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Synthesis of novel macrocyclic peroxides by bis(sym-collidine)iodine (I) hexafluorophosphate-mediated cyclization of unsaturated hydroperoxides and unsaturated alcohols

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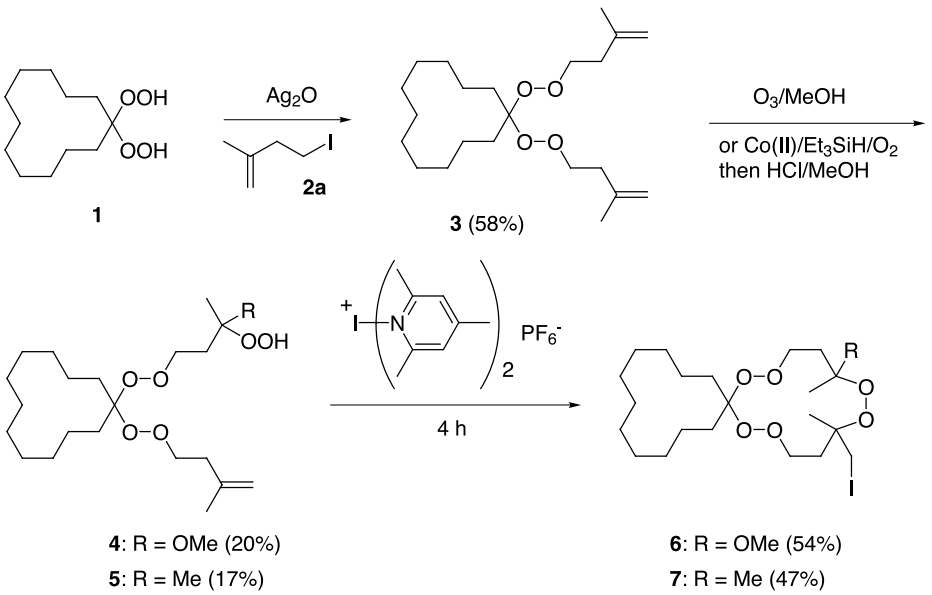
Abstract—Bis(sym-collidine)iodine (I) hexafluorophosphate-mediated cyclization of unsaturated hydroperoxides, prepared by a variety of different methods, afforded the corresponding 10- to 20-membered macrocyclic peroxides having two or three peroxide units located within one ring in moderate yields. By analogy, cyclization of unsaturated alcohols having one or two peroxide bond in the chain afforded the corresponding cyclic ethers. The efficiency of the latter reactions were found to be a function of the structure of the alcohols. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

During the last decade, the chemistry of cyclic peroxides has enjoyed a resurgence of interest with the increasing appreciation that such compounds occur widely in nature and often possess desirable pharmacological properties.[1] Thus, considerable effort has gone into developing short, efficient synthetic routes to 6- to 9-membered cyclic peroxides and identifying the key structure–activity relationships for the antimalarial activity against



Scheme 1.

Keywords: macrocyclic peroxide; iodonium ion-mediated cyclization; unsaturated hydroperoxide; unsaturated alcohol.

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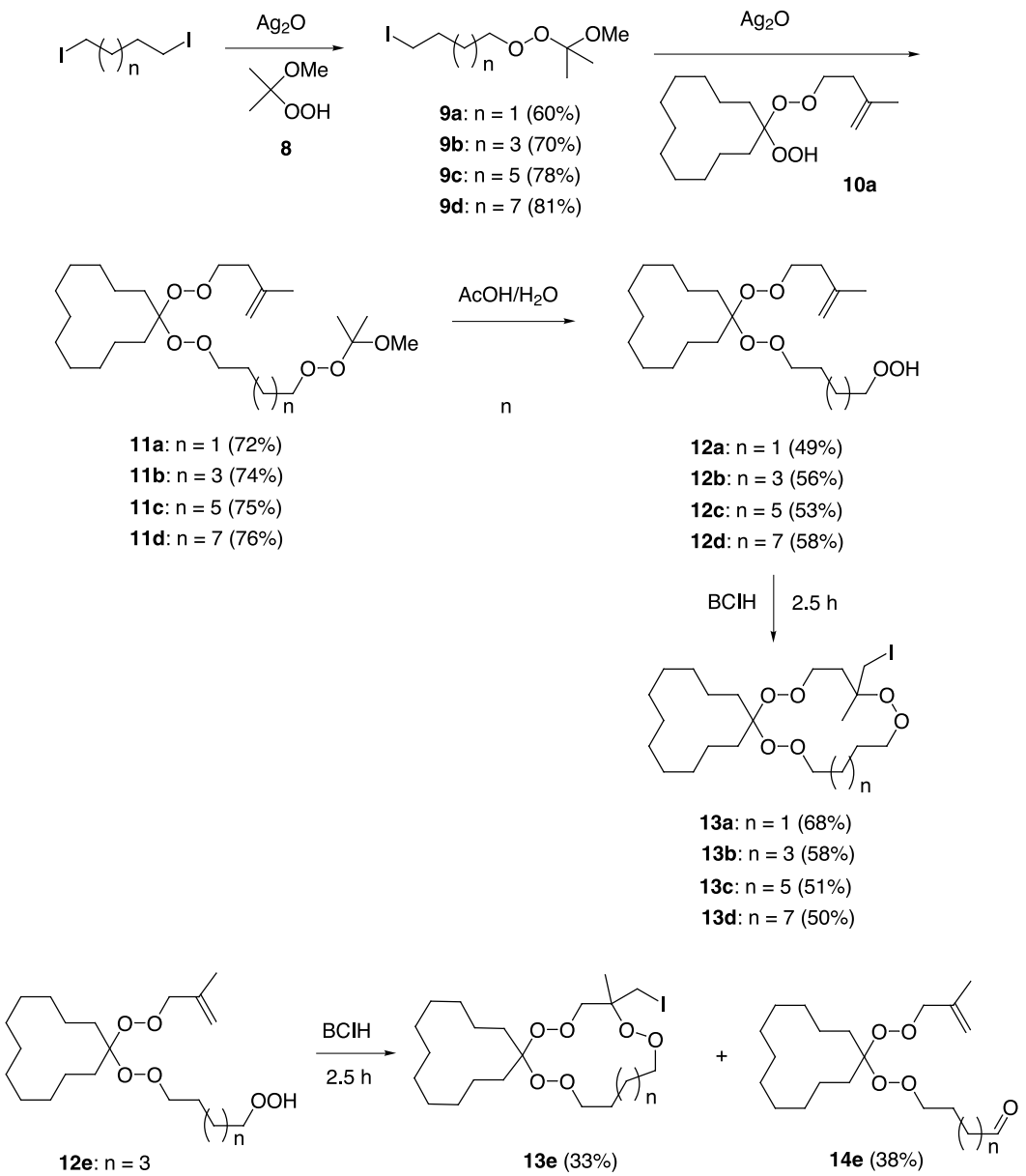
drug-resistant forms of malarial such as *P. falciparum*.[2] In contrast, examples of macrocyclic peroxides are comparatively scarce.[3–5] Moreover, they are usually derived from unexpected oligomerization of key intermediates such as diradicals. In this respect, we recently reported that bis(sym-collidine)iodine(I) hexafluorophosphate (BCIH)-promoted cyclization[6,7] of some unsaturated hydroperoxides provides novel macrocyclic peroxides.[8] We report herein the scope and limitation of these cyclization reactions including new methods of preparation for a variety of unsaturated hydroperoxides and extension of this cyclization methodology to the synthesis of macrocyclic ethers from unsaturated alcohols having one or more peroxide bond in the chain.

2. Results and discussion

2.1. Macrocyclization of unsaturated hydroperoxides

A first approach to the synthesis of the required unsaturated hydroperoxides was based on the mono-ozonolysis of the symmetrical bis(alkenylperoxy)cyclododecane **3**,[9] which was prepared by alkylation of the bishydroperoxide **1** with 2 equiv. of 4-iodo-2-methylbutene in the presence of Ag_2O (Scheme 1).[7] Reaction of diene **3** with 1.3 equiv. of ozone in $MeOH–CH_2Cl_2$ gave the unsaturated hydroperoxide **4** (20%) accompanied by di-ozonolysis product (31%) and unreacted diene **2** (23%) (see Experimental). This suggests that ozone reacts with diene **3** and the mono-ozonolysis product **4** at similar rates. In a second method for the synthesis of unsaturated hydroperoxides, the cobalt(II)-catalyzed triethylsilylperoxidation of diene **3** with molecular oxygen and triethylsilane was investigated.[10] Thus, treatment of a solution of diene **3** and a catalytic amount of cobalt(II) acetylacetonate in dry ethanol with triethylsilane at room temperature for 16 h under an oxygen atmosphere at slightly positive pressure followed by removal of triethylsilyl group afforded the hydroperoxide **5** in 17% yield, together with cyclododecanone (23%) and unreacted diene **3** (36%). Subsequent reaction of **4** with



Scheme 2.

