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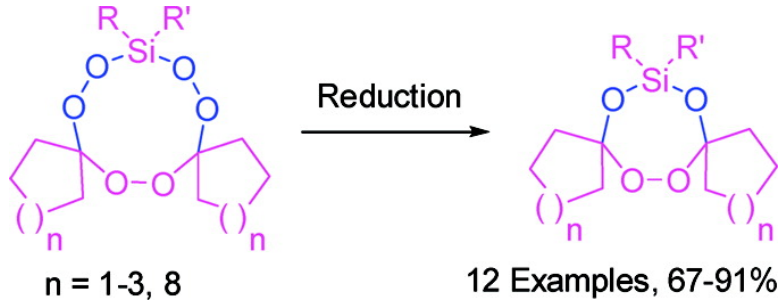

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Ring Contraction of 1,2,4,5,7,8-Hexaoxa-3-silonanes by Selective Reduction of COOSi Fragments. Synthesis of New Silicon-Containing Rings, 1,3,5,6-Tetraoxa-2-silepanes

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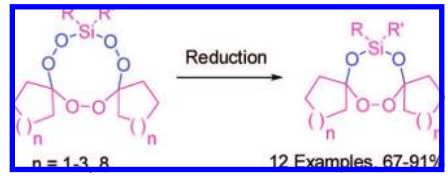

The reducing agents Ph_3P, $(C_8H_{17})_3P$, or $NH_2C(S)NH_2$ promote the ring contraction of nine-membered triperoxides, viz., 1,2,4,5,7,8-hexaoxa-3-silonanes, giving rise to seven-membered rings belonging to the previously unknown class of monoperoxides, viz., 1,3,5,6-tetraoxa-2-silepanes, in yields from 67% to 91%. Therefore, the selective reduction of the SiOOC fragments to SiOC in molecules containing simultaneously the COOC fragment was performed for the first time.

Introduction

In the last decades, methods for the synthesis and reactions of organic peroxides have been extensively developed. These compounds have attracted much attention because many structural types of peroxides showed pronounced antimalarial[1] and antitumor activities.[2] The reduction has a special place among various reactions of organic peroxides, because peroxides are traditionally considered as strong oxidizers and, consequently, the O−O bond cleavage in these compounds primarily occurs even if molecules contain other groups capable of being reduced. As a rule, the reduction of peroxides, for example, with H_2/Pd−C,[3] thiourea,[3a,4] $LiAlH_4$,[4c,5] iodine,[6] $NaBH_4$,[7] or Zn/CH_3COOH,[8] affords alcohols.[3−8] Recently a simple one-pot method has been reported to prepare dioxabicyclo[2.2.1]heptane derivatives from readily available 1,2,4-trioxane frameworks, under catalytic hydrogenation conditions over a platinum surface.[9]

Methods for the selective reduction of functional groups in molecules containing simultaneously the peroxide COOC fragments, which remain intact, have been extensively developed with the aim of preparing semisynthetic drug derivatives of artemisinin (natural cyclic peroxide). The latter are used for malaria treatment. In one of the early studies, the reduction was carried out with the use of $NaBH_4$.[10] As a result, the six-membered lactone ring in artemisinin was transformed into lactol in good yield. The reaction of artemisinin with $LiAlH_4$ led to

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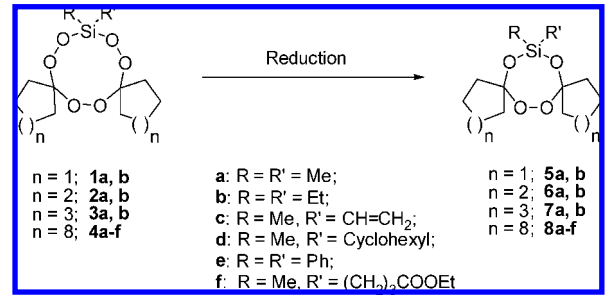
noticeable cleavage of the peroxide bond.[11] The C═O group in artemisinin was transformed into the CH_2 group with the use of diborane, which was prepared by the one-pot method from $NaBH_4-BF_3\cdot Et_2O$,[12] and by successive reduction with DIBAL-H and $Et_3SiH-BF_3\cdot Et_2O$.[13] The ester group in the side chain of artemisinin derivatives was selectively reduced to the aldehyde and alcoholic group with the use of DIBAL-H.[14a] In addition, the reduction of acrylic ester with DIBAL-H proceeded with high selectivity and afforded allylic alcohol, the O−O bond of the monoperoxyketal fragment in the polyfunctional molecule remaining intact.[14b]

