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Facile and Selective Procedure for the Synthesis of Bridged 1,2,4,5-Tetraoxanes; Strong Acids As Cosolvents and Catalysts for Addition of Hydrogen Peroxide to β-Diketones

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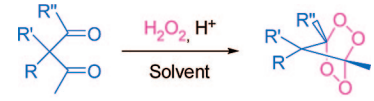
Received February 2, 2009



12 Examples; Yield 44-77%

A facile, experimentally simple, and selective method was developed for the synthesis of bridged 1,2,4,5-tetraoxanes based on the reaction of hydrogen peroxide with β-diketones catalyzed by strong acids (H_2SO_4, $HClO_4$, HBF_4, or BF_3). The yields of the target products vary from 44% to 77%. 1,2,4,5-Tetraoxanes can easily be separated from other reaction products by column chromatography. A high concentration of a strong acid is a key factor determining the selectivity of formation and the yield of 1,2,4,5-tetraoxanes. Unlike many compounds containing the O−O bond, which undergo rearrangements in acidic media, the resulting cyclic peroxides are quite stable under these conditions.

Introduction

In the past two decades, organic peroxides have come to the attention of chemists and researchers in the field of drug design because certain representatives of these compounds exhibit antimalarial[1−3] and antitumor[4] activities. This has stimulated the development of methods for the synthesis of these compounds. Nowadays, cyclic compounds, such as tetraoxanes, ozonides, and trioxanes, are considered as the most promising synthetic peroxides having such activities. Some of these compounds exhibit high activity[5] comparable to or higher than that of the natural peroxide artemisinin, which is widely used for the treatment of malaria. The design of explosives based on cyclic peroxides is of particular interest. For example, triacetone triperoxide is one of the most sensitive known explosives, whose power is similar to that of trinitrotoluene.[6]

Most of known symmetrical tetraoxanes were synthesized by the acid-catalyzed cyclocondensation of hydrogen peroxide with

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10.1021/jo900226b CCC: $40.75 © 2009 American Chemical Society
Published on Web 03/19/2009

ketones or benzaldehydes;[1f,2d,j,7−14] the trimethylsilyl trifluoromethanesulfonate (TMSOTf)-catalyzed cyclocondensation of bis(trimethylsilyl) peroxides with carbonyl compounds;[2a,15] the ozonolysis of olefins,[10,16] enol ethers,[17] and O-alkyl oximes;[18−20] the BF_3-catalyzed rearrangement of dioxetanes;[21] and the rearrangement of ozonides in the presence of catalytic amounts of $SbC1_5$ or $ClSO_3H$.[22]

Because unsymmetrical tetraoxanes are of great interest for the design of antimalarial drugs, methods for their preparation have attracted more attention. The synthesis of these peroxides is based on the cyclocondensation of ketones or aldehydes with steroid[2j,4f,g,23] or alicyclic *gem*-bishydroperoxides (in the presence of H_2SO_4 as the catalyst[24]), with aliphatic or alicyclic *gem*-bishydroperoxides (in the presence of the $MeRhO_3-HBF_4$ system[2h] or HBF_4[5a] as the catalyst), the reaction of ketones with *gem*-bis(trimethylsilyldioxy)alkanes (TMSOTf[2a] as the catalyst), and the BF_3-catalyzed reaction of acetals with alicyclic *gem*-bishydroperoxides.[25]

In the present study, we report the synthesis of bridged 1,2,4,5-tetraoxanes by the acid-catalyzed reaction of β-diketones with hydrogen peroxide. Attempts to prepare tetraoxane from the simplest β-diketone (acetylacetone) have been made earlier. In the study,[26] the corresponding tetraoxane was synthesized in a total yield of 18.5% in two steps involving the reaction of acetylacetone with hydrogen peroxide in a neutral medium giving rise to 5-hydroperoxy-3,5-dimethyl-1,2-dioxolan-3-ol followed by the intramolecular cyclization of the latter compound in the presence of P_2O_5 in diethyl ether. It was also noted that this tetraoxane is formed in trace amounts in the course of the sulfuric acid catalyzed synthesis of 3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane from acetylacetone and hydrogen peroxide. Tetraoxane derived from acetylacetone was prepared by heating the presynthesized 5-hydroperoxy-3,5-dimethyl-1,2-dioxolan-3-ol in acetic acid (the yield was not reported).[27] In some other studies of the reactions of β-diketones with hydrogen peroxide, the formation of tetraoxanes was not documented.[28] In the study,[29] presumably bis-tetraoxane was synthesized in high yield from tetraketone (1,1,3,3-tetraacetylpropane) by the sulfuric acid catalyzed reaction with hydrogen peroxide in water at elevated temperature (80 °C). This result is apparently attributed to the specific reactivity of this tetraketone, its good solubility in water, and the relatively high thermal stability of the resulting peroxide.

