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Improved synthesis of tocopherol fatty alcohols and analogs: microglial activation modulators

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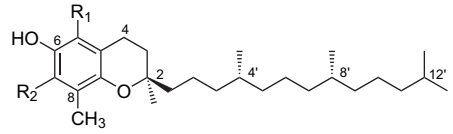
Abstract—The synthesis of tocopherol fatty alcohols (TFAs), potent microglial activation modulators, was achieved via *C*-alkylation of trimethylhydroquinone. Several analogs, in particular water-soluble prodrugs, have been synthesized using a Wittig reaction and their antioxidant activities have been evaluated.

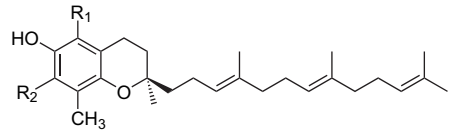
1. Introduction

Vitamin E, the most important fat-soluble antioxidant in biological systems, occurs naturally in eight main isoforms: α, β, γ, and δ-tocopherols and four corresponding tocotrienols (Scheme 1).[1] Both groups are composed of differentially methylated 2-substituted 3,4-dihydro-2*H*-1-benzopyrans, the chromans and a phytyl side chain for the tocopherols and an unsaturated farnesyl chain for the tocotrienols.[2]



Tocopherol

α : $R_1 = R_2 = CH_3$ γ : $R_1 = H$, $R_2 = CH_3$
β : $R_1 = CH_3$, $R_2 = H$ δ : $R_1 = R_2 = H$



Tocotrienol

Scheme 1. Tocopherols and tocotrienols.

Although γ-tocopherol is generally the most abundant form in the diet, α-tocopherol accounts for over 90% of the total vitamin E retained in the body.[1] Naturally occurring α-tocopherol is optically active, having three chiral centers whereas most synthetic supplements are mixtures of the eight possible stereoisomers.

Several groups have identified an α-tocopherol transfer protein (α-TTP) acting mainly in the liver.[3] Studies on the distribution and chiral discrimination of deuterated tocopherols have shown that the 2*R*-isomer of the trimethylated chroman ring dominates the biokinetics. The naturally occurring α-tocopherol is as such preferentially retained by the liver and then redistributed to the tissues.[3b]

α-Tocopherol is therefore the member of the vitamin E family presenting the highest biological activities. Besides its well-known role of being the most effective chain-breaking phenolic antioxidant in mammalian tissues,[4] α-tocopherol has numerous important clinical effects. It acts as a regulator of heme synthesis and an inhibitor of platelet aggregation.[5] Vitamin E plays also an important role in the brain immune system and thus in the prevention of degenerative neuropathies by acting mainly as a neuroprotective agent.[6]

Previous studies showed that *n*-hexacosanol, a long chain primary alcohol extracted from *Hygrophila erecta*, a plant known in the traditional Chinese medicine for its wound healing properties, increases the survival rate and induces the differentiation of fetal mice neurons in vitro.[7] The chain length and the ω-hydroxyl function are crucial factors for this biological activity which is similar to that of naturally occurring growth factors, namely neurotrophic factors.

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In order to combine the neurotrophic activity and the neuroprotective effects of antioxidant molecules, we investigated hybrid compounds composed of a neurotrophic ω-alkanol structure and an antioxidant moiety. This approach led to the syntheses of 3-(15-hydroxy-pentadecyl)-2,4,4-trimethyl-cyclohexen-1-one (tCFA-15)[7b] and 18-(5-methoxy-1*H*-indol-3-yl)octadecane-1-ol.[8] These compounds are strong neural stem cells differentiation inducers, which present antioxidant and neuroprotective activities. In addition, they increase the axonal outgrowth and counteract the axonal growth inhibitory properties of semaphorin 3A and myelin-associated proteins[9] and can therefore be considered as compounds suitable for the treatment of neurological diseases.

In a previous study, we showed that tocopherol fatty alcohols (TFAs), combining the trimethylated chroman ring of α-tocopherol and an ω-alkanol side chain, modulate microglial activation.[10] Microglial cells, the brain resident monocyte-macrophage cell population are found as quiescent cells throughout the brain parenchyma, where they represent around 15% of the cell population.[11] Upon appropriate stimulation, typically after brain injury or infection, as well as during the development of neuropathies like Alzheimer's disease and multiple sclerosis, microgliocytes continue their previously halted differentiation process to become immunocompetent phagocytic cells. Activated microglia produces pro-inflammatory cytokines and a series of free radicals which induce neurodegenerative events comparable to those observed in Alzheimer's disease.[12] TFAs (Scheme 2), specifically the 2-(12-hydroxy-dodecyl)-2,5,7,8-tetramethyl-chroman-6-ol, the TFA bearing 12 carbon atoms on the side chain (n=12), significantly decreases the production of TNF-α and NO radicals by activated microglial cells.[10] In order to further investigate these potent anti-neuroinflammatory properties and their possible applications in the treatment of degenerative neuropathies, larger quantities of TFAs and their water-soluble prodrug forms as well as their optically pure isomers are required.

2. Results and discussion

Here we report an optimized synthesis of different TFAs based on *C*-alkylation of trimethylhydroquinone (THQ) as well as the syntheses of optically active isomers. Several analog compounds are also synthesized in order to investigate the roles of the side chain and the nucleus. Finally, the syntheses of a range of highly water-soluble prodrug forms designed for animal testings are described (Scheme 2).

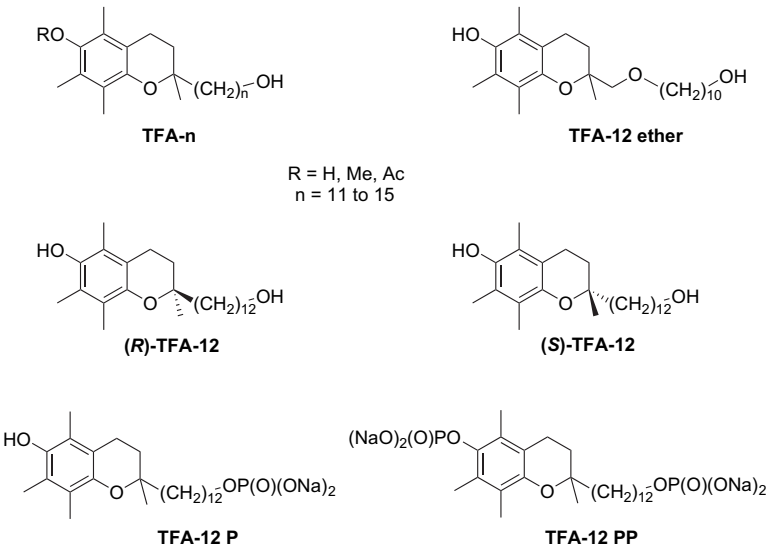
TFAs being able to modulate microglial activation,[10] we wanted to investigate if and to what extend the antioxidative capacity provided by the chroman ring takes part in this activity. In this aim, two new series AcTFAs and MeTFAs were synthesized. Both series have the phenol function, essential for their antioxidant activity, protected by a more or less stable group in biological environment.

In order to investigate the importance of the linking atom between the chroman ring and the ω-alkanol side chain, TFA-12 ether having an oxygen-linking atom was synthesized.

As previously described, the 2*R*-isomer of vitamin E dominates the biokinetics. In order to determine a possible stereogenic effect in the modulation of microglial activation, (*R*)-TFA-12 and (*S*)-TFA-12 were synthesized.

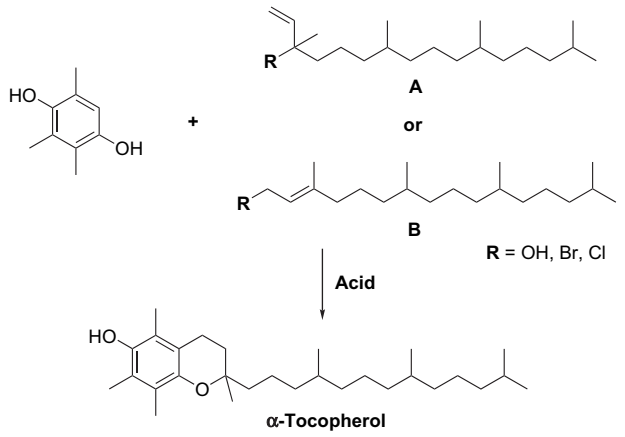
Finally, in order to determine the ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties of TFA-12 and to study its effects on an animal model of multiple sclerosis, the syntheses of water-soluble prodrugs TFA-12 P and TFA-12 PP were developed.

Vitamin E is a very common antioxidant used for food conservation and has thus evoked large synthetic interest.[13] Most industrial preparation processes of (all-*rac*)-α-tocopherol are based on a Lewis or Broensted acid catalyzed condensation of THQ with isophytol **A** (R=OH),[14] phytol



Scheme 2. Different tocopherol fatty alcohols.

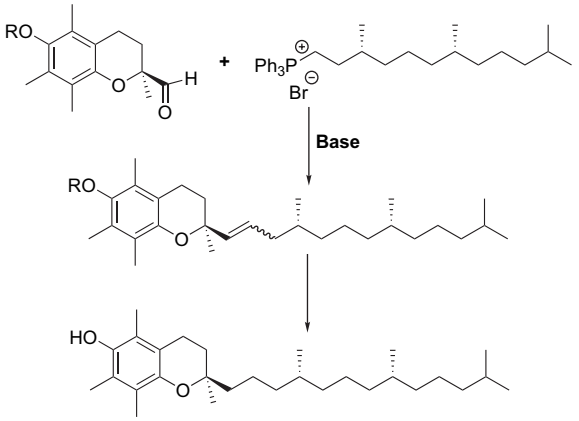
B (R=OH),[15] or the corresponding halides **A** (R=Br or Cl)[16] or **B** (R=Br or Cl)[17] (Scheme 3).



Scheme 3. Industrial synthesis of (all-*rac*)-α-tocopherol.

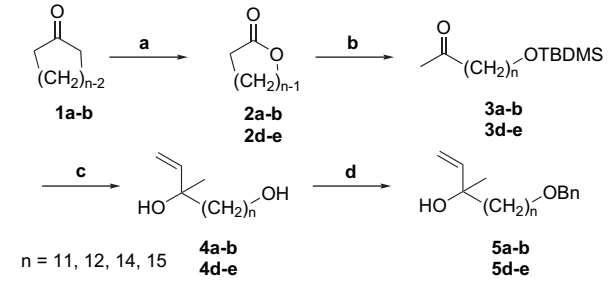
Industrial chroman ring formation can also be achieved by a regioselective Rh(I)-catalyzed arylation of β-springene with THQ.[18]

Several methods have been developed to synthesize chiral chromans or optically active α-tocopherol.[19] Most procedures are based on Wittig[2,3b,20] (Scheme 4) or Julia[6] type couplings of an activated chroman moiety with the corresponding side chain.



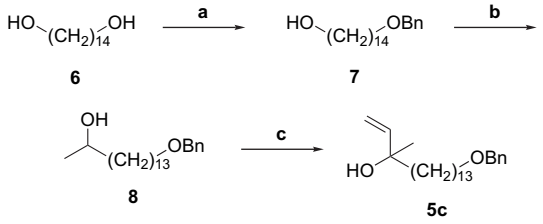
Scheme 4. Synthesis of (2*R*,4′*R*,8′*R*)-α-tocopherol.

TFAs were first synthesized through *C*-alkylation of THQ using ω-benzyloxy allylic alcohols **5a–e** (Scheme 5). These



Scheme 5. Reagents and conditions: (a) *m*-CPBA, CF_3CO_2H, CH_2Cl_2, reflux (80–85%); (b) (i) NHMeOMe·HCl, MeLi, (ii) MeLi, (iii) TBDMSCl, imidazole, THF, 0 °C to rt (68–76%); (c) (i) $CH_2CHMgBr$, THF, 0 °C to rt, (ii) TBAF (66–88%); (d) NaH, BnBr, THF, reflux (73–81%).

key intermediates were obtained starting either from the corresponding cyclic ketones and lactones (Schemes 5 and 6) or from the corresponding 1,ω-diol (Scheme 6).



Scheme 6. Reagents and conditions: (a) NaH, BnBr, NBu_4Br, THF, reflux (32%); (b) $(CO)_2Cl_2$, DMSO, NEt_3, MeMgBr, THF, −78 to 0 °C (66%); (c) $(CO)_2Cl_2$, DMSO, NEt_3, $CH_2CHMgBr$, THF, −78 to 0 °C (75%).

A Baeyer–Villiger type oxidation of ketones **1a–b** in the presence of trifluoroacetic acid gave lactones **2a–b** (Scheme 5).[21] Lactones **2d** and **2e** are commercially available. Formation of the Weinreb methyl hydroxamate using its salt in the presence of methyllithium followed by a subsequent addition of methyllithium gave the methylketones.[22] Finally silylation of the generated ω-hydroxyl function allowed us to obtain the protected hydroxyketones **3a–b,d–e** from the corresponding lactones **2a–b,d–e** in a one-step procedure with satisfactory overall yields.

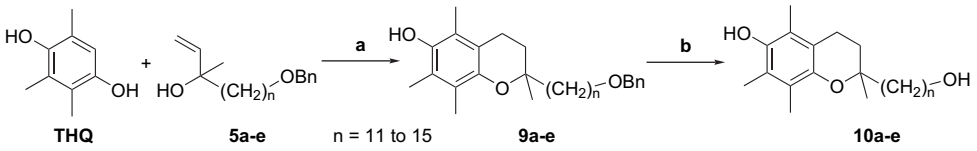
Nucleophilic addition of vinylmagnesium bromide followed by an *in situ* desilylation gave the corresponding ω-hydroxyl allylic alcohols **4a–b,d–e** which were then submitted to a regioselective benzylation in order to generate ω-benzyloxy allylic alcohols **5a–b,d–e**. The use of silylethers as temporary protecting groups remained necessary as all attempts to benzylate the ω-hydroxyl methylketones resulted in low yields. The silyl groups had nevertheless to be replaced by benzylethers as the *C*-alkylation of THQ using silyloxy allylic alcohols did not proceed.

The synthesis of ω-benzyloxy allylic alcohol **5c** was achieved by a monobenzylation of 1,14-tetradecandiol **6** followed by two subsequent Swern–Ireland[23] reactions using, respectively, methylmagnesium bromide and vinylmagnesium bromide as nucleophiles (Scheme 6).

