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FULL PAPER

Synthesis and Liver Microsomal Metabolic Stability Studies of a Fluoro-Substituted δ-Tocotrienol Derivative

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Abstract: A fluoro-substituted δ-tocotrienol derivative, DT3-F2, was synthesized. This compound was designed to stabilize the metabolically labile terminal methyl groups of δ-tocotrienol by replacing one C-H bond on each of the two methyl groups with a C-F bond. However, *in vitro* metabolic stability studies using mouse liver microsomes revealed an unexpected rapid enzymatic C-F bond hydrolysis of DT3-F2. To the best of our knowledge, this is the first report of an unusual metabolic hydrolysis of allylic C-F bonds.

Introduction

Naturally occurring Vitamin E has two major forms, tocotrienols and tocopherols, both of them have α-, β-, γ-, and δ-homologues and share a common 6-hydroxychroman moiety. The difference between these two forms is that tocotrienols have an unsaturated farnesyl side chain while tocopherols bear a saturated phytyl side chain.[1] Although structurally closely related, tocotrienols, especially γ- and δ-tocotrienol (Figure 1), are often more potent than tocopherols in many biological effects and have unique bioactivities that are not observed with tocopherols.[1] However, both γ- and δ-tocotrienol have low bioavailability and short plasma elimination half-lives,[2] which limit their exposure in systemic circulation and require administration of large doses to be effective *in vivo*.[3,4] It is believed that the low bioavailability and short elimination half-lives of tocotrienols are, at least in part, caused by rapid liver metabolism.[5] The major metabolic pathway of tocotrienols is the CYP450 ω-hydroxylase pathway where ω-hydroxylation is the rate-limiting metabolic step (Figure 1),[6–8] indicating that the terminal C-H bonds on the farnesyl side chain are the potential metabolic labile site.

The unique physicochemical properties of fluorine have rendered it an important element that can be incorporated into bioactive molecules to improve bioactivity, physicochemical and/or pharmacokinetic properties.[9,10] Over 150 fluorine-containing drugs have reached market since the first approval of fludrocortisone by the FDA in 1955.[11–13] A widely used strategy in drug design is to replace a metabolically labile C-H bond with a strong C-F bond to slow down CYP450 mediated metabolism.[13]

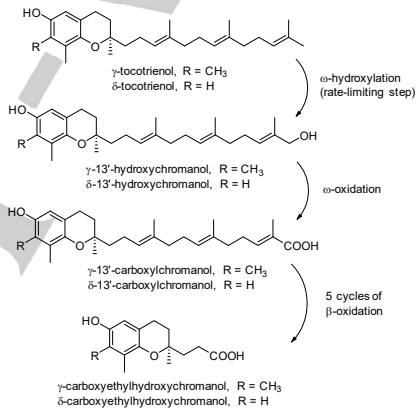


Figure 1. CYP450 ω-hydroxylase metabolic pathway of tocotrienols.

In an attempt to improve the metabolic stability of δ-tocotrienol, herein, we report the synthesis of DT3-F2 ((*R*)-2-((3*E*,7*E*)-13-fluoro-12-(fluoromethyl)-4,8-dimethyltrideca-3,7,11-trien-1-yl)-2,8-dimethylchroman-6-ol, **1**), in which two terminal hydrogen atoms on the side chain of δ-tocotrienol are replaced by two fluorine atoms (Figure 2). *In vitro* metabolic stability of **1** was evaluated using mouse liver microsomes and an unexpected, NADPH-independent, rapid hydrolysis of one or both C-F bonds of **1** was observed.

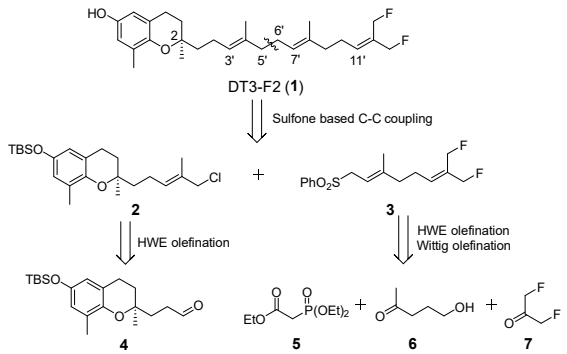
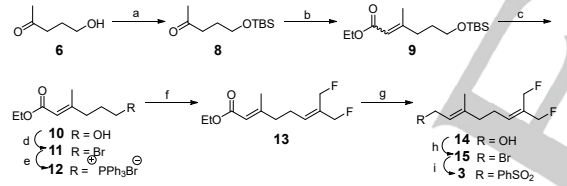


Figure 2. Initial retrosynthetic analysis of DT3-F2 (**1**).

Results and Discussion

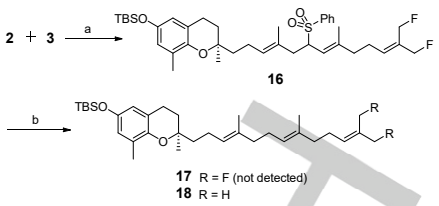
Synthesis of DT3-F2

Several synthetic strategies were investigated for the preparation of DT3-F2 (**1**). Our initial retrosynthetic analysis of **1** is delineated in Figure 2. It was envisioned that bond breakage at C5′-C6′ of **1** would lead to segments **2** and **3**, which could be connected through a sulfone based C-C coupling reaction. Segment **3** could be constructed from commercially available starting materials using Horner-Wadsworth-Emmons (HWE) and Wittig olefination reactions. We have previously reported the synthesis of chloride **2** via aldehyde **4** using δ-tocotrienol as a starting material.[14]



Scheme 1. Reagents and conditions: a) TBSCl, imidazole, DMF, rt, 50%; b) **5**, NaH, THF, 0 °C, 78% for *Z/E* mixture; c) *n*-$Bu_4N^+F^-$, THF, rt, 58% for *E* isomer; d) PPh_3, CBr_4, 0 °C, CH_2Cl_2, 95%; e) PPh_3, toluene, reflux, 90%; f) **7**, LiHMDS, THF, -78 °C-rt, 68%; g) DIBAL-H, CH_2Cl_2, -78 °C, 54%; h) PBr_3, THF 0 °C; i) sodium benzenesulfinate, DMF, rt, 70% (over 2 steps).

Synthesis of sulfone **3** started from commercially available 5-hydroxypentan-2-one (**6**). Protection of the hydroxyl group of **6** with *tert*-butyldimethylsilyl (TBS) gave compound **8**, which was converted to ester **9** as a mixture of *Z/E* isomers[15] in a ratio of ~1:2 (determined by GC-MS analysis). Removal of the TBS protection afforded the corresponding alcohols, from which the *E*-isomer **10** was isolated. Treating **10** with triphenylphosphine (PPh_3) and carbon tetrabromide (CBr_4), followed by heating with PPh_3 in toluene afforded phosphonium bromide **12**. Wittig olefination between ylide generated from **12** and 1,3-difluoroacetone (**7**) yielded ester **13**. Reduction of **13** with DIBAL-H to alcohol **14**, followed by converting to bromide **15** and treating with sodium benzenesulfinate in DMF, furnished sulfone **3** (Scheme 1).



Scheme 2. Reagents and conditions: a) *n*-BuLi, THF, HMPA, -78 °C, 83%; (b) $Pd(dppp)Cl_2$, $LiBHEt_3$, THF; or Na(Hg)/MeOH, THF; or Al(Hg)/MeOH, THF.

Coupling of **2**[14] and **3** yielded **16**. However, subsequent attempts to remove the phenylsulfonyl group of **16** using $LiBHEt_3$/palladium catalyst, sodium amalgam, or aluminum amalgam failed to produce the desired product **17**. Instead, compound **18** was obtained, where simultaneous desulfonylation and defluorination occurred. This is likely due to the two fluorine atoms are residing at the allylic position, making them good leaving groups under the reductive desulfonylation conditions (Scheme 2).

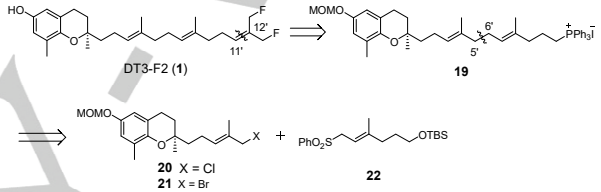
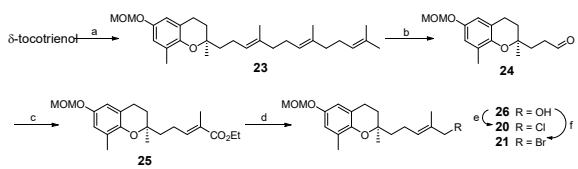


Figure 3. The second retrosynthetic analysis of DT3-F2 (**1**).

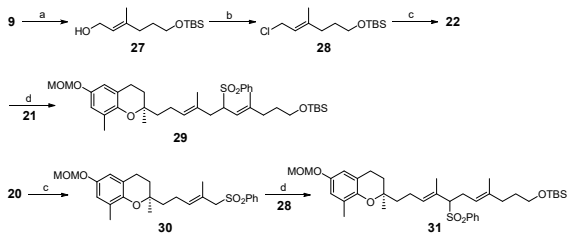
With the initial synthetic strategy unsuccessful, a second method was tested (Figure 3). As we learned from the previous method that the fluorine atoms at the allylic position cannot tolerate the reductive desulfonylation conditions, we decided to rearrange the reaction sequence. Disconnection at C11′-C12′ of **1** would lead to Wittig olefination partners **19** and **7**. Disconnection at C5′-C6′ of **19** would lead to chloride/bromide **20/21** and sulfone **22**.



Scheme 3. Reagents and conditions: a) MOMCl, NaH, DMF, 0 °C, 92%; b) i. OsO_4 (5 mol%), NMO (4 equiv), 2,6-lutidine (6 equiv), acetone/H_2O (10:1); ii. $PhI(OAc)_2$ (4 equiv), acetone/H_2O (10:1), rt, 64%; c) triethyl 2-phosphonopropionate, NaH, THF, 0 °C, 48% (*E*-isomer); d) DIBAL-H, CH_2Cl_2, -78 °C, 92%; e) Me_2S, NCS, CH_2Cl_2, 0 °C; f) i. $MeSO_2Cl$, TEA, THF; ii. LiBr.

