Synthesis of α-tocopherol and naphthotocopherol analogs with a carboxyl group in the side chain

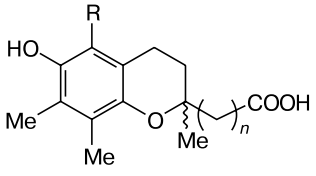
A. Yu. Spivak, O. V. Knyshenko, M. I. Mallyabaeva, and V. N. Odinokov★

Institute of Petrochemistry and Catalysis, Russian Academy of Sciences,
141 prosp. Oktyabrya, 450075 Ufa, Russian Federation
Fax: +7 (347 2) 31 2750. E-mail: ink@anrb.ru

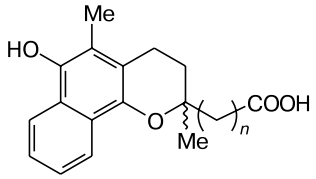
On the basis of ozonolysis of short-chain α-tocopherol and naphthotocopherol analogs with a terminal isopropylidene group in the side chain, a general approach to the synthesis of 6-hydroxy-2,5,7,8-tetrtamethylchroman-2-yl- and 6-hydroxy-2,5-dimethyl-3,4-dihydro-2*H*-naphtho[1,2-*b*]pyran-2-ylpropionic and -acetic acid derivatives, which are hydrophilic tocopherol analogs, was proposed.

Key words: α-tocopherol, naphthotocopherol, carboxylic acids, aldehydes, enol acetates, ozonolysis.

3,4-Dihydro-2*H*-benzopyran-2-ylalkanoic acids are known as the main water-soluble metabolites of Vitamin E (see Refs 1—3) and are of interest for their biological activities.[4—12] They are also used in the enantioselective synthesis of optically active tocopherols and tocotrienols.[13—15] Racemic 6-hydroxy-2-carboxy-2,5,7,8-tetramethylchromane (**1**) known as Trolox, its homolog **2**, and their ammonium, phosphonium, and sulfonium salts are efficient water-soluble antioxidants and cardioprotectors.[4,5] Racemic acids **1** and **2** were used to synthesize compounds with combined pharmacological properties useful in the therapy of the pathological disorders caused by peroxide radicals. The compounds obtained exhibited high antioxidant,[6] antitumor,[7] antiinflammatory,[8,9] and antiarrhythmic activities.[10]



1—4



5, **6**

R = Me (**1—3**), H (**4**); *n* = 0 (**1**), 1 (**2**, **5**), 2 (**3**, **4**, **6**)

Of particular interest are the recently discovered water-soluble D-α-tocopherol and D-γ-tocopherol metabolites and their racemic analogs, 2-carboxyethyl-6-hydroxy-2,5,7,8-tetramethylchromane (**3**) (α-CEHC) and 2-carboxyethyl-6-hydroxy-2,7,8-trimethylchromane (**4**) (γ-CEHC). Unlike tocopherol, these acids were found to exhibit a sodium uretic action, irrespective of the configuration of C(2), apparently, due to their interaction with proteins as endogenic ligands.[3] The CEHC metabolites show a high antioxidant activity *in vitro*.[11,12]

The unique properties found for acids **1—4** aroused interest in their use in biology and medicine. However, known synthetic routes to these compounds are restricted to two approaches based on condensation of methylated hydroqiunones with methyl vinyl ketone[13—19] or γ-methyl-γ-vinylbutyrolactone.[1,2,20]

Recent publications[21] report a high antioxidant activity of (2*RS*)-6-hydroxy-2,5-dimethyl-2-(4*RS*,8*RS*,12-trimethyltridecan-1-yl)-3,4-dihydro-2*H*-naphtho[1,2-*b*]-pyran (naphthotocopherol), which was 6.9 times as high as the activity of α-tocopherol. In this connection, it is pertinent to synthesize ω-carboxyl-containing analogs of naphthotocopherol, in particular, 6-hydroxy-2,5-dimethyl-3,4-dihydro-2*H*-naphtho[1,2-*b*]pyran-2-ylacetic and -propionic acids (**5** and **6**).

Results and Discussion

The condensation of trimethylhydroquinone (TMHQ) or menadiol acetate (AMD) with linalool (**7**) on treatment with (+)-camphor-10-sulfonic acid (CSA) or TsOH gave compounds **8**, **11** (their yield was markedly higher

