Ring-expansion reaction of 1-hydroperoxy-16-oxabicyclo[10.4.0]hexadecane catalyzed by copper ions: use in the synthesis of 15-pentadecanolide

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A catalytic procedure has been developed for the synthesis of 15-pentadecanolide (**1**) from readily available 1-hydroperoxy-16-oxabicyclo[10.4.0]hexadecane (**2**). The method is based on the reaction of hydroperoxide **2** with copper acetate (0.15—5 mol.%). Ring expansion occurred as a result of generation of tertiary bicyclohexadecyloxyl radicals **4** from hydroperoxide **2** under the action of Cu^I ions, β-scission of the radicals accompanied by regioselective cleavage of the bridge bond to form macrocyclic C-centered radicals **5**, and their oxidation by Cu^{II} ions to (*E*)-11- and (*E*)-12-pentadecen-15-olides (**6**). The products obtained were converted into 15-pentadecanolide by subsequent catalytic hydrogenation over a Pd catalyst in a yield of more than 90% with respect to hydroperoxide **2**.

Key words: 1-hydroperoxy-16-oxabicyclo[10.4.0]hexadecane, ring expansion, (*E*)-11- and (*E*)-12-pentadecen-15-olides, 15-pentadecanolide, cyclododecanone, allyl alcohol, 2-(3-hydroxypropyl)cyclododecanone, 13-oxabicyclo[10.4.0]hexadec-1(12)-ene, hydrogenation.

15-Pentadecanolide (**1**) possesses a unique musk-amber odor and is capable of fixing odors of other aromatic principles due to which **1** is widely used in production of perfumes and cosmetics. A large number of various multistage procedures for the synthesis of this macrocyclic lactone are known.[1—18] However, only one of these procedures is used for producing this lactone. This method involves ring expansion of 1-hydroperoxy-16-oxabicyclo[10.4.0]hexadecane (**2**) as the key stage.[7] Compound **2** is prepared by the addition of hydrogen peroxide to 13-oxabicyclo[10.4.0]hexadec-1(12)-ene (**3**). Compound **3** is synthesized according to different procedures from cyclododecanone.[7a,19—21]

Four procedures for the initiation of ring expansion of hydroperoxide **2** and its analogs are known, namely, boiling in xylene,[7b] photoirradiation,[7b] the reaction with a threefold excess of a mixture of sodium sulfite and sodium bisulfite in a solution of equal volumes of chloroform and isopropyl alcohol,[7] and the reaction with a one-and-a-half-fold excess of an equimolar mixture of copper(II) acetate and iron(II) sulfate heptahydrate in methanol.[22,23]

We carried out this reaction with the use of copper acetate as a catalyst. Ring expansion of hydroperoxide **2** occurred as a result of generation of tertiary bicyclohexadecyloxyl radicals (**4**) from hydroperoxide **2** under the action of copper ions, β-scission of the radicals accompanied by regioselective cleavage of the bridge bond to form macrocyclic radicals (**5**), and their oxidation by Cu^{II} ions to (*E*)-11- and (*E*)-12-pentadecen-15-olides (**6**). The products obtained were converted into 15-pentadecanolide (**1**) by subsequent catalytic hydrogenation over a Pd catalyst in a yield of more than 90% with respect to hydroperoxide **2** (Scheme 1).

The initial hydroperoxide **2** was prepared from cyclododecanone (**7**) and allyl alcohol *via* 2-(3-hydroxypropyl)cyclododecane (**8**) and 13-oxabicyclo[10.4.0]hexadec-1(12)-ene (**3**) according to Scheme 2.

Ring expansion of hydroperoxide **2** was carried out in the presence of $CuO(Ac)_2$ (0.0015—0.07 equiv.) by adding a suspension of hydroperoxide **2** in an organic solvent to an intensively stirred boiling solution or suspension of copper acetate in the same solvent. The reaction mixture was boiled with stirring until decomposition of hydroperoxide was completed. When 0.05 equivalents of copper acetate (this amount is optimum) were used, decomposition was completed in from 2 to 40 h depending on the nature of the solvent and the boiling temperature of the reaction mixture (Table 1). The yields of pentadecenolides **6** were up to 96.5%. 4-Methylpentan-2-one is the best solvent for the transformation of hydroperoxide **2** into compounds **6** as regards the selectivity of the reaction and the quality of the target product obtained by catalytic hydrogenation of **6**. Butan-2-one is only insignificantly inferior to 4-methylpentan-2-one. When aromatic hydrocarbons