The selective reduction of functional groups (without reducing the peroxide fragment) was performed with the use of $LiAlH(OBu^t)_3$,[15] $LiAlH_4$,[16] and $LiBH_4$.[17] The reduction of the ester group to the alcoholic group without reducing the 1,2-dioxane ring in the presence of lithium aluminum hydride and lithium borohydride was studied in detail.[18] The soft and selective reduction was found to proceed in the presence of $LiBH_4$.

The ester and azido groups were successfully reduced to the hydroxyl and amino groups, respectively, with $LiAlH_4$ in the synthesis of peroxide structures having high antimalarial activity; in these reactions the 1,2,4,5-tetraoxane ring remained intact.[19]

SCHEME 1. Reduction of 1,2,4,5,7,8-Hexaoxa-3-silonanes 1−4 Giving Rise to 1,3,5,6-Tetraoxa-2-silepanes 5−8



As opposed to the reduction of organic peroxides, the reduction of organosilicon peroxides containing SiOOC[20] and SiOOSi fragments[20c−e,21] was studied in much less detail. These peroxides were reduced with the use of trialkyl- and triphenylphosphines as reducing agents. For example, the SiOOC fragment was transformed into SiOC by the reaction of norbornanone peroxysilyl ether, which was prepared by the reaction of singlet oxygen with norbornene silyl ether, with PPh_3.[20a,b] Analogously, the corresponding alcohol, viz., 2-hydroxy-5-methoxy-2-methylindan-1-one, was synthesized from 2-(*tert*-butyldimethylsilylperoxy)-5-methoxyindan-1-one.[20c] *tert*-Butyl trimethylsilyl peroxide was transformed into *tert*-butyl trimethylsilyl ether by the reaction with triisopropylphosphine.[20d] The reduction of SiOOC with Me_3P was the key step in the synthesis of optically active triols from the ozonolysis products of γ-silyl allylic alcohol and their ethers.[20e]

Results and Discussion

In the present study, the reduction of peroxides containing simultaneously the COOC and SiOOC fragments was carried out for the first time. The conditions were found under which it is possible to perform the transformation 2SiOOC → 2SiOC in cyclic peroxides, 1,2,4,5,7,8-hexaoxa-3-silonanes **1**−**4**, with the use of certain reducing agents, the COOC fragment and other structural fragments of the molecules remaining intact. Nine-membered triperoxides **1**−**4** are transformed into the previously unknown seven-membered monoperoxides, 1,3,5,6-tetraoxa-2-silepanes **5**−**8** (Scheme 1).

In the first step of the study, we chose the conditions and reducing agents for the selective transformation of nine-membered peroxides into seven-membered peroxides using the reduction of **4a** into **8a** as an example. Then we examined the applicability of these conditions to related peroxides **1**−**4**, which

