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A new method for synthesis of n-(3-acyloxypropyl)-substituted six- to thirteen-membered alkan-n-olides

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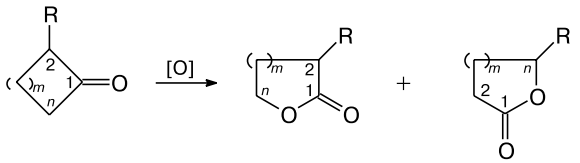
A new method for the synthesis of n-(3-acyloxypropyl)-substituted six- to thirteen-membered alkan-n-olides was developed. The method is based on the H_2SO_4-catalyzed reactions of oxabicycloalkenes, obtained from 2-(3-acetoxypropyl)cycloalkanes, with H_2O_2 and formic or acetic acid. The method includes the subsequent transformations of oxabicycloalkenes into bicyclic hydroperoxides, peroxy ethers, and, at the final stage, into target lactones formed in 56—71% yields. These transformations are carried as a one-pot reaction.

Key words: 2-oxabicyclo[*n*.4.0]alkenes, hydrogen peroxide, sulfuric acid, lowest alkanoic acids, 1-hydroperoxy-2-oxabicycloalkanes, 1-acylperoxy-2-oxabicycloalkanes, rearrangement, n-(3-acyloxypropyl)alkan-n-olides, 2-(3-acetoxypropyl)cycloalkanones, Baeyer—Villiger reaction.

Lactones are usually synthesized from cycloalkanones using the Baeyer—Villiger reaction,[1] which has been known for more than half a century. In this reaction, 2-substituted cycloalkanones produce, as a rule, mixtures of 2- and n-substituted alkan-n-olides.[2—6]



In this work we report a new method for the synthesis of lactones, which, unlike the Baeyer—Villiger reaction, affords only n-substituted lactones from 2-(3-acetoxypropyl)cycloalkanones (**1**) (Scheme 1). This approach is based on the preliminary transformation of ketones **1** into oxabicycloalkenes **2** and on the subsequent transformation of **2** (as a one-pot reaction) by hydrogen peroxide in a lowest alkanoic acid in the presence of a catalytic amount of H_2SO_4 first into hydroperoxides **3** and then into target lactones **4** and **5**.

In order to select the optimum conditions for the transformation of oxabicycloalkenes **2a—d** into lactones **4a—d** and **5a—d**, we studied the influence of formic, acetic, and propionic acids, the molar ratio of reactants and catalyst as well as conditions and procedure of the process on this reaction. The best results were achieved when a 2—3-fold

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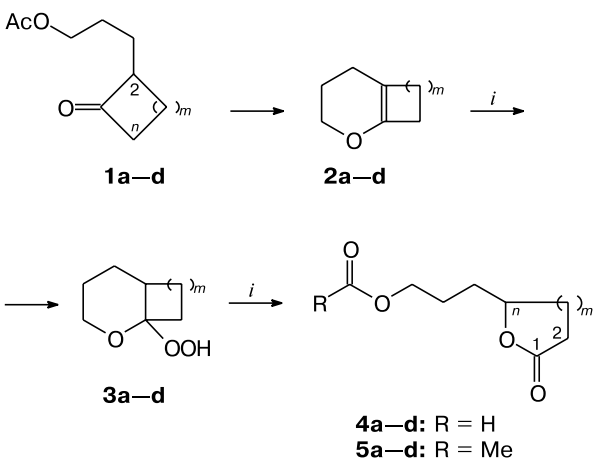
Scheme 1

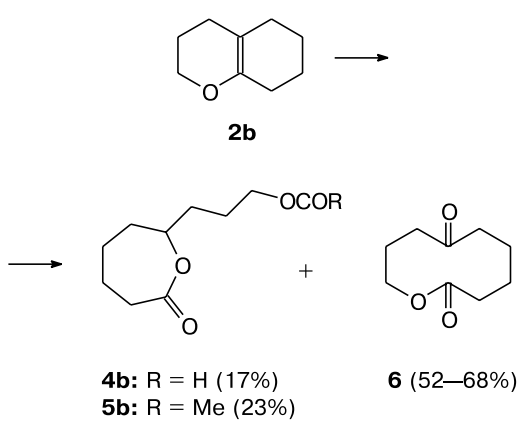


m = 2 (**a**), 3 (**b**), 4 (**c**), 9 (**d**)

