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Synthesis of Fluorine Analogues of Vitamin E. II.[1] Synthesis of 2-(3-Chloropropyl)-2,5,7,8-tetramethyl-6-chromanol and Its Application for Stereocontrolled Wittig Reaction with Trifluoromethyl Ketones[2]

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As the extension of our research to find a biologically active analogue of vitamin E, a more convenient method for the synthesis of fluorine derivatives of 6-chromanol than our previous method was developed. Thus, 2-(3-chloropropyl)-2,5,7,8-tetramethyl-6-chromanol (**3**) was synthesized by the reaction of 6-chloro-3-methyl-2-hexen-1-ol (**2**) and trimethylhydroquinone, and the phosphonium ylides (**5** and **6**) derived from **3** were condensed with trifluoromethylated ketones to give 2-(trifluoroprenyl)-6-chromanol compounds (**1a**, **1b** and **1c**) by means of the Wittig reaction as modified by Schlosser. By the use of this revised procedure, the total yields of the chromanols were much improved. Further, the modified Wittig reaction showed higher stereoselectivity than the previous syntheses of these compounds. The double bonds of the side-chain of the products were reduced to give fluorine derivatives of tocopherol analogues. Compound **3** was found to be a useful intermediate for the facile synthesis of vitamin E derivatives.

Keywords——vitamin E; tocotrienol; fluorine; trifluoromethyl; trifluoroprenyl; Wittig reaction; trifluoromethyl ketone; 6-chromanol; tocol; stereocontrol

Nowadays, many organic fluorine compounds are used as medicinal and agricultural chemicals.[3] As a part of a search for a more biologically active analogue of vitamin E, we have reported the synthesis of 6-chromanol derivatives (**1a**, **1b** and **1c**) with fluorinated side chains at the 2-position by the ring-closure of trifluoroprenols with trimethylhydroquinone in the presence of zinc chloride (see the top of Chart 1).[1]

In this procedure, rather expensive reagents containing fluorine were used for the synthesis of fluorinated prenols at an early stage of the process and the overall yields were very low. Further, the stereoselectivity concerning the *E*/*Z* isomers was unsatisfactory. Now, we should like to report our improved synthesis of the above compounds using phosphonium ylides (**5** and **6**) as key compounds, which were condensed with trifluoromethyl ketones.

At first, 6-chloro-3-methyl-2-hexen-1-ol (**2**), which was obtained from 3-acetyl-γ-lactone, was treated with trimethylhydroquinone in the presence of zinc chloride in acetic acid to give 2-(3-chloropropyl)-2,5,7,8-tetramethyl-6-chromanol (**3**) in the yield of 45%. Compound **3** was treated with triphenylphosphine in the presence of sodium iodide to give the phosphonium salt (**5**). Further, **3** was converted to a phosphonium salt (**6**) after protection of the 6-hydroxy group with a methoxymethyl group. Both compounds **5** and **6** were now ready to use in the Wittig reaction.

To condense the ylides from **5** and **6** with trifluoromethyl ketones more stereoselectively, the Wittig reaction as modified by Schlosser *et al.*[4] was employed. The following procedure was found to be most satisfactory after several trials. First, the salt **5** was treated with butyllithium and lithium bromide. After the addition of trifluoroacetone to the mixture, *tert*-

