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# A Convenient Access to (All-*rac*)-α-Tocopherol Acetate from Linalool and Dihydromyrcene

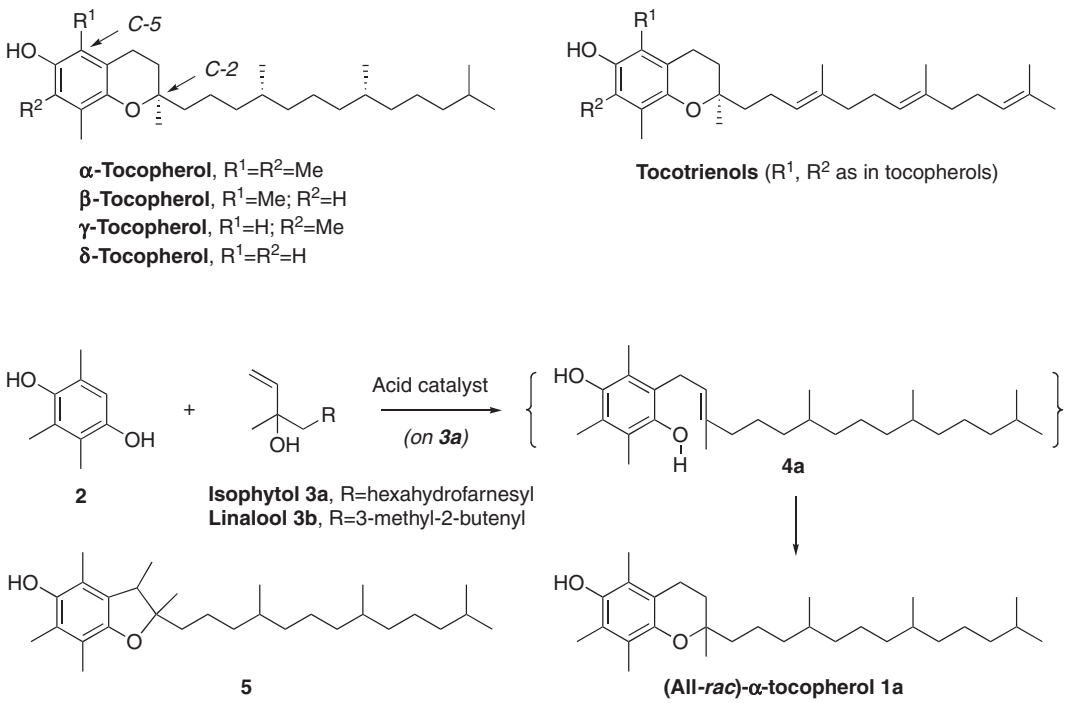
**Vincent Gembus, Nathalie Sala-Jung, and Daniel Uguen**[*,#]

Laboratoire de Synthèse Organique (associé au CNRS), Ecole Européenne de Chimie, Polymères et Matériaux, Université de Strasbourg, 25 rue Becquerel, 67087 Strasbourg, France

Received November 21, 2008; E-mail: uguen@chimie.u-strasbg.fr

Refluxing trimethylhydroquinone **2** in 10:1 dodecane/$CH_2Cl_2$ with linalool **3b** (two-fold excess) and camphorsulfonic acid, then treating the crude condensation product (consisting of a mixture of the chromanols **1b** and **1c**, alongside the tricyclic compounds **9** and **10**) sequentially with $Ac_2O$ and *m*-CPBA afforded, after removal by column chromatography of the **9**/**10** acetates, a mixture of the regioisomeric epoxides **1j**OAc and **1k**OAc (ratio 9:1, total 60%). Treatment of this mixture with Al(O-*i*-Pr)$_3$ followed by CuI-catalysed Wurtz coupling of the acetates of the resulting allylic alcohols with citronellylmagnesium chloride **12a**, and finally hydrogenation then provided the title acetate (overall 46% from **2**).

The term vitamin E refers to the mixtures of chromanols either substituted with a saturated (tocopherol) or unsaturated (tocotrienol) $C_{16}$ side-chain—i.e., vitamers—which are produced by higher plants and photosynthetic bacteria (Scheme 1). Long regarded as a "vitamin in search of a disease,"[1] this vitamin is nowadays considered as essential for health. Experiments on animal models have shown that a deficiency of vitamin E resulted in muscular dystrophy and foetal resorption, that the most efficient vitamer for relieving these syndromes was α-tocopherol, and that, although poorly confirmed by randomized clinical trials, a supplementation in vitamin E would protect against cardiovascular diseases, cancer genesis, and nerve degenerations.[2] The substitution pattern of the α-tocopherol molecule is critical: modifying the lipophilic side-chain, or epimerizing at the C-2 stereogenic centre results in a lower vitamin E activity owing to an improper binding of the resulting molecule to a transport (or associated) protein.[3] Since all of the preceding disorders might be related to an oxidative stress, the reactivity of these compounds with oxygen-centred free radicals has been studied.[4] As an elec-




**Scheme 1.**

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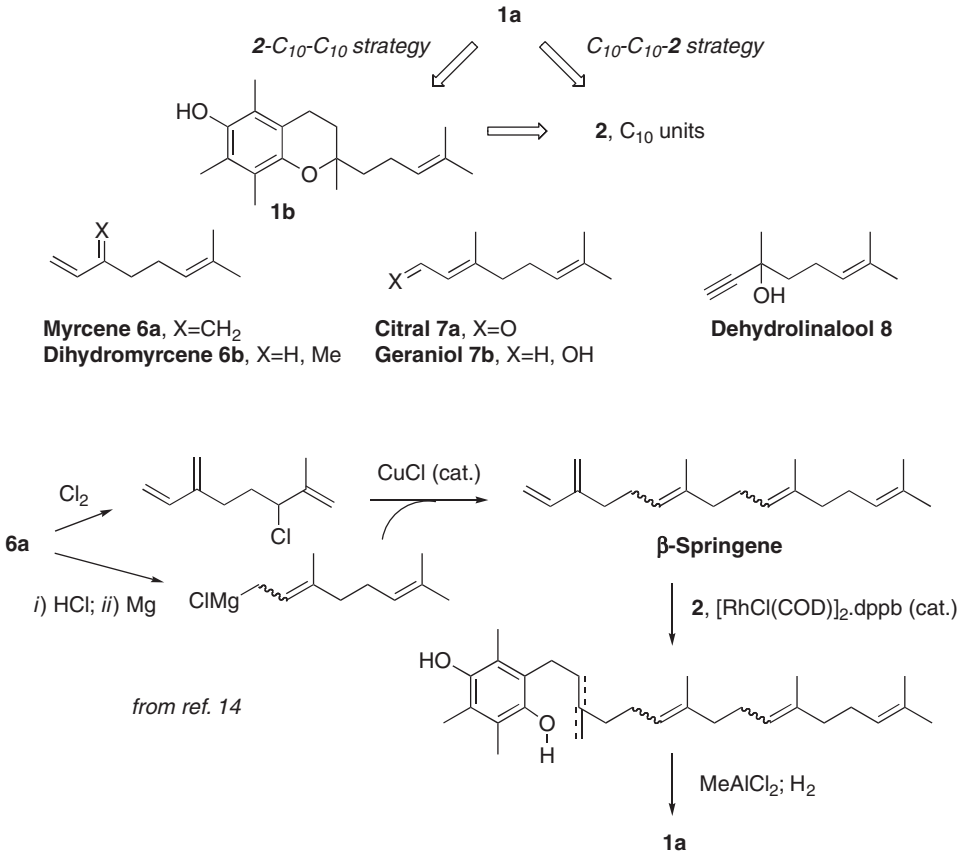
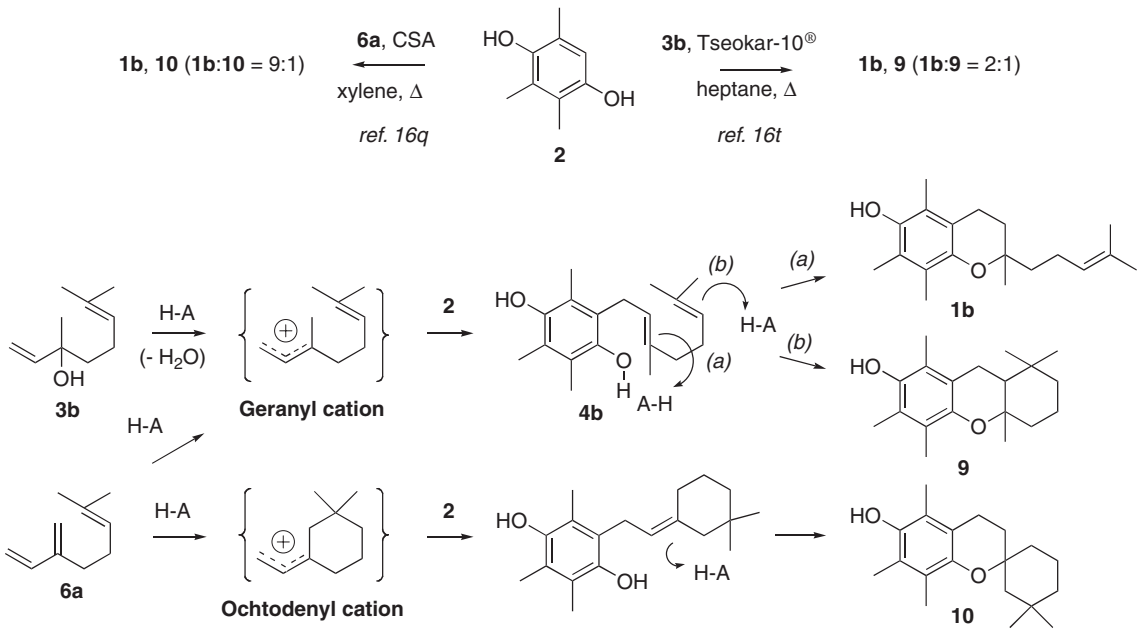



**Scheme 2.**

tron-rich phenol, any tocopherol has the potential to inhibit the lipid autoxidation process, and α-tocopherol was found to be the most active with regards to this property. However, one rationale for this observation is a stereoelectronic effect of the C-5 methyl group.[4b] Other properties (e.g., inhibition of a protein kinase C) have recently been uncovered, making clear that the biology of these compounds merits further investigations.[2b,2c] Nevertheless, it is likely that the activity of vitamin E wholly rests upon the singular ability of the α-tocopherol molecule to quench free radicals issued from the cellular respiration, and thus to protect phospholipids, proteins, and nucleic acids from degradation.

Vitamin E is widely distributed in plants. However, as processing has the potential to lower vitamer contents, the feed industry makes extensive use of synthetic tocopherol acetate. Various asymmetric syntheses of α-tocopherol acetate have been designed,[5] but preference is given to the less active, more cost-effective, mixture of all α-tocopherol acetate stereomers—i.e., (all-*rac*)-α-tocopherol **1a**OAc—to supply this considerable market (ca. 30000 t/year).[2a] The synthesis of **1a**OAc has been extensively studied.[6–8] In all major industrial procedures, trimethylhydroquinone **2** (TMHQ)[7e,9] is condensed with isophytol **3a** to give **1a**, with subsequent acetylation, hydrogenation, and vacuum distillation then affording pure **1a**OAc. Usually a **2**/**3a** mixture is refluxed in a hydrocarbon solvent either with a Lewis or a protic acid (which may be associated with a zinc salt) but improved catalyst and solvent conditions have recently been designed.[8] Mechanistically, **2** would react with protonated **3a** to give **4a**, the acid-catalysed cyclization of which affords **1a**.[7g] The detailed mechanism by which **4a** is formed is not known.[10] O-Isophytylation of the quinol **2**, followed by Claisen rearrangement of the resulting tertiary ether to **4a** has also been considered. The coumaran **5**, possibly formed by acid-induced cyclization of this ether, is observed as trace impurity. Additional impurities are dehydration products of isophytol **3a**, along with a quinone formed by oxidation of **4a** and subsequently converted to **1a**OAc.[11,12]

Isophytol **3a** is most commonly prepared from acetone by means of $C_3$ and $C_2$ homologation processes, although citral **7a** and myrcene **6a** are sometimes used. Though linear, these approaches offer some advantage: standard reagents are used and required substrates such as linalool **3b**, citral **7a**, and dehydrolinalool **8**, a key intermediate to pseudoionone and vitamin A, are also available.[7c,13] However, the attractive convergent strategies summarized in Scheme 2 are not so straightforward. Given the scale at which **1a**OAc is manufactured, only readily available $C_{10}$ terpene derivatives could be used, the same restriction applying to all reagents required for assembling these compounds with **2**. The adverse effect of this constraint is exemplified by the $C_{10}$–$C_{10}$–**2** approach to **1a** from myrcene **6a** (a commodity of the timber industry) summarized in Scheme 2.[14] As shown, the allylic chlorides prepared from **6a** by chlorination and hydrochlorination respectively are coupled to β-springene. Rhodium-catalysed condensation of this polyene with the quinol **2** is followed by treatment with $MeAlCl_2$ and hydrogenation to give **1a**.




**Scheme 3.**

Though concise, this synthesis could hardly develop to a high-scale procedure, owing to the catalyst conditions—i.e., 0.5–1% $[RhCl(COD)]_2$·dppb—required for the allylation step to proceed with an acceptable selectivity.

