Chemistry of Natural Compounds and Bioorganic Chemistry

Synthesis of (±)-furodizinin and (±)-furodizin*

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The racemic forms of natural furanoterpenoids, (±)-furodizinin and (±)-furodizin, were synthesized by cationic cyclization of the α- or β-furylmethyl derivatives of linalool, geraniol, and nerol.

Key words: furanoterpenoids, (±)-furodizinin; (±)-furodizin; derivatives of (±)-linalool, geraniol, and nerol, cationic cyclization; ^1H, ^{13}C, and 2D-NOESY NMR spectra.

Cationic cyclization of the suitable linear precursors of the isoprenoid series is an efficient strategy for constructing the carbon skeleton of bi- and tricyclic natural terpenes (or those containing a larger number of cycles) (see, for example, Ref. 2). We have studied the possibility of using this procedure for the synthesis of furanoterpenoids, namely, (±)-furodizinin (**1**) and (±)-furodizin (**2**). Optically active forms of these compounds have been found among the metabolites of some species of sea sponges.[3] To accomplish the purpose in hand, we obtained a series of α- and β-furylmethyl derivatives of (±)-linalool, geraniol, and nerol (**3**—**6**). Among them, stereoisomers *E*-**3** and *Z*-**3** appeared to be available from dehydrolinalool **7** (see Ref. 4). Similarly, β-substituted furan **4** was synthesized starting from dehydrolinalool **7** and chloride **8** through intermediate alkyne **9**, which was reduced with Li in NH_3 (Scheme 1).

With the aim of obtaining the derivatives of geraniol, *E*-**5** and *E*-**6**, and nerol, *Z*-**5** and *Z*-**6**, we used condensation of citral **10** with furfuryl magnesium chloride **11**, which affords an *E*-**5**/*Z*-**5** mixture with a ratio of 4.5 : 1.

The above-mentioned mixture of alcohols was converted to a mixture of the corresponding acetates without additional purification, and the individual components *E*-**6** and *Z*-**6** of the mixture obtained were isolated by preparative HPLC. The saponification of these compounds afforded the desired allyl alcohols *E*-**5** and *Z*-**5**, respectively. Compounds **4**, **5**, and **6** have not previously been reported. These compounds appear to be moderately labile; their structures were confirmed by the results of NMR (^1H and ^{13}C), IR, and mass spectra, and elemental analysis.

We attempted to find efficient conditions for cationic cyclization of isoprenoids **3**—**6**. A solution of 85% H_3PO_4

* A. M. Moiseenkov (1936—1992), an outstanding Russian organic chemist, would have been sixty on July 6, 1996. He contributed significantly to the chemistry of terpenoids. The scientific heritage of A. M. Moiseenkov is rich and diversified. This work is devoted to the realization of one of his ideas. For the preliminary communication see Ref. 1.

† Deceased

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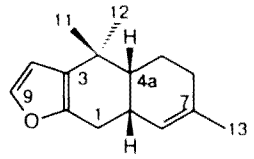
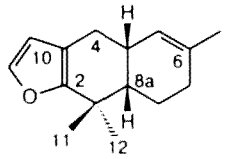


1



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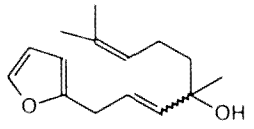
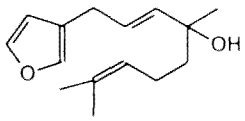


E,Z-**3**



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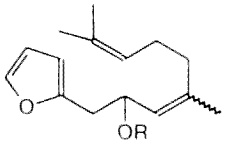
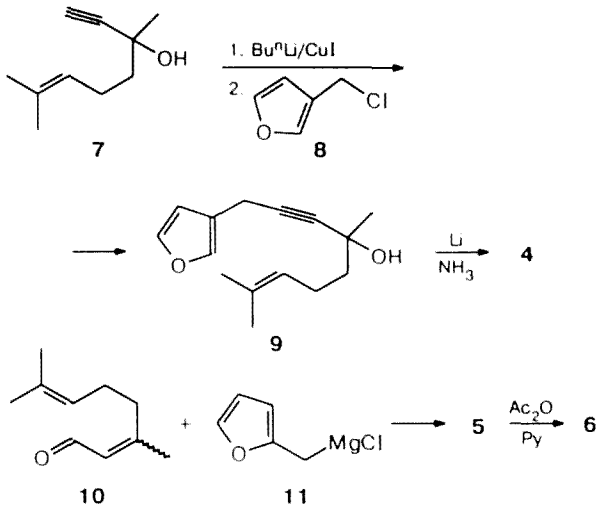


E,Z-**5** (R = H)
E,Z-**6** (R = Ac)

Scheme 1



(~0.2 mole-equivalent) in toluene at 100 °C appeared to be optimum (*cf.* Ref. 5). In this case, mixtures containing identical sets of products were obtained from compounds *E*-**3**, *E*-**5**, and *Z*-**5** in good total yields. (±)-Furodizin **1** was the major component of these mixtures. The minor components were the stereoisomer of (±)-furodizin (**12**) and the derivatives of limonene **13**, which formed, apparently, owing to the interruption of cationic cyclization at the point of the intermediate carbonium ion **16** at the first stage of cyclization of the initial substrates (Scheme 2). In the case of diolefin *Z*-**3**, a noticeable amount of bicyclic compound **14** was present in the reaction mixture in addition to the above-mentioned products. Compound **14** formed, apparently, as a result of the kinetically controlled electrophilic attack at the furan ring in cisoid carbonium intermediate **15a**. In this case, the yield of (±)-furodizinin **1** substantially decreased because of the increase in the proportion of its isomer **12** in the mixture.

In all the cases considered above, traces of furanoterpenoid **17**, which was reported previously[3] without a description of its particular physicochemical characteristics and which is regioisomeric to **1**, were found in the cyclization products (the ^{1}H NMR data). Compound **17** was one of the major components of the mixture that formed under the above-described conditions from acetate *E*-**6**, the complete conversion of which required an increase in the duration of the reaction.

