6,6-ethylenedioxy-1,1,1-trifluoro-2-methyl-2-heptene, which was hydrolyzed to 7,7,7-trifluoro-6-methyl-5-hepten-2-one (**6**). Treatment of **6** with a Wittig–Horner reagent gave ethyl 8,8,8-trifluoro-3,7-dimethyl-2,6-octadienoate (**7**). Reduction of **7** with lithium aluminum hydride gave the objective compound (**8**) (see Chart 2). The trifluoromethylated ketone (**6**) is highly volatile and the isolation yield of this compound was very poor. Therefore, the total yield of this procedure was too low for practical use.

To avoid the above difficulty, another route to **8** was examined. Namely, the ketone **4** was treated with the Wittig–Horner reagent first to give ethyl 6-chloro-3-methyl-2-hexenoate (**9**), which was reduced to the corresponding alcohol. This was converted to a Wittig reagent after protection with tetrahydropyran, and treated with trifluoroacetone to give the tetrahydropyranyl ether of **8**. Hydrolysis of this compound afforded **8** in 59% yield, a much better yield than in the former procedure. Investigation of the fluorine magnetic resonance (^{19}F-NMR) spectrum showed that **8** was a mixture of *Z*- and *E*-isomers (ratio about 2/1). This result is interesting, since the Wittig reaction of trifluoroacetone with triphenylphosphonium ethoxycarbonylmethylide was reported to give the *E*-isomer preferentially (ratio 97/3).[6] In this case, the ylide was stabilized by the ethoxycarbonyl group and the intermediate had a longer life time than in our case. The repulsion between electronegative trifluoromethyl and ethoxycarbonyl groups controlled the stereochemistry of the reaction. In our case, the nonstabilized ylide gave the *Z*-isomer preferentially by kinetic control.

Heating of **8** (*E*/*Z* mixture) with trimethylhydroquinone in the presence of zinc chloride in acetic acid gave 2-(5,5,5-trifluoro-4-methyl-3-penten-1-yl)-2,5,7,8-tetramethyl-6-chromanol (**11**) in the yield of 41% (see Chart 3). The proton nuclear magnetic resonance (^{1}H-NMR) and ^{19}F-NMR spectra of this compound showed that it was a mixture of *E*- and *Z*-isomers (ratio about 1/2). Thus, the peak of the trifluoromethyl group at -1.11 ppm was assigned to the *Z*-isomer, while that of the *E*-isomer was seen at 6.66 ppm. This assignment is based on the results on trifluoro analogues of vitamin A reported by Liu *et al.*, who found that the ^{19}F-NMR signals of the *Z*-isomers appear at lower field than those of the corresponding *E*-isomers.[7]

Elongation of the side chain was next attempted. Thus, for the synthesis of [8-methyl-4-(trifluoromethyl)-2,5,7,8-tetramethyl-2-nona-3,7-dienyl]-6-chromanol (**16**), 3,11-dimethyl-7-(trifluoromethyl)-2,6,10-dodecatrien-1-ol (**15**) was prepared from ethyl trifluoroacetoacetate. The ester was treated with 2-methyl-3-buten-1-ol in the presence of sodium acetate to give 1,1,1-trifluoro-6-methyl-5-hepten-2-one (**12**).[8] The reaction of **12** with the Wittig re-