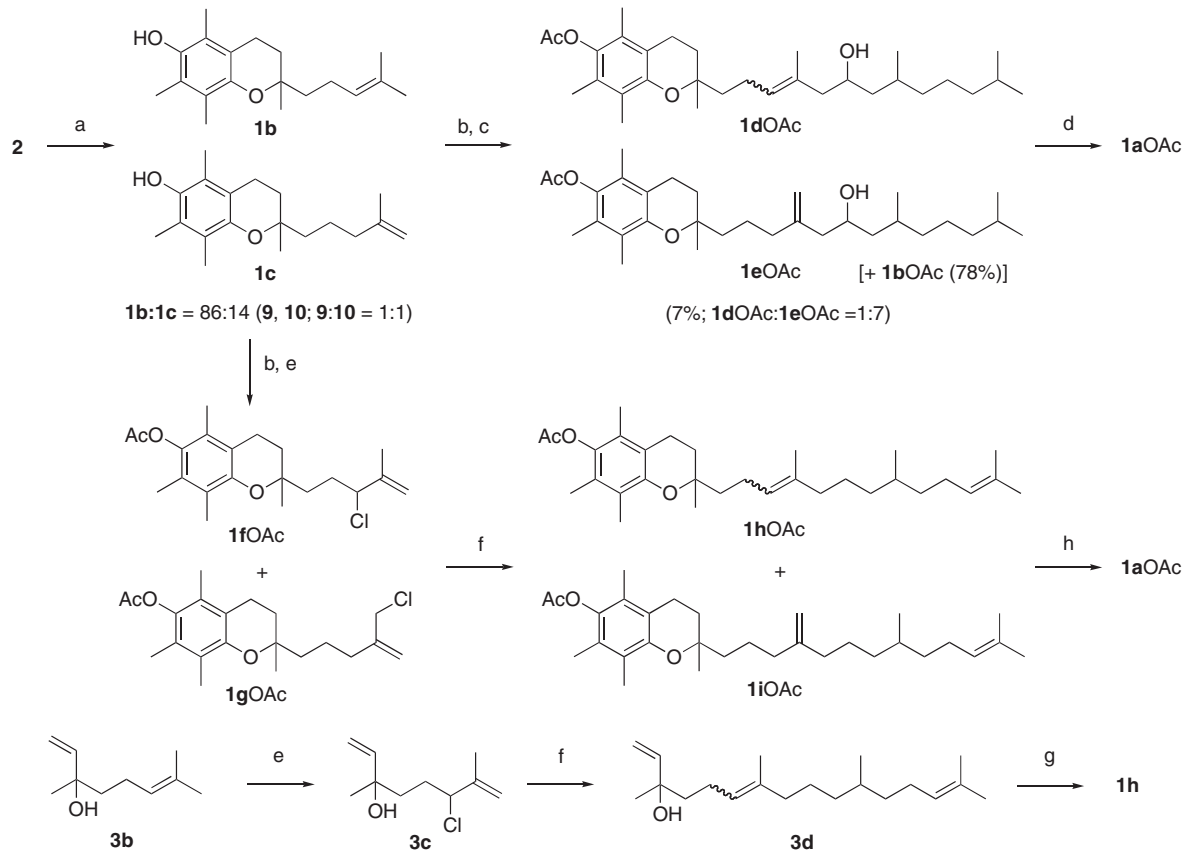
Bearing these considerations in mind with a view to designing a convergent access to **1a**OAc, the condensations of TMHQ **2** with linalool **3b** and citral **7a** respectively have been examined, and in this and the accompanying paper we report our progress and observations.

## Results and Discussion

The reactivity of phenolic compounds with linalool **3b** and geraniol **7b** under acidic conditions has previously been studied in relation to the synthesis of cannabinoids.[15,16] In most cases, rearrangement of the geranyl skeleton occurred and complex mixtures were observed; similar results have been obtained with geranyllinalool and geranylgeraniol, thus rendering impracticable an approach to **1a** from these polyisoprenyl alcohols.[11,17] Detailed descriptions of the planned condensation are scarce, although it was recently reported that refluxing a **2**/**3b** mixture in heptane with the aluminosilicate Tseokar-10® had furnished a 2:1 mixture (69%) of the chromanol **1b** and its tricyclic isomer **9** respectively (Scheme 3),[16t] each product being identified (NMR, GC) with a sample prepared using the previously-described $BF_3$-catalysed condensation of **2** with **7b**.[16c] Varying the conditions invariably gave less satisfactory results. For example, in hot toluene the **1b**/**9** ratio dropped to 1:1 and in refluxing nonane, a complex mixture was observed.

Comparing these results with those obtained independently with myrcene **6a** is worthy of interest (Scheme 3).[16q] Theoretically, as illustrated, linalool **3b** and myrcene **6a** may react with **2** in acidic conditions to give, by way of *o*-geranylTMHQ **4b**, the chromanol **1b**, and the hydroxanthene **9**. A distinct reaction pathway, however, is the formation from **6a** of the ochtodenyl cation, thence the spiro compound **10**, which is indeed observed along with **1b** and **9** by reacting **2** with **6a** in various acid and solvent conditions.[16j,16q] Amazingly, the more severe the conditions, the higher the selectivity in this case. Thus, refluxing **2** in xylene with **6a** and camphorsulfonic acid (CSA) afforded the chromanols **1b** and **10** (**1b**:**10** = 9:1); **9** was not observed. This prompted us to test these conditions with **3b**.

Initial experiments were realized on a mmol scale, the amount of acid catalyst being fixed at 10%. Using an excess of **3b** proved necessary to fully react **2**. As previously observed with **6a**, CSA was more efficient than *p*-toluenesulfonic acid (PTSA) and $MeSO_3H$, which gave complex mixtures. Hence, refluxing **2** in xylene with **3b** (two-fold excess) and CSA for a few hours, then washing out the catalyst and eliminating all volatiles (including $C_{10}$ hydrocarbons, as shown by GC-MS) in vacuo afforded a brown residue. TLC showed a new product, alongside traces of **2** and highly colored polar impurities. Careful column chromatography permitted the isolation of this product (71.5%), whose $^1$H NMR analysis suggested it to be a mixture of the chromanes **1b** and **1c** (**1b**:**1c** = 84:16). This was confirmed as follows. Alkylaluminum chlorides have been shown to promote the selective Alder-ene condensation of 2-methyl-1-alkenes with aliphatic aldehydes, trisubstituted olefins being unreactive in these conditions.[18] Accordingly, the preceding product was acetylated under standard conditions ($Ac_2O$/pyridine), and the resulting acetate mixture was reacted with tetrahydrocitral **11a** in cold (ca. 0 °C) $CH_2Cl_2$ with added $Me_2AlCl$ (excess) (Scheme 4). After a few hours, as judged by TLC analysis, the reaction did not proceed further and the product obtained after hydrolysis was chromatographed to afford, successively, impure **1b**OAc (78%; NMR as literature), and a small amount (7%) of a product whose $^1$H NMR analysis suggested it to be a mixture of **1d**OAc and **1e**OAc. Indeed, hydrogenating this product in acidic conditions ($H_2$, 5% Pd/C, HCl/EtOAc) afforded the tocopherol acetate **1a**OAc. It was verified by a NMR tube experiment [toluene-$d_8$, PTSA (10%); 90–100 °C] that **1b**OAc equilibrates with **1c**OAc in acidic conditions (**1b**OAc:**1c**OAc = 84:16 at equilibrium).

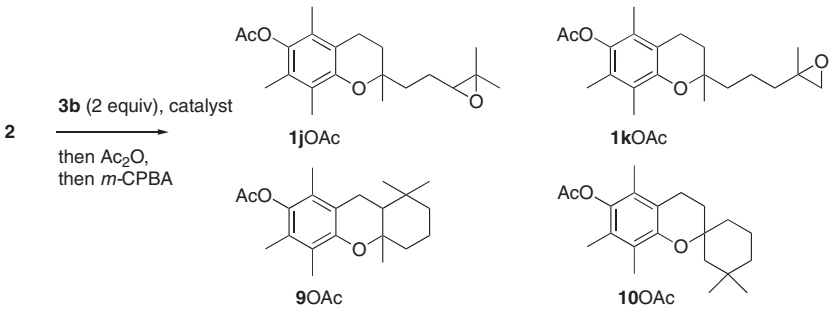



**Scheme 4.** Reagents and conditions (mmol-scale experiments): a) **3b** (2 equiv), CSA (0.1 equiv), xylene; 165–180 °C (bath), 2 h (77%). b) $Ac_2O$ (10 equiv), pyridine (20 equiv); rt, overnight. c) **11a** (0.32 equiv), 1 M (in hexane), $Me_2AlCl$ (0.32 equiv), $CH_2Cl_2$; −78 °C to rt, 8.5 h (7%). d) 1 atm $H_2$, 5% Pd/C, HCl, EtOAc; rt, 24 h (56%). e) $Ca(OCl)_2$ (1.2 equiv), $CO_2$, 10:1 $CH_2Cl_2/H_2O$; rt (72%). f) **12a** (2 equiv), CuI (0.05 equiv), THF; rt, 0.5 h. g) **2** (0.5 equiv), same conditions as in a) (50%). h) $H_2$, 5% Pd/C, EtOAc; rt, 7 h (99%).

Next, the elaboration of **1b**OAc and **1c**OAc to **1a**OAc was examined. A procedure for converting **1b**OAc to **1a**OAc has been patented.[19] As reported, treating **1b**OAc with trichloroisocyanuric acid (or chloramine T), then reacting the resulting allylic chloride with tetrahydrogeranylmagnesium chloride **11b** in THF with added CuCl affords, after hydrogenation, the tocopherol acetate **1a**OAc. Though some doubt could be cast on the selectivity of that chlorination,[20] this approach was studied, citronellylmagnesium chloride **12a** being preferred to **11b** owing to its accessibility from dihydromyrcene **6b** (see experimental). To this end, the preceding **2**/**3b** condensation experiment was duplicated, the only modification being a progressive addition of **3b**. Processing the condensation mixture as above afforded a colored product (same yield and selectivity), which was treated with an excess of $Ac_2O$ in pyridine. The resulting acetate mixture was briefly purified on silica gel before being treated with the $Ca(OCl)_2 \cdot CO_2$ reagent in a two-phase system, conditions selected owing to their efficiency in related cases.[21] After 30 min, a trace of **2** and a new product with close polarity were shown on TLC. Olefinic proton signals in the $^1$H NMR spectra of the sensitive product then isolated were consistent with the structures **1f**OAc and **1g**OAc. Though delicate, purification by column chromatography was realized and gave, successively, a mixture of **9**OAc and **10**OAc (14%; same NMR as literature;[16] **9**OAc:**10**OAc = 1:1), and the chloride product (72%), which was reacted with **12a** in THF and added CuI to give, after purification by column chromatography, a mixture of **1h**OAc and **1i**OAc (72%). Hydrogenating this Wurtz product afforded 94.7% pure **1a**OAc (HPLC-MS). In a converse manner, the chloride **3c**, prepared in moderate yield (54%) by treating linalool **3b** with the $Ca(OCl)_2 \cdot CO_2$ reagent as described,[21] was reacted with **12a** (two-fold excess) under the preceding conditions. The reaction did not proceed to completion and the desired dehydroisophytol **3d** was isolated in low yield (21%). Reacting this alcohol with **2** in xylene with added CSA as above produced the dehydrotocopherol **1h** (50%), which was subsequently converted to **1a**OAc by acetylation followed by hydrogenation (83%).

Though our goal was achieved, a main concern was the tedious elimination of the by-products **9**OAc and **10**OAc. To this end, our plan was modified, with the epoxidation/isomerisation sequence previously designed to convert methyl-substituted olefins to allylic alcohols preferred to the preceding chlorination procedure.[22] The hope was both an increased stability and difference in the polarity of the expected epoxides, as compared to the preceding chlorides, and thus a better evaluation of the selectivity of the chromanisation process. To this end, the **2**/**3b** condensation was realized on a larger scale (ca. 100 mmol), all subsequent operations being realized in the

**Table 1.** Solvent Effect on the Selectivity of the CSA-Catalysed **2**/**3b** Condensation[a)]



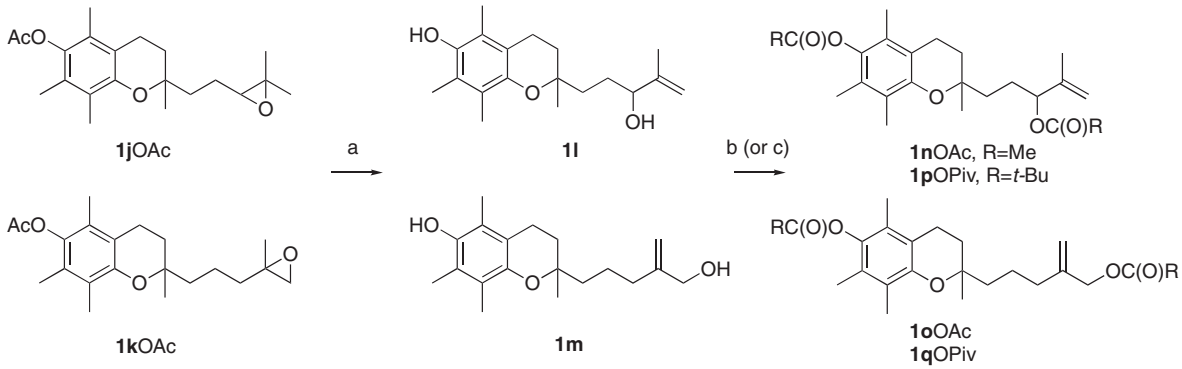

| Solvent | Time/h | Catalyst | Reacted **2**/% | **1j**OAc:**1k**OAc (total %)[b)] | **9**OAc:**10**OAc (total %)[b)] |
|---|---|---|---|---|---|
| Xylene | 2 | CSA | 88 | 86:14 (38) | 1:0 (10) |
| *o*-Dichlorobenzene | 2 | CSA | 100 | 9:1 (51) | 2:1 (9) |
| 10:1 Dodecane/$CH_2Cl_2$ | 2 | CSA | 100 | 10:1 (60) | 1:1 (8) |
| 10:1 Dodecane/$CH_2Cl_2$ | 48 | Tseokar® | 25 | 1:0 (12) | 2:1 (8) |
| Sulfolane | 6 | CSA | 91 | 1:0 (25) | (40)[c)] |

a) 100 mmol-scale experiments;10% CSA, 170–180 °C (bath). b) Isolated. c) **9**OAc, alongside a complex chromane mixture.

absence of air to avoid any degradation. In contrast to the preceding mmol-scale experiments, after 2 h, the reaction was incomplete. The reaction mixture was treated with an excess of $Ac_2O$ in pyridine and the resulting acetate mixture was chromatographed to separate the diacetate of TMHQ **2** (i.e., **2**OAc) from the chromane product (GC-MS), which was immediately treated with *m*-CPBA in $CH_2Cl_2$ to give a mixture of two products, as evidenced by a TLC analysis. This mixture was chromatographed, and the first-eluted product was practically pure **9**OAc (10%), as judged by NMR. Next, a mixture of **1j**OAc and its regioisomer **1k**OAc was obtained in moderate yield (38%). Though more precisely determined, as compared to preceding condensation experiments, this yield appeared abnormally low, another puzzling observation being the exclusive formation of the hydroxanthene **9** as side condensation product. Intrigued by this seeming relation of the selectivity with the scale used, we suspected that this inconsistency was due to the water produced by the chromenisation reaction process. Given that water is slightly soluble in xylene (0.19% w/w at 340 °K),[23] it is apparent that under the temperature and the dilution used, a significant quantity of the water formed in the reaction was in solution. Part of the water distilling out by azeotropy was mechanically retained in the condenser, however. Since the variation of the condensing surface from one experiment to another was small, it could be supposed that this separation was the most significant in mmol-scale experiments and, accordingly, that a dehydration of the condensation medium then occurred. This led us to experiment with various solvent conditions at comparable scale (ca. 100 mmol), in each case with the crude condensation product being treated sequentially with $Ac_2O$ and *m*-CPBA before separation (Table 1).