Reagents and conditions: *i.* HCO_2H or AcOH, H_2O_2 (3—4 equiv.), H_2SO_4 (0.1 equiv.), 0—5 → 35—60 °C.

molar excess of hydrogen peroxide and 0.1 equiv. H_2SO_4 were used along with their gradual addition to a solution of **2a—d** in formic or acetic acid in the temperature interval of the reaction from 0 to 60 °C. Under these conditions, lactones **4a—d** and **5a—d** were obtained in 56—71% yields (Table 1). We found by TLC that lactones **4a—d** and **5a—d** are selectively formed only when the temperature is maintained within 0—5 °C in the hydroperoxidation stage and not higher than 60 °C in the subsequent stages. In addition, the duration of the first stage should be sufficient for the complete transformation of oxabicycloalkenes **2** into hydroperoxides **3**. If these conditions are violated, the H_2SO_4-catalyzed reaction of oxabicycloalkenes with H_2O_2 in formic and acetic acids looses its selectivity. For example, in the case of the reaction of oxabicycloalkene **2b** with H_2O_2 in formic or acetic acid, heating of the reaction mixture at temperature higher than 60 °C before the complete transformation of **2b** into hydroperoxide **3b** substantially decreased the yields of lactones **4b** and **5b** to form 6-oxononano-9-lactone (**6**) as the main product (Scheme 2, Table 1, entries 7 and 19).

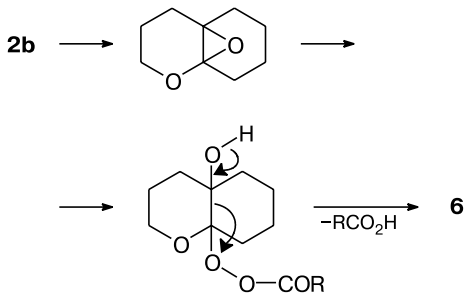
Scheme 2



Reagents and conditions: HCO_2H or AcOH, H_2O_2 (3 equiv.), H_2SO_4 (0.1 equiv.), 0—5 °C → >60 °C.

With respect to alkanolides **4b** and **5b**, lactone **6** is formed in an amount inversely proportional to the duration of interaction of the reactants (τ) at 0—5 °C: with an increase in τ from 15 to 60 min, the yield of **6** decreases to 22—36% (*cf.* entries 7—8 and 19—20). It is known that lactone **6** is formed as the single product (52—92% yield) in the oxidation of bicycloalkene **2b** by peroxycarboxylic acids[7,8] (Scheme 3).

Scheme 3



Reagents and conditions: CH_2Cl_2, MCPBA (1.5 equiv.), CF_3CO_2H (0.2 equiv.), 40 °C, 1 h.

Under the conditions that do not provide the complete conversion of bicycloalkene **2b** to hydroperoxide **3b** (for example, in entries 7—8 and 19—20), the unconverted part of **2b** is transformed into lactone **6**, probably, by peroxyformic or peroxyacetic acids formed under these conditions. However, even under conditions sufficient for the complete conversion of **2b** into **3b**, a mixture of lactones is formed (**4b** and **6** in formic acid and **5b** and **6** in acetic acid) if after the completion of transformation of **2b** into **3b** the reaction mixture is rapidly heated to 100 °C and higher (entries 8 and 20). This is likely caused by the competitive acylation of hydroperoxide **3b** by formic or acetic acid (Scheme 4, route *a*) and its dehydroperoxidation (route *b*) followed by the transformation of bicycloalkene **2b** that formed into lactone **6**.

Performing the reaction in a solution of propionic acid and even with an addition of propionic anhydride, we failed to transform bicycloalkene **2b** and hydroperoxide **3b** into lactone **7** due to a weaker acylating ability of propionic acid compared to formic and acetic acids (entry 23). 2-(3-Propionyloxypropyl)cyclohexanone (**8**) was obtained as the single product under similar conditions (Scheme 5, see Table 1, entry 27).

