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Enantioselective total synthesis and absolute configuration of the alleged structure of crassinervic acid

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ABSTRACT

An enantioselective synthesis of the structure reported for the natural antifungal compound, (−)-crassinervic acid (**1**), has been achieved starting from geraniol and *p*-hydroxybenzoic acid. The key chirality-inducing step is a Sharpless asymmetric epoxidation of an allylic alcohol, on the basis of which the *S* configuration can be assigned to the (−) natural enantiomer. The discrepancies between the spectroscopic data for synthetic and natural crassinervic acid cast some doubts on the structure assigned to the natural compound. A possible revised structure is discussed.

1. Introduction

Piperaceae species have been extensively investigated as a source of new natural products with potential antitumor, antimicrobial, antifungal, and insecticidal activities.[1] The phytochemical profile in *Piper* species is characterized by the production of classes of compounds, such as amides, benzoic acids, and chromenes in addition to lignans, neolignans, and a few alkaloids.[2] Crassinervic acid (**1**) was isolated from leaves of *Piper crassinervium* by Kato and co-workers.[3] Crassinervic acid shows antifungal activity mainly against *Cladosporium cladosporioides* and *Cladosporium sphaerospermum*.

As part of our studies on natural compounds with antifungal activity, we became interested in developing a general method for synthesizing **1** (Fig. 1), which might also be amenable to the synthesis of analogues. As the absolute stereochemistry of (−)-crassinervic acid was not determined in the isolation report, the development of an enantioselective synthesis could also allow assignment of the absolute configuration at C-3′ of the natural product.

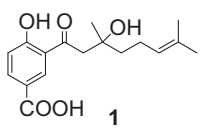

Fig. 1. Structure of crassinervic acid.

2. Results and discussion

We first planned to synthesize racemic **1**, by an aldol reaction between 3-acetyl-4-hydroxybenzoic acid methyl ester and commercially available 6-methyl-5-hepten-2-one, followed by ester hydrolysis under basic conditions to obtain (±)-**1**, then to extend the synthesis to the enantioselective case.

3-Acetyl-4-hydroxybenzoic acid (**2**), obtained by Fries rearrangement of 4-acetoxybenzoic acid, was selectively methylated with $MeOH/H_2SO_4$, to give the acetophenone derivative **3**. Aldol reaction of **3** with commercially available 6-methyl-5-hepten-2-one by using LDA afforded β-hydroxyketone **4**. However deprotection of the carboxyl group using a variety of acidic conditions (TFA; $AlCl_3$/DMA,[4] BBr_3[5]) gave complex mixtures possibly including a product of cyclization of the tertiary alcohol onto the double bond[6] instead of the expected compound **1**. Hydrolysis by using $LiOH\cdot H_2O$ caused retro-aldol reaction to give the starting ketone **2**. Thus, in order to overcome these difficulties, we reduced the ketone group to the corresponding diol **5** by $NaBH_4$/MeOH in 83% yield, which was then hydrolyzed to give acid **6**. Oxidation of the benzylic alcohol was successfully accomplished using IBX in DMSO, to obtain the desired racemic **1** (Scheme 1).

We then focused our attention on the synthesis of enantiopure crassinervic acid by using the same route described above. The key step of our synthetic approach was the aldol addition to a ketone.

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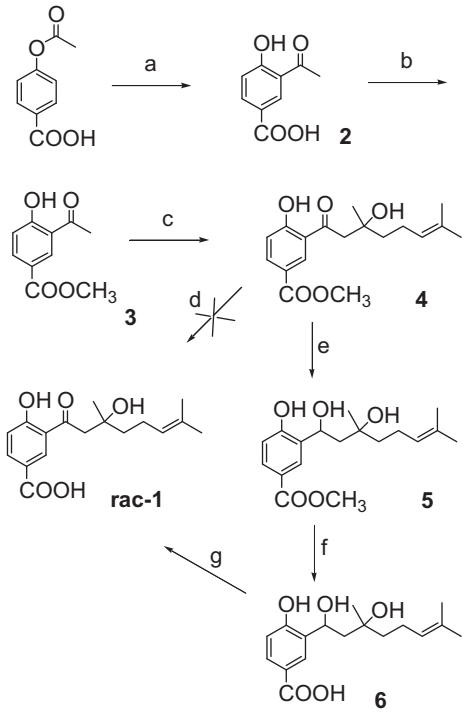


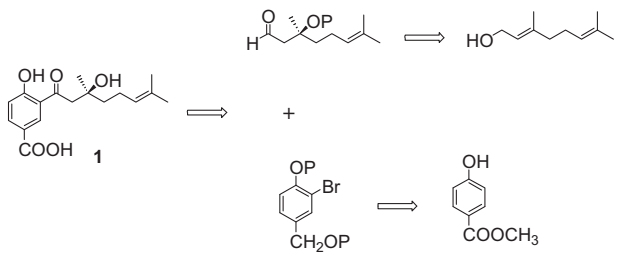
Scheme 1. Reagents and conditions: (a) $AlCl_3$, 160 °C, 5 h, 80%; (b) Concd H_2SO_4, MeOH, reflux, 1 h, 65%; (c) LDA, THF, −78 °C, 1 h; $CH_3CO(CH_2)_2CH{=}C(CH_3)_2$, THF, −78 °C, 3 h, 56%; (d) $LiOH{\cdot}H_2O$, THF/H_2O, rt or $AlCl_3$/DMA or BBr_3, CH_2Cl_2 or TFA; (e) $NaBH_4$, MeOH, 0 °C to rt, 2 h, 83%; (f) $LiOH{\cdot}H_2O$, THF/H_2O, reflux, 9 h, 66%; (g) IBX, DMSO, rt, 3 h, 71%.

The aldol reaction is one of the most important C–C bond-forming reactions and, therefore, there is widespread interest in developing asymmetric variants of this transformation. Reports on the asymmetric aldol condensations using ketones both as aldol acceptors and donors are scarce and so far limited to the use of pyruvates[7] or other activated ketones, such as 1,3-dioxan-5-one derivatives, α-diketones, α-ketonitriles, and α-keto lactams.[8–11]

Notwithstanding the discouraging lack of precedent, it was deemed worthwhile to test different conditions and catalysts to see whether these could be successful in the case of our substrate. We attempted to use chiral lithium amide bases, instead of bonding covalently a chiral auxiliary, which requires removal later on. The use of chiral lithium amides as enantioselective agents for proton removal represents one of the most prominent recent advances in aldol reactions.[12] In principle, treatment of achiral, C_s symmetric ketones with chiral lithium amides leads to the formation of non-racemic lithium enolates. The base discriminates between two enantiotopic protons, and the resulting enolate could be trapped with electrophiles yielding ultimately an enantiomerically enriched chiral product. The potential of this approach has been exploited by numerous research groups.[12]

Attempts using different lithium amides, such as those from (+)-bis[(*R*)-1-phenylethyl]amine,[13] and the tetradentate (*R*)-*N*-[2-(2-methoxyethoxy)ethyl]-1-phenyl-2-piperidinoethylamine,[14] failed to give the desired product. The use of an alkyllithium in tandem with a chiral ligand (BuLi/sparteine and LDA/sparteine) gave only racemic material.[15]

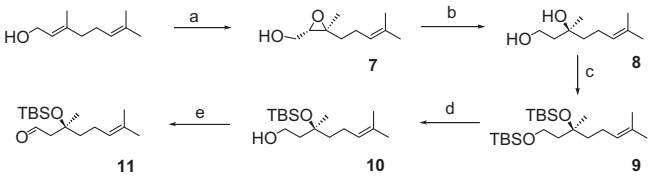
These failures in enantioselective aldol reaction forced us to look for another route for obtaining enantiopure crassinervic acid. The retrosynthetic approach is depicted in Scheme 2. It was envisioned to proceed via a condensation of the monoterpene aldehyde derivative and the bromo arene unit, which could be synthesized from commercially available geraniol and methyl 4-hydroxybenzoate, respectively.