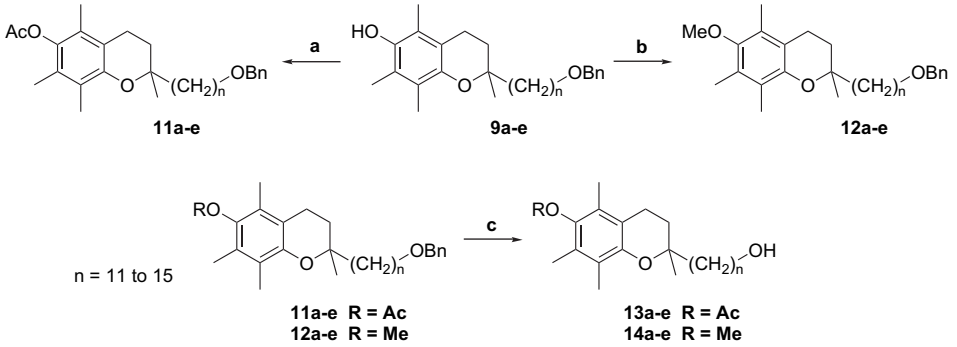
With the ω-benzyloxy allylic alcohols **5a–e** in hand, ω-benzylated TFAs **9a–e** were obtained by an acid catalyzed *C*-alkylation of THQ (Scheme 7). TFAs **10a–e** were finally obtained after treatment with hydrogen over palladium catalyst of compounds **9a–e**.

In order to generate the AcTFA and MeTFA series, the free phenol function of ω-benzylated TFAs **9a–e** was either acetylated in the presence of acetic anhydride in pyridine or methylated using sodium hydride and methyl iodide (Scheme 8). Both series were then submitted to treatment with hydrogen over palladium catalyst to give AcTFAs **13a–e** and MeTFAs **14a–e**, respectively.

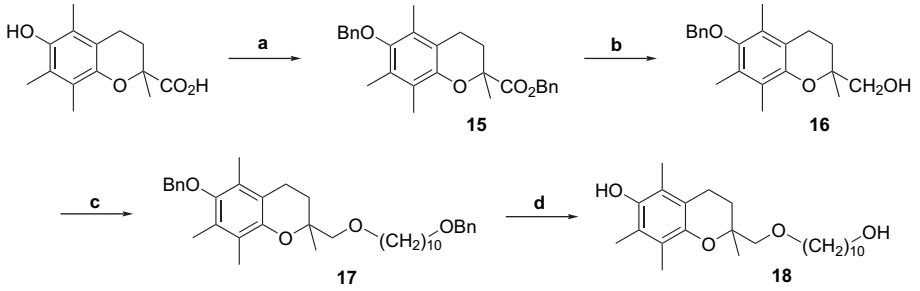
TFA-12 ether **18** was obtained starting from the short chain α-tocopherol analog Trolox® which was dibenzylated using benzyl bromide and potassium carbonate (Scheme 9). Benzyl ester **15** was reduced to its alcohol **16** which in the presence of sodium hydride and 10-iodo-1-(benzyloxy)-decane



Scheme 7. Reagents and conditions: (a) $ZnCl_2$, HCl, EtOAc, rt (68–76%); (b) H_2, Pd/C 5%, EtOH, rt (82–96%).



Scheme 8. Reagents and conditions: (a) Ac_2O, pyridine, rt (85–99%); (b) NaH, MeI, THF, 0 °C (81–99%); (c) H_2, Pd/C 5%, EtOH, rt (83–97%).



Scheme 9. Reagents and conditions: (a) BnBr, K_2CO_3, acetone, reflux (95%); (b) $LiAlH_4$, THF, 0 °C (96%); (c) NaH, 10-iodo-1-(benzyloxy)-decane, THF, reflux (42%); (d) H_2, Pd/C 5%, EtOH, rt (64%).

afforded compound **17**. TFA-12 ether **18** was finally obtained by hydrogenation of **17**.

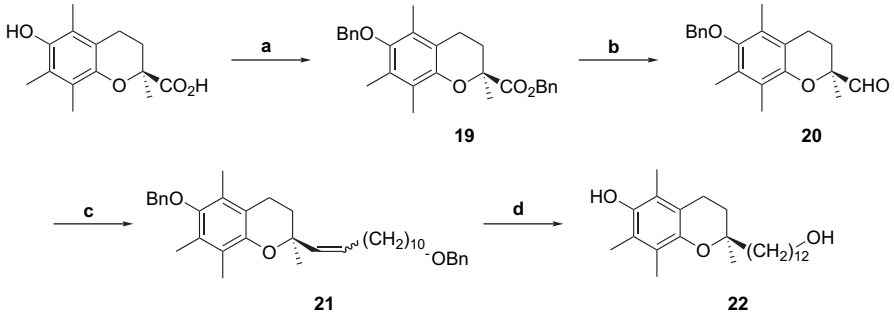
(*R*)-TFA-12 **22** and its enantiomer (*S*)-TFA-12 were synthesized starting either from (*S*)- or (*R*)-Trolox®, respectively.

(*S*)-Trolox® was dibenzylated as previously described (Scheme 10). The benzyl ester **19** was then reduced to its aldehyde **20** using DIBAL-H. A Wittig type coupling using Schlosser's conditions gave alkene **21** which after hydrogenation afforded (*R*)-TFA-12 **22**.

(*S*)-TFA-12 was obtained following the same procedure with identical yields starting from (*R*)-Trolox®.

As TFA-12 is highly lipophilic and thus needs the use of cosolvents (ethanol, dimethyl isosorbide) to achieve a maximum solubility of 1 mg/mL, we synthesized several prodrug forms of TFA-12 which have improved water solubility, namely hemisuccinate or phosphate salts[24] which are readily cleaved by esterases or phosphatases.

In a first attempt, a synthesis of the hemisuccinates prodrugs of TFA-12 was considered (data not shown).[25] Maximum



Scheme 10. Reagents and conditions: (a) BnBr, K_2CO_3, acetone, reflux (95%); (b) DIBAL-H, heptane, −78 °C (79%); (c) *t*-BuLi, *t*-BuOK, 11-benzyloxy-undecanyltriphenylphosphonium bromide, THF, −78 to 0 °C (93%); (d) H_2, Pd/C 5%, EtOH, rt (73%).

water solubility of the bis-hemisuccinate prodrug (4 mg/mL in saline) was insufficient to study the acute toxicity of TFA-12 and so we turned to the synthesis of phosphate prodrugs.

The sodium salt of the phosphoric acid monoester TFA-12 P **25** was synthesized in three steps starting from TFA-12 **10b** (Scheme 11). After protection of the phenolic moiety, the aliphatic alcohol was phosphorylated using the phosphoramidite method developed by Fraser-Reid.[26] The benzyl groups of compound **24** were removed by treatment with hydrogen over palladium catalyst. However, the disodium salt **25**, obtained reacting the corresponding phosphoric acid with NaOH 1 N, still had poor aqueous solubility (<1 mg/mL in saline).

We thus turned to the synthesis of bisphosphate monoester TFA-12 PP **28**. Using the phosphoramidite method resulted in a mixture of by-products due to the oxidation of the chroman ring in the presence of *m*-chloroperoxybenzoic acid.

The method developed by Silverberg[27] which first phosphorylates the phenol group using dibenzyl phosphonate, carbon tetrachloride, *N*,*N*-diisopropylethylamine, and catalytic dimethyl aminopyridine in acetonitrile did not proceed efficiently probably due to the poor solubility of TFA-12 in acetonitrile. Surprisingly, running the reaction in dichloromethane, resulted in complete regioselective phosphorylation of the aliphatic alcohol yielding phosphate **26**. Hence, we then used the phosphoramidite method in order to obtain the bisphosphate **27** (Scheme 12).

After treatment with hydrogen over palladium catalyst, the tetrasodium salt of the bisphosphate monoester TFA-12 PP **28** was obtained with a yield of 82%. This compound has appreciable aqueous solubility (15 mg/mL in saline) and sufficient stability to allow its development for intravenous administration.

In order to determine the antioxidant activity of the different TFAs, their free radical scavenging activity was evaluated by determining the corresponding IC_{50} using the DPPH (2,2′-di(4-*tert*-octylphenyl)-1-picrylhydrazyl)[28] test (Table 1).

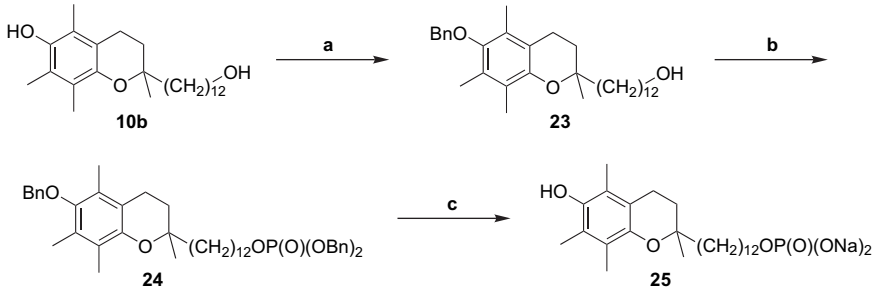
Table 1. IC_{50} of the different TFAs after 15 min in the presence of DPPH

Entry	Compound	IC_{50} (mM)	Error
1	Trolox®	0.08	±0.03
2	α-Tocopherol	0.90	±0.06
3	TFA-12 **10b**	0.90	±0.03
4	TFA-12 ether **18**	1.51	±0.07
5	AcTFA-12 **13b**	>10	—
6	MeTFA-12 **14b**	>10	—
7	TFA-12 PP **28**	>10	—

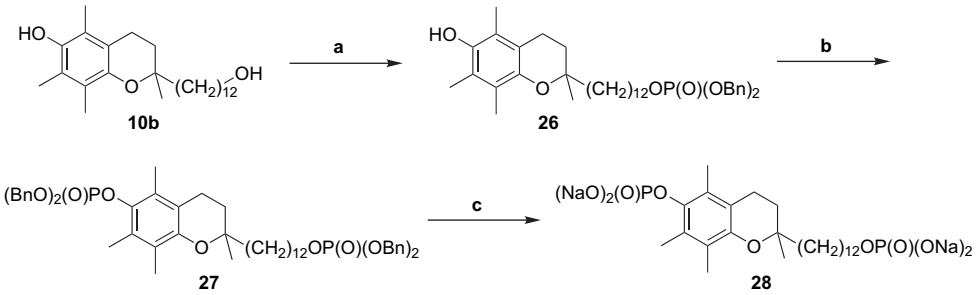
The IC_{50}s of a given series of TFAs were not affected by the length of the side chain (data not shown).

Trolox® and α-tocopherol (entries 1 and 2) were used as control compounds. Trolox® generally has better antioxidant activity because of its increased ethanol solubility compared to α-tocopherol. Vitamin E and TFA-12 (entries 2 and 3) have identical IC_{50}s, whereas AcTFA-12, MeTFA-12, and TFA-12 PP (entries 5–7) did not show any antioxidant activity (IC_{50}>10 mM).

These findings are consistent with the fact that the phenol function of the chroman moiety is crucial for the antioxidant activity.



Scheme 11. Reagents and conditions: (a) BnBr, K_2CO_3, acetone, reflux (73%); (b) (i) $iPr_2NP(OBn)_2$, tetrazole, CH_2Cl_2, rt, (ii) *m*-CPBA, CH_2Cl_2, 0 °C (85%); (c) (i) H_2, Pd/C 5%, EtOH, rt, (ii) NaOH 1 N, EtOH, rt (74%).



Scheme 12. Reagents and conditions: (a) $(BnO)_2P(O)H$, CCl_4, DIEA, DMAP, CH_2Cl_2, −10 °C (78%); (b) (i) $iPr_2NP(OBn)_2$, tetrazole, CH_2Cl_2, rt, (ii) *m*-CPBA, CH_2Cl_2, 0 °C (89%); (c) (i) H_2, Pd/C 5%, EtOH, rt, (ii) NaOH 1 N, EtOH, rt (82%).

3. Conclusion

In order to further investigate the potent neurobiological activities of the TFAs, several series of TFAs have been synthesized. TFAs, AcTFAs, and MeTFAs were prepared via *C*-alkylation of THQ whereas (*R*)-TFA-12, its enantiomer, and the different water-soluble prodrugs were obtained through a Wittig coupling reaction. Both syntheses allowed us to obtain sufficient quantities of products to carry on the biological testings on microglial activation and on animal models of multiple sclerosis.

4. Experimental

4.1. General

Tetrahydrofuran was distilled from sodium/benzophenone under argon prior use. Dichloromethane was distilled from calcium hydride. All reactions involving moisture sensitive reactants were executed under an argon atmosphere using oven dried and/or flame dried glassware. ^{1}H NMR spectra were recorded on a Bruker Advance 300 (300 MHz) spectrometer as solutions in $CDCl_3$ or CD_3OD. Chemical shifts are expressed in parts per million (ppm, δ) downfield from tetramethylsilane (TMS) and are referenced to $CHCl_3$ (7.26 ppm) or CH_3OH (3.31 ppm) as internal standard. *J* values are expressed in hertz (Hz). ^{13}C NMR spectra were recorded on a Bruker Advance 300 (75 MHz) spectrometer as solutions in $CDCl_3$ or CD_3OD. Chemical shifts are expressed in parts per million (ppm, δ) downfield from tetramethylsilane (TMS) and are referenced to $CHCl_3$ (77.4 ppm) or CH_3OH (49.0 ppm) as internal standard. The attribution of different carbons (C, CH, CH_2, CH_3) was determined by ^{13}C to ^{1}H polarization transfer (DEPT). ^{31}P NMR spectra were recorded on a Bruker Advance 300 (121.5 MHz) spectrometer as solutions in $CDCl_3$ or D_2O. Chemical shifts are expressed in parts per million (ppm, δ) downfield with a positive sign relative to external 85% H_3PO_4 in H_2O. Mass spectra (MS) were measured on a MicroTOF Daltonics Electrospray apparatus by direct introduction (a positive ion polarity, a set nebulizer at 1.20 bar, a set capillary at 4500 V, an exit at 120 V, a heater at 150 °C, at 5.5 L/min). Optical rotations was obtained in the indicated solvent at ambient temperature on a Perkin–Elmer 241. Routine monitoring of reactions were performed using 60 F_{254} silica gel TLC plates (Merck), which were dipped in a solution of vanillin (1 g) in EtOH–H_2SO_4 (95:5) and heated on a hot plate. Merck silica gel 60 F_{254} was used for column chromatography.

4.1.1. Oxacyclotridecan-2-one (2a).[29] To a solution of cyclododecanone (3.0 g, 16.44 mmol, 1 equiv) in dry CH_2Cl_2 (35 mL) were added *m*-chloroperbenzoic acid (6.80 g, 39.44 mmol, 2.4 equiv) and acetic acid (1.28 mL, 39.44 mmol, 1 equiv) and the mixture was refluxed in the dark for 24 h. A saturated solution of Na_2CO_3 (100 mL) was added to the reaction mixture and the aqueous layer was extracted with ether (3×100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc: 95:5) to give 2.77 g of a colorless oil (85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.36 (br s, 14H, H-5 to H-11), 1.64 (m, 4H, H-4, H-12), 2.35 (m, 2H, H-3), 4.13 (m, 2H, H-13). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.3–27.6 (C-4 to C-12), 34.4 (C-3), 63.2 (C-13), 173.9 (C-2).