Therefore, despite the results of investigations on the reactions of β-diketones with hydrogen peroxide, appropriate conditions for the selective synthesis of bridged 1,2,4,5-tetraoxanes have not been found hitherto.

Results and Discussion

We succeeded in finding the conditions for the one-pot synthesis of bridged 1,2,4,5-tetraoxanes **2a-l** from β-diketones **1a−l** (Scheme 1) in yields from moderate to good (44−77%).

These results were achieved with the use of large amounts of strong acids (H_2SO_4, $HClO_4$, HBF_4, or BF_3), which act as the catalyst and simultaneously serve as the cosolvent. Unexpectedly, the amount of the acid was found to influence both the formation of tetraoxanes **2** and stability of these peroxides during experiments. It is known that peroxides can be involved in the Baeyer−Villiger,[30] Criegee,[31] and Hock[32] reactions in an acidic medium; these reactions are accompanied by the O−O bond cleavage. Under the proposed conditions, these reactions did not proceed.

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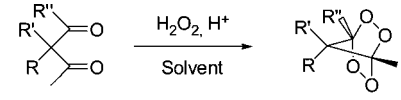
SCHEME 1. Synthesis of 1,2,4,5-Tetraoxanes 2 from β-Diketones 1 and Hydrogen Peroxide



1a-l **2a-l**

a: R = Bu, R' = H, R'' = Me; **b:** R = Bu, R' = Me, R'' = Me; **c:** R = CH_2-CH=CH_2, R' = H; R'' = Me;

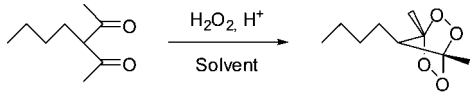
d: R = CH_2CH_2CN, R' = H; R'' = Me; **e:** R = CH_2CH_2COOEt, R' = H, R'' = Me;

f: R = 1-Adamantyl, R' = H, R'' = Me; **g:** R = CH_2Ph, R' = H, R'' = Me; **h:** R = m-$MePhCH_2$, R' = H, R'' = Me;

i: R = p-$MePhCH_2$, R' = H, R'' = Me; **j:** R = o-$MeOPhCH_2$, R' = H, R'' = Me;

k: R = p-NO_2PhCH_2, R' = H, R'' = Me; **l:** R = R'' = -$(CH_2)_4$-, R' = H.

TABLE 1. Synthesis of 7-Butyl-1,4-dimethyl-2,3,5,6-tetraoxabicyclo[2.2.1]heptane 2a from 3-Butyl-2,4-pentanedione[a]



1a **2a**

run	moles of H_2O_2 per mole of **1a**	H_2SO_4 (g) per 0.3 g of **1a**	yield of **2a**, % [b]
1	1	1	27
2	2	1	49
3	3	1	61
4	5	1	61
5	7	1	62
6	3	0.1	5
7	3	0.1	49[c]
8	3	0.5	23
9	3	2	77
10	3	3	45
11	3	4	32
12	3	2	73[d]
13	3	2	48[e]
14	3	1	tr[f]
15	3	2	tr[f]

[a] **General procedure.** A solution of H_2SO_4 (1−40 mmol, 0.1−4 g) in EtOH (*i*-PrOH, THF, CH_3CN; 2 mL) was added with stirring to a mixture of **1a** (1.92 mmol, 0.3 g) and 37% H_2O_2 (1−7 mol per mole of **1a**) in EtOH (*i*-PrOH, THF, CH_3CN; 3 mL) at low temperature (10−15 °C). The reaction mixture was stirred at 20−25 °C for 1 h. [b] The yield based on the isolated product. [c] The reaction time was 20 h. [d] In *i*-PrOH as the solvent. [e] In THF as the solvent. [f] In CH_3CN as the solvent.

