Chem. Pharm. Bull. 43(9) 1466—1474 (1995)   Vol. 43, No. 9

Synthesis of Fluorine Analogs of Vitamin E. IV.[1] Synthesis of Bis(trifluoromethyl)tocopherols[2]

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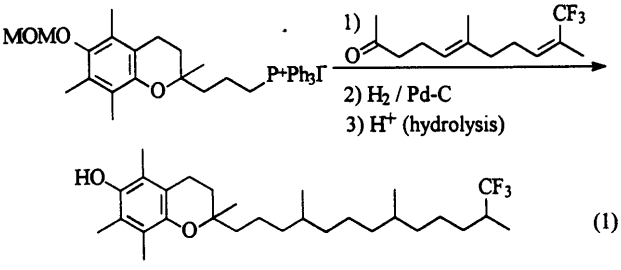
Received March 17, 1995; accepted May 13, 1995

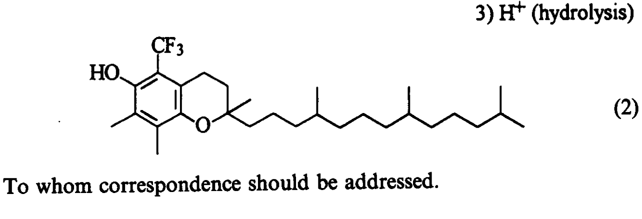
We previously synthesized mono(trifluoromethyl)tocopherols, which were used for investigation of the mobility and orientation of tocopherol in liposomes by ^{19}F-NMR. For more precise investigation of the behavior of vitamin E in liposomes, tocopherols having two trifluoromethyl groups, one on the prenyl side chain and the other on the chromanol ring, were synthesized. Thus, dimethylhydroquinones were treated with 6-chloro-3-methyl-2-hexenol in the presence of zinc chloride to give 2-(3-chloropropyl)trimethylchromanol derivatives. These were converted to phosphonium salts, which, upon condensation with trifluoromethylated ketones followed by hydrogenation, gave tocopherols with a trifluoromethyl group on the side chain and a hydrogen on the chromanol part. These were halogenated on the chromanol part and treated with trifluoromethyl iodide and copper powder to give the title compounds.

Key words tocopherol; fluorine; trifluoromethyl; Wittig reaction; hydroquinone; vitamin E

Many organic fluorine compounds are used as medicinal and agricultural chemicals.[3] Further, some fluorine analogs of biologically active compounds are used as probes for investigation of the biochemical behavior of organic compounds. We have been concerned with syntheses of fluorine analogs of vitamin E.[4] Vitamin E was found about 70 years ago as an anti-impregnancy factor, and named "tocopherol." Since then, its function has been investigated widely and now its activity is believed to be due to its anti-oxidant action on unsaturated fatty acids which are important components of biological membranes.[5] It is suggested that vitamin E is deeply related to senescence. However, its mechanism of action is still not clear. To understand the mechanism of biological activity of vitamin E, it is very important to know the orientation and mobility of vitamin E in biological membranes. On the other hand, fluorine compounds are very rare in biological organisms and their behaviors can be followed by ^{19}F-NMR. Therefore, fluorine analogs of vitamin E should be suitable for the above investigations. We have already synthesized fluorine analogs of vitamin E, in which one of the methyl groups is substituted with a trifluoromethyl group.[4] Two examples of these syntheses are shown in Eqs. 1 and 2.



(1)



(2)

The first equation shows the introduction of a trifluoromethyl group onto the prenyl side chain of α-tocopherol. The second equation shows the introduction of a trifluoromethyl group on the chromanol ring by the method developed by us.[4c] The behavior of these compounds in liposomes was investigated by measuring spin–spin relaxation times (T_2) on fluorine NMR. This study showed us how and where these vitamin E derivatives were incorporated in the liposome, a model of biological membranes.[6] As an extension of this study, we planned to synthesize of fluorine analogs of vitamin E, in which two methyl groups were replaced with two trifluoromethyl groups, one on the chromanol ring and the other on the isoprenoid side chain. More detailed studies using these compounds should improve understanding of the function of vitamin E. We applied our previous reactions to this synthesis. However, we encountered some difficulties, as described in the preliminary communication.[2] Therefore, we carried out some model experiments,[2] and then, using these results, we succeeded in obtaining nine isomers of bis(trifluoromethyl)chromanols. Here, we would like to present details of these experiments.

Previously, we reported that a 2-(3-chloropropyl)chromanol derivative (**2**) was a useful intermediate for synthesis of tocopherols having various side-chains, including a trifluoromethyl group.[4b] For the syntheses of bis(trifluoromethyl)chromanols, we examined the synthesis of chromanols with a short side chain, as model compounds. Thus, 2-(3-chloropropyl)chromanols (**2a**—**c**)[7] were synthesized by the reaction of the corresponding dimethylhydroquinones (**1a**—**c**) with 6-chloro-3-methyl-2-hexen-1-ol in the presence of zinc chloride. Compounds **2a**—**c** were methoxymethylated and converted to the phosphonium salts (**4a**—**c**), which were treated with trifluoroacetone in the presence of bases to give chromanol derivatives (**5a**—**c**) having a short side chain with a trifluoromethyl group as a *ca.* 9 : 1 mixture of *Z*- and *E*-isomers. These results are shown in Chart 1.

All the reactions proceeded as expected from our previous results, and we considerd that this strategy could be used for the introduction of a longer trifluorometh-

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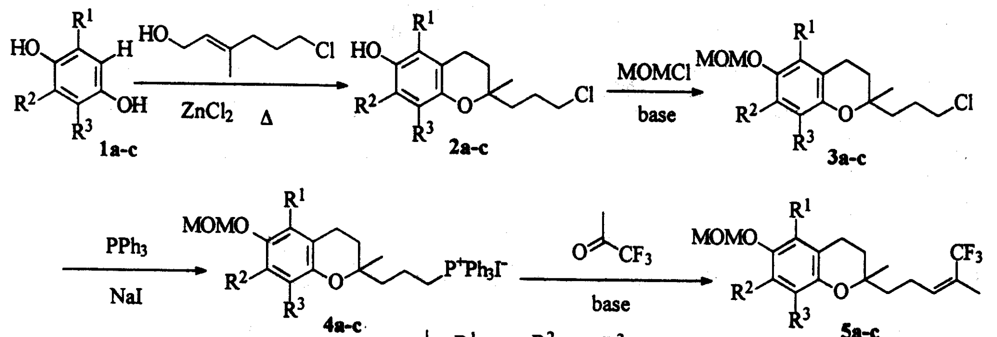


	R^1	R^2	R^3
a	CH_3	CH_3	H
b	H	CH_3	CH_3
c	CH_3	H	CH_3

Chart 1

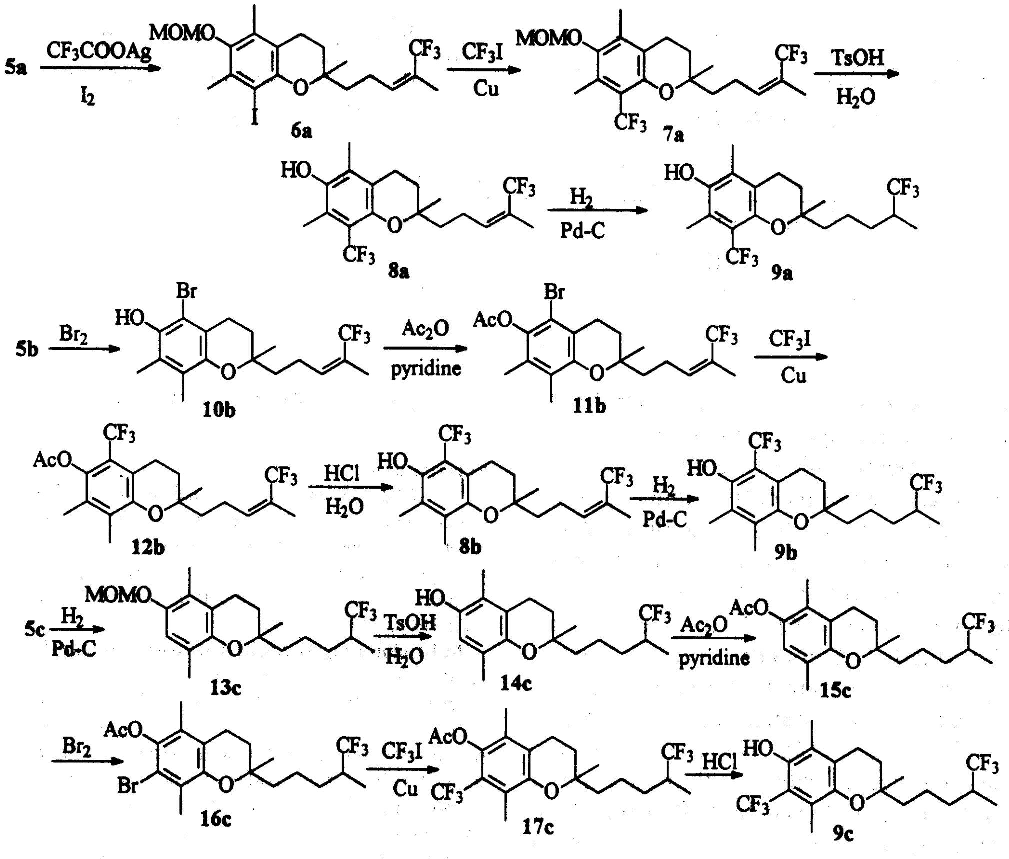
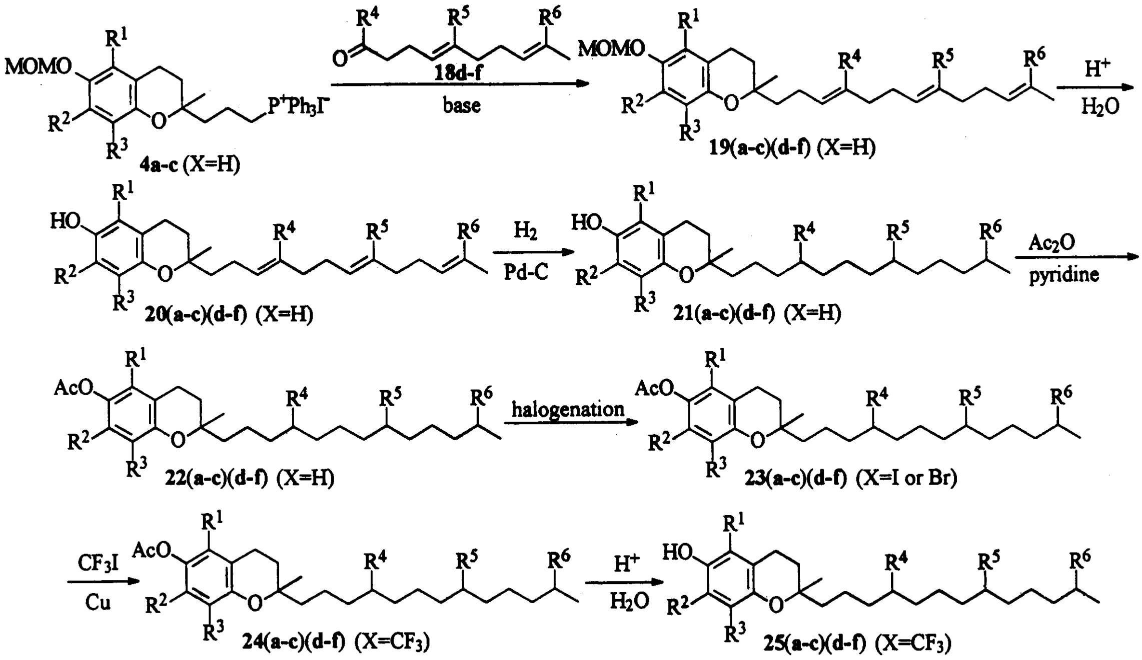


Chart 2

ylated side chain than that of **5**. Next, a trifluoromethyl group had to be introduced onto the chromanol part. We have reported previously the introduction of a trifluoromethyl group onto the chromanol moiety; a chromanol compound was iodinated in the presence of silver trifluoroacetate then treated with trifluoromethyl iodide and copper powder.[4c)] Application of this method to **5a** gave the bis(trifluoromethyl) compound (**7a**), as expected. This compound was hydrolyzed and hydrogenated in the presence of palladium–carbon (Pd–C) to give the bis(trifluoromethyl)chromanol compound (**9a**) as an inseparable diasteremeric mixture. However, the iodination of **5b** resulted in the formation of a bis(chromanol) compound, probably through oxidative coupling of the phenol moiety. To avoid this oxidation, **5b** was brominated first. During this bromination, the methoxymethyl group was hydrolyzed to afford a bromochromanol (**10b**). This chromanol was acetylated and treated with trifluoromethyl iodide and copper powder to give a 5-trifluoromethyl compound (**12b**), which was hydrolyzed and hydrogenated to afford **9b**. The iodination of **5c** resulted in the iodination of the double bond on the side-chain and pheonolic oxidation. Therefore, the double bond was hydrogenated first and the protective group was changed to an acetyl group, then the product was brominated to a bromo acetate (**16c**). This compound was trifluoromethylated as above and hydrolyzed to give a 7-trifluoromethyl compound (**9c**). Compounds **9b** and **9c** are diastereomeric mixtures. These results are shown in Chart 2.

