Synthesis of Fluorine Analogs of Vitamin E. III.[1] Synthesis of 2-[4,8-Dimethyl-12-(trifluoromethyl)tridecyl]-2,5,7,8-tetramethyl-6-chromanol and 2-[4,12-Dimethyl-8-(trifluoromethyl)tridecyl]-2,5,7,8-tetramethyl-6-chromanol

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2-[4,8-Dimethyl-12-(trifluoromethyl)tridecyl]-2,5,7,8-tetramethyl-6-chromanol and 2-[4,12-dimethyl-8-(trifluoromethyl)tridecyl]-2,5,7,8-tetramethyl-6-chromanol, were synthesized by means of the Wittig reaction using the phosphonium salt of 2-(3-chloropropyl)-2,5,7,8-tetramethyl-6-chromanol.

Keywords vitamin E; tocopherol; trifluoromethyl; Wittig reaction; trifluoromethyl ketone; 6-chromanol

Many organic fluorine compounds are used as medicinal and agricultural chemicals.[2] Further, some fluorine analogs of biologically active compounds are used as probes for investigation of biochemical reactions. As a part of a search for a more biologically active analog of vitamin E, we have reported the synthesis of trifluoro analogs of α-tocopherol with a trifluoromethyl group at the 4-position of the prenyl sidechain.[1] We have also reported the synthesis of fluorine analogs of α-tocopherol with a trifluoromethyl group on the benzene ring of the chromanol.[3] These compounds can be used for research on vitamin E in conjunction with the ^{19}F-NMR.[4] Further, other analogs of vitamin E with a fluorine substituent at the opposite end of the prenyl group from the chromanol ring would be useful. Here, we would like to report the synthesis of the title compounds, which have a trifluoromethyl group at the 8- or the 12-position of the prenyl side-chain, *via* the Wittig reaction of the phosphonium salt, which was reported in the previous paper.[1]

To apply the Wittig reaction, we needed the corresponding ketones with a trifluoromethyl group at the appropriate position. The syntheses of these ketones are illustrated in Chart 1.

Thus, the ethylene ketal of 5-chloro-2-pentanone (**1**) was treated with triphenylphosphine and sodium iodide to give the phosphonium salt (**2**), which was allowed to react with butyl lithium and 5-chloro-2-pentanone to afford 2-methyl-2-(7-chloro-4-methyl-3-heptenyl)-1,3-dioxolane (**3**). This was further converted to 6-methyl-10-(trifluoromethyl)-5,9-undecadien-2-one (**5**) through the phosphonium salt (**4**). The ^{1}H- and ^{19}F-NMR spectra of **5** show that it is a mixture of *E*/*Z*-isomers of the 9-double bond in a ratio of 15 : 85.

10-Methyl-6-(trifluoromethyl)-5,9-undecadien-2-one (**7**) was synthesized by a similar Wittig reaction of the phosphonium salt (**2**) with 1,1,1-trifluoro-6-methyl-5-hepten-2-one (**6**), which was obtained by the reaction of ethyl trifluoroacetoacetate with 2-methyl-3-buten-2-ol.[5] The enone **7** is an *E*/*Z* mixture of the 5-double bond in a ratio of 23 : 77.

These ketones were reacted with [3-(6-methoxymethyl-2,5,7,8-tetramethyl-2-chromyl)propyl]triphenylphosphonium iodide (**8**)[1] to give trifluorotocotrienol compounds (**9** and **11**). These were hydrogenated in the presence of Pd–C, followed by hydrolysis to trifluorotocopherols (**10** and **12**). The ^{19}F-NMR spectra of both compounds showed two doublets of equal intensity. ^{1}H-NMR spectra of both compounds showed no diastereomers, and analysis by thin layer chromatography and high-performance liquid chromatography showed only one peak. The results suggested that both products were mixtures of diastereomers, but we could not determine how many isomers were contained.