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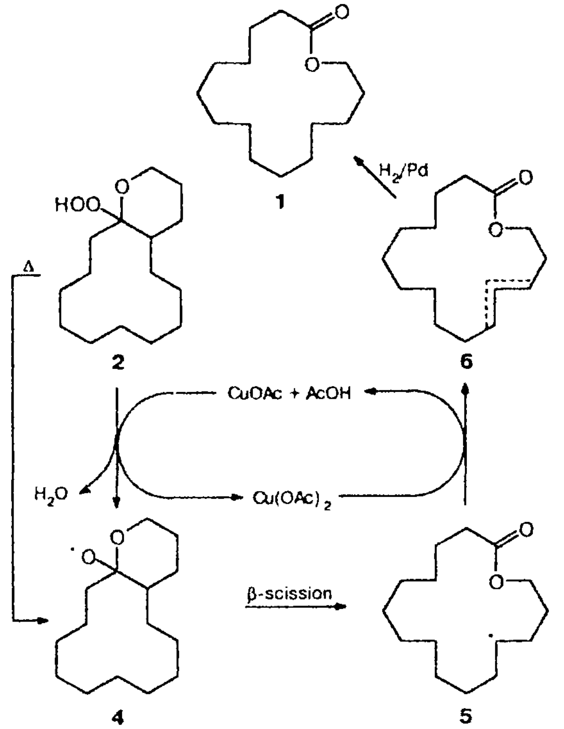
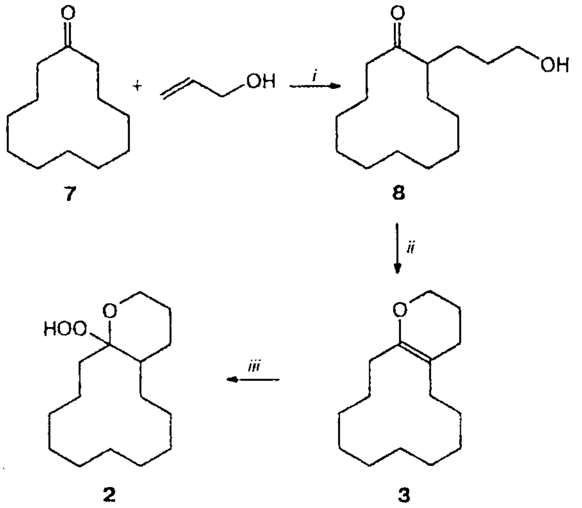
Scheme 1



Scheme 2



Reagents and conditions: *i*. $(Bu^tO)_2$, 140 °C, 8 h; *ii*. *p*-TsOH, $-H_2O$, 115 °C, 1 h, the yield was 60% from 7; *iii*. 30% $H_2O_2/H^{\oplus}$, AcOH, 0 °C, 45 min, the yield was 85%.

Table 1. Catalytic decomposition of 1-hydroperoxy-16-oxabicyclo[10.4.0]hexadecane (**2**) in the presence of copper acetate in different solvents[a]

Solvent	T/°C[b]	Duration of the reaction/h	Yield (%)	
			6[c]	**1**
Acetone	56—57	40	58	8
Butan-2-one	76—77	4	93	1
4-Methylpentan-2-one	102—106	4	96.5	0
Benzene	79—80	4	81	1
Toluene	104—109	3	92	2
m-Xylene	134—138	3	82	1
Chlorobenzene	131—132	2	51	0
Cyclohexane	80—81	6	65	3
n-Butanol	115—116	2	69	10
Chloroform	60—61	2	29	0
CCl_4	76—77	2.5	5	0

[a] Conditions: **2** (0.1 mol), $Cu(OAc)_2$ (0.05 equiv.), and the solvent (250 mL). [b] The boiling temperature of the reaction mixture. [c] Content of **6** of the product was determined from the bromine number.

Table 2. Catalytic decomposition of hydroperoxide **2** in the presence of different amounts of copper acetate in a solution of 4-methylpentan-2-one[a]

$Cu(OAc)_2$ (mol.%)	Yield (%)		$Cu(OAc)_2$ (mol.%)	Yield (%)	
	6[b]	**1**		**6**[b]	**1**
0.15	75	8	3.00	92	0
0.75	87	0	5.00	96.5	0
1.50	90	0	7.00	97	0

[a] Conditions: **2** (0.1 mol) and the solvent (250 mL) (102—106 °C). [b] Content of **6** of the product was determined from the bromine number.