As shown above, the halogenation of the chromanol



	R^1	R^2	R^3
a	CH_3	CH_3	X
b	X	CH_3	CH_3
c	CH_3	X	CH_3

	R^4	R^5	R^6
d	CF_3	CH_3	CH_3
e	CH_3	CF_3	CH_3
f	CH_3	CH_3	CF_3

Chart 3

moiety of tocopherol was found to be a key step for the synthesis of bis(trifluoromethyl)chromanol compounds. Thus, iodination of methoxymethyl ethers having an olefinic side chain might cause oxidative dimerization or iodination of the double bond. Based on these results, syntheses of bis(trifluoromethyl)chromanols were planned. Thus, **4a**—**c** were condensed with trifluorinated 6,10-dimethyl-5,9-undecadien-2-ones (**18d**—**f**) to give trifluorotocotrienol methoxymethyl ethers (**19**) as a 9 : 1 mixture of *Z*- and *E*-isomers. These were hydrolyzed first, then hydrogenated in the presence of palladium and acetylated to give tocopherol acetates (**22**). These acetates were iodinated in the presence of silver trifluoroacetate or brominated with bromine, followed by trifluoromethylation with trifluoromethyl iodide and copper powder to give bis(trifluoromethyl) derivatives (**24**), which were hydrolyzed with hydrochloric acid to give bis(trifluoromethyl)tocopherols (**25**). These results are shown in Chart 3. One exception is that compound **20bd** was first acetylated and hydrogenated to **22bd**, as shown in Experimental. This means that the order of the acetylation and the hydrogenation can be reversed.

In conclusion, all possible isomers of bis(trifluoromethyl)-α-tocopherols, with one trifluoromethyl group on the chromanol ring and the other on the prenyl side chain, were synthesized. The products in this paper are all diastereomeric mixtures, but these will be useful for investigation of the orientation and mobility of vitamin E in liposomes, a model of biological membranes, using ^{19}F-NMR. Studies of the biological properties of these compounds in liposomes are in progress. We are also synthesizing chiral compounds, which will be useful for investigation of biological activity *in vivo*.

Experimental

^{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.

2-(3-Chloropropyl)-2,5,7-trimethyl-6-chromanol (2a) A solution of 2,6-dimethylhydroquinone (**1a**, 0.577 g, 4.18 mmol), 6-chloro-3-methyl-2-hexen-1-ol (0.517 g, 3.48 mmol) and $ZnCl_2$ (110 mg) in AcOH (8 ml) was heated at 90 °C for 16 h. After evaporation of AcOH, the residue was poured into ice-water and extracted with Et_2O. The extract was washed with saturated $NaHCO_3$ and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was refluxed in MeOH (8 ml) containing concentrated HCl (2 ml) for 2 h to hydrolyze the acetate. After evaporation of MeOH, the residue was extracted with Et_2O, then 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–AcOEt, 10 : 1) to give **2a** (0.729 g, 78%). **2a**: A brown oil. Mass spectrum (MS) *m/z*: 268 (M^+). High-resolution mass spectrum (HRMS) Calcd for $C_{15}H_{21}ClO_2$: 268.123. Found: 268.123. ^{1}H-NMR δ: 6.45 (1H, s), 4.23 (1H, s), 3.53 (2H, t, $J=6.3$ Hz), 2.61 (2H, t, $J=6.7$ Hz), 2.18 (3H, s), 2.12 (3H, s), 2.06—1.47 (6H, m), 1.24 (3H, s).

2-(3-Chloropropyl)-2,5,7-trimethyl-6-chromanol Methoxymethyl Ether (3a) A solution of chloromethyl methyl ether (0.742 g, 9.22 mmol) in CH_2Cl_2 (2 ml) was added to a solution of **2a** (0.623 g, 2.32 mmol) and *N*,*N*-diisopropylethylamine (3.2 ml, 18.4 mmol) in CH_2Cl_2 (8 ml). The mixture was stirred at 50 °C for 6 h, poured into ice-water, and extracted twice with CH_2Cl_2. The extract was washed with saturated $NaHCO_3$, 3% HCl 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 **3a** (0.654 g, 90%). **3a**: A colorless oil. ^{1}H-NMR δ: 6.47 (1H, s), 4.88 (2H, s), 3.59 (3H, s), 3.73—3.23 (2H, m), 2.58 (2H, t, $J=6.7$ Hz), 2.21 (3H, s), 2.15 (3H, s), 2.06—1.49 (6H, m), 1.24 (3H, s).

Phosphonium Salt (4a) from (3a) A mixture of **3a** (0.729 g, 2.33 mmol), triphenylphosphine (0.920 g, 3.51 mmol) and NaI (0.70 g, 4.67 mmol) in CH_3CN (8 ml) was stirred at 80 °C for 48 h. After evaporation of the solvent, the residue was taken up in CH_2Cl_2 and filtered. The filtrate was concentrated under vacuum and purified by column chromatography (SiO_2, CH_2Cl_2–MeOH, 20 : 1) to give **4a** (1.346 g, 87%). **4a**: Colorless crystals. ^{1}H-NMR δ: 8.13—7.32 (15H, m), 6.26 (1H, s), 4.87 (2H, s), 3.60 (3H, s), 3.71—3.23 (2H, m), 2.54 (2H, t, $J=6.7$ Hz), 2.19 (3H, s), 2.12 (3H, s), 2.11—1.37 (6H, m), 1.18 (3H, s).

2-(5,5,5-Trifluoro-4-methyl-3-pentenyl)-2,5,7-trimethyl-6-chromanol Methoxymethyl Ether (5a) A solution of **4a** (1.020 g, 1.53 mmol) in THF (2 ml) was added to a suspension of LiBr (133 mg, 1.53 mmol) in (tetrahydrofuran) THF (1.5 ml). To this mixture, *n*-BuLi (15% in hexane, 1 ml, 1.56 mmol) was added dropwise under ice-cooling. The whole was stirred at room temperature for 20 min, then trifluoroacetone (2.0 g, excess) was added at −78 °C under stirring. Stirring was continued for 20 min at this temperature, and the mixture was warmed to room temperature. Further, *n*-BuLi (15% in hexane, 1 ml, 1.56 mmol) was added, and the mixture was stirred for 20 min, cooled to −78 °C, and stirred for 15 min. A solution of *tert*-BuOH (1 ml) and *tert*-BuOK (171 mg, 1.53 mmol) in THF (1.5 ml) was added at this temperature. The mixture was allowed to warm to room temperature. Stirring was continued for 1 h, then saturated NH_4Cl was added, and the whole was extracted with Et_2O. The extract was washed with saturated $NaHCO_3$, water and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography (SiO_2, hexane–Et_2O, 8 : 1) to give **5a** (0.477 g, 84%). **5a**: A pale yellow oil. MS *m/z*: 372 (M^+). HRMS Calcd for $C_{20}H_{27}F_3O_3$: 372.191. Found: 372.190. ^{1}H-NMR δ: 6.48 (1H, s), 6.20—5.92 (0.13H, br), 5.70 (0.87H, t, $J=7.7$ Hz), 4.88 (2H, s), 3.60 (3H, s), 2.59 (2H, t, $J=6.7$ Hz), 2.45—2.26 (2H, m), 2.22 (3H, s), 2.15 (3H, s), 1.82 (3H, s), 1.99—1.43 (4H, m), 1.25 (3H, s). ^{19}F-NMR ppm: −1.22, 6.91 ($Z:E=87:13$).

2-(3-Chloropropyl)-2,7,8-trimethyl-6-chromanol (2b) Reaction of 2,3-dimethylhydroquinone (**1b**, 0.840 g, 6.09 mmol) and 6-chloro-3-methyl-2-hexen-1-ol (0.750 g, 5.05 mmol) in the presence of $ZnCl_2$ (104 mg) in AcOH (10 ml) at 90 °C for 16 h, in the same manner as described for **2a**, gave **2b** (0.826 g, 61%). **2b**: A brown oil. MS *m/z*: 268 (M^+). ^{1}H-NMR δ: 6.34 (1H, s), 3.55 (2H, t, $J=6.4$ Hz), 3.30 (1H, br), 2.68 (2H, t, $J=6.7$ Hz), 2.13 (3H, s), 2.09 (3H, s), 2.20—1.48 (6H, m), 1.24 (3H, s).

2-(3-Chloropropyl)-2,7,8-trimethyl-6-chromanol Methoxymethyl Ether (3b) A solution of **2b** (0.676 g, 2.52 mmol) and *N,N*-diisopropylethylamine (3.5 ml, 20.1 mmol) in CH_2Cl_2 (8 ml) was treated with a solution of chloromethyl methyl ether (0.810 g, 10.1 mmol) in CH_2Cl_2 (2 ml) in the same manner as described for **3a**, and a similar work-up gave **3b** (0.711 g, 90%). **3b**: A colorless oil. ^{1}H-NMR δ: 6.63 (1H, s), 5.09 (2H, s), 3.57 (2H, t, $J=6.3$ Hz), 3.50 (3H, s), 2.74 (2H, t, $J=6.7$ Hz), 2.15 (3H, s), 2.11 (3H, s), 2.23—1.51 (6H, m), 1.26 (3H, s).

Phosphonium Salt (4b) from 3b Reaction of **3b** (0.370 g, 1.18 mmol), triphenylphosphine (0.372 g, 1.42 mmol) and NaI (0.266 g, 1.77 mmol) in CH_3CN (6 ml) in the same manner as described for **4a**, gave **4b** (0.725 g, 92%). **4b**: Colorless crystals. ^{1}H-NMR δ: 8.09—7.51 (15H, m), 6.62 (1H, s), 5.08 (2H, s), 3.49 (3H, s), 4.09—3.11 (2H, m), 2.69 (2H, t, $J=6.7$ Hz), 2.10 (3H, s), 1.83 (3H, s), 2.20—1.43 (6H, m), 1.19 (3H, s).

2-(5,5,5-Trifluoro-4-methyl-3-pentenyl)-2,7,8-trimethyl-6-chromanol Methoxymethyl Ether (5b) A solution of **4b** (1.700 g, 2.55 mmol) in THF (2 ml) was treated with LiBr (222 mg, 2.55 mmol) in THF (4 ml) and *n*-BuLi (15% in hexane) (1.7 ml, 2.66 mmol) followed by reaction with trifluoroacetone (1.7 g, excess) and treatment with bases as in the case of **5a**, giving **5b** (0.838 g, 88%). **5b**: A pale yellow oil. MS *m/z*: 372 (M^+). HRMS Calcd for $C_{20}H_{27}F_3O_3$: 372.191. Found: 372.192. ^{1}H-NMR δ: 6.64 (1H, s), 6.20—5.91 (0.11H, br), 5.71 (0.89H, t, $J=7.7$ Hz), 5.09 (2H, s), 3.49 (3H, s), 2.72 (2H, t, $J=6.7$ Hz), 2.57—2.23 (2H, m), 2.15 (3H, s), 2.10 (3H, s), 1.83 (3H, s), 1.79—1.49 (4H, m), 1.25 (3H, s). ^{19}F-NMR ppm: −4.21, 8.06 ($Z:E=89:11$).

2-(3-Chloropropyl)-2,5,8-trimethyl-6-chromanol (2c) Reaction of 2,5-dimethylhydroquinone (**1c**, 0.482 g, 3.49 mmol) and 6-chloro-3-methyl-2-hexen-1-ol (0.440 g, 2.96 mmol) in the presence of $ZnCl_2$ (110 mg) in AcOH (10 ml) in the same manner as described for **2a**, gave **2c** (0.398 g, 50%). **2c**: A brown oil. MS *m/z*: 268 (M^+). HRMS Calcd for $C_{15}H_{21}ClO_2$: 268.123. Found: 268.123. ^{1}H-NMR δ: 6.47 (1H, s), 3.57 (2H, t, $J=6.4$ Hz), 2.62 (2H, t, $J=6.7$ Hz), 2.08 (6H, s), 2.23—1.50 (6H, m), 1.23 (3H, s).

2-(3-Chloropropyl)-2,5,8-trimethyl-6-chromanol Methoxymethyl Ether (3c) Reaction of **2c** (0.398 g, 1.48 mmol) with chloromethyl methyl ether (0.477 g, 5.92 mmol) in the presence of *N,N*-diisopropylethylamine (2.1 ml, 12.1 mmol) in the same manner as described for **3a**, gave **3c** (0.425 g, 92%). **3c**: A colorless oil. ^{1}H-NMR δ: 6.75 (1H, s), 5.07 (2H, s), 3.49 (3H, s), 3.94—3.23 (2H, m), 2.61 (2H, t, $J=6.7$ Hz), 2.11 (6H, s), 2.25—1.46 (6H, m), 1.23 (3H, s).

Phosphonium Salt (4c) from 3c A solution of **3c** (0.267 g, 0.854 mmol), triphenylphosphine (0.246 g, 0.939 mmol) and NaI (0.192 g, 1.28 mmol) in CH_3CN (3 ml) was treated as in the case of **4a**, to give **4c** (0.526 g, 92%). **4c**: Colorless crystals. ^{1}H-NMR δ: 8.10—7.37 (15H, m), 6.26 (1H, s), 4.91 (2H, s), 3.62 (3H, s), 4.17—3.09 (2H, m), 2.52 (2H, t, $J=6.7$ Hz), 2.20 (3H, s), 2.14 (3H, s), 2.27—1.69 (6H, m), 1.20 (3H, s).