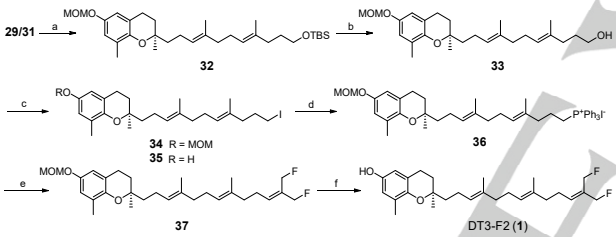
Compounds **20** and **21** were prepared in a similar way to the synthesis of **2**.[14] Briefly, the OH group of δ-tocotrienol was initially protected with a methoxymethyl (MOM) group to afford **23**, which was followed by double bond cleavage to form aldehyde **24** and transformation into α,β-unsaturated esters with *E*-isomer **25** as the major product (*Z/E* ratio of ~1:9, according to GC-MS). Reduction of **25** with DIBAL-H gave alcohol **26**, which was converted into chloride **20** and bromide **21** by standard methods

(Scheme 3). Sulfone **22** was synthesized via a three-step process starting with reduction of **9** (Scheme 1) to alcohol and isolation of the *E*-isomer **27**, followed by chlorination and treatment with sodium benzenesulfinate (Scheme 4).



Scheme 4. Reagents and conditions: a) DIBAL-H, CH_2Cl_2, -78 °C, 63%; b) i. $MeSO_2Cl$, TEA, THF; ii. LiCl; c) sodium benzenesulfinate, DMF, rt, (55% over two steps from alcohol); d) *n*-BuLi, THF/HMPA, -78 °C, 59%.

Unexpectedly, coupling between chloride **20** and sulfone **22** under the same reaction condition used in Scheme 2 did not yield any product. However, the reaction proceeded smoothly when **20** was replaced by bromide **21** to form **29**. Alternatively, we converted **20** into sulfone **30** and coupled with **28** to form **31** (Scheme 4).



Scheme 5. Reagents and conditions: a) $LiBH(Et)_3$, $Pd(dppp)Cl_2$, THF, 90%; b) *n*-Bu4N$^+$F$^-$, THF, 94%; c) i. $MeSO_2Cl$, TEA, THF; ii. NaI, acetone, 89% (over 2 steps); (d) PPh_3, toluene, reflux; (e) **7**, *n*-BuLi, THF, -78 °C, 51% (over 2 steps); (f) 1N HCl in 1,4-dioxane, MeOH, 94%.

The assembled intermediates **29** and **31** were subjected to desulfonylation to afford compound **32** (Scheme 5). Removal of the TBS protection of **32** gave the alcohol **33**, which was then converted to the corresponding iodide **34**. We observed that the MOM group could be removed during the course of iodization when the reaction was allowed to stir for an extended period of time, giving **35** as a byproduct. Indeed, MOM de-protection has been reported under NaI/acetone in the presence of a catalytic amount of acid.[16] Treatment of iodide **34** with PPh_3 in toluene under reflux yielded the Wittig salt **36**, which was coupled with 1,3-difluoroacetone (**7**) to afford **37**. The final product, DT3-F2 (**1**) was obtained upon removal of the MOM group of **37**.

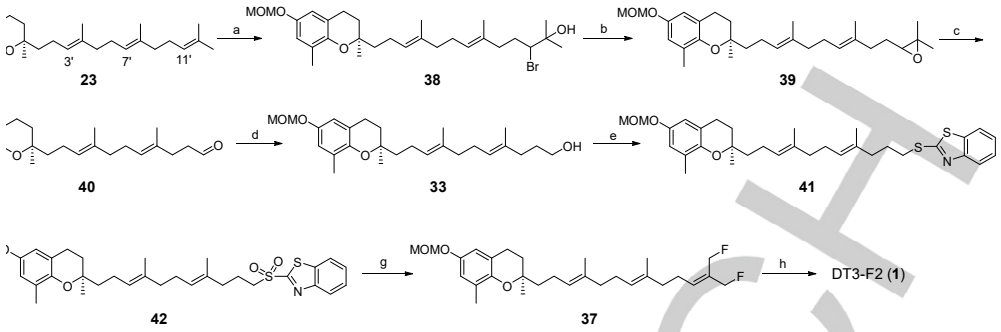
However, the synthetic route for **1** was lengthy with over 10 steps and an overall yield of ~6%. In addition, highly toxic reagent, OsO_4, was used for the side chain cleavage reaction.[14] These disadvantages in this synthetic method prompted the development of an alternative route. We envisioned that selective cleavage of the C11′-C12′ double bond of δ-tocotrienol would lead to a fragment that is ready to be coupled with 1,3-difluoroacetone (**7**). The major challenge for this synthetic strategy, however, is to achieve the regioselective cleavage of the C11′-C12′ double bond with all three double bonds in the farnesyl side chain having similar chemical environment. To this end, we initially tried the NMO/OsO_4 and *m*-CPBA oxidative systems, in attempts to selectively convert C11′-C12′ to a vicinal diol or an epoxide, which can then be cleaved to aldehyde or ketones by oxidants like HIO_4 and $Pb(OAc)_4$.[17] However, neither of these methods gave satisfactory results. To our delight, when we used a condition modified from a previously reported method,[17] treatment of MOM-protected δ-tocotrienol (**23**) with NBS and H_2O in THF at 0 °C, the desired bromohydrin compound **38** was produced (Scheme 6). The optimal ratio between THF and H_2O was studied in order to maximize the region-selectivity and yield. A THF/H_2O ratio of 10/1 and a substrate **23** concentration at ~9 mmol/L gave the best result. Treatment of bromohydrin **38** with K_2CO_3 formed epoxide **39**, which was subsequently treated with HIO_4 to give aldehyde **40**. Reduction of **40** afforded alcohol **33**, which could be converted to the final product by following the chemical transformations in Scheme 5.

The preparation of phosphonium salt **36** (Scheme 5) requires heating **34** with PPh_3 in toluene for a long period of time, resulting in a low yield of compound **37**. Alternatively, we converted alcohol **33** to sulfide **41** and selectively oxidized the sulfur atom using H_2O_2 and ammonium molybdate to form sulfone **42**. The Julia-Kocienski olefination was carried out to couple **42** with 1,3-difluoroacetone (**7**) to afford **37** (Scheme 6). Through this method, DT3-F2 (**1**) was obtained in a ~17% overall yield.

In vitro metabolic stability test

In vitro metabolic stabilities of δ-tocotrienol and synthetic DT3-F2 (**1**) were tested in mouse liver microsomes using propranolol as a positive control (Table 1). A control without NADPH was also performed to reveal any NADPH independent enzymatic degradation or chemical instability. Both δ-tocotrienol and propranolol underwent degradation in the presence of NADPH but remained intact in the absence of NADPH, indicating that NADPH dependent enzymes (CYP450 enzymes) are responsible for their degradation. Unexpectedly, DT3-F2 (**1**) was exhausted (below detection limit) in the incubation mixture, regardless of the presence or the absence of NADPH (Table 1), suggesting factors other than CYP450 enzymes could be also involved in the decomposition of this compound.

To further investigate the rapid decomposition of DT3-F2 (**1**), we incubated DT3-F2 (**1**) with buffer (PBS) alone, inactivated mouse liver microsomes + buffer, mouse liver microsomes + buffer, or mouse liver microsomes + NADPH + buffer. As shown in Figure 4, DT3-F2 (**1**) was stable in buffer or inactivated mouse liver microsomes over the incubation time period, but decreased by ~50% after incubation with active mouse liver microsomes for 10 min. More degradation was observed when NADPH was present. It is worth to note that DT3-F2 (**1**) was stable during synthesis and purification processes and remained intact when stirred in 15% aqueous NaOH for 30 min (data not shown), thus ruling out the chemical instability of this compound during incubation. We also tested the stability of compound **3** (Scheme 1), which contains the ω,ω-difluoro function as in DT3-F2 and has good solubility in the reaction media, in the presence of nucleophilic sulfide



Scheme 6. Reagents and conditions: a) NBS/H_2O, THF, 0 °C, 40-60%; b) K_2CO_3, DMF, 60 °C; c) HIO_4, THF, H_2O, 34% (over 3 steps); d) $NaBH_4$, EtOH, 86%; e) i. $MeSO_2Cl$, TEA, THF 0 °C; ii. then 2-mercaptobenzothiazole, K_2CO_3, DMF, rt, 91% (over 2 steps); f) H_2O_2, $(NH_4)_6Mo_7O_{24}$•$4H_2O$, EtOH, rt, 85%; g) KHMDS, **7**, THF, -78 °C, 82%; h) 1 N HCl in 1,4-dioxane, MeOH, 94%.

Table 1. Metabolic Stability Assay Using Mouse Liver Microsomes.[a]

Compound	% remaining at 30 min[b]		In vitro half-life (min)	$Cl_{in,u}$ (µL/min/mg)[c]
	with NADPH	without NADPH		
Propranolol	14.5 ± 10.4	106.8 ± 8.9	25.0 ± 9.6	124.5 ± 39.9
δ-Tocotrienol	63.7 ± 6.7	100.0 ± 6.6	107.8 ± 17.2	5240 ± 819.7
DT3-F2 (**1**)	0[d]	0[d]	--	--

[a] The concentration of the compounds for the assay was 1 µM. [b] Data are presented as Mean ± SD, n ≥ 3. [c] $Cl_{in,u}$ calculation follows the literature.[18] [d] Below instrument detection limit.

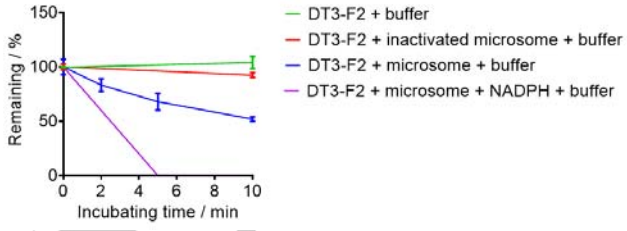


Figure 4. Stability of DT3-F2 when incubated under four different conditions at 37 °C. 1 µM of DT3-F2 was incubated with conditions shown in the legend, percent of compound remaining was determined by comparing with compound concentration at 0 min. Buffer is PBS; compound is DT3-F2; inactivated microsomes was prepared by heating in boiling water for 10 min. Error bars represent Means ± SD, n = 3.

