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Synthesis of 5-(Fluorophenyl)tocopherols as Novel Dioxin Receptor Antagonists

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γ-Tocopherol, a component of the essential nutrient mixture commonly designated as vitamin E, was chemically combined with differently substituted monofluoro- and difluorophenyl moieties to produce potential antagonists for the human aryl hydrocarbon receptor (AhR). 5-Iodo-γ-tocopherol was a very reliable starting material for the Pd-catalyzed reaction with (fluorophenyl)boronic acids (Suzuki coupling). The *ortho*- and *meta*-fluoro-substituted derivatives showed conformational isomerism due to restricted rotation around the interaromatic bond. This effect was investigated by NMR spectroscopy. Three of the derivatives showed very high potency in assays and are promising candidates for further testing.

Introduction

Vitamin E, containing compounds from the tocopherol and tocotrienol family,[1,2] is commonly known as a highly potent natural antioxidant that protects the integrity of tissues against reactive oxygen species.[3–7] Even nowadays, novel non-antioxidant functions of α-tocopherol (**1**), the main constituent of vitamin E, such as gene regulatory properties, cell signaling, and immunological actions, are being discovered.[8–10] The tocopherols are either produced synthetically on an industrial scale,[11–13] or are obtained by extraction of plant oils.[14] In research, tocopherol model compounds that feature a methyl group instead of the isoprenoid C_{16} side chain are frequently employed. This substitution does not alter the in vitro chemical behavior, yet it simplifies handling, crystallization, and analytics of the products (Figure 1).

The quest for novel tocopherol derivatives has intensified within the last decades and was either aimed at achieving special properties such as altered lipophilicity or oxidative lability or at combining the advantages of the vitamin (high oxidative efficiency, physiological compatibility, zero toxicity) with the properties of other chemical systems. Up to date, most alterations of the tocopherol moiety were

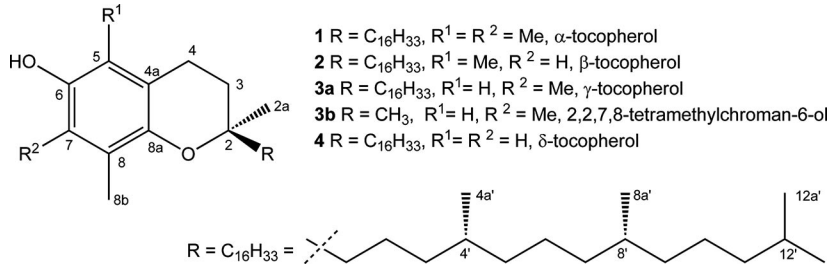

Figure 1. Structures of the four main tocopherol derivatives found in vitamin E (**1**, **2**, **3a**, **4**) and of γ-tocopherol model compound **3b** with a truncated side chain.

achieved by functionalization of the phenolic hydroxy group[1] or by modification of the lipophilic side chain,[15,16] but reports on other modifications of the core are scarce.[17]

Our research efforts were aimed at combining physiologically active moieties with the tocopherol system. In such derivatives, the tocopherol could act either as a lipophilic carrier or as a substance with an individual physiological effect. Of special interest was the aryl hydrocarbon receptor (AhR), also called dioxin receptor. The AhR protein is

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present in most cell and tissue types of the body and is classified as a member of the basic helix-loop-helix/Per-Arnt-Sim (bHLH/PAS) family of ligand-dependent transcription factors.[18–20] Normally inactive and bound to co-chaperones, AhR is activated by binding to ligands, such as environmental pollutants, carcinogens, and drugs. This action makes the chaperones dissociate and allows AhR to translocate into the nucleus.[21,22] Attachment of the receptor to ARNT (AhR nuclear translocator) forms a complex (AhR–ARNT) that binds to dioxin-responsive elements (DRE) and increases their gene transcription rate.[23–25]

Especially polycyclic aromatic hydrocarbons (PAHs) and halogenated aromatic carbons (PACs) have been identified as effective ligands (Figure 2) and their toxic nature, hepatotoxicity, immunotoxicity, and tumor promotion has been shown to be in direct correlation with their ability to bind to AhR.[26] All ligands identified so far comprise planar elements (aromatic systems) and possess some lipophilic character.[27]

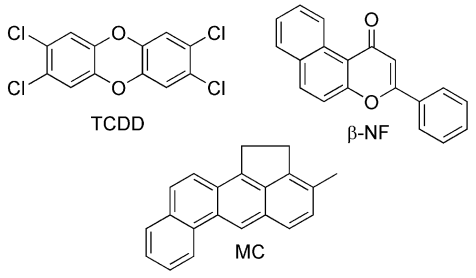


Figure 2. Typical ligands for AhR: 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), methylcholanthrene (MC), and β-naphthoflavone (β-NF).

Based on recent studies that identified *ortho*-(fluorophenyl)phenols as lead structures for AhR antagonists, we reasoned that by combining the antioxidative properties, the lipophilicity (effecting directed transport to the lipophilic action site), and the planar aromatic ring of tocopherol compounds with an additional fluorinated aromatic moiety attached to the chromanol unit would produce very suitable ligands for the AhR target. To test this hypothesis and to provide compounds for assay testing, we synthesized a small library of 5-substituted tocopherols, carrying mono- or difluorinated aromatic substituents. The synthetic approach and the interesting analytical properties of the products are communicated in the present report.

Results and Discussion

Previous studies on the synthesis of novel tocopherol derivatives and on comparative oxidation chemistry of tocopherols showed us an almost complete lack of reports on transition-metal-catalyzed coupling reactions with the aromatic ring of non-α tocopherols (α-tocopherol itself possesses no free aromatic position for such couplings). At first this was surprising, but it became understandable when we realized that 5-bromo-γ-tocopherol, the most obvious starting material, failed in all attempts in our hands. The compound was readily prepared by the reaction of γ-tocopherol with elemental bromine,[28] but showed no conversion under Grignard or Pd-catalyzed coupling reactions. To improve reactivity, the bromine substituent was replaced by the more reactive iodine: γ-tocopheryl acetate (**4a**) was iodinated with elemental iodine in the presence of silver trifluoroacetate according to a modified protocol of the Kumadaki group.[17] The novel *O*-acetyl-5-iodo-γ-tocopherol (**5a**) was recovered in 67% yield besides 4% of 3,4-dehydro-γ-tocopheryl acetate and 3% of unchanged starting material. The iodination reaction was also applied to model compound **4b**, which provided crystalline iodide derivative **5b**, the X-ray structure of which is shown in Figure 3.

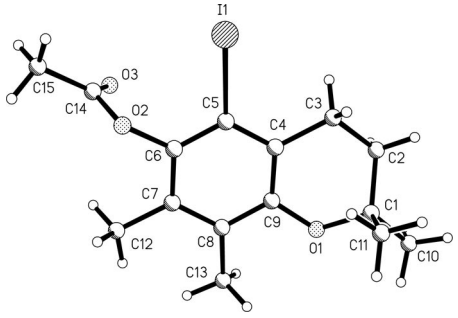


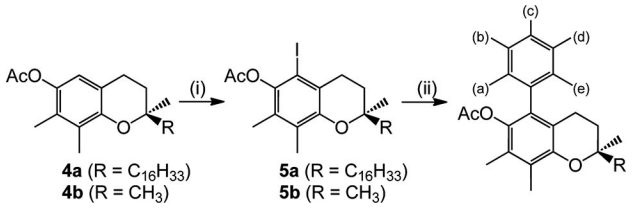
Figure 3. Molecular structure of 5-iodo-2,2,7,8-tetramethylchroman-6-yl acetate (**5b**).