route 2

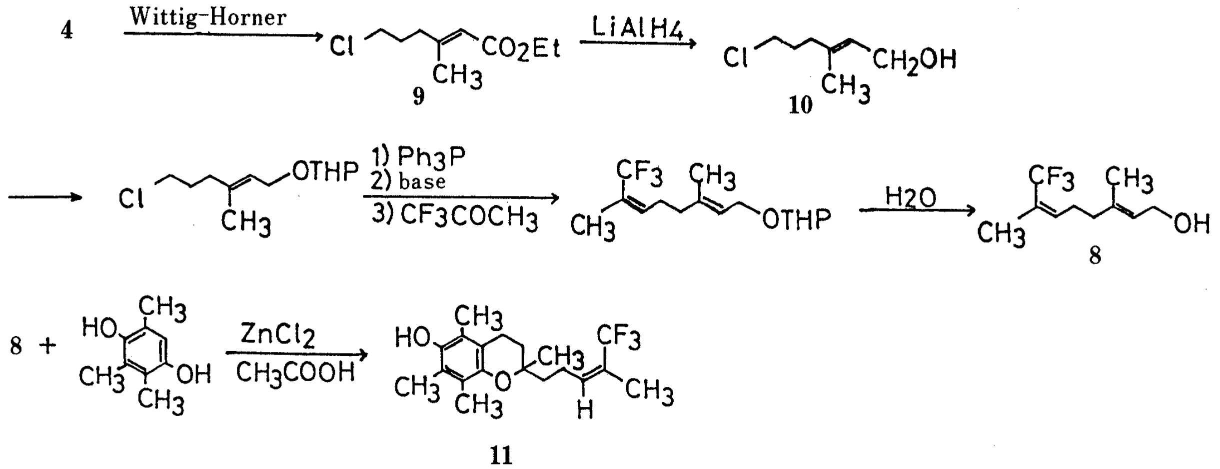

Chart 3

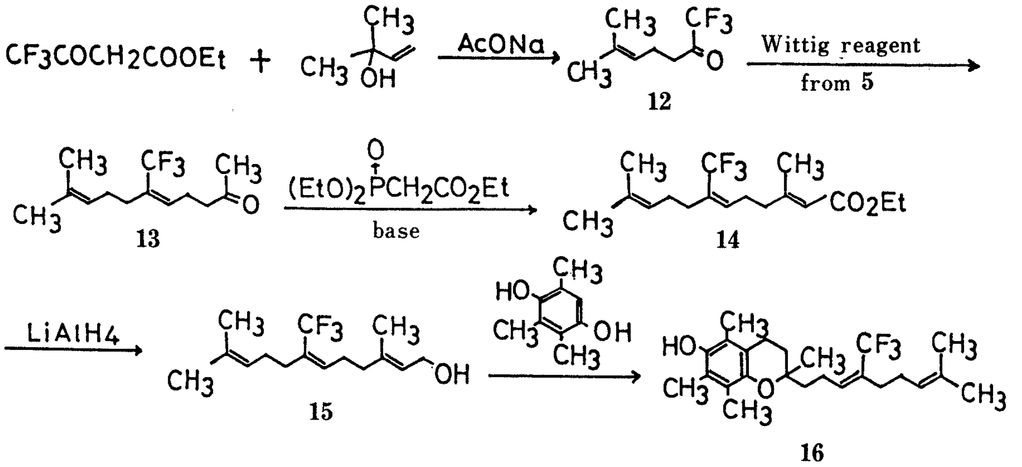

Chart 4

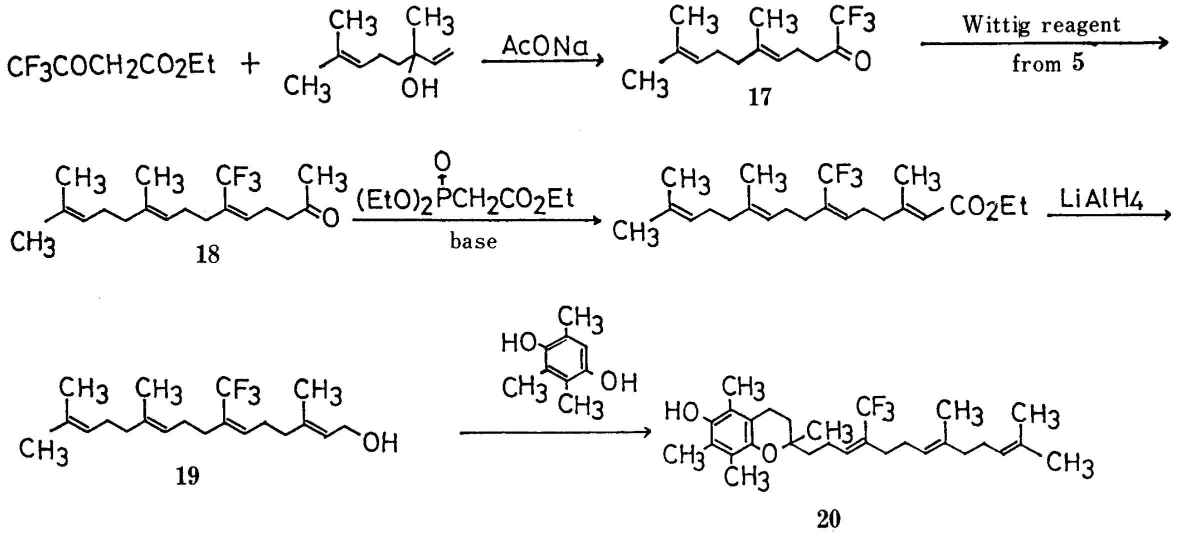

Chart 5

agent from **5** gave 10-methyl-6-(trifluoromethyl)-5,9-undecadien-2-one (**13**, 34%), the ^{19}F-NMR spectrum of which showed that the ratio of Z/E isomers was about 4/1. Compound **13** was condensed with the ethoxycarbonylmethylide to afford an ester (**14**, 76%). Reduction of **14** with lithium aluminum hydride gave **15** (96%). Condensation of **15** with trimethylhydroquinone gave the objective compound (**16**, 30%) (Chart 4).

Finally, a trifluoro analogue of tocotrienol (**20**) was synthesized through a similar route to that used for **16**. Thus, ethyl trifluoroacetoacetate was reacted with linalool to give 1,1,1-trifluoro-6,10-dimethyl-5,19-undecadien-2-one (**17**, E/Z=about 3/1),[8] which was converted to 3,11,15-trimethyl-7-(trifluoromethyl)-2,6,10,14-hexadecatetraen-1-ol (**19**) by repeated Wittig reaction and reduction. The E/Z ratio at the 5-double bond of **18** was estimated by ^{19}F-NMR to be 86/14. The condensation of **19** with hydroquinone gave **20** in the yield of 74% (Chart 5).

