

SUPPORTING INFORMATION (Part 1/2)

Facile and selective procedure for the synthesis of bridged 1,2,4,5-tetraoxanes. Strong acids as cosolvents and catalysts for the addition of hydrogen peroxide to β -diketones.

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General Methods

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. The avoidance of transition metal salts, heating and shaking, should be taken whenever possible. Working with larger amounts of peroxides significantly increases the danger of spontaneous explosions.

NMR spectra were recorded on commercial instruments (200.13 MHz for ^1H , 50.32 MHz for ^{13}C ; 300.13 MHz for ^1H , 75.48 MHz for ^{13}C) in CDCl_3 . The TLC analysis was carried out on standard silica gel chromatography plates. The melting points were determined on a Kofler hot-stage apparatus. Chromatography was performed on silica gel (63-200 mesh). Acetylacetone, 1,3-cyclohexanedione, H_2SO_4 , HClO_4 (60% aqueous solution), HBF_4 (50% aqueous solution), H_3PO_4 , $\text{BF}_3 \cdot \text{Et}_2\text{O}$, 50% MCPBA, tetrahydrofuran (THF), petroleum ether (PE), ethyl acetate (EA), EtOH, MeOH, Et_2O , i-PrOH, CH_3CN , 37% aqueous H_2O_2 solution, benzyl- and alkylbromides, acrylonitrile, and methyl acrylate were purchased from commercial supplier.

Synthesis of β -diketones

β -Diketones were prepared in accordance with known methods.

1a [Bloomfield, J.J. *J. Org. Chem.* **1961**, 26, 4112 – 4115]

1b [Shono, T.; Kashimura, S.; Sawamura, M.; Soejima, T. *J. Org. Chem.* **1988**, 53, 907 – 910]

1c [Kalaitzakis, D.; Rozzell, J. D.; Smonou, I.; Kambourakis, S. *Adv. Synth. Cat.* **2006**, 348, 1958–1969]

1d [Markisz, J.A.; Gettler, J.D. *Can. J. Chem.* **1969**, 47, 1965 – 1979]

1e [Kluiber, R.W.; Oberender, F.; Rossi, C. *J. Org. Chem.* **1960**, 25, 1069 – 1070]

1f [Klimochkin, Yu.N.; Tilli, T.S.; Moiseev, I.K.; *Journal of Organic Chemistry USSR (English Translation)* **1988**, 24, 1605 – 1606 [*Zhurnal Organicheskoi Khimii (Russian)* 1988, 24, 1780 - 1781]

1g [House, H.O.; Gannon, W.F. *J. Org. Chem.* **1958**, 23, 879 – 884]

1i [Sakai, T.; Miyata, K.; Tsuboi, S.; Utaka, M. *Bull. Chem. Soc. Japan* **1989**, 62, 4072 – 4074]

1k [Marquet, J.; Moreno-Manas, M.; Pacheco, P.; Prat, M.; Katritzky, A.R.; Brycki, B. *Tetrahedron* **1990**, 46, 5333 – 5346]

1l [Kaiho, T.; Sannohe, K.; Kajiya, S.; Suzuki, T.; Otsuka, K.; Ito, T., Kamiya, J., Maruyama, M. *J. Med. Chem.* **1989**, 32, 351 – 357]

β -Diketone **1h** was prepared similarly to [Sakai, T.; Miyata, K.; Tsuboi, S.; Utaka, M. *Bull. Chem. Soc. Japan* **1989**, 62, 4072 – 4074] in 38% yield.

β -Diketone **1j** was prepared similarly to [Bloomfield, J.J. *J. Org. Chem.* **1961**, 26, 4112 – 4115] in 32% yield.

NMR spectra of β -diketones:

3-Butylpentane-2,4-dione, 1a.

Colorless oil.

^1H NMR (300.13 MHz, CDCl_3), δ : 0.73-0.87 (m, 3H), 1.03-1.31 (m, 4H), 1.72 (q, 2H, $J = 7.7$ Hz), 2.02 (s, 1.8H), 2.06 (s, 4.2H), 3.51 (t, 0.7H, $J = 7.3$ Hz), 16.57-16.59 (br. s, 0.3H).

3-Butyl-3-methylpentane-2,4-dione, 1b.

Colorless oil.

^1H NMR (300.13 MHz, CDCl_3), δ : 0.85 (t, 3H, $J = 7.3$ Hz), 0.97-1.85 (m, 9H), 2.05 (s, 6H).

3-Allylpentane-2,4-dione, 1c.

Colorless oil.

^1H NMR (300.13 MHz, CDCl_3), δ : 2.04 (s, 3H), 2.13 (s, 3H), 2.53 (m, 1H), 2.93 (d, 1H, $J = 5.1$ Hz), 3.68 (t, 0.5H, $J = 7.3$ Hz), 4.86-5.98 (m, 3H), 16.67-16.69 (br. s, 0.5H).

4-Acetyl-5-oxohexanenitrile, 1d.

White crystals. $\text{Mp} = 72-73$ °C.

^1H NMR (300.13 MHz, CDCl_3), δ : 1.99-2.19 (m, 8H), 2.25-2.43 (m, 2H), 2.57 (t, 0.7H, $J = 7.3$ Hz), 3.77 (t, 0.65H, $J = 6.6$ Hz), 16.82-16.86 (br. s, 0.35H).

