JOC Article

New Preparation of 1,2,4,5,7,8-Hexaoxonanes

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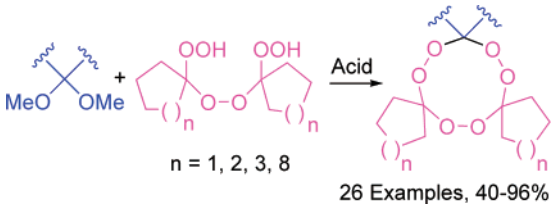

A new versatile procedure was developed for the synthesis of 1,2,4,5,7,8-hexaoxonanes based on the Lewis acid catalyzed reaction of acetals with 1,1′-dihydroperoxydicycloalkyl peroxides. The procedure substantially extends the structural diversity of these compounds and, in most cases, allows the synthesis of these compounds in higher yields (to 96%) and with higher selectivity. Complexation of hexaoxonane with chloroform was documented for the first time. The structures of several triperoxides were established by X-ray diffraction.

Introduction

Triperoxides, 1,2,4,5,7,8-hexaoxonanes, have found application in the synthesis of macrocyclic ketones and lactones produced by thermolysis (Story reaction).[1] Hexaoxonanes were used in the synthesis of unsymmetrical tetraoxanes[2] and as polymerization initiators.[3] Data on high antimalarial activity of related peroxide compounds[4] suggest that hexaoxonanes can be of interest to design antimalarial drugs. A number of studies[5] were concerned with the properties of these cyclic peroxides and methods of their analysis. Of particular interest is triperoxide-based explosives. For example, triacetone triperoxide is one of the most sensitive explosives known, with power close to trinitrotoluene.[5a,b]

Hexaoxonanes can be synthesized according to the following three main methods: acid-catalyzed reactions of ketones with hydrogen peroxide,[6] ozonolysis of unsaturated compounds,[7] and condensation of 1,1′-dihydroperoxydicycloalkyl peroxides with ketones.[1e,8] The drawbacks of the first two methods are low selectivity and difficulties in preparing hexaoxonanes containing bulky substituents. The drawbacks of the third method are moderate yields of the reaction products and a narrow range of ketones suitable for condensation with 1,1′-dihydroperoxydicycloalkyl peroxides. These compounds are limited to reactive ketones, to which hydroperoxide groups are readily added. The

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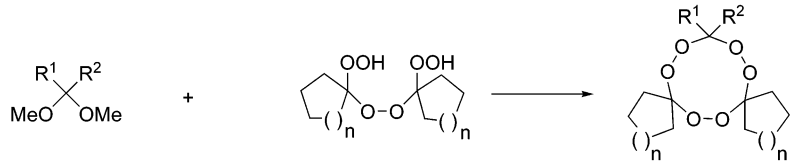
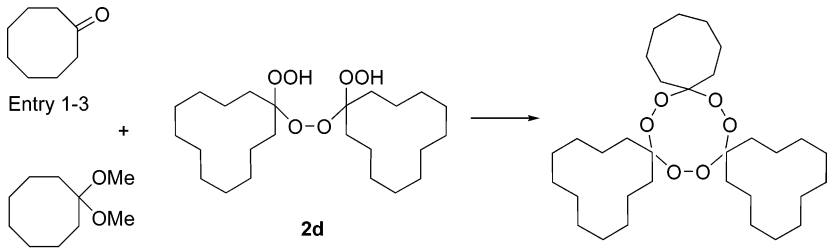
SCHEME 1. General Scheme of the Synthesis of Hexaoxonanes 3−6



1a, **3a - 6a**, $R^1 = R^2 = Me$ — **2a**, n = 1 — **3a-e, g**; n = 1
1b, **3b - 6b**, $R^1 = Me$, $R^2 = {}^iPr$ — **2b**, n = 2 — **4a-h;** n = 2
1c, **3c**, **4c**, **6c**, $R^1 = R^2 = -(CH_2)_4-$ — **2c**, n = 3 — **5a, b, e-g**; n = 3
1d, **3d**, **4d**, **6d**, $R^1 = R^2 = -(CH_2)_5-$ — **2d**, n = 8 — **6a-g**; n = 8
1e, **3e - 6e**, $R^1 = R^2 = -(CH_2)_6-$
1f, **4f - 6f**, $R^1 = R^2 = -(CH_2)_7-$
1g, **3g - 6g**, $R^1 = R^2 = -(CH_2)_{11}-$
1h, **4h**, $R^1 = R^2$ = 2,2 - Adamantyl