The formation of **17** is explained by the acid-catalyzed isomerization of the initially appearing (±)-furodizinin **1**. In the model experiment, the storage of a toluene solution of **1** in the presence of 85% H_3PO_4 (~0.2 mole-equivalent) at 100 °C for 2 h gave a mixture of isomers **1**/**17** in a ratio of ~1 : 3.

The use of alternative cyclizing reagents (protic and Lewis acids) appeared to be less efficient due to the formation of substantial amounts of resinification products. For example, when the derivative of linalool *E*-**3** was treated with HCOOH in cyclohexane, the total yield of compounds **1**, **12**, and **13** was only 35 %.

The mixtures of the products of the cationic cyclization of compounds **3**—**6** were chromatographed on SiO_2 impregnated with 10 % $AgNO_3$. As a result, (±)-furodizinin **1** and its isomer **12** were obtained as individual compounds. We isolated also a mixture of epimeric derivatives of limonene **13** (*cis*/*trans* ≈3 : 1, from ^{1}H NMR data), which was impossible to separate chromatographically, and samples of compounds **14** and **17** as fractions enriched with these compounds.

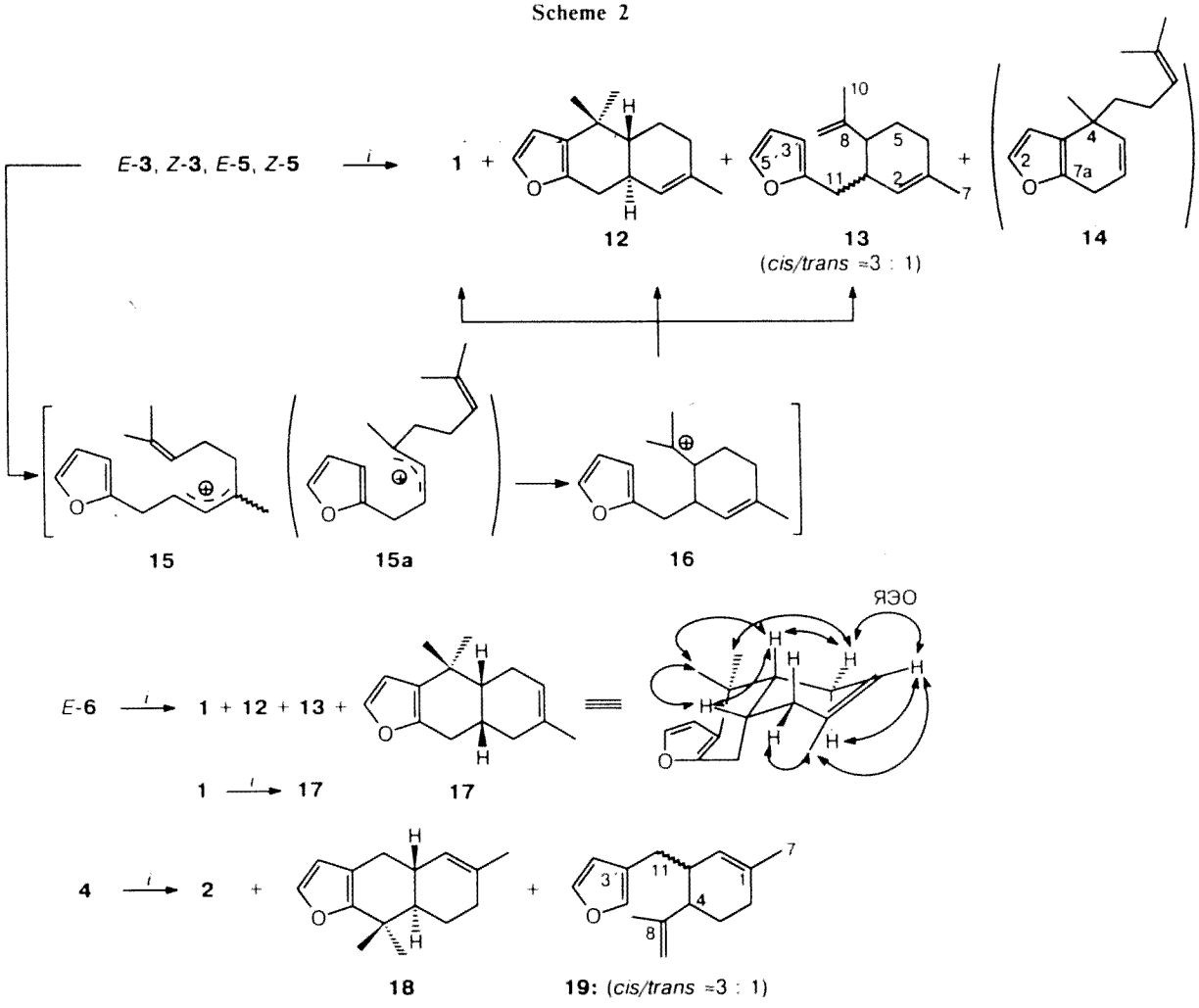
The structures of all compounds obtained by this procedure were confirmed by spectral studies and elemental analysis. In particular, the spectral characteristics (^{1}H and ^{13}C NMR) of (±)-furodizinin **1** virtually coincide with those reported previously.[3,6] The value of the spin-spin interaction constant J_{4a-8a} = 10.4 Hz (*cf.* J_{4a-8a} = 3.6 Hz for **1**) in the ^{1}H NMR spectrum of furanoterpenoid **12** unambiguously indicates that the six-membered cycles in the molecule of **12** are *trans*-fused. The mass spectrum of **12** contains an intense peak at *m*/*z* 122, which corresponds to retrodiene decomposition of the molecular ion typical of these structures (*cf.* Refs. 3 and 7). The derivative of limonene, *trans*-**13**, which has not been reported previously, was reliably identified based on the analysis of the ^{1}H NMR spectrum of the above-mentioned mixture of this derivative with the known *cis*-**13**[4,6b] and on the consideration of the ^{1}H NMR spectrum of the sample of bicyclic compound **14**, which contained *trans*-**13** as a minor component. It is interesting to note that the chemical shifts of the exomethylene protons measured for *cis*-**13** differ by $\Delta\delta \approx 0.17$, whereas in the case of *trans*-**13**, this