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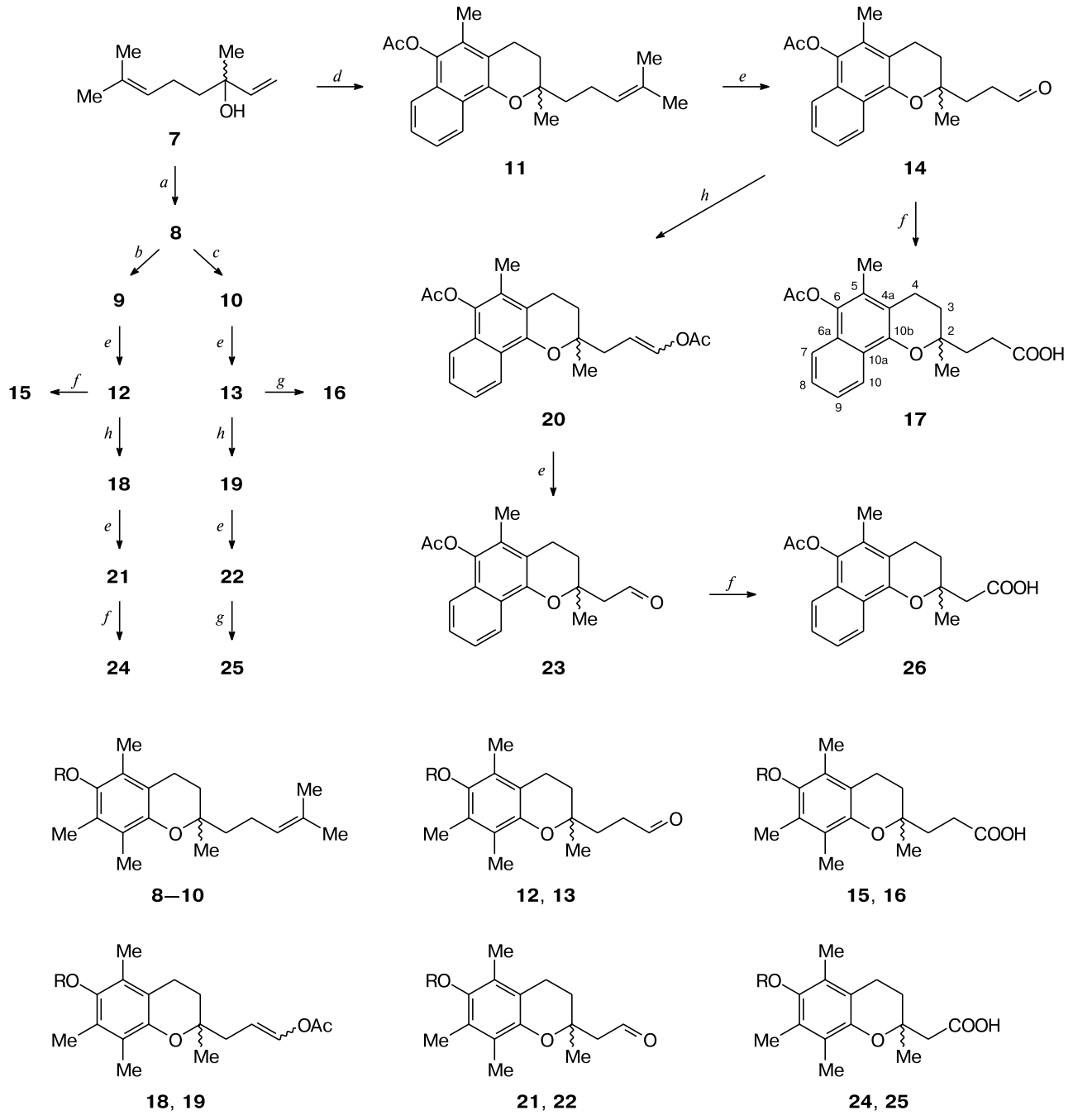
with CSA). The general approach to the synthesis of chroman-2-yl- and benzochroman-2-yl-substituted carboxylic acids, hydrophilic analogs of α-tocopherol and naphthotocopherol, that we developed is based on ozonolysis of the *O*-esters of chromanol **9** and benzochromanol **11** and *O*-ether of chromanol **10** having an unsaturated side chain (Scheme 1). By ozonolysis under reported conditions,[22] olefins **9—11** were converted into

Scheme 1



R = H (**8**), Ac (**9**, **12**, **15**, **18**, **21**, **24**), Bn (**10**, **13**, **16**, **19**, **22**, **25**)

Reagents and conditions: *a*. TMHQ/CSA, *n*-C_8H_{18}; *b*. Ac_2O/Py; *c*. BnCl/K_2CO_3, DMF; *d*. AMD/CSA, *n*-C_8H_{18}; *e*. O_3/$NaHCO_3$, CH_2Cl_2—MeOH (10 : 1), −70 °C, Me_2S; *f*. CrO_3/H_2SO_4/Me_2CO; *g*. $AgNO_3$/NaOH, EtOH; *h*. Ac_2O/AcOK.

aldehydes **12—14**. The subsequent oxidation of acetyl derivatives **12** and **14** with the Jones reagent and oxidation of benzyl ether **13** with an alkaline solution of silver nitrate resulted in acids **15**, **17**, and **16**, respectively.

To prepare noranalogs of acids **15—17**, their precursors, aldehydes **12—14**, were converted into enol acetates **18—20**, whose subsequent ozonolysis gave aldehydes **21—23**, which were further oxidized into the target acids **24—26**.

According to ^{1}H and ^{13}C NMR data, enol acetates **18—20** were mixtures of *E*/*Z* isomers. Their ^{1}H NMR spectra exhibit doublets of triplets for the H(2′) protons in the *Z* isomers at δ 5.05—5.14 (J = 7.8 and 6.4 Hz) and in the *E* isomers at δ 5.52—5.61 (J = 12.0 and 8.3 Hz). From the ratio of the integral intensities of these signals, it follows that the *E*- and *Z*-isomers are formed in 2 : 1 ratio. In the ^{13}C NMR spectra of enol acetates **18—20**, the signals of the C(1′), C(2′), and C(3′) atoms of the *E*-isomers are observed in a somewhat lower field (Δδ 3.2, 1.5, and 1.2.) than the corresponding signals of *Z*-isomers.

The ^{1}H NMR spectra of some of the obtained compounds with functional groups located closely to the C(2) chiral center (**22—24**) show the diastereotopic nature of the protons of the $H_2C(1')$ groups. As a consequence, the spectrum of, *e.g.*, acid **24** contains a signal for two protons of the $H_2C(1')$ group as an AB system at δ 2.43 and δ 2.53 (^2J = 12.3 Hz). The spectra of aldehydes **22** and **23** also show the diastereotopic protons at C(1′) as doublets of an AB-system due to additional vicinal splitting on the aldehyde-group proton. Due to the spin-spin coupling with the diastereotopic $H_2C(1')$ groups, the signals of the aldehyde protons are manifested as a doublet of doublets at δ ≈ 10 (J = 3.4 and 2.5 Hz for compounds **22**, J = 3.2 and 2.0 Hz for compound **23**).