Out of several preliminarily tested coupling procedures, Suzuki reactions – the Pd-catalyzed cross-coupling with phenylboronic acids – were evidently most promising with regard to further optimization towards better yields. Another practical advantage was that the starting materials required for the introduction of fluorophenyl residues, that is, (fluorophenyl)boronic acids, were commercially available. To boost the yield, various Suzuki coupling protocols were employed and the conditions varied; the progress of the reaction between *O*-acetyl-5-iodo-γ-tocopherol (**5a**) and phenylboronic acid was followed by GC–MS. According to the optimized protocol, 95% of 5-substituted tocopherol derivative **6a** was obtained when Pd(dppf)Cl_2·DCM was used as the catalyst and K_2CO_3 as auxiliary base, working in DMF at 80 °C. The addition of some percent of water to the solvent did not change the outcome of the reaction. Even when employing 4-hydroxyphenylboronic acid as a coupling partner, highly labile compound **7** was still obtained in 42%. 4-(Hydroxyphenyl)-γ-tocopherol (**7**) is a phenylogous 5-hydroxy-γ-tocopherol that is highly labile and very readily oxidized to the phenylogous 5,6-chromandione (α-tocored[29]).

With the optimized protocol in hand, a small library of monofluorophenyl and difluorophenyl tocopherol derivatives was established (Table 1), with all possible substitution patterns being included. The monofluoro derivatives (2-fluorophenyl: **8**, 3-fluorophenyl: **9**, 4-fluorophenyl: **10a** with isoprenoid side chain, **10b** with truncation of that chain) were produced smoothly, and only the low yield of the *ortho*-fluoro derivative was remarkable. It is plausible to evoke steric or electronic reasons for the limited success of

the coupling, although possible effects were not studied in detail. With two *ortho*-fluorinated substituents the effect was even more drastic, and no coupling reaction was observed; the 2,6-difluorophenyl derivative was the only of the six bisfluorinated compounds that could not be produced. The isolated yields of bisfluorinated compounds **11**–**15** were satisfying (39 to 70% yield).

Table 1. Preparation of iodide derivatives **5a** and **5b**, followed by Suzuki coupling with F-substituted phenylboronic acids.[a]



Entry		(a)	(b)	(c)	(d)	(e)	R	Yield [%]
1	**6a**	H	H	H	H	H	$C_{16}H_{33}$	95
2	**6b**	H	H	H	H	H	CH_3	83
3	**7**	H	H	OH	H	H	$C_{16}H_{33}$	42
4	**8**	F	H	H	H	H	$C_{16}H_{33}$	20
5	**9**	H	F	H	H	H	$C_{16}H_{33}$	33
6	**10a**	H	H	F	H	H	$C_{16}H_{33}$	95
7	**10b**	H	H	F	H	H	CH_3	75
8	**11**	H	F	F	H	H	$C_{16}H_{33}$	54
9	**12**	H	F	H	F	H	$C_{16}H_{33}$	60
10	**13**	F	H	F	H	H	$C_{16}H_{33}$	40
11	**14**	F	F	H	H	H	$C_{16}H_{33}$	43
12	**15**	F	H	H	F	H	$C_{16}H_{33}$	39
13	**16**	F	H	H	H	F	$C_{16}H_{33}$	no reaction

[a] Reaction conditions: (i) CF_3COOAg, I_2; (ii) Suzuki coupling.

Besides the expected complication of the nuclear magnetic resonance spectral assignment of the tocopherol derivatives due to the additional couplings with ^{19}F, we observed the existence of two conformational isomers (Figure 4) for all compounds that had *ortho*- and/or *meta*-substituents, that is, for all compounds except **10a** and **10b**, which have a *para*-F substituent. In these rotamers the rotation around the C5–C1′ bond that links the two phenyl units is restricted. Compound **12**, having a 3,5-difluorophenyl unit and thus two *meta*-F, is a special case. Due to the symmetric substitution pattern, the two conformers are identical and cannot be distinguished, but the compounds certainly experience rotational barriers similar to those of the other *ortho*- and *meta*-substituted derivatives. In the following, this behavior and the spectral implications are exemplified for tocopherol derivative **9**.

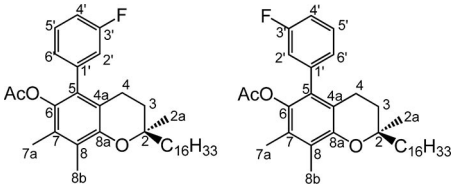


Figure 4. Two possible conformational isomers of 5-(3-fluorophenyl)-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)chroman-6-yl acetate (**9**).

For a detailed analysis and discussion of proton and carbon assignments refer to the Supporting Information. Assignment of the proton signals of the aromatic region of **9** was achieved with the help of ^{19}F decoupled NMR and noncoupled ^1H NMR spectroscopy. Proton 5-H′ appears as a triplet in the ^{19}F decoupled ^1H NMR spectrum at δ = 7.34 ppm with a coupling constant of 7.8 Hz (upper trace in Figure 5), and as a broad multiplet in the ^{19}F coupled spectrum (middle trace in Figure 5) because of the *meta*-coupling to the fluorine atom. The 4-H′ proton shows a homonuclear *ortho*-coupling $J_{H,H}$ to the 5-H′ proton, as a well as two homonuclear *meta*-couplings $J_{H,H}$ to 6-H′ and 2-H′, the former being similar to the heteronuclear *ortho*-$J_{H,F}$ coupling that becomes visible in the decoupled spectrum by the triplet-type splitting. The 6-H′ proton appears as a doublet and shows no detectable coupling to the fluorine atom in the ^{19}F coupled proton experiment. The 2-H′ proton appears as a broad singlet in the ^{19}F decoupled spectrum, and shows *ortho*-$J_{H,F}$ = 9.7 Hz in the nondecoupled spectrum. Carbon resonance assignment of the fluorophenyl substituent was supported by the HSQC spectrum (Figure 5, bottom trace) and crosschecked by HMBC experiments.

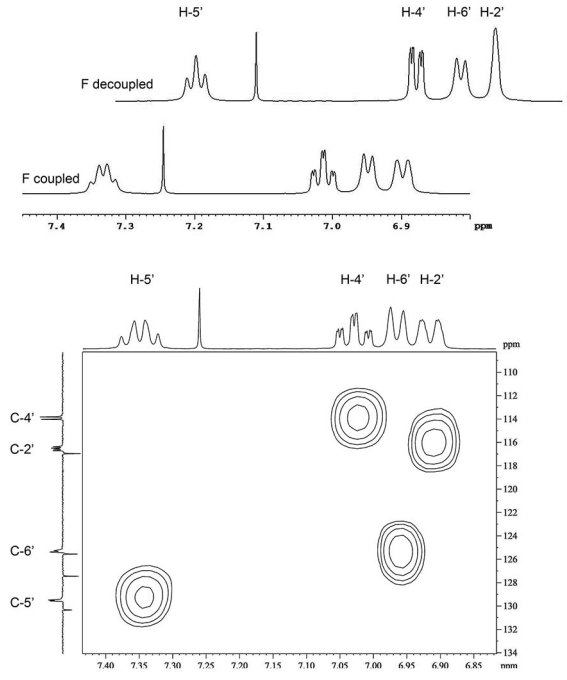


Figure 5. ^1H NMR spectrum with ^{19}F coupling (middle trace, 600 MHz) and ^{19}F decoupled (upper trace, 600 MHz) and HSQC spectrum of **9**.

