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Stereoisomerism in the representative tetracyclic dispiro ozonide derived from (methylene)dicyclohexanone with the 1,5-diketo arrangement

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Table of Contents

1. Experimental

1. Experimental

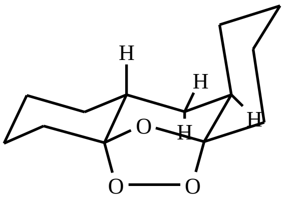
1.1 Materials and methods

All starting materials are commercially available. NMR spectra were recorded with a Bruker Avance-II 400 spectrometer (^{1}H, 400 MHz, and ^{13}C, 100 MHz) in $CDCl_3$. Residual solvent chemical shifts were used as reference and were set to δ 7.26 and δ 77.23 ($CDCl_3$). The ratio of diastereoisomers of initial diketone was established on gas chromatograph Agilent GC 6890 Plus with mass-selective detector 5973N at ionization with electron impact (EI, 70 eV), quartz capillary column HP-5MS (length 30 m, internal diameter 0.25 mm, layer of the stationary phase 0.25 μm thick), carrier gas helium. High-resolution mass spectra were recorded on an Agilent 6210 TOFLC/MS System in electrospray ionization mode with registration of positive and negative ions on a HPLC Agilent 1200 liquid chromatograph.

Monitoring of the reaction progress were done by TLC on Silufol and Sorbfil plates in EtOAc–hexane, 1:5 eluent system, visualization with iodine vapor and under UV light. Melting points were determined on a Buchi B-540 apparatus in a capillary.

1.2 Synthesis of the 1,2,4-trioxolanes (ozonides) 2a, 2b

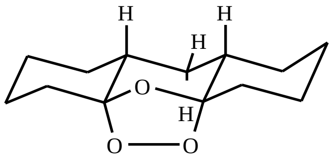
(6R,8R*)-14,15,16-Trioxatetracyclo[11.2.1.0^{1,6}.0^{8,13}]hexadecane (ozonide)* ***2a***



2a

To a solution of diketone *rac*-**1a** (0.2 g, 0.96 mmol, recrystallized from EtOH to 98% purity) in EtOH (2.6 ml), were added with stirring H_2O (1.7 ml), 30% aqueous H_2O_2 (0.2 ml, 1.92 mmol) and conc. HCl (0.26 ml, 2.88 mmol) at 20 °C. After 2-3 minutes, precipitation began. After 30 min, the precipitate was filtered off, washed with water to pH 7, and dried. Yield: 0.19 g (88%). The ratio of isomers **2a/2b** is 94:6. After the recrystallization from ethanol **2a:** mp 69-71°C (mp 69-71 °C [13]). IR (KBr) (ν_{max}/cm^{-1}): 2934, 2861; 972, 919 (-O-O-). LC-MS (APCI-Pos TOF) calcd for $C_{13}H_{20}O_3$ 224,1412, found [M+H$^+$]: 225,1455. ^{13}C NMR (100 MHz, $CDCl_3$): δ 109.7, 109.5, 40.8, 37.2, 32.9, 31.7, 30.8, 30.4, 30.4, 25.4, 25.2, 24.5, 24.0.

(6R,8S*)-14,15,16-Trioxatetracyclo[11.2.1.0^{1,6}.0^{8,13}]hexadecane (ozonide)* ***2b***



2b

To a solution of diketone *rac*-**1a** (0.2 g, 0.96 mmol, recrystallized from EtOH to 98% purity) in ether (2 ml), were added with stirring 30% aqueous H_2O_2 (0.2 ml, 1.92 mmol) and conc. HCl (0.26 ml, 2.88 mmol). The reaction mixture was stirred at 20 °C for 24 h (control by TLC, silufol, in hexane/ethyl acetate ratio 5:1). The reaction was neutralized with Na_2CO_3 solution (pH 9), and the ether layer was separated, and the aqueous layer was extracted with ether (3 × 3 ml). The combined ether extract was washed with water until neutral, dried over $MgSO_4$ and evaporated. Yield: 0.195 g (91%), white crystals. The ratio of isomers **2a**/**2b** is 30:70 (by HPLC-MS, t_R (**2a**) = 17.6 min, t_R (**2b**) = 17.3 min). After recrystallization from ethanol **2b:** mp 119-120 °C (mp 119-120 °C [13]). IR (KBr) (ν_{max}/cm^{-1}): 2938, 2857; 972, 923 (-O-O-). LC-MS (APCI-Pos TOF) calcd for $C_{13}H_{20}O_3$ 224,1412, found [M+H$^+$]: 225,1455. ^{13}C NMR (100 MHz, $CDCl_3$): δ 108.5, 41.2, 32.6, 31.6, 30.8, 25.1, 24.0. The product gives a positive test with 10% KI solution and burns with flash.

1.3. Synthesis in acetic acid

1.3.1 Synthesis in 66% acetic acid

To a solution of diketone **1a** (0.1 g, 0.48 mmol) in glacial AcOH (1 ml) cooled in an ice bath, were added H_2O (0.5 ml), 72% $HClO_4$ (0.0 46 ml, 0.80 mmol), followed by dropwise addition of 30% aqueous H_2O_2 (0. 2 ml, 1.92 mmol). A precipitate begins to form immediately. After 1 h, H_2O (4 ml) was added, the precipitate was filtered off, washed with Na_2CO_3 solution to pH > 7 and then with water to pH 7, and dried. Yield: 0.10 g (94%), white powder. The ratio of isomers **2a/2b** = 70:30.

1.3.2 Synthesis in conc. acetic acid

To a solution of diketone **1a** (0.1 g, 0.48 mmol) in conc. AcOH (1.5 ml) was added with stirring 72% $HClO_4$ (0.046 ml, 0.8 mmol) followed by dropwise addidiotn of 30% H_2O_2 (0.2 ml, 1.92 mmol). The homogeneous solution was left at 20 °C. After 48 h the homogeneous reaction mixture was diluted with water (4 ml), the precipitate was filtered off, washed with Na_2CO_3 solution to pH > 7 then with water to pH 7, and dried. Yield: 0.075 g (70%), white powder. The ratio of isomers **2a/2b** = 30:70.

1.3.3 Isomerization in conc. acetic acid

To a solution of a precipitate from experiment **1.3.1 (**0.1 g, 0.48 mmol) in conc. AcOH (1.5 ml) was added with stirring 72% $HClO_4$ (0.046 ml, 0.8 mmol). The homogeneous solution was left at 20 °C. After 48 h the homogeneous reaction mixture was diluted with water (4 ml), the precipitate was filtered off, washed with Na_2CO_3 solution to pH > 7 then with water to pH 7, and dried. Yield: 0.077 g (77 %), white powder. The ratio of isomers **2a/2b** = 20:80.

