Synthesis of the cyclic isomer of the vitamin K_1 dihydro derivative (naphthotocopherol) and its analogs with the shortened and ω-functionalized side chain*

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(2*RS*,4′*RS*,8′*RS*)-Naphthotocopherol and its optically active short-chain analog were synthesized by the condensation of menadiol acetate with (3*RS*,7*RS*,11*RS*)-isophytol and (3*RS*,4*S*)-3,4,8-trimethylnon-1-en-3-ol (*ee* ~50%) in the presence of aluminosilicate Zeocar-10. Using (+)-camphor-10-sulfonic acid as a catalyst, naphthotocopherol analogs with the unsaturated isoprenoid side chain were obtained from (3*RS*)-linalool or (3*RS*,4*S*)-3,4,8-trimethylnona-1,7-dien-3-ol. Ozonolysis of these compounds produced the corresponding ω-formyl derivatives.

Key words: vitamin K_1, naphthotocopherol, isoprenoids, vinylcarbinols, chromans, ozonolysis, aldehydes, aluminosilicates, condensation.

A cyclic isomer of the dihydro derivative of vitamin K_1,[1] which was found in the product of enzymatic reduction of vitamin K_1 and named naphthotocopherol,[2] determines, in many aspects, the role of vitamin K_1 in various biochemical processes.[3] According to the data of the studies of antioxidant activity of a series of the known phenolic antioxidants, the most active among them is naphthotocopherol, which is 6.9-fold more active than α-tocopherol (vitamin E).[4]

Recently, growing attention has been given to the synthesis of α-tocopherol analogs with the shortened side chain, which have high biological activity.[5,6] Since naphthotocopherol has high antioxidant activity, the synthesis of its analogs is also of interest. Benzochromans with the unsaturated side chain are of particular interest, because the oxidative cleavage of their double bond opens a pathway to the ω-functionalized derivatives, *viz.*, synthons for the preparation of various naphthtocopherols, including water-soluble antioxidants.[5]

Earlier we showed the efficiency of aluminosilicate Zeocar-10 applied in the key step of synthesis of α-tocopherol and its analogs with the shortened and ω-functionalized side chain[7,8] and for the preparation of an optically active diastereomeric mixture of (2*RS*,4′*R*,8′*R*)-naphthotocopherol.[9] In this work, we used this approach to synthesize the naphthotocopherol analogs.

The reaction of menadiol monoacetate (**1**) and a 1 : 1 mixture of (3*R*,4*S*)- and (3*S*,4*S*)-3,4,8-trimethylnon-1-en-3-ols (**2**) (they were synthesized[10] from (*S*)-(+)-dihydromyrcene, *ee* ~50%) in the presence of aluminosilicate Zeocar-10 affords a mixture of olefin **3** and products of its ring closure, *viz.*, diastereomers **4**, which are analogs of naphthotocopheryl acetate with the side chain of eight C atoms (Scheme 1). We failed to separate compounds **3** and **4** by column chromatography.

In this mixture, olefin **3** gives the doublet 2 H(1′) (δ 3.40, J = 6.1 Hz) and related triplet of the vinylic proton H(2′) (δ 5.24, J = 6.1 Hz). The ratio of integral intensities of each of the signals and the triplet with δ 2.75 (the coinciding signals 2 H(4) of diastereomers **4**) show that compounds **3** and **4** exist in a ratio of 2 : 1. In the ^{13}C NMR spectra, a doublet with δ 120.17 and a singlet with δ 137.66 (JMOD mode) correspond to the C(2′) and C(3′) atoms, respectively, of the trisubstituted double bond in compound **3**. The appearance of a signal at δ 13.31 corresponding to the Me group at the double bond and a signal of the allylic C atom (from the side of the tetrasubstituted atom of the $\Delta^{2',3'}$ bond) at δ 42.74 indicates[11] the *trans*-geometry of the double bond in the isoprenoid side chain of compound **3**.

An increase in the reaction time (to 10 h instead of 5 h) results in the formation of only cyclic products: benzochromanyl acetates **4** as a 1 : 1 mixture of (2*R*,1′*S*)- and (2*S*,1′*S*)-diastereomers, which is indicated by the same intensity of the doublet signals at δ 1.04 and 1.15 of the protons of the Me groups at the C(1′) atom of these compounds in the ^{1}H NMR spectrum.

The condensation of acetate **1** with (3*RS*,7*RS*,11*RS*)-isophytol **5** produces a mixture of all the eight possible diastereomeric naphthotocopherol