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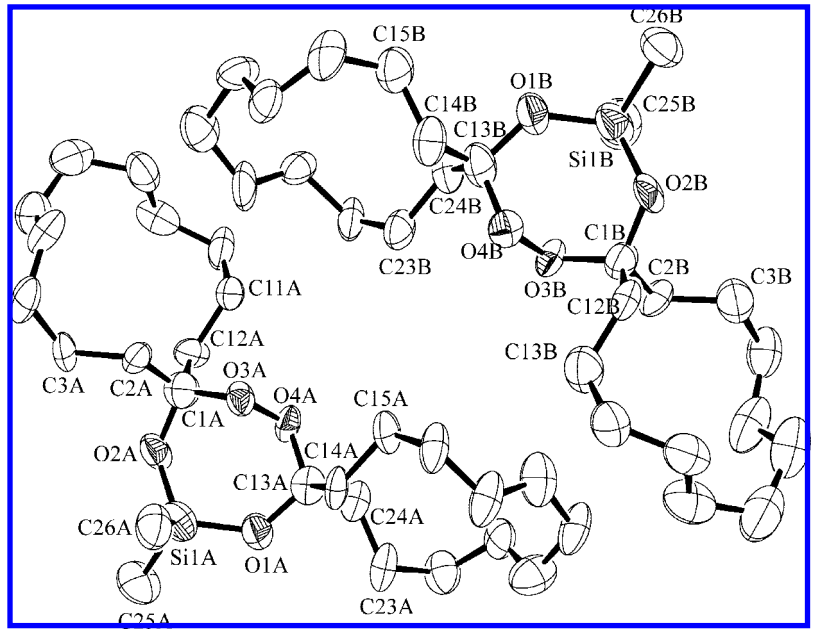

FIGURE 1. Two independent molecules of **8a** in monoclinic polymorph M, showing the atomic numbering and 40% probability displacement ellipsoids. H atoms were omitted for clarity.

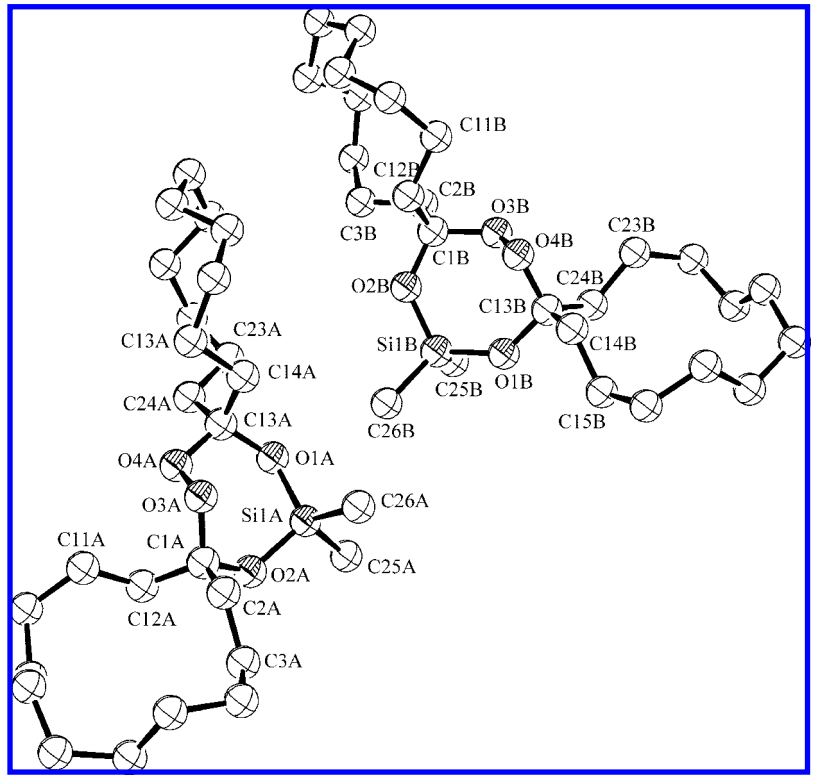

FIGURE 2. Two independent molecules of **8a** in triclinic polymorph T, showing the atomic numbering and 50% probability displacement spheres. H atoms were omitted for clarity.

we have synthesized earlier[22] starting from 1,1′-dihydroperoxydi(cycloalkyl) peroxides with ring sizes of C_5−C_7 and C_{12} and various dialkyldichlorosilanes.

Synthesis of 1,3,5,6-Tetraoxa-2-silepanes by Reduction of 1,2,4,5,7,8-Hexaoxa-3-silonanes. Peroxide **8a** was synthesized from **4a** in tetrahydrofuran with the use of reducing agents of different nature, such as phosphines, phosphites, thiourea, tetrahydrothiopyran, dimethyl sulfoxide, and metal hydrides (Table 1). These reagents are widely used in organic synthesis, in particular, in reactions with peroxides.