Scheme 2. Retrosynthetic analysis of (−)-crassinervic acid **1**.

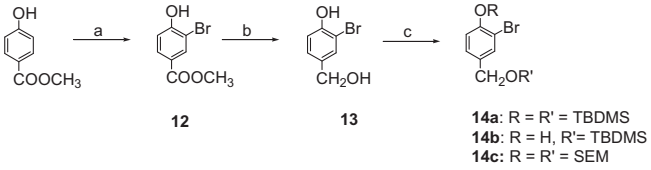
The chiral fragment **11** was obtained by modification of a reported procedure,[16] using as a key step the Sharpless epoxidation of commercially available geraniol, followed by a reductive ring opening. This method has the advantage of providing access to both enantiomers of **11**, if the appropriate tartrate is used.

Initially, we decided to prepare the enantiomer with absolute configuration 3′(*S*). Thus, asymmetric epoxidation of geraniol using L-(+)-diisopropyl tartrate (DIPT)[17] was carried out to give the epoxide **7**. The enantiomeric excess was determined to be 93% by comparing its optical rotation with the data reported in the literature.[16] Regioselective ring opening of **7** using sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) as a reducing agent[18] led to the chiral diol **8** in quantitative yield and without any loss of optical purity $[\alpha]_D^{25}$ +2.7 (*c* 2.5, $CHCl_3$); {lit.,[17] $[\alpha]_D^{25}$ +2.1 (*c* 3, $CHCl_3$)}. Protection of both the hydroxy groups with TBSOTf, gave diprotected diol **9**. It was then selectively deprotected with *p*-TSA/MeOH to obtain the monoprotected diol **10**. Oxidation of the primary alcohol **10**[16] furnished aldehyde **11** (Scheme 3).



Scheme 3. Reagents and conditions: (a) L-(+)-DIPT, MS 4 Å, $Ti(O^iPr)_4$, TBHP, CH_2Cl_2, −23 °C, 4 h, 94%; (b) Red-Al, THF, 0 °C to rt, 4 h, 100%; (c) TBSOTf, 2,6-Lutidine, CH_2Cl_2, 12 h, 100%; (d) *p*TSA, MeOH, 0 °C, 30 min, 100%; (e) $SO_3{\cdot}Py$, TEA, DMSO, rt, 3 h, 92%.

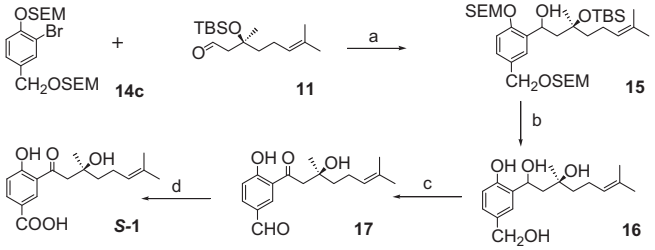
The synthesis of the aromatic fragment **14** is summarized in Scheme 4. Bromination of methyl 4-hydroxybenzoate gave in 95% yield the bromoderivative **12**,[19] that was converted into alcohol **13** using DIBAL as a reducing agent (Scheme 4).



Scheme 4. Reagents and conditions: (a) Br_2, CH_2Cl_2, 0 °C to rt, 24 h, 95%; (b) DIBAL, CH_2Cl_2, −78 °C, 1 h, 68%; (c) TBDMSCl, imidazole, THF, rt, 12 h, 87% (**14a**); TBDMSCl, TEA, DMAP, CH_2Cl_2, rt, 12 h, 86% (**14b**); SEMCl, DIPEA, CH_2Cl_2, 0 °C to rt, 12 h, 87% (**14c**).

Protection of one or both the benzylic and phenolic functionalities as silyl ethers was effected using TBDMSCl, to give compounds **14a**,**b**. Disappointingly, the alkylation reaction with aldehyde **11** by using *t*-BuLi, failed to give the expected product. Eventually, we found that the protection of both the hydroxy functionalities as SEM-ethers (**14c**) followed by treatment with *t*-BuLi (Scheme 5) gave the expected coupling product **15** as a mixture of diastereoisomers in a satisfying 64% yield. However, deprotection of this compound was troublesome, an attempt to

remove both SEM and TBS protecting groups with an excess of tetrabutyl ammonium fluoride (TBAF) in THF did not remove the benzylic SEM. This was accomplished with an excess of tetrabutyl ammonium fluoride (TBAF), 4 Å molecular sieves, and DMPU as solvent.[20] The addition of 4 Å molecular sieves (crushed, activated) was needed to reduce the formation of the corresponding ethoxymethyl ether and to increase the rate of the reaction.



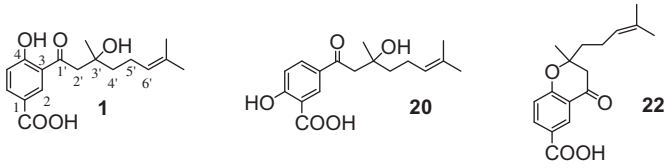
Scheme 5. Reagents and conditions: (a) *t*-BuLi, THF, −78 °C, 2 h, 64%; (b) TBAF, DMPU, reflux, 7 h, 78%; (c) IBX, DMSO, rt, overnight, 65%; (d) $NaClO_2$, $NaH_2PO_4{\cdot}H_2O$, *t*-BuOH, H_2O, 2-methyl-2-butene, 3 h, 75%.

Finally, oxidation of **16** with IBX in DMSO gave the ketoaldehyde **17**, which, by treatment with sodium chlorite furnished (−)-**1** in 75% yield.

Synthetic **1** showed the same (−) sign of specific rotation reported for natural crassinervic acid. As the absolute configuration at C-3′ stereogenic center of synthetic **1** is *S*, due to Sharpless enantioselective epoxidation mechanism, we may safely deduce that the absolute configuration of the natural compound is *S*.

Most of the spectroscopic data of synthetic (−)-1 (^1H, ^{13}C NMR and MS) matched those reported for the natural product,[3] except for the signals of H-2′ and C1′, C3′, and C4′, that showed remarkable discrepancies in chemical shift (Table 1).

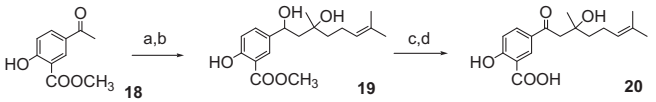
Table 1
^1H and ^{13}C chemical shifts for natural crassinervic acid,[3] and compounds **1**, **20**, and **22**



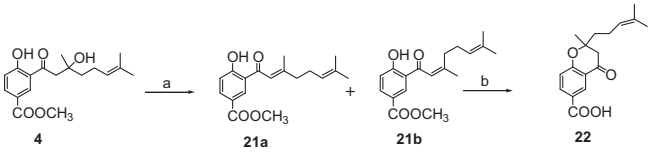
Position[a]	Nat. compd	1	20	22	Position	Nat. compd	1	20	22
OH	12.3	12.06	11.18	12.76	C-1	119.9	119.0	118.5	120.0
H-2	8.56	8.56	8.54	8.64	C-2	129.9	132.0	132.1	130.1
H-6	8.11	8.20	8.14	8.18	C-3	122.1	119.9	132.0	122.0
H-5	6.93	7.06	7.08	7.01	C-4	163.7	166.8	166.3	163.9
H-6′	4.98	5.09	5.09	5.06	C-5	118.8	119.1	129.3	118.9
H-2′a	*2.77*	*3.30*	*3.18*	*2.85*	C-6	137.3	137.8	136.0	137.4
H-2′b	*2.64*	*3.18*	*3.07*	*2.71*	C-1′	*191.5*	*207.1*	*199.6*	*191.6*
H_2-5′	2.03	2.11 −2.18	1.98 −2.18	2.01 −2.18	C-2′	47.2	46.9	46.5	47.3
H_2-4′	1.70	1.65 −1.68	1.58 −1.71	1.61 −1.85	C-3′	*82.3*	*72.2*	*72.8*	*82.5*
H_3-8′	1.58	1.64	1.65	1.66	C-4′	*39.3*	*41.8*	*42.0*	*39.4*
H_3-9′	1.50	1.60	1.61	1.57	C-5′	22.2	22.6	22.9	22.3
H_3-10′	1.37	1.35	1.34	1.44	C-6′	122.9	123.7	124.2	123.0
					C-7′	132.5	133.6	132.3	132.7
					C-8′	25.6	27.0	27.0	25.7
					C-9′	17.5	17.5	17.7	17.7
					C-10′	23.9	25.5	25.7	24.1
					C-11′	170.6	170.0	172.5	171.1

[a] For sake of clarity the same numbering was given to the structurally corresponding atoms.