While the carbon signals of the tocopherol moiety were easily identified on the basis of previous work, the assignment of the carbon resonances in the fluorophenyl substituents was quite interesting: all aromatic signals should appear as doublets in the monofluoro derivatives and as resonances of higher multiplicity in the difluoro derivatives because of the different $J_{C,F}$ couplings. Some of the carbon signals in **9** showed a further line broadening or splitting.

In particular, the signal of C-2′ at ca. 116.5 ppm appears twice. Measurements at different field strengths (150 and 100 MHz) indicate the splitting not to be induced by coupling. It is rather caused by a doubled set of signals with very similar shifts as well as by far equal intensity and $^2J_{C,F}$ coupling (see Figure 6, top). This phenomenon is explained by the existence of two conformational isomers as shown in Figure 4. Four carbon spectra were recorded at different temperatures (298, 312, 322, and 332 K) to facilitate the rotation of the aryl substituent (Figure 6, stack plot at bottom). In this process the two doublets suffer distinct line broadening by converging near the coalescence temperature. Further heating (>332 K) of the sample was not possible because of the low boiling point of the solvent $CDCl_3$.

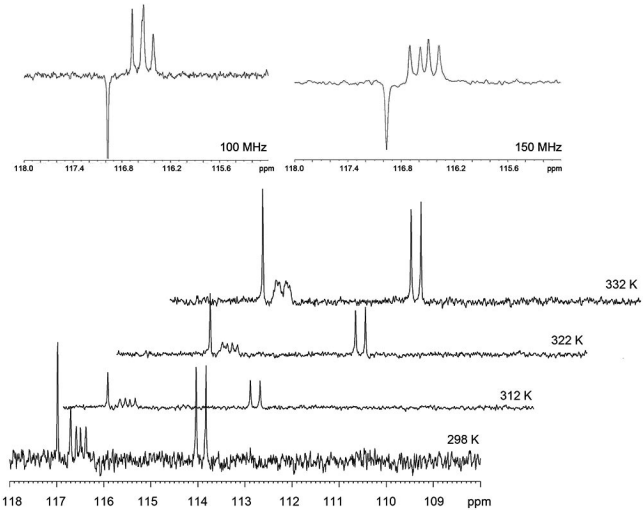


Figure 6. Top: section of the carbon NMR APT spectrum of **9** showing the C-2′ resonance, recorded at 100 MHz (left) and 150 MHz (right). Bottom: stack plot of sections of carbon NMR spectra of **9** recorded at various temperatures, 100 MHz.

To further disprove a coupling-derived phenomenon, the ^{1}H NMR spectrum of compound **9** was additionally recorded on a different spectrometer (600 and 400 MHz). In this case, the coalescence temperature is approx. 288 K leading to significant broadening of the proton signals. An increase in the measurement temperature leads to distinct improvements in the signal resolution caused by faster isomerization of the two different conformational isomers (see Figure 4 and Supporting Information, Figure S1). ^{19}F NMR experiments at various temperatures furnished the unambiguous proof of the existence of at least two conformational isomers. With increasing temperature the rotation barrier is minimized and the two signals unify to a single one, indicating the coalescent point to be between 308 and 318 K. The ^{19}F NMR spectrum clearly shows two signals at room temperature and proves the existence of two conformational isomers at room temperature (Figure 7).

In a preliminary yeast AhR screening following the Miller protocol,[30] we found that compounds 5-(3-fluorophenyl)-γ-tocopherol (**9**), 5-(3,4-difluorophenyl)-γ-tocopherol (**11**), and 5-(3,5-difluorophenyl)-γ-tocopherol (**12**) are quite potent AhR antagonists in vitro, having EC_{50} values of 1.8×10^{-8}, 0.9×10^{-9}, and 8.4×10^{-8} mol/L, respectively. These compounds are two to three orders of magnitude more effective than 3-hydroxymethylindole and bis(indol-3-yl)methane (5.8×10^{-6} and 1.1×10^{-6} mol/L, respectively), which are known from the literature[31,32] to be potent AhR antagonists and were comparable to some of the strongest antagonists hitherto known, such as indolo[3,2-*b*]carbazole (EC_{50} = 1.9×10^{-9}) and formylindolo[3,2-*b*]carbazole (EC_{50} = 3.5×10^{-9}). The *para*-fluorinated compound – the only one of the test candidates not showing rotational isomerism – showed a much more deficient behavior with an EC_{50} value of 3.3×10^{-4}, and the values of the other compounds tested were in the range between 10^{-5} and 10^{-6}. A detailed description of the compound screening in different activity assays will follow.

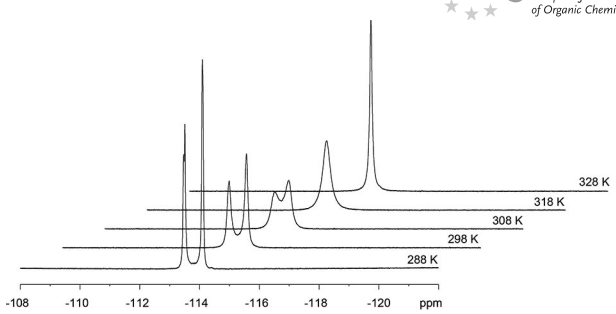


Figure 7. ^{19}F NMR spectrum of **9** recorded at various temperatures, 565 MHz.

Conclusions

O-Acetyl-5-iodo-γ-tocopherol (**5**) was shown to be an excellent starting material for the functionalization of γ-tocopherol by Suzuki coupling with phenylboronic acids, demonstrated with fluorophenyl- and difluorophenylboronic acids in the present case. The products, novel 5-substituted tocopherols, are physiologically relevant as AhR antagonists with promising assay results especially for the 3-fluorophenyl, 3,4-difluorophenyl, and 3,5-difluorophenyl derivatives (i.e., **9**, **11** and **12**, respectively). All compounds besides *para*-F derivatives **10a** and **10b** show conformation isomerism at room temperature with restricted rotation around the C-5–C1′ bond. The Suzuki protocol allowed introduction of a non-hydrolyzable linkage between the tocopherol residue and the attached moiety. At present, the tocopherol hybrid compounds synthesized are screened in receptor binding and expression studies and used as a preliminary basis for establishing quantitative structure–activity relationship (QSAR) models, especially with regard to the possible role of the conformational isomerism as the reason for the observed increased activity.