The conditions of synthesis of tetraoxanes were optimized on the basis of the reaction of 7-butyl-1,4-dimethyl-2,3,5,6-tetraoxabicyclo[2.2.1]heptane **2a**, which was prepared from 3-butyl-2,4-pentanedione **1a**. The influence of the concentration and the nature of the acid and the effect of the amount of hydrogen peroxide on the yield of tetraoxane **2a** were investigated (Table 1).

In runs 1−5, the amount of hydrogen peroxide was varied from 1 to 7 mol per mole of **1a**, the amount of sulfuric acid remaining the same (1 g per 0.3 g of **1a**). The reaction with the use of one-half of the stoichiometric amount of H_2O_2 (run 1) afforded tetraoxane **2a** in 27% yield. The yield of **2a** increases to 49% in the presence of the stoichiometric amount of H_2O_2 (run 2) and then to 61−62% in the reaction with the use of 3−7 moles of H_2O_2 per mole of **1a**. It should be emphasized that the reaction with the use of a 7-fold molar excess of H_2O_2 results only in the addition of two hydrogen peroxide molecules to diketone **1a** giving rise to tetraoxane, whereas the product of the addition of four peroxide molecules is not formed. The latter process could not be excluded in view of the possibility of formation 1,3-di(*gem*-bishydroperoxide) BuCH[CMe$(OOH)_2$]$_2$

Apparently, a 3-fold molar excess of hydrogen peroxide is close to the optimal value. Hence, we used this amount of hydrogen peroxide in subsequent experiments. In runs 6−11, we varied the ratio of sulfuric acid to diketone **1a** from 0.1 to 4 g of H_2SO_4 per 0.3 g of **1a** using the same volume of the solvent (5 mL). The maximum yield of **2a** (77%) was achieved in ethanol, and almost the same yield was obtained in isopropanol (runs 9 and 12, respectively) with the use of 2 g of H_2SO_4 per 0.3 g of **1a**. The reaction in THF (run 13) affords peroxide **2a** in substantially lower yield than in alcohols. In CH_3CN (runs 14 and 15), compound **2a** was detected in trace amounts. An increase in the reaction time to 20 h in run 7 compared to run 6 (1 h) allowed us to obtain peroxide **2a** in 49% yield despite a small amount of sulfuric acid; however, the selectivity of the synthesis was low and unidentified products were formed.

Not only sulfuric acid but also other strong acids, such as $BF_3 \cdot Et_2O$, HBF_4, and $HClO_4$, can be used with advantage in the synthesis of tetraoxanes (Table 2).

The reaction with the use of phosphoric acid afforded tetraoxane **2a** in trace amounts (run 16). Tetrafluoroboric acid (50% aqueous solution) is highly competitive with sulfuric acid. The reaction with the use of tetrafluoroboric acid (from 1 to 5 g per 0.3 g of **1a**) affords tetraoxane in 71−77% yield (runs 17−20). Perchloric acid also proved to be an efficient catalyst (run 21). Tetraoxane **2a** was prepared in a slightly lower yield (43−64%) in an anhydrous medium with the use of Et_2O as the solvent and BF_3 as the catalyst (runs 22−25).

Taking into account the reaction conditions, which were developed as applied to tetraoxane **2a**, we synthesized a series of tetraoxanes **2b−l** containing the alkene fragment (**2c**), the nitrile group (**2d**), the ester moiety (**2e**), the adamantane fragment (**2f**), the nitro group (**2k**), and the aromatic moiety (**2g−k**) (Table 3).

On the basis of the above-considered data, it can be concluded that the yield of tetraoxanes **2a−l** synthesized from diketones **1a−l** (which varies from moderate to good) allows the prediction of the results of this reaction as applied to other structurally similar β-diketones.

