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SYNTHESIS OF 4,4-DIFLUORO-α-TOCOPHEROL USING A CROSS-COUPLING REACTION OF BROMODIFLUOROACETATE WITH ARYL IODIDE IN THE PRESENCE OF COPPER POWDER

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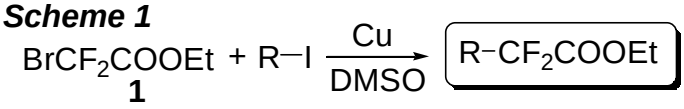
This is dedicated to 70th birthday of Professor James P. Kutney.

Abstract – Using our new methodology for introduction of a CF_2 moiety, 4,4-difluoro-α-tocopherol (**2**) was synthesized. Thus, 1-iodo-2,5-bis(methoxy-methoxy)-3,4,6-trimethylbenzene (**4**) was treated with ethyl bromodifluoroacetate (**1**) in the presence of Cu powder to give a substituted phenyldifluoroacetate (**5**). Compound (**5**) was converted to 4,4-difluorochromanol derivative (**12**). Elongation of the side chain of **12** gave **2**.

Introduction

Nowadays, organofluorine compounds have been attracting much attention in biomedicinal fields, since they have various biological activities.[1] Among them, difluoromethylene (CF_2) compounds are very important, and their syntheses have been reported by many workers.[2] Reformatsky reaction[3] of halodifluoroacetate and aldol reaction[4] using enolate or ketene acetal from halodifluoroacetate are the most common methodologies to introduce a CF_2 moiety. However, these methods give products with one hydroxyl group adjacent to the CF_2 group. This hydroxyl group is very stable and difficult to be removed, although deoxygenation of β-fluoro alcohol through xanthates has been reported.[5] Therefore, it is very difficult to introduce a CF_2 functional group without hydroxyl group using an appropriate synthon.[6] To solve this difficulty, we have developed a cross-coupling reaction of ethyl bromodifluoroacetate (**1**) with alkenyl or aryl iodides (Scheme 1).[7]

Scheme 1



Now, we would like to report the synthesis of the 4,4-difluoro-α-tocopherol (**2**) using our cross-coupling reaction of an organocopper reagent derived from ethyl bromodifluoroacetate (**1**). α-Tocopherol is one of the most important biologically active compounds and has been used in various fields.[8] The main effect of α-tocopherol has been believed to be anti-oxidizing effect but the clinical effect and the biological behavior are not clearly solved.[9] So, we have synthesized α-tocopherols with one or two CF_3 groups (F_3- or F_6-α-tocopherols) in place of the methyl groups. Study of biological behavior of these fluorine analogs of α-tocopherols using ^{19}F-NMR gave interesting results.[10] This prompted us to synthesize α-tocopherol with CF_2 group in chromane ring (F_2-α-tocopherol, **2**) using our new methodology (Figure 1). F_2-α-Tocopherol was expected to be useful for elucidation of biological behavior and effective for the clinical use based on the electronic effect of CF_2.

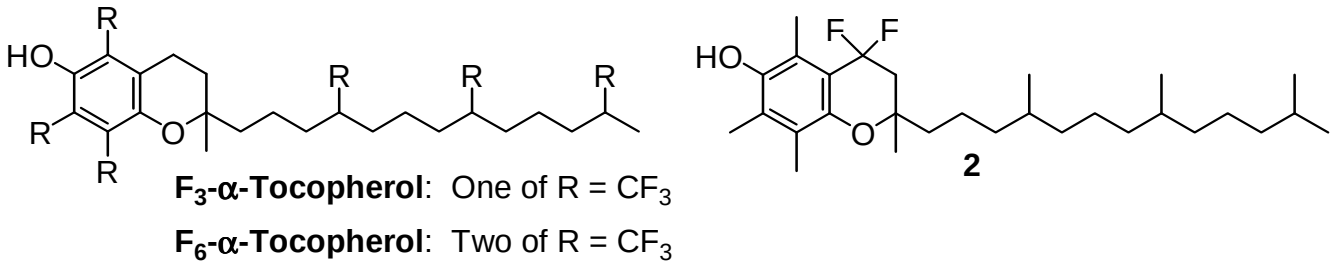
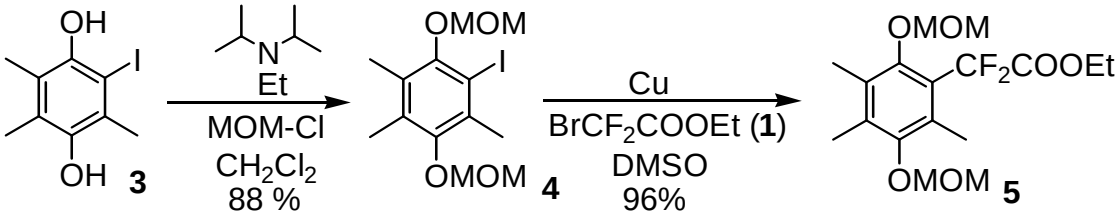