Experimental Section

General: (*all-R*)-Derivatives prepared from (2*R*,4′*R*,8′*R*)-tocopherols were used as starting materials. All other chemicals were obtained from commercial suppliers (Sigma–Aldrich) and used with-

out further purification. Et_2O was dried with sodium with benzophenone (0.2% w/v) as indicator. Dried ether was stored over activated 4 Å molecular sieves. Similarly, CH_2Cl_2 was heated at reflux over calcium hydride (5% w/v) and stored over activated 4 Å molecular sieves. Reagent-grade solvents were used for all extractions and workup procedures. Distilled water was used for all aqueous extractions and for all aqueous solutions. *n*-Hexane, Et_2O, and EtOAc used in chromatography were distilled before use. Yields refer to isolated pure products. All non-aqueous reactions were conducted in oven-dried (140 °C, overnight) or flame-dried glassware under an argon or nitrogen atmosphere; room temperature was 22 °C. Air- or moisture-sensitive liquids were transferred by oven-dried syringes and were introduced into the reaction flasks through rubber septa or through a stopcock under argon or nitrogen positive pressure. Column chromatography was performed on silica gel G_{60} (40–63 μm). Melting points were determined with a Kofler-type micro hot stage with Reichert-Biovar microscope. If not otherwise stated, NMR spectra were measured in $CDCl_3$ and recorded with a Bruker DPX300 or DPX400 spectrometer (300 or 400 MHz for ^1H, 75 or 100 MHz for ^{13}C), ^{19}F NMR spectra were recorded with a Bruker DPX400 (376 MHz), and for compound **9** the NMR spectrum was additionally recorded with a Bruker DRX600 spectrometer (600 MHz for ^1H, 150 MHz for ^{13}C, 565 MHz for ^{19}F). ^{13}C NMR spectra were measured with complete proton decoupling. Chemical shifts are reported in ppm downfield from tetramethylsilane with the solvent reference as the internal standard ($CDCl_3$: δ = 7.26 ppm for ^1H, $CDCl_3$: δ = 77.7 ppm for ^{13}C); chemical shifts for ^{19}F NMR are reported in ppm and trifluoroacetic acid was used as an external standard (–78.51 ppm); ^{13}C resonances were assigned by APT, HMQC, and HMBC spectra. Resonances of the isoprenoid side chain of tocopherols are not influenced by modifications of the chroman ring and are therefore not listed. GC–MS ionization was performed in the EI mode at 70 eV, 230 °C, and 1.5×10^{-5} Torr. For HRMS, a solution of the sample, dissolved in acetonitrile, was injected by a micro wellplate autosampler from Agilent technologies and measured by an Agilent 6210 TOF MS. The MS had been previously tuned with the Agilent tune mix and further reference masses were added to the method to provide a mass accuracy below 2 ppm. Data analysis was performed with Mass Hunter software from Agilent Technologies. Elemental analyses were performed at the Microanalytical Laboratory of the University of Vienna and are reported in percent atomic abundance. X-ray diffraction data were collected with a Bruker AXS Smart APEX CCD diffractometer. For further details, see compound **5b** in the Experimental Section.

***O*-Acetyl-γ-tocopherol (4a):** γ-Tocopherol (3.60 g, 8.294 mmol) was dissolved in dry CH_2Cl_2 (200 mL) followed by the addition of acetic acid anhydride (9 mL) and three drops of conc. H_2SO_4. The mixture was stirred at room temperature for 18 h, then diluted with H_2O (400 mL) and stirred at pH 5 for an additional 1 h. The neutralized reaction mixture ($NaHCO_3$) was filtered through Celite and washed with CH_2Cl_2. The layers were separated, and the organic layer was washed with brine. The aqueous layer was repeatedly extracted with *n*-hexane. The *n*-hexane extracts were combined and washed with brine, then combined with the CH_2Cl_2 layer, dried with Na_2SO_4, and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel (toluene) to afford **4a** (65%). Alternatively, **4a** was prepared following the same procedure as for the preparation of **4b** with acetic anhydride in pyridine to give a yield of 93%. The analytical data for compound **4a** matched the previously published data.[33] ^1H NMR: δ = 1.23 (s, 3 H, 2-Hb), 1.67–1.87 (m, 2 H, 3-H), 2.08 (s, 6 H, 7-Ha, 8-Hb), 2.37 (s, 3 H, CH_3CO), 2.64 (t, ^3J = 6.9 Hz, 2 H, 4-H), 5.29 (s, 1 H, 5-H) ppm.

2,2,7,8-Tetramethylchroman-6-ol: 2,3-Dimethyl-1,4-hydroquinone (3.00 g, 21.70 mmol) was dissolved in a mixture of formic acid (28.00 mL) and THF (4.00 mL), and the mixture was heated to reflux followed by the dropwise addition of 2-methyl-3-buten-2-ol (1.54 mL, 14.80 mmol) dissolved in THF (1.00 mL). The reaction was heated at reflux for 3 h, poured onto crushed ice, then diluted with H_2O and extracted repeatedly with Et_2O. The Et_2O layers were combined, diluted with *n*-hexane (40 mL), and repeatedly washed with H_2O. The organic extracts were dried with Na_2SO_4, filtered, and concentrated. The residue was dissolved in MeOH (40 mL), conc. HCl (0.5 mL) was added, and the mixture was heated at reflux for 20 min to hydrolyze any formate ester that might have been formed in the reaction. The solvent was removed under reduced pressure. The residue was dissolved in Et_2O (100 mL) and washed with H_2O, a saturated aqueous solution of $NaHCO_3$, and then H_2O, dried with Na_2SO_4, and concentrated in vacuo. The residue was extracted by heating at reflux in *n*-hexane (50 mL) for 20 min. After cooling to room temperature, the unreacted 2,3-dimethyl-1,4-hydroquinone (33%) was filtered off. The filtrate was concentrated in vacuo and purified by column chromatography on silica gel (EtOAc/*n*-hexane, 1:9) to give 2,2,7,8-tetramethylchroman-6-ol in 28% yield (42% rel. to unreacted and recycled starting material) and the disubstituted byproduct 3,3,5,6,8,8-hexamethyl-1,2,3,8,9,10-hexahydro-pyrano[3,2-*f*]chromene in 19% yield.[34] Data for 2,2,7,8-tetramethylchroman-6-ol: M.p. 75–77 °C (*n*-hexane/EtOAc). ^1H NMR: δ = 1.29 (s, 6 H, 2a-H, 2b-H), 1.74 (t, ^3J = 6.8 Hz, 2 H, 3-H), 2.10 (s, 3 H, 7a/8b-H), 2.12 (s, 3 H, 8b/7a-H), 2.68 (t, ^3J = 6.8 Hz, 2 H, 4-H), 4.0 (br. s, 1 H, -OH), 6.37 (s, 1 H, 5-H) ppm. ^{13}C NMR: δ = 11.9 (C-7a, C-8b), 22.6 (C-4), 27.0 (C-2a, C-2b), 33.0 (C-3), 73.4 (C-2), 112.1 (C-5), 118.0 (C-4a), 121.6 (C-8), 125.8 (C-7), 145.9 (C-8a), 146.3 (C-6) ppm. Data for 3,3,5,6,8,8-hexamethyl-1,2,3,8,9,10-hexahydropyrano[3,2-*f*]-chromene: M.p. 102–104 °C (*n*-hexane/EtOAc). ^1H NMR: δ = 1.28 (s, 12 H, 3a-H, 3b-H, 8a-H, 8b-H), 1.78 (t, ^3J = 6.8 Hz, 4 H, 2-H, 9-H), 2.09 (s, 6 H, 5a-H, 6b-H), 2.54 (t, ^3J = 6.8 Hz, 4 H, 1-H, 10-H) ppm. ^{13}C NMR**:** δ = 11.8 (C-5a, C-6b), 20.1 (C-1, C-10), 26.8 (C-3a, C-3b, C-8a, C-8b), 32.9 (C-2, C-9), 72.4 (C-3, C-8), 115.6 (C-10a, C-10b), 123.4 (C-5, C-6), 144.7 (C-4a, C-6a) ppm. $C_{18}H_{26}O_2$ (274.40): calcd. C 78.79, H 9.55; found C 78.88, H 9.56.