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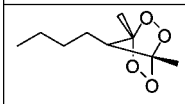
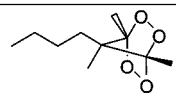
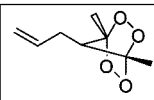
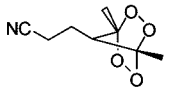
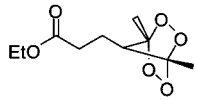
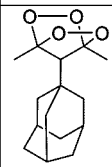
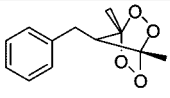
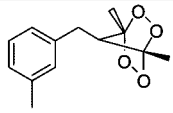
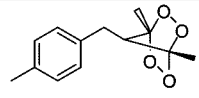
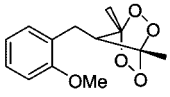
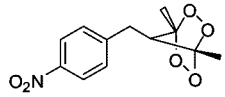
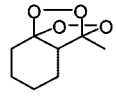
(32) (a) Hock, H.; Lang, S. *Ber. Dtsch. Chem. Ges.* **1944**, *B77*, 257. (b) Jordan, W.; van Barneveld, H.; Gerlich, O.; Boymann, M. K.; Ullrich, J. In *Ullmann's Encyclopedia of Industrial Organic Chemicals*; Gerhartz, W., Ed.; Wiley-VCH: Weinheim, 1985; Vol *A9*, pp 299−312; (c) Nakamura, R.; Obora, Y.; Ishii, Y. *Chem. Commun.* **2008**, 3417–3419. (d) Hamann, H.-J.; Liebscher, J. *J. Org. Chem.* **2000**, *65*, 1873–1876. (e) Hamann, H.-J.; Wlosnewski, A.; Greco, T.; Liebscher, J. *Eur. J. Org. Chem.* **2006**, 2174–2180.

TABLE 2. Influence of Nature of Catalyst on Yield of 7-Butyl-1, 4-dimethyl-2,3,5,6-tetraoxabicyclo[2.2.1]heptane 2a[a]

run	acid	acid (g) per 0.3 g of **1a**	yield of **2a**, %[b]
16	H_3PO_4	1.3	tr
17	HBF_4, 50% aq soln	1	72
18	HBF_4, 50% aq soln	2	77
19	HBF_4, 50% aq soln	3.5	77
20	HBF_4, 50% aq soln	5	71
21	$HClO_4$, 60% aq soln	3.3	69
22	$BF_3 \cdot Et_2O$[c]	0.5	43
23	$BF_3 \cdot Et_2O$[c]	1	50
24	$BF_3 \cdot Et_2O$[c]	4.0	64
25	$BF_3 \cdot Et_2O$[c]	6.0	45

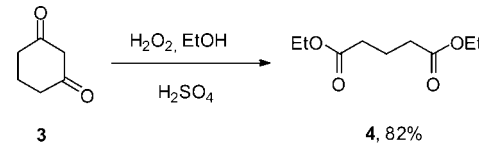
[a] **General procedure.** A solution of acid H_3PO_4, $BF_3 \cdot Et_2O$, HBF_4, or $HClO_4$ (1−10 g) in EtOH, Et_2O (2 mL) was added with stirring to a mixture of **1a** (1.92 mmol, 0.3 g) and 37% H_2O_2 (3 mol per mole of **1a**) in EtOH (3 mL) at low temperature (10−15 °C). The reaction mixture was stirred at 20−25 °C for 1 h. [b] The yield based on the isolated product. [c] Diethyl ether as the solvent and an ethereal solution of H_2O_2 were used (c = 2.53 mol/L).

TABLE 3. Structures and Yields of 1,2,4,5-Tetraoxanes 2a−l[a]

Structures and yields [b] of 1,2,4,5-tetraoxanes, %		
 **2a**, 77	 **2b**, 73	 **2c**, 62 (60, [c] 65 [d])
 **2d**, 47 (44) [e]	 **2e**, 55	 **2f**, 67
 **2g**, 69	 **2h**, 75 (73) [e]	 **2i**, 77
 **2j**, 54 [f]	 **2k**, 58 [f]	 **2l**, 48 [g]

[a] **General procedure.** A 37% aqueous H_2O_2 solution (3 mol of H_2O_2 per mole of β-diketone **1a−l**) was added to a solution of β-diketone **1a−l** (0.3 g) in EtOH (3 mL), the reaction mixture was cooled to 10 °C, and a solution of H_2SO_4 (2 g) in EtOH (2 mL) was added with stirring. The reaction mixture was kept at 20−25 °C for 1 h. [b] The yield based on the isolated product. [c] Experiment on the synthesis of **2c** was scaled with a decrease in the amounts of the reagents by a factor of 3. [d] Experiment on the synthesis of **2c** was scaled with an increase in the amounts of the reagents by a factor of 5. [e] The experiments were carried out with the use of 2 g of HBF_4 (based on the 100% acid) per 0.3 g of **1a**. [f] The reaction was carried out with the use of doubled quantities of EtOH and H_2SO_4; the reaction time was 3 h. [g] Because **2l** is prone to decomposition in an alcohol solution, the synthesis was carried out by adding 37% aqueous H_2O_2 solution (3 mol of H_2O_2 per mole of β-diketone **1l**) to a solution of β-diketone **1l** (0.3 g) in THF (3 mL). The reaction mixture was cooled to 10 °C, and a solution of H_2SO_4 (2 g) in THF (2 mL) was added with stirring. The reaction mixture was kept at 20−25 °C for 0.5 h.

