Efficient Access to $(All-rac)-\alpha$ -Tocopherol Acetate by a Crombie Chromene Synthesis

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In contrast to reports in the literature, the pyridine-catalysed condensation of phenolic compounds and conjugated aldehydes to chromenes was found to be applicable to trimethylhydroquinone 2a with the result of complementary convergent approaches to the title acetate using citral 3a and dihydromyrcene 9 as precursors of the phytyl residue.

(All-rac)- α -tocopherol acetate **1a**OAc, a substitute for vitamin E in the feed industry, is produced by condensing trimethylhydroquinone (TMHQ) 2a with isophytol, which is synthesized from acetone by means of C₃ and C₂ homologation processes.¹ With the aim of designing a convergent access to 1aOAc, we have previously studied the condensation of TMHO 2a and linalool, and shown that refluxing this C_{10} alcohol in 10:1 dodecane/CH2Cl2 with 2a and camphorsulfonic acid mainly afforded the chromanols 1b and 1c, which were subsequently converted to **1a**OAc in few steps.² However, this new approach to 1aOAc suffers from incomplete selectivity of the chromenisation reaction process: unlike isophytol, the linalool molecule incorporates unsaturation at the Δ^6 position, protonation of which results in the formation of chromanol by-products whose large-scale elimination would be problematic. Keeping with a $2a-C_{10}-C_{10}$ strategy, the condensation of the quinol 2a and citral 3a was next examined (Scheme 1).

The reactivity of phenolic compounds with α , β -unsaturated aldehydes has previously been studied in relation to the synthesis of such important compounds as flavonoids, rote-noids, coumarins, and cannabinoids.³ Early investigations were

mainly concerned with the condensation of 5-pentylresorcinol (olivetol) with 3a. With BF₃·Et₂O as catalyst, isomeric tetrahydrocannabinols were produced, a possible reaction pathway being a cationic rearrangement of the initially-formed hydroxygeranylolivetol to corresponding limonene derivatives, which cyclize to the observed cannabinoids.⁴ A different product distribution was observed under base catalysis. As first reported by Crombie,^{5a-5c} and almost simultaneously by others,^{4c,5d,5e} heating (ca. 130-150 °C) olivetol (or a related *m*-diphenol) with **3a** in pyridine afforded a mixture of monoand bis-chromenes, alongside polycyclic compounds formed from these products by isomerization processes involving either a [2 + 2], [2 + 4], or Diels-ene condensation reaction.^{3i,3j} Further investigation of this chromenisation process showed that the use of citral dimethyl acetal 3b permitted shorter reaction times, and thus a reduction in the formation of polycyclic by-products, a result subsequently developed into a preparative procedure.^{3f,6,7} Further refinement of this methodology has dealt with the catalyst conditions, good yields of chromenes being achieved by using calcium hydroxide, or ethylendiamine diacetate, as a catalyst,^{8,9} while in the case of



Scheme 1. Planned strategy.



Scheme 2. Hypothetical mechanism of Crombie chromene synthesis.

monohydric phenols, better results were obtained by refluxing metal phenoxides (Ti^{IV}, Al, and Mg) with α,β -unsaturated aldehyde dimethyl acetals in toluene.⁹ Independently, phenylboronic acid, combined with a carboxylic acid was shown to be an effective catalyst when a conjugated aldehyde was used.¹⁰ Crombie chromene synthesis strongly resembles the condensation of 1,3-dicarbonyl compounds and α,β -unsaturated aldehydes to dihydropyrans.¹¹ Mechanistically, it would proceed by crotonization of the initially-formed aldol-like condensation product to a vinyl o-quinone methide, which isomerizes to the observed chromene (Scheme 2).7d Acid-assisted displacement of the benzylic oxygen atom of the aldol-like intermediate by the phenolic hydroxy might also be considered.^{10c,12} However, as exemplified by the coenzyme Q/ubichromenol interconversion,^{13a-13c} prenylated quinones isomerize to chromenes in basic conditions.¹³ Thus, it is likely that the indicated electrocyclic ring closure operates; indeed, this is a well-documented process,¹⁴ occurring inter alia in the thermal rearrangement of propargyl aryl ethers and o-butadienylphenols to chromenes,¹⁵ and its reversibility is exploited in various photochromic systems.9c-9e

Chromenes being easily hydrogenated to chromanes,¹⁶ the possibility of preparing tocopherol 1a from TMHQ 2a and phytal 3c has previously been studied by Crombie, and although his attempts to condense 2a and 3c in pyridine proved unrewarding^{6f}—"we never succeeded in condensing this (i.e. 2a) or other simple hydroquinones with either phytal (3c) or citral (3a)"-the goal was later achieved using the conditions designed by Casiraghi in the case of weakly acidic phenols.^{9b} Thus, treating 2a with ethylmagnesium bromide (two-fold excess), then refluxing the resulting phenoxide in benzene with phytal dimethyl acetal 3d gave, after acetylation followed by hydrogenation, the tocopherol acetate 1aOAc in moderate yield (26%).¹⁷ As explained in the preceding paper, recourse to expensive reagents to produce this acetate is undesirable. The ready availability of pyridine, coupled with the possibility of in situ acetylation of the chromene product prompted us to re-evaluate the preceding Crombie experiments with this base. The observed reluctance of 2a, compared with

less substituted phenolic compounds, to react with **3b** (or **3d**) could result from a steric effect of its C-5 methyl group, and it is possible that, due to the presence of trace air, a degradation of **2a** occurred. In the event, the prolonged heating of **2a** in pyridine with **3b** under strictly oxygen-free conditions should be beneficial, and proved to be the case.

Results and Discussion

First (Table 1, Entry 1), a mixture of TMHQ 2a, citral dimethyl acetal 3b and pyridine (10 mmol each) was thoroughly degassed (three "freeze-pump-thaw" cycles), then heated at ca. 165-175 °C under a static argon atmosphere. After a few hours, only slow progress was noticed on TLC, but after five days 3b was fully reacted and a new product had formed. Still in absence of air, Ac₂O and pyridine (both in excess) were added and the resulting mixture was stirred overnight to give, after acid hydrolysis and extraction, a brown syrup from which the desired chromene acetate 4aOAc (59%; NMR spectra identical to literature data)^{13h} and the diacetate of TMHQ 2a-i.e., 2aOAc-(22%) were isolated successively by column chromatography. For the sake of comparison, citral 3a was reacted with 2a in the preceding conditions (Entry 2). The reaction proceeded sluggishly and, after 6 days, 4aOAc was obtained in low yield (8%), thus confirming the previously observed greater reactivity of the acetal 3b under these conditions. Next, attempts were made to improve the selectivity of this condensation with regards to the quinol 2a (expressed by the 4aOAc:reacted 2a ratio in Table 1). Varying the reactants-to-pyridine ratio barely affected this selectivity, except when pyridine was used in a two-fold excess (Entries 4-6). When pyridine was omitted, only a trace amount of the chromene 4aOAc was obtained (Entry 7), and this was not improved by adding various rare-earth triflates (in acetonitrile). Collidine and DMAP were also effective (Entries 8 and 9), but without advantage compared with pyridine.

Next, with a view to speeding up this process, and as recommended in a related case,^{3f} an equimolar mixture of **2a**, **3b**, and pyridine was heated in a flask equipped with a Vigreux column, the resulting volatiles being progressively eliminated

	3b (1 ec then Ac then ch 2a	quiv), catalyst, ∆, ₂O/pyridine, romatography	AcO		AcO	OAc
			4aOAc		2a OAc	
Entry	Catalyst (equiv)	Conditions ^{a)}	Time	Reacted 2a/%	4aOAc/% ^{e)}	4aOAc:reacted 2a/%
1	Pyridine (1)	A ^{b)}	5 d	78	59	76
2	Pyridine (1)	A ^{c)}	6 d		8	
3	Pyridine (1)	A ^{d)}	5 d	54	50	93
4	Pyridine (0.1)	A ^{b)}	3 d	52	44	85
5	Pyridine (0.5)	A ^{b)}	3 d	54	49	91
6	Pyridine (2)	A ^{b)}	3 d	46	34	74
7	_	A ^{b)}	3 d	_	4	_
8	Collidine (1)	A ^{b)}	3 d	25	20	80
9	DMAP (1)	A ^{b)}	3 d	45	42	93
10	Pyridine (1)	B ^{b)}	4 h	83	52	63
11	Pyridine (1)	C ^{b)}	1 h	56	42	75

Table 1. Effect of the Conditions on the Selectivity of the 2a/3b Condensation

a) A: 10 mmol scale; 165–175 °C (bath), in a closed vessel. B: 10 mmol scale; 165–175 °C (bath) with progressive elimination of the resulting volatiles. C: 20 mmol scale; slow addition of **3b** diluted with pyridine to a heated (ca. 180–185 °C; bath) **2a**/pyridine mixture with progressive elimination of the resulting volatiles. b) E-**3b**:Z-**3b** = 2:1. c) With citral **3a**. d) With Z-**3b**. e) Isolated.