SCHEME 2. Synthesis of Peroxide 6f



syntheses of hexaoxonanes from less reactive ketones, which are generally solids with high molecular weight, were documented,[8c,d] but these syntheses produced hexaoxonanes in lower yields (10−42%).[8d]

Results and Discussion

Synthesis of Hexaoxonanes by Reaction of Acetals with 1,1′-Dihydroperoxydicycloalkyl Peroxides. In the present study, which is a continuation of our ongoing research into chemistry of geminal peroxide compounds,[9] we developed a new method for the synthesis of 1,2,4,5,7,8-hexaoxonanes (**3**−**6**) based on the acid-catalyzed reaction of acetals (**1**) with 1,1′-dihydroperoxydicycloalkyl peroxides (**2**) in diethyl ether or tetrahydrofuran (Scheme 1).

The advantage of the method is that it is not limited by the reactivity of ketones, allows the use of nearly equimolar amounts of reagents (acetals and peroxides), and, in most cases, gives 1,2,4,5,7,8-hexaoxonanes in high yield (80−96%).

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TABLE 1. Optimization of the Conditions of the Synthesis of Hexaoxonane 6f[a]

entry	catalyst	mole of catalyst per mole of **2d**	reaction time, h	conversion of **2d**, %	yield of **6f**, %
1[b]	BF_3·Et_2O	0.5	15	10	6
2[b]	$SnCl_4$	0.5	15	15	9
3[b]	H_2SO_4	0.5	16	5	1−2
4	BF_3·Et_2O	0.05	38	60	44
5	BF_3·Et_2O	0.05	15	100	37[c]
6	BF_3·Et_2O	0.2	18	90	72
7	BF_3·Et_2O	0.2	6	100	60[c]
8	BF_3·Et_2O	0.5	6	100	84[d]
9	BF_3·Et_2O	0.6	5	100	94
10	BF_3·Et_2O	0.6	2	100	88[c]
11	BF_3·Et_2O	0.6	20	100	88[e]
12	$SnCl_4$	0.2	1.5	100	86
13	$SnCl_4$	0.5	1	100	96
14	$TiCl_4$	0.5	9	90	29
15	$AlCl_3$	0.5	3	100	64
16	$AlBr_3$	0.5	10	100	20
17	H_2SO_4	0.5	7	95	27
18	$TsOH·H_2O$	0.5	23	50	14

[a] Reaction conditions: a catalyst (0.05−0.6 mol of catalyst per mole of **2d**) in THF or Et_2O (0.5 mL) was added to a mixture of dihydroperoxide **2d** (0.465 mmol, 0.2 g) and acetal **1f** (0.604 mmol, 0.104 g) in THF or Et_2O (2 mL), and the reaction mixture was stirred at 20−25 °C; in entries 5, 7, and 10, at 55−60 °C. [b] The reaction with cyclooctanone. [c] The reaction temperature was 55−60 °C. [d] The synthesis was scaled with increasing amounts of the reagents by a factor of 10. [e] Et_2O was used as the solvent.

We performed condensation of 1,1′-dihydroperoxydicyclododecyl peroxide (**2d**) with 1,1-dimethoxycyclooctane (**1f**) and studied the influence of the nature and the amount of the catalyst, the nature of the solvent, and the reaction time on the conversion of **2d** and the yield of hexaoxonane **6f** (Scheme 2, Table 1). For comparison, Table 1 includes the results of the reaction of cyclooctanone with peroxide **2d** (entries 1−3).

The reactions were performed in two temperature modes, at 20−25 and 55−60 °C, by mixing reagents **1f** and **2d** in tetrahydrofuran or diethyl ether in the presence of 0.05−0.6 mol of a catalyst per mole of **2d**.

We chose peroxide **6f** for optimization, taking into account that the synthesis of analogous peroxides from poorly active cycloalkanones with a ring size >6 presents difficulties (earlier, **6f** had been synthesized in 42% yield[8d]).