2-(5,5,5-Trifluoro-4-methyl-3-pentenyl)-2,5,8-trimethyl-6-chromanol Methoxymethyl Ether (5c) Reaction of **4c** (0.500 g, 0.75 mmol) with trifluoroacetone (0.5 g, excess) in the bases as described for **5a**, gave **5c** (0.233 g, 83%). **5c**: A pale yellow oil. MS *m/z*: 372 (M^+). HRMS Calcd for $C_{20}H_{27}F_3O_3$: 372.191. Found: 372.191. ^{1}H-NMR δ: 6.75 (1H, s), 6.23—5.97 (0.1H, br), 5.71 (0.9H, t, $J=7.7$ Hz), 5.08 (2H, s), 3.49 (3H, s), 2.61 (2H, t, $J=6.7$ Hz), 2.49—2.20 (2H, m), 2.11 (6H, s), 1.82 (3H, s), 1.94—1.49 (4H, m), 1.24 (3H, s). ^{19}F-NMR ppm: −1.25, 6.91 ($Z:E=90:10$).

8-Iodo-2-(5,5,5-trifluoro-4-methyl-3-pentenyl)-2,5,7-trimethyl-6-chromanol Methoxymethyl Ether (6a) A solution of I_2 (0.330 mg, 1.27 mmol) in CH_2Cl_2 (20 ml) was added dropwise to a suspension of **5a** (0.474 g, 1.27 mmol) and CF_3COOAg (0.281 g, 1.27 mmol) in CH_2Cl_2 (20 ml) at room temperature under stirring. The mixture was stirred for a further 10 min, and a solution of $NaHCO_3$ (213 mg) and sodium thiosulfate (200 mg) in H_2O (20 ml) was added. The whole was filtered through a Celite layer and the filtrate was extracted with CH_2Cl_2. The extract 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–CH_2Cl_2, 1 : 1) to give **6a** (0.425 g, 67%). **6a**: A yellow oil. MS *m/z*: 498 (M^+). HRMS Calcd for $C_{20}H_{26}F_3IO_3$: 498.088. Found: 498.088. ^{1}H-NMR δ: 6.23—5.94 (0.13H, br), 5.78 (0.87H, t, $J=7.7$ Hz), 4.86 (2H, s), 3.60 (3H, s), 2.60 (2H, t, $J=6.7$ Hz), 2.43 (3H, s), 2.15 (3H, s), 2.49—2.26 (2H, m), 1.94—1.49 (4H, m), 1.81 (3H, s), 1.29 (3H, s).

2-(5,5,5-Trifluoro-4-methyl-3-pentenyl)-2,5,7-trimethyl-8-(trifluoromethyl)-6-chromanol Methoxymethyl Ether (7a) A mixture of Cu powder (500 mg, 7.87 mmol), **6a** (425 mg, 0.853 mmol) and hexamethylphosphoric triamide (HMPA, 10 ml) was sealed in a stainless steel tube and cooled to −78 °C. CF_3I (1.0 ml, 10.2 mmol) was added to the tube by a vacuum-line method and the tube was shaken at 120 °C for 14 h. It was cooled to room temperature, then the content was poured into ice-water, and filtered through a Celite layer. The filtrate was extracted with Et_2O, then the Et_2O layer was washed with H_2O, and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography (SiO_2, hexane–CH_2Cl_2, 2 : 1) to give the starting material (164 mg) and **7a** (180 mg, 78%). **7a**: A yellow oil. MS *m/z*: 440 (M^+). HRMS Calcd for $C_{21}H_{26}F_6O_3$: 440.179. Found: 440.180. ^{1}H-NMR δ: 6.24—5.94 (0.13H, br), 5.74 (0.87H, t, $J=7.7$ Hz), 4.84 (2H, s), 3.61 (3H, s), 2.62 (2H, t, $J=6.7$ Hz), 2.36 (3H, q, $J=3.7$ Hz), 2.20 (3H, s), 2.50—2.02 (2H, m), 1.97—1.37 (4H, m), 1.82 (3H, s), 1.25 (3H, s). ^{19}F-NMR ppm: −10.34 (3F, q, $J=1.8$ Hz), −2.59, 5.24, (3F in total, $Z:E=87:13$).

2-(5,5,5-Trifluoro-4-methyl-3-pentenyl)-2,5,7-trimethyl-8-(trifluoromethyl)-6-chromanol (8a) A solution of **7a** (105 mg, 0.239 mmol) and *p*-TsOH·H_2O (30 mg) in MeOH (4 ml) was stirred at room temperature for 5 h, and then MeOH was evaporated under vacuum. The residue was treated with saturated $NaHCO_3$, and extracted with Et_2O. The extract was washed with brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography (SiO_2, hexane–CH_2Cl_2, 1 : 1) to give **8a** (92 mg, 97%). **8a**: A yellow oil. ^{1}H-NMR δ: 6.23—5.99 (0.13H, br), 5.72 (0.87H, t, $J=7.7$ Hz), 4.37 (1H, s), 2.66 (2H, t, $J=6.7$ Hz), 2.32 (3H, q, $J=2.6$ Hz), 2.14 (3H, s), 2.51—1.97 (2H, m), 1.82 (3H, s), 1.96—1.40 (4H, m), 1.23 (3H, s).

2-(5,5,5-Trifluoro-4-methylpentyl)-2,5,7-trimethyl-8-(trifluoromethyl)-6-chromanol (9a) A solution of **8a** (128 mg, 0.323 mmol) in MeOH (10 ml) was stirred in the presence of Pd–C (10%, 30 mg) in an atmosphere of H_2 at room temperature for 4 h, and at 45 °C for 2 h. The catalyst was filtered off, and the filtrate was concentrated under vacuum. The residue was purified by column chromatography (SiO_2, hexane–Et_2O, 10 : 1) to give **9a** (101 mg, 79%). **9a**: A yellow oil. MS *m/z*: 398 (M^+). HRMS Calcd for $C_{19}H_{24}F_6O_2$: 398.168. Found: 398.168. ^{1}H-NMR δ: 4.36 (1H, s), 2.66 (2H, t, $J=7.1$ Hz), 2.35 (3H, q, $J=2.9$ Hz), 2.15 (3H, s), 1.81 (2H, t, $J=7.0$ Hz), 1.80-1.31 (7H, m), 1.22 (3H, s), 1.10 (3H, d, $J=7.0$ Hz). ^{19}F-NMR ppm: −9.81 (3F, s), 11.04 (3F, d, $J=8.8$ Hz).

5-Bromo-2-(5,5,5-trifluoro-4-methyl-3-pentenyl)-2,7,8-trimethyl-6-chromanol (10b) A solution of Br_2 (100 mg, 0.625 mmol) in CH_2Cl_2 (4 ml) was added dropwise to a solution of **5b** (105 mg, 0.282 mmol) in CH_2Cl_2 (2 ml) at room temperature. The mixture was stirred for 10 min, then saturated $NaHCO_3$ was added and the whole was extracted with CH_2Cl_2. The CH_2Cl_2 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–CH_2Cl_2, 1 : 1) to give **10b** (96 mg, 84%). **10b**: A yellow oil. ^{1}H-NMR δ: 6.12—5.83 (0.11H, br), 5.69 (0.89H, t, $J=7.7$ Hz), 5.20 (1H, s), 2.68 (2H, t, $J=6.7$ Hz), 2.53—2.27 (2H, m), 2.21 (3H, s), 2.08 (3H, s), 1.82 (3H, s), 1.94—1.40 (4H, m), 1.24 (3H, s).

5-Bromo-2-(5,5,5-trifluoro-4-methyl-3-pentenyl)-2,7,8-trimethyl-6-chromanol Acetate (11b) A mixture of **10b** (81 mg, 0.199 mmol), pyridine (0.2 ml) and acetic anhydride (0.2 ml, 2.12 mmol) was stirred at room temperature for 5 h, then was poured into ice-water, and extracted with Et_2O. The Et_2O layer was washed with 5% HCl, 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 **11b** (87 mg, 97%). **11b**: A yellow oil. MS *m/z*: 448 (M^+). HRMS Calcd for $C_{20}H_{24}BrF_3O_3$: 448.086. Found: 448.086. ^{1}H-NMR δ: 6.17—5.89 (0.11H, br), 5.71 (0.89H, t, $J=7.7$ Hz), 2.72 (2H, t, $J=6.7$ Hz), 2.36 (3H, s), 2.49—2.15 (2H, m), 2.07 (6H, s), 1.83 (3H, s), 1.91—1.61 (4H, m), 1.26 (3H, s).

2-(5,5,5-Trifluoro-4-methyl-3-pentenyl)-2,7,8-trimethyl-5-(trifluoromethyl)-6-chromanol Acetate (12b) Compound **11b** (80 mg, 0.178 mmol) was treated with CF_3I (1 ml, 10.2 mmol) and Cu powder (500 mg, 7.87 mmol) in HMPA (10 ml) by a similar method to that used in the case of **7a**, to give **12b** (51 mg, 65%). **12b**: A yellow oil. MS *m/z*: 438 (M^+). HRMS Calcd for $C_{21}H_{24}F_6O_3$: 438.163. Found: 438.163. ^{1}H-NMR δ: 6.28—5.98 (0.11H, br), 5.71 (0.89H, t, $J=7.7$ Hz), 2.91 (2H, t, $J=6.7$ Hz), 2.31 (3H, s), 2.50—2.20 (2H, m), 2.14 (3H, s), 2.04 (3H, s), 1.84 (3H, s), 1.94—1.46 (4H, m), 1.28 (3H, s). ^{19}F-NMR ($CDCl_3$) ppm: −14.45 (3F, s), −4.19, 8.13 (3F in total, $Z:E=89:11$).

2-(5,5,5-Trifluoro-4-methyl-3-pentenyl)-2,7,8-trimethyl-5-(trifluoromethyl)-6-chromanol (8b) A mixture of **12b** (51 mg, 0.116 mmol), MeOH (8 ml) and concentrated HCl (1 ml) was refluxed for 3 h. The solvent was evaporated off under vacuum, and saturated $NaHCO_3$ was added to the residue. The mixture was extracted with Et_2O, then 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–CH_2Cl_2, 2 : 1) to give **8b** (30 mg, 65%). **8b**: A yellow oil. ^{1}H-NMR δ: 6.25—5.86 (0.11H, br), 5.74 (0.89H, t, $J=7.7$ Hz), 5.78 (1H, q, $J=8.2$ Hz), 2.86 (2H, t, $J=6.7$ Hz), 2.59—2.27 (2H, m), 2.17 (6H, s), 1.83 (3H, s), 1.80—1.49 (4H, m), 1.26 (3H, s).

2-(5,5,5-Trifluoro-4-methylpentyl)-2,7,8-trimethyl-5-(trifluoromethyl)-6-chromanol (9b) Compound **8b** (40 mg, 0.101 mmol) in MeOH (5 ml) was hydrogenated in the presence of Pd–C (10%, 30 mg), in the same manner as in the case of **8a**, to give **9b** (34 mg, 85%). **9b**: A yellow oil. MS *m/z*: 398 (M^+). HRMS Calcd for $C_{19}H_{24}F_6O_2$: 398.168. Found: 398.168. ^{1}H-NMR δ: 5.73 (1H, q, $J=8.1$ Hz), 2.85 (2H, t, $J=6.7$ Hz), 2.16 (3H, s), 2.13 (3H, s), 1.74 (2H, t, $J=6.8$ Hz), 1.64—1.34 (7H, m), 1.24 (3H, s), 1.10 (3H, d, $J=6.8$ Hz). ^{19}F-NMR ($CDCl_3$) ppm: −10.66 (3F, d, $J=6.6$ Hz), 10.86 (3F, d, $J=8.0$ Hz).

2-(5,5,5-Trifluoro-4-methylpentyl)-2,5,8-trimethyl-6-chromanol Methoxymethyl Ether (13c) A solution of **5c** (233 mg, 0.63 mmol) in MeOH (10 ml) was stirred in the presence of Pd–C (10%, 20 mg) in an atmosphere of H_2 at room temperature for 3.5 h. The catalyst was filtered off and the filtrate was concentrated under vacuum. The residue was purified by column chromatography (SiO_2, hexane–Et_2O, 20 : 1) to give **13c** (226 mg, 97%). **13c**: A pale yellow oil. ^{1}H-NMR δ: 6.75 (1H, s), 5.08 (2H, s), 3.50 (3H, s), 2.61 (2H, t, $J=6.7$ Hz), 2.11 (6H, s), 1.79 (2H, t, $J=6.8$ Hz), 1.91—1.29 (7H, m), 1.23 (3H, s), 1.09 (3H, d, $J=6.8$ Hz). ^{19}F-NMR ($CDCl_3$) ppm: 10.87 (3F, d, $J=7.9$ Hz).

2-(5,5,5-Trifluoro-4-methylpentyl)-2,5,8-trimethyl-6-chromanol (14c) Compound **13c** (167 mg, 0.447 mmol) was hydrolyzed in the presence of *p*-TsOH·H_2O (50 mg) in MeOH (2 ml), in the same manner as described for the hydrolysis of **7a**, to give **14c** (147 mg, 100%). **14c**: A pale yellow oil. ^{1}H-NMR δ: 6.47 (1H, s), 4.52 (1H, s), 2.62 (2H, t, $J=6.7$ Hz), 2.09 (6H, s), 1.79 (2H, t, $J=6.8$ Hz), 1.66—1.34 (7H, m), 1.23 (3H, s), 1.09 (3H, d, $J=7.0$ Hz).