4.1.2. Oxacyclotetradecan-2-one (2b).[30] Yield 85% (2.53 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.36 (br s, 16H, H-5 to H-12), 1.65 (m, 4H, H-4, H-13), 2.35 (m, 2H, H-3), 4.12 (m, 2H, H-14). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.4–27.6 (C-4 to C-13), 34.4 (C-3), 63.3 (C-14), 173.9 (C-2).

4.1.3. 13-(*tert*-Butyldimethylsilyloxy)tridecan-2-one (3a). To a solution of dimethylhydroxylamine hydrochloride (2.04 g, 20.95 mmol, 1.5 equiv) in dry THF (70 mL) cooled to 0 °C was slowly added MeLi 1.6 M in THF (25.3 mL, 40.51 mmol, 2.9 equiv). After 5 min at 0 °C, a solution of compound **2a** (2.77 g, 13.97 mmol, 1 equiv) in dry THF (40 mL) was slowly added and the resulting mixture was allowed to warm to rt. After 1 h at rt, the mixture was cooled to 0 °C and MeLi 1.6 M in THF (26.2 mL, 41.91 mmol, 3 equiv) was slowly added and the mixture was warmed to rt. After 2 h at rt, *tert*-butyldimethylsilyl chloride (3.16 g, 20.95 mmol, 1.5 equiv) and imidazole (1.43 g, 20.95 mmol, 1.5 equiv) were added. After 2 h, a saturated solution of NH_4Cl (100 mL) was added to the reaction mixture and the aqueous layer was extracted with ether (3×100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc: 9:1) to give 3.11 g of a white solid (68%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.04 (s, 6H, CH_3Si), 0.83 (s, 9H, CH_3C), 1.23 (br s, 14H, H-5 to H-11), 1.52 (m, 4H, H-4, H-12), 2.11 (s, 3H, H-1), 2.39 (t, *J* 7.4 Hz, 2H, H-3), 3.61 (t, *J* 6.6 Hz, 2H, H-13). ^{13}C NMR (75 MHz, $CDCl_3$) δ: −4.5 (CH_3Si), 18.9 (CSi), 23.8 (C-4), 25.7 (C-11), 26.5 (CH_3C), 29.1–29.8 (C-1, C-5 to C-10), 32.8 (C-12), 43.3 (C-3), 63.0 (C-13), 209.5 (C-2).

4.1.4. 14-(*tert*-Butyldimethylsilyloxy)tetradecan-2-one (3b). Yield 73% (2.54 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.04 (s, 6H, CH_3Si), 0.82 (s, 9H, CH_3C), 1.24 (br s, 16H, H-5 to H-12), 1.50 (m, 4H, H-4, H-13), 2.13 (s, 3H, H-1), 2.39 (t, *J* 7.4 Hz, 2H, H-3), 3.61 (t, *J* 6.6 Hz, 2H, H-14). ^{13}C NMR (75 MHz, $CDCl_3$) δ: −4.5 (CH_3Si), 18.9 (CSi), 23.8 (C-4), 25.7 (C-12), 26.5 (CH_3C), 29.0–29.8 (C-1, C-5 to C-11), 32.8 (C-13), 43.3 (C-3), 63.0 (C-14), 209.5 (C-2).

4.1.5. 16-(*tert*-Butyldimethylsilyloxy)hexadecan-2-one (3d). Yield 70% (2.72 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.04 (s, 6H, CH_3Si), 0.82 (s, 9H, CH_3C), 1.26 (br s, 20H, H-5 to H-14), 1.51 (m, 4H, H-4, H-15), 2.12 (s, 3H, H-1), 2.40 (t, *J* 7.4 Hz, 2H, H-3), 3.63 (t, *J* 6.6 Hz, 2H, H-16). ^{13}C NMR (75 MHz, $CDCl_3$) δ: −4.5 (CH_3Si), 18.8 (CSi), 23.8 (C-4), 25.7 (C-14), 26.5 (CH_3C), 29.0–29.8 (C-1, C-5 to C-13), 32.8 (C-15), 43.3 (C-3), 63.0 (C-16), 209.5 (C-2).

4.1.6. 17-(*tert*-Butyldimethylsilyloxy)heptadecan-2-one (3e). Yield 76% (2.4 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.04 (s, 6H, CH_3Si), 0.83 (s, 9H, CH_3C), 1.23 (br s, 22H, H-5 to H-15), 1.52 (m, 4H, H-4, H-16), 2.11 (s, 3H, H-1), 2.39 (t, *J* 7.4 Hz, 2H, H-3), 3.61 (t, *J* 6.6 Hz, 2H, H-17). ^{13}C NMR (75 MHz, $CDCl_3$) δ: −4.5 (CH_3Si), 18.9

(CSi), 23.8 (C-4), 25.7 (C-15), 26.5 (CH_3C), 29.1–29.8 (C-1, C-5 to C-14), 32.8 (C-16), 43.3 (C-3), 63.0 (C-17), 209.5 (C-2).

4.1.7. 12-Methyltetradec-13-ene-1,12-diol (4a). To a solution of compound **3a** (2.14 g, 3.04 mmol, 1 equiv) in dry THF (30 mL) cooled to 0 °C was slowly added vinylmagnesium bromide 1 M in THF (9.1 mL, 9.13 mmol, 3 equiv) and the resulting mixture was allowed to warm to rt. After 3 h at rt, tetrabutylammonium fluoride 1 M in THF (4.6 mL, 4.56 mmol, 1.5 equiv) was added. After 15 h, a saturated solution of NH_4Cl (100 mL) was added to the reaction mixture and the aqueous layer was extracted with ether (3×100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc: 7:3) to give 0.55 g of a white solid (75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.24 (s, 3H, CH_3), 1.24 (br s, 18H, H-3 to H-11), 1.53 (m, 4H, H-2, H-10), 3.60 (t, 2H, J 6.4 Hz, H-1), 5.03 (dd, 1H, J 1.1 Hz, J_Z 10.7 Hz, H-14), 5.17 (dd, 1H, J_E 17.4 Hz, H-14′), 5.91 (dd, 1H, H-13). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.9 (C-10), 25.8 (C-9), 27.5 (CH_3), 29.4–30.1 (C-3 to C-8), 32.8 (C-2), 42.3 (C-11), 63.0 (C-1), 73.4 (C-12), 111.4 (C-14), 145.3 (C-13).

4.1.8. 13-Methylpentadec-14-ene-1,13-diol (4b). Yield 66% (0.98 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.26 (s, 3H, CH_3), 1.24 (br s, 20H, H-3 to H-12), 1.50 (m, 4H, H-2, H-11), 3.60 (t, 2H, J 6.4 Hz, H-1), 5.03 (dd, 1H, J 1.1 Hz, J_Z 10.7 Hz, H-15), 5.17 (dd, 1H, J_E 17.4 Hz, H-15′), 5.89 (dd, 1H, H-14). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.9 (C-11), 25.8 (C-10), 27.5 (CH_3), 29.4–30.1 (C-3 to C-9), 32.7 (C-2), 42.3 (C-12), 63.0 (C-1), 73.4 (C-13), 111.4 (C-15), 145.2 (C-14).

4.1.9. 15-Methylheptadec-16-ene-1,15-diol (4d). Yield 81% (0.38 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.25 (s, 3H, CH_3), 1.24 (br s, 24H, H-3 to H-14), 1.51 (m, 4H, H-2, H-13), 3.61 (t, 2H, J 6.4 Hz, H-1), 5.02 (dd, 1H, J 1.1 Hz, J_Z 10.7 Hz, H-17), 5.18 (dd, 1H, J_E 17.4 Hz, H-17′), 5.89 (dd, 1H, H-16). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.8 (C-13), 25.8 (C-12), 27.6 (CH_3), 29.3–30.1 (C-3 to C-11), 32.7 (C-2), 42.3 (C-14), 63.1 (C-1), 73.3 (C-15), 111.5 (C-17), 145.3 (C-16).

4.1.10. 16-Methyloctadec-17-ene-1,16-diol (4e). Yield 88% (0.35 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.24 (s, 3H, CH_3), 1.25 (br s, 26H, H-3 to H-15), 1.51 (m, 4H, H-2, H-14), 3.62 (t, 2H, J 6.4 Hz, H-1), 5.02 (dd, 1H, J 1.1 Hz, J_Z 10.7 Hz, H-18), 5.18 (dd, 1H, J_E 17.4 Hz, H-18′), 5.90 (dd, 1H, H-17). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.9 (C-14), 25.7 (C-13), 27.5 (CH_3), 29.4–30.0 (C-3 to C-12), 32.8 (C-2), 42.4 (C-15), 63.0 (C-1), 73.3 (C-16), 111.4 (C-18), 145.3 (C-17).

4.1.11. 14-(Benzyloxy)-3-methyltetradec-1-ene-3-ol (5a). To a solution of compound **4a** (0.40 g, 1.65 mmol, 1 equiv) in dry THF (20 mL) was added sodium hydride (0.16 g, 6.60 mmol, 4 equiv) and the resulting suspension was refluxed. After 30 min, benzyl bromide (0.24 mL, 1.98 mmol, 1.2 equiv) was added and the refluxing was continued. After 3 h, a saturated solution of NH_4Cl (100 mL) was added to the reaction mixture and the aqueous layer was extracted with ether (3×100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc: 85:15) to give 0.40 g of a colorless oil (73%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.26 (br s, 19H, H-5 to H-12, CH_3), 1.58 (m, 4H, H-4, H-13), 3.48 (t, 2H, J 6.6 Hz, H-14), 4.50 (s, 2H, CH_2Ph), 5.03 (dd, 1H, J 1.2 Hz, J_Z 10.6 Hz, H-1), 5.21 (dd, 1H, J_E 17.3 Hz, H-1′), 5.91 (dd, 1H, H-2), 7.29 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.9 (C-5), 26.2 (C-6), 27.8 (CH_3), 29.5–30.1 (C-7 to C-14), 42.3 (C-4), 70.5 (C-15), 72.7 (CH_2Ph), 73.3 (C-3), 111.4 (C-1), 127.3, 127.6, 128.5 (Ar-CH), 138.7 (Ar-C), 145.3 (C-2).

4.1.12. 15-(Benzyloxy)-3-methylpentadec-1-ene-3-ol (5b). Yield 76% (0.85 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.26 (br s, 21H, H-5 to H-12, CH_3), 1.58 (m, 4H, H-4, H-14), 3.48 (t, 2H, J 6.6 Hz, H-15), 4.50 (s, 2H, CH_2Ph), 5.03 (dd, 1H, J 1.2 Hz, J_Z 10.6 Hz, H-1), 5.21 (dd, 1H, J_E 17.3 Hz, H-1′), 5.91 (dd, 1H, H-2), 7.29 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.9 (C-5), 26.2 (C-6), 27.8 (CH_3), 29.5–30.1 (C-7 to C-14), 42.3 (C-4), 70.5 (C-15), 72.7 (CH_2Ph), 73.3 (C-3), 111.4 (C-1), 127.3, 127.6, 128.5 (Ar-CH), 138.7 (Ar-C), 145.3 (C-2).

4.1.13. 17-(Benzyloxy)-3-methylheptadec-1-ene-3-ol (5d). Yield 79% (0.89 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.25 (br s, 25H, H-5 to H-14, CH_3), 1.58 (m, 4H, H-4, H-16), 3.49 (t, 2H, J 6.6 Hz, H-17), 4.51 (s, 2H, CH_2Ph), 5.05 (dd, 1H, J 1.2 Hz, J_Z 10.6 Hz, H-1), 5.21 (dd, 1H, J_E 17.3 Hz, H-1), 5.90 (dd, 1H, H-2), 7.29 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.9 (C-5), 26.2 (C-6), 27.7 (CH_3), 29.6–30.1 (C-7 to C-16), 42.3 (C-4), 70.5 (C-18), 72.7 (CH_2Ph), 73.3 (C-3), 111.4 (C-1), 127.3, 127.6, 128.5 (Ar-CH), 138.7 (Ar-C), 145.3 (C-2).

4.1.14. 18-(Benzyloxy)-3-methyloctadec-1-ene-3-ol (5e). Yield 89% (1.06 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.27 (br s, 27H, H-5 to H-16, CH_3), 1.59 (m, 4H, H-4, H-17), 3.47 (t, 2H, J 6.6 Hz, H-18), 4.51 (s, 2H, CH_2Ph), 5.04 (dd, 1H, J 1.2 Hz, J_Z 10.6 Hz, H-1), 5.20 (dd, 1H, J_E 17.3 Hz, H-1), 5.91 (dd, 1H, H-2), 7.30 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.9 (C-5), 26.2 (C-6), 27.7 (CH_3), 29.5–30.0 (C-7 to C-17), 42.4 (C-4), 70.5 (C-18), 72.8 (CH_2Ph), 73.3 (C-3), 111.4 (C-1), 127.4, 127.6, 128.3 (Ar-CH), 138.7 (Ar-C), 145.3 (C-2).

4.1.15. 14-(Benzyloxy)tetradecan-1-ol (7). To a suspension of tetradecan-1,14-diol (3.43 g, 14.89 mmol, 1 equiv) in dry THF (30 mL) was added sodium hydride (0.50 g, 20.84 mmol, 1.4 equiv) and the resulting suspension was refluxed. After 30 min, benzyl bromide (1.80 mL, 14.89 mmol, 1 equiv) and tetrabutylammonium fluoride (0.96 g, 2.98 mmol, 0.2 equiv) were added and the refluxing was continued. After 12 h, a saturated solution of NH_4Cl (100 mL) was added to the reaction mixture and the aqueous layer was extracted with ether (3×100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc: 7:3) to give 1.52 g of a white solid (32%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.27 (br s, 20H, H-3 to H-12), 1.59 (m, 4H, H-2,

H-13), 3.48 (t, *J* 6.6 Hz, 2H, H-14), 3.63 (t, *J* 6.4 Hz, 2H, H-1), 4.52 (s, 2H, C*H*$_2$Ph), 7.32 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 25.7–29.3 (C-3 to C-13), 32.8 (C-2), 63.0 (C-1), 70.5 (C-14), 72.8 (*C*H$_2$Ph), 126.9, 127.4, 128.3 (Ar-CH), 138.7 (Ar-C).

