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Novel tocopherol derivatives. Part 32: On the bromination of pyrano[3,2-*f*] chromenes related to γ-tocopherol

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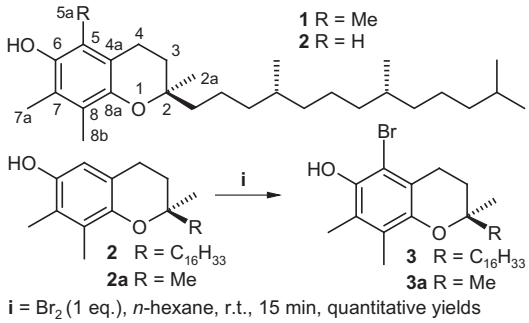
ABSTRACT

While bromination of γ-tocopherol (**2**) with elemental bromine affords 5-bromo-γ-tocopherol quantitatively (**3**), the analogous reaction of its truncated model compound, 2,2,7,8-tetramethylchromanol (**2a**) is known to be accompanied by side reactions and to produce hitherto unknown byproducts. These compounds originate from pyrano[3,2-*f*]chromene (**6**), a byproduct in the synthesis of model compound **2a**, which affords bromochromene **7** as the major product. The reaction mechanism was shown to proceed via chromene **8** and its 1,2-dibromo addition compound **9**, which eliminates HBr in an E1 process to finally afford **7**. Analytical data including crystal structures of both **6** and **7** are reported.

1. Introduction

The compound mixture commonly denoted as vitamin E is actually a blend of tocopherols (saturated side chain) and tocotrienols (unsaturated side chain), which differ in the number and position of methyl groups at the aromatic ring.[1] The main component of vitamin E, α-tocopherol (**1**), has no free aromatic position, whereas γ-tocopherol (**2**), the second main constituent, lacks the 5a-methyl group and offers the 5-position for facile electrophilic substitution at the aromatic core. While α-tocopherol has been intensively studied already due to its antioxidant action, its non-antioxidant action modes currently receive much attention.[2] γ-Tocopherol has been investigated as electrophilic trap, being active in vivo for instance against NO-derived or halogen-derived species.[3]

We have recently provided detailed accounts of the bromination of tocopherols under different conditions, taking into account apolar, polar, and protic conditions[4] as well as different pH values of the reaction medium, which correspond to different halogenating species and to different reaction pathways.[5] Also the bromination behavior of dimeric species derived from α-tocopherol and γ-tocopherol and their detailed reaction mechanisms were studied.[6] The bromination of γ-tocopherol under aprotic conditions proceeds readily and affords a single product, 5-bromo-γ-tocopherol (**3**) (see Scheme 1), which has been described recently, including the crystal structure of its truncated model compound 5-bromo-2,2,7,8-tetramethylchroman-6-ol (**3a**), which carries a methyl group in lieu of the tocopherols' isoprenoid side chain.[7]



Scheme 1. Bromination of γ-tocopherol (**2**) and its truncated model compound 2,2,7,8-tetramethylchroman-6-ol (**2a**).

2. Results and discussion

The truncated model compound of γ-tocopherol, 2,2,7,8-tetramethylchroman-6-ol (**2a**) is commonly used in studies on the reaction behavior of the γ-congener. While γ-tocopherol is commercially available its model compound has to be synthesized from 2,3-dimethylhydroquinone (**4**) by reaction with 2-methylbut-3-en-1-ol (1,1-dimethylallyl alcohol, **5**), see Scheme 2. Double alkylation of the hydroquinone to pyrano[3,2-*f*]chromene **6** cannot be avoided, not even with strictly substoichiometric amounts of the coreactants (0.1 or 0.2 equiv). The best yields of **2a** (41%) were obtained when 0.66 equiv of the alcohol were used. Non-reacted

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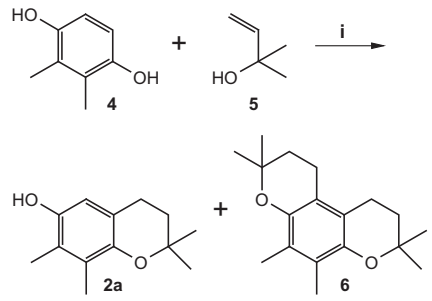
hydroquinone (47%) and bis-alkylated byproduct (**6**, 12%) are separated after the reaction.[8] Using higher stoichiometric amounts of alcohol the amount of bis-alkylation product was disproportionately high: with 1 equiv of **5** only 34% of **2a**, but 33% of **6** were formed.



i: a) HCOOH, THF; b) MeOH, HCl

Scheme 2. Synthesis of the γ-tocopherol model compound **2a** and its byproduct, 3,3,5,6,8,8-hexamethyl-1,2,3,8,9,10-hexahydropyrano[3,2-*f*]chromene (**6**).