In dodecane, a high-boiling solvent in which water is practically insoluble ($\log S = -6.98$), the reaction proceeded sluggishly. A similar observation was made in a control experiment with Tseokar-10® conducted in otherwise identical conditions. This could be due to the insolubility of TMHQ **2** in this solvent. Indeed, adding a little $CH_2Cl_2$ to help dissolve **2** proved beneficial, the reaction then going to completion in less than 2 h. Interestingly, a pretty good yield in epoxides **1j**OAc and **1k**OAc was achieved (60%). Moreover, the selectivity was improved significantly: [**1j**OAc/**1k**OAc]:[**9**OAc/**10**OAc] = 15:2; thus establishing CSA as a more efficient catalyst than the preceding aluminosilicate in these conditions. A lower selectivity was achieved in *o*-dichlorobenzene ($\log S = -3.05$), though better than in xylene however. In sulfolane, the products were **1j**OAc, alongside a mixture of **9**OAc and various unidentified chromanes; **1k**OAc was not observed. Obviously, the question as to whether these chromanes are generated from linalool **3b** or myrcene **6a** is warranted. Observing **10** strongly suggests the involvement of **6a**: no mechanism other than pathway (b) in Scheme 3 could explain the formation of this spiro compound. The extent in which **1b** originates from **6a** can hardly be estimated however. Examination by GC-MS of the volatiles formed in small-scale xylene experiments revealed the presence of ocimene, establishing that linalool **3b** was dehydrated under these conditions. Triene **6a** was not detected, indicating that it reacted with **2** competitively with **3b**. The spirochroman **10** was not observed in the large-scale xylene experiment, suggesting that, unlike the experiment with dodecane (and also small-scale xylene experiments), due to the presence of water in solution the dehydration of **3b** to **6a** was insignificant, thus excluding **10** from the product mixture.

Though not characterised in this study, the geranyl derivative **4b** can be assumed to be an intermediate en route to **1b**, **1c**, and **9**. The cyclization of (*R*,*R*,*E*)-*o*-phytylTMHQ [i.e., (*R*,*R*)-**4a**] to natural (*R*,*R*,*R*)-$\alpha$-tocopherol catalysed by a cyclase isolated from a cyanobacteria has been shown to proceed by protonation of the olefin bond of (*R*,*R*)-**4a** at the *Si*-face and subsequent *Re*-attack of the nearby OH group (anti addition of the phenolic OH group).[24] With the aim of mimicking this biological process, the PTSA-catalysed cyclization of various peptidyl derivatives of (*R*,*R*)-**4a** (homochiral dipeptide residue attached to the C-5 methyl group) has been studied.[25] In one case, good




**Scheme 5.** Reagents and conditions: a) Al(O-*i*-Pr)$_3$ (4 equiv), toluene; reflux, 24 h (95%). b) $Ac_2O$ (10 equiv), 1:1 $CH_2Cl_2$/pyridine; rt, overnight (93%). c) Pivaloyl chloride (3 equiv), 1:1 $CH_2Cl_2$/pyridine; 0 °C to rt, overnight (96%).

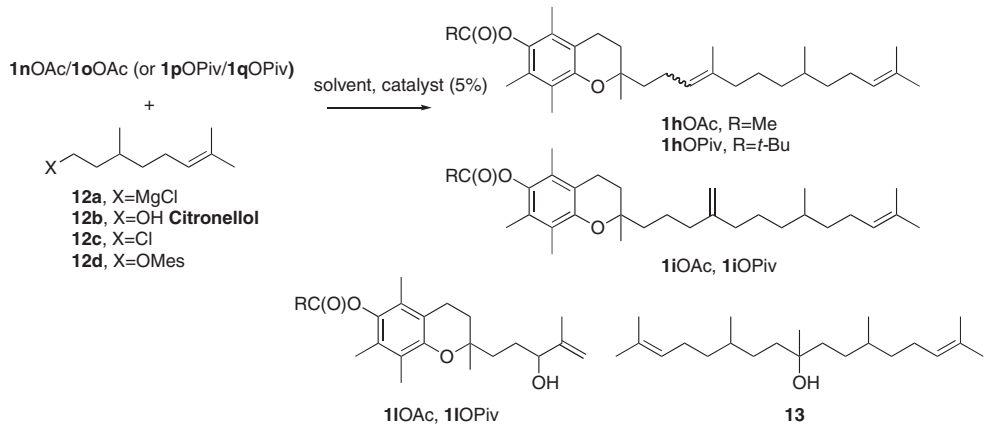
diastereoselectivity was achieved (de 80%), as established by converting the formed chromane into natural tocopherol, thus suggesting a mechanism similar to the biological process; however, no verification of the sense (anti vs. syn) of the addition was made in this case. In contrast to this view, Lewis acid catalysed cyclization of various *o*-geranylphenols to corresponding chromanes are believed to occur by intramolecular 1,6-proton transfer from the coordinated phenolic hydroxy to the nearby olefinic bond, the resulting carbocation immediately being attacked by this OH group to give the observed chromane (syn addition).[16e] A similar mechanism has also been suggested for the Lewis acid catalysed cyclization of *o*-phytylTMHQ **4a** to **1a**.[7g,14,26] Consistent with this view, a linear increase of the chromane/hydroxanthene ratio with temperature has been observed in the $SnCl_4$-catalysed cyclization of *o*-geranylolivetol.[16e] Protonation at an OH group should be kinetically favored over a C=C bond. Therefore, a related intramolecular proton-transfer process is likely to occur in the present case. In the event, on entropy grounds, protonation of **4b** at its terminal olefin bond and ensuing cyclization to **9** [pathway (a) in Scheme 3] should be disfavored at high temperature, the formation of **1b** thus predominating, as observed. Further clarification emerges when considering the polarity of the solvent used. Consistently with results previously obtained by reacting **3b** with diphenols in AcOH, in sulfolane the main product was a mixture of **9**OAc and various chromanes. Due to the polarity of the solvent medium, it is likely that **3b** rearranges to various terpene derivatives, which give with **2** the observed chromanols.[16j] Moreover, by analogy with the related squalene polycyclization process,[27] it may be suggested that the geranyl chain of **4b** adopts a folded conformation in DMSO. In the event, protonation of **4b** at its terminal olefinic bond will be assisted by the internal one, the resulting carbocationic species then cyclizing to **9**, which was indeed found to be the main product in this solvent medium: being accounted for in the ground state, the negative entropy variation accompanying the preceding spatial arrangement does not appear in the activation energy required for this bicyclization process to occur.[28] By contrast, in dodecane, the folding of this chain should be not so favoured. In the event, the preceding entropy term will contribute to the activation energy and, compared to **1b**, the formation of **9** will be limited at high temperature, as observed.[29] As to **1c**, as shown above, **1b** equilibrates with **1c** on treatment with PTSA in hot toluene and this accounts for the observation of these chromanes under most of the conditions used. Acid-induced cleavage of the tricyclic chromanol **9** to **1c**, and isomerization of **4b** prior to its cyclization might also be considered, but was ruled-out by refluxing **9** in xylene with CSA, whereupon neither **1c** nor **1b** were observed. Moreover, as discussed above, protonation of **4b** at its OH group and ensuing cyclization to **1b** should be kinetically favored. Thus, it is likely that **1c** originates from **1b** by acid-induced prototropic shift, such an isomerization not being observed with DMSO owing to a significant drop of the $H_0$ value of CSA in this solvent.

Next, elaboration of the epoxides **1j**OAc and **1k**OAc to **1a**OAc was examined. Refluxing the epoxide mixture generated in the dodecane/$CH_2Cl_2$ experiment in toluene with aluminum isopropoxide[22a] afforded in high yield (95%) a 10:1 mixture ($^1$H NMR) of the respective allylic alcohols **1l** and **1m**. Treating this mixture with an excess of $Ac_2O$ in $CH_2Cl_2$/pyridine then gave the corresponding diacetates **1n**OAc and **1o**OAc (93%) in the same isomeric ratio (Scheme 5).

Wurtz coupling of allylic acetates with alkylmetal species is well documented.[30] Besides control of $\alpha$ vs. $\gamma$ regioselectivity, another potential problem is the competitive nucleophilic addition of the alkylmetal onto the ester carbonyl group. Solutions have been found and, inspired by the literature, the preceding acetate mixture was reacted with citronellylmagnesium chloride **12a** under various catalyst and solvent conditions (Table 2).[31]

Best results were obtained with THF. In this solvent, the dehydrotocopherol acetates **1h**OAc and **1i**OAc were produced in good yield either using CuI, $Li_2CuCl_4$, $Cu(Acac)_2$, or CuOTf as catalyst. No isomeric coupling product was detected and, in each case, hydrogenation afforded **1a**OAc with 94% purity (GC). A few observations are worth noting, however. The use of CuCl, as well as Lipschutz,[30c] Alexakis,[31e] van Koten–Bäckvall,[31b–31d] and Fürstner[31g] catalyst conditions proved ineffective; surprisingly, reductive cleavage occurred with $CoCl_2$·dppp.[31f] In ether, only CuOTf was effective. Whatever the solvent and the catalyst conditions, using an excess of **12a** was necessary for the reaction to complete. This could be due to the addition of **12a** onto an acetoxy group to give deacetylation products and the alcohol **13**, which was indeed observed along with **1h**, **1i**, and **1l**OAc in experiments with

**Table 2.** Screening of Catalyst and Solvent Conditions




| Substrate | Solvent | Catalyst | **12a**/equiv | Products (%) |
|---|---|---|---|---|
| **1n**OAc/**1o**OAc | THF | CuI | 2 | **1h**OAc/**1i**OAc (89) |
| | | CuCl | 2 | — |
| | | CuCN | 2 | — |
| | | CuCN·2LiCl | | — |
| | | CuOTf·0.5Ph | 1.5 | **1h**OAc/**1i**OAc (80) |
| | | Tph-2-$CO_2$Cu | 2 | — |
| | | DMAMPhSCu | 2 | — |
| | | $Li_2CuCl_4$ | 2 | **1h**OAc/**1i**OAc (85) |
| | | $Cu(Acac)_2$ | 1.5 | **1h**OAc/**1i**OAc (82) |
| | | $CoCl_2$·dppp | 5 | **1h**OAc/**1i**OAc (28), **1b**OAc/**1c**OAc (50) |
| | | $Fe(acac)_3$ | 2 | — |
| | Ether | CuI | 2 | **1h**OAc/**1i**OAc (10), **13** (39), **1l**OAc (68) |
| | | CuCN | 2 | **1h**OAc/**1i**OAc (17), **1h**/**1i** (15), **13** (43), **1l**OAc (45) |
| | | $Li_2CuCl_4$ | 2 | **1h**OAc/**1i**OAc (67), **1h**/**1i** (8), **13** (6), **1l**OAc (17) |
| | | CuOTf·0.5Ph | 2 | **1h**OAc/**1i**OAc (81) |
| | | DMAMPhSCu | 2 | **1h**OAc/**1i**OAc (51) |
| **1p**OPiv/**1q**OPiv | THF | $Li_2CuCl_4$ | 2 | **1h**OPiv/**1i**OPiv (86) |
| | | CuCN | 2 | — |
| | | CuI | 2 | — |
| | | Tph-2-$CO_2$Cu | 2 | — |

ether. However, even with THF, when **13** was not formed, the rate of the reaction significantly slowed down at ca. 10% conversion when just a molar-equivalent of **12a** was used. Surprisingly, the same observation was made with the pivalates **1p**OPiv and **1q**OPiv, in which case only Kochi–Schlosser catalyst conditions were effective (compare with Ref. 31a).[32] As is frequently observed in related reactions,[33] it is likely that the partial decomposition of **12a** (or a corresponding organocopper species) occurred.

## Conclusion

Although short, this new approach to **1a**OAc from TMHQ **2** and linalool **3b** hardly surpasses existing procedures owing to incomplete selectivity of the chromanisation reaction process. A few interesting points emerge from this study, however. In contrast to the literature, using a high temperature for reacting **2** with **3b** proved not so detrimental and under selected acid and solvent conditions—viz. 10% CSA, dodecane/$CH_2Cl_2$—the chromanols **1b** and **1c** were produced with fairly good selectivity. Moreover, by using inter alia an epoxidation/aluminum isopropoxide isomerisation sequence, in preference to the more common allylic chlorination process, the chromanol mixture thus obtained could efficiently be converted into (all-*rac*)-$\alpha$-tocopherol **1a**OAc, providing a short, uncomplicated route to this valuable product.

## Experimental

**General.** Infrared (IR) spectra were recorded in KBr pellets on a Perkin-Elmer Spectrum One apparatus. Excepted otherwise indicated $^1$H and $^{13}$C NMR spectra were recorded on a Bruker Avance-300 apparatus at 300 and 75 MHz, respectively. Chemical shifts ($\delta$) are reported in parts per million relative to the solvent resonance as the internal standard [CD(H)$Cl_3$, 7.26 and 77 ppm respectively]. Signal multiplicity is described as s, singlet; d, doublet; t, triplet; m, multiplet. GC-MS analyses were performed on a Shimadzu-QP5050 GCMS apparatus. HPLC-MS analyses were realized at Aventis Industrialisation (Décines, France). GC analyses were performed on a HP 6890 apparatus equipped with a HP-5 crosslinked 5% Ph–Me Siloxane (30 m × 0.32 m × 0.25 mm). TLC analyses were performed on silica gel (60 GF254 Merck); with spot visualisation by exposure to UV light (254 nm)

or treatment with the $H_2SO_4$/vanilline reagent. Column chromatography refers to the Stille method using Merck 60H silica gel (medium pressure of nitrogen with chromanol mixtures); unless it is otherwise stated, a slow gradient (0.5%) of degassed solvents was realized. All experiments were performed in dried glassware, under an argon atmosphere (three freeze–pump–thaw cycles for all condensation and Wurtz-coupling experiments), with magnetic stirring. All solvents used were freshly distilled from an appropriate reagent [Na–benzophenone (ether, THF, and xylene); $CaH_2$ (*o*-dichlorobenzene, sulfolane, DMF, and pyridine); $K_2CO_3$ (EtOAc); $CaH_2$, then $P_4O_{10}$ ($CH_2Cl_2$); $P_4O_{10}$ (pentane and hexane)]. $Ac_2O$ (Acros), 65% calcium hypochlorite (Aldrich) and *m*-CPBA (Aldrich) were used as received. Trimethylhydroquinone **2** (Fluka) was re-crystallized from EtOAc and dried in a desiccator prior to use. Linalool **3b** (Fluka), geraniol **7b** (Fluka), and citronellol **12b** (Acros) were purified by distillation from $CaH_2$ and their purity was verified by NMR and GC analysis. $Li_2CuCl_4$,[32] copper(I) thiophene-2-carboxylate (Tph-2-$CO_2$Cu),[34] copper(I) 2-dimethylaminomethylbenthiolate (DMAMPhSCu),[35] CuOTf·0.5PhH,[36] and CuCN·2LiCl[31a] were prepared according to the literature; the other metal salts in Table 2 were available, and used without purification. pH 7 phosphate buffer was prepared by mixing 0.06 M $Na_2HPO_4$ (500 mL) and 0.06 M $KH_2PO_4$ (500 mL), and pH 2 tartaric buffer by adding NaOH pellets (4.5 g) to 0.7 M tartaric acid (360 mL).