2-(5,5,5-Trifluoro-4-methylpentyl)-2,5,8-trimethyl-6-chromanol Acetate (15c) Compound **14c** (147 mg, 0.445 mmol) was acetylated with acetic anhydride (0.3 ml) and pyridine (0.3 ml) to give **15c** (155 mg, 93%). **15c**: A pale yellow oil. ^{1}H-NMR δ: 6.65 (1H, s), 2.61 (2H, t, $J=6.7$ Hz), 2.29 (3H, s), 2.11 (3H, s), 1.98 (3H, s), 1.79 (2H, t, $J=6.8$ Hz), 1.70—1.36 (7H, m), 1.24 (3H, s), 1.10 (3H, d, $J=6.8$ Hz).

7-Bromo-2-(5,5,5-trifluoro-4-methylpentyl)-2,5,8-trimethyl-6-chromanol Acetate (16c) Compound **15c** (113 mg, 0.304 mmol) was treated with Br_2 (100 mg, 0.625 mmol) in CH_2Cl_2 (3 ml) at room temperature and the mixture was stirred at 45 °C for 3 h. The mixture was worked up as in the case of bromination of **5b**, to give **16c** (90 mg 66%). **16c**: A yellow oil. ^{1}H-NMR δ: 2.59 (2H, t, $J=6.7$ Hz), 2.35 (3H, s), 2.25 (3H, s), 2.04 (3H, s), 1.79 (2H, t, $J=6.8$ Hz), 1.69—1.36 (7H, m), 1.25 (3H, s), 1.10 (3H, d, $J=6.8$ Hz).

2-(5,5,5-Trifluoro-4-methylpentyl)-2,5,8-trimethyl-7-(trifluoromethyl)-6-chromanol Acetate (17c) Compound **16c** (130 mg, 0.288 mmol) was trifluoromethylated with Cu powder (1 g, 15.7 mmol) and CF_3I (1 ml, 10.2 mmol) in HMPA (10 ml), in the same manner as described for the trifluoromethylation of **7a**, to give **17c** (90 mg, 71%). **17c**: A yellow oil. MS *m/z*: 440 (M^+). HRMS Calcd for $C_{21}H_{26}F_6O_3$: 440.179. Found: 440.179. ^{1}H-NMR δ: 2.67 (2H, t, $J=6.7$ Hz), 2.30 (3H, s), 2.26 (3H, q, $J=2.4$ Hz), 1.99 (3H, s), 1.80 (2H, t, $J=6.8$ Hz), 1.69—1.40 (7H, m), 1.25 (3H, s), 1.10 (3H, d, $J=7.0$ Hz). ^{19}F-NMR ($CDCl_3$) ppm: −8.08 (3F, s), 10.85 (3F, d, $J=6.6$ Hz).

2-(5,5,5-Trifluoro-4-methylpentyl)-2,5,8-trimethyl-7-(trifluoromethyl)-6-chromanol (9c) Compound **17c** (78 mg, 0.177 mmol) was hydrolyzed in MeOH (5 ml) and concentrated HCl (0.5 ml) in the same manner as described for the hydrolysis of **12b**, to give **9c** (58 mg, 82%). **9c**: A yellow oil. MS *m/z*: 398 (M^+). HRMS Calcd for $C_{19}H_{24}F_6O_2$: 398.168. Found: 398.169. ^{1}H-NMR δ: 5.72 (1H, q, $J=8.6$ Hz), 2.66 (2H, t, $J=6.7$ Hz), 2.23 (3H, q, $J=2.4$ Hz), 2.12 (3H, s), 1.80 (2H, t, $J=6.8$ Hz), 1.69—1.36 (7H, m), 1.23 (3H, s), 1.09 (3H, d, $J=6.8$ Hz). ^{19}F-NMR ($CDCl_3$) ppm: −10.73 (3F, d, $J=6.6$ Hz), 10.85, 10.90 (3F in total, ratio 1 : 1, both d, $J=9.3$ Hz).

2-[8,12-Dimethyl-4-(trifluoromethyl)-3,7,11-tridecatrienyl]-2,5,7-trimethyl-6-chromanol Methoxymethyl Ether (19ad) A solution of LiBr (156 mg, 1.79 mmol) in THF (2 ml) was added to a solution of the phosphonium salt (**4a**, 1.212 g, 1.82 mmol) in THF (3 ml), and the mixture was cooled in an ice bath, then *n*-BuLi (15% in hexane, 1.35 ml, 2.1 mmol) was added. The mixture was stirred at room temperature for 20 min, then cooled again to −78 °C. A solution of 1,1,1-trifluoro-6,10-dimethyl-5,9-undecadien-2-one (**18d**, 450 mg, 1.81 mmol) in THF (3 ml) was added, and the whole was stirred at the same temperature for 20 min. It was allowed to warm to room temperature, then further *n*-BuLi (15% in hexane, 1.35 ml, 2.1 mmol) was added, and the whole was stirred for 20 min. It was cooled to −78 °C and stirred for 15 min, then a solution of *tert*-BuOH (1.5 ml) and *tert*-BuOK (202 mg, 1.80 mmol) in THF (4 ml) was added. The reaction mixture was allowed to warm up to room temperature, stirred for a further 2 h, then treated with saturated NH_4Cl, and extracted with Et_2O. The Et_2O layer was washed with saturated $NaHCO_3$ and saturated NaCl, and dried over $MgSO_4$. After evaporation of the solvent under vacuum, the residue was purified by column chromatography (SiO_2, hexane–CH_2Cl_2, 2 : 1) to give **19ad** (410 mg, 45%). **19ad**: A pale yellow oil. MS *m/z*: 508 (M^+). HRMS Calcd for $C_{30}H_{43}F_3O_3$: 508.316. Found: 508.317. ^{1}H-NMR ($CDCl_3$) δ: 6.50 (1H, s), 6.24—5.94 (0.19H, br), 5.70 (0.81H, t, $J=7.7$ Hz), 5.24—4.97 (2H, br), 4.89 (2H, s), 3.61 (3H, s), 2.59 (2H, t, $J=6.7$ Hz), 2.23 (3H, s), 2.16 (3H, s), 1.69, 1.60 (9H in total, both s), 2.46—1.40 (14H, m), 1.26 (3H, s). ^{19}F-NMR ($CDCl_3$) ppm: −2.81, 3.83. ($Z:E=81:19$).

2-[8,12-Dimethyl-4-(trifluoromethyl)tridecyl]-2,5,7-trimethyl-6-chromanol (21ad) Compound **19ad** (398 mg, 0.783 mmol) was hydrolyzed in the presence of *p*-TsOH·H_2O (100 mg) in MeOH (10 ml) as in the case of **7a**. Purification of the product by column chromatography (SiO_2, hexane–Et_2O, 5 : 1) gave the deprotected product (**20ad**, 300 mg). A solution of this product in MeOH (15 ml) was stirred under an atmosphere of H_2 in the presence of Pd–C (10%, 60 mg) at room temperature for 3.5 h. After usual work-up, the product was purified by column chromatography (SiO_2, hexane–Et_2O, 5 : 1) to give **21ad** (247 mg, 67%). **21ad**: A pale yellow oil. MS *m/z*: 470 (M^+). HRMS Calcd for $C_{28}H_{45}F_3O_2$: 470.337. Found: 470.337. ^{1}H-NMR ($CDCl_3$) δ: 6.49 (1H, s), 4.23 (1H, s), 2.60 (2H, t, $J=6.7$ Hz), 2.19 (3H, s), 2.13 (3H, s), 1.80 (2H, t, $J=6.7$ Hz), 1.66—0.96 (21H, m), 1.23 (3H, s), 0.86 (9H, d, $J=6.4$ Hz). ^{19}F-NMR ($CDCl_3$) ppm: 6.84 (3F, d, $J=9.2$ Hz).

2-[8,12-Dimethyl-4-(trifluoromethyl)tridecyl]-2,5,7-trimethyl-6-chromanol Acetate (22ad) Compound **21ad** (240 mg, 0.511 mmol) was acetylated with pyridine (1.0 ml, 12.4 mmol) and Ac_2O (1.0 ml, 10.7 mmol) at room temperature for 16 h. After usual work-up the product was purified by column chromatography (SiO$_2$, hexane–Et$_2$O, 7:1) to give **22ad** (254 mg, 97%). **22ad**: A pale yellow oil. ^{1}H-NMR (CDCl$_3$) δ: 6.54 (1H, s), 2.57 (2H, t, $J=6.7$ Hz), 2.32 (3H, s), 2.09 (3H, s), 2.00 (3H, s), 1.79 (2H, t, $J=6.7$ Hz), 1.67—0.97 (21H, m), 1.26 (3H, s), 0.87 (9H, d, $J=6.4$ Hz).

8-Iodo-2-[8,12-dimethyl-4-(trifluoromethyl)tridecyl]-2,5,7-trimethyl-6-chromanol Acetate (23ad) Compound **22ad** (249 mg, 0.486 mmol) was iodinated with CF$_3$COOAg (110 mg, 0.498 mmol) and I$_2$ (130 mg, 0.512 mmol) in CH$_2$Cl$_2$ in the same manner as described for the iodination of **5a**. The product was purified by column chromatography (SiO$_2$, hexane–CH$_2$Cl$_2$, 2:1) to give **23ad** (279 mg, 90%). **23ad**: A yellow oil. MS m/z: 638 (M$^+$), 596 (M−CH$_2$CO). HRMS Calcd for C$_{30}$H$_{46}$F$_3$IO$_3$: 638.245. Found: 638.245. ^{1}H-NMR (CDCl$_3$) δ: 2.63 (2H, t, $J=6.7$ Hz), 2.34 (3H, s), 2.29 (3H, s), 2.00 (3H, s), 1.80 (2H, t, $J=6.7$ Hz), 1.69—0.97 (21H, m), 1.29 (3H, s), 0.87 (9H, d, $J=6.4$ Hz).

2-[8,12-Dimethyl-4-(trifluoromethyl)tridecyl]-2,5,7-trimethyl-8-(trifluoromethyl)-6-chromanol Acetate (24ad) Compound **23ad** (270 mg, 0.423 mmol) was trifluoromethylated with CF$_3$I (1 ml, 10.2 mmol) and Cu powder (300 mg, 4.72 mmol) in HMPA (10 ml) in the same manner as described for the trifluoromethylation of **6a**. The product was purified by column chromatography (SiO$_2$, hexane–CH$_2$Cl$_2$, 2:1) to give **24ad** (136 mg, 55%). **24ad**: A yellow oil. MS m/z: 580 (M$^+$), 538 (M−CH$_2$CO). HRMS Calcd for C$_{31}$H$_{46}$F$_6$O$_3$: 580.335. Found: 580.334. ^{1}H-NMR (CDCl$_3$) δ: 2.63 (2H, t, $J=6.7$ Hz) 2.34 (3H, s) 2.19 (3H, q, $J=3.7$ Hz) 2.02 (3H, s), 1.82 (2H, t, $J=6.7$ Hz), 1.71—0.97 (21H, m), 1.24 (3H, s), 0.86 (9H, d, $J=6.2$ Hz). ^{19}F-NMR (CDCl$_3$) ppm: −8.30 (3F, s), 6.86, 6.99 (3F in total, both d, $J=8.8$ Hz).

2-[8,12-Dimethyl-4-(trifluoromethyl)tridecyl]-2,5,7-trimethyl-8-(trifluoromethyl)-6-chromanol (25ad) Compound **24ad** (139 mg, 0.240 mmol) was hydrolyzed by refluxing in MeOH (10 ml) containing concentrated HCl (1.0 ml) for 7 h. After usual work-up, the product was purified by column chromatography (SiO$_2$, hexane–CH$_2$Cl$_2$, 1:1) to give **25ad** (121 mg, 94%). **25ad**: A pale yellow oil. MS m/z: 538 (M$^+$). HRMS Calcd for C$_{29}$H$_{44}$F$_6$O$_2$: 538.325. Found: 538.325. ^{1}H-NMR (CDCl$_3$) δ: 4.34 (1H, s), 2.63 (2H, t, $J=6.7$ Hz), 2.33 (3H, q, $J=2.6$ Hz), 2.15 (3H, s), 1.81 (2H, t, $J=6.7$ Hz), 1.69—0.97 (21H, m), 1.22 (3H, s), 0.86 (9H, d, $J=6.2$ Hz). ^{19}F-NMR (CDCl$_3$) ppm: −8.86 (3F, s), 6.86, 7.00 (3F in total, both d, $J=8.8$ Hz).

2-[4,12-Dimethyl-8-(trifluoromethyl)-3,7,11-tridecatrienyl]-2,5,7-trimethyl-6-chromanol Methoxymethyl Ether (19ae) The phosphonium salt (**4a**, 0.985 g, 1.48 mmol) was condensed with 10-methyl-6-(trifluoromethyl)-5,9-undecadien-2-one (**18e**, 367 mg, 1.48 mmol) in the same manner as described for **19ad**, and the product was purified by column chromatography (SiO$_2$, hexane–Et$_2$O, 20:1) to give **19ae** (436 mg, 58%). **19ae**: A pale yellow oil. MS m/z: 508 (M$^+$). HRMS Calcd for C$_{30}$H$_{43}$F$_3$O$_3$: 508.316. Found: 508.317. ^{1}H-NMR (CDCl$_3$) δ: 6.49 (1H, s), 6.19—5.91 (0.15H, br), 5.66 (0.85H, t, $J=7.2$ Hz), 5.30—4.94 (2H, br), 4.89 (2H, s), 3.61 (3H, s), 2.58 (2H, t, $J=7.1$ Hz), 2.39—1.37 (14H, m), 2.23 (3H, s), 2.16 (3H, s), 1.69, 1.60 (9H in total, both s), 1.26 (3H, s). ^{19}F-NMR (CDCl$_3$) ppm: −2.95, 3.71 (Z:E=85:15).