SCHEME 2. Oxidation of 1,3-Cyclohexanedione 3



3 **4**, 82%

Unlike acyclic diketones **2a−l**, a cyclic β-diketone, namely, 1,3-cyclohexanedione (**3**), was oxidized with hydrogen peroxide. The reaction was accompanied by the C−C bond cleavage and afforded glutaric acid ester **4** (Scheme 2).

Role of Acids in the Synthesis of Tetraoxanes. The fact that a large excess of acids is favorable for an increase in the selectivity of formation and the yield of the target products seems to be important for the peroxidation reaction. The selective formation of tetraoxane **2b** from disubstituted ketone **1b**, which cannot exist in the enol form containing a double bond conjugated with the carbonyl group, leads us to the conclusion that the role of the acid is not associated with the involvement of reactive enols in the reaction. Apparently, hydrogen peroxide undergoes protonation in concentrated sulfuric acid solutions. This leads to a decrease in the activity of hydrogen peroxide in peroxidation of intermediate hydroxyperoxides thus hindering the formation of tri- and tetraperoxides. This is why only tetraoxanes, which are intramolecular cyclization products of hydroperoxides, are formed even in the presence of a 5- or 7-fold molar excess of hydrogen peroxide with respect to β-diketone.

Reactions of Tetraoxanes with the Use of Some Reagents Commonly Used in Organic Synthesis. With the aim of evaluating the stability of the peroxide bonds in tetraoxanes to reagents widely used in organic synthesis and determining the structures, which are of interest for biological activity assays, we performed the following reactions involving the functional groups in the bridging fragment of tetraoxanes **2c** and **2e**: halogenation, oxidation, alkoxymercuration, hydrolysis, and amidation. In all of these reactions, the tetraoxane ring remained intact (Scheme 3).

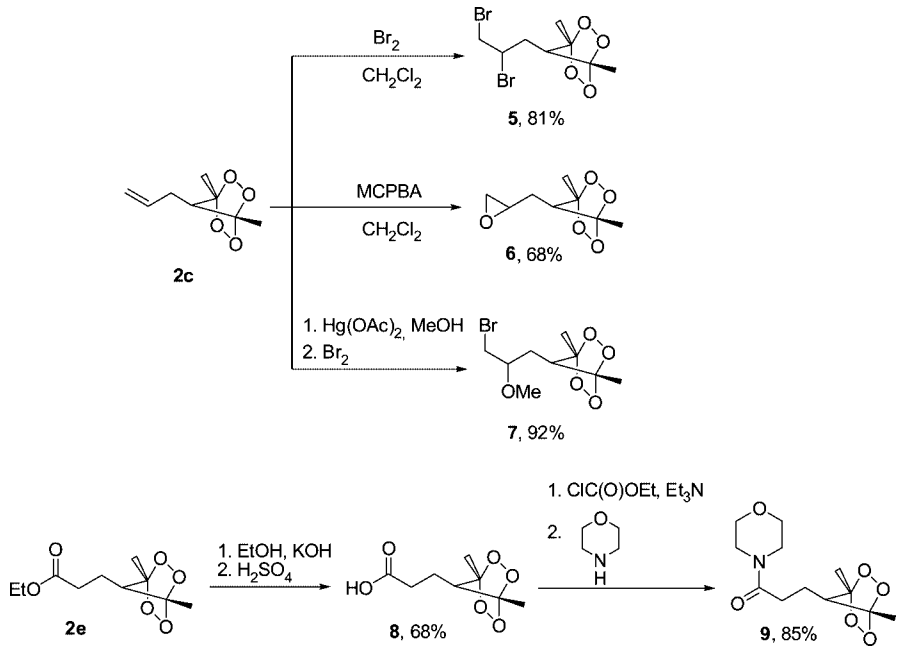
In these reactions, the tetraoxane ring is quite stable and thus the starting structures can be easily modified in such a way that the peroxide fragment remains intact. Tetraoxanes are not decomposed by bromine, MCPBA, $Hg(OAc)_2$, amines, or KOH.