Figure 1. F_3- or F_6-α-Tocopherols and 4,4-difluoro-α-tocopherol (2)

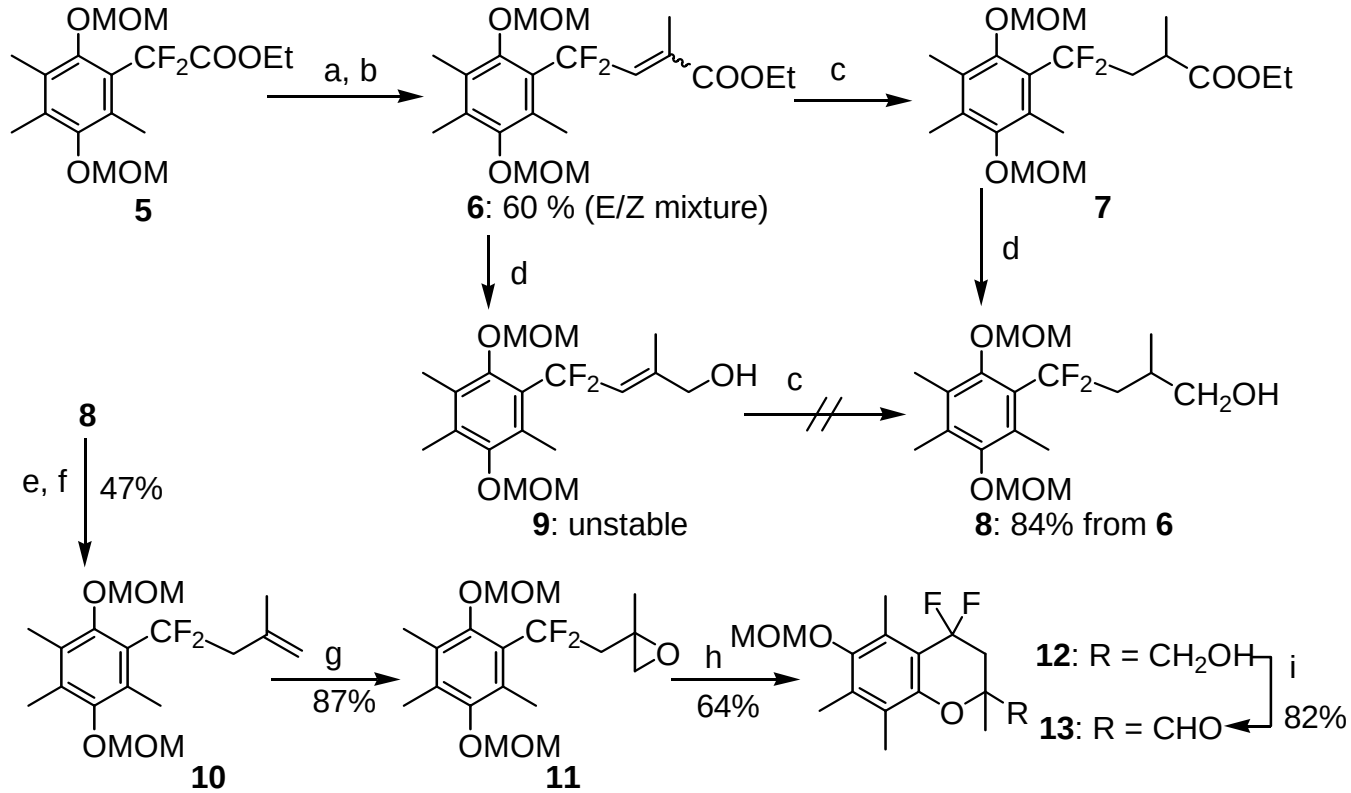
Cross-coupling reaction of 1 with 1-iodo-2,5-bis(methoxymethoxy)-3,4,6-trimethylbenzene (4). First, we synthesized 2-iodo-3,5,6-trimethylhydroquinone (**3**) according to literature[11] for the cross-coupling reaction.[7] The hydroxyl groups of **3** were protected with MOM-Cl to give 1-iodo-2,5-bis(methoxymethoxy)-3,4,6-trimethylbenzene (**4**) in 88% yield (Scheme 2). Compound (**4**) was treated with **1** in the presence of active Cu powder to give ethyl [2,5-bis(methoxymethoxy)-3,4,6-trimethylphenyl]difluoroacetate (**5**) in 96% yield. This result shows that our cross-coupling reaction is not disturbed by large *ortho* substituents and proceeds in an excellent yield. On the other hand, the cross-coupling reactions of the hydroquinone (**3**) or the corresponding quinone themselves did not produce the coupling products at all (Scheme 2).