Ethyl 4-acetyl-5-oxohexanoate, 1e.

Colorless oil.

^1H NMR (300.13 MHz, CDCl_3), δ : 1.16 -1.24 (m, 3H), 2.03-2.57 (m, 10H), 3.69 (t, 0.7H, $J = 7.0$ Hz), 4.02-4.13 (m, 2H), 16.69-16.71 (br. s, 0.3H).

3-(1-Adamantyl)pentane-2,4-dione, 1f.

White crystals. $\text{Mp} = 55-56$ °C.

^1H NMR (300.13 MHz, CDCl_3), δ : 1.56-1.73, 1.92-2.00 (m, 15H), 2.18 (s, 6H), 3.51 (s, 1H).

3-Benzylpentane-2,4-dione, 1g.

Colorless oil.

^1H NMR (300.13 MHz, CDCl_3), δ : 2.08 (s, 3H), 2.13 (s, 3H), 3.15 (d, 1H, $J = 7.3$ Hz), 3.67 (s, 1H), 4.03 (t, 0.5H, $J = 7.3$ Hz), 7.10-7.42 (m, 5H), 16.85-16.87 (br. s, 0.5H).

3-(3-Methylbenzyl)pentane-2,4-dione, 1h.

Colorless oil.

^1H NMR (300.13 MHz, CDCl_3), δ : 2.07 (s, 3H), 2.13 (s, 3H), 2.31, 2.33 (s, 3H), 3.11 (d, 1H, $J = 8.1$ Hz), 3.63 (s, 1H), 4.03 (t, 0.5H, $J = 7.7$ Hz), 6.80-7.32 (m, 4H), 16.84-16.88 (br. s, 0.5H). ^{13}C NMR (75.48 MHz, CDCl_3), δ : 21.1, 21.2, 23.0, 29.5, 32.5, 33.9, 69.5, 108.1, 124.2, 125.3, 126.8, 127.2, 127.9, 128.3, 129.1, 137.8, 138.0, 139.4, 191.6, 203.3. Anal. Calcd for $\text{C}_{13}\text{H}_{16}\text{O}_2$: C, 76.44; H, 7.90. Found: C, 76.64; H, 7.75.

3-(4-Methylbenzyl)pentane-2,4-dione, 1i.

Colorless oil.

^1H NMR (300.13 MHz, CDCl_3), δ : 2.06 (s, 3H), 2.12 (s, 3H), 2.30, 2.32 (s, 3H), 3.10 (d, 1H, $J = 7.3$ Hz), 3.61 (s, 1H), 3.99 (t, 0.5H, $J = 7.3$ Hz), 6.97-7.15 (m, 4H), 16.81-16.83 (br. s, 0.5H).

3-(2-Methoxybenzyl)pentane-2,4-dione, 1j.

White crystals. $\text{Mp} = 86-88$ °C.

^1H NMR (300.13 MHz, CDCl_3), δ : 2.05 (s, 4H), 2.15 (s, 2H), 3.14 (d, 0.7H, $J = 6.6$ Hz), 3.59 (s, 1.3H), 3.85 (s, 1H), 3.88 (s, 2H), 4.09 (t, 0.3H, $J = 7.3$ Hz), 6.81-7.28 (m, 4H), 16.86-16.88 (br. s, 0.7H). ^{13}C NMR (75.48 MHz, CDCl_3), δ : 23.1, 26.8, 55.2, 107.4, 109.8, 120.5, 127.3, 127.7, 157.2, 192.07. Anal. Calcd for $\text{C}_{13}\text{H}_{16}\text{O}_3$: C, 70.89; H, 7.32. Found: C, 70.56; H, 7.13.

3-(4-Nitrobenzyl)pentane-2,4-dione (1k).

Slightly yellow crystals. $\text{Mp} = 90-91$ °C.

^1H NMR (300.13 MHz, CDCl_3), δ : 2.05 (s, 6H), 3.76 (s, 2H), 7.31 (d, 2H, $J = 8.1$ Hz), 8.17 (d, 2H, $J = 8.8$ Hz), 16.84-16.86 (br. s, 1H).

2-Acetylcyclohexanone (1l).

Colorless oil.

^1H NMR (300.13 MHz, CDCl_3), δ : 1.57-1.69 (m, 4H), 2.07 (s, 3H), 2.22-2.32 (m, 4H), 15.85-15.87 (br.s, 1H).

Synthesis of 1,2,4,5-tetraoxanes

Procedure for the synthesis of 1,2,4,5-tetraoxane 2a with the use of H₂SO₄ (Table 1, experiments 1-15).

A solution of H₂SO₄ (0.1-4 g, 0.001-0.04 mol) in EtOH (i-PrOH, THF, CH₃CN; 2 mL) was added with stirring to a mixture of **1a** (0.3 g, 1.92 mmol) and 37% H₂O₂ (0.18-1.24 g, 1.92-13.44 mmol) in EtOH (3 mL) at 10°C. The reaction mixture was stirred at 20-25°C for 1 h. Then CH₂Cl₂ (30 mL) was added. The organic layer was washed with water (2×10 mL), a 5% aqueous NaHCO₃ solution (2×10 mL), and again with water (2×10 mL), dried with Na₂SO₄, 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%.