**Citronellylmagnesium Chloride (12a).** **12a** (in THF) was prepared by reacting dihydromyrcene **6b** with isopropylmagnesium chloride and added dichlorotitanocene, as described,[37] or by treating citronellyl chloride **12c** with magnesium. For the sake of comparison, all the experiments in Table 2 were realized by using solutions (in ether or THF) of **12a** prepared according to the latter procedure. Since being only briefly described in the literature the preparation of citronellyl chloride **12c** from citronellol **12b** (inspired from Ref. 38) and its reduction to **12a** are described thereafter.

Mesyl chloride (9.84 mL, 128 mmol) diluted with pentane (50 mL) was added dropwise to a cooled (ice/methanol bath) solution of citronellol **12b** (10 g, 64 mmol) in the same solvent (250 mL). Pyridine (10.32 mL, 128 mmol), diluted with pentane (50 mL), was slowly added and the temperature was allowed to rise gradually to rt (4 h). The reaction mixture was further stirred for 7 h, and then cooled (ice bath). 1 M HCl (200 mL) was cautiously added and, after 10 mn stirring, the aqueous layer was extracted with pentane (3 × 50 mL). The pooled organic phases were washed with 1 M HCl (200 mL), saturated aqueous $NaHCO_3$ (2 × 200 mL), and dried ($K_2CO_3$). The oily residue left by evaporation of the solvents was purified by chromatography on silica gel (hexane/ether) to give, after evaporation of the solvents in vacuo, the mesylate **12d** as a thick colourless oil (13.9 g, 91%). TLC (hexane:ether = 2:1) $R_f = 0.41$ (vanilline); IR (neat, $cm^{-1}$): 2980, 2926, 1455, 1355, 1175, 974, 943, 890, 528; $^1$H NMR ($CDCl_3$): $\delta$ 0.95 (d, $J = 6.4$ Hz, 3H), 1.15–1.55 (m, 4H), 1.62 (s, 3H), 1.70 (s, 3H), 1.80 (m, 1H), 2.01 (m, 2H), 3.02 (s, 3H), 4.22–4.34 (m, 2H), 5.10 (m, 2H); $^{13}$C NMR ($CDCl_3$): $\delta$ 17.6, 19.1, 25.3, 25.7, 28.9, 35.9, 36.8, 37.4, 68.5, 124.2, 131.6.

Anhydrous LiCl (18 g, 420 mmol) was added to a solution of **12d** (10 g, 42.1 mmol) in DMF (150 mL) and the resulting mixture was refluxed 1 h with stirring before being cooled and poured into an iced mixture of 2 M HCl (100 mL) and hexane (200 mL) with stirring. The aqueous layer was extracted with hexane (3 × 50 mL) and the pooled organic phases were washed with saturated $NaHCO_3$ (2 × 50 mL), brine (50 mL), and dried ($MgSO_4$). The solvents were evaporated and the residue was chromatographed on silica gel (hexane). The product left by evaporation of the solvents was further purified by distillation from $CaH_2$ to afford citronellyl chloride **12c** as a colorless oil (6.75 g, 92%). Bp 95 °C at 13 Torr; TLC (hexane:ether = 3:1) $R_f = 0.92$; IR (neat, $cm^{-1}$): 2964, 2927, 2873, 1650, 1453, 1378, 1286, 1246, 1110, 985, 885, 830, 727, 658; $^1$H NMR ($CDCl_3$): $\delta$ 0.92 (d, $J = 6.4$ Hz, 3H), 1.15–1.45 (m, 4H), 1.62 (s, 3H), 1.71 (s, 3H), 1.82 (m, 1H), 2.01 (m, 2H), 3.59 (m, 2H), 5.12 (m, 2H); $^{13}$C NMR ($CDCl_3$): $\delta$ 17.6, 18.9, 25.3, 25.7, 30.0, 36.7, 39.7, 43.3, 124.4, 140.0.

Magnesium turnings (438 mg) were weighed in a flask and a magnetic stirring-bar was added. Air was evacuated to 0.1 Torr and the flask was flamed before being filled with argon. The dried turnings were vigorously stirred overnight, and then covered with THF (5 mL). An iodine crystal was added and the resulting mixture was warmed-up to ca. 30 °C. After the orange color had discharged a solution of **12c** (3 g, 17.17 mmol) in THF (21 mL) was added progressively and the resulting mixture was refluxed until disappearance of the solids to give a black-gray solution. The concentration of **12a** was estimated by titration with 2-butanol using salicylaldehyde phenylhydrazone as indicator.[39] Solutions of **12a** in ether were similarly prepared.

**Tetrahydrocitral (11a).** Geraniol **7b** was hydrogenated (5% Pd/C, EtOAc, 1 atm $H_2$) to tetrahydrogeraniol **11c**. DMSO (2.15 mL, 30.3 mmol) diluted with $CH_2Cl_2$ (6.5 mL) was slowly added to a cooled (dry ice/acetone bath) solution of oxalyl chloride (1.7 mL, 19.5 mmol) in the same solvent (44 mL) with stirring. After 8 min, a solution of **11c** (2 g, 12.6 mmol) in $CH_2Cl_2$ (17 mL) was slowly added and the resulting mixture was further stirred for 20 min before adding triethylamine (9 mL, 12.6 mmol). After 20 min the cooling bath was removed and the reaction mixture was allowed to warm to rt before being diluted with ether (120 mL) and washed with water (60 mL). The resulting aqueous phase was extracted with ether (30 mL) and the pooled organic phases were repeatedly washed with brine, until neutral, and then dried ($Na_2SO_4$). The residue left by evaporation of the solvents (2.01 g) was purified by distillation to afford tetrahydrocitral **11a** as a colorless oil (1.48 g, 75%). Bp 40–45 °C at 0.2 Torr; TLC (hexane:ether = 19:1) $R_f = 0.28$; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 0.86 (d, $J = 6.6$ Hz, 6H), 0.95 (d, $J = 6.6$ Hz, 3H), 1.05–1.40 (m, 6H), 1.52 (m, 1H), 2.06 (m, 1H), 2.22 (ddd, $J = 15$, 7.6, 2.6 Hz, 1H), 2.40 (ddd, $J = 15$, 6, 2 Hz, 1H), 9.75 (t, $J = 2.4$ Hz, 1H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 19.8, 22.5, 24.6, 27.8, 28.0, 37.1, 38.9, 51.0, 202.3.

**Small-Scale 2/3b Condensation Experiments; 2,5,7,8-Tetramethyl-2-(4-methylpent-3-enyl)chroman-6-ol (1b) and 2,5,7,8-Tetramethyl-2-(4-methylpent-4-enyl)chroman-6-ol (1c).** In a flask equipped with a condenser connected to an argon/vacuum line, trimethylhydroquinone **2** (0.2 g, 1.31 mmol) was diluted with xylene (3 mL) and camphorsulfonic acid (0.031 g, 0.013 mmol) was added. The resulting mixture was thoroughly degassed before being brought to reflux with stirring. After 15 min, linalool **3b** (0.5 mL, 2.6 mmol) diluted with xylene (1 mL) was rapidly added with a syringe, the heating being pursued for 5 h. After cooling the reaction mixture was diluted with ether (5 mL), washed with water (2 × 5 mL), and finally dried ($MgSO_4$). The colored residue left by evaporation of the solvents was chromatographed on silica gel (hexane/EtOAc) to give a mixture of **1b** and **1c** as a pale-yellow oil (270 mg, 71.5%). TLC (hexane:ether = 3:1) $R_f = 0.3$; (hexane:EtOAc = 4:1) $R_f = 0.5$; IR (neat, $cm^{-1}$): 3479, 2928, 1668, 1455, 1286, 1086; $^1$H NMR ($CDCl_3$): $\delta$ 1.27 (s, 3H, $CH_3C$), 1.44–2.15 (m, 6.5H), 1.61/1.68 (2 s, 5H, 2 $CH_3C$=CH), 2.09/2.12/2.16 (3 s,

9H, 3 $CH_3C_{arom}$), 2.62 (t, $J = 7.0$ Hz, 2H, $CH_2C_{arom}$), 4.15 (s, 0.16H, OH), 4.20 (s, 0.84H, OH), 4.69/4.71 (2 s, 0.32H, C=$CH_2$), 5.12 (m, 0.84H, CH=C); $^{13}$C NMR ($CDCl_3$): $\delta$ 11.2/11.9/12.3 ($CH_3C_{arom}$), 17.5/22.7/23.5/26.5 ($CH_3$), 20.7/21.9/22.3/26.4/31.6/38.4/39.9/41.7 ($CH_2$), 74.2 ($CCH_3$), 109.9 (C=$CH_2$), 117.2/118.7/118.9/121.2/122.6 ($C_{arom}$), 124.6 (CH=C), 131.3 (CH=C), 139.2 (C=$CH_2$), 144.6/145.5 ($C_{arom}$); MS (CI-$NH_3$) $m/z$ 289 ($M + H^+$), 288 (M), 220, 204, 166, 153, 136, 122, 108, 92, 82.

**2,5,7,8-Tetramethyl-2-(4-methylpent-3-enyl)chroman-6-yl Acetate (1bOAc) and 2,5,7,8-Tetramethyl-2-(4-methylpent-4-enyl)chroman-6-yl Acetate (1cOAc).** With cooling (ice bath), $Ac_2O$ (2.2 mL) and pyridine (3 mL) were added sequentially to the preceding **1b**/**1c** mixture (261 mg, 0.9 mmol) and the resulting mixture was stirred overnight at rt before being diluted with ether (10 mL) and 1 M HCl (10 mL). The aqueous layer was extracted with ether (3 × 5 mL) and the pooled organic extracts were washed with 1 M HCl (10 mL), brine (3 × 7 mL), and dried ($MgSO_4$). The residue left by evaporation of the solvents was chromatographed on silica gel (hexane/EtOAc) to give an 84:16 mixture ($^1$H NMR) of **1b**OAc and **1c**OAc respectively (263 mg, 88%); TLC (hexane:ether = 3:1) $R_f = 0.45$; IR (neat, $cm^{-1}$): 2928, 1759, 1677, 1455, 1368, 1209, 1079; $^1$H NMR ($CDCl_3$): $\delta$ 1.28 (s, 3H, $CH_3$), 1.39–2.10 (m, 6.5H), 1.63/1.70 (2 s, 5H, 2 $CH_3$C=CH), 2.00/2.05/2.13 (3 s, 9H, 3 $CH_3C_{arom}$), 2.33/2.34 (2 s, 3H, $CH_3$), 2.63 (t, $J = 6.7$ Hz, 2H, $CH_2C_{arom}$), 4.69/4.71 (2 s, 0.32H, C=$CH_2$), 5.15 (m, 0.84H, CH=C); $^{13}$C NMR ($CDCl_3$): $\delta$ 12.0/12.1/12.9 ($CH_3C_{arom}$), 17.5/20.5/22.6/25.7 ($CH_3$), 19.8/20.6/21.4/22.3/27.7/31.1/38.0/40.0/41.7 ($CH_2$), 74.7/74.8 ($CCH_3$), 109.9 (C=$CH_2$), 117.3/118.7/123.0/124.9/126.7 ($C_{arom}$), 124.5 (CH=C), 131.4 (CH=C), 140.6 (C=$CH_2$), 149.4 ($C_{arom}$), 169.6 (C=O); MS (CI-$NH_3$) $m/z$ 330 (M), 287, 208, 166, 153, 137, 122, 108, 92, 82.

**(*E*,*Z*)-2-(6-Hydroxy-4,8,12-trimethyltridec-3-enyl)-2,5,7,8-tetramethylchroman-6-yl Acetate (1dOAc) and 2-(6-Hydroxy-8,12-dimethyl-4-methylenetridecyl)-2,5,7,8-tetramethylchroman-6-yl Acetate (1eOAc).** A flask was charged with the preceding 84:16 mixture of **1b**OAc and **1c**OAc (0.28 g, 0.85 mmol) and tetrahydrocitral **11a** (41.9 mg, 0.27 mmol), and then connected to an argon line. $CH_2Cl_2$ (4.2 mL) was added with a syringe and the resulting solution was cooled to −78 °C (dry ice/acetone bath) before adding 1 M (in hexane) $Me_2AlCl$ (0.27 mL, 0.27 mmol) with a syringe. After 4 h stirring at −78 °C, the cooling bath was removed and the reaction mixture was stirred overnight at rt before being diluted with ether (5 mL), 1 M $NaH_2PO_4$ (1.2 mL), and 2 M HCl (2 mL). After 10 min stirring, the aqueous layer was extracted with ether (3 × 2 mL) and the pooled organic phases were washed with saturated $NaHCO_3$ (2 mL), brine (2 × 2 mL), and dried ($MgSO_4$). The yellow oil left by evaporation of the solvents was chromatographed on silica gel (hexane/$CH_2Cl_2$) to give **1b**OAc (0.22 g, 78%); $^1$H NMR spectra identical to literature data.[16q,16t] Washing the column with ether (100 mL) then afforded, after evaporation of the solvents, a 1:7 ($^1$H NMR) mixture of **1d**OAc and **1e**OAc respectively as a pale-yellow oil (10 mg, 7% Yield). TLC ($CH_2Cl_2$) $R_f = 0.2$; IR (neat, $cm^{-1}$): 3460, 1760, 1644, 1578, 1455, 1366, 1208, 1079, 1009, 920; $^1$H NMR ($CDCl_3$): $\delta$ 0.84–0.98 (m, 9H, 3 $CH_3$), 1.12–2.26 (m, 25H), 1.97/2.02/2.09 (3 s, 9H, 3 $CH_3$), 2.33 (s, 3H, $CH_3$), 2.61 (t, $J =$ 6.5 Hz, 2H, $CH_2$), 3.50–3.85 (m, 1H, CHOH), 4.73–4.98 (m, 1H, C=$CH_2$), 5.25 (t, $J = 6.7$ Hz, 1H, C=CH); $^{13}$C NMR ($CDCl_3$): $\delta$ 11.9/12.2/13.0 ($CH_3C_{arom}$), 16.1/20.4/21.5/22.8/29.0/29.2/29.3 ($CH_3$), 20.7/22.3/24.3/31.2/37.0/38.2/38.4/44.1/45.0/48.3/48.9 ($CH_2$), 66.8/66.9 (CH), 74.7/74.8 (C), 113.3 (C=$CH_2$), 117.3/123.1/125/126.8 ($C_{arom}$), 128.5 (C=CH), 132.3 (C=CH), 140.6 ($C_{arom}$), 146.6 (C=$CH_2$), 149.3 ($C_{arom}$), 169.8 (C=O).