2. NMR study of the synthesized compounds

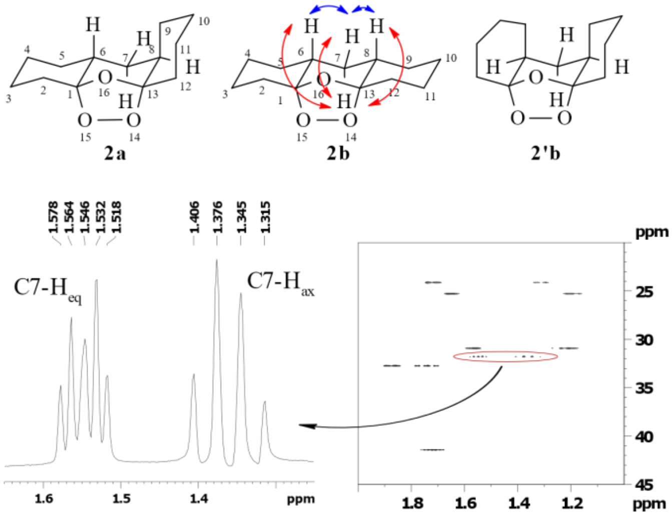
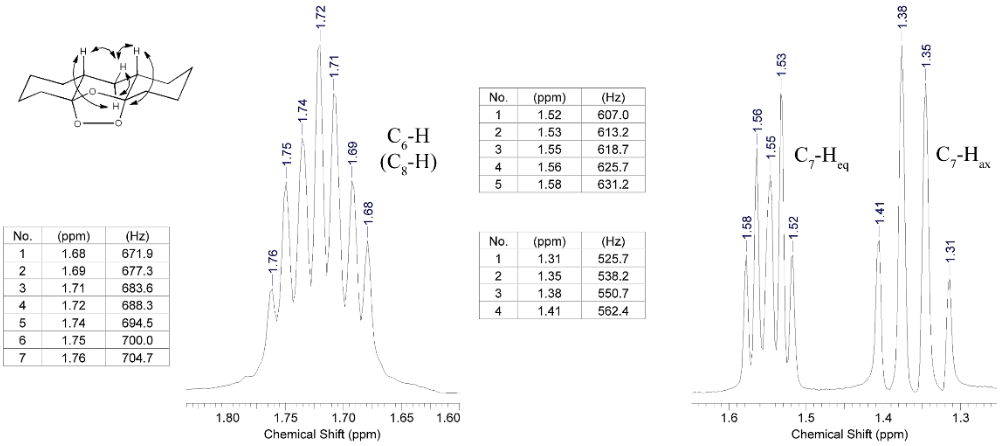


Figure S1. Diastereomeric forms of ozonides **2**. Signals of C^7-H_{ax} and C^7-H_{eq} protons were derived from HSQC spectrum of symmetric isomer **2b**.

^1H and ^{13}C signals were assigned by 2D experiments (COSY, HSQC and HMBC). Figure S2 shows selected proton signals obtained as a 1D projection from the HSQC spectrum of a symmetric product. The multiplet at δ 1.37 ppm was discussed in the main text of the article. The multiplet at δ 1.55 ppm is assigned to the equatorial proton C_7-H_{eq} and can be easily identified as a doublet of triplets. The doublet splitting (J = 13 Hz) corresponds to the geminal coupling constant, and the triplet splitting (J = 5.5 Hz) is a consequence of the vicinal interaction of proton C^7-H_{eq} with protons C^6-H and C^8-H. The multiplet at δ 1.72 in the spectrum of the symmetric isomer is assigned to the protons C^6-H and C^8-H and has the same shape as the multiplet at δ 1.74 in the spectrum of the asymmetric isomer (Figure S3), which is assigned to the proton C^6-H. This fact suggests that the constants of the spin-spin coupling for proton C^6-H are the same in the symmetric and asymmetric isomer. Now we can determine the proton C^7-H_{ax} signal at δ 1.97 ppm (asymmetric isomer, Figure

S2) as a pseudo-triplet of doublets with $J_{ax,ax} \approx J_{gem}$ =13 Hz, $J_{ax,eq}$ =5.5 Hz, and the proton C^7-H_{eq} signal at δ 1.28 as a doublet of pseudo-doublets (J_{gem}=13 Hz, $J_{eq,\ ax}$≈5.5. Hz, $J_{eq,eq}$ is close to zero).

We can now predict the shape of the C_7-H proton multiplets in **2'b** isomer. The signal of equatorial proton C_7-H_{eq} should be a doublet of triplets with very small, or close to zero (considering $J_{eq,eq}$ in asymmetric isomer) triplet splitting, and the C_7-H_{ax} signal should be a doublet of triplets with triplet J = 5.5 Hz. As one can see, the multiplet splitting of the C_7-H proton signals observed in the symmetric product reject the **2'b** structure.

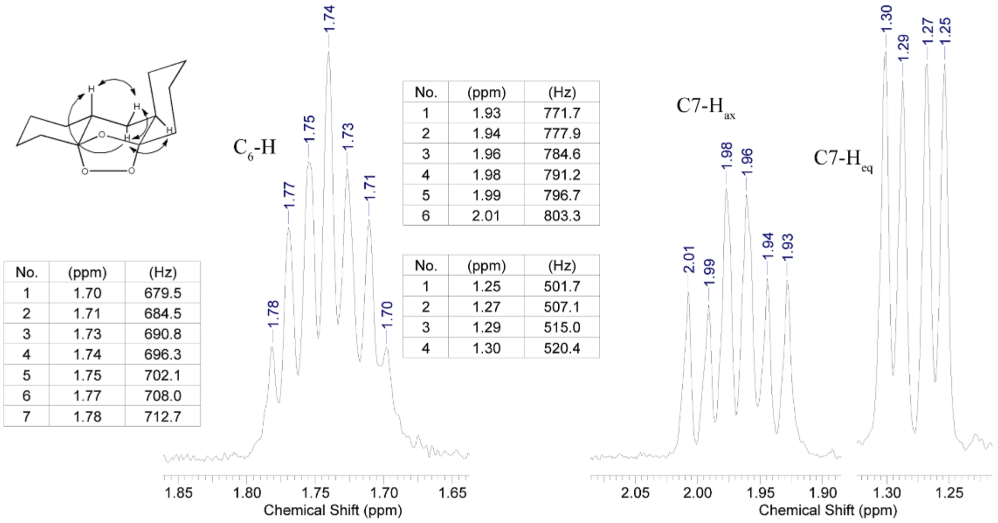


No.	(ppm)	(Hz)
1	1.68	671.9
2	1.69	677.3
3	1.71	683.6
4	1.72	688.3
5	1.74	694.5
6	1.75	700.0
7	1.76	704.7

No.	(ppm)	(Hz)
1	1.52	607.0
2	1.53	613.2
3	1.55	618.7
4	1.56	625.7
5	1.58	631.2

No.	(ppm)	(Hz)
1	1.31	525.7
2	1.35	538.2
3	1.38	550.7
4	1.41	562.4

Figure S2. Multiplet splitting of proton signals C_6-H (C_8-H) and C_7-H in symmetric product (**2b**); 1D projections from HSQC spectrum.