To conclude, we have developed syntheses of α-tocopherol and naphthotocopherol analogs with an ω-carboxyl group, which are of considerable interest for medicine, on the basis of available monoprenylated chromanols and benzochromanols using ozonolysis at the two key steps.

Experimental

IR spectra were recorded on a Specord 75-IR spectrophotometer (in thin layer), and UV spectra were measured on a Specord M-40 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 instrument (operating at 300.13 MHz for ^{1}H and at 75.47 MHz for ^{13}C) in $CDCl_3$ or CD_3OD. The chemical shifts (δ) are given relative to Me_4Si (internal standard). GLC analysis was carried out on a Chrom-5 chromatograph, column 2400×4 mm, SE-30 (5%) on Chromaton N-AW-DMCS as the stationary phase, thermostat temperature 50—300 °C (8 °C min^{-1}), and helium as the carrier gas. TLC was carried out using Silufol UV-254 and Sorbfil in a 1 : 1 *n*-hexane—EtOAc or 1 : 1 $CHCl_3$—MeOH system; the plates were visualized with phosphomolybdic acid and 4-methoxybenzaldehyde. Commercial TMHQ and CSA (Fluka) were used.

(2*RS*)-6-Acetoxy-2,5,7,8-tetramethyl-2-(3-oxopropyl)chromane (12). Linalool (**7**) (0.40 g, 2.6 mmol) was added dropwise (Ar) to a boiling suspension of trimethylhydroquinone (0.4 g, 2.6 mmol) and CSA (0.061 g, 0.26 mmol) in anhydrous *n*-octane (3 mL). The reaction mixture was kept at reflux for 3 h, cooled to ~20 °C, and poured into a saturated solution of $NaHCO_3$ (30 mL). The product was extracted with EtOAc, washed with brine, and dried with $MgSO_4$. The filtrate was concentrated, and the residue was chromatographed on a column with SiO_2 (16 g), using first *n*-hexane and then a 10 : 1 *n*-hexane—EtOAc mixture as eluents to give 0.57 g of compound **8** as a mixture with its cyclic isomer.[23] The condensation products were dissolved in anhydrous pyridine (5.6 mL), then Ac_2O (4.3 mL) was added with stirring, and the mixture was kept for 0.5 h at ~20 °C, poured into ice water (15 mL), and extracted with EtOAc. The solution was washed with 3 *M* HCl, a saturated solution of $NaHCO_3$, and H_2O and dried with $MgSO_4$. Removal of the solvent gave 0.63 g of an oily compound (according to GLC, the product contained 75% compound **9** (*cf.* Ref. 23), which corresponds to 0.47 g (1.43 mmol)). The material was dissolved in a 10 : 1 CH_2Cl_2—anhydrous MeOH mixture (4.4 mL), then $NaHCO_3$ (0.21 g) was added, and an oxygen—ozone mixture was passed through the solution with stirring (−70 °C) at a rate of 30 L h^{-1} for 3 min (1.45 mmol O_3 with an ozone generator productivity of 29 mmol O_3 h^{-1}). The reaction mixture was purged with Ar, then Me_2S (1.6 mL) was added at −40 °C, and the mixture was warmed-up to ~20°C, stirred for 5 h, and concentrated *in vacuo*. The residue was diluted with water (10 mL) and extracted with EtOAc. The extract was washed with brine, dried with $MgSO_4$, and concentrated. The residue was chromatographed on a column with SiO_2 (12 g) using first a 10 : 1 and then a 3 : 1 *n*-hexane—EtOAc mixture as the eluent to give 0.35 g (44% based on **7**) of aldehyde **12** identical (according to IR, UV, and ^{1}H and ^{13}C NMR data) to the sample described previously.[23]

(2*RS*)-6-Benzyloxy-2,5,7,8-tetramethyl-2-(3-oxopropyl)chromane (13). The reaction of trimethylhydroquinone (4.0 g, 26 mmol), linalool (**7**) (4.01 g, 26 mmol), and CSA 0.60 g (2.6 mmol) gave, as described above, a condensation product (6.06 g; according to GLC, the content of **8** was 75%), which was dissolved in anhydrous DMF (42.4 mL). Calcined K_2CO_3 (7.68 g) and benzyl chloride (6.7 g, 52.9 mmol) were added successively. The reaction mixture was kept for 38 h at ~20 °C, poured into ice water, and extracted with EtOAc. The usual workup and column chromatography on SiO_2 gave the benzylation product (4.59 g; the content of **10** was 75%, or 3.44 g, 9.09 mmol). The material was dissolved in a 10 : 1 CH_2Cl_2—anhydrous MeOH mixture (33 mL), $NaHCO_3$ (1.53 g) was added, and an ozone—oxygen mixture was passed through the solution with stirring (−70 °C) at a flow rate of 30 L h^{-1} for 19 min (9.1 mmol O_3 with an ozone generator productivity of 29 mmol O_3 h^{-1}). The mixture was worked-up as described for the synthesis of aldehyde **12**. to give 2.64 g (29% based on **7**) of aldehyde **13** (oily substance).* IR, ν/cm^{-1}: 1710 (C=O), 1210, 1060, 1080 (C—O). UV (MeOH), λ_{max}/nm (ε): 270 (2122); 289

* Since aldehydes **13** and **23** were not obtained in the analytically pure state, no elemental analysis data are presented for these compounds.