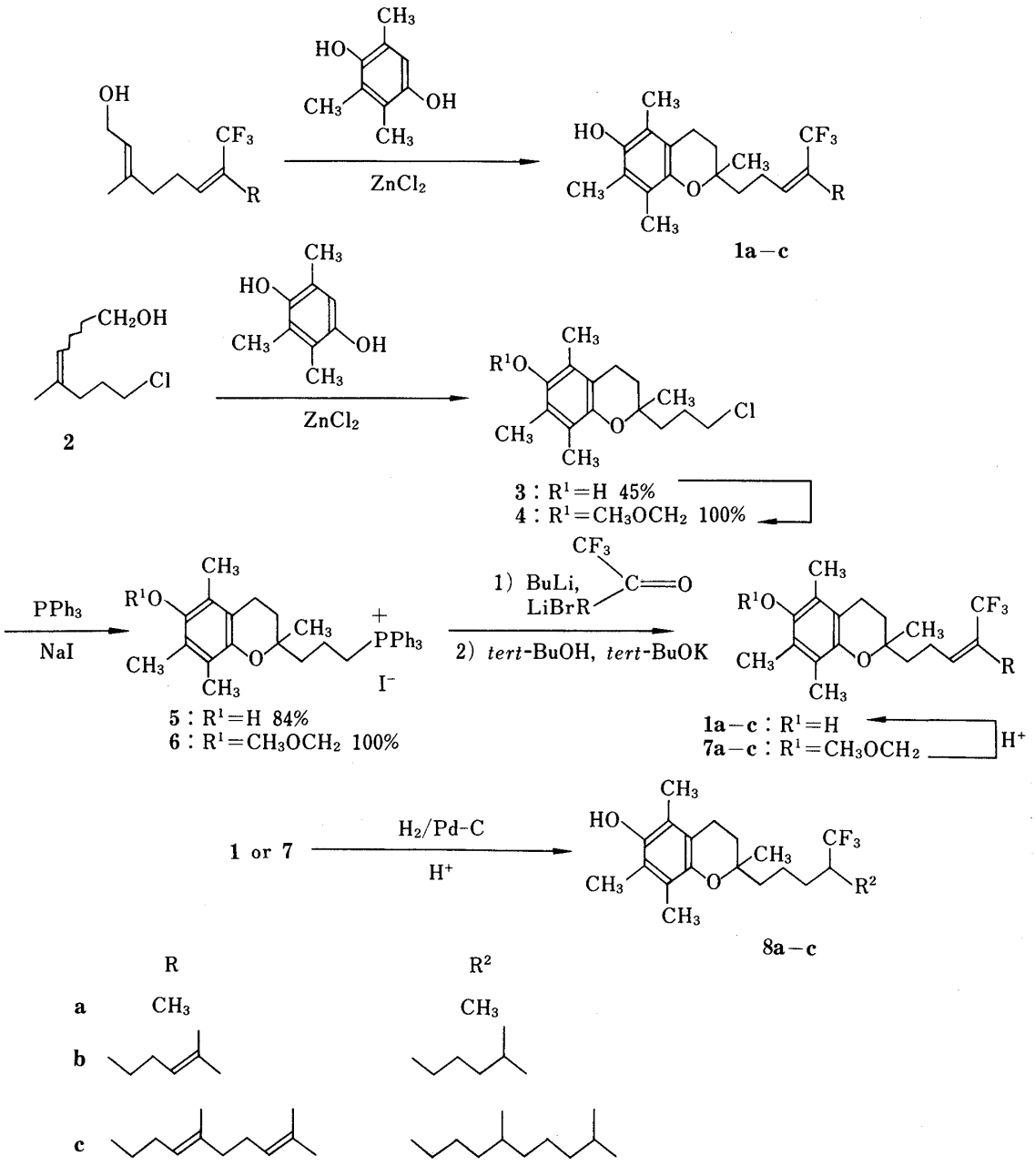

Chart 1

butanol and potassium *tert*-butoxide were added at low temperature. By this procedure, 2,5,7,8-tetramethyl-2-(5,5,5-trifluoro-4-methyl-3-pentenyl)-6-chromanol (**1a**) was obtained in 46% yield. The ^{19}F-nuclear magnetic resonance (^{19}F-NMR) spectrum showed that this product contained two *Z*/*E* isomers in a ratio of 86 : 14. The major product was the *Z*-isomer, as in the previous paper,[1] in which the ratio had been 2 : 1. Thus, the selectivity was greatly improved by the use of this modified Schlosser's method. A similar reaction of the salt **6** gave a 76% yield of the methoxymethyl ether (**7a**), which was hydrolyzed to **1a** in 89% yield. Compounds **1b** and **1c** were obtained similarly from **5** or **6**. The results are summarized in the middle of Chart 1.

Thus, **5** could be condensed with the ketone directly, but the protection of the hydroxyl group with a methoxymethyl group improved the yields of the Wittig reaction, though the *Z*/*E* ratios were not affected. Hydrolysis of the ethers was carried out in acetone in the

TABLE I. Isolation Yields of the Products (%)

	5→1	6→7	7→1	1→8	7→8
a	46	76	89	53	85
b	49	48	65	58	68
c	19	99	55	—	73

presence of *p*-toluenesulfonic acid.

The olefinic side chain of the above products was reduced to give the perhydro compounds, as shown at the bottom of Chart 1. Isolation yields of all the reactions are summarized in Table I.

The biological activities of these compounds are now being investigated, and will be reported elsewhere.