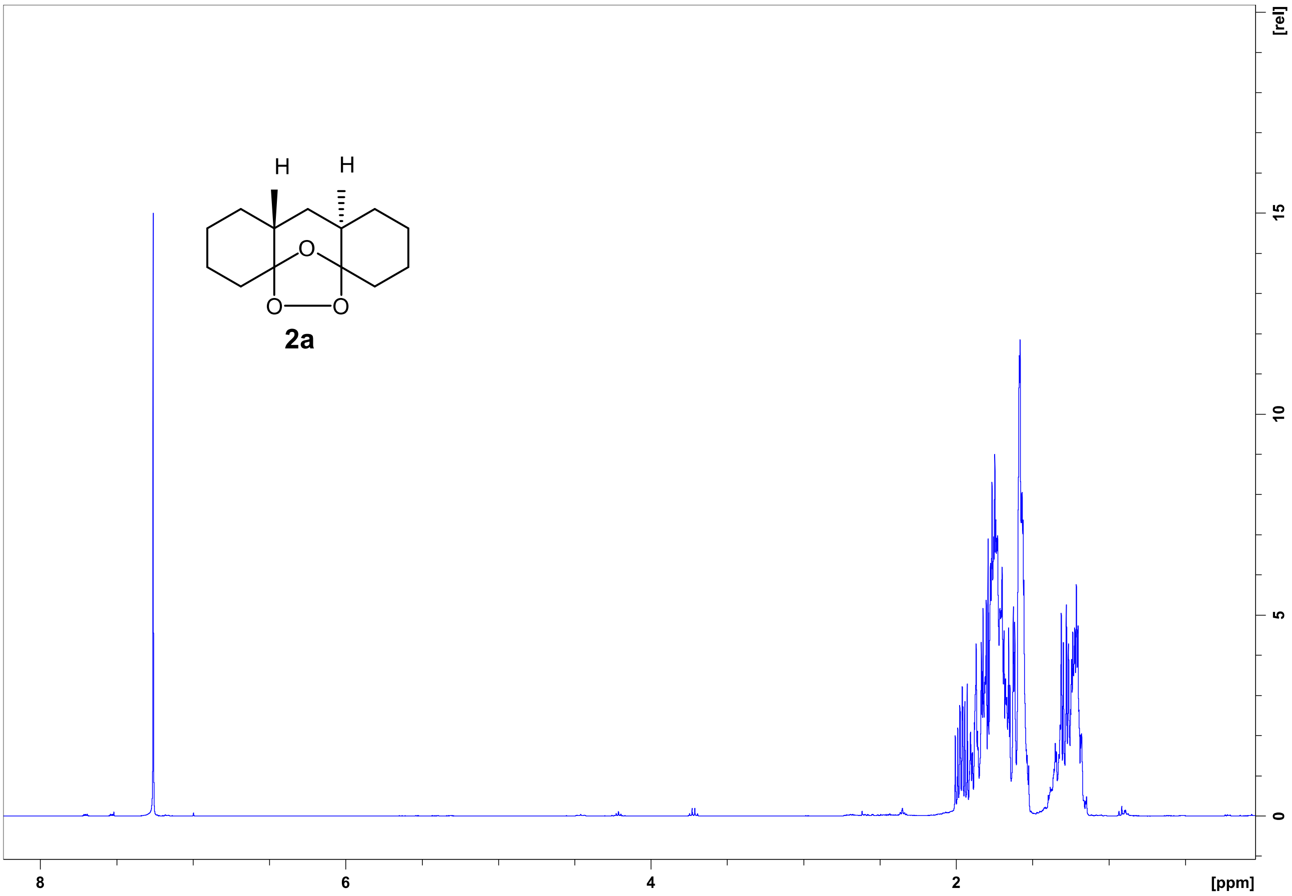


No.	(ppm)	(Hz)
1	1.70	679.5
2	1.71	684.5
3	1.73	690.8
4	1.74	696.3
5	1.75	702.1
6	1.77	708.0
7	1.78	712.7

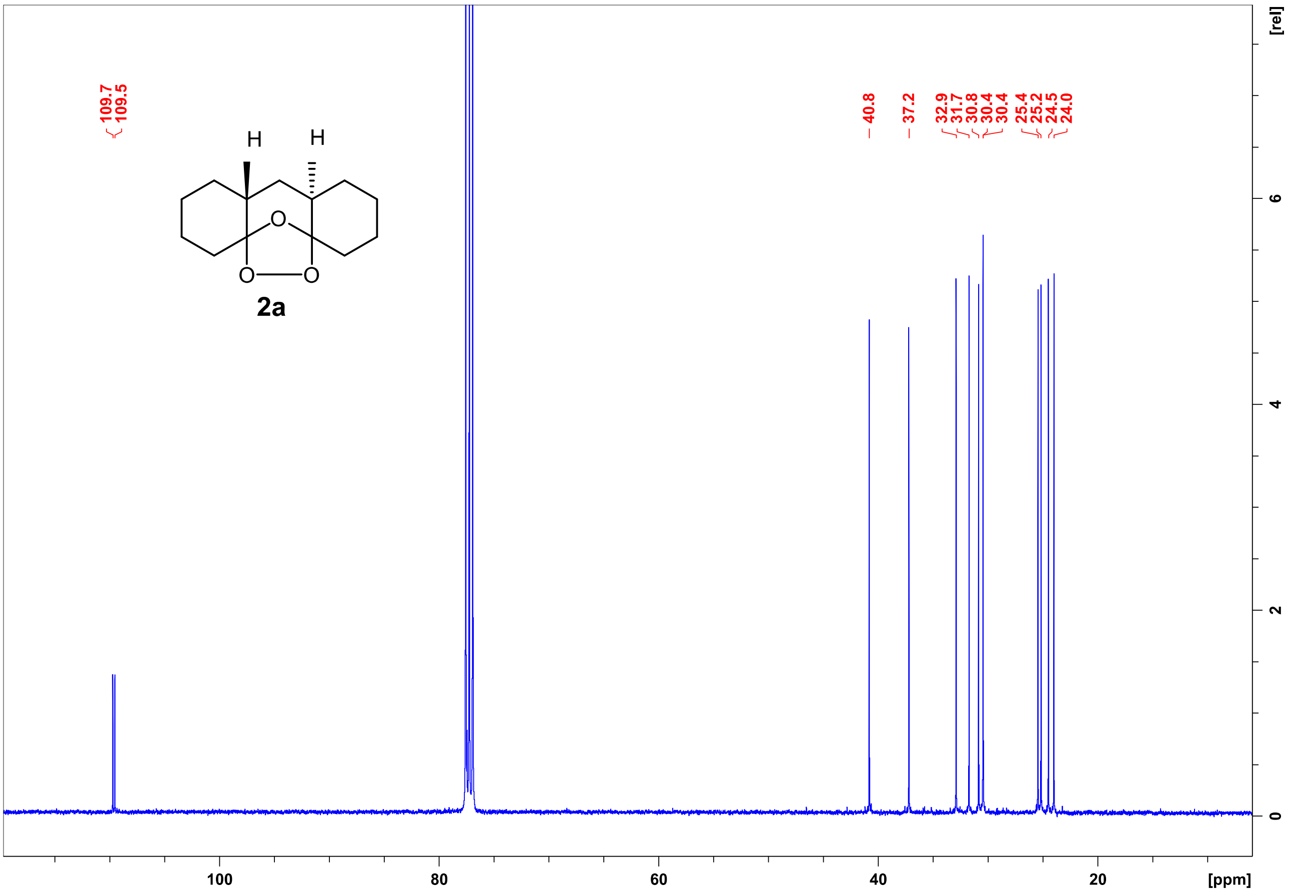
No.	(ppm)	(Hz)
1	1.93	771.7
2	1.94	777.9
3	1.96	784.6
4	1.98	791.2
5	1.99	796.7
6	2.01	803.3