(benzene, toluene, or *m*-xylene) and other solvents (Table 2) were used, additional purification of pentadecanolide **1** was necessary to attain the required consumption quality.

The reaction of ring expansion of hydroperoxide **2**, which is shown in Scheme 1, proceeded according to the chain mechanism with alternating redox cycles of valence transformations of copper ions.[24] In this case, pentadecen-15-olides **6** were obtained without by-products. The high chemoselectivity along with low consumption of the catalyst are the major advantages of this process over alternative methods, in which different procedures for the initiation were used. Thus, under the action of a mixture of sodium sulfite and sodium bisulfite, hydroperoxide **2** gave products **6** (a mixture of *E*- and *Z*-isomers), **1**, **3**, and 12-hydroxypentadecanolide (**9**) in yields of 23, 45, 15, and 7%,[7a] respectively. Thermolysis of **2** in boiling xylene afforded products **6** (a mixture of *E*- and *Z*-isomers), **1**, and **9** in yields of 8, 68, and 22%, respectively.[7b]

Catalytic hydrogenation of pentadecenolides **6** was carried out over three commercial Pd catalysts in a solution of propan-2-ol at a hydrogen pressure of 90—100 atm and at 85—120 °C (Table 3). The highest yield (95%) of target lactone **1** was obtained in the presence

Table 3. Catalytic hydrogenation of pentadecen-15-olides 6[a] over various commercial catalysts

Catalyst (wt.%)	Carrier	Pd content (wt.%)	T/°C	P_0/atm	Time /h	Conversion (%)	Yield of 1 (%)[b]
Pd/C, 3.4	Activated carbon	2	120	100	11	87	81
Pd/Al_2O_3, 6	γ-Al_2O_3	0.45	85	90	14	95	92
Pd/Al_2O_3, 6	Activated carbon	0.45 5[c]	85	100	8	~100	95

[a] A solution of 6 (0.075 mol) in propan-2-ol (30 mL). [b] With respect to the product isolated. [c] Na_2CO_3 content of the catalyst.

of the catalyst that contained 6 wt.% of Pd and 5 wt.% of sodium carbonate on activated alumina.

Therefore, the catalytic procedure for the preparation of pentadecanolide from available hydroperoxide 2 enables the preparative synthesis of this valuable macrolactone in high yield and of quality not requiring complicated purification before use in perfumes and cosmetics. This was confirmed by the production of large batches of 15-pentadecanolide* and by the high appraisal given by perfume experts (4.4 on the 5-number scale).

Experimental

The melting points were determined on a Kofler stage. The IR spectra were recorded on a UR-20 instrument (Carl Zeiss) in a thin layer. The ^1H NMR spectra were recorded on Bruker WM-250 and Bruker AW-300 spectrometers in $CDCl_3$. The mass spectra were obtained on a Varian MAT-311A instrument (EI, 70 eV). The GLC analysis was carried out on a Varian-3700 chromatograph (flame ionization detector; glass columns; 5% Carbowax 20M on Inerton and 5% XE-60 on Chromaton N-AW). The bromine numbers were determined according to a procedure reported in Ref. 25. All reagents and solvents were commercial products. The reagents were used without additional purification. The solvents were purified according to standard procedures.

Synthesis of 2-(3-hydroxypropyl)cyclododecanone (8).[19] A mixture of allyl alcohol (58 g, 1 mol) and di-*tert*-butyl peroxide (26 g, 0.17 mol) was added to an intensively stirred melt of cyclododecanone (7) (600 g, 3.25 mol) at 140—150 °C during 6 h. The reaction mixture was heated with stirring for 3 h. Products of decomposition of di-*tert*-butyl peroxide and unconsumed allyl alcohol (5.8 g, 0.1 mol) were distilled off under atmospheric pressure, and then excess 7 (470 g, 2.55 mol) was distilled off under reduced pressure. The residue was distilled *in vacuo*. Crude adduct 8 was obtained in a yield of 180 g, b.p. 110—131 °C (0.1 Torr). IR, ν/cm^{-1}: 1700, 3410. ^1H NMR, δ: 1.30—2.45 (m, 25 H), 3.30 (br.s, 1 H, OH), 3.50 (t, 2 H, CH_2O).