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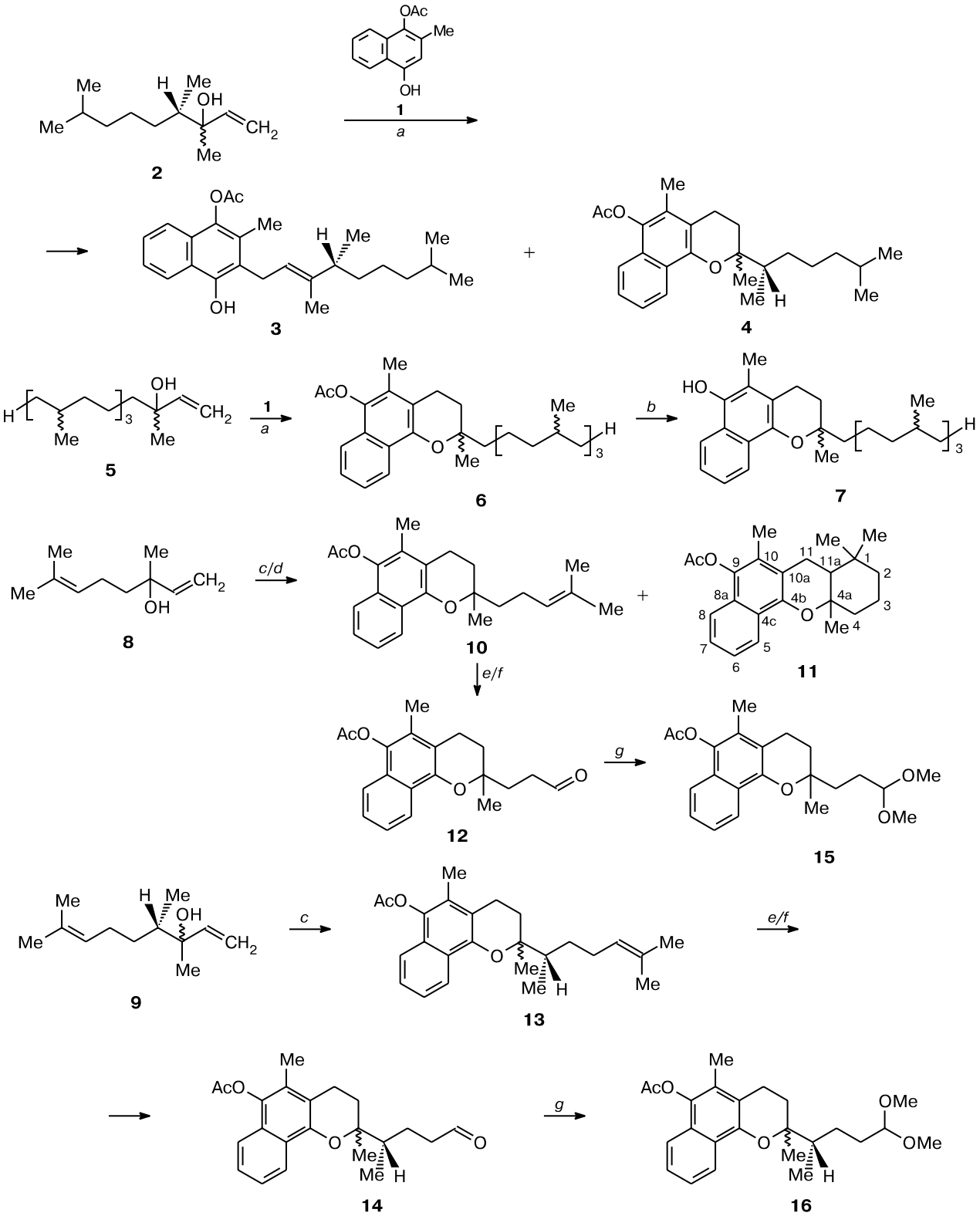
Scheme 1



Reagents and conditions: *a*. Zeocar-10, $PhCH_3$, reflux; *b*. $LiAlH_4/Et_2O$; *c*. **1**/CSA, *n*-C_8H_{18}, reflux, 3 h; *d*. **1**/TsOH, *n*-C_8H_{18}, reflux, 3 h; *e*. $O_3/Ba(OH)_2$, Me_2CO, ~20 °C; *f*. $O_3/NaHCO_3$, CH_2Cl_2—MeOH (10 : 1), −70 °C, then Me_2S; *g*. $MeOH/NH_4Cl$.

acetates (**6**). Naphthotocopherol diastereomers **7** were obtained by reductive cleavage of acetate **6** with $LiAlH_4$.

Thus, aluminosilicate Zeocar-10 can serve as an efficient catalyst in the synthesis of naphthotocopherol and its analogs with the saturated side chain. At the same time, no corresponding naphthotocopherols were obtained by an attempt to involve tertiary allylcarbinols containing the isopropylidene group, *viz.*, (3*R*,*S*)-linalool (**8**) and a 1 : 1 mixture of scalemic (3*R*,4*S*)- and (3*S*,4*S*)-3,4,8-trimethyl-1,7-nonadien-3-ols (**9**), in a similar reaction with acetate **1** in the presence of the Zeocar-10 catalyst. Under these conditions, the reaction of acetate **1** with alcohols **9** affords a complex mixture of products. In the case of (3*RS*)-linalool **8**, a mixture containing 70% (GLC data) of tetracyclic compound **11** is formed. After crystallization, this compound was obtained as an individual diastereomer (^1H and ^{13}C NMR spectra). The structure of tetracyclic compound **11** follows from the data of ^1H and ^{13}C NMR spectroscopy. The characteristic signals in the ^1H and ^{13}C NMR spectra of this compound are close to those in the spectrum of hexamethylperhydroxanthene.[7,12] The ^1H NMR spectrum contains three signals at δ 1.00, 1.10, and 1.30 corresponding to protons of the geminal atom and the Me group at C(4a). The signal of the methylenic proton at C(11) appears as a doublet of doublets at δ 2.80 (J = 16.1 and 5.2 Hz). The ^{13}C NMR spectrum of compound **11** exhibits singlet signals of the C(1) and C(4a) atoms (δ 21.69 and 75.41, respectively), a doublet signal of the C(11a) atom (δ 47.92), and triplet signals of the C atoms in the cyclohexane ring (δ 33.33, 39.71, and 41.50). The relative configuration of the substituents at the asymmetric C(4a) and C(11a) atoms in compound **11** is not determined.