No.	(ppm)	(Hz)
1	1.25	501.7
2	1.27	507.1
3	1.29	515.0
4	1.30	520.4

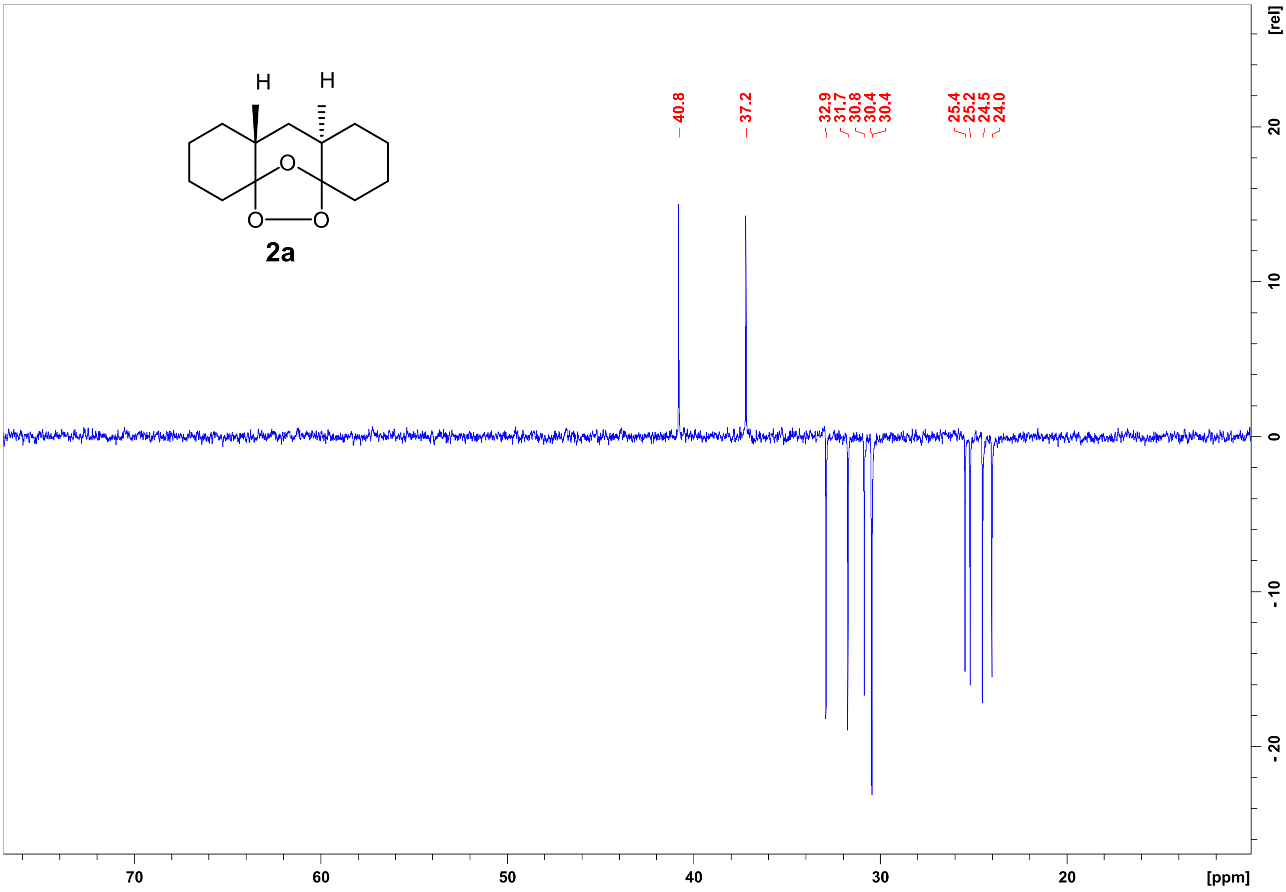
Figure S3. Multiplet splitting of C_6-H and C_7-H proton signals in asymmetric product (**2a**); 1D projections from HSQC spectrum.

