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Efficient Access to (All-*rac*)-α-Tocopherol Acetate by a Crombie Chromene Synthesis

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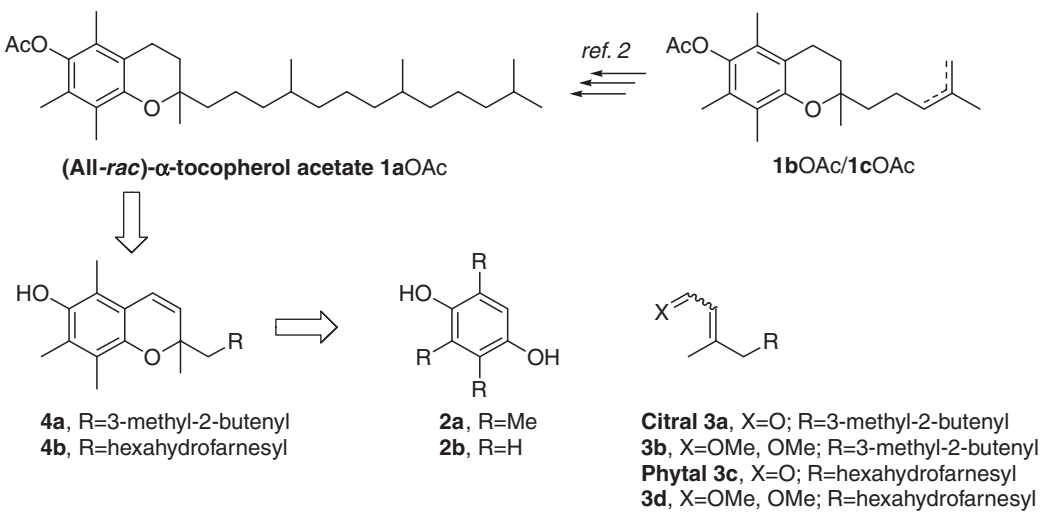
In contrast to reports in the literature, the pyridine-catalysed condensation of phenolic compounds and conjugated aldehydes to chromenes was found to be applicable to trimethylhydroquinone **2a** with the result of complementary convergent approaches to the title acetate using citral **3a** and dihydromyrcene **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 C_3 and C_2 homologation processes.[1] With the aim of designing a convergent access to **1a**OAc, we have previously studied the condensation of TMHQ **2a** and linalool, and shown that refluxing this C_{10} alcohol in 10:1 dodecane/CH_2Cl_2 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 **1a**OAc 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, rotenoids, coumarins, and cannabinoids.[3] Early investigations were mainly concerned with the condensation of 5-pentylresorcinol (olivetol) with **3a**. With $BF_3 \cdot Et_2O$ 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 mono- and 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.

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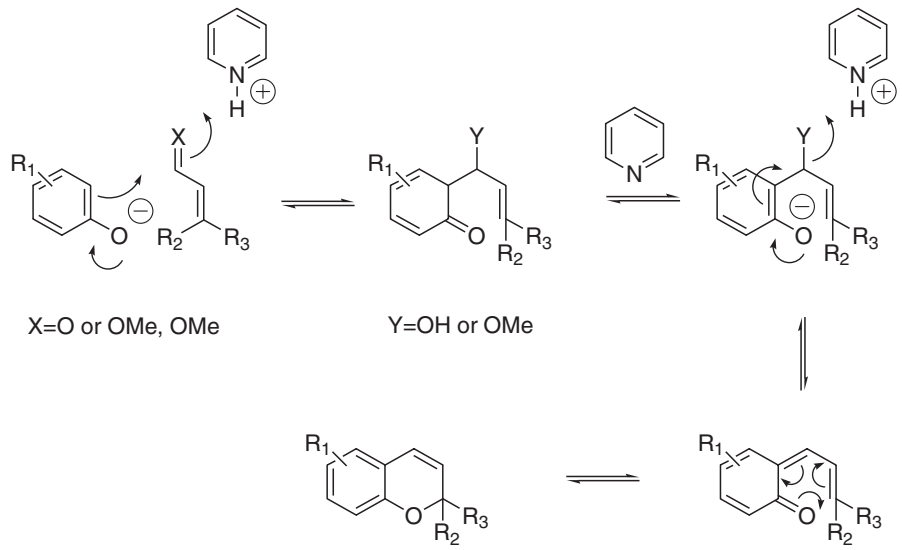


Scheme 2. Hypothetical mechanism of Crombie chromene synthesis.

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]

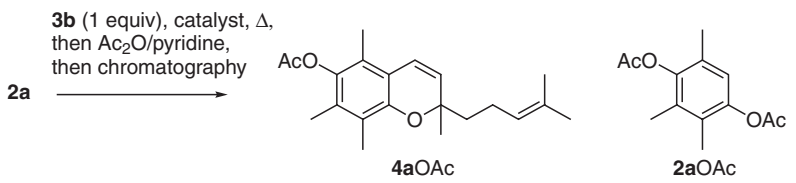
Chromenes being easily hydrogenated to chromanes,[16] the possibility of preparing tocopherol **1a** from TMHQ **2a** and phytal **3c** has previously been studied by Crombie, and although his attempts to condense **2a** and **3c** in pyridine proved unrewarding[6f]—"we never succeeded in condensing 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 **1a**OAc 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, Ac_2O 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 **4a**OAc (59%; NMR spectra identical to literature data)[13h] and the diacetate of TMHQ **2a**—i.e., **2a**OAc—(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, **4a**OAc 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 **4a**OAc: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 **4a**OAc 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.