As can be seen from Table 1, peroxide **6f** was generated from dihydroperoxide **2d** and cyclooctanone in THF in very low yield (1−9%), which confirms that this reaction with ketones is inefficient. The use of acetal instead of ketone in the acid-catalyzed reaction enables the formation of an electrophilic center that is more reactive with respect to the addition of the hydroperoxide group. Subsequent syntheses of **6f** were performed with the use of acetal **1f** in the presence of Lewis acids BF_3·Et_2O, $SnCl_4$, $TiCl_4$, $AlCl_3$, or $AlBr_3$ (entries 4−16), or protic acids H_2SO_4 or $TsOH·H_2O$ (entries 17 and 18) as the catalysts. The best yield of peroxide **6f** was obtained with BF_3·Et_2O and $SnCl_4$ (entries 8−13) in an amount of 0.2−0.6 mol per mole of dihydroperoxide **2d**. However, it should be noted that, in the case of $SnCl_4$, the preparative isolation of the reaction product in pure form presents difficulties because of complications associated with removal of the catalyst residues. Because of low solubility of peroxide **6f** in organic solvents, it is impossible to use a convenient method of its purification from inorganic impurities by filtration through SiO_2; upon recrystallization, $SnCl_4$ residues are poorly removed. The rise of the temperature from 20−25 °C (entries 4, 6, and 9) to 55−60 °C (entries 5, 7, and 10) leads to a decrease in the yield of the target peroxide by 7−12%, but the reaction time is shortened. The reactions with the use of Lewis acids $TiCl_4$, $AlCl_3$, or $AlBr_3$ (entries 14−16) or protic acids H_2SO_4 or $TsOH·H_2O$ (entries 17−18) as the catalyst produce peroxide **6f** in lower yield.

For the purpose of examining the scope of the procedure for the synthesis of hexaoxonanes according to Scheme 1, we tested a broad range of acetals containing a linear fragment, **1a** and **1b**, or a cyclic fragment, **1c**−**h**, in condensation with 1,1′-dihydroperoxydicycloalkyl peroxides **2a**−**d**, which differ in the ring size (C_5, C_6, C_7, and C_{12}; Table 2).

We used diethyl ether as the solvent for peroxides **2a**−**c** with a ring size C_5−C_7, because these compounds are readily soluble in this solvent; for dicyclododecyl peroxide **2d**, we used THF. The amount of the BF_3·Et_2O catalyst was 0.2−0.5 mol per mole of peroxide **2**. The complete conversion of peroxides **2** was achieved in a period of time from 3 to 8 h.

The best yields of hexaoxonanes were achieved in the reactions of dihydroperoxides **2** with acetals **1a**,**b** containing the sterically unhindered reaction center; lower yields were obtained for the reactions with acetals **1f** and **1g**, which were prepared from cyclooctanone and cyclododecanone, respectively. In the reactions of dihydroperoxides **2a** and **2c** with the same acetals, the yields of hexaoxonanes were lower than those in the reactions with dihydroperoxides **2b** and **2d**.

The longest time (6−8 h) for the complete conversion of dihydroperoxides **2** was observed in the synthesis of hexaoxonanes **6** from 1,1′-dihydroperoxydicyclododecyl peroxide **2d**; the reactions with dihydroperoxides **2a** were completed in shorter time (within 3−4 h).

Intermediate Formation in the Reaction of Acetal 1g with Peroxide 2b. When performing the reaction of **1g** and **2b** for a period of time insufficient for the complete conversion of dihydroperoxide **2b**, we succeeded in isolating the intermediate, methoxyhydroperoxyperoxide **7**, in 14% yield (Scheme 3).

This scheme illustrates a two-step formation of 1,2,4,5,7,8-hexaoxonanes. At first, peroxide **7** is produced, which subsequently cyclizes intramolecularly into the nine-membered cycle **4g**. It is likely that peroxides **7** and **4g** are being formed with similar rates. Products of the bimolecular reaction of peroxide **7** with the starting reagents **1g** and **2b** were not obtained.