We succeeded to obtain the desired analogs of naphthotocopherol with the ω-isopropylidene side chain when (+)-camphor-10-sulfonic acid (CSA) was used as a condensation catalyst. CSA has previously been applied successfully for the alkylation of trimethylhydroquinone with myrcene.[13] The reaction of acetate **1** with (3*RS*)-linalool **8** in the presence of CSA affords predominantly the target (2*RS*)-benzochroman **10** (~75%) with admixtures of compound **11** (~15%) and a nonidentified compound (~10%) (GLC data). When CSA is replaced by TsOH, the reaction selectivity with respect to target product **10** decreases to 58%.

The ozonolysis of a mixture of compounds **10** and **11** in acetone in the presence of $Ba(OH)_2$ (see Ref. 14) or in a CH_2Cl_2—MeOH (10 : 1) mixture in the presence of $NaHCO_3$ followed by the treatment with Me_2S [15] produced aldehyde **12** (in 59 and 74% yields, respectively), and unreacted **11** was isolated.

The condensation of acetate **1** with vinylcarbinols **9** in the presence of CSA produces a 1 : 1 mixture of (2*R*,1′*S*)- and (2*S*,1′*S*)-diastereomeric chromanols **13**. Their ozonolysis under the specified conditions[14,15] gave a 1 : 1 mixture of (2*R*,1′*S*)- and (2*S*,1′*S*)-diastereomeric aldehydes **14**, which is indicated by the ^1H NMR spectra containing two doublets of equal intensity at δ 0.90—1.10 corresponding to protons of the Me groups at C(1′) of these stereomers.

The ^{13}C NMR spectra of mixtures of diastereomers **4**, **13**, and **14** exhibit double sets of signals of the C atoms located near the chiral 2- and 1′-centers (*cf.* Ref. 10).

Since aldehydes **12** and **14** are unstable, we could not synthesize them in the analytically pure form and, therefore, each of them was transformed into the corresponding acetal (**15** or **16**). The spectral characteristics and elemental analysis data were obtained for compounds **15** and **16**.

Thus, aluminosilicate Zeocar-10 is efficient in the preparation of naphthotocopherol and its analogs with the saturated side chain by the condensation of menadiol monoacetate with isoprenoid allyl alcohols. The naphthotocopherol analogs with the isopropylidene fragment in the side chain, providing a way to the preparation of ω-functionalized chromans, can be synthesized when (+)-camphor-10-sulfonic acid is used as catalyst.

Experimental

IR spectra were recorded on an Specord 75-IR spectrometer in thin layer. UV spectra were obtained on a Specord M-40 spectrometer. ^1H and ^{13}C NMR spectra were measured on a Bruker AM-300 instrument (^1H, 300.13 MHz; ^{13}C, 75 MHz; solvents $CDCl_3$ and CD_3OD). Chemical shifts are presented in the δ scale relatively to Me_4Si (internal standard). GLC analysis was carried out on an Chrom-5 chromatograph (column 2400×4 mm, stationary phase Chromaton N-AW-DMCS and SE-30 (5%), working temperature 50—300 °C (8 deg min^{-1}), and helium as carrier gas). Specific rotation angles were determined on a Perkin—Elmer-141 polarimeter, and the specific rotation and concentration of solutions are given in deg mL g^{-1} dm^{-1} and g (100 mL)$^{-1}$, respectively. Silufol UV-254 plates in an *n*-hexane—Et_2O (1 : 1) mixture or in $CHCl_3$ were used for TLC (phosphoromolybdic acid was used to develop TLC spots). Menadiol monoacetate (4-acetoxy-3-methyl-1-naphtol, **1**, m.p. 124—125 °C) was synthesized from menadione (m.p. 106—106.5 °C[16]) by reductive acetylation.[9] Zeocar-10, which is an aluminosilicate catalyst containing high-module zeolite Y as an active component (Salavatnefteorgsintez), was activated before use by calcination at 450 °C for 5 h. Vinylcarbinols **5** and **8** were available from Fluka, and vinylcarbinols **2** and **9** were synthesized as described earlier.[10] The parameters of the ^1H and ^{13}C NMR spectra for compounds **3** and **10** were obtained from the spectra of mixtures **3**—**4** and **10**—**11**, respectively.

1-Acetoxy-4-hydroxy-2-methyl-3-(3,4,5,8-trimethyl-2*E*-nonen-1-yl)naphthalene (3) and (2*RS*)-6-acetoxy-2,5-dimethyl-2-(1*S*,5-dimethylhex-1-yl)-3,4-dihydro-2*H*-naphtho[1,2-*b*]pyrans (4). ***A.*** A diastereomeric mixture of alcohols **2** (0.21 g, 1.15 mmol) was slowly added to a boiling suspension of compound **1** (0.50 g, 2.3 mmol) and powdered catalyst Zeocar-10 (1.0 g) in anhydrous toluene (7 mL). The reaction mixture was refluxed for 10 h and cooled to room