(1899). ^{1}H NMR, δ: 1.30 (s, 3 H, C(2)Me); 1.70—2.15 (m, 4 H, H(3), H(1′)); 2.18, 2.24, 2.30 (all s, 9 H, MeC_{arom}); 2.50—2.78 (m, 4 H, H(4), H(2′)); 4.75 (s, 2 H, OCH_2Ph); 7.35—7.70 (m, 5 H, H_{Ph}); 9.83 (t, 1 H, HCO, J = 1.0 Hz). ^{13}C NMR, δ: 11.73, 11.84, 12.70 (MeC_{arom}); 20.34 (C(4)); 23.34 (MeC(2)); 31.28, 31.74 (C(3), C(2′)); 38.38 (C(1′)); 73.51 (OCH_2Ph); 74.52 (C(2)); 117.10, 122.75, 125.96, 127.98 (C(4a), C(5), C(7), C(8)); 127.53, 127.63 (C(2)Ph—C(6)Ph); 137.71 (C(1)Ph); 147.16 (C(8a)); 148.26 (C(6)); 202.38 (CHO).

(2*RS*)-6-Acetoxy-2-(2-carboxyethyl)-2,5,7,8-tetramethylchromane (15). Jones reagent (1.2 mL, 3.36 mmol) (prepared from 1.33 g of CrO_3, 3.8 mL of H_2O, and 1.2 mL of conc. H_2SO_4) was added dropwise with vigorous stirring at 0 °C to a solution of aldehyde **12** (0.86 g, 2.83 mmol) in acetone (20 mL), and the mixture was stirred for 2 h at ~20 °C and extracted with EtOAc. The extract was washed with brine, dried with $MgSO_4$, and concentrated. The residue was chromatographed on a column with SiO_2 (14 g) using methanol as the eluent to give 0.62 g (68%) of acid **15**, m.p. 149—150 °C (*cf.* Ref. 24). Found (%): C, 67.71; H, 7.45. $C_{18}H_{24}O_5$. Calculated (%): C, 67.48; H, 7.55. IR, ν/cm^{-1}: 1210, 1080 (C—O), 1740, 1700 (C=O), 3200—3500 (OH). UV (MeOH), λ_{max}/nm (ε): 278 (1415); 284 (1489). ^{1}H NMR, δ: 1.21 (s, 3 H, MeC(2)); 1.79—2.20 (m, 4 H, H(3), H(1′)); 1.94, 1.97, 2.06 (all s, 9 H, MeC_{arom}); 2.28 (s, 3 H, $MeCO_2$); 2.50—2.75 (m, 4 H, H(4), H(2′)). ^{13}C NMR, δ: 12.02, 12.24, 13.11 (MeC_{arom}); 20.46 ($MeCO_2$); 21.38 (C(4)); 23.59 (MeC(2)); 29.51 (C(2′)); 32.26 (C(3)); 35.68 (C(1′)); 75.33 (C(2)); 118.63, 123.93, 126.30, 127.92 (C(4a), C(5), C(7), C(8)); 142.21 (C(8a)); 150.11 (C(6)); 171.53 ($MeCO_2$); 177.57 (CO_2H).

(2*RS*)-6-Benzyloxy-2-(2-carboxyethyl)-2,5,7,8-tetramethylchromane (16). A solution of $AgNO_3$ (0.32 g, 1.9 mmol) in water (3.8 mL) was added to a solution of aldehyde **13** (0.55 g, 1.6 mmol) in EtOH (25 mL). The mixture was stirred for 5 min at ~20 °C, and a solution of NaOH (0.31 g, 7.8 mmol) in H_2O (8.9 mL) was added dropwise. The mixture was stirred for 2 h at ~20 °C and filtered, and the filtrate was concentrated *in vacuo* to ~5 mL. The residue was dissolved in H_2O (20 mL) and washed with EtOAc. The aqueous solution was acidified with 1 *M* HCl and extracted with EtOAc, and the extract was washed with brine, dried with $MgSO_4$, and concentrated to give 0.43 g (73%) of acid **16**, m.p. 76—78 °C. Found (%): C, 74.63; H, 7.39. $C_{23}H_{28}O_4$. Calculated (%): C, 74.97; H, 7.66. IR, ν/cm^{-1}: 1700 (C=O), 3300—3600 (OH). UV (EtOH), λ_{max}/nm (ε): 203 (62191); 287 (1974). ^{1}H NMR, δ: 1.33 (s, 3 H, MeC(2)); 1.81—2.15 (m, 4 H, H(3), H(1′)); 2.14, 2.23, 2.28 (all s, 9 H, MeC_{arom}); 2.50—2.80 (m, 4 H, H(4), H(2′)); 4.76 (s, 2 H, OCH_2Ph); 7.37—7.57 (m, 5 H, H_{Ph}). ^{13}C NMR, δ: 11.73, 11.92, 12.78 (MeC_{arom}); 20.42 (C(4)); 23.31 (MeC(2)); 28.54 (C(2′)); 31.37 (C(3)); 34.31 (C(1′)); 73.53 (OCH_2Ph); 74.67 (C(2)); 117.20, 122.83, 126.01, 127.95, (C(4a), (C(5), C(7) C(8)); 127.66, 128.38 (C(2)Ph—C(6)Ph); 137.87 (C(1)Ph); 147.34 (C(8a)); 148.36 (C(6)); 180.12 (CO_2H).