N-acetyl cysteine (NAC) No reaction between compound **3** and NAC was observed under our experimental conditions (see Figure S2, Supporting Information). These observations led us to believe that NADPH independent enzymatic degradation processes might play a role in the decomposition of DT3-F2 (**1**) in mouse liver microsomes.

To detect and identify metabolites, we incubated DT3-F2 (**1**) in mouse liver microsomes (no NADPH added) and monitored the reaction with HPLC-UV-MS at 0 min, 10 min, and 30 min (Figure 5A). As shown in the chromatogram, a new peak (peak **b**) with a retention time of ~13 min appeared after 10 min of incubation and grew in intensity after 30 min of incubation, indicating that peak **b** is related to DT3-F2 (**1**). ESI-MS of DT3-F2 (**1**) (peak **a**) gave two major mass peaks at *m/z* 411 and *m/z* 391, which correspond to the $[M\text{-}H\text{-}HF]^-$ ion and $[M\text{-}H\text{-}2HF]^-$ ion, respectively (Figure 5B). The ESI-MS of peak **b** gave two mass peaks at *m/z* 409 and *m/z* 429, which could belong to **M1**, a mono-hydrolyzed product of DT3-F2 (**1**) (Figure 5B). However, because the two fluorine atoms of DT3-F2 (**1**) are not symmetrical, we were interested to explore 1) which C-F bond was hydrolyzed? 2) does peak **b** contain a pair of co-eluting *Z*/*E* isomers? 3) can both C-F bonds be hydrolyzed

to form compound **M2** (Figure 6) if the incubation time is longer? and 4) is the current method sensitive enough to detect small amount of **M2**?

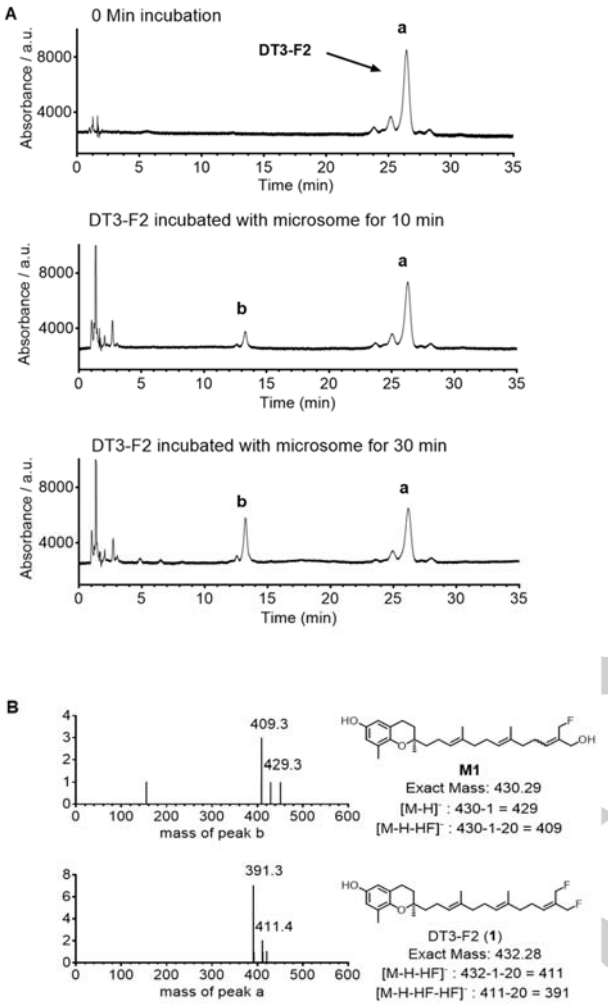


Figure 5. LC (reversed-phase)-UV-MS analyses of DT3-F2 (**1**) incubating with mouse liver microsomes. Peak **b** is the new peak after incubating DT3-F2 with mouse liver microsomes; peak **a** is DT3-F2.

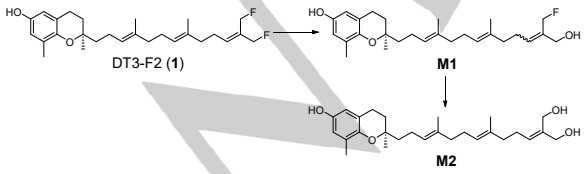


Figure 6. Proposed hydrolysis pathway of DT3-F2 (**1**).

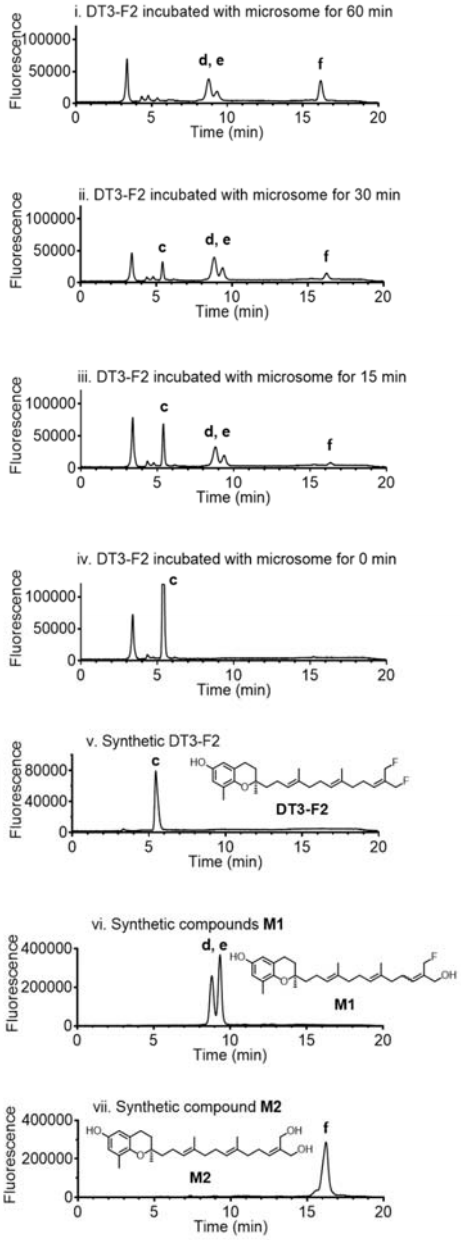


Figure 7. Incubation of DT3-F2 (1) with mouse liver microsomes for indicated time and the metabolites were monitored by using a normal phase LC-fluorescence detection system.

To address these questions, the proposed C-F bond hydrolysis products, **M1** and **M2**, of DT3-F2 (**1**) in mouse liver microsomes were synthesized (See supporting information for the synthesis). Interestingly, **M2**, also known as δ-amplexichromanol, is a natural product present in the stem bark of *Garcinia amplexicaulis*, a shrug found in New Caledonia.[19,20] To the best of our knowledge, the synthesis of this natural product has never been reported. Normal phase chromatography and fluorescence detection ($\lambda_{excitation}$ = 292 nm, $\lambda_{emission}$ = 330 nm) was used for better separation of *Z/E* isomers and improved detection limits. DT3-F2

(**1**) was incubated in mouse liver microsomes for a 60 min period and aliquots of the incubation mixture were analyzed at 0 min, 15 min, 30 min, and 60 min. The DT3-F2 (**1**) peak (peak **c**, Figure 7) decreased over the incubation period and was no longer detectable at 60 min. Peaks **d**, **e**, and **f** (Figure 7) emerged at 15 min and peak **f** grew over time, suggesting that these new peaks correspond to products of DT3-F2 (**1**). Since these product peaks were observable by fluorescence, this further suggests that the chromane ring is still intact with these compounds. Comparing with our synthetic compounds **M1** and **M2**, we found that **M1**, a mixture of *Z/E* isomers, have the same retention times as peaks **d** and **e** (Figure 7), and **M2** has the same retention time as peak **f**, confirming that DT3-F2 (**1**) was initially hydrolyzed to mono-hydroxyl compounds **M1** and then to bis-hydroxyl compound **M2** (Figure 6). Normal phase columns appear to have better separation capability for *Z/E* isomers,[21] as the mixture of two mono-hydroxyl compounds was shown as a single peak under reversed-phase conditions. The two mono-hydroxyl compounds were in different amounts, suggesting some degree of stereoselectivity of the hydrolase(s) involved.

Conclusions

Fluoro-substituted δ-tocotrienol, DT3-F2 (**1**), was synthesized and evaluated for its *in vitro* metabolic stability using mouse liver microsomes. We found that the C-F bonds of DT3-F2 (**1**) were rapidly hydrolyzed to hydroxyl compounds by microsomes in a NADPH independent manner. The instability of DT3-F2 (**1**) could be due to the fluorine atoms reside at the allylic positions.[22] A literature survey failed to find any reports on stability studies of allylic fluorine derivatives. Thus, to the best of our knowledge, our study revealed, for the first time, that fluorine atoms at the allylic position are susceptible to enzymatic hydrolysis. However, it is unclear whether such hydrolysis could occur in other substrates that contain C-F bond(s) at the allylic position. Studies on benzylic fluorides have been shown that hydrogen-bond donor (HBD) solvents such as water can stabilize the leaving fluoride anion by strong solvation thus facilitate nucleophilic substitutions.[23] We tested our model compound **3** under the same conditions and found that compound **3** was able to react with morpholine in HBD solvents at 70 °C (see Figure S3, Supporting Information). It is likely that metabolic enzymes in the microsomes can further reduce the reaction energy thus favor a rapid hydrolysis at 37 °C. It would be interesting to find the enzymes that are responsible for this reaction. It would also be interesting to investigate the stability of the terminal methyl difluorinated or trifluorinated δ-tocotrienol derivatives and identify specific enzyme(s) in liver microsomes that mediate the hydrolysis. Nevertheless, our study provided another cautionary tale about the potential liability of fluorine-containing compounds.[22]

Experimental Section

Chemistry

General methods: δ-Tocotrienol was separated from DeltaGold® using flash column chromatography with silica gel (230-400 mesh) as the stationary phase. Gradient elution was performed with ethyl acetate and hexanes (20/1 to 10/1). DeltaGold® was obtained from American River Nutrition, Inc. THF, CH_2Cl_2, toluene, and DMF were used from a solvent purification system. All other reagents and solvents obtained from commercial sources were used without further purification. If dry and air-free conditions were required, reactions were performed in oven-dried glassware (130 °C) under a positive pressure of argon. Flash chromatography was performed using silica gel (230-400 mesh) as the stationary phase. Reaction progress was monitored by TLC (silica-coated glass plates) and visualized after *p*-anisaldehyde stain solution (recipe: 135 mL alcohol + 5 mL H_2SO_4 + 3.7 mL p-anisaldehyde + 1.5 mL glacial acetic acid) staining, or by GC-MS (Agilent, 5975 series system) or TLC-MS (Advion). NMR spectra were recorded in $CDCl_3$ at 400 MHz for ^{1}H, 100 MHz for ^{13}C NMR, and 600 MHz for ^{19}F NMR. Chemical shifts δ are given in ppm using tetramethylsilane as an internal standard. Multiplicities of NMR signals are designated as singlet (s), broad singlet (*br* s), doublet (d), doublet of doublets (dd), triplet (t), quartet (q), and multiplet (m). MS were recorded on a GC-MS (EI) or Advion Express (APCI or ESI) instrument.