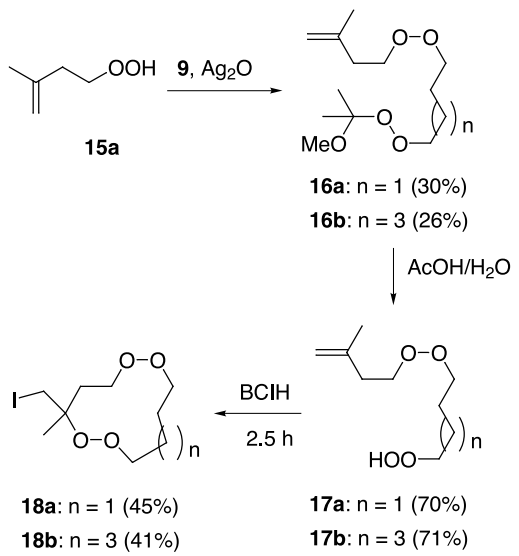
1.5 equiv. of BCIH in CH_2Cl_2 at room temperature for 4 h gave the expected 13-membered macrocyclic triperoxide **6** in 54% yield (a 3:1 mixture of two inseparable stereoisomers). Under similar reaction conditions, the unsaturated hydroperoxide **5** was converted into the cyclic peroxide **7** in 47% yield (Scheme 1). The structure of the 13-membered triperoxide **7** has been unambiguously determined by the X-ray crystallographic analysis.[8]

Thus, BCIH-promoted cyclization of unsaturated hydroperoxides has been proved to be a good procedure for the preparation of macrocyclic peroxides having three peroxide bonds in one ring. The major drawback is the poor selectivity obtained in the mono-peroxidation of diene **3**. Due to the methodology for the preparation of dienes such as **3**, the variation in structure of the derived unsaturated hydroperoxide substrates is also limited. To overcome these limitations, we developed a third method for the preparation of unsaturated hydroperoxide precursors as outlined in Scheme 2. This approach involved the Ag_2O-catalysed alkylation of the hydroperoxide **10a** with the iodoalkyl hemiperketals **9**[11,12] to provide the peroxides **11** in moderate yield (however, as a mixture with ca. 20% of cyclododecanone) (Scheme 2). Subsequent deprotection of the peroxides **11** afforded hydroperoxides **12**, which on BCIH-promoted cyclization gave the corresponding cyclic peroxides **13a–d**. It is noteworthy that the 20-membered cyclic peroxide **13d**, the largest cyclic peroxide hitherto known, could be obtained in an acceptable yield of 50%. The crystal structure of the novel 16-membered triperoxide **13b** has also been unambiguously determined by the X-ray analysis.[8] In the case of the sterically congested **12e**, however, dehydration competed with the intramolecular cyclization process, thereby providing aldehyde **14e** (38%) together with the expected macrocyclic peroxide **13e** (33%). Since the product yields in each step are acceptable and, moreover, the length of the longer tether is readily variable, the procedure outlined in Scheme 2 should offer a convenient synthetic entry to a variety of novel macrocyclic peroxide systems.

The above method was extended to the preparation of unsaturated hydroperoxides **17**. Nucleophilic substitution of the iodide **9** with the hydroperoxide **15a**, followed by deprotection, gave **17a**,**b** in moderate yields (Scheme 3). Subsequent BCIH-promoted cyclization gave the 11- and 13-membered 1,2,4,5-tetraoxacycloalkane derivatives **18a**,**b** in acceptable yields.

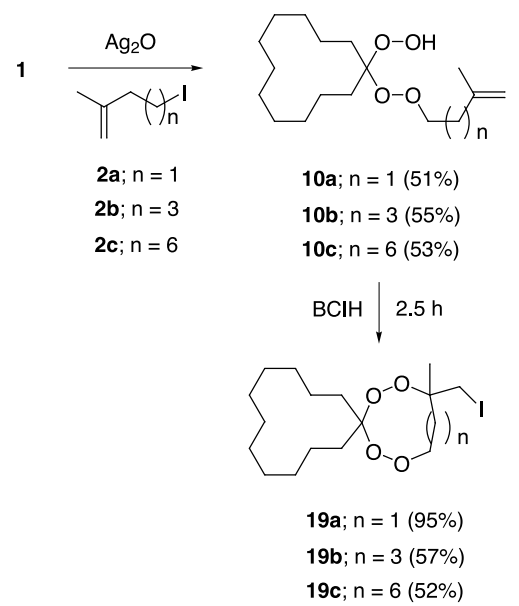
We have previously reported that the tetroxocane derivative **19a** is produced in essentially quantitative yield from an unsaturated hydroperoxide **10a**.[7] Under similar reaction conditions, the larger tetraoxacycloalkane derivatives **19b**,**c** were successfully prepared in around 50% yields from the unsaturated hydroperoxide **10b**,**c** having a longer tether than **10a** (Scheme 4).

In a further approach to the synthesis of unsaturated hydroperoxide precursors **25**, the carbonyl oxide, cyclohexanone *O*-oxide, generated in situ by ozonolysis of the vinyl ether **22**, was captured by (triethylsilyl)dioxy-substituted alcohols **21** to give the corresponding hydroperoxide adducts **23** in moderate yield (Scheme 5).[9]

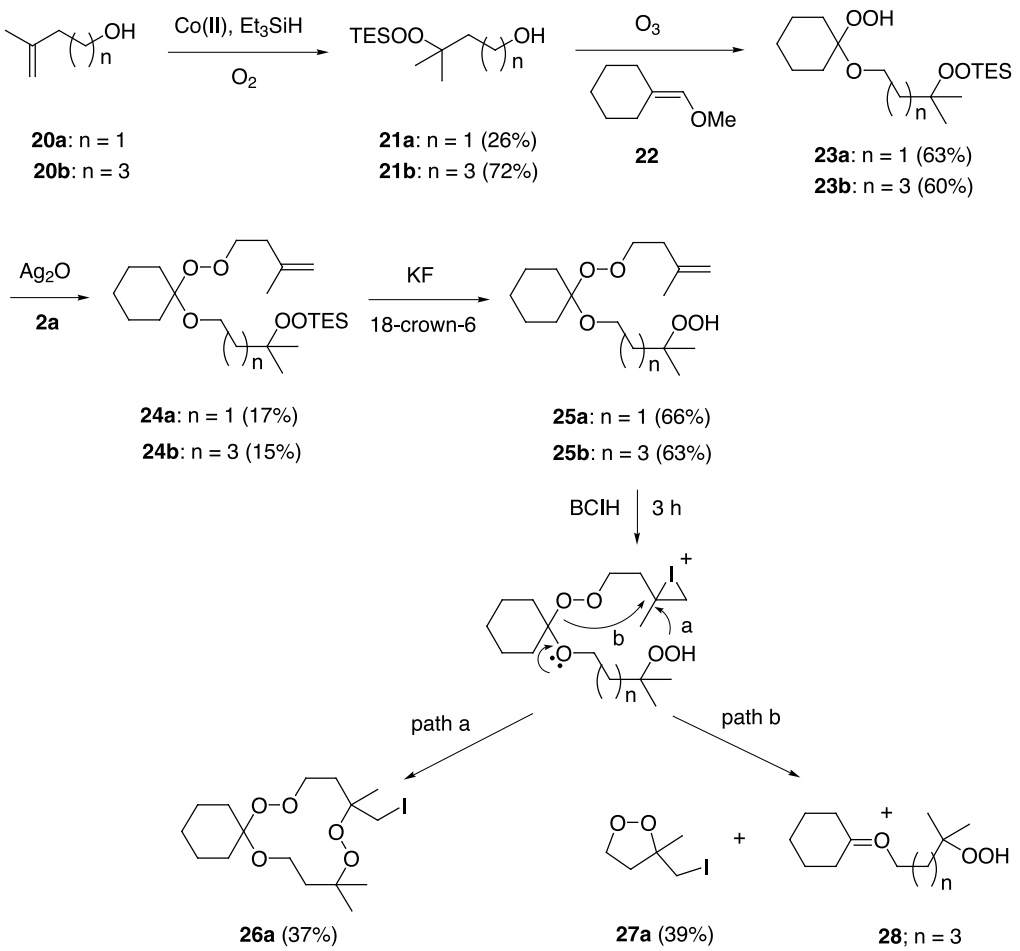


Scheme 3.

Unfortunately, the subsequent Ag_2O-promoted alkylation of **23** afforded the peroxides **24** in poor yield. The desired unsaturated hydroperoxides **25** were then obtained by removal of the triethylsilyl group. The outcome of the BCIH-promoted cyclization of **25** was significantly influenced by the substrate structure: **25a** gave the expected 12-membered cyclic peroxide **26a** whereas **25b**, having the longer chain, underwent cleavage with concomitant elimination of 3-iodomethyl-3-methyl-1,2-dioxolane (**27a**). This implies that formation of the 14-membered cyclic peroxide from **25b** (path a in Scheme 5) is entropically less favorable than the alternative pathway b involving attack on the iodonium ion intermediate by the distal oxygen atom of the inner peroxide bond. In addition to dioxolane **27a**, cleavage path b would result in the formation of a relatively stable oxonium ion intermediate **28**.



Scheme 4.

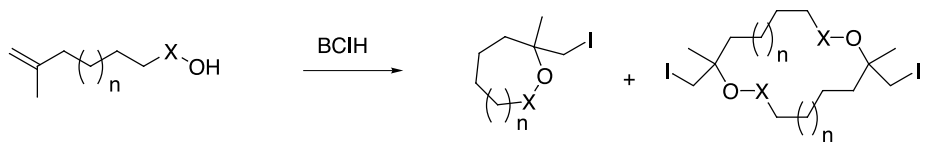


Scheme 5.

2.2. Macrocyclization of unsaturated alcohols

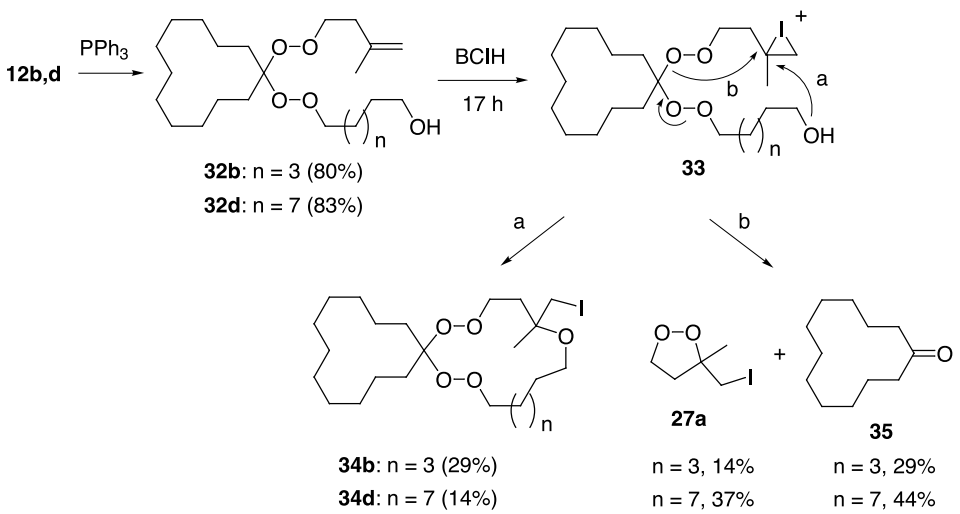
Brunel and Rousseau have reported that the BCIH-promoted cyclization of unsaturated alcohols provides an excellent method for the production of the corresponding oxepanes, whereas the efficiency of formation of the corresponding oxocanes is very poor.[13] Thus, the reaction of an unsaturated alcohol **20c** for 1 h gave the oxepane **29c** in 71% yield. Under similar reaction conditions, the desired oxocane **29d** (9%) and the 16-membered dimer **30d** (14%) were obtained from **20d**. In accordance with this, we also found that the reaction of unsaturated alcohol **20e** at room temperature proceeded very slowly (46% of **20e** was recovered after 17 h reaction) and only the 18-membered cyclic dimer **30e** was obtained in a low yield of 16% (Table 1). These results are at variance with the observation that the BCIH-promoted cyclization reactions of unsaturated carboxylic acids gave the corresponding 7–20-membered lactones in good to moderate yield.[6b] Consequently, we tested the efficiency of the BCIH-promoted cyclization of the relevant unsaturated hydroperoxides **15b**,**c** (Table 1). After 4 h, the reaction of the unsaturated hydroperoxide **15b** with BCIH gave the 1,2-dioxocane **27b** in 63% yield, suggesting that, as compared to alcohol **20d**, the reaction of **15b** is significantly