(2*RS*)-6-Acetoxy-2-(2-carboxyethyl)-2,5-dimethyl-3,4-dihydro-2*H*-naphtho[1,2-*b*]pyran (17). Jones reagent (1.0 mL, 2.8 mmol) was added at 0 °C with vigorous stirring to a solution of aldehyde **14** (0.66 g, 2.0 mmol, prepared as described previously[22]) in acetone (10 mL). The mixture was stirred for 2 h at ~20 °C and then worked-up as described above (see the preparation of acid **15**) to give 0.44 g (64%) of acid **17**, m.p. 150—152 °C. Found (%): C, 69.85; H, 6.63. $C_{20}H_{22}O_5$. Calculated (%): C, 70.16; H, 6.48. IR, ν/cm^{-1}: 1760, 1710 (C=O), 2800—3600 (OH). UV (MeOH), λ_{max}/nm (ε): 242 (19048), 278 (2196), 295 (923), 328 (554). ^{1}H NMR, δ: 1.32 (s, 3 H, MeC(2)); 1.82—2.05 (m, 4 H, H(3), H(1′)); 2.11 (s, 3 H, MeC(5)); 2.42 (s, 3 H, $MeCO_2$); 2.58—2.80 (m, 4 H, H(4), H(2′)); 7.40 (m, 2 H, H(8), H(9)); 7.55, 8.15 (both d, 2 H, H(7), H(10), J = 7.7 Hz). ^{13}C NMR (δ: 12.69 (MeC(5)); 20.55 ($MeCO_2$); 21.51 (C(4)); 23.81 (MeC(2)); 32.23 (C(3)); 33.04 (C(2′)); 37.01 (C(1′)); 76.63 (C(2)); 115.74, 126.08, 127.17, 127.48 (C(4a), C(5), C(6a), C(10a)); 121.44, 122.82, 125.64, 127.14 (C(7)—C(10)); 138.32 (C(10b); 147.59 (C(6)); 171.75 (MeCO); 179.80 (CO_2H).

(2*RS*, 2′*EZ*)-6-Acetoxy-2-(3′-acetoxyprop-2′-en-1′-yl)-2,5,7,8-tetramethylchromane (18). A mixture of aldehyde **12** (2.6 g, 8.5 mmol), Ac_2O (20 mL), and AcOK (0.13 g, 1.3 mmol) was refluxed for 4 h and then concentrated *in vacuo* to ~2 mL, and EtOAc (50 mL) was added. The solution was washed successively with $NaHCO_3$ and H_2O, dried with $MgSO_4$, and concentrated. The residue was chromatographed on SiO_2 (30 g), using a 5 : 1 *n*-hexane—EtOAc mixture as the eluent to give 1.9 g (65%) of a mixture of enol acetates **18** ($E/Z \approx 2 : 1$). Found (%): C, 69.67; H, 7.74. $C_{20}H_{26}O_5$. Calculated (%): C, 69.34; H, 7.56. IR, ν/cm^{-1}: 1760, 1740 (OC=O), 1650 (C=C). UV ($CHCl_3$), λ_{max}/nm (ε): 263 (1951), 286 (2123). ^{1}H NMR, δ: 1.30 (s, 3 H, MeC(2)); 1.72—1.90 (m, 2 H, H(3)); 2.00, 2.05, 2.13 (all s, 12 H, MeC_{arom}, $MeCO_2C(3')$); 2.20—2.47 (m, 2 H, H(1′)); 2.31 (s, 3 H, $MeCO_2Ar$); 2.50—2.72 (m, 2 H, H(4)); 5.05 (dt, ~0.3 H, H(2′) in the *Z*-isomer, J = 7.2, 6.5 Hz); 5.52 (dt, ~0.7 H, H(2′) in the *E*-isomer, J = 12.5, 8.0 Hz); 7.16 (m, 1 H, (H(3′)). ^{13}C NMR, δ: 11.58, 11.81, 12.67 (MeC_{arom}); 13.88 (MeC(2)); 20.22, 20.28, 20.33 ($MeCO_2C(3')$, $MeCO_2Ar$); 22.41 (C(4)); 27.24 (C(1′) in the *Z*-isomer); 30.46 (C(1′) in the *E*-isomer); 31.36 (C(3)); 74.34, 74.52 (C(2)); 108.47 (C(2′) in the *Z*-isomer); 109.52 (C(2′) in the *E*-isomer); 116.86, 116.92, 122.78, 122.69, 124.77, 126.57, 126.62 (C(4a), C(5), C(7), C(8)); 135.64 (C(3′) in the *Z*-isomer); 137.11 (C(3′) in the *E*-isomer); 140.46, 140.58 (C(8a)); 148.78 and 148.72 (C(6)); 167.67 ($MeCO_2(3')$ in the *E*-isomer); 168.67 ($MeCO_2(3')$ in the *Z*-isomer); 169.31 ($MeCO_2Ar$).