Synthesis of Hexaoxonanes by Reaction of Enol Ethers with 1,1′-Dihydroperoxydicycloalkyl Peroxides. The reactions of enol ethers **8d** and **8g** with dihydroperoxides **2b** and **2d** showed that the corresponding hexaoxonanes **4d**, **4g** and **6d, 6g** are produced in yields comparable with their yields from acetals (Scheme 4). This approach extends the scope of the synthesis of hexaoxonanes, because enol ethers derived, for example, from vinyl halides or acetylenes can be used as the starting reagents instead of acetals derived from ketones. An attempt to synthesize hexaoxonanes from 1-trimethylsilyloxo-

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TABLE 2. Synthesis of Hexaoxonanes 3−6

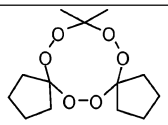
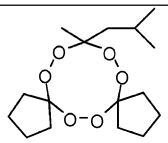
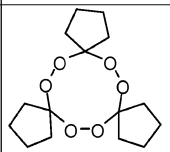
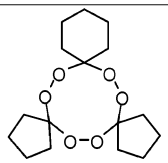
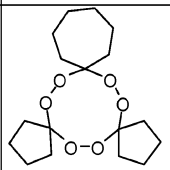
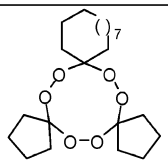
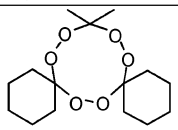
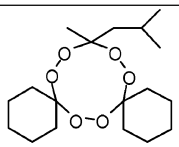
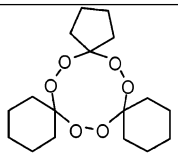
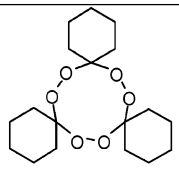
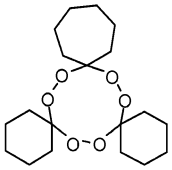
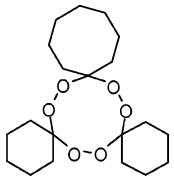
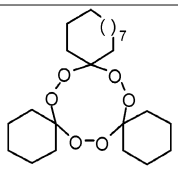
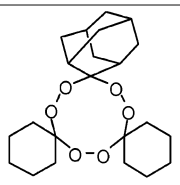
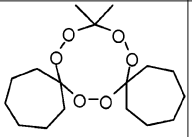
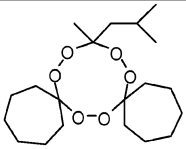
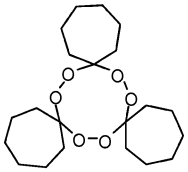
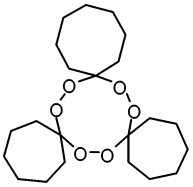
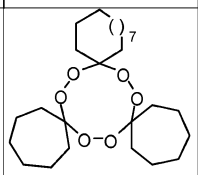
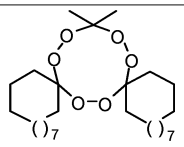
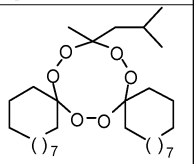
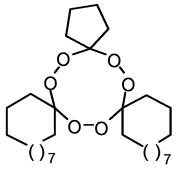
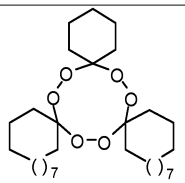
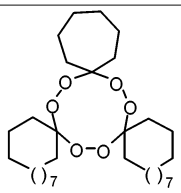
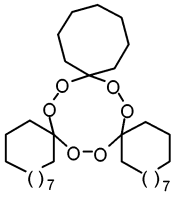
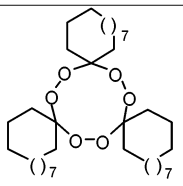
Peroxide, **2** Acetal, **1**	Hexaoxonane **3-6**, yield (%)	Mol BF_3•Et_2O /mol **2;** (reaction time, h)	Peroxide, **2** Acetal, **1**	Hexaoxonane **3-6**, yield (%)	Mol BF_3•Et_2O /mol **2;** (reaction time, h)
2a, 1a	 **3a,** 82	0.2; (3)	**2a, 1b**	 **3b,** 67	0.2; (3)
2a, 1c	 **3c,** 85	0.2; (4)	**2a, 1d**	 **3d,** 65	0.2; (4)
2a, 1e	 **3e,** 77	0.2; (4)	**2a, 1g**	 **3g,** 47	0.2; (4)
2b, 1a	 **4a**, 94	0.2; (3)	**2b, 1b**	 **4b**, 85	0.2; (3)
2b, 1c	 **4c,** 82	0.3; (4)	**2b, 1d**	 **4d,** 74	0.3; (4)
2b, 1e	 **4e**, 81	0.3; (4)	**2b, 1f**	 **4f**, 69	0.3; (5)
2b, 1g	 **4g**, 65	0.3; (4)	**2b, 1h**	 **4h**, 78	0.3; (4)
2c, 1a	 **5a,** 90	0.3; (3)	**2c, 1b**	 **5b,** 84	0.3; (3)

