Superacidic cyclization of ω-hydroxygeraniol diacetate and ω-hydroxygeraniol benzyl ether acetate

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Low-temperature superacidic cyclization of (*E*,*E*)-3,7-dimethylocta-2,6-diene-1,8-diol (ω-hydroxygeraniol) diacetate and (*E*,*E*)-8-acetoxy-1-benzyloxy-3,7-dimethylocta-2,6-diene leads to the same mixtures of two diastereomeric 9-acetoxy-8-hydroxy-*p*-menth-1-enes epimeric at the C(8) atom.

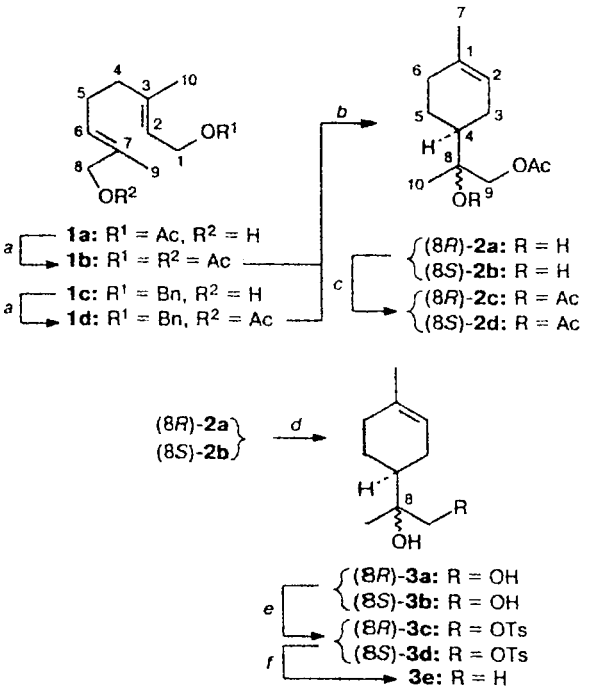
Key words: 1,8-diacetoxy- and 8-acetoxy-1-benzyloxy-3,7-dimethylocta-2,6-dienes, superacidic cyclization; epimeric *p*-menth-1-ene-8,9-diols; α-terpineol.

Previously, as a result of systematic studies, we showed that low-temperature superacidic cyclization of aliphatic and partially cyclized isoprenoids is a highly efficient, structurally and chemically selective, and stereospecific one-step general method for the synthesis of cyclic terpenoids. This method was used to synthesize cyclic terpene alcohols, acids, esters, hydroxy esters, and homo- and bishomoterpene oxides and lactones.[1—4] It was also established that terminal epoxides derived from α- and β-terpenoids react with superacids with isomerization and epoxide ring opening;[5—7] in this reaction, epoxides of α-terpenoids isomerize into the corresponding primary allylic alcohos with *E*-configuration (see, for example, **1a**), which subsequently remain unchanged under the reaction conditions.[7] Under more rigorous conditions, these alcohols are converted into complex mixtures of compounds. However, their acetates react with superacids rather smoothly to give cyclic products.

In this communication, we present data on superacidic cyclization of (*E*,*E*)-3,7-dimethylocta-2,6-diene-1,8-diol diacetate (ω-hydroxygeraniol) (**1b**) and the acetate of 1-*O*-benzyl ether of this diol (**1d**), which were prepared by conventional acetylation (Ac_2O—Py) of the corresponding alcohols, **1a**[7] and **1c**[8] (Scheme 1).