difference is no more than 0.05 p.p.m. This effect is, apparently, typical of compounds of this type (see below). It was also found that when a mixture of epimers of **13** was treated with a solution of 85% H_3PO_4 (~0.2 mole-equivalent) in toluene at 100 °C, both epimers gave a mixture of products **1**, **12**, and **17** in good total yields. This mixture is analogous to that formed upon cyclization of compounds **3**, **5**, and **6**. The regioisomer of (±)-furodizinin **1**, furanoterpenoid **17**, was characterized based on the data of NMR. In particular, the spin-spin interaction constant $J_{4a\text{-}5\alpha}$ = 11.5 Hz observed in the ^{1}H NMR spectrum of **17** indicates that **17** occurs preferentially in steroid conformation in a $CDCl_3$ solution. The nuclear Overhauser effects observed in the 2D-NOESY experiment (see Scheme 2), which additionally confirm the structure of this compound, are also consistent with this conclusion.

The conditions of cyclization of α-substituted furans **3**, **5**, and **6**, which we found, appeared to be efficient also in the case of β-derivative **4**. In this case, the mixture formed contained (±)-furodizin **2** as a major component, its isomer **18**, which was previously unknown, and derivatives of limonene *cis*-/*trans*-**19** (appearing, apparently, analogously to compound **13**) in a ratio of ~6 : 2 : 1, respectively. This ratio was determined based on measurements of the relative integral intensities of diagnostic signals of compounds **2**, **18**, and **19** in the ^{1}H NMR spectrum of the mixture and on the results of the preparative separation of these components on $SiO_2/AgNO_3$.

The structure of (±)-furodizin **2** obtained by this procedure was confirmed by a comparison of its spectral characteristics with those reported previously.[3,6] The conclusions about the structure of its isomer **18** were made based on the data of the mass spectra and ^{1}H and ^{13}C NMR spectra. The obtained mixture of the known[6b] *cis*-**19** and *trans*-**19**, which has not been reported previously, was characterized taking into account criteria analogous to those used for the identification of the stereoisomers of **13**. As in the case of stereoisomers **13**,

Scheme 2



Reagents and conditions: *i*. 85% H_3PO_4 (aq.)/PhMe, 100 °C.

the ^{1}H NMR spectra of compounds **19** show different degrees of nonequivalence of the exomethylene protons of the isopropenyl fragment depending on its location with respect to the furfurylmethyl fragment of the molecule.

Therefore, cationic cyclization of prenyl-substituted furans provides rather simple access to (±)-furodizinin **1** and (±)-furodizin **2**. These compounds are known to be of certain practical interest (see Ref. 8).

Experimental

The melting points (which were not corrected) were determined on a Kofler stage. The IR spectra (ν/cm^{-1}) of solutions in $CHCl_3$ (unless otherwise noted) were recorded on a Specord M-80 instrument. The ^{1}H and ^{13}C NMR spectra (δ, J/Hz) of solutions in $CDCl_3$ were measured on Bruker AC-200, Bruker WM-250, and Bruker AMX-400 spectrometers; the DQF-COSY[9], NOESY,[10] and z-HMQC[11] spectra were obtained on a Bruker AMX-400 instrument. The mass spectra (EI, 70 eV) were recorded on Varian MAT CH-6 and Varian MAT 311A instruments. The values of R_f are given for a fixed Silufol SiO_2 layer (3 : 2 hexane—ether, unless otherwise noted). HPLC was carried out on a column packed with Silasorb 600 (10 μm, 250×24 mm); a heptane–ethyl acetate mixture (9 : 1 by volume, 7 mL min^{-1}) was used as the eluent; the detector was refractometric.

4,8-Dimethyl-1-(3′-furyl)nona-7-en-2-in-4-ol (9). A solution of *n*-BuLi (15.5 mL, 1.35 *M*) in hexane (21 mmol) was added to a solution of compound **7** (1.52 g, 10 mmol) in THF (15 mL) with intense stirring at −20 °C (Ar) over a period of 10 min. After 10 min, CuI (0.3 g, 1.58 mmol) was added to the mixture as one portion, and after 20 min, a solution of chloride **8**[12] (1.16 g, 10 mmol) in THF (3 mL) was added portionwise for 5 min. Then the reaction mixture was heated to 20 °C, kept at this temperature for 20 h, and then diluted with ether and decomposed with a saturated NH_4Cl solution. The organic layer was separated, washed with water, dried with Na_2SO_4, and distilled *in vacuo*. The residue (2.55 g) was chromatographed on SiO_2 (50 g). Elution with a cooled (−5 °C) hexane—ether (4 : 1) mixture afforded a material (1.65 g) from which unreacted **7** (0.5 g) was distilled off, b.p. 37—40 °C (0.03 Torr); the distillation residue (~1 g) was chromatographed on SiO_2 (100 g). Elution under the above-mentioned conditions gave compound **9** (0.81 g, 53 %) as a pale yellow oil, R_f 0.45. IR: 600, 725, 870, 935, 980, 1025, 1115, 1210, 1380, 1450, 1500, 2860—3000, and 3600. ^{1}H NMR: 1.50 (s, 3 H, MeC(4)); 1.62 and 1.70 (br.s, 6 H, MeC(8)); 1.56 (m, 2 H, HC(5)); 2.2 (m, 2 H, HC(6)); 3.38 (br.s, 2 H, HC(1)); 5.15 (br.t, J = 7, 1 H, HC(7)); 6.32 (m, 1 H, HC(4′)); 7.33 and 7.36 (both m, 2 H, HC(2′), HC(5′)). Mass spectrum, m/z: 232 $[M]^+$. Found (%): C, 77.21; H, 8.75. $C_{15}H_{20}O_2$. Calculated (%): C, 77.55; H, 8.68.