Table 2 (Continued)

Peroxide, **2** Acetal, **1**	Hexaoxonane **3-6**, yield (%)	Mol BF_3•Et_2O /mol **2;** (reaction time, h)	Peroxide, **2** Acetal, **1**	Hexaoxonane **3-6**, yield (%)	Mol BF_3•Et_2O /mol **2;** (reaction time, h)
2c, 1e	 **5e,** 91	0.3; (1.5)	**2c, 1f**	 **5f,** 60	0.3; (5)
2c, 1g	 **5g**, 41	0.3; (6)	**2d, 1a**	 **6a** , 94	0.3; (5)
2d, 1b	 **6b**, 84	0.3; (5)	**2d, 1c**	 **6c**, 80	0.3; (6)
2d, 1d	 **6d**, 78	0.3; (6)	**2d, 1e**	 **6e**, 84	0.4; (7)
2d, 1f	 **6f,** 94	0.6; (5)	**2d, 1g**	 **6g,** 40	0.5; (8)

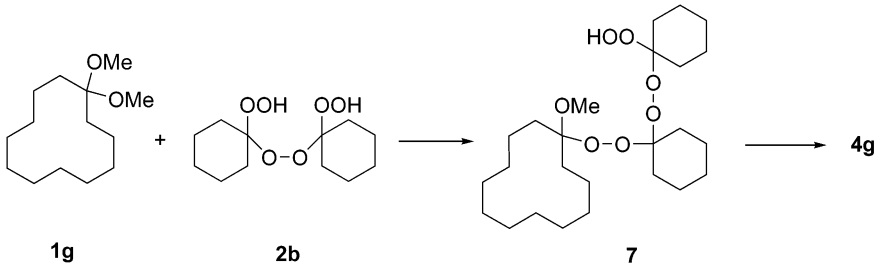
cyclopentene (silyl enol ether) and dihydroperoxide **2b** or **2d** failed, and the target triperoxides were obtained only in trace amounts.

Isolation of Hexaoxonanes. To isolate hexaoxonanes, we used three procedures for the workup of the reaction mixture depending on the structures of the starting dihydroperoxides and acetals (see the Experimental Section). Method A was used for isolation of hexaoxonanes **3a**−**e**, **4a**−**e**, and **5a**,**b**,**e**, which were prepared from dihydroperoxides having a medium-sized ring and water-soluble ketone acetals. In the course of isolation, byproducts, unconsumed acetal, and the hydrolysis product of the latter (ketone) were washed out by water and aqueous methanol. Method B was applied to hexaoxonanes **3g**, **4f**−**h**, and **5f**,**g** derived from water-insoluble ketone acetals. In essence, method B is based on recrystallization of hexaoxonanes from an Et_2O−MeOH mixture with gradual removal of Et_2O, after which the target peroxide precipitates from methanol. Method C was used for isolation of MeOH-insoluble hexaoxonanes **6a**−**g** (contain two C_{12} rings). It should be noted that hexaoxonanes **6a**−**g** are poorly soluble in THF, and major portions precipitate during the synthesis.

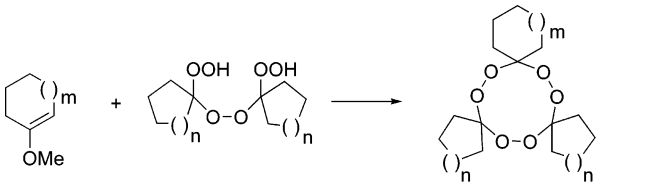
Determination of 1,2,4,5,7,8-Hexaoxonane Structures. The structures of the resulting compounds were established by NMR spectroscopy, mass spectrometry, elemental analysis, and a comparison of their melting points with those published in the literature. The structures of peroxides **4d**, **4h**, **6a**, and **6f** were additionally confirmed by X-ray diffraction.

As a rule, the ^{13}C NMR spectra show two signals of different intensity at δ: 105−120, which is typical of sp^3-hybridized carbon atoms bearing peroxide groups. The more intense signal belongs to the quaternary carbon atoms (the residue of the dihydroperoxide fragment).