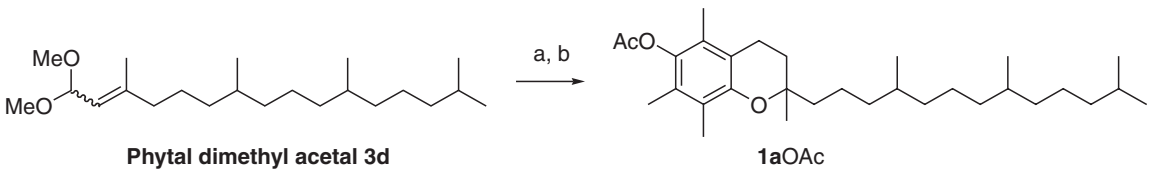
Next, with a view to speeding up this process, and as recommended in a related case,[3f] an equimolar mixture of **2a**, **3b**, and pyridine was heated in a flask equipped with a Vigreux column, the resulting volatiles being progressively eliminated

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



Entry	Catalyst (equiv)	Conditions[a)]	Time	Reacted **2a**/%	**4a**OAc/%[e)]	**4a**OAc: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

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.



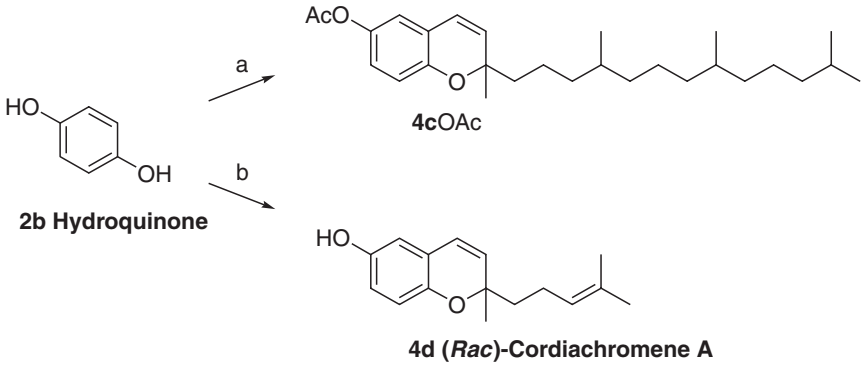
Scheme 3. Reagents and conditions: a) **2a** (1 equiv), pyridine (1 equiv), in conditions B of Table 1, then Ac_2O/pyridine (33%; 70% based on reacted **2a**); b) 1 atm H_2, 5% Pd/C, EtOAc, rt (96%).

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 Ac_2O in pyridine as above to give, after a purification by column chromatography, the chromene **4a**OAc 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** ≈ 2:1), the observed limited selectivity with regards to this reagent—i.e., the yield of **4a**OAc 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 **4a**OAc 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 **4a**OAc was then isolated in lower yield and no more effort was expended in this direction.

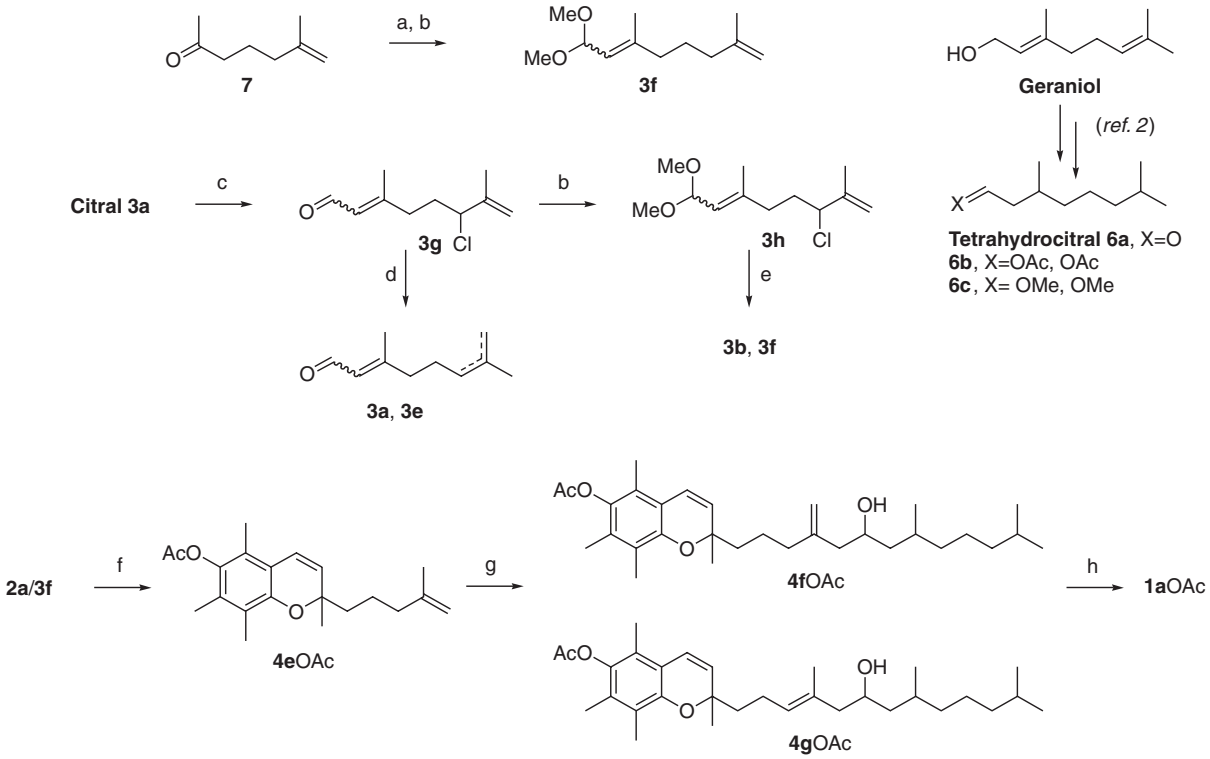
Next, phytal dimethyl acetal **3d**, prepared from commercial phytone **5** as a 1:1 mixture of the E and Z isomers (see experimental), was reacted with **2a** under the conditions of Entry 10 to give, after treatment with Ac_2O/pyridine and chromatography, the chromene acetate **4b**OAc (33%; 70% based 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 **4a**OAc 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 **1b**OAc to **1a**OAc would be inappropriate with