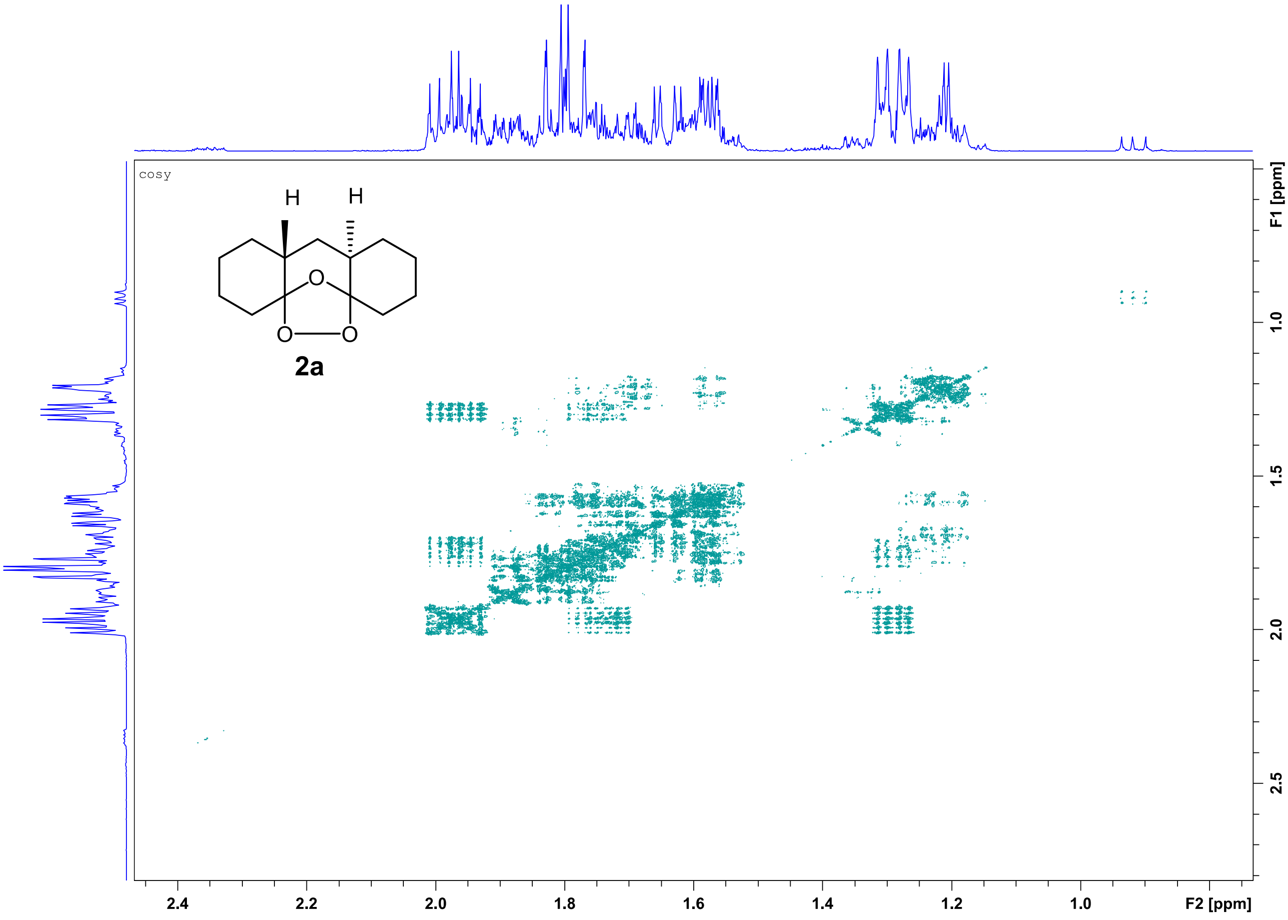


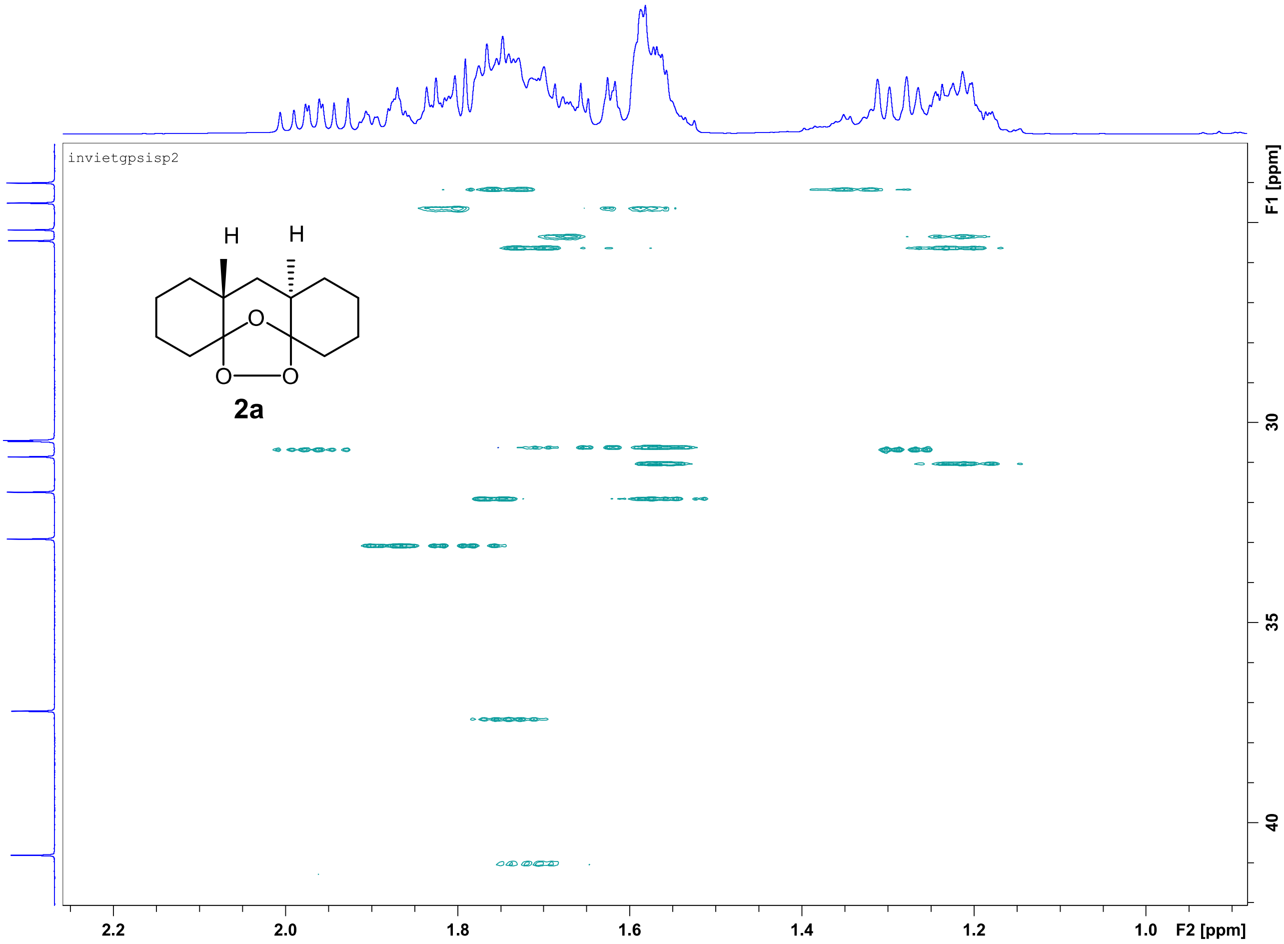
H
H
O
O
O
2a
[rel]
15
10
5
0
8
6
4
2
[ppm]