SCHEME 3. Intermediate 7 in the Synthesis of Peroxide 4g



SCHEME 4. Synthesis of Hexaoxonanes with the Use of Enol Ethers



8d, m = 1
8g, m = 7

2b, n = 2
2d, n = 8

	Yield, %	Time, h
4d	86	5
4g	81	6
6d	80	8
6g	30	15

Compounds **4c**, **5g**, **6c**, **6d**, and **6g** were characterized by informative mass spectra. Studies by electron impact mass spectrometry revealed the Story reaction; the molecular ions of macrocyclic alkanes and lactones corresponding to the molecular formulas of cyclic triperoxides were obtained.

In the present study, it was important to perform X-ray diffraction analysis. The fact is that the formation of diperoxides, 1,2,4,5-tetraoxanes, from peroxides **2**, as well as macrocyclic hexaperoxides from intermediate hydroperoxides (analogous to hydroperoxide **7**), which are produced according to Scheme 3, cannot be a priori excluded in the synthesis of hexaoxonanes. The results of X-ray diffraction experiments conclusively confirmed the structure of 1,2,4,5,7,8-hexaoxonanes. As a result of the single-crystal X-ray diffraction experiment for **4d** grown from $CHCl_3$, we found the first example of complexation of hexaoxonanes with $CHCl_3$.

Compounds **6a**, **6f**, and **4h** did not produce single crystals suitable for the X-ray crystal structure determination and were obtained only as crystalline powders. Therefore, their crystal structures were determined by powder X-ray diffraction methods.[10] Two polymorphic modifications were established for compound **4h**: triclinic (**T**) and monoclinic (**M**), respectively. A similar phenomenon was observed for triacetone triperoxide for which the existence of two conformers in the solid state was obtained from the crystal structure.[5c]

Conclusions

To summarize, we developed a new convenient procedure for the synthesis of 1,2,4,5,7,8-hexaoxonanes by the reactions of 1,1′-bis(hydroperoxy)dicycloalkyl peroxides with acetals using Lewis acids as catalysts. The method substantially extends the structural diversity of these compounds and, in most cases, allows the synthesis of these compounds in higher yields (to 96%) and with higher selectivity. Complexation of hexaoxonanes with chloroform was documented for the first time. The structures of several triperoxides were established by X-ray diffraction.

Experimental Section

Caution: Although we encountered no difficulties in working with hexaoxonanes and dihydroperoxides, precautions such as the use of shields and fume hoods, and avoidance of transition metal salts, heating and shaking should be observed whenever possible.

6,7,13,14,21,22-Hexaoxatrispiro[4.2.4^8.2.5^{15}.2^5]docosane (3d). 1,1-Dimethoxycyclohexane **1d** (0.374 g, 2.6 mmol) was added to a solution of 1,1′-dihydroperoxydi(cyclopentyl)peroxide **2a** (0.472 g, 2 mmol) in Et_2O (1.5 mL). A solution of $BF_3{\cdot}Et_2O$ (0.057 g, 0.4 mmol) in Et_2O (0.5 mL) was added to the reaction mixture at 0−5 °C. Then the mixture was stirred at 20 °C for 4 h. Petroleum ether (30 mL) was added to the reaction mixture. Then the mixture was washed with a 2% NaOH solution (20 mL), water (2 × 20 mL) at 35−45 °C, and 50% aqueous methanol (3 × 20 mL) at 35−45 °C, dried over Na_2SO_4, and filtered. The solvent was evaporated from the filtrate, and analytically pure **3d** (0.408 g, 13 mmol) was isolated by column chromatography on SiO_2 (petroleum ether−ethyl acetate, 20:1). Yield 65%. White crystals. Mp = 53−55 °C (hexane) (Mp^2 = 51−81 °C). R_f 0.41 (TLC, petroleum ether−ethyl acetate, 20:1). ^{1}C NMR (250.13 MHz) δ: 1.45−1.88 (m, 22H), 2.11−2.32 (m, 4H). ^{13}C NMR (50.32 MHz) δ: 22.6, 24.5, 25.4, 30.5, 33.4, 108.1, 118.8. Anal. Calcd for $C_{16}H_{26}O_6$: C, 61.13; H, 8.34. Found: C, 61.37; H, 8.58.