Table 1. Reaction of unsaturated alcohol **20** and unsaturated hydroperoxide **15** with BCIH



Substrate	X	Reaction time (h)	Products	
20c; *n*=1	CH_2	1	**29c**; *n*=l (71%)[a]	
20d; *n*=2	CH_2	1	**29d**; *n*=2 (9%)	**30d**; *n*=2 (14%)[a]
20e; *n*=3	CH_2	17		**30e**; *n*=3 (16%)[b]
15b; *n*=2	O	4	**27b**; *n*=2 (63%)[c]	
15c; *n*=4	O	4	**27c**; *n*=4 (28%)	**31c**; *n*=4 (12%)

[a] Taken from the data in Ref. 6c.
[b] The unreacted alcohol **20e** was recovered in 46%.
[c] 2-Iodomethyl-2-methyloxepane (**29c**) was also obtained in 14% yield.



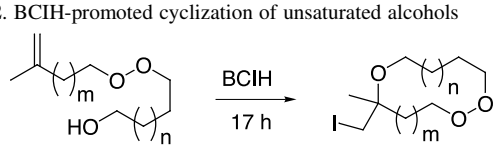
Scheme 6.

faster and the intramolecular cyclization is more efficient. In the case of the unsaturated hydroperoxide **15c**, however, the 20-membered cyclic dimer **31c** (12%) was obtained together with the expected 1,2-dioxecane **27c** (28%). This is in marked contrast to the fact that only the corresponding 1,2,4,6-tetroxecane derivative **19b** is obtained from **10b** in moderate yield (Scheme 4). It is apparent that the number of oxygen atoms must play an important role in determining the extent of Pitzer and transannular strain in the ring formation.[6a,14]

These results clearly demonstrate that, for the steric reasons, the nucleophilicity of the hydroxy group towards the iodonium ion intermediate is substantially lower than that of the hydroperoxy group.[15] Nevertheless, we expected that even in the case of unsaturated alcohols, the presence of oxygen atoms in the chain would make intramolecular cyclization leading to macrocyclic ethers more probable. Thus, we investigated the cyclization reactions of the unsaturated alcohols **32**, prepared by treatment of the corresponding hydroperoxides **12** with 1 equiv. of PPh_3 (Scheme 6). On reaction of **32** with BCIH, the expected cyclic ethers **34** were isolated albeit in poor yield (29% for **34b** and 14% for **34d**) accompanied by significant amounts of 1,2-dioxolane **27a** and cyclododecanone (**35**). This is in marked contrast to the fact that in the case of the corresponding unsaturated hydroperoxides **12b**,**d** only the macrocyclic peroxides **13b**,**d** were obtained in moderate yields of ca. 50%.

To see if this procedure is applicable to the synthesis of monocyclic ethers containing one peroxide bond, cyclization reactions of the unsaturated alcohols **38a**–**c** (for the method of preparation, see Experimental) were carried out. Treatment of **38a** with BCIH for 17 h led to the formation of a 1,2,6-trioxecane derivative **39a** in low yield (11%). Under analogous conditions, **38b** gave the 1,2,6-trioxacyclododecane derivative **39b** in 14% yield and **38c** gave the isomeric 1,2,7-trioxacyclododecane derivative **39c** in 19% yield. In all cases, significant quantities of unchanged starting material were recovered (Table 2).

Table 2. BCIH-promoted cyclization of unsaturated alcohols



Substrate	Yield of **39** (%)	Recovered **38** (%)
38a; *m*=1, *n*=1	11	45
38b; *m*=1, *n*=3	14	55
38c; *m*=3, *n*=1	19	49

3. Conclusion

We designed several methods for the preparation of unsaturated hydroperoxide and alcohol precursors. By the subsequent BCIH-promoted cylization a variety of 10–20-membered macrocyclic peroxides could be prepared, demonstrating that this is a new, reliable synthetic method of a variety of macrocyclic peroxides.

4. Experimental

4.1. General procedure

^1H (270 MHz) and ^{13}C NMR (67.5 MHz) spectra were obtained in $CDCl_3$ with $SiMe_4$ as standard. The precursors **10a**,[7] **15a**–**d**,[16] **20b**,[17] **20e**,[18] 2-(6-iodohexyloxy)tetrahydropyran[19] and 2-(4-iodobutyloxy)tetrahydropyran[19] were prepared by the reported methods.

4.2. Caution

Since organic peroxides are potentially hazardous compounds, they must be handled with due care; avoid exposure to strong heat or light, or mechanical shock, or oxidizable organic materials, or transition metal ions.

4.3. Preparation of 1,1′-cyclododecylidenebis[(3-methyl-3-butenyl) peroxide] (3)

A mixture of cyclododecylidenebishydroperoxide (1392 mg, 6 mmol), 4-iodo-2-methylbutene (2352 mg, 12 mmol) and Ag_2O (2784 mg, 12 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature for 16 h. After removal of the solid material by filtration over celite, ether (100 mL) was added to the filtrate and the mixture was washed with aqueous sodium thiosulfate. After drying the organic layer over anhydrous $MgSO_4$, the solvent was removed from it under reduced pressure and the resulting residue subjected to column chromatography on silica gel. Elution with ether–hexane (2:98) gave peroxide **3** (1271 mg, 58%). Subsequent elution with ether–hexane (2:98) gave cyclododecanone (380 mg, 35%).

4.3.1. 1,1′-Cyclododecylidenebis[(3-methyl-3-butenyl) peroxide] (3). An oil; ^{1}H NMR δ 1.3–1.7 (m, 22H), 1.73 (s, 6H), 2.35 (t, J=6.9 Hz, 4H), 4.18 (t, J=6.9 Hz, 4H), 4.75 (s, 2H), 4.77 (s, 2H); ^{13}C NMR δ 19.23, 21.80, 22.18, 22.70, 25.97, 26.88, 35.80, 73.35, 111.50, 113.14, 142.08. Anal. Calcd for $C_{22}H_{40}O_4$: C, 71.70; H, 10.94. Found: C, 71.66; H, 10.99.

4.4. Preparation and reaction of unsaturated hydroperoxide 4 with bis(sym-collidine)-iodine(I) hexafluorophosphate (BCIH)

A solution of 1,1′-cyclododecylidenebis[(3-methyl-3-butenyl) peroxide] (**3**) (288 mg, 3.5 mmol) in MeOH (10 mL)–CH_2Cl_2 (20 mL) was cooled to −78°C, and a stream of ozone (1.3 equiv.) was bubbled through it at this temperature. Aqueous $NaHCO_3$ was added, and the mixture extracted with ether (70 mL), washed with saturated brine, and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the components of the crude product mixture were separated by column chromatography on silica gel. Elution with ether–hexane (2:98) gave the unreacted **3** (297 mg, 23%). Second fraction (elution with ether–hexane; 20:80) gave 1-methoxy-1-methyl-3-[[1-[(3-methyl-3-butenyl)-dioxy]cyclododecyl]dixoy]propyl hydroperoxide (**4**) (292 mg, 20%). Subsequent elution with ether–hexane (45:55) gave 1,1′-cyclododecylidenebis[(3-hydroperoxy-3-methoxy)butyl peroxide] derived from the reaction of both of the double bonds in **3** with two ozone molecules (501 mg, 31%); an oil; ^{1}H NMR δ 1.2–1.8 (m, 22H), 1.81 (s, 6H), 4.50 (s, 4H), 4.95 (s, 2H). 5.00 (s, 2H); ^{13}C NMR δ 19.34, 19.91, 21.87, 22.25, 26.04, 26.96, 79.12, 113.41, 114.09, 140.81. Anal. Calcd for $C_{20}H_{36}O_4$: C, 70.55; H, 10.66. Found: C, 70.67; H, 10.56. To a solution of the hydroperoxide **4** (200 mg, 0.48 mmol) in CH_2Cl_2 (10 mL) was added BCIH (370 mg, 0.72 mmol) and the mixture was stirred at room temperature for 4 h (the flask was covered by aluminum foil). Ether (70 mL) was added and the organic layer was separated, washed with aqueous $Na_2S_2O_3$ followed by saturated brine, and dried over anhydrous $MgSO_4$. After concentration under reduced pressure, the components of the crude product mixture were separated by column chromatography on silica gel. Elution with diethyl ether–hexane (6:94) gave the iodomethyl-substituted spiro-[11,12]tetracosane **6** (140 mg, 54% yield, a 3:1 mixture of two isomers).

4.4.1. 1-Methoxy-1-methyl-3-[[1-[(3-methyl-3-butenyl)-dioxy]cyclododecyl]dioxy] propyl hydroperoxide (4). An oil; ^{1}H NMR δ 1.2–1.7 (m, 25H), 1.76 (s, 3H), 1.9–2.0 (m, 1H), 2.1–2.2 (m, 1H), 2.35 (t, J=6.9 Hz, 2H), 3.33 (s, 3H), 4.1–4.2 (m, 4H), 4.75 (s, 1H), 4.78 (s, 1H), 8.72 (s, 1H); ^{13}C NMR δ 18.98, 19.18, 21.73, 22.10, 22.64, 25.90, 25.93, 26.78, 33.68, 35.69, 48.65, 70.86, 73.23, 105.55, 111.57, 113.21, 141.99.