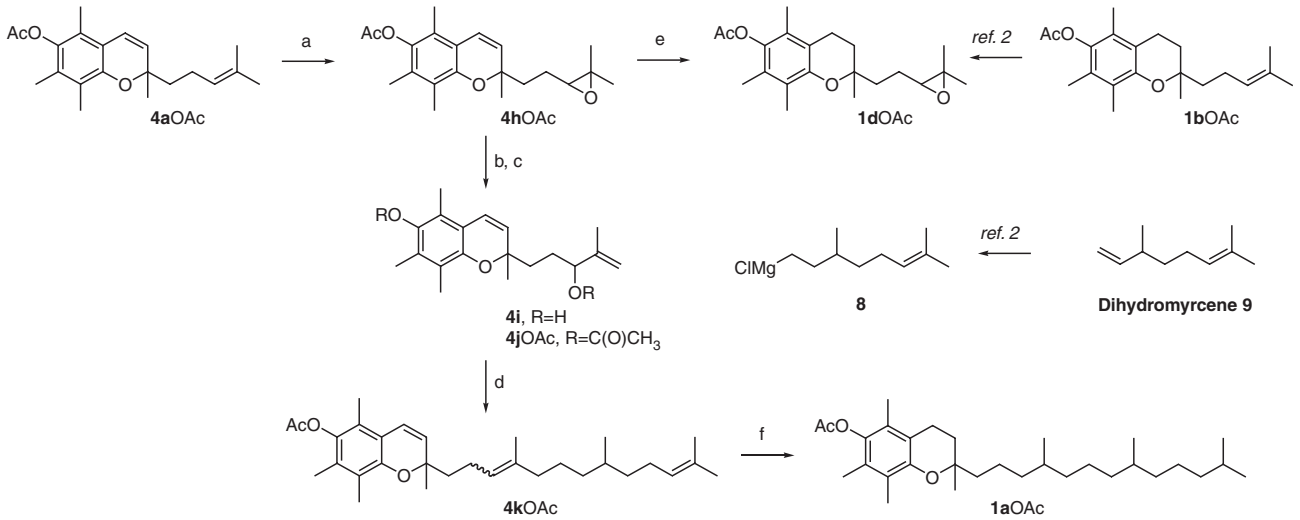
Scheme 4. Reagents and conditions: a) **3d** (0.6 equiv), pyridine (1 equiv), 125 °C, 6 d, then Ac_2O/pyridine (30%); b) **3b** (1 equiv), pyridine (1 equiv), 125 °C, 82 h (40%).



Scheme 5. Reagents and conditions: a) TMSCHLiCH=N*t*Bu, then aqueous HCO_2H according to Ref. 23 (77%). b) MeOH, $CH(OMe)_3$, 1% PPTS (92%). c) $Ca(OCl)_2$, CO_2, H_2O/CH_2Cl_2 (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 Ac_2O/pyridine (52%; 88% based on reacted **2a**). g) **6a**, Me_2AlCl (1.55 equiv), CH_2Cl_2 (58%; **4f**OAc:**4g**OAc = 84:16). h) 1 atm H_2, 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 Snider[21] 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 $Ca(OCl)_2 \cdot CO_2$ 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



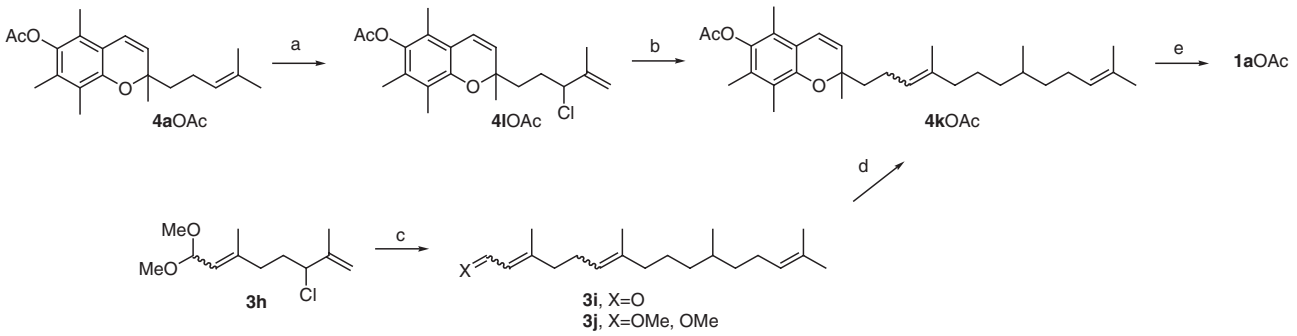
Scheme 6. Reagents and conditions: a) *m*-CPBA (1 equiv), $Ca(OH)_2$, CH_2Cl_2 (93%). b) $Al(O\text{-}i\text{-}Pr)_3$ (4 equiv), toluene (reflux) (95%). c) Ac_2O (excess), 1:1 CH_2Cl_2/pyridine, rt overnight (80% overall from **4h**OAc). d) **8** (2 equiv), CuI (0.05 equiv), THF (84%). e) 1 atm H_2, 10% Pd/C, EtOAc (91%). f) 1 atm H_2, 5% Pd/C, EtOAc (96%).