Our intermediates (**5** or **6**) are expected to be useful intermediates for the synthesis of many kinds of vitamin E analogues.

Experimental

Synthesis of 6-chloro-3-methyl-2-buten-1-ol (**2**) was carried out as described in the previous paper.[1] Proton nuclear magnetic resonance (^{1}H-NMR) spectra were obtained on JNM-FX90Q and JNM-GX400 spectrometers. ^{19}F-NMR spectra were recorded on a JNM-FX90Q spectrometer, using benzotrifluoride as an internal standard (upper field taken as plus).

2-(3-Chloropropyl)-2,5,7,8-tetramethyl-6-chromanol (3)——A mixture of trimethylhydroquinone (1216 mg, 8.0 mmol), **2** (990 mg, 6.66 mmol), and $ZnCl_2$ (89 mg, 0.65 mmol) in AcOH (20 ml) was refluxed for 18 h. After evaporation of the solvent under vacuum, the residue was extracted with CH_2Cl_2. The extract was washed with saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated under vacuum. The residue was purified on an SiO_2 column in hexane–Et_2O (10 : 1) to give **3** (549 mg) and its acetate (815 mg), which was hydrolyzed to **3**, (total yield 45%). **3**: Pale yellow oil, which darkens on standing. Mass spectrum (MS) *m/z*: 282 (M^+). High-resolution mass spectrum (HRMS): Calcd for $C_{16}H_{23}ClO_2$: 282.1380. Found: 282.1374. ^{1}H-NMR ($CDCl_3$) δ: 4.20 (1H, s), 3.53 (2H, t, J= 6.4 Hz), 2.61 (2H, t, J=6.7 Hz), 2.46—2.21 (2H, m), 2.13, 2.10 (9H, s), 2.05—1.63 (4H, m), 1.25 (3H, s).

[3-(6-Hydroxy-2,5,7,8-tetramethyl-2-chromyl)propyl]triphenylphosphonium Iodide (5)——A mixture of **3** (79 mg, 0.28 mmol), triphenylphosphine (112 mg, 0.42 mmol) and NaI (92 mg, 0.61 mmol) in CH_3CN (3 ml) was stirred at 80 °C for 48 h. After the reaction mixture had cooled down to room temperature, CH_2Cl_2 was added. The precipitate was filtered off and washed with CH_2Cl_2. Filtrate and washing were combined and concentrated under vacuum. The residue was purified on an SiO_2 column (CH_2Cl_2–MeOH, 20 : 1) to give **5** as colorless crystals (150 mg, 84%, mp 80—83 °C).

[3-(6-Methoxymethoxy-2,5,7,8-tetramethyl-2-chromyl)propyl]triphenylphosphonium Iodide (6)——Chloromethyl methyl ether (1.114 g, 14.26 mmol) in CH_2Cl_2 (5 ml) was added to a mixture of **3** (1.007 g, 3.56 mmol) and diisopropylethylamine (3.68 g, 28.48 mmol) in CH_2Cl_2 (5 ml) under stirring. The reaction mixture was refluxed for 6 h, then concentrated under vacuum and the residue was purified on an SiO_2 column (hexane–Et_2O, 10 : 1) to give **4** as a colorless oil (1.178 g, quantitative). ^{1}H-NMR ($CDCl_3$) δ: 4.87 (2H, s), 3.60 (3H, s), 3.55 (2H, m), 2.60 (2H, t, J= 6.7 Hz), 2.46—2.21 (2H, m), 2.16 (3H, s), 2.13 (3H, s), 2.07 (3H, s), 1.98—1.54 (4H, m), 1.25 (3H, s). A mixture of **4** (1.812 g, 5.55 mmol), triphenylphosphine (2.18 g, 8.32 mmol) and NaI (1.80 g) was refluxed in CH_3CN (20 ml) for 21 h. By work-up as in the case of **5**, the phosphonium salt (**6**) was obtained in a quantitative yield. ^{1}H-NMR ($CDCl_3$) δ: 7.97—7.36 (15H, m), 4.84 (2H, s), 3.60 (3H, s), 3.87—3.30 (2H, m), 2.53 (2H, t, J=6.6 Hz), 2.40—2.26 (2H, m), 2.14 (6H, s), 2.11 (3H, s), 1.98—1.54 (4H, m), 1.25 (3H, s).