Unfortunately, we were not able to obtain either a sample or copies of the spectra of natural crassinervic acid (M.J. Kato, personal communication, 2010). As the analytical data reported in the isolation paper could also match with the structure of the isomer **20**, we prepared this compound following the route described in Scheme 6. However, not even the spectroscopic NMR data for **20** match with those reported for natural crassinervic acid. As the most striking difference was the chemical shift of C1′ (207.1 ppm vs 191.5 of the reported compound), we reasoned that the carbonyl group in the natural compound could not be involved in an intramolecular hydrogen bond. This pointed to the possibility of the cyclic structure **22**, supported by comparison with spectroscopic NMR data for a farnesyl-derived analogue.[21] Thus, compound **22** was synthesized following the sequence described in Scheme 7. As hypothesized, the NMR spectra of the new derivative completely matched those reported for crassinervic acid. However, the true structure of the natural compound remains open to question, because the mass spectrometric data are consistent with structure **1**, whereas the NMR data correspond to structure **22**. In absence of a direct comparison we may only hypothesize that, if the natural compound is **1**, the reported NMR data were measured on an artifact perhaps due to an acid/base treatment.



Scheme 6. Reagents and conditions: (a) LDA, THF/heptane, −78 °C, 4 h, 59%; (b) $NaBH_4$, MeOH, 2 h, rt, 70%; (c) THF/H_2O, $LiOH{\cdot}H_2O$, 4 h, reflux, 95%; (d) IBX, DMSO, 3 h, rt, 61%.



Scheme 7. Reagents and conditions: (a) TEA, $SOCl_2$, DCM, 0 °C, 2 h, 80%; (b) NaOH, H_2O, rt, overnight, quantitative.

3. Conclusion

In conclusion, the first stereoselective total synthesis of the structure reported[3] for (−)-crassinervic acid **1** was accomplished in 12 steps in 12% overall yield. Crucial steps for our strategy included an enantioselective Sharpless epoxidation of easily available geraniol, followed by a regioselective reduction of the corresponding epoxyalcohol, and a condensation of the monoterpene fragment with lithiated a 4-hydroxymethylphenol. The successful coupling of the two moieties required a careful choice of the protecting groups. The absolute configuration of **1** was assigned as *S*. However, the differences in spectroscopic data for **1** and those reported for crassinervic acid,[3] in absence of a direct comparison, cast doubts on the structure assigned to crassinervic acid. The chromanone analogue **22**, whose NMR data are consistent with those reported for the natural compound, was synthesized.

The synthetic routes developed here could potentially be applied to the synthesis of analogues and other related natural products. Further synthetic studies and the evaluation of biological activity are in progress.

4. Experimental

4.1. General

All reagents and solvents were reagent grade or were purified by standard methods before use. Melting points were determined in open capillaries. IR spectra were recorded on a Perkin–Elmer 177

spectrophotometer. NMR spectra were recorded at 300 MHz. Mass spectra were recorded with a Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometer. Solvents were routinely distilled prior to use; anhydrous tetrahydrofuran (THF) and ether (Et_2O) were obtained by distillation from sodium–benzophenone ketyl; dry dichloromethane was obtained by distillation from phosphorus pentoxide. All reactions requiring anhydrous conditions were performed under a positive nitrogen flow, and all glassware were oven dried and/or flame dried. Isolation and purification of the compounds were performed by flash column chromatography on silica gel 60 (230–400 mesh). Analytical thin-layer chromatography (TLC) was conducted on TLC plates (silica gel 60 F_{254}, aluminum foil) visualized by UV light and spraying with phosphomolybdic acid and *p*-anisaldehyde.

4.2. Synthesis

4.2.1. 3-Acetyl-4-hydroxybenzoic acid[22] (**2**). 4-Acetoxy-benzoic acid (0.350 g, 1.95 mmol) and anhydrous $AlCl_3$ (0.800 g, 6.02 mmol) were mixed and heated at 155–160 °C (oil bath temperature) for 5 h (after 1 h a solid, brown foamy mass formed and stirring was no longer possible). After cooling (ice bath), the reaction mixture was treated with 6.5 mL of 2 N HCl. The acidified reaction mixture was extracted with ethyl acetate (3×10 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated to afford a yellow solid (0.280 g, 80%), which was used without any further purification.

4.2.2. 3-Acetyl-4-hydroxybenzoic acid methyl ester[23] (**3**). Concentrated H_2SO_4 (5 drops) was added to a suspension of 3-acetyl-4-hydroxybenzoic acid **2** (0.250 g, 1.38 mmol) in 12 mL of MeOH at room temperature. The resulting reaction mixture was heated at reflux for 1 h, then it was cooled to room temperature and neutralized using 2 N NaOH. The mixture was allowed to stand for 15 min, before being poured onto an iced H_2O beaker and made up to 42 mL with H_2O. The white precipitate was filtered and dried. The crude product was purified by flash column chromatography (ethyl acetate/hexane 13:87) to give the title compound as a white crystalline solid (0.175 g, 65%). Mp 101–102 °C; [Found: C, 61.80; H, 5.21. $C_{10}H_{10}O_4$ requires C, 61.85; H, 5.19]; R_f 0.62 (ethyl acetate/hexane 35:65); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.65 (s, 1H), 8.48 (d, *J* 1.7 Hz, 1H), 8.21 (dd, *J* 1.7, 8.6 Hz, 1H), 7.01 (d, *J* 8.6 Hz, 1H), 3.90 (s, 3H), 2.70 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 204.3, 165.7 (×2), 136.9, 133.0, 120.8, 118.9, 118.4, 51.9, 26.5.

4.2.3. 4-Hydroxy-3-(3′-hydroxy-3′,7′-dimethyl-oct-6′-enoyl)benzoic acid methyl ester (**4**). A solution of LDA was prepared by adding a 2.7 M solution of *n*-BuLi in heptane (0.595 mL, 1.61 mmol) to a solution of diisopropylamine (0.227 mL, 1.61 mmol) in 4 mL of THF, stirring at 0 °C under argon atmosphere. After 30 min, the solution was cooled to −78 °C and added slowly with a solution of 3-acetyl-4-hydroxybenzoic acid methyl ester (**3**) (0.125 g, 0.64 mmol) in THF (1 mL) over 10 min. The resulting solution was stirred for 1 h at −78 °C (in order to secure the complete formation of the corresponding enolate) prior to slow addition of 6-methyl-5-hepten-2-one (0.143 mL, 0.97 mmol). Stirring was continued for 3 h at −78 °C and then the reaction was quenched with a saturated aqueous NH_4Cl solution. The reaction mixture was allowed to reach room temperature. The layers were separated and the aqueous layer was extracted with diethyl ether (3×5 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexane 15:85) to afford the aldol product **4** as a viscous oil (0.115 g, 56%). [Found: C, 67.45; H, 7.52. $C_{18}H_{24}O_5$ requires C, 67.48; H, 7.55]; R_f 0.74 (ethyl acetate/hexane 1:1); IR ν_{max} (liquid film) 3510, 3080, 2950, 2850, 1720, 1640, 1590, 1480, 1440, 1380, 1280, 1230, 1120, 980, 780 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.61 (s, 1H), 8.50 (d, *J* 2.2 Hz, 1H), 8.18 (dd, *J* 2.2, 8.8 Hz, 1H), 7.02 (d, *J* 8.8 Hz, 1H), 5.06 (m, 1H), 3.95 (s, 1H), 3.30 (d, *J* 16.6 Hz, 1H), 3.20 (d, *J* 16.6 Hz, 1H), 2.10 (m, 2H), 1.80–1.55 (m, 8H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 207.2, 166.0, 165.6, 137.3, 132.6, 131.9, 123.7, 120.9, 119.2, 118.8, 72.0, 52.0, 46.8, 41.8, 26.9, 25.4, 22.5, 17.4. HRMS (ESI^+) calcd for $C_{18}H_{24}O_5Na^+$343.15159, found 343.15882.