As mentioned above, we could synthesize trifluoromethylated 6-chromanol derivatives, **11**, **16** and **20**, by the cyclization of trifluoromethylated allyl alcohols and the hydroquinone. Investigation of the biological effects of the new analogues is in progress. We are now trying to develop a more stereoselective synthesis of these compounds and to convert them to tocopherol derivatives.

Experimental

Ethyl 4,4,4-trifluoro-3-methyl-2-butenoate (**1**) and 4,4,4-trifluoro-3-methyl-2-butenol (**2**) were synthesized according to the literature.[5,6] ^{1}H-NMR spectra were obtained on JNM-FX90Q and JNM-GX400 spectrometers. ^{19}F-NMR spectra were recorded on JNM-FX90Q spectrometer, using benzotrifluoride as an internal standard (upper field taken as plus).

5-Chloro-2-pentanone (4), Ethyl 6-Chloro-3-methyl-2-hexenoate (9) and 6-Chloro-3-methyl-2-hexen-1-ol (10)——Compound **4** was synthesized as reported.[9] Compound **9** was synthesized from **4** by means of the Wittig–Horner reaction.[10] The E- and Z-isomers were separated by column chromatography (SiO_2, hexane–Et_2O, 20:1). Both isomers were reduced with lithium aluminum hydride to give **10** (E- and Z-isomers, respectively). E-**10**: ^{1}H-NMR ($CDCl_3$) δ: 6.03 (1H, t, J=7.4 Hz), 4.17 (2H, d, J=7.4 Hz), 3.54 (2H, t, J=7.0 Hz), 2.13—1.40 (4H, m), 1.68 (3H, s), 1.28 (1H, s). IR (film): 3356, 1670 cm^{-1}. Z-**10**: ^{1}H-NMR ($CDCl_3$) δ: 5.46 (1H, t, J=7.0 Hz), 4.12 (2H, d, J=7.0 Hz), 3.48 (2H, t, J=6.0 Hz), 2.40—1.40 (4H, m), 1.73 (3H, s), 1.42 (1H, s). IR (film): 3356, 1670 cm^{-1}.