In conclusion, the objective compounds were synthesized in good yields. Both are expected to be very useful as probes for investigation of the biophysical properties of vitamin E. A part of that investigation has been published elsewhere.[4] The phosphonium salt (**8**) is a racemate and the products are mixtures of diastereomers. Synthesis of optically active compounds is now in prog-

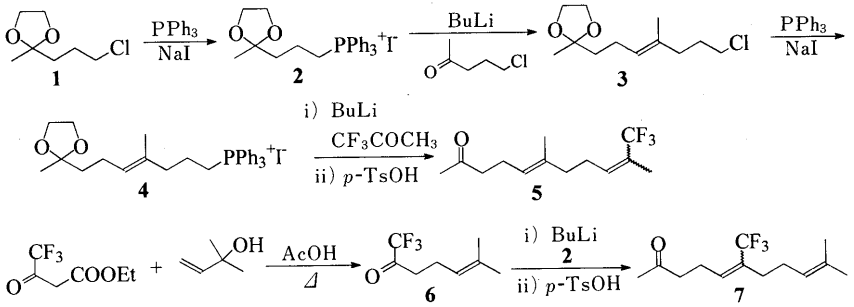

Chart 1

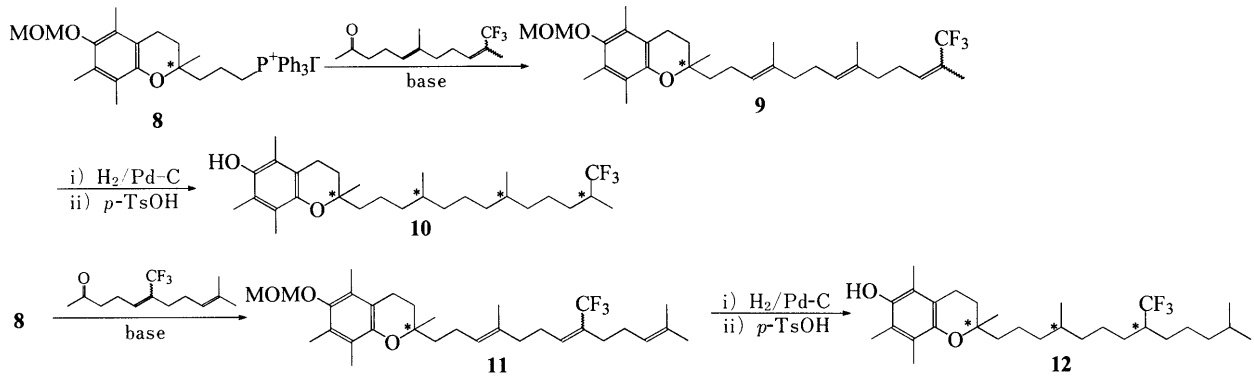

Chart 2

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Experimental

General Melting points were measured on micro melting point apparatus, Model MP (Yanagimoto, Kyoto, Japan) and a melting point apparatus (Ishii Shoten, Tokyo, Japan) without correction. ^{1}H-NMR spectra were recorded on JEOL FX90Q and JNM GX400 spectrometers. ^{19}F-NMR spectra were measured on a Hitachi R-1500 spectrometer. Benzotrifluoride (BTF) was used as an internal standard. The upper field is shown as plus. Abbreviations are: s, singlet; d, doublet; m, multiplet; br s, broad singlet; q, quartet. Mass spectra were recorded on a JEOL JMS-DX300.

Triphenylphosphonium Salt (2) from an Ethylene Ketal of 5-Chloro-2-pentanone (1) A mixture of ethylene ketal of 5-chloro-2-pentanone (**1**, 9.017 g, 54.8 mmol), triphenylphosphine (15.8 g, 60.3 mmol), NaI (16.4 g, 0.109 mol) and CH_3CN (40 ml) was stirred at 80 °C for 44 h, then cooled in an ice-water bath, and CH_2Cl_2 (40 ml) was added to the mixture. The precipitate was filtered off, and the filtrate was concentrated under vacuum. The residue was slurried with Et_2O (15 ml) three times, and on addition of acetone to the slurry, colorless crystals precipitated, which were collected by filtration to give **2** (23.794 g, 83.8%). **2**: Colorless crystals, mp 190—193 °C.