a 1:1 mixture (^{1}H 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 Ac_2O and column chromatography, the chromene acetate **4e**OAc in fair yield (52%). Next, **4e**OAc was reacted with tetrahydocitral **6a** in CH_2Cl_2 and added Me_2AlCl (excess). The reaction proceeded very slowly and additional **6a** proved necessary to observe a useful conversion. ^{1}H NMR analysis of the product then isolated indicated it to be an 84:16 mixture of the isomeric chromenes **4f**OAc and **4g**OAc respectively. Hydrogenating this product in acidic conditions (H_2, 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 Me_2AlCl 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 Ac_2O in the presence of a montmorillonite,[26] was reacted with **4e**OAc 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 **4e**OAc 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 **4a**OAc into **1a**OAc. On electronic grounds, and as illustrated with a parent naphthodihydropyran (vide supra), the $\Delta^{3,4}$ unsaturation of **4a**OAc should be the most reactive with epoxidation reagents. Surprisingly however, it has been observed that the chromene **4b**OAc, prepared by dehydrogenating tocopherol acetate **1a**OAc 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 sp^2 to sp^3) 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 (CH_2Cl_2, 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 (H_2, 5% Pd/C) to a chroman (91%) identified as **1d**OAc (NMR, GC).[2] Refluxing the epoxide **4h**OAc in toluene with aluminum isopropoxide afforded the chromenol **4i**, which was converted to the diacetate **4j**OAc by treatment with Ac_2O in pyridine (overall 80%). Cu^I-catalysed Wurtz coupling of this diacetate with citronellylmagnesium chloride **8** (two-fold excess) then furnished the chromene acetate **4k**OAc, which was hydrogenated to **1a**OAc in high yield (96%; 45% overall from **2a**). Encouraged by this result, the allylic chlorination of **4a**OAc was attempted. NMR features of the product (85%) obtained by treating **4a**OAc with the $CaCl_2 \cdot CO_2$ reagent in a two-phase system as above were consistent with the structure **4l**OAc (Scheme 7).

This sensitive product was immediately reacted with citronellylmagnesium chloride **8** in THF and added CuI to give **4k**OAc (58%), which was subsequently hydrogenated to **1a**OAc (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 **4k**OAc, which was subsequently hydrogenated to **1a**OAc (96%).