From previous work by Dean et al.[9] it was known that pyranochromenes with structures similar to **6** can be brominated in a radical reaction, e.g., by *N*-bromosuccinimide. We were assuming—wrongly, as it turned out later—that upon electrophilic aromatic bromination, i.e., toward ionic bromination, byproduct **6** would behave completely inert, which would allow to brominated **2a** in the presence of **6** without the need for prior chromatographic separation, as **6** would be removed anyway after bromination along with other minor byproducts of that reaction. While bromination of pure **2a** with 1 equiv of elemental bromine proceeded quantitatively to **3a**, the yields were consistently and significantly lower (down to 30% and below!) when pyranochromene **6** was present in the starting material. Hence, compound **6** was evidently not inert under the reaction conditions and was consuming considerable amounts of bromine. Thus, we set out to study the bromination behavior of **6** and the corresponding mechanisms in more detail, and used neat material for this approach. The crystal structure of 3,3,5,6,8,8-hexamethyl-1,2,3,8,9,10-hexahydropyrano[3,2-*f*]chromene (**6**) is shown in Fig. 1.

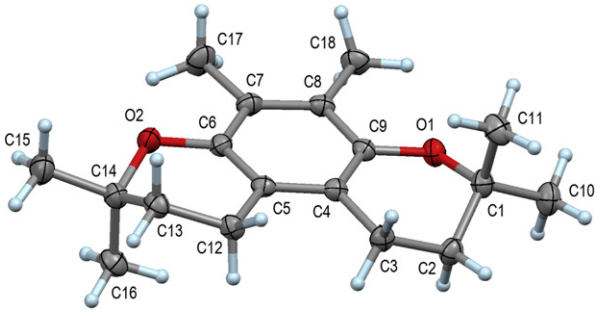


Fig. 1. Thermal ellipsoid plot (30% ellipsoids) of **6**.

Reaction of pyranochromene **6** with bromine consistently provided one main product, independent of the amount of coreacting bromine (between 0.1 and 2 equiv Br_2). 1 equiv of bromine afforded 43% of this main product; in the case of two Br_2 equivalents, the yield increased to 96%, and was thus nearly quantitative. Elemental analysis and MS indicated the presence of one bromine in the product molecule as well as the presence of one additional double bond equivalent, the latter agreeing with an olefin proton resonating at 6.80 ppm (^{1}H NMR). Evaluation of H,C-correlated NMR spectra (HMQC, HMBC) showed the compound to be 9-bromo-3,3,5,6,8,8-hexamethyl-1,2,3,8-tetrahydropyrano-[3,2-*f*]chromene (**7**), which was confirmed by X-ray crystal structure analysis (Fig. 2). The overall reaction with optimum yield in **7** is shown in Scheme 3.

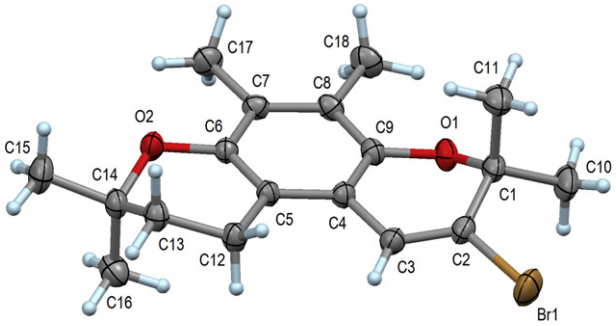
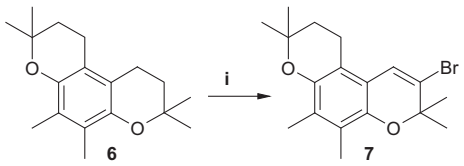