2,5,7,8-Tetramethyl-(5,5,5-trifluoro-4-methyl-3-pentenyl)-6-chromanol (1a)——(a) From **5**: BuLi (15% in hexane, 1.129 ml) and LiBr (0.13 g) in tetrahydrofuran (THF) (1.3 ml) was added to a suspension of **5** (502 mg, 0.79 mmol) in Et_2O (1 ml) and THF (6 ml) under stirring at room temperature. Stirring was continued for 1 h at room temperature, then the mixture was cooled to −78 °C and CF_3COCH_3 (300 mg, excess) was added. Stirring was continued for a further 20 min at −45 °C. BuLi (15% in hexane, 1.129 ml) was added again and the mixture was stirred at room temperature for 30 min. The mixture was cooled to −78 °C and a mixture of *tert*-BuOH (1 ml) and Et_2O (1 ml) was added followed by addition of *tert*-BuOK (0.130 g) in THF (1 ml). Stirring was continued for an additional 1 h. The mixture was treated with saturated NH_4Cl and extracted with Et_2O. The extract was washed with saturated NaCl, dried over $MgSO_4$ and concentrated under vacuum. The residue was passed through an SiO_2 column in hexane–Et_2O

(10 : 1). The effluent was purified on an medium-pressure column (SiO_2, hexane–isopropanol, 200 : 1) to give **1a** as a colorless oil (125 mg, 46%). This was identical with the authentic sample obtained in the previous paper.[1] ^{1}H-NMR ($CDCl_3$) δ: 6.28 (0.16H, m), 5.68 (0.84H, t, J=7.7 Hz), 4.20 (1H, s, OH), 2.61 (2H, t, J=6.7 Hz), 2.36 (2H, m), 2.17 (3H, s), 2.11 (6H, s), 1.94—1.5 (4H, m), 1.82 (3H, s), 1.25 (3H, s). ^{19}F-NMR ($CDCl_3$) ppm from $C_6H_5\underline{C}F_3$: −1.21, 6.68 (both singlet, ratio 84 : 16). This showed that the Z/E ratio was 84 : 16.

(b) From **6**: The salt **6** was dissolved in THF (4 ml) and LiBr (0.127 g) in THF (1 ml) was added. To this mixture, BuLi (15% in hexane, 0.95 ml) was added at room temperature under stirring. After being stirred for 20 min at room temperature, the mixture was cooled to −78 °C and CF_3COCH_3 (0.8 g, excess) was added. The reaction mixture was stirred at −30 °C for 20 min, BuLi (0.95 ml) was added and the whole was stirred at room temperature for 20 min. The mixture was cooled to −78 °C again and stirring was continued for 15 min. Then *tert*-BuOH (1 ml) and *tert*-BuOK (0.164 g in THF 1 ml) were added at this temperature, and the reaction mixture was allowed to warm to room temperature and stirred for a further 1 h. The mixture was treated with saturated NH_4Cl and extracted with Et_2O. The extract was washed with saturated $NaHCO_3$ and saturated NaCl, dried over $MgSO_4$ and concentrated under vacuum. The residue was purified on an SiO_2 column in hexane–Et_2O (10 : 1) to give **7a** as a viscous oil (433 mg, 76%). MS m/z: 386 (M^+), 341, 205. HRMS Calcd for $C_{21}H_{29}F_3O_3$: 386.2077. Found: 386.2085. ^{1}H-NMR ($CDCl_3$) δ: 6.04 (0.16H, m), 5.70 (0.84H, t, J=7.7 Hz), 4.86 (2H, s), 3.60 (3H, s), 2.58 (2H, t, J=6.6 Hz), 2.44—2.26 (2H, m), 2.17 (3H, s), 2.14 (3H, s), 2.06 (3H, s), 1.80 (3H, s), 1.91—1.44 (4H, m), 1.24 (3H, s). ^{19}F-NMR ($CDCl_3$) ppm: −1.20, 6.69 (both singlet, ratio Z/E=84 : 16). The compound (**7a**, 340 mg) was stirred for 48 h at room temperature in acetone (4.5 ml) in the presence of a catalytic amount of *p*-toluenesulfonic acid. The mixture was concentrated under vacuum, treated with saturated $NaHCO_3$ and extracted with Et_2O. The Et_2O layer was washed with saturated NaCl, dried over $MgSO_4$ and concentrated under vacuum. The residue was purified on an SiO_2 column in hexane–Et_2O to give **1a** as a viscous oil (269 mg, 89%). This was identical with the material obtained in (a).