4,8-Dimethyl-1-(3′-furyl)nona-2*E*,7-dien-4-ol (4). A solution of **9** (0.69 g, 3 mmol) in THF (15 mL) was added to a solution of Li (0.21 g, 30 mg-at) in NH_3 (90 mL) with intense stirring at −70 °C (Ar) over a period of 10 min. The reaction mixture was kept at −70 °C for 1 h and then decomposed with an excess of NH_4Cl. NH_3 was evaporated, and the residue was treated with ether and water. The aqueous layer was separated and extracted with ether. A standard treatment of the combined organic layer gave a product (0.7 g), which was chromatographed on SiO_2 (30 g). Elution under the conditions described above gave compound **4** (0.49 g, 70 %) as a colorless oil, R_f 0.46. IR: 600, 740, 880, 980, 1070, 1110, 1205, 1380, 1450, 1500, 2860—3000, and 3600. ^{1}H NMR: 1.28 (s, 3 H, MeC(4)); 1.60 and 1.68 (both br.s, 6 H, MeC(8)); 1.56 (m, 2 H, HC(5)); 2.2 (m, 2 H, HC(6)); 3.18 (br.d, 2 H, HC(1), J = 6); 5.12 (br.t, 1 H, HC(7), J = 7.1); 5.58 (d.t, 1 H, HC(3), J = 15.5 and 1.1); 5.76 (d.t, 1 H, HC(2), J = 15.5 and 5.9); 6.25 (m, 1 H, HC(4′)); 7.20 and 7.35 (both m, 2 H, HC(2′), HC(5′)). Mass spectrum, m/z: 234 $[M]^+$. Found (%): C, 76.70; H, 9.41. $C_{15}H_{22}O_2$. Calculated (%): C, 76.88; H, 9.46.

4,8-Dimethyl-1-(2′-furyl)nona-3*E*,7-dien-2-ol acetate (*E*-6) and 4,8-dimethyl-1-(2′-furyl)nona-3*Z*,7-dien-2-ol acetate (*Z*-6). Furfuryl chloride[13] (2.32 g, 20 mmol) was added to a Mg chip (1.38 g, 60 mg-at) in ether (20 mL) with stirring at −10 °C (Ar) over a period of 2 h. The mixture was kept for 30 min, and **10** (*trans*/*cis* ≈3 : 2, 3.04 g, 20 mmol) was added as one portion to the obtained Grignard reagent **11** at −10 °C. The reaction mixture was heated to 20 °C, kept for 12 h, and decomposed with a saturated NH_4Cl solution. The aqueous layer was separated and extracted with ether. The combined organic layer was washed with water, dried over Na_2SO_4, and evaporated *in vacuo*. Pyridine (1.98 g, 25 mmol), Ac_2O (2.55 g, 25 mmol), and 4-*N*,*N*-dimethylaminopyridine (DMAP) (0.15 g, 1.23 mmol) were added to the residue (~5 g). The reaction mixture was kept for 30 min and treated in the usual fashion. The product was obtained in a yield of 5.3 g and chromatographed on SiO_2 (100 g). Elution with a hexane–ether (4 : 1) mixture gave a mixture of acetates *E*-**6**/*Z*-**6** (1.65 g, 30 %) in the ratio of ~4.5 : 1 as a colorless oil, R_f 0.45. Individual components of this mixture were separated by HPLC. Compounds *Z*-**6** (0.3 g) and *E*-**6** (1.25 g) were obtained in the order of elution.

Acetate *Z*-**6**, colorless viscous liquid, b.p. 76—77 °C (0.02 Torr), n_D^{20} 1.4886. IR: 605, 740, 840, 890, 940, 1020, 1150, 1240, 1380, 1450, 1510, 1600, 1670, 1745, and 2860—2980 (film). ^{1}H NMR: 1.61, 1.68, and 1.72 (br.s, 9 H, MeC(4), MeC(8)); 2.0 (s, 3 H, MeCO); 1.9—2.3 (m, 4 H, HC(5), HC(6)); 2.84 (d.d, 1 H, HC(1), J = 15.0, 6.0); 2.96 (d.d, 1 H, HC(1), J = 15.0, 7.9); 5.09 (m, 1 H, HC(7)); 5.18 (br.d, 1 H, HC(3), J = 9.4); 5.76 (d.d.d, 1 H, HC(2), J = 9.4, 6.9, 6.1); 6.05 (d.d, 1 H, HC(3′), J = 3.2, 0.7); 6.27 (d.d, 1 H, HC(4′), J = 3.2, 1.9); 7.31 (d.d, 1 H, HC(5′), J = 1.9, 0.7). ^{13}C NMR: 17.57, 21.18, 25.64 (MeC(8), MeCO); 23.32 (MeC(4)); 26.40, 33.82 (C-1, C-6); 32.36 (C-5); 69.32 (C-2); 106.92, 110.17 (C-3′, C-4′); 123.09, 123.76 (C-3, C-7); 131.92, 141.54 (C-4, C-8); 141.34 (C-5′); 151.41 (C-2′); 169.96 (C=O). Mass spectrum, m/z: 276 $[M]^+$. Found (%): C, 73.96; H, 8.72. $C_{17}H_{24}O_3$. Calculated (%): C, 73.88; H, 8.75.