Fig. 2. Thermal ellipsoid plots (20% ellipsoids) of brominated pyrano[3,2-*f*]chromene **7**. Selected bond lengths (Å): C2–C3 1.330(3), C2–C1 1.512(3), C2–Br1 1.896(2).



i: Br_2 (2 eq.), CH_2Cl_2, r.t., dark, 18 h, 96%

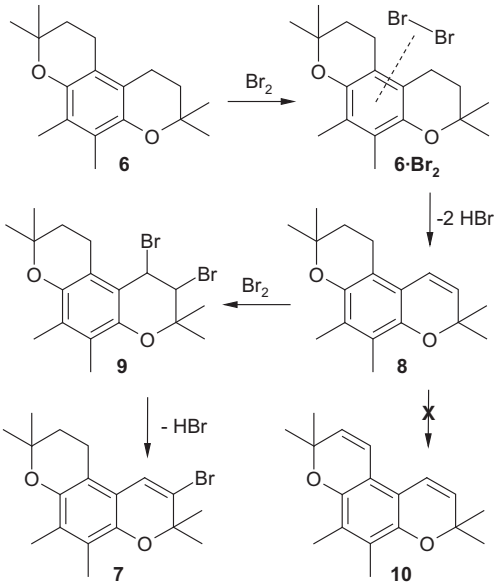
Scheme 3. Overall reaction of the bromination of pyranochromene **6**.

A radical pathway for this reaction was clearly excluded as the process was EPR-silent, proceeded in the dark and also at temperatures of −78 °C, albeit slower at this low temperature but with the same final yield as at room temperature. It was known from previous studies that the bromination of α-tocopherol (**1**) to 5a-bromo-α-tocopherol proceeded through a non-radical, two-step oxidation–addition mechanism involving an *ortho*-quinone methide (*o*-QM) intermediate that adds the evolved HBr.[10] Since an *ortho*-quinone methide cannot be formed in the present case because of the missing free phenolic hydroxyl group, this mechanism is inapplicable.

Carrying out the reaction with 1 equiv of bromine at −78 °C provided a first clue to the mechanism. At this temperature a bright red solution with a similarly colored precipitate formed. Upon warming—at about −45°C—the precipitate dissolved, a gas (HBr) started to evolve and the color changed to a faint yellow. The product was nearly neat 3,3,5,6,8,8-hexamethyl-1,2,3,8-tetrahydropyrano[3,2-*f*]chromene (**8**), see Scheme 4.

We are assuming that pyranochromene **6** is able to form an addition compound with bromine (**6**·$\mathbf{Br_2}$, see Scheme 4) that at low temperatures is relatively stable. Such complexes of bromine with other compounds are well-known in the literature, the most common example being the bromine–dioxane complex.[11] The same complex, indicated by the precipitate and the red color, formed also in other solvents, such as ethanol, chloroform, and dichlorobenzene. When working in ethanol, the addition of KBr dissolved the precipitate and changed the color to dark brown without formation of a gas and without consumption of **6**. This observation would actually be supportive of a bromine complex, since KBr destroys the Br_2 complex by reacting with Br_2 under formation of Br_3^-, which is too weak an oxidant to form **8**.

The dehydrogenation of **6** to afford **8**, basically a conversion of a chroman into a chromene, is a representative of a rather widespread reaction. In tocopherol chemistry for instance, the conversion of *O*-protected tocopherols into the respective 3,4-dehydrotocopherols is a common conversion.[12] It is usually conducted with



Scheme 4. Detailed mechanism of the bromination of pyranochromene **6**.

DDQ as the oxidant, which gives the best yields, but also other dehydrogenating agents, such as platinum black work well. Even bromine can be used, although the yields are inferior due to competitive addition and other side reactions.

Much more surprising than the occurrence of the dehydrogenation itself is the fact that it proceeded strictly on just one 'side' of molecule **6**. We found it impossible to convert chromene **8** to the hypothetical bis-chromene **10** or a bromination product of the latter by using bromine-based chemistry.[13] Brought into contact with bromine at low temperatures, **8** did not form a complex (no color change, no precipitate), but eventually provided brominated pyrano[3,2-*f*]chromene **7** via dibromide **9**. The intermediacy of **9** was proven by working at −78 °C, conducting the reaction in $CDCl_3$ and quickly transferring the mixture into the NMR spectrometer. This allowed acquisition of a proton spectrum and positive identification of the compound, although the degradation into **7** was noticeable. Evidently, GC/MS detection of **9** is unfeasible as elimination of HBr is immediate and only **7** is detected.