2,5,7,8-Tetramethyl-2-[8-methyl-4-(trifluoromethyl)-3,7-nonadienyl]-6-chromanol (1b)——(a) From **5**: The phosphonium salt (**5**) (250 mg, 0.39 mmol) and 1,1,1-trifluoro-6-methyl-5-hepten-2-one (101 mg, 0.56 mmol) were treated in the same manner as in the case of **1a**-(a) to give **1b** as a viscous oil (87 mg, 49%). MS m/z: 410 (M^+). HRMS Calcd for $C_{24}H_{33}F_3O_2$: 410.2437. Found: 410.2442. ^{1}H-NMR ($CDCl_3$) δ: 6.10 (0.15H, m), 5.68 (0.85H, t, J=7.8 Hz), 5.06 (1H, br), 4.19 (1H, s), 2.62 (2H, t, J=6.7 Hz), 2.56—2.47 (2H, m), 2.15 (6H, s), 2.11 (3H, s), 1.64 (3H, s), 1.56 (3H, s), 1.23 (3H, s). ^{19}F-NMR ($CDCl_3$) ppm: −3.03, 4.09 (both singlet, ratio Z/E=85 : 15). This was identical with the authentic sample obtained in the previous paper.[1]

(b) From **6**: The salt (**6**) (1.00 g, 1.47 mmol) and the ketone (0.344 g, 1.9 mmol) were treated as in the case of **1a**-(b) to give the methoxymethyl ether (**7b**, 248 mg, 48%). The Z/E ratio was 83 : 17. This oil (**7b**, 220 mg) was hydrolyzed as above to give **1b** (129 mg, 65%).

2-[8,12-Dimethyl-4-(trifluoromethyl)-3,7,11-tridecatrienyl]-2,5,7,8-tetramethyl-6-chromanol (1c)——(a) From **5**: The salt (**5**) (517 mg, 0.81 mmol) and 1,1,1-trifluoro-6,10-dimethyl-5,9-undecadien-2-one (256 mg, 1.03 mmol) were treated as in the case of **1a**-(a) to give **1c** as a viscous oil (74 mg, 19%). MS m/z: 478 (M^+). HRMS Calcd for $C_{29}H_{41}F_3O_2$: 478.3058. Found: 478.3058. ^{1}H-NMR ($CDCl_3$) δ: 6.11 (0.16H, m), 5.66 (0.84H, t, J=7.8 Hz), 5.06 (2H, br), 4.20 (1H, br), 2.61 (2H, t, J=6.7 Hz), 2.56—2.52 (2H, m), 2.17 (6H, s), 2.11 (3H, s), 1.69, 1.60 (9H in total, s), 1.94—1.06 (12H, m), 1.24 (2H, s). ^{19}F-NMR ($CDCl_3$) ppm: −3.02, 4.10 (both singlet, ratio Z/E=84 : 16). This was identical with the authentic sample obtained in the previous paper.[1]

(b) From **6**: The salt (**6**) (1.00 g, 1.47 mmol) and the ketone (473 mg, 1.91 mmol) were treated as in the case of **1a**-(b) to give the methoxymethyl ether (**7c**) as a viscous oil (758 mg, 99%). MS m/z: 522 (M^+). HRMS Calcd for $C_{31}H_{45}F_3O_3$: 522.3323. Found: 522.3324. ^{1}H-NMR ($CDCl_3$) δ: 6.11 (0.17H, m), 5.68 (0.83H, t, J=7.7 Hz), 5.07 (2H, br), 4.85 (2H, s), 3.60 (3H, s), 2.58 (2H, t, J=6.6 Hz), 2.45—2.22 (2H, m), 2.17 (3H, s), 2.14 (3H, s), 2.07 (3H, s), 2.01—1.40 (12H, m), 1.65 (3H, s), 1.57 (3H, s), 1.23 (3H, s). ^{19}F-NMR ($CDCl_3$) ppm: −3.04, 4.11 (both singlet, ratio Z/E=83 : 17). This ether was treated with acetone and *p*-toluenesulfonic acid to give a 55% of **1c**, which was identical with the sample obtained above.