4.1.16. 15-(Benzyloxy)pentadecan-2-ol (8). To a solution of oxalyl chloride (0.68 mL, 8.03 mmol, 1.05 equiv) in dry THF (15 mL) cooled to −78 °C was slowly added anhydrous DMSO (0.60 mL, 8.41 mmol, 1.1 equiv). The solution was allowed to reach −35 °C and stirred for 5 min at this temperature before being cooled to −78 °C again. A solution of compound **7** (2.45 g, 7.65 mmol, 1 equiv) in THF (18 mL) was slowly added and the resulting mixture was warmed to −35 °C. After 15 min at this temperature, triethylamine (6.4 mL, 45.86 mmol, 6 equiv) was added and stirring was continued at 0 °C for 2 h. The resulting suspension was cooled to −78 °C and methylmagnesium bromide 3 M in ether (12.8 mL, 38.22 mL, 5 equiv) was slowly added. After 2 h at rt, a saturated solution of NH_4Cl (100 mL) was added to the reaction mixture and the aqueous layer was extracted with ether (3×100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc: 8:2) to give 1.69 g of a white solid (66%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.21 (d, 3H, *J* 6.2 Hz, H-1), 1.32 (br s, 20H, H-4 to H-13), 1.40 (m, 2H, H-3), 1.65 (m, 2H, H-14), 3.49 (t, *J* 6.6 Hz, 2H, H-15), 3.80 (t, *J* 5.3 Hz, 2H, H-2), 4.53 (s, 2H, C*H*$_2$Ph), 7.33 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.7 (C-1), 27.1–31.0 (C-4 to C-14), 40.6 (C-3), 69.4 (C-2), 71.8 (C-15), 74.1 (*C*H$_2$Ph), 128.7, 128.9, 129.6 (Ar-CH), 140.0 (Ar-C).

4.1.17. 16-(Benzyloxy)-3-methylhexadec-1-ene-3-ol (5c). To a solution of oxalyl chloride (1.42 mL, 16.57 mmol, 2.4 equiv) in dry THF (16 mL) cooled to −78 °C was slowly added anhydrous DMSO (1.2 mL, 16.92 mmol, 2.45 equiv). The solution was allowed to reach −35 °C and stirred for 5 min at this temperature before being cooled to −78 °C again. A solution of compound **8** (2.31 g, 6.90 mmol, 1 equiv) in THF (22 mL) was slowly added and the resulting mixture was warmed to −35 °C. After 15 min at this temperature, triethylamine (5.76 mL, 41.33 mmol, 6 equiv) was added and stirring was continued at 0 °C for 2 h. The resulting suspension was cooled to −78 °C and vinylmagnesium bromide 1 M in ether (48.33 mL, 48.33 mL, 7 equiv) was slowly added. After 2 h at rt, a saturated solution of NH_4Cl (100 mL) was added to the reaction mixture and the aqueous layer was extracted with ether (3×100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc: 8:2) to give 1.86 g of a white solid (75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.26 (br s, 23H, H-5 to H-14, C*H*$_3$), 1.61 (m, 4H, H-4, H-15), 3.45 (t, *J* 6.6 Hz, 2H, H-16), 4.50 (s, 2H, C*H*$_2$Ph), 5.02 (dd, *J* 1.3 Hz, J_Z 10.7 Hz, 1H, H-1), 5.19 (dd, J_E 17.3 Hz, 1H, H-1′), 5.90 (dd, 1H, H-2), 7.34 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.9 (C-5), 26.5 (C-6), 27.7 (*C*H$_3$), 29.5–30.0 (C-7 to C-15), 42.4 (C-4), 70.5 (C-16), 72.8 (*C*H$_2$Ph), 73.3 (C-3), 111.5 (C-1), 127.5, 127.6, 128.7 (Ar-CH), 138.7 (Ar-C), 145.4 (C-2).

4.1.18. 2-(11-(Benzyloxy)undecyl)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-ol (9a). To a solution of THQ (0.12 g, 0.75 mmol, 1 equiv) in EtOAc (20 mL) were added compound **5a** (0.25 g, 0.75 mmol, 1 equiv), zinc chloride (0.08 g, 0.60 mmol, 0.8 equiv), and HCl 37% aq (0.013 mL, 0.15 mmol, 0.2 equiv) and the resulting mixture was stirred at rt. After 48 h, a saturated solution of $NaHCO_3$ (100 mL) was added to the reaction mixture and the aqueous layer was extracted with ether (3×100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc: 85:15) to give 0.26 g of a white solid (75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.22 (s, 3H, H-2a), 1.24 (br s, 16H, H-2′ to H-9′), 1.57 (m, 4H, H-1′, H-10′), 1.78 (m, 2H, H-3), 2.11 (s, 6H, H-5a, H-7a), 2.15 (s, 3H, H-8a), 2.60 (t, 2H, *J* 6.8 Hz, H-4), 3.47 (t, 2H, *J* 6.6 Hz, H-11′), 4.18 (s, 2H, C*H*$_2$Ph), 7.32 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.3 (C-5a), 11.8 (C-7a), 12.2 (C-8a), 20.8 (C-4), 23.5 (C-2′), 23.8 (C-2a), 26.3 (C-3′), 29.5–30.0 (C-4′ to C-10′), 31.5 (C-3), 39.4 (C-1′), 70.5 (C-11′), 72.7 (*C*H$_2$Ph), 74.5 (C-2), 117.3 (C-5), 118.3 (C-6), 120.9 (C-8), 122.6 (C-7), 127.4, 127.6, 128.3 (Ar-CH), 138.7 (Ar-C), 144.6 (C-4a), 145.6 (C-8b).

4.1.19. 2-(12-(Benzyloxy)dodecyl)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-ol (9b). Yield 68% (0.20 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.23 (s, 3H, H-2a), 1.25 (br s, 18H, H-2′ to H-10′), 1.56 (m, 4H, H-1′, H-11′), 1.78 (m, 2H, H-3), 2.10 (s, 6H, H-5a, H-7a), 2.15 (s, 3H, H-8a), 2.61 (t, 2H, *J* 6.8 Hz, H-4), 3.47 (t, 2H, *J* 6.6 Hz, H-12′), 4.18 (s, 2H, C*H*$_2$Ph), 7.33 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.3 (C-5a), 11.7 (C-7a), 12.2 (C-8a), 20.8 (C-4), 23.5 (C-2′), 23.8 (C-2a), 26.3 (C-3′), 29.5–30.0 (C-4′ to C-11′), 31.5 (C-3), 39.4 (C-1′), 70.5 (C-12′), 72.7 (*C*H$_2$Ph), 74.4 (C-2), 117.2 (C-5), 118.3 (C-6), 120.9 (C-8), 122.6 (C-7), 127.4, 127.6, 128.3 (Ar-CH), 138.5 (Ar-C), 144.7 (C-4a), 145.6 (C-8b).

4.1.20. 2-(13-(Benzyloxy)tridecyl)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-ol (9c). Yield 70% (0.23 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.23 (s, 3H, H-2a), 1.26 (br s, 20H, H-2′ to H-11′), 1.59 (m, 4H, H-1′, H-12′), 1.79 (m, 2H, H-3), 2.12 (s, 6H, H-5a, H-7a), 2.15 (s, 3H, H-8a), 2.61 (t, 2H, *J* 6.8 Hz, H-4), 3.47 (t, 2H, *J* 6.6 Hz, H-13′), 4.19 (s, 2H, C*H*$_2$Ph), 7.33 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.3 (C-5a), 11.8 (C-7a), 12.2 (C-8a), 20.7 (C-4), 23.5 (C-2′), 23.8 (C-2a), 26.3 (C-3′), 29.5–30.0 (C-4′ to C-12′), 31.5 (C-3), 39.4 (C-1′), 70.5 (C-13′), 72.7 (*C*H$_2$Ph), 74.4 (C-2), 117.2 (C-5), 118.5 (C-6), 120.9 (C-8), 122.6 (C-7), 127.4, 127.6, 128.3 (Ar-CH), 138.5 (Ar-C), 144.7 (C-4a), 145.6 (C-8b).

4.1.21. 2-(14-(Benzyloxy)tetradecyl)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-ol (9d). Yield 69% (0.42 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.22 (s, 3H, H-2a), 1.25 (br s, 22H, H-2′ to H-12′), 1.59 (m, 4H, H-1′, H-13′), 1.79 (m, 2H, H-3), 2.12 (s, 6H, H-5a, H-7a), 2.15 (s, 3H, H-8a), 2.61 (t, 2H, *J* 6.8 Hz, H-4), 3.47 (t, 2H, *J* 6.6 Hz, H-14′), 4.19 (s, 2H, C*H*$_2$Ph), 7.33 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.3 (C-5a), 11.8 (C-7a), 12.2 (C-8a), 20.7 (C-4), 23.5 (C-2′), 23.8 (C-2a), 26.3 (C-3′), 29.5–30.0 (C-4′ to C-13′), 31.5 (C-3), 39.4 (C-1′), 70.5 (C-14′), 72.8

(CH_2Ph), 74.4 (C-2), 117.2 (C-5), 118.5 (C-6), 120.9 (C-8), 122.6 (C-7), 127.4, 127.6, 128.3 (Ar-CH), 138.5 (Ar-C), 144.7 (C-4a), 145.6 (C-8b).

4.1.22. 2-(15-(Benzyloxy)pentadecyl)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-ol (9e). Yield 76% (0.29 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.22 (s, 3H, H-2a), 1.25 (br s, 24H, H-2′ to H-13′), 1.58 (m, 4H, H-1′, H-14′), 1.78 (m, 2H, H-3), 2.11 (s, 6H, H-5a, H-7a), 2.16 (s, 3H, H-8a), 2.6 (t, 2H, *J* 6.8 Hz, H-4), 3.46 (t, 2H, *J* 6.6 Hz, H-15′), 4.18 (s, 2H, CH_2Ph), 7.31 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.3 (C-5a), 11.8 (C-7a), 12.2 (C-8a), 20.7 (C-4), 23.6 (C-2′), 23.8 (C-2a), 26.2 (C-3′), 29.5–30.0 (C-4′ to C-14′), 31.5 (C-3), 39.5 (C-1′), 70.5 (C-15′), 72.8 (CH_2Ph, C-16′), 74.5 (C-2), 117.3 (C-5), 118.4 (C-6), 121.0 (C-8), 122.6 (C-7), 127.4, 127.6, 128.3 (Ar-CH), 138.7 (Ar-C), 144.5 (C-4a), 145.6 (C-8b).

4.1.23. 2-(11-Hydroxyundecyl)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-ol (10a). To a solution of compound **9a** (0.45 g, 0.96 mmol, 1 equiv) in EtOH (15 mL) was added palladium on charcoal (5%, 0.20 g, 20% w/w). The mixture was stirred under an atmosphere of hydrogen at rt. After 4 h, the mixture was filtered on Celite and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc: 6:4) to give 0.35 g of a white solid (96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.23 (s, 3H, H-2a), 1.26 (br s, 16H, H-2′ to H-9′), 1.56 (m, 4H, H-1′, H-10′), 1.78 (m, 2H, H-3), 2.13 (s, 6H, H-5a, H-7a), 2.16 (s, 3H, H-8a), 2.61 (t, 2H, *J* 6.8 Hz, H-4), 3.64 (t, 2H, *J* 6.6 Hz, H-11′). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.3 (C-5a), 11.7 (C-7a), 12.2 (C-8a), 20.7 (C-4), 23.6 (C-2′), 23.8 (C-2a), 26.2 (C-3′), 29.5–30.0 (C-4′ to C-10′), 31.5 (C-3), 39.5 (C-1′), 70.5 (C-11′), 74.5 (C-2), 117.4 (C-5), 118.4 (C-6), 121.0 (C-8), 122.7 (C-7), 144.5 (C-4a), 145.6 (C-8b). *m*/*z* (ESI$^+$) 399 (M+Na$^+$). HRMS (ESI$^+$) calcd for $C_{24}H_{40}O_3Na$ (MNa$^+$) 399.2870. Found 399.2864.

4.1.24. 2-(12-Hydroxydodecyl)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-ol (10b). Yield 92% (0.24 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.22 (s, 3H, H-2a), 1.25 (br s, 18H, H-2′ to H-10′), 1.55 (m, 4H, H-1′, H-11′), 1.78 (m, 2H, H-3), 2.13 (s, 6H, H-5a, H-7a), 2.16 (s, 3H, H-8a), 2.61 (t, 2H, *J* 6.8 Hz, H-4), 3.65 (t, 2H, *J* 6.6 Hz, H-12′). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.3 (C-5a), 11.6 (C-7a), 12.2 (C-8a), 20.7 (C-4), 23.6 (C-2′), 23.8 (C-2a), 26.2 (C-3′), 29.5–30.1 (C-4′ to C-11′), 31.5 (C-3), 39.5 (C-1′), 70.5 (C-12′), 74.5 (C-2), 117.4 (C-5), 118.4 (C-6), 121.0 (C-8), 122.7 (C-7), 144.5 (C-4a), 145.6 (C-8b). *m*/*z* (ESI$^+$) 413 (M+Na$^+$). HRMS (ESI$^+$) calcd for $C_{25}H_{42}O_3Na$ (MNa$^+$) 413.3026. Found 413.3017.

4.1.25. 2-(13-Hydroxytridecyl)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-ol (10c). Yield 82% (0.41 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.23 (s, 3H, H-2a), 1.25 (br s, 20H, H-2′ to H-11′), 1.55 (m, 4H, H-1′, H-12′), 1.77 (m, 2H, H-3), 2.13 (s, 6H, H-5a, H-7a), 2.16 (s, 3H, H-8a), 2.61 (t, 2H, *J* 6.8 Hz, H-4), 3.65 (t, 2H, *J* 6.6 Hz, H-13′). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.3 (C-5a), 11.6 (C-7a), 12.3 (C-8a), 20.7 (C-4), 23.6 (C-2′), 23.8 (C-2a), 26.2 (C-3′), 29.6–30.1 (C-4′ to C-12′), 31.5 (C-3), 39.5 (C-1′), 70.5 (C-13′), 74.5 (C-2), 117.4 (C-5), 118.4 (C-6), 121.0 (C-8), 122.7 (C-7), 144.5 (C-4a), 145.6 (C-8b). *m*/*z* (ESI$^+$) 427 (M+Na$^+$). HRMS (ESI$^+$) calcd for $C_{26}H_{44}O_3Na$ (MNa$^+$) 427.3183. Found 427.3138.