(2*RS*, 2′*EZ*)-2-(3′-Acetoxyprop-2′-en-1′-yl)-6-benzyloxy-2,5,7,8-tetramethylchromanes (19). A mixture of aldehyde **13** (0.91 g, 2.6 mmol), Ac_2O (5 mL), and AcOK (0.04 g, 0.41 mmol) was refluxed for 4 h and concentrated *in vacuo* to 1 mL, and EtOAc (20 mL) was added. The solution was washed successively with $NaHCO_3$ and H_2O, dried with $MgSO_4$, and concentrated. The residue was chromatographed on SiO_2 (20 g) using a 5 : 1 *n*-hexane—EtOAc mixture as the eluent to give 0.76 g (74%) of enol acetates **19** ($E/Z \approx 2 : 1$). Found (%): C, 75.82; H, 7.81. $C_{25}H_{30}O_4$. Calculated (%): C, 76.11; H, 7.66. IR, ν/cm^{-1}: 1760 (C=O), 1680 (C=C). UV (EtOH), λ_{max}/nm (ε): 287 (3120). ^{1}H NMR, δ: 1.30, 1.34 (both s, 3 H, MeC(2)); 1.75—2.00 (m, 2 H, H(3)); 2.11, 2.19, 2.24 (all s, 9 H, MeC_{arom}); 2.29 (s, 3 H, $MeCO_2$); 2.40—2.60 (m, 2 H, H(1′)); 2.60—2.95 (m, 2 H, H(4)); 4.75 (s, 2 H, OCH_2Ph); 5.14 (dt, ~0.3 H, H(2′) in the *Z*-isomer, J = 7.0, 6.5 Hz); 5.60 (dt, ~0.7 H, H(2′) in the *E*-isomer, J = 12, 8.0 Hz); 7.20 (m, 1 H, H(3′)); 7.25—7.60 (m, 5 H, H_{Ph}). ^{13}C NMR, δ: 11.50, 11.62, 12.50 (MeC_{arom}); 20.10; 20.49 ($MeCO_2$); 20.26 (C(4)); 23.54, 23.75 (MeC(2)); 30.63, 30.79 (C(3)); 34.02 (C(1′) in the *Z*-isomer); 37.22 (C(1′) in the *E*-isomer); 73.97, 74.17, 74.31 (C(2), OCH_2Ph); 108.47 (C(2′) in the *Z*-isomer)); 109.48 (C(2′) in the *E*-isomer); 116.97, 117.03, 122.58, 125.62, 127.85 (C(4a), C(5), C(7), C(8)); 127.32, 127.39, 128.08, 128.15 (C(2)Ph-C(6)Ph); 135.68, 136.97

(C(3′)); 137.67 (C(1)Ph); 147.19, 147.31 (C(8a)); 148.09 (C(6)); 167.34, 167.49 ($MeCO_2$).

(2*RS*,2′*EZ*)-6-Acetoxy-2-(3′-acetoxyprop-2′-en-1′-yl)-2,5-dimethyl-3,4-dihydro-2*H*-naphtho[1,2-*b*]pyrans (20). A mixture of aldehyde **14** (0.34 g, 1.04 mmol), Ac_2O (3 mL), and AcOK (0.018 g, 0.18 mmol) was refluxed for 4 h and worked-up as described in the synthesis of enol acetates **18** to give 0.28 g (73%) of enol acetates **20** ($E/Z \approx 2:1$). Found (%): C, 71.97; H, 6.38. $C_{22}H_{24}O_5$. Calculated (%): C, 71.72; H, 6.57. IR, ν/cm^{-1}: 1680 (C=C), 1760 (C=O), 1210, 1080, 1060 (C—O). UV (MeOH), λ_{max}/nm (ε): 243 (49677), 302 (16667). ^1H NMR, δ: 1.34 (s, 3 H, MeC(2)); 1.80—1.98 (m, 2 H, H(3)); 2.12 (s, 3 H, MeC(5)); 2.20, 2.21 (both s, 3 H, $MeCO_2C(3')$); 2.34—2.55 (m, 2 H, (H(1′)); 2.48 (s, 3 H, $MeCO_2Ar$); 2.60—2.80 (m, 2 H, H(4)); 5.10 (dt, ~0.3 H, H(2′) in the *Z*-isomer, $J = 7.8$, 6.6 Hz); 5.61 (dt, ~0.7 H, H(2′) in the *E*-isomer, $J = 8.3$, 12.0 Hz); 7.20 (m, 1 H, H(3′)); 7.45 (m, 2 H, H(8), H(9)); 7.67 dd and 8.24 m (2 H, H(7), H(10), $J = 8.0$ Hz, 1.5). ^{13}C NMR, δ: 12.35 (MeC(5)); 13.89 and 13.93 (MeC(2)); 20.07, 20.28, 20.34 ($MeCO_2Ar$, $MeCO_2C(3')$); 20.20 (C(4)); 30.38, 30.74 (C(3)); 31.67 (C(1′) in the *Z*-isomer); 33.81 (C(1′) in the *E*-isomer); 75.00, 75.19 (C(2)); 108.06 (C(2′) in the *Z*-isomer); 109.34 (C(2′) in the *E*-isomer); 113.78, 113.82, 124.48, 125.55, 125.93 (C(4a), C(5), C(6a), C(10a)); 120.11, 120.15, 121.59, 121.63 (C(7)-C(10)); 135.83 (C(3′) in the *Z*-isomer); 136.91 (C(3′) in the *E*-isomer); 136.88 (C(10b), 146.03, 146.15 (C(6)); 167.56, 167.69 ($MeCO_2C(3')$); 169.28 ($MeCO_2Ar$).