2-[4,12-Dimethyl-8-(trifluoromethyl)tridecyl]-2,5,7-trimethyl-6-chromanol (21ae) Compound **19ae** (541 mg, 1.06 mmol) was hydrolyzed with p-TsOH·H$_2$O (100 mg) in MeOH (10 ml) and worked up as in the case of the hydrolysis of **19ad** to give the deprotected product (**20ae**, 465 mg). This compound was hydrogenated in the same manner as described for **20ad**, to give **21ae** (452 mg, 90%). **21ae**: A pale yellow oil. MS m/z: 470 (M$^+$). HRMS Calcd for C$_{28}$H$_{45}$F$_3$O$_2$: 470.337. Found: 470.337. ^{1}H-NMR (CDCl$_3$) δ: 6.47 (1H, s), 4.20 (1H, s), 2.59 (2H, t, $J=7.1$ Hz), 2.18 (3H, s), 2.11 (3H, s), 1.79 (2H, t, $J=7.1$ Hz), 1.67—1.00 (21H, m), 1.23 (3H, s), 0.87 (9H, d, $J=6.2$ Hz). ^{19}F-NMR (CDCl$_3$) ppm: 6.92 (3F, d, $J=9.7$ Hz).

2-[4,12-Dimethyl-8-(trifluoromethyl)tridecyl]-2,5,7-trimethyl-6-chromanol Acetate (22ae) Compound **21ae** (440 mg, 0.936 mmol) was acetylated with acetic anhydride (2.0 ml, 21.3 mmol) and pyridine (2.0 ml, 24.7 mmol) in the same manner as described for **21ad**, to give **22ae** (428 mg, 89.3%). **22ae**: A pale yellow oil. ^{1}H-NMR (CDCl$_3$) δ: 6.54 (1H, s), 2.59 (2H, t, $J=6.7$ Hz), 2.33 (3H, s), 2.07 (3H, s), 2.00 (3H, s), 1.79 (2H, t, $J=6.7$ Hz), 1.67—1.00 (21H, m), 1.25 (3H, s), 0.88 (9H, d, $J=6.2$ Hz).

8-Iodo-2-[4,12-dimethyl-8-(trifluoromethyl)tridecyl]-2,5,7-trimethyl-6-chromanol Acetate (23ae) Compound **22ae** (413 mg, 0.807 mmol) was iodinated with I$_2$ (215 mg, 0.846 mmol) and CF$_3$COOAg (183 mg, 0.828 mmol) in CH$_2$Cl$_2$ as above to give **23ae** (485 mg, 94%). **23ae**: A yellow oil. MS m/z: 638 (M$^+$). 596 (M−CH$_2$CO). HRMS Calcd for C$_{30}$H$_{46}$F$_3$IO$_3$: 638.245. Found: 638.245. ^{1}H-NMR (CDCl$_3$) δ: 2.60 (2H, t, $J=6.7$ Hz), 2.33 (3H, s), 2.27 (3H, s), 1.98 (3H, s), 1.80 (2H, t, $J=6.7$ Hz), 1.69—1.11 (21H, m), 1.28, 0.87 (9H in total, d, $J=5.9$ Hz).

2-[4,12-Dimethyl-8-(trifluoromethyl)tridecyl]-2,5,7-trimethyl-8-(trifluoromethyl)-6-chromanol Acetate (24ae) Compound **23ae** (478 mg, 0.749 mmol) was trifluoromethylated with CF$_3$I (1 ml, 10.2 mmol) and Cu powder (500 mg, 7.87 mmol) in HMPA (12 ml) in the same manner as described for **23ad**, to give **24ae** (338 mg, 78%). **24ae**: A yellow oil. MS m/z: 580 (M$^+$). 538 (M−CH$_2$CO). HRMS Calcd for C$_{31}$H$_{46}$F$_6$O$_3$: 580.335. Found: 580.336. ^{1}H-NMR (CDCl$_3$) δ: 2.63 (2H, t, $J=6.8$ Hz), 2.34 (3H, s), 2.19 (3H, q, $J=3.0$ Hz), 2.02 (3H, s), 1.81 (2H, t, $J=6.8$ Hz), 1.67—1.11 (21H, m), 1.25 (3H, s), 0.87 (9H, d, $J=6.2$ Hz). ^{19}F-NMR (CDCl$_3$) ppm: −8.33 (3F, s), 6.89 (3F, d, $J=8.8$ Hz).

2-[4,12-Dimethyl-8-(trifluoromethyl)tridecyl]-2,5,7-trimethyl-8-(trifluoromethyl)-6-chromanol (25ae) Compound **24ae** (327 mg, 0.564 mmol) was hydrolyzed with concentrated HCl in MeOH in the same manner as described for **24ad**, to give **25ae** (282 mg, 93%). **25ae**: A pale yellow oil. MS m/z: 538 (M$^+$). HRMS Calcd for C$_{29}$H$_{44}$F$_6$O$_2$: 538.325. Found: 538.325. ^{1}H-NMR (CDCl$_3$) δ: 4.37 (1H, s), 2.63 (2H, t, $J=6.8$ Hz), 2.33 (3H, q, $J=3.0$ Hz), 2.14 (3H, s), 1.81 (2H, t, $J=6.8$ Hz), 1.68—0.97 (21H, m), 1.23 (3H, s), 0.87 (9H, d, $J=7.5$ Hz). ^{19}F-NMR (CDCl$_3$) ppm: −8.89 (3F, s), 6.89 (3F, d, $J=8.8$ Hz).

2-(13,13,13-Trifluoro-4,8,12-trimethyl-3,7,11-tridecatrienyl)-2,5,7-trimethyl-6-chromanol Methoxymethyl Ether (19af) The phosphonium salt (**4a**, 1.08 g, 1.62 mmol) was condensed with 11,11,11-trifluoro-6,10-dimethyl-5,9-undecadien-2-one (**18f**, 402 mg, 1.62 mmol) in the same manner as in the case of **19ad**, to give **19af** (413 mg, 50%). **19af**: A pale yellow oil. MS m/z: 508 (M$^+$). HRMS Calcd for C$_{30}$H$_{43}$F$_3$O$_3$: 508.316. Found: 508.316. ^{1}H-NMR (CDCl$_3$) δ: 6.49 (1H, s), 6.20—5.91 (0.1H, br), 5.69 (0.9H, t, $J=7.2$ Hz), 5.39—4.98 (2H, br), 4.88 (2H, s), 3.60 (3H, s), 2.57 (2H, t, $J=6.4$ Hz), 2.21 (3H, s), 2.15 (3H, s), 1.82 (3H, s), 1.67 (3H, s), 1.58 (3H, s), 2.43—1.40 (14H, m), 1.26 (3H, s). ^{19}F-NMR (CDCl$_3$) ppm: −1.20, 6.15 (Z:E=90:10).

2-(13,13,13-Trifluoro-4,8,12-trimethyltridecyl)-2,5,7-trimethyl-6-chromanol (21af) Compound **19af** (372 mg, 0.732 mmol) was hydrolyzed with p-TsOH·H$_2$O in MeOH as described for the hydrolysis of **19ad**, to give the deprotected product (**20af**, 306 mg). This compound was hydrogenated similarly as above to give **21af** (262 mg, 77%). **21af**: A pale yellow oil. MS m/z: 470 (M$^+$). HRMS Calcd for C$_{28}$H$_{45}$F$_3$O$_2$: 470.337. Found: 470.337. ^{1}H-NMR (CDCl$_3$) δ: 6.47 (1H, s), 4.21 (1H, s), 2.59 (2H, t, $J=6.8$ Hz), 2.18 (3H, s), 2.12 (3H, s), 1.79 (2H, t, $J=6.8$ Hz), 1.67—0.97 (21H, m), 1.23 (3H, s), 1.09 (3H, d, $J=7.0$ Hz), 0.95 (6H, d, $J=5.5$ Hz). ^{19}F-NMR (CDCl$_3$) ppm: 9.90, 9.95 (3F in total, ratio 1:1, both d, $J=8.8$ Hz).

2-(13,13,13-Trifluoro-4,8,12-trimethyltridecyl)-2,5,7-trimethyl-6-chromanol Acetate (22af) Compound **21af** (252 mg, 0.536 mmol) was acetylated with acetic anhydride (1.2 ml, 12.8 mmol) and pyridine (1.2 ml, 14.8 mmol) in the same manner as described for the acetylation of **21ad**, to give **22af** (265 mg, 97%). **22af**: A pale yellow oil. ^{1}H-NMR (CDCl$_3$) δ: 6.53 (1H, s), 2.59 (2H, t, $J=6.8$ Hz), 2.31 (3H, s), 2.06 (3H, s), 1.99 (3H, s), 1.80 (2H, t, $J=6.8$ Hz), 1.66—0.97 (21H, m), 1.24 (3H, s), 1.09 (3H, d, $J=6.8$ Hz), 0.85 (6H, d, $J=5.5$ Hz).

8-Iodo-2-(13,13,13-trifluoro-4,8,12-trimethyltridecyl)-2,5,7-trimethyl-6-chromanol Acetate (23af) Compound **22af** (255 mg, 0.498 mmol) was iodinated with I$_2$ (135 mg, 0.531 mmol) and CF$_3$COOAg (120 mg, 0.543 mmol) in CH$_2$Cl$_2$ in the same manner as described for the iodination of **22ad**, to give **23af** (275 mg, 86%). **23af**: A yellow oil. MS m/z: 638 (M$^+$), 596 (M−CH$_2$CO). HRMS Calcd for C$_{30}$H$_{46}$F$_3$IO$_3$: 638.244. Found: 638.244. ^{1}H-NMR (CDCl$_3$) δ: 2.61 (2H, t, $J=6.8$ Hz), 2.33 (3H, s), 2.27 (3H, s), 1.98 (3H, s), 1.80 (2H, t, $J=6.8$ Hz), 1.66—0.96 (21H, m), 1.28 (3H, s), 1.10 (3H, d, $J=6.8$ Hz), 0.87 (6H, d, $J=5.1$ Hz).

2-(13,13,13-Trifluoro-4,8,12-trimethyltridecyl)-2,5,7-trimethyl-8-(trifluoromethyl)-6-chromanol Acetate (24af) Compound **23af** (270 mg, 0.423 mmol) was trifluoromethylated with CF$_3$I (1 ml, 10.2 mmol) and Cu powder (270 mg, 4.25 mmol) in the same manner as described for the trifluoromethylation of **23ad**, to give **24af** (229 mg, 93%). **24af**: A yellow oil. MS m/z: 580 (M$^+$), 538 (M−CH$_2$CO). HRMS Calcd for C$_{29}$H$_{44}$F$_6$O$_2$ (M−CH$_2$CO): 538.325. Found: 538.325. ^{1}H-NMR (CDCl$_3$) δ: 2.62 (2H, t, $J=6.7$ Hz) 2.34 (3H, s), 2.19 (3H, q, $J=3.3$ Hz), 2.02 (3H, s), 1.81 (2H, t, $J=6.7$ Hz), 1.67—0.98 (21H, m), 1.25 (3H, s), 1.09 (3H, d, $J=$ 6.8 Hz), 0.85 (6H, d, $J=5.7$ Hz). ^{19}F-NMR (CDCl$_3$) ppm: −8.33 (3F, s), 9.92, 9.95 (3F in total, both d, $J=8.8$ Hz).

2-(13,13,13-Trifluoro-4,8,12-trimethyltridecyl)-2,5,7-trimethyl-8-

(trifluoromethyl)-6-chromanol (25af) Compound **24af** (220 mg, 0.379 mmol) was hydrolyzed as described for **24ad**, to give **25af** (194 mg, 95%). **25af**: A pale yellow oil. MS *m/z*: 538 (M^+). HRMS Calcd for $C_{29}H_{44}F_6O_2$: 538.324. Found: 538.324. ^{1}H-NMR ($CDCl_3$) δ: 2.63 (2H, t, $J=7.1$ Hz), 2.33 (3H, q, $J=2.5$ Hz), 2.14 (3H, s), 1.81 (2H, t, $J=7.1$ Hz), 1.69—0.94 (21H, m), 1.22 (3H, s), 1.08 (3H, d, $J=7.0$ Hz), 0.85 (6H, d, $J=5.5$ Hz). ^{19}F-NMR ($CDCl_3$) ppm: −8.89 (3F, s), 9.92, 9.95 (3F in total, both d, $J=8.8$ Hz).

2-[8,12-Dimethyl-4-(trifluoromethyl)-3,7,11-tridecatrienyl]-2,7,8-trimethyl-6-chromanol Methoxymethyl Ether (19bd) The phosphonium salt (**4b**, 1.52 g, 2.28 mmol) was condensed with 1,1,1-trifluoro-6,10-dimethyl-5,9-undecadien-2-one (**18d**, 681 mg, 2.74 mmol) as in the case of **19ad**, to give **19bd** (795 mg, 69%). **19bd**: A pale yellow oil. MS *m/z*: 508 (M^+). HRMS Calcd for $C_{30}H_{43}F_3O_3$: 508.316. Found: 508.317. ^{1}H-NMR ($CDCl_3$) δ: 6.58 (1H, s), 6.27—5.93 (0.21H, br), 5.65 (0.79H, t, $J=7.5$ Hz), 5.28—4.83 (2H, br), 5.03 (2H, s), 3.47 (3H, s), 2.70 (2H, t, $J=6.7$ Hz), 2.53—1.40 (14H, m), 2.16 (3H, s), 2.10 (3H, s), 1.68, 1.60 (9H in total, both s), 1.27 (3H, s).