Scheme 3. Reagents and conditions: a) 2a (1 equiv), pyridine (1 equiv), in conditions B of Table 1, then Ac₂O/pyridine (33%; 70% based on reacted 2a); b) 1 atm H₂, 5% Pd/C, EtOAc, rt (96%).

by distillation (Entry 10). After a few hours the distillation ceased, and TLC analysis indicated complete consumption of the acetal **3b**. Removing all volatiles in a vacuum then afforded a brown slurry, which was reacted with Ac₂O in pyridine as above to give, after a purification by column chromatography, the chromene 4aOAc in 52% yield (63% based on reacted 2a). Altough the acetal **3b** was fully reacted, we failed to identify any decomposition product. Since **3b** was a mixture of E and Z isomers (*E*-**3b**:*Z*-**3b** \approx 2:1), the observed limited selectivity with regards to this reagent-i.e., the yield of 4aOAc in Table 1-could result from a difference in the reactivity of these stereomers. This was verified by reacting pure Z-3b with 2a under the conditions of Entry 1 to obtain 4aOAc in 50% yield (Entry 3), to be compared to the 59% yield achieved by using 3b under the same conditions. Another possibility was a self-condensation reaction of these acetals. In the event, lowering the concentration of 3b would be beneficial. Accordingly, the acetal **3b** diluted with a little pyridine was progressively added to a heated (ca. 180-185 °C) mixture of 2a and pyridine, the resulting volatiles being progressively distilled out as in the preceding experiment (Entry 11). After one hour, TLC analysis indicated that **3b** had fully reacted, but, paradoxically, the chromene 4aOAc was then isolated in lower yield and no more effort was expended in this direction.

Next, phytal dimethyl acetal 3d, prepared from commercial phytone 5 as a 1:1 mixture of the E and Z isomers (see

experimental), was reacted with **2a** under the conditions of Entry 10 to give, after treatment with Ac₂O/pyridine and chromatography, the chromene acetate **4b**OAc (33%; 70% based on reacted **2a**), as evidenced by NMR analysis.¹⁸ It is noteworthy that some phytal **3c** (ca. 25%) was recovered. Hydrogenating this acetate afforded (all-*rac*)- α -tocopherol acetate **1a**OAc in high yield (Scheme 3).

Interestingly, HPLC-MS analysis of this product showed it not to contain the isomeric benzofuran derivative found as a trace impurity in a commercial sample of **1a**OAc. The possibility of using hydroquinone **2b** in these condensations was also examined, since hydrogenating the chromene **4c** derived from **2b** and **3d** would deliver a chroman precursor of **1a**OAc.¹⁹ Intriguingly, the reaction of **2b** with **3d** followed by acetylation afforded in low yield the chromene **4c**OAc, alongside bis-chromene by-products (GC-MS). This was exploited in a short synthesis of the racemic form of the naturally-occurring antibiotic cordiachromene A **4d** from **2b** and **3b** (Scheme 4).²⁰

The Isocitral Approach. Epoxidation of a benzochromene having the same substitution pattern at C-2 as 4aOAc with a manganese(III) catalyst has been shown to occur exclusively at the C-3/C-4 unsaturation.^{8f} Although it was later to prove otherwise (vide infra), we surmised that the allylic oxygenation/Wurtz coupling sequence that we had previously used for homologating 1bOAc to 1aOAc would be inappropriate with



4d (Rac)-Cordiachromene A

Scheme 4. Reagents and conditions: a) 3d (0.6 equiv), pyridine (1 equiv), 125 °C, 6 d, then Ac₂O/pyridine (30%); b) 3b (1 equiv), pyridine (1 equiv), 125 °C, 82 h (40%).



Scheme 5. Reagents and conditions: a) TMSCHLiCH=NtBu, then aqueous HCO₂H according to Ref. 23 (77%). b) MeOH, CH(OMe)₃, 1% PPTS (92%). c) Ca(OCl)₂, CO₂, H₂O/CH₂Cl₂ (76%). d) Zn, AcOH, according to Ref. 24 (87%; 3a:3e = 1:1).
e) Zn, MeOH (59% overall from 3g; 3b:3f = 4:1). f) Conditions B of Table 1, then Ac₂O/pyridine (52%; 88% based on reacted 2a). g) 6a, Me₂AlCl (1.55 equiv), CH₂Cl₂ (58%; 4fOAc:4gOAc = 84:16). h) 1 atm H₂, 5% Pd/C, EtOAc/HCl (overall 36% based on reacted 2a).

4aOAc.² Accordingly, the condensation of **2a** and isocitral **3e** was studied. As shown by Snider²¹ and as previously illustrated in the chroman series,² 2-methyl-1-alkenes ene-condense with aliphatic aldehydes in the presence of an alkylaluminum chloride much more readily than 2-alkenes. Hence, our hope was that the chromene **4e**OAc derived from **2a** and isocitral dimethyl acetal **3f** would react with tetrahydrocitral **6a** under these conditions to give a ene-adduct potentially convertible to **1a**OAc by hydrogenolysis.² To this end, the preparation of isocitral **3e** was examined. One possibility was to condense isomethylheptenone **7** and acetylene under basic conditions,^{22a} then to isomerize (Meyer–Schuster rearrangement) the resulting propargylic alcohol to **3e**.^{22a–22e} However, it proved more

convenient to prepare **3e** by means of a Peterson olefination of the ketone **7** using the *t*-butylimine of trimethylsilylacetaldehyde, as described.²³ Next, the reaction of **3e** with methanol in the presence of trimethyl orthoformate and pyridinium tosylate (PPTS) afforded isocitral dimethyl acetal **3f** in good yield (92%) (Scheme 5).

Using the chlorination/reduction methodology designed by Wolinsky to convert citral **3a** to isocitral **3e** was less satisfactory.²⁴ Reacting **3a** with the Ca(OCl)₂·CO₂ reagent in a two-phase system, as described, did indeed afforded chlorocitral **3g**, but in contrast to the observations reported in this otherwise valuable publication, treating this chloroaldehyde (10 g scale) with zinc in acetic acid furnished **3a** and **3e** as



Scheme 6. Reagents and conditions: a) *m*-CPBA (1 equiv), Ca(OH)₂, CH₂Cl₂ (93%). b) Al(O-*i*-Pr)₃ (4 equiv), toluene (reflux) (95%).
c) Ac₂O (excess), 1:1 CH₂Cl₂/pyridine, rt overnight (80% overall from 4hOAc). d) 8 (2 equiv), CuI (0.05 equiv), THF (84%).
e) 1 atm H₂, 10% Pd/C, EtOAc (91%). f) 1 atm H₂, 5% Pd/C, EtOAc (96%).

a 1:1 mixture (¹H NMR), this ratio being essentially unaffected by varying the dilution, the temperature or the zinc activation conditions. Some improvement was gained, however, by first reacting 3g with methanol in the presence of trimethyl orthoformate and PPTS as above, then treating the resulting chloroacetal 3h with zinc in MeOH to obtain a 4:1 mixture of the acetals 3f and 3b respectively. Reacting TMHQ 2a with **3f** under conditions B of Table 1 afforded, after treatment with Ac₂O and column chromatography, the chromene acetate 4eOAc in fair yield (52%). Next, 4eOAc was reacted with tetrahydocitral 6a in CH₂Cl₂ and added Me₂AlCl (excess). The reaction proceeded very slowly and additional 6a proved necessary to observe a useful conversion. ¹HNMR analysis of the product then isolated indicated it to be an 84:16 mixture of the isomeric chromenes 4fOAc and 4gOAc respectively. Hydrogenating this product in acidic conditions (H₂, Pd/C, EtOAc/HCl) furnished, after purification by column chromatography, (all-rac)- α -tocopherol acetate **1a**OAc with a purity of 94.8% (HPLC-MS). Though our goal was achieved, the use of 1.5 molar equivalents of Me₂AlCl altered to some extent the value of this approach. This led us to experiment with the catalytic Diels-ene condensation conditions previously designed by Aggarwal.²⁵ Accordingly, the acylal **6b**, conveniently prepared by treating tetrahydrocitral 6a with Ac₂O in the presence of a montmorillonite,²⁶ was reacted with 4eOAc in acetonitrile in the presence of scandium triflate (10%). No reaction occurred and the addition of more catalyst after a few days provoked decomposition. Reacting 4eOAc with tetrahydrocitral dimethyl acetal **6c** in the presence of $FeCl_3^{27}$ was no more successful and this approach was abandoned.