Scheme 7. Reagents and conditions: a) $Ca(OCl)_2$, CO_2, H_2O/CH_2Cl_2 (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 Ac_2O/pyridine (49%; 82% based on reacted **2a**). e) 1 atm H_2, 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 **1a**OAc 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 **1l**OAc to the tocopherol acetate **1a**OAc 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 C_{10}–C_{10}–**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 ^{1}H and ^{13}C 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 CaH_2 (bp 50 °C at 0.2 Torr). Isocitral **3e** (*E*-**3e**:*Z*-**3e** ≈ 1:1; by ^{1}H NMR) 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** ≈ 3:2; by ^{1}H NMR) 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 CH_2Cl_2 (55 mL) with stirring. The resulting mixture was stirred at rt overnight, then diluted with pH 2 tartaric buffer (210 mL). After 2 h 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 $NaHCO_3$ (100 mL), brine (2 × 50 mL), and dried ($MgSO_4$). The residue left by evaporation of the solvents was purified by column chromatography (hexane/CH_2Cl_2) to give phytal **3c** (*E*-**3c**:*Z*-**3c** ≈ 1.2:1; by ^{1}H NMR) as a pale-yellow oil (4.55 g, 86%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.81–0.89 (m, 12H, 4 CH_3), 0.95–1.65 (m, 19H), 1.97 (d, J = 1 Hz, ca. 1.5H, CH_3C=$CHCHO_{syn}$), 2.15 (d, J = 1 Hz, ca. 1.5H, CH_3C=$CHCHO_{anti}$), 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_{syn}), 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 literature[24] 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 CH_2Cl_2 (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 CH_2Cl_2 (3 × 30 mL) and the pooled organic phases were washed with pH 7 phosphate buffer (40 mL), brine (40 mL), and dried (Na_2SO_4). 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** ≈ 3:1; by ^{1}H NMR). *E*-**3g**: TLC (hexane:ether = 3:1) R_f = 0.44; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.8 (s, 3H, CH_3), 1.96–2.1 (m, 2H, CH_2), 2.17 (s, 3H, CH_3), 2.2–2.45 (m, 2H, CH_2), 4.34 (t, J = 7 Hz, 1H, CHCl), 4.91 (m, 1H, H(H)C=), 5.02 (m, 1H, 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; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.8 (s, 3H, CH_3), 1.99 (s, 3H, CH_3), 2.01–2.12 (m, 2H, CH_2), 2.63 (m, 2H, CH_2), 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 °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 × 10 mL). The pooled organic phases were washed with saturated NH_4Cl (15 mL), brine (2 × 15 mL), and dried ($MgSO_4$). 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 ($CDCl_3$): δ 0.88 (d, $J = 6.3$ Hz, 3H, CH_3), 1.03–1.19 (m, 2H, CH_2), 1.24–1.49 (m, 5H, CH, 2 CH_2), 1.62/1.69 (2 m, 9H, 3 CH_3), 1.9–2.04 (m, 6H, 3 CH_2), 2.16–2.3 (m, 5H, CH, 2 CH_2), 5.11 (m, 2H, 2 CH), 5.9 (m, 1H, CH), 9.99 (4 d, $J = 7.9$ Hz, 1H, CH); ^{13}C NMR ($CDCl_3$): δ 15.9 (CH_3), 17.6 (CH_3), 19.5 (CH_3), 23.3 (CH_3), 25.1 (CH_3), 25.3 (CH_2), 25.5 (CH_2), 32 (CH_2), 32.3 (CH), 36.9 (CH_2), 37.1 (CH_2), 39.9 (CH_2), 40.6 (CH_2), 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-NH_3) m/z 308 ($M + NH_4^+$), 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 Ac_2O (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 $NaHCO_3$ (20 mL), brine (10 mL), and dried (Na_2SO_4). 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 pale-yellow 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, $CDCl_3$): 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, $C(O)CH_3$), 2.07 (s, 3H, $C(O)CH_3$), 6.84 (dd, $J = 6$, 4 Hz, 1H, $CH(OAc)_2$); ^{13}C NMR (50 MHz, $CDCl_3$): 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 × 3.2 mL $mmol^{-1}$) and the pooled organic phases were washed with 1 M NaOH (1.6 mL $mmol^{-1}$), brine (2 × 6 mL $mmol^{-1}$), and dried (K_2CO_3). The residue left by evaporation of the solvents was distilled from CaH_2 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:CH_2Cl_2:EtOAc = 9:9:2) $R_f = 0.75$; ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{22}H_{44}O_2$ 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 ($CDCl_3$): δ 1.49–1.7 (m, 2H, CH_2), 1.72 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 1.96–2.18 (m, 4H, 2 CH_2), 3.31 (s, 6H, 2 OCH_3), 4.66–4.75 (m, 2H, $C{=}CH_2$), 5.01/5.04 (d, $J = 6.5$ Hz, 1H, $CH(OMe)_2$), 5.23–5.31 (m, 1H, C=CH); ^{13}C NMR ($CDCl_3$): δ 16.9 (CH_3), 23.2/23.3 (CH_3), 25.5/25.8 (CH_2), 37.3/37.5 (CH_2), 38.9 (CH_2), 52.2/52.3 (OCH_3), 100/100.4 ($CH(OCH_3)_2$), 110 ($CH_2{=}C$), 121.7/122.5 (C=CH), 142.1/142.4 (C=CH), 145.56 ($CH_2{=}C$); Anal. Found: C, 72.55; H, 11.17%. Calcd for $C_{12}H_{22}O_2$: 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:CH_2Cl_2: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 ($CDCl_3$): δ 1.73 (s, 3H, CH_3), 1.8 (s, 3H, CH_3), 1.86–2.05 (m, 2H, CH_2), 2.0–2.26 (m, 2H, CH_2), 3.31 (s, 6H, 2 OCH_3), 4.35 (t, $J = 7.5$ Hz, 1H, CHCl), 4.9 (m, 1H, CH–$CH(OCH_3)_2$), 5.03 (m, 2H, $CH_2{=}C$), 5.31 (t, $J = 7$ Hz, 1H, CH–$CH(OCH_3)_2$); ^{13}C NMR ($CDCl_3$): δ 17.1/17.6 (CH_3), 23.1 ($CH_3C{=}CH_2$), 34.3/34.7 (CH_2), 36.4/37.5 (CH_2), 52.1/52.3 (2 OCH_3), 66.1/66.2 (CHCl), 99.9/100.2 (CHO), 114.3 ($CH_2{=}C$), 122.6/123.8 (C=CH), 140.5 ($C{=}CH_2$), 144.1/144.2 (C=CH); Anal. Found: C, 62.01; H, 9.12; Cl, 15.01%. Calcd for $C_{12}H_{21}ClO_2$: 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:CH_2Cl_2:EtOAc = 9:9:2) $R_f = 0.69$; ^1H NMR ($CDCl_3$): δ 0.84 (d, $J = 6$ Hz, 3H, CH_3), 1.09–1.34 (2 m, 7H, CH, 3 CH_2), 1.58 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 1.70 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 1.90–2.15 (2 m, 8H, CH_2), 3.31 (s, 6H, 2 OCH_3), 4.09–4.95 (m, 3H, 3 CH), 5.23 (m, 1H, $CHOCH_3$); ^{13}C NMR ($CDCl_3$): δ 16.9 (CH_3), 17.6/19.6 (CH_3), 23.4 (CH_3), 25.3–26.2 (3 CH_2), 25.7 (CH_3), 32 (CH), 36.6–36.9 (2 CH_2), 39.4 (CH_2), 39.9 (CH_2), 51.2/52.2 (2 OCH_3), 100.1/100.2 (CH), 114.3 (CH), 121.6–125 (2 CH), 130.9 ($(CH_3)_2C$), 135.8/136.1 ($CH_2C(CH_3)$), 142/142.1 ($CH_2C(CH_3)$); HRMS found m/z 336.3041, calcd for $C_{22}H_{40}O_2$ 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 10-cm 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 Ac_2O (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 ($MgSO_4$). The residue left by evaporation of the solvents was dried overnight in a vacuum (ca. 0.01 Torr), then chromatographed on silica gel (hexane/CH_2Cl_2) to give, successively, the chromene acetate, and the diacetate of the unreacted quinol.