4.1.26. 2-(14-Hydroxytetradecyl)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-ol (10d). Yield 87% (0.31 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.23 (s, 3H, H-2a), 1.24 (br s, 22H, H-2′ to H-12′), 1.55 (m, 4H, H-1′, H-13′), 1.78 (m, 2H, H-3), 2.13 (s, 6H, H-5a, H-7a), 2.15 (s, 3H, H-8a), 2.61 (t, 2H, *J* 6.8 Hz, H-4), 3.65 (t, 2H, *J* 6.6 Hz, H-14′). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.2 (C-5a), 11.6 (C-7a), 12.3 (C-8a), 20.7 (C-4), 23.6 (C-2′), 23.8 (C-2a), 26.2 (C-3′), 29.4–30.1 (C-4′ to C-13′), 31.5 (C-3), 39.5 (C-1′), 70.5 (C-14′), 74.5 (C-2), 117.4 (C-5), 118.4 (C-6), 121.0 (C-8), 122.7 (C-7), 144.5 (C-4a), 145.6 (C-8b). *m*/*z* (ESI$^+$) 441 (M+Na$^+$). HRMS (ESI$^+$) calcd for $C_{27}H_{46}O_3Na$ (MNa$^+$) 441.3339. Found 441.3319.

4.1.27. 2-(15-Hydroxypentadecyl)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-ol (10e). Yield 88% (0.12 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.22 (s, 3H, H-2a), 1.25 (br s, 24H, H-2′ to H-13′), 1.56 (m, 4H, H-1′, H-14′), 1.78 (m, 2H, H-3), 2.11 (s, 6H, H-5a, H-7a), 2.16 (s, 3H, H-8a), 2.6 (t, 2H, *J* 6.8 Hz, H-4), 3.64 (t, 2H, *J* 6.6 Hz, H-15′). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.3 (C-5a), 11.8 (C-7a), 12.2 (C-8a), 20.7 (C-4), 23.6 (C-2′), 23.8 (C-2a), 26.2 (C-3′), 29.5–30.0 (C-4′ to C-14′), 31.5 (C-3), 39.5 (C-1′), 70.5 (C-15′), 74.5 (C-2), 117.3 (C-5), 118.4 (C-6), 121.0 (C-8), 122.6 (C-7), 144.5 (C-4a), 145.6 (C-8b). *m*/*z* (ESI$^+$) 455 (M+Na$^+$). HRMS (ESI$^+$) calcd for $C_{28}H_{48}O_3Na$ (MNa$^+$) 455.3496. Found 455.3519.

4.1.28. 2-(11-(Benzyloxy)undecyl)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-yl acetate (11a). To a solution of compound **9a** (0.50 g, 1.07 mmol, 1 equiv) in dry pyridine (4 mL) was added acetic anhydride (0.52 mL, 2.36 mmol, 2.2 equiv) and the mixture was stirred at rt. After 24 h, a saturated solution of HCl 1 M (100 mL) was added to the reaction mixture and the aqueous layer was extracted with ether (3×100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc: 9:1) to give 0.52 g of a white solid (96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.25 (s, 3H, H-2a), 1.29 (br s, 16H, H-2′ to H-9′), 1.58 (m, 4H, H-1′, H-10′), 1.78 (m, 2H, H-3), 2.12 (s, 6H, H-5a, H-7a), 2.17 (s, 3H, H-8a), 2.34 (s, 3H, CH_3C=O), 2.60 (t, 2H, *J* 6.8 Hz, H-4), 3.48 (t, 2H, *J* 6.6 Hz, H-11′), 4.52 (s, 2H, CH_2Ph), 7.29 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.3–12.3 (C-5a, C-7a, C-8a, CH_3CO_2), 20.5 (C-4), 20.6 (C-2′), 23.7 (C-2a), 26.2 (C-3′), 29.4–30.1 (C-4′ to C-10′), 31.5 (C-3), 39.6 (C-1′), 70.5 (C-11′), 72.9 (CH_2Ph), 76.5 (C-2), 117.3 (C-5), 123.1 (C-6), 124.9 (C-7), 126.7 (C-8), 127.7–128.3 (Ar-CH), 138.7 (Ar-C), 140.5 (C-4a), 149.8 (C-8b), 169.8 (*C*=O).

4.1.29. 2-(12-(Benzyloxy)dodecyl)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-yl acetate (11b). Yield 85% (0.44 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.25 (s, 3H, H-2a), 1.29 (br s, 18H, H-2′ to H-10′), 1.59 (m, 4H, H-1′, H-11′), 1.77 (m, 2H, H-3), 2.13 (s, 6H, H-5a, H-7a), 2.17 (s, 3H, H-8a), 2.35 (s, 3H, CH_3CO_2), 2.61 (t, 2H, *J* 6.8 Hz, H-4), 3.47 (t, 2H, *J* 6.6 Hz, H-12′), 4.52 (s, 2H, CH_2Ph),

7.30 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.3–12.3 (C-5a, C-7a, C-8a, CH_3CO_2), 20.5 (C-4), 20.6 (C-2′), 23.7 (C-2a), 26.2 (C-3′), 29.4–30.0 (C-4′ to C-11′), 31.5 (C-3), 39.6 (C-1′), 70.5 (C-12′), 72.9 (CH_2Ph), 76.5 (C-2), 117.3 (C-5), 123.1 (C-6), 124.9 (C-7), 126.7 (C-8), 127.7–128.4 (Ar-CH), 138.7 (Ar-C), 140.5 (C-4a), 149.8 (C-8b), 169.6 (C=O).

4.1.30. 2-(13-(Benzyloxy)tridecyl)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-yl acetate (11c). Yield 89% (0.25 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.24 (s, 3H, H-2a), 1.28 (br s, 20H, H-2′ to H-11′), 1.59 (m, 4H, H-1′, H-12′), 1.77 (m, 2H, H-3), 2.13 (s, 6H, H-5a, H-7a), 2.17 (s, 3H, H-8a), 2.36 (s, 3H, CH_3C=O), 2.61 (t, 2H, *J* 6.8 Hz, H-4), 3.47 (t, 2H, *J* 6.6 Hz, H-13′), 4.52 (s, 2H, CH_2Ph), 7.30 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.3–12.3 (C-5a, C-7a, C-8a, CH_3C=O), 20.5 (C-4), 20.6 (C-2′), 23.7 (C-2a), 26.2 (C-3′), 29.3–30.0 (C-4′ to C-12′), 31.5 (C-3), 39.6 (C-1′), 70.5 (C-13′), 72.9 (CH_2Ph), 76.5 (C-2), 117.3 (C-5), 123.1 (C-6), 124.9 (C-7), 126.7 (C-8), 127.7–128.5 (Ar-CH), 138.7 (Ar-C), 140.5 (C-4a), 149.8 (C-8b), 169.4 (C=O).

4.1.31. 2-(14-(Benzyloxy)tetradecyl)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-yl acetate (11d). Yield 97% (0.71 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.26 (s, 3H, H-2a), 1.30 (br s, 22H, H-2′ to H-12′), 1.60 (m, 4H, H-1′, H-13′), 1.78 (m, 2H, H-3), 2.13 (s, 6H, H-5a, H-7a), 2.17 (s, 3H, H-8a), 2.36 (s, 3H, CH_3C=O), 2.61 (t, 2H, *J* 6.8 Hz, H-4), 3.47 (t, 2H, *J* 6.6 Hz, H-14′), 4.53 (s, 2H, CH_2Ph), 7.31 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.3–12.4 (C-5a, C-7a, C-8a, CH_3CO_2), 20.5 (C-4), 20.6 (C-2′), 23.7 (C-2a), 26.2 (C-3′), 29.2–30.0 (C-4′ to C-13′), 31.5 (C-3), 39.6 (C-1′), 70.5 (C-14′), 72.9 (CH_2Ph), 76.5 (C-2), 117.3 (C-5), 123.1 (C-6), 124.9 (C-7), 126.7 (C-8), 127.7–128.5 (Ar-CH), 138.7 (Ar-C), 140.5 (C-4a), 149.8 (C-8b), 169.4 (C=O).

4.1.32. 2-(15-(Benzyloxy)pentadecyl)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-yl acetate (11e). Yield 99% (0.11 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.25 (s, 3H, H-2a), 1.29 (br s, 24H, H-2′ to H-13′), 1.59 (m, 4H, H-1′, H-14′), 1.78 (m, 2H, H-3), 2.11 (s, 6H, H-5a, H-7a), 2.16 (s, 3H, H-8a), 2.34 (s, 3H, CH_3C=O), 2.60 (t, 2H, *J* 6.8 Hz, H-4), 3.48 (t, 2H, *J* 6.6 Hz, H-15′), 4.52 (s, 2H, CH_2Ph), 7.29 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.3–12.2 (C-5a, C-7a, C-8a, CH_3C=O), 20.5 (C-4), 20.6 (C-2′), 23.8 (C-2a), 26.2 (C-3′), 29.5–30.0 (C-4′ to C-14′), 31.5 (C-3), 39.5 (C-1′), 70.5 (C-15′), 72.9 (CH_2Ph), 76.5 (C-2), 117.3 (C-5), 123.1 (C-6), 124.9 (C-7), 126.7 (C-8), 127.7–128.3 (Ar-CH), 138.7 (Ar-C), 140.5 (C-4a), 149.8 (C-8b), 169.8 (C=O).

4.1.33. 2-(11-(Benzyloxy)undecyl)-6-methoxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromene (12a). To a solution of compound **9a** (0.53 g, 1.13 mmol, 1 equiv) in dry THF (12 mL) cooled to 0 °C were added sodium hydride (0.04 g, 1.58 mmol, 1.4 equiv) and methyl iodide (0.21 mL, 3.39 mmol, 3 equiv). After 1 h at 0 °C, a saturated solution of NH_4Cl (100 mL) was added to the reaction mixture and the aqueous layer was extracted with ether (3×100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc: 9:1) to give 0.50 g of a white solid (93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.24 (s, 3H, H-2a), 1.26 (br s, 16H, H-2′ to H-9′), 1.60 (m, 4H, H-1′, H-10′), 1.77 (m, 2H, H-3), 2.12 (s, 3H, H-7a), 2.16 (s, 3H, H-5a), 2.21 (s, 3H, H-8a), 2.59 (t, 2H, *J* 6.8 Hz, H-4), 3.47 (t, 2H, *J* 6.6 Hz, H-11′), 3.64 (s, 3H, OCH_3), 4.52 (s, 2H, CH_2Ph), 7.30 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.7 (C-5a), 11.8 (C-7a), 12.6 (C-8a), 20.7 (C-4), 23.7 (C-2′), 23.9 (C-2a), 26.2 (C-3′), 29.4–31.4 (C-4′ to C-10′), 31.7 (C-3), 39.8 (C-1′), 60.4 (OCH_3), 70.6 (C-11′), 72.9 (CH_2Ph), 74.8 (C-2), 117.5 (C-5), 122.9 (C-6), 125.7 (C-7), 127.6 (C-8), 138.8 (Ar-C), 147.8 (C-4a), 149.4 (C-8b).

4.1.34. 2-(12-(Benzyloxy)dodecyl)-6-methoxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromene (12b). Yield 87% (0.41 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.25 (s, 3H, H-2a), 1.27 (br s, 18H, H-2′ to H-10′), 1.61 (m, 4H, H-1′, H-11′), 1.77 (m, 2H, H-3), 2.12 (s, 3H, H-7a), 2.16 (s, 3H, H-5a), 2.20 (s, 3H, H-8a), 2.58 (t, 2H, *J* 6.8 Hz, H-4), 3.47 (t, 2H, *J* 6.6 Hz, H-12′), 3.64 (s, 3H, OCH_3), 4.52 (s, 2H, CH_2Ph), 7.30 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.7 (C-5a), 11.8 (C-7a), 12.5 (C-8a), 20.7 (C-4), 23.7 (C-2′), 23.8 (C-2a), 26.2 (C-3′), 29.5–31.2 (C-4′ to C-11′), 31.7 (C-3), 39.8 (C-1′), 60.3 (OCH_3), 70.6 (C-12′), 72.9 (CH_2Ph), 74.8 (C-2), 117.5 (C-5), 122.9 (C-6), 125.7 (C-7), 127.6 (C-8), 138.8 (Ar-C), 147.8 (C-4a), 149.4 (C-8b).

4.1.35. 2-(13-(Benzyloxy)tridecyl)-6-methoxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromene (12c). Yield 81% (0.47 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.24 (s, 3H, H-2a), 1.27 (br s, 20H, H-2′ to H-11′), 1.61 (m, 4H, H-1′, H-12′), 1.78 (m, 2H, H-3), 2.12 (s, 3H, H-7a), 2.17 (s, 3H, H-5a), 2.19 (s, 3H, H-8a), 2.58 (t, 2H, *J* 6.8 Hz, H-4), 3.47 (t, 2H, *J* 6.6 Hz, H-13′), 3.64 (s, 3H, OCH_3), 4.52 (s, 2H, CH_2Ph), 7.30 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.7 (C-5a), 11.8 (C-7a), 12.5 (C-8a), 20.7 (C-4), 23.7 (C-2′), 23.8 (C-2a), 26.2 (C-3′), 29.5–31.3 (C-4′ to C-12′), 31.7 (C-3), 39.8 (C-1′), 60.3 (OCH_3), 70.6 (C-13′), 72.9 (CH_2Ph), 74.8 (C-2), 117.5 (C-5), 122.9 (C-6), 125.7 (C-7), 127.6 (C-8), 138.8 (Ar-C), 147.8 (C-4a), 149.4 (C-8b).

4.1.36. 2-(14-(Benzyloxy)tetradecyl)-6-methoxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromene (12d). Yield 99% (0.72 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.24 (s, 3H, H-2a), 1.27 (br s, 22H, H-2′ to H-12′), 1.61 (m, 4H, H-1′, H-13′), 1.78 (m, 2H, H-3), 2.12 (s, 3H, H-7a), 2.16 (s, 3H, H-5a), 2.19 (s, 3H, H-8a), 2.58 (t, 2H, *J* 6.8 Hz, H-4), 3.47 (t, 2H, *J* 6.6 Hz, H-14′), 3.64 (s, 3H, OCH_3), 4.51 (s, 2H, CH_2Ph), 7.30 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.7 (C-5a), 11.8 (C-7a), 12.5 (C-8a), 20.7 (C-4), 23.7 (C-2′), 23.8 (C-2a), 26.2 (C-3′), 29.4–31.3 (C-4′ to C-13′), 31.7 (C-3), 39.8 (C-1′), 60.3 (OCH_3), 70.6 (C-14′), 72.8 (CH_2Ph), 74.8 (C-2), 117.5 (C-5), 122.9 (C-6), 125.7 (C-7), 127.6 (C-8), 138.8 (Ar-C), 147.8 (C-4a), 149.4 (C-8b).