8,8,8-Trifluoro-3,7-dimethyl-2,6-octadien-1-ol (8)——(a) Treatment of the ethylene ketal (**5**) (2.0 g), which was obtained by a conventional procedure, with triphenylphosphine (3.8 g) in benzene (3.5 ml) at 80 °C for 48 h gave phosphonium salt (3.3 g). A solution of this salt (3.0 g) in Et_2O (8 ml) was reacted with BuLi (in hexane, 4 ml) at room temperature, followed by addition of trifluoroacetone (3.6 g) at −78 °C. The reaction mixture was stirred at room temperature for 19 h, treated with ice-water and extracted with Et_2O. The extract was concentrated and purified on an

SiO_2 column in hexane–CH_2Cl_2 (3 : 2) to give a highly volatile colorless oil (0.3 g). Hydrolysis of this oil in Et_2O with 5% HCl gave the ketone (**6**), which was extraordinarily volatile and was detected only as a new and reasonably located peak in gas-liquid chromatography (GLC). Therefore, the ether layer was separated, dried over $MgSO_4$, and subjected to the Wittig–Horner reaction to give a trace of a colorless oil, which was reduced with $LiAlH_4$ to **8** (trace). This was identified by comparison of the spectral data with those of the product obtained in the following experiment (b).

(b) A phosphonium salt, which was obtained by the conventional reaction of the tetrahydropyranyl ether of **10** (*Z*,*E*-mixture, 2 : 1) and triphenylphosphine (2.0 g, 3.71 mmol), was suspended in dry Et_2O (20 ml) and treated with BuLi (15% in hexane, 2.4 ml) at room temperature for 4 h. The mixture was cooled to −78 °C, and trifluoroacetone (2.2 g, 19.6 mmol) was added to the mixture at this temperature. After one hour's stirring at this temperature, the mixture was stirred at room temperature for 18 h. The mixture was treated with ice-water and extracted with Et_2O. The Et_2O layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The residue was passed through a short column of SiO_2 in hexane–CH_2Cl_2 (1 : 1) to remove resinous substances. The effluent was dissolved in MeOH (50 ml) containing a small amount of *p*-toluenesulfonic acid (TsOH) and stirred for 26 h at room temperature. After evaporation of the MeOH, the residue was dissolved in Et_2O, washed with 8% NaOH and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by an SiO_2 column in hexane–AcOEt (5 : 1) to give a colorless oil (0.451 g, 59%). ^{1}H-NMR ($CDCl_3$) δ: 6.03 and 5.60 (1H in total, both m), 5.36 (1H, t, $J=6.8$ Hz), 4.09 (2H, d, $J=6.6$ Hz), 2.63—1.96 (4H, m), 1.83 (3H, s), 1.68 (3H, s), 1.20 (1H, s). ^{19}F-NMR ($CDCl_3$) ppm from $C_6H_5CF_3$ (upper field, +): −1.11 (*Z*-isomer), 6.66 (*E*-isomer) (ratio approximately 2 : 1).

2-(5,5,5-Trifluoro-4-methyl-3-penten-1-yl)-2,5,7,8-tetramethyl-6-chromanol (11)——A mixture of 8,8,8-trifluoro-3,7-dimethyl-2,6-octadien-1-ol (**8**, 210 mg, 1.00 mmol), trimethylhydroquinone (219 mg, 1.44 mmol), $ZnCl_2$ (131 mg, 0.96 mmol) and acetic acid (5 ml) was heated at 120 °C for 18 h. After evaporation of acetic acid under vacuum, the residue was neutralized with saturated $NaHCO_3$ and extracted with Et_2O. The extract was washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The residue was purified on an SiO_2 column in hexane–AcOEt (10 : 1) to give a viscous oil (**11**, 141 mg, 41%). ^{1}H-NMR ($CDCl_3$) δ: 6.08 (m) and 5.68 (t, $J=7.7$ Hz) (1H in total, approximate ratio 1 : 2), 4.20 (1H, s), 2.61 (2H, t, $J=6.7$ Hz), 2.36 (2H, m), 2.17 and 2.11 (9H, s), 1.94—1.50 (4H, m), 1.82 (3H, s), 1.25 (3H, s). ^{19}F-NMR ($CDCl_3$) ppm: −1.21, 6.68 (*Z*/*E* approximately 2/1). IR (film): 3632, 1164, 1124 cm^{-1}. Mass spectrum (MS) *m*/*z*: 242 (M^+), 205, 165. High resolution mass spectrum (HRMS) Calcd for $C_{19}H_{25}F_3O_2$: 342.1803. Found: 342.1800.