temperature. The catalyst was filtered off, and the filtrate was concentrated. The residue was chromatographed on a column with SiO_2 (20 g). A fraction of nonpolar substances (R_f 0.7) was isolated by elution with *n*-hexane, and the evaporation of the next fraction (R_f 0.4), which was eluted with a hexane—Et_2O (10 : 1) mixture, gave a 1 : 1 mixture of *erythro*- and *threo*-diastereomers **4** (0.21 g, 48%) as a viscous oily substance, $[\alpha]_D^{18}$ −1.0 (*c* 2.0, $CHCl_3$). Found (%): C, 78.71; H, 8.91. $C_{25}H_{34}O_3$. Calculated (%): C, 78.49; H, 8.96. IR, ν/cm^{-1}: 1760 (C=O); 1210, 1080 and 1060 (C—O). UV ($CHCl_3$), λ_{max}/nm (ε): 245 (76709), 309 (4883), 330 (4257). ^{1}H NMR, δ: 0.92 (m, 6 H, 2 MeC(5′)); 1.04 (d, 1.5 H, MeC(1′), *J* = 6.7 Hz); 1.15 (d, 1.5 H, MeC(1′), *J* = 6.8 Hz); 1.32 (s, 3 H MeC(2)); 1.20—2.10 (m, 10 H, 2 H(3), H(1′)—H(5′)); 2.25 (s, 3 H, MeC(5)); 2.54 (s, 3 H, MeCO); 2.75 (t, 2 H, H(4), *J* = 6.7 Hz); 7.48 (m, 2 H, H(8), H(9)); 7.70 and 8.28 (both d, 2 H, H(7), H(10), *J* = 8.4 Hz). ^{13}C NMR, δ: 12.56 (MeC(5)); 13.57 and 14.24 (MeC(1′)); 20.30 and 20.38 (C(4)); 20.56 (MeCO); 22.43, 22.64 (MeC(2), 2 MeC(5′)); 25.76 and 25.81 (C(3′)); 27.75, 27.84 (C(5′), C(1′)); 30.77, 31.48 (C(2′), C(3)); 39.13 (C(4′)); 78.27, 78.33 (C(2)); 114.24 and 114.28 (C(5)); 120.19, 121.86, 124.47, 126.02 (C(7)—C(10)); 124.79, 125.72, 126.33 (C(4a), C(6a), C(10a)); 136.67 (C(10b)); 146.48 (C(6)); 169.68 (MeCO).

B. A similar reaction of compound **1** (0.5 g, 2.3 mmol) with reflux for 5 h, under the conditions of experiment ***A***, gave (after column chromatography) a 2 : 1 mixture of compounds **3** and **4** (0.3 g, 68%). The spectroscopic characteristics of compound **3** were found from the spectra of a mixture of **3** and **4**. ^{1}H NMR for **3**, δ: 0.92 (m, 6 H, 2 MeC(8′)); 1.04, 1.10 (both d, 1.5 H each, MeC(4′), *J* = 6.7 Hz); 1.30—2.10 (m, 8 H, H(4′)—H(8′)); 1.75 (s, 3 H, MeC(3′)); 2.29 (s, 3 H, MeC(2)); 2.55 (s, 3 H, MeCO)); 3.40 (d, 2 H, H(1′), *J* = 6.1 Hz); 5.24 (t, 1 H, H(2′), *J* = 6.1 Hz); 6.08 (br.s, 1 H, OH); 7.45 (m, 2 H, H(6), H(7)); 7.70 and 8.10 (both d, 2 H, H(5), H(8), *J* = 7.7 Hz). ^{13}C NMR, δ: 12.51 (MeC(2)); 13.31 (MeC(3′)); 19.86 (MeC(4′)); 20.51 (MeCO); 22.52 (2 MeC(8′)); 25.84 (C(6′)); 26.25 (C(5′)); 27.81 (C(8′)); 35.03 (C(1′)); 38.95 (C(7′)); 42.74 (C(4′)); 120.17 (C(2′)); 120.35, 121.85, 124.44, 125.87 (C(5)—C(8)); 124.80, 125.68, 126.07 (C(2), C(3), C(4a), C(8a)); 137.66 (C(3′)); 142.84 (C(4)); 147.62 (C(1)); 169.80 (MeCO).

(2*RS*)-6-Acetoxy-2,5-dimethyl-2-(4*RS*,8*RS*,12-trimethyldecan-1-yl)-3,4-dihydro-2*H*-naphtho[1,2-*b*]pyrans (6). Isophytol **5** (0.4 g, 1.35 mmol) was slowly added under argon to a boiling suspension of compound **1** (0.56 g, 2.6 mmol) and powdered Zeocar-10 catalyst (1.1 g) in anhydrous toluene (9 mL). The reaction mixture was refluxed for 4 h and cooled to room temperature. The catalyst was filtered off, and the filtrate was concentrated. The residue was chromatographed on a column with SiO_2 (20 g). The fraction of nonpolar substances (R_f 0.7) was eluted with *n*-hexane, and the evaporation of the next fraction (R_f 0.4), which was eluted with an *n*-hexane—Et_2O (10 : 1) mixture, gave diastereomeric mixture **6** (0.56 g, 84%). Found (%): C, 80.42; H, 10.03. $C_{33}H_{50}O_3$. Calculated (%): C, 80.11; H, 10.19. IR, ν/cm^{-1}: 1760 (C=O); 1210, 1080, and 1060 (C—O). UV (EtOH), λ_{max}/nm (ε): 244 (40493), 305 (5365), 328 (3925). ^{1}H NMR, δ: 0.95 (m, 12 H, MeC(4′), MeC(8′), 2 MeC(12′)); 1.00—1.80 (m, 23 H, H(1′)—H(12′), H(3)); 1.35 and 1.40 (both s, 3 H, MeC(2)); 2.28 (s, 3 H, MeC(5)); 2.51 (s, 3 H, MeCO); 2.76 (t, 2 H, H(4), *J* = 6.4 Hz); 7.50 (m, 2 H, H(8), H(9)); 7.70 and 8.30 (both d, 2 H, H(7), H(10), *J* = 8.1 Hz). ^{13}C NMR, δ: 12.56 (MeC(5)); 19.63 and 19.69 (MeC(4′) and MeC(8′)); 20.50 (MeCO); 20.59 and 21.00 (C(4)); 22.58 and 22.68 (2 MeC(12′)); 23.65 (MeC(2)); 24.38, 24.75 (C(2′), C(6′), C(10′)); 27.90 (C(12′)); 30.95 (C(3)); 32.61, 32.70 (C(4′), C(8′)); 37.23, 37.33, 37.50 (C(3′), C(5′), C(7′), C(9′)); 39.31 (C(11′)); 39.99 and 40.06 (C(1′)); 75.65 (C(2)); 113.95 (C(5)); 120.21, 121.90, 124.46, 126.0 (C(7)—C(10)); 124.78, 125.72, 126.33 (C(4a), C(6a), C(10a)); 136.79 (C(10b)); 146.63 (C(6)); 169.54 (MeCO).