Interestingly, the elimination of HBr from **9** is regioselective: always the bromine at the benzylic position—but never the homobenzylic bromine—was lost. This suggests a monomolecular elimination (E1 mechanism): the kinetic rate law is depending on the substrate only, a cationic intermediate is involved and the elimination of a proton occurs in a second step after the elimination of the anion. An intermediate cation as obtained by the release of a bromide anion from **9** is much more stable in benzylic position (due to resonance stabilization with the aromatic ring) than in homobenzylic position where such an electronic stabilization effect is not possible. A bimolecular mechanism would not be able to account for the observed strict regioselectivity, and the fact that no auxiliary base is required for the reaction to proceed additionally disfavors a bimolecular mechanism.

Treating compound **7** with an excess of bromine demonstrated a considerable stability of the compound. At room temperature only negligible consumption was observed, conversion was in the range of 1–2% only.[14] Among these side products, GC/MS indicated a monobrominated derivative of **6** without an additional double bond equivalent, dibrominated **6** with none, one, and two additional double bond equivalents present as well as a monobrominated dimer of **6**. No tri- or tetrabrominated compounds were detected. The position of the bromine substituents and the exact structure of these side products could not be determined from the GC/MS spectra.

In this account, the bromination behavior of a pyranochromene, which is obtained as side product in the synthesis of γ-tocopherol model compound 2,2,7,8-tetramethylchroman-6-ol (**2a**) and has general structural resemblance to tocopherols, was studied. A sequence consisting of bromine complex formation, dehydrogenation (oxidation), bromine addition, and HBr elimination was shown to lead from pyrano[3,2-f]chromene **6** to monobromo derivative **7** while consuming 2 equiv of bromine. When studying the reaction behavior of γ-tocopherol model **2a** care has to be taken that compound **6**, a byproduct from the synthesis of **2a**, is fully removed as it might spoil the outcome of the reaction itself or of kinetic measurements.

3. Experimental

3.1. General

(2*R*,4′*R*,8′*R*)-γ-Tocopherol was used as the starting material.[15] All other chemicals were obtained from commercial suppliers (Sigma–Aldrich). Thin layer chromatography (TLC) was performed on silica gel 60 plates (5×10 cm, 0.25 mm) with fluorescence detection under UV light at 254 nm. Column chromatography was performed on silica gel G_{60} (40–63 μm). Melting points, determined on a Kofler-type micro hot stage with Reichert-Biovar microscope, are uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ at 400 MHz for ^{1}H and at 100 MHz for ^{13}C NMR if not otherwise stated. Chemical shifts, relative to TMS as internal standard, are given in δ values, coupling constants in hertz. ^{13}C peaks were assigned by means of APT, HMQC, and HMBC spectra.

3.2. X-ray crystallographic study

X-ray data collection of compounds **6** and **7** was performed with a Bruker AXS Smart APEX CCD diffractometer and graphite monochromatized Mo Kα radiation, λ=0.71073 Å; corrections for absorption with program SADABS, structure solution with direct methods, structure refinement on F^2 (Bruker AXS, 2004: programs SMART, version 5.626; SAINT, version 6.45; SADABS version 2.10; XPREP, version 6.14; SHELXTL, version 6.3.1. Bruker AXS Inc., Madison, WI, USA). Crystal data for **6**: $C_{18}H_{26}O_2$, M_r=274.39, monoclinic, space group $P2_1/n$, a=11.0779(6), b=9.9874(5), c=15.1287(8) Å, β=107.348(1)°, V=1597.69(14) Å^3 at −100 °C, Z=4, D_x=1.141 g cm^{-3}, F (000)=600, μ=0.072 mm^{-1}, $R1$=0.0468 ($I>2\sigma(I)$). Crystal data for **7**: $C_{18}H_{23}O_2Br$, M_r=351.27, triclinic, space group $P\bar{1}$, a=8.6763(13), b=10.1653(15), c=10.2015(15) Å, α=80.286(3)°, β=75.719(2)°, γ=79.034(3)°, V=849.0(2) Å^3 at 24 °C, Z=2, D_x=1.274 g cm^{-3}, F (000)=364, μ=2.42 mm^{-1}, $R1$=0.0388 ($I>2\sigma(I)$).