2,5,7,8-Tetramethyl-2-(4-methylpent-3-enyl)-2*H*-chromen-6-yl Acetate (4aOAc): Protocol B: In pyridine (0.81 mL, 10 mmol). From TMHQ **2a** (1.52 g, 10 mmol) and citral acetal **3b** (1.98 g, 10 mmol). Isolated: the diacetate **2a**OAc (0.397 g, 17%), and the chromene acetate **4a**OAc (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 **2a**OAc, and 2.795 g (41.5%; 74% based on reacted **2a**) of **4a**OAc. TLC (CH_2Cl_2) $R_f = 0.62$; IR (neat, cm^{-1}): 3046, 2968, 2925, 2860, 1759, 1672, 1644, 1605, 1458, 1368, 1204, 1115, 1089, 1062; ^{1}H NMR ($CDCl_3$): δ 1.37 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 1.6–1.73 (m, 2H, CH_2), 2.02 (s, 3H, CH_3), 2.04–2.16 (m, in which s at 2.04 and 2.1, 8H, CH_2, 2 CH_3), 2.32 (s, 3H, C(O)CH_3), 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); ^{13}C NMR ($CDCl_3$): δ 11.5 (CH_3), 11.8 (CH_3), 13.2 (CH_3), 17.7 (CH_3), 19.6 (CH_3), 22.8 (CH_2), 25.8 (CH_3), 26 (CH_3), 40.8 (CH_2), 78.4 (CO), 116.9 (C_{arom}), 122.6 (C_{arom}), 122.8 (CH), 124.2 (CH), 124.3 (C_{arom}), 129.2 (C_{arom}), 131 (CH), 131.8 ($C(CH_3)_2$), 146.8 (C_{arom}), 149.3 (C_{arom}), 169.4 (C(O)CH_3)); MS (CI-NH_3) m/z 346 (M + NH_4^+), 329 (M + H^+), 313, 286, 273, 245, 203, 159, 105, 91. **2a**OAc: ^{1}H NMR (200 MHz, $CDCl_3$): 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)-2*H*-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**). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.35 (s, 3H, CH_3), 1.55 (m, 4H, 2 CH_2), 1.7 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.09 (s, 3H, $C_{arom}CH_3$), 1.97–2.03 (m, 2H, CH_2), 2.34 (s, 3H, CH_3), 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 $C_{21}H_{28}O_3$ 328.2038.