However, if on completion of the transformation of **2b** into **3b** the reaction mixture is heated to 40 °C only,

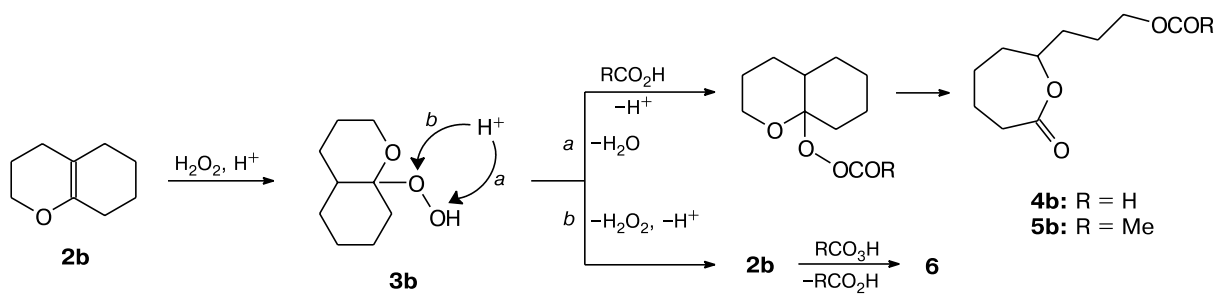
Table 1. Influence of the solvent, molar ratio of reactants, and conditions of the reaction of oxabicyclenes **2a—d** with H_2O_2 on transformations of **2a—d**

Entry	Substrate	Method[a]	Ratio **2** : H_2O_2 [b]	T/°C (τ/min)		Products (yield (%))
				2 → **3**	**3** → **4** and **5**	
			Solvent HCO_2H			
1	**2a**	*A*	1 : 1.5	0—5 (55)	50 (40)	**4a** (68)
2	**2a**	*A*	1 : 3	0—5 (40)	40 (30)	**4a** (70)
3	**2b**	*A*	1 : 2	0—5 (60)	45 (40)	**4b** (62)
4	**2b**	*B*	1 : 3	0—5 (60)	50 (40)	**4b** (49)
5	**2b**	*A*	1 : 3	0—5 (90)	40 (85)	**4b** (61)
6	**2b**	*A*	1 : 3	0—5 (60)	40 (40)	**4b** (56)
7	**2b**	*A*	1 : 3	0—5 (15)	100 (5)	**4b** (17) + 6 (68)
8	**2b**	*A*	1 : 3	0—5 (60)	100 (5)	**4b** (53) + 6 (36)
9	**2c**	*A*	1 : 3	0—5 (60)	50 (40)	**4c** (61)
10	**2d**	*A*	1 : 4	0—5 (90)	50 (40)	**4d** (64)
			Solvent AcOH			
11	**2a**	*A*	1 : 2	0—5 (60)	50 (30)	**5a** (58)
12	**2a**	*A*	1 : 3	0—5 (40)	40 (30)	**5a** (65)
13	**2a**	*B*	1 : 3	0—5 (40)	40 (40)	**5a** (51)
14	**2a**	*C*	1 : 3	0—5 (40)	40 (30)	**5a** (40)
15	**2b**	*A*	1 : 1.5	0—5 (90)	50 (30)	**5a** (55)
16	**2b**	*A*	1 : 2	0—5 (60)	60 (30)	**5a** (65)
17	**2b**	*A*	1 : 3	0—5 (60)	40 (40)	**5b** (64)
18	**2b**	*A*	1 : 4	0—5 (90)	50 (20)	**5b** (71)
19	**2b**	*A*	1 : 3	0—5 (15)	115 (5)	**5b** (23) + 6 (52)
20	**2b**	*A*	1 : 3	0—5 (60)	115 (5)	**5b** (52) + 6 (22)
21	**2c**	*A*	1 : 3	0—5 (60)	50 (40)	**5c** (56)
22	**2d**	*A*	1 : 4	0—5 (90)	50 (40)	**5d** (59)
			Solvent $EtCO_2H$			
23	**2b**	*A*	1 : 3	0—5 (15)	140 (5)	**6** (79)
24	**2b**	*A*	1 : 4	0—5 (120)	40 (40)	**6** (22) + 9 (60)
25	**2b**	*B*	1 : 1 [c]	0—5 (60)	65 (45)	**6** (72) + 8 (18)
26	**2b**	*B*	1 : 2 [c]	0—5 (60)	65 (45)	**6** (86)
			$EtCO_2H$ + $(EtCO)_2O$ (1 : 1)			
27	**2b**	*A*	1 : 3	0—5/15	140/5	**8** (72)