2,2,7,8-Tetramethylchroman-6-yl-acetate (4b): 2,2,7,8-Tetramethylchroman-6-ol (0.50 g, 2.40 mmol) was dissolved in pyridine (10 mL) and cooled to 0 °C followed by the addition of acetic acid anhydride (18.5 mL). The mixture was brought to room temperature and stirred for 18 h. The solvent was evaporated in vacuo and then co-evaporated with toluene. The crude residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 20:1) to afford **4b** in 95% yield. Analytical data was in accordance with the data published in the literature.[35]

***O*-Acetyl-5-iodo-γ-tocopherol (5a):** A solution of I_2 (6.23 g, 24.55 mmol) in dry CH_2Cl_2 (300 mL) was added dropwise to a suspension of **4a** (7.60 g, 16.57 mmol) and silver trifluoroacetate (5.420 g, 24.54 mmol) in CH_2Cl_2 (300 mL) at room temperature whilst stirring (color of the reaction mixture changed from cloudy white to yellow to orange with yellow precipitate during the addition). The mixture was stirred at room temperature for 2 h and an aqueous solution of $NaHCO_3$ (4.2 g) and $Na_2S_2O_3$ (3.9 g) in H_2O (300 mL) was added. The mixture was stirred for 1 h and then filtered through a Celite layer. The filtrate was extracted with CH_2Cl_2. The organic layers were combined, washed with a saturated aqueous solution of $NaHCO_3$ and brine, dried with Na_2SO_4,

filtered, and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel (toluene/*n*-hexane, 1:2 → 1:1) to afford **5a** as a yellow oil in 67% yield. Furthermore 3,4-dehydro-γ-tocopheryl acetate was isolated in a yield of 4% and 3% of unreacted starting material could be recycled. Data for *O*-acetyl-5-iodo-γ-tocopherol: ^{1}H NMR: δ = 1.25 (s, 3 H, 2b-H), 1.67–1.89 (m, 2 H, 3-H), 2.09 (s, 6 H, 7a-H, 8b-H), 2.38 (s, 3 H, CH_3CO), 2.65 (t, ^3J = 6.8 Hz, 2 H, 4-H) ppm. ^{13}C NMR: δ = 12.2/14.1 (C-7a, C-8b), 21.2 (*C*H_3CO), 28.0 (C-2b), 29.6 (C-4), 31.9 (C-3), 76.2 (C-2), 94.7 (C-5), 122.0 (C-4a), 126.3/128.2 (C-7, C-8), 142.4 (C-6), 150.2 (C-8a), 169.1 (CO) ppm. (for full spectra and numeration of **5a** see Supporting Information). MS (EI, 70 eV): *m*/*z* = 584.4, 542.3, 277.0, 151.1, 57.1. Data for 3,4-dehydro-γ-tocopheryl acetate: ^{1}H NMR: δ = 2.04 (s, 3 H, 7a/8b-H), 2.13 (s, 3 H, 8b/7a-H), 2.30 (s, 3 H, CH_3-CO), 5.55 (d, ^3J = 9.8 Hz, 1 H, 3-H), 6.25 (d, ^3J = 9.8 Hz, 1 H, 4-H), 6.51 (s, 1 H, 5-H) ppm.

5-Iodo-2,2,7,8-tetramethylchroman-6-yl Acetate (5b): Compound **5b** was synthesized in the same manner as compound **5a** with I_2 (1.87 g, 7.36 mmol), **4b** (1.22 g, 4.91 mmol), silver trifluoroacetate (1.63 g, 7.36 mmol), and CH_2Cl_2 (400 mL). The crude residue was purified by recrystallization from *n*-hexane to give **5b** in a yield of 52% besides nonreacted starting material. M.p. 130.5–133 °C (*n*-hexane). ^{1}H NMR: δ = 1.30 (s, 6 H, 2a-H, 2b-H), 1.78 (t, ^3J = 6.8 Hz, 2 H, 3-H), 2.09 (s, 6 H, 7a-H, 8b-H), 2.38 (s, 3 H, CH_3CO), 2.66 (t, ^3J = 6.8 Hz, 2 H, 4-H) ppm. ^{13}C NMR: δ = 12.2/14.1 (C-7a, C-8b), 21.2 (*C*H_3CO), 26.6 (C-2a, C-2b), 29.9 (C-4), 33.5 (C-3), 74.1 (C-2), 94.8 (C-5), 121.8 (C-4a), 126.3/128.3 (C-7, C-8), 142.4 (C-6), 150.3 (C-8a), 169.1 (CO) ppm. $C_{15}H_{19}IO_3$ (374.22): calcd. C 48.14, H 5.12; found C 48.09, H 5.16.

General Procedure for Suzuki Coupling: To a solution of aryl iodide dissolved in predegassed DMF (20 mL per 1 mmol starting material) was added K_2CO_3 (2.0 equiv.) and $PdCl_2$(dppf)·DCM (10 mol-%). The resulting suspension was degassed with Ar, and the corresponding boronic acid (1.5 equiv.) was added. The mixture was stirred for 18 h at 80 °C, then diluted with H_2O, and extracted with EtOAc. The organic extracts were combined and washed with brine, dried with Na_2SO_4, filtered, and concentrated in vacuo to afford the crude product.

***O*-Acetyl-5-phenyl-γ-tocopherol (6a):** Following the general procedure for the Suzuki coupling, **5a** (160 mg, 0.274 mmol) was treated with phenylboronic acid (52 mg, 0.411 mmol), K_2CO_3 (76 mg, 0.548 mmol), and $PdCl_2$(dppf)·DCM (10 mol-%). The crude residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 50:1) to afford **6a** (95%). ^{1}H NMR: δ = 1.26 (s, 3 H, 2b-H), 1.50–1.70 (m, 2 H, 3-H), 1.85 (s, 3 H, CH_3CO), 2.06 (s, 3 H, 7a-H), 2.17 (s, 3 H, 8b-H), 2.29–2.41 (m, 2 H, 4-H), 7.14–7.19 (m, 2 H, Ph-H), 7.28–7.33 (m, 1 H, Ph-H), 7.35–7.40 (m, 2 H, Ph-H) ppm. ^{13}C NMR: δ = 12.1 (C-8b), 13.0 (C-7a), 20.2 (*C*H_3CO), 21.4 (C-4), 28.0 (C-2a), 31.0 (C-3), 75.6 (C-2), 117.2 (C-5), 125.0 (C-7/8), 127.3 (C-7/8), 127.0/128.0/129.5 (C-2′, C-3′, C-4′, C-5′, C-6′), 131.6 (C-4a), 137.0 (C-1′), 139.4 (C-6), 149.7 (C-8a), 170.0 (CO) ppm. $C_{36}H_{54}O_3$ (534.83): calcd. C 80.85, H 10.18; found C 80.91, H 10.29.