The Citral Approach. Our interest then returned to the elaboration of the chromene 4aOAc into 1aOAc. On electronic grounds, and as illustrated with a parent naphthodihydropyran (vide supra), the $\Delta^{3,4}$ unsaturation of 4aOAc should be the most reactive with epoxidation reagents. Surprisingly however, it has been observed that the chromene 4bOAc, prepared by dehydrogenating tocopherol acetate 1aOAc with DDQ, epoxidised only very slowly using Jacobsen's catalyst.¹⁸ This low

reactivity could be steric in origin, another possibility being a stereoelectronic effect: a hybridation change (from sp² to sp³) at C-3/C-4 might bring about an interaction of the C-5 methyl group of **4b**OAc with the hydrogen atom at C-4.²⁸ Whatever the validity of these hypotheses, the preceding observation was encouraging. Accordingly, **4a**OAc was reacted with *m*-CPBA under standard conditions (CH₂Cl₂, 0 °C) to give in good yield (93%) a single product (TLC) to which the structure **4h**OAc was assigned by NMR analysis (Scheme 6).

This was confirmed by hydrogenating this product (H₂, 5% Pd/C) to a chroman (91%) identified as 1dOAc (NMR, GC).² Refluxing the epoxide 4hOAc in toluene with aluminum isopropoxide afforded the chromenol 4i, which was converted to the diacetate 4jOAc by treatment with Ac₂O in pyridine (overall 80%). Cu¹-catalysed Wurtz coupling of this diacetate with citronellylmagnesium chloride 8 (two-fold excess) then furnished the chromene acetate 4kOAc, which was hydrogenated to 1aOAc in high yield (96%; 45% overall from 2a). Encouraged by this result, the allylic chlorination of 4aOAc was attempted. NMR features of the product (85%) obtained by treating 4aOAc with the CaCl₂·CO₂ reagent in a two-phase system as above were consistent with the structure 4lOAc (Scheme 7).

This sensitive product was immediately reacted with citronellylmagnesium chloride 8 in THF and added CuI to give 4kOAc (58%), which was subsequently hydrogenated to 1aOAc (40% overall from 2a). In a converse manner, the chloroacetal 3h was similarly reacted with 8. After only a few minutes the reaction was completed, as evidenced by TLC. NMR analysis of the product isolated after acid hydrolysis showed it to be the aldehyde 3i (84%); no isomeric coupling product was detected. Acetalizing this aldehyde with methanol under the above conditions afforded quantitatively the dehydrophytal acetal 3j. Reacting this acetal with 2a in pyridine under the conditions C of the Table 1 afforded in fair yield (49%; 82% based on reacted 2a) the chromene acetate 4kOAc, which was subsequently hydrogenated to 1aOAc (96%).



Scheme 7. Reagents and conditions: a) Ca(OCl)₂, CO₂, H₂O/CH₂Cl₂ (85%). b) 8 (1 equiv), CuI (0.05 equiv), THF (58%). c) 8 (1 equiv), CuI (0.05 equiv), THF, then 1 M HCl, then MeOH, CH(OMe)₃, PPTS (88%). d) 2a (0.5 equiv) in conditions C (see Table 1), then Ac₂O/pyridine (49%; 82% based on reacted 2a). e) 1 atm H₂, 5% Pd/C, EtOAc (94–96%).

Conclusion

In contrast to reports in the literature, the pyridine-catalysed condensation of phenolic compounds and α,β -unsaturated aldehyde dimethyl acetals to chromenes-i.e., Crombie chromene synthesis-was shown to be applicable to trimethylhydroquinone 2a, thereby providing short complementary routes to (all-rac)-tocopherol 1aOAc either from citral 3a, isocitral 3e, or phytal 3c. Of the various ways we have explored, that starting from citral 3a, and leading by way of the chlorochromene 11OAc to the tocopherol acetate 1aOAc appears to be the more efficient, allowing access to this important compound in an acceptable 40% overall yield. However, given the ease with which the chloroacetal 3h was prepared from 3a, the complementary C₁₀-C₁₀-2a approach via the dehydrophytal acetal 3j offers some advantages; besides being highly convergent, the selectivity of the chromenisation step, both with regards to the quinol 2a and the acetal 3j, is fairly good. Alhough citronellylmagnesium chloride 8 is available by hydrometalation of dihydromyrcene 9 (a commodity of the timber industry), eliminating the associated metal wastes could be a limitation. However, this is offset by the simplicity of the conditions, no co-solvent being necessary for the chromenisation reaction process to proceed and all of the reagents used being readily available, features which make these new routes to **1a**OAc attractive in comparison to the existing procedures.

Experimental

General. All general conditions were as described in the preceding paper; except when otherwise stated ¹H and ¹³C NMR at 300 and 75 MHz, respectively. Citral 3a (purissim Fluka; E-3a:Z-3a = 67:33), isomethylheptenone 7 (BASF), phytone 5 (Aventis Animal Nutrition), 65% calcium hypochlorite (Aldrich), KSF montmorillonite (Fluka) and trimethyl orthoformate (Aldrich) were used as received. Hydroquinone 2b (Fluka) was re-crystallized from EtOAc and dried overnight in a desiccator prior to use. Citral dimethyl acetal 3b (Fluka) was purified by distillation from CaH₂ (bp 50 °C at 0.2 Torr). Isocitral **3e** (*E*-**3e**:*Z*-**3e** \approx 1:1; by ¹HNMR) was prepared from the ketone 7 by means of a Peterson olefination using the t-butylimine of trimethylsilylacetaldehyde, as described.²³ Phytonitrile 10 (bp 158 °C at 0.01 Torr) was prepared as a mixture of the E and Z isomers (*E*-10:*Z*-10 \approx 3:2; by ¹HNMR) from phytone 5 according to a reported procedure.²⁹ Tetrahydrocitral 6a and citronellylmagnesium chloride 8 (in THF) were prepared as described in the preceding paper.

(E.Z)-Phytal (3c). 1 M (in hexane) DIBA-H (23.4 mL, 23 mmol) was added dropwise to a cooled (dry ice/acetone bath) solution of phytonitrile 10 (5.15 g, 17.7 mmol) in CH₂Cl₂ (55 mL) with stirring. The resulting mixture was stirred at rt overnight, then diluted with pH 2 tartaric buffer (210 mL). After 2h stirring, the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL) and the pooled organic phases were washed with pH 2 tartaric buffer (100 mL), saturated NaHCO₃ (100 mL), brine $(2 \times 50 \text{ mL})$, and dried (MgSO₄). The residue left by evaporation of the solvents was purified by column chromatography (hexane/CH₂Cl₂) to give phytal 3c (*E*-3c:*Z*-3c \approx 1.2:1; by ¹H NMR) as a pale-yellow oil (4.55 g, 86%). ¹H NMR (200 MHz, CDCl₃): δ 0.81–0.89 (m, 12H, 4 CH₃), 0.95–1.65 (m, 19H), 1.97 (d, J = 1 Hz, ca. 1.5H, CH₃C= CHCHO_{syn}), 2.15 (d, J = 1 Hz, ca. 1.5H, CH₃C=CHCHO_{anti}), 2.18 (t, J = 7 Hz, ca. 1.5H, $CH_2C(CH_3)=C_{anti}$), 2.55 (t, J = 7 Hz, ca. 1.5H, $CH_2C(CH_3)=C_{svn}$, 5.88 (dd, J = 8, 1 Hz, 1H, C=CH), 9.97 (d, J = 8 Hz, 1H, CHO).