**(All-*rac*)-α-Tocopherol Acetate (1aOAc); from 1dOAc/1eOAc.** A stream of dry HCl was passed into EtOAc (10 mL) with cooling (ice bath) for 30 min and the preceding **1d**OAc/**1e**OAc mixture, diluted with EtOAc (1 mL), was added followed by 5% Pd/C (50 mg). The resulting mixture was stirred overnight at rt in a $H_2$ atmosphere, then diluted with $CH_2Cl_2$ (10 mL). The solids were removed by filtration on a short column of silica gel (washings with $CH_2Cl_2$) and the solvents were evaporated to give an oily residue. All these operations were repeated twice and the residue finally obtained was purified by chromatography (hexane/EtOAc) to give a pale-yellow oil (7.2 mg) identified with a sample of **1a**OAc by HPLC-MS analysis (purity 92.7%). TLC ($CH_2Cl_2$) $R_f = 0.73$; IR (neat, $cm^{-1}$): 2924, 1760, 1455, 1372, 1209, 1078, 1011, 921; $^1$H NMR ($CDCl_3$): $\delta$ 0.83–0.89 (m, 12H, CHC$H_3$), 1.00–1.65 (m, 24H, C$H$C$H_3$/C$H_2$/C$CH_3$), 1.72–1.84 (m, 2H, $CH_2$), 1.98/2.03/2.09 (3 s, 9H, 3 $CH_3C_{arom}$), 2.33 (s, 3H, $COCH_3$), 2.59 (t, $J = 6.7$ Hz, 2H, $CH_2C_{arom}$); $^{13}$C NMR ($CDCl_3$): $\delta$ 11.8/12.1/12.9 ($CH_3C_{arom}$), 19.6/19.8/20.5 (3 $CH_3$), 21.0 ($CH_2$), 22.6/22.7 (3 $CH_3$), 24.5/24.8 (2 $CH_2$), 28.0/32.7/32.9 (3 CH), 37.3/37.4/37.5/37.6/39.3/39.4 (6 $CH_2$), 75.0 (C–O), 117.3/123.0/124.9/126.7/140.6/149.4 ($C_{arom}$), 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-(3-Chloro-4-methylpent-4-enyl)-2,5,7,8-tetramethylchroman-6-yl Acetate (1fOAc) and 2-[4-(Chloromethyl)pent-4-enyl]-2,5,7,8-tetramethylchroman-6-yl Acetate (1gOAc).** An 84:16 mixture of **1b**OAc and **1c**OAc (110 mg, 0.34 mmol) was diluted with $CH_2Cl_2$ (2.3 mL) and 65% calcium hypoclorite (45.4 mg, 0.21 mmol), admixed with $H_2O$ (0.23 mL), was added. The resulting mixture was warmed to ca. 30–35 °C (hot-water bath) and, with a vigorous stirring, finely ground dry ice was progressively added (30 min) followed by pH 7 phosphate buffer (3 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3 × 3 mL) and the pooled organic phases were washed with brine (2 × 5 mL), pH 7 phosphate buffer (5 mL), and dried ($Na_2SO_4$). The solvents were evaporated in vacuo and the residue was chromatographed on silica gel (hexane/EtOAc) to give, successively: i) a 1:1 mixture ($^1$H NMR) of **9**OAc and **10**OAc as a thick grey oil (15.3 mg, 13%); TLC (hexane:ether = 3:1) $R_f = 0.45$; IR (neat, $cm^{-1}$): 2946, 1740, 1455, 1368, 1182, 1082, 1070; $^1$H NMR ($CDCl_3$): $\delta$ 0.92/0.95/1.00/1.13/1.15 (5 s, 15H, 5 $CH_3$), 1.30–1.80 (m, 14H, 7 $CH_2$), 1.99/2.00/2.02/2.08 (4 s, 18H, 6 $CH_3C_{arom}$), 2.32/2.33 (2 s, 6H, 2 $COCH_3$), 2.55–2.85 (m, 4H, 2 $CH_2C_{arom}$); diagnostic signals: s at 0.92, 1, and 1.15 ppm (**9**OAc), s at 0.95 and 1.13 ppm (**10**OAc); $^{13}$C NMR ($CDCl_3$): $\delta$ 11.7/11.8/12.1/12.7/12.9 ($CH_3C_{arom}$), 20.5/21.5/32.1/32.4/44.3 (5 $CH_3$), 17.5/19.8/21.6/22.0 (4 $CH_2$), 32.6/33.0/38.9/39.0/39.3/41.5 (6 $CH_2$), 74.5/75.3 (2 C–O), 117.4/117.9 ($C_{arom}$), 122.8/123.3/123.6/124.9/127.3/127.4 ($C_{arom}$), 140.8/140.9/148.8/149.7 ($C_{arom}$), 169.3/169.4 (C=O); MS (CI-$NH_3$) $m/z$ 331 ($M + H^+$), 330 (M), 290, 287, 208, 204, 166, 148, 137, 124, 110, 92, 82; ii) an 84:16 ($^1$H NMR) mixture of **1f**OAc and **1g**OAc, respectively, as a pale-yellow oil (91.2 mg, 72%). TLC (hexane:ether = 3:1) $R_f = 0.36$; $^1$H NMR ($CDCl_3$): $\delta$ 1.25/1.27 (2 s, 3H, $CH_3$), 1.48–2.16 (m, 9H), 1.99/2.03/2.09/2.10 (4 s, 9H, $CH_3C_{arom}$), 2.33/2.38 (2 s, 3H, $CH_3CO$), 4.32–4.41 (m, 1.68H, CHCl), 4.47–4.49 (m, 0.32H, $CH_2Cl$), 4.90/5.02/5.07/5.13 (4 m, 2H, C=$CH_2$); $^{13}$C NMR ($CDCl_3$): $\delta$ 11.8/12.1/12.9 ($CH_3C_{arom}$), 17.0/20.5 ($CH_3$), 19.1/20.6/30.7/30.8/38.1 ($CH_2$), 48.2 ($CH_2Cl$), 67.0/67.2 (CHCl), 74.4 (C–O), 114.4/114.6 (C=$CH_2$), 117.2/123.0/125.0/126.7/140.7 ($C_{arom}$), 144.1/144.3 (C=$CH_2$), 149.4 ($C_{arom}$), 169.7 (C=O); MS (CI-$NH_3$) $m/z$ 382

($M + NH_4^+$), 365 ($M + H^+$), 364 (M), 288, 247, 207, 165, 136, 121.

**(*E*,*Z*)-2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltrideca-3,11-dienyl)chroman-6-yl Acetate (1hOAc) and 2-(8,12-Dimethyl-4-methylenetridec-11-enyl)-2,5,7,8-tetramethylchroman-6-yl Acetate (1iOAc).** In a flask connected to an argon/vacuum line, CuI (2 mg, 0.01 mmol) was heated (hot-air gun) in a vacuum. After cooling to rt the flask was filled with argon and the preceding **1f**OAc/**1g**OAc mixture (70.3 mg, 0.192 mmol) diluted with THF (0.4 mL) was added with a syringe. With cooling (ice/methanol bath), 0.5 M (in THF) **12a** (0.4 mL, 0.2 mmol) was added dropwise with a syringe followed 15 min later by additional **12a** (same amount). The resulting mixture was further stirred for 2 h at ca. −5 °C before being diluted with ether (5 mL) and saturated $NH_4Cl$ (3 mL). The aqueous layer was extracted with ether (3 × 4 mL) and the pooled organic phases were washed with saturated $NH_4Cl$ (7 mL), brine (2 × 10 mL), and dried ($MgSO_4$). The colored oil left by evaporation of the solvents was purified by column chromatography (hexane/ether) to give a mixture of **1h**OAc and **1i**OAc as a pale-yellow oil (65 mg, 72%). TLC (hexane:ether = 3:1) $R_f = 0.51$; IR (neat, $cm^{-1}$): 2927, 1760, 1644, 1578, 1455, 1367, 1208, 1079, 1010, 923; $^1H$ NMR ($CDCl_3$): $\delta$ 0.88 (d, $J = 6.3$ Hz, 3H, C$H_3$CH), 0.99–2.20 (m, 17.3H), 1.27 (s, 3H, $CH_3C$), 1.61/1.67/1.69 (3 s, 8.5H, $CH_3C$=), 1.99/2.04/2.11 (3 s, 9H, $CH_3C_{arom}$), 2.33 (s, 3H, $COCH_3$), 2.61 (t, $J = 6.6$ Hz, 1H, $CH_2C_{arom}$), 4.66/4.73 (2 s, 0.32H, $CH_2$=C), 5.09–5.19 (m, 1.9H, CH=C); $^{13}C$ NMR ($CDCl_3$): $\delta$ 11.8/12.0/12.9 (*C*$H_3C_{arom}$), 17.6/19.6/20.5 ($CH_3$), 20.6/22.0/22.2 ($CH_2$), 23.3 ($CH_3$), 25.3/25.4/25.6 ($CH_2$), 25.7 ($CH_3$), 31.1/31.9 ($CH_2$), 32.4 (CH), 36.6/36.8/37.1/39.9 ($CH_2$), 74.7/74.8 (C–O), 111.6 (*C*$H_2$=C), 117.2/123.0 ($C_{arom}$), 124.0/124.7/125.0 (*C*H=C), 125.0/126.6 ($C_{arom}$), 130.8/135.5/135.7 (CH=*C*), 140.6/149.3 ($C_{arom}$), 169.6 (C=O); MS (CI-$NH_3$) *m*/*z* 487 ($M + NH_4^+$), 469 ($M + H^+$), 428, 427, 245, 207, 165, 136, 121.

**Protocol for Large-Scale 2/3a Condensation Experiments (Table 1).** All these experiments were similarly realized and only that with dodecane is described. In cases where the reaction was incomplete (xylene experiment) the acetylation step was preceded by a brief purification of the crude condensation product as follows. The brown syrup left by removal of the solvents in a vacuum was diluted with a little $CH_2Cl_2$, and then deposited onto a column of silica gel (800 g). The column was washed with hexane to eliminate residual solvents, then with 95:5 hexane/ether to elute the chromanol mixture, and finally with ether to elute the quinol **2**.

**Dodecane/$CH_2Cl_2$ Experiment; 2-[2-(3,3-Dimethyloxiran-2-yl)ethyl]-2,5,7,8-tetramethylchroman-6-yl Acetate (1jOAc) and 2,5,7,8-Tetramethyl-2-[3-(2-methyloxiran-2-yl)propyl]chroman-6-yl Acetate (1kOAc):** A flask equipped with a condenser connected to an argon/vacuum line was charged with TMHQ **2** (15 g, 98.5 mmol) and CSA (2.3 g, 9.85 mmol). $CH_2Cl_2$ (10 mL) was added and the resulting suspension was warmed to 30–35 °C (hot-water bath) with stirring before being diluted with dodecane (85 mL). The resulting mixture was thoroughly degassed, and then brought to reflux. Linalool **3b** (35.3 mL, 197 mmol) was added progressively with a syringe (30 min), reflux being maintained until **2** was fully reacted (2–4 h). After cooling to rt, ether (450 mL) was added followed by water (300 mL). After 10 min stirring the resulting aqueous layer was extracted with ether (3 × 150 mL) and the pooled organic phases were washed with water (3 × 150 mL), dried ($MgSO_4$), and then transferred into a flask equipped with a distillation head, and a receiver connected to an argon/vacuum line. The solvents were removed to dryness by distillation under reduced pressure (hot-water bath) and the residual colored syrup was further dried in a vacuum (ca. 0.01 Torr) for a few hours. The flask was filled with argon and $Ac_2O$ (75 mL, 825 mmol) was added with cooling (ice bath) followed by pyridine (100 mL, 1.1 mol). The resulting mixture was stirred overnight at rt, and then diluted with ether (300 mL) and 1 M HCl (300 mL). After 10 min stirring the aqueous layer was extracted with ether (3 × 150 mL) and the pooled organic phases were washed with 1 M HCl (300 mL), brine (3 × 150 mL), dried ($MgSO_4$), and then filtered on a column of silica gel (washings with ether). The yellow oil left by evaporation of the solvents was diluted with $CH_2Cl_2$ (600 mL) and the resulting solution was cooled to −5 °C (ice/methanol bath). 77% *m*-CPBA (22.2 g, 99 mmol) was progressively added (30 min) and after 1 h stirring at ca. 0 °C (ice bath) saturated $NaHCO_3$ (400 mL) was added. The cooling bath was removed and the resulting mixture was vigorously stirred for 1 h at rt. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 100 mL) and the pooled organic phases were washed with brine (3 × 150 mL), and dried ($MgSO_4$). The solvents were evaporated in vacuo to afford a pale-yellow residue, which was chromatographed on silica gel (hexane/ether) to give, successively, a 1:1 mixture ($^1H$ NMR) of **9**OAc and **10**OAc (2.61 g, 8%) as a white thick oil, and a 91:9 mixture ($^1H$ NMR, GC) of **1j**OAc and **1k**OAc, respectively, as a colorless oil (20.46 g, 60%). TLC (hexane:$CH_2Cl_2$:EtOAc = 9:9:2) $R_f$ = 0.60; IR (neat, $cm^{-1}$): 2930, 1748, 1455, 1370, 1224, 1082, 920; $^1H$ NMR ($CDCl_3$): $\delta$ 1.23–1.34 (m, 8.5H, $CH_3C$), 1.56–1.91 (m, 6.3H, $CH_2$), 1.98/2.02/2.08 (3 s, 9H, $CH_3C_{arom}$), 2.33 (s, 3H, $COCH_3$), 2.56–2.64 (m, 2.3H, $CH_2$–O/$CH_2C_{arom}$), 2.72–2.77 (m, 0.84H, CH–O); $^{13}C$ NMR ($CDCl_3$): $\delta$ 11.8/12.1/12.9 (*C*$H_3C_{arom}$), 18.5/18.6 ($CH_3$), 20.5 ($CH_2$), 20.6 ($CH_3$), 23.3/23.4 ($CH_2$), 24.9 ($CH_3$), 31.4/36.8 ($CH_2$), 58.3/58.4 (C–O), 60.3 ($CH_2$–O), 64.2/64.3 (CH–O), 74.4 (C–O), 117.2/123.0/125.0/126.8/140.7/149.1 ($C_{arom}$), 169.7 (C=O); MS (CI-$NH_3$) *m*/*z* 364 ($M + NH_4^+$), 347 ($M + H^+$), 346 (M), 329, 304, 232, 207, 165, 136, 121; Found: C, 73.01; H, 8.97%. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73%.