Cyclization of diacetate **1b** on treatment with fluorosulfonic acid (a substrate : FSO_3H molar ratio of 1 : 5) at −78 °C gives an unseparable mixture (~1 : 1, according to ^1H and ^{13}C NMR spectroscopy) of two compounds in a high yield. Cyclization of diester **1d** under the same conditions gives the same compounds in the same ratio and in the same yield. The structures of the compounds contained in this mixture were determined by spectroscopy. The IR spectrum of the mixture exhibits bands typical of acetate and hydroxy groups (see Experimental). Its ^1H NMR spectrum contains signals

Scheme 1



Reagents and conditions: *a*. Ac_2O—Py, 22 °C; *b*. FSO_3H/Pr^iNO_2, −78 °C, 15 min; *c*. Ac_2O—Py—DMAP, 22 °C; *d*. KOH/EtOH, −80 °C, 0.5 h; *e*. TsCl—Py/CH_2Cl_2, 0 °C; *f*. $LiAlH_4$/THF, 65 °C, 3 h.

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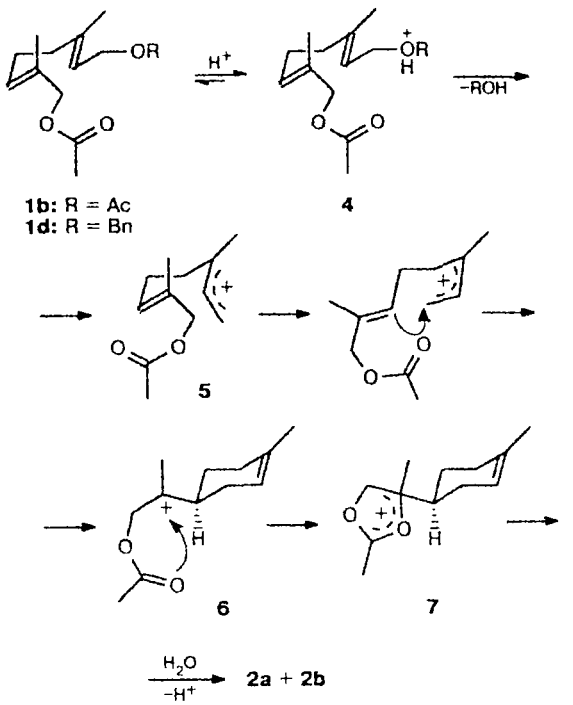
for three methyl groups (at a tertiary carbon atom bearing a hydroxyl group, at a double bond, and in a MeCO group), for an allylic methylene group —CH_2OAc, and for one vinylic group.

Judging from the spectral data, the OH group in the compounds studied is tertiary. This is also consistent with their chemical behavior: they are not oxidized by pyridinium chlorochromate and are not acetylated by the Ac_2O—Py mixture under standard conditions but in the presence of DMAP, they form a mixture of diacetates.

Based on the data of spectroscopic and elemental analysis, it was concluded that the products of superacidic cyclization of compounds **1b** and **1d** are mixtures of C(8) epimeric 9-acetoxy-8-hydroxy-*p*-menth-1-enes (**2a** and **2b**), and the products of their acetylation by the Ac_2O—Py—DMAP system are mixtures of the corresponding diacetates (**2c** and **2d**, see Scheme 1). The structures of the cyclization products were ultimately proved by the chemical method. Alkaline hydrolysis of a mixture of hydroxyacetates **2a** and **2b** affords a mixture of diols **3a** and **3b**. When the latter react with tosyl chloride in pyridine under mild conditions,[9] only primary OH groups are selectively esterified to give a mixture of hydroxy tosylates **3c** and **3d** (see Scheme 1). The reduction of a crude mixture of **3c** and **3d** with lithium aluminum hydride in THF affords (±)-α-terpineol (**3e**), whose chromatographic and spectral characteristics coincide with those of an authentic sample.