Experimental data for Scheme 1

5-((*tert*-Butyldimethylsilyl)oxy)pentan-2-one (8): To a stirring solution of 5-hydroxypentan-2-one (2.65 g, 25.9 mmol) in CH_2Cl_2 (10 mL) was added imidazole (2.7 g, 39.7 mmol) and TBSCl (3.0 g, 19.8 mmol). The resulting mixture was stirred at room temperature overnight, followed by condensation under vacuum. The crude product was chromatographed on silica gel to afford the title compound (2.8 g, 65% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.60 (t, *J* = 6.0 Hz, 2H), 2.50 (t, *J* = 7.2 Hz, 2H), 2.14 (s, 3H), 1.85-1.70 (m, 2 H), 0.88 (s, 9H), 0.03 (s, 6H).

Ethyl (*E*)-6-hydroxy-3-methylhex-2-enoate (10): To a stirring suspension of NaH (60%, 833 mg, 20.8 mmol) in THF at 0 °C was added ethyl 2-(diethoxyphosphoryl)acetate (4 g, 17.9 mmol). The resulting mixture was stirred at 0 °C for 1 h. Compound **8** (3 g, 13.9 mmol) was added to the mixture dropwise. After stirring at room temperature overnight, aqueous NH_4Cl solution was added and the mixture was extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and condensed to give a crude product, which was chromatographed on silica gel (hexanes/ethyl acetate 30:1) to afford compound **9** (3.1 g, 78% yield) as a mixture of *Z/E* isomers (~1:2, GC-MS). To a solution of **9** (4 g, 14.0 mol) in THF (15 mL) was added TBAF•3H_2O (8.8 g, 27.9 mmol) at 0 °C. After stirring at 0 °C for 2 h, water was added and the mixture was extracted with ethyl acetate (40 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and condensed. The crude product was chromatographed on silica gel (hexanes/ethyl acetate 10:1-3:1) to afford the title compound (1.39 g, 58% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.64 (s, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.66-3.54 (m, 2H), 2.18 (t, *J* = 7.7 Hz, 2H), 2.12 (s, 3H), 1.75-1.63 (m, 2H), 1.22 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.84, 159.39, 115.73, 61.92, 59.54, 37.06, 30.20, 18.70, 14.25; GC-MS (EI) *m/z* 172.1 (M^+).

(*E*)-Ethyl-6-bromo-3-methyl-hex-2-enoate (11): CBr_4 (2.9 g, 8.7 mmol) was added to a stirring solution of compound **10** (1.5 g, 8.7 mmol) in CH_2Cl_2 (15 mL), followed by the addition of PPh_3 at 0 °C. The resulting mixture was stirred at 0 °C for 0.5 h, and water was added to quench the reaction. Upon partitioning of the mixture between water and CH_2Cl_2, the CH_2Cl_2 layer was collected, washed with water, dried over anhydrous Na_2SO_4, filtered, and condensed under vacuum to dryness. The crude product was chromatographed on silica gel to afford the title compound (1.9 g, 95% yield) as colorless oil.^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71 (s, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.40 (t, *J* = 6.6 Hz, 2H), 2.31 (t, *J* = 7.4 Hz, 2H), 2.17 (s, 3H), 2.11-1.99 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.43, 157.49, 116.53, 59.52, 38.91, 32.61, 30.16, 18.57, 14.25; GC-MS (EI) *m/z* 234.1/236.1 (M^+).

(*E*)-Ethyl-8-fluoro-7-(fluoromethyl)-3-methylocta-2,6-dienoate (13): To a stirring solution of compound **11** (178 mg, 0.76 mmol) in toluene (2 mL) was added PPh_3 (219.5 mg, 0.84 mmol). The resulting mixture was stirred under reflux for 2 days. Solvent was removed under vacuum and the

resulting solid was washed with diethyl ether for 3-5 times to afford compound **12** (270 mg, yield 72%) as white solid. m.p. 172-175 °C. Compound **12** (270 mg, 0.544 mmol) was dried under vacuum with heating and then suspended in THF (5 mL) and cooled down to -78 °C, LiHMDS (0.54 mL, 1M in THF, 0.544 mmol) was added dropwise. The resulting mixture was allowed to stir at -78 °C for 1 h, 1,3-difluoroacetone (0.047 mL, 0.65 mmol) was then added. After stirring at r.t. overnight, the reaction was quenched with aqueous NH_4Cl solution and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and condensed under vacuum. The crude product was chromatographed (hexanes/ethyl acetate 20:1-15:1) to afford the title compound (85.9 mg, 68% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (s, 1H), 5.69-5.65 (m, 1H), 4.99 (d, J = 47.7 Hz, 2H), 4.87 (d, J = 47.7 Hz, 2H), 4.15 (q, J = 7.1 Hz, 2H), 2.44-2.32 (m, 2H), 2.28-2.22 (m, 2H), 2.17 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.52, 157.65, 135.71(t, $^3J_{CF}$ = 7 Hz), 131.63 (t, $^2J_{CF}$ = 14 Hz), 116.40, 84.36 (d, $^1J_{CF}$ = 165 Hz), 77.36 (d, $^1J_{CF}$ = 162 Hz), 59.62, 40.00, 25.39, 18.62, 14.27; ^{19}F NMR (600 MHz, $CDCl_3$) δ -213.0 (tm, J = 48.0 Hz), -217.2 (t, J = 48.0 Hz); GC-MS (EI) *m/z* 232.0 (M^+).

(*E*)-8-Fluoro-7-(fluoromethyl)-3-methylocta-2,6-dien-1-ol (14): To a stirring solution of compound **13** (232 mg, 1.0 mmol) in CH_2Cl_2 (3 mL) was added DIBAL-H (2.5 mL, 1.2 M in toluene, 3.0 mmol) at -78 °C. The resulting mixture was stirred at -78 °C for 3 h before quenching with MeOH (2 mL). The mixture was poured into Rochelle solution (20 mL) and stirred at room temperature overnight until the mixture layered clearly. The organic phase was collected, dried over anhydrous Na_2SO_4, filtered, and condensed under vacuum. The crude product was chromatographed (hexanes/ethyl acetate 10:1-5:1) to afford the title compound (102 mg, 54% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90-5.80 (m, 1H), 5.46-5.37 (m, 1H), 4.99 (d, J = 48 Hz, 2H), 4.87 (d, J =48 Hz, 2H), 4.15 (d, J = 6.7 Hz, 2H), 2.38-2.26 (m, 2H), 2.13 (t, J = 7.5 Hz, 2H), 1.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.13, 137.33 (t, $^3J_{CF}$ = 5 Hz), 131.25 (t, $^2J_{CF}$ = 14 Hz), 124.7, 84.79 (d, $^1J_{CF}$ = 163 Hz), 77.71(d, $^1J_{CF}$ = 160 Hz), 59.44(t, $^3J_{CF}$ = 5 Hz), 38.82, 25.95, 16.42; ^{19}F NMR (600 MHz, $CDCl_3$) δ -212.0 (tm, J = 48.0 Hz), -216.7 (t, J = 48.0 Hz); GC-MS (EI) *m/z* 190.0 (M^+).

(*E*)-((8-Fluoro-7-(fluoromethyl)-3-methylocta-2,6-dien-1-yl)sulfonyl) benzene (3): To a solution of compound **14** (95 mg, 0.5 mmol) in THF (5 mL) was added PBr_3 (0.06 mL, 0.6 mmol) at 0 °C. After stirring at room temperature for 1 h, aqueous $NaHCO_3$ solution was added to quench the reaction. The resulting mixture was extracted with ethyl acetate for 3 times and the combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and condensed under vacuum to give a residue. The residue was stirred with $PhSO_2Na$ (98.4 mg, 0.6 mmol) in DMF at room temperature overnight, then partitioned between water and ethyl acetate. The organic phase was collected and washed with brine, dried over anhydrous Na_2SO_4, filtered, and condensed under vacuum. The crude product was chromatographed on silica gel to afford the title compound (110 mg, 70% yield over 2 steps) as light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92-7.50 (m, 5H), 5.84-5.74 (m, 1H), 5.21 (t, J = 7.9 Hz, 1H), 4.98 (d, J = 41.3 Hz, 2H), 4.86 (d, J = 41.2 Hz, 2H), 3.82 (d, J = 7.9 Hz, 2H), 2.30-2.18 (m, 2H), 2.11 (t, J = 7.4 Hz, 2H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.95, 138.76, 136.29 (t, $^3J_{CF}$ = 9 Hz), 133.65, 131.31(t, $^2J_{CF}$ = 14 Hz), 129.06, 128.41, 111.33 (d, $^3J_{CF}$ = 6 Hz,), 84.50 (d, $^1J_{CF}$ = 163 Hz), 77.47 (d, $^1J_{CF}$ = 162 Hz), 55.96, 38.89, 25.60, 16.16; ^{19}F NMR (600 MHz, $CDCl_3$) δ -212.7 (tm, J = 48.0 Hz), -216.9 (t, J = 48.0 Hz); GC-MS (EI) *m/z* 314.1 (M^+).