General procedure for the synthesis of tetraoxane 2a with the use of H₃PO₄, HBF₄ (50% aqueous solution), and HClO₄ (60% aqueous solution) (Table 2, experiments 16-21).

A 37% aqueous H₂O₂ solution (0.53 g, 5.76 mmol) and then a solution of H₃PO₄ (50% HBF₄ or 60% HClO₄; 1-5 g, 11.36-56.82 mmol) in EtOH (2 mL) were added with stirring at 10 °C to a solution of β-diketone **1a** (0.3 g, 1.92 mmol) in EtOH (3 mL). The reaction mixture was stirred at 20-25 °C for 1 h. Then CH₂Cl₂ (30 mL) was added. The organic layer was washed with water (2×10 mL), a 5% aqueous NaHCO₃ solution (2×10 mL), and again with water (2×10 mL), dried with Na₂SO₄, 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%.

General procedure for the synthesis of tetraoxane 2a with the use of BF₃•Et₂O (Table 2, experiments 22-25).

A 2.53 M ether H_2O_2 solution (2.28 mL, 5.76 mmol) and then a $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.5–4 g, 3.52–28.17 mmol) solution in Et_2O (2 mL) were added with stirring at 10 °C to a solution of β -diketone **1a** (0.3 g, 1.92 mmol) in Et_2O (3 mL). 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%.

General procedure for the synthesis of tetraoxanes 2a-i (Table 3).

A 37% aqueous H_2O_2 solution (0.41 g, 4.5 mmol) was added to a solution of β -diketone **1a-i** (0.3 g, 1.20–2.14 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. 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-i** 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%.

Synthesis of 7-(2-methoxybenzyl)-1,4-dimethyl-2,3,5,6-tetraoxa-bicyclo[2.2.1]heptane 2j and 1,4-dimethyl-7-(4-nitrobenzyl)-2,3,5,6-tetraoxabicyclo[2.2.1]heptane 2k.

A 37% aqueous H_2O_2 solution (0.37 g, 4.1 mmol) was added to a solution of β -diketone **1j,k** (0.3 g, 1.36 mmol (**1j**) or 1.28 mmol (**1k**)) in EtOH (6 mL), the reaction mixture was cooled to 10 °C, and a solution of H_2SO_4 (4 g, 0.04 mol) in EtOH (4 mL) was added with stirring. The reaction mixture was stirred at 20–25 °C for 3 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

Na₂SO₄, and filtered. The solvent was removed using a water-jet vacuum pump. Products **2j,k** were isolated by silica gel chromatography with elution by a petroleum ether – ethyl acetate mixture using the gradient of the latter from 20 to 50%. Compounds **2j** and **2k** were accordingly obtained in 54% (0.19 g, 0.74 mmol) and 58% (0.2 g, 0.74 mmol) yields.

Synthesis of 3-methylhexahydro-3,7a-epidioxy-1,2-benzodioxole 2l.

A 37% aqueous H₂O₂ solution (0.59 g, 6.42 mmol) and then a solution of H₂SO₄ (2 g, 0.02 mol) in THF (2 mL) were added to a solution of β -diketone **1l** (0.3 g, 2.14 mmol) in THF (3 mL) with stirring at 10°C. The reaction mixture was stirred at 20-25°C for 0.5 h. Then CH₂Cl₂ (30 mL) was added. The organic layer was washed with water (2×10 mL), a 5% aqueous NaHCO₃ solution (2×10 mL), and again with water (2×10 mL), dried with Na₂SO₄, and filtered. The solvent was removed using a water-jet vacuum pump. Product **2l** 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 **2l** was obtained in 48% yield (0.18 g, 1.03 mmol).

Oxidation of 1,3-cyclohexanedione 3. Synthesis of diethyl hexanedioate 4.

A solution of H₂SO₄ (2 g, 0.02 mol) in EtOH (2 mL) was added with stirring to a mixture of **3** (0.3 g, 2.67 mmol) and 37% H₂O₂ (0.74 g, 8.03 mmol) in EtOH (3 mL) at 10°C. The reaction mixture was stirred at 20-25°C for 1 h. Then CH₂Cl₂ (30 mL) was added. The organic layer was washed with water (2×10 mL), a 5% aqueous NaHCO₃ solution (2×10 mL), and again with water (2×10 mL), dried with Na₂SO₄, and filtered. The solvent was removed using a water-jet vacuum pump. Product **4** was isolated by silica gel chromatography with elution by a petroleum ether – ethyl acetate mixture using the gradient of the latter from 0 to 15%. Diethyl hexanedioate **4** was obtained in 82% yield (0.41 g, 2.18 mmol).

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 at 10°C to a solution of **2e** (1 g, 4.31 mmol) in EtOH (5 mL). 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 by H₂SO₄ (0.86 g, 8.8 mmol). Acid **8** was extracted with CH₂Cl₂ (3×30 mL). The combined organic extracts were washed with water (5 mL) and dried with Na₂SO₄. The solvent was removed using a water-jet vacuum pump. Product **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%. 3-(1,4-Dimethyl-2,3,5,6-tetraoxabicyclo[2.2.1]hept-7-yl)propanoic acid **8** was obtained in 68% yield (0.59 g, 2.93 mmol).