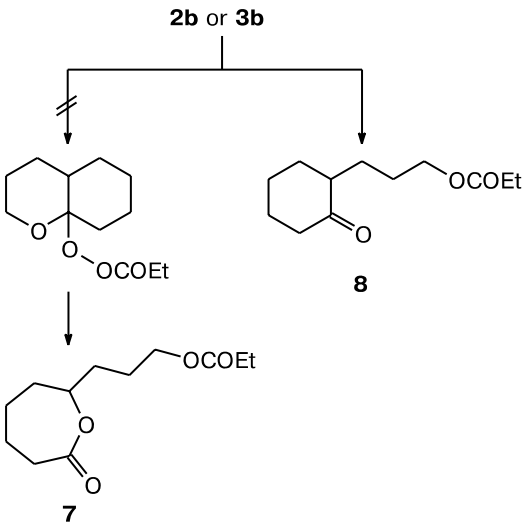
[a] Procedures *A, B,* and *C* are described in Experimental.
[b] H_2SO_4 was used in an amount of 0.1 equiv., except for entries 4 (0.05 equiv.) and 5 (0.20 equiv.).
[c] 90% H_2O_2.

di(2-oxabicyclo[4.4.0]decyl) peroxide (**9**) is formed along with lactone **6** (Scheme 6, procedure *A*, Table 1, entry 24), while ketone **8** is formed (entry 25*)* when an equimolar amount of 90% H_2O_2 is used with an addition of a solution of **2b** in propionic acid (procedure *B*). Only lactone **6** is formed in 86% yield (entry 26) with an in-

Scheme 4

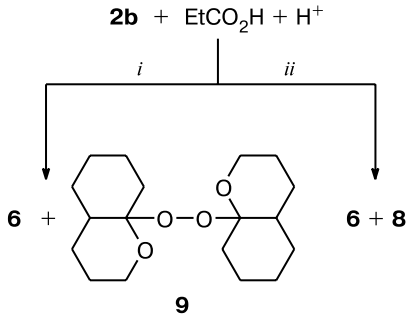


Scheme 5



Reagents and conditions: H_2O_2, $(EtCO)_2$, H^+ or $EtCO_2H + (EtCO)_2O$, H^+.

Scheme 6

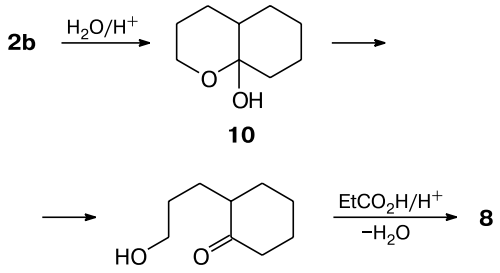


Reagents and conditions: *i*. 50% solution of H_2O_2, procedure *A*. *ii*. 90% solution of H_2O_2, procedure *B*.

crease in the amount of a 90% solution of H_2O_2 to two equivalents.

The formation of peroxide **9** in entry 24 can be accounted for the faster addition of hydroperoxide **3b** to the initial bicyclodecene **2b** than its dehydroperoxidation and transformation into lactone **6**. The partial transformation of bicycloalkene **2b** into ketone **8** in entry 25 and complete transformation in entry 27 are the result, most likely, of the addition of water (which is present in the reaction mixture) to **2b**, decyclization of bicyclic semiketal **10** that formed, and acylation of intermediate 2-(3-hydroxypropyl)cyclohexanone by propionic acid (Scheme 7).