2-[8,12-Dimethyl-4-(trifluoromethyl)-3,7,11-tridecatrienyl]-2,7,8-trimethyl-6-chromanol Acetate (26bd) A solution of **19bd** (790 mg, 1.55 mmol) in MeOH (10 ml) containing *p*-TsOH·H_2O (100 mg) was stirred at room temperature for 6 h, and worked up in a usual manner to give the deprotected product (**20bd**, 495 mg). This product was acetylated with Ac_2O (2.0 ml, 21.2 mmol) and pyridine (1.8 ml, 24.2 mmol) as described for the acetylation of **21ad**, to give **26bd** (500 mg, 64%). **26bd**: A pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 6.48 (1H, s), 6.23—5.87 (0.21H, br), 5.65 (0.79H, t, $J=7.6$ Hz), 4.51—4.77 (2H, br), 2.68 (2H, t, $J=6.5$ Hz), 2.50—1.38 (14H, m), 2.27 (3H, s), 2.10 (3H, s), 2.03 (3H, s), 1.67, 1.40 (9H in total, both s), 1.25 (3H, s).

2-[8,12-Dimethyl-4-(trifluoromethyl)tridecyl]-2,7,8-trimethyl-6-chromanol Acetate (22bd) Compound **26bd** (550 mg, 1.09 mmol) was hydrogenated as described for the hydrogenation of **21ad** in the presence of Pd–C, to give **22bd** (466 mg, 84%). **22bd**: A pale yellow oil. MS *m/z*: 512 (M^+), 470 ($M-CH_2CO$). HRMS Calcd for $C_{30}H_{47}F_3O_3$: 512.348. Found: 512.347. ^{1}H-NMR ($CDCl_3$) δ: 6.50 (1H, s), 5.21 (1H, s), 2.69 (2H, t, $J=6.5$ Hz), 2.27 (3H, s), 2.08 (3H, s), 2.00 (3H, s), 1.90—1.00 (23H, m), 1.25 (3H, s), 0.85 (9H, d, $J=6.0$ Hz).

5-Iodo-2-[8,12-dimethyl-4-(trifluoromethyl)tridecyl]-2,7,8-trimethyl-6-chromanol Acetate (23bd) Compound **22bd** (466 mg, 0.803 mmol) was iodinated with I_2 (245 mg, 0.963 mmol) and CF_3COOAg (213 mg, 0.963 mmol) in CH_2Cl_2 as in the case of **23ad** to give **23bd** (429 mg, 74%). **23bd**: A yellow oil. MS *m/z*: 638 (M^+), 596 ($M-CH_2CO$). HRMS Calcd for $C_{30}H_{46}F_3IO_3$: 638.244. Found: 638.244. ^{1}H-NMR ($CDCl_3$) δ: 5.23 (1H, s), 2.63 (2H, t, $J=6.5$ Hz), 2.34 (3H, s), 2.07 (6H, s), 1.97—1.19 (21H, m), 1.76 (2H, t, $J=6.5$ Hz), 1.23 (3H, s), 0.85 (9H, d, $J=6.0$ Hz).

2-[8,12-Dimethyl-4-(trifluoromethyl)tridecyl]-2,7,8-trimethyl-5-(trifluoromethyl)-6-chromanol Acetate (24bd) Compound **23bd** (429 mg, 0.672 mmol) was trifluoromethylated with CF_3I (1.0 ml, 10.2 mmol) and Cu powder (200 mg, 3.15 mmol) as in the case of trifluoromethylation of **23ad** to give **24bd** (168 mg, 43%). **24bd**: A yellow oil. MS *m/z*: 580 (M^+), 538 ($M-CH_2CO$). HRMS Calcd for $C_{31}H_{46}F_6O_3$: 580.335. Found: 580.336. ^{1}H-NMR ($CDCl_3$) δ: 5.20 (1H, s), 3.10—2.67 (2H, br), 2.27 (3H, s), 2.13 (3H, s), 2.03 (3H, s), 1.33—1.03 (23H, m), 1.24 (3H, s), 0.85 (9H, d, $J=6.0$ Hz).

2-[8,12-Dimethyl-4-(trifluoromethyl)tridecyl]-2,7,8-trimethyl-5-(trifluoromethyl)-6-chromanol (25bd) Compound **24bd** (197 mg, 0.340 mmol) was hydrolyzed as in the case of **24ad**, to give **25bd** (110 mg, 60%). **25bd**: A pale yellow oil. MS *m/z*: 538 (M^+). HRMS Calcd for $C_{29}H_{44}F_6O_2$: 538.324. Found: 538.324. ^{1}H-NMR ($CDCl_3$) δ: 5.66 (1H, q, $J=8.0$ Hz), 3.03—2.60 (2H, br), 2.13 (6H, s), 1.99—1.02 (23H, m), 1.23 (3H, s), 0.85 (9H, d, $J=6.0$ Hz). ^{19}F-NMR ($CDCl_3$) ppm: −10.66 (3F, d, $J=6.6$ Hz), 7.58 (3F, d, $J=6.7$ Hz).

2-[4,12-Dimethyl-8-(trifluoromethyl)-3,7,11-tridecatrienyl]-2,7,8-trimethyl-6-chromanol Methoxymethyl Ether (19be) The phosphonium salt **4b** (1.0 g, 1.5 mmol) was condensed with 10-methyl-6-(trifluoromethyl)-5,9-undecadien-2-one (**18e**, 372 mg, 1.50 mmol) in the same manner as described for **19ad**, and purified similarly to give **19be** (444 mg, 58%). **19be**: A pale yellow oil. MS *m/z*: 508 (M^+). HRMS Calcd for $C_{30}H_{43}F_3O_3$: 508.316. Found: 508.316. ^{1}H-NMR ($CDCl_3$) δ: 6.67 (1H, s), 6.31—6.09 (0.1H, br), 5.67 (0.9H, t, $J=7.5$ Hz), 5.31—4.97 (2H, br), 5.13 (2H, s), 3.54 (3H, s), 2.72 (2H, t, $J=6.7$ Hz), 2.51—1.37 (14H, m), 2.17 (3H, s), 2.14 (3H, s), 1.71, 1.62 (9H in total, s), 1.27 (3H, s). ^{19}F-NMR ($CDCl_3$) ppm: −2.93, 3.74 ($Z:E=90:10$).

2-[4,12-Dimethyl-8-(trifluoromethyl)tridecyl]-2,7,8-trimethyl-6-chromanol (21be) Compound **19be** (395 mg, 0.778 mmol) was hydrolyzed in MeOH (4 ml) containing *p*-TsOH·H_2O (50 mg) at room temperature for 5 h, and worked up as in the case of the hydrolysis of **19ad**, to give the deprotected product **20be** (359 mg). This was hydrogenated similarly to give **21be** (340 mg, 93%). **21be**: A pale yellow oil. MS *m/z*: 470 (M^+). HRMS Calcd for $C_{28}H_{45}F_3O_2$: 470.337. Found: 470.336. ^{1}H-NMR ($CDCl_3$) δ: 6.37 (1H, s), 4.36 (1H, s), 2.67 (2H, t, $J=6.7$ Hz), 2.11 (6H, s), 1.74 (2H, t, $J=6.7$ Hz), 1.63—1.12 (21H, m), 1.25 (3H, s), 0.88 (9H, d, $J=6.4$ Hz). ^{19}F-NMR ($CDCl_3$) ppm: 6.89 (3F, d, $J=8.8$ Hz).

2-[4,12-Dimethyl-8-(trifluoromethyl)tridecyl]-2,7,8-trimethyl-6-chromanol Acetate (22be) Compound **21be** (332 mg, 0.706 mmol) was acetylated with acetic anhydride (1.4 ml, 15.0 mmol) and pyridine (1.4 ml, 17.4 mmol) as in the case of **21ad** and worked up as above to give **22be** (344 mg, 95%). **22be**: A pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 6.57 (1H, s), 2.71 (2H, t, $J=6.7$ Hz), 2.30 (3H, s), 2.11, 2.03 (6H, s), 1.74 (2H, t, $J=6.7$ Hz), 1.71—1.00 (21H, m), 1.26 (3H, s), 0.89 (9H, d, $J=6.0$ Hz).

5-Iodo-2-[4,12-dimethyl-8-(trifluoromethyl)tridecyl]-2,7,8-trimethyl-6-chromanol Acetate (23be) Compound **22be** (338 mg, 0.66 mmol) was iodinated with I_2 (170 mg, 0.669 mmol) and CF_3COOAg (150 mg, 0.679 mmol) in CH_2Cl_2 in the same manner as described for the iodination of **22ad**, to give **23be** (290 mg, 69%). **23be**: A yellow oil. MS *m/z*: 638 (M^+), 596 ($M-CH_2CO$). HRMS Calcd for $C_{30}H_{46}F_3IO_3$: 638.244. Found: 638.244. ^{1}H-NMR ($CDCl_3$) δ: 2.65 (2H, t, $J=6.7$ Hz), 2.39 (3H, s), 2.09 (6H, s), 1.77 (2H, t, $J=6.7$ Hz), 1.66—0.99 (21H, m), 1.25 (3H, s), 0.87 (9H, d, $J=6.0$ Hz).

2-[4,12-Dimethyl-8-(trifluoromethyl)tridecyl]-2,7,8-trimethyl-5-(trifluoromethyl)-6-chromanol Acetate (24be) Compound **23be** (284 mg, 0.445 mmol) was trifluoromethylated with CF_3I (1.0 ml, 10.2 mmol) and Cu powder (300 mg, 4.72 mmol) in the same manner as described for the trifluoromethylation of **23ad**, to give **24be** (194 mg, 75%). **24be**: A yellow oil. MS *m/z*: 580 (M^+), 538 ($M-CH_2CO$). HRMS Calcd for $C_{31}H_{46}F_6O_3$: 580.335. Found: 580.334. ^{1}H-NMR ($CDCl_3$) δ: 3.11—2.70 (2H, br), 2.32 (3H, s), 2.14 (3H, s), 2.04 (3H, s), 1.75 (2H, t, $J=7.0$ Hz), 1.70—0.99 (21H, m), 1.27 (3H, s), 0.88 (9H, d, $J=6.0$ Hz). ^{19}F-NMR ($CDCl_3$) ppm: −7.37 (3F, s), 6.89 (3F, d, $J=8.8$ Hz).

2-[4,12-Dimethyl-8-(trifluoromethyl)tridecyl]-2,7,8-trimethyl-5-(trifluoromethyl)-6-chromanol (25be) Compound **24be** (187 mg, 0.322 mmol) was hydrolyzed in MeOH (10 ml) containing concentrated HCl (0.5 ml) as described for the hydrolysis of **24ad**, to give **25be** (144 mg, 83%). **25be**: A pale yellow oil. MS *m/z*: 538 (M^+). HRMS Calcd for $C_{29}H_{44}F_6O_2$: 538.325. Found: 538.325. ^{1}H-NMR ($CDCl_3$) δ: 5.73 (1H, q, $J=8.4$ Hz), 2.97—2.67 (2H, br), 2.15 (6H, s), 1.74 (2H, t, $J=7.1$ Hz), 1.69—1.00 (21H, m), 1.24 (3H, s), 0.87 (9H, d, $J=6.2$ Hz). ^{19}F-NMR ($CDCl_3$) ppm: −9.63 (3F, d, $J=7.3$ Hz), 6.89 (3F, d, $J=8.8$ Hz).

2-(13,13,13-Trifluoro-4,8,12-trimethyl-3,7,11-tridecatrienyl)-2,7,8-trimethyl-6-chromanol Methoxymethyl Ether (19bf) The phosphonium salt **4b** (1.2 g, 1.8 mmol) was condensed with 11,11,11-trifluoro-6,10-dimethyl-5,9-undecadien-2-one (**18f**, 426 mg, 1.72 mmol) as in the case of **19ad**, to give **19bf** (474 mg, 54%). **19bf**: A pale yellow oil. MS *m/z*: 508 (M^+). HRMS Calcd for $C_{30}H_{43}F_3O_3$: 508.316. Found: 508.316. ^{1}H-NMR ($CDCl_3$) δ: 6.66 (1H, s), 6.14—5.87 (0.03H, br), 5.69 (0.97H, t, $J=7.2$ Hz), 5.34—4.94 (2H, br), 5.11 (2H, s), 3.52 (3H, s), 2.73 (2H, t, $J=6.4$ Hz), 2.17 (3H, s), 2.12 (3H, s), 1.83 (3H, s), 1.69 (3H, s), 1.57 (3H, s), 2.51—1.34 (14H, m), 1.26 (3H, s). ^{19}F-NMR ($CDCl_3$) ppm: −1.31, 6.85 ($Z:E=97:3$).