Scheme 2



Synthesis of the chromane ring. Compound (**5**) was treated with DIBAL-H, followed by Horner-Wadsworth-Emmons (HWE) reaction with triethyl 2-phosphonopropionate to give a 4,4-difluoro-2-butenoate (**6**) in 60% yield as an *E*/*Z* mixture (Scheme 3). Several bases, such as BuLi, were examined for the HWE reaction. Among them, LDA gave the best yield and stereoselectivity was moderate in all cases. Compound (**6**) was reduced by H_2 in the presence of 10% Pd-C, followed by a treatment with LAH to give a saturated alcohol (**8**). On the other hand, the allyl alcohol (**9**) obtained by reduction of **6** with LAH was too unstable to proceed for further synthesis. Since dehydration of **8** through the mesylate was not effective, we adopted Grieco's *o*-nitorophenylselenylation method.[12] Thus, **8** was treated with *o*-nitrophenyl selenocyanate and tributylphosphine, followed by a treatment with 30% H_2O_2 to give the corresponding methylene compound (**10**). Compound (**10**) was epoxidized by *m*CPBA, followed by ring closure with CF_3COOH to give the corresponding chromanol (**12**). Further, **12** was oxidized by Swern reaction to give the aldehyde (**13**) in 18% overall yield from **6**. (Scheme 3)

Scheme 3

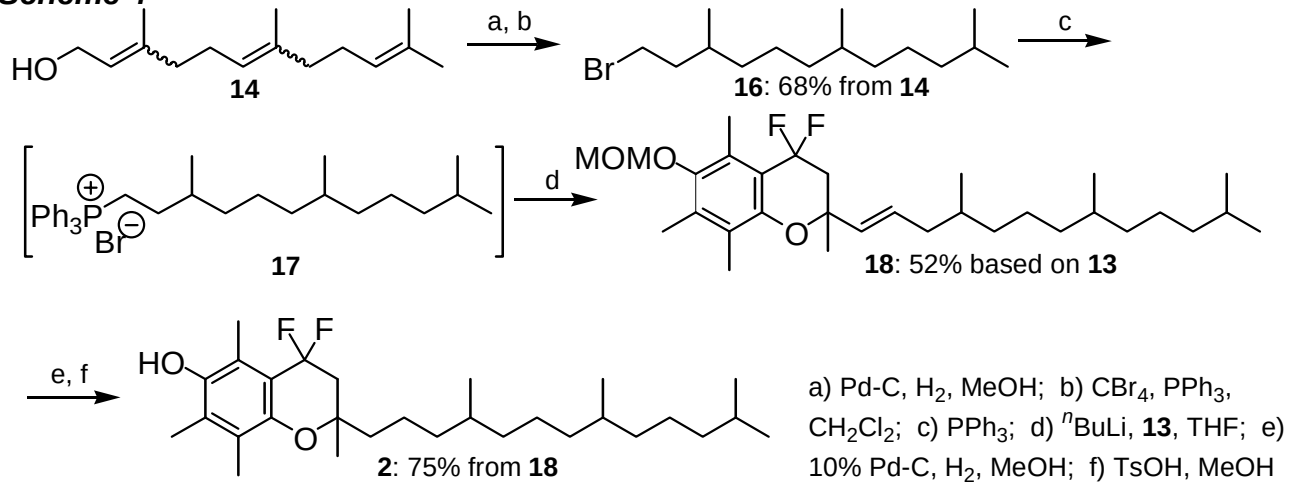


a) 1: DIBAL-H, THF; 2: MeOH, 5% HCl; b) LDA, $(EtO)_2P(O)CHMeCOOEt$, THF; c) 10% Pd-C, H_2, THF; d) $LiAlH_4$, THF; e) *o*-nitrophenyl selenocyanate, Bu_3P, THF; f) 30% H_2O_2, THF; g) *m*CPBA, CH_2Cl_2; h) CF_3COOH, THF, H_2O; i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2

Synthesis of 4,4-difluoro-α-tocopherol (2) by Wittig reaction.[13] For the construction of the side chain, we attempted to join **13** with the Wittig reagent derived from farnesol (**14**), followed by reduction of the double bonds. Unfortunately, catalytic hydrogenation of the Wittig reaction product did not give

the fully saturated side-chain, but a mixture of partially reduced ones. To solve this difficulty, farnesol (**14**) was hydrogenated first in the presence of 10% Pd-C to give 3,7,11-trimethyldodecanol (**15**) in 85% yield. Treatment of **15** with CBr_4 and PPh_3 gave the bromide (**16**) in 80% yield. Compound (**16**) was converted to the phosphonium salt (**17**) by treatment with PPh_3. In this case, the presence of solvent interfered production of the objective phosphonium salt. This salt was an oil and unstable, and used for the Wittig reaction without purification. The ylide obtained from **17** and BuLi was treated with **13** to give 4,4-difluoro-6-methoxymethoxy-2,5,7,8-tetramethyl-2-(4,8,12-trimethyl-1-tridecenyl)chromane (**18**) in 52% yield. Finally, hydrogenation of **18** in the presence of 10% Pd-C afforded **19**, which was hydrolyzed with PTSA to give 4,4-difluoro-α-tocopherol (**2**) in 75% yield from **18**. (Scheme 4)