Acetate *E*-**6**, colorless viscous liquid, b.p. 87—88 °C (0.02 Torr), n_D^{20} 1.4874. IR: 605, 740, 810, 890, 1025, 1085, 1150, 1245, 1380, 1440, 1510, 1600, 1670, 1745, and 2860—2980 (film). ^{1}H NMR: 1.58, 1.61, and 1.66 (br.s, 9 H, MeC(4), MeC(8)); 1.98 (s, 3 H, MeCO); 1.9—2.1 (m, 4 H, HC(5), HC(6)); 2.81 (d.d, 1 H, HC(1), J = 14.8, 6.6); 2.95 (d.d, 1 H, HC(1), J = 14.8, 6.6); 5.02 (m, 1 H, HC(7)); 5.11 (br.d, 1 H, HC(3), J = 9.1); 5.71 (d.d.d, 1 H, HC(2), J = 9.1, 6.7, 6.7); 5.99 (d.d, 1 H, HC(3′), J = 3.1, 0.7); 6.23 (d.d, 1 H, HC(4′), J = 3.1, 1.9); 7.26 (d.d, 1 H, HC(5′), J = 1.9, 0.8). ^{13}C NMR: 16.64 (MeC(4)); 17.74, 21.06, 25.72 (MeC(8), MeCO); 26.28, 33.73 (C-1, C-6); 39.54 (C-5); 69.55 (C-2); 106.90, 110.20 (C-3′, C-4′); 122.75, 123.94 (C-3, C-7); 131.34, 140.91 (C-4, C-8); 141.23 (C-5′); 151.41 (C-2′); 169.36 (C=O). Mass spectrum, m/z: 276 $[M]^+$. Found (%): C, 73.61; H, 8.73. $C_{17}H_{24}O_3$. Calculated (%): C, 73.88; H, 8.75.

4,8-Dimethyl-1-(2′-furyl)nona-3*Z*,7-dien-2-ol (*Z*-5). An emulsion of ***Z*-6** (0.29 g, 1.05 mmol) in a 10% aqueous solution of KOH (0.3 mL) and MeOH (4 mL) were stirred at 20 °C for 2 h; then the mixture was neutralized with a saturated NH_4Cl solution and extracted with ether. The standard treatment of the extract gave a product (0.28 g), which was chromatographed with ether on SiO_2 (15 g). Elution with a cooled (−5 °C) hexane—ether (3 : 2) mixture gave alcohol ***Z*-5** (0.22 g, 92 %) as a colorless oil, R_f 0.48. IR: 605, 730, 840, 890, 930, 1020, 1150, 1380, 1450, 1510, 1600, 1670, 2860—2980, and 3360 (film). ^{1}H NMR: 1.61, 1.69, and 1.73 (br.s, 9 H, MeC(4), MeC(8)); 2.0 (m, 4 H, HC(5), HC(6)); 2.77 (d.d, 1 H, HC(1), J = 14.8, 5.6); 2.86 (d.d, 1 H, HC(1), J = 14.8, 7.0); 4.64 (d.d.d, 1 H, HC(2), J = 8.8, 7.0, 5.8); 5.13 (m, 1 H, HC(7)); 5.25 (br.d, 1 H, HC(3), J = 8.9); 6.11 (d, 1 H, HC(3′), J = 3.1); 6.30 (d.d, 1 H, HC(4′), J = 3.0, 1.9); 7.33 (m, 1 H, HC(5′)). ^{13}C NMR: 17.46 (MeC(8)); 23.13 (MeC(4)); 25.49 (MeC(8)); 26.25, 36.22 (C-1, C-6); 32.12 (C-5); 66.64 (C-2); 106.76, 110.08 (C-3′, C-4′); 123.71, 127.29 (C-3, C-7); 132.14, 139.19 (C-4, C-8); 141.22 (C-5′); 152.41 (C-2′). Mass spectrum, m/z: 234 $[M]^+$. Calculated for $C_{15}H_{22}O_2$.: mol. weight 234.3.

4,8-Dimethyl-1-(2′-furyl)nona-3*E*,7-dien-2-ol (*E*-5). Alcohol ***E*-5** was obtained as described above from ***E*-6** (0.76 g, 2.75 mmol) in a yield of 0.61 g (92 %) as a colorless oil, R_f 0.48. IR: 605, 730, 805, 890, 930, 1020, 1080, 1150, 1380, 1445, 1510, 1600, 1675, 2860—2980, and 3360 (film). ^{1}H NMR: 1.60, 1.62 and 1.68 (br.s, 9 H, MeC(4), MeC(8)); 2.0 (m, 4 H, HC(5), HC(6)); 2.76 (d.d, 1 H, HC(1), J = 14.8, 5.8); 2.87 (d.d, 1 H, HC(1), J = 14.8, 7.0); 4.65 (d.d.d, 1 H, HC(2), J = 8.4, 7.0, 5.8); 5.07 (m, 1 H, HC(7)); 5.23-(br.d, 1 H, HC(3), J = 8.5); 6.08 (d, 1 H, HC(3′), J = 3.1); 6.29 (d.d, 1 H, HC(4′), J = 3.1, 1.9); 7.33 (m, 1 H, HC(5′)). ^{13}C NMR: 16.36 (MeC(4)); 17.59, 25.58 (MeC(8)); 26.21, 36.32 (C-1, C-6); 39.39 (C-5); 67.21 (C-2); 106.89, 110.18 (C-3′, C-4′); 123.79, 126.42 (C-3, C-7); 131.46, 138.91 (C-4), (C-8); 141.28 (C-5′); 152.42 (C-2′). Mass spectrum, m/z: 234 $[M]^+$. Calculated for $C_{15}H_{22}O_2$.: mol. weight 234.3.