Thus, the cyclization of compounds **1b** and **1d** induced by superacids gives a mixture of hydroxyacetates **2a** and **2b** epimeric at the of C(8) atom and having identical configurations at the C(4) atom, because the bulky 1,2-dihydroxylated isopropyl group in their molecules, as in the molecule of α-terpineol **3e**, is equatorial. The epimeric structure of hydroxyacetates **2a** and **2b** accounts for the difficulty of their chromatographic separation. The exclusive formation of products of the *p*-menthane series in the cyclization of compounds **1b** and **1d** indicates that the superacid induces selective solvolysis of the ether or ester group at the C(1) atom in their molecules and after that, the >C=C< bond migrates (Scheme 2). Due to the electronic and steric factors, it is the oxygen-containing functional group at the C(1) atom that is protonated first in the superacid medium, resulting in the formation of the oxonium cation **4**. During solvolysis the latter is converted into carbocation **5** and then into cyclic carbocation **6**, which is stabilized upon an intramolecular attack on the carbenium center by the carbonyl oxygen atom of the acetate group to give a carboxonium ion. Hydration of this ion on treatment of the reaction mixture with water affords a mixture of diastereomeric products **2a** and **2b**.

Scheme 2



Experimental

IR spectra were recorded on a Specord-74 IR instrument in CCl_4, and NMR spectra were measured on Varian GMM-300 (300 MHz) and Bruker AC-80 (80 MHz) spectrometers in $CDCl_3$; the signals are given in the δ scale. GLC analysis was carried out on a Chrom-5 chromatograph (flame ionization detector, a 3500×3 mm glass column, 5% SE-30 on Chromaton N-AW-DCMS as the stationary phase). Column chromatography was performed using silica gels (SiO_2) L (40/100 and 100/160 μm) and Across (60/200 μm); for TLC, silica gel LS 5/40 μm was used. The usual workup of the reaction mixture in organic solvents included exhaustive extraction with diethyl ether and washing with water to a neutral reaction (acidic reaction mixtures were washed with water, a saturated aqueous solution of $NaHCO_3$, and again with water), drying with anhydrous Na_2SO_4, filtration, and evaporation of the solvent *in vacuo*. Petroleum ether with b.p. 50—70 °C was used.

Acetylation of (*E*,*E*)-1-acetoxy-3,7-dimethylocta-2,6-dien-8-ol (1a). Acetic anhydride (5 mL) was added to a solution of 8-hydroxygeraniol acetate (**1a**) (2.5 g, 11.8 mmol) in 15 mL of dry pyridine, and the mixture was kept for 6 h at ~20 °C and worked up by the usual procedure. The product (2.8 g) was chromatographed on a column with 50 g of SiO_2. Elution with a mixture of petroleum ether and AcOEt (93 : 7) gave 2.72 g (90.8%) of diacetate **1b** (a colorless viscous liquid). Found (%): C, 66.03; H, 8.75. $C_{14}H_{22}O_4$. Calculated (%): C, 66.12; H, 8.72. IR, ν/cm^{-1}: 1230, 1730 (OAc). ^{1}H NMR, δ: 1.65 (s, 3 H, C(10)H_3); 1.70 (s, 3 H, C(9)H_3); 2.05 (s, 3 H, OAc); 2.06 (s, 3 H, OAc); 4.45 (br.s, 2 H, C(8)H_2); 4.59 (d, 2 H, C(1)H_2, J = 7.0 Hz); 5.40 (m, 2 H, C(2)H, C(6)H).

Acetylation of (*E*,*E*)-8-acetoxy-1-benzyloxy-3,7-dimethylocta-2,6-diene (1c). The reaction of hydroxy ether **1c** with a mixture of 5.5 mL pyridine and 1.8 mL Ac_2O carried out as described above gave 1.09 g (yield 85%) of ω-hydroxygeraniol benzyl ether acetate (**1d**) (a colorless viscous liquid). Found (%): C, 75.31; H, 8.58. $C_{19}H_{26}O_3$. Calculated (%): C, 75.46; H, 8.67. IR, ν/cm^{-1}: 1020, 1060 (OBn); 1235, 1735 (OAc). ^{1}H NMR, δ: 1.66 (s, 6 H, C(9)H_3, C(10)H_3); 2.06 (s, 3 H, OAc); 4.03 (d, 2 H, C(1)H_2, J = 6.0 Hz); 4.48 (d, 2 H, C(8)H_2,

J = 4.6 Hz); 5.40 (m, 2 H, C(2)H, C(6)H); 7.20—7.30 (m, 5 H, H(Ar)).