CCDC 682758 and 824900 contain the supplementary crystallographic data for **6** and **7**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

3.3. Synthesis of the γ-tocopherol model compound (2a) starting from 2,3-dimethyl-1,4-hydroquinone

2,3-Dimethyl-1,4-hydroquinone (**4**, 3.00 g, 21.70 mmol) was dissolved in formic acid (28.00 mL) and THF (4.00 mL) and heated to reflux. 2-Methyl-3-buten-2-ol (**5**, 1.54 mL, 14.80 mmol) in THF (1.00 mL) was added in three portions. The reaction was refluxed for 3 h and then poured on crushed ice, diluted with H_2O, and extracted repeatedly with diethyl ether. The diethyl ether extract was diluted with *n*-hexane (40 mL) and the resulting mixture was repeatedly washed with H_2O. The organic extracts were dried over Na_2SO_4,

filtered, and evaporated. The residue was dissolved in MeOH (40 mL), concd HCl (0.5 mL) was added, and the mixture was refluxed for 20 min to hydrolyze any formate ester that might have been formed in the reaction. The solvent was evaporated and the residue was dissolved in diethyl ether (100 mL), washed with H_2O, saturated $NaHCO_3$, and again with H_2O, dried over Na_2SO_4, and concentrated in vacuo. The residue was extracted by refluxing in *n*-hexane (50 mL) for 20 min. After cooling to room temperature, the unreacted 2,3-dimethyl-1,4-hydroquinone (47%) was filtered off. The filtrate was concentrated in vacuo and purified by column chromatography on silica gel (EtOAc/*n*-hexane, v/v=1:9) to give 2,2,7,8-tetramethylchroman-6-ol (**2a**) in 41% yield and the disubstituted byproduct 3,3,5,6,8,8-hexamethyl-1,2,3,8,9,10-hexahydropyrano[3,2-*f*]chromene (**6**) in 25% yield. Data agree with previous literature.[16]

*3.3.1. 2,2,7,8-Tetramethylchroman-6-ol (**2a**).* ^{1}H NMR: δ=1.29 (s, 6H, H-2a, H-2b), 1.74 (t, 2H, *J*=6.8 Hz, H-3), 2.10 (s, 3H, H-7a/8b), 2.12 (s, 3H, H-8b/7a), 2.68 (t, 2H, *J*=6.8 Hz, H-4), 4.0 (br s, 1H, −OH), 6.37 (s, 1H, H-5). ^{13}C NMR: δ=11.9 (C-7a, C-8b), 22.6 (C-4), 27.0 (C-2a, C-2b), 33.0 (C-3), 73.4 (C-2), 112.1 (C-5), 118.0 (C-4a), 121.6 (C-8), 125.8 (C-7), 145.9 (C-8a), 146.3 (C-6). Calcd for $C_{13}H_{18}O_2$ (206.29): C 75.69, H 8.80. Found: C 75.80, H 9.02. Mp=75–77 °C.

*3.3.2. 3,3,5,6,8,8-Hexamethyl-1,2,3,8,9,10-hexahydropyrano-[3,2-f] chromene (**6**).* ^{1}H NMR: δ=1.28 (s, 12H, H-3a, H-3b, H-8a, H-8b), 1.78 (t, 4H, *J*=6.8 Hz, H-2, H-9), 2.09 (s, 6H, H-5a, H-6b), 2.54 (t, 4H, *J*=6.8 Hz, H-1, H-10). ^{13}C NMR: δ=11.8 (C-5a, C-6b), 20.1 (C-1, C-10), 26.8 (C-3a, C-3b, C-8a, C-8b), 32.9 (C-2, C-9), 72.4 (C-3, C-8), 115.6 (C-10a, C-10b), 123.4 (C-5, C-6), 144.7 (C-4a, C-6a). Calcd for $C_{18}H_{26}O_2$ (274.40): C 78.79, H 9.55. Found: C 78.88, H 9.56. Mp=102–104 °C (*n*-hexane/EtOAc). The product was recrystallized from *n*-hexane/EtOAc (v/v=19:1) to obtain crystals suitable for X-ray crystallography, see Fig. 2.