2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltridecyl)-2*H*-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**). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.82–0.88 (m, 12H), 1.0–1.7 (m, in which s at 1.33, 24H), 2.02 (s, 3H, CH_3C_{arom}), 2.05 (s, 3H, CH_3C_{arom}), 2.09 (s, 3H, CH_3C_{arom}), 2.32 (s, 3H, CH_3C(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 (CH_2Cl_2) $R_f = 0.51$; ^{1}H NMR (200 MHz, $CDCl_3$): 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)CH_3), 5.58 (d, $J = 10$ Hz, 1H, HC=C), 6.28 (d, $J = 10$ Hz, 1H, HC=C), 6.68–6.81 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): 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 $C_{28}H_{44}O_3$ 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%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.37 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 1.6–1.73 (m, in which s at 1.66, 5H, CH_2, CH_3), 2.04–2.16 (m, 2H, CH_2), 4.51 (s, 1H, OH), 5.09 (t, $J = 7$ Hz, *H*C=C(CH_3)$_2$), 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}); ^{13}C NMR (50 MHz, $CDCl_3$): 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)-2*H*-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** (1.34 g, 3.98 mmol). Isolated: **2a**OAc (371 mg, 39.5%), and the chromene acetate **4k**OAc as a yellow viscous oil (914 mg, 49%, 82% based on reacted **2a**). TLC (hexane:CH_2Cl_2 = 1:1) $R_f = 0.35$; IR (neat, cm^{-1}): 3045, 2966, 2927, 1760, 1672, 1455, 1368, 1206, 1113, 1080, 1063; ^{1}H NMR ($CDCl_3$): δ 0.9 (d, $J = 7$ Hz, 3H, CH_3), 1.08–1.47 (m, in which s at 1.39, 12H, CH, 4 CH_2, CH_3), 1.64 (s, 3H, CH_3), 1.69 (s, 3H, CH_3), 1.70–2.22 (m, in which s at 1.72, 2.06, 2.08, 2.15, and 2.12, 21H, 3 CH_2, 5 CH_3), 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); ^{13}C NMR ($CDCl_3$): δ 11.5 (CH_3), 11.6 (CH_3), 13.2 (CH_3), 15.8 (CH_3), 17.6 (CH_3), 19.6 (CH_3), 20.5 (CH_3), 22.5/22.6 (CH_2), 23.4 (CH_3), 25.3/25.4 (CH_2), 25.7 (CH_2), 25.7/25.8 (CH_3), 32.3/32.4 (CH), 36.6/36.8 (CH_2), 37.1 (CH_2), 40 (CH_2), 40.9/41.2 (CH_2), 77.2/77.3 (C), 117.6 (C_{arom}), 120 (CH), 122.4 (C_{arom}), 122.6 (C_{arom}), 124.6 (C), 125 (C), 129 (C_{arom}), 129.3 (CH), 130.9 (C), 135.6/135.8 (C), 141.3 (C_{arom}), 148.5 (C_{arom}), 169.4 (C); MS (CI-NH_3) m/z 484 (M + NH_4^+), 467 (M + H^+), 385, 329, 272, 245, 230, 203, 174, 147, 95, 81, 69; HRMS found m/z 466.3458, calcd for $C_{31}H_{46}O_3$ 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)-2,5,7,8-tetramethyl-2*H*-chromen-6-yl Acetate (4gOAc). 1 M (in hexane) Me_2AlCl (1.7 mL, 1.7 mmol) was added dropwise to a cooled (ice bath) solution of **4e**OAc (0.361 g, 1.1 mmol) and tetrahydrocitral **6a** (0.26 g, 1.81 mmol) in CH_2Cl_2 (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 HCl (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 $NaHCO_3$ (10 mL), brine (2 × 5 mL), and dried ($MgSO_4$). The solvents were evaporated and the residue (0.58 g) was chromatographed on silica gel (hexane/CH_2Cl_2, then CH_2Cl_2/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 ^{1}H NMR) as a pale-yellow oil (310 mg, 58%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.85–0.92 (m, 9H, 3 CH_3), 1–2.3 (m, ca. 31.5H), 2.33 (s, 3H, C(O)CH_3), 3.78 (m, 1H, C*H*OH), 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 2 h with cooling (ice bath). The preceding **4f**OAc/**4g**OAc 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 H_2 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 pale-yellow oil finally obtained was purified by column chromatography (hexane/CH_2Cl_2). 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 (CH_2Cl_2) R_f = 0.73; IR (neat, cm^{-1}): 2924, 1760, 1455, 1372, 1209, 1078, 1011, 921; ^{1}H NMR ($CDCl_3$): δ 0.83–0.89 (m, 12H, 4 CH_3), 1–1.65 (m, 24H, 3 CH, 9 CH_2, CH_3), 1.72–1.84 (m, 2H, CH_2), 1.98 (s, 3H, $C_{arom}CH_3$), 2.03 (s, 3H, $C_{arom}CH_3$), 2.09 (s, 3H, $C_{arom}CH_3$), 2.33 (s, 3H, CH_3), 2.59 (t, 2H, J = 6.7 Hz, CH_2); ^{13}C NMR ($CDCl_3$): δ 11.8 (CH_3), 12.1 (CH_3), 12.9 (CH_3), 19.6 (CH_3), 19.8 (CH_3), 20.5 (CH_3), 21 (CH_2), 22.6 (CH_3), 22.7 (2 CH_2), 24.5 (CH_2), 24.8 (CH_2), 28 (CH), 32.7 (CH), 32.9 (CH), 37.3–37.6 (4 CH_2), 39.4 (CH_2), 75 (C), 117.3 (C_{arom}), 123 (C_{arom}), 124.9 (C_{arom}), 126.7 (C_{arom}), 140.6 (C_{arom}), 149.4 (C_{arom}), 169.7 (C=O): MS (CI-NH_3) m/z 491 ($M + NH_4^+$), 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 **4a**OAc (500 mg, 1.52 mmol) in CH_2Cl_2 (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 ($MgSO_4$). The residue left by evaporation of the solvents was dried overnight (30 °C, 10^{-2} Torr) to give the epoxychromene **4h**OAc as a colorless oil (485.5 mg, 93%). TLC (hexane:CH_2Cl_2:EtOAc = 9:9:2) R_f = 0.61; ^{1}H NMR ($CDCl_3$): δ 1.23/1.27/1.29 (3 s, 6H, 2 CH_3), 1.36/1.37 (2 s, 3H, CH_3), 1.6–1.88 (m, 4H, 2 CH_2), 2.01 (s, 3H, $C_{arom}CH_3$), 2.05 (s, 3H, $C_{arom}CH_3$), 2.09 (s, 3H, $C_{arom}CH_3$), 2.32 (s, 3H, C(O)CH_3), 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); ^{13}C NMR ($CDCl_3$): δ 11.5 (CH_3), 11.6 (CH_3), 13.2 (s, CH_3), 18.5 (CH_3), 18.6 (CH_3), 20.5 (CH_3), 23.7/24 (CH_2), 24.8 (CH_3), 37.3/37.6 (CH_2), 58.4/58.5 (C), 64.2/64.4 (CH), 76.8/77.1 (C), 111.6 (C_{arom}), 117.3/117.5 (C_{arom}), 120.3/120.4 (CH), 122.5 (C_{arom}), 128.6/129 (CH), 141.4 (C_{arom}), 144.2 (C_{arom}), 148.2 (C_{arom}), 169.4 (C(O)); MS (CI-NH_3) m/z 344 (M), 329, 287, 246, 245, 203; Found: C, 72.91; H, 8.31%. Calcd for $C_{21}H_{28}O_4$: 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 **4h**OAc (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 H_2 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/CH_2Cl_2) to give a thick colorless oil (794 mg, 91%) identified as **1d**OAc (NMR, GC).[2]

2-(3-Hydroxy-4-methylpent-4-enyl)-2,5,7,8-tetramethyl-2*H*-chromen-6-ol (4i). The epoxychromene **4h**OAc (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 × 50 mL) and the pooled organic phases were washed with pH 2 tartaric buffer (50 mL), brine (2 × 50 mL), and dried ($MgSO_4$). The residue left by evaporation of the solvents was filtered on a short column of silica gel (CH_2Cl_2/EtOAc) to give, after evaporation of the solvents, the chromenol **4i** as a colored oil (1.98 g, 95%). TLC (hexane:CH_2Cl_2:EtOAc = 9:9:2) R_f = 0.2; ^{1}H NMR ($CDCl_3$): δ 1.33/1.34 (2 s, 3H, CH_3), 1.6–1.79 (m, in which s at 1.7, 7H, 2 CH_2, CH_3), 2.11 (s, 3H, $C_{arom}CH_3$), 2.14 (s, 3H, $C_{arom}CH_3$), 2.17 (s, 3H, $C_{arom}CH_3$), 4.04–4.06 (m, 1H, CH), 4.5 (s, 1H, OH), 4.82–4.93 (m, 2H, CH_2), 5.58 (d, J = 10 Hz, 1H, CH), 6.51/6.52 (2 d, J = 10 Hz, 1H, CH); ^{13}C NMR ($CDCl_3$): δ 10.8 (CH_3), 11.6 (CH_3), 12.4 (s, CH_3), 17.5/17.6 (CH_3), 25.2/25.5 (CH_3), 29.2/29.3 (CH_2), 36.3 (CH_2), 75.8/76 (CH), 76.5/76.6 (C), 111.1/111.2 (CH_2), 116.5 (C_{arom}), 117.4/117.5 (C_{arom}), 120.4/120.5 (CH), 122.2/123 (C_{arom}), 129.3/129.6 (CH), 144.3/144.4 (C_{arom}), 145.4 (C_{arom}), 147.2/147.3 (C_{arom}); MS (CI-NH_3) m/z 303 ($M + H^+$), 302 (M), 287, 269, 204, 203, 159.