Scheme 4



Concluding Remark Our cross-coupling reaction of bromodifluoroacetate with an aryl iodide was successfully applied for the synthesis of 4,4-difluoro-α-tocopherol (**2**). This result showed that our method is widely applicable for the syntheses of aryldifluoromethylene compounds even in the presence of large substituents in *ortho* positions. Compound (**2**) is a new fluorine derivative of α-tocopherol, and it is expected to have new effect different from those of F_3- or F_6-α-tocopherols.

Experimental

General Procedures

^{1}H-NMR spectra were recorded on JEOL-FX90Q and JNM-GX400 Spectrometer using tetramethylsilane as an internal standard. ^{19}F-NMR spectra were recorded on Hitachi FT-NMR R-1500, JEOL-FX90Q and GE-Omega 600 Spectrometers using benzotrifluoride as an internal standard. MS spectra were obtained by JEOL JMS-DX-300 and JEOL JMS-700T. Gas-liquid chromatography (GLC) was carried out on a Hitachi 263-50 gas chromatograph (column: 5% SE-30 3 mm x 2 m, carrier: N_2 at 30 mL/min). Peak areas were calculated on a Shimadzu C-R5A Chromatopac. The melting point was measured on

an Ishii Shoten Melting Point Apparatus. After the purities of samples were confirmed by TLC or GLC, elemental analyses were obtained by high resolution mass spectra.

1-Iodo-2,5-bis(methoxymethoxy)-3,4,6-trimethylbenzene (4)

Under an atmosphere of Ar, chloromethyl methyl ether (0.52 mL, 6.8 mmol) in CH_2Cl_2 (2.5 mL) was added to a solution of 2-iodo-3,5,6-trimethylhydroquinone (**3**, 480 mg, 1.7 mmol) and *N*,*N*-diisopropylethylamine (2.37 mL, 13.6 mmol) in CH_2Cl_2 (2.5 mL) at rt for 1 h. The mixture was poured into a mixture of ice and 3% HCl, and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with saturated aq. $NaHCO_3$ and saturated aq. NaCl, and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography (SiO_2, AcOEt:hexane=1:9) to give **4** (548 mg, 88%). **4**: Colorless crystals. mp 82.8-83.8 °C. MS *m/z*: 366 (M^+). HRMS Calcd $C_{13}H_{19}O_4I$: 366.033 (M^+) Found: 366.033. ^{1}H-NMR ($CDCl_3$) δ: 4.98 (s, 2H), 4.88 (s, 2H), 3.67 (s, 3H), 3.60 (s, 3H), 2.44 (s, 3H), 2.26 (s, 3H), 2.19 (s, 3H).

Ethyl [2,5-bis(methoxymethoxy)-3,4,6-trimethylphenyl]difluoroacetate (5)

Under an atmosphere of Ar, ethyl bromodifluoroacetate (**1**, 1.49 mL, 11.7 mmol) was added to a suspension of activated Cu powder (1.62 g, 25.8 mmol) and **4** (1.42 g, 3.9 mmol) in DMSO (19.5 mL). After the mixture was stirred at 55 °C for 7 h, it was poured into a mixture of ice and saturated aq. NH_4Cl, and extracted with Et_2O. The Et_2O layer was washed with saturated aq. NH_4Cl and saturated aq. NaCl, and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography (SiO_2, AcOEt:hexane=1:4) to give **5** (1.36 g, 96%). **5**: A pale yellow oil. bp 113-115 °C / 0.017 mmHg. MS *m/z*: 362 (M^+). HRMS Calcd $C_{17}H_{24}O_6F_2$: 362.154 (M^+) Found: 362.154. ^{1}H-NMR ($CDCl_3$) δ: 4.90 (s, 2H), 4.79 (s, 2H), 4.33 (q, 2H, *J*= 7.3 Hz), 3.62 (s, 3H), 3.55 (s, 3H), 2.42 (t, 3H, *J*= 4.4 Hz), 2.24 (s, 3H), 2.20 (s, 3H), 1.31 (t, 3H, *J*= 7.3 Hz). ^{19}F-NMR ($CDCl_3$) ppm: –29.7 (m, 2F).