Experimental data for Scheme 3

(*R*)-6-(Methoxymethoxy)-2,8-dimethyl-2-((3*E*,7*E*)-4,8,12-trimethyltrideca-3,7,11-trien-1-yl)chromane (23): To a stirred suspension of NaH (60% in mineral oil, 1.1 g, 26.5 mmol) in DMF (20 mL) at 0 °C was added a solution of δ-tocotrienol (7 g, 17.7 mmol) in DMF. After bubbles production stopped, MOMCl (1.61 mL, 21.2 mmol) was added dropwise. After stirring at 0 °C for 2 h, saturated aqueous NH_4Cl was added and the resulting mixture was extracted with ether acetate (50 mL × 3). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and condensed under vacuum. The residue was purified by column chromatography on silica gel (hexanes/ethyl acetate 20:1~10:1) to afford the title compound (7.17 g, 92% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (d, J = 2.7 Hz, 1H), 6.61 (d, J = 2.8 Hz, 1H), 5.26-4.96 (m, 5H), 3.50 (d, J = 7.7 Hz, 3H), 2.74 (dd, J = 10.3, 4.2 Hz, 2H), 2.16 (s, 3H), 2.15-2.03 (m, 6H), 1.99 (dd, J = 8.1, 3.8 Hz, 4H), 1.86-1.71 (m, 2H), 1.69 (s, 3H), 1.67-1.63 (m, 1H), 1.63-1.53 (m, 10H), 1.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.74, 147.24, 135.24, 135.07, 131.35, 127.34, 124.52, 124.41, 124.31, 121.05, 117.38, 114.31, 95.45, 75.55, 55.91, 39.93, 39.84, 39.82, 31.43, 26.89, 26.72, 25.83, 24.21, 22.72, 22.30, 17.81, 16.31, 16.13, 16.02; GC-MS (EI) *m/z* 440.4 (M^+).

(*S*)-3-(6-(Methoxymethoxy)-2,8-dimethylchroman-2-yl)propanal (24): To a stirring solution of compound **23** (600 mg, 1.36 mmol) in acetone and water (15 mL/1.5 mL) was added NMO (718 mg, 6.14 mmol), 2,6-lutidine (876 mg, 8.19 mmol), and 2% aqueous OsO_4 (1.0 mL, 0.0816 mmol). The resulting mixture was stirred at room temperature overnight. $PhI(OAc)_2$ (2.20 g, 6.8 mmol) was added. After stirring for 2 h, the reaction was quenched with aqueous $NaSO_3$ solution, and starch KI testing paper was used to make sure the reaction is fully quenched. The mixture was then extracted with ethyl acetate (30 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and condensed under vacuum. The crude product was purified by silica gel column chromatography to afford the title compound (244 mg, 64% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 1H), 6.68 (s, 1H), 6.61 (s, 1H), 5.07 (s, 2H), 3.47 (s, 3H), 2.76 (dd, J = 13.7, 7.0 Hz, 2H), 2.61 (t, J = 7.5 Hz, 2H), 2.12 (s, 3H), 2.04 (dt, J = 14.8, 7.5 Hz, 1H), 1.90 (dt, J = 14.5, 7.5 Hz, 1H), 1.84-1.70 (m, 2H), 1.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.46, 150.01, 146.63, 127.33, 120.76, 117.52, 114.30, 95.32, 74.63, 55.89, 38.60, 32.42, 31.55, 23.73, 22.51, 16.33; MS (EI) *m/z* 278.1 (M^+).

Ethyl (*R*,*E*)-5-(6-(methoxymethoxy)-2,8-dimethylchroman-2-yl)-2-methylpent-2-enoate (25): To a stirring suspension of NaH (60% in mineral oil, 130 mg, 3.24 mmol) in THF was added triethyl 2-phosphonopropionate (0.56 mL, 2.59 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h, followed by adding compound **24** (600 mg, 2.16 mmol) in THF (15 mL). After stirring at 0 °C for an additional hour, the reaction was quenched by aqueous NH_4Cl solution and extracted with ethyl acetate (15 mL × 3). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, and condensed under vacuum. The crude product was purified with column chromatography on silica gel (hexanes/ethyl acetate 10:1~5:1) to afford the title compound (*E* isomer, 380 mg, 48% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83-6.74 (m, 1H), 6.68 (d, J = 2.5 Hz, 1H), 6.60 (d, J = 2.5 Hz, 1H), 5.08 (s, 2H), 4.18 (q, J = 7.2 Hz, 2H), 3.48 (s, 3H), 2.85-2.63 (m, 2H), 2.33 (dd, J = 15.9, 7.9 Hz, 2H), 2.14 (s, 3H), 1.83 (s, 3H), 1.82-1.71 (m, 3H), 1.70-1.60 (m, 1H), 1.31-1.25 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.23, 149.87, 146.91, 142.10, 127.90, 127.30, 120.84, 117.44, 114.27, 95.36, 75.11, 60.47, 55.87, 38.52, 31.50, 23.98, 23.07, 22.58, 16.27, 14.38, 12.31; GC-MS (EI) *m/z* 362.2 (M^+).

(*R*,*E*)-5-(6-(Methoxymethoxy)-2,8-dimethylchroman-2-yl)-2-methylpent-2-en-1-ol (26): To a stirring solution of compound **25** (16 mg, 0.044 mmol) in CH_2Cl_2 (2 mL) was added DIBAL-H (1.0 M in THF, 0.132 mL, 0.132 mmol) at -40 °C. After stirring at -40 °C for 1 h, MeOH was added dropwise to quench the reaction. The resulting mixture was poured into Rochelle solution (10 mL) and stirred overnight until the mixture was clearly layered. The organic phase was separated, dried over anhydrous Na_2SO_4, and condensed under vacuum. The crude product was purified by column chromatography on silica gel (hexanes/ethyl acetate 8:1~3:1) to afford the title compound (13 mg, 92% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (d, J = 2.6 Hz, 1H), 6.60 (d, J = 2.6 Hz, 1H), 5.42 (t, J = 6.8 Hz, 1H), 5.07 (s, 2H), 3.99 (s, 2H), 3.48 (s, 3H), 2.73 (dd, J = 11.8, 6.4 Hz, 2H), 2.23-2.11 (m, 5H), 1.85-1.73 (m, 2H), 1.66 (s, 3H), 1.64-1.53 (m, 2H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.80, 147.16, 134.93, 127.34, 126.33, 121.03, 117.43, 114.35, 95.46, 75.41, 69.10,

55.95, 39.55, 31.50, 24.17, 22.69, 21.97, 16.32, 13.68; GC-MS (EI) *m/z* 320.2 (M^+).

(*R*,*E*)-2-(5-Chloro-4-methylpent-3-en-1-yl)-6-(methoxymethoxy)-2,8-dimethylchromane (20): To a stirring solution of *N*-chlorosuccinamide (37.5 mg, 0.28 mmol) in CH_2Cl_2 (2 mL) was added Me_2S (23 µL, 0.309 mmol) at 0 °C. The resulting milky suspension was stirred at 0 °C for 20 min. A solution of alcohol **26** (45 mg, 0.141 mmol) in CH_2Cl_2 (0.5 mL) was then added. The resulting mixture was stirring at the same temperature until the reaction mixture turned clear. The reaction was then quenched with water and extracted with ethyl acetate (5 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and condensed under vacuum to dryness. The crude product was used in the next step without column purification.

(*R*,*E*)-2-(5-Bromo-4-methylpent-3-en-1-yl)-6-(methoxymethoxy)-2,8-dimethylchromane (21): To a stirring solution of alcohol **26** (65 mg, 0.203 mmol) in THF (3 mL) at 0 °C was added triethylamine (51 µL, 0.365 mmol) and methanesulfonyl chloride (24 µL, 0.305 mmol). The resulting mixture was stirred at 0 °C for 45 min. LiBr (44 mg, 0.508 mmol) was added to the mixture and stirred for an additional hour. The reaction was quenched with water, extracted with ethyl acetate (8 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and condensed under vacuum. The crude product was used in the next step without purification.

Experimental data for Scheme 4

(*E*)-6-((*tert*-Butyldimethylsilyl)oxy)-3-methylhex-2-en-1-ol (27): To a stirring solution of compound **9** (a mixture of *Z* and *E* isomers, *Z*/*E* = 1/2, 4.3 g, 15 mmol) in CH_2Cl_2 (5 mL) was added DIBAL-H (1.2 M in tolulene, 28 mL, 33 mmol) at -78 °C. The mixture was then warmed to room temperature and stirred overnight. MeOH was added to quench to the reaction and the mixture was then poured to Rochelle solution and stirred overnight until the mixture was clearly layered. The organic phase was separated, washed with brine, dried over anhydrous Na_2SO_4, filtered, and condensed under vacuum. The crude product was purified by column chromatography on silica gel (hexanes/ethyl acetate 10:1~5:1) to afford the *E* isomer **27** (2.3 g, 63% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.40 (t, *J* = 6.9 Hz, 1H), 4.12 (d, *J* = 6.9 Hz, 2H), 3.58 (t, *J* = 6.5 Hz, 2H), 2.08-1.94 (m, 2H), 1.70-1.53 (m, 5H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.51, 123.50, 62.86, 59.41, 35.85, 31.00, 26.05, 18.43, 16.36, -5.17; GC-MS (EI) *m/z* 244.1 (M^+).