4.4.2. 20-(Iodomethyl)-17-methoxy-17,20-dimethyl-13,14,18,19,23,24-hexaoxaspiro[11,12]tetracosane (6). A 3:1 mixture of two isomers: mp 115–116°C (from hexane–ether); ^{1}H NMR δ 1.1–1.7 (m, 22H), 1.30 (s, major)+1.41 (s, major)+1.42 (s, minor)+1.47 (s, minor) (6H), 1.9–2.1 (m, 2H), 2.3–2.4 (m, 2H), 3.35 (s, minor)+3.36 (s, major) (3H), 3.40–3.45 (m, 0.7H), 3.54–3.65 (m, 1.3H), 4.0–4.1 (m, 2H), 4.2–4.3 (m, 2H); ^{13}C NMR δ 14.09, 14.14, 15.26, 19.61, 20.79, 21.80, 22.14, 26.87, 22.77, 23.63, 25.91, 26.02, 26.06, 26.81, 26.87, 27.10, 31.52, 33.26, 34.88, 35.42, 35.56, 49.00, 49.18, 70.64, 70.71, 71.29, 71.36, 79.77, 80.43, 104.53, 104.58, 113.32, 113.44. Anal. Calcd for $C_{22}H_{41}IO_7$: C, 48.53; H, 7.59. Found: C, 48.23; H, 7.28.

4.5. Co(II)-catalyzed triethylsilylperoxidation of diene 3, followed by deprotection of the triethylsilyl group and the subsequent BCIH-promoted cyclization

In an oven-dried 50 mL two-necked flask were charged diene **3** (1,960 mg, 5.3 mmol), cobalt(II) acetylacetonate (70 mg, 0.27 mmol) and dry ethanol (5 mL), and then triethylsilane (1230 mg, 10.6 mmol) was added via 1.0 mL gas-tight syringe. The resulting solution was stirred at room temperature for 8 h under slightly positive oxygen atmosphere. After the reaction was complete, the solvent was carefully rotary-evaporated for flash column chromatography on silica gel. Elution with ether–hexane (2:98) gave a 2:1 mixture of the unreacted **3** (711 mg) and 1-[(3-methyl-3-butenyl)dioxy]-1-[[3-methyl-3-[(triethylsilyl)-dioxy]butyl]dioxy]cyclododecane (689 mg, 1.3 mmol, 25%). Subsequent elution with ether–hexane (5:95) gave cyclododecanone (210 mg, 23%). Then, the mixture of **3** and the peroxide obtained above was dissolved in methanol (8 mL) and two drops of conc. HCl was added. After stirring for 15 min, ether (70 mL) was added and the organic layer was separated, washed by saturated brine, and dried over anhydrous $MgSO_4$. After concentration under reduced pressure, the components of the crude product mixture were separated by column chromatography on silica gel. Elution with ether–hexane (2:98) gave diene **3** (550 mg). Subsequent elution with ether–hexane (8:92) gave **5** (361 mg, 17% based on **3**). To a solution of the hydroperoxide **5** (122 mg, 0.30 mmol) in CH_2Cl_2 (10 mL) was added BCIH (231 mg, 0.45 mmol) and the mixture was stirred at room temperature for 4 h. After work-up as described above, the components of the crude product mixture were separated by column chromatography on silica gel. Elution with ether–hexane (2:98) gave the macrocyclic peroxide **7** (72 mg, 47% yield).

4.5.1. 1,1-Dimethyl-3-[[1-[(3-methyl-3-butenyl)dixoy]-cyclododecyl]dioxy]propyl hydroperoxide (5). An oil; ^{1}H NMR δ 1.1–1.8 (m, 22H), 1.24 (s, 6H), 1.76 (s, 3H), 1.97

(t, J=5.9 Hz, 2H), 2.35 (t, J=6.9 Hz, 2H), 4.17 (t, J=6.9 Hz, 2H), 4.23 (t, J=5.9 Hz, 2H), 4.75 (s, 1H), 4.78 (s, 1H), 8.39 (s, 1H, OOH); ^{13}C NMR δ 19.3 (2C), 21.9 (2C), 22.2 (2C), 22.8, 24.5 (2C), 26.0 (2C), 26.1, 26.9 (2C), 35.5, 35.8, 71.2, 73.3, 81.2, 111.6, 113.4, 142.1. Anal. Calcd for $C_{22}H_{42}O_6$: C, 65.64; H, 10.52. Found: C, 65.42; H, 10.79.

4.5.2. 17-(Iodomethyl)-17,20,20-trimethyl-13,14,18,19,23,-24-hexaoxaspiro[11,12]tetracosane (7). Mp 93–94°C (from ether–hexane); ^{1}H NMR δ 1.0–1.7 (m, 22H), 1.17 (s, 3H), 1.23 (s, 3H), 1.34 (s, 3H), 1.8–2.4 (m, 4H), 3.34 (d, J=10.2 Hz, 1H), 3.56 (d, J=10.2 Hz, 1H), 4.1–4.4 (m, 4H); ^{13}C NMR δ 15.4, 19.2 (2C), 21.9 (2C), 22.2 (2C), 23.0 (CH_3), 25.1 (CH_3), 25.8 (CH_3), 26.0 (2C), 26.1, 27.0, 27.1, 32.9, 35.9, 71.4, 71.5, 78.9 (C), 79.9 (C), 113.3 (C). Anal. Calcd for $C_{22}H_{41}IO_6$: C, 50.00; H, 7.82; I, 24.01. Found: C, 49.99; H, 7.90; I, 23.91.

4.6. Preparation of unsaturated hydroperoxide 12 via iodoalkyl hydroperoxide protected by 2-methoxypropene

Preparation of **12a** via **11a** is representative. To a solution of Ag_2O (1160 mg, 5.0 mmol) in CH_2Cl_2, was added 2-methoxy-2-propyl hydroperoxide[15a] (5.0 mmol) (prepared by the ozonolysis of 420 mg of tetramethylethylene in methanol) in methanol–CH_2Cl_2 (30 mL, 1:5) at −78°C, followed by careful evaporation of the solvent under vacuum and 1,4-diiodobutane (3100 mg, 10 mmol), and the mixture was stirred at room temperature for 17 h. After work-up as described before, the resulting residue subjected to column chromatography on silica gel. Elution with ether–hexane (5:95) gave peroxide **9a** (857 mg, 3.0 mmol, 60%). Subsequently, a mixture of hydroperoxide **10a** (553 mg, 1.8 mmol), the iodide **9a** (720 mg, 2.5 mmol) and Ag_2O (418 mg, 1.8 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature for 17 h. The mixture of products was subjected to column chromatography on silica gel. Elution with ether–hexane (5:95) gave a mixture of cyclododecanone (**35**) (71 mg, 22%) and 1-[[4-[(1-methoxy-1-methylethyl)dioxy]butyl]dioxy]-1-[(3-methyl-3-butenyl)dioxy]cyclododecane (**11a**) (576 mg, 72%). Then the mixture was dissolved into aqueous acetic acid (AcOH–H_2O=9:1, 5 mL) and the reaction was continued with stirring at room temperature for 50 min. The mixture of the products was subjected to column chromatography on silica gel. Elution with ether–hexane (10:90) gave hydroperoxide **12a** (249 mg, 49%).

4.6.1. 4-Iodobutyl 1-methoxy-1-methylethyl peroxide (9a). An oil; ^{1}H NMR δ 1.38 (s, 6H), 1.7–2.0 (m, 4H), 3.22 (t, J=6.9 Hz, 2H), 3.30 (s, 3H), 4.03 (t, J=6.3 Hz, 2H); ^{13}C NMR δ 6.33, 22.7 (2C), 28.9, 30.1, 49.2, 73.7, 104.7.

4.6.2. 1-[[4-[(1-Methoxy-1-methylethyl)dioxy]butyl]-dioxy]-1-[(3-methyl-3-butenyl)dioxy]cyclododecane (11a). An oil; ^{1}H NMR (admixture with 21% of **35**) δ 1.0–1.8 (m, 26H), 1.35 (s, 6H), 1.76 (s, 3H), 2.35 (t, J=7.3 Hz, 2H), 3.31 (s, 3H), 3.9–4.0 (m, 4H), 4.07 (t, J=7.3 Hz, 2H), 4.78 (s, 1H), 4.81 (s, 1H); ^{13}C NMR δ 19.2 (2C), 21.7 (2C), 22.2 (2C), 22.4, 22.6 (2C), 24.4, 24.6, 25.9, 26.0 (2C), 26.3, 26.9, 35.8, 49.0, 73.4, 74.4, 74.5, 104.4, 111.5, 113.1, 142.1.

4.6.3. 4-[[1-[(3-Methyl-3-butenyl)dioxy]cyclododecyl]-dioxy]butyl hydroperoxide (12a). An oil; ^{1}H NMR δ 1.1–1.8 (m, 26H), 1.73 (s, 3H), 2.32 (t, J=6.9 Hz, 2H), 3.9–4.1 (m, 4H), 4.15 (t, J=6.9 Hz, 2H), 4.72 (s, 1H), 4.75 (s, 1H), 8.62 (br s, 1H); ^{13}C NMR δ 19.2 (2C), 21.8 (2C), 22.1, 22.2 (2C), 22.8, 24.1, 24.4, 26.0 (2C), 26.9 (2C), 35.7, 73.4, 74.5, 76.5, 111.6, 113.1, 142.2. Anal. Calcd for $C_{21}H_{40}O_6$: C, 64.92; H, 10.38. Found: C, 64.85; H, 10.50.

4.6.4. 6-[[1-[(3-Methyl-3-butenyl)dioxy]cyclododecyl]-dioxy]hexyl hydroperoxide (12b). An oil; ^{1}H NMR δ 1.1–1.8 (m, 30H), 1.73 (s, 3H), 2.33 (t, J=6.9 Hz, 2H), 3.9–4.1 (m, 4H), 4.17 (t, J=6.9 Hz, 2H), 4.72 (s, 1H), 4.75 (s, 1H), 8.36 (br s, 1H); ^{13}C NMR δ 19.3 (2C), 21.8 (2C), 22.2 (2C), 22.7, 25.6, 25.9, 26.0 (2C), 26.9 (2C), 27.4, 27.6, 35.8, 73.4, 74.8, 76.8, 111.5, 113.2, 142.2. Anal. Calcd for $C_{23}H_{44}O_6$: C, 66.31; H, 10.65. Found: C, 66.18; H, 10.54.