2-Methyl-2-(7-chloro-4-methyl-3-heptenyl)-1,3-dioxolane (3) BuLi (15% in hexane, 5.0 ml, 7.8 mmol) was added dropwise to a suspension of **2** (4.013 g, 7.75 mmol) in tetrahydrofuran (THF) (40 ml) under ice-cooling, then the mixture was stirred at room temperature for 1 h. The mixture was cooled to −78 °C, and 5-chloro-2-pentanone (1.030 g, 8.55 mmol) was added at this temperature. The mixture was stirred at this temperature for a further 30 min, then allowed to warm to room temperature, and stirring was continued for 18 h. The mixture was treated with saturated NH_4Cl, and filtered through a Celite layer. The layer was washed with Et_2O, and the filtrate and washing were combined, then extracted with Et_2O. The Et_2O layer was washed with brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography (SiO_2, hexane–Et_2O, 10 : 1) to give **3** (1.302 g, 72.3%). **3**: A colorless oil. MS *m/z*: 232 (M^+). HRMS Calcd for $C_{12}H_{21}ClO_2$: 232.123. Found: 232.123. ^{1}H-NMR δ: 5.15 (1H, t, J=6.4 Hz), 3.91 (4H, s), 3.49 (2H, t, J=6.4 Hz), 1.32 (3H, s), 1.69 (3H, s), 2.34—1.43 (8H, m).

Phosphonium Salt (4) from 3 A mixture of **3** (0.390 g, 1.68 mmol), triphenylphosphine (0.670 g, 2.56 mmol), NaI (0.5 g, 3.33 mol) and CH_3CN (10 ml) was stirred at 80 °C for 23 h. The mixture was cooled to 0 °C, then CH_2Cl_2 (10 ml) was added and the precipitates were filtered off. The filtrate was concentrated under vacuum, and the residue was purified by column chromatography (SiO_2, CH_2Cl_2–MeOH, 20 : 1) to give **4** (0.898 g, 91.4%). **4**: Colorless crystals. ^{1}H-NMR δ: 8.05—7.50 (15H, m), 5.20 (1H, t, J=6.4 Hz), 3.93, 3.89 (4H, s), 3.80—3.35 (2H, m), 1.79 (3H, s), 2.50-1.34 (8H, m), 1.29 (3H, s).

6-Methyl-10-(trifluoromethyl)-5,9-undecadien-2-one (5) BuLi (15% in hexane, 0.8 ml, 1.25 mmol) was added to a solution of **4** (0.694 g, 1.184 mmol) in THF (6 ml) under ice-cooling, then the mixture was stirred at room temperature for 1 h. The mixture was cooled to −78 °C, trifluoroacetone (0.560 g, excess) was added through a cannula, and stirring was continued at this temperature for 30 min, then the whole was allowed to warm to room temperature. Stirring was continued for 18 h, then saturated NH_4Cl was added, and the whole was extracted with Et_2O. The Et_2O layer was washed with saturated $NaHCO_3$ and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was stirred with *p*-TsOH (50 mg) in acetone (10 ml) at room temperature for 16 h, then saturated $NaHCO_3$ was added, and extracted with Et_2O. The Et_2O layer was washed with brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography (SiO_2, hexane–Et_2O, 10 : 1) to give **5** (203 mg, 69.0%). **5**: A colorless oil. MS *m/z*: 248 (M^+). HRMS Calcd for $C_{13}H_{19}F_3O$: 248.139. Found: 248.139. ^{1}H-NMR δ: 6.03 (0.15H, br), 5.64 (0.85H, br), 5.09 (1H, t, J=6.4 Hz), 2.15 (3H, s), 1.83, 1.66, 1.60 (6H, s) 2.72—1.09 (8H, m). ^{19}F-NMR ppm: −1.31, 6.91 (Z : E=85 : 15).

10-Methyl-6-(trifluoromethyl)-5,9-undecadien-2-one (7) BuLi (15% in hexane) (3.2 ml 5.0 mmol) was added to a solution of **2** (2.5 g, 4.83 mmol) in THF (10 ml) under ice-cooling, and the mixture was stirred at room temperature for 1 h. It was cooled to −78 °C, and a solution of 1,1,1-trifluoro-6-methyl-5-hepten-2-one (**6**,[5] 1.701 g, 9.42 mmol) in THF (2 ml) added. After 30 min, the mixture was allowed to warm to room temperature, stirred for 18 h, then treated with saturated NH_4Cl and extracted with Et_2O. The Et_2O layer was washed with saturated $NaHCO_3$ and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was dissolved in acetone (15 ml) containing *p*-TsOH (50 mg), and stirred at room temperature for 16 h. After evaporation of the solvent, the residue was treated with saturated $NaHCO_3$, and extracted with Et_2O. The Et_2O layer was washed with brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography (SiO_2, hexane–Et_2O, 10 : 1) to give **7** (410 mg, 34.3%). **7**: A colorless oil. MS *m/z*: 248 (M^+). HRMS Calcd for $C_{13}H_{19}F_3O$: 248.138. Found: 248.137. ^{1}H-NMR δ: 6.03 (0.23H, t, J=7.7 Hz), 5.66 (0.77H, t, J=7.7 Hz), 5.06 (1H, br), 2.66—2.54 (4H, m), 2.23—1.87 (4H, m), 2.14 (3H, s), 1.61 (3H, s), 1.69 (3H, s). ^{19}F-NMR ppm: −3.08, 4.10 (Z : E=77 : 23).