(2*RS*)-6-Acetoxy-2,5,7,8-tetramethyl-2-(2-oxoethyl)chromane (21). An ozone—oxygen mixture was passed with stirring (−70 °C) at a rate of 30 l h^{-1} for 4.5 min (1.5 mmol O_3, with an ozone generator productivity of 20 mmol O_3 h^{-1}) through a mixture of enol acetates **18** (0.5 g, 1.4 mmol), $NaHCO_3$ (0.16 g), and a 10 : 1 CH_2Cl_2—anhydrous MeOH mixture (2.9 mL). The reaction mixture was purged (Ar), then Me_2S (1.6 mL) was added at −40 °C, and after warming-up to ~20 °C, the mixture was stirred for 5 h and concentrated *in vacuo*. The residue was diluted with water (10 mL) and extracted with EtOAc. The extract was washed with brine, dried with $MgSO_4$, and concentrated. The residue was chromatographed on a column with SiO_2 (5 g), using a 3 : 1 *n*-hexane—EtOAc mixture as the eluent to give 0.32 g (79%) of aldehyde **21**. IR, ν/cm^{-1}: 1720, 1750 (C=O). UV ($CHCl_3$), λ_{max}/nm (ε): 275 (1923); 284 (1769). ^1H NMR, δ: 1.36 (s, 3 H, MeC(2)); 1.76—1.91 (m, 2 H, H(3)); 1.95, 1.99, 2.06 (all s, 9 H, MeC_{arom}); 2.29 (s, 3 H, $MeCO_2$); 2.45—2.70 (m, 4 H, H(4), H(1′)); 9.86 (t, 1 H, HCO, $J = 2.0$ Hz). ^{13}C NMR, δ: 11.85, 11.90, 12.70 (MeC_{arom}); 13.50 (MeC(2)); 19.96 (C(4)); 20.10 ($MeCO_2$); 31.28 (C(3)); 59.93 (C(1′)); 73.46 (C(2)); 116.54, 122.78, 124.92 126.67 (C(4a), (C(5), C(7), C(8)); 140.90 (C(8a)); 148.06 (C(6)); 169.14 ($MeCO_2$); 201.05 (CHO). (for the IR, UV, and ^1H NMR spectra of the *S*-enantiomer, *cf.* Ref. 13).

(2*RS*)-6-Benzyloxy-2,5,7,8-tetramethyl-2-(2-oxoethyl)chromane (22). A similar procedure starting from a enol acetate mixture **19** (0.2 g, 0.51 mmol), $NaHCO_3$ (0.06 g), and a 10 : 1 CH_2Cl_2—anhydrous MeOH mixture (1.1 mL) gave 0.12 g of aldehyde **22** (71%) (slowly crystallizing oil, m.p. 70—80 °C, *cf.* Ref. 25). IR, ν/cm^{-1}: 1720 (C=O), 1080, 1060 (C—O). UV (EtOH), λ_{max}/nm (ε): 264 (1714), 287 (2643). ^1H NMR, δ: 1.47 (s, 3 H, MeC(2)); 1.90—2.01 (m, 2 H, H(3)); 2.15, 2.22, 2.28 (all s, 9 H, MeC_{arom}); 2.60 (dd, 1 H, H_A, $J = 15.0$, 3.4 Hz); 2.68 (m, 2 H, H(4)); 2.76 (dd, 1 H, H_B, $J = 15.0$, 2.5 Hz); 4.76 (s, 2 H, OCH_2Ph); 7.30—7.60 (m, 5 H, H_{Ph}); 9.98 (dd, 1 H, CHO, $J = 3.4$, 2.5 Hz). ^{13}C NMR, δ: 10.59, 10.90, 11.48 (MeC_{arom}); 19.05 (C(4)); 23.49 (MeC(2)); 30.66 (C(3)); 51.19 (C(1′)); 72.58 (OCH_2Ph); 73.72 (C(2)); 116.17, 122.00, 124.52, 127.55 (C(4a), C(5), C(7), C(8)); 126.35; 126.43, 127.00, 127.12 (C(2)Ph-C(6)Ph); 137.16 (C(1)Ph); 146.39 (C(8a)); 148.30 (C(6)); 201.80 (CHO). (The ^1H and ^{13}C NMR spectra for the *R*- and *S*-enantiomers **22** were reported in Ref. 25).

(2*RS*)-6-Acetoxy-2,5-dimethyl-2-(2-oxoethyl)-3,4-dihydro-2*H*-naphtho[1,2-*b*]pyran (23). A similar procedure starting from a mixture of enol acetates **20** (0.17 g, 0.46 mmol), $NaHCO_3$ (0.053 g), and a 10 : 1 CH_2Cl_2—anhydrous MeOH mixture (1.1 mL) gave 0.1 g (71%) of aldehyde **23**. IR, ν/cm^{-1}: 1710, 1760 (C=O), 1210, 1060 (C—O). UV ($CHCl_3$), λ_{max}/nm (ε): 242 (23168), 302 (2622), 328 (1565). ^1H NMR, δ: 1.29 (s, 3 H, MeC(2)); 2.05—2.15 (m, 2 H, H(3)); 2.21 (s, 3 H, MeC(5)); 2.46 (s, 3 H, $MeCO_2$); 2.70 (dd, 1 H, H_A, $J = 12.8$, 3.2 Hz); 2.80 (m, 2 H, H(4)); 2.87 (dd, 1 H, H_B, $J = 12.8$, 2.0 Hz); 7.42 (m, 2 H, H(8), H(9)); 7.66, 8.13 (both d, 2 H, H(7), H(10), $J = 7.5$ Hz); 10.0 (dd, 1 H, HCO, $J = 3.2$, 2.0 Hz). ^{13}C NMR, δ: 12.58 (MeC(5)); 20.43 (C(4)); 20.58 ($MeCO_2$); 29.26 (MeC(2)); 31.67 (C(3)); 53.85 (C(1′)); 74.37 (C(2)); 120.47, 121.62, 125.02, 126.44 (C(7)–C(10)); 113.91, 124.63, 125.73, 126.29 (C(5), C(4a), C(6a), C(10a)); 137.67 (C(10b), 145.71 (C(6)); 169.50 ($MeCO_2$); 201.09 (CHO).