4.6.5. 8-[[1-[(3-Methyl-3-butenyl)dioxy]cyclododecyl]-dioxy]octyl hydroperoxide (12c). An oil; ^{1}H NMR δ 1.2–1.7 (m, 34H), 1.72 (s, 3H), 2.31 (t, J=6.9 Hz, 2H), 3.9–4.1 (m, 4H), 4.14 (t, J=6.9 Hz, 2H), 4.71 (s, 1H), 4.74 (s, 1H), 8.93 (br s, 1H); ^{13}C NMR δ 19.32, 21.8, 22.2, 22.7, 25.7, 25.8, 26.0, 26.9, 27.4, 27.7, 29.2, 29.3, 35.8, 73.4, 74.8, 76.8, 111.5, 113.1, 142.2.

4.6.6. 10-[[1-[(3-Methyl-3-butenyl)dioxy]cyclododecyl]-dioxy]decyl hydroperoxide (12d). ^{1}H NMR δ 1.2–1.7 (m, 38H), 1.74 (s, 3H), 2.34 (t, J=6.9 Hz, 2H), 3.99 (t, J=6.6 Hz, 2H), 4.04 (t, J=6.6 Hz, 2H), 4.17 (t, J=6.9 Hz, 2H), 4.73 (s, 1H), 4.76 (s, 1H), 8.15 (br s, 1H); ^{13}C NMR δ 19.3, 21.9, 22.2, 22.8, 25.8, 26.0, 26.1, 27.0, 27.5, 27.8, 29.4, 29.5, 35.9, 73.5, 74.9, 76.5, 111.5, 113.2, 142.3. Anal. Calcd for $C_{27}H_{52}O_6$: C, 68.60; H, 11.09. Found: C, 68.62; H, 10.64.

4.6.7. 6-[[1-[(2-Methyl-propenyl)dioxy]cyclododecyl]-dioxy]hexyl hydroperoxide (12e). An oil; ^{1}H NMR δ 1.1–2.0 (m, 30H), 1.78 (s, 3H), 3.9–4.1 (m, 4H), 4.46 (s, 2H), 4.91 (s, 1H), 4.97 (s, 1H), 8.62 (br s, 1H); ^{13}C NMR δ 19.3 (2C), 19.9, 21.8 (2C), 22.2 (2C), 25.6, 25.7, 25.9, 26.0 (2C), 26.9 (2C), 27.4, 27.6, 74.7, 76.7, 79.1, 113.2, 114.1, 140.7. Anal. Calcd for $C_{22}H_{42}O_6$: C, 65.64; H, 10.52. Found: C, 65.64; H, 10.49.

4.7. BCIH-promoted cyclization of unsaturated hydroperoxide 12

The synthesis of macrocyclic peroxide **13a** is representative. To a solution of BCIH (391 mg, 0.76 mmol) in CH_2Cl_2 (20 mL) was slowly added the hydroperoxide **12a** (147 mg, 0.38 mmol) in CH_2Cl_2 (20 mL) during 2 h using a syringe and the mixture was stirred at room temperature for additional 0.5 h. After concentration under reduced pressure, the components of the crude product mixture were separated by column chromatography on silica gel. Elution with ether–hexane (2:98) gave the macrocyclic peroxide **13a** (133 mg, 68% yield).

4.7.1. 17-(Iodomethyl)-17-methyl-13,14,18,19,24,25-hexaoxaspiro[11,13]pentacosane (13a). An oil; ^{1}H NMR δ 1.1–2.0 (m, 27H), 1.28 (s, 3H), 2.1–2.2 (m, 1H), 3.36 (d, J=10.6 Hz, 1H), 3.56 (d, J=10.6 Hz, 1H), 3.8–4.2 (m, 5H),

4.3–4.4 (m 1H); ^{13}C NMR δ 15.2, 19.1, 19.2, 21.8 (2C), 22.0 (2C), 22.1 (2C), 25.0, 25.4, 26.0, 26.1, 26.7, 26.9, 32.7, 71.5, 74.0, 76.5, 79.6, 113.0. Anal. Calcd for $C_{21}H_{39}IO_6$: C, 49.03; H, 7.64. Found: C, 49.40; H, 7.54.

4.7.2. 17-(Iodomethyl)-17-methyl-13,14,18,19,26,27-hexaoxaspiro[11,15]heptacosane (13b). Mp 98–99°C (from ether–hexane); ^{1}H NMR δ 1.1–1.8 (m, 30H), 1.28 (s, 3H), 1.9–2.0 (m, 1H), 2.2–2.3 (m, 1H), 3.32 (d, J=10.2 Hz, 1H), 3.58 (d, J=10.2 Hz, 1H), 3.9–4.4 (m, 6H); ^{13}C NMR δ 14.9, 19.2 (2C), 21.8 (2C), 22.1 (2C), 22.8, 25.3, 25.5, 26.0 (2C), 26.1, 26.8 (2C), 27.1, 27.7, 33.2, 71.4, 73.8, 73.9, 79.8, 112.8. Anal. Calcd for $C_{23}H_{43}IO_6$: C, 50.92; H, 7.99. Found: C, 50.95; H, 7.81.

4.7.3. 17-(Iodomethyl)-17-methyl-13,14,18,19,28,29-hexaoxaspiro[11,17]nonacosane (13c). An oil; ^{1}H NMR δ 1.2–1.7 (m, 37H), 1.8–1.9 (m, 1H), 2.1–2.2 (m, 1H), 3.32 (d, J=10.2 Hz, 1H), 3.53 (d, J=10.2 Hz, 1H), 3.9–4.1 (m, 4H), 4.2–4.3 (m, 2H); ^{13}C NMR δ 14.7, 19.3, 21.9, 22.2, 22.6, 24.8, 25.1, 26.0, 26.1, 26.9, 27.0, 27.1, 27.4, 27.6, 31.6, 74.5, 76.5, 80.2, 113.2. Anal. Calcd for $C_{25}H_{47}IO_6$: C, 52.63: H, 8.30; I, 22.24. Found: C, 52.85; H, 8.16; I, 22.31.

4.7.4. 17-(Iodomethyl)-17-methyl-13,14,18,19,30,31-hexaoxaspiro[11,19]hentriacontane (13d). An oil; ^{1}H NMR δ 1.2–1.7 (m, 41H), 1.9–2.3 (m, 2H), 3.34 (d, J=10.2 Hz, 1H), 3.52 (d, J=10.2 Hz, 1H), 4.0–4.2 (m, 6H); ^{13}C NMR δ 14.7, 19.3, 21.8, 22.2, 22.7, 25.3, 25.6, 26.0, 26.1, 26.9, 27.0, 27.3, 27.5, 27.6, 27.8, 27.9, 34.1, 71.0, 74.5, 74.7, 80.3, 113.1. Anal. Calcd for $C_{27}H_{51}IO_6$: C, 54.18; H, 8.59; I, 21.20. Found: C, 54.29; H, 8.31; I, 21.26.

4.7.5. 16-(Iodomethyl)-16-methyl-13,14,17,18,25,26-hexaoxaspiro[11,14]hexacosane (13e). Mp 88–89°C: ^{1}H NMR δ 1.1–1.8 (m, 30H), 1.28 (s, 3H), 3.37 (d, J=10.9 Hz, 1H), 3.61 (d, J=10.9 Hz, 1H), 3.9–4.1 (m, 4H), 4.37 (d, J=9.6 Hz, 1H), 4.61 (d, J=9.6 Hz, 1H); ^{13}C NMR δ 12.2, 19.1 (2C), 21.6, 21.7 (2C), 22.0 (2C), 23.9, 24.4, 25.9 (2C), 26.0, 26.5, 26.6, 26.7, 26.8, 72.5, 73.5, 77.3, 80.3, 113.6. Anal. Calcd for $C_{22}H_{41}IO_6$: C, 50.00; H, 7.82; I, 24.01. Found: C, 49.93; H, 7.76; I, 23.97.

4.7.6. 6-[[1-(2-Methylpropenyl)cyclododecyl]dioxy]hexanal (14e). ^{1}H NMR δ 1.1–1.9 (m, 28H), 1.75 (s, 3H), 2.37 (t, J=5.9 Hz, 2H), 4.03 (t, J=6.6 Hz, 2H), 4.43 (s, 2H), 4.89 (s, 1H), 4.94 (s, 1H), 9.71 (br s, 1H); ^{13}C NMR δ 19.5 (2C), 20.1, 21.9, 22.0 (2C), 22.4 (2C), 25.9, 26.2 (2C), 27.1 (2C), 27.8, 43.9, 74.7, 79.3, 113.4, 114.3, 140.9, 202.5.

4.8. Preparation of unsaturated hydroperoxides 17 and their BCIH-promoted cyclization leading to macrocyclic peroxides 18

The synthesis of **18a** via **17a** is representative. A mixture of hydroperoxide **15a** (163 mg, 1.6 mmol), iodide **9a** (432 mg, 1.5 mmol) and Ag_2O (371 mg, 1.6 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature for 5 h. After conventional work-up as described above, the resulting residue subjected to column chromatography on silica gel. Elution with ether–hexane (7:93) gave 4-[(1-methoxy-1-methylethyl)dioxy]buthyl 3-methyl-3-butenyl peroxide (**16a**) (118 mg, 30%). Then the peroxide **16a** (207 mg, 0.77 mmol) was dissolved into a mixed solvent of acetic acid–THF–H_2O (7.7 mL, 4:2:1.7) and the mixture was stirred at room temperature for 10 h. Column chromatography on silica gel (elution with ether–hexane, 10:90) gave 4-[(3-methyl-3-butenyl)dioxy]butyl hydroperoxide (**17a**) (114 mg, 70%). To a solution of BCIH (447 mg, 0.87 mmol) in CH_2Cl_2 (20 mL) was slowly added the hydroperoxide **17a** (110 mg, 0.58 mmol) in CH_2Cl_2 (20 mL) during 2 h using a syringe and the mixture was stirred at room temperature for additional 0.5 h. After concentration under reduced pressure, the components of the crude product mixture were separated by column chromatography on silica gel. Elution with ether–hexane (2:98) gave the macrocyclic peroxide **18a** (82 mg, 45% yield).