It was found that the COOSi fragment in peroxide **4a** is selectively reduced only with Ph_3P, $(C_8H_{17})_3P$, thiourea, and, to a smaller degree, $(BuO)_3P$; in these reactions, the COOC fragment remains intact. Triphenylphosphine and trioctylphos-

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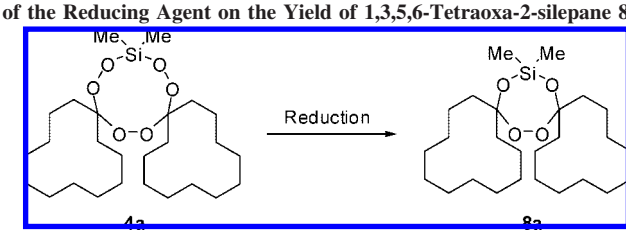
TABLE 1. Influence of the Nature of the Reducing Agent on the Yield of 1,3,5,6-Tetraoxa-2-silepane 8a[a]



Reducing agent	Ph_3P [b]	$(C_8H_{17})_3P$	$(BuO)_3P$	$NH_2C(S)NH_2$ [c]	S	DMSO	$NaBH_4$	$LiAlH_4$
Reaction time, h	12 (7)	2	12	24	24	24	24	2
Yield of **8a**, %	86 (64)	80	5	53	Traces	Traces	0	0
Conversion of **4a**, %	100 (75)	100	5-8	100	Traces	Traces	100 [d]	100 [d]

[a] **General conditions of reduction**: the reducing agent (0.45 mmol) dissolved or suspended in anhydrous THF (2 mL) was added to a suspension of **4a** (100 mg, 0.21 mmol) in anhydrous THF (4 mL) for 2−3 min, then the reaction mixture was stirred at 20−25 °C for 2−24 h. [b] With the use of Ph_3P (55 mg, 0.21 mmol) for 12 h peroxide **8a** was prepared with a yield of 19% along with the mixture of products. [c] Thiourea (0.62 g, 0.81 mmol) was used. [d] The reaction affords a large amount of cyclododecanol.

phine proved to be the best reducing agents. In the presence of these agents, **8a** is produced in 86% and 80% yields, respectively. The conversion of peroxide **4a** upon reduction with triphenylphosphine at 20−25 °C for 7 h is 75%; the complete conversion requires at least 12 h. The reaction in the presence of $(C_8H_{17})_3P$ as the reducing agent affords the target product in high yield, but the use of this agent complicates the experiment. In the latter case, all steps of this reaction should be performed under anaerobic conditions, because $(C_8H_{17})_3P$ is rapidly oxidized in the presence of traces of oxygen. Since triphenylphosphine is oxidized much more slowly than $(C_8H_{17})_3P$, this compound is convenient for solving the problem under consideration. It is much more difficult to reduce **4a** with $(BuO)_3P$. The conversion of the starting peroxide is 5−8%, and the yield of **8a** is 5%.

Satisfactory results were obtained with the use of thiourea for reduction of **4a**. Other sulfur-containing reducing agents (tetrahydrothiopyran and dimethyl sulfoxide) do not react with **4a** at all. The reactions with strong reducing agents, such as $NaBH_4$ and $LiAlH_4$, proceed nonselectively and lead to the cleavage of all peroxide bonds.

The mechanism of the fragment O−O reduction with Ph_3P in cyclic peroxides was investigated in detail.[23] This reduction generally proceeds by initial cleavage of the oxygen−oxygen bond with formation of the O−P−O fragment. For example, the reaction of triphenylphosphine with 2,3-dioxabicyclo-[2.2.1]heptane resulted in the formation of a phosphorane that decomposed in the presence of water to give triphenylphosphine oxide and *trans*-1,3-cyclopentanediol.[23b] The ^{31}P NMR monitoring of peroxide **4a** reduction with Ph_3P at room temperature showed only two peaks corresponding to Ph_3P and Ph_3PO;