2-(3-Acetyloxy-4-methylpent-4-enyl)-2,5,7,8-tetramethyl-2*H*-chromen-6-yl Acetate (4jOAc). Ac_2O (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 × 15 mL) and the pooled organic phases were washed with 1 M HCl (30 mL), brine (3 × 30 mL), and dried ($MgSO_4$). The solvents were evaporated in a vacuum and the residue was filtered on a short column of silica gel (hexane:CH_2Cl_2:EtOAc = 9:9:2) to give the diacetate **4j**OAc as a colorless oil (1.42 g, 96%). TLC (hexane:CH_2Cl_2:EtOAc = 9:9:2) R_f = 0.55; ^{1}H NMR ($CDCl_3$): δ 1.33 (s, 3H, CH_3), 1.58–1.85 (m, in which s at 1.69, 7H, 2 CH_2, CH_3), 2.01 (s, 3H, $C_{arom}CH_3$), 2.02 (2 s, 6H, CH_3, $C_{arom}CH_3$), 2.04 (s, 3H, $C_{arom}CH_3$), 2.32 (s, 3H, CH_3), 4.88–4.93 (m, 2H, CH_2), 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); ^{13}C NMR ($CDCl_3$): δ 11.5 (CH_3), 11.6 (CH_3), 13.2 (CH_3), 17.9/18.1 (CH_3), 20.5 (CH_3), 21.1 (CH_3), 25.9 (CH_3), 26.9 (CH_2), 36.2/36.4 (CH_2), 76.9 (C), 77.3/77.4 (CH), 112.9/113 (C=*C*H_2), 117.3/117.4 (C_{arom}), 120.3 (CH), 122.5 (C_{arom}), 122.6 (C_{arom}), 122.8 (C_{arom}), 128.9/129.1 (CH), 141.4 (C), 142.7 (C_{arom}), 148.2 (C_{arom}), 169.5 (C=O), 170.3 (C=O); MS (CI-NH_3) 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 (350 μL) 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 NH_4Cl (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 NH_4Cl (2 mL), brine (2 × 2 mL), and dried ($MgSO_4$). 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 H_2 atmosphere for 2 h to give, after filtration and evaporation of the solvents, **1a**OAc as a thick white oil (84 mg, 96%).

2-(3-Chloro-4-methylpent-4-enyl)-2,5,7,8-tetramethyl-2*H*-chromen-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 **4a**OAc (469 mg, 1.42 mmol) in CH_2Cl_2 (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 **4a**OAc 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 (Na_2SO_4) and evaporation of the solvents in a vacuum, the chloride **4l**OAc as a colorless oil (440 mg, 85%). TLC (hexane:CH_2Cl_2:EtOAc = 9:9:2) $R_f = 0.71$; ^{1}H NMR ($CDCl_3$): δ 1.35/1.36 (2 s, 3H, CH_3), 1.5–1.73 (m, 4H, 2 CH_2), 1.79/1.8 (2 s, 3H, CH_3), 2.02 (s, 3H, $C_{arom}CH_3$), 2.05 (s, 3H, $C_{arom}CH_3$), 2.09 (s, 3H, $C_{arom}CH_3$), 2.33 (s, 3H, CH_3), 4.38 (t, $J = 7$ Hz, 2H, CH_2), 4.89–5.01 (m, 2H, CH_2), 5.54/5.57 (2 d, $J = 10.2$ Hz, 1H, CH), 6.51/6.54 (2 d, $J = 10.2$ Hz, 1H, CH); ^{13}C NMR ($CDCl_3$): δ 11.5 (CH_3), 11.6 (CH_3), 13.2 (CH_3), 16.9 (CH_3), 20.5 (CH_3), 25.8/26.2 (CH_3), 31.2/34.4 (CH_2), 66.9 (CH), 76.8 (C), 114.4 (C=*C*H_2), 117.3 (C_{arom}), 120.4/120.5 (CH), 122.6 (C_{arom}), 124.3 (C_{arom}), 128.6/128.9 (CH), 141.4 (C_{arom}), 144.2 (C), 148.2 (C_{arom}), 169.5 (C=O); MS (CI-NH_3) *m/z* 380 ($M + NH_4^+$), 363 ($M + H^+$), 362 (M), 344, 327, 311, 269, 245, 203, 165, 121, 105, 91.

(All-*rac*)-Tocopherol Acetate (1aOAc): From the Chloride 4lOAc. CuI (3 mg, 0.05 equiv) was dried in a vacuum for a few hours. After cooling to rt, the chloride **4l**OAc (93 mg, 0.24 mmol) diluted with THF (300 μL) was added with a syringe and the resulting mixture was cooled to −5 °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 NH_4Cl (1 mL). After a few minutes stirring, the aqueous phase was extracted with ether (3 × 1 mL) and the pooled organic extracts were washed with saturated NH_4Cl (2 mL), brine (2 × 2 mL), and dried ($MgSO_4$). 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 **4k**OAc (TLC, NMR). Hydrogenating this product (50 mg, 0.107 mmol) as above afforded **1a**OAc as a thick colorless oil (48 mg, 95%).

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