2-[4,8-Dimethyl-12-(trifluoromethyl)-3,7,11-tridecatrienyl]-2,5,7,8-tetramethyl-6-chromanol Methoxymethyl Ether (9) A solution of LiBr (107 mg, 1.23 mmol) in THF (1 ml) was added to a solution of [3-(6-methoxymethyl-2,5,7,8-tetramethyl-2-chromyl)propyl]triphenylphosphonium iodide (**8**, 835 mg, 1.23 mmol) in THF (3 ml), then BuLi (15% in hexane, 0.8 ml, 1.25 mmol) was added to this mixture under ice-cooling, and the whole was stirred at room temperature for 20 min, and cooled to −78 °C. A solution of **5** (196 mg, 0.79 mmol) in THF (1 ml) was added, and stirring was continued at this temperature for a further 20 min, then the mixture was allowed to warm to room temperature. BuLi (15% in hexane) (0.8 ml, 1.25 mmol) was added again, and the reaction mixture was stirred for 20 min, then cooled to −78 °C. It was further stirred for 15 min, a solution of *tert*-BuOH (1 ml) and *tert*-BuOK (137 mg, 1.23 mmol) in THF (1 ml) was added, and then the mixture was allowed to warm to room temperature. Stirring was continued for 1 h, saturated NH_4Cl was added and the whole was extracted with Et_2O. The Et_2O layer was washed with saturated $NaHCO_3$ and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography (SiO_2, hexane–Et_2O, 10 : 1) to give **9** (244 mg, 59.1%). **9**: A pale yellow oil. MS *m/z*: 522 (M^+). HRMS Calcd for $C_{31}H_{45}F_3O_3$: 522.332. Found: 522.332. ^{1}H-NMR δ: 6.10—5.80 (0.15H, br), 5.65 (0.85H, t, J=7.7 Hz), 5.14 (2H, t, J=6.4 Hz), 4.86 (2H, s), 3.62 (3H, s), 2.59 (2H, t, J=6.7 Hz), 2.09 (3H, s), 2.19 (3H, s), 2.14 (3H, s), 1.80 (3H, s), 1.67 (3H, s), 1.59 (3H, s), 2.47—1.35 (14H, m), 1.24 (3H,

s). ^{19}F-NMR ppm: −1.17, 6.20 ($Z:E=85:15$).

2-[4,8-Dimethyl-12-(trifluoromethyl)tridecyl]-2,5,7,8-tetramethyl-6-chromanol (10) A solution of **9** (225 mg, 0.43 mol) in MeOH (15 ml) was shaken in the presence of Pd–C (10%, 13 mg) in a stream of H_2 at room temperature for 3 h, then at 45 °C for 2 h, and the catalyst was filtered off. After evaporation of the solvent, the residue was purified by column chromatography (SiO_2, hexane–Et_2O, 10 : 1) to give the methyoxymethyl ether of **10** (223 mg). This was dissolved in MeOH (10 ml) containing *p*-TsOH (30 mg), and the solution was stirred at room temperature for 18 h. After evaporation of the solvent under vacuum, the residue was treated with saturated $NaHCO_3$, and extracted with Et_2O. The Et_2O layer was washed with brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography (SiO_2, hexane–Et_2O, 10 : 1) to give **10** (175 mg 83.9%). **10**: A pale yellow oil. MS *m/z*: 484 (M^+). HRMS Calcd for $C_{29}H_{47}F_3O_2$: 484.353. Found: 484.353. ^{1}H-NMR δ: 2.61 (2H, t, $J=6.7$ Hz), 2.15 (3H, s), 2.11 (6H, s), 1.78 (2H, t, $J=6.7$ Hz), 1.60—0.96 (21H, m), 1.22 (3H, s), 1.08 (3H, d, $J=7.1$ Hz), 0.85 (6H, d, $J=5.7$ Hz). ^{19}F-NMR ppm: 9.03, 9.09 (ratio 1 : 1, both d, $J=9.7$ Hz).