(E,Z)-6-Chloro-3,7-dimethylocta-2,7-dienal (3g). Since being only briefly reported in the literature²⁴ the chlorination of citral 3a is described thereafter. In a 500-mL flask, a mixture of Ca(OCl)₂ (3.75 g, 1 equiv) and water (16.4 mL) was added to a solution of citral 3a (5.02 g, 32.98 mmol) in CH₂Cl₂ (164 mL). After 10 min stirring, the resulting mixture was warmed to ca. 35-40 °C (hot-water bath). With a vigorous stirring, finely ground dry ice was progressively added until disappearance of 3a on TLC (25-30 min). After cooling to rt, pH 7 phosphate buffer (20 mL) was added. The aqueous layer was extracted with CH₂Cl₂ $(3 \times 30 \text{ mL})$ and the pooled organic phases were washed with pH 7 phosphate buffer (40 mL), brine (40 mL), and dried (Na₂SO₄). The oily residue left by evaporation of the solvents was purified by distillation to give the chloroaldehyde 3g (4.71 g, 76%) as a pale-yellow oil (bp 86 °C at 0.5 Torr). For sake of analysis, a portion of this product was chromatographed on a thick layer of silica gel (hexane/ether) to separate the E from the Z isomer $(E-3g:Z-3g \approx 3:1; \text{ by } {}^{1}\text{H NMR})$. E-3g: TLC (hexane:ether = 3:1) $R_f = 0.44$; ¹H NMR (CDCl₃, 200 MHz): δ 1.8 (s, 3H, CH₃), 1.96– 2.1 (m, 2H, CH₂), 2.17 (s, 3H, CH₃), 2.2–2.45 (m, 2H, CH₂), 4.34 (t, J = 7 Hz, 1H, CHCl), 4.91 (m, 1H, H(H)C=), 5.02 (m, 1H, H(H)C=)H(H)C=), 5.89 (d, J = 7 Hz, 1H, CH), 10.01 (d, J = 7 Hz, 1H, CH). Z-3g: TLC (hexane:ether = 3:1) $R_f = 0.3$; ¹H NMR (CDCl₃, 200 MHz): δ 1.8 (s, 3H, CH₃), 1.99 (s, 3H, CH₃), 2.01–2.12 (m, 2H, CH₂), 2.63 (m, 2H, CH₂), 4.34 (t, *J* = 7 Hz, 1H, CHCl), 4.91 (m, 1H, H(H)C=), 5.02 (m, 1H, H(H)C=), 5.92 (d, J = 7 Hz, 1H, CH), 9.96 (d, J = 7 Hz, 1H, CH).

(2*E*/*Z*,6*E*/*Z*)-3,7,11,15-Tetramethylhexadeca-2,6,14-trienal (3i). In a flask connected to an argon/vacuum line, CuI (203 mg,

1.06 mmol, 0.049 equiv) was heated (hot-air gun) in a vacuum (ca. 0.01 Torr). After cooling to rt, the flask was filled with argon and a solution of the chloroacetal 3h (4.95 g, 21.48 mmol) in THF (15 mL) was added with a syringe. The resulting mixture was cooled to $-5 \,^{\circ}\text{C}$ (ice/methanol bath) and 1.05 M (in THF) citronellylmagnesium chloride 8 (20.5 mL, 21.5 mmol) was added dropwise with a syringe (10 min). After 5 min stirring, 1 M HCl (20 mL) was slowly added and the resulting aqueous layer was extracted with ether (3 \times 10 mL). The pooled organic phases were washed with saturated NH₄Cl (15 mL), brine (2×15 mL), and dried (MgSO₄). The oily residue left by evaporation of the solvents was purified by column chromatography (hexane/ether) to give the dehydrophytal 3i (5.24 g, 84%) as a thick colorless oil. TLC (hexane:ether = 2:1) $R_f = 0.44$; IR (neat, cm⁻¹): 2927, 2856, 2762, 1678, 1632, 1450, 1377; ¹H NMR (CDCl₃): δ 0.88 (d, J = 6.3 Hz, 3H, CH₃), 1.03-1.19 (m, 2H, CH₂), 1.24-1.49 (m, 5H, CH, 2 CH₂), 1.62/1.69 (2 m, 9H, 3 CH₃), 1.9-2.04 (m, 6H, 3 CH₂), 2.16-2.3 (m, 5H, CH, 2 CH₂), 5.11 (m, 2H, 2 CH), 5.9 (m, 1H, CH), 9.99 (4 d, J = 7.9 Hz, 1H, CH); ¹³C NMR (CDCl₃): δ 15.9 (CH₃), 17.6 (CH₃), 19.5 (CH₃), 23.3 (CH₃), 25.1 (CH₃), 25.3 (CH₂), 25.5 (CH₂), 32 (CH₂), 32.3 (CH), 36.9 (CH₂), 37.1 (CH₂), 39.9 (CH₂), 40.6 (CH₂), 121.8/122.9 (CH), 124.9/125 (CH), 127.4/128.6 (CH), 130.9/131 (C), 136.9/137.8 (C), 163.7/163.8 (C), 190.7/ 191.2 (CH); MS (CI-NH₃) m/z 308 (M + NH₄⁺), 291 (M + H⁺), 273, 247, 217, 197, 179, 163, 149, 137, 121, 109, 95, 81.

3,7-Dimethyl-1-octylidene Diacetate (6b). Tetrahydrocitral 6a (0.41 g, 2.6 mmol) was diluted with Ac₂O (0.8 mL, 8.2 mmol) and KSF montmorillonite (54 mg) was added. The resulting mixture was heated (ca. 125 °C, bath) for 1.5 h with stirring. After cooling to rt, ether (40 mL) was added and the resulting mixture was poured into brine (8 mL) diluted with water (16 mL). The aqueous layer was extracted with ether (10 mL) and the pooled organic phases were washed with saturated NaHCO₃ (20 mL), brine (10 mL), and dried (Na₂SO₄). The solvents were evaporated in vacuo to give a colored residue, which was chromatographed on silica gel (hexane/ether). Bulb-to-bulb distillation of the residue left by evaporation of the solvents afforded the acylal 6b as a palevellow oil (0.55 g, 81%). Bp 80-90 °C (bath) at 0.07 Torr; TLC (hexane:ether = 9:1) $R_f = 0.22$; ¹H NMR (200 MHz, CDCl₃): δ $0.86 (d, J = 7 Hz, 6H, 2 CH_3), 0.93 (d, J = 6 Hz, 3H, CH_3), 1.00-$ 1.88 (m, 10H), 2.06 (s, 3H, C(O)CH₃), 2.07 (s, 3H, C(O)CH₃), 6.84 (dd, J = 6, 4 Hz, 1H, CH(OAc)₂); ¹³C NMR (50 MHz, CDCl₃): δ 19.8, 20.9, 22.6, 22.7, 24.5, 28.0, 28.5, 37.2, 39.1, 40.3, 89.8 (CH(OAc)₂), 168.9 (C=O).

General Protocol for Preparing Dimethyl Acetals. In a flask connected to an argon line, the aldehyde was diluted with trimethyl orthoformate (0.67 mL mmol⁻¹) and anhydrous MeOH (0.4 mL mmol⁻¹). Pyridinium tosylate (2.6 mg mmol⁻¹; 0.01 equiv) was added and the resulting mixture was stirred 24 h at rt before being diluted with aqueous 1 M NaOH (1.6 mL mmol⁻¹) and ether (3.2 mL mmol^{-1}). After 15 min stirring, the aqueous layer was extracted with ether ($4 \times 3.2 \text{ mL mmol}^{-1}$) and the pooled organic phases were washed with 1 M NaOH (1.6 mL mmol⁻¹), brine ($2 \times 6 \text{ mL mmol}^{-1}$), and dried (K₂CO₃). The residue left by evaporation of the solvents was distilled from CaH₂ in a vacuum.

Phytal Dimethyl Acetal (3d): From phytal **3c** (1.5 g, 0.5 mmol), the acetal **3d** was obtained as a colorless oil (1.25 g, 72%) by bulb-to-bulb distillation. Bp 160 °C at 0.008 Torr; TLC (hexane:CH₂Cl₂:EtOAc = 9:9:2) $R_f = 0.75$; ¹³C NMR (100 MHz, CDCl₃): δ 17.35, 19.99, 20.07, 20.10, 20.14, 23.02, 23.12, 23.64, 24.86, 25.06, 25.19, 25.21, 25.42, 25.8, 28.38, 33.08, 33.1, 33.19, 33.25, 37.04, 37.14, 37.32, 37.4, 37.69, 37.71, 37.76, 37.79, 37.83,

39.77, 40.12, 52.62, 52.70, 52.72, 100.54, 100.87, 121.73, 122.55, 142.99, 143.23; HRMS: found m/z 340.3347, calcd for C₂₂H₄₄O₂ 340.3341.

(*E*,*Z*)-3,7-Dimethylocta-2,7-dienal Dimethyl Acetal (3f): From isocitral 3e (5 g, 32.8 mmol), the acetal 3f (*E*-3f:*Z*-3f = 1:1, by GC) was obtained as a colorless oil (5.99 g, 92%). Bp 73–75 °C at 1.4 Torr; TLC (hexane:ether = 3:1) R_f = 0.29; ¹H NMR (CDCl₃): δ 1.49–1.7 (m, 2H, CH₂), 1.72 (s, 3H, CH₃), 1.76 (s, 3H, CH₃), 1.96–2.18 (m, 4H, 2 CH₂), 3.31 (s, 6H, 2 OCH₃), 4.66–4.75 (m, 2H, C=CH₂), 5.01/5.04 (d, *J* = 6.5 Hz, 1H, CH(OMe)₂), 5.23–5.31 (m, 1H, C=CH); ¹³C NMR (CDCl₃): δ 16.9 (CH₃), 23.2/23.3 (CH₃), 25.5/25.8 (CH₂), 37.3/37.5 (CH₂), 38.9 (CH₂), 52.2/52.3 (OCH₃), 100/100.4 (CH(OCH₃)₂), 110 (CH₂=C), 121.7/122.5 (C=CH), 142.1/142.4 (C=CH), 145.56 (CH₂=C); Anal. Found: C, 72.55; H, 11.17%. Calcd for C₁₂H₂₂O₂: C, 72.68; H, 11.18%.