4.2.4. 3-(1′,3′-Dihydroxy-3′,7′-dimethyl-oct-6′-enyl)-4-hydroxybenzoic acid methyl ester (**5**). 4-Hydroxy-3-(3′-hydroxy-3′,7′-dimethyl-oct-6′-enoyl)benzoic acid methyl ester **4** (0.110 g, 0.34 mmol) was dissolved in MeOH (2.5 mL) and then cooled to 0 °C $NaBH_4$ (0.039 g, 0.10 mmol) was added portionwise and the reaction mixture was slowly (without removing ice bath) warmed to room temperature. After 2 h from addition of $NaBH_4$, MeOH was evaporated under vacuo. The residue was diluted with ethyl acetate, followed by addition of a saturated aqueous NH_4Cl solution. The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated to afford **5** as a sticky solid (0.091 g, 83%). [Found: C, 67.13; H, 8.19. $C_{18}H_{26}O_5$ requires C, 67.07; H, 8.13]; R_f 0.40 (ethyl acetate/hexane 1:1). IR ν_{max} (liquid film) 3380, 3080, 2990, 1715, 1430, 1275, 755 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) (mixture of diastereomers ratio 50:50) δ: 9.69 (0.5H, s), 9.62 (0.5H, s), 7.90 (dd, *J* 1.7, 8.6 Hz, 1H), 7.65 (d, *J* 1.7 Hz, 1H), 6.90 (d, *J* 8.6 Hz, 1H), 5.75 (s, 0.5H), 5.70 (s, 0.5H), 5.45–5.35 (m, 1H), 5.25–5.19 (m, 0.5H), 5.15–5.05 (m, 0.5H),3.90 (s, 3H), 2.20–1.50 (m, 15H). ^{13}C NMR (75 MHz, $CDCl_3$) (mixture of diastereomers, some signals overlapped) δ: 166.9, 161.0, 132.9, 130.6, 128.7, 126.7, 123.6, 121.7, 117.4, 75.3, 73.9, 73.6, 51.7, 47.4, 46.9, 44.4, 39.6, 29.7, 29.1, 25.6, 23.3, 22.4, 17.7.

4.2.5. 3-(1′,3′-Dihydroxy-3′,7′-dimethyl-oct-6′-enyl)-4-hydroxybenzoic acid (**6**). 3-(1′,3′-dihydroxy-3′,7′-dimethyl-oct-6′-enyl)-4-hydroxybenzoic acid methyl ester **5** (0.085 g, 0.26 mmol) was taken in THF/H_2O (3:1) (1.5 mL:0.5 mL), followed by addition of $LiOH\cdot H_2O$ (33 mg, 0.79 mmol). The resulting reaction mixture was refluxed for 9 h and then cooled to room temperature. THF was evaporated and the remaining aqueous layer was cooled to 0 °C and acidified to pH 3 by cold 2 N HCl. The resulting white precipitate was filtered, washed with H_2O and dried to afford the acid **6** as a sticky solid (0.051 g, 66%). This crude product was used further without any purification. IR ν_{max} (liquid film) 3400, 3080, 1950, 1690, 1600, 1430, 1280, 910, 750 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) (mixture of diastereomers ratio 50:50) δ: 9.80 (br s, 0.5H), 9.75 (br s, 0.5H), 7.92 (dd, *J* 1.7, 8.6 Hz, 0.5H), 7.85 (dd, *J* 1.7, 8.6 Hz, 0.5H), 7.70 (d, *J* 1.7 Hz, 1H), 6.90 (d, *J* 8.6 Hz, 1H), 5.45 (t, *J* 6.0 Hz, 0.5H), 5.40 (t, *J* 6.0 Hz, 0.5H), 5.25–5.21 (m, 0.5H), 5.10–4.99 (m, 0.5H), 4.12–4.00 (m, 0.5H), 3.55–3.45 (m, 0.5H), 2.30–1.20 (m, 15H). ^{13}C NMR (75 MHz, $CDCl_3$) (mixture of diastereomers, some signals overlapped) δ: 171.3, 161.6, 133.5, 131.4, 129.4, 126.5, 123.4, 120.5, 117.6, 75.5, 74.0, 73.6, 46.7, 44.2, 39.2, 29.0, 25.8, 25.4, 23.2, 22.4, 17.6.

4.2.6. 4-Hydroxy-3-(3′-hydroxy-3′,7′-dimethyl-oct-6′-enoyl)-benzoic acid (rac **1**). To a stirred solution of IBX (136 mg, 0.49 mmol) in DMSO (1.5 mL), 3-(1′,3′-dihydroxy-3′,7′-dimethyl-oct-6′-enyl)-4-hydroxybenzoic acid **6** (0.051 g, 0.16 mmol) in 1 mL DMSO was added dropwise at 0 °C under argon atmosphere. The reaction mixture was warmed to room temperature and stirred for 3 h, then H_2O (2 mL) was added. Stirring was continued for further 10 min. The reaction mixture was filtered through a pad of Celite and the residue was washed with ethyl acetate. The resulting filtrate and washings were combined and dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by reverse phase column chromatography (RP-18) (water/methanol 35:65) to afford *rac* **1** as a white solid (0.036 g, 71%). Mp 148 °C; R_f 0.65 (CH_2Cl_2/MeOH 9:1); IR ν_{max} (Nujol) 3450, 3080, 2980, 1690, 1640, 1432, 1270, 750, 710 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.06 (s,

1H), 8.56 (d, *J* 1.7 Hz, 1H), 8.20 (dd, *J* 1.7, 8.9 Hz, 1H), 7.06 (d, *J* 8.9 Hz, 1H), 5.09 (t, *J* 7.2 Hz, 1H), 3.30 (d, *J* 16.6 Hz, 1H), 3.18 (d, *J* 16.6 Hz, 1H), 2.11 (m, 2H), 1.68 (m, 2H), 1.64 (s, 3H), 1.60 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 207.1, 170.0, 166.8, 137.8, 133.6, 132.0, 123.7, 119.9, 119.1, 119.0, 72.2, 46.9, 41.8, 27.0, 25.5, 22.6, 17.5. HRMS (ESI−) calcd for $C_{17}H_{21}O_5^-$ 305.13945, found 305.13967.