Ethyl 4-[2,5-bis(methoxymethoxy)-3,4,6-trimethylphenyl]-4,4-difluoro-2-methyl-2-butenoate (6)

Under an atmosphere of Ar, DIBAL-H (7.6 mL: 0.94 M in hexane, 7.1 mmol) was added to a solution of **5** (1.08 g, 3.0 mmol) in Et_2O (9.0 mL) at –78 °C and stirred at this temperature for 2 h, then MeOH (1.5 mL) and 5% HCl (3.0 mL) were added to the solution. After the mixture was stirred at rt for 10 min, it was poured into saturated aq. NaCl, and extracted with Et_2O. The Et_2O layer was dried over $MgSO_4$. After evaporation of the solvent, the residue was used for next step without purification. Triethyl phosphonopropionate (0.77 mL, 3.6 mmol) was added at –78 °C to a solution of LDA from ^{n}BuLi (2.3 mL: 1.56 M in hexane, 3.6 mmol) and diisopropylamine (0.5 mL, 3.6 mmol) in THF (12 mL), and then the above residue dissolved in THF (6 mL) was added. After 10 min, the mixture was gradually warmed to rt and stirred for 15 min. The mixture was poured into 10% HCl, and extracted with Et_2O. The Et_2O layer was washed with saturated aq. $NaHCO_3$ and saturated aq. NaCl, and dried over $MgSO_4$.

After evaporation of the solvent, the residue was purified by column chromatography (SiO_2, AcOEt:hexane=1:9) to give (*E*)-**6** (531 mg, 44%) and (*Z*)-**6** (193 mg, 16%). (*E*)-**6**: A pale yellow oil. MS *m/z*: 402 (M^+). HRMS Calcd $C_{20}H_{28}O_6F_2$: 402.185 (M^+) Found: 402.185. ^{1}H-NMR ($CDCl_3$) δ: 6.06 (tq, 1H, *J*= 12.7, 2.0 Hz), 4.87 (s, 2H), 4.84 (s, 2H), 4.11 (q, 2H, *J*= 7.3 Hz), 3.61 (s, 3H), 3.59 (s, 3H), 2.36 (dd, 3H, *J*= 4.9, 4.3 Hz), 2.23 (s, 3H), 2.22 (s, 3H), 2.01 (td, 3H, *J*= 2.9, 2.0 Hz), 1.30 (t, 3H, *J*= 7.3 Hz). ^{19}F-NMR ($CDCl_3$) ppm: –15.6 (m, 2F). (*Z*)-**6**: A pale yellow oil. MS *m/z*: 402 (M^+). HRMS Calcd $C_{20}H_{28}O_6F_2$: 402.185 (M^+) Found: 402.185. ^{1}H-NMR ($CDCl_3$) δ: 7.13 (tq, 1H, *J*= 12.0, 1.5 Hz), 4.88 (s, 2H), 4.85 (s, 2H), 4.22 (q, 2H, *J*= 7.3 Hz), 3.61 (s, 3H), 3.58 (s, 3H), 2.40 (dd, 3H, *J*= 4.8, 4.4 Hz), 2.24 (s, 3H), 2.21 (s, 3H), 1.85 (td, 3H, *J*= 2.9, 1.5 Hz), 1.30 (t, 3H, *J*= 7.3 Hz). ^{19}F-NMR ($CDCl_3$) ppm: –17.3 (m, 2F).

4-[2,5-Bis(methoxymethoxy)-3,4,6-trimethylphenyl]-4,4-difluoro-2-methylbutanol (8)

A THF (10 mL) solution of **6** (525 mg, 1.3 mmol) was vigorously stirred in the presence of 10% Pd-C (13 mg) under an atmosphere of H_2 at rt for 6.5 h. After the catalyst was filtered off, the solvent was evaporated to give the crude **7**, which was added to a solution of $LiAlH_4$ (7.4 mg, 1.95 mmol) in THF (3.7 mL) at 0 °C under an atmosphere of Ar. After 30 min, the mixture was poured into 10% HCl, and extracted with Et_2O. The Et_2O layer was washed with saturated aq. $NaHCO_3$ and saturated aq. NaCl, and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography (SiO_2, AcOEt:hexane=2:3) to give **8** (395 mg, 84% from **6**). **8**: A pale yellow oil. MS *m/z*: 362 (M^+). HRMS Calcd $C_{18}H_{28}O_5F_2$: 362.190 (M^+); Found: 362.190. ^{1}H-NMR ($CDCl_3$) δ: 4.86 (s, 4H), 3.62 (s, 3H), 3.61 (s, 3H), 3.52 (t, 2H, *J*= 5.3 Hz), 2.38-2.52 (m, 1H), 2.34 (dd, 3H, *J*= 5.2, 4.8 Hz), 2.23 (s, 3H), 2.22 (s, 3H), 2.08 (m, 2H), 1.59 (bs, 1H), 1.03 (d, 3H, *J*= 6.8 Hz). ^{19}F-NMR ($CDCl_3$) ppm: –21.6 (m, 2F).