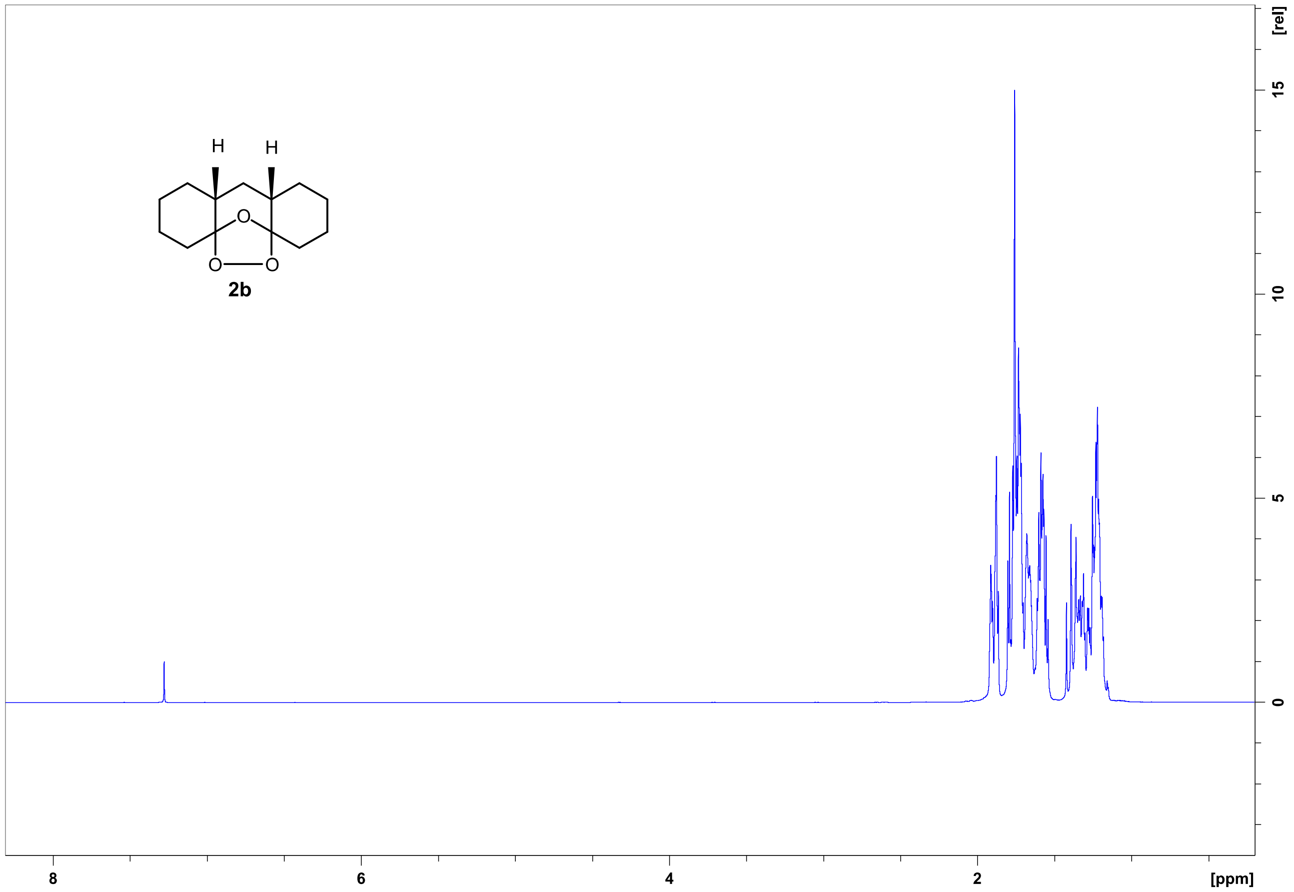


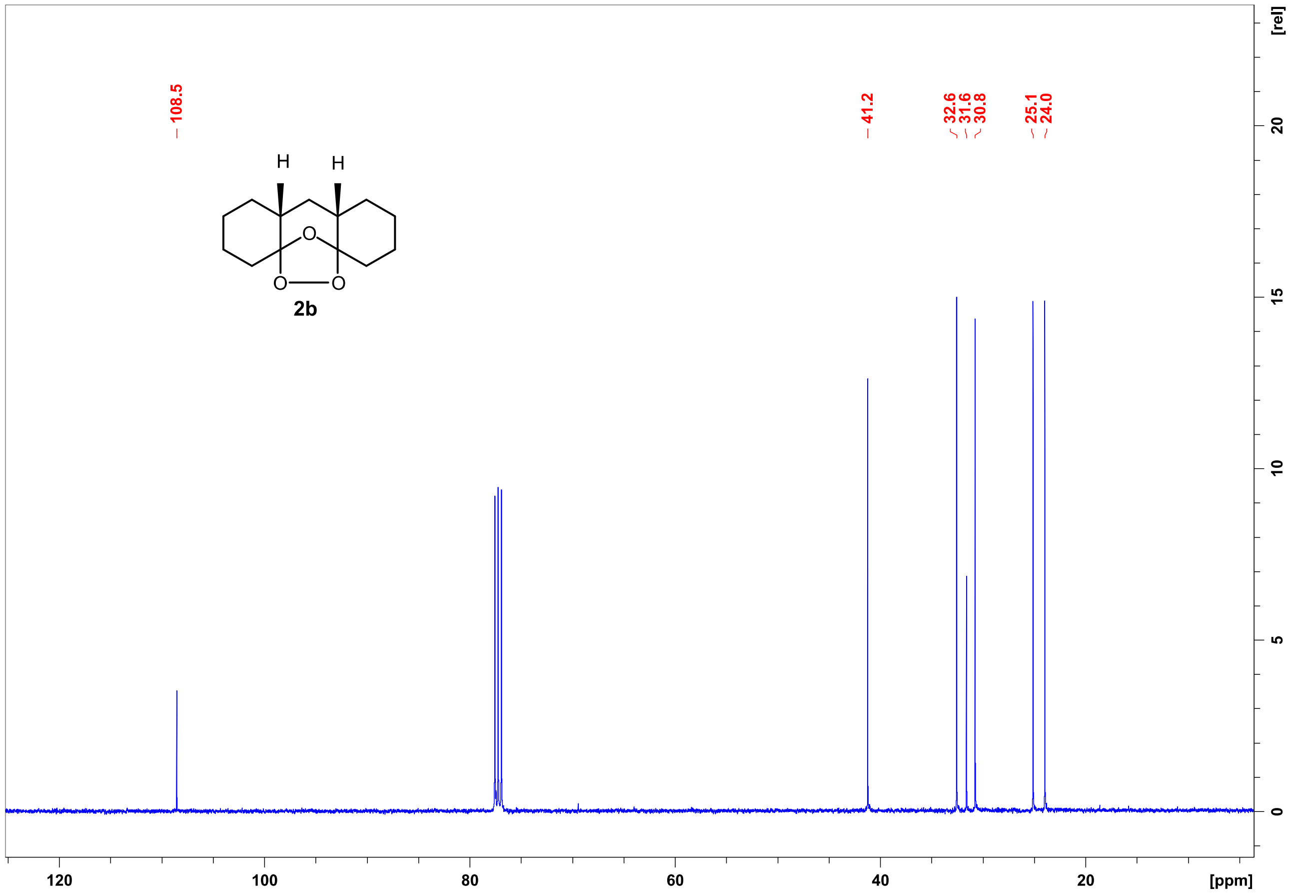
109.7
109.5
40.8
37.2
32.9
31.7
30.8
30.4
30.4
25.4
25.2
24.5
24.0
H
H
O
O
O
2a
[rel]
6
4
2
0
100
80
60
40
20
[ppm]

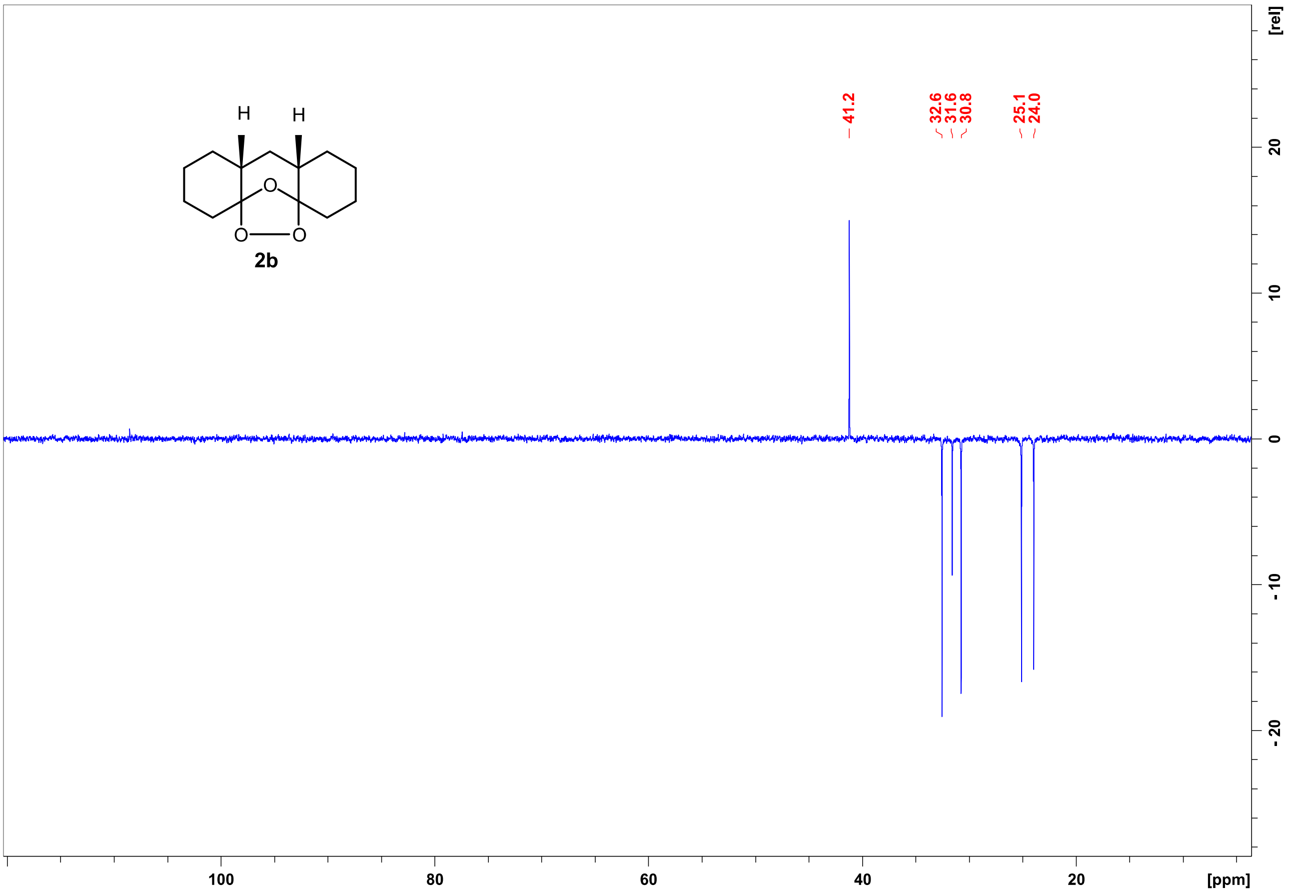

H
H
O
O
O
2a
40.8
37.2
32.9
31.7
30.8
30.4
30.4
25.4
25.2
24.5
24.0
[rel]
20
10
0
-10
-20
70
60
50
40
30
20
[ppm]