(*E*)-*tert*-Butyldimethyl((4-methyl-6-(phenylsulfonyl)hex-4-en-1-yl)oxy)silane (22): To a stirring solution of compound **27** (440 mg, 1.80 mmol) in THF (10 mL) was added triethylamine (0.376 mL, 2.70 mmol) and methanesulfonyl chloride (0.167 mL, 2.16 mmol) at 0 °C. After stirring at this temperature for 1 h, LiCl (191 mg, 4.5 mmol) was added and the resulting mixture was allowed to stir for 2 h. The reaction was quenched with water and extracted with ethyl acetate (15 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and condensed under vacuum. The crude chloride product **28** was used in the next step without purification. To a solution of **28** in DMF (10 mL) was added sodium benzenesulfinate (266 mg, 1.62 mmol). The resulting mixture was stirred at room temperature overnight. Water was added to the reaction and the mixture was then extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and condensed under vacuum. The crude product was purified with column chromatography on silica gel (hexanes/ethyl acetate 10:1) to afford the title compound (364 mg, 55% yield over 2 steps) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90-7.45 (m, 5H), 5.19 (t, *J* = 8.0 Hz, 1H), 3.80 (d, *J* = 8.0 Hz, 2H), 3.55 (t, *J* = 6.4 Hz, 2H), 2.09-1.95 (m, 2H), 1.57-1.46 (m, 2H), 1.30 (s, 3H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.50, 138.78, 133.64, 129.08, 128.64, 110.37, 62.67, 56.21, 36.07, 30.97, 26.05, 18.43, 16.31, -5.15; GC-MS (EI) *m/z* 368.1 (M^+).

***tert*-Butyl(((4*E*,8*E*)-11-((*R*)-6-(methoxymethoxy)-2,8-dimethylchroman-2-yl)-4,8-dimethyl-7-(phenylsulfonyl)undeca-4,8-dien-1-yl)oxy)dimethylsilane (29):** To a stirred solution of compound **22** (50 mg, 0.136 mmol) in THF/HMPA (5 mL/1mL) was added *n*-BuLi (1.6 M in hexane, 0.127 mL, 0.2 mmol) at -78 °C. After stirring at the same temperature for 45 min, a solution of bromide **21** (prepared from 58.5 mg of corresponding alcohol) in THF (0.5 mL) was added. After stirring at -78 °C for 1 h, the reaction was quenched with aqueous NH_4Cl solution and extracted with ethyl acetate (10 mL × 3). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, and condensed under vacuum. The crude product was purified by silica gel column chromatography (hexanes/ethyl acetate 8:1) to afford the title compound (53 mg, 59% yield) as a mixture of two diastereomers which was subject to desulfonylation in the next step.

(*R*,*E*)-6-(Methoxymethoxy)-2,8-dimethyl-2-(4-methyl-5-(phenylsulfonyl)pent-3-en-1-yl)chromane (30): To a stirred solution of compound **20** (prepared from 56 mg alcohol compound **26**) in DMF (6 mL) was added sodium benzenesulfinate (29 mg, 0.177 mmol). After stirring at room temperature overnight, water was added and the mixture was extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and condensed under vacuum. The crude product was purified by column chromatography on silica gel (hexanes/ethyl acetate 8:1) to afford the title compound (51 mg, 66% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.84-7.78 (m, 2H), 7.60-7.43 (m, 3H), 6.68 (d, *J* = 2.6 Hz, 1H), 6.60 (d, *J* = 2.6 Hz, 1H), 5.11-5.01 (m, 3H), 3.70 (s, 2H), 3.48 (s, 3H), 2.79-2.58 (m, 2H), 2.13-2.11 (s, 3H), 2.09-2.02 (m, 2H), 1.77-1.73 (m, 3H), 1.73-1.64 (m, 2H), 1.44-1.23 (m, 2H), 1.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 149.84, 146.95, 138.40, 136.32, 133.58, 128.97, 128.60, 127.23, 123.48, 120.88, 117.43, 114.30, 95.38, 75.09, 66.35, 55.92, 38.71, 31.37, 24.06, 22.64, 22.58, 16.56, 16.27; GC-MS (EI) *m/z* 444.1 (M^+).

***tert*-Butyl(((4*E*,8*E*)-11-((*R*)-6-(methoxymethoxy)-2,8-dimethylchroman-2-yl)-4,8-dimethyl-7-(phenylsulfonyl)undeca-4,8-dien-1-yl)oxy)dimethylsilane (31):** To a stirred solution of compound **30** (50 mg, 0.112 mmol) in THF/HMPA (5 mL/1mL) was added *n*-BuLi (1.6 M in hexane, 0.127 mL) at -78 °C. After stirring at the same temperature for 45 min, a solution of chloride **28** (prepared from 58.5 mg corresponding alcohol) in THF (0.5 mL) was added dropwise. After stirring at -78 °C for 1 h, the reaction was quenched with aqueous NH_4Cl solution and extracted with ethyl acetate (10 mL × 3). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, and condensed under vacuum. The crude product was purified by silica gel column chromatography (hexanes/ethyl acetate 8:1) to afford the title compound (44 mg, 59% yield) as a mixture of two diastereomers which was subject to desulfonylation in the next step.

Experimental data for Scheme 5

***tert*-Butyl(((4*E*,8*E*)-11-((*R*)-6-(methoxymethoxy)-2,8-dimethylchroman-2-yl)-4,8-dimethylundeca-4,8-dien-1-yl)oxy)dimethylsilane (32):** To a stirring solution of compound **29** or **31** (50 mg, 0.075 mmol) in THF (5 mL) was added $Pd(dppp)Cl_2$ (26 mg, 0.045 mmol). The mixture was cooled to 0 °C and $LiBH(Et)_3$ (0.37 mL, 0.373 mmol) was added dropwise. After stirring at 0 °C for 15 min, the reaction was quenched with water and extracted with ethyl acetate (8 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and condensed under vacuum. The crude product was purified by column chromatography on silica gel (hexanes/ethyl acetate 20:1) to yield the title compound (35.6 mg, 90% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 6.68 (d, *J* = 2.8 Hz, 1H), 6.60 (d, *J* = 2.8 Hz, 1H), 5.16-5.09 (m, 2H), 5.08 (s, 2H), 3.58 (t, *J* = 6.6 Hz, 2H), 3.48 (s, 3H), 2.78-2.64 (m, 2H), 2.15 (s, 3H), 2.13-2.03 (m, 4H), 2.02-1.92 (m, 4H), 1.86-1.71 (m, 2H), 1.68-1.53 (m, 10H), 1.27 (s, 3H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 149.75, 147.26, 135.25, 134.81, 127.36, 124.40, 124.38, 121.07, 117.39, 114.32, 95.47, 75.57, 63.05, 55.94, 39.95, 39.83, 35.93,

31.44, 31.32, 26.75, 26.13, 24.22, 22.74, 22.31, 18.51, 16.33, 16.12, 16.04, -5.10; MS (APCI) *m/z* 531.0 $[M+H]^+$.

(4*E*,8*E*)-11-((*R*)-6-(Methoxymethoxy)-2,8-dimethylchroman-2-yl)-4,8-dimethylundeca-4,8-dien-1-ol (33): Method 1: To a stirring solution of compound **32** (93 mg, 0.175 mmol) in THF (2 mL) was added TBAF•H_2O (122 mg, 0.39 mmol). After stirring at room temperature overnight, the mixture was partitioned between ethyl acetate and water. The organic layer was collected, washed with brine, dried over anhydrous Na_2SO_4, filtered, and condensed under vacuum. The crude product was chromatographed on silica gel to afford the title compound (68 mg, 94% colorless). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 6.68 (d, *J* = 2.7 Hz, 1H), 6.60 (d, *J* = 2.7 Hz, 1H), 5.21-5.10 (m, 2H), 5.08 (s, 2H), 3.61 (t, *J* = 6.5 Hz, 2H), 3.48 (s, 3H), 2.73 (dd, *J* = 10.3, 4.0 Hz, 2H), 2.15 (s, 3H), 2.14-1.95(m, 8H), 1.85-1.71 (m, 2H), 1.70-1.62 (m, 3H), 1.60 (s, 3H), 1.59 (s, 3H), 1.58-1.50 (m, 1H), 1.42 (br, 1H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 149.73, 147.25, 135.08, 134.79, 127.35, 124.85, 124.56, 121.09, 117.40, 114.34, 95.47, 75.58, 62.94, 55.94, 39.87, 39.72, 36.12, 31.43, 30.85, 26.60, 24.23, 22.72, 22.30, 16.32, 16.00, 15.98; GC-MS (EI) *m/z* 416.3 (M^+).

(*R*)-2-((3*E*,7*E*)-11-Iodo-4,8-dimethylundeca-3,7-dien-1-yl)-6-(methoxymethoxy)-2,8-dimethylchromane (34): To a solution of alcohol **33** (30 mg, 0.072 mmol) in CH_2Cl_2 (2 mL) was added triethylamine (0.018 mL, 0.13 mmol) and then $MeSO_2Cl$ (8.36 µL, 0.11 mmol) dropwise at 0 °C. After stirring at 0 °C for 15 min, the reaction was quenched with water, extracted with ethyl acetate for 3 times. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and condensed under vacuum to afford a residue. The residue was dissolved in acetone (3 mL), sodium iodide (32.4 mg, 0.22 mmol) was then added. The resulting mixture was stirred under reflux for 3 h. After cooling down to room temperature, the mixture was partitioned between water and ethyl acetate. The organic layer was collected and washed with brine, dried over anhydrous Na_2SO_4, filtered, and condensed under vacuum to give a residue which was chromatographed on silica gel to afford the title compound (34 mg, 89% yield over 2 steps) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 6.68 (d, *J* = 2.9 Hz, 1H), 6.60 (d, *J* = 2.9 Hz, 1H), 5.14 (dd, *J* = 15.5, 7.1 Hz, 2H), 5.08 (s, 2H), 3.48 (s, 3H), 3.13 (dd, *J* = 8.0, 5.9 Hz, 2H), 2.73 (dd, *J* = 10.3, 4.1 Hz, 2H), 2.15 (s, 3H), 2.13-2.02 (m, 6H), 2.01-1.95 (m, 2H), 1.90 (dd, *J* = 14.3, 7.1 Hz, 2H), 1.85-1.70 (m, 2H), 1.68-1.62 (m, 1H), 1.62-1.55 (m, 7H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 149.75, 147.25, 134.99, 132.93, 127.34, 125.90, 124.64, 121.08, 117.39, 114.33, 95.47, 75.56, 55.94, 40.11, 39.89, 39.69, 31.69, 31.45, 26.60, 24.25, 22.74, 22.31, 16.34, 15.96 (2C), 6.83; GC-MS (EI) *m/z* 526.2 (M^+).