4-[2,5-Bis(methoxymethoxy)-3,4,6-trimethylphenyl]-4,4-difluoro-2-methyl-1-butene (10)

Under an atmosphere of Ar, Bu_3P (0.09 mL, 0.38 mmol) was slowly added at 0 °C to a stirred solution of **8** (100 mg, 0.27 mmol) and *o*-nitrophenyl selenocyanate (74 mg, 0.32 mmol) in THF (1 mL), and the mixture was stirred at rt for 24 h. After THF was evaporated from the mixture, the residue was passed through an SiO_2 column (AcOEt:hexane=2:3) to give the corresponding selenide. 30% H_2O_2 (0.31 mL, 2.7 mmol) was slowly added at 0 °C to a solution of the selenide in THF (2 mL), and the mixture was stirred at 0 °C for 1 h and then at rt for 2 h. The mixture was poured into H_2O and was extracted with Et_2O. The Et_2O layer was washed with 10% aq. Na_2CO_3 and saturated aq. NaCl, and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography (SiO_2, AcOEt:hexane=2:3) to give **10** (44 mg, 47% from **8**). **10**: A pale yellow oil. MS *m/z*: 344 (M^+). HRMS Calcd $C_{18}H_{26}O_4F_2$: 344.179 (M^+); Found: 344.179. ^{1}H-NMR ($CDCl_3$) δ: 4.93 (m, 1H), 4.87 (s, 2H), 4.86 (s, 2H), 4.79 (m, 1H), 3.63 (s, 3H), 3.60 (s, 3H), 2.98 (t, 2H, *J*= 17.7 Hz), 2.33 (t, 3H, *J*= 5.2 Hz), 2.23 (s,

6H), 1.77 (s, 3H). ^{19}F-NMR ($CDCl_3$) ppm: –21.0 (m, 2F).

2-[2-{2,5-Bis(methoxymethoxy)-3,4,6-trimethylphenyl}-2,2-difluoroethyl]-2-methyloxirane (11)

Under an atmosphere of Ar, to a stirred solution of *m*CPBA (100 mg, 0.58 mmol) in CH_2Cl_2 (4 mL) was slowly added a solution of **10** (200 mg, 0.58 mmol) in CH_2Cl_2 (6 mL), and the mixture was stirred at rt for 24 h. Further, *m*CPBA (75%, 130 mg, 0.58 mmol) was added to the mixture and stirred for 24 h. After **10** was not detected by TLC, the mixture was poured into saturated aq. $NaHCO_3$ and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with saturated aq. NaCl, and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography (SiO_2, AcOEt:hexane =1:4) to give **11** (181 mg, 87%). **11**: A pale yellow oil. MS *m/z*: 360 (M^+). HRMS Calcd $C_{18}H_{26}O_5F_2$: 360.175 (M^+) Found: 360.175. ^{1}H-NMR($CDCl_3$) δ: 4.86 (s, 2H), 4.86 (s, 2H), 3.62 (s, 3H), 3.61 (s, 3H), 2.77 (m, 1H), 2.70 (d, 1H, *J*= 4.8 Hz), 2.62 (dd, 1H, *J*= 4.8, 1.2 Hz), 2.33 (dd, 3H, *J*= 5.2, 4.8 Hz), 2.29 (m, 1H), 2.23 (s, 3H), 2.22 (s, 3H), 1.42 (s, 3H). ^{19}F-NMR ($CDCl_3$) ppm: –21.0 (m, 2F).

(4,4-Difluoro-6-methoxymethoxy-2,5,7,8-tetramethylchroman-2-yl)methanol (12)

Under an atmosphere of Ar, 50 %(v/v) CF_3COOH-H_2O (0.08 mL) was added dropwise at 0 °C to a solution of **11** (40 mg, 0.11 mmol) in THF (0.22 mL), and the mixture was stirred for 1 h at 0 °C. The mixture was warmed up to rt and stirred for 14 h. The mixture was poured into saturated aq. $NaHCO_3$ and extracted with Et_2O. The Et_2O layer was washed with saturated aq. NaCl, and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography (SiO_2, AcOEt:hexane=2:3) to give **12** (22 mg, 64%). **12**: A pale yellow oil. MS *m/z*: 316 (M^+). HRMS Calcd $C_{16}H_{22}O_4F_2$: 316.149 (M^+) Found: 316.149. ^{1}H-NMR ($CDCl_3$) δ: 4.88 (d, 1H, *J*= 7.7 Hz), 4.87 (d, 1H, *J*= 7.7 Hz), 3.72 (m, 1H), 3.62 (s, 3H), 3.59 (m, 1H), 2.72 (ddd, 1H, *J*= 21.6, 14.7, 14.4 Hz), 2.44 (s, 3H), 2.30 (ddd, 1H, *J*= 17.5, 14.7, 8.5 Hz), 2.22 (s, 3H), 2.08 (s, 3H), 1.95 (bs, 1H), 1.32 (d, 3H, *J*= 1.7 Hz). ^{19}F-NMR ($CDCl_3$) ppm: –16.80 (m, 1F), –18.80 (m, 1F).