2-(13,13,13-Trifluoro-4,8,12-trimethyltridecyl)-2,7,8-trimethyl-6-chromanol (21bf) Compound **19bf** (447 mg, 0.88 mmol) was hydrolyzed with *p*-TsOH·H_2O (50 mg) in MeOH (6 ml) as in the case of **19ad**, to give the deprotected product **20bf** (400 mg). This compound was hydrogenated in the presence of Pd–C (10% 42 mg) as in the case of **20ad**, to give **21bf** (335 mg, 85%). **21bf**: A pale yellow oil. MS *m/z*: 470 (M^+). HRMS Calcd for $C_{28}H_{45}F_3O_2$: 470.337. Found: 470.336. ^{1}H-NMR ($CDCl_3$) δ: 6.39 (1H, s), 4.39 (1H, s), 2.68 (2H, t, $J=7.5$ Hz), 2.12 (6H, s), 1.74 (2H, t, $J=7.5$ Hz), 1.66—0.96 (21H, m), 1.25 (3H, s), 1.10 (3H, d, $J=7.5$ Hz), 0.86 (6H, d, $J=5.0$ Hz). ^{19}F-NMR ($CDCl_3$) ppm: 10.91, 10.95 (both d, ratio 1:1, $J=8.8$ Hz).

2-(13,13,13-Trifluoro-4,8,12-trimethyltridecyl)-2,7,8-trimethyl-6-chromanol Acetate (22bf) Compound **21bf** (321 mg, 0.683 mmol) was acetylated with acetic anhydride (1 ml, 10.7 mmol) and pyridine (1 ml, 12.4 mmol), and worked up as above to give **22bf** (336 mg, 96%). **22bf**: A pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 6.59 (1H, s), 2.71 (2H, t, $J=7.5$ Hz), 2.29 (3H, s), 2.11 (3H, s), 2.03 (3H, s), 1.74 (2H, t, $J=7.5$ Hz), 1.71—0.94 (21H, m), 1.25 (3H, s), 1.1 (3H, d, $J=7.5$ Hz), 0.86 (6H, d, $J=5.0$ Hz).

5-Iodo-2-(13,13,13-trifluoro-4,8,12-trimethyltridecyl)-2,7,8-trimethyl-6-chromanol Acetate (23bf) Compound **22bf** (272 mg, 0.53 mmol) was iodinated with I_2 (145 mg, 0.57 mmol) and CF_3COOAg (133 mg, 0.6 mmol) in CH_2Cl_2 in the same manner as described for the iodination of **22ad**, to give **23bf** (268 mg, 79%): A yellow oil. MS *m*/*z*: 638 (M^+), 596 ($M-CH_2CO$). HRMS Calcd for $C_{30}H_{46}F_3IO_3$: 638.244. Found: 638.244. ^{1}H-NMR ($CDCl_3$) δ: 2.66 (2H, t, $J=7.2$ Hz), 2.40 (3H, s), 2.11 (6H, s), 1.77 (2H, t, $J=7.2$ Hz), 1.66—0.97 (21H. m), 1.26 (3H, s), 1.10 (3H, d, $J=7.5$ Hz), 0.86 (6H, d, $J=5.0$ Hz).

2-(13,13,13-Trifluoro-4,8,12-trimethyltridecyl)-2,7,8-trimethyl-5-(trifluoromethyl)-6-chromanol Acetate (24bf) Compound **23bf** was trifluoromethylated with CF_3I (1.5 ml, 15.3 mmol) and Cu powder (180 mg, 2.83 mmol) in the same manner as described for the trifluoromethylation of **23ad**, to give **24bf** (193 mg, 79%). **24bf**: A yellow oil. MS *m*/*z*: 580 (M^+), 538 ($M-CH_2CO$). ^{1}H-NMR ($CDCl_3$) δ: 3.03—2.71 (2H, br), 2.32 (3H, s), 2.15, 2.05 (6H, s), 1.76 (2H, t, $J=7.5$ Hz), 1.63—0.96 (21H, m), 1.28 (3H, s), 1.10 (3H, d, $J=7.5$ Hz), 0.86 (6H, d, $J=5.0$ Hz). ^{19}F-NMR ($CDCl_3$) ppm: -6.50 (3F, s), 9.93 (3F, d, $J=8.8$ Hz).

2-(13,13,13-Trifluoro-4,8,12-trimethyltridecyl)-2,7,8-trimethyl-5-(trifluoromethyl)-6-chromanol (25bf) Compound **24bf** (178 mg, 0.31 mmol) was hydrolyzed by refluxing in MeOH (5 ml) containing concentrated HCl (0.5 ml) as described for the hydrolysis of **24ad**, to give **25bf** (118 mg, 83%). **25bf**: A pale yellow oil. MS *m*/*z*: 538 (M^+). HRMS Calcd for $C_{29}H_{44}F_6O_2$: 538.325. Found: 538.325. ^{1}H-NMR ($CDCl_3$) δ: 5.75 (1H, q, $J=8.4$ Hz), 2.98—2.66 (2H, br), 2.18 (6H, s), 1.75 (2H, t, $J=7.5$ Hz), 1.63—0.95 (21H, m), 1.29 (3H, s), 1.10 (3H, d, $J=7.5$ Hz), 0.86 (6H, d, $J=5.0$ Hz). ^{19}F-NMR ($CDCl_3$) ppm: -9.64 (3F, d, $J=7.3$ Hz), 9.90, 9.94 (3F in total, ratio 1 : 1, both d, $J=8.8$ Hz).

2-[8,12-Dimethyl-4-(trifluoromethyl)-3,7,11-tridecatrienyl]-2,5,8-trimethyl-6-chromanol Methoxymethyl Ether (19cd) The phosphonium salt **4c** (0.952 g, 1.43 mmol) was condensed with 1,1,1-trifluoro-6,10-dimethyl-5,9-undecadien-2-one (**18d**, 360 mg, 1.45 mmol) in THF in the same manner as described for **19ad**, and the product was purified as above to give **19cd** (415 mg, 57%). **19cd**: A pale yellow oil. MS *m*/*z*: 508 (M^+). HRMS Calcd for $C_{30}H_{43}F_3O_3$: 508.316. Found: 508.316. ^{1}H-NMR ($CDCl_3$) δ: 6.78 (1H, s), 6.17—5.91 (0.2H, br), 5.71 (0.8H, t, $J=7.7$ Hz), 5.23—4.94 (2H, br), 5.11 (2H, s), 3.52 (3H, s), 2.63 (2H, t, $J=6.4$ Hz), 2.14 (6H, s), 1.69, 1.60 (9H in total, both s), 2.50—1.17 (14H, m), 1.26 (3H, s). ^{19}F-NMR ($CDCl_3$) ppm: -2.83, 3.81 ($Z:E=80:20$).

2-[8,12-Dimethyl-4-(trifluoromethyl)tridecyl]-2,5,8-trimethyl-6-chromanol (21cd) Compound **19cd** (353 mg, 0.695 mmol) was hydrolyzed as **19ad** in MeOH (5 ml) containing p-TsOH·H_2O (50 mg) to give the deprotected product (**20cd**, 302 mg). This product was hydrogenated in the presence of Pd–C (10% 50 mg) as in the case of **20ad**, to give **21cd** (286 mg, 88%). **21cd**: A pale yellow oil. MS *m*/*z*: 470 (M^+). HRMS Calcd for $C_{28}H_{45}F_3O_2$: 470.337. Found: 470.338. ^{1}H-NMR ($CDCl_3$) δ: 6.51 (1H, s), 4.27 (1H, s), 2.63 (2H, t, $J=6.7$ Hz), 2.11 (6H, s), 1.80 (2H, t, $J=6.7$ Hz), 1.66-0.94 (21H, m), 1.23 (3H, s), 0.88 (9H, d, $J=6.4$ Hz). ^{19}F-NMR ($CDCl_3$) ppm: 7.88 (d, $J=8.8$ Hz).

2-[8,12-Dimethyl-4-(trifluoromethyl)tridecyl]-2,5,8-trimethyl-6-chromanol Acetate (22cd) Compound **21cd** (277 mg, 0.589 mmol) was acetylated with acetic anhydride (1.0 ml, 10.7 mmol) and pyridine (1.0 ml, 12.4 mmol) as described for the acetylation of **21ad** to give **22cd** (223 mg, 74%). **22cd**: A pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 6.68 (1H, s), 2.62 (2H, t, $J=6.7$ Hz), 2.30 (3H, s), 2.11 (3H, s), 1.99 (3H, s), 1.80 (2H, t, $J=6.7$ Hz), 1.69—0.97 (21H, m), 1.24 (3H, s), 0.88 (9H, d, $J=6.4$ Hz).

7-Bromo-2-[8,12-dimethyl-4-(trifluoromethyl)tridecyl]-2,5,8-trimethyl-6-chromanol Acetate (23cd) A solution of Br_2 (85 mg, 0.531 mmol) in CH_2Cl_2 (5 ml) was added to a solution of **22cd** (223 mg, 0.436 mmol) in CH_2Cl_2 (5 ml). The mixture was stirred at 50 °C for 2 h, then worked up as described in the case of the bromination of **5b**, to give **23cd** (134 mg, 63%) with recovery of the starting material (38 mg). **23cd**: A yellow oil. MS *m*/*z*: 590 (M^+). 548 ($M-CH_2CO$). ^{1}H-NMR ($CDCl_3$) δ: 2.61 (2H, t, $J=6.7$ Hz), 2.37 (3H, s), 2.26 (3H, s), 2.05 (3H, s), 1.80 (2H, t, $J=6.7$ Hz), 1.69—0.96 (21H, m), 1.26 (3H, s), 0.87 (9H, d, $J=6.0$ Hz).

2-[8,12-Dimethyl-4-(trifluoromethyl)tridecyl]-2,5,8-trimethyl-7-(trifluoromethyl)-6-chromanol Acetate (24cd) Compound **23cd** (134 mg, 0.227 mmol) was trifluoromethylated with CF_3I (1.0 ml, 10.2 mmol) and Cu powder (150 mg, 2.36 mmol) in HMPA (8 ml) at 110 °C for 44 h as described for the trifluoromethylation of **23ad**, to give **24cd** (94 mg, 72%). **24cd**: A yellow oil. MS *m*/*z*: 580 (M^+). 538 ($M-CH_2CO$). HRMS Calcd for $C_{29}H_{44}F_6O_2$ ($M-CH_2CO$): 538.324. Found: 538.324. ^{1}H-NMR ($CDCl_3$) δ: 2.66 (2H, t, $J=6.7$ Hz), 2.30 (3H, s), 2.27 (3H, q, $J=2.6$ Hz), 1.99 (3H, s), 1.82 (2H, t, $J=6.7$ Hz), 1.71—1.00 (21H, m), 1.26 (3H, s), 0.86 (9H, d, $J=6.2$ Hz). ^{19}F-NMR ($CDCl_3$) ppm: -7.28 (3F, s), 6.79, 6.85 (3F in total, ratio 1 : 1, both d, $J=8.8$ Hz).

2-[8,12-Dimethyl-4-(trifluoromethyl)tridecyl]-2,5,8-trimethyl-7-(trifluoromethyl)-6-chromanol (25cd) Compound **24cd** (84 mg, 0.145 mmol) was hydrolyzed in MeOH (2 ml) containing concentrated HCl (0.2 ml) as described for **25ad**, to give **25cd** (40 mg, 51%). **25cd**: A pale yellow oil. MS *m*/*z*: 538 (M^+). HRMS Calcd for $C_{29}H_{44}F_6O_2$: 538.324. Found: 538.324. ^{1}H-NMR ($CDCl_3$) δ: 5.76 (1H, q, $J=9.0$ Hz), 2.66 (2H, t, $J=7.1$ Hz), 2.24 (3H, q, $J=2.5$ Hz), 2.12 (3H, s), 1.82 (2H, t, $J=7.1$ Hz), 1.69—1.00 (21H, m), 1.23 (3H, s), 0.86 (9H, d, $J=6.4$ Hz). ^{19}F-NMR ($CDCl_3$) ppm: -9.71 (3F, d, $J=7.3$ Hz), 6.80, 6.94 (3F in total, ratio 1 : 1, both d, $J=7.9$ Hz).

2-[4,12-Dimethyl-8-(trifluoromethyl)-3,7,11-tridecatrienyl]-2,5,8-trimethyl-6-chromanol Methoxymethyl Ether (19ce) The phosphonium salt **4c** (1.0 g, 1.50 mmol) was condensed with 10-methyl-6-(trifluoromethyl)-5,9-undecadien-2-one (372 mg, 1.50 mmol) as described for **19ad**, to give **19ce** (381 mg, 50%). **19ce**: A pale yellow oil. MS *m*/*z*: 508 (M^+). HRMS Calcd for $C_{30}H_{43}F_3O_3$: 508.316. Found: 508.316. ^{1}H-NMR ($CDCl_3$) δ: 6.77 (1H, s), 6.17—5.91 (0.10H, br), 5.66 (0.90H, t, $J=7.1$ Hz), 5.34—4.89 (2H, br), 5.10 (2H, s), 3.51 (3H, s), 2.63 (2H, t, $J=6.7$ Hz), 2.46—1.34 (14H, m), 2.13 (6H, s), 1.69, 1.60 (9H in total, both s), 1.26 (3H, s). ^{19}F-NMR ($CDCl_3$) ppm: -2.93, 3.74. ($Z:E=90:10$).