(*R*)-2-((3*E*,7*E*)-13-Fluoro-12-(fluoromethyl)-4,8-dimethyltrideca-3,7,11-trien-1-yl)-6-(methoxymethoxy)-2,8-dimethylchromane (37): Method 1: To a stirring solution of iodide **34** (34 mg, 0.065 mmol) in toluene (2 mL) was added PPh_3 (169 mg, 0.65 mmol). The mixture was allowed to stir under reflux overnight. Removal of the solvent under vacuum afforded an oil residue which was washed with diethyl ether for 3 times. The residue (**36**) was then dried and dissolved in THF (2 mL), upon cooling down to -78 °C, *n*-BuLi (1.6 M in hexane, 50 uL, 0.097 mmol) was added and the mixture was stirred at -78 °C for 45 min. 1,3-Difluoroacetone (**7**) (12.2 mg, 0.13 mmol) was then added and the resulting mixture was stirred for an additional 45 min. The reaction was then quenched with aqueous NH_4Cl solution and extracted with ethyl acetate. The combined organic layers were collected, washed with brine, dried over anhydrous Na_2SO_4, filtered, and condensed under vacuum. The crude product was chromatographed on silica gel to afford the title compound (15.7 mg, 51% yield over 2 steps) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 6.68 (d, *J* = 2.6 Hz, 1H), 6.60 (d, *J* = 2.7 Hz, 1H), 5.88-5.79 (m, 1H), 5.16-5.09 (m, 2H), 5.08 (s, 2H), 4.99 (d, *J* = 47.9 Hz, 2H), 4.86 (d, *J* = 47.9 Hz, 2H), 3.48 (s, 3H), 2.73 (dd, *J* = 8.1, 5.6 Hz, 2H), 2.32-2.20 (m, 2H), 2.17-2.01 (m, 9H), 2.00-1.93 (m, 2H), 1.85-1.69 (m, 2H), 1.66-1.51 (m, 8H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 149.75, 147.25, 137.88, 135.10, 133.61, 132.93, 127.36, 125.54, 124.53, 121.08, 117.40, 114.33, 95.48, 84.82 (d, $^1J_{CF}$ = 164 Hz), 77.6 (d,$^1J_{CF}$ = 170 Hz), 75.56, 55.96, 39.92, 39.70, 39.01, 31.44, 26.69, 26.23, 24.23, 22.73, 22.31, 16.33, 16.06, 16.02; ^{19}F NMR (600 MHz, $CDCl_3$) *δ* -211.8 (tm, *J* = 48.0 Hz), -216.8 (t, *J* = 48.0 Hz); MS (APCI) *m/z* 477.0 $[M+H]^+$.

(*R*)-2-((3*E*,7*E*)-13-Fluoro-12-(fluoromethyl)-4,8-dimethyltrideca-3,7,11 -trien-1-yl)-2,8-dimethylchroman-6-ol (DT3-F2, 1): To a stirring solution of compound **37** (20 mg, 0.049 mmol) in MeOH (1.5 mL) was added HCl (4.0 N in 1,4-dioxane, 0.5 mL). The resulting mixture was stirred at room temperature for 2 h. Saturated aqueous $NaHCO_3$ was added and the mixture was extracted with ethyl acetate for 3 times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and condensed under vacuum to give a residue which was chromatographed on silica gel to yield the title compound (17 mg, 94% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 6.47 (s, 1H), 6.38 (s, 1H), 5.88-5.79 (m, 1H), 5.17-5.08 (m, 2H), 4.99 (d, *J* = 47.7 Hz, 2H), 4.86 (d, *J* = 47.7 Hz, 2H), 4.13 (br, 1H), 2.73-2.65 (m, 2H), 2.32-2.21 (m, 2H), 2.15-2.00 (m, 9H), 2.00-1.92 (m, 2H), 1.82-1.70 (m, 2H), 1.63-1.50 (m, 6H), 1.57-1.50 (m, 2H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 147.84, 146.11, 137.88, 135.07, 133.62, 130.78, 127.50, 125.52, 124.55, 121.36, 115.75, 112.70, 84.85 (d, *J* = 166 Hz), 77.71 (d, 162 Hz), 75.44, 39.74, 39.69, 39.01, 31.50, 26.66, 26.24, 24.20, 22.61, 22.30, 16.21, 16.06, 16.00; ^{19}F NMR (600 MHz, $CDCl_3$) *δ* -211.8 (tm, *J* = 48.0 Hz), -216.8 (t, *J* = 48.0 Hz); MS (APCI) *m/z* 431.0 $[M-H]^-$.

Experimental data for Scheme 6

(4*E*,8*E*)-11-((*R*)-6-(Methoxymethoxy)-2,8-dimethylchroman-2-yl)-4,8-dimethylundeca-4,8-dienal (40): To a stirring solution of compound **23** (1.28 g, 2.9 mmol) in THF/H_2O (30 mL/3 mL) at 0 °C was added NBS (600 mg, 3.2 mmol) in portions within 2 h. The mixture was allowed to stir at 0 °C for an additional hour. Water was added and the resulting mixture was extracted with ethyl acetate for 3 times. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and condensed under vacuum to give a residue which was chromatographed on silica gel to afford **38** (730 mg, 47%). To a stirring solution of **38** (730 mg, 1.4 mmol) in DMF (15 mL) was added K_2CO_3 (470 mg, 3.4 mmol). The resulting mixture was stirred at 60 °C overnight. Upon cooling down to room temperature, the mixture was partitioned between water and ethyl acetate. The organic layer was collected and washed with brine, dried over sodium sulfate, filtered, and condensed under vacuum to give the crude epoxide **39**, which was used in the next step without further purification. To a solution of **39** obtained above in THF (10 mL) was added a solution of HIO_4 (294 mg, 1.29 mmol) in water (1 mL). After stirring at room temperature for 2 h, aqueous Na_2SO_3 solution was added and the resulting mixture was extracted with ethyl acetate for 3 times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and condensed under vacuum. The crude product was purified on silica gel to give the title compound (400 mg, 71% yield over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 9.73 (s, 1H), 6.68 (s, 1H), 6.60 (s, 1H), 5.13 (d, *J* = 6.4 Hz, 2H), 5.07 (s, 2H), 3.48 (s, 3H), 2.72 (t, *J* = 6.5 Hz, 2H), 2.49 (t, *J* = 7.5 Hz, 2H), 2.30 (t, *J* = 7.4 Hz, 2H), 2.15 (s, 3H), 2.13-2.02 (m, 4H), 1.97 (t, *J* = 7.4 Hz, 2H), 1.88-1.69 (m, 2H), 1.67-1.49 (m, 8H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 202.77, 149.74, 147.22, 134.90, 133.04, 127.31, 125.44, 124.64, 121.05, 117.38, 114.31, 95.44, 75.53, 55.91, 42.25, 39.86, 39.57, 31.95, 31.42, 26.58, 24.22, 22.70, 22.27, 16.30, 16.20, 15.96; GC-MS (EI) *m/z* 414.2 (M^+).

(4*E*,8*E*)-11-((*R*)-6-(Methoxymethoxy)-2,8-dimethylchroman-2-yl)-4,8-dimethylundeca-4,8-dien-1-ol (33): Method 2: To a solution of compound **40** (590 mg, 1.4 mmol) in ethanol was added $NaBH_4$ (191 mg, 5.2 mmol), the resulting mixture was partitioned between ethyl acetate and water after stirring at room temperature for 30 min. The organic layer was collected and washed with brine, dried over anhydrous Na_2SO_4, filtered, and condensed under vacuum to afford a residue which was chromatographed on silica gel to yield the title compound (500 mg, 86% yield). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 6.68 (d, *J* = 2.7 Hz, 1H), 6.60 (d, *J* = 2.7 Hz, 1H), 5.21-5.10 (m, 2H), 5.08 (s, 2H), 3.61 (t, *J* = 6.5 Hz, 2H), 3.48 (s, 3H), 2.73 (dd, *J* =

10.3, 4.0 Hz, 2H), 2.15 (s, 3H), 2.14-1.95(m, 8H), 1.85-1.71 (m, 2H), 1.70-1.62 (m, 3H), 1.60 (s, 3H), 1.59 (s, 3H), 1.58-1.50 (m, 1H), 1.42 (br, 1H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.73, 147.25, 135.08, 134.79, 127.35, 124.85, 124.56, 121.09, 117.40, 114.34, 95.47, 75.58, 62.94, 55.94, 39.87, 39.72, 36.12, 31.43, 30.85, 26.60, 24.23, 22.72, 22.30, 16.32, 16.00, 15.98; GC-MS (EI) *m/z* 416.3 (M^+).

2-(((4*E*,8*E*)-11-((*R*)-6-(Methoxymethoxy)-2,8-dimethylchroman-2-yl)-4,8-dimethylundeca-4,8-dien-1-yl)thio)benzothiazole (41): To a stirring solution of alcohol **33** (50 mg, 0.095 mmol) in THF (1.5 mL) was added triethylamine (25 µL, 0.14 mmol) and then $MeSO_2Cl$ (11.1 µL, 0.11 mmol). After stirring at 0 °C for 0.5 h, the mixture was partitioned between water and ethyl acetate. The organic layer was collected and washed with brine, dried over anhydrous Na_2SO_4, filtered, and condensed under vacuum to give a residue which was dissolved in DMF (2 mL). To the DMF solution was added 2-mercaptobenzolthiozole (22 mg, 0.13 mmol) and then K_2CO_3 (33 mg, 0.24 mmol). The mixture was allowed to stir at room temperature overnight and then partitioned between water and ethyl acetate. The organic layer was collected, washed with brine, dried over anhydrous Na_2SO_4, filtered, and condensed under vacuum to give the crude product which was purified by chromatography on silica gel to afford the title compound (62 mg, 91% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88-7.83 (m, 1H), 7.76-7.72 (m, 1H), 7.40 (ddd, *J* = 8.3, 7.3, 1.2 Hz, 1H), 7.27 (ddd, *J* = 8.2, 4.7, 1.0 Hz, 1H), 6.68 (d, *J* = 2.7 Hz, 1H), 6.59 (d, *J* = 2.7 Hz, 1H), 5.19-5.10 (m, 2H), 5.07 (s, 2H), 3.47 (s, 3H), 3.31-3.26 (m, 2H), 2.71 (dd, *J* = 10.5, 4.2 Hz, 2H), 2.19-2.05 (m, 9H), 1.88-2.00 (m, 4H), 1.81-1.67 (m, 2H), 1.66-1.51 (m, 8H), 1.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.43, 153.50, 149.73, 147.24, 135.30, 135.04, 133.49, 127.34, 126.10, 125.78, 124.59, 124.21, 121.57, 121.07, 121.02, 117.38, 114.32, 95.45, 75.55, 55.93, 39.90, 39.71, 38.59, 33.07, 31.41, 27.42, 26.65, 24.20, 22.72, 22.29, 16.33, 15.98, 15.94; MS ($APCI^+$) *m/z* 566.1 $[M+H]^+$.