4.8.1. 4-[(1-Methoxy-1-methylethyl)dioxy]butyl 3-methyl-3-butenyl peroxide (16a). An oil; ^{1}H NMR δ 1.35 (s, 6H), 1.6–1.7 (m, 4H), 1.72 (s, 3H), 2.29 (t, J=6.9 Hz, 2H), 3.27 (s, 3H), 3.9–4.1 (m, 4H), 4.04 (t, J=6.9 Hz, 2H), 4.70 (s, 1H), 4.75 (s, 1H); ^{13}C NMR δ 22.6, 22.7, 24.5, 35.9, 49.1, 72.6, 73.7, 104.5, 111.7, 142.0.

4.8.2. 4-[(3-Methyl-3-butenyl)dioxy]butyl hydroperoxide (17a). An oil; ^{1}H NMR δ 1.6–1.7 (m, 4H), 1.72 (s, 3H), 2.31 (t, J=6.9 Hz, 2H), 3.9–4.0 (m, 4H), 4.01 (t, J=6.9 Hz, 2H), 4.71 (s, 1H), 4.72 (s, 1H), 8.60 (br s, 1H); ^{13}C NMR δ 22.5, 24.1, 24.2, 35.8, 72.4, 73.7, 76.5, 11.8, 141.9. Anal. Calcd for $C_9H_{18}O_4$: C, 56.82; H, 9.54. Found: C, 56.95; H, 9.44.

4.8.3. 3-(Iodomethyl)-3-methyl-1,2,6,7-tetraoxacycloundecane (18a). An oil; ^{1}H NMR δ 1.20 (s, 3H), 1.5–2.0 (m, 4H), 2.3–2.5 (m, 2H), 3.28 (d, J=10.2 Hz, 1H), 3.53 (d, J=10.2 Hz, 1H), 3.9–4.1 (m, 6H); ^{13}C NMR δ14.7, 23.1, 25.2, 25.9, 34.3, 70.5, 73.6, 74.0, 80.1. Anal. Calcd for $C_9H_{17}IO_4$: C, 34.19; H, 5.42. Found: C, 34.31; H, 5.13.

4.8.4. 3-(Iodomethyl)-3-methyl-1,2,6,7-tetraoxacyclotridecane (18b). An oil; ^{1}H NMR δ1.18 (s, 3H), 1.1–1.6 (m, 8H), 1.9–2.0 (m, 1H), 2.5–2.6 (m, 1H), 3.27 (d, J=10.2 Hz, 1H), 3.56 (d, J=10.2 Hz, 1H), 3.9–4.2 (m, 6H); ^{13}C NMR δ15.3, 22.6, 24.9, 25.1, 26.5, 26.6, 32.6, 70.4, 73.3, 73.7, 79.8; HRMS (EI) m/z calcd for $C_{11}H_{21}IO_4$ (M^+) 344.0485, found 344.0485. Anal. Calcd for $C_{11}H_{21}IO_4$: C, 38.39; H, 6.15. Found: C, 38.91; H, 5.77.

4.9. Preparation of tetraoxacycloalkane 19 from unsaturated hydroperoxide 10

The preparation of **19c** is representative. A mixture of bishydroperoxide 1 (1044 mg, 4.5 mmol), 9-iodo-2-methyl-1-nonene (798 mg, 3 mmol) and Ag_2O (696 mg, 3 mmol) in CH_2Cl_2 (40 mL) was stirred at room temperature for 17 h. By column chromatography on silica gel (elution with ether–hexane 5:95) was obtained 1-[(8-methyl-8-nonenyl)dioxy]cyclododecyl hydroperoxide (**10c**) (600 mg, 53%). Then, to the solution of BCIH (1645 mg, 2.4 mmol) in CH_2Cl_2 (20 mL) was slowly added the hydroperoxide **10c** (600 mg, 1.6 mmol) in CH_2Cl_2 (20 mL) during 2 h using a syringe. After concentration under reduced pressure, the components of the crude product mixture were separated by column chromatography on silica gel. Elution with ether–hexane (2:98) gave the macrocyclic peroxide **19c** (412 mg, 52% yield).

4.9.1. 1-[(8-Methyl-8-nonenyl)dioxy]cyclododecyl hydroperoxide (10c). An oil; ^{1}H NMR δ1.1–1.8 (m, 32H), 1.68 (s, 3H), 1.94 (t, J=6.9 Hz, 2H), 4.02 (t, J=6.6 Hz, 2H), 4.60 (s, 1H), 4.62 (s, 1H), 8.28 (br s, 1H); ^{13}C NMR δ19.3, 21.9, 22.2, 22.4, 26.0, 26.1, 26.5, 27.5, 27.8, 29.1, 29.3, 37.7, 40.3, 75.2, 109.5, 113.8, 145.8. Anal. Calcd for $C_{22}H_{42}O_4$: C, 71.31; H, 11.42. Found: C, 71.64; H, 11.50.

4.9.2. 15-(Iodomethyl)-15-methyl-13,14,23,24-tetraoxaspiro[11,12]tetracosane (19c). Mp 71–72°C; ^{1}H NMR δ 1.1–1.8 (m, 34H), 1.23 (s, 3H), 3.27 (d, J=10.2 Hz, 1H), 3.39 (d, J=10.2 Hz, 1H), 4.0–4.1 (m, 2H); ^{13}C NMR δ 15.1, 19.5, 20.9, 22.0, 22.4, 23.3, 24.4, 26.1, 26.2, 26.3, 27.2, 27.3, 27.4, 35.1, 74.3, 81.3, 112.1. Anal. Calcd for $C_{22}H_{41}IO_4$: C, 53.22; H, 8.32. Found: C, 53.08; H, 8.00.

4.9.3. 3-(Iodomethyl)-3-methyl-1,2,6,7-tetraoxaspiro-[7.11]nonadecane (19a). A 7:3 mixture of two conformers: mp 61–63°C (from methanol); ^{1}H NMR δ 1.3–1.7 (m, 24.4H), 1.81 (d, J=6.7 Hz, 0.3H), 1.97 (d, J=6.3 Hz, 0.3H), 2.03 (d, J=6.3 Hz, 0.3H), 2.1–2.2 (m, 0.7H), 2.4–2.5 (m, 0.7H), 2.7–2.9 (m, 0.3H), 3.4–3.5 (m, 2H), 4.0–4.2 (m, 1H), 4.3–4.4 (m, 1H); ^{13}C NMR δ 15.56, 15.65, 19.05, 19.12, 19.30, 19.34, 19.45, 20.07, 21.62, 21.80, 21.85, 21.96, 22.09, 22.30, 25.54, 25.81, 25.90, 25.95, 26.00, 26.06, 26.11, 26.18, 28.14, 28.14, 31.23, 38.30, 38.55, 70.49, 71.86, 80.50, 81.44, 111.75, 113.19. Anal. Calcd for $C_{17}H_{31}IO_4$: C, 47.89; H, 7.33; I, 29.77. Found: C, 47.76; H, 7.15; I, 29.52.

4.9.4. 3-(Iodomethyl)-3-methyl-1,2,8,9-tetraoxaspiro-[9.11]henicosane (19b). Mp 95–97°C; ^{1}H NMR δ 1.1–1.6 (m, 26H), 1.15 (s, 3H), 2.32 (br s, 1H), 2.58 (br s, 1H), 3.13 (d, J=10.2 Hz, 1H), 3.54 (d, J=10.2 Hz, 1H), 3.7–3.8 (m, 1H), 4.0–4.1 (m, 1H); ^{13}C NMR δ 19.3, 19.5, 21.9, 22.0, 22.3, 22.4, 26.0, 26.1, 26.2, 26.6, 26.7, 76.6, 81.7, 110.9; HRMS (EI) m/z Calcd for $C_{19}H_{35}IO_4$ (M^+) 454.1581. Found: 454.1581.

4.10. Co(II)-catalyzed peroxidation of unsaturated alcohols 20

In a 50 mL two-necked flask were charged 3-methyl-3-butenol **20a** (430 mg, 5.0 mmol), bis(1-morpholinocarbamoyl-4,4-dimethyl-1,3-pentanedionato)-cobalt(II) (135 mg, 0.25 mmol) and dichloroethane (10 mL), and then triethylsilane (1160 mg, 10 mmol) was added via 1.0 mL gas-tight syringe. The resulting solution was stirred at room temperature for 3 h under slightly positive oxygen atmosphere. After the reaction was complete, the products were separated by column chromatography on silica gel. Elution with ether–hexane (2:98) gave 1,1-dimethyl-3-(triethylsiloxy)propyl triethylsilyl peroxide (452 mg, 26%); an oil; ^{1}H NMR δ 0.5–0.7 (m, 12H), 0.8–1.0 (m, 18H), 1.19 (s, 6H), 1.84 (t, J=7.6 Hz, 2H), 3.72 (t, J=7.6 Hz, 2H); ^{13}C NMR δ3.87 (3C), 4.41 (3C), 6.63 (3C), 6.78 (3C), 24.7 (2C), 41.6, 59.1, 81.3. Anal. Calcd for $C_{17}H_{40}O_3Si_2$: C, 58.56; H, 11.56. Found: C, 58.62; H, 11.63. Subsequent elution with ether–hexane (10:90) gave 3-methyl-3-[(triethylsilyl)dioxy]-butanol (**21a**) (284 mg, 26%). From the final fraction (elution with ether–hexane, 12:88) was obtained 3-methyl-3-(triethylsiloxy)butanol (287 mg, 24%); an oil; ^{1}H NMR δ 0.62 (q, J=7.9 Hz, 6H), 0.95 (t, J=7.9 Hz, 9H), 1.21 (s, 6H), 1.22 (br s, 1H), 1.69 (t, J=5.6 Hz, 2H), 3.89 (t, J=5.6 Hz, 2H); ^{13}C NMR δ 4.09 (3C), 6.65 (3C), 29.12 (2C), 42.8, 60.5, 70.9. Anal. Calcd for $C_{11}H_{26}O_2Si$: C, 60.49; H, 12.00. Found: C, 60.22; H, 11.74.

4.10.1. 3-Methyl-3-[(triethylsilyl)dioxy]butanol (21a). An oil; ^{1}H NMR δ0.69 (q, J=7.9 Hz, 6H), 0.97 (t, J=7.9 Hz, 9H), 1.23 (s, 6H), 1.86 (t, J=5.9 Hz, 2H), 2.91 (br s, 1H, OH), 3.73 (t, J=5.9 Hz, 2H); ^{13}C NMR δ3.74 (3C), 6.65 (3C), 24.7 (2C), 41.1, 58.8, 82.6. Anal. Calcd for $C_{11}H_{26}O_3Si$: C, 56.36; H, 11.18. Found: C, 56.54; H, 10.86.