Superacidic cyclization of (*E,E*)-3,7-dimethylocta-2,6-diene-1,8-diol diacetate (1b). A solution of FSO_3H (1.93 g, 19.3 mmol) in 2.5 mL of Pr^iNO_2, cooled to −78 °C, was added with vigorous stirring to a solution of diacetate **1b** (980 mg, 3.86 mmol) in 15 mL Pr^iNO_2, cooled to the same temperature. The reaction mixture was stirred for 15 min at this temperature, 15 mL of a solution of Et_3N in petroleum ether (1 : 1) was added, and the mixture was worked up in the usual way. The reaction product (1.87 g) was chromatographed on a column with 45 g of SiO_2. Elution with a 97 : 3 mixture of petroleum ether and AcOEt gave 276 mg (28.2%) of the initial diacetate **1b**. Elution with a 93 : 7 mixture of the same solvents gave 408 mg (69.4% with allowance for the recovered compound **1b**) of a mixture (~1 : 1) of diastereomeric 9-acetoxy-8-hydroxy-*p*-menth-1-enes **2a** and **2b** (a colorless viscous liquid). Found (%): C, 67.74; H, 9.42. $C_{12}H_{20}O_3$. Calculated (%): C, 67.89; H, 9.50. IR, ν/cm^{-1}: 1040, 1105, 3520, 3640 (OH); 1240, 1750 (OAc). ^1H NMR (300 MHz), δ: 1.12, 1.16 (both s, 1.5 H each, C(10)H_3); 1.65 (s, 3 H, C(7)H_3); 2.10, 2.11 (both s, 1.5 H each, OAc); 3.97—4.13 (m, 2 H, C(9)H_2); 5.35, 5.40 (both m, 0.5 H each, C(2)H). ^{13}C NMR, δ: 133.7, 134.1 (both s, C(1)); 119.9, 120.3 (both d, C(2)); 25.7, 26.7 (both t, C(3)); 40.8, 41.0 (both d, C(4)); 22.9, 24.0 (both t, C(5)); 30.7, 30.8 (both t, C(6)); 23.2, 23.8 (both q, C(7)); 69.8, 70.0 (both s, C(8)); 73.2, 73.3 (both t, C(9)); 20.0, 20.8 (both, q, C(10)); 171.1 (s, $CH_3\underline{C}O$); 21.1 (q, $\underline{C}H_3CO$).

Superacidic cyclization of (*E,E*)-8-acetoxy-1-benzyloxy-3,7-dimethylocta-2,6-diene (1d). A solution of FSO_3H (365 mg, 3.65 mmol) in 0.8 mL of Pr^iNO_2, cooled to −78 °C, was added with vigorous stirring to a solution of ester **1d** (220 mg, 0.728 mmol) in 3.6 mL of Pr^iNO_2, cooled to the same temperature. The reaction mixture was stirred for 15 min at this temperature, 3 mL of a solution of Et_3N in petroleum ether (1 : 1) was added, and the mixture was worked up in the usual way. The reaction product (202 mg) was chromatographed on a column with 4.6 g of SiO_2. Elution with a 97 : 3 mixture of petroleum ether and AcOEt gave 20 mg (9%) of the initial ester **1d**. Elution with a 93 : 7 mixture of the same solvents gave 96 mg (68.4% with allowance for the recovered initial compound **1d**) of a mixture (~1 : 1) of diastereomeric hydroxyacetates **2a** and **2b**, identical to that obtained in the previous experiment.