2-(((4E,8E)-11-((R)-6-(Methoxymethoxy)-2,8-dimethylchroman-2-yl)-4,8-dimethylundeca-4,8-dien-1-yl)sulfonyl)benzo[d]thiazole (42): To a stirring solution of compound **41** (20 mg, 0.035 mmol) in EtOH (2 mL) was added ammonium molybdate (4.3 mg, 0.0035 mmol) and H_2O_2 (35%, 0.046 mL, 0.47 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 2-3 h. Saturated aqueous Na_2SO_3 solution was added and the mixture was then extracted with ethyl acetate for 3 times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and condensed under vacuum to give a residue which was chromatographed on silica gel to give the title compound (18 mg, 84% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24-8.19 (m, 1H), 8.03-7.99 (m, 1H), 7.67-7.57 (m, 2H), 6.68 (d, *J* = 2.7 Hz, 1H), 6.59 (d, *J* = 2.7 Hz, 1H), 5.11 (m, 2H), 5.07 (s, 2H), 3.48 (s, 3H), 3.46-3.41 (m, 2H), 2.76-2.67 (m, 2H), 2.14 (s, 3H), 2.13-2.01 (m, 6H), 1.96 (dd, *J* = 15.0, 7.9 Hz, 4H), 1.84-1.68 (m, 2H), 1.67-1.60 (m, 1H), 1.58 (s, 3H), 1.56-1.50 (m, 4H), 1.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.07, 152.87, 149.74, 147.25, 136.89, 134.90, 132.39, 128.12, 127.77, 127.35, 126.89, 125.59, 124.69, 122.48, 121.09, 117.39, 114.33, 95.47, 55.95, 54.08, 39.88, 39.61, 37.88, 31.41, 27.00, 26.62, 24.21, 22.73, 22.29, 20.42, 16.34, 15.97, 15.65; MS ($APCI^+$) *m/z* 598.8 $[M+H]^+$.

(*R*)-2-((3*E*,7*E*)-13-Fluoro-12-(fluoromethyl)-4,8-dimethyltrideca-3,7,11-trien-1-yl)-6-(methoxymethoxy)-2,8-dimethylchromane (37) method 2: To a stirring solution of compound **42** (15 mg, 0.025 mmol) in THF at -78 °C was added KHMDS (0.5 M in hexane, 75 µL, 0.038 mmol). After stirring at the same temperature for 45 min, 1,3-difluroacetone (**7**) (4.7 mg, 0.5 mmol) was added, the resulting mixture was stirred at -78 °C for an additional 45 min, and aqueous NH_4Cl solution was then added to quench the reaction. The mixture was partitioned between water and ethyl acetate. The organic layer was collected, washed with brine, dried over anhydrous Na_2SO_4, filtered, and condensed under vacuum to give crude product which was purified on silica gel to afford the title compound (9.8 mg, 82%).^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (d, *J* = 2.6 Hz, 1H), 6.60 (d, *J* = 2.7 Hz, 1H), 5.88-5.79 (m, 1H), 5.16-5.09 (m, 2H), 5.08 (s, 2H), 4.99 (d, *J* = 47.9 Hz, 2H), 4.86 (d, *J* = 47.9 Hz, 2H), 3.48 (s, 3H), 2.73 (dd, *J* = 8.1, 5.6 Hz, 2H), 2.32-2.20 (m, 2H), 2.17-2.01 (m, 9H), 2.00-1.93 (m, 2H), 1.85-1.69 (m, 2H), 1.66-1.51 (m, 8H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.75, 147.25, 137.88, 135.10, 133.61, 132.93, 127.36, 125.54, 124.53, 121.08, 117.40, 114.33, 95.48, 84.82 (d, $^1J_{CF}$ = 164 Hz), 77.6 (d,$^1J_{CF}$ = 170 Hz), 75.56, 55.96, 39.92, 39.70, 39.01, 31.44, 26.69, 26.23, 24.23, 22.73, 22.31, 16.33, 16.06, 16.02; ^{19}F NMR (600 MHz, $CDCl_3$) δ -211.8 (tm, *J* = 48.0 Hz), δ -216.8 (t, *J* = 48.0 Hz); MS (APCI) *m/z* 477.0 $[M+H]^+$.

Microsomal metabolic stability assay

Metabolic stability in microsomes with or without NADPH. A solution of the test compound in DMSO/ACN (V/V, 20/80) (1.64 µL 137.5 µM) was added to 178.4 µL mouse liver microsome suspension prepared by mixing mouse liver microsomes (Corning® Gentest™, 20 mg protein/mL) with EDTA (Corning® Gentest™, 0.5 M) and 758 µL potassium phosphate buffer (PBS, pH 7.4, 0.1 M) in a 25:2:765 ratio. After incubating at 37 °C for 30 min, 45 µL NADPH generating solution which was freshly prepared by mixing solution A ($NADP^+$; Glc-6-PO_4; $MgCl_2$, Corning® Gentest™), solution B (G_6PDH, Corning® Gentest™), and PBS (pH 7.4, 0.1 M) in a 5:1:14 ratio, was added to initiate the reaction. For control groups, equal volume of PBS buffer was added instead of NADPH generating solution. After incubation for 30 min, the reaction was quenched by adding 450 µL cold acetonitrile containing internal standard. The sample was then extracted with 900 µL hexane. The upper layer was transferred to a glass tube and dried under a stream of nitrogen and then reconstituted with 50 µL acetonitrile. An aliquot of this solution was then analyzed by HPLC-UV-MS. Propranolol was used as metabolism reference standard.

Comparing stability of DT3-F2 in PBS buffer, microsomes, microsomes+NADPH, and inactivated microsomes. A solution of DT3-F2 in DMSO/ACN (V/V, 20/80) (8.2 µL 137.5 µM) was added to 1117 µL PBS buffer, 28.2 µL microsomes + 1088.8 µL buffer, 28.2 µL microsomes + 225 µL NADPH + 863.7 buffer, or 28.2 µL inactivated microsomes + 225 µL NADPH + 863.7 buffer. The resulting mixtures were then incubated at 37 °C. 225 µL aliquots of the mixture were taken at 0 min, 2 min, 5 min, and 10 min and quenched with cold acetonitrile. The samples were then extracted with hexane, and the up-layers were transferred to newly labeled glass tubes and dried under a stream of nitrogen. The pellets were reconstituted with 50 µL acetonitrile and analyzed with LC-UV.

Stability of DT3-F2 in microsomes and comparing metabolites with synthetic compounds. A solution of DT3-F2 in DMSO/ACN (V/V, 20/80) (8.2 µL 1.375 mM) was added to 1117 µL microsome suspension. The resulting mixture was incubated at 37 °C and 225 µL aliquots quenched at 0 min, 15 min, 30 min, or 60 min by adding 450 µL cold acetonitrile. The mixture was extracted with 990 µL hexane and the up-layers were transferred to a glass tube and dried over nitrogen. The dried residue was reconstituted with acetonitrile and analyzed with LC-fluorescence. For comparison, the same analytic condition was applied to synthetic compounds **M1** and **M2**.

HPLC-UV-MS (Reversed Phase) and HPLC-fluorescence (Normal Phase) analysis. For LC-UV-MS analysis, Waters™ 2695 HPLC system and Betabasic™3.5 µm, 4.6 * 150 mm, C-18 column was used for the separation, Waters™ 2489 UV/Visible detector was used for UV detection with absorption wavelength set at 298 nm, Waters™ Q-Tof micro Mass Spectrometer was used for mass analysis. Mobile phase was 80% methanol/20% water containing 6 mM NH_4OH. Flow rate was set at 1 mL/min, injection volume was 20 µL. For LC-fluorescence analysis, Waters™ 2695 HPLC system and Astec CYCOBOND™ I 2000 HP-RSP, 5 µm, 25 cm *4.6 mm column were used for separation. Shimadzu® RF-10AXL fluorescence detector with excitation wavelength set at 292 nm and emission wavelength set at 330 nm was used for detection. Mobile phase was isopropanol and n-heptane with isopropanol/n-heptane ratio ranging from 5/95 to 95/5. Injection volume was 2 µL.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: tocotrienol • fluorination • metabolic stability • synthesis • C-F bond hydrolysis

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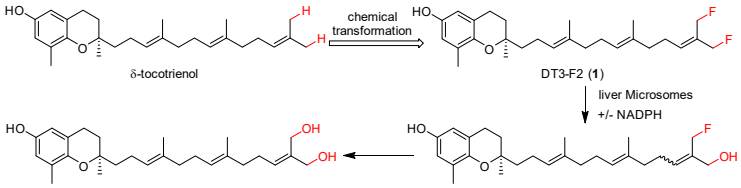

In an attempt to improve metabolic stability of δ-tocotrienol, we designed and synthesized DT3-F2 (**1**). However, subsequent *in vitro* metabolic studies using mouse liver microsomes revealed that the C-F bonds of DT3-F2 were rapidly hydrolyzed to form the hydroxyl metabolites. This unexpected C-F bond hydrolysis appeared to be enzymatic and NADPH-independent.