2,5,7,8-Tetramethyl-2-(1,1,1-trifluoro-4-methylpentyl)-6-chromanol (8a)——(a) From **1a**: A solution of **1a** (53 mg, 0.16 mmol) in EtOH (2 ml) was stirred at 80 °C in an atmosphere of hydrogen in the presence of Pd–C (10%, 10 mg) for 6 h. The catalyst was filtered off and washed with Et_2O. The filtrate and washings were combined and concentrated under vacuum. The residue was purified on an SiO_2 column in hexane–Et_2O (10 : 1) to give **8a** as a viscous oil (29 mg, 53%) with recovery of 2 mg of the starting material. **8a**: MS m/z: 344. HRMS Calcd for $C_{19}H_{27}F_3O_2$: 344.1958. Found: 344.1954. ^{1}H-NMR ($CDCl_3$) δ: 4.22 (1H, br), 2.60 (2H, t, J=7.2 Hz), 2.15 (3H, s), 2.10 (6H, s), 1.77 (2H, t, J=7.0 Hz), 1.87—1.00 (7H, m), 1.22 (3H, s), 1.08 (3H, d, J=7.0 Hz). ^{19}F-NMR ($CDCl_3$) ppm: 10.51, 10.55 (both doublets, J_{H-F}=9.2 Hz, ratio 1 : 1). This shows that the product is a 1 : 1 mixture of two diastereoisomers.

(b) From the Methoxymethyl Ether **7a**: The ether (**7a**, 484 mg) was stirred in EtOH (4 ml) containing a few drops of 10% HCl in an atmosphere of hydrogen in the presence of Pd–C (10%, 40 mg) at 60 °C for 6 h. The reaction mixture was treated as above to give **8a** (367 mg, 85%).

2,5,7,8-Tetramethyl-2-[8-methyl-4-(trifluoromethyl)nonyl]-6-chromanol (8b)——(a) From **1b**: A solution of **1b** (67 mg, 0.16 mmol) in EtOH (2 ml) was treated in a similar manner as in the case of **8a**-(a) to give **8b** as a viscous oil

(39 mg, 58%). MS *m/z*: 414 (M^+). HRMS Calcd for $C_{24}H_{37}F_3O_2$: 414.2741. Found: 414.2737. ^{1}H-NMR ($CDCl_3$) δ: 4.18 (1H, br), 2.62 (2H, t, J=7.2 Hz), 2.16 (3H, s), 2.10 (6H, s), 1.77 (2H, m), 1.86—0.98 (14H, m), 1.23 (3H, s), 0.87 (6H, d, J=6.2 Hz). ^{19}F-NMR ($CDCl_3$) ppm: 7.29, 7.40 (both doublets, J=9.3 Hz, ratio approximately 2:1). This result shows that the product is a 2:1 mixture of two diastereoisomers.

(b) From the Methoxymethyl Ether **7b**: A solution of the ether (**7b**, 752 mg) in EtOH (4 ml) was treated as in the case of **8a**-(b) to give **8b** as a viscous oil (470 mg, 68%), which was identical with the product of the above experiment.

2-[8,12-Dimethyl-4-(trifluoromethyl)tridecyl]-2,5,7,8-tetramethyl-6-chromanol (8c)——The methoxymethyl ether (**7c**, 828 mg) was treated as in the case of **8a**-(b) to give **8c** as a viscous oil (562 mg, 73%). MS *m/z*: 484 (M^+). HRMS Calcd for $C_{29}H_{47}F_3O_2$: 484.3524. Found: 484.3521. ^{1}H-NMR ($CDCl_3$) δ: 4.18 (1H, br s), 2.60 (2H, t, J=6.5 Hz), 2.14 (3H, s), 2.10 (6H, s), 1.75 (2H, m), 1.56—1.0 (21H, m), 1.21 (3H, s), 0.86 (6H, d, J=6.3 Hz). ^{19}F-NMR ($CDCl_3$) ppm: 7.29, 7.38 (both doublets, J=9.3 Hz, each peak is split by 0.1 Hz). This result shows that this is a mixture of four diastereoisomers.

References and Notes

1) Part I: I. Kumadaki, M. Tamura, A. Ando, T. Nagai, M. Koyama, and T. Miki, *Chem. Pharm. Bull.*, **36**, 515 (1988).
2) Part of this work was reported at the 107th Annual Meeting of the Pharmaceutical Society of Japan in Kyoto, April 1987.
3) For details of the biological activity, see "Biomedicinal Aspects of Fluorine Compounds," ed. by R. Filler and Y. Kobayashi, Kodansha, Tokyo, 1982.
4) M. Schlosser, H. B. Tuong, and B. Schaub, *Tetrahedron Lett.*, **26**, 311 (1985).