Cationic cyclization of alcohols 3, 4, and 5, acetate *E*-6, and derivatives of limonene 13 (the general procedure). A solution of ***E*-3** (936 mg, 4 mmol) in PhMe (1 mL) was added as one portion with intense stirring to an emulsion of 85% (aq.) H_3PO_4 (92 mg, 0.8 mmol) in PhMe (6 mL) at 100 °C (Ar). The mixture was kept at 100 °C for 20 min, then rapidly (in 3 min) cooled to 20 °C and treated with ether. The ether extract was washed with a 5% $NaHCO_3$ solution and then with water, dried over Na_2SO_4, and evaporated *in vacuo*. The residue (0.9 g) was chromatographed on SiO_2 (50 g) Elution with hexane gave a mixture (588 mg, 68 %) of **1** : **12** : *cis*-**13** : *trans*-**13** : **17** ≈ 65 : 20 : 9 : 3 : 3 (the ^{1}H NMR data) as a colorless oil, R_f 0.38 (hexane). The mixture was chromatographed on SiO_2 (100 g) impregnated with 10 % $AgNO_3$. Elution in a hexane—benzene (85 : 15) mixture gave (in order of elution) **1** (0.36 g, 42 %), **12** (115 mg, 13 %), and a mixture *cis*-**13** : *trans*-**13** ≈3 : 1 (60 mg, 7 %).

(±)-Furodizinin **1**, colorless needles, m.p. 47—51 °C (hexane). ^{1}H NMR: 1.20 and 1.24 (s, 6 H, HC(11), HC(12)); 1.30 (m, 1 H, HC(5)); 1.53 (m, 1 H, HC(4a)); 1.64 (br.s, 3 H, HC(13)); 1.65 (m, 1 H, HC(5)); 1.93 (m, 2 H, HC(6)); 2.43 (d.d, 1 H, HC(1), J = 15.3, 10.2); 2.63 (m, 1 H, HC(8a)); 2.79 (d.d, 1 H, HC(1), J = 15.3, 5.6); 5.56 (br.d, 1 H, HC(8), J = 5.6); 6.22 (d, 1 H, HC(10), J = 1.9); 7.21 (br.s, 1 H, HC(9)). ^{13}C NMR: 19.3 (C-5); 23.2 (C-13); 26.2 (C-12); 27.6 (C-1); 31.2 (C-8a); 31.7 (C-6); 32.8 (C-11); 33.1 (C-4); 44.5 (C-4a); 108.1 (C-10); 124.6 (C-3); 126.1 (C-8); 133.6 (C-7); 140.4 (C-9), 147.4 (C-2). High-resolution mass spectrum, m/z 216 $[M]^+$. Found: mol. weight 216.15178; calculated for $C_{15}H_{20}O$: mol. weight 216.15131.

4,4,7-Trimethyl-1,4,4aα,5,6,8aβ-hexahydronaphtho[2,3-*b*]furan (**12**), colorless prisms, m.p. 33—37 °C (hexane). IR: 600, 690, 840, 900, 1050, 1140, 1270, 1330, 1380, 1445, 1470, 1510, 1640, and 2820—3005. ^{1}H NMR: 1.02 (s, 3 H, HC(11)); 1.23 (s, 3 H, HC(12)); 1.30 (m, 1 H, HC(4a)); 1.37 (m, 1 H, HC(5)); 1.71 (br.s, 3 H, HC(13)); 1.90 (m, 1 H, HC(5)); 2.06 (m, 2 H, HC(6)); 2.22 (d.d, 1 H, HC(1), J = 15.6, 11.7); 2.42 (m, 1 H, HC(8a)); 2.71 (d.d, 1 H, HC(1), J = 15.6, 5.3); 5.30 (m, 1 H, HC(8)); 6.30 (br.s, 1 H, HC(10)); 7.25 (br.s, 1 H, HC(9)). ^{13}C NMR: 22.9 (C-5); 23.3 (C-13); 24.4 (C-11); 27.7 (C-12); 30.6 (C-1); 31.4 (C-6); 33.3 (C-4); 34.2 (C-8a); 46.8 (C-4a); 108.2 (C-10); 125.4 (C-8); 127.5 (C-3); 134.2 (C-7); 140.4 (C-9); 148.4 (C-2). High-resolution mass spectrum, m/z 216 $[M]^+$. Found: mol. weight 216.15231; calculated for $C_{15}H_{20}O$: mol. weight 216.15131.

A mixture (~3 : 1) of *cis*-4-isopropenyl-1-methyl-3-(2′-furyl)methylcyclohex-1-ene (*cis*-**13**) and *trans*-4-isopropenyl-1-methyl-3-(2′-furyl)methylcyclohex-1-ene (*trans*-**13**), colorless oil, R_f 0.38 (hexane). For *cis*-**13**, ^{1}H NMR: 1.5—2.2 (m, 8 H, HC, H_2C); 1.68 and 1.80 (br.s, 6 H, Me); 4.73 and 4.90 (br.s, 2 H, H_2C=); 5.37 (m, 1 H, HC=); 6.0, 6.3, 7.3 (m, 3 H, HC(3′), HC(4′), HC(5′)). For *trans*-**13**, ^{1}H NMR: 1.50 and 1.72 (br.s, 6 H, Me); 1.5—2.1 (m, 5 H, HC(4), HC(5), HC(6)); 2.22 (d.d, 1 H, HC(11), J = 14.2, 10.0); 2.40 (m, 1 H, HC(3)); 2.82 (br.d.d, 1 H, HC(11), J = 14.2, 3.4); 4.80 (m, 2 H, H_2C=); 5.26 (m, 1 H, HC=); 5.96 (br.d, 1 H, HC(3′), J = 3.1); 6.25 (d.d, 1 H, HC(4′), J = 3.1, 1.9); 7.28 (br.d, 1 H, HC(5′), J = 1.9). High-resolution mass spectrum, m/z 216 $[M]^+$. Found: mol. weight 216.15215; calculated for $C_{15}H_{20}O$: mol. weight 216.15131.