10-Methyl-6-(trifluoromethyl)-5,9-undecadien-2-one (13)——A phosphonium salt, which was obtained by the conventional reaction of the ketal (**5**) with triphenylphosphine (7.236 g, 14.5 mmol), was suspended in dry Et_2O and treated with BuLi (15% in hexane, 9.4 ml) at room temperature for 1 h under stirring. The mixture was cooled to −78 °C and 1,1,1-trifluoro-6-methyl-5-hepten-2-one (**12**,[8] 2.004 g, 11.1 mmol) in Et_2O (5 ml) was added at this temperature. After 30 minutes' stirring at this temperature, the mixture was allowed to warm up gradually to room temperature and stirred for a further 18 h. A saturated solution of $NaHCO_3$ was added to the mixture and the precipitate was filtered off. The Et_2O layer was collected, washed with brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was passed through a short column of SiO_2 in hexane–CH_2Cl_2 (10 : 1). The effluent was dissolved in MeOH (15 ml) containing a small amount of TsOH and stirred at room temperature for 26 h. After evaporation of the MeOH, the residue was dissolved in Et_2O, washed with aqueous $NaHCO_3$, and dried over $MgSO_4$. The residue obtained by the evaporation of the solvent was purified on an SiO_2 column in hexane–CH_2Cl_2 (3 : 2) to give a colorless oil (0.934 g, 34.0%). This was found to be a mixture of the *Z*- and *E*-isomers of **13**. ^{1}H-NMR ($CDCl_3$) δ: 6.11 (0.23H, m), 5.70 (0.77H, t, $J=7.7$ Hz), 5.08 (1H, br), 2.66—2.54 (4H, m), 2.23—1.87 (4H, m), 2.14 (3H, s), 1.66 (3H, s), 1.58 (3H, s). ^{19}F-NMR ($CDCl_3$) ppm: −3.08, 4.12 (ratio 77 : 23). IR (film): 1724, 1160, 1124 cm^{-1}.

Ethyl 3,11-Dimethyl-7-(trifluoromethyl)-2,6,10-dodecatrienoate (14)——Triethyl phosphonoacetate (406 mg, 1.81 mmol) was added to a suspension of NaH in oil (50%, 103 mg) and the mixture was stirred at room temperature for 1 h, then cooled to −78 °C, and **13** (300 mg, 1.2 mmol) was added. Stirring was continued at this temperature for 30 min, then the mixture was allowed to warm to room temperature. Stirring was continued for 18 h, then the mixture was treated with ice-water and extracted with ether. The extract was washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The residue was purified over an SiO_2 column in CH_2Cl_2 solution to give a colorless oil (**14**) (294 mg, 76.0%). ^{1}H-NMR ($CDCl_3$) δ: 6.03 (0.23H, m), 5.67 (1.77H, m), 5.03 (1H, m), 4.15 (2H, q, $J=7.1$ Hz), 2.53—1.78 (8H, m), 2.16 (3H, s), 1.66, 1.57 (6H, s), 1.23 (3H, t, $J=7.1$ Hz). ^{19}F-NMR ($CDCl_3$) ppm: −2.86, 4.15 (*Z*/*E*=77/23).