4.1.37. 2-(15-(Benzyloxy)pentadecyl)-6-methoxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromene (12e). Yield 96% (0.52 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.25 (s, 3H, H-2a), 1.26 (br s, 24H, H-2′ to H-13′), 1.60 (m, 4H, H-1′, H-14′), 1.78 (m, 2H, H-3), 2.11 (s, 3H, H-7a), 2.16 (s, 3H, H-5a), 2.20 (s, 3H, H-8a), 2.59 (t, 2H, *J* 6.8 Hz, H-4), 3.48

(t, 2H, *J* 6.6 Hz, H-15′), 3.65 (s, 3H, OC*H*$_3$), 4.52 (s, 2H, C*H*$_2$Ph), 7.31 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 11.7 (C-5a), 11.8 (C-7a), 12.6 (C-8a), 20.7 (C-4), 23.7 (C-2′), 23.9 (C-2a), 26.2 (C-3′), 29.5–31.3 (C-4′ to C-14′), 31.7 (C-3), 39.8 (C-1′), 60.4 (O*C*H$_3$), 70.6 (C-15′), 72.9 (*C*H$_2$Ph), 74.8 (C-2), 117.5 (C-5), 122.9 (C-6), 125.7 (C-7), 127.6 (C-8), 138.8 (Ar-C), 147.8 (C-4a), 149.4 (C-8b).

4.1.38. 2-(11-Hydroxyundecyl)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-yl acetate (13a). To a solution of compound **11a** (0.54 g, 1.06 mmol, 1 equiv) in EtOH (15 mL) was added palladium on charcoal (5%, 0.11 g, 20% w/w). The mixture was stirred under an atmosphere of hydrogen at rt. After 4 h, the mixture was filtered on Celite and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc: 6:4) to give 0.43 g of a white solid (97%). ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 1.22 (s, 3H, H-2a), 1.25 (br s, 16H, H-2′ to H-9′), 1.56 (m, 4H, H-1′, H-10′), 1.76 (m, 2H, H-3), 1.99 (s, 3H, H-7a), 2.01 (s, 3H, H-8a), 2.12 (s, 3H, C*H*$_3$C═O), 2.58 (t, 2H, *J* 6.8 Hz, H-4), 3.63 (t, 2H, *J* 6.6 Hz, H-11′). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 11.7–12.9 (C-5a, C-7a, C-8a, C*H*$_3$C═O), 20.5 (C-4), 20.6 (C-2a), 23.7 (C-2′), 25.7 (C-3′), 29.4–30.1 (C-4′ to C-10′), 32.8 (C-3), 39.5 (C-1′), 63.1 (C-11′), 75.4 (C-2), 117.4 (C-5), 123.1 (C-6), 124.9 (C-7), 126.6 (C-8), 140.5 (C-4a), 149.4 (C-8b), 169.8 (*C*═O). *m*/*z* (ESI$^+$) 441 (M+Na$^+$). HRMS (ESI$^+$) calcd for $C_{26}H_{42}O_4Na$ (MNa$^+$) 441.2975. Found 441.2909.

4.1.39. 2-(12-Hydroxydodecyl)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-yl acetate (13b). Yield 83% (0.35 g). ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 1.23 (s, 3H, H-2a), 1.25 (br s, 18H, H-2′ to H-10′), 1.55 (m, 4H, H-1′, H-11′), 1.75 (m, 2H, H-3), 1.98 (s, 3H, H-7a), 2.01 (s, 3H, H-8a), 2.12 (s, 3H, C*H*$_3$C═O), 2.58 (t, 2H, *J* 6.8 Hz, H-4), 3.63 (t, 2H, *J* 6.6 Hz, H-12′). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 11.7–12.8 (C-5a, C-7a, C-8a, *C*H$_3$C═O), 20.5 (C-4), 20.6 (C-2a), 23.7 (C-2′), 25.7 (C-3′), 29.5–30.1 (C-4′ to C-11′), 32.8 (C-3), 39.5 (C-1′), 63.1 (C-12′), 75.3 (C-2), 117.4 (C-5), 123.1 (C-6), 124.9 (C-7), 126.6 (C-8), 140.5 (C-4a), 149.3 (C-8b), 169.7 (*C*═O). *m*/*z* (ESI$^+$) 455 (M+Na$^+$). HRMS (ESI$^+$) calcd for $C_{27}H_{44}O_1Na$ (MNa$^+$) 455.3132. Found 455.3111.

4.1.40. 2-(13-Hydroxytridecyl)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-yl acetate (13c). Yield 85% (0.17 g). ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 1.24 (s, 3H, H-2a), 1.26 (br s, 20H, H-2′ to H-11′), 1.54 (m, 4H, H-1′, H-12′), 1.74 (m, 2H, H-3), 1.98 (s, 3H, H-7a), 2.01 (s, 3H, H-8a), 2.11 (s, 3H, C*H*$_3$C═O), 2.58 (t, 2H, *J* 6.8 Hz, H-4), 3.64 (t, 2H, *J* 6.6 Hz, H-13′). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 11.8–12.8 (C-5a, C-7a, C-8a, *C*H$_3$C═O), 20.4 (C-4), 20.6 (C-2a), 23.7 (C-2′), 25.7 (C-3′), 29.5–30.1 (C-4′ to C-12′), 32.8 (C-3), 39.5 (C-1′), 63.1 (C-13′), 75.3 (C-2), 117.4 (C-5), 123.1 (C-6), 124.9 (C-7), 126.6 (C-8), 140.5 (C-4a), 149.4 (C-8b), 169.9 (*C*═O). *m*/*z* (ESI$^+$) 469 (M+Na$^+$). HRMS (ESI$^+$) calcd for $C_{28}H_{46}O_4Na$ (MNa$^+$) 469.3288. Found 469.3218.

4.1.41. 2-(14-Hydroxytetradecyl)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-yl acetate (13d). Yield 97% (0.54 g). ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 1.24 (s, 3H, H-2a), 1.25 (br s, 22H, H-2′ to H-12′), 1.54 (m, 4H, H-1′, H-13′), 1.75 (m, 2H, H-3), 2.00 (s, 3H, H-7a), 2.01 (s, 3H, H-8a), 2.11 (s, 3H, C*H*$_3$C═O), 2.59 (t, 2H, *J* 6.8 Hz, H-4), 3.64 (t, 2H, *J* 6.6 Hz, H-14′). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 11.8–12.9 (C-5a, C-7a, C-8a, *C*H$_3$CO), 20.4 (C-4), 20.6 (C-2a), 23.7 (C-2′), 25.7 (C-3′), 29.5–30.1 (C-4′ to C-13′), 32.8 (C-3), 39.5 (C-1′), 63.1 (C-14′), 75.3 (C-2), 117.5 (C-5), 123.1 (C-6), 124.9 (C-7), 126.6 (C-8), 140.5 (C-4a), 149.4 (C-8b), 169.7 (*C*═O). *m*/*z* (ESI$^+$) 483 (M+Na$^+$). HRMS (ESI$^+$) calcd for $C_{29}H_{48}O_4Na$ (MNa$^+$) 483.6782. Found 483.6775.

4.1.42. 2-(15-Hydroxypentadecyl)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-yl acetate (13e). Yield 87% (0.54 g). ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 1.22 (s, 3H, H-2a), 1.25 (br s, 24H, H-2′ to H-13′), 1.55 (m, 4H, H-1′, H-14′), 1.76 (m, 2H, H-3), 1.99 (s, 3H, H-7a), 2.00 (s, 3H, H-8a), 2.10 (s, 3H, C*H*$_3$C═O), 2.58 (t, 2H, *J* 6.8 Hz, H-4), 3.63 (t, 2H, *J* 6.6 Hz, H-15′). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 11.8–12.9 (C-5a, C-7a, C-8a, *C*H$_3$C═O), 20.5 (C-4), 20.6 (C-2a), 23.6 (C-2′), 25.7 (C-3′), 29.5–30.0 (C-4′ to C-14′), 32.8 (C-3), 39.5 (C-1′), 63.1 (C-15′), 75.4 (C-2), 117.4 (C-5), 123.0 (C-6), 124.9 (C-7), 126.6 (C-8), 140.5 (C-4a), 149.4 (C-8b), 169.8 (*C*═O). *m*/*z* (ESI$^+$) 497 (M+Na$^+$). HRMS (ESI$^+$) calcd for $C_{30}H_{50}O_4Na$ (MNa$^+$) 497.3601. Found 497.3592.

4.1.43. 11-(6-Methoxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-2-yl)undecan-1-ol (14a). Yield 87% (0.34 g). ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 1.22 (s, 3H, H-2a), 1.25 (br s, 16H, H-2′ to H-9′), 1.56 (m, 4H, H-1′, H-10′), 1.77 (m, 2H, H-3), 2.12 (s, 6H, H-5a, H-7a), 2.18 (s, 3H, H-8a), 2.60 (t, 2H, *J* 6.8 Hz, H-4), 3.63 (s, 3H, OC*H*$_3$), 3.65 (t, 2H, *J* 6.6 Hz, H-11′). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 11.7 (C-5a), 11.7 (C-7a), 12.4 (C-8a), 20.7 (C-4), 23.6 (C-2′), 23.9 (C-2a), 25.7 (C-3′), 29.4–31.3 (C-4′ to C-10′), 32.8 (C-3), 39.7 (C-1′), 60.4 (O*C*H$_3$), 63.1 (C-11′), 74.5 (C-2), 117.5 (C-5), 118.5 (C-6), 121.0 (C-8), 122.6 (C-7), 144.4 (C-4a), 145.6 (C-8b). *m*/*z* (ESI$^+$) 413 (M+Na$^+$). HRMS (ESI$^+$) calcd for $C_{25}H_{42}O_3Na$ (MNa$^+$) 413.3026. Found 413.3005.

4.1.44. 12-(6-Methoxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-2-yl)dodecan-1-ol (14b). Yield 85% (0.22 g). ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 1.23 (s, 3H, H-2a), 1.25 (br s, 18H, H-2′ to H-10′), 1.57 (m, 4H, H-1′, H-11′), 1.78 (m, 2H, H-3), 2.10 (s, 6H, H-5a, H-7a), 2.18 (s, 3H, H-8a), 2.60 (t, 2H, *J* 6.8 Hz, H-4), 3.63 (s, 3H, OC*H*$_3$), 3.65 (t, 2H, *J* 6.6 Hz, H-12′). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 11.7 (C-5a), 11.8 (C-7a), 12.5 (C-8a), 20.7 (C-4), 23.6 (C-2′), 23.9 (C-2a), 25.7 (C-3′), 29.5–31.3 (C-4′ to C-11′), 32.8 (C-3), 39.7 (C-1′), 60.5 (O*C*H$_3$), 63.1 (C-12′), 74.5 (C-2), 117.5 (C-5), 118.5 (C-6), 121.1 (C-8), 122.6 (C-7), 144.4 (C-4a), 145.6 (C-8b). *m*/*z* (ESI$^+$) 427 (M+Na$^+$). HRMS (ESI$^+$) calcd for $C_{26}H_{44}O_3Na$ (MNa$^+$) 427.3183. Found 427.3215.

4.1.45. 13-(6-Methoxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-2-yl)tridecan-1-ol (14c). Yield 93% (0.27 g). ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 1.23 (s, 3H, H-2a), 1.25 (br s, 20H, H-2′ to H-11′), 1.58 (m, 4H, H-1′, H-12′), 1.78 (m, 2H, H-3), 2.11 (s, 6H, H-5a, H-7a), 2.18 (s, 3H, H-8a), 2.61 (t, 2H, *J* 6.8 Hz, H-4), 3.63 (s, 3H, OC*H*$_3$), 3.65

(t, 2H, *J* 6.6 Hz, H-13′). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.7 (C-5a), 11.8 (C-7a), 12.5 (C-8a), 20.7 (C-4), 23.6 (C-2′), 23.9 (C-2a), 25.7 (C-3′), 29.5–31.3 (C-4′ to C-12′), 32.8 (C-3), 39.7 (C-1′), 60.5 (O*C*H$_3$), 63.1 (C-13′), 74.6 (C-2), 117.5 (C-5), 118.5 (C-6), 121.1 (C-8), 122.6 (C-7), 144.4 (C-4a), 145.6 (C-8b). *m*/*z* (ESI$^+$) 441 (M+Na$^+$). HRMS (ESI$^+$) calcd for $C_{27}H_{46}O_3Na$ (MNa$^+$) 441.3339. Found 441.3317.

4.1.46. 14-(6-Methoxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-2-yl)tetradecan-1-ol (14d). Yield 95% (0.45 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.22 (s, 3H, H-2a), 1.26 (br s, 22H, H-2′ to H-12′), 1.58 (m, 4H, H-1′, H-13′), 1.78 (m, 2H, H-3), 2.11 (s, 6H, H-5a, H-7a), 2.18 (s, 3H, H-8a), 2.61 (t, 2H, *J* 6.8 Hz, H-4), 3.63 (s, 3H, OCH$_3$), 3.65 (t, 2H, *J* 6.6 Hz, H-14′). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.7 (C-5a), 11.8 (C-7a), 12.5 (C-8a), 20.7 (C-4), 23.5 (C-2′), 23.9 (C-2a), 25.7 (C-3′), 29.5–31.4 (C-4′ to C-13′), 32.8 (C-3), 39.7 (C-1′), 60.5 (O*C*H$_3$), 63.1 (C-14′), 74.6 (C-2), 117.5 (C-5), 118.5 (C-6), 121.1 (C-8), 122.6 (C-7), 144.4 (C-4a), 145.6 (C-8b). *m*/*z* (ESI$^+$) 455 (M+Na$^+$). HRMS (ESI$^+$) calcd for $C_{28}H_{48}O_3Na$ (MNa$^+$) 455.3496. Found 455.3516.

4.1.47. 15-(6-Methoxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-2-yl)pentadecan-1-ol (14e). Yield 89% (0.29 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.22 (s, 3H, H-2a), 1.26 (br s, 24H, H-2′ to H-13′), 1.57 (m, 4H, H-1′, H-14′), 1.77 (m, 2H, H-3), 2.11 (s, 6H, H-5a, H-7a), 2.18 (s, 3H, H-8a), 2.60 (t, 2H, *J* 6.8 Hz, H-4), 3.63 (s, 3H, OC*H*$_3$), 3.64 (t, 2H, *J* 6.6 Hz, H-15′). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.7 (C-5a), 11.8 (C-7a), 12.5 (C-8a), 20.7 (C-4), 23.5 (C-2′), 23.9 (C-2a), 25.7 (C-3′), 29.4–31.2 (C-4′ to C-14′), 32.8 (C-3), 39.7 (C-1′), 60.4 (O*C*H$_3$), 63.1 (C-15′), 74.5 (C-2), 117.5 (C-5), 118.4 (C-6), 121.0 (C-8), 122.6 (C-7), 144.5 (C-4a), 145.6 (C-8b). *m*/*z* (ESI$^+$) 455 (M+Na$^+$). HRMS (ESI$^+$) calcd for $C_{29}H_{50}O_3Na$ (MNa$^+$) 469.3652. Found 469.3689.