(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*]pyrans (7). A solution of diastereomeric mixture **6** (0.28 g, 0.57 mmol) and lithium alumohydride (0.02 g, 0.53 mmol) in anhydrous diethyl ether (22.7 mL) was refluxed for 1 h (Ar) with stirring. The reaction mixture was cooled to 0 °C, and wet ether (2 mL) and then 3 *M* hydrochloric acid (0.5 mL) were added. The ethereal layer was separated, washed with water to the neutral pH, dried with $MgSO_4$, and concentrated *in vacuo*. Compound **7** was obtained in 77% yield (0.2 g) as a viscous dark yellow oil. IR, ν/cm^{-1}: 1080, 1060 (C—O); 3400 (OH). The UV and ^{1}H NMR spectra are identical to those presented earlier.[4] ^{13}C NMR, δ: 15.27 (MeC(5)); 19.78, 19.86 (MeC(4′), MeC(8′)); 21.01 and 21.18 (C(4)); 22.75 and 22.85 (2 MeC(12′)); 23.60 (MeC(2)); 24.56, 24.93 (C(2′), C(6′), C(10′)); 28.07 (C(12′)); 31.52 (C(3)); 32.78, 32.87 (C(4′), C(8′)); 37.39, 37.49, 37.69 (C(3′), C(5′), C(7′), C(9′)); 39.47 (C(11′)); 39.91 and 39.96 (C(1′)); 75.12 (C(2)); 114.48 (C(5)); 117.50, 124.44, 124.57 (C(4a), C(6a), C(10a)); 120.63, 121.66, 124.44, 125.08 (C(7)—C(10)); 141.08 (C(10b)); 142.88 (C(6)).

(2*RS*)-6-Acetoxy-2,5-dimethyl-2-(4-methylpent-3-en-1-yl)-3,4-dihydro-2*H*-naphtho[1,2-*b*]pyran (10) and 9-acetoxy-1,1,4a,10-tetramethyl-1,2,3,4,4a*RS*,11a-hexahydro-1*H*-benzo[*h*]xanthene (11). ***A.*** Linalool **8** (0.22 g, 1.4 mmol) was slowly added under argon to a boiling suspension of compound **1** (0.60 g, 2.8 mmol) and powdered Zeocar-10 catalyst (1.0 g) in anhydrous toluene (9 mL). The reaction mixture was refluxed for 5 h and cooled to room temperature. The catalyst was filtered off, and the filtrate was concentrated. The residue was chromatographed on a column with SiO_2 (20 g). A fraction of nonpolar substances (R_f 0.7) was isolated by elution with *n*-hexane, and the next fraction (R_f 0.4) was eluted with an *n*-hexane—Et_2O (10 : 1) mixture. Evaporation of this fraction gave a viscous oil (0.45 g), which crystallized on standing. After treatment with *n*-hexane, product **11** was filtered off. The yield was 0.31 g (63%), m.p. 191—193 °C. Found (%): C, 78.16; H, 7.81. $C_{23}H_{28}O_3$. Calculated (%): C, 78.38; H, 8.01. IR, ν/cm^{-1}: 1760 (C=O); 1210, 1080, 1060 (C—O). UV ($CHCl_3$), λ_{max}/nm (ε): 245 (34650), 308 (6410), 330 (5396). ^{1}H NMR, δ: 1.00, 1.10 (both s, 6 H, 2 MeC(1)); 1.30 (s, 3 H, MeC(4a)); 1.40—1.90 (m, 6 H, H(2)—H(4)); 2.15 (m, 1 H, H(11a)); 2.28 (s, 3 H, MeC(10)); 2.50 (m, 1 H, H(11), 3 H, MeCO); 2.80 (dd, 1 H, H(11), *J* = 16.1 Hz, *J* = 5.2 Hz); 7.48 (m, 2 H, H(6), H(7)); 7.70 and 8.28 (both d, 2 H, H(8), H(5), *J* = 8.0 Hz). ^{13}C NMR, δ: 12.60 (MeC(10)); 20.55 (2 MeC(1), MeCO); 21.69 (C(1)); 32.03 (MeC(4a)); 33.33 (C(3), C(11)); 39.71 (C(2)); 41.50 (C(4)); 47.92 (C(11a)); 75.41 (C(4a)); 114.00 (C(10a)); 120.04, 120.15, 121.97, 124.43, 124.62, 125.91, 125.99 (C(5)—C(8), C(4C), C(8a), C(10)); 136.86 (C(4b)); 146.01 (C(9)); 169.66 (MeCO).