*3.3.3. 5-Bromo-2,2,7,8-tetramethyl-chroman-6-ol (**3a**).* 2,2,7,8-Tetramethylchroman-6-ol (**2a**, 6.05 g, 29.33 mmol) was dissolved in *n*-hexane (300 mL), and a solution of Br_2 (1.53 mL, 30 mmol) in *n*-hexane (30 mL) was added in one shot at 0 °C. One drop of H_2SO_4 concd was added[17] and the mixture was stirred at ambient temperature for 2 h. The mixture was washed with aqueous $NaHCO_3$ and water, and was dried over Na_2SO_4. The solvent was removed in vacuo. The crude residue was purified by column chromatography on silica gel (EtOAc/*n*-hexane, v/v=1:30) to give 5-bromo-2,2,7,8-tetramethylchroman-6-ol (**3a**) in 95% yield. ^{1}H NMR: δ=1.29 (s, 6H, H-2a and H-2b), 1.78 (2H, t, H-3, *J*=7.2 Hz), 2.08 (3H, s, H-7a), 2.21 (3H, s, H-8b), 2.68 (2H, t, H-4, *J*=7.2 Hz), 5.19 (1H, s, OH). ^{13}C NMR: δ=11.8 (C-7a), 12.9 (C-8b), 24.3 (C-4), 26.5 (C-2a and C-2b), 33.0 (C-3), 73.3 (C-2), 109.3 (C-5), 117.1 (C-4a), 122.4 (C-7), 125.4 (C-8), 143.4 (C-6), 146.0 (C-8a). Calcd for $C_{13}H_{17}BrO_2$ (285.18): C, 54.75; H, 6.01; Br, 28.02; found: C, 74.81; H, 5.92; Br 28.28.

*3.3.4. 5-Bromo-γ-tocopherol ((R,R,R)-5-bromo-2,7,8-trimethyl-2-(4,8,12-trimethyl-tridecyl)-chroman-6-ol, **3**).* The preparation followed the above procedure for the preparation of **3a**, employing γ-tocopherol (2, 0.6 g, 1.44 mmol) and bromine (1.5 mmol, 76 μl) as the starting materials. ^{1}H NMR: δ=1.22 (s, 3H, H-2a), 1.68–1.87 (2H, m, H-3), 2.07 (6H, s, H-7a, H-8b), 2.65 (2H, t, H-4, *J*=7.2 Hz), 5.17 (1H, s, br, OH). ^{13}C NMR: δ=11.8 (C-7a), 12.9 (C-8b), 24.1 (C-4), 23.7 (C-2a), 31.5 (C-3), 75.4 (C-2), 109.3 (C-5), 117.3 (C-4a), 122.4 (C-7), 125.4 (C-8), 143.4 (C-6), 145.9 (C-8a), resonances of the isoprenoid side chain are not listed. Calcd for $C_{28}H_{47}BrO_2$ (495.59 g mol^{-1}): C 67.86, H 9.56, Br 16.12; found C 67.99, H 9.82.

*3.3.5. 9-Bromo-3,3,5,6,8,8-hexamethyl-1,2,3,8-tetrahydro-pyrano [3,2-f] chromene (**7**).* Pyranochromene **6** (800 mg, 2.91 mmol) was dissolved in dichloromethane (40 mL) and Br_2 (0.30 mL, 0.942 g, 5.9 mmol, 2.02 equiv), dissolved in dichloromethane (10 mL), was added to the solution in one shot. One drop of H_2SO_4 concd was added and the reaction mixture was stirred in a closed flask at ambient temperature for 18 h. The mixture was washed with aqueous $NaHCO_3$ and water and was dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude residue was purified by column chromatography using toluene/*n*-hexane on silica gel (gradient from v/v=1:100 to v/v=2:1) as mobile phase to give the monobrominated compound **7** in a yield of 96%. ^{1}H NMR: δ=1.28 (s, 6H, H-3a, H-3b), 1.49 (s, 6H, H-8a, H-8b), 1.76 (t, 2H, *J*=6.8 Hz, H-2), 2.07, 2.08 (2×s, 2×3H, H-5a, H-6b), 2.64 (t, 2H, *J*=6.8 Hz, H-1), 6.80 (s, 1H, H-10). ^{13}C NMR: δ=11.6 (C-5a/6b), 12.1 (C-5a/6b), 19.6 (C-1), 26.1/26.7 (C-3a, C-3b, C-8a, C-8b), 32.6 (C-2), 72.9 (C-8), 78.5 (C-3), 112.2 (C-10b), 117.4 (C-10a), 122.9 (C-10), 123.6 (C-5/6), 124.6 (C-9), 126.2 (C-5/6), 142.3 (C-6a), 145.9 (C-4a). Mp=85–87 °C. Elemental analysis calcd for $C_{18}H_{23}BrO_2$ (351.28): C 61.54, H 6.60. Found: C 61.24, H 6.72. GC/MS: *m*/*z* 350.1, 335.1, 281.0, 271.2, 215.1. Small crystals from acetic acid, see Fig. 2.