(*E*,*Z*)-6-Chloro-3,7-dimethylocta-2,7-dienal Dimethyl Acetal (3h): From the chloroaldehyde 3g (15 g, 80.4 mmol), the acetal 3h was obtained as a colorless oil (14.65 g, 78.2%). Bp 67 °C at 0.25 Torr; TLC (hexane:CH₂Cl₂:EtOAc = 9:9:2) R_f = 0.8; IR (neat, cm⁻¹): 3080, 2949, 2827, 1672, 1647, 1448, 1377, 1131, 1053, 963, 907; ¹H NMR (CDCl₃): δ 1.73 (s, 3H, CH₃), 1.8 (s, 3H, CH₃), 1.86–2.05 (m, 2H, CH₂), 2.0–2.26 (m, 2H, CH₂), 3.31 (s, 6H, 2 OCH₃), 4.35 (t, *J* = 7.5 Hz, 1H, CHCl), 4.9 (m, 1H, CH-CH(OCH₃)₂); ¹³C NMR (CDCl₃): δ 17.1/17.6 (CH₃), 23.1 (CH₃C=CH₂), 34.3/34.7 (CH₂), 36.4/37.5 (CH₂), 52.1/52.3 (2 OCH₃), 66.1/66.2 (CHCl), 99.9/100.2 (CHO), 114.3 (CH₂=C), 122.6/123.8 (C=CH), 140.5 (*C*=CH₂), 144.1/144.2 (*C*=CH); Anal. Found: C, 62.01; H, 9.12; Cl, 15.01%. Calcd for C₁₂H₂₁CIO₂: C, 61.92; H, 9.09; Cl, 15.23%.

(2*E*/*Z*,6*E*/*Z*)-3,7,11,15-Tetramethylhexadeca-2,6,14-trienal Dimethyl Acetal (3j): From the aldehyde 3i (1.44 g, 4.96 mmol), the acetal 3j was obtained as a colorless oil (1.51 g, 100%). TLC (hexane:CH₂Cl₂:EtOAc = 9:9:2) R_f = 0.69; ¹H NMR (CDCl₃): δ 0.84 (d, *J* = 6 Hz, 3H, CH₃), 1.09–1.34 (2 m, 7H, CH, 3 CH₂), 1.58 (s, 3H, CH₃), 1.66 (s, 3H, CH₃), 1.70 (s, 3H, CH₃), 1.75 (s, 3H, CH₃), 1.90–2.15 (2 m, 8H, CH₂), 3.31 (s, 6H, 2 OCH₃), 4.09–4.95 (m, 3H, 3 CH), 5.23 (m, 1H, CHOCH₃); ¹³C NMR (CDCl₃): δ 16.9 (CH₃), 17.6/19.6 (CH₃), 23.4 (CH₃), 25.3–26.2 (3 CH₂), 25.7 (CH₃), 32 (CH), 36.6–36.9 (2 CH₂), 39.4 (CH₂), 39.9 (CH₂), 51.2/52.2 (2 OCH₃), 100.1/100.2 (CH), 114.3 (CH), 121.6–125 (2 CH), 130.9 ((CH₃)₂C), 135.8/136.1 (CH₂C(CH₃)), 142/142.1 (CH₂C(CH₃)); HRMS found *m*/*z* 336.3041, calcd for C₂₂H₄₀O₂ 336.3028.

General Protocols of Chromenisation Reaction Experiments (Table 1). Protocol A: A flask equipped with a condenser connected to an argon/vacuum line was charged with the quinol, the acetal and the base (10 mmol each). The resulting mixture was thoroughly degassed (three freeze-pump-thaw cycles) and a static atmosphere of argon was established. The flask was immersed in a thermostated oil bath (ca. 165-175 °C) for the indicated time. **Protocol B**: Similarly to protocol A in a flask equipped with a 10cm Vigreux column, a distillation head, and a receiver connected to an argon/vacuum line, the heating being pursued until the distillation of the resulting volatiles ceased (bp 35-65 °C). Protocol C: A flask equipped with a Vigreux column, a distillation head, and a receiver, as in protocol B, and an addition funnel with a pressure-equalizing system was charged with the quinol and pyridine (0.5 equiv). The resulting mixture was thoroughly degassed and the flask was filled with argon. A degassed solution of the acetal (1 equiv) in pyridine (0.5 equiv) was introduced into

the funnel with a syringe and the flask was immersed in a thermostated oil bath (ca. 180-185 °C). The acetal was added dropwise (1 h) while the resulting volatiles were progressively distilled out (bp 40–65 °C). Whatever the protocol used, after cooling to ca. 0 °C (ice bath) pyridine (10 equiv) and Ac₂O (7.5 equiv) were added sequentially with a syringe and the resulting mixture was stirred at rt overnight before being diluted with ether (10 mL mmol⁻¹) and 1 M HCl (10 mL mmol⁻¹). After 1 h stirring, the aqueous layer was extracted with ether (4 × 3 mL mmol⁻¹) and the pooled organic extracts were washed with 1 M HCl (5 mL mmol⁻¹), brine (3 × 5 mL mmol⁻¹), and dried (MgSO₄). The residue left by evaporation of the solvents was dried overnight in a vacuum (ca. 0.01 Torr), then chromatographed on silica gel (hexane/CH₂Cl₂) to give, successively, the chromene acetate, and the diacetate of the unreacted quinol.

2,5,7,8-Tetramethyl-2-(4-methylpent-3-enyl)-2H-chromen-6yl Acetate (4aOAc): Protocol B: In pyridine (0.81 mL, 10 mmol). From TMHO 2a (1.52 g, 10 mmol) and citral acetal 3b (1.98 g, 10 mmol). Isolated: the diacetate 2aOAc (0.397 g, 17%), and the chromene acetate 4aOAc (1.7 g, 52%; 62% based on reacted 2a). Protocol C: In pyridine (1.7 mL, 21 mmol). From TMHQ 2a (3.12 g, 20.5 mmol) and citral dimethyl acetal 3b (4.07 g, 20.48 mmol). Isolated: 2.144 g (44%) of 2aOAc, and 2.795 g (41.5%; 74% based on reacted 2a) of 4aOAc. TLC (CH₂Cl₂) $R_f = 0.62$; IR (neat, cm⁻¹): 3046, 2968, 2925, 2860, 1759, 1672, 1644, 1605, 1458, 1368, 1204, 1115, 1089, 1062; ¹H NMR (CDCl₃): δ 1.37 (s, 3H, CH₃), 1.57 (s, 3H, CH₃), 1.66 (s, 3H, CH₃), 1.6-1.73 (m, 2H, CH₂), 2.02 (s, 3H, CH₃), 2.04-2.16 (m, in which s at 2.04 and 2.1, 8H, CH₂, 2 CH₃), 2.32 (s, 3H, C(O)CH₃), 5.1 (t, J = 7 Hz, 1H, CH), 5.57 (d, J = 10.2 Hz, 1H, CH), 6.5 (d, J = 10.2 Hz, 1H, CH); ¹³C NMR (CDCl₃): δ 11.5 (CH₃), 11.8 (CH₃), 13.2 (CH₃), 17.7 (CH₃), 19.6 (CH₃), 22.8 (CH₂), 25.8 (CH₃), 26 (CH₃), 40.8 (CH₂), 78.4 (CO), 116.9 (C_{arom}), 122.6 (Carom), 122.8 (CH), 124.2 (CH), 124.3 (Carom), 129.2 (Carom), 131 (CH), 131.8 (C(CH₃)₂), 146.8 (C_{arom}), 149.3 (C_{arom}), 169.4 $(C(O)CH_3)$; MS (CI-NH₃) m/z 346 (M + NH₄⁺), 329 (M + H⁺), 313, 286, 273, 245, 203, 159, 105, 91. 2aOAc: ¹HNMR (200 MHz, CDCl₃): δ 2.05 (s, 3H), 2.07 (s, 3H), 2.11 (s, 3H), 2.31 (s, 3H), 2.34 (s, 3H), 6.75 (s, 1H).