Synthesis of 7-(2,3-dibromopropyl)-1,4-dimethyl-2,3,5,6-tetraoxa-bicyclo[2.2.1]heptane **5 from 7-allyl-1,4-dimethyl-2,3,5,6-tetraoxa-bicyclo[2.2.1]heptane **2c**.**

Bromine (0.31 g, 1.94 mmol) was added in portions to a solution of **2c** (0.3 g, 1.74 mmol) in CH₂Cl₂ (10 mL) at 0°C. The reaction mixture was stirred at 0°C for 20 min. Methylene chloride was removed using a water-jet vacuum pump. Product **5** 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%. 7-(2,3-Dibromopropyl)-1,4-dimethyl-2,3,5,6-tetraoxa-bicyclo[2.2.1]heptane **5** was obtained in 81% yield (0.47 g, 1.41 mmol).

Synthesis of 1,4-dimethyl-7-(oxiran-2-ylmethyl)-2,3,5,6-tetraoxabicyclo[2.2.1]heptane **6 from 7-allyl-1,4-dimethyl-2,3,5,6-tetraoxa-bicyclo[2.2.1]heptane **2c**.**

50% MCPBA (0.6 g, 3.48 mmol) was added to a solution of **2c** (0.3 g, 1.74 mmol) in Et₂O (5 mL). The reaction mixture was stirred at 20-25°C for 96 h. Methylene chloride (20 mL) was added and the organic

layer was washed with water (2×10 mL), a 5% water solution of NaHCO₃ (4×5 mL), and again with water (2×10 mL). The solvent was removed using a water-jet vacuum pump. Product **6** was isolated by silica gel chromatography with elution by a petroleum ether – ethyl acetate mixture using the gradient of the latter from 20 to 50%. 1,4-Dimethyl-7-(oxiran-2-ylmethyl)-2,3,5,6-tetraoxabicyclo[2.2.1]heptane **6** was obtained in 68% yield (0.23 g, 1.2 mmol).

Synthesis of 7-(3-bromo-2-methoxypropyl)-1,4-dimethyl-2,3,5,6-tetraoxabicyclo[2.2.1]heptane 7 from 7-allyl-1,4-dimethyl-2,3,5,6-tetraoxa-bicyclo[2.2.1]heptane 2c.

Hg(OAc)₂ (0.67 g, 2.09 mmol) was added to a solution of **2c** (0.3 g, 1.74 mmol) in MeOH (5 mL). The reaction mixture was stirred at 20-25°C for 1 h. Bromine (0.28 g, 1.74 mmol) was added and reaction mixture was stirred for 20 min at 20-25°C. Methylene chloride (20 mL) was added and the organic layer was washed with water (3×10 mL). The solvent was removed using a water-jet vacuum pump. Product **7** was isolated by silica gel chromatography with elution by a petroleum ether – ethyl acetate mixture using the gradient of the latter from 20 to 50%. 7-(3-Bromo-2-methoxypropyl)-1,4-dimethyl-2,3,5,6-tetraoxabicyclo[2.2.1]heptane **7** was obtained in 92% yield (0.45 g, 1.60 mmol).

Synthesis of 4-[3-(1,4-dimethyl-2,3,5,6-tetraoxabicyclo[2.2.1]hept-7-yl)propanoyl]morpholine 9 from 3-(1,4-dimethyl-2,3,5,6-tetraoxabicyclo[2.2.1]hept-7-yl)propanoic acid 8.

An Et₃N (0.20 g, 1.96 mmol) and then ethylchloroformate (0.21 g, 1.96 mmol) were added to a solution of **8** (0.2 g, 0.98 mmol) in CH₂Cl₂ (20 mL) at 0°C. The reaction mixture was stirred at 0°C for 1h. Then morpholine (0.26 g, 2.94 mmol) was added and reaction mixture was stirred for 1 h at 0°C. Methylene chloride (20 mL) was added and the organic phase was washed with water (10 mL), a 5% water solution of H₂SO₄ (2×10 mL), a 5% water solution of NaHCO₃ (2×10 mL), and again with water (10 mL). Organic layer was dried over Na₂SO₄, filtered, and the solvent was removed using a water-jet

vacuum pump. Product **8** was isolated by silica gel chromatography with elution by a petroleum ether – ethyl acetate mixture using the gradient of the latter from 30 to 90%. 4-[3-(1,4-Dimethyl-2,3,5,6-tetraoxabicyclo[2.2.1]hept-7-yl)propanoyl]morpholine **9** was obtained in 85% yield (0.23 g, 0.82 mmol).

NMR spectra of 1,2,4,5-tetraoxanes.

7-butyl-1,4-dimethyl-2,3,5,6-tetraoxa-bicyclo[2.2.1]heptane, 2a.

Oil. R_f=0.61 (TLC, hexane – EA, 5:1).