2,2,7,8-Tetramethyl-5-phenylchroman-6-yl Acetate (6b): Following the general procedure for the Suzuki coupling, **5b** (200 mg, 0.534 mmol) was treated with phenylboronic acid (101 mg, 0.801 mmol), K_2CO_3 (147 mg, 1.068 mmol), and $PdCl_2$(dppf)·DCM (10 mol-%). The crude residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 50:1) to afford **6b** (83%). M.p. 108–110 °C. ^{1}H NMR: δ = 1.31 (s, 6 H, 2a-H, 2b-H), 1.65 (t, ^3J = 6.8 Hz, 2 H, 3-H), 1.85 (s, 3 H, CH_3CO), 2.06 (s, 3 H, 7a-H), 2.16 (s, 3 H, 8b-H), 2.32–2.41 (m, 4-H), 7.14–7.19 (m, 2 H, Ph-H), 7.29–7.34 (m, 1 H, Ph-H), 7.34–7.40 (m, 2 H, Ph-H) ppm. ^{13}C NMR: δ = 12.1 (C-8b), 13.0 (C-7a), 20.2 (*C*H_3CO), 21.7 (C-4), 27.1 (C-2b), 32.6 (C-3), 73.5 (C-2), 117.0 (C-5), 125.0 (C-7/8), 127.3 (C-7/8), 127.0/128.0/129.5 (C-2′, C-3′, C-4′, C-5′, C-6′), 131.7 (C-4a), 136.9 (C-1′), 139.5 (C-6), 149.7 (C-8a), 170.0 (CO) ppm. $C_{21}H_{24}O_3$ (324.42): calcd. C 77.75, H 7.86; found C 77.70, H 7.68.

5-(4-Hydroxyphenyl)-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-chroman-6-yl Acetate (7): Following the general procedure for the Suzuki coupling, **5a** (217 mg, 0.371 mmol) was treated with 4-hydroxyphenylboronic acid (77 mg, 0.557 mmol), K_2CO_3 (104 mg, 0.742 mmol), and $PdCl_2$(dppf)·DCM. The crude residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 100:1) to afford **7** (42%). ^{1}H NMR: δ = 1.26 (s, 3 H, 2b-H), 1.90 (s, 3 H, CH_3CO), 2.07 (s, 3 H, 7a-H), 2.16 (s, 3 H, 8b-H), 2.27–2.45 (m, 2 H, 4-H), 4.80–5.40 (br. s, 1 H, OH), 6.83 (br. d, 2 H, 2′-H, 4′-H), 7.03 (br. d, 2 H, 3′-H, 5′-H) ppm. ^{13}C NMR: δ = 12.1 (C-8b), 12.9 (C-7a), 20.3 (*C*H_3CO), 21.4 (C-4), 24.2 (C-2b), 31.0 (C-3), 75.6 (C-2), 115.0 (C-2′, C-6′), 117.6 (C-5), 125.0/127.1 (C-7, C-8), 129.1 (C-4a), 130.8/130.7 (C-3′, C-5′), 131.2 (C-1′), 139.7 (C-6), 149.7 (C-8a), 154.6 (C-4′), 170.4 (CO) ppm.

5-(2-Fluorophenyl)-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-chroman-6-yl Acetate (8): Following the general procedure for the Suzuki coupling, **5a** (173 mg, 0.295 mmol) was treated with 2-fluorophenylboronic acid (62 mg, 0.443 mmol), K_2CO_3 (83 mg, 0.591 mmol), and $PdCl_2$(dppf)·DCM (10 mol-%). The crude residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 5:1) to afford **8** (20%). ^{1}H NMR: δ = 1.27 (s, 6 H, 2a-H), 1.89 (s, 3 H, CH_3CO), 2.08 (s, 3 H, 7a-H), 2.18 (s, 3 H, 8b-H), 2.31–2.43 (m, 2 H, 4-H), 7.10–7.20 (m, 3 H, Ph-H), 7.30–7.37 (m, 1 H, Ph-H) ppm. ^{13}C NMR: δ = 12.2 (C-8b), 13.0 (C-7a), 20.2 (*C*H_3CO), 21.0 (C-4), 30.9 (C-3), 75.7 (C-2), 115.5 (d, $^2J_{C,F}$ = 22.3 Hz, C-3′), 117.8 (C-5), 123.8 (d, C-4′/C-5′/C-6′), 124.1 (d, $^2J_{C,F}$ = 17.7 Hz, C-1′), 125.2 (C-7/C-8), 126.0 (C-4a), 127.4 (C-7/C-8), 129.3 ("q", $J_{C,F}$ = 7.9 Hz, C-4′/C-5′/C-6′), 131.8 (d, C-4′/C-5′/C-6′), 139.6 (C-6), 149.7 (C-8a), 159.7 (d, $^1J_{C,F}$ = 246.2 Hz, C-2′), 170.1 (CO) ppm. ^{19}F NMR: δ = –116.9 (s), –115.9 (s) ppm.

5-(3-Fluorophenyl)-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-chroman-6-yl Acetate (9): Following the general procedure for the Suzuki coupling, **5a** (278 mg, 0.478 mmol) was treated with 3-fluorophenylboronic acid (101 mg, 0.718 mmol), K_2CO_3 (133 mg, 0.957 mmol), and $PdCl_2$(dppf)·DCM (10 mol-%). The crude residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 5:1) to afford **9** (33%). ^{1}H NMR: δ = 1.27 (s, 3 H, 2a-H), 1.91 (s, 3 H, CH_3CO), 2.07 (s, 3 H, 7a-H), 2.18 (s, 3 H, 8b-H), 2.25–2.48 (m, 2 H, 4-H), 7.35 (m, 1 H, 5′-H), 7.03 (m, 1 H, 4′-H), 6.97 (m, 1 H, 6′-H), 6.92 (m, 1 H, 2′-H) ppm. ^{13}C NMR: δ = 12.1 (C-8b), 12.9 (C-7a), 20.2 (*C*H_3CO), 21.3 (C-4), 31.0 (C-3), 75.7 (C-2), 113.9 (d, $^2J_{C,F}$ = 20.8 Hz, C-4′), 116.5 (d, $^2J_{C,F}$ = 20.7 Hz, C-2′), 117.0 (C-5), 125.3 (d, $^4J_{C,F}$ < 3 Hz, C-6′), 125.6 (C-7/8), 127.4 (C-7/8), 129.5 (d, $^3J_{C,F}$ = 8.3 Hz, C-5′), 130.3 (C-4a), 139.2 (C-6), 139.2 (d, $^3J_{C,F}$ = 8.4 Hz, C-1′), 149.7 (C-8a), 162.5 (d, $^1J_{C,F}$ = 246.0 Hz, C-3′), 169.8 (CO) ppm. ^{19}F NMR (298 K): δ = –113.6 (s), –114.2 (s) ppm. ^{19}F NMR (308 K): δ = –114.1 (s) ppm.