4.11. Preparation of unsaturated hydroperoxides 25, followed by BCIH-promoted cyclization

The preparation of **25a** and its reaction is representative. To a solution of methoxymethylenecyclohexane (**22**) (245 mg, 1.9 mmol) and an unsaturated alcohol **21a** (1334 mg, 5.7 mmol) in CH_2Cl_2 (25 mL) was passed a slow stream of ozone (1.5 equiv) at −70 °C. After concentration under reduced pressure, the components of the crude mixture were separated by column chromatography on silica gel. Elution with ether–hexane (5:95) gave 1-[[3-methyl-3-(triethylsilyl)dioxy]butoxy]cyclohexyl hydroperoxide (**23a**) (425 mg, 63%). Then, the mixture of **23a** (470 mg, 1.4 mmol), 4-iodo-2-methyl-1-butene (549 mg, 2.8 mmol) and Ag_2O (325 mg, 1.4 mmol) in CH_2Cl_2 (40 mL) was stirred at room temperature for 17 h. Column chromatography on silica gel (elution with ether–hexane, 2:98) gave 1-[[3-methyl-3-(triethylsilyl)dioxy]butoxy]cyclohexyl 3-methyl-3-butenyl peroxide (**24a**) (99 mg, 17%). Subsequently, a mixture of **24a** (120 mg, 0.29 mmol), KF (17 mg, 0.29 mmol) and 18-crown-6 (37 mg, 0.14 mmol) in THF was stirred at room temperature for 17 h. Ether (100 mL) was added and the organic layer was washed with saturated brine. Column chromatography on silica gel (elution with ether–hexane, 7:93) gave 1,1-dimethy1-3-[[1-(2-methyl-1-butenyl)dioxy]cyclohexyloxy]propyl hydroperoxide (**25a**) (56 mg, 66%). Treatment of **25a** (56 mg, 0.19 mmol) with BCIH (129 mg, 0.25 mmol) in CH_2Cl_2 (10 mL) at room temperature for 3 h, followed by column chromatography on silica gel, was obtained **26a** (30 mg, 37%).

4.11.1. 1-[[3-Methyl-3-(triethylsilyl)dioxy]butoxy]cyclohexyl hydroperoxide (23a). An oil; ^{1}H NMR δ0.71 (q, J=7.9 Hz, 6H), 0.99 (t, J=7.9 Hz, 9H), 1.27 (s, 6H), 1.2–1.8 (m, 10H), 1.91 (t, J=6.6 Hz, 2H), 3.66 (t, J=6.6 Hz, 2H), 8.62 (s, 1H); ^{13}C NMR δ 3.69 (3C), 6.65 (3C), 22.6 (2C), 25.2 (2C), 25.5, 31.5 (2C), 38.1, 56.0, 82.1 105.1. Anal. Calcd for $C_{17}H_{36}O_5Si$: C, 58.58; H, 10.41. Found: C, 58.43; H, 10.16.

4.11.2. 1-[[3-Methyl-3-(triethylsilyl)dioxy]butoxy]cyclohexyl 3-methyl-3-butenyl peroxide (24a). An oil; ^{1}H NMR δ0.66 (q, J=7.9 Hz, 6H), 0.98 (t, J=7.9 Hz, 9H), 1.22 (s, 6H), 1.1–1.8 (m, 10H), 1.76 (s, 3H), 1.91 (t, J=7.9 Hz, 2H), 2.34 (t, J=6.9 Hz, 2H), 3.62 (t, J=7.9 Hz, 2H), 4.12 (t, J=6.9 Hz, 2H), 4.74 (s, 1H), 4.78 (s, 1H); ^{13}C NMR δ 3.88 (3C), 6.81 (3C), 22.8 (2C), 24.6, 24.7 (2C), 25.6, 32.1 (2C), 36.0, 38.8, 56.7, 73.5, 81.5, 104.9, 111.7, 142.3.

4.11.3. 1,1-Dimethy1-3-[[1-(2-methyl-1-butenyl)dioxy]-cyclohexyloxy]propyl hydroperoxide (25a). An oil; ^{1}H

NMR δ 1.1–1.8 (m, 10H), 1.21 (s, 6H), 1.73 (s, 3H), 1.88 (t, *J*=5.3 Hz, 2H), 2.33 (t, *J*=6.9 Hz, 2H), 3.67 (t, *J*=5.3 Hz, 2 Hz), 4.11 (t, *J*=6.9 Hz, 2H), 4.72 (s, 1H), 4.76 (s, 1H), 9.44 (br s, 1H); ^{13}C NMR δ22.6 (2C), 22.8, 24.7 (2C), 25.3, 31.9 (2C), 35.8, 37.8, 56.3, 73.4, 81.1, 105.1, 111.7, 142.1.

4.11.4. 11-(Iodomethyl)-11,14,14-trimethyl-7,8,12,13,17-pentaoxaspiro[5,11]heptadecane (26a). An oil; ^{1}H NMR δ 0.9–2.1 (m, 13H), 0.96 (s, 3H), 1.07 (s, 3H), 1.26 (s, 3H), 2.5–2.7 (m, 1H), 3.21 (d, *J*=10.6 Hz, 1H), 3.4–3.6 (m, 1H), 3.54 (d, *J*=10.4 Hz, 1H), 3.7–4.1 (m, 2H), 4.4–4.6 (m, 1H); ^{13}C NMR δ15.7, 22.7, 22.8, 23.8, 25.4, 26.1, 29.7, 31.3, 31.6, 33.3, 36.6, 56.3, 72.7, 78.7, 80.0, 106.6; MS (EI) *m/z* 428 (M^+); HRMS (EI) *m/z* calcd for $C_{16}H_{29}IO_5$ 428.1060, found 428.1061.

4.12. Reaction of unsaturated alcohol 20e with BCIH

Treatment of 8-methyl-8-nonean-1-ol (**20e**) (312 mg, 2.0 mmol) with BCIH (1542 mg, 3.0 mmol) in CH_2Cl_2 (40 mL) at room temperature for 4 h, followed by column chromatography on silica gel (elution with ether–hexane 5:95) was obtained **30e** (91 mg, 16%). Further elution with ether–hexane (30:70) gave the unreacted alcohol **20e** (142 mg, 46%).

4.12.1. 2,11-Di(iodomethyl)-2,11-dimethyl-1,10-dioxacyclooctadecane (30e). An oil; ^{1}H NMR δ 1.1–1.7 (m, 24H), 1.22 (s, 6H), 3.1–3.3 (m, 8H); ^{13}C NMR δ 17.2, 17.5, 22.6, 22.9, 24.3, 24.5, 25.9, 26.0, 29.1, 29.2, 29.7, 29.8, 30.0, 35.4, 35.8, 60.7, 60.8, 73.8, 73.9; HRMS (EI) *m/z* calcd for $C_{20}H_{38}I_2O_2$ (M^+) 564.0962, found 564.0973.

4.13. Reaction of unsaturated hydroperoxide 15 with BCIH

Reaction of **15c** is representative. To the solution of BCIH (925 mg, 1.8 mmol) in CH_2Cl_2 (20 mL) was slowly added 8-methyl-8-nonenyl hydroperoxide (**15c**) (200 mg, 1.2 mmol) in CH_2Cl_2 (20 mL) during 3 h using a syringe and the mixture was stirred at room temperature for additional 1 h. The monitoring by TLC suggested that the hydroperoxide **15c** reacted completely. After concentration under reduced pressure, the components of the crude product mixture were separated by column chromatography on silica gel. First fraction (elution with benzene–hexane, 30:70) gave the monomeric peroxide **27c** (98 mg, 28%). From the second fraction (elution with benzene–hexane, 40:60) was obtained the dimeric peroxide **31c** (83 mg, 12%).

4.13.1. 3-(Iodomethyl)-3-methyl-1,2-dioxecane (27c). An oil; ^{1}H NMR δ1.18 (s, 3H), 1.4–2.2 (m, 12H), 3.24 (d, *J*=10.2 Hz, 1H), 3.52 (d, *J*=10.2 Hz, 1H), 3.9–4.0 (m, 1H), 4.1–4.2 (m, 1H); ^{13}C NMR δ 16.6, 22.0, 22.4, 22.5, 25.1, 25.6, 27.8, 29.5, 75.5, 81.1; HRMS (EI) *m/z* calcd for $C_{10}H_{19}IO_2$ 298.0430, found 298.0437. Anal. Calcd for $C_{10}H_{19}IO_2$: C, 40.28; H, 6.42; I, 42.56. Found: C, 40.03; H, 6.19; I, 42.56.

4.13.2. 3,13-Di(iodomethyl)-3,13-dimethyl-1,2,11,12-tetraoxacycloicosane (31c). An oil; ^{1}H NMR δ 1.12 (s, 3H), 1.21 (s, 3H), 0.9–1.8 (m, 24H), 3.2–3.2 (m, 2H), 3.4–3.5 (m, 2H), 3.8 (m, 4H); ^{13}C NMR δ 15.4, 16.2, 22.4, 22.6, 23.7, 24.1, 26.1, 26.2, 27.9, 29.2, 29.5, 29.9, 30.2, 35.2, 35.4, 73.9, 74.3, 80.9, 81.1; HRMS (EI) *m/z* calcd for $C_{20}H_{38}I_2O_4$ (M^+) 596.0860, found 596.0873. Anal. Calcd for $C_{20}H_{38}I_2O_4$: C, 40.28; H, 6.42; I, 42.56. Found: C, 40.35; H, 6.30; I, 42.62.

4.13.3. 3-(Iodomethyl)-3-methyl-1,2-dioxocane (27b). An oil; ^{1}H NMR δ 1.13 (s, 3H), 1.1–2.0 (m, 8H), 3.20 (d, *J*=10.4 Hz, 1H), 3.51 (d, *J*=10.4 Hz, 1H), 3.6–3.7 (m, 1H), 4.0–4.2 (m, 1H); ^{13}C NMR δ16.7, 21.6, 24.6, 25.7, 28.2, 32.2, 74.7, 81.1; HRMS (EI) *m/z* calcd for $C_8H_{15}IO_2$: 270.0117, found 270.0122.