Synthesis of 13-oxabicyclo[10.4.0]hexadec-1(12)-ene (3).[7a,19] Crude adduct 8 (179 g) was heated in the presence of *p*-toluenesulfonic acid (1.1 g) at 115 °C *in vacuo* (40 Torr) for 1 h with simultaneous distillation of the water that formed. Subsequent distillation ot the mixture *in vacuo* afforded compound 3 in a yield of 95 g (60% with respect to converted 7), b.p. 138—145 °C (1 Torr), n_D^{20} 1.5060. IR, ν/cm^{-1}: 1660. ^1H δ: 1.35—2.15 (m, 24 H), 3.78 (t, 2 H). MS, m/z (I_{rel} (%)): 222 $[M]^+$ (15).

Synthesis of 1-hydroperoxy-16-oxabicyclo[10.4.0]hexadecane (2).[7a] A mixture of a 30% aqueous solution of H_2O_2 (47 mL, 0.415 mol) and 50% H_2SO_4 (11 g, 0.057 mol) was added to a stirred solution of 3 (50 g, 0.22 mol) in AcOH (250 mL) cooled to 0 °C during 30 min. The reaction mixture was stirred for 15 min. The precipitate of hydroperoxide 2 that formed was filtered off, washed with a 50% aqueous solution of AcOH (40 mL) and then with water until the aqueous extracts became neutral (4×100 mL), and dried in a desiccator over $CaCl_2$. Product 2 (96% purity) was obtained in a yield of 48.5 g (85%), m.p. 108—110 °C. IR (KBr), ν/cm^{-1}: 3300. ^1H NMR, δ: 1.32—1.75 (m, 25 H), 3.75 (t, 2 H, CH_2O), 7.40 (br.s, 1 H, OOH).

Conversion of hydroperoxide 2 into a mixture of (*E*)-11- and (*E*)-12-pentadecen-15-olides (6) catalyzed by copper acetate (general procedure). A suspension of hydroperoxide 2 (26 g, 0.1 mol) in 4-methylpentan-2-one (125 mL) was added portionwise to an intensively stirred boiling solution of $Cu(OAc)_2$ (0.9 g, 5 mmol) in 4-methylpentan-2-one (125 mL) during 1 h. The reaction mixture was boiled with stirring for 3 h, cooled, and filtered off from copper salts that precipitated. The filtrate was washed with hot water (2×200 mL) and concentrated. Compound 6 was obtained in a yield of 23 g (96.5%) and was purified by distillation *in vacuo*, b.p. 140—145 °C (1 Torr), n_D^{20} 1.4790 (Ref. 26: n_D^{20} 1.4778). IR, ν/cm^{-1}: 960, 1735. ^1H NMR, δ: 1.33—1.61 (m, 16 H), 1.71—2.55 (m, 6 H), 4.10 (t, 2 H, J = 5.2 Hz), 5.35 (t, 2 H). MS, m/z (I_{rel} (%)): 238 $[M]^+$ (25).

Preparation of 15-pentadecanolide (1) by catalytic hydrogenation of a mixture of pentadecen-15-olides 6 (general procedure). A solution of pentadecen-15-olide 6 (18 g, 75 mmol) in isopropyl alcohol (30 mL) was hydrogenated in an autoclave in the presence of the commercial Pd/Al_2O_3 catalyst (1.5 g) containing Pd (6 wt.%) and Na_2CO_3 (5 wt.%) at 85 °C and at the initial H_2 pressure of 100 atm. The course of hydrogenation was monitored by TLC and by determining the bromine numbers. After completion of hydrogenation of 6 (8 h), the reaction mixture was filtered off from the catalyst. The filtrate was concentrated at the residual pressure of 100 Torr. Distillation of the residue *in vacuo* afforded 1 (17.3 g, 95%), b.p. 137—142 °C (1 Torr), m.p. 31.5—33 °C. The IR spectra, ^1H and ^{13}C NMR spectra, and mass spectra of synthesized lactone 1 are identical to the corresponding spectra of 15-pentadecanolide reported in the literature.[8,21,27] Samples of macrolactone 1 for perfume tests were prepared by recrystallization of the product from 70% aqueous ethanol.

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