Scheme 7

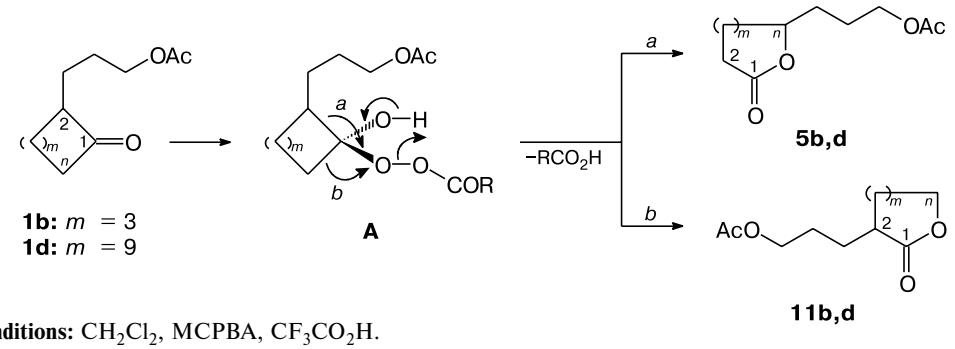


Substrates **2** are most effectively transformed into lactones **4** and **5** by a two- to threefold molar excess of 50% H_2O_2 in the presence of 0.1—0.2 equiv. H_2SO_4. With a smaller excess and a lower concentration of H_2O_2, as well as in the presence of a smaller amount of the catalyst, the time necessary for completion of this reaction substantially increases, and without a catalyst the reaction does not occur at all.

The structures of lactones **4a—d**, **5a—d**, and **6** were established by ^1H and ^{13}C NMR, IR, and mass spectra and comparison of these spectra with those obtained in Ref. 7 for the same compounds. The structures of lactones **5b** and **5d** were additionally confirmed by their independent doubtless synthesis, *i.e.*, Baeyer—Villiger oxidation of ketones **1b,d** (Scheme 8).[9]

6-(3-Acetoxypropyl)hexan-6-olide (**5b**) was obtained by this method in 34% yield as a mixture with isomeric 2-(3-acetoxypropyl)hexan-6-olide (**11b**) (20% yield). However, this method afforded 12-(3-acetoxypropyl)dodecan-12-olide (**5d**) only in 7% yield along with isomeric 2-(3-acetoxypropyl)dodecan-12-olide (**11d**) (3% yield).

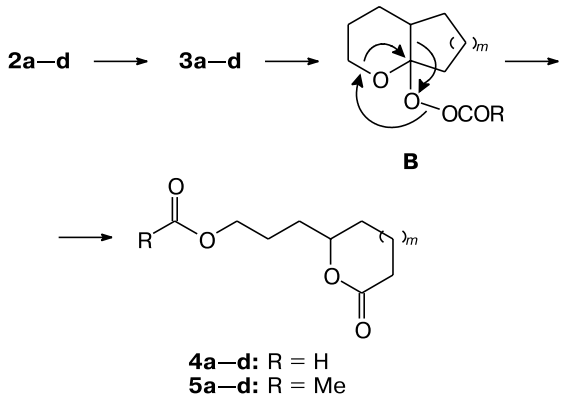
Scheme 8



Reagents and conditions: CH_2Cl_2, MCPBA, CF_3CO_2H.

Thus, unlike the Baeyer—Villiger reaction, the new method proposed for the synthesis of n-substituted lactones allows their regiospecific formation from 2-acetoxypropyl-substituted cycloalkanones through the successive transformation of these substrates into 2-oxabicycloalkenes and 1-hydroperoxy-2-oxabicycloalkenes. The distinction between the results of these two processes is caused by the different structures of the key intermediates that formed, which are conventionally called the "Criegee intermediates." [5] We have shown[10] that, in the case of the synthesis of lactones through oxabicycloalkenes and hydroperoxides, bicyclic peroxy ethers **B** are such intermediates (Scheme 9), whereas for the Baeyer—Villiger oxidation of ketones, these are monocyclic peroxy ethers **A** [5] (Scheme 8), whose rearrangement is less selective. The latter is due, most likely, to a less rigid structure **A** with respect to that of bicyclic peroxy ethers **B** and the substantial influence of the electronic, conformational, and steric factors on the regioselectivity in the Baeyer—Villiger reaction.[11,12]