2,5,7,8-Tetramethyl-2-(4-methylpent-4-enyl)-2H-chromen-6-yl Acetate (4eOAc): Protocol B (165 °C, 1 day): In pyridine (0.37 mL, 4.6 mmol). From TMHQ **2a** (0.7 g, 4.6 mmol) and isocitral dimethyl acetal **3f** (0.9 g, 4.54 mmol). Isolated: the diacetate **2a**OAc (0.46 g, 42.3%), and the chromene acetate **4e**OAc as a clear oil (0.77 g, 52%; 88% based on reacted **2a**). ¹H NMR (200 MHz, CDCl₃): δ 1.35 (s, 3H, CH₃), 1.55 (m, 4H, 2 CH₂), 1.7 (s, 3H, CH₃), 2.02 (s, 3H, CH₃), 2.04 (s, 3H, CH₃), 2.09 (s, 3H, CH₃), 1.97–2.03 (m, 2H, CH₂), 2.34 (s, 3H, CH₃), 4.68 (m, 1H, *H*HC=C), 4.71 (m, 1H, H*H*C=C), 5.59 (d, *J* = 10 Hz, 1H), 6.5 (d, *J* = 10 Hz, 1H). HRMS found *m/z* 328.2043, calcd for C₂₁H₂₈O₃ 328.2038.

2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-chromen-6-yl Acetate (4bOAc): Protocol B (165–175 °C, 6 h): In pyridine (0.1 mL, 1.24 mmol). From TMHQ **2a** (0.189 g, 1.24 mmol) and phytal dimethyl acetal **3d** (0.422 g, 1.24 mmol). Isolated: the diacetate **2a**OAc (0.155 g, 53%), impured (TLC) phytal **3c** (0.091 g, 25%), and the chromene acetate **4b**OAc (0.192 g, 33%; 70% based on reacted **2a**). ¹H NMR (200 MHz, CDCl₃): δ 0.82–0.88 (m, 12H), 1.0–1.7 (m, in which s at 1.33, 24H), 2.02 (s, 3H, CH₃C_{arom}), 2.05 (s, 3H, CH₃C_{arom}), 2.09 (s, 3H, CH₃C_{arom}), 2.32 (s, 3H, CH₃C(O)), 5.59 (d, *J* = 10 Hz, 1H, CH), 6.48 (d, *J* = 10 Hz, 1H, CH).

2-Methyl-2-(4,8,12-trimethyltridecyl)-2*H***-chromen-6-yl Acetate (4cOAc): Protocol B (125 °C, 6 days): In pyridine (0.21 mL, 2.6 mmol). From hydroquinone 2b** (0.279 g, 2.53 mmol, 1.5 equiv) and phytal dimethyl acetal **3d** (0.562 g, 1.65 mmol). Isolated: hydroquinone diacetate **2b**OAc (0.242 g, 49%), and the chromene acetate **4c**OAc as a pale-yellow oil (0.214 g, 30%). TLC (CH₂Cl₂) $R_f = 0.51$; ¹H NMR (200 MHz, CDCl₃): δ 0.81–0.88 (m, 12H), 0.95–1.7 (m, in which s at 1.36, 24H), 2.26 (s, 3H, OC(O)CH₃), 5.58 (d, J = 10 Hz, 1H, HC=C), 6.28 (d, J = 10 Hz, 1H, HC=C), 6.68–6.81 (m, 3H); ¹³C NMR (50 MHz, CDCl₃): δ 19.69, 19.74, 19.8, 19.86, 21.16, 21.57, 22.75, 22.75, 22.84, 24.57, 24.92, 26.53, 28.07, 32.79, 32.86, 37.38, 37.43, 37.47, 37.52, 39.47, 41.66, 79.01, 116.66, 119.07, 121.62, 121.75, 122.33, 130.89, 144.02, 150.83, 169.92; HRMS found *m/z* 428.3292, calcd for C₂₈H₄₄O₃ 428.3290.

2-Methyl-2-(4-methylpent-3-enyl)-2*H***-chromen-6-ol: (***rac***)-Cordiachromene A (4d):** Protocol B (125 °C, 82 h): In pyridine (0.2 mL, 2.48 mmol). From citral dimethyl acetal **3b** (0.505 g, 2.54 mmol) and hydroquinone **2b** (0.278 g, 2.52 mmol). Purification by column chromatography (hexane/ether) of the crude condensation product afforded, after evaporation of the solvents, cordiachromene **4d** as a pale-yellow oil (0.244 g, 40%). ¹H NMR (200 MHz, CDCl₃): δ 1.37 (s, 3H, CH₃), 1.57 (s, 3H, CH₃), 1.6–1.73 (m, in which s at 1.66, 5H, CH₂, CH₃), 2.04–2.16 (m, 2H, CH₂), 4.51 (s, 1H, OH), 5.09 (t, *J* = 7 Hz, *H*C=C(CH₃)₂), 5.6 (t, *J* = 10 Hz, 1H, CH), 6.27 (d, *J* = 10 Hz, CH), 6.48 (d, *J* = 3 Hz, 1H, HC_{arom}), 6.57 (dd, *J* = 8, 3 Hz, 1H, HC_{arom}), 6.65 (d, *J* = 8 Hz, 1H, HC_{arom}); ¹³C NMR (50 MHz, CDCl₃): δ 17.75, 22.84, 25.81, 26.04, 40.89, 78.42, 113.19, 115.7, 116.87, 122.18, 122.8, 124.21, 131.02, 131.85, 146.86, 149.33.

2.5.7.8-Tetramethyl-2-(4.8,12-trimethyltrideca-3,11-dienyl)-2H-chromen-6-yl Acetate (4kOAc): Protocol C (180 °C, 2 h): In pyridine (0.31 mL, 3.82 mmol). From TMHQ 2a (604 mg, 3.97 mmol) and the dehydrophytal dimethyl acetal 3j (1.34g, 3.98 mmol). Isolated: 2aOAc (371 mg, 39.5%), and the chromene acetate 4kOAc as a yellow viscous oil (914 mg, 49%, 82% based on reacted **2a**). TLC (hexane:CH₂Cl₂ = 1:1) $R_f = 0.35$; IR (neat, cm⁻¹): 3045, 2966, 2927, 1760, 1672, 1455, 1368, 1206, 1113, 1080, 1063; ¹H NMR (CDCl₃): δ 0.9 (d, J = 7 Hz, 3H, CH₃), 1.08– 1.47 (m, in which s at 1.39, 12H, CH, 4 CH₂, CH₃), 1.64 (s, 3H, CH₃), 1.69 (s, 3H, CH₃), 1.70-2.22 (m, in which s at 1.72, 2.06, 2.08, 2.15, and 2.12, 21H, 3 CH₂, 5 CH₃), 5.15 (m, 2H, 2 CH), 5.62/5.64 (d, J = 10.2 Hz, 1H, CH), 6.54 (d, J = 10.2 Hz, 1H, CH); ¹³C NMR (CDCl₃): δ 11.5 (CH₃), 11.6 (CH₃), 13.2 (CH₃), 15.8 (CH₃), 17.6 (CH₃), 19.6 (CH₃), 20.5 (CH₃), 22.5/22.6 (CH₂), 23.4 (CH₃), 25.3/25.4 (CH₂), 25.7 (CH₂), 25.7/25.8 (CH₃), 32.3/ 32.4 (CH), 36.6/36.8 (CH₂), 37.1 (CH₂), 40 (CH₂), 40.9/41.2 (CH₂), 77.2/77.3 (C), 117.6 (C_{arom}), 120 (CH), 122.4 (C_{arom}), 122.6 (Carom), 124.6 (C), 125 (C), 129 (Carom), 129.3 (CH), 130.9 (C), 135.6/135.8 (C), 141.3 (Carom), 148.5 (Carom), 169.4 (C); MS (CI-NH₃) m/z 484 (M + NH₄⁺), 467 (M + H⁺), 385, 329, 272, 245, 230, 203, 174, 147, 95, 81, 69; HRMS found m/z 466.3458, calcd for C₃₁H₄₆O₃ 466.3447.