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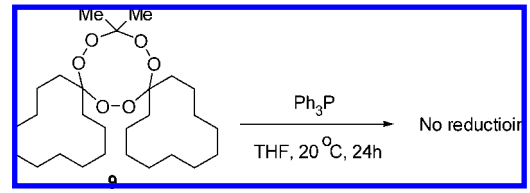
SCHEME 2. Reaction of Triphenylphosphine with Hexaoxonane 9



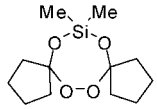
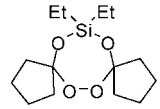
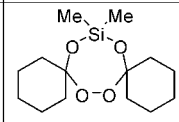
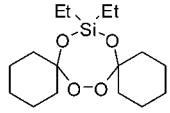
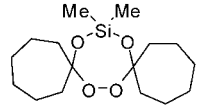
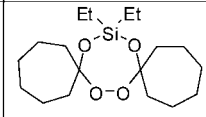
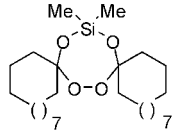
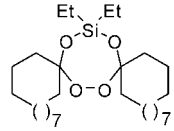
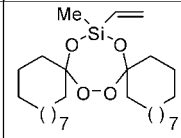
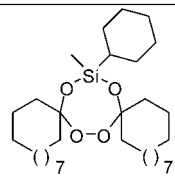
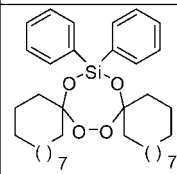
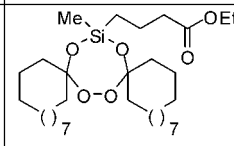
characteristic signals for the O−P−O fragment (region ca. −50 to −70 ppm)[23d] were not detected. It is probable that the insertion of the phosphine into the peroxide bond is the rate limitating step of the SiOOC fragment reduction after which Ph_3PO rapidly eliminates with formation of the SiOC fragment.

The lack of characteristic signals for the O−P−O fragment also makes it possible to suppose that the SiOOC fragment is reduced without a phosphorane formation. Phosphine attack occurs on the less crowded silyl part of the molecule likely on the silicon-bonded oxygen. Selectivity of the SiOOC fragment reduction in comparison with the COOC fragment is also probably the result of formation of a weak P−Si complex, which makes it possible to draw together reductant (phosphine) and oxidant (peroxide fragment).

An attempt to perform the ring contraction by the reduction of hexaoxonane **9**, which is the carbocyclic analogue of compound **4a**, with triphenylphosphine failed. At room temperature, the conversion of **9** did not proceed within 1 day. At higher temperature (60 °C), the conversion was virtually absent within 2 h (Scheme 2).

Taking into account the reaction conditions found for the synthesis of **8a**, we performed the reduction of compounds **1**−**4** containing different substituents in the peroxide ring (spiro-fused carbocycles C_5−C_7 and C_{12} at the carbon atoms; Me, Et, vinyl, cyclohexyl, phenyl, and carbethoxypropane substituents at the silicon atom) with the use of a small excess of triphenylphosphine as the reducing agent (2.2 mol per mol of 1,2,4,5,7,8-hexaoxa-3-silonanes). The reactions were performed at room

TABLE 2. Structures and Yields of 1,3,5,6-Tetraoxa-2-silepanes[a]

Run	1,3,5,6-Tetraoxa-2-silepane, yield,[b] (reaction time, h)	Run	1,3,5,6-Tetraoxa-2-silepane, yield, [b] (reaction time, h)	Run	1,3,5,6-Tetraoxa-2-silepane, yield, [b] (reaction time, h)
1	 **5a, 89, (6)**	2	 **5b, 67, (12)**	3	 **6a, 91, (6)**
4	 **6b, 90, (12)**	5	 **7a, 79, (6)**	6	 **7b, 83, (12)**
7	 **8a, 86, (12)**	8	 **8b, 88, (42)**	9	 **8c, 67, (12)**
10	 **8d, 68, (30)**	11	 **8e, 71, (12)**	12	 **8f, 69, (40)**

[a] **General reaction conditions**: peroxide **1**−**4** (0.72 mmol) was dissolved or suspended in anhydrous THF (9−12 mL), a solution of PPh_3 (1.60 mmol) in anhydrous THF (5 mL) was added for 4−6 min, and the reaction mixture was stirred at 20−25 °C for 6−42 h until the complete conversion of peroxides **1**−**4** was achieved. [b] The yield based on the isolated product.

temperature for 6−42 h until the complete conversion of compounds **1**−**4** was achieved (Table 2).