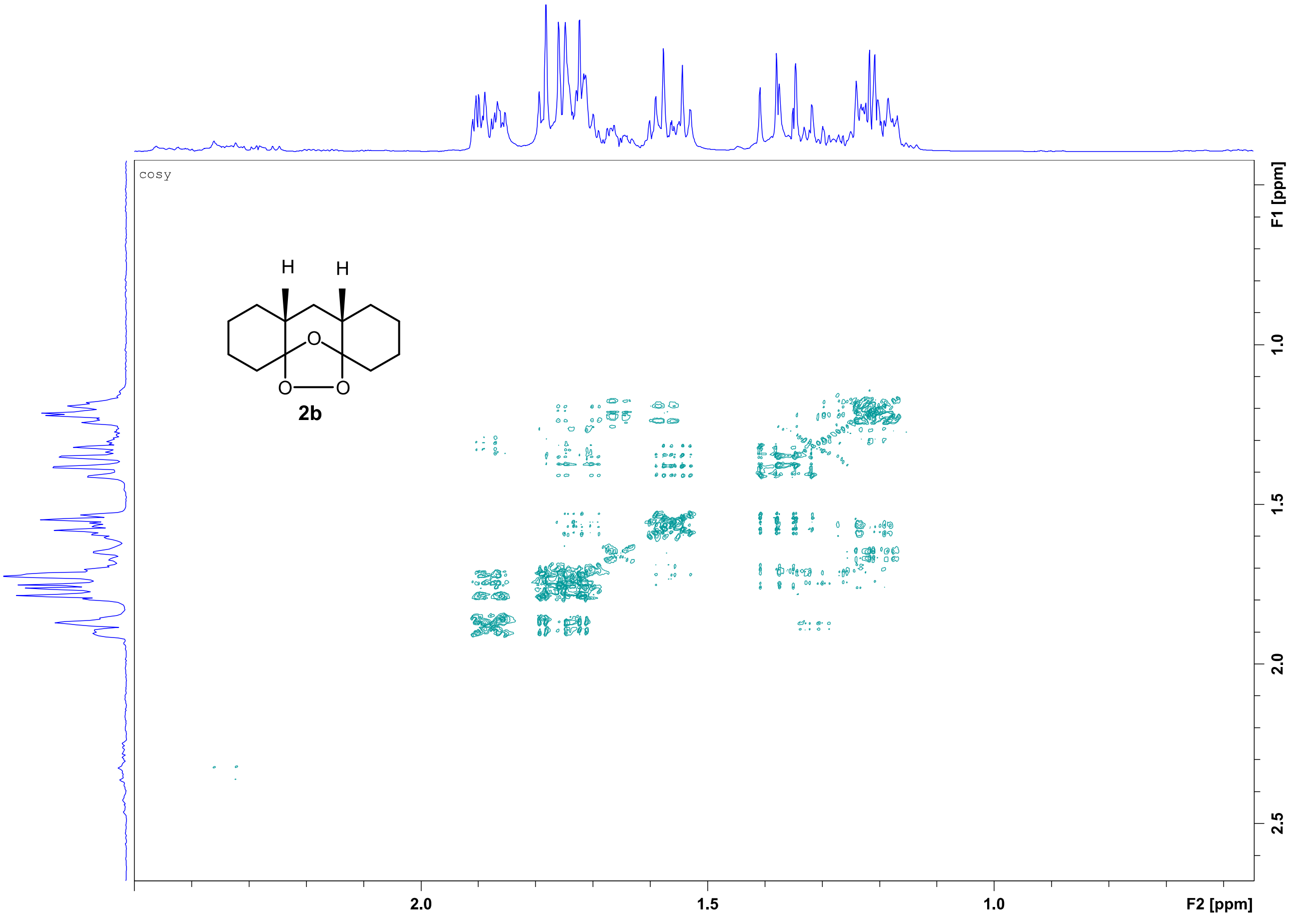

cosy
H
H
O
O
O
2a
F1 [ppm]
1.0
1.5
2.0
2.5
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
F2 [ppm]