3,11-Dimethyl-7-(trifluoromethyl)-2,6,10-dodecatrien-1-ol (15)——The ester (**14**) (26 mg, 0.08 mmol) in Et_2O (2 ml) was added to an ice-cooled suspension of $LiAlH_4$ (18 mg) in Et_2O (1 ml) under stirring. The mixture was allowed to warm to room temperature and stirring was continued for a further 4 h. A small amount of water was added, then the mixture was filtered through a celite layer and extracted with Et_2O. The extract was washed with brine, dried over $MgSO_4$ and evaporated under vacuum. The residue was purified through an SiO_2 column in hexane–CH_2Cl_2 (1 : 2) to give a colorless oil (**15**) (22 mg, 96%). ^{1}H-NMR ($CDCl_3$) δ: 6.03 (0.23H, m), 5.64 (0.77H, t, $J=7.5$ Hz), 5.40 (1H, m), 5.06 (1H, m), 4.14 (2H, m), 3.39 (1H, s), 2.54—1.91 (8H, m), 1.71 (3H, s), 1.67 (3H, s), 1.56 (3H, s). ^{19}F-NMR

($CDCl_3$) ppm: -2.95, 4.06 ($Z/E=77/23$).

2-[8-Methyl-4-(trifluoromethyl)-2,5,7,8-tetramethyl-3,7-nonadienyl]-6-chromanol (16)——A similar reaction of trimethylhydroquinone (216 mg) with the allyl alcohol (**15**) (250 mg) in the presence of $ZnCl_2$ (809 mg) in acetic acid (20 ml) as in the case of **11** gave a colorless oil (**16**) (75 mg, 30%). ^1H-NMR ($CDCl_3$) δ: 6.03 (m) and 5.67 (t, $J=7.8$ Hz) (1H in total), 5.04 (1H, m), 4.19 (1H, s), 2.60 (2H, t, $J=6.7$ Hz), 2.47—2.36 (2H, m), 2.36—1.73 (8H, m), 2.15 and 2.10 (9H, s), 1.64 and 1.56 (6H, s), 1.23 (3H, s). ^{19}F-NMR ($CDCl_3$) ppm: -3.03, 4.09 ($Z/E=70/30$). IR (film): 3636, 1162, 1122 cm^{-1}. MS m/z: 410 (M^+). HRMS Calcd for $C_{24}H_{33}F_3O_2$: 410.2437. Found: 410.2442.

10,14-Dimethyl-6-(trifluoromethyl)-5,9,13-tridecatrien-2-one (18)——The phosphonium salt obtained by the reaction of the ketal (**5**) with triphenylphosphine (2.626 g, 5.25 mmol) was suspended in Et_2O (20 ml) and BuLi (15% in hexane, 3.41 ml) was added at room temperature. After one hour's stirring at room temperature, the mixture was cooled to -78 °C and 1,1,1-trifluoro-6,10-dimethyl-5,9-undecadien-2-one (**17**)[8] (1.085 g, 4.37 mmol) in Et_2O (5 ml) was added at this temperature. Stirring was continued for 30 min at this temperature, then the mixture was warmed to room temperature and stirred for 28 h. Work-up as in the case of **13** gave a colorless oil (**18**) (0.429 g, 26%). ^1H-NMR ($CDCl_3$) δ: 6.11 (0.14H, t, $J=6.7$ Hz), 5.64 (0.86H, t, $J=7.7$ Hz), 5.08 (2H, br), 2.62—2.37 (4H, m), 2.30—1.94 (8H, m), 2.15 (3H, s), 1.68, 1.60 (9H, s). ^{19}F-NMR ($CDCl_3$) ppm: -2.92, 4.26 ($Z/E=86/14$).

Ethyl 3,11,15-Trimethyl-7-(trifluoromethyl)-2,6,10,14-hexadecatetraenoate——The title compound was obtained by a procedure similar to that used in the case of **14**, starting from the ketone (**18**) (235 mg). The solvent used for the last stage of chromatography was hexane–Et_2O (30 : 1). The yield was 214 mg (74.0%). ^1H-NMR ($CDCl_3$) δ: 6.04 (0.14H, m), 5.66 (0.86H, m), 5.07 (2H, br), 4.12 (2H, q, $J=7.0$ Hz), 2.57—1.80 (12H, m), 2.17 (3H, s), 1.67, 1.59 (9H, s), 1.27 (3H, t, $J=7.0$ Hz). ^{19}F-NMR ($CDCl_3$) ppm: -2.88, 4.18 ($Z/E=86/14$).