4.1.48. Benzyl 6-(benzyloxy)-2,5,7,8-tetramethylchroman-2-carboxylate (15). To solution of Trolox® (0.60 g, 2.40 mmol, 1 equiv) in acetone (35 mL) were added potassium carbonate (2.98 g, 21.57 mmol, 9 equiv) and benzyl bromide (0.87 mL, 7.19 mmol, 3 equiv) and the resulting mixture was refluxed. After 40 h, a saturated solution of NH_4Cl (100 mL) was added to the reaction mixture and the aqueous layer was extracted with ether (3×100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–CH_2Cl_2: 9:1) to give 2.58 g of a colorless oil (95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.64 (s, 3H, H-2a), 1.87 (m, 1H, H-3), 2.10 (s, 3H, H-7a), 2.16 (s, 3H, H-5a), 2.23 (s, 3H, H-8a), 2.46 (m, 2H, H-4), 2.58 (m, 1H, H-3), 4.50 (s, 2H, C*H*$_2$Ph), 5.04 (d, *J* 12.5 Hz, 1H, C═OC*H*H′Ph), 5.16 (d, 1H, C═OCH*H*′Ph), 7.29 (m, 10H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.9 (C-5a), 12.0 (C-7a), 12.9 (C-8a), 20.9 (C-4), 25.5 (C-2a), 30.7 (C-3), 66.4 (C═O*C*H$_2$Ph), 74.7 (*C*H$_2$Ph), 77.1 (C-2), 117.3 (C-5), 123.1 (C-6), 126.0 (C-7), 127.8 (C-8), 127.6–128.5 (Ar-CH), 135.8 (Ar-C), 137.9 (Ar-C), 148.1 (C-4a), 148.9 (C-8b), 173.8 (*C*═O).

4.1.49. (6-(Benzyloxy)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-2-yl)methanol (16). To a solution of compound **15** (0.50 g, 1.15 mmol, 1 equiv) in dry THF (10 mL) cooled to 0 °C was added lithium aluminum hydride (0.05 g, 1.15 mmol, 1 equiv). After 1 h at this temperature, a saturated solution of NH_4Cl (100 mL) was added to the reaction mixture and the aqueous layer was extracted with ether (3×100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc: 7:3) to give 0.36 g of a colorless oil (96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.24 (s, 3H, H-2a), 1.75 (m, 2H, H-3), 2.11 (s, 3H, H-7a), 2.18 (s, 3H, H-5a), 2.23 (s, 3H, H-8a), 2.60 (d, *J* 11.3 Hz, 1H, CH_2OH), 2.67 (d, *J* 11.3 Hz, 1H, CH_2OH), 4.70 (s, 2H, C*H*$_2$Ph), 7.40 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.9 (C-5a), 12.0 (C-7a), 12.9 (C-8a), 20.2 (C-4), 20.5 (C-2a), 27.7 (C-3), 65.4 (*C*H$_2$OH), 69.4 (*C*H$_2$Ph), 74.8 (C-2), 117.6 (C-5), 122.9 (C-6), 126.3 (C-7), 127.0–128.6 (Ar-CH), 137.9 (Ar-C), 147.2 (C-4a), 148.6 (C-8b).

4.1.50. 10-Iodo-1(benzyloxy)-decane. To a suspension of 1,10-decandiol (3 g, 17.21 mmol, 1 equiv) in toluene (45 mL) was added HI 57% aq (6.8 mL, 51.63 mmol, 3 equiv) and the resulting mixture was heated at 90 °C. After 6 h, a saturated solution of $Na_2S_2O_3$ (100 mL) was added to the reaction mixture and the aqueous layer was extracted with ether (3×100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc: 7:3) to give 3.82 g of a colorless oil (78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.28 (br s, 12H, H-3 to H-8), 1.54 (m, 2H, H-2), 1.82 (m, 2H, H-9), 3.18 (t, *J* 7.1 Hz, 2H, H-10), 3.62 (t, *J* 6.4 Hz, 2H, H-1). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 7.3 (C-10), 25.5 (C-9), 28.5–32.7 (C-3 to C-8), 33.5 (C-2), 63.0 (C-1). To a solution of 10-iododecan-1-ol (3.85 g, 13.55 mmol, 1 equiv) in dry THF (15 mL) was added sodium hydride (0.45 g, 18.97 mmol, 1.4 equiv) and the resulting mixture was refluxed. After 30 min, benzyl bromide (1.97 mL, 16.27 mmol, 1.2 equiv) was added and refluxing was continued. After 24 h, a saturated solution of NH_4Cl (100 mL) was added to the reaction mixture and the aqueous layer was extracted with ether (3×100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc: 8:2) to give 4.81 g of a colorless oil (95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.26 (br s, 12H, H-3 to H-8), 1.62 (m, 2H, H-2), 1.78 (m, 2H, H-9), 3.35 (t, *J* 6.7 Hz, 2H, H-10), 3.45 (t, *J* 6.4 Hz, 2H, H-1), 4.49 (s, 2H, C*H*$_2$Ph), 7.33 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 7.5 (C-10), 26.3 (C-3), 27.8 (C-8), 29.6–29.9 (C-2, C-4 to C-6), 32.9 (C-9), 70.6 (C-1), 73.0 (*C*H$_2$Ph), 127.3, 128.2, 128.4 (Ar-CH), 141.3 (Ar-C).

4.1.51. 6-(Benzyloxy)-2-((10-(benzyloxy)decyloxy)-methyl)-2,5,7,8-tetramethyl-3,4-tetrahydroxy-2*H*-chromene (17). To a solution of compound **16** (0.20 g, 0.62 mmol, 1 equiv) in dry THF (6 mL) was added sodium hydride (0.02 g, 0.80 mmol, 1.3 equiv) and the resulting mixture was refluxed. After 30 min, a solution of 10-iodo-1(benzyloxy)-decane (0.58 g, 1.55 mmol, 2.5 equiv) was added and the refluxing was continued. After 20 h, a saturated solution of NH_4Cl (100 mL) was added to the reaction

mixture and the aqueous layer was extracted with ether (3×100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc: 9:1) to give 0.19 g of a colorless oil (42%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.24 (br s, 15H, H-3′ to H-8′, H-2a), 1.55 (m, 4H, H-2′ to H-9′), 1.75 (m, 3H, H-3, H-10′), 1.96 (m, 1H, H-3), 2.10 (s, 3H, H-7a), 2.11 (s, 3H, H-5a), 2.15 (s, 3H, H-8a), 2.61 (t, *J* 6.8 Hz, 2H, H-4), 3.48 (m, 4H, C*H*$_2$O-alkyl, H-1′), 4.47 (s, 2H, alkyl-OC*H*$_2$Ph), 4.65 (s, 2H, Ar-OC*H*$_2$-Ph), 7.53 (m, 10H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.3 (C-5a), 11.9 (C-7a), 12.3 (C-8a), 20.3 (C-4), 20.4 (C-2a), 25.7–29.7 (C-2′ to C-9′), 32.8 (C-3), 63.1 (C-10′), 72.0 (C-1′), 72.9 (alkyl-OCH$_2$Ph), 74.7 (Ar-OCH$_2$Ph), 74.8 (*C*H$_2$O-alkyl), 74.8 (C-2), 117.5 (C-5), 118.7 (C-6), 121.3 (C-7), 122.5 (C-8), 127.5–128.7 (Ar-CH), 137.3 (Ar-C), 144.8 (C-4a), 145.4 (C-8b).

4.1.52. 2-((10-Hydroxydecyloxy)methyl)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-ol (18). To a solution of compound **17** (0.14 g, 0.24 mmol, 1 equiv) in EtOH (8 mL) was added palladium on charcoal (5%, 0.03 g, 20% w/w). The mixture was stirred under an atmosphere of hydrogen at rt. After 72 h, the mixture was filtered on Celite and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc: 7:3) to give 0.06 g of a colorless oil (64%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.27 (br s, 15H, H-3′ to H-8′, H-2a), 1.55 (m, 4H, H-2′, H-9′), 1.75 (m, 1H, H-3), 1.96 (m, 1H, H-3), 2.10 (s, 3H, H-7a), 2.11 (s, 3H, H-5a), 2.15 (s, 3H, H-8a), 2.61 (t, *J* 6.8 Hz, 2H, H-4), 3.48 (m, 6H, C*H*$_2$O-alkyl, H-1′, H-10′), 4.55 (br s, 1H, Ph-O*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.3 (C-5a), 11.9 (C-7a), 12.3 (C-8a), 20.3 (C-4), 20.4 (C-2a), 25.7–29.7 (C-2′ to C-9′), 32.8 (C-3), 63.1 (C-10′), 72.0 (C-1′), 74.8 (*C*H$_2$O-alkyl), 74.8 (C-2), 117.5 (C-5), 118.7 (C-6), 121.3 (C-7), 122.5 (C-8), 144.8 (C-4a), 145.4 (C-8b). *m*/*z* (ESI$^+$) 415 (M+Na$^+$). HRMS (ESI$^+$) calcd for $C_{24}H_{40}O_4Na$ (MNa$^+$) 415.2819. Found 415.2635.

4.1.53. (*S*)-Benzyl 6-(benzyloxy)-2,5,7,8-tetramethylchroman-2-carboxylate (19).[31] Compound **19** ($[\alpha]_D^{20}$ −3.5 (*c* 0.5, $CHCl_3$)) and its (*R*)-enantiomer ($[\alpha]_D^{20}$ +3.4 (*c* 0.5, $CHCl_3$)) were obtained as described for the racemic mixture **15**. All analytical data were identical to that of **15**.

4.1.54. (*S*)-6-(Benzyloxy)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromene-2-carbaldehyde (20). To a solution of compound **19** (0.87 g, 2.03 mmol, 1 equiv) in dry heptane (30 mL) cooled to −78 °C was added over a period of 1.5 h 30 DIBAL-H 1 M in hexane (2.19 mL, 2.19 mmol, 1.08 equiv). After an additional hour at −78 °C, a saturated solution of sodium tartrate (100 mL) was added to the reaction mixture and the aqueous layer was extracted with ether (3×100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–CH_2Cl_2: 9:1) to give 0.52 g of a colorless oil (79%). $[\alpha]_D^{20}$ −0.3 (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.42 (s, 3H, H-2a), 1.85 (m, 1H, H-3), 2.14 (s, 3H, H-7a), 2.21 (s, 3H, H-5a), 2.25 (s, 3H, H-8a), 2.29 (m, 1H, H-3), 2.58 (m, 2H, H-4), 4.71 (s, 2H, C*H*$_2$Ph), 7.41 (m, 5H, Ar-H), 9.65 (s, 1H, C*H*O). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.9 (C-5a), 12.0 (C-7a), 12.9 (C-8a), 20.3 (C-4), 21.6 (C-2a), 27.8 (C-3), 74.7 (*C*H$_2$Ph), 80.5 (C-2), 117.8 (C-5), 123.2 (C-6), 126.4 (C-7), 127.8–128.6 (Ar-CH), 128.5 (C-8), 137.8 (Ar-C), 147.5 (C-4a), 149.2 (C-8b), 204.4 (*C*HO).

4.1.55. 11-Benzyloxyundanyltriphenylphosphonium bromide. To a solution of 11-bromo-1-(benzyloxy)-undecane (13.6 g, 39.48 mmol, 1 equiv) in CH_3CN (50 mL) was added triphenylphosphine (12.5 g, 47.81 mmol, 2 equiv) and the resulting mixture was refluxed. After 44 h, CH_3CN was evaporated and several washings of the residue in hexane and ether gave 22.85 g of a white solid (96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.15 (br s, 14H, H-3 to H-9), 1.56 (m, 4H, H-2, H-10), 3.42 (t, *J* 6.6 Hz, 2H, H-11), 3.69 (m, 2H, H-1), 4.45 (s, 2H, C*H*$_2$Ph), 7.28 (m, 5H, Ar-H), 7.73 (m, 15H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.7 (C-1), 23.4 (C-2), 26.2 (C-9), 29.2–30.6 (C-3 to C-8, C-10), 70.6 (C-11), 72.9 (*C*H$_2$Ph), 117.6, 119.3 (Ar-CH), 127.5, 127.6, 128.4 (Ar-CH), 130.4, 130.7, 133.6, 133.8, 135.1 (Ar-CH), 138.7 (Ar-C).

4.1.56. (*S*)-6-(Benzyloxy)-2-(12-(benzyloxy)dodec-1-enyl)-2,5,7,8-tetramethyl-3,4-tetrahydro-2*H*-chromene (21). To a suspension of 11-benzyloxyundanyltriphenylphosphonium bromide (0.49 g, 0.82 mmol, 1.2 equiv) in dry THF (5 mL) cooled to −78 °C was slowly added *t*-BuLi 1.6 M in hexane (0.51 g, 0.82 mmol, 1.2 equiv). The resulting mixture was allowed to warm to rt and after 15 min was cooled to 0 °C and potassium *tert*-butoxide (0.10 g, 0.82 mmol, 1.2 equiv) was added. After 15 min to the solution cooled to −78 °C was slowly added a solution of compound **20** (0.22 g, 0.68 mmol, 1 equiv) in dry THF (5 mL). After 1 h at −78 °C, the solution was allowed to warm to 0 °C. After 1.5 h 30, a saturated solution of NH_4Cl (100 mL) was added to the reaction mixture and the aqueous layer was extracted with ether (3×100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–CH_2Cl_2: 9:1) to give 0.36 g of a colorless oil (93%). $[\alpha]_D^{20}$ −6.4 (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.24 (br s, 14H, H-3′ to H-10′), 1.48 (s, 3H, H-2a), 1.59 (m, 2H, H-11′), 1.78 (m, 1H, H-3), 2.01 (m, 1H, H-3), 2.16 (s, 3H, H-7a), 2.21 (s, 3H, H-5a), 2.26 (s, 3H, H-8a), 2.59 (m, 2H, H-4), 3.46 (t, *J* 6.6 Hz, 2H, H-12′), 4.50 (s, 2H, alkyl-OC*H*$_2$Ph), 4.69 (s, 2H, Ar-OC*H*$_2$Ph), 5.34 (m, 2H, H-1′, H-2′), 7.45 (m, 10H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 12.0 (C-5a), 12.1 (C-7a), 12.9 (C-8a), 21.1 (C-4), 26.2 (C-3′), 27.3–29.9 (C-4′ to C-11′), 27.3 (C-2a), 33.3 (C-3), 70.5 (C-12′), 72.9 (alkyl-OCH$_2$Ph), 74.7 (Ar-OCH$_2$Ph), 75.8 (C-2), 118.0 (C-5), 122.8 (C-6), 125.9 (C-8), 127.8 (C-7), 127.5–128.5 (Ar-CH), 132.7, 133.2 (C-1′, C-2′), 137.0, 137.8 (Ar-C), 147.5 (C-4a), 149.2 (C-8b).