*4.2.7. (2S-trans)-3-Methyl-3-(4′-methyl-pent-3′-enyl)oxiranylmethanol (**7**).* A mixture of powdered, activated 4-Å molecular sieves (0.040 g) and CH_2Cl_2 (2 mL) was cooled to 0 °C (+) diisopropyl tartrate (0.016 mL, 0.08 mmol) and $Ti(O^iPr)_4$ (0.015 mL, 0.05 mmol) were added sequentially. After the mixture was cooled to −10 °C *t*-BuOOH (0.274 mL, 1.51 mmol) was added and the resulting mixture was stirred for 20 min. The mixture was cooled to −23 °C and geraniol (0.176 mL, 1.0 mmol) was added at a rate sufficient to ensure that the temperature remained below −20 °C. The mixture was stirred at −23 °C for an additional 4 h and water was added with vigorous stirring. After 30 min a 30% aqueous solution of NaOH saturated with NaCl was added, and the mixture was stirred at room temperature for an additional 25 min until a phase separation was observed. The suspension was filtered then over a Buchner funnel to separate the residues of the molecular sieves from the solution. After separating the liquid phases, the cloudy, aqueous phase was extracted CH_2Cl_2 (3×5 mL), the combined organic phases were dried over anhydrous Na_2SO_4, filtered, and the solvent removed in vacuo. The residue was purified by flash column chromatography (ethyl acetate/hexane 35:65) to afford **7** as a colorless liquid (0.161 g, 94%). [Found: C, 70.52; H, 10.68. $C_{10}H_{18}O_2$ requires C, 70.55; H, 10.66]; R_f 0.51 (ethyl acetate/petroleum ether 1:1); $[\alpha]_D^{20}$ −5.4 (*c* 3, $CHCl_3$); {lit.,[16] $[\alpha]_D^{25}$ −5.3 (*c* 3, $CHCl_3$)}; IR ν_{max} (liquid film) 3420, 3000, 2980, 2860, 1680, 1450, 1380, 1220, 1190, 1040, 870 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.08 (t, *J* 7.1 Hz, 1H), 3.83 (dd, *J* 3.8, 11.6 Hz, 1H), 3.68 (dd, *J* 11.6, 6.9 Hz, 1H), 2.97 (dd, *J* 3.81, 6.9 Hz, 1H), 2.10−1.98 (m, 2H),1.68 (s, 3H), 1.61 (s, 3H), 1.40−1.70 (m, 2H), 1.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 132.3, 123.4, 63.0, 61.6, 61.3, 38.6, 25.7, 23.8, 17.7, 16.8.

*4.2.8. (3S)-3,7-Dimethyl-oct-6-ene-1,3-diol (**8**).* The compound was prepared following the procedure described in Ref. 17.

*4.2.9. (6S)-6,8-Bis-(tert-butyldimethylsilanyloxy)-2,6-dimethyl-oct-2-ene (**9**).* To an ice-cold stirred solution of **8** (0.145 g, 0.84 mmol) in CH_2Cl_2 (5 mL), 2,6-lutidine (0.390 mL, 3.36 mmol) and TBSOTf (0.464 mL, 2.02 mmol) were added at 0 °C. The resulting mixture was warmed to room temperature and stirred for 12 h, then water (3 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (ethyl acetate/hexane 98:2) to obtain **9** as a viscous oil, (0.337 g, 100%). [Found: C, 65.90; H, 12.11. $C_{22}H_{48}O_2Si_2$ requires C, 65.93; H, 12.07]; R_f 0.89 (ethyl acetate/petroleum ether 5:95); $[\alpha]_D^{20}$ +1.3 (*c* 3, $CHCl_3$); IR ν_{max} (liquid film) 3000, 2960, 2920, 2905, 2860, 1610, 1540, 1495, 1465, 1410, 1360, 1240, 1100, 990, 840 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.08 (t, *J* 6.7 Hz, 1H), 3.71 (t, *J* 7.4 Hz, 2H), 2.10−1.90 (m, 2H), 1.80−1.65 (m, 5H), 1.60 (s, 3H), 1.50−1.35 (m, 2H), 1.21 (s, 3H), 0.89 (s, 9H), 0.86 (s, 9H), 0.07 (s, 6H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 131.2, 124.8, 74.9, 60.0, 45.0, 43.1, 28.0, 26.1, 26.0, 25.8, 23.1, 18.4, 17.7, −1.9, −5.5.

*4.2.10. (3S)-3-(tert-Butyldimethylsilanyloxy)-3,7-dimethyl-oct-6-en-1-ol[16] (**10**).* An ice-bath cooled solution of the bis-TBS ether **9** (0.325 g, 0.81 mmol) in MeOH (4 mL) was treated with *p*-TsOH (0.019 g, 0.10 mmol) as a solid. The reaction mixture was stirred at the same temperature for 30 min. The reaction mixture was quenched with solid $NaHCO_3$ and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (ethyl acetate/petroleum ether 12:88) to afford **10** as a colorless liquid (0.232 g, 100%). [Found: C, 67.09; H, 11.99. $C_{16}H_{34}O_2Si$ requires C, 67.07; H, 11.96.]; R_f 0.49 (ethyl acetate/petroleum ether 15:85); $[\alpha]_D^{20}$ +4.13 (*c* 3, $CHCl_3$); IR ν_{max} (liquid film) 3405, 3080, 2965, 2940, 2870, 1630, 1460, 1380, 1360, 1275, 1150, 1097, 842, 750 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.08 (t, *J* 7.1 Hz, 1H), 3.80 (t, *J* 5.7 Hz, 2H), 2.72 (t, *J* 5.7 Hz, 2H), 1.97 (m, 2H), 1.69 (s, 3H), 1.60 (s, 3H), 1.80−1.50 (m, 2H), 1.20 (s, 3H), 0.87 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 131.7, 124.3, 77.3, 60.0, 42.9, 42.8, 27.8, 26.0, 25.8, 25.4, 25.3, 23.4, 18.2, 17.7, −1.3.

*4.2.11. (3S)-3-(tert-Butyldimethylsilanyloxy)-3,7-dimethyl-oct-6-enal (**11**).* The compound was prepared following the procedure described in Ref. 16.

*4.2.12. 3-Bromo-4-hydroxybenzoic acid methyl ester (**12**).* The compound was prepared following the procedure described in Ref. 19.

*4.2.13. 2-Bromo-4-hydroxymethylphenol[24] (**13**).* To a solution of **12** (0.185 g, 0.80 mmol) in dry CH_2Cl_2 (14 mL), a solution of DIBAL-H in THF (1.0 M) (1.92 mL, 1.92 mmol) was added at −78 °C. The solution was stirred for 1 h and then it was quenched by addition of MeOH and water. A saturated solution of Na^+ and K^+ tartrate was added; the mixture was stirred for an additional hour and the aqueous layer was extracted with ethyl acetate (3×20 mL). The organic layers were combined and washed with a 10% aqueous solution of $NaHCO_3$ and water, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexane 1:1) to afford **13** as white solid (0.111 g, 68%). Mp 125 °C; [Found: C, 41.45; H, 3.42. $C_7H_7BrO_2$ requires C, 41.41; H, 3.48]; R_f 0.6 (ethyl acetate/hexane 65:35); IR ν_{max} (Nujol) 3510, 3060, 2982, 1610, 1505, 1425, 1270, 905, 750, 710 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ: (s, 1H), 7.38 (d, *J* 2.0 Hz, 1H), 7.08 (dd, *J* 2.0, 8.2 Hz, 1H), 6.87 (d, *J* 8.2 Hz, 1H), 5.07 (t, *J* 5.7 Hz, 1H), 4.34 (d, *J* 5.7 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 153.3, 135.4, 131.6, 127.6, 116.5, 109.4, 62.5.