Scheme 9



Experimental

NMR spectra were recorded on Bruker WM-250 (250.13 MHz for ^1H) and Bruker AM-300 (75.4 MHz for ^{13}C) spectrometers in solutions of $CDCl_3$. IR spectra were recorded on a UR-20 spectrometer (Carl Zeiss, Jena). Mass spectra were obtained on a Varian MAT-311A instrument (EI, 70 eV). GLC analysis was carried out on Varian-3700 (a flame-ionization detector, a glass column 2000×3 mm, 5% Carbowax 20M on Inerton) and LKhM-80 chromatographs (a flame-ionization detector, a steel column 1000×4 mm, 5% XE-60 on Chromaton N-AW). TLC analysis was performed using Silufol UV-254 chromatographic plates. Neutral Al_2O_3 and a diethyl ether—petroleum ether mixture (30—70% Et_2O) was used as the eluent in flash chromatography.

A commercial 50% aqueous solution of H_2O_2 (Acros Organics); acetic, formic, and propionic acids; 96% H_2SO_4 (Reakhim); trifluoroacetic acid (Lancaster); propionic anhydride and MCPBA (Aldrich) were used. A solution of 90% H_2O_2 was prepared by concentrating a 37% aqueous solution of H_2O_2 in a vacuum desiccator above P_2O_5 at 20 °C for 5 days. The concentration of H_2O_2 was determined by iodometric titration.

We have previously[10,13] described the synthesis of initial 2-(3-acetoxypropyl)cycloalkanones **1a—d**, oxabicycloalkenes **2a—d**, and 1-hydroperoxy-2-oxabicyclo[4.4.0]decane (**3b**).

Synthesis of n-acyloxyalkano-n-lactones 4a—d and 5a—d from oxacycloalkenes 2a—d (general procedures) (molar ratios of reactants, particular conditions of experiments, and yields of lactones are presented in Table 1). ***A.*** An aqueous solution of H_2O_2 containing a catalytic amount of H_2SO_4 was added dropwise for 5—10 min to a vigorously stirred and cooled to 0—5 °C solution of oxabicycloalkene **2** (5—10 mmol) in a lowest alkanoic acid (5—10 mL). The reaction mixture was stirred at this temperature until **2** completely converted (30—120 min) (TLC monitoring) and then heated at 40—60 °C for 20—45 min. Then the mixture was diluted with water (15 mL) and extracted with Et_2O (2×30 mL). The organic layer was neutralized with solid Na_2CO_3 (3 g), filtered, and concentrated by evaporation. The residue was distilled *in vacuo* (10—30 Torr) using a Hickmann flask (this distillation results in the thermal depolymerization of lactone oligomers, which can be formed under the reaction conditions), and the distillate was purified by flash chromatography if necessary.

B. A solution of oxabicycloalkene **2** (5—10 mmol) in a lowest alkanoic acid (5—10 mL) was added dropwise (for 5—10 min) to an aqueous solution of H_2O_2, which was vigorously stirred and cooled to 0—5 °C and contained a catalytic amount of H_2SO_4. The reaction mixture was stirred for this temperature until compound **2** converted completely (40—60 min) (TLC monitoring) and then heated at 40—50 °C for 40—45 min. For the further treatment of the mixture, see procedure *A*.

C. An aqueous solution of H_2O_2 containing a catalytic amount of H_2SO_4 was added dropwise (10 min) at ~20 °C to a vigorously stirred solution of oxabicycloalkene **2** (5 mmol) in a lowest alkanoic acid (5 mL). The reaction mixture was stirred to the complete conversion of **2** (40 min) (TLC monitoring) and heated at 40 °C for 30 min. Then the mixture was treated similarly to the treatment described in procedure *A*.