4.1.57. (*R*)-2-(12-Hydroxydodecyl)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-ol (22). To a solution of compound **21** (0.36 g, 0.64 mmol, 1 equiv) in EtOH (14 mL) was added palladium on charcoal (5%, 0.08 g, 20% w/w). The mixture was stirred under an atmosphere of hydrogen at rt. After 48 h, the mixture was filtered on Celite and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel

(hexane–EtOAc: 7:3) to give 0.18 g of a white solid (73%). $[\alpha]_D^{20}$ −0.4 (*c* 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.23 (s, 3H, H-2a), 1.25 (br s, 18H, H-2′ to H-10′), 1.54 (m, 4H, H-1′, H-11′), 1.78 (m, 2H, H-3), 2.14 (s, 6H, H-5a, H-7a), 2.16 (s, 3H, H-8a), 2.60 (t, 2H, *J* 6.8 Hz, H-4), 3.65 (t, 2H, *J* 6.6 Hz, H-12′). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.4 (C-5a), 11.6 (C-7a), 12.2 (C-8a), 20.7 (C-4), 23.6 (C-2′), 23.8 (C-2a), 26.2 (C-3′), 29.5–30.2 (C-4′ to C-11′), 31.5 (C-3), 39.5 (C-1′), 70.5 (C-12′), 74.5 (C-2), 117.4 (C-5), 118.4 (C-6), 121.0 (C-8), 122.7 (C-7), 144.5 (C-4a), 145.6 (C-8b).

4.1.58. 12-(6-(Benzyloxy)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-2-yl)dodecan-1-ol (23). To a solution of compound **10b** (450 mg, 1.15 mmol, 1 equiv) in dry acetone (12 mL) were added potassium carbonate (0.478 mg, 3.46 mmol, 3 equiv) and benzyl bromide (0.25 mL, 3.46 mmol, 3 equiv). The stirred mixture was refluxed under argon. After 10 h, a saturated solution of NH_4Cl (50 mL) was added to the reaction mixture and the aqueous layer was extracted with EtOAc (3×50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (heptane–EtOAc: 8:2) to give 0.402 g of a colorless oil (73%). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.24 (s, 3H, H-2a), 1.27 (br s, 18H, H-2′ to H-10′), 1.39–1.61 (m, 4H, H-1′, H-11′), 1.78 (m, 2H, H-3), 2.10 (s, 3H, H-7a), 2.17 (s, 3H, H-5a), 2.22 (s, 3H, H-8a), 2.59 (t, *J* 6.9 Hz, 2H, H-4), 3.64 (t, *J* 6.6 Hz, 2H, H-12′), 4.70 (s, 2H, Ar-OC*H*$_2$Ph), 7.42 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.8 (C-5a), 12.0 (C-7a), 12.9 (C-8a), 20.7 (C-4), 23.6 (C-2′), 23.9 (C-2a), 25.7 (C-10′), 29.4–30.2 (C-3′ to C-9′, C-11′), 31.3 (C-3), 39.7 (C-1′), 63.1 (C-12′), 74.7 (C-2, Ar-O*C*H$_2$Ph), 117.6 (C-5), 122.9 (C-7, C-8), 126.0 (C-4a), 127.7 (Ar-CH), 127.9 (Ar-CH), 128.4 (Ar-CH), 138.0 (Ar-C), 147.9 (C-8b), 148.1 (C-6).

4.1.59. Dibenzyl 12-(6-(benzyloxy)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-2-yl)dodecyl phosphate (24). To a solution of compound **23** (0.385 g, 0.80 mmol, 1 equiv) in CH_2Cl_2 (4 mL) were added 1*H*-tetrazole (0.112 g, 1.60 mmol, 2 equiv) and dibenzyl diisopropyl phosphoramidite (0.32 mL, 0.96 mmol 1.2 equiv) and the resulting mixture was stirred at rt. After 3 h, the mixture was cooled to 0 °C and a solution of *m*-chloroperoxybenzoic acid (0.27 g, 77% w/w, 1.20 mmol, 1.5 equiv) in CH_2Cl_2 (2 mL) was added, maintaining the temperature at 0 °C. After 1 h, a saturated solution of $Na_2S_2O_3$ (30 mL) was added to the reaction mixture and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined extracts were successively washed with H_2O (30 mL), saturated $NaHCO_3$ (30 mL), and brine (30 mL) before being dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (heptane–EtOAc: 85:15 to 8:2) to give 0.503 g of a colorless oil (85%). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.24 (br s, 21H, H-2a, H-2′ to H-10′), 1.39–1.61 (m, 4H, H-1′, H-11′), 1.78 (m, 2H, H-3), 2.10 (s, 3H, H-7a), 2.16 (s, 3H, H-5a), 2.22 (s, 3H, H-8a), 2.59 (t, *J* 6.6 Hz, 2H, H-4), 3.97 (q, *J* 6.9 Hz, 2H, H-12′), 4.69 (s, 2H, Ar-OC*H*$_2$Ph), 5.03 (dd, *J* 8.1, 2.1 Hz, 4H, P-OC*H*$_2$Ph), 7.36 (m, 15H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.8 (C-5a), 12.0 (C-7a), 12.9 (C-8a), 20.7 (C-4), 23.6 (C-2′), 23.9 (C-2a), 25.6 (C-3′), 29.1–30.2 (C-4′ to C-11′), 31.3 (C-3), 39.8 (C-1′), 68.0 (C-12′), 69.1 (P-O*C*H$_2$Ph), 74.7 (C-2, Ar-O*C*H$_2$Ph), 117.6 (C-5), 122.9 (C-7, C-8), 126.0 (C-4a), 127.7 (Ar-CH), 127.9 (Ar-CH), 128.5 (Ar-CH), 138.0 (Ar-C), 147.9 (C-8b), 148.1 (C-6). ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: −3.56.

4.1.60. Sodium 12-(6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-2-yl)dodecyl phosphate (25). To a solution of compound **24** (0.48 g, 0.65 mmol, 1 equiv) in EtOH (5 mL) was added palladium on charcoal (10%, 0.096 g, 20% w/w). The mixture was stirred under an atmosphere of hydrogen at rt. After 4 h, the mixture was filtered on Celite and concentrated under reduced pressure. A saturated solution of $NaHCO_3$ (50 mL) was added to the residue and the aqueous layer was extracted with EtOAc (3×50 mL). The combined extracts were washed with brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was diluted in water (5 mL), treated with a solution of NaOH (1 M) until pH 7.5 was reached. The mixture was lyophilized to give 0.327 g of a white solid (74%). ^1H NMR (300 MHz, CD_3OD) δ: 1.26 (br s, 21H, H-2a, H-2′ to H-10′), 1.36–1.62 (m, 4H, H-1′, H-11′), 1.76 (m, 2H, H-3), 2.04 (s, 3H, H-7a), 2.08 (s, 3H, H-5a), 2.12 (s, 3H, H-8a), 2.57 (t, *J* 6.8 Hz, 2H, H-4), 3.94 (q, *J* 6.9 Hz, 2H, H-12′). ^{13}C NMR (75 MHz, CD_3OD) δ: 10.8 (C-5a), 11.0 (C-7a), 11.7 (C-8a), 20.5 (C-4), 23.4 (C-2′), 25.3 (C-2a, C-3′), 29.0–30.1 (C-4′ to C-11′), 31.6 (C-3), 39.1 (C-1′), 65.7 (C-12′), 74.2 (C-2), 117.0 (C-5), 120.7 (C-8), 121.8 (C-7), 123.1 (C-4a), 147.8 (C-6), 148.1 (C-8b). ^{31}P NMR (121.5 MHz, D_2O) δ: 3.89. *m*/*z* (ESI^+) 515 ($M+H^+$). HRMS (ESI^+) calcd for $C_{25}H_{42}O_6Na_2P$ (MH^+) 515.2509. Found 515.2505.

4.1.61. Dibenzyl 12-(6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-2-yl)dodecyl phosphate (26). To a solution of compound **10b** (0.40 mg, 1.02 mmol, 1 equiv) in CH_2Cl_2 (10 mL) cooled to −10 °C, were added carbon tetrachloride (1 mL, 10.24 mmol, 10 equiv), *N*,*N*-diisopropylethylamine (0.90 mL, 5.15 mmol, 5 equiv), and *N*,*N*-dimethyl aminopyridine (0.50 g, 0.41 mmol, 0.4 equiv). Dibenzyl phosphite (0.70 mL, 3.1 mmol, 3 equiv) was then added dropwise and the temperature was kept at or below −10 °C. After 3 h, a solution of KH_2PO_4 (0.5 M, 30 mL) was added and the mixture was allowed to warm to rt. After 30 min, the mixture was extracted with EtOAc (3×50 mL). The combined extracts were washed successively with water (50 mL) and brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to give 0.518 g of a white solid (78%). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.22 (s, 3H, H-2a), 1.25 (br s, 18H, H-2′ to H-10′), 1.39–1.56 (m, 4H, H-1′, H-11′), 1.76 (m, 2H, H-3), 2.11 (s, 6H, H-5a, H-7a), 2.16 (s, 3H, H-8a), 2.60 (t, *J* 6.6 Hz, 2H, H-4), 3.97 (q, *J* 6.9 Hz, 2H, H-12′), 5.03 (m, 4H, P-OC*H*$_2$Ph), 7.34 (m, 10H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.3 (C-5a), 11.8 (C-7a), 12.2 (C-8a), 20.8 (C-4), 23.6 (C-2′), 23.8 (C-2a), 25.8 (C-3′), 29.1–30.1 (C-4′ to C-11′), 31.5 (C-3), 39.5 (C-1′), 68.0 (C-12′), 69.1 (P-O*C*H$_2$Ph), 69.2 (P-O*C*H$_2$Ph), 74.5 (C-2), 117.3 (C-5), 118.5 (C-8), 121.0 (C-7), 122.6 (C-4a), 127.9 (Ar-CH), 128.5 (Ar-CH), 136.0 (Ar-C), 144.6 (C-6), 145.5 (C-8b). ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: −3.43.

4.1.62. Dibenzyl 2-(dibenzyl 12-dodecyl phosphate)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-yl phosphate (27). To a solution of compound **26** (0.50 g, 0.77 mmol, 1 equiv) in CH_2Cl_2 (2 mL) were added 1*H*-tetrazole (0.108 g, 1.54 mmol, 2 equiv), dibenzyl diisopropyl phosphoramidite (0.30 mL, 0.92 mmol 1.2 equiv) and the resulting mixture was stirred at rt. After 3.5 h, the mixture was cooled to 0 °C and a solution of *m*-chloroperoxybenzoic acid (0.190 g, 77% w/w, 0.85 mmol, 1.2 equiv) in CH_2Cl_2 (1.5 mL) was added, maintaining the temperature at 0 °C. After 1 h, a saturated solution of $Na_2S_2O_3$ (30 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined extracts were successively washed with H_2O (30 mL), a saturated solution of $NaHCO_3$ (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (heptane–EtOAc: 85:15 to 80:20) to give 0.625 g of a colorless oil (89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.22 (s, 3H, H-2a), 1.25 (br s, 18H, H-2′ to H-10′), 1.40–1.62 (m, 4H, H-1′, H-11′), 1.76 (m, 2H, H-3), 2.05 (s, 3H, H-7a), 2.14 (s, 3H, H-5a), 2.18 (s, 3H, H-8a), 2.54 (t, *J* 6.6 Hz, 2H, H-4), 3.98 (q, *J* 6.6 Hz, 2H, H-12′), 5.04 (m, 8H, P-OC*H*$_2$Ph), 7.31 (m, 20H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.9 (C-5a), 13.0 (C-7a), 13.9 (C-8a), 20.7 (C-4), 23.6 (C-2′), 23.8 (C-2a), 25.6 (C-3′), 29.1–30.2 (C-4′ to C-11′), 31.2 (C-3), 39.7 (C-1′), 68.0 (C-12′), 69.1 (P-O*C*H$_2$Ph), 69.7 (P-O*C*H$_2$Ph), 75.0 (C-2), 117.6 (C-5), 123.2 (C-8), 125.3 (C-7), 127.2 (Ar-CH), 127.9 (Ar-CH), 128.0 (Ar-CH), 128.4 (Ar-CH), 128.5 (Ar-CH), 128.7 (Ar-CH), 135.8 (Ar-C), 135.9 (Ar-C), 140.7 (C-6), 148.8 (C-8b). ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 0.49, −3.67.

4.1.63. Sodium 2-(12-dodecyl phosphate)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-yl phosphate (28). To a solution of compound **27** (0.58 mg, 0.64 mmol, 1 equiv) in EtOH (3 mL) was added palladium on charcoal (10%, 0.058 g). The mixture was stirred under an atmosphere of hydrogen at rt. After 4 h, the mixture was filtered on Celite and concentrated under reduced pressure. The residue was dissolved in water (5 mL), treated with a solution of NaOH (1 M) until pH 8 was reached. The mixture was then purified by DEAE-Trisacryl ion-exchange column with a NaCl solution (step gradient 0.5 M, 1 M, 2 M), subjected to size exclusion chromatography and then lyophilized to give 0.333 g of a white solid (82%). ^{1}H NMR (300 MHz, D_2O) δ: 1.27 (br s, 21H, H-2a, H-2′ to H-10′), 1.41–1.62 (m, 4H, H-1′, H-11′), 1.85 (m, 2H, H-3), 2.09 (s, 3H, H-7a), 2.19 (s, 3H, H-5a), 2.23 (s, 3H, H-8a), 2.65 (t, *J* 6.6 Hz, 2H, H-4), 3.78 (q, *J* 6.9 Hz, 2H, H-12′). ^{13}C NMR (75 MHz, D_2O) δ: 11.1 (C-7a), 12.6 (C-5a), 13.2 (C-8a), 20.7 (C-4), 23.6 (C-2′), 23.8 (C-2a), 25.4 (C-3′), 29.1–30.2 (C-4′ to C-11′), 31.5 (C-3), 39.1 (C-1′), 65.7 (C-12′), 74.2 (C-2), 117.6 (C-5), 123.2 (C-8), 125.3 (C-7), 127.2 (C-4a), 140.5 (C-6), 148.6 (C-8b). ^{31}P NMR (121.5 MHz, D_2O) δ: 0.57, 4.01. *m*/*z* (ESI^-) 549 ($M-3Na^+ + 3H^+$). HRMS (ESI^-) calcd for $C_{25}H_{43}O_9NaP_2$ ($M-3Na^+ + 3H^+$) 549.2377. Found 549.2378.

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