Ene-Condensation of the Chromene Acetate 4eOAc and Tetrahydrocitral 6a: 2-(6-Hydroxy-8,12-dimethyl-4-methylenetridecyl)-2,5,7,8-tetramethyl-2*H*-chromen-6-yl Acetate (4fOAc) and (*E*)-2-(6-Hydroxy-4,8,12-trimethyltridec-3-enyl)-2,5,7,8tetramethyl-2*H*-chromen-6-yl Acetate (4gOAc). 1 M (in hexane) Me₂AlCl (1.7 mL, 1.7 mmol) was added dropwise to a cooled (ice bath) solution of 4eOAc (0.361 g, 1.1 mmol) and tetrahydrocitral 6a (0.26 g, 1.81 mmol) in CH₂Cl₂ (5.5 mL). The resulting mixture was stirred overnight at rt. An excess of tetrahydrocitral **6a** (0.5 mL, 0.5 mmol) was added with a syringe and the resulting mixture was further stirred (16 h), then diluted with ether (10 mL), pH 7 phosphate buffer (4 mL) and 3 M HCI (3 mL). After 30 min stirring the aqueous layer was extracted with ether (2 × 5 mL) and the pooled organic extracts were washed with saturated NaHCO₃ (10 mL), brine (2 × 5 mL), and dried (MgSO₄). The solvents were evaporated and the residue (0.58 g) was chromatographed on silica gel (hexane/CH₂Cl₂, then CH₂Cl₂/ ether) to give, successively, **4e**OAc (78.8 mg, 22%), and a mixture of **4f**OAc and **4g**OAc (**4f**OAc:**4g**OAc = 84:16; by ¹H NMR) as a pale-yellow oil (310 mg, 58%). ¹H NMR (200 MHz, CDCl₃): δ 0.85–0.92 (m, 9H, 3 CH₃), 1–2.3 (m, ca. 31.5H), 2.33 (s, 3H, C(O)CH₃), 3.78 (m, 1H, CHOH), 4.84 (m, ca. 0.15H, *H*HC=C), 4.88 (m, ca. 0.15H, H*H*C=C), 5.25 (m, ca. 0.7H, HC=C), 5.57 (d, J = 10 Hz, 1H), 6.57/6.6 (d, J = 1.6 Hz, 1H).

(All-rac)-Tocopherol Acetate (1aOAc): From the Ene-Adduct 4fOAc/4gOAc. A stream of HCl was passed into EtOAc (5 mL) for 2h with cooling (ice bath). The preceding 4fOAc/4gOAc mixture was diluted with the HCl solution thus obtained and 5% Pd/C (100 mg) was added. The resulting mixture was stirred overnight at rt in a H₂ atmosphere. The solids were removed by filtration on Celite (washings with ether) and the solvents were evaporated. All these operations were repeated twice and the paleyellow oil finally obtained was purified by column chromatography (hexane/CH₂Cl₂). The residue left by evaporation of the solvents was dried overnight (30 °C, 10^{-2} Torr) to give **1a**OAc as a thick colorless oil (170 mg, 36% overall, based on reacted 2a). TLC (CH₂Cl₂) $R_f = 0.73$; IR (neat, cm⁻¹): 2924, 1760, 1455, 1372, 1209, 1078, 1011, 921; ¹H NMR (CDCl₃): δ 0.83–0.89 (m, 12H, 4 CH₃), 1-1.65 (m, 24H, 3 CH, 9 CH₂, CH₃), 1.72-1.84 (m, 2H, CH₂), 1.98 (s, 3H, C_{arom}CH₃), 2.03 (s, 3H, C_{arom}CH₃), 2.09 (s, 3H, $C_{arom}CH_3$), 2.33 (s, 3H, CH₃), 2.59 (t, 2H, J = 6.7 Hz, CH₂); ¹³C NMR (CDCl₃): δ 11.8 (CH₃), 12.1 (CH₃), 12.9 (CH₃), 19.6 (CH₃), 19.8 (CH₃), 20.5 (CH₃), 21 (CH₂), 22.6 (CH₃), 22.7 (2 CH₂), 24.5 (CH₂), 24.8 (CH₂), 28 (CH), 32.7 (CH), 32.9 (CH), 37.3–37.6 (4 CH₂), 39.4 (CH₂), 75 (C), 117.3 (C_{arom}), 123 (C_{arom}), 124.9 (Carom), 126.7 (Carom), 140.6 (Carom), 149.4 (Carom), 169.7 (C=O): MS (CI-NH₃) m/z 491 (M + NH₄⁺), 473 (M + H⁺), 472 (M), 430, 245, 207, 203, 165.

2-[2-(3,3-Dimethyloxiran-2-yl)ethyl]-2,5,7,8-tetramethylchroman-6-yl Acetate (4hOAc). With stirring, m-CPBA (341.3 mg, 1 equiv) was added progressively to a cooled (ice bath) solution of the chromene acetate 4aOAc (500 mg, 1.52 mmol) in CH₂Cl₂ (25 mL). After 1 h stirring at ca. 0 °C, finely ground Ca(OH)₂ (130 mg, 1.15 equiv) was added and the resulting mixture was further stirred for 1 h before being filtered on a pad of Celite. The solids were washed with CH_2Cl_2 (6 × 10 mL) and the pooled organic extracts were dried (MgSO₄). The residue left by evaporation of the solvents was dried overnight (30 °C, 10⁻² Torr) to give the epoxychromene 4hOAc as a colorless oil (485.5 mg, 93%). TLC (hexane:CH₂Cl₂:EtOAc = 9:9:2) $R_f = 0.61$; ¹H NMR (CDCl₃): δ 1.23/1.27/1.29 (3 s, 6H, 2 CH₃), 1.36/1.37 (2 s, 3H, CH₃), 1.6-1.88 (m, 4H, 2 CH₂), 2.01 (s, 3H, C_{arom}CH₃), 2.05 (s, 3H, CaromCH₃), 2.09 (s, 3H, CaromCH₃), 2.32 (s, 3H, C(O)CH₃), 2.69–2.76 (m, 1H, CH), 5.56/5.59 (2 d, J = 10 Hz, 1H, CH), 6.52/ 6.53 (2 d, J = 10 Hz, 1H, CH); ¹³C NMR (CDCl₃): δ 11.5 (CH₃), 11.6 (CH₃), 13.2 (s, CH₃), 18.5 (CH₃), 18.6 (CH₃), 20.5 (CH₃), 23.7/24 (CH₂), 24.8 (CH₃), 37.3/37.6 (CH₂), 58.4/58.5 (C), 64.2/ 64.4 (CH), 76.8/77.1 (C), 111.6 (Carom), 117.3/117.5 (Carom), 120.3/120.4 (CH), 122.5 (Carom), 128.6/129 (CH), 141.4 (Carom), 144.2 (Carom), 148.2 (Carom), 169.4 (C(O)); MS (CI-NH₃) m/z 344 (M), 329, 287, 246, 245, 203; Found: C, 72.91; H, 8.31%. Calcd for C₂₁H₂₈O₄: C, 73.23; H, 8.19%.

2-[2-(3,3-Dimethyloxiran-2-yl)ethyl]-2,5,7,8-tetramethylchroman-6-yl Acetate (1dOAc). The epoxychromene 4hOAc (867 mg, 2.52 mmol) was diluted with EtOAc (6 mL) and 10% Pd/C (10 mg) was added. The resulting mixture was degassed, and then stirred in a H₂ atmosphere until the absorption ceased (1.5 h). The solids were removed by filtration on a pad of Celite (washings with ether). The oily residue left by evaporation of the solvents in a vacuum was purified by column chromatography (hexane/CH₂Cl₂) to give a thick colorless oil (794 mg, 91%) identified as 1dOAc (NMR, GC).²

2-(3-Hydroxy-4-methylpent-4-enyl)-2,5,7,8-tetramethyl-2Hchromen-6-ol (4i). The epoxychromene 4hOAc (2.37 g, 6.92 mmol) was refluxed in toluene (36 mL) with aluminum isopropoxide (5.66 g, 27.7 mmol) for 24 h with stirring. After cooling to rt, the resulting mixture was slowly added to a stirred mixture of ether (100 mL) and pH 2 tartaric buffer (100 mL). After 1 h stirring, the aqueous layer was extracted with ether $(3 \times 50 \text{ mL})$ and the pooled organic phases were washed with pH 2 tartaric buffer (50 mL), brine $(2 \times 50 \text{ mL})$, and dried (MgSO₄). The residue left by evaporation of the solvents was filtered on a short column of silica gel (CH2Cl2/EtOAc) to give, after evaporation of the solvents, the chromenol 4i as a colored oil (1.98 g, 95%). TLC (hexane:CH₂Cl₂:EtOAc = 9:9:2) $R_f = 0.2$; ¹HNMR (CDCl₃): δ 1.33/1.34 (2 s, 3H, CH₃), 1.6–1.79 (m, in which s at 1.7, 7H, 2 CH₂, CH₃), 2.11 (s, 3H, C_{arom}CH₃), 2.14 (s, 3H, C_{arom}CH₃), 2.17 (s, 3H, CaromCH₃), 4.04–4.06 (m, 1H, CH), 4.5 (s, 1H, OH), 4.82– 4.93 (m, 2H, CH₂), 5.58 (d, J = 10 Hz, 1H, CH), 6.51/6.52 (2 d, J = 10 Hz, 1H, CH); ¹³C NMR (CDCl₃): δ 10.8 (CH₃), 11.6 (CH₃), 12.4 (s, CH₃), 17.5/17.6 (CH₃), 25.2/25.5 (CH₃), 29.2/29.3 (CH₂), 36.3 (CH₂), 75.8/76 (CH), 76.5/76.6 (C), 111.1/111.2 (CH₂), 116.5 (C_{arom}), 117.4/117.5 (C_{arom}), 120.4/120.5 (CH), 122.2/123 (Carom), 129.3/129.6 (CH), 144.3/144.4 (Carom), 145.4 (C_{arom}), 147.2/147.3 (C_{arom}); MS (CI-NH₃) m/z 303 (M + H⁺), 302 (M), 287, 269, 204, 203, 159.