¹H NMR (300.13 MHz, CDCl₃), δ: 0.92 (t, 3H, J= 6.6 Hz), 1.30-1.61 (m, 12H), 2.59 (t, 1H, J= 5.9 Hz).

¹³C NMR (50.32 MHz, CDCl₃), δ: 9.8, 13.8, 22.8, 23.5, 29.7, 59.0, 110.8. Anal. Calcd for C₉H₁₆O₄: C, 57.43; H, 8.57. Found: C, 57.27; H, 8.77.

7-butyl-1,4,7-trimethyl-2,3,5,6-tetraoxabicyclo[2.2.1]heptane, 2b.

Oil. R_f=0.63 (TLC, hexane – EA, 5:1).

¹H NMR (300.13 MHz, CDCl₃), δ: 0.88 (t, 3H, J= 6.6 Hz), 1.14 (s, 3H), 1.28-1.59 (m, 12H). ¹³C NMR (75.48 MHz, CDCl₃), δ: 8.7, 13.2, 13.8, 23.5, 26.3, 30.0, 58.4, 111.9. Anal. Calcd for C₁₀H₁₈O₄: C, 59.39; H, 8.97. Found: C, 59.47; H, 8.76.

7-Allyl-1,4-dimethyl-2,3,5,6-tetraoxa-bicyclo[2.2.1]heptane, 2c.

Oil. R_f= 0.47 (TLC, hexane – EA, 5:1).

¹H NMR (300.13 MHz, CDCl₃), δ: 1.50 (s, 6H), 2.35 (t, 2H, J= 7.0 Hz), 2.75 (t, 1H, J= 6.6 Hz), 4.96-5.26 (m, 2H), 5.65-5.91 (m, 1H). ¹³C NMR (75.48 MHz, CDCl₃), δ: 9.8, 28.4, 57.6, 110.5, 117.8, 133.9. Anal. Calcd for C₈H₁₂O₄: C, 55.81; H, 7.02. Found: C, 55.97; H, 7.24.

3-(1,4-Dimethyl-2,3,5,6-tetraoxa-bicyclo[2.2.1]heptan-7-yl)propanenitrile, 2d.

White crystals. Mp= 79-80 °C. R_f= 0.53 (TLC, hexane – EA, 1:2).

¹H NMR (300.13 MHz, CDCl₃), δ: 1.59 (s, 6H), 1.97 (q, 2H, J= 6.6 Hz), 2.57 (t, 2H, J= 7.3 Hz), 2.83 (t, 1H, J= 5.9 Hz). ¹³C NMR (75.48 MHz, CDCl₃), δ: 9.8, 15.6, 20.1, 57.3, 110.4, 118.4. Anal. Calcd for C₈H₁₁NO₄: C, 51.89; H, 5.99; N, 7.56. Found: C, 52.14; H, 6.10; N, 7.55.

Ethyl 3-(1,4-dimethyl-2,3,5,6-tetraoxabicyclo[2.2.1]hept-7-yl)propanoate, 2e.

Oil. R_f= 0.62 (TLC, hexane – EA, 2:1).

¹H NMR (200.13 MHz, CDCl₃), δ: 1.22 (t, 3H, J= 7.1 Hz), 1.51 (s, 6H), 1.86 (q, 2H, J= 6.8 Hz), 2.45 (t, 2H, J= 7.3 Hz), 2.63 (t, 1H, J= 5.9 Hz), 4.11 (q, 2H, J= 7.1 Hz). ¹³C NMR (50.32 MHz, CDCl₃), δ:

9.6, 14.0, 18.9, 31.6, 58.0, 60.7, 110.6, 172.3. Anal. Calcd for C₁₀H₁₆O₆: C, 51.72; H, 6.94. Found: C, 51.72; H, 6.94.

7-(1-Adamantyl)-1,4-dimethyl-2,3,5,6-tetraoxabicyclo[2.2.1]heptane, 2f.

White crystals. Mp= 130-131 °C (partially decomposed). Rf= 0.60 (TLC, hexane – EA, 5:1).

¹H NMR (300.13 MHz, CDCl₃), δ: 1.63-2.04 (m, 21H), 2.37 (s, 1H). ¹³C NMR (75.48 MHz, CDCl₃), δ: 12.7, 28.3, 33.0, 36.7, 40.6, 66.8, 110.6. Anal. Calcd for C₁₅H₂₂O₄: C, 67.64; H, 8.33. Found: 67.28; H, 8.69.

7-Benzyl-1,4-dimethyl-2,3,5,6-tetraoxa-bicyclo[2.2.1]heptane, 2g.

White crystals. Mp= 58-60 °C. Rf= 0.45 (TLC, hexane – EA, 5:1).

¹H NMR (300.13 MHz, CDCl₃), δ: 1.41 (s, 6H), 2.96 (d, 2H, J= 7.3 Hz), 3.13 (t, 1H, J= 7.0 Hz), 7.24-7.40 (m, 4H). ¹³C NMR (75.48 MHz, CDCl₃), δ: 9.8, 30.2, 59.2, 110.6, 126.9, 128.3, 128.8, 137.2. Anal. Calcd for C₁₂H₁₄O₄: C, 64.85; H, 6.35. Found: C, 64.96; 6.38.