B. Compound **8** (0.71 g, 4.6 mmol) was slowly added under argon to a boiling suspension of compound **1** (1.0 g, 4.6 mmol) and CSA catalyst (0.11 g, 0.47 mmol) in anhydrous *n*-octane (9 mL). The reaction mixture was refluxed for 3 h, then cooled

to room temperature, and poured into a saturated solution of $NaHCO_3$ (60 mL). According to the GLC data, the mixture consisted of benzochroman **10** (75%, retention time 25.81 min), xanthene **11** (15%, retention time 26.88 min), and a non-identified product (10%, retention time 24.46 min). The resulting mixture was extracted with EtOAc, and the organic layers were washed with a saturated solution of NaCl and dried over $MgSO_4$. The filtrate was concentrated, and the residue was chromatographed on a column with SiO_2 (60 g). A fraction of nonpolar substances (R_f 0.7) was eluted with *n*-hexane, and the next fraction (R_f 0.4) was eluted with an *n*-hexane—Et_2O (10 : 1) mixture. The evaporation of this fraction gave 1.07 g of an oily substance (**10—11**, ~6 : 1, GLC data, compound **10** was characterized by the spectra of the mixture). IR, ν/cm^{-1}: 1730 (C=O); 1210, 1080, 1060 (C—O). UV ($CHCl_3$), λ_{max}/nm (ε): 245 (35137), 309 (5383), 328 (4595). ^{1}H NMR, δ: 1.48 (s, 3 H, MeC(2)); 1.60—2.10 (m, 6 H, H(1′), H(2′), H(3)); 1.74 and 1.78 (both s, 3 H each, 2 MeC(4′)); 2.28 (s, 3 H, MeC(5)); 2.50 (s, 3 H, MeCO); 2.80 (t, 2 H, H(4), J = 6.5 Hz); 5.28 (t, 1 H, H(3′), J = 7.0 Hz); 7.50 (m, 2 H, H(8), H(9)); 7.75 and 8.32 (both d, 2 H, H(7), H(10), J = 8.5 Hz). ^{13}C NMR, δ: 12.42 (MeC(5)); 17.96 (MeC(4′)); 20.41 (MeCO); 20.42 (C(4)); 22.12 (C(2′)); 26.50 (MeC(2), C(5′)); 30.89 (C(3)); 33.18 (C(1′)); 75.34 (C(2)); 113.89 (C(5)); 124.37 (C(3′)); 120.14, 121.74, 124.20, 126.10 (C(7)—C(10)); 124.52, 125.73, 126.10 (C(4a), C(6a), C(10a)); 131.31 (C(4′)); 136.75 (C(10b)); 146.81 (C(6)); 169.37 (MeCO).

C. An oily material (0.22 g, **10—11**, ~4 : 1, the content of **10** is 58%) was obtained from compound **1** (0.2 g, 0.9 mmol), compound **8** (0.14 g, 0.9 mmol), and *p*-TsOH (0.017 g, 0.1 mmol) under the conditions of a previous experiment.

(2*RS*)-6-Acetoxy-2,5-dimethyl-2-(3-oxoprop-1-yl)-3,4-dihydro-2*H*-naphtho[1,2-*b*]pyran (12). ***A.*** An ozone—oxygen mixture was passed at a rate of 30 L h^{-1} (1.5 mmoles of O_3 at a productivity of the ozonator of 10 mmol O_3 h^{-1}) through a mixture (0.74 g) of nonpurified compound **10** (the content of **10** was 75%, *i.e.* 0.56 g (1.6 mmol)), $Ba(OH)_2$ (0.65 g, 3.8 mmol), H_2O (0.1 mL), and acetone (6 mL) at room temperature for 11 min. Then, the solid was filtered off, and the filtrate was concentrated *in vacuo*. The resulting material was dissolved in Et_2O (15 mL), dried with $MgSO_4$, and concentrated. The residue was chromatographed on a column with SiO_2 (20 g). A fraction with R_f 0.7 was eluted with an *n*-hexane—Et_2O (10 : 1) mixture, and evaporation of this fraction gave unreacted compound **11** (0.1 g). Then, the fraction (R_f 0.5) containing aldehyde **12** (0.31 g, 59%), which is an oily substance, was eluted with an *n*-hexane Et_2O (10 : 3) mixture. IR, ν/cm^{-1}: 1710, 1740 (C=O); 1210, 1060, 1080 (C—O). UV ($CHCl_3$), λ_{max}/nm (ε): 243 (19275), 275 (3264), 303 (2834), 326 (2061). ^{1}H NMR, δ: 1.20 (s, 3 H, MeC(2)); 1.70—2.00 (m, 4 H, H(3), H(1′)); 2.02 (s, 3 H, MeC(5)); 2.32 (s, 3 H, MeCO); 2.53 (m, 2 H, H(2′)); 2.65 (t, 2 H, H(4), J = 6.7 Hz); 7.30 (m, 2 H, H(8), H(9)); 7.55 and 8.05 (both d, 2 H, H(7), H(10), J = 7.3 Hz); 9.65 (s, 1 H, HCO). ^{13}C NMR, δ: 15.04 (MeC(5)); 20.22 (MeCO); 20.29 (C(4)); 28.97 (MeC(2)); 30.93 (C(3)); 38.19 (C(1′)); 53.57 (C(2′)); 74.40 (C(2)); 113.87 (C(5)); 120.19, 121.17, 124,43, 125.94 (C(7)—C(10)); 124.56, 125.59, 125.88 (C(4a), C(6a), C(10a)); 137.02 (C(10b)); 145.85 (C(6)); 169.32 (MeCO); 201.96 (HCO).