7,8,15,16,29,30-Hexaoxatrispiro[5.2.5.2.11.2]triacontane (4g). 1-Methoxycyclododecene **8g** (0.51 g, 2.6 mmol) was added to a solution of 1,1′-dihydroperoxydi(cyclohexyl)peroxide **2b** (0.524 g, 2 mmol) in Et_2O (1.5 mL). A solution of boron trifluoride etherate (0.142 g, 1 mmol) in diethyl ether (0.5 mL) was added to the reaction mixture at 20−25 °C. The mixture was stirred at 20−25 °C for 6 h. Et_2O (10 mL) and dry K_2CO_3 (0.5 g) were added to the reaction mixture. The reaction mixture was stirred for 30 min and filtered. The solvent was evaporated, methanol (10 mL) was added to the residue (a sticky white precipitate was obtained), and Et_2O was added dropwise to the reaction mixture until the latter was homogenized (~10 mL). Then the mixture was stirred under atmospheric pressure for 0.5 h, during which the major portion of the ether was evaporated. The residue was cooled at 0 to −5 °C. The crystals of **4g** that precipitated were filtered off and washed with MeOH (2 × 3 mL) at 0 °C. Analytically pure **4g** (0.692 g, 16.2 mmol) was isolated by column chromatography on SiO_2 (petroleum ether−ethyl acetate, 20:1). Yield 81%. Mp 57−59 °C (hexane). R_f 0.45 (TLC, petroleum ether−ethyl acetate, 20:1). ^{1}C NMR (250.13 MHz) δ: 1.17−1.93 (m, 42H). ^{13}C NMR (62.9 MHz) δ: 19.4, 22.1, 22.3, 22.8, 25.6, 26.0, 26.3, 26.8, 30.4, 107.6, 111.6. Anal. Calcd for $C_{24}H_{42}O_6$: C, 67.57; H, 9.92. Found: C, 67.31; H, 9.61.

(10) (a) *Structure Determination from Powder Diffraction Data;* David, W. I. F., Shankland, K., McCusker, L. B., Baerlocher, C., Eds; Oxford University Press: New York, 2002. (b) Baerlocher, C.; McCusker, L. B. *Z. Kristallogr.* **2004**, *219*, 782. (c) Harris, K. D. M.; Cheung, E. Y. *Chem. Soc. Rev.* **2004**, *33*, 526−538. (d) Chernyshev, V. V. *Russ. Chem. Bull.* **2001**, *50*, 2273−2292; *Izv. Acad. Nauk, Ser. Khim.* **2001**, 2171−2190. (e) Zhukov, S. G.; Chernyshev, V. V.; Babaev, E. V.; Sonneveld, E. J.; Schenk, H. *Z. Kristallogr.* **2001**, *216*, 5−9.

9,10,23,24,37,38-Hexaoxatrispiro[7.2.11^{11}.2.11^{25}.2^{8}]-octatriacontane (6f). 1,1-Dimethoxycyclooctane **1f** (0.447 g, 2.6 mmol) was added to a suspension of 1,1′-dihydroperoxydi-(cyclododecyl)peroxide **2d** (0.862 g, 2 mmol) in THF (8 mL). A solution of BF_3·Et_2O (0.17 g, 1.2 mmol) in THF (0.5 mL) was added to the reaction mixture at 20 °C. Then the mixture was stirred at 20−25 °C for 5 h. A major portion of solvent (∼$^3/_4$) was evaporated from the reaction mixture, and cooled MeOH (15 mL) was added. The white crystals that precipitated were filtered off and washed with cooled MeOH (3 × 5 mL). The purity of the compounds was ∼95%. Analytically pure **6f** (1.01 g, 18.8 mmol) was isolated by column chromatography on SiO_2 (petroleum ether−ethyl acetate, 20:1). Yield 94%. Mp = 198−200 °C (MeOH). (Mp^{8d} = 185−187 °C). R_f 0.86 (TLC, PE−EA, 20:1). ^{1}H NMR (250.13 MHz) δ: 1.20−1.84 (m, 58H). ^{13}C NMR (62.9 MHz) δ: 19.4, 22.0, 22.2, 25.0, 26.0, 26.2, 26.7, 26.8, 28.1, 28.3, 111.5, 111.6. Anal. Calcd for $C_{32}H_{58}O_6$: C, 71.33; H, 10.85. Found: C, 71.57; H, 10.46.

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Supporting Information Available: Experimental procedures, ^{1}H and ^{13}C NMR spectra, and details of X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

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