1,4-Dimethyl-7-(3-methylbenzyl)-2,3,5,6-tetraoxa-bicyclo[2.2.1]heptane, 2h.

White crystals. Mp= 76-77 °C. Rf= 0.54 (TLC, hexane – EA, 5:1).

¹H NMR (300.13 MHz, CDCl₃), δ: 1.39 (s, 6H), 2.34 (s, 3H), 2.89 (d, 2H, J= 7.3 Hz), 3.09 (t, 1H J= 7.0 Hz), 6.98-7.27 (m, 4H). ¹³C NMR (75.48 MHz, CDCl₃), δ: 9.8, 21.4, 30.2, 59.3, 110.7, 125.8, 127.6, 128.7, 129.6, 137.1, 138.5. Anal. Calcd for C₁₃H₁₆O₄: C, 66.09; H, 6.83. Found: C, 65.81; H, 7.29.

1,4-Dimethyl-7-(4-methylbenzyl)-2,3,5,6-tetraoxa-bicyclo[2.2.1]heptane, 2i.

White crystals. Mp= 60-62 °C. Rf= 0.62 (TLC, hexane – EA, 2:1).

¹H NMR (300.13 MHz, CDCl₃), δ: 1.39 (s, 6H), 2.33 (s, 3H), 2.90 (d, 2H, J= 7.3 Hz), 3.08 (t, 1H, J= 7.3), 7.14 (s, 4H). ¹³C NMR (75.48 MHz, CDCl₃), δ: 9.8, 21.0, 29.8, 59.3, 110.6, 128.6, 129.4, 134.0, 136.5. Anal. Calcd for C₁₃H₁₆O₄: C, 66.09; H, 6.83. Found: C, 66.20; H, 7.14.

7-(2-Methoxybenzyl)-1,4-dimethyl-2,3,5,6-tetraoxa-bicyclo[2.2.1]heptane, 2j.

White crystals. Mp= 46-48 °C, Rf=0.38 (TLC, hexane – EA, 5:1).

¹H NMR (300.13 MHz, CDCl₃), δ: 1.45 (s, 6H), 2.91 (d, 2H, J= 6.6 Hz), 3.19 (t, 1H, J= 6.6 Hz), 3.88 (s, 3H), 6.88-7.32 (m, 4H). ¹³C NMR (75.48 MHz, CDCl₃), δ: 9.6, 26.0, 55.2, 57.8, 110.3, 110.9, 120.4, 125.8, 128.3, 130.9, 157.4. Anal. Calcd for C₁₃H₁₆O₅: C, 61.90; H, 6.39. Found: C, 62.32; H, 6.68.

1,4-Dimethyl-7-(4-nitrobenzyl)-2,3,5,6-tetraoxabicyclo[2.2.1]heptane, 2k.

Yellowish crystals. Mp= 141-142 °C (with decomposition). Rf= 0.68 (TLC, hexane – EA, 2:1).

¹H NMR (300.13 MHz, CDCl₃), δ: 1.40 (s, 6H), 3.05 (d, 2H, J= 6.6), 3.13 (t, 1H, J= 7.3 Hz), 7.46 (d, 2H, J= 8.8 Hz), 8.22 (d, 2H, J= 8.8). ¹³C NMR (75.48 MHz, CDCl₃), δ: 9.9, 30.2, 58.6, 110.4, 124.1, 129.7, 144.9, 147.1. Anal. Calcd for C₁₂H₁₃NO₆: C, 53.93; H, 4.90; N, 5.24. Found: C, 53.90; H, 4.98; N, 5.22.

3-Methylhexahydro-3,7a-epidioxy-1,2-benzodioxole, 2l.

White crystals. Mp=31-33 °C. Rf=0.44 (TLC, hexane – EA, 5:1).

¹H NMR (300.13 MHz, CDCl₃), δ: 1.20-2.13 (m, 11H), 2.59 (m, 1H). ¹³C NMR (75.48 MHz, CDCl₃), δ: 9.0, 21.3, 21.7, 23.1, 23.3, 58.0, 108.9, 109.3.

Anal. Calcd for C₈H₁₂O₄: C, 55.81; H, 7.02. Found: 55.74; H, 7.15.

Diethyl pentanedioate, 4.

¹H NMR (300.13 MHz, CDCl₃) 1.19 (t, 6H, J=7.2 Hz), 1.88 (m, 2H), 2.32 (m, 4H), 4.06 (q, 4H, J=7.2 Hz).

7-(2,3-Dibromopropyl)-1,4-dimethyl-2,3,5,6-tetraoxa-bicyclo[2.2.1]heptane, 5.

Oil. Rf=0.47 (TLC, hexane – EA, 2:1).

¹H NMR (300.13 MHz, CDCl₃), δ: 1.57, 1.60 (s, 6H), 1.91-2.04, 2.52-2.63 (m, 2H), 2.98 (dd, 1H, J= 2.6, 5.2 Hz), 3.62 (m, 1H), 3.92 (m, 1H), 4.14-4.25 (m, 1H). ¹³C NMR (75.48 MHz, CDCl₃), δ: 9.6, 9.8, 31.1, 35.5, 49.6, 57.1, 110.5, 110.8. Anal. Calcd for C₈H₁₂Br₂O₄: C, 28.94; H, 3.64; Br, 48.14. Found: C, 28.73; H, 3.67; Br, 48.31.