4.14. Preparation of unsaturated alcohols 32 and their cyclization

The preparation and cyclization of **32b** is representative. To a solution of hydroperoxide **12b** (430 mg, 1.0 mmol) in CH_2Cl_2 (25 mL) was added PPh_3 (262 mg, 1.0 mmol) at 0°C during 30 min. After evaporation of the solvent under reduced pressure, the crude products were separated by column chromatography on silica gel. Elution with ether–hexane (30:70) gave 6-[[1-[(3-methyl-3-butenyl)dioxy]-cyclododecyl]dioxy]hexanol (**32b**) (330 mg, 80%). To the solution of BCIH (216 mg, 0.42 mmol) in CH_2Cl_2 (20 mL) was slowly added unsaturated hydroperoxide **32b** (85 mg, 0.21 mmol) in CH_2Cl_2 (20 mL) during 3 h using a syringe and the mixture was stirred at room temperature for 17 h. After concentration under reduced pressure, the components of the crude product mixture were separated by column chromatography on silica gel. First fraction (elution with ether–hexane, 1:99) contained the cyclic peroxide **34b** (33 mg, 29%). From the second fraction (elution with ether–hexane, 3:97) was obtained the dioxolane **27a** (7 mg, 14%). The final fraction (elution with ether–hexane, 5:95) contained cyclododecanone (**35**) (11 mg, 29%).

4.14.1. 6-[[1-[(3-Methyl-3-butenyl)dioxy]cyclododecyl]-dioxy]hexanol (32b). An oil; ^{1}H NMR δ1.3–1.7 (m, 31H), 1.74 (s, 3H), 2.33 (t, *J*=6.9 Hz, 2H), 3.62 (t, *J*=6.3 Hz, 2H), 4.05 (t, *J*=6.6 Hz, 2H), 4.17 (t, *J*=6.9 Hz, 2H), 4.72 (s, 1H), 4.76 (s, 1H); ^{13}C NMR δ19.3, 21.9, 22.2, 22.8, 25.5, 25.9, 26.0, 27.0, 27.8, 32.6, 35.8, 62.8, 73.5, 74.8, 111.5, 113.2, 142.3. Anal. Calcd for $C_{23}H_{44}O_5$: C, 68.96; H, 11.07. Found: C, 68.67; H, 10.92.

4.14.2. 17-(Iodomethyl)-17-methyl-13,14,18,25,26-pentaoxaspiro[11,14]hexacosane (34b). An oil; ^{1}H NMR δ 1.2–1.7 (m, 30H), 1.33 (s, 3H), 1.7–1.8 (m, 1H), 2.0–2.1 (m, 1H), 3.26 (d, *J*=10.6 Hz, 1H), 3.24 (d, *J*=10.6 Hz, 1H), 3.39 (t, *J*=6.6 Hz, 2H), 4.09 (t, *J*=5.6 Hz, 2H), 4.2–4.3 (m, 2H); ^{13}C NMR δ16.3, 19.3, 21.8, 22.2, 23.9, 24.5, 25.0, 26.0, 26.1, 26.9, 27.0, 27.4, 28.4, 34.7, 60.5, 71.5, 73.4, 113.0. Anal. Calcd for $C_{23}H_{43}IO_5$: C, 52.47; H, 8.23. Found: C, 52.76; H, 7.81.

4.14.3. 3-(Iodomethyl)-3-methyl-1,2-dioxolane (27a). An oil; ^{1}H NMR δ1.55 (s, 3H), 2.3–2.4 (m, 1H), 2.7–2.8 (m, 1H), 3.36 (s, 2H), 4.1–4.2 (m, 2H); ^{13}C NMR δ13.8, 23.4, 45.0, 70.9, 83.4; HRMS (EI) *m/z* calcd for $C_5H_9IO_2$ (M^+) 227.9648, found 227.9649.

4.14.4. 17-(Iodomethyl)-17-methyl-13,14,18,29,30-pentaoxaspiro[11,18]triacontane (34d). An oil; ^{1}H NMR δ1.2–1.7 (m, 38H), 1.33 (s, 3H), 2.0–2.1 (m, 1H), 2.2–2.3 (m, 1H), 3.26 (d, *J*10.6 Hz, 1H), 3.33 (d, *J*=10.6 Hz, 1H), 3.34 (t, *J*=7.3 Hz, 2H), 4.09 (t, *J*=6.6 Hz, 2H), 4.1–4.2 (m, 2H); ^{13}C NMR δ16.5, 19.3, 21.9, 22.2, 23.4, 25.0, 25.3, 26.0, 26.1, 26.9, 27.0, 27.1, 27.4, 27.5, 27.6, 29.0, 35.3, 60.8, 70.9, 73.3, 74.7, 113.3. Anal. Calcd for $C_{27}H_{51}IO_5$: C, 55.66; H, 8.82. Found: C, 55.80; H, 8.53.

4.15. Synthesis of macrocyclic peroxides 39 from unsaturated alcohol 38

The synthesis of **39b** is representative. A mixture of hydroperoxide **15a** (612 mg, 6.0 mmol), 2-(6-iodohexyloxy)tetrahydropyran (**36b**) (2808 mg, 19.0 mmol) and Ag_2O (1392 mg, 6.0 mmol) in CH_2Cl_2 (40 mL) was stirred at room temperature for 17 h. By column chromatography on silica gel (elution with ether-hexane, 8:92) was obtained 2-[6-[(3-methyl-3-butenyl)dioxy]hexyloxy]tetrahydropyran (**37b**) (1230 mg, 72%). The peroxide **37b** (1230 mg, 4.3 mmol) was dissolved in AcOH (4 mL)–THF (2 mL)–H_2O (1 mL) and the mixture was stirred at room temperature for 2 days to give 6-[(3-methyl-3-butenyl)-dioxy]hexanol (**38b**) (626 mg, 72%) the solution of BCIH (1542 mg, 3.0 mmol) in CH_2Cl_2 (20 mL) was slowly added unsaturated hydroperoxide (**38b**) (400 mg, 2.0 mmol) in CH_2Cl_2 (20 mL) during 3 h using a syringe and the mixture was stirred at room temperature for 17 h. After concentration under reduced pressure, the components of the crude product mixture were separated by column chromatography on silica gel. First fraction (elution with ether–hexane, 1:99) contained the cyclic peroxide **39b** (87 mg, 14%). From the second fraction (elution with ether–hexane, 30:70) was obtained unreacted alcohol **38b** (220 mg, 55%).

4.15.1. 2-[6-[(3-Methyl-3-butenyl)dioxy]hexyloxy]tetrahydropyran (37b). An oil; ^{1}H NMR δ 1.3–1.9 (m, 14H), 1.79 (s, 3H), 2.33 (t, *J*=6.8 Hz, 2H), 3.3–3.5 (m, 2H), 3.6–3.9 (m, 2H), 3.98 (t, *J*=6.6 Hz, 2H), 4.08 (t, *J*=6.9 Hz, 2H), 4.57 (t, *J*=3.9 Hz, 1H), 4.74 (s, 1H), 4.79 (s, 1H); ^{13}C NMR δ 19.7, 22.6, 25.5, 25.9, 26.1, 27.8, 29.6, 30.7, 35.9, 62.2, 67.3, 72.4, 74.0, 98.7, 111.6, 141.9.

4.15.2. 6-[(3-Methyl-3-butenyl)dioxy]hexanol (38b). An oil; ^{1}H NMR δ1.1–1.6 (m, 9H), 1.78 (s, 3H), 2.26 (t, *J*=6.9 Hz, 2H), 3.54 (t, *J*=6.6 Hz, 2H), 3.93 (t, *J*=6.4 Hz, 2H), 4.01 (t, *J*=6.8 Hz, 2H), 4.67 (s, 1H), 4.72 (s, 1H); ^{13}C NMR δ22.6, 25.5, 25.8, 27.8, 32.5, 35.9, 62.5, 72.4, 73.9, 111.6, 141.9. Anal. Calcd for $C_{11}H_{22}O_3$; C, 65.31; H, 10.96. Found: C, 65.01; H, 11.10.

4.15.3. 5-(Iodomethyl)-5-methyl-1,2,6-trioxacyclododecane (39b). An oil; ^{1}H NMR δ1.31 (s, 3H), 1.4–2.2 (m, 10H), 3.16 (d, *J*=10.6 Hz, 1H), 3.28 (d, *J*=10.6 Hz, 1H), 3.4–3.5 (m, 2H), 4.0–4.1 (m, 4H); ^{13}C NMR δ16.2, 20.2, 21.6, 25.3, 26.3, 28.3, 31.2, 58.9, 68.4, 68.8, 73.6; HRMS calcd for $C_{11}H_{21}IO_3$ (M^+) 328.0536, found 328.0534. Anal. Calcd for $C_{11}H_{21}IO_3$: C, 40.26; H, 6.45; I, 38.67. Found: C, 40.54; H, 6.29; I, 38.53.

4.15.4. 5-(Iodomethyl)-5-methyl-1,2,6-trioxacyclodecane (39a). An oil; ^{1}H NMR δ 1.36 (s, 3H), 1.4–1.8 (m, 6H), 3.16 (d, *J*=10.6 Hz, 1H), 3.27 (d, *J*10.6 Hz, 1H), 3.5–3.7 (m, 2H), 3.9–4.1 (m, 4H); ^{13}C NMR δ 16.7, 22.6, 25.4, 28.3, 29.7, 59.9, 69.9, 74.0, 75.3; HRMS (EI) *m/z* calcd for $C_9H_{17}IO_3$ 300.0223, found 300.0221.

4.15.5. 8-(Iodomethyl)-8-methyl-1,2,7-trioxacyclododecane (39c). An oil; ^{1}H NMR δ 1.23 (s, 3H), 1.2–1.9 (m, 10H), 3.24 (d, *J*=10.6 Hz, 1H), 3.37 (d, *J*=10.6 Hz, 1H), 3.4–3.5 (m, 2H), 3.8–4.0 (m, 4H); ^{13}C NMR δ 17.7, 19.7, 23.4, 24.6, 25.3, 27.5, 33.3, 62.1, 70.7, 74.0, 74.7; HRMS (CI) *m/z* calcd for $C_{11}H_{21}IO_3$: 329.0614, found 329.0613.

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