2-(3-Acetyloxy-4-methylpent-4-enyl)-2,5,7,8-tetramethyl-2Hchromen-6-yl Acetate (4jOAc). Ac₂O (2.7 mL, 28.3 mmol) was progressively added to a cooled (ice bath) solution of the chromenol 4i (1.16 g, 3.83 mmol) in pyridine (6 mL, 76.6 mmol). The resulting mixture was stirred at rt overnight, then diluted with ether (50 mL) and 1 M HCl (30 mL). After 1 h stirring, the aqueous layer was extracted with ether $(4 \times 15 \text{ mL})$ and the pooled organic phases were washed with 1 M HCl (30 mL), brine ($3 \times 30 \text{ mL}$), and dried (MgSO₄). The solvents were evaporated in a vacuum and the residue was filtered on a short column of silica gel (hexane:CH₂Cl₂:EtOAc = 9:9:2) to give the diacetate 4jOAc as a colorless oil (1.42 g, 96%). TLC (hexane: CH_2Cl_2 :EtOAc = 9:9:2) $R_f = 0.55$; ¹H NMR (CDCl₃): δ 1.33 (s, 3H, CH₃), 1.58–1.85 (m, in which s at 1.69, 7H, 2 CH₂, CH₃), 2.01 (s, 3H, CaromCH₃), 2.02 (2 s, 6H, CH₃, C_{arom}CH₃), 2.04 (s, 3H, C_{arom}CH₃), 2.32 (s, 3H, CH₃), 4.88-4.93 (m, 2H, CH₂), 5.14-5.16 (m, 1H, CH), 5.54 (d, J = 10 Hz, 1H, CH), 6.51/6.52 (2 d, J = 10 Hz, 1H, CH); ¹³C NMR (CDCl₃): δ 11.5 (CH₃), 11.6 (CH₃), 13.2 (CH₃), 17.9/ 18.1 (CH₃), 20.5 (CH₃), 21.1 (CH₃), 25.9 (CH₃), 26.9 (CH₂), 36.2/ 36.4 (CH₂), 76.9 (C), 77.3/77.4 (CH), 112.9/113 (C=CH₂), 117.3/117.4 (Carom), 120.3 (CH), 122.5 (Carom), 122.6 (Carom), 122.8 (Carom), 128.9/129.1 (CH), 141.4 (C), 142.7 (Carom), 148.2 (Carom), 169.5 (C=O), 170.3 (C=O); MS (CI-NH₃) m/z 386 (M), 371, 327, 269, 246, 245, 204, 203, 159.

Wurtz Coupling of 4jOAc and Citronellylmagnesium Chloride 8: (E,Z)-2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltrideca-3,11-dienyl)-2*H*-chromen-6-yl Acetate (4kOAc). In a flask connected to an argon/vacuum line, CuI (3 mg, 0.05 equiv) was flamed in a vacuum. After cooling to rt, the diacetate **4j**OAc (100 mg, 0.256 mmol) diluted with THF (350μ L) was added with a syringe and the resulting mixture was cooled to -5 °C (ice/ methanol bath). A 0.82 M solution of the Grignard reagent **8** in THF (0.65 mL, 0.54 mmol) was added dropwise followed, 10 min later, by ether (2 mL) and saturated NH₄Cl (1 mL). After 10 min stirring, the aqueous phase was extracted with ether (3 × 1 mL) and the pooled organic extracts were washed with saturated NH₄Cl (2 mL), brine (2 × 2 mL), and dried (MgSO₄). The residue left by evaporation of the solvents was purified by column chromatography (hexane/ether) to give a thick colorless oil (102 mg, 84%) identified as **4k**OAc (TLC, NMR).

(All-*rac*)-Tocopherol Acetate (1aOAc): From 4kOAc. The preceding acetate (87 mg, 0.186 mmol) was diluted with EtOAc (2 mL) and 5% Pd/C (50 mg) was added. The resulting mixture was stirred in a H₂ atmosphere for 2 h to give, after filtration and evaporation of the solvents, 1aOAc as a thick white oil (84 mg, 96%).

2-(3-Chloro-4-methylpent-4-enyl)-2,5,7,8-tetramethyl-2Hchromen-6-yl Acetate (4lOAc). Ca(OCl)₂ (173 mg, 0.78 mmol), admixed with water (0.92 mL), was added to a solution of the chromene 4aOAc (469 mg, 1.42 mmol) in CH₂Cl₂ (9.2 mL). The resulting mixture was warmed to ca. 35-40 °C. With a vigorous stirring, finely ground dry ice was progressively added until disappearance of 4aOAc on TLC (30 min). pH 7 buffer (3 mL) was then added and the mixture was worked-up as above (see the 3a chlorination) to give, after drying (Na₂SO₄) and evaporation of the solvents in a vacuum, the chloride 4IOAc as a colorless oil (440 mg, 85%). TLC (hexane:CH₂Cl₂:EtOAc = 9:9:2) $R_f = 0.71$; ¹H NMR (CDCl₃): δ 1.35/1.36 (2 s, 3H, CH₃), 1.5–1.73 (m, 4H, 2 CH₂), 1.79/1.8 (2 s, 3H, CH₃), 2.02 (s, 3H, C_{arom}CH₃), 2.05 (s, 3H, CaromCH3), 2.09 (s, 3H, CaromCH3), 2.33 (s, 3H, CH3), 4.38 (t, $J = 7 \text{ Hz}, 2 \text{H}, \text{CH}_2$, 4.89–5.01 (m, 2H, CH₂), 5.54/5.57 (2 d, J = 10.2 Hz, 1H, CH), 6.51/6.54 (2 d, J = 10.2 Hz, 1H, CH); ¹³C NMR (CDCl₃): δ 11.5 (CH₃), 11.6 (CH₃), 13.2 (CH₃), 16.9 (CH₃), 20.5 (CH₃), 25.8/26.2 (CH₃), 31.2/34.4 (CH₂), 66.9 (CH), 76.8 (C), 114.4 (C=CH₂), 117.3 (C_{arom}), 120.4/120.5 (CH), 122.6 (Carom), 124.3 (Carom), 128.6/128.9 (CH), 141.4 (Carom), 144.2 (C), 148.2 (C_{arom}), 169.5 (C=O); MS (CI-NH₃) m/z 380 (M + NH₄⁺), 363 (M + H⁺), 362 (M), 344, 327, 311, 269, 245, 203, 165, 121, 105.91.

(All-rac)-Tocopherol Acetate (1aOAc): From the Chloride 4IOAc. CuI (3 mg, 0.05 equiv) was dried in a vacuum for a few hours. After cooling to rt, the chloride 4IOAc (93 mg, 0.24 mmol) diluted with THF (300 µL) was added with a syringe and the resulting mixture was cooled to $-5 \,^{\circ}\text{C}$ (ice/methanol bath). A 0.44 M solution of the Grignard reagent 8 in THF (0.58 mL, 0.24 mmol) was added dropwise. The cooling bath was removed and the reaction mixture was diluted with ether (2 mL) and saturated NH₄Cl (1 mL). After a few minutes stirring, the aqueous phase was extracted with ether $(3 \times 1 \text{ mL})$ and the pooled organic extracts were washed with saturated NH₄Cl (2 mL), brine $(2 \times 2 \text{ mL})$, and dried (MgSO₄). The residue left by evaporation of the solvents was purified by column chromatography (hexane/ ether) to give, after removal of the solvents in a vacuum, a thick colorless oil (64.5 mg, 58%) identified as 4kOAc (TLC, NMR). Hydrogenating this product (50 mg, 0.107 mmol) as above afforded 1aOAc as a thick colorless oil (48 mg, 95%).

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