As described above for ***E*-3**, a product (0.46 g) was obtained from ***Z*-3** (468 mg, 2 mmol) and 85% H_3PO_4 (aq.) (46 mg, 0.4 mmol) in PhMe (3 mL) after 40 min, and then chromatographed on SiO_2 (20 g). Elution with hexane gave a mixture (285 mg, 66 %) of **1** : **12** : *cis*-**13** : *trans*-**13** : **14** : **17** ≈ 30 : 35 : 3 : 7 : 20 : 5 (the ^{1}H NMR data) as a colorless oil, R_f 0.38. The mixture was chromatographed under the conditions of the previous experiment on SiO_2 (30 g) impregnated with 10 % $AgNO_3$ to isolate the samples of compounds **1** and **12**; the ^{1}H NMR spectra of these compounds are virtually identical to those reported above. A mixture (20 mg) of bicyclic product **14** and the derivative of limonene *trans*-**13** was obtained in a ratio of ~2 : 1 (^{1}H NMR data) as a colorless oil, R_f 0.38 (hexane). The high-resolution mass spectrum, m/z 216 $[M]^+$. Found: mol. weight 216.15203; calculated for $C_{15}H_{20}O$: mol. weight 216.15131.

For 4-methyl-4-(4′-methylpent-3′-en-1′-yl)-4,7-dihydrobenzofuran (**14**), ^{1}H NMR: 1.24 (s, 3 H, MeC(4)); 1.50 and 1.60 (br.s, 6 H, Me); 1.5—2.1 (m, 4 H, CH_2); 3.23 (d.d, 2 H, HC(7), J = 3.4, 2.2); 5.0 (m, 1 H, HC(3′)); 5.49 (d.t, 1 H, HC(5), J = 10.0, 2.2); 5.79 (d.t, 1 H, HC(6), J = 10.0, 3.4); 6.22 (d, 1 H, HC(3), J = 1.9); 7.28 (br.s, 1 H, HC(2)).

Similarly, a **1** : **12** : *cis*-**13** : *trans*-**13** : **17** mixture was obtained from ***E*-5** (702 mg, 3 mmol) and 85% (aq.) H_3PO_4 (69 mg, 0.2mmol) in PhMe (4.5 mL) after 30 min in a yield of 356 mg (55 %); the ratio of components in the mixture was virtually identical to that obtained in the case of cationic cyclization of ***E*-3** (^{1}H NMR data).

Similarly, a **1** : **12** : *cis*-**13** : *trans*-**13** : **17** mixture was obtained from ***Z*-5** (234 mg, 1 mmol) and 85% (aq.) H_3PO_4 (23 mg, 0.6 mmol) in PhMe (1.5 mL) after 20 min in a yield

of 166 mg (77 %) in a ratio virtually identical to that obtained in the case of cationic cyclization of ***E*-3** (^{1}H NMR data).

Similarly, a **1** : **12** : *cis*-**13** : *trans*-**13** : **17** mixture was obtained from ***E*-6** (414 mg, 1.5 mmol) and 85% (aq.) H_3PO_4 (35 mg, 0.3 mmol) in PhMe (2 mL) after 1.5 h in a yield of 107 mg (33 %) in the ratio ~ 3 : 3 : 1 : 3 (^{1}H NMR data).

As described above for ***E*-3**, the reaction of a ~3 : 1 *cis*-**13** : *trans*-**13** mixture (110 mg, 0.51 mmol) and 85% (aq.) H_3PO_4 (12 mg, 0.1 mmol) in PhMe (0.7 mL) after 1.5 h gave a product (0.1 g), which was chromatographed on SiO_2 (2 g). Elution with hexane gave a **1** : **12** : *cis*-**13** : *trans*-**13** : **17** mixture in a yield of 75 mg (68 %) in the ratio ~7 : 3 : 1 : 2 : 7 (^{1}H NMR data) as a colorless oil, R_f 0.38 (hexane).

As described above for ***E*-3**, the reaction of **4** (468 mg, 2 mmol) and 85% (aq.) H_3PO_4 (46 mg, 0.4 mmol) in PhMe (3 mL) after 20 min gave a product in a yield of 0.46 g. This material was chromatographed on SiO_2 (20 g). Elution with hexane gave a **2** : **18** : (*cis*-**19**+*trans*-**19**) mixture in a yield of 259 mg (60 %) in the ratio ≈ 66 : 22 : 12 (^{1}H NMR data) as a colorless oil, R_f 0.38 (hexane). The mixture was chromatographed on SiO_2 (50 g) impregnated with 10 % $AgNO_3$. Elution in a hexane—benzene (85 : 15) system gave (in order of elution) **2** (168 mg, 39 %), **18** (54 mg, 12 %), and the *cis*-**19** : *trans*-**19** mixture (≈3 : 1) (28 mg, 6 %).

(±)-Furodizin **2**, colorless crystals, m.p. 58—61 °C (hexane). ^{1}H NMR: 1.26 (s, 3 H, HC(11)); 1.28 (s, 3 H, HC(12)); 1.38 (m, 1 H, HC(8)); 1.59 (m, 1 H, HC(8a)); 1.67 (br.s, 3 H, HC(13)); 1.74 (m, 1 H, HC(8)); 2.0—2.1 (m, 2 H, HC(7)); 2.20 (d.d, 1 H, HC(4), J = 17.4, 12.5); 2.56 (d.d, 1 H, HC(4), J = 17.4, 5.7); 2.60 (m, 1 H, HC(4a)); 5.61 (m, 1 H, HC(5)); 6.11 (d, 1 H, HC(10), J = 1.8); 7.24 (d, 1 H, HC(9), J = 1.8). ^{13}C NMR: 19.5 (C-8); 23.2 (C-13); 23.8 (C-12); 27.3 (C-4); 30.7 (C-11); 31.6 (C-4a); 31.8 (C-7); 34.6 (C-1); 45.6 (C-8a); 109.8 (C-5); 112.9 (C-3); 126.4 (C-10); 133.1 (C-2); 140.4 (C-9); 156.8 (C-6).