5-(4-Fluorophenyl)-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-chroman-6-yl Acetate (10a): Following the general procedure for the Suzuki coupling, **5a** (217 mg, 0.371 mmol) was treated with 4-fluorphenylboronic acid (78 mg, 0.557 mmol), K_2CO_3 (104 mg, 0.742 mmol), and $PdCl_2$(dppf)·DCM (10 mol-%). The crude residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 5:1) to afford **10a** (95%). ^{1}H NMR: δ = 1.25 (s, 3 H, 2a-H), 1.88 (s, 3 H, CH_3CO), 2.06 (s, 3 H, 7a-H), 2.16 (s, 3 H, 8b-

H), 2.26–2.38 (m, 2 H, 4-H), 7.00–7.10 (m, 2 H, 3′-H, 5′-H), 7.10–7.18 (m, 2 H, 2′-H, 6′-H) ppm. ^{13}C NMR: δ = 12.1 (C-8b), 12.9 (C-7a), 20.2 (*C*H$_3$CO), 21.4 (C-4), 31.0 (C-3), 75.6 (C-2), 115.0 (d, $^2J_{C,F}$ = 21.0 Hz, C-3′, C-5′), 117.3 (C-5), 125.4 (C-7/8), 127.4 (C-7/8), 130.6 (C-4a), 131.1 (d, $^3J_{C,F}$ = 8.1 Hz, C-2′/C-6′), 131.2 (d, $^3J_{C,F}$ = 8.1 Hz, C-2′/C-6′), 132.8 (d, $^4J_{C,F}$ = 3.4 Hz, C-1′), 139.6 (C-6), 149.7 (C-8a), 161.9 (d, $^1J_{C,F}$ = 245.5 Hz, C-4′), 169.8 (CO) ppm. ^{19}F NMR: δ = –117.54 (s) ppm.

5-(4-Fluorophenyl)-2,2,7,8-tetramethylchroman-6-yl Acetate (10b): Following the general procedure for the Suzuki coupling, **5b** (200 mg, 0.534 mmol) was treated with 4-fluorophenylboronic acid (112 mg, 0.801 mmol), K_2CO_3 (147 mg, 1.068 mmol), and PdCl$_2$(dppf)·DCM (10 mol-%). The crude residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 5:1) to afford **10b** (75%). ^{1}H NMR: δ = 1.32 (s, 6 H, 2a-H, 2b-H), 1.66 (t, ^3J = 6.7 Hz, 2 H, 3-H), 1.89 (s, 3 H, CH$_3$CO), 2.06 (s, 3 H, 7a-H), 2.16 (s, 3 H, 8b-H), 2.27–2.40 (m, 2 H, 4-H), 7.03–7.10 (m, 2 H, 3′-H, 5′-H), 7.10–7.17 (m, 2 H, 2′-H, 6′-H) ppm. ^{13}C NMR: δ = 12.1 (C-8b), 13.0 (C-7a), 20.2 (*C*H$_3$CO), 21.7 (C-4), 27.1 (C-2a, C-2b), 32.6 (C-3), 73.6 (C-2), 115.0 (d, $^2J_{C,F}$ = 21.2 Hz, C-3′, C-5′), 117.1 (C-5), 125.4 (C-7/8), 127.4 (C-7/8), 130.6 (C-4a), 131.2 (d, $^3J_{C,F}$ = 7.9 Hz, C-2′, C-6′), 132.8 (d, $^4J_{C,F}$ = 3.6 Hz, C-1′), 139.6 (C-6), 149.8 (C-8a), 161.9 (d, $^1J_{C,F}$ = 245.0 Hz, C-4′), 169.9 (CO) ppm. ^{19}F NMR: δ = –118.11 (s) ppm. $C_{21}H_{23}FO_3$ (342.41): calcd. C 73.66, H 6.77; found C 73.36, H 7.00.

5-(3,4-Difluorophenyl)-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-chroman-6-yl Acetate (11): Following the general procedure for the Suzuki coupling, **5a** (300 mg, 0.513 mmol) was treated with 3,4-difluorphenylboronic acid (122 mg, 0.770 mmol), K_2CO_3 (144 mg, 1.026 mmol), and PdCl$_2$(dppf)·DCM (10 mol-%). The crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 5:1) to afford **11** (54%). ^{1}H NMR: δ = 1.29 (s, 3 H, 2a-H), 1.95 (s, 3 H, CH$_3$CO), 2.08 (s, 3 H, 7a-H), 2.19 (s, 3 H, 8b-H), 2.27–2.44 (m, 2 H, 4-H), 6.89–6.97 (m, 1 H, 6′-H), 7.03 (m, 1 H, 2′-H), 7.19 (m, 1 H, 5′-H) ppm. ^{13}C NMR: δ = 12.2 (C-8b), 13.0 (C-7a), 20.3 (*C*H$_3$CO), 21.4 (C-4), 31.0 (C-3), 75.7 (C-2), 117.0 (C-5), 117.0/118.6/125.9 (m, C-2′/C-5′/C-6′), 125.9 (C-7/8), 127.5 (C-7/8), 129.6 (C-4a), 133.8 (m, C-1′), 139.3 (C-6), 149.8 (C-8a), 149.5 (dd, $^1J_{C,F}$ = 248.4 Hz, $^3J_{C,F}$ = 12.8 Hz, C-3′/4′), 150.0 (dd, $^1J_{C,F}$ = 248.4 Hz, $^3J_{C,F}$ = 12.8 Hz, C-3′/4′), 169.7 (CO) ppm. ^{19}F NMR: δ = –140.02 (d, J = 21.2 Hz), –141.97 (br. d) ppm.

5-(3,5-Difluorophenyl)-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-chroman-6-yl Acetate (12): Following the general procedure for the Suzuki coupling, **5a** (310 mg, 0.530 mmol) was treated with 3,5-difluorphenylboronic acid (126 mg, 0.800 mmol), K_2CO_3 (149 mg, 1.060 mmol), and PdCl$_2$(dppf)·DCM (10 mol-%). The crude residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 5:1) to afford **12** (60%). ^{1}H NMR: δ = 1.27 (s, 3 H, 2a-H), 1.96 (s, 3 H, CH$_3$CO), 2.07 (s, 3 H, 7a-H), 2.18 (s, 3 H, 8b-H), 2.27–2.44 (m, 2 H, 4-H), 6.71–6.76 (m, 2 H, 2′-H, 6′-H), 6.76–6.83 (m, 1 H, 4′-H) ppm. ^{13}C NMR: δ = 12.2 (C-8b), 13.0 (C-7a), 20.2 (*C*H$_3$CO), 21.2 (C-4), 30.9 (C-3), 75.8 (C-2), 102.6/112.6 (m, C-2′/C-4′/C-6′), 116.7 (C-5), 126.1 (C-7/8), 127.7 (C-7/8), 129.4 (C-4a), 139.0 (C-6), 140.4 (m, C-1′), 149.8 (C-8a), 162.7 (dd, $^1J_{C,F}$ = 248.7 Hz, $^3J_{C,F}$ = 12.7 Hz, C-3′, C-5′), 169.7 (CO) ppm. ^{19}F NMR: δ = –112.21 (d, J = 231.5 Hz) ppm.