(2*RS*)-6-Acetoxy-2-carboxymethyl-2,5,7,8-tetramethylchromane (24). Jones reagent (0.5 mL, 1.4 mmol) was added dropwise with vigorous stirring at 0 °C to a solution of aldehyde **21** 0.25 g (0.86 mmol) in acetone (2 mL). The mixture was stirred for 2 h at ~20 °C and extracted with EtOAc. The extract was washed with brine, dried with $MgSO_4$, and concentrated. The residue was chromatographed on a column with SiO_2 (4 g) using methanol as the eluent to give 0.15 g (58%) of acid **24**, m.p. 132—134 °C (*cf.* Ref. 13). IR, ν/cm^{-1}: 3500—2800 (OH), 1710 (C=O), 1750 (OC=O). UV (MeOH), λ_{max}/nm (ε): 203 (4114); 221 (1286); 278 (1906). ^1H NMR, δ: 1.43 (s, 3 H, MeC(2)); 1.93, 1.96, 2.05 (all s, 9 H, MeC_{arom}); 2.08—2.21 (m, 2 H, H(3)); 2.28 (s, 3 H, $MeCO_2$); 2.43 (d, 1 H, H_A, $J = 12.9$ Hz); 2.53 (d, 1 H, H_B, $J = 12.9$ Hz); 2.58—2.79 (m, 2 H, H(4)) (*cf.* Ref. 13). ^{13}C NMR, δ: 12.04, 12.20, 13.07 (MeC_{arom}); 20.49 (MeC(2)); 21.73 (C(4)); 25.45 ($MeCO_2$); 31.94 (C(3)); 48.20 (C(1′)); 75.87 (C(2)); 119.07, 123.94, 126.09, 127.63 (C(4a), C(5), C(7), C(8)); 142.10 (C(8a)); 150.39 (C(6)); 171.71 ($MeCO_2$); 179.18 (CO_2H).

(2*RS*)-6-Benzyloxy-2-carboxymethyl-2,5,7,8-tetramethylchromane (25). A solution of $AgNO_3$ (0.11 g, 0.65 mmol) in water (1.3 mL) was added to a solution of aldehyde **22** (0.19 g, 0.56 mmol) in EtOH (8.6 mL). The mixture was stirred for 5 min at ~20 °C, a solution of NaOH (0.11 g, 2.75 mmol) in H_2O (3 mL) was added dropwise, the mixture was stirred for 2 h and filtered, and the filtrate was concentrated *in vacuo*. The residue was dissolved in H_2O (6 mL), and the solution was washed with EtOAc. The aqueous solution was acidified with 1 *M* HCl and extracted with EtOAc, and the extract was washed with brine, dried with $MgSO_4$, and concentrated to give 0.12 g (61%) of acid **25**, m.p. 131—133 °C (*cf.* Ref. 18). IR, ν/cm^{-1}: 3500—2800 (OH), 1700 (C=O). UV (MeOH), λ_{max}/nm (ε): 267 (1648), 286 (1444). ^1H NMR, δ: 1.29 (s, 3 H, MeC(2)); 1.92—2.08 (m, 2 H, H(3)); 2.12, 2.19, 2.24 (all s, 9 H, MeC_{arom}); 2.61—2.72 (m, 4 H, H(4), H(1′)); 4.69 (s, 2 H, OCH_2Ph); 7.20—7.60 (m, 5 H, H_{Ph}) (*cf.* Ref. 18). ^{13}C NMR, δ: 11.70, 11.89, 12.77 (MeC_{arom}); 20.42 (C(4)); 24.55 (MeC(2)); 29.60 (C(3));

43.84 (C(1′)); 73.40 (O<u>C</u>H_2Ph); 74.67 (C(2)); 117.16, 123.13, 126.06, 128.24 (C(4a), C(5), C(7), C(8)); 127.67, 127.74, 128.38 (C(2)Ph-C(6)Ph); 137.76 (C(1)Ph); 146.87 (C(8a)); 148.65 (C(6)); 175.45 (CO_2H).

(2*RS*)-6-Acetoxy-2-carboxymethyl-2,5-dimethyl-3,4-dihydro-2*H*-naphtho[1,2-*b*]pyran (26). Jones reagent (0.5 mL, 1.4 mmol) was added dropwise with vigorous stirring at ~0 °C to a solution of aldehyde **23** (0.4 g, 1.28 mmol) in acetone (2 mL). The mixture was stirred for 2 h at ~20 °C and worked-up as in the synthesis of acid **24** to give 0.29 g (69%) of acid **26** as a glassy material. Found (%): C, 69.23; H, 6.32. $C_{19}H_{20}O_5$. Calculated (%): C, 69.50; H, 6.14. IR, ν/cm^{-1}: 1705, 1740 (C=O), 3200—3600 (OH). UV ($CHCl_3$), λ_{max}/nm (ε): 243 (49000), 265 (4215), 301 (2273), 329 (1239). ^{1}H NMR, δ: 1.25 (s, 3 H, MeC(2)); 1.50—1.90 (m, 2 H, H(3)); 2.18 (s, 3 H, MeC(5)); 2.47 (s, 3 H, Me<u>C</u>O_2); 2.72—2.90 (m, 4 H, H(4), H(1′)); 7.45 (m, 2 H, H(8), H(9)); 7.64, 8.18 (both d, 2 H, H(7), H(10), J = 7.8 Hz). ^{13}C NMR, δ: 12.54 (<u>Me</u>C(5)); 14.04 (<u>Me</u>C(2)); 20.47 (<u>Me</u>CO_2); 20.58 (C(4)); 29.62 (C(3)); 30.62 (C(1′)); 74.17 (C(2)); 120.28, 121.78, 124.63, 126.29 (C(7)—C(10)); 114.02, 124.83, 125.71, 126.11 (C(5), C(4a), C(6a), C(10a)); 137.39 (C(10b); 145.74 (C(6)); 169.69 (Me<u>C</u>O_2); 175.11 (CO_2H).

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