B. An ozone—oxygen mixture was passed with stirring (−70 °C) for 70 min at a rate of 30 L h^{-1} (9.8 mmoles of O_3) through a mixture (4.6 g) of nonpurified compound **10** (the content of **10** is 75% or 3.45 g (9.8 mmol)), and $NaHCO_3$ (1.6 g) in a CH_2Cl_2—anhydrous MeOH (10 : 1) mixture (36 mL). Then, argon was passed through the reaction mixture, and Me_2S (11 mL) was added at −40 °C. After the mixture was heated to room temperature, it was stirred for 5 h and concentrated *in vacuo*. The residue was diluted with water (40 mL) and extracted with Et_2O. The extract was washed with a saturated solution of NaCl, dried with $MgSO_4$, and concentrated. The residue was chromatographed on a column with SiO_2 (100 g) as described in experiment ***A***. Compounds **11** (0.8 g) and **12** (2.38 g, 74%) were obtained. Their IR, UV, and ^{1}H, ^{13}C NMR spectra are identical to those presented for experiment ***A***.

(2*RS*)-6-Acetoxy-2,5-dimethyl-2-(1*S*,5-dimethylhex-4-en-1-yl)-3,4-dihydro-2*H*-naphtho[1,2-*b*]pyrans (13). A mixture of diastereomers **13** (0.27 g, 51%) was obtained as an oily material with $[\alpha]_D^{20}$ −4.1 (*c* 4.0, $CHCl_3$) by refluxing (3 h, Ar) a mixture of menadiol monoacetate **1** (0.3 g, 1.4 mmol), vinylcarbinol **9** (0.25 g, 1.4 mmol), CSA (0.033 g, 0.14 mmol), and *n*-octane (4 mL) followed by the treatment as described in experiment ***B***. Found (%): C, 78.77; H, 8.36. $C_{25}H_{32}O_3$. Calculated (%): C, 78.91; H, 8.48. IR, ν/cm^{-1}: 1730 (C=O); 1210, 1080 (C—O). UV ($CHCl_3$), λ_{max}/nm (ε): 242 (25897), 309 (4712), 333 (3585). ^{1}H NMR, δ: 1.10 (d, 1.5 H, MeC(1′), J = 6.6 Hz); 1.18 (d, 1.5 H, MeC(1′), J = 6.7 Hz); 1.35 (s, 3 H, MeC(2)); 1.72 and 1.82 (both s, 6 H, 2 MeC(5′)); 1.60—2.10 (m, 7 H, H(1′)—H(3′), H(3)); 2.25 (s, 3 H, MeC(5)); 2.50 (s, 3 H, MeCO); 2.75 (t, 2 H, H(4), J = 6.6 Hz); 5.10 and 5.25 (both t, 1 H, H(4′), J = 7.3 Hz); 7.50 (m, 2 H, H(8), H(9)); 7.73 and 8.31 (both d, 2 H, H(7), H(10), J = 7.3 Hz). ^{13}C NMR, δ: 12.38 (MeC(5)); 13.39 and 14.03 (MeC(1′)); 17.40 and 17.52 (MeC(5′)); 20.22 (C(4)); 20.32 (MeCO); 25.34 (MeC(2)); 25.64 (C(6′)); 26.27 and 26.31 (C(3′)); 30.88, 31.54 (C(2′), C(3)); 39.37 (C(1′)); 78.12 and 78.16 (C(2)); 114.20 and 114.24 (C(5)); 120.18, 121.76, 121.80, 124.51, 125.75 (C(7)—C(10)); 124.36 and 124.39 (C(4′)); 124.75, 124.78, 125.53, 126.04 (C(4a), C(6a), C(10a)); 131.39, 131.20 (C(5′)); 136.75 (C(10b)); 146.37, 146.33 (C(6)); 169.34, 169.29 (MeCO).

(2*RS*)-6-Acetoxy-2,5-dimethyl-2-(1*S*-methyl-4-oxobut-1-yl)-3,4-dihydro-2*H*-naphtho[1,2-*b*]pyrans (14). ***A.*** An ozone—oxygen mixture was passed at room temperature for 13 min at a rate of 30 L h^{-1} (1.7 mmoles of O_3 at a productivity of the ozonator of 10 mmol O_3 h^{-1}) through a mixture of compound **13** (0.65 g, 1.7 mmol), $Ba(OH)_2$ (0.5 g, 2.9 mmol), H_2O (0.1 mL), and acetone (9 mL). Then, the mixture was treated as described in experiment ***A*** for the synthesis of compound **12**. Compound **14** was obtained in 58% yield (0.35 g), $[\alpha]_D^{20}$ −1.75 (*c* 5.4, $CHCl_3$). IR, ν/cm^{-1}: 1740 (C=O); 1210, 1080, 1060 (C—O). UV ($CHCl_3$), λ_{max}/nm (ε): 243 (24316), 277 (2068), 308 (2166), 333 (1824). ^{1}H NMR, δ: 0.95 and 1.10 (both d, 3 H, MeC(1′), J = 6.9 Hz); 1.22 (s, 3 H, MeC(2)); 1.40—2.0 (m, 5 H, H(1′), H(2′), H(3)); 2.15 (s, 3 H, MeC(5)), 2.40 (m, H(3′)); 2.44 (s, 3 H, MeCO); 2.70 (m, 2 H, H(4)); 7.40 (m, 2 H, H(8), H(9)); 7.62 and 8.15 (both d, 2 H, H(7), H(10), J = 7.2 Hz); 9.75 (s, 1 H, HCO). ^{13}C NMR, δ: 12.41 (MeC(5)); 13.35 and 13.95 (MeC(1′)); 19.92 (MeC(2)); 20.56 (MeCO); 20.30 (C(4)); 22.79 (C(3)); 29.65 (C(1′)); 42.41 (C(2′)); 60.16 (C(3′)); 75.11 (C(2)); 114.15 (C(5)); 120.93, 121.55, 124.65, 129.95 (C(7)—C(10)); 125.58, 125.64 (C(4a), C(6a), C(10a)); 136.76 (C(10b)); 145.95, 146.03 (C(6)); 169.50 (MeCO); 202.60 and 202.34 (HCO).