**2-(3-Hydroxy-4-methylpent-4-enyl)-2,5,7,8-tetramethylchroman-6-ol (1l) and 2-[4-(Hydroxymethyl)pent-4-enyl]-2,5,7,8-tetramethylchroman-6-ol (1m).** The preceding epoxide mixture (320 mg, 0.92 mmol) was refluxed in toluene (6 mL) with Al(O-*i*-Pr)$_3$ (756 mg, 3.7 mmol) for 24 h with stirring. After cooling to rt the reaction mixture was poured into a well-stirred mixture of ether (10 mL) and pH 2 tartaric buffer (10 mL). After 10 min stirring, the aqueous layer was extracted with ether (3 × 5 mL) and the pooled organic extracts were washed with tartaric buffer (5 mL), brine (2 × 5 mL), and dried ($MgSO_4$). The residue left by evaporation of the solvents was filtered on a short column of silica gel (hexane:$CH_2Cl_2$:EtOAc = 9:9:2) to give, after evaporation of the solvents, a mixture of **1l** and **1m** as a red oil (267.5 mg, 95%). TLC (hexane:EtOAc = 3:1) $R_f = 0.21$; IR (neat, $cm^{-1}$): 3391, 2929, 1648, 1452, 1377, 1258, 1086, 901; $^1H$ NMR ($CDCl_3$): $\delta$ 1.23 (s, 3H, $CCH_3$), 1.47–1.87 (m, 8.8H), 2.11/2.16 (2 s, 9H, $CH_3C_{arom}$), 2.62 (t, $J = 6.7$ Hz, 2H, $CH_2C_{arom}$), 3.98–4.12 (m, 1.2H, C*H*OH/C$H_2$OH), 4.23 (m, 1H, OH), 4.84/4.88/4.94/5.02 (4 s, 2H, $CH_2$=C); $^{13}C$ NMR ($CDCl_3$): $\delta$ 11.3/11.8/12.2 (*C*$H_3C_{arom}$), 17.5 ($CH_3$), 20.7 ($CH_2$), 23.4/23.5 ($CH_3$), 28.7/28.9/31.5/31.8/35.7 ($CH_2$), 65.9 ($CH_2$OH), 74.2 (C–O), 76.2 (CHOH), 111.2/111.4 (*C*$H_2$=C), 117.3/118.7/121.2/122.6 ($C_{arom}$), 144.7/145.3 ($CH_2$=*C*), 147.2/147.5 ($C_{arom}$); MS (CI-$NH_3$) *m*/*z* 304 (M), 287 (M − OH), 243, 205, 198, 165, 136, 121.

**2-(3-Acetoxy-4-methylpent-4-enyl)-2,5,7,8-tetramethylchroman-6-yl Acetate (1nOAc) and 2-[4-(Acetoxymethyl)pent-4-enyl]-2,5,7,8-tetramethylchroman-6-yl Acetate (1oOAc).** The

preceding **1l**/**1m** mixture (235.7 mg, 0.77 mmol) was diluted with $CH_2Cl_2$ (1.5 mL). With cooling (ice bath), $Ac_2O$ (0.78 mL, 8.2 mmol) and pyridine (1.5 mL) were added sequentially and the resulting mixture was stirred overnight at rt before being poured into a mixture of ether (10 mL) and 1 M HCl (5 mL). The aqueous layer was extracted with ether (4 × 5 mL) and the pooled organic phases were washed with 1 M HCl (2 × 7 mL), brine (2 × 10 mL), and dried ($MgSO_4$). The solvents were evaporated in vacuo and the residual oil was filtered on a short column of silica gel (EtOAc:hexane = 95:5) to give, after evaporation of the solvents, a mixture of the diacetates **1n**OAc and **1o**OAc as a viscous colorless oil (281 mg, 93%). TLC (hexane:EtOAc = 3:1) $R_f$ = 0.52; IR (neat, $cm^{-1}$): 2933, 1760, 1731, 1652, 1455, 1372, 1205, 1047, 901; $^1$H NMR ($CDCl_3$): $\delta$ 1.23 (s, 3H, $CCH_3$), 1.53–1.88 (m, 8.8H), 1.98/2.02/2.09 (3 s, 9H, $CH_3C_{arom}$), 2.04 (s, 3H, $CH_3CO$), 2.32/2.33 (2 s, 3H, $CH_3CO$), 2.60 (t, $J$ = 6.5 Hz, 2H, $CH_2C_{arom}$), 4.90/4.95/5.00/5.04 (4 s, 2H, $CH_2$=C), 5.13–5.22 (m, 1.2H, C*H*OAc/C*H*$_2$OAc); $^{13}$C NMR ($CDCl_3$): $\delta$ 11.8/12.0/12.9 (*C*H$_3$C$_{arom}$), 18.0/20.5/21.1 ($CH_3$), 20.5 ($CH_2$), 22.6 ($CH_3$), 26.4/29.0/31.2/33.4/41.3 ($CH_2$), 66.8 (*C*H$_2$OAc), 74.4 (C–O), 77.3 (*C*HOAc), 112.9/113.0 (*C*H$_2$=C), 117.1/123.0/124.9/126.7/126.8/140.7 ($C_{arom}$), 142.8 ($CH_2$=*C*), 149.1 ($C_{arom}$), 169.6/170.3 (C=O); MS (CI-$NH_3$) $m/z$ 407 ($M + NH_4^+$), 389 ($M + H^+$), 346 (M − Ac), 329, 286, 247, 203, 165, 121.

**2-(3-Pivalyloxy-4-methylpent-4-enyl)-2,5,7,8-tetramethylchroman-6-yl Pivalate (1pOPiv) and 2-[4-(Pivalyloxymethyl)pent-4-enyl]-2,5,7,8-tetramethylchroman-6-yl Pivalate (1qOPiv).** Pyridine (1.75 mL) and pivaloyl chloride (0.61 mL, 5 mmol) were added sequentially to a cooled (ice bath) solution of the preceding **1l**/**1m** mixture (506 mg, 1.66 mmol) in $CH_2Cl_2$ (5 mL). After 24 h stirring at rt, the reaction mixture was diluted with ether (10 mL) and washed with 1 M HCl (5 mL). The aqueous layer was extracted with ether (4 × 5 mL) and the pooled organic extracts were washed with 1 M HCl (2 × 7 mL), brine (2 × 10 mL), and dried ($MgSO_4$). The residue left by evaporation of the solvents was filtered on a short column of silica gel (hexane:EtOAc = 9:1) to give, after evaporation of the solvents, a mixture of the dipivalates **1p**OPiv and **1q**OPiv as a colorless viscous oil (752 mg, 96%). TLC (hexane:EtOAc = 3:1) $R_f$ = 0.68; IR (neat, $cm^{-1}$): 2932, 1755, 1576, 1455, 1368, 1210, 1080, 917, 737; $^1$H NMR ($CDCl_3$): $\delta$ 1.23 (s, 3H, $CCH_3$), 1.27/1.40 (2 s, 18H, $CH_{3Piv}$), 1.53–1.88 (m, 6H, 3 $CH_2$), 1.71 (s, 3H, $CH_3C$=), 1.94/1.97/2.07 (3 s, 9H, $CH_3C_{arom}$), 2.60 (t, $J$ = 6.4 Hz, 2H, $CH_2C_{arom}$), 4.87/4.94 (2 s, 2H, $CH_2$=), 5.08–5.15 (m, 1H, C*H*OPiv); $^{13}$C NMR ($CDCl_3$): $\delta$ 11.8/11.9/12.7 (*C*H$_3$C$_{arom}$), 18.2 (*C*H$_3$C=), 20.5 (*C*H$_2$C$_{arom}$), 23.9 (C*C*H$_3$), 27.1/27.7 ($CH_{3Piv}$), 26.6/31.0/31.4/39.2 (4 $CH_2$), 34.7/35.8 ($C_{Piv}$), 74.3 (*C*CH$_3$), 76.7/76.8 (*C*HOPiv), 112.4 (*C*H$_2$=C), 117.1/122.9/124.9/126.8/140.6 ($C_{arom}$), 143.2 (*C*=CH$_2$), 148.9 ($C_{arom}$), 177.5/177.6 (C=O); MS (CI-$NH_3$) $m/z$ 473 ($M + H^+$), 472 (M), 388, 371, 289, 249, 205, 165, 121.

**General Protocol for Catalyst Screening Experiments (Table 2).** The diester (1 mmol) diluted with THF (or ether) (1.4 mL) was added to the catalyst (0.05 mmol). The resulting mixture was thoroughly degassed, then cooled to −5 °C (ice/methanol bath) before adding a solution of **12a** (1 mmol) in THF (or ether) with a syringe. The reaction was monitored by TLC (hexane:ether = 3:1). After 1 h stirring, an excess of **12a** was added portionwise (0.5 mmol each). In each case the reaction mixture was processed as described above for the Wurtz-coupling experiment with **1f**OAc/**1g**OAc and the residue left by evaporation of the solvents was chromatographed on silica gel (hexane/ether);

**2,6,9,12,16-Pentamethylheptadeca-2,15-dien-9-ol (13):** TLC (hexane:ether = 3:1) $R_f$ = 0.27; $^1$H NMR ($CDCl_3$): $\delta$ 0.88 (d, $J$ = 6.3 Hz, 6H, 2 C*H*$_3$CH), 1.14 (s, 3H, C*H*$_3$COH), 1.18–1.50 (m, 14H, 6 $CH_2$, 2 CH), 1.60/1.68 (2 s, 12H, 4 $CH_3C$=), 1.88–2.06 (m, 4H, 2 C*H*$_2$CH=), 5.09 (m, 2H, 2 CH=C); $^{13}$C NMR ($CDCl_3$): $\delta$ 17.6/19.6/25.7 (6 $CH_3$), 27.0/27.1 (*C*H$_3$COH), 25.5/30.8 (4 $CH_2$), 32.9 (2 CH), 37.0/37.1/39.0/39.1 (4 $CH_2$), 72.9 (COH), 124.9 (2 *C*H=C), 131.1 (2 *C*=CH);

**2-(3-Hydroxy-4-methylpent-4-enyl)-2,5,7,8-tetramethylchroman-6-yl Acetate (1lOAc):** TLC (hexane:ether = 3:1) $R_f$ = 0.05; $^1$H NMR ($CDCl_3$): $\delta$ 1.23 (s, 3H), 1.50–1.88 (m, 6H), 1.71 (2 s, 3H), 1.98/2.02/2.09 (3 s, 9H), 2.33 (s, 3H), 2.61 (t, $J$ = 6.6 Hz, 2H), 4.03–4.08 (m, 1H), 4.31 (s, 1H, OH), 4.84/4.94 (2 m, 2H); $^{13}$C NMR ($CDCl_3$): $\delta$ 11.8/12.0/12.9 ($CH_3$), 17.4/17.5 ($CH_3$), 20.5 ($CH_3$), 20.6 ($CH_2$), 24.2 ($CH_3$), 28.4/28.5 ($CH_2$), 31.5/31.6 ($CH_2$), 35.6/35.8 ($CH_2$), 74.3 (C), 77.3 (CH–O), 111.2/111.4 (C=*C*H$_2$), 117.1/117.2 ($C_{arom}$), 123.0 ($C_{arom}$), 124.9 ($C_{arom}$), 126.7/126.8 ($C_{arom}$), 140.7 ($C_{arom}$), 147.2/147.5 (C), 149.1 ($C_{arom}$), 169.6/170.3 (C).

**6-Chloro-3,7-dimethylocta-1,7-dien-3-ol (3c).** Linalool **3b** (500 mg, 3.24 mmol) was chlorinated with $Ca(OCl)_2$ (363.6 mg, 1.65 mmol) as described above for the **1b**OAc/**1c**OAc chlorination.[21] The oily residue left by evaporation of the solvents was chromatographed on silica gel (hexane/ether) to give **3c** as a yellow oil (360.4 mg, 59%). TLC (hexane:ether = 2:1) $R_f$ = 0.66; IR (neat, $cm^{-1}$): 3419, 2970, 1645, 1452, 1375, 1113, 996, 920; $^1$H NMR ($CDCl_3$) $\delta$ 1.28/1.29 (2 s, 3H, C*H*$_3$COH), 1.40–1.96 (m, 4H, $CH_2$), 1.78 (s, 3H, C*H*$_3$C=CH$_2$), 4.35 (t, $J$ = 7.3 Hz, 1H, CHCl), 4.91 (m, 2H, $CH_2$=C), 5.07 (dd, $J$ = 10.7, 1.2 Hz, 1H, CH*H*=CH), 5.21 (dd, $J$ = 17.3, 1.2 Hz, 1H, C*H*H=CH), 5.87 (dd, $J$ = 17.3, 10.7 Hz, 1H, CH$_2$=C*H*); $^{13}$C NMR ($CDCl_3$): $\delta$ 16.9/17.0 (*C*H$_3$C=CH$_2$), 28.0/28.2 (*C*H$_3$COH), 31.0/31.1 ($CH_2$), 39.1/39.2 ($CH_2$), 67.0/67.1 (CHCl), 72.7/72.8 (COH), 112.1/112.2 (*C*H$_2$=CH), 114.1/114.2 (*C*H$_2$=C), 144.0/144.3 (*C*=CH$_2$), 144.5/144.6 (*C*H=CH$_2$); MS (CI-$NH_3$) $m/z$ 137 (M − Cl), 130, 107, 90, 70, 61.