4,4-Difluoro-6-methoxymethoxy-2,5,7,8-tetramethyl-2-chromancarbaldehyde (13)

Under an atmosphere of Ar, a solution of DMSO (0.037 mL, 0.52 mmol) in CH_2Cl_2 (0.065 mL) was added dropwise at –78 °C to a solution of $(COCl)_2$ (0.023 mL, 0.26 mmol) in CH_2Cl_2 (0.32 mL), and the mixture was stirred for 30 min at that temperature. A solution of **12** (67 mg, 0.21 mmol) in CH_2Cl_2 (0.4 mL) was added to the mixture at –78 °C, and the mixture was stirred for 30 min, followed by slow addition of Et_3N (0.148 mL, 1.06 mmol) at –78 °C. The mixture was gradually warmed up to rt, and was poured into saturated aq. NaCl and extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography (SiO_2, AcOEt:hexane=1:4) to give **13** (54 mg, 82%). **13**: A pale yellow oil. MS *m/z*: 314 (M^+). HRMS Calcd $C_{16}H_{20}O_4F_2$: 314.133 (M^+) Found: 314.133. ^{1}H-NMR ($CDCl_3$) δ: 9.64 (dd, 1H, *J*= 1.4, 0.8 Hz), 4.89 (d, 1H, *J*= 6.6 Hz), 4.87 (d, 1H, *J*= 6.6 Hz), 3.62 (s, 3H), 2.81 (ddd, 1H, *J*= 16.1, 14.7, 9.2 Hz), 2.49 (ddd,

1H, *J*= 19.8, 14.7, 12.1 Hz), 2.40 (s, 3H), 2.25 (s, 3H), 2.18 (s, 3H), 1.48 (d, 3H, *J*= 1.0 Hz). ^{19}F-NMR ($CDCl_3$) ppm: –14.82 (ddd, 1F, *J*= 263.7, 19.8, 16.1 Hz), –23.54 (ddd, 1F, *J*= 263.7, 12.1, 9.2 Hz).

3,7,11-Trimethyldodecanol (15)

A MeOH (140 mL) solution of farnesol (**14**, 1.0 g, 4.50 mmol) was vigorously stirred in the presence of 10% Pd-C (150 mg) under an atmosphere of H_2 at rt for 4 h. After removal of the catalyst and evaporation of the solvent, the residue was purified by column chromatography (SiO_2, AcOEt:hexane =1:1) to give **15** (872 mg, 85%) as a mixture of diastereomers. **15**: A colorless oil: MS *m/z*: 227 (M^+–1). HRMS Calcd $C_{15}H_{32}O$: 227.238 (M^+–1) Found: 227.237. ^{1}H-NMR($CDCl_3$) δ: 3.68 (m, 2H), 1.47-1.66 (m, 3H), 1.00-1.44 (m, 15H), 0.89 (d, 3H, *J*= 6.1 Hz), 0.86 (d, 6H, *J*= 6.7 Hz), 0.84 (dd, 3H, *J*= 6.6, 0.6 Hz).

1-Bromo-3,7,11-trimethyldodecane (16)

Under an atmosphere of Ar, to CBr_4 (1.3 g, 3.4 mmol) was added a solution of **15** (711 mg, 3.1 mmol) in CH_2Cl_2 (13 mL) and a solution of PPh_3 (892 mg, 3.4 mmol) in CH_2Cl_2 (3 mL) at 0 °C, and the mixture was stirred at rt for 1 h. MeOH (3 mL) was added to the mixture, and stirred for 1 h. After evaporation of the solvent, the residue was purified by column chromatography (SiO_2, AcOEt:hexane =1:1) and vacuum distillation to give **16** (729 mg, 81%) as a mixture of diastereomers. **16**: A colorless oil. bp 110-115 °C / 4 mmHg. MS *m/z*: 290 (M^+), 292 (M^++2). HRMS Calcd $C_{15}H_{31}Br$: 290.161 (M^+) Found: 290.160. ^{1}H-NMR ($CDCl_3$) δ: 3.44 (m, 2H), 1.87 (m, 1H), 1.46-1.72 (m, 3H), 1.01-1.43 (m, 13H), 0.89 (d, 3H, *J*= 6.2 Hz), 0.87 (d, 6H, *J*= 6.8 Hz), 0.85 (d, *H, *J*= 6.8 Hz), 0.85 (d, *H, *J*= 7.2 Hz); *H is total 3H.