*4.2.14. 2-Bromo-4-(tert-butyldimethylsilyloxymethylphenoxy)(tert-butyl)dimethylsilane (**14a**).* To a solution of **13** (0.100 g, 0.49 mmol) in THF (3.0 mL) at 0 °C, imidazole was added in one portion followed by addition of TBDMSCl (0.192 mL, 1.08 mmol). The resulting reaction mixture was warmed to room temperature and stirred for 12 h, then the reaction mixture was diluted with water and extracted with ethyl acetate (3×5 mL). The organic layers were combined and dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (ethyl acetate/petroleum ether 3:97) to afford **14a** as colorless thick oil (0.370 g, 87%). [Found: C, 52.92; H, 8.19. $C_{19}H_{35}BrO_2Si_2$ requires C, 52.88; H, 8.17]; R_f 0.81 (ethyl acetate/petroleum ether 30:70); IR ν_{max} (liquid film) 3050, 2950, 2850, 1600, 1495, 1300, 1250, 1090, 930, 850, 760 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.46 (d, *J* 2.2 Hz, 1H), 7.09 (dd, *J* 2.2, 8.2 Hz), 6.81 (d, *J* 8.2 Hz), 4.62 (s, 2H), 1.02 (s, 9H), 0.92 (s, 9H), 0.22 (s, 6H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.5, 135.7, 131.2, 126.1, 120.0, 115.1, 64.1, 26.0, 25.8, 18.4, 16.6, −5.1, −4.1.

*4.2.15. 2-Bromo-4-(tert-butyldimethylsilyloxymethyl)phenol (**14b**).* To a solution of **13** (0.150 g, 0.74 mmol) in CH_2Cl_2 (5.0 mL) at 0 °C, was added TEA (0.154 mL, 1.11 mmol) and DMAP (0.005 g, 0.04 mmol) followed by slow addition of TBDMSCl (0.111 g, 0.74 mmol). The resulting reaction mixture was warmed to room temperature and stirred for 12 h. After 12 h, a saturated aqueous NH_4Cl solution was added to the reaction mixture, followed by

extraction with ethyl acetate (3×5 mL). The organic layers were combined and dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (ethyl acetate/petroleum ether 25:75) to afford **14b** as a colorless oil (0.200 g, 86%). [Found: C, 49.27; H, 6.65. $C_{13}H_{21}BrO_2Si$ requires C, 49.21; H, 6.67]; R_f 0.40 (ethyl acetate/petroleum ether 30:70); IR ν_{max} (liquid film) 3500, 3045, 2960, 2920, 1605, 1495, 1260, 1100, 845 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.53 (d, *J* 1.7 Hz, 1H), 7.16 (dd, *J* 1.7 Hz, 8.2 Hz), 6.85 (d, *J* 8.2 Hz, 1H), 4.59 (s, 2H), 1.04 (s, 9H), 0.24 (s, 6H).

*4.2.16. 2-(2′-Bromo-4′-(2″-(trimethylsilylethoxymethoxymethyl)-phenoxy)methoxyethyl)trimethyl silane (**14c**).* To a solution of **13** (0.100 g, 0.49 mmol) in CH_2Cl_2 (3.5 mL) at 0 °C, *N*,*N*′-diisopropylethylamine (0.683 mL, 3.9 mmol) was added dropwise, followed by slow addition of 2-trimethylsilanylethoxymethoxy chloride (0.192 mL, 1.08 mmol). The resulting reaction mixture was warmed to room temperature and stirred for 12 h, then it was diluted with water. The organic layer was separated, washed with H_2O and dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexane 6:96) to afford **14c** as colorless thick liquid (0.198 g, 87%). [Found: C, 49.28; H, 7.66. $C_{19}H_{35}BrO_4Si_2$ requires C, 49.23; H, 7.61]; R_f 0.62 (Ethyl acetate/hexane 10:90); IR ν_{max} (liquid film) 3080, 2950, 1650, 1490, 1250, 1100, 840 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.55 (d, *J* 2.0 Hz, 1H), 7.22 (dd, *J* 2.0, 8.4 Hz, 1H), 7.14 (d, *J* 8.4 Hz, 1H), 5.28 (s, 2H), 4.73 (s, 2H), 4.51 (s, 2H), 3.79 (t, 2H), 3.65 (t, *J* 8.5 Hz, 2H), 0.90–1.00 (m, 4H), 0.03 (s, 9H), 0.00 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.0, 153.6, 133.0, 128.2, 116.1, 112.8, 97.6, 94.2, 93.7, 68.3, 66.7, 65.4, 18.1, −1.3.

*4.2.17. (3S)-3-(tert-Butyldimethylsilyloxy)-3,7-dimethyl-1-[2′-2″-(trimethylsilylethoxymethoxy)-5′-2″-(trimethylsilylethoxyethoxymethyl)-phenyl]-oct-6-en-1-ol (**15**).* To a solution of **14c** (0.190 g, 0.40 mmol) in THF (4 mL) 1.7 M *t*-BuLi (0.264 mL, 0.45 mmol) was added at −78 °C under argon atmosphere. Aldehyde **11** (0.117 g, 0.40 mmol) was added immediately to the above solution. After additional 2 h at −78 °C, a saturated aqueous NH_4Cl solution was added and the reaction mixture was allowed to reach room temperature. The product was extracted by diethyl ether (3×10 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (diethyl ether/petroleum ether 12:88) to afford **15** (0.175 g, 64%) as a colorless thick liquid. [Found: C, 65.21; H, 10.25. $C_{30}H_{56}O_5Si_2$ requires C, 65.17; H, 10.21]; R_f 0.47 (diethyl ether/petroleum ether 20:80); IR ν_{max} (liquid film) 3470, 3050, 2950, 1500, 1250, 1100, 1070, 980, 850 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (mixture of diastereomers ratio 60:40) δ: 7.58 (s, 1H), 7.18 (d, *J* 8.5 Hz, 1H), 7.06 (d, *J* 8.5 Hz, 0.6H), 7.02 (d, *J* 8.5 Hz, 0.4H), 5.40–5.35 (m, 1H), 5.21 (s, 2H), 5.20–5.15 (m, 0.6H), 5.01–4.95 (m, 0.4H), 4.74 (s, 2H), 4.56 (br s, 0.6H), 4.55 (s, 2H), 4.24 (br s, 0.4H), 3.69–3.65 (m, 4H), 2.05–1.95 (m, 2H), 1.78–1.55 (m, 16H), 0.99–0.85 (m, 13H), 0.18 (s, 6H), 0.03 (s, 9H), 0.02 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) (mixture of diastereomers, some signals overlapped) δ:153.0, 134.0, 131.7, 131.2, 127.6, 126.4, 124.2, 124.1, 113.3, 94.1, 92.8, 78.8, 78.4, 69.3, 66.3, 66.2, 66.0, 65.2, 47.7, 44.6, 41.0, 27.0, 26.1, 26.0, 25.7, 23.8, 23.1, 18.2, 18.1, 17.7, −1.3.

*4.2.18. (3′S)-1-(2′-Hydroxy-5′-hydroxymethylphenyl)-3,7-dimethyl-oct-6-ene-1,3-diol (**16**).* A solution of tetrabutyl ammonium fluoride in THF (1 M, 3.70 mL, 3.70 mmol) was added to the SEM protected compound **15** (0.165 g, 0.25 mmol) and the solution was concentrated in vacuo. The resulting oil was dissolved in anhydrous DMPU (1.5 mL). Powdered activated 4 Å molecular sieves were added (ca. 0.160 g), and the resultant suspension was heated to 80 °C for 7 h. Then the reaction mixture was cooled to room temperature, and the contents diluted with diethyl ether and poured onto water. The solution was extracted with diethyl ether (3×10 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. The resulting oil was washed with hexane to remove residual DMPU and subjected to flash column chromatography (ethyl acetate/petroleum ether 80:20) to afford **16** as a colorless liquid (0.056 g, 78%). [Found: C, 69.39; H, 8.86. $C_{17}H_{26}O_4$ requires C, 69.36; H, 8.90]; R_f 0.54 (ethyl acetate/petroleum ether 90:10); IR ν_{max} (liquid film) 3480, 3080, 2980, 1440, 1270 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (mixture of diastereomers ratio 60:40) δ: 8.90 (br s, 1H), 7.11 (dd, *J* 2.0, 8.7 Hz, 1H), 6.92 (d, *J* 2.0 Hz, 1H), 6.82 (d, *J* 8.7 Hz, 1H), 5.35–5.15 (m, 2H+0.6H), 5.12–5.02 (m, 0.4H) 4.55 (s, 2H), 2.25–2.00 (m, 2H), 1.85–1.55 (m, 13H), ^{13}C NMR (75 MHz, $CDCl_3$) (mixture of diastereomers, some signals overlapped) δ: 155.9, 132.9, 132.1, 127.9, 127.1, 126.0, 125.9, 123.7, 117.5, 75.2, 75.1, 74.0, 73.5, 65.2, 47.1, 46.7, 44.3, 39.6, 29.8, 29.0, 25.8, 25.5, 23.3, 22.5, 17.9. HRMS (ESI^+) calcd for $C_{17}H_{26}O_4Na^+$317.17233, found 317.17645.