1,4-Dimethyl-7-(oxiran-2-ylmethyl)-2,3,5,6-tetraoxabicyclo[2.2.1]heptane, 6.

Oil. Rf=0.46 (TLC, hexane – EA, 1:1).

¹H NMR (300.13 MHz, CDCl₃), δ: 1.58 (br.s, 6H), 2.01-2.11 (m, 2H), 2.54-2.58 (m, 1H), 2.82-2.91 (m, 2H), 3.02-3.10 (m, 1H). ¹³C NMR (75.48 MHz, CDCl₃), δ: 9.6, 9.8, 27.4, 47.2, 49.9, 56.7, 110.6, 110.8. Anal. Calcd for C₈H₁₂O₅: C, 51.06; H, 6.43. Found: C, 51.25; H, 6.49.

7-(3-Bromo-2-methoxypropyl)-1,4-dimethyl-2,3,5,6-tetraoxabicyclo[2.2.1]heptane, 7.

White crystals. Mp= 125-126 °C. Rf= 0.41 (TLC, hexane – EA, 2:1).

¹H NMR (300.13 MHz, CDCl₃), δ: 1.53, 1.55 (s, 6H), 1.67-1.80 (m, 2H), 2.19-2.29 (m, 1H, dd, J = 3.7, 8.8 Hz), 2.53 (m, 1H, dd, J = 5.5, 6.6 Hz), 2.90 (m, 1H), 3.38 (s, 3H), 3.88-3.99 (m, 1H). ¹³C NMR (75.48 MHz, CDCl₃), δ: 9.8, 10.1, 34.0, 41.2, 56.0, 56.6, 77.7, 110.7, 111.2. Anal. Calcd for C₉H₁₅BrO₅: C, 38.18; H, 5.34; Br, 28.22. Found: C, 38.22; H, 5.40; Br, 28.47.

3-(1,4-Dimethyl-2,3,5,6-tetraoxabicyclo[2.2.1]hept-7-yl)propanoic acid, 8.

White crystals. Mp = 92-93 °C. Rf = 0.43 (TLC, hexane – EA, 1:1).

¹H NMR (300.13 MHz, CDCl₃), δ: 1.55 (s, 6H), 1.92 (q, 2H, J = 7.1 Hz), 2.56 (t, 2H, J = 7.3 Hz), 2.70 (t, 1H, J = 5.9 Hz), 9.14-9.48 (br. s, 1H). ¹³C NMR (75.48 MHz, CDCl₃), δ: 9.7, 18.8, 31.5, 58.0, 110.7, 178.3. Anal. Calcd for C₈H₁₂O₆: C, 47.06; H, 5.92. Found: C, 47.33; H, 5.78.

4-[3-(1,4-Dimethyl-2,3,5,6-tetraoxabicyclo[2.2.1]hept-7-yl)propanoyl]morpholine, 9.

White crystals. Mp= 112-113 °C. Rf= 0.46 (TLC, EA).

¹H NMR (300.13 MHz, CDCl₃), δ: 1.54 (s, 6H), 1.90 (q, 2H, J = 6.6 Hz), 2.46 (t, 2H, J = 7.0 Hz), 2.72 (t, 1H, J = 5.5 Hz), 3.40-3.68 (m, 8H). ¹³C NMR (75.48 MHz, CDCl₃), δ: 9.7, 18.8, 30.0, 41.9, 45.6, 58.3, 66.4, 66.7, 110.7, 169.9. Anal. Calcd for C₁₂H₁₉NO₆: C, 52.74; H, 7.01; N, 5.13. Found: C, 52.48; H, 7.12; N, 5.34.

X-Ray single-crystal diffraction of **2h** and **2d**.

The single-crystal X-ray diffraction experiments were carried out on a CAD-4 diffractometer (Nonius BV, The Netherlands) at room temperature using graphite monochromated CuK α radiation. The structures were solved with *SHELXS97*¹ and refined with *SHELXL97*². All hydrogen atoms were located on a difference Fourier map, then placed in idealized positions (C-H 0.93-0.98 Å), and refined as riding with $U_{iso}(H)=1.2-1.5U_{eq}(C)$. The crystallographic data for **2h** and **2d** are summarized in Table. Molecular structures of **2h** and **2d**, drawn with ORTEP-III³, are shown in Fig. 1 and 2, respectively.

In both compounds, all bond lengths and angles in the rigid 2,3,5,6-tetraoxabicyclo[2.2.1]heptane fragment are normal – in **2h**: the averaged values of O-O and C-O bond lengths are 1.502(3) and 1.426(3) Å, respectively, and the averaged values of C-C-O and O-C-O bond angles are 103.5(2) and 107.3(2) $^{\circ}$, respectively; and in **2d**: the averaged values of O-O and C-O bond lengths are 1.501(3) and 1.428(3) Å, respectively, and the averaged values of C-C-O and O-C-O bond angles are 103.6(2) and 107.5(2) $^{\circ}$, respectively. Interestingly, the search for molecules containing the 2,3,5,6-tetraoxabicyclo[2.2.1]heptane fragment in the Cambridge Structural Database (CSD, Version 5.29 with updates)⁴ showed no hits.