1-(4,4-Difluoro-6-methoxymethoxy-2,5,7,8-tetramethylchroman-2-yl)-4,8,12-trimethyl-1-tridecene (18)

Under an atmosphere of Ar, PPh_3 (89 mg, 0.34 mmol) and **16** (100 mg, 0.34 mmol) was stirred at 200 °C for 17 h without a solvent. After the mixture was cooled to rt, THF (3 mL) was added to the mixture. ^{n}BuLi (0.25 mL: 1.56 M in hexane, 0.4 mmol) was slowly added at 0 °C to the solution and stirred for 15 min. A solution of **13** (54 mg, 0.17 mmol) in THF (2 mL) was added to the mixture and stirred at rt for 2 h and then at 50 °C for 30 min. The mixture was poured into saturated aq. NH_4Cl, and extracted with Et_2O. The Et_2O layer was washed with saturated aq. NH_4Cl and saturated aq. NaCl, and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography (SiO_2, AcOEt:hexane=1:9) to give **18** (45 mg, 52%) as *E-Z* and diastereo mixture. **18**: A pale yellow oil. MS *m/z*: 508 (M^+). HRMS Calcd $C_{31}H_{50}O_3F_2$: 508.371 (M^+) Found: 508.372. ^{1}H-NMR ($CDCl_3$) δ: 5.50 (m, 1H), 5.40 (m, 1H), 4.87 (d, 1.6H, *J*= 0.6 Hz), 4.86 (s, 0.4H), 3.62 (s, 2.4H), 3.61 (s, 0.6H), 2.42 (s, 3H), 2.22 (s, 3H), 2.13 (s, 3H), 1.70-2.70 (m, 5H), 0.87 (d, *H, *J*= 6.8 Hz), 0.86 (d, 6H, *J*= 6.8 Hz), 0.84 (dd, *H, *J*= 6.8, 0.4 Hz), 0.83 (d, **H, *J*= 6.4 Hz), 0.81 (d, **H, *J*= 6.4 Hz), 0.74 (d, *H, *J*= 6.8 Hz), 0.71 (d, *H,

J= 6.8 Hz), *H is total 3H, **H is total 3H. ^{19}F-NMR ($CDCl_3$) ppm: –18.6 (t, 2F, *J*= 14.6 Hz).

1-(4,4-Difluoro-6-methoxymethoxy-2,5,7,8-tetramethylchroman-2-yl)-4,8,12-trimethyltridecane (19)

A MeOH (3 mL) solution of **18** (45 mg, 0.09 mmol) was vigorously stirred in the presence of 10% Pd-C (3 mg) under an atmosphere of H_2 at rt for 12 h. After removal of the catalyst and the evaporation of the solvent, the residue was purified by column chromatography (SiO_2, AcOEt:hexane=1:9) to give **19** (42 mg, 93%) as a mixture of diastereomers. **19**: A pale yellow oil. MS *m/z*: 510 (M^+). HRMS Calcd $C_{31}H_{52}O_3F_2$: 510.388 (M^+) Found: 510.376. ^{1}H-NMR ($CDCl_3$) δ: 4.87 (s, 2H), 3.61 (s, 3H), 2.43 (s, 3H), 2.26-2.52 (m, 2H), 2.21 (s, 3H), 2.08 (s, 3H), 1.00-1.75 (m, 24H), 0.87 (d, 6H, *J*= 6.8 Hz), 0.85 (dd, 3H, *J*= 6.8, 0.4 Hz), 0.84 (d, 3H, *J*= 6.8 Hz). ^{19}F-NMR ($CDCl_3$) ppm: –18.0 (m, 2F).

4,4-Difluoro-α-tocopherol (2)

Under an atmosphere of Ar, a solution of **19** (42 mg, 0.08 mmol) and *p*-toluenesulfonic acid·H_2O (5 mg) in MeOH (2 mL) was stirred at rt for 24 h. The mixture was poured into saturated aq. $NaHCO_3$ and extracted with Et_2O. The Et_2O layer was washed with saturated aq.NaCl, and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography (SiO_2, AcOEt:hexane=1:19) to give **2** (31 mg, 81%) as a mixture of diastereomers. **2**: A pale yellow oil. MS *m/z*: 466 (M^+). HRMS Calcd $C_{29}H_{48}O_2F_2$: 466.362 (M^+) Found: 466.362. ^{1}H-NMR ($CDCl_3$) δ: 4.37 (s, 1H), 2.38 (s, 3H), 2.26-2.52 (m, 2H), 2.19 (s, 3H), 2.10 (s, 3H), 0.95-1.75 (m, 24H), 0.87 (d, 6H, *J*= 6.8 Hz), 0.85 (d, 3H, *J*= 6.8 Hz), 0.84 (d, 3H, *J*= 6.8 Hz). ^{19}F-NMR ($CDCl_3$) ppm: –16.7 (dd, 2F, *J*= 30.8, 15.0 Hz).

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