*4.2.19. (3′S)-4-Hydroxy-3-(3′-hydroxy-3′,7′-dimethyl-oct-6′-enoyl)-benzaldehyde (**17**).* Alcohol **16** (0.050 g, 0.17 mmol) was dissolved in DMSO (1 mL), and IBX (0.119 g, 0.424 mmol) was added. The resulting mixture was stirred overnight at room temperature; added with water and stirred for 5 min. The precipitate was filtered through a Celite pad and the filtrate was extracted with ethyl acetate (3×5 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude was purified by flash chromatography (ethyl acetate/hexane 35:65) to afford **17** (0.032 g, 65%) as a colorless liquid; [Found: C, 52.83; H, 8.11. $C_{17}H_{22}O_4$ requires C, 52.88; H, 8.17]; R_f 0.67 (ethyl acetate/petroleum ether 1:1); $[\alpha]_D^{20}$ −12.0 (*c* 0.15, $CHCl_3$); IR ν_{max} (liquid film) 3380, 3080, 2950, 1700, 1640, 1270, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 12.74 (s, 1H), 9.90 (s, 1H), 8.31 (d, *J* 2.1 Hz, 1H), 8.08 (dd, *J* 2.1, 8.7 Hz, 1H), 7.11 (d, *J* 8.7 Hz, 1H), 5.12–5.04 (m, 1H), 3.29 (d, *J* 16.6 Hz, 1H), 3.17 (d, *J* 16.6 Hz, 1H), 2.18–1.98 (m, 2H), 1.75–1.55 (m, 2H), 1.64 (s, 3H), 1.60 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 207.4, 189.7, 167.6, 137.3, 133.5, 132.3, 128.3, 124.0, 119.9, 72.4, 47.4, 42.2, 27.3, 25.7, 22.8, 17.8.

*4.2.20. (3′S)-4-Hydroxy-3-(3′-hydroxy-3′,7′-dimethyl-oct-6′-enoyl)-benzoic acid (S-**1**).* To a solution of **17** (0.020 g, 0.07 mmol) in *t*-BuOH (1.0 mL) and 2-methyl-2-butene (0.033 mL, 0.31 mmol) was added a solution of $NaH_2PO_4 \cdot H_2O$ (0.02 g, 0.14 mmol) in water (0.5 mL) and $NaClO_2$ (0.019 g, 0.21 mmol). The reaction was stirred for 3 h at room temperature. The reaction was then quenched by dropwise addition of saturated aqueous NH_4Cl solution. The aqueous layer was extracted with ethyl acetate (3×5 mL), washed with brine, and dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by reverse phase column chromatography (water/methanol 35:65) to afford the title compound as a white solid (0.016 g, 75%). Mp 148 °C; R_f 0.65 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D^{25}$ −10.6 (*c* 0.15, $CHCl_3$); {lit.,[3] $[\alpha]_D^{25}$ −6.70 (*c* 0.15, $CHCl_3$); IR ν_{max} (Nujol) 3450, 3080, 2980, 1690, 1640, 1432, 1270, 750, 710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 12.06 (s, 1H), 8.56 (d, *J* 1.7 Hz, 1H), 8.20 (dd, *J* 1.7, 8.9 Hz, 1H), 7.06 (d, *J* 8.9 Hz, 1H), 5.09 (t, *J* 7.2 Hz, 1H), 3.30 (d, *J* 16.6 Hz, 1H), 3.18 (d, *J* 16.6 Hz, 1H), 2.18–2.11 (m, 2H), 1.68–1.65 (m, 2H), 1.64 (s, 3H), 1.60 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 207.1, 170.0, 166.8, 137.8, 133.6, 132.0, 123.7, 119.9, 119.1, 119.0, 72.2, 46.9, 41.8, 27.0, 25.5, 22.6, 17.5. {lit.,[3] ^1H NMR (500 MHz, $CDCl_3$) δ: 12.3 (s, 1H), 8.56 (d, *J* 2.4 Hz, 1H, H-2), 8.11 (dd, *J* 2.4, 8.9 Hz, 1H, H-6), 6.93 (d, *J* 8.9 Hz, 1H, H-5), 4.98 (t, *J* 7.2 Hz, 1H, H-6′), 2.77 (d, *J* 16.5 Hz, 1H, H-2′a), 2.64 (d, *J* 16.5 Hz, 1H, H-2′b), 2.03 (m, 2H, H-5′), 1.70 (m, 2H, H-4′), 1.58 (br s, 3H, H-8′), 1.50 (br s, 3H, H-9′); 1.37 (s, 3H, H-10′) ^{13}C NMR (125 MHz, $CDCl_3$) δ: 191.5, 170.6, 163.7, 137.3, 132.5, 129.9,

122.9, 122.1, 119.9, 118.8, 82.3, 47.2, 39.3, 25.6, 22.2 17.5}. HRMS (ESI−) calcd for $C_{17}H_{21}O_5^-$ 305.13945, found 305.13967.

*4.2.21. 5-(1′,3′-Dihydroxy-3′,7′-dimethyl-oct-6′-enyl)-2-hydroxybenzoic acid methyl ester (**19**).* Under argon atmosphere, LDA (1.8 M in THF/heptane, 21.4 mL, 0.038 mol) was added to solution of 5-acetyl-2-hydroxybenzoic acid methyl ester (3.000 g, 0.015 mol) in dry THF (100 mL) at −78 °C. The resulting solution was stirred for 30 min at −78 °C, followed by addition of 6-methyl-5-hepten-2-one (2.921 g, 0.023 mol). Stirring was continued for 4 h at −78 °C, then the reaction was quenched with saturated aqueous NH_4Cl. The reaction mixture was allowed to reach room temperature. The layers were separated and the aqueous phase was extracted with diethyl ether (3×80 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexane 12:88) to afford 2-Hydroxy-5-(3′-hydroxy-3′,7′-dimethyl-oct-6′-enoyl)-benzoic acid methyl ester as a sticky solid (4.911 g, 59%); [Found: C, 67.45; H, 7.58. $C_{18}H_{24}O_5$ requires C, 67.48; H, 7.55]; R_f 0.7 (ethyl acetate/hexane 1:1); IR ν_{max} (Nujol) 3420, 3045, 2965, 2220, 1680, 1440, 1380, 1270 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 11.28 (s, 1H), 8.47 (d, *J* 1.7 Hz, 1H), 8.08 (dd, *J* 1.7, 8.9 Hz, 1H), 7.05 (d, *J* 8.9 Hz, 1H), 5.14–5.04 (m, 1H), 4.01 (s, 3H), 3.13 (d, *J* 17.1 Hz, 1H), 3.03 (d, *J* 17.1 Hz, 1H), 2.18–1.99 (m, 2H), 1.71–1.60 (m, 2H), 1.65 (s, 3H), 1.60 (s, 3H), 1.30 (s, 3H). The above compound (0.500 g, 1.560 mmol) was dissolved in MeOH (12 mL) and then cooled to 0 °C $NaBH_4$ (0.171 g, 4.535 mmol) was added portionwise and the reaction was warmed to room temperature. After 2 h MeOH was evaporated under vacuo. The residue was diluted with ethyl acetate, followed by addition of a saturated aqueous NH_4Cl solution. The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexane 15:85) to afford **19** as a sticky solid (0.350 g, 70%); [Found: C, 67.04; H, 8.10. $C_{18}H_{26}O_5$ requires C, 67.06; H, 8.13]; R_f 0.5 (ethyl acetate/hexane 1:1). ^1H NMR (300 MHz, $CDCl_3$) (mixture of diastereomers ratio 60:40) δ: 10.72 (s, 0.4H), 10.69 (s, 0.6H), 7.85 (d, *J* 1.7 Hz, 0.6H), 7.82 (d, *J* 1.7 Hz, 0.4H), 7.45 (dd, *J* 1.7, 8.9 Hz, 1H), 6.96 (d, *J* 8.9 Hz, 1H), 5.21–4.96 (m, 2H), 3.95 (s, 3H), 2.15–1.99 (m, 2H), 2.20–1.20 (m, 15H).