Structure Determination of Bridged Tetraoxanes. Peroxides **2a−c,e**, **5**, and **6** are liquids; the other peroxides are solids with melting points from 31−33 °C (**2l**) to 141−142 °C (**2k**). The structures of these compounds were established by ^1H and ^{13}C NMR spectroscopy and elemental analysis. In the ^{13}C NMR spectra, the signals for the carbon atoms of the OOCOO fragments are most informative. The chemical shifts of these atoms (108.9−111.9 ppm) are similar to those for the OOCOO fragment of geminal bisperoxide compounds. The upfield chemical shift (from 8.7 to 12.7 ppm) of the methyl groups at positions 1 and 4 of the tetraoxane ring observed in the ^{13}C NMR spectra is characteristic of the resulting bridged tetraoxanes.

Determination of active oxygen content in the bridged tetraoxanes by iodine liberation procedure with a KI-CH_3COOH-H_2O system does not give a quantitative result. However this system can be useful for qualitative analysis of the tetraoxanes.

It is always difficult to reliably establish the structures of organic peroxides (even though the compounds are characterized by NMR spectroscopy) because the condensation of several molecules through peroxide bridges or the acid-catalyzed rearrangements accompanied by changes in the carbon skeleton

SCHEME 3. Reactions in Which the Tetraoxane Ring Remains Intact



and the formation of the ester rather than peroxide group cannot be excluded. Hence, we established the structures of **2d** and **2h** belonging to the poorly known class of bridged tetraoxanes by X-ray diffraction. The X-ray data proved the structures of these compounds.

Conclusions

A facile and experimentally simple procedure for the synthesis of bridged 1,2,4,5-tetraoxanes was developed. This method affords the target compounds in 44−77% yield. The method is based on the acid-catalyzed reaction of β-diketones with hydrogen peroxide. A high concentration of strong acids, such as H_2SO_4, HBF_4, or $HClO_4$, is a key factor determining the selectivity of formation and the yield of 1,2,4,5-tetraoxanes. Under these conditions, the target compounds are formed selectively even in the presence of an excess hydrogen peroxide. Bridged 1,2,4,5-tetraoxanes are rather stable to reagents commonly used in organic synthesis, such as Br_2, MCPBA, $Hg(OAc)_2$, morpholine, and KOH, which offers considerable scope for structural modifications of this class of peroxides.

Experimental Section

Caution: Generally peroxides are extremely dangerous materials, which may lead to severe and spontaneous explosions under impact, friction, and temperature changes. The synthesis of these substances may only be carried out by qualified personnel, using appropriate safety measures (reinforced goggles and gloves, splinter-proof vessels, etc.) and in small quantities. Transition metal salts, heating, and shaking should be avoided whenever possible. Working with larger amounts of peroxides significantly increases the danger of spontaneous explosions.

Synthesis of 7-Butyl-1,4-dimethyl-2,3,5,6-tetraoxabicyclo[2.2.1]-heptane 2a with H_2SO_4 (Run 9, Table 1). A solution of H_2SO_4 (2 g, 0.02 mol) in EtOH (2 mL) was added with stirring to a mixture of **1a** (1.92 mmol, 0.3 g) and 37% H_2O_2 (0.53 g, 5.76 mmol) in EtOH (3 mL) at 10−15 °C. The reaction mixture was stirred at 20−25 °C for 1 h. Then CH_2Cl_2 (30 mL) was added. The organic layer was washed with water (2 × 10 mL), a 5% aqueous $NaHCO_3$ solution (2 × 10 mL), and again with water (2 × 10 mL), dried with Na_2SO_4, and filtered. The solvent was removed using a water-jet vacuum pump. Product **2a** was isolated by silica gel chromatography with elution by a petroleum ether−ethyl acetate mixture using the gradient of the latter from 0 to 30%. Product **2a** was obtained in 77% yield (0.28 g, 1.48 mmol) as an oil. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ: 0.94 (t, 3H, J = 6.6 Hz), 1.30−1.64 (m, 12H), 2.61 (t, 1H, J = 5.9 Hz). ^{13}C NMR (50.32 MHz, $CDCl_3$) δ: 9.7, 13.7, 22.7, 23.4, 29.6, 58.9, 110.7. Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.61; H, 8.44.