2-[4,12-Dimethyl-8-(trifluoromethyl)tridecyl]-2,5,8-trimethyl-6-chromanol (21ce) Compound **19ce** (323 mg, 0.636 mmol) was hydrolyzed in MeOH (10 ml) containing p-TsOH·H_2O (50 mg) as described for **19ad**, to give the deprotected product (**20ce**, 317 mg). This compound was hydrogenated in the presence of Pd–C (10%, 60 mg) as described for the hydrogenation of **20ad**, to give **21ce** (248 mg, 83%). **21ce**: A pale yellow oil. MS *m*/*z*: 470 (M^+). HRMS Calcd for $C_{28}H_{45}F_3O_2$: 470.337. Found: 470.337. ^{1}H-NMR ($CDCl_3$) δ: 6.46 (1H, s), 4.38 (1H, s), 2.60 (2H, t, $J=7.0$ Hz), 2.09 (6H, s), 1.78 (2H, t, $J=7.0$ Hz), 1.66—1.00 (21H, m), 1.23 (3H, s), 0.87 (9H, d, $J=6.5$ Hz). ^{19}F-NMR ($CDCl_3$) ppm: 6.92 (3F, d, $J=9.2$ Hz).

2-[4,12-Dimethyl-8-(trifluoromethyl)tridecyl]-2,5,8-trimethyl-6-chromanol Acetate (22ce) Compound **21ce** (245 mg, 0.521 mmol) was acetylated with acetic anhydride (1.2 ml, 12.8 mmol) and pyridine (1.2 ml, 14.8 mmol) as described for **22ad**, to give **22ce** (266 mg, 100%). **22ce**: A pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 6.65 (1H, s), 2.61 (2H, t, $J=6.7$ Hz), 2.30 (3H, s), 2.13, 1.99 (6H, s), 1.80 (2H, t, $J=6.7$ Hz), 1.69—0.97 (21H, m), 1.23 (3H, s), 0.88 (9H, d, $J=6.4$ Hz).

7-Bromo-2-[4,12-dimethyl-8-(trifluoromethyl)tridecyl]-2,5,8-trimethyl-6-chromanol Acetate (23ce) Compound **22ce** (268 mg, 0.523 mmol) was brominated with Br_2 (90 mg, 0.563 mmol) in the same manner as described for **16c**, to give **23ce** (240 mg, 78%). **23ce**: A yellow oil. MS *m*/*z*: 590 (M^+). 548 ($M-CH_2CO$). HRMS Calcd for $C_{28}H_{44}BrF_3O_2$ ($M-CH_2CO$): 548.248. Found: 548.247. ^{1}H-NMR ($CDCl_3$) δ: 2.59 (2H, t, $J=7.1$ Hz), 2.37 (3H, s), 2.26 (3H, s), 2.05 (3H, s), 1.80 (2H, t, $J=7.1$ Hz), 1.68—1.00 (21H, m), 1.25 (3H, s), 0.88 (9H, d, $J=6.4$ Hz).

2-[4,12-Dimethyl-8-(trifluoromethyl)tridecyl]-2,5,8-trimethyl-7-(trifluoromethyl)-6-chromanol Acetate (24ce) Compound **23ce** (230 mg, 0.389 mmol) was trifluoromethylated with CF_3I (0.5 ml, 5.1 mmol) and Cu powder (300 mg, 4.72 mmol) as described for the trifluoromethylation of **23ad**, to give **24ce** (156 mg, 69%). **24ce**: A yellow oil. MS *m*/*z*: 580 (M^+). 538 ($M-CH_2CO$). HRMS Calcd for $C_{29}H_{44}F_6O_2$ ($M-CH_2CO$): 538.324. Found: 538.324. ^{1}H-NMR ($CDCl_3$) δ: 2.66 (2H, t, $J=7.1$ Hz), 2.33 (3H, s), 2.27 (3H, q, $J=2.8$ Hz), 2.01 (3H, s), 1.81 (2H, t, $J=7.1$ Hz), 1.69—0.97 (21H, m), 1.26 (3H, s), 0.89 (9H, d, $J=6.4$ Hz). ^{19}F-NMR ($CDCl_3$) ppm: -7.32 (3F, s), 6.89 (3F, d, $J=8.8$ Hz).

2-[4,12-Dimethyl-8-(trifluoromethyl)tridecyl]-2,5,8-trimethyl-7-(trifluoromethyl)-6-chromanol (25ce) Compound **24ce** (149 mg, 0.257 mmol) was hydrolyzed in MeOH (8 ml) containing concentrated HCl (0.8 ml) in the same manner as described for **25ad**, to give **25ce** (113 mg, 82%). **25ce**: A pale yellow oil. MS *m*/*z*: 538 (M^+). HRMS Calcd for $C_{29}H_{44}F_6O_2$: 538.325. Found: 538.325. ^{1}H-NMR ($CDCl_3$) δ: 5.71 (1H, q, $J=8.6$ Hz), 2.64 (2H, t, $J=7.1$ Hz), 2.23 (3H, q, $J=2.4$ Hz), 2.11 (3H, s), 1.87 (2H, t, $J=7.1$ Hz), 1.69—1.00 (21H, m), 1.23 (3H, s), 0.87 (9H, d, $J=6.2$ Hz). ^{19}F-NMR ($CDCl_3$) ppm: -9.71 (3F, d, $J=7.3$ Hz), 6.89 (3F, d, $J=9.2$ Hz).

2-(13,13,13-Trifluoro-4,8,12-trimethyl-3,7,11-tridecatrienyl)-2,5,8-trimethyl-6-chromanol Methoxymethyl Ether (19cf) The phosphonium salt **4c** (1.0 g, 1.50 mmol) was condensed with 11,11,11-trifluoro-6,10-

dimethyl-5,9-undecadien-2-one (**18f**, 372 mg, 1.50 mmol) in the same manner as described for **19ad**, to give **19cf** (431 mg, 57%). **19cf**: A pale yellow oil. MS *m/z*: 508 (M^+). HRMS Calcd for $C_{30}H_{43}F_3O_3$: 508.316. Found: 508.316. ^{1}H-NMR ($CDCl_3$) δ: 6.77 (1H, s), 6.11—5.86 (0.10H, br), 5.67 (0.90H, t, $J=7.2$ Hz), 5.37—4.90 (2H, br), 5.10 (2H, s), 3.53 (3H, s), 2.63 (2H, t, $J=6.4$ Hz), 2.14 (6H, s), 1.83 (3H, s), 1.67 (3H, s), 1.59 (3H, s), 2.40—1.31 (14H, m), 1.26 (3H, s). ^{19}F-NMR ($CDCl_3$) ppm: -1.17, 6.20. ($Z:E=90:10$).

2-(13,13,13-Trifluoro-4,8,12-trimethyltridecyl)-2,5,8-trimethyl-6-chromanol (21cf) Compound **19cf** (420 mg, 0.827 mmol) was hydrolyzed in MeOH (10 ml) containing *p*-TsOH·H_2O (50 mg) as described for the hydrolysis of **19ad**, to give the deprotected product (**20cf**, 368 mg). This compound (**20cf**) was hydrogenated as described for **21ad**, to give **21cf** (365 mg, 94%). **21cf**: A pale yellow oil. MS *m/z*: 470 (M^+). HRMS Calcd for $C_{28}H_{45}F_3O_2$: 470.337. Found: 470.338. ^{1}H-NMR ($CDCl_3$) δ: 6.49 (1H, s), 4.31 (1H, s), 2.60 (2H, t, $J=7.0$ Hz), 2.10 (6H, s), 1.79 (2H, t, $J=7.0$ Hz), 1.66—0.94 (21H, m), 1.23 (3H, s), 1.09 (3H, d, $J=6.8$ Hz), 0.85 (6H, d, $J=5.7$ Hz). ^{19}F-NMR ($CDCl_3$) ppm: 9.91, 9.95 (both d, $J=8.8$ Hz, ratio 1:1).

2-(13,13,13-Trifluoro-4,8,12-trimethyltridecyl)-2,5,8-trimethyl-6-chromanol Acetate (22cf) Compound **21cf** (365 mg, 0.777 mmol) was acetylated with Ac_2O (1.2 ml, 12.8 mmol) and pyridine (1.2 ml, 14.8 mmol) and worked up as usual to give **22cf** (384 mg, 97%). **22cf**: A pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 6.66 (1H, s), 2.60 (2H, t, $J=7.0$ Hz), 2.29 (3H, s), 2.11 (3H, s), 1.99 (3H, s), 1.78 (2H, t, $J=7.0$ Hz), 1.66—0.94 (21H, m), 1.23 (3H, s), 1.10 (3H, d, $J=6.8$ Hz), 0.86 (6H, d, $J=5.7$ Hz).

7-Bromo-2-(13,13,13-trifluoro-4,8,12-trimethyltridecyl)-2,5,8-trimethyl-6-chromanol Acetate (23cf) Compound **22cf** (300 mg, 0.586 mmol) was brominated with Br_2 (120 mg, 0.75 mmol) in CH_2Cl_2 at 50 °C for 4 h, and worked up as described in the case of **16c**, to give **23cf** (257 mg, 83%) with recovery of the starting material (30 mg). **23cf**: A yellow oil. MS *m/z*: 590 (M^+), 548 ($M-CH_2CO$). ^{1}H-NMR ($CDCl_3$) δ: 2.59 (2H, t, $J=7.0$ Hz), 2.38 (3H, s), 2.26, 2.04 (6H, s), 1.94 (2H, t, $J=7.0$ Hz), 1.66—0.97 (21H, m), 1.26 (3H, s), 1.09 (3H, d, $J=6.8$ Hz), 0.86 (6H, d, $J=5.7$ Hz).

2-(13,13,13-Trifluoro-4,8,12-trimethyltridecyl)-2,5,8-trimethyl-7-(trifluoromethyl)-6-chromanol Acetate (24cf) Compound **23cf** was trifluoromethylated with CF_3I (2.0 ml, 20.4 mmol) and Cu powder (300 mg, 4.72 mmol) in the same manner as described for **24ad**, to give **24cf** (139 mg, 47%). **24cf**: A yellow oil. MS *m/z*: 580 (M^+), 538 ($M-CH_2CO$). HRMS Calcd for $C_{29}H_{44}F_6O_2$ ($M-CH_2CO$): 538.325. Found: 538.325. ^{1}H-NMR ($CDCl_3$) δ: 2.66 (2H, t, $J=6.8$ Hz), 2.30 (3H, s), 2.26 (3H, q, $J=2.6$ Hz), 1.99 (3H, s), 1.80 (2H, t, $J=6.8$ Hz), 1.69—0.97 (21H, m), 1.25 (3H, s), 1.08 (3H, d, $J=7.0$ Hz), 0.85 (6H, d, $J=5.7$ Hz). ^{19}F-NMR ($CDCl_3$) ppm: -7.32 (3F, s), 9.91, 9.95 (3F in total, ratio 1:1, both d, $J=8.8$ Hz).

2-(13,13,13-Trifluoro-4,8,12-trimethyltridecyl)-2,5,8-trimethyl-7-(trifluoromethyl)-6-chromanol (25cf) Compound **24cf** (129 mg, 0.222 mmol) was hydrolyzed in MeOH (5 ml) containing concentrated HCl (0.5 ml) as described for **25ad** to give **25cf** (82 mg, 78%) with recovery of the starting material (17 mg). **25cf**: A pale yellow oil. MS *m/z*: 538 (M^+). HRMS Calcd for $C_{29}H_{44}F_6O_2$: 538.324. Found: 538.324. ^{1}H-NMR ($CDCl_3$) δ: 5.71 (1H, q, $J=8.6$ Hz), 2.64 (2H, t, $J=6.8$ Hz), 2.23 (3H, q, $J=2.4$ Hz), 2.12 (3H, s), 1.80 (2H, t, $J=6.8$ Hz), 1.60—0.89 (21H, m), 1.24 (3H, s), 1.09 (3H, d, $J=6.8$ Hz), 0.86 (6H, d, $J=5.7$ Hz). ^{19}F-NMR ($CDCl_3$) ppm: -9.72 (3F, s), 9.92, 9.95 (3F in total, ratio 1:1, both d, $J=8.8$ Hz).

Acknowledgment This work was partly supported by the Sasakawa Scientific Research Grant from the Japan Science Society to M. K. and a Grant-in-Aid for Scientific Research (C) from the Minstry of Education, Science and Culture, Japan.

References and Notes

1) Part III: Koyama M., Tamura M., Ando A., Kumadaki I., *Chem. Pharm. Bull.*, **42**, 2154 (1994).
2) A part of this work was reported at the 114th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, March 1994. Preliminary communication: Koyama M., Takagi T., Ando A., Kumadaki I., *Heterocycles*, **37**, 163 (1994).
3) For details of the biological activity, see "Biomedicinal Aspects of Fluorine Compounds," ed. by Filler R., Kobayashi Y., Kodansha, Tokyo, 1982, and "Selective Fluorination in Organic and Bioorganic Chemistry," ed. by Welch J. T., American Chemical Society Symposium Series, 456, Washington DC, 1991.
4) *a*) Kumadaki I., Tamura M., Ando A., Nagai T., Koyama M., Miki T., *Chem. Pharm. Bull.*, **36**, 515 (1988); *b*) Koyama M., Tamura M., Ando A., Nagai T., Miki T., Kumadaki I., *Chem. Pharm. Bull.*, **36**, 2950 (1988); *c*) Kumadaki I., Hirai M., Koyama M., Nagai T., Ando A., Miki T., *Synth. Commun.*, **19**, 173 (1989).
5) Burton G. W., Ingold K. U., *Acc. Chem. Res.*, **19**, 194 (1986).
6) Urano S., Matsuo M., Sakanaka T., Uemura I., Kumadaki I., Koyama M., Fukuzawa K., *Arch. Biochem. Biophys.*, **303**, 10 (1993).
7) Postscripts **a**, **b** and **c** show the types of the chromanol parts, and **d**, **e** and **f** show the position of the CF_3 group.