1,3,5,6-Tetraoxa-2-silepanes **5**−**8** were prepared in yields from 67% to 91%. The yield depends only slightly on the structures of the starting compounds. The nature of the substituents in the starting 1,2,4,5,7,8-hexaoxa-3-silonanes has a substantial effect on the reaction time required to achieve the complete conversion of **1**−**4**. The reduction time increases with increasing ring size of the substituent spiro-fused to the peroxide ring. Thus, the reactions with compounds containing the C_5, C_6, or C_7 rings are completed in 6−12 h, whereas the reaction time in the case of compounds containing the C_{12} ring increases (in certain cases) to 42 h. The reduction time increases with increasing bulkiness of the substituent at the Si atom. Thus, the time of the synthesis starting from compounds containing ethyl substituents instead of methyl groups increases by a factor of 2 or more.

Properties and Structures of Peroxides 5−8. Peroxides **5a**,**b**, **6a**,**b**, and **7b** are liquids. Compounds **7a** and **8a**−**f** are solid compounds with melting points from 36 °C (**7a**) to 137 °C (**8e**). Their structures were established by ^1H, ^{13}C, and ^{29}Si NMR spectroscopy and elemental analysis. In the ^{13}C NMR spectra, the characteristic signals for the carbon atoms of the monoperoxyacetal OCOO fragments[1q,24] of the seven-membered rings are most informative. The chemical shifts of these fragments (105−116 ppm) are similar to those for the bisperoxide OOCOO fragments of the starting nine-membered rings (108−120 ppm). The ^{29}Si NMR spectra are also informative. The chemical shifts in the spectra of compounds **2a** and **4a** are 8.44 and 7.56 ppm, respectively; after reduction the shifts in the spectra are −7.50 (**6a**) and −8.25 ppm (**8a**), respectively.

Since 1,3,5,6-tetraoxa-2-silepanes have been previously unknown, it was important to obtain direct evidence for the existence of these compounds by X-ray diffraction. The X-ray diffraction study was carried out for compound **8a**. Peroxide **8a** was obtained as a crystalline powder, which contained a small amount of single crystals suitable for X-ray diffraction. The X-ray analysis has shown that **8a** crystallizes in two polymorphic modifications: monoclinic (M) and triclinic (T), respectively. The solid state crystal structure of M (Figure 1) was obtained from X-ray single-crystal diffraction data, while the crystal structure of T (Figure 2) was determined by powder diffraction methods.

Conclusion

It was demonstrated that the COOSi fragment in organosilicon peroxides can be selectively reduced in molecules containing

(24) (a) Ito, T.; Tokuyasu, T.; Masuyama, A.; Nojima, M.; McCullough, K. J. *Tetrahedron* **2003**, *59*, 525–536. (b) Dussault, P. H.; Eary, C. T. *J. Am. Chem. Soc.* **1998**, *120*, 7133–7134. (c) Zmitek, K.; Zupan, M.; Stavber, S.; Iskra, J. *J. Org. Chem.* **2007**, *72*, 6534–6540.

simultaneously the COOC fragment at the same geminal peroxide center. The reduction of 1,2,4,5,7,8-hexaoxa-3-silonanes affords 1,3,5,6-tetraoxa-2-silepanes belonging to a new class of cyclic organosilicon peroxides. The reactions with phosphines and thiourea proceed selectively. In the presence of other reducing agents, such as $(BuO)_3P$, $(CH_2)_5S$, DMSO, $NaBH_4$, or $LiAlH_4$, either all peroxide groups are completely reduced or the conversion is not observed at all.