The physical properties and spectra of synthesized n-(3-formyloxypropyl)alkano-n-lactones (**4a—d**) and n-(3-acetoxypropyl)alkano-n-lactones (**5a—d**) were identical to those of lactones synthesized from hydroperoxides **3a—d**.[10] 6-Oxononano-9-lactone (**6**) was similar in physical and spectroscopic properties to the ketolactone synthesized by the reaction of 2-oxabicyclo[4.4.0]dec-1(6)-ene (**2b**) with MCPBA.[7,8]

2-(3-Propionyloxypropyl)cyclohexanone (8) was isolated by distillation of the residue obtained in entry 25. B.p. 170—173 °C (30 Torr). IR (KBr), ν/cm^{-1}: 1707 (C=O), 1736 (O—C=O). ^1H NMR, δ: 1.10—1.64 (m, 11 H, CH_2, CH_3); 1.88—2.12 (m, 5 H, CH_2, CH); 2.63 (q, 2 H, CH_2C=O, J = 2.3 Hz); 3.93 (t, 2 H, CH_2O, J = 4.0 Hz). Found (%): C, 67.71; H, 9.72. $C_{12}H_{20}O_3$. Calculated (%): C, 67.89; H, 9.50.

Di(1-oxadecahydronaphthalen-8a-yl) peroxide (9) was isolated by flash chromatography of the residue obtained in entry 22. R_f 0.2 (Et_2O—petroleum ether, 1 : 1), oil manifesting a positive for peroxide reaction with an acidifed solution of KI. IR (NaCl), ν/cm^{-1}: 864 (O—O). ^1H NMR, δ: 1.10—1.80 (m, 26 H, CH_2, CH); 3.55—4.31 (m, 4 H, CH_2O). ^{13}C NMR, δ: 22.5, 24.6, 25.6, 26.0, 29.2 (CH_2); 32.0 (CH); 43.5 (CH_2—C—O);

61.4 (CH_2O); 103.4 (C—O). Found (%): C, 69.28; H, 10.11. $C_{18}H_{30}O_4$. Calculated (%): C, 69.64; H, 9.74.

Independent synthesis of n-acetoxy- and α-(3-acetoxypropyl)-substituted alkano-n-lactones (5b,d and 11b,d). A solution of cyclohexanone **1b** or cyclododecanone **1d** (10 mmol) in chloroform (10 mL) was added at 20—25 °C to a stirred solution of MCPBA (15 mmol) in a mixture of chloroform (20 mL) and CF_3CO_2H (4 mL). Then the reaction mixture was stirred until the initial substrate completely converted (1 h, GLC and TLC monitoring) and extracted with diethyl ether (45 mL). The ether extract was washed with a 5% aqueous solution of sodium hydrocarbonate (3×15 mL), dried above $MgSO_4$, and concentrated. Lactones **5b,d** and **11b,d** were isolated by flash chromatography of the residue using an Et_2O—petroleum ether (2 : 1) mixture as the eluent.

6-(3-Acetoxypropyl)hexano-6-lactone (5b), 34% yield. R_f 0.8 (Et_2O—petroleum ether, 2 : 1), identical by the ^1H and ^{13}C NMR spectra to the corresponding lactone obtained from hydroperoxide **3b**.[10]

12-(3-Acetoxypropyl)dodecano-12-lactone (5d), 7% yield. R_f 0.7 (Et_2O—petroleum ether, 2 : 1), identical by the ^1H and ^{13}C NMR spectra to the corresponding lactone obtained from hydroperoxide **3d**.[10]

2-(3-Acetoxypropyl)hexano-6-lactone (11b),[15] 20% yield. R_f 0.8 (Et_2O—petroleum ether, 2 : 1). IR, ν/cm^{-1}: 1715. ^1H NMR, δ: 1.48—2.10 (m, 8 H, CH_2); 2.03 (s, 3 H, CH_3); 2.28—2.60 (m, 1 H, CHC=O); 3.98—4.23 (m, 2 H, CH_2O); 4.29—4.38 (m, 2 H, CH_2O).

2-(3-Acetoxypropyl)dodecano-12-lactone (11d), 3% yield. R_f 0.7 (Et_2O—petroleum ether, 2 : 1). IR, ν/cm^{-1}: 1715. ^1H NMR, δ: 1.13—2.12 (m, 22 H, CH_2); 2.02 (s, 3 H, CH_3); 2.16.—2.45 (m, 1 H, CHC=O); 3.93—4.15 (m, 4 H, CH_2O, HC—O). Found (%): C, 68.73; H, 9.83%. $C_{17}H_{30}O_4$. Calculated (%): C, 68.42; H, 10.13.

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