B. An ozone—oxygen mixture was passed with stirring (−70 °C) for 6 min at a rate of 30 L h^{-1} (0.85 mmoles of O_3)

through a mixture of compound **13** (0.32 g, 0.84 mmol) and $NaHCO_3$ (0.16 g) in a CH_2Cl_2—anhydrous MeOH (10 : 1) mixture (3.6 mL). Then, the mixture was treated as described in experiment ***B*** for the synthesis of aldehyde **12**. A mixture of diastereomeric aldehydes **14** was obtained in 67% yield (0.2 g). Their IR, UV, and ^1H, ^{13}C NMR spectra are identical to those presented above.

(2*RS*)-6-Acetoxy-2,5-dimethyl-2-(3,3-dimethoxyprop-1-yl)-3,4-dihydro-2*H*-naphtho[1,2-*b*]pyran (15). Vacuum-dried (5 Torr, 50 °C) NH_4Cl (0.03 g, 0.56 mmol) was added to a solution of aldehyde **12** (0.29 g, 0.89 mmol) in anhydrous MeOH (2.5 mL). The mixture was kept for 48 h at room temperature, and a 10% methanolic solution of MeONa (0.3 mL) was added until the alkaline pH was achieved. Then the mixture was concentrated *in vacuo*, and the residue was diluted with Et_2O, washed with a saturated solution of NaCl, dried with $MgSO_4$, and concentrated. Acetal **15** was obtained in 85% yield (0.28 g). Found (%): C, 70.84; H, 7.48. $C_{22}H_{28}O_5$. Calculated (%): C, 70.94; H, 7.58. IR, ν/cm^{-1}: 1750 (C=O); 1200, 1060 (C—O). UV ($CHCl_3$), λ_{max}/nm (ε): 244 (35805), 305 (4450), 327 (3445). ^1H NMR, δ: 1.28 (s, 3 H, MeC(2)); 1.78—2.10 (m, 6 H, H(3), H(1′), H(2′)); 2.18 (s, 3 H, MeC(5)); 2.45 (s, 3 H, MeCO); 2.74 (t, 2 H, H(4), J = 6.5 Hz); 3.30 and 3.32 (both s, 6 H, OMe); 4.40 (t, 1 H, H(3′), J = 5.0 Hz); 7.40 (m, 2 H, H(8), H(9)); 7.65 and 8.20 (both d, 2 H, H(7), H(10), J = 7.5 Hz). ^{13}C NMR, δ: 12.39 (MeC(5)); 20.34 (MeCO); 20.39 (C(4)); 23.38 (MeC(2)); 26.56 (C(2′)); 29.50 (C(3)); 31.73 (C(1′)); 52.39 and 52.67 (2 OMe); 74.96 (C(2)); 104.53 (C(3′)); 113.95 (C(5)); 120.17, 121.68, 124.45, 125.80 (C(7)—C(10)); 124.63, 125.80, 125.95 (C(4a), C(6a), C(10a)); 136.90 (C(10b)); 146.28 (C(6)); 169.31 (MeCO).

(2*RS*)-6-Acetoxy-2,5-dimethyl-2-(4,4-dimethoxybut-1-yl)-3,4-dihydro-2*H*-naphtho[1,2-*b*]pyrans (16) were obtained similarly to a previous procedure from a diastereomeric mixture of aldehyde **14** (0.17 g, 0.48 mmol). The yield was 0.167 g (87%). Found (%): C, 72.09; H, 8.40. $C_{24}H_{32}O_5$. Calculated (%): C, 71.97; H, 8.05. IR, ν/cm^{-1}: 1750 (C=O); 1200, 1060 (C—O). UV ($CHCl_3$), λ_{max}/nm (ε): 243 (22742), 272 (4416), 305 (3034), 329 (2248). ^1H NMR, δ: 0.95 and 1.07 (both d, 3 H, MeC(1′), J = 6.5 Hz); 1.23 (s, 3 H, MeC(2)); 1.40—2.0 (m, 7 H, H(3), H(1′)—H(3′)); 2.13 and 2.18 (both s, 3 H, MeC(5)); 2.46 (s, 3 H, MeCO); 2.72 (t, 2 H, H(4), J = 6.4 Hz); 3.31, 3.32 and 3.35 (all s, 6 H, OMe); 4.34 (m, 1 H, H(4′)); 7.40 (m, 2 H, H(8), H(9)); 7.60 and 8.20 (both m, 2 H, H(7), H(10)). ^{13}C NMR, δ: 12.51 (MeC(5)); 13.59 and 14.23 (MeC(1′)); 16.25 (MeC(2)); 20.50 (MeCO); 20.31 and 20.38 (C(4)); 27.98, 28.48 (C(3) (C(3′)); 29.18 (C(1′)); 31.05 and 31.17 (C(2′)); 52.81, 52.73, 52,67 and 52.59 (2 OMe); 78.25 (C(2)); 104.39 and 104.65 (C(4′)); 114.31 (C(5)); 120.27, 121.84, 124.53, 125.72 (C(7)—C(10)); 124.83, 126.03, 126.14 (C(4a), C(6a), C(10a)); 136.90 (C(10b)); 146.44 (C(6)); 169.51 (MeCO).

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