1,1,6-Trimethyl-1,4,4aα,7,8,8aβ-hexahydronaphtho[2,3-*b*]furan (**18**), colorless crystals, m.p. 32—35 °C (hexane). IR: 610, 700, 840, 940, 1020, 1080, 1120, 1150, 1180, 1280, 1370, 1380, 1450, 1500, 1570, 1630, 1680, and 2740—3020. ^{1}H NMR: 1.10 (s, 3 H, HC(11)); 1.30 (s, 3 H, HC(12)); 1.39 (m, 2 H, HC(8), HC(8a)); 1.70 (br.s, 3 H, HC(13)); 1.86 (m, 1 H, HC(8)); 2.04 (m, 2 H, HC(7)); 2.05 (d.d, 1 H, HC(4), J = 15.3, 11.6); 2.30 (m, 1 H, HC(4a)); 2.50 (d.d, 1 H, HC(4), J = 15.3, 5); 5.30 (m, 1 H, HC(5)); 6.15 (br.s, 1 H, HC(10)); 7.25 (br.s, 1 H, HC(9)). ^{13}C NMR: 22.1 (C-11); 22.6 (C-8); 23.2 (C-13); 25.2 (C-12); 29.7 (C-4); 31.1 (C-7); 34.6 (C-4a); 35.0 (C-1); 47.3 (C-8a); 109.8 (C-10); 114.4 (C-3); 125.6 (C-5); 133.6 (C-6); 140.2 (C-9); 158.0 (C-2). High-resolution mass spectrum, m/z 216 $[M]^+$. Found: mol. weight 216.15223; calculated for $C_{15}H_{20}O$: mol. weight 216.15131.

A mixture (~3 : 1) of *cis*-4-isopropenyl-1-methyl-3-(3′-furyl)methylcyclohex-1-ene (*cis*-**19**) and *trans*-4-isopropenyl-1-methyl-3-(3′-furyl)methylcyclohex-1-ene (*trans*-**19**) was obtained as a colorless oil, R_f 0.38 (hexane). For *cis*-**19**, ^{1}H NMR: 1.5—2.2 (m, 8 H, HC, H_2C); 1.65 and 1.80 (both br.s, 6 H, Me); 4.73 and 4.90 (both br.s, 2 H, H_2C=); 5.4 (m, 1 H, HC=); 6.25, 7.15, 7.35 (all m, 3 H, HC(4′), HC(2′), HC(5′)). For *trans*-**19**, ^{1}H NMR: 1.5—2.2 (m, 8 H, HC, H_2C); 1.55 and 1.75 (both br.s, 6 H, Me); 4.78 and 4.82 (both br.s, 2 H, H_2C=); 5.4 (m, 1 H, HC=); 6.25, 7.15, 7.35 (all m, 3 H, HC(4′), HC(2′), HC(5′)). High-resolution mass spectrum, m/z 216 $[M]^+$. Found: mol. weight 216.15185; calculated for $C_{15}H_{20}O$: mol. weight 216.15131.

Isomerization of (±)-furodizinin 1. A solution of **1** (100 mg, 0.46 mmol) in PhMe (0.2 mL) was added as one portion with stirring to an emulsion of 85% (aq.) H_3PO_4 (10 mg, 0.1 mmol) in PhMe (0.7 mL) at 100 °C (Ar). The mixture was kept at 100 °C for 2 h, then rapidly cooled to 20 °C and diluted with ether. The usual treatment of the ether extract gave a **1**/**17** mixture (98 mg) in the ratio ~1 : 3 (^{1}H NMR data). The mixture was chromatographed on SiO_2 (20 g) impregnated with $AgNO_3$ (10 %). Elution in the hexane—benzene (85 : 15) system gave a fraction (20 mg) enriched with compound **17** (>80 %) as a colorless oil, R_f 0.38 (hexane).

For 4,4,7-trimethyl-1,4,4aα,5,8,8aα-hexahydronaphtho[2,3-*b*]furan **17**, ^{1}H NMR: 1.14 (s, 3 H, HC(11)); 1.23 (s, 3 H, HC(12)); 1.65 (d.d.d, 1 H, HC(4a), J = 11.5, 5.2, 2.1); 1.68 (br.s, 3 H, HC(13)); 1.76 (m, 1 H, HC(5)); 1.83 (br.d, 1 H, HC(8), J = 17.8); 1.96 (m, 1 H, HC(5)); 2.38 (m, 1 H, HC(8)); 2.4—2.6 (m, 3 H, HC(1), HC(8a)); 5.37 (m, 1 H, HC(6)); 6.24 (d, 1 H, HC(10), J = 1.9); 7.22 (br.d, HC(9)). ^{13}C NMR: 23.4 (C-13); 23.6 (C-5); 24.8 (C-1); 25.8 (C-11); 29.4 (C-8a); 31.4 (C-12); 33.9 (C-4); 36.7 (C-8); 42.9 (C-4a); 108.4 (C-10); 120.7 (C-6); 123.8 (C-3); 130.9 (C-7); 140.4 (C-9), 148.6 (C-2). High-resolution mass spectrum, m/z 216 $[M]^+$. Found: mol. weight 216.15082; calculated for $C_{15}H_{20}O$: mol. weight 216.15131.

Cyclization of alcohol *E*-3 under the action of HCO_2H. HCO_2H (2.32 g, 50.4 mmol) was added as one portion with intense stirring to a solution of ***E*-3** (468 mg, 2 mmol) in cyclohexane (8 mL) at 20 °C (Ar). The mixture was kept for 5 min and treated with a 5% $NaHCO_3$ solution. The organic layer was separated, washed with water, dried over Na_2SO_4, and evaporated *in vacuo*. The residue (0.5 g) was chromatographed on SiO_2 (30 g). Elution with hexane gave a **1** : **12** : *cis*-**13** : *trans*-**13** mixture (151 mg, 35 %) in the ratio of ~ 70 : 20 : 7 : 3 (^{1}H NMR data) as a colorless oil, R_f 0.38 (hexane).

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