*3.3.6. 3,3,5,6,8,8-Hexamethyl-1,2,3,8-tetrahydropyrano[3,2-f] chromene (**8**).* Pyranochromene **6** (200 mg, 0.73 mmol) was dissolved in dichloromethane (50 mL) and the mixture was cooled to −78 °C in an acetone/dry ice bath. Br_2 (38 μl, 0.12 g, 1 equiv), dissolved in dichloromethane (10 mL), was added dropwise to the cooled solution. The color changed to bright red and a red solid started to precipitate. The reaction mixture was stirred in a closed flask for 30 min, and was then allowed to slowly reach ambient temperature. During warming the precipitate dissolved, the color changed into a pale yellow and a gas (HBr) evolved. At room temperature, the mixture was stirred for another 2 h, washed with water, and dried over Na_2SO_4. The solvent was removed in vacuo and the crude residue was purified by column chromatography using toluene/*n*-hexane on silica gel (v/v=1:50) to give compound **8** in 84% yield. ^{1}H NMR: δ=1.32 (s, 12H, H-3a, H-3b, H-8a, H-8b), 2.12 (s, 6H, H-5a/6a), 5.66 (d, 2H, *J*=10.0 Hz, H-2, H-9), 6.50 (d, 2H, *J*=10.0 Hz, H-1, H-10). ^{13}C NMR: δ=11.8 (C-5a/6a), 26.1, 26.4 (C-3a, C-3b, C-8a, C-8b), 73.5 (C-3, C-8), 116.4 (C-1a, C-10a), 120.1 (C-1, C-10), 122.9 (C-5, C-6), 132.1 (C-2, C-9), 144.6 (C-4a, C-7a). Mp=72–74 °C. Elemental analysis calcd for $C_{18}H_{22}O_2$ (270.37): C 79.96, H 8.20. Found: C 80.16, H 8.34.

*3.3.7. 1,2-Dibromo-3,3,5,6,8,8-hexamethyl-1,2,3,8,9,10-hexa-hydropyrano[3,2-f]chromene (**9**).* Compound **8** (15 mg, 55 μmol) was dissolved in $CDCl_3$ (0.3 mL) in an NMR tube and the mixture was cooled to −78 °C in an acetone/dry ice bath. A solution (0.3 mL) of Br_2 (0.28 mL in 3 mL of $CDCl_3$), also cooled to the same temperature, was added. The tube was vortexed, left at −78 °C for 10 min, and then quickly transferred into the NMR spectrometer. ^{1}H NMR: δ=1.27 (s, 6H, H-3a, H-3b), 1.46 (s, 6H, H-8a, H-8b), 1.76 (t, 2H, ^3J=6.8 Hz, H-9), 2.08, 2.10 (2×s, 2×3H, H-5a and H-6b), 2.64 (t, 2H, *J*=6.8 Hz, H-10), 4.25 (d, 1H, *J*=9.9 Hz, H-2), 4.75 (d, 1H, *J*=9.9 Hz, H-1).

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References and notes

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13. By contrast, DDQ allows a fast conversion of **8** into **10**, and also of **6** into **10** via **8**.
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17. This addition was found to eliminate byproducts, which are otherwise formed up to 15%, and additionally to moderately accelerate the reaction. The effect could be due to both simple 'drying' by binding traces of water or by an activation of bromine facilitating generation of transient bromonium species.