Acetylation of a mixture of 9-acetoxy-8-hydroxy-*p*-menth-1-enes (2a and 2b). Acetic anhydride (0.1 mL) and 5 mg of DMAP were added to a solution of a mixture of cycloolefins **2a** and **2b** (50 mg, 0.236 mmol) in 1.2 mL of dry pyridine, and the mixture was allowed to stand for 18 h at 20 °C and worked up in the usual way. The reaction product (54 mg) was chromatographed on a column with 1.60 g of SiO_2. Elution with a mixture of petroleum ether and AcOEt (93 : 7) gave 37.2 mg (62%) of a mixture (~1 : 1) of 8,9-diacetoxy-*p*-menth-1-enes **2c** and **2d** (a colorless viscous liquid). Found (%): C, 65.98; H, 8.79. $C_{14}H_{22}O_4$. Calculated (%): C, 66.12; H, 8.72. IR, ν/cm^{-1}: 1215, 1732 (OAc). ^1H NMR (300 MHz), δ: 1.39, 1.41 (both s, 1.5 H each, C(1)H_3); 1.65 (s, 3 H, C(7)H_3); 2.00, 2.01 (both s, 1.5 H each, 8-OAc); 2.07, 2.08 (both s, 1.5 H each, 9-OAc); 4.27 (d, 1 H, C(9)H_2, J = 3.0 Hz); 4.30 (d, J_{AB} = 11.8 Hz) and 4.53 (d, J_{AB} = 11.8 Hz, AB system, 1 H, C(9)H_2); 5.37 (m, 1 H, C(2)H).

Alkaline hydrolysis of a mixture of 9-acetoxy-8-hydroxy-*p*-menth-1-enes (2a and 2b). A 10% solution of KOH (3 mL) was added to a solution of a mixture of hydroxyacetates **2a** and **2b** (110 mg, 0.519 mmol) in 1 mL of EtOH, and the mixture was refluxed for 30 min. The usual workup gave 77.8 mg (88%) of a mixture (~1 : 1) of 8,9-dihydroxy-*p*-menth-1-enes **3a** and **3b** (a colorless viscous liquid). Found (%): C, 70.45; H, 10.59. $C_{10}H_{18}O_2$. Calculated (%): C, 70.55; H, 10.66. IR, ν/cm^{-1}: 1065, 3340, 3550 (OH). ^1H NMR (300 MHz), δ: 1.06, 1.10 (both s, 1.5 H each, C(10)H_3); 1.62 (s, 3 H, C(7)H_3); 1.90—1.98 (m, 2 H, 2 OH); 3.38—3.64 (m, 2 H, C(9)H_2); 5.38 (m, 1 H, C(2)H).

Transformation of diastereomeric *p*-menth-1-ene-8,9-diols (3a + 3b) into (±)-α-terpineol (3e). *p*-Toluenesulfonyl chloride (135 mg, 0.707 mmol) was added to a solution of a mixture of diols **3a** and **3b** (80 mg, 0.471 mmol) in 0.7 mL of dry CH_2Cl_2 and 0.1 mL of anhydrous pyridine cooled to 0 °C. The reaction mixture was stirred (2.5 h) at this temperature. The usual workup gave 131.8 mg of a mixture of monotosylates **3c** and **3d**, which was used in the next step without additional purification.

$LiAlH_4$ (152 mg, 4.01 mmol) was added to a solution of 130 mg of a mixture of tosylates **3c** and **3d** in 1.8 mL of dry THF, and the reaction mixture was refluxed for 3 h. The usual workup gave a product (59.2 mg), which was chromatographed on a column with 1.1 g of SiO_2. Elution with a 95 : 5 mixture of petroleum ether and AcOEt gave 41.2 mg (57%) of (±)-α-terpineol (**3e**) (a colorless viscous liquid). IR, ν/cm^{-1}: 1040, 1100, 3340, 3620 (OH). ^1H NMR (80 MHz),* δ: 1.10 (s, 6 H, C(9)H_3, C(10)H_3); 1.70 (s, 3 H, C(7)H_3); 5.30 (m, 1 H, C(2)H). The product was identified by comparison with an authentic sample.

* The ^1H NMR spectrum of compound **3e** was recorded on an instrument operating at 80 MHz, because we compared it with the corresponding spectrum given in a handbook,[10] which had been recorded on an instrument operating at 60 MHz. We do not present all signals because at a frequency of 80 MHz, this would make the description of the spectrum rather subjective.

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