**3,7,11,15-Tetramethylhexadeca-1,6,14-trien-3-ol (3d).** Chlorolinalool **3c** (943 mg, 5 mmol) was reacted with **12a** (11 mmol) in THF with added CuI (0.25 mmol) as described above. The product isolated after hydrolysis was purified by column chromatography (hexane/ether) to give, successively, the dehydroisophytol **3d** as a colorless oil (310 mg, 21%), and unreacted **3c** (530 mg, 56%). TLC (hexane:ether = 3:1) $R_f$ = 0.29; IR (neat, $cm^{-1}$): 3401, 2970, 1644, 1452, 1376, 1113, 995, 920; $^1$H NMR ($CDCl_3$): $\delta$ 0.85/0.87 (2 d, $J$ = 6.4 Hz, 3H, C*H*$_3$CH), 1.06–1.48 (m, 9H, 4 $CH_2$/C*H*CH$_3$), 1.28 (s, 3H, C*H*$_3$COH), 1.58/1.66 (2 s, 3H, $CH_3C$=), 1.60/1.68 (2 s, 6H, 2 $CH_3C$=), 1.88–2.08 (m, 6H, 3 $CH_2$), 5.12 (m, 2H, 2 C=CH), 5.06 (2 d, $J$ = 10.8 Hz, 1H, C*H*H=CH), 5.22 (2 d, $J$ = 17.6 Hz, 1H, CH*H*=CH), 5.86–5.98 (2 dd, $J$ = 17.5, 10.8 Hz, 1H, C*H*=CH$_2$); $^{13}$C NMR ($CDCl_3$): $\delta$ 15.9/17.6/19.5/25.5 ($CH_3$), 22.5/22.7 ($CH_2$), 27.4 (*C*H$_3$COH), 25.3/25.4 (2 $CH_2$), 32.3 (*C*HCH$_3$), 36.5/36.8/36.9/37.1/39.9/42.1/42.3 (4 $CH_2$), 73.5 (COH), 111.6/111.7 (*C*H$_2$=CH), 123.9/124.6/125.0/125.1 (2 C=*C*H), 130.9 (*C*=CH), 136.0/136.1 (*C*=CH), 145.0 (*C*H=CH$_2$); MS (CI-$NH_3$) $m/z$ 293 ($M + H^+$), 275 (M − OH), 177, 163, 149, 135, 121, 109, 93, 80, 69, 55.

**(*E*,*Z*)-2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltrideca-3,11-dienyl)chroman-6-ol (1h).** A mixture of TMHQ **2** (50 mg, 0.33 mmol) and CSA (8 mg, 0.03 mmol) was diluted with xylene (0.8 mL) in a flask equipped with a condenser connected to an argon/vacuum line. The resulting mixture was thoroughly degassed and the flask was immersed in a thermostated bath (165–180 °C). After 15 min stirring, the dehydroisophytol **3d** (144.4 mg, 0.49 mmol) diluted with xylene (0.4 mL) was added with a syringe

and the heating was pursued for 5 h. The reaction mixture was processed as above to give a colored residue, which was chromatographed on silica gel (hexane/EtOAc) to give, successively, **1h** as a red viscous oil (70.3 mg, 50%), and TMHQ **2** (15 mg, 29%). TLC (hexane:ether = 3:1) $R_f = 0.78$; IR (neat, $cm^{-1}$): 3474, 2927, 1673, 1455, 1279, 1082; $^1$H NMR ($CDCl_3$): $\delta$ 0.86–1.85 (m, 17H), 1.60/1.62/1.70 (3 s, 9H, $CH_3C$=), 1.80–2.12 (m, 6H, $CH_2$), 2.12/2.13/2.17 (3 s, 9H, $CH_3C_{arom}$), 2.59 (m, 2H, $CH_2C_{arom}$), 4.20 (s, 1H, OH), 5.09–5.16 (m, 2H, C=CH); $^{13}$C NMR ($CDCl_3$): $\delta$ 11.2/11.8/12.2 ($CH_3C_{arom}$), 15.8/17.6/19.5/23.7/25.6 ($CH_3$), 20.7/22.0/25.4/25.5/31.5 ($CH_2$), 33.1/33.3 ($CHCH_3$), 37.0/39.0/39.5/39.9 ($CH_2$), 74.3/74.4 (C–O), 117.2/118.4/121.0/122.5 ($C_{arom}$), 124.1/124.4/125.0 (C=CH), 134.5/134.7 (C=CH), 145.5/146.5.

**(All-*rac*)-α-Tocopherol Acetate (1aOAc); from 1hOAc/1iOAc.** A **1h**OAc/**1i**OAc mixture (162 mg, 0.346 mmol) was diluted with EtOAc (2 mL) and 5% Pd/C (16 mg) was added. The resulting mixture was stirred in a $H_2$ atmosphere (7 h), then filtered on a column of Celite (washings with ether). The residue left by evaporation of the solvents was chromatographed on silica gel (hexane/$CH_2Cl_2$) to give, after removal of the solvents, a white thick oil (162 mg, 99%) identified as **1a**OAc (NMR, GC-MS; purity ca. 94%).

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## References

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1 a) T. M. Shevlin, *Biochemistry*, John Wiley, New York, **1982**, p. 970. The only pathology clearly associated to shortage in vitamin E is a syndrome designated as AVED, for *A*taxia and *V*itamin *E D*eficiency: people suffering from this genetic disorder cannot walk: b) L. Cavalier, K. Ouahchi, H. J. Kayden, S. Donato, L. Reutenauer, J.-L. Mandel, M. Koenig, *Am. J. Hum. Genet.* **1998**, *62*, 301, and cited references.

2 a) P. M. Bramley, I. Elmadfa, A. Kafatos, F. J. Kelly, Y. Manios, H. E. Roxborough, W. Schuch, P. J. A. Sheehy, K.-H. Wagner, *J. Sci. Food Agric.* **2000**, *80*, 913. b) A. Azzi, *Eur. J. Nutr.* **2004**, *43*, i18. c) R. Brigelius-Flohé, F. J. Kelly, J. T. Salonen, J. Neuzil, J.-M. Zingg, A. Azzi, *Am. J. Clin. Nutr.* **2002**, *76*, 703.

3 A. Hosomi, M. Arita, Y. Sato, C. Kiyose, T. Ueda, O. Igarashi, H. Arai, K. Inoue, *FEBS Lett.* **1997**, *409*, 105; S. Zimmer, A. Stocker, M. N. Sarbolouki, S. E. Spycher, J. Sassoon, A. Azzi, *J. Biol. Chem.* **2000**, *275*, 25672; M. G. Traber, H. Arai, *Annu. Rev. Nutr.* **1999**, *19*, 343; H. Lei, J. Atkinson, *J. Org. Chem.* **2000**, *65*, 2560; G. W. Burton, M. G. Traber, R. V. Acuff, D. N. Walter, H. Jayden, L. Hughes, K. U. Ingold, *Am. J. Clin. Nutr.* **1998**, *67*, 669; S. Morley, C. Panagabko, D. Shineman, B. Mani, A. Stocker, J. Atkinson, D. Manor, *Biochemistry* **2004**, *43*, 4143.

4 a) V. W. Bowry, K. U. Ingold, *Acc. Chem. Res.* **1999**, *32*, 27. b) G. W. Burton, K. U. Ingold, *Acc. Chem. Res.* **1986**, *19*, 194. c) A. Kamal-Eldin, L.-Å. Appelqvist, *Lipids* **1996**, *31*, 671. d) J. F. Keaney, Jr., D. I. Simon, J. E. Freedman, *FASEB J.* **1999**, *13*, 965. e) W. A. Pryor, *Free Radic. Biol. Med.* **2000**, *28*, 141. f) M. J. Burkitt, *Arch. Biochem. Biophys.* **2001**, *394*, 117. g) E. Niki, N. Noguchi, *Acc. Chem. Res.* **2004**, *37*, 45. h) P. Franchi, M. Lucarini, G. F. Pedulli, L. Valgimigli, B. Lunelli, *J. Am. Chem. Soc.* **1999**, *121*, 507. i) T. Rosenau, A. Potthast, T. Elder, T. Lange, H. Sixta, P. Kosma, *J. Org. Chem.* **2002**, *67*, 3607. j) W. Gregor, G. Grabner, C. Adelwöhrer, T. Rosenau, L. Gille, *J. Org. Chem.* **2005**, *70*, 3472. k) G. Gramlich, J. Zhang, W. M. Nau, *J. Am. Chem. Soc.* **2004**, *126*, 5482.

5 K.-K. Chan, A. C. Specian, Jr., G. Saucy, *J. Org. Chem.* **1978**, *43*, 3435; C. H. Heathcock, E. T. Jarvi, *Tetrahedron Lett.* **1982**, *23*, 2825; G. Bérubé, P. Deslongchamps, *Bull. Soc. Chim. Fr.* **1987**, 103; S. Takano, T. Sugihara, K. Ogasawara, *Synlett* **1990**, 451; S. Takano, T. Yoshimitsu, *Synlett* **1994**, 119; C. Y. Chen, S. Nagumo, *Chem. Pharm. Bull.* **1996**, *44*, 2153; R. Chênevert, M. Desjardins, *J. Org. Chem.* **1996**, *61*, 1219; L. F. Tietze, J. Görlitzer, *Synlett* **1996**, 1041; L. F. Tietze, J. Görlitzer, *Synlett* **1997**, 1049; L. F. Tietze, J. Görlitzer, *Synthesis* **1997**, 877; T. A. Ayers, R. A. Schnettler, G. Marciniak, K. T. Stewart, R. K. Mishra, D. J. Krysan, B. R. Bernas, P. Bhardwaj, T. L. Fevig, *Tetrahedron: Asymmetry* **1997**, *8*, 45; B. M. Trost, N. Asakawa, *Synthesis* **1999**, 1491; S. Huo, J.-C. Shi, E. Negishi, *Angew. Chem., Int. Ed.* **2002**, *41*, 2141; F. M. Dean, D. A. Matkin, M. O. A. Orabi, *J. Chem. Soc., Perkin Trans. 1* **1981**, 1437; B. M. Trost, H. C. Shen, L. Dong, J.-P. Surivet, C. Sylvain, *J. Am. Chem. Soc.* **2004**, *126*, 11966; L. F. Tietze, K. M. Sommer, J. Zinngrebe, F. Stecker, *Angew. Chem., Int. Ed.* **2004**, *44*, 257; L. F. Tietze, F. Stecker, J. Zinngrebe, K. M. Sommer, *Chem.—Eur. J.* **2006**, *12*, 8770; For synthesis of all α-tocopherol stereomers, see: N. Cohen, C. G. Scott, C. Neukom, R. J. Lopresti, G. Weber, G. Saucy, *Helv. Chim. Acta* **1981**, *64*, 1158. The vitamin E activity (measured on animal models) of these stereomers varies from 0.21 to 1 international unit (IU), 1 IU being defined as the vitamin E activity of 1 mg of natural α-tocopherol acetate (see Ref. 2a).

6 P. Karrer, H. Fritzsche, B. H. Ringier, H. Salomon, *Helv. Chim. Acta* **1938**, *21*, 820; L. I. Smith, H. E. Ungnade, J. R. Stevens, C. C. Christman, *J. Am. Chem. Soc.* **1939**, *61*, 2615; P. Karrer, O. Isler, U.S. Patent 2, 411, 967, **1946**; P. Karrer, O. Isler, *Chem. Abstr.* **1947**, *41*, 8102; P. Karrer, H. Fritzsche, B. H. Ringier, H. Salomon, *Helv. Chim. Acta* **1938**, *21*, 520; P. Karrer, H. Fritzsche, B. H. Ringier, H. Salomon, *Nature* **1938**, *141*, 1057; L. I. Smith, H. E. Ungnade, W. W. Pritchard, *Science* **1938**, *88*, 37.

7 a) R. M. Parkhurst, W. A. Skinner, *Chromanols and Tocopherols* in *The Chemistry of Heterocyclic Compounds*, ed. by G. P. Ellis, New York, Chichester, Brisbane, Toronto, **1981**, Vol. 36, p. 59. b) T. Netscher, *Synthesis and Production of Vitamins E*; *Lipids Synthesis and Manufacture*, Sheffield Academic Press, Sheffield, **1999,** p. 250. c) *Ullmann's Encyclopedia of Industrial Chemistry*, VCH, Weinheim, **1997**, Vol. A28. d) C. Mercier, P. Chabardes, *Pure Appl. Chem.* **1994**, *66*, 1509. e) W. Bonrath, T. Netscher, *Appl. Catal., A* **2005**, *280*, 55. f) O. Isler, G. Brubacher, S. Ghisla, B. Kräutler, *Vitamins*, Thieme, Stuttgart, **1988**, Vol. 2, p. 126. g) P. A. Wehrli, R. I. Fryer, W. Metlesics, *J. Org. Chem.* **1971**, *36*, 2910. h) L. I. Smith, *Chem. Rev.* **1940**, *27*, 287. i) B. Stalla-Bourdillon, *Ind. Chim. Belg.* **1970**, *35*, 13.

8 F. M. D. Ismail, M. J. Hilton, M. Stefinovicic, *Tetrahedron Lett.* **1992**, *33*, 3795; W. Bonrath, A. Haas, E. Hoppmann, T. Netscher, H. Pauling, F. Schager, A. Wilderman, *Adv. Synth. Catal.*

**2002**, *344*, 37; M. Matsui, N. Karibe, K. Hayashi, H. Yamamoto, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 3569; T. Netscher, *Chimia* **1996**, *50*, 563; M. Schneider, K. Zimmermann, F. Aquino, W. Bonrath, *Appl. Catal., A* **2001**, *220*, 51; F. Schager, W. Bonrath, *J. Catal.* **1999**, *182*, 282; V. N. Odinokov, A. Y. Spivak, G. A. Emelyanova, M. I. Malliabaeva, O. V. Nazarova, U. M. Dzhemilev, *ARKIVOC* **2003**, Part xiii, 101; M. Matsui, H. Yamamoto, *Bull. Chem. Soc. Jpn.* **1996**, *69*, 137; S. Wang, W. Bonrath, H. Pauling, F. Kienzle, *J. Supercrit. Fluids* **2000**, *17*, 135; A. Hasegawa, K. Ishihara, H. Yamamoto, *Angew. Chem., Int. Ed.* **2003**, *42*, 5731; V. N. Odinokov, A. Y. Spivak, G. A. Emelyanova, E. V. Syutkina, Z. I. Ushakova, L. M. Khalilov, *Russ. Chem. Bull., Int. Ed.* **2000**, *49*, 1620; Y. Kokubo, A. Hasegawa, S. Kuwata, K. Ishihara, H. Yamamoto, T. Ikariya, *Adv. Synth. Catal.* **2005**, *347*, 220; W. Bonrath, C. Dittel, L. Giraudi, T. Netscher, T. Pabst, *Catal. Today* **2007**, *121*, 65.