Synthesis of 7-Butyl-1,4-dimethyl-2,3,5,6-tetraoxabicyclo[2.2.1]-heptane 2a with HBF_4 (Run 18, Table 2). A 50% aqueous HBF_4 solution (4 g, 0.023 mol) in EtOH (2 mL) was added with stirring to a mixture of diketone **1a** (1.92 mmol, 0.3 g) and 37% H_2O_2 (0.53 g, 5.76 mmol) in EtOH (3 mL) at 10−15 °C. The reaction mixture was stirred at 20−25 °C for 1 h. The product was isolated as described in run 9 (Table 1). Compound **2a** was obtained in 77% yield (0.28 g, 1.48 mmol).

Synthesis of Ethyl 3-(1,4-Dimethyl-2,3,5,6-tetraoxabicyclo[2.2.1]-hept-7-yl)propanoate 2e (Table 3). A 37% aqueous H_2O_2 solution (0.41 g, 4.5 mmol) was added to a solution of β-diketone **1e** (0.3 g, 1.5 mmol) in EtOH (3 mL), the reaction mixture was cooled to 10 °C, and a solution of H_2SO_4 (2 g, 0.02 mol) in EtOH (2 mL) was added with stirring. The reaction mixture was stirred at 20−25 °C for 1 h. The product was isolated as described in run 9 (Table 1). Compound **2e** was obtained in 55% yield (0.19 g, 0.82 mmol) as an oil. ^{1}H NMR (200.13 MHz, $CDCl_3$) δ: 1.25 (t, 3H, J = 7.1 Hz), 1.54 (s, 6H), 1.89 (q, 2H, J = 6.8 Hz), 2.48 (t, 2H, J = 7.3 Hz), 2.66 (t, 1H, J = 5.9 Hz), 4.14 (q, 2H, J = 7.1 Hz). ^{13}C NMR (50.32 MHz, $CDCl_3$) δ: 9.5, 14.0, 18.9, 31.5, 58.0, 60.6, 110.6, 172.3. Anal. Calcd for $C_{10}H_{16}O_6$: C, 51.72; H, 6.94. Found: C, 51.57; H, 6.81.

Synthesis of 3-(1,4-Dimethyl-2,3,5,6-tetraoxabicyclo[2.2.1]hept-7-yl)propanoic Acid 8 by Hydrolysis of Ethyl 3-(1,4-Dimethyl-2,3,5,6-tetraoxabicyclo[2.2.1]hept-7-yl)propanoate 2e. A solution of KOH (0.48 g, 8.62 mmol) in water (2 mL) was added with stirring to a solution of ester **2e** (1 g, 4.31 mmol) in EtOH (5 mL) at 10 °C. The reaction mixture was stirred at 20−25 °C for 1 h. Water (10 mL) was added, and the water layer was washed with methylene chloride (30 mL) and acidified with H_2SO_4 (0.86 g, 8.8 mmol). Acid **8** was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with water (5 mL), dried with Na_2SO_4, and filtered. The solvent was removed using a water-jet vacuum

pump. Acid **8** was isolated by silica gel chromatography with elution by a petroleum ether−ethyl acetate mixture using the gradient of the latter from 50 to 90%. Acid **8** was obtained in 68% yield (0.6 g, 2.93 mmol) as white crystals. Mp = 92−93 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ: 1.57 (s, 6H), 1.94 (q, 2H, J = 7.1 Hz), 2.58 (t, 2H, J = 7.3 Hz), 2.72 (t, 1H, J = 5.9 Hz), 9.13−9.49 (br s, 1H). ^{13}C NMR (75.48 MHz, $CDCl_3$) δ: 9.9, 19.0, 31.6, 58.2, 110.8, 178.5. Anal. Calcd for $C_8H_{12}O_6$: C, 47.06; H, 5.92. Found: C, 47.24; H, 5.83.

Acknowledgment. This work is supported by the Program for Support of Leading Scientific Schools of the Russian Federation (Grant NSh 2942.2008.3) and the Grant of President of the Russian Federation (no. MK-3515.2007.3).

Supporting Information Available: Experimental procedures for the synthesis of 1,2,4,5-tetraoxanes, ^{1}H and ^{13}C NMR spectra for 1,2,4,5-tetraoxanes and β-diketones, and details of X-ray data for **2d** and **2h**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO900226B