References to the X-ray section:

1. Sheldrick, G.M. *SHELXS97*. Program for crystal structure solution. (1997). University of Göttingen, Göttingen, Germany.
2. Sheldrick, G.M. *SHELXL97*. Program for crystal structure refinement. (1997). University of Göttingen, Göttingen, Germany.
3. Farrugia, L.J. (1999). *J. Appl. Cryst.* **32**, 837-838.
4. Allen, F.H. (2002). *Acta Cryst.* **B58**, 380-388.

Crystallographic data for **2h** (CCDC no. 695764) and **2d** (CCDC no. 695765) have also been deposited with the Cambridge Crystallographic Data Center [CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: +44-1233-336033; E-mail: deposit@ccdc.cam.ac.uk or www: <http://www.ccdc.cam.ac.uk>)]

Table. Crystallographic data of 2h and 2d.

	2h	2d
Chemical formula	C ₁₃ H ₁₆ O ₄	C ₈ H ₁₁ NO ₄
M_r	236.3	185.2
Cell setting, space group	<i>Monoclinic, P2₁/c</i>	<i>Monoclinic, P2₁/n</i>
a (Å)	10.6396(8)	5.5187(10)
b (Å)	10.8659(11)	9.6577(15)
c (Å)	11.1091(12)	17.276(3)
β (°)	106.62(2)	94.944(13)
V (Å ³)	1226.9(2)	917.3(3)
Z	4	4
Radiation type	CuK $_{\alpha}$	CuK $_{\alpha}$
θ_{\max} (°)	70	70
No. of independent (observed) reflections	2313 (1307)	1742 (866)
No. of parameters	155	120
Refinement on	F^2	F^2
$R[F^2 > 2\sigma(F^2)], wR(F^2), S$	0.073, 0.154, 1.016	0.039, 0.095, 0.934

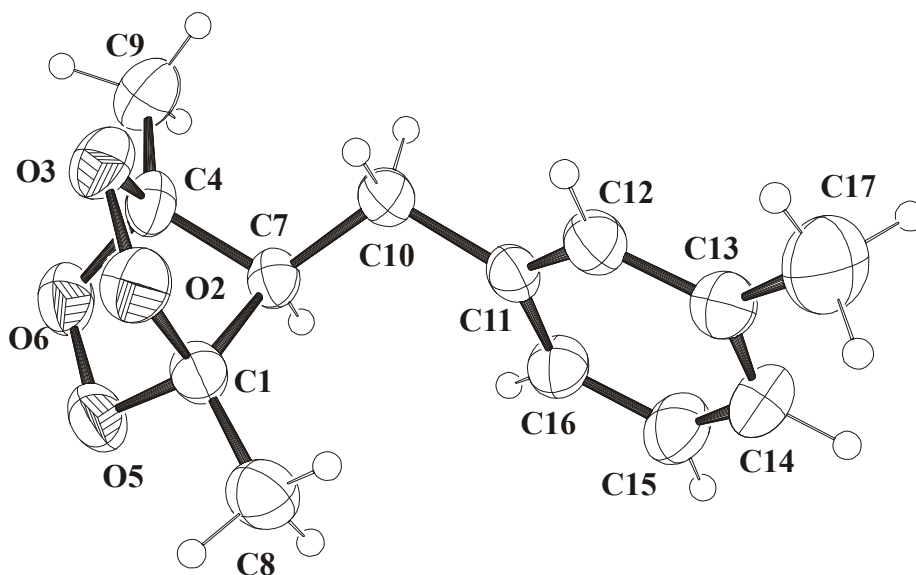


Fig. 1. The molecular structure of **2h**, showing the atomic numbering and 40% probability displacement ellipsoids.

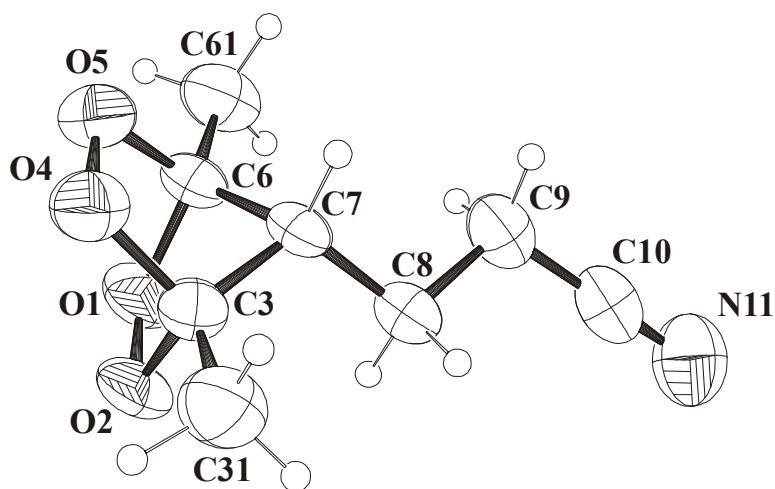


Fig. 2. The molecular structure of **2d**, showing the atomic numbering and 40% probability displacement ellipsoids.