Experimental Section

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

Influence of the Nature of the Reducing Agent on the Yield of 1,3,5,6-Tetraoxa-2-silepane (8a, Table 1). A reducing agent (0.45 mmol) dissolved or suspended in anhydrous THF (2 mL) was added to a suspension of **4a** (100 mg, 0.21 mmol) in anhydrous THF (4 mL) for 2−3 min. The reaction mixture was stirred at 20−25 °C for 2−24 h. Then the solvent was evaporated (if the precipitate was present, the mixture was initially filtered through a thin layer of silica gel) and methanol (10 mL) was added. The reaction mixture was cooled to −10 °C, and the precipitate was filtered off and washed with MeOH (5 × 2 mL). Peroxide **8a** was dried under a pressure of 0.5−1 mmHg for 1 h.

Synthesis of 28,28-Dimethyl-13,14,27,29-tetraoxa-28-siladispiro[11.2.11.3]nonacosane Peroxide (8a) by Reduction of 4a with Triphenylphosphine (Table 1). Hexaoxasilonane **4a** (100 mg, 0.21 mmol) was suspended in anhydrous tetrahydrofuran (4 mL). Then a solution of PPh_3 (120 mg, 0.45 mmol) in anhydrous THF (2 mL) was added for 2 min. The reaction mixture was stirred at 20−25 °C for 12 h. The general procedure for the isolation of peroxides **8a**−**f** involved the following steps. The solvent was evaporated and methanol (10 mL) was added. The reaction mixture was cooled to −10 °C, the precipitate was filtered off and washed with MeOH (5 × 2 mL), and the product was dried under a pressure of 0.5−1 mmHg for 1 h. Compound **8a** was obtained in a yield of 86% (82 mg, 0.18 mmol). White crystals; mp 127−129 °C (MeOH); R_f 0.61 (TLC, petroleum ether−EtOAc, 20:1); ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 0.19 (s, 6H), 1.25−1.95 (m, 44H); ^{13}C NMR (75.48 MHz, $CDCl_3$) δ 0.5, 19.8, 20.1, 22.0, 22.1, 22.3, 22.4, 26.07, 26.10, 31.7, 32.2, 109.7. Anal. Calcd for $C_{26}H_{50}O_4Si$: C, 68.67; H, 11.08; Si, 6.18. Found: C, 68.81; H, 11.29; Si, 6.03.

Synthesis of 18,18-Diethyl-8,9,17,19-tetraoxa-18-siladispiro-[6.2.6.3]nonadecane (7b). Peroxide **3b** (270 mg, 0.72 mmol) was dissolved in anhydrous THF (9 mL). Then a solution of PPh_3 (420 mg, 1.60 mmol) in anhydrous THF (5 mL) was added for 4 min. The reaction mixture was stirred at 20−25 °C for 12 h until the complete conversion of peroxide **3b** was achieved. The general procedure for the isolation of peroxides **5**−**7** involved the following steps. A solution of hydrogen peroxide (35 mg, 1.0 mmol) in Et_2O (1 mL) was added to the reaction mixture to oxidize excess triphenylphosphine. Then the solvent was removed under reduced pressure at room temperature. Peroxide **7b** was isolated by silica gel chromatography with use of a hexane/EA = 20/1 mixture. The eluent was evaporated under a pressure of 0.5−1 mmHg for 0.5 h. Compound **7b** was obtained in a yield of 83% (204 mg, 0.59 mmol). Colorless oil; R_f 0.65 (TLC, petroleum ether−EtOAc, 20:1); ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 0.63 (q, 4H, J = 11.4 Hz), 0.98 (t, 6H, J = 8 Hz), 1.47−1.83 (m, 20H), 1.98−2.10 (m, 4H); ^{13}C NMR (75.48 MHz, $CDCl_3$) δ 6.4, 6.7, 22.3, 22.6, 29.17, 29.21, 37.9, 39.4, 109.8. Anal. Calcd for $C_{18}H_{34}O_4Si$: C, 63.11; H, 10.00; Si, 8.20. Found: C, 63.37; H, 10.12; Si, 8.11.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for 1,3,5,6-tetraoxa-2-silepanes **5**−**8**, and X-ray data for **8a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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