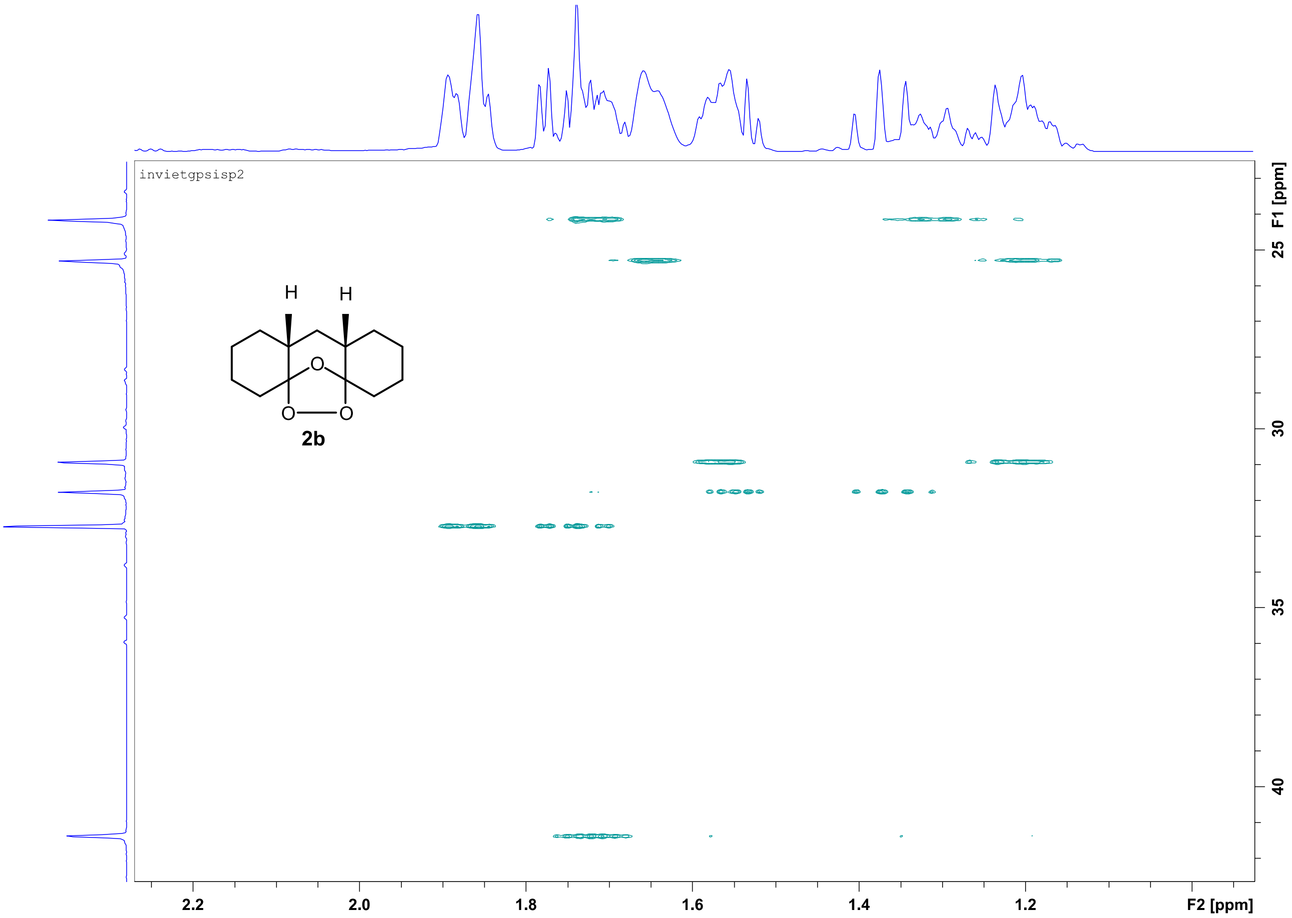

invietgpsisp2
H
H
O
O
O
2a
F1 [ppm]
30
35
40
2.2
2.0
1.8
1.6
1.4
1.2
1.0
F2 [ppm]

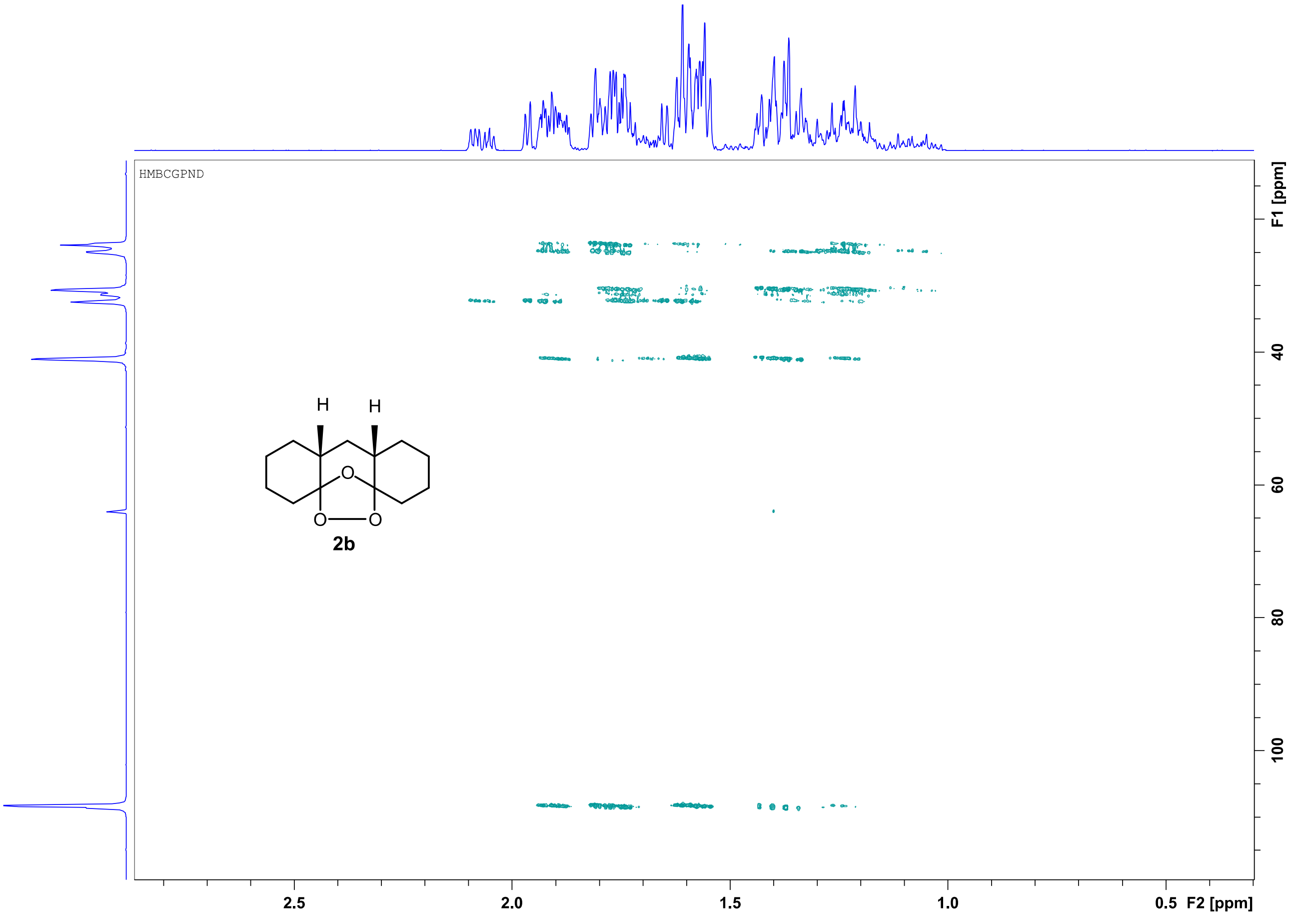

H
H
O
O
O
2b
[rel]
15
10
5
0
8
6
4
2
[ppm]


108.5
41.2
32.6
31.6
30.8
25.1
24.0
H
H
O
O
O
2b
[rel]
20
15
10
5
0
120
100
80
60
40
20
[ppm]


H
H
O
O
O
2b
41.2
32.6
31.6
30.8
25.1
24.0
[rel]
20
10
0
- 10
- 20
100
80
60
40
20
[ppm]

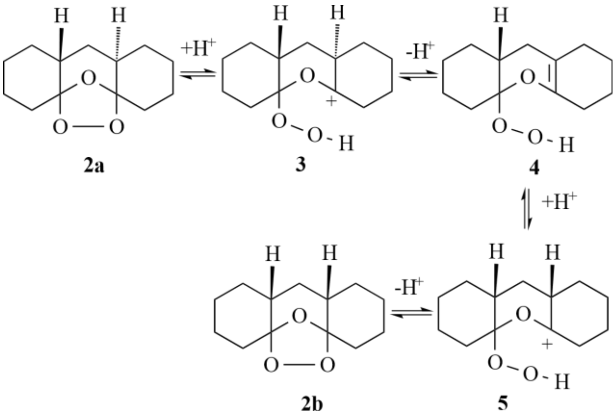

cosy
H
H
O
O
O
2b
F1 [ppm]
1.0
1.5
2.0
2.5
2.0
1.5
1.0
F2 [ppm]


invietgpsisp2
H
H
O
O
O
2b
F1 [ppm]
25
30
35
40
2.2
2.0
1.8
1.6
1.4
1.2
F2 [ppm]


HMBCGPND
H
H
O
O
O
2b
F1 [ppm]
40
60
80
100
2.5
2.0
1.5
1.0
0.5
F2 [ppm]

The proposed mechanism of stereoisomerization of ozonides

The proposed mechanism of stereoisomerization of ozonide **2a** to **2b** is shown in Scheme S2. Protonation of the peroxide bond in an acidic medium lead to the formation of carbocation **3**, which, after the elimination of the methine proton, is converted into intermediate unsaturated compound **4**. Further, the double bond of the hydropyran ring, activated by the proximity to the oxygen atom, attaches a proton to form the carbocation **5** with the subsequent addition of the hydroperoxide fragment and the formation of the *meso*-form **2b**:



Scheme S2. The proposed mechanism of stereoisomerization of ozonide **2a** to **2b**