9 H. Sun, K. Harms, J. Sundermeyer, *J. Am. Chem. Soc.* **2004**, *126*, 9550; R. A. Sheldon, J. K. Kochi, *Metal-Catalyzed Oxidation of Organic Compounds*, Academic Press, New York, **1981**, p. 373; A. Corma, H. García, *Chem. Rev.* **2002**, *102*, 3837; P. A. Wehrli, R. I. Fryer, F. Pigott, G. Silverman, *J. Org. Chem.* **1972**, *37*, 2340; N. Iwasawa, K. Narasaka, *Top. Curr. Chem.* **2000**, *207*, 69.

10 A. V. Ermolaev, A. N. Malkin, N. S. Tyukavkina, R. P. Evstineeva, I. K. Sarycheva, E. J. Bulychev, *Khim. Farmat. Zhur.* **1980**, *14*, 63; A. V. Ermolaev, A. N. Malkin, N. S. Tyukavkina, R. P. Evstineeva, I. K. Sarycheva, E. J. Bulychev, *Chem. Abstr.* **1980**, *93*, 204190; U. Svanholm, V. D. Parker, *J. Chem. Soc., Chem. Commun.* **1972**, 645; U. Svanholm, V. D. Parker, *J. Chem. Soc., Perkin Trans. 2* **1974**, 169; D. McHale, S. Marcinkiewicz, J. Green, *J. Chem. Soc. C* **1966**, 1427; For related examples, see: J.-Y. Goujon, A. Duval, B. Kirschleger, *J. Chem. Soc., Perkin Trans. 1* **2002**, 496; C. J. Davis, C. J. Moody, *Synlett* **2002**, 1874; N. Cairns, L. M. Harwood, D. P. Astles, *J. Chem. Soc., Chem. Commun.* **1986**, 750.

11 P. Schudel, H. Mayer, J. Metzger, R. Rüegg, O. Isler, *Helv. Chim. Acta* **1963**, *46*, 2517.

12 D. J. McHale, J. Green, *J. Chem. Soc.* **1965**, 5060; K. A. Parker, T. L. Mindt, *Org. Lett.* **2001**, *3*, 3875; V. N. Odinokov, A. Y. Spivak, G. A. Emelyanova, B. I. Kutepov, *Russ. Chem. Bull., Int. Ed.* **2002**, *51*, 526; E. K. Aleksandrova, L. I. Bunina-Krivorukova, K. V. Balyan, *Zh. Org. Khim.* **1980**, *16*, 459; S. Nakamura, K. Ishihara, H. Yamamoto, *J. Am. Chem. Soc.* **2000**, *122*, 8131; This oxidation is of key importance in the ubiquinone chemistry, see: H. Mayer, O. Isler, *Methods in Enzymology, Vitamins and Coenzymes,* Part C, Academic Press, New York, London, **1971**, Vol. 18, p. 228; B. O. Linn, C. H. Shunk, E. L. Wong, K. Folkers, *J. Am. Chem. Soc.* **1963**, *85*, 239.

13 J. Paust, *Pure Appl. Chem.* **1991**, *63*, 45.

14 J.-E. Ancel, H. Bienaymé, P. Meilland, Eur. Pat. Appl. EP 400, 998, **1996**; J.-E. Ancel, H. Bienaymé, P. Meilland, *Chem. Abstr.* **1996**, *126*, 75101; H. Bienaymé, J.-E. Ancel, P. Meilland, J.-P. Simonato, *Tetrahedron Lett.* **2000**, *41*, 3339; For a related approach, see: M. Mulhauser, P. Chabardès, Eur. Pat. Appl. EP 17739, **1986**; M. Mulhauser, P. Chabardès, *Chem. Abstr.* **1986**, *105*, 227086.

15 For a review on cannabinoids, see: S. Morimoto, F. Taura, Y. Shoyama, *Curr. Top. Phytochem.* **1999**, *2*, 103.

16 a) J. Green, D. McHale, G. B. Patent 949,715, **1964**; J. Green, D. McHale, *Chem. Abstr.* **1964**, *60*, 75329. b) G. D. Daves, Jr., H. W. Moore, D. E. Schwab, R. K. Olsen, J. J. Wilczynski, K. Folkers, *J. Org. Chem.* **1967**, *32*, 1414. c) T. Ichikawa, T. Kato, *Bull. Chem. Soc. Jpn.* **1968**, *41*, 1224. d) Y. Ichikawa, T. Yamaji, Y. Tanaka, Jpn. Kokai Tokkyo Koho 51016672, **1976**; Y. Ichikawa, T. Yamaji, Y. Tanaka, *Chem. Abstr.* **1976**, *85*, 33227. e) R. Mechoulam, B. Yagen, *Tetrahedron Lett.* **1969**, *10*, 5349. f) S. Yamada, T. Katagiri, J. Tanaka, *J. Synth. Org. Chem., Jpn.* **1971**, *29*, 81; S. Yamada, T. Katagiri, J. Tanaka, *Chem. Abstr.* **1971**, *75*, 6119. g) H. Sugihara, M. Sasaki, Y. Kawamatsu, H. Miromoto, *Justus Liebigs Ann. Chem.* **1972**, *763*, 121. h) G. Manners, L. Jurd, K. Stevens, *Tetrahedron* **1972**, *28*, 2949, and cited references. i) A. A. Svishchuk, E. D. Basalkevich, *Fiziol. Aktiv. Veshchestva Respub. Mezhvedom. Sb.* **1971**, 256; A. A. Svishchuk, E. D. Basalkevich, *Chem. Abstr.* **1972**, *77*, 88217. j) M. H. Stern, T. H. Regan, D. P. Maier, C. D. Robeson, J. G. Thweatt, *J. Org. Chem.* **1973**, *38*, 1264. k) L. L. Crombie, W. M. L. Crombie, R. Forbes, A. Whitaker, *J. Chem. Res., Synop.* **1977**, 114. l) M. Teruo, S. Shinkichi, N. Tado, I. Masaaki, Jpn. Kokai Tokkyo Koho 60075475, **1985**; M. Teruo, S. Shinkichi, N. Tado, I. Masaaki, *Chem. Abstr.* **1985**, *103*, 141820. m) S. Ohta, A. Nozaki, N. Ohashi, M. Matsukawa, M. Okamoto, *Chem. Pharm. Bull.* **1988**, *36*, 2239. n) B. Liu, L. Gu, J. Zhang, *Rec. Trav. Chim. Pays-Bas* **1991**, 104. o) C.-N. Yook, S.-H. Baek, S.-D. Cho, N.-Y. Park, *Bull. Korean Chem. Soc.* **1992**, *13*, 457. p) S.-H. Baek, C.-N. Yook, D. S. Han, *Bull. Korean Chem. Soc.* **1995**, *16*, 293. q) M. Matsui, T. Yamamoto, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 2663. r) M. Matsui, T. Yamamoto, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 2657. s) M. Matsui, T. Yamamoto, Jpn. Kokai Tokkyo Koho 08151376, **1996**; M. Matsui, T. Yamamoto, *Chem. Abstr.* **1996**, *125*, 168389. t) V. N. Odinokov, A. Y. Spivak, G. A. Emelyanova, B. I. Kutepov, L. M. Khalilov, *Russ. Chem. Bull., Int. Ed.* **2001**, *50*, 2227. u) R. A. Miller, H. C. S. Wood, *J. Chem. Soc. C* **1968**, 1837.

17 P. Karrer, H. Rentschler, *Helv. Chim. Acta* **1944**, *27*, 1297; D. McHale, J. Green, S. Marcinkiewicz, J. Feeney, L. H. Sutcliffe, *J. Chem. Soc.* **1963**, 784.

18 B. B. Snider, in *Comprehensive Organic Synthesis*, ed. by I. Fleming, Pergamon, Oxford, **1991**, Vol. 2, p. 527; B. B. Snider, *Acc. Chem. Res.* **1980**, *13*, 426.

19 K. Hamamura, N. Hirose, K. Shizumasa, Jpn. Kokai Tokkyo Koho 01249765, **1989**; K. Hamamura, N. Hirose, K. Shizumasa, *Chem. Abstr.* **1990**, *112*, 179520; T. Miyakoshi, K. Onomura, K. Takayama, M. Nagahama, *Yukagaku* **1995**, 316; T. Miyakoshi, K. Onomura, K. Takayama, M. Nagahama, *Chem. Abstr.* **1995**, *122*, 314876; T. Takahashi, N. Hirata, Y. Miyamoto, Jpn. Kokai Tokkyo Koho 11014767, **1998**; T. Takahashi, N. Hirata, Y. Miyamoto, *Chem. Abstr.* **1998**, *126*, 28107.

20 Chlorination of pentamethyl-6-hydroxychromane has been claimed to afford the corresponding 5-chloromethylchromanol: K. Murase, J. Matsumoto, K. Tamazawa, K. Takahashi, M. Murakami, *Yamanouchi Seiyaku Kenkyu Hokoku* **1974**, 66; K. Murase, J. Matsumoto, K. Tamazawa, K. Takahashi, M. Murakami, *Chem. Abstr.* **1976**, *84*, 30811.

21 S. G. Hegde, M. K. Vogel, J. Saddler, T. Hrinyo, N. Rockwell, R. Haynes, M. Olivier, J. Wolinsky, *Tetrahedron Lett.* **1980**, *21*, 441.

22 a) S. Terao, M. Shiraishi, K. Kato, *Synthesis* **1979**, 467. b) D. Eren, E. Keinan, *J. Am. Chem. Soc.* **1988**, *110*, 4356.

23 M. H. Abraham, J. Le, *J. Pharm. Sci.* **1999**, *88*, 868; F. S. Chernoglazova, Y. N. Simulin, *Zh. Fiz. Khim.* **1976**, *50*, 809; F. S. Chernoglazova, Y. N. Simulin, *Chem. Abstr.* **1976**, *84*, 185519.

24 A. Stocker, G. Derungs, W.-D. Woggon, T. Netscher, A. Rüttimann, R. K. Müller, H. Schneider, L. J. Todaro, *Helv. Chim. Acta* **1994**, *77*, 1721.

25 C. Grütter, E. Alonso, A. Chougnet, W.-D. Woggon,

*Angew. Chem., Int. Ed.* **2006**, *45*, 1126.

26 Phenolic compounds coordinated to $SnCl_4$ indeed catalyse the cyclization of parent geranyl derivatives: H. Ishibashi, K. Ishihara, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 11122; K. Kumazawa, K. Ishihara, H. Yamamoto, *Org. Lett.* **2004**, *6*, 2551; K. Ishihara, S. Nakamura, H. Yamamoto, *J. Am. Chem. Soc.* **1999**, *121*, 4906; H. Nakamura, K. Ishihara, H. Yamamoto, *J. Org. Chem.* **2002**, *67*, 5124; H. Ishibashi, K. Ishihara, H. Yamamoto, *Chem. Rec.* **2002**, *2*, 177.

27 E. E. Van Tamelen, *Acc. Chem. Res.* **1968**, *1*, 111; E. E. Van Tamelen, *Acc. Chem. Res.* **1975**, *8*, 152; W. S. Johnson, *Angew. Chem.* **1976**, *88*, 33.

28 O. Kronja, M. Orlovic, K. Humski, S. Borcic, *J. Am. Chem. Soc.* **1991**, *113*, 2306.

29 Interestingly, the cationic polycyclization of a epoxypolyene on a zeolite has been shown to proceed with good selectivity, which has been explained by stabilisation of the corresponding transition state by negatively-charged oxygen atoms at the surface of the used aluminosilicate: S. E. Sen, Y. Z. Zhang, S. M. Smith, J. C. Huffman, *J. Org. Chem.* **1998**, *63*, 4459. This might provide a rationale for the enhanced formation of **9** in the experiment with Tseokar-10®, as compared with the experiment with CSA.

30 a) *Organometallics in Synthesis*, ed. by M. Schlosser, Wiley, Chichester, **1994**. b) G. H. Posner, *Org. React.* **1975**, *22*, 253. c) B. H. Lipshutz, S. Sengupta, *Org. React.* **1992**, *41*, 135. d) R. M. Magid, *Tetrahedron* **1980**, *36*, 1901. e) N. Krause, A. Gerold, *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 186.

31 a) C. C. Tseng, S. D. Paisley, H. L. Goering, *J. Org. Chem.* **1986**, *51*, 2884, and previous papers in this series. b) E. S. M. Persson, M. van Klaveren, D. M. Grove, J.-E. Bäckvall, G. van Koten, *Chem.—Eur. J.* **1995**, *1*, 351. c) G. J. Meuzelaar, A. S. E. Karlström, M. van Klaveren, E. S. M. Persson, A. del Villar, G. van Koten, J.-E. Bäckvall, *Tetrahedron* **2000**, *56*, 2895. d) J.-E. Bäckvall, M. Sellén, B. Grant, *J. Am. Chem. Soc.* **1990**, *112*, 6615. e) K. Tissot-Croset, D. Polet, S. Gille, C. Hawner, A. Alexakis, *Synthesis* **2004**, 2586. f) T. Tsuji, H. Yorimitsu, K. Oshima, *Angew. Chem., Int. Ed.* **2002**, *41*, 4137. g) A. Fürstner, M. Méndez, *Angew. Chem., Int. Ed.* **2003**, *42*, 5355.

32 M. Tamura, J. K. Kochi, *Synthesis* **1971**, 303; M. Schlosser, H. Bossert, *Tetrahedron* **1991**, *47*, 6287.

33 H. L. Goering, S. S. Kantner, *J. Org. Chem.* **1984**, *49*, 422.

34 G. D. Allred, L. S. Liebeskind, *J. Am. Chem. Soc.* **1996**, *118*, 2748.

35 D. M. Knotter, H. L. van Maanen, D. M. Grove, A. L. Spek, G. van Koten, *Inorg. Chem.* **1991**, *30*, 3309.

36 R. G. Salomon, J. K. Kochi, *J. Chem. Soc., Chem. Commun.* **1972**, 559; R. G. Salomon, J. K. Kochi, *J. Am. Chem. Soc.* **1973**, *95*, 1889.

37 J.-E. Ancel, K. Couture, Eur. Pat. Appl. EP 1179520, **2002**; J.-E. Ancel, K. Couture, *Chem. Abstr.* **2002**, *136*, 167528.

38 G. Stork, M. Gregson, P. A. Grieco, *Tetrahedron Lett.* **1969**, *10*, 1391.

39 B. E. Love, E. G. Jones, *J. Org. Chem.* **1999**, *64*, 3755.