2-[4,12-Dimethyl-8-(trifluoromethyl)-3,7,11-tridecatrienyl]-2,5,7,8-tetramethyl-6-chromanol Methoxymethyl Ether (11) A solution of LiBr (111 mg, 1.28 mmol) in THF (1 ml) was added to a solution of [3-(6-methoxymethyl-2,5,7,8-tetramethyl-2-chromyl)propyl]triphenylphosphonium iodide (**8**, 869 mg, 1.28 mmol) in THF (3 ml) under ice-cooling, and BuLi (15% in hexane, 0.82 ml, 1.28 mmol) was added dropwise, thereto. The mixture was stirred at room temperature for 20 min, then cooled to −78 °C. A solution of **7** (264 mg, 1.06 mmol) in THF (1 ml) was added dropwise, and the whole was stirred for a further 20 min. It was allowed to warm to room temperature, then BuLi (15% in hexane, 0.82 ml, 1.28 mmol) was added. The reaction mixture was stirred for 20 min, cooled to −78 °C, then stirred at this temperature for 15 min, and a solution of *tert*-BuOH (1 ml) and *tert*-BuOK (143 mg, 1.28 mmol) in THF (3 ml) was added. The whole was allowed to warm to room temperature, treated with saturated NH_4Cl, and extracted with Et_2O. The Et_2O layer was washed with saturated $NaHCO_3$ and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography (SiO_2, hexane–Et_2O, 10 : 1) to give **11** (278 mg, 50.0 %). **11**: A pale yellow oil. MS *m/z*: 522 (M^+). HRMS Calcd for $C_{31}H_{45}F_3O_3$: 522.332. Found: 522.331. ^{1}H-NMR δ: 6.10—5.90 (0.23H, br), 5.63 (0.77H, t, $J=7.7$ Hz), 5.15 (2H, s), 3.61 (3H, s), 2.59 (2H, t, $J=6.7$ Hz), 2.18 (3H, s), 2.14 (3H, s), 2.09 (3H, s), 1.67 (6H, s), 1,59 (3H, s), 2.47—1.33 (14H, m), 1.24 (3H, s). ^{19}F-NMR ppm: −2.91, 3.76 ($Z:E=77:23$).

2-[4,12-Dimethyl-8-(trifluoromethyl)tridecyl]-2,5,7,8-tetramethyl-6-chroman-ol (12) A solution of **11** (243 mg, 0.466 mol) in MeOH (15 ml) was shaken with Pd–C (10%, 15 mg) in a stream of H_2 at room temperature for 3 h, then at 45 °C for 3 h, and at room temperature for a further 18 h. The catalyst was filtered off. After evaporation of the solvent, the residue was purified by column chromatography (SiO_2, hexane–Et_2O, 10 : 1) to give the methyoxymethyl ether of **12** (217 mg). This was dissolved in MeOH (10 ml) containing *p*-TsOH (30 mg), and the solution was stirred at room temperature for 18 h. After evaporation of MeOH, the residue was treated with saturated $NaHCO_3$, and extracted with Et_2O. The Et_2O layer was washed with brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography (SiO_2, hexane–Et_2O, 10 : 1) to give **12** (217 mg, 96.4%). **12**: A pale yellow oil. MS *m/z*: 484 (M^+). HRMS Calcd for $C_{29}H_{47}F_3O_2$: 484.353. Found: 484.353. ^{1}H-NMR δ: 4.16 (1H, s), 2.60 (2H, t, $J=6.7$ Hz), 2.14 (3H, s), 2.08 (6H, s), 1.77 (2H, t, $J=6.7$ Hz), 1.62—1.00 (21H, m), 1.20 (3H, s), 0.85 (9H, d, $J=6.4$ Hz). ^{19}F-NMR ppm: 5.83, 5.86 (ratio 1 : 1, both d, $J=9.7$ Hz).

References and Notes

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