3,11,15-Trimethyl-7-(trifluoromethyl)-2,6,10,14-hexadecatetraen-1-ol (19)——The above ester (41 mg) in Et_2O (2 ml) was added to an ice-cooled suspension of $LiAlH_4$ (28 mg) in Et_2O (1 ml) under stirring. After 4 hours' stirring at room temperature, the reaction mixture was treated as in the case of **15**. Purification on an SiO_2 column in hexane–CH_2Cl_2 (1 : 2) gave a colorless oil (**19**) (25 mg, 67%). ^1H-NMR ($CDCl_3$) δ: 6.03 (m), 5.62 (t, $J=7.4$ Hz) (1H in total), 5.39 (1H, m), 5.03 (2H, m), 5.27 (1H, s), 4.13 (2H, d, $J=6.5$ Hz), 2.54—1.77 (12H, m), 1.74, 1.66, 1.59 (12H, s). ^{19}F-NMR ($CDCl_3$) ppm: -2.92, 4.08 (both s, ratio $Z/E=86/14$).

2-[8,12-Dimethyl-4-(trifluoromethyl)-3,7,11-tridecatrienyl]-2,5,7,8-tetramethyl-6-chromanol (20)——A reaction of trimethylhydroquinone (93 mg) and the allyl alcohol (**19**) (141 mg) in the presence of $ZnCl_2$ (417 mg) in acetic acid (15 ml) as in the case of **11** gave a colorless oil (**20**) (130 mg, 74%) with recovery of **19** (16 mg). ^1H-NMR ($CDCl_3$) δ: 6.11 and 5.66 (1H in total, both m), 5.06 (2H, m), 4.20 (1H, s), 2.61 (2H, t, $J=6.7$ Hz), 2.56—2.52 (2H, m), 2.17 and 2.11 (9H, s), 1.69 and 1.60 (9H, s), 1.24 (3H, s), 1.94—1.06 (12H, m). ^{19}F-NMR ($CDCl_3$) ppm: -3.02, 4.10 ($Z/E=$ approximately 2/1). IR (film): 3636, 1168, 1120 cm^{-1}. MS m/z: 478 (M^+), 205, 165. HRMS Calcd for $C_{29}H_{41}F_3O_2$: 478.3058. Found: 478.3058.

References and Notes

1) Part of this work was presented at the 18th Congress of Heterocyclic Chemistry, Fukuoka, October 1986.
2) H. M. Evans and K. S. Bishop, *Science*, **56**, 650 (1922). For the synthesis, the analysis, the extraction and the biosynthesis of vitamin E, see "Methods in Enzymology," Vol. 18C, ed. by D. B. McCormick and L. D. Wright, Academic Press, New York, 1971, p. 241.
3) Concerning the biological effect of fluorine, see "Biomedicinal Aspects of Fluorine Chemistry," ed. by R. Filler and Y. Kobayashi, Kodansha, Tokyo, 1982, p. 1.
4) For example: Eisai Co., Ltd., Japan Kokai Tokkyo Koho, 8094382 (1980) [*Chem. Abstr.*, **94**, 30568 (1981)].
5) D. H. Dull, I. Baxter, and H. S. Mosher, *J. Org. Chem.*, **32**, 1622 (1967).
6) C. D. Poulter, D. M. Satterwhite, and H. C. Rilling, *J. Am. Chem. Soc.*, **98**, 3376 (1976).
7) D. Mead, R. Loh, A. E. Asato, and R. S. H. Liu, *Tetrahedron Lett.*, **26**, 2873 (1985).
8) F. Camps, R. Canela, J. Coll, A. Messeguer, and A. Roca, *Tetrahedron*, **34**, 2179 (1978).
9) G. W. Cannon, R. C. Ellis, and J. R. Leal, "Organic Synthesis," Coll. Vol. IV, John Wiley and Sons, Inc., New York, 1963, p. 597.
10) J. Balsevich, *Can. J. Chem.*, **61**, 1053 (1983).