5-(2,4-Difluorophenyl)-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-chroman-6-yl Acetate (13): Following the general procedure for the Suzuki coupling, **5a** (300 mg, 0.513 mmol) was treated with 2,4-difluorphenylboronic acid (122 mg, 0.770 mmol), K_2CO_3 (144 mg, 1.026 mmol), and PdCl$_2$(dppf)·DCM (10 mol-%). The crude residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 5:1) to afford **13** (70%). ^{1}H NMR: δ = 1.23 (s, 3 H, 2a-H), 1.94 (s, 3 H, CH$_3$CO), 2.08 (s, 3 H, 7a-H), 2.18 (s, 3 H, 8b-H), 2.27–2.43 (m, 2 H, 4-H), 6.86–6.96 (m, 2 H, 5′-H, 6′-H), 7.15 (m, 1 H, 3′-H) ppm. ^{13}C NMR: δ = 12.2 (C-8b), 13.0 (C-7a), 20.2 (*C*H$_3$CO), 21.0 (C-4), 30.9 (C-3), 75.8 (C-2), 103.9/111.0/132.5 (m, C-3′/5′/6′), 117.9 (C-5), 120.2 (m, C-1′), 126.3 (C-4a), 124.3 (C-7/8), 127.4 (C-7/8), 139.8 (C-6), 149.8 (C-8a), 159.5/162.5 (dd, $^1J_{C,F}$ = 249.0 Hz, $^3J_{C,F}$ = 12.0 Hz, C-2′, C-4′), 169.7 (CO) ppm. ^{19}F NMR: δ = –110.1 to –112.3 (br. d), –112.96 (d, J = 7.4 Hz) ppm.

5-(2,3-Difluorophenyl)-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-chroman-6-yl Acetate (14): Following the general procedure for the Suzuki coupling, **5a** (150 mg, 0.257 mmol) was treated with 2,3-difluorphenylboronic acid (61 mg, 0.385 mmol), K_2CO_3 (71 mg, 513 mmol), and PdCl$_2$(dppf)·DCM (10 mol-%). The crude residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 5:1) to afford **14** (43%). ^{1}H NMR: δ = 0.82–0.89 (m, 12 H, 4a′, 8a′, 12a′, 13), 0.99–1.81 (m, 23 H, 3, 1′, 2′, 3′, 4′, 5′, 6′, 7′, 8′, 9′, 10′, 11′, 12′-H), 1.27 (s, 3 H, 2a-H), 1.92 (s, 3 H, *C*H$_3$CO), 2.07 (s, 3 H, 7a-H), 2.18 (s, 3 H, 8b-H), 2.26–2.45 (m, 2 H, 4-H), 6.92 (t, J = 6.9 Hz, 1 H, 4′-H), 7.03–7.21 (m, 5 H, 5′-H, 6′-H) ppm. ^{13}C NMR: δ = 12.2 (C-8b), 13.0 (C-7a), 19.6 (C-8a′), 19.7 (C-4a′), 20.2 (*C*H$_3$CO), 20.9 (C-4), 21.0 (C-2′), 22.6 (C-2a), 22.7 (C-12a′, C-13), 24.4 (C-10′), 24.8 (C-6′), 28.0 (C-12′), 30.9 (C-3), 32.6 (C-4′), 32.8 (C-8′), 37.6 (C-9′), 37.7 (C-5′), 37.8 (C-7′), 37.8 (C-11′), 37.8 (C-3′), 37.3 (C-9′), 37.4 (C-5′), 37.4 (C-7′), 37.4 (C-11′), 37.4 (C-3′), 39.6 (C-1′)75.8 (C2), 116.4 (d, $^2J_{C,F}$ = 17.1 Hz, Ph-C4′), 117.7 (C4a), 123.7 (Ph-C5′), 126.4 (Ph-C6′), 126.5 (C5), 126.5 (C8), 126.7 ($^2J_{C,F}$ = 14 Hz, Ph-C1′), 127.6 (C7), 139.6 (C6), 147.9 ($^2J_{C,F}$ = 10 Hz, $^1J_{C,F}$ = 246 Hz, Ph-C2′), 149.5 (C8a), 150.7 ($^1J_{C,F}$ = 249 Hz, $^2J_{C,F}$ = 14 Hz, Ph-C3′) ppm. ^{19}F NMR: δ = –139.0 (s), –137.9 (s) ppm.

5-(2,5-Difluorophenyl)-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-chroman-6-yl Acetate (15): Following the general procedure for the Suzuki coupling, **5a** (150 mg, 0.257 mmol) was treated with 2,5-difluorphenylboronic acid (61 mg, 0.385 mmol), K_2CO_3 (71 mg, 513 mmol), and PdCl$_2$(dppf)·DCM (10 mol-%). The crude residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 5:1) to afford **15** (39%). ^{1}H NMR: δ = 0.82–0.93 (m, 12 H, 4a′, 8a′, 12a′, 13-H), 0.98–1.83 (m, 23 H, 3, 1′, 2′, 3′, 4′, 5′, 6′, 7′, 8′, 9′, 10′, 11′, 12′-H), 1.26 (s, 3 H, 2a-H), 1.94 (s, 3 H, *C*H$_3$CO), 2.07 (s, 3 H, 7a-H), 2.17 (s, 3 H, 8b-H), 2.25–2.59 (m, 2 H, 4-H), 6.89 (m, 1 H, Ph-6 H), 6.96–7.13 (m, 2 H, Ph-3 H, Ph-4 H) ppm. ^{13}C NMR: δ = 12.5 (C-8b), 13.4 (C-7a), 19.9 (C-8a′), 20.1 (C-4a′), 20.5 (*C*H$_3$CO), 21.1 (C-4), 21.3 (C-2′), 23.0 (C-2a), 23.1 (C-12a′, C-13), 24.8 (C-10′), 25.2 (C-6′), 28.3 (C-12′), 31.2 (C-3), 33.0 (C-4′), 33.1 (C-8′), 37.6 (C-9′), 37.7 (C-5′), 37.8 (C-7′), 37.8 (C-11′), 37.9 (C-3′), 39.7 (C-1′), 76.2 (C-2), 116.0 (dd, $^3J_{C,F}$ = 7.4 Hz, $^2J_{C,F}$ = 23.2 Hz, Ph-C3), 116.8 (dd, $^3J_{C,F}$ = 9.3 Hz, $^2J_{C,F}$ = 25.9 Hz, Ph-C4), 117.9 (C-4a), 118.4 (dd, $^3J_{C,F}$ = 11.1 Hz, $^2J_{C,F}$ = 24.1 Hz, Ph-C6), 126.0 (dd, $^3J_{C,F}$ = 7.6 Hz, $^2J_{C,F}$ = 20.9 Hz, Ph-C1), 126.8 (C5), 126.8 (C8), 128.0 (C7), 139.8 (C6), 150.1 (C8a) 156.2 ($^1J_{C,F}$ = 249 Hz, Ph-C2), 158.6 ($^1J_{C,F}$ = 243 Hz, Ph-C5), 169.5 (CH3*C*O) ppm. ^{19}F NMR: δ = –120.2 (s), –119.1 (s) ppm.

X-ray Single-Crystal Diffraction: Data were collected with a Bruker AXS Smart APEX CCD diffractometer and graphite monochromated Mo-K_α. There was only one useful crystal available, which was bent, gave poor reflection profiles and consequently furnished modest reflection data. Corrections for absorption was performed with program SHELXA, The structure was solved and refined with program SHELXTL (version 6.10. Bruker AXS Inc., Madison, WI, USA) using anisotropic displacement parameters only for iodine. Crystal data and information on the structure refinement are given

in the Supporting Information. CCDC-795835 (for **5b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Detailed information to structural analysis, schematically shown for compound **9**; ^{1}H NMR and ^{13}C NMR spectra for compounds **5a**, **5b**, **6b**,**7**, **9**, and **10b**. Complete spectral assignments of compounds **8**–**13**. Crystal data and structure refinement data for **5b**.

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