*4.2.22. 2-Hydroxy-5-(3′-hydroxy-3′,7′-dimethyl-oct-6′-enoyl)-benzoic acid (**20**).* Compound **19** (0.350 g, 1.080 mmol) was dissolved in THF/H_2O (3:1), then LiOH·H_2O (0.136 g, 3.241 mmol) was added. The resulting reaction mixture was refluxed for 4 h and then cooled to room temperature. THF was evaporated and the remaining aqueous layer was cooled to 0 °C and acidified to pH 3 by 2 N HCl. The resulting precipitate was taken in ethyl acetate. The organic layer was dried on anhydrous Na_2SO_4 and concentrated to afford 5-(1′,3′-dihydroxy-3′,7′-dimethyl-oct-6′-enyl)-2-hydroxy-benzoic acid as a semisolid product (0.320 g, 95%). R_f 0.25 (ethyl acetate/hexane 1:1). This crude product was used without any further purification.

The above acid (0.050 g, 0.162 mmol) dissolved in DMSO (1 mL) was added dropwise at 0 °C, under argon atmosphere, to a stirred solution of IBX (0.068 g, 0.243 mmol) in DMSO (1 mL). The reaction mixture was warmed to room temperature and stirred for 3 h, then it was filtered through a pad of Celite. The residue was washed with ethyl acetate. The resulting filtrate and washings were combined and dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by reverse phase column chromatography (water/methanol 60:40) to afford *rac*-**20** as a faint brownish solid (0.030 g, 61%). Mp 97 °C; [Found: C, 66.61; H, 7.26. $C_{17}H_{22}O_5$ requires C, 66.65; H, 7.24]; R_f 0.6 (CH_2Cl_2/MeOH 9:1); IR ν_{max} (Nujol) 3380, 3080, 2950, 1700, 1590, 1275, 745, 710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 11.18 (s, 1H), 8.54 (d, *J* 1.7 Hz, 1H), 8.14 (dd, *J* 1.7, 8.9 Hz, 1H), 7.08 (d, *J* 8.9 Hz, 1H), 5.09 (t, *J* 7.5 Hz, 1H), 3.18 (d, *J* 17.1 Hz, 1H), 3.07 (d, *J* 17.1 Hz, 1H), 2.18–1.98 (m, 2H), 1.71–1.58 (m, 2H), 1.65 (s, 3H), 1.61 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 199.6, 172.5, 166.3, 136.0, 132.3, 132.1, 132.0, 129.3, 124.2, 118.5, 72.8, 46.5, 42.0, 27.0, 25.7, 22.9, 17.7. HRMS (ESI−) calcd for $C_{17}H_{21}O_5^-$ 305.13945, found 305.13911.

*4.2.23. E,Z 3-(3′,7′-Dimethyl-octa-2′,6′-dienoyl)-4-hydroxybenzoic acid methyl ester (**21**).* To an ice-cooled solution of **4** (0.425 g, 1.326 mmol) and TEA (0.424 g, 0.580 mL, 4.190 mmol) in dry DCM (5 mL) thionyl chloride (0.289 g, 0.178 mL, 2.430 mmol) was added dropwise during 30 min under a nitrogen atmosphere. The mixture was stirred for 2 h, poured onto crushed ice and extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with cold 1 M HCl, a saturated $NaHCO_3$ solution and brine, then it was dried and concentrated under vacuum. The residue was purified by flash column chromatography (ethyl acetate/hexane 4:96) to afford **21** as a sticky solid (0.318 g, 80%); [Found: C, 71.52; H, 7.28. $C_{18}H_{22}O_4$ requires C, 71.50; H, 7.33]; R_f 0.51; 0.42 (ethyl acetate/hexane 1:9). IR ν_{max} (liquid film) 3080, 2980, 1720, 1635, 1580, 1485, 1440, 1370, 1270, 1220, 750, 710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (mixture of diastereomers 50:50) δ: 13.35 (s, 1H), 8.52 (d, *J* 1.7 Hz, 0.5H), 8.50 (d, *J* 1.7 Hz, 0.5H), 8.09 (dd, *J* 1.7, 8.9 Hz, 1H), 6.99 (d, *J* 8.9 Hz, 1H), 5.20–5.05 (m, 1H), 3.91 (s, 3H), 2.72–2.61 (m, 1H), 2.39–2.20 (m, 3H), 2.21 (s, 1.5H), 2.08 (s, 1.5H), 1.71 (s, 3H), 1.64 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) (mixture of diastereomers, some signals overlapped) δ: 198.2, 195.9, 177.2, 177.1, 167.1, 166.3, 163.6, 143.2, 136.6, 136.2, 133.1, 132.3, 122.8, 120.7, 120.2, 119.6, 119.0, 118.7, 52.2, 42.0, 31.2, 29.8, 26.3, 25.8, 20.4, 17.9.

*4.2.24. 2-Methyl-2-(4′-methyl-pent-3′-enyl)-4-oxo-chroman-6-carboxylic acid (**22**).* Compound **21** (0.058 g, 0.192 mmol) was added with NaOH 2.5 N in H_2O (1.5 mL). The reaction mixture was stirred overnight at room temperature, then it was acidified to pH 3 by addition of an ice-cooled solution of 2 N HCl. The aqueous phase was extracted with ethyl acetate (3×5 mL). The collected organic extracts were dried and evaporated to give a pale yellow solid (0.054 g, quantitative). Mp 128–131 °C; [Found: C, 70.77; H, 7.02. $C_{17}H_{20}O_4$ requires C, 70.81; H, 6.99]; R_f 0.78 (ethyl acetate/hexane 75:25). IR ν_{max} (Nujol) 3350, 3040, 2850, 1695, 1620, 1420, 1280, 1140, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 12.76 (s, 1H), 8.64 (d, *J* 2.1 Hz, 1H), 8.18 (dd, *J* 2.1, 8.7 Hz, 1H), 7.01 (d, *J* 8.7 Hz, 1H), 5.06 (t, *J* 7.2 Hz, 1H), 2.85 (d, *J* 16.3 Hz, 1H), 2.71 (d, J 16.3 Hz, 1H), 2.18–2.00 (m, 2H), 1.85–1.61 (m, 2H), 1.66 (s, 3H), 1.57 (s, 3H), 1.44 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 191.6, 171.1, 163.9, 137.4, 132.7, 130.1, 123.0, 122.0, 120.0, 118.9, 82.5, 47.3, 39.4, 25.7, 24.1, 22.3, 17.7. HRMS (ESI−) calcd for $C_{17}H_{19}O_4^-$ 287.12888, found 287.12859.

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